Catalytic Asymmetric Synthesis of Cyclic Acetals and Dearomatization Reactions of Indoles & Naphthols

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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June 2024

Dedicated

to

My Family

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Catalytic Asymmetric Synthesis of Cyclic Acetals and Dearomatization Reactions of Indoles & Naphthols***" is the outcome of the research work carried out by me under the supervision of **Prof. Subhas Chandra Pan**, Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

In harmony with the general practice of reporting scientific observations, due acknowledgements have been made if the work is established on the findings of other investigators.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Catalytic Asymmetric Synthesis of Cyclic Acetals and Dearomatization Reactions of Indoles & Naphthols***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Amit Shikari (Roll No: 176122103) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati

June, 2024

Prof. Subhas Chandra Pan

Supervisor

~Acknowledgements~

I would like to appreciate all the peoples around me who have assisted and guided me throughout my academic journey. It would have been impossible to finish all the work presented in this thesis without the help of many individuals.

First of all, I would like to express my sincere gratitude to my supervisor **Prof. Subhas Chandra Pan** for giving me an opportunity to work in such a beautiful research environment and for introducing me to this challenging yet fascinating field of asymmetric catalysis. I am extremely grateful to him for his inspiring guidance, support, helpful discussions throughout my research work.

I would like to acknowledge my doctoral committee members **Prof. Anil Kumar Saikia** (Chairman), **Dr. Dipankar Srimani** and **Dr. Krishna Pada Bhabak** for their valuable suggestions and encouragements which helped a lot to improve my thesis.

I extend my sincere thanks to the **Dr. Kalishankar Bhattacharyya** for his collaborative assistance during my research work.

I am thankful to IIT Guwahati for the fellowship and also thankful to IIT Guwahati, Department of Chemistry and Central Instruments Facilities (CIF) for providing research facilities and instrumental facilities. I will always remain thankful to the staff members of CIF and department of chemistry.

My deepest gratitude to my dear lab mates Dr. Utpal Nath, Dr. Keshab Mondal, Dr. Rajendra Maity, Dr. Buddhadeb Mondal, Dr. Soumendra Nath Mukhopadhyay, Dr. Subas Chandra Sahoo, Dr. Megha Balha, Dr. Chandan Gharui, Dr. Nimisha Bania, Dr. Chandrakanta Parida, Subhankar Biswas, Rupkumar Khuntia, Dipankar Barman, Jyotish Barman, Ramji Meher, Gaurav Jaiswal and Dipali Digangana Sahoo for their great support during my Ph.D. period. Their constant help definitely

smoothen this journey. I sincerely thank to my project student Soumili Pal for her contribution in my works.

I am thankful to all NMR, XRD and HRMS operators.

I am grateful to all my teachers throughout my academic career for their constant encouragement and guidance starting from my school life, until today.

I would like to thank all my friends, Ph.D. batch mates, seniors and juniors who helped during my work and for making a friendly environment.

My PhD endeavor could not be completed without the endless love, support and blessing from my parents. My heartfelt gratitude goes to my father Dilip Kumar Shikari, mother Anu Shikari and my elder sisters Munmun Shikari. It is my pleasure to thank Sanchari Rakshit for her constant support and always being there in difficult times. I am blessed to have these pillars of strength in my life. I thank the Almighty for making all this possible and giving me strength and determination to work

Sincerely,

Amit Shikari

¤ *Table of Contents* ¤

Abbreviation

Ac	Acetyl
AcOH	Acetic acid
anh.	Anhydrous
aq.	Aqueous
Å	Angstrom
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
br.	Broad
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
Bu	Butyl
CCDC	Cambridge crystallographic data centre
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
^{o}C	Degree celsius
d	Doublet or day
δ	Chemical shift or delta
DACH	*trans*-(1,2)-Diaminocyclohexane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
δ	Delta
EtOAc	Ethyl acetate
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 seives
MTBE	Methy tertiary butyl ether
NHC	N-Heterocyclic carbene
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
q	Quartet
rac	Racemic
RCM	Ring-closing metathesis
rt	Room temperature
s	Singlet
THF	Tetrahydrofuran
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TES	*tert*-Butyldiethylsilyl
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
Ts	*p*-Tolylsulfonyl
uv	Ultra violet
XRD	X-ray diffraction

Abstract

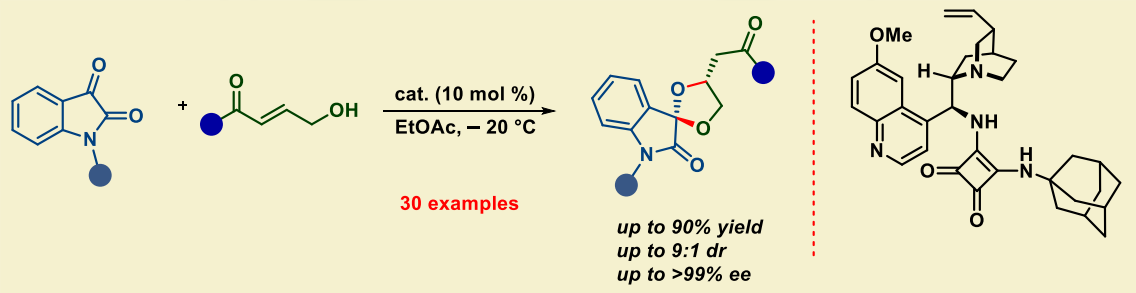
The contents of the present thesis entitled as "***Catalytic Asymmetric Synthesis of Cyclic Acetals and Dearomatization Reactions of Indoles & Naphthols***" have been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the Ph.D. research programme.

Chapter I: Overview

Chapter I is divided in two parts. First part contains a brief discussion on asymmetric organocatalysis particularly, bifunctional thiourea and squaramide catalysis and chiral phosphoric acid. A brief description of Michael reaction is also presented here. And second part contains a brief discussion on dearomatization of arene systems mainly focused on indole and naphthol motifs.

Chapter II: Organocatalytic Asymmetric Synthesis of Cyclic Acetals with Spirooxindole Skeleton

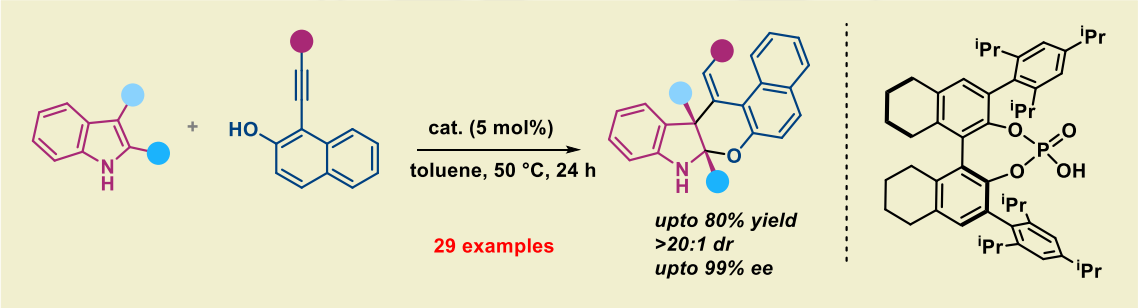
In this chapter, a method for synthesizing a cyclic acetal with a spirooxindole structure asymmetrically using organocatalysis has been devised. This involves a domino reaction between isatin and γ-hydroxy enones. Among the catalysts tested, the bifunctional squaramide catalyst featuring an adamantyl motif exhibited the highest efficiency in promoting the cascade reaction. The cyclic acetal products are obtained with good to high yields, high enantioselectivities, and moderate diastereoselectivities.



Reference: Shikari, A.; Mandal, K.; Chopra, D.; Pan, S. C. *Adv. Synth. Catal.* **2022**, *364*, 58 – 63.

Chapter III: Catalytic Asymmetric Dearomatization of 2,3-Disubstituted Indoles by a [4 + 2] Cycloaddition Reaction with In Situ Generated Vinylidene ortho-Quinone Methides (VQM)

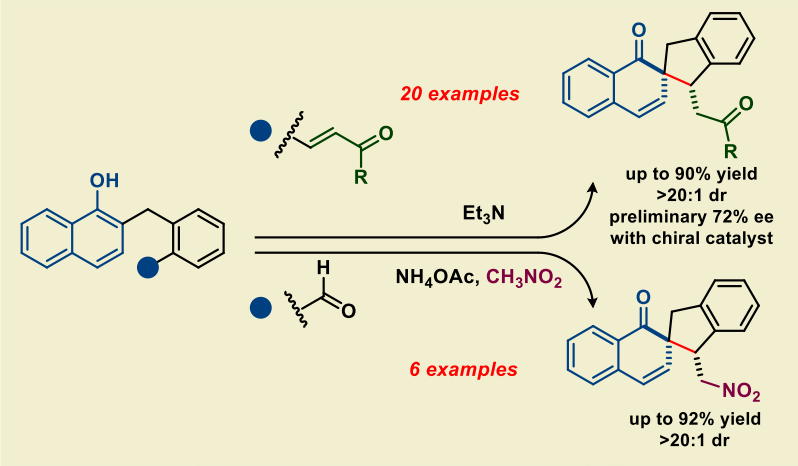
A method for the enantioselective dearomatization of 2,3-disubstituted indoles through an organocatalytic intermolecular [4 + 2] cycloaddition reaction with in situ generated vinylidene *ortho*-quinone methide has been detailed. This protocol enables the efficient synthesis of a broad spectrum of polycyclic 2,3-fused indolines featuring vicinal quaternary carbon stereocenters, achieved with high yields and outstanding diastereo- and enantioselectivities.



Reference: Shikari, A.; Parida, C.; Pan, S. C. *Org. Lett.* **2024**, *26*, 5057 – 5062.

Chapter IV: Organocatalytic Dearomative Spirocyclization Reaction of Enone-Tethered *α*-and *β*-Naphthols and Dearomatization Reaction of In Situ Generated Nitro-Olefin-Tethered *α*-Naphthols

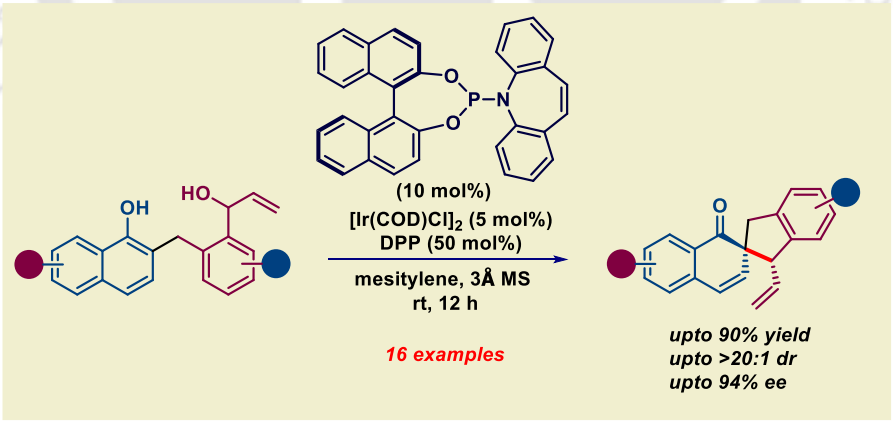
In this study, we present a catalytic dearomative spirocyclization reaction involving novel substrates containing aryl/alkyl enone-tethered *α*- and *β*-naphthols, as well as a dearomatization reaction of in situ generated nitro-olefin-tethered *α*-naphthols. The resulting spirocarbocycles were obtained in moderate to good yields, showcasing high diastereoselectivities. Additionally, we introduced a preliminary catalytic asymmetric variant of this reaction. Furthermore, we explored a few applications such as hydrogenations and epoxidation reactions. Complementary to the experimental work, a theoretical study was conducted to elucidate the high diastereoselectivity observed in the triethylamine-catalyzed spirocyclization reaction.



Reference: Shikari, A.; Sharma, M.; Bhattacharyya, K.; Pan, S. C. *J. Org. Chem*. **2024**, *89*, 9769.

Chapter V: Cooperative Iridium and Brønsted Acid Catalyzed Intramolecular Asymmetric Allylic Dearomatization of *α*- and *β*-Naphthols

A method for the asymmetric allylic dearomatization of novel substrates containing secondary racemic allyl alcohol-tethered *α*- and *β*-naphthols. Using iridium/Brønsted acid dual catalysis, the resulting naphthalenone spirocarbocycles were achieved in high yields and enantioselectivities with notable diastereoselectivities.



Reference: Shikari, A.; Pan, S. C. *Manuscript communicated.*

Chapter I

Overview

PART 1

1.1 Introduction

In French scientific literature, the term "dissymmetry" was documented as early as 1820, preceding the work of Louis Pasteur. Pasteur, a prominent French scientist, employed the term "dissymmetric" in his 1860 lecture titled "*Recherches sur la Dissymétrie Moléculaire des Produits Organiques Naturels*." This term was later translated into English as "asymmetric."[1] Molecules that are chiral have a non-superimposable mirror image and they are known as enantiomers. Although, they possess identical chemical and physical properties such as boiling points, refractive indices, reactivity, melting points, solubility, but often behave differently under the external influence of chiral environment. Moreover, the different enantiomers can have different odor, taste and more importantly different pharmacological properties. For example, the natural (*S*)-(+)-linalool **1** has an odor like petitgrain oil, whereas (*R*)-(+)-linalool *ent*-**1** smells like lavender (Figure 1).[2]

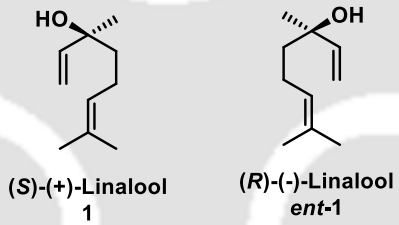


Figure 1: The enantiomers of linalool.

On the other hand (*S*)-(-)-asparagine **2** has bitter taste whereas (*R*)-(+)-asparagine *ent*-**2** is sweet (Figure 2).[3]

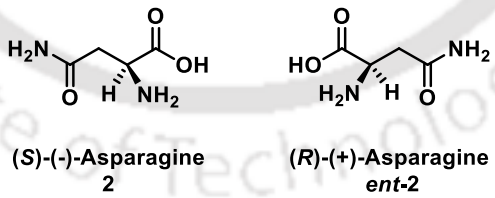


Figure 2: The enantiomers of asparagine.

Enzymes in living systems are chiral and mostly exist as single enantiomeric form. Thus, they are able to distinguish between enantiomers. One enantiomer of a drug may have a desired valuable effect while the other may cause serious and even harmful side effects. For example, dopamine is an effective drug for Parkinson's disease, and only (*S*)-Dopa **3** is effective in restoring nerve function while (*R*)-Dopa *ent*-**3** is toxic (Figure 3).[4]

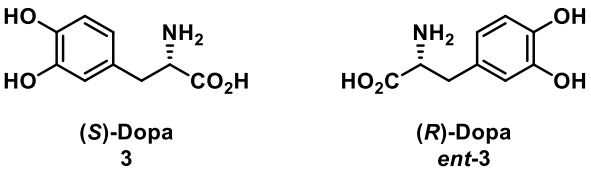


Figure 3: The enantiomers of Dopa.

Countless examples can be found in nature where biological systems respond in a different way to the opposite enantiomers. Hence, it is crucial to synthesize natural products or drug molecules in enantiomerically pure forms to ensure they exhibit the desired physical, chemical, and biological properties.

Enantiomerically pure compounds can be obtained either by mechanical or chemical resolution of the corresponding racemic starting materials. However, a major drawback of chiral resolution of racemates is the maximum theoretical yield of only 50% and the undesired enantiomer needs to be discarded. This is where asymmetric synthesis came into being fruitful. Asymmetric synthesis, by which achiral or prochiral starting materials can be converted to the chiral products under the influence of a chiral environment.

1.2 Asymmetric catalysis

It is a type of catalysis in which a chiral catalyst directs the formation of a chiral compound such that formation of one particular stereoisomer is favored. Asymmetric synthesis can be classified into four major categories: (a) substrate-controlled methods, (b) auxiliary-controlled methods, (c) reagent-controlled methods, and (d) catalyst-controlled methods. The first three methods require either valuable chiral reagents or chiral substrates in stoichiometric amounts which make the processes expensive. In contrast, catalyst-controlled methods are economical and sustainable. Catalyst-controlled methods can be classified into three main categories, based on the nature of catalysts used:

i) Biocatalysis[5] is the chemical process through which enzymes or other biological catalysts are used as for regio-, chemo- and stereoselective transformations.

ii) Metal catalysis[6] have become one of the most actively studied due to unthinkable transformations could be easily performed with the help of metal catalysts.

iii) Organocatalysis[7], the use of small chiral organic molecules as catalysts for stereoselective reactions has had a significant impact in chemical synthesis.

1.3 Asymmetric Organocatalysis

Asymmetric organocatalysis has been established as the third essential foundation in asymmetric catalysis, alongside enzymes and metal-based catalysts, and has become integral to the work of scientists in both academic research and industrial applications. Unique concepts and methods have been developed, leading to rapid advancements in this field, particularly over the past two decades.[8] It has also been publicly recognized by numerous prestigious awards, *i.e.* the 2021 Nobel prize in chemistry which was awarded to Benjamin List and David MacMillan for "*the development of asymmetric organocatalysis*". Among various organocatalytic methodologies, there are different types of activation and two main areas can be identified on the mechanistic basis:
(i) covalent organocatalysis and (ii) non-covalent organocatalysis.

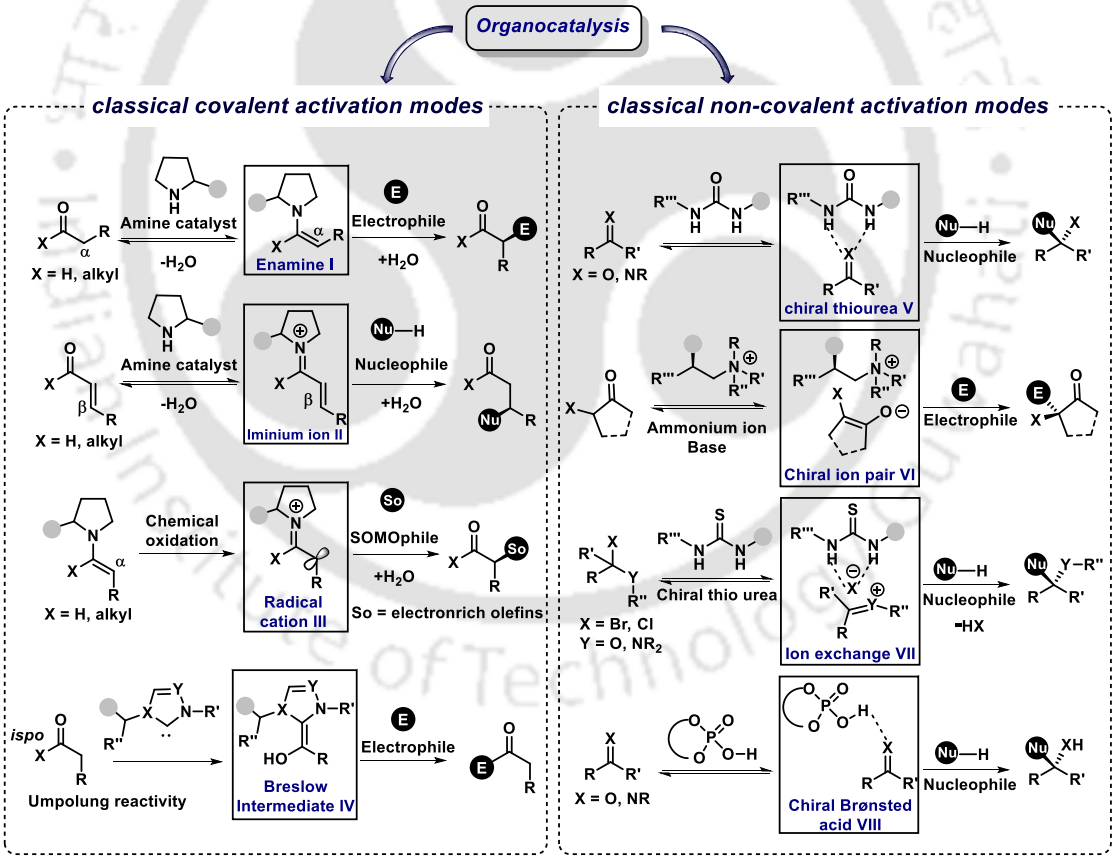


Figure 4: Generic mechanisms of organocatalytic reactivity

Covalent-based modes of activation exploit the ability of an organic catalyst to covalently bind a substrate in a reversible fashion and form a reactive intermediate that can participate

in many reaction types with consistently high enantioselectivity. Chiral primary and secondary amines belong to this class, activating carbonyl substrates *via* the formation of nucleophilic enamines **I**[9] (from enolizable aldehydes and ketones), electrophilic iminium ions **II**[10] (from unsaturated carbonyl compounds), and *α*-iminyl radical cation intermediates **III**[11] (upon single-electron oxidation of enamines by a chemical oxidant). *N*-heterocyclic carbene catalysts **IV**[12] offer an alternative activation mechanism for aldehydes, conferring an inverted (umpolung) reactivity to the normally electrophilic carbonyl carbon atom upon formation of Breslow intermediate **IV**[13], which acts as an acyl anion equivalent[14,15]. These activation modes, which rely on strong, directional interactions, enable the stereoselective functionalization of unmodified carbonyl compounds at the *ipso*, *α*, and *β* positions.

Non-covalent approaches are based on the cooperation of several weak attractive interactions between the catalyst and a basic functional group on the substrates[16]. Although the catalyst–substrate interactions are generally weaker and less directional than their covalent counterparts, they operate in concert to ensure a high level of transition state organization, resulting in a high degree of enantioselectivity. Hydrogen-bonding activation **V**[17], phase-transfer catalysis **VI**[18], anion-binding activation **VII**[19], and Brønsted acid catalysis **VIII**[20] is all useful organocatalytic strategies for making chiral molecules[21].

- ***1.3.1 Asymmetric Hydrogen Bonding Promoted Catalysis:***

During the last decade, diverse H-bonding catalysts were developed and applied to a wide range of asymmetric organic transformations. The catalysts according to their activation patterns can be simply classified as three categories: (Figure 5)

i) double hydrogen bond catalyst[22], the simultaneous donations of dual hydrogen bonds are proved to be an efficient strategy for the electrophile activation.

ii) single hydrogen bond catalyst[23], asymmetric transformations involving the donation of a single H-bond for the activation are less common than those double H-bonding activation.

iii) acid/base bifunctional catalyst[24], the mostly investigated strategy among the hydrogen bonding catalyses in recent years is the simultaneous activation of both nucleophiles and electrophiles, by Brønsted base and Brønsted acid moieties, respectively.

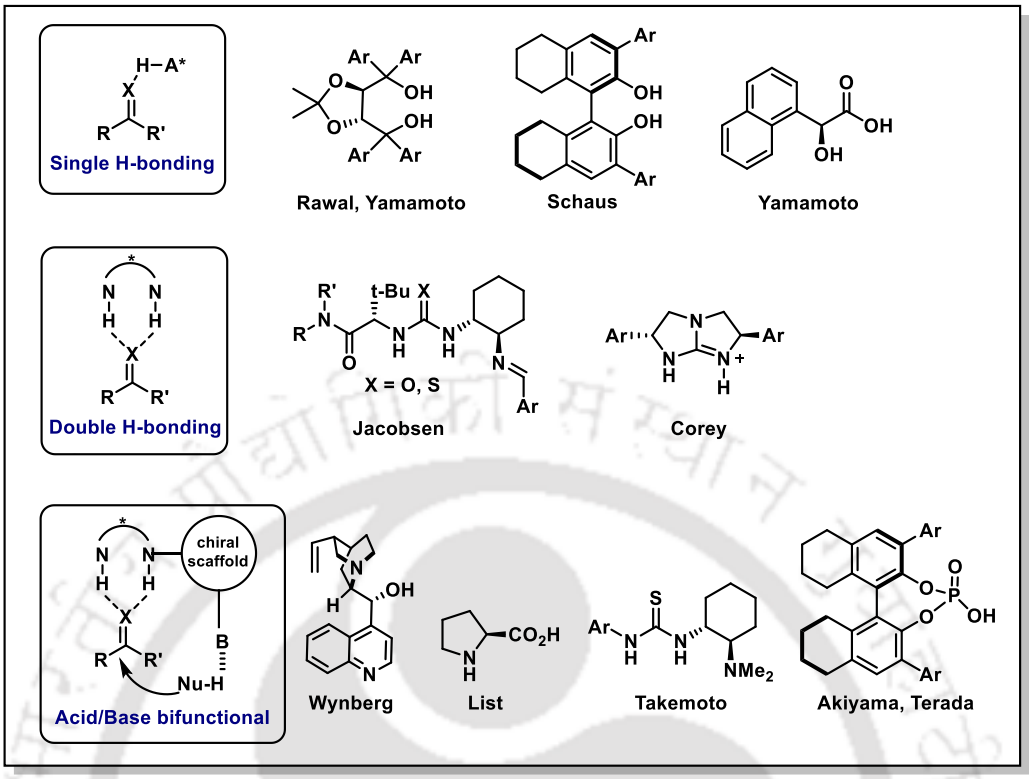
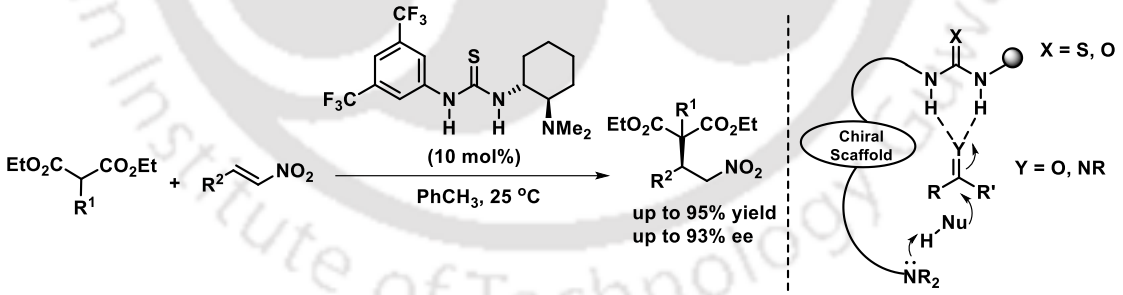


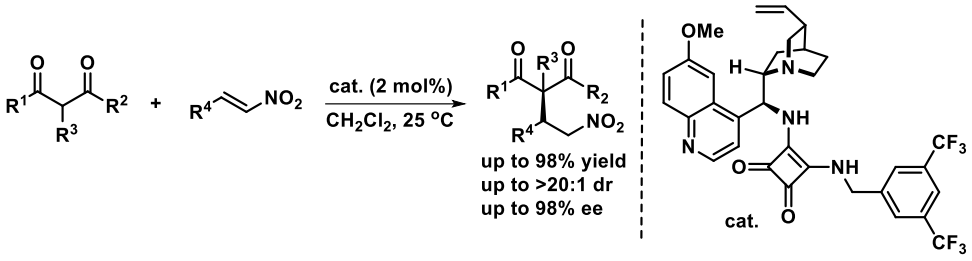
Figure 5: H-bonding catalysts

In 2003, bifunctional thiourea catalyst was first reported by Takemoto and co-workers,[25] they have developed a tertiary amino thiourea based bifunctional organocatalyst (scheme 1).



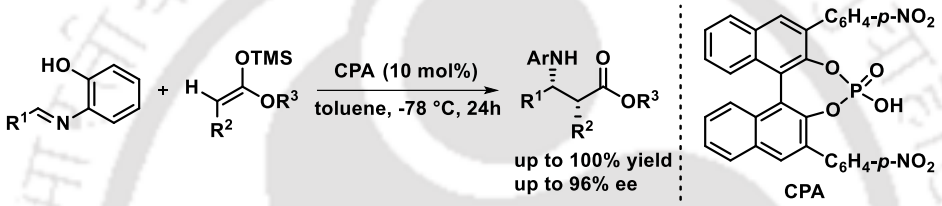
Scheme 1: Enantioselective Michael addition of malonates to nitroolefins using bifunctional thiourea catalyst

In 2008, Rawal and co-workers first reported cinchona alkaloid derived bifunctional squramide catalyzed enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins[26] (scheme 2).



Scheme 2: The first bifunctional squaramide catalyzed reaction

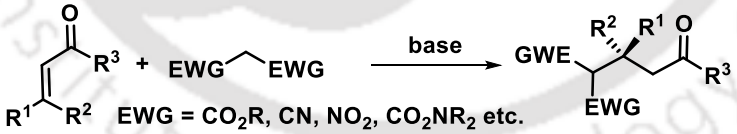
Although the use of BINOL-derived phosphoric acids has been known for over 50 years in organic synthesis, their usage as catalysts started about 20 years ago. Akiyama is widely credited as one of the pioneers of the field with his report in 2004 on the chiral Brønsted acid-catalyzed Mannich reaction[27] (scheme 3).



Scheme 3: Brønsted acid-catalyzed Mannich reaction

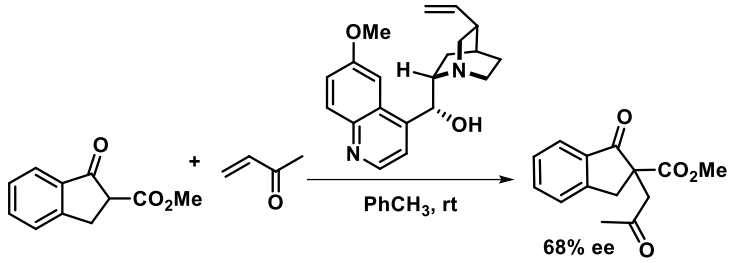
1.4 Michael reaction

The Michael reaction is one of the most important reactions in organic chemistry. In 1887 Arthur Michael discovered the addition of carbon nucleophiles to conjugate acceptor systems, which is commonly known as Michael addition (Scheme 4).[28]



Scheme 4: The Michael reaction

The first example of asymmetric Michael reaction was discovered by Wynberg in 1975. He utilized optically active quinine as catalyst in the Michael addition of 1-oxo-2-indanecarboxylate to methyl vinyl ketone and the desired product was obtained in 68 % ee (Scheme 5).[29]



Scheme 5: The first asymmetric Michael reaction by Wynberg.

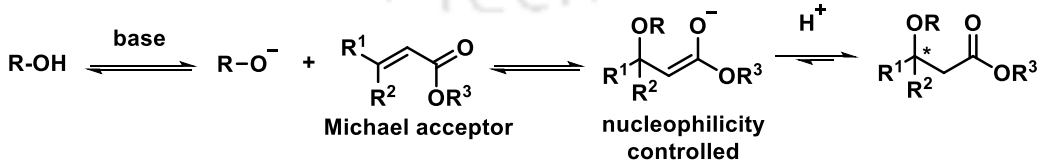
- ***Classification of the Michael addition***

Depending on the nature of the nucleophile (Michael donor), Michael addition can be classified into the following types:

- *Carba*-Michael addition
- *Aza*-Michael addition
- *Oxa*-Michael addition
- *Phospha*-Michael addition
- *Thia*-Michael addition

The present thesis is focused on *oxa*-Michael addition. The details of other types of Michael additions, namely *carba*-,[30] *aza*-[31], *phospha*-[32] and *thia*-Michael[33] additions can be found elsewhere.

The first example of an *oxa*-Michael addition was reported by Loydl in 1878 for the synthesis of malic acid (Scheme 6).[34] Major challenges of *oxa*-Michael reactions are the reversibility in the alcohol addition step as well as low reactivity of the employed alcohols. Pleasingly, during recent years a variety of approaches have been developed for the enhancement of reactivity and stereoselectivity.



Scheme 6: The *oxa*-Michael reaction

PART 2

1.5 Introduction

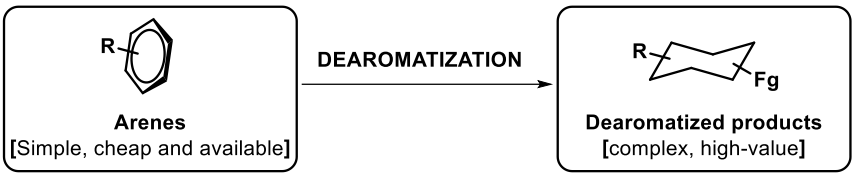
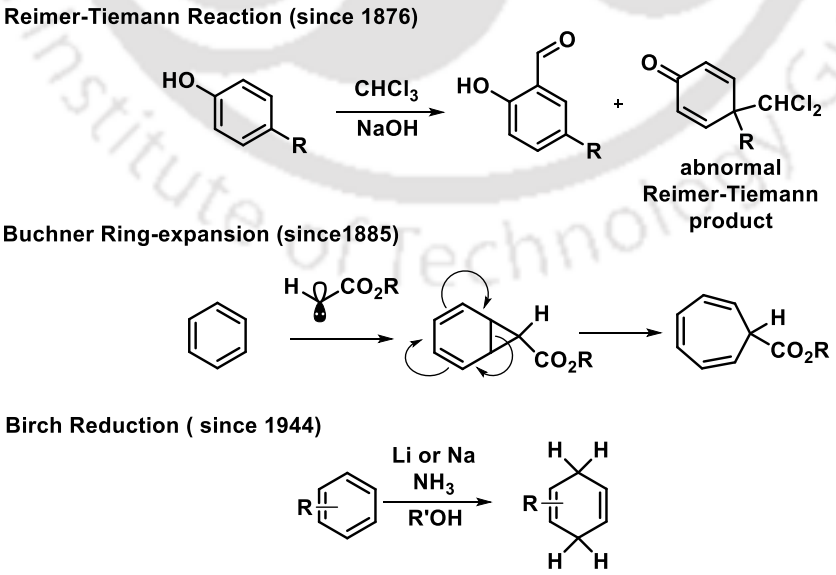


Figure 6: Dearomatization

A dearomatization reaction involves the transformation of aromatic compounds (arenes) into non-aromatic compounds, thereby losing the characteristic stability and properties of aromatic systems.[35] Since Michael Faraday's discovery of benzene in 1825[36], aromatic compounds have profoundly influenced both academic research and industrial applications for nearly two centuries. These compounds are essential as bulk and fundamental chemical feedstocks, playing a prominent role in organic synthesis. Due to their "aromaticity," which arises from the delocalization of π-electrons, aromatic compounds primarily undergo substitution reactions.[37] These reactions involve the replacement of a hydrogen atom on the aromatic ring with a functional group, while maintaining the aromaticity of the molecule.[38] On the other hand, dearomatization represents a general but comparatively underdeveloped transformation of aromatic compounds. In dearomatization reactions, a functional group is introduced onto the aromatic ring, resulting in the permanent loss or

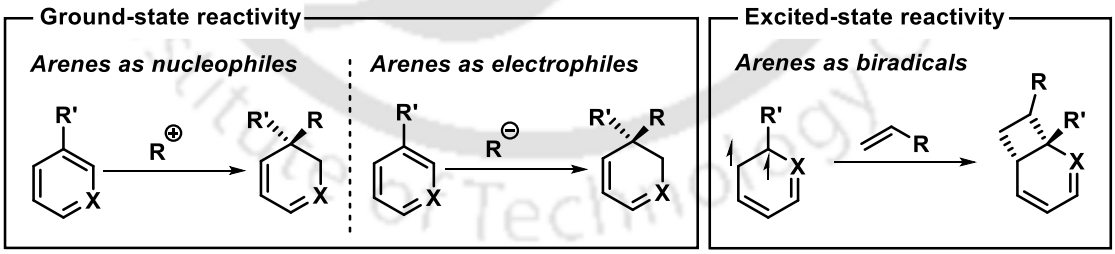


Scheme 7. Classical Named reactions for Dearomatization

significant reduction of its aromaticity. In the past, the Reimer-Tiemann[39], Buchner ring-expansion[40] and the Birch reduction[41] reaction were among the few named reactions known for dearomatization (scheme 7).

1.6 Strategies for catalytic asymmetric dearomatization reactions

In recent years, one of the most dynamic areas of asymmetric catalysis has been the expansion of functional groups compatible with diverse transformations, including those traditionally considered "inert." Catalytic asymmetric dearomatization (CADA)[42] reactions have emerged as a potent synthetic strategy over the past decade. These reactions enable various aromatic compounds to be converted into reactive functionalities for asymmetric synthesis. This advancement has significantly broadened the scope of reactions and applications in organic chemistry, offering new routes to complex molecules with high levels of stereochemical control. However, catalytic asymmetric dearomatization reactions face several challenges that must be addressed. Primarily, the exceptional stability of aromatic compounds renders the dearomatization process thermodynamically unfavorable. Creating and refining chiral catalytic systems is crucial for overcoming the energetic barriers of dearomatization and effectively distinguishing between subtle diastereomeric transition states. These are few representative examples in which aromatic compounds participate in asymmetric dearomatization reactions as nucleophiles, electrophiles, and excited state biradicals (Scheme 8).



Scheme 8. General strategies for CADA reactions

1.7 Importance of dearomatization

The ongoing effectiveness of this dearomatization approach hinges on the capability to transform readily available planar 2D molecules into intricate 3D polycyclic molecular structures. Moreover, the increased saturation resulting from dearomatization reactions,

along with the introduction of new stereogenic centers, significantly enriches the libraries of products available through catalytic asymmetric dearomatization. These transformations are particularly appealing in drug discovery due to the diversity and complexity they introduce into molecular structures. The ability to control stereochemistry in these reactions enhances the potential for discovering novel drug candidates with desired pharmacological properties.[43] As a result, catalytic asymmetric dearomatization has become a valuable tool in medicinal chemistry (figure 7).

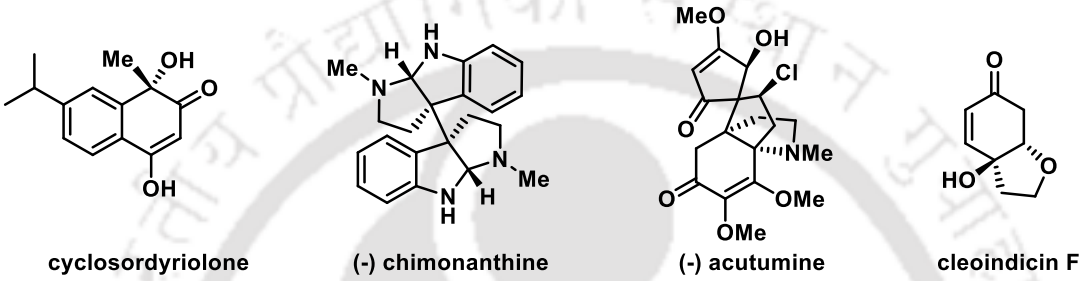


Figure 7. Selected natural alkaloids and bioactive molecules containing dearomatized core

1.8 Different Arene systems for the dearomatization

In principle, every aromatic compound can undergo dearomatization. However, heteroaromatics such as furan, pyrrole, or pyridine are more susceptible to dearomative transformations compared to arenes like benzene.[44] This increased susceptibility is due to the lower resonance stabilization energy in heteroaromatic compounds. Electron-rich heteroaromatics such as indole, pyrrole, benzofuran, as well as benzene-like systems like phenol and naphthol, have been extensively studied in dearomative reactions.[45] These compounds offer energetically favourable reaction profiles that can be effectively utilized in synthetic transformations.

1.9 Types of Catalytic Asymmetric Dearomatization reactions of indole and naphthol derivatives

In this context, indole derivatives and α-/β-naphthols represent important platforms to create synthetically intriguing heterocyclic motifs *via* catalytic asymmetric dearomatization (CADA) reactions. These methodologies are characterized by their ability

to install new C–C and C–X bonds while simultaneously generating stereogenic centers (figure 8).

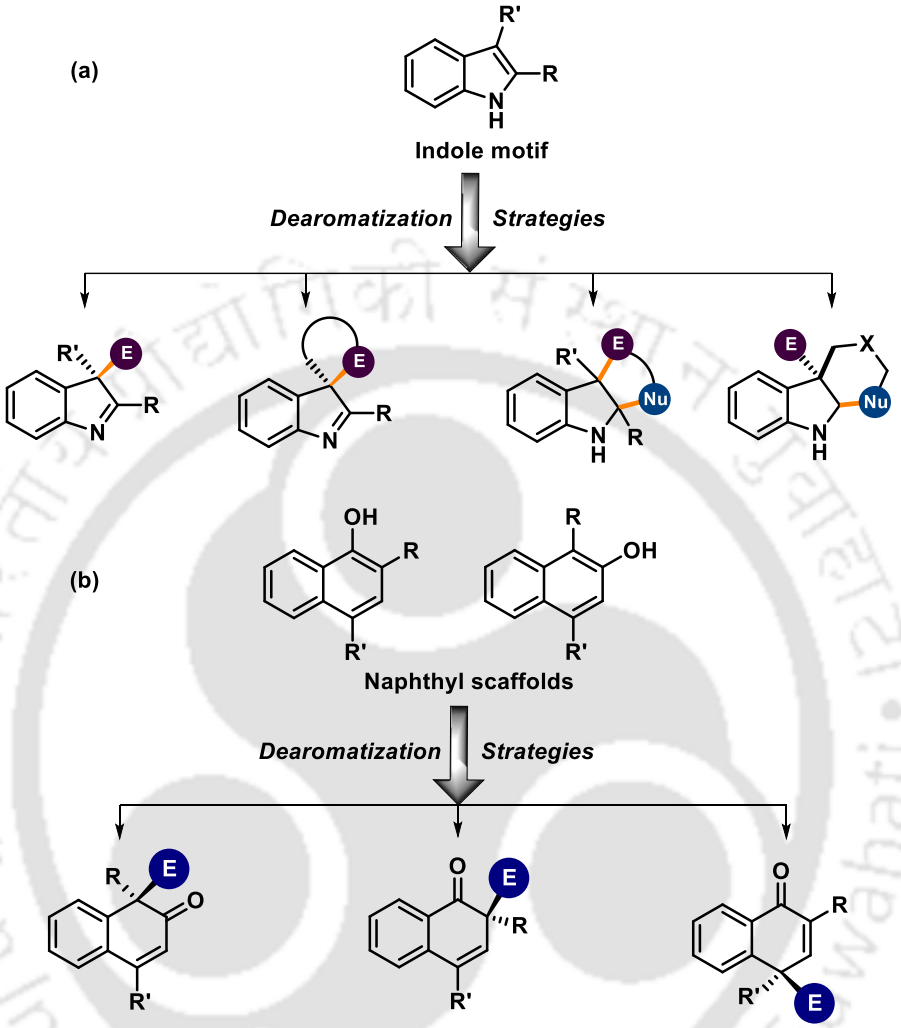


Figure 8. Schematic representation of catalytic dearomatizations of **(a)** indoline and indolenine cores from indole derivatives and **(b)** Naphthalenone cores from naphthol derivatives

Figure **8a** categorizes organo-CADA reactions of indole derivatives[45a] into four distinct categories, each based on different types of indole derivatives. It provides an overview of the key characteristics and types of reactions associated with each category. The first category involves organo-CADA reactions of C3- and/or C2-substituted indoles. Essentially, these indole derivatives leverage the nucleophilicity at the C3 position to interact with electrophiles (E), thereby facilitating organo-CADA reactions and forming indolenine frameworks. The second category pertains to organo-CADA reactions of C3-functionalized indoles equipped with an electrophilic site. These indole derivatives utilize

their C3-nucleophilicity to undergo intramolecular addition reactions with the internal electrophilic site, thereby forming enantio-enriched spiro-indolenine frameworks. The third category is if a nucleophilic site (Nu) is linked to the electrophiles, a [2 + n] cycloaddition could occur with substituted indoles to construct chiral indoline-fused cyclic skeletons. The last category involves organo-CADA reactions of tryptamines, tryptophols, and their analogues. These compounds can utilize the C3-nucleophilicity of the indole ring to attack electrophiles (E) and initiate a cascade cyclization process, thereby achieving the organo-CADA reaction.

Naphthols play a crucial role as aromatic feedstocks in organic chemistry. α- or β-naphthols can undergo reactions with intramolecular or intermolecular nucleophiles to produce chiral functionalized cyclic ketones (Figure **8b**).[45b,c] In case of β-naphthols with substitution on α-position, the reaction occurs from α-position providing a β-naphthalenone motifs as product. In case of α-naphthols with substitution on 2 and/or 4-position, the reaction mainly takes place from *ortho*-position providing a α-naphthalenone core motifs. Depending upon the structural configuration of naphthol derivatives, the reaction could also happen from C4 position providing a α-naphthalenone cores. Mostly intramolecular dearomatizations are known for this type of reactivity.

1.10 Conclusion and focal theme of the present work

The focal theme of this thesis is to utilize bifunctional tertiary amine thiourea, squaramide catalysts and chiral phosphoric acid catalysts in various organocascade reactions.

Chapter 2 includes use of bifunctional tertiary amine thiourea and squaramide catalyst and Michael reactions to synthesize chiral oxindole derivatives with acetal motifs.

Chapter 3 describes the use of chiral phosphoric acid catalysts for the dearomatization reaction of disubstituted indole derivatives.

And lastly in chapter 4 and 5 intramolecular dearomative spirocyclization reactions have been presented on α- and β-naphthols.

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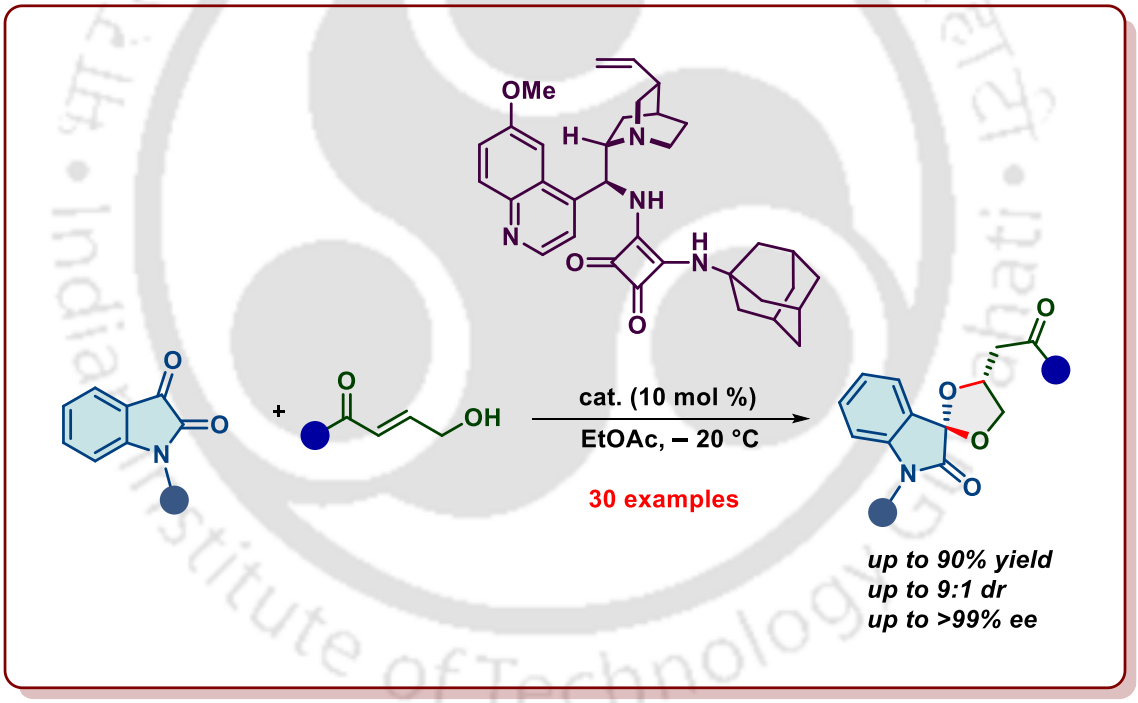
Chapter II

Organocatalytic Asymmetric Synthesis of Cyclic Acetals with Spirooxindole Skeleton

ABSTRACT: In this chapter, a method for synthesizing a cyclic acetal with a spirooxindole structure asymmetrically using organocatalysis has been devised. This involves a domino reaction between isatin and γ-hydroxy enones. Among the catalysts tested, the bifunctional squaramide catalyst featuring an adamantyl motif exhibited the highest efficiency in promoting the cascade reaction. The cyclic acetal products are obtained with good to high yields, high enantioselectivities, and moderate diastereoselectivities.



Adv. Synth. Catal. **2022**, *364*, 58.

2.1 Introduction

Optically active cyclic *O,O*-acetals and ketals play a crucial role in nature, serving as essential structural elements found in various natural products and pharmaceuticals. These compounds contribute to a diverse array of biological activities.[1] For example, in figure 1, first structure exhibits anticonvulsant activities[2] whereas second compound is an inhibitor of *Mycobacterium tuberculosis* (*Mtb*) acetyltransferase Eis[3]. Consequently, considerable attention has been directed toward asymmetric synthesis methods for these compounds in recent years. Various sophisticated approaches have been devised to achieve this goal.[4]

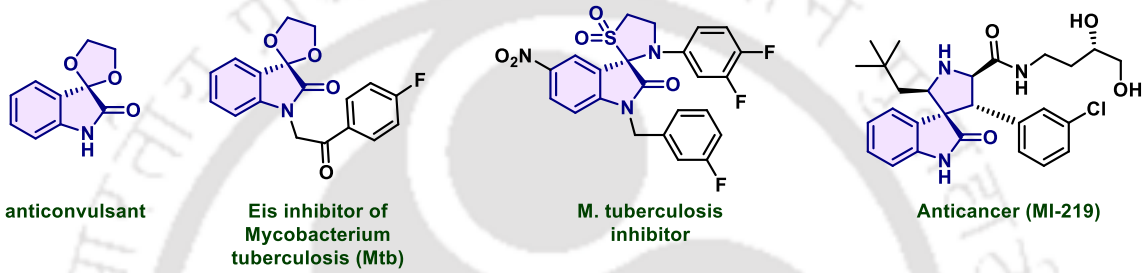


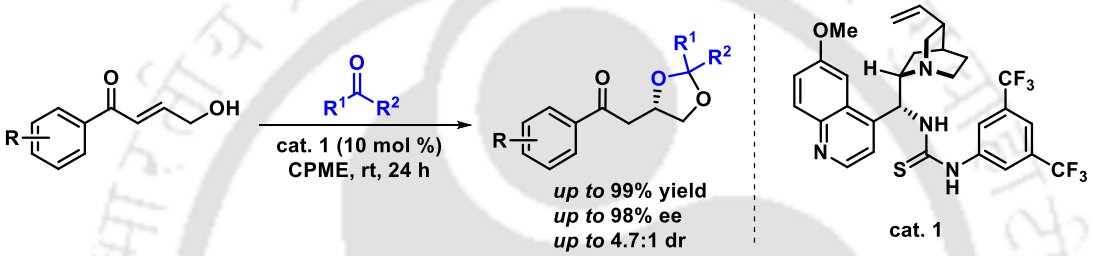
Figure 1: Selected biologically active spirooxindole motifs

However, the preparation of optically active acetals predominantly relies on chiral starting materials or stoichiometric chiral reagents. Catalytic asymmetric syntheses are relatively rare in this context. Additionally, catalytic asymmetric cycloaddition, despite its potential to efficiently build multiple bonds in a single step, has not been extensively explored, limiting its application in divergent synthesis.[5] A number of scientists have been engaged to prepare enantiopure spirocyclic oxindole frameworks over the past years. In particular, isatin derivatives have been found to be a popular substrate, and a range of asymmetric reactions including cyclization methods have been developed.[6]

2.2 Previous known strategies

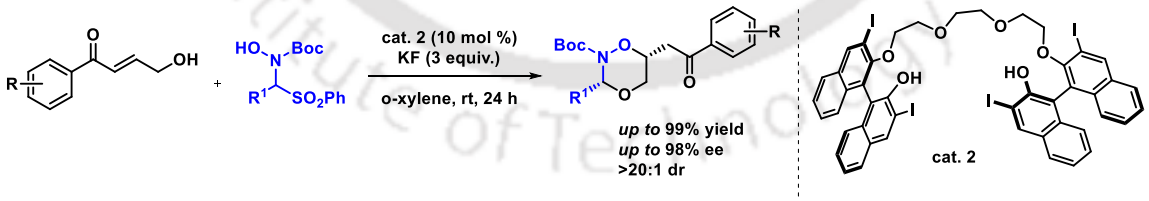
2.2.1 Previous reports on enantioselective reaction of *γ*-hydroxy-*α,β*-unsaturated ketones:

In 2012, Matsubara and co-workers reported[7] a novel method for synthesizing 1,3-dioxolanes through an asymmetric formal [3 + 2] cycloaddition reaction. The process employs cinchona alkaloid-thiourea-based bifunctional organocatalysts. It operates by generating hemiacetal intermediates from *γ*-hydroxy-*α,β*-unsaturated ketones and aldehydes. This approach offers promising prospects for organic synthesis due to its innovative catalyst design and reaction pathway (scheme 1).



Scheme 1: Formal [3 + 2] cycloaddition reaction of *γ*-hydroxyenones and aldehydes

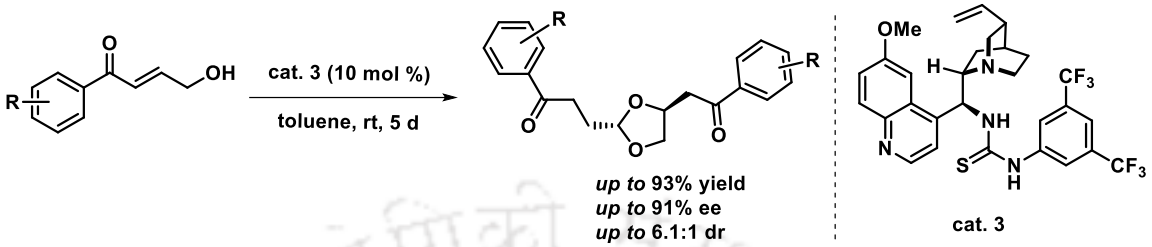
In 2016, Yan and co-workers[8] showed an unprecedented formal cycloaddition of *N*-Boc-*N*-hydroxy amido sulfones as the nitrone precursors with terminal-hydroxy *α,β*-unsaturated carbonyls in the presence of Song's chiral oligoethylene glycol as a cation binding catalyst and KF as a base to afford a wide range of highly enantio- and diastereo-enriched six-membered dioxazinane and seven-membered dioxazepane heterocycles (Scheme 2)



Scheme 2: Reaction between *γ*-hydroxyenones and ethyl cyanoformates

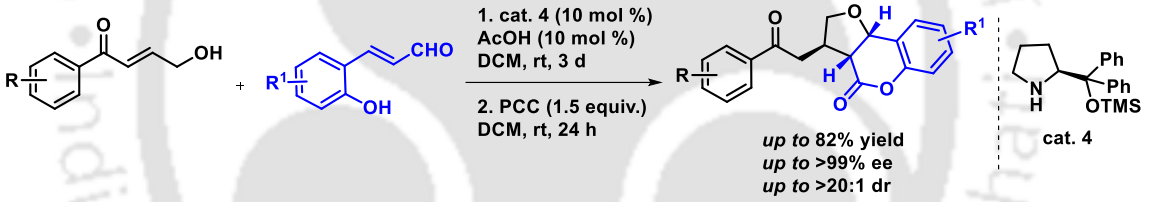
In 2017, Pan *et al*. reported[9] a new technique for the organocatalytic dimerization of *γ*-hydroxyenones. This method involves a redox isomerization/acetal formation process. The resulting stereogenic acetal products are derived from hemiacetal intermediates, which then undergo cyclization. Using bifunctional thiourea catalysts, the reaction achieves high

yields and exceptional enantioselectivities across a range of acetal products under mild reaction conditions. This advancement holds promise for efficient and precise synthesis in organic chemistry (Scheme 3).



Scheme 3: Dimerization of γ-hydroxyenones

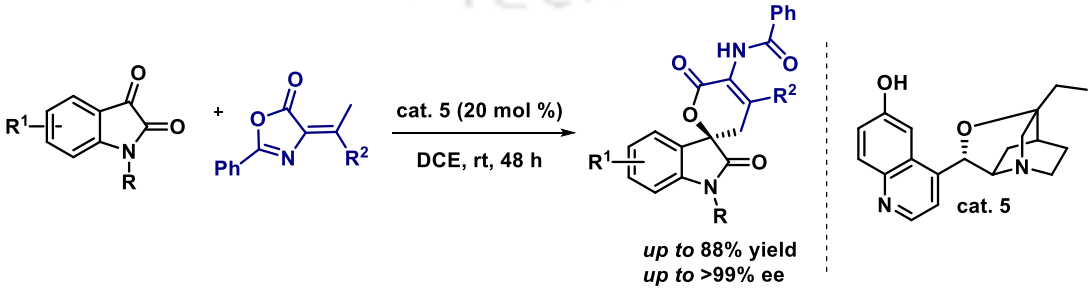
In 2018, Pan *et al*. developed[10] the first organocatalytic asymmetric synthesis of tetrahydrofuran fused 3,4-dihydrocoumarin *via* a cascade reaction between 2-hydroxy cinnamaldehydes and γ-hydroxy enones followed by pyridinium chlorochromate oxidation. The desired products were obtained in high enantio- and diastereoselectivities (Scheme 4).



Scheme 4: Cascade reaction between 2-hydroxy cinnamaldehydes and γ-hydroxy enones

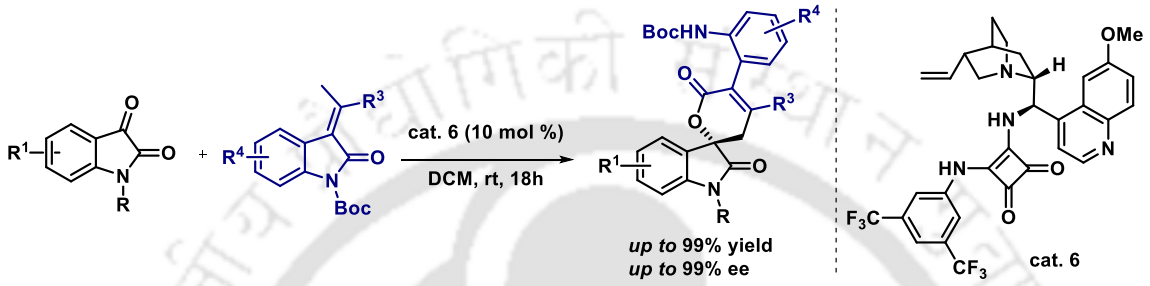
2.2.2 Previous reports on enantioselective reaction of substituted Isatins:

In 2014, Xu group reported[11] a catalytic asymmetric hetero-Diels–Alder (HDA) reaction through hydrogen-bond directed γ-addition of olefinic azlactones to isatins. This methodology provides an efficient access to spirooxindole dihydropyranones in moderate to good yields and with excellent enantioselectivities (Scheme 5).



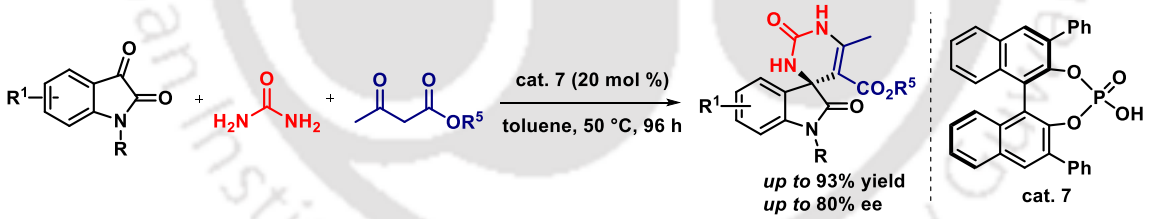
Scheme 5: Hetero-Diels–Alder reaction of olefinic azlactones and isatins

In 2016, Chang group[12] reported a highly enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles to isatins using bifunctional organocatalysts. The unexpected intramolecular lactonization which follows the initial aldol reaction, leading to the cleavage of the oxindole ring and generation of enantioenriched spirooxindole dihydropyranones in good to excellent yields with high enantioselectivities (scheme 6).



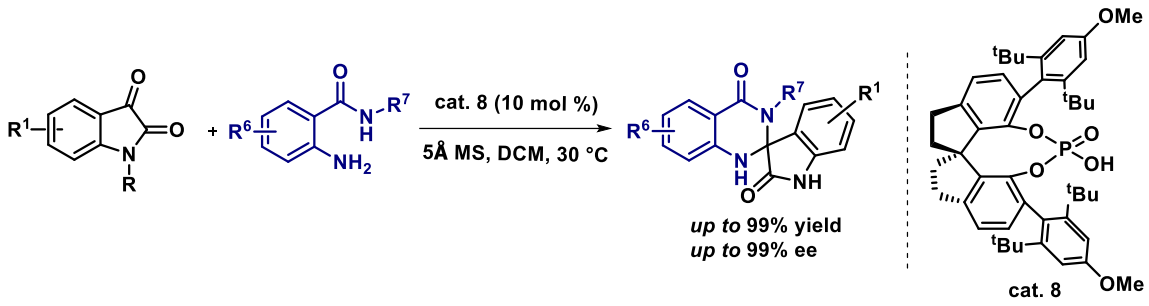
Scheme 6: Vinylogous Aldol-cyclization of 3-alkylidene oxindoles with isatins

In 2016, Silvani group[13] described Brønsted acid catalyzed Biginelli-like reaction of ketones, using *N*-substituted isatins as carbonyl substrates, and urea and alkyl acetoacetates as further components. BINOL-derived phosphoric acid catalysts have been used to achieve the synthesis of enantioenriched spiro(indoline-pyrimidine)diones derivatives (Scheme 7).



Scheme 7: Biginelli-like reaction of *N*-substituted isatins

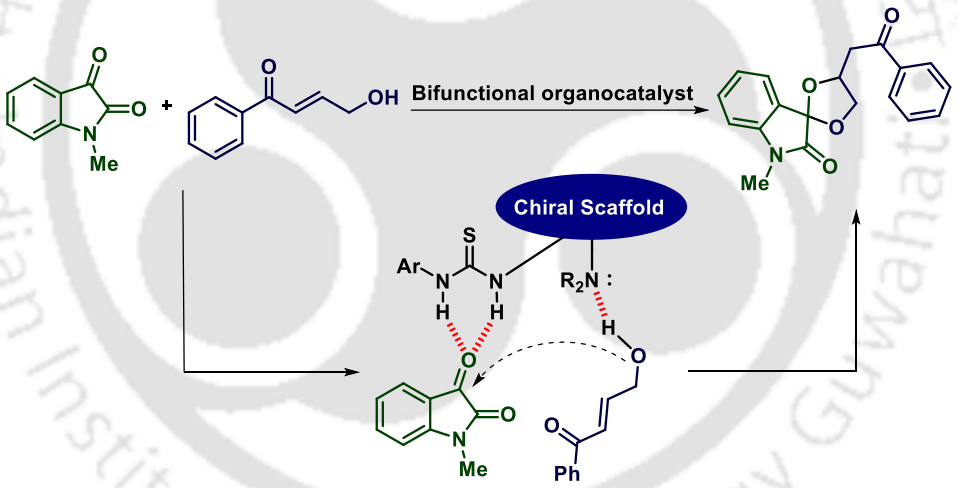
In 2018, Zuo *et al*. developed[14] enantioenriched 3-*N*-substituted spirooxindole dihydro-quinazolinones by cyclization reactions involving 2-amino-*N*-substituted benzamides and isatins catalyzed by SPINOL-CPA catalyst in a highly enantioselective manner with excellent ee values (up to 99%) and good yields (up to 99%) (Scheme 8).



Scheme 8: Cyclization reactions between *N*-substituted anthranilamides and isatins

2.3 Concept

Several convenient catalytic asymmetric cyclization reactions with isatin derivatives have been documented in recent years. However, the asymmetric synthesis of spiro-oxindole containing cyclic acetals is not known. So, we envisioned that the reaction between isatin and *γ*-hydroxyenones would result in the formation of cyclic acetals through *O*-addition followed by an *oxa*-Michael reaction.

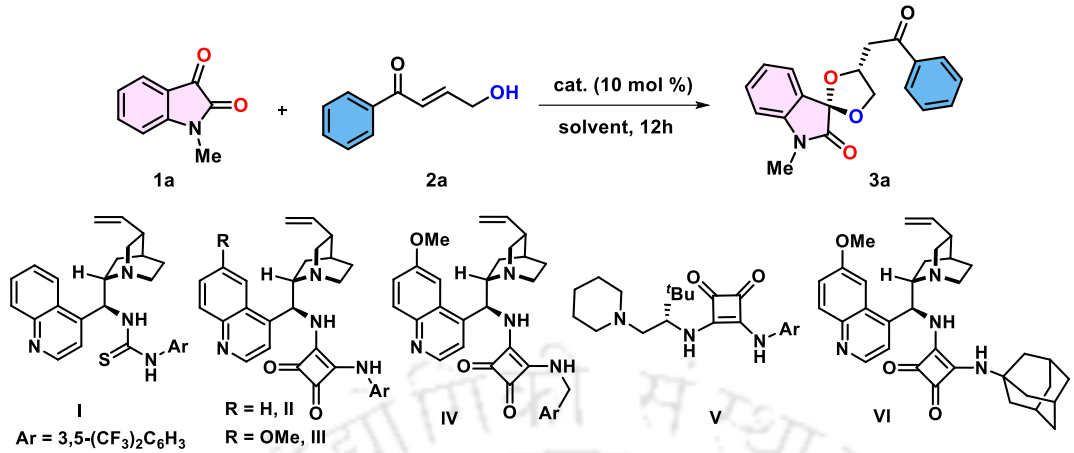


Scheme 9: Proposed route to spiro-oxindole containing cyclic acetals

2.4 Result and Discussion

2.4.1 Catalyst, solvent and reaction condition optimization:

Our investigation began with a model reaction involving *N*-methyl isatin **(1a)** and 3-benzoyl prop-2-en-1-ol **(2a)** in toluene at room temperature, utilizing a cinchonidine-derived bifunctional thiourea catalyst. Encouragingly, after 12 hours of stirring, the desired cascade reaction proceeded, yielding spirooxindole-acetal **3a** in 45 % yield with a diastereomeric ratio (d.r.) of 1.1:1. The enantiomeric excess (ee) of the major diastereomer



entry[a]	catalyst	solvent	temp.	yield (%)[b]	dr[c]	ee(%)[d]
1	**I**	toluene	r.t.	45	1:1	64
2	**II**	toluene	r.t.	55	1.3:1	53
3	**III**	toluene	r.t.	75	1.3:1	88
4	**IV**	toluene	r.t.	67	1.2:1	88
5	**V**	toluene	r.t.	60	1:1	87
6	**VI**	toluene	r.t.	72	1.2:1	99
7[e]	**VI**	toluene	0 °C	60	1.3:1	99
8[f]	**VI**	Toluene	- 20 °C	67	1.6:1	99
9	**VI**	$PhCF_3$	- 20 °C	60	3.2:1	99
10	**VI**	THF	- 20 °C	80	3:1	93
11	**VI**	CH_3CN	- 20 °C	75	2.8:1	99
12	**VI**	MeOH	- 20 °C	75	2.3:1	81
13	**VI**	DCM	- 20 °C	90	1:1	70
14	**VI**	MeOAc	- 20 °C	82	3.5:1	99
15	**VI**	**EtOAc**	**- 20 °C**	**88**	**5:1**	**99**
16[g]	**VI**	EtOAc	- 20 °C	83	3.3:1	98
17[h]	**VI**	EtOAc	- 20 °C	86	4.6:1	98
18[i]	**VI**	EtOAc	- 20 °C	72	2:1	99

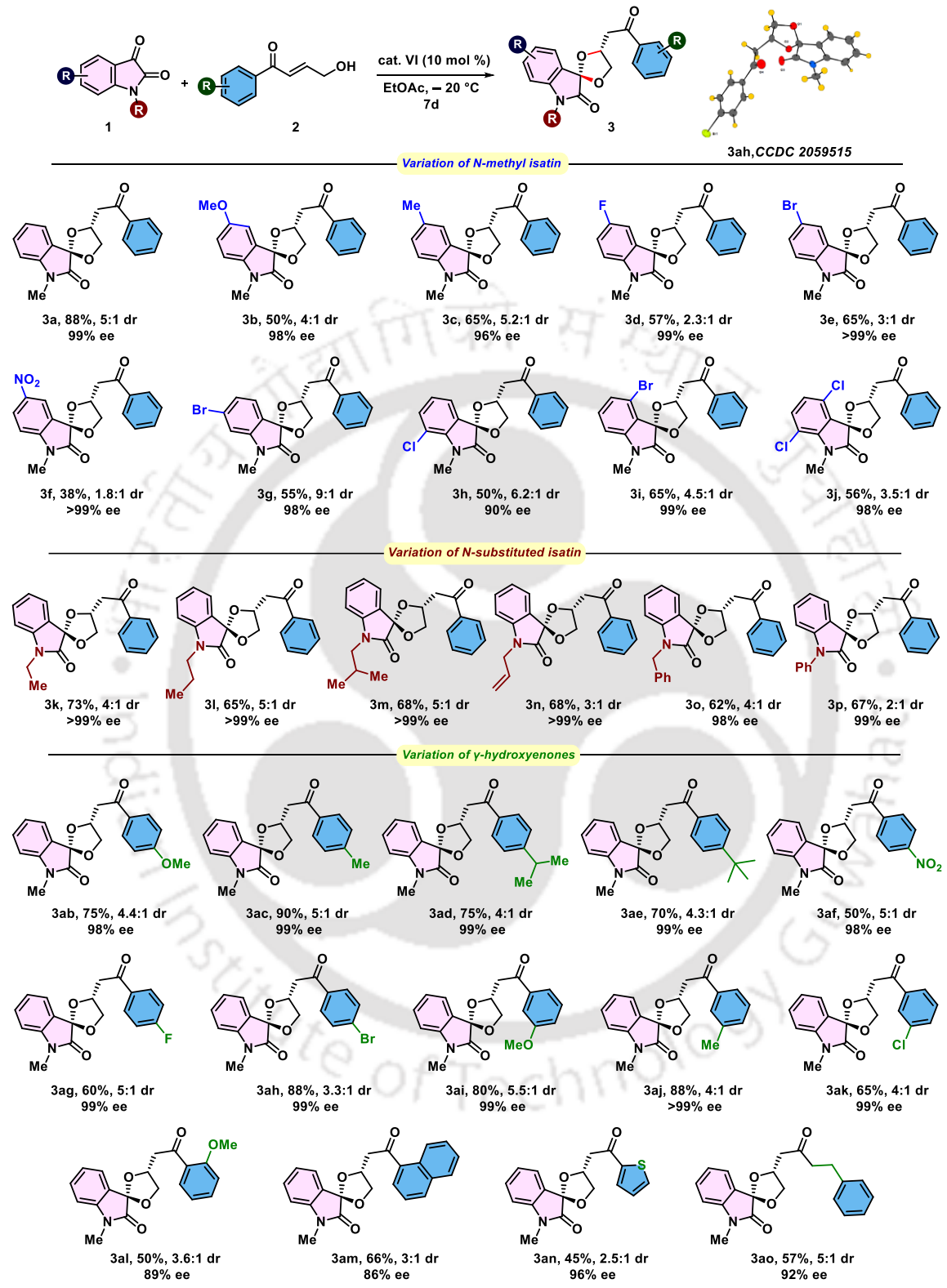
[a] 0.1 mmol of **1a** with 0.15 mmol of **1b** in 0.5 ml solvent using 10 mol% catalyst at room temperature for 12 hours. [b] Isolated combined yield after silica gel column chromatography. [c] Determined by 1H NMR. [d] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [e] Reaction temperature 0 °C and stirred for 4 days. [f] Reaction temperature -20 °C and stirred for 7 days. [g] Reaction carried with 5 mol % catalyst. [h] Reaction carried with 4Å MS. [i] Reaction temperature -40 °C and stirred for 9 days.

