Organocatalytic Asymmetric Acyl Transfer Reaction and the Synthesis of C-C and C-N Atropisomers

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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Dedicated to

My Parents and Well Wishers

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Organocatalytic Asymmetric Acyl Transfer Reaction and the Synthesis of C-C and C-N Atropisomers***" is the result of investigations 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 wherever the work described is based on the findings of other investigators.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Organocatalytic Asymmetric Acyl Transfer Reaction and the Synthesis of C-C and C-N Atropisomers***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Chandrakanta Parida (Roll No: 176122118) 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
May, 2023

Prof. Subhas Chandra Pan
Supervisor

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Chandrakanta Parida

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Abbreviation

Ar	Aryl group	h	Hours
AcOH	Acetic Acid	HPLC	High performance liquid chromatography
Bu	Butyl	HRMS	High Resolution Mass Spectrometry
CCDC	Cambridge Crystallographic Data Centre	Hz	Hertz
COSY	Correlation spectroscopy	Hex	Hexane
^{o}C	Degrees Celsius	*i*	Iso
CAN	ceric ammonium nitrate	*i*-PrOH	2-propapnol
CH_3CN	Acetonitrile	*J*	Coupling Constant
C_6H_6	Benzene	KBr	Potassium bromide
$CHCl_3$	Chloroform	m	Multiplet
$PhCh_3$	Toluene	*m*	*meta*
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene	*m*CPBA	*meta*-Chloroperoxybenzoic acid
DCE	1,2-Dichloroethane	Me	Methyl
DCM	Dichloromethane	mg	Miligram
DIPEA	*N*,*N*-Diisopropylethylamine	mL	Millilitre
DMAP	4-Dimethylaminopyridine	mmol	Milimole
DMF	*N*,*N*-Dimethylformamide	mp	Melting point
DMSO	Dimethylsulfoxide	MTBE	Methyl tertiary butyl ether
dr	Diastereomeric ratio	MS	Molecular sieves
DTBP	Di-*tert*-butyl peroxide	ppm	Parts per million
EA	Ethyl acetate	q	Quartet
ee	Enantiomeric excess	s	Singlet
equiv	Equivalent	t	triplet

ESI	Electrospray ionization	d	Doublet
Et	Ethyl	dd	Doublet of doublet
n	Normal	*t*	*tert*
NMR	Nuclear magnetic resonance	TC	Thiocarboxylate
NOESY	Nuclear Overhauser effect spectroscopy	TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program	TFA	Trifluoroacetic acid
o	*ortho*	TFAA	Trifluoroacetic anhydride
p	*para*	UV	Ultra violet
Ph	Phenyl	THF	Tetrahydrofuran
ppm	Parts per million	TMS	Tetramethylsilane
Pr	Propyl	TBHP	tert-Butyl hydroperoxide
PS	Proton sponge	TBAI	Tetra^{n}butylammonium iodide
PTSA	*para*-Toluenesulfonic acid	Ts	*p*-Toluenesulfonyl
$PhCF_3$	Trifluorotoluene	UV	Ultra violet
PPA	Polyphosphoric acid	XRD	X-ray diffraction
rt	Room temperature	δ	Chemical shift
VQM	Vinylidene *ortho*-quinone methide		

General Remarks

The present investigations are carried out in Department of Chemistry, Indian Institute of Technology Guwahati, during the period from April-2018 to May-2023 as a Ph.D. student under the supervision of Prof. Subhas Chandra Pan.

Mostly, all reactions were carried under air using oven dried glassware and magnetic stirring. All solvents and reagents were used as received from Aldrich, Merck and Spectrochem without purification.

But reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. Methanol and ethanol were freshly distilled from magnesium/iodine under argon. THF and diethylether (Et_2O) were freshly distilled from Sodium under argon. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane ($ClCH_2CH_2Cl$) were freshly distilled from calcium hydride (CaH_2). Chloroform ($CHCl_3$) was distilled calcium chloride ($CaCl_2$) and store under argon. *N*, *N*-diisopropylethylamine (DIPEA) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene, toluene and were distilled from calcium hydride (CaH_2) before use. Trifluorotoluene ($PhCF_3$) was used as received from Sigma Aldrich India. All other solvents and reagents were purified according to standard procedures.

^{1}H &^{13}C NMR spectroscopy: *Bruker DRX 400 MHz, Bruker DRX 500 MHz* and *Bruker DRX 600 MHz*. Chemical shifts, δ (in ppm), are reported relative to TMS (δ (1H) 0.0 ppm, δ (13C) 0.0 ppm) which was used as the inner reference. Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.23 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.15 ppm) were used for calibration.

Column chromatography: Merck or Spectrochem silica gel 60-120, 230-400 mesh or neutral alumina (Merck or Fischer Scientific) under gravity. After purifications the solvent was usually removed in Büchi R-114V rotavapour.

MS (ESI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

XRD: X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo-Kα radiation (l = 0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS-97 and refined with full matrix least squares on *F*2 using SHELXL-97.

HPLC: HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic materials.

TLC: Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm).

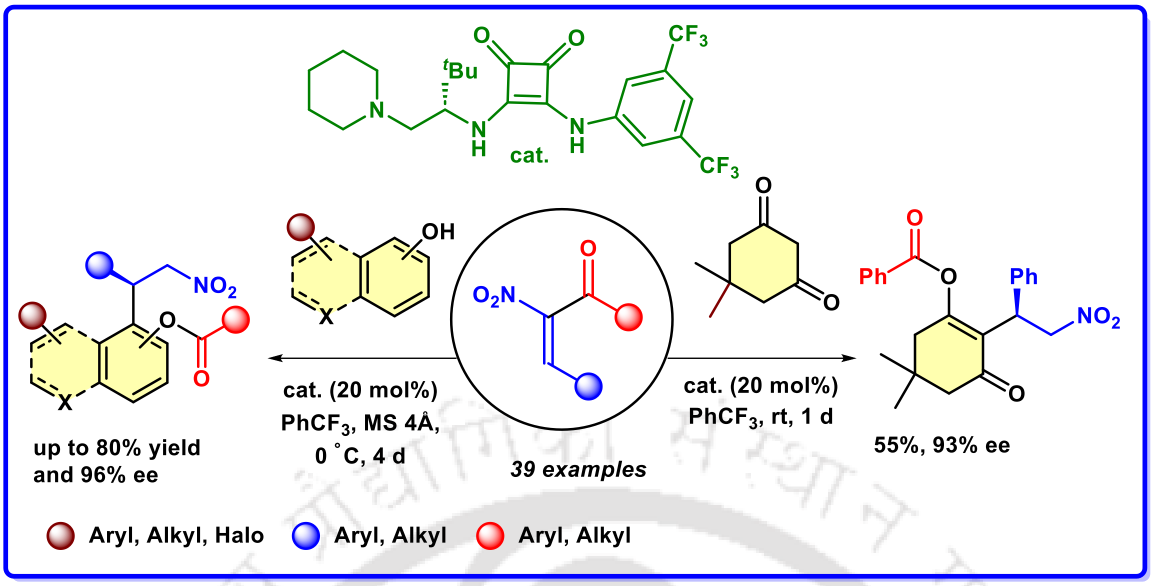
Melting Point: Melting points were measured using BüCHI melting point B-540 apparatus.

Abstract

The contents of the present thesis entitled as "***Organocatalytic Asymmetric Acyl Transfer Reaction and the Synthesis of C-C and C-N Atropisomers***" have been divided into six chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

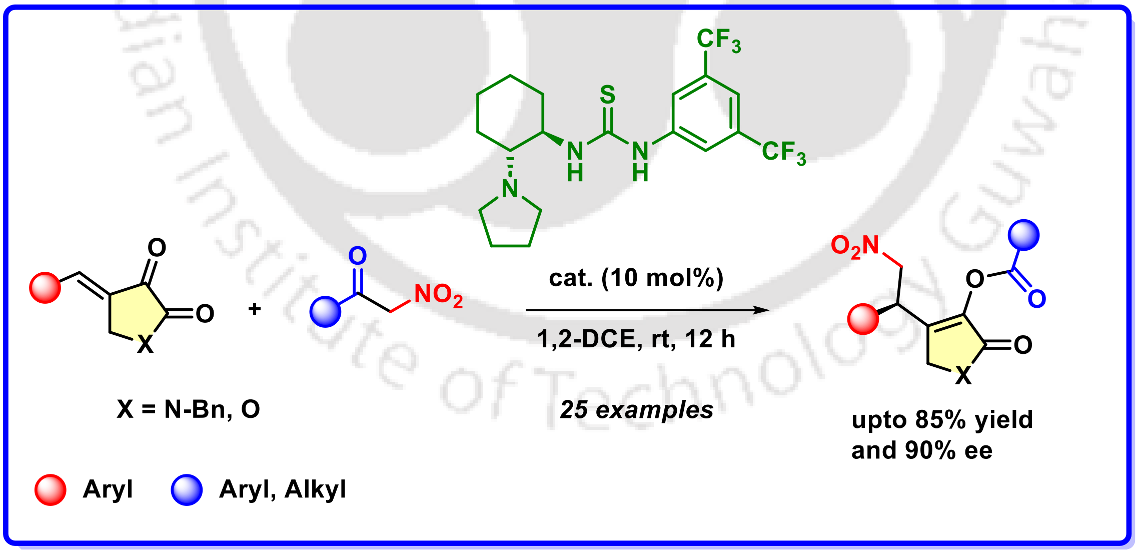
Chapter 1 is of two parts, first part contains a brief overview of asymmetric synthesis, details organocatalytic mechanistic approaches and in part two describes the details study about the atropisomer.

Chapter 2 In this chapter, highlights the α-nitro-α, β-unsaturated ketones as efficient electrophilic acyl transfer reagents, and they were employed in Friedel−Crafts as well as in Michael reactions. This strategy features broad substrate scope (39 examples), high atom economy, as well as α-nitro-α, β-unsaturated ketones as efficient electrophilic acyl transfer reagents in asymmetric cascade reactions for the first time. The desired acyl transfer products of these reactions were obtained in high yields with high to excellent enantioselectivities with *t*-leucine-derived squaramide catalyst under mild reaction conditions. Few applications including a synthesis of the isoxazoline motif have been demonstrated.



Scheme 1

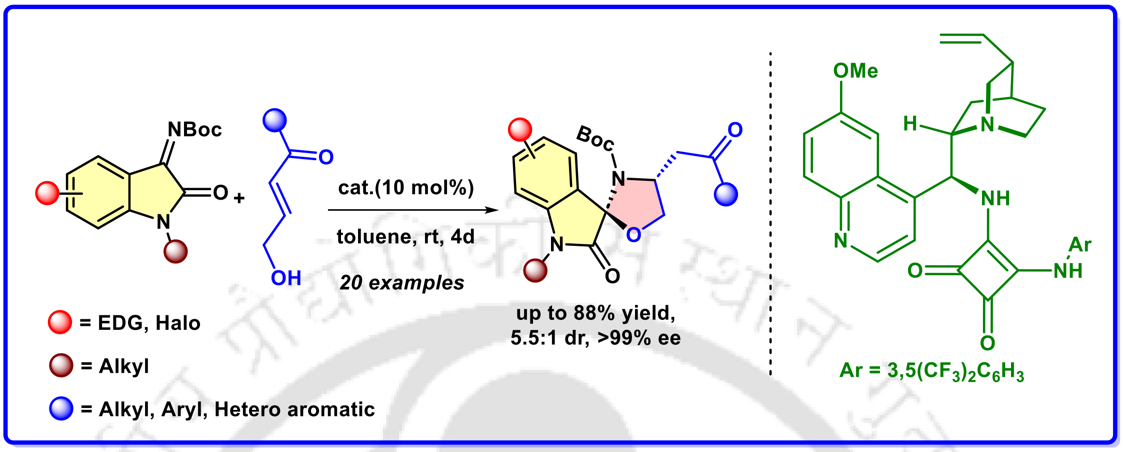
Chapter 3 represents an organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones is reported. A bifunctional thiourea catalyst was found to be effective for this reaction. With 10 mol % of the catalyst, good results were attained for a variety of 1,5-dihydro-2H-pyrrol-2-ones under mild reaction conditions.



Scheme 2

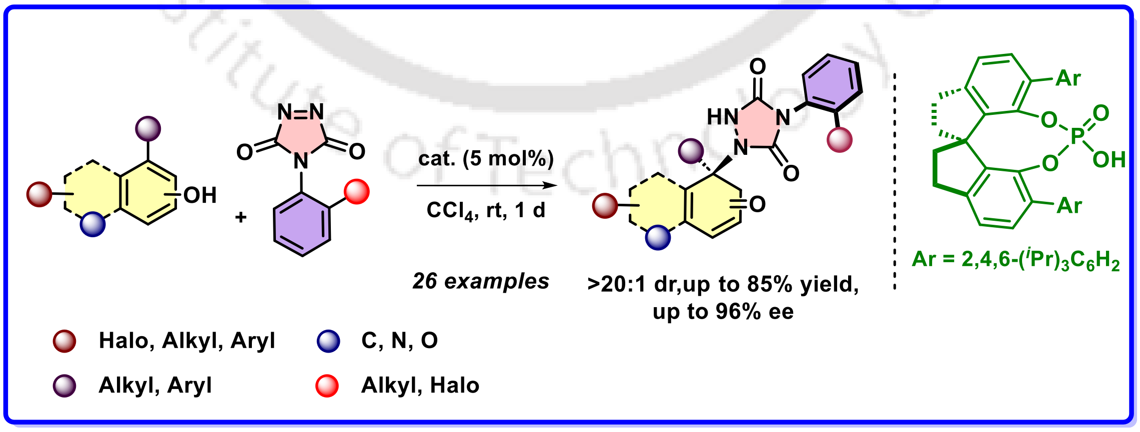
Chapter 4 describes the first organocatalytic asymmetric synthesis of spirooxindole embedded oxazolidines has been developed via a domino reaction involving hemiaminal formation, followed by an unprecedented *aza*-Michael reaction between isatin derived *N*-

Boc ketimines and γ-hydroxy enones. A quinine derived bifunctional squaramide catalyst was found to be efficient for this reaction, and the products were obtained in good diastereoselectivity and with high enantioselectivity.



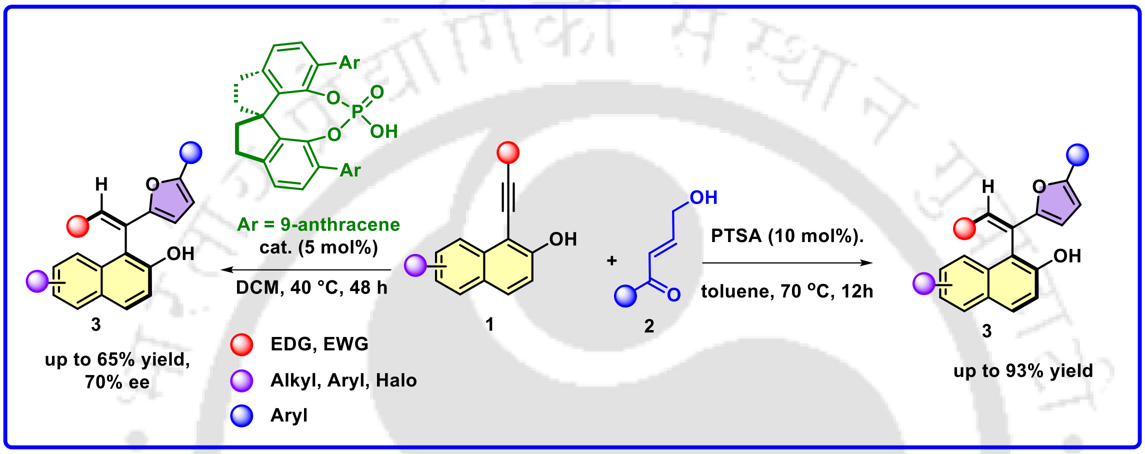
Scheme 3

Chapter 5 demonstrates a catalytic asymmetric dearomatization reaction of β-naphthols with 4- aryl-1,2,4-triazole-3,5-diones. A chiral phosphoric acid with spiro motif was found to be effective for this reaction. The chiral urazole embedded naphthalenones having both axial and central chirality were obtained in good to high yields (70–85%) with high diastereo- and enantioselectivities (up to >20:1, 96% ees), having C-N rotational energy barrier 31.54 kaclmol^{-1} and $t^{1/2}{}_{25\ ^\circ\mathrm{C}}$=589.8 years. The scope of the reaction was broad and few applications including a bromo-amination reaction have been demonstrated.



Scheme 4

Chapter 6 demonstrate the synthesis of furan embedded styrene atropisomer *via* the reaction between 1-(aryl-ethynyl)-naphthalen-2-ol and γ-hydroxyenone. With a catalytic quantity of PTSA, the styrene derivatives were produced with moderate to good yields, and in high diastereoselectivities. Moderate enantioselectivities up to (70% ee) were achieved with chiral phosphoric acid. Few applications such as triazole formation and cross-coupling reactions have been demonstrated. C-C rotational energy barrier 30.1 kaclmol^{-1} and $t_{1/2}^{25\,°C}$ = 21.2 years.



Each of these chapters contain introduction, previous reported works, present result and discussion, experimental section, references, along with characterization data of products including few selective spectral data. Overall, this thesis demonstrates some new and efficient approaches for organocatalytic asymmetric acyl transfer reaction and the synthesis of C-C and C-N atropisomers.

Chapter 1

Overview

PART 1

1.1 Introduction

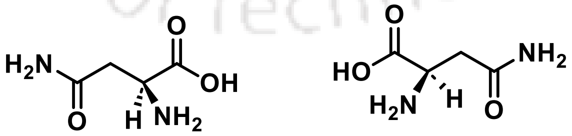
The word dissymmetric which was translated as asymmetric in the modern chemistry. In 1848 the great French scientist Louis Pasteur disclosed the evidence of chirality in nature.[1] Most of the naturally occurring compounds are optically active: they are not superimposable on their mirror images. Although, they possess identical chemical and physical properties such as boiling points, refractive indices, reactivity, melting points, solubility; enantiomers often behave differently under the external influence of chiral environment. Moreover, the different enantiomers can have different odor, taste and more importantly different pharmacological properties. For example, the natural (*S*)-(+)-linalool **1** has an odor like petitgrain oil, whereas (*R*)-(+)-linalool *ent*-**1** smells like lavender (Figure 1).[2]

(*S*)-(+)-Linalool
1

(*R*)-(-)-Linalool
***ent*-1**

Figure 1: The enantiomers of linalool.

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

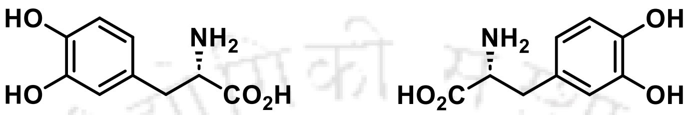


(*S*)-(-)-Asparagine
2

(*R*)-(+)-Asparagine
***ent*-2**

Figure 2: The enantiomers of asparagine.

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



(*S*)-Dopa
3

(*R*)-Dopa
***ent*-3**

Figure 3: The enantiomers of Dopa.

Countless examples can be found in nature where biological systems respond in a different way to the opposite enantiomers. Therefore, it is highly required to prepare natural products or drug molecules in enantiomerically pure forms to have the desired physical, chemical and biological properties.

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

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

i) Bio-catalysis
ii) Metal catalysis and
iii) Organocatalysis

Biocatalysis[6] is the chemical process through which enzymes or other biological catalysts perform regio-, chemo- and stereoselective transformations. This process usually requires mild reaction conditions. However, there are few disadvantages of biocatalysts such as substrate specificity, sensitivity to high pH and temperature and most importantly, the unavailability of the enzyme for synthesizing the opposite enantiomer as enzymes exist in nature as single enantiomeric form.

Metal catalysis and particularly organometallic catalysts have become the most actively studied due to unthinkable transformations could be easily performed with the help of metal catalysts such as asymmetric hydrogenation, epoxidation and dihydroxylation of olefins, cross-coupling reactions, olefin metathesis etc. Although metal catalysis has several advantages but, toxicity and laborious removal of trace metal impurities are some of the unavoidable drawbacks of transition-metal catalysis.[7]

Between these two extremes, a third general approach has appeared which is called organocatalysis. Organocatalysis has had a significant impact in chemical synthesis. Organocatalysis is the process of accelerating chemical reactions with a sub stoichiometric number of organic molecules, which do not contain a metal element in their active principle.[8]

1.2 Asymmetric organocatalysis

Asymmetric organocatalysis is an economical and environment-friendly process where a purely organic small molecule is used to catalyze organic transformations. Organocatalysis is often devoid of the drawbacks associated with transition-metal catalysis and bio-catalysis. Organocatalysts have several advantages. They are usually easy to handle, robust, bench-stable, inexpensive and in certain cases commercially available. Particularly, organocatalysts have attracted increasing attention of synthetic organic chemists for the preparation of pharmaceutical products that should not contain metal contamination.

1.2.1 Generic mechanisms of organocatalytic reactivity:

Organic catalysts can exert their functions by following two different substrate activation patterns (Figure 4):

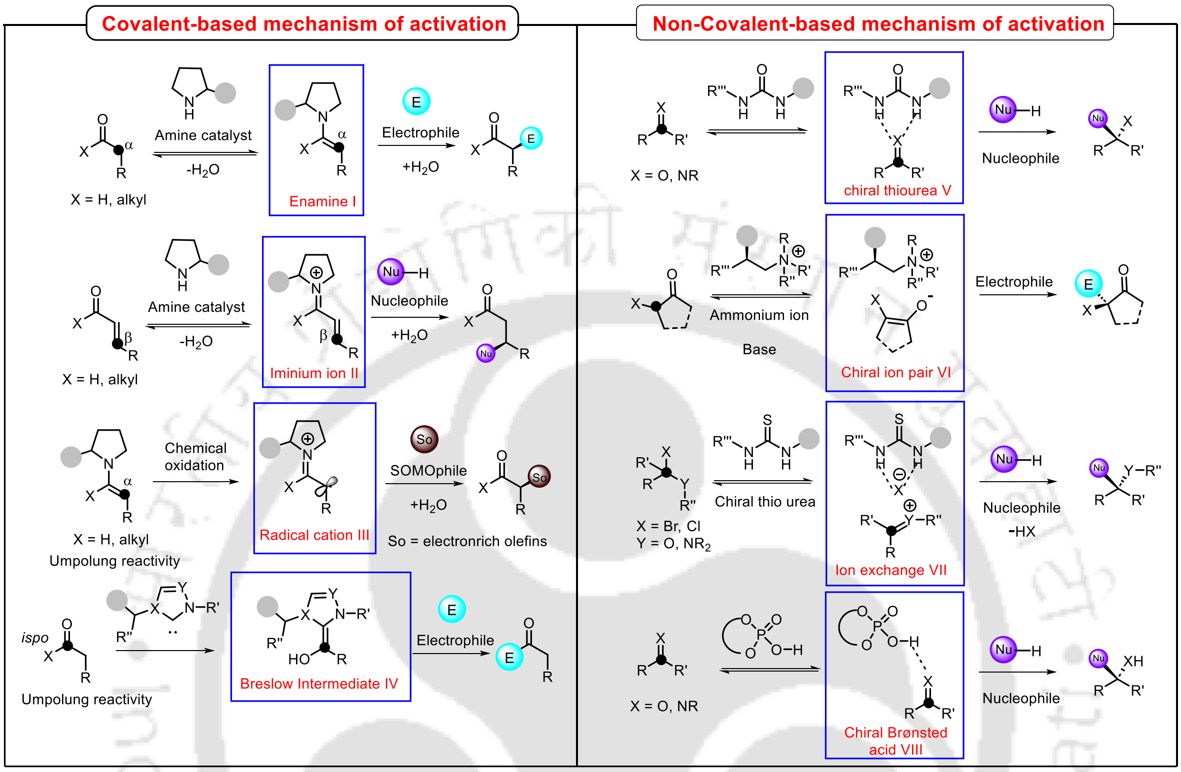


Figure 4: Generic mechanisms of organocatalytic reactivity.

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

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

1.2.2 Asymmetric Hydrogen Bonding Promoted Catalysis:

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

i) double hydrogen bond catalyst

ii) single hydrogen bond catalyst

iii) acid/base bifunctional catalyst.

Firstly, in the case of double hydrogen bond catalyst, the simultaneous donations of dual hydrogen bonds are proved to be an efficient strategy for the electrophile activation. The pioneering result in this category is the Schiff base, which was developed by Jacobsen in 1998, for the purpose of promoting asymmetric Strecker synthesis (Figure 5). The birth of this catalyst is interesting, because it was originally designed and synthesized as a potential ligand for Lewis acidic metal. However, surprisingly, an efficient enantioselective catalytic Strecker reaction was achieved even in the absence of metal additive[22]. This discovery opened up the field of asymmetric catalysis using H-bond catalysts and attracted a number of further researchers.

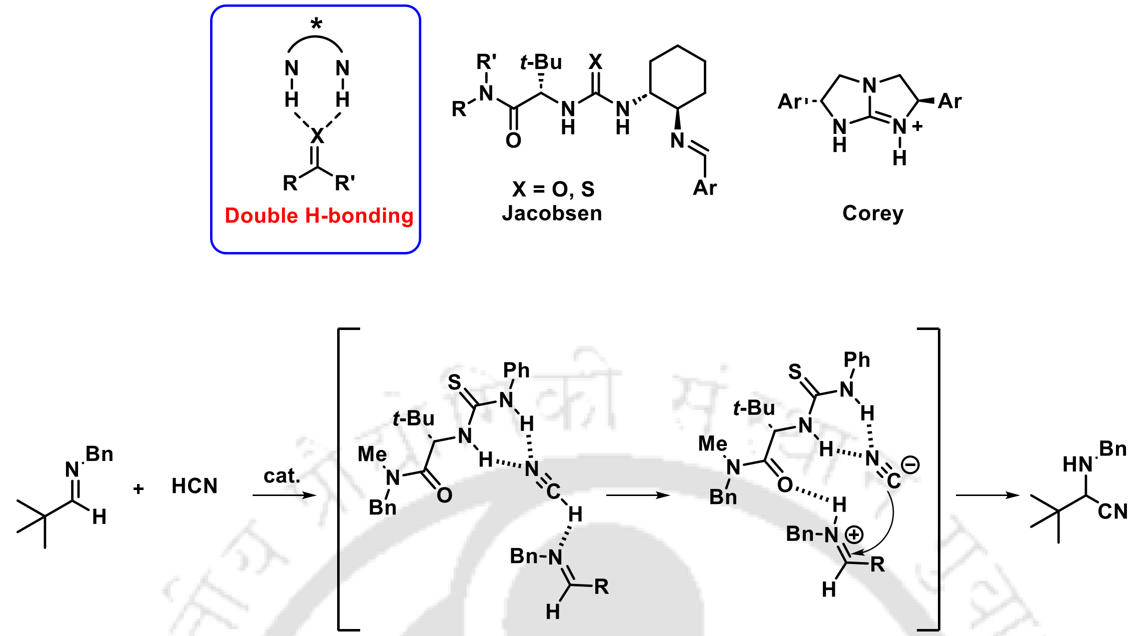


Figure 5: Double hydrogen bond catalyst.

Asymmetric transformations involving the donation of a single H-bond for the activation are less common than those double H-bonding activation. As an example of this type, intramolecular hydrogen bonding is observed in the chiral diol catalyst such as TADDOL,[23] which is a remarkably efficient chiral promoter for some asymmetric syntheses. One of the hydrogen atoms of the alcohol group participates in an intramolecular hydrogen bond and the other functions as H-bond donor for substrate binding. These properties were studied by X-ray crystallographic analysis. This molecule was employed as a chiral "BBA catalyst (Brønsted acid assisted Brønsted acid catalyst, which was termed by Yamamoto[24])" by Rawal and co-workers.[25] They showed that hetero-Diels–Alder reaction in the presence of axially chiral biaryl diol was remarkably enantioselective and provided only one of the enantiomers of the desired product[26] (figure 6).

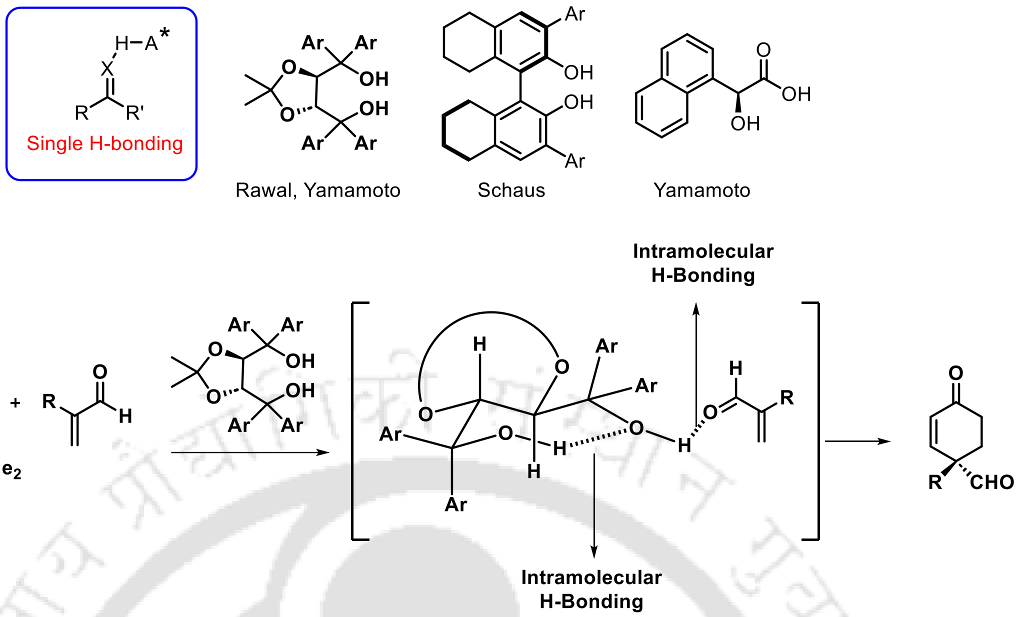


Figure 6: single hydrogen bond catalyst.

The mostly investigated strategy among the hydrogen bonding catalyses in recent years is the simultaneous activation of both nucleophiles and electrophiles, by Brønsted base and Brønsted acid moieties, respectively. Beginning with naturally occurring catalyst such as cinchona alkaloid[27] and proline,[28] chiral acid/base bifunctional catalysts have been widely investigated and which brought significant progress in this field. The representative example is the asymmetric Michael addition reaction of 1,3-dicarbonyl compounds to nitroolefins using Takemoto's thiourea catalyst.[29] Recently, two plausible mechanisms on this catalysis were suggested by means of quantum chemical calculation (path A)[30] and experimental approach (path B)[31] (figure 7) which gave same product.

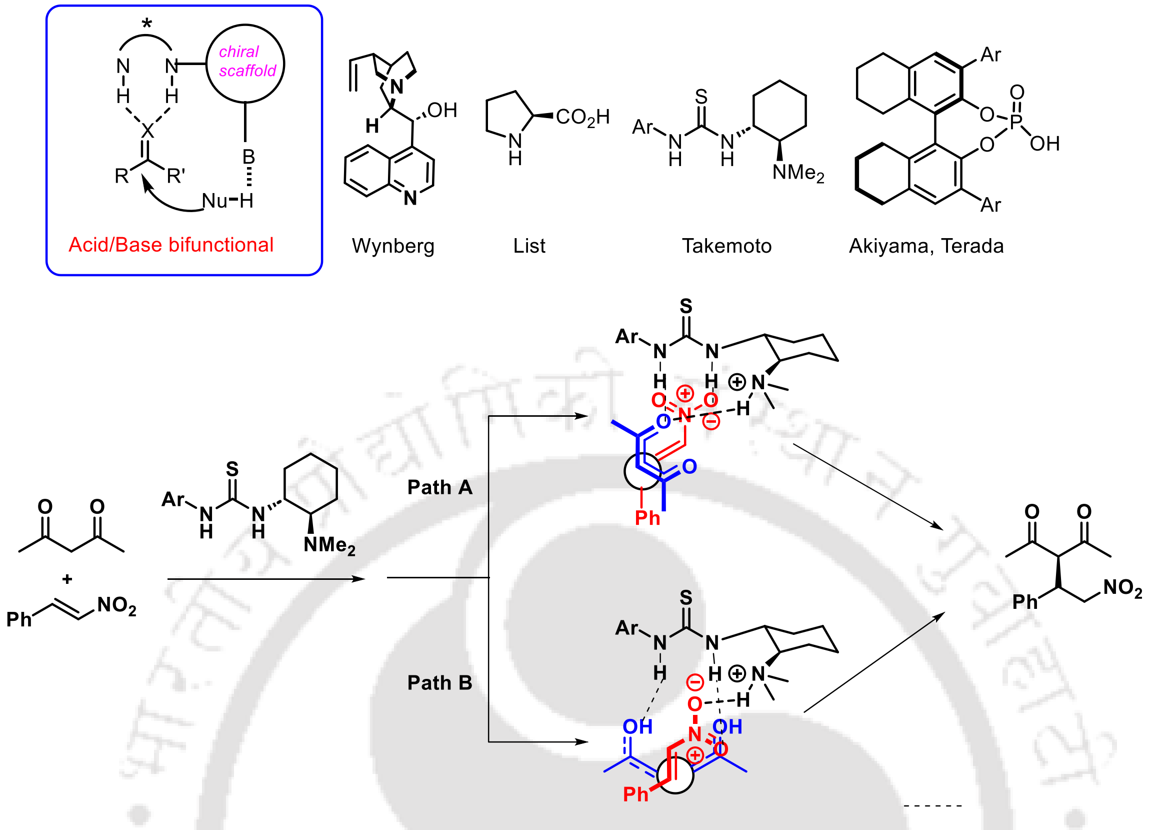
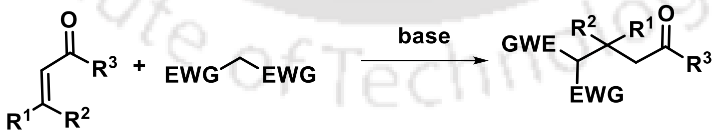


Figure 7: Activation of acid/base bifunctional catalyst.

1.3 Michael reaction

The Michael reaction is one of the most important reactions in organic chemistry. In 1887 Arthur Michael discovered the addition of carbon nucleophiles to conjugate acceptor systems, which is commonly known as Michael addition (Scheme 11).[32]

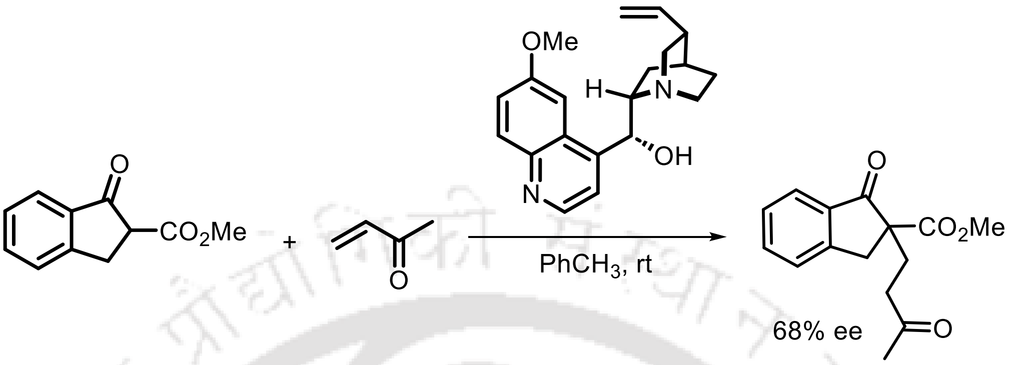


EWG = CO_2R, CN, NO_2, CO_2NR_2 etc.

Scheme 1: The Michael reaction.

The first example of asymmetric Michael reaction was discovered by Wynberg in 1975. He utilized optically active quinine as catalyst in the Michael addition of 1-oxo-2-

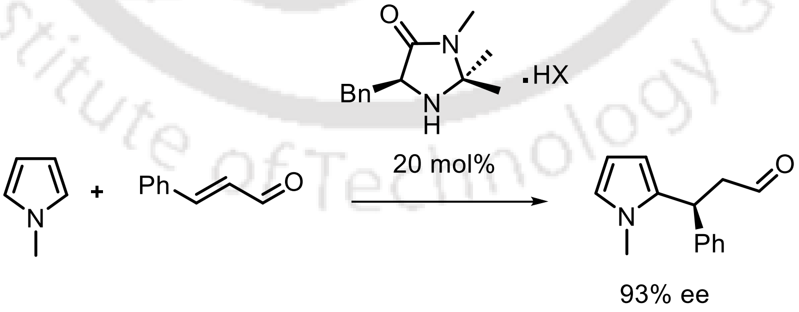
indanecarboxylate to methyl vinyl ketone and the desired product was obtained in 68% ee (Scheme 12).[33]



Scheme 2: The first asymmetric Michael reaction by Wynberg.

1.4 Friedel−Crafts reaction

In 1877, Charles Friedel and James Mason Crafts reported a special kind of carbon−carbon bond formation reaction[34]. The Friedel-Crafts reaction requires a catalyst to proceed, and the traditional catalysts include Lewis acids such as $AlCl_3$, $FeCl_3$, BF_3, $ZnCl_2$, and $TiCl_4$; Brønsted acids such as HF, H_2SO_4, and H_3PO_4; and acidic oxide catalysts such as silica-alumina type and cation-exchange resins[35]. First example of organocatalytic asymmetric Friedel−Crafts reaction was discovered by MacMillan group in 2001. They reported enantioselective Friedel-Crafts alkylation of pyrroles with ***α***,***β***-unsaturated aldehydes to generate ***β***-pyrrolyl carbonyls with 93% ee (Scheme 3).[36]



Scheme 3: First example of organocatalytic asymmetric Friedel−Crafts reaction.

Part 2

1.5 Introduction:

Atropisomeric compounds, referring to the compounds which show restricted rotation of a single bond primarily due to electronic or steric effects of flanking substituents[37]. Richard Kuhn in 1933 Coins the term atropisomer.[38] It was derived from the Greek word atropos, meaning "without turn." G. H. Christie & J. Kenner in 1922, are the first to observe *enantiomers* about a chiral axis in 6,6'-dinitro-2,2'-diphenic acid[39] (Figure 8).

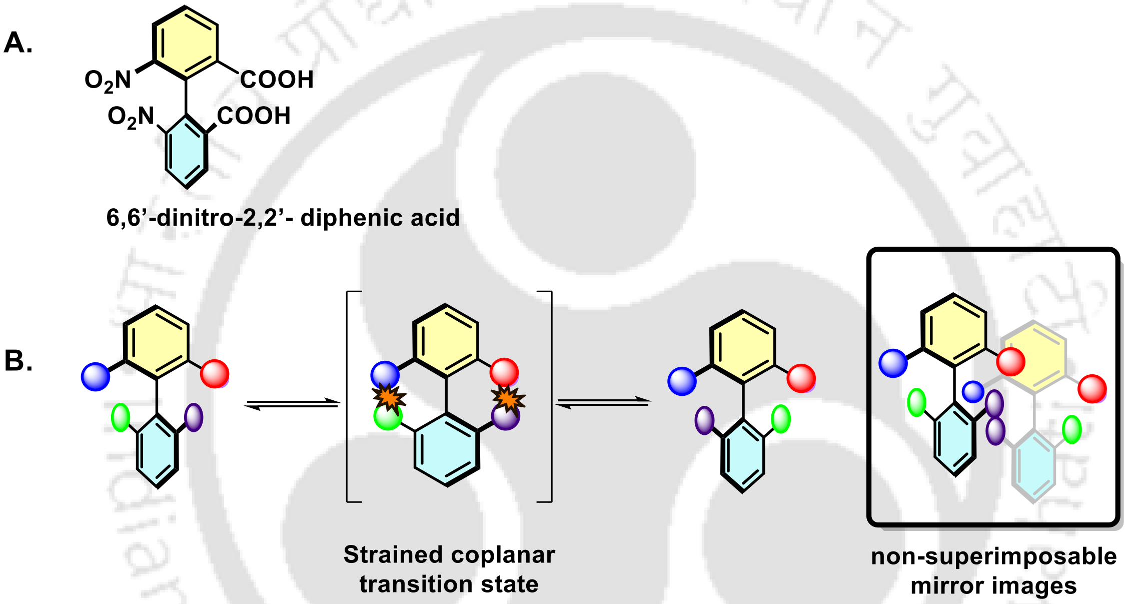


Figure 8: Atropisomeric compounds.

1.6 Importance of atropisomer: Molecules exhibiting atropisomerism were found in many bio-active compounds such as Korupensamine A[40], Marinopyrrole[41] and Steganacin[42]. Also, these compounds are used in asymmetric synthesis for example chiral BINAP[43] used as a ligand for many metals catalysed reactions. Similarly chiral phosphoric acids are used as catalyst for many enantioselective reactions[44]. Atropisomeric compounds also find wide-ranging utilities in material sciences[45] which have been incorporated in molecular machines and atropisomeric receptor, among others. Importantly, as with the case of drugs bearing stereogenic center(s), the handedness of biological targets leads to differential recognition of antipodal atropisomers. As regulations tightened for chiral drugs and more potent candidates are sought, atropisomerism in compound library[46] becomes a focus of increasing attentions (Figure 9).

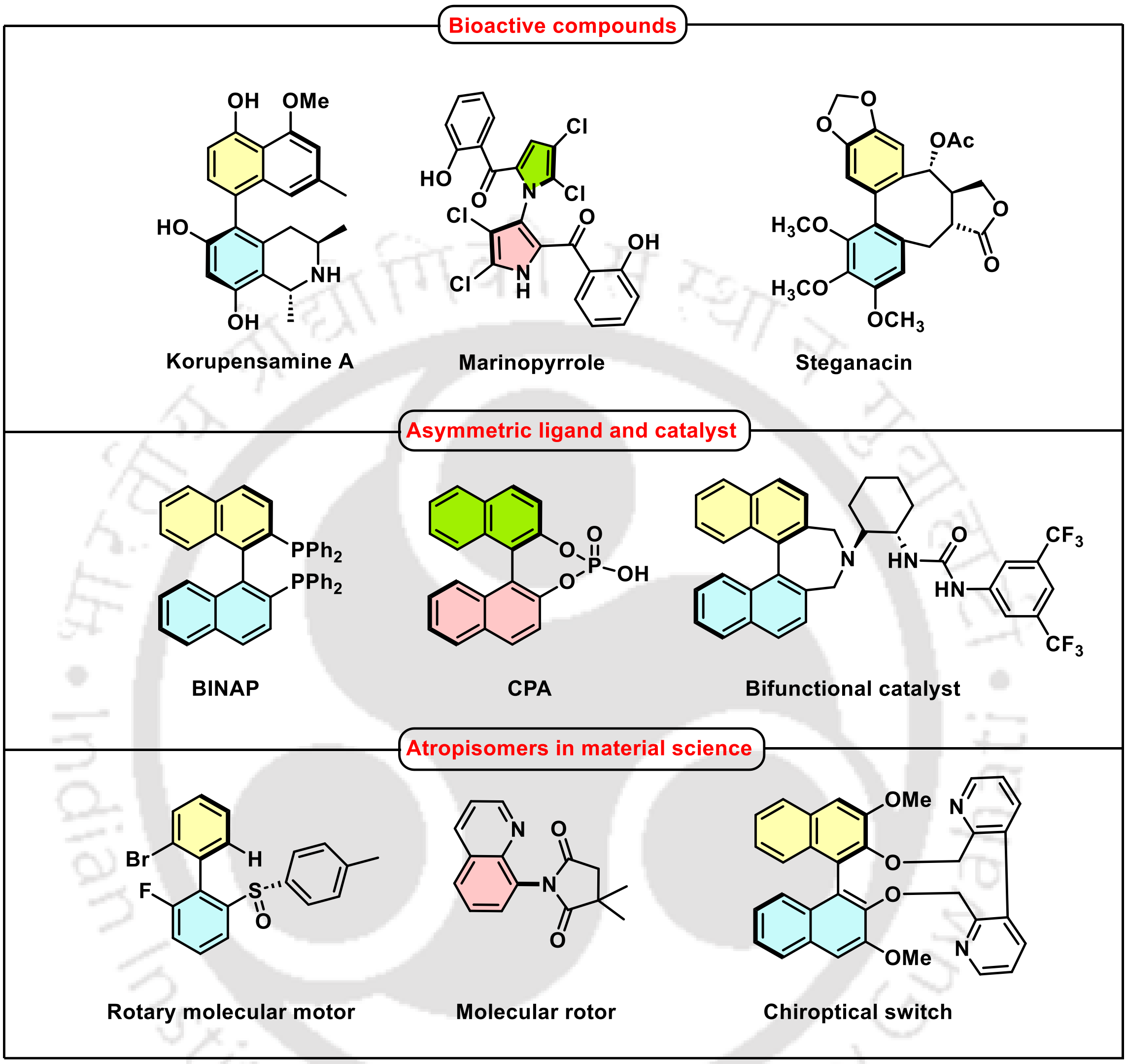


Figure 9: Representative atropisomers in various scientific disciplines.

1.7 Types of atropisomers:

During the last decade, diverse atropisomers were developed. So, they can be classified in categories like C-C, C-N, C-B, C-O, C-S and N-N etc. Among different atropisomers, the C–C atropisomers were well explored; there were numerous efficient strategies for the atroposelective synthesis of C-C axially chiral biaryls,[47] heterobiaryls,[48] arylalkenes,[49] arylquinoids,[50] heteroarylalkenes,[51] and arylamides[52] (Figure 10). In addition, many innovative approaches have been established to synthesize C-N axially chiral molecules such as *N*-aryl heteroaryls,[53] anilides,[54] urazoles,[55] imides,[56] quinazolinones,[57] pyridinones,[58] and N-arylquinoids[59] in an atroposelective manner.

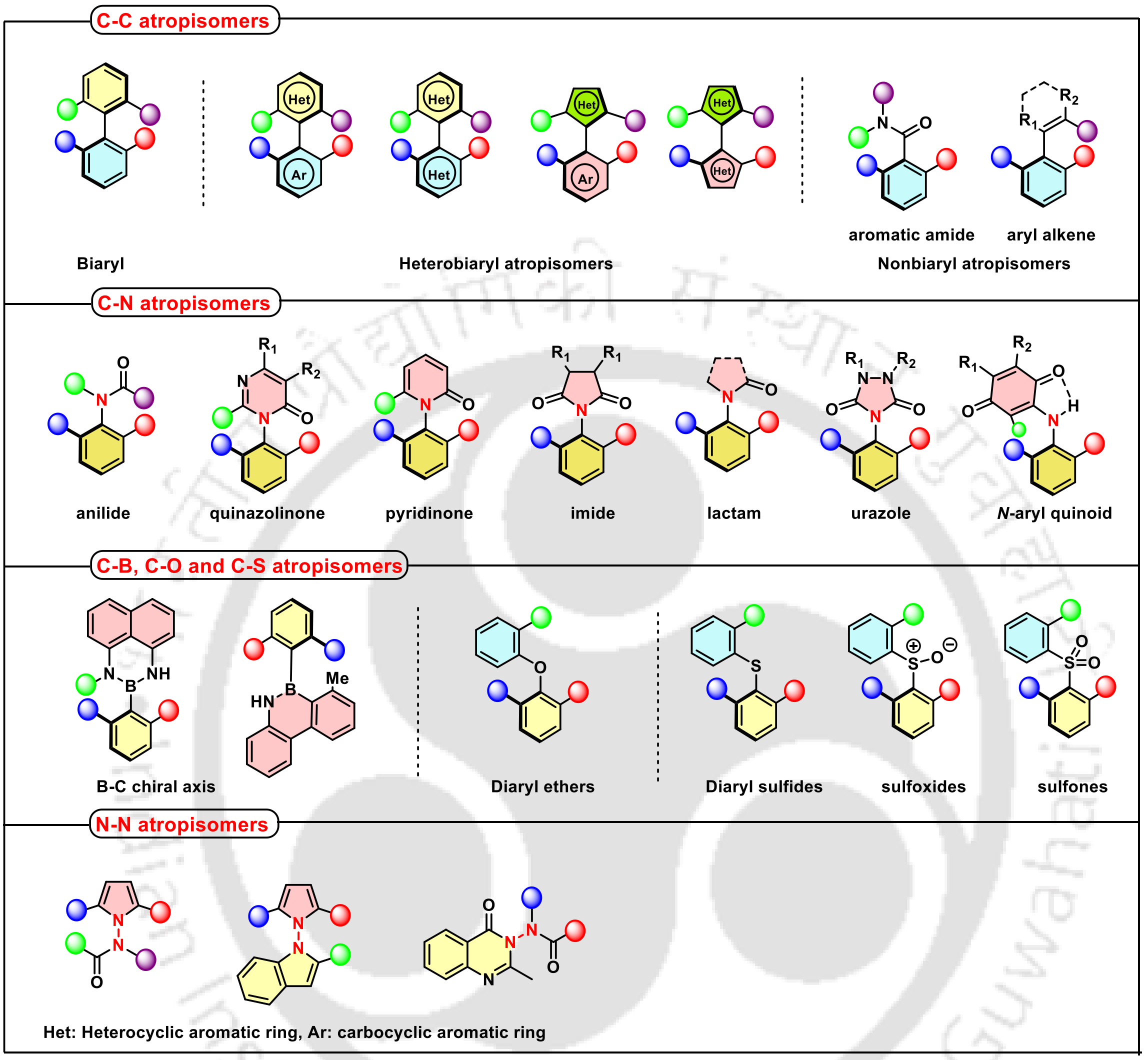


Figure 10: Different types of biaryl, heterobiaryl, and nonbiaryl atropisomers.

On the other hand, atropisomers beyond the C–C and C-N axis, e.g., about the C–B, C–O, C-S and N-N bonds, have been studied to a much less extent, which may be likely due to the reduced rotation barrier induced by the deplanarization of the heteroatom-containing plane. Synthesis of C-B atropisomers is more challenging as the C–B bond is longer than the corresponding C–C and C–N bonds, which lowers the rotational barrier. There were two approaches for synthesis of C-B axially chiral molecules:

the construction of axially chiral arylborons *via* atroposelective Miyaura borylation[60a] and enantioselective construction of C–B stereogenic axis through a desymmetrization strategy[60b]. Similarly, an example on the enantioselective synthesis of C–O atropisomers was reported by Turner and Clayden[61] *via* biocatalytic approach. This is the sole instance of a C-O atropisomer as of yet. Similar to this, little is known about C-S atropisomers. There was only one report from the Clayden[62] group. Dynamic resolution with thermodynamic control is used to create the C-S atropisomer of diarylsulfones in an asymmetric fashion. It is very difficult to make N-N axially chiral compounds because rotational deplanarization of the two N-containing planes results in a low rotational barrier. However, given that the N-N bond is shorter, the creation of such an N-N axis may be encouraged. In addition, the electronic barrier resulting from the repulsive interaction between the two nitrogen atoms' lone pairs is projected to result in a denser N-N axis. N-allylic alkylation[63] and the de novo ring creation of N-N axially chiral indoles and pyrroles are two methods for synthesising N-N axially chiral compounds (Figure 10).[64]

1.8 Conclusion and focal theme of the present work

The focal theme of this thesis is to utilize bifunctional tertiary amine thiourea, squaramide and chiral phosphoric acid catalysts in various organocascade reactions. Bifunctional thiourea and squaramides are used as catalysts in chapters 2, 3, and 4. Chapter 2 includes, α-nitro-α,β-unsaturated ketones: an electrophilic acyl transfer reagent and utilized in asymmetric Friedel−Crafts and Michael reactions.

Similar to this, chapter 3 describes the asymmetric Michael/acyl transfer reaction involve-ing 4-arylidene-pyrrolidine-2,3-diones and α-nitroketones.

Bifunctional squaramide catalysed synthesis of spirooxindole embedded oxazolidines are reported in the fourth chapter.

The detailed investigations for the enantioselective construction of C-N and C-C atropisomers using chiral phosphoric acid, are presented in the chapter 5 and 6 of the thesis.

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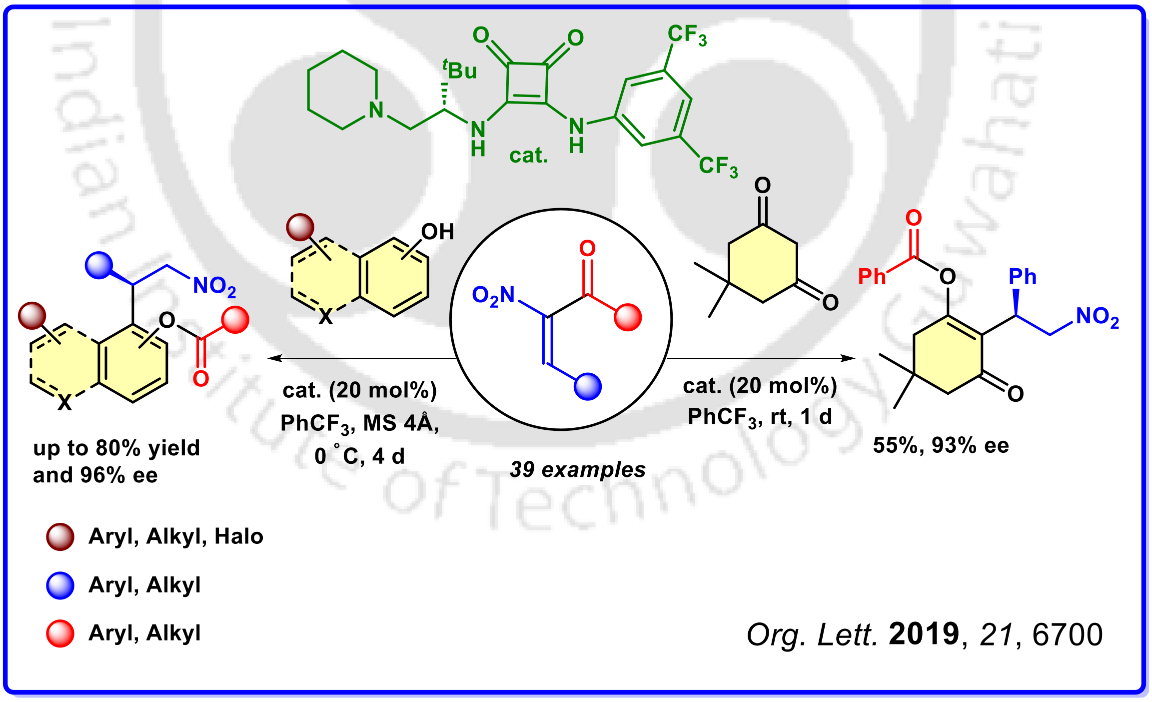
Chapter 2

α-Nitro-α,β-Unsaturated Ketones: An Electrophilic Acyl Transfer Reagent in Catalytic Asymmetric Friedel−Crafts and Michael Reactions

Abstract: In this chapter, we introduce *α*-nitro-*α*, *β*-unsaturated ketones as efficient electrophilic acyl transfer reagents, and they were employed in Friedel−Crafts as well as in Michael reactions. This strategy features broad substrate scope (39 examples), high atom economy, as well as *α*-nitro-*α*, *β*-unsaturated ketones as efficient electrophilic acyl transfer reagents in asymmetric cascade reactions for the first time. The desired acyl transfer products of these reactions were obtained in high yields with high to excellent enantioselectivities with *t*-leucine-derived squaramide catalyst under mild reaction conditions. Few applications including a synthesis of the isoxazoline motif have been demonstrated.



Org. Lett. **2019**, *21*, 6700

2.1 Introduction

Enantioselective acyl transfer reactions have attracted considerable attention in biological as well as in synthetic chemistry. For example, acetyl coenzyme A is an important molecule involved in the metabolism of proteins, carbohydrates, and lipids. Acyl CoA is an important molecule used in fatty acid metabolism[1,2] (Figure 1). It is a group of coenzymes. During the past few decades, acyl transfer reactions have been applied as powerful chemical tools for the construction of complex chiral compounds.

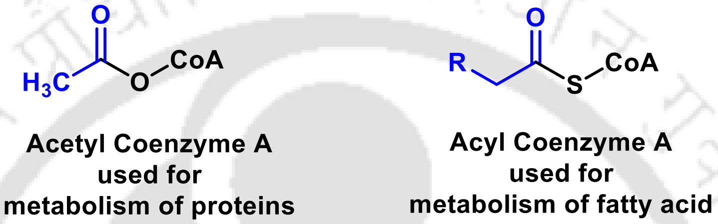


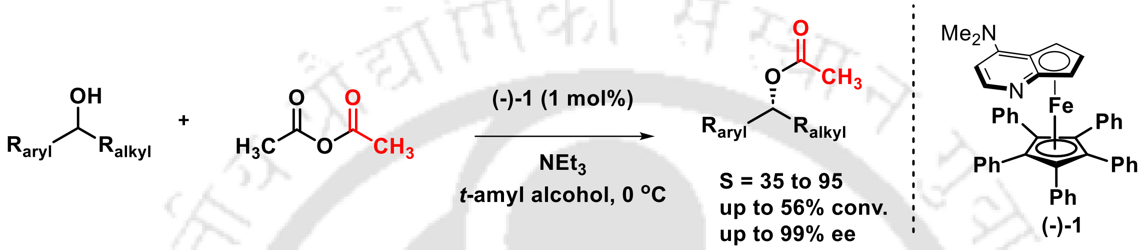
Figure 1: Biological use of Acyl group.

Acyl group transfer is one of the most popular and very effective preparative relevant enantioselective organocatalytic transformations.[3] The reasons are manifold: Typical acylation reagents such as anhydrides, acyl halogenides, and carboxylic acids are commercially available and can be handled easily; reactions can be performed under mild conditions and a large variety of catalysts have been developed. The design of new acyl-transfer organocatalysts is a vibrant area of research, and many mechanistic details are being elucidated in the course of applying these catalysts to an ever-growing number of substrates.

The Friedel-Crafts (F-C) reaction is one of the powerful methods for C-C bond formation in organic chemistry and has been widely utilized for the synthesis of aromatic and heteroaromatic frameworks.[4] A range of aromatic compounds, including benzenes with electron-donating substituents, furans, pyrroles, and indoles, have been successfully employed in a number of F-C reactions with diverse electrophiles. A variety of organocatalytic approaches[5] have been reported for the development of enantioselective variants.[6] Electron-rich arene derivatives[7] and β-naphthols[8] have also been recently employed in Friedel-Crafts reactions.

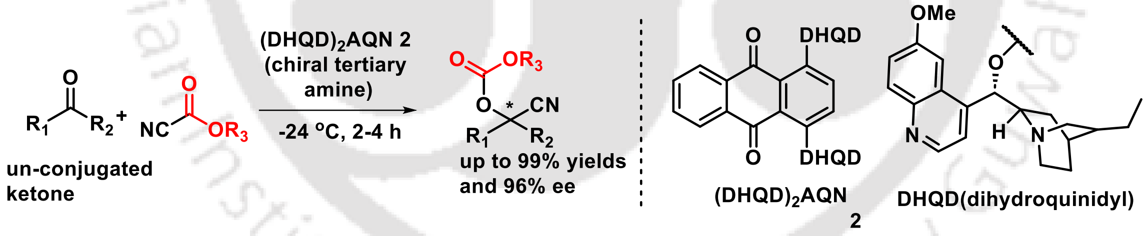
2.2 Previous known strategies:

2.2.1 In 1998 Fu and co-workers reported[9] kinetic resolution of secondary alcohols with chiral DMAP catalyst *via in situ* generation of acyl-DMAP species as shown in (Scheme 1). They modified the chiral DMAP catalyst, in which greatly enhanced enantioselectivity as well as the selectivity (s) (32-95) was achieved. Furthermore, they applied this system for the first time to racemic and meso diols.



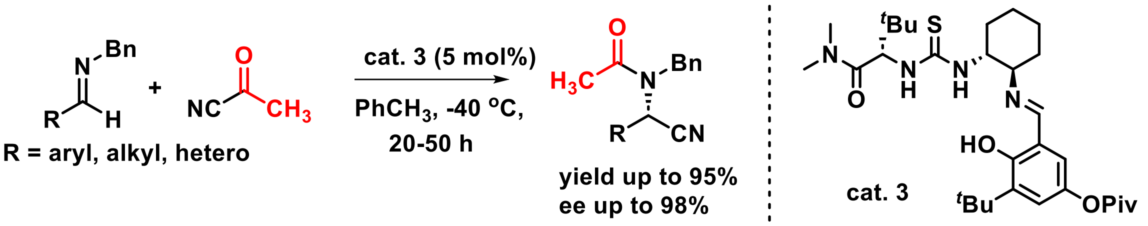
Scheme 1: Performance and applications of Fu's catalyst

2.2.2 In 2001, Deng and co-workers showed an efficient cyanoethoxycarbonylation of ketones with ethylcyanoformate.[10] A highly enantioselective chiral Lewis base-catalyzed reaction giving rise to desired product with high yield (up to 99%) as well as high enantioselectivity was reported (up to 96%) (Scheme 2).



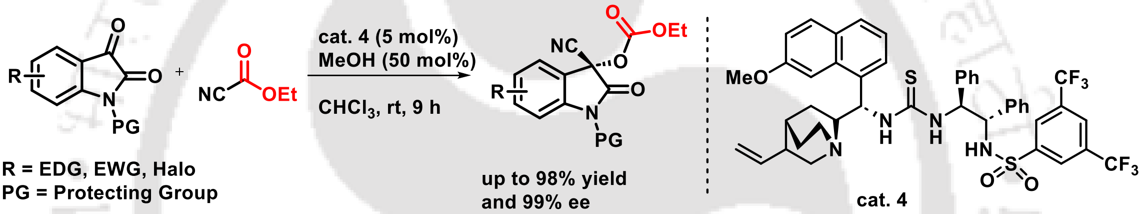
Scheme 2: Reaction between ketone and ethylcyanoformate

2.2.3 In 2007, the List group reported[11] catalytic asymmetric acylcyanation of imines with acetylcyanide as the reagent. In this method they used less problematic acetyl cyanide instead of toxic HCN for the highly enantioselective acyl-Strecker-type reaction. In the presence of an *N*-benzylimine and a catalytic amount of Jacobsen's catalyst **3**, the desired α-amidonitriles are obtained in excellent enantioselectivities and yields (Scheme 3).



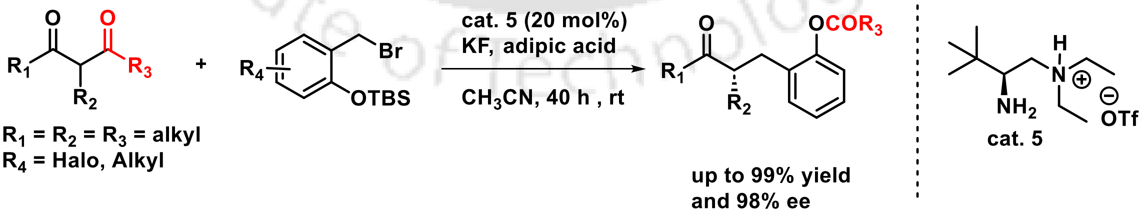
Scheme 3: Reaction between imines and acetylcyanide.

2.2.4 In 2011 Deng group, developed[12] the first enantioselective cyanoethoxycarbonylation of isatins by using the Lewis base–Brønsted acid cooperative catalyst. The Lewis basic site of caused nucleophilic activation of ethyl cyanoformate, and the Brønsted acidic, deep, and flexible cavity simultaneously stabilized and selectively recognized the *R* alkoxy anion intermediate to promote asymmetric acylation (Scheme 4).



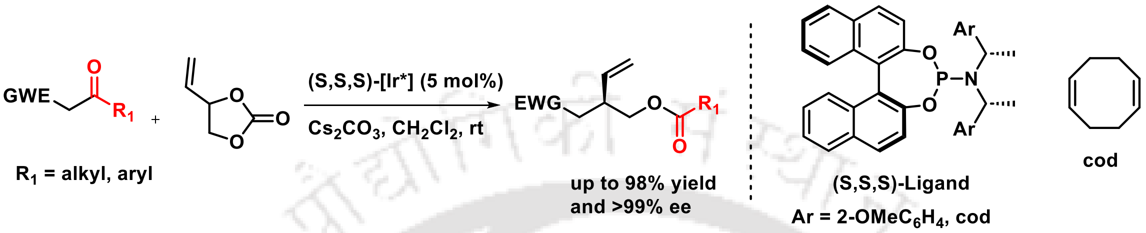
Scheme 4: Reaction of isatin and ethylcyanoformate.

2.2.5 In 2016 Luo group reported[13] an enamine-based asymmetric retro-Claisen reaction of β-diketones by primary amine catalysis. The reaction proceeds *via* a sequence of stereoselective C–C formation, C–C cleavage, and a highly stereospecific enamine protonation to afford chiral α-alkylated ketones or macrolides with high yields and enantioselectivities (Scheme 5).



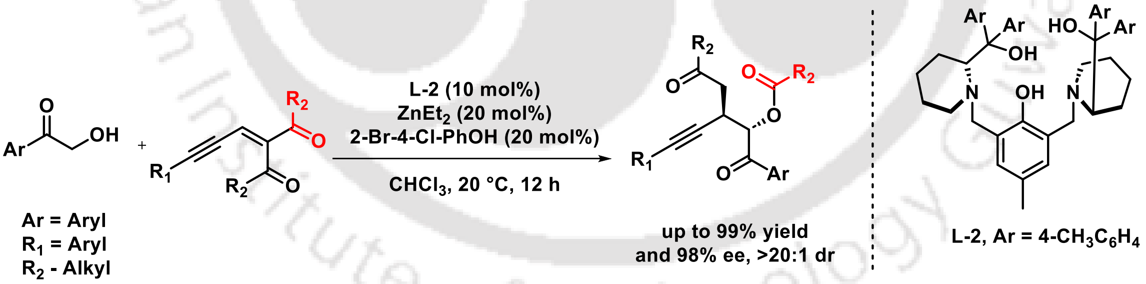
Scheme 5: Asymmetric retro-Claisen reaction by chiral primary amine catalysis.

2.2.6 In 2022 Wang group[14] reported Ir-catalyzed asymmetric cascade allylation/retro-Claisen reaction of 1,3-diketones with vinylethylene carbonate (VEC) was successfully designed and developed. A wide range of highly functionalized chiral 3-hydroxymethyl pentenal derivatives could be readily accessible in good yields with excellent enantioselectivities. The efficient protocol is also amenable to a series of *β*-functionalized ketones containing various functional groups on the β-position (Scheme 6).



Scheme 6: Iridium catalysed acyl transfer reaction between 1,3-diketones with vinylethylene carbonate.

2.2.7 In 2023 Jia group[15] described a neoteric enantioselective cascade Michael/acyl transfer reaction of enynones and *α*-hydroxy aryl ketones catalyzed by dinuclear zinc cooperative catalysis. A series of structurally diverse chiral 1,5-dicarbonyl compounds were synthesized in good yields with excellent stereoselectivities. This strategy features broad substrate scope, high atom economy, as well as enynones as efficient electrophilic acyl transfer reagents in asymmetric cascade reactions (Scheme 7).

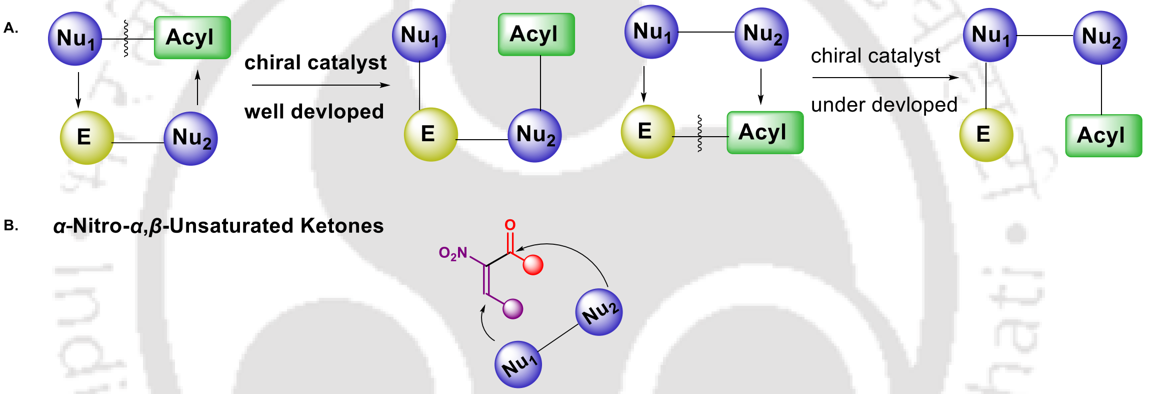


Scheme 7: Enynones as an electrophilic acyl transfer reagent.

2.3 Concept:

However, in contrast, catalytic asymmetric Michael/acyl transfer reactions with electrophilic acyl transfer reagents remained largely underdeveloped (Scheme 8a). Mainly the acyl transfer reagent consists of a nucleophilic site and an acyl group, at first

the nucleophilic site reacts with electrophilic substrate generate a nucleophilic site, that nucleophile react with the acyl group. So we exploited the asymmetric Michael/acyl transfer reactions, using *α*-nitro-*α*,*β*-unsaturated ketones as kinds of new electrophilic acyl transfer reagents with which a dinucleophilic substrate reacts *via* Friedel−Crafts and Michael Reactions pathway (Scheme 8b).

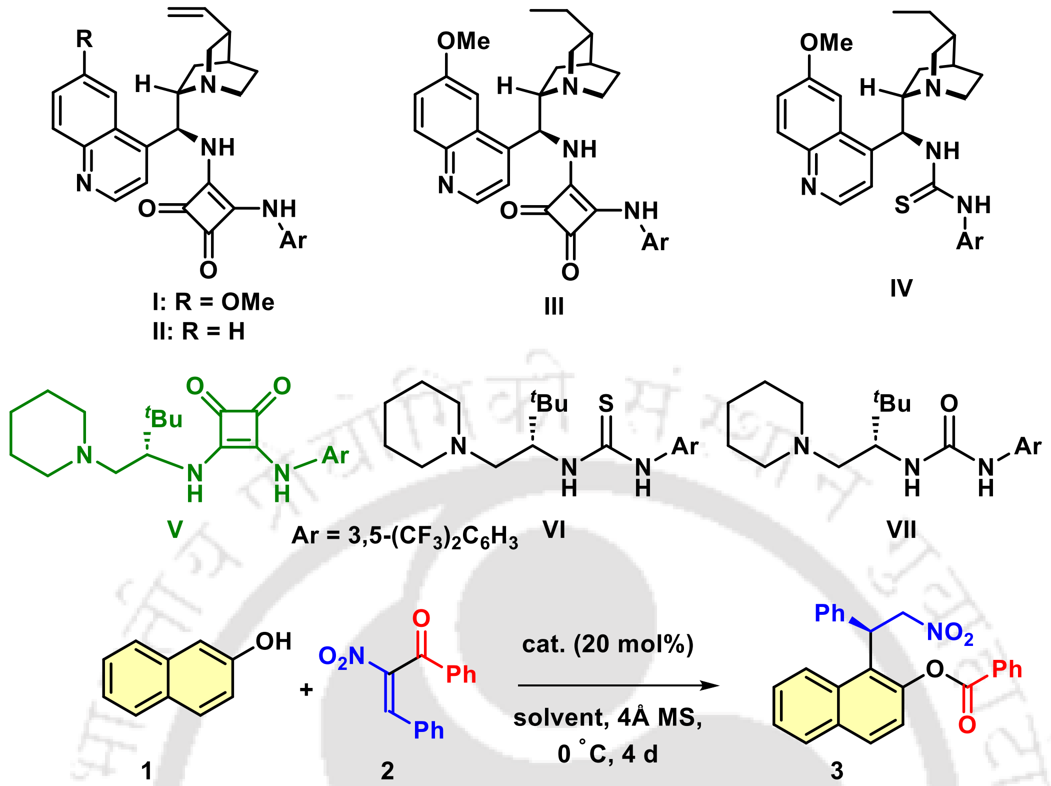


Scheme 8: A) General concept. B) Our hypothesis.

2.4 Result and Discussion:

2.4.1 Catalyst, solvent and reaction condition optimization for Friedel-Crafts acyl transfer reaction:

We initiated our exploration by performing a model reaction between β-naphthol (**1a**) and (*E*)-2-nitro-1,3-diphenylprop-2- en-1-one (**2a**) with quinine-derived squaramide catalyst **I** in toluene solvent at 0℃ with MS 4 Å as an additive (Table 1, entry 1). Gratifyingly, the desired cascade Friedel-Crafts acyl transfer reaction took place, and the desired product **3a** was obtained in 63% yield with 82% ee. The yield and enantioselectivity were slightly improved with cinchonidine derived catalyst **II** (entry 2). Then hydroquinine-derived squramide catalysts **III** was screened in the reaction; however, similar levels of



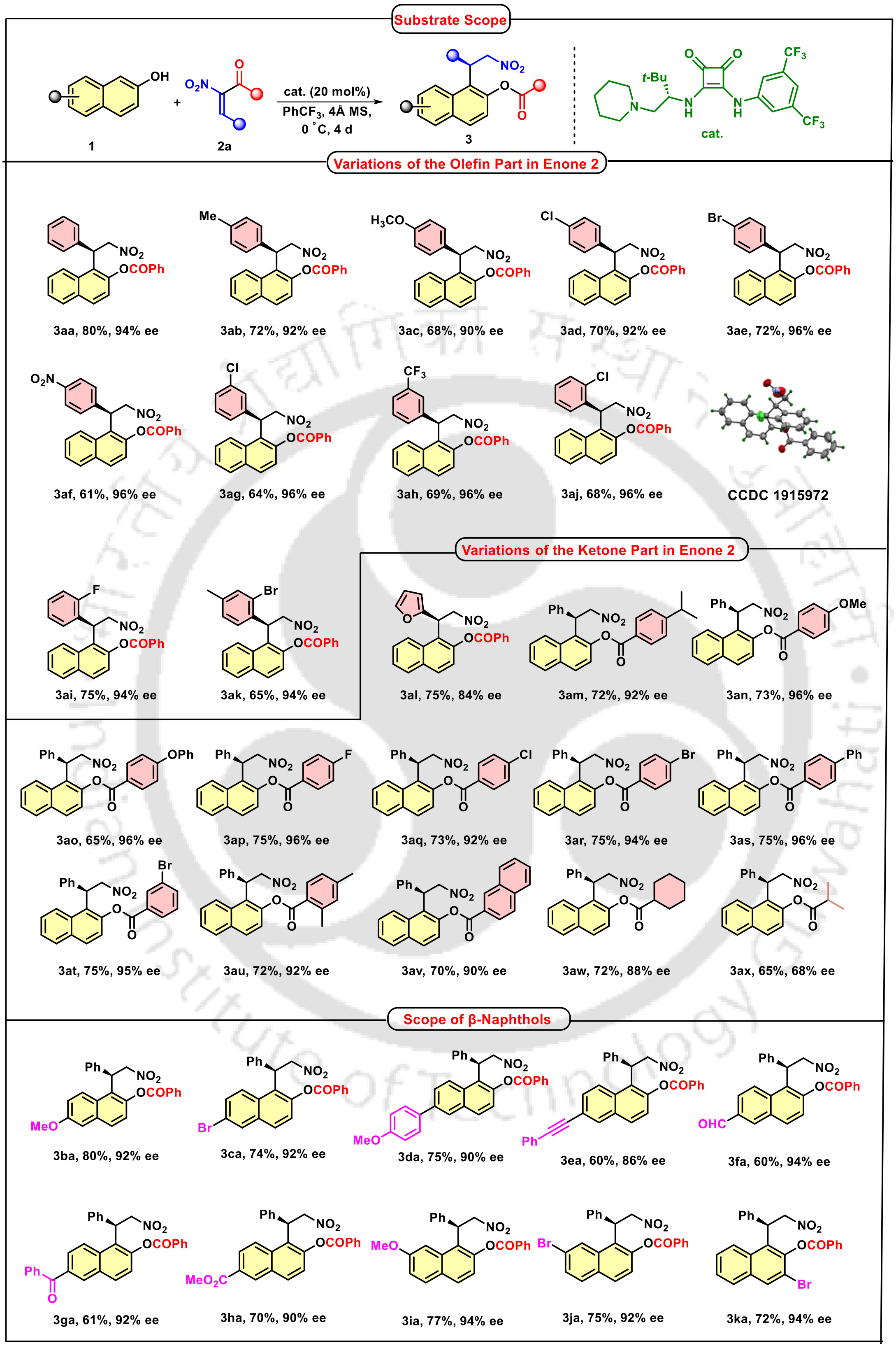
entry[a]	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	I	$PhCH_3$	63	82
2	II	$PhCH_3$	70	84
3	III	$PhCH_3$	60	84
4	IV	$PhCH_3$	42	50
5	V	$PhCH_3$	70	92
6	VI	$PhCH_3$	55	80
7	VII	$PhCH_3$	57	82
8	V	CH_2Cl_2	60	73
9	V	Et_2O	70	91
10	**V**	**$PhCF_3$**	**80**	**94**
11	V	PhCl	65	86
12[d]	V	$PhCF_3$	79	92
13[e]	V	$PhCF_3$	55	80

[a] All reactions were carried out with 0.1 mmol of 1 with 0.1 mmol of 2 in 1.2 mL solvent. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC. [d] Reaction carried with 10 mol% of catalyst. [e] Reaction carried out at -10 ℃.

Table 1: Catalyst and solvent optimization.

enentioselectivities were attained (entries 3). Replacement of the squaramide motif with thiourea was detrimental for the reaction (entry 4). Then *t*-leucine-derived squaramide catalyst **V** was prepared and employed in the reaction. Delightfully, this catalyst was found to be efficient and provided product **3a** in 70% yield with 92% ee (entry 5). After that *t*-leucine-derived thiourea **VI** and urea **VII** motif was used, decrease in enantioselectivities were observed (entry 6 and 7). To further improve the enantioselectivity, other solvents were screened (entries 8-11). Dichloromethane was not a suitable solvent for the reaction, although high enantioselectivity was obtained in diethyl ether solvent (entries 8 and 9). Finally, *α,α,α*-trifluoro toluene emerged as the best solvent, and the product **3a** was attained in 80% yield with 94% ee (entry 10). When we decreased the catalyst loading to 10 mol%, slight decrease in enantioselectivity was observed 92% (entry 12). Similarly, with further decrease in temperature of the reaction to -10 ℃ enantioselectivity got dropped to 80% (entry 13).

After the optimized conditions were established, the generality and scope of the reaction were studied. Initially, different nitroenones **2** having variations in the olefin group were investigated, and gratifyingly, excellent results were achieved irrespective of the electronic nature of the aryl group (Scheme 9). At the beginning, both electron-donating groups (−Me and −OMe), and electron-withdrawing groups (−Cl, −Br and−NO_2) on the *para* position were screened to deliver the corresponding products (**3ab-3ac** and **3ad-3af**) in high levels of enantioselectivities (90−96% ee values). A variety of *meta*- (**3ag-3ah**), *ortho*- (**3ai-3aj**), and *di*-substituted (**3ak**) phenyl substrates may also enable the acyl transfer reactions to produce the required product with ee values ranging from 94 to 96%. Finally, furyl-substituted enone **2l** was engaged in the reaction, and slightly less enantioselectivity was detected for product **3al**. Then, the ketone part of the enone **2** was varied. It turned out that a range of substitutions on the aryl group could be installed, and excellent outcome was maintained. Initially, different *para*-substitutions both electron-donating groups (−*iso*-propyl, −OMe and −OPh), and halogen groups (−F, −Cl, and −Br) were checked, and the corresponding products (**3am-3ar**) were obtained in good yields (65-75%) with high enantioselectivities (92-96%) (Scheme 9).

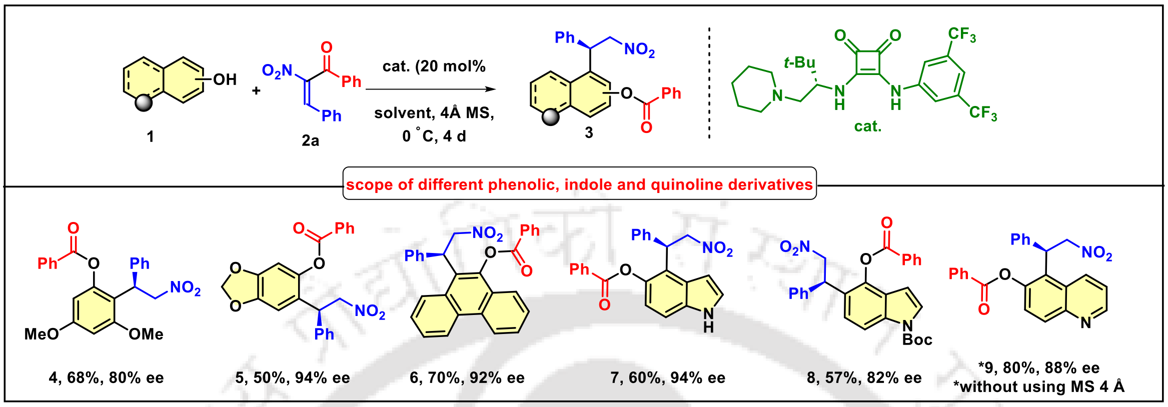


Scheme 9: Substrate scope of Friedel−Crafts reaction.

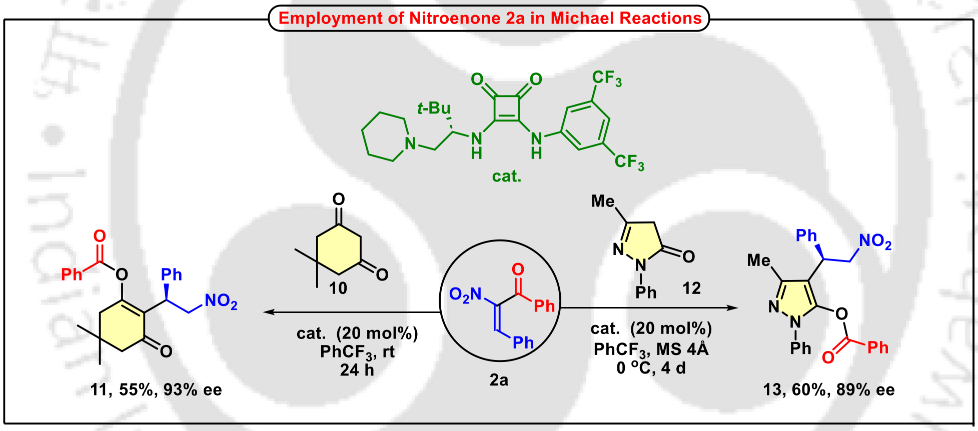
Delightfully, 4-biphenyl group containing enone smoothly reacted to afford product **3as** in 75% yield with 96% ee. *Meta*-substituted enone **2t** and 2,4-dimethyl-substituted enone **2u** underwent the reaction, delivering the products **3at** and **3au** in 95% ee and 92% ee respectively. The outcome was also excellent with a sterically bulkier group (R = 2-naphthyl) and the desired product **3av** was isolated in 70% yield with 92% ee value. Then, aliphatic group containing enones (cyclohexyl and isopropyl) were engaged in the reaction, and gratifyingly, 88-68% ee were achieved. In the next phase, different β-naphthol derivatives were employed in the reaction. As can be seen, a variety of substitutions were tolerated at 6-, 7-, and 3-positions, and high enantioselectivities were obtained. Initially, 6-position was substituted with a methoxy group, and the corresponding product **3ba** was obtained in 80% yield with 92% ee. Substitutions with a bromo or aryl group did not alter the enantioselectivity. The phenylacetylene group **3ea** could also be incorporated, and good result was detected. Then different electron-poor carbonyl functionalities (−CHO, −COPh, $-CO_2Me$) were installed, and delightfully the reactions progressed efficiently to provide products (**3fa**-**3ha**) in high enantioselectivities (90-94%). 7-Substituted methoxy and bromo-containing naphthols also participated in the reaction, delivering the products **3ia** and **3ja** in 94% ee and 92% ee, respectively. Moreover, 3-bromo-substituted β- naphthol **1k** can also be employed, and it was found that the steric effect did not hinder the formation of the product **3ka** (Scheme 9).

The absolute structure of the product **3aj** was determined to be (*S*) by single-crystal X-ray crystallography. Since the priority changes when the 2-chlorophenyl group is replaced by the phenyl group, the (*S*) becomes (*R*) but have similar structure.

Then we explored other phenolic derivatives in the reaction (Scheme 10). At first 3,4-dimethoxy phenol was employed, and gratifyingly the desired product **4** was attained in acceptable yield with 80% ee. The enantioselectivity was high for product **5** derived from sesamol. The reaction also took place with 9-phenanthrol, and the desired product **6** was isolated in 70% yield with 92% ee. Then we carried out reactions with hydroxy indole compounds, and it turned out that our methodology was suitable to provide desired products **7** and **8**. In particular, an excellent 94% ee was obtained for product **7**. Hydroxyquinoline can also be employed in the reaction, and the best result 88% ee was obtained without using MS 4 Å.

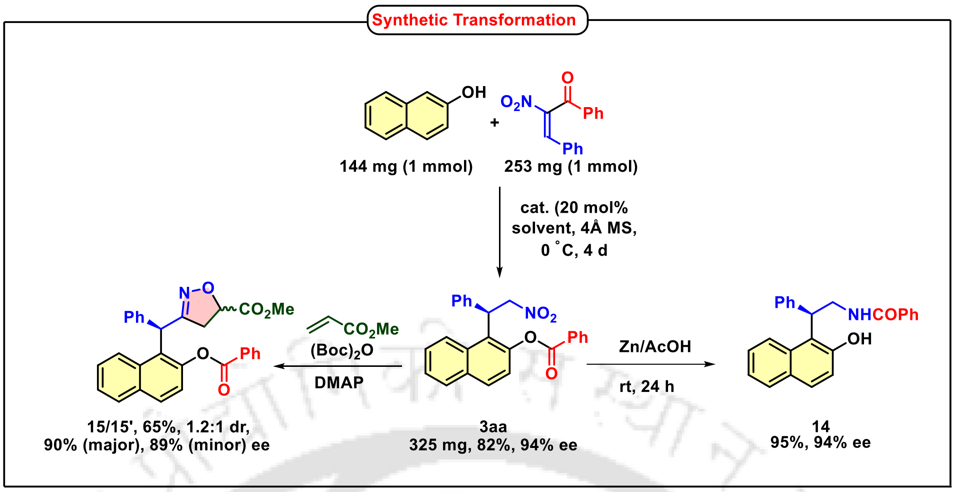


Scheme 10: Scope of other phenolic substrate.



Scheme 11: Substrate scope of Michael reaction.

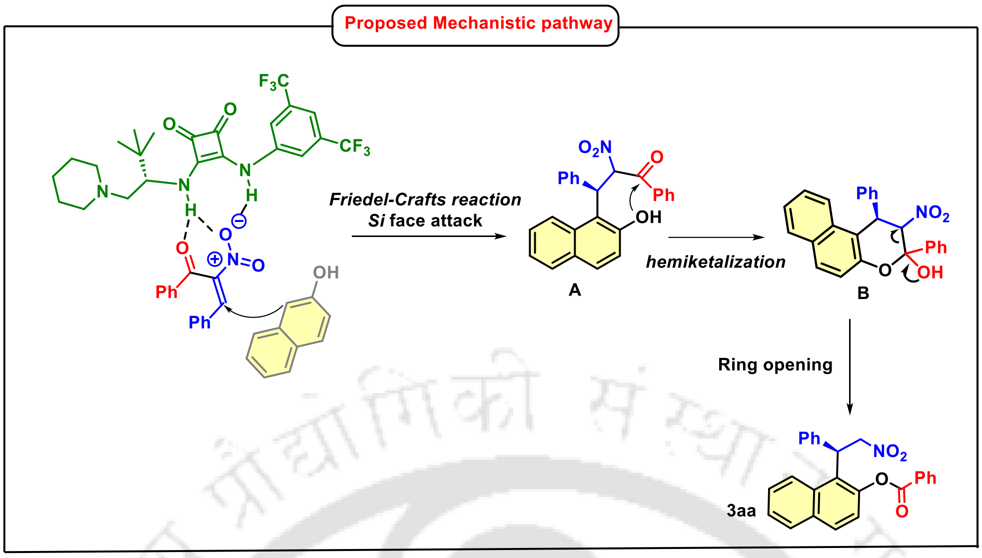
Then, we looked for the feasibility of our strategy in a Michael-acyl transfer reaction (Scheme 11). Thus, enone **2a** was treated with a 1,3-dicarbonyl compound dimedone (**10**) in the presence of *t*-leucine-derived squaramide catalyst at room temperature. Gratifyingly, after stirring for 24 h, the desired Michael-acyl transfer product **11** was isolated in 55% yield with 93% ee. Then, pyrazolone **12** was employed in the reaction. The best result was attained after mixing **2a** and **12** at 0℃ with MS 4 Å. Delightfully, the chiral pyrazole product **13** was obtained in 60% yield with 89% ee.



