Organocatalytic acyl transfer reaction of 1,3-diketones and convenient synthesis of Pyrazolone derivatives

A thesis

submitted for the degree of

Doctor of Philosophy

By

Nimisha Bania
Roll. No. 156122007

Under the guidance of
Prof. Subhas Chandra Pan

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, Assam, India

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June 2022

In matters of science, a thousand proclamations by so-called experts are outweighed by the humble reasoning of a single individual.

- Galileo Galilei

Dedicated to my family

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry

Declaration

*The work in this thesis entitled "***Organocatalytic acyl transfer reaction of 1,3-diketones and convenient synthesis of Pyrazolone derivatives***" has been carried out by me under the supervision of Prof. Subhas Chandra Pan, Department of Chemistry, Indian Institute of Technology Guwahati. No part of this thesis has been submitted elsewhere for award of any other degree or qualification. The research works have been carried out in the period from August 2015 to December 2021. In keeping with general practice of reporting scientific observations, due acknowledgments have been made wherever the work described is based on the findings of other investigations.*

Place: *IIT Guwahati*
Date: *03/06/2022*

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Certificate

This is to certify that the research work contained in this thesis entitled "**Organocatalytic acyl transfer reaction of 1,3-diketones and convenient synthesis of Pyrazolone derivatives**" by Miss Nimisha Bania, a Ph.D. student of the Department of Chemistry, IIT Guwahati was carried out under my supervision. This work is original and has not been submitted elsewhere for award of any degree.

Place: IIT Guwahati
Date: 03/06/2022

Prof. Subhas Chandra Pan
Supervisor

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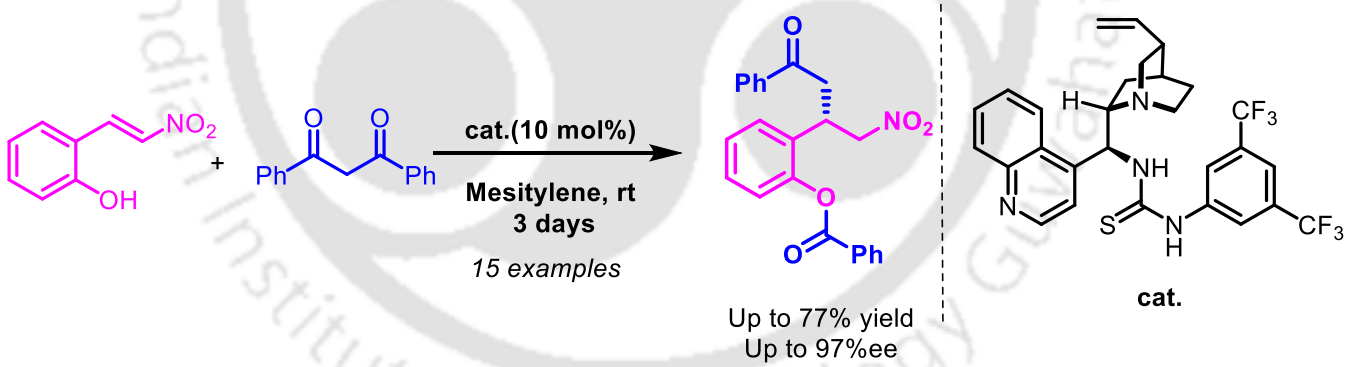
I thank all the people who have been in direct or indirect association with me for my research work and have helped me in even the slightest possible manner. Above all, I thank the Divine for everything - just everything.

Abstract

The contents of the present thesis entitled as "***Organocatalytic acyl transfer reaction of 1,3-diketones and convenient synthesis of Pyrazolone derivatives***" has been divided into five chapters based on the results achieved from the experimental works performed during the entire course of the Ph.D. research programme.

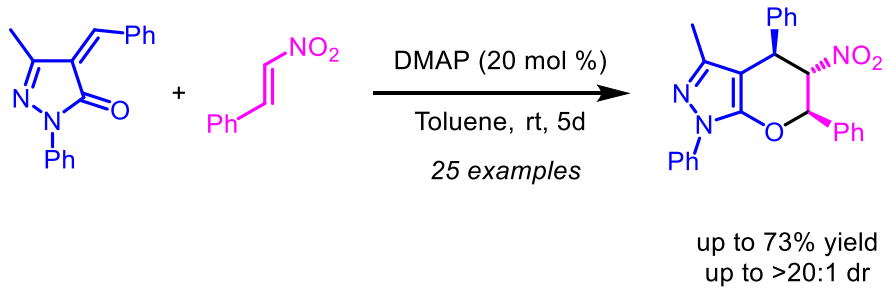
Chapter I of this thesis gives a brief review of Organocatalytic Michael reaction and Rauhut Currier reactions. This chapter mainly focuses on cinchona-derived catalysts as they were utilized primarily in the demonstrated works. A brief discussion has also been made on the Pyrazolone moiety.

Chapter II describes the bifunctional thiourea catalyzed asymmetric organocatalytic Michael/Hemiketalization/ Retro-Aldol Reaction between 1,3-diketones and (E)-2-(2-nitrovinyl) phenols. Using Cinchonidine derived thiourea catalysts, high yields and excellent enantioselectivities were obtained (Scheme 1).



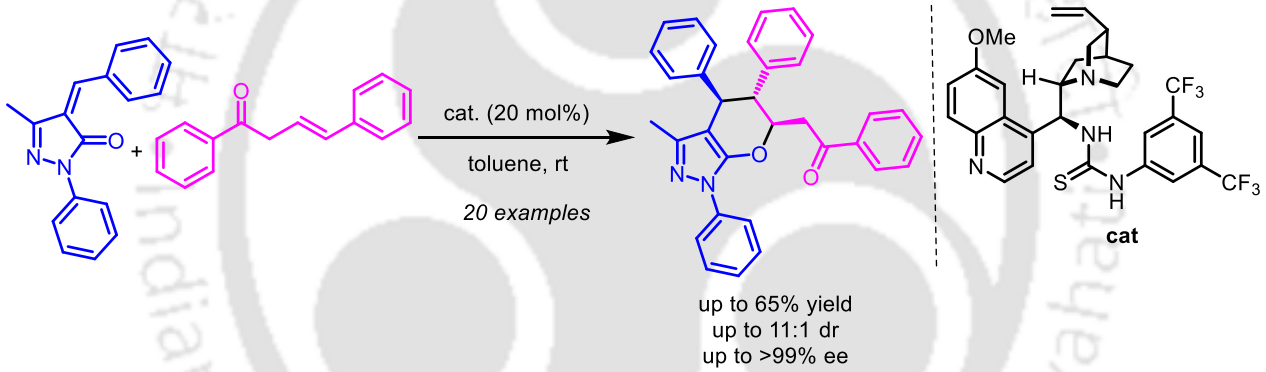
Scheme 1

Chapter III demonstates DMAP Catalyzed Domino Rauhut-Currier Cyclization Reaction between Alkylidene Pyrazolones and Nitro-olefins to give Tetrahydropyrano[2,3-c]Pyrazoles. The products were obtained in moderate to high yields with excellent diastereoselectivities under ambient reaction conditions with DMAP catalyst. Chiral DMAP catalysts were used to perform a preliminary catalytic asymmetric variant (Scheme 2).



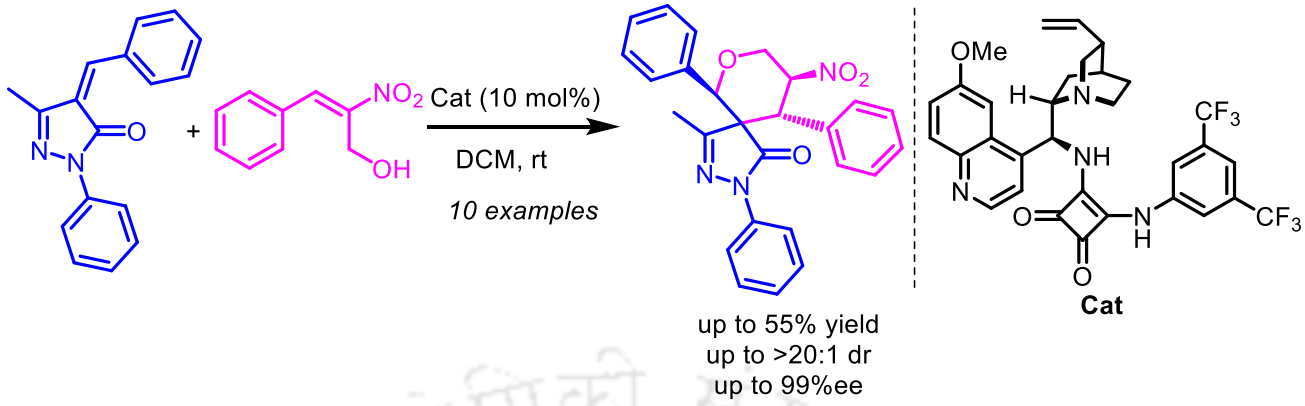
Scheme 2

Chapter IV presents an Organocatalytic Asymmetric Inverse-Electron-Demand Oxa-Diels-Alder Reaction of Allyl Ketones with unsaturated pyrazolones. Quinine derive thiourea catalysts were used to form tetrahydropyrano[2,3-c]pyrazole products with in moderate to good yields with high diastereo- and enantioselectivities under ambient reaction conditions (Scheme 3).



Scheme 3

Chapter V describes Quinine derived squaramide catalyzed synthesis of spiro-tetrahydropyran-pyrazolones via Organocatalytic asymmetric oxa-Michael-Michael reaction between 3-aryl-2-nitroprop-2-enols and unsaturated pyrazolones. The products were furnished in acceptable yields with perfect diastereomeric ratios as well as good to excellent enantioselectivities. This is the first report of utilization of 3-aryl-2-nitroprop-2-enol as O-nucleophile in enantioselective catalysis (Scheme 4).



Scheme 4

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
anh.	Anhydrous
aq.	Aqueous
Å	Angstrom
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
br.	Broad
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
Bu	Butyl
CCDC	Cambridge crystallographic data centre
COSY	Correlation spectroscopy
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
^{o}C	Degree Celsius
d	Doublet or day
δ	Chemical shift or delta
DACH	*trans*-(1,2)-Diaminocyclohexane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
δ	Delta
EtOAc	Ethyl acetate
ee	Enantiomeric excess
er	Enantiomeric ratio
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
EDG	Electron donating group
FT-IR	Fourier-transform infrared spectroscopy
g	Grams
γ	Gamma
h	Hours

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

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General Information:

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra are recorded on 500/600 MHz spectrometer. ^{13}C NMR spectra were recorded on 126/151 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak is used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity is indicated as follows**:** s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants are reported in Hertz (Hz). Using ESI mode HRMS spectra wewre recorded. For visualizing the products, UV light and I_2 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).

Chapter 1: Introduction

Chapter I. Introduction

1.1 Asymmetric synthesis:

Asymmetric synthesis is a chemical reaction, which affects the structural symmetry in the molecules of a compound resulting unequal proportions of compounds and a new chiral stereogenic unit is created. It is a subclass of stereoselective reactions. The new stereogenic unit can be a chiral centre, a chiral axis or a chiral plane. Enantiomerically pure compounds are important in pharmaceutical industry, academics and others and as such the development of methods for acquiring them attracts the attention. Different diastereomers or enantiomers show different biological properties, as S-Dopa helps to restore nerve function in human body; R-Dopa is toxic in nature. Developments of new asymmetric synthetic methodologies are highly essential due to the growing demand of chiral molecules. Two synthetic approaches such as chiral pool synthesis or chiral auxiliary approaches were used to synthesize enantiopure natural products and drugs. The targeted optically active molecules can be synthesized from naturally occurring enantiomerically pure compounds in chiral pool strategy whereas in case of chiral auxiliary approach, chiral inducing agent can be temporarily incorporated in an achiral substrate to form enantiomerically enriched compound through stereoselective reaction with the substrate followed by release of the catalyst. In asymmetric catalysis, a chiral catalyst directs the formation of a chiral compound such that formation of one particular stereoisomer is favored. Asymmetric synthesis can be categorized 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, making the processes expensive. However, catalyst-controlled methods are economical and sustainable. Based on the nature of catalysts used, catalyst-controlled methods can be classified into three main categories:

i) Biocatalysis

ii) Metal catalysis and

iii) Organocatalysis

Ezymes or other biological catalysts are used in biocatalysis, for regio-, chemo- and stereoselective transformations. Usually mild reaction conditions are required in this process. However, there are few drawbacks of biocatalysts as they are substrate specific, sensitive to high pH and temperature