Table 1: Catalyst and solvent optimization

was 64 %. To enhance both diastereo- and enantioselectivity, various cinchona alkaloid-derived bifunctional squaramides were tested, yielding promising results. Although the cinchonidine-derived bifunctional squaramide **II** did not enhance the enantioselectivity, a higher yield and enantioselectivity (88% ee) were achieved with quinine-derived squaramide **III**. Subsequently, catalyst **IV**, featuring a bis trifluoromethyl benzyl group, was utilized, but the enantioselectivity remained unchanged. The *t*-Leucine-derived bifunctional squaramide catalyst **V** also failed to enhance the enantioselectivity, yielding only 87% ee. Finally, bifunctional squaramide **VI**, incorporating quinine and a 1-adamantyl group, was employed, resulting in a gratifying 99% enantiomeric excess; however, the diastereoselectivity remained low (1.2:1 dr). To enhance the diastereoselectivity, we conducted temperature and solvent optimizations, which proved successful. The reaction was carried out at 0 °C and – 20 °C, stirred for 4 and 7 days, respectively. The diastereomeric ratio slightly improved to 1.6:1 at – 20 °C. Subsequently, at this temperature, we tested different solvents and achieved better results. Notably, in trifluorotoluene, the diastereoselectivity was enhanced to 3.2:1 while maintaining 99% ee. Similar diastereomeric ratios were obtained in tetrahydrofuran and acetone. Ultimately, the most favorable outcome was observed in ethyl acetate, yielding product 3aa in an 88% combined yield with a 5:1 dr and 99% ee (Table 1).

2.4.2 Substrate scope:

After determining the most optimized conditions, the reaction's generality and scope were explored. Initially, various N-methyl isatins with different substituents on the aryl ring were tested. Encouragingly, satisfactory outcomes were obtained for the desired products. For instance, when using 5-methoxy substituted *N*-methyl isatin, product **3b** was isolated with 50% yield, 4:1 diastereomeric ratio, and 98% enantiomeric excess. For the 5-Me substitution, 65% yield with 5.2:1 dr and 96% ee was achieved. Notably, high enantioselectivity was attained for products with 5-halo substitution (**3d** and **3e**). Additionally, an electron-withdrawing nitro group could be introduced at the 5-position, although a lower yield was observed for product **3f** but high enantioselectivity was maintained. After using 6-bromo substituted isatin in the process, product **3g** showed acceptable enantio- and diastereoselectivity. For 7-halo substitution, product **3i** was



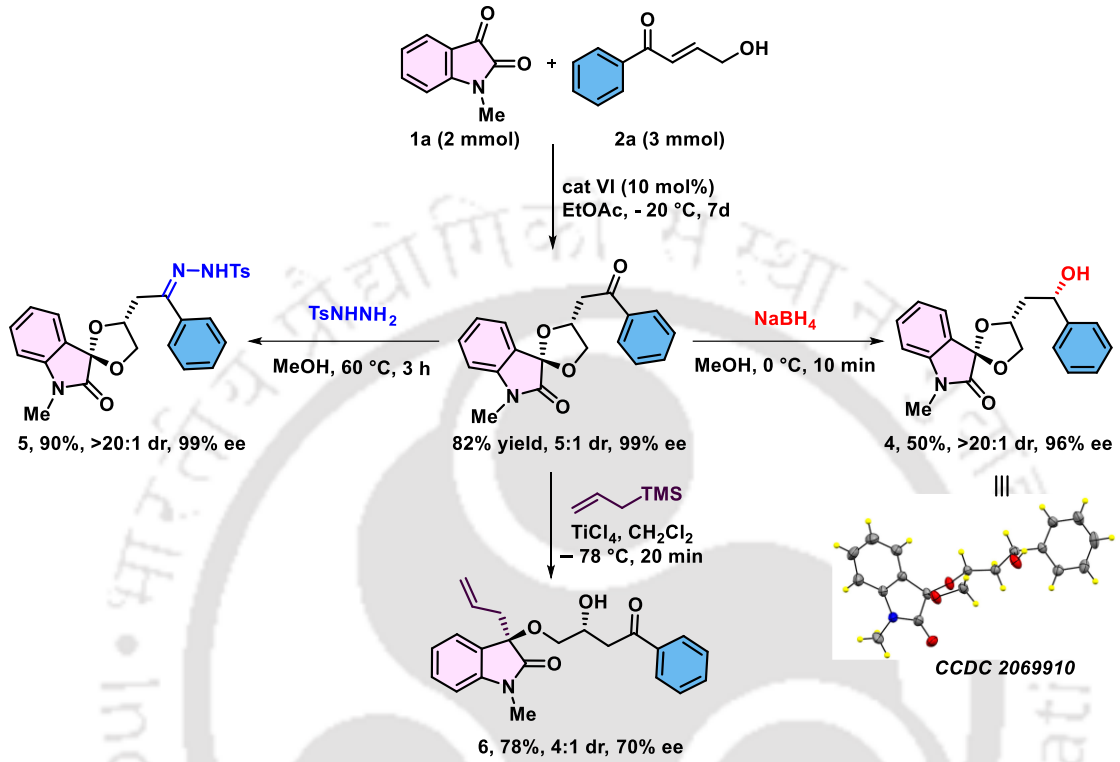
Scheme 10: Substrate scope

isolated with 90% ee. Lastly, **3j** was produced in 98% ee with 3.5:1 dr using 4,7-dichloro substituted isatin. Next, *N*-substitution on isatin was changed, and similarly good outcomes were obtained. To check the reaction, many *N*-alkyl and allyl groups containing isatins were first produced and in all cases >99% ee was obtained. *N*-benzyl isatin **1o** also participated in the reaction and produced the product with 62% yield, 4:1 dr and 98% ee. Upon screening *N*-phenyl isatin in the process, the intended product **3p** was successfully recovered in 99% ee. After that, *γ*-hydroxyenones were examined, and happily, good outcomes were obtained here as well. To obtain the required products, *γ*-hydroxyenones with para-substituted aryl groups were used in the initial steps. Anisoline-containing product **3ab** exhibited high diastereo- and enantioselectivity (4.4:1 dr, 98% ee). Subsequently, distinct 4-alkyl and 4-halogen substituted *γ*-hydroxyenones were utilized in the procedure, yielding satisfactory enantioselectivity (99% ee). In the reaction, the nitro group is likewise tolerated, and product **3af** was produced in 5:1 dr with 98% ee. In addition, several meta-substituted enones **2i – 2k** took part in the process and produced the expected results with high diastereo- and enantioselectivities. Although slightly lower enantiomeric excesses (89%) were found for **3al**, ortho-Substitution. The reaction also included naphthyl substituted enone **2m**, which delivered product **3am** in 86% ee with 5:1 d.r. The thiophene with *γ*-hydroxyenone **2n** was likewise appropriate for our reaction circumstances. Despite having a lower diastereomeric excess, product **3an** showed 96% enantioselectivity. Lastly, the synthesis used a hydrocinnamyl group containing enone **2o**. The response went smoothly and produced **3ao** in 5:1 dr with 92% ee (Scheme 10).

2.4.3 Synthetic transformation:

Scale-up reaction of **1a** and **2a** in 2 mmol scale was performed to verify the practicability of this method. 82% yield with 97% ee of main diastereomer and 5:1 dr were obtained with only 10 mol% catalyst **VI**. Next, on pure diastereomer of enantiopure **3a**, a few synthetic modifications were performed. Sodium borohydride was first applied to **3a** at 0 °C. It's interesting to note that the reduction only occurred from the top face, resulting in the 50% yield and 96% ee production of alcohol **4** as a single diastereomer. X-ray crystallography was utilized to verify the structure of **4**. After that, *p*-toluenesulfonyl hydrazide was used to transform **3a** into hydrazone **5**. The enatiopurity was preserved here

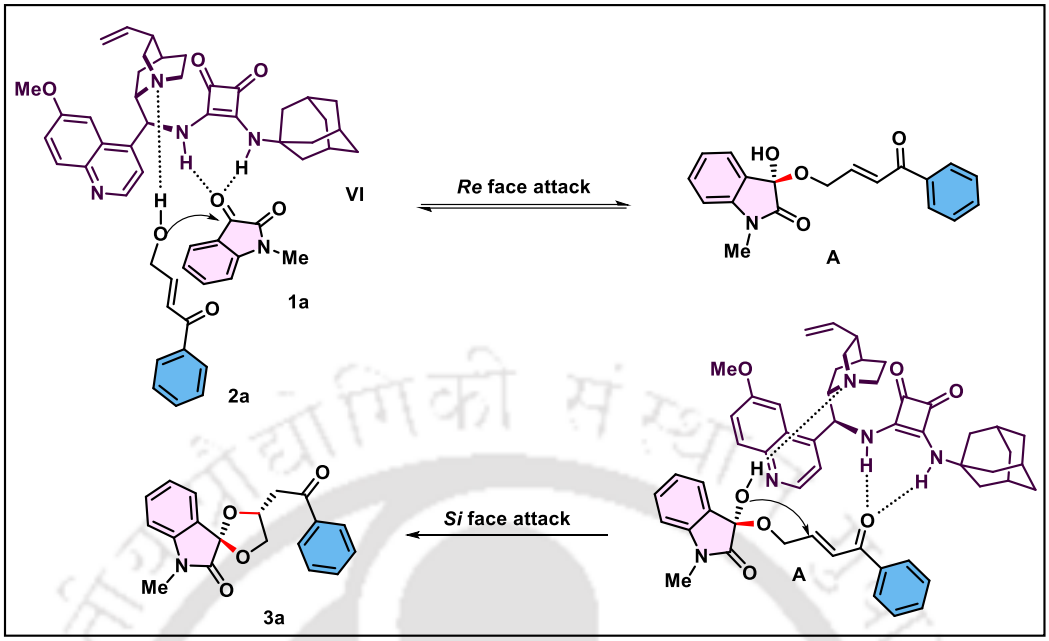
as well. Next, titanium tetrachloride and allyltrimethylsilane were used to treat **3a** in order to cleave the acetal ring. Remarkably, allylated alcohol **6** was produced in a 78% yield at 4:1 dr, despite a slight loss in enantioselectivity (Scheme 11).



Scheme 11: Scale up reaction and Synthetic transformation

2.4.4 Mechanistic pathway:

Based on the absolute configuration, a plausible mechanism has been proposed (Scheme 11). A bifunctional mode of activation of catalyst **VI** operates. It is expected that two carbonyl groups of **1a** will co-ordinate with the squaramide NH of catalyst **VI** and OH group of **2a** will be activated by the quinuclidine motif of **VI**. Thus *Si* face of **1a** is blocked and the addition of **2a** takes place from the *Re* face to provide hemiacetal **A**. Then the intramolecular *oxa*-Michael reaction proceeds from the *Si* face of the enone and product **3a** is generated. We did a model reaction of benzyl alcohol with *N*-methyl isatin (**1a**) under the same reaction conditions; however, no product is formed. Thus, it is assumed that hemiacetal **A** is not stable and either can go back to starting materials or undergoes *oxa*-Michael reaction to provide **3a**. Thus, the diastereoselectivity is expected to generate at the acetal carbon (Scheme 12).



Scheme 12: Proposed Mechanistic pathway

2.5 Conclusion

In summary, this report presents a method for catalytically synthesizing spirooxindole-containing cyclic acetals. The process employs a domino strategy, starting with bifunctional squaramide-catalyzed hemiacetal formation, followed by an *oxa*-Michael reaction. Both the reactants and the catalyst can be prepared with minimal steps. Several synthetic transformations, including a stereoselective ketone reduction, have been showcased.

2.6 Experimental section

2.6.1 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 were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA, IB, ID, IF and AD-H 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. 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).

2.6.2 General procedure for the synthesis of *γ*-hydroxyenones

γ-hydroxyenones were synthesized according to the general procedure.[15]

2.6.3 General procedure for the synthesis of *N*-substituted isatins

N-substituted isatins were synthesized according to the general procedure.[16]

2.6.4 General procedure for the synthesis of catalyst VI

Bifunctional squaramide VI having quinine and 1-adamantyl groups synthesized according to the general procedure.[17]

2.6.5 General procedure for the synthesis of compound 3:

In an oven dried round bottom flask, **1a** (16.1 mg, 0.1 mmol), **2a** (24.3 mg, 0.15 mmol) and 10 mol% of catalyst (**VI**) were taken. 0.5 mL EtOAc of was added to the reaction mixture and stirred at – 20 °C for 7 days. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10 – 20 %) to afford desired products **3aa – 3pa** and **3ab – 3ao**.

2.6.6 General procedure for the synthesis of compound 4:

To a stirrer solution of (3*S*,4'*R*)-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one **(3aa)** (0.1 mmol) in 1 mL dry MeOH under argon at 0 °C, $NaBH_4$ (2 equiv.) was added at once. The resulting reaction mixture was stirred for 10 min at 0 °C. After completion of the reaction, aq. NH_4Cl solution was added. Then organic layer was extracted with EtOAc. At the end, it was purified by silica gel column chromatography

using (15 – 30 %) Hexane/EtOAc to obtain the pure product (3*S*,4'*R*)-4'-((*S*)-2-hydroxy-2-phenylethyl)-1-methylspiro[indoline-3,2'-[1,3]dioxolan]-2-one **(4)** with 50 % yield.

2.6.7 General procedure for the synthesis of compound 5[18]:

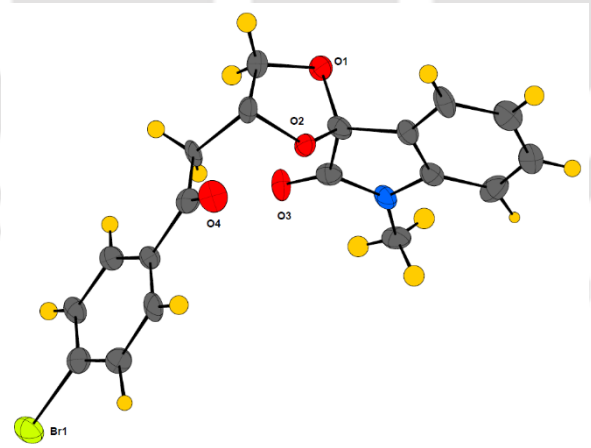
To an oven dried round-bottom flask previously equipped with a magnetic stir bar, was charged with hydrazide (0.1 mmol) in dry methanol (0.5 mL) at 60 °C, (3*S*,4'*R*)-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one **(3aa)** (0.1 mmol) was added. After the completion of reaction, the product began to precipitate. The crude product was filtered and purified by silica gel column chromatography with Hexane/ethyl acetate (20 – 30 %) and dried to afford the pure hydrazone **(5)** with 90 % yield.

2.6.8 General procedure for the synthesis of compound 6[19]:

To a stirred solution of (3*S*,4'*R*)-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one **(3aa)** (0.1 mmol) and allyltrimethylsilane (0.37 mmol) in dry CH_2Cl_2 (2 mL) was added titanium tetrachloride (0.14 mmol) rapidly in –78 °C under argon, and the mixture was stirred at – 78 °C for 20 min. CH_3OH (0.1 mL) was added to the solution, and the mixture was stirred at – 78 °C for 30 min and subsequently warmed to ambient temperature. H_2O was added to the solution, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash silica gel column chromatography using 20% hexane/ethyl acetate as an eluent gave (*R*)-3-allyl-3-((*R*)-2-hydroxy-4-oxo-4-phenylbutoxy)-1-methylindolin-2-one **(6)** with 78 % yield.

2.7 Crystal Data analysis for compound 3ah

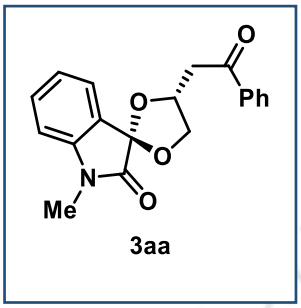
CCDC No.	**2059515**
Empirical formula	$C_{19}H_{16}BrNO_4$
Formula weight	402.2440
Crystal habit, colour	block / clear colourless
Crystal size, mm^3	0.08x0.196x0.268
Temperature, *T*	100 K
Wavelength, λ (Å)	0.71073
Crystal system	Monoclinic
Space group	*'P 21'*
Unit cell dimensions	*a=11.5270(12) b=6.6108(7) c=12.0061(15)*
	alpha=90 beta=114.134(8) gamma=90
Theta(max)	29.124
Data completeness	1.78/0.96
R(reflections)	0.0800(2171)
wR2(reflections)	0.1961(4324)



Ortep Diagram with 30 % ellipsoid probability of compound 3ah

2.8 Characterisation of the products

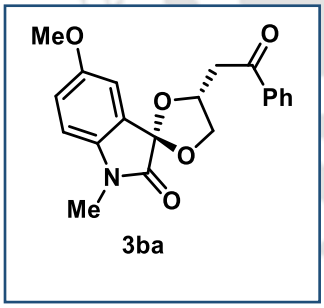
(3S,4'R)-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3aa)



3aa

Pale yellow semi solid, 88% (28mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 – 7.96 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.34 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.06 (tt, *J* = 7.7, 5.7 Hz, 1H), 4.75 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.88 (dd, *J* = 17.9, 5.3 Hz, 1H), 3.60 (dd, *J* = 17.9, 7.8 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.9, 173.5, 144.5, 136.4, 133.5, 131.7, 128.7, 128.2, 124.8, 124.2, 123.5, 108.6, 102.7, 74.5, 71.3, 43.7, 25.9. **FT-IR (KBr):** 3061, 2925, 1728, 1679, 1618, 1471, 1310, 1245, 1120, 1019, 794, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. for $C_{19}H_{17}NO_4$ $[M+H]^+$ 324.1230, found 324.1230. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.9 min, t_{minor} = 17.3 min).

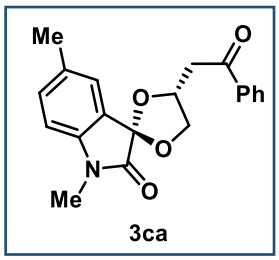
(3S,4'R)-5-methoxy-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3] dioxolan]-2-one (3ba)



3ba

Light yellow sticky solid, 50% (17mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.63 – 7.54 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 2.6 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.7 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 5.06 (tt, *J* = 7.8, 7.3, 5.3 Hz, 1H), 4.75 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.40 (t, *J* = 8.1 Hz, 1H), 3.89 (dd, *J* = 17.9, 5.4 Hz, 1H), 3.81 (s, 3H), 3.61 (dd, *J* = 17.9, 7.7 Hz, 1H), 3.12 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.1, 173.6, 156.8, 137.9, 136.6, 133.7, 128.8, 128.4, 125.4, 117.1, 111.3, 109.5, 103.1, 74.8, 71.5, 56.1, 43.9, 26.2. **FT-IR (KBr):** 2925, 1721, 1680, 1608, 1499, 1354, 1264, 1113, 1039, 732, 703 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. for $C_{20}H_{19}NO_5$ $[M+H]^+$ 354.1336, found 354.1337. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.9 min, t_{minor} = 12.5 min).

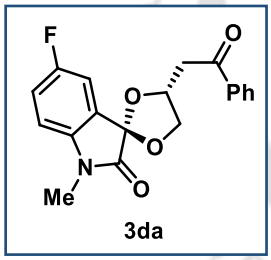
(3S,4'R)-1,5-dimethyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ca)



3ca

Yellow solid, 65% (22mg) yield. Melting Point 155-165 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.03 – 7.95 (m, 2H), 7.62 – 7.54 (m, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 1.9 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 5.06 (tt, *J* = 7.8, 5.8 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.88 (dd, *J* = 18.0, 5.4 Hz, 1H), 3.60 (dd, *J* = 17.9, 7.7 Hz, 1H), 3.12 (s, 3H), 2.33 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.1, 173.7, 142.2, 136.6, 133.7, 133.4, 132.0, 128.8, 128.4, 125.7, 124.3, 108.6, 103.1, 74.7, 71.5, 43.9, 26.1, 21.1. **FT-IR (KBr):** 2923, 1723, 1680, 1627, 1501, 1448, 1300, 1244, 1114, 1011, 793, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_4$ $[M+H]^+$ 338.1387, found 338.1399. **HPLC Analysis:** ee of major diasteromer= 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.1 min, t_{minor} = 14.3 min).

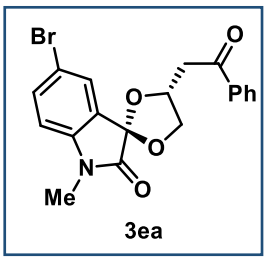
(3S,4'R)-5-fluoro-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan] 2-one (3da)



3da

Colourless sticky solid, 57% (19mg) yield. Diastereomeric mixture (dr ratio 2.3:1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.7 Hz, 2.67H), 7.59 (t, *J* = 7.7 Hz, 1.43H), 7.49 (q, *J* = 8.1 Hz, 2.59H), 7.19 – 7.13 (m, 1H), 7.09 (d, *J* = 8.5 Hz, 1.61H), 6.72 (dd, *J* = 8.7, 3.9 Hz, 1H), 5.42 – 5.32 (m, 0.43H), 5.05 (m, 1H), 4.98 – 4.87 (m, 0.43H), 4.81 – 4.69 (m, 1H), 4.38 (t, *J* = 8.2 Hz, 1H), 4.03 (t, *J* = 6.7 Hz, 0.43H), 3.88 (dd, *J* = 17.9, 5.4 Hz, 1H), 3.71 (dd, *J* = 17.2, 4.8 Hz, 0.42H), 3.59 (dd, *J* = 17.9, 7.6 Hz, 1H), 3.33 (dd, *J* = 17.2, 8.2 Hz, 0.42H), 3.13 (s, 4.19H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9, 197.1, 173.6, 173.0, 160.9, 160.8, 158.5, 140.9, 140.5, 136.6, 136.5, 133.8, 133.7, 129.0, 128.9, 128.4, 128.3, 126.1, 126.0, 118.3, 118.2, 118.0, 117.9, 113.4, 113.2, 113.1, 113.0, 109.5, 109.5, 102.6, 102.6, 74.9, 73.9, 71.6, 71.2, 43.8, 43.5, 26.2, 26.1. **FT-IR (KBr):** 2924, 1727, 1680, 1625, 1496, 1355, 1272, 1187, 1109, 1028, 794, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}FNO_4$ $[M+H]^+$ 342.1136, found 342.1136. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.8 min, t_{minor} = 16.9 min).

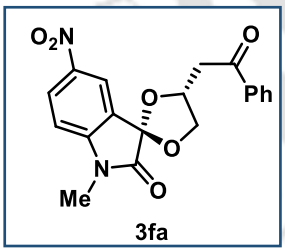
(3S,4'R)-5-bromo-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ea)



3ea

Pale yellow semi solid, 65% (26mg) yield. Diastereomeric mixture (dr ratio 3:1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 7.9 Hz, 2.46H), 7.59 (t, *J* = 7.7 Hz, 1.26H), 7.55 – 7.40 (m, 4.65H), 6.67 (d, *J* = 8.1 Hz, 1.21H), 5.41 – 5.29 (m, 0.3H), 5.05 (m, 1H), 4.91 (t, *J* = 7.4 Hz, 0.29H), 4.74 (t, *J* = 7.3 Hz, 1H), 4.36 (t, *J* = 8.1 Hz, 1H), 4.02 (t, *J* = 6.9 Hz, 0.29H), 3.87 (dd, *J* = 17.9, 5.4 Hz, 1H), 3.71 (dd, *J* = 17.2, 4.8 Hz, 0.31H), 3.57 (dd, *J* = 17.7, 7.5 Hz, 1H), 3.33 (dd, *J* = 17.3, 8.4 Hz, 0.32H), 3.12 (s, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.8, 197.1, 173.2, 144.0, 143.7, 136.5, 136.5, 134.7, 134.6, 133.9, 133.7, 129.0, 128.9, 128.4, 128.4, 128.3, 126.4, 125.7, 116.2, 116.0, 110.3, 102.4, 74.9, 73.9, 71.6, 71.2, 43.7, 43.5, 26.2, 26.1. **FT-IR (KBr):** 2921, 1732, 1680, 1614, 1489, 1356, 1286, 1241, 1112, 1027, 793, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}BrNO_4$ $[M+H]^+$ 402.0335, found 402.0337. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 26.4 min, t_{minor} = 33.8 min).

(3S,4'R)-1-methyl-5-nitro-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3fa)

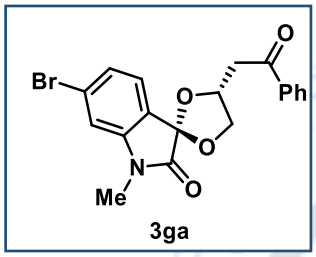


3fa

Light yellow solid, 38% (14mg) yield. Melting Point 135 – 145 °C. Diastereomeric mixture (dr ratio 1.8:1) **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.35 (dd, *J* = 8.7, 2.3 Hz, 1.4H), 8.29 (d, *J* = 2.3 Hz, 1H), 8.22 (d, *J* = 2.3 Hz, 0.5H), 7.99 (dt, *J* = 6.2, 3.0 Hz, 3H), 7.60 (t, *J* = 7.5 Hz, 1.5H), 7.54 – 7.40 (m, 3H), 6.89 (d, *J* = 8.6 Hz, 1.5H), 5.39 (m, 0.55H), 5.17 – 5.06 (m, 1H), 4.93 (t, *J* = 7.5 Hz, 0.54H), 4.80 (dd, *J* = 8.5, 6.1 Hz, 1H), 4.37 (t, *J* = 8.1 Hz, 1H), 4.07 (dd, *J* = 8.0, 5.9 Hz, 0.53H), 3.88 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.75 (dd, *J* = 17.4, 5.0 Hz, 0.54H), 3.56 (dd, *J* = 17.9, 7.6 Hz, 1H), 3.37 (dd, *J* = 17.4, 8.2 Hz, 0.59H), 3.21 (s, 4.5H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.6, 197.0, 173.8, 173.2, 150.5, 150.1, 144.2, 144.0, 136.5, 136.4, 134.0, 133.8, 129.0, 128.9, 128.8, 128.7, 128.3, 128.3, 125.6, 124.9, 121.2, 121.1, 108.6, 101.6, 101.3, 75.2, 74.2, 71.8, 71.4, 43.6, 43.3, 26.6, 26.5. **FT-IR (KBr):** 2923, 1742, 1680, 1619, 1522, 1494, 1336, 1237,

1109, 1026, 793, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}N_2O_6$ $[M+H]^+$ 369.1081, found 369.1081. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 45.2 min, t_{minor} = 53.8 min).

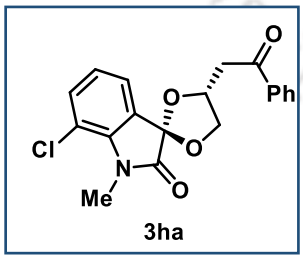
(3S,4'R)-6-bromo-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ga)



3ga

Yellow solid, 55% (22mg) yield. Melting Point 120-130 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.9 Hz, 2H), 7.55 (dt, *J* = 67.2, 7.6 Hz, 3H), 7.28 (q, *J* = 8.2 Hz, 2H), 6.97 (s, 1H), 5.06 (tt, *J* = 6.9 Hz, 1H), 4.75 (t, *J* = 7.4 Hz, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 3.89 (dd, *J* = 18.1, 5.2 Hz, 1H), 3.59 (dd, *J* = 18.0, 7.9 Hz, 1H), 3.14 (s, 3H).**13C NMR (100 MHz, $CDCl_3$)** δ 197.7, 173.4, 145.8, 136.3, 133.5, 128.7, 128.2, 126.3, 126.1, 125.5, 123.1, 112.2, 102.2, 74.6, 71.3, 43.6, 26.0. **FT-IR (KBr):** 2922, 1731, 1638, 1613, 1493, 1369, 1236, 1120, 1027, 793, 689 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}BrNO_4$ $[M+H]^+$ 402.0335, found 402.0366. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.4 min, t_{minor} = 21.7 min).

(3S,4'R)-7-chloro-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ha)

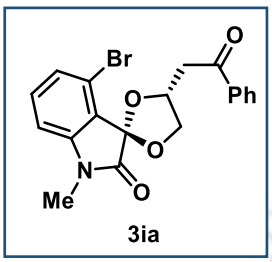


3ha

Light yellow sticky solid, 50% (18mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 – 7.94 (m, 2H), 7.62 – 7.56 (m, 1H), 7.48 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.30 (ddd, *J* = 8.3, 5.3, 1.2 Hz, 2H), 7.01 (dd, *J* = 8.3, 7.3 Hz, 1H), 5.05 (tt, *J* = 7.8, 5.8 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.37 (t, *J* = 8.2 Hz, 1H), 3.87 (dd, *J* = 17.9, 5.4 Hz, 1H), 3.57 (dd, *J* = 17.9, 7.7 Hz, 1H), 3.50 (s, 3H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.0, 174.0, 140.5, 136.6, 134.1, 133.7, 128.9, 128.4, 127.4, 124.5, 123.7, 116.2, 101.9, 74.9, 71.6, 43.8, 29.5. **FT-IR (KBr):** 2923, 1729, 1636, 1460, 1300, 1245, 1121, 1011, 793, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}ClNO_4$ $[M+H]^+$ 358.0841, found 358.0854. **HPLC Analysis:** ee of major diasteromer= 90%, Chiralpak

ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.0 min, t_{minor} = 13.3 min).

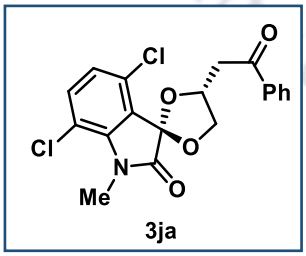
(3S,4'R)-4-bromo-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ia)



3ia

Yellow solid, 65% (26mg) yield. Melting Point 155-165 °C. Diastereomeric mixture (dr ratio 4.5:1) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.06 – 7.96 (m, 2.3H), 7.59 (t, *J* = 7.2 Hz, 1.22H), 7.48 (t, *J* = 7.5 Hz, 2.3H), 7.24 – 7.14 (m, 2.11H), 6.73 (dd, *J* = 6.5, 2.2 Hz, 1.12H), 5.42 (m, 0.22H), 5.19 (m, 1H), 4.94 (t, *J* = 7.1 Hz, 0.22H), 4.87 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.36 (t, *J* = 8.1 Hz, 1H), 4.08 (t, *J* = 7.5 Hz, 0.21H), 3.88 (ddd, *J* = 17.7, 5.1 Hz, 1.22H), 3.57 (dd, *J* = 17.8, 8.1 Hz, 1H), 3.40 (dd, *J* = 17.4, 8.3 Hz, 0.21H), 3.12 (s, 3.42H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.9, 197.2, 173.8, 173.2, 146.9, 146.6, 136.6, 136.5, 133.7, 133.7, 133.0, 132.9, 128.9, 128.8, 128.4, 128.3, 127.7, 127.5, 123.0, 122.3, 120.1, 120.0, 107.9, 107.8, 103.5, 102.9, 75.5, 74.5, 72.4, 71.9, 44.0, 42.7, 26.2, 26.1. **FT-IR (KBr):** 2925, 1733, 1680, 1609, 1455, 1354, 1274, 1121, 1028, 793, 689 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}BrNO_4$ $[M+H]^+$ 402.0335, found 402.0336. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.9 min, t_{minor} = 17 min).

(3S,4'R)-4,7-dichloro-1-methyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'[1,3] dioxolan]-2-one (3ja)

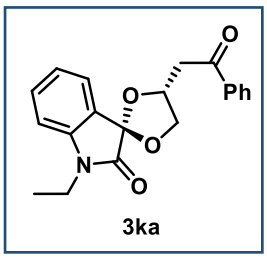


3ja

White solid, 56% (22mg) yield. Melting Point 150-160 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 – 7.95 (m, 2H), 7.63 – 7.56 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 5.13 (tt, *J* = 8.0, 5.6 Hz, 1H), 4.83 (t, *J* = 8.2, 6.0 Hz, 1H), 4.32 (t, *J* = 8.1 Hz, 1H), 3.88 (dd, *J* = 17.8, 5.2 Hz, 1H), 3.58 – 3.52 (dd, 1H), 3.50 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.8, 173.5, 142.0, 136.5, 134.8, 133.7, 131.1, 128.9, 128.4, 125.5, 123.8, 114.8, 102.3, 75.6, 72.5, 43.8, 29.6. **FT-IR (KBr):** 2923, 1737, 1677, 1606, 1448, 1404, 1273, 1121, 1042, 793, 685 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{15}Cl_2NO_4$ $[M+H]^+$ 392.0451, found

392.0479. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.1 min, t_{minor} = 14.0 min).

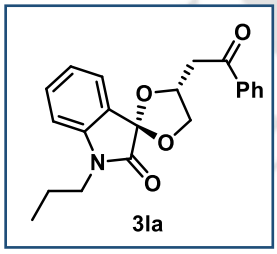
(3S,4'R)-1-ethyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one(3ka)



3ka

Yellow semi solid, 73% (25mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 5.11 – 5.01 (m, 1H), 4.74 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 3.89 (dd, *J* = 17.9, 5.4 Hz, 1H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.59 (dd, *J* = 17.9, 7.7 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9, 173.1, 143.6, 136.5, 133.4, 131.6, 128.6, 128.2, 125.0, 124.5, 123.2, 108.7, 102.7, 74.5, 71.2, 43.6, 34.5, 12.4. **FT-IR (KBr):** 3120, 2925, 1726, 1681, 1618, 1468, 1400, 1211, 1120, 1046, 754, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_4$ $[M+H]^+$ 338.1387, found 338.1387. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.6 min, t_{minor} = 21.5 min).

(3S,4'R)-4'-(2-oxo-2-phenylethyl)-1-propylspiro[indoline-3,2'-[1,3]dioxolan]-2-one (3la)

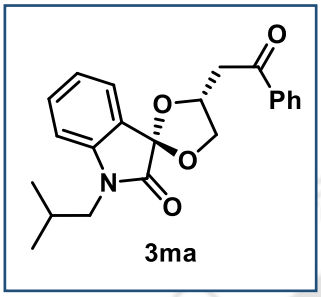


3la

Yellow sticky solid, 65% (23mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.41 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.07 (tt, *J* = 7.6, 5.7 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.89 (dd, *J* = 17.8, 5.4 Hz, 1H), 3.59 (qd, *J* = 7.7, 4.1 Hz, 3H), 1.70 (q, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.0, 173.6, 144.0, 136.5, 133.4, 131.6, 128.6, 128.2, 124.9, 124.4, 123.2, 108.9, 102.7, 74.6, 71.2, 43.6, 41.4, 20.6, 11.3. **FT-IR (KBr):** 2923, 1725, 1680, 1618, 1467, 1366, 1287, 1201, 1122, 1013, 793, 689 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{21}H_{21}NO_4$ $[M+H]^+$ 352.1543, found 352.1544. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak

IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.5 min, t_{minor} = 18.9 min).

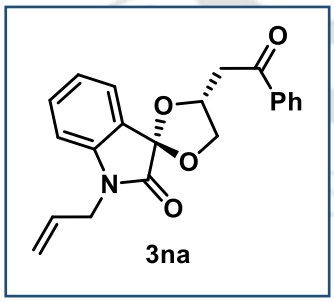
(3S,4'R)-1-isobutyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ma)



3ma

Orange solid, 68% (25mg) yield. Melting Point 80-90 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 7.7 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.07 (p, *J* = 6.8 Hz, 1H), 4.74 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.89 (dd, *J* = 17.8, 5.5 Hz, 1H), 3.57 (dd, *J* = 17.7, 7.6 Hz, 1H), 3.43 (qd, *J* = 14.0, 7.5 Hz, 2H), 2.11 (dt, *J* = 13.8, 6.9 Hz, 1H), 0.96 (dd, *J* = 6.4, 3.0 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.0, 173.9, 144.3, 136.5, 133.4, 131.5, 128.6, 128.2, 124.9, 124.3, 123.2, 109.1, 74.6, 71.2, 47.3, 43.6, 26.9, 20.2, 20.1. **FT-IR (KBr):** 2923, 1728, 1681, 1618, 1468, 1375, 1270, 1203, 1121, 1016, 793, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{22}H_{23}NO_4$ $[M+H]^+$ 366.1700, found 366.1700. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.1 min, t_{minor} = 10.5 min).

(3S,4'R)-1-allyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one(3na)

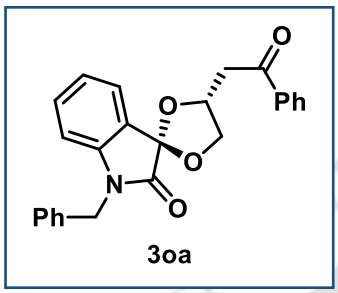


3na

Yellow solid, 68% (24mg) yield. Melting Point 100-110 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.05 – 7.97 (m, 2H), 7.62 – 7.55 (m, 1H), 7.52 – 7.40 (m, 3H), 7.33 (td, *J* = 7.8, 1.4 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.83 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.31 – 5.20 (m, 2H), 5.08 (tt, *J* = 7.7, 5.7 Hz, 1H), 4.75 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.40 (t, *J* = 8.1 Hz, 1H), 4.26 (dt, *J* = 5.4, 1.8 Hz, 2H), 3.89 (dd, *J* = 17.8, 5.4 Hz, 1H), 3.60 (dd, *J* = 17.9, 7.7 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9, 173.3, 143.7, 136.4, 133.5, 131.5, 130.8, 128.6, 128.2, 124.9, 124.3, 123.4, 117.9, 109.5, 102.6, 74.6, 71.3, 43.6, 42.1. **FT-IR (KBr):** 2920, 1728, 1679, 1618, 1467, 1356, 1287, 1186, 1122, 1013, 793, 689 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{21}H_{19}NO_4$ $[M+H]^+$ 350.1387, found

350.1387. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.7 min, t_{minor} = 21.7 min).

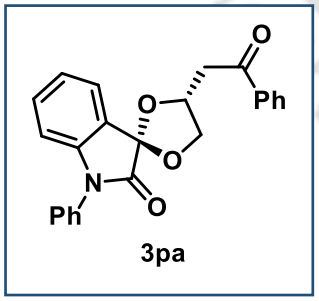
(3S,4'R)-1-benzyl-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3oa)



3oa

Yellow sticky solid, 62% (25mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.33 – 7.24 (m, 7H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.10 (ddd, *J* = 13.5, 7.7, 5.9 Hz, 1H), 4.84 (d, *J* = 7.4 Hz, 1H), 4.81 – 4.75 (m, 1H), 4.44 (t, *J* = 8.1 Hz, 1H), 3.93 (dd, *J* = 17.8, 5.5 Hz, 1H), 3.83 (d, *J* = 9.1 Hz, 1H), 3.61 (dd, *J* = 17.8, 7.7 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.1, 173.9, 143.8, 136.6, 135.3, 133.7, 132.9, 131.8, 129.0, 128.8, 128.4, 127.9, 127.3, 125.1, 123.7, 109.9, 103.0, 74.9, 71.5, 55.6, 43.8. **FT-IR (KBr):** 3117, 2928, 1726, 1677, 1618, 1401, 1211, 1180, 1130, 1011, 793, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{25}H_{21}NO_4$ $[M+H]^+$ 400.1543, found 400.1543. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 26.5 min, t_{minor} = 30.6 min).

(3S,4'R)-4'-(2-oxo-2-phenylethyl)-1-phenylspiro[indoline-3,2'-[1,3]dioxolan]-2-one (3pa)

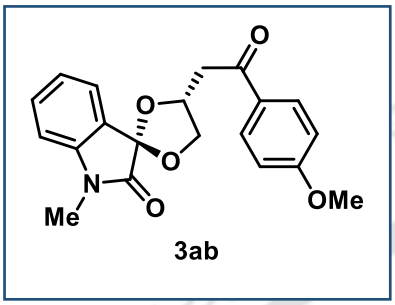


3pa

Yellow sticky solid, 67% (26mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.04 – 7.93 (m, 2H), 7.62 – 7.35 (m, 9H), 7.31 (td, *J* = 7.8, 1.4 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.14 (p, *J* = 7.0 Hz, 1H), 4.80 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.45 (t, *J* = 8.1 Hz, 1H), 3.90 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.66 – 3.60 (m, 1H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.9, 133.7, 133.4, 131.6, 129.6, 128.6, 128.2, 128.2, 126.3, 125.2, 123.9, 109.9, 74.7, 71.3, 43.7. **FT-IR (KBr):** 2922, 1735, 1619, 1498, 1466, 1299, 1197, 1121, 794, 700 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{24}H_{19}NO_4$ $[M+H]^+$ 386.1387, found 386.1387. **HPLC Analysis:**

ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.7 min, t_{minor} = 19.6 min).

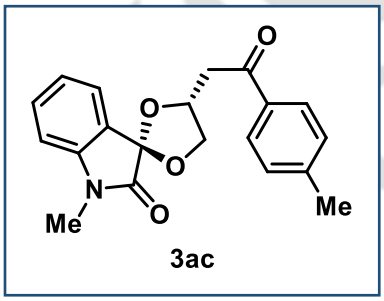
(3S,4'R)-4'-(2-(4-methoxyphenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'[1,3] dioxolan]-2-one (3ab)



3ab

Orange semi solid, 75% (26mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.00 – 7.94 (m, 2H), 7.42 – 7.33 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.05 (tt, *J* = 7.7, 5.7 Hz, 1H), 4.72 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 3.82 (dd, *J* = 17.5, 5.4 Hz, 1H), 3.53 (dd, *J* = 17.5, 7.8 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.6, 173.8, 164.0, 144.7, 131.8, 130.7, 130.0, 125.0, 124.7, 123.6, 114.0, 108.7, 102.9, 75.0, 71.6, 55.7, 43.5, 26.1. **FT-IR (KBr):** 2922, 1725, 1616, 1469, 1309, 1261, 1121, 1018, 793, 636 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_5$ $[M+H]^+$ 354.1336, found 354.1336. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 34.6 min, t_{minor} = 32.3 min).

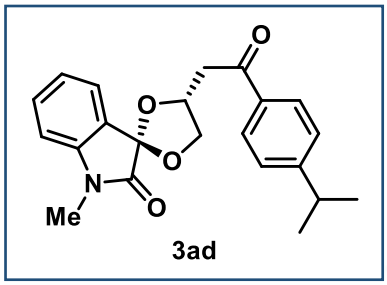
(3S,4'R)-1-methyl-4'-(2-oxo-2-(p-tolyl)ethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ac)



3ac

White solid, 90% (30mg) yield. Melting Point 145-155 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.97 – 7.87 (m, 2H), 7.49 – 7.35 (m, 2H), 7.30 – 7.24 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.05 (tt, *J* = 7.7, 5.6 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 3.85 (dd, *J* = 17.8, 5.3 Hz, 1H), 3.57 (dd, *J* = 17.8, 7.8 Hz, 1H), 3.14 (s, 3H), 2.41 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.5, 173.6, 144.5, 144.3, 134.0, 131.7, 129.3, 128.3, 124.8, 124.3, 123.4, 108.6, 102.6, 74.6, 71.3, 43.5, 25.9, 21.7. **FT-IR (KBr):** 3059, 2923, 1727, 1618, 1471, 1373, 1246, 1112, 1019, 793, 692 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_4$ $[M+H]^+$ 338.1387, found 338.1387. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 19.8 min, t_{minor} = 18.6 min).

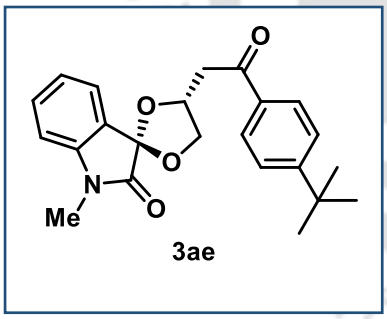
(3S,4'R)-4'-(2-(4-isopropylphenyl)-2-oxoethyl)-1-methylspiro[indoline3,2'[1,3] dioxolan]-2-one (3ad)



3ad

Yellow semi solid, 75% (27mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.30 (m, 4H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.05 (ddd, *J* = 13.6, 7.8, 5.6 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 3.86 (dd, *J* = 17.8, 5.3 Hz, 1H), 3.57 (dd, *J* = 17.7, 7.8 Hz, 1H), 3.14 (s, 3H), 2.97 (p, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 7H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.5, 173.5, 155.0, 144.5, 134.4, 131.6, 128.4, 126.7, 124.8, 123.4, 108.5, 102.7, 74.7, 71.3, 43.5, 34.2, 25.9, 23.6. **FT-IR (KBr):** 2959, 2924, 1729, 1618, 1469, 1309, 1245, 1110, 1018, 793, 692 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{22}H_{23}NO_4$ $[M+H]^+$ 366.1700, found 366.1700. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 17.1 min, t_{major} = 20.5 min).

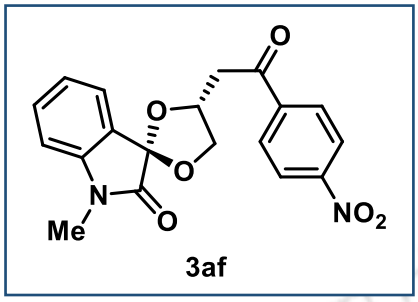
(3S,4'R)-4'-(2-(4-(tert-butyl)phenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'-[1,3] dioxolan]-2-one (3ae)



3ae

White sticky solid, 70% (26mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 – 7.91 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.44 – 7.34 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.05 (tt, *J* = 7.9, 5.6 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.38 (t, *J* = 8.1 Hz, 1H), 3.86 (dd, *J* = 17.8, 5.3 Hz, 1H), 3.57 (dd, *J* = 17.8, 7.9 Hz, 1H), 3.14 (s, 3H), 1.34 (s, 9H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.5, 157.3, 144.4, 133.9, 131.6, 128.1, 125.6, 124.8, 124.3, 123.4, 108.6, 74.6, 71.3, 43.5, 35.1, 31.0, 25.9. **FT-IR (KBr):** 2924, 1727, 1619, 1469, 1266, 1121, 1018, 793, 667 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{23}H_{25}NO_4$ $[M+H]^+$ 380.1856, found 380.1855. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 16.9 min, t_{major} = 19.5 min).

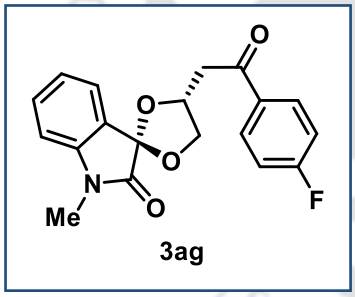
(3S,4'R)-1-methyl-4'-(2-(4-nitrophenyl)-2-oxoethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3af)



3af

Yellow sticky solid, 50% (18.4mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.32 (d, *J* = 8.4 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.26 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 5.08 (p, *J* = 6.8 Hz, 1H), 4.72 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.41 (t, *J* = 7.9 Hz, 1H), 3.96 (dd, *J* = 17.7, 6.0 Hz, 1H), 3.58 (dd, *J* = 17.8, 6.8 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.7, 179.5, 157.3, 156.1, 144.7, 141.1, 132.0, 129.5, 125.1, 124.1, 123.7, 108.9, 97.2, 74.4, 71.2, 44.4, 26.1. **FT-IR (KBr):** 2921, 1729, 1636, 1466, 1345, 1265, 1121, 1090, 793, 667 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}N_2O_6$ $[M+H]^+$ 369.1081, found 369.1085. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 50.9 min, t_{minor} = 74.9 min).

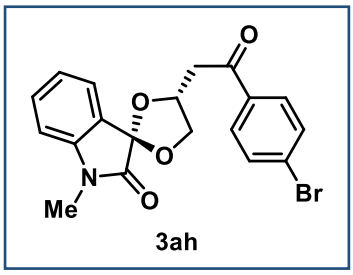
(3S,4'R)-4'-(2-(4-fluorophenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'-[1,3] dioxolan]-2-one (3ag)



3ag

White semi solid, 60% (20mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 – 7.98 (m, 2H), 7.45 – 7.34 (m, 2H), 7.20 – 7.06 (m, 3H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.06 (tt, *J* = 7.5, 5.8 Hz, 1H), 4.73 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.39 (t, *J* = 8.0 Hz, 1H), 3.86 (dd, *J* = 17.8, 5.5 Hz, 1H), 3.55 (dd, *J* = 17.7, 7.5 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.3, 173.6, 167.0 (J_{C-F} = 253.8 Hz), 144.5, 133.0 (J_{C-F} = 3 Hz), 131.7, 130.9 (J_{C-F} = 9.1 Hz), 124.8, 124.2, 123.5, 115.9 (J_{C-F} = 21.7 Hz), 108.6, 102.8, 74.5, 71.2, 43.6, 25.9. **^{19}F NMR (470 MHz, $CDCl_3$)** δ -62.75, -104.57. At -62.75 ppm, singlet due to internal standard $PhCF_3$. **FT-IR (KBr):** 2923, 2853, 1726, 1618, 1470, 1309, 1245, 1109, 1018, 793, 692 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}FNO_4$ $[M+H]^+$ 342.1136, found 342.1136. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.6 min, t_{minor} = 20.6 min).

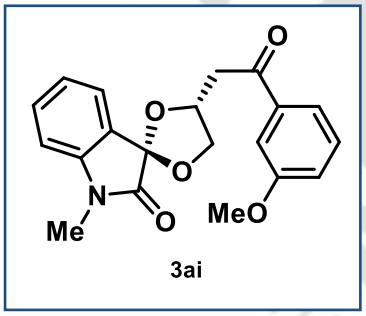
(3S,4'R)-4'-(2-(4-bromophenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'-[1,3] dioxolan]-2-one (3ah)



3ah

White solid, 85% (34mg) yield. Melting Point 160-170 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.33 (m, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.05 (p, *J* = 5.4 Hz, 1H), 4.72 (dd, *J* = 8.5, 6.2 Hz, 1H), 4.38 (t, *J* = 8.0 Hz, 1H), 3.85 (dd, *J* = 17.8, 5.7 Hz, 1H), 3.53 (dd, *J* = 17.8, 7.4 Hz, 1H), 3.13 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.9, 173.5, 144.4, 135.2, 132.0, 131.7, 129.7, 128.7, 124.8, 124.1, 123.5, 108.6, 102.8, 74.4, 71.1, 43.6, 25.9. **FT-IR (KBr):** 3442, 2923, 1721, 1617, 1468, 1397, 1260, 1121, 1018, 794, 636 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}BrNO_4$ $[M+H]^+$ 402.0335, found 402.0335. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 22.3 min, t_{minor} = 26.8 min).

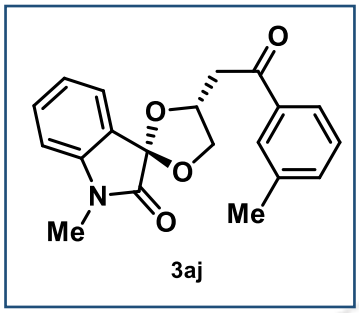
(3S,4'R)-4'-(2-(3-methoxyphenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'[1,3] dioxolan]-2-one (3ai)



3ai

Yellow sticky solid, 80% (28mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.50 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.46 – 7.27 (m, 3H), 7.20 – 7.01 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.05 (tt, *J* = 7.7, 5.8 Hz, 1H), 4.74 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.85 (s, 4H), 3.57 (dd, *J* = 17.9, 7.7 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.7, 173.5, 159.8, 144.5, 137.7, 131.7, 129.7, 124.8, 124.2, 123.4, 121.0, 120.2, 112.0, 108.6, 102.7, 74.5, 71.3, 55.4, 43.8, 25.9. **FT-IR (KBr):** 2923, 2355, 1725, 1618, 1469, 1311, 1247, 1121, 1089, 793, 636 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_5$ $[M+H]^+$ 354.1336, found 354.1336. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.9 min, t_{minor} = 22.1 min).

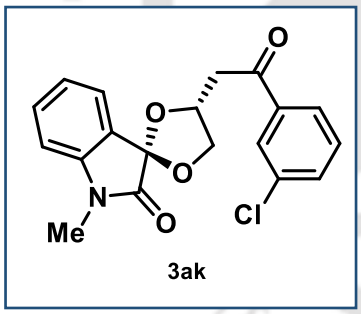
(3S,4'R)-1-methyl-4'-(2-oxo-2-(m-tolyl)ethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3aj)



3aj

Yellow sticky solid, 88% (30mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 6.4 Hz, 2H), 7.38 (dq, *J* = 15.7, 7.8 Hz, 4H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.06 (p, *J* = 6.9 Hz, 1H), 4.80 – 4.71 (m, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.87 (dd, *J* = 17.9, 5.3 Hz, 1H), 3.59 (dd, *J* = 17.9, 7.8 Hz, 1H), 3.14 (s, 3H), 2.41 (s, 3H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.1, 173.6, 144.4, 138.4, 136.4, 134.2, 131.7, 128.7, 128.5, 125.4, 124.8, 124.2, 123.4, 108.6, 102.7, 74.6, 71.3, 43.7, 25.9, 21.3. **FT-IR (KBr):** 2923, 1727, 1677, 1618, 1470, 1309, 1244, 1120, 1018, 793, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_4$ $[M+H]^+$ 338.1387, found 338.1387. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.4 min, t_{minor} = 14.5 min).

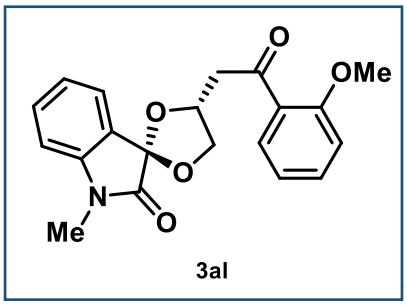
(3S,4'R)-4'-(2-(3-chlorophenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'-[1,3] dioxolan]-2-one (3ak)



3ak

Yellow sticky solid, 65% (23mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.96 (t, *J* = 1.9 Hz, 1H), 7.87 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.0, 2.2, 1.1 Hz, 1H), 7.45 – 7.34 (m, 3H), 7.14 – 7.07 (m, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 5.05 (tt, *J* = 7.5, 5.9 Hz, 1H), 4.73 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.39 (t, *J* = 8.1 Hz, 1H), 3.87 (dd, *J* = 17.9, 5.7 Hz, 1H), 3.54 (dd, *J* = 17.9, 7.4 Hz, 1H), 3.14 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.7, 173.5, 144.5, 137.9, 135.0, 133.4, 131.7, 130.0, 128.3, 126.3, 124.8, 124.1, 123.5, 108.6, 102.8, 74.3, 71.1, 43.8, 25.9. **FT-IR (KBr):** 2922, 1725, 1617, 1468, 1309, 1245, 1121, 1090, 1017, 793, 636 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{16}ClNO_4$ $[M+H]^+$ 358.0841, found 358.0841. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.3 min, t_{minor} = 17.9 min).

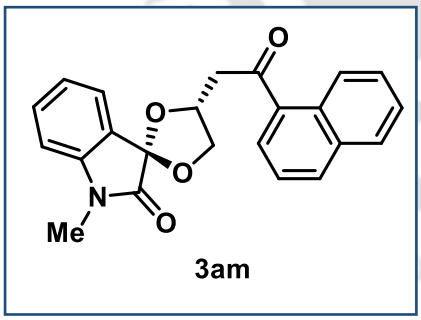
(3S,4'R)-4'-(2-(2-methoxyphenyl)-2-oxoethyl)-1-methylspiro[indoline-3,2'[1,3] dioxolan]-2-one (3al)



3al

Yellow sticky solid, 50% (18mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.76 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.48 (ddd, *J* = 8.8, 7.3, 1.9 Hz, 1H), 7.40 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.35 (td, *J* = 7.7, 1.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.99 (dt, *J* = 10.1, 8.0 Hz, 2H), 6.77 (d, *J* = 7.7 Hz, 1H), 5.00 (tt, *J* = 8.0, 5.6 Hz, 1H), 4.72 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.36 (t, *J* = 8.3 Hz, 1H), 3.93 (s, 3H), 3.86 (dd, *J* = 13.8, 4.7 Hz, 1H), 3.62 (dd, *J* = 18.6, 8.1 Hz, 1H), 3.12 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 199.3, 173.7, 159.4, 144.7, 134.2, 131.7, 130.6, 127.6, 125.0, 125.0, 123.5, 120.8, 111.9, 108.7, 102.7, 74.9, 71.7, 55.7, 48.8, 26.1. **FT-IR (KBr):** 2922, 1726, 1680, 1617, 1468, 1301, 1244, 1110, 1018, 750, 693 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{20}H_{19}NO_5$ $[M+H]^+$ 354.1336, found 354.1336. **HPLC Analysis:** ee of major diasteromer= 89%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.9 min, t_{minor} = 22.8 min).

(3S,4'R)-1-methyl-4'-(2-(naphthalen-1-yl)-2-oxoethyl)spiro[indoline-3,2'-[1,3] dioxolan]-2-one (3am)

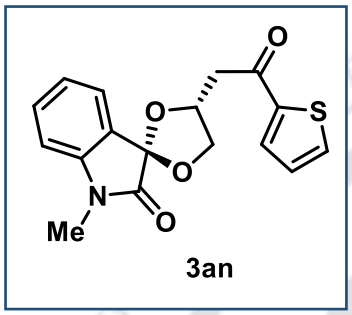


3am

Yellow sticky solid, 66% (25mg) yield. Diastereomeric mixture (dr ratio 5:1). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.77 – 8.71 (m, 1H), 8.06 – 7.99 (m, 2H), 7.89 – 7.86 (m, 1.36H), 7.60 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1.32H), 7.56 – 7.49 (m, 3H), 7.45 – 7.41 (m, 1H), 7.37 (td, *J* = 7.8, 1.3 Hz, 1H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.15 (m, 1H), 4.78 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.67 (m, 0.21H), 4.46 (t, *J* = 8.1 Hz, 1H), 3.97 (dd, *J* = 17.6, 5.6 Hz, 1H), 3.70 (dd, *J* = 17.6, 7.4 Hz, 1H), 3.25 (s, 0.6H), 3.14 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 201.7, 201.6, 173.8, 148.2, 144.7, 138.5, 134.8, 134.2, 133.6, 133.4, 132.6, 132.0, 131.9, 130.4, 130.3, 129.2, 129.0, 128.6, 128.5, 128.4, 128.4, 126.7, 126.6, 126.1, 126.0, 125.5, 125.0, 124.6, 124.6, 124.5, 124.5, 124.0, 123.6, 110.0, 108.8, 103.1, 103.0, 75.0, 72.9, 71.5, 71.1, 46.8, 45.8, 26.6, 26.1. **FT-IR**

(KBr): 2923, 1725, 1672, 1615, 1470, 1371, 1246, 1109, 1018, 803, 752 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{23}H_{19}NO_4$ $[M+H]^+$ 374.1387, found 374.1387. **HPLC Analysis:** ee of major diasteromer= 86%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.3 min, t_{minor} = 22.4 min).

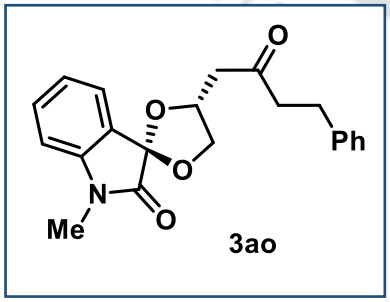
(3S,4'R)-1-methyl-4'-(2-oxo-2-(thiophen-2-yl)ethyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3an)



3an

Light orange solid, 45% (15mg) yield. Melting Point 120-130 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.66 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.47 – 7.29 (m, 2H), 7.14 (dd, *J* = 5.1, 3.8 Hz, 1H), 7.12 – 7.07 (m, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.04 (tt, *J* = 7.6, 6.0 Hz, 1H), 4.69 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.41 (t, *J* = 8.1 Hz, 1H), 3.84 (dd, *J* = 17.0, 6.0 Hz, 1H), 3.47 (dd, *J* = 17.0, 7.3 Hz, 1H), 3.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 190.6, 173.5, 144.5, 143.9, 134.2, 132.9, 131.7, 128.2, 124.8, 124.1, 123.4, 108.6, 102.8, 74.3, 71.1, 44.0, 25.9. **FT-IR (KBr):** 2924, 1724, 1617, 1469, 1309, 1245, 1121, 1016, 793, 636 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{17}H_{15}NO_4S$ $[M+H]^+$ 330.0795, found 330.0795. **HPLC Analysis:** ee of major diasteromer= 96%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 19.2 min, t_{minor} = 23.7 min).

(3S,4'R)-1-methyl-4'-(2-oxo-4-phenylbutyl)spiro[indoline-3,2'-[1,3]dioxolan]-2-one (3ao)

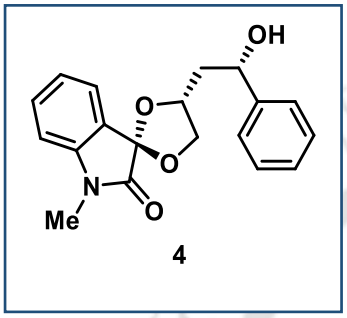


3ao

Yellow sticky solid, 57% (20mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.34 (m, 2H), 7.30 – 7.26 (m, 2H), 7.23 – 7.14 (m, 3H), 7.12 – 7.06 (m, 1H), 6.81 – 6.75 (m, 1H), 4.85 (dq, *J* = 7.8, 6.3 Hz, 1H), 4.59 (dd, *J* = 8.3, 6.2 Hz, 1H), 4.26 (t, *J* = 8.1 Hz, 1H), 3.28 (dd, *J* = 17.6, 6.3 Hz, 1H), 3.12 (s, 3H), 2.97 (dd, *J* = 17.6, 6.9 Hz, 1H), 2.94 – 2.87 (m, 2H), 2.84 – 2.77 (m, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.9, 173.6, 144.6, 140.9, 131.9, 128.7, 128.5, 126.3, 125.0, 124.4, 123.6, 108.8, 102.9, 74.1, 71.1, 47.6, 45.0, 29.6, 26.1. **FT-IR (KBr):** 3060, 2924, 1726, 1617, 1470, 1309, 1245, 1109, 1018, 793,

700 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{21}H_{21}NO_4$ $[M+H]^+$ 352.1543, found 352.1543. **HPLC Analysis:** ee of major diasteromer= 92%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.4 min, t_{minor} = 19.7 min).

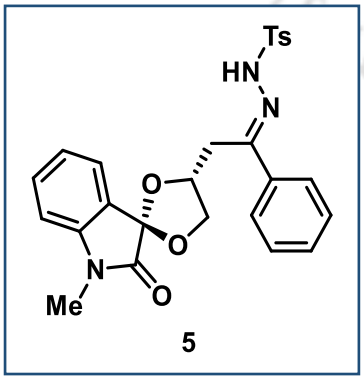
(3S,4'R)-4'-((S)-2-hydroxy-2-phenylethyl)-1-methylspiro[indoline-3,2'-[1,3]dioxolan]-2-one (4)



4

White solid, 50% (16mg) yield. Melting Point 210-220 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 – 7.31 (m, 6H), 7.30 – 7.26 (m, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 5.01 (dd, *J* = 9.8, 2.8 Hz, 1H), 4.76 (m, *J* = 8.4, 5.9, 4.2 Hz, 1H), 4.44 (dd, *J* = 8.2, 5.9 Hz, 1H), 4.33 (t, *J* = 8.3 Hz, 1H), 3.14 (s, 3H), 2.39 (ddd, *J* = 14.4, 8.4, 2.9 Hz, 1H), 2.27 (s, 1H), 2.13 (ddd, *J* = 14.2, 9.7, 4.2 Hz, 1H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.6, 144.7, 144.5, 131.8, 128.7, 127.8, 125.8, 125.0, 124.8, 123.5, 108.8, 102.8, 76.0, 71.4, 71.1, 42.7, 26.1. **FT-IR (KBr):** 3454, 2922, 1727, 1617, 1470, 1373, 1309, 1246, 1113, 1032, 753, 702 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1387, found 326.1386. **HPLC Analysis:** ee of major diasteromer= 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.2 min, t_{minor} = 11.4 min).

4-methyl-N'-((E)-2-((3S,4'R)-1-methyl-2-oxospiro[indoline-3,2'-[1,3]dioxolan]-4'-yl)-1-phenylethylidene)benzenesulfonohydrazide (5)

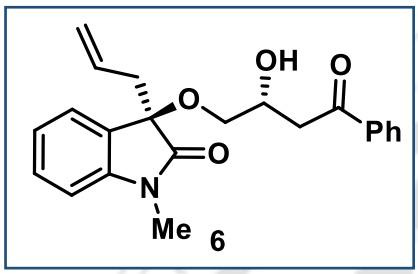


5

Yellow sticky solid, 90% (44mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.06 (s, 1H), 7.65 – 7.59 (m, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.45 (td, *J* = 7.8, 1.4 Hz, 1H), 7.36 – 7.33 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.9 Hz, 3H), 4.56 (m, *J* = 10.6, 7.2, 2.7 Hz, 1H), 4.47 (dd, *J* = 8.2, 6.3 Hz, 1H), 4.40 (t, *J* = 7.9 Hz, 1H), 3.43 (dd, *J* = 14.6, 11.0 Hz, 1H), 3.28 (s, 3H), 3.00 (dd, *J* = 14.6, 2.9 Hz, 1H), 2.23 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 174.1, 150.1, 144.7, 143.4, 136.3, 136.2, 132.3, 129.7, 129.2, 128.7, 127.8, 126.5, 126.5, 125.2, 123.8, 109.2, 103.7,

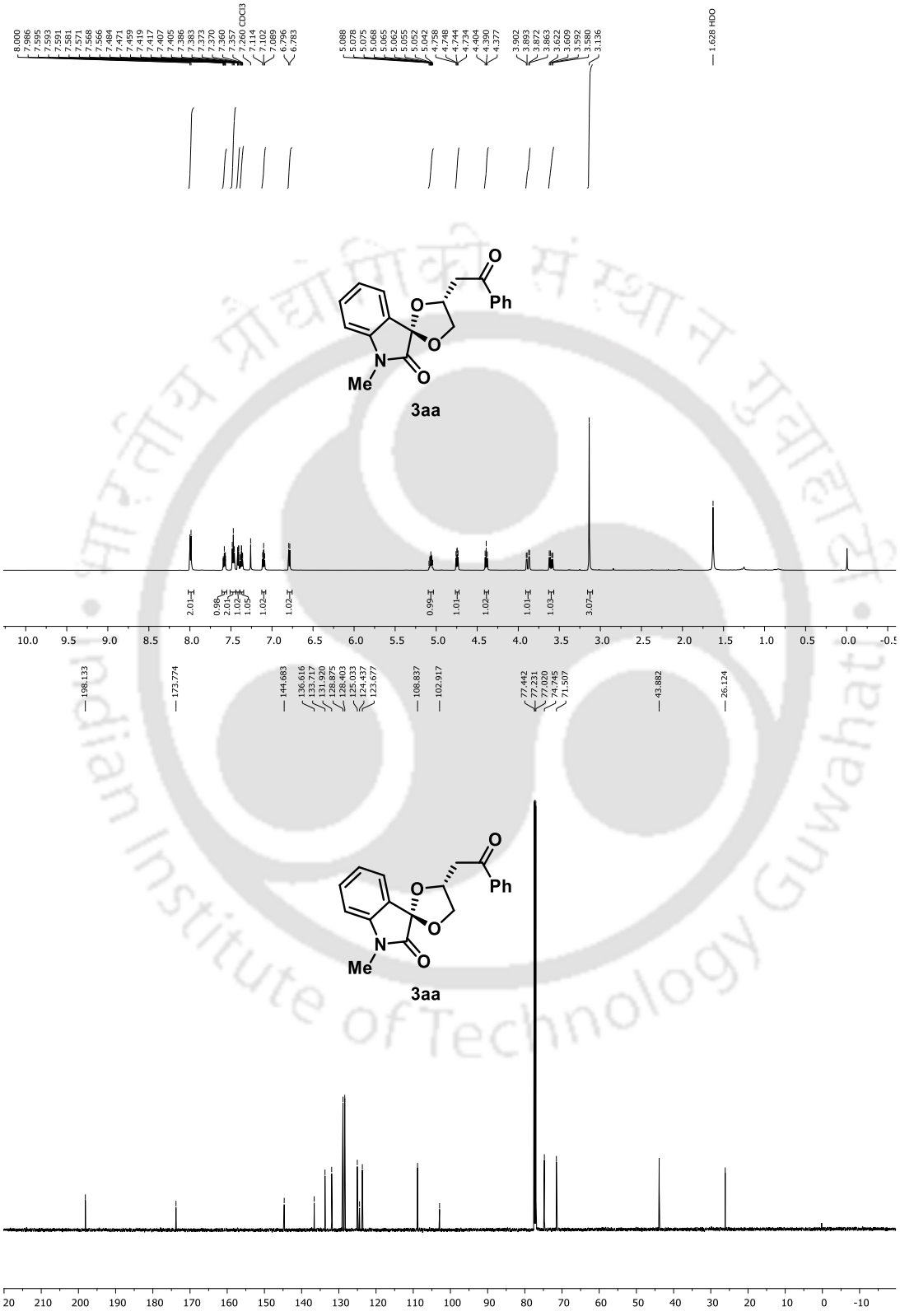
76.1, 70.6, 32.3, 26.5, 21.6. **FT-IR (KBr):** 3219, 2925, 1718, 1617, 1470, 1308, 1264, 1167, 1113, 1018, 734, 702 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{26}H_{25}N_3O_5S$ $[M+H]^+$ 492.1588, found 492.1590. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 71.3 min, t_{minor} = 81.5 min).

(R)-3-allyl-3-((R)-2-hydroxy-4-oxo-4-phenylbutoxy)-1-methylindolin-2-one (6)



Colourless liquid, 78% (28mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.99 – 7.94 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.56 – 5.47 (m, 1H), 5.03 – 4.96 (m, 2H), 4.31 (d, *J* = 3.8 Hz, 1H), 3.33 (dd, *J* = 17.5, 3.9 Hz, 1H), 3.25 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.20 (s, 3H), 3.18 – 3.12 (m, 2H), 3.08 (dd, *J* = 17.6, 8.0 Hz, 1H), 2.76 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.62 (dd, *J* = 13.5, 8.1 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 199.8, 175.7, 143.7, 136.8, 133.4, 130.5, 129.9, 128.6, 128.2, 126.7, 124.5, 123.0, 119.7, 108.3, 82.0, 68.5, 66.9, 42.1, 41.9, 26.1. **FT-IR (KBr):** 3443, 2923, 1720, 1613, 1470, 1374, 1252, 1115, 1021, 753, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** calcd. For $C_{22}H_{23}NO_4$ $[M+H]^+$ 366.1700, found 366.1718. **HPLC Analysis:** ee of major diasteromer= 70%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 29.3 min, t_{minor} = 31.1 min). ee of minor diasteromer= 59%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 35.6 min, t_{minor} = 52.3 min).

2.9 NMR and HPLC spectra of the products



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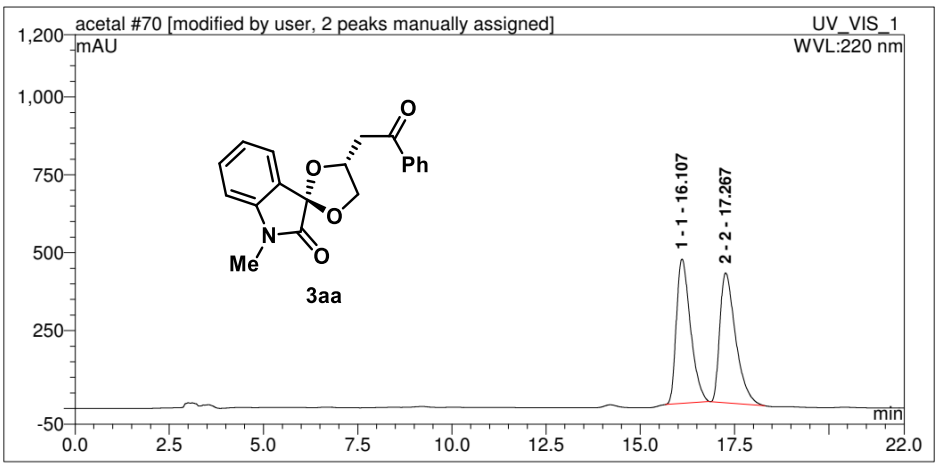
12/19/2019 7:07 PM



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2	2	17.27	203.121	50.23096563	416.635	n.a.