Scheme 12: Synthetic transformation.

One millimole-scale reaction was conducted to test the viability of our techniques, and the resultant product, **3aa**, was produced with a good yield of 82% and 94% ee. A few reactions were then carried out on **3aa** to demonstrate the synthetic potential of our technique. (Scheme 12). Initially, **3aa** was treated with Zn/AcOH. In this case, not only the nitro group was reduced to amine but also concomitant acyl transfer took place to provide **14** in 95% yield with preservation of enantiopurity. Then, a Michael-cyclization reaction was performed by mixing **3aa** with methyl acrylate and $(Boc)_2O$ in the presence of DMAP to provide isoxazoline **15/15′** as a mixture of diastereomers in good yield, though slight erosion in enantioselectivity was detected.

Based on the absolute configuration, a plausible mechanism has been proposed (Scheme 13). Since the *Re* face of enone **2a** is blocked by the catalyst, Friedel-Crafts reaction only takes place from the *Si* face, and intermediate **A** is generated. Hemiketalization of **A** leads to the formation of **B**, which undergoes ring-opening reaction to deliver product **3aa**.



Scheme 13: Proposed Mechanistic pathway.

2.5 Conclusion

In summary, we have demonstrated *α*-nitro-*α*,*β*-unsaturated ketones as an efficient electrophilic acyl transfer reagent in Friedel-Crafts as well as in Michael addition reactions for the first time. This is also the first report for the enantioselective Friedel-Crafts reaction with concomitant acyl transfer. The products having nitro and acyl groups were obtained in high yields with high to excellent enantioselectivities under mild reaction conditions. Synthetic applications such as reduction and isoxazoline synthesis have also been shown.

2.6 Experimental section:

2.6.1 General Information:

Chemicals and solvents were purchased from commercial suppliers and used as received. 1H NMR spectra were recorded on 400 MHz, and 600 MHz spectrometer. 13C NMR spectra were recorded on 100 MHz, and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA, IF and AD-H Column. For visualizing the products UV light and I2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

2.6.2 General procedure for the synthesis of *α*-nitro-*α,β*-unsaturated ketones[16]:

α-nitro-*α,β*-unsaturated ketones were synthesized according to the general procedure[16]

2.6.3 General procedure for the synthesis 2-Naphthol derivative[17]

2-Naphthol were synthesized according to the general procedure[17]

2.6.4 General procedure for the synthesis of catalyst[18]:

tert-Lucine squaramide synthesized according to the general procedure[18]

2.6.5 General procedure for the synthesis of compound 3 to 13:

In an oven dried round bottom flask, **1a** (14.4 mg, 0.1 mmol), **2a** (25.3 mg, 0.1 mmol), 20 mol% of catalyst (**VI**) and 20 mg 4Å MS activated were taken. 1.2 mL $PhCF_3$ was added to the reaction mixture and stirred at 0˚C for 4 days. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (5 %) to afford desired product **3aa to 13**.

2.6.6 General procedure for the synthesis of compound 14 and 15/15'

To a stirrer solution of (*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (**3aa**) (0.1 mmol) in 1 mL acetic acid activated Zn powder (134 mg) was added. The resulting reaction mixture was stirred for 1 day at room temperature. After completion of the reaction, the mixture was filtered through celite pad and concentrated in *vacuo*. Then the residue was dissolved in aqueous sodium carbonate and extracted with DCM. At the end it was purified by silica gel column chromatography using 30% Hexane/EtOAc to obtain the pure product (*R*)-*N*-(2-(2-hydroxynaphthalen-1-yl)-2-phenylethyl)benzamide (**14**) with 95% yield.

Di *tert*-butyl dicarbonate and methyl acrolate were dissolved in ACN and DMAP was added to it. The nitro compound (**3aa**) dissolved in ACN was added slowly to the above solution. Then the reaction proceeded further for 3 h. At the end it was purified by silica gel column chromatography using 10-30% Hexane/EtOAc to obtain the pure product **15/15'** with 65% yield.

2.7 Crystal Data analysis for compound 3aj:

CCDC = 1915972

Bond precision: C-C = 0.0120 A Wavelength=0.71073

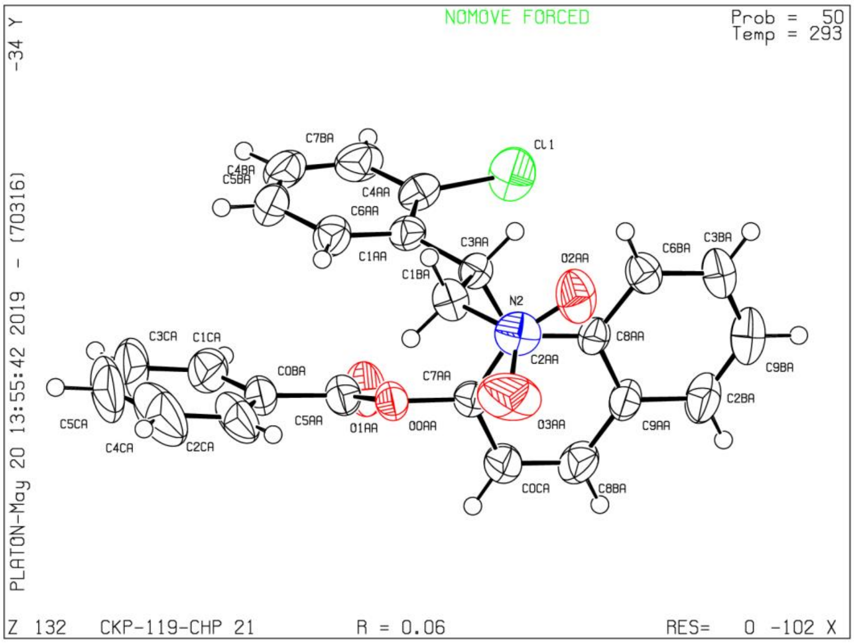
Cell: a=7.8453(9) b=15.3587(12) c=9.4930(13)

alpha=90 beta=111.352(14) gamma=90

Temperature: 293 K

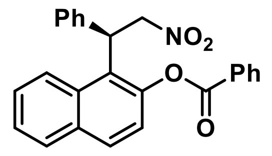
	Reported
Volume	1065.3 (2)
Space group	P 21
Hall group	P 2yb
Moiety formula	$C_{25}H_{18}ClNO_4$
Sum formula	$C_{25}H_{18}ClNO_4$
Mr	431.85
Dx, g cm^{-3}	1.346
Z	2
Mu (mm^{-1})	0.211
F000	448.0
F000’	448.50
H, k, l_{max}	10, 19, 12
N_{ref}	3386

Theta (max)	28.852
R (reflections)	0.0588 (2228)
S	0.906
N_{par}	280
Flack parameter	0.03



2.8 Characterisation of the products:

(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate) (3aa)

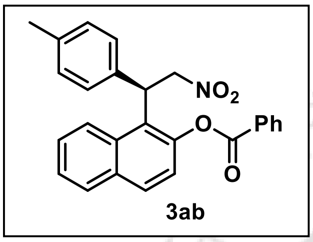


3aa

Light yellow solid, 80% (24 mg) yield. M.P. = 121-123 °C. ^{1}**H NMR (400 MHz, CDCl$_3$)** δ 8.09 (d, *J* = 6.9 Hz, 3H), 7.91 (dd, *J* = 8.9, 5.2 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.0 Hz, 4H), 7.31 (d, *J* = 8.9 Hz, 1H), 7.15 (s, 5H), 6.00 (t, *J* = 7.1 Hz, 1H), 5.48 (dd, *J* = 13.0, 8.5 Hz, 1H), 5.10 (ddd, *J* = 13.3, 6.1, 1.3 Hz, 1H). ^{13}**C NMR (100 MHz, CDCl$_3$)** δ 165.0, 139.0, 134.1, 132.7, 130.4, 130.2, 129.4, 129.1, 129.0, 129.0, 127.5, 127.1, 126.8, 126.3, 126.0, 124.0, 122.5, 77.0, 40.1. **FT-IR**

(KBr): 3063, 2924, 2853, 1730, 1600, 1556, 1375, 1208, 1145, 1002 cm^{-1}. **ESI-MS** m/z calcd. for $C_{25}H_{19}NO_4$ $[M+NH_4]^+$ 415.1652, found 415.1652. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 23.6 min, t_{minor} = 26.5 min.

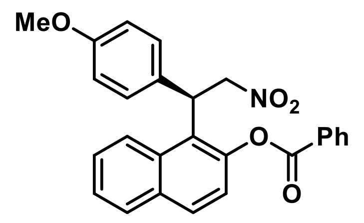
(*R*)-1-(2-nitro-1-(*p*-tolyl)ethyl)naphthalen-2-yl benzoate (3ab)



3ab

Grey semi solid, 72% (29.5 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.08 (t, *J* = 11.7 Hz, 3H), 7.90 (dd, *J* = 9.1, 6.1 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 (dd, *J* = 10.0, 5.6 Hz, 4H), 7.31 (d, *J* = 8.9 Hz, 1H), 6.99 (dd, *J* = 26.8, 8.0 Hz, 4H), 5.98 – 5.90 (m, 1H), 5.44 (dd, *J* = 13.2, 8.4 Hz, 1H), 5.08 (dd, *J* = 13.2, 6.1 Hz, 1H), 2.23 (s, 3H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.1, 147.8, 136.8, 136.0, 134.1, 132.7, 132.3, 130.4, 130.1, 129.70, 129.4, 129.1, 128.9, 127.5, 126.7, 126.3, 125.9, 124.0, 122.5, 78.8, 40.0, 21.0. **FT-IR (KBr):** 3063, 2923, 2854, 1735, 1625, 1554, 1492, 1375, 1314, 1259, 1023 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{21}NO_4$ $[M+NH_4]^+$ 429.1809, found 429.1834. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.5 min, t_{minor} = 26.9 min.

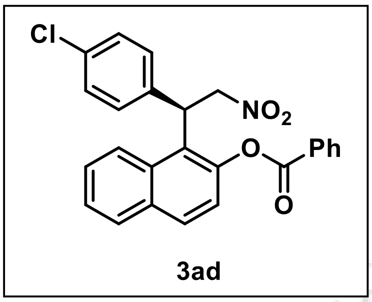
(*R*)-1-(1-(4-methoxyphenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ac)



3ac

White sticky solid, 68% (29 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.09 (t, *J* = 12.9 Hz, 3H), 7.90 (t, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.52 (dd, *J* = 10.6, 4.8 Hz, 4H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 5.96 – 5.85 (m, 1H), 5.42 (dd, *J* = 13.1, 8.5 Hz, 1H), 5.08 (dd, *J* = 13.2, 6.1 Hz, 1H), 3.70 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.2, 158.6, 147.8, 134.2, 132.7, 132.4, 131.00, 130.4, 130.5, 129.4, 129.1, 129.0, 128.0, 127.5, 126.7, 126.0, 124.0, 122.5, 114.4, 78.5, 55.4, 39.8. **FT-IR (KBr):** 2957, 2924, 2852, 1636, 1554, 1451, 1250, 1209, 1178, 1083 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{21}NO_5$ $[M+NH_4]^+$ 445.1758, found 445.1788. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 28.1 min, t_{minor} = 34.5 min.

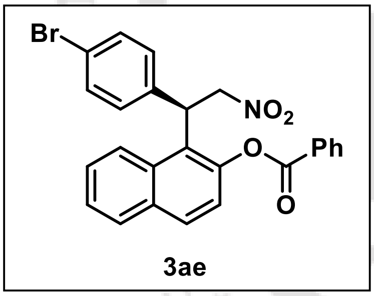
(*R*)-1-(1-(4-chlorophenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ad)



3ad

Yellow semi solid, 70% (30 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.06 (d, *J* = 7.3 Hz, 3H), 7.92 (dd, *J* = 9.0, 5.2 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.53 (dd, *J* = 10.7, 4.8 Hz, 4H), 7.30 (d, *J* = 8.9 Hz, 1H), 7.08 (dd, *J* = 21.3, 8.5 Hz, 4H), 5.94 (dd, *J* = 8.4, 5.9 Hz, 1H), 5.43 (dd, *J* = 13.4, 8.7 Hz, 1H), 5.05 (dd, *J* = 13.4, 5.7 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.1, 147.9, 137.5, 134.3, 133.1, 130.5, 130.8, 129.5, 129.2, 129.00, 128.9, 128.3, 127.8, 126.1, 125.8, 122.6, 77.8, 39.8. **FT-IR (KBr):** 3062, 2924, 2853, 1739, 1554, 1401, 1210, 1013, 752, 699 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}ClNO_4$ $[M+NH_4]^+$ 449.1263, found 449.1260. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, n-Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 26.4 min, t$_{minor}$ = 35.7 min.

(*R*)-1-(1-(4-bromophenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ae)

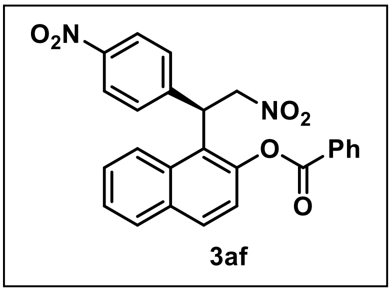


3ae

Light yellow sticky solid, 72% (34 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.19 – 7.86 (m, 5H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 4H), 7.27 (dd, *J* = 18.3, 7.9 Hz, 4H), 6.99 (d, *J* = 8.3 Hz, 2H), 5.92 (dd, *J* = 8.4, 5.8 Hz, 1H), 5.42 (dd, *J* = 13.4, 8.7 Hz, 1H), 5.03 (dd, *J* = 13.4, 5.7 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.1, 147.9, 138.1, 134.33, 132.7, 132.1, 130.5, 130.4, 129.6, 129.0, 128.9, 128.6, 127.8, 126.2, 125.7, 123.6, 122.6, 121.2, 77.5, 39.8. **FT-IR (KBr):** 3061, 2924, 2853, 1737, 1554, 1465, 1375, 1072, 1010, 520 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrNO_4$ $[M+NH_4]^+$ 493.0757, found 493.0766. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 37.5 min, t$_{minor}$ = 45.2 min.

(*R*)-1-(2-nitro-1-(4-nitrophenyl)ethyl)naphthalen-2-yl benzoate (3af)

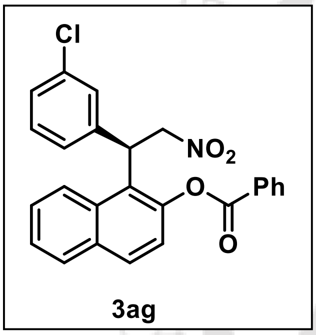
Brown semi solid, 65% (29 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.09 – 7.87 (m, 5H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.33 – 7.26 (m, 2H), 6.05 (dd, *J* = 8.7,



3af

5.4 Hz, 1H), 5.51 (dd, J = 13.7, 8.9 Hz, 1H), 5.06 (dd, J = 13.7, 5.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 173.3, 148.0, 146.9, 146.5, 134.6, 132.7, 131.0, 130.2, 130.1, 129.7, 129.2, 129.1, 128.9, 128.6, 128.2, 127.9, 126.4, 125.1, 124.1, 122.6, 77.4, 40.0. **FT-IR (KBr):** 2923, 2852, 1637, 1555, 1517, 1346, 1176, 1061, 701 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}N_2O_6$ $[M+NH_4]^+$ 460.1503, found 460.1539. **HPLC Analysis:** ee = 96%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.0 min, t_{minor} = 41.8 min.

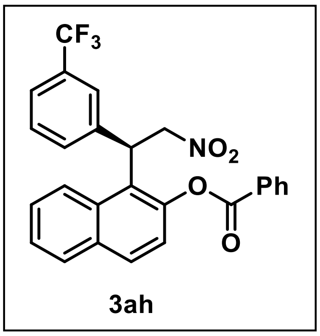
(*R*)-1-(1-(3-chlorophenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ag)



3ag

Light yellow sticky solid, 70% (30 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.07 (d, J = 7.2 Hz, 3H), 7.96 – 7.89 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.62 – 7.49 (m, 4H), 7.30 (d, J = 8.9 Hz, 1H), 7.15 – 7.04 (m, 3H), 7.00 (d, J = 7.3 Hz, 1H), 5.99 – 5.93 (m, 1H), 5.44 (dd, J = 13.4, 8.6 Hz, 1H), 5.05 (dd, J = 13.5, 5.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.0, 147.9, 141.1, 135.05, 134.3, 132.7, 132.2, 130.6, 130.4, 130.3, 129.5, 129.1, 128.9, 127.9, 127.5, 127.0, 126.6, 125.7, 125.3, 123.6, 122.6, 77.5, 39.8. **FT-IR (KBr):** 3062, 2924, 2853, 1736, 1592, 1433, 1375, 873, 847, 628 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}ClNO_4$ $[M+NH_4]^+$ 449.1263, found 449.1263. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 27.6 min, t_{minor} = 29.9 min.

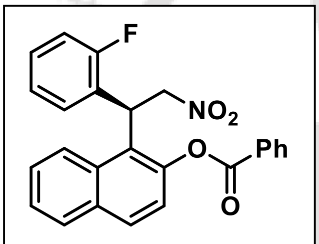
(*R*)-1-(2-nitro-1-(4-(trifluoromethyl)phenyl)ethyl)naphthalen-2-yl benzoate (3ah)



3ah

Yellow oil, 72% (33.5 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.96 (dd, *J* = 32.3, 24.0 Hz, 5H), 7.68 – 7.48 (m, 5H), 7.40 (d, *J* = 6.4 Hz, 2H), 7.32 – 7.26 (m, 3H), 6.06 – 5.99 (m, 1H), 5.53 – 5.43 (m, 1H), 5.10 (dd, *J* = 13.5, 5.9 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.9, 147.9, 140.1, 134.4, 132.6, 131.4, 131.1, 130.8, 130.7, 130.3, 129.6, 129.0, 128.6, 127.9, 126.2, 125.5, 124.8, 124.2, 124.2, 123.1, 123.0, 122.9, 122.6, 77.5, 40.0. **FT-IR (KBr):** 2923, 2853, 1637, 1555, 1451, 1329, 1060, 803, 701 cm^{-1}. **ESI HRMS:** calcd. For $C_{26}H_{18}CF_3NO_4$ $[M+NH_4]^+$ 483.1526, found 483.1541. **HPLC Analysis:** ee = 96%, Chiralpak IF Column, n-Hexane/i-PrOH = 96/4, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 11.2 min, t$_{minor}$ = 12.9 min.

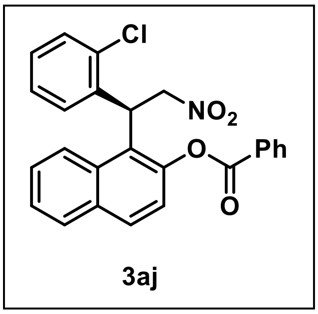
(*S*)-1-(1-(2-fluorophenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ai)



3ai

Grey semi solid 75% (31 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.22 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 7.3 Hz, 4H), 7.90 (t, *J* = 8.5 Hz, 4H), 7.68 (t, *J* = 7.5 Hz, 2H), 7.63 – 7.47 (m, 8H), 7.26 (t, *J* = 4.4 Hz, 3H), 7.23 – 7.08 (m, 4H), 6.95 (dd, *J* = 10.0, 8.4 Hz, 2H), 6.82 (t, *J* = 7.5 Hz, 2H), 6.23 – 6.11 (m, 2H), 5.42 (dd, *J* = 13.6, 8.6 Hz, 2H), 5.11 (dd, *J* = 13.6, 6.6 Hz, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.1, 161.6, 159.9, 148.0, 134.2, 130.4, 130.4, 129.4, 129.1, 128.9, 128.5, 127.7, 126.1, 124.5, 122.5, 116.2, 116.0, 76.6, 35.8. **FT-IR (KBr):** 2957, 2853, 1736, 1603, 1554, 1375, 1153, 852, 760 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}FNO_4$ $[M+NH_4]^+$ 433.1558, found 433.1555. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 22.1 min, t$_{minor}$ = 24.8 min.

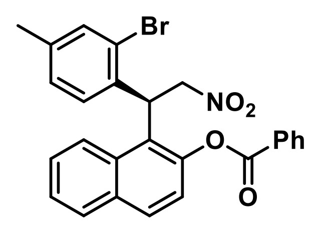
(*S*)-1-(1-(2-chlorophenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3aj)



3aj

White solid, 68% (29.3 mg) yield, M.P = 171-172 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.22 (d, *J* = 8.6 Hz, 2H), 8.06 (d, *J* = 7.3 Hz, 4H), 7.90 (t, *J* = 9.1 Hz, 4H), 7.64 (dt, *J* = 14.3, 7.4 Hz, 4H), 7.53 (dd, *J* = 7.3, 5.8 Hz, 6H), 7.34 (d, *J* = 1.0 Hz, 2H), 7.28 – 7.20 (m, 5H), 7.09 (td, *J* = 7.8, 1.3 Hz, 2H), 6.87 (t, *J* = 7.5 Hz, 2H), 6.20 (t, *J* = 7.9 Hz, 2H), 5.28 (dd, *J* = 14.0, 8.6 Hz, 2H), 5.10 (dd, *J* = 14.0, 7.3 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.3, 148.3, 135.6, 134.3, 132.6, 132.5, 130.5, 130.4, 130.4, 129.4, 129.1, 128.9, 128.8, 128.7, 127.8, 127.4, 126.0, 123.8, 123.4, 122.7, 76.0, 39.9. **FT-IR (KBr):** 3030, 2924, 1739, 1624, 1554, 1375, 1210, 1076, 740 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}ClNO_4$ $[M+NH_4]^+$ 449.1263, found 449.1264. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.0 min, t_{minor} = 23.8 min.

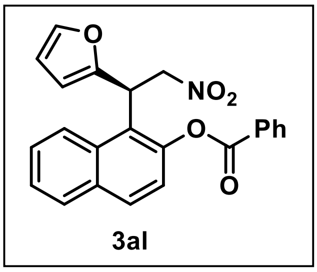
(*S*)-1-(1-(2-bromo-4-methylphenyl)-2-nitroethyl)naphthalen-2-yl benzoate (3ak)



3ak

White solid, 65% (32 mg) yield, M.P = 110-112 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.18 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 2H), 7.89 (dd, *J* = 13.8, 8.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 14.9, 7.2 Hz, 3H), 7.38 (s, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.15 – 7.10 (m, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.11 (t, *J* = 8.0 Hz, 1H), 5.20 (dd, *J* = 14.2, 8.4 Hz, 1H), 5.10 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.18 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.1, 147.9, 139.1, 134.0, 133.9, 133.7, 132.5, 132.2, 130.3, 130.1, 129.1, 128.9, 128.7, 128.64, 128.6, 127.6, 125.8, 124.0, 123.6, 123.3, 122.5, 75.7, 41.9,20.5. **FT-IR (KBr):** 2971, 2924, 1733, 1637, 1552, 1375, 1247, 1163, 1081 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{20}BrNO_4$ $[M+NH_4]^+$ 507.0914, found 507.0918. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 99/1, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 30.2 min, t_{minor} = 34.1 min.

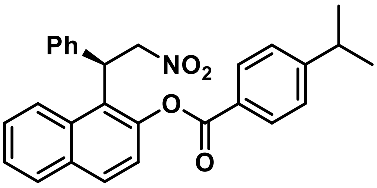
(*R*)-1-(1-(furan-2-yl)-2-nitroethyl)naphthalen-2-yl benzoate (3al)



3al

Yellow sticky solid, 75% (29 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 (d, *J* = 7.5 Hz, 2H), 8.07 (s, 1H), 7.96 – 7.86 (m, 2H), 7.58 (ddd, *J* = 24.2, 11.3, 4.7 Hz, 5H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.20 (s, 1H), 6.21 – 6.14 (m, 1H), 5.98 (dd, *J* = 14.3, 5.1 Hz, 2H), 5.45 (dd, *J* = 13.5, 8.4 Hz, 1H), 5.00 (dd, *J* = 13.5, 5.8 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.1, 151.6, 147.8, 142.0, 134.2, 132.6, 132.2, 130.5, 130.4, 129.4, 129.0, 128.9, 127.6, 126.0, 123.5, 122.4, 110.8, 106.9, 76.53, 35.6. **FT-IR (KBr):** 2923, 2853, 1633, 1514, 1374, 1207, 1080, 705 cm^{-1}. **ESI HRMS**: calcd. For $C_{23}H_{17}NO_5$ [M+NH$_4$]$^+$ 405.1445, found 405.1468. **HPLC Analysis:** ee = 84%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 22.6 min, t$_{minor}$ = 30.13 min.

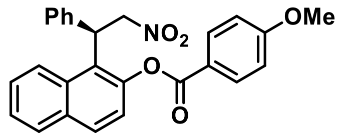
(*S*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-isopropylbenzoate (3am)



3am

Red semi solid, 72% (31.6 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 6.3 Hz, 3H), 7.90 (t, *J* = 9.2 Hz, 2H), 7.50 (d, *J* = 6.9 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 5H), 6.00 – 5.96 (m, 1H), 5.47 (dd, *J* = 12.8, 8.6 Hz, 1H), 5.09 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.02 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.2, 155.8, 147.9, 139.1, 132.6, 132.3, 130.6, 130.1, 129.4, 129.0, 127.5, 127.1, 127.0, 126.9, 126.6, 126.2, 125.8, 123.9, 122.6, 78.1, 40.3, 23.8, 23.8. **FT-IR (KBr):** 2925, 2854, 1637, 1555, 1375, 1262, 1080, 1074 cm^{-1}. **ESI HRMS**: calcd. For $C_{28}H_{25}NO_4$ [M+NH$_4$]$^+$ 457.2122, found 457.2121. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 21.0 min, t$_{minor}$ = 24.5 min.

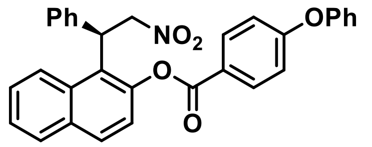
(*S*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-methoxybenzoate) (3an)



3an

White semi solid, 73% (31 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.90 (t, *J* = 9.5 Hz, 2H), 7.75 (dd, *J* = 15.9, 8.5 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.32 (dd, *J* = 13.7, 8.3 Hz, 1H), 7.21 – 7.11 (m, 5H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.04 – 5.94 (m, 1H), 5.47 (dd, *J* = 12.9, 8.6 Hz, 1H), 5.09 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.91 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.4, 147.9, 139.1, 132.6, 130.1, 130.0, 129.4, 129.0, 127.9, 127.5, 127.1, 126.9, 126.6, 126.5, 126.2, 125.8, 123.9, 123.7, 122.6, 121.2, 117.9, 114.2, 109.6, 78.1, 55.7, 40.2. **FT-IR (KBr):** 2924, 2852, 1637, 1511, 1462, 1259, 1162, 695 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{21}NO_5$ $[M+NH_4]^+$ 445.1758, found 445.1754. **HPLC Analysis:** ee = 96%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 47.9 min, t_{minor} = 53.6 min.

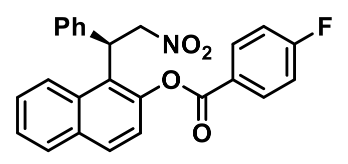
(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-phenoxybenzoate(3ao)



3ao

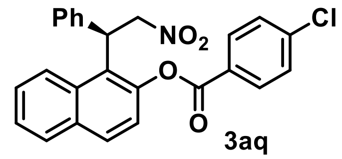
Light yellow semi solid, 65% (32 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.03 (d, *J* = 7.5 Hz, 3H), 7.89 (t, *J* = 9.7 Hz, 2H), 7.46 (ddd, *J* = 26.3, 14.3, 7.3 Hz, 6H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.16 (dd, *J* = 11.2, 5.6 Hz, 5H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.00 – 5.96 (m, 1H), 5.46 (dd, *J* = 13.0, 8.5 Hz, 1H), 5.08 (dd, *J* = 13.3, 6.0 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.5, 147.9, 139.1, 136.2, 132.6, 130.1, 129.4, 129.0, 128.9, 128.5, 127.7, 127.2, 127.1, 126.9, 126.2, 125.8, 122.6, 121.4, 115.0, 78.0, 70.4, 40.9. **FT-IR (KBr):** 2958, 2853, 1735, 1637, 1554, 1375, 1208, 1074, 699 cm^{-1}. ESI HRMS: calcd. For $C_{31}H_{23}NO_5$ $[M+NH_4]^+$ 507.1914, found 507.1925. **HPLC Analysis:** ee = 96%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 60.0 min, t_{minor} = 69.2 min.

(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-fluorobenzoate) (3ap)


3ap

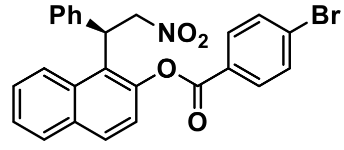
Light pink semi solid, 75% (31 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.09 (s, 2H), 7.91 (t, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 6.1 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.16 (ddd, *J* = 26.4, 18.7, 7.8 Hz, 7H), 5.99 (t, *J* = 7.1 Hz, 1H), 5.52 – 5.41 (m, 1H), 5.07 (dd, *J* = 13.3, 6.2 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 167.3, 165.7, 164.1, 147.74, 139.0, 133.1, 133.0, 132.7, 130.3, 129.4, 129.0, 127.6, 127.1, 126.8, 126.2, 126.0, 125.2, 122.4, 116.2, 116.1, 77.9, 40.1. **FT-IR (KBr):** 2958, 2853, 1735, 1637, 1554, 1375, 1208, 1074, 699 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}FNO_4$ $[M+NH_4]^+$ 433.1558, found 433.1558. **HPLC Analysis:** ee = 96%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 20.8 min, t_{minor} = 23.1 min.

(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-chlorobenzoate (3aq)


3aq

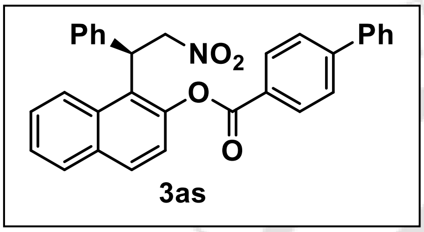
Red semi solid, 73% (31.4 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.96 (dd, *J* = 32.4, 24.8 Hz, 5H), 7.53 (dd, *J* = 18.9, 7.4 Hz, 4H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.22 – 7.10 (m, 5H), 6.01 (t, *J* = 7.1 Hz, 1H), 5.56 – 5.44 (m, 1H), 5.09 (dd, *J* = 13.3, 6.3 Hz, 1H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.2, 147.6, 140.7, 138.9, 132.7, 132.3, 131.7, 130.3, 129.4, 129.3, 129.0, 127.6, 127.4, 127.2, 126.7, 126.2, 126.0, 123.9, 122.3, 77.8, 40.0. **FT-IR (KBr):** 2924, 2853, 1736, 1554, 1488, 1375, 1210, 1031, 804 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}ClNO_4$ $[M+NH_4]^+$ 449.1263, found 449.1268. **HPLC Analysis:** ee = 92%, Chiralpak IF Column Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.2 min, t_{minor} = 24.4 min).

(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 4-bromobenzoate(3ar)


3ar

Brown solid, 75% (35.7 mg) yield. M.P. = 115-117 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.91 (t, *J* = 8.5 Hz, 5H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 6.7 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 1H), 7.16 (s, 3H), 7.11 (d, *J* = 7.0 Hz, 2H), 5.99 (t, *J* = 7.2 Hz, 1H), 5.46 (dd, *J* = 12.5, 8.5 Hz, 1H), 5.07 (dd, *J* = 13.3, 6.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.4, 147.6, 138.9, 132.7, 132.3, 131.8, 130.3, 129.4, 129.4, 129.0, 127.9, 127.6, 127.2, 126.7, 126.2, 126.0, 122.3, 77.8, 40.0. **FT-IR (KBr):** 2924, 2853, 1736, 1625, 1554, 1375, 1257, 1173, 782, 626 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrNO_4$ $[M+NH_4]^+$ 493.0757, found 493.0751. **HPLC Analysis:** ee = 94%, Chiralpak IF Column *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 24.1 min, t_{minor} = 26.3 min.

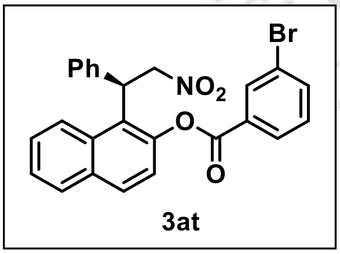
(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl [1,1'-biphenyl]-4-carboxylate (3as)



3as

White semi solid, 75% (35.4 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.16 (s, 5H), 7.92 (dd, *J* = 8.8, 5.8 Hz, 4H), 7.75 (d, *J* = 8.3 Hz, 4H), 7.69 (d, *J* = 7.5 Hz, 4H), 7.52 (t, *J* = 7.6 Hz, 8H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.18 (s, 10H), 6.03 (d, *J* = 6.9 Hz, 2H), 5.51 (dd, *J* = 12.9, 8.4 Hz, 2H), 5.13 (dd, *J* = 13.3, 6.2 Hz, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.0, 147.8, 146.9, 139.9, 139.0, 132.6, 130.9, 130.2, 129.4, 129.2, 129.0, 128.6, 127.7, 127.5, 127.5, 127.2, 126.9, 126.2, 125.9, 122.5, 78.0, 40.2. **FT-IR (KBr):** 2924, 2853, 1734, 1629, 1555, 1375, 1075, 1017, 746, 697 cm^{-1}. ESI HRMS: calcd. For $C_{31}H_{23}NO_4$ $[M+NH_4]^+$ 491.1965, found 491.1973. **HPLC Analysis:** ee = 96%, Chiralpak IF Column *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 36.0 min, t_{minor} = 39.9 min.

(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 3-bromobenzoate one (3at)

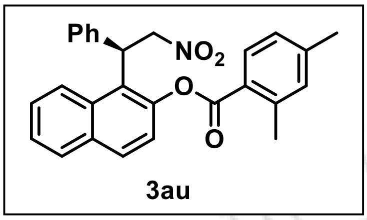


3at

Red semi solid, 75% (35.7 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.23 (s, 1H), 8.09 (s, 1H), 8.00 (t, *J* = 8.4 Hz, 2H), 7.90 – 7.82 (m, 2H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.49 (dd, *J* = 16.1, 8.1 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.26 – 7.18 (m, 4H), 6.08 (t, *J* = 7.1 Hz, 1H), 5.54 (d, *J* = 8.3 Hz, 1H), 5.14 (dd, *J* = 13.3, 6.2 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.9, 147.6, 138.9, 137.1, 134.7, 133.3, 132.7, 130.9, 130.4, 130.4, 130.0, 129.4, 129.1, 128.9, 127.9, 127.7, 127.2, 126.7, 126.7, 126.5, 126.3, 126.1, 123.8, 122.9, 122.2, 117.9, 109.6, 77.7, 40.0. **FT-IR (KBr):** 3062, 2924, 2853, 1737, 1588, 1554, 1398, 1375, 1072, 750, 698 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrNO_4$ $[M+NH_4]^+$ 495.0757, found 493.0770.

HPLC Analysis: ee = 95%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 27.15 min, t_{minor} = 29.7 min.

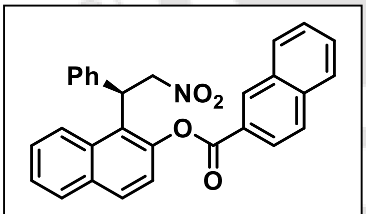
(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 2,4-dimethylbenzoate (3au)



3au

White sticky solid, 72% (30.6 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.19 – 7.95 (m, 2H), 7.90 (t, *J* = 9.5 Hz, 2H), 7.51 (dd, *J* = 15.3, 7.7 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.20 – 7.05 (m, 7H), 6.01 – 5.92 (m, 1H), 2.47 (s, 3H), 2.41 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.2, 147.9, 144.1, 142.3, 139.1, 133.2, 132.5, 132.6, 131.4, 130.0, 129.3, 128.9, 127.5, 127.0, 126.9, 126.4, 125.8, 124.9, 123.8, 122.7, 77.8, 40.1, 22.0, 21.7. **FT-IR (KBr):** 2924, 2853, 1633, 1555, 1450, 1375, 1207, 1053, 764, 607 cm^{-1}. **ESI HRMS**: calcd. For $C_{27}H_{23}NO_4$ $[M+NH_4]^+$ 443.1965, found 443.1984. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.9 min, t_{minor} = 25.1 min.

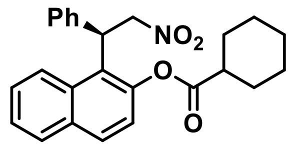
(*S*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl 2-naphthoate (3av)



3av

Light brown semi solid, 70% (31.2 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.62 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 8.00 – 7.91 (m, 5H), 7.69 – 7.59 (m, 2H), 7.53 (dd, *J* = 9.9, 4.6 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 1H), 7.16 (s, 5H), 6.05 (dd, *J* = 8.0, 6.4 Hz, 1H), 5.50 (dd, *J* = 13.3, 8.3 Hz, 1H), 5.13 (dd, *J* = 13.3, 6.2 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.3, 147.9, 139.1, 136.1, 132.6, 132.3, 130.2, 129.8, 129.4, 129.1, 129.0, 128.7, 128.0, 127.6, 127.2, 127.1, 126.8, 126.3, 126.1, 126.0, 125.4, 123.9, 122.8, 77.9, 40.1. **FT-IR (KBr):** 2924, 2853, 1629, 1553, 1463, 1375, 1277, 1186, 1075 cm^{-1}. **ESI HRMS**: calcd. For $C_{29}H_{21}NO_4$ $[M+NH_4]^+$ 465.1809, found 465.1811. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 35.3 min, t_{minor} = 38.4 min.

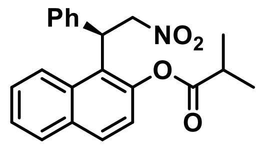
(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl cyclohexanecarboxylate (3aw)



3aw

Pale yellow semi solid, 72% (29 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.03 – 7.81 (m, 3H), 7.45 (d, *J* = 3.8 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.23 – 7.15 (m, 4H), 5.92 – 5.82 (m, 1H), 5.53 (dd, *J* = 13.3, 8.9 Hz, 1H), 4.97 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.48 (s, 1H), 2.10 (d, *J* = 11.6 Hz, 1H), 1.90 (s, 1H), 1.86 – 1.76 (m, 2H), 1.69 (d, *J* = 11.6 Hz, 1H), 1.38 – 1.27 (m, 4H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 174.5, 147.7, 139.3, 132.6, 132.2, 130.1, 129.3, 129.1, 127.3, 127.2, 126.7, 126.0, 125.7, 124.0, 122.3, 78.1, 43.3, 28.7, 25.8, 25.6, 25.4, 22.9. **FT-IR (KBr):** 2924, 2853, 1633, 1554, 1462, 1378, 1261, 1147, 951 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{24}NO_4$ $[M+NH_4]^+$ 421.2122, found 421.2126. **HPLC Analysis:** ee = 88%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.2 min, t_{minor} = 16.3 min.

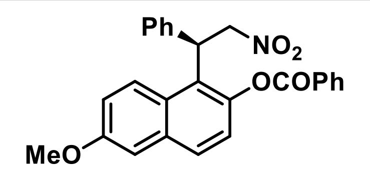
(*R*)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl isobutyrate (3ax)



3ax

Gray semi solid, 65% (24.7 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.86 (dd, J = 11.7, 6.7 Hz, 3H), 7.46 (dd, J = 6.2, 3.0 Hz, 2H), 7.31 – 7.24 (m, 3H), 7.24 – 7.18 (m, 2H), 7.16 (s, 1H), 5.91 (dd, J = 8.4, 5.6 Hz, 1H), 5.53 (dd, J = 13.5, 8.7 Hz, 1H), 4.98 (dd, J = 13.5, 5.4 Hz, 1H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 175.5, 147.7, 139.3, 132.6, 130.2, 129.6, 129.1, 127.4, 127.2, 126.7, 126.0, 125.8, 122.3, 78.11, 39.8, 34.3, 19.2, 18.7. **FT-IR (KBr):** 2922, 2853, 1759, 1554, 1462, 1378, 1127, 492, 458 cm^{-1}. **ESI HRMS:** calcd. For $C_{22}H_{21}NO_4$ [M+NH$_4$]+ 364.1543, found 364.1547. **HPLC Analysis**: ee = 68%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 10.2 min, t_{minor} = 12.0 min.

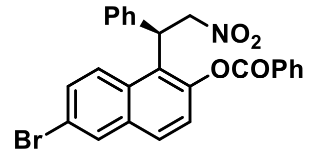
(*R*)-6-methoxy-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ba)



3ba

White semi solid, 80% (34 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.80 (dd, *J* = 10.7, 9.0 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.25 – 7.08 (m, 8H), 5.91 (dd, *J* = 8.3, 6.1 Hz, 1H), 5.48 (dd, *J* = 13.2, 8.5 Hz, 1H), 5.07 (dd, *J* = 13.2, 6.0 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.2, 158.7, 148.4, 139.2, 134.1, 133.6, 130.8, 130.4, 129.9, 129.0, 129.0, 128.9, 128.0, 127.1, 126.8, 125.1, 119.8, 118.2, 103.2, 77.7, 55.4, 40.4. **FT-IR (KBr):** 2923, 2851, 1636, 1553, 1450, 1242, 1208, 1175, 1081 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{21}NO_5$ $[M+NH_4]^+$ 445.1798, found 445.1794. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 47.7 min, t_{minor} = 54.9 min.

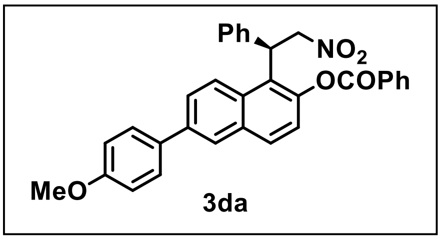
(*R*)-6-bromo-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ca)



3ca

Light brown sticky solid, 74% (35 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.07 (t, *J* = 5.7 Hz, 3H), 7.90 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 1H), 7.16 (s, 3H), 7.10 (d, *J* = 7.2 Hz, 2H), 5.93 (t, *J* = 7.3 Hz, 1H), 5.44 (dd, *J* = 13.1, 8.1 Hz, 1H), 5.11 (dd, *J* = 13.2, 6.6 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.9, 148.0, 138.6, 134.3, 133.8, 131.3, 130.8, 130.4, 129.3, 129.1, 128.9, 128.8, 127.3, 126.8, 126.6, 125.7, 123.8, 120.1, 77.8, 40.1. **FT-IR (KBr):** 3061, 2853, 1737, 1588, 1554, 1375, 1306, 1173, 750 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrNO_4$ $[M+NH_4]^+$ 493.0757, found 493.0766. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 29.8 min, t_{minor} = 34.5 min.

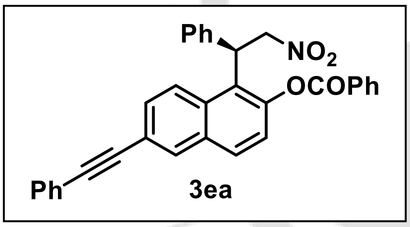
(*R*)-6-(4-methoxyphenyl)-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3da)



3da

Light yellow semi solid, 75% (37.7 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.07 (dd, *J* = 18.7, 4.6 Hz, 4H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.62 (m, 3H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.15 (d, *J* = 14.0 Hz, 5H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.04 – 5.96 (m, 1H), 5.49 (dd, *J* = 13.2, 8.3 Hz, 1H), 5.13 (dd, *J* = 13.2, 6.3 Hz, 1H), 3.88 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.1, 159.7, 147.6, 139.1, 138.3, 134.1, 133.1, 132.2, 131.1, 130.4, 130.3, 129.1, 129.0, 128.9, 128.5, 127.2, 127.0, 126.9, 126.3, 126.2, 124.5, 122.9, 114.6, 78.0, 55.6, 40.3. **FT-IR (KBr):** 2924, 2853, 1638, 1553, 1500, 1376, 1210, 1176, 752 cm^{-1}. **ESI HRMS:** calcd. For $C_{26}H_{21}NO_5$ [M+NH4]$^+$ 521.2071, found 521.2073. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 46.05 min, t$_{minor}$ = 52.7 min.

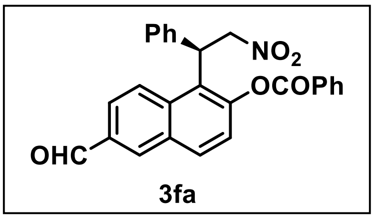
(*R*)-1-(2-nitro-1-phenylethyl)-6-(phenylethynyl)naphthalen-2-yl benzoate (3ea)



3ea

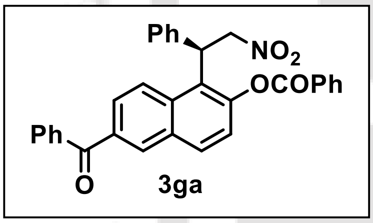
Light yellow semi solid, 60% (30 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 – 7.97 (m, 4H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.68 – 7.49 (m, 6H), 7.39 – 7.31 (m, 4H), 7.20 – 7.11 (m, 5H), 6.01 – 5.94 (m, 1H), 5.47 (dd, *J* = 13.2, 8.2 Hz, 1H), 5.11 (dd, *J* = 13.3, 6.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.0, 148.5, 138.8, 134.2, 132.6, 132.3, 131.9, 131.7, 130.4, 130.1, 130.0, 129.1, 128.9, 128.7, 128.6, 127.3, 126.8, 126.5, 124.1, 123.3, 123.2, 121.0, 90.8, 89.1, 77.9, 40.2. **FT-IR (KBr):** 2923, 2853, 1637, 1555, 1497, 1375, 1259, 1080, 755 cm^{-1}. **ESI HRMS:** calcd. For $C_{33}H_{23}NO_4$ [M+NH$_4$]$^+$ 515.1965, found 515,1980. **HPLC Analysis:** ee = 86%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 32.7 min, t$_{minor}$ = 42.4 min.

(*R*)-6-formyl-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3fa)


3fa

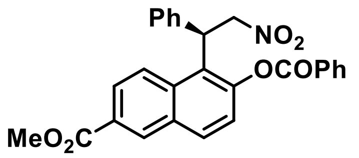
Yellow oil, 60% (25.5 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 10.17 (s, 1H), 8.40 (d, *J* = 1.3 Hz, 1H), 8.21 – 8.04 (m, 4H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.21 – 7.09 (m, 5H), 6.01 (t, *J* = 7.3 Hz, 1H), 5.47 (dd, *J* = 13.1, 7.8 Hz, 1H), 5.15 (dd, *J* = 13.1, 6.9 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 191.8, 164.8, 150.3, 138.4, 135.7, 135.0, 134.4, 133.8, 132.0, 131.1, 130.4, 129.1, 129.0, 128.6, 127.4, 127.0, 126.8, 125.1, 124.6, 124.0, 77.8, 40.2. **FT-IR (KBr):** 2923, 2852, 1738, 1693, 1623, 1554, 1497, 1376, 1208, 1080 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{19}NO_5$ $[M+NH_4]^+$ 443.1601, found 443.1617. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 25.6 min, t_{minor} = 30.0 min.

(*R*)-6-benzoyl-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ga)


3ga

Light yellow semi solid, 68% (31 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.34 (d, *J* = 1.5 Hz, 1H), 8.12 (t, *J* = 10.8 Hz, 3H), 7.99 (t, *J* = 7.0 Hz, 2H), 7.88 (d, *J* = 7.1 Hz, 2H), 7.74 – 7.61 (m, 2H), 7.55 (t, *J* = 7.5 Hz, 4H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.23 – 7.11 (m, 5H), 6.04 (t, *J* = 7.3 Hz, 1H), 5.50 (dd, *J* = 13.1, 7.9 Hz, 1H), 5.18 (dd, *J* = 13.2, 6.8 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.3, 164.9, 149.7, 138.6, 137.6, 134.8, 134.3, 132.8, 132.7, 131.6, 130.4, 130.3, 129.1, 129.0, 128.7, 128.6, 127.5, 127.4, 126.8, 126.6, 124.4, 123.6, 77.8, 40.2. **FT-IR (KBr):** 2924, 2852, 1736, 1654, 1553, 1468, 1375, 1177, 1001 cm^{-1}. **ESI HRMS**: calcd. For $C_{32}H_{23}NO_5$ $[M+H]^+$ 502.1649, found 502.1649. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 35.6 min, t_{minor} = 39.8 min.

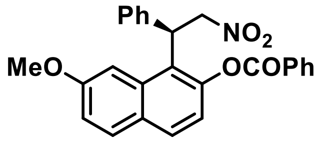
Methyl (*R*)-6-(benzoyloxy)-5-(2-nitro-1-phenylethyl)-2-naphthoate (3ha)



3ha

Pale yellow semi solid, 70% (32.6 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.65 (s, 1H), 8.05 (dd, *J* = 28.1, 8.0 Hz, 5H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.14 (dt, *J* = 7.5, 4.0 Hz, 5H), 6.00 (t, *J* = 7.3 Hz, 1H), 5.47 (dd, *J* = 13.2, 8.0 Hz, 1H), 5.13 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.99 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 166.9, 164.9, 149.7, 138.6, 134.7, 134.3, 132.1, 131.8, 131.5, 130.4, 129.1, 129.0, 128.83, 127.6, 127.3, 126.9, 126.8, 126.6, 123.5, 77.8, 52.5, 40.2. **FT-IR (KBr):** 2957, 2851, 1629, 1555, 1471, 1375, 1206, 1080, 748 cm^{-1}. **ESI HRMS**: calcd. For $C_{227}H_{21}NO_6$ $[M+NH_4]^+$ 473.1707, found 473.1710. **HPLC Analysis:** ee = 90%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.2 min, t_{minor} = 28.4 min.

(*R*)-7-methoxy-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ia)

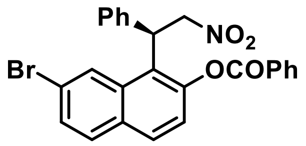


3ia

Light yellow semi solid, 77% (33 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.10 (d, *J* = 7.4 Hz, 2H), 7.95 (s, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.11 (m, 9H), 5.94 (d, *J* = 6.6 Hz, 1H), 5.48 (dd, *J* = 13.2, 8.3 Hz, 1H), 5.10 (dd, *J* = 13.2, 6.2 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.2, 157.5, 146.1, 139.0, 134.1, 130.4, 129.1, 129.0, 128.9, 127.1, 126.8, 126.3, 123.0, 120.0, 107.5, 78.0, 55.6, 40.2. **FT-IR (KBr):** 2923, 2852, 1735, 1627, 1554, 1462, 1375, 1138, 1059, 832 cm^{-1}. **ESI HRMS**: calcd. For $C_{26}H_{21}NO_5$ $[M+NH_4]^+$ 445.1798, found 445.1798. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 28.3 min, t_{minor} = 32.5 min.

(*R*)-7-bromo-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ja)

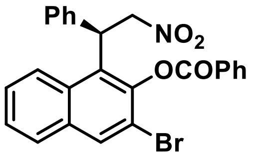
Grey semi solid, 75% (35.7 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.23 (s, 1H), 8.06 (d, *J* = 6.9 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.12 (dd,



3ja

J = 20.1, 17.1 Hz, 5H), 5.89 (t, *J* = 7.3 Hz, 1H), 5.44 (dd, *J* = 13.2, 8.1 Hz, 1H), 5.12 (dd, *J* = 13.3, 6.7 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.9, 148.7, 148.7, 138.4, 134.3, 130.9, 130.4, 130.1, 129.5, 129.1, 129.0, 128.8, 127.4, 126.8, 126.3, 125.6, 123.1, 77.7, 77.5, 40.2. **FT-IR (KBr):** 2956, 2924, 1737, 1588, 1554, 1433, 1398, 1173, 1072, 804 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrNO_4$ $[M+NH_4]^+$ 493.0757, found 493.0766. **HPLC Analysis:** ee = 92%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 22.4 min, t_{minor} = 24.4 min.

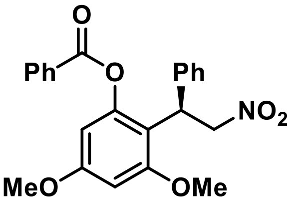
(*R*)-3-bromo-1-(2-nitro-1-phenylethyl)naphthalen-2-yl benzoate (3ka)



3ka

Brown sticky, 72% (34 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.26 – 8.05 (m, 3H), 7.96 – 7.77 (m, 2H), 7.68 (t, *J* = 7.9 Hz, 1H), 7.61 – 7.42 (m, 4H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 26.3 Hz, 3H), 6.04 – 5.91 (m, 1H), 5.41 (s, 1H), 5.13 – 4.92 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.1, 138.8, 134.5, 134.2, 133.5, 133.3, 130.9, 130.5, 129.2, 129.09, 128.9, 128.9, 128.7, 128.5, 128.3, 127.8, 127.3, 127.2, 126.9, 126.9, 126.8, 124.2, 116.3, 110.8, 77.9, 41.1. **FT-IR (KBr):** 2924, 2857, 1738, 1589, 1560, 1433, 1375, 1145, 1072, 804 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{18}BrO_4$ $[M+NH_4]^+$ 493.0757, found 493.0793. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 19.5 min, t_{minor} = 22.5 min.

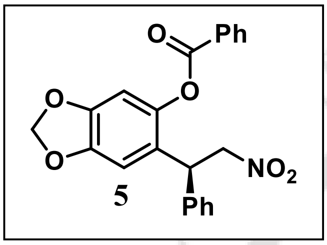
(*R*)-3,5-dimethoxy-2-(2-nitro-1-phenylethyl)phenyl benzoate (4)



4

light yellow semi solid, 68% (27.5 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.25 (d, *J* = 7.3 Hz, 2H), 7.76 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.25 (ddd, *J* = 10.9, 10.1, 4.3 Hz, 5H), 6.47 (dd, *J* = 22.2, 2.3 Hz, 2H), 5.39 – 5.31 (m, 2H), 5.18 (dd, *J* = 12.6, 7.0 Hz, 1H), 3.86 (d, *J* = 3.8 Hz, 6H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.9, 160.3, 159.3, 150.5, 139.3, 134.1, 130.4, 129.1, 128.9, 128.5, 127.3, 126.9, 113.4, 100.2, 97.7, 77.5, 55.9, 55.6, 39.3. **FT-IR (KBr):** 3030, 2924, 1739, 1619, 1552, 1452, 1328, 1261, 1095, 708 cm^{-1}. **ESI HRMS**: calcd. For $C_{23}H_{21}NO_6$ $[M+NH_4]^+$ 425.1707, found 425.1708. **HPLC Analysis:** ee = 80%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 15.9 min, t_{minor} = 24.0 min.

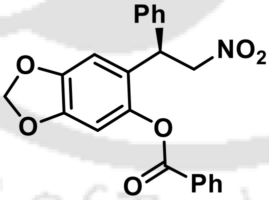
(*S*)-6-(2-nitro-1-phenylethyl)benzo[d][1,3]dioxol-5-yl benzoate (5)



5

This compound was characterized by reported literature [19]. White semi solid 50% (19.5 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 (d, *J* = 7.1 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.24 (dd, *J* = 6.5, 4.2 Hz, 4H), 7.18 – 7.12 (m, 2H), 6.71 (s, 1H), 6.66 (s, 1H), 5.99 (dd, *J* = 7.3, 1.3 Hz, 2H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.93 (dt, *J* = 12.8, 8.9 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.2, 147.6, 146.2, 142.8, 138.3, 134.1, 130.4, 129.1, 129.0, 128.9, 127.8, 127.7, 124.4, 107.3, 105.0, 102.2, 78.3, 42.8. **FT-IR (KBr):** 2923, 1737, 1636, 1554, 1483, 1375, 1261, 1153, 1038, 933 cm^{-1}. **ESI HRMS**: calcd. For $C_{22}H_{17}NO_6$ $[M+NH_4]^+$ 409.1394, found 409.1397. **HPLC Analysis:** ee = 92%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 92/8, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 32.0 min, t_{minor} = 42.0 min.

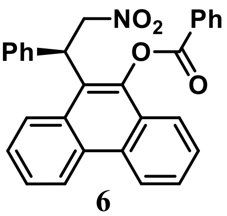
From known literature:



(*R*)-6-(2-nitro-1-phenylethyl)benzo[d][1,3]dioxol-5-yl benzoate. **HPLC Analysis:** ee = 96%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 92/8, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 41.1 min, t_{minor} = 31.8 min.

(*R*)-10-(2-nitro-1-phenylethyl)phenanthren-9-yl benzoate (6)

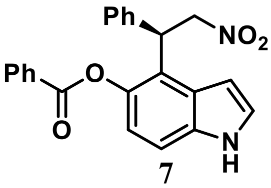
light yellow semi solid, 70% (31.2 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.76 (dd, *J* = 23.1, 6.7 Hz, 2H), 8.25 (s, 2H), 8.02 – 7.38 (m, 9H), 7.23 (d, *J* = 65.2 Hz, 6H), 6.06 (d,



6

J = 4.8 Hz, 1H), 5.56 (dd, *J* = 44.9, 32.4 Hz, 1H), 5.09 (d, *J* = 7.1 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 165.7, 139.2, 134.5, 134.3, 131.6, 130.9, 130.6, 129.2, 129.1, 128.7, 128.5, 128.0, 127.7, 127.5, 127.1, 126.7, 126.3, 125.4, 123.9, 123.7, 123.1, 122.9, 122.7, 78.1, 40.2. **FT-IR (KBr):** 2923, 2852, 1737, 1638, 1554, 1448, 1374, 1240, 1178, 1085, 710 cm^{-1}. **ESI HRMS**: calcd. For $C_{29}H_{21}NO_4$ [M+NH4]$^+$ 465.1808, found 465.1800. **HPLC Analysis:** ee = 92%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 26.8 min, t_{minor} = 31.6 min.

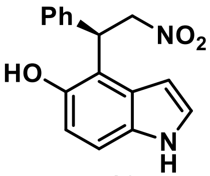
(*R*)-4-(2-nitro-1-phenylethyl)-1H-indol-5-yl benzoate (7)



7

The stereochemistry of this compound **7** was confirmed after base hydrolysis of ester and comparing that HPLC data with known reported literature [20].

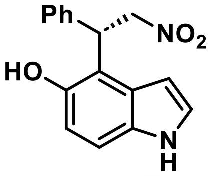
Light yellow semi solid, 60% (23 mg) yield**. ^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.32 (s, 1H), 8.18 – 8.14 (m, 2H), 7.68 – 7.62 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.23 – 7.13 (m, 6H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.44 (s, 1H), 5.59 – 5.52 (m, 1H), 5.38 (dd, *J* = 13.0, 8.6 Hz, 1H), 5.10 (dd, *J* = 13.0, 6.7 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 166.0, 142.7, 139.0, 134.3, 133.8, 130.4, 129.6, 128.8, 127.5, 127.3, 127.2, 125.8, 122.7, 117.8, 111.7, 101.9, 77.6, 42.1. **FT-IR (KBr):** 2924, 1633, 1554, 1493, 1450, 1348, 1267, 1178, 1091, 710 cm^{-1}. **ESI HRMS**: calcd. For $C_{23}H_{18}N_2O_4$ [M+NH$_4$]$^+$ 404.1605, found 404.1605. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 9.0 min, t_{minor} = 11.2 min.



16

HPLC Analysis: ee = 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 12.6 min, t_{minor} = 13.7 min.

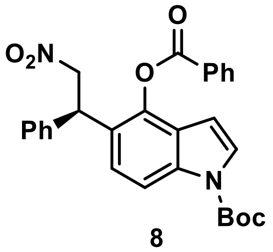
From known literature:



(*S*)-4-(1-Phenyl-2-nitroethyl)-1H-indol-5-ol.

HPLC Analysis: ee = 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 15.3 min, t_{minor} = 13.8 min.

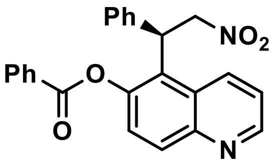
(*R*)-1-((λ^1-methyl)(λ^1-oxidaneyl)boraneyl)-5-(2-nitro-1-phenylethyl)-1H-indol-4-yl benzoate (8)



8

Light green semi solid, 57% (27.7 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.23 (d, *J* = 7.2 Hz, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.56 (dd, *J* = 15.9, 8.0 Hz, 3H), 7.25 – 7.14 (m, 6H), 6.37 (d, *J* = 3.6 Hz, 1H), 5.25 (t, *J* = 8.0 Hz, 1H), 5.05 (ddd, *J* = 20.4, 12.9, 8.1 Hz, 2H), 1.65 (s, 9H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.5, 141.4, 138.8, 130.6, 129.0, 128.9, 127.8, 127.6, 123.8, 114.1, 104.2, 78.6, 42.7, 29.9, 29.8, 28.3. **FT-IR (KBr):** 2924, 2853, 1639, 1555, 1434, 1372, 1340, 1287, 1132, 1022, 764 cm^{-1}. **ESI HRMS**: calcd. For $C_{28}H_{26}N_2O_6$ $[M+NH_4]^+$ 504.2129, found 504.2128. **HPLC Analysis:** ee =84%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 92/8, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 20.6 min, t_{minor} = 30.8 min.

(*R*)-5-(2-nitro-1-phenylethyl)quinolin-6-yl benzoate (9)

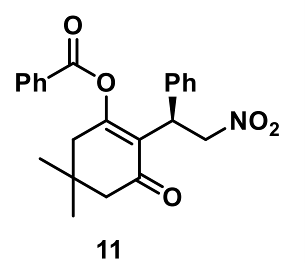


9

Yellow semi solid, 80% (31.8 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.94 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.40 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 8.08 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.58 – 7.50 (m, 3H), 7.44 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.21 – 7.07 (m, 5H), 5.92 (t, *J* = 7.3 Hz, 1H), 5.43

(dd, J = 13.2, 7.9 Hz, 1H), 5.13 (dd, J = 13.2, 6.8 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.9, 150.2, 148.0, 147.4, 138.5, 134.3, 132.2, 131.8, 130.4, 129.2, 129.0, 128.8, 127.6, 127.5, 126.9, 126.5, 126.3, 122.1, 77.9, 40.2. **FT-IR (KBr):** 2924, 2854, 1705, 1557, 1434, 1375, 1362, 1287, 1132, 1064, 764 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{22}NO_4$ [M+H]$^+$ 399.1339, found 399.1343. **HPLC Analysis:** ee = 88%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 15.4 min, t$_{minor}$ = 27.2 min.

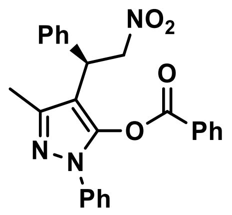
(*R*)-5,5-dimethyl-2-(2-nitro-1-phenylethyl)-3-oxocyclohex-1-en-1-yl benzoate (11)



11

Light yellow semi solid, 55% (21.6 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.13 – 8.05 (m, 2H), 7.68 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.24 – 7.15 (m, 5H), 5.32 – 5.18 (m, 1H), 4.99 (ddd, J = 15.4, 10.4, 6.7 Hz, 2H), 2.65 (d, J = 12.4 Hz, 2H), 1.60 (s, 2H), 1.12 (s, 3H), 1.08 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 198.5, 166.4, 163.3, 138.0, 134.6, 130.5, 129.2, 129.1, 129.1, 128.9, 128.3, 127.7, 127.5, 126.0, 76.9, 51.8, 43.0, 39.6, 33.0, 28.3, 27.9. **FT-IR (KBr):** 2924, 2852, 1639, 1552, 1451, 1375, 1236, 1147, 1081, 736, 656 cm^{-1}. **ESI HRMS**: calcd. For $C_{23}H_{23}NO_5$ [M+H]$^+$ 394.1649, found 394.1656. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 11.1 min, t$_{minor}$ = 12.0 min.

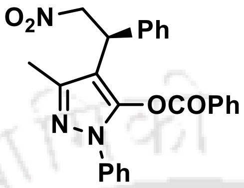
3-methyl-4-(*R*)-2-nitro-1-phenylethyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl benzoate (13)



13

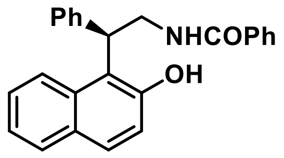
This compound was characterized by reported literature [21]. light yellow semi solid, 60% (25.6 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.07 – 8.00 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 4H), 7.34 (t, J = 7.8 Hz, 2H), 7.29 – 7.19 (m, 6H), 5.06 – 4.85 (m, 3H), 2.24 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 163.4, 147.7, 142.1, 137.9, 137.7, 134.9, 130.7, 129.4, 129.1, 129.1, 127.7, 127.6, 127.5, 127.31, 123.0, 107.1, 77.5, 39.0, 13.6. **FT-IR (KBr):** 2924, 2853, 1639, 1553, 1451, 1315, 1235, 1178, 1011, 759, 696 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{21}N_3O_4$ $[M+NH_4]^+$ 428.1605, found 428.1618. **HPLC Analysis:** ee = 89%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 8.0 min, t_{minor} = 10.5 min.

From known literature:



3-methyl-4-(*S*)-2-nitro-1-phenylethyl)-1-phenyl-4,5-dihydro-1H-pyrazol-5-yl benzoate. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 11.94 min, t_{minor} = 8.6 min.

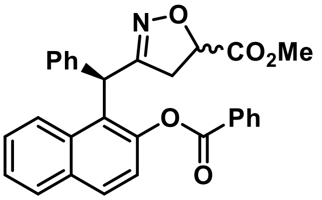
(*R*)-*N*-(2-(2-hydroxynaphthalen-1-yl)-2-phenylethyl)benzamide (14)



14

White solid, 95% (38 mg) yield. **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 9.64 (s, 1H), 8.48 – 8.34 (m, 1H), 7.97 (s, 1H), 7.72 – 7.59 (m, 4H), 7.42 – 7.28 (m, 6H), 7.19 – 7.01 (m, 5H), 5.28 (s, 1H), 4.65 – 4.51 (m, 1H), 3.84 – 3.70 (m, 1H). **^{13}C NMR (100 MHz, DMSO-d$_6$)** δ 166.8, 153.7, 143.7, 135.3, 131.3, 129.0, 128.8, 128.6, 128.4, 128.3, 127.5, 125.9, 122.5, 120.6, 119.2, 60.2, 42.8. **FT-IR (KBr):** 2924, 2853, 1639, 1553, 1451, 1315, 1235, 1178, 1011, 759, 696 cm^{-1}. **ESI HRMS**: calcd. For $C_{25}H_{16}NO_2$ $[M+NH_4]^+$ 368.1645, found 368.1643. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 93/7, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 43.4 min, t_{minor} = 48.5 min.

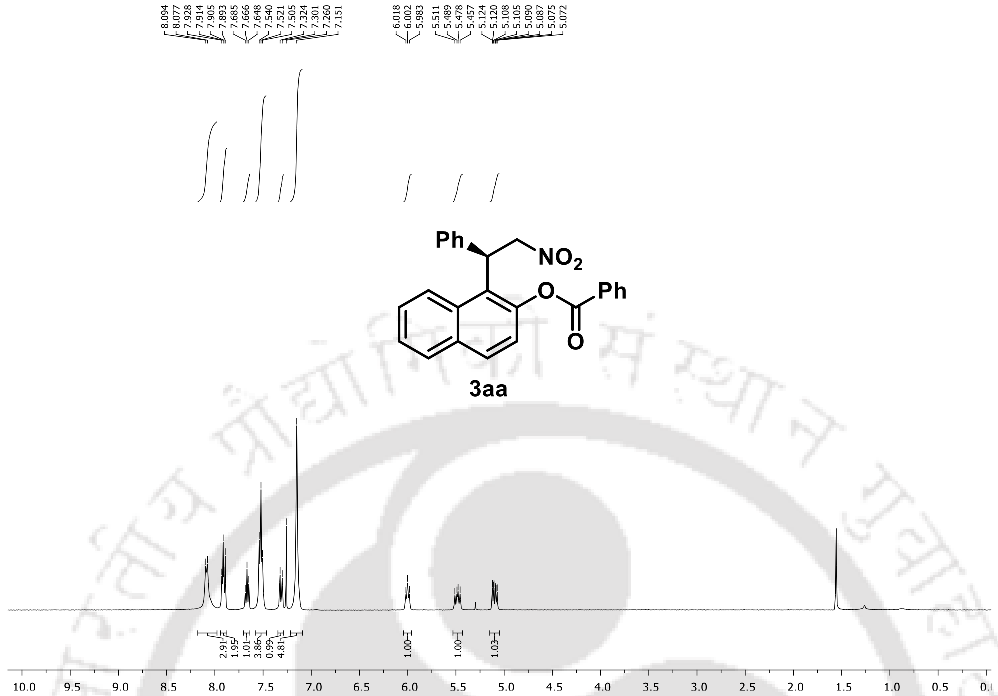
Methyl 3-(*R*)-(2-(benzoyloxy)naphthalen-1-yl)(phenyl)methyl)-4,5-dihydroisoxazole-5-carboxylate (15/15')

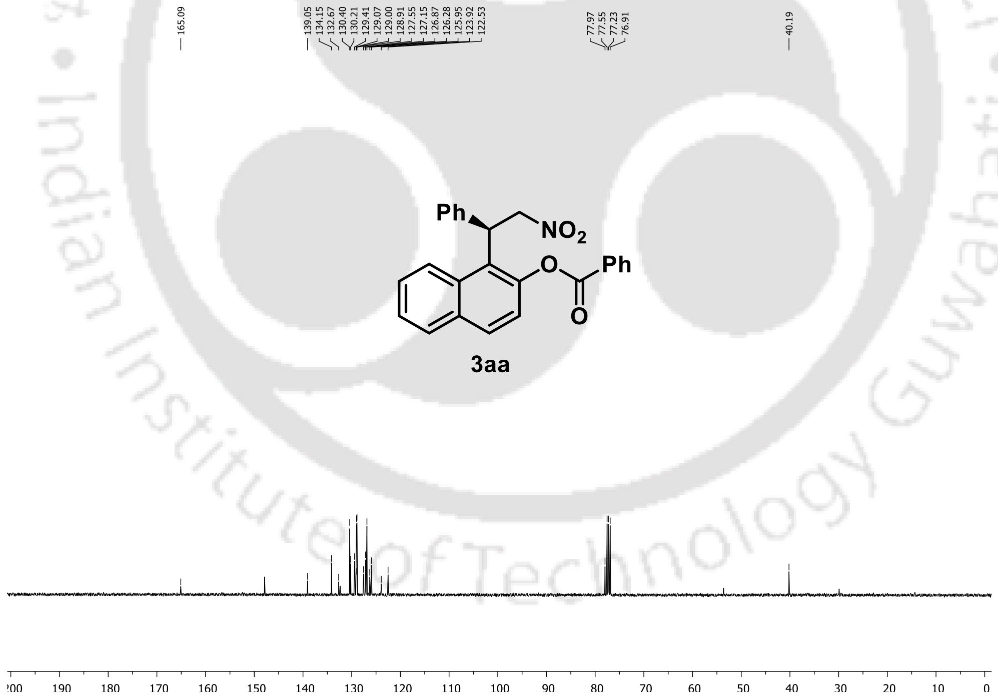


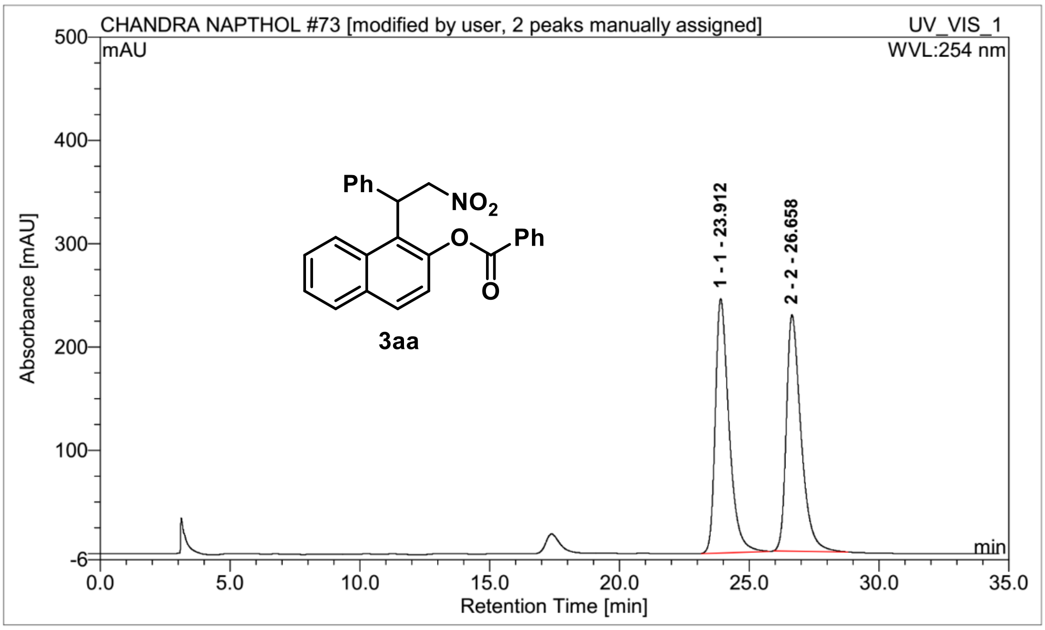
15/15'

Red semi solid, 65% (26 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.09 (d, J = 7.6 Hz, 1H), 8.04 (d, J = 7.9 Hz, 3H), 7.99 (s, 2H), 7.92 (t, J = 7.6 Hz, 4H), 7.63 (dd, J = 11.0, 7.4 Hz, 2H), 7.48 (dd, J = 9.2, 4.7 Hz, 9H), 7.39 (d, J = 2.1 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 7.4 Hz, 2H), 7.25 – 7.12 (m, 8H), 6.19 (s, 1H), 6.03 (s, 1H), 4.96 – 4.87 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.29 – 3.09 (m, 4H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 170.9, 170.8, 165.3, 165.2, 158.9, 158.9, 158.7, 158.7, 147.9, 147.9, 138.6, 138.0, 138.0, 134.1, 134.1, 134.0, 134.0, 132.6, 132.6, 130.5, 130.5, 130.4, 130.4, 130.3, 130.3, 130.2, 130.2, 129.2, 129.2, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 127.9, 127.9, 127.3, 127.3, 127.2, 127.2, 127.0, 127.0, 126.9, 126.9, 125.9, 125.9, 125.9, 125.9, 125.0, 125.0, 124.9, 124.8, 124.2, 124.8, 122.5, 122.5, 122.4, 122.4, 77.7, 77.7, 77.6, 77.6, 77.5, 52.8, 52.8, 52.7, 52.7, 42.2, 42.2, 41.7, 41.7, 41.6, 41.6, 40.9, 40.9. **IR (KBr):** 2924, 2853, 1639, 1553, 1451, 1315, 1235, 1178, 1011, 759, 696 cm-1. **ESI HRMS:** calcd. For $C_{29}H_{17}NO_5$ [M+NH$_4$]$^+$ 466.1649, found 466.1654. **HPLC Analysis:** Major dr ee = 90%, Minor dr ee = 89%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (major dr) t_{major} = 36.8 min, t_{minor} = 22.4 min, (Minor dr) t_{major} = 47.4 min, t_{minor} = 20.3 min.

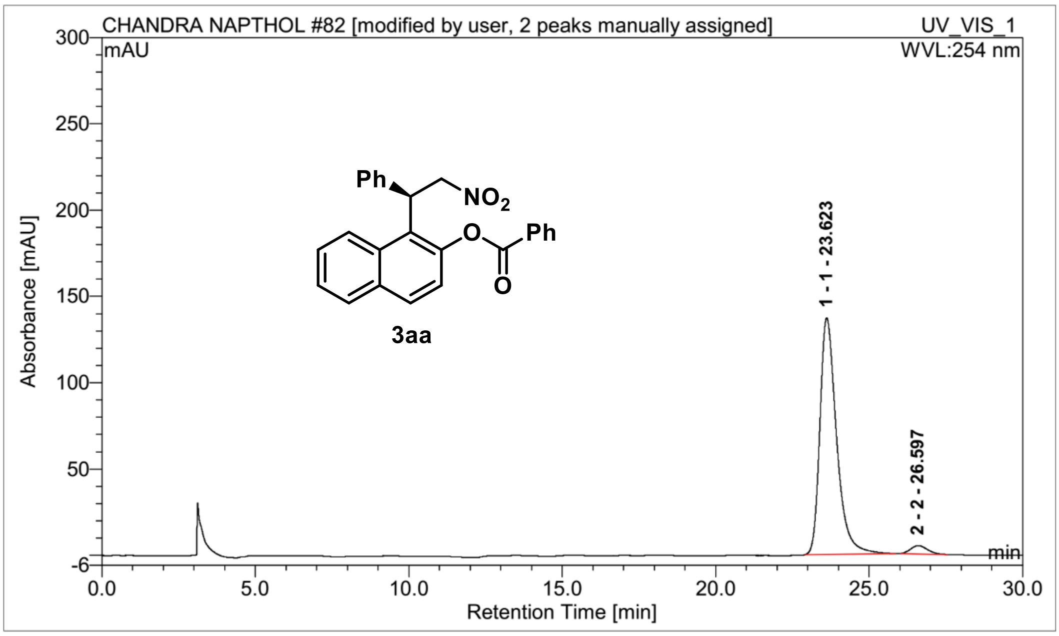
2.9 NMR and HPLC spectra of the products







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	23.91	150.0356	50.13772933	245.8428	n.a.
2	2	26.66	149.211	49.86227067	228.461	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	23.62	86.31921	96.66280413	137.1281	n.a.
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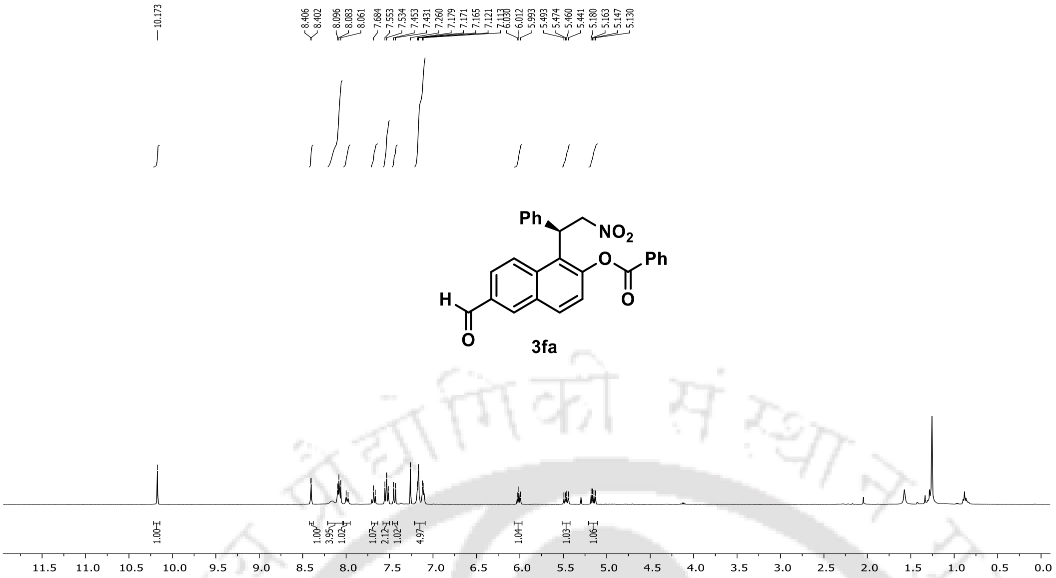
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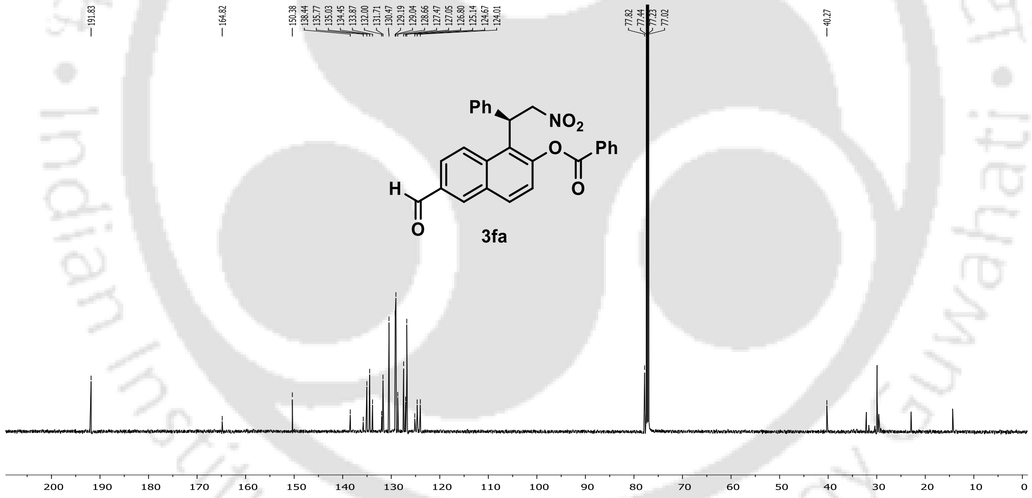
7.171
7.165
7.121
7.113
6.030
6.012
5.993
5.493
5.474
5.460
5.441
5.180
5.163
5.147
5.130
Ph
NO2
O
Ph
O
H
O
3fa
1.00
1.00
3.95
1.02
1.07
2.12
1.02
4.97
1.04
1.03
1.06
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0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128.66
127.47
127.05
126.80
125.14
124.67
124.01
77.82
77.44
77.23
77.02
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Ph
NO2
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H
O
3fa
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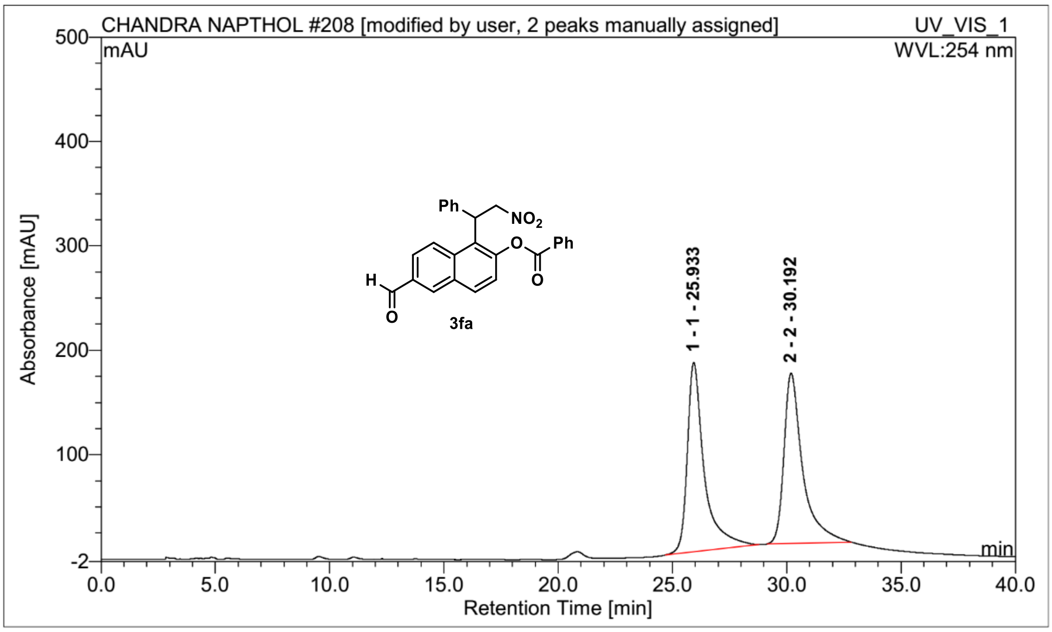
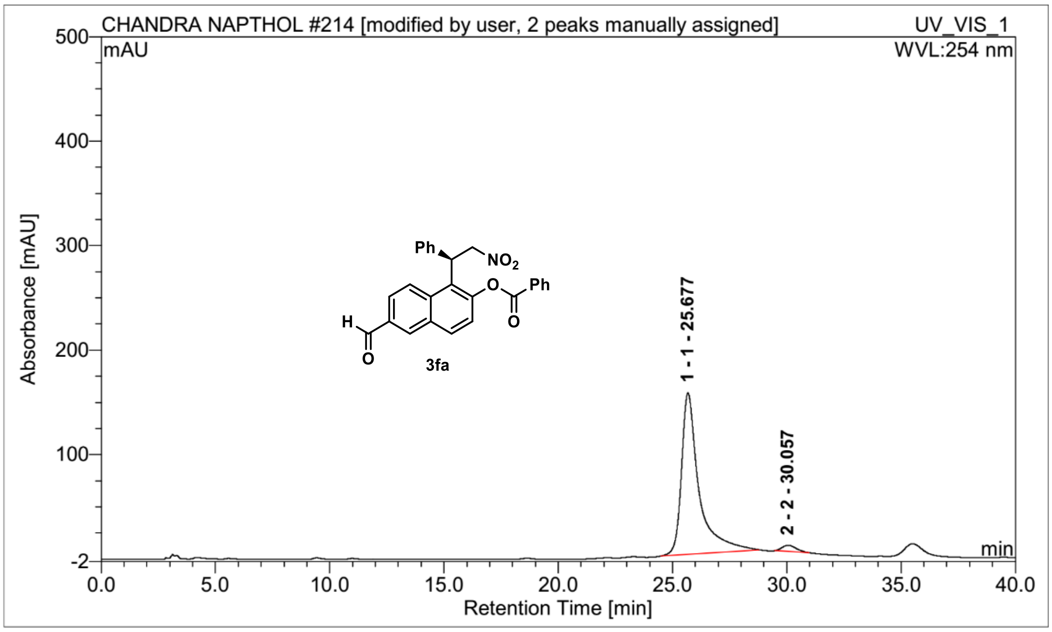


