Organocatalytic Enantioselective Synthesis of Aza-Spirooxindoles and Construction of Quaternary Stereocenters by Desymmetrization Reactions

A Dissertation

Submitted in Partial Fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Organocatalytic Enantioselective Synthesis of Aza-Spirooxindoles and Construction of Quaternary Stereocenters by Desymmetrization Reactions***" 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 "***Organocatalytic Enantioselective Synthesis of Aza-Spirooxindoles and Construction of Quaternary Stereocenters by Desymmetrization Reactions***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Subhankar Biswas (Roll No: 196122035) 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 **Prof. Subhas Chandra Pan**

December, 2024 **Supervisor**

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Sincerely,

Subhankar Biswas

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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*
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

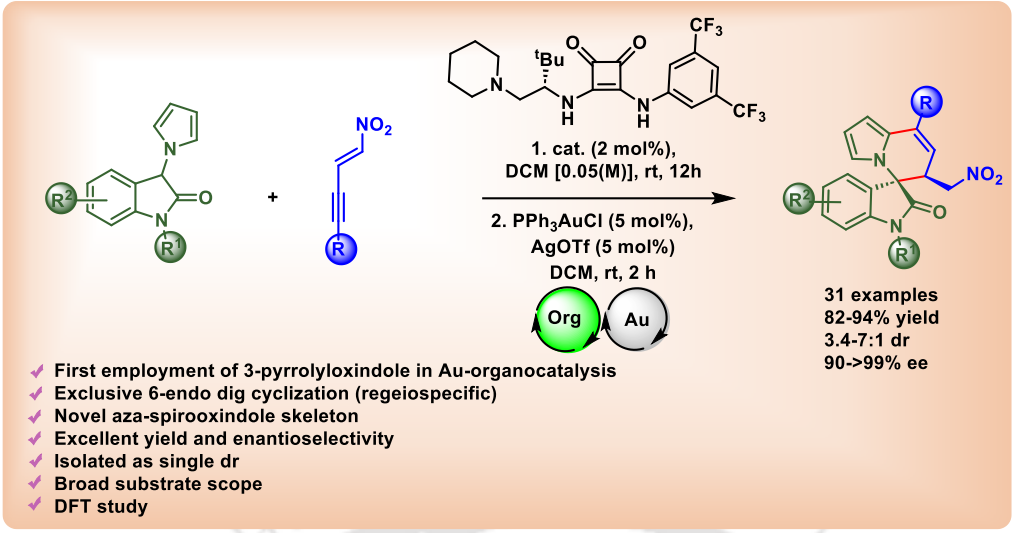
The contents of the present thesis entitled as "***Organocatalytic Enantioselective Synthesis of Aza-Spirooxindoles and Construction of Quaternary Stereocenters by Desymmetrization Reactions***" have been divided into five chapters based on the results achieved from the experimental works performed during 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 on enantioselective merged gold/organocatalysis. And second part contains a brief discussion on construction of quaternary stereocenters by desymmetrization reactions.

Chapter II: Sequential Organo and Metal Catalyzed Reaction Between 3-Pyrrolyloxindoles and Linear Nitroenynes: Access to Cyclic Aza-Spirooxindoles

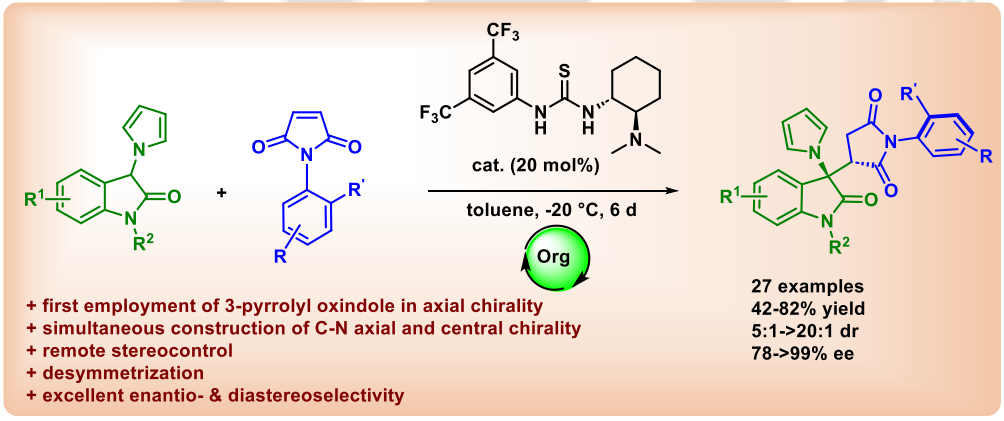
An asymmetric Michael addition/hydroarylation reaction sequence, catalyzed by a sequential catalytic system consisting of a squaramide and a combination of silver and gold salts, provides a new series of cyclic aza-spirooxindole derivatives in excellent yields (up to 94%) and high diastero- and enantioselectivities (up to 7:1 dr, up to >99% ee). Computational study has also been performed.



Reference: **Biswas, S**.; Purkayastha, S. K.; Guha, A. K.; Pan, S. C. *Chem. Comm.*, **2023**, *59*, 12156.

Chapter III: Organocatalytic Asymmetric Synthesis of C-N Atropisomers with Pyrrole, Oxindole and Succinimide Scaffold

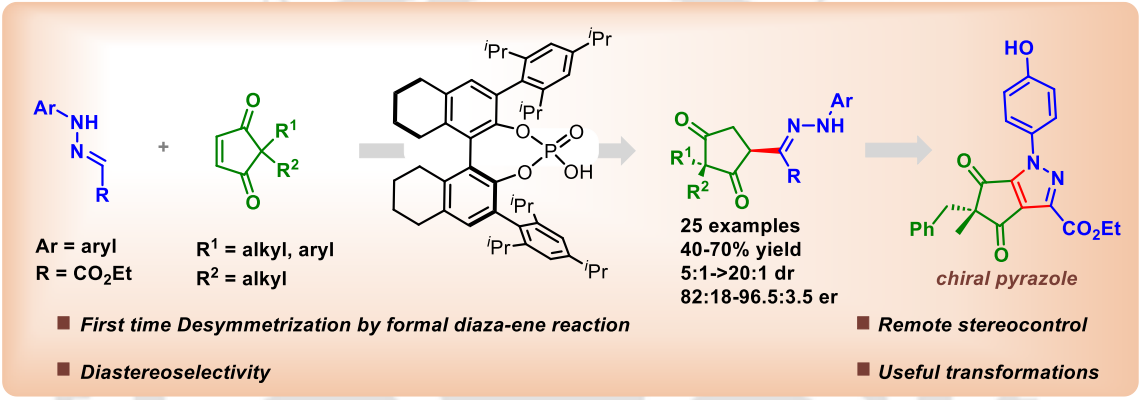
Organocatalytic desymmetric Michael addition of 3-pyrrolyloxindole with prochiral N-aryl maleimides was used to create an asymmetric synthesis of C-N atropisomers with pyrrole, oxindole, and succinimide moities. High diasteroselectivities and enantioselectivities (>20:1 dr, up to >99% ee) were obtained for the C-N atropisomers in acceptable yields. Additionally, the C-N rotational energy barrier has been determined.



Reference: **Biswas, S.**; Kundu, S.; Pan, S. C. *Chem Asian J.* **2025**, *20,* e202401132.

Chapter IV: Organocatalytic Asymmetric Desymmetrization of Cyclopentene-1,3-diones via Formal Diaza-ene Reaction with Donor–Acceptor Hydrazones

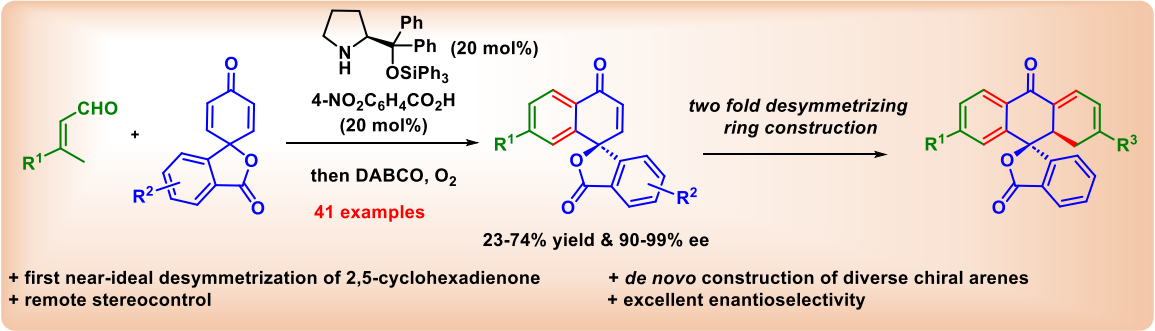
Here in, we disclose a catalytic asymmetric desymmetrization of cyclopentene-1,3-diones through formal diaza-ene reaction/tautomerization with donor-acceptor hydrazones. It was found that H8-TRIP chiral phosphoric acid worked well for this process. Chiral cyclopentane 1,3-diones embedded with the hydrazone motif were obtained in good to high yields with excellent diastereo- and good to high enantioselectivities. The scope of the reaction was broad, and some synthetic application, such as chiral pyrazole synthesis have been shown.



Reference: **Biswas, S.**; Pan, S. C. *Organic Chemistry Frontiers.* **2025**, *12,* 2651.

Chapter V: Catalytic Asymmetric Desymmetrizing [4+2] Cycloaddition/Base Mediated Oxidative Aromatization Sequence: *De Novo* Synthesis of Isobenzofuranone Embedded Chiral Arenes

Asymmetric desymmetrizing [4+2] cycloaddition/base-mediated oxidative aromatization reaction between *β*-methyl cinnamaldehydes and spirophthalide 2,5-cyclohexadienones has been developed here. The reaction progressed through the formation of an in situ chiral dienamine intermediate resulting in densely functionalised spirocyclic isoben-zofuranone embedded chiral arenes with high yields and excellent enantioselectivities. Additionally, a twofold desymmetrization reaction was carried out, yielding products with high enantioselectivities.



Reference: **Biswas, S.**; Pan, S. C. *Org. Lett.* **2025**, *27* (1), 309.

Chapter I

Overview

PART 1

Enantioselective Merged Gold/Organocatalysis

1.1 Introduction

The term "asymmetric" refers to a lack of equality or equivalence between parts or aspects of something, which could be anything from nature, molecules, or the human body. In 1801, René Just Haüy, a French mineralogist, first discovered chirality in quartz crystals. Louis Pasteur discovered molecular chirality in 1847 while examining *para*-tartrate crystals.[1] He observed that tartaric acid crystals can exist in two forms. These two forms were later identified as mirror images. Such compounds are known as enantiomers.[2-3] Molecular chirality is the foundation of stereochemistry, and his research revealed that asymmetry was one of the most fundamental properties of living things. Enantiomers interact differently in the chiral environment, despite having the same chemical and physical properties in the achiral one. Physical properties include melting point, colour, hardness, density, etc. Enantiomers behave differently in response to plane-polarized light. One rotates the plane-polarized light to the right (+) is dextrorotatory *d*-(+), while the other rotates it to the left is levorotatory *l*-(-). The extent of rotation in the two cases is identical, with the exception of the direction of rotation, which is opposite. For example, orange and lemon smell differently, being the left and right –handed version of the same molecule, i.e., they are enantiomeric form of limonone (Figure 1).[4] Because our nasal receptors are made up of chiral molecules, we can distinguish between the two isomers. Enantiomers are chiral molecules that are not superimposable mirror images of one another.

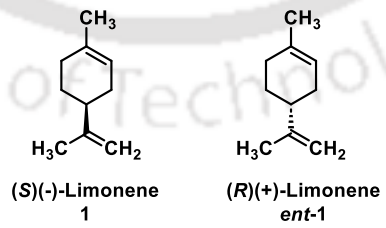


Figure 1. The enantiomers of limonene

Living organisms are the primary source of optically active substances, producing mostly one of the isomers. One of the most fundamental and universal rules of biological activity is chiral determination, or the ability to distinguish a molecule's structure from its mirror

image.[5] In biological systems, enzymes are the essential catalysts that are optically active; thus, stereochemical specificity is the norm rather than the exception. The biological activity of many drugs varies depending on their enantiomers.[6] 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).[7]

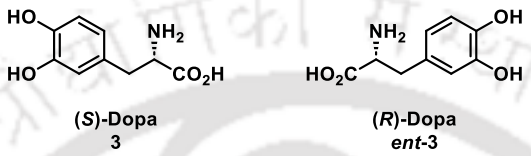


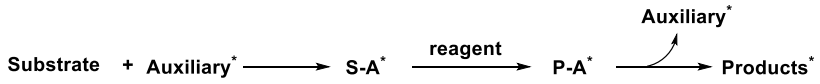
Figure 2: The enantiomers of Dopa.

Because the two enantiomers of a chiral molecule frequently have opposite effects on cells, it is critical to prepare drug molecules in enantiomerically pure forms. These are the most important processes in modern chemistry, particularly in pharmaceuticals. Here is where asymmetric synthesis comes into play. Asymmetric synthesis is the process of forming preferentially one stereoisomer (enantiomer or diastereomer) over another. Asymmetric synthesis is divided into four major categories: (1) substrate-controlled methods; (2) auxiliary-controlled methods; (3) reagent-controlled methods; and (4) catalyst-controlled methods.

Substrate-controlled asymmetric synthesis: Diastereoselective reactions in which the formation of a new chiral centre is influenced by an existing chiral centre in the substrate.

Scheme 1: Substrate-controlled asymmetric synthesis

Auxiliary-controlled asymmetric synthesis: A chiral auxiliary, or chiral molecular unit, is temporarily attached to an achiral substrate to direct the selective formation of one of two stereoisomers. Chiral auxiliaries are optically active compounds that introduce chirality into previously achiral starting materials. A chiral auxiliary physically prevents one of two possible attack trajectories on an achiral substrate, leaving only the desired pathway open for the reaction. Steric considerations can be used to explain the new chiral center's stereochemistry.



Scheme 2: Auxiliary-controlled asymmetric synthesis

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

Scheme 3: Reagent-controlled asymmetric synthesis

During the early decades of asymmetric synthesis, chiral pool synthesis and the use of chiral auxiliaries were popular strategies.[8] However, in terms of the step- and atom-economical aspects of synthesis, catalytic methods have emerged as a more powerful tool in recent decades.

Catalyst-controlled asymmetric synthesis: Chiral catalysts direct the formation of a new chiral centre. This method requires a catalytic amount of catalysts, making it very cost-effective and sustainable.

Scheme 4: Catalyst -controlled asymmetric synthesis

Catalyst-controlled methods can be classified into three main categories, based on the nature of catalysts used:

i) Biocatalysis[9] is the chemical process through which enzymes or other biological catalysts are used as for regio-, chemo- and stereoselective transformations.

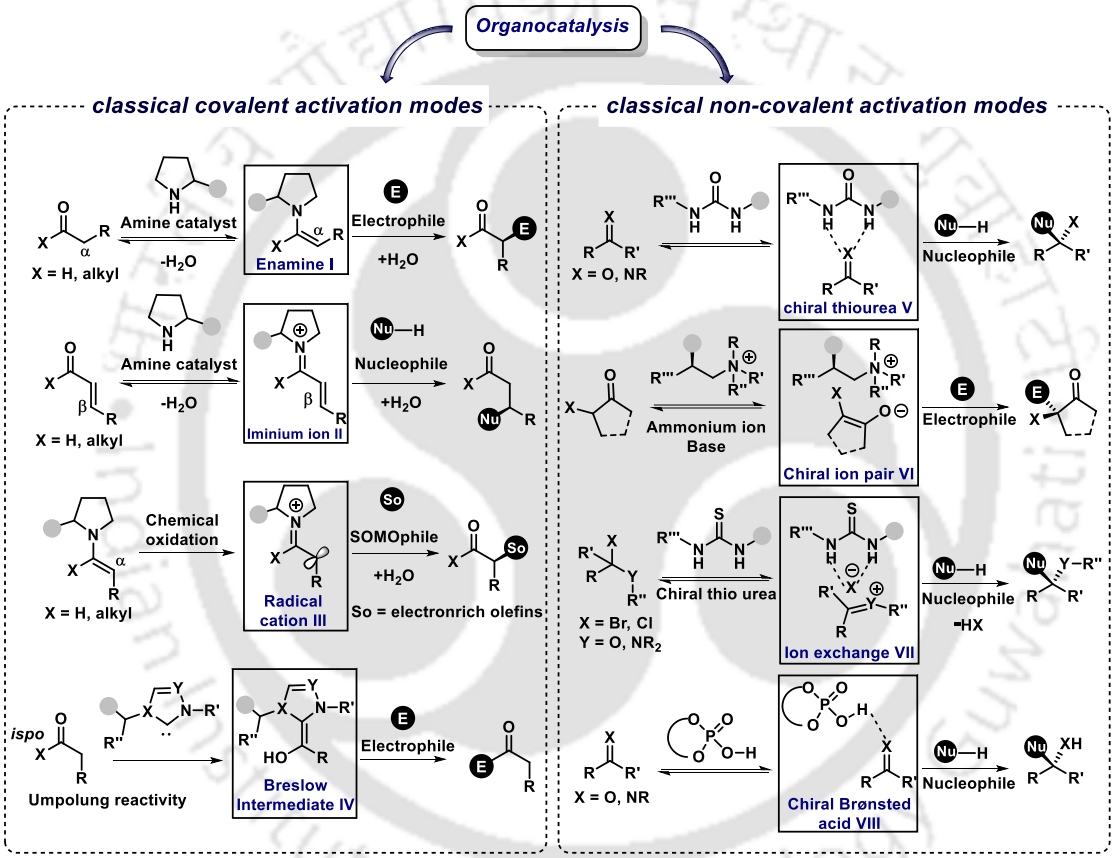
ii) Metal catalysis[10] have become one of the most actively studied due to unthinkable transformations could be easily performed with the help of metal catalysts.

iii) Organocatalysis[11] is the use of small chiral organic molecules as catalysts for stereoselective reactions has had a significant impact in chemical synthesis.

1.2 Asymmetric Organocatalysis

Along with enzymes and metal-based catalysts, asymmetric organocatalysis has been recognized as the third fundamental pillar of asymmetric catalysis and has become a crucial component of scientists' work in both academic and industry settings. Particularly

in the last 20 years, this discipline has advanced quickly due to the development of novel ideas and techniques.[12] Numerous distinguished honours have also been given to it, such as the 2021 Nobel Prize in Chemistry, which was given to David MacMillan and Benjamin List for "the development of asymmetric organocatalysis." diverse activation types exist among diverse organocatalytic techniques, and two primary categories can be distinguished based on their mechanisms: (i) covalent organocatalysis and (ii) non-covalent organocatalysis (Scheme 5).



Scheme 5: Generic mechanisms of organocatalytic reactivity

The ability of an organic catalyst to covalently bind a substrate in a reversible manner and create a reactive intermediate that can take part in a variety of reaction types with consistently high enantioselectivity is exploited by covalent-based modes of activation. This class includes chiral primary and secondary amines, which activate carbonyl substrates by forming nucleophilic enamines **I**[13] from enolizable aldehydes and ketones, electrophilic iminium ions **II**[14] from unsaturated carbonyl compounds and α-iminyl radical

cation intermediates **III**[15] from enamines that have been single-electron oxidized by a chemical oxidant. N-heterocyclic carbene catalysts **IV**[16] provide an alternative method of aldehyde activation by giving the normally electrophilic carbonyl carbon atom an inverted (umpolung) reactivity upon the formation of the Breslow intermediate **IV**[17], which functions as an equivalent of an acyl anion.[18, 19] Stereoselective functionalization of unmodified carbonyl compounds at the *ipso*, *α*, and *β* locations is made possible by these activation mechanisms, which depend on strong, directed contacts.

Non-covalent methods rely on the catalyst and a basic functional group on the substrates cooperating through a number of weakly attractive interactions.[20] The catalyst-substrate interactions work together to guarantee a high degree of transition state organization, which leads to a high degree of enantioselectivity, despite the fact that they are often weaker and less directed than their covalent counterparts. Effective organocatalytic techniques for creating chiral compounds include hydrogen-bonding activation **V**,[21] phase-transfer catalysis **VI**,[22] anion-binding activation **VII**,[23] and Brønsted acid catalysis **VIII**.[24]

One of the key tactics in the field of non-covalent asymmetric organocatalysis is hydrogen bonding catalysis. This catalysis is crucial for organocatalytic enantioselective chemical

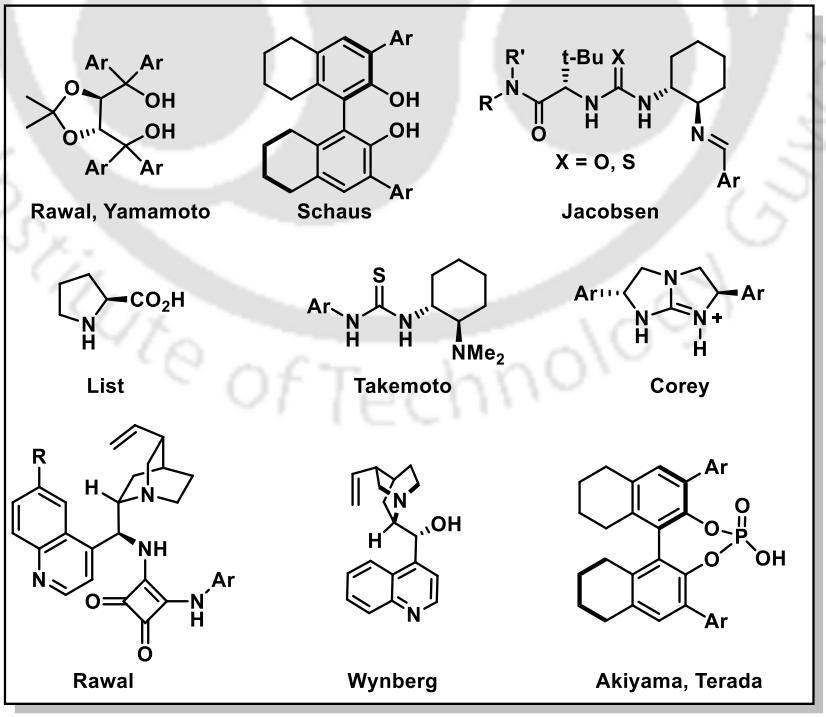
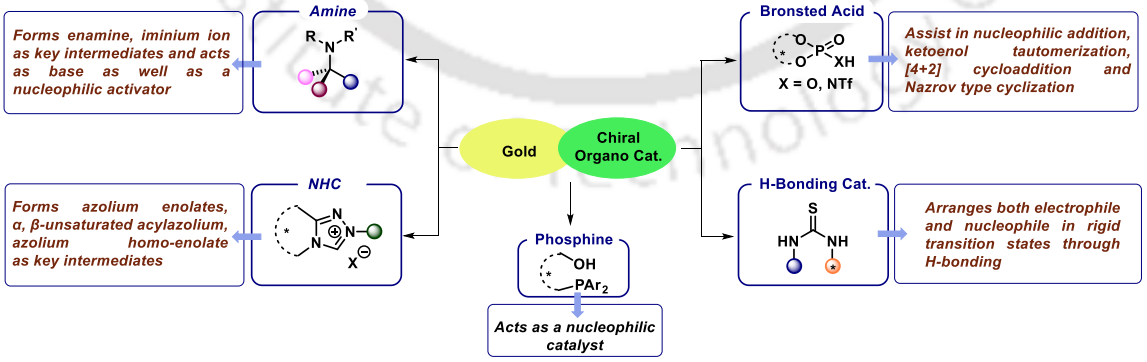


Figure 3: H-bonding catalysts

processes and has significant uses in molecular recognition.[25] As a result, the synthetic community found it intriguing to advance this sector. Prominent examples of bifunctional hydrogen bonding catalysts possessing both Brønsted acidic and Lewis basic sites concurrently inside a single molecule are BINOL-based chiral phosphoric acids,[26] cinchona alkaloids,[27] thiourea[28] and urea[29] (Figure 3). Consequently, hydrogen bond creation enables the synergistic dual activation of electrophile and nucleophile to support numerous stereoselective reactions.

1.3 Enantioselective Merged Gold/Organocatalysis

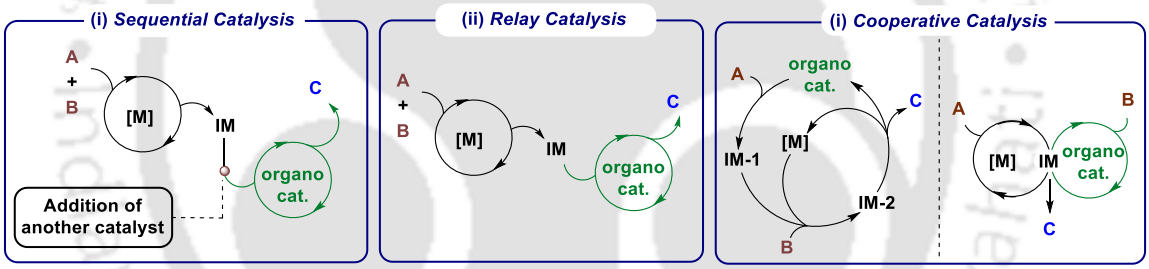
Creating highly enantiopure chemicals by asymmetric catalysis has been considered one of the most important research areas.[30] Transition metal catalysis[31] and organocatalysis have been used to make significant strides in the field of asymmetric synthesis.[32] The idea of dual catalysis has drawn a lot of interest as a cutting-edge technique for creating a wide range of enantioselective transformations in addition to these traditional methods.[33] By using two catalysts that function in unison to facilitate a single synthetic transformation, the basis for dual catalysis has been established. In order to create distinctive molecular scaffolds with superior degrees of chemo-, regio-, and stereoselectivity, a number of dual catalytic systems combining metal–metal,[34] organo–organo,[35] and metal–organocatalysts[36] have been developed. The technique of combining transition metals and chiral organocatalysts is one of these combined catalytic systems that has been widely used in the field of asymmetric organic synthesis.[36]



Scheme 6: Enantioselective merged gold/organocatalysis

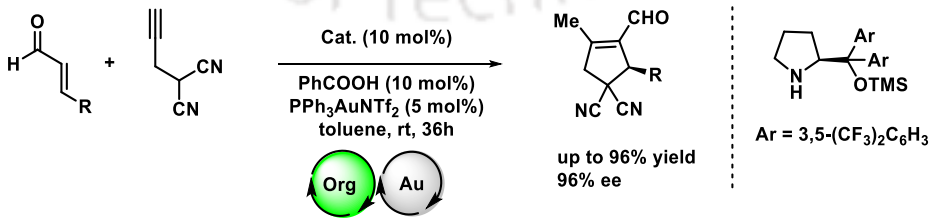
Gold catalysts' distinct π affinity for carbon–carbon multiple bonds have attracted a lot of attention. Under gold catalysis, a number of reactions have been accomplished by utilizing the carbophilic mechanism of activation.[37] Combining gold and organocatalysis has emerged as a viable method for causing enantioselectivity in asymmetric reactions that are catalyzed by gold (Scheme 6). This is primarily due to the benefits, which include: (a) using the complementary reactivities provided by gold and organocatalysts, which rely on the chemoselective activation of particular functional groups; and (b) having access to various reactivities and selectivities that neither catalyst alone can produce. This approach does have certain drawbacks, though, including: (a) catalyst inhibition brought on by unwanted coordination between gold and organocatalysts; and (b) coherence between the two catalytic cycles to prevent discrepancies in their respective kinetic rates.

Based on the mode of activation by catalyst, these methods can be classified into three main categories: (i) sequential, (ii) relay and (iii) cooperative catalysis (Scheme 7).[38]



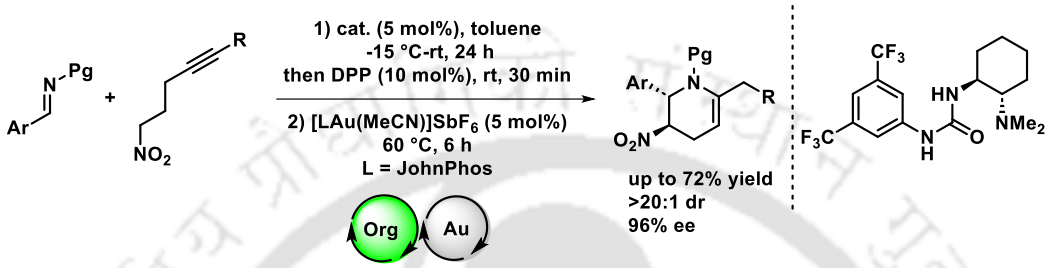
Scheme 7: schematic representation of sequential, relay and cooperative modes of catalysis

In 2010, using the mutual cooperativity of Ph_3AuNTf_2 and chiral pyrrolidine amine, Jørgensen and colleagues demonstrated carbocyclization of enals with alkyne-tethered malononitrile, exhibiting high enantioselectivity (ee up to 96%) (Scheme 8).[39]



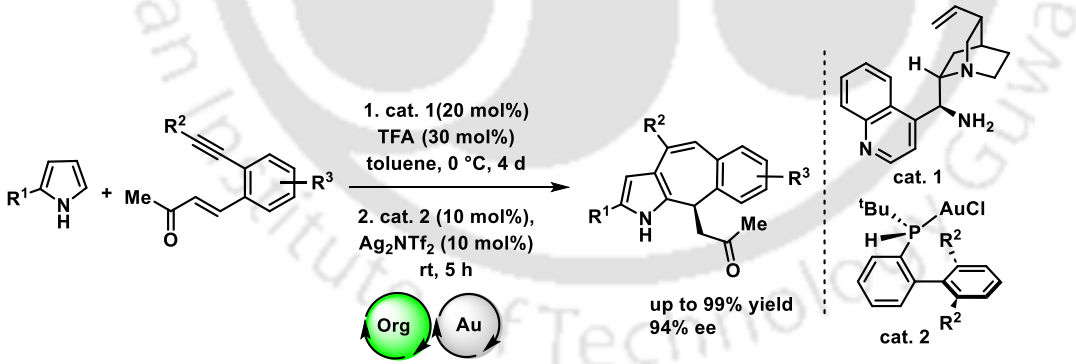
Scheme 8: Gold/chiral amine-catalyzed enantioselective carbocyclization of *α,β*-unsaturated aldehydes with propargylated malononitrile

In 2012, Dixon group delineated a sequential catalysis protocol that merged Echavarren's gold(I) catalyst with Takemoto's catalyst (Scheme 9).[40] Using a nitro-Mannich/hydroamination reaction sequence between N-protected aldimines and nitro-alkynes, a diastereo- and enantioselective synthesis of tetrahydropyridine derivatives has been accomplished up to 96% ee.



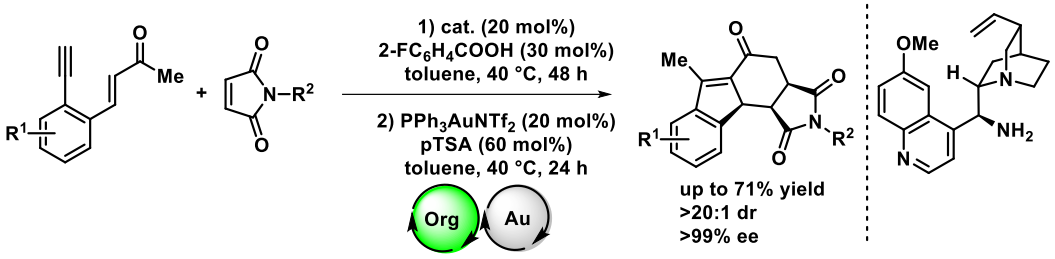
Scheme 9: Gold/chiral amine-catalyzed enantioselective nitro-Mannich/ hydroamination cascade reaction

In 2014, In 2014, Enders' group used a sequential catalytic system that included chiral cinchona alkaloid-derived primary amine and JohnPhosAuCl to dialkylate pyrrole at positions C-2 and C-3 (Scheme 10).[41] By combining amine and JhonPhosAuCl to pyrroles and enones, an enantiopure seven-membered ring containing 2,3-annulated pyrrole (up to 94% ee) is accessible.



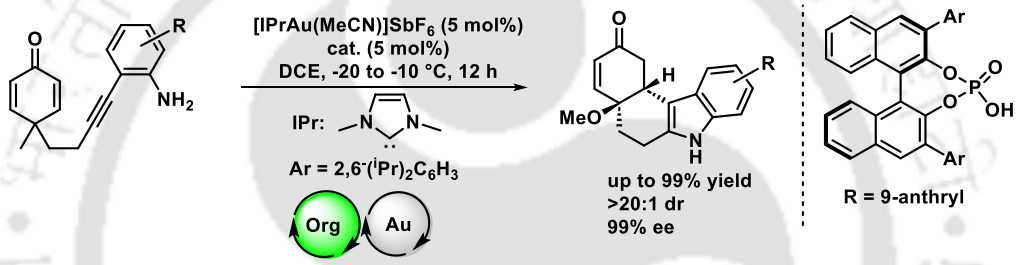
Scheme 10: Synthesis of annulated pyrroles by chiral primary amine and a Au^{I}-phosphine catalyst

In 2014, Wu and colleagues reported the asymmetric synthesis of [6,5,6]-carbotricyclic compounds in excellent ee (up to >99%) and high dr (up to >20: 1), utilising the mutual cooperativity of the gold(I) catalyst and Cinchona alkaloid-based amine (Scheme 11).[42]



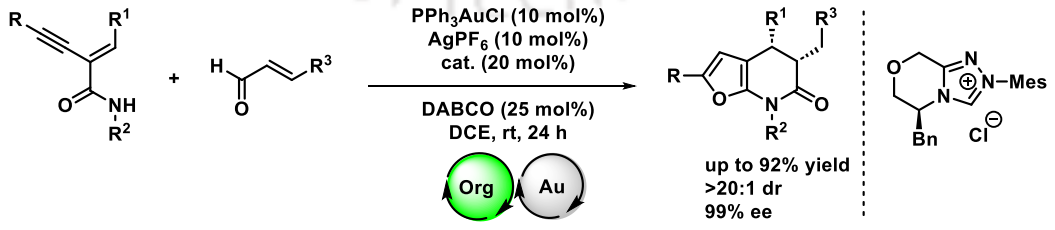
Scheme 11: Gold/chiral amine-catalyzed enantioselective Diels–Alder/ carboannulation cascade reaction

In 2016, Han and colleagues described a hydroamination/Michael addition cascade that produced enantiopure tetrahydrocarbazoles through the relay catalysis of a gold complex and chiral Brønsted acid (Scheme 12).[43]



Scheme 12: Gold/chiral Brønsted acid-catalyzed enantioselective synthesis of tetrahydrocarbazoles

The group of Pan and Chi revealed the first report of combining gold and chiral NHC catalysis in a diastereo- and enantioselective cycloisomerization/azadiene-Diels-Alder reaction in 2020 (Scheme 13).[44] A gold catalyst activated the ynamide substrate to create an unsaturated ketimine intermediate, which then successfully reacted with the enals (through an azolium enolate intermediate produced with NHC) to produce bicyclic lactam products with superior diastereo- and enantio-selectivities.



Scheme 13: Gold/chiral NHC-catalyzed enantioselective cycloisomerization/cyclization reaction of ynamides and enals

PART 2

Construction of Quaternary Stereocenters by Desymmetrization Reactions

1.4 Introduction

Highly structurally diverse fully substituted carbons are created when any other atom or group replaces the remaining hydrogen atom on a tertiary carbon. Quaternary carbons[45,46] are those that have four carbon neighbours, while tetrasubstituted carbons, which are found in tertiary alcohols or thiols, α-tertiary amines, and other compounds, are those that have heteroatom substitutions.[47] Natural products, medications, and bioactive compounds frequently contain quaternary or tetrasubstituted carbon stereogenic centres (Figure 4), which are created when the four substituents are different. Modifying organic compounds by adding fully substituted carbon stereocenters to increase biological activity is a successful drug design strategy due to their structural diversity and improved conformational constraints when compared to the corresponding tertiary carbon stereocenters. The conformational restriction imposed by spiro ring fusion, for instance, lowers the conformational entropy penalty upon interacting with a protein target, making spirocyclic systems increasingly useful in drug discovery.[48]

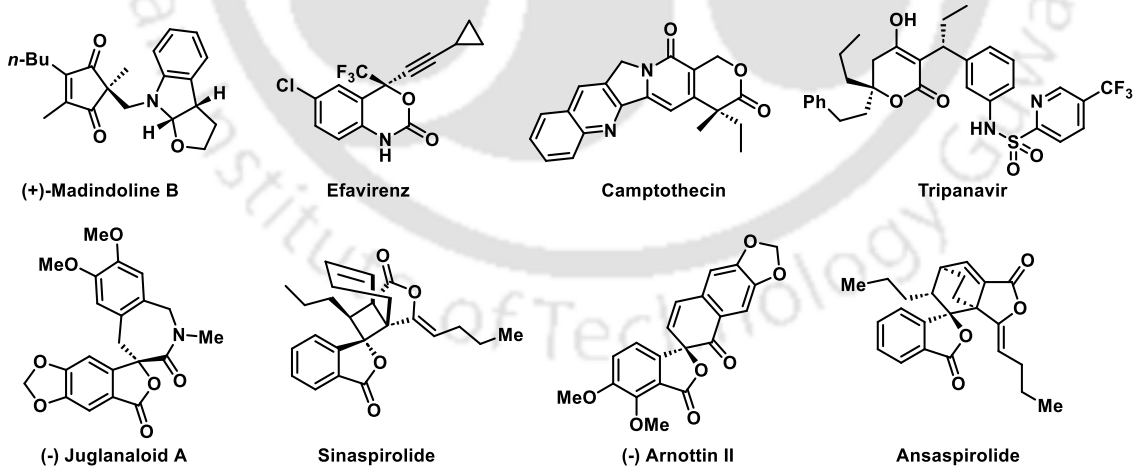


Figure 4. Selected examples of molecules (natural and artificial) bearing a chiral quaternary centre

The development of effective techniques for the stereocontrolled construction of quaternary and tetrasubstituted carbon stereocenters has thus received a great deal of

attention.[49-51] The catalytic enantioselective formation of quaternary carbon stereocenters, bonded by four distinct carbon substituents, remains a long-term challenge despite notable advancements.[50-54] Although 12% of the top 200 prescription medications sold in the US in 2011 contained molecules with a quaternary carbon stereocenter, as recently noted by Quasdorf and Overman,[52] the synthesis of these medications depends on the use of natural product precursors to supply the quaternary stereocenters. Reliable techniques for creating such structural motifs are obviously desired, as evidenced by the almost lack of approved drugs with chemically synthesised chiral quaternary carbon stereocenters.

1.5 Synthetic Strategies and Challenges to Synthesize All-Carbon Quaternary Stereogenic Centers

By looking at established synthetic techniques, the difficulties involved in the enantioselective formation of quaternary carbon stereocenters can be completely comprehended. There are three main methods for providing quaternary carbon stereocenters, as illustrated in Figure 5: (i) C-C bond-forming reactions on a sp^2-hybridized prochiral carbon, as present in organic compounds like 1,1-disubstituted olefins, fully substituted metal carbenoids, enolates, and their equivalent; (ii) desymmetrization of prochiral molecules with a prochiral quaternary carbon or meso-compounds with preexisting stereogenic quaternary carbons; (iii) kinetic resolution reaction of racemic compounds bearing quaternary stereocenters. Obviously, prochiral carbons that form quaternary carbon stereocenters need to be completely substituted by carbon groups, whereas those that form tertiary stereocenters require a hydrogen atom.

Two specific difficulties arise from this: (i) the increased steric repulsion that occurs when a carbon substituent replaces the smallest atom, hydrogen, makes it harder for the two reaction partners to approach one another and makes the transition state more crowded; and (ii) it is more difficult to achieve excellent enantiofacial discrimination (or enantiotopic group discrimination) because there is less steric dissimilarity between two carbon substituents on the prochiral centre than there is between a carbon substituent and a H atom. The efficient production of quaternary carbon stereocenters from basic starting materials in a stereocontrollable and operationally friendly manner is therefore a difficult

task; this is seen as a test site for novel catalysts and novel synthetic approaches to prove them worth.[53]

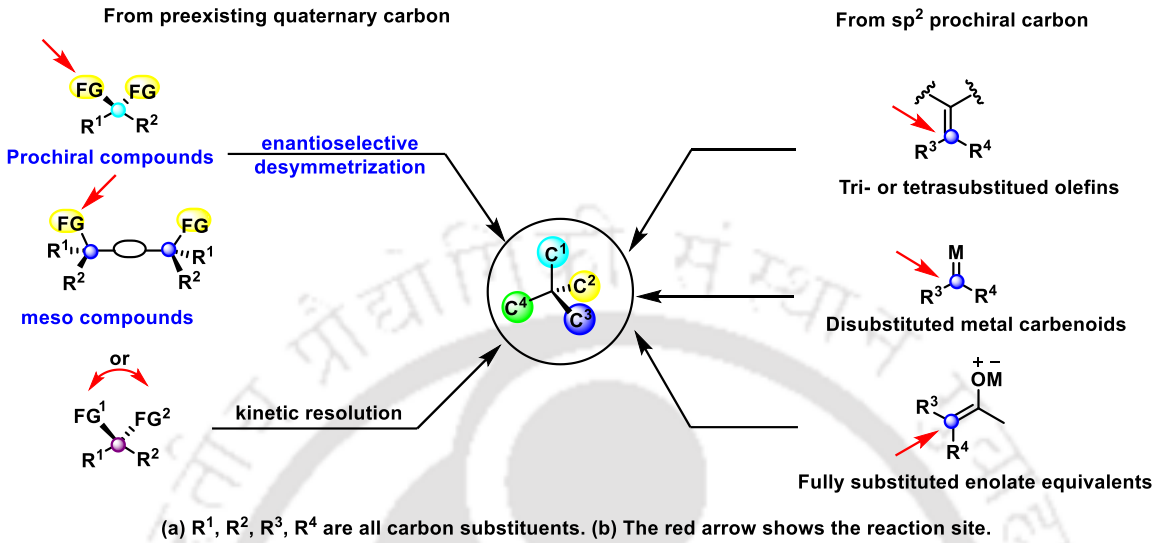


Figure 5. Synthetic strategies to all-carbon quaternary stereogenic centers

1.6 Advantages of Catalytic Enantioselective Desymmetrization

A potential and appealing approach that divides the task of C-C production from the problem of its enantiofacial selectivity is catalytic enantioselective desymmetrization[54] of prochiral compounds or meso-compounds. There might be some special benefits to this tactic. Firstly, since a quaternary carbon stereocenter is simultaneously generated regardless of the type of reaction occurring at one of the two identical functional groups connected to the pre-existing quaternary carbon, it theoretically makes advantage of all catalytic processes for enantioselective synthesis. On the other hand, a sp^2 prochiral carbon must be converted in order for enantioselective C-C bond formation events to occur. Second, because the reactive site is at least one covalent bond away from the existing quaternary carbon, if no additional quaternary carbon stereocenter is generated, unfavourable steric repulsion is somewhat mitigated as the reaction proceeds at the tethered functionality rather than the existing quaternary carbon. Third, the yield of the kinetic resolution reaction cannot be greater than 50%, although the theoretical yield of the desymmetric process is 100%. Fourth, it is frequently simple to create the symmetric substrates. Fifth, quaternary carbon stereocenters with a functionality that is challenging

to introduce through an enantioselective C-C bond-forming process on a sp^2-prochiral carbon (such as an ethynyl group) can be created utilising preorganized substrates. Additionally, the desymmetrization of meso-compounds permits the simultaneous production of many quaternary carbon stereocenters.

Because of these benefits, there is a growing interest in creating quaternary carbon stereocenters using enantioselective desymmetrizing processes. Numerous amazing methods and their use in the enantioselective total synthesis of natural products and physiologically active chemicals have shown how effective this strategy is.

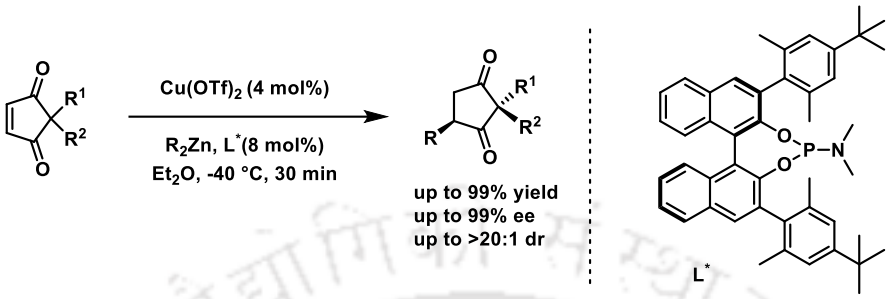
1.7 Desymmetrization of Prochiral Enones and Malemides

For enantioselective desymmetric reactions to create quaternary carbon stereogenic centers from prochiral enone, there are mainly two types of moiety are available: 2,2-disubstituted cyclopentene-1,3-diones and 4,4-disubstituted cyclohexadienones. The electron-deficient olefin functionality of the two classes of substrates makes it possible to employ a wide variety of nucleophiles to create desymmetric conjugate addition, cycloaddition, and tandem reactions. These reactions easily yield multisubstituted cyclohexane or cyclopentane derivatives with a quaternary carbon stereogenic centre. Furthermore, both bicyclic and polycyclic compounds can be created by substituting an appropriate functionality attached to the prochiral carbon, regardless of whether these cyclic compounds have heteroatoms or not.

Prochiral 2,2-disubstituted cyclopentene-1,3-diones can be readily prepared from 2-substituted cyclopentene-1,3-diones by base promoted nucleophilic addition with a corresponding halide, followed by oxidation. They are highly active substrates for the synthesis of optically active quaternary cyclopentanes and cyclopentenes, which are fundamental structures of numerous natural products and bioactive compounds.[55]

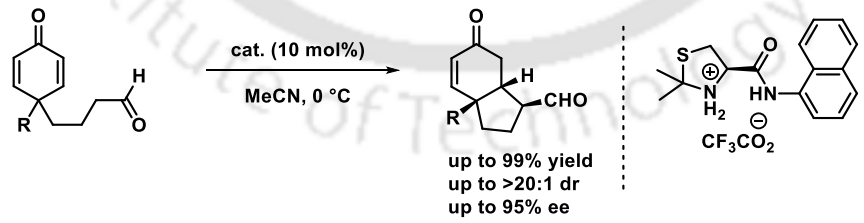
This scaffold was initially applied to enantioselective desymmetric reactions by Mikami group in 2012 (Scheme 14). Excellent stereoselectivity was achieved by installing a coordinating benzyloxy group and using a chiral ligand. In presence of Cu(II) salt, the Michael addition of dialkylzinc reagents to 1,3-diones with both aryl and alkyl substituents

at the prochiral center functioned well to produce functionalised cyclopentane derivatives in high to excellent stereoselectivity.



Scheme 14: Copper(I)-catalyzed asymmetric desymmetrization of prochiral cyclopentene-1,3-diones

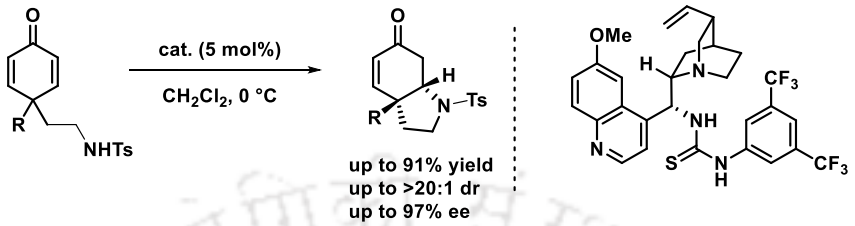
Six-membered cyclic compounds with a quaternary carbon stereocenter are widely found in many natural products and pharmaceutically active compounds. This led to extensive use of 4,4-disubstituted cyclohexadienones in organic synthesis. In 2005, Hayashi and colleagues were the first to try using this framework to build quaternary carbon stereocenters (Scheme 15).[56] They described the creation of the well-known bicyclo[4.3.0]nonene carbon skeletons by a desymmetric intramolecular Michael reaction of prochiral dienones with a 3-formylpropyl group. At 0°C, the transformation proceeded smoothly with the enamine catalysis provided by 10 mol% trifluoroacetic salt of cysteine-derived aminocatalyst, which produced the desired cis-product in 99% yield, up to >20:1 dr and 95% ee for the cis isomer.



Scheme 15: Desymmetric intramolecular Michael reaction to 4,4-disubstituted cyclohexadienones

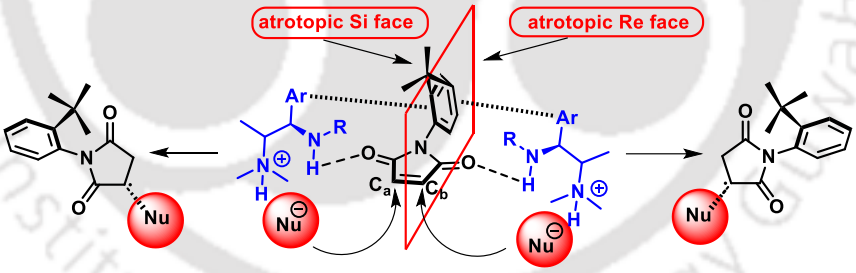
In 2011, Gu and You created an efficient desymmetric intramolecular aza-Michael addition to produce optically active nitrogen-containing heterocyclic compounds by attaching an amine moiety to the C4 substituent of prochiral cyclohexadienones (Scheme

16).[57] A range of differently substituted dienones functioned effectively to provide the enantioenriched pyrrolidine derivatives in high to excellent yield and ee value when 5 mol% cinchonine-derived bifunctional thiourea was present.



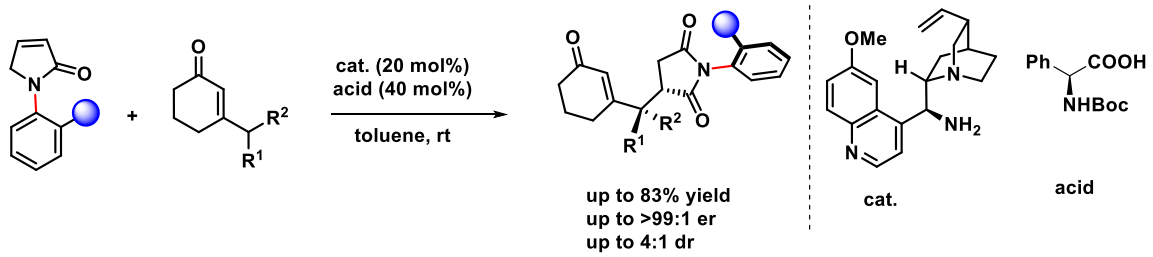
Scheme 16: Aza-Michael addition prochiral cyclohexadienones

In this regard, simultaneous construction of quaternary stereocenter and chiral C-N axis through desymmetrization strategy can also be achieved by nucleophilic addition to prochiral N-aryl malemides in presence of a suitable catalyst. The feasibility of these atroposelective transformations relies on the hindered rotation along the maleimide $C_{Ar–N}$ single bond and on the ability of the catalyst to break the maleimide symmetry plane through the controlled regiochemical addition to one of the two carbon atoms C_a or C_b (Scheme 17).



Scheme 17: Organocatalytic maleimide desymmetrization by means of a nucleophilic Michael addition reaction.

In 2014, Bencivenni *et al*. developed a method for the atroposelective synthesis of succinimides using a new vinylogous Michael addition of enones to maleimides (Scheme 18).[58] Primary amine catalysis was fundamental for the enantioselective desymmetrization to occur with simultaneous and exclusive remote control of the chiral axis and the newly formed stereocenters.



Scheme 18: Atroposelective synthesis of succinimides by Michael addition of enones to maleimides

1.8 Conclusion and Focal Theme of the Present Work

Chapter I of this thesis is divided into two parts which is enantioselective merged gold/organocatalysis and construction of quaternary stereocenters by desymmetrization reactions.

Chapter II includes sequential organo and metal catalyzed reaction between 3-pyrrolyloxindoles and linear nitroenynes: access to cyclic aza-spirooxindoles.

Chapter III describes organocatalytic ssymmetric synthesis of C-N atropisomers with pyrrole, oxindole and succinimide scaffold.

Chapter IV describes organocatalytic asymmetric desymmetrization of cyclopentene-1,3-diones via formal diaza-ene reaction with donor–acceptor hydrazones.

Lastly in chapter V catalytic asymmetric desymmetrizing [4+2] cycloaddition/base mediated oxidative aromatization sequence: *de novo* synthesis of isobenzofuranone embedded chiral arenes has been described.

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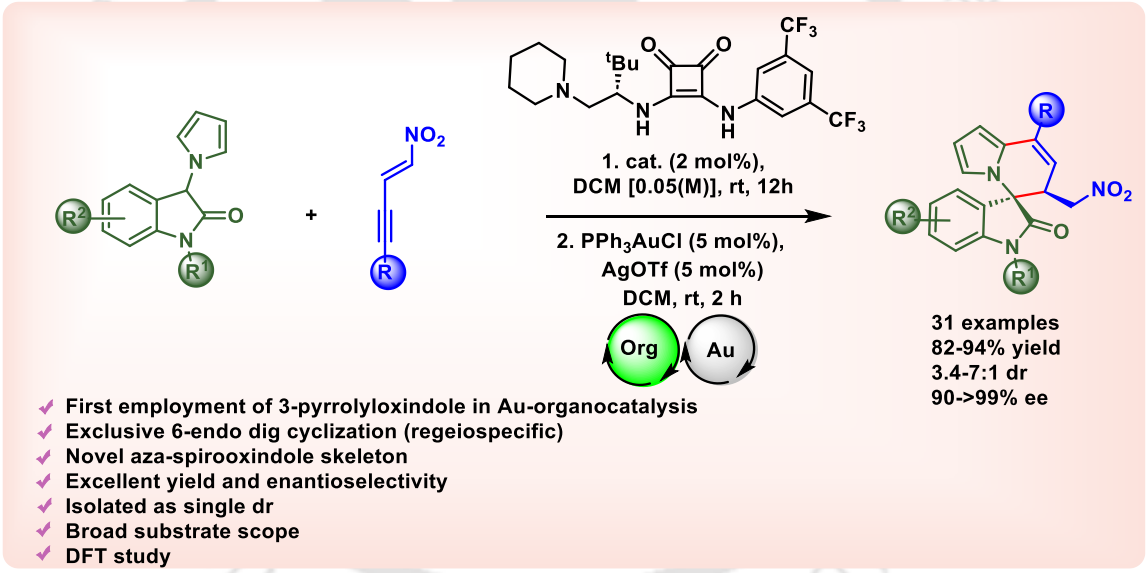
Chapter II

Sequential Organo and Metal Catalyzed Reaction Between 3-Pyrrolyloxindoles and Linear Nitroenynes: Access to Cyclic Aza-Spirooxindoles

Abstract: An asymmetric Michael addition/hydroarylation reaction sequence, catalyzed by a sequential catalytic system consisting of a squaramide and a combination of silver and gold salts, provides a new series of cyclic aza-spirooxindole derivatives in excellent yields (up to 94%) and high diastero- and enantioselectivities (up to 7:1 dr, up to >99% ee). Computational study has also been performed.



2.1 Introduction

Spirooxindole is included in the structural frameworks of numerous natural substances and pharmaceutical drugs.[1] Specifically, a number of bioactive natural compounds have been reported to contain the aza-spirooxindole unit.[2] For example, (-)-vincatine is an alkaloid of Aspidosperma.[3] Elacomine has been shown to exhibit anti-cancer properties.[4] Currently undertaking Phase II clinical investigations, ciprgamin has proven to be a powerful, fast-acting, and dose-dependent antimalarial medication candidate.[5] It has been demonstrated that Compound D is very successful in blocking the interaction between p53 and MDM2.[6] As a result, there has been a lot of interest in the stereoselective production of functionalized aza-spirooxindole scaffolds in recent years.[1]

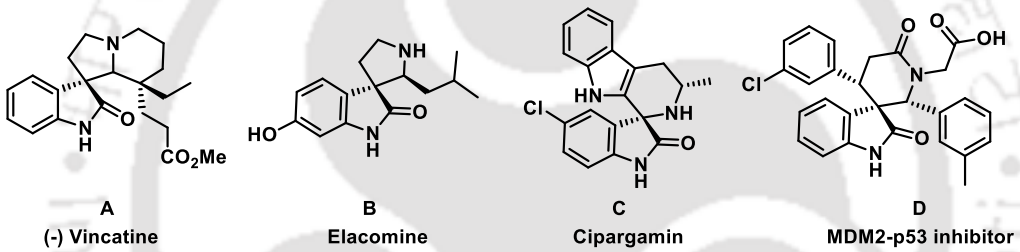


Figure 1. Examples of aza-spirooxindoles in bioactive compounds

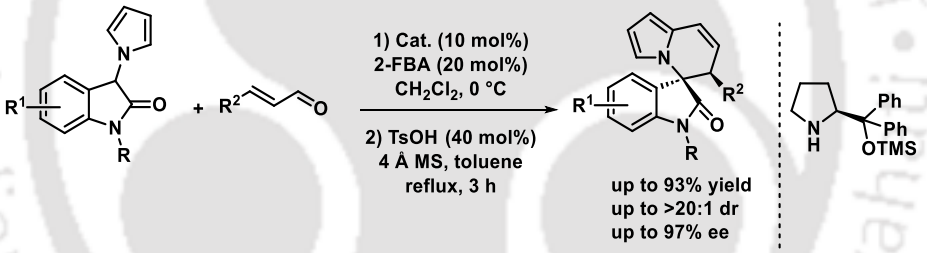
For efficient access to spiropyrrolidine oxindoles, most of the methods focused on formal [3+2] cyclizations.[7] On the other hand, little attention was given to generating spiropiperidinyl oxindole using an asymmetric procedure.[8] Under organocatalysis, 3-pyrrolyloxindoles are useful synthetic building blocks for the synthesis of several 3,3′-disubstituted oxindoles.[9] Furthermore, the pyrrole moiety with an oxindole at the C3 position enabled the Friedel-Crafts reaction with a range of electrophiles, providing a practical and attractive way to produce chiral aza-spirooxindoles.[11] Even though there aren't many reports, it is still very desirable to look into creative ways to make novel spirocyclic oxindole molecules accessible. This is especially true given that a molecule's specificity of action and potentially useful biological properties are usually linked to its structural complexity and well-defined architecture. It has been discovered that electron-poor 1,3-enynes are a crucial synthon for creating densely functionalized skeletons. Because the related Michael adducts include a triple bond, 1,3-enynes with a strong

electron-poor nitro group at the C1 (linear) position are a valuable Michael acceptor. Numerous carbonyl compounds have been used as nucleophiles in the organocatalytic 1,4-addition of nitroenynes, yielding a range of heterocyclic molecules.[12]

2.2 Literature Survey

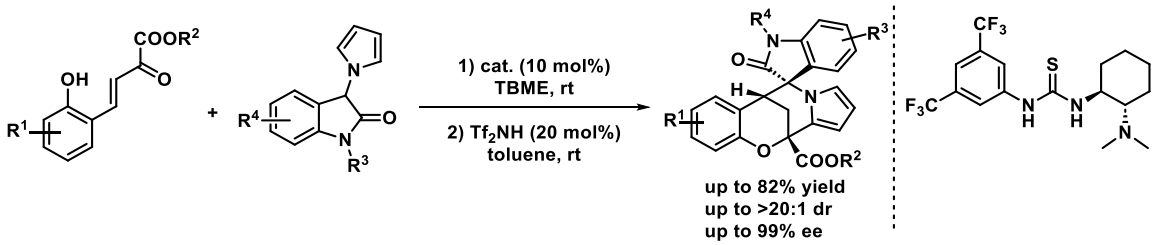
2.2.1 Previous reports on organocatalytic enantioselective reaction with 3-pyrrolyloxindoles:

In 2015, Yuan *et al.* developed an efficient and unprecedented organocatalytic asymmetric reaction of 3-pyrrolyl-oxindoles with *α,β*-unsaturated aldehydes to generate spirocyclic oxindole (Scheme 1).[10a] Diphenylprolinol silyl ether and 2-fluorobenzoic acid catalyzed the reactions through an asymmetric Michael/Friedel–Crafts cascade process. A wide range of structurally diverse spiro[5,6-dihydropyrido[1,2-a]pyrrole-3,3′-oxindole] derivatives were obtained in high yields (up to 93%) and with high to excellent diastereo- and enantioselectivities (up to >99:1 dr and 97% ee).



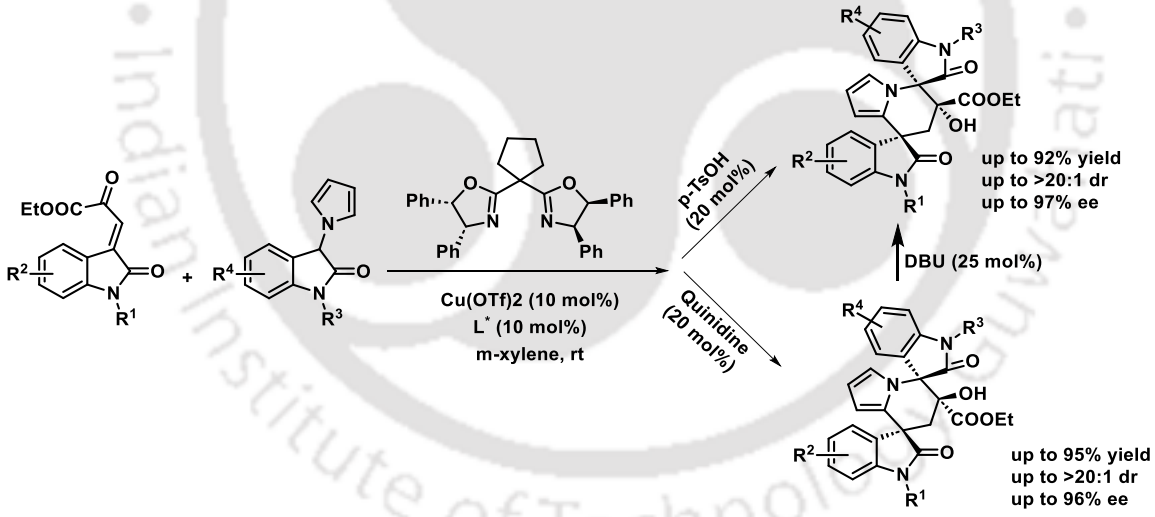
Scheme 1: Synthesis of za-spirooxindoles with 3-pyrrolyloxindoles and *α,β*-unsaturated aldehydes

In 2017, Wang group using a Takemoto thiourea catalyst and a triflimide as cooperative catalysts reported a Michael-hemiketalization-oxa-Pictet-Spengler cyclization to create chiral bridged and spiro heterocyclic skeletons with one spiro stereogenic carbon center and two bridgehead carbon centers (Scheme 2).[10b] The products were obtained in high yields (up to 82%) with excellent enantioselectivity (up to 99%). For this cyclization reaction, an oxocarbenium ion in particular serves as a crucial intermediary.



Scheme 2: Asymmetric Michael-hemiketalization-oxa-Pictet-Spengler cyclization for bridged and spiro heterocyclic skeletons

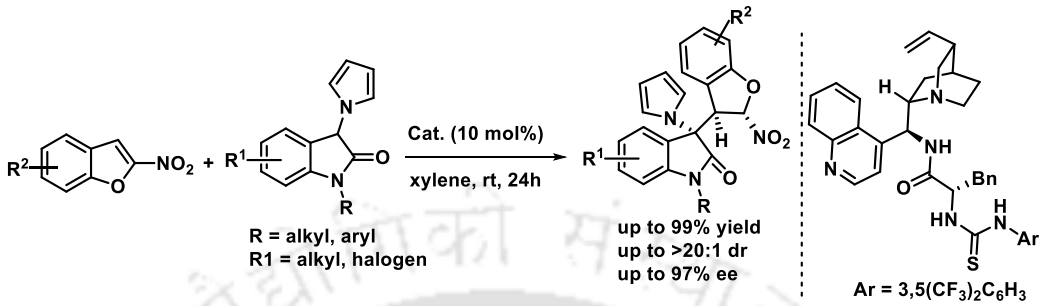
In 2018 Wang group demonstrated a metal- and organo-catalyzed asymmetric Friedel–Crafts/aldol tandem reaction with 3-pyrrolyl-oxindoles and isatin-derived *β,γ*-unsaturated *α*-ketoesters (Scheme 3).[10d] Here two types of diastereoisomeric bispirooxindoles bearing three quaternary stereocentres are constructed in high yields (up to 95%) with excellent enantioselectivity (up to 97%). Mechanistically, the stereodivergent synthesis of optically active bispirooxindoles formation goes through the equilibrium of the hemiketal formation under co-catalyst assistance of a Brønsted acid or a Lewis base.



Scheme 3: Diastereodivergent synthesis of bispirooxindoles *via* asymmetric Friedel–Crafts/aldol cascade reaction

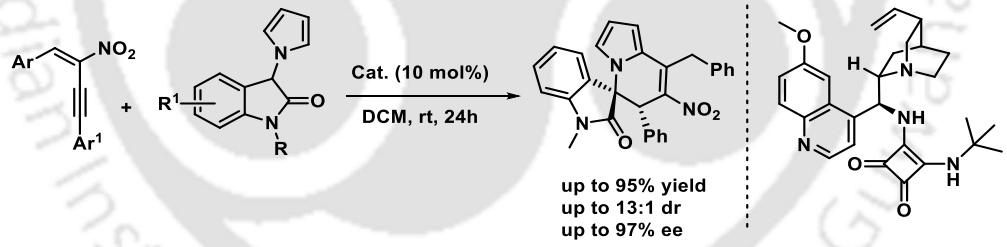
In 2020, Yuan *et. al.* reported an asymmetric dearomatization of 2-nitrobenzofurans by organocatalyzed one-step Michael addition to access 3,3' -disubstituted oxindoles using a chiral multiple hydrogen-bonding thiourea (Scheme 4).[9e] Under mild conditions, a variety of structurally diverse disubstituted oxindoles with three contiguous stereocenters including one quaternary and two tertiary, could be obtained with ease using the developed

protocol, yielding excellent results (up to 99% yield, >20: 1 dr and 96% ee). The 2-pyrrolyl-substitutedoxindole and 2,3-dihydrobenzofuran substructures are two privileged motifs that are intriguingly combined in these products.



Scheme 4: Dearomatization of 2-nitrobenzofurans by organocatalysis

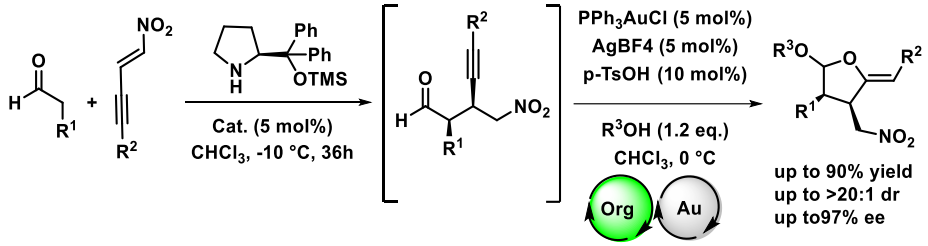
In 2021, Song *et al.* reported an organocatalytic asymmetric [3+3] cyclization with 1,3-nitroenynes and 3-pyrrolyl-oxindoles using a chiral bifunctional squaramide catalyst (Scheme 5).[10e] Under mild reaction conditions, this Michael/Friedel-Crafts cascade approach offers a simple and effective way to obtain enantioenriched polycyclic aza-spirooxindoles with 32–95% isolated yields and good stereocontrol.



Scheme 5: Synthesis of aza-spirooxindoles via Michael/Friedel–Crafts cascade reaction

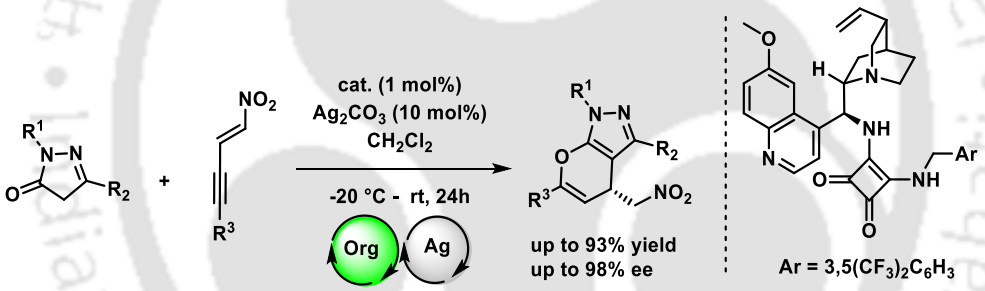
2.2.2 Previous reports on enantioselective merged metal/organocatalysis with linear nitroenyne:

In 2009, Alexakis *et. al.* demonstrated a one-pot process consisting of an enantioselective organocatalytic Michael addition to a nitroenyne and a subsequent gold-catalyzed acetalization/cyclization (Scheme 6).[12a] This was first report on merging of gold catalysis with organocatalysis. This sequence leads to highly substituted tetrahydrofuranyl ethers with high diastereo- and enantioselectivities.



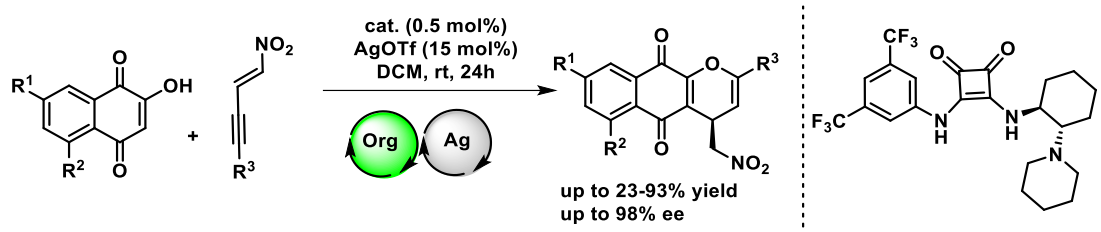
Scheme 6: Synthesis of highly substituted tetrahydrofuranyl ethers by Au[1] and organocatalysis.

In 2015, Enders group reported a new method for creating chiral pyrano-annulated pyrazoles using silver catalysis and squaramide (Scheme 7).[12c] Excellent yields and enantioselectivities were obtained from the potentially bioactive pyrano-annulated pyrazoles under mild reaction conditions and with low catalyst loading using a sequential catalytic system that involved an asymmetric Michael addition followed by a subsequent hydroalkoxylation.



Scheme 7: Synthesis of pyrano-annulated pyrazoles by combining silver- and organocatalysis

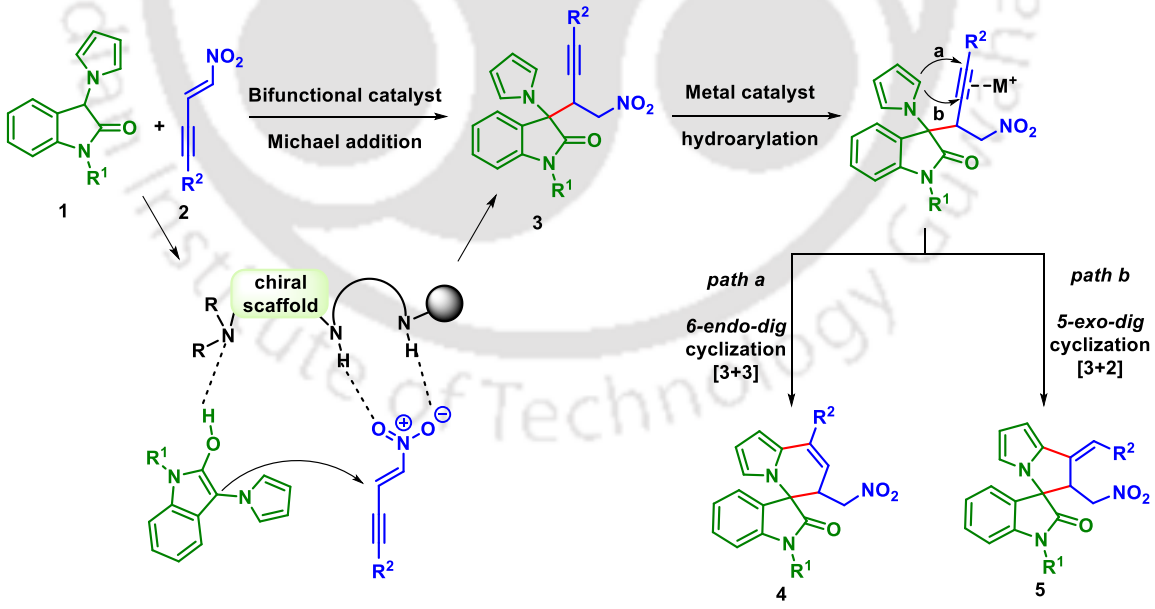
In 2016, Enders *et al.* again delineated cinchona-derived squaramide and a silver(I) salt catalyzed an enantioselective one-pot Michael addition/hydroalkoxylation reaction between 2-hydroxy-1,4-naphthoquinones and alkyne-tethered nitroalkenes (Scheme 8).[12d] At a very low catalyst loading (0.5 mol%) of the squaramide, the sequential procedure offers direct access to 4H-pyranonaphthoquinones in moderate to very good yields and good to excellent enantioselectivities.



Scheme 8: Synthesis of 4*H*-pyranonaphthoquinones via sequential squaramide and silver catalysis

2.3 Concept

From the previous literature survey, we hypothesised that the linear nitroenynes could also be used as biselectrophiles to start the asymmetric Michael addition with 3-pyrrolyloxindoles by bifunctional organocatalysis (Scheme 9). This will produce Michael adduct **3**, which can take part in metal catalyzed intramolecular hydroarylation. We envisioned that metal catalyst can activate the triple bond of the nitroenyne **1**. Now the pyrrole ring can undergo hydroarylation either by path a or by path b (Scheme 9). Here possibilities of both *6-endo-dig* and *5-exo-dig* cyclization can occur, which can lead to either [3+3] or [3+2] cyclized product. Hence controlling enantioselectivity and regioselective cycloaddition remains the main challenge for this reaction.

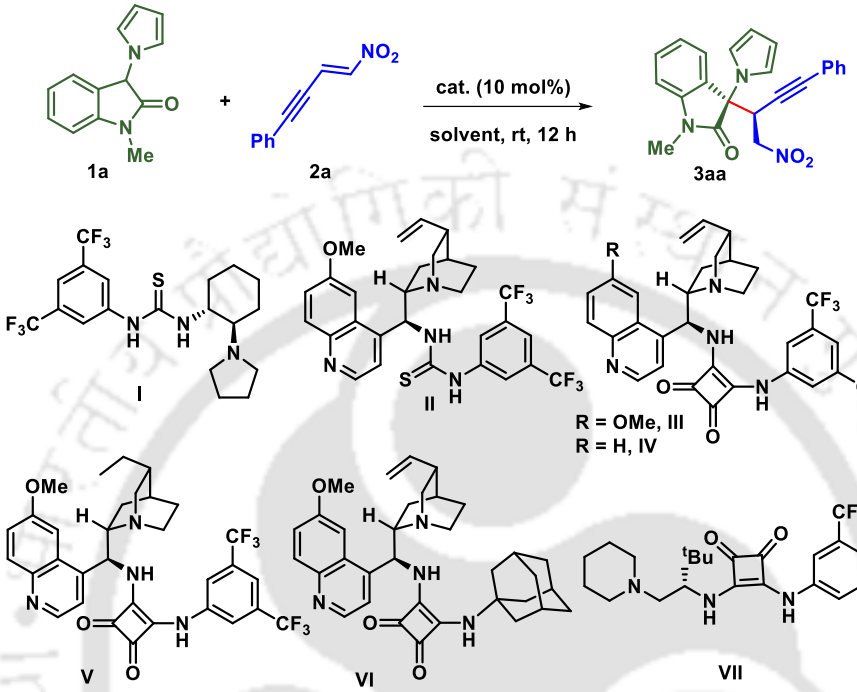


Scheme 9: Proposed route for merged metal/organo- dual catalysis to access aza-spirooxindoles

2.4 Results and Discussion

2.4.1 Optimization of catalyst and reaction conditions:

Table 1. Catalyst screening and optimization of reaction conditions



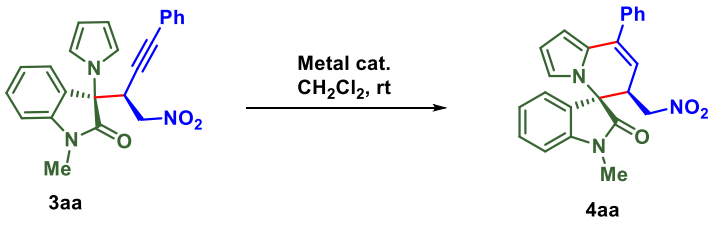
entry[a]	catalyst	solvent	yield[b]	dr[c]	ee[d]
1	**I**	toluene	86	1.2:1	50
2	**II**	toluene	88	1.1:1	62
3	**III**	toluene	85	1.1:1	80
4	**IV**	toluene	92	1.4:1	85
5	**V**	toluene	88	1.3:1	82
6	**VI**	toluene	84	0.6:1	53
7	**VII**	toluene	88	2.8:1	90
8	**VII**	$PhCF_3$	90	5:1	97
9	**VII**	$CHCl_3$	92	5.1:1	97
10	**VII**	CH_2Cl_2	96	5.2:1	97
11[e]	**VII**	CH_2Cl_2	95	6:1	97
12[f]	**VII**	**CH_2Cl_2**	**95**	**6:1**	**97**

[a]Unless otherwise mentioned, 0.1 mmol of **1a** and 0.1 mmol of **2a** were stirred in 1 mL solvent at room temperature with 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by 1H NMR. [d]Determined by HPLC. [e]In 2 mL solvent. [f]With 2 mol% catalyst.

Initially, we started our investigation by focusing on catalytic asymmetric Michael addition. Thus, in toluene at ambient temperature, a model reaction between 3-pyrrolyloxindole **1a** and linear nitroenyne **2a** was carried out (Table 1). The Michael reaction was first facilitated by Takemoto catalyst **I**, which produced product **3aa** in 86% yield with 1.2:1 dr and 50% ee (Table 1, entry 1). A minor improvement in enantioselectivity was then noted when we employed quinine-derived bifunctional thiourea catalyst **II** (entry 2). Bifunctional squaramide catalysts produced from cinchona alkaloids were then used in the process, and pleasantly improved outcomes were observed (entries 3-6). The best catalyst, *t*-leucine derived bifunctional squaramide catalyst **VII**, was ultimately discovered to have 90% ee of **3aa** (entry 7). The enantioselectivity was then increased by using catalyst **VII** with various solvents (entry 8–10). As can be shown, *α,α,α*-trifluorotoluene (entry 8) boosted both diastereo- and enantioselectivity. After that, halogenated solvents like dichloromethane and chloroform were examined, and we were thrilled to discover excellent results (entries 9–10). Specifically, dichloromethane was found to be the most effective solvent, yielding **3aa** in 96% yield with 5.2:1 dr and 97% ee (entry 10). Next, we measured the concentration of the solvent. Remarkably, the enantioselecitivity did not alter when the molarity was reduced to 0.05 M, whereas the diastereoselectivity increased to 6:1 (entry 11). After that, we concentrated on lowering the catalyst loading. Interestingly, adding 2 mol% of the catalyst had no effect on the reaction's conclusion (entry 12).

Following organocatalytic step optimization, we turned our attention to the metal-catalyzed cyclization reaction (Table 2). We hypothesized that when the alkyne was π-activated by different silver and gold compounds, the hydroarylation process of the pyrrole

Table 2. Optimization studies for the metal catalyzed cyclization



Entry	catalyst	Time (h)	Yield[b]	dr[c]	*ee*[d]
1.	Ag_2O	24	-	-	-
2.	$AgNO_3$	24	-	-	-
3.	Ag_2CO_3	24	-	-	-
4.	$AgBF_4$	24	-	-	-
5.	AgOTf	24	-	-	-
6.	$AgNTf_2$	24	-	-	-
7.	PPh_3AuCl	24	-	-	-
8.	PPh_3AuCl/AgOTf	1	98	>20:1	97
9.	$PPh_3AuCl/AgNTf_2$	4	82	>20:1	97
10.[e]	**PPh_3AuCl/AgOTf**	**2**	**98**	**>20:1**	**97**

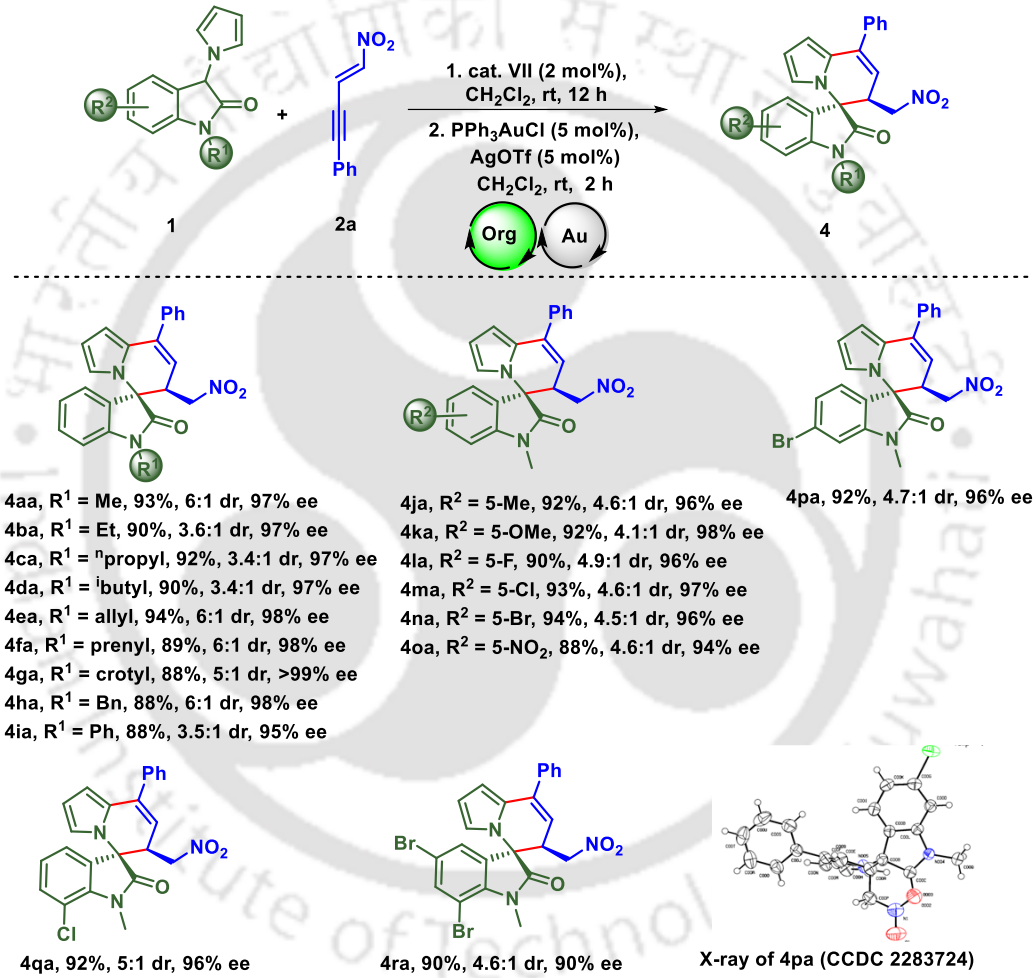
[a] Reaction conditions: 0.10 mmol of **3aa**, 10 mol% of catalyst, DCM 2 mL, rt. [b] Yield of isolated **4aa** after flash chromatography. [c] Determined by 1HNMR after flash chromatography. [d] Determined by HPLC analysis on a chiral stationary phase. [e] 5 mol% of catalyst was used.

motif would produce either a five- or six-membered ring. At room temperature, however, no cyclization was seen with Ag_2O, $AgNO_3$, Ag_2CO_3, $AgBF_4$, AgOTf, $AgNTf_2$, or PPh_3AuCl in dichloromethane. Remarkably, compound **3aa** underwent clean cyclization in 2 hours with good regioselectivity to generate the *6-endo-dig* derived compound **4aa** in the presence of 5 mol% PPh_3AuCl and 5 mol% AgOTf, although no *5-exo-dig* product was seen (Table 2).

2.4.2 Substrate scope:

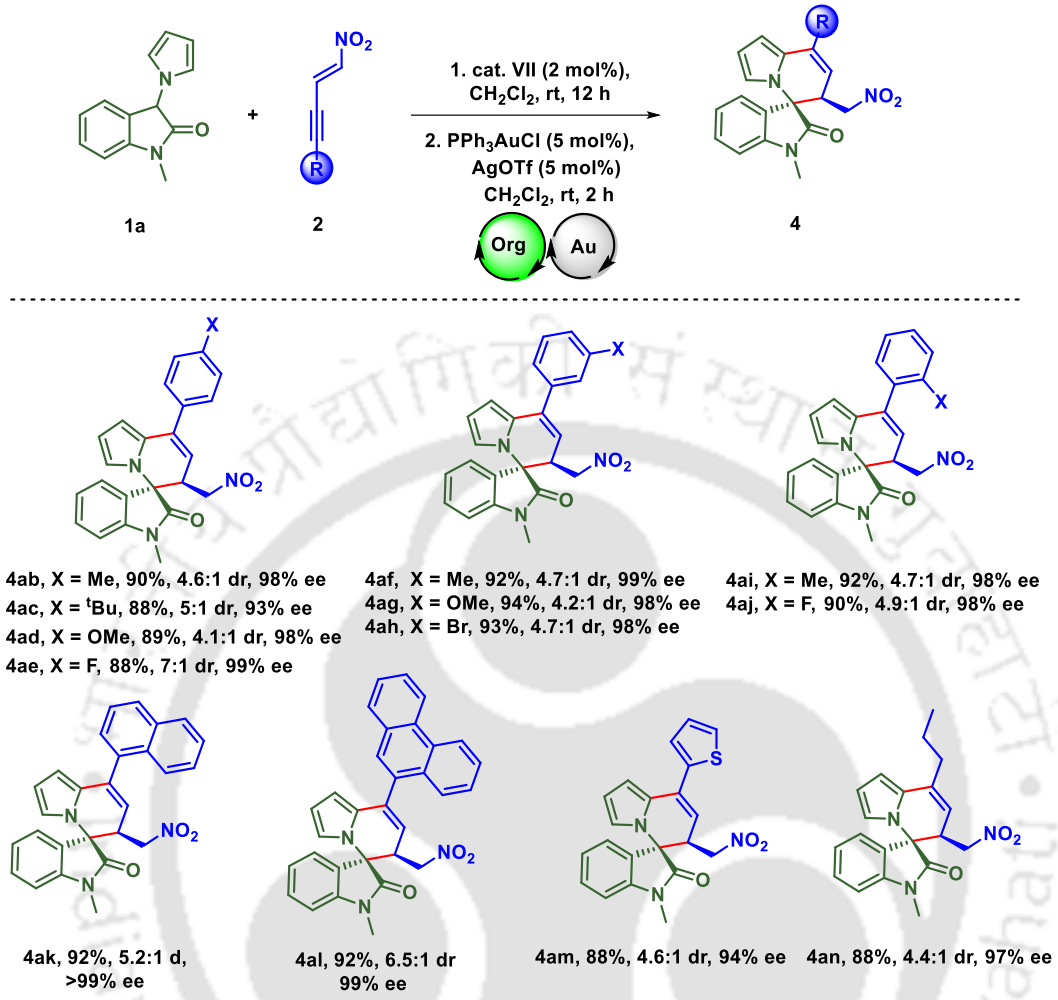
Building on our optimized conditions, we carried out the hydroarylation reaction after doing a short column of the reaction mixture obtained in the first step. To our delight, major diastereomer was isolated in pure form by column chromatography. Initially we explored the generality of this reaction with a variety of 3-pyrollyl-oxindole (Scheme 10). After checking various N-substitutions on 3-pyrrolyloxindole **1**, all cases yielded gratifyingly high yields and excellent enantioselectivities. Specifically, with >99% ee, product **4ga** with an *N*-crotyl substituent was extracted in 5:1 dr (Scheme 10). Substitutions on the phenyl ring of **1** were then investigated. Initially, several oxindoles **1ja**-**1oa** with 5-

substituted phenyl groups were made and used in the procedure. Excellent enantioselectivities and high yields of the target compounds **4ja**-**4oa** were obtained (Scheme 10). We obtained the X-ray crystal structure of **4pa** to ascertain the absolute configuration, and the results were comparable for oxindoles **1pa**-**1qa** with 6- and 7-substitutions, respectively. Additionally, oxindole **1ra** with a 5,7-disubstuted phenyl group was involved in the reaction, and 90% ee was found for the product **4ra**.



Scheme 10. Scope of 3-pyrollyloxindole[a,b]

[a]All reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 2 ml CH_2Cl_2 with 2 mol % **VII** for the first step. Then 5 mol% metal catalyst and 1 ml CH_2Cl_2 was used for the second step. [b]Yields correspond to the isolated yields after silica gel column chromatography, dr was determined by ^{1}H NMR and ee was determined by HPLC.