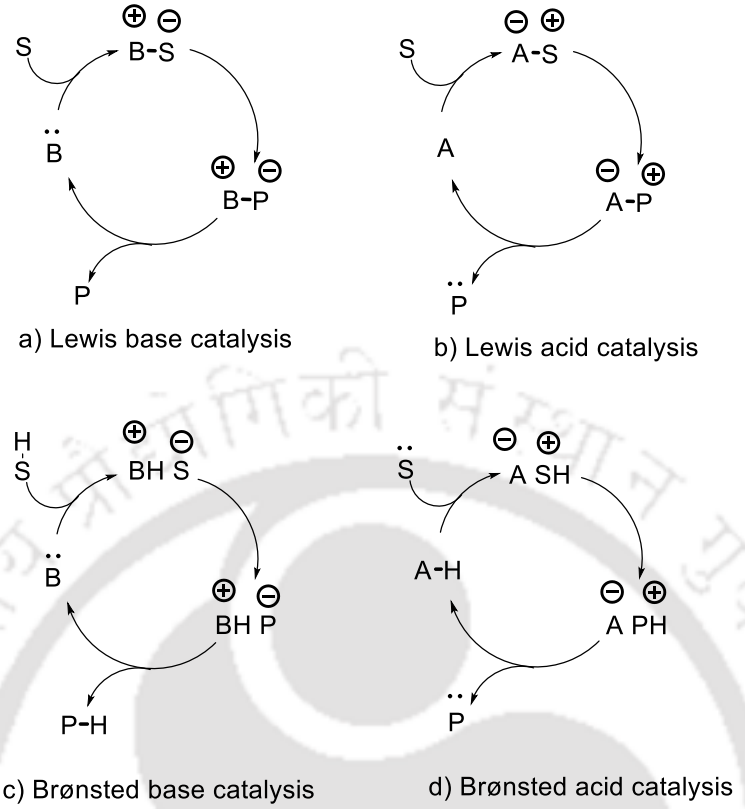
and most importantly, the unavailability of the enzyme for synthesizing the opposite enantiomer as enzymes exist in nature as single enantiomeric form.[1]

In metal catalysis, organometallic catalysts have become the most actively studied due to unthinkable transformations that could be easily performed. Transformations such as asymmetric hydrogenation, epoxidation and dihydroxylation of olefins, cross-coupling reactions, olefin metathesis etc are commonly known. But, due to highy toxicity and laborious removal of trace metal impurities, transition-metal catalysis face the drawbacks.[2]

Organocatalysis is the third general approach and has had a significant impact in chemical synthesis. Organocatalysis is the process of accelerating chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element in their active principle.[3]

1.2. Asymmetric organocatalysis

Until year 2000, we knew only about two classes of chiral catalysts enzyme, that speed up in essence all reactions in living organisms, and metal complexes which were tremendously used in asymmetric synthesis. However, in the year 2000, organocatalysis became prominent. Then Benjamin List and David W C MacMillan independently reported that we can use small organic molecules to do the same job as big enzymes and metal catalysts and used in reactions that are precise, cheap and environmentally safe. Asymmetric organocatalysis is an economical and environment-friendly process where a purely organic small molecule is used to catalyze organic transformations. Organocatalysts are advantageous as they are usually non-toxic, robust, bench-stable, inexpensive and in certain cases commercially available. Organocatalysts have attracted increasing attention, particularly of synthetic organic chemists for the preparation of pharmaceutical products that do not contain metal contamination.



Scheme 1: Different modes of organocatalysis.

Organocatalysis can be classified into four types such as Lewis base, Lewis acid, Bronsted base and Bronsted acid.[4] But, in terms of mechanistic way organocatalysts are mainly divided into two types, covalent and non-covalent bonding catalysis. In covalent bonding catalysis, substrates interact with catalyst via covalent bond either by Lewis acid-Lewis base reaction or formation of imine/enamine intermediates. Whereas, in the non-covalent bonding catalysis, reactants and catalysts interact through hydrogen bonding or formation of ion pair intermdediates.

In a Lewis base catalysis, the reaction is initiated by the nucleophilic addition of the catalyst (**B:**) to the substrate (**S**) and the resulting complex undergoes a reaction followed by release of the product (**P**) and catalyst regeneration for further turnover (Scheme 1a). In Lewis acid catalysis, the catalyst (**A**) activates nucleophilic substrates (**S:**) to form an activated complex (Scheme 1b). After the reaction, product (**P:**) is released and catalyst in a similar manner. Brønsted base catalytic cycles are initiated by partial or full deprotonation of the substrate (**S-H**) by the catalyst (**B:**) followed by the chemical transformation to give the product (**P-H**) and regeneration of the catalyst (Scheme 1c). Similarly Brønsted acid catalytic cycles start with partial or full protonation of the

substrate (**S:**) by the catalyst (**A-H**) and the resulting ion-pair reacts to give the product (**P:**) followed by the catalyst regeneration (Scheme 1d).

1.2.1. Bifunctional (thio)urea catalysts:

Activation of a substrate or an intermediate by organocatalysts may not always be restricted to any individual mode. Presence of different functional groups in the same catalyst result in more than one mode of activation which can operate synergistically. Such catalysts are termed as multifunctional organocatalysts.[5] The major domain of multifunctional catalysis is occupied by bifunctional catalysis[6] and used to provide dual activation of nucleophile and electrophile with two activating sites, either through hydrogen bonding or Brønsted acid-Lewis/Brønsted base activation (Figure 1).

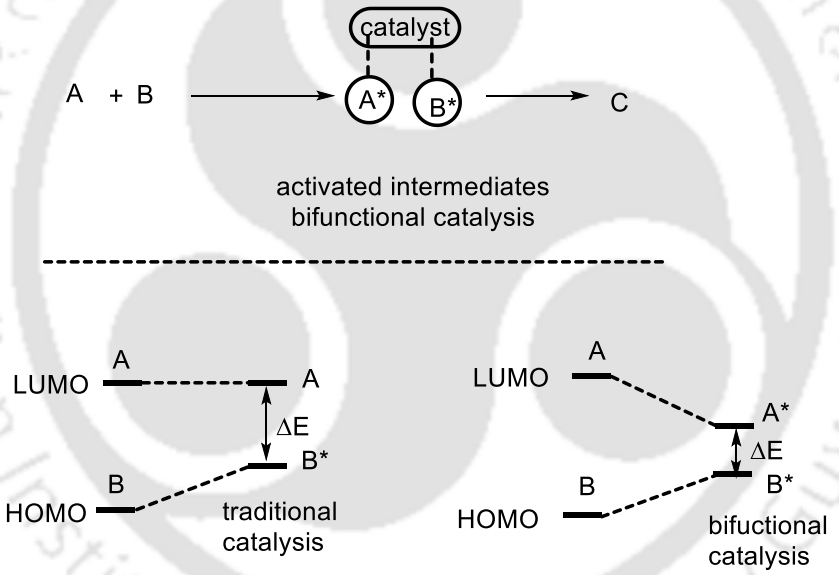
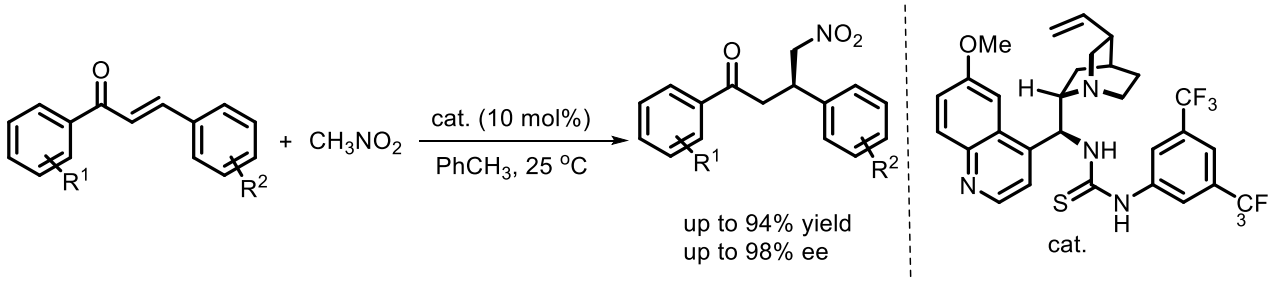


Figure 1. The concept of bifunctional catalysis.

In 2005, Soós and co-workers developed a cinchona alkaloid derived bifunctional thiourea catalyst and their application in the asymmetric Michael addition of nitromethane to chalcones (Scheme 2).[7] In the same year, similar type of cinchona- derived bifunctional thiourea catalyzed asymmetric Michael addition of malonates to nitroolefins was independently disclosed by Dixon and Connon group.[8]



Scheme 2: Asymmetric Michael addition of nitromethane to chalcones using quinine-derived bifunctional thiourea organocatalyst by Soós et al.

1.2.2. Bifunctional squaramides

Squaramide catalysts emerged as an effective alternative to urea/thiourea and guanidine catalysts. Also, squaramide functionality differs significantly from its closest urea or thiourea analogues in several aspects. Squaramide acts as a ditopic binder as it contains two H-bond donor (N-H) and two H-bond acceptor (C=O) functionalities in the same molecular framework (Figure 2a).[9] The N-H acidity of squaramide is higher than urea/thiourea derivative due to their vinylogous amide nature. The delocalization of nitrogen lone pair occurs through carbon-oxygen double bond thus providing a polarized nitrogen moiety. Hence, the squaramide scaffold is more rigid, which accounts for limited conformational changes (Figure 2b).[10]

In the case of squaramide the distance between the two NH groups (~2.72 Å) is about 0.6 Å longer than that of thiourea (~2.13 Å). The pKa value of squaramide is lower compared to its thiourea and urea analogous. In the case of squaramide further delocalization occurrs through cyclobutenedione system and it leads to stronger hydrogen-bonding and increased catalytic activity (Figure 2c and 2d).

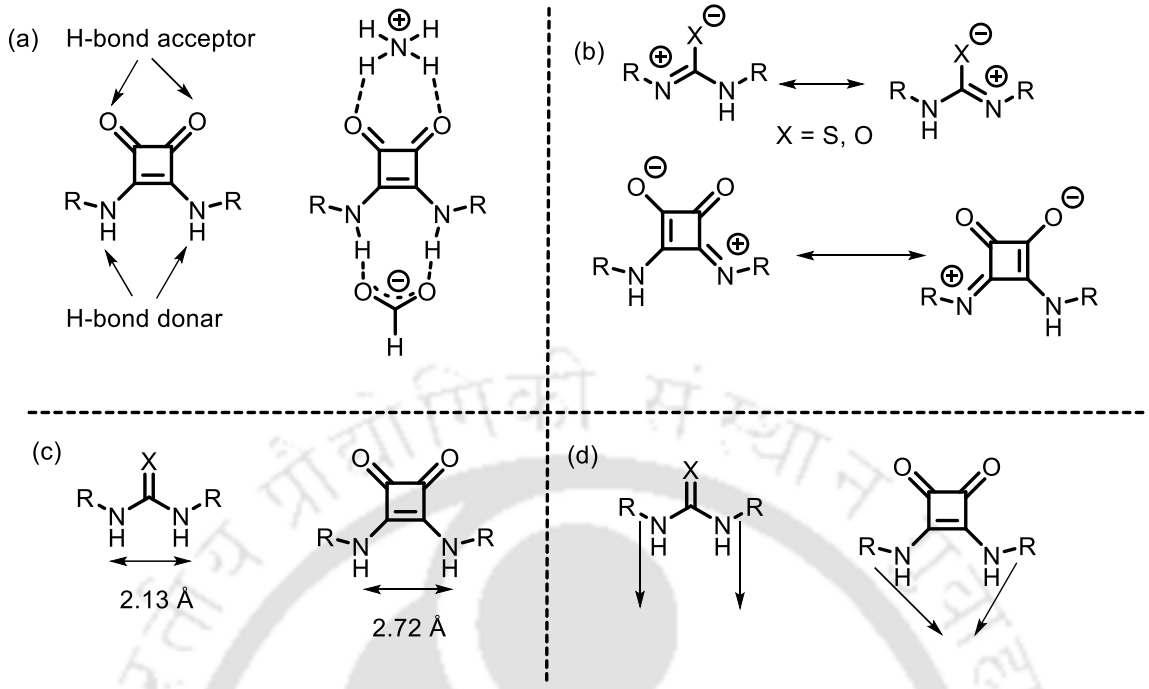
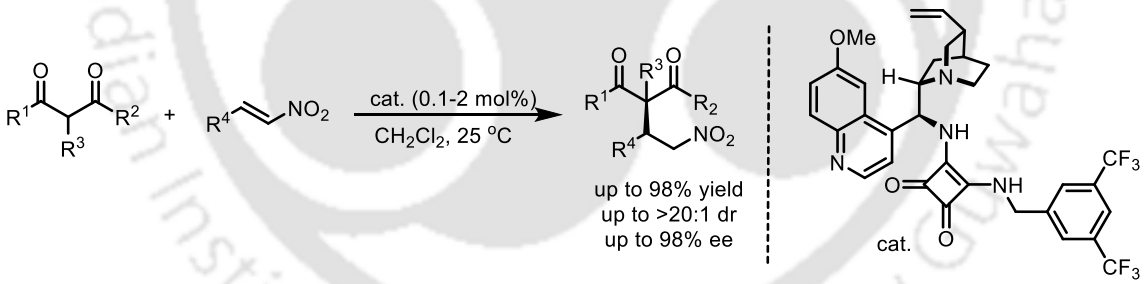


Figure 2: Comparison between squaramide and (thio)urea.