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	25.93	156.6524	50.24251095	181.2582	n.a.
2	2	30.19	155.140	49.75748905	163.165	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	25.68	137.5331	97.03009049	154.5052	n.a.
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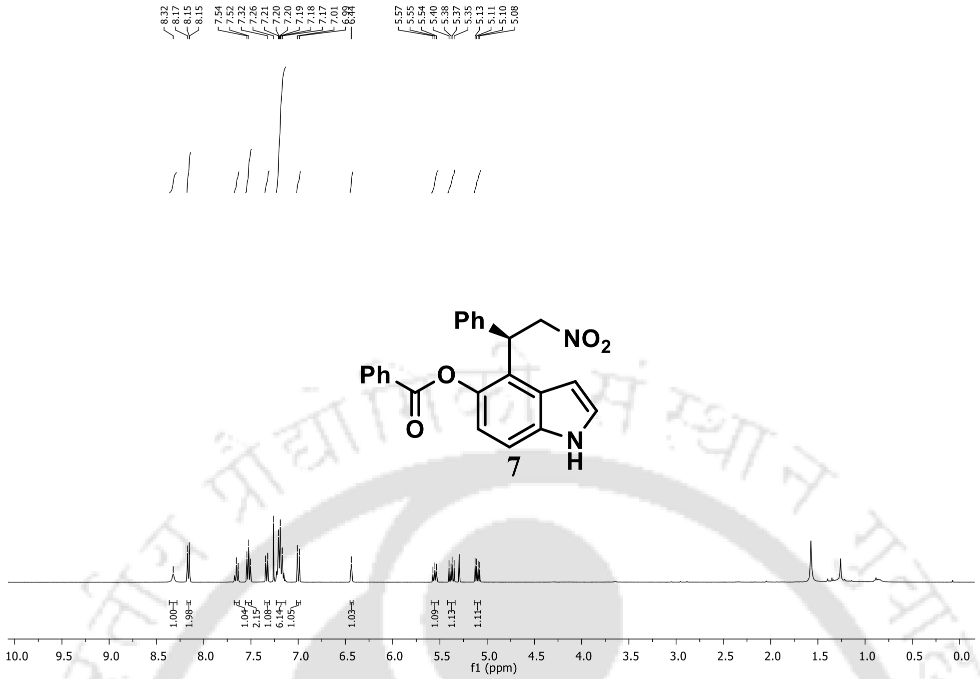
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7.17
7.01
6.99
6.44
5.57
5.55
5.54
5.40
5.38
5.37
5.35
5.13
5.11
5.10
5.08
Ph
NO2
Ph
O
O
N
H
7
1.00
1.99
1.04
2.15
1.08
6.14
1.05
1.03
1.09
1.13
1.11
10.0
9.5
9.0
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8.0
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7.0
6.5
6.0
5.5
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4.5
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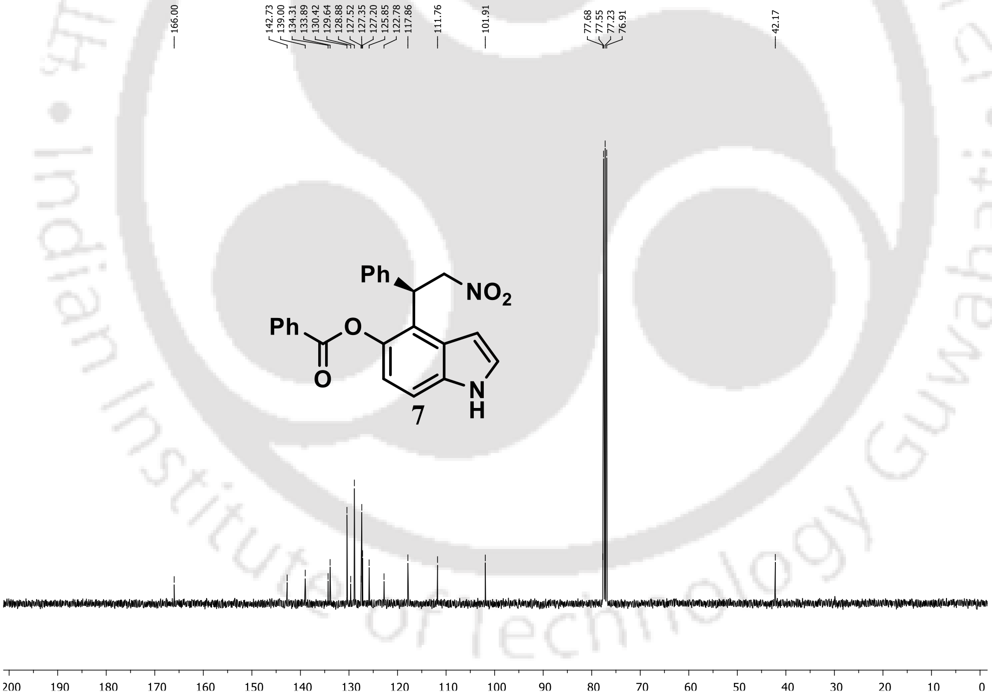
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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128.88
127.52
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122.78
117.86
111.76
101.91
77.68
77.55
77.23
76.91
42.17
Ph
NO2
Ph
O
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N
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50
40
30
20
10
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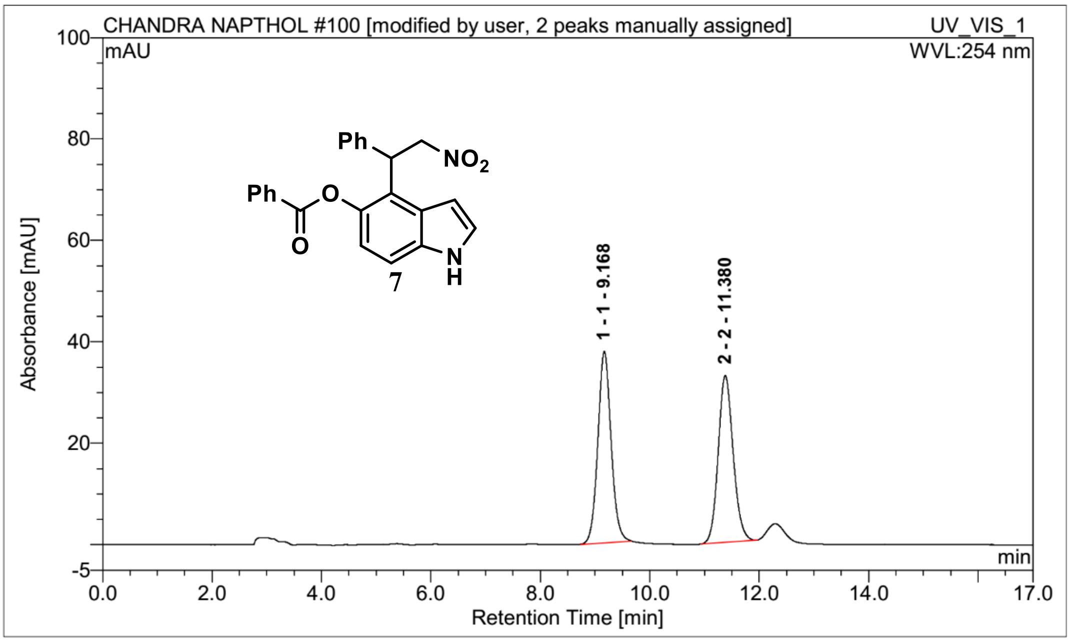

No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.17	10.57269	50.44082786	37.76749	n.a.
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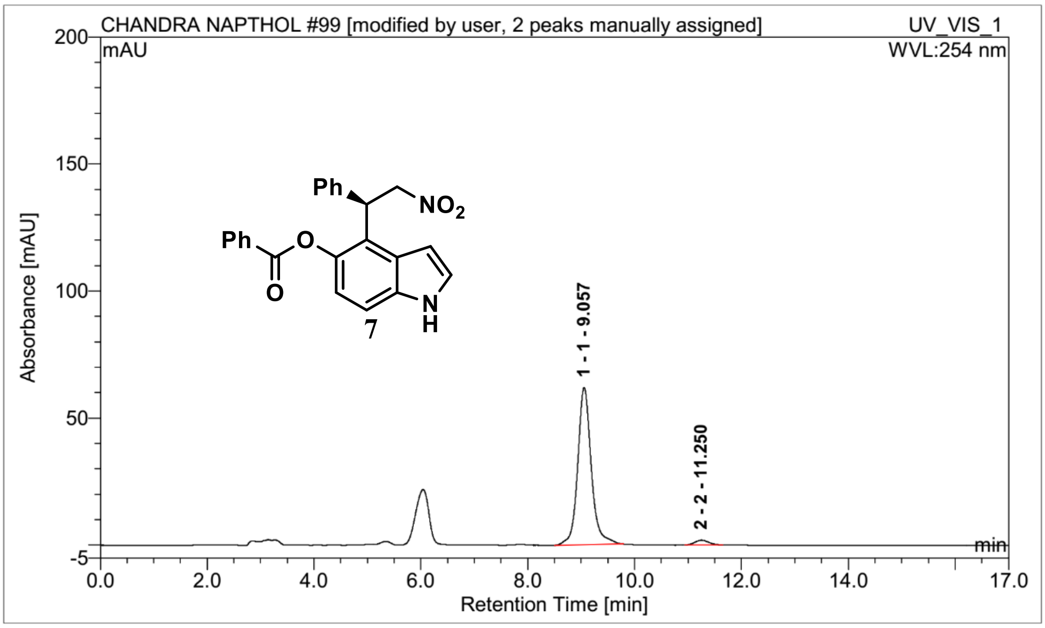
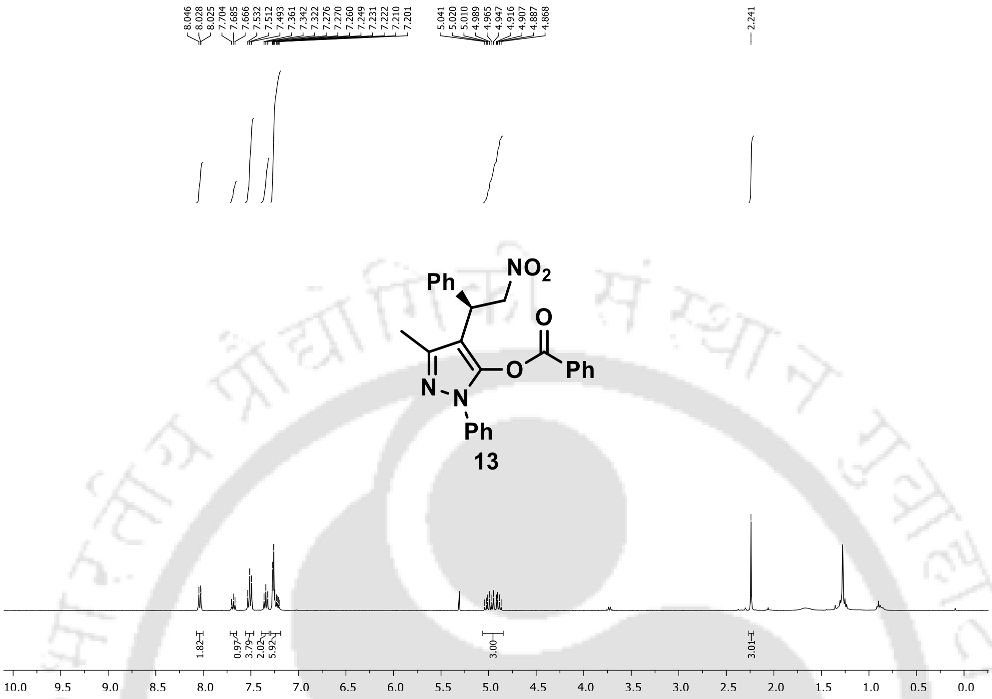


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.06	18.19122	97.01746694	61.93246	n.a.
2	2	11.25	0.559	2.982533062	1.860	n.a.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7.276
7.270
7.260
7.249
7.231
7.222
7.210
7.201
5.041
5.020
5.010
4.989
4.965
4.947
4.916
4.907
4.887
4.868
2.241
Ph
NO2
O
O
Ph
N
N
Ph
13
1.82
0.97
3.79
2.02
5.92
3.00
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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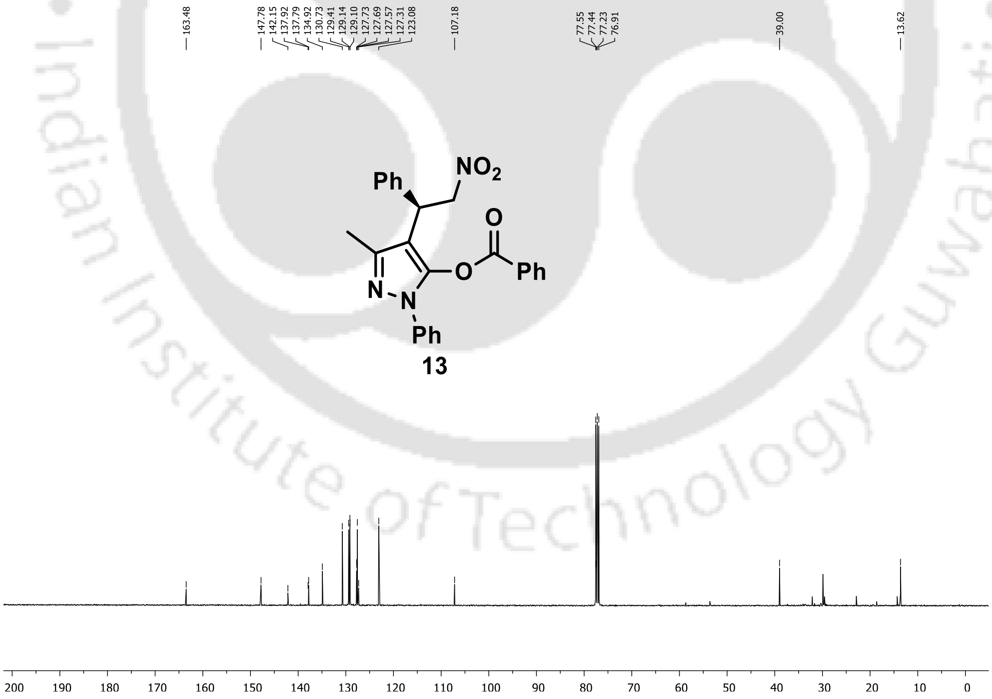
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129.10
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127.57
127.31
123.08
107.18
77.55
77.44
77.23
76.91
39.00
13.62
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O
O
Ph
N
N
Ph
13
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70
60
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40
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20
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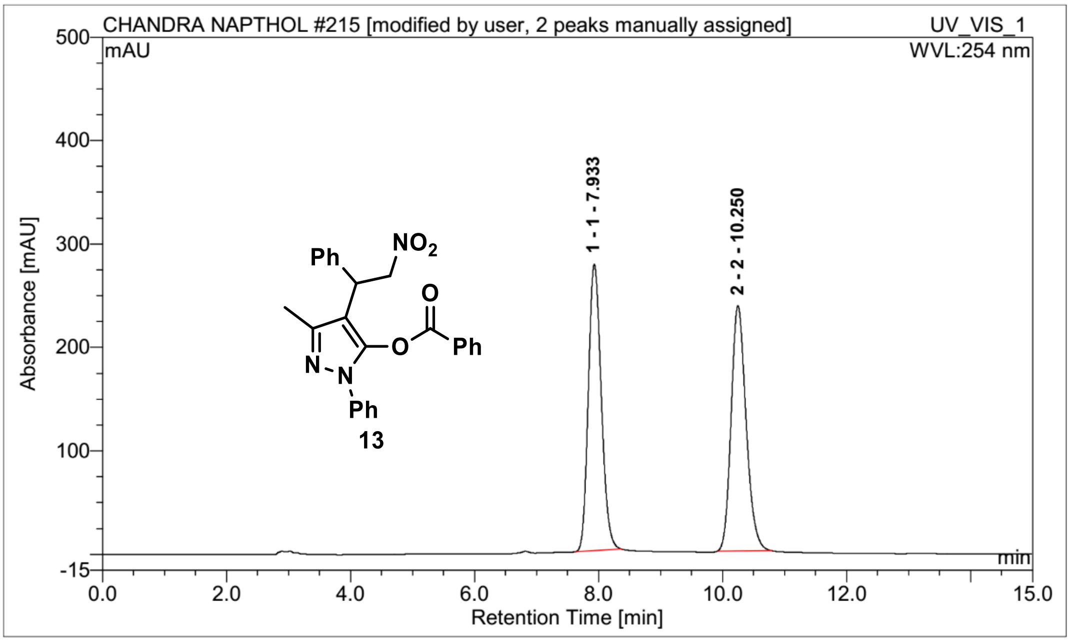
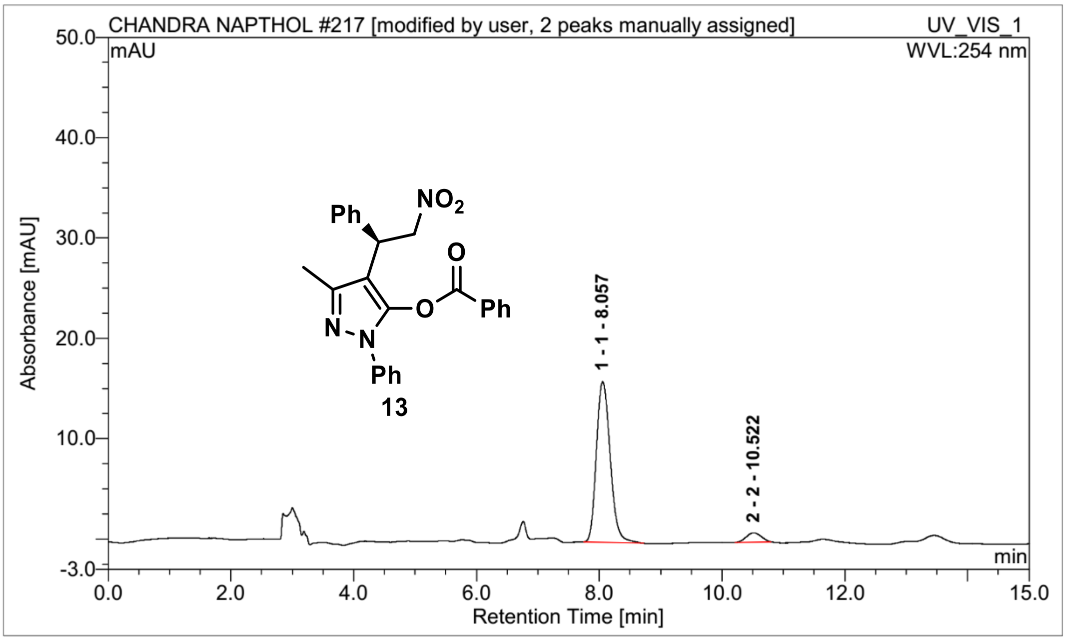


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	7.93	66.77523	50.15474177	277.012	n.a.
2	2	10.25	66.363	49.84525823	237.316	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.06	4.174897	94.07590722	16.00823	n.a.
2	2	10.52	0.263	5.924092778	0.929	n.a.

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(7) For selected examples, see: (a) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Chen, J.-P. *Org. Lett.* **2010**, *12*, 1096. (b) Enders, D.; Seppelt, M.; Beck, T. *Adv. Synth. Catal.* **2010**, *352*, 1413. (c) Li, G.-X.; Qu, J. *Chem. Commun*. **2012**, *48*, 5518.

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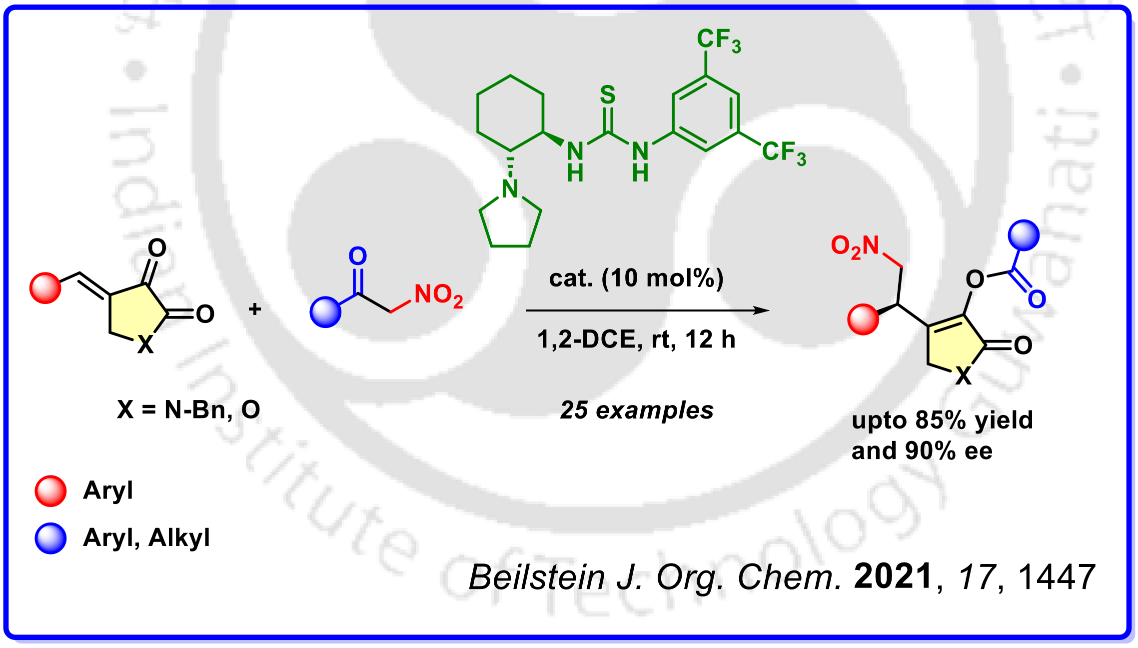
(21) Maity, R.; Gharui, C.; Sil, A. K.; Pan, S. C. *Org. Lett*. **2017**, *19*, 662.

Chapter 3

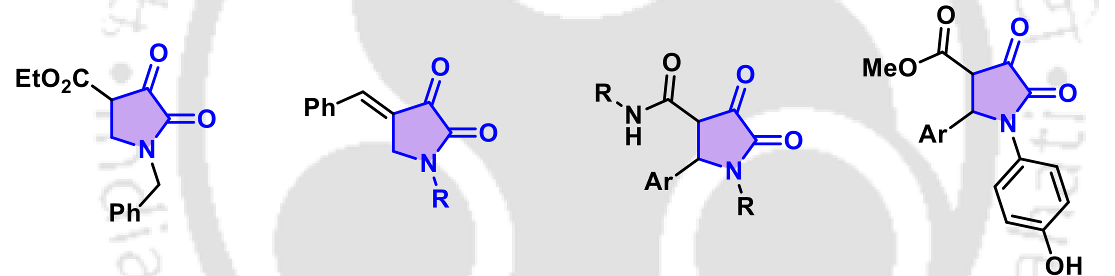
Organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones

ABSTRACT: An organocatalytic asymmetric Michael/acyl transfer reaction between *α*-nitroketones and 4-arylidenepyrrolidine-2,3-diones is reported. A bifunctional thiourea catalyst was found to be effective for this reaction. With 10 mol % of the catalyst, good results were attained for a variety of 1,5-dihydro-2H-pyrrol-2-ones under mild reaction conditions.



3.1 Introduction

Compounds containing the pyrrolidine ring are widely distributed in nature. Pyrrolidinediones and related compounds play an important role in organic synthesis, as well as in modern therapeutics due to their wide range of biological and pharmacological activities. A number of functionalized pyrrolidine-2,3-diones are receiving attention from the point of view of interesting biological activities. 1-Benzyl-4-carboethoxy-2,3-pyrrolidinedione is reported as a highly specific aldose reductase inhibitor **A**,[1] and a series of the 4-arylidene derivatives have been found to be inhibitors of blood platelet aggregation **B**.[2] A number of 4-carboxamido-2,3-pyrrolidinediones have been reported as potent HIV-1 inhibitors **C**,[3] and a series of chiral peptide derivatives related to 2,3-pyrrolidinedione have good anti-inflammatory and analgesic activities **D**.[4] In addition, the total synthesis of leopolic acid A, a natural 2,3-pyrrolidinedione, with antimicrobial activity has been reported **E** (Figure 1).[5]

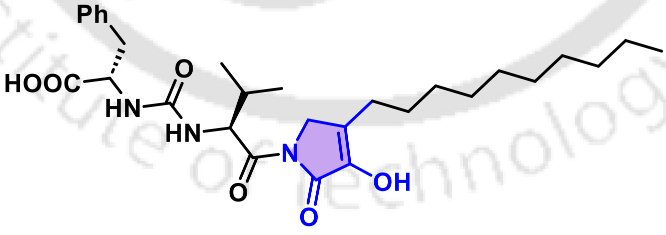


A
Aldose reductase inhibitor

B
Inhibitior of blood platelet aggregation

C
HIV inhibitor

D
Antimicrobial



E
Leopolic acid
Antimicrobial

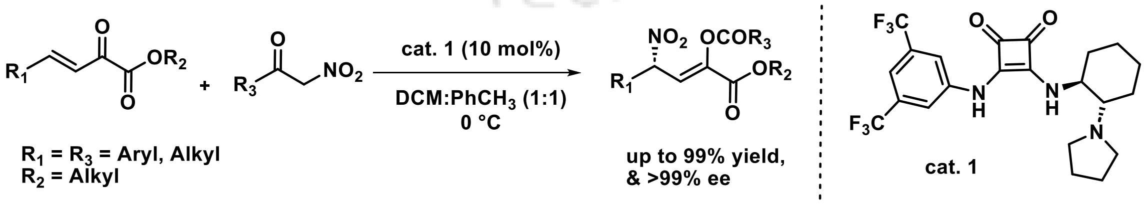
Figure 1: A number of bioactive 2,3-pyrrolidinediones

The Michael reaction is a powerful reaction that has been so far applied for the formation of carbon–carbon and carbon–heteroatom bonds in organic synthesis[6,7]. After the renaissance of organocatalysis in the year 2000, this field has been applied tremendously for the development of catalytic asymmetric conjugate addition reactions[8-10]. In particular, the conjugate addition of nitroalkanes and their derivatives to enones has drawn the attention of organic chemists as the corresponding products can be chemoselectively converted to a variety of useful structures[11]. Thus, a variety of methods has been developed with a range of different catalysts[12-14]. One of the challenges is to employ highly substituted enones in the reaction. Indeed, additional substituents, especially at the *α*-position of enones/activated olefins, decreases the reactivity significantly because of unfavourable steric interactions. To overcome this problem, reactive Michael donors must be used to achieve a good conversion in the reaction. In recent years, α-nitroketones have emerged as active nucleophiles in Michael reactions and a range of substrates have been explored[15]. Also, *α*-nitroketones have been found to be a popular nucleophilic acyl transfer reagent.

3.2 Literature Survey

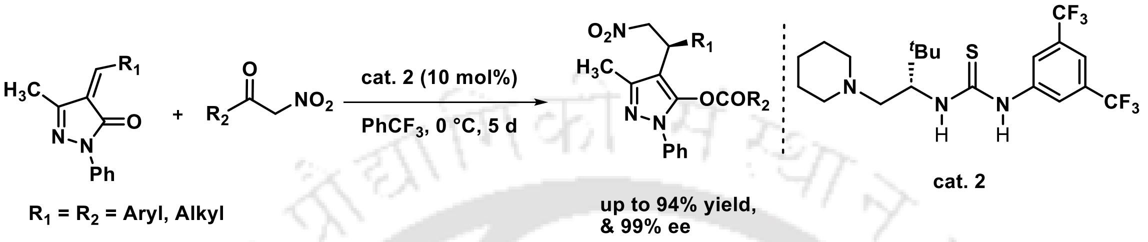
3.2.1 Previous reports on enantioselective acyl transfer reactions using *α*-nitroketones:

In 2011, Yan et al. reported[16], organocatalytic asymmetric conjugate addition of *α*-nitroketones to *β*,*γ*-unsaturated *α*-keto esters. A pyrrolidine-based thiourea–tertiary amine was identified as the best catalyst. The reaction was found to proceed *via* cascade conjugate addition and acyl transfer reaction. 5-Nitro-2-acyloxypent-2-enoates were obtained in good yields (up to 99%) and enantioselectivities (up to 99% ee) (Scheme 1).



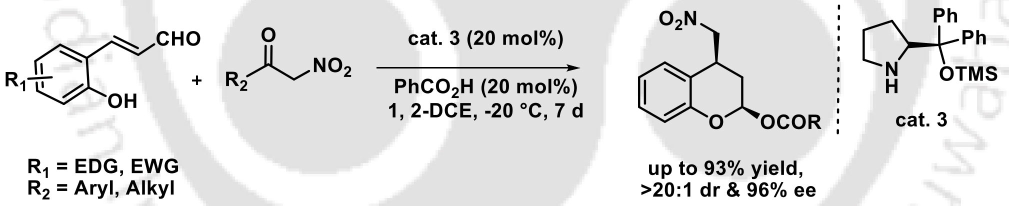
Scheme 1: Reaction of α-nitroketones to *β*,*γ*-unsaturated *α*-keto esters

In 2017, Pan *et al*. reported[17], an organocatalytic asymmetric cascade Michael/hemiketalization/retro-aldol reaction between unsaturated pyrazolones and α-nitroketones. A bifunctional thiourea catalyst was found to be efficient for this reaction. With 10 mol % of catalyst, high yields as well as excellent enantioselectivities are attained for a variety of 3-acyloxy pyrazoles under mild reaction conditions (Scheme 2).



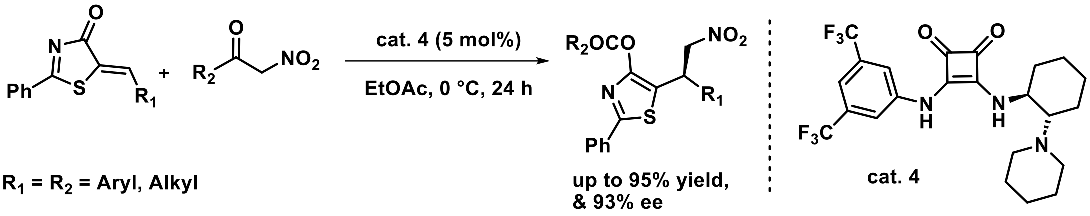
Scheme 2: Reaction between unsaturated pyrazolones and α-nitroketones.

Later in 2018, Pan *et al.* reported[18], an organocatalytic asymmetric cascade Michael/hemiketalization/acyl transfer reaction between *o*-hydroxycinnamaldehydes and α-nitroketones. Prolinol TMS ether catalyst in combination with benzoic acid was found to be the most effective for this reaction which proceeds through an equilibrium of lactols to provide a single diastereomer of enantiopure 2,4-disubstituted chromans (Scheme 3).



Scheme 3: Reaction between *o*-hydroxycinnamaldehydes and α-nitroketones

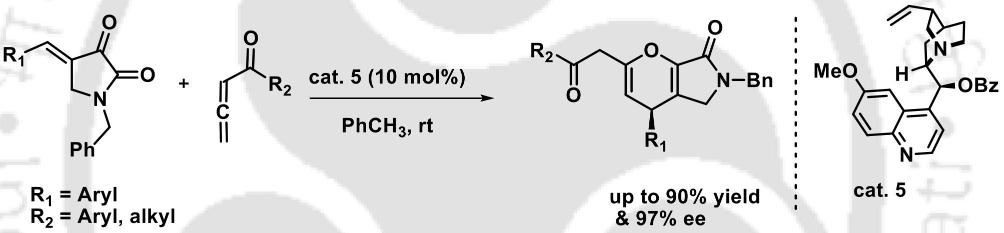
After that in 2019, Du *et al.* reported[19], an efficient and practical organocatalytic asymmetric cascade Michael/hemiketalization/retro-aldol reaction of unsaturated thiazolones with α-nitroketones by using cyclohexanediamine-derived bifunctional squaramide as the catalyst. Under mild conditions, a broad range of chiral 4-acyloxythiazole derivatives were obtained in high yields (up to 98% yield) with excellent enantioselectivities (up to 95% *ee*) (Scheme 4).



Scheme 4: Reaction between unsaturated thiazolones with α-nitroketones.

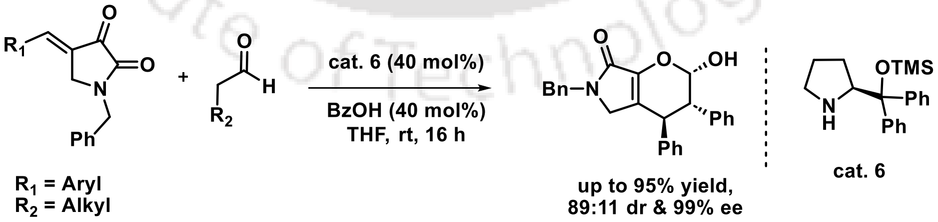
3.2.2 Previous reports on enantioselective reaction of 4-Arylidene-pyrrolidine-2,3-diones:

In 2015, Xu *et al.* reported[20], an efficient cinchona alkaloid-derived amine catalyzed asymmetric [4 + 2] cycloaddition reaction. 4*H*-Pyran fused pyrrolin-2-one products are readily obtained in moderate to high yields with good enantioselectivites by employing allene ketones and 2,3-dioxopyrrolidine derivatives as substrates (Scheme 5).



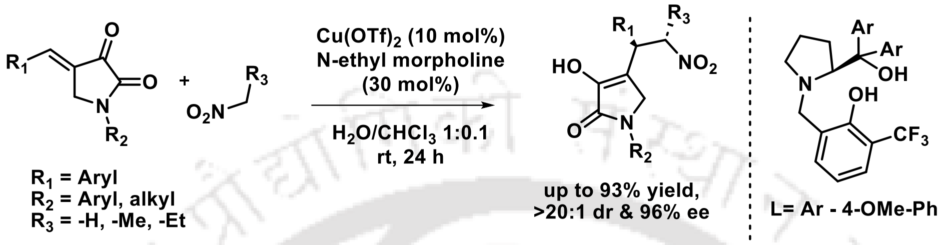
Scheme 5: Reaction between allene ketones and 2,3-dioxopyrrolidine.

In 2016, Gou *et al.* reported[21], a highly enantioselective organocatalytic inverse-electron-demand *oxo*-Diels–Alder reaction involving aqueous acetaldehyde. The reaction, in which cyclic enones serve as dienes in the presence of readily available secondary amine catalysts, allows facile construction of optically active bicyclic dihydropyrans (Scheme 6).



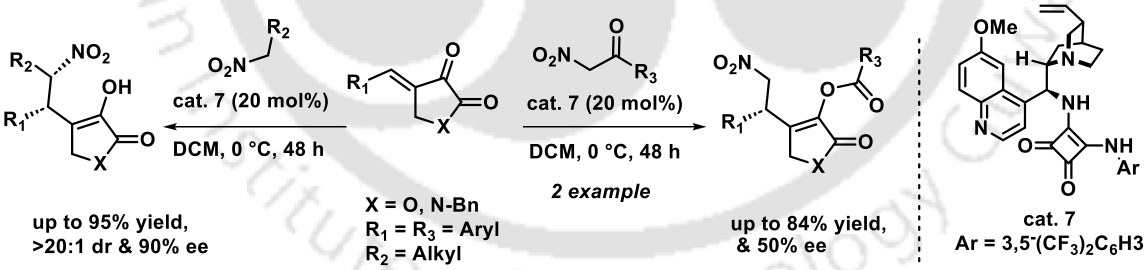
Scheme 6: Reaction between aqueous acetaldehyde and 2,3-dioxopyrrolidine.

In 2020, Wang *et al*. reported[22], a good diastereo- and enantioselective 1,4-addition Michael reaction catalyzed by a chiral copper complex in aqueous media. A series of nitro-containing pyrrolidones could be gained in high yields with excellent diastereoselectivities and good ee values by virtue of this developed method. It affords a facile access to construct carbon–carbon bonds with water and air tolerance (Scheme 7).



Scheme 7: Michael reaction between nitromethane and 2,3-dioxopyrrolidine in aqueous media.

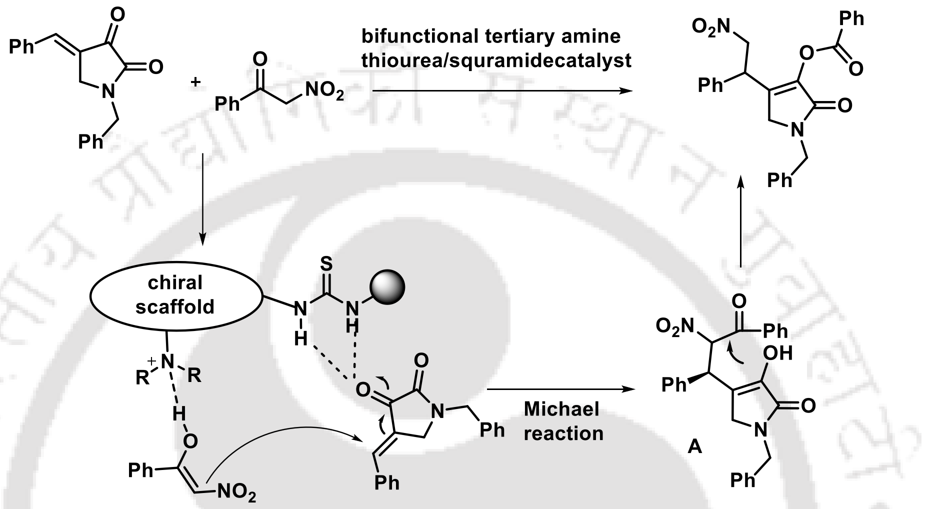
Later in 2020, during the progress of our work Bugaut *et al*. reported[23] organocatalyzed addition of various nitroalkanes to *β*-arylidene-*α*-ketolactones and *α*-ketolactams. The highly functionalized products and were obtained with moderate to good yields and diastereocontrol, but with high enantioselectivities. They have also shown two examples for the reaction of 2-nitroacetophenone with 4-benzylidenepyrrolidine-2,3-dione and only moderate enantioselectivity (50% ee) was found (Scheme 8).



Scheme 8: Synthesis of *β*-arylidene-*α*-ketolactones and *α*-ketolactams.

3.3 Concept:

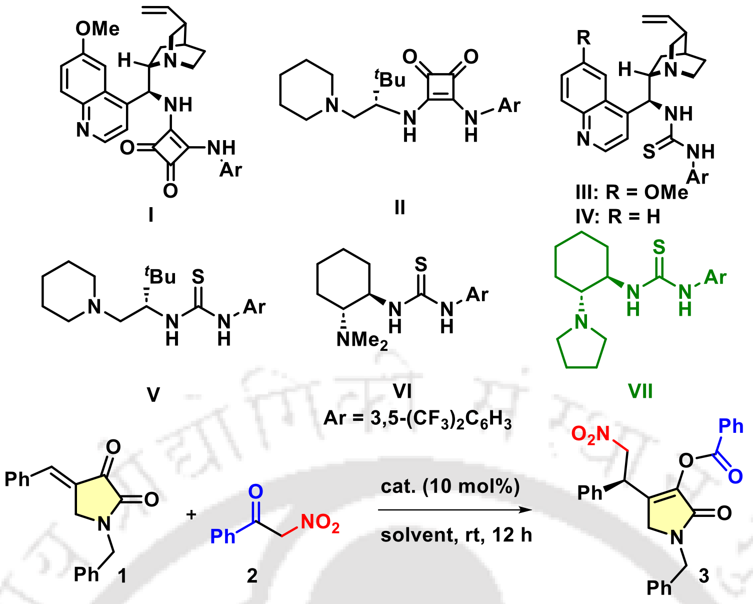
From the previous literature survey, we found that 4-arylidenepyrrolidine-2,3-diones have been explored mainly for the preparation of bicyclic dihydropyran derivatives through the catalytic inverse-electrondemand hetero-Diels–Alder reaction. So, we postulated that 4-arylidenepyrrolidine-2,3-diones could also be suitable reaction partners of asymmetric acyl transfer reaction with α-nitroketones. We postulate that enol form of α-nitroketone and 4-arylidenepyrrolidine-2,3-diones might be activated by the bifunctional thiourea/squaramide catalysts. After this, domino Michael/acyl transfer reaction will provide the desired products in an enantioselective fashion (Scheme 9).



Scheme 9: Proposed route to 1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate derivatives.

3.4 Result and Discussion:

Thus, initially a model reaction was examined between *N*-benzyl-4-benzylidenepyrrolidine-2,3-dione (**1a**) and 2-nitro-1-phenylethanone (**2a**) in the presence of the quinine-derived bifunctional squaramide catalyst **I** in dichloromethane at room temperature (Table 1). Delightfully, after stirring for 12 hours, a product was isolated in 70% yield that was characterized as compound **3a** and was supposed to be formed through conjugate addition followed by benzoyl-transfer reaction. However, only 20% enantiomeric excess was achieved. Then, the *tert*-leucine derived squaramide catalyst **II** was employed and here both yield and ee slightly improved. Next, we turned our attention to bifunctional thiourea catalysts that proved to be fruitful. Thus, the quinine and



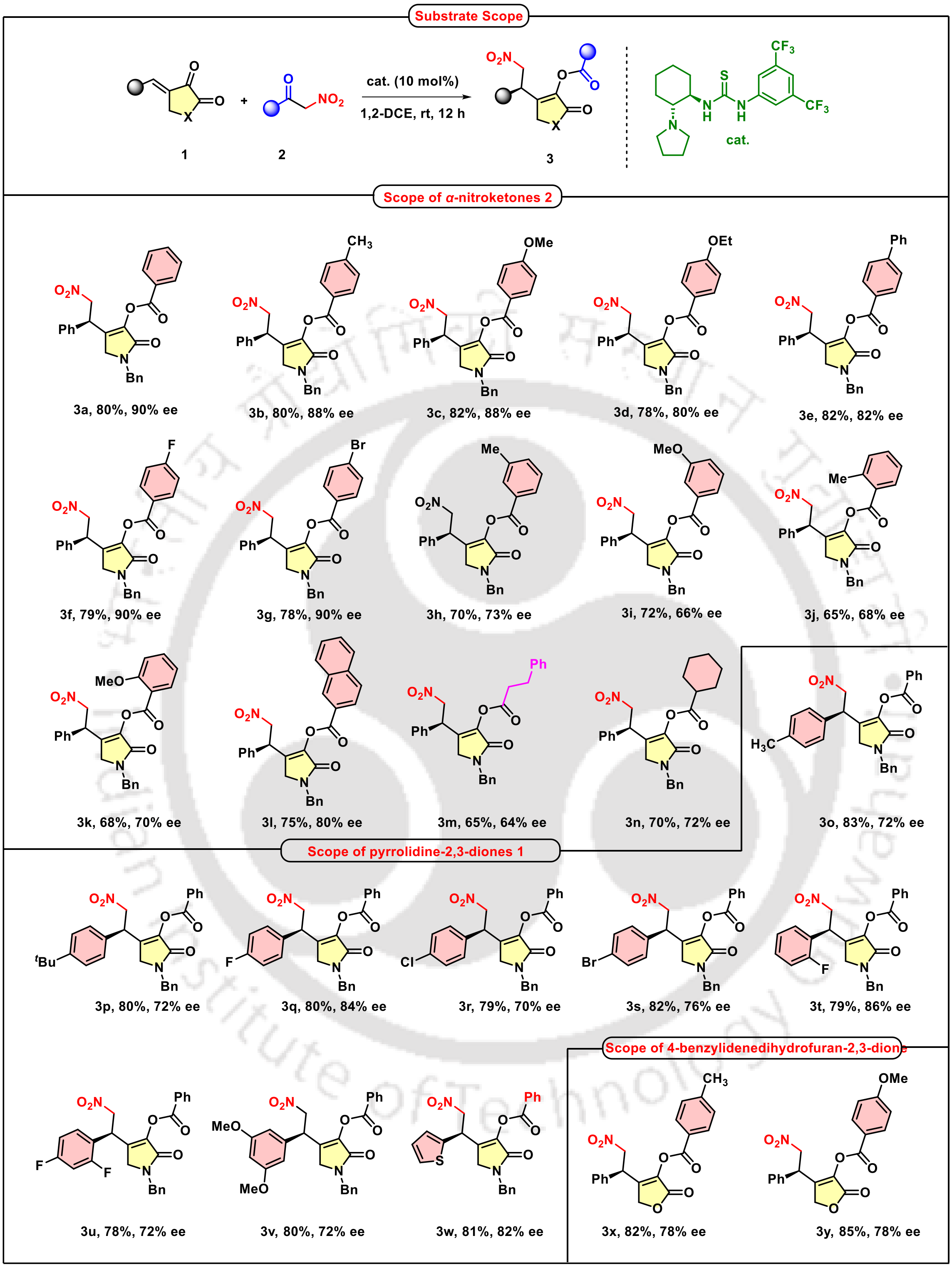
entry[a]	catalyst	solvent	Yield (%)[b]	ee (%)[c]
1	I	CH_2Cl_2	70	20
2	II	CH_2Cl_2	73	34
3	III	CH_2Cl_2	76	55
4	IV	CH_2Cl_2	78	52
5	V	CH_2Cl_2	80	74
6	VI	CH_2Cl_2	75	50
7	VII	CH_2Cl_2	80	80
8	VII	$PhCH_3$	80	75
9	VII	$PhCF_3$	79	78
10	VII	THF	60	80
11	VII	$CHCl_3$	81	86
12	**VII**	**$(CH_2Cl)_2$**	**82**	**90**
13[d]	VII	$(CH_2Cl)_2$	80	85
14[e]	VII	$(CH_2Cl)_2$	75	60

[a] Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2** in 0.6 mL solvent at 25 °C for 12 hours. [b] isolated yield after silica gel column chromatography. [C] determined by chiral HPLC. [d] Reaction carried with 5 mol% of catalyst. [e] Reaction carried out at 0 °C for 2 d.

Table 1: Catalyst, solvent and reaction condition optimization,

cinchonidine-derived bifunctional thiourea catalysts **III** and **IV** were employed in the reaction and moderate enantiomeric excesses were achieved. The yield and enantioselectivity further improved when using the *tert*-leucine derived thiourea catalyst **V**. Also, Takemoto's catalyst **VI** was suitable for the reaction though a moderate enantiomeric excess was detected. Finally, the best catalyst turned out to be the pyrrolidine-containing bifunctional thiourea catalyst **VII** and the desired product was isolated in 80% yield with 80% ee. Then, solvent optimization was carried out to obtain better enantioselectivities. A similar enantioselectivity was attained in $PhCF_3$ and THF as the solvent, whereas in $CHCl_3$ a slightly improved enantioselectivity of 86% ee was observed. Finally, the best solvent was found to be 1,2-DCE and the product **3a** was obtained in 82% yield with 90% ee. After that the reaction was carried with 5 mol% of catalyst as well as in at 0℃ for 2 days, but decrease in enantioselectivity was observed (entry 12 and 13).

After having identified the optimized conditions, we ventured in the scope and generality of the reaction. Initially a variety of *α*-nitroketones **1** having different aryl substituents were tested (scheme 10). In fact, different *ortho*-, *meta*-, and *para*-substitutions on the phenyl group were compatible with the reaction conditions and satisfactory results were obtained (**3a-3n**). For example, at first different electron donating groups at the *para* position (-Me, -OMe and -OEt) was checked and the products **3b**, **3c** and **3d** were obtained with 88%, 88% and 80% ee respectively. Also, a biphenyl group was tolerated and a good result was achieved (**3e** with 82% ee). Then, 4-fluoro and 4-bromo-containing nitroketones **2f** and **2f** and **2g** were employed in the reaction and gratifyingly the same 90% ee were obtained for both products **3f** and **3g** (Scheme 10). *meta*-Substitutions were also tolerated in the reaction although decreased enantioselectivities were detected for the products **3h** and **3i**. Then, *o*-methyl- *and o*-methoxyphenyl-substituted nitroketones **2j** and **2k** provided products **3j** and **3k** in moderate yields and enantioselectivities. The 2-naphthyl-substituted nitroketone **2l** also participated in the reaction to deliver **3l** in 80% ee. Moreover, the alkyl substituted nitroketone like hydrocinnamyl and cyclohexyl group giving the corresponding product **3m and 3n** with 64% and 72% ee respectively. In the next step, we investigated



Scheme 10: Substrate scope of 1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate derivatives.

the scope of different pyrrolidine-2,3-diones **1** having different benzylidene substituents under the optimized conditions. Initially, *para*-substitutions were checked e.g various EDG, such as (-CH$_3$ and -^{t}Bu), and halogen groups, such as (-F, -Cl, and -Br), which easily yielded products **3o-3s** with good enantioselectivity up to 80%. The *ortho*-fluoroarylidene-substituted pyrrolidine-2,3-dione deliver product **3t** in 86% ee. 2,4-Disubstitution at the aromatic ring was also tolerated in the reaction and a moderate enantioselectivity was observed. Finally, pyrrolidine-2,3-dione **1j** containing a heteroaromatic group was also screened and an acceptable enantioselectivity for the 2-thienyl-substituted product **3w** was witnessed (Scheme 10). To further expand the scope of the reaction, 4-benzylidenedihydrofuran-2,3-dione **1x** and **1y** was prepared and reacted with nitroketones **2b** and **2c**, respectively. To our delight, the reactions proceeded smoothly at room temperature providing the desired products **3x** and **3y** in good yields and enantioselectivities (Scheme 10).

3.5 Determination of absolute stereochemistry:

From the literature study[23] it was found that the specific rotation of compound **(*S*)-3a** was +20.69 (*c* 1.03, CHCl$_3$, 25.1 °C) with 50% ee having *S* configuration. Then specific rotation of compound **(*R*)-3a** was taken and it was found as -35.00 (c 1.03, CHCl$_3$, 27.5 °C) with 90% ee. So we assume that it should be *R* configuration (Scheme 11). The absolute configuration of other products was expected to be the same by analogy.

(*S*)-3a, 50% ee

(*S*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl benzoate

$[a]^{D}_{25}$ = 20.69 (*c* 1.03, CHCl$_3$, 25.1 °C)

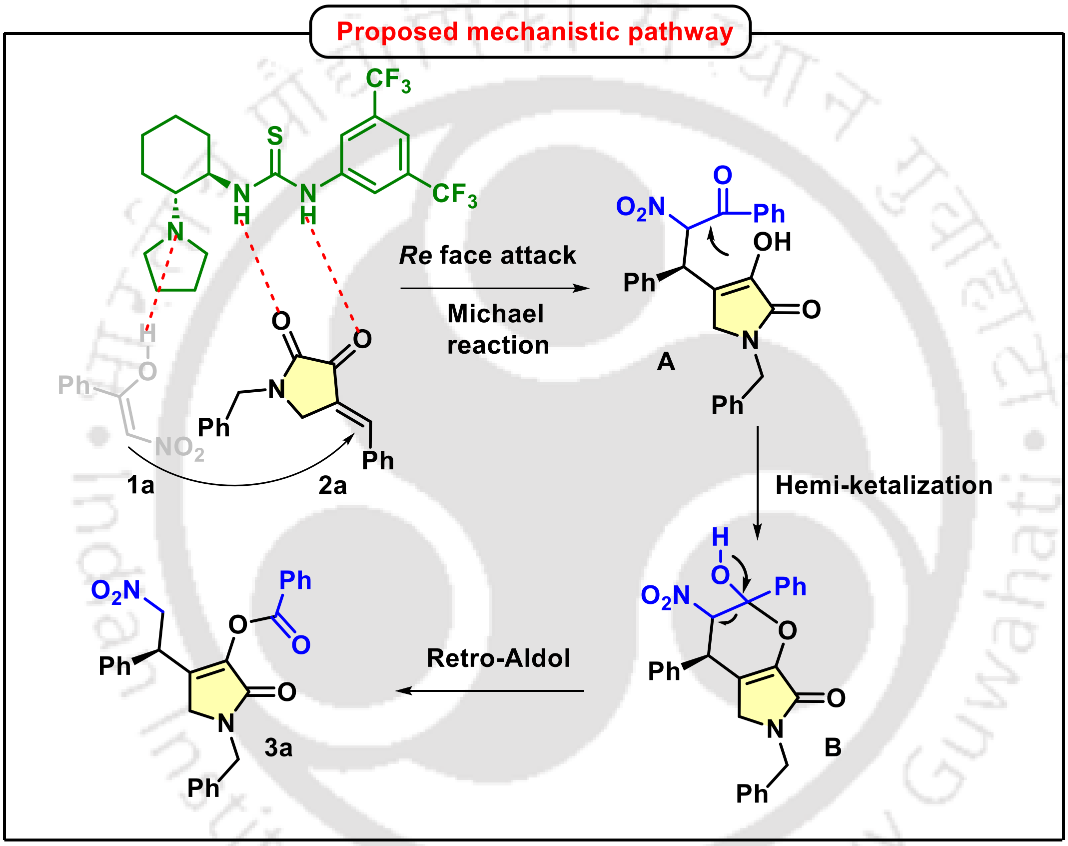
(*R*)-3a, 90% ee

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl) -2-oxo-2,5-dihydro-1*H*-pyrrol-3-yl benzoate

$[a]^{D}_{27}$ = -41.11 (c 1.03, CHCl$_3$, 27.5 °C)

Scheme 11: Determination of absolute stereochemistry.

Based on the absolute configuration a plausible mechanism has been depicted in Scheme 11. It is expected that nitroketone **2a** is activated by the pyrrolidine moiety of the catalyst **VII** whereas a thiourea motif binds with *N*-benzyl-4- benzylidenepyrrolidine-2,3-dione **1a**. Since the *Si* face of **1a** is blocked by catalyst **VII**, addition takes place from the *Re* face to provide intermediate **A**. Then **A** is converted to **B** *via* hemiketalization. Finally, a retro-aldol reaction of **B** delivers product **3a** (Scheme 12).



Scheme 12: Proposed mechanistic pathway.

In summary, in this chapter we reported an organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones/4-benzylidenedihydrofuran-2,3-dione. The products were obtained in good yields with moderate to high enantioselectivities. An easily available bifunctional thiourea catalyst was employed in the methodology.

3.6 Experimental section:

3.6.1 General Information.

Chemicals and solvents were purchased from commercial suppliers and used as received. 1H NMR spectra were recorded on 400 MHz, 500MHz and 600 MHz spectrometer. 13C NMR spectra were recorded on 100 MHz, and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA, IF, ID and AD-H Column. For visualizing the products UV light and I2 were used. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

3.6.2. General procedure for the synthesis of 4-Arylidene-pyrrolidine-2,3-diones:[23]

4-Arylidene-pyrrolidine-2,3-diones was prepared according to reported procedures.

3.6.3. General procedure for the synthesis of *α*-nitro ketone:[17]

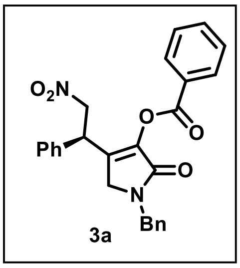
α-nitro ketone was prepared according to reported procedures.

3.6.4. General procedure for the synthesis of compound 3 and 5:

In an oven dried round bottom flask, **1a** (27.7 mg, 0.1 mmol), **2a** (16.5 mg, 0.1 mmol) and 10 mol% of catalyst (**VII**) were taken. 0.6 mL 1,2-DCE of was added to the reaction mixture and stirred at room temperature for 12h. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10-12%) to afford desired product **3a-y**.

3.7 Characterisation of the products:

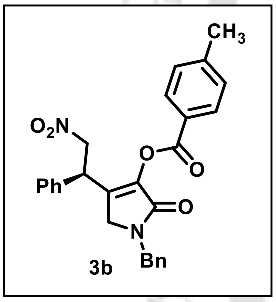
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3a)



3a

Yellow sticky, 80% (35 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.21 – 8.15 (m, 2H), 7.70 – 7.64 (m, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.37 – 7.27 (m, 6H), 7.22 (ddd, J = 7.8, 3.7, 1.6 Hz, 4H), 4.99 (dd, J = 13.5, 8.0 Hz, 1H), 4.78 (dd, J = 13.5, 8.0 Hz, 1H), 4.66 (d, J = 15.1 Hz, 1H), 4.60 (t, J = 7.9 Hz, 1H), 4.52 (d, J = 15.1 Hz, 1H), 3.70 (s, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.4, 163.9, 140.8, 136.4, 136.2, 135.9, 134.5, 130.9, 129.7, 129.1, 128.9, 128.8, 128.2, 128.0, 127.9, 127.6, 77.0, 48.9, 46.9, 42.7. **ESI HRMS**: calcd. For $C_{26}H_{22}N_2O_5$ $[M+H]^+$ 443.1601, found 443.1601. **HPLC Analysis:** ee = 90%, IF Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$= 20.9 min, t$_{minor}$ = 23.3 min).

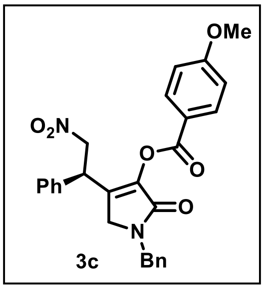
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 4-methylbenzoate(3b).



3b

light orange sticky, 80% (36 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.07 (d, J = 8.2 Hz, 2H), 7.41 – 7.26 (m, 8H), 7.26 – 7.15 (m, 4H), 4.98 (dd, J = 13.5, 7.9 Hz, 1H), 4.77 (dd, J = 13.5, 8.0 Hz, 1H), 4.67 (d, J = 15.1 Hz, 1H), 4.57 (t, J = 8.0 Hz, 1H), 4.51 (d, J = 15.1 Hz, 1H), 3.69 (d, J = 3.0 Hz, 2H), 2.46 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.5, 163.9, 145.6, 140.8, 136.5, 136.0, 135.9, 130.9, 129.8, 129.7, 129.1, 128.8, 128.2, 128.0, 127.8, 125.1, 76.9, 48.9, 46.9, 42.8, 22.1. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_5$ $[M+H]^+$ 457.1758, found 457.1758. **HPLC Analysis:** ee = 88%, IF Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$= 24.6 min, t$_{minor}$ = 26.5 min.

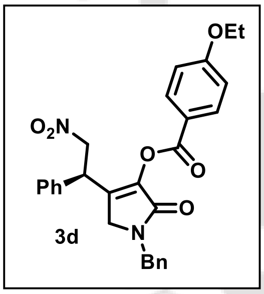
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 4-methoxybenzoate (3c).



3c

Colourless sticky solid, 82% (38 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (d, J = 8.9 Hz, 2H), 7.42 – 7.27 (m, 6H), 7.22 (dt, J = 10.5, 4.1 Hz, 4H), 7.04 – 6.96 (m, 2H), 4.99 (dd, J = 13.5, 7.9 Hz, 1H), 4.77 (dd, J = 13.5, 8.0 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.57 (t, J = 8.0 Hz, 1H), 4.50 (d, J = 15.1 Hz, 1H), 3.91 (s, 3H), 3.68 (d, J = 3.1 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.7, 164.6, 163.6, 140.8, 136.5, 135.9, 135.9, 133.2, 129.7, 129.1, 128.8, 128.2, 128.0, 127.9, 120.1, 114.2, 76.9, 55.7, 48.9, 46.9, 42.8. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_6$ $[M+H]^+$ 473.1707, found 473.1707. **HPLC Analysis:** ee = 80%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 43.5 min, t_{minor} = 47.4 min.

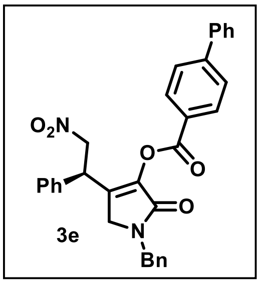
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 4-ethoxybenzoate (3d)



3d

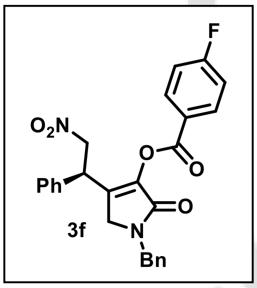
Pale yellow semi solid, 78% (38mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.12 (d, J = 8.9 Hz, 2H), 7.38 – 7.26 (m, 6H), 7.25 – 7.18 (m, 4H), 6.98 (d, J = 8.9 Hz, 2H), 4.96 (s, 1H), 4.78 (s, 1H), 4.65 (s, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 4.13 (d, J = 7.0 Hz, 2H), 3.68 (d, J = 3.4 Hz, 2H), 1.46 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.6, 164.2, 163.6, 140.9, 136.5, 135.9, 135.9, 133.1, 129.7, 129.1, 128.8, 128.2, 128.0, 127.9, 119.8, 114.7, 76.9, 64.1, 48.9, 46.9, 42.8, 14.8. **ESI HRMS**: calcd. For $C_{28}H_{26}N_2O_6$ $[M+H]^+$ 487.1864, found 487.1863. **HPLC Analysis:** ee = 80%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 38.6 min, t_{minor} = 44.5 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl [1,1'-biphenyl]-4-carboxylate (3e)


3e

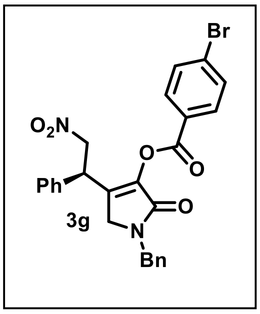
Light yellow sticky solid, 82% (42 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.28 – 8.23 (m, 2H), 7.78 – 7.73 (m, 2H), 7.67 (dd, J = 5.2, 3.3 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.46 – 7.41 (m, 1H), 7.37 – 7.28 (m, 6H), 7.23 (dt, J = 10.8, 4.1 Hz, 4H), 5.01 (dd, J = 13.5, 8.0 Hz, 1H), 4.79 (dd, J = 13.5, 7.9 Hz, 1H), 4.68 (d, J = 15.1 Hz, 1H), 4.61 (t, J = 8.0 Hz, 1H), 4.53 (d, J = 15.1 Hz, 1H), 3.71 (d, J = 2.2 Hz, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.5, 163.8, 147.3, 140.8, 139.9, 136.5, 136.1, 135.9, 131.5, 129.8, 129.2, 129.1, 128.9, 128.6, 128.3, 128.1, 127.9, 127.6, 127.6, 126.5, 77.4, 48.9, 46.9, 42.8. **ESI HRMS**: calcd. For $C_{32}H_{26}N_2O_5$ $[M+H]^+$ 519.1914, found 519.1914. **HPLC Analysis:** ee = 82%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 45.7 min, t_{minor} = 51.5 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 4-fluorobenzoate (3f)


3f

Yellow semi solid, 79% (36 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.26 – 8.12 (m, 2H), 7.38 – 7.27 (m, 6H), 7.26 – 7.14 (m, 6H), 4.97 (dd, J = 13.5, 8.3 Hz, 1H), 4.76 (dd, J = 13.5, 7.6 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 8.0 Hz, 1H), 4.52 (d, J = 15.1 Hz, 1H), 3.70 (s, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 168.1, 165.6, 164.3, 162.9, 140.7, 136.4, 136.2, 135.7, 133.7, 133.6, 129.8, 129.2, 128.9, 128.2, 128.1, 127.8, 124.2, 124.2, 116.4, 116.2, 77.4, 48.9, 46.9, 42.7. **ESI HRMS**: calcd. For $C_{26}H_{21}FN_2O_5$ $[M+H]^+$ 461.1507, found 461.1506. **HPLC Analysis:** ee = 90%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 39.3 min, t_{minor} = 42.7 min.

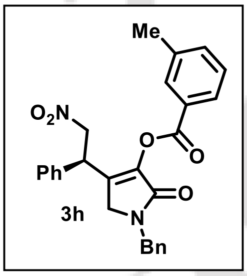
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 4-bromobenzoate (3g)



3g

Light yellow sticky solid, 78% (40 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.03 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.38 – 7.26 (m, 6H), 7.21 (d, J = 6.9 Hz, 4H), 4.96 (dd, J = 13.5, 8.4 Hz, 1H), 4.75 (dd, J = 13.5, 7.5 Hz, 1H), 4.66 (d, J = 15.0 Hz, 1H), 4.60 (t, J = 8.0 Hz, 1H), 4.52 (d, J = 15.1 Hz, 1H), 3.70 (s, 2H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.2, 163.2, 140.7, 136.4, 136.2, 135.7, 132.4, 132.3, 130.0, 129.8, 129.1, 128.9, 128.2, 128.1, 127.8, 126.8, 77.4, 48.9, 47.0, 42.7. **ESI HRMS**: calcd. For $C_{26}H_{21}BrN_2O_5$ $[M+H]^+$ 521.0707, found 521.0708. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 43.6 min, t_{minor} = 47.9 min).

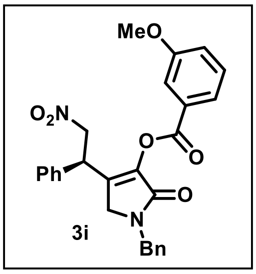
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 3-methylbenzoate (3h)



3h

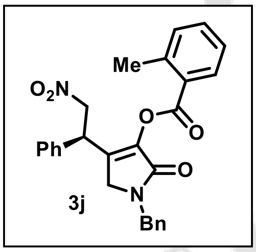
Yellow sticky, 70% (32 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.01 – 7.96 (m, 2H), 7.48 (d, J = 7.4 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.24 – 7.19 (m, 4H), 4.99 (dd, J = 13.5, 7.9 Hz, 1H), 4.78 (dd, J = 13.5, 8.1 Hz, 1H), 4.67 (d, J = 15.1 Hz, 1H), 4.58 (t, J = 8.0 Hz, 1H), 4.51 (d, J = 15.1 Hz, 1H), 3.70 (d, J = 5.5 Hz, 2H), 2.45 (s, 3H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.4, 164.1, 140.8, 138.8, 136.5, 136.1, 135.8, 135.4, 131.4, 129.7, 129.1, 128.8, 128.8, 128.2, 128.0, 127.8, 127.8, 76.9, 48.9, 46.9, 42.7, 21.5. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_5$ $[M+H]^+$ 457.1758, found 457.1757. **HPLC Analysis:** ee = 72%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 21.0 min, t_{minor} = 23.3 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 3-methoxybenzoate (3i)


3i

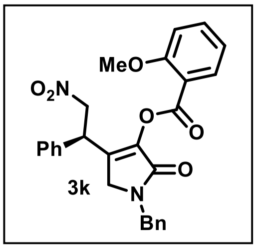
Orange semi solid, 72% (34 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.79 (dt, J = 7.6, 1.2 Hz, 1H), 7.68 (dd, J = 2.7, 1.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.36 – 7.27 (m, 6H), 7.22 (ddd, J = 6.8, 4.6, 2.5 Hz, 5H), 5.00 (dd, J = 13.6, 8.3 Hz, 1H), 4.76 (dd, J = 13.6, 7.7 Hz, 1H), 4.68 (d, J = 15.1 Hz, 1H), 4.58 (t, J = 8.0 Hz, 1H), 4.51 (d, J = 15.1 Hz, 1H), 3.89 (s, 3H), 3.70 (d, J = 4.8 Hz, 2H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.3, 163.7, 159.9, 140.7, 136.4, 136.0, 135.7, 129.9, 129.7, 129.1, 129.0, 128.9, 128.2, 128.0, 127.8, 123.3, 121.5, 114.8, 76.9, 55.7, 48.9, 46.9, 42.7. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_6$ [M+H]$^+$ 473.1707, found 473.1714. **HPLC Analysis:** ee = 66%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 22.4 min, t_{minor} = 18.5 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 2-methylbenzoate (3j)


3j

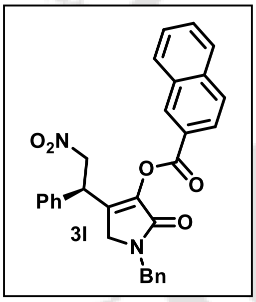
Pale yellow semi solid, 65% (29 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.14 (dd, J = 8.2, 1.5 Hz, 1H), 7.51 (td, J = 7.5, 1.5 Hz, 1H), 7.41 – 7.26 (m, 8H), 7.22 (ddd, J = 7.7, 4.0, 1.6 Hz, 4H), 5.00 (dd, J = 13.4, 7.8 Hz, 1H), 4.79 (dd, J = 13.4, 8.1 Hz, 1H), 4.67 (d, J = 15.1 Hz, 1H), 4.59 (t, J = 7.9 Hz, 1H), 4.53 (d, J = 15.0 Hz, 1H), 3.70 (d, J = 2.0 Hz, 2H), 2.70 (s, 3H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.5, 164.1, 142.4, 140.9, 136.4, 136.0, 135.9, 133.7, 132.2, 131.9, 129.7, 129.1, 128.8, 128.2, 128.0, 127.8, 126.9, 126.3, 77.4, 48.9, 46.9, 42.7, 22.1. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_5$ [M+H]$^+$ 457.1758, found 457.1757. **HPLC Analysis:** ee = 68%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 15.9 min, t_{minor} = 14.9 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 2-methoxybenzoate (3k)



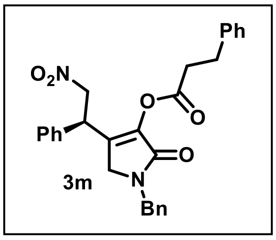
Yellow sticky solid, 68% (32 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.04 (dd, J = 7.8, 1.8 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.35 – 7.27 (m, 8H), 7.23 – 7.19 (m, 2H), 7.09 – 7.03 (m, 2H), 5.10 (dd, J = 13.5, 6.9 Hz, 1H), 4.94 (dd, J = 13.6, 9.0 Hz, 1H), 4.68 (d, J = 15.0 Hz, 1H), 4.56 – 4.47 (m, 2H), 3.96 (s, 3H), 3.68 (d, J = 10.5 Hz, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.5, 163.3, 160.1, 136.5, 136.3, 135.9, 135.3, 133.2, 129.7, 129.0, 128.8, 128.2, 128.0, 128.0, 120.6, 117.5, 112.2, 77.4, 56.2, 49.1, 46.9, 42.9. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_6$ $[M+H]^+$ 473.1707, found 473.1711. **HPLC Analysis:** ee = 70%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 59.0 min, t_{minor} = 72.9 min.

(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 2-naphthoate (3l)



White sticky solid, 75% (37 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.78 (s, 1H), 8.15 (dd, J = 8.6, 1.8 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.66 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.60 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.34 (td, J = 7.8, 7.3, 1.7 Hz, 4H), 7.30 (dd, J = 7.4, 2.0 Hz, 2H), 7.24 (ddd, J = 11.1, 6.9, 1.8 Hz, 4H), 5.03 (dd, J = 13.6, 8.1 Hz, 1H), 4.79 (dd, J = 13.6, 7.9 Hz, 1H), 4.69 (d, J = 15.1 Hz, 1H), 4.63 (t, J = 8.0 Hz, 1H), 4.53 (d, J = 15.1 Hz, 1H), 3.73 (d, J = 4.2 Hz, 2H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.4, 164.1, 140.8, 136.4, 136.3, 136.2, 135.8, 133.1, 132.6, 129.9, 129.7, 129.2, 129.1, 128.8, 128.8, 128.2, 128.0, 127.8, 127.2, 125.7, 125.0, 76.9, 48.9, 46.9, 42.7. **ESI HRMS**: calcd. For $C_{30}H_{24}N_2O_5$ $[M+H]^+$ 493.1758, found 493.1767. **HPLC Analysis:** ee = 80%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 35.9 min, t_{minor} = 40.3 min.

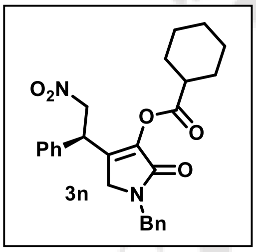
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl 3-phenylpropanoate (3m)



3m

Colourless semi solid, 65% (31mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.33 – 7.27 (m, 10H), 7.21 – 7.16 (m, 3H), 7.11 – 7.07 (m, 2H), 4.62 (dtd, J = 21.6, 13.5, 8.0 Hz, 3H), 4.50 – 4.40 (m, 2H), 3.60 (d, J = 8.6 Hz, 2H), 3.09 (t, J = 7.6 Hz, 2H), 3.00 – 2.95 (m, 2H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 170.1, 164.4, 140.4, 139.9, 136.3, 135.9, 135.8, 129.7, 129.1, 128.9, 128.8, 128.6, 128.2, 128.1, 127.8, 126.8, 77.4, 48.8, 46.9, 42.5, 35.4, 30.8. **ESI HRMS**: calcd. For $C_{28}H_{26}N_2O_5$ $[M+H]^+$ 479.1914, found 479.1915. **HPLC Analysis:** ee = 72%, Chiralpak IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 37.3 min, t$_{minor}$ = 35.4 min.

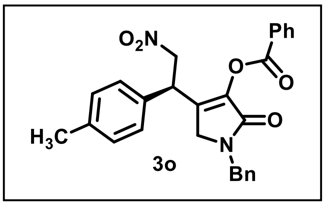
(*R*)-1-benzyl-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl cyclohexanecarboxylate (3n)



3n

Pale yellow semi solid, 70% (31 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36 – 7.29 (m, 5H), 7.28 – 7.26 (m, 1H), 7.21 – 7.14 (m, 4H), 4.95 – 4.87 (m, 1H), 4.80 – 4.73 (m, 1H), 4.66 – 4.58 (m, 1H), 4.54 – 4.45 (m, 2H), 3.67 – 3.56 (m, 2H), 2.68 – 2.60 (m, 1H), 2.15 – 2.07 (m, 2H), 1.89 – 1.80 (m, 2H), 1.72 – 1.65 (m, 2H), 1.43 – 1.27 (m, 4H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 173.2, 164.4, 140.7, 136.4, 136.0, 135.4, 129.7, 129.0, 128.8, 128.2, 128.0, 127.8, 48.8, 46.8, 42.9, 42.6, 29.0, 25.8, 25.4. **ESI HRMS**: calcd. For $C_{26}H_{28}N_2O_5$ $[M+H]^+$ 449.2071, found 449.2072. **HPLC Analysis:** ee = 72%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 16.7 min, t$_{minor}$ = 15.5 min.

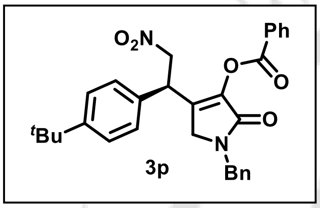
(*R*)-1-benzyl-4-(2-nitro-1-(p-tolyl)ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3o)



3o

Light yellow semi solid, 83% (38 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.17 (dd, J = 8.3, 1.2 Hz, 2H), 7.72 – 7.64 (m, 1H), 7.53 (dd, J = 10.8, 4.8 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.23 – 7.19 (m, 4H), 7.06 – 6.99 (m, 2H), 4.97 (dd, J = 13.4, 7.7 Hz, 1H), 4.77 – 4.65 (m, 2H), 4.59 – 4.49 (m, 2H), 3.69 (d, J = 5.2 Hz, 2H), 1.60 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.3, 163.9, 140.9, 136.3, 135.8, 134.6, 131.6, 131.6, 130.9, 129.7, 129.6, 129.1, 129.0, 128.3, 128.1, 127.8, 116.9, 116.7, 77.0, 48.9, 46.9, 42.1. **ESI HRMS**: calcd. For $C_{27}H_{24}N_2O_5$ $[M+H]^+$ 457.1758, found 457.1766. **HPLC Analysis:** ee = 72%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 24.5 min, t_{minor} = 21.4 min.

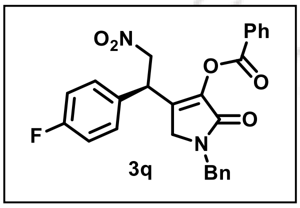
(*R*)-1-benzyl-4-(1-(4-(tert-butyl)phenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3p)



3p

White semi solid, 72% (40 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.21 – 8.15 (m, 2H), 7.71 – 7.62 (m, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.38 – 7.27 (m, 5H), 7.24 – 7.19 (m, 2H), 7.14 (d, J = 8.3 Hz, 2H), 4.97 (dd, J = 13.5, 8.2 Hz, 1H), 4.75 (dd, J = 13.5, 7.7 Hz, 1H), 4.67 (d, J = 15.1 Hz, 1H), 4.55 (dd, J = 19.1, 11.5 Hz, 2H), 3.73 (s, 2H), 1.27 (s, 10H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.5, 163.8, 151.9, 140.6, 136.5, 136.4, 134.5, 132.6, 130.9, 129.1, 128.9, 128.2, 128.0, 127.9, 127.5, 126.6, 77.0, 49.0, 46.9, 42.2, 31.3. **ESI HRMS**: calcd. For $C_{30}H_{30}N_2O_5$ $[M+H]^+$ 499.2227, found 499.2228. **HPLC Analysis:** ee = 72%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 10.5 min, t_{minor} = 11.8 min.

(*R*)-1-benzyl-4-(1-(4-fluorophenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3q)

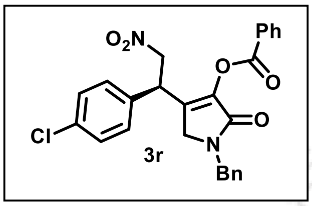


3q

Pale Yellow semi solid, 80% (37 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.21 – 8.14 (m, 2H), 7.71 – 7.65 (m, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.38 – 7.27 (m, 3H), 7.25 – 7.17 (m, 4H), 7.10 – 6.96 (m, 2H), 4.97 (dd, J = 13.4, 7.6 Hz, 1H), 4.75 (dd, J = 13.4, 8.3 Hz, 1H), 4.68 (d, J = 15.0 Hz, 1H), 4.57 (t, J = 8.0 Hz, 1H), 4.52 (d, J = 15.0 Hz, 1H), 3.75 – 3.63 (m, 2H).**^{13}C NMR (125 MHz, CDCl$_3$)** δ 164.1, 163.7, 163.6, 161.7, 140.7, 136.2, 135.6, 134.4, 131.5, 131.4, 130.7, 129.4, 129.4, 128.9, 128.8, 128.1, 127.9, 127.6, 116.7, 116.5, 48.7, 46.8, 41.9, 29.7. **ESI HRMS**: calcd. For $C_{26}H_{21}FN_2O_5$ $[M+H]^+$ 461.1507, found 461.1513. **HPLC Analysis:** ee = 84%, Chiralpak

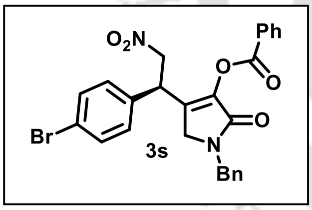
IF Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 33.3 min, t_{minor} = 42.0 min.

(*R*)-1-benzyl-4-(1-(4-chlorophenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3r)



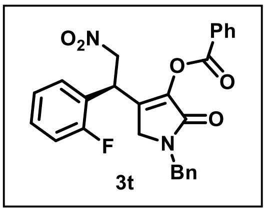
Yellow semi solid, 79% (38 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.16 (dd, J = 8.2, 1.0 Hz, 2H), 7.68 (dd, J = 10.6, 4.3 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.37 – 7.28 (m, 5H), 7.25 – 7.14 (m, 4H), 4.96 (dd, J = 13.5, 7.6 Hz, 1H), 4.75 (dd, J = 13.5, 8.3 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.60 – 4.49 (m, 2H), 3.69 (d, J = 4.4 Hz, 2H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.2, 163.9, 141.0, 136.3, 135.5, 135.0, 134.7, 134.3, 130.9, 130.0, 129.2, 129.1, 129.0, 128.3, 128.1, 76.7, 48.8, 47.0, 42.1. **ESI HRMS**: calcd. For $C_{26}H_{21}ClN_2O_5$ $[M+H]^+$ 477.1212, found 477.1224. **HPLC Analysis:** ee = 76%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 12.7 min, t_{minor} = 14.8 min.

(*R*)-1-benzyl-4-(1-(4-bromophenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3s)



Yellow semi solid, 82% (76 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.20 – 8.13 (m, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.8 Hz, 2H), 7.49 – 7.42 (m, 2H), 7.39 – 7.28 (m, 3H), 7.25 – 7.19 (m, 2H), 7.11 (d, J = 8.4 Hz, 2H), 4.96 (dd, J = 13.5, 7.6 Hz, 1H), 4.75 (dd, J = 13.5, 8.3 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.59 – 4.49 (m, 2H), 3.69 (d, J = 4.4 Hz, 2H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.2, 163.9, 141.1, 136.3, 135.4, 134.8, 134.7, 132.9, 130.9, 129.5, 129.1, 129.0, 128.3, 128.1, 127.7, 123.1, 76.7, 48.8, 47.0, 42.2. **ESI HRMS**: calcd. For $C_{26}H_{21}BrN_2O_5$ $[M+H]^+$ 521.0707, found 521.0726. **HPLC Analysis:** ee = 76%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 25.6 min, t_{minor} = 21.3 min.

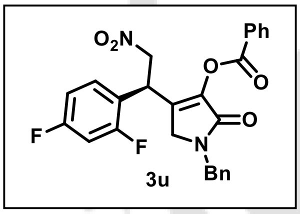
(*S*)-1-benzyl-4-(1-(2-fluorophenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3t)



3t

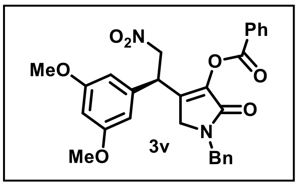
Yellow semi solid, 79% (36 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.15 (dd, J = 8.3, 1.1 Hz, 2H), 7.70 – 7.63 (m, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.38 – 7.27 (m, 4H), 7.26 – 7.19 (m, 3H), 7.12 – 7.03 (m, 2H), 5.01 (dd, J = 11.4, 6.1 Hz, 1H), 4.91 – 4.80 (m, 2H), 4.67 (d, J = 15.0 Hz, 1H), 4.56 (d, J = 15.0 Hz, 1H), 3.78 (s, 2H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.3, 163.6, 161.8, 159.3, 141.3, 136.4, 134.9, 134.5, 130.8, 130.8, 130.7, 129.6, 129.5, 129.1, 128.9, 128.2, 128.1, 127.9, 125.4, 125.4, 122.7, 122.6, 116.7, 116.4, 75.4, 75.3, 48.9, 46.9, 36.8, 36.7. **ESI HRMS**: calcd. For $C_{26}H_{21}FN_2O_5$ $[M+H]^+$ 461.1507, found 461.1516. **HPLC Analysis:** ee = 86%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 75/25, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 56.1 min, t_{minor} = 68.1 min.

(*S*)-1-benzyl-4-(1-(2,4-difluorophenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3u)



3u

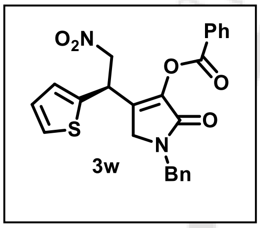
White sticky solid, 78% (37 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.18 – 8.09 (m, 2H), 7.70 – 7.64 (m, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.26 – 7.18 (m, 3H), 6.88 – 6.78 (m, 2H), 5.02 – 4.93 (m, 1H), 4.82 (dq, J = 15.5, 7.7 Hz, 2H), 4.67 (d, J = 15.0 Hz, 1H), 4.56 (d, J = 15.0 Hz, 1H), 3.77 (d, J = 4.3 Hz, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 163.9, 163.4, 141.3, 136.1, 134.4, 134.3, 130.6, 130.3, 130.2, 128.9, 128.7, 128.1, 127.9, 127.5, 118.5, 112.6, 112.4, 105.2, 104.9, 104.7, 75.1, 48.7, 46.8, 36.2, 36.1, 29.7. **ESI HRMS**: calcd. For $C_{26}H_{20}F_2N_2O_5$ $[M+H]^+$ 479.1413, found 479.1424. **HPLC Analysis:** ee = 72%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 11.4 min, t_{minor} = 10.1 min.



3v

(*R*)-1-benzyl-4-(1-(3,5-dimethoxyphenyl)-2-nitroethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3v) light yellow semi solid, 80% (40 mg) yield. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.20 – 8.15 (m, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.29 (dd, J = 8.5, 6.0 Hz, 1H), 7.22 (d, J = 7.0 Hz, 2H), 6.80 – 6.72 (m, 3H), 4.98 (dd, J = 13.5, 8.1 Hz, 1H), 4.73 (dd, J = 13.5, 7.9 Hz, 1H), 4.68 (d, J = 15.1 Hz, 1H), 4.55 – 4.48 (m, 2H), 3.83 (d, J = 3.0 Hz, 6H), 3.71 (d, J = 4.6 Hz, 2H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.4, 164.0, 149.9, 149.3, 140.6, 136.5, 136.4, 134.6, 130.8, 129.1, 129.0, 128.2, 128.0, 127.9, 119.9, 111.8, 110.7, 77.2, 56.20, 56.1, 49.0, 46.9, 42.5. **ESI HRMS**: calcd. For $C_{28}H_{26}N_2O_7$ [M+H]$^+$ 503.1813, found 503.1814. **HPLC Analysis:** ee = 72%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 37.1 min, t$_{minor}$ = 32.4 min.

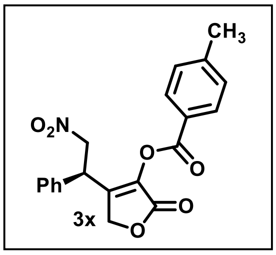
(*R*)-1-benzyl-4-(2-nitro-1-(thiophen-2-yl)ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl benzoate (3w)



3w

light brown semi solid, 81% (36 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.24 – 8.14 (m, 2H), 7.67 (dd, J = 10.6, 4.3 Hz, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.38 – 7.29 (m, 3H), 7.27 – 7.22 (m, 3H), 6.94 (d, J = 3.4 Hz, 2H), 4.98 – 4.91 (m, 2H), 4.85 – 4.79 (m, 1H), 4.63 (d, J = 3.4 Hz, 2H), 3.81 (d, J = 5.0 Hz, 2H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 164.2, 163.5, 140.8, 137.7, 136.4, 135.5, 134.5, 130.9, 130.3, 129.1, 128.9, 128.6, 128.2, 128.1, 127.9, 127.7, 126.7, 126.3, 77.3, 48.6, 47.0, 37.4. **ESI HRMS**: calcd. For $C_{24}H_{20}N_2O_5S$ [M+H]$^+$ 449.1166, found 449.1167. **HPLC Analysis:** ee = 82%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t$_{major}$ = 34.1 min, t$_{minor}$ = 36.9 min.

(*R*)-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydrofuran-3-yl 4-methylbenzoate (3x)

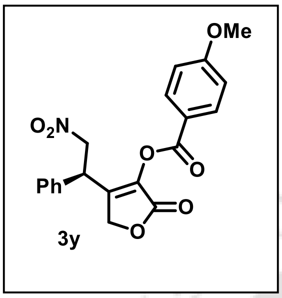


3x

light yellow semi solid, 82% (30 mg) yield. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 8.03 (d, J = 8.2 Hz, 2H), 7.42 – 7.28 (m, 5H), 7.26 (dd, J = 6.6, 2.1 Hz, 2H), 5.04 (dd, J = 13.8, 8.3 Hz, 1H), 4.83 – 4.79 (m, 1H), 4.75 (s, 1H), 4.70 (d, J = 16.8 Hz, 1H), 4.65 (t, J = 7.9 Hz, 1H), 2.46 (s, 3H).**^{13}C NMR (150 MHz, CDCl$_3$)** δ 166.7, 163.3, 146.1, 145.6, 135.9, 134.4, 130.9, 130.0, 129.8, 129.4, 127.8, 124.3, 76.1, 68.6, 42.2, 22.1. **ESI HRMS**: calcd. For $C_{20}H_{17}NO_6$ [M+Na]$^+$ 390.0948, found 390.0957.

HPLC Analysis: ee = 78%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 85/25, flow rate 1.0 mL/min, λ = 200 nm, t_{major} = 12.5 min, t_{minor} = 13.5 min.