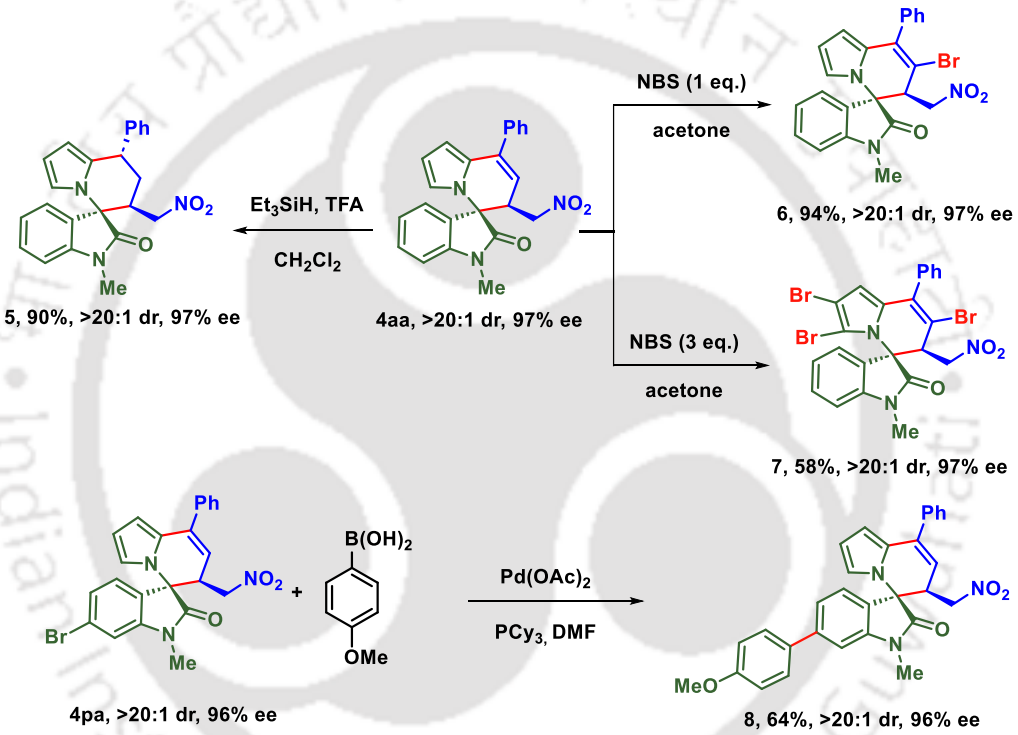
Scheme 11. Scope of linear nitroenyne[a,b]

[a]All reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 2 ml CH_2Cl_2 with 2 mol % **VII** for the first step. Then 5 mol% metal catalyst and 1 ml CH_2Cl_2 was used for the second step. [b]Yields correspond to the isolated yields after silica gel column chromatography, dr was determined by ^{1}H NMR and ee was determined by HPLC.

Nitroenynes **2** with various alkyne substituents were used to further investigate the range of the sequential Michael-hydroarylation cyclization reaction (Scheme 11). Several nitroenynes **2b**-**2e** with aryl groups that had substitutions at the *para*-position were first examined, and the products **4ab**-**4ae** (Scheme 11) produced gratifyingly good results. Subsequent screening of nitroenynes **2f**-**2h** with *meta*-substitutions on the phenyl group revealed similar results (Scheme 11). *Ortho*-substitutions were likewise accepted, and both products (**4ai** and **4aj**) showed 98% ee. Nitroenynyes **2k**-**2n** with additional aryl, heteroaryl, and alkyl substituents likewise underwent a smooth reaction (Scheme 11).

2.4.3 Synthetic transformation:

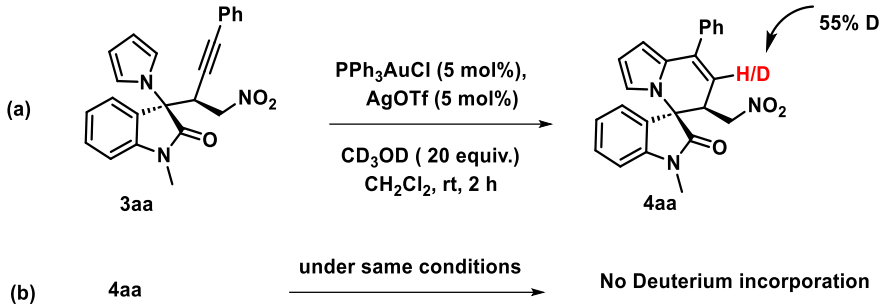
Additionally, to demonstrate the synthetic potential of our method, some reactions were conducted on **4aa** and **4pa** (Scheme 12). At first **4aa** using Et_3SiH/TFA, consequently compound **5** was produced in 90% yield while maintaining enantiopurity and perfect diastereoselectivity.Then **4aa** was treated NBS. It was that that product **6** was formed with one equivalent NBS and that product **7** was tribrominated with three equivalents. Lastly, a Suzuki coupling reaction was performed at **4pa**, and a moderate yield of product **8** was produced.



Scheme 12. Synthetic transformations

2.4.4 Deuterium exchange experiment:

To gain understanding of the mechanism, we conducted a deuteration test using 3aa (Scheme 13). PPh_3AuCl (5 mol%), AgOTf (5 mol%), and CD_3OD (20 equiv.) in CH_2Cl_2 were thus used to treat **3aa**. 55% of the deuterium was incorporated at the C7'-position, according to a ^1H nuclear magnetic resonance (NMR) analysis of **4aa**. Pure 4aa showed no signs of deuterium incorporation under comparable circumstances. Therefore, in the cyclisation step, coordination through a π-acidic AuI complex activates the triple bond.



Scheme 13. Deuterium exchange experiment

2.4.5 Computational study:

Computational details for the Michael Step:

The topology of electron density was analyzed within the realm of quantum theory of atoms in molecules (QTAIM).[13a] To understand the nature of intramolecular interactions within the molecule AIM analysis was performed using Multiwfn program code.[13b] For obtaining a better insight about the nature of non-covalent interactions in both the major and minor products, non-covalent interaction (NCI) index analysis was done.[13c,13d] For visualization of such NCI surfaces we have used visual molecular dynamics (VMD) software based on the files exported from Multiwfn program code.[13e]

To investigate the reason behind the formation of the major product, the electron density for both the isomers were analyzed. It is evident form figure 2 that the major isomer (**3aa**) contains more intramolecular non-covalent interactions compared to the minor one (**3aa'**). Atoms in molecules analysis reveals the formation of C-H π interaction in the major product which has also been confirmed by the presence of attractive zone in the NCI plots. From the coloured NCI plots, we can confirm the presence of non-covalent interactions. The light bluish green colour denotes attractive interactions, the green region tells us the C-H π interactions and the bluish green region H-bonding interactions. The presence of significant intramolecular non-covalent interactions makes the *Re*-face product more stable, whereas, no such interactions were observed for the *Si*-face product.

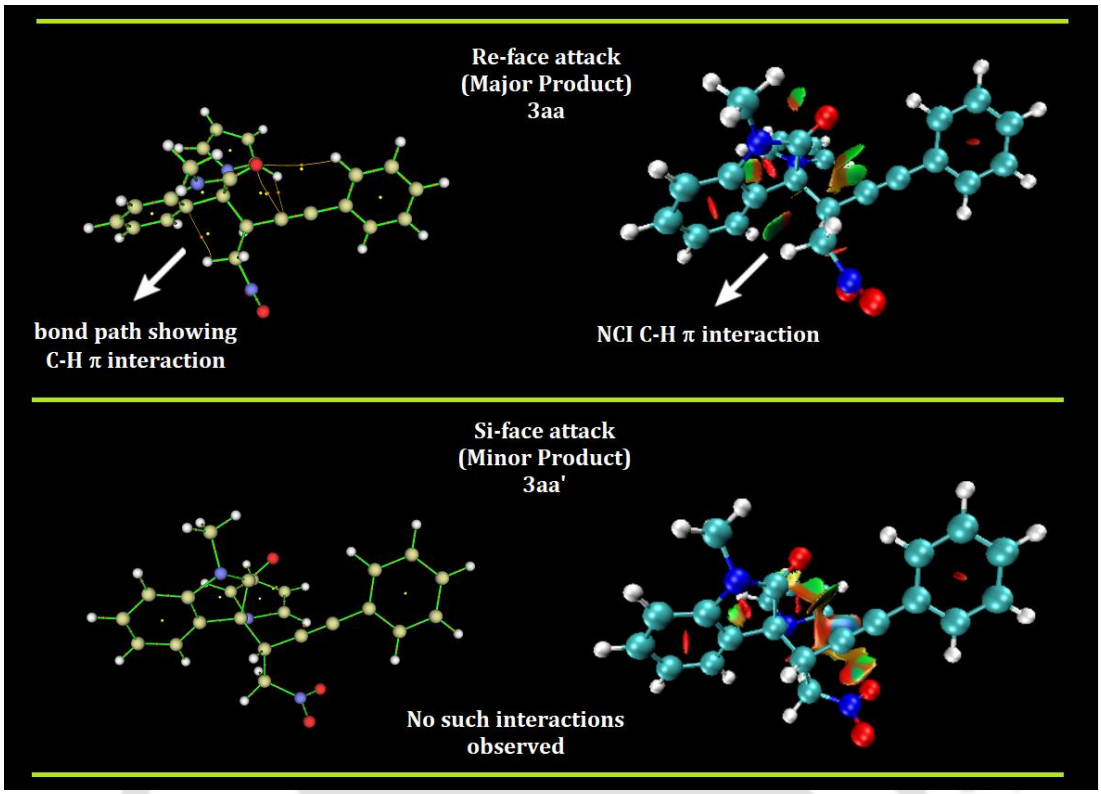


Figure 2. Non-covalent interactions (NCI) plots

Computational details for the hydroarylation step:

All the structures were fully optimized without any symmetry constraint using M06-1X/def2-TZVP level.[13f] Harmonic vibrational frequency calculations were performed at the same level to understand the nature of stationary points. Intermediates were characterized as true minima with all real values of the Hessian matrix while transition states were characterized with one imaginary value. All calculations were performed at gas phase and at ambient condition (298K and 1 atm). Energies are zero-point and thermal corrected. All these calculations were performed using Gaussian16 suite of program.

Figure 3 shows the energy profile diagram for the Au catalyzed formation of Aza-Spirooxindoles. Both endo and exo-cyclization process were considered. Binding of $[Au]^+$

to the C≡C triple bond of **3aa** to generate intermediate **A** is found to exergonic by 6.7kcal/mol. Intermediate **A** then converts to **C** or **E** through two different pathways.

Formation of **C** involves endo cyclization which involves a barrier of 17.2 kcal/mol. Similarly, formation of **E** involving exo-cyclization has a higher barrier of 21.8 kcal/mol. As a consequence, construction of the endo product **4aa** is more likely compared to exo product **F**.

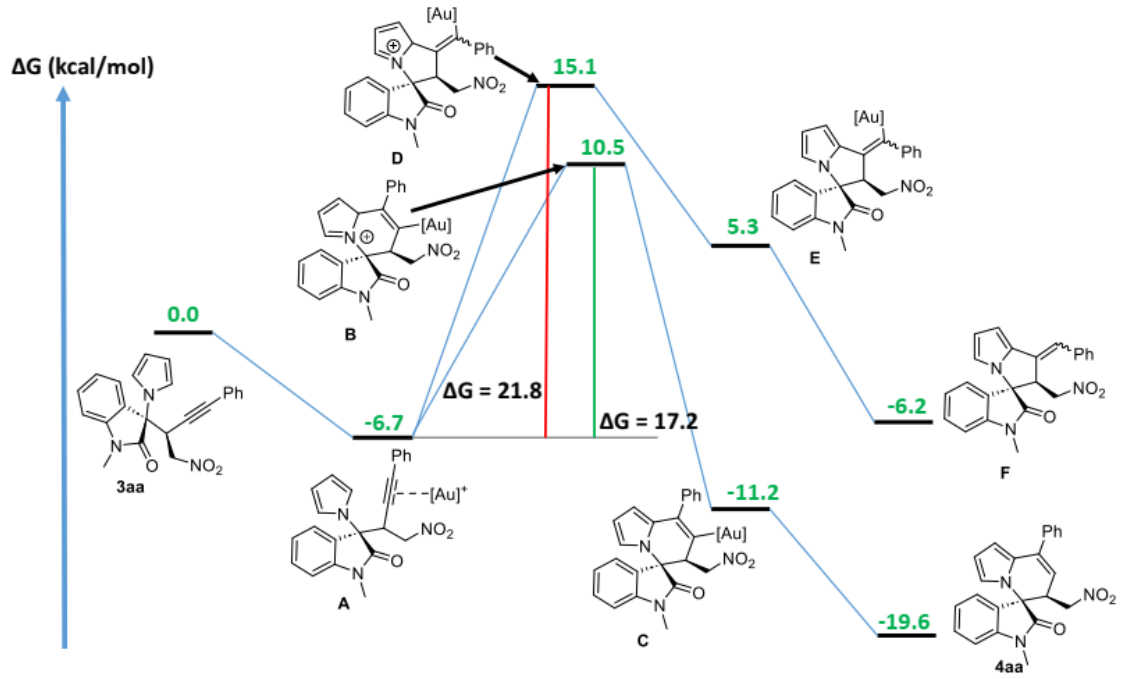
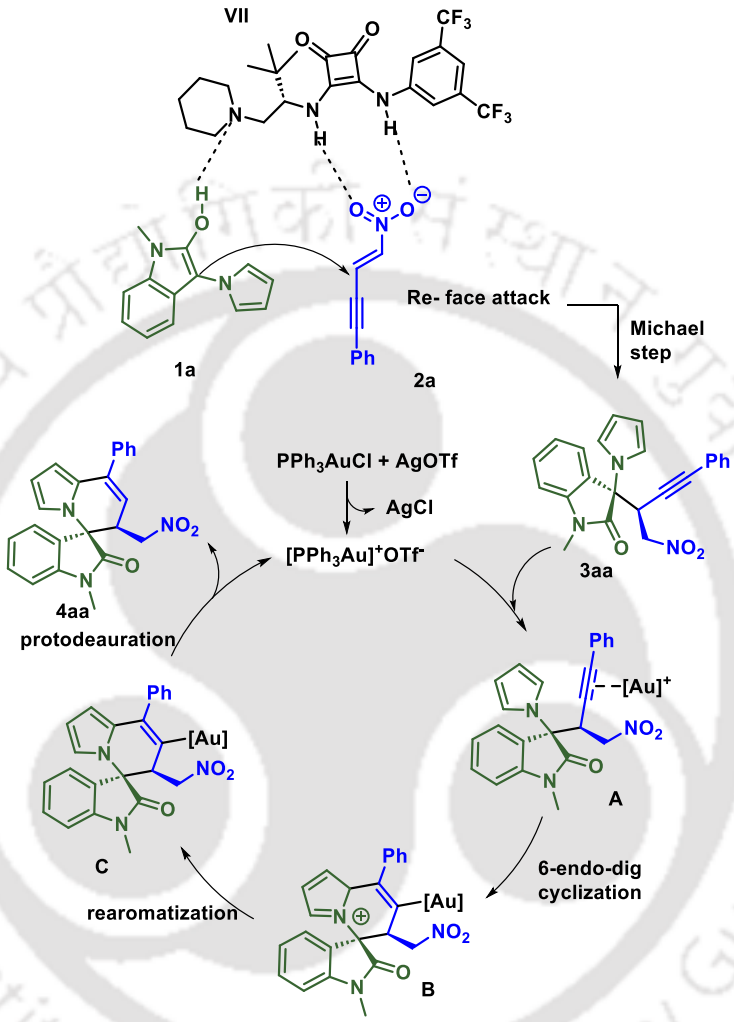


Figure 3. Energy (ΔG_{298}, kcal/mol) profile diagram for the formation of aza-spirooxindoles.

2.4.6 Plausible reaction mechanism:

A plausible mechanism has been suggested based on the absolute configuration (Scheme 14). It is anticipated that the squaramide catalyst **VII**'s N-H moieties will bind to the nitro group of nitroeneyne **2a** while the catalyst **VII**'s nitrogen deprotonates 3-pyrrolyloxindole **1a**. The single attack intermediate **3aa** is then produced by the conjugate addition of 3-pyrrolyloxindole **1a** from the *Re face* of **2a**. The gold-catalyzed cycle can now be entered by the intermediate **3aa**. We anticipated that an initiating *6-endo-dig* cyclisation of the

more nucleophilic 2-position of pyrrole to the internal alkyne can explain the mechanism for the gold-catalyzed step.



Scheme 14. Plausible reaction mechanism

2.5 Conclusion

In conclusion, for the synthesis of a new series of cyclic aza-spirooxindole derivatives, we have created a sequential organo- and metal-catalyzed reaction between 3-pyrrolyloxindoles and linear nitroenynes. In this report, 3-pyrrolyloxindoles are used for the first time in sequential organo-gold catalysis. Excellent yields of the potentially bioactive spiropiperidinyl oxindoles with high diastereo- and excellent enantioselectivities were obtained with low catalyst loading and mild reaction conditions. Additionally, few

synthetic application reactions have been carried out. The Michael-hydroarylation reaction's selectivity has been better understood through the use of DFT-based computational analysis.

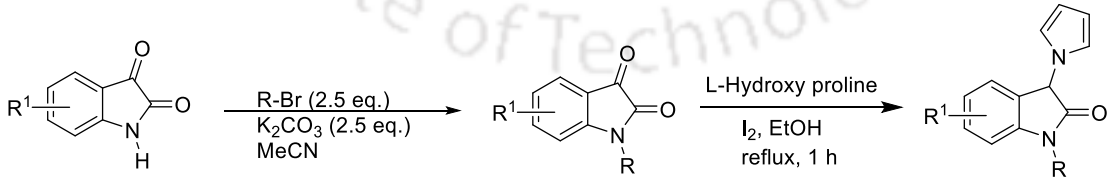
2.6 Experimental section

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 ($CDCl_3$: δ 7.260), carbon ($CDCl_3$: δ 77.16). 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 ID Column, Daicel Chiralpak IE Column, Daicel Chiralpak IF Column, and Daicel Chiralpak ADH Column. For visualizing the products UV light and I_2 were used. DCM was distilled over CaH_2 under argon and stored over 4A° molecular sieves. Silica gel (230-400 mesh size) was used for the flash column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

2.6.2 General procedure for the synthesis of 3-pyrrolyloxindoles:

3-pyrrolyloxindoles were prepared according to reported procedure.[14]



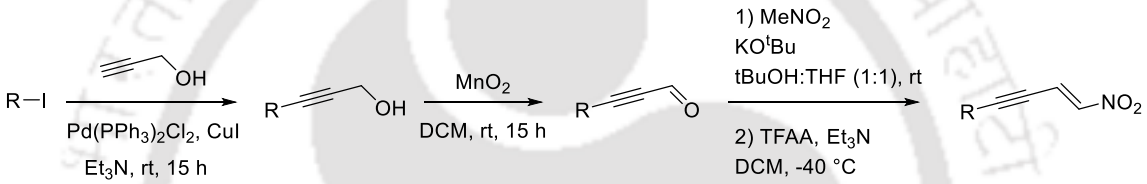
Isatin (3.0 mmol, 1.0 eq.) is dissolved in 15 mL of acetonitrile before potassium carbonate (2.5 eq.) is added. The appropriate amount of bromide (2.5eq.) was then added, and the reaction was stirred at reflux for the remainder of the day. The mixture was then added to

water (15mL) and extracted with EtOAc following TLC analysis. In order to produce N-substituted isatins (yield of 80–90%), the combined organic sections were first washed with water and brine, dried over sodium sulphate, and then concentrated.

The N-substituted isatin (10 mmol), L-hydroxyproline (10 mmol), and iodine (200 mg) were combined with ethanol (20 mL). For 12 hours, the mixture was heated in a reflux system. Following that, the reaction was extracted with DCM (100 mL) and quenched with water (6 mL). The mixed organic phase was concentrated using rotor vapour after being rinsed with saturated sodium carbonate (50 mL). To eventually get a white solid, the residue was purified by flash chromatography using hexane/EtOAc (10/1) as an eluent.

2.6.3 General procedure for the synthesis of nitrolefines:

Nitrolefines were prepared according to reported procedures.[15]



To a solution of the corresponding aryl iodide (13.4 mmol) in NEt_3 (100mL) was added at room temperature $PdCl_2(PPh_3)_2$ (0.47g, 0.07 mmol), CuI (0.13g, 0.07 mmol) and propargylalcohol (1.0 mL, 17.4 mmol). The resulting dark reaction mixture was stirred during 15 hours at room temperature. Then NEt_3 was removed by concentration over reduced pressure and the resulting black oil was purified by flash column chromatography on silica gel using a mixture of ethyl acetate and cyclohexane. Then to a solution of the purified alcohol (13.4 mmol) in dry dichloromethane (100 mL) was added at room temperature MnO_2 (23g, 268 mmol). The resulting dark reaction mixture was stirred during 15 hours at room temperature. Then filtration on celite, concentration under reduced pressure and purification by flash column chromatography on silica gel using a mixture of ethyl acetate and n-hexane gave the expected propargylic aldehyde.

Under an atmosphere of argon, nitromethane (1.5 eq.) and KO^tBu (1 eq.) were added to a solution of aldehyde (1 eq.) in a solution of THF and ^tBuOH (1:1, 0.5 M), and the mixture was stirred overnight. Then a solution of NH_4Cl was added, the product was extracted twice with Et_2O, the combined organic phases were washed with brine and dried over

$MgSO_4$. The solvent was removed under reduced pressure and the crude product was subjected to flash chromatography on silica (n-hexane/Et_2O 5:1 to 1:1).

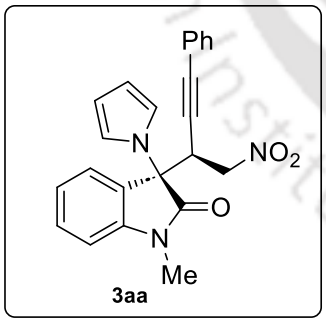
2.6.4 General procedure for the synthesis of catalysts:

The catalyst (**I, II, III, IV, V, VI** and **VII**) was prepared according to reported procedures.[16]

2.6.5 General procedure for the enantioselective synthesis of compound 4:

In an oven dried 5 mL round bottom flask, 3-pyrrole oxindole **1** (0.1 mmol), nitroenyne **2** (0.1 mmol) and 2 mol% of catalyst (**VII**) were taken. Then 2 mL of CH_2Cl_2 was added to the reaction mixture and stirred at rt for 16 h. Progress of the reaction was monitored by TLC. After the completion of reaction, reaction mixture was passed through a short silica gel eluting with hexane/ethyl acetate (90/10) to afford the intermediate **3**. Then the intermediate **3** was then treated with 5 mol% PPh_3AuCl and 5 mol% AgOTf catalyst in 1 ml CH_2Cl_2 at rt and the reaction was monitored by TLC (2 h). After complete consumption of the intermediate, the reaction mixture was subjected to directly in flash chromatography eluting with hexane/ethyl acetate (90/10) to afford the product **4**.

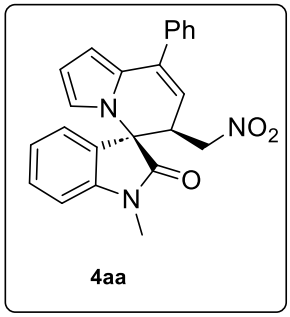
(R)-1-methyl-3-((S)-1-nitro-4-phenylbut-3-yn-2-yl)-3-(1H-pyrrol-1-yl)indolin-2-one (3aa)



3aa

White solid (36.5 mg, combined yield: 95%); M.P. 189-192 °C; R_f = 0.50 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.52 (td, *J* = 7.8, 1.2 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.20 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.08 – 7.01 (m, 4H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.25 (t, *J* = 2.2 Hz, 2H), 4.75 – 4.66 (m, 2H), 4.46 (dd, *J* = 11.8, 2.3 Hz, 1H), 3.21 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.46, 144.88, 131.82, 131.28, 128.95, 128.34, 126.19, 124.30, 123.21, 121.58, 119.34, 110.36, 109.37, 86.13, 81.61, 74.72, 66.67, 39.50, 26.78. **ESI HRMS**: calcd. for $C_{23}H_{19}N_3O_3$ $[M+H]^+$ 386.1499, found 386.1505. **HPLC Analysis**: *ee* = 97%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.3 min, t_{minor} = 24.6 min).

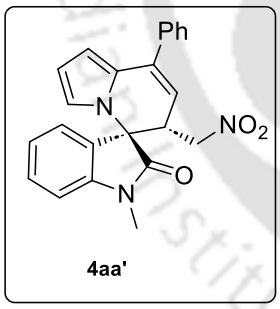
(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4aa)



4aa

White solid (35.8 mg, combined yield: 93%); M.P. 175-178 °C; R_f = 0.42 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.63 – 7.53 (m, 2H), 7.48 – 7.35 (m, 4H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.44 – 6.36 (m, 1H), 6.28 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.65 (d, *J* = 5.3 Hz, 1H), 4.82 (dd, *J* = 13.7, 5.7 Hz, 1H), 4.43 (dd, *J* = 13.7, 8.5 Hz, 1H), 3.76 (dt, *J* = 8.5, 5.5 Hz, 1H), 3.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.76, 142.42, 138.10, 136.64, 130.65, 129.23, 128.63, 128.58, 128.27, 128.04, 124.61, 123.87, 120.88, 113.04, 111.51, 110.20, 109.10, 74.69, 63.76, 41.58, 26.81. **ESI HRMS**: calcd. for $C_{23}H_{19}N_3O_3$ $[M+H]^+$ 386.1499, found 386.1506. **HPLC Analysis**: *ee* = 97%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.5 min, t_{minor} = 17.5 min).

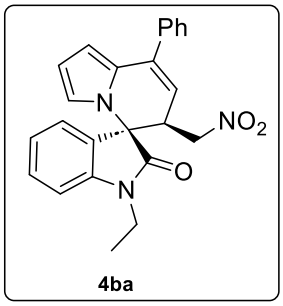
(3R,6'R)-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4aa′)



4aa'

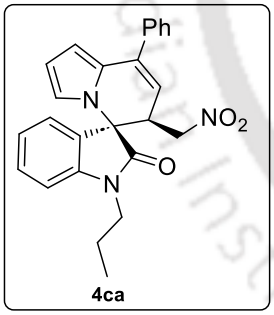
Red solid; M.P. 182-185 °C; R_f = 0.41 in 1:9 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.61 – 7.57 (m, 2H), 7.47 – 7.40 (m, 3H), 7.36 (td, *J* = 7.8, 1.2 Hz, 1H), 7.16 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.44 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.7, 1.4 Hz, 1H), 6.15 (t, *J* = 3.3 Hz, 1H), 5.58 (d, *J* = 2.8 Hz, 1H), 4.23 (ddd, *J* = 9.8, 4.8, 2.8 Hz, 1H), 4.14 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.07 (dd, *J* = 12.8, 9.7 Hz, 1H), 3.37 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 173.64, 141.84, 138.00, 135.98, 130.74, 129.39, 128.67, 128.59, 128.15, 125.57, 124.77, 123.93, 120.44, 113.53, 111.08, 110.35, 109.44, 75.07, 64.99, 41.95, 27.08. **ESI HRMS**: calcd. for $C_{23}H_{19}N_3O_3$ $[M+H]^+$ 386.1499, found 386.1506.

(3R,6'S)-1-ethyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ba)



White solid (35.9 mg, combined yield: 90%); M.P. 163-166 °C; R_f = 0.44 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 3.6:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.62 – 7.53 (m, 2H), 7.48 – 7.35 (m, 4H), 7.31 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.15 (dd, *J* = 3.7, 2.8 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 4.81 (dd, *J* = 13.8, 6.0 Hz, 1H), 4.41 (dd, *J* = 13.8, 8.0 Hz, 1H), 3.88 (dd, *J* = 14.2, 7.2 Hz, 1H), 3.79 (dtd, *J* = 12.5, 7.1, 6.3, 3.5 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.36, 141.49, 138.07, 136.57, 130.58, 129.17, 128.61, 128.56, 128.27, 128.23, 124.78, 123.65, 120.78, 113.00, 111.41, 110.17, 109.21, 74.37, 63.54, 41.50, 35.38, 12.74. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_3$ $[M+H]^+$ 400.1656, found 400.1676. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.5 min, t_{minor} = 16.7 min).

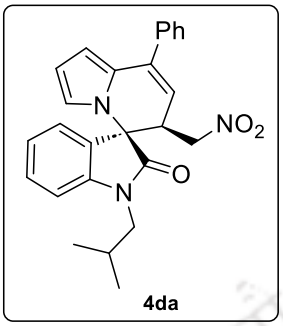
(3R,6'S)-6'-(nitromethyl)-8'-phenyl-1-propyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ca)



White solid (37.9 mg, combined yield: 92%); M.P. 171-174 °C; R_f = 0.46 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 3.4:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.62 – 7.54 (m, 2H), 7.48 – 7.39 (m, 3H), 7.37 (td, *J* = 7.8, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.39 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.65 (d, *J* = 5.2 Hz, 1H), 4.81 (dd, *J* = 13.7, 5.8 Hz, 1H), 4.42 (dd, *J* = 13.7, 8.3 Hz, 1H), 3.78 (dtd, *J* = 14.2, 7.2, 4.6 Hz, 2H), 3.71 (dt, *J* = 14.2, 7.4 Hz, 1H), 1.78 (h, *J* = 7.3 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.72, 141.97, 138.13, 136.62, 130.58, 129.26, 128.64, 128.58, 128.28, 128.18, 124.79, 123.65, 120.82, 113.08, 111.49, 110.22, 109.39, 74.63, 63.63, 42.23, 41.61, 20.86, 11.56. **ESI HRMS**: calcd. for $C_{25}H_{23}N_3O_3$ $[M+H]^+$ 414.1812, found 414.1836. **HPLC Analysis**: *ee* = 97%, Chiralpak IE

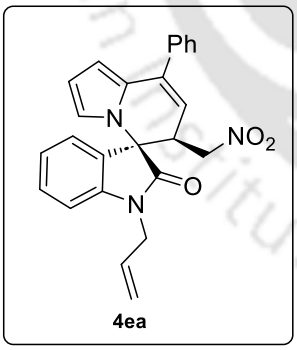
Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.0 min, t_{minor} = 15.3 min).

(3R,6'S)-1-isobutyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4da)



White solid (38.4 mg, combined yield: 90%); M.P. 155-158 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 3.4:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.62 – 7.53 (m, 2H), 7.47 – 7.39 (m, 3H), 7.36 (td, *J* = 7.8, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.03 (td, *J* = 7.6, 0.9 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.40 (dd, *J* = 2.8, 1.5 Hz, 1H), 6.29 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.66 (d, *J* = 5.2 Hz, 1H), 4.81 (dd, *J* = 13.5, 5.6 Hz, 1H), 4.44 (dd, *J* = 13.5, 8.6 Hz, 1H), 3.77 (dt, *J* = 8.6, 5.4 Hz, 1H), 3.66 – 3.51 (m, 2H), 2.21 (tt, *J* = 14.3, 7.1 Hz, 1H), 1.01 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.97, 142.31, 138.12, 136.63, 130.54, 129.27, 128.64, 128.59, 128.29, 128.05, 124.77, 123.64, 120.82, 113.12, 111.53, 110.23, 109.65, 74.81, 63.63, 48.15, 41.67, 27.16, 20.42. **ESI HRMS**: calcd. for $C_{26}H_{25}N_3O_3$ $[M+H]^+$ 428.1969, found 428.1966. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.1 min, t_{minor} = 12.3 min).

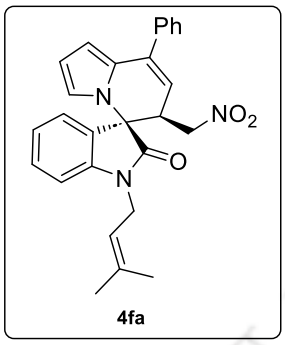
(3R,6'S)-1-allyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ea)



White solid (38.6 mg, combined yield: 94%); M.P. 159-162 °C; R_f = 0.45 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.60 – 7.54 (m, 2H), 7.45 – 7.39 (m, 3H), 7.38 – 7.30 (m, 2H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.29 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.18 – 6.15 (m, 1H), 5.88 (ddt, *J* = 16.2, 10.6, 5.4 Hz, 1H), 5.65 (d, *J* = 5.1 Hz, 1H), 5.31 (d, *J* = 1.6 Hz, 1H), 5.29 (dq, *J* = 7.4, 1.3 Hz, 1H), 4.80 (dd, *J* = 13.7, 5.8 Hz, 1H), 4.47 – 4.34 (m, 3H), 3.82 (dt, *J* = 8.3, 5.5 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 172.50, 141.68, 138.10, 136.64, 130.78, 130.58, 129.31, 128.65, 128.60, 128.28, 127.99, 124.72, 123.86, 120.81, 118.58, 113.03, 111.55, 110.31, 110.01, 74.55, 63.67, 42.87, 41.70. **ESI HRMS**: calcd. for $C_{25}H_{21}N_3O_3$ $[M+H]^+$ 412.1656,

found 412.1663. **HPLC Analysis**: *ee* = 98%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.3 min, t_{minor} = 14.8 min).

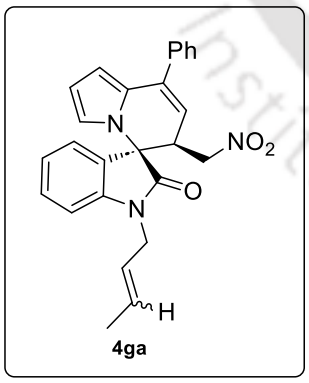
(3R,6'S)-1-(3-methylbut-2-en-1-yl)-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4fa)



4fa

White solid (39.0 mg, combined yield: 89%); M.P. 176-179 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.60 – 7.55 (m, 2H), 7.47 – 7.40 (m, 3H), 7.38 – 7.29 (m, 2H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.16 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 5.20 (ddt, *J* = 6.7, 5.0, 1.4 Hz, 1H), 4.79 (dd, *J* = 13.7, 5.6 Hz, 1H), 4.48 – 4.39 (m, 2H), 4.32 (dd, *J* = 15.5, 6.8 Hz, 1H), 3.79 (dt, *J* = 8.5, 5.4 Hz, 1H), 1.85 (s, 3H), 1.77 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.24, 141.85, 138.11, 138.03, 136.54, 130.54, 129.22, 128.62, 128.56, 128.27, 128.12, 124.63, 123.67, 120.82, 117.56, 113.06, 111.43, 110.15, 109.79, 74.60, 63.67, 41.60, 38.69, 25.83, 18.42. **ESI HRMS**: calcd. for $C_{27}H_{25}N_3O_3$ $[M+H]^+$ 440.1969, found 440.1976. **HPLC Analysis**: *ee* = 98%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.5 min, t_{minor} = 14.5 min).

(3R,6'S)-1-((E)-but-2-en-1-yl)-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ga)

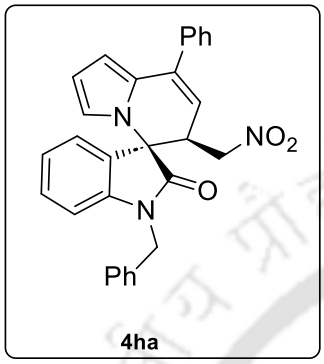


4ga

White solid (37.4 mg, combined yield: 88%); M.P. 188-191 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.57 (d, *J* = 7.1 Hz, 3H), 7.43 (q, *J* = 6.7 Hz, 4H), 7.38 – 7.28 (m, 3H), 7.04 (q, *J* = 7.6, 6.3 Hz, 1H), 6.93 (dd, *J* = 17.6, 7.9 Hz, 1H), 6.39 (d, *J* = 6.7 Hz, 1H), 6.28 (d, *J* = 3.7 Hz, 1H), 6.16 (d, *J* = 4.3 Hz, 1H), 5.86 – 5.74 (m, 1H), 5.65 (d, *J* = 4.9 Hz, 1H), 5.51 (dd, *J* = 14.6, 7.1 Hz, 1H), 4.79 (dt, *J* = 10.3, 5.3 Hz, 1H), 4.50 – 4.21 (m, 4H), 3.80 (dt, *J* = 8.9, 5.3 Hz, 1H), 1.86 (d, *J* = 7.0 Hz, 1H), 1.73 (d, *J* = 6.6 Hz, 3H).**^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.35, 141.79, 138.09, 136.57, 130.52, 129.63, 129.23, 128.62, 128.57, 128.26, 128.03, 124.63, 123.70,

123.59, 120.82, 113.04, 111.46, 110.19, 110.00, 74.53, 63.59, 42.34, 41.61, 17.87. **ESI HRMS**: calcd. for $C_{26}H_{23}N_3O_3$ $[M+H]^+$ 426.1812, found 426.1830. **HPLC Analysis**: *ee* = >99%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.6 min, t_{minor} = 20.0 min).

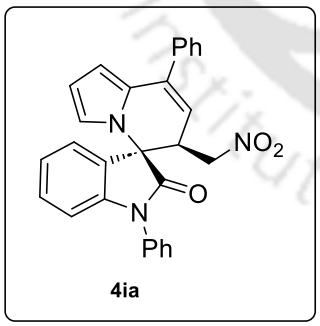
(3R,6'S)-1-benzyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ha)



4ha

White solid (40.5 mg, combined yield: 88%); M.P. 203-206 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.58 (d, *J* = 7.0 Hz, 2H), 7.43 (q, *J* = 7.2, 6.6 Hz, 3H), 7.31 (ddd, *J* = 32.3, 16.3, 9.0 Hz, 7H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.44 – 6.37 (m, 1H), 6.30 (d, *J* = 3.7 Hz, 1H), 6.18 (t, *J* = 3.3 Hz, 1H), 5.66 (d, *J* = 5.1 Hz, 1H), 4.97 (s, 2H), 4.78 (dd, *J* = 13.7, 5.6 Hz, 1H), 4.44 (dd, *J* = 13.7, 8.5 Hz, 1H), 3.85 (dt, *J* = 8.6, 5.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.89, 141.75, 138.10, 136.60, 135.18, 130.62, 129.39, 129.21, 128.65, 128.60, 128.29, 128.24, 127.96, 127.52, 124.76, 123.95, 120.80, 113.10, 111.60, 110.37, 110.18, 74.63, 63.75, 44.45, 41.80. **ESI HRMS**: calcd. for $C_{29}H_{23}N_3O_3$ $[M+H]^+$ 462.1812, found 462.1831. **HPLC Analysis**: *ee* = 98%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.1 min, t_{minor} = 21.4 min).

(3R,6'S)-6'-(nitromethyl)-1,8'-diphenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ia)

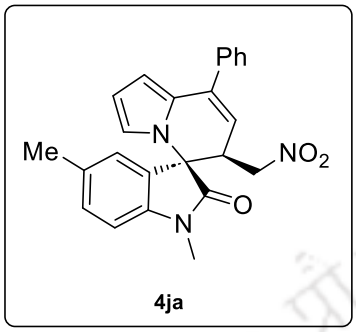


4ia

White solid (39.3 mg, combined yield: 88%); M.P. 239-242 °C; R_f = 0.44 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 3.5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.58 (p, *J* = 9.1, 7.5 Hz, 4H), 7.50 – 7.36 (m, 7H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.53 (s, 1H), 6.31 (d, *J* = 3.7 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 5.66 (d, *J* = 5.2 Hz, 1H), 4.90 (dd, *J* = 14.0, 6.3 Hz, 1H), 4.48 (dd, *J* = 14.0, 7.5 Hz, 1H), 3.96 (q, *J* = 6.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.25, 142.56, 138.04, 136.66, 133.52, 130.57, 130.00, 129.28, 128.90, 128.63, 128.59, 128.25, 127.75, 126.69, 124.87, 124.29, 120.94, 112.86, 111.61, 110.44, 110.40, 74.28, 63.76, 41.90. **ESI HRMS**: calcd. for $C_{28}H_{21}N_3O_3$ $[M+H]^+$ 448.1656, found 448.1673. **HPLC Analysis**: *ee* = 95%, Chiralpak IE

Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.5 min, t_{minor} = 25.7 min).

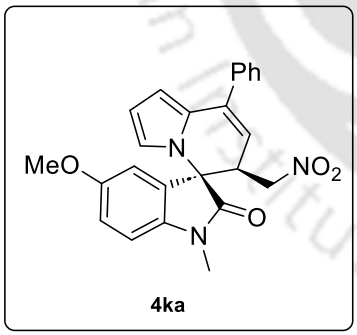
(3R,6'S)-1,5-dimethyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ja)



4ja

White solid (36.7 mg, combined yield: 92%); M.P. 215-218 °C; R_f = 0.46 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.60 – 7.54 (m, 2H), 7.47 – 7.39 (m, 3H), 7.19 (ddd, *J* = 7.9, 1.7, 0.8 Hz, 1H), 7.12 (d, *J* = 1.7 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.38 (dd, *J* = 2.8, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.16 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.63 (d, *J* = 5.0 Hz, 1H), 4.75 (dd, *J* = 13.5, 5.5 Hz, 1H), 4.43 (dd, *J* = 13.5, 8.8 Hz, 1H), 3.78 (dt, *J* = 8.8, 5.3 Hz, 1H), 3.27 (s, 3H), 2.28 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.59, 140.12, 138.20, 136.46, 133.67, 130.96, 129.35, 128.63, 128.52, 128.27, 127.92, 125.30, 120.84, 113.12, 111.34, 110.12, 108.88, 74.76, 63.82, 41.63, 26.80, 21.36. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_3$ $[M+H]^+$ 400.1656, found 400.1656. **HPLC Analysis**: *ee* = 96%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.9 min, t_{minor} = 19.8 min).

(3R,6'S)-5-methoxy-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ka)

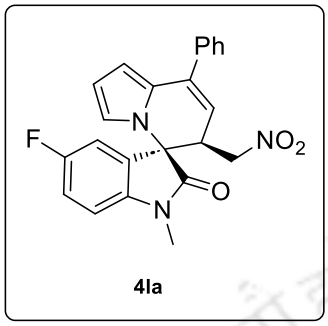


4ka

White solid (38.1 mg, combined yield: 92%); M.P. 199-202 °C; R_f = 0.34 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.1:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.60 – 7.51 (m, 2H), 7.47 – 7.37 (m, 3H), 6.95 – 6.87 (m, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.41 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.28 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 4.83 (dd, *J* = 13.7, 5.6 Hz, 1H), 4.43 (dd, *J* = 13.6, 8.6 Hz, 1H), 3.75 (dt, *J* = 8.6, 5.4 Hz, 1H), 3.71 (s, 3H), 3.27 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.40, 156.66, 138.10, 136.60, 135.59, 129.16, 129.15, 128.63, 128.55, 128.22, 120.95, 114.89, 113.00, 111.85, 111.52, 110.23, 109.60, 74.71, 64.00, 55.86, 41.51, 26.87. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_4$ $[M+H]^+$ 416.1605, found 416.1594. **HPLC Analysis**: *ee* = 98%, Chiralpak IE

Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.0 min, t_{minor} = 27.2 min).

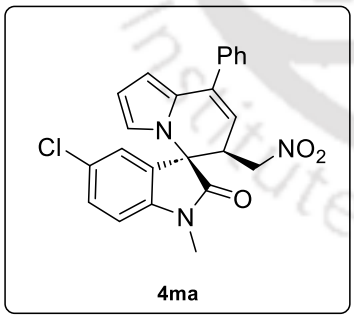
(3R,6'S)-5-fluoro-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4la)



4la

White solid (36.2 mg, combined yield: 90%); M.P. 175-178 °C; R_f = 0.41 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.9:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.61 – 7.53 (m, 2H), 7.50 – 7.41 (m, 3H), 7.08 (td, *J* = 8.7, 2.6 Hz, 1H), 7.02 (dd, *J* = 7.7, 2.6 Hz, 1H), 6.88 (dd, *J* = 8.5, 4.0 Hz, 1H), 6.44 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.31 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.19 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 4.96 (dd, *J* = 13.9, 6.1 Hz, 1H), 4.42 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.68 (dt, *J* = 8.0, 5.9 Hz, 1H), 3.32 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.72, 160.64, 158.22, 137.99 (d, $J_{C\text{-}F}$ = 3.03 Hz), 137.80 (d, $J_{C\text{-}F}$ = 87.87 Hz), 129.75 (d, $J_{C\text{-}F}$ = 8.08 Hz), 128.78, 128.76, 128.74, 128.22, 121.04, 117.00 (d, $J_{C\text{-}F}$ = 23.23 Hz), 113.03 (d, $J_{C\text{-}F}$ = 25.25 Hz), 112.60, 111.91, 110.50, 109.89 (d, $J_{C\text{-}F}$ = 8.08 Hz), 74.39, 63.80 (d, $J_{C\text{-}F}$ = 2.02 Hz), 41.12, 27.06. **^{19}F NMR (377 MHz, $CDCl_3$)** δ -117.78. **ESI HRMS**: calcd. for $C_{23}H_{18}FN_3O_3$ $[M+H]^+$ 404.1405, found 404.1428. **HPLC Analysis**: *ee* = 96%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.6 min, t_{minor} = 29.8 min).

(3R,6'S)-5-chloro-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ma)

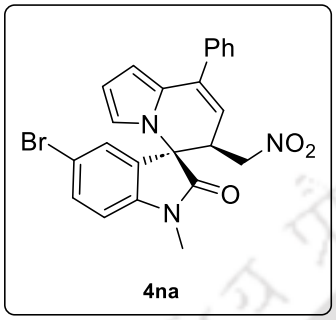


4ma

White solid (38.9 mg, combined yield: 93%); M.P. 161-164 °C; R_f = 0.43 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.62 – 7.52 (m, 2H), 7.51 – 7.40 (m, 3H), 7.36 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.24 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.43 (dd, *J* = 2.9, 1.4 Hz, 1H), 6.30 (dd, *J* = 3.7, 1.4 Hz, 1H), 6.19 (t, *J* = 3.3 Hz, 1H), 5.67 (d, *J* = 5.7 Hz, 1H), 4.94 (dd, *J* = 14.0, 6.1 Hz, 1H), 4.42 (dd, *J* = 13.9, 7.9 Hz, 1H), 3.69 (dt, *J* = 7.8, 5.9 Hz, 1H), 3.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.59, 140.63, 137.84, 136.96, 130.50, 129.81, 129.17, 128.86, 128.77, 128.75, 128.24, 125.08, 121.02, 112.60, 111.93, 110.56, 110.15, 74.31, 63.65, 41.15, 27.04. **ESI**

HRMS: calcd. for $C_{23}H_{18}ClN_3O_3$ $[M+H]^+$ 420.1109, found 420.1105. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.4 min, t_{minor} = 26.3 min).

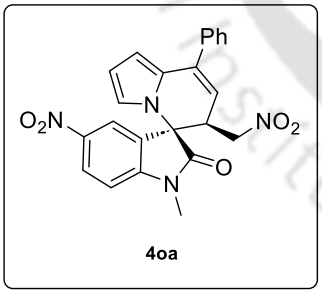
(3R,6'S)-5-bromo-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4na)



4na

White solid (43.6 mg, combined yield: 94%); M.P. 219-222 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.59 – 7.53 (m, 2H), 7.53 – 7.49 (m, 1H), 7.48 – 7.40 (m, 3H), 7.38 (d, *J* = 1.9 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.46 – 6.37 (m, 1H), 6.30 (dd, *J* = 3.5, 1.7 Hz, 1H), 6.19 (d, *J* = 3.3 Hz, 1H), 5.66 (d, *J* = 5.7 Hz, 1H), 4.93 (dd, *J* = 14.0, 6.1 Hz, 1H), 4.42 (dd, *J* = 14.0, 7.9 Hz, 1H), 3.74 – 3.64 (m, 1H), 3.31 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.47, 141.14, 137.85, 136.95, 133.42, 130.13, 128.89, 128.74, 128.23, 127.79, 121.01, 116.39, 112.60, 111.92, 110.62, 110.57, 74.27, 63.59, 41.17, 27.00. **ESI HRMS**: calcd. for $C_{23}H_{18}BrN_3O_3$ $[M+H]^+$ 464.0604, found 464.0611. **HPLC Analysis**: *ee* = 96%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.3 min, t_{minor} = 27.1 min).

(3R,6'S)-1-methyl-5-nitro-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4oa)

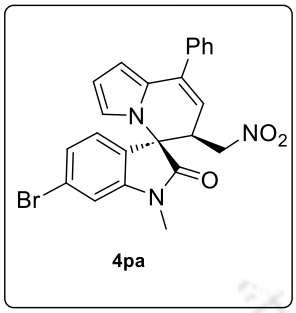


4oa

White solid (37.8 mg, combined yield: 88%); M.P. 209-212 °C; R_f = 0.28 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 8.37 – 8.31 (m, 1H), 8.17 – 8.10 (m, 1H), 7.63 – 7.54 (m, 2H), 7.51 – 7.41 (m, 3H), 7.05 (dd, *J* = 8.7, 1.2 Hz, 1H), 6.44 (dt, *J* = 2.8, 1.4 Hz, 1H), 6.36 – 6.29 (m, 1H), 6.24 – 6.15 (m, 1H), 5.73 – 5.65 (m, 1H), 5.08 – 4.99 (m, 1H), 4.43 (ddd, *J* = 14.5, 6.7, 1.2 Hz, 1H), 3.70 (q, *J* = 6.5, 6.0 Hz, 1H), 3.40 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.42, 147.32, 143.97, 137.50, 129.08, 128.92, 128.84, 128.16, 127.28, 121.06, 120.33, 112.51, 112.17, 111.07, 109.00, 73.64, 63.23, 40.94, 27.40. **ESI HRMS**: calcd. for $C_{23}H_{18}N_4O_5$ $[M+H]^+$ 431.1350, found 431.1373. **HPLC**

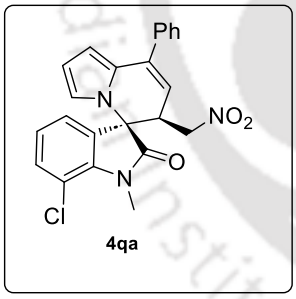
Analysis: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 26.9 min, t_{minor} = 35.7 min).

(3R,6'S)-6-bromo-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4pa)



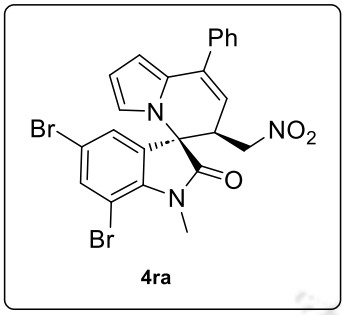
White solid (42.6 mg, combined yield: 92%); M.P. 245-248 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.7:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.55 (dd, *J* = 7.1, 2.6 Hz, 2H), 7.48 – 7.40 (m, 3H), 7.19 – 7.07 (m, 3H), 6.40 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.29 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.17 (dd, *J* = 3.7, 2.8 Hz, 1H), 5.65 (d, *J* = 5.5 Hz, 1H), 4.88 (dd, *J* = 13.9, 6.0 Hz, 1H), 4.41 (dd, *J* = 13.9, 8.1 Hz, 1H), 3.70 (dt, *J* = 8.0, 5.8 Hz, 1H), 3.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.73, 143.51, 137.83, 136.83, 128.92, 128.74, 128.71, 128.20, 127.00, 126.64, 125.83, 124.39, 120.90, 112.73, 112.67, 111.83, 110.49, 74.32, 63.44, 41.23, 26.99. **ESI HRMS**: calcd. for $C_{23}H_{18}BrN_3O_3$ $[M+H]^+$ 464.0604, found 464.0610. **HPLC Analysis**: *ee* = 96%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.1 min, t_{minor} = 15.1 min).

(3R,6'S)-7-chloro-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4qa)



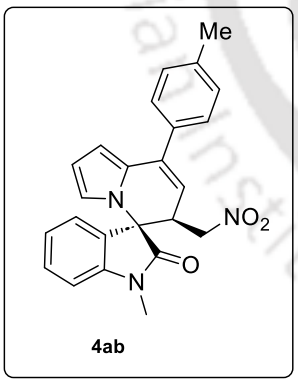
White solid (38.5 mg, combined yield: 92%); M.P. 215-218 °C; R_f = 0.43 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.61 – 7.51 (m, 2H), 7.48 – 7.39 (m, 3H), 7.34 – 7.28 (m, 1H), 7.21 – 7.15 (m, 1H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.40 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.30 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.18 (t, *J* = 3.3 Hz, 1H), 5.62 (d, *J* = 5.4 Hz, 1H), 4.83 (dd, *J* = 13.9, 6.0 Hz, 1H), 4.41 (dd, *J* = 13.9, 8.0 Hz, 1H), 3.72 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.67 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.22, 138.22, 137.87, 136.74, 132.86, 130.76, 128.98, 128.71, 128.69, 128.22, 124.59, 123.07, 120.98, 116.47, 112.59, 111.81, 110.51, 74.43, 63.21, 41.65, 30.33. **ESI HRMS**: calcd. for $C_{23}H_{18}ClN_3O_3$ $[M+H]^+$ 420.1109, found 420.1093. **HPLC Analysis**: *ee* = 96%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.7 min, t_{minor} = 12.3 min).

(3R,6'S)-5,7-dibromo-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ra)



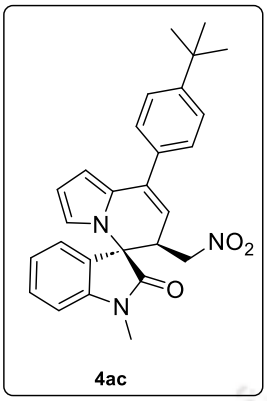
White solid (48.8 mg, combined yield: 90%); M.P. 241-244 °C; R_f = 0.60 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.64 (q, *J* = 1.7 Hz, 1H), 7.53 (dt, *J* = 6.7, 1.9 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 3H), 7.29 (d, *J* = 2.2 Hz, 1H), 6.44 – 6.38 (m, 1H), 6.33 – 6.27 (m, 1H), 6.20 (d, *J* = 3.0 Hz, 1H), 5.62 (d, *J* = 5.8 Hz, 1H), 4.91 (dd, *J* = 14.2, 6.4 Hz, 1H), 4.39 (dd, *J* = 14.2, 7.4 Hz, 1H), 3.67 (s, 3H), 3.65 (d, *J* = 7.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.17, 138.73, 138.02, 137.71, 137.05, 132.63, 128.84, 128.78, 128.19, 126.79, 121.12, 116.56, 112.24, 112.23, 110.91, 103.75, 74.10, 63.09, 41.43, 30.60. **ESI HRMS**: calcd. for $C_{23}H_{17}Br_2N_3O_3$ $[M+H]^+$ 543.9689, found 543.9706. **HPLC Analysis**: *ee* = 90%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.6 min, t_{minor} = 16.5 min).

(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-(p-tolyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ab)



White solid (35.9 mg, combined yield: 90%); M.P. 179-182 °C; R_f = 0.46 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.37 (td, *J* = 7.8, 1.3 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.06 – 6.98 (m, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.40 (dd, *J* = 2.8, 1.5 Hz, 1H), 6.29 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.15 (t, *J* = 3.3 Hz, 1H), 5.62 (d, *J* = 5.4 Hz, 1H), 4.84 (dd, *J* = 13.7, 5.8 Hz, 1H), 4.41 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.73 (dt, *J* = 8.3, 5.5 Hz, 1H), 3.30 (s, 3H), 2.41 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.81, 142.28, 138.47, 136.47, 135.15, 130.55, 129.30, 129.19, 128.10, 124.58, 123.79, 120.80, 112.48, 111.41, 110.09, 109.07, 74.64, 63.69, 41.43, 26.80, 21.38. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_3$ $[M+H]^+$ 400.1656, found 400.1656. **HPLC Analysis**: *ee* = 98%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.8 min, t_{minor} = 20.5 min).

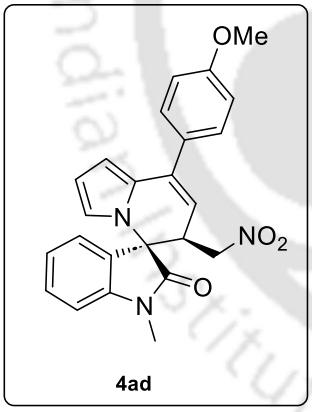
(3R,6'S)-8'-(4-(tert-butyl)phenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ac)



4ac

White solid (38.8 mg, combined yield: 88%); M.P. 177-180 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.56 – 7.49 (m, 2H), 7.49 – 7.42 (m, 2H), 7.37 (td, *J* = 7.8, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.05 – 7.00 (m, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.41 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.33 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.65 (d, *J* = 5.4 Hz, 1H), 4.86 (dd, *J* = 13.7, 5.8 Hz, 1H), 4.41 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.73 (dt, *J* = 8.3, 5.6 Hz, 1H), 3.30 (s, 3H), 1.37 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 172.89, 151.73, 142.28, 136.47, 135.13, 130.55, 129.18, 128.20, 127.92, 125.56, 124.65, 123.81, 120.82, 112.57, 111.54, 110.12, 109.06, 74.69, 63.74, 41.48, 34.82, 31.50, 26.83. **ESI HRMS**: calcd. for $C_{27}H_{27}N_3O_3$ $[M+H]^+$ 442.2125, found 442.2120. **HPLC Analysis**: *ee* = 93%, Chiralpak IF Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.2 min, t_{minor} = 10.1 min).

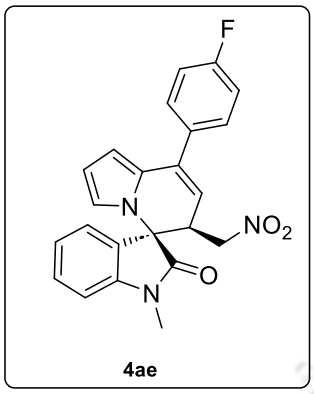
(3R,6'S)-8'-(4-methoxyphenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ad)



4ad

White solid (36.9 mg, combined yield: 89%); M.P. 176-179 °C; R_f = 0.40 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.1:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.54 – 7.47 (m, 2H), 7.38 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.00 – 6.89 (m, 3H), 6.44 – 6.32 (m, 1H), 6.28 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.15 (t, *J* = 3.3 Hz, 1H), 5.59 (d, *J* = 5.4 Hz, 1H), 4.82 (dd, *J* = 13.6, 5.7 Hz, 1H), 4.41 (dd, *J* = 13.6, 8.5 Hz, 1H), 3.86 (s, 3H), 3.72 (dt, *J* = 8.5, 5.6 Hz, 1H), 3.30 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 172.83, 160.05, 142.36, 136.11, 130.58, 130.54, 129.40, 129.35, 128.12, 124.62, 123.82, 120.79, 114.04, 112.03, 111.40, 110.09, 109.06, 74.77, 63.74, 55.51, 41.53, 26.80. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_4$ $[M+H]^+$ 416.1605, found 416.1599. **HPLC Analysis**: *ee* = 98%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 25.0 min, t_{minor} = 30.4 min).

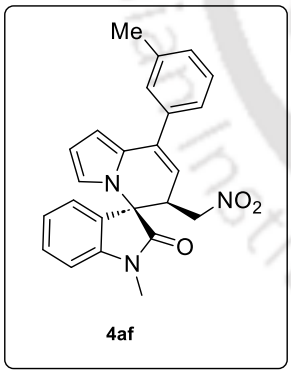
(3R,6'S)-8'-(4-fluorophenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ae)



4ae

White solid (35.4 mg, combined yield: 88%); M.P. 155-158 °C; R_f = 0.42 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 7:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.59 – 7.48 (m, 2H), 7.40 (td, *J* = 7.7, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.17 – 7.03 (m, 3H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.38 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.24 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.15 (t, *J* = 3.3 Hz, 1H), 5.60 (d, *J* = 5.0 Hz, 1H), 4.74 (dd, *J* = 13.5, 5.5 Hz, 1H), 4.42 (dd, *J* = 13.5, 8.8 Hz, 1H), 3.78 (dt, *J* = 8.8, 5.3 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.56, 164.03 (248.22 Hz), 142.56, 135.55, 134.10 (3.78 Hz), 130.77, 129.94 (7.56 Hz), 129.20, 127.76, 124.55, 123.93, 120.97, 115.63 (21.42 Hz), 113.05, 111.40, 110.23, 109.15, 74.68, 63.72, 41.63, 26.77. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -113.45. **ESI HRMS**: calcd. for $C_{23}H_{18}FN_3O_3$ $[M+H]^+$ 404.1405, found 404.1397. **HPLC Analysis**: *ee* = 99%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.6 min, t_{minor} = 18.7 min).

(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-(m-tolyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4af)

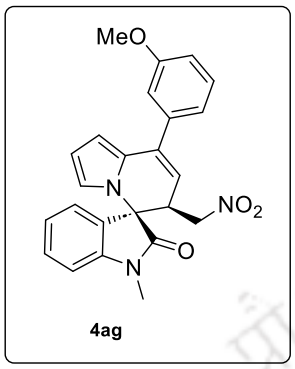


4af

White solid (36.7 mg, combined yield: 92%); M.P. 167-170 °C; R_f = 0.46 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.7:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.42 – 7.28 (m, 5H), 7.25 – 7.20 (m, 1H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.29 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.15 (dd, *J* = 3.7, 2.9 Hz, 1H), 5.64 (d, *J* = 5.3 Hz, 1H), 4.82 (dd, *J* = 13.7, 5.7 Hz, 1H), 4.42 (dd, *J* = 13.7, 8.5 Hz, 1H), 3.75 (dt, *J* = 8.5, 5.5 Hz, 1H), 3.30 (s, 3H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.82, 142.42, 138.33, 138.06, 136.72, 130.63, 129.35, 129.33, 128.90, 128.52, 128.10, 125.38, 124.65, 123.88, 120.83, 112.86, 111.53, 110.17, 109.09, 74.72, 63.78, 41.59, 26.81, 21.60. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_3$ $[M+H]^+$ 400.1656, found 400.1656. **HPLC Analysis**: *ee* =

99%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 17.0 min, t_{minor} = 19.9 min).

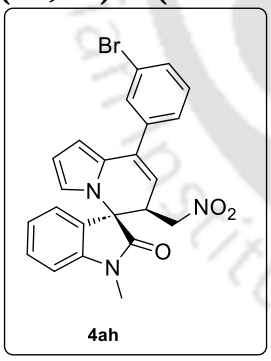
(3R,6'S)-8'-(3-methoxyphenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ag)



4ag

White solid (39.0 mg, combined yield: 94%); M.P. 190-193 °C; R_f = 0.39 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.2:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.42 – 7.27 (m, 3H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 2.1 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.99 – 6.89 (m, 2H), 6.42 – 6.35 (m, 1H), 6.34 – 6.29 (m, 1H), 6.15 (t, *J* = 3.3 Hz, 1H), 5.66 (d, *J* = 5.2 Hz, 1H), 4.80 (dd, *J* = 13.7, 5.7 Hz, 1H), 4.41 (dd, *J* = 13.7, 8.4 Hz, 1H), 3.85 (s, 3H), 3.76 (dt, *J* = 8.4, 5.5 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.74, 159.83, 142.46, 139.51, 136.47, 130.66, 129.65, 129.15, 128.04, 124.62, 123.89, 120.90, 120.76, 114.17, 113.88, 113.09, 111.54, 110.23, 109.09, 74.65, 63.74, 55.52, 41.60, 26.79. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_4$ $[M+H]^+$ 416.1605, found 416.1602. **HPLC Analysis**: *ee* = 98%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.4 min, t_{minor} = 29.2 min).

(3R,6'S)-8'-(3-bromophenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ah)

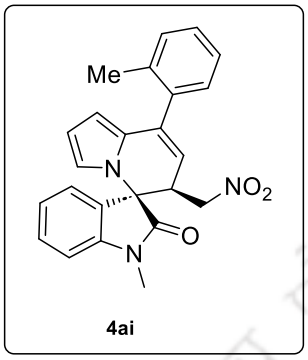


4ah

White solid (43.1 mg, combined yield: 93%); M.P. 196-199 °C; R_f = 0.49 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.7:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.72 (s, 1H), 7.51 (dd, *J* = 22.9, 7.9 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 8.1 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.42 – 6.33 (m, 1H), 6.26 (d, *J* = 3.7 Hz, 1H), 6.16 (t, *J* = 3.3 Hz, 1H), 5.64 (d, *J* = 5.0 Hz, 1H), 4.72 (dd, *J* = 13.7, 5.5 Hz, 1H), 4.41 (dd, *J* = 13.6, 8.7 Hz, 1H), 3.81 (dt, *J* = 9.8, 5.2 Hz, 1H), 3.28 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.48, 142.65, 140.15, 135.28, 131.60, 131.14, 130.85, 130.20, 128.86, 127.65, 126.96, 124.57, 124.01, 122.69, 121.10, 113.87, 111.49, 110.36, 109.18, 74.56, 63.70, 41.71, 26.78. **ESI HRMS**: calcd. for $C_{23}H_{18}BrN_3O_3$ $[M+H]^+$ 464.0604, found 464.0582. **HPLC Analysis**: *ee* = 98%,

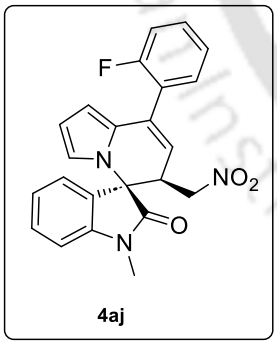
Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.8 min, t_{minor} = 19.1 min).

(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-(o-tolyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ai)



White solid (36.7 mg, combined yield: 92%); M.P. 170-173 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.7:1; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.40 (m, 2H), 7.33 – 7.21 (m, 4H), 7.16 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.29 – 6.22 (m, 1H), 6.08 (t, *J* = 3.4 Hz, 1H), 5.90 (d, *J* = 3.6 Hz, 1H), 5.44 (d, *J* = 4.1 Hz, 1H), 4.56 (dd, *J* = 13.4, 5.6 Hz, 1H), 4.46 (dd, *J* = 13.4, 8.7 Hz, 1H), 3.94 (dt, *J* = 9.3, 4.8 Hz, 1H), 3.26 (s, 3H), 2.39 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.48, 143.17, 137.61, 136.81, 135.67, 130.98, 130.55, 130.43, 129.68, 128.13, 127.76, 125.68, 124.69, 124.07, 120.46, 113.91, 111.05, 110.49, 109.09, 74.88, 64.09, 42.18, 26.66, 20.11. **ESI HRMS**: calcd. for $C_{24}H_{21}N_3O_3$ $[M+H]^+$ 400.1656, found 400.1651. **HPLC Analysis**: *ee* = 98%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.8 min, t_{minor} = 15.6 min).

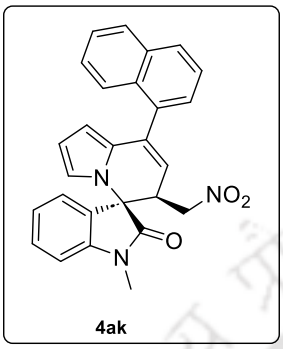
(3R,6'S)-8'-(2-fluorophenyl)-1-methyl-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4aj)



White solid (36.2 mg, combined yield: 90%); M.P. 168-171 °C; R_f = 0.43 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.9:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.52 – 7.42 (m, 2H), 7.41 – 7.34 (m, 2H), 7.23 – 7.12 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.37 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.11 (dd, *J* = 8.8, 3.4 Hz, 2H), 5.67 (d, *J* = 5.2 Hz, 1H), 4.85 (dd, *J* = 13.9, 5.9 Hz, 1H), 4.45 (dd, *J* = 13.9, 8.1 Hz, 1H), 3.79 (dt, *J* = 8.2, 5.7 Hz, 1H), 3.30 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.66, 161.14 (248.22 Hz), 142.20, 131.18 (2.52 Hz), 130.67, 130.51, 129.97 (7.56 Hz), 128.99, 128.02, 125.44 (15.12 Hz), 124.52 (1.26 Hz), 124.12 (3.78 Hz), 123.81, 120.75, 116.05 (22.68 Hz), 115.41 (2.52 Hz), 110.95, 110.31, 108.95, 74.33, 63.72, 41.50, 26.67. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -114.03. **ESI HRMS**: calcd. for $C_{23}H_{18}FN_3O_3$

$[M+H]^+$ 404.1405, found 404.1395. **HPLC Analysis**: *ee* = 98%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 95/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 29.8 min, t_{minor} = 27.0 min).

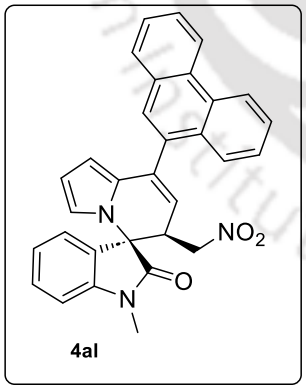
(3R,6'S)-1-methyl-8'-(naphthalen-1-yl)-6'-(nitromethyl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4ak)



4ak

White solid (40.0 mg, combined yield: 92%); M.P. 230-233 °C; R_f = 0.46 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 5.2:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 7.4 Hz, 1H), 7.88 (dt, *J* = 6.9, 3.6 Hz, 2H), 7.72 – 7.42 (m, 6H), 7.21 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.27 (s, 1H), 6.12 – 5.98 (m, 1H), 5.84 (d, *J* = 22.1 Hz, 1H), 5.63 (d, *J* = 3.7 Hz, 1H), 4.51 (q, *J* = 8.1, 7.5 Hz, 2H), 4.11 (td, *J* = 7.8, 7.2, 3.7 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.37, 143.57, 135.98, 134.73, 133.81, 132.56, 131.44, 131.18, 128.61, 128.03, 127.36, 126.81, 126.55, 126.39, 126.13, 125.24, 124.86, 124.23, 120.37, 115.15, 111.46, 110.54, 109.14, 74.84, 64.20, 42.70, 26.69. **ESI HRMS**: calcd. for $C_{27}H_{21}N_3O_3$ $[M+H]^+$ 436.1656, found 436.1660. **HPLC Analysis**: *ee* = >99%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.0 min, t_{minor} = 24.2 min).

(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-(phenanthren-9-yl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4al)

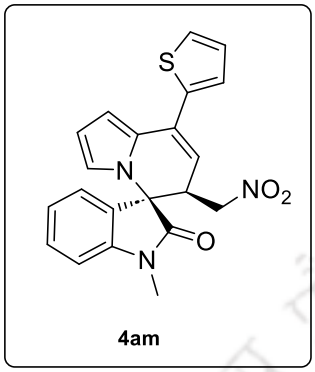


4al

White solid (44.6 mg, combined yield: 92%); M.P. 215-218 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 6.5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 8.73 (d, *J* = 8.3 Hz, 2H), 8.45 (d, *J* = 8.0 Hz, 1H), 7.92 (q, *J* = 7.4 Hz, 1H), 7.80 (d, *J* = 3.4 Hz, 1H), 7.74 – 7.41 (m, 6H), 7.25 (q, *J* = 7.9, 6.0 Hz, 1H), 6.98 (dd, *J* = 7.9, 3.4 Hz, 1H), 6.27 (d, *J* = 12.1 Hz, 1H), 6.09 – 5.99 (m, 1H), 5.93 – 5.81 (m, 1H), 5.71 (dd, *J* = 7.7, 3.9 Hz, 1H), 4.62 – 4.38 (m, 2H), 4.18 (tt, *J* = 5.8, 3.4 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.30, 143.78, 134.87, 134.83, 131.59, 131.44, 131.30, 130.66, 130.53, 128.82, 127.87, 127.36, 127.16, 126.99, 126.84, 124.91, 124.34, 122.75, 122.63, 120.33, 115.22, 111.42, 110.61, 109.16, 74.81, 64.23, 42.90, 26.67. **ESI HRMS**: calcd. for $C_{31}H_{23}N_3O_3$ $[M+H]^+$ 486.1812,

found 486.1804. **HPLC Analysis**: *ee* = 99%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.6 min, t_{minor} = 18.2 min).

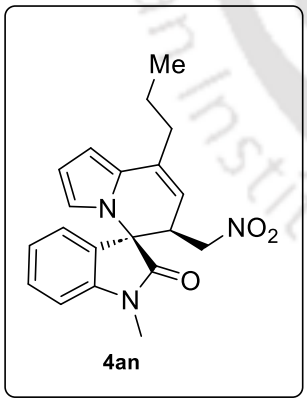
(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-(thiophen-2-yl)-6'H-spiro[indoline-3,5'-indolizin]-2-one (4am)



4am

White solid (34.4 mg, combined yield: 88%); M.P. 172-175 °C; R_f = 0.47 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.6:1; ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44 – 7.29 (m, 3H), 7.28 – 7.23 (m, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.59 (dd, *J* = 3.7, 1.5 Hz, 1H), 6.41 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.19 (dd, *J* = 3.8, 2.9 Hz, 1H), 5.82 (d, *J* = 5.5 Hz, 1H), 4.81 (dd, *J* = 14.0, 5.8 Hz, 1H), 4.39 (dd, *J* = 13.9, 8.1 Hz, 1H), 3.77 (dt, *J* = 8.1, 5.6 Hz, 1H), 3.29 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.62, 142.38, 139.84, 130.69, 129.77, 128.15, 127.83, 127.59, 126.18, 125.50, 124.65, 123.92, 121.21, 112.78, 111.70, 110.20, 109.12, 74.24, 63.53, 41.56, 26.83. **ESI HRMS**: calcd. for $C_{21}H_{17}N_3O_3S$ $[M+H]^+$ 392.1063, found 392.1058. **HPLC Analysis**: *ee* = 94%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.7 min, t_{minor} = 25.0 min).

(3R,6'S)-1-methyl-6'-(nitromethyl)-8'-propyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (4an)



4an

White solid (30.8 mg, combined yield: 88%); M.P. 145-148 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Crude diastereomeric ratio**: 4.4:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.38 (td, *J* = 7.7, 1.3 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.35 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.26 (dd, *J* = 2.9, 1.5 Hz, 1H), 6.13 (t, *J* = 3.3 Hz, 1H), 5.36 (dt, *J* = 4.8, 1.3 Hz, 1H), 4.67 (dd, *J* = 13.7, 5.8 Hz, 1H), 4.33 (dd, *J* = 13.7, 8.3 Hz, 1H), 3.69 – 3.61 (m, 1H), 3.26 (s, 3H), 2.52 – 2.39 (m, 2H), 1.76 – 1.67 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.85, 142.50, 134.72, 130.56, 130.44, 128.30, 124.45, 123.77, 120.18, 111.01, 110.18, 108.99, 108.28, 74.85, 64.00, 41.47, 34.45, 26.71, 22.11, 14.18. **ESI HRMS**: calcd. for $C_{20}H_{21}N_3O_3$ $[M+H]^+$ 352.1656, found

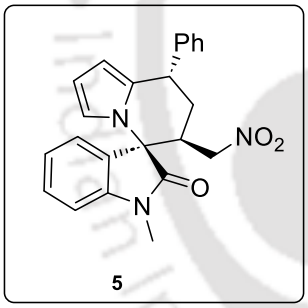
352.1647. **HPLC Analysis**: *ee* = 97%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.3 min, t_{minor} = 11.4 min).

2.6.6 Procedure for synthetic transformations:

a. Procedure for the synthesis of compound 5:

Triethylsilane (0.6 mmol, 68 mg) was added to a solution of **4aa** (0.1 mmol, 38.5 mg) and trifluoroacetic acid (1 mmol, 80 µL) in CH_2Cl_2 (2 mL) at 0 °C and slowly allowed to warm to room temperature and the progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. The reaction mixture was quenched with saturated K_2CO_3 and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with brine, drying (Na_2SO_4), and evaporation of the solvent gave a residue that was purified on flash chromatography eluting with hexane/ethyl acetate (90/10) to give the product **5** (34.8 mg, 90% yield, white sticky solid).

(3R,6'S,8'R)-1-methyl-6'-(nitromethyl)-8'-phenyl-7',8'-dihydro-6'H-spiro[indoline-3,5'-indolizin]-2-one (5)



5

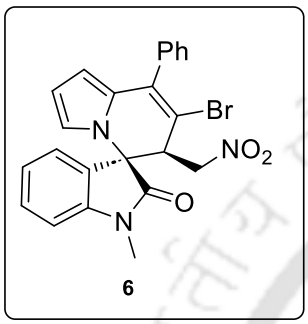
White sticky olid (34.8 mg, yield: 90%); R_f = 0.38 in 1:9 ethyl acetate/hexane; **Diastereomeric ratio**: >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.48 (dd, *J* = 15.4, 7.6 Hz, 3H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.04 (t, *J* = 3.3 Hz, 1H), 5.97 – 5.89 (m, 1H), 5.59 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.21 (ddd, *J* = 22.5, 12.6, 7.7 Hz, 2H), 3.95 (dd, *J* = 12.8, 4.1 Hz, 1H), 3.44 (ddt, *J* = 13.0, 9.5, 3.5 Hz, 1H), 3.25 (s, 3H), 2.94 (q, *J* = 12.7 Hz, 1H), 2.06 (ddd, *J* = 13.2, 5.8, 2.9 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.14, 144.18, 143.68, 134.46, 131.35, 128.70, 127.22, 127.18, 124.73, 124.51, 117.07, 110.15, 109.01, 107.84, 75.92, 64.01, 42.20, 41.55, 30.17, 26.64. **ESI HRMS**: calcd. for $C_{23}H_{21}N_3O_3$ $[M+H]^+$ 388.1656, found 388.1661. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.6 min, t_{minor} = 16.4 min).

b. Procedure for the synthesis of compound 6:

Under air atmosphere in a 5ml round bottom flask, **4aa** (38.5 mg, 0.1 mmol) in acetone (1.0 mL) was taken and NBS (17.7 mg, 0.1 mmol) was added slowly at 0 °C. Then it was

stirred at rt for 10 min. At the end of the reaction, the solvent was removed in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (95/5) to give the product **4** (43.6 mg, 94% yield, white solid).

(3R,6'S)-7'-bromo-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (6)



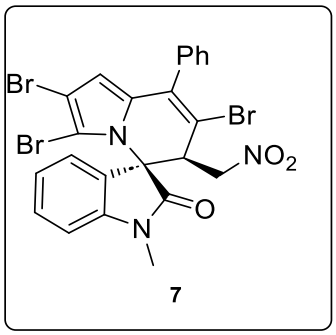
6

White solid (43.6 mg, yield: 94%); M.P. 245-248 °C; R_f = 0.48 in 1:9 ethyl acetate/hexane; **Diastereomeric ratio**: >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.47 (q, *J* = 7.2, 6.7 Hz, 5H), 7.39 (td, *J* = 7.8, 1.2 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.48 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.08 (t, *J* = 3.3 Hz, 1H), 5.92 (dd, *J* = 3.7, 1.5 Hz, 1H), 5.31 (dd, *J* = 15.6, 8.2 Hz, 1H), 4.53 (dd, *J* = 15.6, 3.2 Hz, 1H), 3.96 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.33 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 172.62, 141.53, 136.82, 135.86, 130.60, 129.82, 129.42, 128.85, 128.81, 128.49, 123.97, 123.78, 121.78, 112.53, 110.98, 109.47, 108.23, 71.43, 63.87, 50.61, 27.03. **ESI HRMS**: calcd. for $C_{23}H_{18}BrN_3O_3$ $[M+H]^+$ 466.0584, found 466.0573. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.6 min, t_{minor} = 13.6 min).

c. Procedure for the synthesis of compound 7:

Under air atmosphere, **4aa** (67.2 mg, 0.1 mmol) and NBS (53.1 mg, 0.3 mmol) in acetone (1.0 mL) was stirred under room temperature for 5 min. At the end of the reaction, the solvent was removed in vacuo. The residue was purified by flash chromatography eluting with hexane/ethyl acetate (95/5) to give the product **4** (36.0 mg, 58% yield, white solid).

(3R,6'S)-3',7'-dibromo-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (7)



7

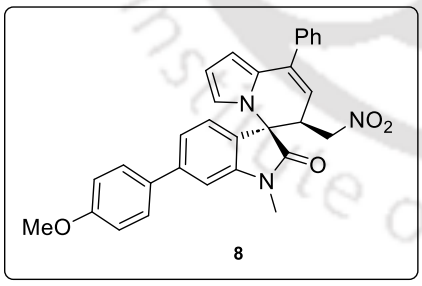
White solid (36.0 mg, yield: 58%); M.P. 259-262 °C; R_f = 0.52 in 1:9 ethyl acetate/hexane; **Diastereomeric ratio**: >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** 1H NMR (600 MHz, Chloroform-d) δ 7.51 – 7.45 (m, 3H), 7.43 (td, J = 7.8, 1.3 Hz, 1H), 7.39 (d, J = 6.4 Hz, 1H), 7.21 (dd, J = 7.4, 1.3

Hz, 1H), 7.10 – 7.06 (m, 1H), 7.00 (d, J = 7.8 Hz, 1H), 6.11 (d, J = 3.9 Hz, 1H), 5.86 (d, J = 3.9 Hz, 1H), 5.59 (dd, J = 15.5, 8.0 Hz, 1H), 4.54 (dd, J = 15.5, 3.0 Hz, 1H), 3.90 (dd, J = 8.1, 3.0 Hz, 1H), 3.32 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 171.81, 141.83, 136.22, 135.66, 132.32, 130.84, 128.97, 128.61, 127.69, 123.88, 123.50, 115.08, 113.20, 109.55, 108.32, 103.99, 71.84, 64.08, 51.00, 27.24. **ESI HRMS**: calcd. for $C_{23}H_{16}Br_3N_3O_3$ $[M+H]^+$ 621.8795, found 621.8795. **HPLC Analysis**: *ee* = 97%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.7 min, t_{minor} = 16.7 min).

d. Procedure for the synthesis of compound 8:

To a round bottom flask 10 ml **4pa** (0.1 mmol), $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), 4-methoxy phenyl boronic acid and Na_2CO_3 (0.2 mmol) were added under nitrogen atomosphere. Then 0.5 ml DMF was added to the reaction mixture and the reaction mixture was stirred at room temperature for overnight. Next H_2O was added to the mixture and the mixture was extracted with ethyl acetate. Then the combined organic layers were again washed with H_2O twice and the organic layer was dried over Na_2SO_4 and concentrated in vacuo and the crude product was purified by flash chromatography eluting with hexane/ethyl acetate (85/15) to give the product **4** (31.4 mg, 64% yield, white sticky solid).

(3R,6'S)-6-(4-methoxyphenyl)-1-methyl-6'-(nitromethyl)-8'-phenyl-6'H-spiro[indoline-3,5'-indolizin]-2-one (8)



8

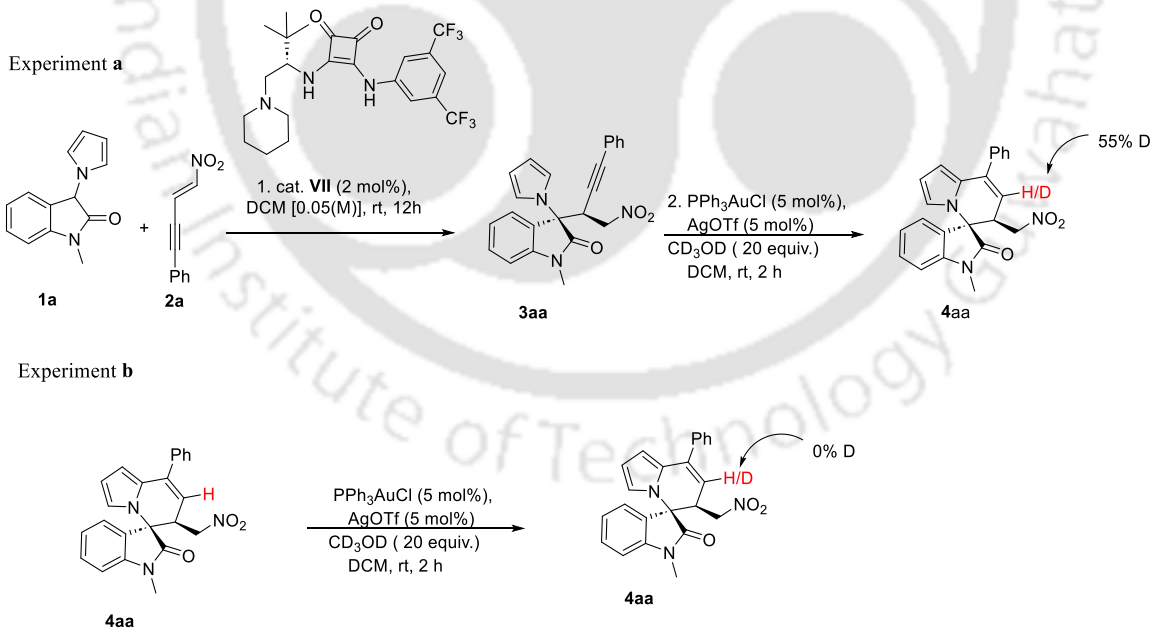
White sticky solid (31.4 mg, yield: 64%); M.P. 195-198 °C; R_f = 0.38 in 1:9 ethyl acetate/hexane; **Diastereomeric ratio**: >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.61 – 7.56 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 3H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.07 (d, *J* = 1.5 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 2H), 6.44 (dd, *J* = 2.9, 1.4 Hz, 1H), 6.30 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.17 (t, *J* = 3.3 Hz, 1H), 5.68 (d, *J* = 5.2 Hz, 1H), 4.85 (dd, *J* = 13.6, 5.6 Hz, 1H), 4.45 (dd, *J* = 13.6, 8.6 Hz, 1H), 3.86 (s, 3H), 3.80 (dt, *J* = 8.9, 5.5 Hz, 1H), 3.35 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 173.01, 159.96, 143.92, 142.99, 138.15, 136.67, 132.92, 129.30, 128.66, 128.60, 128.41, 128.30, 126.19, 124.82, 122.30, 120.92, 114.59, 113.13, 111.55,

110.25, 107.57, 74.73, 63.74, 55.55, 41.68, 26.88. **ESI HRMS**: calcd. for $C_{30}H_{25}N_3O_4$ $[M+H]^+$ 492.1918, found 492.1914. **HPLC Analysis**: *ee* = 96%, Chiralpak IE Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 42.8 min, t_{minor} = 50.2 min).

2.6.7 Procedure for deuterium exchange experiment:

Here we have performed D-exchange experiment with d^4-MeOH (Scheme 13). In experiment **a**, the Michael adduct **3aa** was treated with PPh_3AuCl/ AgOTf (5 mol%) and 20 equivalent d^4-MeOH and after 2 hours the final product **4aa** was isolated. We found that the olefinic proton of the 6-membered ring was deuterated by 55% and also the protons of pyrrole ring were deuterated to some extent.

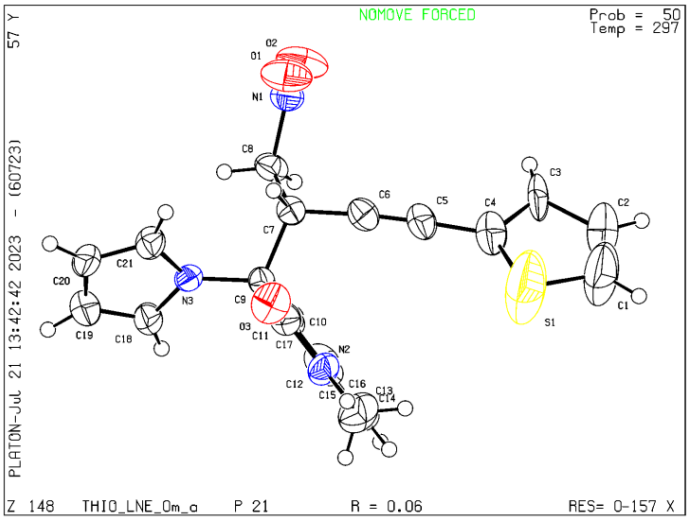
After that we put a reaction with the product **4aa** under the same condition (experiment **b**) and found that no deuteration of the olefinic proton of the 6-membered ring was observed and again the pyrrole ring proton was deuterated to some extent.