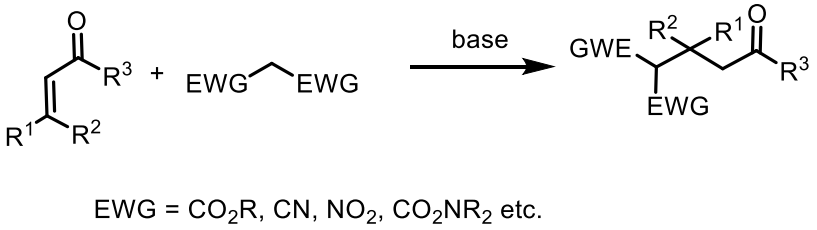
Rawal and co-workers first reported cinchona alkaloid derived bifunctional squramide catalyzed enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins. (Scheme 3).[11]



Scheme 3: The first bifunctional squaramide catalyzed reaction by Rawal et al.

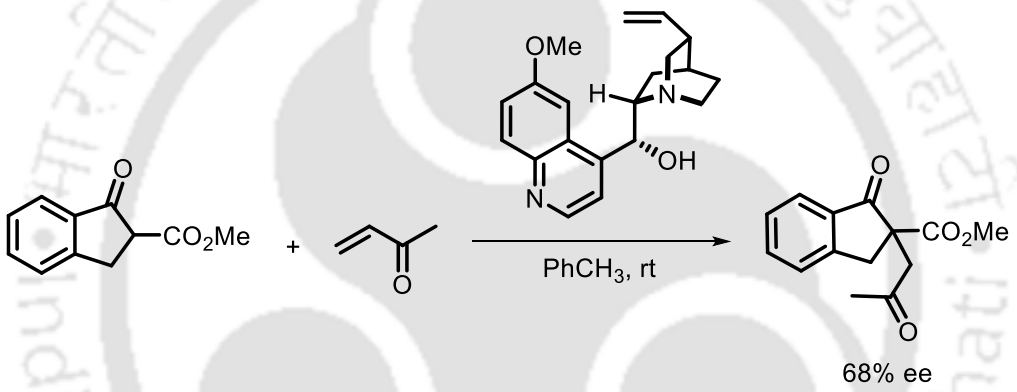
1.3. Michael reaction

The Michael reaction is one of the most important reactions in organic chemistry. It is the nucleophilic addition of a carbanion or another nucleophile to an unsaturated carbonyl compound containing an electron-withdrawing group. Arthur Michael first discovered Michael addition in 1887, by reaction between ethyl malonates and ethyl esters of cinnamic acid, in presence of sodium acetate base (Scheme 4).[12]



Scheme 4: The Michael reaction.

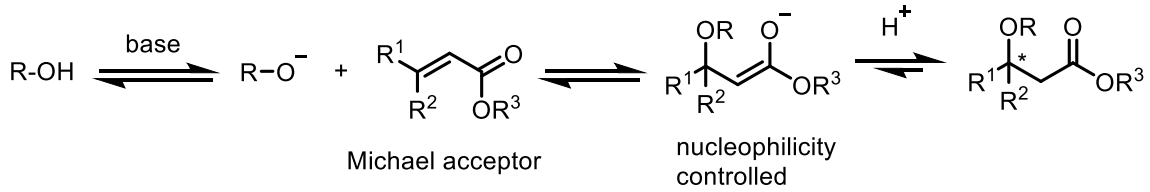
In 1975, Wynberg discovered the first organocatalytic Michael addition, by addition of 1-oxo-2-indanecarboxylate to methyl vinyl ketone catalyzed by optically active quinine. The desired product was obtained in 68 % ee (Scheme 5).[13]



Scheme 5: The first asymmetric Michael reaction by Wynberg.

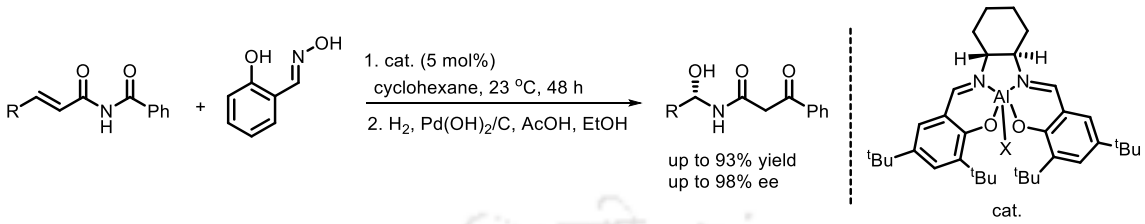
1.3.1. Oxa-Michael reaction:

The first example of an oxa-Michael addition was reported by Loydl in 1878 for the synthesis of malic acid (Scheme 6).[14] Major challenges of oxa-Michael reactions are the reversibility in the alcohol addition step as well as low reactivity of the employed alcohols. Pleasingly, during recent years a variety of approaches have been developed for the enhancement of reactivity and stereoselectivity.



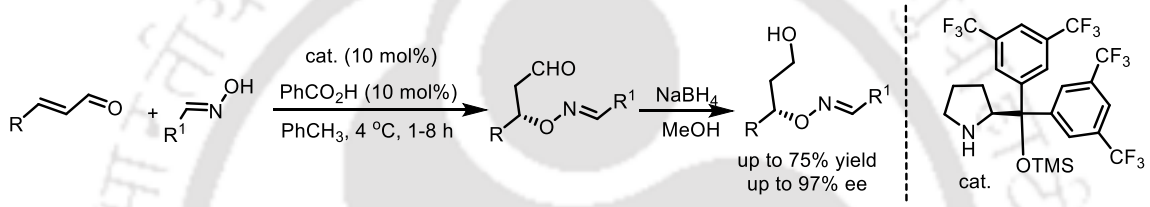
Scheme 6: The oxa-Michael reaction.

In 2005, Jacobsen and co-workers reported enantioselective hydration of *α,β*-unsaturated imides catalyzed by aluminium-salen. (Scheme 7).[15]



Scheme 7: Enantioselective hydration of *α,β*-unsaturated imides by Jacobsen et al.

Jørgensen and group reported addition of benzaldoxime to *α,β*-unsaturated aldehyde catalyzed by diaryl prolinol ether. (Scheme 8).[16]

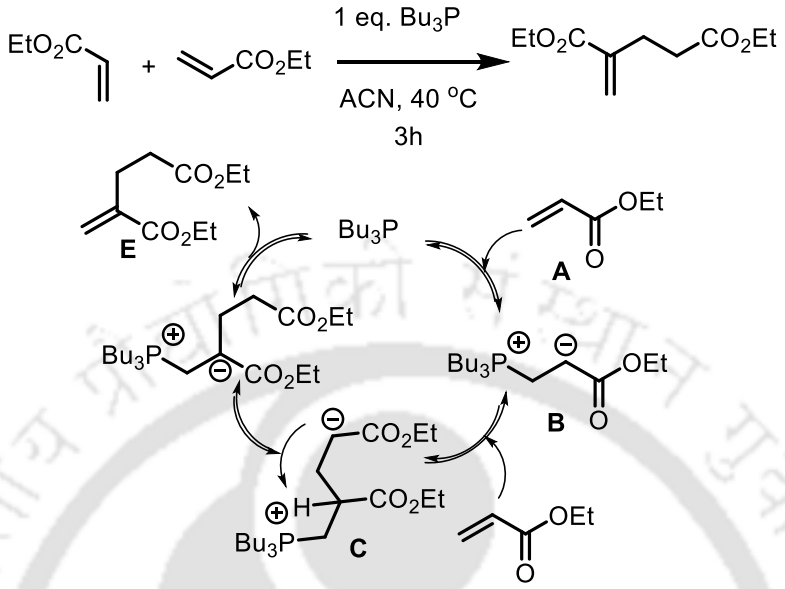


Scheme 8: Enantioselective addition of benzaldoxime to *α,β*-unsaturated aldehyde by Jørgensen et al.

1.4. Rauhut-Currier reactions:

The Rauhut-Currier reaction is a prominent reaction describing C-C bonds between two Michael acceptors in the presence of a nucleophilic catalyst.[17] This reaction is also known as the vinylogous Morita-Baylis-Hilman reaction. The RC reaction is important as it facilitates the C-C bond formation required for biologically active molecules and natural products. This reaction is also advantageous as in it is atom economic, feasible under mild conditions, generates chiral centre and forms densely substituted valuable adducts. Despite various advantages, this reaction suffers from shortcomings such as lack of selectivity and low availability of reactants. The analogous Morita−Baylis−Hillman (MBH) reaction has been found to be more progressive as compared to the cross-RC reaction. The cross RC reaction faces the challenge of control of the chemoselectivity especially in the asymmetric versions. However, Krische and co-workers and Roush and co-workers overcame this challenge, in 2002, by employemnet of bis-enones as substrates.[18] As a result they could react compounds with different electophilicity or having sufficient stereo control. Nevertheless, in recent years, a number of reactions are reported to use reactants that are

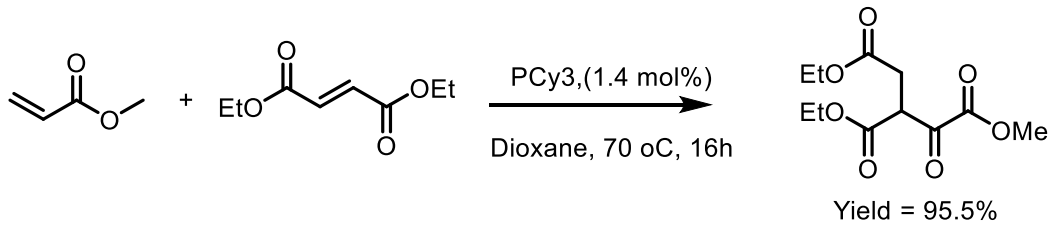
pre activated and helps in selectivity. In addition, a number of catalysts has been developed to overcome this situation.



Scheme 9: Rauhut Currier reaction catalysed by tributylphosphine and its mechanism

Phosphines are the most common catalysts used for this kind of reaction. In fact, Phosphine-catalysed dimerization of ethyl acrylate and acrylonitrile were the reactions reported by Rauhut and Currier in 1963.[17] The mechanism of the reaction is believed to be proceed via reversible conjugate addition of a nucleophilic catalyst, like tributylphosphine (Bu_3P), to the activated alkene A generating zwitterionic species B. This is followed by Michael reaction of the enolate with a second equivalent of the activated alkene A. This generates intermediate C, which is followed by a proton shift, eventually resulting in the expulsion of the phosphine catalyst. Thus, the RC product E is generated. (Scheme 9)

The cross-RC reaction, where there are two different Michael receptors, is challenging as it proceeds with two different activated alkenes and it proceeds with poor selectivity. Most common form of cross-RC reaction is one in which a mono- or di- substituted akene is reacted with another electron deficient alkene. Morita and Kobayashi reported in 1969, where activated alkenes like methyl acrylate and acrylonitrile reacted with fumaric/maleic esters. Tricyclohexylphosphine (PCy_3) was used as the catalyst and a high yield of 95.5% was obtained when Methyl acrylate was coupled with diethyl fumarate to give 3-butene1,2,3-tricarboxylic acid 1,2-diethyl-3-methyl ester (Scheme 10). [19]

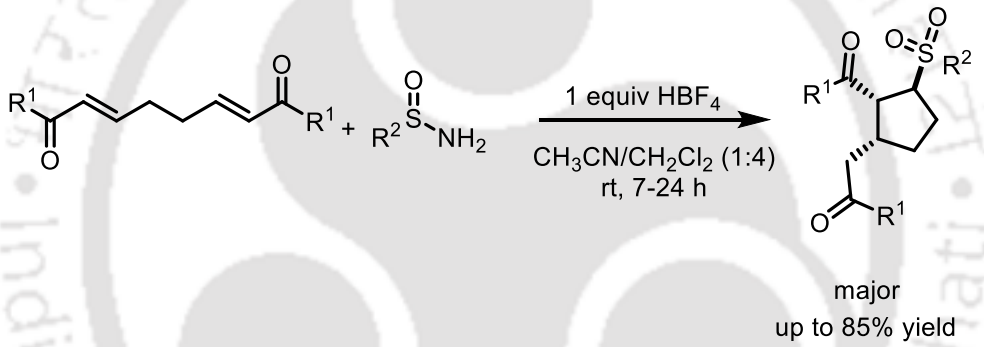


Scheme 10: Morita and Kobayashi reported cross-RC reaction

1.4.1. Recent reports on cross-RC reactions:

1.4.1.1. Highly Functionalized Sulfonated Cyclopentanes synthesis.

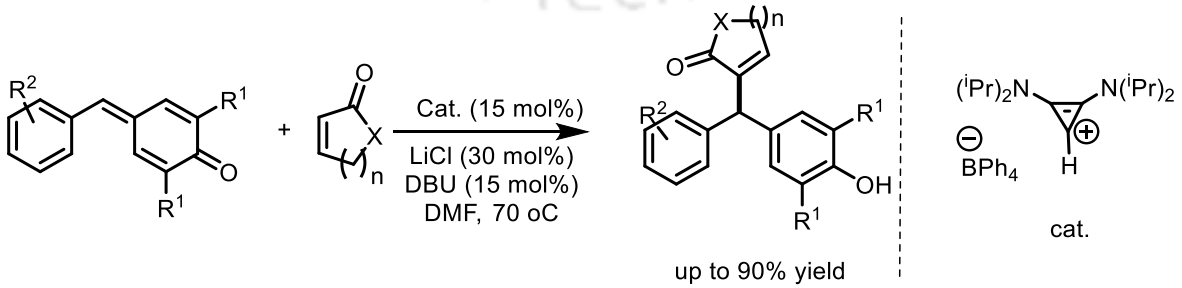
Joseph et al. reported an unexpected acid-mediated Rauhut–Currier cascade reaction by conjugate addition of sulfinamides to dienediones to synthesize sulfonated cyclopentanes with three contiguous stereogenic centers in a single step (Scheme 11).[20]



Scheme 11: Highly Functionalized Sulfonated Cyclopentanes synthesis Josheph et al.