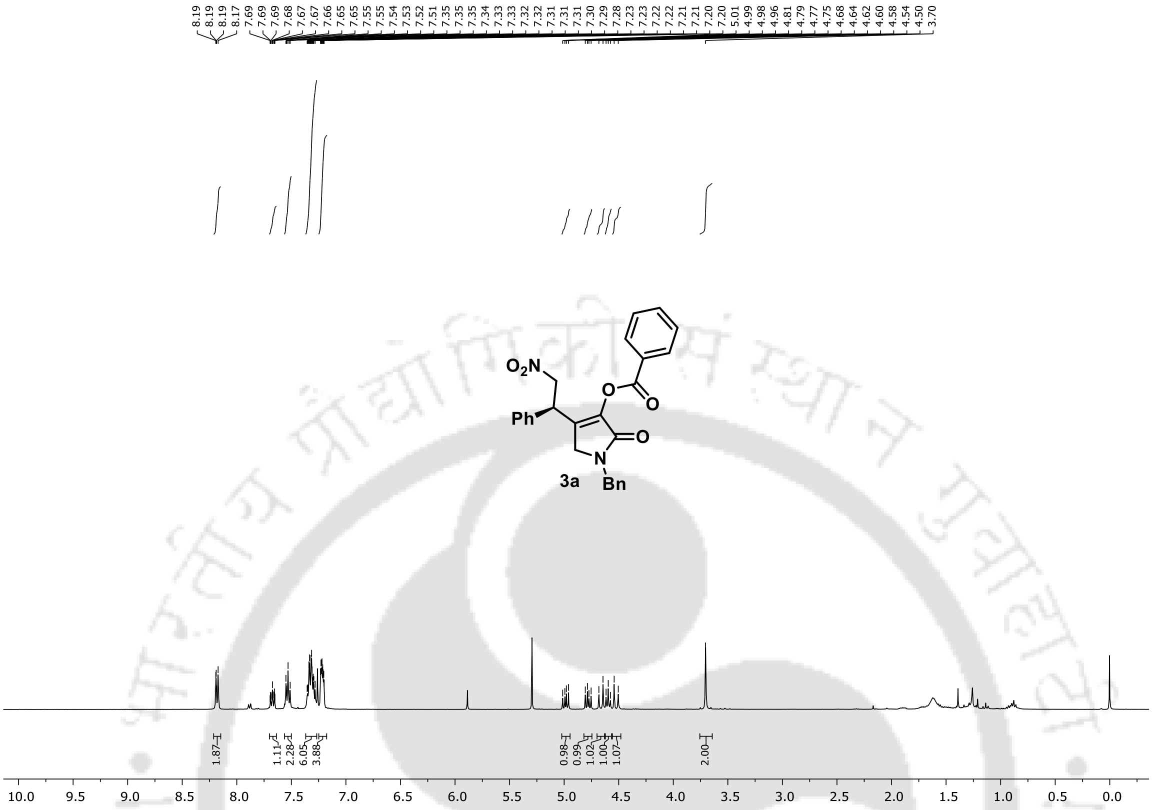
(*R*)-4-(2-nitro-1-phenylethyl)-2-oxo-2,5-dihydrofuran-3-yl 4-methoxybenzoate (3y)

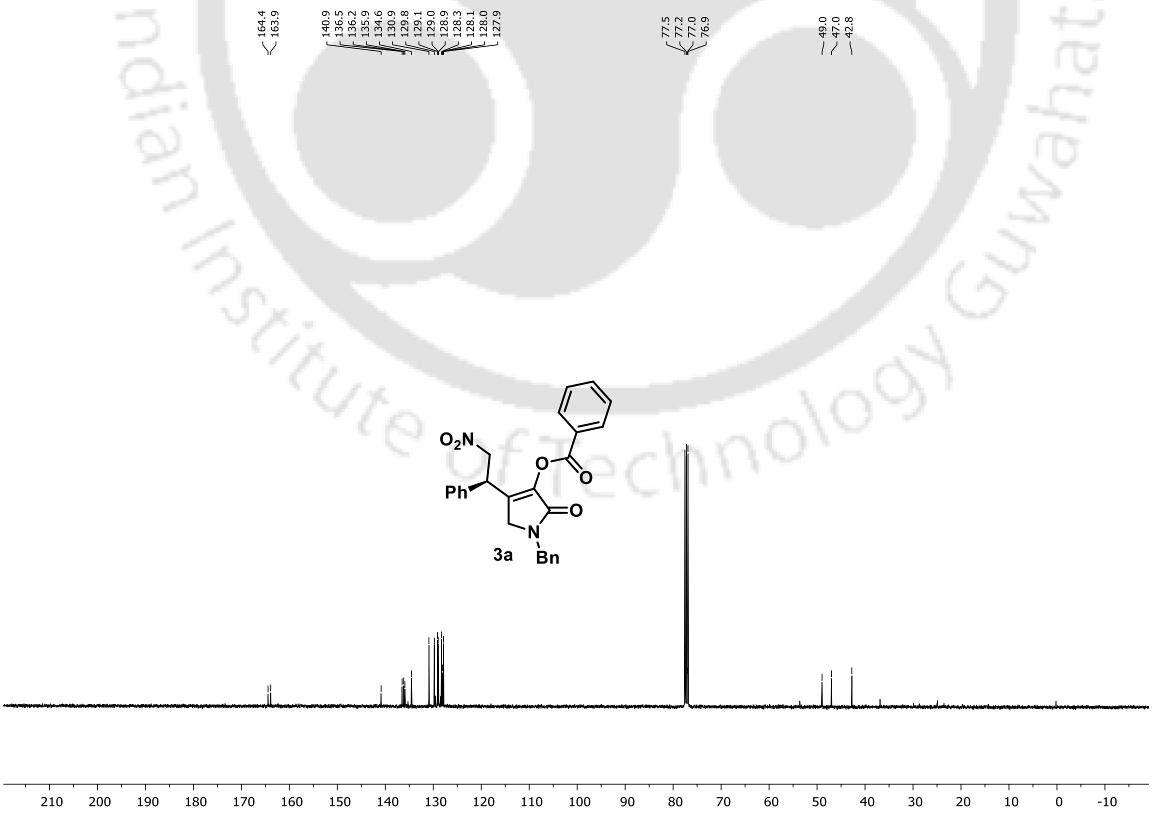


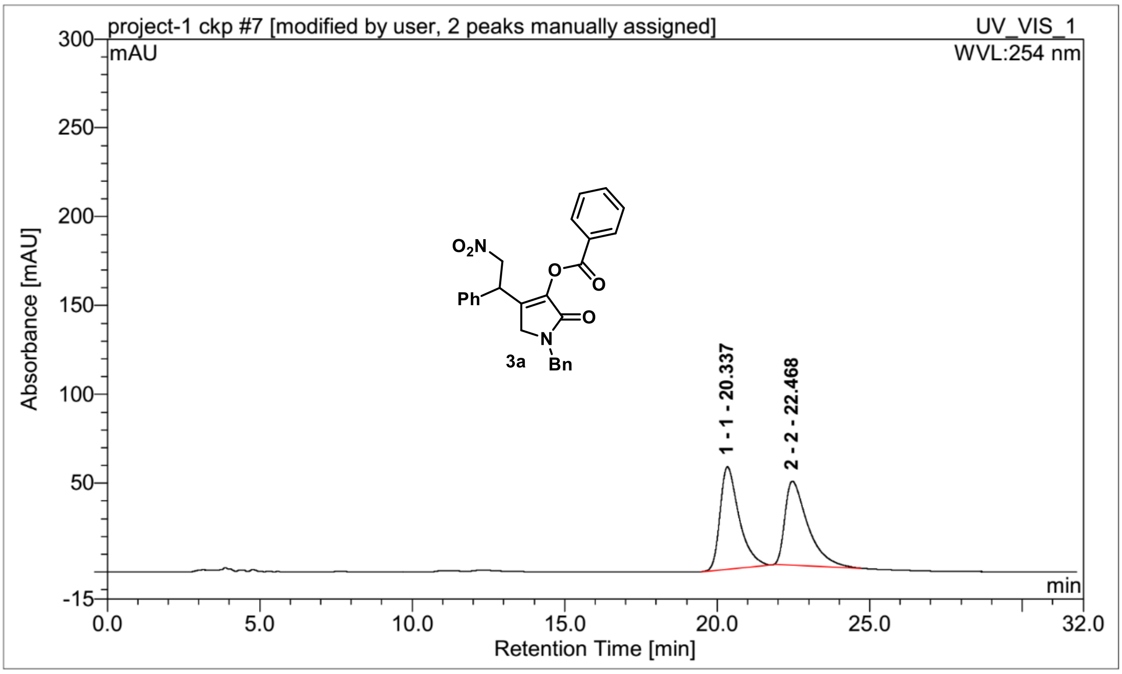
3y

light yellow semi solid, 85% (33 mg) yield. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.02 (d, J = 8.5 Hz, 2H), 7.30 (dd, J = 13.0, 7.0 Hz, 3H), 7.22 – 7.16 (m, 2H), 6.93 (d, J = 8.5 Hz, 2H), 4.97 (dd, J = 13.9, 8.4 Hz, 1H), 4.76 – 4.55 (m, 4H), 3.83 (s, 3H).**^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.7, 165.0, 162.9, 145.5, 134.6, 133.2, 130.0, 129.3, 127.9, 119.4, 114.4, 76.2, 68.5, 55.8, 42.2. **ESI HRMS**: calcd. For $C_{20}H_{17}NO_7$ $[M+H]^+$ 384.1078, found 384.1087. **HPLC Analysis:** ee = 78%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 19.1 min, t_{minor} = 20.8 min.

3.8 NMR and HPLC spectra:







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
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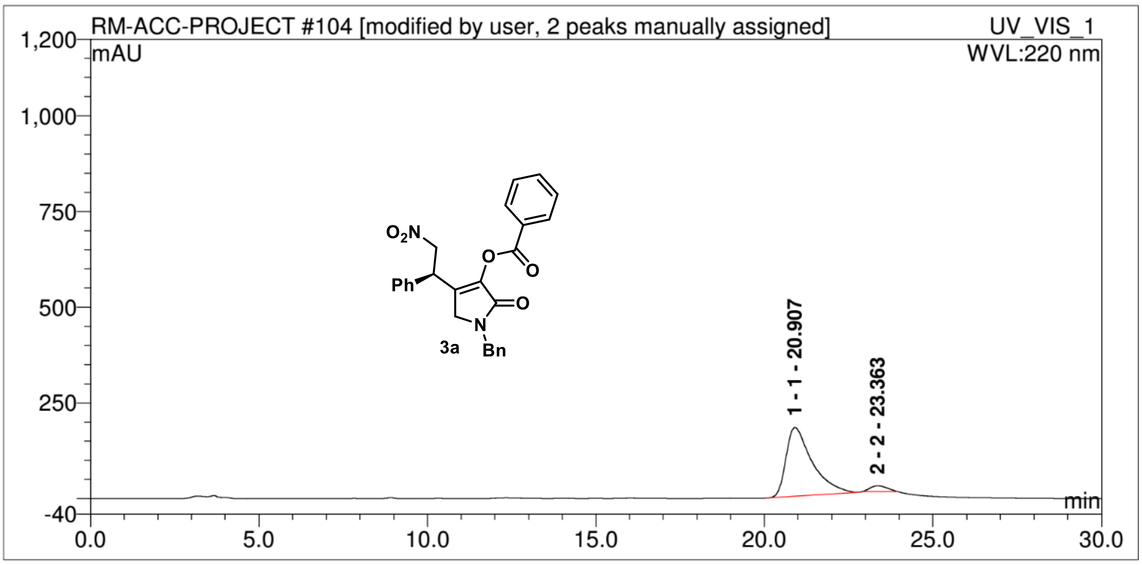
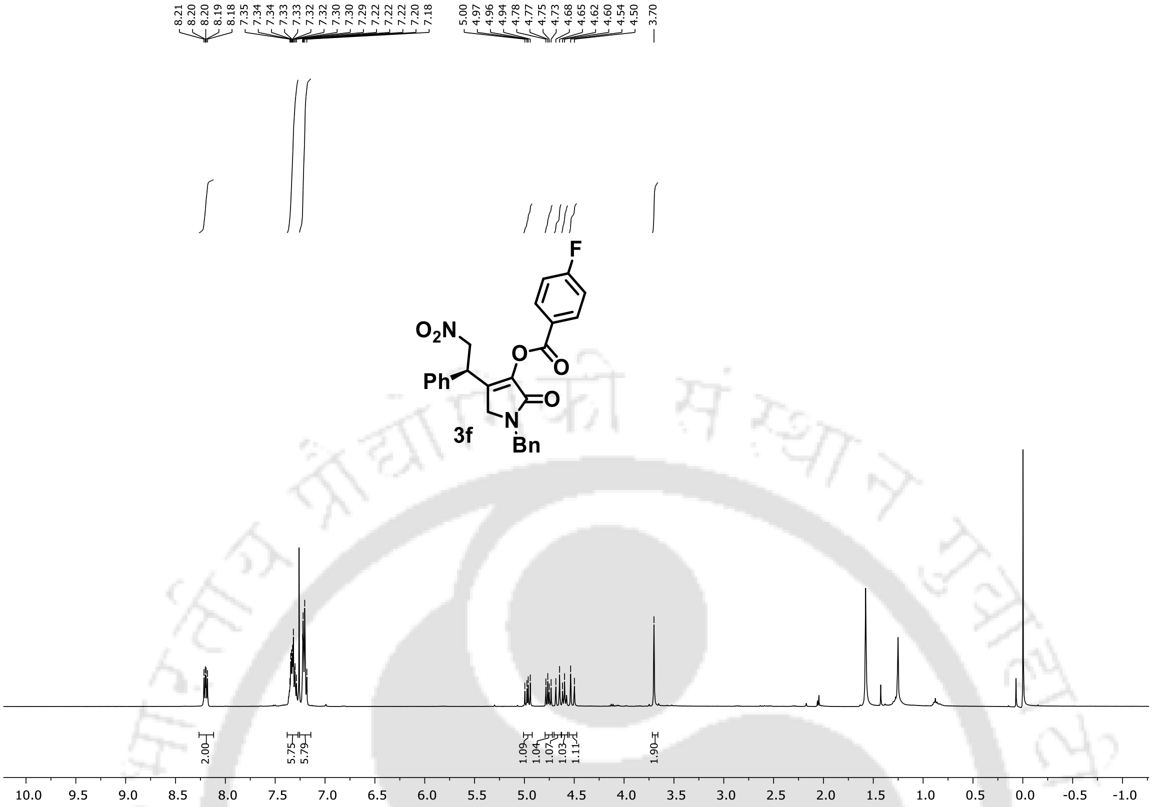


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	20.91	161.7176	94.83129978	179.7468	n.a.
2	2	23.36	8.814	5.168700222	14.981	n.a.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3f
Bn
2.00
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1.04
1.07
1.03
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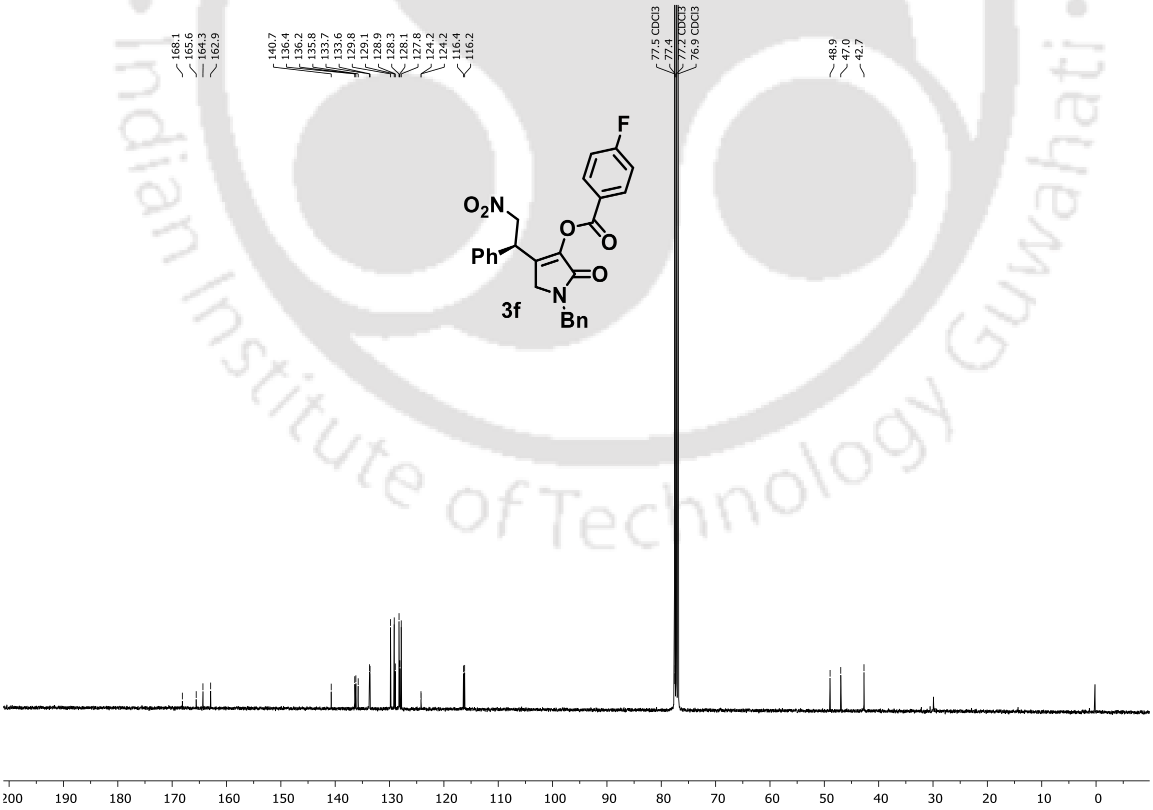
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127.8
124.2
124.2
116.4
116.2
77.5 CDCl3
77.4
77.2 CDCl3
76.9 CDCl3
48.9
47.0
42.7
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Ph
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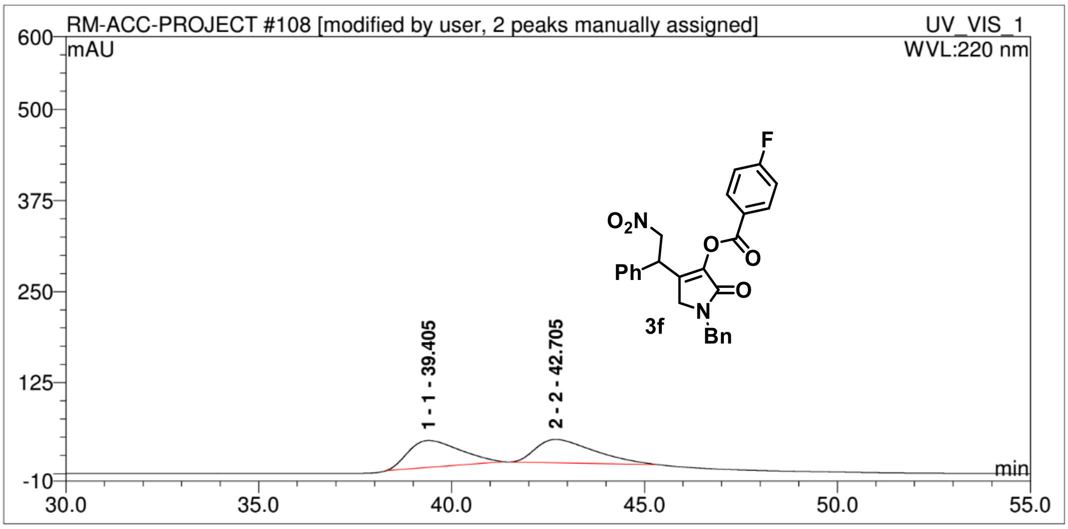

No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
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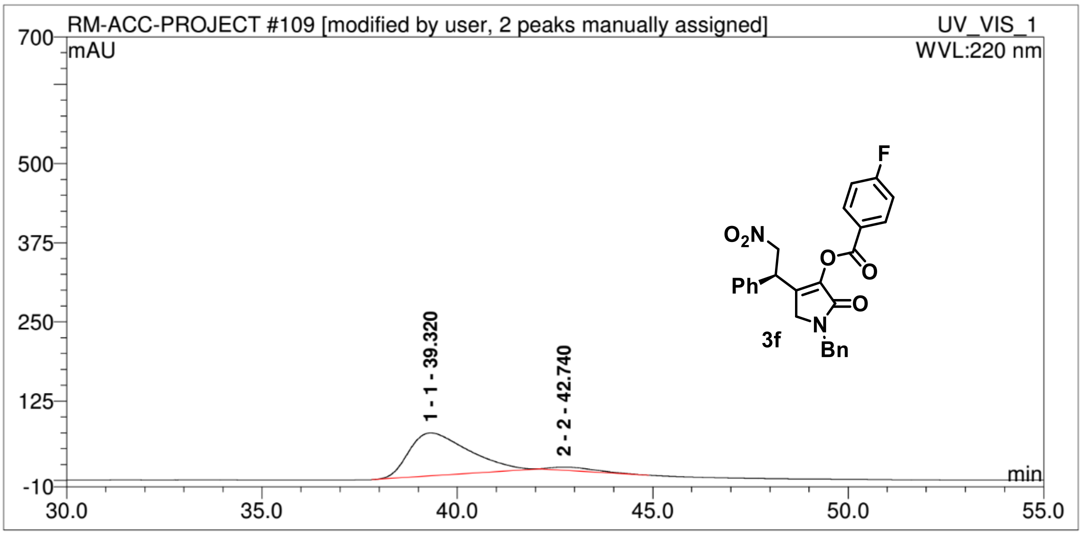

No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	39.32	119.8521	94.53301927	67.85756	n.a.
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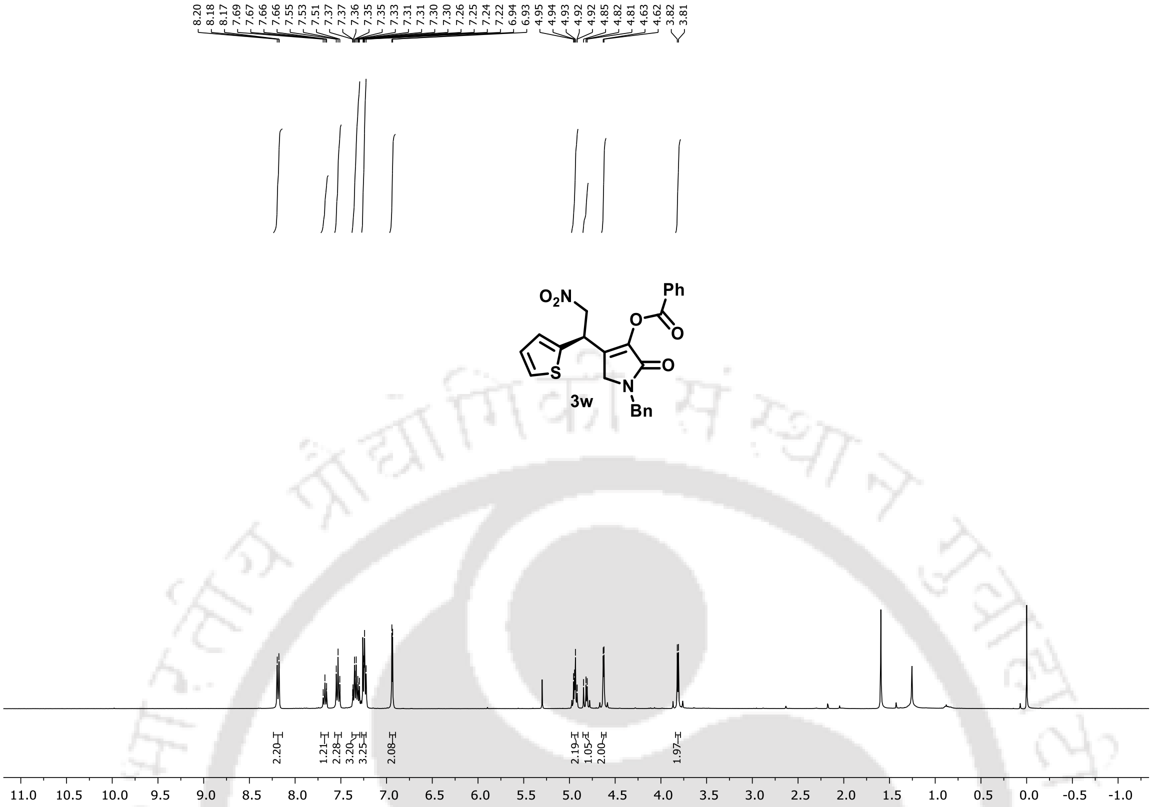
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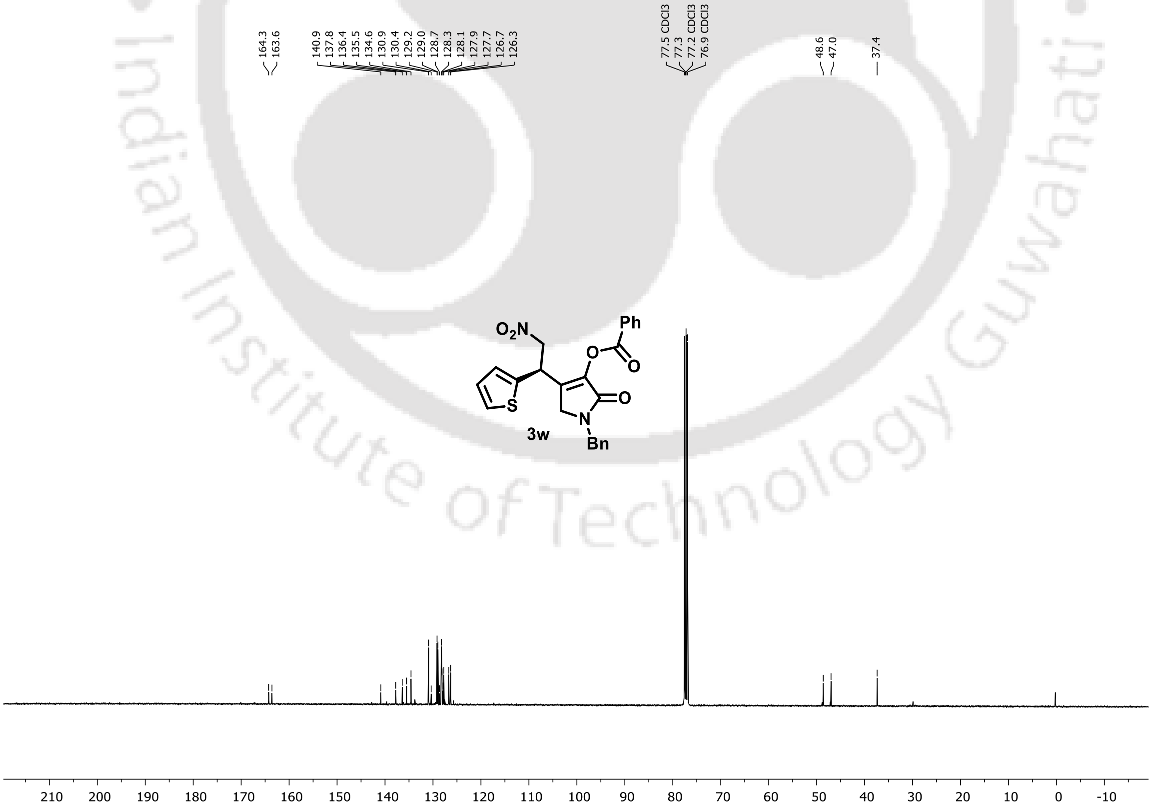
O2N
Ph
O
O
O
N
S
Bn
3w
2.20
1.21
2.28
3.20
3.25
2.08
2.19
1.05
2.00
1.97
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0


164.3 163.6
140.9 137.8 136.4 135.5 134.6 130.9 130.4 129.2 129.0 128.7 128.3 128.1 127.9 127.7 126.7 126.3
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48.6 47.0
37.4
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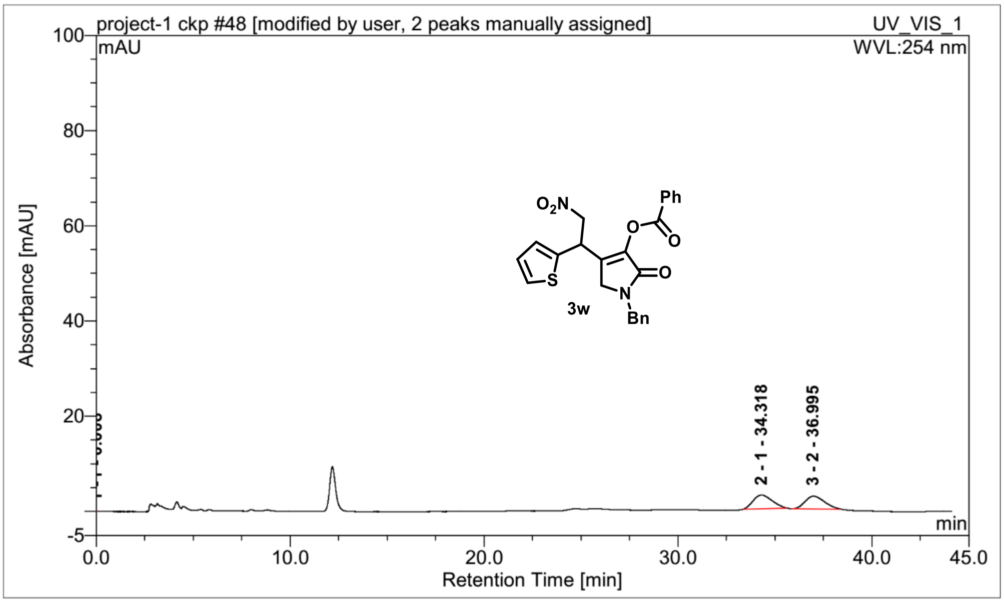

No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
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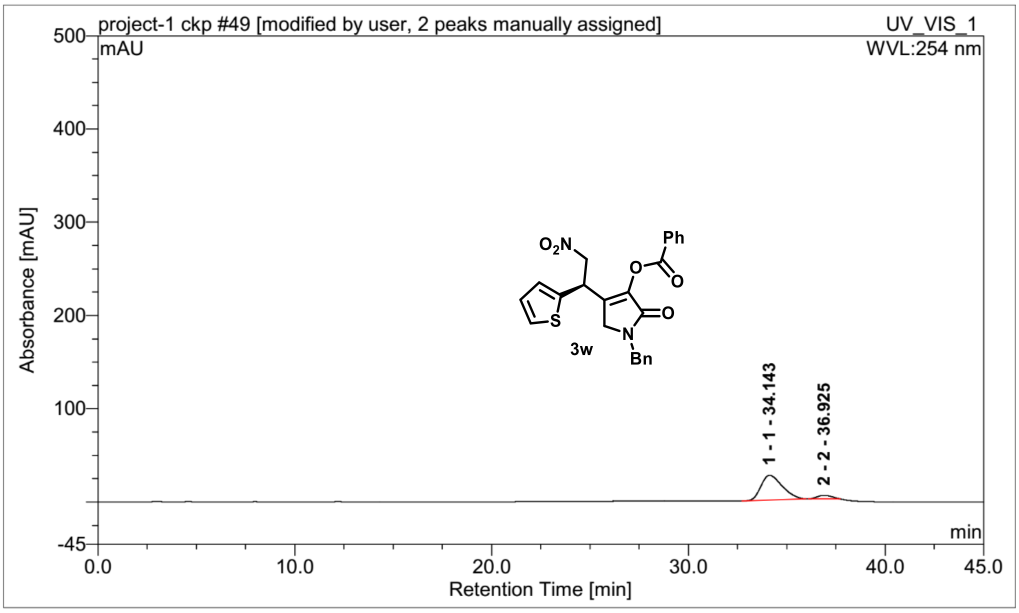

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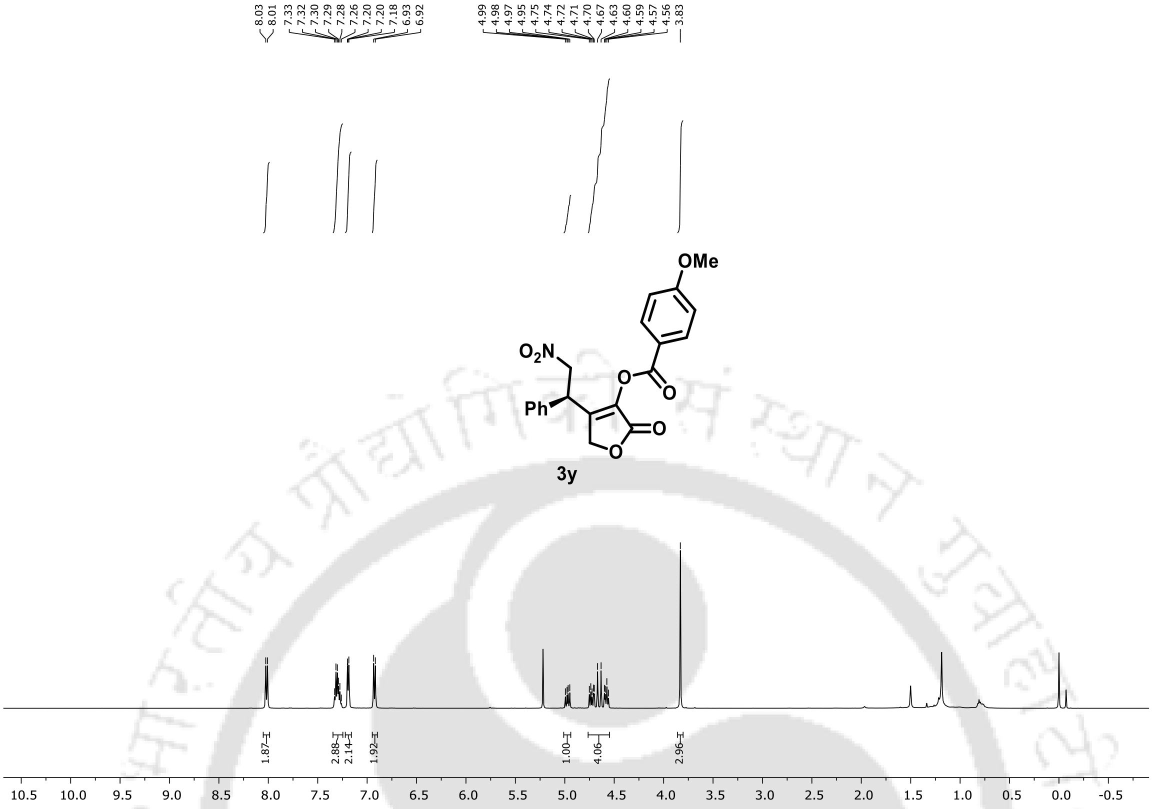
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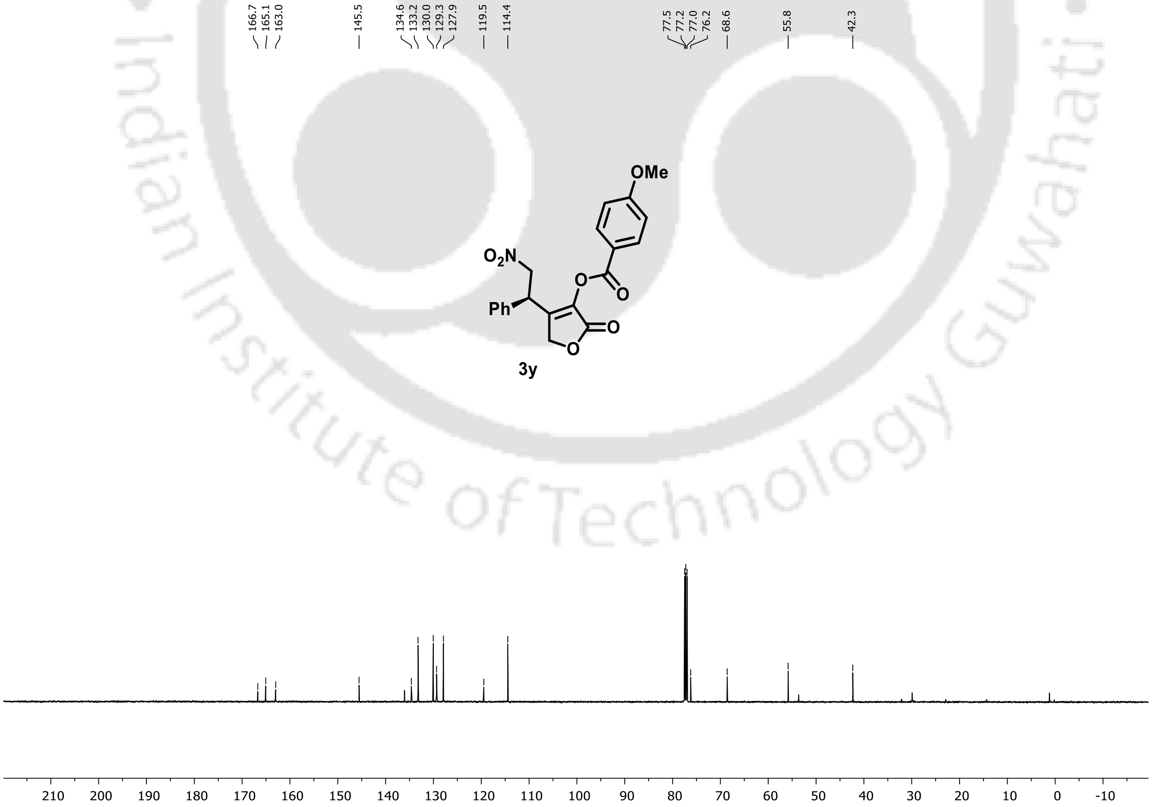
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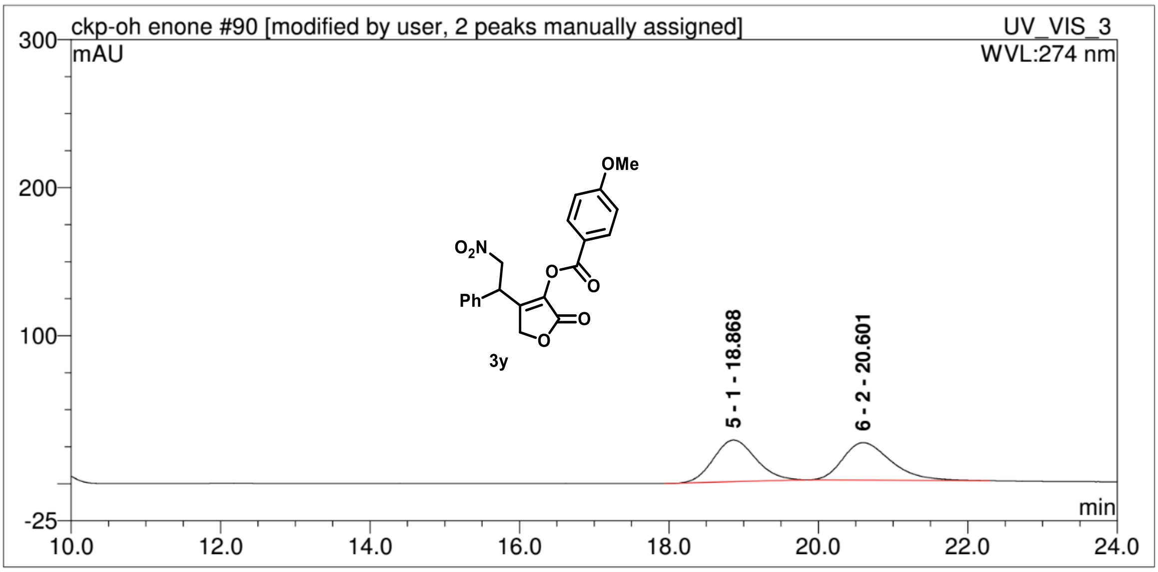

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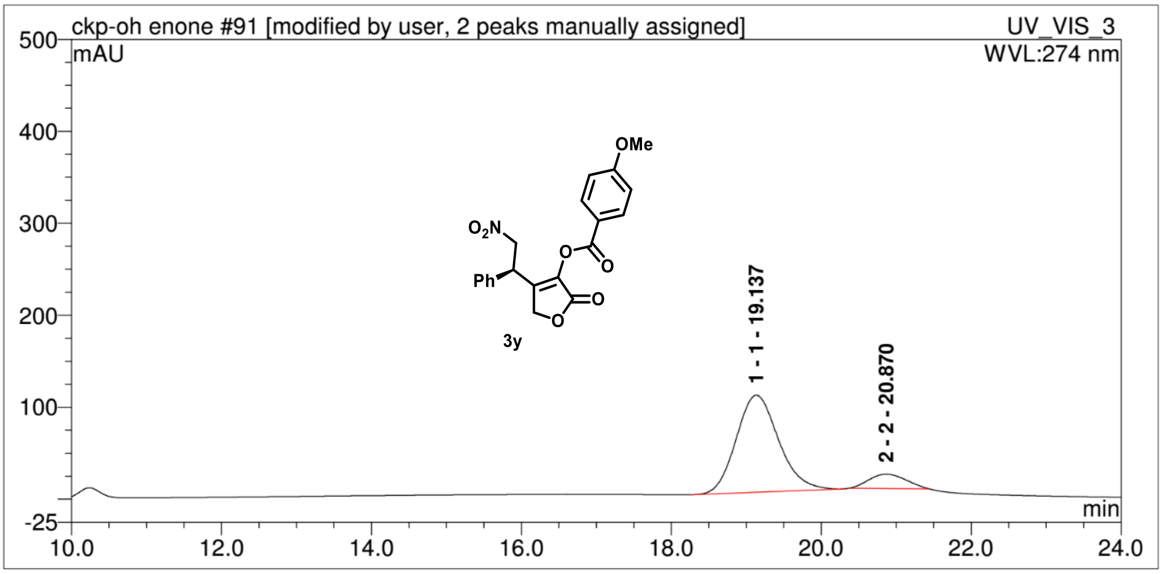

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1	1	19.14	69.07896	88.55887293	105.4466	n.a.
2	2	20.87	8.924	11.44112707	15.558	n.a.

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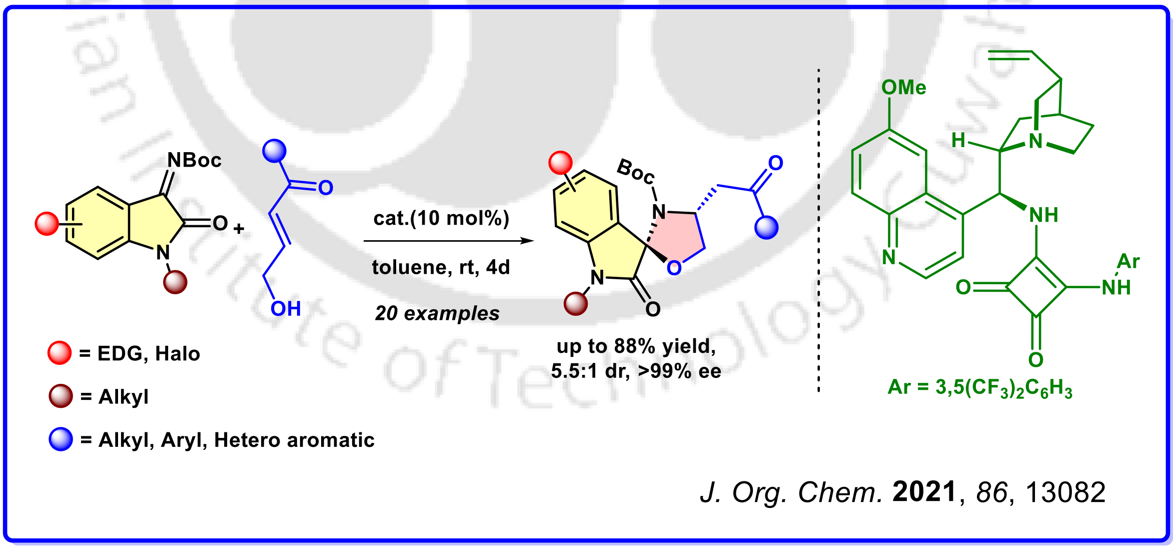
Chapter 4

Organocatalytic Asymmetric Synthesis of Spirooxindole Embedded Oxazolidines

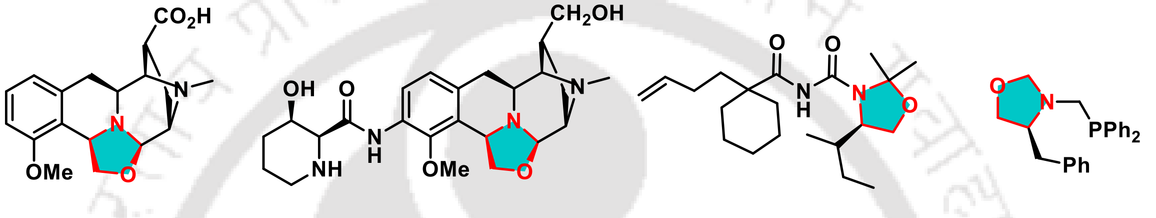
ABSTRACT: The first organocatalytic asymmetric synthesis of spirooxindole embedded oxazolidines has been developed via a domino reaction involving hemiaminal formation, followed by an unprecedented *aza*-Michael reaction between isatin derived *N*-Boc ketimines and γ-hydroxy enones. A quinine derived bifunctional squaramide catalyst was found to be efficient for this reaction, and the products were obtained in good diastereoselectivities and with high enantioselectivities.



J. Org. Chem. **2021**, *86*, 13082

4.1. Introduction

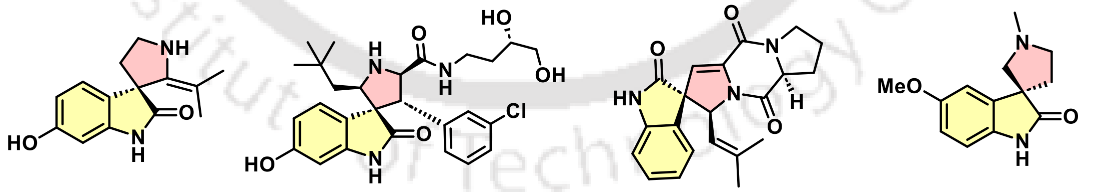
Multifunctional heterocyclic compounds play an essential role in organic and medicinal chemistry, as well as in drug discovery. Notably, nearly 70% of marketed drugs contain heterocycles. Chiral oxazolidine rings are common pharmacophores that comprise potent antitumor tetrahydroisoquinoline based natural products including quinocarcin (**I**) and tetrazomine (**II**). In addition, chiral oxazolidines are used as chiral auxiliaries (**III**)[1] and chiral ligands (**IV**) in a variety of asymmetric transformations.[2]



Quinocarcin (I) **Tetrazomine (II)** **Chiral auxiliary (III)** **Chiral ligand (IV)**

Figure 1: Importance of oxazolidines frame-work.

Chiral spirooxindoles belong to a class of unique spiro-cyclic frameworks, which bear a spiro-ring fused at the C3-position of the oxindole core. These privileged heterocyclic motifs have been widely found in natural alkaloids and pharmaceutical molecules with a broad range of biological activities, such as anti-cancer (**V** and **VI**), antimicrobial (**VII**), antimalarial and traditional herbal medicine (generally used as a pain killer drug) (**VIII**) (Fig. 2).[3]



(+)-Elacomine (V)
Natural anti-cancer agent

Anticancer (MI-219) (VI)

(-)-Spirotrypostatin B (VII)
Anti-mitotic property

(-)-Horsfiline (VIII)
Pain killer drug

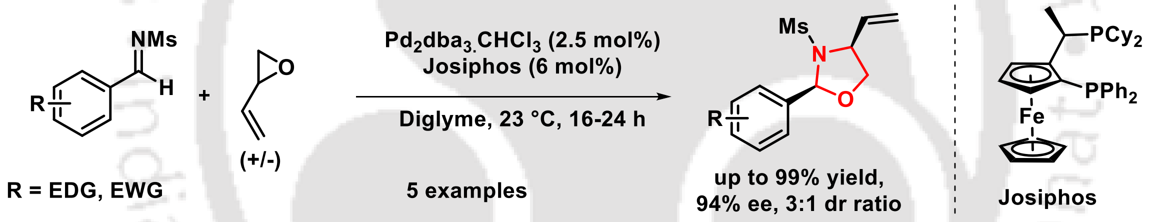
Figure 2: Importance of chiral spirooxindoles frame-work.

Due to the importance of chiral oxazolidine and chiral spirooxindoles motifs, it has received significant attention. Though few metal catalyzed asymmetric syntheses of oxazolidines have been developed, organocatalytic approaches are much less. Similarly, a number of scientists have been engaged to prepare enantiopure spirocyclic oxindole frameworks over the past years.[4] In particular, isatin derived ketimines have been found to be a popular substrate, and a range of asymmetric reactions including cyclization methods have been developed.

4.2 Literature Study:

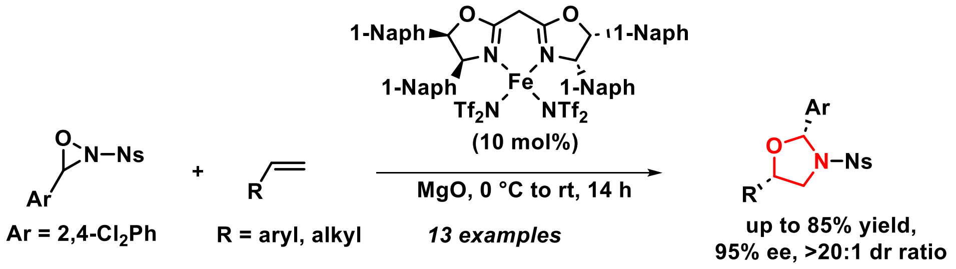
4.2.1 Known strategies for metal catalyzed asymmetric syntheses of oxazolidines:

In 2011, Jarvo et al. reported[5] a complementary stereo convergent reaction for enantioselective synthesis of 1,3-oxazolidines. In this report, reaction of racemic butadiene monoxide, in the presence of a chiral palladium provides an enantioselective synthesis of 1,3-oxazolidines (up to 94% ee).



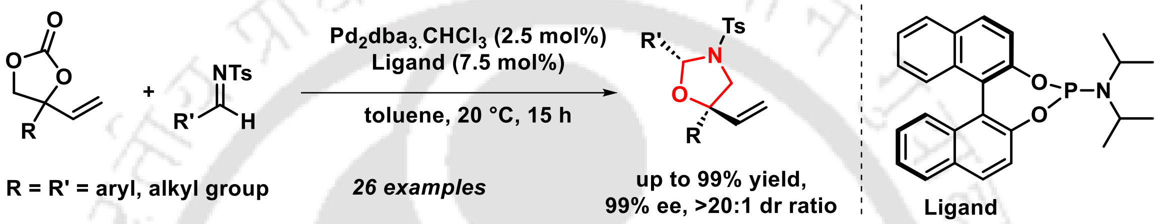
Scheme 1: Complementary stereo convergent reactions for enantioselective synthesis of 1,3-oxazolidines

In 2012, Yoon *et al.* reported[6], the regioselective and enantioselective oxyamination of alkenes with *N*-sulfonyl oxaziridines catalyzed by a novel iron (II) bis(oxazoline) complex. This protocol allowed efficient synthesis of enantioenriched oxazolidine products with good yields and excellent enantioselectivities with single regioisomer. (Scheme 2).



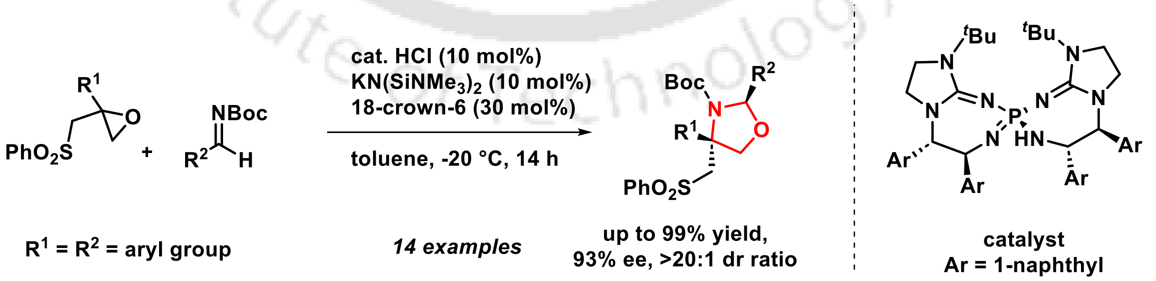
Scheme 2: Iron catalyzed asymmetric oxyamination of olefins

In 2015, Zhang *et al*. reported[7], an efficient method for the enantioselective synthesis of β-tertiary β-amino alcohol derivatives through Pd-catalyzed decarboxylative cycloaddition of vinylethylene carbonates with imines. By using a palladium complex generated in situ from [$Pd_2(dba)_3$]·$CHCl_3$ and phosphoramidite as a catalyst under mild reaction conditions, the process provided 4-substituted-4-vinyloxazolidines in good to high yields with high levels of enantio- and diastereoselectivities (Scheme 3).



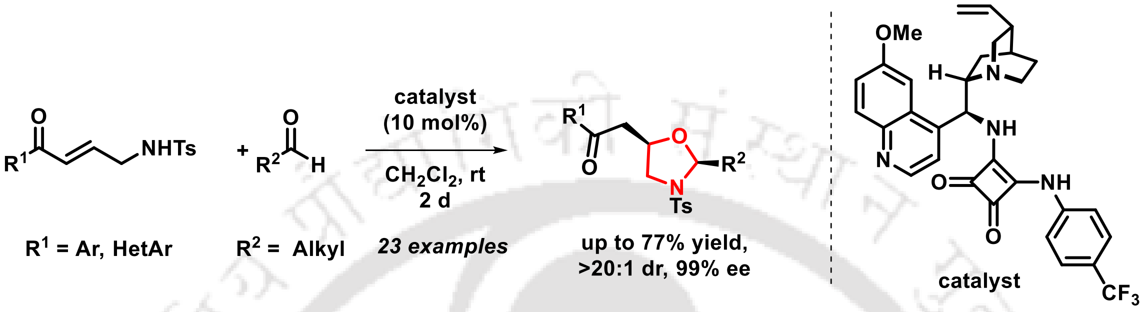
Scheme 3: Pd-Catalyzed asymmetric decarboxylative cycloaddition of vinylethylene carbonates with imines

After the metal catalysed synthesis of oxazolidines, few organocatalytic reports were there. In 2018, Tereda *et al*. postulated[8], a novel enantioselective formal [3+2] cycloaddition of epoxides under Brønsted base catalysis. Due to its high basicity and capacity for good stereocontrol, the bis(guanidino)iminophosphorane, acting as a chiral organosuperbase catalyst, allowed the enantioselective reaction of *β,γ*-epoxysulfones with imines to produce enantioenriched 1,3-oxazolidines with two stereogenic centres, including a quaternary one, in a highly diastereo- and enantiocontrol (Scheme 4).



Scheme 4: Chiral organosuperbase catalysed synthesis of 1,3-oxazolidines

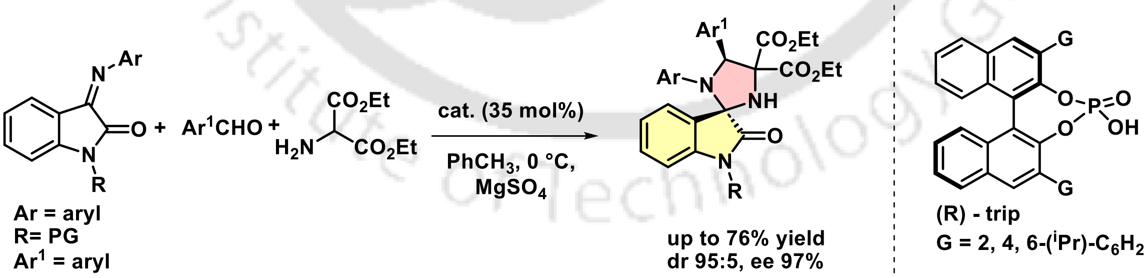
In 2018, Pan *et al*. reported[9], the first organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines *via* hemiaminal formation between alkyl aldehydes and *N*-tosyl aminomethyl enones followed by intramolecular *oxa*-Michael reaction. Quinine derived bifunctional squaramide catalyst was found to be efficient for this reaction and a variety of alkyl aldehydes and *N*-tosyl aminomethyl enones were employed.



Scheme 5: Organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines

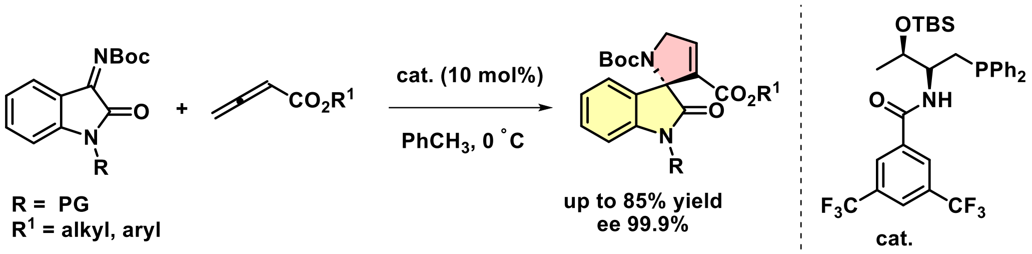
4.2.2 Known strategies for asymmetric syntheses of chiral spiro-oxindoles motifs:

Using a three-component reaction of isatin-derived imines, aldehydes, and an amino-ester in the presence of chiral phosphoric acid, Shi et al. reported[10] a catalytic asymmetric chemoselective 1,3-dipolar cycloaddition (1,3-DC) of an azomethine ylide with imines in 2016. This reaction successfully constructed biologically significant spiro[imidazolidine-2,3′-oxindole] frameworks in good yields, and with high diastereo- and enantioselectivities (Scheme 6).



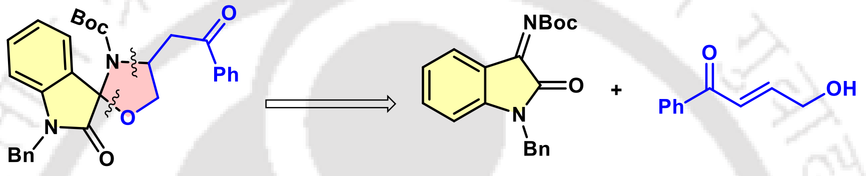
Scheme 6: construction of a spiro[imidazolidine-2,3′-oxindole] framework.

In 2016, Wang et al. reported[11] a highly enantioselective [3+2] cycloaddition reaction that makes the use of isatin-derived ketimines as reaction partners. Both simple and γ-substituted allenoates could be utilized, and various 3,2′-pyrrolidinyl spirooxindoles with a tetrasubstituted stereocenter were obtained in excellent yields and with nearly perfect enantioselectivities (Scheme 7).



Scheme 6: construction of a 3,2′-pyrrolidinyl spirooxindoles framework.

4.3 Concept



3 1 2

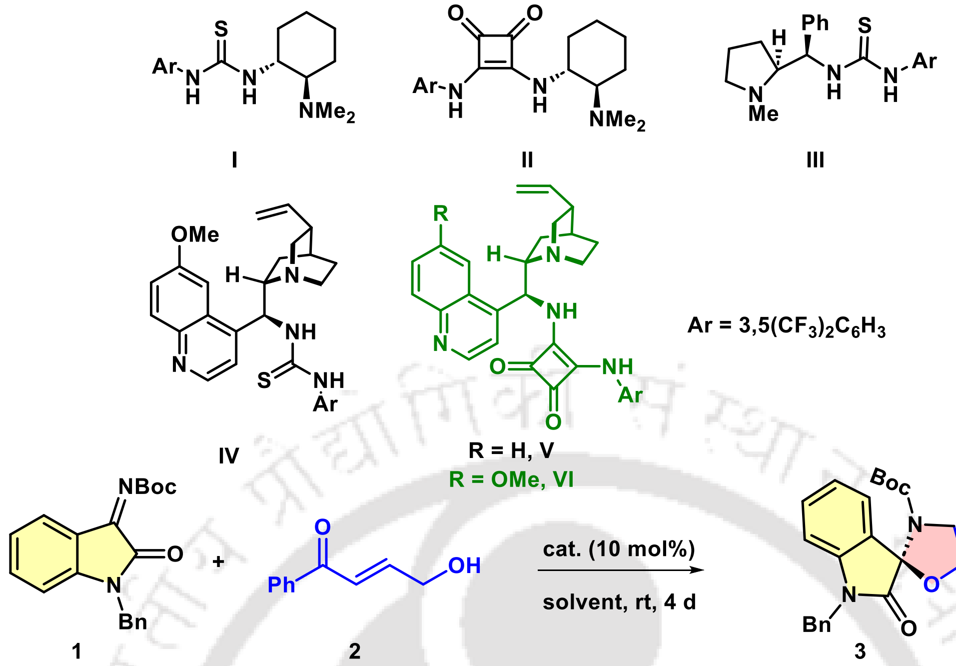
Scheme 7: Concept.

According to literature survey, there is no information on the asymmetric synthesis of spirooxindole-embedded oxazolidines, thus this motif can be created using the isatin-derived ketimine **1** and γ-hydroxyenones **2** as indicated in Scheme 7.

4.4 Results and discussion

4.4.1 Catalyst, Solvent and Reaction condition Optimization

The investigation was initiated by running a model reaction between isatin derived *N*-Boc ketimine **1** and 3-benzoyl prop- 2-en-1-ol (**2**) in the presence of Takemoto catalyst **I** in toluene at room temperature (Table 1). Gratifyingly, after stirring for 4 days, the desired spiro-oxindole-oxazolidine products **3a/3a′** were isolated in 72% combined yield as a mixture of diastereomers (1.1:1 dr), and the ee of the major diastereomer was 88% (Table 1, entry 1). Then we moved our attention to use cyclohexyl diamine based bifunctional squaramide catalyst **II**, and gratifyingly, both enantioselectivity and diastereoselectvity got enhanced (Table 1, entry 2). Proline derived thiourea catalyst **III** was not suitable for the reaction, and moderate yield and enantioselectivity was detected (Table 1, entry 3). The enantioselectivity of the major diastereomer got improved to 95% ee with quinine derived thiourea catalyst **IV** in 1.9:1, though the minor diastereomer



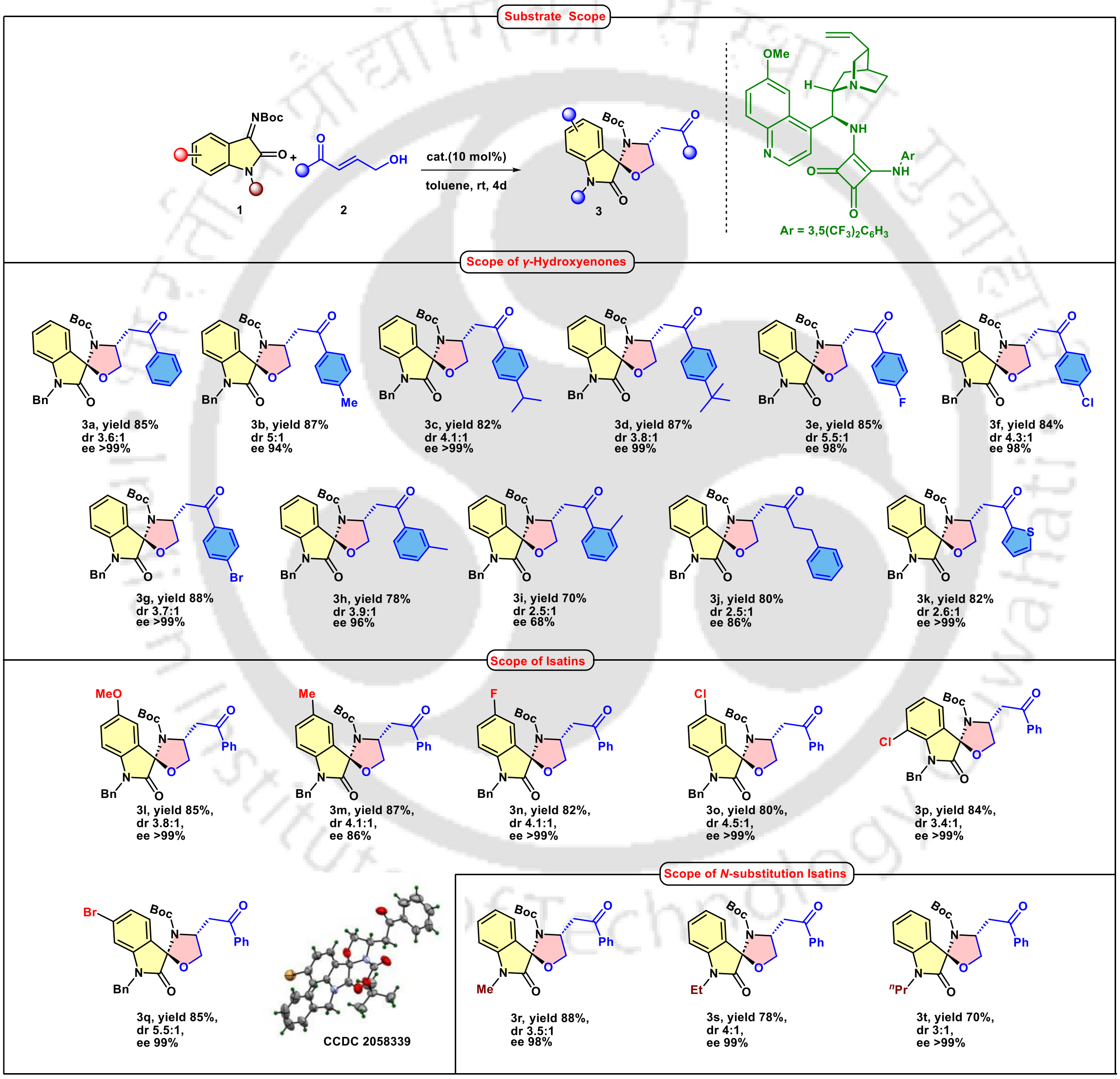
entry[a]	catalyst	solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCH_3$	72	1.1:1	88/36
2	**II**	$PhCH_3$	75	1.5:1	95/0
3	**III**	$PhCH_3$	40	1.1:1	68/10
4	**IV**	$PhCH_3$	67	1.9:1	97/14
5	**V**	$PhCH_3$	83	3.5:1	>99/75
6	**VI**	**$PhCH_3$**	**85**	**3.6:1**	**>99/81**
7	**VI**	$PhCF_3$	80	3.5:1	>99/80
8	**VI**	xylene	81	3.5:1	>99/79
9	**VI**	CH_2Cl_2	74	2.6:1	>99/80
10	**VI**	MTBE	71	2.1:1	>99/75
11[e]	**VI**	$PhCH_3$	83	3.6:1	97/80
12[f]	**VI**	$PhCH_3$	87	3.6:1	60/-

[a] Reaction condition: 0.11 mmol of **1** and 0.1 mmol of **2** in 0.5 mL solvent using 10 mol% catalyst. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}HNMR. [d] Determined by HPLC and of the major diastereomers. [e] reaction carried out at 5 mol% catalyst loading. [f] reaction carried out at 40 °C for 2 d.

Table 1: Catalyst, solvent and reaction condition optimization.

was isolated as a racemic mixture (Table 1, entry 4). Inspired by this result, cinchonidine derived squaramide catalyst **V** having a bis-trifluoromethyl substituted aryl group was screened, and delightfully, the diastereoselectivity got improved to 3.5:1 and enantiomeric excesses of the diastereomers were 99% and 75%, respectively (Table 1, entry 5). Finally, the best catalyst turned out to be quinine derived squaramide catalyst **VI** and the diastereomeric products **3a/3a′** were obtained in 3.6:1 dr with 99% and 81% ees, respectively (Table 1, entry 6). Different solvents were also checked, but a better result was not found. For example, the diastereoselectivity got decreased in *α,α,α*-trifluorotoluene, xylene, dichloromethane and also in MTBE (Table 1, entries 7-10). After that reaction was carried out at 40 °C, to reduce the reaction time but decrease in enantioselectivity was observed (entry 12).

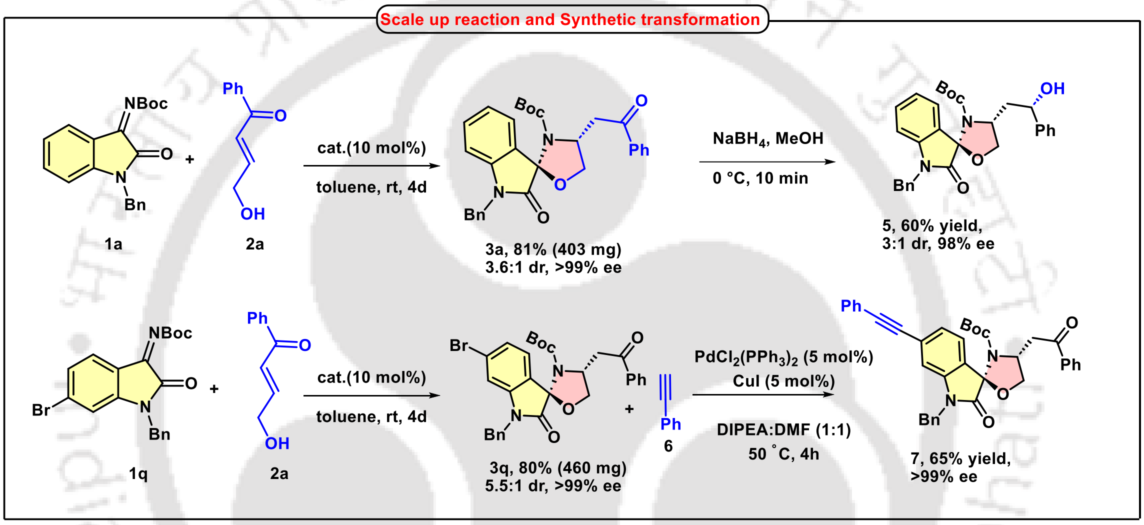
After finalizing the optimized conditions, the scope and generality of the methodology for spirooxindole embedded oxazolidine synthesis was investigated. Initially, different *para* substituted aryl group containing *γ*-hydroxyenones were employed, and gratifyingly, good results were detected (scheme 8). For example, product **3b** having a *p*-tolyl motif was obtained in high diastereo- and enantioselectivity (5:1 dr, 94% ee). Also, other 4-alkyl substituted enones **2c** and **2d** provided the products **3c** and **3d** in high enantioselectivities.Different 4-halo substituted *γ*-hydroxyenones were tolerated in the reaction, providing the products in high diastereo- and enantioselectivities (up to 5.5:1 dr and >99% ee). In particular, product **3e** was isolated in 5.5 dr with 98% ee. A *meta*-tolyl group containing enone **2h** also participated in the reaction to deliver product **3h** in 3.9:1 dr with 96% ee. Then *ortho*-tolyl substituted enone **2i** was engaged in the reaction. Though a smooth conversion was detected for product **3i**, the enantioselectivity was less. Moreover, our methodology is also suitable for hydrocinnamyl substituted enone **2j**, and an acceptable enantioselectivity 86%was detected for product **3j**. Then heteroaromatic 2-thienyl group containing enone **2k** was screened, and gratifyingly, product **3k** was obtained in excellent >99% ee. In the next, the scope of isatin derived ketimine **1** was investigated. *N*-substitutions as well as the substitutions on the aryl part were tolerated (Scheme 8). First, good results (up to >99% ee) were obtained using a variety of substituents at the 5-position, including both electron-donating (OMe and Me) and withdrawing (F and Cl). 7-Chloro substituted ketimine **1g** also took part in the reaction to deliver product **3p** in perfect enantioselectivity. Then 6-bromosubstituted ketimine was engaged in the reaction to provide product **3q** in 5.5:1 dr with 99% ee (Scheme 8). Then different *N*-substitutions were checked, and gratifyingly, different *N*-alkyl groups were tolerated and excellent enantioselectivities were maintained for products **3r**, **3s**, and **3t**.



Scheme 8: Substrate scope

The absolute configuration of the product **3q** was solved to be (3*R*,4′*R*) by *X*-ray crystallography. The absolute structure of other products is expected to be the same by analogy.

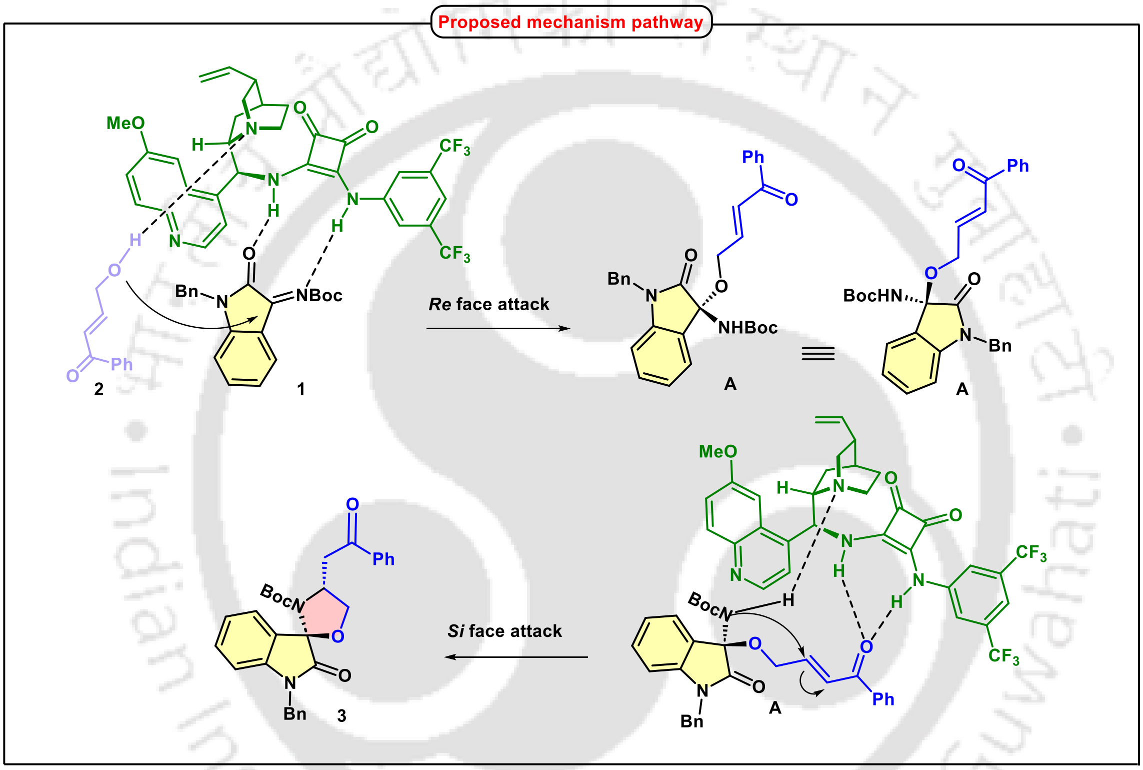
To confirm the feasibility of this strategy for practical use, scale-up reactions were conducted in 1 mmol scale for **1a** and **1q**, and good yields with excellent enantioselectivities were achieved in the presence of only 10 mol % catalyst **VI** (Scheme 9). These results indicated that this reaction has good potential for scaled-up production.



Scheme 9: Scale up reaction and synthetic transformation

The synthetic utility of our method was demonstrated by performing a few reactions on **3a** and **3q** (Scheme 9). Initially, compound **3a** was treated with sodium borohydride. This resulted in the formation of the alcohol **5** in 60% yield with 98% ee, and the relative stereochemistry was solved by NOE experiment. Then the Sonogashira reaction was carried out between **3q** (pure diastereomer) and phenyl acetylene (**6**). The reaction progressed smoothly to deliver product **7** in 65% yield with retention of enantiopurity.

A probable mechanism has been shown in Scheme 10 to explain the stereochemistry of the product. A bifunctional mode of activation of catalyst **VI** operates. It is assumed that the keto and imine groups of **1a** are activated by the squaramide moiety of the catalyst **VI**, whereas the alcohol group of **2a** is deprotonated by the tertiary amino motif of **VI**. Since the *Si* face of **1a** is blocked by catalyst **VI**, addition of **2a** takes place from the *Re* face to provide hemiaminal **A**. Hemiaminal **A** then undergoes an intramolecular *aza*-Michael reaction with Boc carbamate as the nucleophile. Here also, catalyst **VI** blocks the *Re* face of the enone, and thus Michael addition takes place from the *Si* face to generate product **3a**. Since the hemiaminal chiral centre is stable,[12] the diastereoselectiviity of this reaction might be due to the *aza*-Michael step.



Scheme 10: Proposed mechanism

In summary, this report delineates the first organocatalytic asymmetric synthesis of spirooxindole embedded oxazolidines. Our work also represents the first bifunctional thiourea/ squaramide catalyzed *aza*-Michael reaction of the *N*-Boc group. Easily available isatin derived *N*-Boc ketimines and *γ*-hydroxy enones were used as the substrates. The oxazolidine products were isolated in good yields and with good diastereoselectivity and high enantioselectivity. Also, a few synthetic transformations have been demonstrated, including a Sonogashira reaction.

4.5 Experimental section:

4.5.1. General Information.

Chemicals and solvents were purchased from commercial suppliers and used as received. 1H NMR spectra were recorded on 400, 500, and 600 MHz spectrometers. 13C{H} NMR spectra were recorded on 100 and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in hertz (Hz). Using ESI mode, HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA, IC, IB, IE, Chiralpak lux Amylose-1 and AD-H Column. For visualizing the products, UV light and I2 were used. Melting points were measured using a BüCHI melting point B-540 apparatus. All melting points were measured in an open glass capillary, and values are uncorrected. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 GF254 (0.25 mm).

4.5.2. General Procedure for the Synthesis of Isatin Derived Ketimine (1a): Isatin derived ketimines (**1a**) were prepared according to the known reported procedure[13].

4.5.3. General Procedure for the Synthesis of γ-Hydroxyenones (2a): γ-Hydroxyenones (**2a**) were prepared according to the known reported procedure[14].

4.5.4. General Procedure for the Catalyst Preparation: The best catalyst, i.e., quinine derived squaramide catalyst **VI**, was prepared according to the previously reported procedure[14].

4.5.5. General Procedure for the Synthesis of Compound 3: In an oven-dried round-bottom flask (5 mL) were taken **1a** (37 mg, 0.11 mmol), **2a** (16.2 mg, 0.1 mmol), and 10 mol % of catalyst (**VI**). Toluene (0.5 mL) was added to the reaction mixture and stirred at room temperature for 4 days. Completion of the reaction was checked by TLC. After completion of the reaction, solvent was concentrated and the reaction mixture was directly purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (4- 8%) to afford the desired products **3a**-**3t**.

4.5.6. General Procedure for the Synthesis of Compounds 5 and 7: To a stirred solution of *tert*-butyl (3*R*,4′**R**)-1-benzyl-2-oxo 4′-(2-oxo-2-phenylethyl)spiro[indoline-3,2′-oxazolidine]-3′-carboxylate (**3a**) (0.1 mmol) in 1 mL of dry MeOH under argon at 0 °C was added NaBH$_4$ (2 equiv) at once. The resulting reaction mixture was stirred for 10 min at 0 °C. After completion of the reaction, water was added. Then the organic layer was extracted with EtOAc. At the end, it was purified by silica gel column chromatography using (5-15)% EtOAc/hexane to obtain the pure product *tert*-butyl (3*R*,4′*R*)-1- benzyl-4′-((*S*)-2-hydroxy-2-phenylethyl)-2-oxospiro[indoline-3,2′-oxazolidine]-3′-carboxylate (**5**) with 60% yield.

In an oven-dried round-bottom flask were taken *tert*-butyl (3*R*,4′*R*)-1-benzyl-6-bromo-2-oxo-4′-(2-oxo-2-phenylethyl) spiro- [indoline-3,2′-oxazolidine]-3′-carboxylate (**3q**), Cl$_2$Pd (PPh$_3$)$_2$ (5 mol %), and CuI (5 mol %) under an argon atmosphere. DMF: DIPEA (1:1) and phenyl acetylene (1.1 equiv) were added to the reaction mixture. The resulting reaction mixture was stirred for 4 h at 50 °C. After completion of the reaction, water was added and the organic part was extracted with EtOAc. At the end, it was purified by silica gel column chromatography using (5-10) % EtOAc/hexane to obtain the pure product *tert*-butyl (3*R*,4′*R*)-1-benzyl-2-oxo-4′-(2-oxo-2-phenylethyl)-6-(phenylethynyl)spiro[indoline-3,2′-oxazolidine]-3′-carboxylate (**7**) with 65% yield.

4.6 Crystal structure of product 3p:

CCDC No.	2058339
Empirical formula	$C_{30}H_{29}BrN_2O_5$
Formula weight	576.12
Crystal habit, colour	block / white
Crystal size, mm^3	0.36×0.33×0.33

Temperature, *T*	296 K
Wavelength, *λ* (Å)	0.71073
Crystal system	Monoclinic
Space group	*'C 2'*
Unit cell dimensions	*a=21.999(4) b=9.9929(14) c=26.101(5)* *alpha=90 beta=105.083(6) gamma=90*

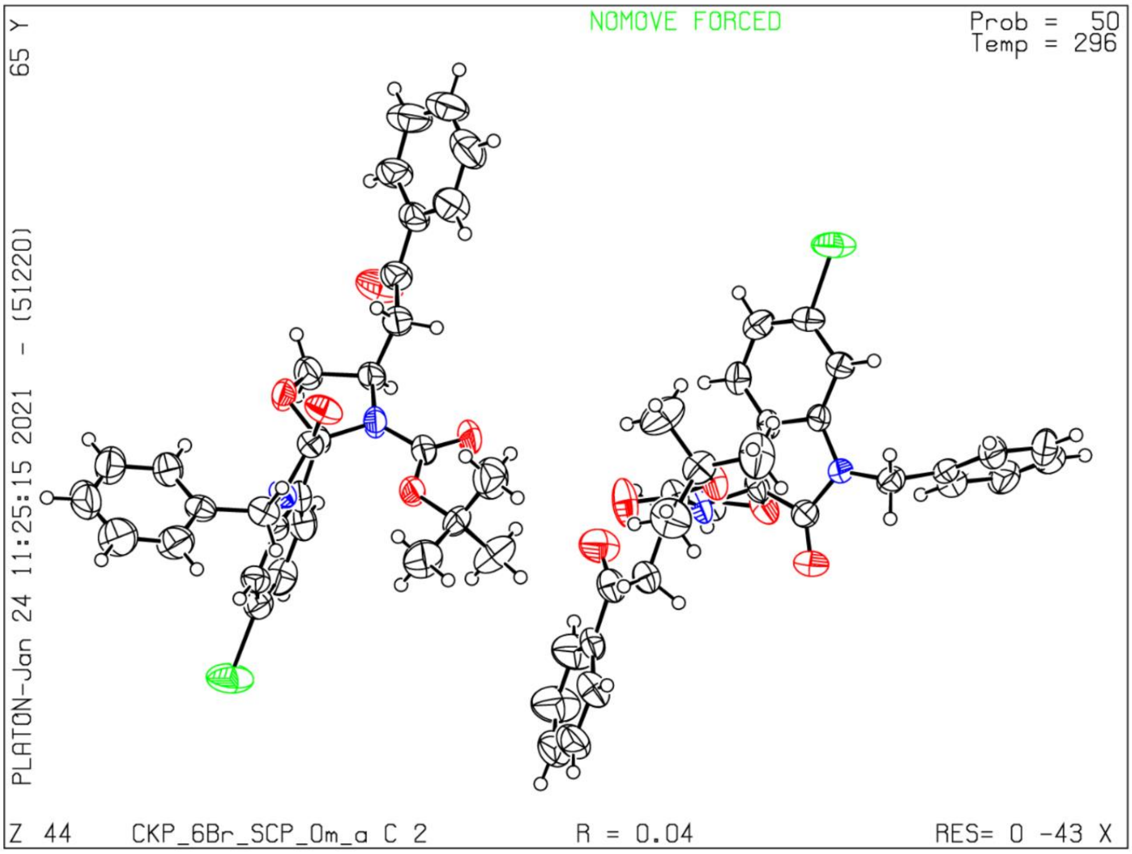
Theta(max)= 25.048

Data completeness= 1.87/0.99

R(reflections)= 0.0406(7139)

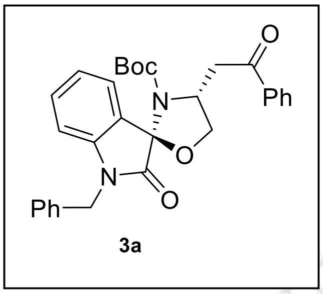
wR2(reflections)=0.0967(9735)

Datablock CKP_6Br_SCP_0m_a - ellipsoid plot



4.7 Characterisation of the products:

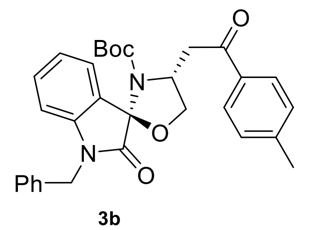
tert-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3a)



3a

Orange sticky, 85% (42 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.10 (d, J = 7.0 Hz, 0.55H), 8.07 (d, J = 7.5 Hz, 2H), 7.63 (d, J = 7.1 Hz, 0.28H), 7.60 (t, J = 7.4 Hz, 1H), 7.53 (d, J = 7.5 Hz, 0.55H), 7.49 (t, J = 7.7 Hz, 2H), 7.40 (d, J = 7.4 Hz, 2.55H), 7.35 (dd, J = 15.4, 7.5 Hz, 3.83H), 7.31 – 7.26 (m, 2.54H), 7.08 (t, J = 7.5 Hz, 1.27H), 6.77 (d, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 0.28H), 5.12 (d, J = 15.5 Hz, 1H), 4.98 (d, J = 14.9 Hz, 0.28H), 4.89 – 4.86 (m, 1H), 4.81 (d, J = 3.2 Hz, 0.27H), 4.70 – 4.63 (m, 2H), 4.31 (dd, J = 9.0, 3.5 Hz, 1H), 4.26 (d, J = 8.8 Hz, 0.27H), 4.16 – 4.12 (m, 1H), 4.11 (d, J = 2.5 Hz, 0.54H), 3.95 – 3.89 (m, 0.27H), 3.78 (d, J = 18.2 Hz, 0.27H), 3.70 (dd, J = 18.1, 10.4 Hz, 1H), 1.40 (s, 2.57H), 1.00 (s, 9H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.1, 173.2, 150.9, 143.4, 136.6, 135.4, 133.5, 130.7, 129.0, 128.7, 128.4, 128.3, 128.1, 128.0, 127.8, 123.4, 123.4, 109.6, 90.0, 81.1, 71.8, 54.0, 44.2, 41.2, 27.8. **ESI-MS** m/z calcd. for $C_{30}H_{30}N_2O_5$ $[M+H]^+$ 499.2227, found 499.2227.**HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 8.3 min, t_{minor} = 33.3 min.

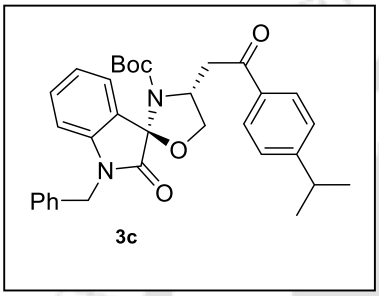
tert-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-(p-tolyl)ethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3b)



3b

light orange sticky, 87% (45 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.86 (d, J = 8.3 Hz, 2.34H), 7.29 (t, J = 7.5 Hz, 3.66H), 7.24 – 7.22 (m, 2.43H), 7.21 – 7.17 (m, 4.91H), 6.98 (t, J = 7.3 Hz, 1.24H), 6.66 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 7.9 Hz, 0.20H), 5.02 (d, J = 15.4 Hz, 1H), 4.89 (s, 0.22H), 4.80 – 4.75 (m, 1.25H), 4.61 – 4.52 (m, 2.41H), 4.20 (dd, J = 9.0, 3.6 Hz, 1H), 4.08 (d, J = 7.0 Hz, 0.26H), 4.00 (dd, J = 18.0, 2.6 Hz, 1H), 3.76 (d, J = 9.8 Hz, 0.22H), 3.60 – 3.52 (m, 1H), 3.04 – 2.99 (m, 0.25H), 2.34 (s, 3.59H), 0.94 (s, 1.78H), 0.90 (s, 9H). **13C NMR (100 MHz, $CDCl_3$)** δ 198.8, 173.2, 151.0, 144.3, 143.5, 135.5, 134.3, 130.7, 129.4, 129.1, 128.5, 127.8, 123.5, 123.4, 109.6, 90.0, 81.5, 71.9, 54.1, 44.2, 41.1, 27.9, 21.9· **ESI HRMS**: calcd. For $C_{31}H_{32}N_2O_5$ $[M+H]^+$ 513.2384, found 513.2384. **HPLC Analysis:** ee of major diasteromer= 94%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 47.1 min, t_{major} = 84.0 min.

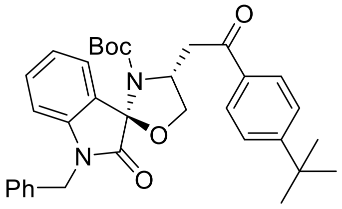
***tert*-butyl (3R,4'R)-1-benzyl-4'-(2-(4-isopropylphenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3c)**



3c

Colourless sticky solid, 82% (44 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91 (t, J = 9.4 Hz, 2H), 7.82 (ddd, J = 11.7, 7.7, 4.8 Hz, 0.45H), 7.29 (t, J = 7.8 Hz, 3.82H), 7.23 (dd, J = 7.3, 6.0 Hz, 7.06H), 7.18 (d, J = 3.7 Hz, 1.25H), 6.98 (t, J = 7.3 Hz, 1.23H), 6.66 (d, J = 7.7 Hz, 1H), 6.60 – 6.56 (m, 0.25H), 5.02 (d, J = 15.4 Hz, 1H), 4.88 (d, J = 6.9 Hz, 0.48H), 4.79 – 4.74 (m, 1H), 4.62 – 4.50 (m, 2H), 4.45 (d, J = 15.5 Hz, 0.21H), 4.19 (dt, J = 9.9, 5.0 Hz, 1H), 4.07 (d, J = 7.7 Hz, 0.24H), 4.01 (dd, J = 18.0, 2.5 Hz, 1H), 3.86 (d, J = 16.1 Hz, 0.24H), 3.55 (dd, J = 18.0, 10.5 Hz, 1H), 3.24 (dd, J = 16.1, 10.6 Hz, 0.24H), 3.02 (t, J = 7.4 Hz, 0.23H), 2.91 – 2.87 (m, 1H), 1.21 – 1.18 (m, 7.77H), 0.93 (d, J = 9.2 Hz, 2.09H), 0.92 (d, J = 18.5 Hz, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.8, 173.3, 155.1, 151.0, 144.1, 143.5, 135.5, 134.7, 130.7, 129.0, 128.6, 128.2, 128.0, 127.8, 127.0, 126.8, 123.4, 123.4, 109.6, 90.0, 81.5, 71.95, 54.2, 44.2, 41.2, 34.4, 27.8, 23.8. **ESI HRMS**: calcd. For $C_{33}H_{36}N_2O_5$ $[M+H]^+$ 541.2697, found 547.2696. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 11.3 min, t_{minor} = 14.6 min.

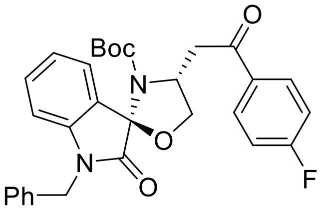
***tert*-butyl (3R,4'R)-1-benzyl-4'-(2-(4-(tert-butyl)phenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3d)**



3d

Pale yellow semi solid, 80% (44 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.91 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 6.9 Hz, 0.49H), 7.47 – 7.36 (m, 3.78H), 7.29 (t, J = 7.5 Hz, 2.80H), 7.27 – 7.20 (m, 3.98H), 7.19 (t, J = 3.9 Hz, 2.31H), 7.12 (d, J = 7.8 Hz, 0.31H), 6.98 (t, J = 7.4 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 7.8 Hz, 0.24H), 5.02 (d, J = 15.5 Hz, 1H), 4.89 (d, J = 7.8 Hz, 0.27H), 4.77 (ddd, J = 13.3, 6.4, 3.4 Hz, 1.27H), 4.60 – 4.53 (m, 2H), 4.20 (dd, J = 9.0, 3.6 Hz, 1H), 4.10 (d, J = 6.7 Hz, 0.23H), 4.02 (dd, J = 18.1, 2.3 Hz, 1H), 3.77 (d, J = 9.9 Hz, 0.22H), 3.55 (dd, J = 17.9, 10.5 Hz, 1H), 3.49 – 3.44 (m, 0.28H), 3.03 (t, J = 7.5 Hz, 0.52H), 1.27 (d, J = 2.6 Hz, 14.07H), 0.90 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.9, 173.2, 157.31, 151.0, 143.5, 135.5, 134.2, 130.7, 129.1, 128.4, 128.2, 128.2, 128.1, 127.8, 125.8, 125.7, 123.4, 123.4, 109.6, 90.0, 81.5, 71.9, 54.1, 44.2, 35.3, 31.3, 27.9. **ESI HRMS**: calcd. For $C_{34}H_{38}N_2O_5$ $[M+H]^+$ 555.2853, found 555.2853. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 40.5 min, t_{minor} = 106.1 min.