2.6.8 Single crystal X-ray diffraction analysis:

(a) Single crystal X-ray diffraction analysis of 3am:

CCDC No.	2283728
Empirical formula	$C_{21}H_{17}N_3O_3S$
Formula weight	391.43
Crystal habit, colour	Block / colourless
Temperature, T	297 K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P 21'
Unit cell dimensions	a = 6.4614(4) Å
	b = 10.7877(7) Å
	c = 14.3616(9) Å
	α = 90°, β = 101.675°, γ = 90°
Volume, V ($Å^3$)	980.35(11)
Z	2
Calculated density, $g·cm^{-3}$	1.326
F (000)	408.0
Refinement method	'SHELXL−2019/1'
Goodness−of−fit on F^2	1.073
Theta(max)	24.985
Data completeness	1.89/1.00
R(reflections)	0.0609 (2877)
wR2(reflections)	0.1715 (3441)

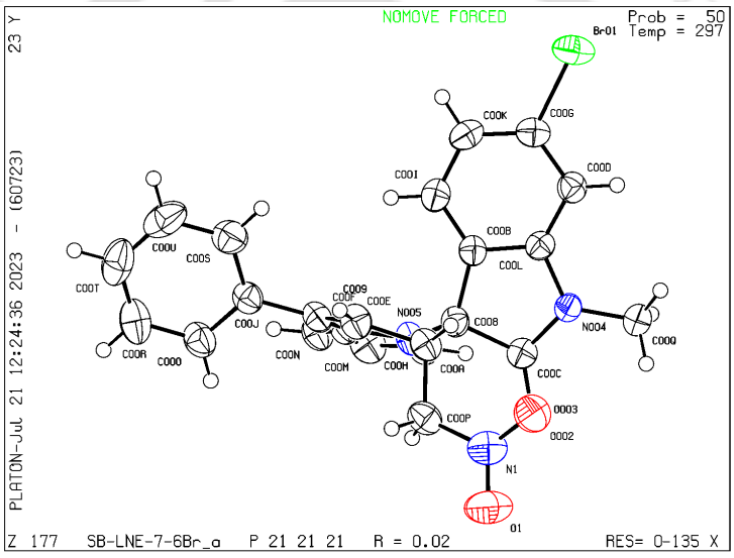


ORTEP diagram of 3am

(b) Single crystal X-ray diffraction analysis of 4pa:

CCDC No.	2283724
Empirical formula	$C_{23}H_{18}BrN_3O_3$
Formula weight	464.31
Crystal habit, colour	Block / colourless
Temperature, T	297 K
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	'P 21'
Unit cell dimensions	a = 10.1820(6) Å
	b = 10.2729(6) Å
	c = 19.3413(12) Å
	α = 90°, β = 90°, γ = 90°
Volume, V ($Å^3$)	2023.1(2)
Z	4

Calculated density, g·cm^{-3}	1.524
F (000)	944.0
Refinement method	'SHELXL–2019/1'
Goodness–of–fit on F^2	1.013
Theta(max)	24.996
Data completeness	1.73/0.99
R(reflections)	0.0228 (3323)
wR2(reflections)	0.0604 (3531)

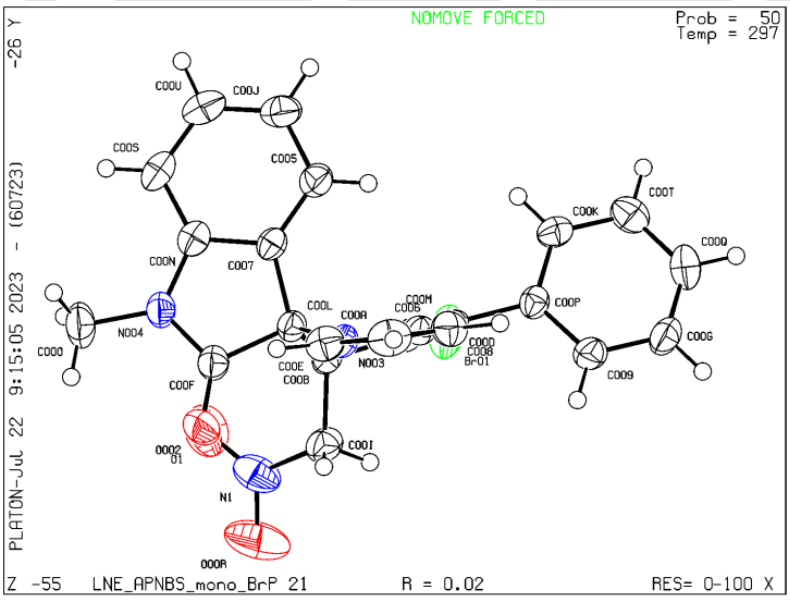


ORTEP diagram of 4pa

(c) Single crystal X-ray diffraction analysis of 6:

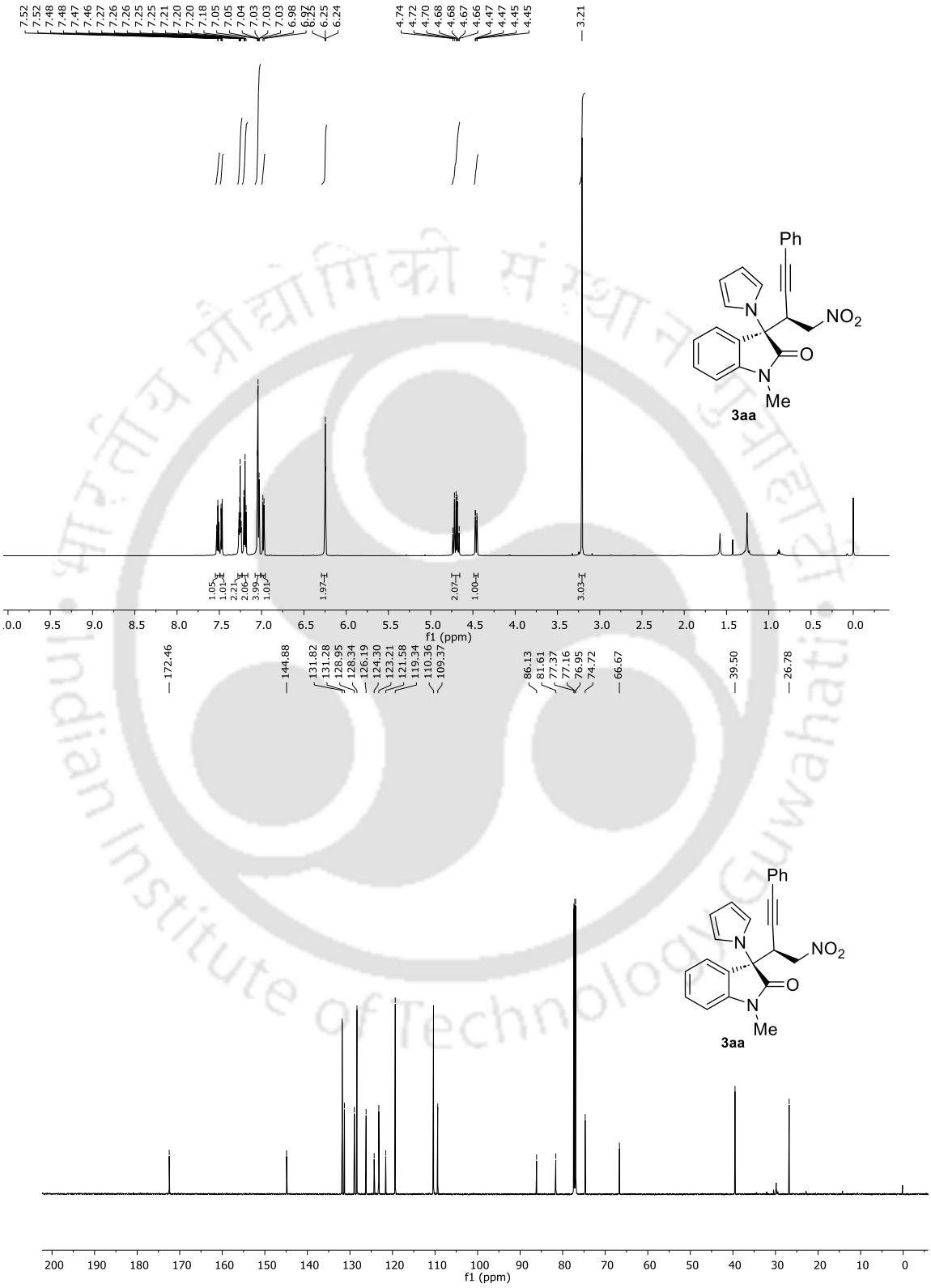
CCDC No.	2283725
Empirical formula	$C_{23}H_{18}BrN_3O_3$
Formula weight	464.31
Crystal habit, colour	Block / colourless
Temperature, T	297 K
Wavelength, λ (Å)	0.71073

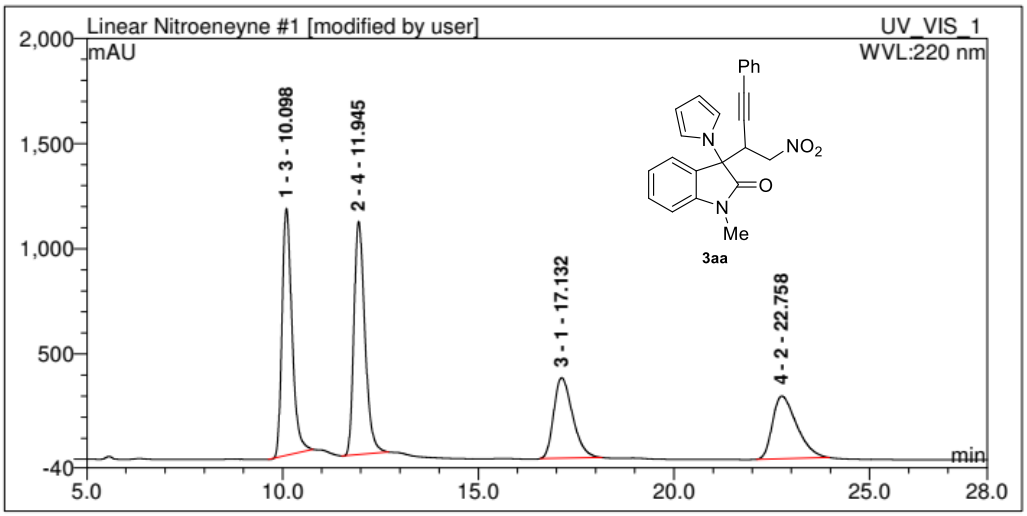
Crystal system	monoclinic
Space group	'P 21'
Unit cell dimensions	a = 7.7574(7) Å
	b = 13.9180(14) Å
	c = 9.8197(9) Å
	α = 90°, β = 107.102°, γ = 90°
Volume, V (Å^3)	1013.33(17)
Z	2
Calculated density, g·cm^{-3}	1.522
F (000)	472.0
Refinement method	'SHELXL–2019/1'
Goodness–of–fit on F^2	0.709
Theta(max)	24.493
Data completeness	1.83/0.96
R(reflections)	0.0234 (3025)
wR2(reflections)	0.0570 (3224)



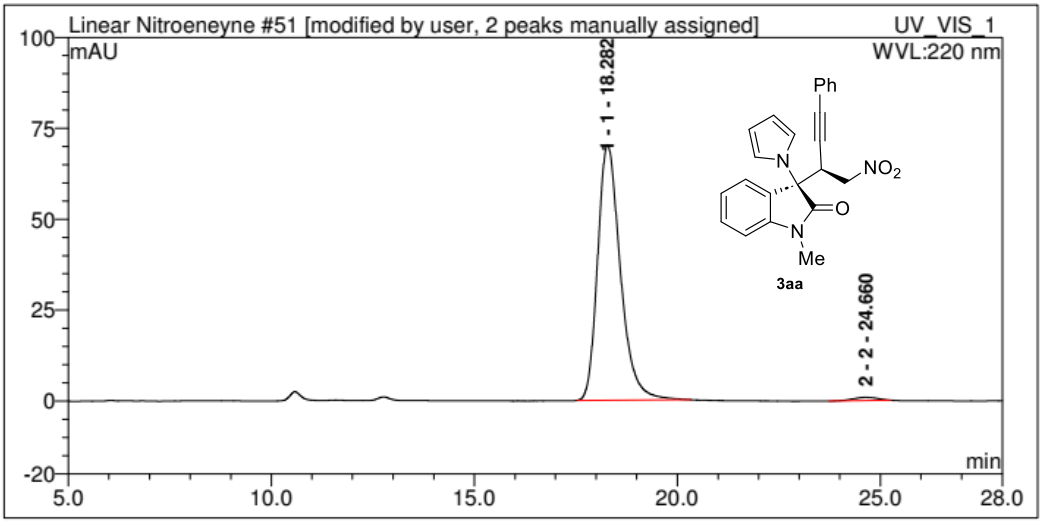
ORTEP diagram of 6

2.6.9 NMR spectra and HPLC chromatograms of selected products:

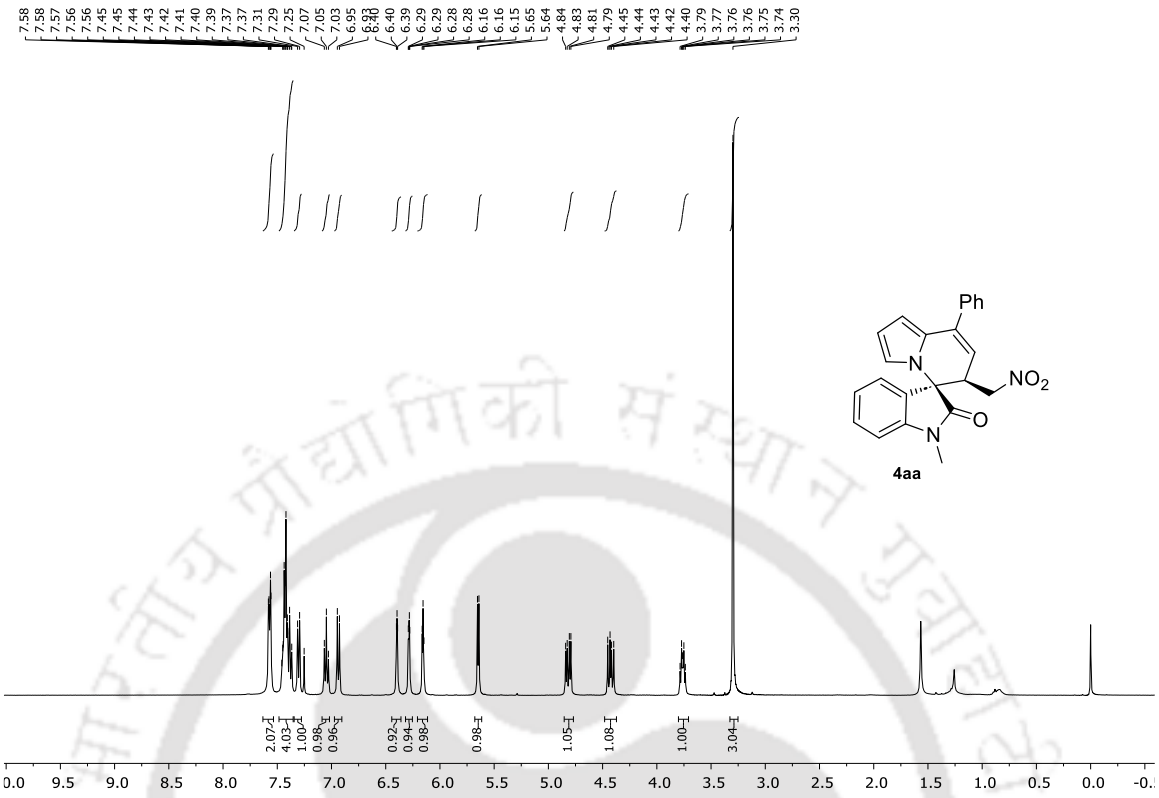


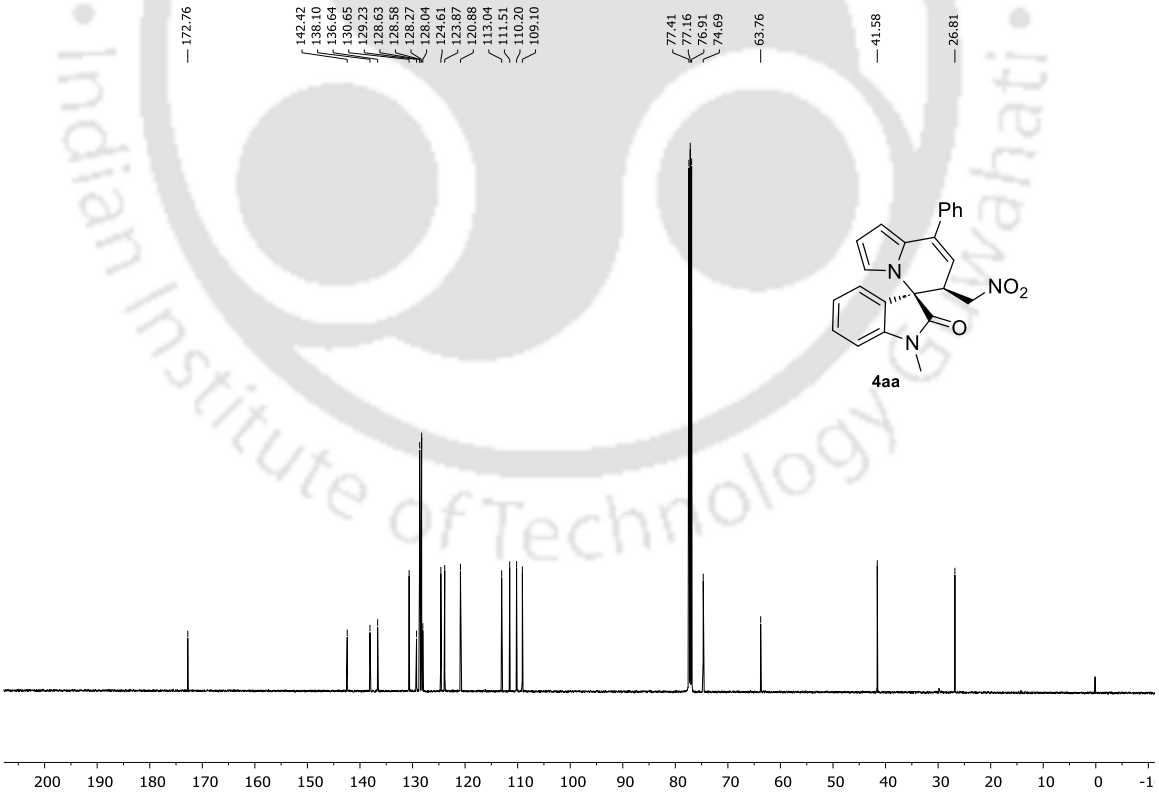


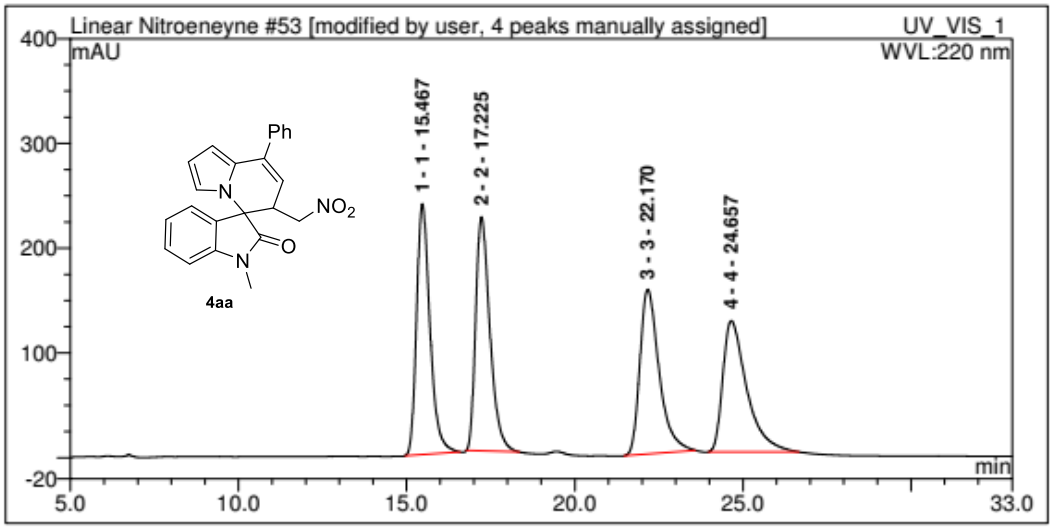
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	3	10.10	344.8536	30.4078974	1173.906	n.a.
2	4	11.95	361.204	31.84960864	1108.19	n.a.
3	1	17.13	214.4226	18.90698065	382.8223	n.a.
4	2	22.76	213.612	18.83551331	297.619	n.a.



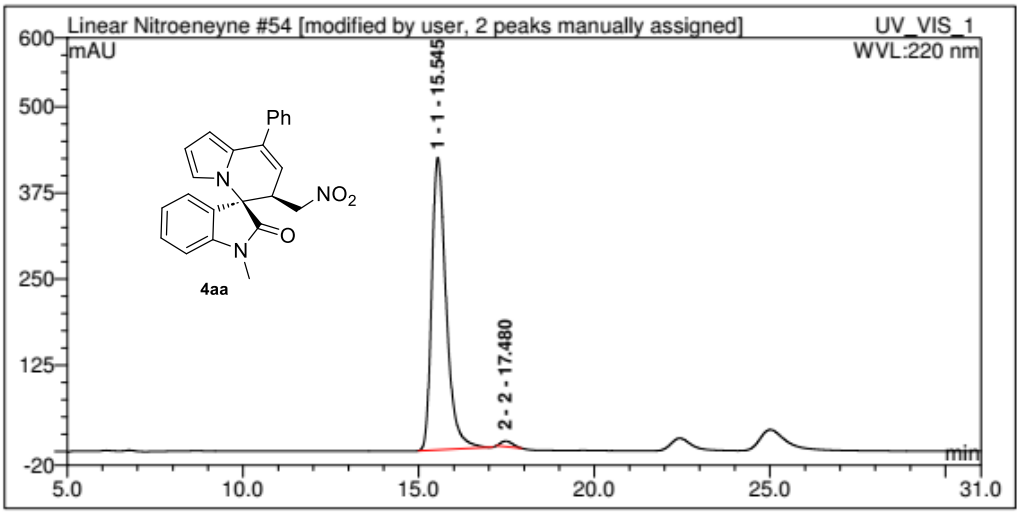
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	18.28	45.70046	98.64582791	70.28438	n.a.
2	2	24.66	0.627	1.35417209	0.890	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	15.47	110.5138	25.80394602	239.2405	n.a.
2	2	17.23	109.8557	25.65029197	223.4079	n.a.
3	3	22.17	104.4018	24.37686502	157.086	n.a.
4	4	24.66	103.511	24.16889699	125.252	n.a.



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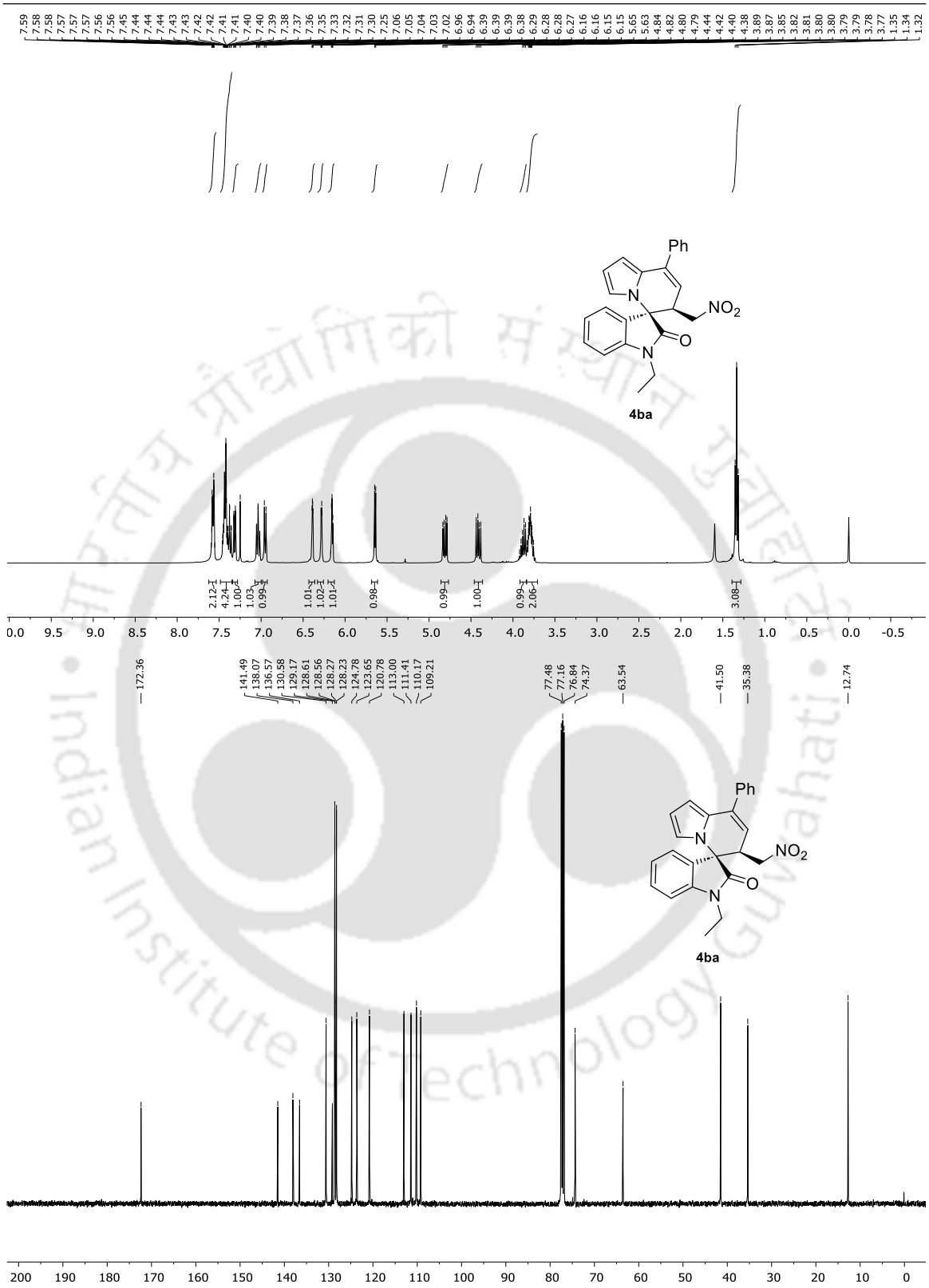

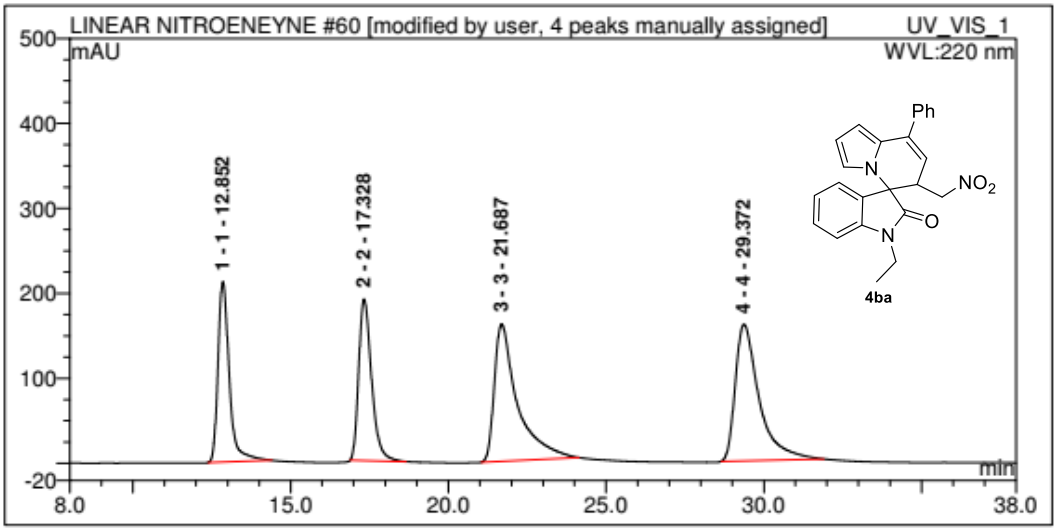

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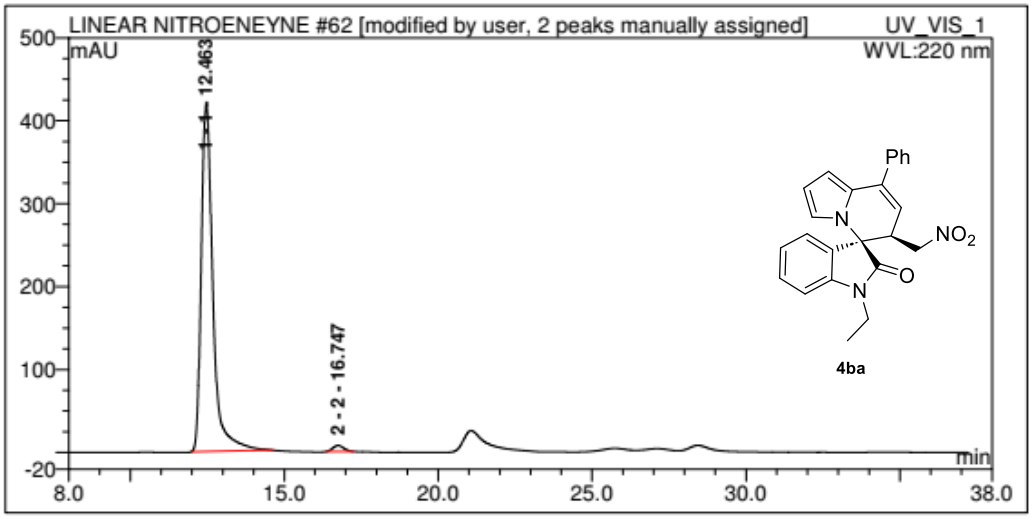
1	1	12.85	88.2105	19.31917069	212.4018	n.a.
2	2	17.33	90.06438	19.72519406	190.2734	n.a.
3	3	21.69	137.2872	30.06755643	161.5053	n.a.
4	4	29.37	141.034	30.88807882	160.593	n.a.



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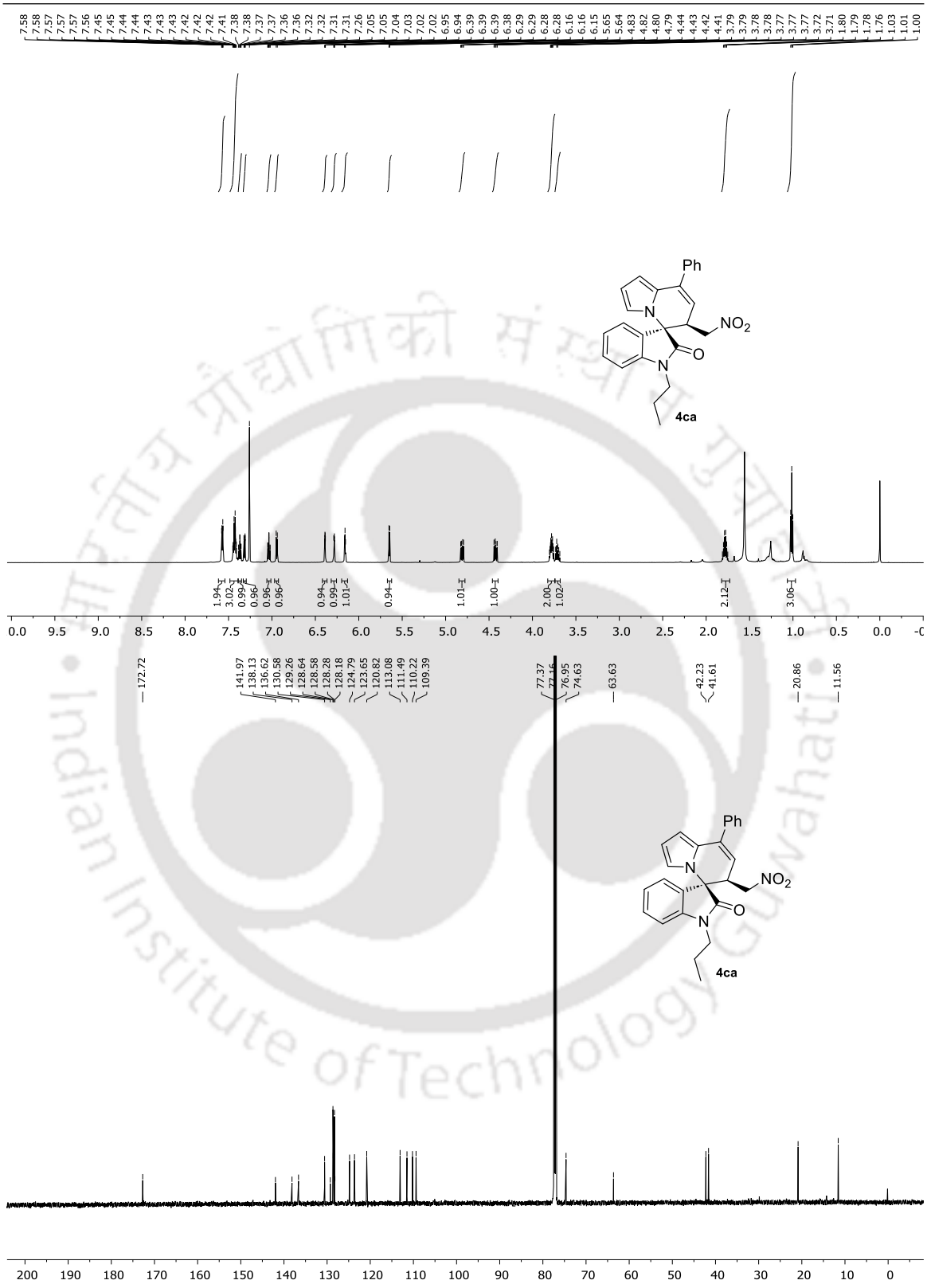

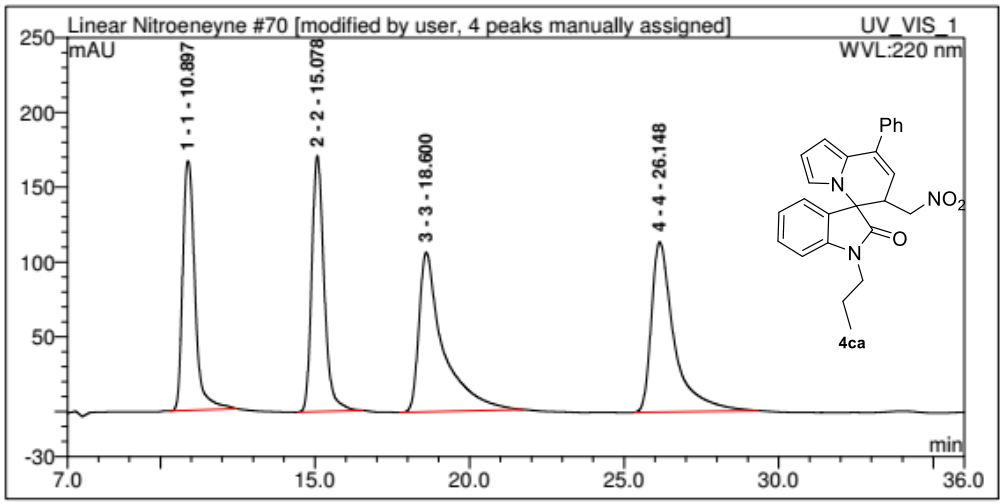

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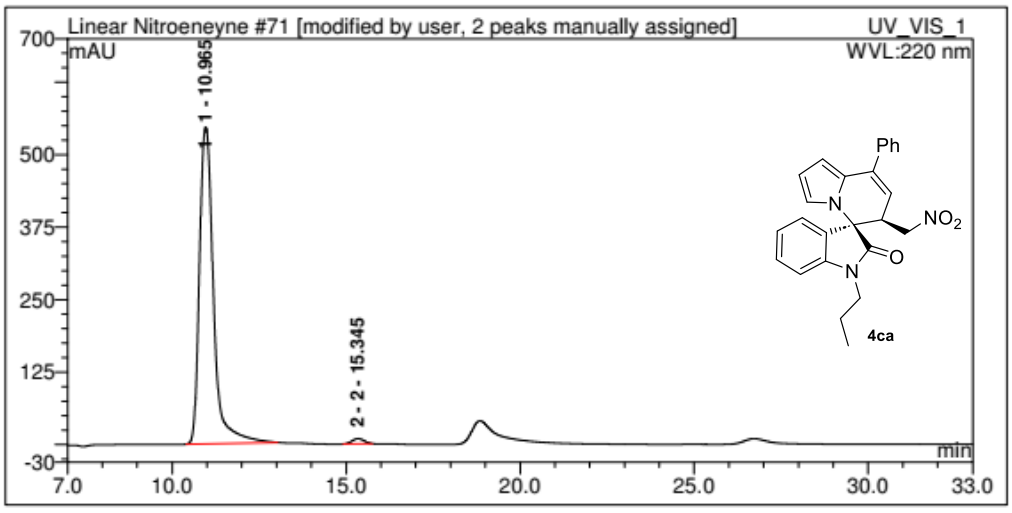
1	1	10.90	76.55668	21.83859404	166.8177	n.a.
2	2	15.08	79.48459	22.67381017	171.1378	n.a.
3	3	18.60	96.60364	27.55719712	106.5947	n.a.
4	4	26.15	97.912	27.93039867	113.718	n.a.



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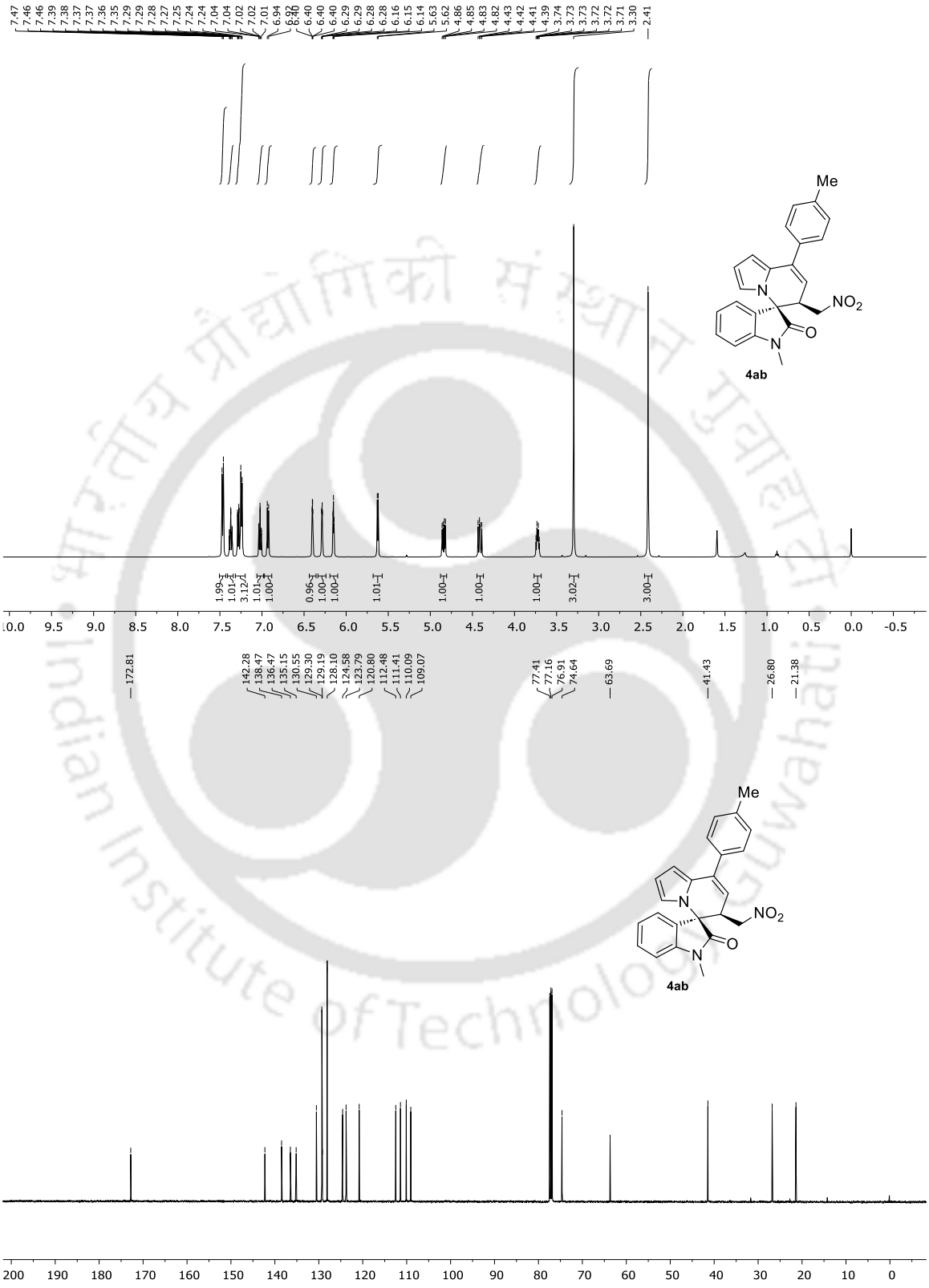
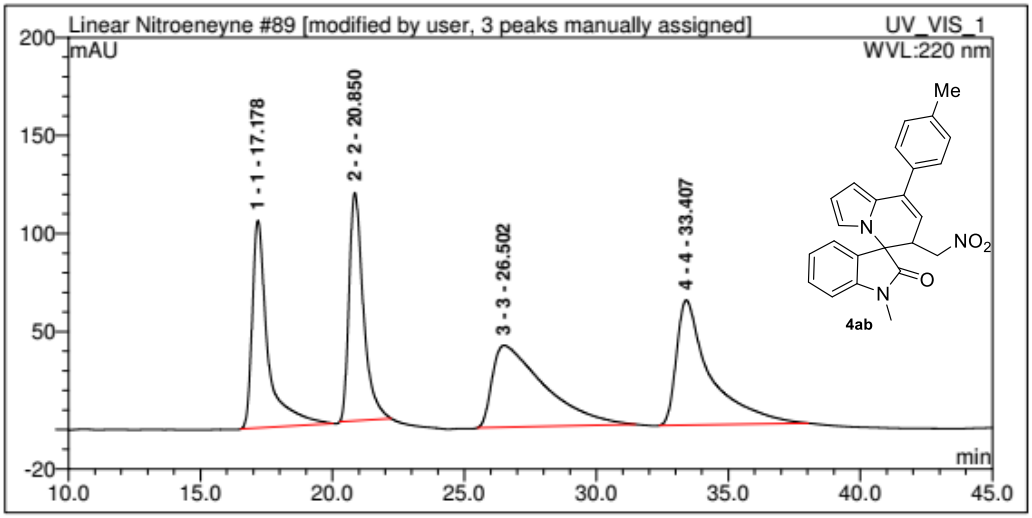
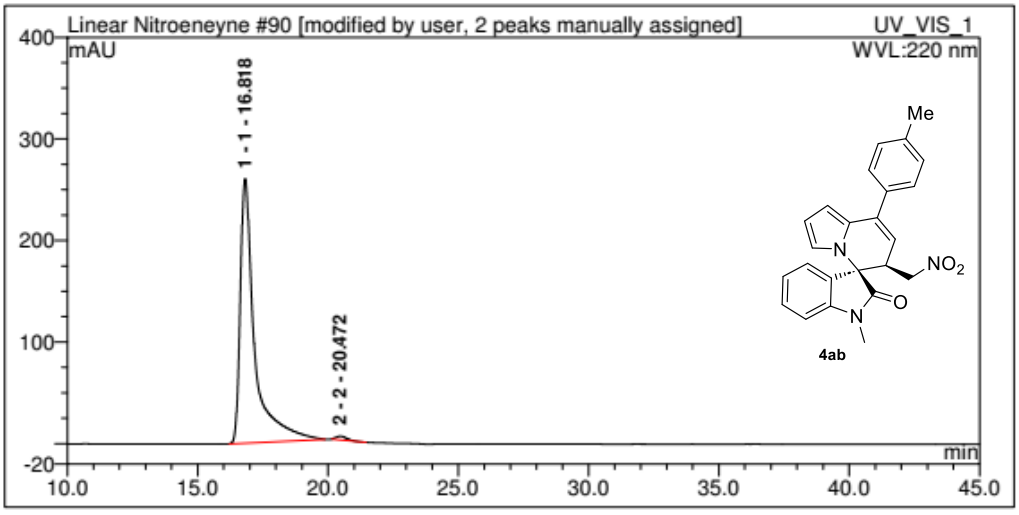




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.18	72.85568	21.71594095	105.7782	n.a.
2	2	20.85	73.23062	21.82770066	116.3425	n.a.
3	3	26.50	94.83294	28.26665776	41.6863	n.a.
4	4	33.41	94.575	28.18970062	63.673	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	16.82	166.4706	99.00003695	260.2522	n.a.
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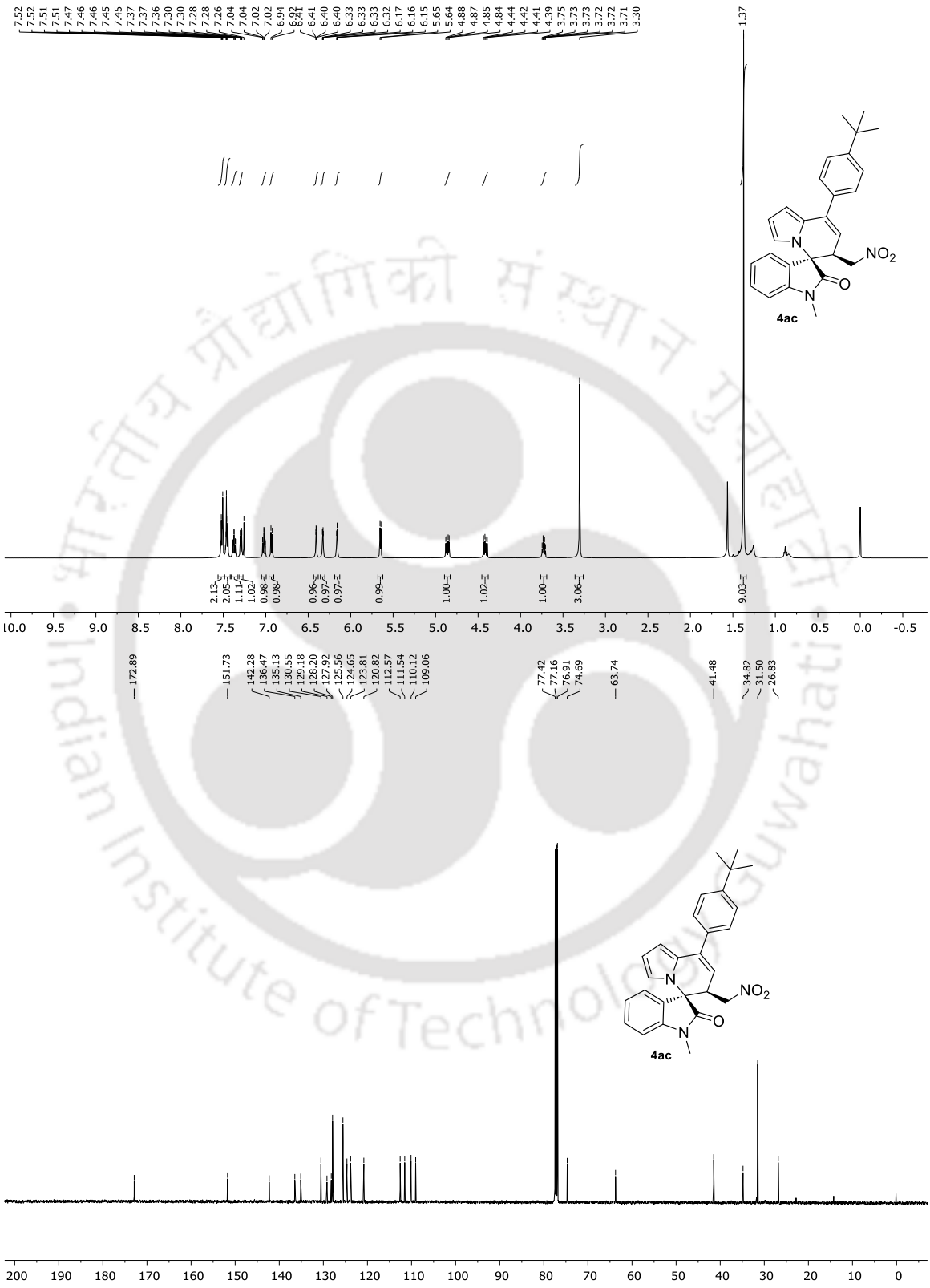
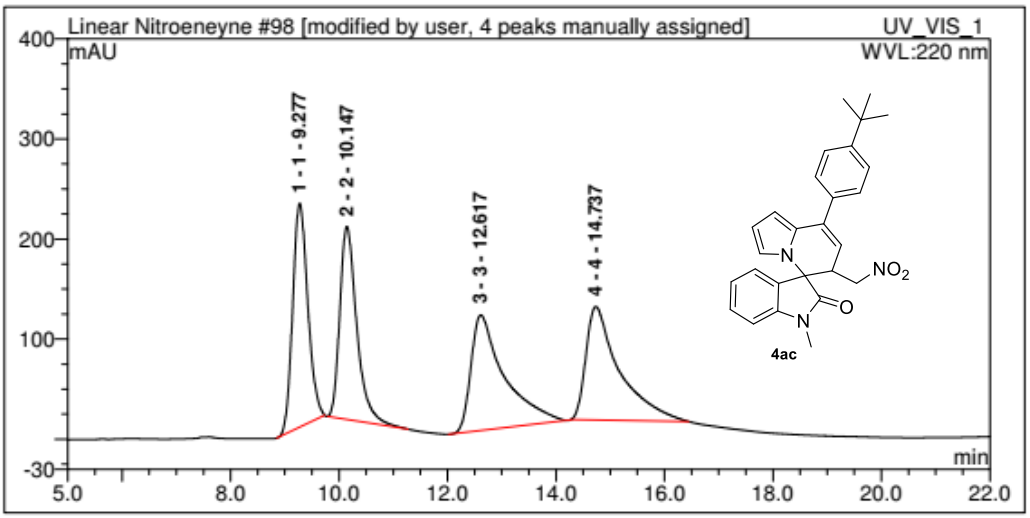
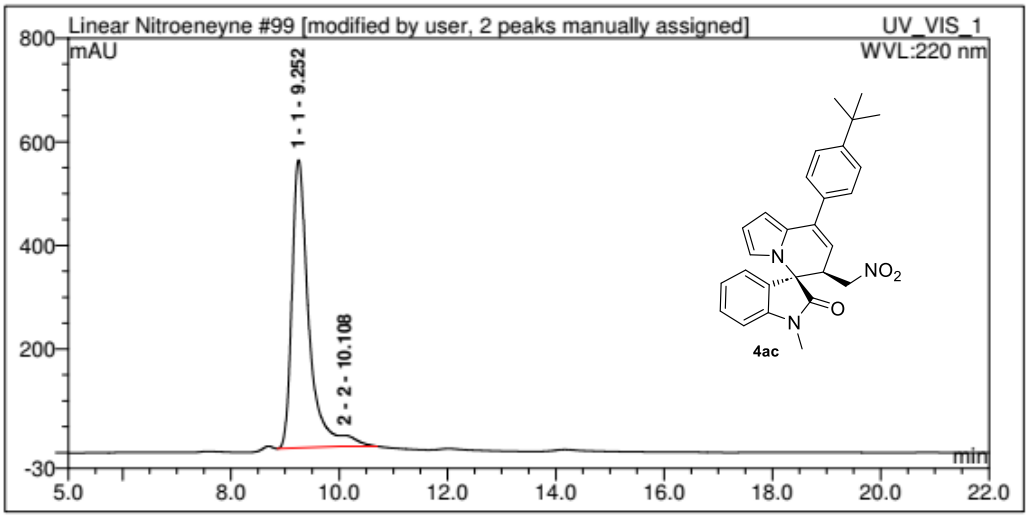




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.28	72.06837	23.65491113	223.7512	n.a.
2	2	10.15	70.10619	23.01086768	193.1048	n.a.
3	3	12.62	81.68529	26.81145906	115.4634	n.a.
4	4	14.74	80.806	26.52276213	113.274	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.25	195.3936	96.47992369	556.1837	n.a.
2	2	10.11	7.129	3.520076312	20.921	n.a.

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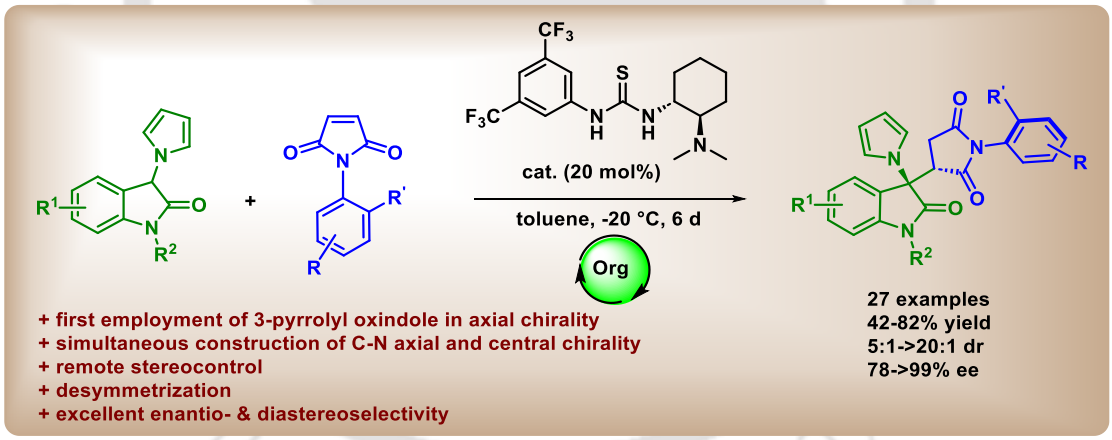
Chapter III

Organocatalytic Asymmetric Synthesis of C-N Atropisomers with Pyrrole, Oxindole and Succinimide Scaffold

Abstract: Organocatalytic desymmetric Michael addition of 3-pyrrolyloxindole with prochiral N-aryl maleimides was used to create an asymmetric synthesis of C-N atropisomers with pyrrole, oxindole, and succinimide moities. High diasteroselectivities and enantioselectivities (>20:1 dr, up to >99% ee) were obtained for the C-N atropisomers in acceptable yields. Additionally, the C-N rotational energy barrier has been determined.



3.1 Introduction

The synthesis of atropisomers using safe and efficient metal-free techniques has grown in importance as a study area in organic chemistry. One Since the majority of these transformations are catalytic and enantioselective, the scientific community is interested in them. Additionally, the use of these molecules in a variety of science and biology fields has rekindled interest in axial chirality resulting from limited rotation around the C-N bond.[1,2] Marinopyrrole, murrastifoline-F, and ancistrocladinium are some of the examples of bioactive substances (Figure 1).[3] Hindered anilides and imides are primarily studied as C–N atropisomers that represent the basic structure of important molecules. They have been employed as ligands for asymmetric synthesis,[4] "internal chirality transfer devices" in asymmetric radical processes,[5] and stereochemical relays.[6]

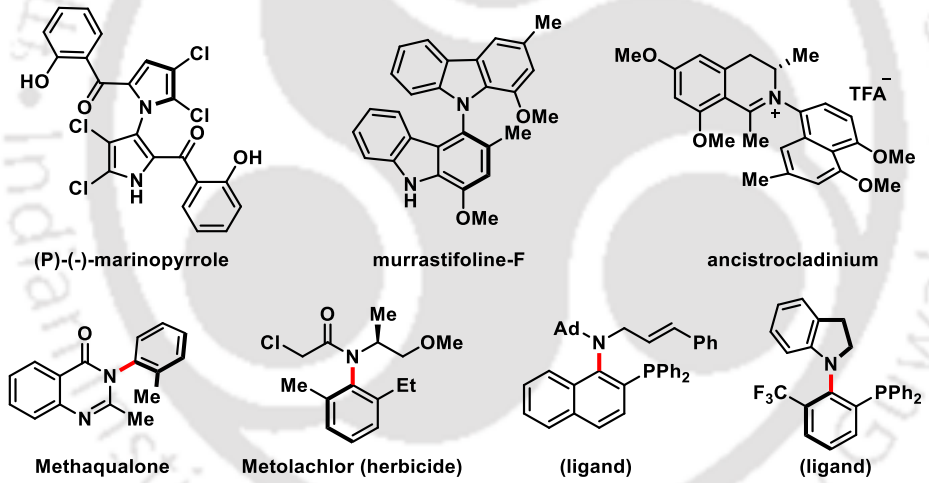


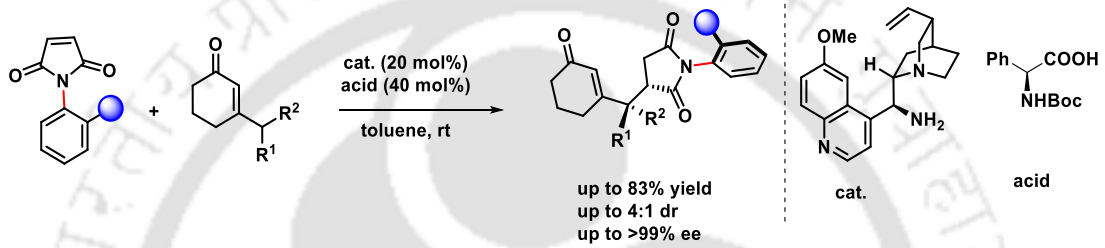
Figure 1. Examples of Bioactive compounds and ligands with C-N axial chirality

Because of the restricted rotation around the C-N bond, a maleimide derivative with a suitably ortho-substituted aryl group offers the perfect platform for axial chirality in this situation.[7] This type of maleimide has a symmetry plane (σ). Hence, the organocatalytic desymmetrization of maleimide derivatives can produce succinimide compounds through conjugate addition processes or enantioselective cycloaddition. [8]

3.2 Literature Survey

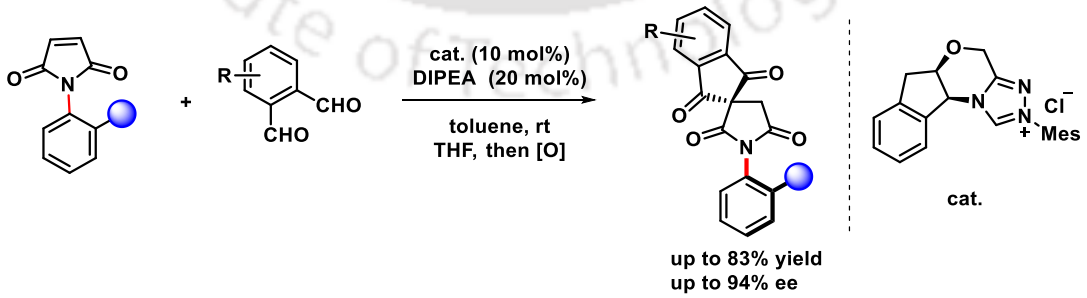
3.2.1 Previous reports on enantioselective construction of C–N atropisomers with N-aryl malemide:

In 2014, Bencivenni *et al*. developed a method for the atroposelective synthesis of succinimides using a new vinylogous Michael addition of enones to maleimides (Scheme 1).[9a] Primary amine catalysis was fundamental for the enantioselective desymmetrization to occur with simultaneous and exclusive remote control of the chiral axis and the newly formed stereocenters.



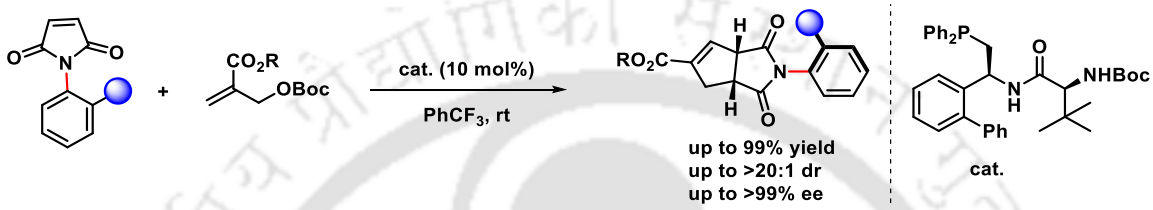
Scheme 1: Atroposelective synthesis of succinimides by Michael addition of enones to maleimides

In 2021, Biju group documented the desymmetrization of N-aryl maleimides for the enantioselective synthesis of N-aryl succinimides with an axially chiral C-N bond (Scheme 2).[9e] The intermolecular Stetter reaction, intramolecular aldol reaction, and subsequent oxidation are the sequential steps in this carbene-involved process. Notable characteristics of this reaction are its broad scope, gentle settings, and remote axial chirality control. The products were obtained in high yields (up to 83%) with excellent enantioselectivity (up to 97:3 er).



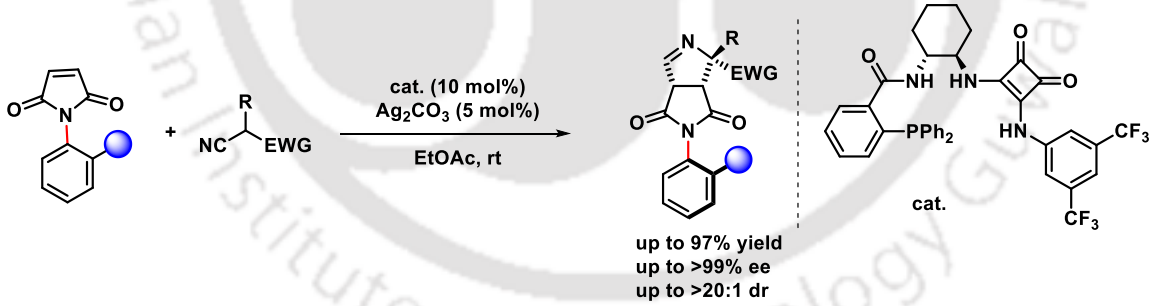
Scheme 2: Desymmetrization of N-aryl maleimides for the enantioselective synthesis of N-aryl succinimides

In 2022 Lin group reported a [3 + 2] annulation of MBH carbonates and N-aryl maleimides were under chiral phosphine to create a novel approach for the enantioselective synthesis of axially chiral N-aryl succinimides (Scheme 3).[9f] This desymmetrization technique enables the rapid formation of a remote $C_{Ar–N}$ atropisomeric chirality as well as two stereogenic carbon centers. Good to outstanding yields, diastereoselectivities, and enantioselectivities were obtained for a range of structurally varied N-aryl succinimides.



Scheme 3: Enantioselective [3 + 2] annulation desymmetrization

In 2022, Liao et. al. demonstrated desymmetrizative [3 + 2] cycloaddition of prochiral N-aryl maleimides with activated isocyanides, which is catalyzed by silver, and which simultaneously creates three contiguous stereogenic carbon centers and a distant C–N stereogenic axis (Scheme 4).[9h] This approach has great efficiency, good to excellent stereoselectivity, a broad substrate scope, and ease of operation.

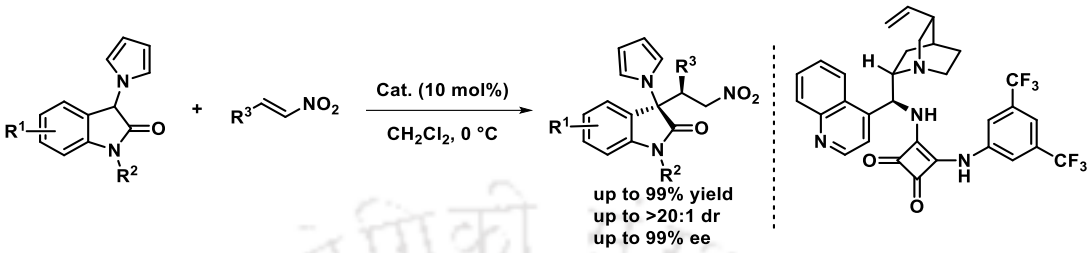


Scheme 4: Enantioselective desymmetrizative [3 + 2] cycloaddition of prochiral N-aryl maleimides with activated isocyanides

3.2.2 Previous reports on organocatalytic enantioselective reaction with 3-pyrrolyloxindoles:

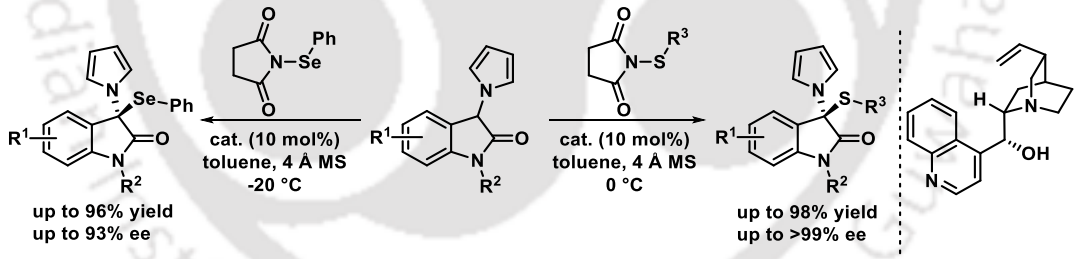
In 2015, Yuan *et al.* first developed an efficient technique, which used a chiral squaramide-substituted cinchona alkaloid catalyst, involved adding 3-pyrrolyl-oxindoles as nucleophiles to nitroalkenes (Scheme 5).[10a] Under mild circumstances, the typical Michael

addition reactions offer access to a wide variety of 3-pyrrolyl oxindoles with vicinal quaternary/tertiary stereocenters in high yields (up to 99%) and with high to excellent diastereo- and enantioselectivities (up to >20:1 dr and 99% ee).



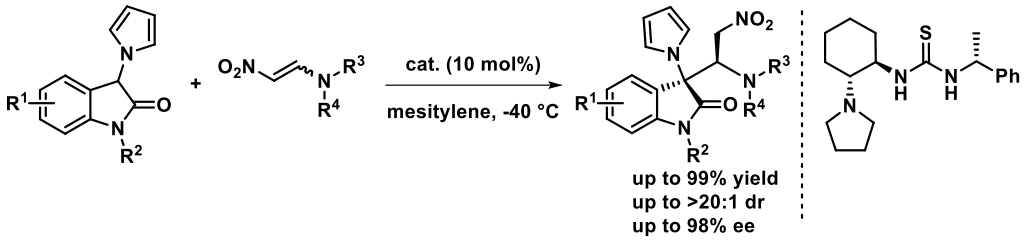
Scheme 5: 3-Pyrrolyl-oxindoles as an efficient nucleophile with nitrostyrene

In 2015, Yuan *et al.* again demonstrated asymmetric sulfenylation and selenenylation of 3-pyrrolyl-oxindoles using a commercially available cinchonidine catalyst in order to create 3,3-disubstituted oxindoles with two distinct heteroatoms at the C3 position (Scheme 6).[10c] Under mild circumstances, a variety of optically active 3-thio-3-pyrrolyl-oxindoles and 3-seleno-3-pyrrolyl-oxindoles were obtained in excellent yields (up to 98%) with excellent enantioselectivity (up to >99%).



Scheme 6: Organocatalyzed sulfenylation and selenenylation of 3-pyrrolyl-oxindoles

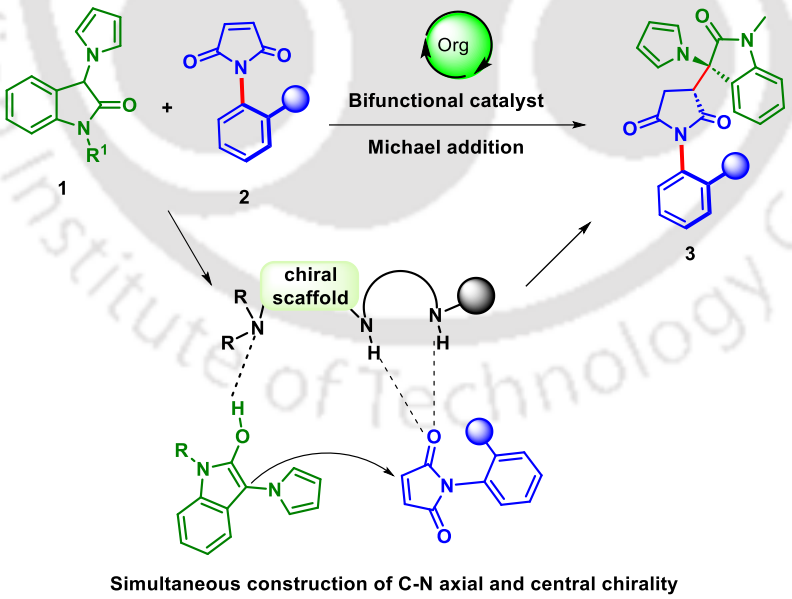
In 2016, Yuan *et al.* created an effective asymmetric Michael addition reaction between 3-pyrrolyloxindoles and β-phthalimidonitroethene using a bifunctional thiourea-tertiary amine catalyst (Scheme 7).[10d] The creation of 3,3′-disubstituted oxindoles with a contiguous 3,*α*,*β*-triamino functionality was made possible by this technique. A variety of 3,3′-disubstituted oxindoles we obtained in high yields (up to 99%) with good diastereoselectivities (>20:1) and high enantioselectivities (up to 99%) using the established approach.



Scheme 7: Organocatalytic asymmetric Michael addition of 3-pyrrolyloxindoles to *β*-phthalimidonitroethene

3.3 Concept

Despite the previous efforts, it is unknown whether a desymmetrization reaction will produce a compound with a pyrrole and succinimide motif. Therefore, we started working on creating an organocatalytic desymmetric Michael addition of prochiral N-aryl maleimides to 3-pyrrolyl-oxindole. The proposed desymmetrization strategy will enable to construct simultaneous C-N axial and central chirality by remote stereocontrol through generation of one quaternary stereocenter, one tertiary stereocenter and one chiral C-N axis.

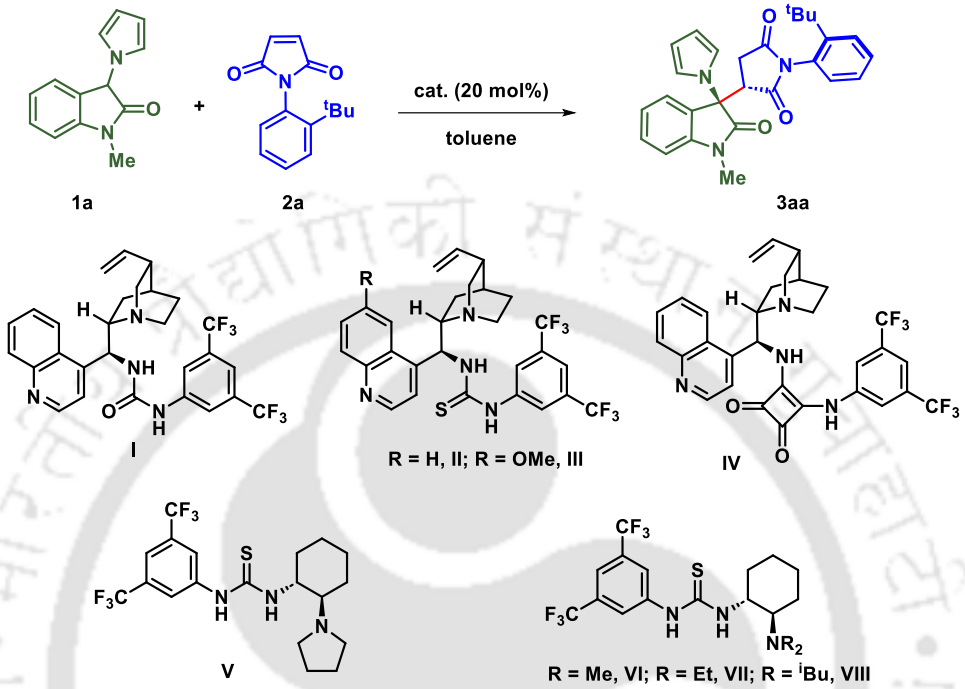


Scheme 8: Proposed route for simultaneous construction of C-N axial and central chirality

3.4 Results and Discussion

3.4.1 Optimization of catalyst and reaction conditions:

Table 1. Catalyst screening and optimization of reaction conditions



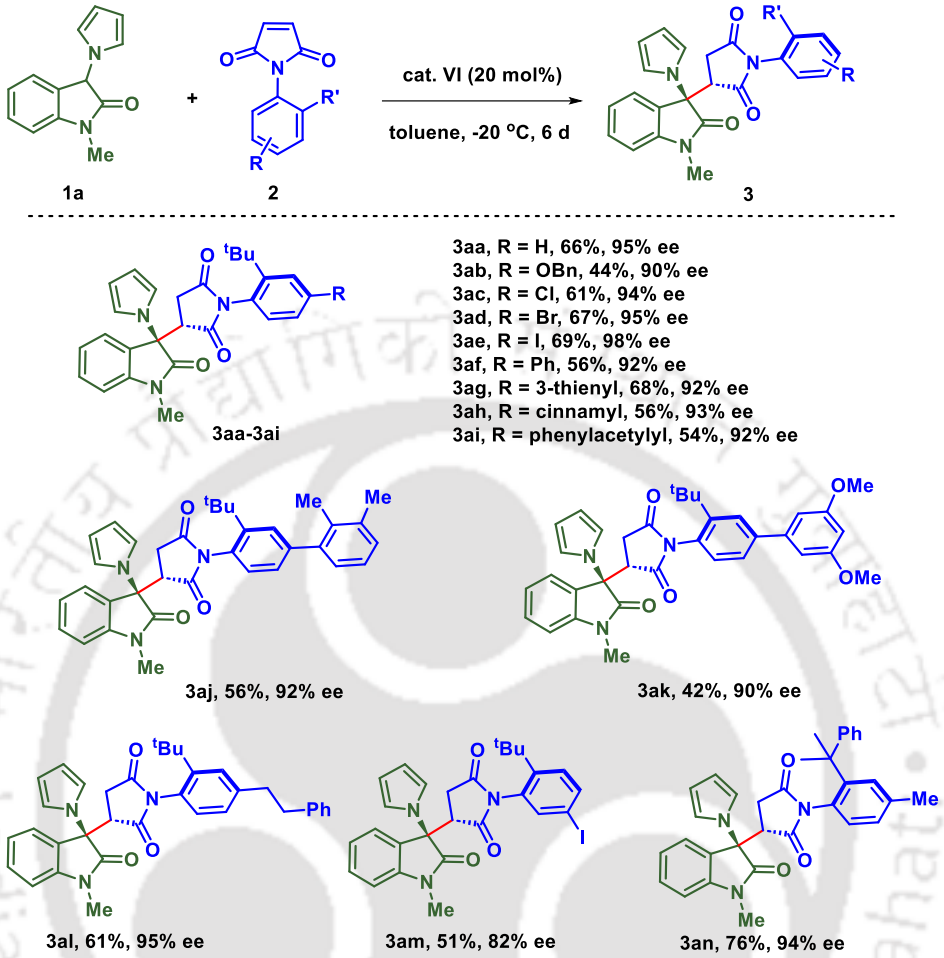
entry[a]	catalyst	temp (°C)	yield[b]	dr[c]	ee[d]
1	**I**	25	60	>20:1	50
2	**II**	25	55	>20:1	22
3	**III**	25	55	>20:1	7
4	**IV**	25	20	>20:1	11
5	**V**	25	56	>20:1	63
6	**VI**	25	68	>20:1	84
7	**VII**	25	62	>20:1	80
8	**VIII**	25	60	>20:1	80
9[e]	**VI**	0	62	>20:1	90
10[e]	**VI**	-20	55	>20:1	95
11[e,f]	**VI**	**-20**	**66**	**>20:1**	**95**

[a]Unless otherwise mentioned, 0.1 mmol of **1a** and 0.1 mmol of **2a** were stirred in 1 mL toluene at room temperature for 4 days with 20 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]Reaction time 6 days. [f]With 1.5 equiv of of **2a** and in 0.5 mL toluene.

We began our investigation by conducting a model reaction between N-(2-tert-butylphenyl)maleimide **2a** and 3-pyrrolyloxindole **1a** in toluene at room temperature (Table 1). The reaction proceeded effectively to yield the desired product **3aa** in 60% yield with >20:1 dr and 50% ee after cinchonidine-derived urea derivative **I** was initially selected as the catalyst (Table 1, entry 1). The enantioselectivity of **3aa** got reduced using bifunctional thiourea catalysts **II** and **III** that were derived from cinchonidine and quinine (entries 2-3). Additionally, catalyst **IV**, a bifunctional squaramide derived from cinchonidine, was unsuitable for the reaction (entry 4). When thiourea catalysts derived from cyclohexyl diamine were used in the reaction, pleasantly improved outcomes were seen (entries 5-8). The pyrrolidine motif of bifunctional thiourea catalyst **V** improved the enantioselectivity of 3aa (entry 5). Ultimately, Takemoto catalyst **VI** proved to be the most effective catalyst, detecting 84% ee of **3aa** (entry 6). With catalysts **VII** and **VIII** containing diethylamino and diisobutyl groups, respectively, slightly reduced enantioselectivities were noted (entries 7-8). The enantioselectivity was then increased to 90% ee (entry 9) after the reaction was conducted for six days at 0 °C using catalyst **VI**. Although the yield dropped, the enantioselectivity rose to 95% ee after the reaction was run at -20 °C (entry 10). 1.5 equivalents of **2a** were used, and the reaction was conducted at a concentration of 0.2 (M) in order to boost the yield (entry 11). Other solvents were also examined but better enantioselectivity was not detected.

3.4.2 Substrate scope:

After optimizing the reaction conditions, we concentrated on the reaction's scope (Scheme 9). Initially, a range of N-arylmaleimides **2** were analysed, and thankfully, in every instance, only one diastereomer was found. A number of N-arylmaleimides with different substitutions at the *para*-position and the ^{t}butyl group holding at the *ortho*-position of the aryl group were employed to test the scope. The aryl group of maleimide **2b**, which had 4-*O*-benzyl substitution on it, reacted smoothly to produce product **3ab** in 90% ee. The products **3ac**, **3ad**, and **3ae** were then obtained in high enantioselectivities after various

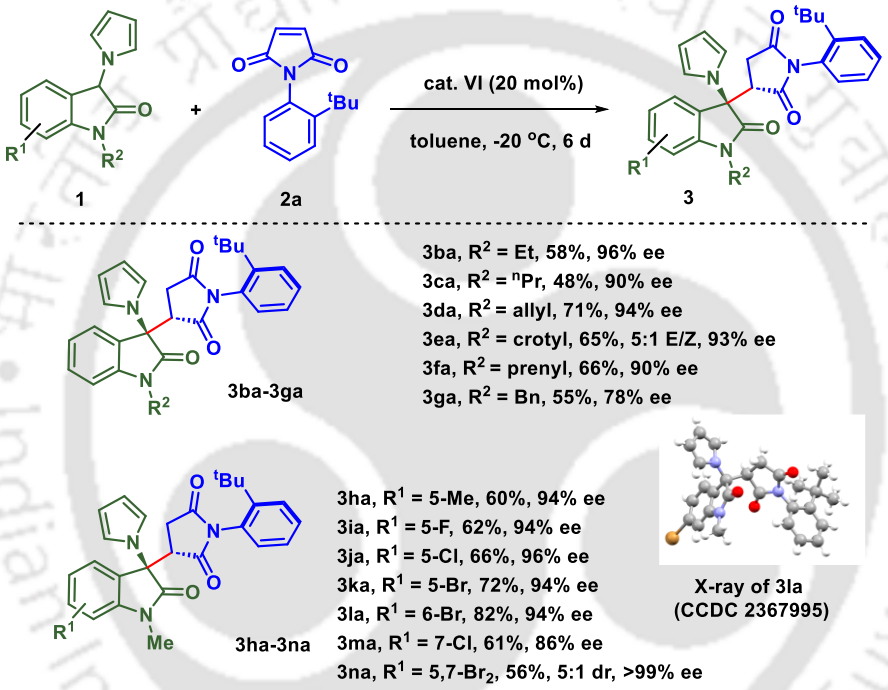


Scheme 9. Scope of N-aryl maleimides[a,b]

[a]All reactions were carried out with 0.1 mmol of **1a** and 0.15 mmol of **2** in 0.5 mL toluene at -20 °C for 6 days. [b]Yields correspond to the isolated yields after silica gel column chromatography, dr (>20:1 in all cases) was determined by ^{1}H NMR after coloumn chromatography and ee was determined by HPLC.

halo-substitutions were examined at the 4-position. In particular, compound **3ae** with 4-iodo substitution showed an outstanding 98% ee. The reaction's outcome was similar with substitutions of 4-phenyl and 4(3)-thienyl, and both products **3af** and **3ag** formed in the same 92% ee. The product **3ah** was isolated in 56% yield with 93% ee, and a cinnamonyl group was also tolerated. Then, under the reaction conditions, maleimide **2i** with a 4-phenylacetyl substituent reacted with **1a** to produce the product **3ai** in an acceptable yield with 92% ee. Following that, maleimides **2j** and **2k** with aryl groups substituted at position 4 were made and added to the reaction. The intended products **3aj** and **3ak** showed high

enantioselectivities. Additionally, the homobenzyl group at 4-position was well tolerated, and product **3al** was isolated with high enantioselectivity (95% ee) and an acceptable yield. The desired product **3am** was then obtained with somewhat reduced enantioselectivity when we concentrated on maleimide **2m** that had 3-iodo and 6-^{t}butyl substitutions on the aryl group. Lastly, a dimethyl benzyl substituent was added to maleimide **2n** in place of the tbutyl group, and another methyl substituent was added. Thankfully, the reactions proceeded smoothly, yielding **3an**.



Scheme 10. Scope of linear 3-pyrrolyl-oxindole [a,b]

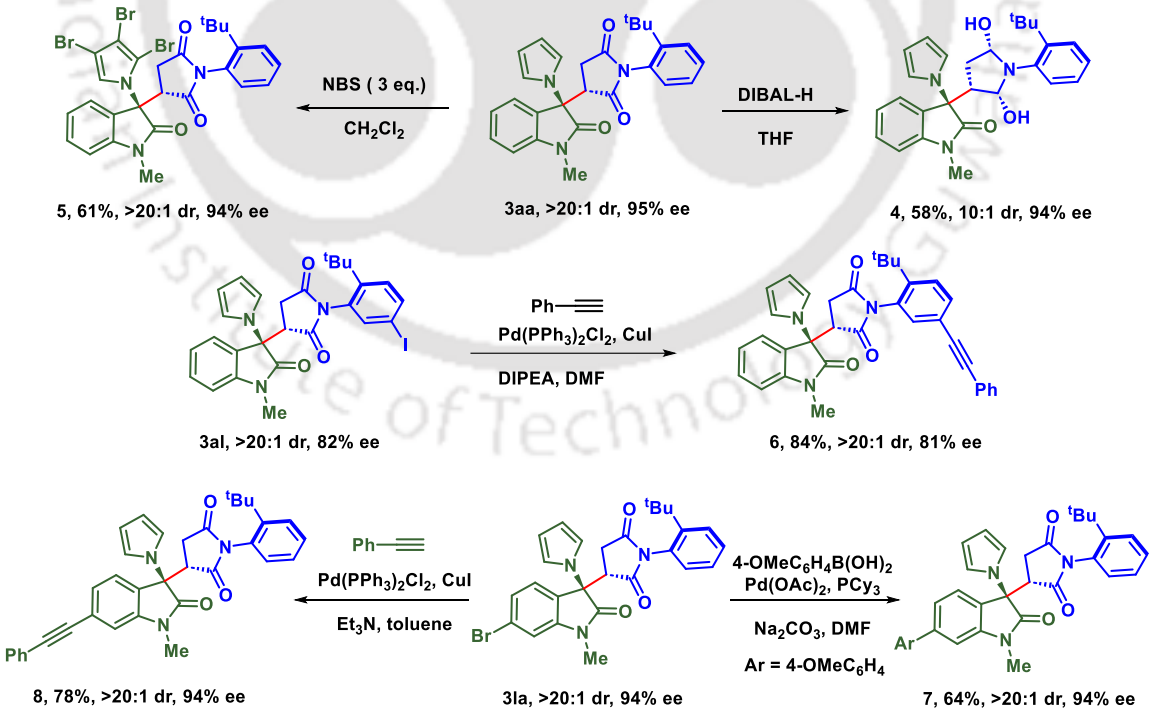
[a]Same as Table 2. [b]Yields correspond to the isolated yields after silica gel column chromatography, dr (>20:1 in all cases except **3na**) was determined by 1H NMR after coloumn chromatography and ee was determined by HPLC.

After that, the scope of 3-pyrrolyloxindole **1** was investigated, and pleasingly, the detection of a single diastereomer in every instance produced positive results as well (Scheme 10). First, various N-substitutions on 3-pyrrolyloxindole **1** were examined, high enantioselectivities and acceptable yields were obtained. In addition to simple alkyl groups, other groups such as allyl, crotyl, prenyl, and benzyl were also tolerated and high enantioselectivities were found. Only product **3ga** with N-benzyl substitution showed a

slightly lower enantioselectivity (78% ee). Next, various substitutions were examined on the phenyl ring of **1**. Initially, various oxindoles **1h-1k** with 5-substituted phenyl groups were synthesised and employed in the procedure. Excellent enantioselectivities and moderate yields of the corresponding products **3ha-3ka** were obtained. For oxindoles **1l-1m** with 6- and 7- substitutions, respectively, the results were comparable. Following that, a 5,7-disubstituted phenyl group containing oxindole **1n** was involved in the reaction. The product **3na** was found to have excellent enantioselectivity (>99% ee) (Scheme 10).

3.4.3 Synthetic transformation:

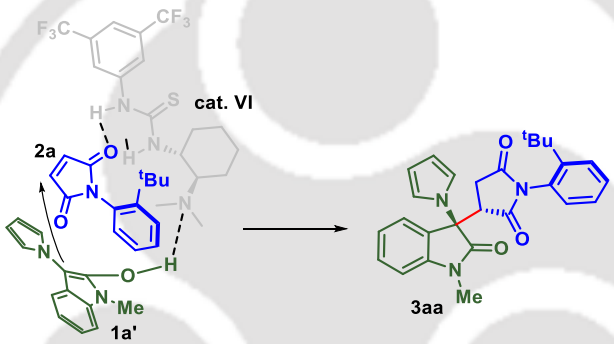
The synthetic potential of our approach was then demonstrated by a few reactions on **3aa**, **3al**, and **3la** (Scheme 11). Initially, **3aa** was reduced using DIBAL-H in a chemo- and stereoselective manner. Consequently, compound **4** containing the pyrrolidine-2,5-diol motif was produced with enantioselectivity in 58% yield and 10:1 dr. Three equivalents of NBS were applied to the **3aa**, and the pyrrole moiety's tribromination was noted. As a result, compound **5** was produced in 61% yield while maintaining enantio- and diastereo-selectivity. The Sonogoshira reaction between **3al** and phenylacetylene was then carried out.



Scheme 11. Synthetic transformations

3.4.4 Proposed transition state:

The X-ray crystal structure of compound **3la** was used to determine its absolute configuration.[12] It is anticipated that other items would have the same exact structure. Scheme 12 suggests a tenable TS based on the absolute structure. Attack occurs from the Si face as a result of catalyst **VI**'s tertiary amino group activating **1a'** (the enol from **1a**) from the Re face. Additionally, catalyst **VI**'s thiourea motif concurrently activates the carbonyl group of **2a**.



Scheme 12. Proposed transition state

3.4.5 Determination of rotational barrier of C–N bond of 3aa:

Given that product **3aa** has a chiral C(sp^2)-N(sp^3) axis, the rotational barrier was then ascertained.[13] The C(sp^2)-N(sp^3) axis is a persistent stereogenic element at room temperature, as shown by the observation of rotamer of compound **3aa** that is **3aa'** following six hours of heating at 120 °C (Figure 2). As a result, compound **3aa** in toluene-D8 was heated gradually between 60 and 100 °C. But since rotamer **3aa'** emerged at 110 °C, we took hourly ^{1}H NMR readings at 120 °C. We computed the C-N rotational energy barrier from this experiment, and the results are as follows: $t_{1/2}^{25^{\circ}C}$ = 1049 years at room temperature and $t_{1/2}^{120^{\circ}C}$ = 14.4 hours at 120°C, and 31.98 K.Cal/mol at room temperature.

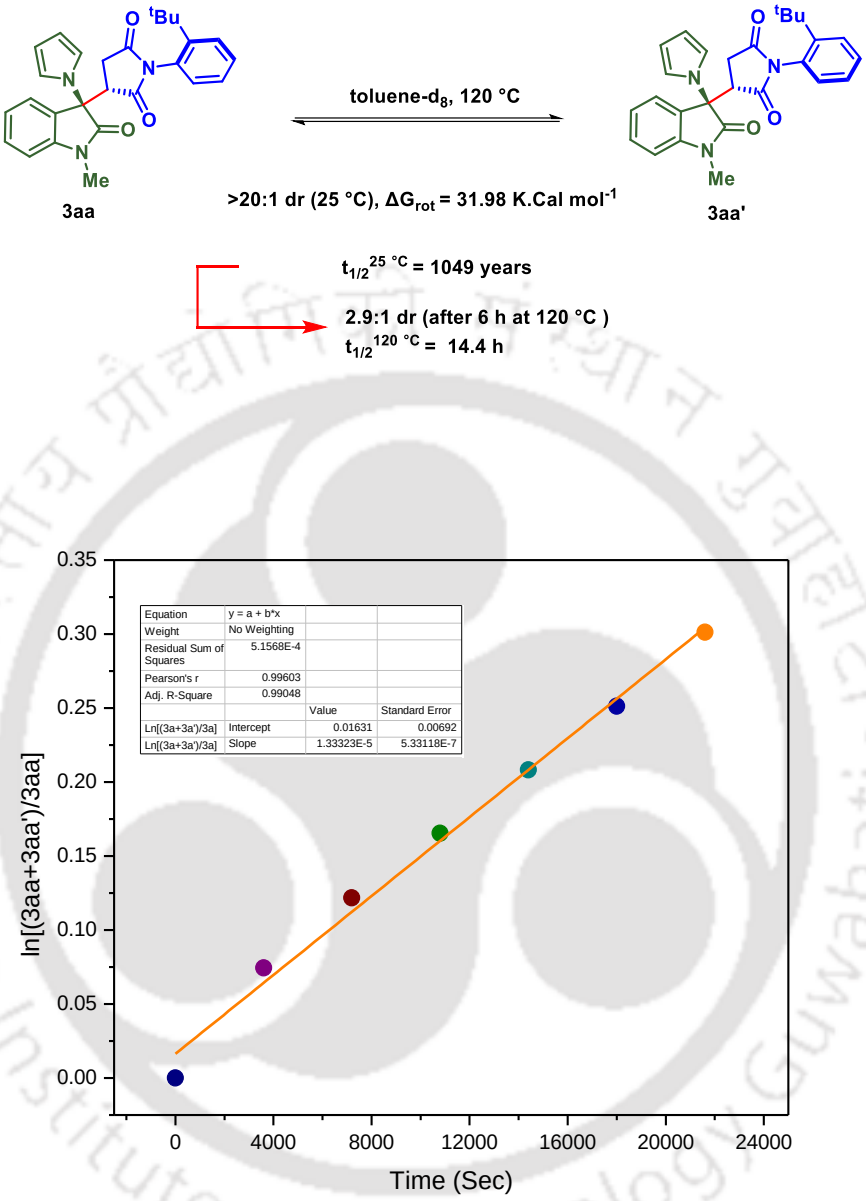


Figure 2. Effect of temperature on the diastereoselectivity

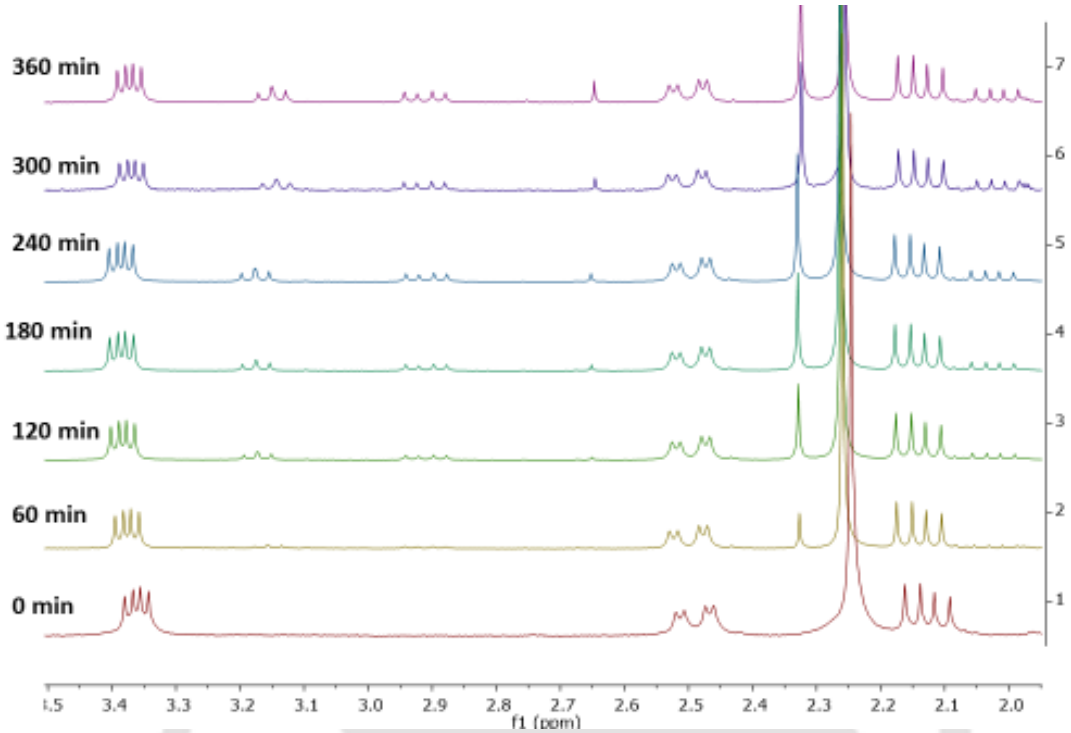


Figure 3. Stacked ^{1}H NMR data at 120 °C, at 1-hour gap duration

3.5 Conclusion

For the synthesis of new series of C-N atropisomers containing pyrrole, oxindole, and succinimide moieties, we have created an organocatalytic asymmetric Michael addition of 3-pyrrolyloxindole to prochiral N-aryl maleimides. This work is the first to create atropisomers using 3-pyrrolyloxindoles. Under gentle reaction conditions, moderate yields of the potentially bioactive C-N atropisomers with high diastereo- and enantioselectivities were obtained. Few synthetic application reactions and experiments on the C-N rotational energy barrier have been performed.