1.4.1.2 Bis(amino)cyclopropenylidene Catalyzed Rauhut−Currier Reaction

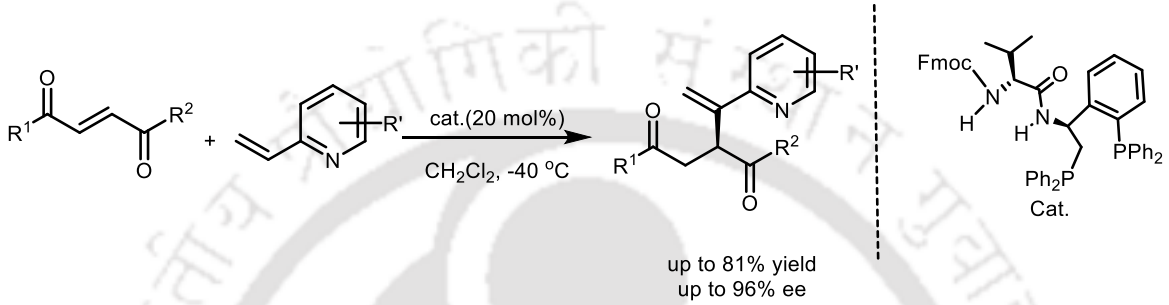
In 2018, Ramaswamy and group reported an intermolecular Rauhut−Currier reaction between *α,β*-unsaturated carbonyl compounds and p-quinone methides catalysed by bis(amino)-cyclopropenylidene to give a variety of vinyl diarylmethane derivatives in moderate to good yields. (Scheme 12).[21]



Scheme 12: Bis(amino)cyclopropenylidene Catalyzed Rauhut−Currier Reaction by Ramasamy and group.

1.4.1.3 Chiral Phosphine Catalyzed Enantioselective Cross Rauhut−Currier Reaction

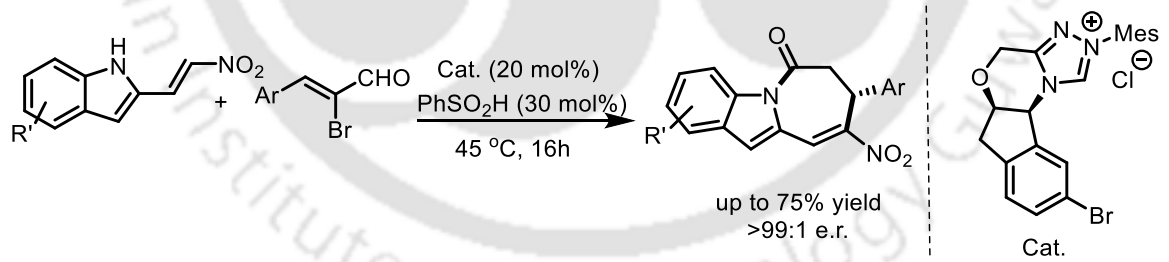
Wang and co-workers reported an asymmetric cross Rauhut−Currier reaction with 2-Vinylpyridines activated by a newly designed chiral phosphine catalyst with 2-Ene-1,4-diones (scheme 13).[22]



Scheme 13: Chiral Phosphine Catalyzed Enantioselective Cross Rauhut−Currier Reaction by

1.4.1.4 Sulfinate and Carbene Co-catalyzed Rauhut–Currier Reaction

Chi et al disclosed a carbene and sulfinate co-catalyzed intermolecular Rauhut–Currier reaction between enals and nitrovinyl indoles to synthesise Azepino[1,2-α]indoles. The carbene catalyst activates the enal and the sulfinate co-catalyst activates the nitrovinyl indole (scheme 14).[23]



Scheme 14: Sulfinate and Carbene Co-catalyzed Rauhut–Currier Reaction by Chi et al.

1.5. The Pyrazolone moiety:

Pyrazoles and pyrazolones are important nitrogen containing heterocyclic motifs and are predominant in most of the bioactive compounds having pharmaceutical and agricultural activities.[24] In particular, 3-hydroxypyrazole derivative are obtained by aromatization of pyrazolones. 3-hydroxypyrazole derivatives have interesting enzyme inhibition and activation properties, and have been broadly used in antidiabetic, anticancer, anti-inflammatory,

antipsychosis, insecticidal and herbicidal studies. The development of efficient methods for the enantioselective construction of 3-hydroxypyrazoles are important for the discovery of new chiral drugs and other utilities. This thesis mainly focuses on the synthesis of tetrahydropyano-pyrazoles and spiro-pyrazolones.

1.5.1. Tetrahydropyrano-pyrazolone derivative

Tetrahydropyran (THP) skeleton is a common structural unit found in a number of biologically active natural products such as acetogenins, polyether antibiotics, and ladderlike marine polycyclic ethers. In recent years, Pyrazole and tetrahydropyran derivatives have intensively attracted much attention due to their diverse applications in the field of drug discovery and agricultural research. Among numerous pyrazoles and tetrahydropyran derivatives, tetrahydropyrano[2,3-*c*]pyrazoles that contain both cores of tetrahydropyran and pyrazole are especially of synthetic and pharmaceutical interest. The tetrahydropyrano[2,3-*c*]pyrazole moiety is present in many biologically important compounds (figure 3). Syntheses of tetrahydropyranopyrazoles (THPPs) from pyrazolones were reported by groups of Enders, Jeong, Ye, Biju, Kesavan, Zhou and others.[25] Whereas, unsaturated pyrazolones for the synthesis of THPPs were employed by Wang, Pericàs and Pan Group.[26]

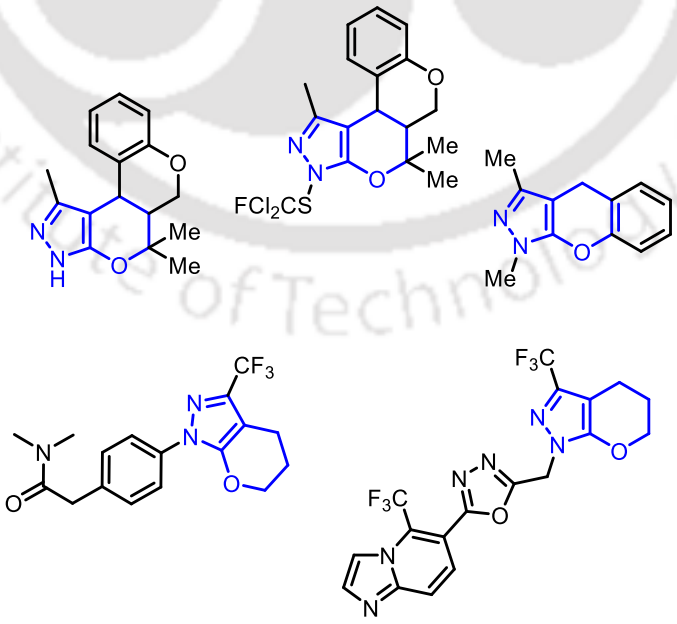


Figure 3: Selective bioactive compounds containg tetrahydropyrano[2,3-*c*]pyrazolescore frameworks.

1.5.2. Spiro-pyrazolone derivative

Chiral spiropyrazolones, with a spiro-ring fused at the 4-position of the pyrazolone core, are widely found in a large family medicinally relevant compounds. Chiral spiropyrazolones exhibit biological activities such as antitumor, antimicrobial, insecticidal, and analgesic activities, as well as an inhibitory effect for acetyl-CoA carboxylase and type 4-phosphodiesterase. Enantiopure spiropyrazolone derivatives act as significant synthesis intermediates or products and receive constant attention from chemists and the industry worldwide owing to their importance in medicinal chemistry. Various methods to access the structurally diverse spiropyrazolone derivatives have been developed, including asymmetric organocatalysis, which is among the most effective and environment-friendly strategies.

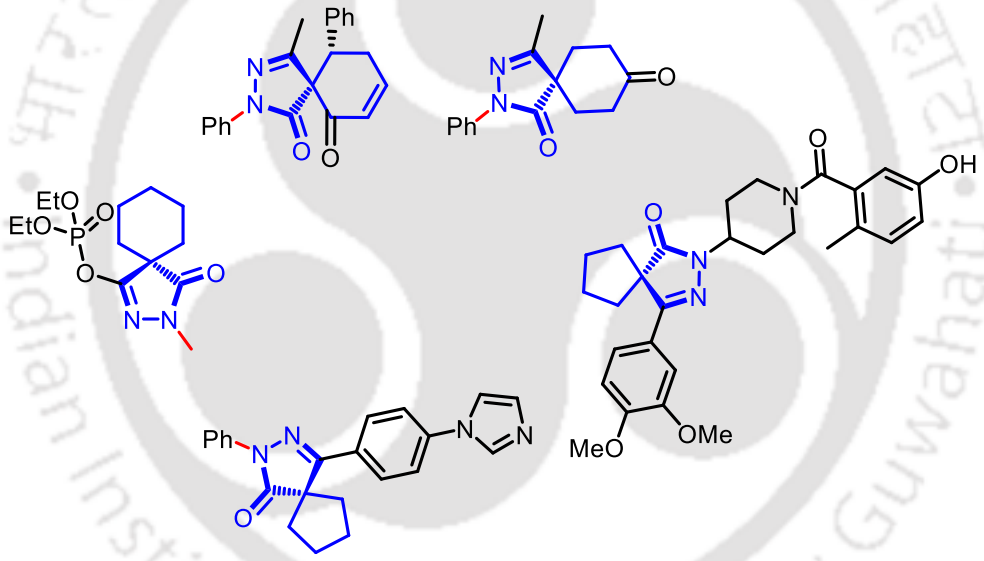


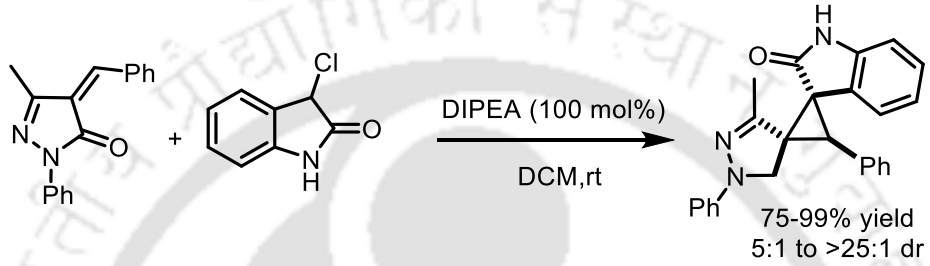
Figure 4: Selective bioactive compounds containing spiropyrazolone core frameworks.

Pyrazolone derivatives are versatile synthons in organic synthesis. The construction of spiropyrazolones fused with diverse cycle have increased as they are useful raw materials. By using these pyrazolone derivatives as starting materials in catalytic reactions, various enantiopure spiropyrazolones fused with three-, five-, and six-membered carbocycle or nitrogen-, oxygen-, sulfur-heterocycle have been achieved.