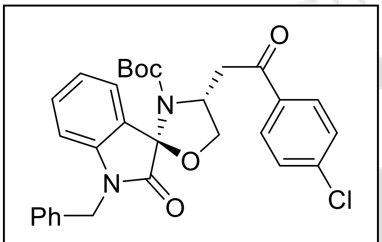
***tert*-butyl (3R,4'R)-1-benzyl-4'-(2-(4-fluorophenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3e)**



3e

Light yellow sticky solid, 85% (44 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (dd, J = 8.8, 5.4 Hz, 2.34H), 7.29 (t, J = 7.1 Hz, 3.52H), 7.26 – 7.21 (m, 3.70H), 7.18 (dd, J = 4.3, 2.5 Hz, 2.20H), 7.06 (t, J = 8.6 Hz, 2.40H), 6.98 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 7.5 Hz, 0.17H), 6.67 (d, J = 7.7 Hz, 1H), 6.59 (d, J = 7.8 Hz, 0.18H), 5.01 (d, J = 15.4 Hz, 1H), 4.76 (ddd, J = 9.3, 6.4, 3.3 Hz, 1.23H), 4.57 (dd, J = 15.1, 7.9 Hz, 2H), 4.46 (d, J = 15.5 Hz, 0.19H), 4.20 (dd, J = 9.0, 3.5 Hz, 1H), 4.08 (t, J = 6.7 Hz, 0.33H), 3.99 (dd, J = 18.1, 2.7 Hz, 1H), 3.86 (d, J = 16.1 Hz, 0.17H), 3.55 (dd, J = 18.0, 10.3 Hz, 1H), 3.22 (dd, J = 15.2, 8.8 Hz, 0.19H), 0.94 (s, 1.62H), 0.89 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.5, 173.2, 167.4, 164.8, 151.0, 144.1, 143.5, 135.8, 133.2, 133.2, 131.1, 131.0, 130., 129.1, 128.1, 127.8, 123.4, 116.0, 115.8, 109.6, 90.0, 81.6, 71.8, 54.0, 44.2, 41.2, 27.8. **ESI HRMS**: calcd. For $C_{30}H_{29}FN_2O_5$ $[M+H]^+$ 517.2133, found 517.2133. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 37.6 min, t_{minor} = 72.9 min.

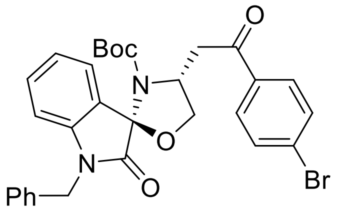
tert-butyl (3R,4'R)-1-benzyl-4'-(2-(4-chlorophenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3f)



3f

Yellow semi solid, 84% (45 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.91 (d, J = 8.8 Hz, 2.67H), 7.38 (t, J = 6.8 Hz, 2.70H), 7.29 – 7.21 (m, 8.60H), 6.98 (d, J = 7.3 Hz, 1.27H), 6.67 (d, J = 7.7 Hz, 1.22H), 5.01 (d, J = 15.4 Hz, 1H), 4.89 (s, 0.24H), 4.76 (dd, J = 7.2, 3.1 Hz, 1.23H), 4.57 (dd, J = 15.2, 6.7 Hz, 2H), 4.48 (s, 0.26H), 4.19 (dd, J = 9.0, 3.5 Hz, 1H), 4.06 (d, J = 7.4 Hz, 0.46H), 3.99 (dd, J = 18.2, 2.7 Hz, 1H), 3.85 (d, J = 12.6 Hz, 0.24H), 3.55 (dd, J = 18.1, 10.3 Hz, 1H), 3.23 (d, J = 3.4 Hz, 0.26H), 0.94 (s, 2.27H), 0.89 (s, 9H). **13C NMR (150 MHz, CDCl$_3$)** δ 197.9, 173.2, 151.0, 143.5, 140.0, 135.4, 135.1, 131.1, 130.8, 129.8, 129.8, 129.2, 129.1, 129.1, 129.0, 128.8, 128.1, 128.0, 127.9, 127.8, 127.6, 123.8, 123.4, 123.5, 123.2, 109.6, 109.5, 90.0, 81.3, 71.2, 54.0, 44.2, 41.2, 27.9, 27.8. **ESI HRMS**: calcd. For $C_{30}H_{29}ClN_2O_5$ $[M+H]^+$ 533.1838, found 533.1841. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 28.6 min, t_{major} = 51.0 min.

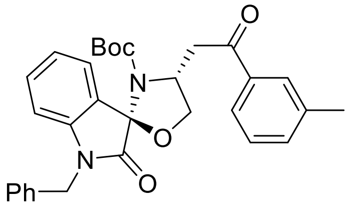
tert-butyl (3R,4'R)-1-benzyl-4'-(2-(4-bromophenyl)-2-oxoethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3g)



3g

Light yellow sticky solid, 88% (49 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (t, J = 8.7 Hz, 2.23H), 7.54 (dd, J = 13.4, 8.5 Hz, 2.52H), 7.29 (d, J = 7.2 Hz, 2.66H), 7.22 (d, J = 7.3 Hz, 2.54H), 7.19 – 7.15 (m, 2.70H), 7.11 – 7.05 (m, 1.27H), 6.98 (t, J = 7.3 Hz, 1.29H), 6.67 (d, J = 7.7 Hz, 1H), 6.62 – 6.56 (m, 0.26H), 5.00 (d, J = 15.5 Hz, 1H), 4.88 (d, J = 3.6 Hz, 0.30H), 4.83 (d, J = 6.5 Hz, 0.30H), 4.78 – 4.72 (m, 1.26H), 4.60 – 4.53 (m, 2H), 4.46 (d, J = 15.5 Hz, 0.27H), 4.18 (dd, J = 9.0, 3.5 Hz, 1H), 4.05 (s, 0.29H), 3.98 (dd, J = 18.1, 2.7 Hz, 1H), 3.84 (d, J = 15.5 Hz, 0.28H), 3.53 (dd, J = 18.1, 10.2 Hz, 1H), 3.26 – 3.17 (m, 0.29H), 0.93 (s, 2.38H), 0.89 (s, 9H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.1, 172.2, 150.0, 143.1, 142.5, 134.5, 134.4, 134.4, 131.2, 131.1, 129.8, 128.9, 128.2, 128.1, 127.7, 127.4, 127.1, 127.0, 126.8, 124.5, 122.4, 108.6, 89.0, 80.1, 70.7, 53.1, 53.0, 43.2, 40.2, 26.8. **ESI HRMS**: calcd. For $C_{30}H_{29}BrN_2O_5$ $[M+H]^+$ 577.1333, found 577.1332. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 51.9 min, t_{major} = 95.8 min.

***tert*-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-(m-tolyl)ethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3h)**

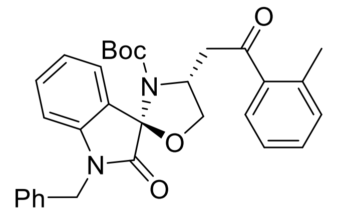


3h

Yellow sticky, 78% (40 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 – 7.74 (m, 2.51H), 7.29 (t, J = 6.8 Hz, 4.96H), 7.20 (ddd, J = 14.6, 8.2, 5.1 Hz, 5.54H), 7.09 (s, 0.24H), 6.98 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.59 (d, J = 7.1 Hz, 0.27H), 5.03 (d, J = 15.5 Hz, 1H), 4.88 (s, 0.26H), 4.84 (d, J = 8.3 Hz, 0.20H), 4.80 – 4.75 (m, 1H), 4.71 (s, 0.26H), 4.61 – 4.53 (m, 2H), 4.20 (dd, J = 9.0, 3.6 Hz, 1H), 4.09 (t, J = 6.6 Hz, 0.27H), 4.01 (dd, J = 18.3, 2.5 Hz, 1H), 3.83 – 3.74 (m, 0.23H), 3.70 – 3.62 (m, 0.27H), 3.56 (dd, J = 18.2, 10.4 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 0.71H), 1.30 (s, 2.32H), 0.90 (s, 9H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.4, 173.2, 151.0, 143.5, 138.5, 136.7, 135., 134.37, 130.7, 129.2, 129.1, 128.8, 128.6, 128.4, 128.1, 127.8, 125.6, 123.4, 123.4, 109.6, 90.1, 81.6, 71.9, 54.1, 44.2, 41.3, 27.9, 21.5. **ESI HRMS**: calcd. For $C_{31}H_{32}N_2O_5$

[M+H]$^+$ 513.2384, found 513.2385. **HPLC Analysis:** ee of major diasteromer= 96%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 66.3 min, t_{minor} = 74.5 min.

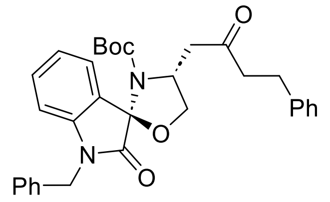
***tert*-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-(o-tolyl)ethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3i)**



3i

Orange semi solid 70% (36 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, J = 7.7 Hz, 1.25H), 7.42 – 7.28 (m, 13.15H), 7.09 (s, 0.25H), 7.05 (d, J = 7.4 Hz, 1H), 6.78 (s, 0.25H), 6.72 (d, J = 7.6 Hz, 1H), 5.13 (d, J = 15.5 Hz, 1H), 5.13 (d, J = 15.5 Hz, 1H), 4.93 (s, 1H), 4.90 (d, J = 8.4 Hz, 1.43H), 4.87 – 4.81 (m, 1H), 4.68 – 4.60 (m, 0.45H), 4.53 (d, J = 15.5 Hz, 1H), 4.32 – 4.27 (m, 0.38H), 4.17 – 4.14 (m, 1H), 4.11 – 4.04 (m, 0.41H), 3.88 (d, J = 16.5 Hz, 1H), 3.67 – 3.61 (m, 0.41H), 3.32 (dd, J = 17.0, 10.6 Hz, 1H), 2.54 (d, J = 5.4 Hz, 4..27H), 1.26 (s, 3.43H), 1.01 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 202.1, 173., 151.43, 144.2, 138.9, 138.5, 137.1, 135.6, 132.4, 132.5, 131.0, 129.2, 129.0, 128.4, 128.4, 128.0, 127.9, 127.6, 126.0, 125.6, 124.0, 123.1, 123.2, 111.2, 109.5, 89.8, 81.5, 71.2, 54.2, 44.9, 44.2, 44.0, 27.9, 21.8. **ESI HRMS**: calcd. For $C_{31}H_{32}N_2O_5$ [M+H]$^+$ 513.2384, found 513.2387. **HPLC Analysis:** ee of major diasteromer= 68%, Chiralpak lux Amylose-1 Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 25.2 min, t_{minor} = 119.7 min.

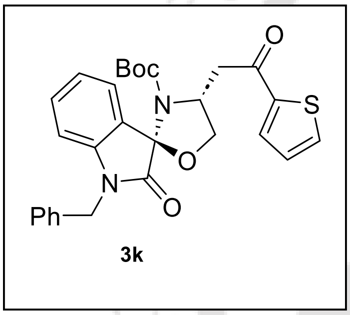
***tert*-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-4-phenylbutyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3j)**



3j

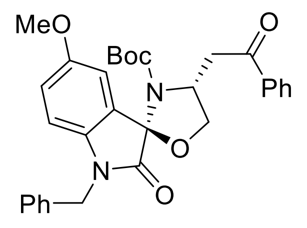
Yellow sticky solid, 86% (43 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 (s, 4.02H), 7.23 – 7.18 (m, 7.05H), 7.13 (d, J = 6.1 Hz, 5.52H), 6.98 (d, J = 7.5 Hz, 1.50H), 6.64 (t, J = 7.5 Hz, 1.33H), 5.07 – 4.97 (m, 1.39H), 4.86 (s, 0.44H), 4.77 – 4.69 (m, 1H), 4.58 – 4.54 (m, 1.49H), 4.51 – 4.46 (m, 1.47H), 4.08 (dd, J = 8.9, 3.7 Hz, 1H), 3.91 (s, 0.40H), 3.48 (dd, J = 18.2, 2.7 Hz, 1H), 3.26 (s, 0.48H), 3.01 (dd, J = 18.4, 10.0 Hz, 1.18H), 2.85 (t, J = 7.2 Hz, 2.92H), 2.79 – 2.74 (m, 3.19H), 0.91 (s, 3.82H), 0.87 (s, 9H).^{13}**C NMR (100 MHz, $CDCl_3$)** δ 208.9, 173.2, 150.9, 144.1, 143.5, 141.0, 135.6, 135.5, 131.0, 130.8, 129.1, 128.8, 128.7, 128.5, 128.1, 127.8, 126.3, 123.4, 123.4, 109.6, 89.9, 81.6, 71.7, 53.4, 45.0, 44.6, 44.2, 27.8. **ESI HRMS**: calcd. For $C_{32}H_{34}N_2O_5$ $[M+H]^+$ 527.2540, found 527.2540. **HPLC Analysis:** ee of major diasteromer= 86%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 24.1 min, t_{minor} = 39.5 min.

tert-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-(thiophen-2-yl)ethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3k)



Pale yellow semi solid, 82% (41 mg) yield. ^{1}**H NMR (400 MHz, $CDCl_3$)** δ 7.87 (dd, J = 7.6, 3.5 Hz, 0.36H), 7.82 (d, J = 3.6 Hz, 1H), 7.61 (d, J = 4.7 Hz,0.401H), 7.57 (d, J = 4.9 Hz, 1H), 7.32 – 7.14 (m, 10.52H), 7.10 (dd, J = 8.7, 4.4 Hz, 0.42H), 7.06 (t, J = 4.3 Hz, 1H), 6.96 (dt, J = 20.4, 7.4 Hz, 1.46H), 6.67 (d, J = 7.8 Hz, 1H), 6.58 (t, J = 10.1 Hz, 0.35H), 5.02 (d, J = 15.4 Hz, 1H), 4.89 (dd, J = 35.0, 16.1 Hz, 0.60H), 4.76 – 4.73 (m, 1H), 4.73 – 4.66 (m, 0.42H), 4.55 (dd, J = 9.1, 6.5 Hz, 2H), 4.48 (dd, J = 28.0, 10.6 Hz, 0.34H), 4.25 (dd, J = 9.0, 3.4 Hz, 1H), 4.17 (dd, J = 24.1, 8.7 Hz, 0.38H), 3.98 (dd, J = 17.3, 2.9 Hz, 1H), 3.72 (dd, J = 84.9, 22.6 Hz, 0.69H), 3.49 (dd, J = 17.3, 10.3 Hz, 1H), 1.29 (s, 2.98H), 0.89 (s, 9H).^{13}**C NMR (150 MHz, $CDCl_3$)** δ 191.8, 173.1, 150.9, 144.0, 143.4, 135.4, 134.1, 133.1, 131.0, 130.7, 129.0, 128.4, 127.8, 123.4, 109.6, 90.0, 81.6, 71.8, 54.4, 54.1, 53.9, 44.2, 41.6, 27.8.**ESI HRMS**: calcd. For $C_{28}H_{28}N_2O_5S$ $[M+H]^+$ 505.1792, found 505.1791. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 17.8 min, t_{minor} = 36.6 min.

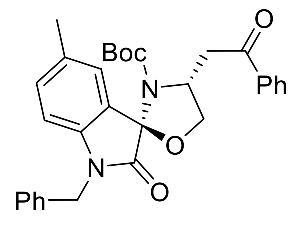
tert-butyl (3R,4'R)-1-benzyl-5-methoxy-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3l)



3l

Reddish sticky solid, 85% (45 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 (t, J = 9.8 Hz, 2.32H), 7.50 (t, J = 7.4 Hz, 1.18H), 7.40 (t, J = 7.6 Hz, 2.54), 7.35 – 7.22 (m, 6.12H), 7.08 (d, J = 2.7 Hz, 0.30H), 6.95 (dd, J = 8.6, 2.7 Hz, 0.25H), 6.84 (d, J = 2.5 Hz, 1H), 6.70 (dd, J = 8.5, 2.5 Hz, 1H), 6.60 (d, J = 8.6 Hz, 0.26H), 6.56 (d, J = 8.5 Hz, 1H), 5.01 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 12.8 Hz, 1H), 4.77 (dd, J = 6.8, 3.3 Hz, 1H), 4.74 – 4.69 (m, 0.29H), 4.64 – 4.56 (m, 1H), 4.52 (d, J = 15.4 Hz, 1H), 4.21 (dd, J = 8.9, 3.7 Hz, 1H), 4.16 (d, J = 10.0 Hz, 0.34H), 4.04 (dd, J = 18.2, 2.8 Hz, 1H), 3.95 (d, J = 5.9 Hz, 0.23H), 3.81 (d, J = 9.8 Hz, 0.28H), 3.70 (d, J = 3.0 Hz, 4H), 3.60 (dd, J = 18.1, 10.4 Hz, 1H), 1.32 (s, 2.26H), 0.94 (s, 9H).**^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2, 173.0, 156.6, 151.0, 136.7, 136.6, 135.5, 133.5, 129.08, 128.7, 128.4, 128.0, 127.8, 115.3, 110.3, 110.2, 90.3, 81.6, 71.9, 56.1, 54.1, 44.3, 41.2, 32.1, 29.9. **ESI HRMS**: calcd. For $C_{31}H_{32}N_2O_6$ $[M+H]^+$ 529.2333, found 529.2333. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IC Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 20.9 min, t_{minor} = 78.8 min.

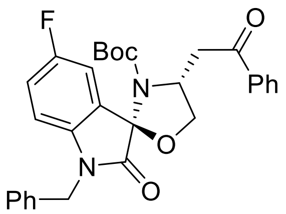
***tert*-butyl (3R,4'R)-1-benzyl-5-methyl-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3am).**



3m

Orange semi solid, 87% (45 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, J = 7.2 Hz, 0.45H), 7.97 (d, J = 7.5 Hz, 2H), 7.48 (s, 0.50H), 7.40 (d, J = 7.7 Hz, 2H), 7.32 – 7.15 (m, 7.67H), 7.06 (s, 1.23H), 6.97 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 7.8 Hz, 0.24H), 6.54 (d, J = 7.9 Hz, 1H), 6.49 – 6.44 (m, 0.25H), 5.05 (s, 0.23H), 5.00 (d, J = 15.5 Hz, 1H), 4.85 (d, J = 14.2 Hz, 0.48H), 4.81 – 4.73 (m, 1.25H), 4.59 (dd, J = 8.7, 6.3 Hz, 1H), 4.52 (d, J = 15.5 Hz, 1H), 4.20 (dd, J = 9.0, 3.6 Hz, 1H), 4.16 (d, J = 8.3 Hz, 0.23H), 4.03 (dd, J = 18.2, 2.6 Hz, 1H), 3.84 (dd, J = 18.2, 10.2 Hz, 0.26H), 3.68 (d, J = 17.3 Hz, 0.25H), 3.58 (dd, J = 18.1, 10.4 Hz, 1H), 2.22 (d, J = 4.7 Hz, 3.73H), 1.31 (s, 2.26H), 0.91 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2, 173.2, 151.1, 141.1, 136.6, 135.5, 133.5, 133.1, 130.8, 129.0, 128.7, 128.4, 128.0, 127.8, 124.2, 109.4, 90.2, 81.5, 71.8, 54.1, 44.2, 41.3, 29.9, 27.8. **ESI HRMS**: calcd. For $C_{31}H_{32}N_2O_6$ [M+H]$^+$ 513.2384, found 513.2384. **HPLC Analysis:** ee of major diasteromer= 86%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 9.7 min, t_{minor} = 25.8 min.

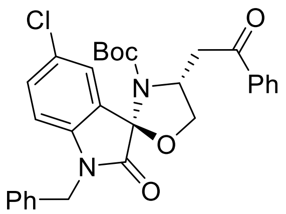
***tert*-butyl (3R,4'R)-1-benzyl-5-fluoro-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3n)**



3n

Orange semi solid, 82% (48 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.05 (t, J = 8.6 Hz, 2.47H), 7.58 (dd, J = 10.3, 4.3 Hz, 1.23H), 7.47 (t, J = 7.6 Hz, 2.50H), 7.36 – 7.31 (m, 6.30H), 7.07 (dd, J = 7.2, 2.6 Hz, 1.30H), 6.96 (td, J = 8.8, 2.6 Hz, 1.28H), 6.66 (dd, J = 8.5, 3.9 Hz, 1H), 6.58 – 6.56 (m, 0.26H), 5.09 (d, J = 15.5 Hz, 1H), 4.95 (s, 0.65H), 4.87 – 4.81 (m, 1.23H), 4.67 – 4.58 (m, 2H), 4.49 (d, J = 15.5 Hz, 0.24H), 4.29 (dd, J = 9.0, 3.5 Hz, 1H), 4.10 (dd, J = 12.3, 5.0 Hz, 1H), 3.92 – 3.88 (m, 0.24H), 3.67 (dd, J = 18.2, 10.5 Hz, 1H), 3.37 – 3.28 (m, 0.26H), 1.26 (s, 2.12H), 1.01 (s, 9H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 199.1, 173.1, 160.4, 158.8, 150.7, 139.3, 136.6, 135.1, 133.6, 129.1, 129.0, 128.9, 128.7, 128.3, 128.2, 127.8, 127.2, 116.9, 116.7, 111.7, 111.5, 110.3, 110.2, 89.8, 81.9, 72.0, 54.1, 44.4, 41.2, 27.9. **ESI HRMS**: calcd. For $C_{30}H_{29}FN_2O_5$ [M+H]$^+$ 517.2133, found 517.2135. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 11.7 min, t_{minor} = 81.4 min).

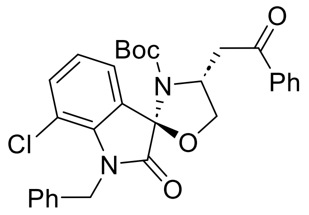
***tert*-butyl (3R,4'R)-1-benzyl-5-chloro-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3o)**



3o

Light yellow semi solid, 80% (42 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.05 (dd, J = 12.6, 7.9 Hz, 2.49H), 7.59 (dd, J = 13.3, 6.5 Hz, 1.21H), 7.49 (dd, J = 16.7, 8.9 Hz, 2.50H), 7.32 (dd, J = 13.3, 5.6 Hz, 7.27H), 7.25 – 7.21 (m, 1H), 7.16 (d, J = 7.2 Hz, 0.23H), 6.66 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 3.9 Hz, 0.23H), 5.09 (d, J = 15.5 Hz, 1H), 4.94 (s, 0.49H), 4.87 – 4.80 (m, 1.25H), 4.68 – 4.56 (m, 2H), 4.49 (d, J = 15.5 Hz, 0.22H), 4.28 (dd, J = 9.2, 3.5 Hz, 1H), 4.14 – 4.07 (m, 1H), 3.91 – 3.85 (m, 0.26H), 3.76 (s, 0.24H), 3.65 (dd, J = 18.1, 10.5 Hz, 1H), 3.37 – 3.32 (m, 0.22H), 1.40 (s, 2.24H), 1.01 (s, 9H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.1, 172.8, 150.7, 141.9, 136.6, 135.0, 133.6, 130.4, 129.8, 129.2, 129.0, 128.9, 128.9, 128.8, 128.4, 128.3, 127.8, 110.6, 89.7, 81.9, 72.1, 54.2, 44.3, 41.2, 27.9. **ESI HRMS**: calcd. For $C_{30}H_{29}ClN_2O_5$ [M+H]+ 533.1838, found 533.1840. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IB Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.7 min, t_{minor} = 73.6 min.

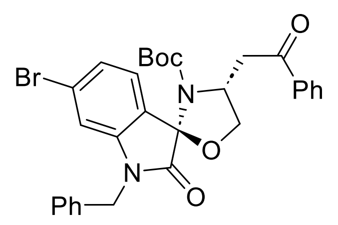
***tert*-butyl (3R,4'R)-1-benzyl-7-chloro-2-oxo-4'-(2-oxo-2-phenylethyl)spiro [indoline-3,2'-oxazolidine]-3'-carboxylate (3p)**



3p

Yellow semi solid, 84% (43 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.07 (s, 0.55H), 8.04 – 8.01 (m, 2H), 7.60 (s, 0.31H), 7.57 (t, J = 7.4 Hz, 1H), 7.51 (d, J = 6.4 Hz, 0.56H), 7.46 (t, J = 7.7 Hz, 2H), 7.34 – 7.30 (m, 5.21H), 7.26 – 7.22 (m, 3.91H), 7.01 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.0 Hz, 0.28H), 5.40 (d, J = 16.0 Hz, 1H), 5.36 (s, 0.28H), 5.28 (d, J = 5.1 Hz, 1H), 5.23 (s, 0.31H), 4.85 (ddd, J = 13.3, 6.4, 3.3 Hz, 1.28H), 4.69 (dd, J = 8.8, 6.2 Hz, 1H), 4.65 – 4.60 (m, 0.30H), 4.28 (dd, J = 9.0, 3.7 Hz, 1H), 4.23 (d, J = 9.0 Hz, 0.32H), 4.11 (dd, J = 18.1, 2.7 Hz, 1H), 3.91 – 3.84 (m, 0.29H), 3.74 (d, J = 17.1 Hz, 0.35H), 3.64 (dd, J = 18.2, 10.4 Hz, 1H), 1.39 (s, 2.74H), 1.09 (s, 9H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 199.0, 174.2, 150.7, 139.5, 136.9, 136.6, 133.6, 133.2, 131.2, 128.8, 128.7, 128.3, 127.6, 126.9, 124.4, 122.1, 116.2, 89.1, 82.0, 72.2, 54.1, 45.3, 41.2, 27.9. **ESI HRMS**: calcd. For $C_{30}H_{29}ClN_2O_5$ $[M+H]^+$ 533.1838, found 533.1843. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IC Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 13.6 min, t_{minor} = 41.5 min.

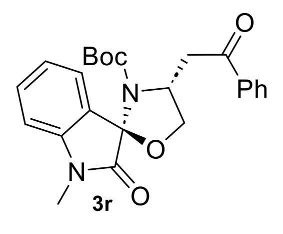
***tert*-butyl (3R,4'R)-1-benzyl-6-bromo-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3q)**



3q

White solid, 85% (44 mg) yield. Melting Point 165-170 °C **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.03 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1.16H), 7.48 (dt, J = 15.3, 7.8 Hz, 2.92H), 7.37 – 7.28 (m, 6.94H), 7.23 – 7.16 (m, 2.67H), 6.90 (d, J = 0.9 Hz, 1H), 5.06 (d, J = 15.5 Hz, 7H), 4.92 (s, 1H), 4.86 – 4.80 (m, 0.56H), 4.66 – 4.57 (m, 1.17H), 4.49 (d, J = 15.6 Hz, 2H), 4.27 (dd, J = 9.1, 3.6 Hz, 0.18H), 4.13 – 4.07 (m, 1H), 3.85 (d, J = 9.9 Hz, 0.18H), 3.76 (s, 0.17H), 3.64 (dd, J = 18.2, 10.4 Hz, 1H), 1.38 (s, 1.75H), 1.01 (s, 9H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 199.1, 173.1, 150.7, 144.8, 136.6, 134.9, 133.6, 129.2, 128.8, 128.3, 127.8, 126.2, 124.7, 124.3, 112.9, 89.6, 81.9, 72.0, 54.1, 44.3, 41.2, 27.9. **ESI HRMS**: calcd. For $C_{30}H_{29}BrN_2O_5$ $[M+H]^+$ 577.1333, found 577.1338. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IC Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 14.5 min, t_{minor} = 28.8 min.

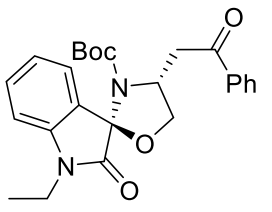
tert-butyl (3R,4'R)-1-methyl-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3r)



3r

Yellow semi solid, 88% (37 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.97 (t, J = 8.1 Hz, 2.56H), 7.50 (t, J = 7.4 Hz, 1.22H), 7.40 (dd, J = 13.9, 6.2 Hz, 2.58H), 7.29 (dd, J = 10.0, 5.4 Hz, 1.3H), 7.23 (t, J = 6.8 Hz, 1.34H), 7.02 (t, J = 7.4 Hz, 1.26H), 6.73 (t, J = 7.7 Hz, 1.28H), 4.78 – 4.74 (m, 1.29H), 4.56 (dd, J = 8.7, 6.3 Hz, 1H), 4.16 (dd, J = 9.0, 3.2 Hz, 1H), 4.07 – 4.03 (m, 0.61H), 3.97 (dd, J = 18.1, 2.3 Hz, 1H), 3.86 (d, J = 16.7 Hz, 0.3H), 3.55 (dd, J = 18.1, 10.4 Hz, 1H), 3.29 (dd, J = 11.6, 4.9 Hz, 0.29H), 3.12 (s, 3H), 3.09 (s, 0.83H), 1.02 (s, 2.39H), 0.97 (s, 9H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 199.1, 172.7, 150.9, 144.3, 136.6, 133.5, 128.8, 128.7, 128.3, 128.1, 123.3, 123.3, 108.5, 89.9, 81.4,71.8, 53.8, 41.0, 28.4, 27.9, 26.4. **ESI HRMS**: calcd. For $C_{24}H_{26}N_2O_5$ $[M+H]^+$ 423.1914, found 423.1918. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 98/2, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 50.1 min, t_{major} = 93.0 min.

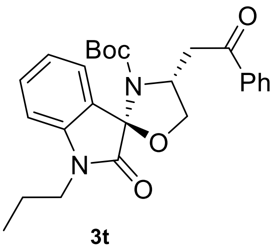
***tert*-butyl (3R,4'R)-1-ethyl-2-oxo-4'-(2-oxo-2-phenylethyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3s)**



3s

Yellow semi solid, 88% (87 mg) yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 – 7.94 (m, 2.52H), 7.52 – 7.47 (m, 1.23H), 7.42 (dd, J = 14.7, 7.7 Hz, 2.53H), 7.26 (dd, J = 13.2, 7.6 Hz, 2.54H), 7.05 (d, J = 7.5 Hz, 0.24H), 7.00 (d, J = 7.4 Hz, 1H), 6.83 (d, J = 7.8 Hz, 0.25H), 6.77 (d, J = 7.9 Hz, 1H), 4.78 – 4.74 (m, 1.24H), 4.56 (dd, J = 8.7, 6.3 Hz, 1H), 4.16 (dd, J = 9.0, 3.4 Hz, 1H), 4.04 (d, J = 7.6 Hz, 0.25H), 3.98 (dd, J = 18.2, 2.4 Hz, 1H), 3.85 (s, 0.25H), 3.83 – 3.76 (m, 1.27H), 3.72 (dd, J = 14.5, 7.2 Hz, 1H), 3.57 (d, J = 7.5 Hz, 1H), 3.47 – 3.43 (m, 0.24H), 3.29 – 3.23 (m, 0.26H), 1.24 (t, J = 5.9 Hz, 3.85H), 1.01 (s, 2.33H), 0.97 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.1, 172.5, 150.9, 144.1, 143.5, 138.5, 136.6, 133.5, 130.8, 128.9, 128.7, 128.3, 128.2, 125.6, 123.8, 123.5, 123.1, 110.2, 108.7, 108.6, 89.9, 81.5, 71.7, 54.0, 41.2, 35.2, 27.9, 12.9. **ESI HRMS:** calcd. For $C_{25}H_{28}N_2O_5$ $[M+H]^+$ 437.2071, found 437.2070. **HPLC Analysis:** ee of major diasteromer= 99%, Chiralpak IE Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 24.7 min, t_{major} = 32.9 min.

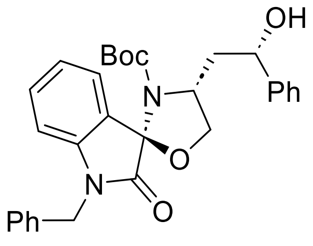
***tert*-butyl (3R,4'R)-2-oxo-4'-(2-oxo-2-phenylethyl)-1-propylspiro[indoline-3,2'-oxazolidine]-3'-carboxylate (3t)**



3t

Yellow semi solid, 70% (31 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (d, J = 7.3 Hz, 2H), 8.01 (dd, J = 11.5, 4.2 Hz, 0.64H), 7.60 (dd, J = 13.2, 5.8 Hz, 1.34H), 7.53 (s, 0.70H), 7.49 (t, J = 7.7 Hz, 2H), 7.38 – 7.36 (m, 1.37H), 7.34 (s, 1.31H), 7.10 (t, J = 7.4 Hz, 1.38H), 6.85 (d, J = 7.8 Hz, 1H), 6.82 (s, 0.34H), 4.99 – 4.95 (m, 0.31H), 4.87 – 4.84 (m, 1.44H), 4.66 (dd, J = 8.7, 6.3 Hz, 1H), 4.27 (dd, J = 9.1, 3.4 Hz, 1H), 4.22 (d, J = 9.0 Hz, 0.29H), 4.16 – 4.12 (m, 0.40H), 4.07 (dd, J = 18.3, 2.7 Hz, 1H), 3.97 (d, J = 16.6 Hz, 0.30H), 3.83 (dd, J = 14.2, 7.3 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.63 – 3.60 (m, 0.35H), 3.50 (dt, J = 14.0, 7.1 Hz, 1H), 3.35 (dd, J = 10.3, 6.9 Hz, 0.38H), 1.76 (dd, J = 14.7, 7.4 Hz, 2.72H), 1.10 (s, 2.92H), 1.06 (s, 9H), 1.05 – 1.02 (m, 3.74H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2, 173.0, 151.0, 143.8, 136.6, 133.6, 133.5, 131.9, 130.7, 128.9, 128.9, 128.7, 128.4, 128.3, 128.3, 128.2, 123.4, 123.1, 108.9, 89.9, 81.5, 71.8, 54.0, 42.1, 41.2, 29.9, 28.0, 27.9, 21.0, 20.7, 14.3. **ESI HRMS**: calcd. For $C_{26}H_{30}N_2O_5$ $[M+H]^+$ 451.2227, found 451.2226. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.6 min, t_{minor} = 17.9 min.

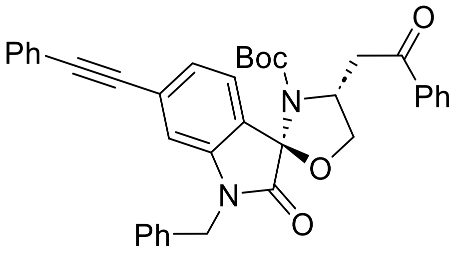
***tert*-butyl (3R,4'R)-1-benzyl-4'-((S)-2-hydroxy-2-phenylethyl)-2-oxospiro[indoline-3,2'-oxazolidine]-3'-carboxylate (5)**



5

White sticky solid, 60% (30 mg) yield. **^{1}H NMR (600 MHz, $CDCl_3$)** 1H NMR (600 MHz, CDCl3) δ 7.49 – 7.43 (m, 2.62H), 7.41 – 7.26 (m, 13H), 7.08 (t, J = 7.4 Hz, 1H), 7.04 (d, J = 7.4 Hz, 0.31H), 6.78 (d, J = 7.9 Hz, 1H), 6.71 (d, J = 7.8 Hz, 0.31H), 5.21 – 5.15 (m, 0.3H), 5.13 – 5.07 (m, 1H), 4.98 (ddd, J = 26.4, 18.2, 9.3 Hz, 2H), 4.87 – 4.82 (m, 0.27H), 4.79 – 4.74 (m, 0.32H), 4.66 – 4.59 (m, 2H), 4.53 (dt, J = 9.1, 5.6 Hz, 1.36H), 4.45 (dd, J = 8.5, 6.7 Hz, 1H), 4.16 – 4.07 (m, 0.3H), 4.02 (t, J = 6.8 Hz, 0.25H), 3.76 (s, 1H), 3.42 (s, 0.31H), 2.44 (ddd, J = 11.0, 8.8, 3.3 Hz, 1.33H), 1.28 (s, 2.98H), 0.98 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 172.46, 152.86, 144.29, 143.44, 135.45, 130.73, 129.09, 128.47, 128.09, 127.85, 127.07, 125.70, 123.32, 122.90, 109.73, 90.17, 82.32, 77.44, 77.23, 77.02, 72.00, 70.28, 54.77, 54.59, 44.80, 44.35, 27.77. **ESI HRMS**: calcd. For $C_{30}H_{32}N_2O_5$ $[M+H]^+$ 501.2384, found 501.2384. **HPLC Analysis:** ee of major diasteromer= 98%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.0 min, t_{minor} = 21.5 min.

***tert*-butyl (3R,4'R)-1-benzyl-2-oxo-4'-(2-oxo-2-phenylethyl)-6-(phenylethynyl)spiro[indoline-3,2'-oxazolidine]-3'-carboxylate (7)**

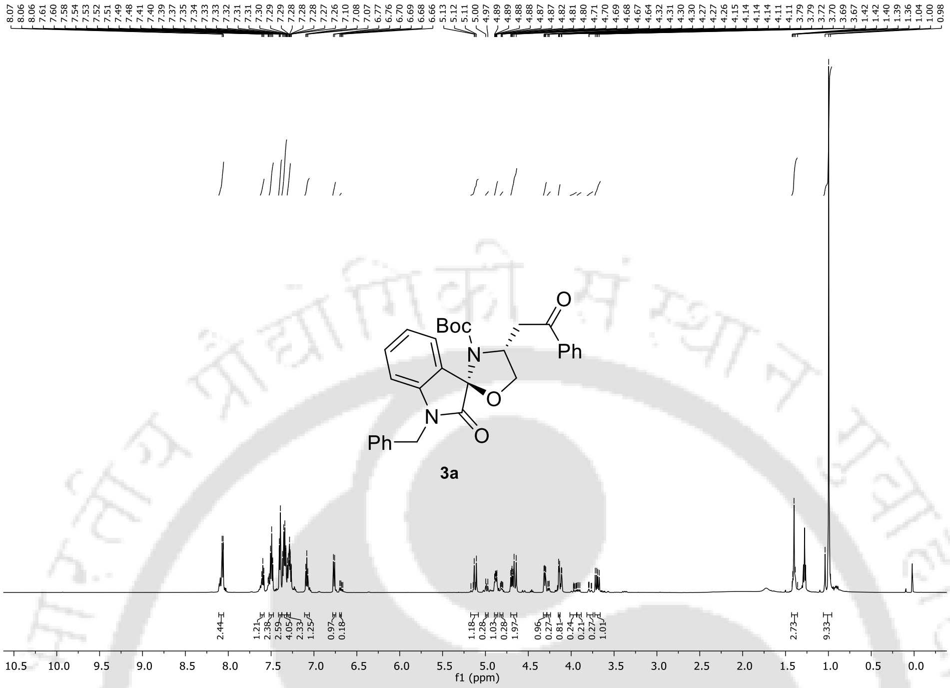


7

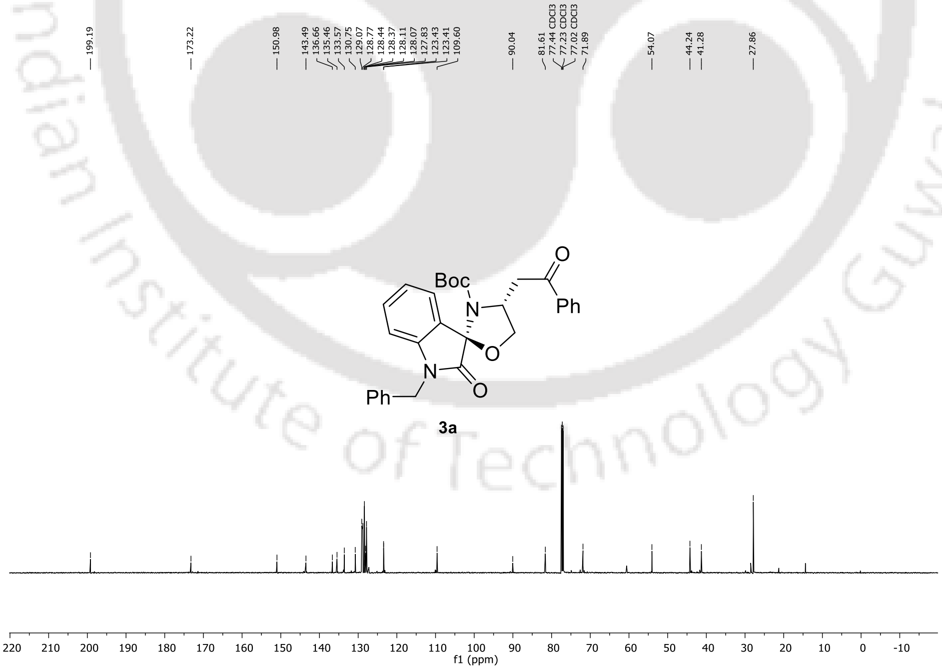
light brown semi solid, 65% (39 mg) yield. **^{1}H NMR (400 MHz, CDCl$_3$)** 1H NMR (400 MHz, CDCl3) δ 8.04 (d, J = 7.5 Hz, 2H), 7.61 – 7.27 (m, 15H), 6.89 (s, 1H), 5.10 (d, J = 15.5 Hz, 1H), 4.88 – 4.81 (m, 1H), 4.66 (dd, J = 15.1, 5.1 Hz, 2H), 4.29 (dd, J = 9.1, 3.4 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.70 – 3.61 (m, 1H), 1.02 (s, 9H).**^{13}C NMR (100 MHz, CDCl$_3$)** δ 199.1, 173.1, 150.8, 143.6, 135.2, 133.6, 131.8, 129.0, 128.2, 128.8, 128.6, 128.4, 128.2, 127.7, 125.7, 123.4, 112.0, 90.82, 89.7, 89.1, 81.9, 76.9, 71.9, 54.3, 44.3, 41.1, 29.5. **ESI HRMS**: calcd. For $C_{38}H_{34}N_2O_5$ [M+H]$^+$ 599.2540, found 599.2540. **HPLC Analysis:** ee of major diasteromer= >99%, Chiralpak IC Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm, t$_{major}$ = 16.4 min, t$_{minor}$ = 25.0 min.

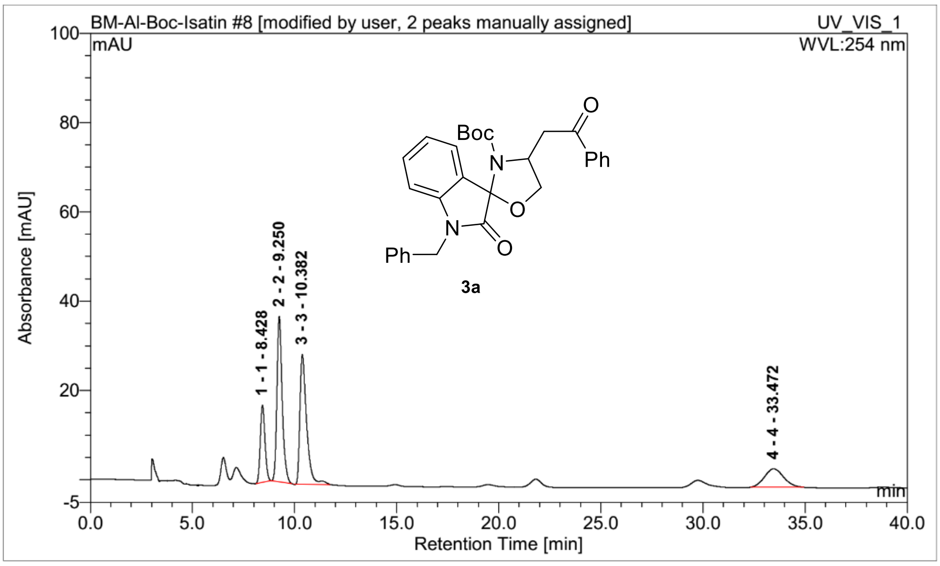
4.8 NMR and HPLC spectra:

^{1}H NMR of 3a (600 MHz, CDCl$_3$)

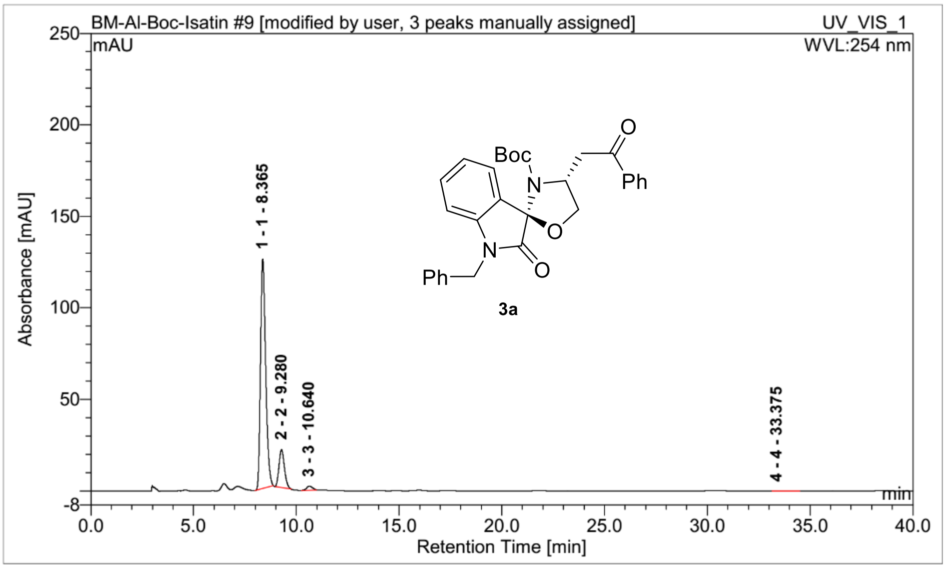


^{13}C{^{1}H} NMR of 3a (150 MHz, CDCl$_3$)



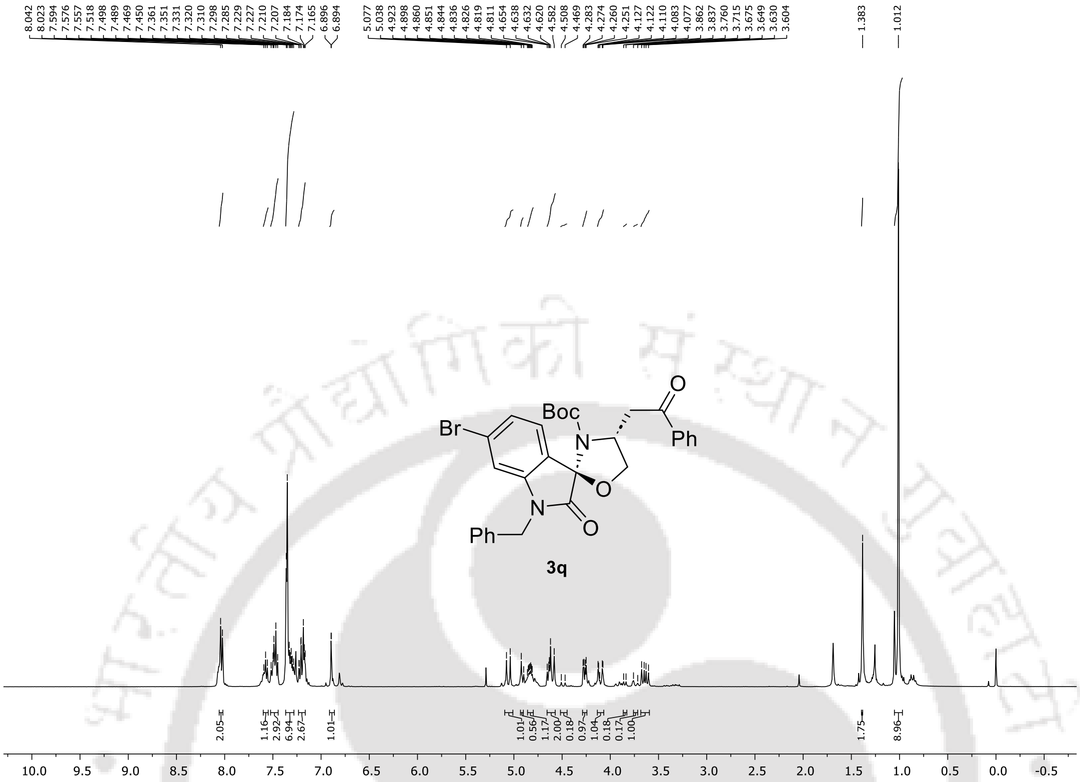


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.43	4.598752	14.71878624	17.32299	n.a.
2	2	9.25	11.10295	35.5361508	37.00582	n.a.
3	3	10.38	11.09309	35.50457969	29.06306	n.a.
4	4	33.47	4.449	14.24048327	4.108	n.a.

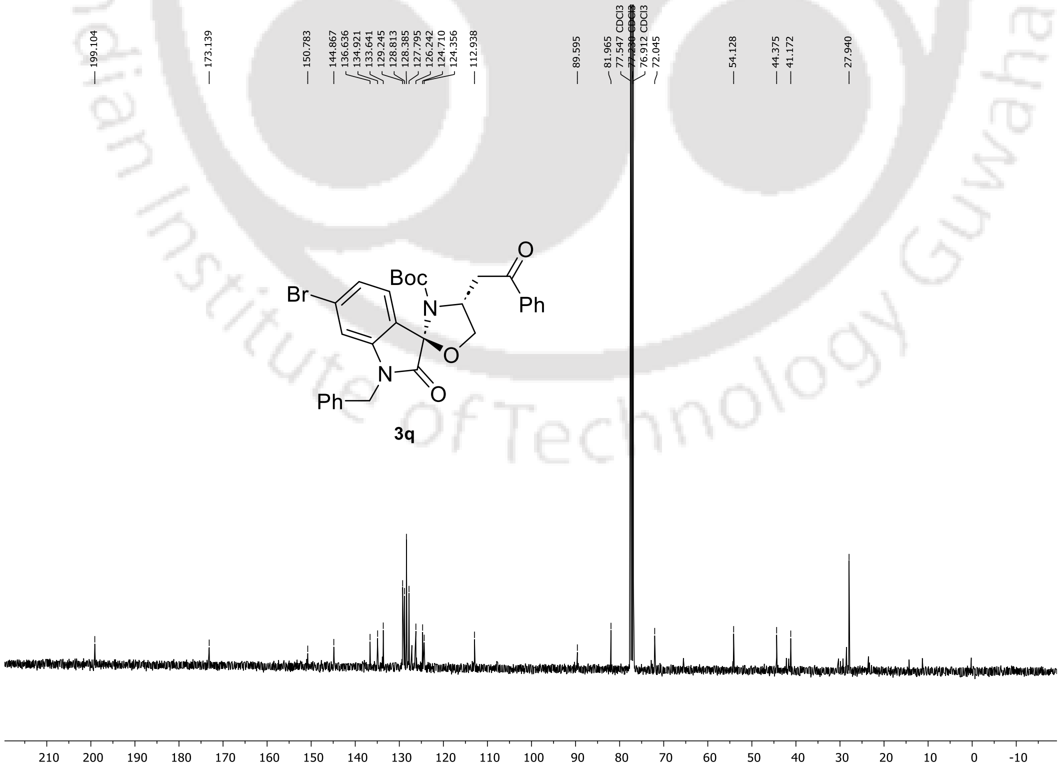


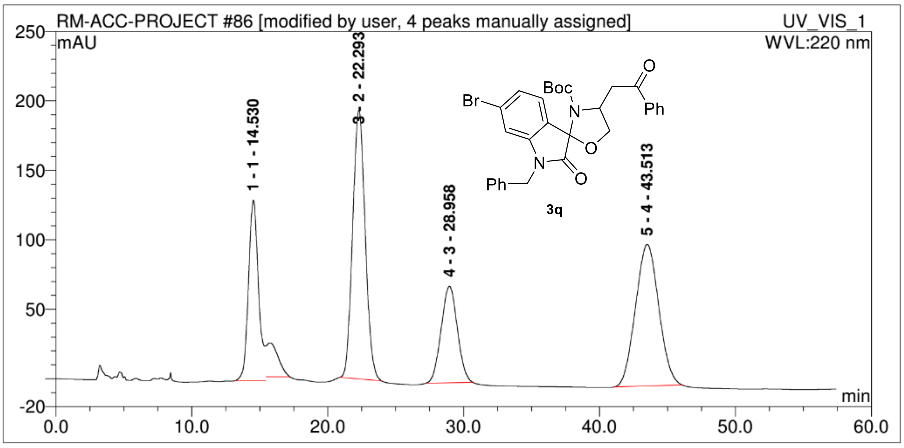
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.37	36.60123	83.77327251	125.3329	n.a.
2	2	9.28	6.370305	14.58041763	20.74822	n.a.
3	3	10.64	0.702765	1.608494905	2.18771	n.a.
4	4	33.38	0.017	0.03781495844	0.027	n.a.

^{1}H NMR of 3q (400 MHz, CDCl$_3$)

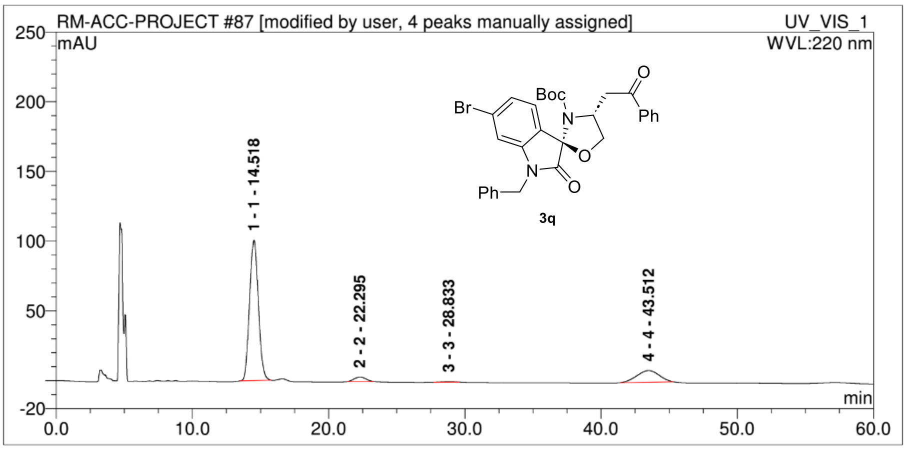


^{13}C{^{1}H} NMR of 3q (100 MHz, CDCl$_3$)



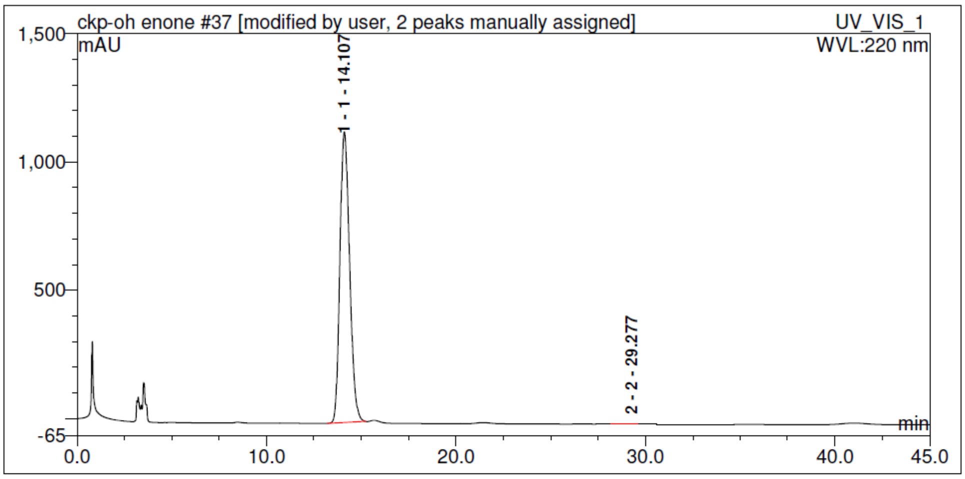


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.53	111.8582	18.12053499	129.913	n.a.
3	2	22.29	206.9793	33.52972618	193.1365	n.a.
4	3	28.96	96.02905	15.55627932	69.54516	n.a.
5	4	43.51	202.434	32.79345951	101.909	n.a.



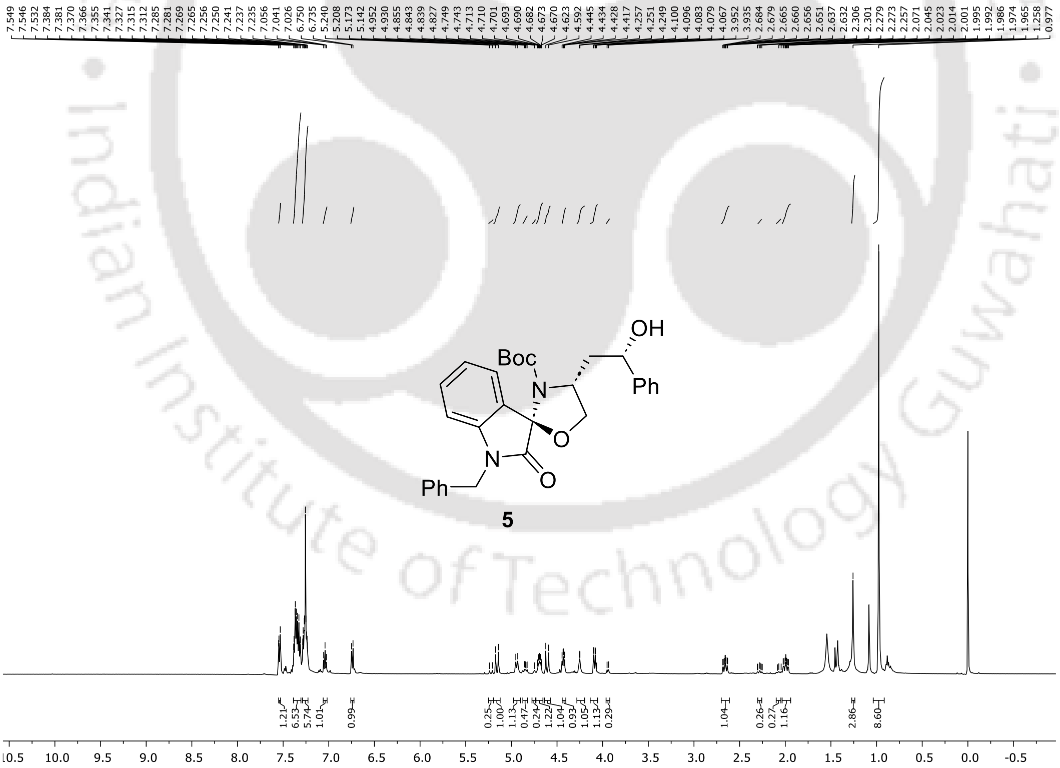
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.52	75.76645	79.492893	100.7805	n.a.
2	2	22.30	3.275752	3.436863849	3.31143	n.a.
3	3	28.83	0.477623	0.5011145545	0.45682	n.a.
4	4	43.51	15.792	16.5691286	8.383	n.a.

After crystallization HPLC of the compound **3q** was taken and we observed only two peaks corresponding to the major diasteromer; there was no peak corresponding to the minor diasteromer.

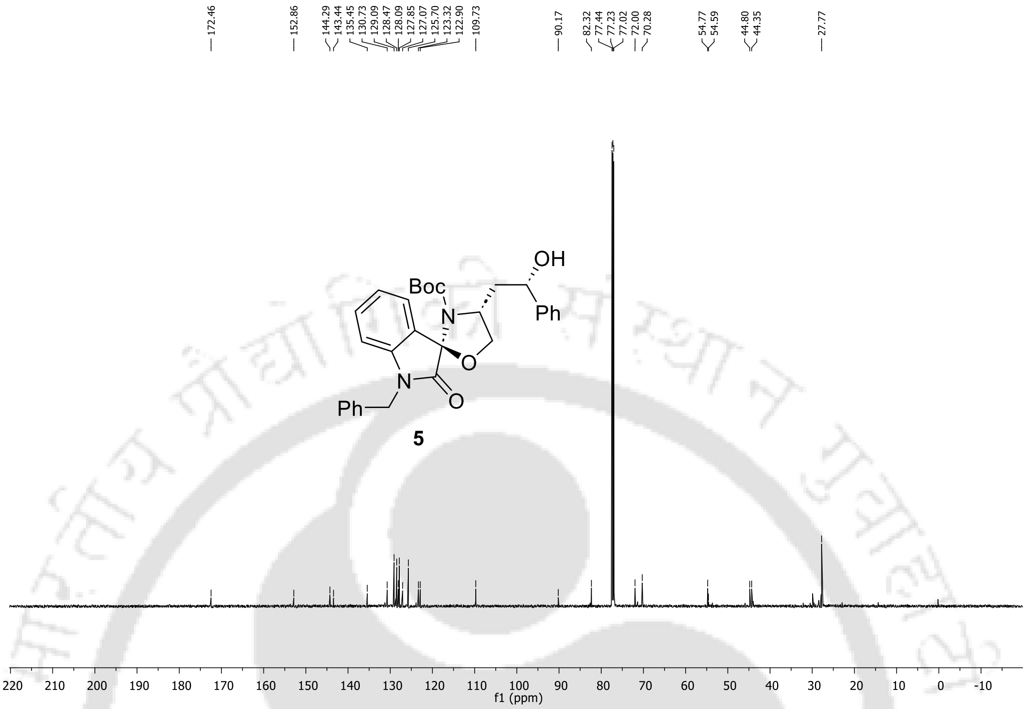


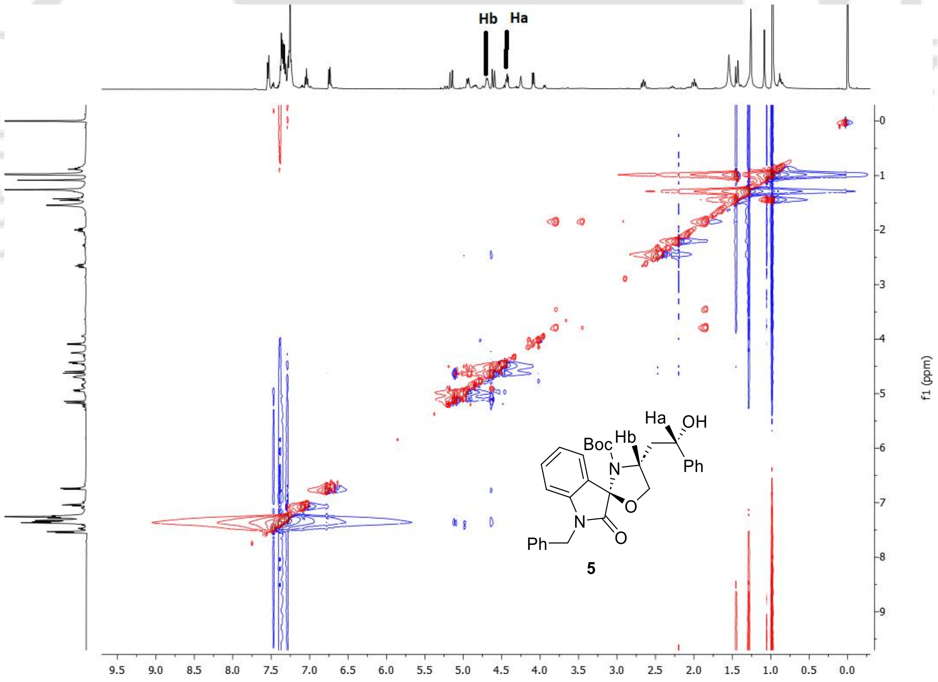
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.11	669.9503	99.9864743	1132.082	n.a.
2	2	29.28	0.091	0.01352570398	0.090	n.a.

^{1}H NMR of 5 (500 MHz, $CDCl_3$)

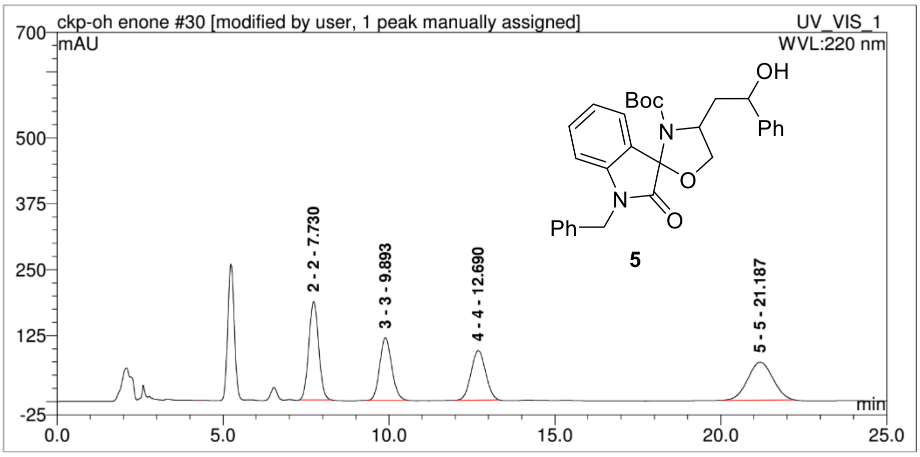


$^{13}C\{^1H\}$ NMR of 5 (150 MHz, $CDCl_3$)

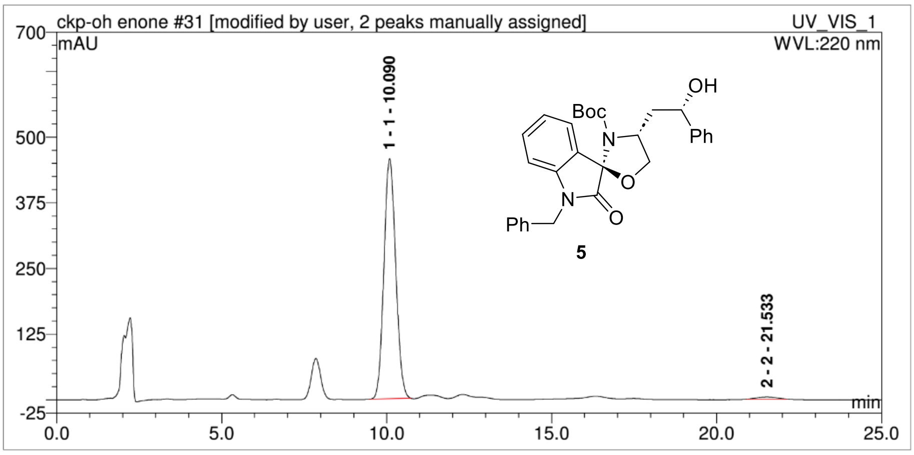




NOESY spectra of compound **5** exhibiting the strong interaction between the protons (marked as Ha and Hb), so we can conclude that both the Ha and Hb are in the same plane.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
2	2	7.73	64.40954	28.59432292	186.3859	n.a.
3	3	9.89	50.01692	22.20478455	118.8388	n.a.
4	4	12.69	47.67819	21.16651706	93.85453	n.a.
5	5	21.19	63.148	28.03437547	71.689	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.09	189.3571	98.55073094	457.106	n.a.
2	2	21.53	2.785	1.449269061	4.044	n.a.

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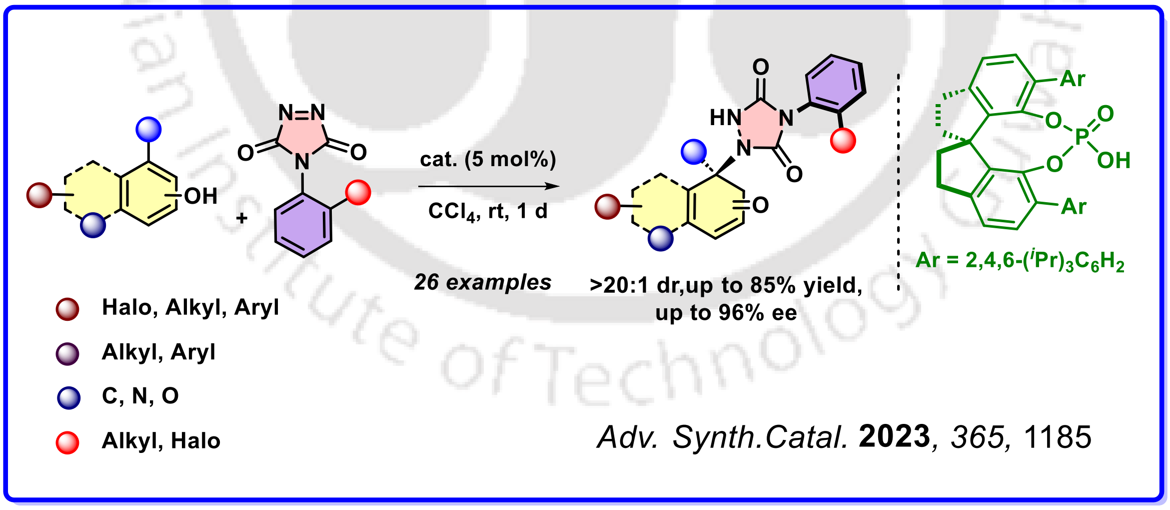
Chapter 5

Organocatalytic Asymmetric Dearomatization Reaction for the Construction of Axially Chiral Urazole Embedded Naphthalenones

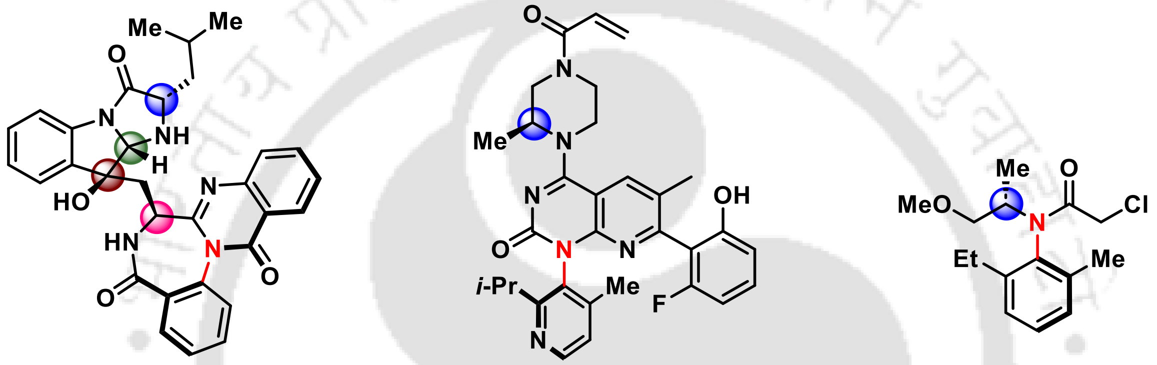
ABSTRACT: Herein we disclose a catalytic asymmetric dearomatization reaction of β-naphthols with 4- aryl-1,2,4-triazole-3,5-diones. A chiral phosphoric acid with spiro motif was found to be effective for this reaction. The chiral urazole embedded naphthalenones having both axial and central chirality were obtained in good to high yields (70–85%) with high diastereo- and enantioselectivities (>20:1, 8–96% ees), having C-N rotational energy barrier 31.54 kcalmol^{-1} and $t^{1/2}{}_{25\,^{\circ}\mathrm{C}}$=589.8 years. The scope of the reaction was broad and few applications including a bromo-amination reaction have been demonstrated.



Adv. Synth.Catal. **2023**, *365*, 1185

5.1 Introduction

Compounds bearing both C−N axial and central chirality exhibit broad bio-activities and have found wide applications as pharmaceuticals or agrochemicals. Asperlicin[1] is a nonpeptide cholecystokinin antagonist produced by Aspergillus alliaceus, possessing a C−N stereogenic axis and four stereogenic carbon centers. Sotorasib[2] (AMG 510), that has been approved in May 2021 by the US FDA for the treatment of non-small cell lung cancer (NSCLC). Metolachlor[3] is one of the most widely used herbicides.



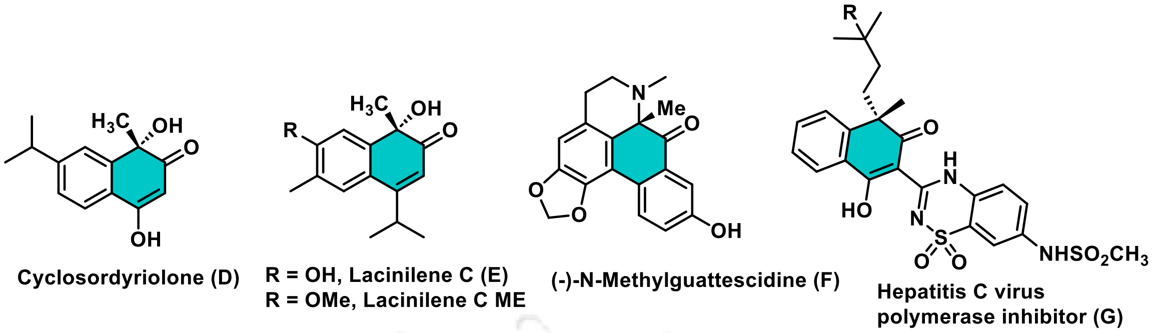
Asperlicin (A)
Cholescystokinin antagonist

Sotorasib (AMG 510) (B)
Antitumor drug

Metolachlor (C)
Herbicide

Figure 1: Importance of compound having both C−N axial and central chirality.

Catalytic asymmetric dearomatization (CADA) reaction has established itself as a powerful method for converting planar aromatic structures into stereoselective chiral motifs. Electron-rich heteroaromatics (i.e. indole, pyrrole, benzofuran) as well as benzene like systems (i.e. phenol, naphthol) have been extensively investigated in dearomative procedures over the last decade and many catalytic asymmetric transformations have been developed. In this context, *α*- and *β*-naphthols turned out to be important platforms to generate highly functionalized three dimensional naphthalenone cores *via* dearomatization reactions.[4] These partially dearomatized naphthalenone cores are present in bioactive naturally occurring compounds as well as in therapeutic reagents, such as (−)-N-methylguattescidine, cyclosordyriolone, lacinilenes and HCV polymerase inhibitor (Figure 2).[5] Thus recent years have witnessed significant efforts from various research groups for the construction of naphthalenone core.



Cyclosordyriolone (D)

R = OH, Lacinilene C (E)
R = OMe, Lacinilene C ME

(-)-N-Methylguattescidine (F)

Hepatitis C virus
polymerase inhibitor (G)

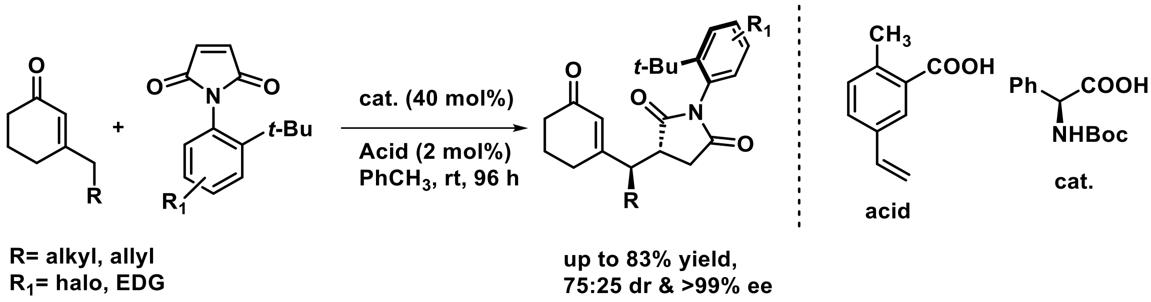
Figure 2: Naphthalenone cores present in bioactive molecules.

Similarly, urazoles i.e 1,2,4-triazolidine-3,5-diones are important heterocyclic compounds with potential applications in drug discovery and valuable uses in the area of protein modification chemistry.[6] Urazoles are also favorable motif because of their simple chemical synthesis and ease of optimization of reaction conditions. In addition, oxidation of urazoles provides a very useful class of persistent cyclic hydrazyl radicals for different transformations. As a consequence, there is a huge demand for the easy access to a variety of these compounds.[7] In particular, the development of the synthesis of chiral urazoles in a catalytic enantioselective manner is highly desirable.

5.2 Literature Study:

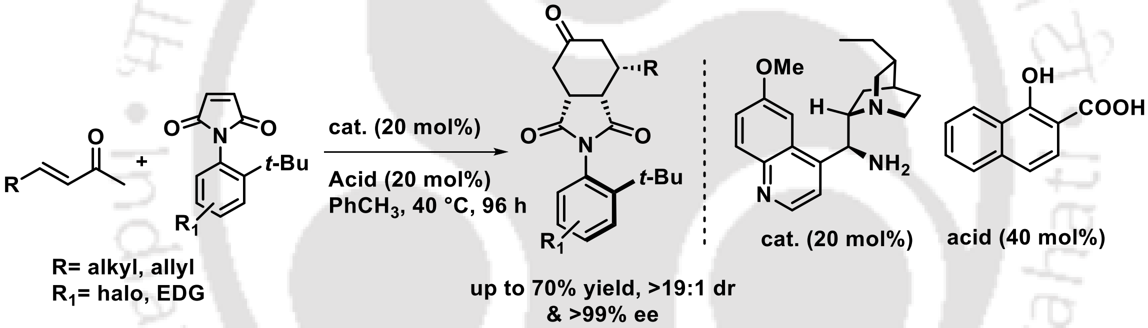
5.2.1 Known strategies for compound having both C−N axial and central chirality:

Using the vinylogous Michael addition of 3-substituted cyclohexenones to *N*-(2-*t*-*butyl*phenyl)maleimides, Bencivenni et al. reported[8] in 2014 that it was possible to remotely control the axial chirality of N-(2-t-butylphenyl)succinimides. Enantioselective desymmetrization was aided by 9-amino(9-deoxy)*epi*-quinine, producing atropisomeric succinimides with two neighbouring stereocenters (Scheme1).



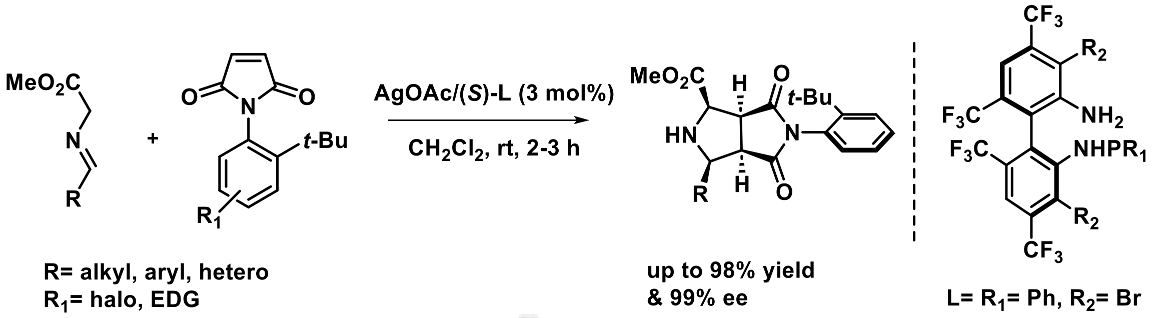
Scheme 1: Desymmetrization of rotationally constrained N-(2-*t-butyl*phenyl)maleimide.

The atroposelective desymmetrization of N-arylmaleimides utilising a primary amine catalysed Diels-Alder reaction of enones was reported[9] later in 2015 by the same group. The chiral axis as new element of chirality is generated under remote control of the catalyst that selectively drives the formal Diels–Alder reaction through an exclusive stereochemical outcome (Scheme 2).



Scheme 2: The atroposelective desymmetrization of *N*-arylmaleimides *via* Diels–Alder reaction of enones.

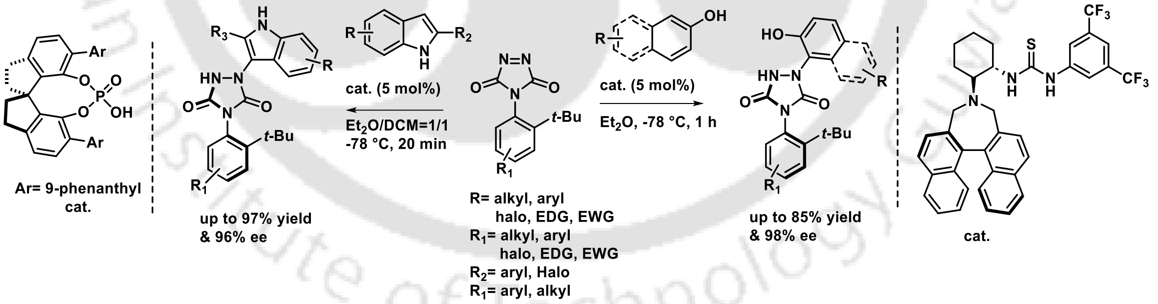
In 2015, Wang *et al*. reported[10], a highly efficient Ag(I)-catalyzed atroposelective desymmetrization of N-(2-*t-butyl*phenyl)maleimide via 1,3-dipolar cycloaddition of in situ generated azomethine ylides, affording a facile access to a series of biologically important and enantioenriched octahydropyrrolo[3,4-c]pyrrole derivatives in generally high yields (up to 99%) with excellent levels of diastereo-/enantioselectivities (up to 99% ee, >20:1 dr).



Scheme 3: desymmetrization of *N*-arylmaleimides *via* 1,3-dipolar cycloaddition of in situ generated azomethine ylides.

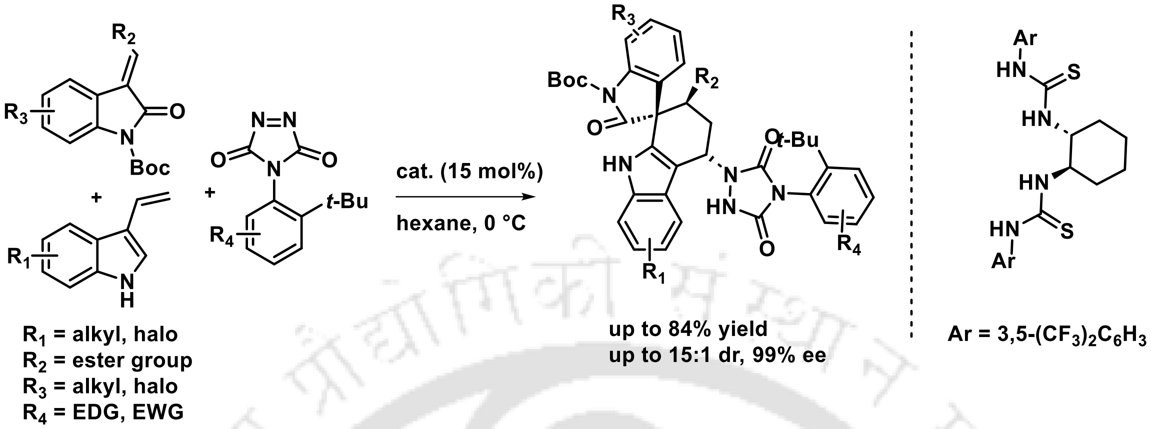
5.2.3 Known strategies for synthesis for axially chiral urazole:

In 2016, Tan *et al.* reported[11] an organocatalytic asymmetric tyrosine click-like reaction in high yields with excellent enantioselectivity under mild reaction conditions in an excellent remote enantiocontrol manner. The reaction represents a very convenient approach to an interesting class of axially chiral urazole derivatives, with potential biological activities and potential application as effective chiral organocatalysts/ligands. The excellent remote enantiocontrol of the process stems from the efficient discrimination of the two reactive sites in the triazoledione-involving phenols or indoles as nucleophile and transferring the chirality of the catalyst into the axial chirality of urazoles at the remote position far from the reactive site (Scheme 4).



Scheme 4: Asymmetric tyrosine click-like reaction.

In 2018, Tan *et al.* reported[12], for the first time, a desymmetrization strategy empowered the assembly of a class of optically pure spirooxindole–urazoles possessing an *N*-Ar stereogenic axis *via* remote control of axial chirality in an asymmetric three-component reaction. This transformation was realized by a tandem bisthiourea-catalyzed asymmetric Diels–Alder reaction and substrate-controlled asymmetric *ene* reaction. Under favourable conditions, the consecutive ene reaction was caused by the driving force of aromatization and the strong reactivity of 4-aryl-1,2,4-triazole-3,5-dione enophiles (Scheme 5).

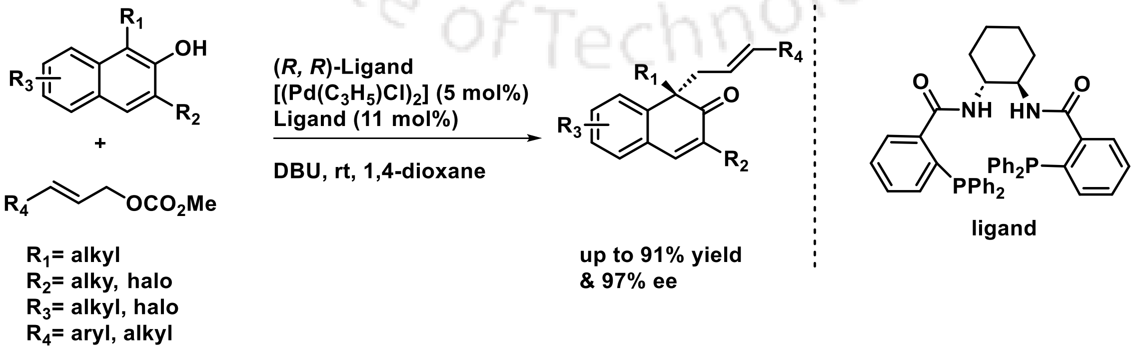


Scheme 5: Synthesis of spirooxindole–urazoles *via* desymmetrization of ATAD.

5.2.4 Known strategies for catalytic asymmetric dearomatization (CADA) of β-naphthols:

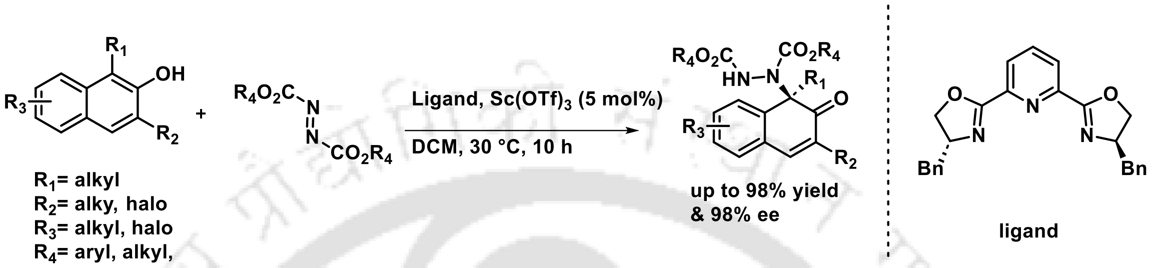
A variety of electrophiles such as nitroethylenes,[13] azodicarboxylates,[14] aziridines,[15] halogenation reagents,[16] activated propargylic compounds,[17] allyl alcohols,[18] allenes,[19] allylic carbonates,[20] quinones[21] etc. have been successfully employed in the CADA reaction with β-naphthols. Few examples are shown below.

In 2013, You *et al.* reported[20a] first palladium-catalyzed intermolecular asymmetric allylic dearomatization reaction of 2-naphthol derivatives. The 2-naphthalenones bearing an all-carbon quaternary chiral centre could be easily accessed from simple aromatic naphthol derivatives in good to excellent yields, and excellent chemo- and enantioselectivities (Scheme 6).



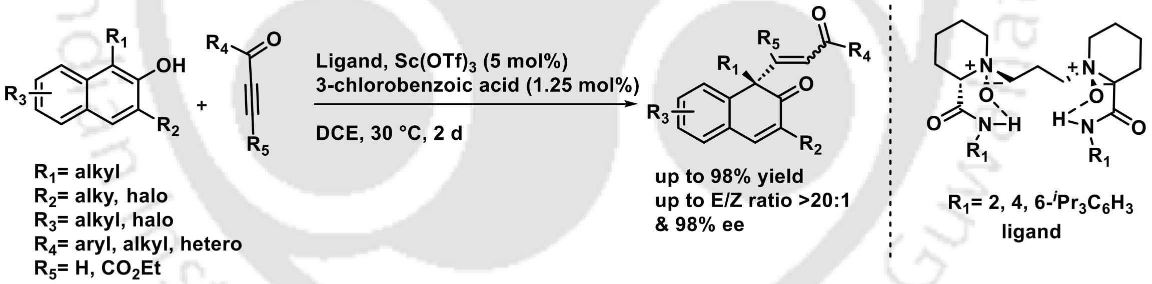
Scheme 6: construction of a spiro[imidazolidine-2,3′-oxindole] framework

In 2015, Luan *et al*. reported[14b] an unprecedented scandium-catalyzed asymmetric aminative dearomatization reaction of substituted 2-naphthols, thus leading to the formation of nitrogen-containing quaternary carbon stereocenter containing products with excellent enantioselectivities (up to 98%ee). This method represents the first example of a catalytic, enantioselective carbon–nitrogen bond forming reaction through direct dearomatization of phenol derivatives (Scheme 7).