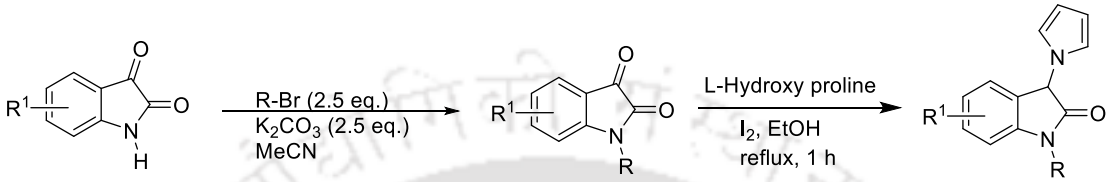
3.6 Experimental section

3.6.1 General Information:

Same as Chapter II.

3.6.2 General procedure for the synthesis of 3-pyrrolyloxindoles:

3-pyrrolyloxindoles were prepared according to reported procedure. [14]

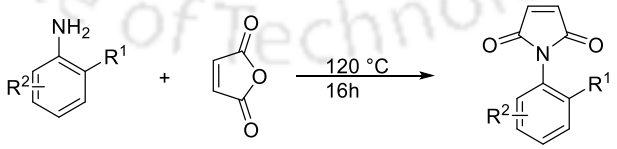


Isatin (3.0 mmol, 1.0 eq.) is dissolved in 15 mL of acetonitrile before potassium carbonate (2.5 eq.) is added. The appropriate amount of bromide (2.5eq.) was then added, and the reaction was stirred at reflux for the remainder of the day. The mixture was then added to water (15mL) and extracted with EtOAc following TLC analysis. In order to produce N-substituted isatins (yield of 80–90%), the combined organic sections were first washed with water and brine, dried over sodium sulphate, and then concentrated.

The N-substituted isatin (10 mmol), L-hydroxyproline (10 mmol), and iodine (200 mg) were combined with ethanol (20 mL). For 12 hours, the mixture was heated in a reflux system. Following that, the reaction was extracted with DCM (100 mL) and quenched with water (6 mL). The mixed organic phase was concentrated using rotor vapour after being rinsed with saturated sodium carbonate (50 mL). To eventually get a white solid, the residue was purified by flash chromatography using hexane/EtOAc (10/1) as an eluent.

3.6.3 General procedure for the synthesis of malemides:

Malemides were prepared according to the reported procedures. [15]



N-Aryl maleimide derivatives are prepared by a modified literature procedure,1a The corresponding aniline (1 equiv) and maleic anhydride (3 equiv) were mixed in a round-bottomed flask and heated to 120 °C for 16 h. After cooling to room temperature, the solid was taken up in EtOAc and filtered through Celite. After evaporation, the residue was purified by column chromatography.

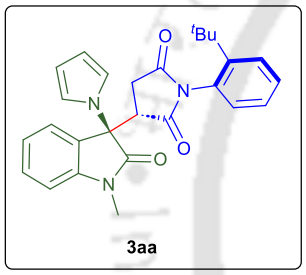
3.6.4 General procedure for the synthesis of catalyst:

The catalyst (**I, II, III, IV, V, VI** and **VII**) was prepared according to reported procedures.[16]

3.6.5 General procedure for the synthesis of compound 3:

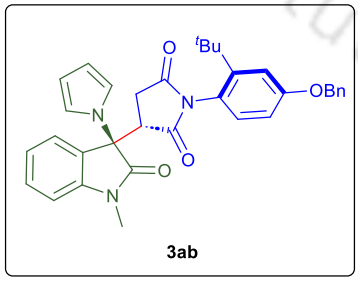
In an oven dried 5 mL reaction vial, 3-pyrrole oxindole **1** (0.1 mmol), N-aryl malemide **2** (0.15 mmol) and 20 mol% of catalyst (**VI**) were taken. Then 0.5 mL of pre-cooled toluene was added to the reaction mixture and stirred at -20 °C for 6d. Progress of the reaction was monitored by TLC. Then the reaction mixture was subjected to directly in flash chromatography eluting with hexane/ethyl acetate (90/10) to afford the product **3**.

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3aa)



White solid (29.2 mg, yield: 66%); M.P. 203-206 °C; R_f = 0.42 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.56 – 7.49 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.29 – 7.20 (m, 2H), 6.98 (t, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.17 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.25 (s, 3H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.49 (dd, *J* = 18.7, 5.3 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.05, 174.87, 172.45, 148.09, 144.17, 131.33, 130.50, 130.05, 129.96, 129.03, 127.54, 125.46, 125.23, 123.88, 119.26, 109.72, 109.68, 65.38, 45.83, 35.82, 31.80, 31.39, 26.75. **ESI HRMS**: calcd. for $C_{27}H_{28}N_3O_3$ $[M+H]^+$ 442.2126, found 442.2126. **HPLC Analysis**: *ee* = 95%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.0 min, t_{minor} = 30.2 min).

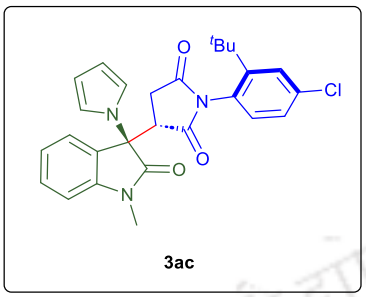
(S)-1-(4-(benzyloxy)-2-(tert-butyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ab)



White solid (24.1 mg, yield: 44%); M.P. 189-192 °C; R_f = 0.35 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.35 (m, 5H), 7.32 (t, *J* = 6.9 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.97 (t, *J* = 2.2 Hz, 2H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.22 (t, *J* = 2.3 Hz, 2H), 5.03 (s, 2H), 4.15 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.23 (s, 3H), 2.90 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.48 (dd, *J* = 18.6, 5.2 Hz, 1H), 1.21 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.33, 175.13, 172.44, 159.50, 149.61, 144.12, 136.69, 131.53, 131.26, 128.76, 128.22, 127.63, 125.37, 123.83, 122.87, 119.23, 116.32, 112.73, 109.69, 109.64, 70.30, 65.36, 45.71, 35.81, 31.61, 31.27, 26.71. **ESI HRMS**: calcd. for $C_{34}H_{34}N_3O_4$ $[M+H]^+$ 548.2544, found 548.2545. **HPLC Analysis**: *ee* = 90%, Chiralpak

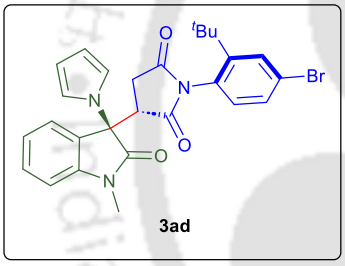
ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.0 min, t_{minor} = 13.5 min).

(S)-1-(2-(tert-butyl)-4-chlorophenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ac)



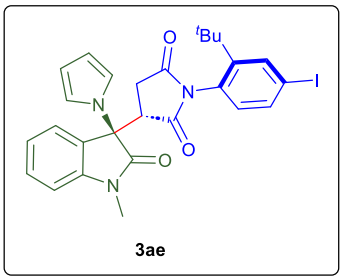
White solid (29.0 mg, yield: 61%); M.P. 185-188 °C; R_f = 0.48 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.55 – 7.41 (m, 3H), 7.27 – 7.20 (m, 2H), 7.00 – 6.87 (m, 3H), 6.69 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.21 – 4.12 (m, 1H), 3.24 (s, 3H), 2.98 – 2.85 (m, 1H), 2.55 (dd, *J* = 18.6, 5.2 Hz, 1H), 1.23 (s, 9H)**. ^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.85, 174.74, 172.40, 150.21, 144.04, 135.91, 131.90, 131.31, 129.33, 128.76, 127.75, 125.54, 125.15, 123.90, 119.20, 109.84, 109.71, 65.31, 45.98, 35.98, 31.54, 31.40, 26.74. **ESI HRMS**: calcd. for $C_{27}H_{27}ClN_3O_3$ $[M+H]^+$ 476.1735, found 476.1739. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.2 min, t_{minor} = 25.2 min).

(S)-1-(4-bromo-2-(tert-butyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ad)



White solid (34.8 mg, yield: 67%); M.P. 181-184 °C; R_f = 0.5 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.64 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.45 (td, *J* = 7.8, 1.2 Hz, 1H), 7.40 (dt, *J* = 8.3, 2.0 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.03 – 6.89 (m, 3H), 6.62 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.23 (t, *J* = 2.1 Hz, 2H), 4.16 (ddd, *J* = 9.7, 5.2, 1.9 Hz, 1H), 3.25 (s, 3H), 2.91 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.55 (dd, *J* = 18.5, 5.2 Hz, 1H), 1.23 (d, *J* = 1.4 Hz, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.79, 174.69, 172.39, 150.48, 144.02, 132.29, 132.15, 131.31, 130.78, 129.32, 125.53, 125.13, 124.29, 123.90, 119.19, 109.84, 109.71, 65.30, 45.99, 35.97, 31.55, 31.41, 26.74. **ESI HRMS**: calcd. for $C_{27}H_{27}BrN_3O_3$ $[M+H]^+$ 520.1230, found 520.1230. **HPLC Analysis**: *ee* = 95%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.9 min, t_{minor} = 27.0 min).

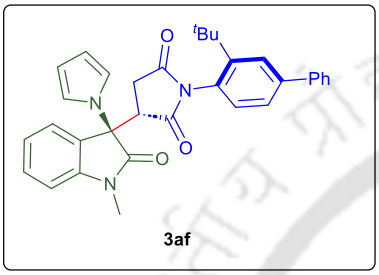
(S)-1-(2-(tert-butyl)-4-iodophenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ae)



White solid (39.1 mg, yield: 69%); M.P. 190-193 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.83 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.02 – 6.90 (m, 3H), 6.46 (d, *J* = 8.2 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.16 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.25 (s, 3H), 2.91 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.55 (dd, *J* = 18.8, 5.2 Hz, 1H), 1.22 (s, 9H). **^{13}C NMR (126**

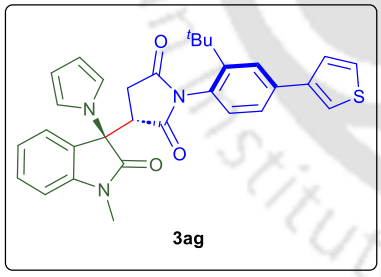
MHz, $CDCl_3$) δ 174.77, 174.66, 172.40, 150.54, 144.04, 138.36, 136.83, 132.26, 131.32, 130.11, 125.52, 125.17, 123.91, 119.20, 109.85, 109.72, 96.52, 65.31, 46.01, 35.85, 31.58, 31.43, 26.75. **ESI HRMS**: calcd. for $C_{27}H_{27}IN_3O_3$ $[M+H]^+$ 568.1092, found 568.1094. **HPLC Analysis**: *ee* = 98%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 24.7 min, t_{minor} = 28.4 min).

(S)-1-(3-(tert-butyl)-[1,1'-biphenyl]-4-yl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3af)



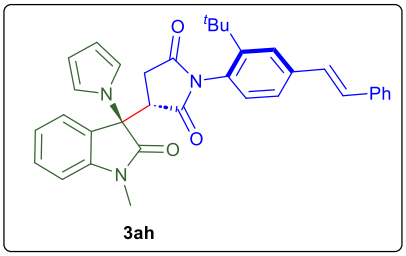
White solid (29.0 mg, yield: 56%); M.P. 215-218 °C; R_f = 0.37 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.70 (d, *J* = 2.2 Hz, 1H), 7.58 – 7.51 (m, 3H), 7.49 – 7.40 (m, 4H), 7.36 (td, *J* = 7.2, 1.4 Hz, 1H), 7.26 – 7.21 (m, 1H), 6.99 (q, *J* = 2.2 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.84 – 6.79 (m, 1H), 6.29 – 6.19 (m, 2H), 4.19 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.26 (s, 3H), 2.95 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.55 (dd, *J* = 18.5, 5.2 Hz, 1H), 1.30 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.17, 175.01, 172.45, 148.34, 144.11, 142.96, 140.81, 131.30, 130.86, 129.18, 128.92, 128.16, 127.78, 127.47, 126.47, 125.37, 123.89, 119.25, 109.76, 109.69, 65.39, 45.94, 35.98, 31.82, 31.43, 26.75. **ESI HRMS**: calcd. for $C_{32}H_{32}N_3O_3$ $[M+H]^+$ 518.2438, found 518.2442. **HPLC Analysis**: *ee* = 92%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 35.4 min, t_{minor} = 39.4 min).

(S)-1-(2-(tert-butyl)-4-(thiophen-3-yl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ag)



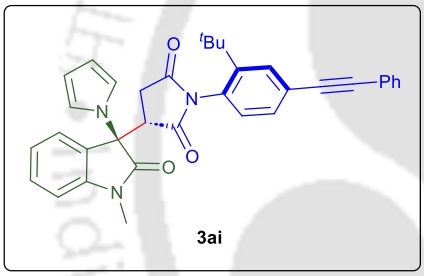
White solid (35.6 mg, yield: 68%); M.P. 169-172 °C; R_f = 0.45 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.71 (dd, *J* = 2.0, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.50 – 7.41 (m, 3H), 7.38 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.33 (dt, *J* = 5.0, 1.1 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.02 – 6.97 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.77 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.24 (dd, *J* = 3.1, 1.4 Hz, 2H), 4.18 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.26 (s, 3H), 2.94 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.53 (dd, *J* = 18.5, 5.3 Hz, 1H), 1.29 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.11, 174.94, 172.45, 148.45, 144.15, 141.89, 137.58, 131.32, 130.97, 128.96, 127.31, 126.59, 126.55, 125.79, 125.39, 123.89, 121.30, 119.26, 109.76, 109.69, 65.39, 45.91, 35.90, 31.79, 31.42, 26.75. **ESI HRMS**: calcd. for $C_{31}H_{30}N_3O_3S$ $[M+H]^+$ 524.2002, found 524.2005. **HPLC Analysis**: *ee* = 92%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.7 min, t_{minor} = 22.8 min).

(S)-1-(2-(tert-butyl)-4-((E)-styryl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ah)



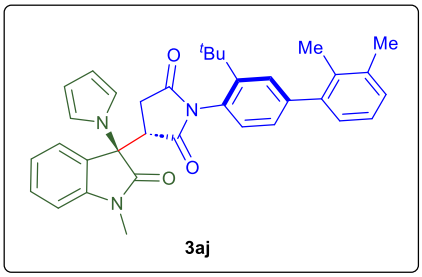
White solid (30.4 mg, yield: 56%); M.P. 219-222 °C; R_f = 0.47 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.59 (d, *J* = 1.9 Hz, 1H), 7.56 – 7.49 (m, 3H), 7.49 – 7.42 (m, 2H), 7.39 – 7.32 (m, 2H), 7.30 – 7.19 (m, 2H), 7.08 (s, 2H), 6.98 (t, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.17 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.25 (s, 3H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.51 (dd, *J* = 18.5, 5.4 Hz, 1H), 1.28 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.07, 174.89, 172.45, 148.33, 144.16, 138.93, 137.08, 131.33, 130.87, 130.20, 129.19, 128.83, 128.05, 127.73, 126.77, 125.43, 124.94, 123.88, 119.26, 109.75, 109.69, 65.40, 45.87, 35.83, 31.77, 31.41, 26.75. **ESI HRMS**: calcd. for $C_{35}H_{34}N_3O_3$ $[M+H]^+$ 544.2595, found 544.2596. **HPLC Analysis**: *ee* = 93%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 40.7 min, t_{minor} = 53.0 min).

(S)-1-(2-(tert-butyl)-4-(phenylethynyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ai)



White solid (29.2 mg, yield: 54%); M.P. 201-204 °C; R_f = 0.45 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.68 (t, *J* = 2.0 Hz, 1H), 7.57 – 7.50 (m, 3H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.41 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.35 (dq, *J* = 5.7, 3.6 Hz, 3H), 7.26 – 7.21 (m, 1H), 7.02 – 6.91 (m, 3H), 6.73 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.17 (dd, *J* = 9.3, 5.0 Hz, 1H), 3.25 (s, 3H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.52 (dd, *J* = 18.8, 5.2 Hz, 1H), 1.27 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.85, 174.72, 172.43, 148.44, 144.12, 132.37, 131.82, 131.35, 130.75, 130.51, 130.10, 128.65, 128.50, 125.32, 125.14, 123.91, 123.01, 119.24, 109.80, 109.71, 90.40, 88.83, 65.36, 45.93, 35.87, 31.69, 31.44, 26.75. **ESI HRMS**: calcd. for $C_{35}H_{32}N_3O_3$ $[M+H]^+$ 542.2438, found 542.2448. **HPLC Analysis**: *ee* = 92%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 29.2 min, t_{minor} = 49.3 min).

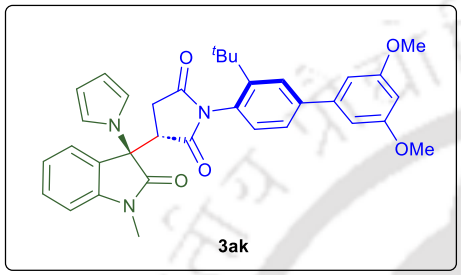
(S)-1-(3-(tert-butyl)-2',3'-dimethyl-[1,1'-biphenyl]-4-yl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3aj)



White solid (30.5 mg, yield: 56%); M.P. 180-183 °C; R_f = 0.50 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.59 – 7.52 (m, 1H), 7.50 – 7.42 (m, 2H), 7.26 – 7.12 (m, 4H), 7.06 (d, *J* = 6.7 Hz, 1H), 7.00 (q, *J* = 2.1 Hz, 2H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.77 (dd, *J* = 7.9, 2.1 Hz, 1H), 6.24 (t, *J* = 2.1 Hz, 2H), 4.22 – 4.16 (m, 1H), 3.26 (s, 3H), 2.94 (dd, *J* = 18.5, 9.6 Hz, 1H), 2.59 – 2.47 (m, 1H), 2.33

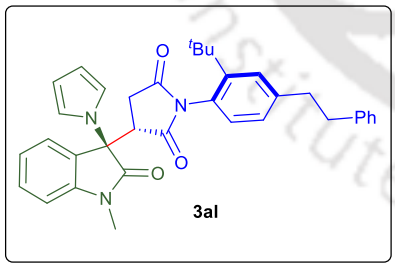
(s, 3H), 2.14 (s, 3H), 1.27 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.15, 175.06, 172.44, 147.51, 144.17, 143.93, 141.58, 137.48, 134.14, 131.34, 130.46, 130.10, 129.26, 128.44, 127.72, 125.46, 125.44, 123.89, 119.26, 109.73, 109.69, 65.38, 45.88, 35.95, 31.84, 31.40, 26.76, 20.78, 17.15. **ESI HRMS**: calcd. for $C_{35}H_{36}N_3O_3$ $[M+H]^+$ 546.2751, found 546.2755. **HPLC Analysis**: *ee* = 92%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.7 min, t_{minor} = 24.5 min).

(S)-1-(3-(tert-butyl)-3',5'-dimethoxy-[1,1'-biphenyl]-4-yl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ak)



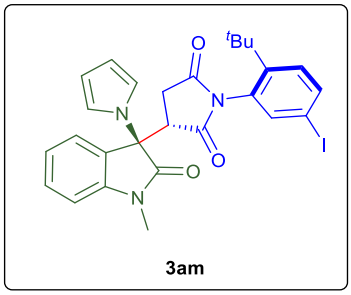
White solid (24.2 mg, yield: 42%); M.P. 179-182 °C; R_f = 0.2 in 2:8 ethyl acetate/hexane; dr = >20:1**;** **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.67 (d, *J* = 2.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.27 – 7.21 (m, 1H), 6.99 (t, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 2.2 Hz, 2H), 6.48 (t, *J* = 2.2 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.19 (dd, *J* = 9.6, 5.2 Hz, 1H), 3.83 (s, 6H), 3.26 (s, 3H), 2.94 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.56 (dd, *J* = 18.6, 5.3 Hz, 1H), 1.29 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.13, 174.98, 172.44, 161.16, 148.33, 144.11, 143.07, 142.93, 131.29, 130.80, 129.42, 128.18, 126.51, 125.34, 123.89, 119.24, 109.76, 109.68, 105.91, 99.51, 65.38, 55.55, 45.97, 35.97, 31.80, 31.44, 26.75. **ESI HRMS**: calcd. for $C_{35}H_{36}N_3O_5$ $[M+H]^+$ 578.2649, found 578.2655. **HPLC Analysis**: *ee* = 90%, Chiralpak IB Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 19.3 min, t_{minor} = 13.5 min).

(S)-1-(2-(tert-butyl)-4-phenethylphenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3al)



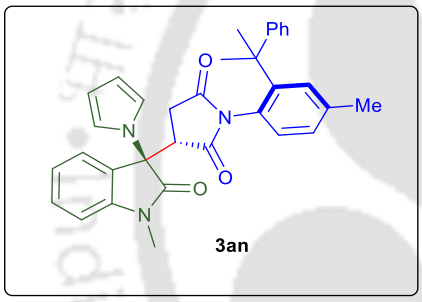
White solid (33.2 mg, yield: 61%); M.P. 219-222 °C; R_f = 0.46 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.15 (m, 5H), 7.10 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.97 (t, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.15 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.24 (s, 3H), 2.94 – 2.86 (m, 5H), 2.47 (dd, *J* = 18.9, 5.2 Hz, 1H), 1.20 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.14, 174.96, 172.45, 147.67, 144.18, 143.38, 141.52, 131.31, 130.37, 129.30, 128.59, 128.50, 127.79, 127.55, 126.11, 125.49, 125.20, 123.85, 119.26, 109.69, 109.66, 65.40, 45.76, 37.88, 37.71, 35.69, 31.75, 31.35, 26.73. **ESI HRMS**: calcd. for $C_{35}H_{36}N_3O_3$ $[M+H]^+$ 546.2752, found 546.2750. **HPLC Analysis**: *ee* = 95%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 32.5 min, t_{minor} = 27.0 min).

(S)-1-(2-(tert-butyl)-5-iodophenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3am)



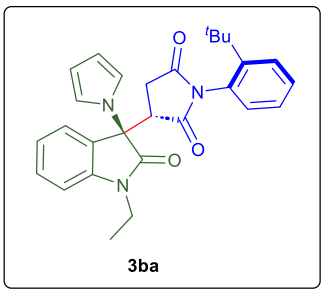
White solid (28.9 mg, yield: 51%); M.P. 188-191 °C; R_f = 0.56 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.64 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.31 – 7.22 (m, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 7.01 – 6.92 (m, 3H), 6.24 (t, *J* = 2.2 Hz, 2H), 4.16 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.27 (s, 3H), 2.93 (dd, *J* = 18.7, 9.7 Hz, 1H), 2.52 (dd, *J* = 18.8, 4.7 Hz, 1H), 1.22 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.72, 174.60, 172.23, 148.28, 144.00, 139.05, 138.76, 131.46, 131.43, 130.68, 125.36, 125.06, 123.90, 119.19, 109.82, 109.77, 91.21, 65.39, 45.94, 35.80, 31.56, 31.34, 26.80. **ESI HRMS**: calcd. for $C_{27}H_{27}IN_3O_3$ $[M+H]^+$ 568.1092, found 568.1092. **HPLC Analysis**: *ee* = 82%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.4 min, t_{minor} = 23.8 min).

(S)-1-(4-methyl-2-(2-phenylpropan-2-yl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3an)



White solid (39.3 mg, yield: 76%); M.P. 209-212 °C; R_f = 0.46 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.41 (td, *J* = 7.8, 1.3 Hz, 1H), 7.36 – 7.24 (m, 4H), 7.21 – 7.12 (m, 3H), 7.09 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.84 – 6.73 (m, 2H), 6.51 (d, *J* = 7.8 Hz, 1H), 6.19 (t, *J* = 2.2 Hz, 2H), 3.33 (dd, *J* = 9.7, 5.5 Hz, 1H), 3.16 (s, 3H), 2.39 (s, 3H), 2.25 – 2.15 (m, 1H), 1.89 (dd, *J* = 18.2, 5.4 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.00, 173.82, 172.52, 149.04, 146.91, 144.25, 139.93, 131.25, 130.57, 129.38, 128.62, 128.55, 127.54, 126.38, 126.19, 125.61, 124.74, 123.66, 119.26, 109.50, 109.37, 65.17, 44.31, 42.88, 32.05, 31.81, 30.73, 26.61, 21.67. **ESI HRMS**: calcd. for $C_{32}H_{32}N_3O_3$ $[M+H]^+$ 518.2438, found 518.2440. **HPLC Analysis**: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 29.7 min, t_{minor} = 33.6 min).

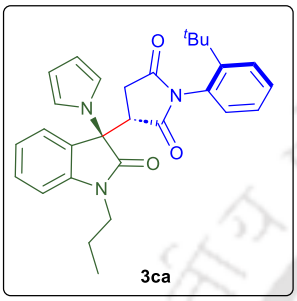
(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1-ethyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ba)



White solid (26.4 mg, combined yield: 58%); M.P. 201-204 °C; R_f = 0.43 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.59 – 7.49 (m, 2H), 7.48 – 7.41 (m, 1H), 7.35 (td, *J* = 7.7, 1.5 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.03 – 6.92 (m, 3H), 6.74 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.31 – 6.14 (m, 2H), 4.17 (dd, *J* = 9.7, 5.4 Hz, 1H), 3.87 (dq, *J* = 14.5, 7.2 Hz, 1H), 3.73 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.53 (dd, *J* = 18.5, 5.3 Hz, 1H), 1.26 (d, *J* = 10.7 Hz, 12H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.12, 174.81,

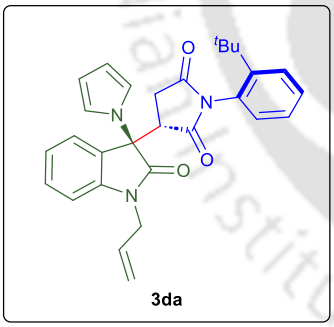
172.11, 148.08, 143.20, 131.21, 130.57, 130.09, 129.95, 129.00, 127.51, 125.73, 125.56, 123.70, 119.21, 109.76, 109.71, 65.20, 45.82, 35.81, 35.40, 31.80, 31.35, 12.58.
ESI HRMS: calcd. for $C_{28}H_{30}N_3O_3$ $[M+H]^+$ 456.2282, found 456.2282.
HPLC Analysis: *ee* = 96%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 25.8 min, t_{minor} = 17.5 min).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-2-oxo-1-propyl-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ca)



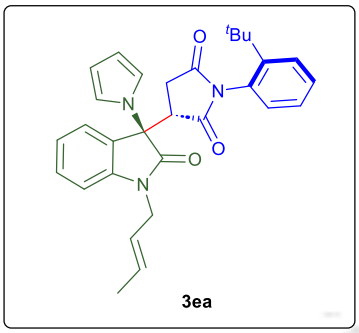
White solid (22.5 mg, yield: 48%); M.P. 171-174 °C; R_f = 0.44 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.53 (dt, *J* = 8.1, 1.4 Hz, 2H), 7.44 (td, *J* = 7.8, 1.2 Hz, 1H), 7.35 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.21 (td, *J* = 7.6, 1.0 Hz, 1H), 7.00 – 6.93 (m, 3H), 6.74 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.22 (t, *J* = 2.2 Hz, 2H), 4.18 (dd, *J* = 9.7, 5.4 Hz, 1H), 3.78 – 3.63 (m, 2H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.60 – 2.47 (m, 1H), 1.72 (tt, *J* = 13.8, 7.1 Hz, 2H), 1.25 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.1, 174.8, 172.5, 148.0, 143.6, 131.2, 130.6, 130.0, 129.9, 129.0, 127.5, 125.5, 123.7, 119.2, 109.9, 109.7, 65.2, 45.7, 42.2, 35.8, 31.8, 31.4, 20.8, 11.5. **ESI HRMS**: calcd. for $C_{29}H_{32}N_3O_3$ $[M+H]^+$ 470.2438, found 470.2445. **HPLC Analysis**: *ee* = 90%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 24.2 min, t_{minor} = 16.1 min).

(S)-3-((R)-1-allyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-1-(2-(tert-butyl)phenyl)pyrrolidine-2,5-dione (3da)



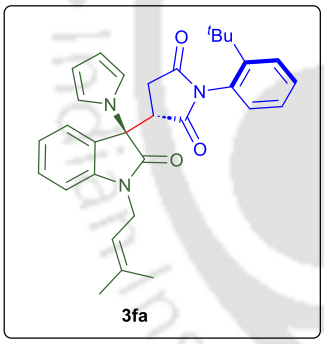
White solid (33.2 mg, yield: 71%); M.P. 169-172 °C; R_f = 0.44 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 7.8, 4.3 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.03 – 6.89 (m, 3H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.34 – 6.17 (m, 2H), 5.79 (ddt, *J* = 16.0, 10.5, 5.4 Hz, 1H), 5.24 (dd, *J* = 13.9, 8.1 Hz, 2H), 4.43 (dd, *J* = 16.3, 5.4 Hz, 1H), 4.31 (dd, *J* = 16.3, 5.5 Hz, 1H), 4.19 (ddd, *J* = 9.9, 5.4, 1.9 Hz, 1H), 2.93 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.59 (dd, *J* = 18.8, 5.1 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.09, 174.77, 172.22, 148.05, 143.23, 131.09, 130.66, 130.41, 130.06, 129.95, 128.96, 127.50, 125.70, 125.30, 123.86, 119.19, 118.88, 110.52, 109.81, 65.27, 45.85, 42.90, 35.80, 31.80, 31.40. **ESI HRMS**: calcd. for $C_{29}H_{30}N_3O_3$ $[M+H]^+$ 468.2282, found 468.2282. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.5 min, t_{minor} = 17.0 min).

(S)-3-((R)-1-((E)-but-2-en-1-yl)-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-1-(2-(tert-butyl)phenyl)pyrrolidine-2,5-dione (3ea)



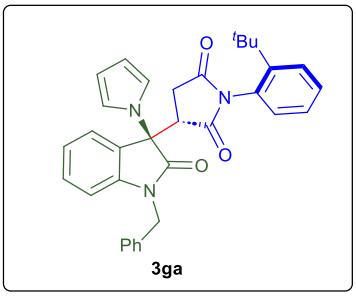
White solid (31.5 mg, yield: 65%); M.P. 181-184 °C; R_f = 0.44 in 2:8 ethyl acetate/hexane; E/Z ratio = 5:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.56 (dt, *J* = 7.6, 1.5 Hz, 2H), 7.45 (td, *J* = 7.8, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.28 (td, *J* = 7.6, 1.4 Hz, 1H), 7.24 (tt, *J* = 7.6, 1.3 Hz, 1H), 7.02 – 6.97 (m, 3H), 6.76 (dt, *J* = 7.9, 1.4 Hz, 1H), 6.26 (t, *J* = 2.3 Hz, 2H), 5.83 – 5.74 (m, 1H), 5.46 (dtd, *J* = 15.4, 6.0, 1.7 Hz, 1H), 4.39 (ddt, *J* = 15.7, 5.8, 1.5 Hz, 1H), 4.29 – 4.19 (m, 2H), 2.96 (ddd, *J* = 18.7, 9.7, 2.2 Hz, 1H), 2.55 (d, *J* = 16.0 Hz, 1H), 1.89 – 1.86 (m, 1H), 1.70 (dd, *J* = 6.5, 1.6 Hz, 3H), 1.29 (s, 11H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.14, 174.75, 172.07, 148.05, 143.49, 131.15, 130.69, 130.55, 130.03, 129.91, 128.98, 127.49, 125.41, 123.69, 123.27, 119.21, 110.55, 109.68, 65.23, 45.71, 42.39, 35.80, 31.78, 31.31, 17.84. **ESI HRMS**: calcd. for $C_{30}H_{32}N_3O_3$ $[M+H]^+$ 482.2438, found 482.2448. **HPLC Analysis**: for major dr, *ee* = 93% and for minor dr, *ee* = 86%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 95/5, flow rate 0.7 mL/min, λ = 220 nm (for major dr: t_{major} = 70.8 min, t_{minor} = 52.5 min and for minor dr: t_{major} = 77.0 min, t_{minor} = 56.3 min).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1-(3-methylbut-2-en-1-yl)-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3fa)



White solid (32.7 mg, yield: 66%); M.P. 188-191 °C; R_f = 0.44 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.52 (ddd, *J* = 7.5, 3.8, 1.4 Hz, 2H), 7.43 (td, *J* = 7.8, 1.2 Hz, 1H), 7.35 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.30 – 7.16 (m, 2H), 6.97 (t, *J* = 2.2 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.72 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.22 (t, *J* = 2.2 Hz, 2H), 5.12 (qd, *J* = 4.9, 2.5 Hz, 1H), 4.40 (dd, *J* = 15.6, 6.7 Hz, 1H), 4.27 (dd, *J* = 15.5, 6.8 Hz, 1H), 4.18 (dd, *J* = 9.6, 5.3 Hz, 1H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.48 (dd, *J* = 18.5, 5.3 Hz, 1H), 1.83 (s, 3H), 1.72 (s, 3H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.1, 174.8, 172.0, 148.1, 143.6, 138.1, 131.2, 130.6, 130.1, 129.9, 129.0, 127.5, 125.5, 125.3, 123.7, 119.3, 117.3, 110.3, 109.6, 65.3, 45.7, 38.7, 35.8, 31.8, 31.3, 25.8, 18.4. **ESI HRMS**: calcd. for $C_{31}H_{34}N_3O_3$ $[M+H]^+$ 496.2595, found 496.2598. **HPLC Analysis**: *ee* = 90%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.0 min, t_{minor} = 15.0 min).

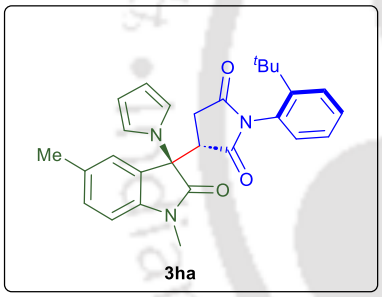
(S)-3-((R)-1-benzyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-1-(2-(tert-butyl)phenyl)pyrrolidine-2,5-dione (3ga)



3ga

White solid (28.4 mg, yield: 55%); M.P. 170-173 °C; R_f = 0.45 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.31 – 7.25 (m, 5H), 7.20 (dtd, *J* = 16.1, 7.6, 1.2 Hz, 2H), 6.98 (t, *J* = 2.3 Hz, 2H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.70 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.25 (t, *J* = 2.2 Hz, 2H), 4.98 – 4.87 (m, 2H), 4.24 (dd, *J* = 9.7, 5.5 Hz, 1H), 2.93 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.55 (d, *J* = 18.6 Hz, 1H), 1.26 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.05, 174.79, 172.70, 148.01, 143.29, 134.79, 131.18, 130.61, 129.99, 129.93, 129.17, 128.97, 128.20, 127.52, 127.36, 125.37, 123.93, 119.23, 110.67, 109.84, 65.32, 45.69, 44.48, 35.80, 31.79, 31.33. **ESI HRMS**: calcd. for $C_{33}H_{32}N_3O_3$ $[M+H]^+$ 518.2438, found 518.2448. **HPLC Analysis**: *ee* = 78%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 8.3 min, t_{minor} = 4.5 min).

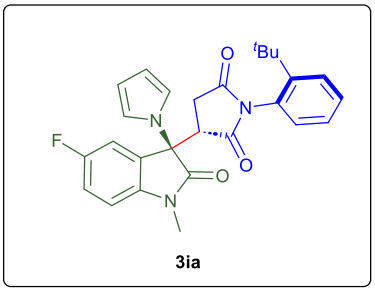
(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1,5-dimethyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ha)



3ha

White solid (27.3 mg, yield: 93%); M.P. 204-207 °C; R_f = 0.45 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.29 – 7.22 (m, 2H), 6.98 (t, *J* = 2.3 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.22 (t, *J* = 2.2 Hz, 2H), 4.16 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.22 (s, 3H), 2.92 (dd, *J* = 18.6, 9.7 Hz, 1H), 2.41 (s, 4H), 1.26 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.11, 174.94, 172.41, 148.18, 141.92, 133.56, 131.77, 130.47, 130.07, 129.94, 129.11, 127.43, 126.34, 124.62, 119.32, 109.56, 109.47, 65.60, 45.53, 35.85, 31.79, 31.35, 26.75, 21.29. **ESI HRMS**: calcd. for $C_{28}H_{30}N_3O_3$ $[M+H]^+$ 456.2282, found 456.2282. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.0 min, t_{minor} = 32.2 min).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-5-fluoro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ia)

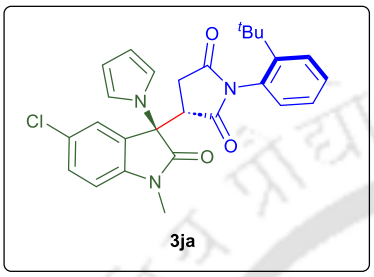


3ia

White solid (28.5 mg, yield: 62%); M.P. 201-204 °C; R_f = 0.4 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.52 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.36 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.12 (td, *J* = 8.7, 2.6 Hz, 1H), 6.93 (t, *J* = 2.3 Hz, 2H), 6.84 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.75 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.25 (t, *J* = 2.2 Hz, 2H), 4.13 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.23 (s, 3H), 2.93 (dd, *J* = 18.7, 9.7 Hz, 1H), 2.73 (d, *J* = 18.5 Hz, 1H), 1.24 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 175.00, 174.79, 172.07, 160.40 (d, J_{C-F} = 243.11 Hz), 148.00, 139.65, 130.44, 130.01, 129.96,

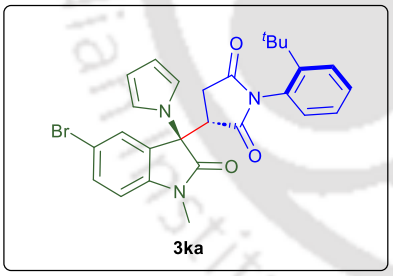
128.92, 127.66, 119.00, 117.44(d, J_{C-F} = 22.65 Hz), 113.16 (d, J_{C-F} = 25.67 Hz), 110.32 (d, J_{C-F} = 7.55 Hz), 110.15, 65.33, 46.13, 35.73, 31.74, 31.38, 26.84. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -117.64. **ESI HRMS**: calcd. for $C_{27}H_{27}FN_3O_3$ $[M+H]^+$ 460.2031, found 460.2037. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.5 min, t_{minor} = 18.1 min).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-5-chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ja)



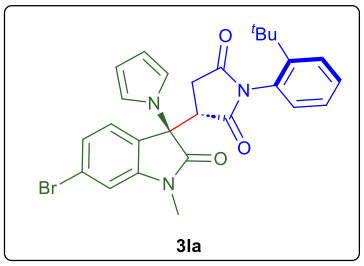
White solid (31.4 mg, yield: 66%); M.P. 199-202 °C; R_f = 0.43 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.49 (d, *J* = 2.1 Hz, 1H), 7.41 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 6.93 (t, *J* = 2.2 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.76 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.25 (t, *J* = 2.2 Hz, 2H), 4.14 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.23 (s, 3H), 2.93 (dd, *J* = 18.7, 9.7 Hz, 1H), 2.62 (d, *J* = 18.8 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.94, 174.79, 171.99, 148.01, 142.39, 131.06, 130.56, 130.04, 129.93, 129.39, 128.97, 127.71, 125.46, 119.08, 110.60, 110.15, 65.28, 45.94, 35.78, 31.78, 31.34, 26.86. **ESI HRMS**: calcd. for $C_{27}H_{27}ClN_3O_3$ $[M+H]^+$ 476.1735, found 476.1740. **HPLC Analysis**: *ee* = 96%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.0 min, t_{minor} = 17.8 min).

(S)-3-((R)-5-bromo-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-1-(2-(tert-butyl)phenyl)pyrrolidine-2,5-dione (3ka)



White solid (37.4 mg, yield: 72%); M.P. 239-242 °C; R_f = 0.46 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.63 (d, *J* = 1.9 Hz, 1H), 7.57 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.2, 7.3, 1.5 Hz, 1H), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H), 6.94 (t, *J* = 2.2 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.77 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.25 (t, *J* = 2.2 Hz, 2H), 4.14 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.23 (s, 3H), 2.94 (dd, *J* = 18.7, 9.7 Hz, 1H), 2.57 (d, *J* = 18.6 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.93, 174.78, 171.90, 148.01, 142.96, 134.05, 130.63, 130.05, 129.90, 128.98, 128.24, 127.74, 119.11, 116.62, 111.07, 110.13, 65.27, 45.83, 35.79, 31.78, 31.31, 26.85. **ESI HRMS**: calcd. for $C_{27}H_{27}BrN_3O_3$ $[M+H]^+$ 520.1230, found 520.1232. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.6 min, t_{minor} = 19.1 min).

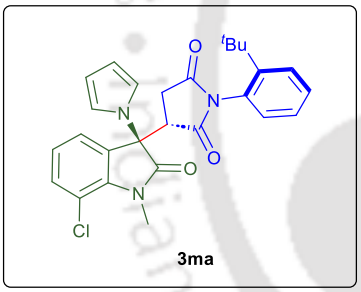
(S)-3-((R)-6-bromo-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-1-(2-(tert-butyl)phenyl)pyrrolidine-2,5-dione (3la)



3la

White solid (42.6 mg, yield: 82%); M.P. 248-251 °C; R_f = 0.46 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.52 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.39 – 7.32 (m, 3H), 7.30 – 7.24 (m, 1H), 7.08 (d, *J* = 1.5 Hz, 1H), 6.91 (t, *J* = 2.2 Hz, 2H), 6.71 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.23 (t, *J* = 2.2 Hz, 2H), 4.13 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.22 (s, 3H), 2.91 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.66 (dd, *J* = 18.5, 5.4 Hz, 1H), 1.24 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.85, 174.80, 172.25, 148.04, 145.10, 130.43, 130.01, 129.96, 128.98, 127.60, 126.72, 126.17, 125.08, 124.99, 119.04, 113.20, 110.10, 64.99, 45.97, 35.75, 31.76, 31.37, 26.83. **ESI HRMS**: calcd. for $C_{27}H_{27}BrN_3O_3$ $[M+H]^+$ 520.1230, found 520.1235. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.4 min, t_{minor} = 12.1 min).

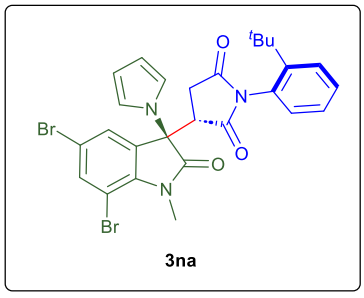
(S)-1-(2-(tert-butyl)phenyl)-3-((R)-7-chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3ma)



3ma

White solid (29.0 mg, yield: 61%); M.P. 209-212 °C; R_f = 0.43 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.52 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.42 – 7.31 (m, 3H), 7.30 – 7.22 (m, 1H), 7.15 – 7.07 (m, 1H), 6.90 (t, *J* = 2.2 Hz, 2H), 6.74 (dt, *J* = 7.8, 1.4 Hz, 1H), 6.29 – 6.19 (m, 2H), 4.14 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.63 (s, 3H), 2.93 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.77 (dd, *J* = 18.7, 5.2 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.96, 174.78, 172.79, 148.03, 139.74, 133.24, 130.46, 130.02, 129.35, 128.95, 127.63, 124.58, 123.21, 119.04, 117.04, 110.15, 64.81, 46.26, 35.76, 31.77, 31.48, 30.23. **ESI HRMS**: calcd. for $C_{27}H_{27}ClN_3O_3$ $[M+H]^+$ 476.1735, found 476.1739. **HPLC Analysis**: *ee* = 86%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.7 min, t_{minor} = 20.8 min).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-5,7-dibromo-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (3na)



3na

White solid (33.4 mg, yield: 56%); M.P. 207-210 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr = 5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.67 (d, *J* = 1.9 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.37 (td, *J* = 7.7, 1.5 Hz, 1H), 7.29 (td, *J* = 7.5, 1.5 Hz, 1H), 6.85 (t, *J* = 2.2 Hz, 2H), 6.76 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.29 – 6.24 (m, 2H), 4.11 (dd, *J* = 9.3, 5.5 Hz, 1H), 3.62 (s, 3H), 2.95 (dd, *J* = 18.6, 9.5 Hz, 1H), 2.84 (dt, *J* = 19.5, 4.4 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 174.83, 174.70, 172.57, 148.02, 138.38, 130.59,

130.12, 129.95, 128.95, 127.78, 126.65, 118.94, 116.78, 110.61, 104.33, 64.75, 46.37, 35.78, 31.80, 31.51, 30.49. **ESI HRMS**: calcd. for $C_{27}H_{26}Br_2N_3O_3$ $[M+H]^+$ 598.0335, found 598.0342. **HPLC Analysis**: *ee* = >99%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 8.6 min, t_{minor} = 18.4 min).

3.6.6 Scale up reaction:

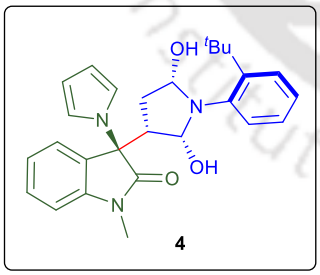
In an oven dried 10 mL reaction vial, 3-pyrrole oxindole **1a** (1 mmol), N-aryl malemide **2a** (1.5 mmol) and 20 mol% of catalyst (**VI**) were taken. Then 5 mL of pre-cooled toluene was added to the reaction mixture and stirred at -20 °C for 6 d. Progress of the reaction was monitored by TLC. Then the reaction mixture was subjected to directly in flash chromatography eluting with hexane/ethyl acetate (90/10) to afford the product **3** (278.0 mg, 63% yield, white solid).

3.6.7 Procedure for the synthetic transformations:

a. Procedure for the synthesis of compound 4:

In a 5 ml round bottom flask under Ar atmosphere, DIBAL-H [1 (M) solution in toluene] (0.3 ml, 0.3 mmol) was added to **3aa** (44.1 mg, 0.1 mmol) in THF (1.0 mL) at -78 °C and was stirred for 1 h at room temperature. The reaction was quenched with 1 (N) HCl and the precipitate was filtered off through a pad of celite with EtOAc. The organic layer was separated, evaporated and was subjected to directly in flash chromatography eluting with hexane/ethyl acetate (90/10) to afford the product **4** (25.8 mg, 58% yield, white solid).

(R)-3-((2R,3S,5S)-1-(2-(tert-butyl)phenyl)-2,5-dihydroxypyrrolidin-3-yl)-1-methyl-3-(1H-pyrrol-1-yl)indolin-2-one (4)



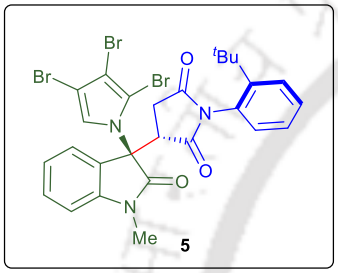
4

White solid (25.8 mg, yield: 58%); M.P. 245-248 °C; R_f = 0.40 in 2:8 ethyl acetate/hexane; dr = 10:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.06 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.96 (t, *J* = 2.2 Hz, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.32 (t, *J* = 2.2 Hz, 2H), 5.03 (dd, *J* = 12.9, 7.3 Hz, 1H), 4.30 (d, *J* = 11.1 Hz, 1H), 4.03 (d, *J* = 11.1 Hz, 1H), 3.31 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.05 (ddd, *J* = 14.9, 11.4, 7.3 Hz, 1H), 2.78 (s, 3H), 2.27 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.03 (d, *J* = 17.4 Hz, 1H), 1.31 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.64, 153.95, 147.64, 133.80, 132.36, 130.88, 129.46, 128.98, 128.77, 127.03, 124.93, 120.68, 118.02, 109.58, 109.33, 85.03, 68.52, 67.39, 48.88, 35.98, 35.82, 32.02, 31.12. **ESI HRMS**: calcd. for $C_{27}H_{32}N_3O_3$ $[M+H]^+$ 446.2439, found 446.2435. **HPLC Analysis**: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 28.6 min, t_{minor} = 17.3 min).

b. Procedure for the synthesis of compound 5:

Under Ar atmosphere, NBS (53.1 mg, 0.3 mmol) was added to **3aa** (44.1 mg, 0.1 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C and then it was stirred at room temperature for 30 min. At the end of the reaction, water was added, and extracted by CH_2Cl_2. The solvent was removed in vacuo and the residue was purified by flash chromatography eluting with hexane/ethyl acetate (90/10) to give the product **5** (41.3 mg, 61% yield, white solid).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(2,3,4-tribromo-1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (5)

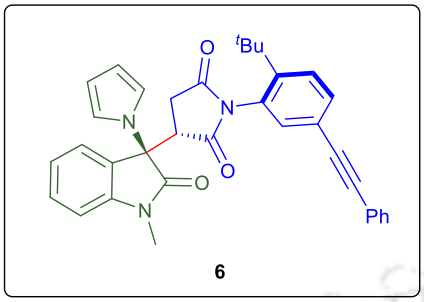


White solid (41.3 mg, yield: 61%); M.P. 237-240 °C; R_f = 0.44 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.53 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.36 (td, *J* = 7.8, 1.5 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.16 (dd, *J* = 15.4, 7.7 Hz, 2H), 6.91 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 4.48 (t, *J* = 7.5 Hz, 1H), 3.30 (s, 3H), 3.12 – 2.94 (m, 2H), 1.26 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.33, 174.17, 171.58, 148.04, 143.80, 131.43, 130.43, 130.12, 129.92, 129.03, 127.63, 124.72, 124.52, 122.77, 109.59, 106.28, 101.74, 99.84, 68.09, 45.21, 35.81, 31.97, 31.80, 27.01.
ESI HRMS: calcd. for $C_{27}H_{25}Br_3N_3O_3$ $[M+H]^+$ 677.9421, found 677.9416.
HPLC Analysis: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.7 min, t_{minor} = 19.6 min).

c. Procedure for the synthesis of compound 6:

Under Ar atmosphere to a mixture of **3al** (56.7 mg, 0.1 mmol) in DMF (1 mL) were added $Pd(PPh_3)_2Cl_2$ (7 mg, 0.1 equiv) and CuI (3.8 mg, 0.2 equiv). After the reaction mixture was stirred for 5 min. at rt, DIPEA (51.6 mg, 70 µL, 4 equiv) was added by a syringe. The reaction mixture was then heated at 70 °C and phenylacetylene (12.24 mg, 13.16 µL, 1.2 equiv) was added. After stirring the reaction mixture for 16 h at 70 °C, the reaction mixture was washed with saturated aq. NH_4Cl and water, and then extracted with EtOAc, dried over anhydrous Na_2SO_4 and concentrated under vacuum. Subsequent purification via silica gel flash column chromatography (Pet. ether /EtOAc = 90/10) of the crude reaction mixture afforded **6** as a yellow solid (45.4 mg, 84% yield).

(S)-1-(2-(tert-butyl)-5-(phenylethynyl)phenyl)-3-((R)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (6)



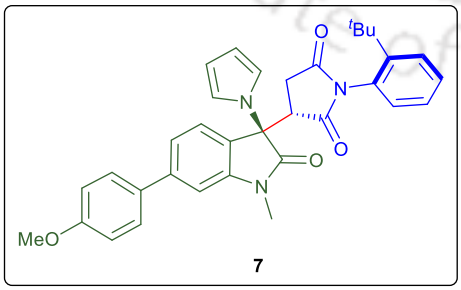
6

White solid (45.5 mg, yield: 84%); M.P. 212-215 °C; R_f = 0.39 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.57 – 7.45 (m, 6H), 7.39 – 7.33 (m, 3H), 7.28 – 7.23 (m, 1H), 6.98 (t, *J* = 2.2 Hz, 2H), 6.97 – 6.89 (m, 2H), 6.24 (t, *J* = 2.2 Hz, 2H), 4.17 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.28 (s, 3H), 2.93 (dd, *J* = 18.6, 9.6 Hz, 1H), 2.54 (dd, *J* = 18.5, 5.1 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.83, 174.69, 172.35, 148.55, 144.09, 133.69, 132.74, 131.74, 131.44, 130.24, 129.22, 128.61, 128.54, 125.50, 123.97, 123.15, 122.81, 119.24, 109.79, 109.72, 90.44, 87.86, 65.39, 45.96, 35.98, 31.67, 31.40, 26.79. **ESI HRMS**: calcd. for $C_{35}H_{32}N_3O_3$ $[M+H]^+$ 542.2438, found 542.2438. **HPLC Analysis**: *ee* = 81%, Chiralpak IB Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.1 min, t_{minor} = 21.0 min).

d. Procedure for the synthesis of compound 7:

To a round bottom flask 10 ml **3la** (0.1 mmol), $Pd(OAc)_2$ (0.05 eq.), PCy_3 (0.05 eq.), 4-methoxy phenyl boronic acid (1.5 eq.) and Na_2CO_3 (2 eq.) were added under Ar atomosphere. Then 0.5 ml DMF was added to the reaction mixture and the reaction mixture was stirred at room temperature for 20 h. Next H_2O was added to the mixture and the mixture was extracted with ethyl acetate. Then the combined organic layers were again washed with H_2O twice and the organic layer was dried over Na_2SO_4 and concentrated in rota-vap and the crude product was purified by flash chromatography eluting with hexane/ethyl acetate (80/20) to give the product **7** (35.0 mg, 64% yield, white sticky solid).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-6-(4-methoxyphenyl)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (7)



7

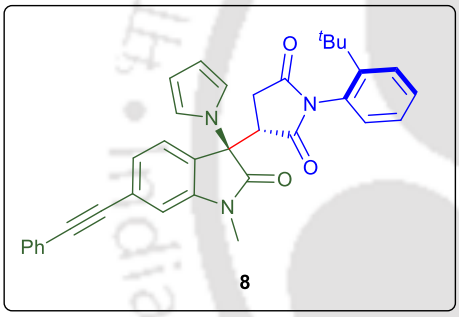
White solid (35.0 mg, yield: 64%); M.P. 199-202 °C; R_f = 0.25 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 – 7.50 (m, 4H), 7.41 – 7.32 (m, 2H), 7.29 – 7.24 (m, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.05 – 6.97 (m, 4H), 6.76 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.24 (t, *J* = 2.2 Hz, 2H), 4.20 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.87 (s, 3H), 3.30 (s, 3H), 2.98 – 2.88 (m, 1H), 2.51 (dd, *J* = 18.5, 5.3 Hz, 1H), 1.26 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 175.11, 174.99, 172.73, 160.02, 148.11, 144.77, 144.60, 132.66, 130.54, 130.06, 129.98, 129.06, 128.51, 127.58, 125.75, 122.28, 119.30, 114.57, 109.72, 108.12, 65.39, 55.54, 45.82, 35.85, 31.82, 31.47, 26.82. **ESI HRMS**: calcd. for $C_{34}H_{34}N_3O_4$ $[M+H]^+$ 548.2544,

found 548.2549. **HPLC Analysis**: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 60.7 min, t_{minor} = 53.2 min).

e. Procedure for the synthesis of compound 8:

To a dry flask under argon containing **3la** (0.1 mmol, 1.0) was sequentially added Et_3N (1.0 mL), phenyl acetylene (13.0 µL, 0.12 mmol, 1.2 equiv.), $PdCl_2(PPh_3)_2$ (3.5 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 90 °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 hexane/ethyl acetate (85/15) to afford compound **7** (42.1 mg, 78% yield, white sticky solid).

(S)-1-(2-(tert-butyl)phenyl)-3-((R)-1-methyl-2-oxo-6-(phenylethynyl)-3-(1H-pyrrol-1-yl)indolin-3-yl)pyrrolidine-2,5-dione (8)



8

White solid (42.2 mg, yield: 78%); M.P. 208-211 °C; R_f = 0.4 in 2:8 ethyl acetate/hexane; dr = >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.57 – 7.49 (m, 4H), 7.42 – 7.35 (m, 5H), 7.30 – 7.26 (m, 1H), 7.09 (s, 1H), 6.99 – 6.94 (m, 2H), 6.74 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.28 – 6.21 (m, 2H), 4.17 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.27 (s, 3H), 2.94 (dd, *J* = 18.7, 9.6 Hz, 1H), 2.57 (d, *J* = 18.7 Hz, 1H), 1.25 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 174.92, 174.83, 172.37, 148.09, 144.21, 131.88, 130.51, 130.03, 130.00, 129.05, 128.99, 128.61, 127.62, 127.36, 126.53, 125.26, 122.65, 119.20, 112.35, 109.95, 91.62, 88.39, 65.25, 45.90, 35.83, 31.81, 31.40, 26.85. **ESI HRMS**: calcd. for $C_{35}H_{32}N_3O_3$ $[M+H]^+$ 542.2438, found 542.2446. **HPLC Analysis**: *ee* = 94%, Chiralpak IB Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 25.5 min, t_{minor} = 20.4 min).

3.6.8 Determination of rotational barrier of C–N bond of 3aa:

The C–N rotational barrier in 3aa is determined following the method of Jørgensen et al.[13]

To an oven-dried sealed tube equipped with a magnetic stirring bar was taken **3aa** (30 mg, in 2.5 mL d^8-toluene. The resulting solution was allowed to heat in pre-equilibrated oil bath with electronic controller at 120 °C. After one hour, it was taken out, cooled to rt for 3-4 min. Then 100 µL aliquot was taken out in a NMR tube and another 0.4 ml d^8-toluene was added to the NMR tube. Then analyzed by ^{1}H NMR spectroscopy periodically in every

1 hour, in order to determine the **3aa/3aa'** ratio over time. The ratio was plotted against time, and the barrier of rotation was calculated from the plot.

Then Applying the method of initial rates:

$$k = \frac{\ln[\frac{C(3aa) + C(3aa')}{C(3aa)}]}{t}$$

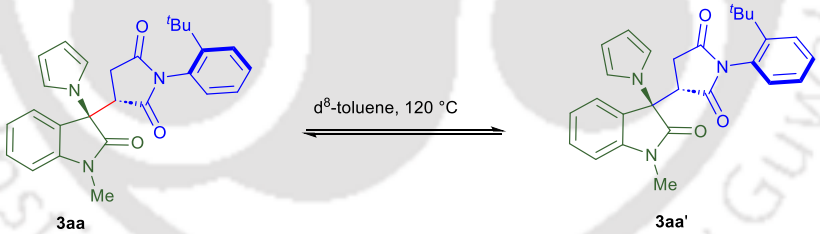
Where C (concentration of the species in the sample) is determined by the relative **3aa/3aa'** signal ratio in the 1H spectrum. Constant k is extrapolated by the graph shown. Then applying the Eyring equation:

$$\Delta G^{rot} = \mathrm{RTln}(\frac{k_b T}{kh})$$

Where: R = 8.31451 J. K^{-1}.mol; h = 6.62608.10^{-34} J.s (Planck constant); k_B = 1.38066·10^{-23} J·K^{-1} (Boltzmann constant) and *k* is the previously calculated kinetic constant Finally, the half-life time is calculated as follows:

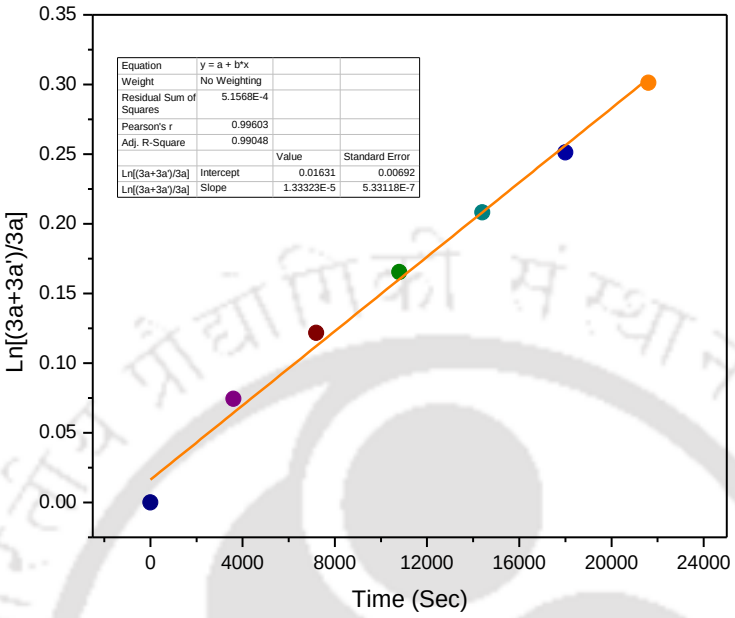
$$k^{\mathrm{T}} = \frac{k_b T}{h} e^{\frac{-\Delta G^{rot}}{RT}}$$

$$t_{1/2}^{T} = \frac{ln(2)}{k^{T}}$$



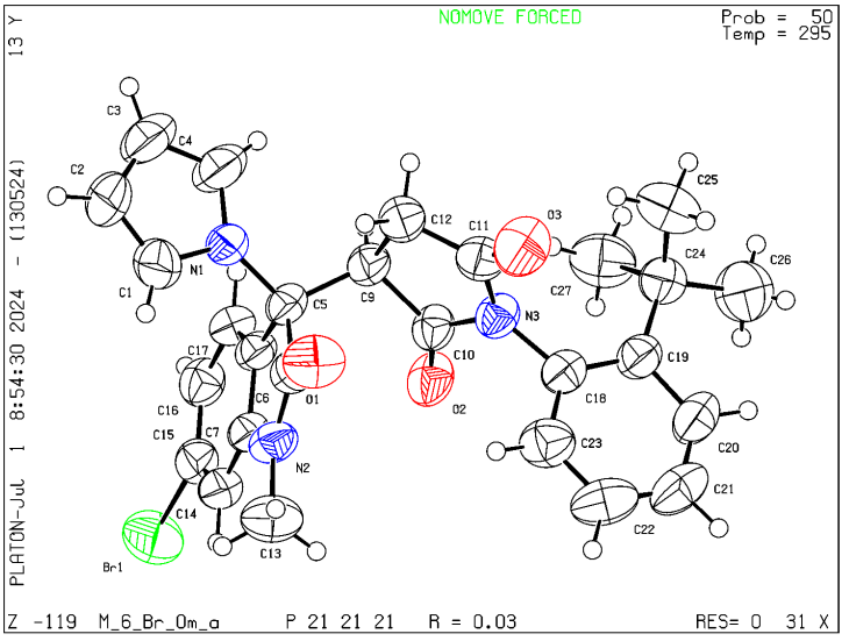
3aa **3aa'**

Time (sec.)	3aa/(3aa+3aa')	ln[(3aa+3aa')/3aa]
0	1	0
3600	0.9375	0.064
7200	0.8765	0.1317
10800	0.8475	0.1653
14400	0.8120	0.2082
18000	0.7780	0.2513
21600	0.7700	0.2612



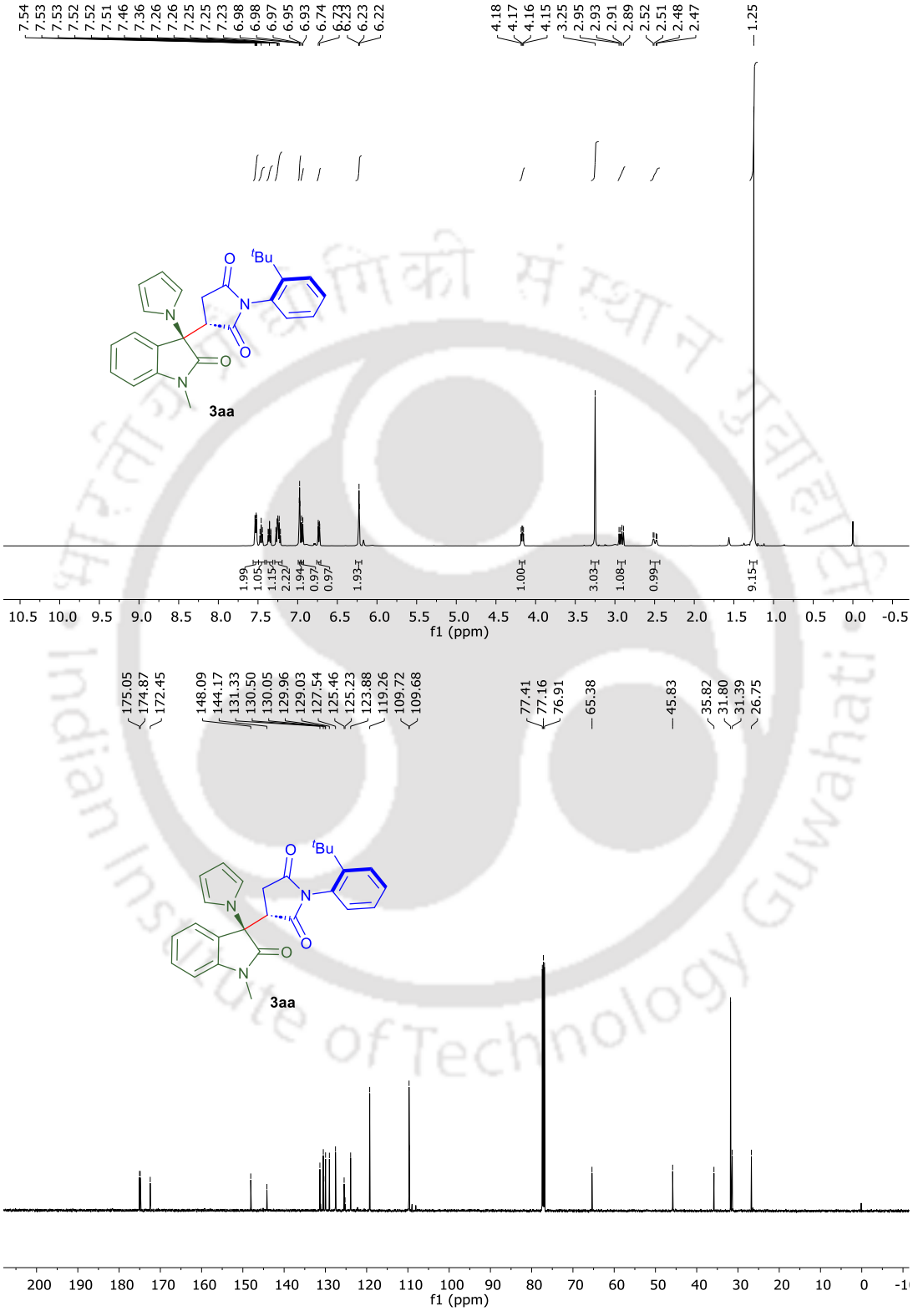
3.6.9 Single crystal X-ray diffraction analysis of 3la:

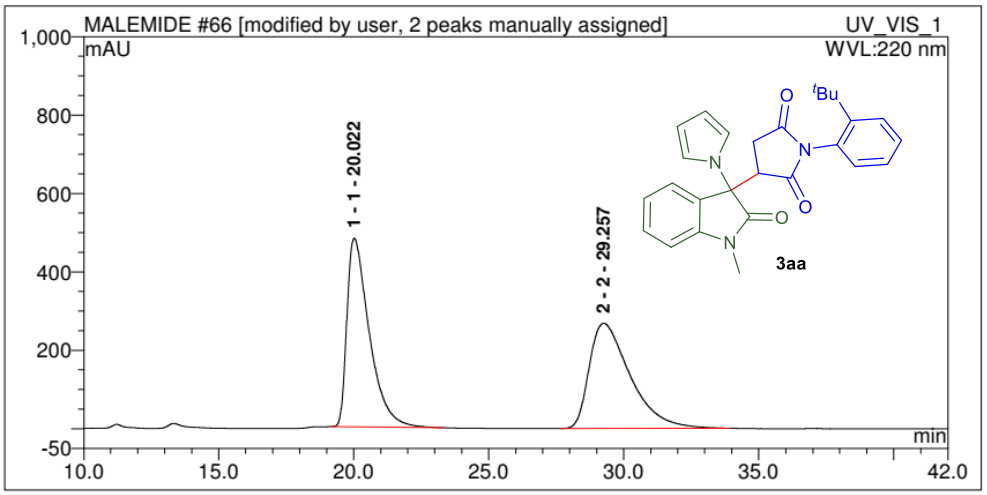
CCDC No.	2367995
Empirical formula	$C_{27}H_{26}BrN_3O_3$
Formula weight	520.42
Crystal habit, colour	Block / colourless
Temperature, T	295 K
Wavelength, λ (Å)	0.71073
Crystal system	orthorhombic
Space group	'P 21'
Unit cell dimensions	a = 9.3307(6) Å b = 16.3598(10) Å c = 16.5024(10) Å α = 90°, β = 101.675°, γ = 90°
Volume, V ($Å^3$)	2519.1(3)
Z	4
Calculated density, $g·cm^{-3}$	1.372
F (000)	1072.0
Refinement method	'SHELXL–2019/1'
Goodness–of–fit on F^2	0.865
Theta(max)	25.026
Data completeness	1.75/1.00
R(reflections)	0.0324 (3266)
wR2(reflections)	0.1225 (4448)



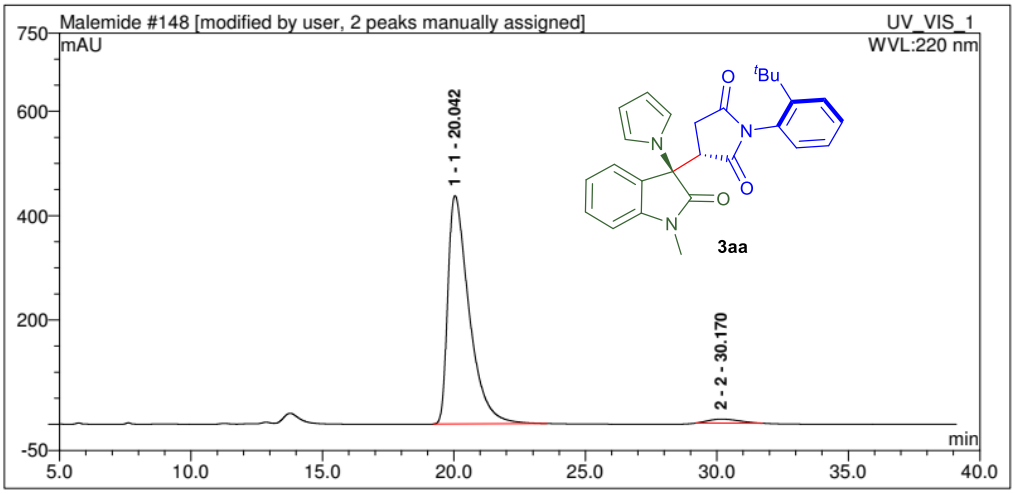
ORTEP diagram of 3la

3.6.10 NMR spectra and HPLC chromatograms of selected products:

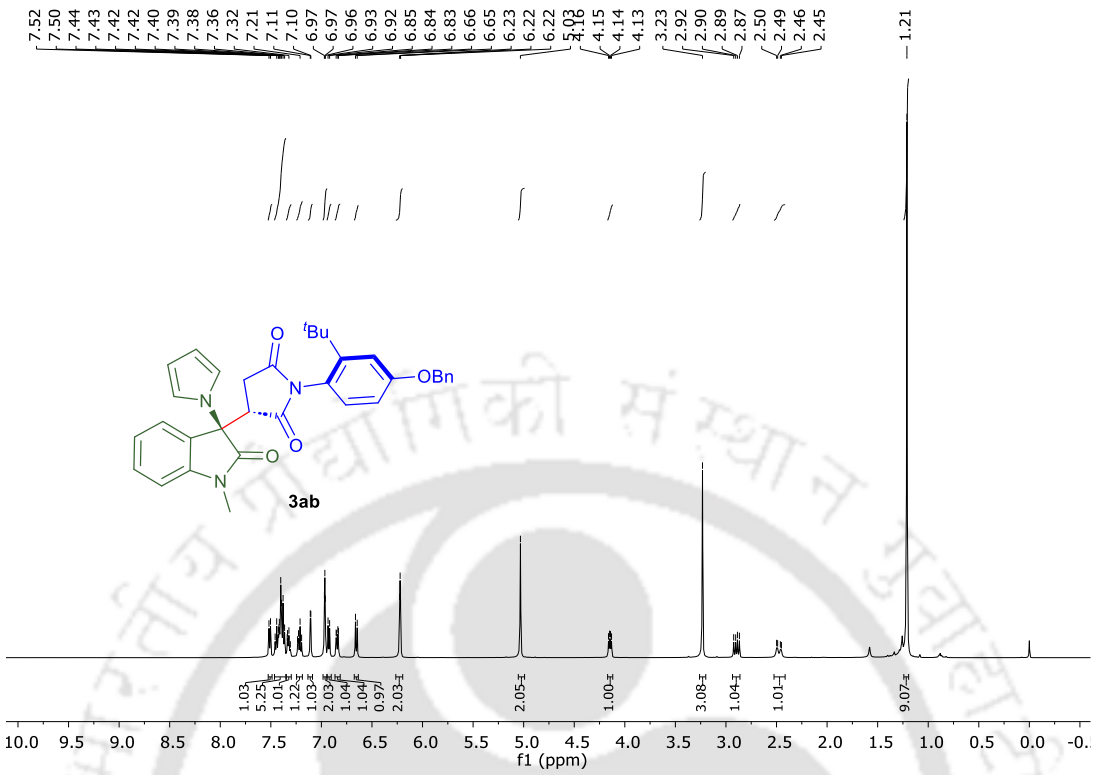


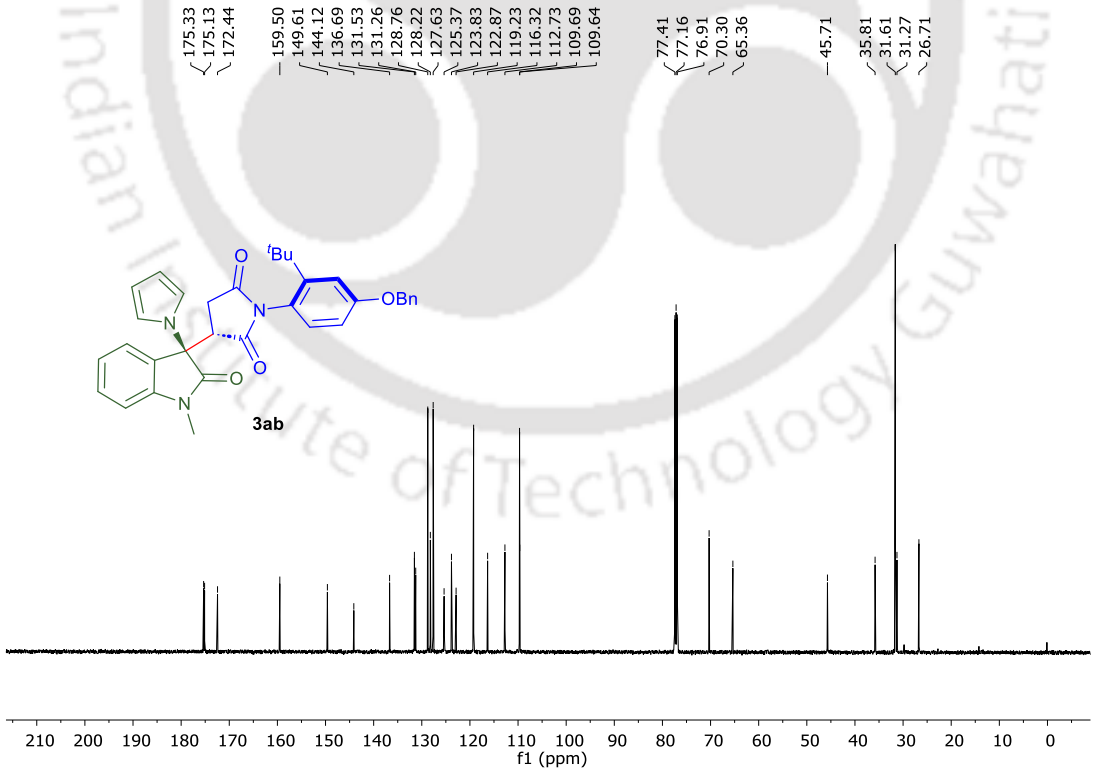


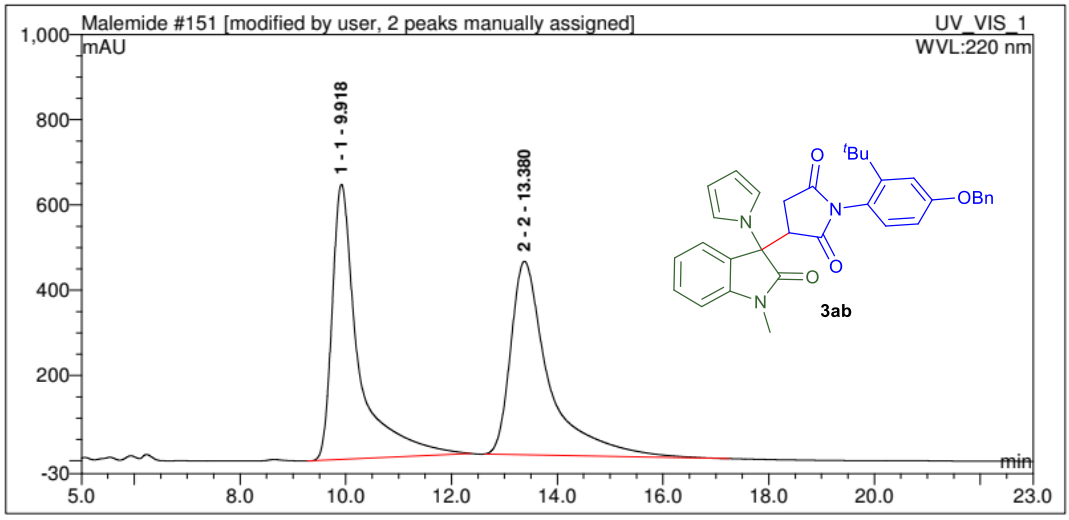
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.02	462.6273	49.5411176	481.3509	n.a.
2	2	29.26	471.198	50.4588824	268.302	n.a.



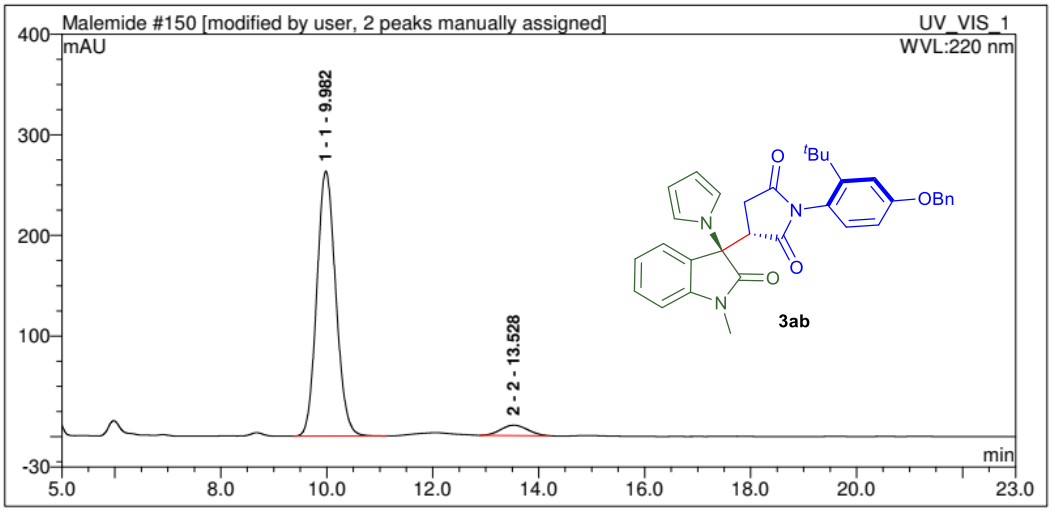
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.04166667	410.6984	97.51690426	437.9088	n.a.
2	2	30.17	10.45771	2.483095744	7.73625	n.a.



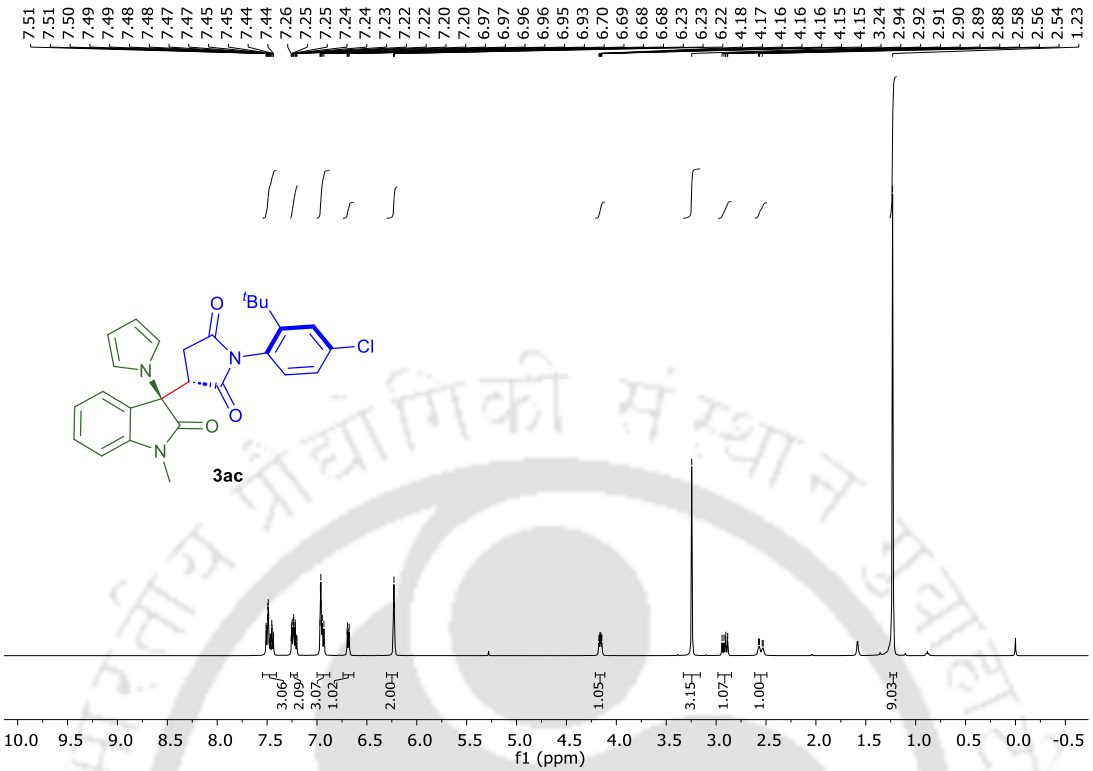


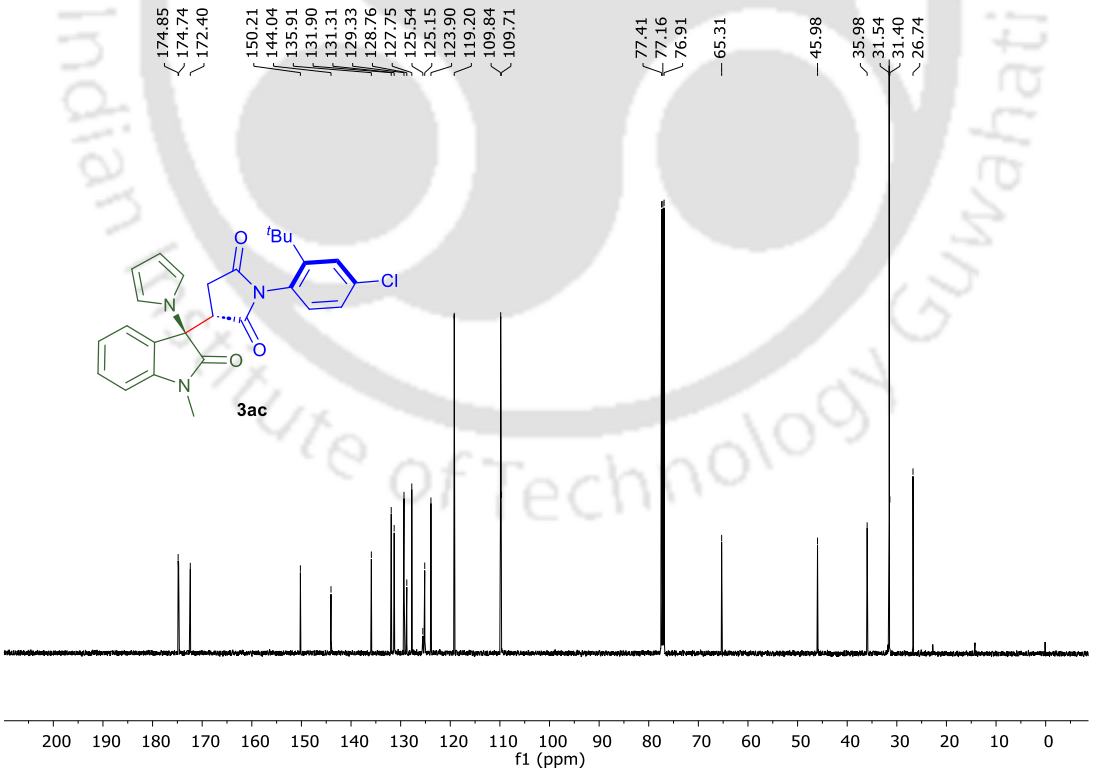


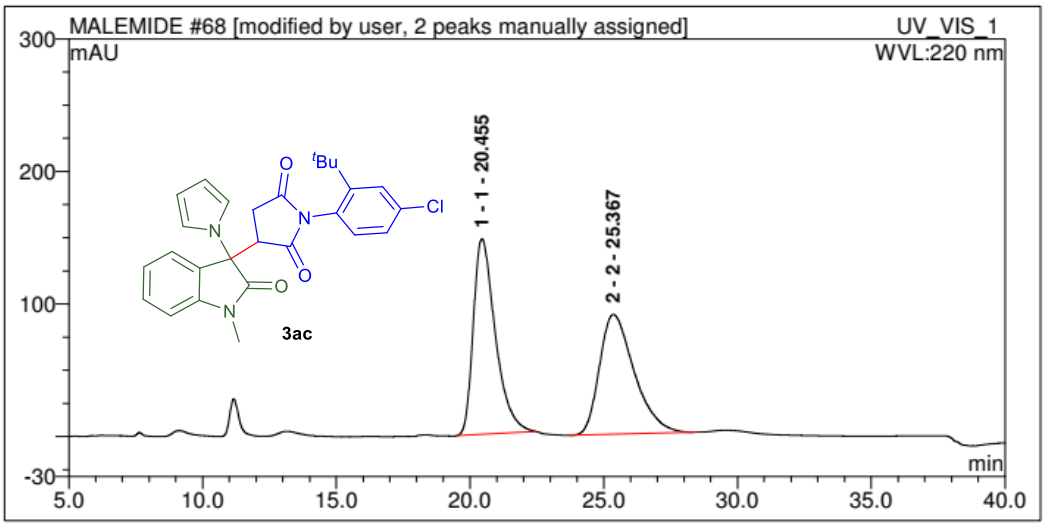
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.918333333	374.0892	49.64500484	645.4455	n.a.
2	2	13.38	379.4392	50.35499516	453.6413	n.a.