Operator:user Timebase:SCP_HPLC-2 Sequence:acetal

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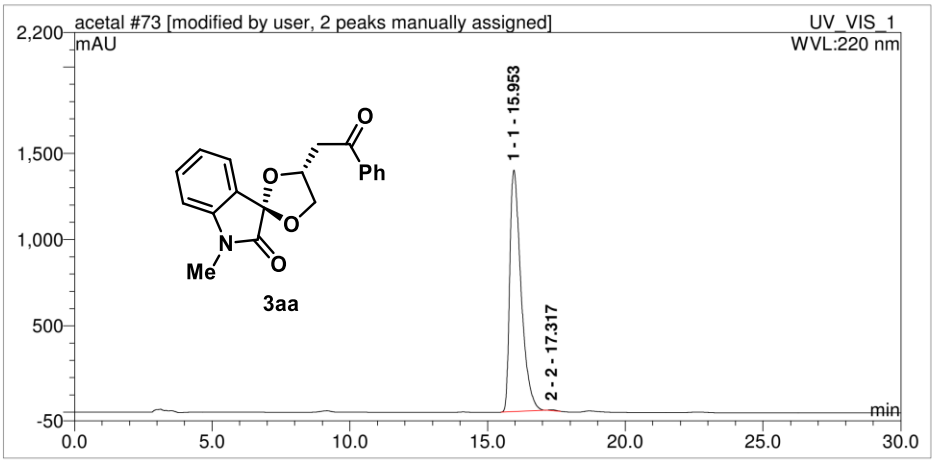
12/19/2019 7:09 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
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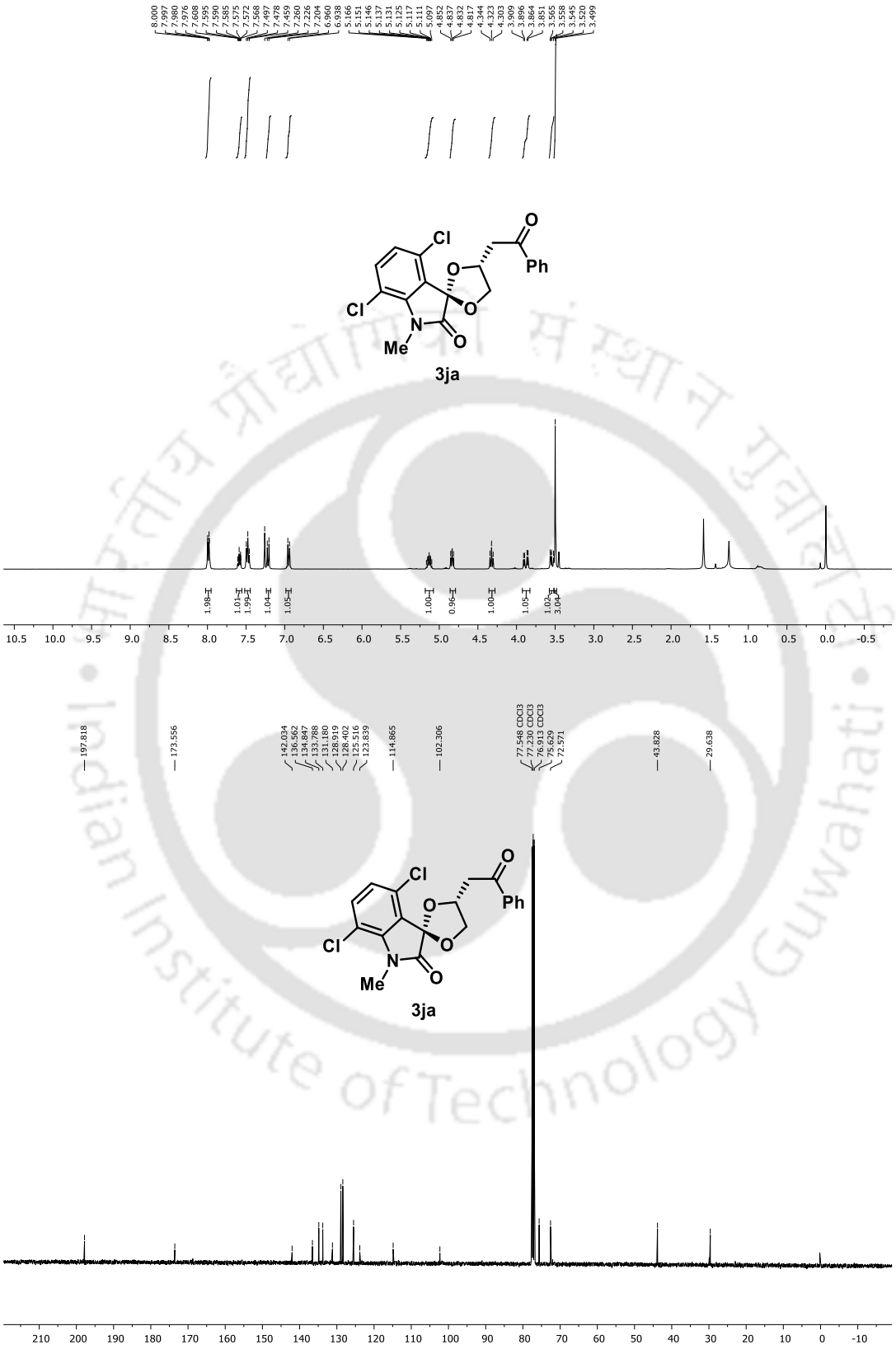
2	2	17.32	1.520	0.2279186068	4.835	n.a.



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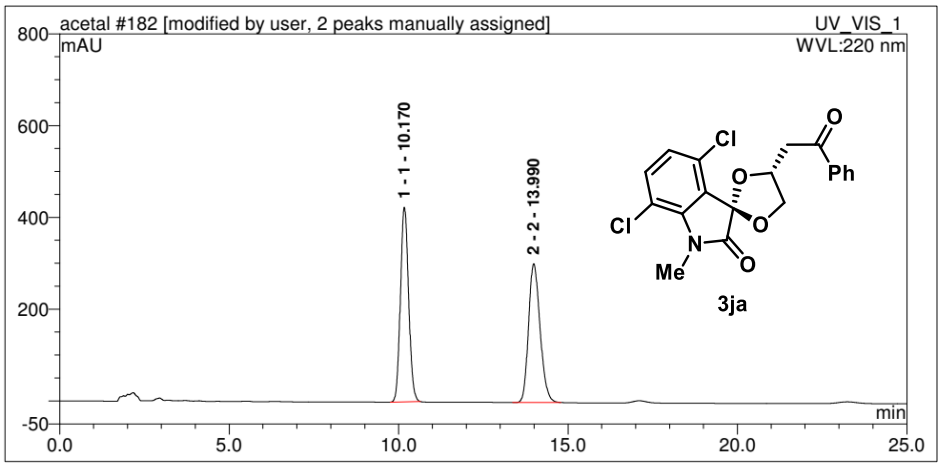
12/19/2019 5:27 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.17	118.9243	49.88335255	424.102	n.a.
2	2	13.99	119.481	50.11664745	302.443	n.a.

Operator:user Timebase:SCP_HPLC-2 Sequence:acetal

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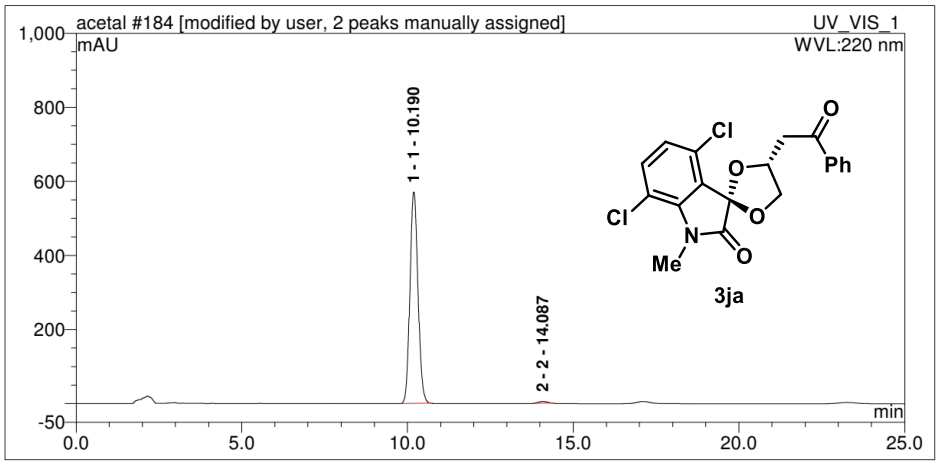
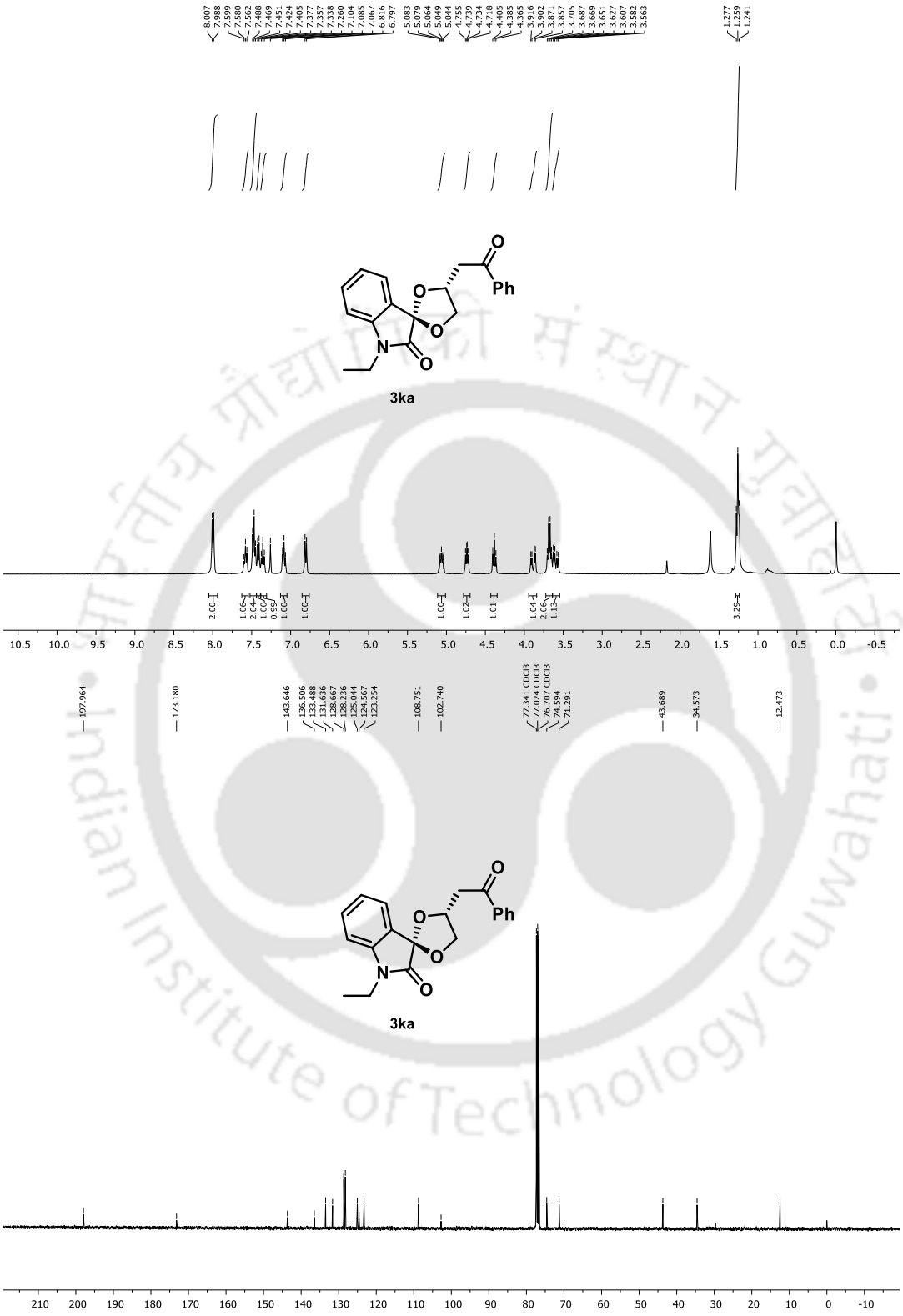
12/19/2019 5:29 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.19	160.3295	99.04431076	570.6456	n.a.
2	2	14.09	1.547	0.9556892439	4.918	n.a.



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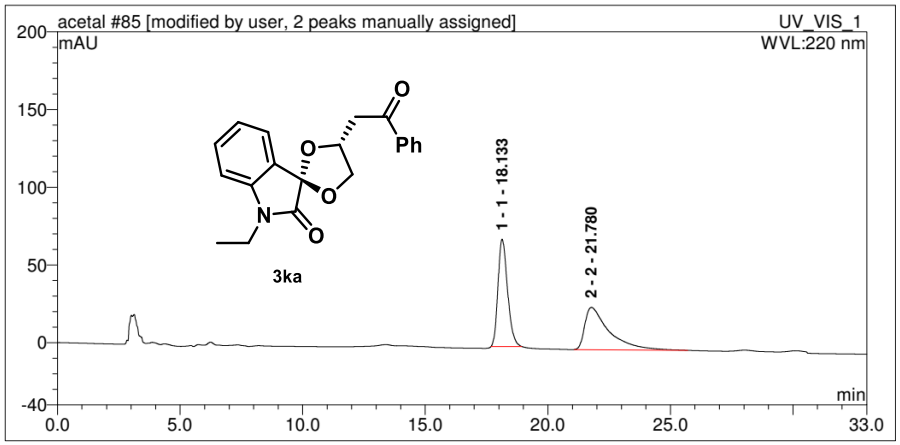
12/19/2019 6:34 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	18.13	31.19716	49.98169266	69.09405	n.a.
2	2	21.78	31.220	50.01830734	27.188	n.a.

Operator:user Timebase:SCP_HPLC-2 Sequence:acetal

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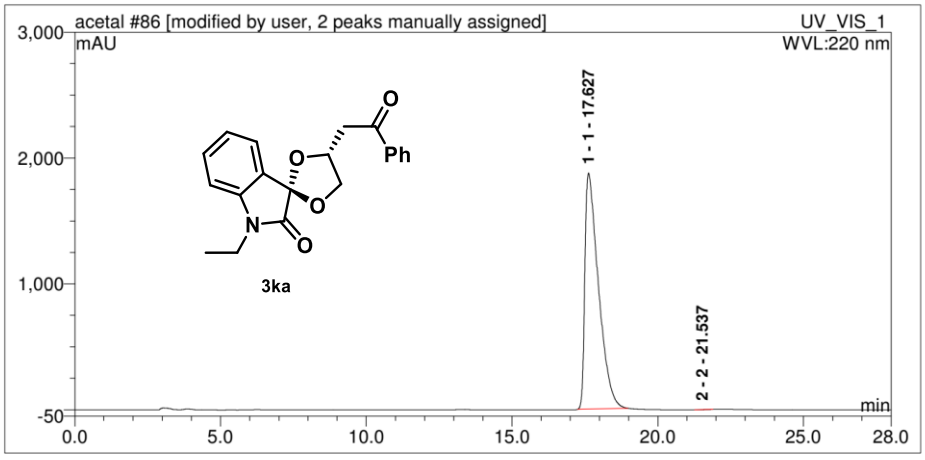
12/19/2019 6:39 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.63	1011.237	99.97151242	1875.753	n.a.
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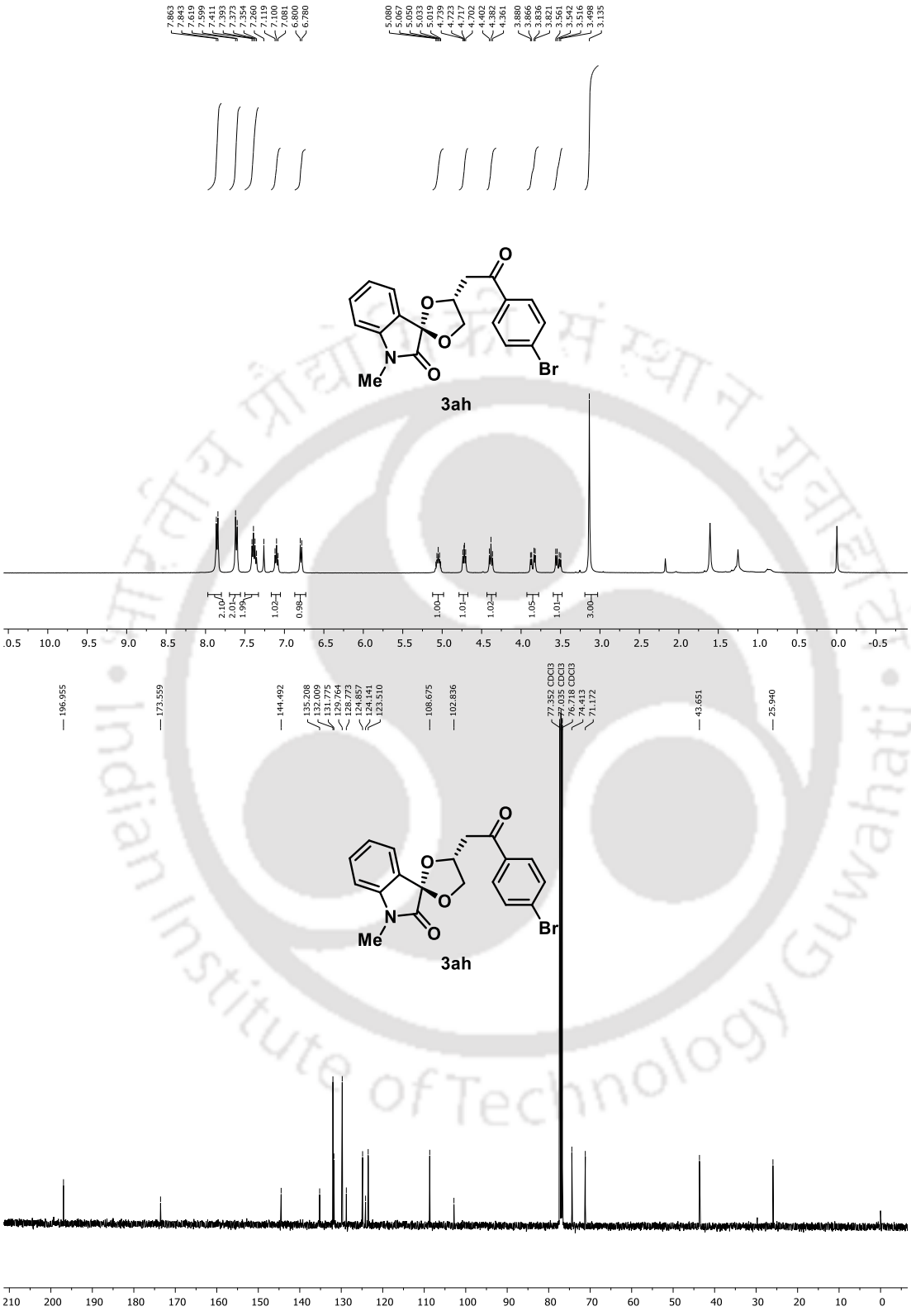

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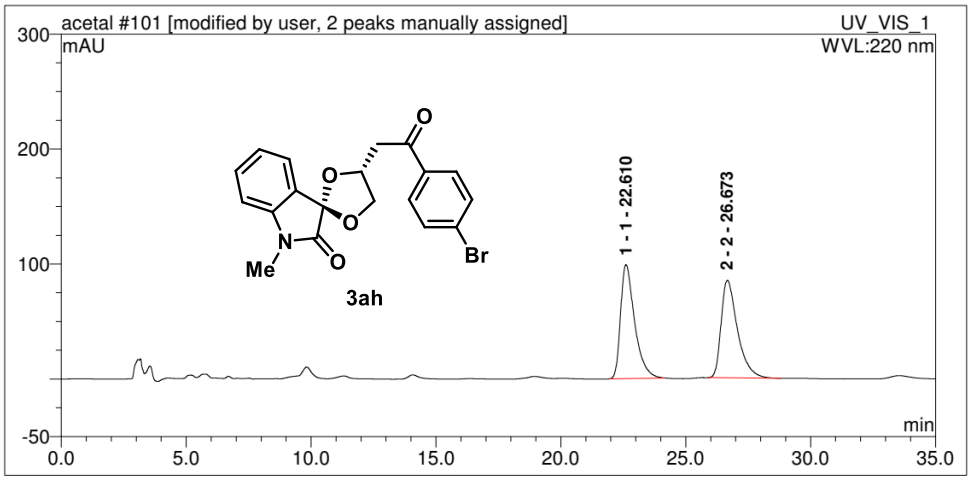
12/21/2019 11:59 AM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	22.61	64.72377	50.1223654	99.04385	n.a.
2	2	26.67	64.408	49.8776346	84.911	n.a.

Operator:user Timebase:SCP_HPLC-2 Sequence:acetal

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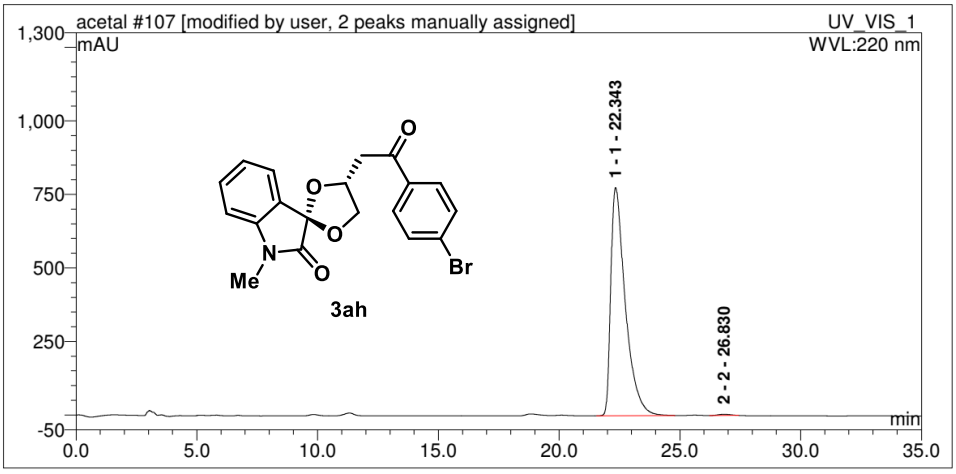
12/21/2019 12:00 PM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	22.34	541.606	99.52900046	775.6369	n.a.
2	2	26.83	2.563	0.470999538	4.265	n.a.

2.10 References

1. (a) Felix, W.; Rimbach, G.; Wengenroth, H. *Arzeim.-Forsch.* **1969**, *19*, 1860. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (c) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (d) Mavragani, C. P.; Moutsopoulos, H. M. Clinic Rev. *Allerg. Immunol.* **2007**, *32*, 287. e) Palmes, J. A.; Aponick, A. *Synthesis* **2012**, 3699.

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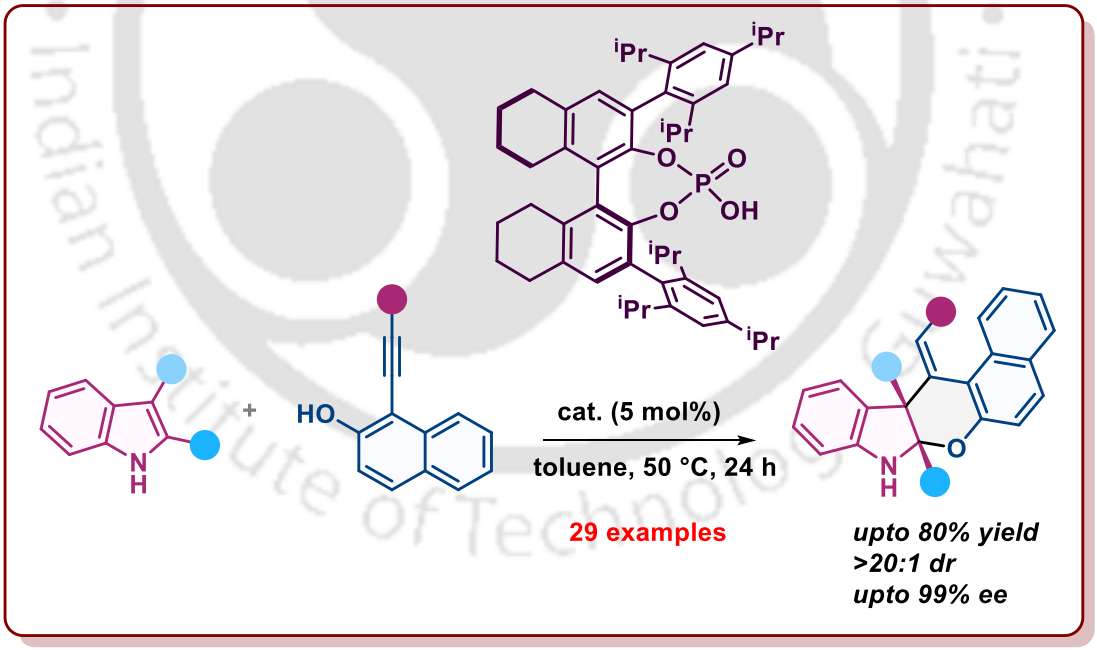
Chapter III

Catalytic Asymmetric Dearomatization of 2,3-Disubstituted Indoles by a [4 + 2] Cycloaddition Reaction with In Situ Generated Vinylidene ortho-Quinone Methides (VQM)

ABSTRACT: A method for the enantioselective dearomatization of 2,3-disubstituted indoles through an organocatalytic intermolecular [4 + 2] cycloaddition reaction with *in situ* generated vinylidene *ortho*-quinone methide has been detailed. This protocol enables the efficient synthesis of a broad spectrum of polycyclic 2,3-fused indolines featuring vicinal quaternary carbon stereocenters, achieved with high yields and outstanding diastereo- and enantioselectivities.



Org. Lett. **2024**, *26*, 5057 – 5062.

3.1 Introduction

The *N*-containing polycyclic motifs serve as crucial scaffold segments within the framework of numerous biologically active compounds.[1-2] Within this category, fused polycyclic indoline derivatives stand out, featuring contiguous stereogenic centers, including one or more quaternary carbon stereocenter. These *N*-heterocycles hold significance as they are prevalent in a diverse array of bioactive molecules and natural products.[3-7] Representative naturally occurring polycyclic indolines such as kopsnone, pleiomaltinine, vincorine, communesin K are shown in Figure 1.

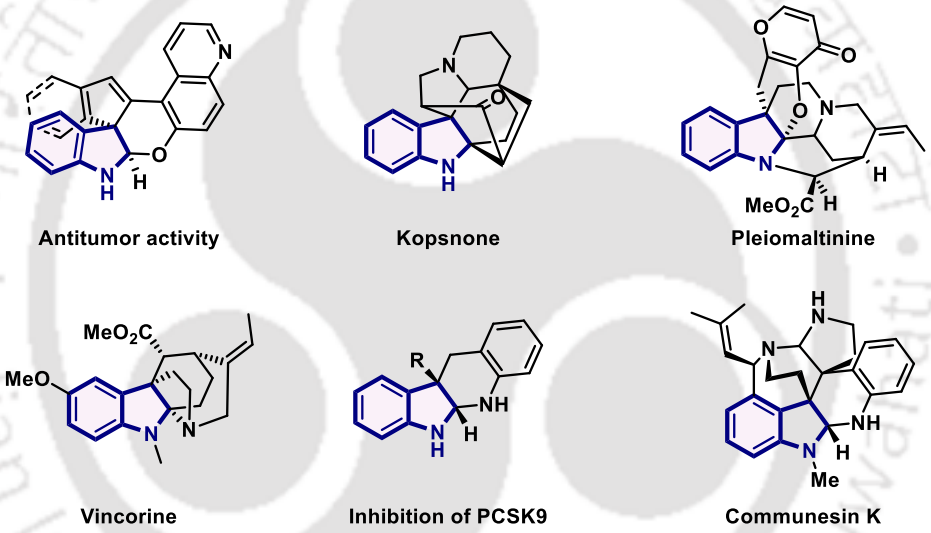


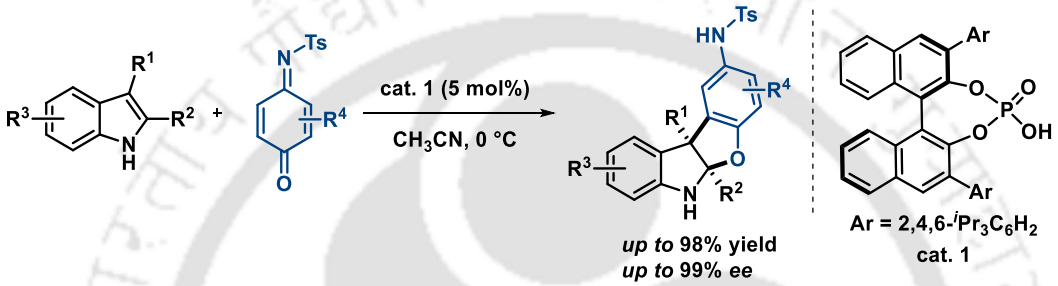
Figure 1: Selected bioactive molecules and natural products containing 2,3-fused indolines motifs

Certainly, the synthesis of these fused polycyclic scaffolds poses significant challenges, largely due to the presence of quaternary carbon stereocenters, which render the molecules structurally less flexible. In the past two decades, substantial efforts have been directed towards the progress of practical and effective regio- and enantioselective construction methods, as well as the functionalization of these scaffolds.[8] Among these strategies, catalytic asymmetric dearomatization (CADA) [9] reactions of indole derivatives emerge as a swift and efficient approach to access these crucial structural motifs in an enantioselective manner.

3.2 Literature Survey

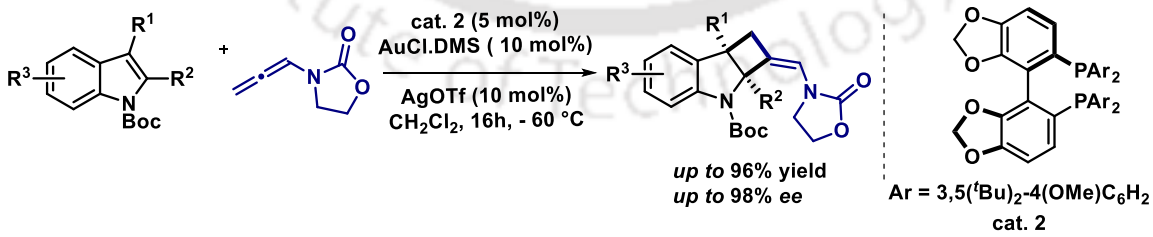
3.2.1 Previous reports on enantioselective cycloaddition of substituted indoles:

In 2014, Zhang *et al.* reported[10], a process involving highly enantioselective [3+2] coupling of 3-substituted indoles with quinone monoimines, facilitated by a chiral phosphoric acid. This method has yielded a diverse range of benzofuroindolines in moderate to high yields, reaching up to 98%. Notably, the enantioselectivities achieved were consistently excellent (up to 99% ee) (Scheme 1).



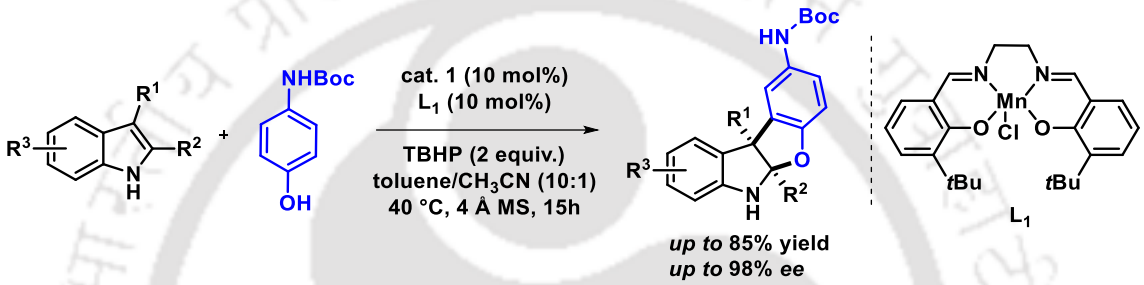
Scheme 1: Reaction of 3-substituted indoles with quinone monoimines

In 2015, Bandini *et al*. reported[11], a highly enantioselective method for synthesizing densely functionalized 2,3-indoline-cyclobutanes using chiral gold catalysis. Through intermolecular formal [2+2]-cycloaddition reactions between substituted indoles and allenamides, direct synthesis of methylenecyclobutane-fused indolines has been achieved. Notably, this approach yields products with two consecutive quaternary stereogenic centers, demonstrating excellent stereochemical control with a diastereomeric ratio of >20:1 and enantiomeric excess up to 99%. (Scheme 2).



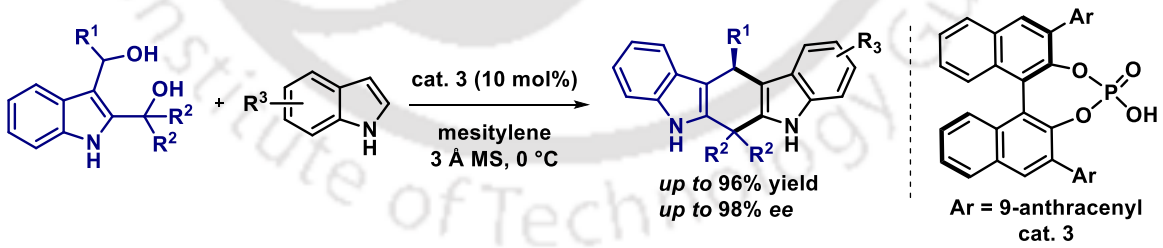
Scheme 2: Reaction between substituted indoles and allenamides

Later in 2019, Zhong *et al*.[12] used a (salen) Mn (III) complex as a biomimetic surrogate of the metallocofactor of phenol-oxidizing enzymes, in combination with chiral phosphoric acid relay catalysis, enabling an enantioselective direct oxidative phenol-indole [3 + 2] coupling reaction to access structurally diverse chiral benzofuroindolines. Differing from previous methods that exclusively make use of isolatable quinones or their imines, this system is capable of harnessing transient *N*-Boc quinone imines and highlights its synthetic potential with high yield and high enantioselectivities (Scheme 3).



Scheme 3: Reaction between substituted indoles and *p*-aminophenols

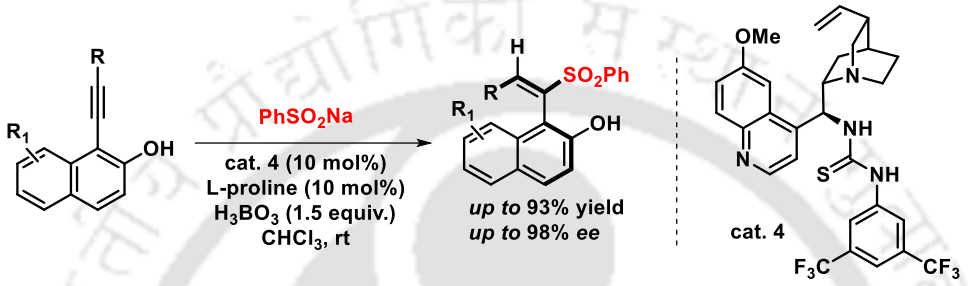
After that in 2023, Shi *et al*. reported[13], first catalytic asymmetric (4 + 2) cycloadditions of 2,3-indolyldimethanols by using indoles as suitable reaction partners under the catalysis of chiral phosphoric acids, constructing enantioenriched indole-fused six-membered rings in high yields with excellent enantioselectivities. (Scheme 4).



Scheme 4: Reaction between 2,3-indolyldimethanols and indoles

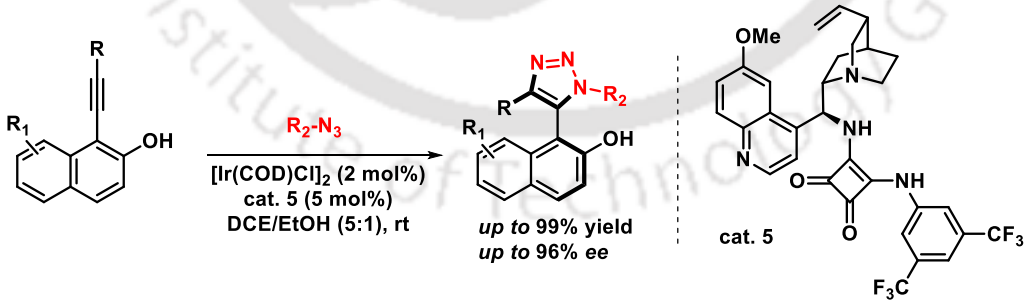
3.2.2 Previous reports on enantioselective reaction of vinylidene *o*-quinone methide (*VQM*):

In 2018, Yan *et al*. reported[14], a method using organocatalysis to selectively create axially chiral sulfone-containing styrenes. They successfully synthesized a range of these compounds with high enantioselectivity, achieving > 99% ee, as well as nearly complete *E/Z* selectivity, > 99% *E/Z*. (Scheme 5).



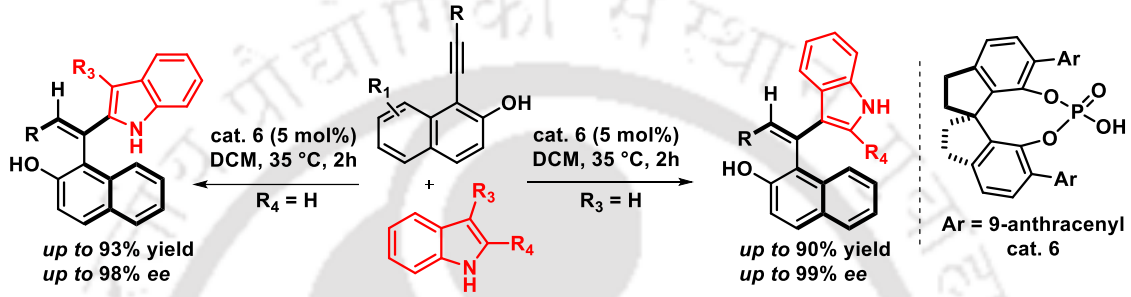
Scheme 5: Reaction between *o*-alkynylnaphthols and sodium benzenesulfinates

In 2022, Xu *et al*. reported[15], a novel cooperative catalytic approach employing Ir(I)/squaramide has been pioneered for the atroposelective synthesis of axially chiral aryltriazoles. This method enabled the synthesis of diverse aryltriazole structures, which were previously inaccessible through traditional click reactions, yielding good product yields with outstanding enantioselectivity. Notably, both enantiomers were readily accessible using a pair of diastereoisomeric squaramides derived from natural quinidine and quinine. (Scheme 6).



Scheme 6: Reaction between *o*-alkynylnaphthols and benzyl azides

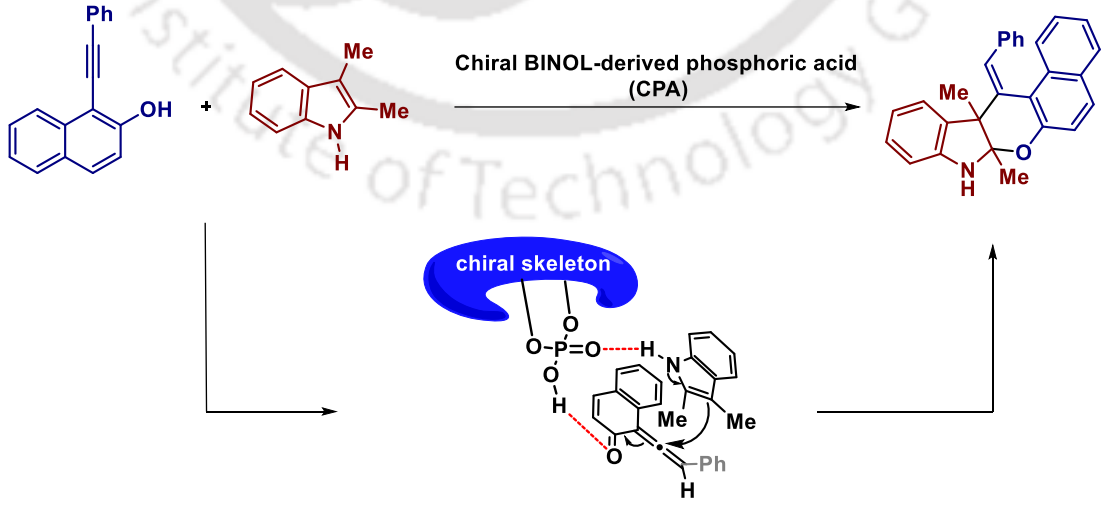
In 2022, Jian *et al*. reported[16], a chiral phosphoric acid-catalyzed intermolecular C2 Friedel−Crafts alkylation reaction involving ortho-alkynylnaphthols and a range of substituted indoles. This method yields axially chiral alkenes with impressive yields of up to 93%, coupled with high *E/Z* selectivity ratios >20:1, and exceptional enantiomeric excess levels reaching up to 98%. Notably, these reactions occur under mild conditions, highlighting the versatility and practicality of this synthetic approach. (Scheme 7).



Scheme 7: Reaction between *o*-alkynylnaphthols and substituted indoles

3.3 Concept

From the previous literature survey, we found that vinylidene *o*-quinone methide (*VQM*) have been explored mainly for the preparation of axially chiral derivatives.[17] So, we postulated that *VQM* could also be suitable reaction partners of asymmetric intermolecular [4 + 2] cycloaddition reaction with 2,3-disubstituted indoles for the preparation of polycyclic fused indolines with vicinal quaternary carbon stereocenters (Scheme 8).

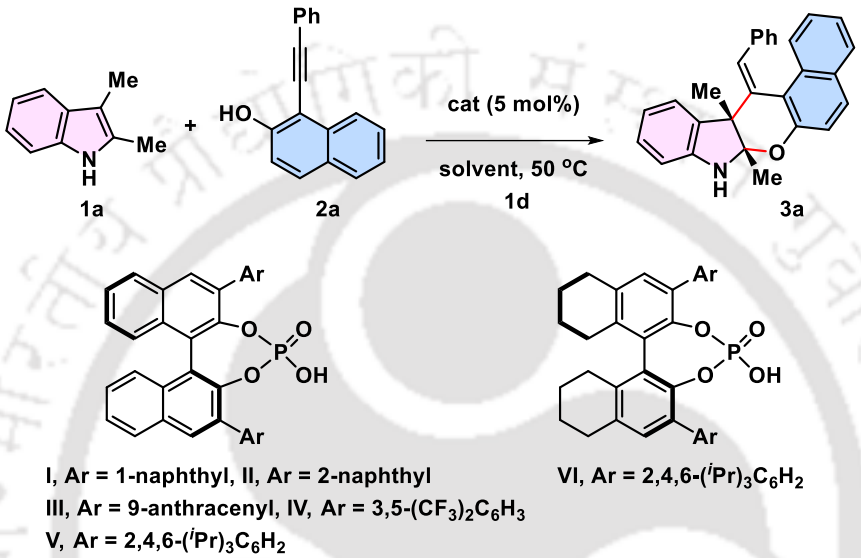


Scheme 8: Proposed route to polycyclic fused indolines derivatives

3.4 Result and Discussion

3.4.1 Optimization of catalyst and reaction conditions:

In the initial trial, a reaction between 2,3-dimethyl-1H-indole (**1a**) and 1-(phenylethynyl)naphthalen-2-ol (**2a**) conducted in toluene at 50 °C utilizing phosphoric



Entry[a]	Catalyst	Solvent	Yield[b] (%)	d.r[c]	ee[d] (%)
1	**I**	toluene	45	>20:1	35
2	**II**	toluene	45	>20:1	8
3	**III**	toluene	60	>20:1	18
4	**IV**	toluene	65	>20:1	84
5	**V**	toluene	60	>20:1	90
6	**VI**	**toluene**	**65**	**>20:1**	**98**
7	**VI**	mesitylene	64	>20:1	92
8	**VI**	$PhCF_3$	50	>20:1	91
9	**VI**	DCE	55	>20:1	92

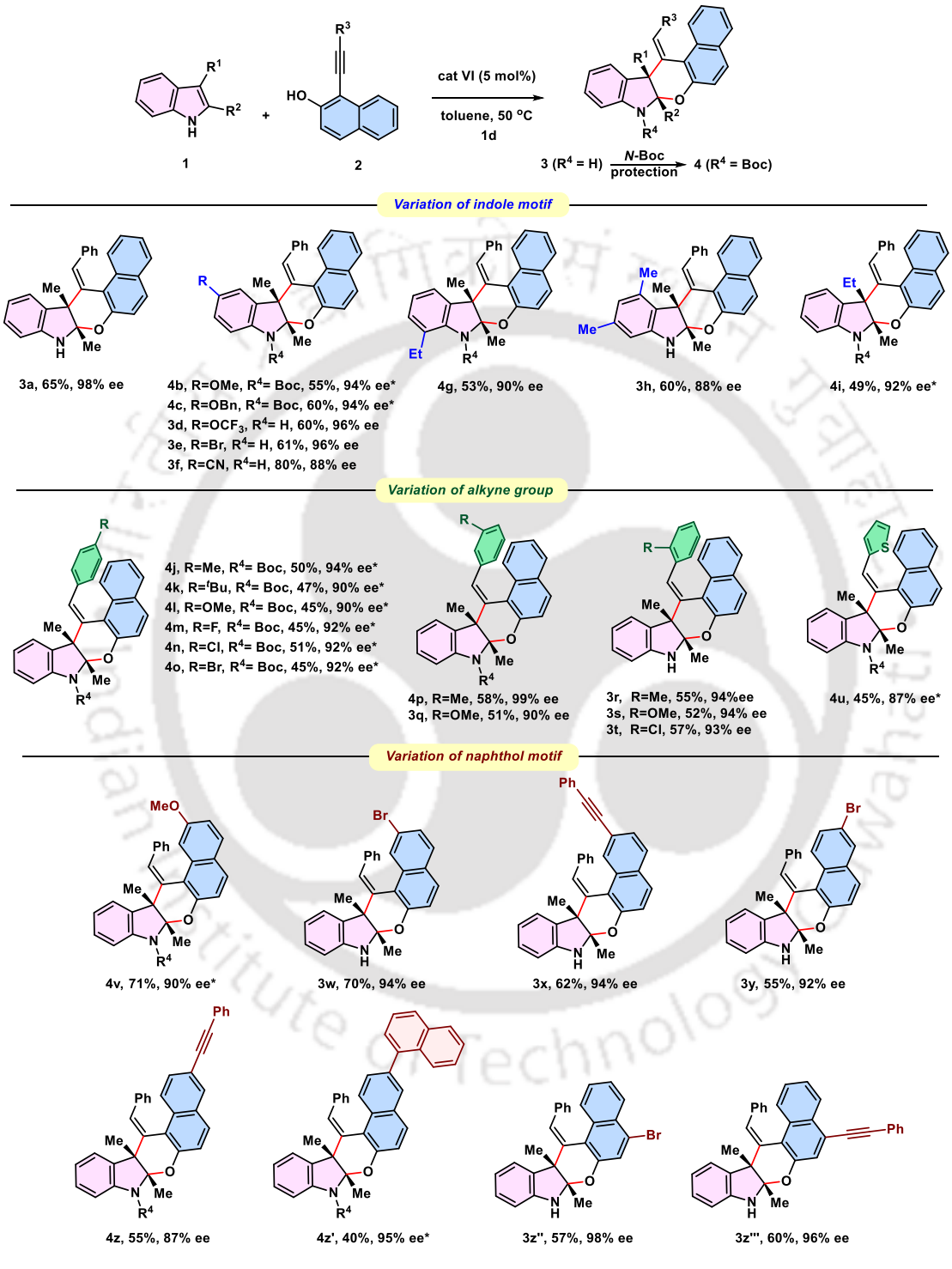
[a] Reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2a** in 8 ml solvent at 50 °C. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^1H NMR. [d] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Table 1: Catalyst and solvent optomization

acid catalyst **I**, as indicated in Table **1**. Encouragingly, within 12 hours, a successful conversion was achieved, yielding the formation of [4+2]-cycloadduct **3a**. While excellent diastereoselectivity was evident for **3a**, only moderate enantioselectivity was observed (entry **1**). Catalysts **II** and **III**, featuring 2-naphthyl and 9-anthracenyl substituents respectively, proved unsuitable for the reaction. Notably, a substantial improvement in enantiomeric excess (*ee*) was noted with catalyst **IV**, featuring bis(trifluoromethyl)phenyl substituents. Enantioselectivity was further enhanced to 90% ee with TRIP catalyst **V**. Ultimately, the most effective catalyst was identified as H_8-TRIP catalyst **VI**, yielding **3a** in 65% yield with 98% *ee*. Although alternative solvents were explored, superior enantioselectivity was not observed.

3.4.2 Substrate scope:

Once the ideal reaction conditions were established, we proceeded to ascertain the substrate range of this novel [4+2] annulation. Initially, the scope of 2,3-disubstituted indole **1** was checked and gratifyingly good results were obtained. To our delight, only a single diastereomer was detected in all cases and high to excellent enantioselectivities were obtained for different indoles. In some cases, the products were isolated as *N*-Boc derivatives **4**. At first, 5-substituted indoles **1b**-**1f** were prepared and reacted with **2a**. The reactions went smoothly and delivered product in acceptable yields with excellent enantioselectivities. Compound **1g** with 7-ethyl substitution similarly showed a smooth conversion, delivering the intended product **4g** in moderate yield with 90% ee. The reaction outcome also did not change with 2,3,4,6-tetramethyl indole (**1h**) and the desired product **3h** was attained in high enantioselectivity. Then we varied the substitution at the 3-position. To our delight, 2-methyl-3-ethyl indole (**1i**) reacted smoothly to provide *N*-Boc derivative **4i** in moderate yield with 92% ee. In the next stage, a range of naphthol **2** with various substitutions on the alkyne group were examined (Table 2). We were pleased to see positive outcomes for *N*-Boc derivatives **4j**-**4o** with *para*-alkyl, -alkoxy and -halo substituted aryl groups. The halo substitutions could be elaborated to other functionalities *via* cross-coupling reactions. Next, *meta*-substitutions were checked, and here also good results were obtained for products **4p** and **3q**.



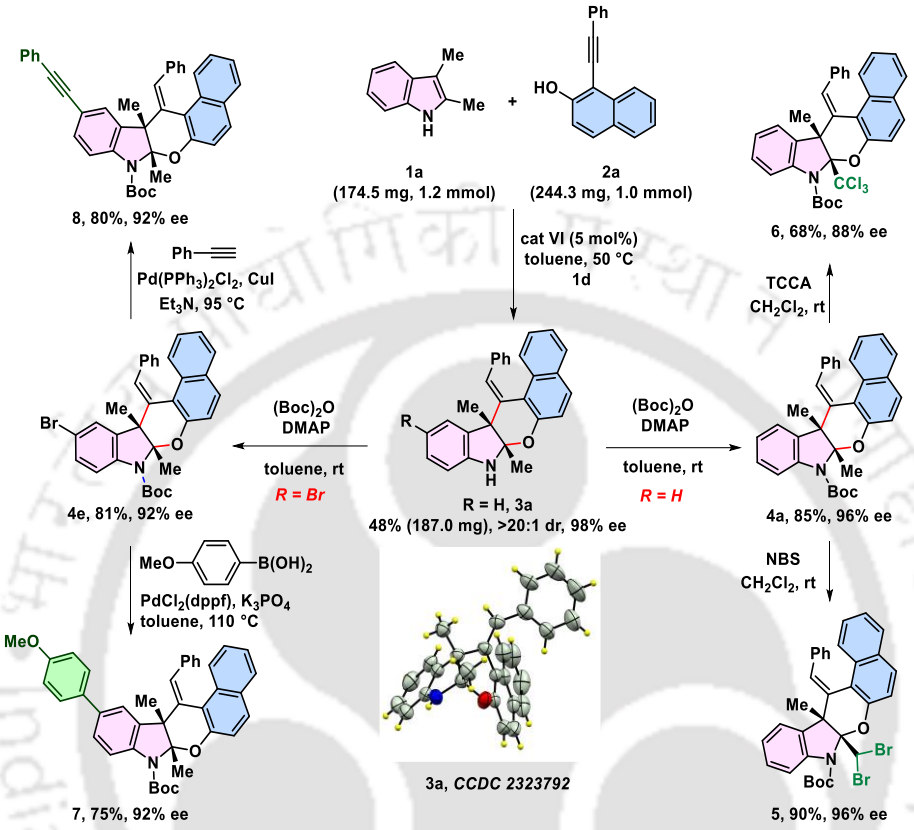
Scheme 9: Substrate scope

The reaction outcome did not alter with *ortho*-substituents and excellent enantioselectivities were detected for products **3r-3t**. An heteroaromatic thienyl substitution was also tolerated in the reaction and the desired *N*-Boc derivative **4u** was isolated in 87% ee. Then different substitutions on the aromatic ring of naphthol **2** were checked. Delightfully, good results were obtained in all cases. Initially, different substituents were attached at the 7-position of naphthol **2**. *N*-Boc derivative **4v** with 7-methoxy substituent was attained 75% yield with 90% ee. Slightly higher enantioselectivities were observed for products **3w** and **3x** having 7-bromo and 7-alkynyl substituents respectively. The reaction was then investigated with 6-substituted naphthols. Gratifyingly, 6- bromo, 6-alkynyl and 6-Naphthyl substitutions were tolerated; and acceptable yields and high enantioselectivities were obtained for the desired products **3y** and *N*-Boc derivative **4z**, **4z'**. Finally, naphthols having variation in the 4-position were screened in the reaction. Delightfully reactions progressed efficiently to afford 4-bromo and 4-alkynyl substituted products **3z''** and **3z'''** respectively in excellent enantioselectivities.

3.4.3 Synthetic transformations:

Following this, a scale-up reaction was conducted using 1.2 mmol of **1a** and 1 mmol of **2a**. Gratifyingly, the reaction proceeded smoothly, affording **3a** in 48% yield with 98% ee. To showcase the synthetic versatility of our approach, several transformations were performed on **3a** and **3e**. Initially, the NH group of **3a** was protected as Boc, yielding compound **4a** in 85% yield with 96% ee. Subsequently, compound **4a** was subjected to treatment with NBS (*N*-bromosuccinimide), resulting in an unusual dibromination reaction on the methyl group and yielding compound **5** in 90% yield with retention of enantioselectivity. Compound **4a** was then combined with TCAA (trichloroisocyanuric acid) in dichloromethane, leading to the formation of an unexpected product **6** containing a trichloromethyl group in 68% yield with slight erosion in enantioselectivity. Following this, *N*-Boc protection was carried out on **3e**, affording compound **4e** in 81% yield with 92% ee. Suzuki coupling reaction of **4e** with *p*-anisyl boronic acid resulted in the formation of compound **7** in acceptable yield with retention of enantioselectivity. Finally, a

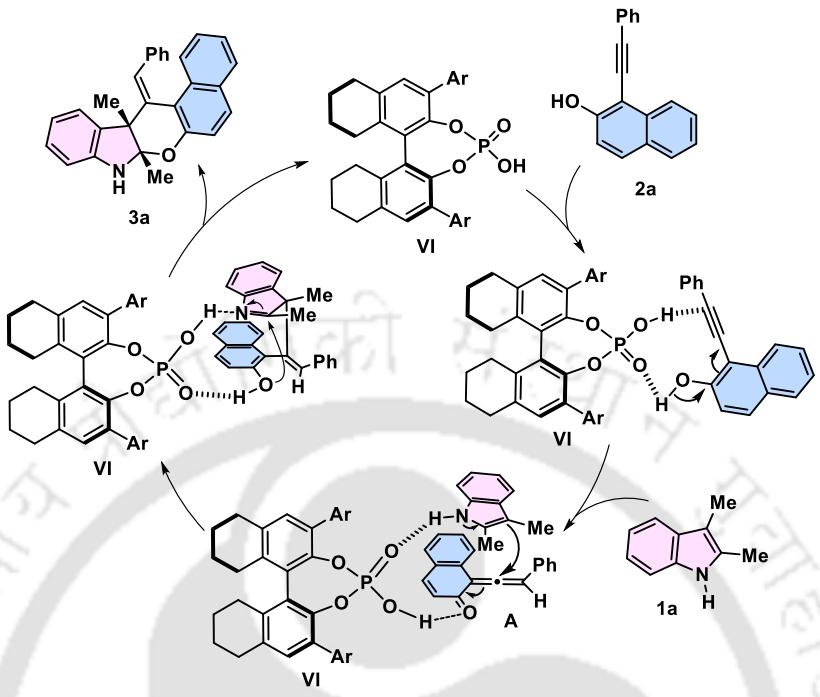
Sonogoshira reaction was performed between **4e** and phenyl acetylene, yielding compound **8** with an alkyne motif in 80% yield, with enantioselectivity preserved.



Scheme 10: Scale up reaction and synthetic transformations

3.4.4 The proposed mechanism:

Drawing upon previous reports of phosphoric acid catalyzed reactions[18], a plausible reaction mechanism has been proposed. In this scheme, the chiral phosphoric acid serves as a bifunctional catalyst. Initially, non-racemic *VQM* intermediate **A** is formed as a transient species from **2a** through the action of phosphoric acid catalyst **VI** *via* prototropic rearrangement. Subsequently, chiral catalyst **VI** activates both **1a** and *VQM* **A**, facilitating an inverse electron demand [4+2] cycloaddition and yielding indoline **3a** with high enantioselectivity.



Scheme 11: Proposed mechanistic pathway

3.5 Conclusion

In summary, we've pioneered the first enantioselective intermolecular [4+2] reaction involving in situ generated vinylidene *ortho*-quinone methides with 2,3-disubstituted indoles. This methodology has yielded a range of polycyclic 2,3-fused indolines featuring vicinal carbon quaternary centers, achieved with high yields and outstanding diastereo- and enantioselectivities. Additionally, we've reported several synthetic transformations, including rare trichlorination and dibromination of methyl groups.

3.6 Experimental section

3.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. All dry solvents were dried using activated 4Å molecular sieves and stored under argon. ^{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 and acetone δ 2.05), carbon (chloroform δ 77.23 and acetone δ 29.84). Multiplicity was indicated as follows**:** s = singlet, d = doublet, dd = double doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet, bs = broad singlet. Coupling constants were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using Daicel Chiral PAK IA, IF and ADH Columns, Phenomenex Chiral LC Lux Cellulose-1 and Cellulose-4 Columns, YMC Chiral ART Amylose-C Column. For visualizing the products UV light and/or I_2 were used. Silica gel (230-400 mesh size) was used for the flash column chromatography. Reactions were monitored by TLC on silica gel 60 with fluorescence indicator F254 (0.25 mm).

3.6.2 Preparation of Starting materials

- ***3.6.2.1 General procedure for synthesis of 2,3-disubstituted indoles:***

2,3-disbustitued indoles were known compounds and were prepared according to the literature procedure.[19]

- ***3.6.2.2 General procedure for synthesis of different o-alkynylnaphthols:***

o-Alkynylnaphthols were known compounds and were synthesized as described in the literature.[20]

3.6.3 General Procedure for acid catalysed [4+2] cycloaddition reaction

- ***3.6.3.1 General procedure for synthesis of racemic compounds:***

In an oven dried round bottom flask, **1a** (17.5 mg, 0.12 mmol, 1.2 equiv.), **2a** (24.5 mg, 0.1 mmol, 1.0 equiv.) and 10 mol% of *p*-toluene sulfonic acid (1.75 mg) were taken under argon atmosphere. 2.0 mL dry toluene was added to the reaction mixture and stirred at 50 °C in a pre-heated oil bath for 24 hours. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (2 – 3 %) to afford desired products.

- ***3.6.3.2 General procedure for the synthesis of chiral compound:***

In an oven dried round bottom flask, **1a** (17.5 mg, 0.12 mmol, 1.2 equiv.), **2a** (24.5 mg, 0.1 mmol, 1.0 equiv.) and 5 mol% of catalyst VI (3.8 mg) were taken under argon

atmosphere. 8.0 mL dry toluene was added to the reaction mixture and stirred at 50 °C in a pre-heated oil bath for 24 hours. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (2 – 3 %) to afford desired products.

3.6.4 Synthetic transformations

- ***3.6.4.1 General Procedure for Boc protection of compound 3:***

In an oven dried round bottom flask, compound **3a** (39.0 mg, 0.1 mmol, 1.0 equiv.) was taken and DMAP (0.4 mg, 0.003 mmol, 0.03 equiv.) was added under argon atmosphere. Then 1.0 mL of toluene was added to the reaction mixture. Di-*tert*-butyl dicarbonate (25 µL, 0.11 mmol, 1.1 equiv.) was added dropwise to the reaction mixture. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (10 %) to afford desired products **4**.

- ***3.6.4.2 General procedure for the synthesis of compound 5:***

In an oven dried round bottom flask, N-Bromosuccinimide (27.0 mg, 0.15 mmol, 1.5 equiv.) was added to a solution of compound **4a** (49.0 mg, 0.1 mmol, 1.0 equiv.) in dichloromethane (1.0 mL) under argon atmosphere. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (3 – 4 %) to afford desired product **5** with 90 % yield.

- ***3.6.4.3 General procedure for the synthesis of compound 6:***

In an oven dried round bottom flask, trichloroisocyanuric acid (35.0 mg, 0.15 mmol, 1.5 equiv.) was added to a solution of compound **4a** (49.0 mg, 0.1 mmol, 1.0 equiv.) in dichloromethane (1.0 mL) under argon atmosphere. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (3 – 4 %) to afford desired product **6** with 68 % yield.

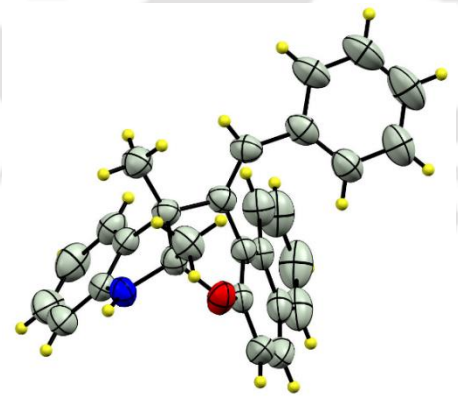
➢ ***3.6.4.4 General procedure for the synthesis of compound 7[21]:***

To a dry flask under argon containing **4e** (53.0 mg, 0.1 mmol, 1.0 equiv.) was sequentially added *p*-methoxy phenylboronic acid (76.0 mg, 0.5 mmol, 5.0 equiv.), $PdCl_2$(dppf) (8.2 mg, 0.01 mmol, 0.01 equiv.), K_3PO_4 (106.0 mg, 0.5 mmol, 5.0 equiv.). The mixture was stirred for 3 h at 110 °C in a pre-heated oil bath. Completion of reaction was checked by TLC. After the completion of reaction, water was added to the mixture and extracted with ethyl acetate. Removal of solvent under reduced pressure afforded a residue which is purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (10 – 12 %) to afford compound **7** with 75 % yield.

➢ ***3.6.4.5 General procedure for the synthesis of compound 8:***

To a dry flask under argon containing **4e** (53.0 mg, 0.1 mmol, 1.0 equiv.) was sequentially added Et_3N (1.0 mL), phenyl acetylene (13.0 µL, 0.12 mmol, 1.2 equiv.), $PdCl_2(PPh_3)_2$ (2.0 mg, 0.005 mmol, 0.05 equiv.), CuI (2.0 mg, 0.01 mmol, 0.1 equiv.). The mixture was stirred for 12 h at 95 °C in a pre-heated oil bath. Then the mixture was filtered through a pad of celite. Removal of solvent under reduced pressure afforded a residue which is purified by column chromatography on silica gel eluting with ethyl-acetate: hexane (10 – 12 %) to afford compound **8** with 80 % yield.

3.7 Single crystal X-ray diffraction analysis of 3a



Ortep Diagram with 30 % ellipsoid probability of 3a

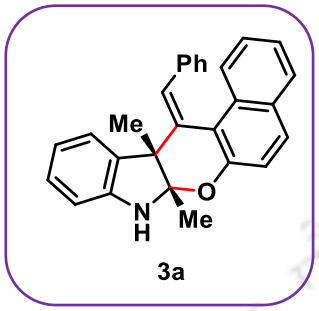
- ***Method for crystal growth:***

In a round bottom flask, compound 3a dissolved in minimum amount of hexane/DCM (3:1) and it kept in dark place at room temperature for slow evaporation to get yellow crystal of 3a.

CCDC No.	**2323792**
Empirical formula	$C_{28}H_{23}NO$
Formula weight	389.47
Crystal habit, colour	block / light yellow
Crystal size mm^3	0.25 x 0.20 x 0.15 mm^3
Device type	Bruker APEX-II CCD
Temperature, *T*	293 K
Wavelength, λ	0.71073 Å
Crystal system	triclinic
Space group	P 1
Unit cell dimensions	a=8.8362(8) Å α=111.560(2)° b=14.9866(13) Å β=95.286(2)° c=17.7229(16) Å γ=92.395(3)°
Volume	2166.2(3) $Å^3$
Z	4
Density (calculated)	1.194 g/cm^3
Absorption coefficient	0.072 mm^{-1}
F(000)	824.0
Theta(max)	24.996°
Data completeness	0.97
R(reflections)	0.0724 (10575)
wR2(reflections)	0.1280 (14805)

3.8 Characterisation of the products

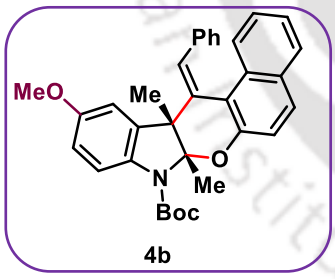
(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-7a,8,12b,13-tetrahydrobenzo [5,6] chromeno[2,3-b]indole (3a)



3a

Light yellow crystalline solid, M.P. 161 – 164 °C, 65% (25.3 mg) yield, >20:1 *dr*, 98% *ee*. **^{1}H NMR (500 MHz, Acetone-d$_6$)** δ 7.52 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.18 (s, 1H), 7.00 (dd, *J* = 11.2, 5.2 Hz, 4H), 6.94 (dd, *J* = 8.1, 2.7 Hz, 4H), 6.71 (d, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 6.23 (s, 1H), 6.19 (t, *J* = 7.4 Hz, 1H), 1.75 (s, 3H), 1.71 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d$_6$)** δ 155.6, 148.8, 138.4, 136.0, 134.4, 130.3, 130.2, 129.8, 129.8, 128.6, 128.6, 128.0, 127.6, 127.5, 126.2, 125.6, 123.7, 122.5, 121.3, 119.5, 118.8, 108.3, 103.5, 58.6, 22.9, 22.7. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{23}NO$: 390.1853, found 390.1853. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 5.3 min, t_{major} = 6.8 min).

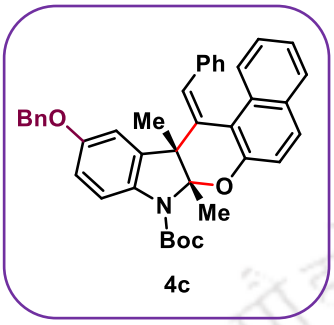
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-11-methoxy-7a, 12b-dimethyl-12b,13-dihydrobenzo[5,6]chromeno[2,3-b] indole-8(7aH)-carboxylate (4b)



4b

Yellow semi solid, 55% (28.6 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.94 (m, 1H), 7.76 – 7.70 (m, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.26 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.23 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.01 (s, 1H), 6.97 – 6.90 (m, 3H), 6.86 (dt, *J* = 8.0, 1.9 Hz, 2H), 6.66 (d, *J* = 2.3 Hz, 1H), 6.62 – 6.57 (m, 1H), 3.32 (s, 3H), 2.45 (s, 3H), 1.55 (s, 3H), 1.42 (s, 9H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 184.3, 157.4, 151.3, 148.2, 146.4, 146.2, 136.0, 134.2, 133.4, 131.9, 131.5, 128.9, 128.9, 128.5, 128.1, 127.5, 127.3, 126.6, 126.1, 125.6, 121.7, 119.9, 113.5, 109.4, 83.7, 64.7, 55.4, 27.7, 23.3, 16.6. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_4$: 520.2483, found 520.2484. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm (t_{minor} = 10.5 min, t_{major} = 12.0 min).

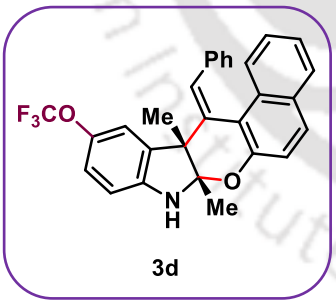
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-11-(benzyloxy)-7a,12b-dimethyl-12b,13-dihydrobenzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4c)



4c

Yellow sticky solid, 60% (35.7 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.97 – 7.91 (m, 1H), 7.76 – 7.71 (m, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.20 (m, 10H), 7.05 (s, 1H), 6.98 – 6.92 (m, 3H), 6.90 – 6.85 (m, 2H), 6.71 (q, *J* = 3.8, 2.9 Hz, 1H), 6.68 – 6.62 (m, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.28 (d, *J* = 11.4 Hz, 1H), 2.45 (s, 3H), 1.57 (s, 3H), 1.39 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 184.4, 156.6, 151.4, 148.4, 146.4, 146.1, 137.3, 136.0, 134.3, 133.4, 131.9, 131.5, 128.9, 128.9, 128.5, 128.1, 127.9, 127.7, 127.7, 127.5, 127.3, 126.6, 126.2, 125.6, 121.8, 119.9, 114.4, 110.5, 83.7, 70.4, 64.7, 27.7, 23.4, 16.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{40}H_{37}NO_4$: 596.2796, found 596.2798. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15 min, t_{minor} = 19.4 min).

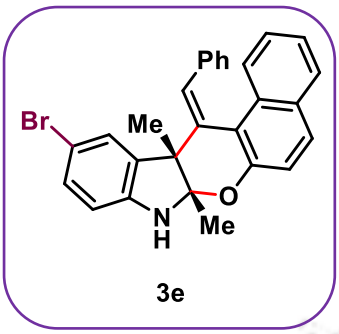
(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-11-(tri fluoromethoxy)-7a,8,12b,13-tetrahydrobenzo[5,6]chromeno [2,3-b]indole (3d)



3d

Light yellow semi solid, 60% (28.4 mg) yield, >20:1 *dr*, 96% *ee*. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 7.57 (dd, *J* = 8.5, 3.6 Hz, 2H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.23 (s, 1H), 7.02 – 7.07 (m, 4H), 6.94 – 6.99 (m, 4H), 6.70 (s, 1H), 6.56 (dd, *J* = 8.4, 2.7 Hz, 1H), 6.50 (s, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 1.80 (s, 3H), 1.79 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 155.3, 148.0, 141.7, 138.2, 137.6, 133.6, 130.4, 130.2, 130.0, 129.9, 128.7, 128.6, 128.0, 127.7, 126.4, 125.4, 124.0, 121.9, 121.2, 120.4 (q, *J* = 252.5 Hz), 119.6, 116.5, 107.9, 103.9, 59.1, 23.0, 22.3. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{29}H_{22}F_3NO_2$: 474.1676, found 474. 1678. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm (t_{minor} = 4.8 min, t_{major} = 6.0 min).

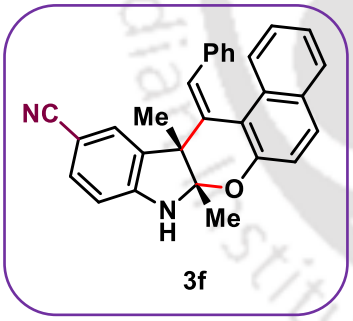
(7aS,12bS)-13-((E)-benzylidene)-11-bromo-7a,12b-dimethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3e)



3e

Yellow semi solid, 61% (28.6 mg) yield, >20:1 *dr*, 96% *ee*. **^{1}H NMR (600 MHz, Acetone-d$_6$)** δ 7.58 (dd, *J* = 8.7, 2.7 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.21 (s, 1H), 7.08 – 7.03 (m, 2H), 7.02 – 6.95 (m, 6H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.55 (s, 1H), 6.30 (dd, *J* = 8.3, 1.7 Hz, 1H), 1.77 (s, 3H), 1.75 (s, 3H). **^{13}C NMR (150 MHz, Acetone-d$_6$)** δ 155.3, 148.1, 138.6, 138.2, 133.4, 130.7, 130.3, 130.2, 130.0, 129.8, 128.7, 128.6, 128.0, 127.6, 126.4, 125.6, 125.4, 124.0, 121.5, 119.6, 109.9, 109.6, 103.5, 58.9, 22.9, 22.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{22}BrNO$: 468.0958, found 468.0958. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 5.6 min, t_{major} = 7.0 min).