Some reports on spiropyrazolones fused with three, five and six membered rings

1.5.2.1. Spiropyrazolones fused with three-membered ring structure

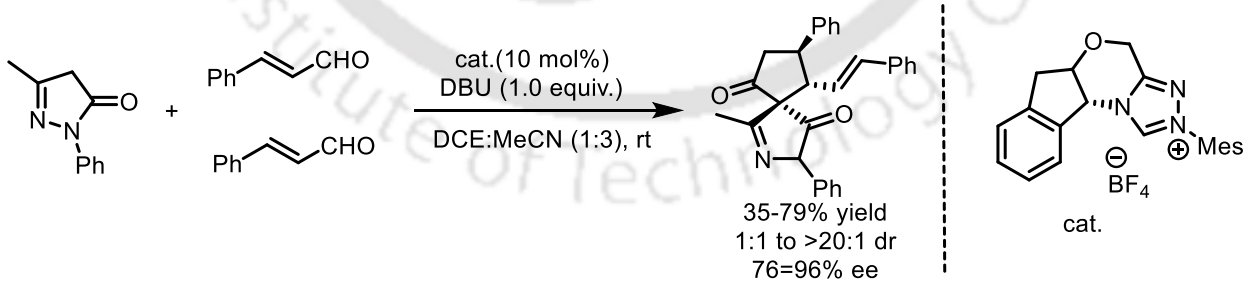
In 2015, the Du group developed a Michael/alkylation cascade reaction between arylidenepyrazolones 1 and 3-chlorooxindoles 2 with 100% N,N-diisopropylethylamine (DIPEA) base to synthesize multi-substituted spiropyrazolone- cyclopropane-oxindole derivatives (Scheme 15).[27]



Scheme 15: Three-membered spiropyrazolones reported by Du et al.

1.5.2.2. Spiropyrazolones fused with five-membered ring structure

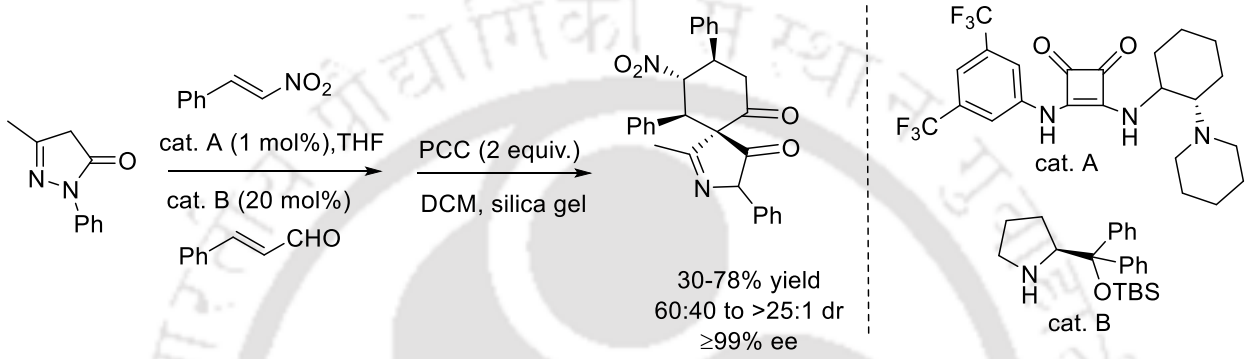
The Enders group reported a three-component, one pot reaction for the synthesis of spiro-cyclic pyrazolones through an aldol condensation/N-heterocyclic carbine (NHC)-catalyzed [1+2+2] annulation between pyrazolones and enals. The enals provided two molecules as substrates. The the optimal conditions were obtained by use of 1,5-dizzabicyclo [5.4.0]undecen-5-ene (DBU) base and a mixture of 1,2- dichloroethane (DCE) and acetonitrile (1:3) as solvent (Scheme 16). [28]



Scheme 16: Five-membered spiropyrazolones reported by Enders and co-workers.

1.5.2.3. Spiropyrazolones fused with six-membered ring structure

In 2016, the Du group reported a Michael/Michael/aldol cascade reaction catalyzed by the combination of the bifunctional squaramide catalyst and diphenylprolinol silyl ether catalyst, in reactions between pyrazolones, (*E*)-*β*-nitrostyrenes and cinnamaldehydes, This was followed by the oxidation with pyridinium chlorochromate (PCC) and cyclohexanone-fused spirospyrazolones containing four consecutive stereocenters were synthesized (Scheme 17). [29]



Scheme 17: Six-membered spiropyrazolones reported by Du et al.

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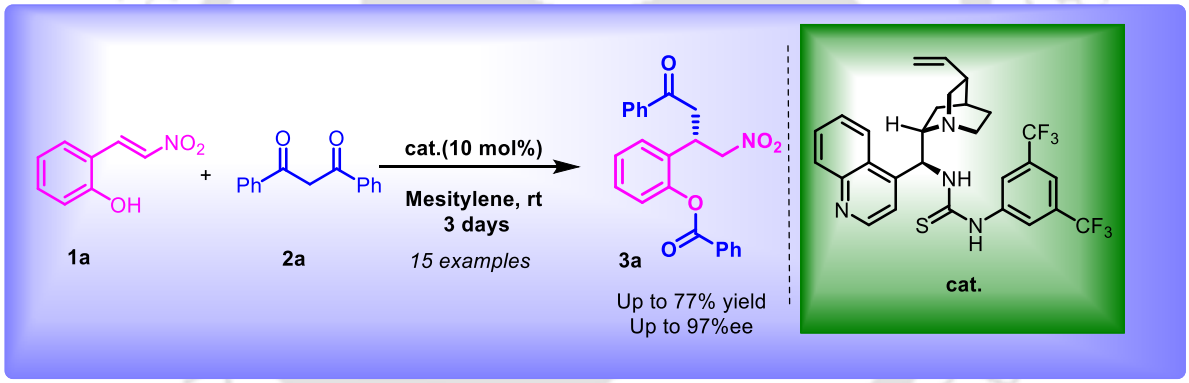
Chapter 2: Asymmetric Organocatalytic Michael/Hemiketalization/ Retro-Aldol Reaction between 1,3-diketones and (E)-2-(2-nitrovinyl) phenols.



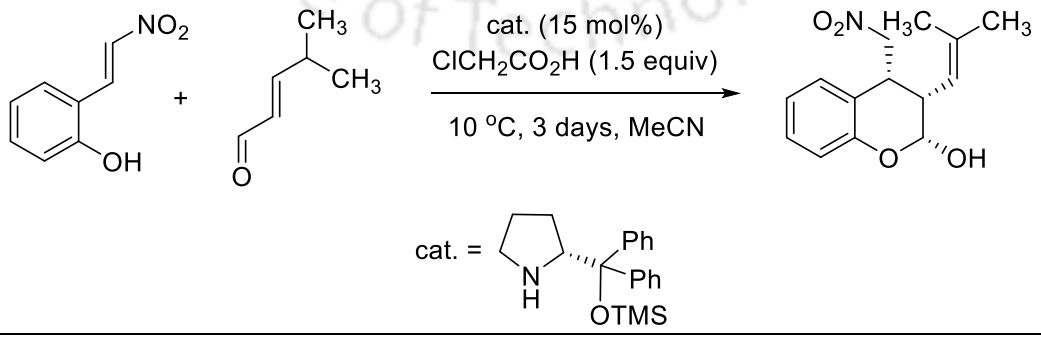
2.1 Introduction

The Michael reaction of carbon-centered nucleophiles with nitro olefins represents one of the direct and fascinating routes to nitroalkanes, which are important synthetic intermediates in organic chemistry as diverse transformations of the nitro group into other functional groups could be possible. The organocatalytic asymmetric versions of such processes have been studied extensively in recent years by a large number of synthetic organic chemistry groups.[1] Also, Michael addition reaction-triggered cascade reactions have drawn significant attention because of the ultimate formation of different structural frameworks having multiple stereocentres.[2] Thus the development of new organocatalytic asymmetric Michael based cascade reactions is an important arena of research.

In this regard, (*E*)-2-(2-nitrovinyl)phenols have been broadly utilized as bidentate substrate and a range of asymmetric organocatalytic one-pot double Michael or Michael-cyclization reactions has been developed with the induction of neighboring *ortho* hydroxyl group.[3] The conjugate addition of 1,3-dicarbonyl compounds to these substrates could potentially lead to different types of products.

2.2. Selected previously reported strategies for the asymmetric organocatalytic one-pot double Michael or Michael-cyclization with induction of neighboring *ortho* hydroxyl group:

2.2.1 Organocatalytic asymmetric chromanol synthesis:

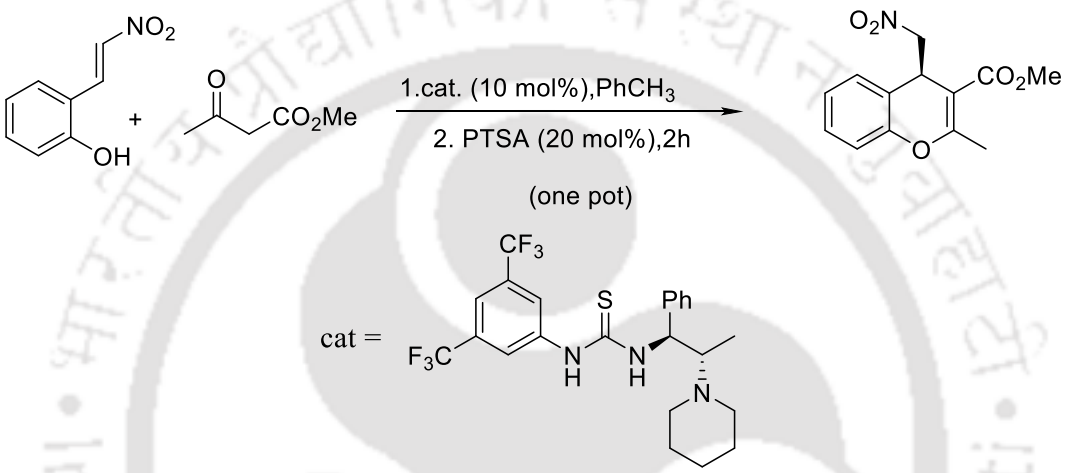


Scheme 1: Organocatalytic Michael–hemiacetalization reactions between (*E*)-2-(2-nitrovinyl)phenols and aldehydes by Enders et al.

Enders group, in 2011, predicted (*E*)-2-(2-nitrovinyl)phenols and α,β-unsaturated aldehydes as potential substrates for a new Michael addition–hemiacetalization reaction, a process initiated by a dienamine-mediated Michael addition (Scheme 1).[4]

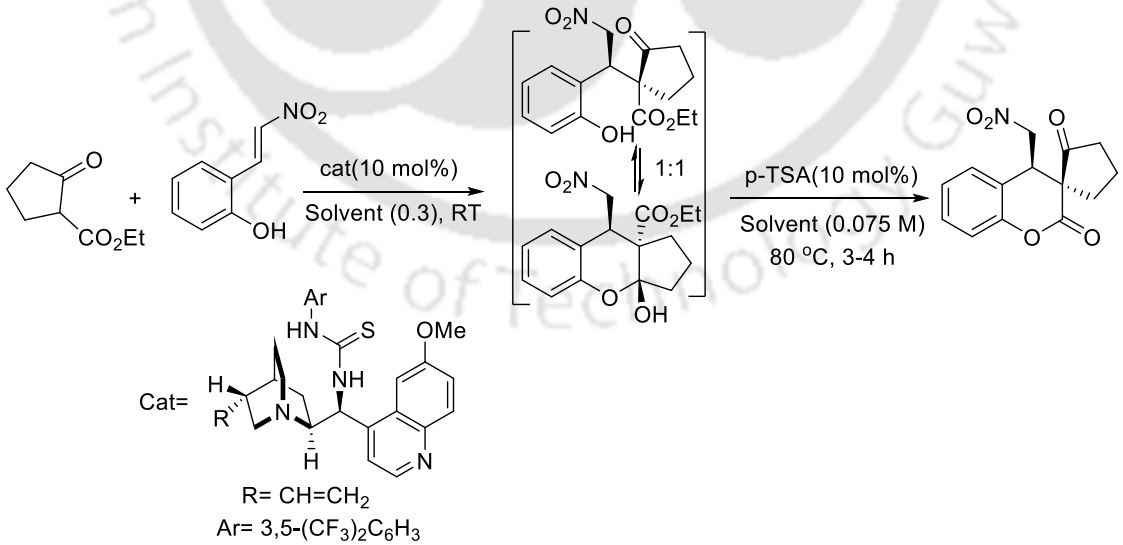
2.2.2 Organocatalytic Asymmetric Synthesis of Functionalized 4*H*-Chromenes:

In 2012, Enders and co-workers disclosed organocatalytic asymmetric synthesis of polyfunctionalized 4*H*-Chromenes via a one-pot Domino Michael-Hemiacetalization and dehydration sequence (Scheme 2).[5]



Scheme 2: Organocatalytic Asymmetric Synthesis of Functionalized 4*H*-Chromenes by Enders et al

2.2.3 Organocatalytic asymmetric sequential Michael-lactonization reactions:

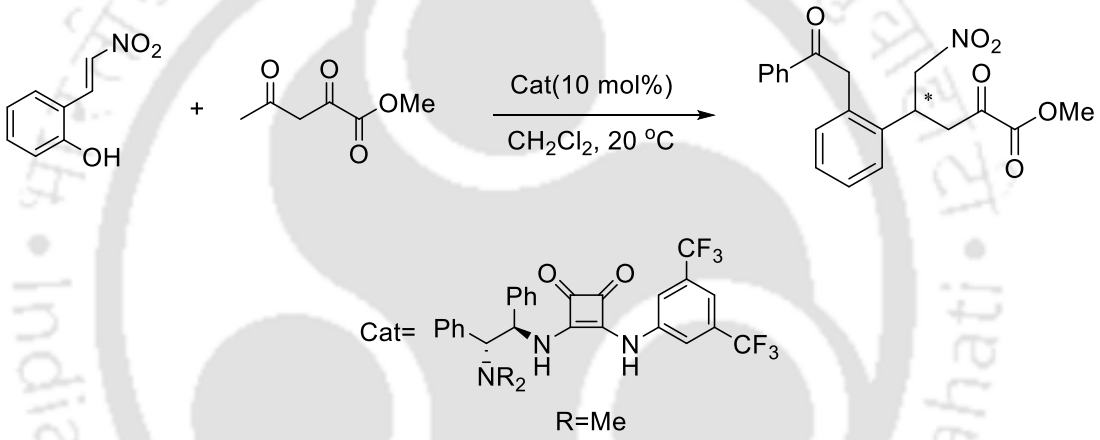


Scheme 3: Organocatalytic asymmetric sequential Michael-lactonization reactions by Ramachary et al.