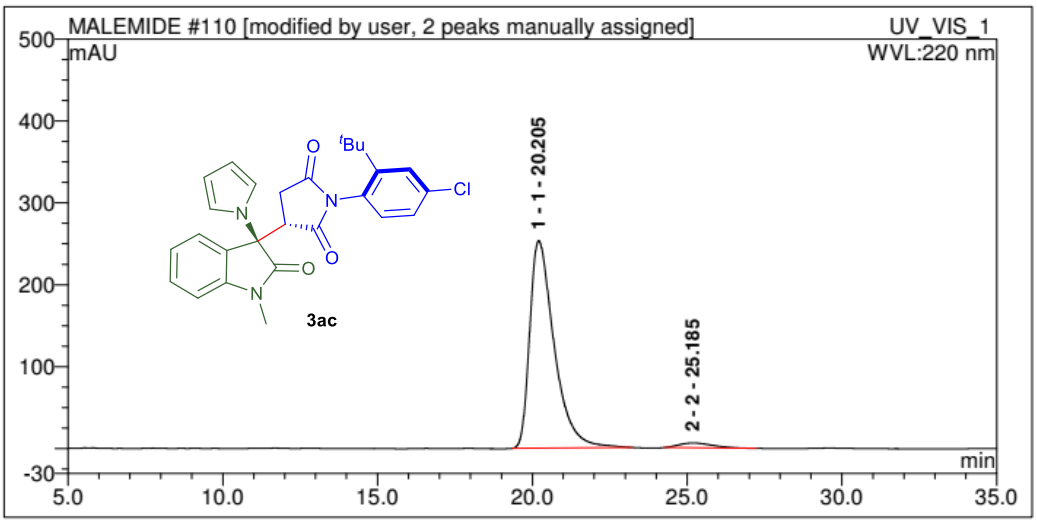
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.981666667	109.0603	94.79307076	263.4513	n.a.
2	2	13.52833333	5.990618	5.206929238	10.22345	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.46	141.1377	50.90720225	147.5536	n.a.
2	2	25.37	136.107	49.09279775	90.378	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.21	232.2214	96.944035	253.3744	n.a.
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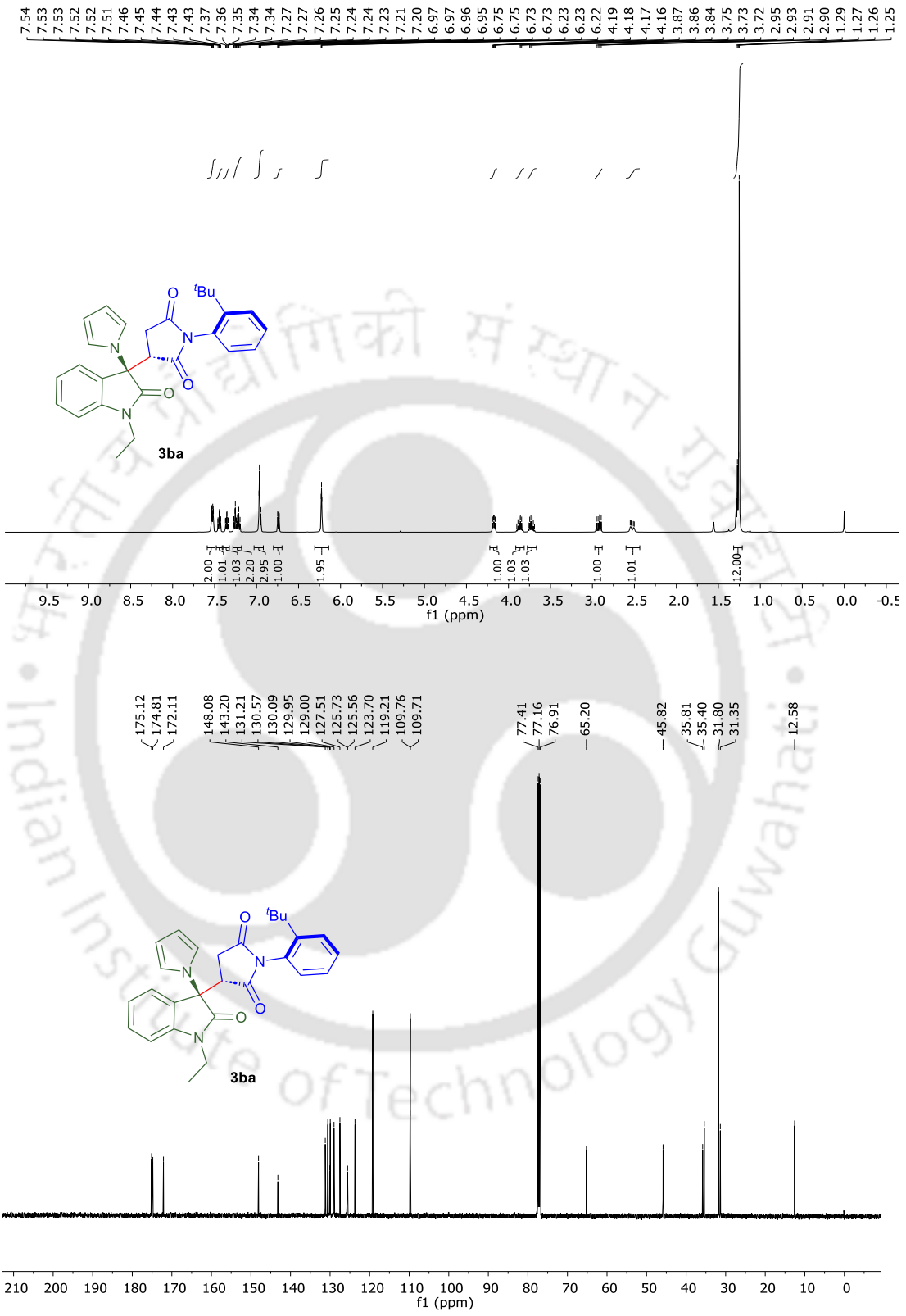
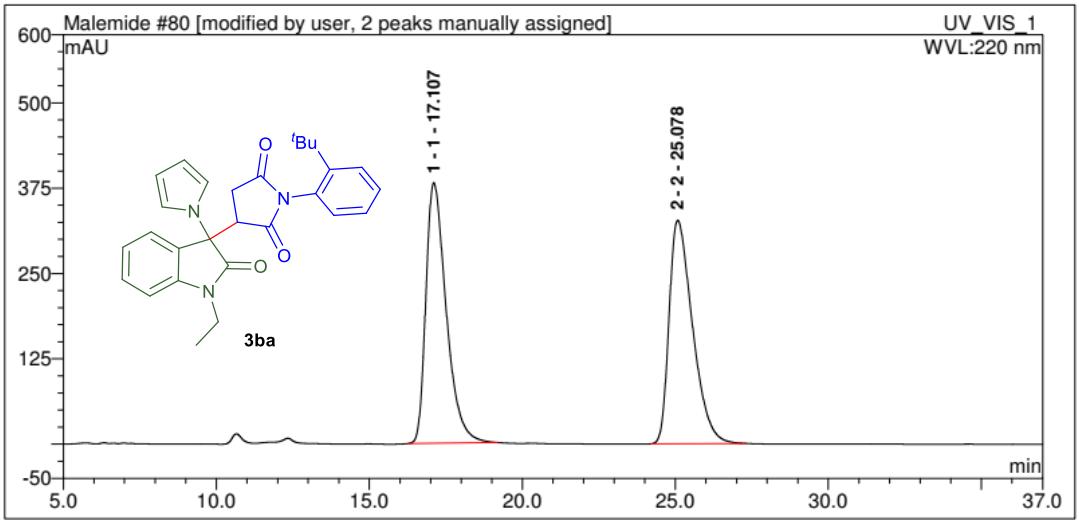
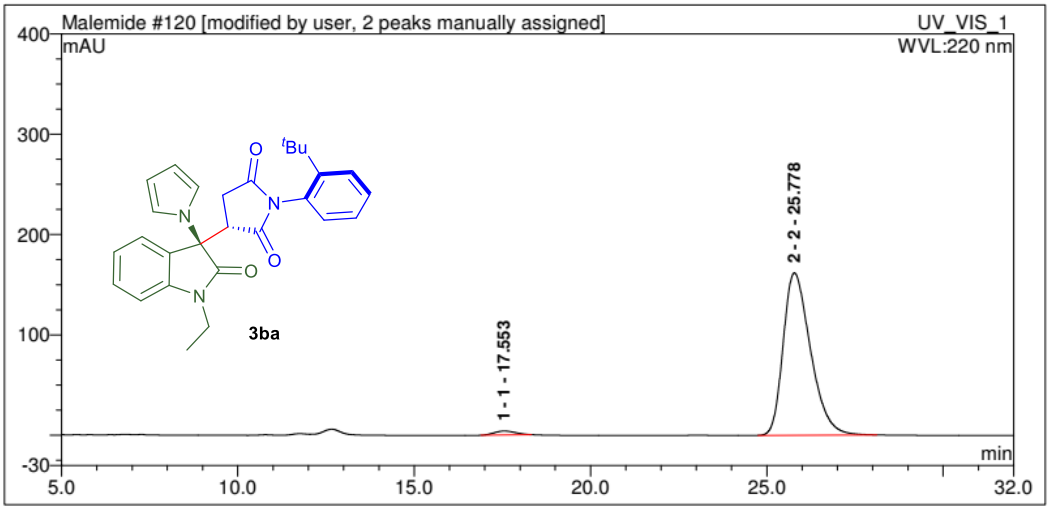
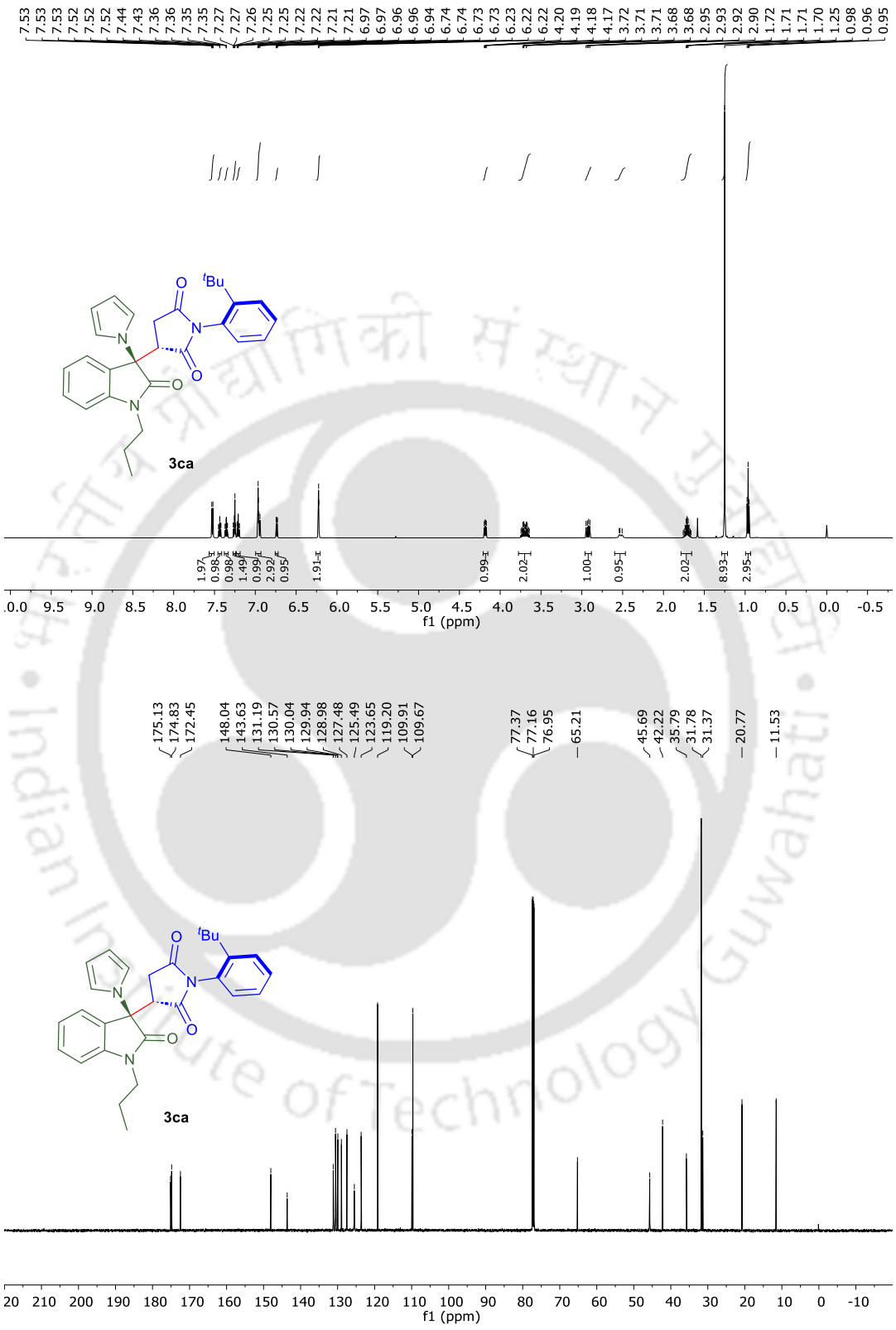


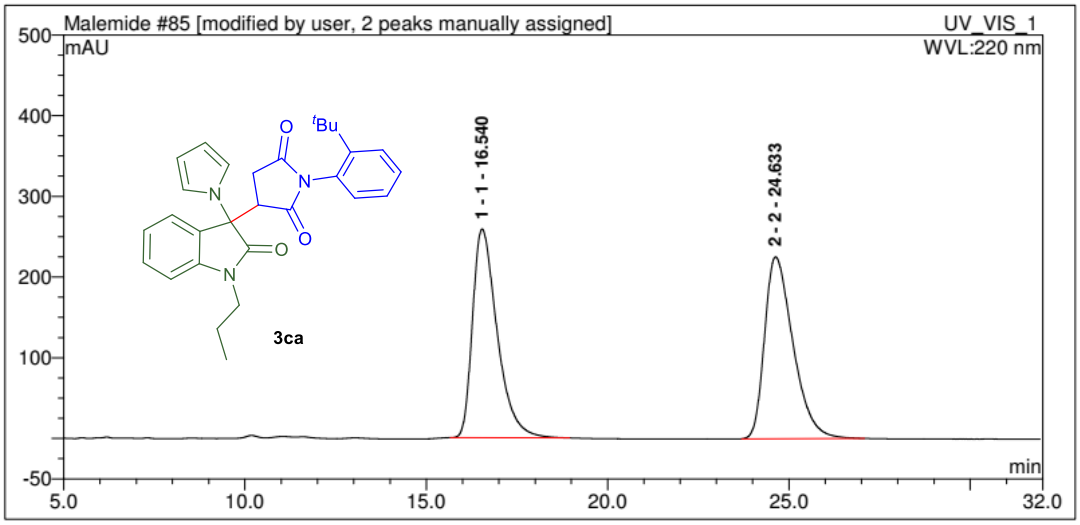


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.10666667	293.7917	50.28170575	381.6226	n.a.
2	2	25.07833333	290.4997	49.71829425	327.5708	n.a.

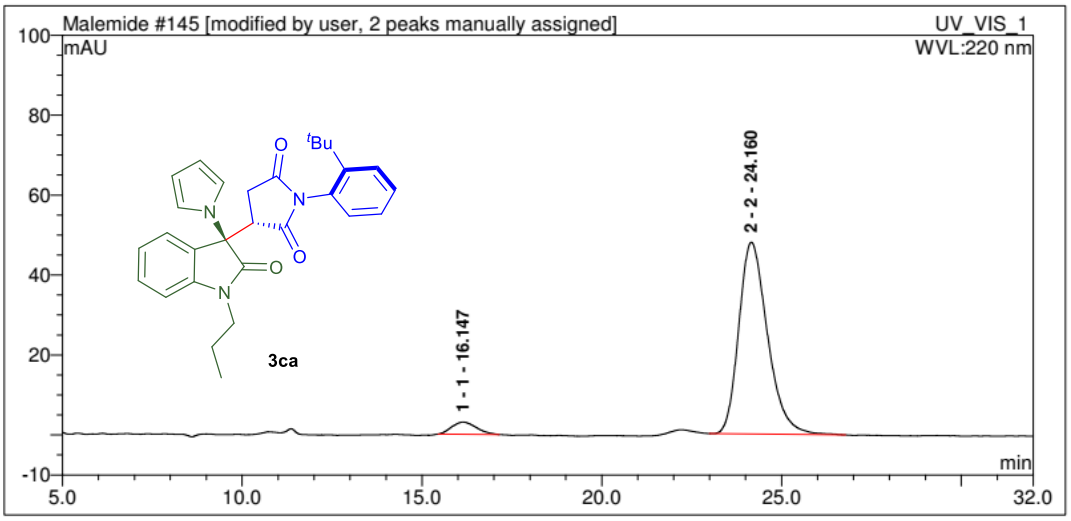


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.55333333	2.765239	1.865653177	3.92613	n.a.
2	2	25.77833333	145.453	98.13434682	161.6892	n.a.





No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	16.54	203.8467	49.84770565	258.8156	n.a.
2	2	24.63333333	205.0923	50.15229435	225.3354	n.a.



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1	1	16.14666667	2.422557	5.164480905	3.0659	n.a.
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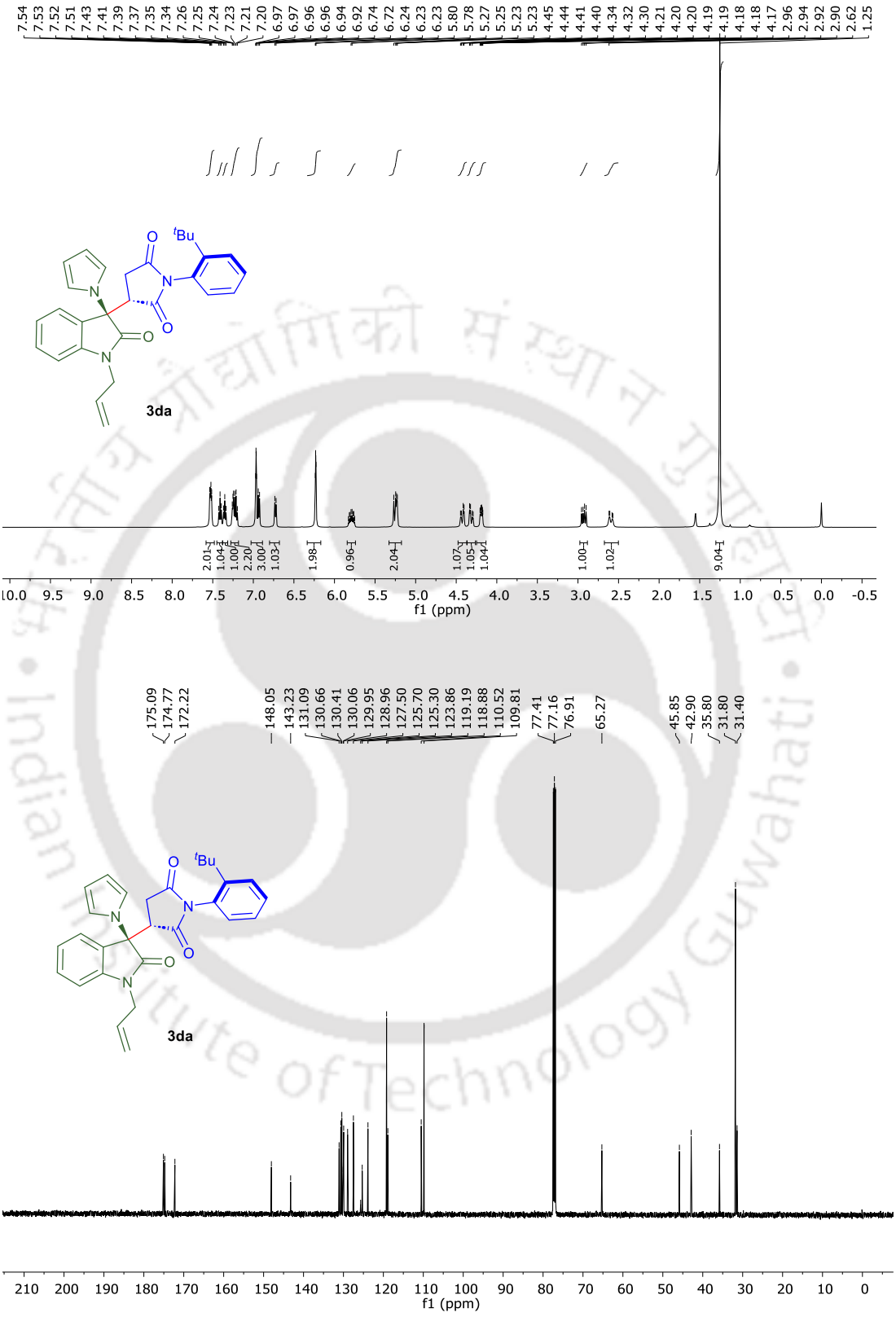
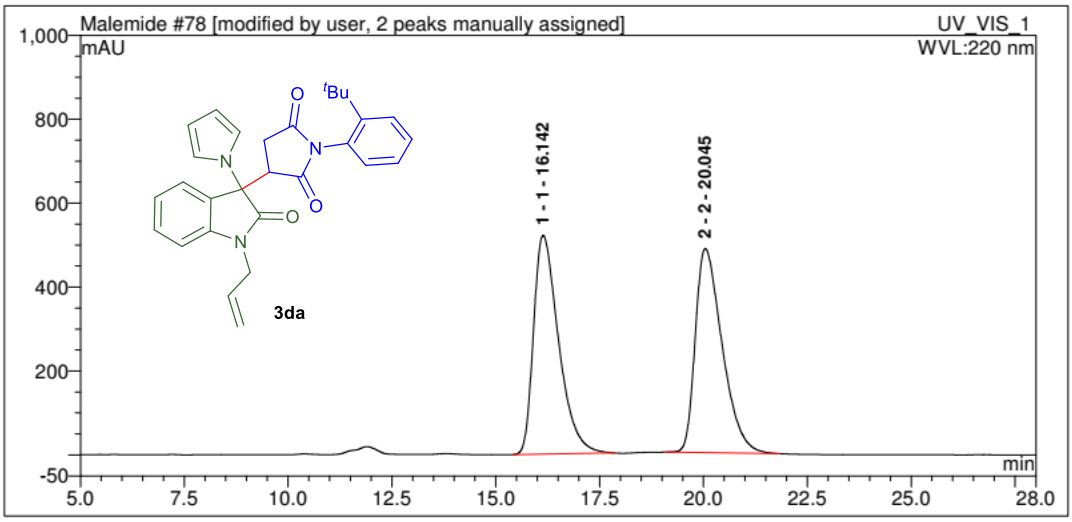
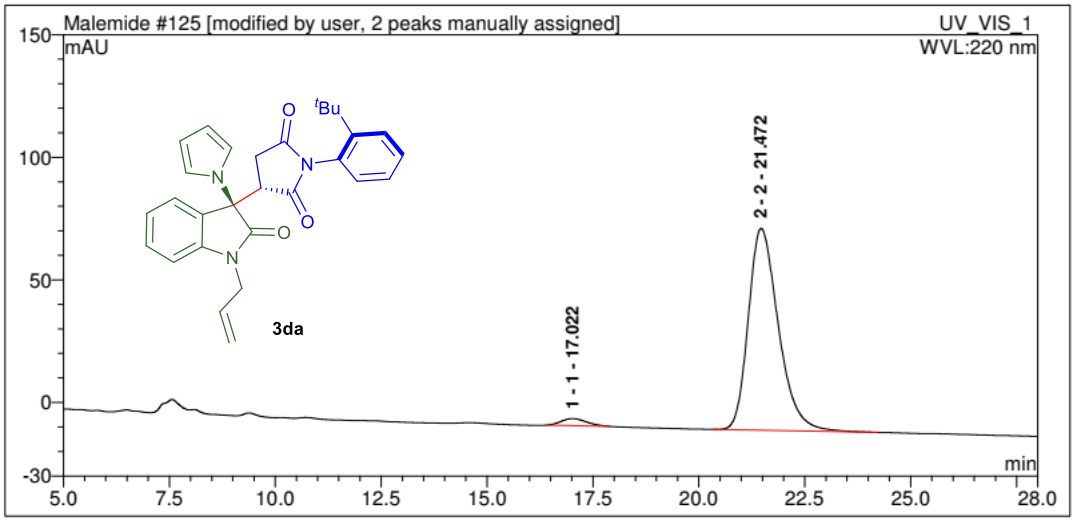




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	16.14166667	364.0194	49.94707897	521.3576	n.a.
2	2	20.045	364.7907	50.05292103	486.129	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.02166667	1.992352	2.847678573	2.85437	n.a.
2	2	21.47166667	67.97173	97.15232143	82.34522	n.a.

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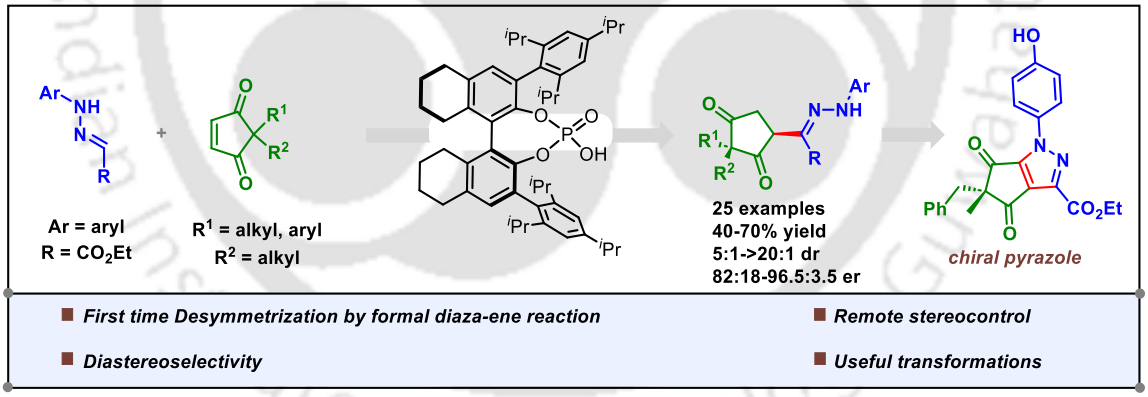
Chapter IV

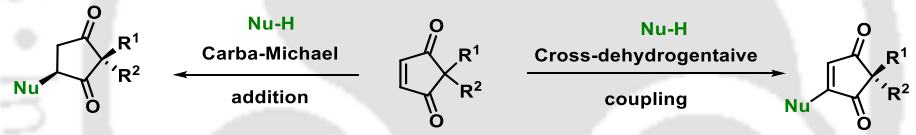
Organocatalytic Asymmetric Desymmetrization of Cyclopentene-1,3-diones via Formal Diaza-ene Reaction with Donor–Acceptor Hydrazones

Abstract: Here in, we disclose a catalytic asymmetric desymmetrization of cyclopentene-1,3-diones through formal diaza-ene reaction/tautomerization with donor-acceptor hydrazones. It was found that H8-TRIP chiral phosphoric acid worked well for this process. Chiral cyclopentane 1,3-diones embedded with the hydrazone motif were obtained in good to high yields with excellent diastereo- and good to high enantioselectivities. The scope of the reaction was broad, and some synthetic application, such as chiral pyrazole synthesis have been shown.



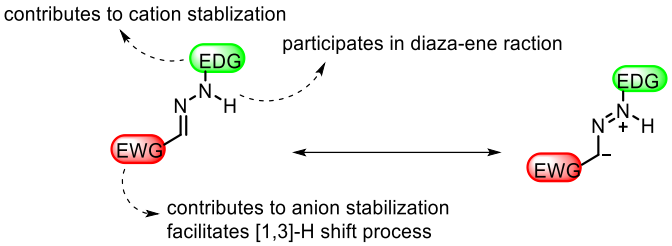
4.1 Introduction

One of the most effective techniques in organic synthesis is the enantioselective desymmetrization process of meso or prochiral molecules.[1] It often leads to the synthesis of stereochemically complicated molecules with several stereogenic centers in a single step. One advantage of desymmetrization reactions is that the symmetric precursors can be produced quickly either from simple starting materials or from readily available precursors. As a result, over time, numerous reports on desymmetrization reactions have been released. An effective technique for producing valuable synthons for bioactive chemicals is the desymmetrization of prochiral cyclopentene-1,3-dione by alkylation.[2] Consequently, throughout the past few years, numerous research groups have worked significantly to achieve desymmetrization of prochiral cyclopentene-1,3-dione using diverse nucleophiles (Scheme 1).[3]



Scheme 1. Strategies for desymmetrization of prochiral cyclopentenedione

On the other hand, hydrazones can be used as formyl anion equivalents in organic synthesis because of their broad spectrum of reactivity.[4] Initially, N,N-dialkylhydrazones were shown to be effective ligands and catalysts in asymmetric processes.[5] Aldehydes, trifluoromethyl ketones, α-keto esters, imines, *α,β*-unsaturated ketones, and other electrophiles have all been functionalized using the unique aza-enamine (nucleophilic) properties of formaldehyde N,N-dialkyl hydrazones.[6] In comparison, asymmetric conjugate addition of donor-acceptor N-monosubstituted hydrazones in organocatalysis still remains problematic and challenging because of their dual nature (Scheme 1B).[7] In fact both aza-Michael addition[8] and carbo-Michael addition[9] (formal diaza-ene reaction) were reported and the site selectivity was dependent on the nature of N-monosubstituted hydrazones used in each organocatalytic reaction.

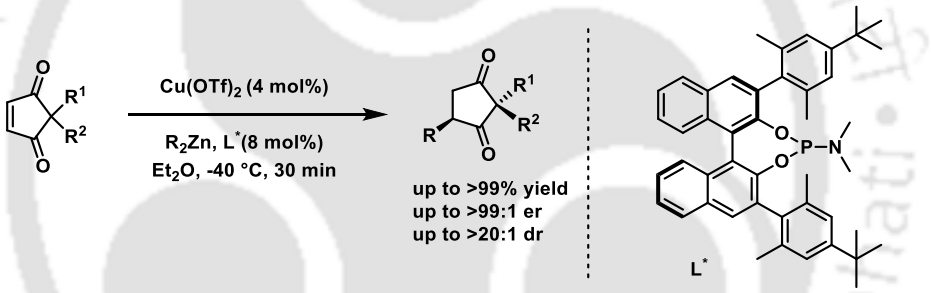


Scheme 2. Reactivity of donor-acceptor hydrazone

4.2 Literature Survey

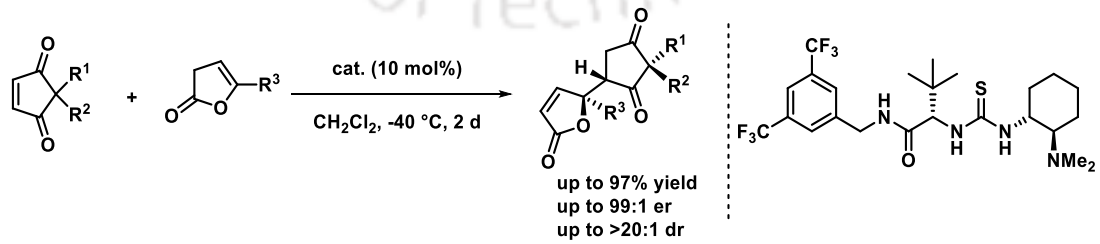
4.2.1 Previous reports on enantioselective desymmetrization of cyclopentene-1,3-diones:

In 2012 Mikami group reported Cu and ligand catalyzed enantioselective desymmetrization of achiral cyclopentene-1,3-diones (Scheme 3).[3a] By this procedure using a minimal catalyst loading in a one-pot operation, a range of complex cyclopentane derivatives were obtained with excellent enantioselectivities (up to >99% ee).



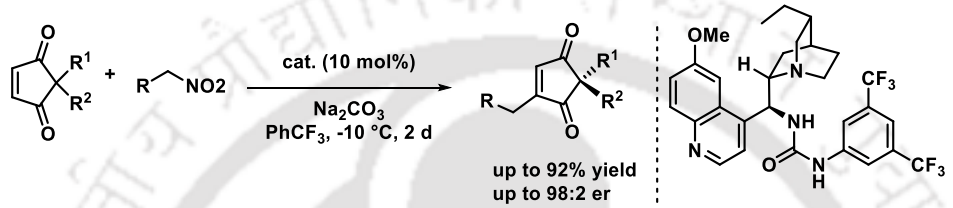
Scheme 3: Copper(I)-catalyzed asymmetric desymmetrization of prochiral cyclopentene-1,3-diones

In 2014, Mukherjee group used a tertiary amine-thiourea bifunctional catalyst to facilitate the direct vinylogous nucleophilic addition of deconjugated butenolides, resulting in a highly effective desymmetrization process for 2,2-disubstituted cyclopentene-1,3-diones (Scheme 4).[3b] Excellent enantioselectivity and high diastereoselectivity were achieved by the products with two quaternary and a tertiary stereocenter.



Scheme 4. Desymmetrization of 2,2-disubstituted cyclopentene-1,3-diones via direct vinylogous nucleophilic addition of deconjugated butenolides

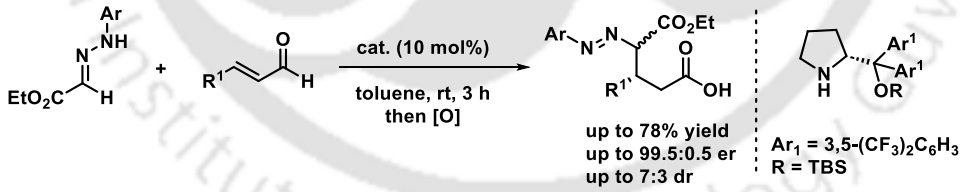
In 2015, using a dihydroquinine-based bifunctional urea derivative as a catalyst, Mukherjee group created an enantioselective alkylative desymmetrization of prochiral 2,2-disubstituted cyclopentene-1,3-diones (Scheme 5).[3c] Using readily available, inexpensive, and air-stable nitroalkanes as the alkylating agent, this formal C(sp^2)-H alkylation is a near-ideal desymmetrization that yields products with an all-carbon quaternary stereogenic center in high enantioselectivities and in good to excellent yields.



Scheme 5. Desymmetrization by organocatalytic enantioselective formal C(sp^2)-H alkylation

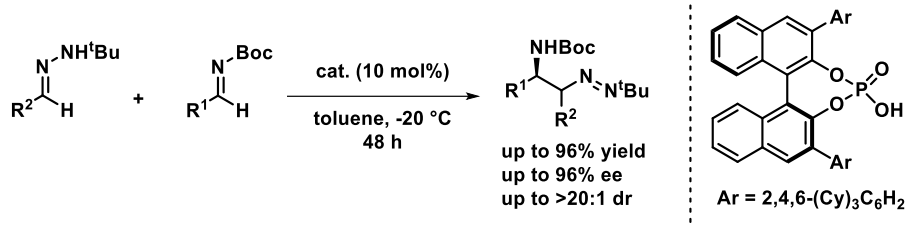
4.2.2 Previous reports on enantioselective reactions of hydrazones:

In 2012 Vicario group demonstrated that, in presence of a chiral secondary amine catalyst, donor-acceptor hydrazones can take part in enantioselective formal diaza-ene reactions with *α,β*-unsaturated aldehydes via imiminium activation (Scheme 6).[8b] The process produces *γ*-azoaldehydes, which undergo an oxidation/[1,3]-hydride shift sequence to get enantiopure *γ*-hydrazono carboxylic acids.



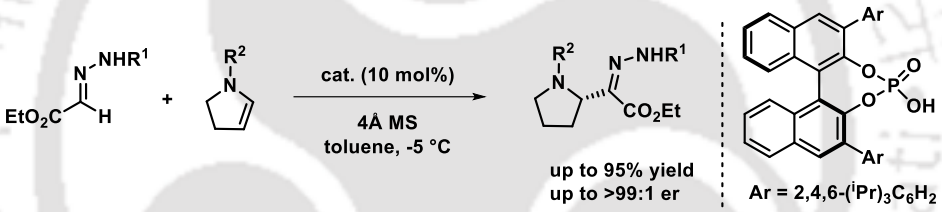
Scheme 6. Enantioselective conjugate addition of donor-acceptor hydrazones to *α,β*-unsaturated aldehydes

In 2017 Zhu described chiral phosphoric acid catalyzed enantioselective imino aza-enamine reaction between N-tert-butyl hydrazones and N-Boc imines for the synthesis of enantioenriched *β*-amino diazenylalkanes (Scheme 7).[8f] This was the first instance of a catalytic asymmetric transformation employing N-alkyl hydrazones as *α*-azo carbanion equivalents to produce two continuous stereocenters in a highly chemo-, diastereo-, and enantioselective way.



Scheme 7. Organocatalytic nucleophilic addition of hydrazones to imines

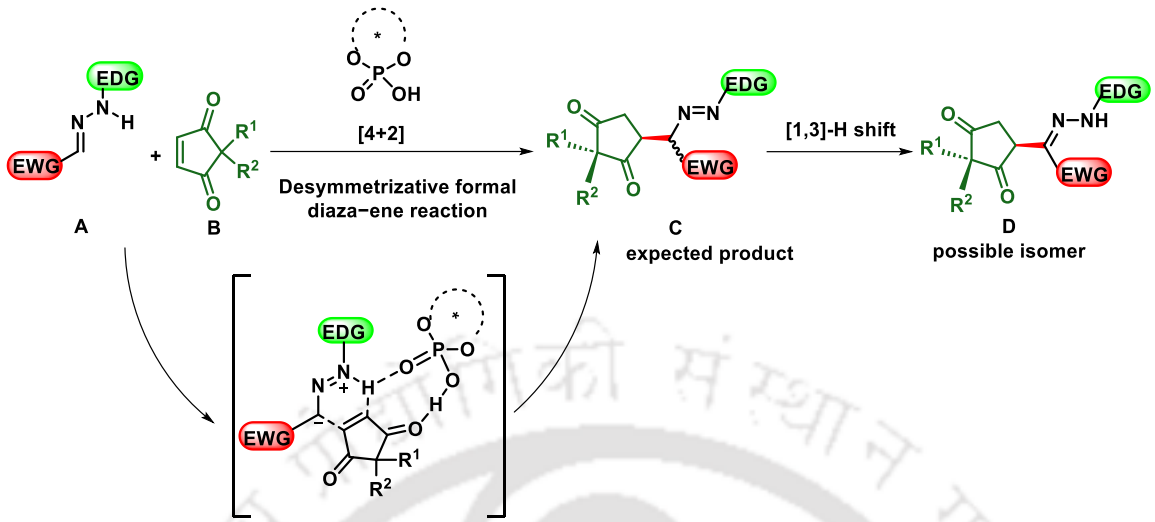
In 2018, Vicario group have shown that in the presence of a potent chiral Brønsted acid catalyst dihydropyrrole derivatives are effective substrates for the generation of chiral quaternary N-acyliminium salt intermediates (Scheme 8).[8g] A broad variety of enantiopure α-hydrazono proline derivatives were produced in good yields by their reaction with N-monosubstituted hydrazones. Starting from β-disubstituted enamides, two contiguous stereocentres can even be produced.



Scheme 8. Enantioselective addition of hydrazones to enamides

4.3 Concept

As far as the chemical literature is concerned, the use of donor-acceptor hydrazone in catalytic enantioselective desymmetrization through formal diaza-ene-type reactions is still novel. It is still unknown whether this reaction can even be performed asymmetrically in the absence of metal. Therefore, it is still very desirable to find new synthetic methods for the organocatalytic asymmetric desymmetrization of cyclopentenediones via the formal diaza-ene reaction. From the previous literature survey, we hypothesised that in presence of chiral phosphoric acid, donor-acceptor hydrazone **A** can undergo desymmetrizing formal diaza-ene reaction with prochiral 2,2-disubstituted cyclopentene-1,3-dione **B** to form adduct **C**. Additionally, there is also a possibility this adduct **4** can undergo 1,3-H shift to form product **D**.

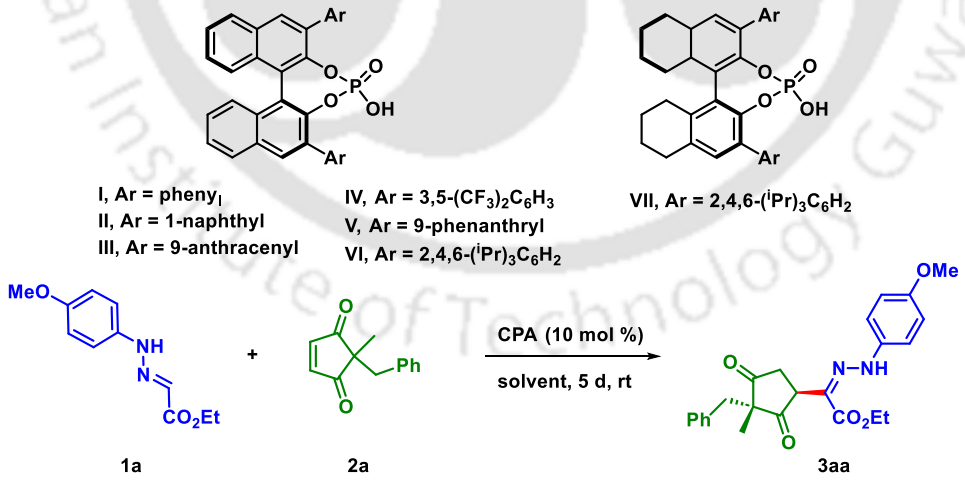


Scheme 9: Proposed route for desymmetrization of cyclopentenediones with hydrazone

4.4 Results and Discussion

4.4.1 Optimization of catalyst and reaction conditions:

Table 1. Catalyst screening and optimization of reaction conditions



entry[a]	catalyst	solvent	yield[b]	dr[c]	er[d]
1	**I**	toluene	48	7:1	69:31
2	**II**	toluene	32	9:1	55:45
3	**III**	toluene	36	7:1	73:27
4	**IV**	toluene	52	6:1	60:40
5	**V**	toluene	28	5:1	61:39
6	**VI**	toluene	50	16:1	85:15
7	**VII**	toluene	72	>20:1	89:11
8	**VII**	xylene	73	>20:1	90:10
9[e]	**VII**	xylene	70	>20:1	94.5:5.5
10[f]	**VII**	**xylene**	**68**	**>20:1**	**95.5:4.5**

[a]Unless mentioned, 0.075 mmol of **1a** and 0.05 mmol of **2a** were stirred in 0.5 mL solvent at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC. [e]With 5 mol% catalyst. [f]With 5 mol% catalyst and in 1.0 ml solvent.

To begin our investigation, we used 3,3'-phenyl substituted phosphoric acid **I** to conduct a model reaction between hydrazone **1a** and cyclopentene-1,3-dione **2a** in toluene at room temperature (Table 1, entry 1). To our delight after stirring for five days at room temperature, the desymmetrization product **3aa** was obtained in 48% yield with 7:1 dr and 69:31 er. The reaction did not benefit from naphthyl substituted phosphoric acid **II** (Table 1, entry 2). Enantioselectivity of **3aa** was marginally enhanced with 9-anthracenyl substituted phosphoric acid **III** (Table 1, entry 3). Additionally, catalysts **IV** and **V** were unsuitable for the reaction, which contained 3,5-ditrifluro-methylphenyl and 9-phenanthryl substituents, respectively (Table 1, entries 4-5). Higher yield and enantioselectivity were achieved with TRIP catalyst **VI** (Table 1, entry 6). Finally, H8-TRIP **VII** was proved to be the best catalyst and product **3aa** was obtained in 72% yield with 89:11 er as a single diastereomer (Table 1, entry 7). To further improve the enantioselectivity, various solvents were tested. The enantioselectivity was somewhat improved in xylene (Table 1, entry 8). Next, using 5 mol% of catalyst **VII**, the reaction was examined (Table 1, entry 9). We were surprised to find that the enantioselectivity increased to 94.5:5.5 er with minimal impact on the reaction's yield (Table 1, entry 9).

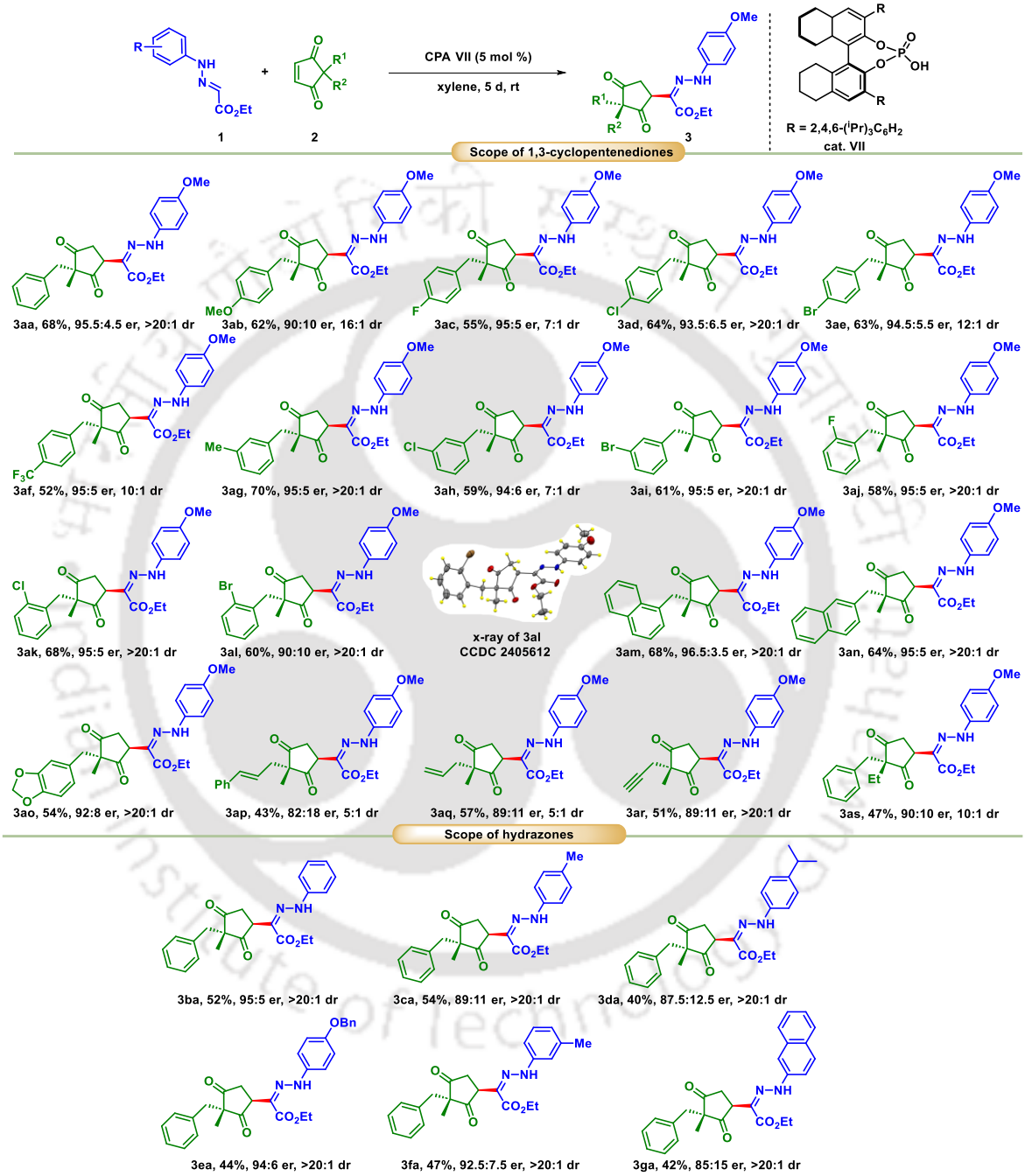
Finally, product **3aa** was isolated in 68% yield with 95.5:4.5 er after the reaction was examined in 0.05(M) xylene (Table 1, entry 10).

4.4.2 Substrate scope:

Following the establishment of optimal conditions, the scope of this desymmetrization process was examined. First, hydrazone **1a** was used to test cyclopentene-1,3-diones **2** with various substituents at the aryl group (Scheme 10). Remarkably, only single diastereomer was formed in the majority of cases. Initially, different *para*-substitutions were investigated, and the products **3aa**-**3af** showed promising results. Cross-coupling reactions could be used to further elaborate the halo substituted products **3ac**-**3ae**. Following that, a number of *meta*-substitutions were examined, and the outcomes for products **3ag**-**3ai** were comparable. *Ortho*-Substitutions were also tolerated, and the products **3aj**-**3ak** with 2-fluoro and 2-chloro substitutions, respectively, showed positive outcomes. The enantioselectivity of compound **3al**, which had 2-bromo substitution, was marginally reduced. The structure of **3al** was ambiguously confirmed from X-ray crystallography. After checking for 1-naphthyl substitution, the product **3am** was isolated in 68% yield with 96.5:3.5 er. Thus, cyclopentene-1,3-dione **2n** with a 2-naphthyl group was examined in the reaction, and the product **3an** was obtained in a satisfactory yield with 95:5 er. Product **3ao**, which contains the 1,3-dioxolane motif, was found to have somewhat lower enantioselectivity. Cinnamyl group containing substrate **2p**, also takes part in the reaction, however, product **3ap** showed moderate enantioselectivity. Additionally, the products **3aq** and **3ar** demonstrated moderate enantioselectivities when aliphatic moieties such as allyl and propargyl groups were examined. Also, somewhat lower enantioselectivity was observed for product **3as**, where the methyl group is replaced with an ethyl group.

After that, hydrazones **1** with different aryl group substitutions were prepared and employed in the reaction (Scheme 10). First, hydrazone **1b** with a phenyl group was screened, and product **3ba** was isolated with a 95:5 er and 52% yield. After that, 4-alkyl substitutions were examined, and the products **3ca** and **3da** showed gratifyingly positive outcomes. The reaction was then initiated with hydrazone **1e** having a 4-benzyloxy group, and product **3ea** was isolated in moderate yield with 94:6 er. A meta-tolyl group containing

hydrazone **1f** also took part in the reaction to produce compound **3fa** with 92.5:7.5 er. Furthermore, 2-naphthyl substituted hydrazone **1g** also produce the product **3ga** with moderate enantioselectivity.

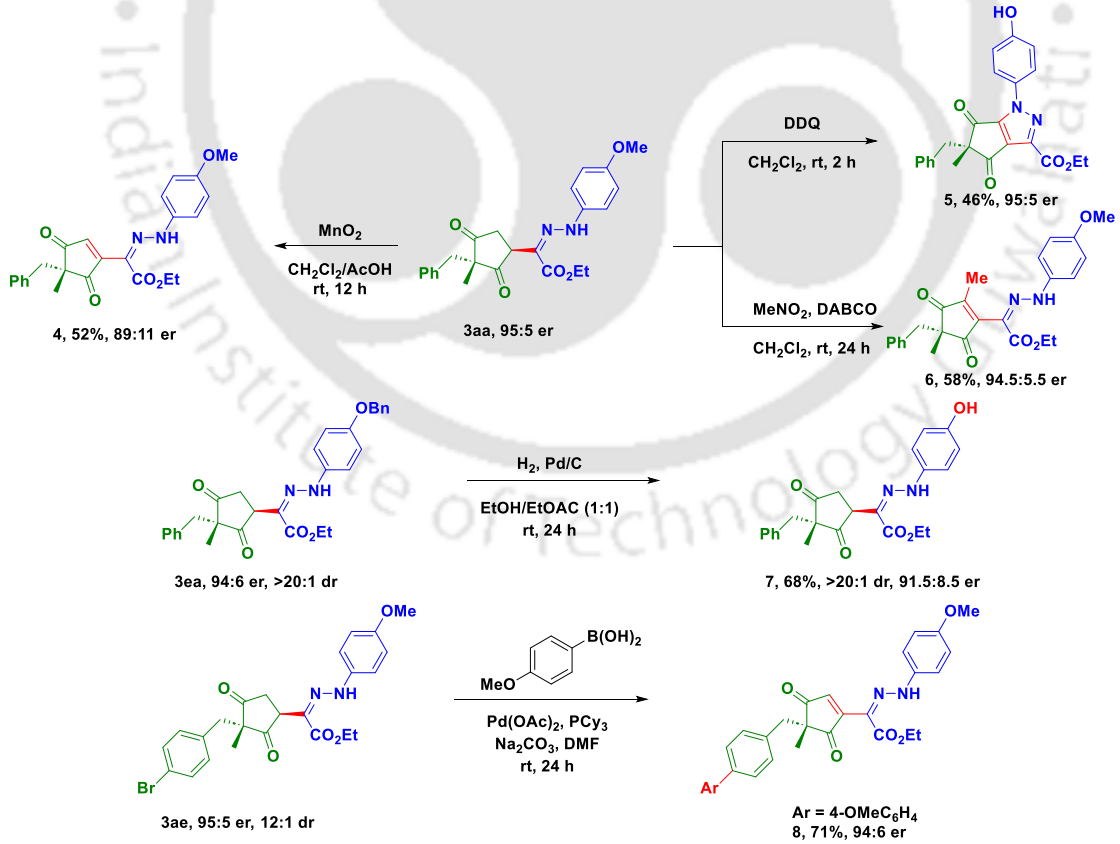


Scheme 10. Substrate scope[a]

[a]The reactions were carried out in the conditions as indicated above with 0.15 mmol of **1**, 0.1 mmol of **2** and 5 mol% cat. in 2 ml dry xylene. Yields correspond to the isolated yields after silica gel column chromatography, dr was determined by ^{1}H NMR and ee was determined by HPLC.

4.4.3 Synthetic transformation:

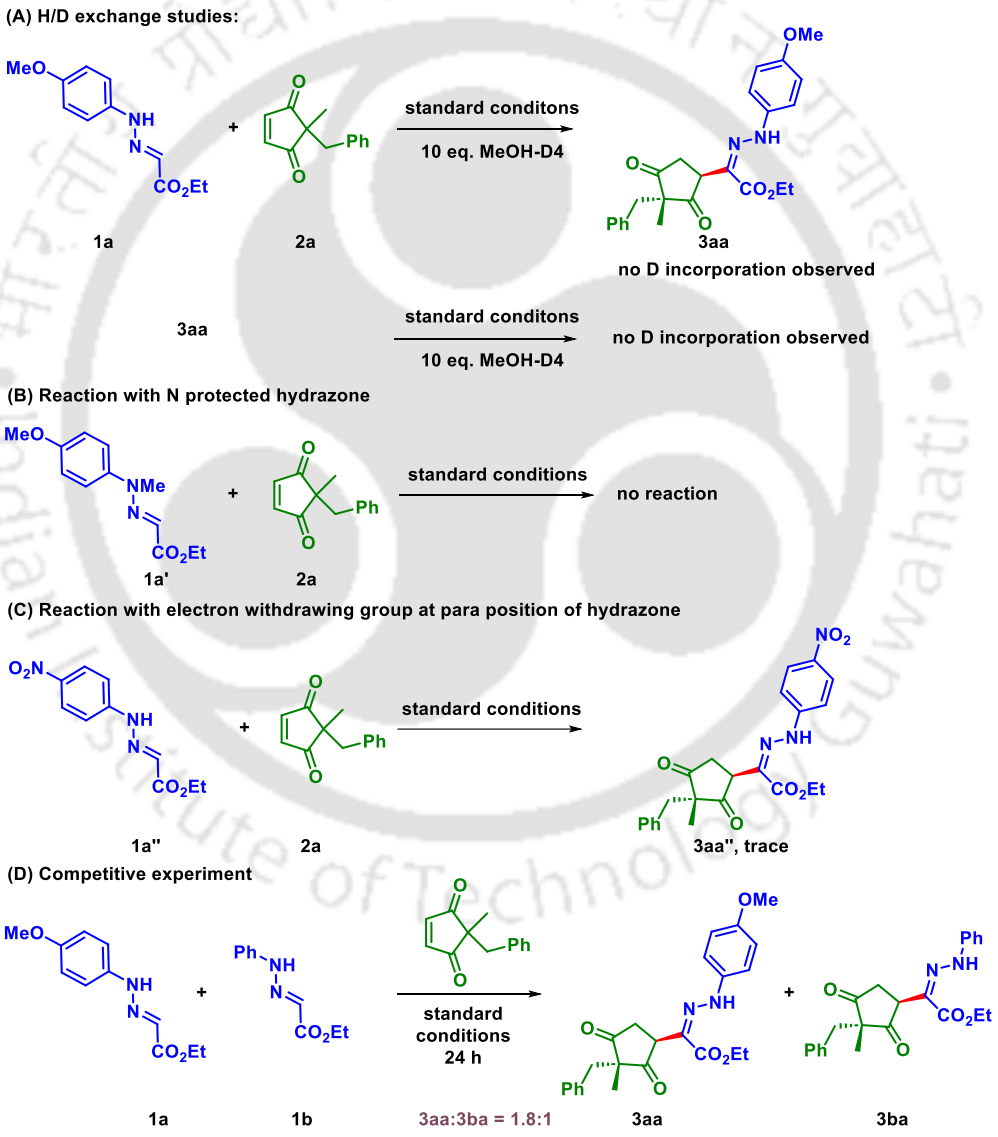
To demonstrate the synthetic potential of our method, a series of synthetic transformation reactions were carried out (Scheme 11). First, **3aa** was subjected to an oxidation reaction with MnO_2. This led to formation of **4** in 52% yield with a slight enantioselectivity erosion. After that, **3aa** was treated with DDQ. To our surprise, the cyclization reaction and O-benzyl group deprotection occurred simultaneously to produce pyrazole product **5** in moderate yield while retaining enantioselectivity. Compound **3aa** was then treated with nitromethane in presence of DABCO. To our delight, one pot oxidation, Michael addition, and nitro group removal resulted in a 58% yield of methylated compound **6** with no enantioselectivity erosion. The *O*-benzyl group deprotection process was then carried out on **3da** with Pd/C in the presence of hydrogen, producing compound **7** in 68% yield with nearly intact enantiopurity. Lastly, Suzuki coupling reaction was performed with **3ae** and 4-methoxyphenylboronic acid and coupling product **8** was obtained with concomitant oxidation of the cyclopentadiene ring where enantioselectivity was also preserved.



Scheme 11. Synthetic transformation

4.4.4 Mechanistic studies:

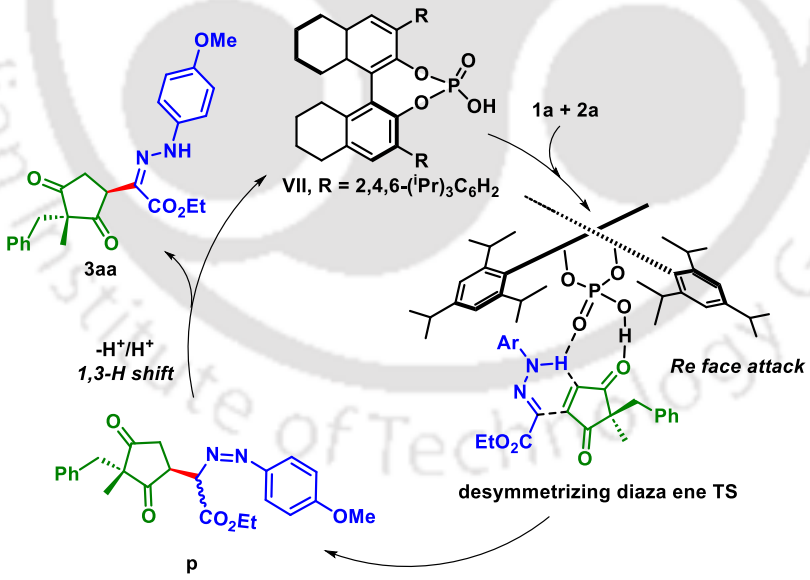
In order to understand the reaction mechanism, we conducted few experiments (Scheme 12). Initially, methanol-D4 solvent was used in deuterium incorporation experiments. At first, 10 equivalents of methanol-D4 were used under standard reaction conditions; however, the isolated product **3aa** (Scheme 12A) showed no signs of D-incorporation. The product **3aa** was then employed in the same experiment. No D-incorporation was discovered here either.



Scheme 12. Mechanistic studies

These experiments suggest the formal diaza-ene pathway for the reaction. Next, under standard reaction conditions, N-protected hydrazone **1a'** was reacted with **2a** (Scheme 12B). However, there was no product formation observed. It suggests that N-H is crucial for the catalyst's activation of substrate **1a**. Similarly, we believed that an electron-withdrawing substituent containing hydrazone might not be able to undergo the reaction because of its electron-withdrawing deactivation effect on hydrazone in order to further illustrate the push-pull effect on hydrazone **1**. As a result, *para*-NO_2 substituted hydrazone **1h** was employed in this reaction (Scheme 12C). As expected, only a trace amount of product was produced, suggesting that the reaction needs an electron-donating/electron-neutral group at hydrazone nitrogen atom. A competition experiment between electronically different substrates were performed and it was found out that reaction with electron-rich *para*-methoxy substituted hydrazone **1a** proceeded 1.8 times faster than the hydrazone **1b** (Scheme 12D). This further indicates the role of the electron-donating group on hydrazone for the observed product formation.

4.4.5 Plausible reaction mechanism:



Scheme 13. Plausible reaction mechanism

Based on the absolute configuration a plausible mechanism has been suggested (Scheme 13). It is anticipated that catalyst **VII** will favour the formal diaza-ene reaction by simultaneously activating hydrazone **1a** and cyclopentene-1,3-dione **2a**. Additionally, the

intermediate **P** is created as a result of this cycloaddition occurring on the *Re face* of the double bond of **2a**. Lastly, product **3aa** is produced by tautomerization of intermediate **P**.

4.5 Conclusion

In conclusion, we have shown a catalytic asymmetric desymmetrization of cyclopentene-1,3-diones via a formal diaza-ene reaction/tautomerization using donor-acceptor hydrazones. The use of donor-acceptor hydrazones in an enantioselective desymmetrization reaction has never been reported before, until now. Under ambient reaction conditions, the readily available H8-TRIP catalyst produced the desired chiral cyclopentane 1,3-diones embedded with a hydrazone motif in good to high yields with excellent diastereo- and good to high enantioselectivities. Synthetic transformation like MnO_2 oxidation and pyrazole formation, direct SP^2 C-H funtionalization, oxidative Suzuki coupling have also been demonstrated.

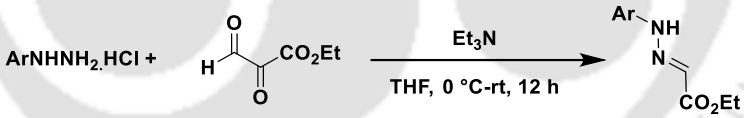
4.6 Experimental section

4.6.1 General Information:

Same as Chapter II.

4.6.2 General procedure for the synthesis of hydrazones (1):

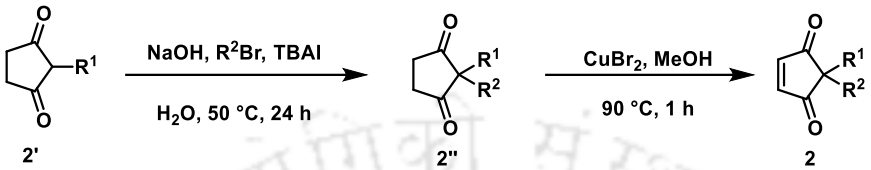
Hydrazones were prepared according to reported procedure.[11]



Hydrazone derivatives were prepared according to literature procedure as followed. A suspension of the corresponding hydrazine hydrochloride (10 mmol, 1.0 eq.) in anhydrous tetrahydrofuran (10 mL) was treated with triethylamine (10 mmol, 1.0 eq.) before the corresponding aldehyde (10 mmol, 1.0 eq.) was added dropwise to the reaction mixture at 0 °C. The mixture was stirred at this temperature for 30 minutes and then for 12 h at room temperature. The crude was filtered under vacuum and the filtrates were concentrated in vacuo. The resulting solids were dissolved in dichloromethane (15 mL) and washed with HCl 1M (2 × 10 mL) and water (2 × 10 mL). The resulting organic layer was dried over Na_2SO_4 and concentrated in vacuo. The resulting solids were triturated with diethyl ether or purified by flash column chromatography to obtain the desired hydrazone.

4.6.3 General procedure for the synthesis of 2,2-disubstituted cyclopentene-1,3-dione (2):

2,2-disubstituted cyclopentene-1,3-dione were prepared according to reported procedures.[12]



To a solution of **2'** (20 mmol, 1.0 equiv.) in H_2O (80 mL) was added NaOH (20 mmol, 1.0 equiv.) and TBAI (0.2 mmol, 0.01 equiv.). The mixture was stirred at room temperature for 20 min. Then R^2Br (30 mmol, 1.5 equiv.) was added. The reaction mixture was stirred at 50 °C for 24 h and then cooled to room temperature. The reaction mixture was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford target compounds.

To a solution of **2''** (2.41 g, 11.92 mmol, 1.0 equiv.) in 86 mL of MeOH was added copper(II) bromide (5.86 g, 26.22 mmol, 2.2 equiv.) and the resulting brown solution was stirred at 90 °C under argon atmosphere. After 1 h the reaction mixture was cooled to r.t., quenched with 20 mL of distilled water followed by 20 mL of 1 M aq. HCl solution, 50 mL of Et2O was added and the organic phase was separated from aqueous phase. Aqueous phase was back-extracted with Et2O (2 × 20 mL). The combined organic phase was dried over anh. MgSO4 and concentrated under reduced pressure. The crude reaction mixture was purified by silica-gel column chromatography (10% EtOAc in petroleum ether) to obtain a yellow crystalline solid.

4.6.4 General procedure for the synthesis of catalysts:

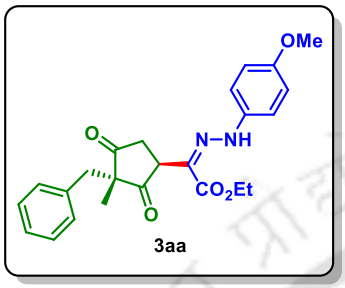
The catalyst (**I-VII**) was prepared according to reported procedures.[13]

4.6.5 General procedure for the catalytic enantioselective synthesis of 3:

In an oven dried 5 mL rb, hydrazone **1** (0.15 mmol), 2,2-disubstituted cyclopentene-1,3-dione **2** (0.1 mmol) and 20 mol% of catalyst **VII** were taken under Ar. Then 2 mL of dry xylene was added to the reaction mixture and stirred at rt for 5 days. Progress of the

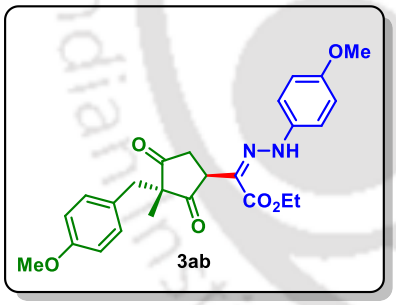
reaction was monitored by TLC. After the completion of reaction, the reaction mixture was subjected to directly in flash chromatography to obtain the product **3** (5-10% EtOAc in petroleum ether).

Ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3aa)



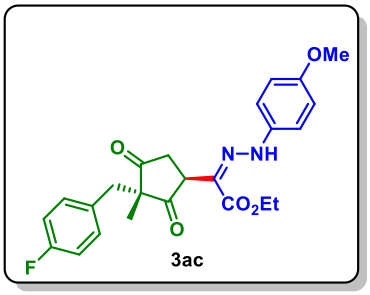
Yellow solid (28.7 mg, yield: 68%); M.P. 198-201 °C; R_f = 0.5 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.14 (s, 1H), 7.31 – 7.26 (m, 3H), 7.11 – 7.06 (m, 2H), 7.06 – 7.01 (m, 2H), 6.89 – 6.82 (m, 2H), 4.32 – 4.13 (m, 2H), 3.78 (s, 3H), 3.22 (dd, *J* = 11.4, 7.9 Hz, 1H), 2.97 (q, *J* = 12.8 Hz, 2H), 2.76 (dd, *J* = 19.0, 7.9 Hz, 1H), 2.41 (dd, *J* = 19.0, 11.4 Hz, 1H), 1.28 (m, 6H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 216.62, 216.07, 162.43, 155.81, 136.64, 135.60, 129.79, 128.85, 127.60, 123.62, 115.34, 114.83, 61.24, 58.80, 55.73, 52.17, 44.50, 42.02, 19.88, 14.38. **ESI HRMS**: calcd. for $C_{24}H_{27}N_2O_5$ $[M+H]^+$ 423.1914, found 423.1914. **HPLC Analysis**: er = 95.5:4.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.5 min, t_{minor} = 11.1 min).

ethyl (Z)-2-((1S,3R)-3-(4-methoxybenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ab)



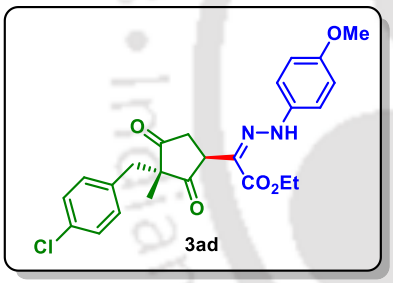
Yellow solid (28.0 mg, yield: 62%); M.P. 212-215 °C; R_f = 0.3 in 2:8 ethyl acetate/hexane; dr 16:1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 12.14 (s, 1H), 7.08 – 6.96 (m, 4H), 6.89 – 6.77 (m, 4H), 4.27 (dq, *J* = 10.1, 7.2 Hz, 1H), 4.19 (qd, *J* = 7.1, 3.9 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.27 (dd, *J* = 11.4, 7.7 Hz, 1H), 2.92 (q, *J* = 13.1 Hz, 2H), 2.75 (dd, *J* = 18.9, 7.8 Hz, 1H), 2.44 (dd, *J* = 18.9, 11.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 216.83, 216.30, 162.41, 158.99, 155.81, 136.66, 130.83, 127.55, 123.74, 115.35, 114.83, 114.17, 61.22, 58.91, 55.70, 55.34, 52.16, 43.79, 42.06, 19.67, 14.36. **ESI HRMS**: calcd. for $C_{25}H_{29}N_2O_6$ $[M+H]^+$ 453.2020, found 453.2024. **HPLC Analysis**: er = 90:10, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 31.6 min, t_{minor} = 14.1 min).

ethyl (Z)-2-((1S,3R)-3-(4-fluorobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ac)



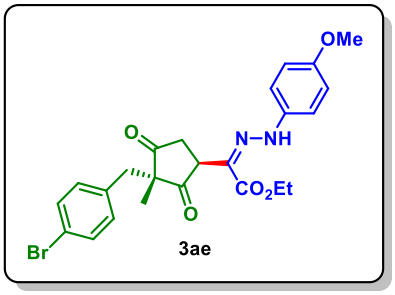
Yellow solid (24.2 mg, yield: 55%); M.P. 200-203 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr 7:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.15 (s, 1H), 7.08 – 7.02 (m, 4H), 7.01 – 6.95 (m, 2H), 6.87 – 6.83 (m, 2H), 4.28 (dq, *J* = 10.5, 7.2 Hz, 1H), 4.19 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.83 (s, 1H), 3.78 (s, 3H), 3.26 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.01 – 2.89 (m, 2H), 2.81 (dd, *J* = 18.9, 8.1 Hz, 1H), 2.46 (dd, *J* = 18.9, 11.2 Hz, 1H), 1.30 – 1.26 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.35, 215.81, 162.41, 155.87, 136.59, 131.45, 131.40, 123.41, 115.79, 115.64, 115.37, 114.85, 61.26, 58.64, 55.71, 52.18, 43.13, 41.96, 20.00, 14.38. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -114.75. **ESI HRMS**: calcd. for $C_{24}H_{26}FN_2O_5$ $[M+H]^+$ 441.1820, found 441.18221. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 24.4 min, t_{minor} = 13.5 min).

ethyl (Z)-2-((1S,3R)-3-(4-chlorobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ad)



Yellow solid (29.2 mg, yield: 64%); M.P. 222-225 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 12.17 (s, 1H), 7.30 – 7.25 (m, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.30 (dt, *J* = 10.9, 7.1 Hz, 1H), 4.25 – 4.18 (m, 1H), 3.80 (s, 3H), 3.31 (dd, *J* = 11.2, 8.1 Hz, 1H), 2.99 (d, *J* = 13.0 Hz, 1H), 2.92 (d, *J* = 13.1 Hz, 1H), 2.85 (dd, *J* = 18.9, 8.1 Hz, 1H), 2.50 (dd, *J* = 18.9, 11.2 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.28 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.11, 215.59, 162.42, 155.87, 136.58, 134.19, 133.55, 131.21, 128.97, 123.34, 115.37, 114.85, 61.27, 58.52, 55.71, 52.14, 43.08, 41.93, 20.12, 14.38. **ESI HRMS**: calcd. for $C_{24}H_{26}ClN_2O_5$ $[M+H]^+$ 457.1525, found 457.1528. **HPLC Analysis**: er = 93.5:6.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 28.1 min, t_{minor} = 15.8 min).

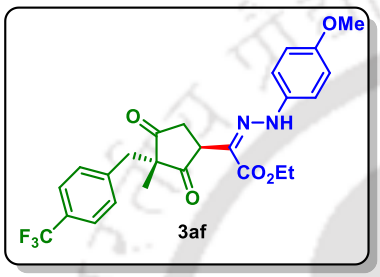
ethyl (Z)-2-((1S,3R)-3-(4-bromobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ae)



Yellow solid (31.5 mg, yield: 63%); M.P. 248-251 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr 12:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.44 – 7.39 (m, 2H), 7.07 – 7.03 (m, 2H), 6.98 – 6.93 (m, 2H), 6.87 – 6.83 (m, 2H), 4.31 – 4.25 (m, 1H), 4.20 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.78 (s, 3H), 3.30 (dd, *J* = 11.2, 8.1 Hz, 1H),

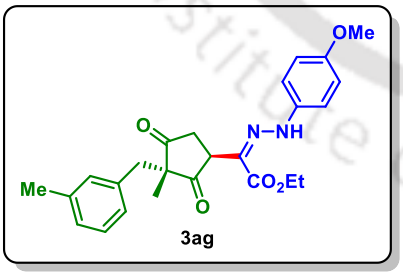
2.97 – 2.87 (m, 2H), 2.84 (dd, *J* = 18.9, 8.1 Hz, 1H), 2.48 (dd, *J* = 18.9, 11.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 3H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 216.10, 215.58, 162.43, 155.87, 136.57, 134.69, 131.94, 131.57, 123.31, 121.68, 115.38, 114.85, 61.28, 58.46, 55.72, 52.14, 43.10, 41.93, 20.15, 14.40. **ESI HRMS**: calcd. for $C_{24}H_{26}BrN_2O_5$ $[M+H]^+$ 501.1020, found 501.1025. **HPLC Analysis**: er = 94.5:5.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 26.7 min, t_{minor} = 13.9 min).

ethyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-((1S,3R)-3-methyl-2,4-dioxo-3-(4-(trifluoromethyl)benzyl)cyclopentyl)acetate (3af)



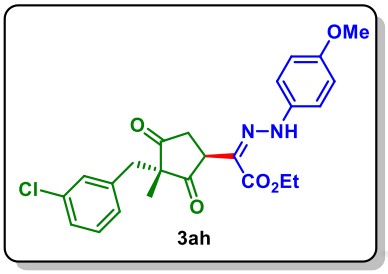
Yellow solid (25.4 mg, yield: 52%); M.P. 201-204 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr 10:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.18 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.08 – 7.03 (m, 2H), 6.90 – 6.84 (m, 2H), 4.29 (dd, *J* = 11.0, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.80 (s, 3H), 3.31 (dd, *J* = 11.0, 8.4 Hz, 1H), 3.08 (d, *J* = 12.7 Hz, 1H), 3.00 (d, *J* = 13.0 Hz, 1H), 2.91 (dd, *J* = 18.9, 8.4 Hz, 1H), 2.53 (dd, *J* = 18.8, 11.1 Hz, 1H), 1.32 – 1.27 (m, 7H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 215.67, 215.12, 162.46, 155.93, 139.89, 136.56, 130.32, 125.70 (q, J_{C-F} = 3.02 Hz), 123.09, 117.20, 115.37, 115.09, 114.88, 61.29, 58.34, 55.72, 52.12, 42.97, 41.80, 20.34, 14.35. **^{19}F NMR (471 MHz, CDCl$_3$)** δ -62.56. **ESI HRMS**: calcd. for $C_{25}H_{25}F_3N_2NaO_5$ $[M+Na]^+$ 513.1608, found 513.1610. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.4 min, t_{minor} = 10.1 min).

ethyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-((1S,3R)-3-methyl-3-(3-methylbenzyl)-2,4-dioxocyclopentyl)acetate (3af)



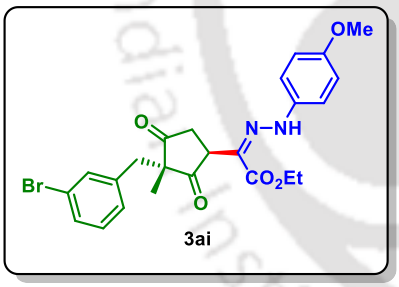
Yellow solid (30.5 mg, yield: 70%); M.P. 192-195 °C; R_f = 0.65 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.14 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.01 (m, 3H), 6.90 – 6.82 (m, 4H), 4.32 – 4.13 (m, 2H), 3.78 (s, 3H), 3.24 (dd, *J* = 11.4, 7.7 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.74 (dd, *J* = 19.0, 7.7 Hz, 1H), 2.42 (dd, *J* = 19.0, 11.4 Hz, 1H), 2.32 (s, 3H), 1.29 – 1.26 (m, 6H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 216.67, 216.14, 162.41, 155.80, 138.46, 136.65, 135.47, 130.45, 128.72, 128.34, 126.80, 123.71, 115.32, 114.83, 61.23, 58.83, 55.71, 52.21, 44.57, 42.07, 21.49, 19.78, 14.37. **ESI HRMS**: calcd. for $C_{25}H_{29}N_2O_5$ $[M+H]^+$ 437.2071, found 437.2071. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.8 min, t_{minor} = 10.7 min).

ethyl (Z)-2-((1S,3R)-3-(3-chlorobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ah)



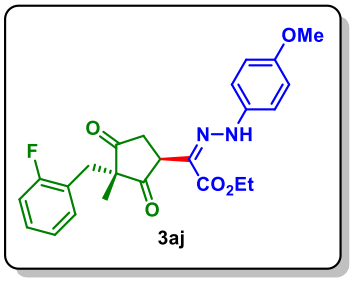
Yellow solid (26.9 mg, yield: 59%); M.P. 198-201 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr 7:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.26 – 7.21 (m, 2H), 7.08 (q, *J* = 2.0 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.0 Hz, 2H), 6.99 – 6.94 (m, 1H), 6.87 – 6.83 (m, 2H), 4.29 (tt, *J* = 8.4, 5.3 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.83 (s, 1H), 3.78 (s, 3H), 3.34 (dd, *J* = 11.2, 8.3 Hz, 1H), 3.00 – 2.89 (m, 2H), 2.87 (dd, *J* = 18.9, 8.2 Hz, 1H), 2.51 (dd, *J* = 18.9, 11.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 215.89, 215.35, 162.50, 155.88, 137.71, 136.62, 134.62, 130.07, 129.88, 128.11, 127.84, 123.27, 115.38, 114.87, 61.30, 58.42, 55.73, 52.09, 43.22, 41.79, 20.12, 14.41. **ESI HRMS**: calcd. for $C_{24}H_{26}ClN_2O_5$ $[M+H]^+$ 457.1525, found 457.1526. **HPLC Analysis**: er = 94:6, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 32.3 min, t_{minor} = 21.7 min).

ethyl (Z)-2-((1S,3R)-3-(3-bromobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ai)



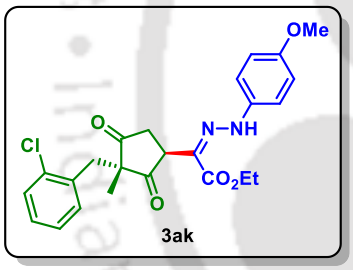
Yellow solid (30.5 mg, yield: 61%); M.P. 237-240 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.41 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.24 (d, *J* = 1.9 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.07 – 7.03 (m, 2H), 7.02 (dt, *J* = 7.8, 1.4 Hz, 1H), 6.88 – 6.83 (m, 2H), 4.25 (ddq, *J* = 50.3, 10.9, 7.1 Hz, 2H), 3.78 (s, 3H), 3.34 (dd, *J* = 11.2, 8.3 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.88 – 2.83 (m, 1H), 2.52 (dd, *J* = 18.9, 11.2 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 215.90, 215.36, 162.49, 155.88, 138.00, 136.62, 132.77, 130.79, 130.35, 128.59, 123.28, 122.82, 115.39, 114.86, 61.32, 58.44, 55.74, 52.12, 43.15, 41.81, 20.12, 14.43. **ESI HRMS**: $C_{24}H_{26}BrN_2O_5$ $[M+H]^+$ 501.1020, found 501.1022. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 22.9 min, t_{minor} = 16.2 min).

ethyl (Z)-2-((1S,3R)-3-(2-fluorobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3aj)



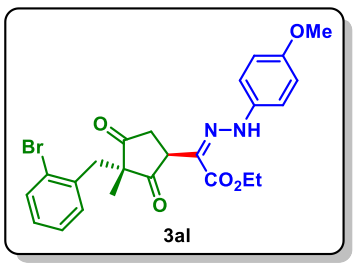
Yellow solid (25.5 mg, yield: 58%); M.P. 174-177 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.30 – 7.24 (m, 1H), 7.16 – 6.98 (m, 5H), 6.88 – 6.82 (m, 2H), 4.26 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.17 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.84 – 3.75 (m, 4H), 2.98 (s, 2H), 2.92 (dd, *J* = 19.0, 11.5 Hz, 1H), 2.82 (dd, *J* = 19.0, 7.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 214.76, 214.41, 162.35, 161.96 (d, J_{C-F} = 247.64 Hz), 155.83, 136.65, 132.42 (d, J_{C-F} = 3.02 Hz), 129.67 (d, J_{C-F} = 9.06 Hz), 124.33 (d, J_{C-F} = 4.53 Hz), 123.84, 122.23 (d, J_{C-F} = 16.61 Hz), 115.80 (d, J_{C-F} = 22.65 Hz), 115.40, 114.83, 61.30, 57.69, 55.72, 51.39, 41.50, 36.26 (d, J_{C-F} = 3.02 Hz), 17.84, 14.30. **^{19}F NMR (471 MHz, $CDCl_3$)** δ -114.75. **ESI HRMS**: calcd. for $C_{24}H_{26}FN_2O_5$ $[M+H]^+$ 441.1820, found 441.18223. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.0 min, t_{minor} = 16.8 min).

ethyl (Z)-2-((1S,3R)-3-(2-chlorobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ak)



Yellow solid (31.0 mg, yield: 68%); M.P. 200-203 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.41 – 7.35 (m, 1H), 7.25 – 7.19 (m, 2H), 7.19 – 7.13 (m, 1H), 7.10 – 7.04 (m, 2H), 6.88 – 6.82 (m, 2H), 4.26 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.78 (s, 3H), 3.18 – 3.10 (m, 2H), 2.91 (dd, *J* = 19.0, 11.7 Hz, 1H), 2.82 (dd, *J* = 19.0, 7.4 Hz, 1H), 1.27 – 1.24 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 214.89, 214.50, 162.37, 155.84, 136.67, 134.88, 133.14, 132.34, 130.08, 129.11, 126.98, 123.84, 115.41, 114.84, 61.29, 57.67, 55.73, 51.59, 41.81, 39.95, 18.18, 14.32. **ESI HRMS**: $C_{24}H_{26}ClN_2O_5$ $[M+H]^+$ 457.1525, found 457.1529. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 22.5 min, t_{minor} = 18.3 min).

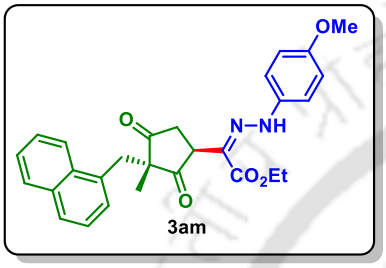
ethyl (Z)-2-((1S,3R)-3-(2-bromobenzyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3al)



Yellow solid (30.0 mg, yield: 60%); M.P. 222-225 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.16 (s, 1H), 7.57 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.20 – 7.10 (m, 2H), 7.09 – 7.05 (m, 2H), 6.87 – 6.83 (m, 2H), 4.26 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.78 (s, 3H), 3.20 – 3.14 (m, 2H), 2.92 (dd, *J* = 19.0,

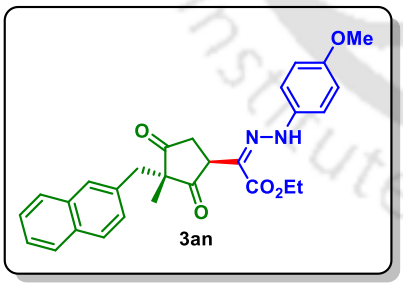
11.7 Hz, 1H), 2.82 (dd, *J* = 19.0, 7.4 Hz, 1H), 1.27 – 1.24 (m, 6H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 214.89, 214.49, 162.37, 155.85, 136.67, 134.98, 133.51, 132.16, 129.26, 127.60, 125.58, 123.83, 115.41, 114.85, 61.29, 57.67, 55.73, 51.70, 42.20, 41.93, 18.29, 14.34. **ESI HRMS**: $C_{24}H_{26}BrN_2O_5$ $[M+H]^+$ 501.1020, found 501.1025. **HPLC Analysis**: er = 90:10, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 25.3 min, t_{minor} = 20.0 min).

ethyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-((1S,3R)-3-methyl-3-(naphthalen-1-ylmethyl)-2,4-dioxocyclopentyl)acetate (3am)



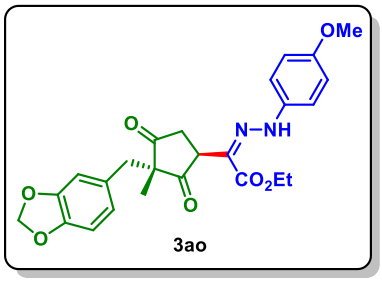
Yellow solid (32.0 mg, yield: 68%); M.P. 236-239 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.05 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.51 (dddd, *J* = 23.1, 8.0, 6.8, 1.3 Hz, 2H), 7.41 (dd, *J* = 8.2, 7.0 Hz, 1H), 7.27 (dd, *J* = 7.0, 5.8 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.84 – 6.79 (m, 2H), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.09 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.77 (s, 3H), 3.55 – 3.43 (m, 2H), 2.96 (dd, *J* = 11.7, 7.3 Hz, 1H), 2.58 (dd, *J* = 19.1, 7.4 Hz, 1H), 2.10 (dd, *J* = 19.1, 11.8 Hz, 1H), 1.38 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 216.78, 216.30, 162.28, 155.78, 136.62, 133.97, 132.00, 131.90, 128.82, 128.65, 128.53, 126.56, 126.13, 125.42, 124.20, 123.71, 115.30, 114.79, 61.15, 58.86, 55.71, 52.26, 42.27, 40.77, 19.96, 14.29. **ESI HRMS**: calcd. for $C_{28}H_{28}N_2NaO_5$ $[M+Na]^+$ 495.1890, found 495.1892. **HPLC Analysis**: er = 96.5:3.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 39.2 min, t_{minor} = 21.9 min).

ethyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-((1S,3R)-3-methyl-3-(naphthalen-2-ylmethyl)-2,4-dioxocyclopentyl)acetate (3an)



Yellow solid (30.2 mg, yield: 64%); M.P. 194-197 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 12.11 (s, 1H), 7.88 – 7.73 (m, 3H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.48 (td, *J* = 5.8, 5.3, 3.2 Hz, 2H), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.02 – 6.95 (m, 2H), 6.86 – 6.78 (m, 2H), 4.23 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.76 (s, 3H), 3.23 – 3.08 (m, 3H), 2.76 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.37 (dd, *J* = 19.0, 11.3 Hz, 1H), 1.33 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 216.56, 216.03, 162.42, 155.79, 136.61, 133.46, 133.21, 132.64, 128.64, 128.52, 127.99, 127.80, 127.78, 126.44, 126.17, 123.53, 115.32, 114.80, 61.19, 58.89, 55.70, 52.12, 44.50, 42.06, 20.15, 14.33. **ESI HRMS**: calcd. for $C_{28}H_{28}N_2NaO_5$ $[M+Na]^+$ 495.1890, found 495.1897. **HPLC Analysis**: er = 95:5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 25.8 min, t_{minor} = 18.2 min).

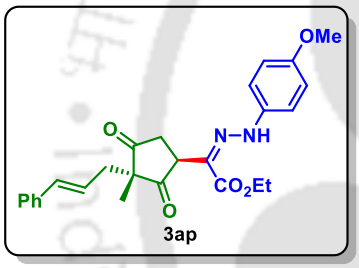
ethyl (Z)-2-((1S,3R)-3-(benzo[d][1,3]dioxol-5-ylmethyl)-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ao)



3ao

Yellow semi-solid (25.1 mg, yield: 54%); M.P. 200-203 °C; R_f = 0.25 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)** δ 12.16 (s, 1H), 7.08 – 7.03 (m, 2H), 6.87 – 6.83 (m, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.58 – 6.51 (m, 2H), 5.95 (s, 2H), 4.31 – 4.25 (m, 1H), 4.19 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.78 (s, 3H), 3.36 (dd, *J* = 11.3, 8.0 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.81 (dd, *J* = 18.9, 8.0 Hz, 1H), 2.52 (dd, *J* = 18.9, 11.3 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.24 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.58, 216.01, 162.47, 155.81, 147.82, 146.98, 136.63, 129.19, 123.54, 123.01, 115.36, 114.82, 110.15, 108.56, 101.22, 61.26, 58.81, 55.71, 52.16, 44.09, 41.98, 19.81, 14.37. **ESI HRMS**: calcd. for $C_{25}H_{27}N_2O_7$ $[M+H]^+$ 467.1813, found 467.1818. **HPLC Analysis**: er = 92:8, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 31.3 min, t_{minor} = 19.4 min).