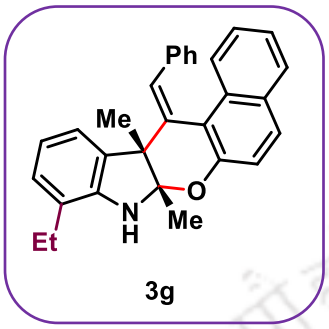
(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-7a,8,12b,13-tetrahydrobenzo[5,6] chromeno[2,3-b]indole-11-carbonitrile (3f)



3f

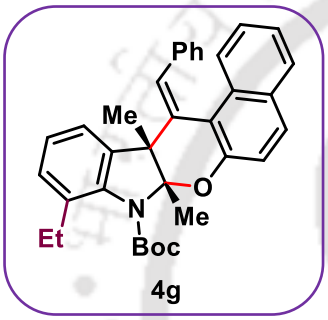
Light pink solid, M.P. 190 – 193 °C, 80% (36.5 mg) yield, >20:1 *dr*, 88% *ee*. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.51 (dd, *J* = 8.5, 4.2 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.11 – 6.89 (m, 11H), 6.26 (d, *J* = 8.1 Hz, 1H), 5.14 (s, 1H), 1.78 (s, 3H), 1.72 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 153.6, 150.8, 136.7, 136.0, 133.3, 131.9, 129.8, 129.7, 129.2, 129.1, 128.1, 128.0, 127.7, 127.4, 126.4, 125.5, 124.6, 123.9, 121.2, 120.3, 118.6, 107.3, 101.9, 100.9, 57.8, 22.8, 22.3. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{29}H_{22}N_2O$: 415.1805, found 415.1812. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 5.0 min, t_{major} = 6.6 min).

(7aS,12bS)-13-((E)-benzylidene)-9-ethyl-7a,12b-dimethyl-7a,8,12b,13-tetrahydrobenzo [5,6]chromeno[2,3-b]indole (3g)



3g

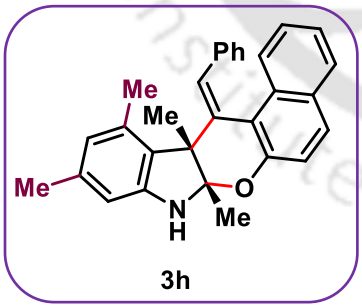
Light yellow semi solid, 53% (22.0 mg) yield, >20:1 *dr*, 90% *ee*. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{30}H_{27}NO$: 418.2166, found 418.2166. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 4 min, t_{major} = 5.2 min).



4g

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.39 – 7.24 (m, 3H), 7.17 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.99 – 6.86 (m, 5H), 6.84 – 6.75 (m, 3H), 2.92 (m, 2H), 2.40 (s, 3H), 1.49 (s, 3H), 1.43 (s, 9H), 1.23 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 185.3, 152.5, 151.4, 146.3, 145.4, 136.1, 135.5, 134.2, 133.2, 131.8, 131.6, 129.0, 128.9, 128.4, 128.1, 127.4, 127.2, 127.2, 126.4, 126.4, 125.7, 124.9, 121.6, 120.9, 83.6, 64.6, 27.8, 24.3, 22.6, 17.1, 15.5.

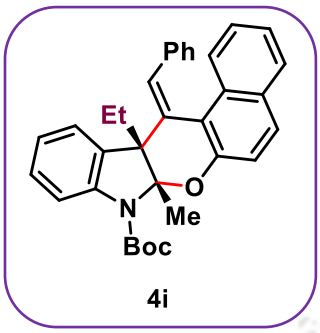
(7aS,12bS)-13-((E)-benzylidene)-7a,10,12,12b-tetramethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3h)



3h

Yellow semi solid, 60% (25.0 mg) yield, >20:1 *dr*, 88% *ee*. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 7.61 – 7.49 (m, 3H), 7.22 (s, 1H), 7.07 – 7.01 (m, 3H), 6.99 – 6.92 (m, 5H), 6.13 (s, 1H), 6.12 (s, 1H), 5.89 (s, 1H), 2.14 (s, 3H), 1.94 (s, 3H), 1.75 (s, 3H), 1.72 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 155.1, 148.4, 137.9, 136.6, 134.4, 133.2, 129.4, 129.3, 128.9, 128.8, 128.1, 127.8, 127.8, 126.9, 126.6, 125.3, 125.0, 122.6, 121.8, 118.9, 118.3, 106.8, 102.7, 57.1, 21.6, 20.4, 19.6, 16.7. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{30}H_{27}NO$: 418.2166, found 418.2165. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 97/3, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 8.4 min, t_{major} = 10.2 min).

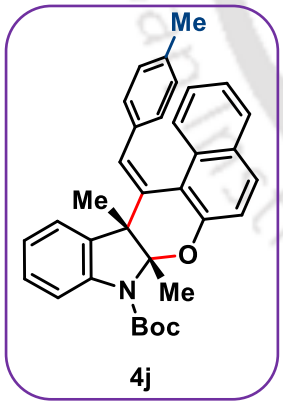
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-12b-ethyl-7a-methyl-12b,13-dihydrobenzo [5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4i)



4i

Light yellow sticky liquid, 49% (24.5 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.23 (dd, *J* = 8.9, 1.3 Hz, 1H), 7.09 (q, *J* = 7.4 Hz, 2H), 6.99 (d, *J* = 1.5 Hz, 1H), 6.95 – 6.89 (m, 3H), 6.85 – 6.79 (m, 2H), 6.76 (t, *J* = 7.5 Hz, 1H), 2.40 (s, 3H), 2.28 – 2.35 (m, 1H), 2.00 – 2.07 (m, 1H), 1.42 (s, 9H), 0.41 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 185.2, 155.5, 151.3, 146.3, 142.5, 136.1, 133.9, 133.4, 132.0, 131.5, 128.9, 128.9, 128.4, 128.1, 127.6, 127.4, 126.6, 126.1, 125.7, 124.5, 123.7, 121.6, 119.5, 83.6, 69.6, 28.6, 27.8, 17.1, 8.3. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_3$: 504.2534, found 504.2535. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 7.9 min, t_{minor} = 8.8 min).

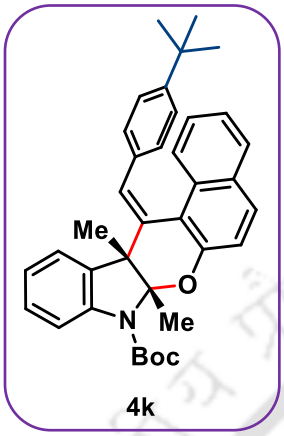
tert-butyl (7aS,12bS)-7a,12b-dimethyl-13-((E)-4-methylbenzylid ene)-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4J)



4j

Light yellow sticky liquid, 50% (24.9 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.27 – 7.19 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.88 (s, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.72 (q, *J* = 8.3 Hz, 4H), 2.44 (s, 3H), 2.10 (s, 3H), 1.51 (s, 3H), 1.42 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.7, 154.6, 151.4, 146.4, 145.3, 137.3, 133.3, 133.2, 132.6, 131.9, 131.6, 128.9, 128.9, 128.4, 127.6, 127.4, 126.6, 126.3, 125.7, 124.7, 123.4, 121.7, 119.7, 83.6, 64.6, 27.8, 22.8, 21.2, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_3$: 504.2534, found 504.2534. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1 mL/min, λ = 274 nm (t_{minor} = 5.4 min, t_{major} = 6.9 min).

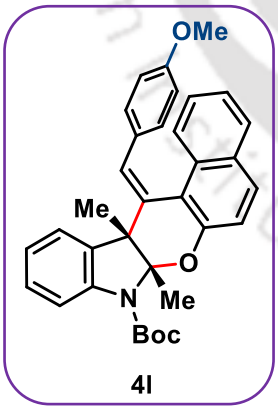
tert-butyl (7aS,12bS)-13-((E)-4-(tert-butyl)benzylidene)-7a,12b-dimethyl-12b,13-dihydrobenzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4k)



4k

Light yellow sticky liquid, 47% (25.6 mg) yield, >20:1 *dr*, 90% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.39 (dt, *J* = 14.4, 7.1 Hz, 3H), 7.30 – 7.17 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.91 (s, 1H), 6.74 (t, *J* = 7.5 Hz, 3H), 2.44 (s, 3H), 1.52 (s, 3H), 1.36 (s, 9H), 1.11 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.7, 154.5, 151.3, 150.6, 146.1, 145.2, 133.1, 133.0, 132.7, 132.1, 131.6, 128.9, 128.8, 128.4, 127.6, 127.4, 126.6, 126.4, 125.8, 125.1, 124.6, 123.4, 121.8, 119.6, 83.6, 64.7, 34.6, 31.2, 27.7, 22.7, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{37}H_{39}NO_3$: 546.3003, found 546.3003. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 0.5 mL/min, λ = 254 nm (t_{minor} = 12.9 min, t_{major} = 16.1 min).

tert-butyl (7aS,12bS)-13-((E)-4-methoxybenzylidene)-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8 (7aH)-carboxylate (4l)

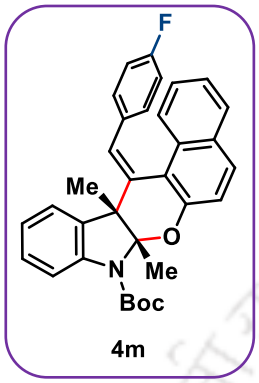


4l

Light yellow sticky liquid, 45% (23.4 mg) yield, >20:1 *dr*, 90% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.3 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.28 – 7.21 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.83 (s, 1H), 6.77 (dd, *J* = 18.0, 8.1 Hz, 3H), 6.46 (d, *J* = 8.9 Hz, 2H), 3.59 (s, 3H), 2.44 (s, 3H), 1.49 (s, 3H), 1.42 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.8, 158.9, 154.6, 151.5, 146.5, 145.4, 132.8, 131.8, 131.7, 131.1, 130.3, 129.0, 128.8, 128.5, 127.6, 127.5, 126.6, 126.3, 125.8, 124.7, 123.4, 121.7, 119.6, 113.5, 83.6, 64.5, 55.2, 27.8, 22.7, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_4$: 520.2483, found 520.2485. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C

Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 7.1 min, t_{major} = 10.2 min).

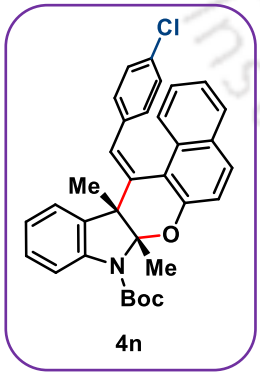
tert-butyl (7aS,12bS)-13-((E)-4-fluorobenzylidene)-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8 (7aH)-carboxylate (4m)



4m

Light yellow sticky liquid, 45% (22.8 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.27 (dd, *J* = 8.5, 3.1 Hz, 2H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 6.87 (s, 1H), 6.82 (ddd, *J* = 7.3, 4.7, 1.8 Hz, 3H), 6.63 (t, *J* = 8.8 Hz, 2H), 2.46 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 186.5, 162.8 (J_{C-F} = 246 Hz), 161.1, 154.5, 151.5, 146.5, 145.2, 133.6, 132.2, 132.1 (J_{C-F} = 3 Hz), 132.1, 131.7, 131.6, 130.6 (J_{C-F} = 9 Hz), 130.6, 129.3, 128.6, 127.7, 127.0, 126.7, 126.0, 125.9, 124.8, 123.4, 121.7, 119.7, 115.1 (J_{C-F} = 21 Hz), 115.0, 83.8, 64.5, 27.8, 22.6, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{30}FNO_3$: 508.2283, found 508.2283. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 5.5 min, t_{major} = 7.1 min).

tert-butyl (7aS,12bS)-13-((E)-4-chlorobenzylidene)-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4n)

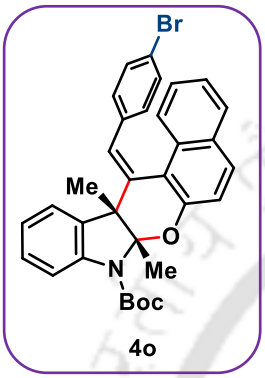


4n

Light yellow sticky liquid, 51% (26.7 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.39 (m, 3H), 7.28 – 7.22 (m, 2H), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.84 (s, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 2.43 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.3, 154.6, 151.5, 146.4, 145.2, 134.8, 134.5, 133.2, 132.1, 131.7, 131.5, 130.1, 129.3, 128.6, 128.3, 127.8, 126.8, 126.8, 126.0, 125.9, 124.8, 123.4, 121.7, 119.8, 83.8, 64.6, 27.8, 22.6, 17.0. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{30}ClNO_3$: 524.1987, found 524.1987. **HPLC Analysis:** The enantiomeric excess was

determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 5.9 min, t_{major} = 6.9 min).

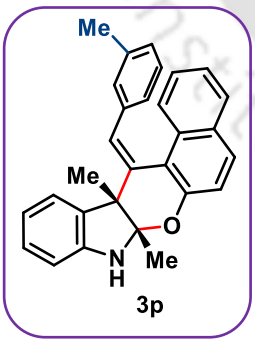
tert-butyl (7aS,12bS)-13-((E)-4-bromobenzylidene)-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4o)



4o

Light yellow sticky liquid, 45% (25.5 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.83 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.43 – 7.35 (m, 3H), 7.28 – 7.22 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 2.43 (s, 3H), 1.49 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.3, 154.6, 151.5, 146.4, 145.2, 135.0, 134.9, 132.2, 131.7, 131.5, 131.3, 130.4, 129.3, 128.6, 127.8, 126.8, 126.0, 125.9, 124.8, 123.4, 121.7, 121.5, 119.8, 83.9, 64.6, 27.8, 22.6, 17.0. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{30}BrNO_3$: 568.1482, found 568.1482. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 6.0 min, t_{major} = 6.93 min).

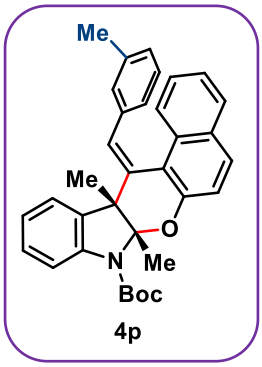
(7aS,12bS)-7a,12b-dimethyl-13-((E)-3-methylbenzylidene)-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3p)



3p

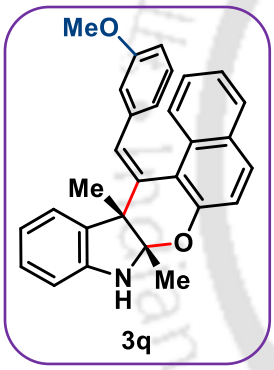
Light yellow sticky solid, 58% (29.2 mg) yield, >20:1 *dr*, 99% *ee*. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_3$: 404.2009, found 404.2009. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 4.6 min, t_{major} = 6.4 min).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.86 (m, 1H), 7.74 – 7.70 (m, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.41 – 7.32 (m, 3H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.90 (s, 1H), 6.80 – 6.74 (m, 3H), 6.72 (s, 1H), 6.57 (dd, *J* = 5.7, 3.1 Hz, 1H), 2.45 (s, 3H), 2.02 (s, 3H), 1.52 (s, 3H), 1.43 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.6, 154.6, 151.4, 146.4, 145.2, 137.4, 135.9, 133.7, 133.5, 131.8, 131.5, 130.1, 128.9, 128.4, 128.2, 128.0, 127.6, 127.3, 126.5, 126.2, 125.7, 125.5, 124.7, 123.4, 121.6, 119.7, 83.6, 64.5, 27.8, 22.8, 21.2, 16.9. **HRMS (ESI-TOF)** ***m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_3$: 504.2534, found 504.2534.



4p

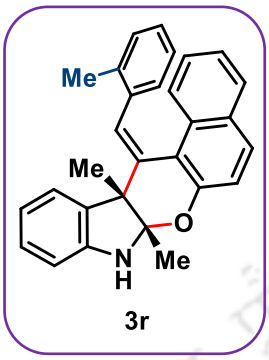
(7aS,12bS)-13-((E)-3-methoxybenzylidene)-7a,12b-dimethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3q)



3q

Reddish semi solid, 51% (21.4 mg) yield, >20:1 *dr*, 90% *ee*. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 7.58 - 7.54 (m, 3H), 7.17 (s, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.74 (t, *J* = 9.2 Hz, 2H), 6.64 (t, *J* = 7.7 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.47 (s, 1H), 6.37 (d, *J* = 8.0 Hz, 1H), 6.22 (dd, *J* = 13.7, 6.1 Hz, 2H), 3.18 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 160.1, 155.6, 148.8, 139.5, 136.0, 134.5, 130.5, 130.2, 129.7, 129.5, 128.7, 128.0, 127.5, 126.3, 125.7, 123.8, 122.8, 122.6, 121.5, 119.6, 118.9, 114.4, 114.2, 108.3, 103.5, 58.8, 54.8, 23.3, 22.7. **HRMS (ESI-TOF)** ***m/z***: $[M+H]^+$ calculated for $C_{29}H_{25}NO_2$: 420.1959, found 420.1956. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK AD-H Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 5.8 min, t_{major} = 8.9 min).

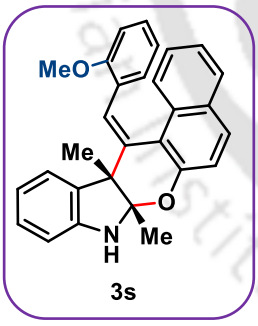
(7aS,12bS)-7a,12b-dimethyl-13-((E)-2-methylbenzylidene)-7a,8, 12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3r)



3r

Orange solid, 55% (22.2 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (dd, *J* = 8.4, 4.0 Hz, 2H), 7.28 – 7.21 (m, 1H), 7.13 (s, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.94 – 6.82 (m, 2H), 6.78 – 6.69 (m, 2H), 6.58 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.53 (t, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 6.35 (t, *J* = 7.4 Hz, 1H), 4.70 (bs, 1H), 2.48 (s, 3H), 1.81 (s, 3H), 1.73 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 154.5, 147.2, 136.8, 135.7, 133.7, 130.0, 129.3, 129.3, 129.2, 127.8, 127.5, 127.1, 126.1, 125.4, 125.3, 124.5, 123.0, 122.2, 121.6, 120.6, 119.9, 119.6, 118.2, 112.4, 108.5, 57.4, 22.8, 22.3, 20.4. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{29}H_{25}NO$: 404.2009, found 404.2009. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 4.5 min, t_{major} = 5.9 min).

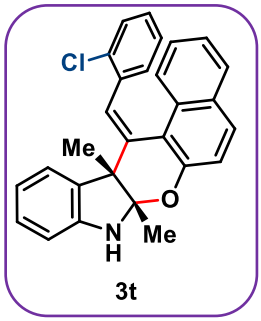
(7aS,12bS)-13-((E)-2-methoxybenzylidene)-7a,12b-dimethyl-7a, 8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3s)



3s

Orange semi solid, 52% (21.8 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (600 MHz, Acetone-d_6)** δ 7.48 (t, *J* = 9.0 Hz, 3H), 7.29 (s, 1H), 7.01 – 6.93 (m, 5H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 6.22 (td, *J* = 8.3, 7.8, 5.0 Hz, 3H), 3.98 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H). **^{13}C NMR (150 MHz, Acetone-d_6)** δ 157.9, 155.7, 148.8, 136.2, 133.8, 130.4, 130.3, 130.2, 129.5, 129.2, 128.5, 128.0, 127.6, 126.0, 125.4, 123.5, 123.5, 122.5, 121.2, 120.3, 119.3, 118.9, 111.3, 108.4, 103.6, 58.2, 56.1, 22.9, 22.7. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{29}H_{25}NO_2$: 420.1959, found 420.1956. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 5.0 min, t_{major} = 7.6 min).

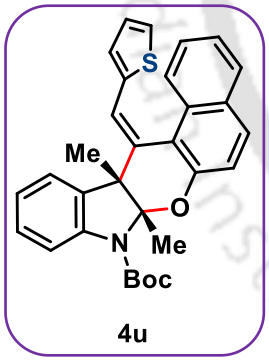
(7aS,12bS)-13-((E)-2-chlorobenzylidene)-7a,12b-dimethyl-7a,8, 12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3t)



3t

Yellow semi solid, 57% (24.2 mg) yield, >20:1 *dr*, 93% *ee*. **^{1}H NMR (600 MHz, Acetone-d$_6$)** δ 7.54 – 7.48 (m, 2H), 7.40 (dd, *J* = 8.3, 4.8 Hz, 2H), 7.23 (s, 1H), 7.02 – 6.94 (m, 4H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.58 (t, *J* = 7.5 Hz, 1H), 6.56 – 6.52 (m, 1H), 6.39 (d, *J* = 7.7 Hz, 1H), 6.31 (s, 1H), 6.27 (t, *J* = 7.4 Hz, 1H), 1.81 (s, 3H), 1.77 (s, 3H). **^{13}C NMR (150 MHz, Acetone-d$_6$)** δ 155.9, 148.8, 137.3, 136.8, 135.7, 133.9, 131.4, 130.4, 130.0, 129.9, 129.2, 128.6, 128.2, 126.9, 126.3, 124.8, 124.6, 123.7, 122.5, 121.9, 120.1, 119.3, 119.0, 108.4, 103.5, 58.3, 23.1, 22.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{22}ClNO$: 424.1463, found 424.1464. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 4.5 min, t_{major} = 5.8 min).

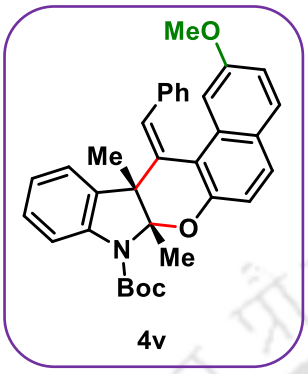
tert-butyl (7aS,12bS,E)-7a,12b-dimethyl-13-(thiophen-2-yl methylene)-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4u)



4u

Yellow semi solid, 45% (22.3 mg) yield, >20:1 *dr*, 87% *ee*. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 (p, *J* = 4.1 Hz, 1H), 7.82 – 7.72 (m, 2H), 7.46 – 7.35 (m, 3H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.16 (s, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 6.86 (d, *J* = 5.0 Hz, 1H), 6.80 – 6.67 (m, 3H), 2.46 (s, 3H), 1.57 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 186.3, 154.5, 151.1, 146.5, 144.7, 139.7, 132.5, 131.8, 131.7, 129.5, 128.8, 128.5, 127.8, 127.4, 126.8, 126.6, 126.2, 125.9, 125.8, 125.8, 124.7, 123.5, 121.9, 119.8, 83.7, 64.1, 27.8, 22.8, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{31}H_{29}NO_3S$: 496.1941, found 496.1941. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 6.9 min, t_{major} = 8.5 min).

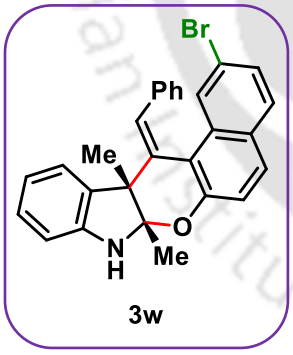
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-2-methoxy-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8 (7aH)-carboxylate (4v)



4v

Yellow sticky liquid, 71% (37 mg) yield, >20:1 *dr*, 90% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.65 (d, *J* = 8.8 Hz, 2H), 7.43 (dd, *J* = 15.5, 7.6 Hz, 2H), 7.19 – 7.12 (m, 2H), 7.06 – 7.01 (m, 2H), 6.98 – 6.90 (m, 5H), 6.88 – 6.83 (m, 2H), 3.61 (s, 3H), 2.35 (s, 3H), 1.52 (s, 3H), 1.43 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.6, 158.3, 154.5, 151.4, 147.1, 145.9, 136.2, 134.3, 133.5, 133.1, 130.0, 128.9, 128.7, 128.1, 127.8, 127.5, 127.1, 126.2, 125.1, 123.3, 119.9, 119.2, 118.4, 104.8, 83.6, 64.5, 55.2, 27.8, 23.3, 17.2. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{34}H_{33}NO_4$: 520.2483, found 520.2483. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 4.9 min, t_{major} = 9.6 min).

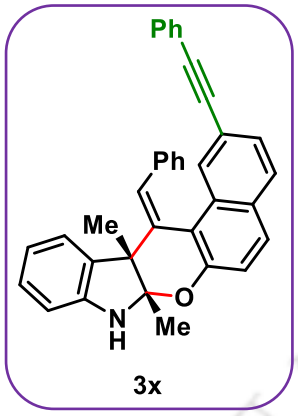
(7aS,12bS)-13-((E)-benzylidene)-2-bromo-7a,12b-dimethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3w)



3w

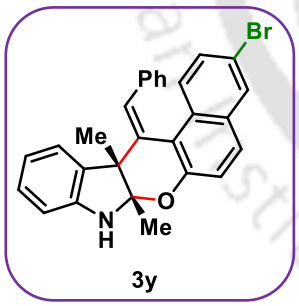
Yellow solid, 70% (32.8 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (500 MHz, Acetone-d_6)** δ 7.63 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 7.25 (s, 1H), 7.11 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.06 – 6.96 (m, 6H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.68 (t, *J* = 7.8 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 6.29 (dd, *J* = 17.8, 10.2 Hz, 2H), 1.78 (s, 3H), 1.73 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d_6)** δ 156.8, 148.7, 138.3, 135.9, 133.9, 131.4, 130.6, 129.9, 129.7, 128.7, 128.5, 128.3, 128.2, 128.0, 127.8, 126.7, 122.5, 120.6, 120.1, 120.0, 119.1, 108.6, 104.1, 58.2, 22.7, 22.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{22}BrNO$: 468.0958, found 468.0958. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK ADH Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 0.5 mL/min, λ = 254 nm(t_{minor} = 23.8 min, t_{major} = 41.4 min).

(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-2-(phenyl ethynyl)-7a,8,12b,13-tetrahydrobenzo[5,6]chromeno[2,3-b] indole (3x)



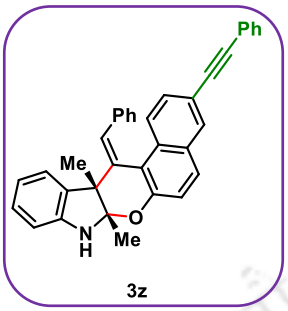
Brown solid, 62% (30.4 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (600 MHz, Acetone-d$_6$)** δ 7.70 (s, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.51 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.44 – 7.39 (m, 3H), 7.27 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.07 – 7.00 (m, 7H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.32 (s, 1H), 6.27 (t, *J* = 7.4 Hz, 1H), 1.79 (s, 3H), 1.74 (s, 3H). **^{13}C NMR (150 MHz, Acetone-d$_6$)** δ 156.5, 148.7, 138.4, 136.0, 134.1, 133.0, 132.3, 129.8, 129.7, 129.5, 129.4, 129.2, 129.0, 128.7, 128.3, 128.1, 127.8, 126.7, 126.0, 124.3, 122.6, 120.9, 120.8, 120.3, 119.1, 108.5, 103.9, 91.0, 89.5, 58.3, 22.8, 22.6. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{36}H_{27}NO$: 490.2166, found 490.2165. **HPLC Analysis:** The enantiomericexcess was determined using ChiralPAK ADH Column, *n*-Hexane/*i*-PrOH = 97/3, flow rate 0.5 mL/min, λ = 274 nm (t_{minor} = 28.2 min, t_{major} = 40.3 min).

(7aS,12bS)-13-((E)-benzylidene)-3-bromo-7a,12b-dimethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3y)



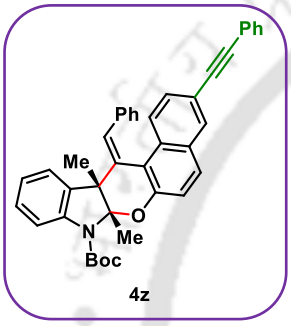
Yellow solid, 55% (25.8 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (400 MHz, Acetone-d$_6$)** δ 7.56 (dd, *J* = 8.5, 4.0 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.17 – 7.11 (m, 3H), 7.06 – 7.00 (m, 2H), 6.94 (dd, *J* = 8.9, 2.2 Hz, 2H), 6.73 (d, *J* = 7.3 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 6.29 (s, 1H), 6.20 (t, *J* = 7.4 Hz, 1H), 1.76 (s, 3H), 1.72 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d$_6$)** δ 155.7, 148.8, 137.8, 135.8, 135.5, 131.6, 130.3, 130.1, 128.8, 128.1, 126.4, 126.3, 125.4, 123.9, 122.5, 120.9, 120.2, 119.6, 118.9, 111.3, 110.8, 108.3, 103.5, 58.7, 22.9, 22.6. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{22}BrNO$: 468.0958, found 468.0960. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{minor} = 5.2 min, t_{major} = 6.1 min).

(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-3-(phenyl ethynyl)-7a,8,12b,13-tetrahydrobenzo[5,6]chromeno[2,3-b] indole (3z)



3z

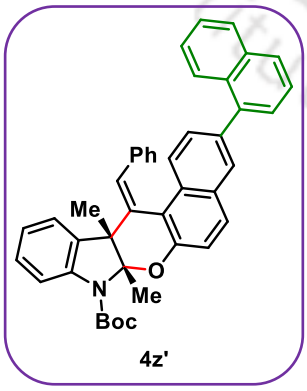
Yellow semi solid, 55% (27.0 mg) yield, >20:1 *dr*, 87% *ee*. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{41}H_{35}NO_3$: 490.2166, found 490.2165. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm (t_{minor} = 5.3 min, t_{major} = 6.6 min).



4z

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.64 (d, *J* = 9.1 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.46 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.40 – 7.32 (m, 4H), 7.26 (d, *J* = 8.9 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 (s, 1H), 6.98 – 6.92 (m, 3H), 6.86 – 6.82 (m, 2H), 6.80 – 6.75 (m, 1H), 2.46 (s, 3H), 1.57 (s, 3H), 1.44 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.3, 154.6, 151.3, 147.1, 144.8, 135.9, 133.8, 133.7, 131.9, 131.8, 131.2, 131.2, 129.2, 128.8, 128.8, 128.6, 128.2, 127.8, 127.6, 127.4, 126.3, 124.8, 123.3, 123.3, 122.4, 120.5, 119.8, 90.4, 89.5, 83.9, 64.5, 27.8, 22.9, 16.8. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{41}H_{35}NO_3$: 590.2690, found 590.2691.

tert-butyl (7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-3-(naphthalen-1-yl)-12b,13-dihydrobenzo[5,6]chromeno[2,3 -b]indole-8(7aH)-carboxylate (4z')

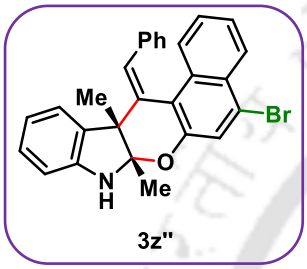


4z'

Yellow sticky liquid, 40% (24.6 mg) yield, >20:1 *dr*, 95% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 1H), 7.57 – 7.53 (m, 1H), 7.53 – 7.48 (m, 3H), 7.47 – 7.41 (m, 2H), 7.37 – 7.34 (m, 1H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.15 (td, *J* = 7.6, 1.2 Hz, 1H), 7.04 – 6.99 (m, 4H), 6.96 – 6.93 (m, 2H), 6.87 (t, *J* = 7.5 Hz, 1H), 2.51 (s, 3H), 1.61 (s, 3H), 1.45 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 186.7, 154.5, 151.4, 146.4, 145.1, 139.8, 138.0, 136.0, 134.0, 133.9, 133.4, 131.8, 131.5, 131.0, 129.2,

129.2, 129.0, 129.0, 128.6, 128.2, 128.0, 127.8, 127.6, 127.4, 127.1, 126.3, 126.1, 126.0, 125.6, 124.7, 123.5, 122.1, 119.7, 114.3, 83.7, 64.7, 27.8, 22.6, 17.0. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{43}H_{37}NO_3$: 616.2847, found 616.2847. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 7.7 min, t_{major} = 14.0 min).

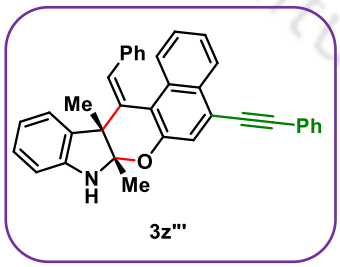
(7aS,12bS)-13-((E)-benzylidene)-5-bromo-7a,12b-dimethyl-7a,8,12b,13-tetrahydro benzo[5,6]chromeno[2,3-b]indole (3z'')



3z''

Orange solid, 57% (26.7 mg) yield, >20:1 *dr*, 98% *ee*. **^{1}H NMR (500 MHz, Acetone-d$_6$)** δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.38 (s, 1H), 7.26 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.08 – 6.93 (m, 6H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 22.2 Hz, 2H), 6.23 (t, *J* = 7.6 Hz, 1H), 1.79 (s, 3H), 1.73 (s, 3H). **^{13}C NMR (125 MHz, Acetone-d$_6$)** δ 155.4, 148.7, 138.1, 135.6, 133.7, 131.1, 129.8, 128.7, 128.3, 128.2, 127.8, 127.3, 127.2, 126.3, 125.3, 123.6, 122.7, 122.6, 121.9, 120.8, 119.1, 108.5, 104.6, 58.6, 23.3, 22.6. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{28}H_{22}BrNO$: 468.0958, found 468.0959. **HPLC Analysis:** The enantiomeric excess was determined using Chiral LC Lux Cellulose-1 Column, *n*-Hexane/*i*-PrOH = 99/1, flow rate 0.5 mL/min, λ = 254 nm (t_{minor} = 48.1 min, t_{major} = 59.0 min).

(7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-5-(phenylethynyl)-7a,8,12b,13-tetrahydrobenzo[5,6] chromeno[2,3-b]indole (3z''')

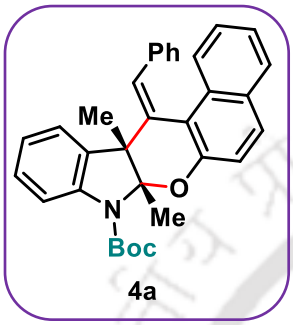


3z'''

Orange semi solid, 60% (29.4 mg) yield, >20:1 *dr*, 96% *ee*. **^{1}H NMR (400 MHz, Acetone-d$_6$)** δ 9.63 (s, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.05 (s, 1H), 7.78 – 7.71 (m, 3H), 7.56 (s, 1H), 7.53 (s, 1H), 7.51 – 7.46 (m, 3H), 7.44 – 7.39 (m, 1H), 7.38 – 7.30 (m, 3H), 7.10 – 7.01 (m, 6H), 2.30 (s, 3H), 2.17 (s, 3H). **^{13}C NMR (150 MHz, Acetone-d$_6$)** δ 206.2, 152.1, 138.6, 136.8, 136.7, 134.9, 134.4, 133.2, 132.5, 130.2, 130.1, 129.7, 129.6, 129.5, 129.3, 128.8, 127.9, 127.5, 127.0, 126.3, 125.0, 124.0, 123.1, 123.0, 122.4, 118.2, 118.0, 109.7, 106.9, 95.2, 87.9, 11.4, 8.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{36}H_{27}NO$: 490.2166, found 490.2165. **HPLC Analysis:**

The enantiomeric excess was determined using ChiralPAK ADH Column, *n*-Hexane/*i*-PrOH = 97/3, flow rate 0.5 mL/min, λ = 254 nm (t_{minor} = 21.7 min, t_{major} = 34.7 min).

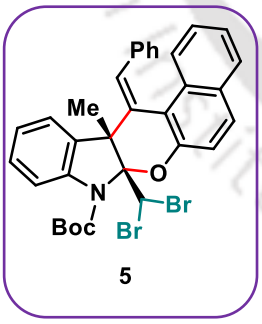
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-12b,13-dihydrobenzo[5,6] chromeno[2,3-b]indole-8(7aH)-carboxylate (4a)



4a

Pale yellow sticky liquid, 85% (41.6 mg) yield, >20:1 *dr*, 96% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.89 – 7.84 (m, 1H), 7.77 – 7.72 (m, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.30 (s, 1H), 7.26 – 7.15 (m, 3H), 6.99 – 6.90 (m, 4H), 6.89 – 6.83 (m, 2H), 2.44 (s, 3H), 1.51 (s, 3H), 1.42 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 187.1, 153.6, 151.4, 146.9, 146.3, 135.7, 133.5, 133.0, 131.7, 131.5, 130.7, 129.2, 128.9, 128.5, 128.2, 127.7, 126.8, 126.7, 126.6, 125.9, 125.9, 121.6, 120.9, 118.5, 83.9, 65.1, 27.8, 22.2, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{31}NO_3$: 490.2377, found 490.2373. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 5.5 min, t_{major} = 7.3 min).

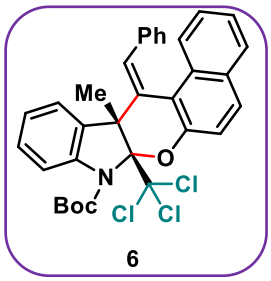
tert-butyl (7aR,12bS)-13-((E)-benzylidene)-7a-(dibromomethyl -12b-methyl-12b,13-dihydrobenzo[5,6]chromeno[2,3-b]indole- 8(7aH)-carboxylate (5)



5

Yellow sticky liquid, 90% (58.0 mg) yield, >20:1 *dr*, 96% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 8.9 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 16.0, 8.0 Hz, 2H), 7.50 – 7.43 (m, 2H), 7.41 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.30 (td, *J* = 7.5, 1.1 Hz, 1H), 6.96 – 6.87 (m, 3H), 6.81 – 6.76 (m, 2H), 6.52 (s, 1H), 6.37 (s, 1H), 1.46 (s, 9H), 1.38 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 183.9, 153.3, 151.5, 147.3, 147.2, 135.4, 135.3, 132.2, 131.4, 130.1, 129.7, 129.1, 128.9, 128.5, 128.1, 128.0, 127.8, 127.4, 126.4, 126.3, 125.2, 123.8, 122.1, 122.0, 84.3, 64.5, 33.5, 27.8, 21.6. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{29}Br_2NO_3$: 646.0567, found 646.0566. **HPLC Analysis:** The enantiomeric excess was determined using Chiral LC Lux Cellulose-4 Column, *n*-Hexane/*i*-PrOH = 99/1, flow rate 0.5 mL/min, λ = 220 nm (t_{minor} = 20.3 min, t_{major} = 22.7 min).

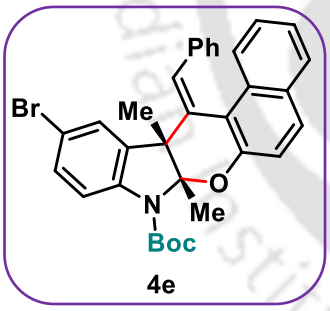
tert-butyl (7aR,12bS)-13-((E)-benzylidene)-12b-methyl-7a-(trichloromethyl)-12b,13-dihydrobenzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (6)



6

Pale yellow sticky liquid, 68% (40.3 mg) yield, >20:1 *dr*, 88% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.95 – 7.91 (m, 1H), 7.67 – 7.61 (m, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.41 (s, 1H), 7.35 – 7.30 (m, 2H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.03 (td, *J* = 7.6, 1.2 Hz, 1H), 6.98 (q, *J* = 5.8, 4.5 Hz, 6H), 6.73 (td, *J* = 7.6, 1.1 Hz, 1H), 2.14 (s, 3H), 1.43 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 179.3, 151.8, 150.8, 147.1, 144.9, 136.5, 135.9, 132.0, 131.7, 131.4, 129.2, 129.0, 128.2, 128.1, 128.0, 127.7, 126.9, 126.8, 126.0, 125.9, 125.5, 123.2, 122.0, 121.7, 94.1, 83.7, 65.8, 27.8, 23.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{28}Cl_3NO_3$: 592.1208, found 592.1208. **HPLC Analysis:** The enantiomeric excess was determined using Chiral LC Lux Cellulose-4 Column, *n*-Hexane/*i*-PrOH = 99/1, flow rate 0.5 mL/min, λ = 254 nm (t_{minor} = 13.4 min, t_{major} = 18.0 min).

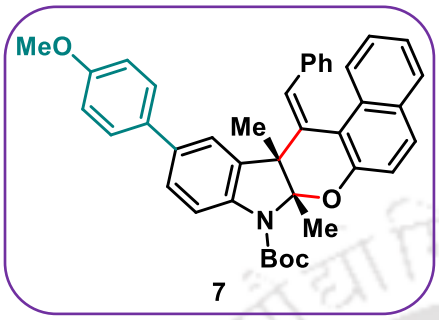
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-11-bromo-7a,12b-dimethyl-12b,13-dihydro benzo[5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (4e)



4e

Pale yellow sticky liquid, 81% (46.0 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.86 (dd, *J* = 6.4, 3.3 Hz, 1H), 7.76 (dd, *J* = 6.3, 3.2 Hz, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.41 (dd, *J* = 6.4, 3.2 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.27 – 7.16 (m, 3H), 7.00 – 6.90 (m, 4H), 6.90 – 6.83 (m, 2H), 2.44 (s, 3H), 1.51 (s, 3H), 1.42 (s, 9H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 187.2, 153.6, 151.4, 147.0, 146.4, 135.7, 133.6, 133.1, 131.7, 131.6, 130.7, 129.2, 128.9, 128.6, 128.2, 127.7, 126.9, 126.8, 126.6, 126.0, 125.9, 121.6, 120.9, 118.5, 83.9, 65.2, 27.8, 22.2, 16.9. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{33}H_{30}BrNO_3$: 568.1482, found 568.1482. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 10.2 min).

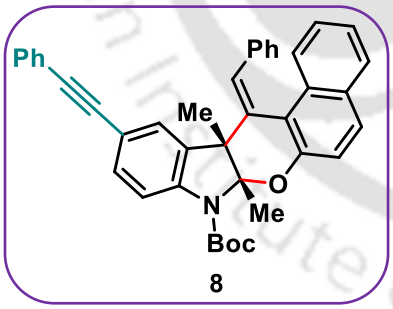
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-11-(4-methoxyphenyl)-7a,12b-dimethyl-12b,13-dihydro benzo [5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (7)



7

Brown solid, 75% (44.7 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.06 – 8.01 (m, 1H), 7.78 – 7.73 (m, 1H), 7.59 (d, *J* = 8.9 Hz, 1H), 7.46 (h, *J* = 4.7 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.28 – 7.24 (m, 1H), 7.18 – 7.13 (m, 2H), 7.01 – 6.94 (m, 4H), 6.91 (dt, *J* = 7.9, 1.8 Hz, 2H), 6.77 – 6.71 (m, 2H), 6.71 – 6.65 (m, 2H), 3.79 (s, 3H), 2.55 (s, 3H), 1.72 (s, 3H), 1.40 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 186.2, 158.8, 153.5, 151.3, 146.2, 144.4, 137.2, 136.1, 134.8, 134.1, 133.4, 132.1, 131.5, 128.9, 128.8, 128.6, 128.2, 128.2, 127.6, 127.6, 126.9, 126.3, 126.3, 125.5, 122.0, 121.7, 119.7, 113.9, 83.6, 64.6, 55.5, 27.8, 24.1, 16.5. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{40}H_{37}NO_4$: 596.2796, found 596.2796. **HPLC Analysis:** The enantiomeric excess was determined using ChiralPAK IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.4 min, t_{minor} = 26.8 min).

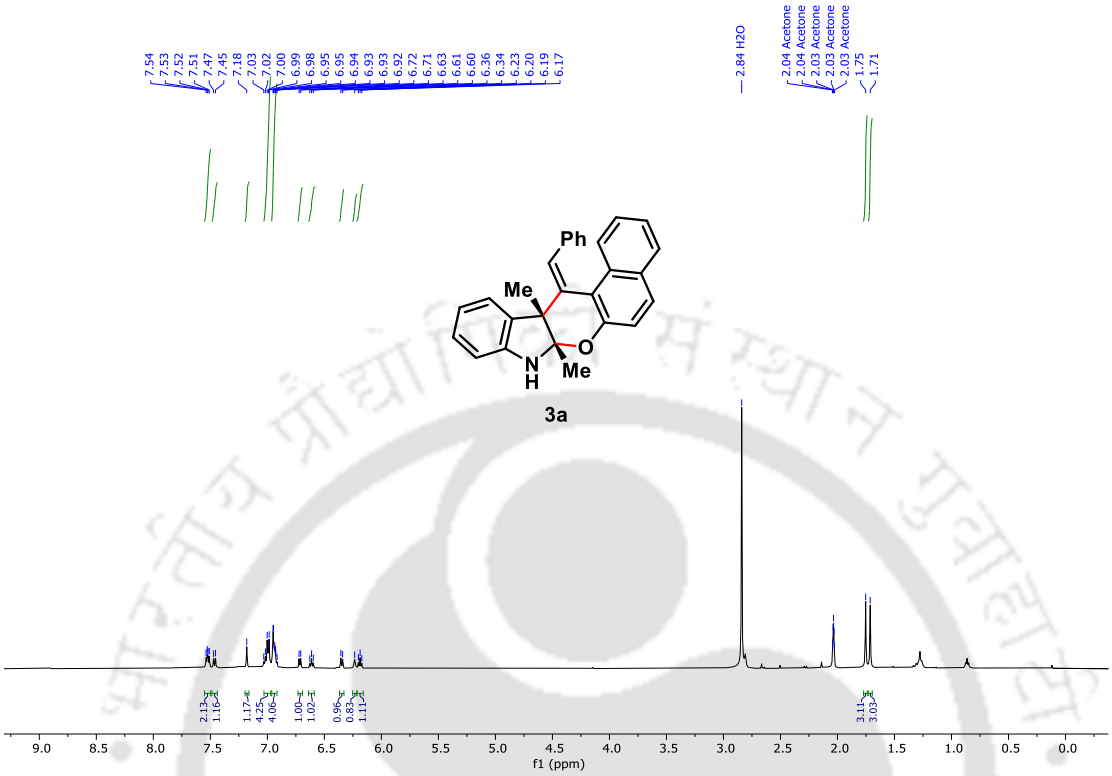
tert-butyl (7aS,12bS)-13-((E)-benzylidene)-7a,12b-dimethyl-11-(phenylethynyl)-12b, 13-dihydrobenzo [5,6]chromeno[2,3-b]indole-8(7aH)-carboxylate (8)

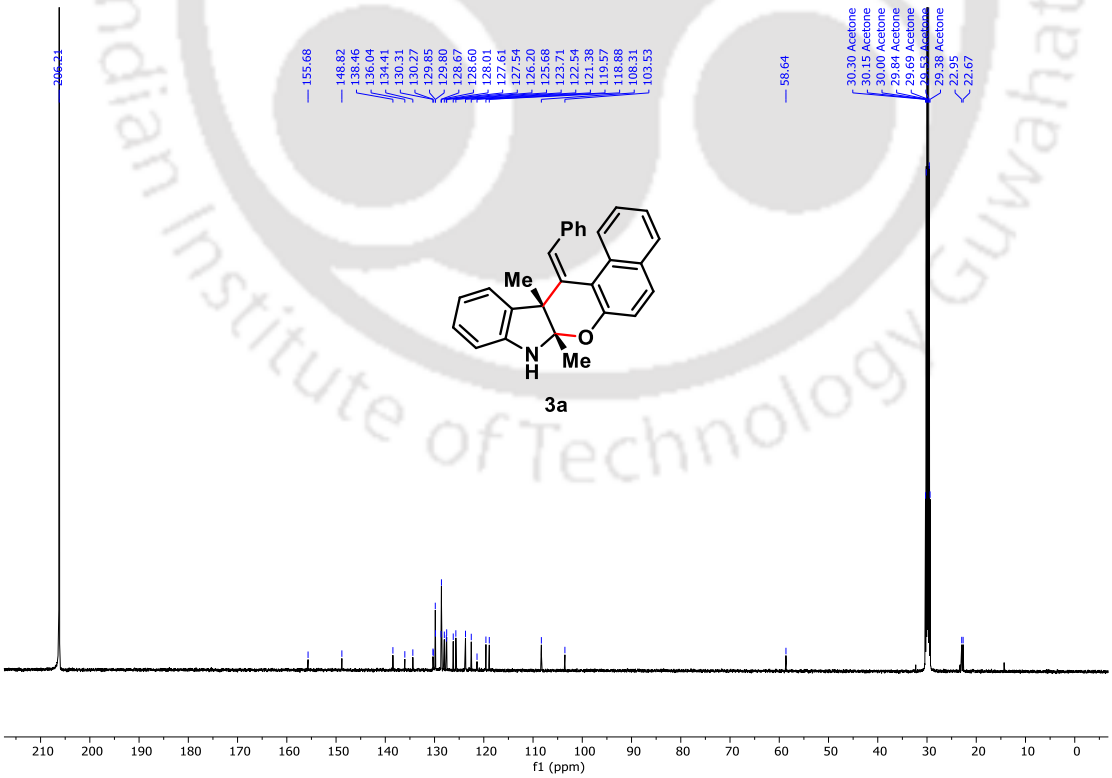


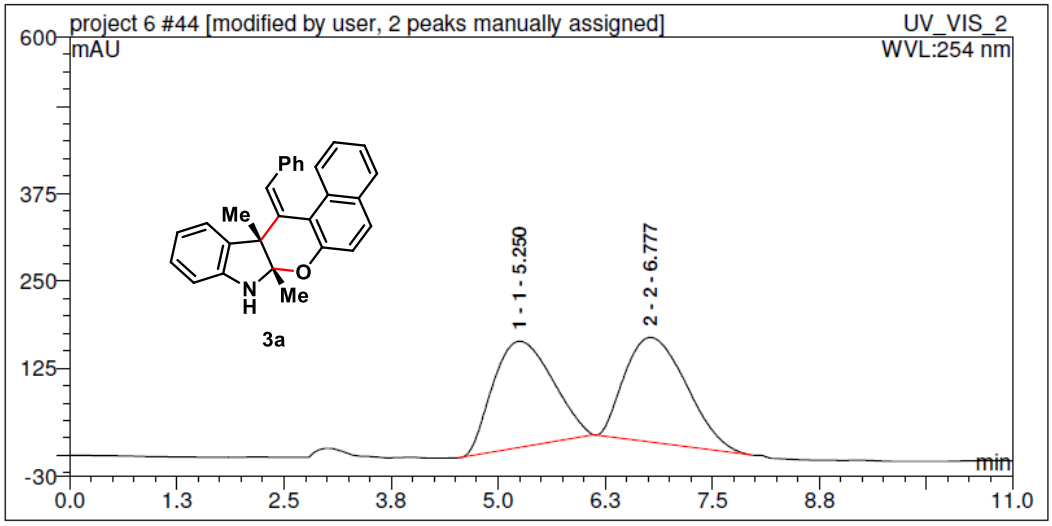
8

Red sticky liquid, 80% (47.2 mg) yield, >20:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.88 – 7.83 (m, 1H), 7.79 – 7.73 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.37 (m, 5H), 7.35 – 7.28 (m, 5H), 7.25 (d, *J* = 7.1 Hz, 1H), 6.97 – 6.92 (m, 4H), 6.89 – 6.85 (m, 2H), 2.43 (s, 3H), 1.53 (s, 3H), 1.40 (s, 9H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 188.0, 154.7, 151.5, 146.4, 145.3, 135.8, 133.5, 133.3, 131.8, 131.6, 129.3, 128.9, 128.6, 128.5, 128.2, 127.6, 126.9, 126.8, 126.7, 126.2, 125.8, 123.8, 121.7, 119.6, 119.6, 90.2, 89.0, 83.8, 64.8, 27.8, 22.3, 17.1. **HRMS (ESI-TOF) *m/z***: $[M+H]^+$ calculated for $C_{41}H_{35}NO_3$: 590.2690, found 590.2690. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{minor} = 7.0 min, t_{major} = 9.2 min).

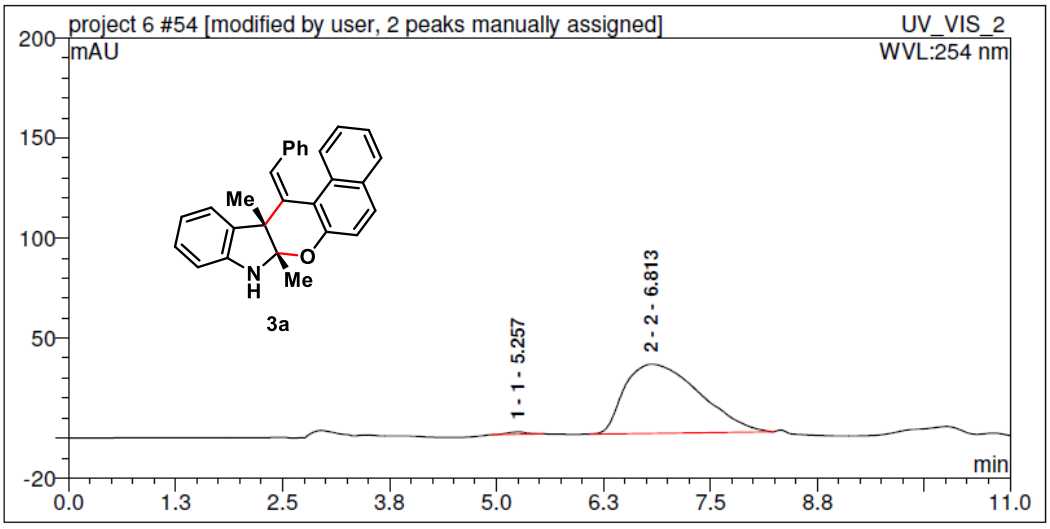
3.9 NMR and HPLC spectra



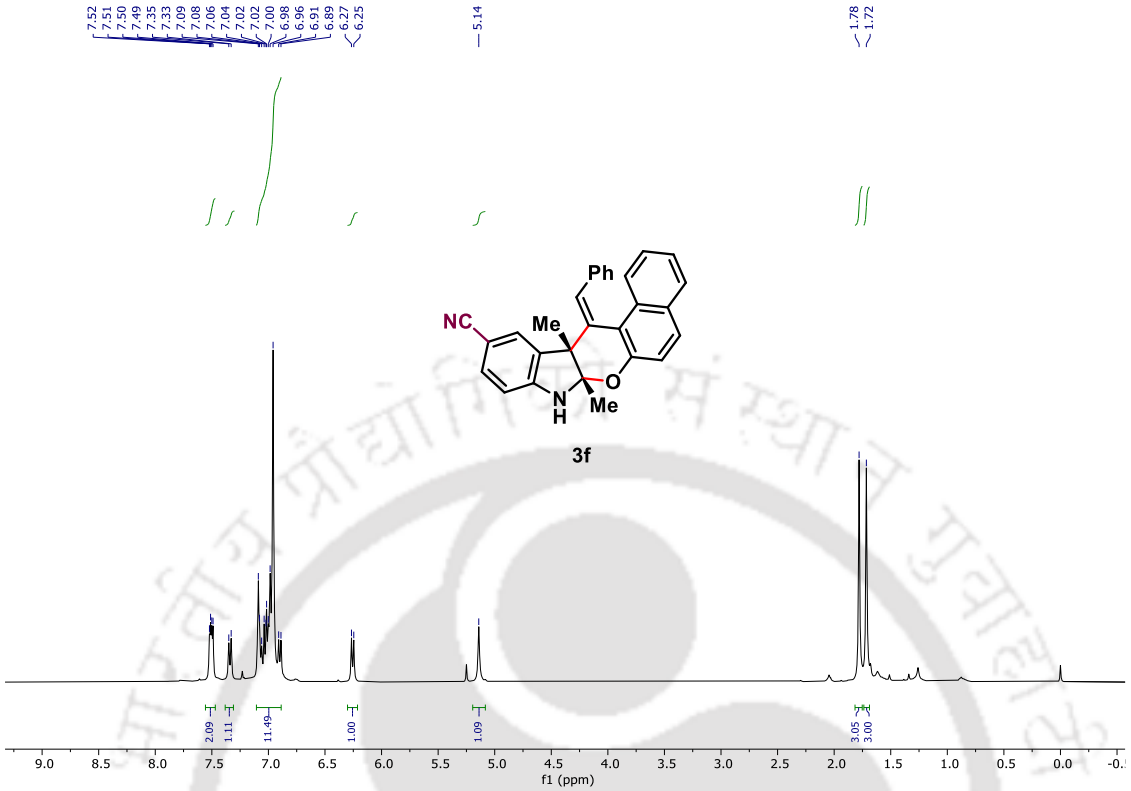


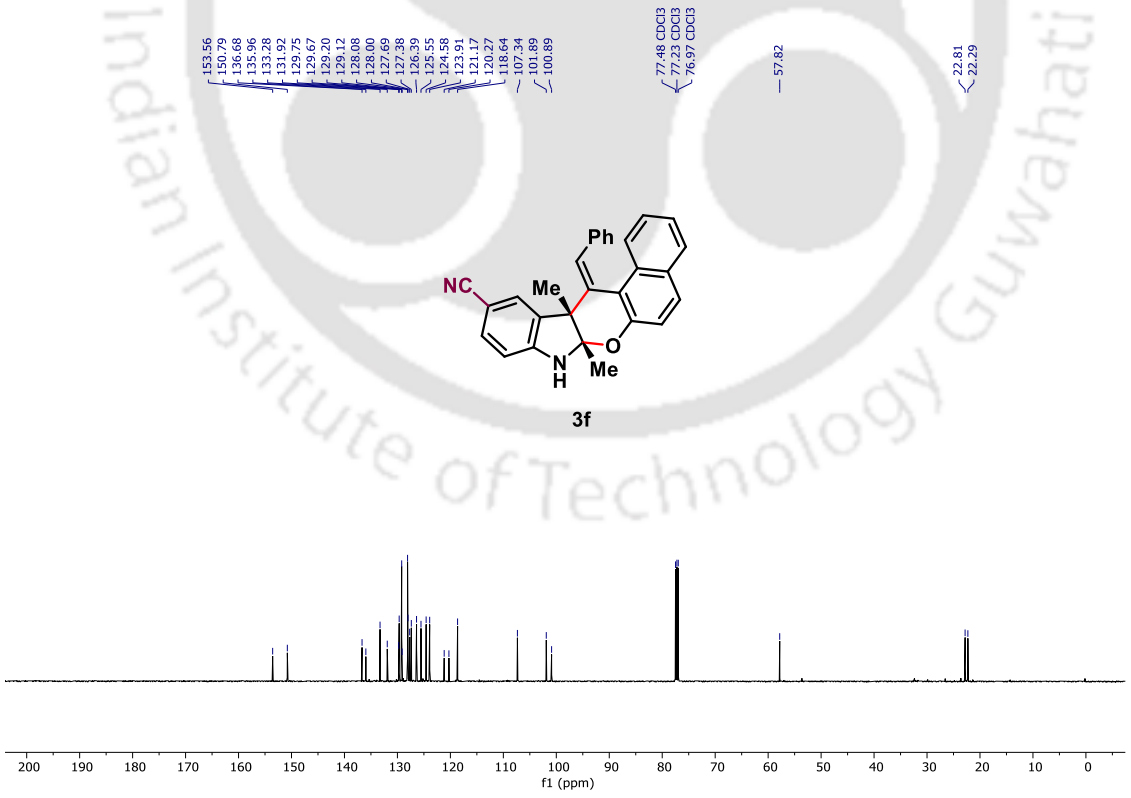


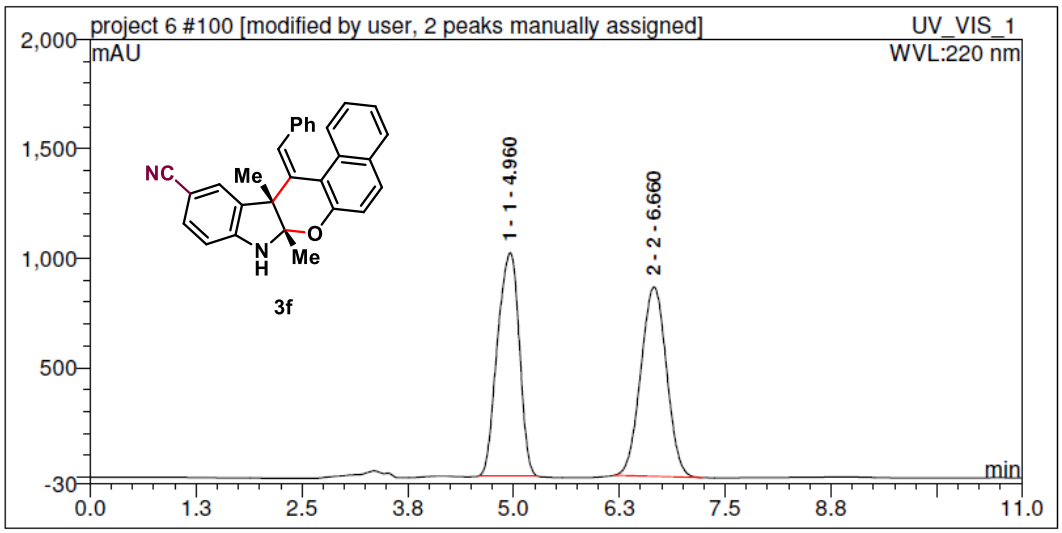
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.25	122.3316	49.28907401	152.1443	n.a.
2	2	6.78	125.861	50.71092599	150.087	n.a.



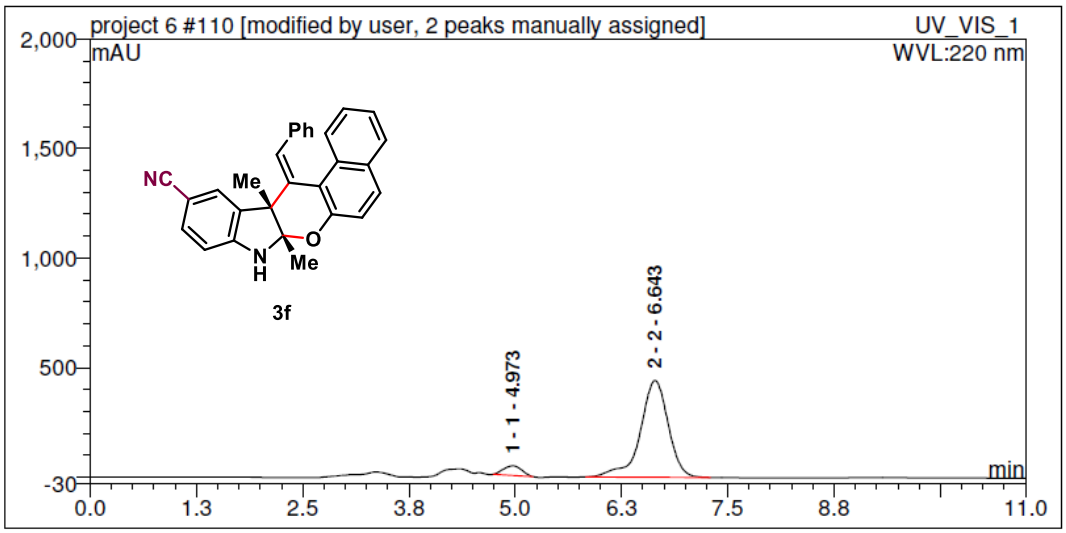
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.26	0.322454	0.9143289145	1.22628	n.a.
2	2	6.81	34.944	99.08567109	34.471	n.a.



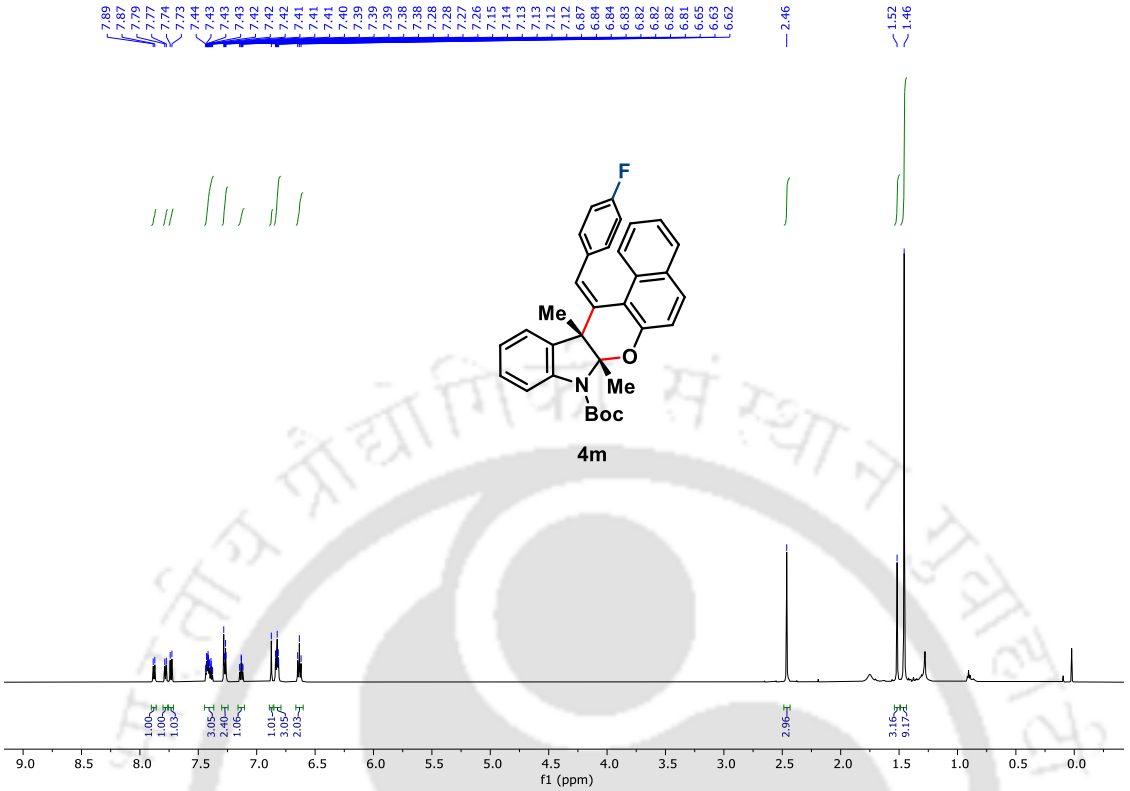


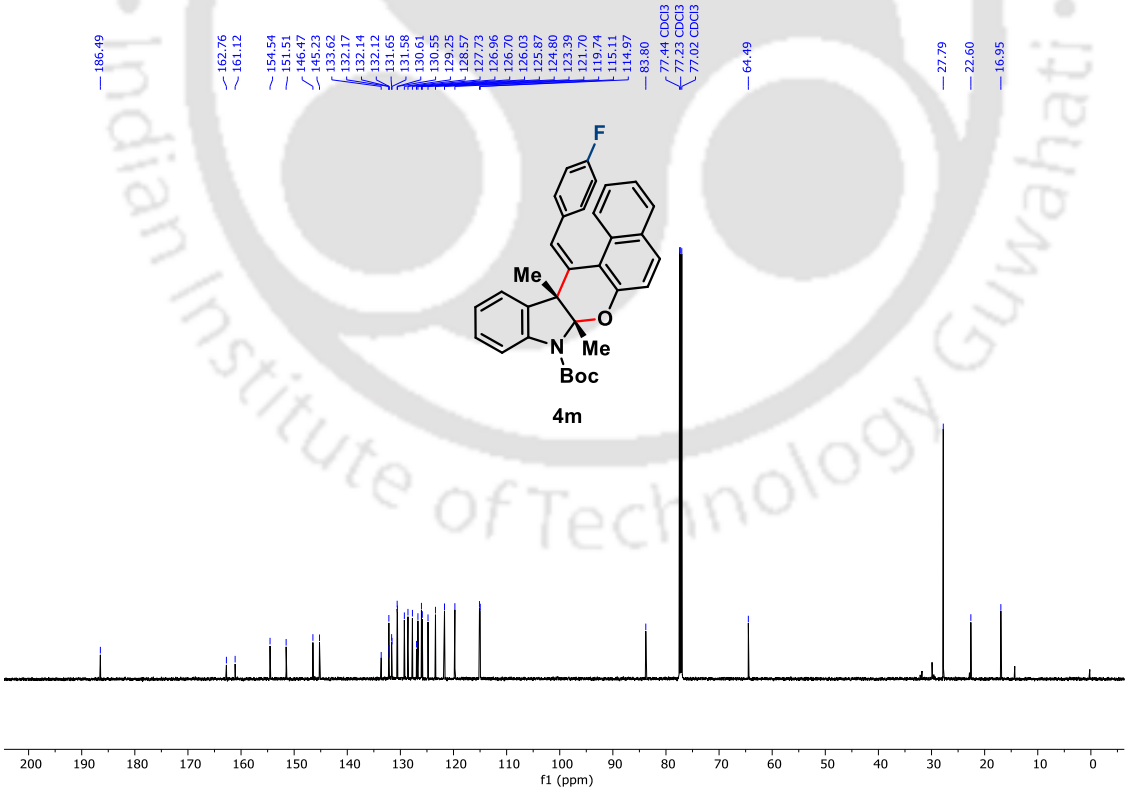


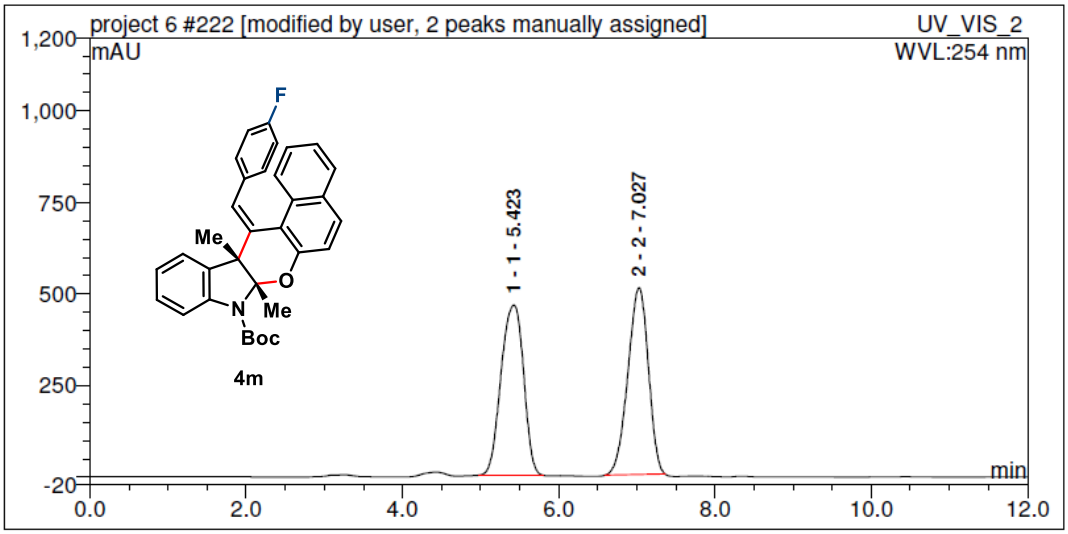
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	4.96	306.5371	50.1082019	1021.761	n.a.
2	2	6.66	305.213	49.8917981	864.589	n.a.



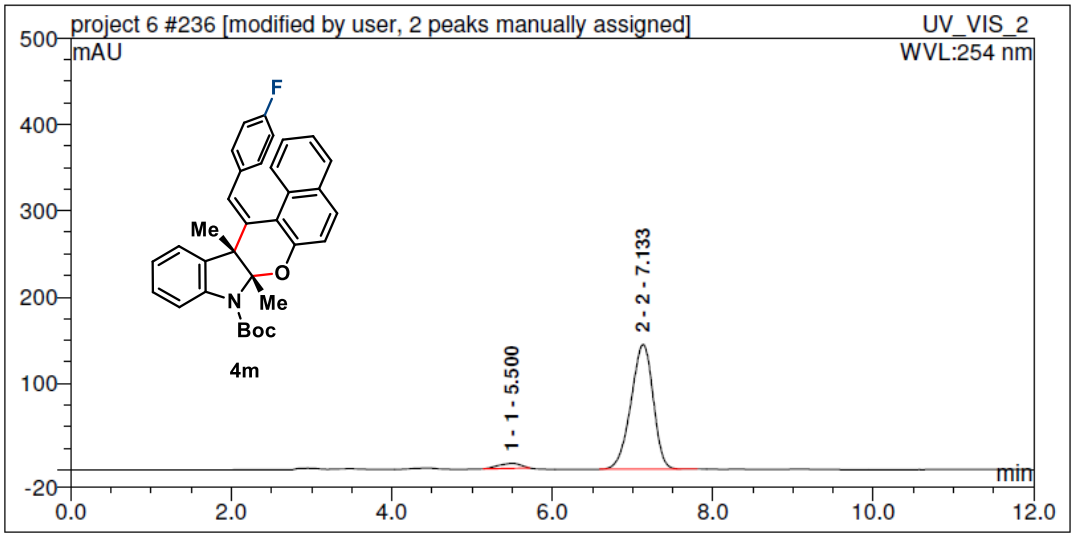
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	4.97	10.78978	6.009888234	43.44252	n.a.
2	2	6.64	168.744	93.99011177	441.135	n.a.