Ramachary and group in 2012, reported asymmetric synthesis of highly substituted spirodihydrocoumarins with a quaternary stereocenter achieved through neighboring ortho-hydroxyl group induced sequential Michael–lactonization reactions on 2-(2-nitrovinyl)phenols with alkyl cyclopentanone-2-carboxylates in the presence of a catalytic amount of quinine–NH–thiourea followed by p-TSA (Scheme 3).[6]

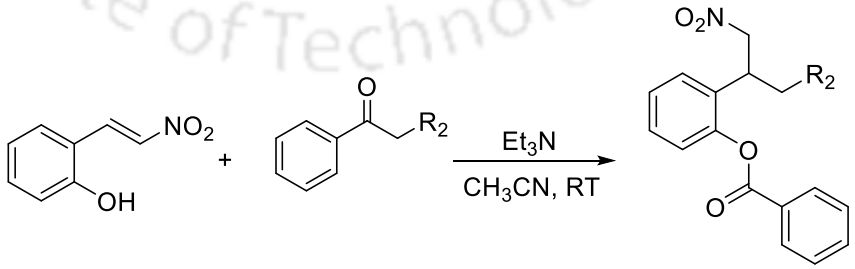
2.2.4. Asymmetric Organocatalytic Cascade Michael/Hemiketalization/Retro-Aldol Reaction of 2-[(E)-2-Nitrovinyl]phenols with 2,4-Dioxo-4-arylbutanoates:

In 2013, Tang and co-workers developed an organocatalytic Michael-acyl transfer reaction between 2,4-dioxo-4-arylbutanoates and (*E*)-2-(2-nitrovinyl)phenols (Scheme 4).[7]



Scheme 4: Asymmetric Organocatalytic Cascade Michael/Hemiketalization/Retro-Aldol Reaction of 2-[(E)-2-Nitrovinyl]phenols with 2,4-Dioxo-4-arylbutanoates by Tang et al.

2.2.5. One-Pot Synthesis of Aliphatic Nitro Compounds by Michael/retro-Claisen Fragmentation Domino Reaction:

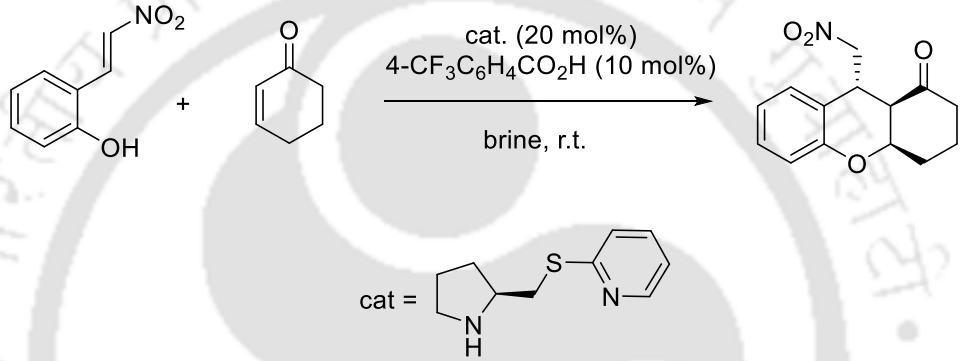


Scheme 5: One-Pot Synthesis of Aliphatic Nitro Compounds by Michael/retro-Claisen Fragmentation Domino Reaction by Wang et al.

Wang and co-workers developed an achiral method to synthesize γ-nitro-ketones from acyclic 1,3-diketones and (*E*)-2-(2-nitrovinyl)phenols (Scheme 5).[8]

2.2.6. Enantioselective Cascade Oxa-Michael–Michael Reactions of 2-Hydroxynitrostyrenes with Enones Using a Prolinol Thioether Catalyst:

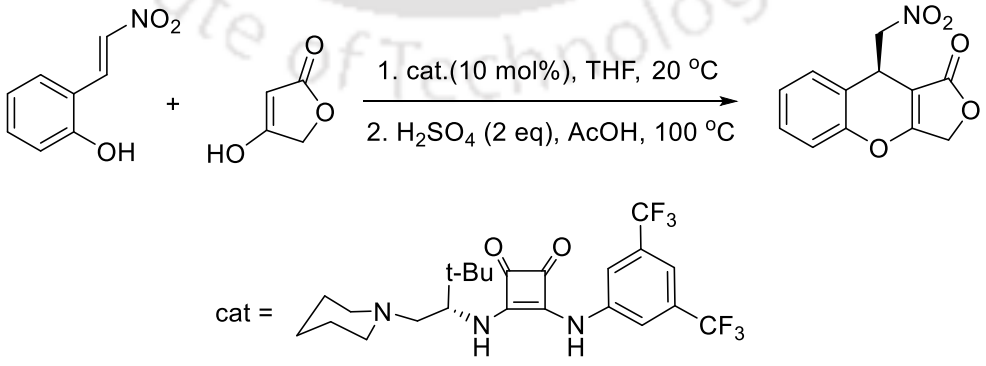
A highly chemo-, diastereo- and enantioselective synthesis of functionalized tetrahydroxanthenones and chromanes, with three contiguous stereocenters, catalyzed by prolinol thioether , was developed by Xu et al (Scheme 6).[9]



Scheme 6: Enantioselective Cascade Oxa-Michael–Michael Reactions of 2-Hydroxynitrostyrenes with Enones Using a Prolinol Thioether Catalyst by Xu et al.

2.2.7. Stereocontrolled construction of 3*H*-furo[3,4-*b*]chromen-1(9*H*)-one scaffold via organocatalyzed Michael addition followed by intramolecular dehydration:

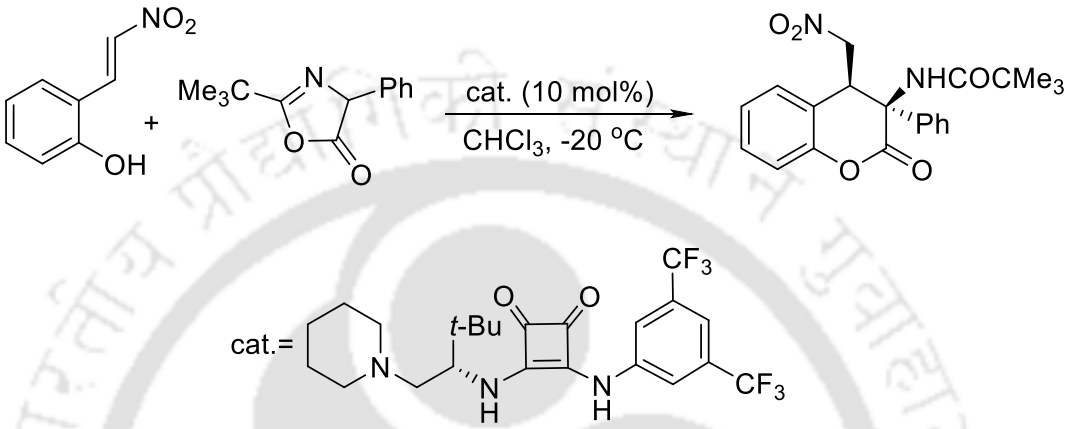
Through a sequential Michael addition/intramolecular dehydration strategy, Zhou and co-workers, in 2015, synthesized 3H-furo[3,4-b]chromen-1(9H)-one scaffold (Scheme 7).[10]



Scheme 7: Organocatalyzed Michael addition followed by intramolecular dehydration by Zhou et al.

2.2.8. Chiral Squaramide Catalyzed Cascade Michael Addition–Lactonization Reaction:

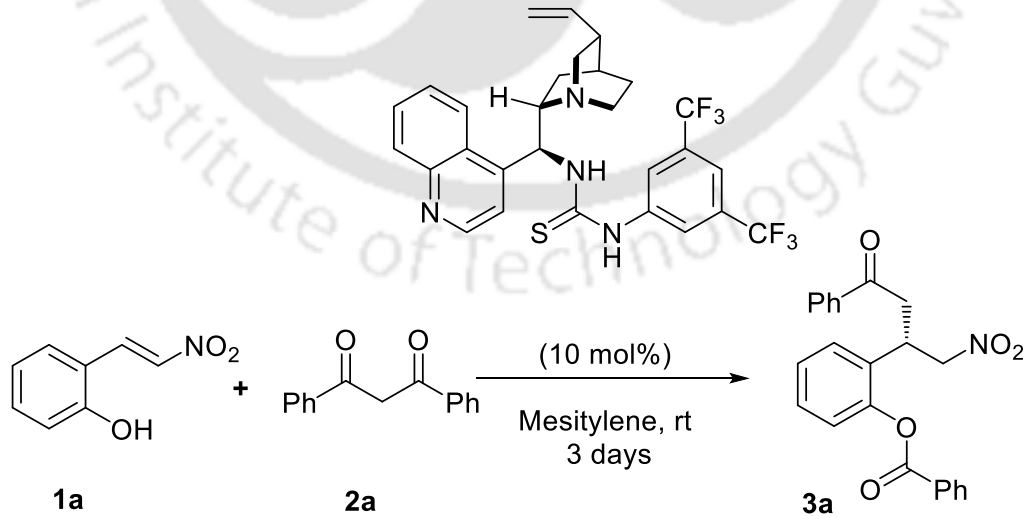
Zhou and co-workers, in 2016, constructed 3,4-dihydrocoumarin backbones with a quaternary amino acid moiety via an asymmetric tandem Michael addition–lactonization between ortho-nitrovinylphenols and azalactones, using chiral squaramide derived from L-tert-leucine catalyst (Scheme 8).[11]



Scheme 8: Chiral Squaramide Catalyzed Cascade Michael Addition–Lactonization Reaction by Zhou et al.

2.3 Concept

Realizing the potential of γ-nitrocarbonyl compounds, we envisaged in developing an asymmetric Michael/hemiacetalization/retro-aldol reaction[12] between linear 1,3-diketones and (*E*)-2-(2-nitrovinyl)phenols (Scheme 9).

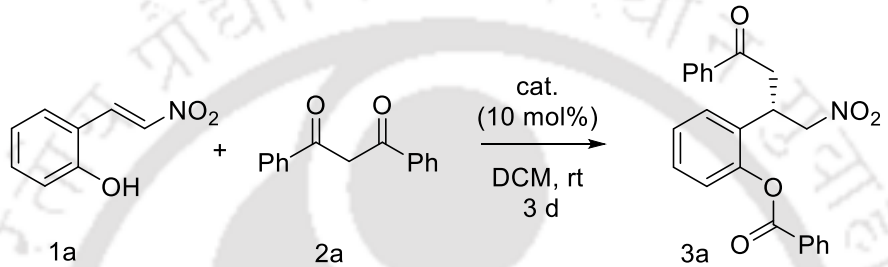


Scheme 9: The present work.