Scheme 7: construction of a spiro[imidazolidine-2,3′-oxindole] framework.

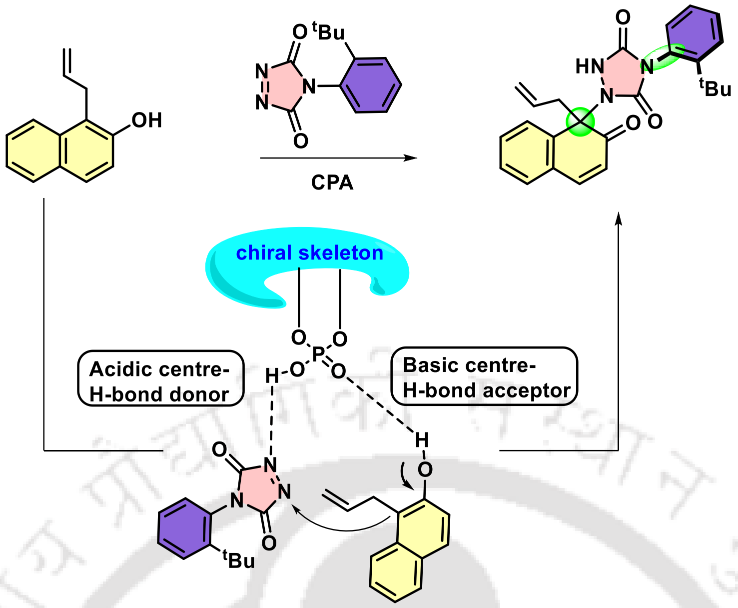
In 2017, Feng *et al*. reported[22] an efficient chiral *N*,*N′*-dioxide–Sc(OTf)$_3$ complex catalytic system for the asymmetric dearomatization of β-naphthols with electron-deficient alkynes. The corresponding β-naphthalenones were obtained with excellent *Z*/*E* selectivities (up to >20/1) and excellent enantioselectivities (up to 98% ee) (Scheme 8).



Scheme 8: construction of a spiro[imidazolidine-2,3′-oxindole] framework

5.3 Concept:

A catalytic asymmetric dearomatization reaction has not been utilized for the synthesis of urazole derivatives having both axial and central chirality. Thus, we envisioned to make such derivatives *via* reaction of 1-substituted β-naphthol and 4-aryl-1,2,4-triazole-3,5-dione (ATAD) (Scheme 9).

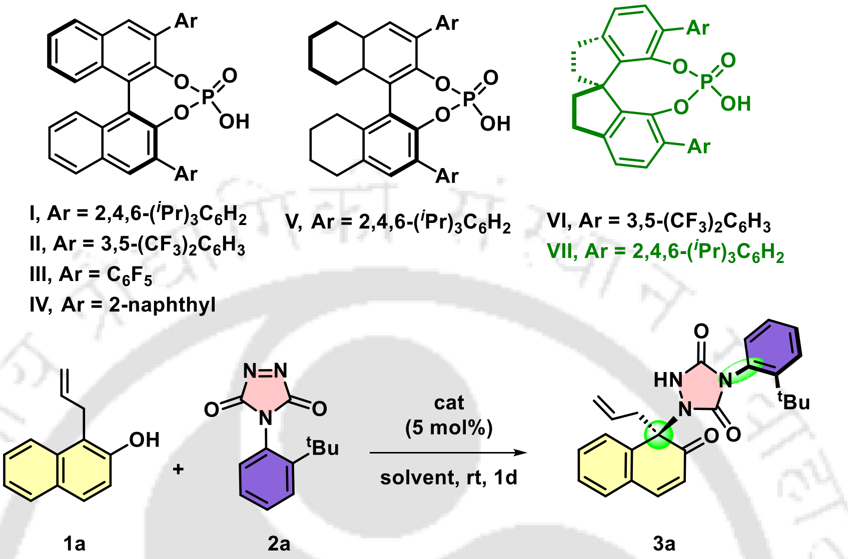


Scheme 9: Concept

5.4 Results and discussion

We initiated our study by performing a model reaction between 1-allyl-*β*-naphthol (**1a**) and ATAD **2a** in toluene at room temperature (Table 1). At first, TRIP (**I**) was employed as the catalyst. Delightfully, after stirring for 1 day at room temperature, the desired dearomatization product **3a** was obtained in 70% yield with >20:1 dr and 36% ee (Table 1, entry 1). The enantioselectivity of **3a** got slightly improved with phosphoric acid **II** having 3,5-di trifluromethylphenyl substituents (Table 1, entry 2). Catalysts **III** and **IV** having pentafluoro phenyl and 2-naphthyl substituents respectively were not suitable for the reaction (Table 1, entries 3-4). Better yield and enantioselectivity was attained with H8-TRIP catalyst **V** (Table 1, entry 5). Similar enantioselectivity was detected with spiro-phosphoric acid **VI** having 3,5-di trifluoromethylphenyl substituent (Table 1, entry 6). Finally, the best catalyst turned out to be spiro-TRIP **VII** and product **3a** was attained in 78% yield with 70% ee (Table 1, entry 7). To further improve the enantioselectivity, different solvents were tested (Table 1, entries 8-11). The enantioselectivity got slightly increased in *o*-xylene (Table 1, entry 8). Then halogenated solvents were screened and this found to be fruitful (Table 1, entries 9-11). For example, 80% and 86% ees were observed in chloroform and dichloromethane respectively (Table 1, entries 9-10). Finally, carbon tetrachloride emerged as the best solvent and product **3a** was isolated in 80% yield with

90% ee (Table 1, entry 11). Also reaction carried out with low catalyst loading (2.5 mol%), decrease in enantioselectivity was observed (entry 12).

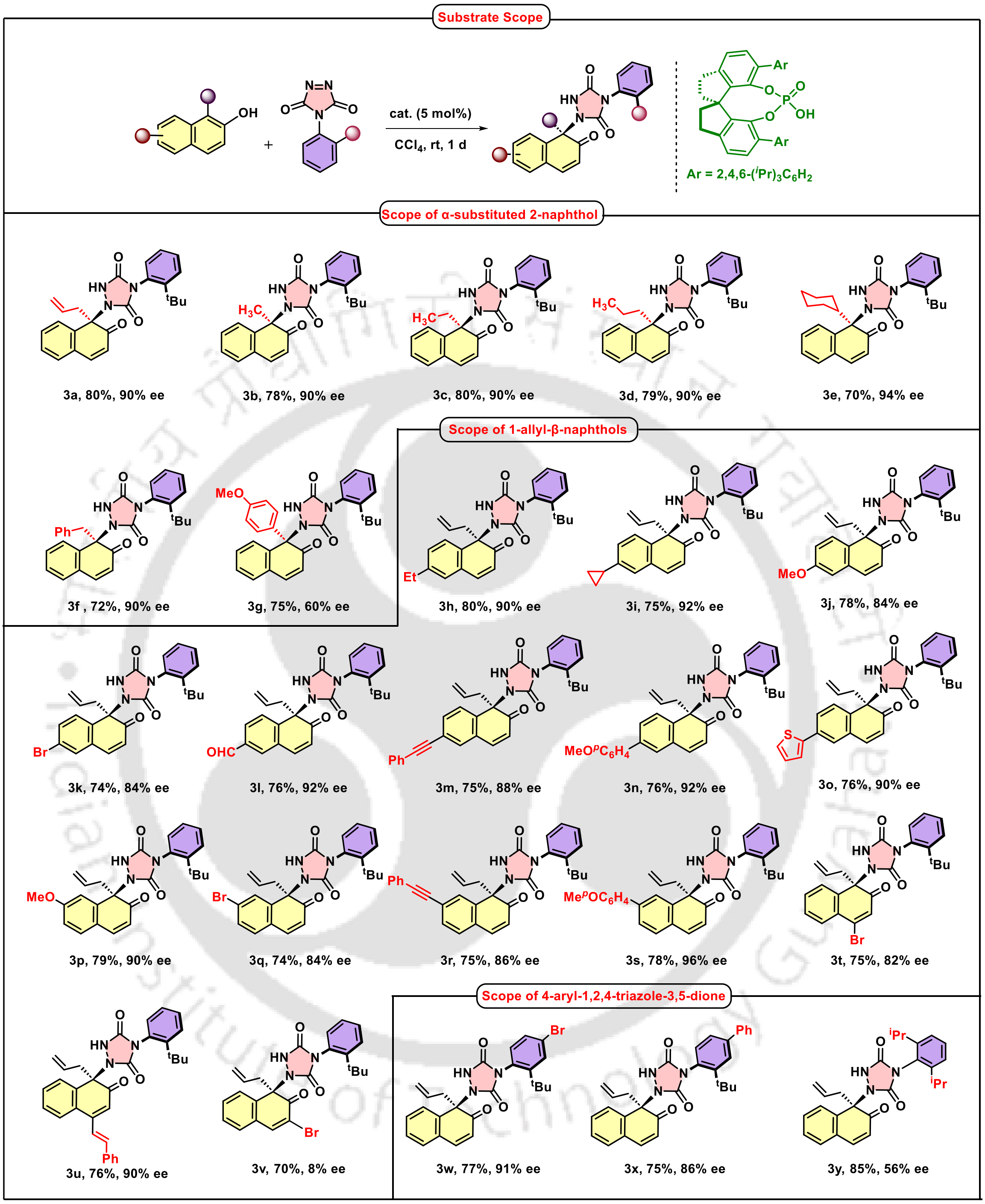


Entry[a]	catalyst	solvent	Yield (%)[b]	d.r[c]	ee (%)[d]
1	**I**	toluene	70	>20:1	36
2	**II**	toluene	73	>20:1	42
3	**III**	toluene	72	>20:1	34
4	**IV**	toluene	70	>20:1	26
5	**V**	toluene	78	>20:1	62
6	**VI**	toluene	75	>20:1	62
7	**VII**	toluene	78	>20:1	70
8	**VII**	*o*-xylene	78	>20:1	74
9	**VII**	$CHCl_3$	79	>20:1	80
10	**VII**	CH_2Cl_2	78	>20:1	86
11	**VII**	**CCl_4**	**80**	**>20:1**	**90**
12[e]	**VII**	CCl_4	80	>20:1	88

[a] Reaction condition: 0.1 mmol of **1** and 0.1 mmol of **2** in 1.25 mL solvent using 5 mol% catalyst. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}HNMR. [d] Determined by HPLC and of the major diastereomers. [e] Reaction carried with 2.5 mol% catalyst loading.

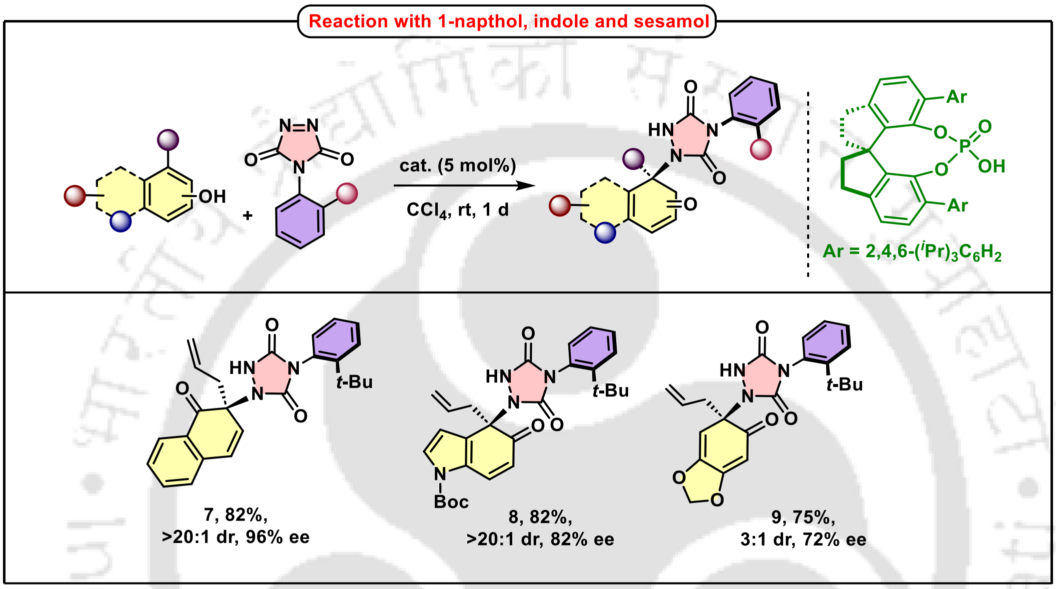
Table 1: Catalyst and solvent optimization.

Following the establishment of the optimal conditions, the scope of this dearomatization process was examined. Initially, naphthols **1** having different substituents at the *α*-position were prepared and reacted with ATAD **2a** (Scheme 10). Gratifyingly, in all cases a single diastereomer was attained. Different linear aliphatic groups such as methyl, ethyl and ^{n}propyl could be tolerated well, and the corresponding compounds **3b**–**3d** were produced in high yields with identical enantioselectivities (Scheme 10). Then cyclohexyl substitution was checked and gratifyingly the product **3e** was isolated in 70% yield with 94% ee. Then *α*-benzyl substituted *β*-naphthol gave the product **3f** with 70% yield and 90% ee. Aryl substitution was also tested but moderate enantioselectivity was obtained for product **3g.** Then β-naphthol **1** having substitutions at other positions were prepared and employed in the reaction. Initially, substitutions at 6-position with different EDG (-Ethyl, -cyclopropane and -OMe) were checked and gratifyingly good results were detected (**3h**, **3i** and **3j**) up to 92% ee. Then halo substitution was checked and acceptable enantioselectivity was detected for product **3k**. *β*-Naphthol **1l** with an aldehyde motif also took part in the reaction to deliver product **3l** in 92% ee. Then *β*-naphthol **1m** with an alkyne motif in 6-position was employed in the reaction and product **3m** was isolated in 75% yield with 88% ee. An aryl motif was also incorporated at the 6 position and the corresponding product **3n** was obtained in 92% ee. Smooth conversion was also detected for thiophene substituted naphthol **1o** to provide product **3o** in high enantioselectivity. Then we focussed to incorporate substitutions at the 7-position of *β*-naphthol **1** (Scheme 10). Thus, naphthol **1p** having 7-methoxy substituent was prepared and engaged in the reaction. This resulted in the formation of **3p** in 90% ee. The reaction also progressed efficiently with 7-bromo substituted naphthol **1q** to deliver **3q** in 74% yield with 84% ee. An alkyne substituent was also tolerated at the 7-position and product **3r** was isolated in 75% yield with 86% ee. Gratifyingly, an enhancement in enantioselectivity (96% ee) was observed for product **3s** with a 7-aryl substituent. Then we turned our attention to check different substituents at the 4-position of *β*-naphthols **1** (Scheme 10). To our delight, here also the outcome was good. For example, 82% ee was attained for product **3t** with 4-bromo substituent. A styryl substituted β- naphthol **1u** was employed in the reaction to provide product **3u** in acceptable enantioselectivity. 3-Substituted naphthol **1v** was also checked



Scheme 10: Substrate scope pf dearomatized product.

but surprisingly poor enantioselectivity was detected for **3v**. Then we checked the scope of 4-aryl-1,2,4-triazole- 3,5-dione (Scheme 10). Initially different *para*-substitutions were explored and good results were obtained for the corresponding urazoles. High enantioselectivity (91% ee) was attained for the product **3w** with *p*-bromo substitution. Similarly, an aryl group can be incorporated at the *para*-position without much change in enantioselectivity. Then we made the *N*-aryl group symmetrical of 1,2,4-triazole-3,5-dione and thus axial chirality was lost for the product. Interestingly, a significant drop in enantioselectivity was observed for product **3y**.



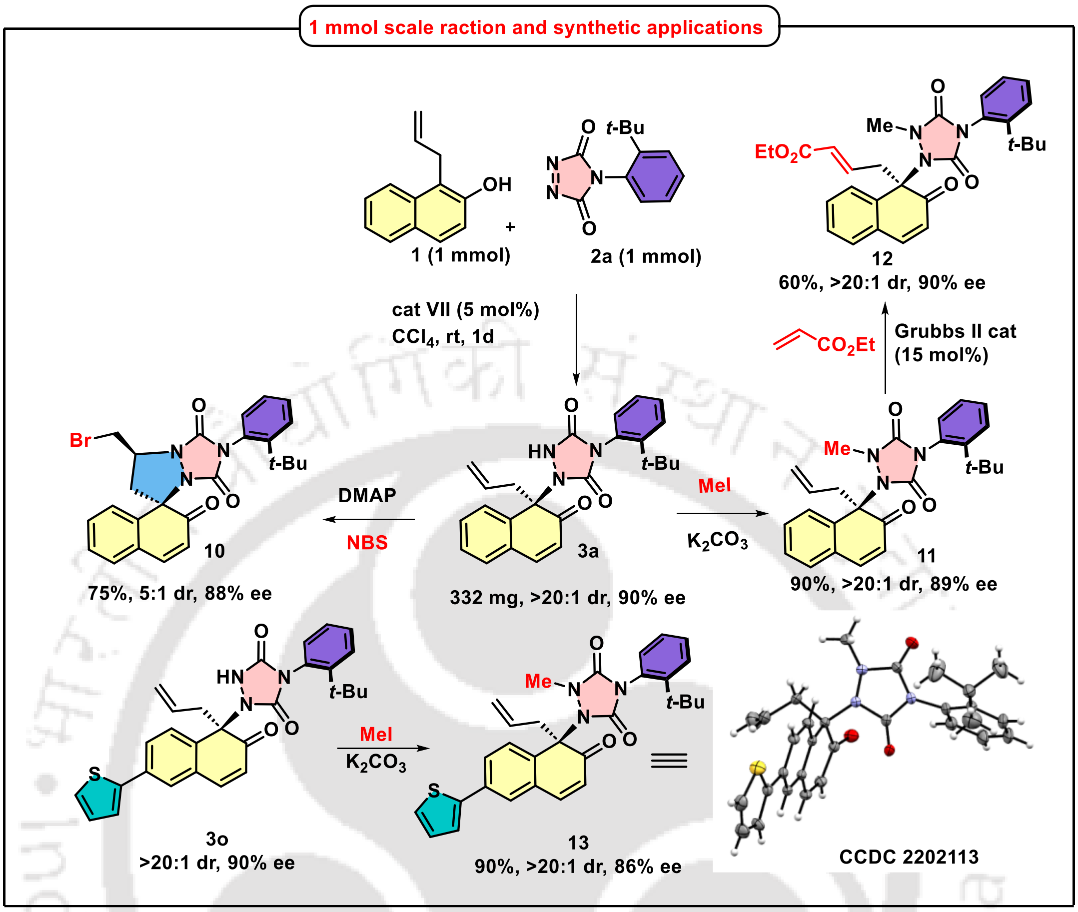
7, 82%,
>20:1 dr, 96% ee

8, 82%,
>20:1 dr, 82% ee

9, 75%,
3:1 dr, 72% ee

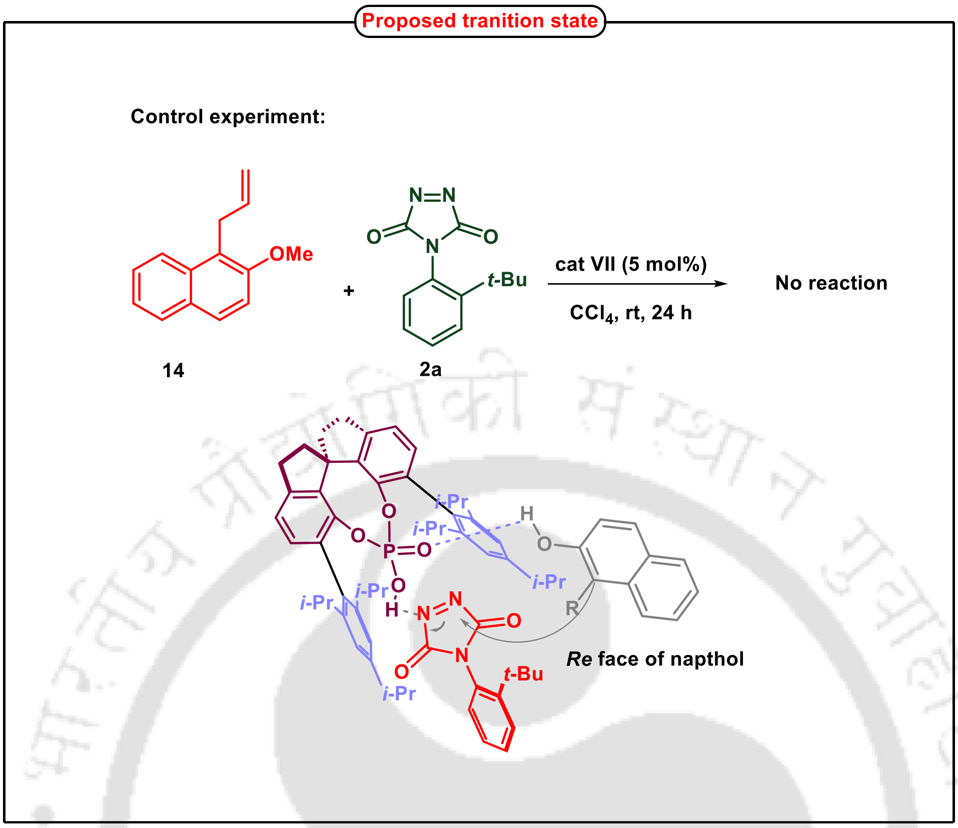
Scheme 11: Reaction with 1-napthol, indole and sesamol.

After that, we became interested to employ other compounds having phenolic OH group (Scheme 11). Thus, 2-allyl-*α*-naphthol **4** was prepared and treated with **2a**. Gratifyingly, the reaction proceeded smoothly to deliver product **7** as a single diastereomer in 82% yield with 96% ee. An indole derivative **5** also took part in the reaction and product **8** was obtained as a single diastereomer in 82% yield and 82% ee. Finally, a sesamol derivative **6** was prepared and engaged in the reaction. The product **9** was obtained in slight less enantioselectivity and 3:1 diastereomeric ratio was detected (Scheme 11).



Scheme 12: 1 mmol scale reaction and synthetic applications.

By carrying out a few reactions, our methods' synthetic potential was shown (Scheme 12). At first 1 mmol scale reaction was carried out, product **3a** was obtained in good yield (80%, 332 mg) and 90% ees. Then an electrophilic bromination followed by intramolecular cyclization reaction was performed on **3a**. This led to the formation of **10** in 5:1 dr and with 88% ee. Then **3a** was subjected to *N*-methylation with iodomethane. Thus, **11** was formed in 89% yield and both diastereo- and enantioselectivity got retained. Then Grubbs **II** catalyzed cross-metathesis reaction was carried out with ethyl acrylate and to our delight, product **12** was obtained in 60% yield with no erosion in enantioselectivity. Finally, *N*-methylation reaction was performed on **3o** to get **13** with 86% enantioselectivity. The absolute configuration the compound **13** was determined by X-ray diffraction analysis of a single crystal.



Scheme 13: Control experiment and proposed transition state.

No product was formed from the reaction of methoxy compound **14** with **2a** (Scheme 7). From this we conclude that -OH group is crucial for the reaction. Thus, in the proposed reaction mechanism, at first CPA activates naphthol and ATAD *via* H-bonding, then nucleophilic attack takes place from *Re* face of *α*- position of 2-naphthol as shown below (Scheme 13) generate product **3a**.

Next, we determined the rotational barriers[23], As we observed product **3a** as a single chiral C(sp^2)−C(sp^3) atropisomer. Heating compound **3a** at 120 °C for 6 hours resulted

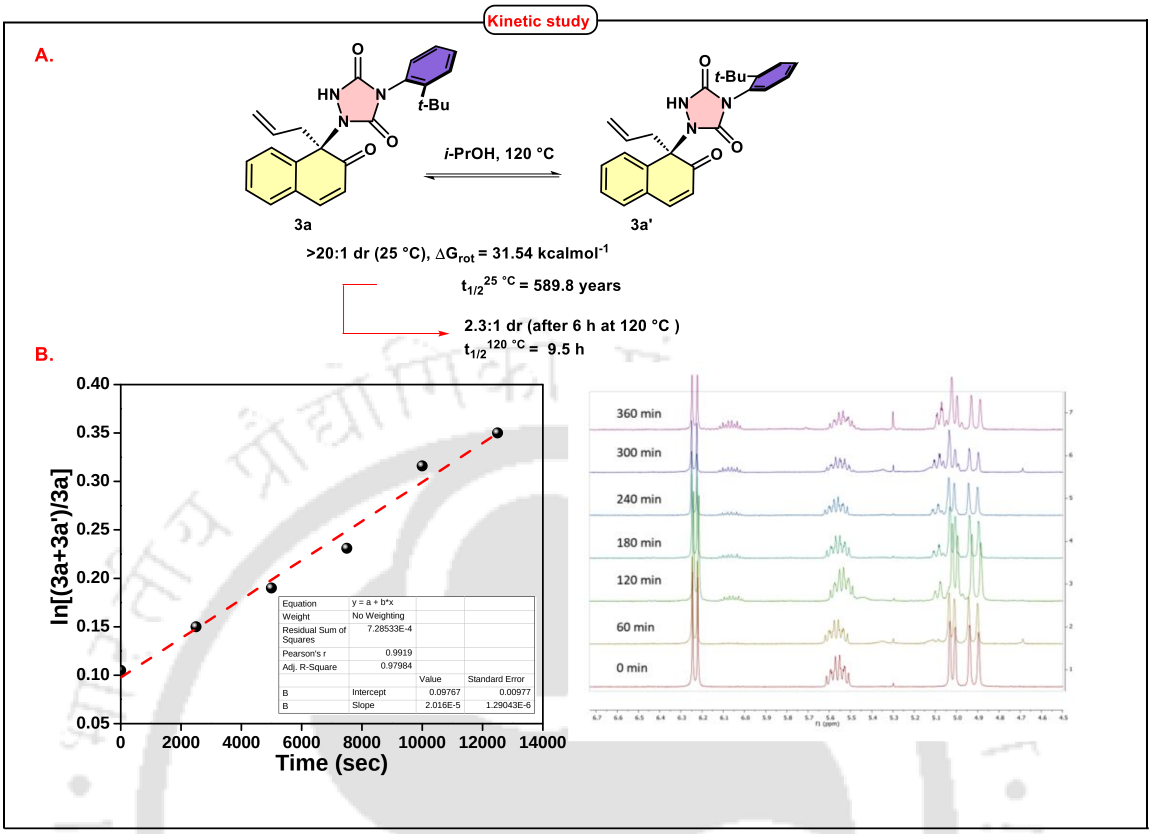


Figure 3: A: Effect of temperature on the diastereoselective. B: Stacked ^{1}H NMR data at 120°C at 1-hour gap duration.

in the observation of its rotamer **3a'** confirming that the C(sp^2)–C(sp^3) axis is a stable stereogenic element at room temperature. For this compound **3a** in ^{i}PrOH was gradually heated, starting at 60 °C to 100 °C , but product **3a'** started appering at 110 °C, so we record ^{1}H NMR in 120 °C in every 1 hr duration. The ratio was plotted against time, and the barrier of rotation was calculated from the plot. Then applying the method of initial rates:

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

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

$$\Delta G^{rot} = RTln\left(\frac{k_B\,T}{kh}\right)$$

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:

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

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

From this experiment we calculate the C-N rotational energy barrier found to be 31.54 kcalmol^{-1} and $t^{25\,°C}_{1/2} = 589.8\,years$ at room temprature and $t^{120\,°C}_{1/2} = 9.5\,hour$ at 120 °C (figure 2).

In conclusion, we present a catalytic asymmetric dearomatization for the synthesis of axially chiral urazole derived naphthalenones. The desired products were obtained in good to high yields with high diastereo- and enantioselectivities under ambient reaction conditions with easily available spiro-TRIP catalyst. The reaction scope was extended to other substrates such as 1-naphthol and 5-hydroxy indole derivatives. Synthetic applications including bromoamination and cross-metathesis have been demonstrated.

5.5 Experimental section

5.5.1 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 {1H} NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz).

Using ESI mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA, Daicel Chiralpak ID and Daicel Chiralpak AD-H Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Silica gel (100-200 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

5.5.2 General procedure of synthesis of compounds

General Procedure for the Synthesis of different α-substituted-2-napthol[24]: General Procedure for the Synthesis of different α-substituted-2-napthol.

General Procedure for the Synthesis of ATAD complex (2a)[25]: ATAD (**2a**) were prepared according to the known reported procedure.

General Procedure for the Catalyst Preparation[26]: The best catalyst, i.e., spiro trip phosphoric acid was prepared according to the previously reported procedure.

General Procedure for the Synthesis of Compound 3:

In an oven dried round bottom flask, **1** (0.1 mmol), **2** (0.1 mmol), 5 mol% of catalyst (*S*)-spiro TRIP were taken under argon atmosphere. 1.25 mL dry CCl_4 of was added to the reaction mixture and stirred at rt for 1 day. Completion of the reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with DCM/acetone (2-5%) to afford desired products **3 to 9**.

General procedure for the synthesis of compound 10:

A flame-dried reaction tube was cooled to room temperature and filled with argon. In this flask, **3a** (41.5 mg, 0.1 mmol, 90% ee) and dimethylaminopyridine (10 mol %) were dissolved in dichloromethane (1 mL). After the resultant solution was stirred for 5 minutes, *N*-bromo succinimide (36 mg, 0.2 mmol) was added to this tube. The reaction mixture was stirred at room temperature. After the reaction was complete (monitored by TLC), the reaction mixture was quenched with aq. $Na_2S_2O_3$ and extracted with DCM. The DCM layer was washed with brine, dried over Na_2SO_4 and filtrated. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate/hexane =15-20%) to afford product **10** (37 mg, 75% yield, 90% ee, 5:1 dr).

General procedure for the synthesis of compound 11:

In an oven dried round bottom flask, **3a** (41.4mg, 0.1 mmol) and K_2CO_3 (2.5 eq.) were taken.1.25 mL 1,4-dioxane was added. To the flask methyl iodide (2.5 eq) was added. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl acetate/hexane =15-20% to afford desired products **11** with 90% (39 mg) yield as well as ee.

General procedure for the synthesis of compound 12:

Compound **11** (42.9 mg, 0.1 mmol), ethyl acrylate (10 eq.) and Grubbs catalyst (15 mol%) were dissolved in DCM (1 mL, 0.1 M). the reaction mixture was stirred at 40 °C for 4 h. After 4 h, the mixture was directly purified by column chromatography on silica gel eluting with ethyl acetate/hexane =15-20% to afford desired products **12** with 60% (30 mg) yield and 90% ee.

General procedure for the synthesis of compound 13:

In an oven dried round bottom flask, **3o** (49.7 mg, 0.1 mmol) and K_2CO_3 (2.5 eq.) were taken. Then 1.25 mL 1,4-dioxane was added. To the flask methyl iodide (2.5 eq) was added. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with ethyl acetate/hexane =15-20% to afford the desired product **13** with 90% (46 mg) yield as well as in high ee.

5.6 Crystal data of compound 13

CCDC = 2202113

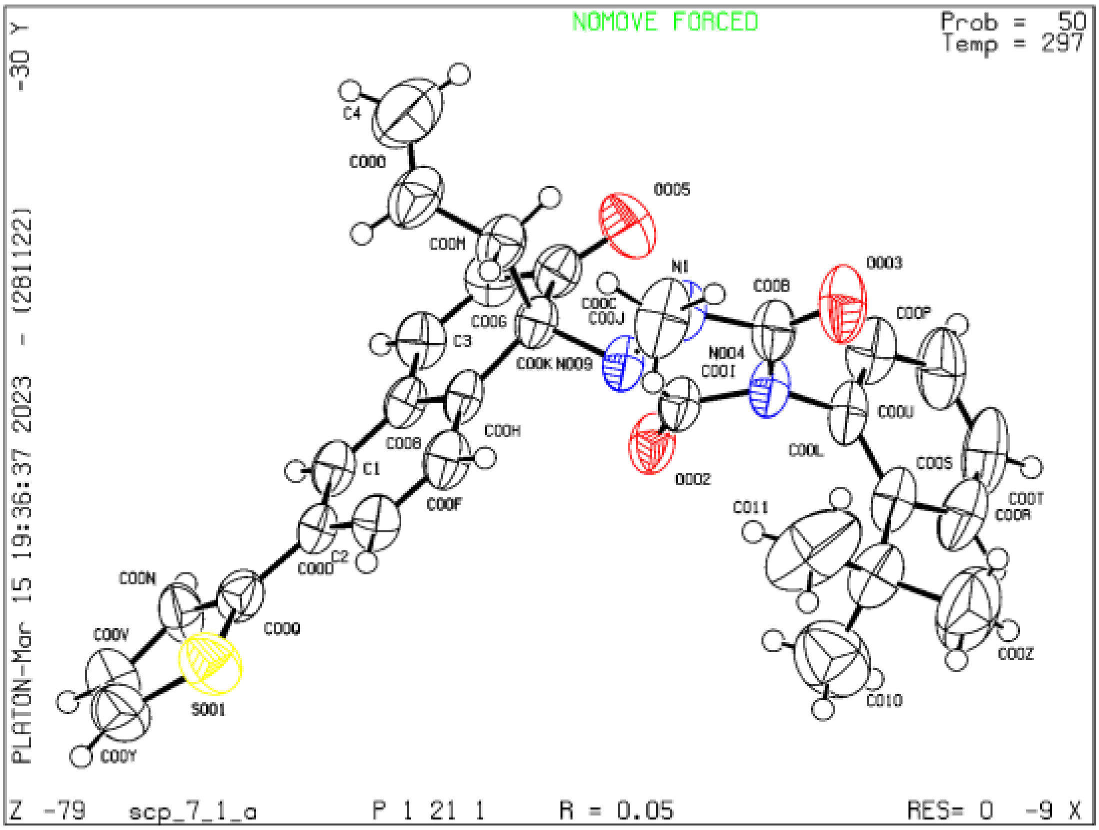
Bond precision: C-C = 0.0118 A Wavelength=0.71073

Cell: a=9.690(5) b=12.089(6) c=13.334(7) alpha=90 beta=96.853(15) gamma=90

Temperature: 297 K

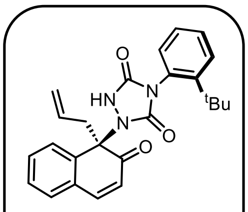
	Reported
Volume	1550.7 (14)
Space group	P 21
Hall group	P 2yb
Moiety formula	$C_{30}H_{29}N_3O_3S$
Sum formula	$C_{30}H_{29}N_3O_3S$
Mr	511.62
Dx, g cm^{-3}	1.096
Z	2
Mu (mm^{-1})	0.136
F000	540.0
H, k, l_{max}	11, 14, 15
N_{ref}	5468
T_{min}, T_{max}	0.636, 0.745
T_{min}’	0.959
Data completeness	1.89/0.99
Theta (max)	25.042
R (reflections)	0.0475 (4446)
S	1.086
N_{par}	339
Flack parameter	0.08

Datablock scp_7_1_a - ellipsoid plot



5.7 Characterisation of the products:

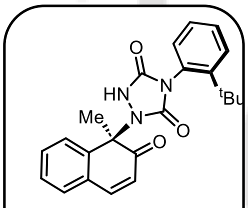
(*R*, *R_a*)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3a)



3a

White sticky solid**,** yield: 80%, 33 mg. **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.61 (d, J = 7.7 Hz, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.48 – 7.36 (m, 5H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 7.23 (dd, J = 7.5, 1.6 Hz, 1H), 6.23 (d, J = 9.9 Hz, 1H), 5.56 (ddt, J = 17.1, 10.2, 7.6 Hz, 1H), 5.02 (dd, J = 10.2, 1.5 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 3.24 (dd, J = 13.5, 6.5 Hz, 1H), 3.09 (dd, J = 13.5, 8.0 Hz, 1H), 1.39 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d**) δ 198.8, 156.8, 155.1, 149.3, 145.6, 139.8, 131.7, 130.6, 130.6, 130.4, 130.3, 130.1, 129.1, 129.1, 128.8, 127.7, 126.9, 124.9, 121.1, 74.9, 43.9, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{25}N_3O_3$ $[M+H]^+$ 416.1969, found 416.1966. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 10.3 min, t_{minor} = 5.1 min.

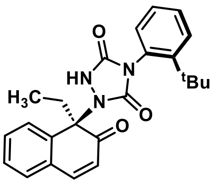
(*R*, *R_a*)-4-(2-(*tert*-butyl)phenyl)-1-(1-methyl-2-oxo-1,2-dihydronaphthalen-1-yl)-1,2,4-triazolidine-3,5-dione (3b)



3b

White sticky solid, yield: 78%, 30 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.68 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.45 (d, J = 9.9 Hz, 1H), 7.40 (dd, J = 10.6, 6.3 Hz, 3H), 7.33 – 7.29 (m, 2H), 7.08 (s, 1H), 6.24 (d, J = 9.9 Hz, 1H), 1.99 (s, 3H), 1.41 (s, 9H).**^{13}C NMR (100 MHz, Chloroform-d)** δ 198.9, 155.8, 155.6, 149.5, 145.5, 142.8, 131.7, 131.1, 130.4, 130.2, 129.3, 129.2, 128.8, 128.5, 127.6, 126.0, 124.1, 77.5, 77.2, 76.9, 69.8, 35.7, 31.5, 27.3. **HRMS (ESI):** m/z calcd. for $C_{23}H_{23}N_3O_3$ $[M+H]^+$ 390.1812, found 390.1819. **HPLC Analysis:** ee = 90%, Chiralpak ID Column, *n*-Hexane/*i*-PrOH = 70/30, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 23.5 min, t_{minor} = 12.6 min.

(*R*, *R_a*)-4-(2-(*tert*-butyl)phenyl)-1-(1-ethyl-2-oxo-1,2-dihydronaphthalen-1-yl)-1,2,4-triazolidine-3,5-dione (3c)

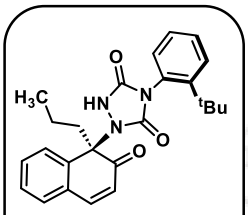


3c

Pale yellow sticky solid, yield: 80%, 32 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.63 (d, J = 7.8 Hz, 1H), 7.56 (dd, J = 8.2, 1.6 Hz, 1H), 7.47 – 7.35 (m, 5H), 7.29 (t, J = 7.6 Hz, 1H), 7.21 – 7.14 (m, 1H), 6.25 (dd, J = 10.0, 2.1 Hz, 1H), 2.46 (tt, J = 15.0, 6.1 Hz, 2H), 1.38 (s, 9H), 0.83 – 0.78 (m, 3H). **^{13}C NMR (125 MHz,**

Chloroform-d) δ 199.3, 156.4, 155.2, 149.3, 145.5, 140.3, 131.7, 130.8, 130.7, 130.3, 130.2, 129.2, 129.0, 128.7, 127.7, 126.6, 125.2, 75.2, 35.9, 33.1, 31.8, 8.0. **HRMS (ESI):** m/z calcd. for $C_{24}H_{25}N_3O_3$ $[M+H]^+$ 404.1969, found 404.1974. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 200 nm, t_{major} = 5.8 min, t_{minor} = 3.3 min.

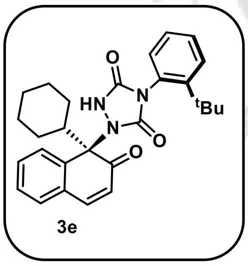
(*R*, *R*$_a$)-4-(2-(*tert*-butyl)phenyl)-1-(2-oxo-1-propyl-1,2-dihydronaphthalen-1-yl)-1,2,4-triazolidine-3,5-dione (3d)



3d

Yellow sticky solid, yield: 79%, 32 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.64 (d, J = 7.7 Hz, 1H), 7.56 (dd, J = 8.0, 1.5 Hz, 1H), 7.49 – 7.37 (m, 5H), 7.30 (td, J = 7.6, 1.6 Hz, 1H), 7.21 (dd, J = 7.6, 1.7 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H), 2.41 – 2.33 (m, 2H), 1.39 (s, 9H), 1.26 (d, J = 3.2 Hz, 2H), 0.78 (t, J = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, Chloroform-d**) δ 198.8, 155.8, 155.1, 149.6, 145.4, 140.8, 131.6, 130.7, 130.7, 130.2, 130.2, 129.3, 128.9, 128.5, 127.6, 126.7, 125.3, 72.6, 41.9, 35.7, 31.5, 16.9, 14.0. **HRMS (ESI):** m/z calcd. for $C_{25}H_{27}N_3O_3$ $[M+H]^+$ 418.2125, found 418.2131. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 4.8 min, t_{minor} = 3.1 min.

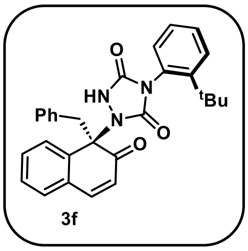
(*R*, *R*$_a$)-4-(2-(*tert*-butyl)phenyl)-1-(1-cyclohexyl-2-oxo-1,2-dihydronaphthalen-1-yl)-1,2,4-triazolidine-3,5-dione (3e)



3e

White solid, Yield: 70%, 31 mg, melting point: 248-250 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.63 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.36 (dd, J = 9.3, 5.8 Hz, 3H), 7.28 (d, J = 7.4 Hz, 3H), 7.05 (d, J = 7.6 Hz, 1H), 6.22 (d, J = 9.9 Hz, 1H), 2.67 (d, J = 17.5 Hz, 1H), 1.85 – 1.77 (m, 2H), 1.60 (d, J = 13.5 Hz, 1H), 1.51 (t, J = 16.6 Hz, 2H), 1.33 (s, 9H), 1.22 – 1.13 (m, 2H), 1.03 (dd, J = 12.2, 3.3 Hz, 1H), 0.93 – 0.87 (m, 2H). **^{13}C NMR (100 MHz, Chloroform-d**) δ 199.3, 155.8, 155.2, 149.7, 145.4, 139.0, 131.7, 131.6, 130.1, 130.0, 129.8, 129.5, 128.8, 128.4, 127.9, 127.4, 126.1, 76.3, 47.4, 35.7, 31.5, 28.2, 27.1, 26.2, 26.1, 26.0. **HRMS (ESI):** m/z calcd. for $C_{28}H_{31}N_3O_3$ $[M+Na]^+$ 480.2258, found 480.2274. **HPLC Analysis:** ee = 94%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 3.8 min, t_{minor} = 5.3 min.

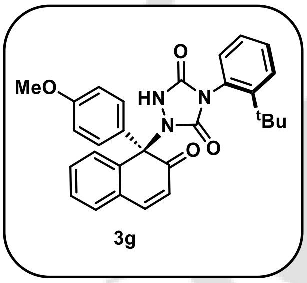
(*R*, *R*$_a$)-1-(1-benzyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidin-3-one (3f)



3f

White solid, yield: 72%, 33 mg, melting point: 194-196 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.61 – 7.57 (m, 1H), 7.49 – 7.29 (m, 7H), 7.20 (dd, J = 7.2, 1.6 Hz, 1H), 7.12 (dd, J = 8.4, 6.3 Hz, 1H), 7.07 (d, J = 9.9 Hz, 1H), 7.01 (dd, J = 8.4, 6.7 Hz, 2H), 6.67 – 6.61 (m, 2H), 6.03 (d, J = 9.9 Hz, 1H), 3.92 – 3.80 (m, 2H), 1.42 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d)** δ 199.2, 157.6, 154.8, 149.3, 145.0, 139.4, 132.9, 131.8, 131.3, 130.9, 130.5, 130.3, 130.1, 129.2, 129.1, 128.8, 127.8, 127.4, 127.2, 125.2, 76.2, 45.3, 36.0, 31.8. **HRMS (ESI):** m/z calcd. for $C_{29}H_{27}N_3O_3$ $[M+H]^+$ 466.2125, found 466.2129. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm (t$_{major}$ = 12.5 min, t$_{minor}$ = 7.2 min).

(*R*, *R*$_a$)-4-(2-(*tert*-butyl)phenyl)-1-(1-(4-methoxyphenyl)-2-oxo-1,2-dihydro naphthalen-1-yl)-1,2,4-triazolidine-3,5-dione (3g)

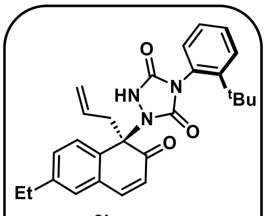


3g

White solid, yield: 75%, 36 mg, melting point: 183-185 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.75 (d, J = 7.7 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 9.9 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.85 (dd, J = 14.0, 7.9 Hz, 3H), 6.15 (d, J = 9.9 Hz, 1H), 3.76 (s, 3H), 1.42 (s, 9H).**^{13}C NMR (125 MHz, Chloroform-d)** δ 194.7, 160.8, 154.6, 149.6, 144.3, 140.5, 131.5, 131.1, 130.5, 130.4, 130.4, 130.3, 129.3, 128.9, 128.8, 127.5, 127.2, 125.8, 124.4, 114.7, 73.7, 55.6, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{29}H_{27}N_3O_4$ $[M+H]^+$ 482.2074, found 482.2080. **HPLC Analysis:** ee = 60%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 36.5 min, t$_{minor}$ = 9.3 min.

(*R*, *R*$_a$)-1-(1-allyl-6-ethyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)

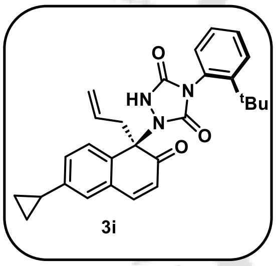
-1,2,4-triazolidine-3,5-dione (3h)



3h

Yellow solid, yield: 80%, 35 mg, melting point: 183-185 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.61 (d, J = 7.7 Hz, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.48 – 7.36 (m, 5H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 7.23 (dd, J = 7.5, 1.6 Hz, 1H), 6.23 (d, J = 9.9 Hz, 1H), 5.56 (ddt, J = 17.1, 10.2, 7.6 Hz, 1H), 5.02 (dd, J = 10.2, 1.5 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 3.24 (dd, J = 13.5, 6.5 Hz, 1H), 3.09 (dd, J = 13.5, 8.0 Hz, 1H), 1.39 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d)** δ 198.8, 156.8, 155.1, 149.3, 145.6, 139.8, 131.7, 130.6, 130.6, 130.4, 130.3, 130.1, 129.1, 129.1, 128.8, 127.7, 126.9, 124.9, 121.1, 74.9, 43.9, 35.9, 32.1, 31.8. **HRMS (ESI):** m/z calcd. for $C_{27}H_{29}N_3O_3$ $[M+H]^+$ 444.2282, found 444.2288. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 12.4 min, t_{minor} = 4.5 min.

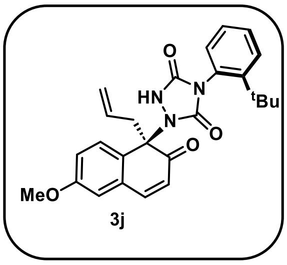
(*R*, *R_a*)-1-(1-allyl-6-cyclopropyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3i)



3i

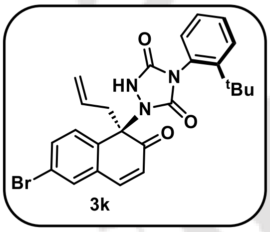
White solid, yield: 75%, 34 mg, melting point: 195-197 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.57 (dd, J = 8.1, 1.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 7.24 (dd, J = 7.7, 1.6 Hz, 1H), 7.16 (dd, J = 8.0, 1.9 Hz, 1H), 7.05 (s, 1H), 6.87 (s, 1H), 6.21 (d, J = 9.9 Hz, 1H), 5.57 (dq, J = 17.0, 8.0 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.95 (dd, J = 17.0, 1.7 Hz, 1H), 3.22 (dd, J = 13.5, 6.4 Hz, 1H), 3.09 (dd, J = 13.5, 8.1 Hz, 1H), 1.92 (ddd, J = 13.4, 8.6, 5.0 Hz, 1H), 1.39 (s, 9H), 1.04 (dt, J = 10.0, 3.2 Hz, 2H), 0.73 (td, J = 6.0, 4.9, 3.6 Hz, 2H). **^{13}C NMR (100 MHz, Chloroform-d)** δ 199.0, 156.8, 155.0, 149.3, 145.8, 145.4, 136.5, 131.7, 130.5, 130.3, 130.2, 129.2, 128.7, 127.9, 127.7, 127.7, 126.9, 124.9, 120.9, 74.7, 43.8, 35.9, 31.8, 15.2, 9.7, 9.7. **HRMS (ESI):** m/z calcd. for $C_{28}H_{29}N_3O_3$ $[M+H]^+$ 456.2282, found 456.2280. **HPLC Analysis:** ee = 92%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 14.2 min, t_{minor} = 5.2 min.

(*R*, *R*$_a$)-1-(1-allyl-6-methoxy-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3j)



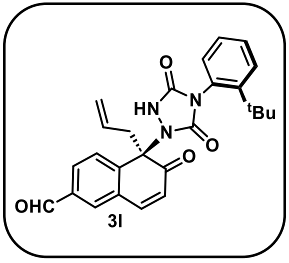
Pale yellow sticky solid, yield: 78%, 35 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.61 – 7.51 (m, 2H), 7.40 (td, J = 7.7, 1.6 Hz, 1H), 7.35 (d, J = 10.0 Hz, 1H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 7.22 (dd, J = 7.8, 1.6 Hz, 1H), 7.06 (s, 1H), 6.98 (dd, J = 8.6, 2.7 Hz, 1H), 6.87 (d, J = 2.7 Hz, 1H), 6.23 (d, J = 9.9 Hz, 1H), 5.56 (dddd, J = 16.8, 10.2, 8.1, 6.4 Hz, 1H), 5.06 – 4.89 (m, 2H), 3.84 (s, 3H), 3.15 (ddd, J = 62.0, 13.5, 7.3 Hz, 2H), 1.38 (s, 9H). **^{13}C NMR (125 MHz, Chloroform-d)** δ 198.9, 159.9, 156.9, 155.0, 149.3, 145.5, 131.8, 131.7, 131.4, 130.3, 130.3, 129.1, 128.8, 128.2, 127.8, 125.4, 121.0, 115.9, 115.5, 74.5, 55.7, 44.0, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{26}H_{27}N_3O_4$ $[M+H]^+$ 446.2074, found 446,2080. **HPLC Analysis:** ee = 84%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 21.0 min, t_{minor} = 6.5 min.

(*R*, *R*$_a$)-1-(1-allyl-6-bromo-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3k)



White sticky solid, yield: 74%, 36 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.91 (s, 1H), 7.57 (dd, J = 8.1, 1.5 Hz, 1H), 7.51 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (dd, J = 5.2, 3.1 Hz, 2H), 7.41 (td, J = 7.7, 1.5 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.31 – 7.29 (m, 1H), 7.16 (dd, J = 7.8, 1.6 Hz, 1H), 6.25 (d, J = 9.9 Hz, 1H), 5.51 (dddd, J = 16.8, 10.1, 8.0, 6.5 Hz, 1H), 5.09 – 4.84 (m, 2H), 3.16 (dd, J = 13.5, 6.5 Hz, 1H), 3.02 (dd, J = 13.4, 8.0 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR (125 MHz, Chloroform-d)** δ 198.0, 156.4, 155.4, 149.3, 144.0, 138.6, 133.2, 132.8, 132.3, 131.6, 130.3, 129.6, 129.0, 128.8, 128.7, 127.7, 126.0, 122.9, 121.5, 73.9, 43.8, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ $[M+H]^+$ 494.1074, found 494.1086. **HPLC Analysis:** ee = 84%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 18.7 min, t_{minor} = 7.1 min.

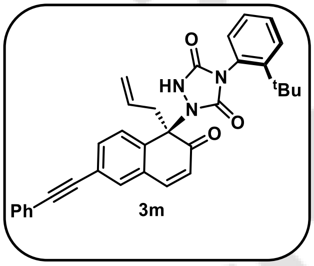
(*R*, *R*$_a$)-5-allyl-5-(4-(2-(*tert*-butyl)phenyl)-3,5-dioxo-1,2,4-triazolidin-1-yl)-6-oxo-5,6-dihydronaphthalene-2-carbaldehyde (3l)



3l

White solid, yield: 76%, 33 mg, melting point: 198-200 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 9.98 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 7.48 (d, J = 10.0 Hz, 1H), 7.41 (td, J = 7.7, 1.6 Hz, 1H), 7.30 (td, J = 7.6, 1.6 Hz, 1H), 7.15 (dd, J = 7.7, 1.7 Hz, 1H), 6.33 (s, 1H), 5.59 – 5.48 (m, 1H), 5.03 (d, J = 10.2 Hz, 1H), 4.90 (d, J = 17.0 Hz, 1H), 3.22 (dd, J = 13.6, 6.6 Hz, 1H), 3.04 (dd, J = 13.5, 7.9 Hz, 1H), 1.36 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d**) δ 197.7, 190.8, 156.4, 155.5, 149.4, 145.8, 144.3, 136.7, 131.6, 131.4, 131.3, 130.5, 130.4, 129.5, 129.4, 128.9, 128.8, 127.9, 127.7, 126.1, 121.7, 74.4, 43.8, 35.9, 31.7. **HRMS (ESI):** m/z calcd. for $C_{26}H_{25}N_3O_4$ $[M+H]^+$ 444.1918, found 444.1923. **HPLC Analysis:** ee = 92%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 38.4 min, t_{minor} = 12.3 min.

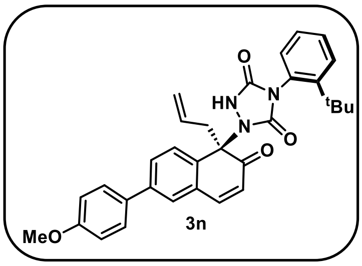
(*R*, *R*$_a$)-1-(1-allyl-2-oxo-6-(phenylethynyl)-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3m)



3m

Yellow sticky solid, yield: 75%, 38 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.62 – 7.51 (m, 5H), 7.52 – 7.47 (m, 1H), 7.38 (td, J = 5.7, 2.4 Hz, 5H), 7.30 (td, J = 7.4, 1.5 Hz, 1H), 7.20 (dt, J = 7.6, 2.0 Hz, 1H), 6.26 (d, J = 9.9 Hz, 1H), 5.62 – 5.45 (m, 1H), 5.02 (d, J = 10.4 Hz, 1H), 4.91 (d, J = 16.6 Hz, 1H), 3.21 (dd, J = 13.3, 6.4 Hz, 1H), 3.06 (dd, J = 13.4, 8.1 Hz, 1H), 1.38 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d**) δ 198.2, 156.5, 155.4, 149.3, 144.9, 139.3, 133.3, 133.0, 131.9, 131.6, 130.7, 130.3, 129.8, 129.1, 128.9, 128.7, 128.6, 127.7, 127.2, 125.6, 124.4, 122.8, 121.3, 91.3, 88.0, 74.3, 43.9, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{33}H_{29}N_3O_3$ $[M+H]^+$ 516.2282, found 516.2287. **HPLC Analysis:** ee = 88%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 18.6 min, t_{minor} = 8.1 min.

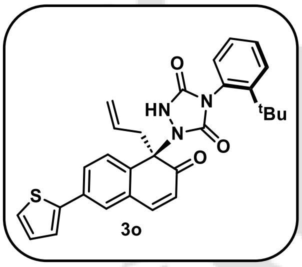
(*R*, *R*$_a$)-1-(1-allyl-6-(4-methoxyphenyl)-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3n)



3n

Gray sticky solid, yield: 76%, 39 mg, **^{1}H NMR (400 MHz, DMSO-d6)** δ 10.87 (s, 1H), 7.93 – 7.82 (m, 2H), 7.82 – 7.68 (m, 4H), 7.61 (dd, J = 8.0, 1.5 Hz, 1H), 7.45 (td, J = 7.7, 1.6 Hz, 1H), 7.32 (td, J = 7.4, 1.5 Hz, 1H), 7.15 – 7.06 (m, 2H), 6.96 (dd, J = 7.6, 1.5 Hz, 1H), 6.29 (d, J = 9.9 Hz, 1H), 5.38 (ddt, J = 17.0, 9.9, 7.2 Hz, 1H), 5.03 – 4.87 (m, 2H), 3.86 (s, 3H), 3.06 (qd, J = 13.0, 7.2 Hz, 2H), 1.34 (s, 9H). **^{13}C NMR (100 MHz, DMSO-d6)** δ 198.3, 160.2, 155.5, 155.1, 149.7, 146.6, 140.5, 140.0, 132.6, 131.9, 131.6, 130.6, 130.4, 130.3, 129.2, 128.8, 128.7, 128.0, 126.0, 121.3, 115.4, 70.5, 56.1, 45.5, 36.1, 32.1. **HRMS (ESI):** m/z calcd. for $C_{32}H_{31}N_3O_4$ $[M+H]^+$ 522.2387, found 522.2393. **HPLC Analysis:** ee = 92%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 13.0 min, t_{minor} = 5.8 min.

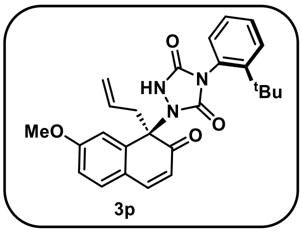
(*R*, *R*$_a$)-1-(1-allyl-2-oxo-6-(thiophen-2-yl)-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3o)



3o

White solid, yield: 76%, 37 mg, melting point: 123-125 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.70 (dd, J = 8.1, 1.9 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 1.9 Hz, 1H), 7.56 (dd, J = 8.2, 1.5 Hz, 1H), 7.45 (d, J = 9.9 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.33 – 7.28 (m, 1H), 7.23 (dd, J = 7.8, 1.6 Hz, 1H), 7.13 (dd, J = 5.1, 3.6 Hz, 1H), 7.03 (s, 1H), 6.28 (d, J = 9.9 Hz, 1H), 5.66 – 5.56 (m, 1H), 5.06 (d, J = 10.1 Hz, 1H), 4.98 (dd, J = 17.0, 1.6 Hz, 1H), 3.26 (dd, J = 13.5, 6.5 Hz, 1H), 3.11 (dd, J = 13.6, 8.0 Hz, 1H), 1.39 (s, 9H). **^{13}C NMR (150 MHz, Chloroform-d)** δ 198.6, 156.8, 155.2, 149.2, 145.3, 142.4, 138.2, 135.3, 131.6, 131.0, 130.3, 130.0, 128.9, 128.7, 128.5, 127.8, 127.6, 127.6, 127.5, 126.1, 125.4, 124.3, 121.4, 74.5, 43.8, 35.9, 31.7. **HRMS (ESI):** m/z calcd. for $C_{29}H_{27}N_3O_3S$ $[M+Na]^+$ 520.1665, found 520.1673. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 20.0 min, t_{minor} = 8.3 min.

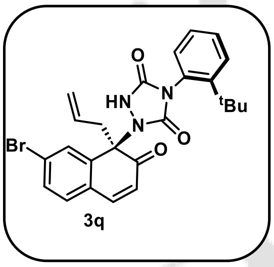
(*R, Ra*)-1-(1-allyl-7-methoxy-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3p)



3p

Pale yellow solid, yield: 79%, 35 mg, melting point: 199-201 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.71 (s, 1H), 7.57 (dd, J = 8.0, 1.4 Hz, 1H), 7.40 (td, J = 8.1, 7.6, 2.0 Hz, 1H), 7.38 – 7.24 (m, 4H), 7.10 (s, 1H), 6.82 (ddt, J = 6.3, 4.5, 2.4 Hz, 1H), 6.07 (d, J = 9.8 Hz, 1H), 5.57 (dt, J = 16.8, 8.7 Hz, 1H), 5.01 (d, J = 10.1 Hz, 1H), 4.91 (d, J = 17.0 Hz, 1H), 3.73 (s, 3H), 3.24 (dd, J = 13.6, 6.4 Hz, 1H), 3.04 (dd, J = 13.7, 8.3 Hz, 1H), 1.37 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d)** δ 198.9, 161.8, 157.1, 155.3, 149.4, 145.7, 141.8, 132.1, 131.8, 130.3, 130.2, 129.3, 128.6, 127.7, 123.5, 122.1, 120.9, 114.4, 113.2, 75.5, 55.7, 44.0, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{26}H_{27}N_3O_4$ $[M+H]^+$ 446.2074, found 446,2080. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 17.9 min, t_{minor} = 6.1 min.

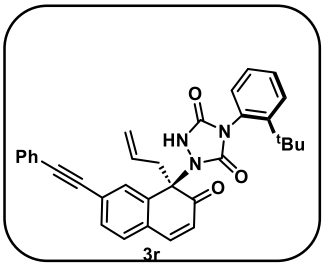
(*R, Ra*)-1-(1-allyl-7-bromo-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3q)



3q

White solid, yield: 74%, 36 mg, melting point: 196-199 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.73 (d, J = 1.9 Hz, 1H), 7.58 (dd, J = 8.4, 1.3 Hz, 1H), 7.52 (dd, J = 8.1, 2.0 Hz, 1H), 7.40 (td, J = 7.7, 1.7 Hz, 1H), 7.36 (d, J = 9.9 Hz, 1H), 7.32 (td, J = 7.4, 1.6 Hz, 1H), 7.23 (dd, J = 7.3, 5.0 Hz, 2H), 6.25 (d, J = 10.0 Hz, 1H), 5.64 – 5.50 (m, 1H), 5.08 (d, J = 10.3 Hz, 1H), 4.96 (d, J = 17.0 Hz, 1H), 3.20 (dd, J = 13.6, 6.5 Hz, 1H), 3.05 (dd, J = 13.6, 8.0 Hz, 1H), 1.40 (s, 9H). **^{13}C NMR (100 MHz, Chloroform-d)** δ 197.8, 156.7, 155.3, 149.4, 144.5, 141.9, 132.3, 131.7, 131.5, 130.4, 130.1, 129.8, 129.4, 129.1, 128.8, 127.8, 125.5, 125.2, 121.6, 74.3, 43.9, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ $[M+H]^+$ 494.1074, found 494.1079. **HPLC Analysis:** ee = 84%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 8.9 min, t_{minor} = 4.2 min.

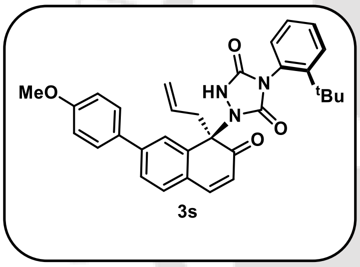
(*R, Ra*)-1-(1-allyl-2-oxo-7-(phenylethynyl)-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3r)



3r

White solid, yield: 75%, 38 mg, melting point: 185-187 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.76 – 7.72 (m, 1H), 7.64 – 7.48 (m, 4H), 7.40 (q, J = 4.9, 3.0 Hz, 5H), 7.36 – 7.22 (m, 4H), 6.25 (d, J = 9.9 Hz, 1H), 5.68 – 5.53 (m, 1H), 5.13 – 5.03 (m, 1H), 4.97 (d, J = 16.5 Hz, 1H), 3.23 (dd, J = 13.7, 6.6 Hz, 1H), 3.14 (dd, J = 13.6, 8.0 Hz, 1H), 1.41 (s, 9H). **^{13}C NMR (125 MHz, Chloroform-d)** δ 198.3, 156.6, 155.2, 149.4, 144.8, 140.3, 132.1, 132.0, 131.7, 130.3, 130.2, 130.2, 129.9, 129.7, 129.2, 129.1, 128.7, 128.7, 127.7, 125.9, 125.2, 122.7, 121.4, 93.1, 88.7, 74.4, 44.0, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{33}H_{29}N_3O_3$ $[M+H]^+$ 516.2282, found 516.2295. **HPLC Analysis:** ee = 86%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 14.7 min, t_{minor} = 5.2 min.

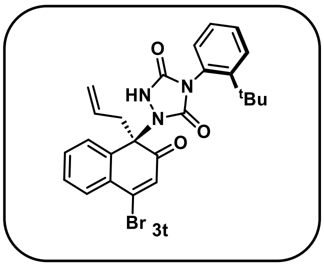
(*R*, *R$_a$*)-1-(1-allyl-7-(4-methoxyphenyl)-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3s)



3s

White sticky solid, yield: 78%, 40 mg, **^{1}H NMR (400 MHz, DMSO-d6)** δ 10.73 (s, 1H), 7.90 (s, 1H), 7.84 – 7.68 (m, 4H), 7.61 (d, J = 7.9 Hz, 2H), 7.44 (t, J = 7.7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 7.8 Hz, 1H), 6.25 (d, J = 9.9 Hz, 1H), 5.43 (dq, J = 16.9, 8.0 Hz, 1H), 5.06 – 4.80 (m, 2H), 3.87 (s, 3H), 3.18 (dd, J = 13.0, 6.4 Hz, 1H), 3.00 (dd, J = 13.0, 8.1 Hz, 1H), 1.35 (s, 9H). **^{13}C NMR (100 MHz, DMSO-d6)** δ 198.7, 160.4, 155.8, 155.5, 149.7, 146.3, 142.5, 142.4, 132.5, 132.4, 131.0, 130.6, 130.6, 130.4, 129.5, 129.1, 129.0, 127.9, 126.8, 125.6, 125.1, 121.2, 115.4, 71.6, 56.2, 45.5, 36.1, 32.1. **HRMS (ESI):** m/z calcd. for $C_{32}H_{31}N_3O_4$ $[M+H]^+$ 522.2387, found 522.2399. **HPLC Analysis:** ee = 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 7.1 min, t_{minor} = 5.6 min.

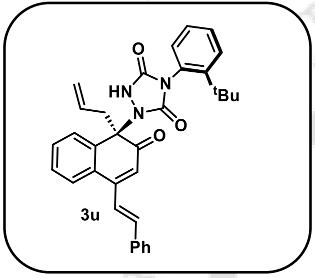
(*R*, *R$_a$*)-1-(1-allyl-4-bromo-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3t)



3t

Yellow sticky solid, yield: 75%, 37 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.95 (d, J = 7.7 Hz, 1H), 7.63 (dd, J = 7.7, 1.5 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.52 (dd, J = 7.6, 1.5 Hz, 1H), 7.47 (td, J = 7.6, 1.4 Hz, 1H), 7.41 (td, J = 7.7, 1.6 Hz, 1H), 7.31 (td, J = 7.5, 1.5 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 6.80 (s, 1H), 5.62 – 5.47 (m, 1H), 5.06 (d, J = 10.5 Hz, 1H), 4.93 (d, J = 16.9 Hz, 1H), 3.23 (dd, J = 13.5, 6.5 Hz, 1H), 3.11 (dd, J = 13.5, 8.1 Hz, 1H), 1.38 (s, 9H).**^{13}C NMR (125 MHz, Chloroform-d)** δ 195.4, 156.7, 155.2, 149.3, 145.4, 138.6, 131.6, 131.6, 130.9, 130.4, 129.9, 129.6, 129.3, 129.0, 128.8, 128.7, 127.8, 126.5, 121.6, 74.9, 44.1, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ $[M+H]^+$ 494.1074, found 494.1070. **HPLC Analysis:** ee = 82%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 7.8 min, t_{minor} = 4.7 min.

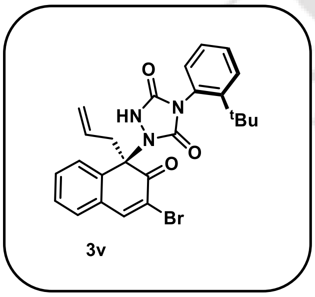
(*R, E, R$_a$*)-1-(1-allyl-2-oxo-4-styryl-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3u)



3u

White sticky solid, yield: 76%, 39 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.76 – 7.68 (m, 2H), 7.60 – 7.53 (m, 3H), 7.50 (t, J = 7.5 Hz, 1H), 7.39 (dtd, J = 15.1, 8.3, 3.1 Hz, 5H), 7.33 – 7.20 (m, 4H), 7.12 (dd, J = 7.7, 1.6 Hz, 1H), 6.50 (s, 1H), 5.60 (dt, J = 17.0, 8.6 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.22 – 3.08 (m, 2H), 1.36 (s, 9H).**^{13}C NMR (100 MHz, Chloroform-d)** δ 197.9, 155.7, 155.6, 151.9, 149.6, 140.1, 137.3, 136.1, 131.7, 130.7, 130.6, 130.5, 130.3, 129.5, 129.3, 129.,2 128.8, 128.6, 127.6, 127.6, 127.3, 126.8, 123.4, 121.0, 120.3, 72.9, 44.3, 35.8, 31.6. **HRMS (ESI):** m/z calcd. for $C_{33}H_{31}N_3O_3$ $[M+H]^+$ 518.2438, found 518.2428. **HPLC Analysis:** ee = 90%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 9.2 min, t_{minor} = 4.9 min.

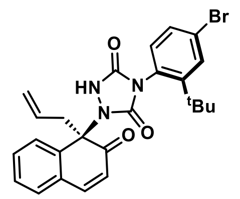
***(R, Ra)*-1-(1-allyl-3-bromo-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3v).**



3v

Pale yellow sticky solid, yield: 70%, 34 mg, **^{1}H NMR (500 MHz, Acetone-d6)** δ 9.49 (s, 1H), 8.12 (s, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.62 – 7.48 (m, 3H), 7.45 (td, J = 7.5, 1.3 Hz, 1H), 7.39 (td, J = 7.7, 1.6 Hz, 1H), 7.30 (td, J = 7.6, 1.6 Hz, 1H), 7.06 (dd, J = 7.8, 1.6 Hz, 1H), 5.37 (dddd, J = 16.6, 10.1, 8.0, 6.5 Hz, 1H), 5.01 – 4.86 (m, 2H), 3.21 – 3.07 (m, 2H), 1.22 (s, 9H).**^{13}C NMR (125 MHz, Acetone-d6)** δ192.8, 156.3, 156.1, 150.0, 147.9, 141.7, 132.7, 131.7, 131.5, 130.8, 130.6, 130.3, 130.0, 129.6, 129.0, 128.0, 127.9, 121.7, 121.3, 72.5, 46.2, 36.0, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ $[M+H]^+$ 494.1074, found 494.1078. **HPLC Analysis:** ee = 08%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 97/03, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 52.6 min, t_{minor} = 17.8 min.

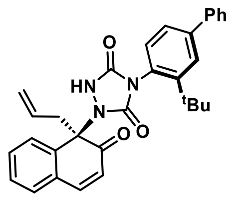
(*R*, *R*$_a$)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(4-bromo-2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (3w)



3w

White sticky solid, yield: 77%, 37 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.69 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.40 (dd, J = 6.6, 1.5 Hz, 2H), 7.16 (d, J = 8.3 Hz, 1H), 6.96 (s, 1H), 6.23 (d, J = 9.9 Hz, 1H), 5.63 – 5.51 (m, 1H), 5.03 (d, J = 11.0 Hz, 1H), 4.92 (d, J = 17.1 Hz, 1H), 3.27 – 3.21 (m, 1H), 3.09 – 3.03 (m, 1H), 1.38 (s, 9H).**^{13}C NMR (125 MHz, Chloroform-d)** δ 198.5, 155.5, 155.0, 151.9, 145.7, 140.1, 133.3, 131.9, 130.7, 130.6, 130.4, 130.2, 129.7, 128.9, 128.5, 127.0, 125.0, 124.6, 121.2, 72.2, 44.3, 35.9, 31.3. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ $[M+H]^+$ 494.1074, found 494.1072. **HPLC Analysis:** ee = 91%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 95/05, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 20.3 min, t$_{minor}$ = 6.7 min.

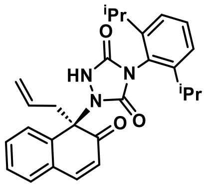
(*R*, *R*$_a$)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(3-(*tert*-butyl)-[1,1'-biphenyl]-4-yl)-1,2,4-triazolidine-3,5-dione (3x)



3x

Pale yellow sticky solid, yield: 75%, 33 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.83 (dd, J = 7.9, 1.8 Hz, 1H), 7.78 – 7.56 (m, 3H), 7.53 – 7.39 (m, 6H), 7.19 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 6.24 (d, J = 10.0 Hz, 1H).**^{13}C NMR (100 MHz, Chloroform-d)** δ 199.0, 173.1, 162.2, 156.7, 154.9, 151.7, 145.8, 139.3, 136.6, 133.4, 132.2, 131.0, 130.6, 130.5, 130.1, 129.3, 128.3, 127.1, 124.8, 124.7, 121.2, 119.5, 117.7, 75.9, 43.7, 36.2, 31.6. **HRMS (ESI):** m/z calcd. for $C_{31}H_{29}N_3O_3$ $[M+H]^+$ 492.2282, found 492.2287. **HPLC Analysis:** ee = 86%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 36.2 min, t$_{minor}$ = 18.9 min.

(*R*)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2,6-diisopropylphenyl)-1,2,4-triazolidine-3,5-dione (3y)

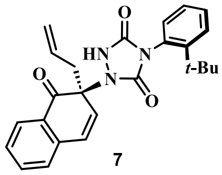


3y

White sticky solid, yield: 85%, 38 mg, **^{1}H NMR (400 MHz, DMSO-d6)** δ 11.02 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 9.9 Hz, 1H), 7.60 (td, J = 7.5, 1.6 Hz, 1H), 7.54 (dd, J = 7.6, 1.5 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.30 (dd, J = 7.7, 1.4 Hz, 1H), 7.24 (dd, J = 7.7, 1.5 Hz, 1H), 6.25 (d, J = 10.0 Hz, 1H), 5.29 (ddt, J = 17.1, 10.0, 7.2 Hz, 1H), 4.98 – 4.85 (m, 2H), 3.03 (d, J = 7.2 Hz, 2H), 2.81 (hept, J

= 6.8 Hz, 1H), 2.44 (p, J = 6.8 Hz, 1H), 1.19 (d, J = 6.9 Hz, 3H), 1.11 (t, J = 6.8 Hz, 6H), 0.81 (d, J = 6.8 Hz, 3H).**^{13}C NMR (100 MHz,DMSO-d6)** δ 199.0, 173.1, 162.2, 156.7, 154.9, 151.7, 145.8, 139.3, 136.6, 133.4, 132.2, 131.0, 130.6, 130.5, 130.1, 129.3, 128.3, 127.1, 124.8, 124.7, 121.2, 119.5, 117.7, 75.9, 43.7, 36.2, 31.6. **HRMS (ESI):** m/z calcd. for $C_{27}H_{29}N_3O_3$ $[M+H]^+$ 444.2282, found 444.2286. **HPLC Analysis:** ee = 56%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 5.1 min, t_{minor} = 4.1 min.

(*S*, *R*$_a$)-1-(2-allyl-1-oxo-1,2-dihydronaphthalen-2-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (7)

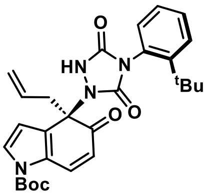


7

White solid, yield: 82%, 34 mg, melting point: 120-122 °C,

^{1}H NMR (500 MHz, Chloroform-d) δ 8.03 (dd, J = 7.8, 1.4 Hz, 1H), 7.66 – 7.52 (m, 2H), 7.38 (tt, J = 7.8, 1.5 Hz, 2H), 7.29 – 7.23 (m, 2H), 7.06 (dd, J = 7.8, 1.5 Hz, 1H), 6.74 (d, J = 9.9 Hz, 1H), 6.39 (d, J = 9.9 Hz, 1H), 5.78 (ddt, J = 17.3, 10.2, 7.2 Hz, 1H), 5.26 – 5.09 (m, 2H), 3.03 – 2.87 (m, 2H), 1.38 (s, 9H).**^{13}C NMR (125 MHz, Chloroform-d)** δ 197.3, 155.6, 155.6, 149.3, 137.1, 135.4, 131.6, 131.5, 130.4, 130.3, 129.4, 129.0, 128.9, 128.8, 128.0, 127.9, 127.6, 121.1, 70.1, 41.5, 35.9, 31.8. **HRMS (ESI):** m/z calcd. for $C_{25}H_{25}N_3O_3$ $[M+H]^+$ 416.1969, found 416.1985. **HPLC Analysis:** ee = 96%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 13.1 min, t_{minor} = 7.3 min.

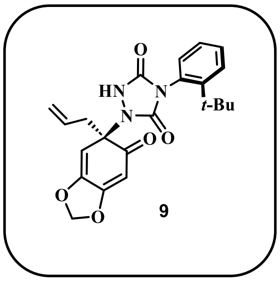
tert-butyl (*R*, *R*$_a$)-4-allyl-4-(4-(2-(*tert*-butyl)phenyl)-3,5-dioxo-1,2,4-triazolidin-1-yl)-5-oxo-4,5-dihydro-1H-indole-1-carboxylate (8)



8

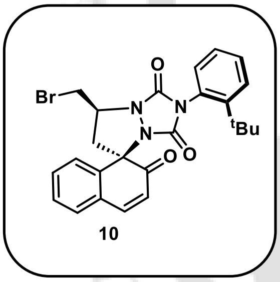
Yellow sticky solid, yield: 82%, 41 mg, **^{1}H NMR (500 MHz, Chloroform-d)** 1H NMR (500 MHz, Chloroform-d) δ 8.09 (d, J = 10.3 Hz, 1H), 7.54 (dd, J = 8.2, 1.5 Hz, 1H), 7.44 (d, J = 3.3 Hz, 1H), 7.37 (td, J = 7.8, 1.6 Hz, 1H), 7.27 (d, J = 1.4 Hz, 1H), 6.98 (dd, J = 7.8, 1.6 Hz, 1H), 6.48 (d, J = 3.3 Hz, 1H), 5.98 (d, J = 10.3 Hz, 1H), 5.75 – 5.60 (m, 1H), 5.15 – 5.06 (m, 2H), 3.10 (dd, J = 13.3, 6.5 Hz, 1H), 3.00 (dd, J = 13.3, 7.9 Hz, 1H), 1.64 (s, 9H), 1.35 (s, 9H). **^{13}C NMR (125 MHz, Chloroform-d)** δ 198.6, 156.3, 155.4, 149.3, 148.5, 135.4, 131.6, 131.4, 130.3, 130.0, 128.9, 128.8, 127.7, 127.3, 125.6, 121.4, 121.0, 109.9, 85.9, 70.6, 42.8, 35.9, 31.8, 28.2. **HRMS (ESI):** m/z calcd. for $C_{28}H_{32}N_4O_5$ $[M+H]^+$ 505.2445, found 505.2447. **HPLC Analysis:** ee = 82%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 6.1 min, t_{minor} = 4.4 min.

(*R*, *R*$_a$)-1-(5-allyl-6-oxo-5,6-dihydrobenzo[d][1,3]dioxol-5-yl)-4-(2-(*tert*-butyl)phenyl)-1,2,4-triazolidine-3,5-dione (9)



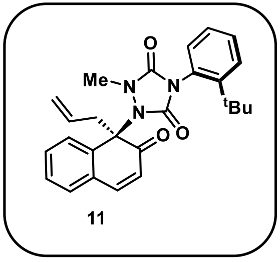
White sticky solid, yield: 75%, 30 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.59 – 7.55 (m, 1H), 7.40 (ddd, J = 8.1, 5.6, 1.6 Hz, 1H), 7.30 (td, J = 7.5, 1.6 Hz, 1H), 7.09 (dd, J = 7.7, 1.7 Hz, 1H), 5.86 – 5.62 (m, 5H), 5.49 (s, 1H), 5.22 – 5.13 (m, 2H), 3.11 (dd, J = 13.4, 6.9 Hz, 1H), 2.92 (dd, J = 13.7, 7.5 Hz, 1H), 1.35 (s, 9H).**^{13}C NMR (100 MHz, Chloroform-d)** δ 196.1, 164.0, 154.8, 149.4, 146.9, 131.8, 130.3, 130.2, 128.9, 127.7, 127.6, 121.0, 102.4, 102.0, 98.8, 77.4, 70.1, 35.9, 31.8, 31.7. **HRMS (ESI):** m/z calcd. for $C_{22}H_{23}N_3O_5$ [M+H]$^+$ 410.1710, found 410.1714. **HPLC Analysis:** ee = 72%, Chiralpak ADH Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t$_{major}$ = 20.7 min, t$_{minor}$ = 11.1 min.

(1*R*, 7'*S*, *R*$_a$)-7'-(bromomethyl)-2'-(2-(*tert*-butyl)phenyl)-6',7'-dihydro-1'H,2H-spiro[naphthalene-1,5'-pyrazolo[1,2-a][1,2,4]triazole]-1',2,3'(2'H)-trione (10)



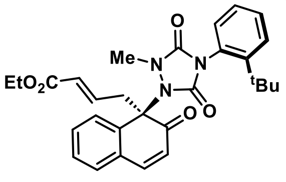
Pale yellow sticky solid, yield: 75%, 37 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.84 (d, J = 7.7 Hz, 1H), 7.61 – 7.50 (m, 3H), 7.43 – 7.34 (m, 3H), 7.27 (dd, J = 3.4, 1.6 Hz, 1H), 7.09 (dd, J = 7.7, 1.6 Hz, 1H), 6.24 (d, J = 9.9 Hz, 1H), 4.51 – 4.40 (m, 1H), 3.91 (dd, J = 10.6, 3.1 Hz, 1H), 3.75 (dd, J = 10.6, 7.8 Hz, 1H), 3.18 – 3.10 (m, 1H), 2.65 (dd, J = 13.6, 10.6 Hz, 1H), 1.47 (s, 9H).**^{13}C NMR (100 MHz, Chloroform-d)** δ 198.0, 153.9, 152.7, 150.5, 147.2, 139.3, 131.8, 131.5, 130.3, 130.2, 129.9, 129.7, 129.4, 128.9, 127.4, 126.9, 122.7, 70.0, 54.5, 49.6, 35.9, 31.7, 29.9. **HRMS (ESI):** m/z calcd. for $C_{25}H_{24}N_3O_3Br$ [M+H]$^+$ 494.1074, found 494.1081. **HPLC Analysis:** ee = 88%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 200 nm, t$_{major}$ = 14.4 min, t$_{minor}$ = 13.0 min.

(*R*, *R*$_a$)-1-(1-allyl-2-oxo-1,2-dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-2-methyl-1,2,4-triazolidine-3,5-dione (11)



White solid, yield: 90%, 39 mg, melting point: 127-129 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.80 (d, J = 7.8 Hz, 1H), 7.54 (qd, J = 7.7, 1.6 Hz, 2H), 7.46 – 7.35 (m, 4H), 7.29 (td, J = 7.4, 1.6 Hz, 1H), 7.21 (dd, J = 7.6, 1.7 Hz, 1H), 6.26 (d, J = 9.9 Hz, 1H), 5.31 (dddd, J = 16.6, 10.2, 8.1, 6.1 Hz, 1H), 4.92 – 4.80 (m, 2H), 3.37 (dd, J = 12.8, 8.2 Hz, 1H), 3.23 (dd, J = 12.9, 6.4 Hz, 1H), 2.79 (s, 3H), 1.37 (s, 9H).^{13}**C NMR (100 MHz, Chloroform-d)** δ 197.9, 157.5, 157.0, 149.0, 145.7, 141.2, 131.7, 130.6, 130.4, 130.2, 130.0, 129.5, 129.5, 129.0, 128.8, 128.3, 127.8, 125.7, 121.0, 74.3, 46.0, 38.0, 36.0, 31.9. **HRMS (ESI):** m/z calcd. for $C_{26}H_{27}N_3O_3$ $[M+H]^+$ 430.2125, found 430.2128. **HPLC Analysis:** ee = 89%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm, t_{major} = 11.5 min, t_{minor} = 13.9 min.

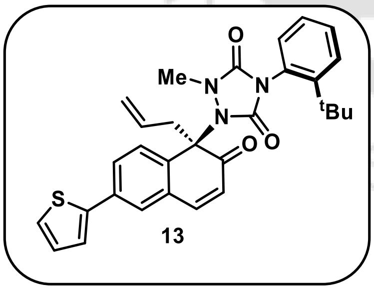
ethyl (*R*, *E*, *R*$_a$)-4-(1-(4-(2-(*tert*-butyl)phenyl)-2-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-2-oxo-1,2-dihydronaphthalen-1-yl)but-2-enoate (12)



12

Yellow sticky solid, yield: 60%, 29 mg, ^{1}**H NMR (500 MHz, Chloroform-d)** δ 7.76 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 8.1 Hz, 2H), 7.45 (dd, J = 14.6, 8.5 Hz, 2H), 7.39 (d, J = 6.4 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.45 (dq, J = 15.3, 7.6 Hz, 1H), 6.26 (d, J = 9.9 Hz, 1H), 5.61 (d, J = 15.5 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.40 (dd, J = 13.0, 8.5 Hz, 1H), 3.31 (dd, J = 13.1, 6.7 Hz, 1H), 2.96 (s, 3H), 1.36 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H).^{13}**C NMR (125 MHz, Chloroform-d)** δ 197.1, 165.6, 156.7, 156.2, 149.7, 145.8, 141.3, 139.3, 131.6, 131.0, 130.3, 130.3, 130.2, 129.9, 129.4, 128.6, 127.8, 127.6, 126.6, 125.4, 72.4, 60.5, 44.2, 37.8, 35.7, 31.5, 14.3. **HRMS (ESI):** m/z calcd. for $C_{29}H_{31}N_3O_5$ $[M+Na]^+$ 524.2156, found 524.2163. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, *n*-Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 8.5 min, t_{minor} = 10.0 min.