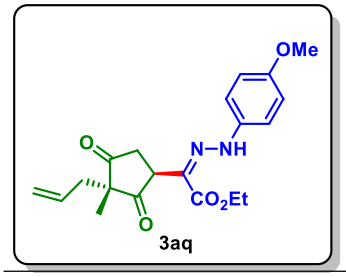
ethyl (Z)-2-((1S,3R)-3-cinnamyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3ap)



3ap

Yellow semi-solid (19.2 mg, yield: 43%); M.P. 193-196 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; dr 5:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 12.20 (s, 1H), 7.36 – 7.28 (m, 5H), 7.24 (td, *J* = 7.0, 6.4, 3.5 Hz, 2H), 7.10 – 7.05 (m, 2H), 6.93 (d, *J* = 9.0 Hz, 1H), 6.88 – 6.82 (m, 2H), 6.45 (d, *J* = 15.7 Hz, 1H), 6.03 (dt, *J* = 16.1, 7.9 Hz, 1H), 4.33 – 4.24 (m, 2H), 4.24 – 4.17 (m, 1H), 3.99 (dd, *J* = 11.3, 7.6 Hz, 1H), 3.82 (s, 1H), 3.78 (s, 3H), 3.06 (dd, *J* = 18.9, 11.3 Hz, 1H), 2.91 (dd, *J* = 18.9, 7.6 Hz, 1H), 2.63 – 2.58 (m, 1H), 2.52 (ddd, *J* = 7.9, 5.3, 1.3 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 1H), 1.26 (t, *J* = 2.6 Hz, 3H), 1.24 (s, 1H), 1.23 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 215.39, 215.03, 162.40, 155.87, 136.69, 136.64, 135.15, 128.75, 127.93, 126.52, 123.83, 122.42, 115.42, 114.86, 61.34, 57.50, 55.73, 51.68, 41.74, 40.71, 18.11, 14.34. **ESI HRMS**: calcd. for $C_{26}H_{29}N_2O_5$ $[M+H]^+$ 449.2071, found 449.2075. **HPLC Analysis**: er = 82:18, Chiralpak Phenomenex Lux C4 Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 19.2 min, t_{minor} = 15.8 min).

ethyl (Z)-2-((1S,3R)-3-allyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3aq)

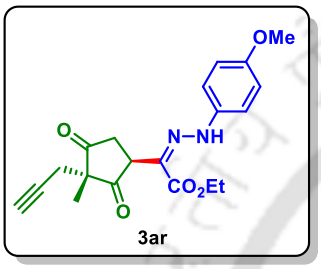


3aq

Yellow semi-solid (21.2 mg, yield: 57%); M.P. -206 °C; R_f = 0.75 in 2:8 ethyl acetate/hexane; dr 5:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.20 (s, 1H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 5.66 (ddt, *J* = 17.4, 10.1, 7.5 Hz, 1H), 5.20 – 5.10 (m, 2H), 4.24 (ddq, *J* = 41.7, 10.8, 7.1 Hz, 2H), 3.99 (dd, *J* = 11.4, 7.5 Hz, 1H), 3.79 (s, 3H), 3.06 (dd, *J* = 19.0,

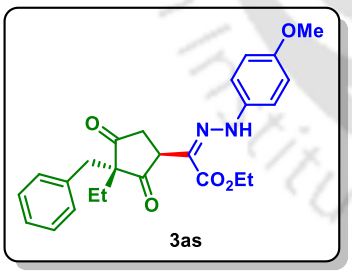
11.4 Hz, 1H), 2.90 (dd, *J* = 18.9, 7.5 Hz, 1H), 2.42 – 2.31 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.19 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 215.22, 214.80, 162.37, 155.89, 136.67, 131.24, 123.92, 120.36, 115.44, 114.87, 61.33, 57.23, 55.73, 51.75, 41.67, 41.50, 17.83, 14.35. **ESI HRMS**: calcd. for $C_{20}H_{24}N_2NaO_5$ $[M+Na]^+$ 395.1577, found 395.1580. **HPLC Analysis**: er = 89:11, Chiralpak Phenomenex Lux C4 Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.6 min, t_{minor} = 11.8 min).

ethyl (Z)-2-(2-(4-methoxyphenyl)hydrazineylidene)-2-((1S,3R)-3-methyl-2,4-dioxo-3-(prop-2-yn-1-yl)cyclopentyl)acetate (3ar)



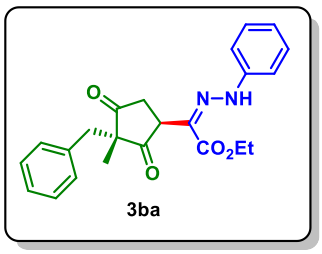
Yellow semi-solid (18.8 mg, yield: 51%); R_f = 0.75 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.22 (s, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.37 – 4.20 (m, 2H), 4.14 (dd, *J* = 11.2, 7.9 Hz, 1H), 3.79 (s, 3H), 3.16 (dd, *J* = 18.9, 11.2 Hz, 1H), 2.99 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.48 (t, *J* = 3.0 Hz, 2H), 2.11 (t, *J* = 2.7 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 214.55, 214.09, 162.43, 155.93, 136.64, 123.77, 115.46, 114.89, 78.65, 71.72, 61.37, 55.75, 55.52, 52.63, 42.36, 26.12, 19.10, 14.41. **ESI HRMS**: calcd. for $C_{20}H_{23}N_2O_5$ $[M+H]^+$ 371.1601, found 371.1606. **HPLC Analysis**: er = 89:11, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 36.4 min, t_{minor} = 27.0 min).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-ethyl-2,4-dioxocyclopentyl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (3as)



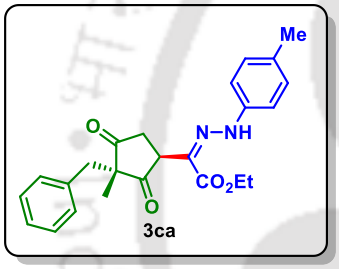
Yellow semi-solid (20.4 mg, yield: 47%); R_f = 0.55 in 2:8 ethyl acetate/hexane; dr 10:1 **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.18 (s, 1H), 7.30 – 7.24 (m, 3H), 7.11 – 7.06 (m, 2H), 7.02 – 6.98 (m, 2H), 6.84 – 6.81 (m, 2H), 4.30 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.21 – 4.14 (m, 1H), 3.77 (s, 3H), 3.15 – 3.04 (m, 2H), 2.97 – 2.85 (m, 2H), 2.49 (dd, *J* = 18.8, 10.7 Hz, 1H), 1.84 (h, *J* = 7.3 Hz, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.79, 215.90, 163.16, 155.68, 136.83, 135.89, 129.87, 128.77, 127.38, 122.36, 115.14, 114.84, 63.88, 61.02, 55.72, 51.37, 42.96, 42.51, 28.74, 14.35, 9.46. **ESI HRMS**: calcd. for $C_{25}H_{28}N_2NaO_5$ $[M+Na]^+$ 459.1890, found 459.1892. **HPLC Analysis**: er = 90:10, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.8 min, t_{minor} = 7.2 min).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-phenylhydrazineylidene)acetate (3ba)



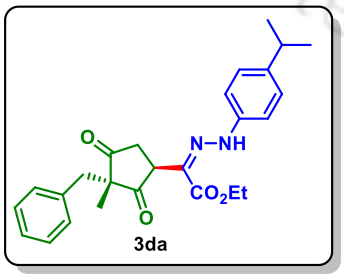
Yellow solid (20.3 mg, yield: 52%); M.P. 212-215 °C; R_f = 0.6 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 12.13 (s, 1H), 7.32 – 7.25 (m, 5H), 7.13 – 7.05 (m, 4H), 6.98 (t, *J* = 7.3 Hz, 1H), 4.24 (ddq, *J* = 46.7, 11.0, 7.2 Hz, 2H), 3.24 (dd, *J* = 11.3, 8.0 Hz, 1H), 3.04 – 2.92 (m, 2H), 2.78 (dd, *J* = 19.0, 8.0 Hz, 1H), 2.43 (dd, *J* = 19.0, 11.3 Hz, 1H), 1.30 – 1.26 (m, 6H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 216.38, 215.77, 162.29, 142.76, 135.58, 129.78, 129.46, 128.84, 127.61, 124.83, 122.91, 114.14, 61.41, 58.80, 52.19, 44.47, 41.84, 19.87, 14.34. **ESI HRMS**: calcd. for $C_{23}H_{25}N_2O_4$ $[M+H]^+$ 393.1809, found 393.1809. **HPLC Analysis**: *er* = 95:5, Chiralpak Phenomenex Lux C4 Column, n-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.0 min, t_{minor} = 17.2 min).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(p-tolyl)hydrazineylidene)acetate (3ca)



Yellow solid (21.9 mg, yield: 54%); M.P. 208-211 °C; R_f = 0.65 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 12.11 (s, 1H), 7.32 – 7.26 (m, 3H), 7.08 (dd, *J* = 7.8, 1.5 Hz, 4H), 7.02 – 6.96 (m, 2H), 4.23 (ddq, *J* = 55.3, 10.9, 7.1 Hz, 2H), 3.24 (dd, *J* = 11.3, 7.9 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.77 (dd, *J* = 19.0, 7.9 Hz, 1H), 2.42 (dd, *J* = 19.0, 11.3 Hz, 1H), 2.29 (s, 3H), 1.29 – 1.26 (m, 6H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 216.51, 215.93, 162.36, 140.50, 135.61, 132.46, 129.99, 129.79, 128.84, 127.60, 124.11, 114.13, 61.30, 58.80, 52.16, 44.47, 41.95, 20.87, 19.89, 14.37. **ESI HRMS**: calcd. for $C_{24}H_{27}N_2O_4$ $[M+H]^+$ 407.1965, found 407.1966. **HPLC Analysis**: er = 89:11, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.8 min, t_{minor} = 13.8 min).

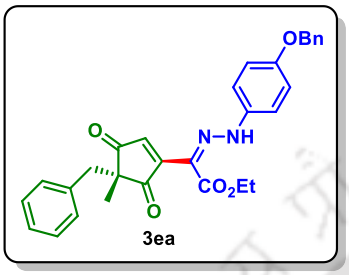
ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-isopropylphenyl)hydrazineylidene)acetate (3da)



Yellow solid (17.3 mg, yield: 40%); M.P. 182-185 °C; R_f = 0.68 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.12 (s, 1H), 7.30 – 7.26 (m, 3H), 7.16 – 7.13 (m, 2H), 7.08 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.04 – 7.00 (m, 2H), 4.32 – 4.24 (m, 1H), 4.22 – 4.15 (m, 1H), 3.25 (dd, *J* = 11.3, 7.9 Hz, 1H), 2.97 (q, *J* = 12.9 Hz, 2H), 2.89 – 2.83 (m, 1H), 2.78 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.41 (dd, *J* = 19.0, 11.3 Hz, 1H), 1.28 (d, *J* = 3.0 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.61, 215.96, 162.38, 143.70, 140.72, 135.61, 129.79, 128.85, 127.60, 127.38, 124.10, 114.18, 61.31, 58.80, 52.12, 44.44, 41.96, 33.61, 24.21, 19.94, 14.37. **ESI**

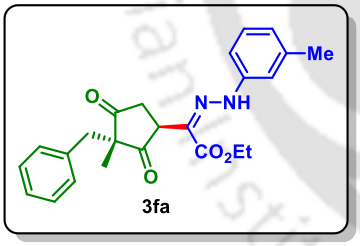
HRMS: calcd. for $C_{26}H_{30}N_2NaO_4$ $[M+Na]^+$ 457.2098, found 457.2099. **HPLC Analysis**: er = 87.5:12.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.8 min, t_{minor} = 14.0 min).

ethyl (R,Z)-2-(4-benzyl-4-methyl-3,5-dioxocyclopent-1-en-1-yl)-2-(2-(4-(benzyloxy)phenyl)hydrazineylidene)acetate (3ea)



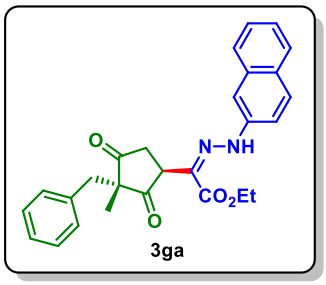
Yellow semi-solid (21.8 mg, yield: 44%); R_f = 0.52 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)** δ 12.16 (s, 1H), 7.47 – 7.43 (m, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.29 (m, 4H), 7.13 – 7.08 (m, 2H), 7.08 – 7.03 (m, 2H), 6.96 – 6.92 (m, 2H), 5.06 (s, 2H), 4.29 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.20 (dq, *J* = 10.9, 7.2 Hz, 1H), 3.25 (dd, *J* = 11.3, 7.9 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.78 (dd, *J* = 18.9, 7.9 Hz, 1H), 2.44 (dd, *J* = 18.9, 11.3 Hz, 1H), 1.31 – 1.28 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.56, 216.00, 162.41, 154.98, 137.20, 136.87, 135.60, 129.78, 128.84, 128.70, 128.08, 127.61, 127.59, 123.72, 115.98, 115.31, 70.63, 61.25, 58.80, 52.16, 44.49, 41.98, 19.87, 14.37. **ESI HRMS**: calcd. for $C_{30}H_{29}N_2O_5$ $[M+H]^+$ 497.2071, found 497.2071. **HPLC Analysis**: er = 94:6, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 43.0 min, t_{minor} = 26.8 min).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(m-tolyl)hydrazineylidene)acetate (3fa)



Yellow semi-solid (19.0 mg, yield: 47%); R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 12.10 (s, 1H), 7.32 – 7.24 (m, 3H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.95 – 6.85 (m, 2H), 6.80 (d, *J* = 7.6 Hz, 1H), 4.28 (dq, *J* = 9.3, 7.0 Hz, 1H), 4.19 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.25 (dd, *J* = 11.3, 7.9 Hz, 1H), 3.03 – 2.93 (m, 2H), 2.78 (dd, *J* = 19.0, 7.9 Hz, 1H), 2.42 (dd, *J* = 18.8, 11.6 Hz, 1H), 2.33 (s, 3H), 1.29 (d, *J* = 7.4 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 216.53, 215.89, 162.27, 142.71, 139.43, 135.57, 129.78, 129.31, 128.86, 127.61, 124.57, 123.82, 114.76, 111.36, 61.39, 58.81, 52.21, 44.49, 41.90, 21.67, 19.85, 14.36. **ESI HRMS**: calcd. for $C_{24}H_{26}N_2NaO_4$ $[M+Na]^+$ 429.1785, found 429.1789. **HPLC Analysis**: er = 92.5:7.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.1 min, t_{minor} = 20.1 min).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(naphthalen-2-yl)hydrazineylidene)acetate (3ga)



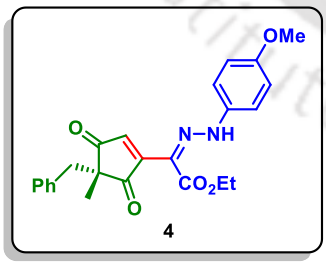
Yellow semi-solid (18.5 mg, yield: 42%); R_f = 0.55 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 12.33 (s, 1H), 7.79 – 7.70 (m, 3H), 7.46 – 7.40 (m, 2H), 7.38 – 7.27 (m, 5H), 7.10 (dd, *J* = 7.5, 2.0 Hz, 2H), 4.31 (dq, *J* = 10.9, 7.2 Hz, 1H), 4.22 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.30 (dd, *J* = 11.4, 8.0 Hz, 1H), 3.05 – 2.94 (m, 2H), 2.82 (dd, *J* = 19.0, 8.0 Hz, 1H), 2.47 (dd, *J* = 19.0, 11.4 Hz, 1H), 1.32 – 1.27 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 216.37, 215.77, 162.33, 140.45, 135.60, 134.32, 130.39, 129.82, 129.60, 128.89, 127.96, 127.65, 127.21, 126.86, 125.29, 124.34, 115.41, 109.66, 61.52, 58.85, 52.32, 44.54, 41.89, 19.87, 14.37. **ESI HRMS**: calcd. for $C_{27}H_{27}N_2O_4$ $[M+H]^+$ 443.1965, found 443.1965. **HPLC Analysis**: er = 85:15, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.5 min, t_{minor} = 14.8 min).

4.6.6 Procedure for the synthetic transformations:

a. Procedure for the synthesis of compound 4:

In a screw cap vial, equipped with a magnetic stirring bar, to a solution of **3aa** (0.05 mmol) in AcOH:DCM (1:1) 1 mL was added MnO_2 (0.5 mmol, 10 equiv). The mixture was stirred at room temperature for overnight. After full conversion of **3aa**, the crude reaction mixture was directly purified by silica-gel flash column chromatography (5-10% EtOAc in petroleum ether) to obtain **4** as a yellow solid (10.9 mg, 52% yield).

ethyl (R,Z)-2-(4-benzyl-4-methyl-3,5-dioxocyclopent-1-en-1-yl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (4)

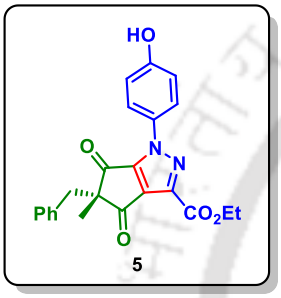


Yellow solid (10.9 mg, yield: 52%); M.P. 201-204 °C; R_f = 0.4 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 13.03 (s, 1H), 7.38 – 7.30 (m, 2H), 7.15 – 7.07 (m, 3H), 7.06 – 6.98 (m, 3H), 6.98 – 6.90 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.09 – 2.97 (m, 2H), 1.33 – 1.28 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 206.35, 204.41, 163.55, 157.44, 152.71, 139.86, 136.10, 135.97, 130.00, 128.29, 126.93, 117.65, 117.10, 115.07, 61.43, 55.75, 53.37, 41.80, 19.73, 14.21. **ESI HRMS**: calcd. for $C_{24}H_{25}N_2O_5$ $[M+H]^+$ 421.1758, found 421.1760. **HPLC Analysis**: er = 89:11, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 30.3 min, t_{minor} = 12.5 min).

b. Procedure for the synthesis of compound 5:

In a screw cap vial, equipped with a magnetic stirring bar, to a solution of **3aa** (0.05 mmol) in 0.5 mL DCM was added DDQ (0.15 mmol, 3 eq.) and the mixture was stirred for 2 h at room temperature. After full conversion of **3aa**, the crude reaction mixture was directly purified by silica-gel flash column chromatography (5-10% EtOAc in petroleum ether) to obtain **5** as a yellow semi-solid (9.2 mg, 46% yield).

ethyl (S)-5-benzyl-1-(4-hydroxyphenyl)-5-methyl-4,6-dioxo-1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carboxylate (5)

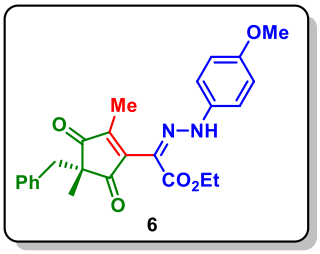


Yellow semi-solid (9.2 mg, yield: 46%); R_f = 0.38 in 2:8 ethyl acetate/hexane; **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.77 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.08 (ddd, *J* = 13.2, 7.8, 5.9 Hz, 3H), 7.03 – 6.98 (m, 2H), 6.98 – 6.93 (m, 2H), 4.48 (q, *J* = 7.0 Hz, 2H), 3.21 (d, *J* = 13.4 Hz, 1H), 3.10 (d, *J* = 13.3 Hz, 1H), 1.49 – 1.43 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 190.66, 189.25, 159.96, 156.88, 150.25, 137.70, 136.38, 135.62, 131.10, 129.79, 128.51, 128.30, 127.35, 123.42, 117.12, 116.21, 65.60, 62.39, 42.16, 20.68, 14.34. **ESI HRMS**: calcd. for $C_{23}H_{21}N_2O_5$ $[M+H]^+$ 405.1445, found 405.1446. **HPLC Analysis**: er = 95:5, Chiralpak IC Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.1 min, t_{minor} = 18.2 min).

c. Procedure for the synthesis of compound 6:

In a screw cap vial, equipped with a magnetic stirring bar, to a solution of **3aa** (0.05 mmol) in DCM (1 mL) was added CH_3NO_2 (10 equiv) and DABCO (1.5 equiv). The mixture was stirred at room temperature for 24 h. The reaction was monitored by TLC. After full conversion of **3aa**, the crude reaction mixture was directly purified by silica-gel flash column chromatography (5-10% EtOAc in petroleum ether) to obtain **6** as a yellow solid (12.5 mg, 58% yield).

ethyl (R,Z)-2-(4-benzyl-2,4-dimethyl-3,5-dioxocyclopent-1-en-1-yl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (6)



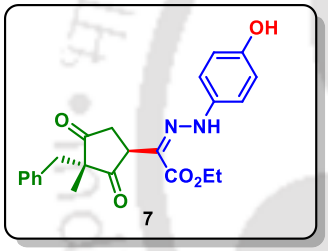
Yellow solid (12.5 mg, yield: 58%); M.P. 199-202 °C; R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.56 (s, 1H), 7.20 – 7.07 (m, 5H), 6.99 (dd, *J* = 7.4, 2.1 Hz, 2H), 6.92 – 6.83 (m, 2H), 4.21 (qt, *J* = 7.3, 3.7 Hz, 2H), 3.80 (s, 3H), 3.02 (s, 2H), 1.94 (s, 3H), 1.29 – 1.22 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.77, 204.19,

162.90, 156.65, 154.23, 150.69, 136.19, 129.99, 128.21, 126.89, 118.04, 116.10, 114.93, 61.11, 55.74, 52.11, 41.34, 19.84, 14.13, 10.46. **ESI HRMS**: calcd. for $C_{25}H_{27}N_2O_5$ $[M+H]^+$ 435.1914, found 435.1918. **HPLC Analysis**: er = 94.5:5.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 93/7, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.3 min, t_{minor} = 24.0 min).

d. Procedure for the synthesis of compound 7:

In an oven dried 5 mL rb, **3ea** (0.05 mmol) was dissolved in 1 ml methanol/ethyl acetate (1:1), and Pd/C (10 mol %) was added. The resulting mixture was stirred at room temperature under H_2 atmosphere. The reaction was monitored by TLC. After full conversion of **3ea**, the crude reaction mixture was directly purified by silica-gel flash column chromatography (10-20% EtOAc in petroleum ether) to obtain **7** as a yellow semi-solid (13.8 mg, 68% yield).

ethyl (Z)-2-((1S,3R)-3-benzyl-3-methyl-2,4-dioxocyclopentyl)-2-(2-(4-hydroxyphenyl)hydrazineylidene)acetate (7)



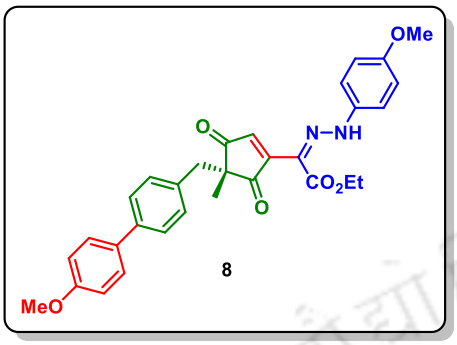
7

Yellow semi-solid (13.8 mg, yield: 68%); R_f = 0.3 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 12.11 (s, 1H), 7.29 (dt, *J* = 7.2, 2.6 Hz, 3H), 7.13 – 7.05 (m, 2H), 7.03 – 6.94 (m, 2H), 6.85 – 6.72 (m, 2H), 4.34 – 4.14 (m, 2H), 3.22 (dd, *J* = 11.4, 7.9 Hz, 1H), 2.98 (q, *J* = 12.9 Hz, 2H), 2.75 (dd, *J* = 19.0, 7.9 Hz, 1H), 2.41 (dd, *J* = 19.0, 11.4 Hz, 1H), 1.30 – 1.26 (m, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 216.69, 216.22, 162.43, 151.70, 136.71, 135.59, 129.80, 128.87, 127.62, 123.59, 116.28, 115.52, 61.28, 58.85, 52.18, 44.52, 42.02, 19.88, 14.38. **ESI HRMS**: calcd. for $C_{23}H_{25}N_2O_5$ $[M+H]^+$ 409.1758, found 409.1760. **HPLC Analysis**: er = 91.5:8.5, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 19.9 min, t_{minor} = 23.4 min).

e. Procedure for the synthesis of compound 8:

To a round 5 ml round bottom flask, **3ae** (0.05 mmol), $Pd(OAc)_2$ (5 mol%), PCy_3 (5 mol%), 4-methoxy phenyl boronic acid (1.5 eq.) and Na_2CO_3 (2 eq.) were added under nitrogen atomosphere. Then 0.5 ml DMF was added to the reaction mixture and the reaction mixture was stirred at room temperature for 24 h. Next H_2O was added to the mixture and the mixture was extracted with ethyl acetate. Then the combined organic layers were again washed with H_2O twice and the organic layer was dried over Na_2SO_4 and concentrated in vacuo and the crude product was purified by flash chromatography (10-20% EtOAc in petroleum ether) to obtain **8** as a yellow solid (18.6 mg, 71% yield).

ethyl (R,Z)-2-(4-((4'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-3,5-dioxocyclopent-1-en-1-yl)-2-(2-(4-methoxyphenyl)hydrazineylidene)acetate (8)



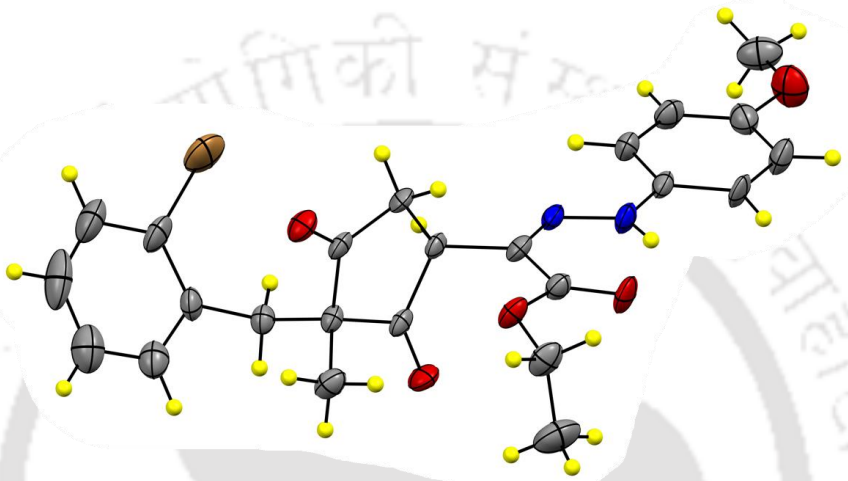
8

Yellow solid (18.6 mg, yield: 71%); M.P. 222-225 °C; R_f = 0.3 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.92 – 7.83 (m, 2H), 7.26 – 7.21 (m, 2H), 7.05 – 6.97 (m, 2H), 6.95 – 6.87 (m, 2H), 6.83 – 6.70 (m, 5H), 4.86 (s, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.16 (d, *J* = 13.5 Hz, 1H), 3.05 (d, *J* = 13.5 Hz, 1H), 1.49 – 1.40 (m, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 190.33, 188.84, 160.52, 159.81, 153.83, 150.00, 149.77, 137.95, 136.27, 134.68, 131.64, 130.99, 123.15, 121.40, 116.17, 114.95, 114.64, 65.39, 62.40, 55.92, 55.78, 40.76, 21.25, 14.33. **ESI HRMS**: calcd. for $C_{31}H_{31}N_2O_6$ $[M+H]^+$ 527.2177, found 527.2180. **HPLC Analysis**: er = 94:6, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 43.3 min, t_{minor} = 26.8 min).

4.6.7 Single crystal X-ray diffraction analysis:

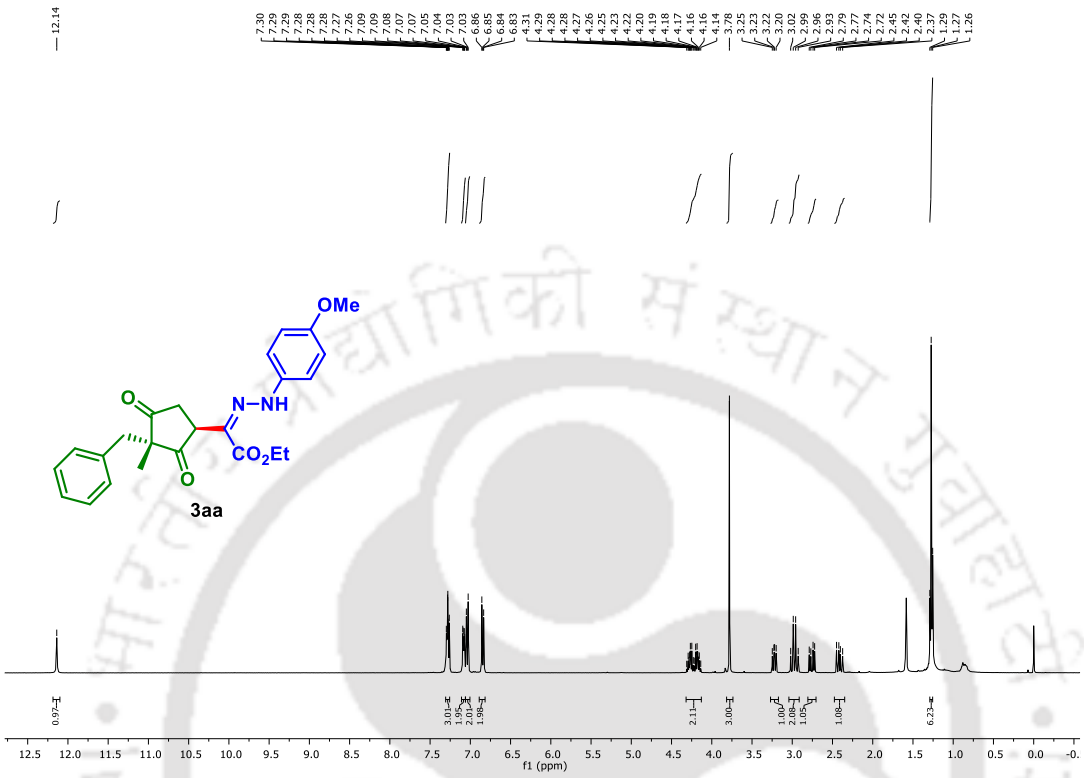
CCDC No.	2405612
Empirical formula	$C_{24}H_{25}BrN_2O_5$
Formula weight	501.36
Crystal habit, colour	needle / yellow
Temperature, T	295 K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P 21'
Unit cell dimensions	a = 5.5791(8) Å
	b = 31.801(4) Å
	c = 12.9476(18) Å
	α = 90°, β = 90°, γ = 90°
Volume, V (Å^3)	2297.2(5)
Z	2
Calculated density, g·cm^{-3}	1.450
F (000)	1032.0
Refinement method	'SHELXL–2018/3'

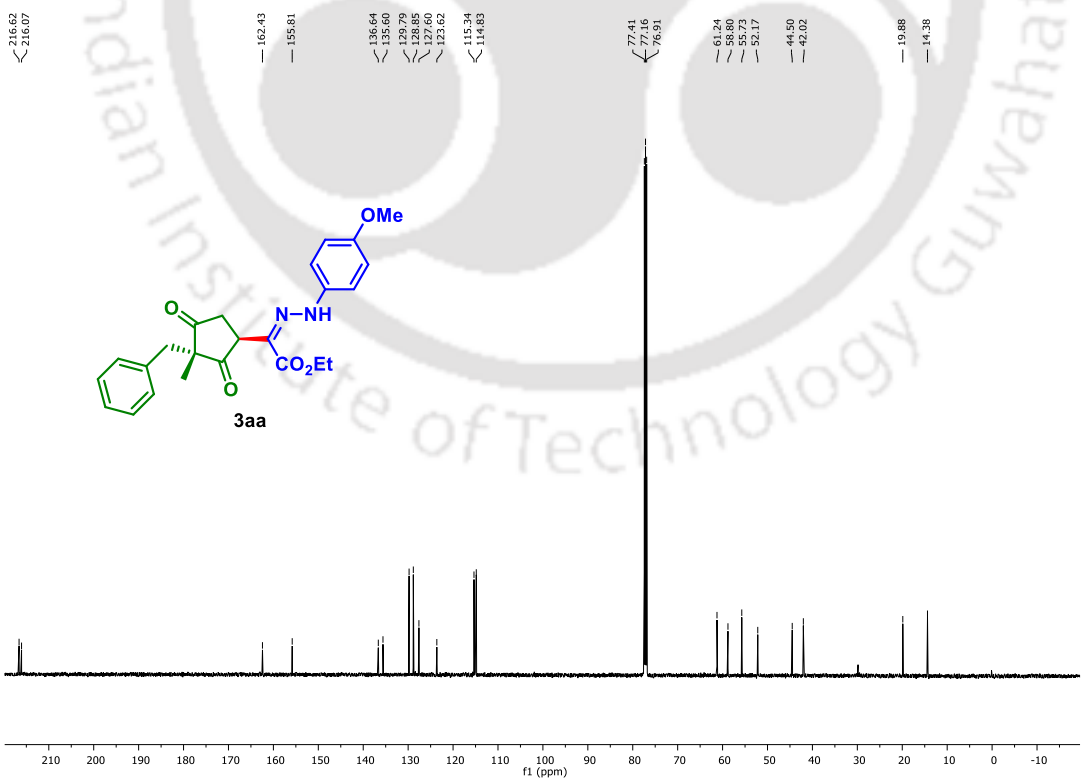
Goodness–of–fit on F^2	0.999
Theta(max)	25.245
Data completeness	1.96/1.00
R(reflections)	0.0747 (4457)
wR2(reflections)	0.2014 (8329)

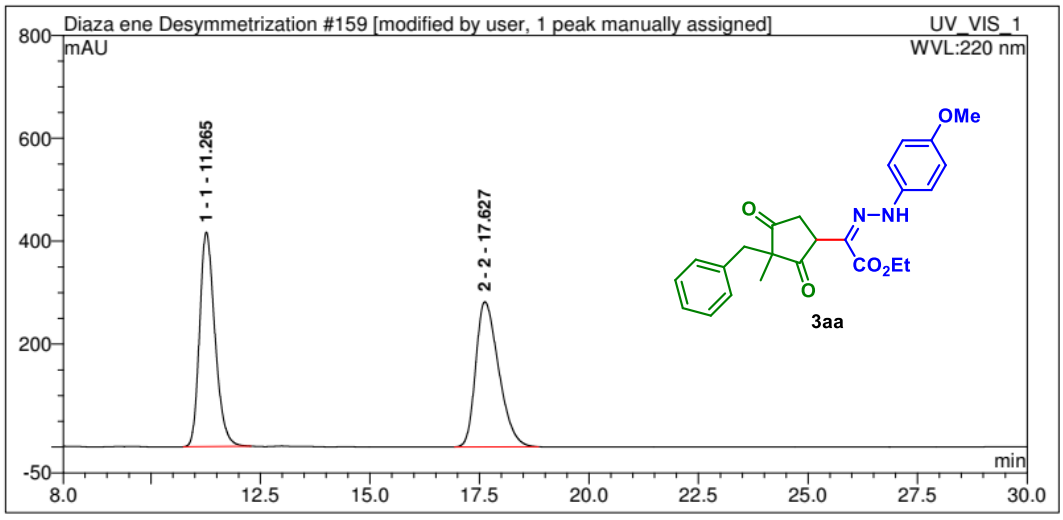


ORTEP representation of the X-ray structure of **3al** (thermal ellipsoids at 30% probability)

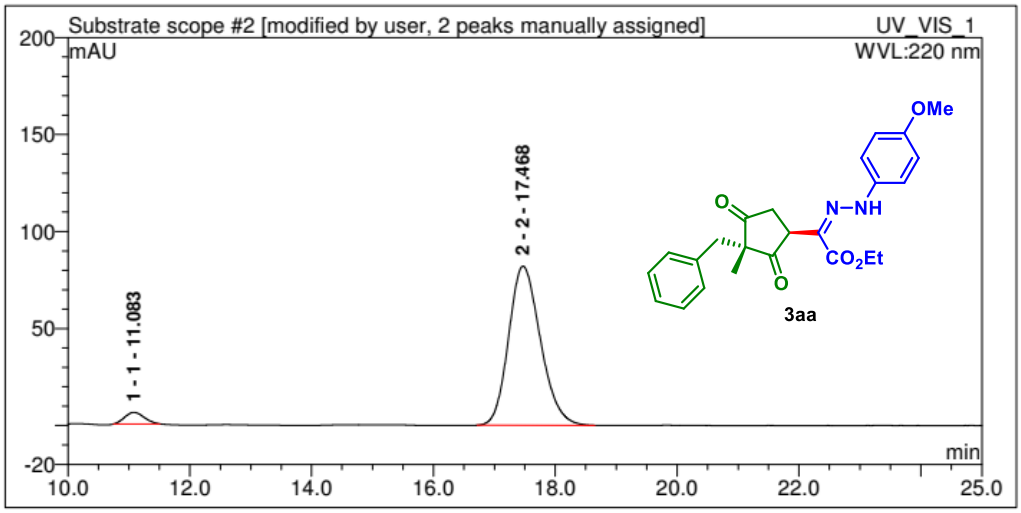
4.6.8 NMR spectra and HPLC chromatograms of selected products:



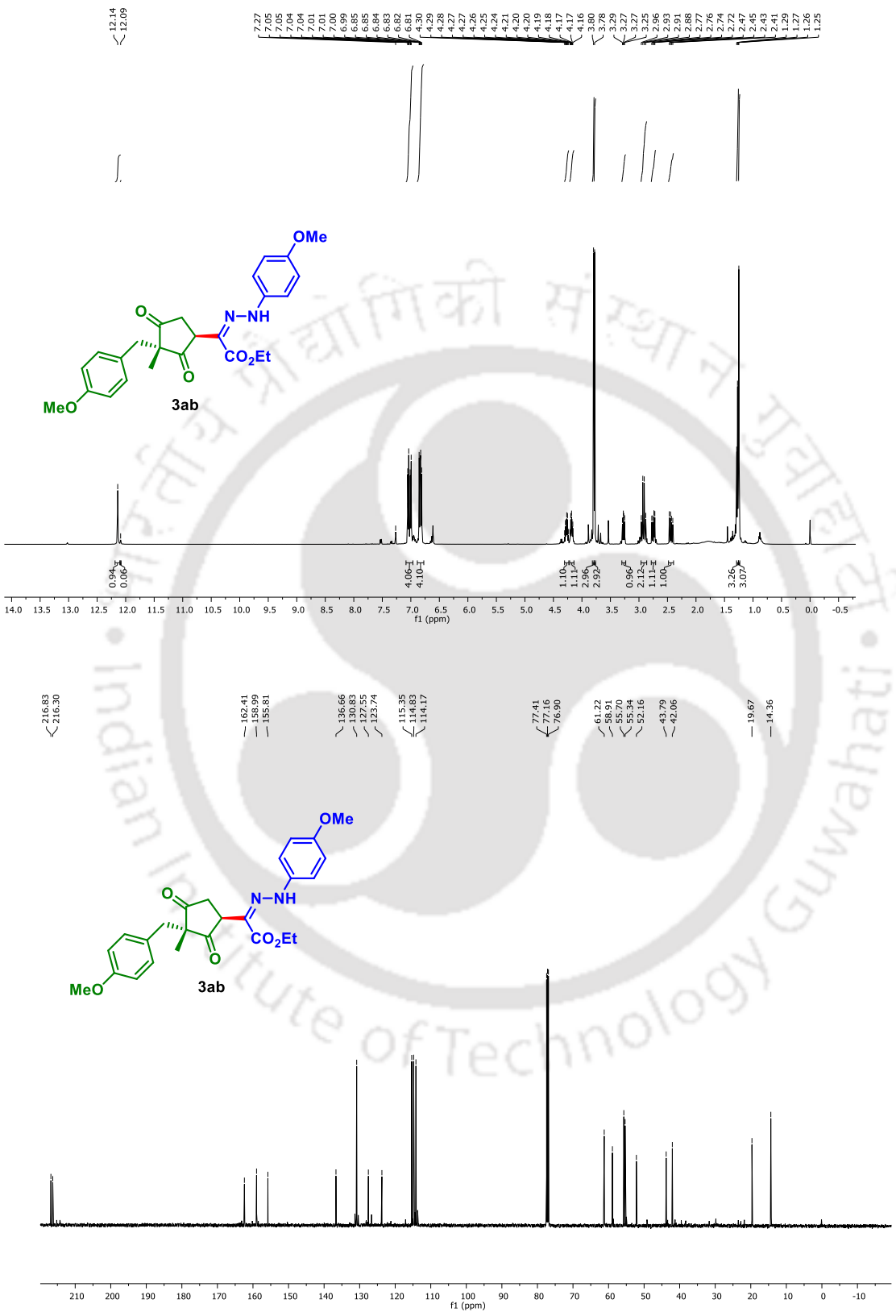


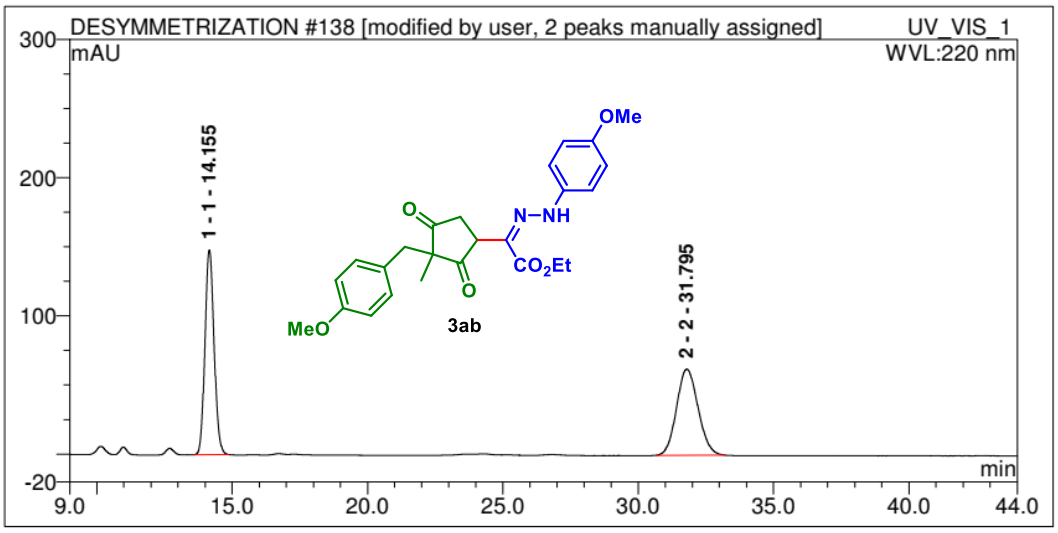


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.265	169.5394	49.7435331	417.0445	n.a.
2	2	17.62666667	171.2876	50.2564669	281.9515	n.a.

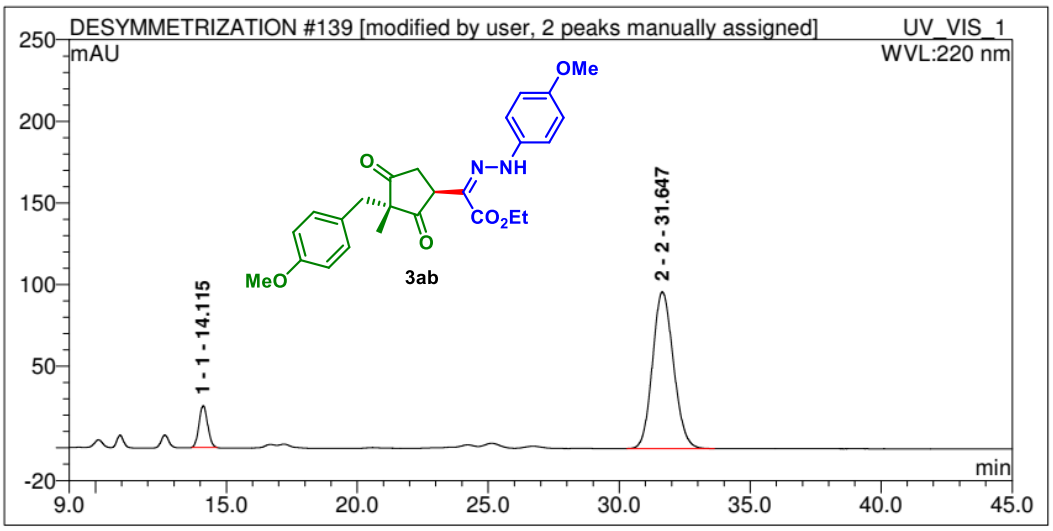


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.08	2.205346	4.255002122	5.96611	n.a.
2	2	17.47	49.624	95.74499788	81.998	n.a.

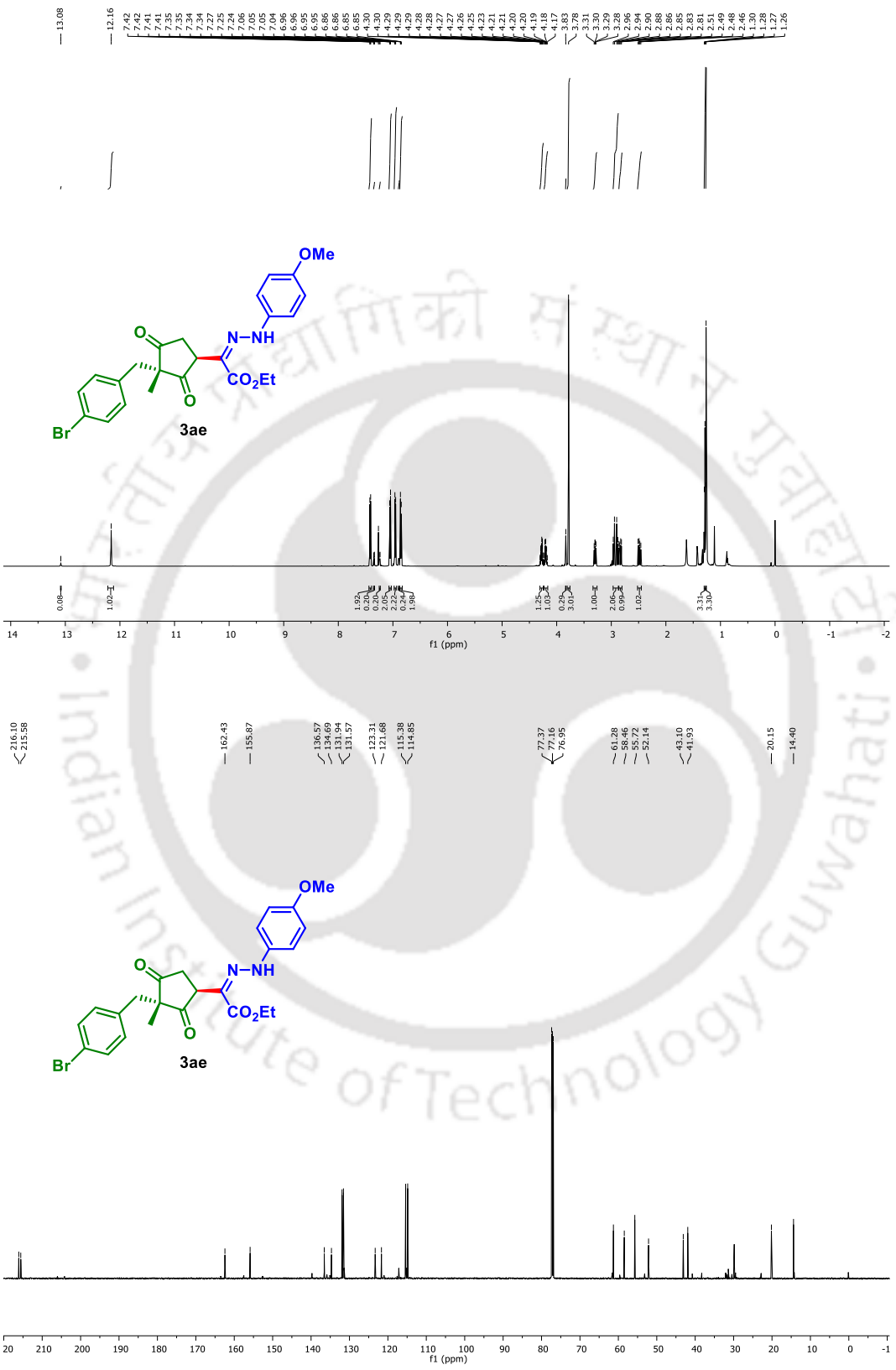


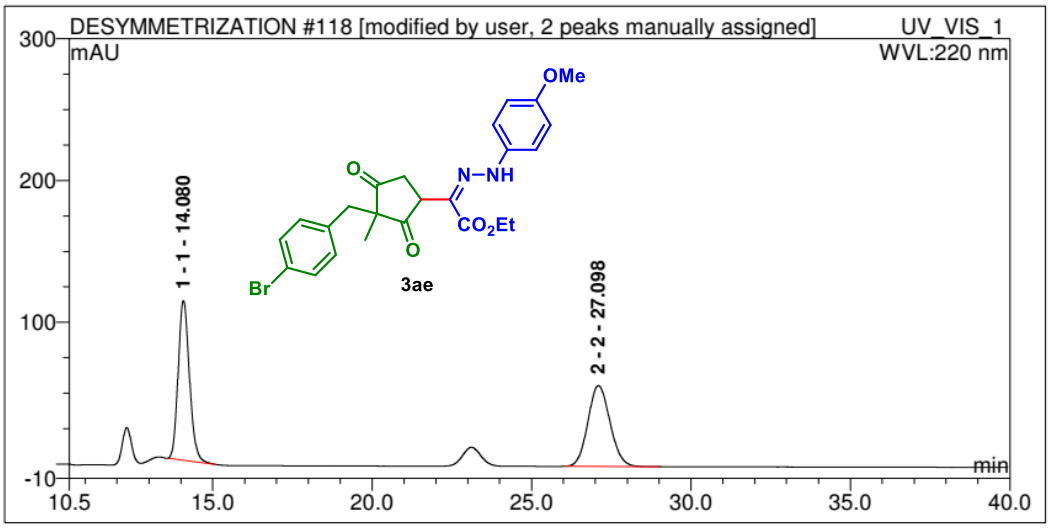


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.16	57.77494	50.20144409	147.7121	n.a.
2	2	31.80	57.311	49.79855591	62.286	n.a.

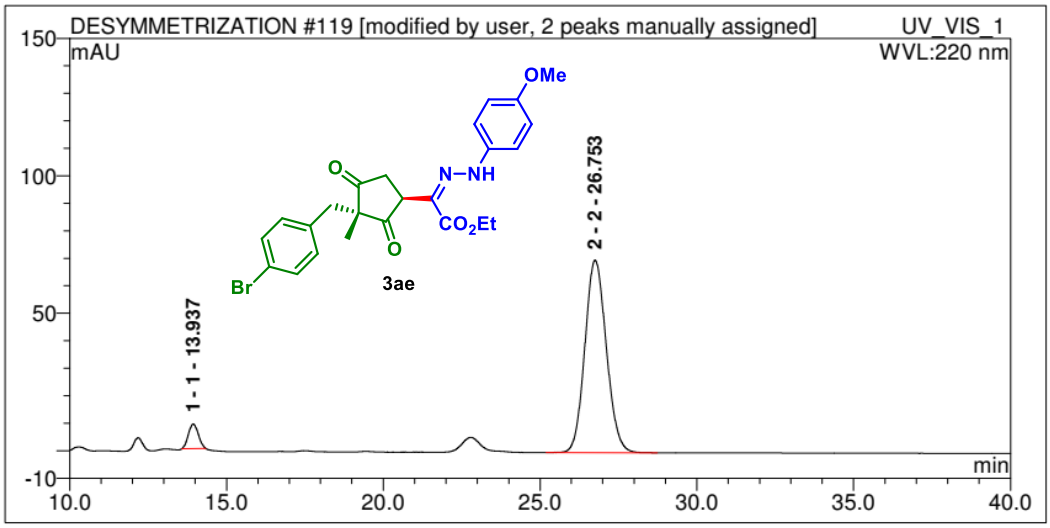


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.12	9.809155	9.911373824	25.6382	n.a.
2	2	31.65	89.160	90.08862618	95.974	n.a.

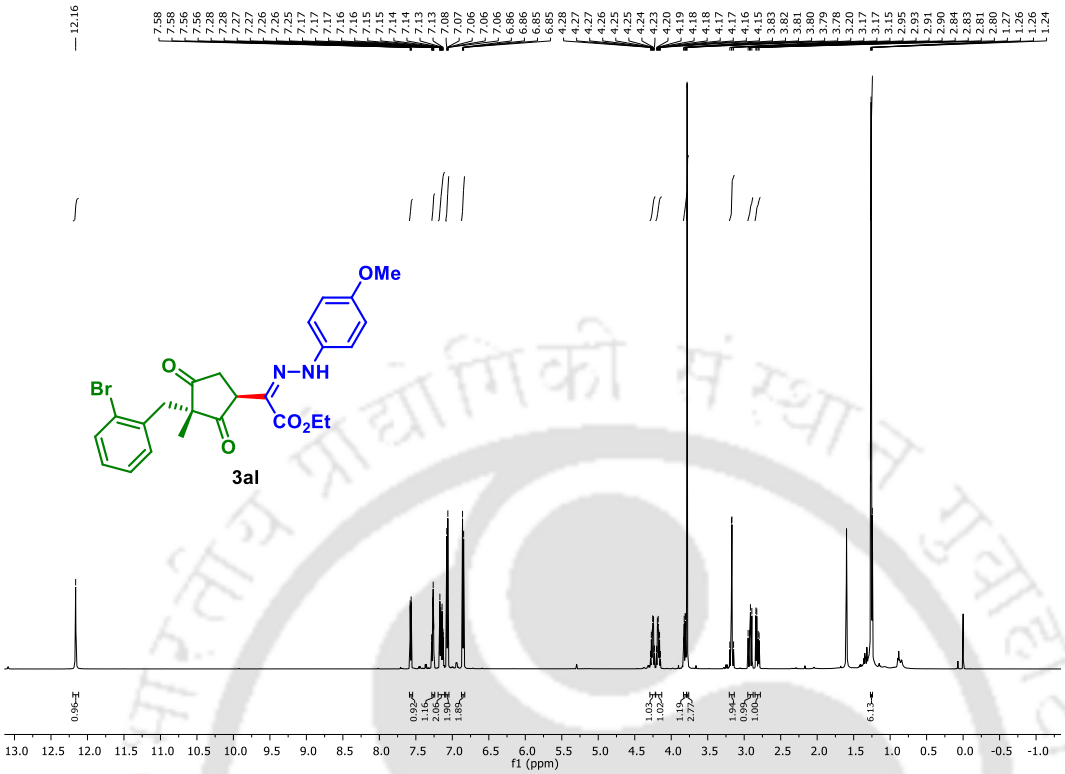


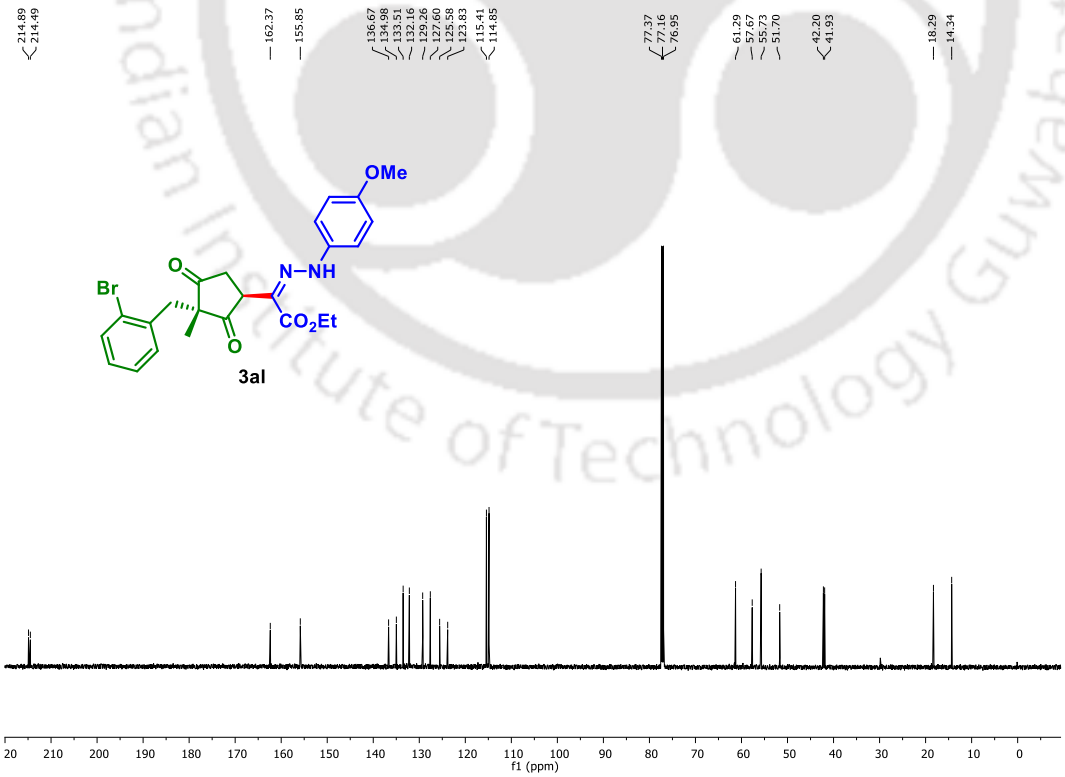


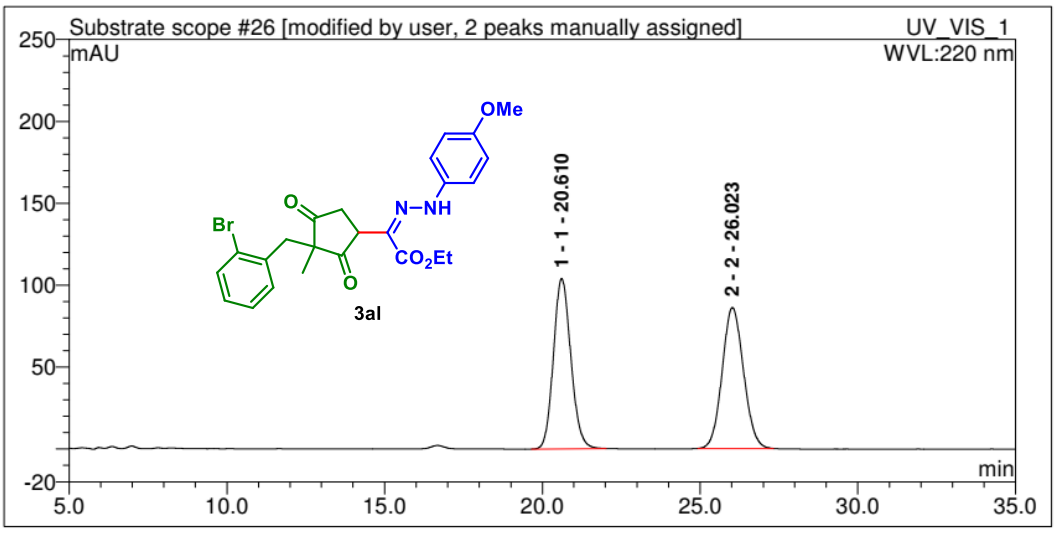
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.08	46.20699	50.24918728	112.5857	n.a.
2	2	27.10	45.749	49.75081272	57.027	n.a.



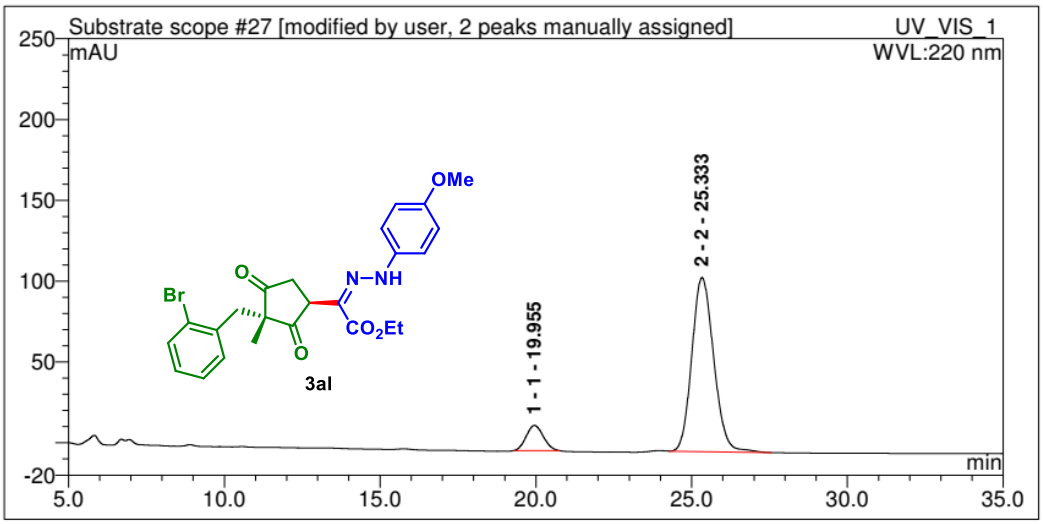
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	13.94	3.28822	5.576105392	8.97443	n.a.
2	2	26.75	55.682	94.42389461	70.055	n.a.







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.61	66.62214	49.62100584	104.0277	n.a.
2	2	26.02	67.640	50.37899416	85.978	n.a.



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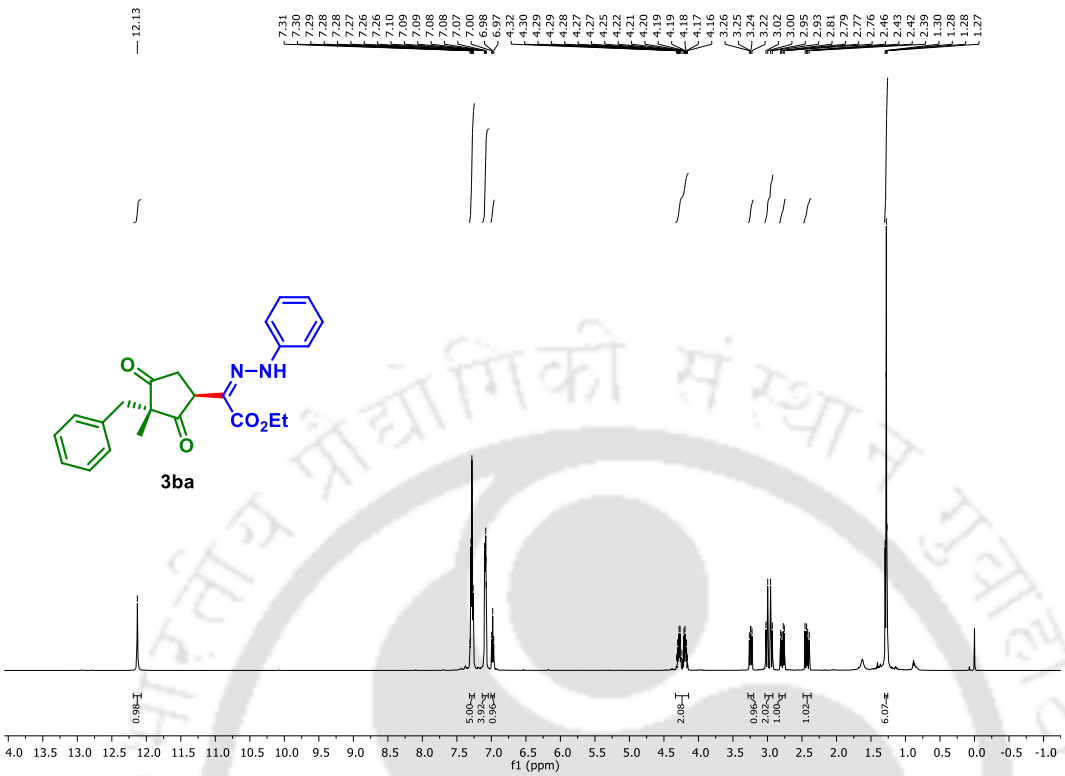

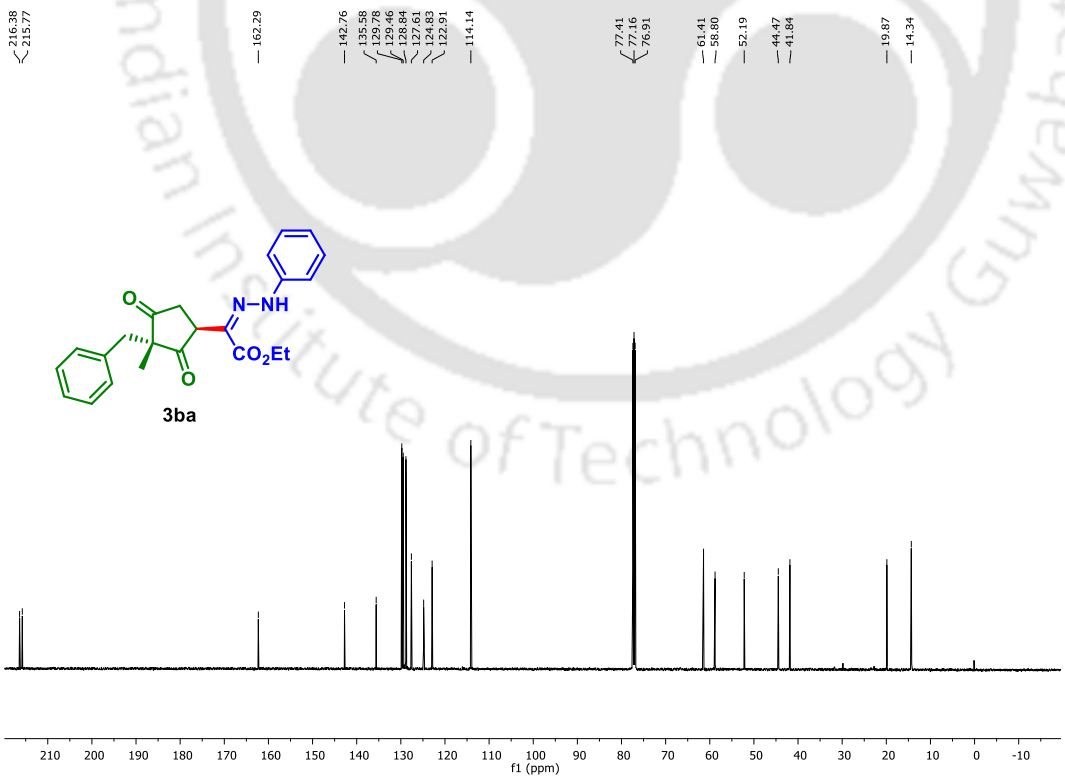

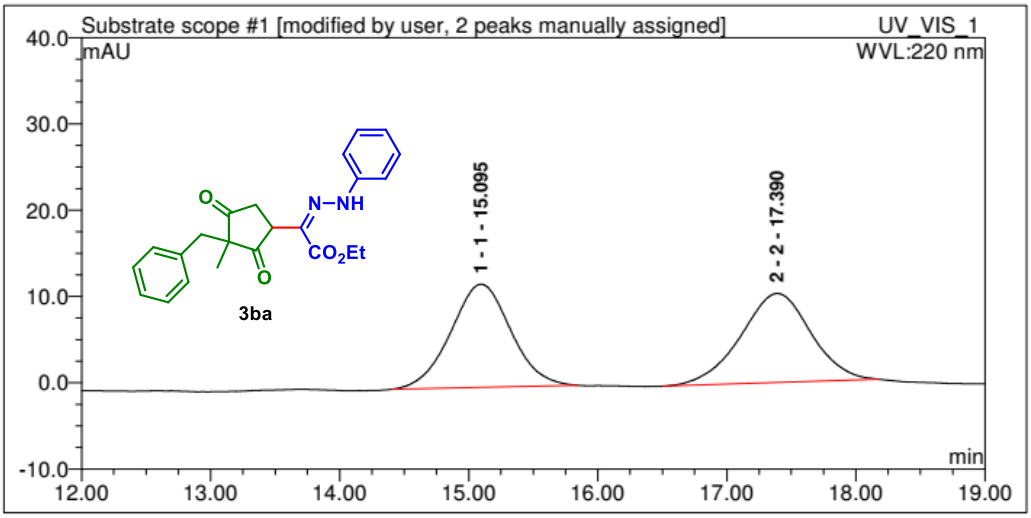

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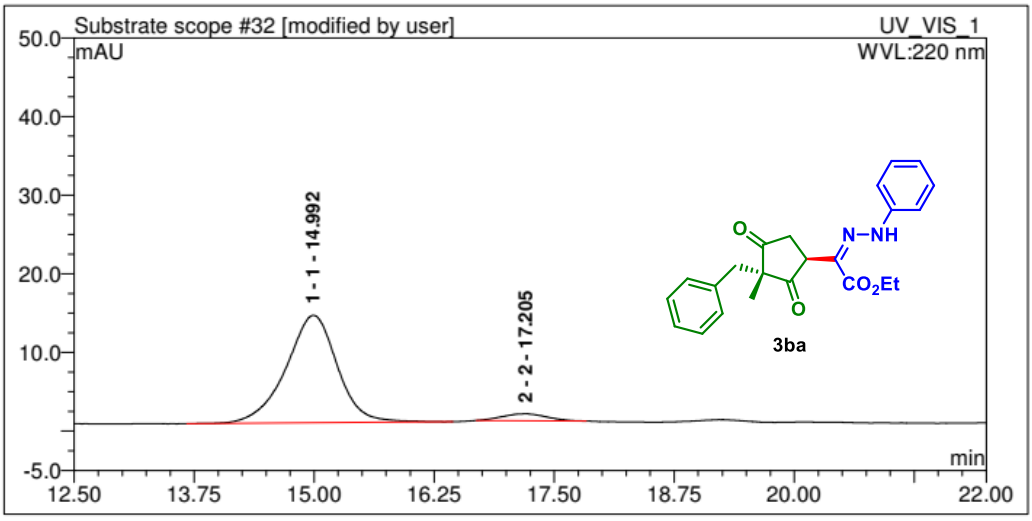

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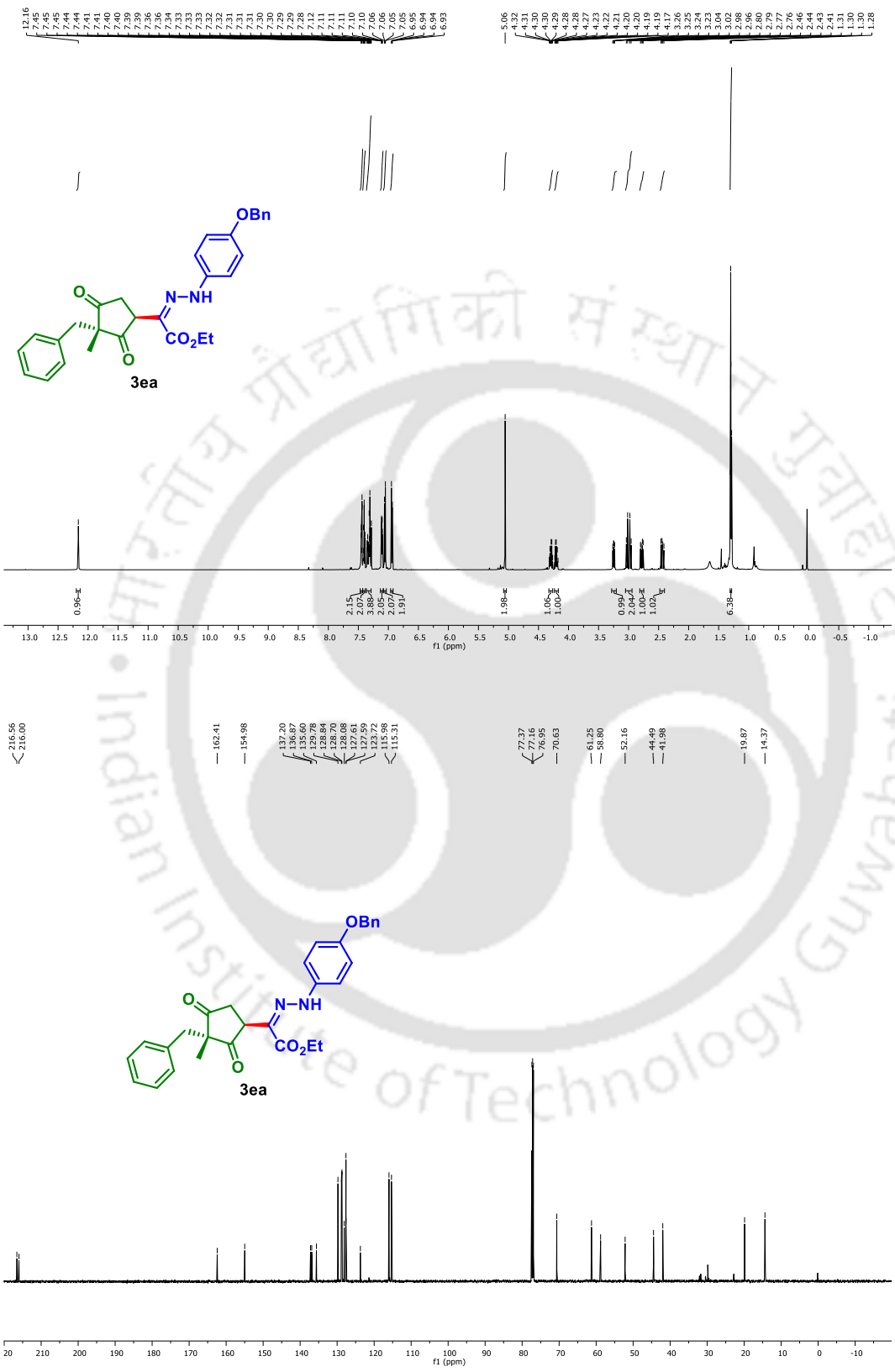

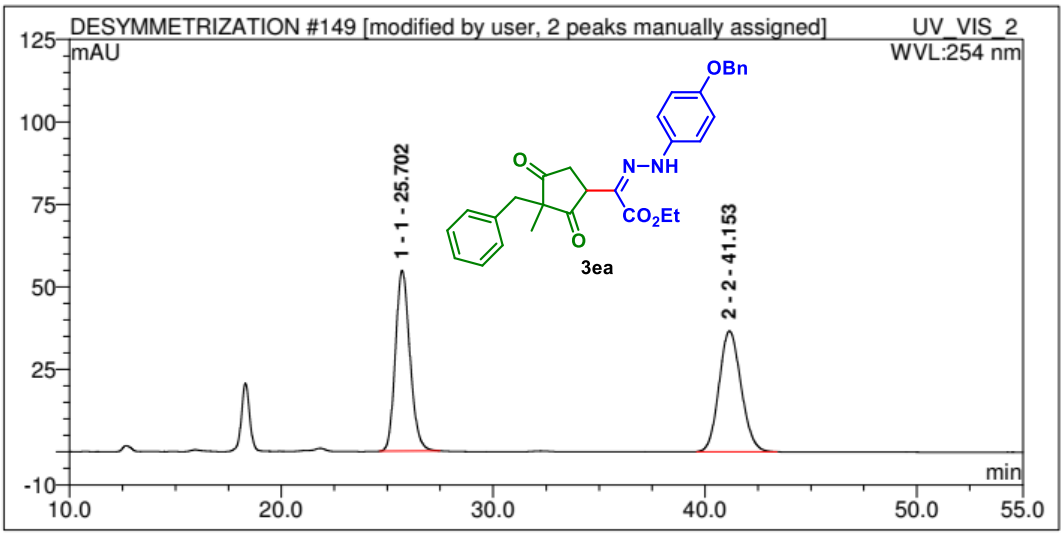

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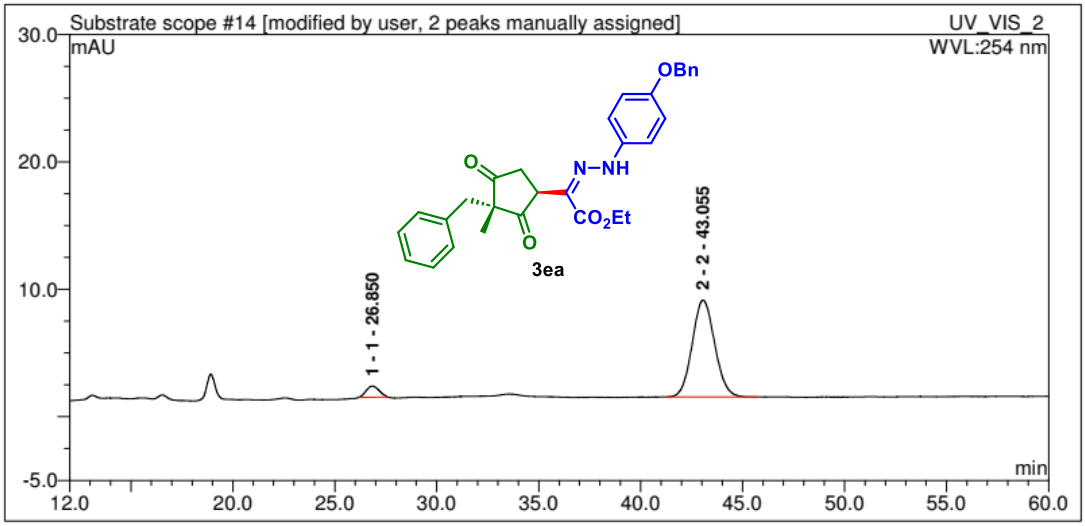

No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	26.85	0.63896	6.172187589	0.87808	n.a.
2	2	43.055	9.713284	93.82781241	7.59159	n.a.

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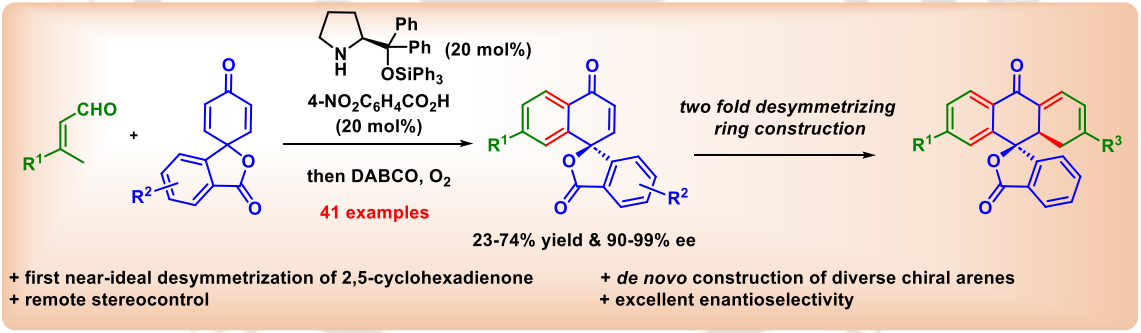
Chapter V

Catalytic Asymmetric Desymmetrizing [4+2] Cycloaddition/Base Mediated Oxidative Aromatization Sequence: de novo Synthesis of Isobenzofuranone Embedded Chiral Arenes

Abstract: Asymmetric desymmetrizing [4+2] cycloaddition/base-mediated oxidative aromatization reaction between *β*-methyl cinnamaldehydes and spirophthalide 2,5-cyclohexadienones has been developed here. The reaction progressed through the formation of an in situ chiral dienamine intermediate resulting in densely functionalised spirocyclic isoben-zofuranone embedded chiral arenes with high yields and excellent enantioselectivities. Additionally, a twofold desymmetrization reaction was carried out, yielding products with high enantioselectivities.



5.1 Introduction

The synthesis of benzene-fused γ-lactones, such as benzofuranones and isobenzofuranones has long piqued the interest of the organic synthesis community because they are crucial structural elements of many naturally occurring chemicals and synthetically produced bioactive molecules.[1] The isobenzofuranone unit, also known as phthalide, is the building block of phthalein dyes, a significant class of organic dyes.[2] Furthermore, chiral natural compounds like butylphthalide (**A**), an essential part of cerery oil that is used to treat cerebral ischaemia, contain the isobenzofuranone framework (Figure 1).[3] Furthermore, spiro-cyclic isobenzofuranones, which occur naturally, have emerged as significant motifs for biological evaluations (Figure 1). For example, sinaspirolide (**B**) is used in traditional Chinese medicine,[4] (-)-arnottin II (**C**) has antibacterial qualities[5] and (-)-juglanaloid A (**D**) fights Alzheimer's disease.[6] The synthetic spirocyclohexane isobenzo-furanone (**E**) is an antagonist of the Y-5 receptor.[7] While the naturally occurring spirocyclohexane isobenzo-furanone ansaspirolide (**F**) is a serotonin receptor (5-HT7) binding molecule.[4] Due to these diverse biological properties asymmetric synthesis of spirocyclic isobenzofuranone systems is highly desired.[8]

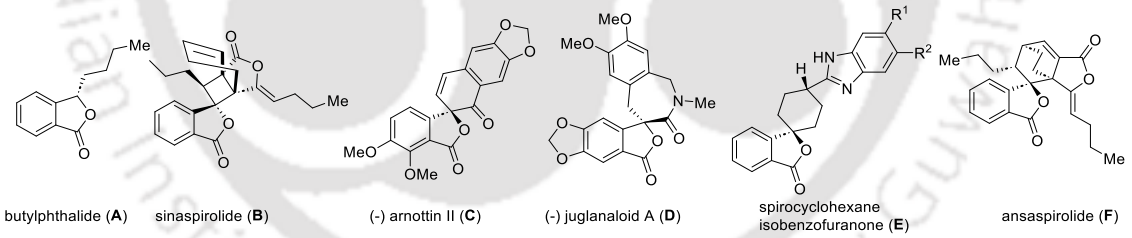


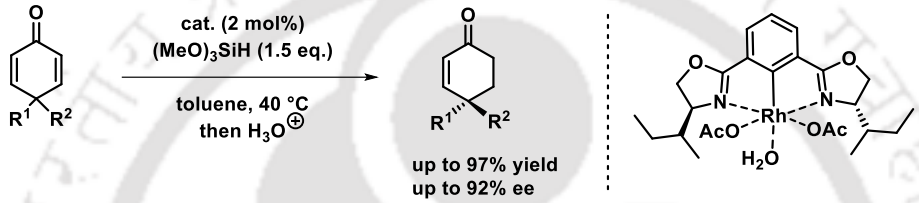
Figure 1: Representative bioactive isobenzofuranone

A versatile and affordable method for creating enantioenriched products with complex structures and numerous stereogenic centres is catalytic asymmetric desymmetrization strategy, which is achieved by differentiating two enantiotopic groups on the readily accessible symmetric or prochiral molecules.[9] Recently, desymmetrizations of 2,5-cyclohexadienones catalysed by organocatalysts or transition metals have emerged as useful techniques for obtaining enantiopure entities.[10] Few studies have been conducted on intermolecular desymmetrizations, whereas the majority of organocatalytic 2,5-cyclohexadienone desymmetrization processes have been developed intramolecularly.[11]

5.2 Literature Survey

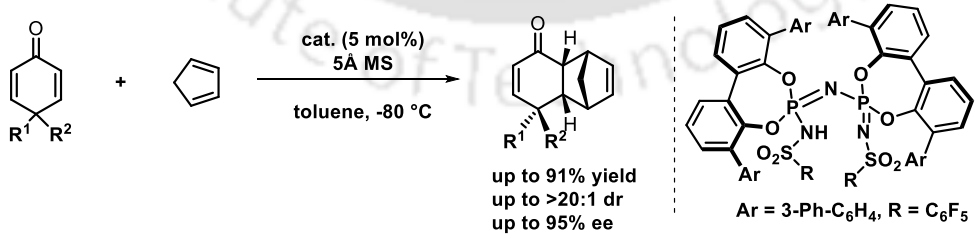
5.2.1 Previous reports on enantioselective desymmetrization of 2,5-cyclohexadienones:

In 2016, Nishiyama group demonstrated enantioselective desymmetrizing conjugate hydrosilylation of prochiral differently *γ,γ*-disubstituted cyclohexadienone derivatives to the corresponding cyclohexenones with a remote chiral all-carbon quaternary centre at the γ-position (Scheme 1).[12a] For this transformation, chiral rhodium-bis(oxazolinyl)-phenyl complexes was used as catalysts.



Scheme 1: Asymmetric induction at remote quaternary centers of cyclohexadienones by rhodium-catalyzed conjugate hydrosilylation

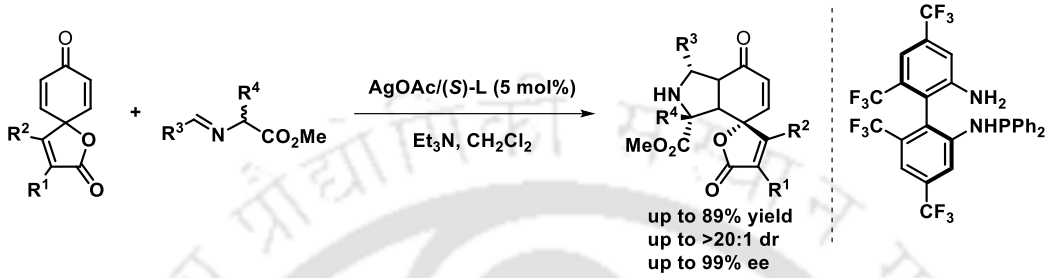
In 2020, List group have created an effective asymmetric intermolecular Diels-Alder reaction between cross-conjugated dienones with electronically unbiased quaternary centres and cyclopentadiene, which is catalysed by Brønsted acid and yields complex products (Scheme 2).[12b] The cycloaddition is guided by IDPi catalyst's high acidity and confined structure, producing the corresponding adducts with up to five stereo-centers in excellent yields, enantio- and diastereoselectivities.



Scheme 2: Catalytic asymmetric Diels–Alder reactions of cyclohexadienones with cyclopentadiene

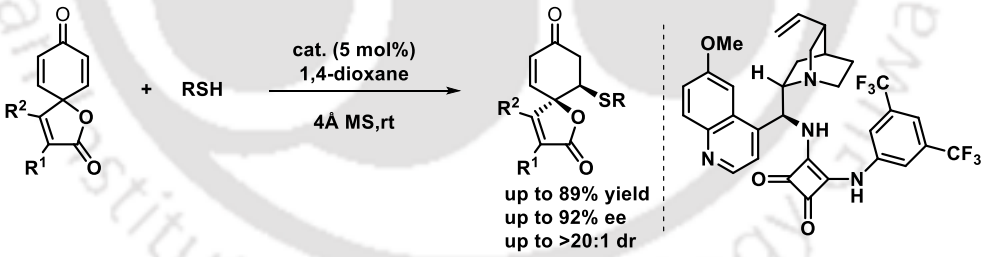
Wang group have reported catalytic asymmetric synthesis of highly functional spirolactone-pyrrolidine derivatives with five contiguous stereocenters and one unique

spiro quaternary stereocenter through the enantioselective desymmetrization of a prochiral spirodienone-lactone via silver-catalyzed asymmetric 1,3-dipolar cycloaddition (Scheme 3).[12c] This catalytic system demonstrated a wide range of substrates, good diastereoselectivity, and enantioselectivity.



Scheme 3: Silver-catalyzed enantioselective synthesis of spirolactone-pyrrolidines

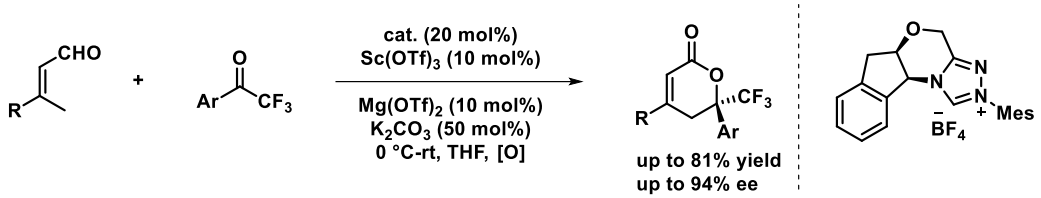
In 2023, Chauhan *et al.* demonstrated squaramide-catalyzed desymmetrization reaction for asymmetric synthesis of spirocyclic isobenzofuranones (Scheme 4).[11b] A bifunctional squaramide catalyst catalyses the reactions of spiro-phthalide 2,5-cyclohexadienones with aryl thiols, producing isobenzofuranones with a cyclohexenone ring as single diastereomers in moderate to good enantioselectivities (up to 92% ee).



Scheme 4: Asymmetric synthesis of spirocyclic isobenzofuranones via a squaramide-catalysed desymmetrizing sulfa-Michael addition

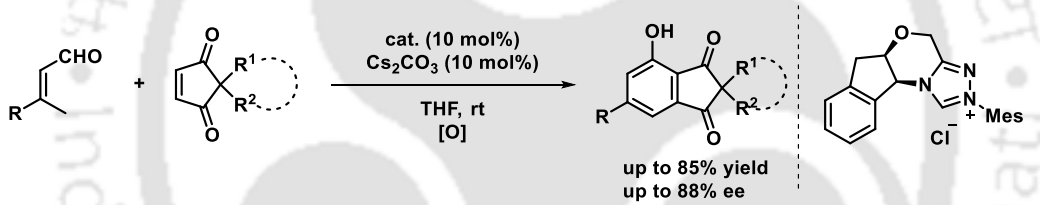
5.2.2 Previous reports on enantioselective cyclization reaction with *α,β*-unsaturated aldehydes :

In 2012, Chi *et al.* demonstrated N-heterocyclic carbene (NHC) catalyzed the oxidative γ-functionalization of enals to produce unsaturated δ-lactones (Scheme 5).[13a] Lewis acid [$Sc(OTf)_3$ or combined $Sc(OTf)_3/Mg(OTf)_2$] and NHC cooperative catalysis was used to control enantioselectivity with the relatively distant enal γ-carbon.