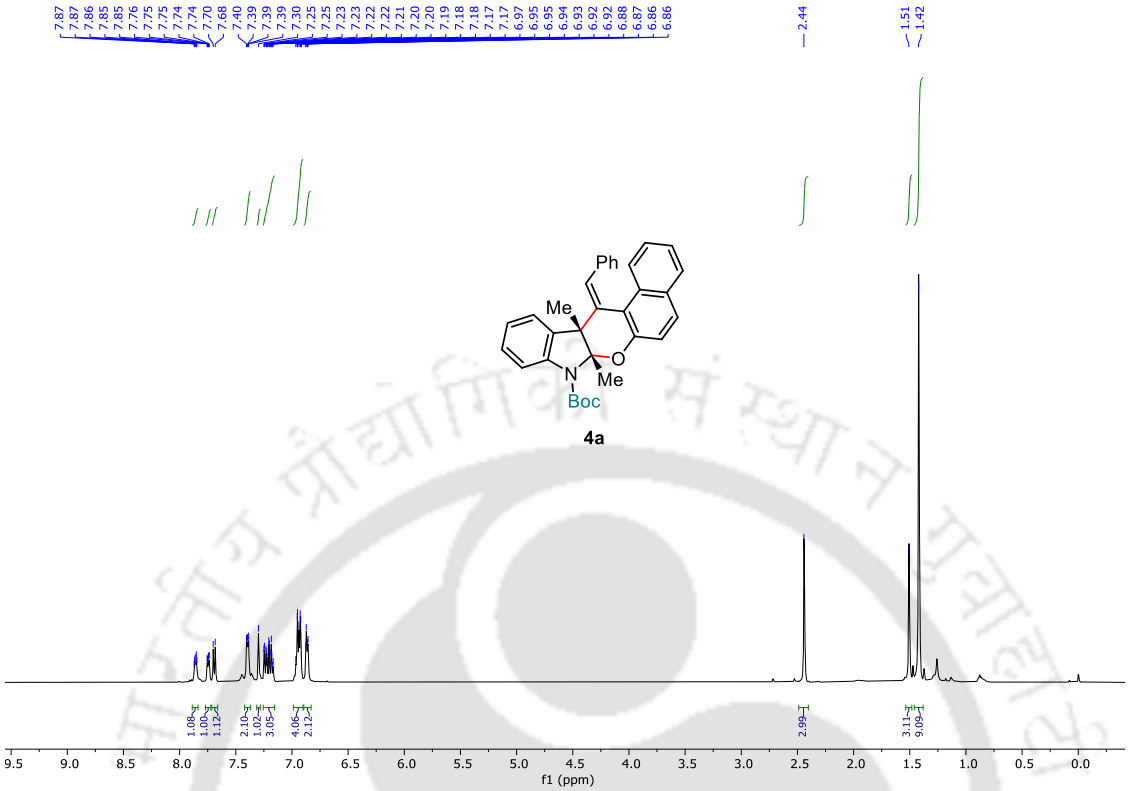


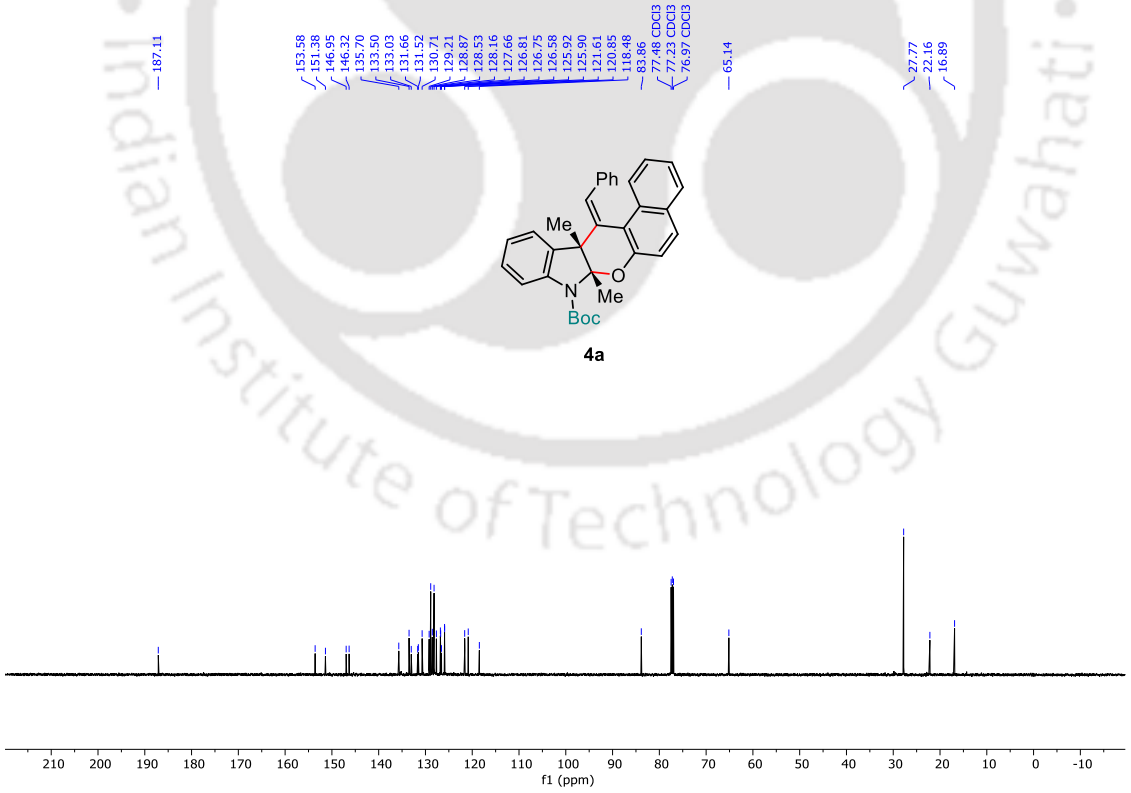


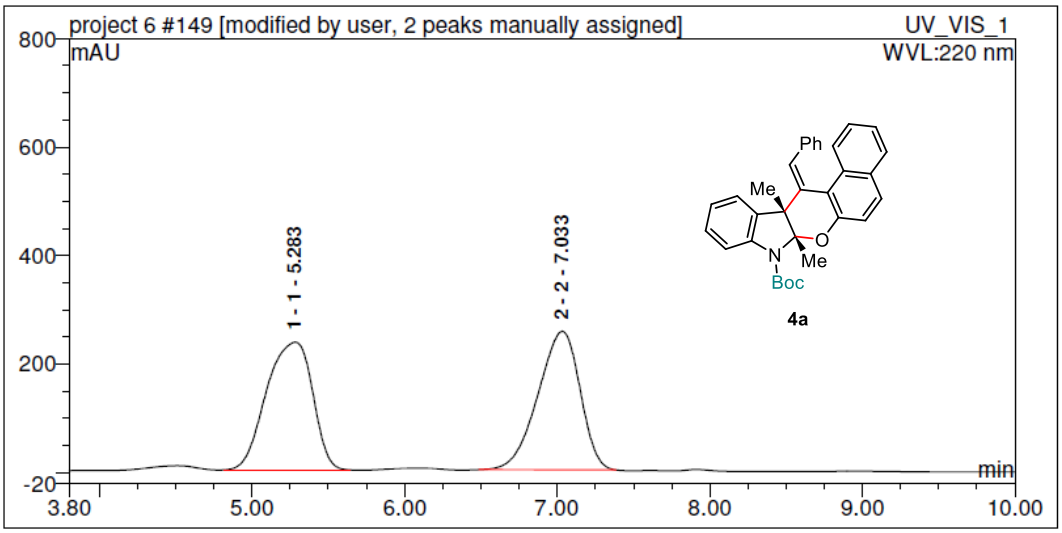
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.42	155.5157	50.12756934	464.6881	n.a.
2	2	7.03	154.724	49.87243066	509.930	n.a.



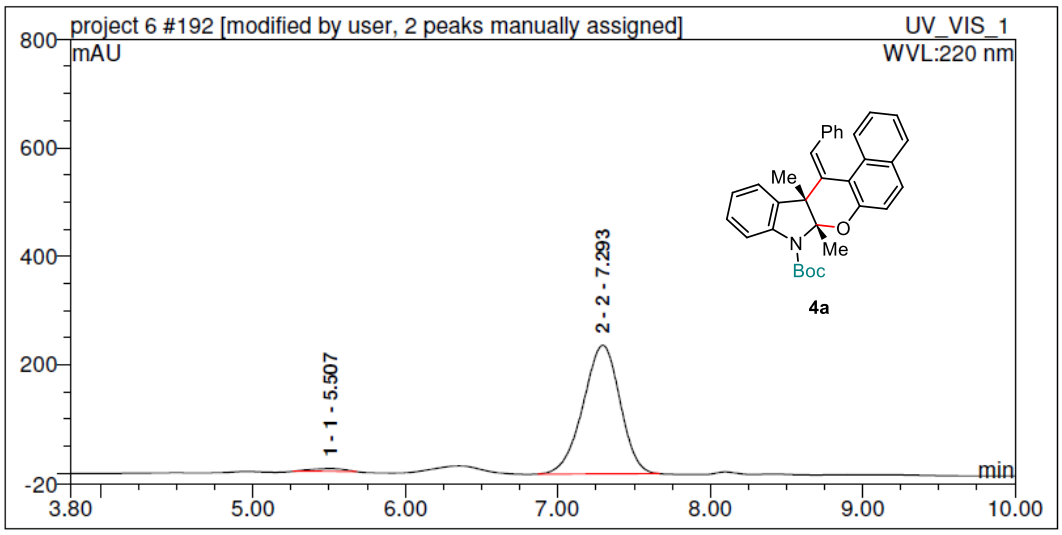
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.50	1.823726	3.77849671	5.62251	n.a.
2	2	7.13	46.442	96.22150329	144.324	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.28	82.65361	50.28662499	235.4938	n.a.
2	2	7.03	81.711	49.71337501	255.276	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.51	1.3913	2.041225387	5.41576	n.a.
2	2	7.29	66.769	97.95877461	236.885	n.a.

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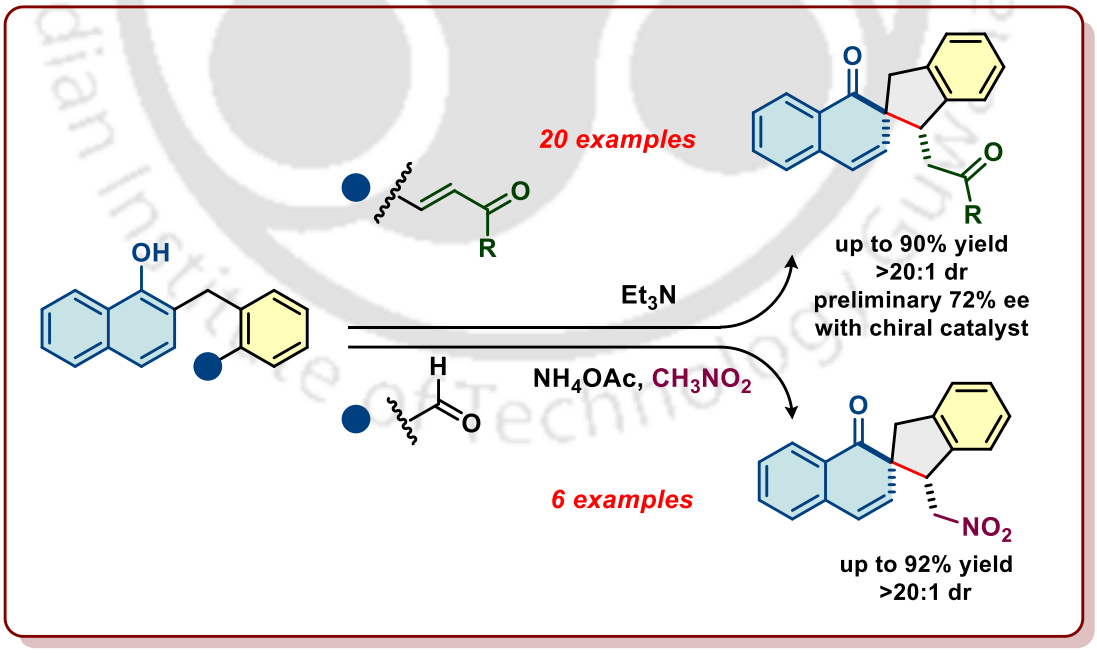
Chapter IV

Organocatalytic Dearomative Spirocyclization Reaction of Enone-Tethered α-and β-Naphthols and Dearomatization Reaction of In Situ Generated Nitro-Olefin-Tethered α-Naphthols

ABSTRACT: In this study, we present a catalytic process for the dearomative spirocyclization of novel substrates containing aryl/alkyl enone-linked α- and β-naphthols, as well as a dearomatization reaction of α-naphthols tethered with in situ generated nitro-olefins. The resulting spirocarbocycles were achieved in moderate to good yields with notable diastereoselectivity. Additionally, we introduced a preliminary catalytic asymmetric variant. A theoretical investigation was also conducted to elucidate the high diastereoselectivity observed in the triethylamine catalyzed spirocyclization reaction.



J. Org. Chem. **2024**, *89*, 9769.

4.1 Introduction

Spirocarbocycles have captured the close attention of organic chemists because of their distinctive structural features, which include quaternary carbon centers. Furthermore, spirocarbocycles can be found in a variety of naturally occurring products and biologically active compounds (Figure 1).[1] Developing a synthetically relevant methodology for the synthesis of quaternary carbon centers is a highly demanding task for chemists due to their relatively crowded carbon center.[2] Therefore, the organic synthetic community continues to place a high demand on the development of mild, efficient and streamlined synthetic pathways.

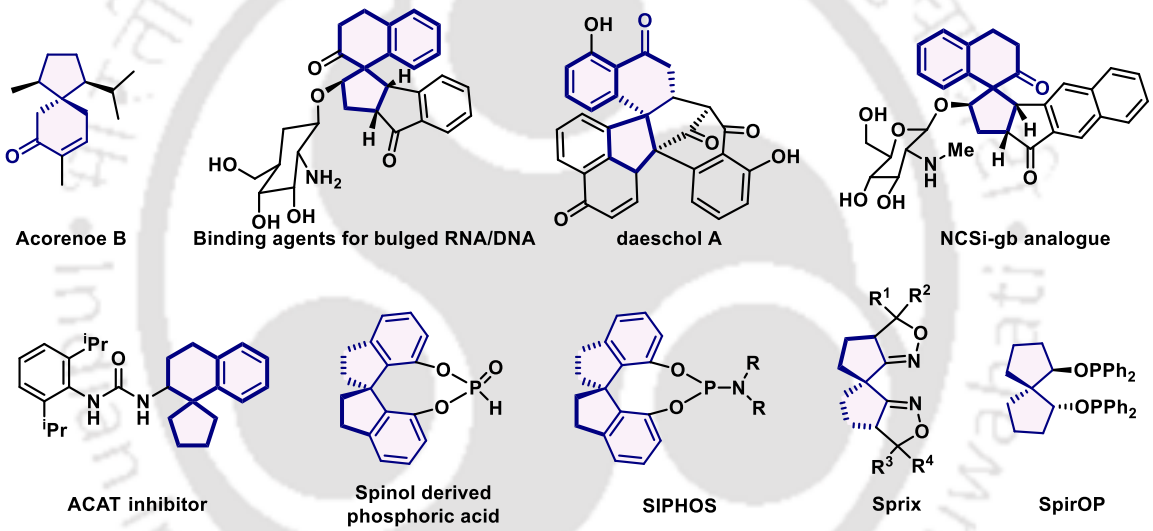


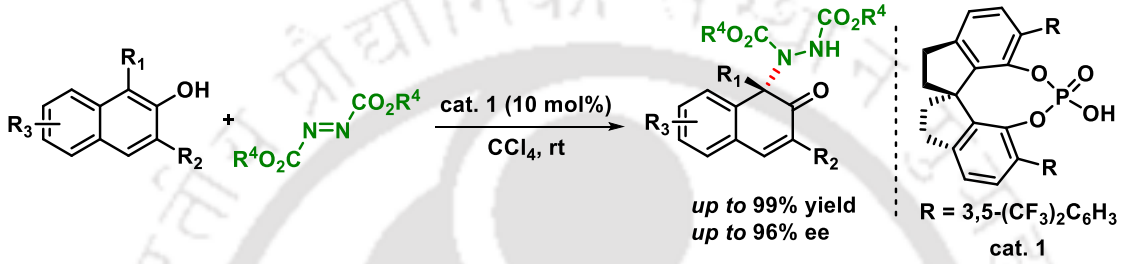
Figure 1: Selected bioactive compounds and ligands with spirocarobocycle skeleton

Meanwhile, electron-rich heteroaromatics as well as benzene-like systems (i.e. phenol, naphthol) have been extensively investigated in dearomative procedures enabling energetically favorable reaction profiles for the synthesis of highly functionalized spirocarbocyclic with quaternary carbon centers.[3] In this context, *α*- and *β*-naphthols turned out to be important platforms to generate highly functionalized three-dimensional naphthalenone cores *via* dearomatization reactions.[4] These dearomatized naphthalenones with spirocarbocyclic quaternary carbon centers are present in bioactive naturally occurring compounds as well (Figure 1). Thus, recent years have witnessed significant efforts from various research groups for the construction of naphthalenone core.[5]

4.2 Literature Survey

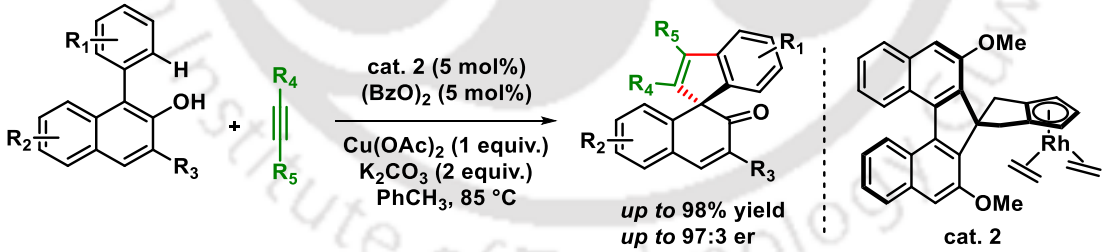
4.2.1 Previous reports on intermolecular dearomatization of *α*- and *β*-naphthols:

In 2014, You *et al.* reported[6], a highly efficient catalytic asymmetric dearomatization of naphthols by an electrophilic amination reaction catalysed by chiral phosphoric acid. This protocol provides a facile access to functionalized *β*-naphthalenone compounds with a chiral quaternary carbon centre in excellent yields and enantioselectivity (Scheme 1).



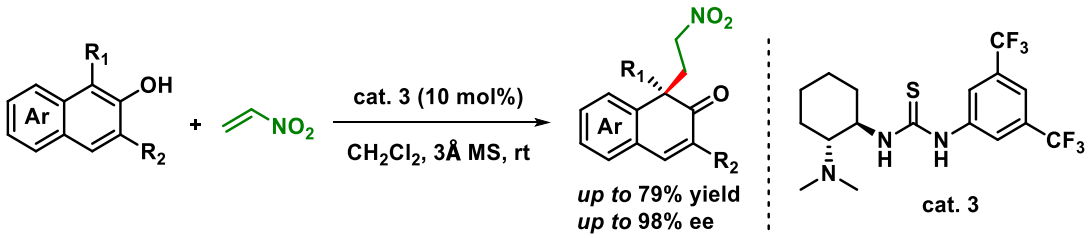
Scheme 1: Dearomatization of *β*-naphthols through an amination reaction

In 2015, You *et al.* reported[7], a Rh-catalyzed enantioselective dearomatization of 1-aryl-2-naphthols with internal alkynes *via* C–H functionalization reaction. In the presence of a chiral Cp/Rh catalyst and combined oxidants of $Cu(OAc)_2$ and air (oxygen), various highly enantioenriched spirocyclic enones bearing an all-carbon quaternary stereogenic centre could be synthesized in up to 98% yields with up to 97:3 er (Scheme 2).



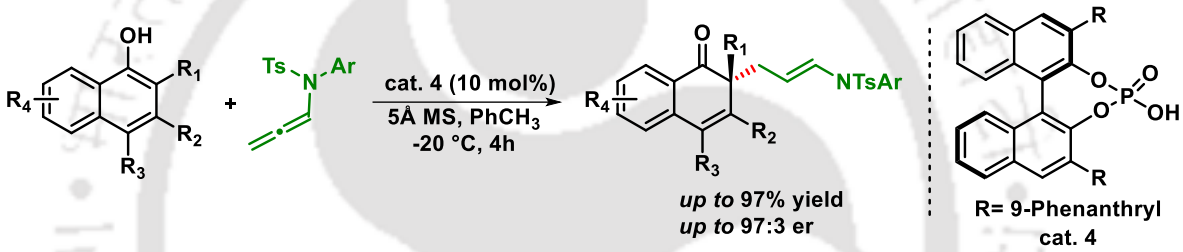
Scheme 2: Dearomatization of *β*-naphthols *via* C(sp^2)–H functionalization/annulation reaction

In 2015, You *et al.* reported[8], an intermolecular asymmetric dearomatization reaction of *β*-naphthols with nitroethylene through a chiral-thiourea-catalyzed Michael reaction. Enantioenriched functionalized *β*-naphthalenones with an all-carbon quaternary stereogenic centre was constructed in good yields and excellent ee (Scheme 3).



Scheme 3: Dearomatization of *β*-naphthols through Michael reaction

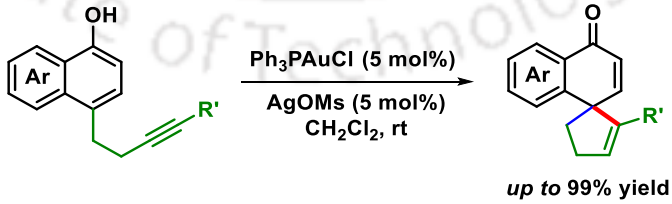
After that in 2019, Shao *et al*. reported[9], highly stereoselective intermolecular catalytic asymmetric allylic dearomatization of *α*-naphthols through C–C bond formation by chiral organocatalysis. These reactions provided enantioriched *α*-naphthalenones in good yields and excellent enantioselectivity (Scheme 4).



Scheme 4: Allylic dearomatization of naphthols

4.2.2 Previous reports on intramolecular dearomatization of *α*- and *β*-naphthol systems:

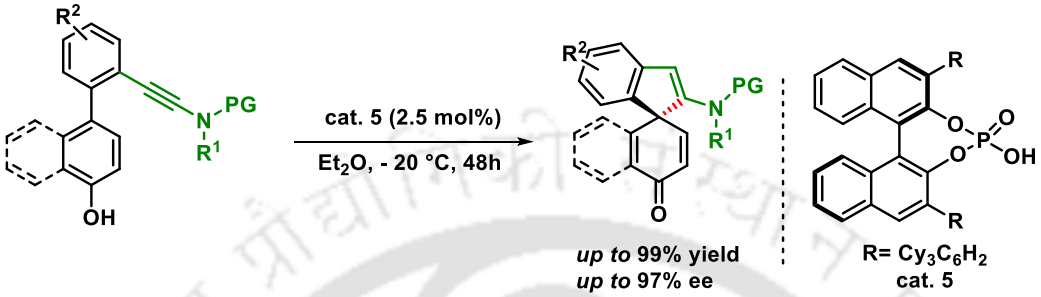
In 2016, You *et al*. reported[10], a highly efficient, gold-catalyzed intramolecular dearomatization reaction of naphthols *via* 5-endo-dig cyclization to produce spirocarbocycles in excellent yields under mild conditions (Scheme 5).



Scheme 5: Intramolecular dearomatization of naphthols tethered with terminal alkynes

In 2021, Ye *et al*. reported[11], chiral Brønsted acids enabled catalytic asymmetric dearomatization reactions of naphthol-, phenol- and pyrrole-ynamides by the direct

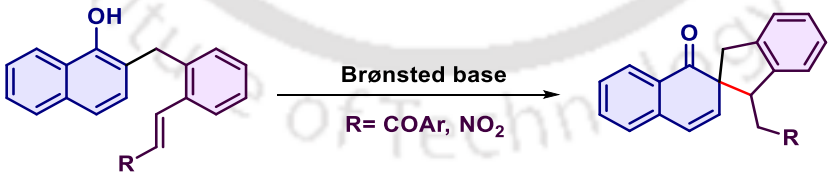
activation of alkynes. This method leads to the practical and atom-economic construction of various valuable spirocyclic enones and 2H-pyrroles that bear a chiral quaternary carbon stereocentre in generally good-to-excellent yields with excellent chemo-, regio- and enantioselectivities. (Scheme 6).



Scheme 6: Dearomatization reactions of naphthol-ynamides

4.3 Our Aim

From the previous literature survey, we found that metal-free methods are less. A few metal-free techniques such radical cyclization[12] and halogen electrophiles[13] have been developed for the synthesis of the spirocarbocycles. There is still a great need for efficient synthetic techniques to create structurally distinct spirocarbocycles from readily available starting materials. So, we like to demonstate Brønsted base catalyzed dearomative intramolecular spirocyclization of newly designed substrates having aryl/alkyl enonetethered *α*-and *β*-naphthol moieties and a deraomatization reaction of *in situ* generated nitro-olefin-tethered *α*-naphthols (Scheme 7).

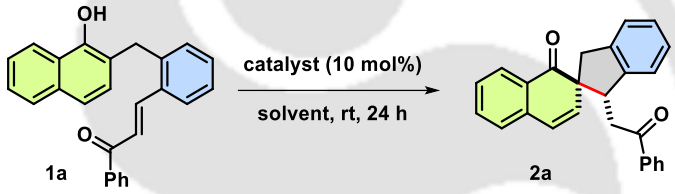


Scheme 7: Intramolecular dearomatization of naphthols

4.4 Result and Discussion

4.4.1 Optimization of catalyst and reaction conditions:

Initially, we synthesized (*E*)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (**1a**) through a series of steps. Subsequently, we conducted the desired dearomative spirocyclization in dichloromethane at room temperature using various organic bases. Initially, DBU served as the catalyst (10 mol%) and after 1 day of stirring, the desired dearomatization product **2a** was obtained in 60% yield with >20:1 dr. The yield of **2a** decreased slightly with DABCO, and DIPEA yielded 52% yield. DMAP, imidazole and 1,1,3,3-tetramethylguanidine (TMG) proved unsuitable for the reaction (Table 1).



entry[a]	catalyst	solvent	yield[b] (%)	dr[c]
1	DBU	CH_2Cl_2	60	>20:1
2	DABCO	CH_2Cl_2	49	>20:1
3	DIPEA	CH_2Cl_2	52	>20:1
4	DMAP	CH_2Cl_2	10	>20:1
5	Imidazole	CH_2Cl_2	16	>20:1
6	TMG	CH_2Cl_2	12	>20:1
7	Et_3N	CH_2Cl_2	90	>20:1
8	Et_3N	$CHCl_3$	85	>20:1
9	Et_3N	EtOAc	50	>20:1
10	Et_3N	Toluene	60	>20:1
11	Et_3N	CH_3CN	50	>20:1
12	Et_3N	Acetone	25	>20:1

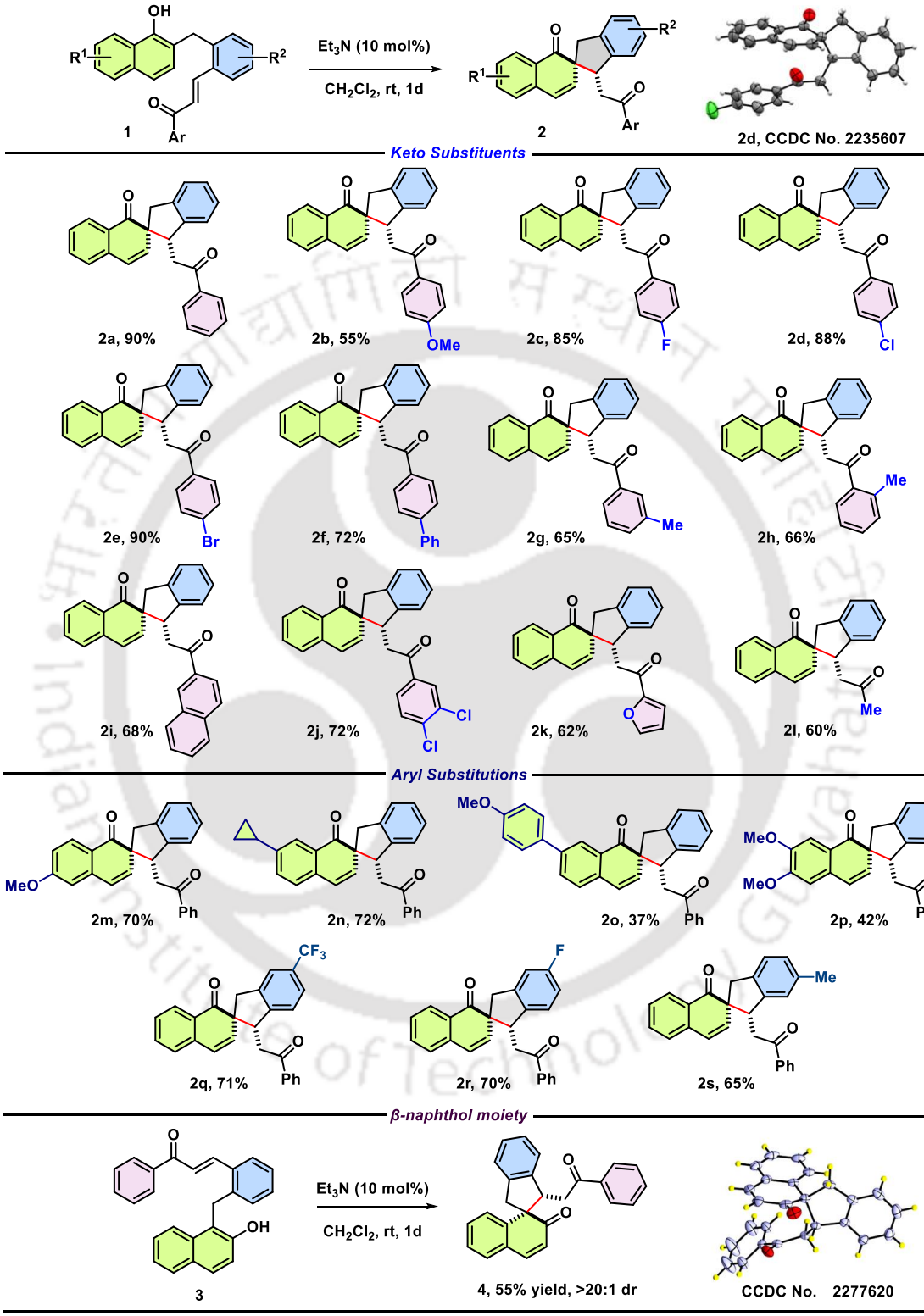
[a] Reactions were carried out 0.1 mmol of **1** in 1 mL dichloromethane at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR.

Table 1: Catalyst and solvent optimization

Ultimately, Et_3N emerged as the most effective catalyst, yielding **2a** in 90% yield with >20:1 dr. We also explored different solvents to enhance the yield but observed no improvement (Table 1).

4.4.2 Substrate scope:

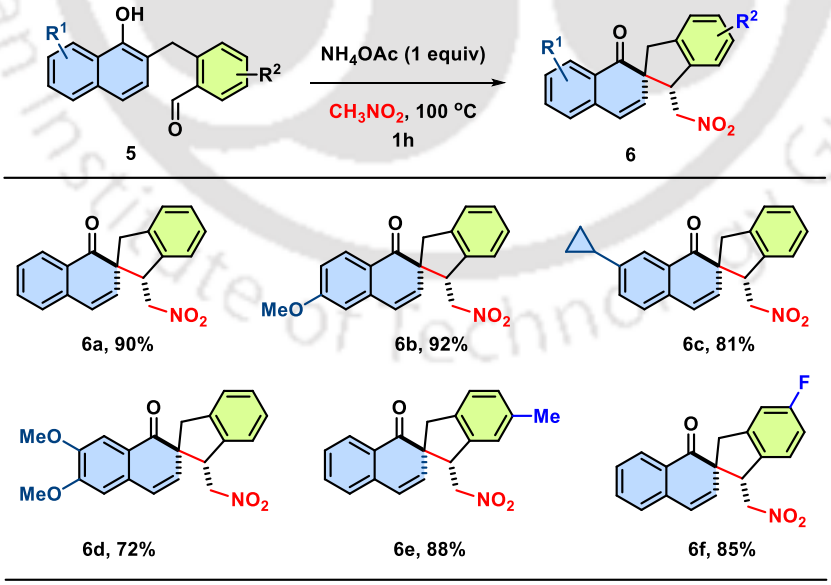
After establishing the optimal conditions, we explored the scope of the dearomative spirocyclization process. Initially, substrates **1** with various keto substituents were prepared and reacted with Et_3N at room temperature. Encouragingly, a single diastereomer was obtained in all cases. We began by testing various *para*-substitutions on the aryl group, all of which proceeded smoothly. For instance, the *para*-anisyl-substituted enone **1b** yielded the spirocyclized product **2b** in 55% yield as a single diastereomer. We then examined different halo substitutions and got the products with excellent yields. Enone **1f** containing a biphenyl group also underwent the reaction smoothly, affording product **2f** in 72% yield. Product **2g** bearing a *meta*-anisyl group obtained in good yield. Even *ortho*-substitution was tolerated, with enone **1h** smoothly converted to product **2h**, isolated in 66% yield. A moderate yield of 68% was also observed for product **2i** with a naphthyl substituent. Substrate **1j** containing a 3,4-dichloro substituted phenyl group provided good results. Furthermore, heteroaromatic 2-furyl group-containing enone yielded product **2k** in a 62% yield. Enone **1l**, containing a aliphatic ketone, participated smoothly, providing **2l** in 60% yield. In the subsequent phase, we examined the scope of enone **1** with different substitutions on the aryl group. Here too, positive outcomes were obtained in almost all cases. Initially, substrates **1** with various substitutions on the naphthol motif were prepared and reacted with Et_3N. Substrate **1m**, with a 6-OMe substituent, smoothly yielded product **2m** in 70% yield, also yielding a single diastereomer. Product **2n** and **2o**, featuring a 7-cyclopropyl and 7-anisyl substituent respectively, showed positive results. Enone **1p**, with 6,7-dimethoxy substitution, also provided a reasonable yield for **2p**. We then explored substitutions on the aryl group of the enone motif in **1** with acceptable results. For instance, smooth conversions were achieved for 4-trifluoromethyl, 4-fluoro, and 5-methyl substituted naphthols **1q**, **1r**, and **1s**, respectively, yielding products **2q**, **2r**, and **2s** in good yields (Scheme 8).



Scheme 8: Substrate scope of enone tethered *α*-and *β*-naphthols

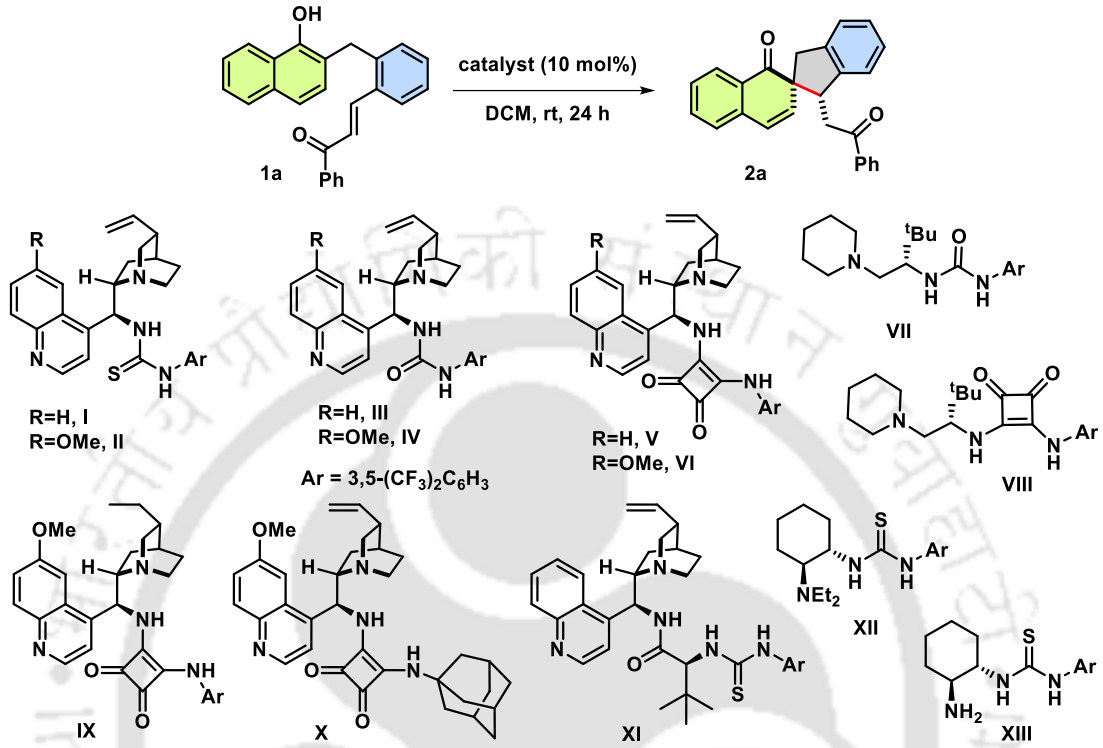
To demonstrate the versatility of this method, we prepared *β*-naphthol-derived enone **3** and subjected it to the reaction conditions. To our satisfaction, it underwent dearomatization smoothly, yielding the desired product **4** in 55% yield with perfect diastereoselectivity (Scheme 8).

Upon considering the synthesis of nitro-olefin tethered *α*-naphthol, we initially attempted the formation of this compound using naphthol **5a** containing an aldehyde group. Surprisingly, when subjected to nitro-olefin formation with ammonium acetate and nitromethane at 100 °C for 1 hour, a concurrent nitro-olefin formation and dearomatization reaction occurred, leading to the formation of product **6a** in 90% yield with perfect diastereoselectivity. Motivated by this discovery, we proceeded to test various substrates **5b – 5d** with different substitutions on the naphthol motif, yielding promising results. For instance, substrate **5b**, featuring a 6-OMe substituent, underwent smooth conversion to deliver product **6b** in 92% yield. Acceptable yields were also obtained for products **6c** and **6d**, bearing 7-cyclopropyl and 6,7-dimethoxy substituents, respectively. We then explored different substitutions on the aryl group of the aldehyde motif in **5**, and pleasingly, smooth conversions were achieved with 5-methyl and 5-fluoro-substituted naphthols **5e** and **5f**, resulting in high yields of products **6e** and **6f**, respectively (Scheme 9).



Scheme 9: Substrate scope of in situ generated nitro-olefin-tethered *α*-naphthols

4.4.3 Catalytic Asymmetric Variant:

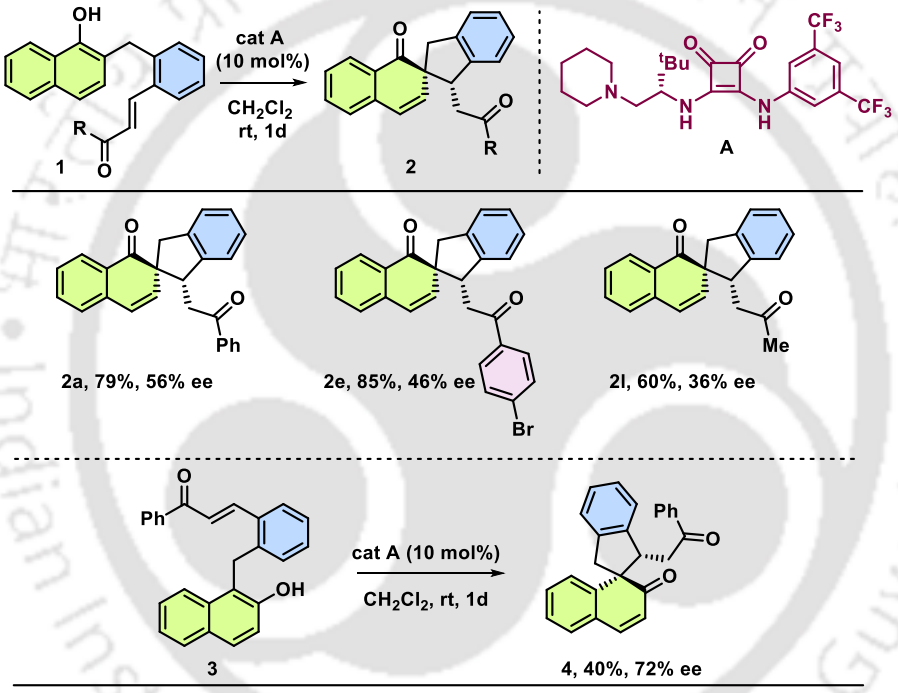


entry[a]	catalyst	yield[b] (%)	dr[c]	ee[d] (%)
1	I	66	>20:1	45
2	II	62	>20:1	44
3	III	74	>20:1	49
4	IV	61	>20:1	20
5	V	74	>20:1	46
6	VI	70	>20:1	54
7	VII	71	>20:1	28
8	**VIII**	**79**	**>20:1**	**56**
9	IX	77	>20:1	50
10	X	68	>20:1	34
11	XI	50	>20:1	20
12	XII	42	>20:1	18
13	XIII	25	>20:1	32
14[e]	VIII	61	>20:1	56
15[f]	VIII	47	>20:1	50

[a]Unless otherwise mentioned, 0.1 mmol of **1a** was stirred in 1.0 mL solvent at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC. [e]Reaction temperature 0 °C and stirred for 2 days. [f]4Å MS added.

Table 2: Chiral catalyst and condition optimization

We became intrigued by the prospect of developing an asymmetric variant of the dearomatization reaction of enone-tethered naphthols. After screening various bifunctional thiourea and squaramide catalysts, we found that *tert*-leucine-derived bifunctional squaramide catalyst **A** was the most effective for the reaction of **1a**. (Table **2**) However, while perfect diastereoselectivity was achieved, the enantioselectivity was only moderate (56% ee). Moderate enantioselectivities were also observed for products **2e** and **2l**. Subsequently, we examined the reaction of **3** with catalyst **A**, and gratifyingly, product **4** was obtained with 72% ee (Scheme **10**).

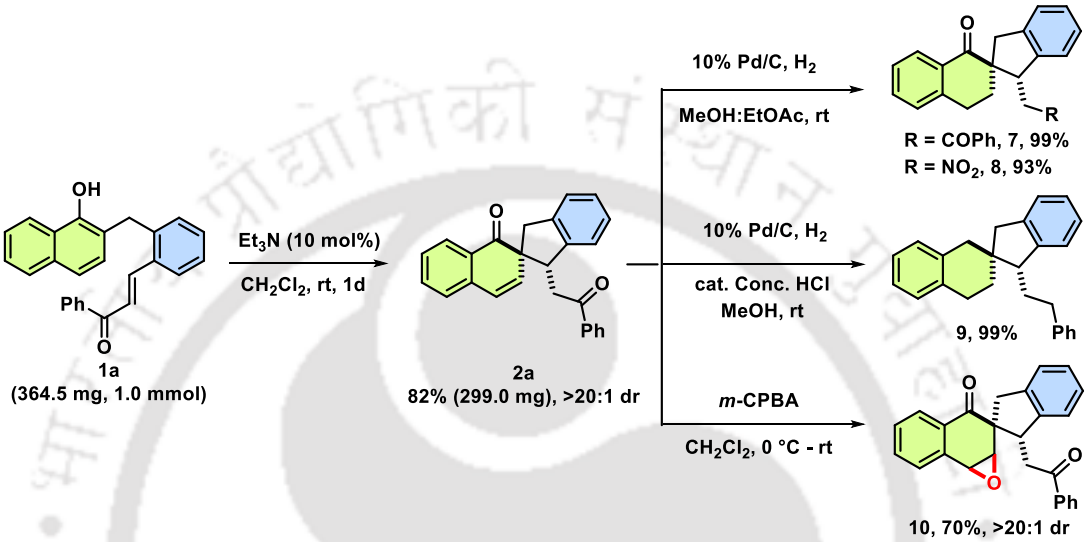


Scheme 10: Catalytic asymmetric variant

4.4.4 Synthetic transformations:

A scale-up reaction was conducted using 1 mmol of **1a**, yielding the desired product **2a** in 82% yield. Subsequently, to showcase the synthetic versatility of our reaction, experiments were performed on both **2a** and **6a** (Scheme 11). Initially, a hydrogenation reaction was executed with 10% Pd/C in a mixed solvent of methanol and ethyl acetate, resulting in the desired product **7** in 99% yield from **2a**. Under identical conditions, substrate **6a** afforded hydrogenated product **8** in 93% yield. Intriguingly, when the hydrogenation reaction of **2a**

was conducted in methanol with a catalytic amount of hydrochloric acid, simultaneous reduction of both the double bond and keto group occurred, yielding product **9** in 99% yield. Finally, treatment of compound **2a** with *m*-CPBA led to the formation of epoxide **10** in 70% yield.

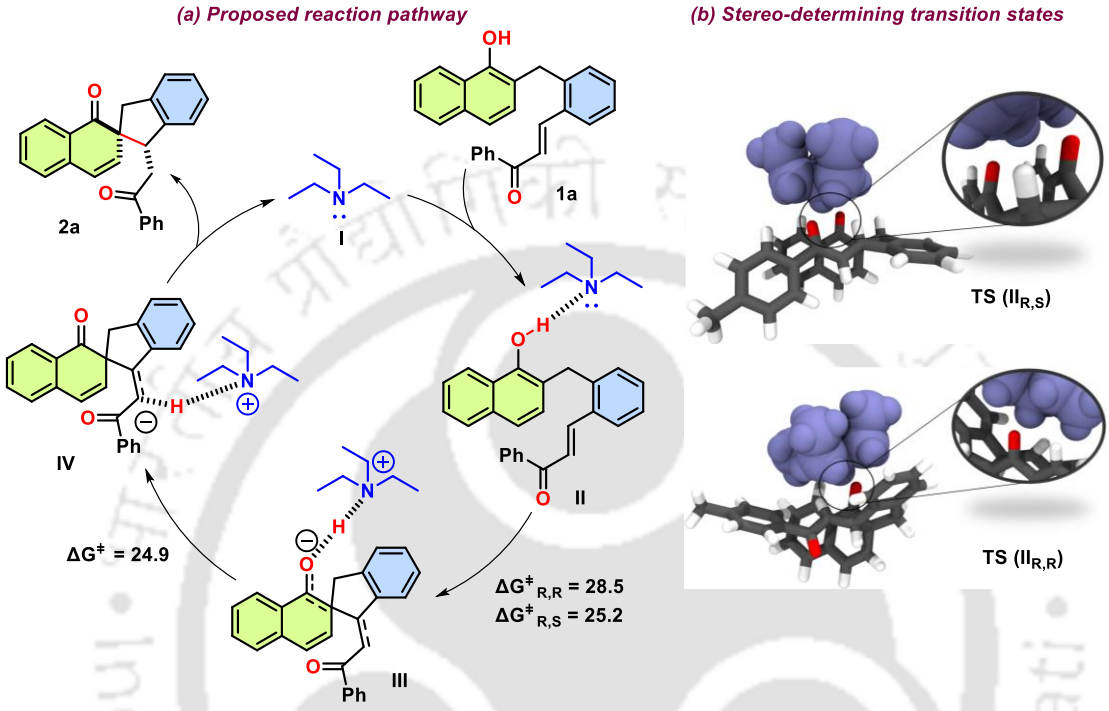


Scheme 11: Scale up reaction and synthetic transformations

4.4.5 The proposed mechanism:

To gain insight into the reaction mechanism of the diastereoselective dearomatization of *α*-naphthol catalyzed by Et_3N (**I**), we conducted DFT calculations. Consistent with experimental observations, the calculations reveal a notable preference for the coordination of **I** with the *α*-naphthol motif of **1a**. This coordination is characterized by a hydrogen bonding interaction between **I** and the adjacent -OH group of naphthol, maintaining a distance of 1.78 Å in species **II**. The transition state corresponding to $\mathbf{II}_{R,S}$ ($\Delta G^{\ddagger}$ = 25.2 kcal/mol) is lower than $\mathbf{II}_{R,R}$ ($\Delta G^{\ddagger}$ = 28.5 kcal/mol) leading to the exclusive formation of the *R,S* product. Furthermore, species **II** demonstrates a significant activation of the naphthalic moieties during the introduction of **I**. It is well-known that **I** acts as a base, forming hydrogen bonding interactions with the substrates. Intermediate **II** proceeds through a ring-attack, accompanied by a concurrent proton transfer from the naphthol -OH group to the nitrogen centre of **I**. This concerted process results in the formation of species

III. Subsequently, species **III** can undergo further evolution through proton transfer through the **TS**$_{\mathbf{III\text{-}IV}}$, producing the final product **2a** with the regeneration of catalyst **I** (Scheme 12).



Scheme 12: Proposed mechanistic pathway

4.5 Conclusion

In summary, we've outlined the dearomative intramolecular spirocyclization of newly devised substrates, including aryl/alkyl enonetethered α- and β-naphthols, and a dearomatization reaction involving in situ generated nitro-olefin-tethered α-naphthols. These reactions yielded spirocyclic products in moderate to good yields with high diastereoselectivities, all conducted under ambient conditions. Additionally, an asymmetric version was detailed, showcasing moderate enantioselectivities. We explored synthetic applications such as hydrogenation and epoxidation reactions.

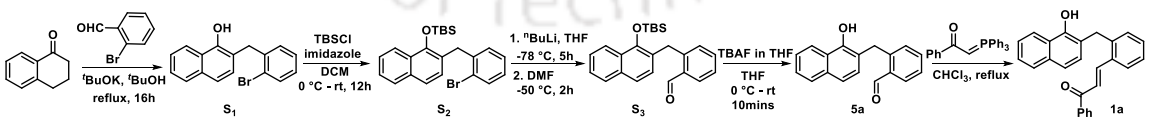
4.6 Experimental section

4.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. All dry solvents were dried using activated 4Å molecular sieves and stored under argon. ^{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 and DMSO δ 2.50), carbon (chloroform δ 77.23 and DMSO δ 39.58). Multiplicity was indicated as follows**:** s = singlet, d = doublet, dd = double doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet, bs = broad singlet. Coupling constants were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using Daicel Chiral PAK IA. Melting point was measured using BÜCHI melting point B-540 apparatus. Melting point was measured in open glass capillary and values are uncorrected. For visualizing the products UV light and/or I_2 were used. Silica gel (230 – 400 mesh size) was used for the flash column chromatography. Reactions were monitored by TLC on silica gel 60 with fluorescence indicator F254 (0.25 mm).

4.6.2 Preparation of Starting materials

- ***General Procedure for the Synthesis of Enone-Tethered Naphthols (1a – 1s & 3) and aldehydes (5a – 5f):***



Procedure A[14a]**:** A solution of 1-tetralone (1.0 g, 6.85 mmol, 1.0 equiv.) and benzaldehyde (1.3 g, 6.85 mol, 1.0 equiv.) in tert-butyl alcohol (70.0 mL) was treated with potassium tert-butoxide (1.6 g, 13.7 mmol, 2.0 equiv.) and heated at reflux in a pre-heated oil bath under nitrogen for 16 h. The mixture was cooled, acidified with 1 N HCl, and concentrated

to remove the tert-butyl alcohol. The aqueous residue was extracted with ethyl acetate, and the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, the crude product (**S_1**) was obtained and used in the next step without further purification.

Procedure B[14b]**:** In a round bottom flask, above obtained aryl alcohol (1.0 equiv.) was dissolved in dichloromethane (27.0 mL). The solution was then charged with imidazole (930 mg, 13.7 mmol, 2.0 equiv.) and tert-butyldimethylchlorosilane (1.5 g, 10.3 mmol, 1.5 equiv.) and stirred until the starting alcohol was fully consumed. The reaction was diluted with 25.0 mL dichloromethane, washed with deionized H_2O (3 × 50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash column chromatography (hexane/ethyl acetate) on silica gel to afford the aryl silyl ether (**S_2**).

Procedure C[14c]**:** The above obtained product (1.95 g, 4.56 mmol, 1.0 equiv.) was dissolved in 25.0 mL of dry THF under argon. The stirred solution was cooled to – 78 °C, and 10.0 mL of *n*-BuLi in *n*-hexane (2 M) (20.1 mmol, 4.4 equiv.) was added at such a rate to keep the temperature at – 70 °C. Temperature was measured using an internal probe in the reaction flask. After 5 h, dimethylformamide (1.8 mL, 22.8 mmol, 5.0 equiv.) was added, keeping the temperature below – 50 °C. The solution was stirred at – 50 °C for 2 h. The reaction mixture was poured into HCl/ice under vigorous stirring and allowed to reach room temperature overnight. The reaction mixture was extracted three times with dichloromethane, and the combined organic phases were washed twice with deionized water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude (**S_3**) was used in the next step without further purification.

Procedure D[14d]**:** To a cold (0 ºC) solution of the above crude product (1.0 equiv.) in dry tetrahydrofuran (50 mL), was added tetra-*n*-butylammonium fluoride (TBAF) (5.0 mL of a 1 M solution in tetrahydrofuran, 5.0 mmol, 1.1 equiv.) and the resulting solution stirred for 10 minutes allowing the mixture to warm to room temperature. The resulting solution was diluted with dichloromethane and quenched with water. The organic layer was extracted with brine and dried over Na_2SO_4, followed by solvent reduction in *vacuo* and purification was carried out by silica gel flash column chromatography hexane/ethyl acetate to afford aldehyde derivative (**5a – 5f**).

Procedure E[14e]**:** Following the general procedure, in dry chloroform (10.0 mL) aldehyde **5** (1022 mg, 3.9 mmol, 1.0 equiv.) and 1-phenyl-2-(triphenylphosphanylidene)ethanone (2162 mg, 4.7 mmol, 1.2 equiv.) stirred at reflux in a pre-heated oil bath for 16 h. The reaction was cooled to rt, concentrated in *vacuo* and the crude product purified by silica gel flash column chromatography hexane/ethyl acetate (90:10 – 80:20) to give desired naphthol derivatives **(1a – 1s** and **3)** with 40 – 55 % overall yield.

4.6.3 General procedure for the synthesis of compounds 2a – 2s and 4

In an oven dried round bottom flask, **1a** (36.5 mg, 0.1 mmol), 10 mol% of triethylamine were taken and 1.0 mL dichloromethane was added to the reaction mixture and stirred at room temperature for 24 h. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford desired product **2a – 2s** and **4**.

4.6.4 General procedure for the synthesis of compound 6a – 6f

In an oven dried round bottom flask, **5** (26.5 mg, 0.1 mmol), ammonium acetate (0.1 mmol) were taken and 1.0 mL nitromethane was added to the reaction mixture and stirred at 100 °C in a pre-heated oil bath for an hour. Completion of reaction was checked by TLC. After the completion of reaction, the reaction mixture was quenched with saturated $NaHCO_3$ solution and excess nitromethane was removed under reduced pressure. The mixture was diluted with water and extracted with ethyl acetate 3 times. Then it was dried over Na_2SO_4 and solvent was concentrated under reduced pressure. Then the reaction mixture was purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford desired product **6a – 6f**.

4.6.5 Synthetic transformations

➢ 4.6.5.1 General procedure for the synthesis of compound 7 – 8[15]

The *α*-naphthalenone **2a** (36.5 mg, 0.1 mmol) was dissolved in methanol/ ethyl acetate (1:1), and added Pd/C (10 mol%). The resulting mixture was stirred at room temperature under H_2 atmosphere. When the reaction was completed by the monitoring of TLC, the solution was filtered and concentrated in *vacuo*. Then water was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash column chromatography hexane/ethyl acetate to afford **7** and **8**.

➢ 4.6.5.2 General procedure for the synthesis of compound 9[16]

To a flask containing a solution of **2a** (36.5 mg, 0.1 mmol) in MeOH (2.0 mL) were added 10 mol% Pd/C and HCl (conc. 10.0 μL). Then the mixture was stirred under H_2 (1 atm) at room temperature until TLC showed complete consumption of starting material. After the removal of Pd/C, water was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, separated, dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash column chromatography (Hexane/ethyl acetate) to afford **9** with 99% yield.

➢ 4.6.5.3 General procedure for the synthesis of compound 10[17]

Under the protection of argon, with dry DCM as solvent, add *m*-CPBA (2 equiv.) in solution of **2a** (36.5 mg, 0.1 mmol) at 0 °C and then heat the mixture to room temperature for 24 h. After the reaction is complete, the aqueous solution of Na_2SO_3 was added, the mixture was extracted with ethyl acetate (3 × 10 mL), dried using Na_2SO_4 and filtered. After that, flash column chromatography (Hexane/ethyl acetate = 9/1) was done to afford the product **10** with 70% yield.

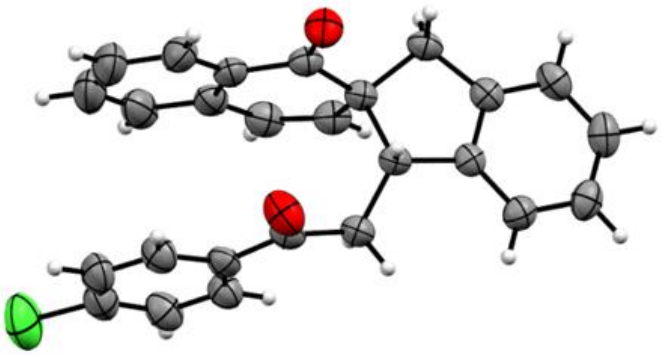
4.7 Single crystal X-ray diffraction analysis

➢ 4.7.1 Single crystal X-ray diffraction analysis of 2d:

Method for crystal growth:

In a round bottom flask, compound **2d** dissolved in minimum amount of hexane/DCM (3:1) and it kept in for slow evaporation at room temperature to get colourless crystal of **2d**.

CCDC No.	**2235607**
Empirical formula	$C_{26}H_{19}ClO_2$
Formula weight	398.86
Crystal habit, colour	block / clear colourless
Crystal size mm^3	0.25 x 0.20 x 0.15 mm^3
Diffraction measurement device type	Bruker APEX-II CCD
Diffraction measurement method	\ f and \ w scans
Temperature, *T*	299 K
Wavelength, λ	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a=7.3773(5) Å α=90° b=6.7935(4) Å β=94.163(2)° c=38.701(2) Å γ=90°
Volume	1934.5(2) $Å^3$
Z	4
Density (calculated)	1.370 g/cm^3
Absorption coefficient	0.218 mm^{-1}
F(000)	832.0
Theta(max)	24.997°
Data completeness	0.994
R(reflections)	0.0448 (3018)
wR2(reflections)	0.1171 (3370)



Ortep Diagram with 30 % ellipsoid probability of compound 2d

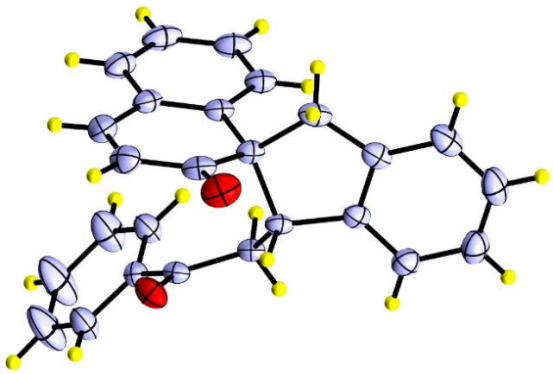
➢ 4.7.2 Single crystal X-ray diffraction analysis of 4:

Method for crystal growth:

In a round bottom flask, compound **4** dissolved in minimum amount of hexane/DCM (3:1) and it kept in for slow evaporation at room temperature to get colourless crystal of **4**.

CCDC No.	**2277620**	
Empirical formula	$C_{26}H_{20}O_2$	
Formula weight	364.42	
Crystal habit, colour	block / clear colourless	
Crystal size mm^3	0.25 x 0.20 x 0.15 mm^3	
Diffraction measurement device type	Bruker APEX-II CCD	
Diffraction measurement method	\ f and \ w scans	
Temperature, *T*	298 K	
Wavelength, λ	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a=10.2869(3) Å b=10.8850(3) Å c=17.5167(6) Å	α=98.509(1)° β=91.194(1)° γ=104.257(1)°
Volume	1876.70(10) $Å^3$	
Z	4	

Density (calculated)	1.290 g/cm^3
Absorption coefficient	0.080 mm^{-1}
F(000)	768.0
Theta(max)	27.115°
Data completeness	0.988
R(reflections)	0.0508 (4450)
wR2(reflections)	0.1395 (8186)



Ortep Diagram with 30 % ellipsoid probability of compound 4

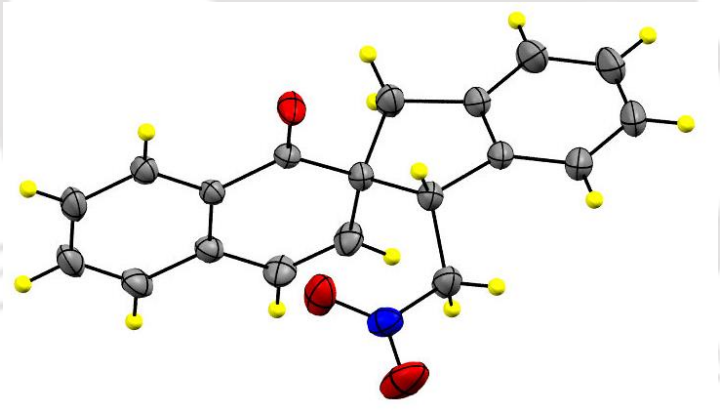
- **4.7.3 Single crystal X-ray diffraction analysis of 6a:**

Method for crystal growth:

In a round bottom flask, compound **6a** dissolved in minimum amount of hexane/ethylacetate (3:1) and it kept in for slow evaporation at room temperature to get colourless crystal of **6a**.

CCDC No.	**2300684**
Empirical formula	$C_{19}H_{15}NO_3$
Formula weight	305.32
Crystal habit, colour	block / clear colourless
Crystal size mm^3	0.25 x 0.20 x 0.15 mm^3
Diffraction measurement device type	Bruker APEX-II CCD
Diffraction measurement method	\ f and \ w scans

Temperature, *T*	293 K
Wavelength, λ	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a= 8.0549(13)Å α=90° b=17.935(3) Å β=90.693(4)° c=10.6527(18) Å γ=90°
Volume	1538.9(4) $Å^3$
Z	4
Density (calculated)	1.318 g/cm^3
Absorption coefficient	0.090 mm^{-1}
F(000)	640.0
Theta(max)	24.995°
Data completeness	0.989
R(reflections)	0.0566
wR2(reflections)	0.1212

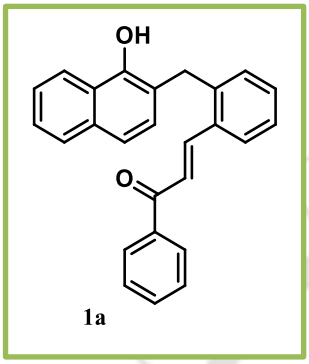


Ortep Diagram with 30 % ellipsoid probability of compound 6a

4.8 Characterisation of the products

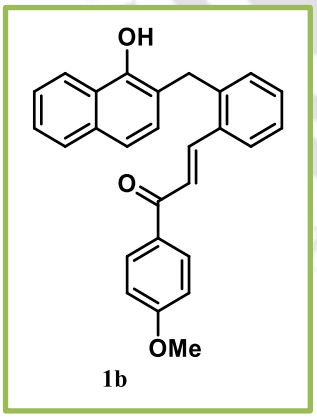
(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (1a)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, overall yield: 55% (1371 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.31 (d, *J* = 15.6 Hz, 1H), 8.12 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.91 – 7.86 (m, 2H), 7.77 – 7.73 (m, 1H), 7.71 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.57 – 7.52 (m, 1H), 7.48 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.39 – 7.34 (m, 2H), 7.33 – 7.28 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.04 (bs, 1H), 4.36 (s, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 191.4, 148.3, 143.2, 140.7, 138.1, 134.4, 133.7, 133.1, 130.8, 130.5, 128.7, 128.7, 128.4, 128.0, 127.3, 127.2, 125.9, 125.7, 125.7, 123.7, 121.3, 121.3, 121.1, 33.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{21}O_2$ 365.1536; found 365.1512.



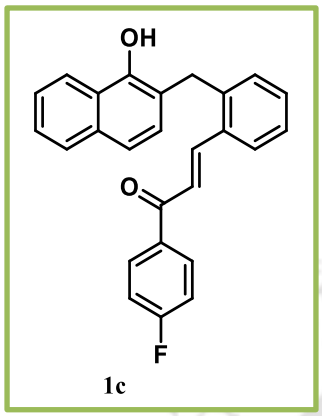
(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (1b)

The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20) as pale yellow solid, overall yield: 52% (1403 mg). **^{1}H NMR (500 MHz, DMSO)** δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.01 (m, 4H), 7.80 – 7.72 (m, 2H), 7.49 – 7.41 (m, 2H), 7.39 – 7.30 (m, 3H), 7.20 (dd, *J* = 7.3, 1.7 Hz, 1H), 6.98 (t, *J* = 9.3 Hz, 3H), 4.32 (s, 2H), 3.83 (s, 3H). **^{13}C{H} NMR (125 MHz, DMSO)** δ 187.7, 163.2, 149.6, 140.6, 133.7, 133.2, 131.0, 130.7, 130.4, 130.3, 128.0, 127.6, 127.3, 126.8, 125.5, 125.3, 125.0, 123.5, 122.1, 120.9, 119.4, 114.1, 55.6, 32.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_3$ 395.1642; found 395.1655.



(E)-1-(4-fluorophenyl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1c)

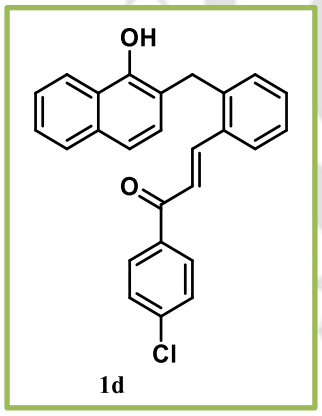
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow semi solid, overall yield: 49% (1282 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.28 (d, *J* = 15.6 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.75 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.51 – 7.40 (m, 2H), 7.39 – 7.33 (m, 2H), 7.33 – 7.22 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.08 – 6.98 (m, 2H), 6.11 (s, 1H), 4.35 (s, 2H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 189.8, 148.3, 143.4, 140.7, 134.3, 133.7, 131.4, 131.3, 130.9, 130.6, 128.3, 128.0, 127.4, 127.2, 125.9, 125.8, 125.6, 123.3, 121.3, 121.2, 121.1, 116.0, 115.7, 33.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}FO_2$ 383.1442; found 383.1447.



1c

(E)-1-(4-chlorophenyl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1d)

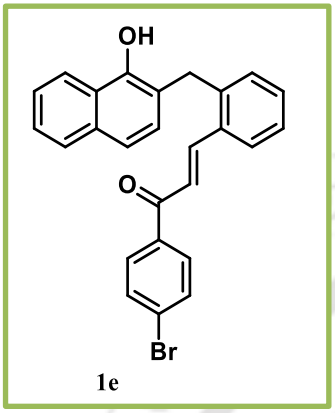
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale yellow solid, overall yield: 52% (1417 mg**). ^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.27 (d, *J* = 15.5 Hz, 1H), 8.13 – 8.07 (m, 1H), 7.81 – 7.73 (m, 3H), 7.71 – 7.66 (m, 1H), 7.45 (m, 2H), 7.39 – 7.27 (m, 6H), 7.27 – 7.22 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.04 (s, 1H), 4.34 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 190.1, 148.2, 143.7, 140.7, 139.5, 136.3, 134.3, 133.7, 130.9, 130.7, 130.1, 129.0, 128.3, 128.0, 127.4, 127.2, 126.0, 125.8, 125.5, 123.2, 121.3, 121.1, 121.0, 33.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}ClO_2$ 399.1146; found 399.1150.



1d

(E)-1-(4-chlorophenyl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1e)

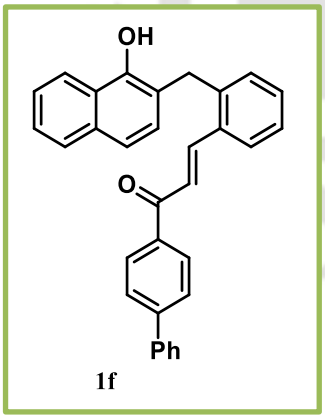
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, overall yield: 50% (1513 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.25 (d, *J* = 15.6 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.67 (m, 3H), 7.50 – 7.40 (m, 4H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.28 (td, *J* = 7.6, 5.7 Hz, 2H), 7.21 (d, *J* = 15.5 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.16 (s, 1H), 4.33 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 190.3, 148.3, 143.7, 140.7, 136.7, 134.2, 133.6, 132.0, 130.9, 130.6, 130.2, 128.3, 128.1, 128.0, 127.3, 127.2, 125.9, 125.8, 125.5, 123.1, 121.2, 121.1, 121.0, 33.8. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}BrO_2$ 443.0641; found 443.0634.



1e

(E)-1-([1,1'-biphenyl]-4-yl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1f)

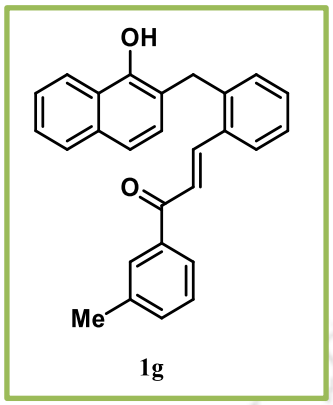
The product was purified by flash column chromatography (hexane/ethyl acetate = 87:13) as light pink solid, overall yield: 47% (1416 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.32 (d, *J* = 15.5 Hz, 1H), 8.15 – 8.10 (m, 1H), 7.99 – 7.93 (m, 2H), 7.74 (ddd, *J* = 9.6, 7.7, 1.6 Hz, 2H), 7.64 – 7.59 (m, 4H), 7.50 – 7.35 (m, 8H), 7.34 – 7.30 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.08 (s, 1H), 4.38 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 190.9, 148.3, 145.7, 143.1, 140.7, 140.0, 136.8, 134.5, 133.7, 130.8, 130.6, 129.4, 129.1, 128.4, 128.4, 128.0, 127.5, 127.4, 127.4, 127.2, 125.9, 125.7, 125.7, 123.8, 121.3, 121.2, 33.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{32}H_{25}O_2$ 441.1849; found 441.1848.



1f

(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-(m-tolyl)prop-2-en-1-one (1g)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

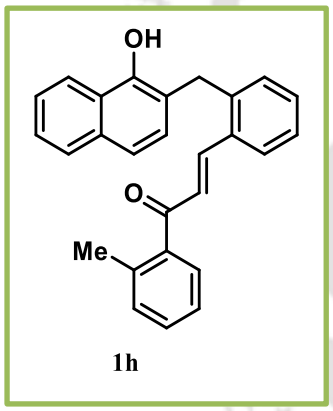


1g

as yellow gummy solid, overall yield: 53% (1372 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 15.6 Hz, 1H), 8.12 (d, *J* = 7.4 Hz, 1H), 7.75 – 7.62 (m, 4H), 7.47 – 7.22 (m, 10H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.32 (s, 1H), 4.33 (s, 2H), 2.35 (s, 3H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 191.6, 148.4, 143.1, 140.7, 138.6, 138.1, 134.4, 133.9, 133.7, 130.7, 130.5, 129.2, 128.6, 128.4, 127.9, 127.2, 127.1, 125.9, 125.8, 125.7, 125.6, 123.8, 121.3, 121.2, 33.8, 21.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693; found 379.1709.