(*R*, *R*$_a$)-1-(1-allyl-2-oxo-6-(thiophen-2-yl)-1,2 dihydronaphthalen-1-yl)-4-(2-(*tert*-butyl)phenyl)-2-methyl-1,2,4-triazolidine-3,5-dione (13)

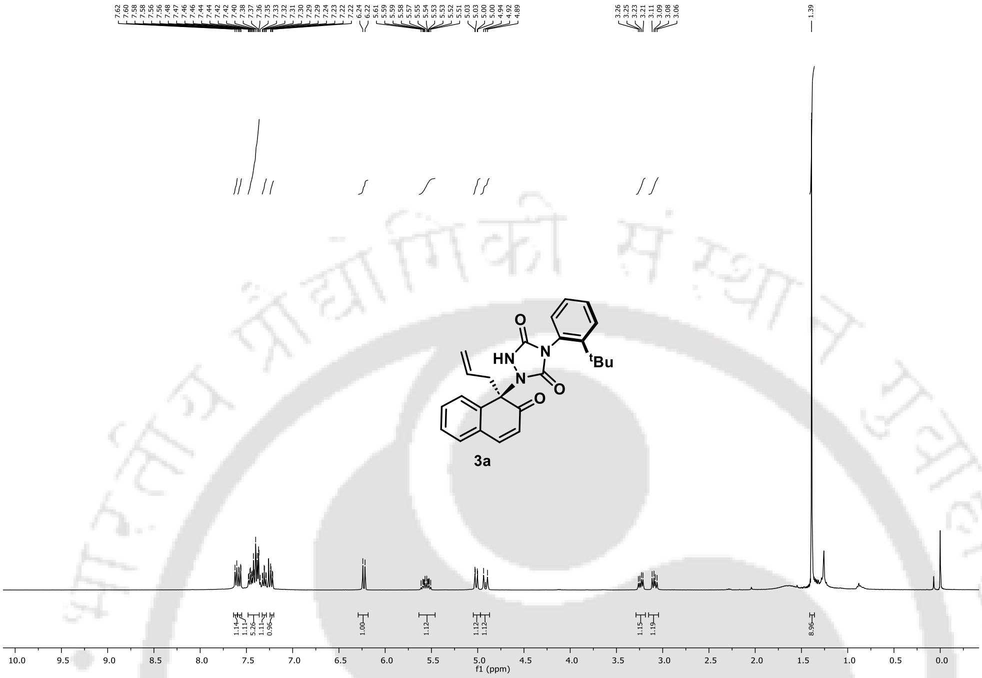


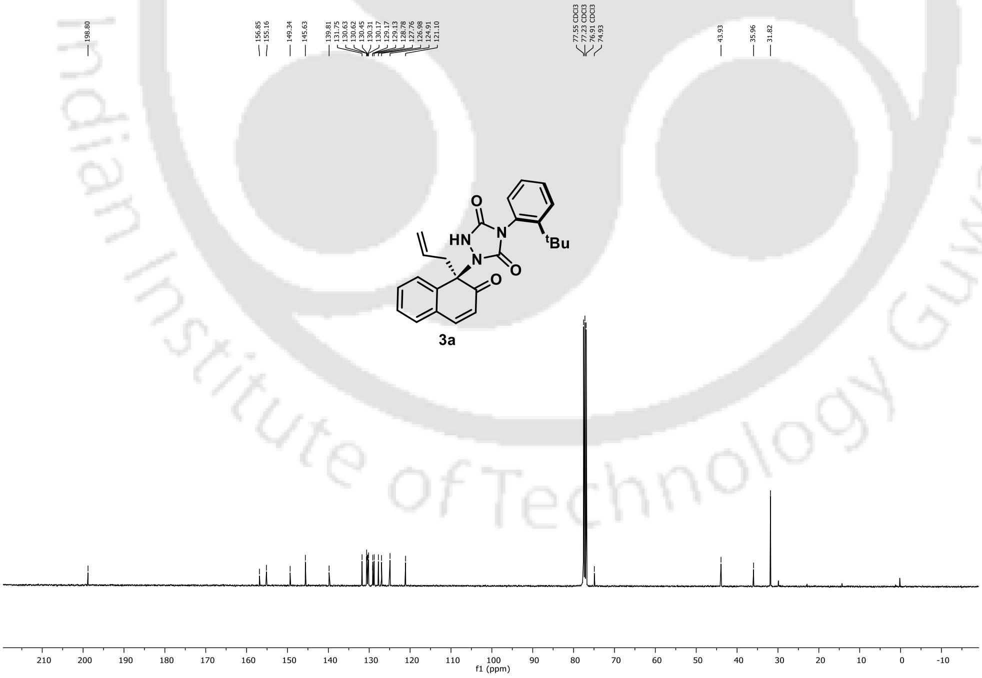
13

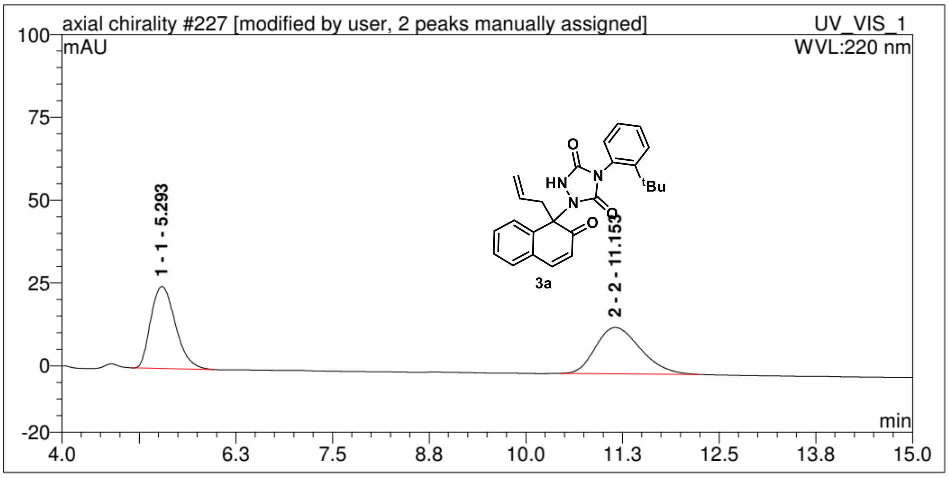
White solid, yield: 90%, 46 mg, melting point: 140-142 °C, ^{1}**H NMR (500 MHz, Chloroform-d)** δ 7.78 – 7.70 (m, 2H), 7.56 (d, J = 1.9 Hz, 1H), 7.52 (dd, J = 8.1, 1.5 Hz, 1H), 7.44 (d, J = 10.0 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 7.13 (dd, J = 5.1, 3.6 Hz, 1H), 7.05 (dd, J = 7.8, 1.5 Hz, 1H), 6.29 (d, J = 9.9 Hz, 1H), 5.36 (ddt, J = 17.1, 9.9, 7.1 Hz, 1H), 4.97 – 4.87 (m, 2H), 3.30 (dd, J = 12.5, 7.9 Hz, 1H), 3.15 (s, 4H), 1.31 (s, 9H).^{13}**C NMR (100 MHz, Chloroform-d)** δ 197.8, 157.2, 156.4, 149.4, 145.1, 142.6, 140.5, 135.1, 131.6, 131.1, 130.2, 129.8, 129.1, 128.5, 128.5, 128.1, 127.9, 127.7, 126.9, 126.5, 126.0, 124.2, 121.2, 72.7, 46.2, 38.7, 35.6, 31.9, 31.5.**HRMS (ESI):** m/z calcd. for $C_{30}H_{29}N_3O_3S$ $[M+Na]^+$ 534.1822, found 534.1826. **HPLC Analysis:** ee = 86%, Chiralpak IA Column, *n*Hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 200 nm, t_{major} = 28.0 min, t_{minor} = 31.1 min.

5.8 NMR and HPLC spectra:

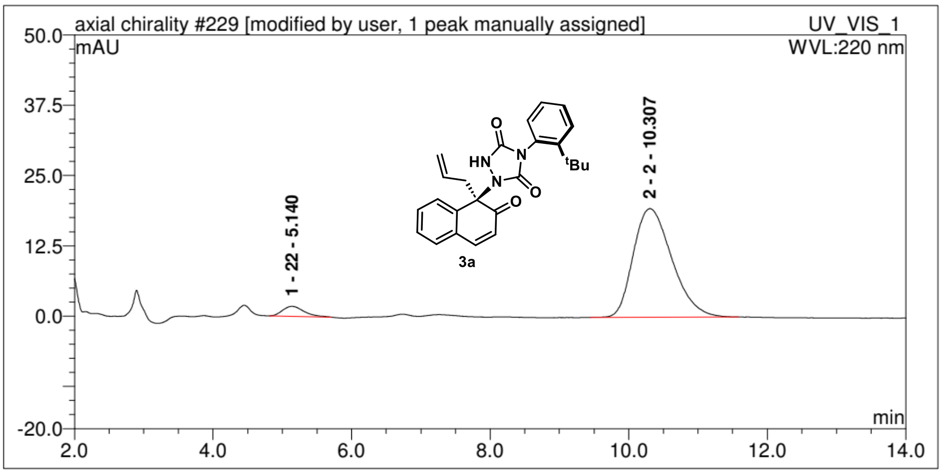
^{1}H and ^{13}C{H} spectra of compound 3a:





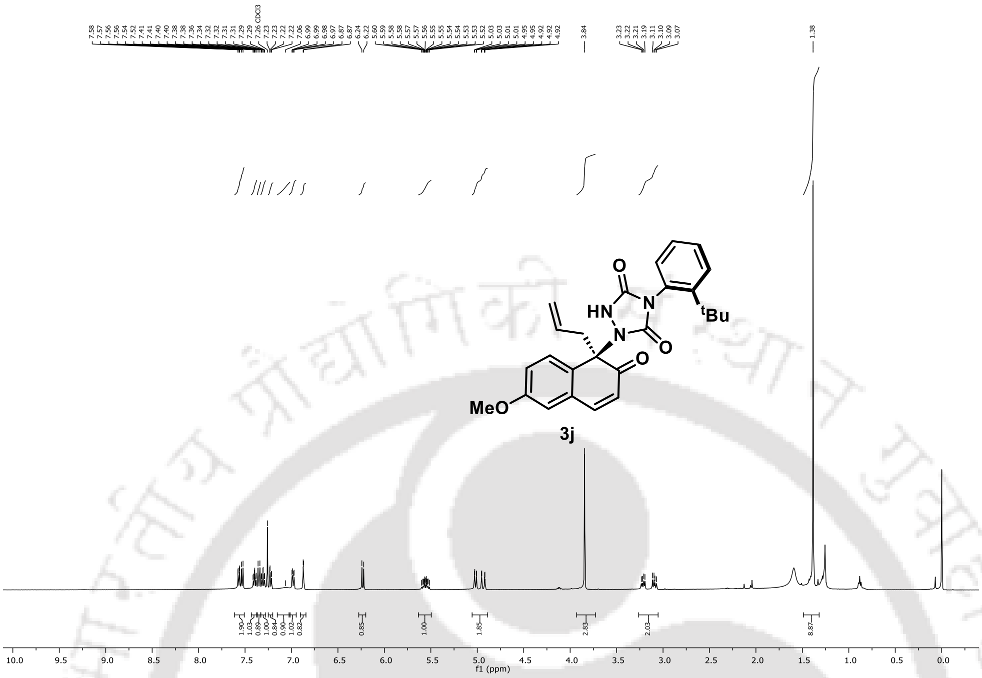


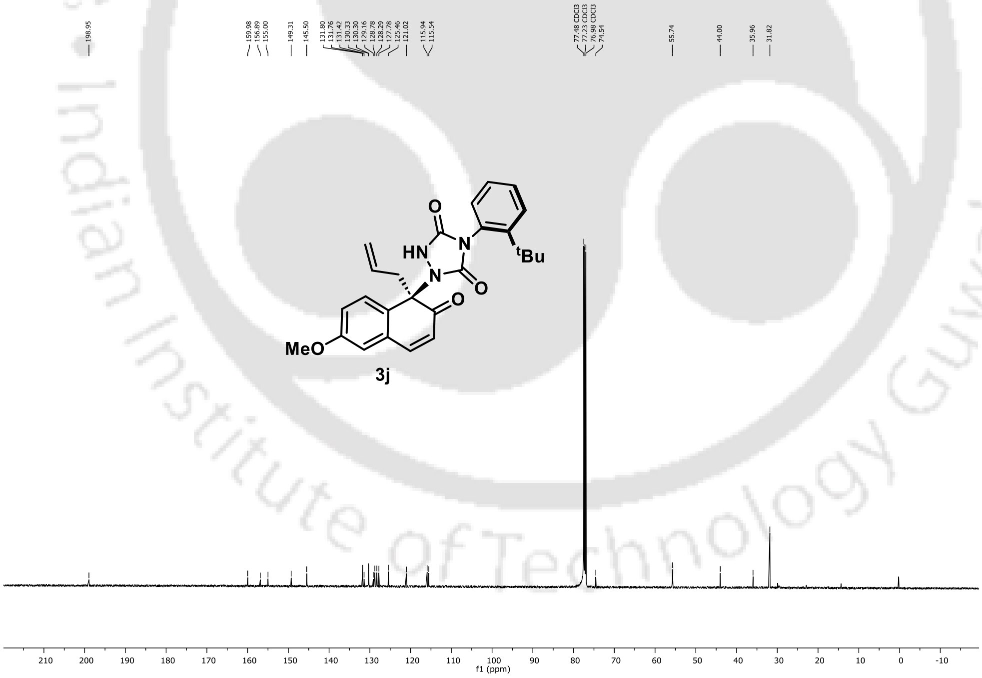
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.29	9.184013	49.41778191	24.74234	n.a.
2	2	11.15	9.400	50.58221809	13.981	n.a.

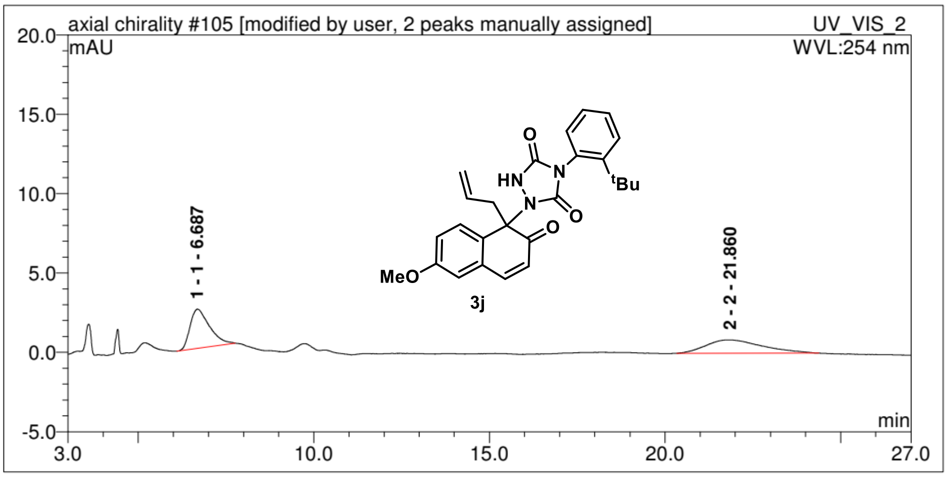


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	22	5.14	0.633644	4.832740915	1.76197	n.a.
2	2	10.31	12.478	95.16725909	19.301	n.a.

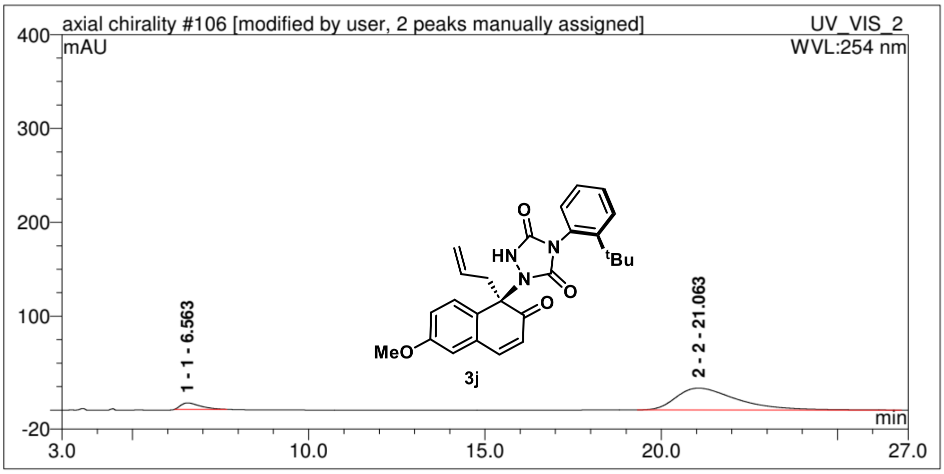
^{1}H and ^{13}C{H} spectra of compound 3j:





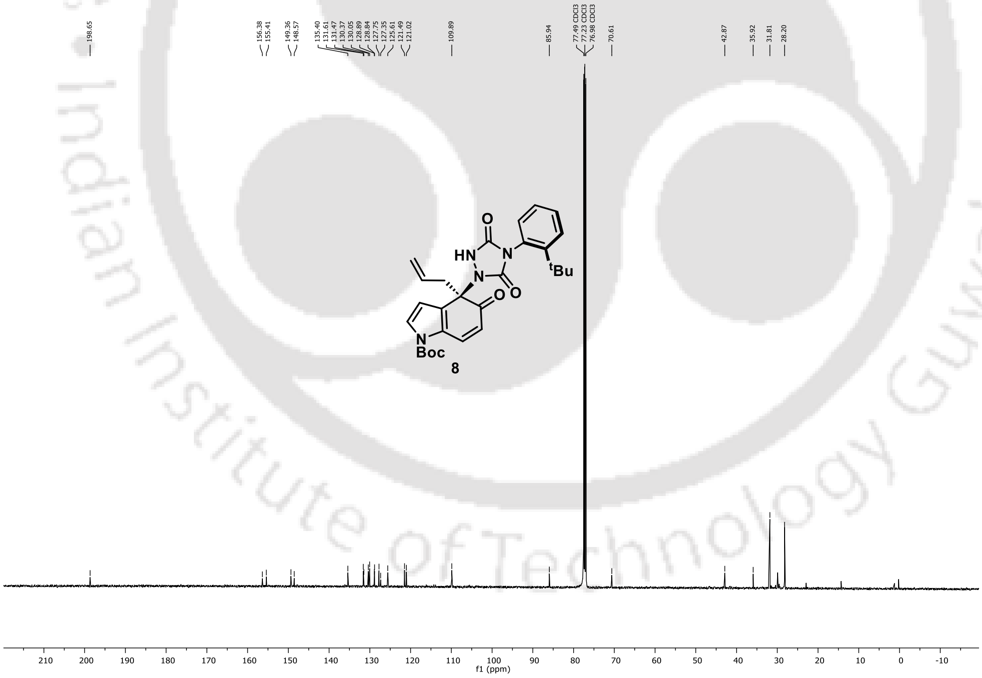


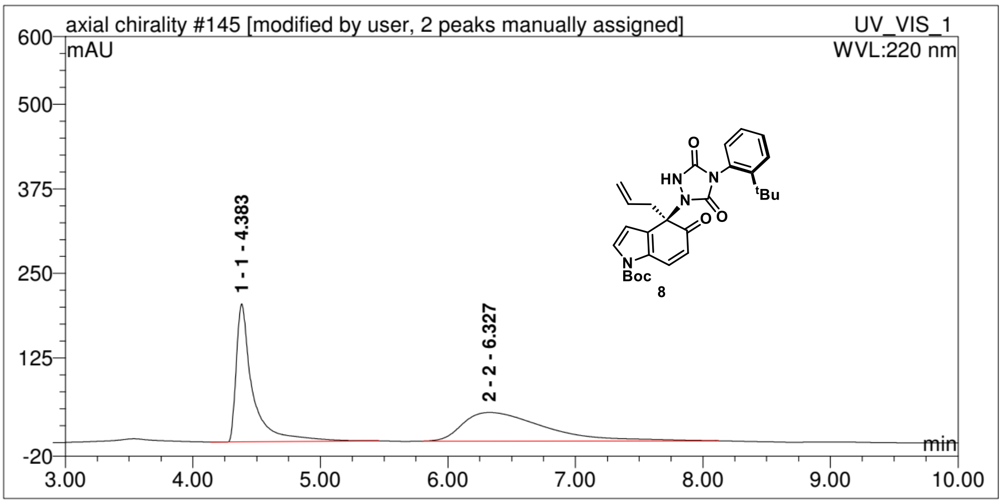
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	6.69	1.585143	50.26476994	2.47333	n.a.
2	2	21.86	1.568	49.73523006	0.841	n.a.



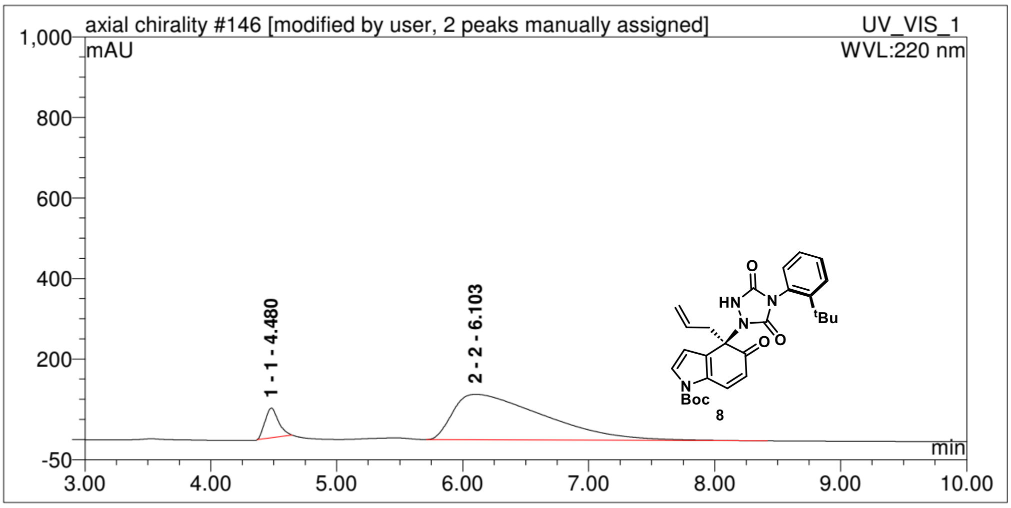
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	6.56	4.326581	8.494504821	6.77839	n.a.
2	2	21.06	46.607	91.50549518	23.276	n.a.

^{1}H and ^{13}C{H} spectra of compound 8:



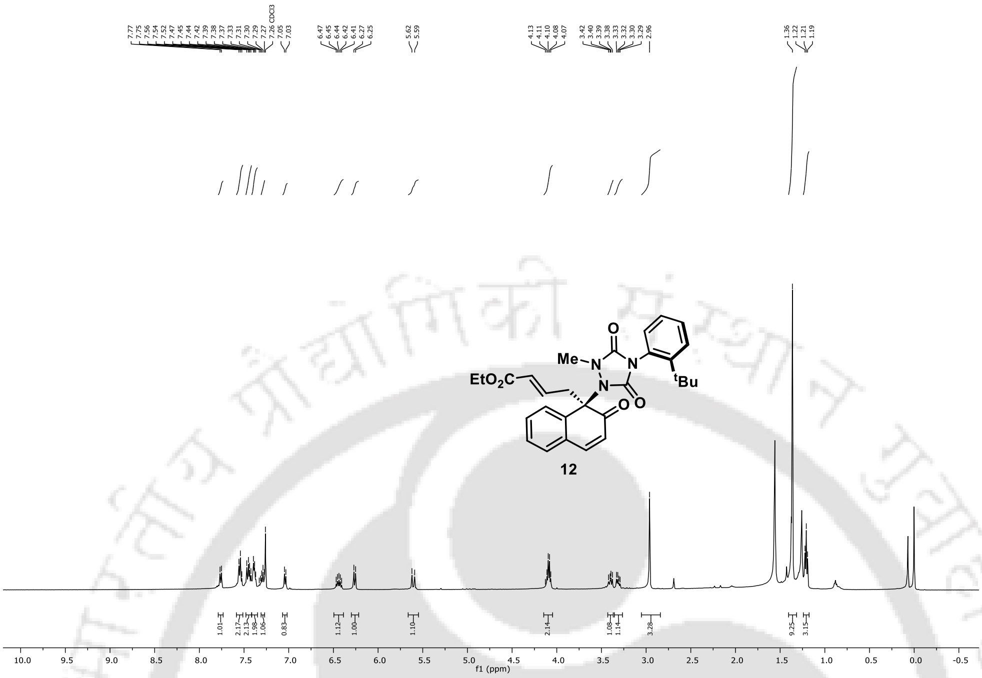


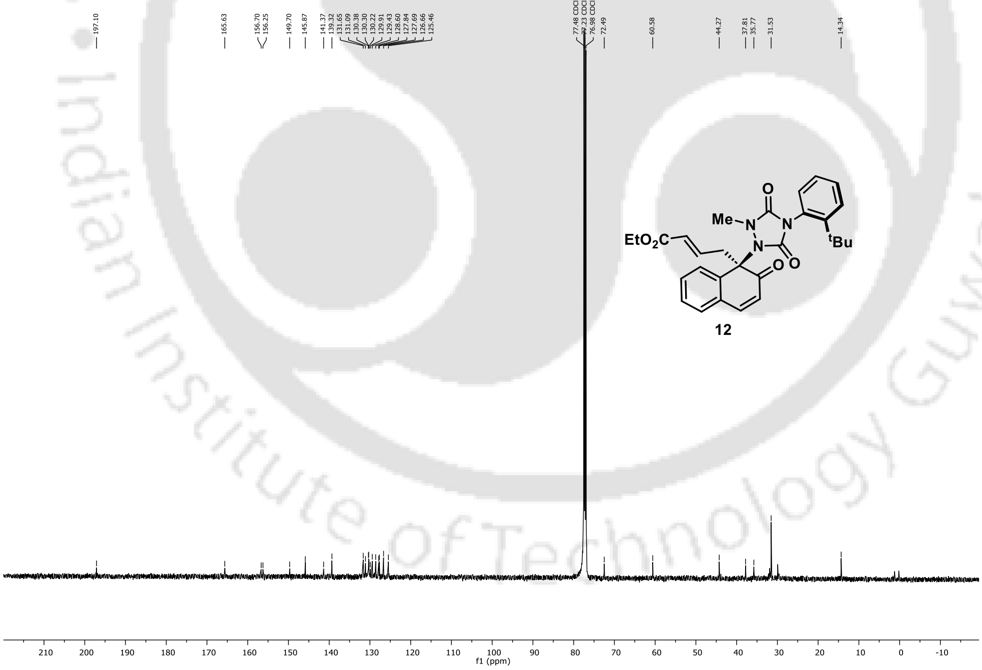
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	4.38	30.35407	49.29519221	204.009	n.a.
2	2	6.33	31.222	50.70480779	42.247	n.a.

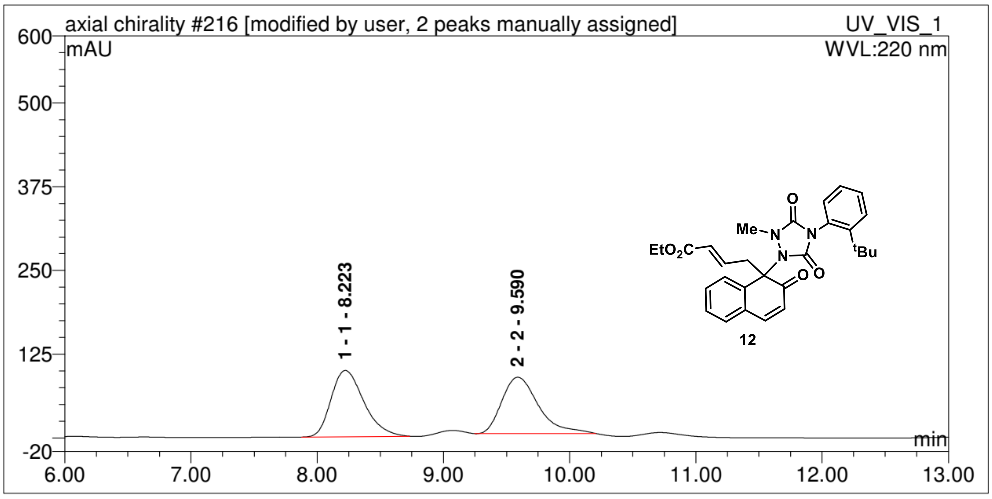


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	4.48	9.164072	8.825146797	73.93691	n.a.
2	2	6.10	94.676	91.1748532	112.967	n.a.

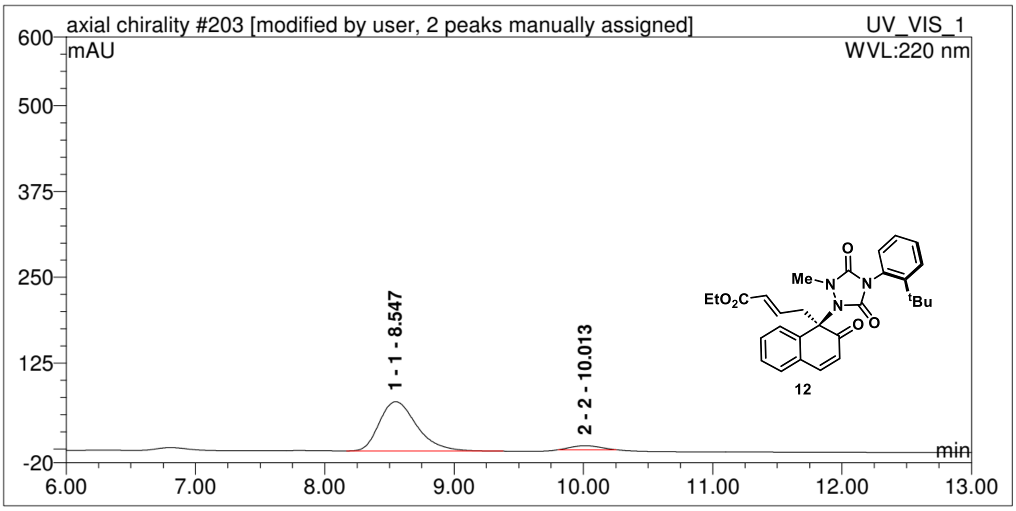
^{1}H and ^{13}C{H} spectra of compound 12:







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.22	29.79152	51.20876629	98.90759	n.a.
2	2	9.59	28.385	48.79123371	84.148	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.55	24.21126	94.09405423	71.8654	n.a.
2	2	10.01	1.520	5.90594577	5.817	n.a.

5.9 References

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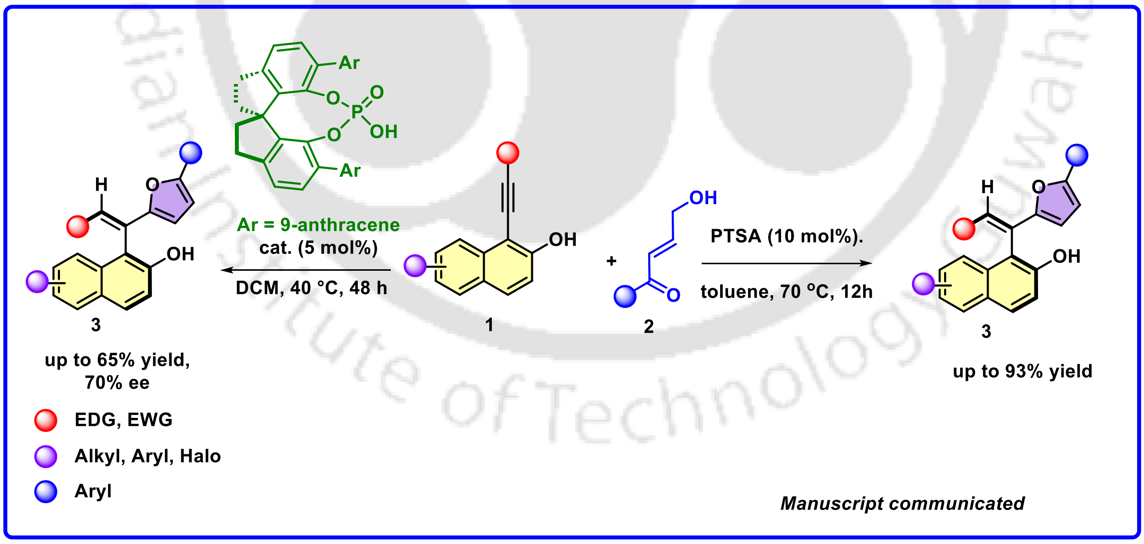
Chapter 6

Organocatalytic Synthesis of Furan Embedded Styrene Atropisomers

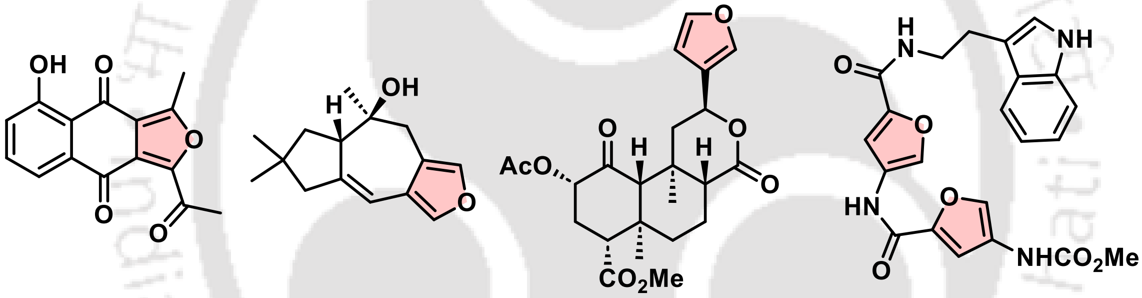
ABSTRACT: Herein we report the synthesis of furan embedded styrene atropisomer *via* the reaction between 1-(aryl-ethynyl)-naphthalen-2-ol and *γ*-hydroxyenone. With a catalytic quantity of PTSA, the styrene derivatives were produced with moderate to good yields, and in high diastereoselectivities. Moderate enantioselectivities up to (70% ee) were achieved with chiral phosphoric acid. Few applications such as triazole formation and cross-coupling reactions have been demonstrated. C-C rotational energy barrier 30.1 kcalmol^{-1} and $t^{1/2}{}_{25\ °C}$=21.2 years.



Manuscript communicated

6.1 Introduction

The furan ring is present in a variety of natural products. The biological activity of many of these compounds is strong; some are sex pheromones, some are defence substances, and many have been used in clinical trials to treat a wide range of diseases. For example, Bhimamycin B (**I**) shows antibacterial property, Furoscrobiculins (**II**) are a series of lactarane sesquiterpenes that were isolated from basidiomycetes of mushrooms. These molecules show mushrooms' chemical defence against various predators such as bacteria, fungi, animals and insects, and also show antifeedant properties against the storage pests. Similarly, Salvinorin A (**III**) possesses potent hallucinogenic activity and the Proximicins C (**IV**) are novel naturally occurring peptides with a 2,4-disubstituted furan amino acid as a core structure. They show a moderate cytotoxic activity (Figure 1)[1].



Bhimmamycin B
Antinacterial
I

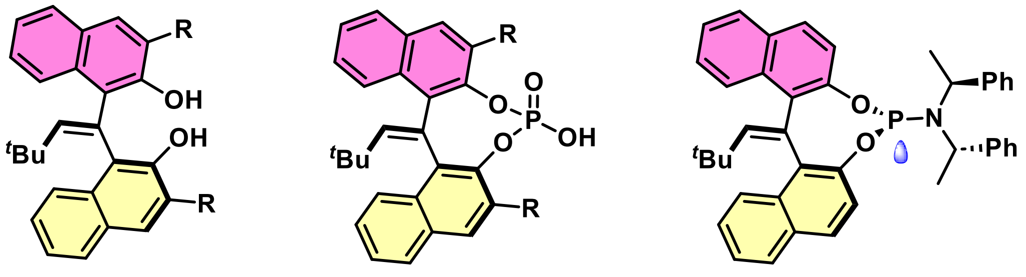
Furoscrobiculin B
Mushroom's chemical defense
II

Salvinorin A
Psychoactive
III

Proximicin C
Cytotoxic
IV

Figure 1: Bio-active compound containing furan motif.

Axially chiral styrenes have been used for chiral catalysts and ligands. Synthetic chemists have also been very interested in them because of their potential to be employed as substrates for chemical processes that induce selectivity. Consequently, protocols toward the enantioselective preparation of axially chiral styrenes are highly desirable. For examples, EBINOL **V** is used as a chiral phosphoric acid **VI**, similarly compound **VII** is used as phosphoramidite ligand for metal catalysed asymmetric reactions[2] (Figure 2).



EBINOL
V

EBINOL-CPA
VI

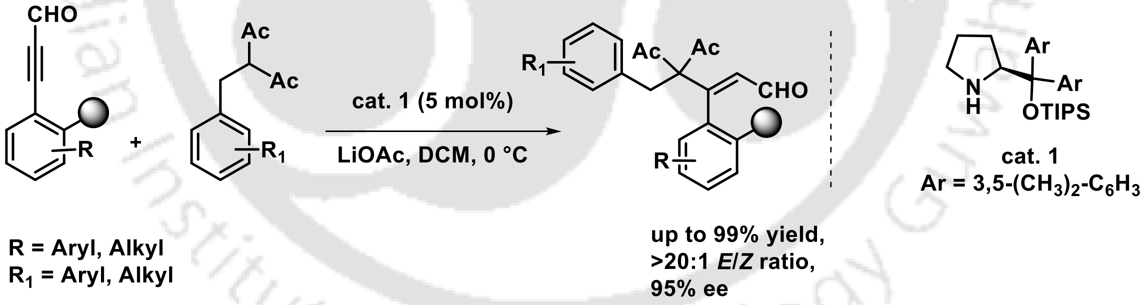
EBINOL-derived phosphoramidite
VII

Figure 2: Importance of compound containing axial chiral styrene motif.

6.2 Literature Study:

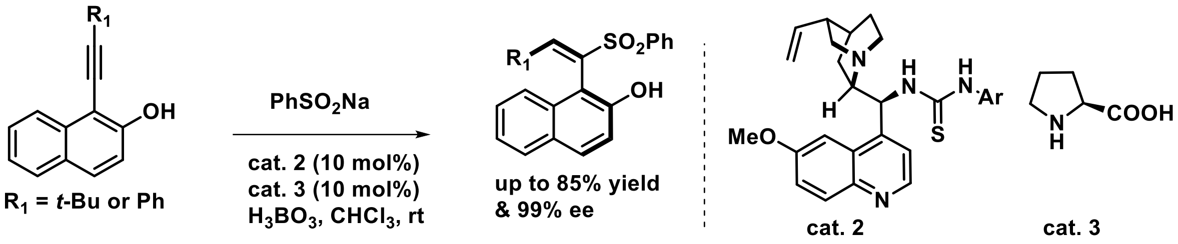
6.2.1 Known strategies for synthesis of axially chiral stryenes:

In 2017 Tan *et al*, discovered an asymmetric organocatalytic approach for a direct Michael addition reaction of substituted diones/ketone esters/malononitrile to alkynals. The axially chiral styrene compounds were produced with good chemical yields, enantioselectivities and almost complete *E*/*Z*-selectivities through a secondary amine-catalysed iminium activation strategy under mild conditions[3](Scheme 1).



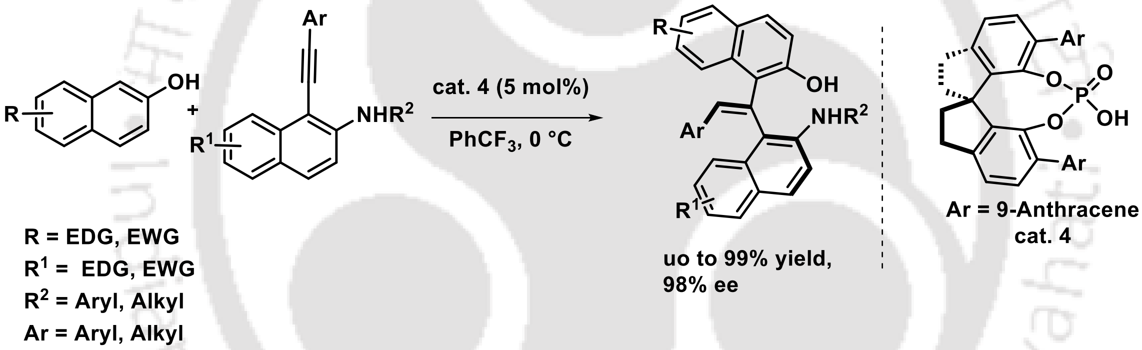
Scheme 1: Organocatalytic atroposelective synthesis of axially chiral styrenes

Later in 2018, Yan group reported an organocatalytic enantioselective approach for the the construction of axially chiral sulfone-containing styrenes. Various axially chiral sulfone-containing styrene compounds were prepared with excellent enantioselectivities (up to >99% ee) and almost complete *E*/*Z* selectivities (>99% *E*/*Z*)[4] (Scheme 2).



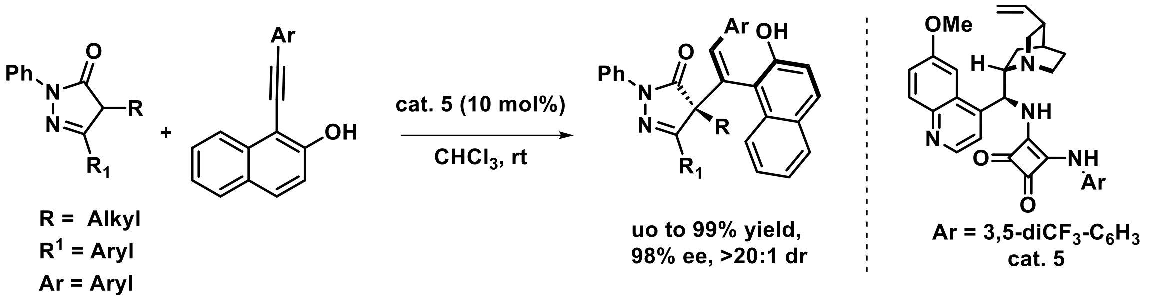
Scheme 2: Organocatalytic enantioselective construction of axially chiral sulfone-containing styrenes.

In 2019, Tan *et al*. reported[11] an axially chiral structural scaffold EBINOL. To construct this skeleton enantioselectively, they developed the effective chiral phosphoric acid-catalysed asymmetric hydroarylation of alkynes *via* a concerted 1,5-H transfer to form the chiral vinylidene *ortho*-quinone methide (VQM) intermediate. This approach gives expedient access to EBINOLs with good to high yields (up to 99%), excellent enantioselectivities (up to 98% ee) and in complete *E*/*Z*-selectivity control[2] (Scheme 3).



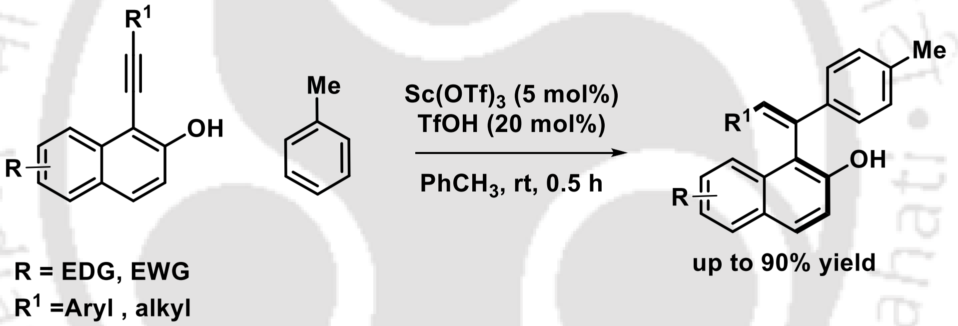
Scheme 3: Axially chiral structural scaffold EBINOL.

In 2021, Wang *et al*. reported[10], an organocatalytic asymmetric process for the sterically precise construction of C-4 alkenyl substituted pyrazolone derivatives bearing multiple stereoelements. A series of interesting products featuring the union of a centrally chiral pyrazolone moiety and an axially chiral styrene unit were obtained in high yields with excellent diastereoselectivities and enantioselectivities (up to 99% ee, >20:1 dr). The process has the characteristics of mild reaction conditions, simple operation and broad substrate scope[5] (Scheme 4).



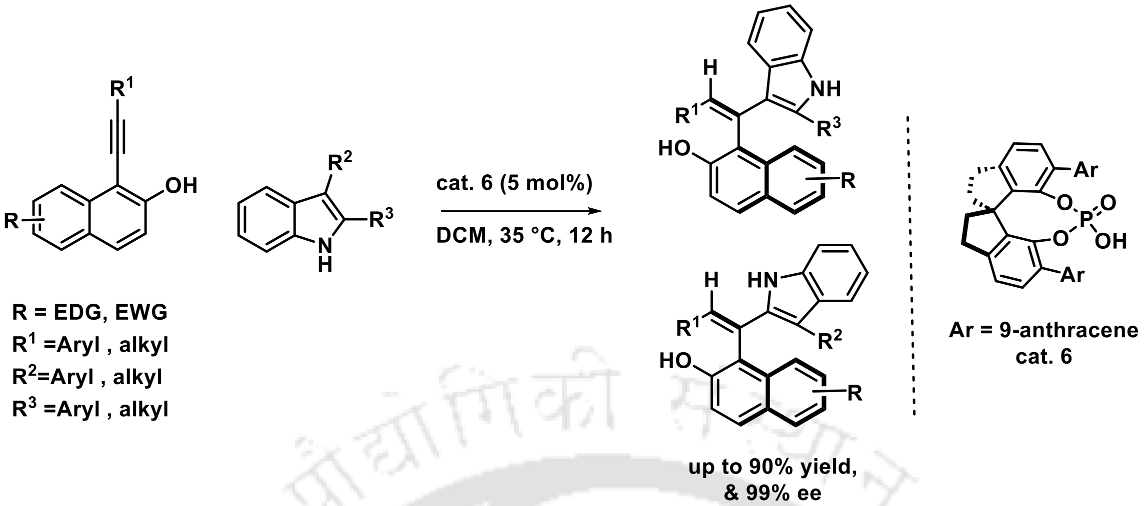
Scheme 4: Asymmetric catalytic construction of pyrazolone and an axially chiral styrene unit.

In 2021, Lv *et al.* reported[12], a binary acid Sc(OTf)$_3$/TfOH-catalyzed alkenylation of arenes with alkynes. In this system, the high-energy vinyl carbocations with activated and weakly coordinating trifluoromethanesulfonate anions by Lewis acid Sc(III) can undergo facile Friedel–Crafts reactions with arenes to give the desired adducts in up to 90% yield and with high *Z*-selectivity[6] (Scheme 5).



Scheme 5: Binary acid catalyzed alkenylation of arenes with alkynes

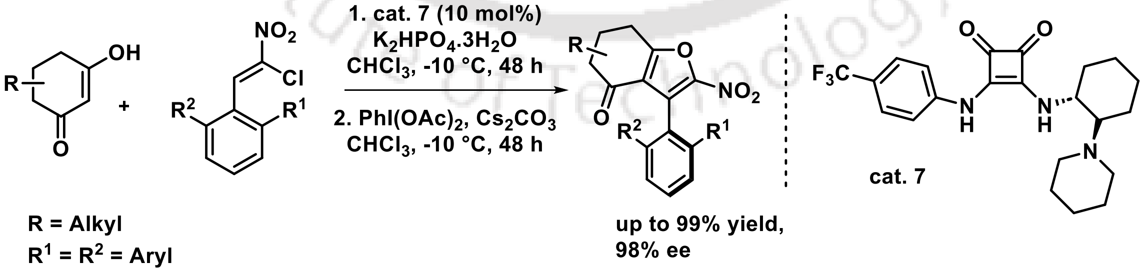
In 2013, You *et al.* reported[20a] a chiral phosphoric acid-catalyzed intermolecular C2 Friedel–Crafts alkylation reaction between *ortho*-alkynylnaphthols and various 3-substituted indoles, affording axially chiral alkenes with up to 93% yields (*E/Z* > 20:1) and up to 98% ee under mild reaction condition. Other substituted indole derivatives could be also tolerated in this system, giving the corresponding axially chiral alkenes with high yields and in excellent enantioselectivities[7] (Scheme 6).



Scheme 6: Axially chiral styrenes linking an indole moiety

6.2.2 Known strategies for synthesis of axially chiral furan:

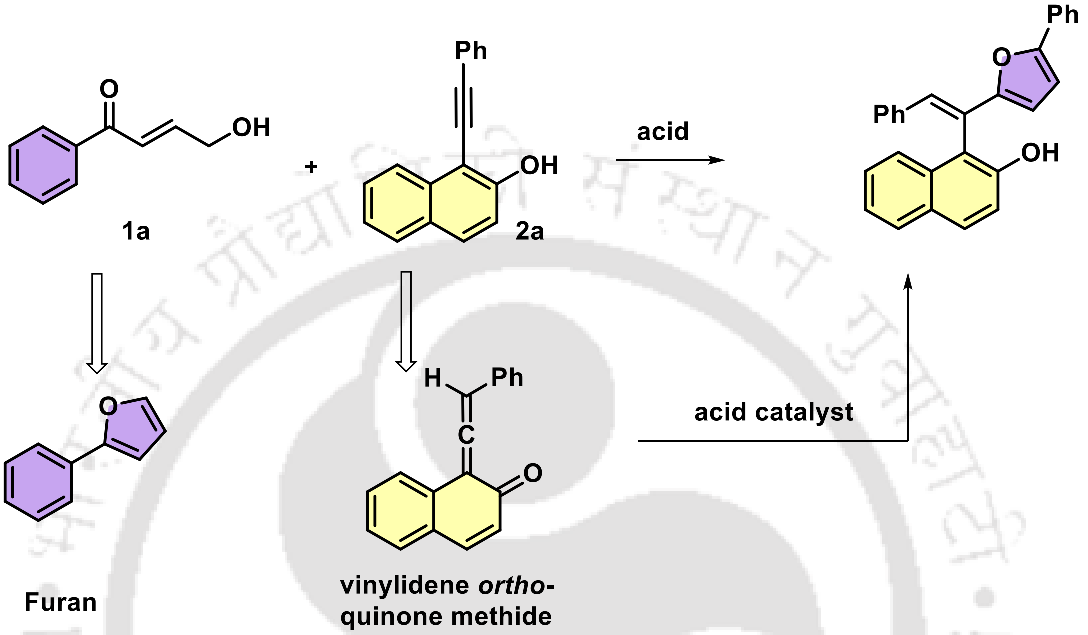
In 2017, Rodriguez *et al*. reported[8] an enantioselective synthesis of herto unknown furan atropisomers using a central-to-axial chirality conversion strategy based on the formation of the furan heterocycle, from acyclic precursors, and with the concomitant creation of the chiral axis. Two structurally different optically active heteroatropisomeric families displaying a five-membered heterocycle could be obtained with great efficiency from readily available substrates. The crucial central chirality in the dihydrofuran precursor is mastered by an enantioselective organocatalyzed *C*–*O*-heterocyclization sequence, and the chiral axis is revealed with good to excellent cp by an oxidative dehydrogenation with either $PhI(OAc)_2$ (Scheme 7).



Scheme 7: construction of furan based axial chirality.

6.3 Concept:

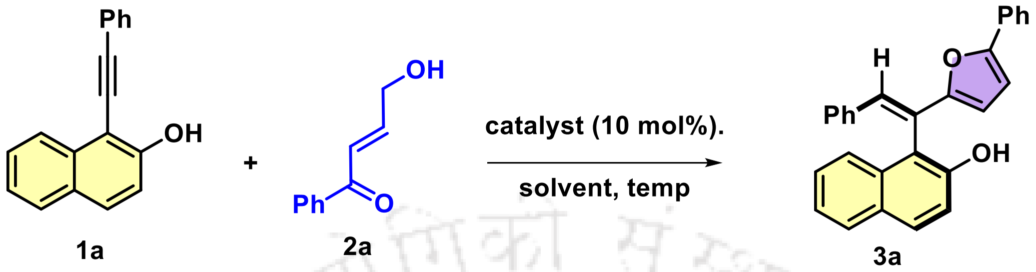
After the study of the importance of axial chiral compounds, we planned to put a reaction between hydroxy enone and 1-alkynyl-2-naphthol. The reaction procceds *via* generating a vinylidene *ortho*-quinone methide intermediate (VQM) (Scheme 8).



Scheme 8: Concept

6.4 Results and discussion

We first reacted1-(phenylethynyl)naphthalen-2-ol (**1a**) and (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**2a**) with diphenyl phosphate (DPP) catalyst in toluene (Table 1). After stirring for 3 days at 40 °C, the desired furyl substituted styrene atropisomer **3aa** was formed in low yield (Table 1, entry 1). The yield got improved to 40% with *p*-toluenesulfonic acid (Table 1, entry 2). Slight less yield was observed with trifluoroacetic acid (TFA). Interestingly, triflic acid (TfOH), AcOH, Tf_2NH and $Sc(OTf)_3$ were not suitable for the reaction (Table 1, entries 4-7). Moderate yield was detected with $BF_3.OEt_2$ (Table 1, entry 8). Then we focused on increasing the temperature of the reaction and this found to be fruitful. Gratifyingly, the yield got enhanced to 90% after stirring the reaction at 70 °C and the reaction time got shortened to 12 hours (Table 1, entry 7). Other solvents such as DCE, dioxane, ACN and EtOAc were also checked but better result was not achieved. Also, additive such as 4 Å MS and magnesium sulfate were used but trace amount of product was formed.

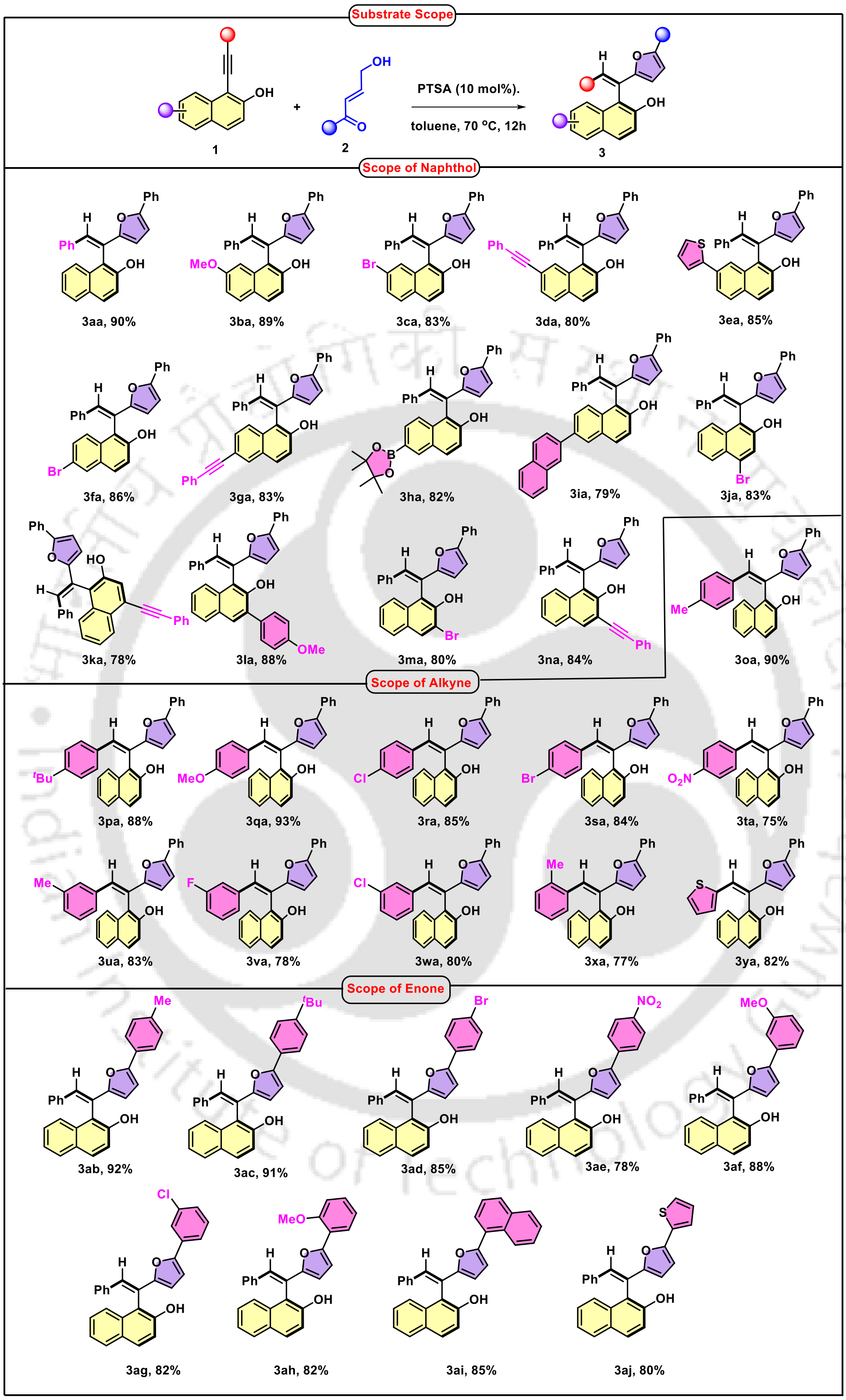


Entry[a]	catalyst	solvent	Temp (˚C)	Time (h)[b]	Yield (%)[d]
1	DPP	$PhCH_3$	40	72	10
2	PTSA	$PhCH_3$	40	72	40
3	TFA	$PhCH_3$	40	72	35
4	TfOH	$PhCH_3$	40	72	>5
5	AcOH	$PhCH_3$	40	72	-
6	Tf_2NH	$PhCH_3$	40	72	-
7	$Sc(OTf)_3$	$PhCH_3$	40	72	0
8	$BF_3.OEt_2$	$PhCH_3$	40	72	30
9	**PTSA**	**$PhCH_3$**	**70**	**12**	**90**
10	PTSA	1,2-DCE	70	12	85
11	PTSA	1,4-dioxane	70	12	50
12	PTSA	ACN	70	12	80
13	PTSA	EtOAc	70	12	75
14	PTSA + 4 Å MS	$PhCH_3$	70	12	20
15	PTSA + $MgSO_4$	$PhCH_3$	70	12	trace

[a]0.1 mmol of **1a** and 0.15 mmol of **2a** were stirred in 1.0 mL toluene. [b]Isolated yield after silica gel column chromatography. DPP = Diphenyl phosphate

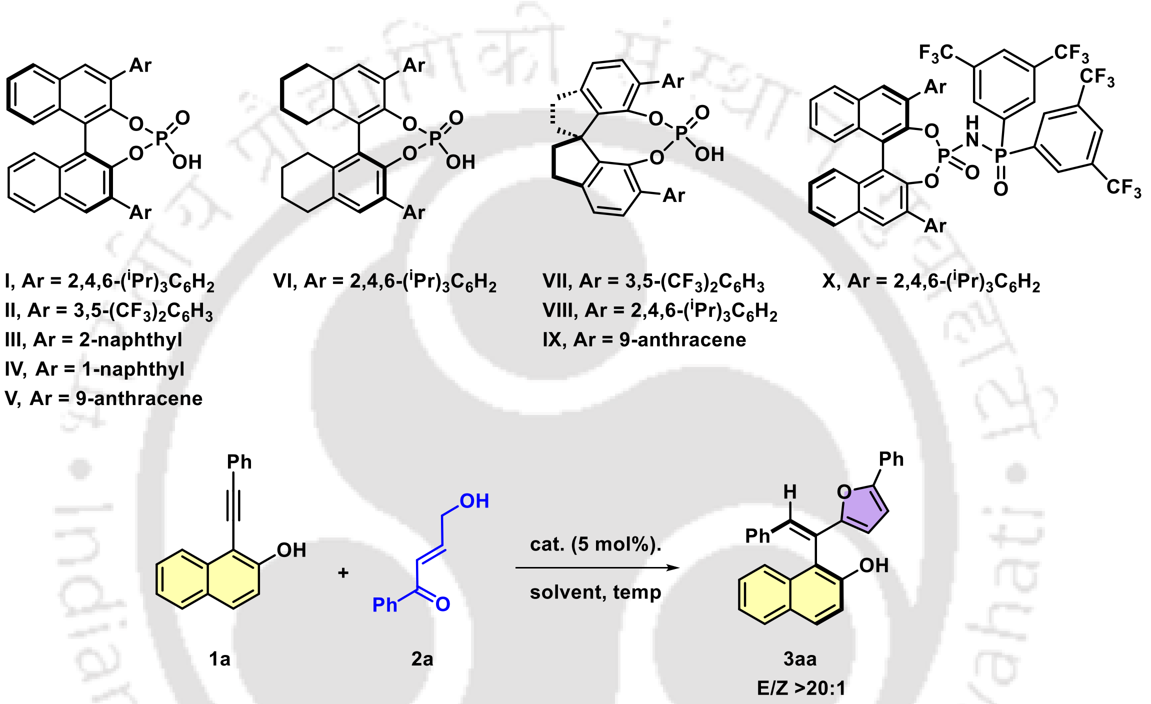
Table 1: Catalyst and solvent optimization

After identifying the optimized conditions, the reaction's range and generality were examined. Initially, naphthols **1** having varied substitutions on the aromatic ring were prepared and reacted with **2** (Scheme 9). To our delight, good results were achieved in all cases. At first, different substituents were incorporated at the 7-position of naphthol **1** and the corresponding products **3ba-3da** were obtained in good yields (up to 89%). Then we prepared 6-substituted naphthols **1f-1i** and were engaged in the reaction. To our delight, different substituents such as alkynyl, pinacol boronate, naphthyl etc were tolerated and good yields were attained for the products **3fa-3ia**. Then, substitutions at the 4-position of naphthol **1** were checked and good yields were observed for the products **3ja** and **3ka**. Smooth conversions were also detected with 3-substituted naphthols **1l-1n** and the corresponding products **3la-3na** were isolated in 80-88% yields (Scheme 9). The scope of naphthol **1** with various substitutions on the alkyne group was examined in the next stage. (Scheme 9). Here also, good results were attained in almost all cases. Initially, naphthols **1o-1t** having alkyne aryl groups with different *para*-substitutions were prepared and reacted with **2a** (Scheme 9). Then meta-substitutions were checked and here also, smooth conversions were detected for naphthols **1u-1w** to deliver products **3ua-3wa** in 75-83% yields. The halo substitutions could be further elaborated to other functionalities via cross-coupling reactions. Finally, a thienyl substituted naphthol **1y** participated in the reaction and the desired product **3ya** was formed in 82% yield. The scope of γ-hydroxy enones **2** was checked in the following stage. Here also, a range of substitutions were tolerated and good results were observed in all cases (Scheme 9). Initially aryl groups with varied substitutions at the *para*-position with EDG (-Me, -^{t}Bu) and EWG (-Br, -NO_2) was checked and gratifyingly good outcome was detected. Then, *meta*-substitutions were checked and to our delight, acceptable yields were observed for the products **3af** and **3ag.** *Ortho*-substitution was also tolerated and a good yield of 82% was observed for product **3ah**.1-Naphthyl substituted enone **2i** also took part in the reaction to deliver product **3ai** in 85% yield (Table 3, entry 8). The finally reaction outcome did not change much with 2-thienyl substituted enone **2j** (Scheme 9).



Scheme 9: Substrate scope pf dearomatized product.

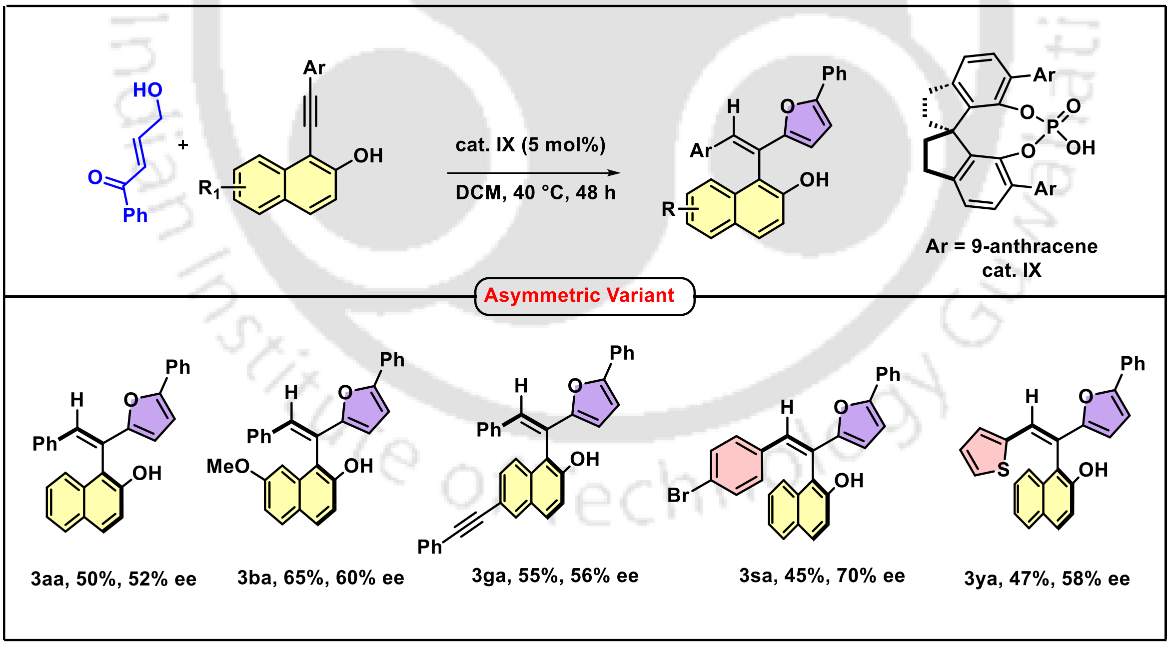
The development of an asymmetric variant of the reaction piqued our curiosity at that point. The optimum chiral spiro-phosphoric acid catalyst for the reaction was discovered after testing several different phosphoric acid catalysts. It was also found that at 70 °C, only racemic product was achieved, thus reaction temperature was decreased to 40 °C and CH_2Cl_2 was chosen as the solvent. Nevertheless, moderate enantioselectivities were achieved under these conditions (Table 2, entry 14).



entry[a]	solvent	catalyst	Temp. (° C)	Yield (%)[b]	ee (%)[c]
1	$PhCH_3$	I	70 (12 h)	70	10
2	$PhCH_3$	II	70 (12 h)	73	10
3	$PhCH_3$	III	70 (12 h)	72	4
4	$PhCH_3$	IV	70 (12 h)	70	2
5	$PhCH_3$	V	70 (12 h)	75	20
6	$PhCH_3$	VI	70 (12 h)	80	5
7	$PhCH_3$	VII	70 (12 h)	78	20
8	$PhCH_3$	VIII	70 (12 h)	75	32
9	$PhCH_3$	IX	70 (12 h)	78	36

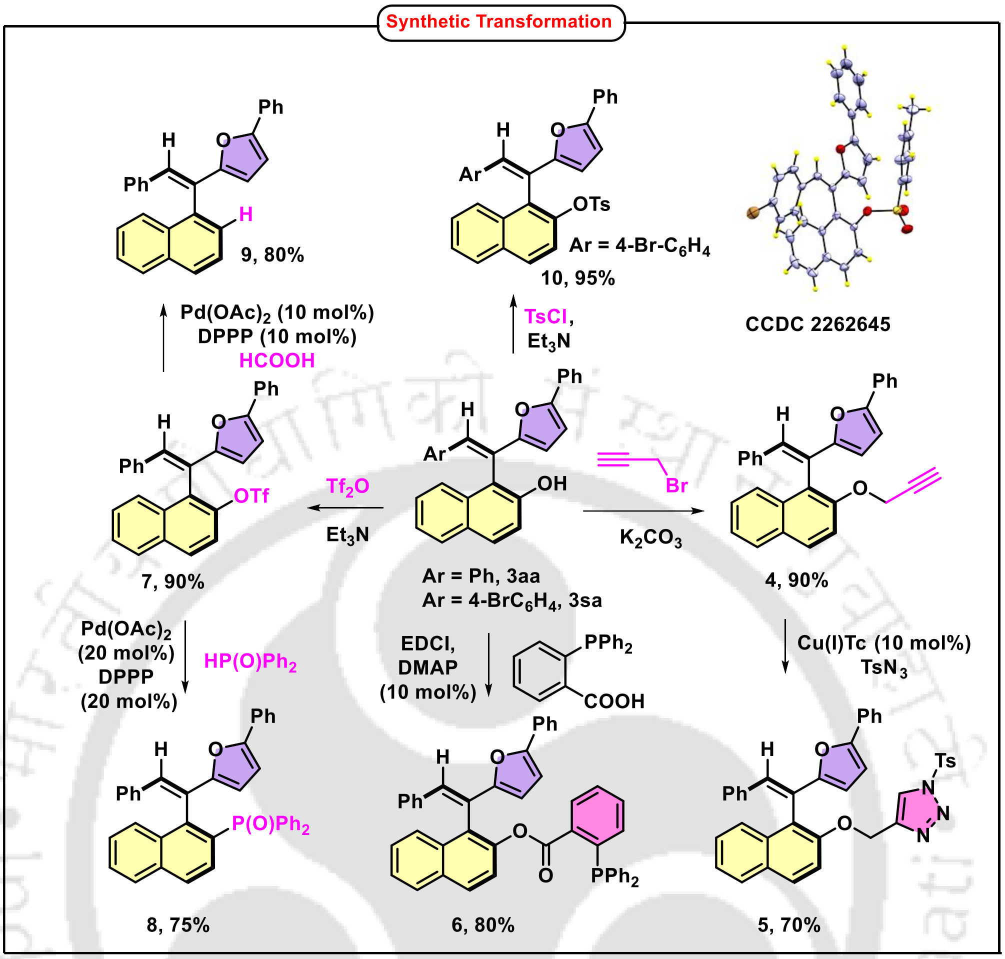
10	$PhCH_3$	X	70 (12 h)	60	10
11	$PhCH_3$	IX	40 (48 h)	30	40
12	$PhCF_3$	IX	40 (48 h)	40	30
13	1,2-DCE	IX	40 (48 h)	45	45
14	**DCM**	**IX**	**40 (48 h)**	**50**	**52**
15	THF	IX	40 (48 h)	-	-
16	ACN	IX	40 (48 h)	20	10
17	DCM + 4Å MS	IX	40 (48 h)	10	-
18	DCM + $MgSO_4$	IX	40 (48 h)	<5	-
19	DCM+$Sc(OTf)_3$ (10 mol%) + 4Å MS, 60 °C	IX	40 (48 h)	-	-

Table 2: Catalyst and solvent optimization for asymmetric variant.



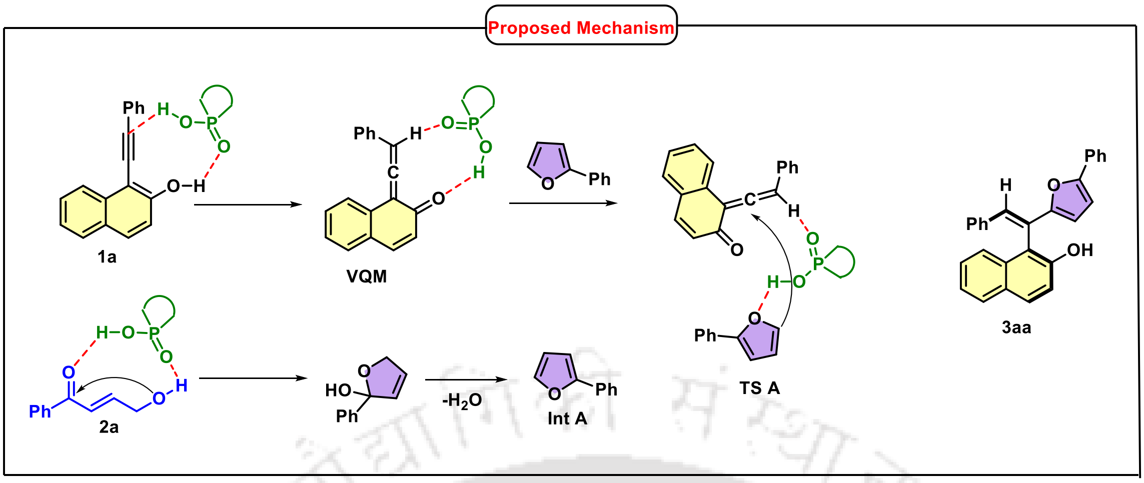
Scheme 10: Asymmetric variant.

After that scope of asymmetric variant was verified compound **3aa** was obtained in 50% yield with 52% ee. Slightly higher enantioselectivities were detected for **3ba**, **3ga**, **3sa** and **3ya** (Scheme 10).



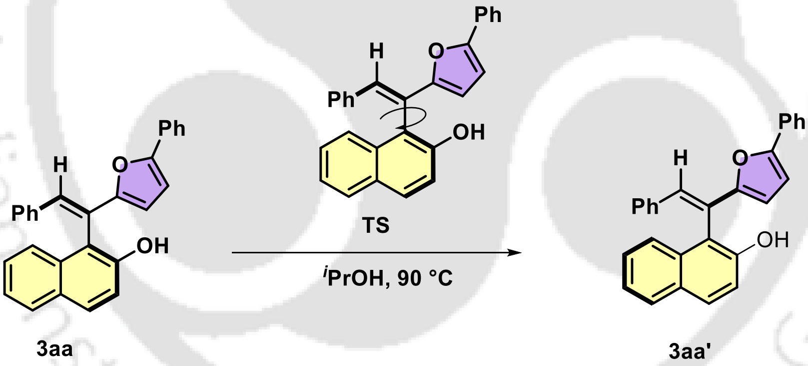
Scheme 11: Synthetic transformation.

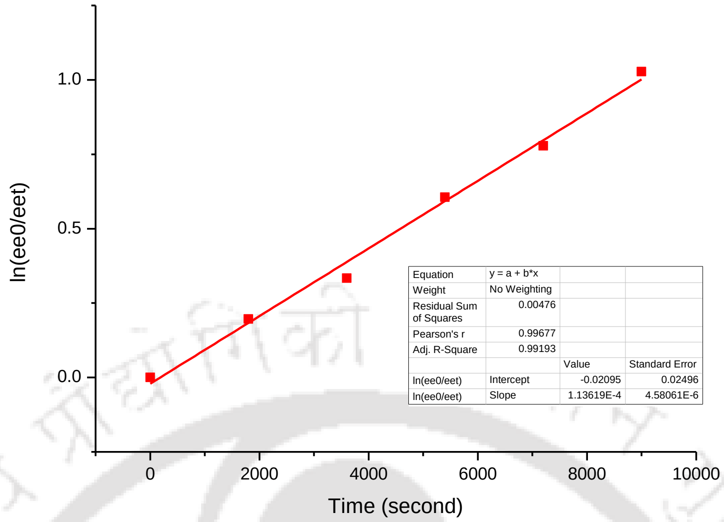
Then, several reactions were carried out on **3aa** and **3sa** to show our methodology's synthetic potential. Initially, **3aa** was reacted with propargyl bromide to provide **4** in 90% yield (Scheme 4). Then Cu(I) catalyzed click reaction generated triazole **5** in 70% yield. Also, esterification of **3aa** with 2-(diphenylphosphaneyl) benzoic acid led to the formation of **6** with 80% yield. Then **3aa** and triflic anhydride were reacted to produce **7** in 90% yield. Then Pd catalyzed coupling reactions of **8** with diphenyl phosphine oxide and formic acid respectively formed **8** and **9** in acceptable yields. Finally, **3sa** was converted to **10** by tosyl chloride. The structure of **10** was unambiguously confirmed from *X*-ray crystallography and thus other compounds **3** have similar structure.



Scheme 12: Proposed mechanism.

In proposed mechanism part, phosphoric acid activated the compound **1a** generating a VQM intermediate, simultaneously, in presence of phosphoric acid, compound **2a** gives an intermediate **Int A**, which further underwent via a transition state **TS A**, giving rise to product **3aa** (scheme 12).





Equation	y = a + b*x		
Weight	No Weighting		
Residual Sum of Squares	0.00476		
Pearson's r	0.99677		
Adj. R-Square	0.99193		
		Value	Standard Error
ln(ee0/eet)	Intercept	-0.02095	0.02496
ln(ee0/eet)	Slope	1.13619E-4	4.58061E-6

Figure 3: Racemization barriers.

$$k_{\text{rac}} = 2k_{\text{rot}} = \frac{k_B T}{h} e^{\frac{-\Delta G^{\neq}_{rot}}{RT}}$$

$$t_{1/2} = \frac{\ln 2}{k_{rac}} = 21.2 \text{ years at } 25\,℃ \qquad k_{rot} = \frac{slope}{2}$$

$$\boldsymbol{k^{\neq}_{rot}} = \frac{k_{rot} h}{T k_B}$$

$$\Delta G^{\neq}_{rot} = -RT\ln k^{\neq}_{rot} = 30\ kCalmol^{-1}$$

The rate of racemization of **3aa** was measured at 90 °C by following Curran[9] *et al*, and from these experiments, the rotational barrier of the C–C axis in **3aa** was found to be about 30 kcal/mol, and $t_{1/2}$ of racemization at 25 °C is estimated to be approximately 21.2 years.

In summary, we have described the synthesis of furan embedded styrene atropisomer, and the reaction was catalyzed by PTSA. The reaction progressed through acid catalyzed furan formation followed by addition to vinyl *ortho*-quinone methide that was generated from

1. Synthetic applications such as triazole formation and cross-coupling reactions have been performed.

6.5 Experimental section

6.5.1 General procedure of synthesis of compounds

General Procedure for the Synthesis of different-substituted-2-napthol[4]: Substituted naphthol (**1a**) were prepared according to the known reported procedure.

General Procedure for the Synthesis of γ-Hydroxyenones (2a)[10]: γ-Hydroxyenones (**2a**) were prepared according to the known reported procedure.

General Procedure for the Catalyst Preparation[11]: The best catalyst, i.e., quinine derived squaramide catalyst **IX**, was prepared according to the previously reported procedure.

General Procedure for the Synthesis of Compound 3:

In an oven dried round bottom flask, **1a** (0.1 mmol), **2** (0.15 mmol), 10 mol% of *p*-toluene-sulfonic acid were taken under argon atmosphere. 1.00 mL dry toluene of was added to the reaction mixture and stirred at 70 °C for 12 hours. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel (230-400 mesh size) eluting with ethyl-acetate: hexane (1-2%) to afford desired products **3aa to 3aj**.

General procedure for the synthesis of chiral compound 3aa, 3ba, 3sa and 3ya:

In an oven dried round bottom flask, **1** (0.1 mmol), **2a** (0.15 mmol), 5 mol% of (*S*)-Spiro-anthracene chiral phosphoric acid were taken under argon atmosphere. 1.00 mL dry CH_2Cl_2 of was added to the reaction mixture and stirred at 40 °C for 48 hours. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel (230-400 mesh size) eluting with ethyl-acetate: hexane (1-2%) to afford desired products.

General procedure for the synthesis of compound 4:

To a solution of **3aa** (39.0 mg, 0.1 mmol, 1.0 eq) in acetone (2.0 mL) were sequentially added propargyl bromide (35.7 mg, 0.3 mmol, 3.0 eq) and K2CO3 (64.9 mg, 0.5 mmol, 5.0 eq). The reaction mixture was stirred for 12 h before it was filtered and concentrated. The residue was purified by silica gel flash chromatography to afford the desired product (ethyl acetate/hexane 0.5-1% as the eluent) as white sticky solid in 90% yield (38.3 mg).

General procedure for the synthesis of compound 5:

A flame dried 5 mL vial, equipped with a stir bar, was charged with **4** (26 mg, 0.06 mmol, 1.0 eq) and freshly distilled toluene (1.2 mL). Tosyl azide (18 mg, 0.092 mmol, 1.5 equiv) was added to the solution at rt. And copper(I) thiophene-2-carboxylate (0.1 equiv) was added, respectively. After stirring for 12 h, the reaction mixture was monitored by TLC. The mixture was then purified by silica gel flash chromatography to afford the desired product (ethyl acetate/petroleum ether = 3-5% as the eluent) as white powder in 70% yield (43 mg)

General procedure for the synthesis of compound 6:

To a solution of 2-(diphenylphosphino)benzoic acid (33.7 mg, 0.11 mmol, 1.1 eq) in DCM (1.0 mL), **3aa** (39.0 mg, 0.1 mmol, 1.0 eq), *N* -ethylcarbodiimide hydrochloride (EDCI) (17.1 mg, 0.11 mmol, 1.1 eq), 4-dimethylaminopyridine (DMAP) (1.2 mg, 0.01 mmol, 0.1 eq) were added. The reaction was stirred at room temperature until the reaction was complete (about 24 h). Upon completion, the mixture was filtrated, washed with 10% $NaHCO_3$, and extracted with dichloromethane. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to afford the desired product (ethyl acetate/hexane = 3-5% as the eluent) as pale-yellow solid in 80% yield (54 mg).

General procedure for the synthesis of compound 7:

At 0 °C, to a solution of **3aa** (116.52 mg, 0.3 mmol, 1.0 eq) and Et3N (0.083 mL, 0.6 mmol, 2.0 eq) in DCM (6 mL) was slowly added Tf2O (0.06 mL, 0.36 mmol, 1.2 eq) over 1 min. The reaction mixture was stirred at 0 °C for 30 min. Then stirred at room temperature for 3.5 hours. Next, water (3 mL) was added, and the reaction mixture was extracted with DCM (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel flash chromatography to afford the desired product (ethyl acetate/hexane 0.5-1% as the eluent) as a yellow viscous oil in 90% yield (140.4 mg).

General procedure for the synthesis of compound 8:

Under argon atmosphere, dry DMSO (1.0 mL) was added to the mixture of **7** (52 mg, 0.1 mmol, 1.0 eq), diphenylphosphine oxide (1.5 eq), $Pd(OAc)_2$ (20 mol%), dppp (20 mol %) and DIPEA (2.5 eq). The mixture was heated with an oil bath at 120 °C and stirred for 2 hours. Then, the reaction mixture was concentrated and purified by silica gel flash chromatography (ethyl acetate/petroleum ether = 40-50% as the eluent) to afford the desired product as white powder in 75% yield (43 mg).

General procedure for the synthesis of compound 9:

To an oven-dried 5 mL round bottom flask were successively added a magnetic stir bar, $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 eq), dppp (3.1 mg, 0.01 mmol, 0.1 eq), **7** (52 mg, 0.1 mmol, 1.0 eq), DMF (1.0 mL), Et_3N (139 µL, 1.0 mmol, 10.0 eq) and HCOOH (38.0 µL, 1.0 mmol, 10.0 eq) under argon. The mixture was allowed to heat with an oil bath at 80 °C and stir for 60 h. Upon completion, saturated brine was added (5 mL). The aqueous layer was extracted with EtOAc for twice (10 mL x 2). Then the combined organic phases were washed with brine for three times (10 mL x 3) and dried over Na_2SO_4. After filtration, the organic solution was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/petroleum ether = 1-2% as the eluent) to afford the product **9** as a pale-yellow powder in 80% yield (29.7 mg).

General procedure for the synthesis of compound 10:

Under argon atmosphere, dry DCM (1.0 mL) was added to the mixture of **3sa** (47 mg, 0.1 mmol, 1.0 eq), triethyl amine (2 eq) and tosyl chloride (2.5 eq). The mixture was stirred for 6 hours at room temprature. Then, the reaction mixture was concentrated and purified by silica gel flash chromatography (ethyl acetate/petroleum ether = 2-3% as the eluent) to afford the desired product **10** as white powder in 95% yield (59 mg).

6.6 Crystal data of compound 10

CCDC = 2262645

Bond precision: C-C = 0.0118 A Wavelength=0.71073

Cell: a=9.690(5) b=12.089(6) c=13.334(7)

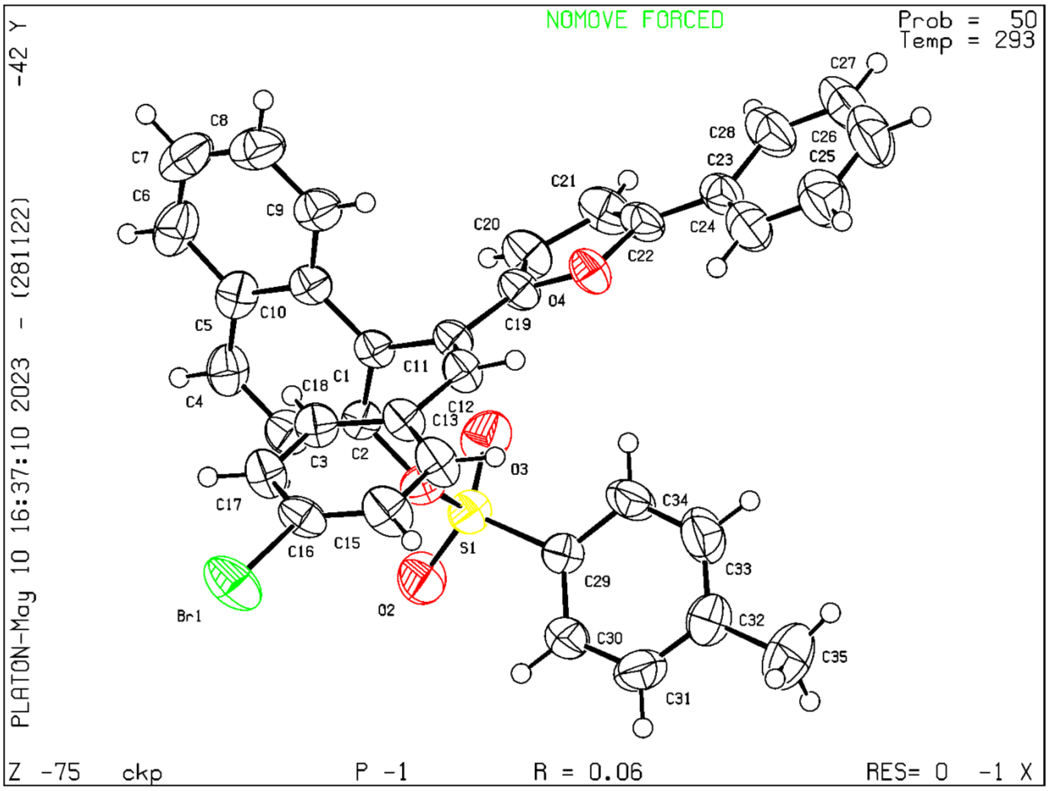
alpha=90 beta=96.853(15) gamma=90

Temperature: 297 K

	Reported
Volume	1464.4 (3)
Space group	P -1
Hall group	-P1
Moiety formula	$C_{35}H_{25}BrO_4S$
Sum formula	$C_{35}H_{25}BrO_4S$
Mr	621.52
Dx, g cm^{-3}	1.410
Z	2
Mu (mm^{-1})	1.513
F000	636.0

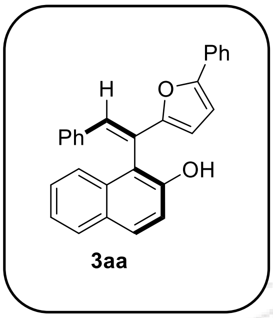
H, k, l_{max}	15, 15, 18
N_{ref}	6615
T_{min}, T_{max}	0.259, 1.000
T_{min}’	0.557
Data completeness	0.850
Theta (max)	28.976
R (reflections)	0.0571 (3870)
S	1.008
N_{par}	371

Datablock ckp - ellipsoid plot



6.7 Characterisation of the products:

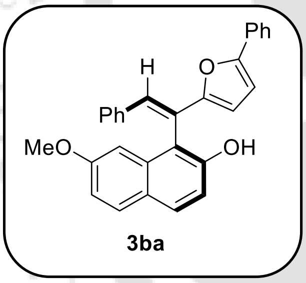
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3aa)



3aa

Pale yellow solid, yield: 90%, 35.2 mg. **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.90 (d, J = 8.9 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.80 (d, J = 8.2 Hz, 3H), 7.76 – 7.71 (m, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.33 (d, J = 7.2 Hz, 1H), 7.28 (s, 1H), 7.13 – 7.03 (m, 5H), 6.59 (d, J = 3.5 Hz, 1H), 5.78 (d, J = 3.5 Hz, 1H), 5.45 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.4, 153.5, 150.6, 135.7, 133.0, 130.7, 130.5, 129.4, 129.0, 128.9, 128.8, 128.7, 128.4, 128.10, 128.0, 127.2, 124.8, 124.2, 123.9, 122.9, 117.8, 115.8, 112.7, 107.8. **HRMS (ESI):** m/z calcd. for $C_{28}H_{20}O_2$ $[M+H]^+$ 389.1536, found 389.1520. **HPLC Analysis:** ee = 52%, Chiralpak OD Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 8.2 min, t_{minor} = 10.3 min.

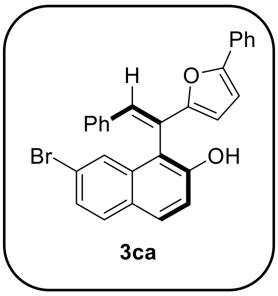
(*E*)-7-methoxy-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ba)



3ba

White Sticky solid, yield: 89%, 36.49 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.83 – 7.77 (m, 4H), 7.74 (d, J = 8.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.09 (ddd, J = 8.9, 3.9, 1.8 Hz, 6H), 7.04 – 6.97 (m, 2H), 6.59 (d, J = 3.5 Hz, 1H), 5.83 (d, J = 3.5 Hz, 1H), 5.42 (s, 1H), 3.70 (s, 3H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 158.8, 154.4, 153.3, 151.3, 135.8, 134.4, 130.7, 130.3, 129.9, 129.0, 128.9, 128.8, 128.7, 128.1, 127.9, 124.7, 124.1, 123.1, 116.1, 115.2, 115.1, 112.7, 107.8, 103.5, 55.46. **HRMS (ESI):** m/z calcd. for $C_{29}H_{21}O_3$ $[M+H]^+$ 416.1642, found 416.1652. **HPLC Analysis:** ee = 60%, Chiralpak OD Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 200 nm (t_{major} = 12.3 min, t_{minor} = 15.8 min).

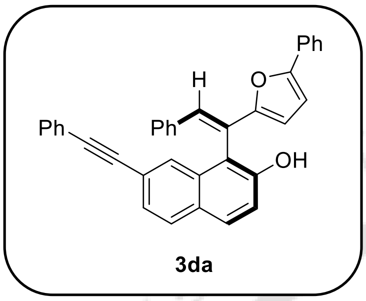
(*E*)-7-bromo-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ca)



3ca

Pale yellow solid, yield: 83%, 38.18 mg, melting point: 125 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.87 – 7.81 (m, 2H), 7.81 – 7.76 (m, 3H), 7.70 (d, J = 8.7 Hz, 1H), 7.43 (q, J = 9.4, 8.5 Hz, 3H), 7.32 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 4.3 Hz, 1H), 7.09 (q, J = 6.8, 6.0 Hz, 3H), 7.01 (d, J = 7.3 Hz, 2H), 6.58 (d, J = 3.5 Hz, 1H), 5.75 (d, J = 3.5 Hz, 1H), 5.51 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.7, 153.0, 151.5, 135.5, 134.3, 130.6, 130.2, 130.0, 129.2, 129.0, 128.9, 128.7, 128.3, 128.1, 127.8, 127.4, 126.8, 124.2, 122.1, 121.8, 118.3, 115.3, 112.7, 107.9. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$ 467.0641, found467.0646.