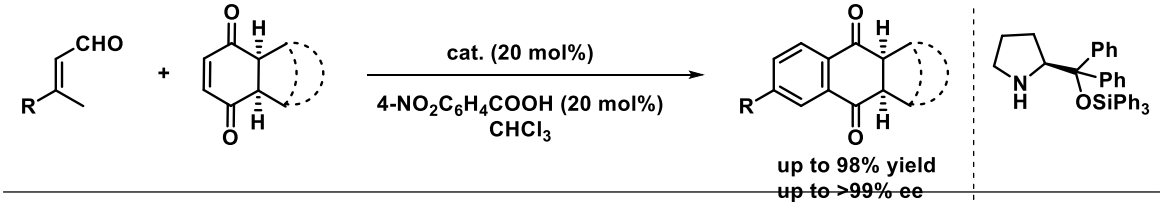
Scheme 5: Oxidative γ-addition of enals to trifluoromethyl ketones by Lewis acid and NHC cooperative catalysis

In 2019 Chi group again demonstrated the enantioselective formal [4+2] construction of multi substituted phenol by NHC catalysis (Scheme 6).[13b] This approach offers using readily available enals and diketones to build a phenol framework while simultaneously installing a distant all-carbon quaternary chiral centre in a highly enantioselective manner through desymmetrization.



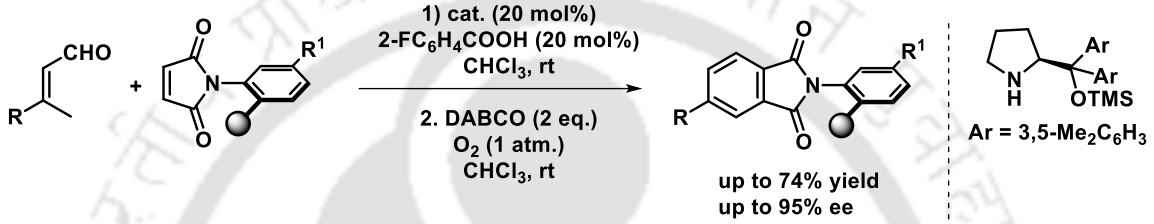
Scheme 6: NHC catalysed desymmetrization of cyclopentene-1,3-dione

In 2022, Mukherjee group reported a desymmetrization approach for enantioselective *de novo* construction of centrally chiral unfunctionalized arenes (Scheme 7).[13d] This straightforward procedure, which typically does not need an external oxidant, is based on a [4+2]-cycloaddition between polycyclic meso-cyclohexene-diones and *α,β*-unsaturated aldehydes. This reaction, which is catalysed by a diphenylprolinol silyl ether, proceeds via a dienamine intermediate and significantly streamlines the process of obtaining chiral arenes that are diversely substituted and possess outstanding enantioselectivities (up to >99%).



Scheme 7: *de novo* construction of chiral arenes through desymmetrizing oxidative [4+2]-cycloaddition

In 2022, Mukherjee group again reported a *de novo* arene construction strategy to create the atroposelective desymmetrization of prochiral N-aryl maleimides by converting them to axially chiral phthalimides (Scheme 8).[13e] Through oxidative [4 + 2]-cycloaddition with *α,β*-unsaturated aldehydes, this reaction is catalyzed by a prolinol TMS-ether and produces only a chiral C−N axis distant from the reaction sites with high enantioselectivity (up to 95% ee).

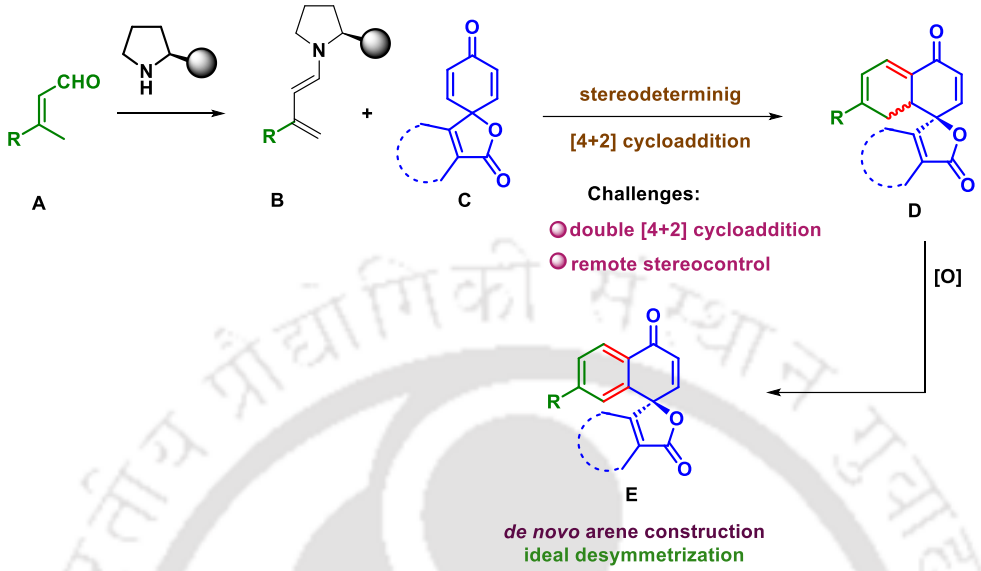


Scheme 8: Asymmetric catalytic generation of remote C−N axial chirality through atroposelective de novo arene construction

5.3 Concept

As far as our literature survey, prochiral 2,5-spirocyclohexadienones do not exhibit any other known organocatalytic asymmetric intermolecular annulation reactions. Here, we envisioned a catalytic enantioselective *de novo* synthesis of chiral arenes (**E**) with spirocyclohexenone isobenzofuranone motif (**C**) using spirophthalide 2,5-cyclohexadienone desymmetrization (Scheme 9). In order to begin this operation, we suggested a [4+2]-cycloaddition between prochiral spirophthalide 2,5-cyclohexadienone (**C**) and the electron-rich dienamine intermediate (**B**), which is generated from *α,β*-unsaturated aldehyde (**A**) (Scheme 9). This will produce intermediate **D** and an oxidation process would yield the necessary chiral arene **E** where the enantiocontrol occurs remotely by the aldehyde group. Also double [4+2] cycloaddition can occur with spirocyclohexenone isobenzofuranone (**C**). Hence remote stereocontrol and controlling double [4+2] cycloaddition are the main challenges of this work. By this way we can

achieve ideal desymmetrization of 2,5-spirocyclohexadienone (without generation of any new chiral center).

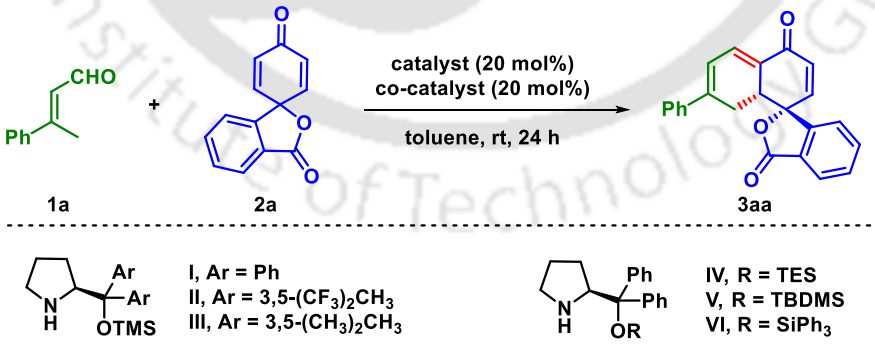


Scheme 9: Proposed route for desymmetrization of 2,5-spirocyclohexadienone for *de novo* synthesis of isobenzofuranone embedded chiral arenes

5.4 Results and Discussion

5.4.1 Optimization of catalyst and reaction conditions:

Table 1. Catalyst screening and optimization of the [4+2] cycloaddition step



Entry[a]	Catalyst	Co-catalyst	Yield[%][b]	ee[%][c]
1	**I**	$PhCO_2H$	64	76
2	**I**	4-FC_6H_4COOH	45	83

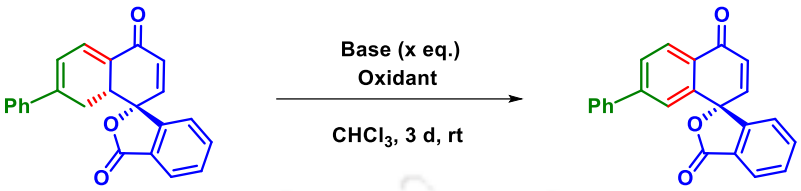
3	**I**	4-BrC_6H_4COOH	42	80
4	**I**	4-$NO_2C_6H_4COOH$	72	84
5	**II**	4-$NO_2C_6H_4COOH$	35	16
6	**III**	4-$NO_2C_6H_4COOH$	45	64
7	**IV**	4-$NO_2C_6H_4COOH$	65	95
8	**V**	4-$NO_2C_6H_4COOH$	70	96
9	**VI**	4-$NO_2C_6H_4COOH$	76	98
10[d]	**VI**	**4-$NO_2C_6H_4COOH$**	**85**	**98**

[a]Unless otherwise mentioned, reactions were carried out with 0.15 mmol of **1a** with 0.1 mmol of **2a** in 1 mL toluene using 20 mol% catalyst, 20 mol% co-catalyst at rt for 24 h. [b]Isolated yield after silica gel column chromatography and dr>20:1 in all cases. [c]Determined by chiral HPLC. [d]Reaction was run with 2 equivalents of **1a** in 0.2 (M) toluene.

With the above mentioned concept we put a model reaction between *β*-methyl cinnamal-dehyde **1a** and spirocyclohexadienone **2a** with 20 mol% (S)-diphenylprolinol trimethylsilyl (TMS)-ether **I** and 20 mol% benzoic acid as co-catalyst in toluene (Table 1, entry 1). To our delight, after 24 h spirocyclic isobenzofuranone **3aa** was isolated in 64% yield with 76% ee as a single diastereomer and the structure was confirmed by ^{1}H, ^{13}C NMR spectroscopy and X-ray crystallography. Then, using catalyst **I**, we evaluated other acid co-catalysts. Interestingly, 4-nitrobenzoic acid proved to be the best co-catalyst, significantly increasing yield and ee (entry 4). To improvise ee, we then considered increasing steric crowding on the diphenylprolinol silyl ether's silyl protecting group, and this worked well. With (S)-diphenylprolinol triethylsilyl (TES)-ether **IV**, the enantioselectivity increased to 95% ee (entry 7). Slight improvement in enantioselectivity was seen with ^{t}butyldimethylsilyl-protected (S)-diphenylprolinol **V** (entry 8). Ultimately, the optimal catalyst was proved to be triphenylsilyl-protected diphe-nylprolinol catalyst **VI**, which yielded product **3aa** in 76% yield with 98% ee (entry 9). The yield got enhanced

to 85% by running the reaction with 2 equivalents of **1a** (entry 10). Further, although additional solvents were investigated, improved yield was not attained.

Table 2: Optimization of reaction conditions for oxidative aromatization



3aa 4aa

Entry	Base (x eq.)	oxidant	yield (%)[b]	ee(%)[c]
1.	-	DDQ (2 eq.)	<10	98
2.	-	MnO_2 (2 eq.)	<10	98
3.	Pyrrolidine (1.2)	O_2	21	98
4.	DBU (1.2)	O_2	15	98
5.	DABCO (1.2)	O_2	42	98
6.	DABCO (2)	O_2	56	98
7.	**DABCO (4)**	**O_2**	**80**	**98**
8.	DABCO (6)	O_2	75	98

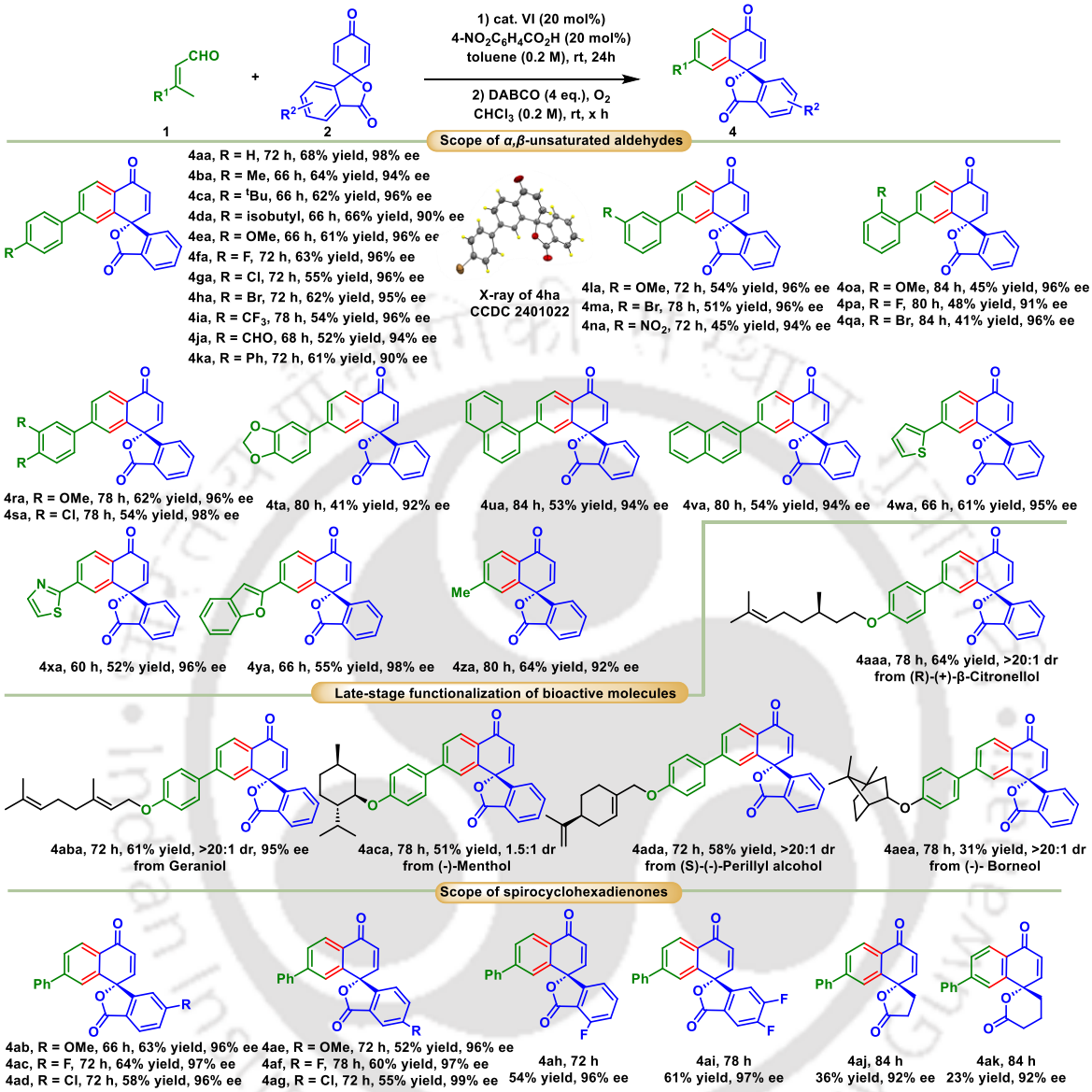
[a] Unless otherwise mentioned, reactions were carried out with 0.05 mmol of **3aa** in 0.2 (M) $CHCl_3$ under O_2 balloon at room temperature for 3 d. [b] Yields correspond to isolated yield. [c] Enantiomeric excess was determined by HPLC analysis using a stationary phase chiral column.

After getting the optimized condition for [4+2]-cycloaddition step, we focussed on the oxidative aromatization of **3aa** to 7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione **4aa** (Table 2). Initially, oxidants like DDQ and MnO_2 were tested, however the product **4aa** was obtained in poor yields (entries 1-2). Following that, base-mediated oxidative aromatization was examined and found to be successful. Both pyrrolidine and DBU can promote the oxidative aromatization reaction in the presence of oxygen balloon and provided the product **4aa** in 21% and 15% yields respectively (entries 3-4). The enantioselectivity was unchanged. A higher yield of 42% was detected with DABCO (entry 5). Then the number of equivalents of DABCO was varied and a higher yield of 56% was achieved with two equivalents of DABCO (entry 6). Ultimately, four

equivalents of DABCO produced the highest yield of 80% (entry 7), while adding more DABCO produced a lower yield of **4aa** (entry 8).

5.4.2 Substrate scope:

With the optimized conditions in hand, we next examined the substrate range for this [4+2]-cycloaddition-oxidative aromatization reaction sequence (Scheme 10). Initially, a variety of *β*-methyl cinnamaldehydes were investigated. At first various substitutions were incorporated at the *para*-position of the aryl group of **1a** and excellent results were obtained. For instance, *para*-alkyl substituted *β*-methyl cinnamaldehydes **1b**-**1d** reacted smoothly to produce products **4ba**-**4da** with high enantioselectivities and acceptable overall yields. Also the results for product **4ea** with the *para*-anisyl group remained unchanged. The reaction was then conducted using various halo-substituted *β*-methyl cinnamaldehydes **1f**-**1h**. Results for the **4fa**-**4ha** products were gratifyingly excellent. The structure of **4ha** was confirmed from X-ray crystallography. Cross-coupling reactions could be used to further refine these products. The intended products, **4ia** and **4ja**, were obtained in moderate yields with high enantioselectivities when electron-poor trifluoromethyl and CHO groups were introduced. Product **4ka** having a biphenyl substituent was obtained in 90% ee. Additionally, the reaction produced products **4la**-**4na** in moderate overall yields with excellent enantioselectivities when meta-substituted aryl groups containing *β*-methyl cinammaldehydes **1l**-**1n** were employed. Also, the products **4oa**-**4qa** with *ortho*-substitution was obtained in acceptable yields with high enantioselectivities. In case of 3,4-disubstituted aryl groups containing *β*-methyl cinnamaldehydes **1r**-**1t,** excellent results were obtained for products **4ra**-**4ta**. Specifically, **4sa** showed an outstanding 98% ee. Naphthyl substitution also performed well and high enantioselectivities were found for products **4ua** and **4va**. Various heterocyclic groups containing *β*-methyl cinnamaldehydes **1w**-**1y** also participated in the reaction and the products **4wa**-**4ya** were obtained in excellent enantioselectivities. The reaction was then initiated with an aliphatic aldehyde, 3-methylbut-2-enal (**1z**), and the desired product **4za**, was obtained in 64% overall yield with 92% ee.



Scheme 10. Substrate scope[a]

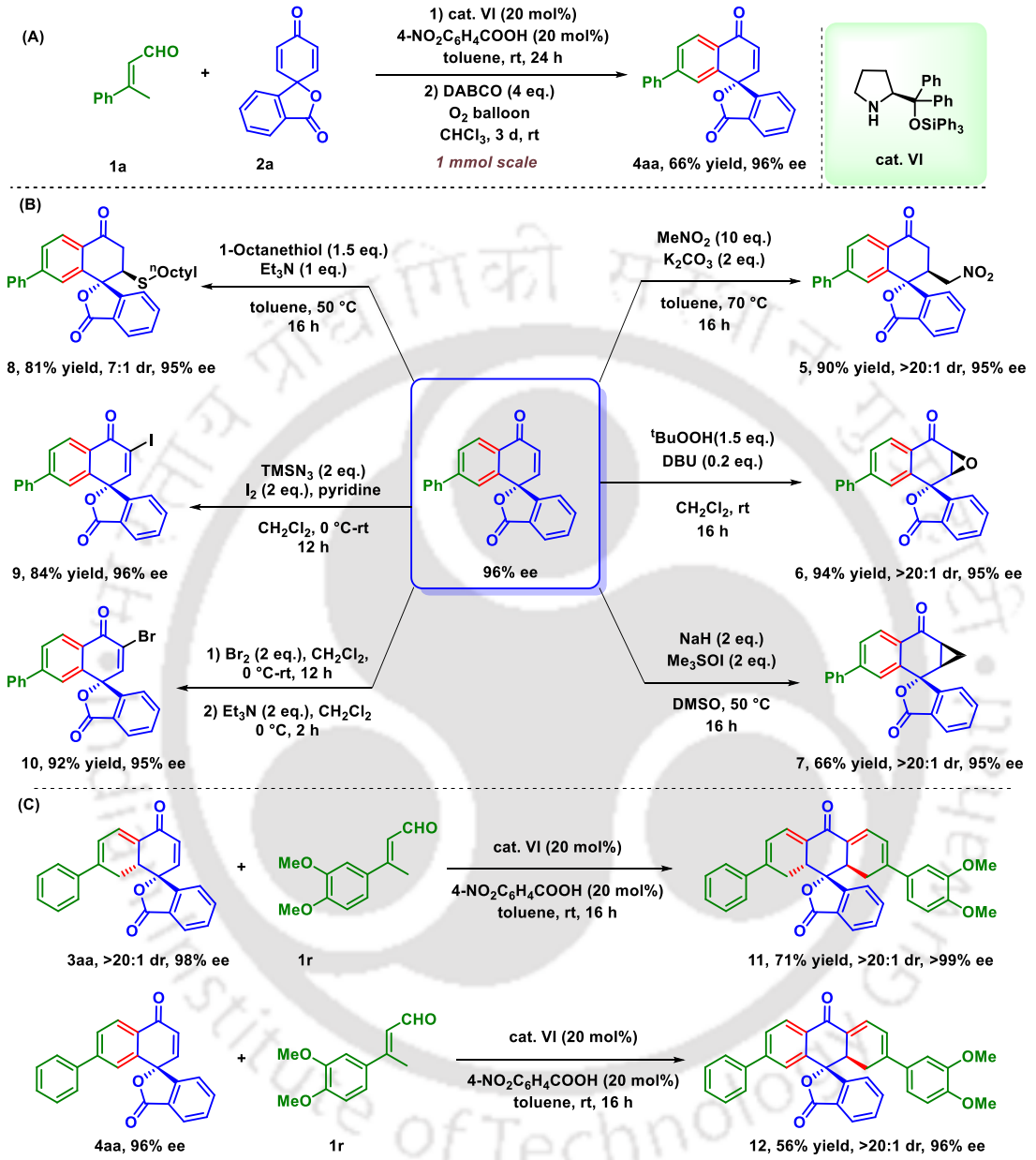
[a]The reactions were carried out in the conditions as indicated in scheme 10 with 0.2 mmol of **1** and 0.1 mmol of **2**. Yields correspond to the isolated yields after silica gel column chromatography and ee was determined by HPLC. Time refers to the reaction time required for the oxidative aromatization step.

Then a series of late stage functionalization of bioactive molecule was performed with our protocol (Scheme 10). First, substrate **1aa**, which is derived from (*R*)-citronellol, was used in the reaction. Pleasingly, the reaction proceeded smoothly, yielding product **4aaa** in 64%

yield as a single diastereomer. Similarly, geraniol derived substrate **1ab** undergoes the reaction, forming product **4aba** in acceptable yield of 61% and high enantioselectivity (95%). The reaction also went well with a (-) menthol motif substrate **1ac** and obtained the product **4aca** in 51% yield and 1.5:1 dr. Also substrate **1ad**, which was derived from (S)-perillyl alcohol, employed in the reaction and the product **4ada** was obtained as a single diastereomer in a 58% yield. Lastly, Substrate **1ae**, which is derived from (-)-Borneol, also took part in the reaction to produce **4aea**. A moderate yield of 31% was noted, even though high diastereoselectivity for **4aea** was detected.

The scope of spirocyclohexadienones was then examined (Scheme 10). Hence various spirocyclohexadienones **2** was prepared and performed reaction with *β*-methyl cinnamaldehyde **1a**. At first, various aryl substitutions were tested, and the results were gratifyingly good. For instance, 4-methoxy substituted spirocyclohexadienone **2b** and *β*-methyl cinnamaldehyde **1a** were employed under standard reaction condition and the desired spiro compound **4ab** obtained with a 63% overall yield and 96% ee. Also, for 4-halo substituted products **4ac** and **4ad**, enantioselectivities and yields were excellent. Next, we screened the reaction for spirocyclohexadienones **2e-2g** that contained a 5-substituted aryl group. To our delight, the reactions proceeded smoothly, yielding products **4ae**-**4ag** with outstanding enantioselectivities and acceptable overall yields. Then 6- position having fluoro substitution was performed and the product **4ah** was isolated in 54% overall yield with 96% ee. With 4,5-disubstituted spirocycloexadione **2i**, the intended product **4ai** was produced in 61% yield with 97% ee. Finally, aliphatic spirocyclohexadienones **2j** with a butyrolactone motif and **2k** with a tetrahydro-2H-pyran-2-one moiety was employed in the reaction. Despite of lower yields was found for the products **4aj** and **4ak**, high enantioselectivities was observed in both the cases.

5.4.3 (A) Scale-up experiment. (B) Synthetic elaborations of 4aa. (C) Further ring constructions with 3aa and 4aa.



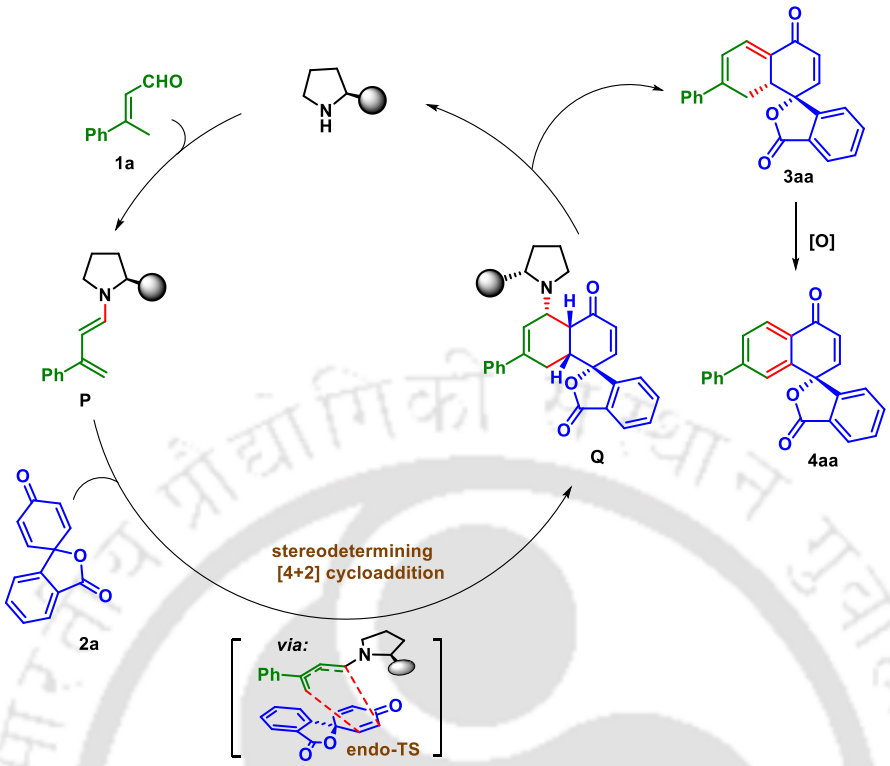
Scheme 11. Scale up reaction and synthetic transformations

These enantioselective desymmetrization reactions are scalable as demonstrated for the scale-up synthesis of **4aa** (Scheme 11A). A scale-up process in 1 mmol scale was performed and product **4aa** was then produced in 66% yield with 96% ee. The polycyclic molecule **4aa** was then subjected to a number of chemical transformations in order to

illustrate synthetic potential of our strategy (Scheme 11B). At first, base-mediated Michael addition of nitromethane was carried out and the intended product **5** was produced as a single diastereomer in 90% yield with retention in enantioselectivity. With a catalytic quantity of DBU present, the epoxidation reaction with ^{t}butyl hydroperoxide was effective, and compound **6** was obtained as a single diastereomer in high yield. After that, **4aa** was subjected to the Corey Chaykovosky cyclopropanation reaction using sodium hydride and trimethylsulfoxonium iodide in DMSO. Remarkably, the reaction proceeded effectively, preserving enantioselectivity while producing cyclopropanated product **7** in acceptable yield. Then base-mediated thia-Michael addition was performed by 1-octanethiol and the desired product **8** was obtained in 90% yield with 7:1 dr while preserving enantioselectivity. Trimethylsilyl azide and iodine were then used in an iodination process. As a result, compound **9** was formed in 84% yield with no enantioselectivity erosion. Similarly, brominated product **10** was synthesized by treating with bromine and triethylamine. Finally, for further arene ring constuction compounds **3aa** and **4aa** were treated with enal **1r** in the presence of catalytic quantities of **VI** and *para*-nitrobenzoic acid (Scheme 11C). Pleasingly, the twofold desymmetrized products **11** and **12** were obtained in outstanding enantioselectivities. To the best of our knowledge, no prior reports of this type of double desymmetrized arene construction was performed.

5.4.4 Proposed reaction mechanism:

A plausible mechanism has been suggested based on the absolute configuration of the product (Scheme 12). Our synthetic strategy is based on the [4+2]-cycloaddition[14] process via dienamine catalysis,[15] initially developed by Jørgensen *et al*.[16] Accordingly, for the formation of cyclohexene derivative **Q**, we suggested a [4+2]-cycloaddition between the prochiral spirophthalide 2,5-cyclohexadienone **2a** and the electron-rich dienamine intermediate **P**, which is generated from *α,β*-unsaturated aldehyde **1a** (Scheme 12). The amine catalyst would then be easily removed from **Q** to generate intermidiate **3aa**, and an oxidation procedure would produce the required chiral arene **4aa**.



Scheme 12. Plausible reaction mechanism

5.5 Conclusion

In conclusion, asymmetric desymmetrizing [4+2] cycloaddition/base mediated oxidative aromatization reaction sequence between β-methyl cinnamaldehydes and spirophthalide 2,5-cyclohexadienones has been created. Using a readily available triphenylsilyl-protected diphenylprolinol catalyst, the highly functionalized spirocyclic isobenzofuranone embedded chiral arenes were produced in high yield with excellent enantioselectivities. Additionally, a twofold desymmetrization reaction and late stage functionalization of bioactive compounds have been shown. A seriers of synthetic transformations like base mediated Michael addition, iodination, bromination, epoxidation and Corey Chaykovosky cyclopropanation have also been carried out. Given the great medicinal utility of densely functionalized isobenzofuranones, our technique may prove beneficial.

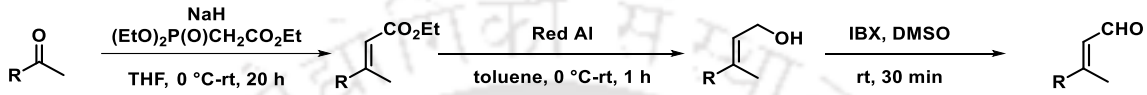
5.6 Experimental section

5.6.1 General Information:

Same as Chapter II.

5.6.2 General procedure for the synthesis of aldehydes (1):

α,β-unsaturated aldehydes were prepared according to previously reported procedures. [1]



To a suspension of NaH (60% dispersion in mineral oil, 15 mmol, 1.5 equiv) in anhydrous THF [0.5(M)] was added dropwise triethyl phosphonoacetate (16 mmol, 1.6 equiv) over 15 min at 0 °C. After 30 min, corresponding ketone (10 mmol, 1.00 equiv) was added to the reaction mixture, which was then allowed to warm to rt. After 20 h, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, quenched by the addition of sat. aq. NH_4Cl (25 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (1-5% petroleum ether/EtOAc) to yield the corresponding ester as a colorless oil.

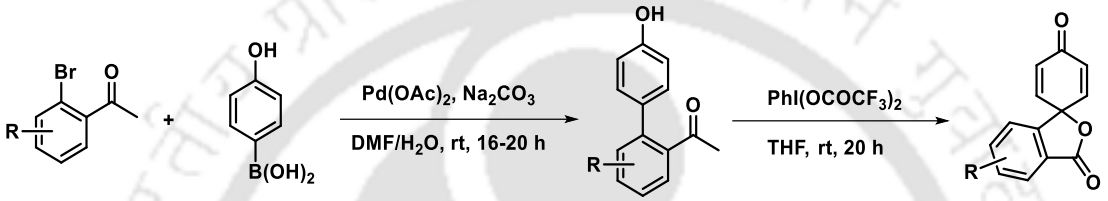
To a stirred solution of the ester (1.00 equiv) in anhydrous toluene (10 mL) at 0 °C was added dropwise Red-Al (60 wt% solution in toluene, 1.15 equiv). The mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 30 min, the completion of the reaction was confirmed by TLC control. The reaction mixture was cooled to 0 °C, diluted with EtOAc (20 mL), quenched by the addition of 1 M HCl (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by flash column chromatography (10-30% petroleum ether /EtOAc) to yield the corresponding alcohol as a colorless oil.

To a stirred solution of the obtained allylic alcohol (1.0 equiv) in anhydrous DMSO (0.2 M) was added a solution of IBX (1.5 eq.) in DMSO (0.4 M), and the whole solution was

stirred for 30 min at room temperature. Then H_2O was added to the reaction mixture, and the resulting cloudy suspension was filtered through celite and washed with EtOAc. The filtrate was extracted with EtOAc, and the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure after filtration. The residue was purified by flash chromatography (5-10% petroleum ether/EtOAc) to afford *α,β*-unsaturated aldehyde.

5.6.3 General procedure for the synthesis of spirocyclohexadienones (2):

Spirocyclohexadienones were prepared according to previously reported procedures. [2]



To a solution of substituted 2-bromoacetophenone derivatives (6.0 mmol, 1.0 eq.) and Na_2CO_3 (2.0 eq.) in DMF:H_2O (v:v = 2 :1, 16 mL) was added phenylboronic acid (7.2 mmol, 1.2 eq.). The reaction mixture was stirred at room temperature for 5 minutes. Palladium (II) acetate (5 mol%) was then added, and the reaction mixture was allowed to stir at room temperature for 16-20 h (monitored by TLC). After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with water and brine and dried over anhydrous Na_2SO_4. The organic phase was filtered and concentrated under vacuum to yield the crude product, which was purified by silica gel flash column chromatography (10-25% petroleum ether/EtOAc) to afford the coupling intermediate.

To a solution of the coupling product (2 mmol, 1.0 eq.) in THF (14.0 mL) was added $C_6H_5I(OCOCF_3)_2$ (6.0 eq.). The mixture was stirred at room temperature in the air for 20-24 h (monitored by TLC). The solvent was removed under reduced pressure, and the residue was directly purified by silica gel flash column chromatography (10-25% petroleum ether/EtOAc) to afford the desired products.

5.6.4 General procedure for the synthesis of catalyst:

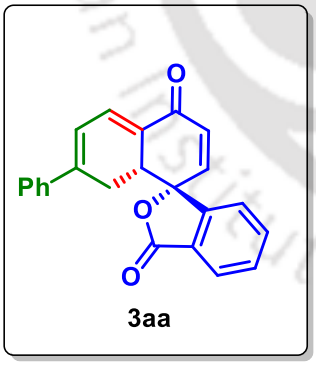
The catalyst (**I - IX**) was prepared according to reported procedures. [3]

5.6.5 General procedure for the catalytic enantioselective synthesis of 4:

A screw cap vial, equipped with a magnetic stirring bar, was charged with **2** (0.1 mmol, 1.0 equiv), 4-$NO_2C_6H_4CO_2H$ (0.02 mmol, 0.2 equiv), and cat. **VI** (0.02 mmol, 0.2 equiv) followed by addition of 0.5 mL dry toluene. Then freshly prepared **1** (0.2 mmol, 2.0 equiv) was added to the reaction mixture and was stirred at rt until TLC revealed complete consumption of **2** (typically 24 h). The crude residue was directly purified by silica gel flash column chromatography (10-20% EtOAc in petroleum ether) to obtain **3**, which was taken in an oven-dried 10 mL round-bottom flask along with DABCO (4.0 equiv) in $CHCl_3$ [0.2(M)] under oxygen atmosphere. The resulting mixture was stirred at 25 °C until TLC revealed complete consumption of **3** (typically 3 days). The crude residue was directly purified by silica gel flash column chromatography to obtain **4** (5-15% EtOAc in petroleum ether).

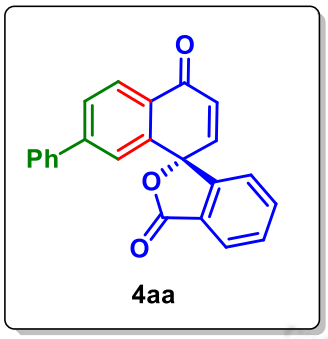
(**N.B.** ee of the 1st step might decrease for prolonged reaction run time. Therefore, coloumn of the 1st step with in 24 h is recommended. Also, liquid packing need to be done for the 1st step to avoid erosion of ee (no need to prepare slurry).

(1S,8a'R)-7'-phenyl-8',8a'-dihydro-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (3aa)



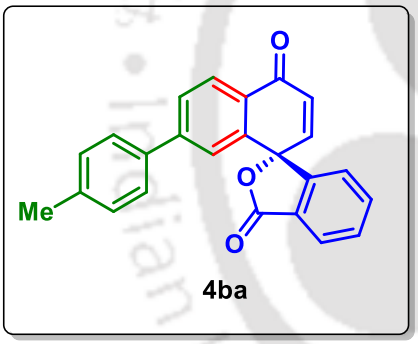
Yellow solid (28.9 mg, yield: 85%); M.P. 202-205 °C, R_f = 0.55 in 3:7 ethyl acetate/hexane, >20:1 dr; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.00 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.78 (td, *J* = 7.5, 1.2 Hz, 1H), 7.66 (td, *J* = 7.5, 1.0 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.43 (dd, *J* = 6.1, 2.9 Hz, 1H), 7.27 (d, *J* = 5.3 Hz, 5H), 6.56 (dd, *J* = 8.9, 2.2 Hz, 3H), 3.76 (ddd, *J* = 19.3, 7.8, 3.0 Hz, 1H), 2.82 (ddd, *J* = 19.3, 16.5, 2.9 Hz, 1H), 2.02 – 1.95 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 184.2, 169.2, 150.8, 143.8, 141.2, 139.2, 135.6, 135.4, 134.0, 130.5, 129.0, 128.7, 127.1, 126.4, 126.3, 125.6, 121.5, 120.5, 82.1, 40.7, 25.6. **ESI HRMS**: calcd. for $C_{23}H_{17}O_3$ $[M+H]^+$ 341.1172, found 341.1173. **HPLC Analysis**: *ee* = 98%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.7 min, t_{minor} = 13.0 min).

(S)-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4aa)



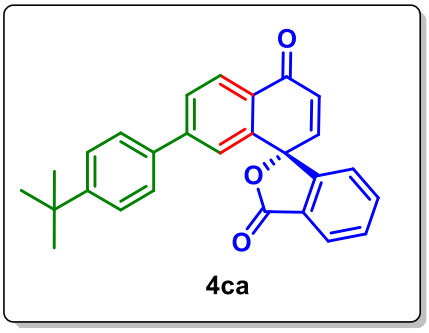
Pale yellow solid (22.9 mg, yield: 68%); M.P. 208-211 °C, R_f = 0.5 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.61 (dtd, *J* = 21.1, 7.4, 1.2 Hz, 2H), 7.46 (dt, *J* = 6.0, 1.4 Hz, 2H), 7.42 – 7.39 (m, 2H), 7.38 – 7.35 (m, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.14 – 7.10 (m, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 146.6, 144.9, 139.6, 139.2, 135.5, 130.4, 130.2, 129.1, 129.1, 128.8, 128.4, 128.0, 127.5, 126.7, 125.1, 125.1, 122.7, 81.9. **ESI HRMS**: calcd. for $C_{23}H_{15}O_3$ $[M+H]^+$ 339.1016, found 339.1016. **HPLC Analysis**: *ee* = 98%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.5 min, t_{minor} = 10.8 min).

(S)-7'-(p-tolyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ba)



Pale yellow solid (22.5 mg, yield: 64%); M.P. 212-215 °C, R_f = 0.52 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.70 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.39 – 7.34 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.07 (m, 2H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.2 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 146.6, 144.8, 139.6, 139.0, 136.3, 135.5, 130.4, 130.2, 129.9, 128.8, 128.1, 127.9, 127.3, 126.6, 125.1, 124.8, 122.7, 81.9, 21.3. **ESI HRMS**: calcd. for $C_{24}H_{17}O_3$ $[M+H]^+$ 353.1172, found 353.1176. **HPLC Analysis**: *ee* = 94%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.9 min, t_{minor} = 15.9 min).

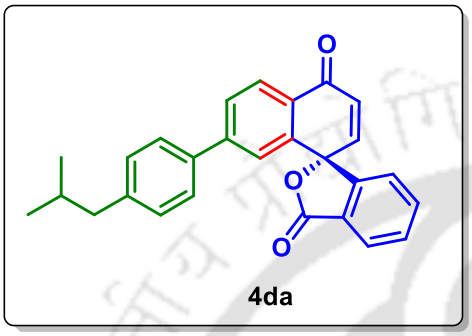
(S)-7'-(4-(tert-butyl)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ca)



Pale yellow solid (24.4 mg, yield: 62%); M.P. 192-195 °C, R_f = 0.7 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.02 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.44 – 7.40 (m, 4H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.11 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 1.32 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 152.2, 150.4, 146.5, 144.8, 139.6, 136.3, 135.5,

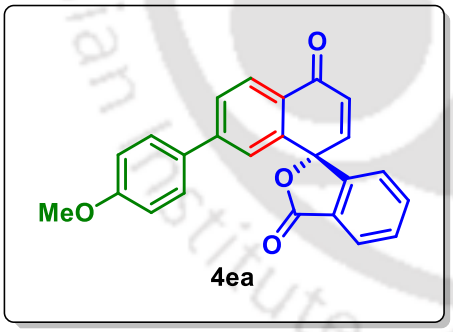
130.4, 130.3, 128.9, 128.2, 127.9, 127.2, 126.6, 126.1, 125.1, 125.0, 122.7, 81.9, 34.8, 31.4. **ESI HRMS**: calcd. for $C_{27}H_{23}O_3$ $[M+H]^+$ 395.1642, found 395.1647. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.0 min, t_{minor} = 9.7 min).

(S)-7'-(4-isobutylphenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4da)



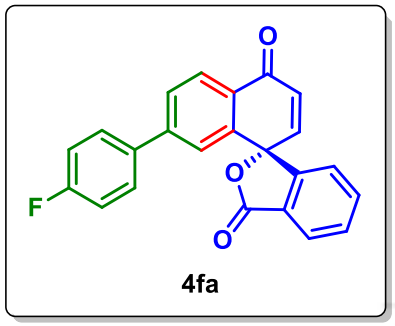
Pale yellow solid (26.0 mg, yield: 66%); M.P. 187-190 °C, R_f = 0.66 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.03 (dt, *J* = 7.3, 1.0 Hz, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.60 (dtd, *J* = 20.6, 7.4, 1.2 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.19 – 7.17 (m, 2H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.11 (dt, *J* = 7.7, 1.0 Hz, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.86 (dq, *J* = 13.5, 6.8 Hz, 1H), 0.90 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 146.6, 144.8, 142.8, 139.6, 136.5, 135.5, 130.4, 130.2, 129.9, 128.8, 128.2, 127.9, 127.1, 126.6, 125.1, 124.8, 122.7, 81.9, 45.1, 30.3, 22.5, 22.5. **ESI HRMS**: calcd. for $C_{27}H_{23}O_3$ $[M+H]^+$ 395.1642, found 395.1640. **HPLC Analysis**: *ee* = 90%, Chiralpak IF Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.6 min, t_{minor} = 19.4 min).

(S)-7'-(4-methoxyphenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ea)



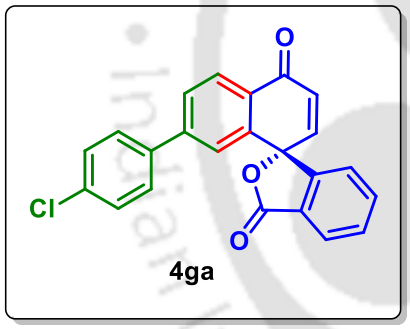
Pale yellow solid (22.4 mg, yield: 61%); M.P. 182-185 °C, R_f = 0.4 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.25 (d, *J* = 8.2 Hz, 1H), 8.05 – 8.01 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.60 (dtd, *J* = 21.0, 7.3, 1.2 Hz, 2H), 7.42 – 7.40 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.61 (d, *J* = 10.1 Hz, 1H), 3.82 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 160.4, 150.5, 146.2, 144.7, 139.6, 135.7, 135.5, 131.5, 130.4, 130.2, 128.6, 128.0, 127.8, 126.6, 125.1, 124.4, 122.7, 114.6, 82.0, 55.5. **ESI HRMS**: calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$ 369.1121, found 369.1128. **HPLC Analysis**: *ee* = 96%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 23.6 min, t_{minor} = 27.2 min).

(S)-7'-(4-fluorophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4fa)



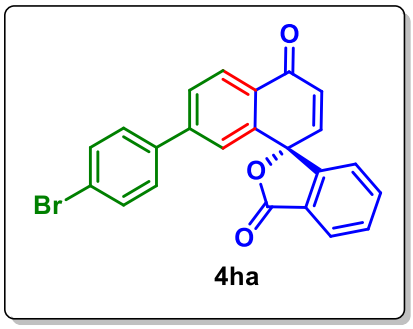
Pale yellow solid (22.4 mg, yield: 63%); M.P. 215-218 °C, R_f = 0.5 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.46 – 7.40 (m, 2H), 7.14 – 7.07 (m, 4H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.4, 169.9, 164.2 (d, $J_{C\text{-}F}$ = 249.15 Hz), 150.3, 145.6, 144.9, 139.7, 135.6, 135.3 (d, $J_{C\text{-}F}$ = 3.02 Hz), 130.5, 130.2, 129.2 (d, $J_{C\text{-}F}$ = 249.15 Hz), 129.1, 128.2, 128.1, 126.7, 125.1, 124.8, 122.7, 116.2(d, $J_{C\text{-}F}$ = 22.65 Hz), 81.9. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -113.0.**ESI HRMS**: calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$ 357.0921, found 357.0922. **HPLC Analysis**: *ee* = 96%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.6 min, t_{minor} = 10.3 min).

(S)-7'-(4-chlorophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ga)



Pale yellow solid (20.4 mg, yield: 55%); M.P. 208-211 °C, R_f = 0.5 in 2:8 ethyl acetate/hexane; **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.1 Hz, 1H), 8.09 – 7.99 (m, 1H), 7.68 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.43 – 7.34 (m, 4H), 7.11 (dd, *J* = 4.8, 2.9 Hz, 2H), 6.80 (dd, *J* = 9.7, 1.9 Hz, 1H), 6.63 (dd, *J* = 10.1, 1.8 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** 183.3, 169.9, 150.3, 145.3, 144.9, 139.8, 137.6, 135.6, 135.1, 130.5, 130.1, 129.3, 129.3, 128.7, 128.2, 128.1, 126.7, 125.1, 124.8, 122.7, 81.8. **ESI HRMS**: calcd. for $C_{23}H_{14}ClO_3$ $[M+H]^+$ 373.0626, found 373.0620. **HPLC Analysis**: *ee* = 96%, Chiralpak OD Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.0 min, t_{minor} = 13.6 min).

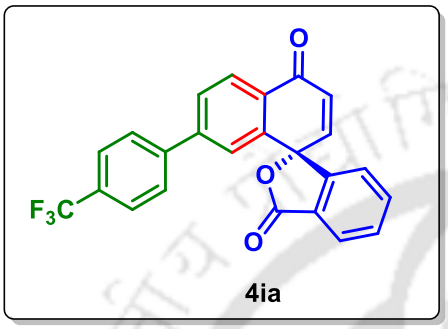
(S)-7'-(4-bromophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ha)



Pale yellow solid (25.7 mg, yield: 62%); M.P. 205-208 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.64 (dqd, *J* = 21.8, 7.8, 7.3, 1.5 Hz, 3H), 7.56 – 7.50 (m, 2H), 7.35 – 7.30 (m, 2H), 7.16 – 7.07 (m, 2H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.3, 169.9, 150.2, 145.4, 144.9, 139.8, 138.0, 135.6, 132.3, 130.5, 130.2, 129.3, 129.0, 128.2, 128.1, 126.7, 125.1,

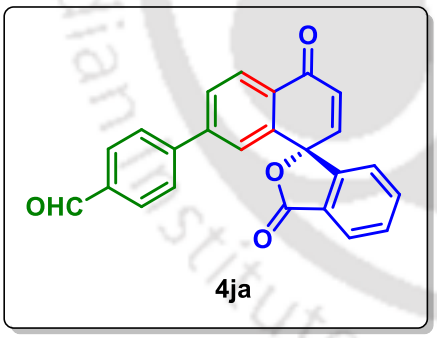
124.8, 123.3, 122.7, 81.8. **ESI HRMS**: calcd. for $C_{23}H_{14}BrO_3$ $[M+H]^+$ 417.0121, found 417.0122. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 22.3 min, t_{minor} = 20.9 min).

(S)-7'-(4-(trifluoromethyl)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ia)



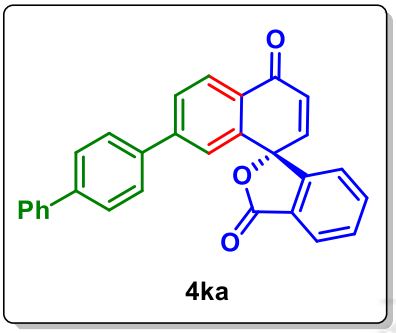
Pale yellow solid (21.9 mg, yield: 54%); M.P. 169-172 °C, R_f = 0.5 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.32 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.68 – 7.55 (m, 6H), 7.19 – 7.09 (m, 2H), 6.82 (d, *J* = 10.1 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.3, 169.8, 150.2, 145.1, 145.0, 142.7, 139.9, 135.6, 130.5, 130.1, 129.7, 128.6, 128.2, 127.9, 126.8, 126.1 (q, J_{C-F} = 3.02 Hz), 125.3, 125.1, 122.7, 81.7. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -62.7. **ESI HRMS**: calcd. for $C_{24}H_{14}F_3O_3$ $[M+H]^+$ 407.0890, found 407.0898. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.7 min, t_{minor} = 8.9 min).

(S)-4-(3,4'-dioxo-3H,4'H-spiro[isobenzofuran-1,1'-naphthalen]-7'-yl)benzaldehyde (4ja)



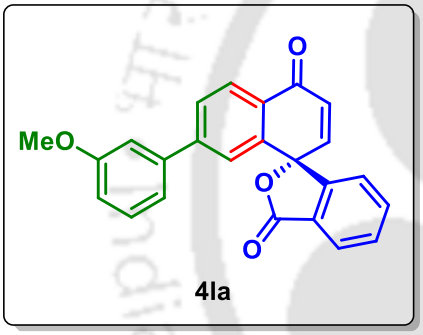
Pale yellow solid (19.0 mg, yield: 52%); M.P. 165-168 °C, R_f = 0.35 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 10.04 (s, 1H), 8.33 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.95 – 7.90 (m, 2H), 7.77 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.67 – 7.60 (m, 4H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.13 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.83 (d, *J* = 10.1 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 191.7, 183.3, 169.8, 150.1, 145.1, 144.9, 139.9, 136.2, 135.6, 130.6, 130.4, 130.1, 129.9, 128.6, 128.2, 128.2, 126.8, 125.4, 125.1, 122.7, 81.7. **ESI HRMS**: calcd. for $C_{24}H_{15}O_4$ $[M+H]^+$ 367.0965, found 367.0974. **HPLC Analysis**: *ee* = 94%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.1 min, t_{minor} = 23.3 min).

(S)-7'-([1,1'-biphenyl]-4-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ka)



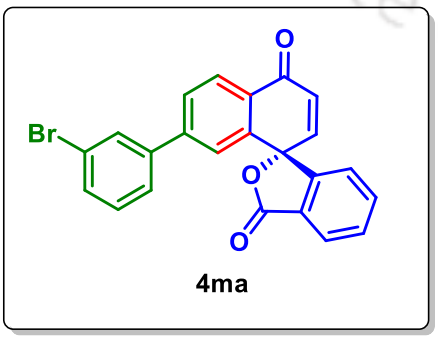
Pale yellow solid (25.2 mg, yield: 61%); M.P. 202-205 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.30 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.67 – 7.53 (m, 8H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.64 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 146.1, 144.9, 141.8, 140.3, 139.7, 138.0, 135.6, 130.4, 130.2, 129.1, 129.0, 128.2, 128.1, 127.9, 127.2, 126.7, 125.1, 124.9, 122.8, 81.9. **ESI HRMS**: calcd. for $C_{29}H_{19}O_3$ $[M+H]^+$ 415.1329, found 415.1325. **HPLC Analysis**: *ee* = 90%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 24.0 min, t_{minor} = 22.7 min).

(S)-7'-(3-methoxyphenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4la)



Pale yellow solid (19.8 mg, yield: 54%); M.P. 222-225 °C, R_f = 0.42 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.27 (d, *J* = 8.2 Hz, 1H), 8.09 – 7.98 (m, 1H), 7.71 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.61 (pd, *J* = 7.3, 1.4 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.15 – 7.08 (m, 2H), 7.03 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.97 (t, *J* = 2.1 Hz, 1H), 6.91 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 3.82 (s, 3H**). ^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 169.9, 160.1, 150.3, 146.5, 144.9, 140.7, 139.6, 135.5, 130.4, 130.2, 130.2, 129.2, 128.5, 127.9, 126.7, 125.2, 125.1, 122.7, 119.9, 113.9, 113.4, 81.9, 55.5. **ESI HRMS**: calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$ 369.1121, found 369.1128. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.8 min, t_{minor} = 11.7 min).

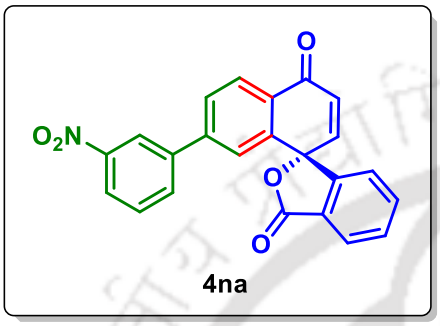
(S)-7'-(3-bromophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ma)



Pale yellow solid (21.2 mg, yield: 51%); M.P. 182-185 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.29 (d, *J* = 8.2 Hz, 1H), 8.11 – 8.02 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.50 (ddd, *J* = 7.9, 2.0, 1.1 Hz, 1H), 7.37 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.11 (dt, *J* = 4.1, 1.9 Hz, 2H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.3, 169.9, 150.2, 145.1, 145.1, 141.3, 139.8, 135.6, 131.7, 130.6, 130.5, 130.4, 130.1, 129.5, 128.5, 128.1, 126.8, 126.2, 125.1, 123.3, 122.7, 81.8. **ESI HRMS**:

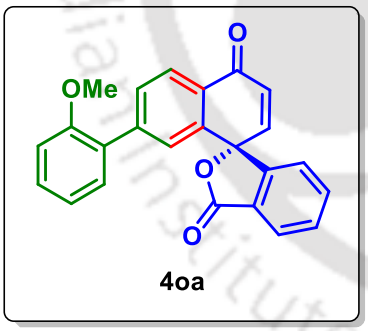
calcd. for $C_{23}H_{14}BrO_3$ $[M+H]^+$ 417.0121, found 417.0123. **HPLC Analysis**: *ee* = 96%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.7 min, t_{minor} = 11.9 min).

(S)-7'-(3-nitrophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4na)



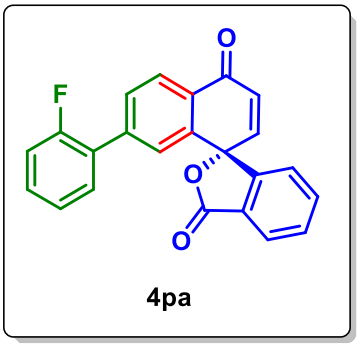
Pale yellow solid (17.2 mg, yield: 45%); M.P. 200-203 °C, R_f = 0.25 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.40 – 8.29 (m, 2H), 8.23 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.11 – 8.02 (m, 1H), 7.81 – 7.71 (m, 2H), 7.69 – 7.57 (m, 3H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.16 – 7.09 (m, 1H), 6.83 (d, *J* = 10.1 Hz, 1H), 6.65 (d, *J* = 10.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.1, 169.7, 150.1, 148.9, 145.2, 144.1, 141.0, 140.1, 135.7, 133.5, 130.6, 130.2, 130.1, 130.0, 128.6, 128.4, 126.9, 125.2, 125.1, 123.4, 122.7, 122.3, 81.7. **ESI HRMS**: calcd. for $C_{23}H_{14}NO_5$ $[M+H]^+$ 384.0866, found 384.0872. **HPLC Analysis**: *ee* = 94%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.3 min, t_{minor} = 24.9 min).

(S)-7'-(2-methoxyphenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4oa)



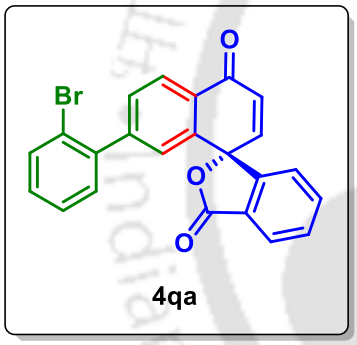
Pale yellow solid (16.5 mg, yield: 45%); M.P. 212-215 °C, R_f = 0.42 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.23 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.71 – 7.56 (m, 3H), 7.34 – 7.29 (m, 1H), 7.17 (ddd, *J* = 22.0, 6.2, 2.5 Hz, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 10.2 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 3.67 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.6, 170.0, 156.4, 150.5, 144.5, 144.2, 138.7, 135.4, 130.7, 130.7, 130.4, 130.2, 130.1, 128.7, 128.5, 127.8, 127.0, 126.5, 125.3, 122.9, 121.2, 111.5, 81.9, 55.5. **ESI HRMS**: calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$ 369.1121, found 369.1121. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.9 min, t_{minor} = 10.7 min).

(S)-7'-(2-fluorophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4pa)



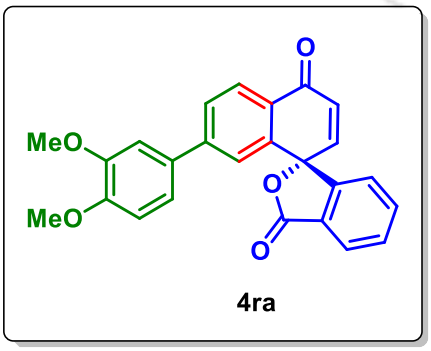
Pale yellow solid (17.0 mg, yield: 48%); M.P. 169-172 °C, R_f = 0.5 in 2:8 ethyl acetate/hexane;**^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.06 – 7.99 (m, 1H), 7.71 (dt, *J* = 8.2, 1.8 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.36 – 7.29 (m, 2H), 7.20 – 7.08 (m, 4H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.64 (d, *J* = 10.2 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.4, 169.9, 160.5(d, J_{C-F} = 250.66 Hz), 150.2, 144.9, 141.4, 139.3, 135.5, 130.7 (d, J_{C-F} = 3.02 Hz), 130.5 (d, J_{C-F} = 9.06 Hz), 130.4, 130.3 (d, J_{C-F} = 4.53 Hz), 130.2, 129.3, 127.5, 127.2 (d, J_{C-F} = 12.08 Hz), 127.1 (d, J_{C-F} = 3.02 Hz), 126.7, 125.1, 124.8 (d, J_{C-F} = 3.02 Hz), 122.8, 116.5 (d, J_{C-F} = 21.14 Hz), 81.7. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -117.3. **ESI HRMS**: calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$ 357.0921, found 442.2126. **HPLC Analysis**: *ee* = 91%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.0 min, t_{minor} = 15.7 min).

(S)-7'-(2-bromophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4qa)



Pale yellow solid (17.0 mg, yield: 41%); M.P. 182-185 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.07 – 8.00 (m, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.65 – 7.55 (m, 2H), 7.47 – 7.45 (m, 1H), 7.43 – 7.36 (m, 3H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.13 – 7.08 (m, 1H), 6.80 (d, *J* = 10.2 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.35, 146., 144.9, 139.6, 139.2, 135.5, 130.4, 130.2, 129.1, 129.0, 128.8, 128.4, 128.0, 127.5, 126.7, 125.1, 122.7, 81.9. **ESI HRMS**: calcd. for $C_{23}H_{14}BrO_3$ $[M+H]^+$ 417.0121, found 417.0126. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.2 min, t_{minor} = 17.6 min).

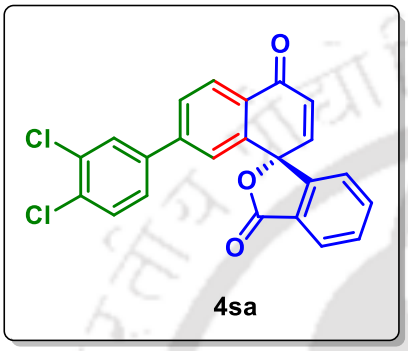
(S)-7'-(3,4-dimethoxyphenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ra)



Pale yellow solid (24.6 mg, yield: 62%); M.P. 212-215 °C, R_f = 0.2 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.26 (d, *J* = 8.2 Hz, 1H), 8.06 – 8.01 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.66 – 7.56 (m, 2H), 7.14 – 7.09 (m, 2H), 7.03 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 3.90 (d, *J* = 1.9 Hz, 6H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 149.9, 149.5, 146.5, 144.8, 139.6, 135.5, 132.0, 130.4, 130.2,

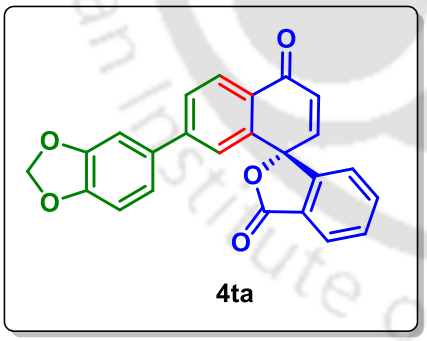
128.6, 128.0, 127.9, 126.6, 125.0, 124.6, 122.7, 120.2, 111.6, 110.5, 81.9, 56.2, 56.1. **ESI HRMS**: calcd. for $C_{25}H_{19}O_5$ $[M+H]^+$ 399.1227, found 399.1227. **HPLC Analysis**: *ee* = 96%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.7 min, t_{minor} = 20.5 min).

(S)-7'-(3,4-dichlorophenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4sa)



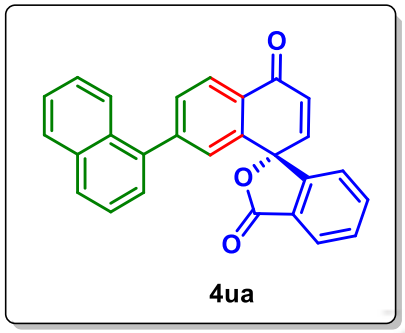
Pale yellow solid (21.9 mg, yield: 54%); M.P. 197-200 °C, R_f = 0.6 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.30 (dd, *J* = 8.2, 2.1 Hz, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.69 – 7.59 (m, 3H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.13 – 7.08 (m, 2H), 6.81 (dd, *J* = 10.1, 2.1 Hz, 1H), 6.64 (dd, *J* = 10.2, 2.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.2, 169.8, 150.1, 145.1, 144.1, 139.9, 139.1, 135.6, 133.4, 133.2, 131.1, 130.6, 130.1, 129.7, 129.2, 128.3, 128.3, 126.8, 126.7, 125.0, 124.9, 122.7, 81.7. **ESI HRMS**: calcd. for $C_{23}H_{13}Cl_2O_3$ $[M+H]^+$ 407.0236, found 407.0241. **HPLC Analysis**: *ee* = 98%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.8 min, t_{minor} = 15.0 min).

(S)-7'-(benzo[d][1,3]dioxol-5-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ta)



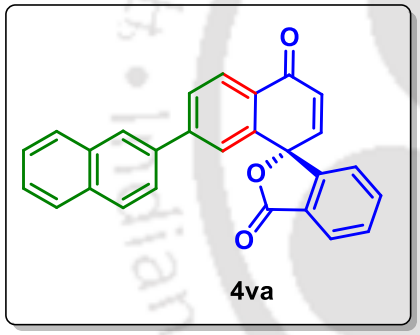
Pale yellow solid (15.6 mg, yield: 41%); M.P. 213-216 °C, R_f = 0.25 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.04 (dt, *J* = 7.4, 0.9 Hz, 1H), 7.65 – 7.58 (m, 3H), 7.12 – 7.10 (m, 1H), 7.07 (d, *J* = 1.8 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 5.98 (s, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.4, 170.0, 150.4, 148.5, 148.4, 146.3, 144.8, 139.6, 135.5, 133.3, 130.4, 130.2, 128.7, 128.0, 128.0, 126.7, 125.1, 124.6, 122.7, 121.5, 108.9, 107.7, 101.6, 81.9. **ESI HRMS**: calcd. for $C_{24}H_{15}O_5$ $[M+H]^+$ 383.0914, found 383.0915. **HPLC Analysis**: *ee* = 92%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.1 min, t_{minor} = 17.7 min).

(S)-7'-(naphthalen-1-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ua)



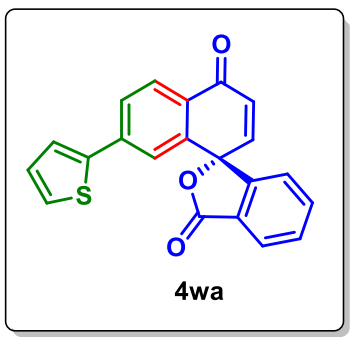
Pale yellow solid (20.5 mg, yield: 53%); M.P. 212-215 °C, R_f = 0.48 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 8.0 Hz, 1H), 7.96 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.69 – 7.63 (m, 2H), 7.57 (td, *J* = 7.5, 1.0 Hz, 2H), 7.49 – 7.44 (m, 2H), 7.39 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 10.2 Hz, 1H), 6.67 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 169.8, 150.3, 146.5, 144.8, 139.3, 138.1, 135.5, 133.9, 131.5, 131.0, 130.4, 130.3, 129.2, 128.9, 128.6, 128.3, 127.3, 127.2, 126.8, 126.7, 126.2, 125.4, 125.2, 125.1, 122.7, 81.7. **ESI HRMS**: calcd. for $C_{27}H_{17}O_3$ $[M+H]^+$ 389.1172, found 389.1182. **HPLC Analysis**: *ee* = 94%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.1 min, t_{minor} = 14.1 min).

(S)-7'-(naphthalen-2-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4va)



Pale yellow solid (20.9 mg, yield: 54%); M.P. 202-205 °C, R_f = 0.49 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.33 (d, *J* = 8.2 Hz, 1H), 8.09 – 8.01 (m, 1H), 7.94 (d, *J* = 1.9 Hz, 1H), 7.91 – 7.81 (m, 4H), 7.66 – 7.55 (m, 3H), 7.54 – 7.45 (m, 2H), 7.28 (d, *J* = 1.8 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 10.1 Hz, 1H), 6.64 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 150.4, 146.6, 144.9, 139.7, 136.4, 135.6, 133.5, 133.2, 130.4, 130.2, 129.1, 129.0, 128.7, 128.5, 128.1, 127.8, 126.9, 126.8, 126.7, 126.7, 125.3, 125.1, 125.1, 122.7, 82.0. **ESI HRMS**: calcd. for $C_{27}H_{17}O_3$ $[M+H]^+$ 389.1172, found 389.1166. **HPLC Analysis**: *ee* = 94%, Chiralpak ADH Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.9 min, t_{minor} = 15.4 min).

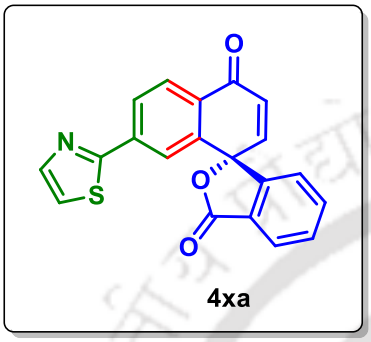
(S)-7'-(thiophen-2-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4wa)



Pale yellow solid (20.9 mg, yield: 61%); M.P. 162-165 °C, R_f = 0.45 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.22 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.72 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.34 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.30 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.16 (d, *J* = 1.8 Hz, 1H), 7.13 – 7.10 (m, 1H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.77 (d, *J* = 10.2 Hz, 1H), 6.61 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.1, 169.9, 150.3,

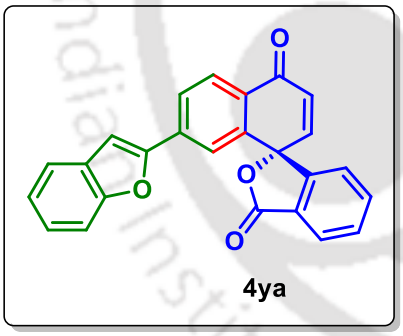
144.8, 142.1, 139.9, 139.6, 135.6, 130.5, 130.1, 128.9, 128.6, 128.2, 127.4, 126.9, 126.7, 125.6, 125.0, 123.2, 122.7, 81.8. **ESI HRMS**: calcd. for $C_{21}H_{13}O_3S$ $[M+H]^+$ 345.0580, found 345.0582. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 22.7 min, t_{minor} = 21.3 min).

(S)-7'-(thiazol-2-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4xa)



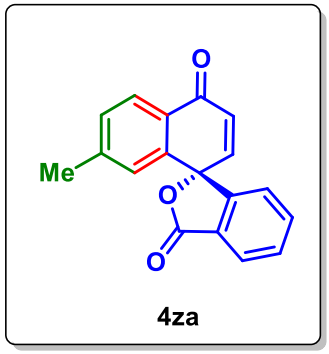
Pale yellow solid (17.9 mg, yield: 52%); M.P. 166-169 °C, R_f = 0.35 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.33 – 8.27 (m, 1H), 8.11 – 8.04 (m, 2H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.39 (d, *J* = 3.2 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.80 (d, *J* = 10.2 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.1, 169.7, 165.9, 150.0, 145.4, 144.5, 140.0, 138.2, 135.0, 130.9, 130.6, 129.9, 128.3, 127.7, 126.9, 125.2, 124.4, 122.7, 120.8, 81.6. **ESI HRMS**: calcd. for $C_{20}H_{12}NO_3S$ $[M+H]^+$ 346.0532, found 346.0533. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.4 min, t_{minor} = 17.3 min).

(S)-7'-(benzofuran-2-yl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ya)



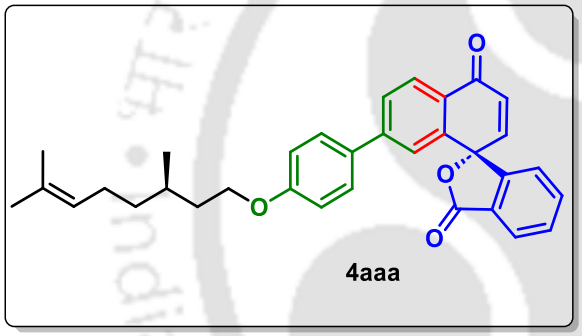
Pale yellow solid (20.7 mg, yield: 55%); M.P. 215-218 °C, R_f = 0.45 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.29 (d, *J* = 8.3 Hz, 1H), 8.11 – 8.08 (m, 1H), 7.96 (dt, *J* = 8.2, 1.3 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 7.11 (s, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.1, 170.0, 155.4, 153.6, 150.3, 145.0, 139.9, 135.6, 135.4, 130.5, 130.1, 129.6, 128.7, 128.1, 126.8, 125.7, 125.1, 123.5, 122.7, 122.4, 121.6, 111.6, 104.9, 81.8. **ESI HRMS**: calcd. for $C_{25}H_{15}O_4$ $[M+H]^+$ 379.0965, found 379.0959. **HPLC Analysis**: *ee* = 98%, Chiralpak OD Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.4 min, t_{minor} = 14.0 min).

(S)-7'-methyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4za)



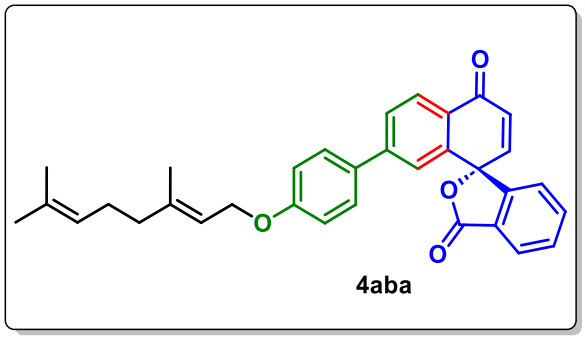
Pale yellow solid (17.6 mg, yield: 64%); M.P. 175-178 °C, R_f = 0.35 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.10 (d, *J* = 8.0 Hz, 1H), 8.07 – 8.00 (m, 1H), 7.65 – 7.58 (m, 2H), 7.30 (ddd, *J* = 7.9, 1.6, 0.8 Hz, 1H), 7.11 – 7.04 (m, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.74 (d, *J* = 10.1 Hz, 1H), 6.57 (d, *J* = 10.1 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.6, 170.0, 150.5, 144.8, 144.5, 139.0, 135.4, 130.6, 130.3, 130.2, 128.0, 127.4, 126.8, 126.5, 125.1, 122.7, 81.8, 21.9. **ESI HRMS**: calcd. for $C_{18}H_{13}O_3$ $[M+H]^+$ 277.0859, found 277.0862. **HPLC Analysis**: *ee* = 92%, Chiralpak Phenomenex Lux C4 Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 17.8 min, t_{minor} = 26.3 min).

(S)-7'-(4-(((R)-3,7-dimethyloct-6-en-1-yl)oxy)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4aaa)



Pale yellow solid (31.5 mg, yield: 64%); M.P. 202-205 °C, R_f = 0.38 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.43 – 7.37 (m, 2H), 7.11 (dd, *J* = 6.6, 1.6 Hz, 2H), 6.95 – 6.88 (m, 2H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.61 (d, *J* = 10.1 Hz, 1H), 5.10 (ddt, *J* = 8.6, 5.6, 1.4 Hz, 1H), 4.00 (dddd, *J* = 9.2, 7.5, 5.2, 2.7 Hz, 2H), 2.00 (dp, *J* = 22.3, 7.2 Hz, 2H), 1.87 – 1.79 (m, 1H), 1.69 – 1.66 (m, 3H), 1.60 (s, 4H), 1.43 – 1.34 (m, 1H), 1.31 – 1.19 (m, 2H), 0.95 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.4, 170.0, 159.9, 150.4, 146.2, 144.7, 139.6, 135.5, 131.4, 131.2, 130.3, 130.2, 128.5, 128.4, 127.9, 127.7, 126.6, 125.1, 124.7, 124.3, 122.7, 115.1, 81.9, 66.5, 37.2, 36.1, 29.6, 25.8, 25.5, 19.6, 17.8. **ESI HRMS**: calcd. for $C_{33}H_{33}O_4$ $[M+H]^+$ 493.2373, found 493.2379.

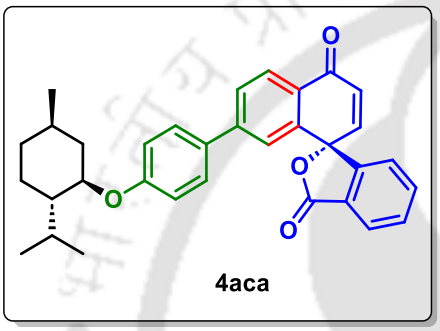
(S,E)-7'-(4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4aba)



Pale yellow solid (29.9 mg, yield: 61%); M.P. 198-201 °C, R_f = 0.35 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.43 – 7.37 (m, 2H), 7.14 – 7.07 (m, 2H), 6.97 – 6.89 (m, 2H), 6.78 (d, *J* = 10.2 Hz, 1H), 6.61

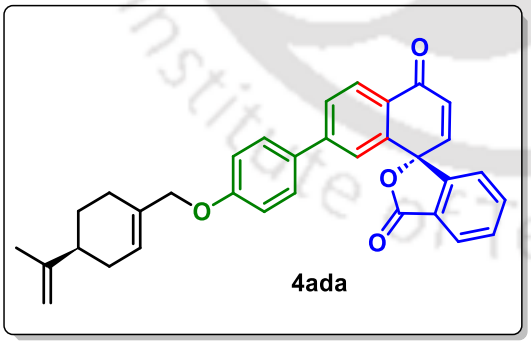
(d, *J* = 10.1 Hz, 1H), 5.47 (tt, *J* = 5.0, 2.5 Hz, 1H), 5.08 (ddq, *J* = 6.8, 5.4, 1.5 Hz, 1H), 4.55 (d, *J* = 6.5 Hz, 2H), 2.10 (dtt, *J* = 11.2, 8.0, 4.4 Hz, 4H), 1.73 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 183.5, 170.0, 159.7, 150.4, 146.2, 144.7, 141.7, 139.6, 135.5, 131.9, 131.3, 130.3, 130.2, 128.5, 128.4, 127.9, 127.7, 126.6, 125.1, 124.3, 123.8, 122.7, 119.3, 115.3, 81.9, 65.1, 39.6, 26.4, 25.8, 17.8, 16.8. **ESI HRMS**: calcd. for $C_{33}H_{31}O_4$ $[M+H]^+$ 491.2217, found 491.2220. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.3 min, t_{minor} = 10.1 min).

(S)-7'-(4-(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4aca)



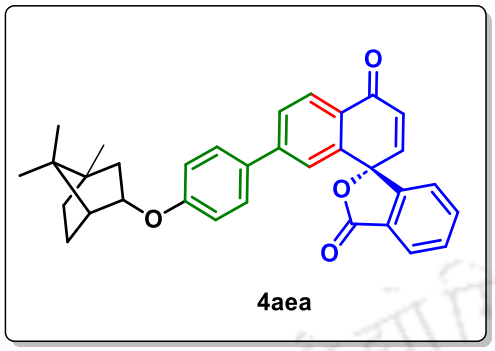
Pale yellow solid (25.0 mg, yield: 51%); M.P. 171-174 °C, R_f = 0.35 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.07 – 7.99 (m, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.60 (pd, *J* = 7.3, 1.4 Hz, 3H), 7.47 – 7.36 (m, 4H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.11 (dd, *J* = 6.7, 1.6 Hz, 3H), 6.96 – 6.87 (m, 2H), 6.78 (dd, *J* = 9.5, 7.6 Hz, 1H), 6.61 (d, *J* = 10.2 Hz, 1H), 4.75 – 4.55 (m, 1H), 2.06 (dt, *J* = 13.8, 2.8 Hz, 1H), 1.84 – 1.40 (m, 8H), 1.08 – 0.63 (m, 17H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 183.5, 170.0, 159.1, 150.5, 146.4, 144.7, 139.6, 135.7, 135.5, 130.8, 130.3, 130.3, 128.7, 127.9, 127.7, 127.5, 126.6, 124.4, 122.7, 116.0, 82.0, 73.5, 47.8, 37.7, 35.1, 29.4, 26.3, 24.9, 22.4, 21.2, 20.9. **ESI HRMS**: calcd. for $C_{33}H_{33}O_4$ $[M+H]^+$ 493.2373, found 493.2371.

(S)-7'-(4-(((S)-4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methoxy)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ada)



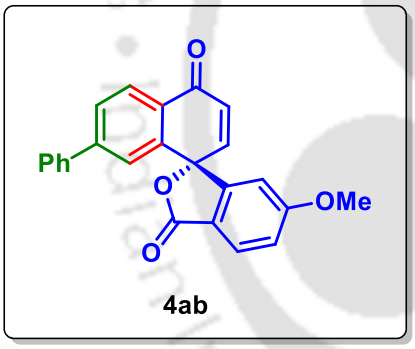
Pale yellow solid (28.3 mg, yield: 58%); M.P. 165-168 °C, R_f = 0.38 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.24 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 6.9 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.11 (d, *J* = 6.3 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.61 (d, *J* = 10.1 Hz, 1H), 5.84 (s, 1H), 4.72 (d, *J* = 6.6 Hz, 2H), 4.40 (s, 2H), 2.17 (q, *J* = 9.9, 6.3 Hz, 4H), 2.01 (d, *J* = 14.3 Hz, 1H), 1.90 – 1.83 (m, 1H), 1.74 (s, 3H), 1.52 (dt, *J* = 11.9, 6.0 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 183.5, 170.0, 159.8, 150.5, 149.7, 146.2, 144.7, 139.6, 135.5, 133.3, 131.4, 130.4, 130.2, 128.5, 128.5, 128.0, 127.8, 126.6, 125.6, 125.1, 124.3, 122.7, 115.4, 108.9, 82.0, 72.5, 41.0, 30.6, 27.5, 26.4, 20.9. **ESI HRMS**: calcd. for $C_{23}H_{29}O_4$ $[M+H]^+$ 489.2060, found 489.2066.

(S)-7'-(4-(((1R,2S,4R)-4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)phenyl)-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4aea)



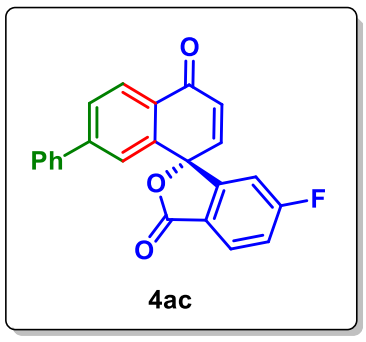
Pale yellow solid (15.1 mg, yield: 31%); M.P. 176-179 °C, R_f = 0.39 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.24 (dd, *J* = 8.2, 2.5 Hz, 1H), 8.03 (dt, *J* = 6.6, 1.9 Hz, 1H), 7.67 (ddd, *J* = 8.2, 4.4, 1.9 Hz, 1H), 7.61 (qt, *J* = 7.1, 1.4 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.13 – 7.08 (m, 2H), 7.04 – 6.93 (m, 1H), 6.88 – 6.85 (m, 1H), 6.78 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.61 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.05 (t, *J* = 5.3 Hz, 1H), 1.83 – 1.74 (m, 3H), 1.37 – 1.28 (m, 2H), 1.11 (qd, *J* = 8.8, 2.6 Hz, 2H), 1.03 (s, 3H), 0.97 (s, 3H), 0.87 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.5, 170.0, 158.8, 150.5, 146.4, 144.7, 139.6, 135.5, 130.8, 130.3, 130.3, 128.5, 127.9, 127.9, 127.7, 126.6, 124.3, 123.2, 122.7, 116.0, 85.9, 82.0, 49.4, 47.2, 45.4, 39.6, 34.3, 27.5, 20.4, 20.2, 11.9. **ESI HRMS**: calcd. for $C_{33}H_{31}O_4$ $[M+H]^+$ 491.2217, found 491.2225.

(S)-6-methoxy-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ab)



Pale yellow solid (23.1 mg, yield: 63%); M.P. 220-223 °C, R_f = 0.42 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.43 – 7.40 (m, 2H), 7.39 – 7.36 (m, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 7.07 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 10.1 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 3.77 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.6, 169.6, 165.8, 153.2, 146.7, 145.1, 139.8, 139.2, 130.1, 129.1, 129.0, 128.8, 128.3, 128.1, 127.9, 127.5, 125.1, 118.2, 117.2, 106.1, 81.1, 56.2. **ESI HRMS**: calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$ 369.1121, found 369.1121. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.4 min, t_{minor} = 13.5 min).

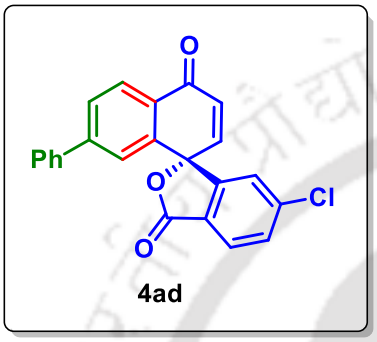
(S)-6-fluoro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ac)



Pale yellow solid (22.7 mg, yield: 64%); M.P. 207-210 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.29 (d, *J* = 8.2 Hz, 1H), 8.03 (dd, *J* = 8.5, 4.6 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.48 (d, *J* = 7.0 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.40 – 7.37 (m, 1H), 7.29 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 6.82 – 6.76 (m, 2H), 6.65 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.1, 168.7, 168.1 (d, J_{C-F} = 259.72 Hz), 153.3 (d, J_{C-F} = 10.57 Hz), 146.8, 144.1, 139.1 (d, J_{C-F} =

16.61 Hz), 130.6, 129.2, 129.1 (d, J_{C-F} = 10.57 Hz), 1289.0, 128.9, 128.7, 128.1, 127.5, 125.0, 121.2 (d, J_{C-F} = 3.02 Hz), 118.9 (d, J_{C-F} = 24.16 Hz), 110.2 (d, J_{C-F} = 24.16 Hz), 81.2 (d, J_{C-F} = 1.51 Hz). **^{19}F NMR (565 MHz, $CDCl_3$)** δ -99.6. **ESI HRMS**: calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$ 357.0921, found 357.0924. **HPLC Analysis**: *ee* = 97%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.2 min, t_{minor} = 12.3 min).

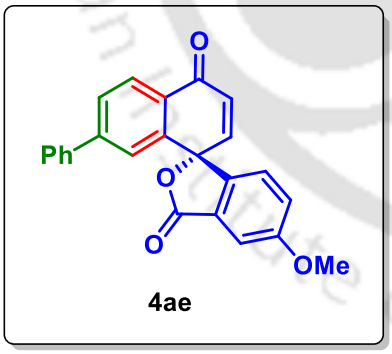
(S)-6-chloro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ad)



4ad

Pale yellow solid (21.5 mg, yield: 58%); M.P. 222-225 °C, R_f = 0.56 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.29 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.75 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.44 – 7.37 (m, 3H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.09 (d, *J* = 1.7 Hz, 1H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 183.1, 168.7, 152.0, 146.8, 144.0, 142.3, 139.0, 138.9, 131.3, 130.6, 129.2, 129.0, 128.9, 128.7, 128.1, 127.8, 127.5, 125.0, 123.5, 123.1, 81.3. **ESI HRMS**: calcd. for $C_{23}H_{14}ClO_3$ $[M+H]^+$ 373.0626, found 373.0627. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 7.5 min, t_{minor} = 8.6 min).

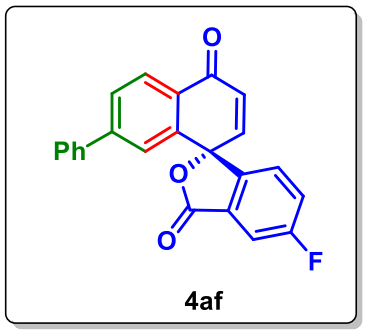
(S)-5-methoxy-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ae)



4ae

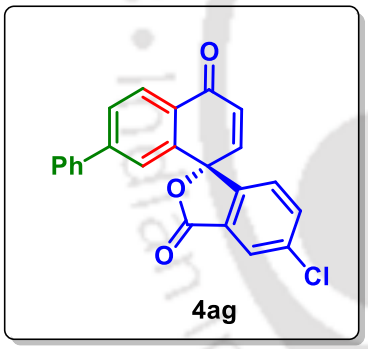
Pale yellow solid (19.1 mg, yield: 52%); M.P. 204-207 °C, R_f = 0.42 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.27 (d, *J* = 8.2 Hz, 1H), 7.71 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.43 – 7.40 (m, 3H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.15 (m, 2H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 10.1 Hz, 1H), 6.60 (d, *J* = 10.1 Hz, 1H), 3.89 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.6, 170.0, 161.6, 146.6, 145.1, 142.5, 139.8, 139.3, 135.7, 130.0, 129.1, 128.8, 128.3, 127.9, 127.5, 126.6, 125.1, 124.5, 123.6, 108.3, 81.7, 56.1. **ESI HRMS**: calcd. for $C_{24}H_{17}O_4$ $[M+H]^+$ 369.1121, found 369.1122. **HPLC Analysis**: *ee* = 96%, Chiralpak ID Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.8 min, t_{minor} = 16.3 min).

(S)-5-fluoro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4af)



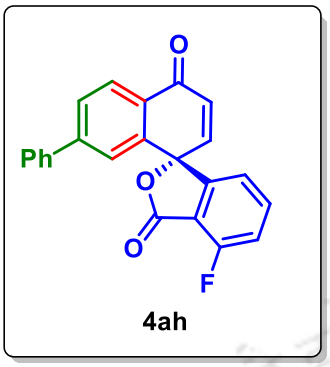
Pale yellow solid (21.3 mg, yield: 60%); M.P. 218-221 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.67 (dd, *J* = 6.9, 2.4 Hz, 1H), 7.48 – 7.46 (m, 2H), 7.44 – 7.40 (m, 2H), 7.40 – 7.36 (m, 1H), 7.34 (td, *J* = 8.5, 2.4 Hz, 1H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.10 (dd, *J* = 8.5, 4.1 Hz, 1H), 6.78 (d, *J* = 10.1 Hz, 1H), 6.63 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 183.2, 168.6 (d, J_{C-F} = 3.02 Hz), 164.7 (d, J_{C-F} = 252.17 Hz), 146.8, 145.9 (d, J_{C-F} = 1.51 Hz), 144.3, 139.2 (d, J_{C-F} = 12.08 Hz), 130.4, 129.2, 129.0, 128.9, 128.6, 128.1, 127.4, 127.3 (d, J_{C-F} = 9.06 Hz), 125.0, 124.7 (d, J_{C-F} = 9.06 Hz), 123.7 (d, J_{C-F} = 9.06 Hz), 113.1 (d, J_{C-F} = 25.16 Hz), 81.8. **^{19}F NMR (565 MHz, CDCl$_3$)** δ -109.1. **ESI HRMS**: calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$ 357.0921, found 357.0928. **HPLC Analysis**: *ee* = 97%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 8.9 min, t_{minor} = 9.7 min).