2.4 Results and discussion:

2.4.1. Catalyst screening:

Initially, the reaction between (*E*)-2-(2-nitrovinyl)phenol (**1a**) and 1,3-diphenyl-1,3-propane-1,3-dione (**2a**) was examined with cinchonal alkaloid derived bifunctional thiourea catalysts (**I-III**)[13] in dichloromethane solvent at room temperature (Table 1, entry 1). To our delight, the reaction progressed well in 3 days with quinidine derived thiourea **I** to deliver the Michael-acyl transfer product **3a** in 70% yield, however the enantioselectivity



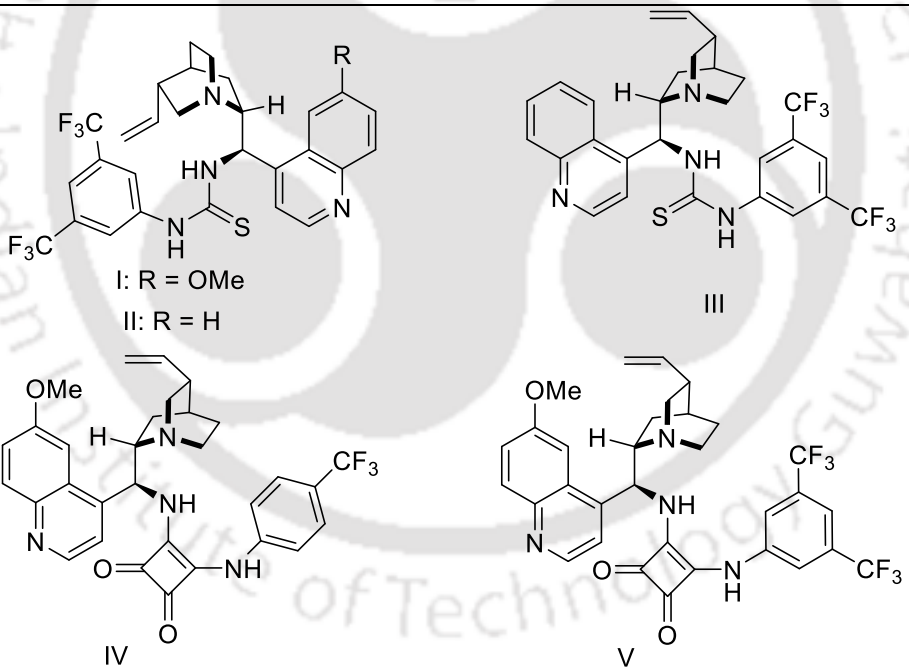


Table 1: Catalyst screening

Entry[a]	Catalyst	Solvent	Yield[b] (%)	ee(%)[c]
1	I	DCM	70	47
2	II	DCM	67	47
3	**III**	**DCM**	**71**	**92**

4	IV	DCM	70	64
5	V	DCM	69	82

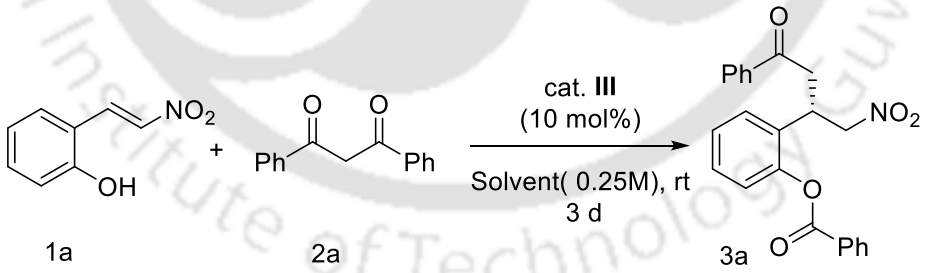
[a]Reactions were carried out with 0.05 mmol of **1a** with 0.055 mmol of **2a** in 0.2 ml solvent using 10 mol% catalyst at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral HPLC.

was moderate (47% ee, Table 1, entry 1). The enantioselectivity did not improve with cinchonine derived thiourea catalyst **II** (entry 2). Then cinhonidine derived catalyst **III** was employed in the reaction and gratifyingly a big jump to 92% ee was observed (entry 3). Bifunctional squaramide catalysts **IV-V** were also screened but lower enantioselectivities were detected (entries 4-5).

2.4.2. Solvent screening:

Then we turned our attention on the solvent optimization and this proved to be rewarding. For example, the enantiomeric excess got enhanced to 94% ee in toluene and similar conversion was observed (entry 2). Xylene as a solvent also afforded similar enantioselectivity (entry 3). With 4CF_3-toluene, the enantioselectivity remained similar (entry 4).With mesitylene, the enantioselectivity increased to 96% and yield to 73% (entry 5). Other solvents such as Chloroform and MTBE, did not improve the ee (entry 6&7). Thus, the best solvent was found to be mesitylene and we obtained our optimized condition.

Table 2: Solvent screening



1a 2a 3a

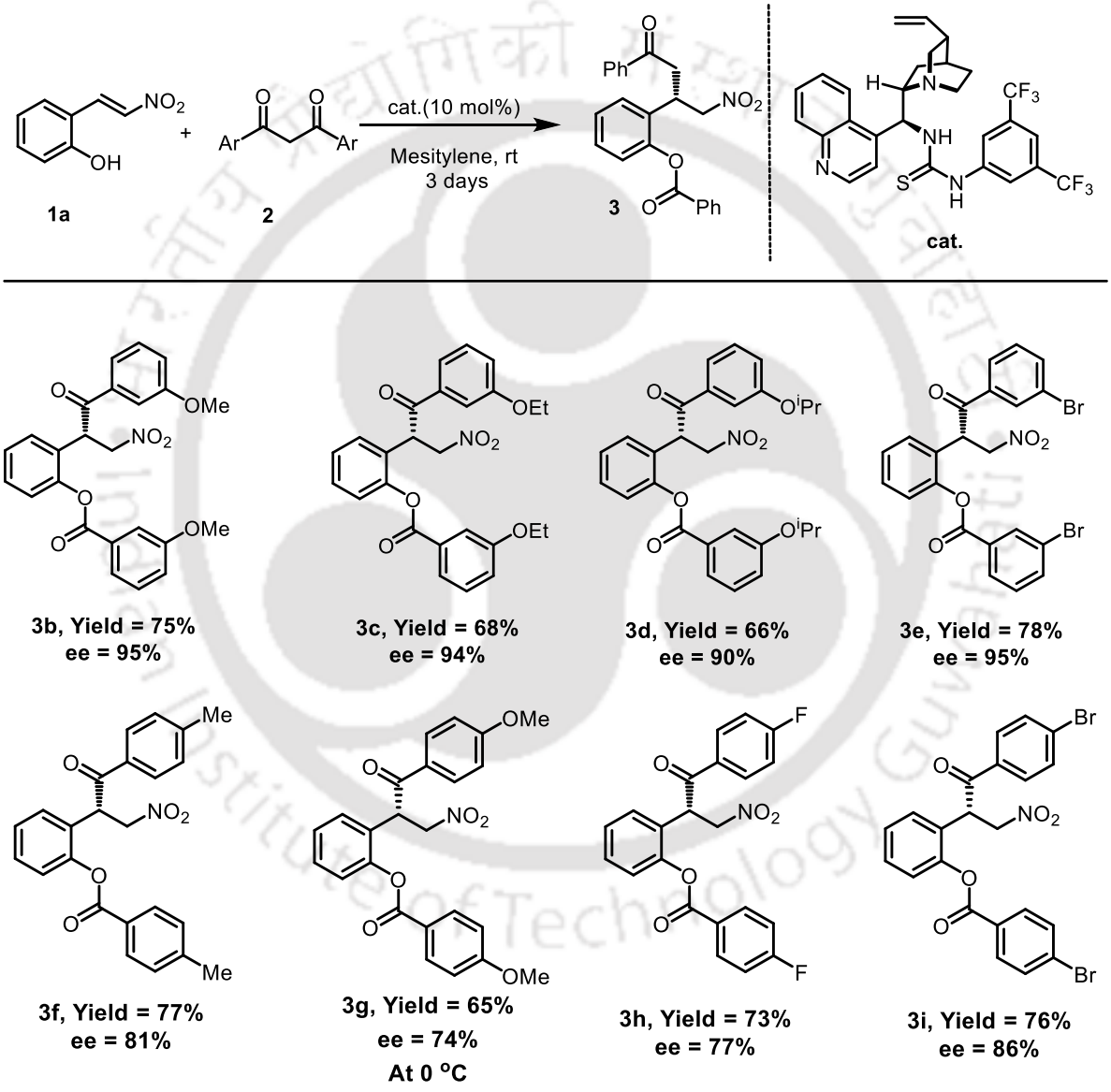
Entry[a]	Solvent	Yield (%)[b]	ee(%)[c]
1	DCM	71	92
2	Toluene	73	94
3	Xylene	72	95
4	$PhCF_3$	68	94
5	**Mesitylene**	**73**	**96**

6	$CHCl_3$	70	92
7	MTBE	75	92

[a] Reaction condition: 0.05 mmol of **1a** and 0.055 mmol of **2a** in 0.2 mL solvent using 10 mol% catalyst **III**. [b] Isolated yield after silica gel column chromatography. [c] Determined by HPLC.

2.4.3. Substrate scope:

2.4.3.1 Scope of 1,3-propandiones:



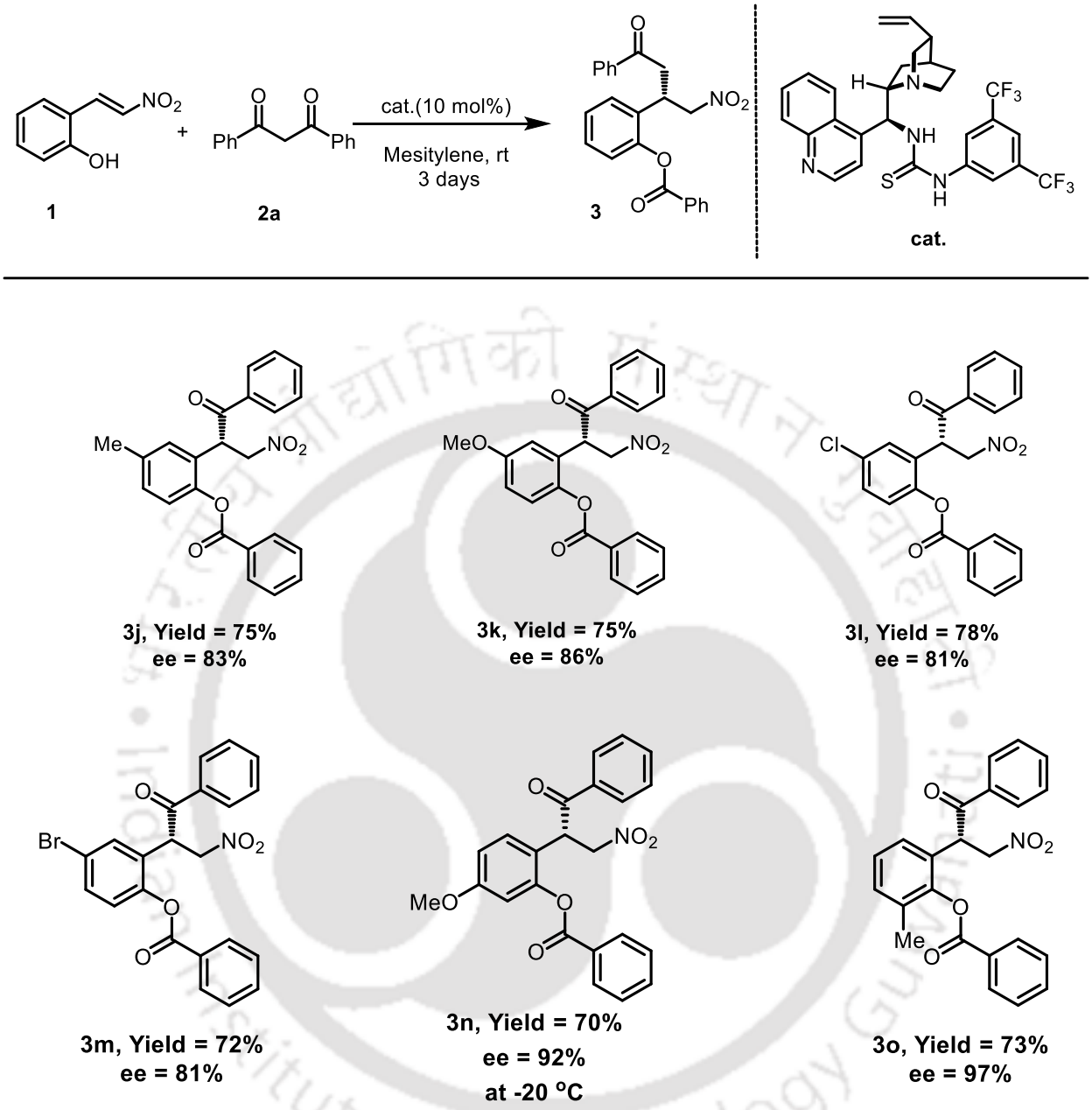
Scheme 10: Scope of 1,3-propandiones

After the identification of suitable conditions, the scope and generality of the reaction was investigated. Initially a range of 1,3-propanediones **2** having different aryl groups were

tested and the results are shown in Scheme 10. Gratifyingly quite a number of substituents can be incorporated in the *ortho*-, *meta*- and *para*-position of the aryl group and good results were achieved. At first, different *meta*-substituted diaryl propanediones **2b-d** were screened and the products **3b-e** were isolated in good yields with high enantioselectivities. For example, 3-methoxy substituted diarylpropanedione **2b** reacted smoothly to provide product **3b** in 78% yield with 95% ee. Inspired by this result, other 3-alkoxy propanediones **2c** and **2d** were employed and high enantioselectivities were detected for the products **3c** and **3d** respectively. 3-Bromo substituted propanedione **2e** also participated in the reaction delivering the product **3e** in 78% yield with 95% ee. Then different *para*-substituted propane diones **2f-2i** were prepared and engaged in the reaction. Propanedione **2f** having tolyl groups afforded the corresponding product **3f** in 77% yield with 81% ee. The enantiomeric excess for product **3g** having anisyl substituents was less at room temperature, thus the reaction was studied at 0^{o}C to obtain acceptable enantioselectivity. Further lowering of the reaction temperature could not improve the enantioselectivity. 4-Halo substitutions were also tolerated in the reaction and the products **3h-3i** were obtained in similar yields. Although the enantiomeric excess for product **3h** was moderate, product **3i** was isolated in high enantioselectivity. These halo substituted products could be further elaborated via cross-coupling reactions.