(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-(o-tolyl)prop-2-en-1-one (1h)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

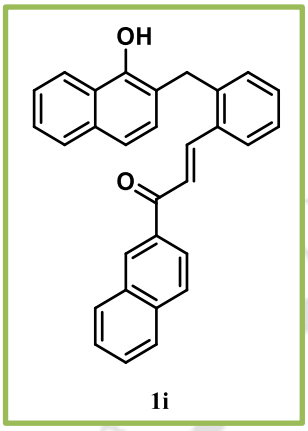


1h

as yellow gummy solid, overall yield: 52% (1346 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.74 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.51 – 7.41 (m, 2H), 7.39 – 7.24 (m, 6H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 – 6.88 (m, 2H), 5.50 (s, 1H), 4.21 (s, 2H), 2.21 (s, 3H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 197.5, 147.9, 144.3, 140.6, 139.1, 137.1, 134.0, 133.6, 131.3, 130.9, 130.9, 130.4, 128.2, 128.2, 128.1, 128.1, 127.5, 127.1, 125.9, 125.6, 125.6, 125.1, 121.2, 121.1, 120.9, 33.8, 20.1. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693; found 379.1743.

(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-(naphthalen-2-yl)prop-2-en-1-one (1i)

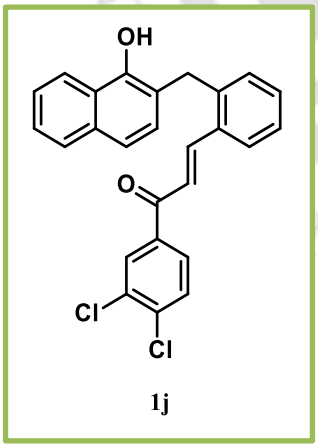
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pink solid, overall yield: 42% (1191 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.43 – 8.33 (m, 2H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.98 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.85 (dd, *J* = 8.5, 6.5 Hz, 3H), 7.78 – 7.71 (m, 2H), 7.59 (ddd, *J* = 7.9, 6.9, 1.3 Hz, 1H), 7.52 (td, *J* = 7.3, 6.8, 1.3 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.39 – 7.27 (m, 4H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.24 (s, 1H), 4.38 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.1, 148.3, 143.2, 140.7, 135.6, 135.4, 135.2, 134.5, 133.7, 132.6, 130.8, 130.6, 130.3, 130.0, 129.7, 128.7, 128.6, 128.4, 127.9, 127.3, 127.3, 126.9, 125.9, 125.7, 124.6, 124.3, 123.7, 121.3, 121.2, 33.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{30}H_{23}O_2$ 415.1693, found 415.1704.



1i

(E)-1-(3,4-dichlorophenyl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1j)

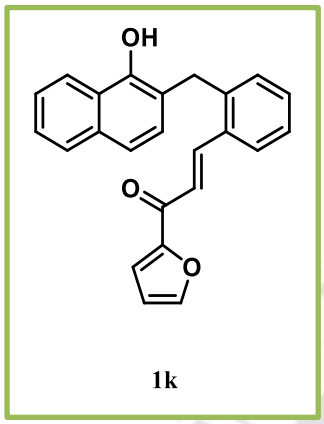
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, overall yield: 45% (1331 mg). **^{1}H NMR (400 MHz, DMSO)** δ 9.42 (s, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.29 – 8.22 (m, 1H), 8.18 – 8.09 (m, 2H), 8.00 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.85 – 7.73 (m, 3H), 7.50 – 7.29 (m, 5H), 7.23 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 4.33 (s, 2H). **^{13}C{H} NMR (100 MHz, DMSO)** δ 187.2, 149.4, 142.4, 141.1, 137.6, 135.9, 133.2, 133.1, 131.9, 131.0, 130.8, 130.6, 130.4, 128.5, 128.0, 127.5, 127.4, 126.7, 125.5, 125.2, 124.9, 122.5, 122.0, 120.8, 119.3, 32.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{19}Cl_2O_2$ 433.0757, found 433.0749.



1j

(E)-1-(furan-2-yl)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)prop-2-en-1-one (1k)

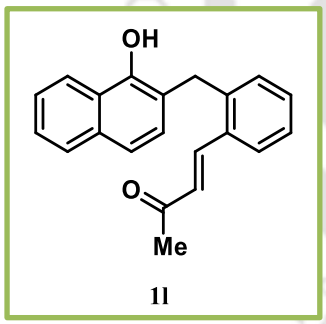
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale yellow solid, overall yield: 50% (1212 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.39 (d, *J* = 15.7 Hz, 1H), 8.17 – 8.13 (m, 1H), 7.74 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.68 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.26 (m, 3H), 7.21 – 7.19 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.39 (s, 1H), 4.37 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 178.7, 153.6, 148.4, 146.9, 142.4, 141.0, 134.1, 133.7, 130.8, 130.4, 128.5, 127.9, 127.2, 127.0, 125.9, 125.8, 125.7, 122.5, 121.3, 121.3, 121.2, 118.2, 112.7, 33.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{24}H_{19}O_3$ 355.1329, found 355.1368.



1k

(E)-4-(2-((1-hydroxynaphthalen-2-yl)methyl)phenyl)but-3-en-2-one (1l)

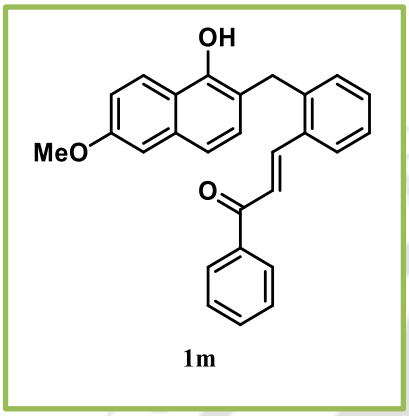
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as white solid, overall yield: 49% (1013 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.09 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.96 (d, *J* = 16.1 Hz, 1H), 7.77 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.46 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.34 (td, *J* = 7.1, 6.7, 1.4 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 16.2 Hz, 1H), 5.94 (s, 1H), 4.31 (s, 2H), 2.25 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 199.3, 148.4, 141.4, 140.1, 133.9, 133.7, 130.8, 130.5, 128.4, 128.3, 128.0, 127.5, 127.1, 126.0, 125.8, 125.3, 121.2, 120.9, 120.6, 34.0, 27.8. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{19}O_2$ 303.1380, found 303.1398.



1l

(E)-3-(2-((1-hydroxy-6-methoxynaphthalen-2-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (1m)

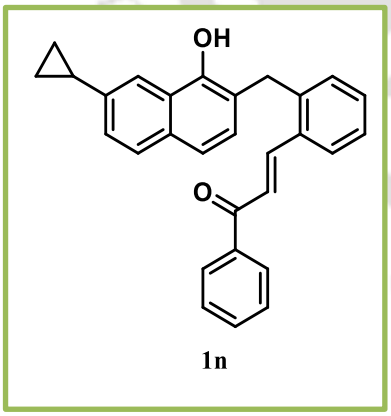
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, overall yield: 55% (1484 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.27 (d, *J* = 15.6 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.69 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.35 (td, *J* = 7.6, 1.7 Hz, 1H), 7.32 – 7.24 (m, 4H), 7.12 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.08 – 7.02 (m, 2H), 5.99 (s, 1H), 4.30 (s, 2H), 3.88 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.4, 157.8, 148.6, 143.2, 140.8, 138.1, 135.1, 134.4, 133.0, 130.7, 130.4, 129.2, 128.7, 127.3, 127.2, 123.7, 123.0, 121.0, 120.2, 119.1, 118.2, 106.1, 55.4, 33.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_3$ 395.1642; found 395.1660.



1m

(E)-3-(2-((7-cyclopropyl-1-hydroxynaphthalen-2-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (1n)

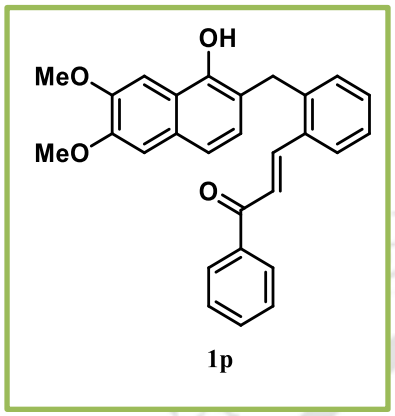
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as red semi solid, overall yield: 52% (1439 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.28 (d, *J* = 15.6 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 2H), 7.79 (s, 1H), 7.68 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.22 (m, 6H), 7.13 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.93 (s, 1H), 4.32 (s, 2H), 2.05 (tt, *J* = 8.3, 5.1 Hz, 1H), 1.07 – 0.94 (m, 2H), 0.80 (m, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 191.4, 147.8, 143.3, 141.4, 140.7, 138.1, 134.4, 133.0, 132.1, 130.7, 130.4, 128.7, 128.7, 128.0, 127.4, 127.2, 127.1, 125.6, 124.6, 123.7, 121.1, 121.0, 117.1, 33.8, 16.1, 9.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{29}H_{25}O_2$ 405.1849, found 405.1852.



1n

(E)-3-(2-((1-hydroxy-6,7-dimethoxynaphthalen-2-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (1p)

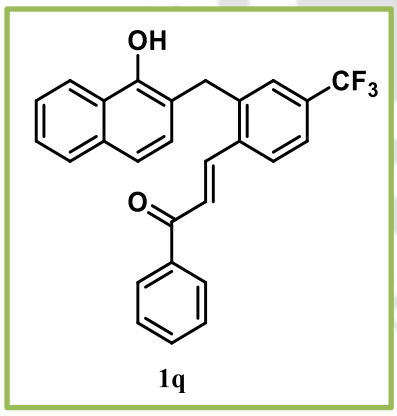
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as red semi solid, overall yield: 43% (1249 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.28 (d, *J* = 15.6 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.41 (dd, *J* = 14.7, 7.1 Hz, 3H), 7.37 – 7.24 (m, 5H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.02 (s, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.05 (s, 1H), 4.31 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.3, 149.6, 149.4, 147.7, 143.2, 140.7, 138.0, 134.4, 133.1, 130.8, 130.4, 129.6, 128.7, 128.7, 127.3, 127.2, 126.7, 123.6, 121.1, 119.8, 119.7, 106.5, 100.7, 56.0, 55.9, 34.0. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{28}H_{25}O_4$ 425.1747, found 425.1791.



1p

(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)-4-(trifluoromethyl)phenyl)-1-phenylprop-2-en-1-one (1q)

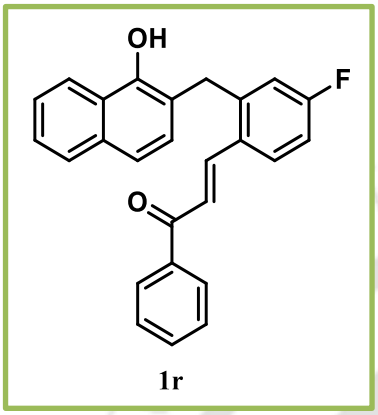
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, overall yield: 41% (1213 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.29 (d, *J* = 15.6 Hz, 1H), 8.19 – 8.13 (m, 1H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.78 – 7.72 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.50 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.43 (m, 2H), 7.38 (t, *J* = 8.6 Hz, 3H), 7.32 (d, *J* = 15.6 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.39 (s, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 191.2, 148.5, 142.0, 141.9, 137.8, 137.5, 133.7, 133.4, 132.2, 131.9, 131.7, 131.5, 128.8, 128.8, 128.1, 128.0, 127.4, 127.3, 127.3, 127.3, 126.0, 125.8, 125.7, 125.6, 125.2, 124.9, 123.8, 123.8, 123.8, 123.7, 123.1, 121.4, 121.1, 120.6, 33.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{20}F_3O_2$ 433.1410; found 433.1391.



1q

(E)-3-(4-fluoro-2-((1-hydroxynaphthalen-2-yl)methyl) phenyl)-1-phenylprop-2-en-1-one (1r)

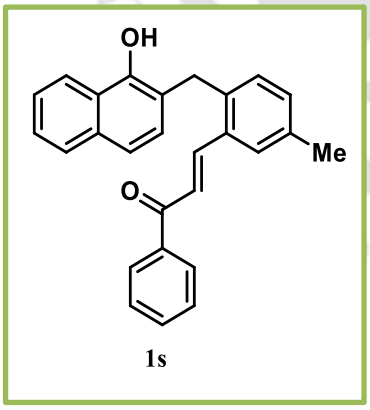
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale yellow solid, overall yield: 46% (1203 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.26 (d, *J* = 15.5 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 8.3, 5.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.36 (m, 5H), 7.29 – 7.20 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.25 (s, 1H), 4.33 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.2, 165.2, 163.2, 148.4, 143.9, 143.8, 142.1, 138.0, 133.8, 133.1, 130.5, 130.4, 129.0, 128.9, 128.8, 128.7, 128.3, 128.1, 126.0, 125.8, 125.6, 123.2, 121.5, 121.0, 120.6, 117.5, 117.3, 114.4, 114.2, 33.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}FO_2$ 383.1442, found 383.1447.



1r

(E)-3-(2-((1-hydroxynaphthalen-2-yl)methyl)-5-methylphenyl)-1-phenylprop-2-en-1-one (1s)

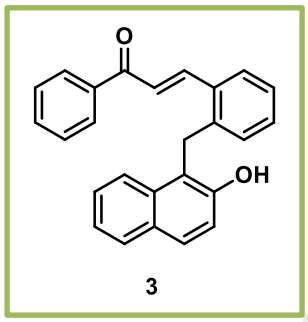
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale-yellow gummy solid, overall yield: 49% (1269 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.24 (dd, *J* = 15.6, 2.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.32 (m, 5H), 7.27 (dd, *J* = 15.6, 2.3 Hz, 1H), 7.13 (s, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.19 (s, 1H), 4.29 (s, 2H), 2.34 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.4, 148.4, 143.3, 138.1, 137.7, 136.8, 134.2, 133.7, 133.0, 131.6, 130.4, 128.7, 128.7, 128.4, 127.9, 127.7, 125.8, 125.6, 125.6, 123.4, 121.3, 121.2, 121.2, 33.5, 21.1. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693, found 379.1727.



1s

(E)-3-(2-((2-hydroxynaphthalen-1-yl)methyl)phenyl)-1-phenylprop-2-en-1-one (3)

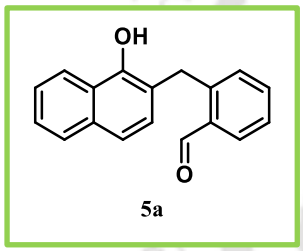
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale yellow solid, overall yield: 54% (1346 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.55 (d, *J* = 15.5 Hz, 1H), 8.11 – 8.04 (m, 2H), 7.75 – 7.65 (m, 3H), 7.63 – 7.58 (m, 1H), 7.56 – 7.46 (m, 4H), 7.27 – 7.17 (m, 4H), 7.14 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.46 (s, 1H), 4.55 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 191.3, 151.7, 143.5, 140.8, 138.3, 134.1, 133.9, 133.2, 130.7, 129.5, 129.0, 128.9, 128.8, 128.8, 128.6, 126.8, 126.7, 126.5, 123.4, 123.3, 123.2, 118.2, 117.5, 28.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{21}O_2$ 365.1536, found 365.1538.



3

2-((1-hydroxynaphthalen-2-yl)methyl)benzaldehyde (5a)

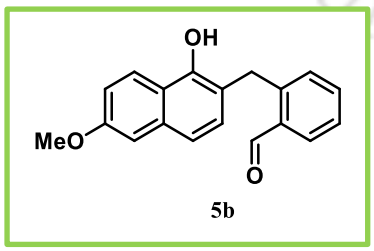
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as yellow solid, yield: 57% (1021 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 10.04 (s, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 13.0 Hz, 1H), 7.77 (dd, *J* = 6.9, 2.8 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.43 (m, 4H), 7.43 – 7.33 (m, 3H), 4.50 (s, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 196.8, 149.6, 141.9, 135.9, 134.5, 133.7, 133.1, 132.2, 128.6, 127.4, 127.1, 126.0, 125.5, 125.3, 122.4, 120.1, 118.9, 32.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{18}H_{15}O_2$ 263.1067; found 263.1067.



5a

2-((1-hydroxy-6-methoxynaphthalen-2-yl)methyl)benzaldehyde (5b)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as reddish semi solid, yield: 56% (1120 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.00 (s, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.89 (s, 1H), 7.65 (dt, *J* = 8.1, 2.3 Hz, 1H), 7.49 – 7.42 (m, 2H), 7.34 (td, *J* = 7.2, 6.7, 1.9 Hz, 1H), 7.23 (q, *J* = 8.3 Hz, 2H), 7.07 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.00 (d, *J* = 2.6 Hz, 1H), 4.40 (s, 2H), 3.84 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 196.7, 157.9, 149.9, 142.3, 135.8, 135.1, 134.5, 133.2, 132.1, 129.3, 127.1, 124.1, 120.8, 119.0, 117.7, 117.0, 105.6,

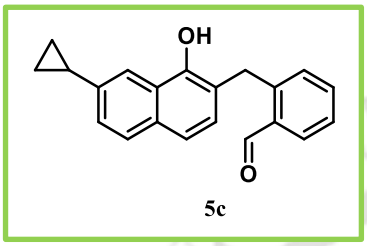


5b

55.3, 32.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{19}H_{17}O_3$ 293.1172; found 293.1150.

2-((7-cyclopropyl-1-hydroxynaphthalen-2-yl)methyl)benzaldehyde (5c)

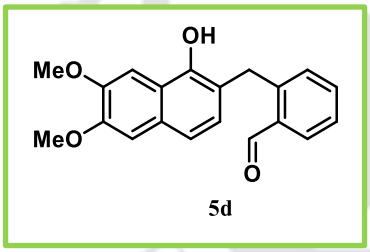
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as orange solid, yield 54% (1117 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 10.07 (s, 1H), 8.04 – 7.94 (m, 2H), 7.70 (m, 2H), 7.53 (p, *J* = 7.5, 6.8 Hz, 2H), 7.45 – 7.34 (m, 2H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.20 (ddd, *J* = 7.2, 4.9, 2.1 Hz, 1H), 4.50 (s, 2H), 2.10 (m, 1H), 1.05 (m, 2H), 0.87 (q, *J* = 5.8, 5.1 Hz, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 196.7, 149.0, 142.0, 141.0, 135.7, 134.4, 133.1, 132.1, 127.5, 127.4, 127.4, 127.0, 125.4, 124.8, 119.8, 119.0, 118.0, 32.8, 16.0, 9.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{19}O_2$ 303.1380; found 303.1380.



5c

2-((1-hydroxy-6,7-dimethoxynaphthalen-2-yl)methyl)benzaldehyde (5d)

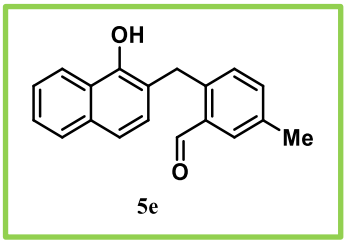
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow solid, yield: 46% (1014 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.06 (s, 1H), 8.01 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.48 (m, 3H), 7.41 (ddd, *J* = 8.2, 5.3, 3.3 Hz, 1H), 7.22 (d, *J* = 1.7 Hz, 2H), 7.03 (s, 1H), 4.45 (s, 2H), 3.99 (s, 3H), 3.96 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 197.1, 149.7, 149.1, 148.9, 142.3, 136.2, 134.6, 133.2, 132.4, 129.7, 127.1, 126.9, 120.7, 118.6, 117.7, 106.1, 101.5, 56.0, 55.9, 32.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{19}O_4$ 323.1278; found 323.1278.



5d

2-((1-hydroxynaphthalen-2-yl)methyl)-5-methyl benzaldehyde (5e)

The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as orange solid, yield: 51% (964 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.99 (s, 1H), 8.30 (t, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 17.0 Hz, 1H), 7.81 – 7.72 (m, 1H), 7.52 – 7.42 (m, 3H), 7.39 (m, 2H), 7.34 (dd, *J* = 15.5, 7.7 Hz, 2H), 4.44 (s, 2H), 2.37 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 197.1, 149.7, 138.9,

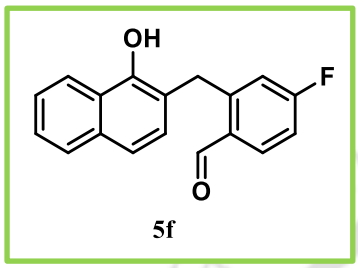


5e

137.0, 136.5, 135.4, 133.7, 133.0, 132.2, 128.6, 127.4, 126.0, 125.5, 125.3, 122.5, 120.0, 119.2, 32.4, 20.8. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{19}H_{17}O_2$ 277.1223; found 277.1225.

4-fluoro-2-((1-hydroxynaphthalen-2-yl)methyl) benzaldehyde (5f)

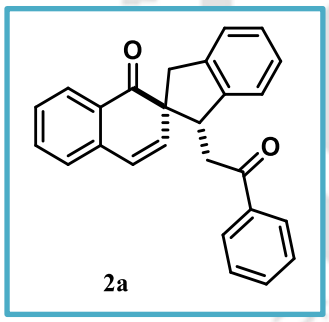
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as yellow solid, yield: 49% (939 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 10.05 (s, 1H), 8.26 – 8.21 (m, 1H), 7.80 – 7.74 (m, 2H), 7.49 – 7.42 (m, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 9.7, 2.5 Hz, 1H), 7.09 (td, *J* = 8.2, 2.5 Hz, 1H), 4.51 (s, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 194.8, 167.2, 165.1, 149.7, 146.0, 145.9, 138.6, 138.5, 133.9, 130.0, 130.0, 128.4, 127.6, 126.3, 125.6, 125.5, 122.3, 120.5, 119.5, 119.3, 118.2, 114.6, 114.4, 32.8. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{18}H_{14}FO_2$ 281.0972; found 281.0961.



5f

1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2a)

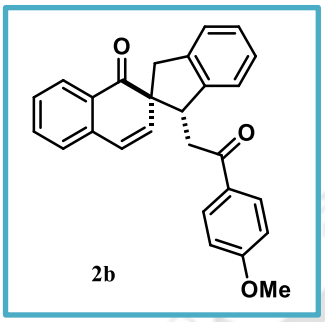
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as light pink semi solid, yield: 90% (33 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.50 (m, 2H), 7.36 (m, 3H), 7.21 (m, 3H), 7.12 (dd, *J* = 9.8, 6.4 Hz, 2H), 6.53 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 4.60 (t, *J* = 7.2 Hz, 1H), 3.71 (d, *J* = 15.4 Hz, 1H), 3.35 (dd, *J* = 17.5, 6.8 Hz, 1H), 3.17 (dd, *J* = 17.6, 7.5 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.3, 198.3, 143.4, 140.4, 137.4, 137.1, 135.8, 134.4, 133.1, 130.5, 128.6, 128.2, 128.0, 127.6, 127.5, 127.4, 127.2, 125.2, 124.8, 123.9, 60.7, 51.2, 45.5, 39.6. FT-IR (KBr): 1670, 1595, 1448, 1363, 1271, 1214, 1001, 798, 689, 563 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{21}O_2$ 365.1536; found 365.1570. **HPLC Analysis:** ee of major diasteromer= 56%, Chiralpak IA Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.3 min, t_{minor} = 15.1 min).



2a

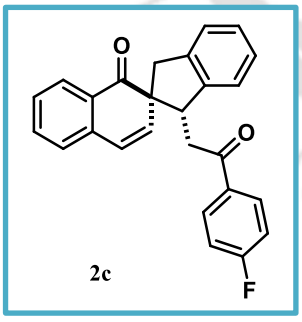
1-(2-(4-methoxyphenyl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2b)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as orange semi solid, yield: 55% (22 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 7.22 (dd, *J* = 5.7, 3.7 Hz, 3H), 7.13 (dd, *J* = 12.4, 6.4 Hz, 2H), 6.86 – 6.80 (m, 2H), 6.54 (d, *J* = 9.9 Hz, 1H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 3.83 (s, 3H), 3.71 (d, *J* = 15.4 Hz, 1H), 3.30 (dd, *J* = 17.2, 6.9 Hz, 1H), 3.11 (dd, *J* = 17.2, 7.4 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 196.9, 163.5, 143.6, 140.5, 137.5, 135.9, 134.4, 130.5, 130.4, 130.2, 128.2, 127.6, 127.5, 127.4, 127.3, 125.2, 124.8, 124.0, 113.7, 60.8, 55.6, 51.4, 45.5, 39.2. FT-IR (KBr): 1674, 1599, 1457, 1364, 1261, 1233, 1170, 1030, 800, 749, 563 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_3$ 395.1642; found 395.1655.



1-(2-(4-fluorophenyl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2c)

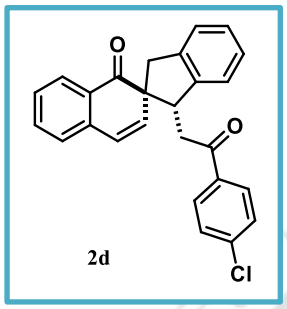
The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07) as yellow semi solid, yield: 85% (32 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.80 – 7.68 (m, 2H), 7.53 (m, 1H), 7.39 (m, 1H), 7.22 (dd, *J* = 5.6, 3.7 Hz, 3H), 7.16 – 7.07 (m, 2H), 7.06 – 6.97 (m, 2H), 6.53 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 3.70 (d, *J* = 15.4 Hz, 1H), 3.32 (dd, *J* = 17.4, 6.6 Hz, 1H), 3.16 (dd, *J* = 17.4, 7.8 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 201.3, 196.8, 167.1 (d, J_{C-F} = 253 Hz), 143.3, 140.4, 137.4, 135.7, 134.5, 133.5 (d, J_{C-F} = 3 Hz), 130.7 (d, J_{C-F} = 9 Hz), 130.4, 128.3, 127.7, 127.5, 127.4, 127.3, 125.3, 124.9, 123.8, 115.8 (d, J_{C-F} = 22 Hz), 60.7, 51.3, 45.6, 39.4. **FT-IR (KBr):** 1688, 1650, 1471, 1421, 1340, 1264,



1154, 985, 703, 556 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}FO_2$ 383.1442; found 383.1454.

1-(2-(4-chlorophenyl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2d)

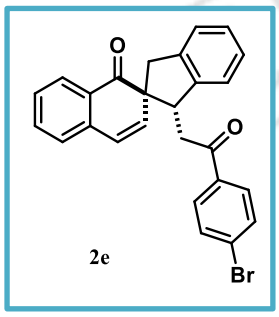
The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07)



as colourless crystalline solid, yield: 88% (35 mg). M.P. 125 – 128 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.23 (m, 3H), 7.16 – 7.07 (m, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.70 (d, *J* = 15.4 Hz, 1H), 3.31 (dd, *J* = 17.5, 6.5 Hz, 1H), 3.15 (dd, *J* = 17.5, 7.9 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 201.3, 197.2, 143.2, 140.4, 139.6, 137.4, 135.7, 135.3, 134.5, 130.4, 129.5, 128.9, 128.3, 127.7, 127.5, 127.4, 127.3, 125.3, 124.9, 123.8, 60.7, 51.3, 45.6, 39.5. **FT-IR (KBr):** 1673, 1589, 1482, 1400, 1309, 1265, 1091, 1029, 797, 701 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}ClO_2$ 399.1146, found 399.1150.

1-(2-(4-bromophenyl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2e)

The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07)

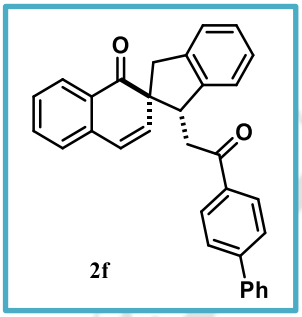


as light brown semi solid, yield: 90% (40 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (d, *J* = 7.7 Hz, 1H), 7.59 – 7.50 (m, 3H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.11 (dd, *J* = 13.2, 6.4 Hz, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 4.58 (t, *J* = 7.2 Hz, 1H), 3.70 (d, *J* = 15.4 Hz, 1H), 3.29 (dd, *J* = 17.4, 6.5 Hz, 1H), 3.15 (dd, *J* = 17.4, 7.8 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 201.3, 197.4, 143.2, 140.5, 137.4, 135.8, 135.7, 134.5, 131.9, 130.4, 129.6, 128.4, 128.3, 127.7, 127.5, 127.4, 127.3, 125.4, 124.9, 123.8, 60.7, 51.3, 45.6, 39.5. **FT-IR (KBr):** 1685, 1674, 1585, 1482, 1398, 1273, 1212, 1070, 984, 766, 702 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}BrO_2$ 443.0641, found 443.0634. **HPLC Analysis:** ee of major diasteromer= 46%,

Chiralpak IA Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.1 min, t_{minor} = 19.0 min).

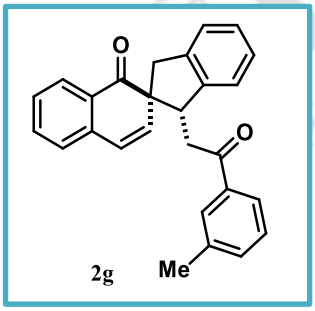
1-(2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2f)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as orange semi solid, yield: 72% (32 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.62 – 7.56 (m, 4H), 7.53 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 – 7.36 (m, 4H), 7.28 – 7.20 (m, 3H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.55 (d, *J* = 9.9 Hz, 1H), 6.13 (d, *J* = 9.9 Hz, 1H), 4.63 (t, *J* = 7.2 Hz, 1H), 3.72 (d, *J* = 15.4 Hz, 1H), 3.39 (dd, *J* = 17.5, 6.7 Hz, 1H), 3.21 (dd, *J* = 17.4, 7.6 Hz, 1H), 2.90 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 198.0, 145.8, 143.5, 140.5, 140.0, 137.5, 135.8, 135.7, 134.4, 130.5, 129.1, 128.7, 128.4, 128.3, 127.7, 127.5, 127.4, 127.4, 127.3, 127.3, 125.3, 124.9, 123.9, 60.7, 51.3, 45.6, 39.6. **FT-IR (KBr):** 1674, 1669, 1601, 1483, 1403, 1363, 1310, 1271, 1122, 1026, 798, 698 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{32}H_{25}O_2$ 441.1849, found 441.1848.



1-(2-oxo-2-(m-tolyl)ethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2g)

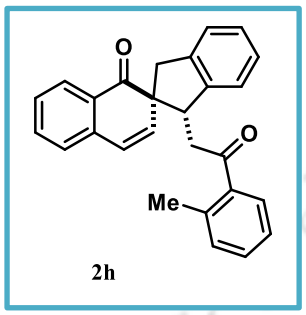
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as orange semi solid, yield: 65% (25 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.53 (m, 3H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.26 – 7.21 (m, 5H), 7.13 (ddd, *J* = 12.4, 7.8, 2.3 Hz, 2H), 6.54 (d, *J* = 9.9 Hz, 1H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.59 (t, *J* = 7.1 Hz, 1H), 3.71 (d, *J* = 15.4 Hz, 1H), 3.34 (dd, *J* = 17.4, 6.8 Hz, 1H), 3.16 (dd, *J* = 17.5, 7.5 Hz, 1H), 2.89 (d, *J* = 15.4 Hz, 1H), 2.33 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 198.6, 143.5, 140.5, 138.4, 137.5, 137.2, 135.8, 134.4, 133.9,130.5,128.6, 128.5, 128.3, 127.6, 127.5, 127.4, 127.3, 125.3, 125.2, 124.9, 124.0, 60.7, 51.3, 45.6, 39.7,



21.5. **FT-IR (KBr):** 1678, 1643, 1596, 1481, 1362, 1273, 1159, 1064, 923, 797, 690, 563 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693, found 379.1703.

1-(2-oxo-2-(o-tolyl)ethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2h)

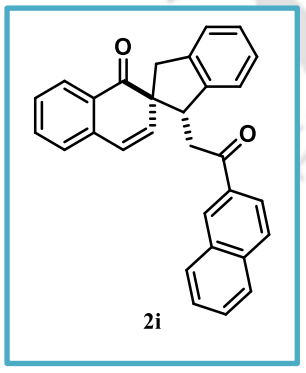
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as yellow semi solid, yield: 66% (25 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (d, *J* = 7.2 Hz, 1H), 7.54 (m, 2H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.19 – 7.11 (m, 4H), 6.56 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 4.55 (t, *J* = 7.1 Hz, 1H), 3.71 (d, *J* = 15.4 Hz, 1H), 3.36 (dd, *J* = 17.8, 6.3 Hz, 1H), 3.10 (dd, *J* = 17.9, 8.1 Hz, 1H), 2.89 (d, *J* = 15.5 Hz, 1H), 2.15 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.9, 201.4, 143.5, 140.5, 138.7, 137.5, 137.5, 135.9, 134.4, 132.2, 131.5, 130.6, 128.7, 128.3, 127.7, 127.5, 127.4, 125.7, 125.1, 124.9, 123.9, 60.6, 51.4, 45.9, 42.6, 21.2. **FT-IR (KBr):** 1736, 1675, 1596, 1482, 1360, 1273, 1194, 977, 800, 749, 685, 566 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693, found 379.1702.



2h

1-(2-(naphthalen-2-yl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2i)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pink semi solid, yield: 68% (28 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.25 (s, 1H), 8.21 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.80 (m, 1H), 7.80 – 7.73 (m, 2H), 7.57 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 1H), 7.51 (m, 2H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.24 (m, 3H), 7.20 – 7.15 (m, 1H), 7.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 4.67 (t, *J* = 7.1 Hz, 1H), 3.73 (d, *J* = 15.5 Hz, 1H), 3.47 (dd, *J* = 17.2, 6.6 Hz, 1H), 3.34 (dd, *J* = 17.3, 7.7 Hz, 1H), 2.91 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 198.4, 143.5, 140.5, 137.5, 135.8, 135.7, 134.4, 134.4, 132.6, 130.5, 129.7, 129.7, 128.6, 128.5, 128.3, 127.9, 127.7, 127.5, 127.4, 127.3, 126.9, 125.3, 124.9, 123.9, 60.8, 51.6, 45.6, 39.7. **FT-IR (KBr):** 1674, 1595, 1469, 1368, 1264, 1182,

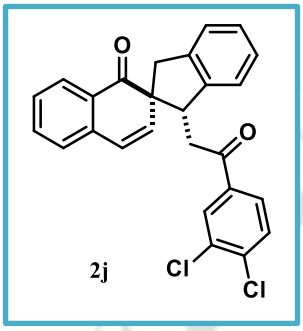


2i

895, 860, 797, 732, 703, 556 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{30}H_{23}O_2$ 415.1693, found 415.1697.

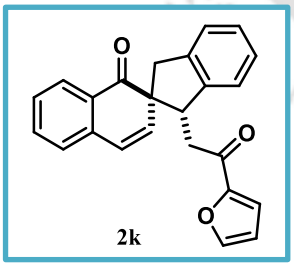
1-(2-(3,4-dichlorophenyl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2j)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale-yellow semi solid, yield: 72% (31 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.45 – 7.37 (m, 2H), 7.24 (dt, *J* = 9.4, 4.0 Hz, 3H), 7.15 – 7.07 (m, 2H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 4.60 – 4.54 (m, 1H), 3.70 (d, *J* = 15.4 Hz, 1H), 3.28 (dd, *J* = 17.3, 6.2 Hz, 1H), 3.16 (dd, *J* = 17.4, 8.2 Hz, 1H), 2.89 (d, *J* = 15.5 Hz, 1H**). ^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.2, 196.3, 142.9, 140.4, 137.8, 137.3, 136.6, 135.6, 134.6, 133.3, 130.8, 130.4, 130.1, 128.5, 127.9, 127.5, 127.5, 127.3, 127.1, 125.5, 125.0, 123.7, 60.6, 51.4, 45.6, 39.5. **FT-IR (KBr):** 1671, 1643, 1594, 1481, 1389, 1272, 1198, 1029, 878, 798, 736, 535 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{19}Cl_2O_2$ 433.0757, found 433.0749.



1-(2-(furan-2-yl)-2-oxoethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2k)

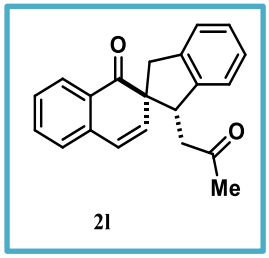
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as orange semi solid, yield: 62% (22 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 (d, *J* = 1.7 Hz, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 7.22 (dt, *J* = 6.0, 3.8 Hz, 3H), 7.17 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.01 (d, *J* = 3.6 Hz, 1H), 6.58 (d, *J* = 9.9 Hz, 1H), 6.44 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.12 (d, *J* = 9.9 Hz, 1H), 4.55 (t, *J* = 7.2 Hz, 1H), 3.69 (d, *J* = 15.3 Hz, 1H), 3.22 (dd, *J* = 17.0, 7.2 Hz, 1H), 3.00 (dd, *J* = 17.1, 7.1 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.2, 187.5, 152.8, 146.3, 143.4, 140.4, 137.6, 135.7, 134.5, 130.4, 128.3, 127.6, 127.5, 127.4, 127.3, 125.4, 124.8, 124.0, 117.0, 112.4, 61.0, 50.7, 45.4, 39.3. **FT-IR (KBr):** 1672, 1595, 1568, 1467, 1396, 1272,



1156, 1021, 883, 797, 735, 594 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{24}H_{19}O_3$ 355.1329, found 355.1337.

1-(2-oxopropyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2l)

The product was purified by flash column chromatography (hexane/ethyl acetate = 92:08)

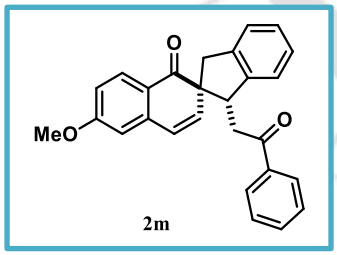


2l

as pale-yellow semi solid, yield: 60% (18 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.5, 1.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.08 – 7.01 (m, 1H), 6.62 (d, *J* = 9.9 Hz, 1H), 6.06 (d, *J* = 9.9 Hz, 1H), 4.40 (t, *J* = 7.2 Hz, 1H), 3.65 (d, *J* = 15.4 Hz, 1H), 2.88 (d, *J* = 7.5 Hz, 1H), 2.85 (d, *J* = 5.8 Hz, 1H), 2.59 (dd, *J* = 17.7, 7.6 Hz, 1H), 2.03 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 206.9, 201.3, 143.2, 140.4, 137.5, 135.7, 134.6, 130.4, 128.4, 127.7, 127.6, 127.4, 127.3, 125.1, 124.9, 123.7, 60.7, 50.5, 45.7, 44.5, 30.1. **FT-IR (KBr):** 1693, 1651, 1549, 1470, 1387, 1264, 1195, 895, 731, 703, 541, 511 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{19}O_2$ 303.1380, found 303.1398. **HPLC Analysis:** ee of major diasteromer= 36%, Chiralpak IA Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 7.6 min, t_{minor} = 13.4 min).

6'-methoxy-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2m)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

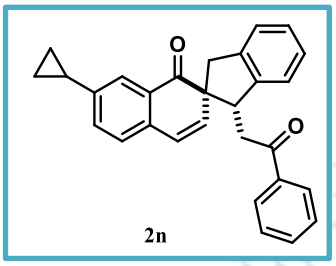


2m

as yellow semi solid, yield: 70% (28 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.86 – 7.77 (m, 3H), 7.53 – 7.47 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.25 (s, 1H), 7.20 (m, 2H), 7.13 – 7.09 (m, 1H), 6.81 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.53 (d, *J* = 9.7 Hz, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 4.07 (t, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 3.65 (d, *J* = 16.0 Hz, 1H), 3.52 (dd, *J* = 18.0, 7.6 Hz, 1H), 3.15 (dd, *J* = 18.0, 5.9 Hz, 1H), 2.98 (d, *J* = 16.0 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 199.8, 198.6, 164.8, 144.6, 141.1, 140.4, 140.1, 137.3, 133.1, 129.4, 128.7, 128.2, 127.4, 127.2, 125.0, 124.3, 124.1, 123.7, 114.3, 111.3, 58.5, 55.7, 51.0, 42.6, 41.2. **FT-IR (KBr):** 1683, 1661, 1591, 1490, 1448, 1331, 1262, 1196, 1027, 896, 741, 691 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_3$ 395.1642, found 395.1649.

7'-cyclopropyl-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2n)

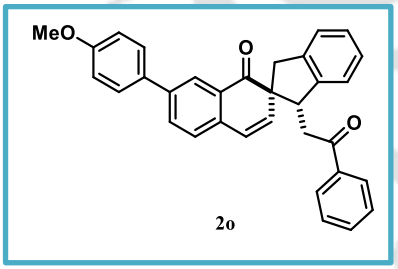
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)



as pale-yellow semi solid, yield: 72% (29 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (s, 1H), 7.77 (d, *J* = 7.7 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.24 (m, 3H), 7.15 – 7.11 (m, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.53 (d, *J* = 9.8 Hz, 1H), 6.06 (d, *J* = 9.8 Hz, 1H), 4.62 (t, *J* = 7.1 Hz, 1H), 3.72 (d, *J* = 15.4 Hz, 1H), 3.37 (dd, *J* = 17.6, 7.0 Hz, 1H), 3.18 (dd, *J* = 17.6, 7.2 Hz, 1H), 2.89 (d, *J* = 15.4 Hz, 1H), 1.99 (tt, *J* = 9.0, 5.2 Hz, 1H), 1.04 (m, 2H), 0.82 (dd, *J* = 9.5, 5.3 Hz, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 201.6, 198.3, 144.6, 143.5, 140.5, 137.0, 135.0, 134.5, 133.1, 132.1, 130.3, 128.6, 128.1, 127.5, 127.4, 127.3, 125.0, 124.8, 123.9, 123.8, 60.7, 51.1, 45.5, 39.6, 15.6, 9.8, 9.7. **FT-IR (KBr):** 1680, 1662, 1580, 1482, 1441, 1330, 1268, 1191, 1023, 890, 745, 690 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{29}H_{25}O_2$ 405.1849, found 405.1850.

7'-(4-methoxyphenyl)-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2o)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

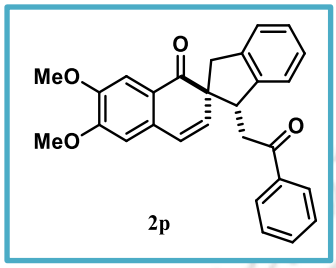


as purple semi solid, yield: 37% (17 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 2.1 Hz, 1H), 7.75 (td, *J* = 6.5, 3.3 Hz, 3H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.47 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.18 (m, 4H), 7.15 – 7.10 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 9.9 Hz, 1H), 6.12 (d, *J* = 9.8 Hz, 1H), 4.63 (t, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.74 (d, *J* = 15.4 Hz, 1H), 3.38 (dd, *J* = 17.5, 6.8 Hz, 1H), 3.20 (dd, *J* = 17.6, 7.4 Hz, 1H), 2.92 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 201.5, 198.4, 159.7, 143.5, 140.7, 140.5, 137.0, 135.8, 135.4, 133.1, 132.5, 132.3, 130.7, 128.6, 128.2, 128.1, 128.0, 127.6, 127.4, 125.1, 124.9, 124.9, 123.9, 114.5, 60.8, 55.5, 51.2, 45.6, 39.6. **FT-IR (KBr):** 1682, 1663,

1589, 1494, 1442, 1335, 1268, 1192, 1029, 899, 748, 698 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{33}H_{27}O_3$ 471.1955, found 471.1956.

6',7'-dimethoxy-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2p)

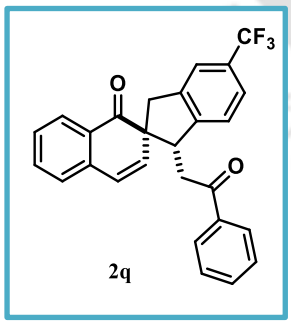
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as red semi solid, yield: 42% (18 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.67 (s, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 3.9 Hz, 3H), 7.13 – 7.08 (m, 1H), 6.57 (s, 1H), 6.47 (d, *J* = 9.8 Hz, 1H), 6.07 (d, *J* = 9.8 Hz, 1H), 4.60 (t, *J* = 7.1 Hz, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.71 (d, *J* = 15.3 Hz, 1H), 3.31 (dd, *J* = 17.4, 6.9 Hz, 1H), 3.15 (dd, *J* = 17.4, 7.2 Hz, 1H), 2.86 (d, *J* = 15.3 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 200.2, 198.4, 154.4, 149.2, 143.7, 140.7, 137.2, 135.2, 133.1, 132.9, 128.6, 128.2, 127.6, 127.4, 124.9, 124.7, 124.3, 123.9, 109.2, 108.9, 60.4, 56.4, 56.3, 51.5, 45.4, 39.5. **FT-IR (KBr):** 1683, 1659, 1591, 1509, 1457, 1384, 1278, 1157, 1060, 751, 692 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{28}H_{25}O_4$ 425.1747, found 425.1759.



2p

5-trifluoromethyl-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2q)

The product was purified by flash column chromatography (hexane/ethyl acetate = 92:08) as pale-yellow semi solid, yield: 71% (31 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 6.9 Hz, 1H), 7.75 (d, *J* = 7.1 Hz, 2H), 7.56 (td, *J* = 7.5, 1.5 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.45 – 7.34 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.58 (d, *J* = 9.9 Hz, 1H), 6.07 (d, *J* = 9.8 Hz, 1H), 4.64 (t, *J* = 7.4 Hz, 1H), 3.74 (d, *J* = 15.7 Hz, 1H), 3.36 (dd, *J* = 17.7, 7.1 Hz, 1H), 3.20 (dd, *J* = 17.7, 7.2 Hz, 1H), 2.95 (d, *J* = 15.7 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 200.8, 197.9, 147.7, 141.5, 137.3, 136.8, 134.8, 134.7, 133.4, 130.2, 130.2, 128.7, 128.5, 128.0, 127.7, 127.3, 125.7, 125.4, 124.7, 124.7, 124.7, 124.6, 124.4, 121.8, 121.8, 121.7, 121.7, 60.6, 51.0, 45.1, 39.3. **FT-IR (KBr):** 1673, 1649, 1592, 1489, 1362, 1271, 1239,

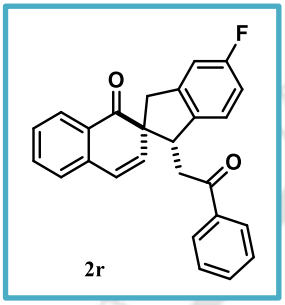


2q

1006, 924, 790, 758, 683 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{20}F_3O_2$ 433.1410, found 433.1395.

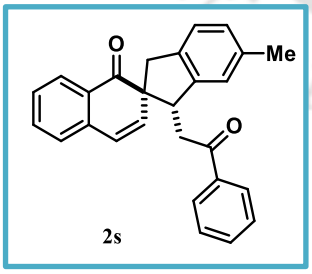
5-fluoro-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2r)

The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07) as pale-yellow semi solid, yield: 70% (27 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.77 – 7.70 (m, 2H), 7.57 – 7.46 (m, 2H), 7.43 – 7.34 (m, 3H), 7.19 – 7.13 (m, 1H), 7.04 (dd, *J* = 8.0, 5.1 Hz, 1H), 6.91 (t, *J* = 8.7 Hz, 2H), 6.56 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 4.52 (t, *J* = 7.3 Hz, 1H), 3.69 (d, *J* = 15.7 Hz, 1H), 3.30 (dd, *J* = 17.6, 7.0 Hz, 1H), 3.16 (dd, *J* = 17.6, 7.2 Hz, 1H), 2.86 (d, *J* = 15.7 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.0, 198.2, 163.8 (d, J_{C-F} = 242.5 Hz), 142.8 (d, J_{C-F} = 8.7 Hz), 138.9 (d, J_{C-F} = 2.5 Hz), 137.4, 137.0, 135.3, 134.6, 133.3, 130.4, 128.7, 128.4, 128.1, 127.6, 127.4, 125.5 (d, J_{C-F} = 8.7 Hz), 114.3 (d, J_{C-F} = 22.5 Hz), 112.2 (d, J_{C-F} = 22.5 Hz), 60.9, 50.5, 45.2, 45.2, 39.7. **FT-IR (KBr):** 1682, 1644, 1597, 1486, 1365, 1272, 1234, 1002, 942, 799, 750, 689 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{20}FO_2$ 383.1442, found 383.1447.



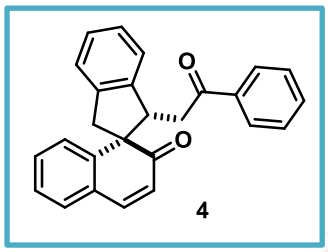
6-methyl-1-(2-oxo-2-phenylethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2s)

The product was purified by flash column chromatography (hexane/ethyl acetate = 94:06) as yellow semi solid, yield: 65% (25 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.17 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.41 – 7.32 (m, 3H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.11 (d, *J* = 9.9 Hz, 1H), 4.57 (t, *J* = 7.2 Hz, 1H), 3.65 (d, *J* = 15.3 Hz, 1H), 3.34 (dd, *J* = 17.6, 6.6 Hz, 1H), 3.17 (dd, *J* = 17.6, 7.6 Hz, 1H), 2.84 (d, *J* = 15.3 Hz, 1H), 2.33 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 198.4, 143.6, 137.5, 137.4, 137.1, 137.0, 136.0, 134.4, 133.1, 130.5, 128.6, 128.4, 128.2, 128.1, 127.5, 127.3, 125.2, 124.6, 60.9, 51.1, 45.2, 39.7, 21.6. **FT-IR (KBr):** 1672,



1643, 1596, 1448, 1363, 1272, 1180, 1001, 885, 799, 688, 570 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{23}O_2$ 379.1693, found 379.1702.

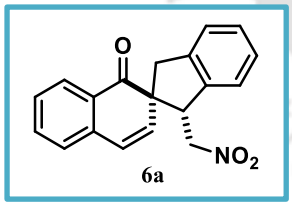
1-(2-oxo-2-phenylethyl)-1,3-dihydro-2'H-spiro[indene-2,1'-naphthalen]-2'-one (4)



The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as colorless crystalline solid, yield: 55% (20 mg), M.P. 127 – 130 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.51 – 7.43 (m, 1H), 7.35 – 7.24 (m, 6H), 7.19 – 7.11 (m, 3H), 7.09 – 7.01 (m, 1H), 7.01 – 6.92 (m, 1H), 6.35 (d, *J* = 9.8 Hz, 1H), 4.67 (t, *J* = 7.1 Hz, 1H), 4.03 (d, *J* = 16.2 Hz, 1H), 3.23 (d, *J* = 16.2 Hz, 1H), 3.01 (dd, *J* = 7.1, 3.8 Hz, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 203.4, 198.3, 144.6, 144.5, 143.8, 142.5, 136.9, 133.1, 129.8, 129.8, 128.6, 127.9, 127.7, 127.6, 127.4, 126.8, 124.2, 123.8, 61.9, 54.5, 47.3, 39.8. **FT-IR (KBr):** 1671, 1597, 1448, 1363, 1271, 1215, 1003, 798, 690, 565 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{21}O_2$ 365.1536, found 365.1537. **HPLC Analysis:** ee of major diastereomer= 72%, Chiralpak IA Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.3 min, t_{minor} = 14.5 min).

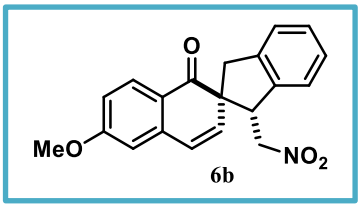
1-(nitromethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (6a)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as colourless crystalline solid, yield: 90% (27 mg), M.P. 102 – 105 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.60 (m, 1H), 7.41 (m, 1H), 7.33 – 7.20 (m, 4H), 7.08 (dd, *J* = 6.8, 1.8 Hz, 1H), 6.68 (d, *J* = 9.8 Hz, 1H), 6.06 (d, *J* = 9.9 Hz, 1H), 4.77 – 4.67 (m, 2H), 4.50 – 4.41 (m, 1H), 3.63 (d, *J* = 15.5 Hz, 1H), 2.92 (d, *J* = 15.5 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 200.1, 140.2, 139.1, 137.2, 135.0, 133.2, 129.7, 128.7, 128.6, 127.8, 127.7, 127.3, 126.5, 125.2, 123.5, 75.1, 59.5, 52.2, 45.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{19}H_{16}NO_3$ 306.1125, found 306.1125.



6'-methoxy-1-(nitromethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (6b)

The product was purified by flash column chromatography (hexane/ethyl acetate = 85:15)

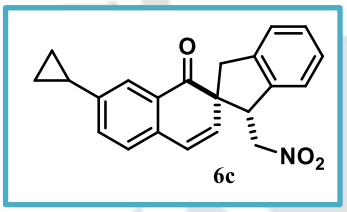


6b

as light-yellow semi solid, yield: 92% (31 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.7 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.95 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.74 (d, *J* = 2.5 Hz, 1H), 6.66 (d, *J* = 9.9 Hz, 1H), 6.11 (d, *J* = 9.8 Hz, 1H), 4.78 – 4.71 (m, 2H), 4.50 – 4.43 (m, 1H), 3.92 (s, 3H), 3.68 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.93 (d, *J* = 15.5 Hz, 1H).**^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 198.5, 165.2, 140.5, 139.6, 139.4, 134.5, 130.2, 128.6, 127.8, 126.6, 125.3, 123.6, 123.5, 114.8, 112.1, 75.3, 59.5, 55.8, 52.3, 45.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{18}NO_4$ 336.1230, found 336.1231.

7'-cyclopropyl-1-(nitromethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (6c)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

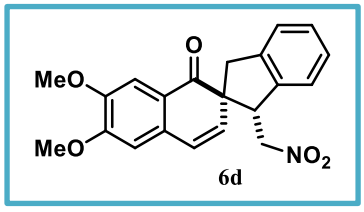


6c

as light-yellow semi solid, yield: 81% (28 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.82 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.31 – 7.21 (m, 3H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 6.7 Hz, 1H), 6.65 (d, *J* = 9.8 Hz, 1H), 5.98 (d, *J* = 9.9 Hz, 1H), 4.78 – 4.67 (m, 2H), 4.51 – 4.39 (m, 1H), 3.63 (d, *J* = 15.4 Hz, 1H), 2.90 (d, *J* = 15.5 Hz, 1H), 1.96 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.02 (m, 2H), 0.79 (m, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 200.5, 145.3, 140.5, 139.4, 134.8, 132.8, 132.0, 129.7, 128.6, 127.9, 127.8, 126.4, 125.3, 124.0, 123.6, 75.3, 59.7, 52.3, 45.8, 15.7, 9.9, 9.8. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{22}H_{20}NO_3$ 346.1438, found 346.1444.

6',7'-dimethoxy-1-(nitromethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (6d)

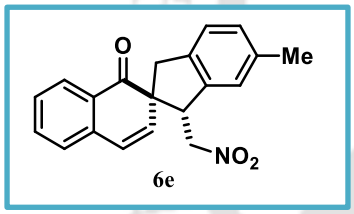
The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20) as yellow semi solid, yield: 72% (26 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.65 (s, 1H), 7.32 – 7.25 (m, 3H), 7.11 (d, *J* = 7.0 Hz, 1H), 6.71 (s, 1H), 6.62 (d, *J* = 9.8 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 4.77 – 4.69 (m, 2H), 4.48 – 4.40 (m, 1H), 3.98 (s, 6H), 3.66 (d, *J* = 15.4 Hz, 1H), 2.90 (d, *J* = 15.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 199.0, 155.0, 149.6, 140.6, 139.5, 132.8, 132.7, 128.6, 127.8, 126.0, 125.4, 123.6, 123.6, 109.5, 108.9, 75.3, 59.2, 56.4, 56.4, 52.6, 45.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}NO_5$ 366.1336, found 366.1337.



6d

6-methyl-1-(nitromethyl)-1,3-dihydro-1'H-spiro [indene-2,2'-naphthalen]-1'-one (6e)

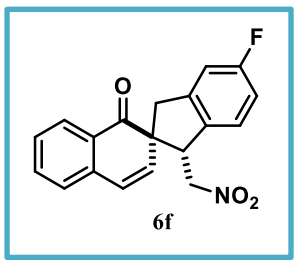
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as light-yellow semi solid, yield: 88% (28 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.11 (q, *J* = 7.8 Hz, 2H), 6.90 (s, 1H), 6.68 (d, *J* = 9.9 Hz, 1H), 6.08 (d, *J* = 9.9 Hz, 1H), 4.77 – 4.67 (m, 2H), 4.45 (dd, *J* = 12.2, 6.1 Hz, 1H), 3.59 (d, *J* = 15.3 Hz, 1H), 2.88 (d, *J* = 15.4 Hz, 1H), 2.35 (s, 3H).**^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 200.3, 139.4, 137.6, 137.3, 137.3, 135.1, 133.5, 129.9, 129.4, 128.8, 127.9, 127.5, 126.5, 125.1, 124.2, 75.3, 59.8, 52.2, 45.4, 21.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{18}NO_3$ 320.1281, found 320.1281.



6e

5-fluoro-1-(nitromethyl)-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (6f)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as light pink semi solid, yield: 85% (27 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.62 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 9.0, 5.0 Hz, 1H), 6.95 (dd, *J* = 8.9, 6.5 Hz, 2H), 6.70 (d, *J* = 9.9 Hz, 1H), 6.06 (d, *J* = 10.0 Hz, 1H), 4.73 – 4.60 (m, 2H), 4.44 (dd, *J* = 13.5, 7.1 Hz, 1H), 3.63 (d, *J* = 15.8 Hz, 1H), 2.90 (d, *J* = 15.7 Hz, 1H).**^{13}C{H} NMR (125 MHz, $CDCl_3$)**

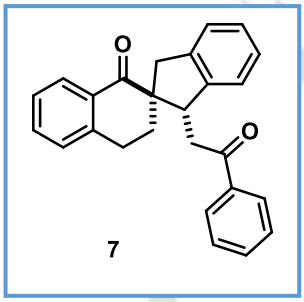


6f

δ 199.8, 164.3 (d, J_{C-F} = 245 Hz), 142.8 (d, J_{C-F} = 8.8 Hz), 137.2, 135.2, 134.8 (d, J_{C-F} = 2.5 Hz), 132.8, 129.7, 128.9, 128.0, 127.5, 126.9, 124.9 (d, J_{C-F} = 8.8 Hz), 114.8 (d, J_{C-F} = 22.5 Hz), 112.8 (d, J_{C-F} = 22.5 Hz), 75.2, 59.8, 51.5, 45.3, 45.3. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{19}H_{15}FNO_3$ 324.1030, found 324.1030.

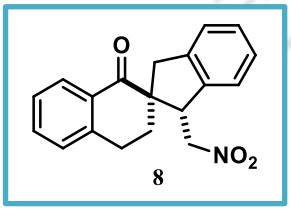
1-(2-oxo-2-phenylethyl)-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (7)

The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05) as colourless liquid, yield: 99% (36.3 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.08 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.98 (dd, *J* = 7.4, 1.7 Hz, 2H), 7.59 – 7.51 (m, 1H), 7.51 – 7.41 (m, 3H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.20 (m, 1H), 7.15 (d, *J* = 2.0 Hz, 4H), 4.85 – 4.73 (m, 1H), 3.31 (dd, *J* = 16.7, 7.9 Hz, 1H), 3.26 – 3.13 (m, 3H), 3.01 (d, *J* = 15.6 Hz, 1H), 2.92 (ddd, *J* = 17.3, 4.9, 3.1 Hz, 1H), 2.19 (td, *J* = 12.8, 5.0 Hz, 1H), 1.97 (ddd, *J* = 13.4, 4.8, 3.0 Hz, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 199.9, 199.2, 145.3, 142.9, 139.5, 137.2, 133.4, 133.3, 132.4, 128.8, 128.8, 128.5, 128.4, 127.1, 127.1, 127.0, 124.7, 124.2, 57.6, 45.2, 39.7, 39.5, 27.6, 26.1. **FT-IR (KBr):** 1672, 1635, 1595, 1448, 1363, 1271, 1214, 1007, 793, 699, 560 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{23}O_2$ 367.1693, found 367.1697.



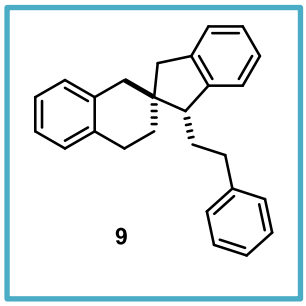
1-(nitromethyl)-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (8)

The product was purified by flash column chromatography (hexane/ethyl acetate = 92:08) as colourless semi solid, yield: 93% (29 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.52 (m, 1H), 7.37 – 7.30 (m, 1H), 7.30 – 7.20 (m, 4H), 7.17 (d, *J* = 6.4 Hz, 1H), 4.58 (m, 2H), 4.08 (t, *J* = 7.0 Hz, 1H), 3.78 (d, *J* = 16.2 Hz, 1H), 3.25 (ddd, *J* = 17.4, 8.9, 4.7 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.89 (d, *J* = 16.3 Hz, 1H), 2.32 (ddd, *J* = 13.8, 6.5, 4.7 Hz, 1H), 2.19 (ddd, *J* = 13.7, 8.9, 4.7 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 198.9, 143.4, 140.6, 140.3, 134.2, 131.9, 129.0, 128.5, 128.3, 127.6, 127.3, 125.5, 124.5, 77.1, 56.8, 48.8, 41.7, 34.0, 26.1. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{19}H_{18}NO_3$ 308.1281, found 308.1255.



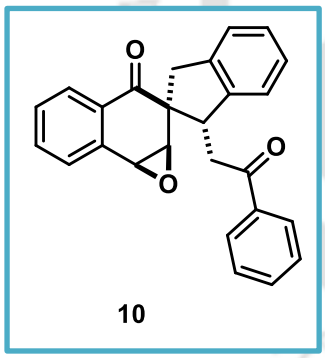
1-phenethyl-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-naphthalene] (9)

The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02) as colorless liquid, yield: 99% (33.5 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.22 (m, 3H), 7.17 (q, *J* = 3.9, 3.2 Hz, 6H), 7.12 – 7.03 (m, 3H), 6.92 (d, *J* = 7.4 Hz, 1H), 2.96 – 2.87 (m, 3H), 2.84 – 2.78 (m, 2H), 2.72 (d, *J* = 16.5 Hz, 1H), 2.61 (d, *J* = 15.7 Hz, 3H), 2.03 (ddd, *J* = 12.1, 7.5, 5.7 Hz, 1H), 1.88 (dq, *J* = 15.6, 6.2 Hz, 2H), 1.74 – 1.65 (m, 1H). **^{13}C{H} NMR (100 MHz, $CDCl_3$)** δ 147.3, 142.9, 142.3, 136.3, 136.2, 129.9, 128.9, 128.6, 126.6, 126.0, 126.0, 125.8, 125.8, 125.6, 125.4, 53.9, 46.0, 42.0, 41.7, 34.5, 32.5, 28.8, 27.3. **FT-IR (KBr):** 1495, 1476, 1453, 1264, 1181, 1029, 808, 738, 699, 545, 497 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{27}$ 339.2107, found 339.2104.

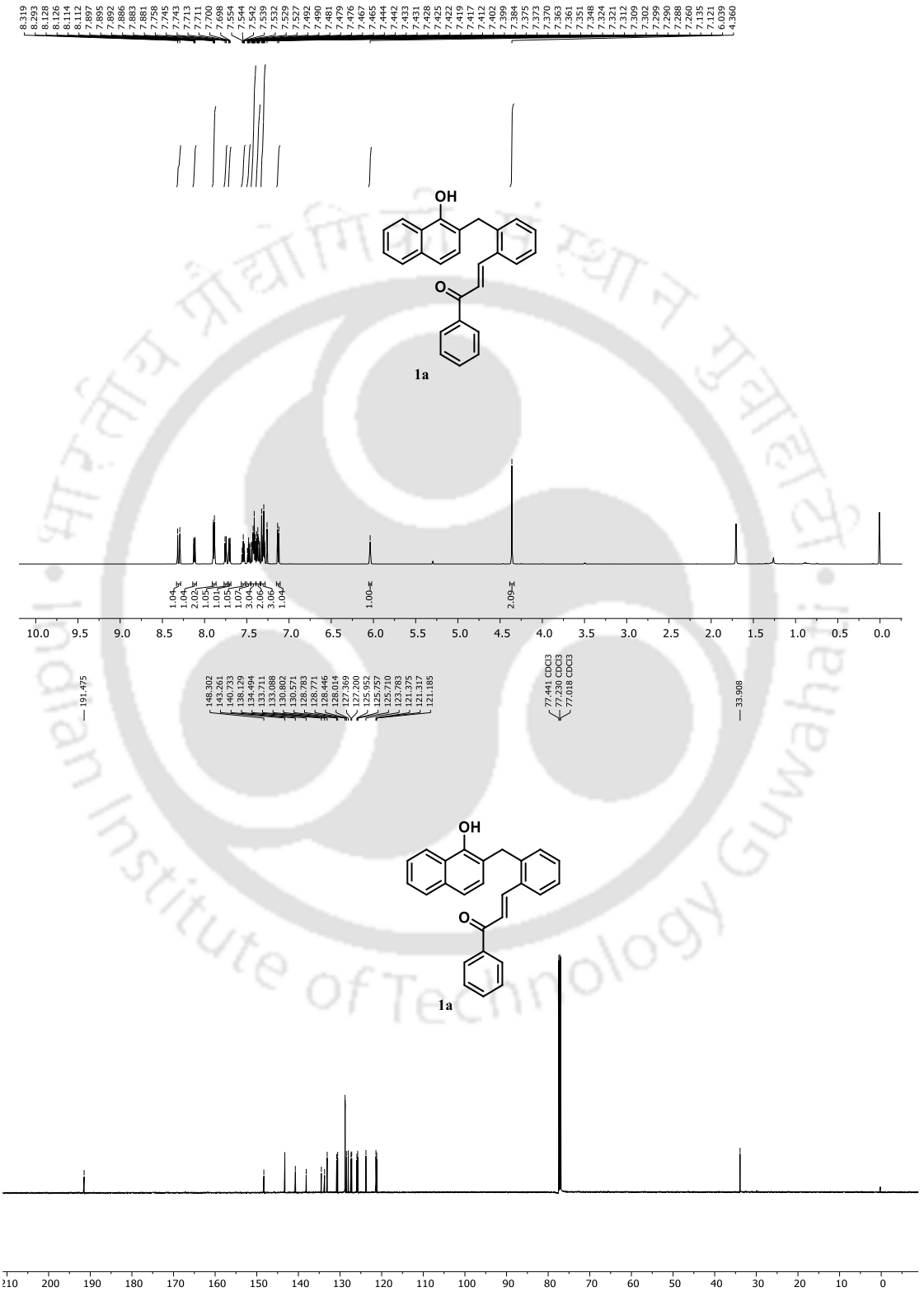


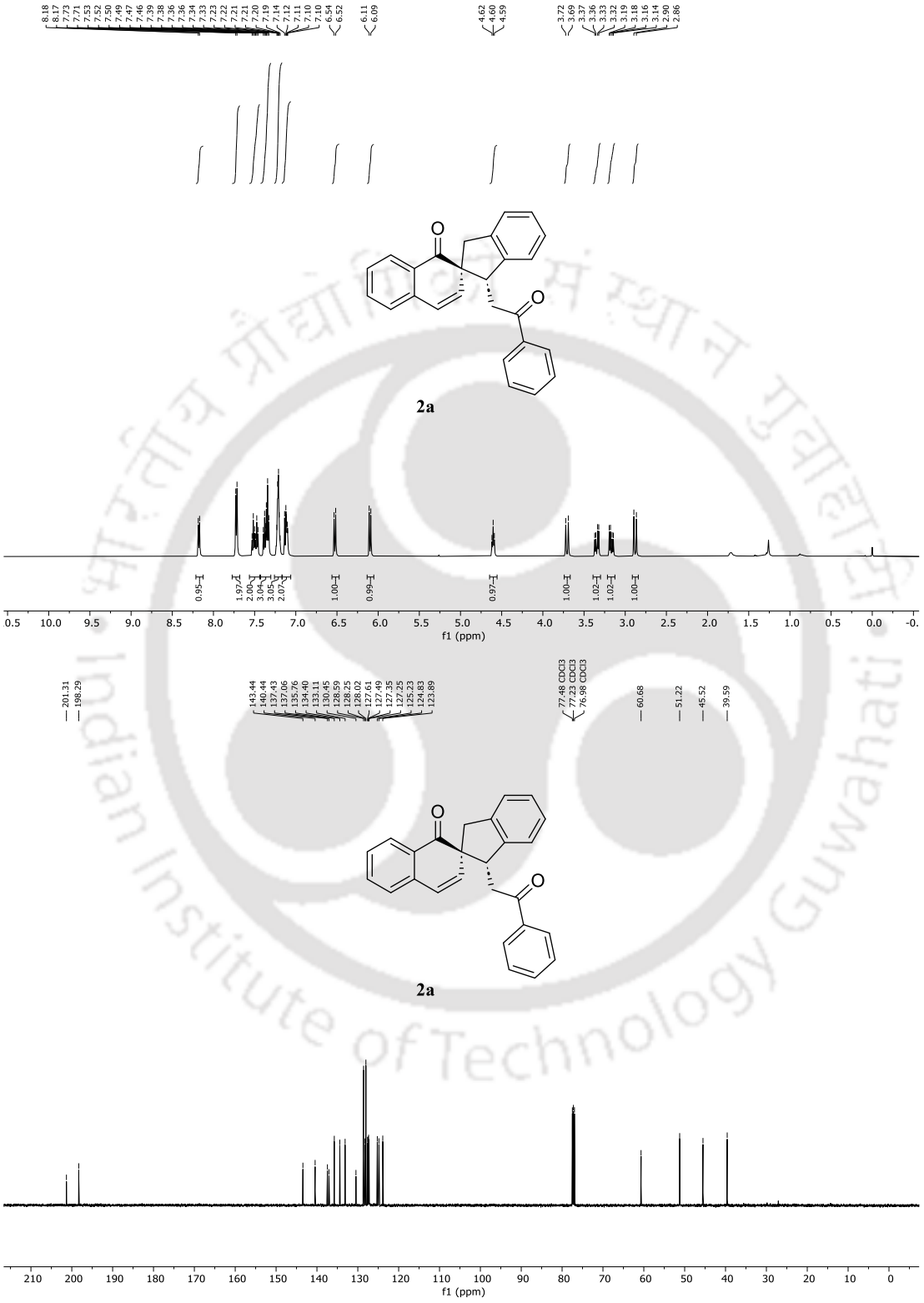
1-(2-oxo-2-phenylethyl)-1,1a',3,7b'-tetrahydro-3'H-spiro[indene-2,2'-naphtho[1,2-b] oxiren]-3'-one (10)

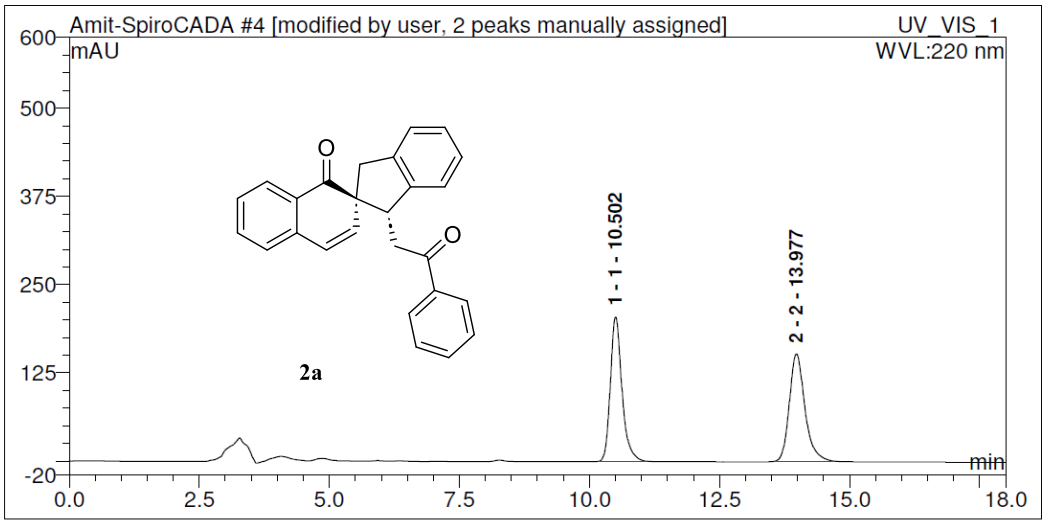
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as colorless gummy solid, yield: 70% (26.6 mg). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 2.0 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.59 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.27 – 7.23 (m, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 4.06 (d, *J* = 3.8 Hz, 1H), 3.76 (d, *J* = 3.8 Hz, 1H), 3.37 – 3.20 (m, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 197.5, 197.0, 142.2, 141.2, 138.3, 136.6, 133.6, 133.5, 132.2, 129.9, 129.8, 129.0, 128.8, 128.1, 127.9, 127.4, 125.1, 123.6, 58.6, 58.0, 54.1, 48.7, 40.7, 38.8. **FT-IR (KBr):** 1683, 1599, 1449, 1369, 1274, 1228, 988, 764, 750, 692, 540 cm^{-1}. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{26}H_{21}O_3$ 381.1485, found 381.1494.