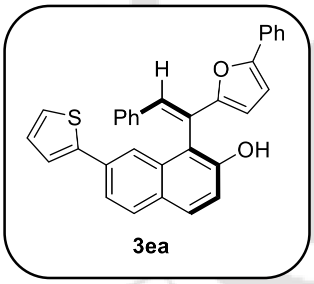
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-7-(phenylethynyl)naphthalen-2-ol (3da)



3da

Orange sticky solid, yield: 80%, 38.4 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.84 (s, 1H), 7.79 (d, J = 8.9 Hz, 1H), 7.77 – 7.70 (m, 4H), 7.44 – 7.36 (m, 5H), 7.25 – 7.17 (m, 5H), 7.02 (q, J = 6.1 Hz, 3H), 6.97 (d, J = 6.5 Hz, 2H), 6.52 (d, J = 3.4 Hz, 1H), 5.70 (d, J = 3.5 Hz, 1H), 5.41 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.5, 153.3, 151.2, 135.6, 132.8, 131.8, 130.6, 130.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 126.7, 124.2, 123.3, 122.4, 122.0, 118.5, 115.8, 112.8, 108.0, 90.3, 90.2. **HRMS (ESI):** m/z calcd. for $C_{36}H_{24}O_2$ $[M+H]^+$ 489.1849, found 489.1853.

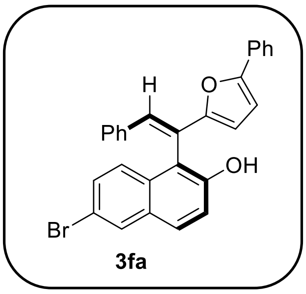
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-7-(thiophen-2-yl)naphthalen-2-ol (3ea)



3ea

Grey sticky solid, yield: 85%, 39.95 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.94 (d, J = 1.9 Hz, 1H), 7.90 – 7.85 (m, 3H), 7.85 – 7.82 (m, 2H), 7.64 (dd, J = 8.5, 1.8 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.24 (t, J = 2.8 Hz, 1H), 7.12 (d, J = 4.0 Hz, 5H), 7.04 (dd, J = 5.1, 3.6 Hz, 1H), 6.61 (d, J = 3.5 Hz, 1H), 5.85 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.5, 153.3, 151.3, 144.8, 135.7, 133.3, 133.1, 130.7, 130.3, 129.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.2, 128.1, 127.9, 125.3, 124.2, 123.8, 122.7, 122.7, 121.2, 117.8, 116.0, 112.8, 107.9. **HRMS (ESI):** m/z calcd. for $C_{32}H_{22}O_2S$ $[M+H]^+$471.1413, found 471.1419.

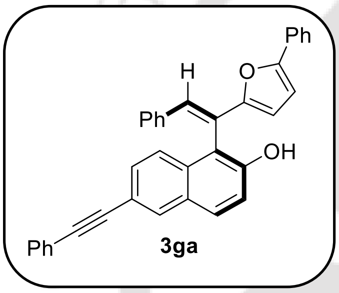
(*E*)-6-bromo-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3fa)



3fa

Pale yellow sticky solid, yield: 86%, 39.56 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.98 (d, J = 2.1 Hz, 1H), 7.76 (ddd, J = 6.0, 4.3, 2.2 Hz, 4H), 7.57 (d, J = 8.9 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.33 – 7.28 (m, 1H), 7.24 (s, 1H), 7.12 – 7.04 (m, 3H), 6.99 (dt, J = 6.8, 1.7 Hz, 2H), 6.56 (d, J = 3.5 Hz, 1H), 5.72 (d, J = 3.5 Hz, 1H), 5.44 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.6, 153.1, 151.0, 135.5, 131.6, 130.6, 130.5, 130.5, 130.4, 129.6, 129.1, 129.0, 128.8, 128.7, 128.3, 128.1, 126.6, 124.2, 122.3, 119.0, 117.7, 116.1, 112.7, 107.8. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$467.0641, found 467.0647.

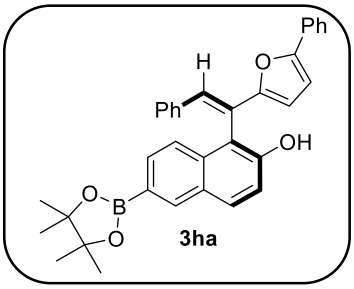
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-6-(phenylethynyl)naphthalen-2-ol (3ga)



3ga

White sticky solid, yield: 83%, 39.84 mg, melting point: 160 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.04 (s, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 8.2 Hz, 3H), 7.67 (d, J = 8.6 Hz, 1H), 7.53 (dd, J = 6.8, 2.1 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.32 (dq, J = 15.0, 7.5, 6.7 Hz, 5H), 7.24 (d, J = 4.0 Hz, 1H), 7.07 (q, J = 6.6, 6.1 Hz, 3H), 7.01 (d, J = 7.3 Hz, 2H), 6.56 (d, J = 3.6 Hz, 1H), 5.76 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.6, 153.2, 151.4, 135.6, 132.6, 131.9, 131.8, 130.6, 130.5, 129.8, 129.0, 128.9, 128.7, 128.5, 128.4, 128.2, 128.0, 125.0, 124.2, 123.6, 122.5, 118.6, 118.5, 116.1, 112.7, 107.8, 89.9, 89.6. **HRMS (ESI):** m/z calcd. for $C_{36}H_{24}O_2$ $[M+H]^+$ 489.1849, found 489.1854. **HPLC Analysis:** ee = 60%, Chiralpak OD Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.2 min, t_{minor} = 14.8 min).

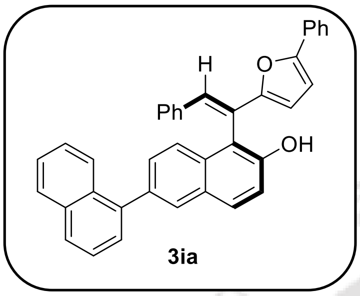
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (3ha)



3ha

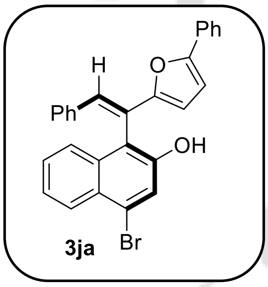
Orange sticky solid, yield: 82%, 41.82 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.38 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.79 (d, J = 1.9 Hz, 2H), 7.78 – 7.76 (m, 1H), 7.74 (dd, J = 8.4, 1.2 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.24 (d, J = 8.9 Hz, 1H), 7.10 – 7.00 (m, 5H), 6.56 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 3.5 Hz, 1H), 5.55 (s, 1H), 1.37 (s, 12H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.4, 153.4, 151.6, 136.7, 135.7, 134.9, 131.9, 131.4, 130.7, 129.0, 128.8, 128.8, 128.6, 128.0, 127.9, 124.2, 123.9, 122.8, 117.7, 115.8, 112.7, 107.8, 84.0, 25.2, 25.1. **HRMS (ESI):** m/z calcd. for $C_{34}H_{31}BO_4$ $[M+H]^+$ 515.2388, found 515.2382.

(*E*)-5'-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-[1,2'-binaphthalen]-6'-ol (3ia)


3ia

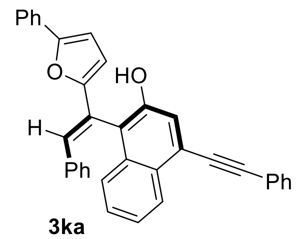
Pale yellow solid, yield: 79%, 40.29 mg, melting point: 130 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.01 – 7.96 (m, 2H), 7.95 – 7.91 (m, 2H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.85 (s, 1H), 7.84 – 7.80 (m, 3H), 7.58 – 7.53 (m, 3H), 7.52 – 7.47 (m, 2H), 7.46 – 7.43 (m, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.15 (p, J = 3.8 Hz, 5H), 6.63 (d, J = 3.5 Hz, 1H), 5.89 (d, J = 3.5 Hz, 1H), 5.51 (s, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.5, 153.5, 150.8, 140.3, 136.3, 135.8, 134.1, 132.2, 131.9, 130.7, 130.7, 129.8, 129.4, 129.2, 129.0, 129.0, 128.9, 128.7, 128.5, 128.2, 127.9, 127.8, 127.4, 126.3, 126.2, 125.9, 125.6, 124.6, 124.2, 122.9, 118.2, 115.9, 112.8, 107.9. **HRMS (ESI):** m/z calcd. for $C_{38}H_{26}O_2$ $[M+H]^+$ 515.2006, found 515.2011.

(*E*)-4-bromo-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ja)


3ja

Red solid, yield: 83%, 38.18 mg, melting point: 178 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.18 (s, 1H), 7.78 (dd, J = 10.8, 3.1 Hz, 4H), 7.75 – 7.70 (m, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.38 (ddt, J = 10.0, 6.7, 3.6 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.08 (h, J = 3.4 Hz, 3H), 7.00 (dd, J = 7.6, 2.2 Hz, 2H), 6.57 (d, J = 3.5 Hz, 1H), 5.78 (s, 1H), 5.73 (d, J = 3.5 Hz, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.4, 153.3, 147.1, 135.8, 132.5, 132.4, 130.7, 129.9, 129.0, 128.8, 128.7, 128.4, 128.0, 127.9, 127.6, 127.4, 125.0, 124.9, 124.2, 123.2, 117.8, 112.3, 112.0, 107.7. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$ 467.0641, found 467.0647.

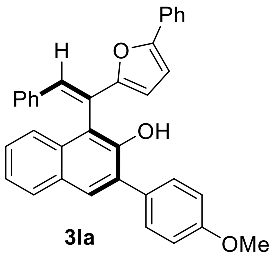
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-4-(phenylethynyl)naphthalen-2-ol (3ka)



3ka

Grey sticky solid, yield: 78%, 37.44 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.51 – 8.46 (m, 1H), 7.84 – 7.76 (m, 4H), 7.74 – 7.68 (m, 2H), 7.57 (s, 1H), 7.50 – 7.42 (m, 7H), 7.33 (t, J = 7.4 Hz, 1H), 7.11 (dqd, J = 10.0, 5.6, 5.2, 2.1 Hz, 5H), 6.59 (d, J = 3.5 Hz, 1H), 5.79 (d, J = 3.6 Hz, 1H), 5.46 (s, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.5, 153.1, 150.0, 135.5, 133.0, 131.9, 130.6, 129.4, 129.0, 128.9, 128.8, 128.7, 128.7, 128.2, 128.0, 127.8, 126.7, 125.2, 124.8, 124.2, 123.3, 123.2, 122.5, 121.7, 117.3, 112.7, 107.8, 95.2, 87.2. **HRMS (ESI):** m/z calcd. for $C_{36}H_{24}O_2$ $[M+H]^+$ 489.1849, found 489.1854.

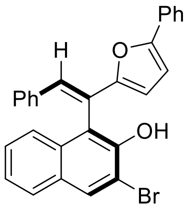
(*E*)-3-(4-methoxyphenyl)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3la)



3la

Yellow sticky solid, yield: 88%, 43.12 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.90 (s, 1H), 7.89 – 7.85 (m, 1H), 7.82 (d, J = 2.3 Hz, 2H), 7.79 (s, 1H), 7.76 – 7.71 (m, 1H), 7.62 – 7.58 (m, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.39 – 7.35 (m, 2H), 7.34 – 7.30 (m, 1H), 7.10 (s, 5H), 7.03 – 6.98 (m, 2H), 6.59 (d, J = 3.5 Hz, 1H), 5.84 (d, J = 3.5 Hz, 1H), 5.63 (s, 1H), 3.86 (s, 3H).**^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 159.4, 154.3, 153.6, 148.3, 135.9, 132.3, 130.8, 130.7, 130.3, 130.2, 130.1, 129.4, 128.9, 128.9, 128.6, 128.3, 128.0, 127.9, 126.9, 124.7, 124.2, 124.1, 123.5, 116.5, 114.1, 112.6, 107.8, 55.55. **HRMS (ESI):** m/z calcd. for $C_{35}H_{26}O_3$ $[M+H]^+$ 495.1955, found 495.1952.

(*E*)-3-bromo-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ma)

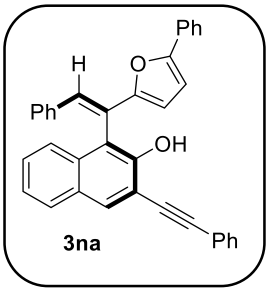


3ma

Pale yellow solid, yield: 80%, 36.8 mg, melting point: 110 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.26 (dd, J = 8.4, 1.4 Hz, 1H), 7.82 – 7.72 (m, 4H), 7.63 (s, 1H), 7.48 – 7.40 (m, 4H), 7.32 (td, J = 7.3, 1.4 Hz, 1H), 7.16 – 7.08 (m, 3H), 7.08 – 7.02 (m, 2H), 6.57 (d, J = 3.5 Hz, 1H), 5.75 (d, J = 3.5 Hz, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.6, 153.0, 150.3, 135.4, 133.7, 130.6, 129.1, 129.0, 128.8, 128.8, 128.3, 128.0, 128.0, 127.6, 125.2, 124.5, 124.2, 122.2, 122.0, 116.1, 112.8, 107.8. **HRMS (ESI):**

m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$ 467.0641, found 467.0645.

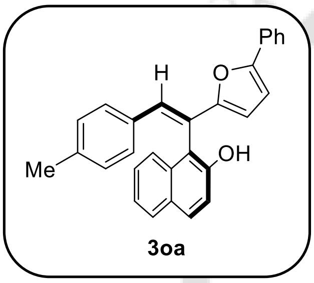
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)-3-(phenylethynyl)naphthalen-2-ol (3na)



3na

White sticky solid, yield: 84%, 40.32 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.15 (s, 1H), 7.85 – 7.73 (m, 5H), 7.60 – 7.54 (m, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.41 – 7.34 (m, 5H), 7.31 (t, J = 7.4 Hz, 1H), 7.08 (t, J = 3.7 Hz, 5H), 6.58 (d, J = 3.5 Hz, 1H), 5.97 (s, 1H), 5.77 (d, J = 3.5 Hz, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.2, 153.8, 149.9, 136.2, 133.3, 133.3, 131.9, 130.8, 129.0, 128.9, 128.8, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 127.7, 124.8, 124.6, 124.1, 123.4, 122.6, 116.6, 112.4, 112.0, 107.7, 96.1, 84.3. **HRMS (ESI):** m/z calcd. for $C_{36}H_{24}O_2$ [M+H]$^+$ 489.1849, found 489.1854.

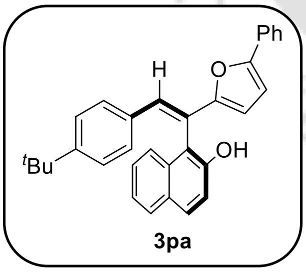
(*E*)-1-(1-(5-phenylfuran-2-yl)-2-(*p*-tolyl)vinyl)naphthalen-2-ol (3oa)



3oa

Grey sticky solid, yield: 90%, 36 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.90 – 7.84 (m, 2H), 7.79 (s, 1H), 7.79 – 7.76 (m, 2H), 7.75 – 7.71 (m, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.33 – 7.29 (m, 1H), 7.26 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 6.57 (d, J = 3.5 Hz, 1H), 5.74 (d, J = 3.5 Hz, 1H), 5.46 (s, 1H), 2.21 (s, 3H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.2, 153.6, 150.6, 138.2, 133.0, 132.9, 130.7, 130.4, 129.4, 129.4, 129.0, 128.8, 128.3, 127.8, 127.2, 124.8, 124.1, 123.8, 121.9, 117.7, 116.0, 112.3, 107.8, 21.4. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_3$ [M+H]$^+$ 403.1693, found 403.1690.

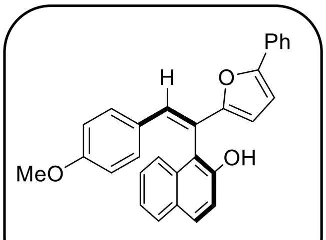
(*E*)-1-(2-(4-(*tert*-butyl)phenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3pa)



3pa

Red sticky solid, yield: 88%, 39.6 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.90 (d, J = 8.9 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.79 (d, J = 8.3 Hz, 3H), 7.75 – 7.70 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.36 (dq, J = 6.6, 4.7, 3.4 Hz, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.11 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 3.4 Hz, 1H), 5.72 (d, J = 3.4 Hz, 1H), 5.47 (s, 1H), 1.21 (s, 9H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.3, 153.7, 151.3, 150.6, 133.0, 132.8, 130.7, 130.4, 129.4, 129.0, 128.8, 128.7, 128.4, 127.8, 127.2, 125.7, 124.8, 124.1, 123.9, 121.8, 117.8, 116.1, 112.3, 107.8, 34.7, 31.3. **HRMS (ESI):** m/z calcd. for $C_{32}H_{28}O_2$ [M+H]$^+$ 445.2162, found 445.2167.

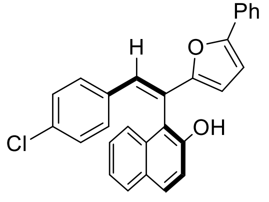
(*E*)-1-(2-(4-methoxyphenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3qa)



3qa

Pale yellow sticky solid, yield: 93%, 38.13 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.90 – 7.85 (m, 2H), 7.80 – 7.76 (m, 2H), 7.75 (s, 1H), 7.74 – 7.71 (m, 1H), 7.43 (d, J = 7.7 Hz, 2H), 7.38 – 7.35 (m, 2H), 7.34 – 7.30 (m, 1H), 7.27 (s, 1H), 6.98 (d, J = 8.9 Hz, 2H), 6.66 – 6.60 (m, 2H), 6.56 (d, J = 3.5 Hz, 1H), 5.71 (d, J = 3.5 Hz, 1H), 5.49 (s, 1H), 3.70 (s, 3H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 159.5, 154.0, 153.7, 150.7, 133.0, 130.8, 130.4, 130.3, 129.4, 128.9, 128.5, 128.4, 128.3, 127.8, 127.2, 124.8, 124.0, 123.9, 120.6, 117.7, 116.0, 114.2, 111.8, 107.8, 55.3. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_3$ $[M+H]^+$ 419.1642, found 419.1647.

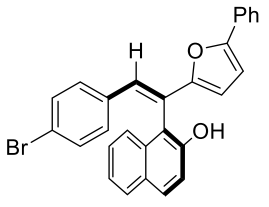
(*E*)-1-(2-(4-chlorophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ra)



3ra

Brown sticky solid, yield: 85%, 37.7 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.84 (d, J = 8.9 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.75 – 7.71 (m, 2H), 7.68 (s, 1H), 7.66 – 7.62 (m, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 7.3 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.01 – 6.96 (m, 2H), 6.92 – 6.88 (m, 2H), 6.53 (d, J = 3.5 Hz, 1H), 5.74 (d, J = 3.5 Hz, 1H), 5.35 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.7, 153.2, 150.6, 134.3, 133.7, 132.8, 130.7, 130.6, 130.0, 129.4, 129.0, 128.8, 128.5, 128.0, 127.4, 127.3, 124.6, 124.2, 124.0, 123.6, 117.8, 115.4, 113.1, 107.9. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}ClO_2$ $[M+H]^+$ 423.1146, found 423.1151.

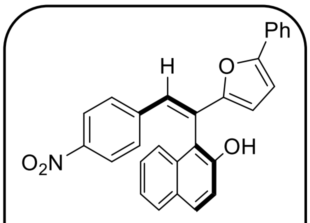
(*E*)-1-(2-(4-bromophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3sa)



3sa

Pale yellow sticky solid, yield: 84%, 37.64 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.86 – 7.79 (m, 2H), 7.77 – 7.71 (m, 2H), 7.66 (s, 1H), 7.65 – 7.61 (m, 1H), 7.40 (t, J = 7.8 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.26 (m, 1H), 7.20 (d, J = 8.8 Hz, 1H), 7.17 – 7.12 (m, 2H), 6.86 – 6.81 (m, 2H), 6.53 (d, J = 3.5 Hz, 1H), 5.75 (d, J = 3.5 Hz, 1H), 5.34 (s, 1H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 154.7, 153.1, 150.5, 134.7, 132.8, 131.8, 130.8, 130.6, 130.2, 129.4, 129.0, 128.5, 128.1, 127.4, 127.3, 124.5, 124.2, 124.0, 123.7, 122.0, 117.8, 115.4, 113.1, 107.9. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$ 467.0641, found 467.0638. **HPLC Analysis:** ee = 70%, Chiralpak OD Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.9 min, t_{minor} = 11.3 min).

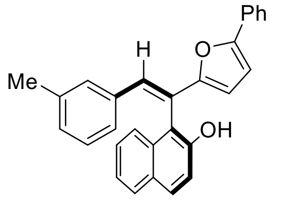
(*E*)-1-(2-(4-nitrophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3ta)



3ta

Grey sticky solid, yield: 75%, 32.25 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.91 (dd, J = 8.9, 7.3 Hz, 3H), 7.89 – 7.87 (m, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.80 (d, J = 4.3 Hz, 2H), 7.67 (dt, J = 8.2, 2.9 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.41 – 7.36 (m, 3H), 7.28 (s, 1H), 7.14 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 3.6 Hz, 1H), 5.93 (d, J = 3.6 Hz, 1H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 155.5, 152.8, 150.7, 146.5, 142.5, 132.7, 131.1, 130.3, 129.4, 129.1, 129.0, 128.6, 128.4, 127.6, 125.7, 124.3, 124.2, 124.2, 124.2, 123.9, 118.0, 114.9, 114.9, 108.2. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}NO_4$ $[M+H]^+$ 434.1387, found 434.1392.

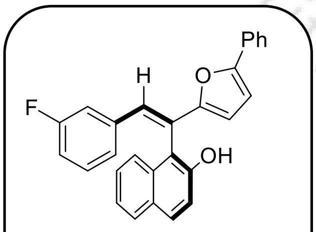
(*E*)-1-(1-(5-phenylfuran-2-yl)-2-(*m*-tolyl)vinyl)naphthalen-2-ol (3ua)



3ua

Orange sticky solid, yield: 83%, 33.2 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.89 (d, J = 8.9 Hz, 1H), 7.88 – 7.85 (m, 1H), 7.82 – 7.79 (m, 2H), 7.78 (s, 1H), 7.76 – 7.71 (m, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.37 (ddd, J = 6.6, 3.9, 1.8 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.28 (d, J = 1.9 Hz, 1H), 6.96 – 6.91 (m, 3H), 6.77 (dq, J = 7.0, 2.8, 2.3 Hz, 1H), 6.59 (d, J = 3.4 Hz, 1H), 5.78 (d, J = 3.5 Hz, 1H), 5.45 (s, 1H), 2.15 (s, 3H).**^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.3, 153.5, 150.6, 138.0, 135.6, 133.0, 130.7, 130.4, 130.2, 129.4, 129.0, 128.9, 128.5, 128.3, 127.9, 127.2, 125.5, 124.8, 124.1, 123.8, 122.7, 117.7, 116.0, 112.5, 107.8, 21.5. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_2$ $[M+H]^+$ 403.1693, found 403.1696.

(*E*)-1-(2-(3-fluorophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3va)



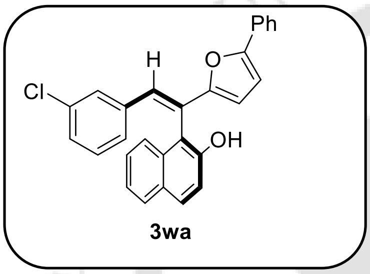
3va

Pale yellow solid, yield: 78%, 31.2 mg, melting point: 185 °C, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.83 (d, J = 8.9 Hz, 1H), 7.80 – 7.77 (m, 1H), 7.75 – 7.70 (m, 2H), 7.67 (s, 1H), 7.64 – 7.60 (m, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.29 (ddd, J = 13.0, 6.7, 4.2 Hz, 3H), 7.22 – 7.17 (m, 1H), 6.97 (td, J = 8.0, 6.1 Hz, 1H), 6.79 – 6.76 (m, 1H), 6.72 (ddd, J = 9.1, 5.8, 1.7 Hz, 1H), 6.61 (dt, J = 10.7, 2.1 Hz, 1H), 6.51 (d, J = 3.5 Hz, 1H), 5.74 (d, J = 3.5 Hz, 1H), 5.32 (s, 1H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 164.07, 161.64, 154.8, 153.0, 150.6, 137.99, 137.91, 132.8, 130.8, 130.5, 130.03, 129.95, 129.4, 129.0, 128.5, 128.1, 127.36, 127.3, 124.81, 124.78, 124.5, 124.2, 124.2, 124.0, 117.8, 115.3, 115.30, 115.08, 115.00, 114.79, 113.4, 107.9.

The coupling constants between C-F are as follow,

$^{1}J_{CF}$ = (164.07-161.64) x 100 = 240Hz
$^{2}J_{CF}$ = (115.30-115.08) x 100 = 22Hz
$^{2'}J_{CF}$ = (115.00-114.79) x 100 = 21Hz
$^{3}J_{CF}$ = (137.99-137.91) x 100 = 8Hz
$^{3'}J_{CF}$ = (130.03-129.95) x 100 = 8Hz
$^{4}J_{CF}$ = (124.81-124.78) x 100 = 3Hz
HRMS (ESI): m/z calcd. for $C_{28}H_{19}FO_2$ $[M+H]^+$ 407.1442, found 407.1447.

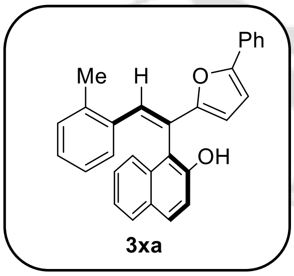
(*E*)-1-(2-(3-chlorophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-ol (3wa)



3wa

White sticky solid, yield: 80%, 33.6 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.83 (d, J = 9.0 Hz, 1H), 7.79 (dd, J = 6.5, 2.8 Hz, 1H), 7.74 – 7.70 (m, 2H), 7.64 (s, 1H), 7.63 – 7.59 (m, 1H), 7.38 (t, J = 7.7 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.21 – 7.17 (m, 1H), 7.01 (t, J = 1.9 Hz, 1H), 6.98 (dd, J = 8.0, 2.1 Hz, 1H), 6.87 (t, J = 7.9 Hz, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.51 (d, J = 3.5 Hz, 1H), 5.75 (d, J = 3.5 Hz, 1H), 5.31 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.8, 153.0, 150.6, 137.6, 134.4, 132.8, 130.8, 130.5, 129.8, 129.4, 129.2, 129.0, 128.5, 128.1, 127.9, 127.4, 127.1, 126.3, 124.6, 124.4, 124.2, 124.0, 117.8, 115.3, 113.4, 107.9. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}ClO_2$ $[M+H]^+$ 423.1146, found 423.1152.

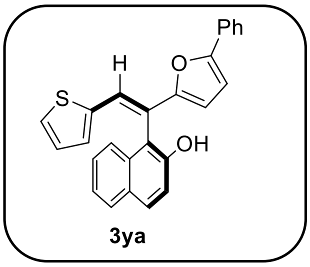
(*E*)-1-(1-(5-phenylfuran-2-yl)-2-(o-tolyl)vinyl)naphthalen-2-ol (3xa)



3xa

Brown sticky solid, yield: 77%, 30.8 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.97 (s, 1H), 7.81 (dd, J = 9.1, 2.9 Hz, 2H), 7.79 – 7.75 (m, 2H), 7.73 (d, J = 8.3 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.38 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.17 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.99 (td, J = 7.4, 1.5 Hz, 1H), 6.73 – 6.70 (m, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.58 (d, J = 3.5 Hz, 1H), 5.77 (d, J = 3.5 Hz, 1H), 5.39 (s, 1H), 2.56 (s, 3H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.3, 153.5, 150.7, 136.9, 134.5, 133.4, 130.7, 130.3, 130.3, 129.3, 129.0, 128.4, 128.0, 127.9, 127.5, 127.1, 127.0, 125.9, 124.9, 124.1, 123.7, 123.6, 117.6, 115.8, 112.6, 107.8, 20.6. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_2$ $[M+H]^+$ 403.1693, found 403.1689.

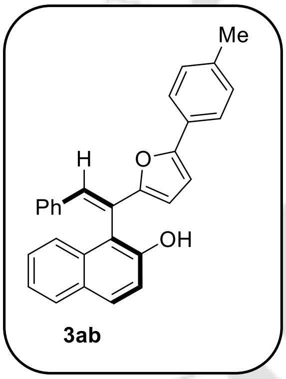
(*E*)-1-(1-(5-phenylfuran-2-yl)-2-(thiophen-2-yl)vinyl)naphthalen-2-ol (3ya)



3ya

Grey sticky solid, yield: 82%, 31.98 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.99 (s, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.87 (dd, J = 6.2, 3.3 Hz, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.65 (dt, J = 7.1, 3.5 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.34 (ddt, J = 22.0, 7.8, 3.6 Hz, 4H), 7.09 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 5.0 Hz, 1H), 6.87 (t, J = 4.4 Hz, 1H), 6.59 (d, J = 3.5 Hz, 1H), 5.83 (d, J = 3.5 Hz, 1H), 5.44 (d, J = 2.2 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.4, 153.0, 151.6, 139.6, 133.1, 131.2, 130.6, 129.9, 129.7, 129.0, 128.3, 127.9, 127.3, 126.6, 124.2, 124.1, 124.0, 122.4, 120.0, 118.0, 114.8, 112.5, 108.0. **HRMS (ESI):** m/z calcd. for $C_{29}H_{18}O_2S$ $[M+H]^+$ 395.1100, found 395.1105. **HPLC Analysis:** ee = 58%, Chiralpak OD Column, *n*-Hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 200 nm (t_{major} = 19.9 min, t_{minor} = 14.7 min).

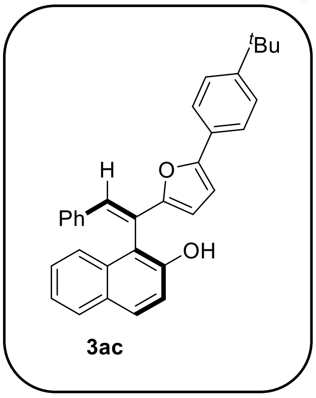
(*E*)-1-(2-phenyl-1-(5-(*p*-tolyl)furan-2-yl)vinyl)naphthalen-2-ol (3ab)



3ab

Red sticky solid, yield: 92%, 36.8 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.89 (dd, J = 10.4, 7.7 Hz, 2H), 7.80 (s, 1H), 7.76 – 7.73 (m, 1H), 7.70 (d, J = 7.9 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.28 (s, 3H), 7.08 (ddd, J = 15.1, 6.9, 4.5 Hz, 5H), 6.53 (d, J = 3.5 Hz, 1H), 5.76 (d, J = 3.5 Hz, 1H), 5.47 (s, 1H), 2.43 (s, 3H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 154.7, 153.1, 150.6, 137.9, 135.8, 133.0, 130.5, 129.7, 129.4, 128.9, 128.6, 128.5, 128.4, 128.0, 128.0, 127.2, 124.8, 124.1, 123.9, 123.0, 117.8, 115.9, 112.7, 107.1, 21.6. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_2$ $[M+H]^+$ 403.1693, found 403.1698.

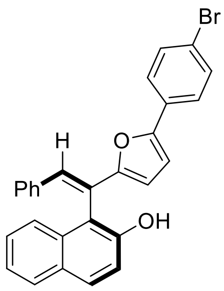
(*E*)-1-(1-(5-(4-(*tert*-butyl)phenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ac)



3ac

Yellow sticky solid, yield: 91%, 40.04 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.91 – 7.85 (m, 2H), 7.80 (s, 1H), 7.75 – 7.72 (m, 2H), 7.52 – 7.47 (m, 2H), 7.40 – 7.36 (m, 2H), 7.28 (s, 2H), 7.12 – 7.08 (m, 3H), 7.05 (dq, J = 5.5, 2.8 Hz, 2H), 6.54 (d, J = 3.4 Hz, 1H), 5.77 (d, J = 3.5 Hz, 1H), 5.47 (s, 1H), 1.40 (s, 9H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 154.7, 153.1, 151.1, 150.6, 135.8, 133.0, 130.5, 129.4, 128.9, 128.8, 128.6, 128.5, 128.3, 128.0, 127.2, 125.9, 124.8, 124.0, 123.8, 123.0, 117.8, 115.9, 112.7, 107.2, 34.93, 31.49. **HRMS (ESI):** m/z calcd. for $C_{32}H_{28}O_2$ $[M+H]^+$ 445.2162, found 445.2167.

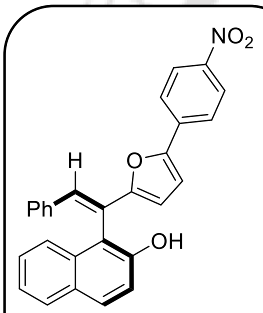
(*E*)-1-(1-(5-(4-bromophenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ad)



3ad

Pale yellow sticky solid, yield: 85%, 39.1 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.90 – 7.85 (m, 2H), 7.79 (s, 1H), 7.74 – 7.69 (m, 1H), 7.66 – 7.62 (m, 2H), 7.59 – 7.55 (m, 2H), 7.39 – 7.34 (m, 2H), 7.26 (d, J = 8.9 Hz, 1H), 7.12 – 7.03 (m, 5H), 6.57 (d, J = 3.5 Hz, 1H), 5.76 (d, J = 3.5 Hz, 1H), 5.43 (s, 1H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 153.8, 153.3, 150.6, 135.6, 132.9, 132.1, 130.6, 129.6, 129.4, 129.2, 128.9, 128.7, 128.4, 128.2, 127.2, 125.6, 124.7, 123.9, 122.8, 121.7, 117.8, 115.7, 112.7, 108.4. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}BrO_2$ $[M+H]^+$ 467.0641, found 467.0646.

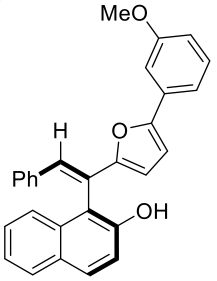
(*E*)-1-(1-(5-(4-nitrophenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ae)



3ae

White solid, yield: 78%, 33.54 mg, melting point: 130 °C, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.31 – 8.26 (m, 2H), 7.91 – 7.82 (m, 5H), 7.71 – 7.66 (m, 1H), 7.37 (qd, J = 6.7, 3.5 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.15 – 7.03 (m, 5H), 6.78 (d, J = 3.7 Hz, 1H), 5.82 (d, J = 3.6 Hz, 1H), 5.41 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 155.7, 151.9, 150.6, 146.7, 136.2, 135.3, 132.9, 130.8, 130.6, 129.4, 129.1, 128.8, 128.6, 128.5, 127.3, 124.6, 124.5, 124.2, 124.0, 122.6, 117.8, 115.3, 112.9, 111.8. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}NO_4$ $[M+H]^+$ 434.1387, found 434.1383.

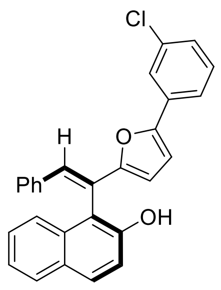
(*E*)-1-(1-(5-(3-methoxyphenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3af)



3af

Grey sticky solid, yield: 88%, 35.08 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.89 – 7.83 (m, 2H), 7.79 (s, 1H), 7.74 – 7.70 (m, 1H), 7.38 – 7.34 (m, 4H), 7.33 – 7.32 (m, 1H), 7.27 – 7.22 (m, 1H), 7.10 – 7.03 (m, 5H), 6.87 (dt, J = 6.9, 2.4 Hz, 1H), 6.56 (d, J = 3.5 Hz, 1H), 5.75 (d, J = 3.5 Hz, 1H), 5.46 (s, 1H), 3.90 (s, 3H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 160.2, 154.2, 153.5, 150.6, 135.7, 133.0, 132.0, 130.5, 130.1, 129.4, 128.9, 128.9, 128.6, 128.4, 128.1, 127.2, 124.8, 123.9, 122.9, 117.8, 116.8, 115.8, 113.4, 112.7, 109.8, 108.2. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_3$ $[M+H]^+$ 419.1642, found 419.1647.

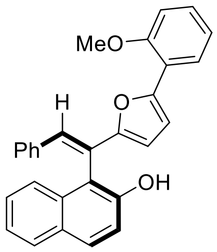
(*E*)-1-(1-(5-(3-chlorophenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ag)



3ag

Pale yellow sticky solid, yield: 82%, 33.44 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.89 – 7.82 (m, 2H), 7.79 (s, 1H), 7.75 (t, J = 1.9 Hz, 1H), 7.71 – 7.67 (m, 1H), 7.62 (dt, J = 7.8, 1.4 Hz, 1H), 7.35 (td, J = 7.9, 7.2, 3.4 Hz, 3H), 7.28 – 7.22 (m, 2H), 7.10 – 7.01 (m, 5H), 6.57 (d, J = 3.6 Hz, 1H), 5.74 (d, J = 3.5 Hz, 1H), 5.42 (s, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.0, 152.8, 150.6, 135.5, 135.0, 133.0, 132.3, 130.6, 130.3, 129.3, 129.0, 128.7, 128.4, 128.2, 127.8, 127.2, 124.7, 124.0, 123.9, 122.7, 122.2, 117.8, 115.6, 112.6, 108.9. **HRMS (ESI):** m/z calcd. for $C_{28}H_{19}ClO_2$ $[M+H]^+$ 423.1146, found 423.1141.

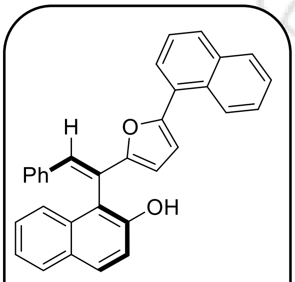
(*E*)-1-(1-(5-(2-methoxyphenyl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ah)



3ah

Red sticky solid, yield: 82%, 33.62 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.08 (dd, J = 7.8, 1.8 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.79 (s, 1H), 7.74 – 7.69 (m, 1H), 7.38 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 7.27 – 7.23 (m, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.09 – 7.03 (m, 5H), 6.98 (d, J = 8.3 Hz, 1H), 6.86 (d, J = 3.5 Hz, 1H), 5.78 (d, J = 3.5 Hz, 1H), 5.45 (s, 1H), 3.92 (s, 3H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 155.9, 152.4, 150.9, 150.6, 135.8, 133.1, 130.5, 129.4, 128.8, 128.7, 128.6, 128.6, 128.3, 127.9, 127.1, 126.2, 124.9, 123.8, 123.0, 121.0, 119.7, 117.8, 116.0, 113.0, 112.8, 111.3, 55.6. **HRMS (ESI):** m/z calcd. for $C_{29}H_{22}O_3$ $[M+H]^+$ 419.1642, found 419.1645.

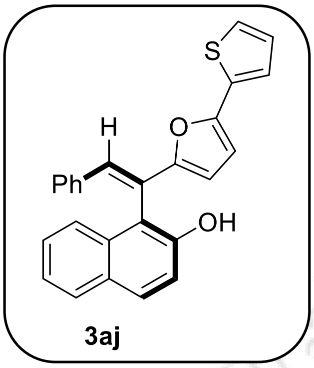
(*E*)-1-(1-(5-(naphthalen-1-yl)furan-2-yl)-2-phenylvinyl)naphthalen-2-ol (3ai)



3ai

Orange sticky solid, yield: 85%, 36.55 mg, **^{1}H NMR (400 MHz, Chloroform-d)** δ 8.50 – 8.46 (m, 1H), 7.91 – 7.87 (m, 2H), 7.87 – 7.85 (m, 2H), 7.85 – 7.83 (m, 1H), 7.79 (s, 1H), 7.78 – 7.74 (m, 1H), 7.56 – 7.51 (m, 3H), 7.40 – 7.32 (m, 3H), 7.23 (d, J = 4.5 Hz, 1H), 7.06 – 7.04 (m, 2H), 7.02 (q, J = 2.7, 2.0 Hz, 2H), 6.63 (d, J = 3.4 Hz, 1H), 5.87 (d, J = 3.4 Hz, 1H), 5.47 (s, 1H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 154.0, 153.9, 150.6, 135.7, 134.2, 133.0, 130.6, 130.4, 129.4, 129.0, 129.0, 128.9, 128.9, 128.7, 128.4, 128.3, 128.1, 127.3, 126.9, 126.4, 126.2, 125.6, 125.5, 124.8, 123.9, 123.0, 117.8, 115.9, 112.2, 112.0. **HRMS (ESI):** m/z calcd. for $C_{32}H_{22}O_2$ $[M+H]^+$ 439.1693, found 439.1689.

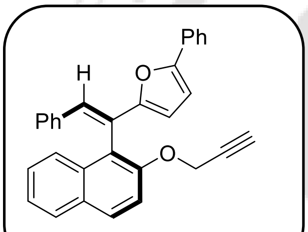
(*E*)-1-(2-phenyl-1-(5-(thiophen-2-yl)furan-2-yl)vinyl)naphthalen-2-ol (3aj)



3aj

Pale yellow sticky solid, yield: 80%, 33.2 mg**, ^{1}H NMR (400 MHz, Chloroform-d)** δ 7.91 – 7.85 (m, 2H), 7.77 (s, 1H), 7.76 – 7.71 (m, 1H), 7.42 – 7.37 (m, 3H), 7.32 (dd, J = 5.1, 1.2 Hz, 1H), 7.28 (d, J = 3.5 Hz, 1H), 7.13 – 7.09 (m, 4H), 7.07 – 7.03 (m, 2H), 6.43 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 3.6 Hz, 1H), 5.44 (s, 1H). **^{13}C{H} NMR (100 MHz, Chloroform-d)** δ 153.0, 150.6, 150.0, 135.7, 133.6, 133.0, 130.6, 129.4, 128.9, 128.9, 128.7, 128.4, 128.1, 128.0, 127.2, 124.9, 124.8, 123.9, 123.3, 122.6, 117.8, 115.75, 112.6, 107.8. **HRMS (ESI):** m/z calcd. for $C_{26}H_{18}O_2S$ $[M+H]^+$ 395.1100, found 395.1106.

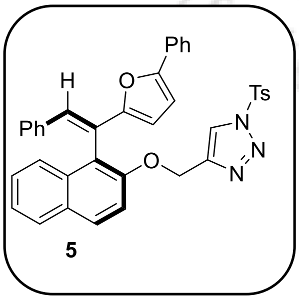
(*E*)-2-phenyl-5-(2-phenyl-1-(2-(prop-2-yn-1-yloxy)naphthalen-1-yl)vinyl)furan (4)



4

Pale whie sticky solid, yield: 90%, 38.3 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.96 (d, J = 9.0 Hz, 1H), 7.88 – 7.81 (m, 2H), 7.81 – 7.75 (m, 2H), 7.69 (s, 1H), 7.52 (d, J = 9.1 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.36 (tt, J = 6.7, 5.1 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.04 – 6.96 (m, 5H), 6.56 (d, J = 3.5 Hz, 1H), 5.70 (d, J = 3.5 Hz, 1H), 4.65 (d, J = 2.4 Hz, 2H), 2.35 (t, J = 2.4 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 154.8, 153.6, 152.8, 136.9, 133.1, 131.0, 130.0, 129.9, 128.9, 128.2, 128.1, 127.6, 127.2, 127.1, 126.7, 125.2, 125.1, 124.6, 124.0, 121.8, 116.0, 111.4, 107.7, 79.3, 75.6, 57.3. **HRMS (ESI):** m/z calcd. for $C_{31}H_{22}O_2$ $[M+H]^+$ 427.1693, found 427.1683.

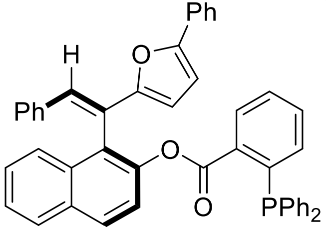
(*E*)-4-(((1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-yl)oxy)methyl)-1-tosyl-1H-1,2,3-triazole (5)



5

White powder, yield: 70%, 43 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.89 (dd, J = 11.2, 8.6 Hz, 2H), 7.82 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 7.5 Hz, 2H), 7.56 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.45 (dd, J = 8.3, 7.0 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.37 – 7.34 (m, 2H), 7.30 – 7.25 (m, 1H), 7.24 (s, 1H), 7.11 (d, J = 7.9 Hz, 3H), 6.99 – 6.94 (m, 1H), 6.89 (dd, J = 13.6, 6.5 Hz, 3H), 6.39 (d, J = 3.2 Hz, 1H), 6.17 (d, J = 16.9 Hz, 1H), 5.86 (d, J = 10.8 Hz, 1H), 5.53 (d, J = 3.4 Hz, 1H), 2.33 (s, 3H). **^{13}C{H} NMR (125 MHz, Chloroform-d)** δ 165.2, 153.8, 153.6, 147.0, 143.3, 138.6, 136.2, 132.6, 132.6, 132.1, 130.8, 129.6, 129.4, 128.9, 128.8, 128.3, 128.3, 127.7, 127.4, 127.4, 127.3, 126.9, 126.4, 126.0, 125.8, 125.2, 124.0, 123.4, 122.1, 112.1, 107.6, 21.7. **HRMS (ESI):** m/z calcd. for $C_{38}H_{29}N_3O_4S$ $[M+H]^+$ 624.1952, found 624.1960.

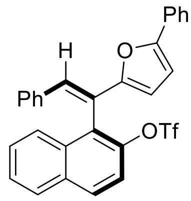
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-yl 2 (diphenylphosphaneyl)benzoate (6)



6

Pale yellow solid**,** yield: 80%, 54 mg, **^{1}H NMR (500 MHz, Chloroform-d)** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.83 (dq, *J* = 8.6, 5.2, 4.5 Hz, 4H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.60 (s, 1H), 7.39 (td, *J* = 7.5, 3.3 Hz, 3H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.20 (tt, *J* = 15.1, 6.4 Hz, 13H), 7.07 (d, *J* = 8.9 Hz, 1H), 6.99 – 6.94 (m, 3H), 6.94 – 6.88 (m, 2H), 6.82 (dd, *J* = 7.7, 4.0 Hz, 1H), 6.42 (d, *J* = 3.6 Hz, 1H), 5.66 (d, *J* = 3.5 Hz, 1H).**^{13}C NMR (125 MHz, Chloroform-d)** δ 164.73, 164.72, 154.13, 153.44, 146.69, 141.83, 141.61, 138.10, 138.00, 137.95, 137.86, 136.45, 134.28, 134.27, 134.17, 134.11, 133.37, 133.23, 132.49, 132.41, 132.01, 131.27, 131.25, 131.01, 129.62, 128.96, 128.93, 128.79, 128.72, 128.66, 128.63, 128.60, 128.57, 128.39, 128.36, 128.30, 127.60, 127.38, 127.30, 127.12, 126.01, 125.79, 125.66, 124.16, 124.03, 122.49, 112.21, 108.02. **HRMS (ESI):** m/z calcd. for $C_{47}H_{33}PO_3$ $[M+H]^+$ 677.2240, found 677.2241.

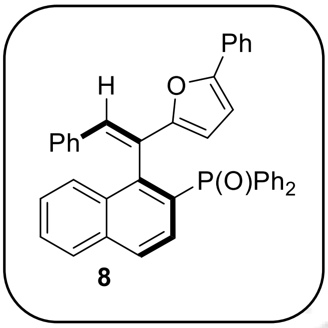
(*E*)-1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-yl trifluoromethanesulfonate (7)



7

Yellow oil**,** yield: 90%, 140.4 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.03 (d, J = 9.1 Hz, 1H), 7.98 (t, J = 8.2 Hz, 2H), 7.78 (d, J = 7.7 Hz, 2H), 7.75 (s, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.49 (dd, J = 8.9, 6.3 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.05 (q, J = 8.4, 7.0 Hz, 3H), 6.89 (d, J = 7.4 Hz, 2H), 6.59 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 3.5 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d**) δ 154.0, 153.5, 144.8, 135.9, 132.9, 132.7, 131.0, 130.7, 128.9, 128.7, 128.5, 128.4, 128.3, 127.8, 127.7, 127.7, 127.5, 126.6, 124.9, 122.3, 119.9, 112.1, 107.6. **^{19}F NMR (471 MHz, Chloroform-d**) δ -74.36. **HRMS (ESI):** m/z calcd. for $C_{29}H_{19}F_3O_4S$ $[M+H]^+$ 521.1029, found 521.1035.

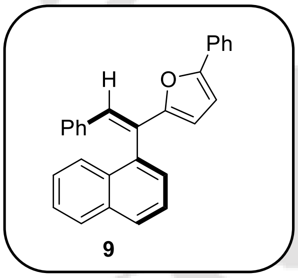
(*E*)-diphenyl(1-(2-phenyl-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-yl)phosphine oxide (8)



8

White powder, yield: 75%, 43 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 8.06 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.85 (t, J = 2.1 Hz, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.35 (dd, J = 12.0, 7.5 Hz, 5H), 7.30 (d, J = 7.7 Hz, 2H), 7.20 – 7.12 (m, 4H), 7.06 – 7.04 (m, 1H), 7.01 (t, J = 7.5 Hz, 2H), 6.90 (d, J = 1.9 Hz, 1H), 6.71 (d, J = 7.6 Hz, 2H), 6.51 (d, J = 3.7 Hz, 1H), 5.62 (d, J = 3.5 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d**) δ 154.87, 153.02, 140.01, 139.94, 136.27, 134.85, 134.84, 134.13, 133.30, 133.22, 132.45, 132.37, 132.18, 132.10, 131.47, 131.45, 131.40, 131.37, 130.87, 129.95, 129.87, 129.40, 128.86, 128.64, 128.58, 128.45, 128.43, 128.08, 127.98, 127.92, 127.65, 127.58, 127.55, 127.35, 127.03, 126.17, 126.13, 124.04, 112.89, 107.72. **HRMS (ESI):** m/z calcd. for $C_{40}H_{29}PO_3$ $[M+H]^+$ 573.1978, found 573.1978.

(*E*)-2-(1-(naphthalen-1-yl)-2-phenylvinyl)-5-phenylfuran (9)

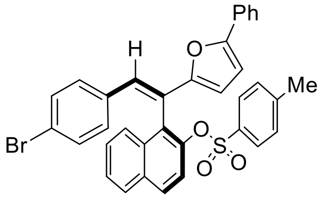


9

Pale yellow solid, yield: 80%, 29.7 mg, **^{1}H NMR (500 MHz, Chloroform-d)** δ 7.96 – 7.90 (m, 3H), 7.78 (d, J = 7.7 Hz, 2H), 7.60 (s, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.40 – 7.36 (m, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.01 (dd, J = 5.2, 2.2 Hz, 3H), 6.93 – 6.87 (m, 2H), 6.56 (d, J = 3.5 Hz, 1H), 5.67 (d, J = 3.5 Hz, 1H). (d, J = 9.1 Hz, 1H), 7.98 (t, J = 8.2 Hz, 2H), 7.78 (d, J = 7.7 Hz, 2H), 7.75 (s, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.49 (dd, J = 8.9, 6.3 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.05 (q, J = 8.4, 7.0 Hz, 3H), 6.89 (d, J = 7.4 Hz, 2H), 6.59 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 3.5 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d**) δ 155.5, 153.7, 136.6, 135.5, 134.1, 132.1, 130.9, 129.5, 129.3, 128.9, 128.6, 128.5, 128.3, 127.8, 127.7, 127.1, 126.6, 126.3, 126.1, 126.0, 125.9, 124.1, 112.2, 107.6. **HRMS (ESI):** m/z calcd. for $C_{28}H_{20}PO_3$ $[M+H]^+$ 373.1587, found 373.1597.

(*E*)-1-(2-(4-bromophenyl)-1-(5-phenylfuran-2-yl)vinyl)naphthalen-2-yl 4-methylbenzenesulfonate (10)

White solid**,** yield: 95%, 59 mg,

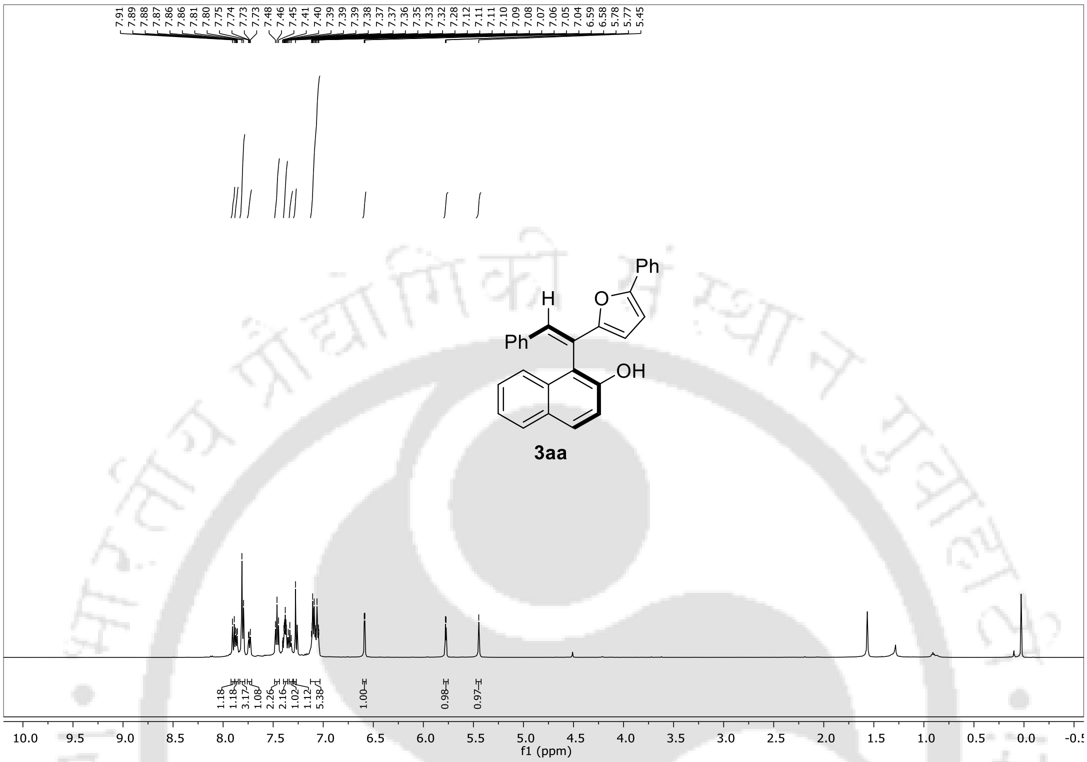


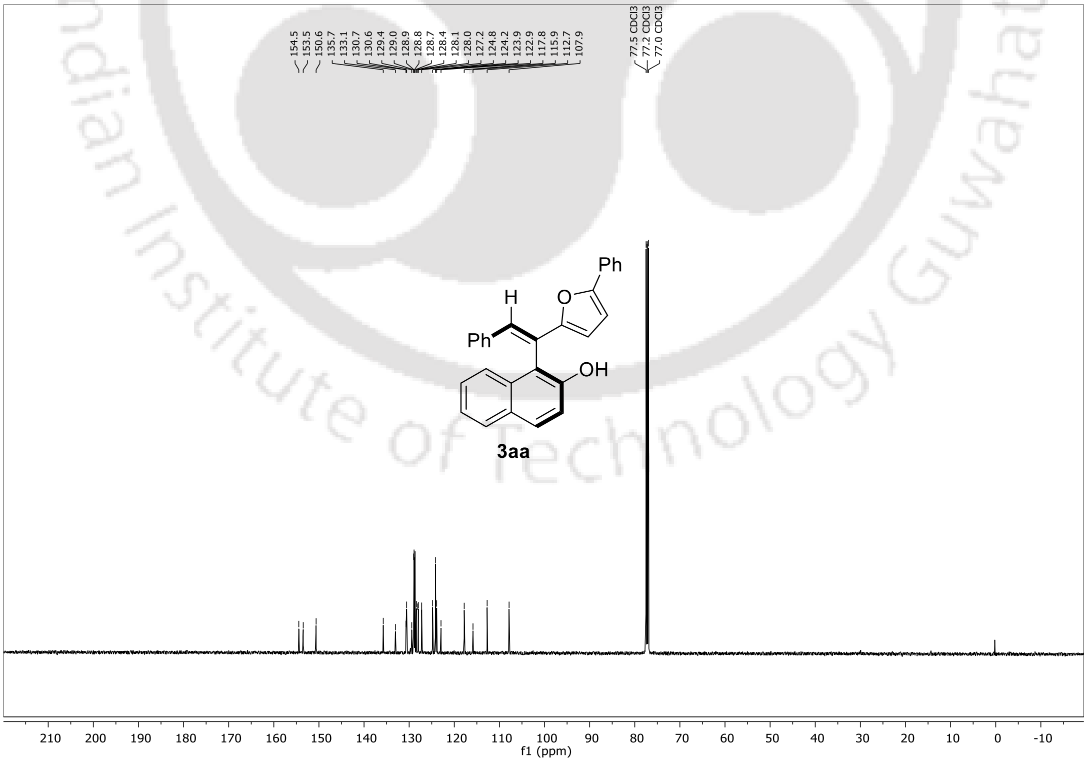
10

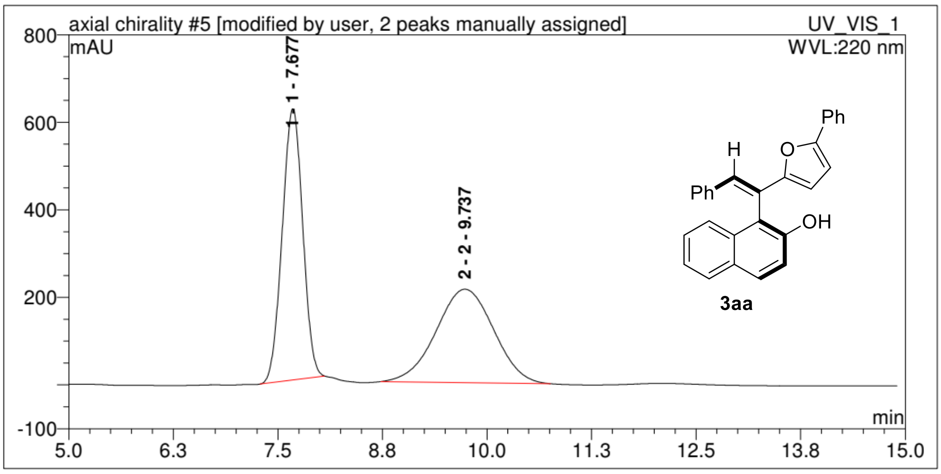
^{1}H NMR (500 MHz, Chloroform-d) δ 7.96 – 7.90 (m, 3H), 7.78 (d, J = 7.7 Hz, 2H), 7.60 (s, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.4 Hz, 1H), 7.46 – 7.41 (m, 3H), 7.40 – 7.36 (m, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.01 (dd, J = 5.2, 2.2 Hz, 3H), 6.93 – 6.87 (m, 2H), 6.56 (d, J = 3.5 Hz, 1H), 5.67 (d, J = 3.5 Hz, 1H). (d, J = 9.1 Hz, 1H), 7.98 (t, J = 8.2 Hz, 2H), 7.78 (d, J = 7.7 Hz, 2H), 7.75 (s, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.49 (dd, J = 8.9, 6.3 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H), 7.05 (q, J = 8.4, 7.0 Hz, 3H), 6.89 (d, J = 7.4 Hz, 2H), 6.59 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 3.5 Hz, 1H). **^{13}C{H} NMR (125 MHz, Chloroform-d**) δ 155.5, 153.7, 136.6, 135.5, 134.1, 132.1, 130.9, 129.5, 129.3, 128.9, 128.6, 128.5, 128.3, 127.8, 127.7, 127.1, 126.6, 126.3, 126.1, 126.0, 125.9, 124.1, 112.2, 107.6. **HRMS (ESI):** m/z calcd. for $C_{35}H_{25}BrO_4S$ $[M+H]^+$ 621.0730, found 621.0730.

6.8 NMR and HPLC spectra:

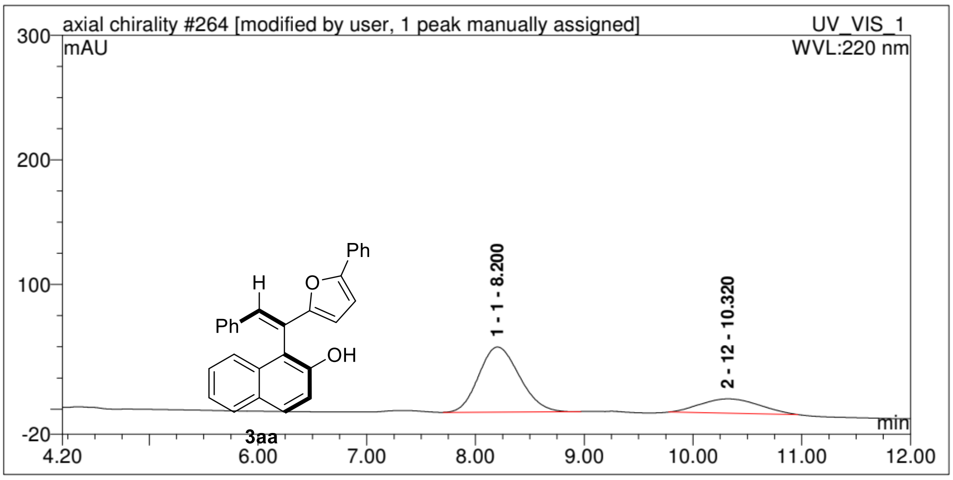
^{1}H and ^{13}C{H} spectra of compound 3aa:





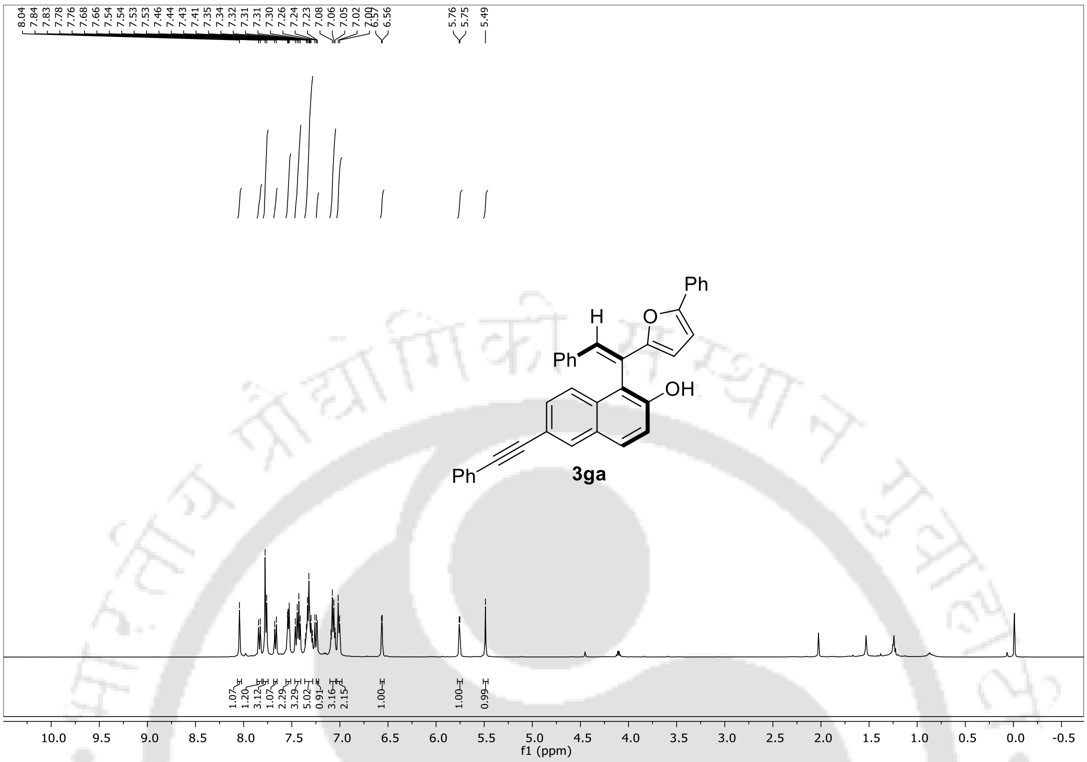


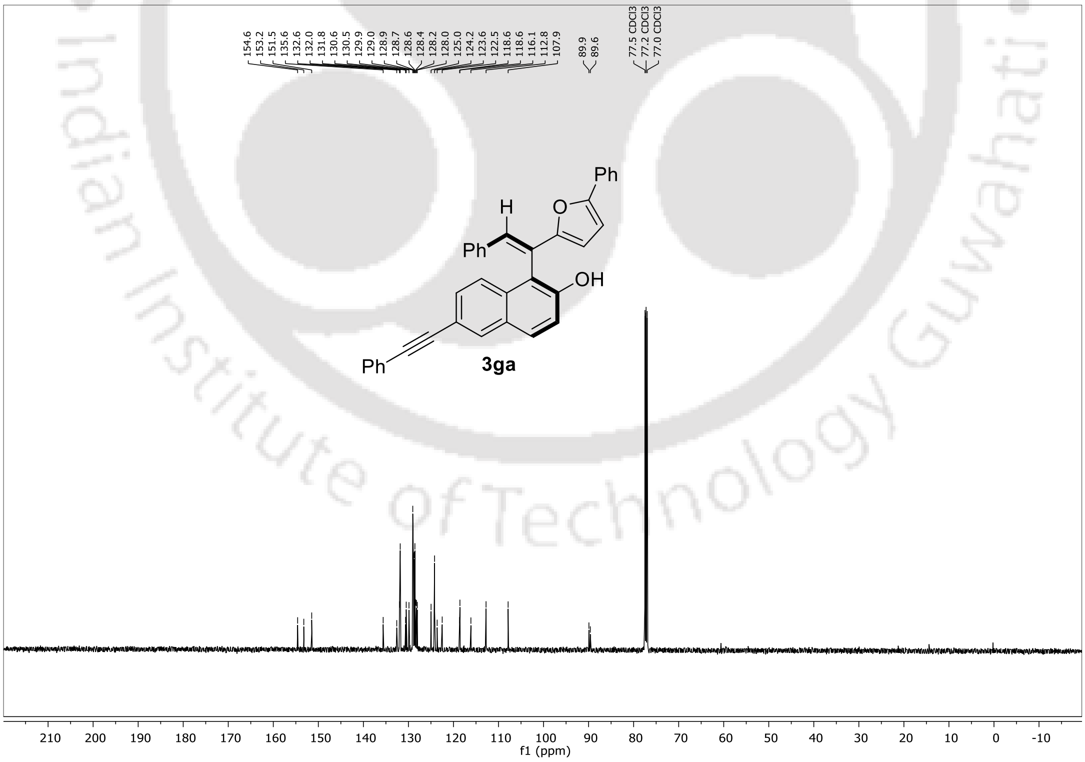
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	7.68	176.0151	50.7728353	619.8133	n.a.
2	2	9.74	170.657	49.2271647	213.494	n.a.

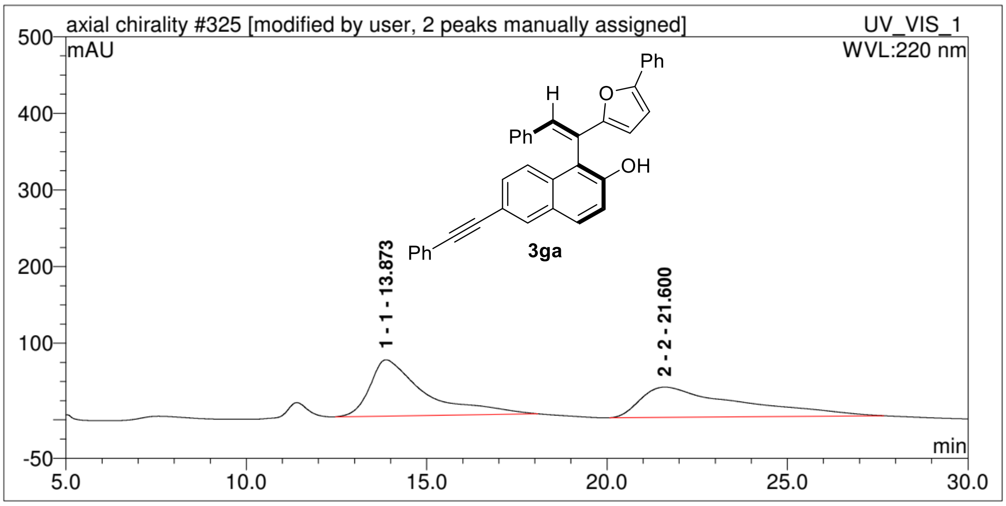


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.20	22.52492	75.67820096	52.14151	n.a.
2	12	10.32	7.239	24.32179904	11.521	n.a.

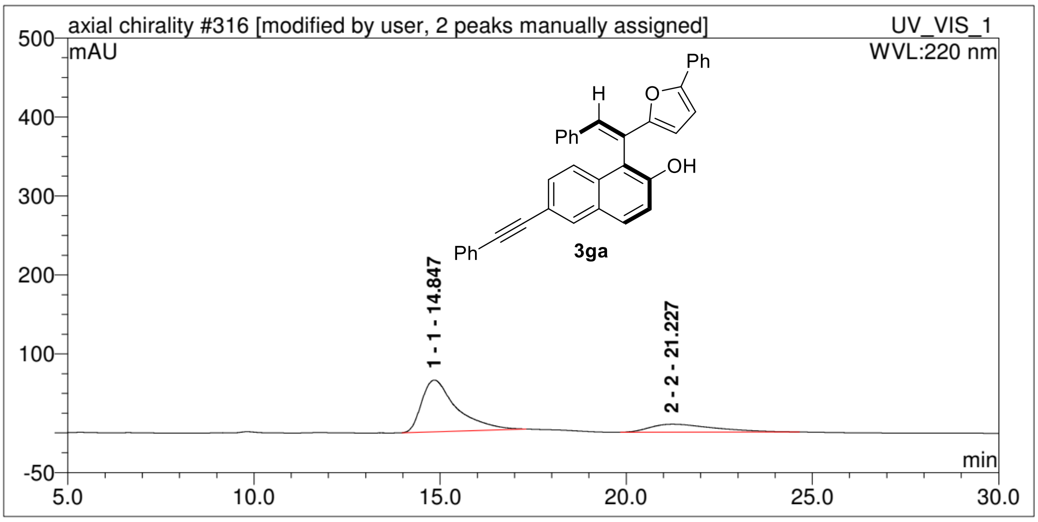
^{1}H and ^{13}C{H} spectra of compound 3ga:





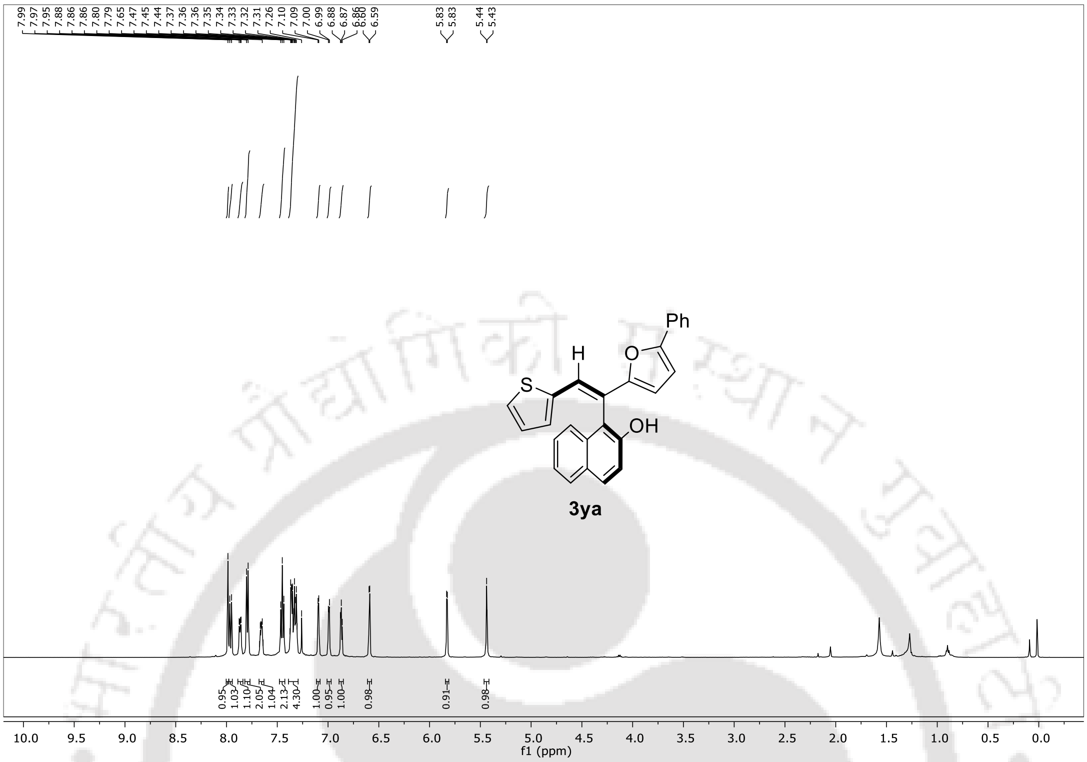


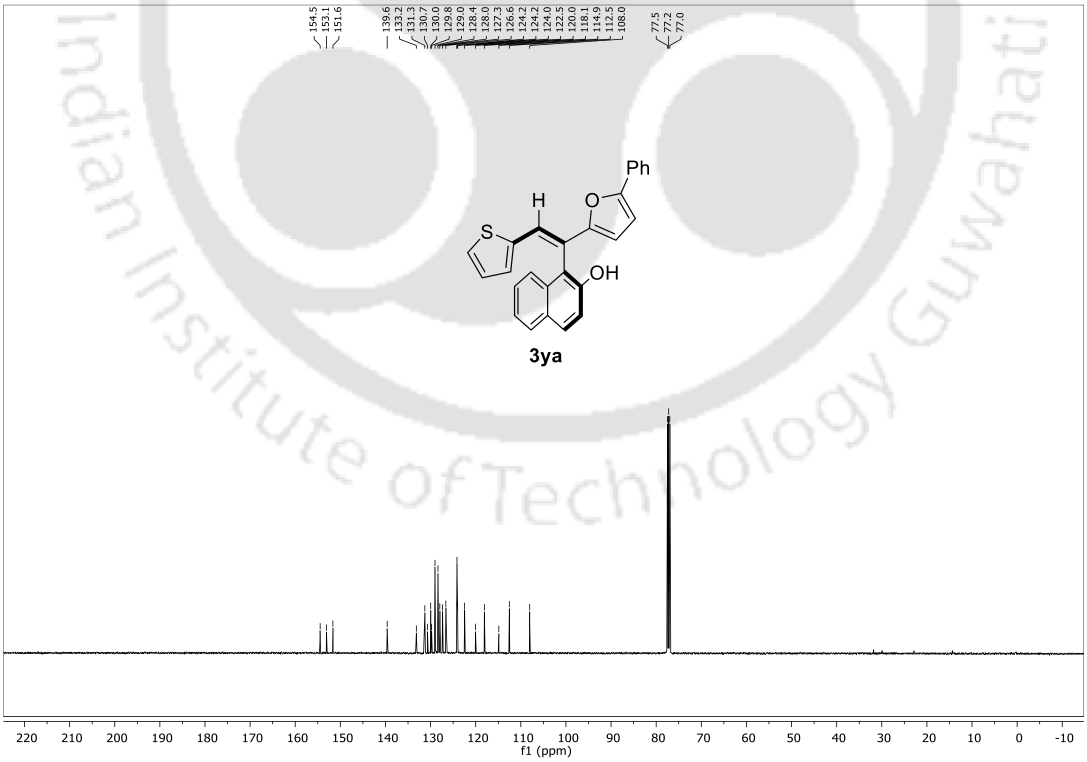
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	13.87	128.5724	50.7950089	73.42131	n.a.
2	2	21.60	124.548	49.2049911	39.426	n.a.

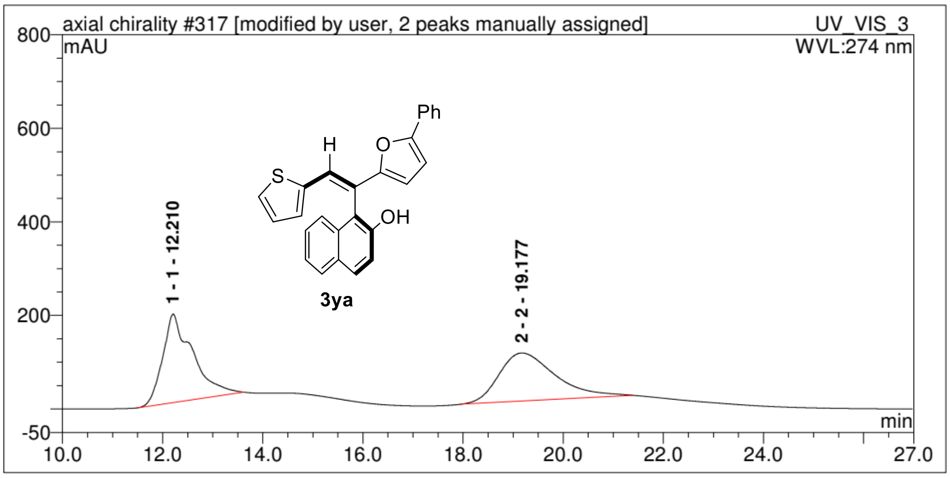


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.85	70.80262	77.65960445	65.37815	n.a.
2	2	21.23	20.368	22.34039555	10.147	n.a.

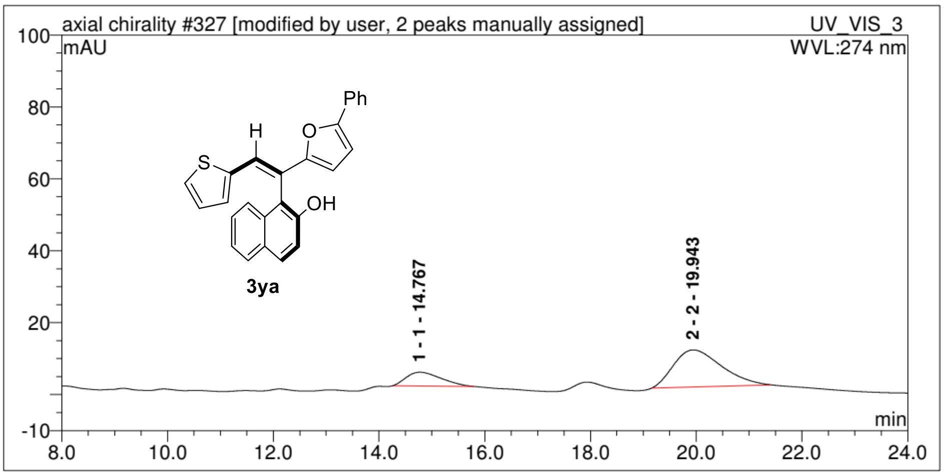
^{1}H and ^{13}C{H} spectra of compound 3ya:





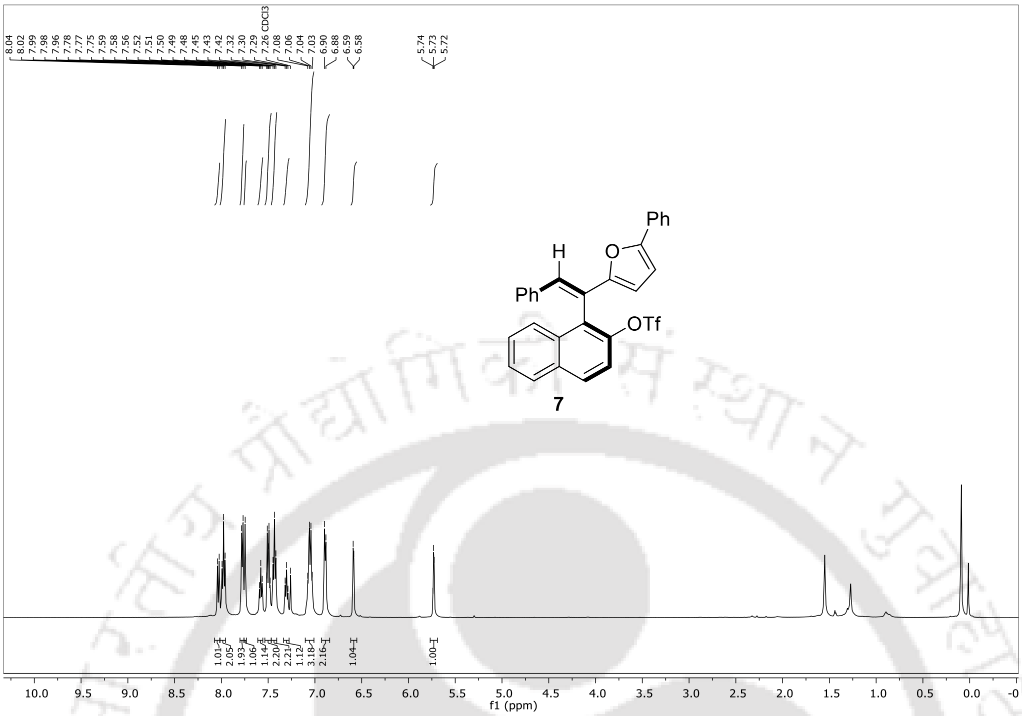


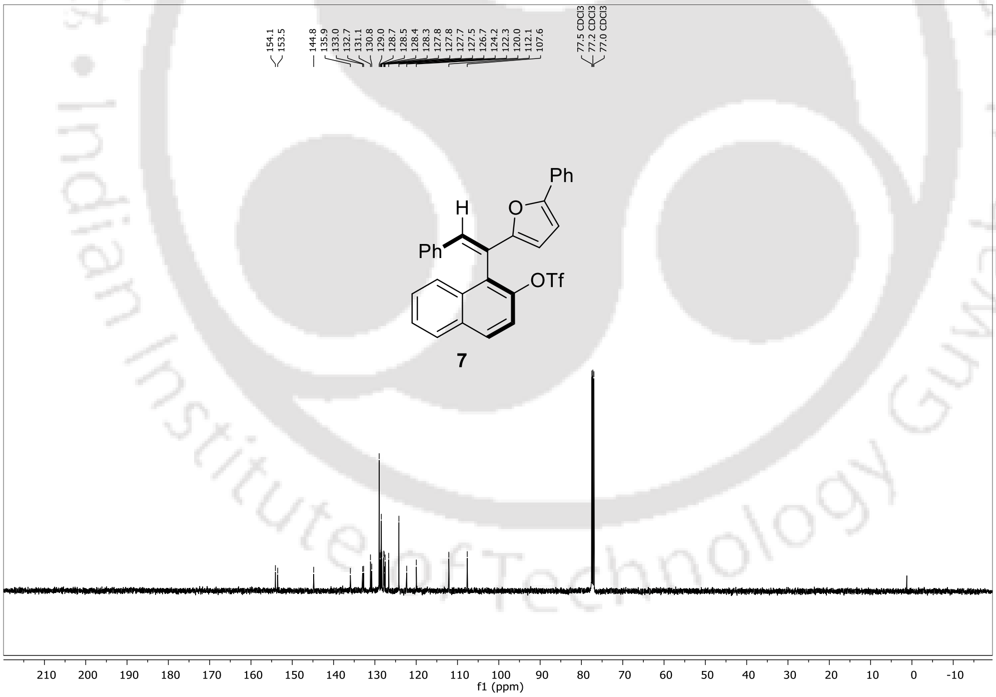
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	12.21	131.5902	49.63729744	189.3699	n.a.
2	2	19.18	133.513	50.36270256	102.733	n.a.

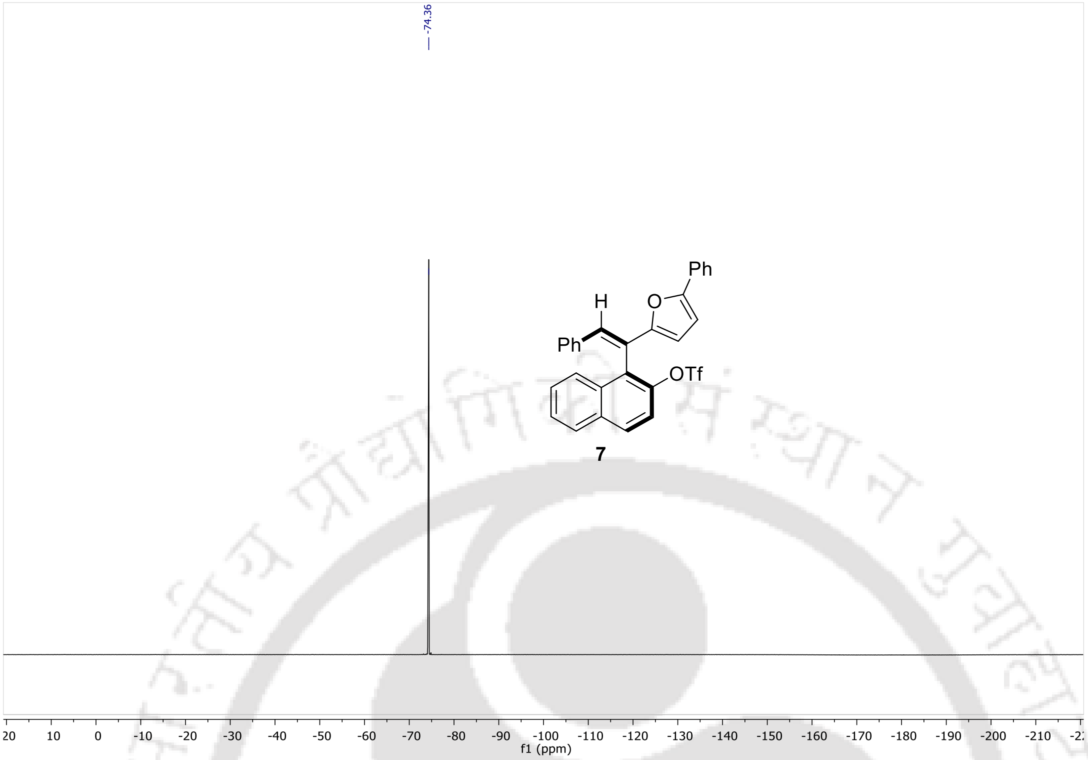


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	14.77	2.879722	21.02388999	3.79648	n.a.
2	2	19.94	10.818	78.97611001	10.305	n.a.

^{1}H, $^{13}C\{H\}$, ^{19}F spectra of compound 7:






-74.36
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-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

6.9 References

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List of publications and presentations

1. α-Nitro-α, β-Unsaturated Ketones: An Electrophilic Acyl Transfer Reagent in Catalytic Asymmetric Friedel–Crafts and Michael Reactions, C. Parida, R. Maity, S. C. Sahoo, S. C. Pan*, *Org. Lett.* **2019**, *21*, 6700.
2. Organocatalytic Asymmetric Synthesis of Spirooxindole Embedded Oxazolidines, C. Parida, B. Mondal, A. Ghosh, S. C. Pan*, *J. Org. Chem.* **2021**, *86*, 13082.
3. Organocatalytic Asymmetric Addition of Aromatic α-Cyanoketones to o-Quinone Methides: Synthesis of 3,4-Dihydrocoumarins and Tetrasubstituted Chromans, C. Gharui, C. Parida, S. C. Pan*, *J. Org. Chem.* **2021**, *86*, 13071.
4. Organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2, 3-diones, C. Parida, S. C. Pan*, *Beilstein J. Org. Chem.* **2021**, *17*, 1447.
5. Organocatalytic Asymmetric *Ene* Reactions, M. Balha$^{\neq}$, C. Parida$^{\neq}$, S. C. Pan*, *Asian J. Org.Chem.* **2021**,*10*, 2440 (≠ contributed equally).
6. Organocatalytic Asymmetric Dearomatization Reaction for the Construction of Axially Chiral Urazole Embedded Naphthalenones, C. Parida, S. K. Dave, K. Das, S. C. Pan*, *Adv. Synth. Catal.* **2023**, *365*, 1185. (This article selected for very important publication)
7. Organocatalytic Synthesis of Furan Embedded Styrene Atropisomers, C. Parida, S. C. Pan*, *Manuscript under preparation*.

Presentations

- Participated In the poster presentation On "Chemical Research Society of India (CRSI)-2019", Organized by Department of Chemistry, Indian Institute of Technology Kanpur, Utter Pradesh, India. [July 2019]
- Participated in the poster presentation in "International Conference on Chemistry for Human Devlopment (ICCHD)" Organised by Dperatment of Chemistry, Culcutta university, WestBengal, India. [January 2020]
- Participated in the poster presentation in "Chemical Research Society of India (CRSI)-2022", Organized by Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, Assam, India. [Mar 2022]