(S)-5-chloro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ag)



Pale yellow solid (20.4 mg, yield: 55%); M.P. 225-228 °C, R_f = 0.58 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 1.9 Hz, 1H), 7.74 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.47 (d, *J* = 6.9 Hz, 2H), 7.40 (dt, *J* = 22.8, 6.9 Hz, 3H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 10.1 Hz, 1H), 6.64 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 183.2, 168.5, 148.5, 146.8, 144.1, 139.0, 139.0, 137.0, 135.9, 130.5, 129.2, 129.0, 128.9, 128.6, 128.1, 127.5, 126.9, 126.5, 125.0, 124.0, 81.8. **ESI HRMS**: calcd. for $C_{23}H_{14}ClO_3$ $[M+H]^+$ 373.0626, found 373.0628. **HPLC Analysis**: *ee* = 99%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 9.1 min, t_{minor} = 9.8 min).

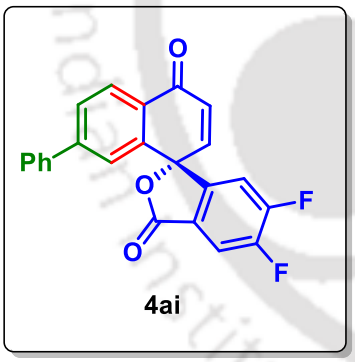
(S)-4-fluoro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ah)



4ah

Pale yellow solid (19.2 mg, yield: 54%); M.P. 200-203 °C, R_f = 0.55 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.75 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.62 (td, *J* = 7.9, 4.4 Hz, 1H), 7.49 (dt, *J* = 6.3, 1.4 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.40 – 7.37 (m, 1H), 7.24 – 7.20 (m, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 10.1 Hz, 1H), 6.64 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.2, 165.9, 160.7 (d, J_{C-F} = 267.27 Hz), 152.7, 146.8, 144.1, 139.1(d, J_{C-F} = 10.57 Hz), 138.1 (d, J_{C-F} = 9.06 Hz), 135.7, 130.5, 129.2, 128.9, 128.6, 128.1, 127.5, 125.0, 118.8(d, J_{C-F} = 4.53 Hz), 117.5 (d, J_{C-F} = 18.12 Hz), 113.1(d, J_{C-F} = 15.1 Hz), 81.5. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -111.8. **ESI HRMS**: calcd. for $C_{23}H_{14}FO_3$ $[M+H]^+$ 357.0921, found 357.0930. **HPLC Analysis**: *ee* = 96%, Chiralpak IF Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.2 min, t_{minor} = 14.8 min).

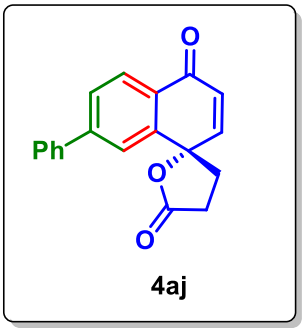
(S)-5,6-difluoro-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (4ai)



4ai

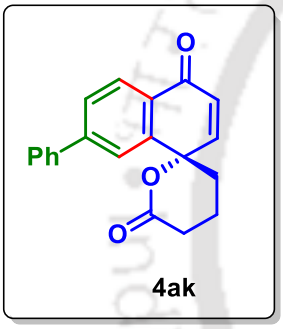
Pale yellow solid (22.8 mg, yield: 61%); M.P. 195-198 °C, R_f = 0.62 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.29 (d, *J* = 8.2 Hz, 1H), 7.83 – 7.79 (m, 1H), 7.76 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.44 – 7.38 (m, 3H), 7.14 (d, *J* = 1.7 Hz, 1H), 6.93 (dd, *J* = 8.1, 6.1 Hz, 1H), 6.77 (d, *J* = 10.1 Hz, 1H), 6.65 (d, *J* = 10.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 182.9, 167.9, 156.6 (d, J_{C-F} = 15.1 Hz), 154.9 (d, J_{C-F} = 13.54 Hz), 153.3 (d, J_{C-F} = 13.54 Hz), 151.6 (d, J_{C-F} = 13.54 Hz), 147.2 (d, J_{C-F} = 7.55 Hz), 147.0, 143.6, 139.0 (d, J_{C-F} = 69.46 Hz), 130.8, 129.2, 129.0 (d, J_{C-F} = 21.14 Hz), 128.9, 128.2, 127.5, 124.9, 121.5 (d, J_{C-F} = 7.55 Hz), 115.2 (d, J_{C-F} = 18.12 Hz), 112.0 (d, J_{C-F} = 19.63 Hz), 81.3. **^{19}F NMR (565 MHz, $CDCl_3$)** δ -121.8 (d, J_{C-F} = 22.6 Hz), -131.0 (d, J_{C-F} = 22.6 Hz). **ESI HRMS**: calcd. for $C_{23}H_{13}F_2O_3$ $[M+H]^+$ 375.0827, found 375.0831. **HPLC Analysis**: *ee* = 97%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 7.4 min, t_{minor} = 8.2 min).

(S)-7'-phenyl-3,4-dihydro-4'H,5H-spiro[furan-2,1'-naphthalene]-4',5-dione (4aj)



Pale yellow solid (10.4 mg, yield: 36%); M.P. 182-185 °C, R_f = 0.32 in 2:8 ethyl acetate/hexane; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.66 (d, *J* = 1.7 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.51 – 7.48 (m, 2H), 7.46 – 7.42 (m, 1H), 7.06 (d, *J* = 10.3 Hz, 1H), 6.48 (d, *J* = 10.2 Hz, 1H), 3.00 – 2.88 (m, 2H), 2.64 – 2.54 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.2, 175.9, 146.8, 146.5, 143.4, 139.5, 129.2, 129.0, 128.9, 128.7, 128.1, 127.8, 127.5, 124.2, 80.5, 37.1, 28.8. **ESI HRMS**: calcd. for $C_{19}H_{15}O_3$ $[M+H]^+$ 291.1016, found 291.1020. **HPLC Analysis**: *ee* = 92%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.0 min, t_{minor} = 17.7 min).

(S)-7-phenyl-4',5'-dihydro-4H-spiro[naphthalene-1,2'-pyran]-4,6'(3'H)-dione (4ak)



Pale yellow solid (7.0 mg, yield: 23%); M.P. 175-178 °C, R_f = 0.28 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.63 (dd, *J* = 7.2, 1.9 Hz, 2H), 7.52 – 7.47 (m, 2H), 7.45 – 7.41 (m, 1H), 7.20 (d, *J* = 10.4 Hz, 1H), 6.45 (d, *J* = 10.4 Hz, 1H), 2.90 – 2.75 (m, 2H), 2.23 – 2.07 (m, 4H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.1, 169.6, 147.2, 146.5, 144.3, 139.7, 129.2, 128.9, 128.8, 128.4, 127.8, 127.7, 127.6, 125.1, 79.9, 37.8, 29.5, 17.8. **ESI HRMS**: calcd. for $C_{20}H_{17}O_3$ $[M+H]^+$ 305.1172, found 305.1179. **HPLC Analysis**: *ee* = 92%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.7 min, t_{minor} = 22.3 min).

5.6.6 Procedure for the scale-up experiment:

In a 25 ml rb, equipped with a magnetic stirring bar, was charged with **2a** (212.0 mg, 1 mmol, 1.0 equiv), 4-$NO_2C_6H_4CO_2H$ (33.4 mg, 0.2 mmol, 0.2 equiv), and cat. **VI** (102.0 mg, 0.2 mmol, 0.2 equiv) followed by addition of 5 mL dry toluene. Then freshly prepared **1a** (292.0 mg, 2 mmol, 2.0 equiv) was added to the reaction mixture and was stirred at rt until TLC revealed complete consumption of **2a** (24 h). The crude residue was directly purified by silica gel flash column chromatography (10-20% EtOAc in petroleum ether) to obtain **3aa** (286.0 mg), which was taken in an oven-dried 10 mL round-bottom flask along with DABCO (376.8 mg, 3.36 mmol, 4.0 equiv) in 4.5 ml $CHCl_3$ under oxygen atmosphere. The resulting mixture was stirred at 25 °C until TLC revealed complete consumption of **3aa** (72 h). The crude residue was directly purified by silica gel flash

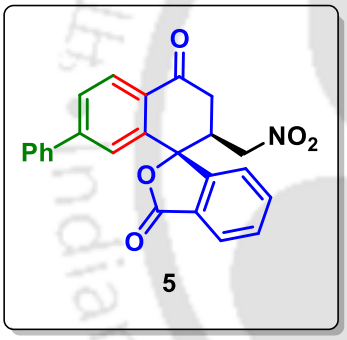
column chromatography to obtain **4aa** (5-15% EtOAc in petroleum ether) (223.0 mg, 66% yield, 96% ee).

5.6.7 Procedure for synthetic transformations:

a. Procedure for the preparation of 5:

In a screw cap vial, equipped with a magnetic stirring bar, **4aa** (0.05 mmol, 1.0 equiv.), K_2CO_3 (0.1 mmol, 2 equiv.) was taken in 0.5 ml dry toluene. To this nitromethane (10 eq.) was added and the resulting suspension was heated at 70 °C for 16 h. After full conversion of **4aa**, the reaction mixture was cooled to r.t. The crude reaction mixture was directly purified by silica-gel flash column chromatography (10-15% EtOAc in petroleum ether) to obtain **5** as a pale yellow solid (17.9 mg, 90% yield).

(1S,2'S)-2'-(nitromethyl)-7'-phenyl-2',3'-dihydro-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (5)

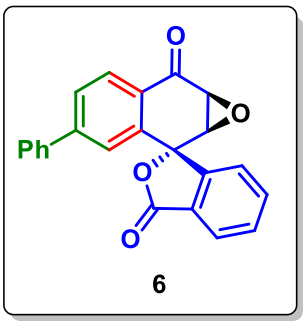


Pale yellow solid (17.9 mg, yield: 90%); M.P. 201-204 °C, R_f = 0.45 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.26 (d, *J* = 8.1 Hz, 1H), 8.07 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.82 (td, *J* = 7.6, 1.2 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.40 – 7.35 (m, 5H), 6.86 (d, *J* = 1.7 Hz, 1H), 4.30 (dd, *J* = 13.4, 8.4 Hz, 1H), 4.24 (dd, *J* = 13.4, 4.8 Hz, 1H), 3.77 (ddt, *J* = 10.6, 8.7, 4.7 Hz, 1H), 3.19 (dd, *J* = 17.4, 10.8 Hz, 1H), 3.09 (dd, *J* = 17.4, 4.5 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 192.9, 168.3, 148.7, 148.0, 139.7, 139.0, 135.7, 131.3, 130.5, 129.4, 129.2, 129.0, 128.7, 127.4, 126.8, 126.6, 125.5, 123.25, 85., 75.4, 41.7, 38.2. **ESI HRMS**: calcd. for $C_{24}H_{18}O_5N$ $[M+H]^+$ 400.1179, found 400.1181. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 43.4 min, t_{minor} = 49.6 min).

b. Procedure for the preparation of 6:

In a screw cap vial, equipped with a magnetic stirring bar, *tert*-butyl hydroperoxide (70 wt% in water, 0.075 mmol, 1.5 eq.) and DBU (0.01 mmol, 0.2 eq) were added to a solution of **4aa** (0.05 mmol) in CH_2Cl_2 (1 ml). Then resulting suspension was stirred for 16 h at rt. After full conversion of **4aa**, the crude reaction mixture was directly purified by silica-gel flash column chromatography (10-15% EtOAc in petroleum ether) to obtain **6** as a pale yellow solid (16.6 mg, 94% yield).

(1S,1a'R,7a'S)-4'-phenyl-1a',7a'-dihydro-3H,7'H-spiro[isobenzofuran-1,2'-naphtho[2,3-b]oxirene]-3,7'-dione (6)

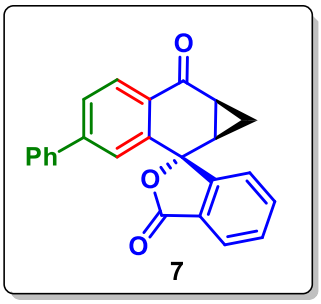


Pale yellow solid (16.6 mg, yield: 94%); M.P. 164-167 °C, R_f = 0.4 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.07 (d, *J* = 8.1 Hz, 1H), 8.02 (dd, *J* = 6.8, 1.5 Hz, 1H), 7.71 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.54 – 7.47 (m, 2H), 7.43 – 7.36 (m, 4H), 7.04 (dd, *J* = 7.2, 1.4 Hz, 1H), 3.94 (d, *J* = 4.1 Hz, 1H), 3.83 (d, *J* = 4.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 192.7, 169.4, 149.6, 148.2, 139.1, 137.2, 135.4, 130.8, 129.2, 129.0, 128.9, 128.5, 127.5, 127.3, 127.0, 124.8, 123.8, 122.4, 84.4, 56.3, 53.6. **ESI HRMS**: calcd. for $C_{23}H_{15}O_4$ $[M+H]^+$ 355.0965, found 355.0969. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.7 min, t_{minor} = 14.9 min).

c. Procedure for the preparation of 7:

To a Schlenk tube equipped with a magnetic stirring bar was added $Me_3S(O)I$ (0.1 mmol, 2 eq.) and NaH (0.1 mmol, 2 equiv.) in 0.5 ml dry DMSO under Ar at rt. To this solution, **4aa** (0.05 mmol, 1.0 equiv.) in 1 ml dry DMSO was added dropwise and the reaction mixture was heated to 50 °C and stirred for 16 h. After full conversion of **4aa**, the reaction was quenched with H_2O (0.5 mL) and diluted with EtOAc (5 mL), the layers were separated the aq. layer was extracted with EtOAc (3 x 3 mL), and combined org. layers were washed with brine. The org. layer was dried over Na_2SO4, filtered and concentrated in vacuo. The crude mixture was purified by silica-gel flash column chromatography (10-15% EtOAc in petroleum ether) to give the product **7** (11.6 mg, 66%) as a white semi-solid.

(1aR,2S,7aS)-4-phenyl-1a,7a-dihydro-3'H-spiro[cyclopropa[b]naphthalene-2,1'-isobenzofuran]-3',7(1H)-dione (7)



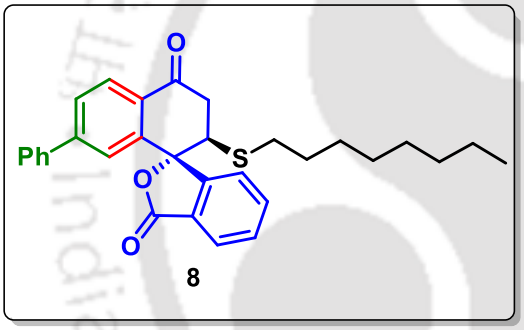
White semi-solid (11.6 mg, yield: 66%); R_f = 0.4 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 15.0, 7.6 Hz, 3H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 2.51 (td, *J* = 8.3, 4.6 Hz, 1H), 2.08 (td, *J* = 8.0, 7.0, 5.4 Hz, 1H), 1.59 (dt, *J* = 8.3, 4.2 Hz, 1H), 1.42 (q, *J* = 5.4 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 195.7, 170.2, 154.2, 147.5, 139.2, 137.7, 135.2, 129.9, 129.1, 128.8, 128.7, 128.2, 127.5, 127.4, 126.4, 123.8, 123.6, 122.2, 85.1, 24.8, 22.9, 14.7. **ESI HRMS**: calcd. for $C_{24}H_{17}O_3$

$[M+H]^+$ 353.1172, found 353.1179. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 10.0 min, t_{minor} = 12.7 min).

d. Procedure for the preparation of 8:

In a screw cap vial, equipped with a magnetic stirring bar, **4aa** (0.05 mmol, 1.0 equiv.), 1-Octanethiol (0.075 mmol, 1.5 equiv.) and Et_3N (0.05 mmol, 1 eq.) were taken in 0.5 ml dry toluene. The resulting suspension was heated at 50 °C for 16 h. After full conversion of **4aa**, the reaction mixture was cooled to r.t. Then the crude reaction mixture was directly purified by silica-gel flash column chromatography (5-7% EtOAc in petroleum ether) to obtain **8** as a pale yellow semi solid (19.6 mg, 81% yield).

(1S,2'R)-2'-(octylthio)-7'-phenyl-2',3'-dihydro-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (8)



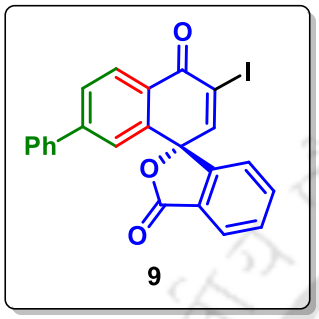
Pale yellow semi-solid (19.6 mg, yield: 81%); R_f = 0.7 in 2:8 ethyl acetate/hexane; dr 7:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.23 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.74 (td, *J* = 8.4, 7.9, 1.5 Hz, 2H), 7.69 (td, *J* = 7.5, 0.9 Hz, 1H), 7.36 (tq, *J* = 4.5, 2.7, 2.0 Hz, 6H), 6.92 (d, *J* = 1.8 Hz, 1H), 3.78 (dd, *J* = 12.9, 4.3 Hz, 1H), 3.36 (dd, *J* = 17.1, 12.9 Hz, 1H), 3.24 (dd, *J* = 17.1, 4.3 Hz, 1H), 2.18 (dt, *J* = 12.2, 7.3 Hz, 1H), 2.03 (dt, *J* = 12.3, 7.4 Hz, 1H), 1.33 – 1.27 (m, 5H), 1.23 – 1.16 (m, 5H), 1.13 (td, *J* = 7.3, 2.5 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 194.7, 169.2, 150.3, 147.5, 140.3, 139.2, 134.4, 131.1, 130.4, 129.2, 129.1, 128.8, 128.6, 128.3, 127.4, 127.0, 126.0, 122.7, 87.6, 49.6, 43.2, 32.7, 31.9, 29.5, 29.2, 29.1, 28.6, 22.7, 14.2. **ESI HRMS**: calcd. for $C_{31}H_{33}O_3S$ $[M+H]^+$ 485.2145, found 485.2146. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.2 min, t_{minor} = 14.6 min).

e. Procedure for the preparation of 9:

To an ice cold solution of **4aa** (0.05 mmol) in anhydrous methylene chloride (0.5 mL) at 0 °C was added $TMSN_3$ (0.1 mmol, 2 eq.). The reaction mixture was stirred under argon at 0 °C for 2 h before the addition of I_2 (0.1 mmol, 2 eq.) in methylene chloride (0.5 mL) and pyridine (76 μL). The resultant mixture was gradually warmed to room temperature and stirred for 12 h, diluted with ether (5 mL), washed with H_2O (5 mL), followed by

$Na_2S_2O_3$ (5 mL) and brine (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Then the crude reaction mixture was purified by silica-gel flash column chromatography (5-10% EtOAc in petroleum ether) to obtain **9** as a pale yellow solid (19.4 mg, 84% yield).

(S)-3'-iodo-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (9)

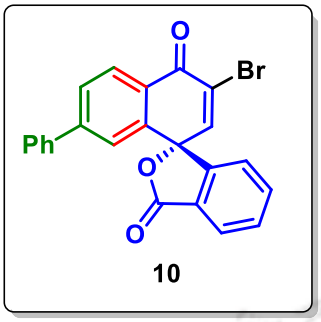


Pale yellow solid (19.4 mg, yield: 84%); M.P. 228-231 °C, R_f = 0.62 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.33 (d, *J* = 8.2 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.55 (s, 1H), 7.49 – 7.36 (m, 5H), 7.14 (dt, *J* = 3.7, 1.6 Hz, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 178.0, 169.4, 152.4, 149.2, 147.0, 139.6, 138.9, 135.8, 130.7, 129.4, 129.2, 129.0, 128.7, 127.5, 126.8, 126.5, 125.2, 125.0, 122.8, 106.6, 83.7. **ESI HRMS**: calcd. for $C_{23}H_{14}O_3I$ $[M+H]^+$ 464.9982, found 464.9986. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 44.8 min, t_{minor} = 40.4 min).

f. Procedure for the preparation of 10:

In an oven-dried screw-capped test tube equipped with a magnetic stir bar, **4aa** (0.05 mmol) was dissolved in dry DCM (0.5 mL) and cooled to 0 °C. Br_2 (0.1 mmol, 2 eq.) was added dropwise to the above solution, and the mixture was allowed to warm to room temperature and stirred for 12 h. After completion, the reaction mixture was again cooled to 0 °C, and Et_3N (0.1 mmol, 2 eq.) was added dropwise and stirred at the same temperature for 2 h. After completion of the reaction, the mixture was diluted with H_2O (5 mL), and extracted with EtOAc (3x10 mL), washed with brine (5 mL), and the organic layer dried over Na_2SO_4. The crude residue was purified using silica-gel flash column chromatography (5-10% EtOAc in petroleum ether) to afford **10** as a pale yellow solid (19.2 mg, 92% yield).

(S)-3'-bromo-7'-phenyl-3H,4'H-spiro[isobenzofuran-1,1'-naphthalene]-3,4'-dione (10)

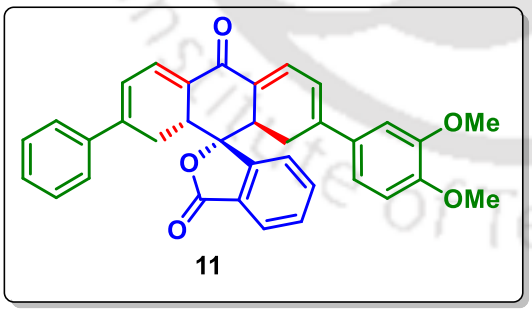


Pale yellow solid (19.2 mg, yield: 92%); M.P. 232-235 °C, R_f = 0.58 in 2:8 ethyl acetate/hexane; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 8.2 Hz, 1H), 8.04 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.74 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.69 – 7.60 (m, 2H), 7.49 – 7.36 (m, 5H), 7.24 (s, 1H), 7.19 – 7.07 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 177.1, 169.4, 149.3, 147.2, 144.7, 139.3, 138.8, 135.8, 130.7, 129.2, 129.1, 129.0, 128.8, 127.8, 127.5, 126.9, 126.8, 125.2, 125.0, 122.8, 83.1. **ESI HRMS**: calcd. for $C_{23}H_{14}O_3Br$ $[M+H]^+$ 417.0121, found 417.0121. **HPLC Analysis**: *ee* = 95%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.5 min, t_{minor} = 14.3 min).

g. Procedure for the preparation of 11:

A screw cap vial, equipped with a magnetic stirring bar, was charged with **3aa** (0.05 mmol, 1.0 equiv), 4-$NO_2C_6H_4CO_2H$ (0.01 mmol, 0.2 equiv), and cat. **VI** (0.01 mmol, 0.2 equiv) followed by addition of 0.25 mL dry toluene. Then freshly prepared **1r** (0.1 mmol, 2.0 equiv) was added to the reaction mixture and was stirred at rt for 16 h. The crude residue was directly purified by silica gel flash column chromatography (20-30% EtOAc in petroleum ether) to obtain **11** as a yellow solid (18.7 mg, 71% yield).

(8aR,9R,9aS)-2-(3,4-dimethoxyphenyl)-7-phenyl-1,8,8a,9a-tetrahydro-3'H,10H-spiro[anthracene-9,1'-isobenzofuran]-3',10-dione (11)

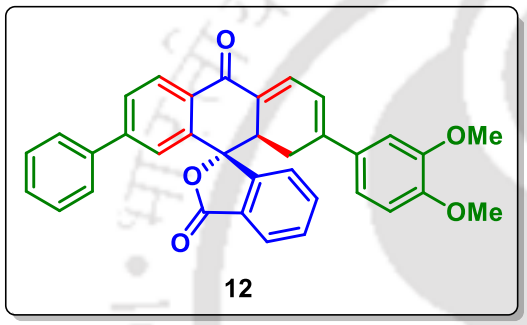


Yellow solid (18.7 mg, yield: 71%); M.P. 240-243 °C, R_f = 0.2 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.94 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.68 (td, *J* = 7.6, 1.2 Hz, 1H), 7.56 (td, *J* = 7.5, 0.9 Hz, 1H), 7.45 – 7.28 (m, 8H), 6.94 (d, *J* = 7.7 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 5.8, 2.4 Hz, 1H), 6.49 (dd, *J* = 6.1, 2.6 Hz, 1H), 3.88 (s, 6H), 3.86 – 3.82 (m, 1H), 3.44 (ddd, *J* = 19.1, 7.1, 2.8 Hz, 1H), 2.91 – 2.71 (m, 3H), 2.12 (ddd, *J* = 19.0, 16.7, 2.8 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 186.5, 169.4, 151.1, 150.4, 149.2, 145.2, 143.9, 139.2, 134.9, 134.6, 134.4, 131.7, 130.9, 129.8, 129.5, 128.9, 128.8, 126.4, 126.2, 125.8, 123.8, 121.4, 119.2, 119.2, 111.2, 108.9, 87.8, 56.2, 56.1, 41.9, 40.4, 29.0, 27.6. **ESI HRMS**: calcd. for $C_{35}H_{29}O_5$ $[M+H]^+$ 529.2010, found 529.2012. **HPLC Analysis**: *ee* = >99%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 54.9 min, t_{minor} = 39.9 min).

h. Procedure for the preparation of 12:

A screw cap vial, equipped with a magnetic stirring bar, was charged with **4aa** (0.05 mmol, 1.0 equiv), 4-$NO_2C_6H_4CO_2H$ (0.01 mmol, 0.2 equiv), and cat. **VI** (0.01 mmol, 0.2 equiv) followed by addition of 0.25 mL dry toluene. Then freshly prepared **1r** (0.1 mmol, 2.0 equiv) was added to the reaction mixture and was stirred at rt for 16 h. The crude residue was directly purified by silica gel flash column chromatography (20-25% EtOAc in petroleum ether) to obtain **12** as a yellow solid (14.7 mg, 56% yield).

(9S,9aR)-2-(3,4-dimethoxyphenyl)-7-phenyl-1,9a-dihydro-3'H,10H-spiro[anthracene-9,1'-isobenzofuran]-3',10-dione (12)



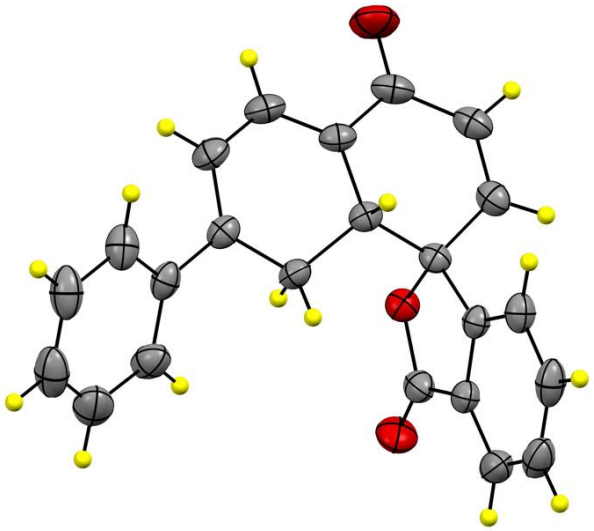
Yellow solid (14.7 mg, yield: 56%); M.P. 237-240°C, R_f = 0.3 in 2:8 ethyl acetate/hexane; dr >20:1; **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.34 (d, *J* = 8.1 Hz, 1H), 8.08 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.87 (td, *J* = 7.5, 1.1 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.67 (dd, *J* = 6.2, 2.9 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.33 (m, 5H), 6.89 – 6.85 (m, 2H), 6.76 (d, *J* = 1.2 Hz, 2H), 6.56 (dd, *J* = 6.2, 2.8 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.68 (ddd, *J* = 19.1, 16.3, 2.9 Hz, 1H), 2.03 (dd, *J* = 16.4, 7.6 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 183.6, 169.0, 150.2, 149.1, 149.1, 146.7, 143.6, 139.6, 139.3, 135.2, 135.1, 133.6, 132.0, 130.6, 129.4, 129.3, 129.1, 128.6, 128.2, 127.4, 127.1, 126.3, 125.2, 122.7, 119.4, 118.8, 111.0, 108.7, 86.3, 56.1, 56.1, 41.2, 26.4. **ESI HRMS**: calcd. for $C_{35}H_{27}O_5$ $[M+H]^+$ 527.1853, found 527.1856. **HPLC Analysis**: *ee* = 96%, Chiralpak IA Column, n-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 27.1 min, t_{minor} = 32.3 min).

5.6.8 Single crystal X-ray diffraction analysis:

(a) Single crystal X-ray diffraction analysis of 3aa:

Method for crystal growth: In a round bottom flask, compound **3aa** dissolved in minimum amount of hexane/DCM (1:1) and it kept in dark place at room temperature for slow evaporation to get crystal of **3aa**. The needle shaped crystal was then subjected to X-ray diffraction.

CCDC No.	2400979
Empirical formula	$C_{23}H_{16}O_3$
Formula weight	340.36
Crystal habit, colour	needle / yellow
Temperature, T	295 K
Wavelength, λ (Å)	0.71073
Crystal system	orthorhombic
Space group	'P 21'
Unit cell dimensions	a = 5.6163(2) Å
	b = 10.3847(4) Å
	c = 29.9173(11) Å
	α = 90°, β = 90°, γ = 90°
Volume, V ($Å^3$)	1744.88(11)
Z	4
Calculated density, $g \cdot cm^{-3}$	1.296
F (000)	712.0
Refinement method	'SHELXL–2018/3'
Goodness–of–fit on F^2	1.190
Theta(max)	24.997
Data completeness	1.68/1.00
R(reflections)	0.0404 (2564)
wR2(reflections)	0.0883 (3074)



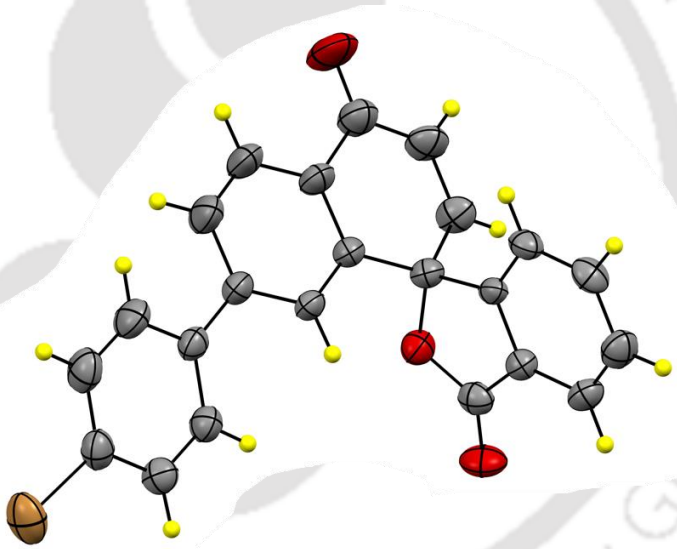
ORTEP representation of the X-ray structure of **3aa** (thermal ellipsoids at 30% probability)

(b) Single crystal X-ray diffraction analysis of 4ha:

Method for crystal growth: In a round bottom flask, compound **4ha** dissolved in minimum amount of hexane/DCM (1:1) and it kept in dark place at room temperature for slow evaporation to get crystal of **4ha**. The needle shaped crystal was then subjected to X-ray diffraction.

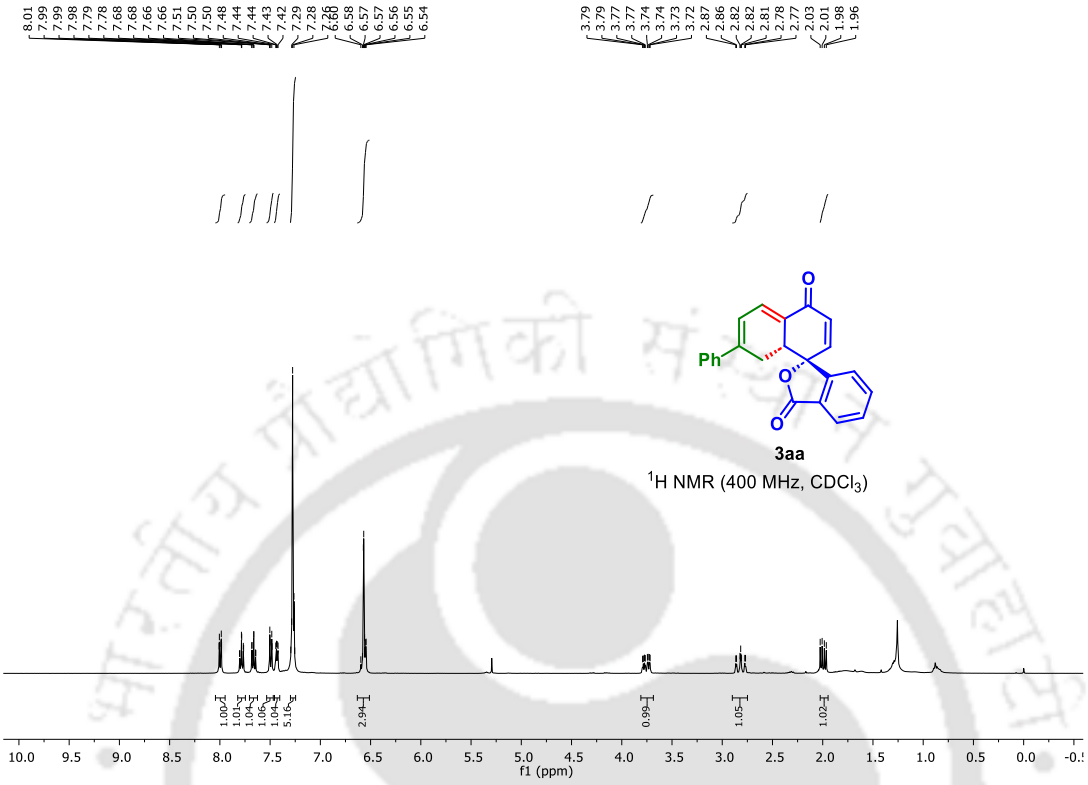
CCDC No.	2401022
Empirical formula	$C_{23}H_{13}BrO_3$
Formula weight	417.24
Crystal habit, colour	needle / colourless
Temperature, T	301 K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	'P 21'
Unit cell dimensions	a = 10.7381(10) Å
	b = 8.2262(8) Å
	c = 21.255(2) Å
	α = 90°, β = 102.995°, γ = 90°

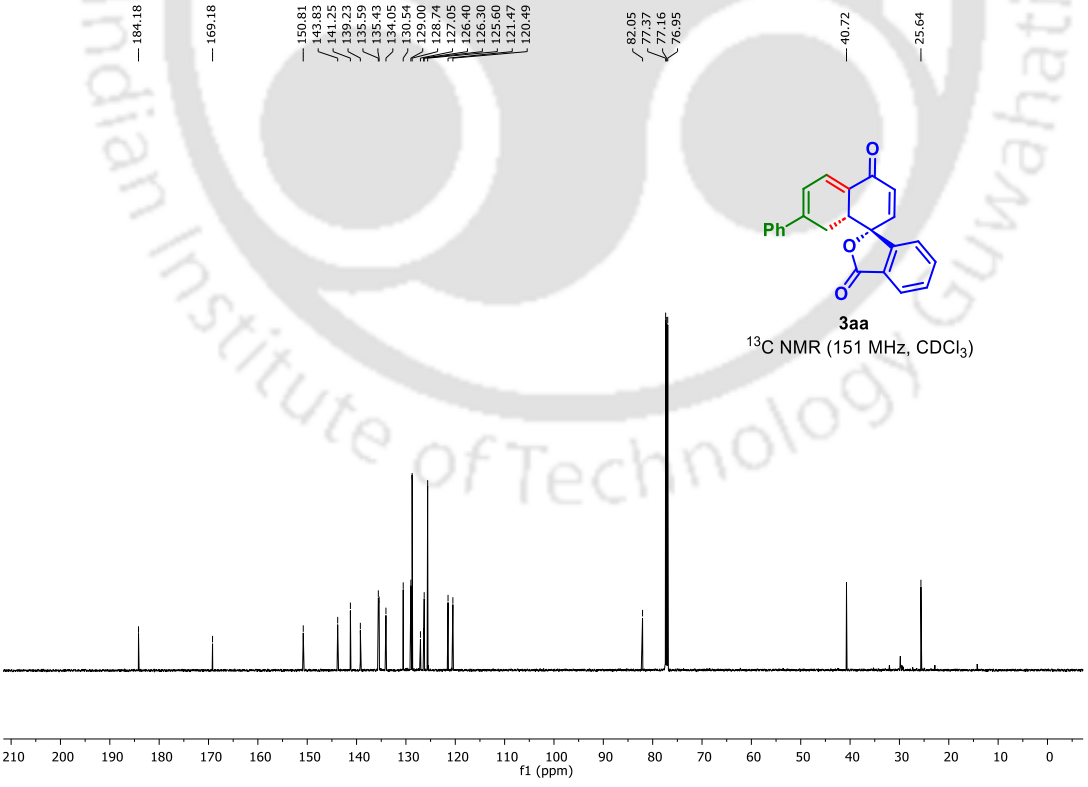
Volume, V (Å^3)	1829.5(3)
Z	4
Calculated density, g·cm^{-3}	1.515
F (000)	840.0
Refinement method	'SHELXL–2019/1'
Goodness–of–fit on F^2	1.059
Theta(max)	25.051
Data completeness	1.85/0.99
R(reflections)	0.0511 (3768)
wR2(reflections)	0.1507 (6433)

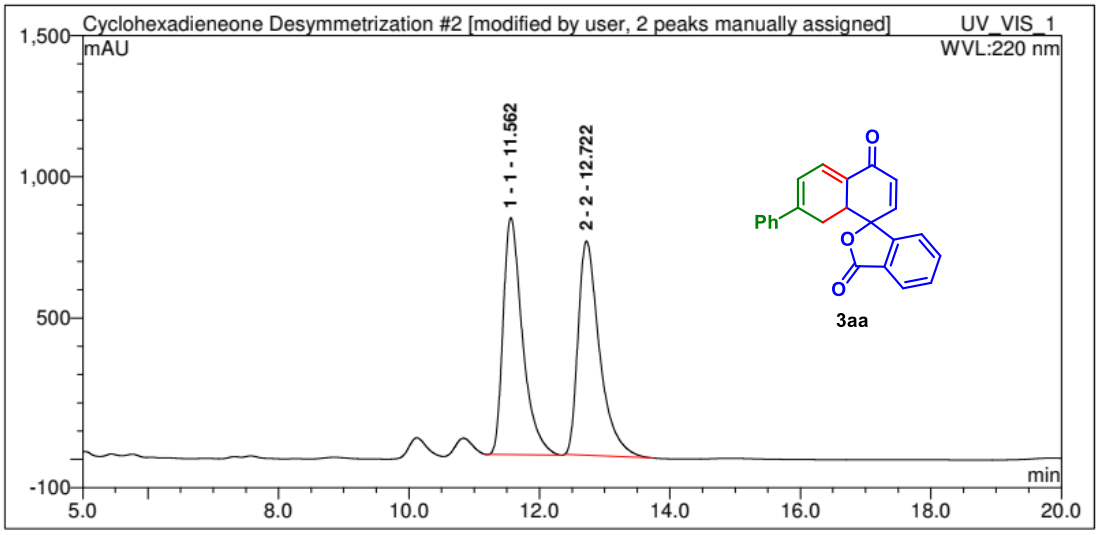


ORTEP representation of the X-ray structure of **4ha** (thermal ellipsoids at 30% probability)

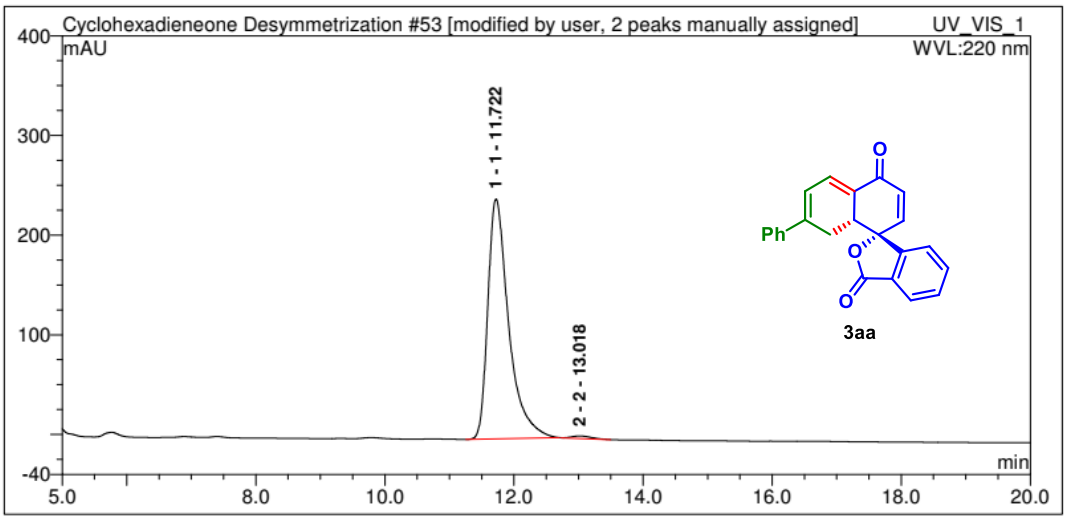
5.6.9 NMR spectra and HPLC chromatograms of selected products:



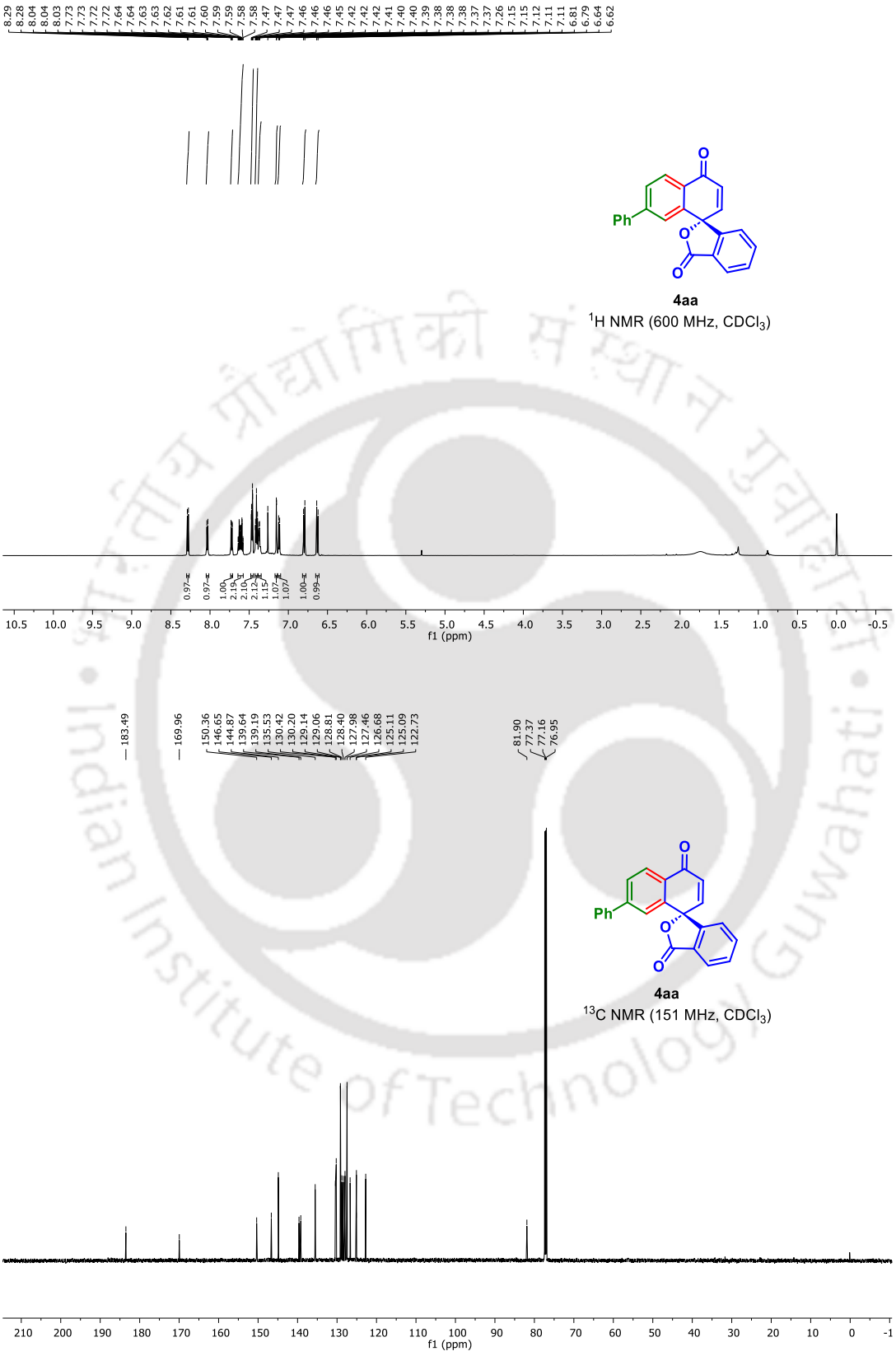


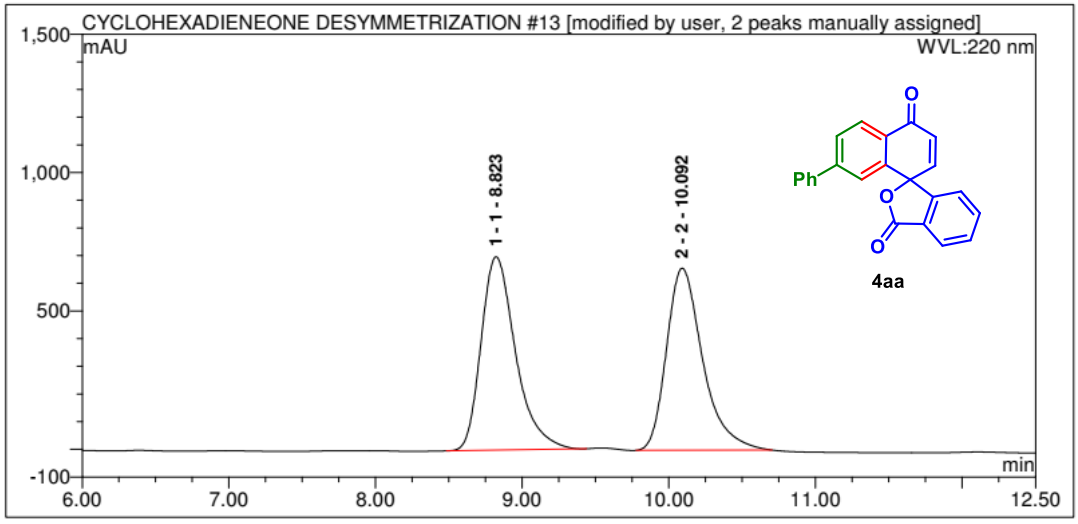


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.56166667	288.1372	49.88268326	838.2055	n.a.
2	2	12.72166667	289.4925	50.11731674	758.4835	n.a.

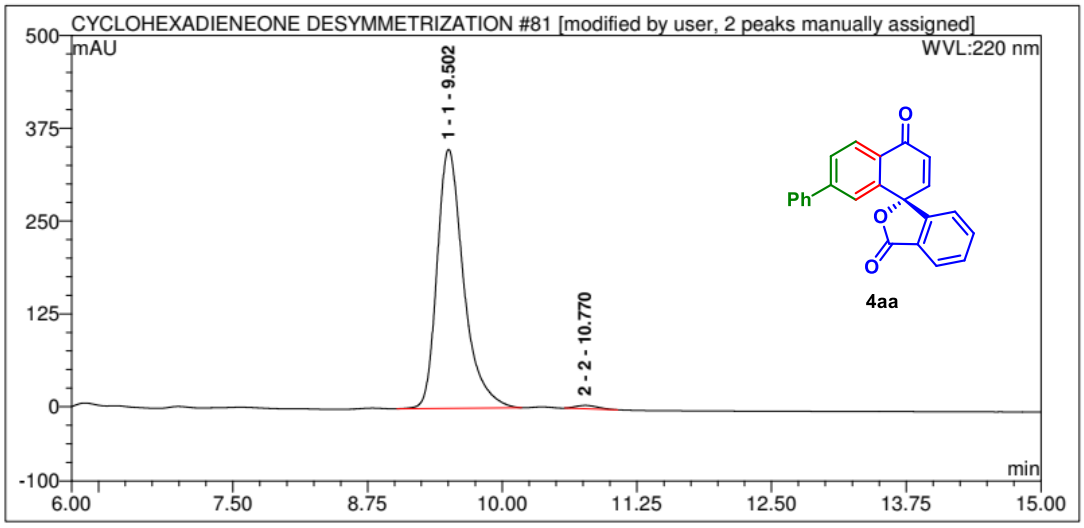


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.72166667	90.09098	99.06582341	240.6059	n.a.
2	2	13.01833333	0.849545	0.9341765884	2.50893	n.a.

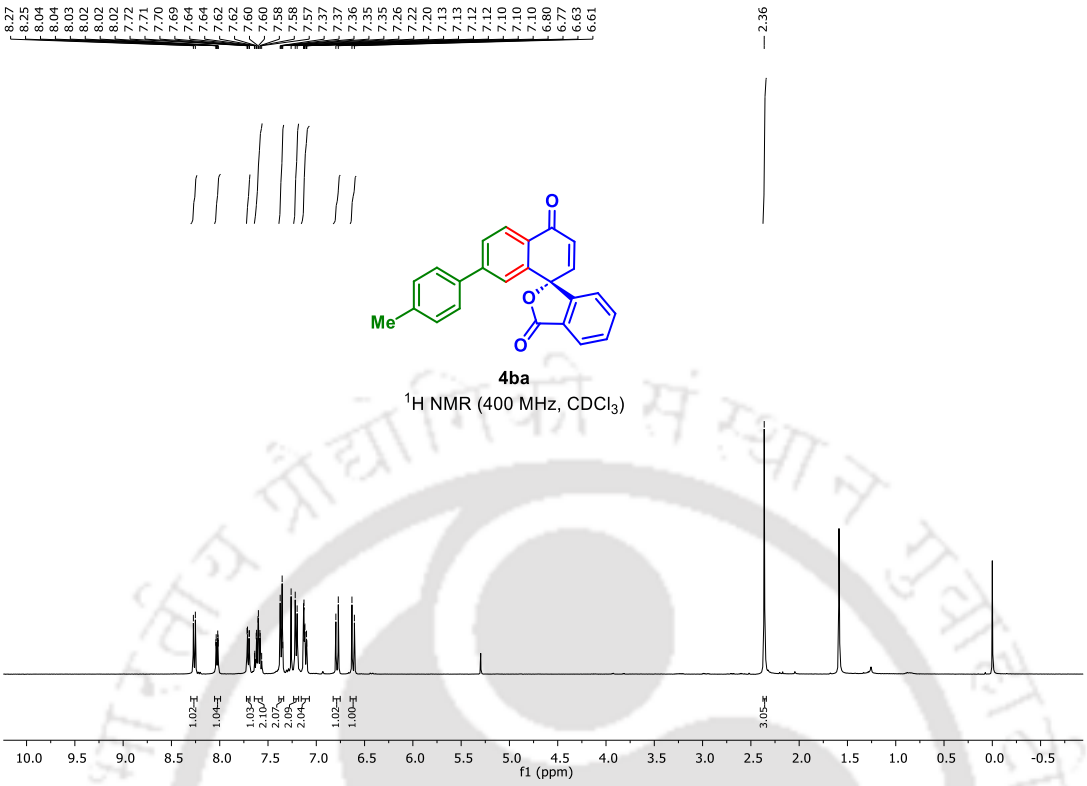




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.823333333	190.4686	50.26300317	698.6874	n.a.
2	2	10.09166667	188.4753	49.73699683	657.6913	n.a.

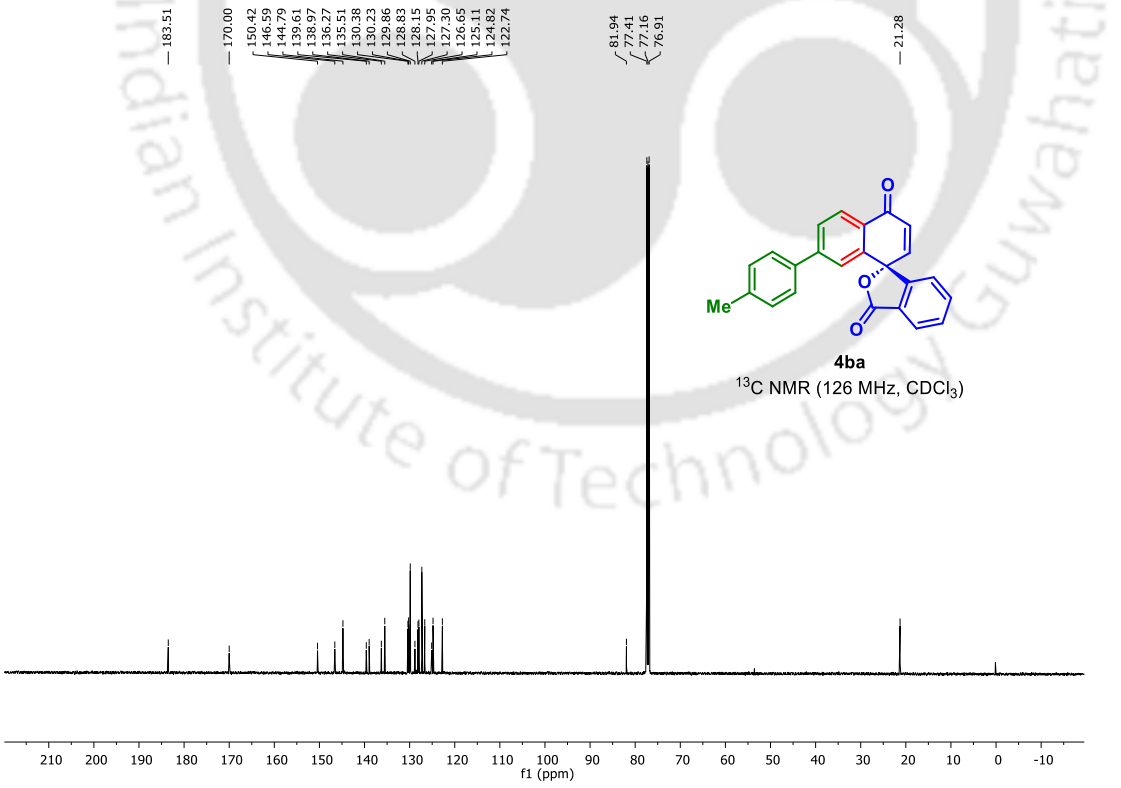


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.501666667	99.67268	98.93615783	348.7466	n.a.
2	2	10.77	1.071762	1.063842167	4.51409	n.a.



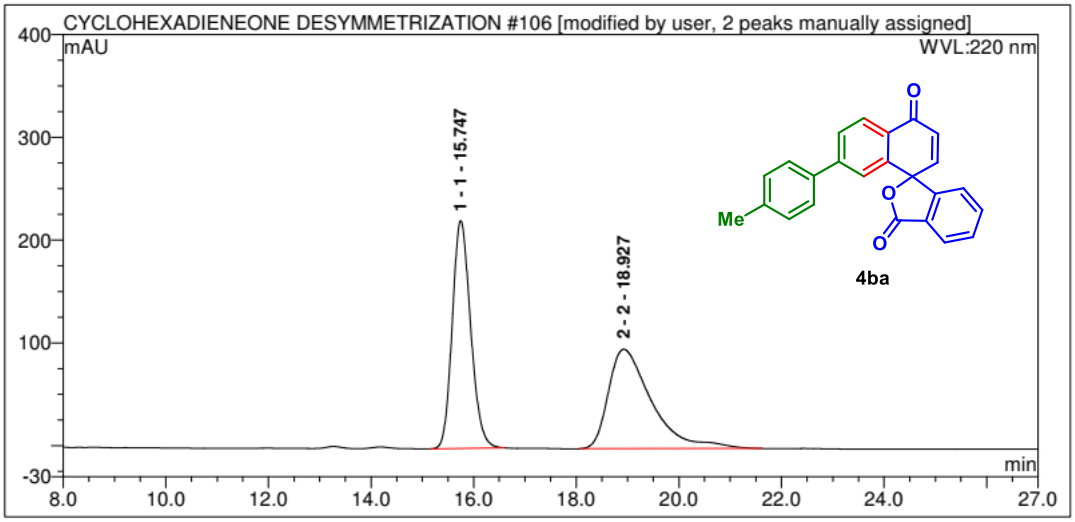
4ba

^{1}H NMR (400 MHz, $CDCl_3$)

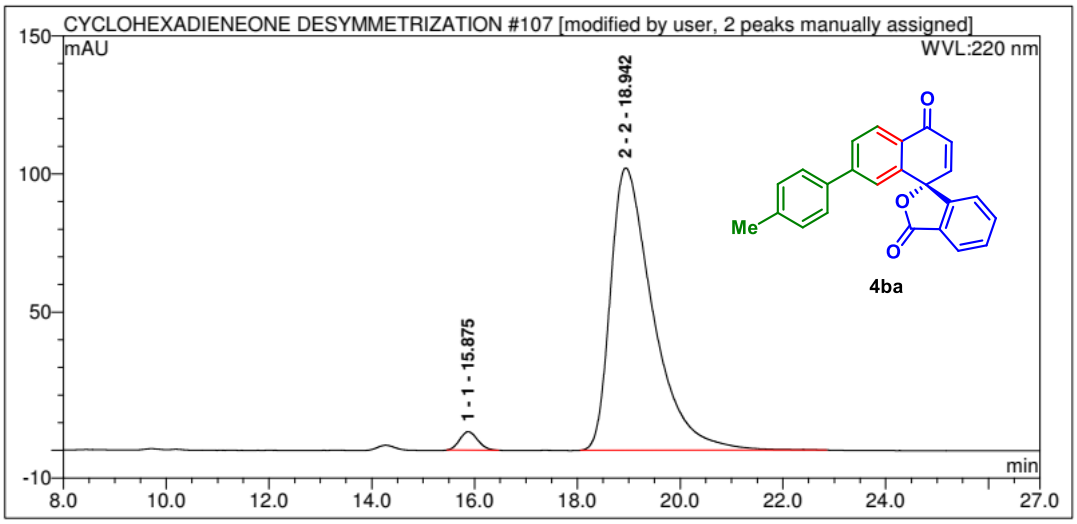


4ba

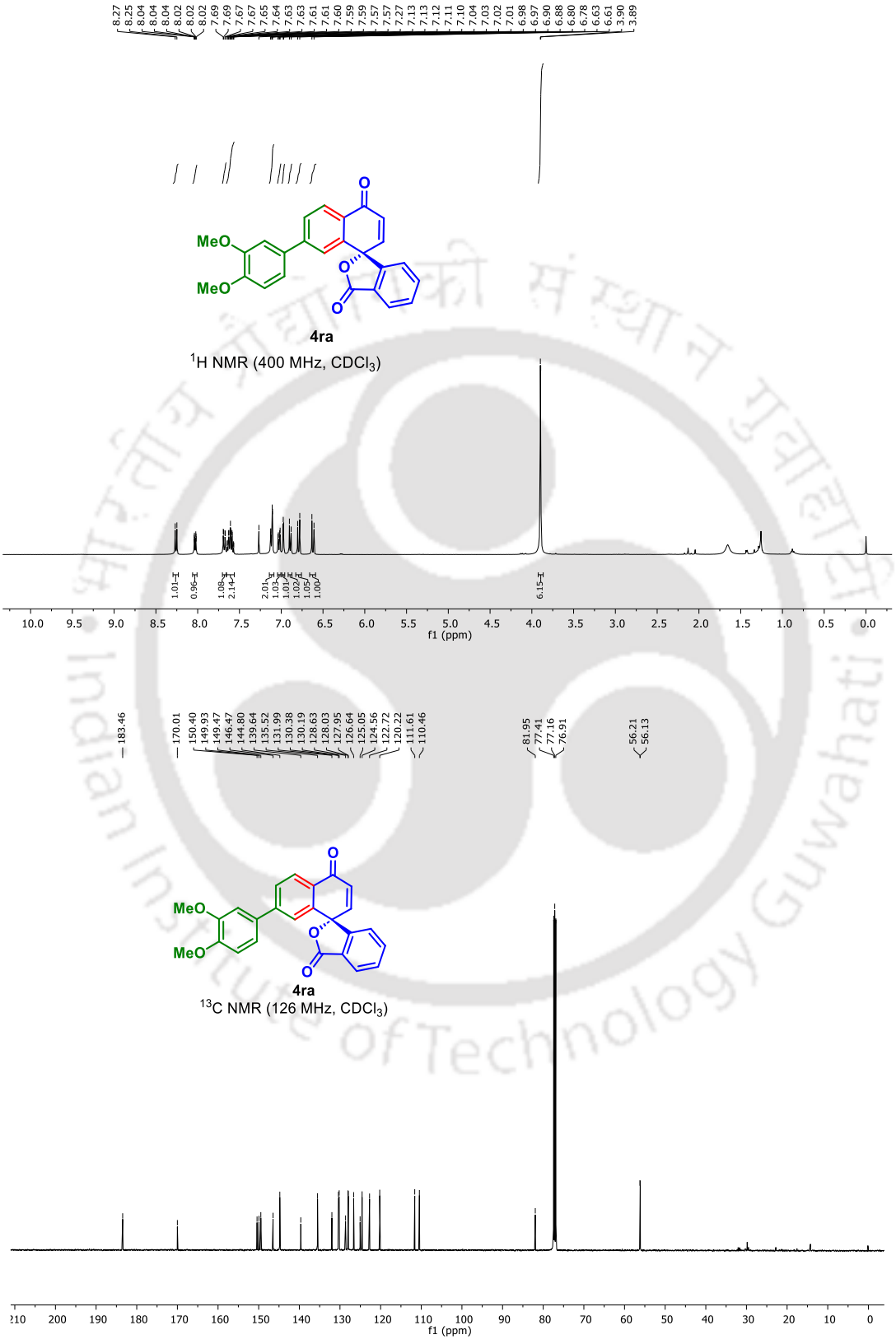
^{13}C NMR (126 MHz, $CDCl_3$)

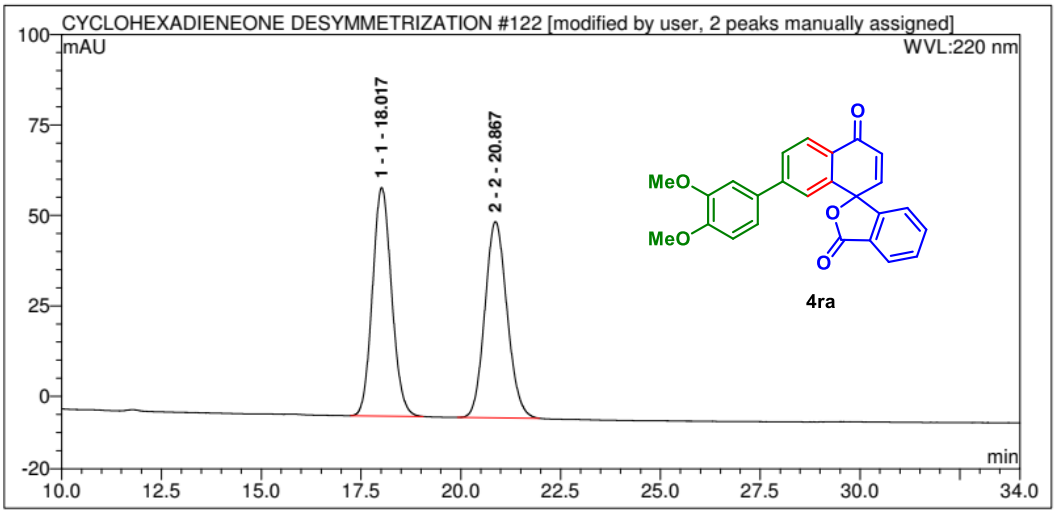


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	15.74666667	92.00029	49.4247896	221.3831	n.a.
2	2	18.92666667	94.14171	50.5752104	96.70176	n.a.

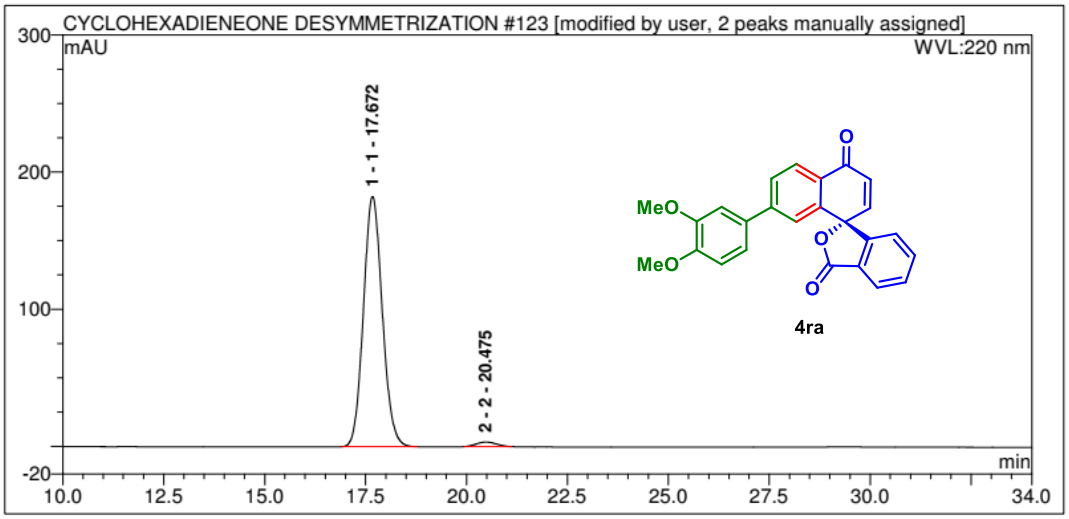


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	15.875	2.7102	2.695270413	6.66477	n.a.
2	2	18.94166667	97.84374	97.30472959	102.1576	n.a.

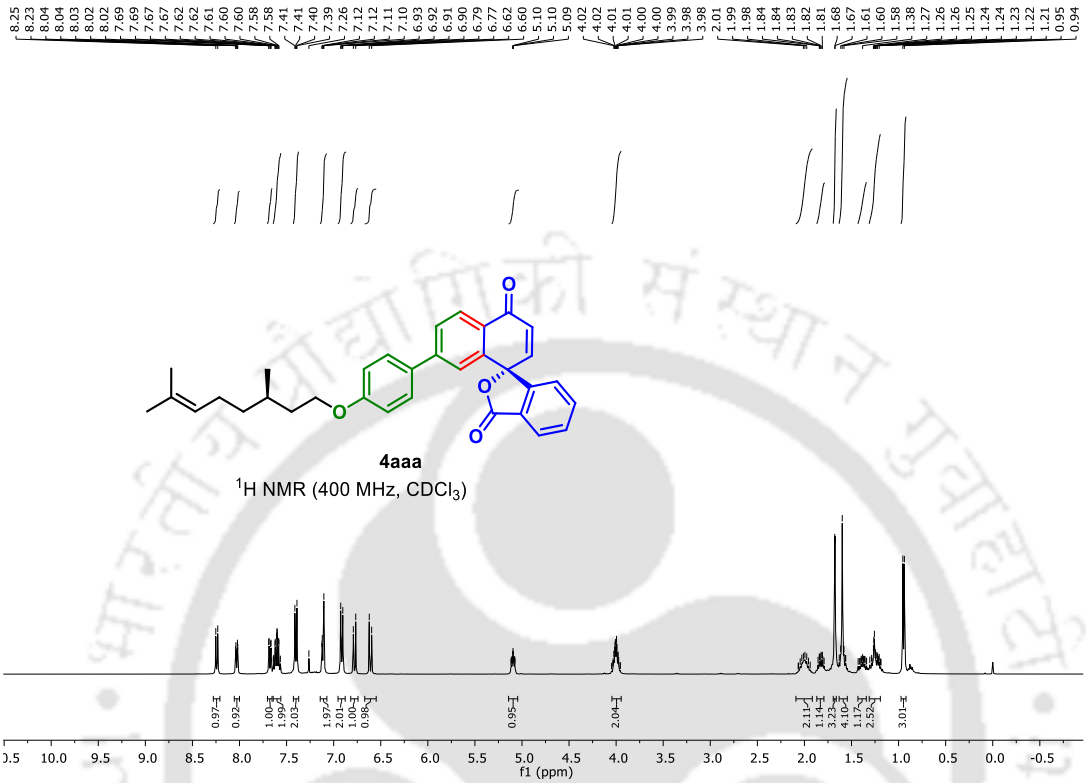




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	18.01666667	35.17934	50.09050895	63.16096	n.a.
2	2	20.86666667	35.0522	49.90949105	54.2136	n.a.

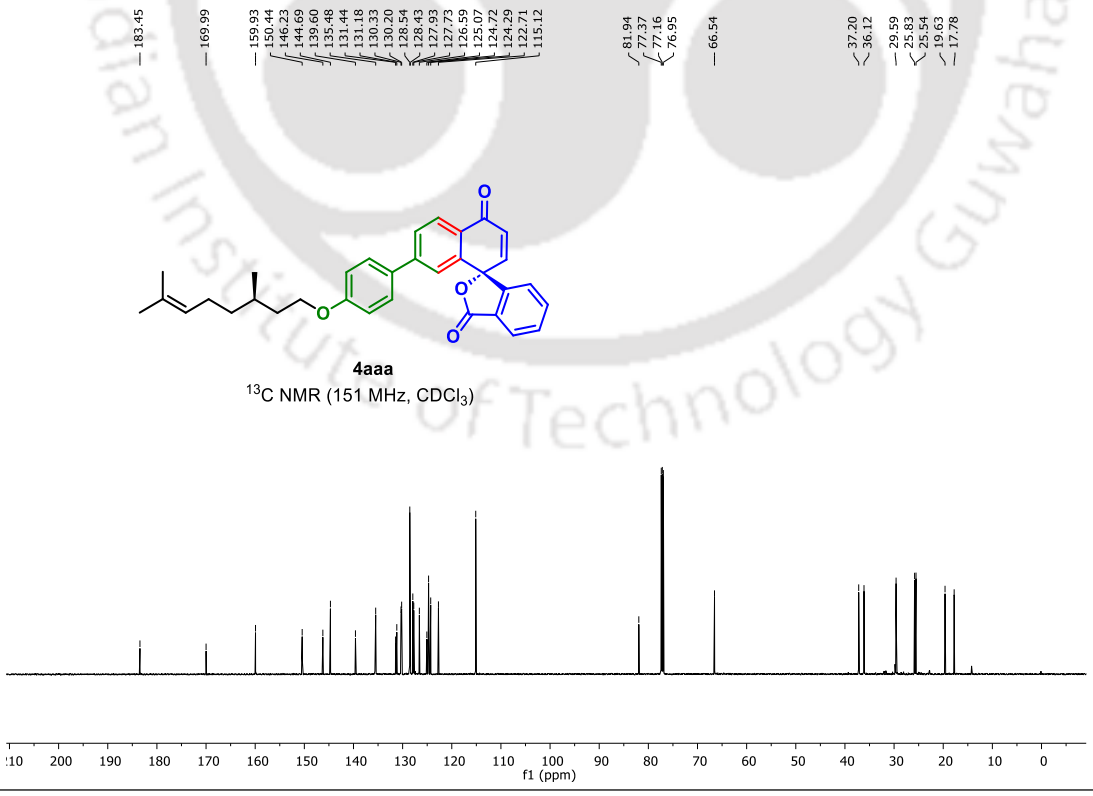


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	17.67166667	98.81428	98.09016062	182.4042	n.a.
2	2	20.475	1.923938	1.909839381	3.35958	n.a.



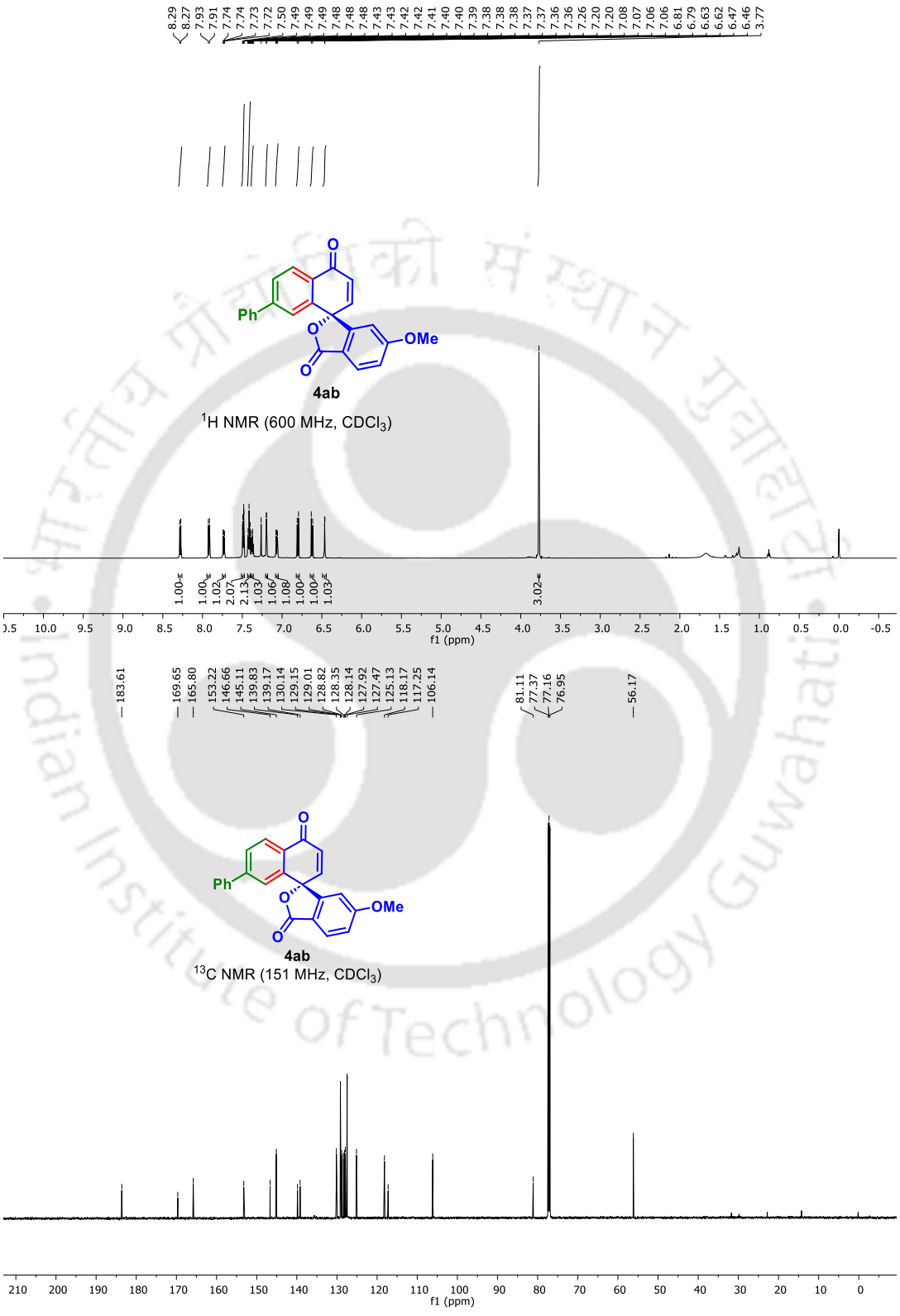
4aaa

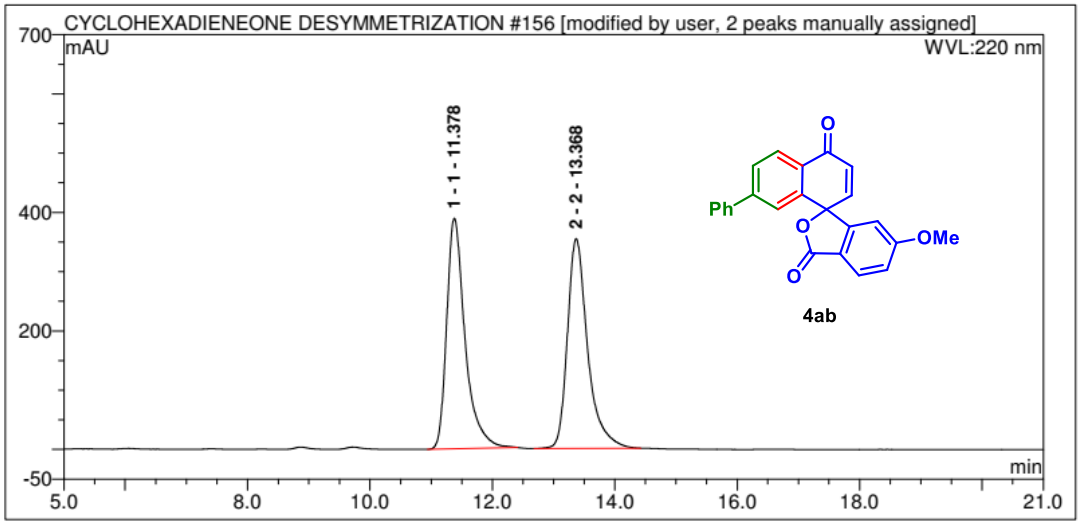
^{1}H NMR (400 MHz, $CDCl_3$)



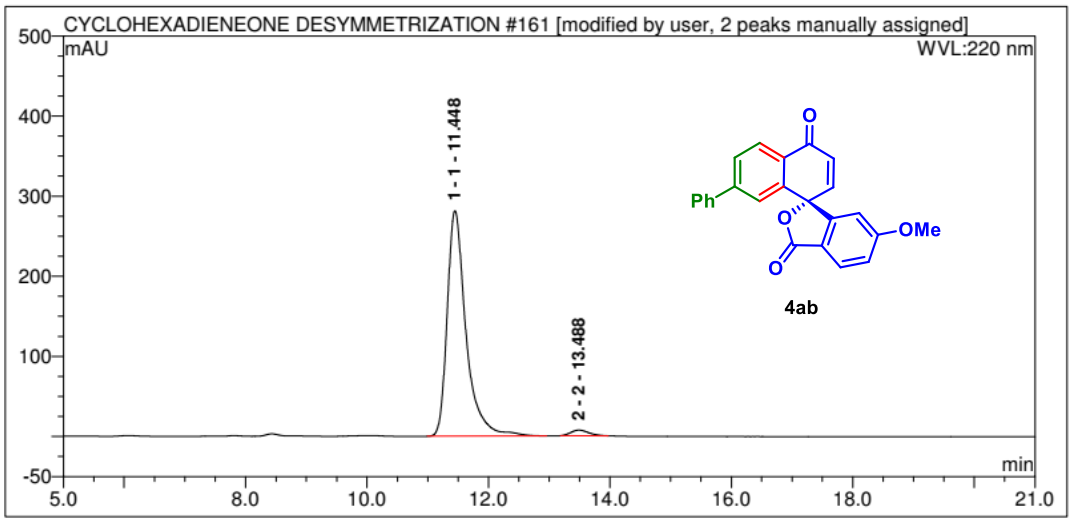
4aaa

^{13}C NMR (151 MHz, $CDCl_3$)

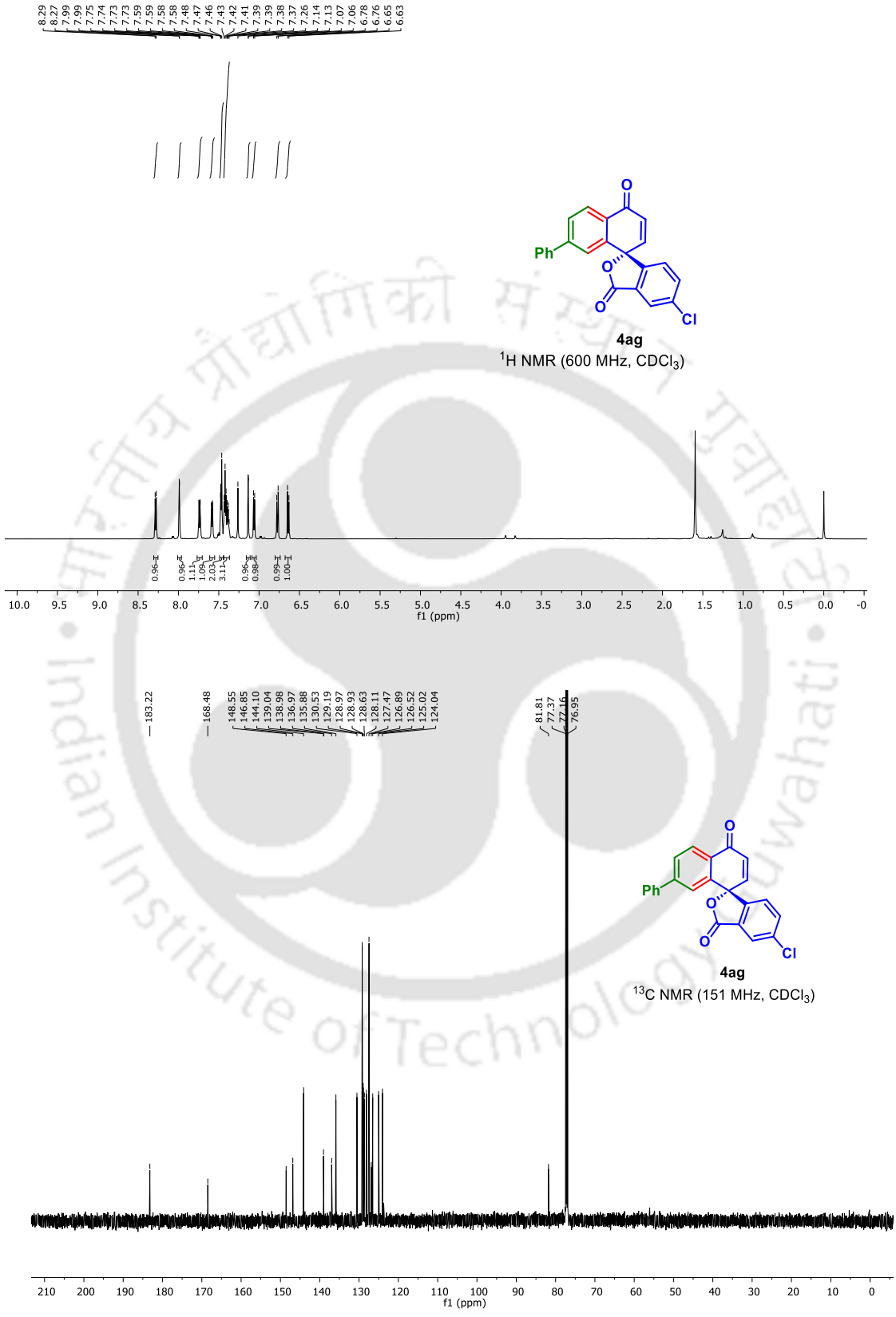


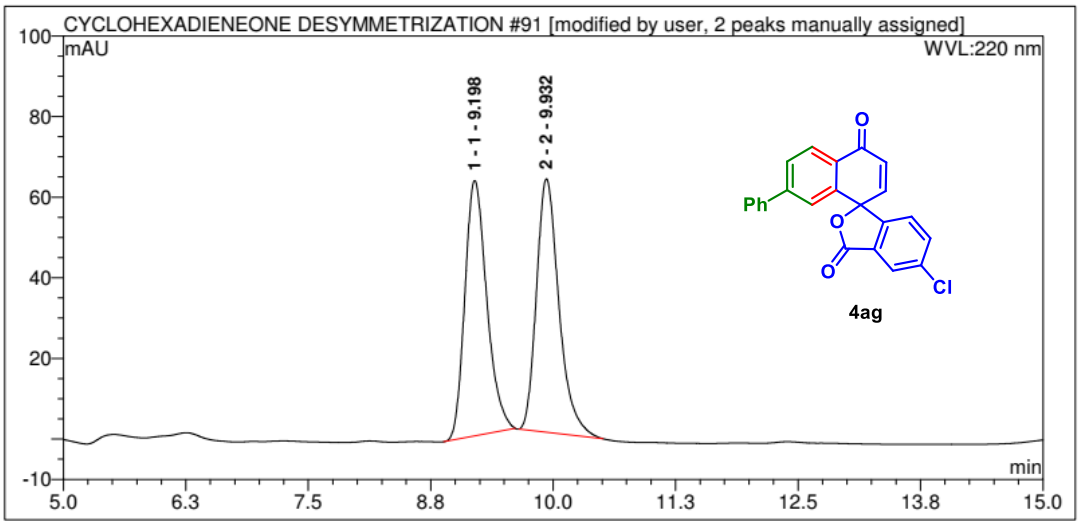


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.37833333	135.3605	49.93903809	389.2392	n.a.
2	2	13.36833333	135.6909	50.06096191	354.3415	n.a.

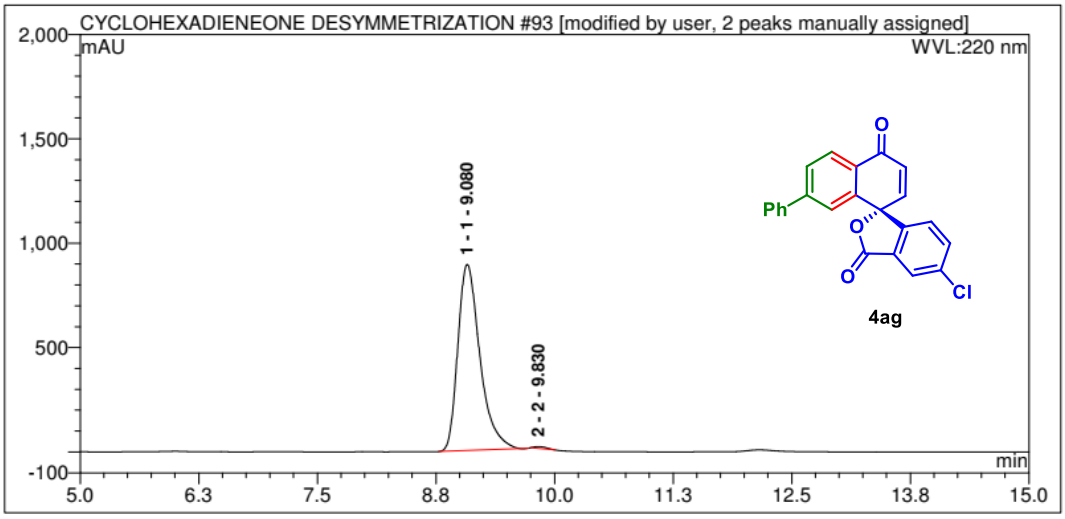


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	11.44833333	101.032	97.66286103	281.3547	n.a.
2	2	13.48833333	2.417764	2.337138971	7.08275	n.a.





No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.198333333	16.46174	49.58678041	63.36753	n.a.
2	2	9.931666667	16.7361	50.41321959	62.8847	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.08	240.2097	99.42804301	890.6577	n.a.
2	2	9.83	1.3818	0.5719569898	8.85828	n.a.

5.7 References

(1) For a review on the naturally occurring benzene-fused γ-lactones, see: (a) Beck, J. J.; Chou, S.-C. *J. Nat. Prod.* **2007**, *70*, 891. For selected examples, see: (b) Piacente, S.; Montoro, P.; Oleszek, W.; Pizza, C. *J. Nat. Prod.* **2004**, *67*, 882. (c) Sontag, B.; Rüth, M.; Spiteller, P.; Arnold, N.; Steglich, W.; Reichert, M.; Bringmann, G. *Eur. J. Org. Chem.* **2006**, *2006*, 1023. (d) Kwon, Y.-J.; Sohn, M.-J.; Zheng, C.-J.; Kim, W.-G. *Org. Lett.* **2007**, *9*, 2449. (e) Ge, H. M.; Zhu, C. H.; Shi, D. H.; Zhang, L. D.; Xie, D. Q.; Yang, J.; Ng, S. W.; Tan, R. X. *Chem. - Eur. J.* **2008**, *14*, 376. (f) Ding, G.; Zheng, Z.; Liu, S.; Zhang, H.; Guo, L.; Che, Y. *J. Nat. Prod.* **2009**, *72*, 942. (g) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213.

(2) R. W. Sabnis, *Kirk-Othmer Encyclopedia of Chemical Technology*, 2010, DOI: 10.1002/0471238961.phthsabn.a01.

(3) Barton, D. H. R.; de Vries, J. X. *J. Chem. Soc*. **1963**, 1916.

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Publications:

- **Biswas, S.**; Pan, S. C. Organocatalytic Asymmetric Desymmetrization of Cyclopentene-1,3-diones via Formal Diaza-ene Reaction with Donor-Acceptor Hydrazones. *Org. Chem. Front.* **2025**, *12*, 2651.

- **Biswas, S.**; Pan, S. C. Catalytic Asymmetric Desymmetrizing [4+2] Cycloaddition/Base Mediated Oxidative Aromatization Sequence: *de novo* Synthesis of Isobenzofuranone Embedded Chiral Arenes. *Org. Lett.* **2025**, *27*(1), 309.

- **Biswas, S.**; Kundu, S.; Pan, S. C. Organocatalytic Asymmetric Synthesis of C-N Atropisomers with Pyrrole, Oxindole and Succinimide Scaffold. *Chem Asian J.* **2025**, *20*, e202401132.

- **Biswas, S**.; Purkayastha, S. K.; Guha, A. K.; Pan, S. C. Sequential Organo and Metal Catalyzed Reaction between 3-Pyrrolyloxindoles and Linear Nitroenynes: access to cyclic aza-spirooxindoles. *Chem. Comm.*, **2023**, *59*, 12156.

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Conferences:

- Participated in poster presentation in **Indo French Seminar on Catalysis for Sustainability** (December 2023) at IISER Thiruvananthapuram.
- Participated in poster presentation **in Frontiers in Chemical Sciences** (December 2022) at IIT Guwahati.
- Participated in poster presentation in **North-East Research Conclave** (May 2022) at IIT Guwahati.
- Participated in poster presentation in 28th **CRSI National Symposium in Chemistry** (March 2022) at IIT Guwahati.