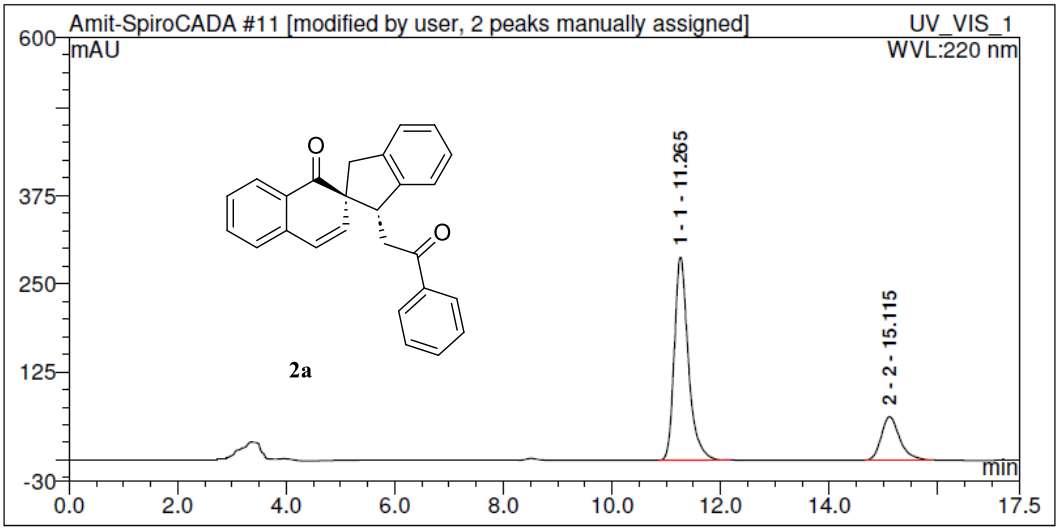
4.9 NMR and HPLC spectra



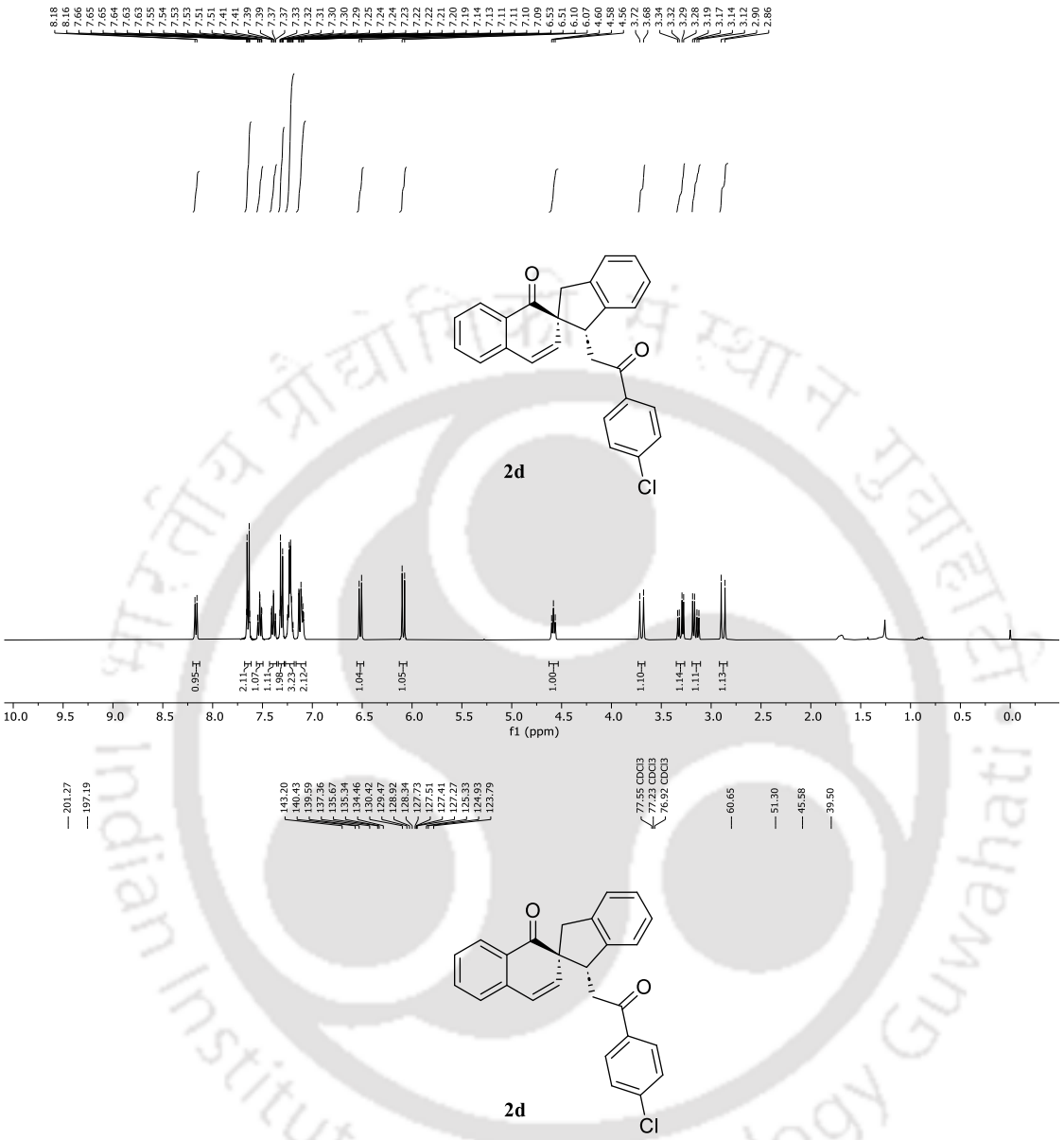


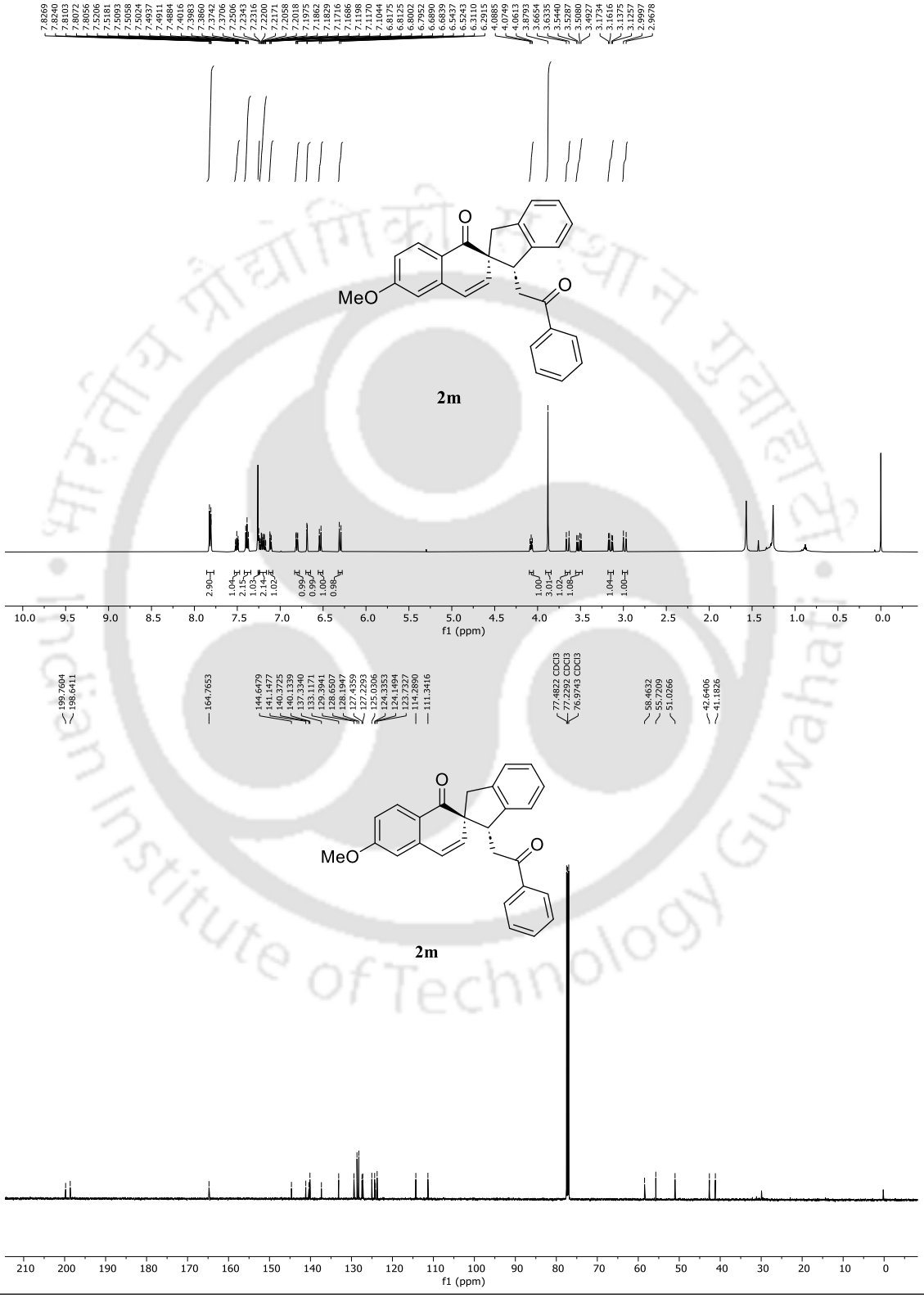


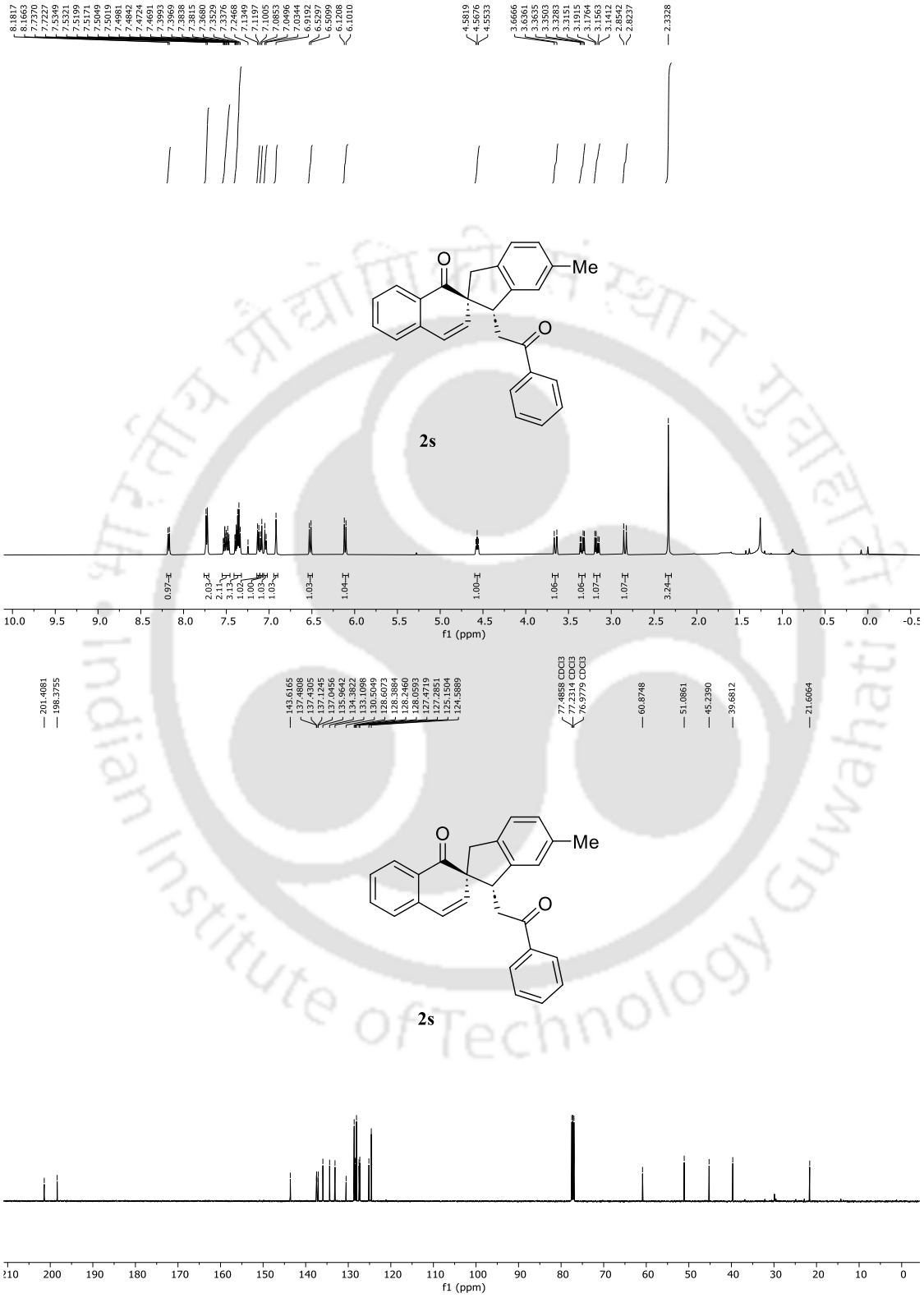
Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 1	10.50	52.98567	50.15360289	204.4312	n.a.
2 2	13.98	52.661	49.84639711	152.143	n.a.

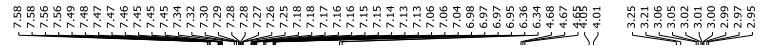


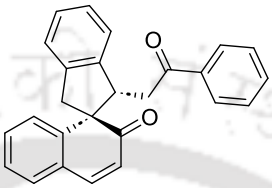
Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 1	11.27	86.2699	77.95245169	287.8667	n.a.
2 2	15.12	24.400	22.04754831	61.633	n.a.



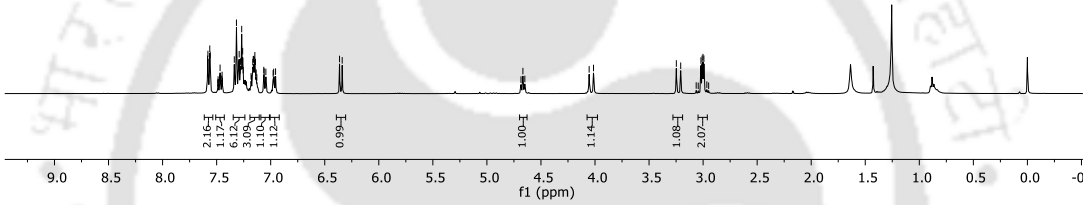


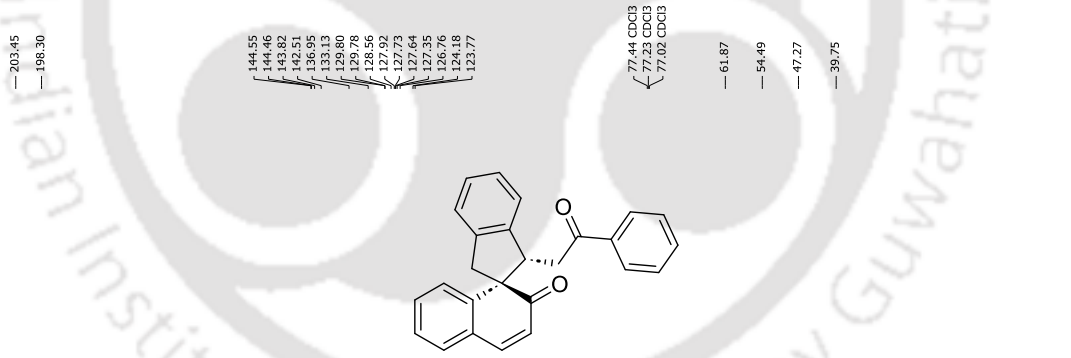






4





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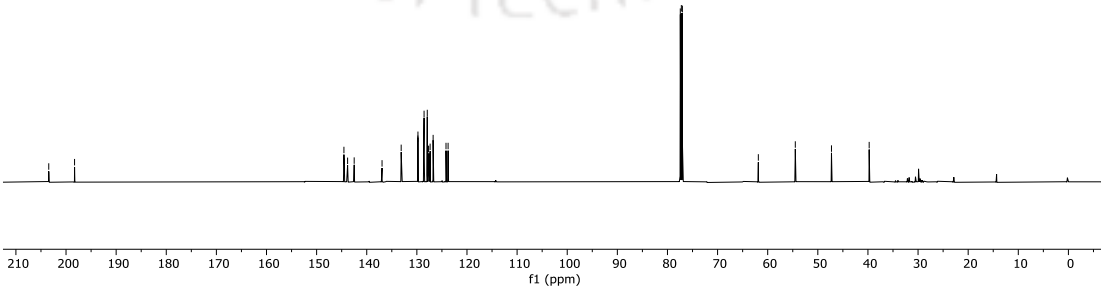
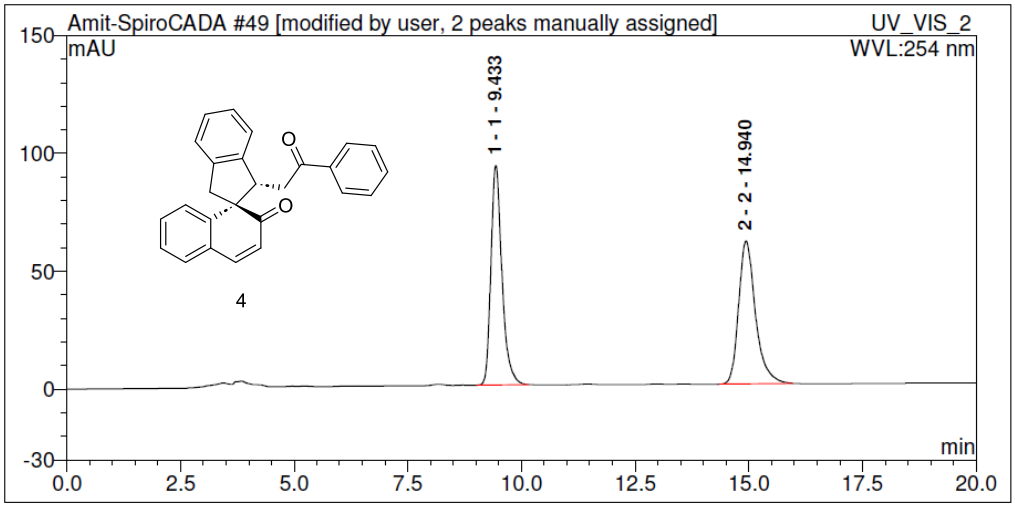
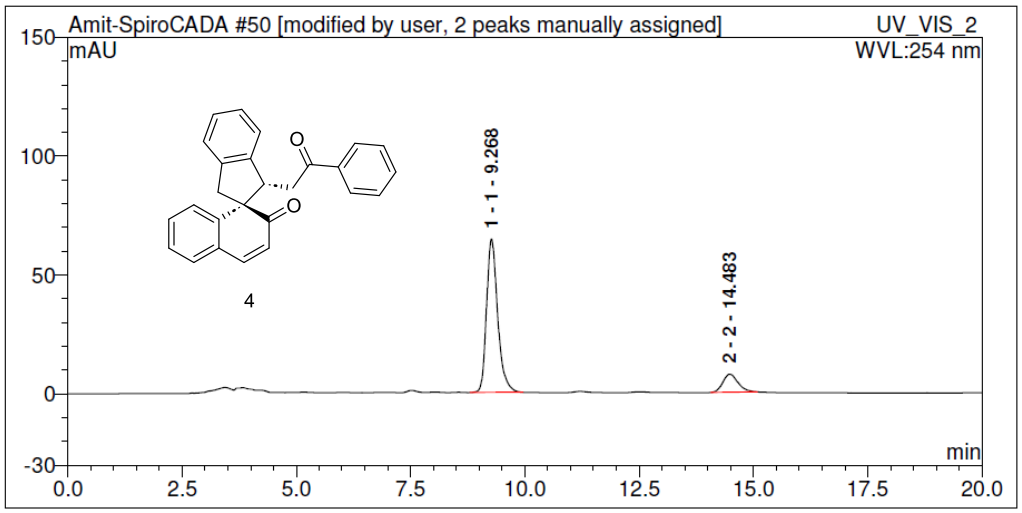
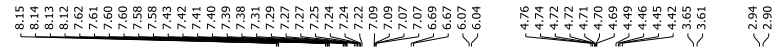




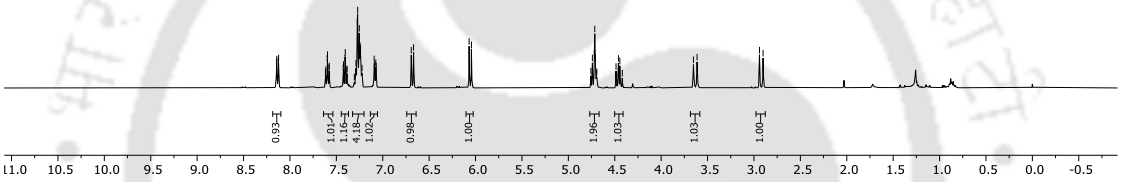
	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.43	26.29942	50.22119373	93.09261	n.a.
2	2	14.94	26.068	49.77880627	60.674	n.a.

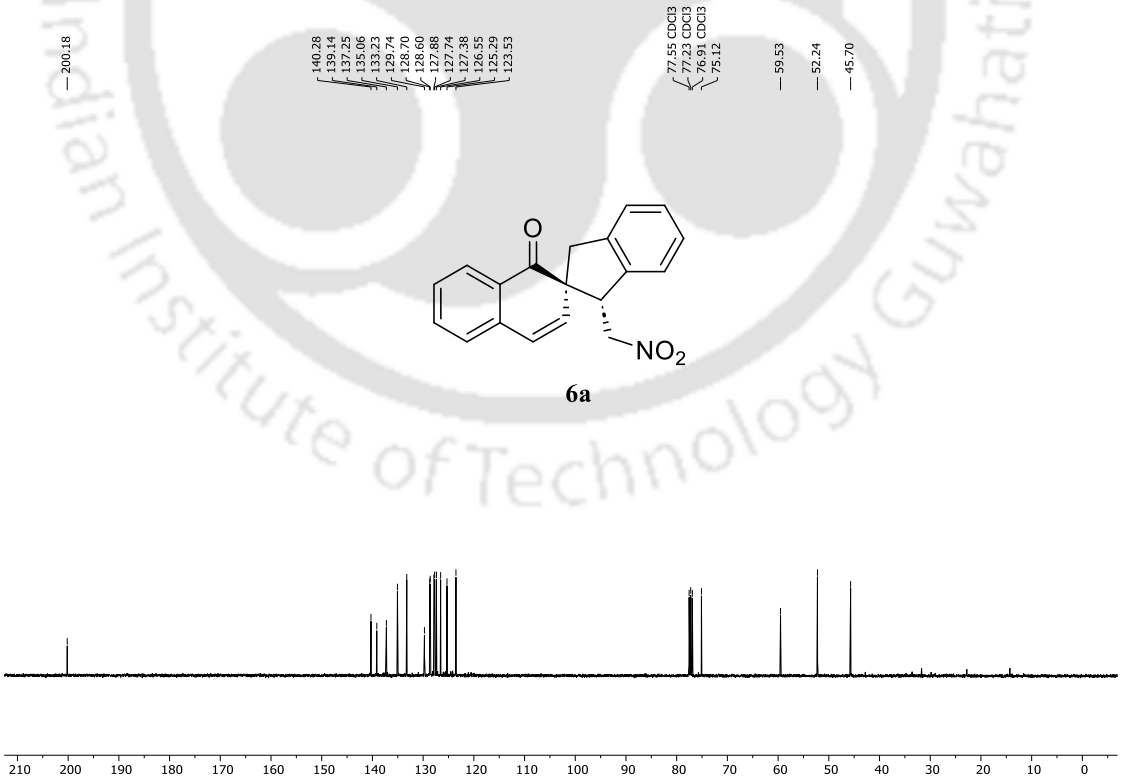


	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.27	18.2778	86.2445435	64.61284	n.a.
2	2	14.48	2.915	13.7554565	7.579	n.a.



6a





6a

4.10 References

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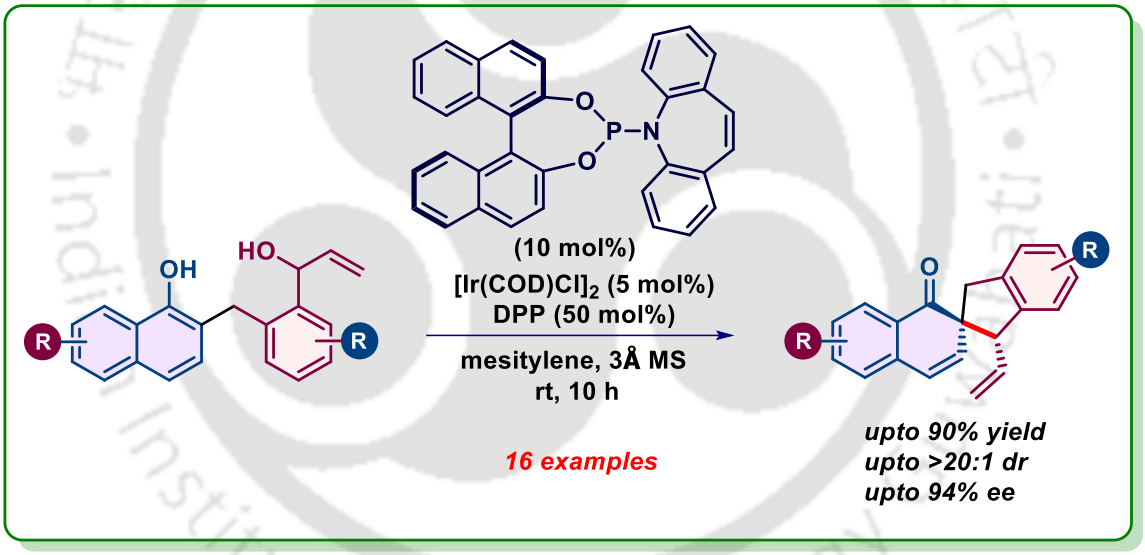
Chapter V

Cooperative Iridium and Brønsted Acid Catalyzed Intramolecular Asymmetric Allylic Dearomatization of α- and β-Naphthols

ABSTRACT: A method for the asymmetric allylic dearomatization of novel substrates containing secondary racemic allyl alcohol-tethered *α*- and *β*-naphthols. Using iridium/Brønsted acid dual catalysis, the resulting naphthalenone spirocarbocycles were achieved in high yields and enantioselectivities with notable diastereoselectivities.



Manuscript communicated.

5.1 Introduction

Asymmetric catalytic reactions involving C−C bond formation have provided synthetic pathways to biologically significant molecules. Among these reactions, asymmetric allylic alkylation (AAA)[1] has been extensively researched due to its ability to form diverse bonds and its wide-ranging applications in total synthesis. Highly regio- and enantioselective allylic substitution reactions have been achieved using activated precursors of π-allyl fragments such as allyl halides, esters, and carbonates, among others, with various nucleophiles.[2-3] However, successful applications of naphthols in allylic substitution reactions remain limited. Recently, a few groups independently reported successful inter- and intra-molecular asymmetric allylic dearomatization (AADA) of naphthols using allyl carbonates.[4] This approach yielded β-naphthalenones in good yields with outstanding chemo- and enantioselectivities. Nevertheless, in all instances, the electrophiles utilized were allyl carbonates. And because of that, there has been a growing trend toward substituting synthetically reliable alcohols for allyl carbonates in AAA reactions due to their high synthetic efficiency and favourable environmental impact (with water as the sole stoichiometric by-product).[5] So, a few groups have shown that the racemic secondary alcohols might be employed as versatile and useful substrates *via* chiral iridium catalysis in a number of asymmetric allylic substitution processes and also in enantioselective intermolecular dearomatization of naphthol derivatives.[6] However, an intramolecular dearomatization report with secondary allyl alcohol is not known. And this intramolecular asymmetric allylic dearomatization (AADA) of naphthols would offer a direct route to enantiopure spirocarbocycles, which serve as a widely used structural motif in many biologically significant natural products and pharmaceuticals (Figure 1) because of their distinctive structural features, which include quaternary carbon centers.[7]

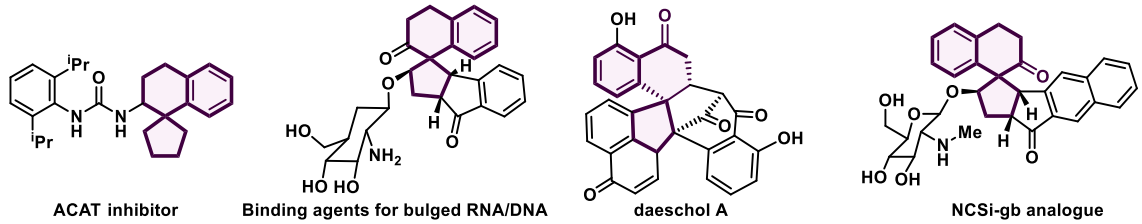
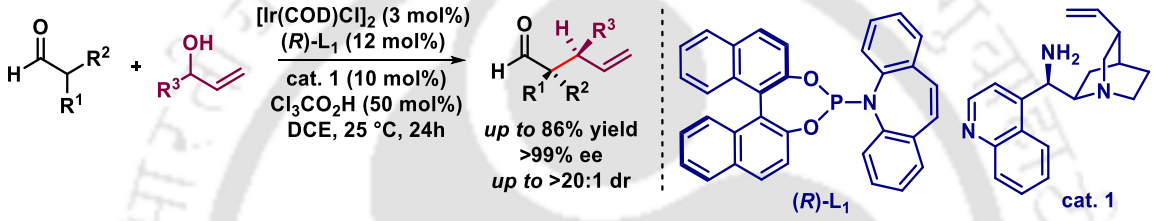


Figure 1: Selected bioactive compounds with spirocarobocycle skeleton

5.2 Literature Survey

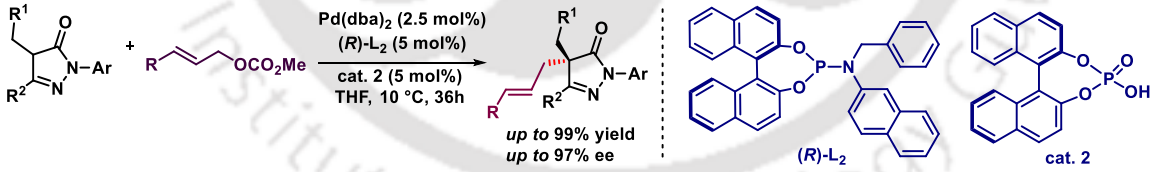
5.2.1 Previous reports on intermolecular asymmetric allylic alkylation (AAA) reactions:

In 2013, Carreira *et al.* reported[8], a fully stereodivergent dual-catalytic synthesis of *γ,δ*-unsaturated aldehydes bearing vicinal quaternary/tertiary stereogenic centers. The reaction was performed using chiral iridium and amine catalysts, which activate the allylic alcohol and aldehyde substrates, respectively. They isolated the products with high yields and excellent enantioselectivity (>99% *ee*) in all cases (Scheme 1).



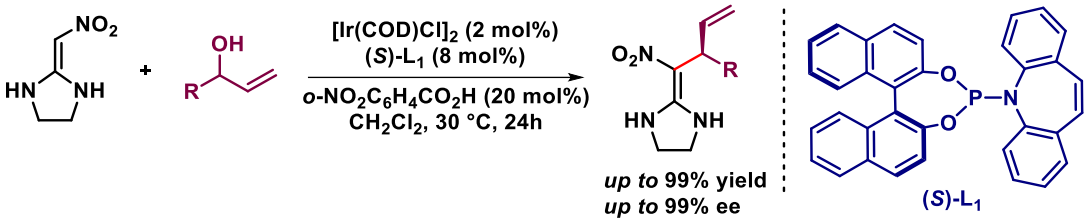
Scheme 1: Synthesis of *γ,δ*-unsaturated aldehydes using chiral iridium and amine catalysts

In 2013, Gong *et al.* used a palladium complex with a chiral phosphoramidite ligand and a chiral phosphoric acid for the first highly efficient asymmetric allylic alkylation of pyrazol-5-ones with allylic alcohols. affording multiply functionalized heterocyclic products in high yields with excellent enantioselectivities (Scheme 2).[9]



Scheme 2: Asymmetric allylic alkylation of pyrazol-5-ones

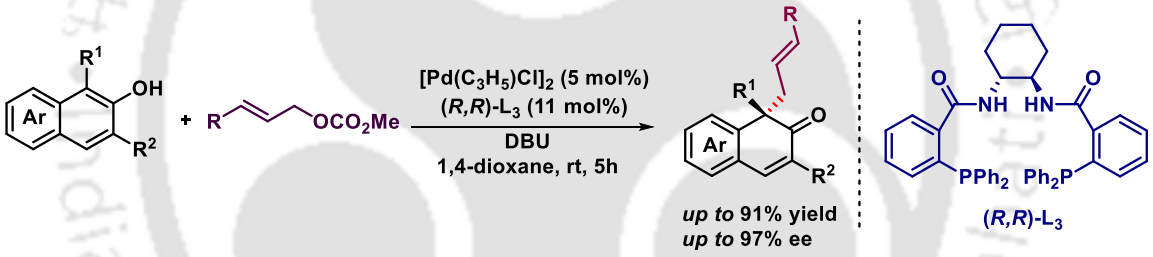
After that in 2024, Yang *et al.* reported[10], the enantioselective allylic alkylation of nitro ketene aminals with racemic allylic alcohols by iridium/acid dual catalysis. An allyl group was installed on the *α*-position of nitro ketene aminals in a branched-selective manner with excellent conversions and enantioselectivities (Scheme 3).



Scheme 3: Enantioselective allylic alkylation of nitro ketene aminals

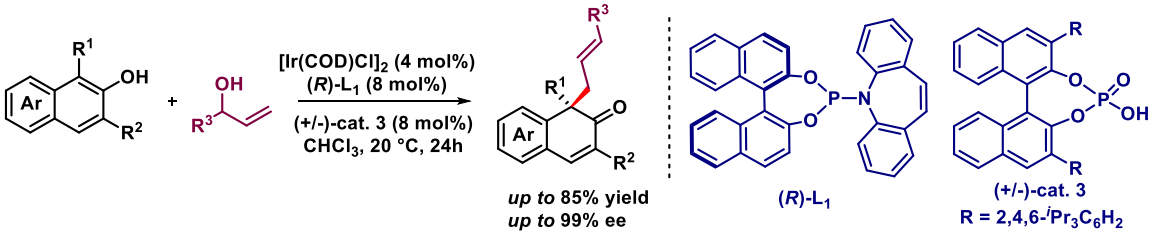
5.2.2 Previous reports on intermolecular asymmetric allylic dearomatization (AADA) reactions:

In 2013, You *et al*. synthesized *β*-naphthalenone moiety bearing an all-carbon quaternary center from substituted naphthols and cinnamyl carbonate, using [{Pd(C_3H_5)Cl}$_2$] and the Trost ligand. The asymmetric allylic dearomatization reaction proceeded smoothly with good conversions, as well as excellent chemo- and enantioselectivities (Scheme 4).[11]



Scheme 4: Dearomatization of *β*-naphthols through asymmetric allylic alkylation reaction

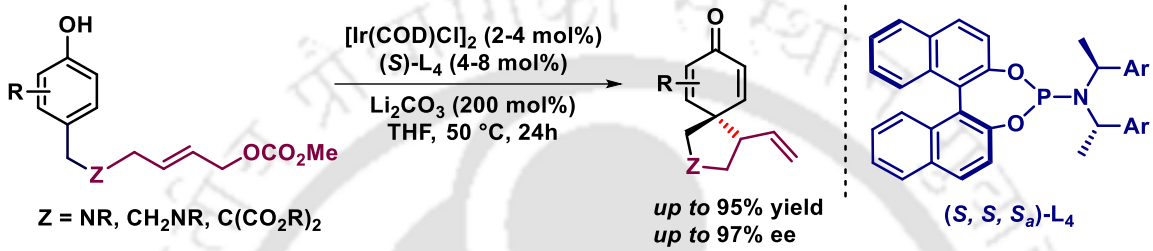
After that in 2017, Zhong *et al*. demonstrated[12], the combination of a transition-metal catalyst and organocatalyst to achieve a highly enantioselective system for the allylic dearomatization reaction of naphthols with racemic secondary allylic alcohols. The desired *β*-naphthalenones, bearing an all-carbon quaternary center, were obtained in good yields with high chemo- and enantioselectivities. (Scheme 5).



Scheme 5: Allylic dearomatization of naphthols

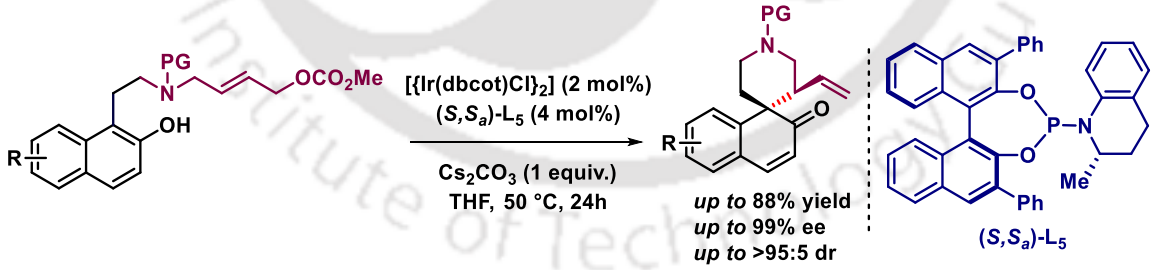
5.2.3 Previous reports on intramolecular asymmetric allylic dearomatization (AADA) reaction of phenolic systems:

In 2011, You *et al*. demonstrated[13], intramolecular asymmetric allylic dearomatization of phenols in the presence of [{Ir(cod)Cl}$_2$] and a binol-derived phosphoramidite ligand. In this method, spirocyclohexadienone derivatives were obtained with excellent yields and up to 97 % *ee* (Scheme 6).



Scheme 6: Intramolecular asymmetric allylic dearomatization of phenols

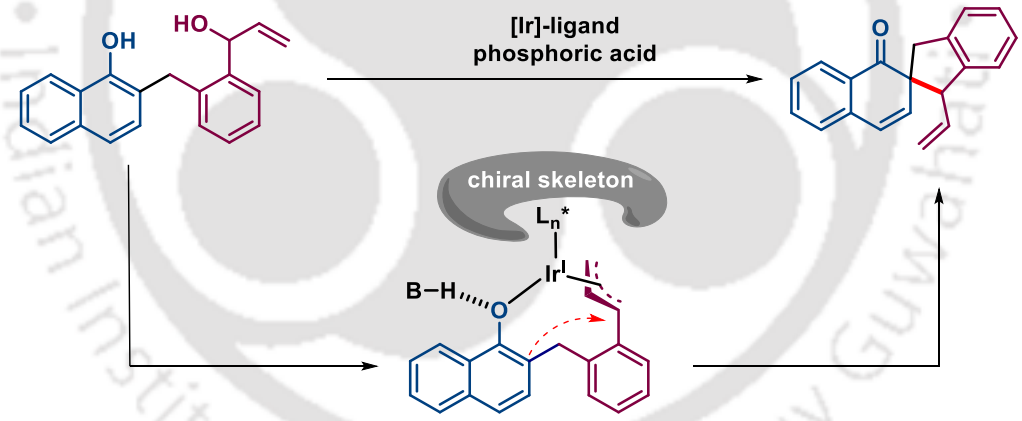
In 2016 You *et al*. reported[14] iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of naphthol derivatives. In the presence of an iridium catalyst, generated from [{Ir(dbcot)Cl$_2$] and *THQ*phos ligand, various spiro-naphthalenones were obtained with >95:5 *C/O* selectivity, excellent conversions and excellent diastereo- as well as enantioselectivities (Scheme 7).



Scheme 7: Intramolecular asymmetric allylic dearomatization of naphthols

5.3 Our Aim

From the previous literature survey, we found that asymmetric allylic alkylation (AAA) reactions have emerged as a powerful tool for the construction of carbon−carbon and carbon−hetero atom bonds in organic synthesis. However, the direct asymmetric dearomatization reaction where the dearomatization and asymmetric allylic alkylation occur in one step is highly desirable but very challenging and because of that very few methods are been reported of the same. So, we like to demonstate iridium-catalyzed allylic intramolecular dearomative spirocyclization of a newly designed substrate having secondary allyl alcohol motif tethered with naphthol moiety (Scheme 8). The challenges confronted in this reaction include chemoselectivity between carbon and oxygen atoms as nucleophilic centers, diastereoselectivity when contiguous chiral centers are generated, and enantioselective control for constructing an all-carbon quaternary stereocenter.

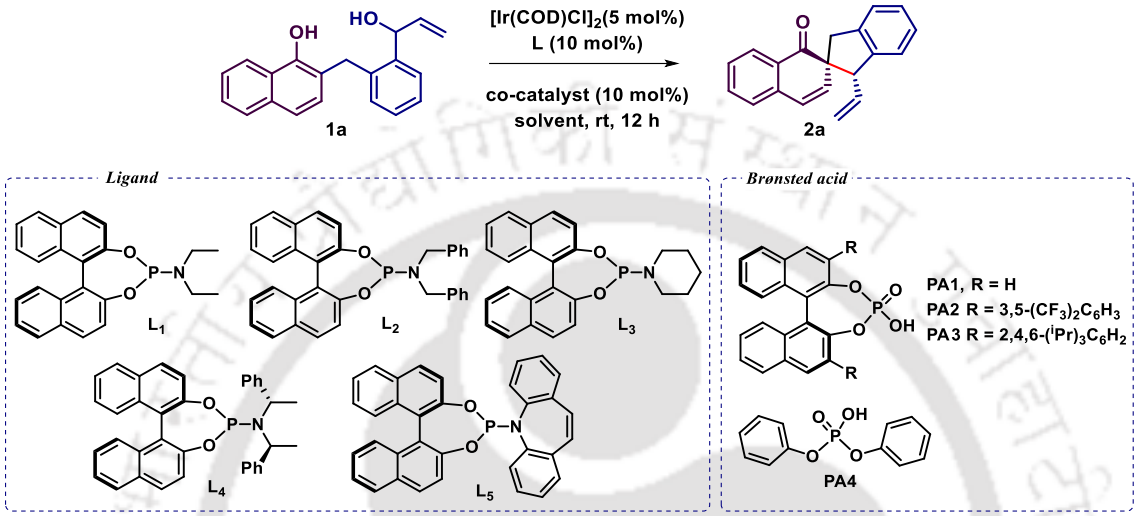


Scheme 8: Allylic intramolecular dearomative spirocyclization of naphthols

5.4 Result and Discussion

5.4.1 Optimization of catalyst and reaction conditions:

To realize this proposal, we began examining the AADA reaction of α-naphthol **1a** in the presence of chiral iridium complexes along with Brønsted acid as co-catalysts.



entry[a]	L	co-catalyst	solvent	additive	yield[b]	d.r[c]	ee[d]
1	L1	PA1	toluene	-	30	7:1	15
2	L2	PA1	toluene	-	55	9:1	34
3	L3	PA1	toluene	-	47	10:1	38
4	L4	PA1	toluene	-	65	9:1	28
5	L5	PA1	toluene	-	80	6:1	70
6	L5	PA2	toluene	-	78	7:1	74
7	L5	PA3	toluene	-	88	12:1	74
8	L5	PA4	toluene	-	90	10:1	70
9	L5	PA3	DCM	-	90	7:1	60
10	L5	PA3	EtOAc	-	76	11:1	72
11	L5	PA3	mesitylene	-	85	12:1	74
12	L5	PA3	toluene	3Å MS	78	12:1	84
13	L5	PA3	toluene	4Å MS	81	12:1	82
14	L5	PA3	toluene	5Å MS	60	12:1	66
15	L5	PA3	toluene	$MgSO_4$	64	9:1	78
16	L5	PA3	mesitylene	3Å MS	79	12:1	87
17	L5	PA4[e]	mesitylene	3Å MS	90	10:1	94

[a]Reactions were carried out 0.1 mmol of **1a** in 3 mL dichloromethane at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]50 mol% co-catalyst PA4.

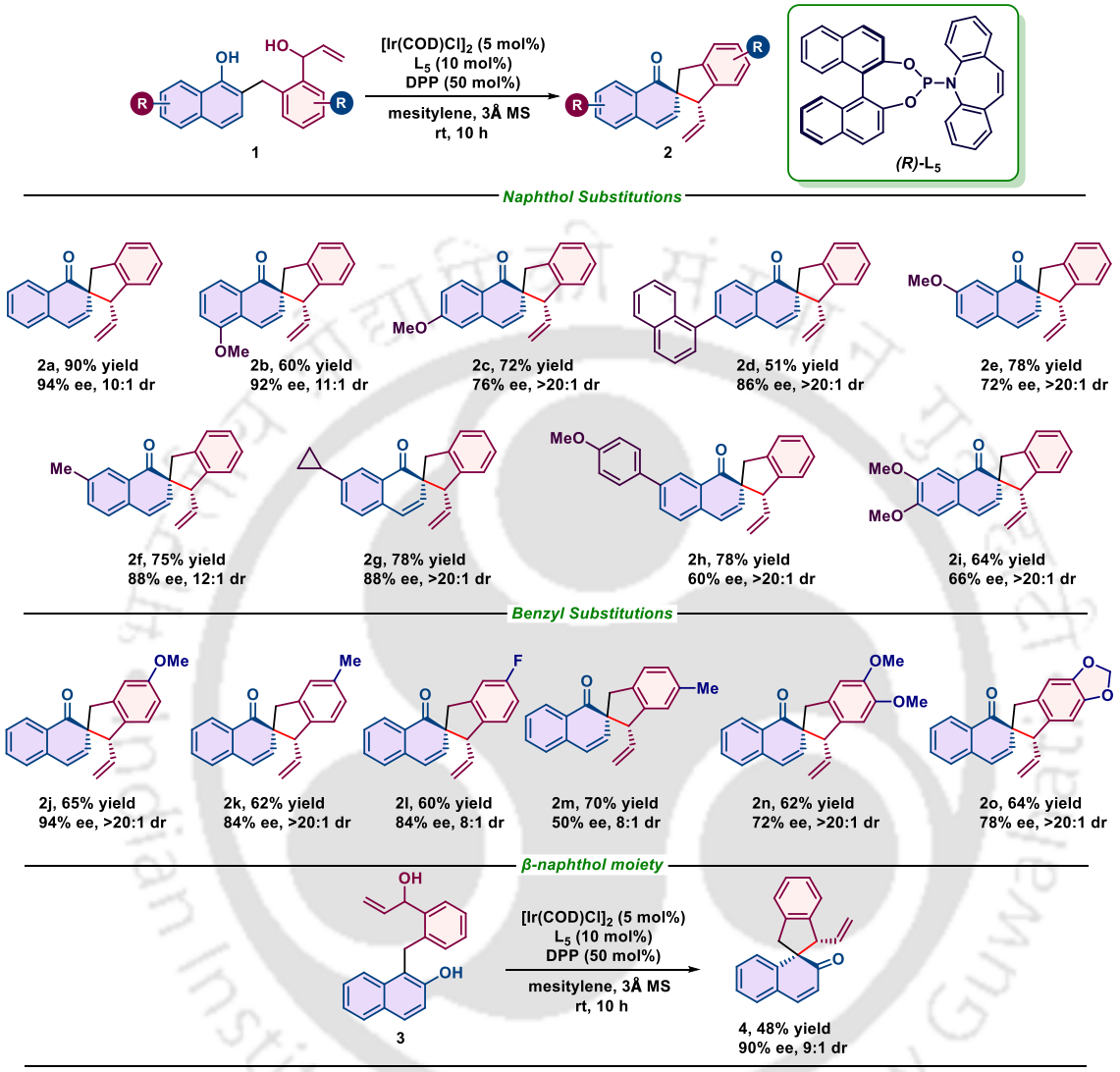
Table 1: Catalyst, solvent and condition optimization

To our delight, with the combination of ligand (*R*)-**L1** and Brønsted acid (*S*)-**PA1**, the AADA reaction progressed as expected to deliver the desired product **2a** but the yield and enantioselectivity was poor. Though ligand (*R*)-**L2**, (*R*)-**L3** and (*R*)-**L4** shown improved results but it was not suitable for the reaction. A higher enantioselectivity (70% ee) was achieved with ligand (*R*)-**L5**. Then we focused on screening several phosphoric acid catalysts generated from BINOL and diphenyl phosphate in the reaction. Phosphoric acid (*S*)-**PA2** with bis(trifluoromethyl)phenyl substituents was screened in the reaction. Though there was a small improvement in enantioselectivity, diastereoselectivity declined. Similar enantioselectivity but better diastereoselectivity (12:1 dr) was detected with (*S*)-TRIP catalyst (*S*)-**PA3**. With diphenyl phosphate we got 70% ee with 90% yield and 10:1 dr. After establishment of (*R*)-**L5** as our best ligand and (*S*)-**PA3** as the optimal co-catalyst, different conditions, such as solvents, additives were subsequently tested. When we used different solvents like DCM and EtOAc, the enantioselectivity got slightly decreased but in case of mesitylene, we got the similar result with 74% ee and 12:1 dr. Addition of molecular sieves (MS 3Å) was found to be beneficial and both the diastero- and enantioselectivity got improved. When we used mesitylene solvent with 3Å MS, A higher enantioselectivity (87% ee) was achieved. Interestingly, upon using diphenyl phosphate at 50 mol% with 3Å MS and mesitylene solvent, the enantioselectivity enhanced to 94% with slightly less diastereoselectivity (10:1 dr) (Table 1).

5.4.2 Substrate scope:

After establishing the optimal conditions, we explored the scope of the AADA reaction. Initially, substrates **1** with various substituents on naphthols were prepared and reacted in our optimized conditions. We began by testing 5-OMe substitutions on the naphthol group, **1b** yielded the spirocyclized dearomatized product **2b** in 60% yield, 92% ee and 11:1 dr. We then examined different substitutions on 6- and 7-position and got the products with good yields and moderate to high enantioselectivities. For example, with 1-naphthyl substitution on 6-position, we got the product **2d** in 51% yield and 86% ee. And while using 7-Me and 7-cyclopropyl groups, we isolated the products **2f** and **2g** respectively with

moderate yield and 88% ee. A moderate yield of 64% and 66% ee was also observed for product **2i** with dimethoxy substituent (Scheme 9).



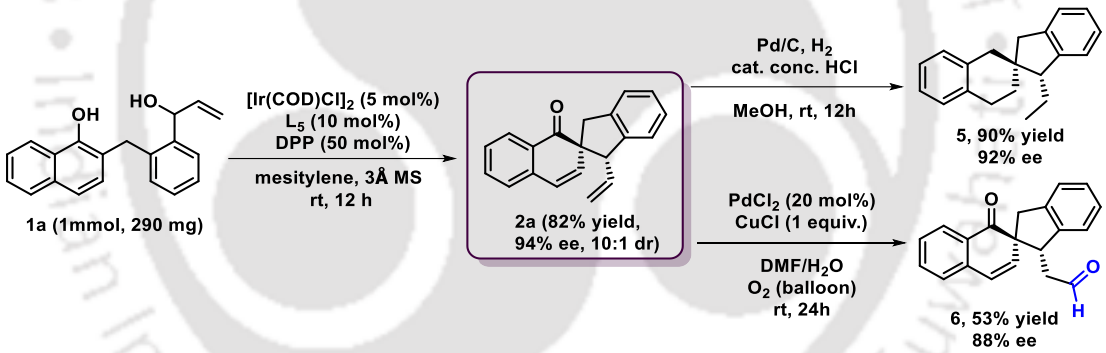
Scheme 9: Substrate scope of α-and β-naphthols

In the next stage, we investigated the range of compound **1** by substituting various aryl groups. Similarly, positive results were achieved in nearly every instance here as well. Initially, substrates **1** with various 5-substitutions on the aryl motif were prepared and reacted. Substrate **1j**, with a 5-OMe substituent, smoothly yielded product **2j** in 65% yield and 94% ee with yielding a single diastereomer. Product **2k** and **2l**, featuring a 5-methyl and 5-fluoro substituent respectively, showed positive results as we got 84% ee in both cases. Smooth conversion was achieved for 4-methyl substitution, yielding products **2m**

in good yield 70% with 50% ee and 8:1 dr. Compound **1n**, with 5,6-dimethoxy substitution, also provided a reasonable yield 62% for **2n** with 72% ee and >20:1 dr. To showcase how adaptable this approach can be, we used *β*-naphthol-derivative **3** and subjected it to the reaction conditions. It underwent dearomatization smoothly, yielding the desired product **4** in 48% yield with 90% ee and 9:1 dr (Scheme 9).

5.4.3 Synthetic transformations:

A scale-up reaction was conducted using 1 mmol of **1a**, yielding the desired product **2a** in 82% yield. Subsequently, to showcase the synthetic versatility of our reaction, experiments were performed on **2a** (Scheme 10). Initially, a hydrogenation reaction was executed with 10% Pd/C in methanol, resulting in the desired product **5** in 90% yield and 92% ee from **2a**. Treatment of compound **2a** with $PdCl_2$ and CuCl in DMF led to the formation of an aldehyde product **6** in 53% yield and 88% ee.

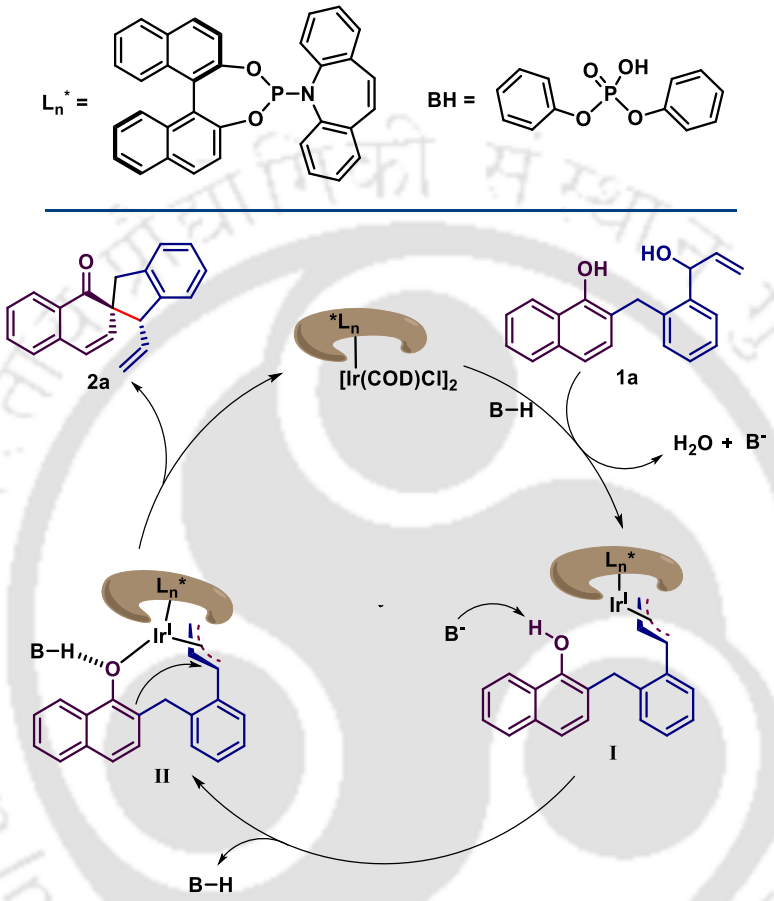


Scheme 10: Synthetic transformations

5.4.4 The proposed mechanism:

Based on experimental observations and literature[9,10,12], a plausible mechanism is proposed in Scheme 11. Initially, the chiral iridium complex and acid promoter react with the allylic alcohol part of **1a**, resulting in the formation of intermediate **A** with the elimination of water and generation of the conjugate base of the acid. Subsequently, the naphthol part undergoes deprotonation by the base and forms intermediate **B**, where a hydrogen bond is established between the acid and naphthol. The asymmetric allylic dearomatization (AADA) reaction then proceeds *via* an intramolecular nucleophilic

addition reaction. The highly sterically hindered chiral iridium complex enhances enantioselectivity significantly, yielding product **2a** with a high enantiomeric excess. Finally, the iridium complex is regenerated, completing the catalytic cycle for subsequent reactions. (Scheme 11).



Scheme 11: Proposed mechanistic pathway

5.5 Conclusion

In summary, we have devised a method for asymmetric dearomatization of naphthol derivatives using iridium-catalyzed asymmetric allylic substitution reactions. This process yields naphthalenones featuring an all-carbon quaternary center and an adjacent tertiary chiral center. Our novel catalytic system demonstrates exceptional selectivity across multiple fronts, encompassing chemo-, diastereo-, and enantioselectivity. The broad substrate scope, mild reaction conditions, and versatile transformations underscore the practical potential of this approach.

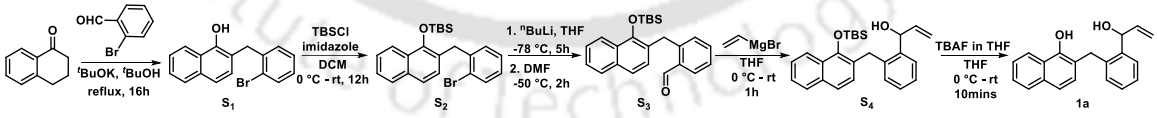
5.6 Experimental section

5.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. All dry solvents were dried using activated 4Å molecular sieves and stored under argon. ^{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 and DMSO δ 2.50), carbon (chloroform δ 77.23 and DMSO δ 39.58). Multiplicity was indicated as follows**:** s = singlet, d = doublet, dd = double doublet, ddd = doublet of doublet of doublets, t = triplet, q = quartet, dt = doublet of triplets, m = multiplet, bs = broad singlet. Coupling constants were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using Daicel Chiral PAK ID, IF and ADH. For visualizing the products UV light and/or I_2 were used. Silica gel (230 – 400 mesh size) was used for the flash column chromatography. Reactions were monitored by TLC on silica gel 60 with fluorescence indicator F254 (0.25 mm).

5.6.2 Preparation of Starting materials

➢ **5.6.2.1** ***General Procedure for the Synthesis of Naphthols (1a – 1o & 3):***



Procedure A[15a]**:** A solution of 1-tetralone (1.0 g, 6.85 mmol, 1.0 equiv.) and benzaldehyde (1.3 g, 6.85 mol, 1.0 equiv.) in *tert*-butyl alcohol (70.0 mL) was treated with potassium *tert*-butoxide (1.6 g, 13.7 mmol, 2.0 equiv.) and heated at reflux in a pre-heated oil bath under nitrogen for 16 h. The mixture was cooled, acidified with 1 N HCl, and concentrated to remove the *tert*-butyl alcohol. The aqueous residue was extracted with ethyl acetate, and

the organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, the crude product (**S_1**) was obtained and used in the next step without further purification.

Procedure B[15b]**:** In a round bottom flask, above obtained aryl alcohol (1.0 equiv.) was dissolved in dichloromethane (27.0 mL). The solution was then charged with imidazole (930 mg, 13.7 mmol, 2.0 equiv.) and *tert*-butyldimethylchlorosilane (1.5 g, 10.3 mmol, 1.5 equiv.) and stirred until the starting alcohol was fully consumed. The reaction was diluted with 25.0 mL dichloromethane, washed with deionized H_2O (3 × 50 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified by flash column chromatography (hexane/ethyl acetate) on silica gel to afford the aryl silyl ether (**S_2**).

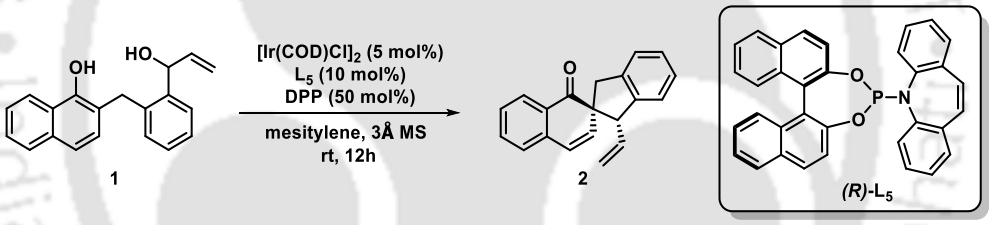
Procedure C[15c]**:** The above obtained product (1.95 g, 4.56 mmol, 1.0 equiv.) was dissolved in 25.0 mL of dry THF under argon. The stirred solution was cooled to – 78 °C, and 10.0 mL of *n*-BuLi in *n*-hexane (2 M) (20.1 mmol, 4.4 equiv.) was added at such a rate to keep the temperature at – 70 °C. Temperature was measured using an internal probe in the reaction flask. After 5 h, dimethylformamide (1.8 mL, 22.8 mmol, 5.0 equiv.) was added, keeping the temperature below – 50 °C. The solution was stirred at – 50 °C for 2 h. The reaction mixture was poured into HCl/ice under vigorous stirring and allowed to reach room temperature overnight. The reaction mixture was extracted three times with dichloromethane, and the combined organic phases were washed twice with deionized water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude (**S_3**) was used in the next step without further purification.

Procedure D[15d]**:** Following the general procedure, under argon, a flame-dried 25mL round-bottomed flask with a stirrer bar was charged with dry THF (10.0 mL) and aldehyde **S3** (1.0 equiv.), followed by the dropwise addition of vinyl magnesium bromide (5.0 mL of a 1 M solution in tetrahydrofuran, 5.0 mmol, 1.2 equiv.) at 0 °C with stirring. The reaction was warmed to room temperature and kept for 1 hour with stirring. Completion of reaction was checked in TLC and after that, the reaction was quenched with sat. aq. NH_4Cl and water. EtOAc was added and the mixture was transferred to a separatory funnel. The organic layer was collected, and the aqueous phase was washed with EtOAc

twice. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated in *vacuo*. It was used directly in the next step without further purification.

Procedure E[15e]**:** To a cold (0 ºC) solution of the above crude product **S4** (1.0 equiv.) in dry tetrahydrofuran (45 mL), was added tetra-*n*-butylammonium fluoride (TBAF) (4.6 mL of a 1 M solution in tetrahydrofuran, 4.6 mmol, 1.1 equiv.) and the resulting solution stirred for 10 minutes allowing the mixture to warm to room temperature. The resulting solution was diluted with dichloromethane and quenched with water. The organic layer was extracted with brine and dried over Na_2SO_4, followed by solvent reduction in *vacuo* and purification was carried out by silica gel flash column chromatography hexane/ethyl acetate to afford our desired derivatives (**1a – 1o** and **3**).

5.6.3 General procedure for the synthesis of compounds 2a – 2o and 4



Under an argon atmosphere, an oven dried round bottom flask was charged with $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 5 mol %), Carreira's ligand (*R*)-L_5 (5.1 mg, 0.01 mmol, 10 mol %). After the flask was evacuated and backfilled with argon, dry mesitylene (3.0 mL) was added, then stirred at rt for 15 minutes. Then **1a** (29.0 mg, 0.1 mmol) and DPP (12.5 mg, 0.04 mmol, 50 mol %) were added sequentially. The reaction mixture was stirred at room temperature until compound **1a** were consumed (monitored by TLC). After the completion of reaction, mixture was directly purified by flash column chromatography on silica gel with hexane/ethyl acetate to afford desired product **2a – 2o** and **4**.

5.6.4 Synthetic transformations

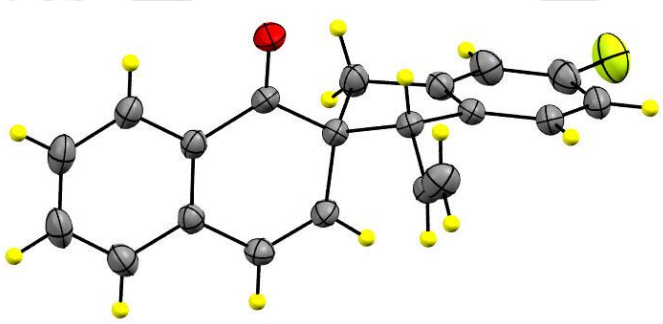
➢ 5.6.4.1 General procedure for the synthesis of compound 5[16]

The *α*-naphthalenone **2a** (36.5 mg, 0.1 mmol) was dissolved in methanol, and added Pd/C (10 mol%) and catalytic amount of conc. HCl. The resulting mixture was stirred at room temperature under H_2 atmosphere. When the reaction was completed by the monitoring of TLC, the solution was filtered and concentrated in *vacuo*. Then water was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer dried over Na_2SO_4 and filtered. After the solvent was removed under reduced pressure, the residue was purified by silica gel flash column chromatography hexane/ethyl acetate to afford **5**.

➢ 5.6.4.2 General procedure for the synthesis of compound 6[17]

To a Schlenk tube were added $PdCl_2$ (4.0 mg, 0.02 mmol, 20 mol%) and CuCl (10.0 mg, 0.1 mmol, 1.0 equiv.). After the flask was evacuated and refilled with O_2 for three times, DMF and water were added. After stirring for 10 min, a DMF solution of **2a** (30 mg, 0.1 mmol) was added and the mixture was stirred with O_2 bubbled. After the reaction was complete (monitored by TLC), the reaction was filtered by Celite, concentrated in vacuo and purified by silica gel column chromatography (hexane/ ethyl acetate) to afford **6**.

5.7 Single crystal X-ray diffraction analysis of *2l*

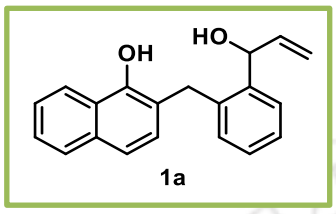


Ortep Diagram with 30 % ellipsoid probability of compound 2l

5.8 Characterisation of the products

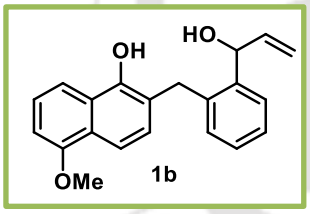
2-(2-(1-hydroxyallyl)benzyl)naphthalen-1-ol (1a)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as colourless solid, overall yield: 59% (1173 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.17 – 8.11 (m, 1H), 7.94 (bs, 1H), 7.79 – 7.73 (m, 1H), 7.44 – 7.34 (m, 4H), 7.24 – 7.09 (m, 4H), 6.17 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.51 – 5.44 (m, 1H), 5.31 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.24 (d, *J* = 15.6 Hz, 1H), 4.09 (d, *J* = 15.6 Hz, 1H), 3.16 (bs, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 149.9, 138.9, 138.9, 138.1, 134.0, 130.9, 129.8, 128.8, 128.0, 127.6, 126.7, 125.9, 125.3, 125.2, 122.1, 119.9, 119.6, 116.2, 74.7, 33.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{18}O_2$ 291.1380; found 291.1380.



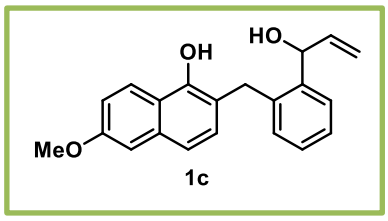
2-(2-(1-hydroxyallyl)benzyl)-5-methoxynaphthalen-1-ol (1b)

The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20) as light pink solid, overall yield: 57%. **^{1}H NMR (400 MHz, DMSO)** δ 9.31 (s, 1H), 7.84 – 7.77 (m, 1H), 7.64 – 7.56 (m, 1H), 7.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 7.6 Hz, 1H), 7.21 (td, *J* = 7.5, 1.6 Hz, 1H), 7.15 (td, *J* = 7.4, 1.6 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.94 – 6.87 (m, 1H), 5.93 (ddd, *J* = 17.1, 10.4, 5.3 Hz, 1H), 5.62 (d, *J* = 4.4 Hz, 1H), 5.41 – 5.34 (m, 1H), 5.22 (dt, *J* = 17.1, 1.8 Hz, 1H), 5.04 (dt, *J* = 10.3, 1.7 Hz, 1H), 4.27 – 4.14 (m, 2H), 3.93 (s, 3H). **^{13}C{H} NMR (125 MHz, DMSO)** δ 154.8, 149.4, 141.8, 141.2, 137.7, 129.7, 127.8, 126.9, 126.7, 126.3, 126.0, 124.9, 124.9, 122.0, 114.2, 113.4, 112.8, 103.9, 70.1, 55.4, 31.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_3$ 321.1485; found 321.1486.



2-(2-(1-hydroxyallyl)benzyl)-6-methoxynaphthalen-1-ol (1c)

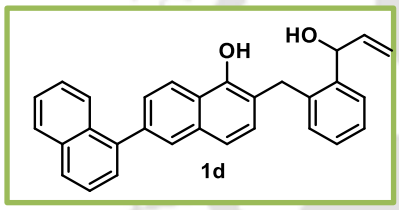
The product was purified by flash column chromatography (hexane/ethyl acetate = 85:15)



as yellow semi solid, overall yield: 60%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 9.1 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.34 (s, 1H), 7.26 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.18 (m, 2H), 7.14 – 7.08 (m, 2H), 6.23 (m, 1H), 5.52 (m, 1H), 5.41 – 5.34 (m, 1H), 5.34 – 5.28 (m, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 4.12 (d, *J* = 15.6 Hz, 1H), 3.93 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 157.8, 150.2, 139.1, 139.0, 138.1, 135.3, 130.9, 130.6, 128.7, 128.0, 126.6, 123.9, 120.7, 118.5, 118.0, 117.7, 116.1, 105.7, 74.6, 55.4, 33.2. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_3$ 321.1485; found 321.1485.

6'-(2-(1-hydroxyallyl)benzyl)-[1,2'-binaphthalen]-5'-ol (1d)

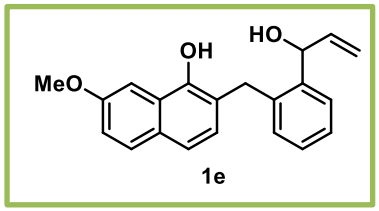
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)



as yellow solid, overall yield: 40%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.29 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.99 – 7.90 (m, 4H), 7.63 – 7.56 (m, 2H), 7.56 – 7.50 (m, 2H), 7.49 (s, 2H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.33 (dt, *J* = 7.2, 1.9 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.25 – 7.18 (m, 2H), 6.36 – 6.29 (m, 1H), 5.63 (dd, *J* = 6.2, 1.9 Hz, 1H), 5.46 (d, *J* = 17.2 Hz, 1H), 5.39 (d, *J* = 10.6 Hz, 1H), 4.38 (d, *J* = 15.5 Hz, 1H), 4.25 (d, *J* = 15.5 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 150.1, 140.5, 139.1, 139.0, 138.3, 138.2, 134.0, 131.9, 130.9, 130.3, 128.8, 128.5, 128.4, 128.0, 127.8, 127.8, 127.3, 126.7, 126.4, 126.2, 126.0, 125.6, 124.5, 122.0, 120.1, 119.7, 116.2, 108.2, 74.8, 33.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{30}H_{24}O_2$ 417.1849; found 417.1846.

2-(2-(1-hydroxyallyl)benzyl)-7-methoxynaphthalen-1-ol (1e)

The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20)

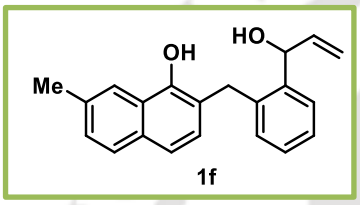


as yellow solid, overall yield: 55% (1205 mg). **^{1}H NMR (600 MHz, DMSO-d_6)** δ 9.22 (s, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 2.8 Hz, 1H), 7.43 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.21 (td, *J* = 7.5, 1.5 Hz, 1H), 7.15 (td, *J* = 7.5, 1.6 Hz, 1H), 7.10 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.02 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.93

(d, *J* = 8.3 Hz, 1H), 5.94 (ddd, *J* = 17.1, 10.4, 5.3 Hz, 1H), 5.62 (d, *J* = 4.4 Hz, 1H), 5.41 – 5.37 (m, 1H), 5.23 (dt, *J* = 17.1, 1.8 Hz, 1H), 5.06 (dt, *J* = 10.4, 1.7 Hz, 1H), 4.20 (d, *J* = 2.6 Hz, 2H), 3.88 (s, 3H). **^{13}C{H} NMR (150 MHz, DMSO-*d*$_6$)** δ 157.3, 149.0, 142.2, 141.7, 138.3, 130.2, 129.6, 129.0, 127.4, 127.1, 126.6, 126.6, 126.5, 122.4, 119.5, 118.2, 113.9, 101.1, 70.6, 55.6, 32.3. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_3$ 321.1485; found 321.1481.

2-(2-(1-hydroxyallyl)benzyl)-7-methylnaphthalen-1-ol (1f)

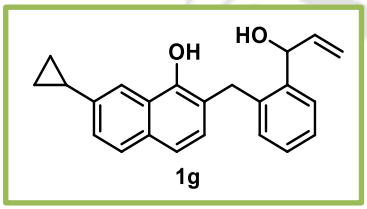
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as light yellow solid, overall yield: 58% (1208 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.98 (s, 2H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.23 (dd, *J* = 7.3, 2.1 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.23 (ddd, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.53 – 5.47 (m, 1H), 5.37 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.31 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.28 (d, *J* = 15.6 Hz, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 3.36 (bs, 1H), 2.52 (s, 3H). **^{13}C{H} NMR (150 MHz, CDCl$_3$)** δ 149.2, 139.0, 138.9, 138.2, 134.9, 132.2, 130.8, 128.8, 128.7, 128.1, 127.9, 127.5, 126.6, 125.4, 121.0, 120.1, 119.5, 116.0, 74.5, 33.3, 22.0. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_2$ 305.1536; found 305.1536.



1f

7-cyclopropyl-2-(2-(1-hydroxyallyl)benzyl)naphthalen-1-ol (1g)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as yellow gummy solid, overall yield: 49%. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.90 (s, 1H), 7.73 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.24 – 7.15 (m, 4H), 6.23 (ddd, *J* = 16.0, 10.5, 5.1 Hz, 1H), 5.52 (d, *J* = 5.4 Hz, 1H), 5.42 – 5.35 (m, 1H), 5.32 (d, *J* = 10.6 Hz, 1H), 4.27 (d, *J* = 15.6 Hz, 1H), 4.14 (d, *J* = 15.6 Hz, 1H), 3.19 (s, 1H), 2.06 (tt, *J* = 8.5, 5.1 Hz, 1H), 1.01 (h, *J* = 4.4 Hz, 2H), 0.82 (d, *J* = 5.4 Hz, 2H). **^{13}C{H} NMR (150 MHz, CDCl$_3$)** δ 149.3, 141.0, 139.0, 138.1, 132.4, 130.9, 128.8, 128.7, 127.9, 127.6, 126.6, 125.4, 124.8,

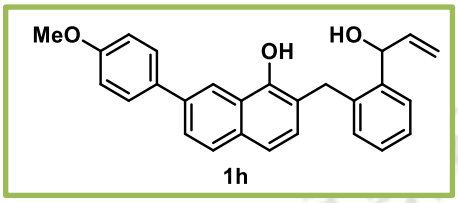


1g

120.1, 119.4, 117.8, 116.1, 74.6, 33.4, 16.0, 9.4, 9.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{23}H_{22}O_2$ 331.1693; found 331.1701.

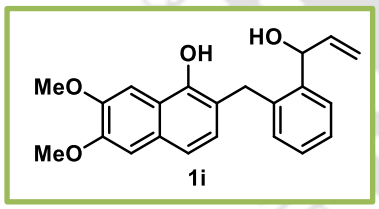
2-(2-(1-hydroxyallyl)benzyl)-7-(4-methoxyphenyl)naphthalen-1-ol (1h)

The product was purified by flash column chromatography (hexane/ethyl acetate = 70:30) as yellow solid, overall yield: 35%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.37 (d, *J* = 1.7 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.72 – 7.64 (m, 3H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.18 (pd, *J* = 8.6, 7.2, 2.2 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.25 (ddd, *J* = 17.2, 10.5, 5.2 Hz, 1H), 5.60 – 5.56 (m, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.5 Hz, 1H), 4.31 (d, *J* = 15.6 Hz, 1H), 4.17 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 159.2, 150.2, 139.0, 139.0, 138.1, 137.5, 134.1, 132.8, 130.9, 129.6, 128.8, 128.6, 128.1, 128.0, 126.7, 125.6, 125.3, 120.2, 119.4, 119.3, 116.2, 114.4, 74.8, 55.5, 33.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{24}O_3$ 397.1798; found 397.1800.



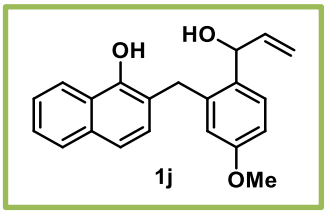
2-(2-(1-hydroxyallyl)benzyl)-6,7-dimethoxynaphthalen-1-ol (1i)

The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20) as pink solid, overall yield: 52%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98 (s, 1H), 7.47 (s, 1H), 7.32 – 7.27 (m, 2H), 7.24 (ddd, *J* = 13.7, 7.3, 1.9 Hz, 2H), 7.17 (m, 2H), 7.09 (s, 1H), 6.25 (m, 1H), 5.53 (d, *J* = 4.7 Hz, 1H), 5.38 (m, 1H), 5.32 (ddd, *J* = 11.8, 3.9, 2.3 Hz, 1H), 4.26 (d, *J* = 15.6 Hz, 1H), 4.14 – 4.08 (m, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.23 (s, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 149.5, 149.1, 149.0, 139.2, 139.0, 138.0, 130.9, 129.8, 128.8, 128.1, 128.0, 126.6, 120.5, 118.7, 118.1, 116.1, 106.2, 101.1, 74.8, 55.9, 55.9, 33.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{22}H_{22}O_4$ 351.1591; found 351.1591.



2-(2-(1-hydroxyallyl)-5-methoxybenzyl)naphthalen-1-ol (1j)

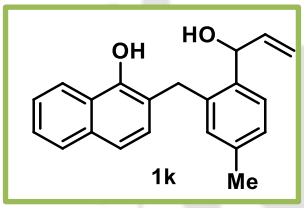
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)



as yellow solid, overall yield: 52%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.22 – 8.18 (m, 1H), 8.10 (s, 1H), 7.81 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.19 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 8.5, 2.8 Hz, 1H), 6.24 (ddd, *J* = 17.2, 10.5, 5.1 Hz, 1H), 5.54 – 5.48 (m, 1H), 5.38 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.25 (d, *J* = 15.5 Hz, 1H), 4.14 (d, *J* = 15.4 Hz, 1H), 3.67 (s, 3H), 3.22 (s, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 159.7, 150.0, 140.7, 139.2, 134.0, 130.6, 129.7, 129.3, 127.5, 125.8, 125.4, 125.2, 122.2, 119.7, 119.6, 116.7, 115.9, 111.5, 74.1, 55.2, 33.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_3$ 321.1485; found 321.1492.

2-(2-(1-hydroxyallyl)-5-methylbenzyl)naphthalen-1-ol (1k)

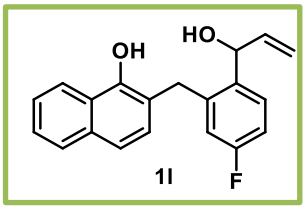
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)



as pale yellow gummy solid, overall yield: 58%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.21 – 8.17 (m, 1H), 7.83 – 7.79 (m, 1H), 7.47 – 7.39 (m, 4H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.22 (m, 1H), 5.55 – 5.47 (m, 1H), 5.40 – 5.33 (m, 1H), 5.32 – 5.25 (m, 1H), 4.25 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.5 Hz, 1H), 2.20 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 150.0, 139.2, 138.7, 138.5, 135.3, 134.0, 131.6, 129.9, 128.0, 127.5, 127.4, 125.8, 125.4, 125.2, 122.2, 120.0, 119.5, 115.9, 74.5, 33.4, 21.3. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_2$ 305.1536; found 305.1537.

2-(5-fluoro-2-(1-hydroxyallyl)benzyl)naphthalen-1-ol (1l)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

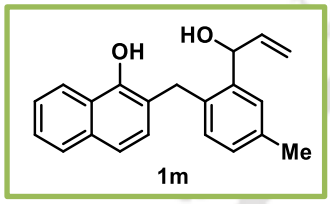


as white solid, overall yield: 50%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.17 (d, *J* = 8.2 Hz, 1H), 8.12 – 7.88 (m, 1H), 7.81 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.6, 5.8 Hz, 1H), 6.87 (dd, *J* = 10.1, 2.8 Hz, 1H), 6.82

(m, 1H), 6.18 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.50 – 5.45 (m, 1H), 5.37 – 5.28 (m, 2H), 4.23 (d, *J* = 15.6 Hz, 1H), 4.10 (d, *J* = 15.6 Hz, 1H), 3.27 (s, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 163.7, 162.1, 149.9, 141.9, 141.8, 138.7, 134.1, 133.9, 133.9, 129.8, 129.7, 129.6, 127.7, 126.1, 125.4, 125.3, 122.0, 119.9, 119.3, 117.6, 117.5, 116.4, 113.5, 113.4, 74.0, 33.3. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{17}FO_2$ 309.1285; found 309.1288.

2-(2-(1-hydroxyallyl)-4-methylbenzyl)naphthalen-1-ol (1m)

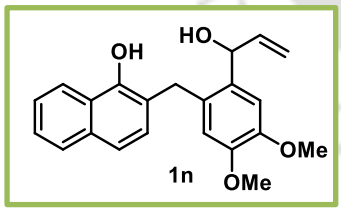
The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)



as yellow solid, overall yield: 58%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.1 Hz, 1H), 8.01 (s, 1H), 7.84 – 7.79 (m, 1H), 7.48 – 7.39 (m, 4H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 1.7 Hz, 1H), 6.99 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.21 (ddd, *J* = 17.3, 10.5, 5.2 Hz, 1H), 5.49 – 5.44 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.5 Hz, 1H), 4.25 (d, *J* = 15.6 Hz, 1H), 4.09 (d, *J* = 15.6 Hz, 1H), 3.31 (s, 1H), 2.28 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 149.8, 139.0, 137.9, 136.2, 135.7, 133.9, 130.8, 129.8, 129.5, 128.7, 127.5, 125.8, 125.3, 125.2, 122.1, 120.2, 119.6, 116.0, 74.7, 33.1, 21.1. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{20}O_2$ 305.1536; found 305.1536.

2-(2-(1-hydroxyallyl)-4,5-dimethoxybenzyl)naphthalen-1-ol (1n)

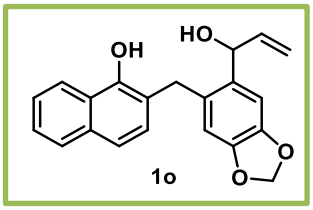
The product was purified by flash column chromatography (hexane/ethyl acetate = 70:30)



as red semi solid, overall yield: 50%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.80 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.38 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H), 6.69 (s, 1H), 6.25 – 6.17 (m, 1H), 5.50 (d, *J* = 5.1 Hz, 1H), 5.37 (d, *J* = 17.1 Hz, 1H), 5.30 (d, *J* = 10.6 Hz, 1H), 4.21 (d, *J* = 15.5 Hz, 1H), 4.09 (d, *J* = 15.5 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 149.9, 149.0, 147.3, 139.1, 133.9, 131.2, 130.5, 129.4, 127.5, 125.8, 125.4, 125.2, 122.1, 119.9, 119.6, 115.9, 113.6, 111.1, 74.0, 56.1, 55.9, 33.1. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{22}H_{22}O_4$ 351.1591; found 351.1591.

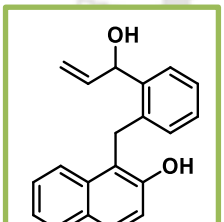
2-((6-(1-hydroxyallyl)benzo[d][1,3]dioxol-5-yl)methyl)naphthalen-1-ol (1o)

The product was purified by flash column chromatography (hexane/ethyl acetate = 80:20) as red semi solid, overall yield: 40%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.43 (dt, *J* = 7.3, 5.0 Hz, 3H), 7.36 (d, *J* = 8.3 Hz, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 6.22 – 6.14 (m, 1H), 5.84 (d, *J* = 9.7 Hz, 2H), 5.48 (d, *J* = 5.2 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.30 (d, *J* = 10.7 Hz, 1H), 4.17 – 4.08 (m, 2H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 149.9, 147.7, 146.1, 139.0, 133.9, 132.8, 131.6, 129.6, 127.5, 125.8, 125.3, 125.2, 122.0, 119.9, 119.6, 116.0, 110.6, 107.9, 101.2, 73.7, 33.2. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{19}O_4$ 335.1278; found 335.1272.



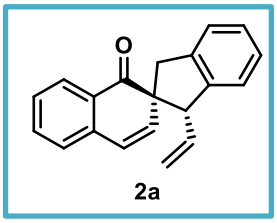
1-(2-(1-hydroxyallyl)benzyl)naphthalen-2-ol (3)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10) as pale yellow solid, overall yield: 50%. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (dd, *J* = 8.8, 3.3 Hz, 1H), 7.85 (dd, *J* = 8.7, 3.3 Hz, 1H), 7.73 (dd, *J* = 8.9, 3.6 Hz, 1H), 7.53 (q, *J* = 8.3, 6.1 Hz, 1H), 7.45 – 7.27 (m, 3H), 7.22 – 7.03 (m, 3H), 6.99 – 6.89 (m, 1H), 6.39 – 6.28 (m, 1H), 5.69 (d, *J* = 5.0 Hz, 1H), 5.47 (d, *J* = 17.2 Hz, 1H), 5.39 (d, *J* = 10.5 Hz, 1H), 4.60 – 4.45 (m, 2H), 3.26 (s, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 152.5, 139.2, 138.7, 138.6, 134.3, 129.7, 129.4, 128.8, 128.8, 128.7, 127.6, 127.0, 126.6, 123.3, 123.1, 118.6, 118.1, 116.2, 74.3, 26.9. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{18}O_2$ 291.1380; found 291.1380.



(1S,2R)-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2a)

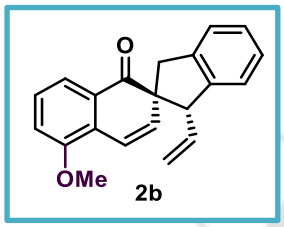
The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02) as colorless semisolid, 90% (24.5 mg) yield, 10:1 *dr*, 94% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.5, 1.5 Hz, 1H), 7.37 (td, *J* = 7.7, 1.2 Hz, 1H), 7.24 (m, 4H), 7.09 (dd, *J* = 8.4, 4.8 Hz, 1H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.76 (m, 1H), 5.12 – 5.03 (m, 2H), 4.47 (d, *J* = 9.4 Hz, 1H), 3.67 (d, *J* = 15.3 Hz, 1H), 2.87 (d, *J* = 15.2 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 201.8, 143.2, 140.4,



138.4, 136.0, 135.0, 134.8, 130.2, 128.0, 127.7, 127.6, 127.3, 127.2, 125.0, 124.7, 124.5, 119.3, 62.7, 61.0, 44.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{16}O$ 273.1274; found 273.1274. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.97 min, t_{minor} = 7.6 min).

(1S,2R)-5'-methoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2b)

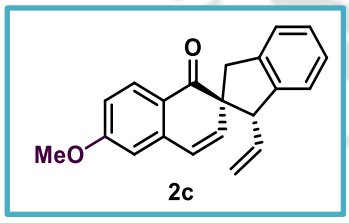
The product was purified by flash column chromatography (hexane/ethyl acetate = 94:06)



as colorless semi solid, yield: 60% (18 mg). 11:1 *dr*, 92% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.24 (m, 3H), 7.13 – 7.02 (m, 3H), 6.15 (d, *J* = 10.2 Hz, 1H), 5.77 (m, 1H), 5.15 – 5.02 (m, 2H), 4.45 (d, *J* = 9.4 Hz, 1H), 3.89 (s, 3H), 3.66 (d, *J* = 15.1 Hz, 1H), 2.86 (d, *J* = 15.2 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 202.2, 155.2, 143.3, 140.4, 135.1, 135.0, 131.0, 128.4, 127.7, 127.6, 127.2, 125.0, 124.5, 119.2, 119.0, 118.2, 116.1, 62.4, 61.0, 56.1, 44.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O_2$ 303.1380; found 303.1371. **HPLC Analysis:** The enantiomeric excess was determined using Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.02 min, t_{minor} = 11.02 min).

(1S,2R)-6'-methoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2c)

The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)

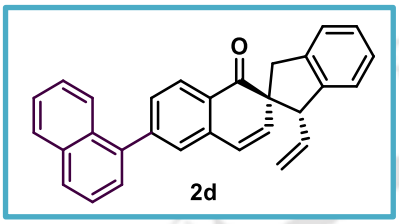


as colorless semi solid, 72% (21.7 mg) yield, >20:1 *dr*, 76% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 8.7 Hz, 1H), 7.23 (dt, *J* = 7.4, 3.9 Hz, 3H), 7.12 – 7.05 (m, 1H), 6.88 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.55 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 5.75 (dt, *J* = 16.8, 9.7 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.46 (d, *J* = 9.4 Hz, 1H), 3.88 (s, 3H), 3.67 (d, *J* = 15.3 Hz, 1H), 2.84 (d, *J* = 15.3 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 200.1, 164.9, 143.3, 140.6, 140.5, 137.2, 135.1, 129.8, 127.6, 127.2, 124.9, 124.7, 124.5, 124.1, 119.2, 114.2, 111.5, 62.5, 61.0, 55.7, 44.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O_2$ 303.1380; found 303.1381. **HPLC Analysis:** The enantiomeric excess was determined using Chiral PAK IF Column, *n*-

Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.57 min, t_{minor} = 11.42 min).

(1S,2R)-6'-(naphthalen-1-yl)-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2d)

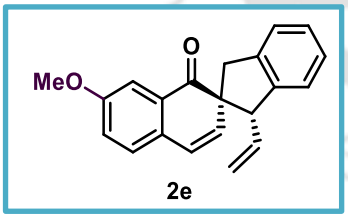
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)



as colourless semisolid, 51% (20.3 mg) yield, >20:1 *dr*, 86% *ee*. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.19 – 7.50 (m, 7H), 7.49 (s, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.76 (m, 1H), 5.12 – 5.03 (m, 2H), 4.47 (d, *J* = 9.4 Hz, 1H), 3.67 (d, *J* = 15.3 Hz, 1H), 2.87 (d, *J* = 15.2 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.8, 143.2, 140.4, 138.4, 136.0, 135.0, 134.8, 130.2, 128.6, 128.0, 127.7, 127.6, 127.3, 127.2, 126.7, 126.4, 126.2, 126.0, 125.6, 125.0, 124.7, 124.5, 122.0, 120.1, 119.7, 116.2, 108.2, 62.7, 61.0, 44.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{30}H_{22}O$ 399.1743, found 399.1744. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.81 min, t_{minor} = 10.76 min).

(1S,2R)-7'-methoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2e)

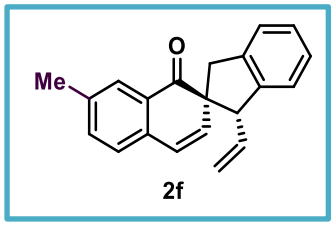
The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07)



as colorless semisolid, 78% (23.6 mg) yield, >20:1 *dr*, 72% *ee*. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 – 7.21 (m, 5H), 7.12 –6.81 (d, *J* = 2.5 Hz, 2H), 6.55 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 5.75 (m, 1H), 5.11 – 5.02 (m, 2H), 4.46 (d, *J* = 9.4 Hz, 1H), 3.91 (s, 3H), 3.67 (d, *J* = 15.3 Hz, 1H), 2.89 (d, *J* = 15.3 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 200.2, 164.9, 143.3, 140.6, 140.5, 137.2, 135.1, 129.8, 127.6, 127.2, 124.9, 124.7, 124.5, 124.1, 119.2, 114.2, 111.5, 62.7, 61.2, 55.6, 44.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O_2$ 303.1380, found 303.1379. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.02 min, t_{minor} = 10.84 min).

(1S,2R)-7'-methyl-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2f)

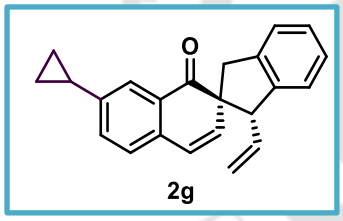
The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02)



as colorless semisolid, 75% (21.5 mg) yield, 12:1 *dr*, 88% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 1.9 Hz, 1H), 7.37 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.08 (q, *J* = 5.3, 3.9 Hz, 1H), 6.56 (d, *J* = 10.3 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 5.76 (m, 1H), 5.11 – 5.02 (m, 2H), 4.46 (d, *J* = 9.4 Hz, 1H), 3.66 (d, *J* = 15.2 Hz, 1H), 2.84 (d, *J* = 15.2 Hz, 1H), 2.39 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 202.0, 143.2, 140.4, 137.9, 135.9, 135.6, 135.1, 134.8, 130.0, 127.6, 127.5, 127.4, 127.2, 124.9, 124.5, 124.4, 119.1, 62.6, 60.9, 44.6, 21.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O$ 287.1431, found 287.1433. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.88 min, t_{minor} = 7.99 min).

(1S,2R)-7'-cyclopropyl-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2g)

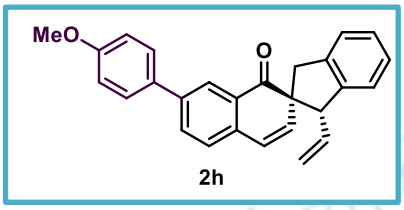
The product was purified by flash column chromatography (hexane/ethyl acetate = 96:04)



as colorless semisolid, 78% (24.4 mg) yield, >20:1 *dr*, 88% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 2.3 Hz, 1H), 7.30 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.23 (m, 3H), 7.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.56 (d, *J* = 9.8 Hz, 1H), 6.09 (dd, *J* = 9.8, 1.7 Hz, 1H), 5.75 (m, 1H), 5.14 – 5.01 (m, 2H), 4.46 (d, *J* = 9.4 Hz, 1H), 3.64 (d, *J* = 15.2 Hz, 1H), 2.84 (d, *J* = 15.2 Hz, 1H), 1.95 (m, 1H), 1.00 (m, 2H), 0.77 (m, 2H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 202.1, 144.4, 143.3, 140.4, 135.9, 135.1, 134.7, 132.5, 130.1, 127.6, 127.5, 127.2, 124.9, 124.5, 124.2, 123.7, 119.2, 62.6, 60.9, 44.8, 15.6, 9.8, 9.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{23}H_{20}O$ 313.1587, found 313.1587. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.36 min, t_{minor} = 9.02 min).

(1S,2R)-7'-(4-methoxyphenyl)-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2h)

The product was purified by flash column chromatography (hexane/ethyl acetate = 90:10)

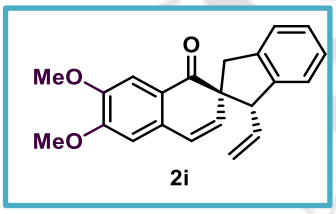


2h

as yellow semi solid, 78% (29.0 mg) yield, >20:1 *dr*, 60% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.21 (d, *J* = 7.2 Hz, 1H), 7.54 (m, 2H), 7.40 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.19 – 7.11 (m, 3H), 6.56 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 5.75 (m, 1H), 5.11 – 5.02 (m, 2H), 4.46 (d, *J* = 9.4 Hz, 1H), 4.01 (s, 3H), 3.77 (d, *J* = 15.3 Hz, 1H), 2.99 (d, *J* = 15.3 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 200.2, 160.9, 143.3, 140.6, 140.5, 137.2, 135.1, 129.8, 128.8, 128.6, 128.1, 128.0, 127.6, 127.2, 124.9, 124.7, 124.5, 124.1, 119.2, 114.2, 111.5, 62.7, 61.2, 55.6, 44.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{27}H_{22}O_2$ 379.1693, found 379.1693. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.8 min, t_{minor} = 23.6 min).

(1S,2R)-6',7'-dimethoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2i)

The product was purified by flash column chromatography (hexane/ethyl acetate = 93:07)

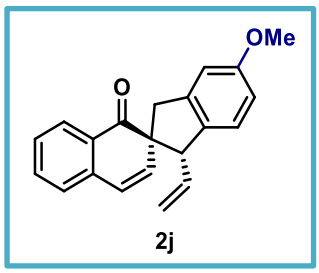


2i

as colorless semisolid, 64% (21.3 mg) yield, >20:1 *dr*, 66% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.25 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.20 – 7.15 (m, 2H), 7.09 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.52 (d, *J* = 9.9 Hz, 1H), 6.15 (d, *J* = 9.9 Hz, 1H), 5.77 – 5.70 (m, 1H), 5.10 – 5.02 (m, 2H), 4.39 (d, *J* = 9.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.61 – 3.31 (m, 1H), 2.80 (d, *J* = 15.0 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 153.5, 152.5, 140.6, 140.5, 137.5, 135.8, 134.4, 132.6, 130.5, 129.7, 128.3, 127.9, 127.4, 126.9, 125.3, 124.9, 62.7, 61.4, 56.4, 56.3, 44.4. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{22}H_{20}O_3$ 333.1486, found 333.1477. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.88 min, t_{minor} = 18.62 min).

(1S,2R)-5-methoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2j)

The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)

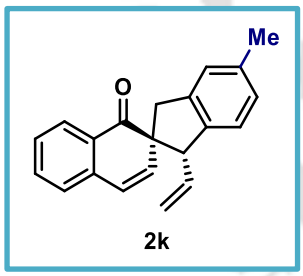


2j

as colorless semisolid, 65% (19.7 mg) yield, >20:1 *dr*, 94% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 2H), 6.61 (d, *J* = 9.9 Hz, 1H), 6.18 (d, *J* = 9.9 Hz, 1H), 5.74 (dt, *J* = 17.0, 9.7 Hz, 1H), 5.11 – 5.00 (m, 2H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 3.66 (d, *J* = 15.3 Hz, 1H), 2.82 (d, *J* = 15.3 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.7, 159.9, 141.9, 138.4, 136.1, 135.4, 135.1, 134.8, 130.2, 128.0, 127.5, 127.2, 125.1, 124.7, 118.9, 112.8, 110.7, 62.8, 60.3, 55.7, 44.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O_2$ 303.1380, found 303.1381. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.23 min, t_{minor} = 13.53 min).

(1S,2R)-5-methyl-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2k)

The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02)

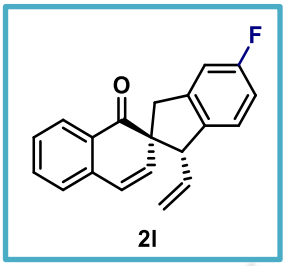


2k

as colorless semisolid, 62% (17.7 mg) yield, >20:1 *dr*, 84% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.75 (m, 1H), 5.10 – 5.00 (m, 2H), 4.42 (d, *J* = 9.3 Hz, 1H), 3.64 (d, *J* = 15.3 Hz, 1H), 2.82 (d, *J* = 15.3 Hz, 1H), 2.36 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.9, 140.5, 140.2, 138.4, 137.4, 136.2, 135.3, 134.7, 130.2, 128.0, 127.5, 127.2, 125.7, 125.2, 124.6, 124.3, 119.0, 62.8, 60.6, 44.5, 21.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for 287.1431, found 287.1429. **HPLC Analysis:** The enantiomeric excess was determined using Chiral ART Amylose-C Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.55 min, t_{minor} = 7.44 min).

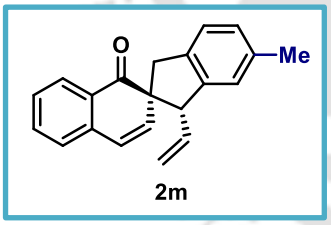
(1S,2R)-5-fluoro-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2l)

The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02) as colorless solid, 60% (17.4 mg) yield, 8:1 *dr*, 84% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.5, 1.6 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.18 (m, 1H), 7.01 (dd, *J* = 8.1, 5.4 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 9.9 Hz, 1H), 6.14 (d, *J* = 10.0 Hz, 1H), 5.79 – 5.68 (m, 1H), 5.11 – 5.01 (m, 2H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.65 (d, *J* = 15.5 Hz, 1H), 2.83 (d, *J* = 15.5 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.4, 164.0, 162.0, 142.6, 142.5, 138.5, 138.5, 138.3, 138.0, 135.5, 134.9, 130.1, 128.1, 127.6, 127.2, 125.6, 125.5, 125.0, 119.4, 114.1, 113.9, 112.3, 112.1, 62.8, 60.2, 44.2. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{15}FO$ 291.1180, found 291.1179. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.82 min, t_{minor} = 7.77 min).



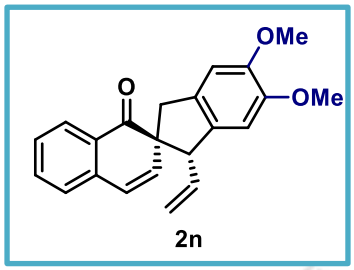
(1S,2R)-6-methyl-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2m)

The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02) as colorless semisolid, 70% (20 mg) yield, 8:1 *dr*, 50% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 6.59 (d, *J* = 9.9 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.75 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.11 – 5.02 (m, 2H), 4.43 (d, *J* = 9.4 Hz, 1H), 3.61 (d, *J* = 15.1 Hz, 1H), 2.82 (d, *J* = 15.1 Hz, 1H), 2.34 (s, 3H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 201.8, 143.3, 138.4, 137.3, 136.9, 136.1, 135.2, 134.7, 130.2, 128.4, 128.0, 127.5, 127.1, 125.2, 124.7, 124.6, 119.1, 62.8, 60.9, 44.2, 21.5. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{18}O$ 287.1431, found 287.1423. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ID Column, *n*-Hexane/*i*-PrOH = 98/02, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.73 min, t_{minor} = 8.81 min).



(1S,2R)-5,6-dimethoxy-1-vinyl-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1'-one (2n)

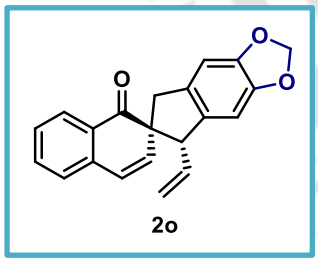
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)



as colorless semisolid, 62% (20.5 mg) yield, >20:1 *dr*, 74% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.10 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.58 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.25 (dd, *J* = 7.7, 1.2 Hz, 1H), 6.77 (s, 1H), 6.61 (d, *J* = 9.8 Hz, 2H), 6.22 (d, *J* = 9.9 Hz, 1H), 5.77 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.10 – 5.02 (m, 2H), 4.39 (d, *J* = 9.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.61 (dt, *J* = 14.9, 1.3 Hz, 1H), 2.80 (d, *J* = 15.0 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 201.8, 149.0, 148.8, 138.3, 136.3, 135.5, 134.8, 134.6, 131.7, 130.1, 128.0, 127.5, 127.2, 124.6, 119.0, 108.2, 107.7, 62.8, 60.9, 44.2. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{22}H_{20}O_3$ 333.1486, found 333.1478. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK IF Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.36 min, t_{minor} = 19.87 min).

(5S,6R)-5-vinyl-5,7-dihydro-1'H-spiro[indeno[5,6-d][1,3]dioxole-6,2'-naphthalen]-1'-one (2o)

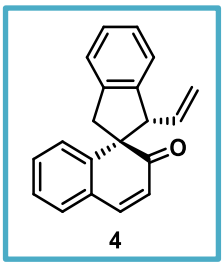
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)



as colorless semisolid, 64% (20.0 mg) yield, >20:1 *dr*, 78% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 8.1 Hz, 1H), 7.75 (td, *J* = 6.5, 3.3 Hz, 2H), 7.51 – 7.47 (m, 1H), 6.77 (s, 1H), 6.64 (s, 1H), 6.58 (d, *J* = 9.9 Hz, 1H), 6.12 (d, *J* = 9.8 Hz, 1H), 5.84 (d, *J* = 9.7 Hz, 2H), 5.79 – 5.68 (m, 1H), 5.11 – 5.01 (m, 2H), 4.38 (d, *J* = 9.4 Hz, 1H), 3.65 (d, *J* = 15.5 Hz, 1H), 2.83 (d, *J* = 15.5 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 201.5, 149.9, 147.7, 146.1, 140.7, 137.0, 135.8, 133.1, 132.5, 132.3, 130.7, 128.6, 127.6, 127.4, 125.1, 114.5, 110.2, 60.8, 55.5, 51.2, 45.6, 39.6. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{21}H_{16}O_3$ 317.1172, found 317.1172. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.39 min, t_{minor} = 13.45 min).

(1S,2R)-1-vinyl-1,3-dihydro-2'H-spiro[indene-2,1'-naphthalen]-2'-one (4)

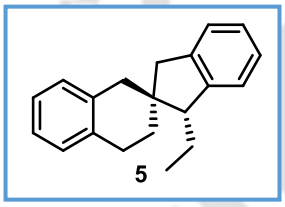
The product was purified by flash column chromatography (hexane/ethyl acetate = 98:02)



as colorless semisolid, 48% (13 mg) yield, 9:1 *dr*, 90% *ee*. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 9.9 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.26 – 7.22 (m, 2H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 2H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.09 – 4.93 (m, 3H), 4.29 – 4.18 (m, 2H), 3.23 (d, *J* = 16.3 Hz, 1H). **^{13}C{H} NMR (125 MHz, $CDCl_3$)** δ 203.4, 146.2, 144.0, 143.0, 142.4, 134.8, 130.1, 129.9, 129.5, 127.9, 127.4, 127.2, 126.5, 126.0, 124.9, 124.0, 119.6, 65.4, 64.5, 43.3. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{17}O$ 273.1274, found 273.1271. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 6.57 min, t_{minor} = 8.55 min).

(1R,2S)-1-ethyl-1,3,3',4'-tetrahydro-1'H-spiro[indene-2,2'-naphthalene] (5)

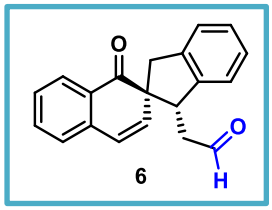
The product was purified by flash column chromatography (hexane/ethyl acetate = 94:06)



as colorless liquid, yield: 90% (23.5 mg), 92% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 – 7.29 (m, 1H), 7.22 (m, 3H), 7.19 (d, *J* = 6.0 Hz, 2H), 7.15 – 7.12 (m, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 3.02 – 2.95 (m, 3H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.72 – 2.65 (m, 3H), 2.01 – 1.92 (m, 2H), 1.89 – 1.83 (m, 1H), 1.49 – 1.43 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 147.4, 142.2, 136.4, 136.2, 129.9, 128.9, 126.4, 125.8, 125.8, 125.8, 125.7, 125.3, 55.6, 45.8, 42.1, 41.7, 28.8, 27.3, 23.1, 12.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{22}$ 263.1795, found 263.1799. **HPLC Analysis:** The enantiomeric excess was determined using Phenomenex Lux Cellulose1 Column, *n*-Hexane/*i*-PrOH = 99.5/0.5, flow rate 0.3 mL/min, λ = 254 nm (t_{minor} = 16.23 min, t_{major} = 20.34 min).

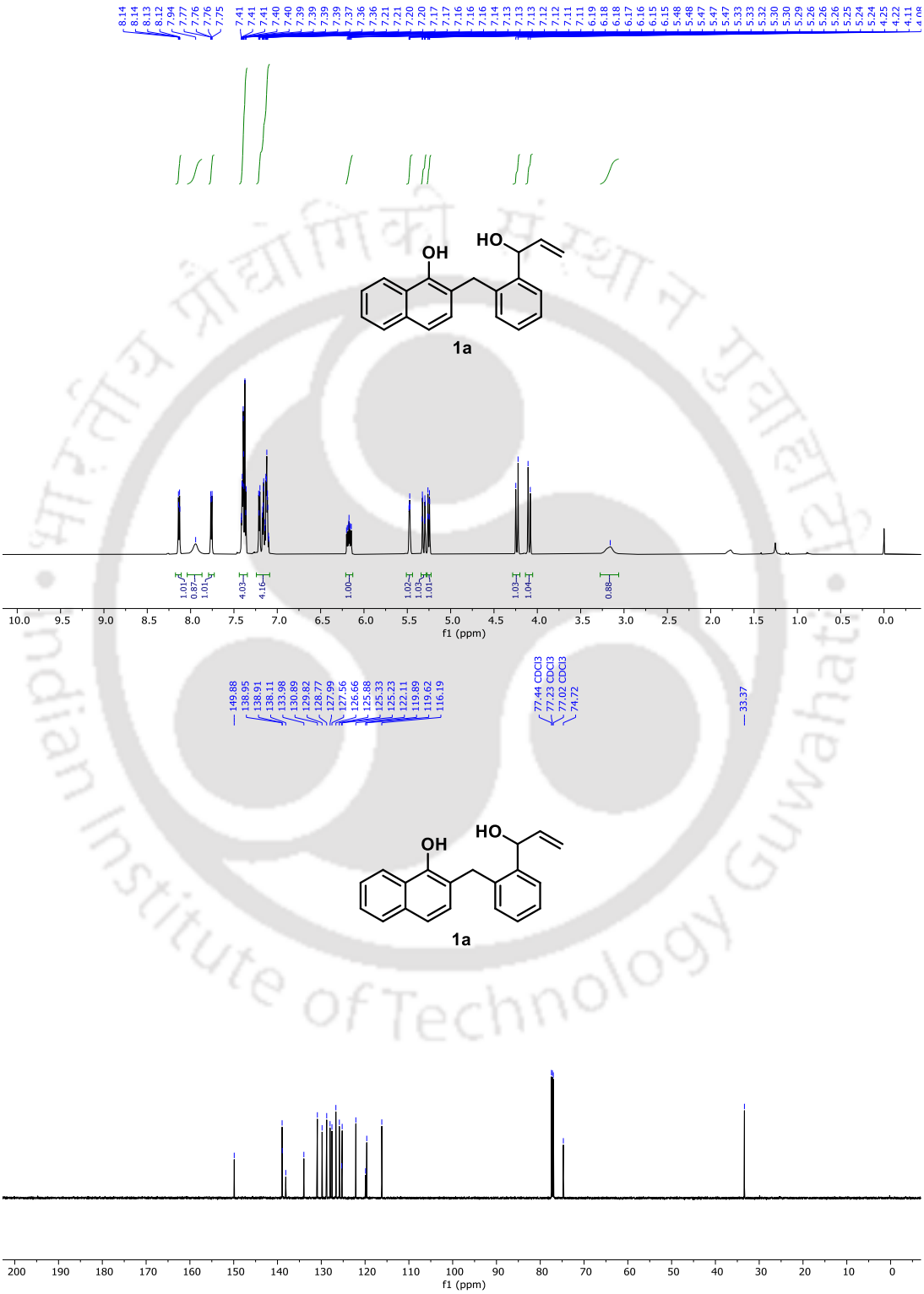
2-((1S,2R)-1'-oxo-1,3-dihydro-1'H-spiro[indene-2,2'-naphthalen]-1-yl)acetaldehyde(6)

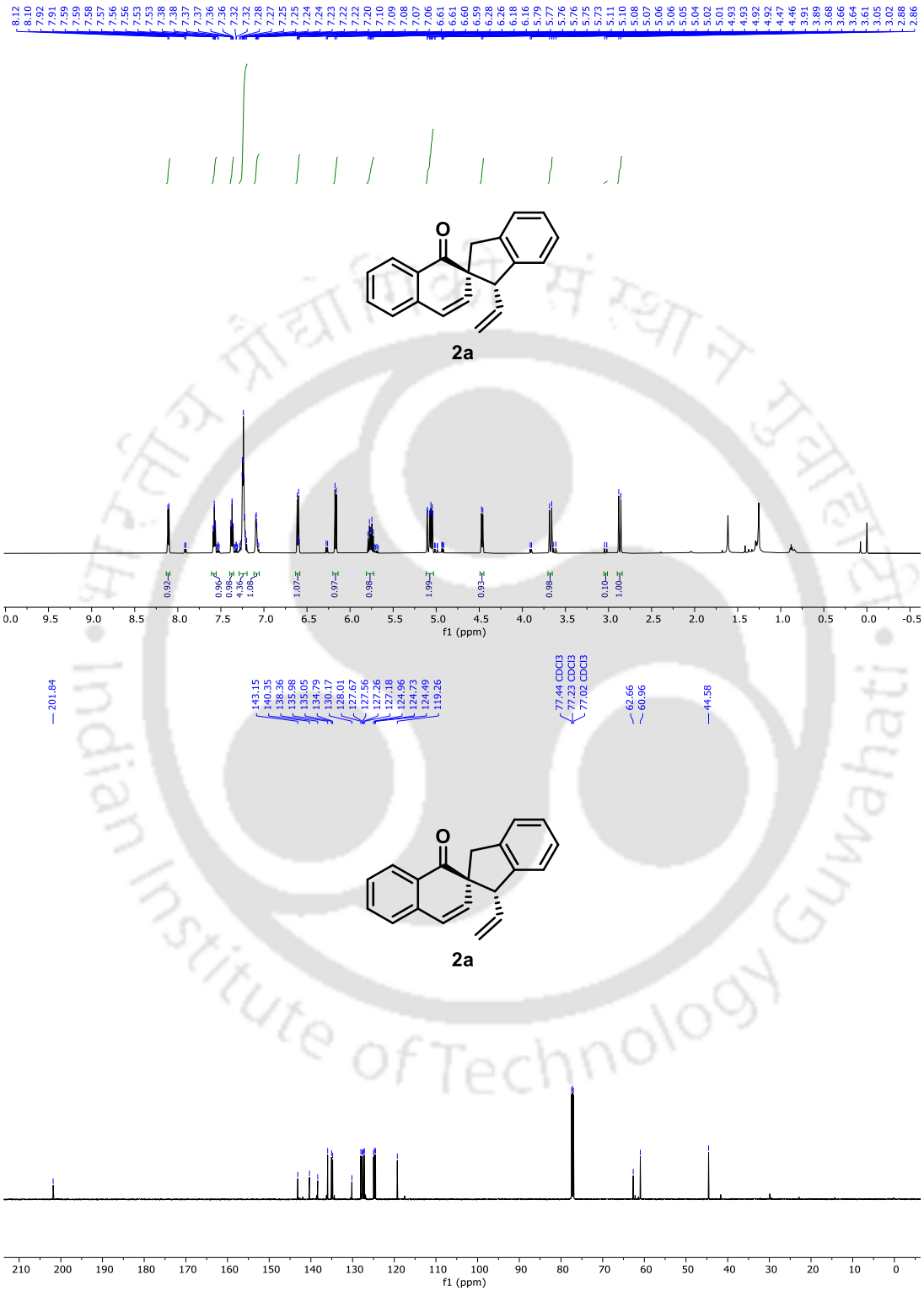
The product was purified by flash column chromatography (hexane/ethyl acetate = 95:05)

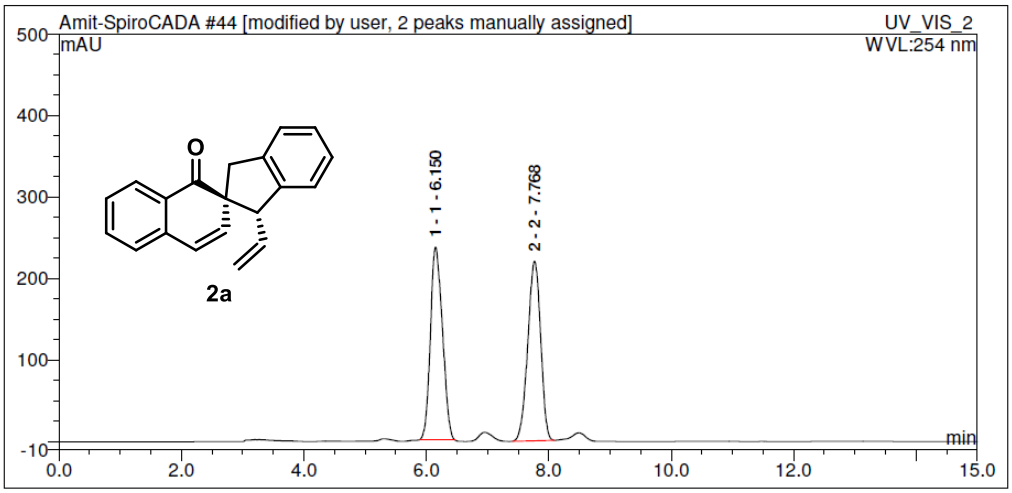


as yellow semi solid, yield: 53% (15.0 mg), 88% *ee*. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 9.68 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.28 (q, *J* = 4.5, 4.1 Hz, 3H), 7.25 – 7.23 (m, 1H), 7.12 – 7.06 (m, 1H), 6.67 (d, *J* = 9.9 Hz, 1H), 6.10 (d, *J* = 9.9 Hz, 1H), 4.47 (t, *J* = 7.2 Hz, 1H), 3.69 (d, *J* = 15.3 Hz, 1H), 2.94 – 2.85 (m, 2H), 2.62 (dd, *J* = 17.9, 7.6 Hz, 1H). **^{13}C{H} NMR (150 MHz, $CDCl_3$)** δ 201.4, 200.6, 142.7, 140.3, 137.6, 135.3, 134.9, 130.1, 128.5, 127.9, 127.7, 127.5, 127.4, 125.5, 125.0, 123.6, 60.9, 49.3, 45.6, 44.7. **HRMS (ESI-TOF) *m/z*:** $[M+H]^+$ calcd. for $C_{20}H_{16}O_2$ 289.1224, found 289.1218. **HPLC Analysis:** The enantiomeric excess was determined using Daicel Chiral PAK ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.84 min, t_{minor} = 7.61 min).

5.9 NMR and HPLC spectra







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
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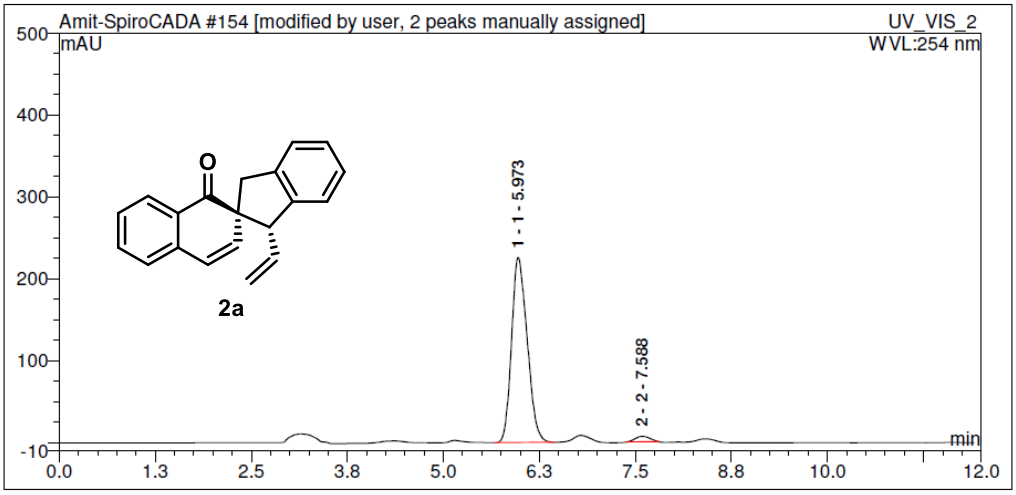
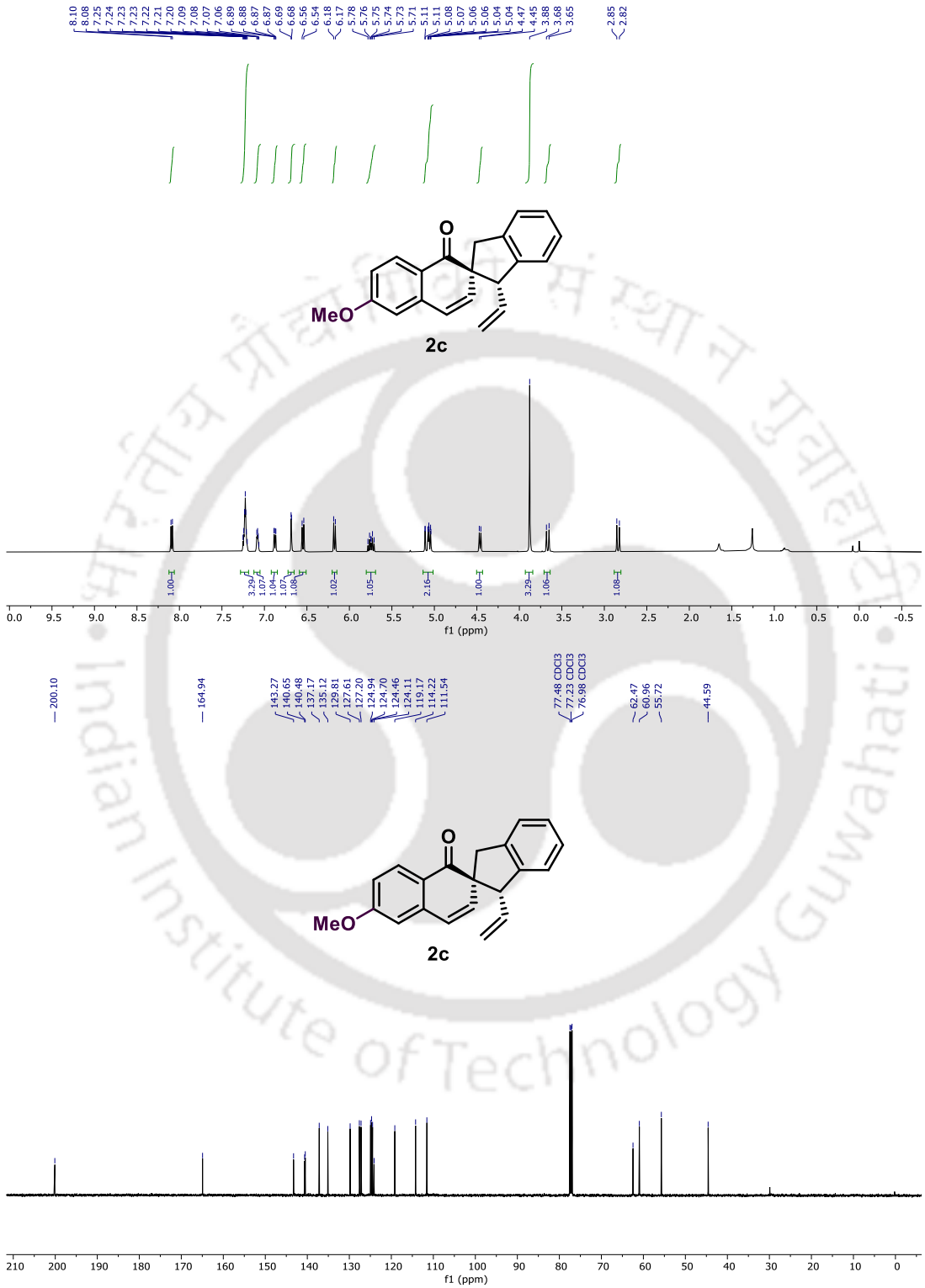
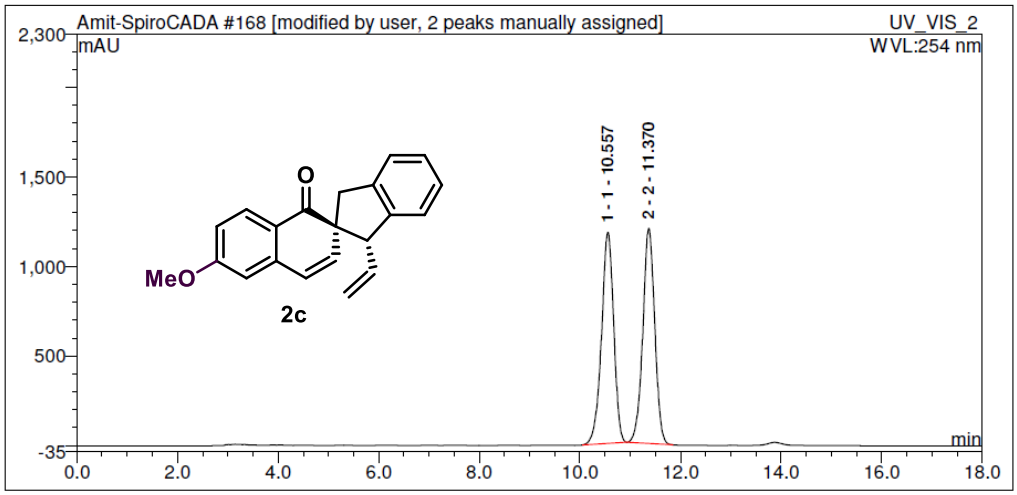
2	2	7.768333333	53.68573	49.98350511	220.0511	n.a.

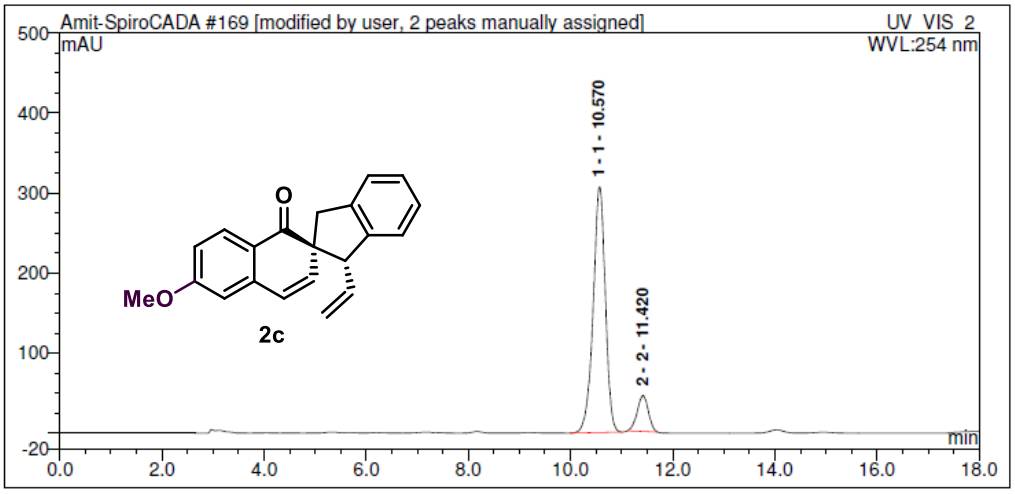


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.973333333	53.2375	97.23166705	225.7843	n.a.
2	2	7.588333333	1.515752	2.768332946	6.78143	n.a.

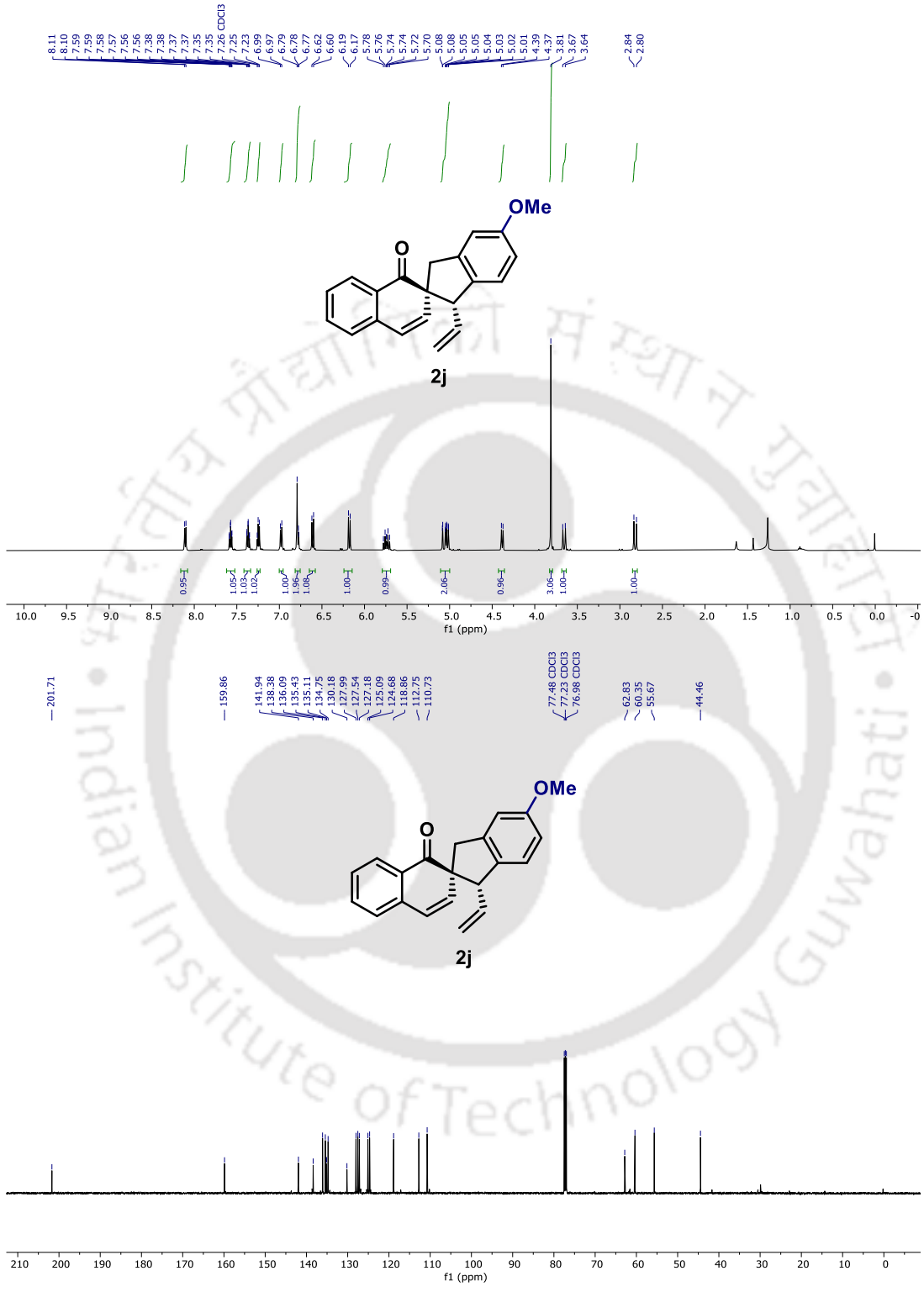


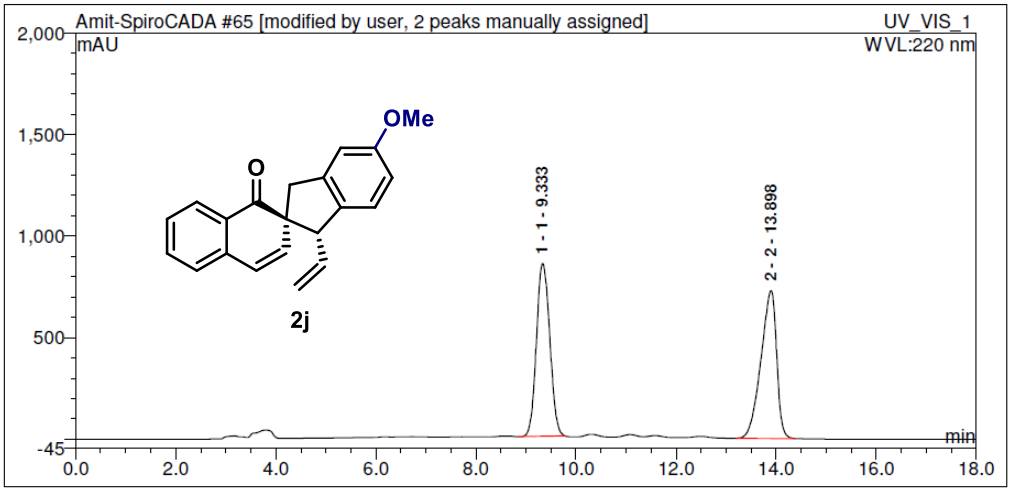


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.55666667	330.9201	49.97220518	1179.878	n.a.
2	2	11.37	331.2882	50.02779482	1202.311	n.a.

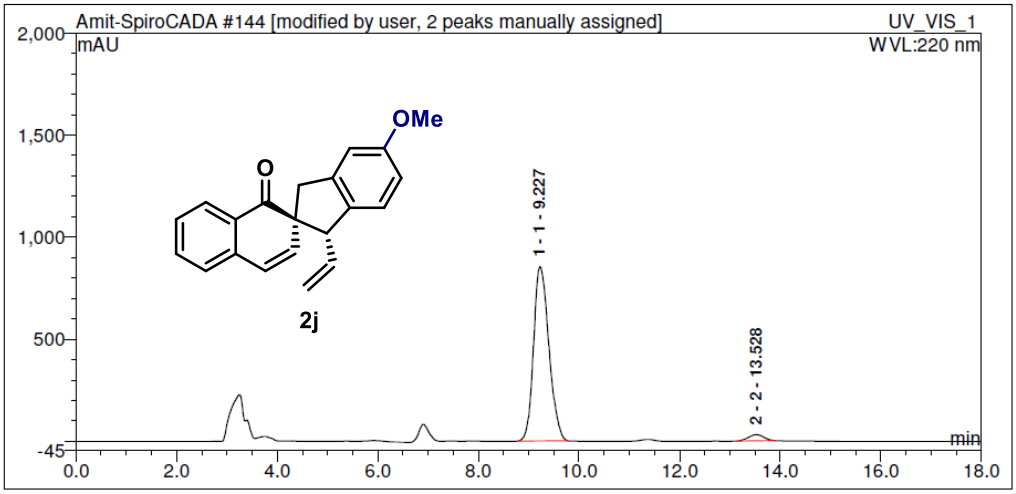


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.57	84.84127	88.22510828	306.6224	n.a.
2	2	11.42	11.32327	11.77489172	44.75728	n.a.

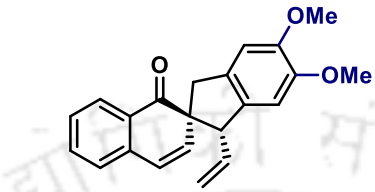




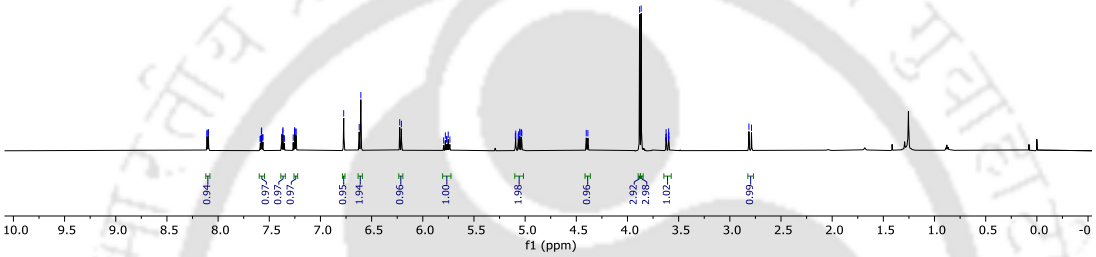
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.333333333	262.7458	49.82862978	850.4853	n.a.
2	2	13.89833333	264.5531	50.17137022	727.2678	n.a.

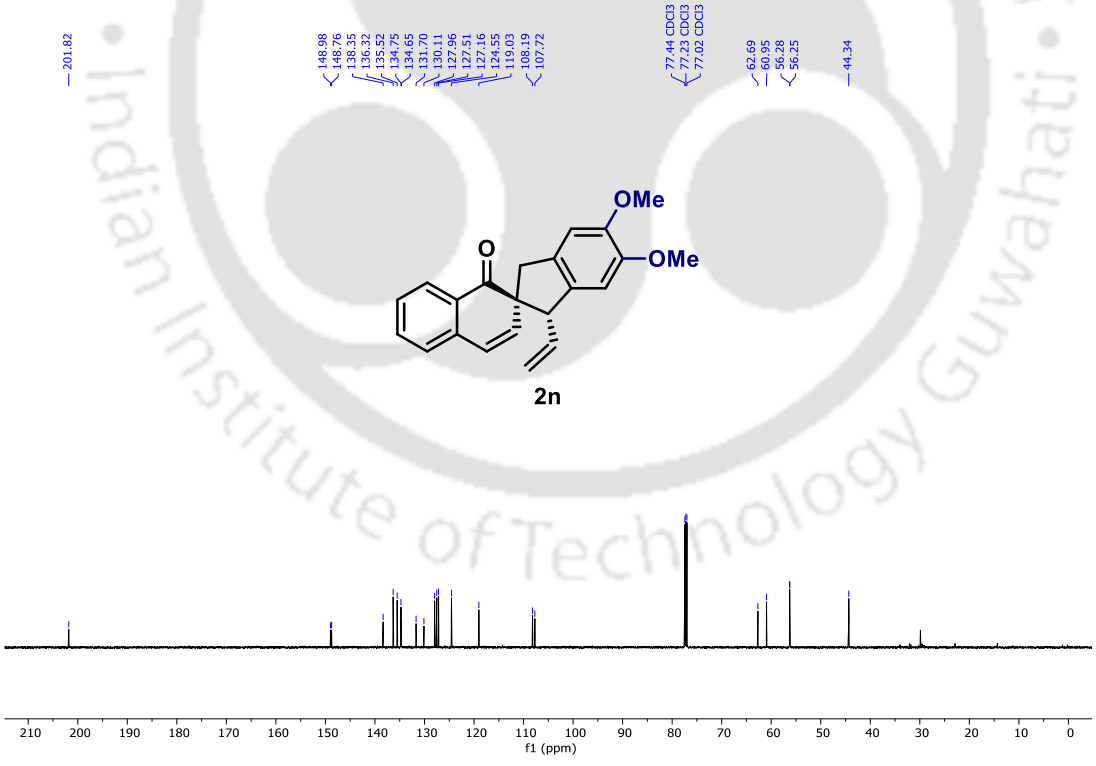


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.226666667	301.4235	96.67667335	853.1542	n.a.
2	2	13.52833333	10.36164	3.323326652	29.71269	n.a.

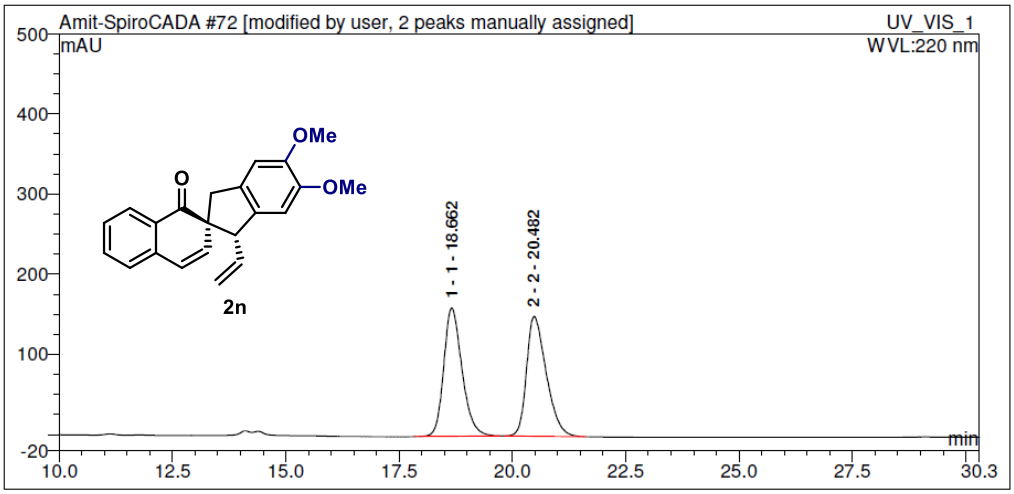


2n

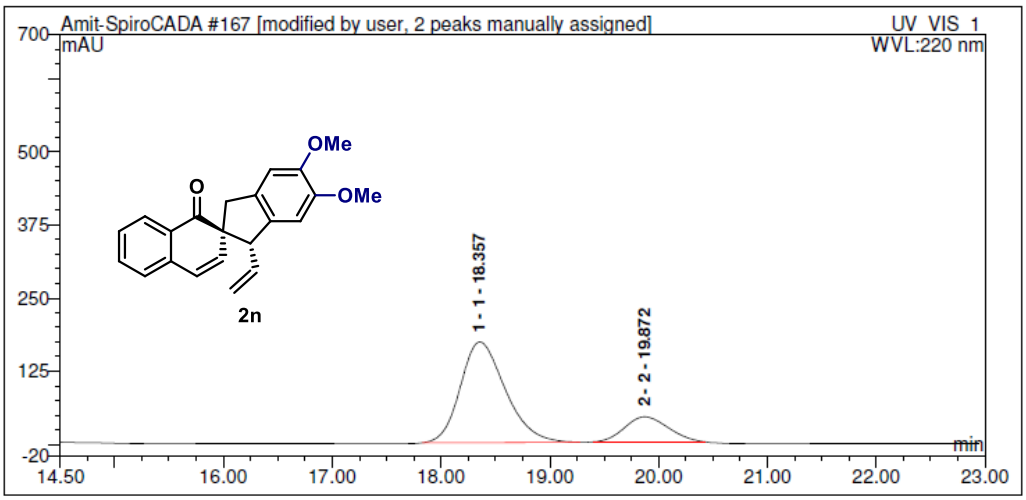




2n



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	18.66166667	74.9	49.84702755	159.9562	n.a.
2	2	20.48166667	75.35971	50.15297245	149.2729	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	18.35666667	82.3749	80.59652283	171.8939	n.a.
2	2	19.87166667	19.83162	19.40347717	42.70021	n.a.

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List of publications

1. "Organocatalytic Asymmetric Synthesis of Cyclic Acetals with Spirooxindole Skeleton." **Shikari**, **A**.; Mandal, K.; Chopra, D.; Pan, S. C. *Adv. Synth. Catal*. **2022**, *364*, 58 – 63.
2. "Catalytic Asymmetric Dearomatization of 2,3-Disubstituted Indoles by a [4 + 2] Cycloaddition Reaction with In Situ Generated Vinylidene ortho-Quinone Methides: Access to Polycyclic Fused Indolines." **Shikari**, **A**.; Parida, C.; Pan, S. C. *Org. Lett.* **2024**, *26*, 5057 – 5062.
3. "Organocatalytic Dearomative Spirocyclization Reaction of Enone-Tethered *α*-and *β*-Naphthols and Dearomatization Reaction of In Situ Generated Nitro-Olefin-Tethered *α*-Naphthols." **Shikari**, **A**.; Sharma, M.; Bhattacharyya, K.; Pan, S. C. *J. Org. Chem*. **2024**, *89*, 9769.
4. "Cooperative Iridium and Brønsted Acid Catalyzed Intramolecular Asymmetric Allylic Dearomatization of *α*- and *β*-Naphthols." **Shikari**, **A**.; Pan, S. C. *Manuscript communicated.*

Conferences Attended

1. Presented a poster in **International Conference on Chemistry for Human Development (ICCHD-2020)** held at Heritage Institute of Technology, Kolkata, India.
2. Presented a poster in **Chemical Research Society of India 28th National Symposium in Chemistry** (**CRSI NSC-2022)** held at IIT Guwahati, India.
3. Presented a poster in **North-East Research Conclave (NERC-2022)** held at IIT Guwahati, India.
4. Presented a poster in **Frontiers in Chemical Sciences** (**FICS-2022**) held at IIT Guwahati, India.