2.4.3.2 Scope of (E)-2-(2-nitrovinyl)phenol:

Next, the scope of (*E*)-2-(2-nitrovinyl)phenol was studied and here also good results were achieved with different substitutions (Scheme 11). Initially different 4-substituted nitrovinylphenols were employed in the reaction and acceptable yields were detected. Though 4-methyl substitution lowered the enantioselectivity a little, high enantioselectivity was obtained for product **3k** having 4-methoxy substitution. 4-chloro and 4-bromo gave similar enantioselectivities. The reaction was also found to be smooth with 5-methoxy substituted nitrophenol **1e;** however, less enantioselectivity was obtained at room temperature**.** Gratifyingly lowering the temperature to -20^{o}C could improve the enantioselectivity to 92% ee. Finally, 6-substitutions were also tolerated in the reaction and 6-methyl substituted nitrovinylphenol **1g** emerged as the best substrate for the reaction providing product **3o** in 73% yield with 96% ee.

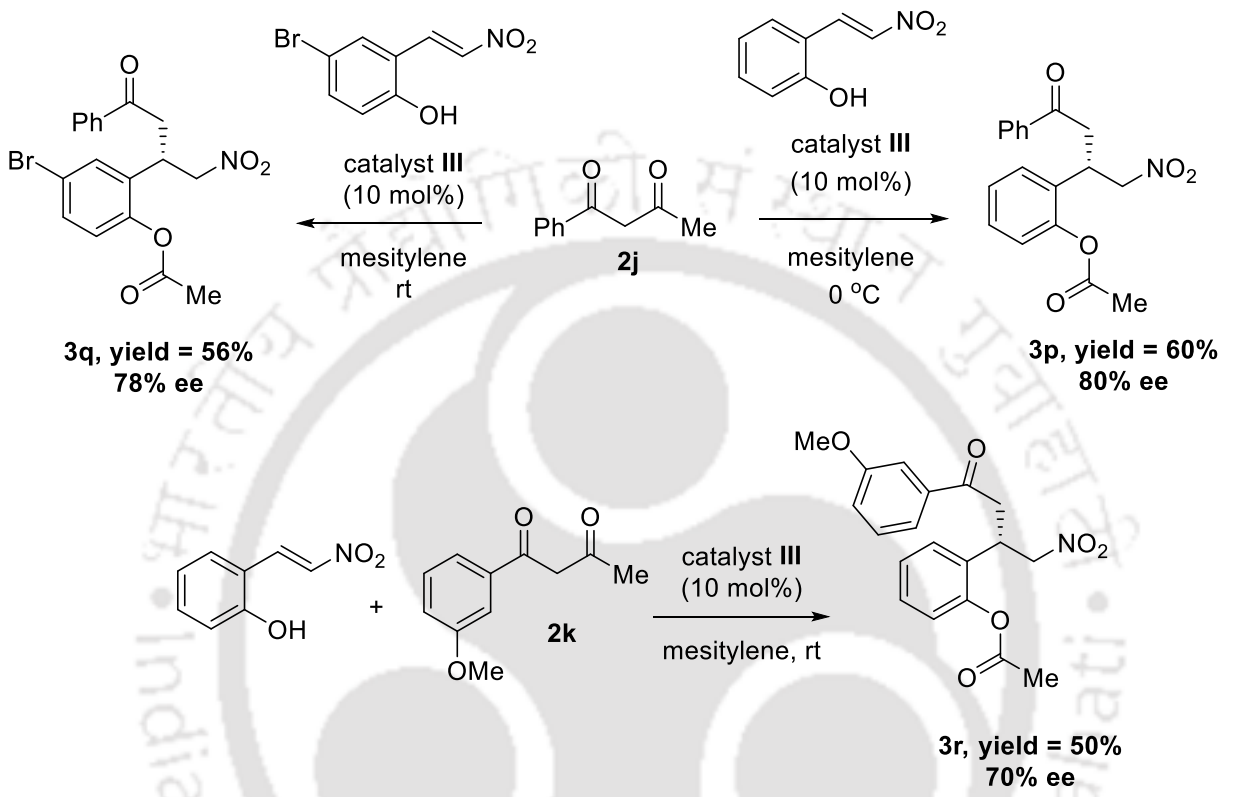


Scheme 11: Scope of (*E*)-2-(2-nitrovinyl)phenol

2.4.3.3 Scope of unsymmetrical 1,3-diketones:

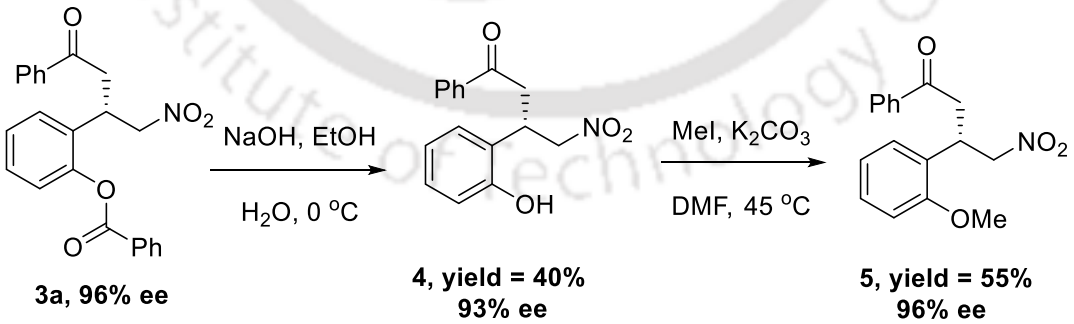
The scope of the reaction was then further extended by incorporating unsymmetrical 1,3-diketones in the reaction. Thus initially 4-phenyl,1,4-butanedione **2j** was prepared and reacted with (*E*)-2-(2-nitrovinyl)phenols **1a** and **1d** (Scheme 12). Pleasingly the reactions progressed smoothly to deliver major *O*-acetyl containing products **3p** and **3q** in good yields. The enantioselectivity of **3p**

was moderate at room temperature and thus the reaction was performed at 0°C to improve the ee (80%). Another unsymmetrical diketone **2k** having methoxy substituent was also prepared and engaged in the reaction. This resulted in the formation of 3r in 70% ee.



Scheme 12: Scope of unsymmetrical 1,3-diketones

2.4.4. Synthetic transformations and structure determination:



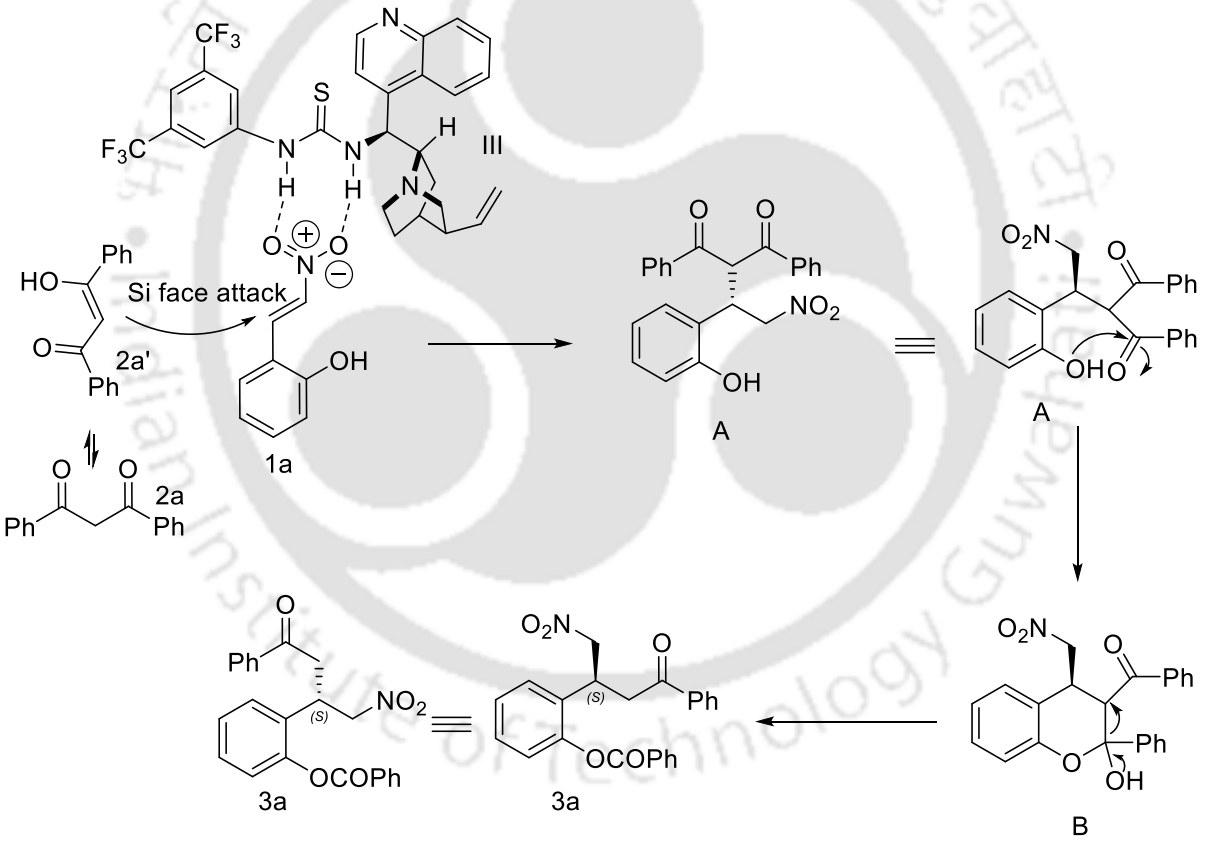
Scheme 13: Synthetic transformations

To strengthen our methodology, a few derivatizations were performed on **3a** (Scheme 3). At first, the ester moiety of **3a** was hydrolyzed with sodium hydroxide to provide phenol **4** in 40% yield and enantioselectivity was almost retained. Then methoxy protection with iodomethane delivered

5 with retention in enantioselectivity. (Scheme 2). Based on the HPLC chromatogram of **5** as reported by Kwiatkowski and co-workers[14], the absolute configuration of product **3a** was assigned to be (*S*).

2.4.5. Plausible mechanism:

A plausible mechanism has been shown in Scheme 14 to explain the stereochemistry of the product. It is believed that the nitro functionality of (*E*)-2-(2-nitrovinyl)phenol **1a** will co-ordinate with the thiourea motif of the catalyst **III**. Since the *Re* face of the nitroolefin is blocked by the catalyst, the addition of enol **2a'** occurs only from the *Si* face to provide intermediate **A**. Intramolecular hemiketalization then generates **B**. Finally retro-aldol reaction of **B** delivers product **3a**.



Scheme 14: Plausible mechanism

2.5 Conclusion:

In summary, this work has shown the development of an efficient Michael-hemiketalization-acyl transfer reaction between 1,3-propanediones and (*E*)-2-(2-nitrovinyl)phenols. The products having nitro, keto and ester functionalities were obtained in moderate to good yields with good to high enantioselectivities. Also selective acetyl transfer was observed from unsymmetrical 1,3-

diketones. Given the high importance of chiral nitroalkanes in synthetic organic chemistry, our method might be useful to prepare these compounds in a convenient way.

2.6 Experimental section:

2.6.1. General procedure for the synthesis of (*E*)-2-(2-ntrovinyl)phenols:

(*E*)-2-(2-ntrovinyl)phenols are prepared according to reported procedure.[15]

2.6.2. General procedure for the synthesis of 1,3-propanediones:

1,3-propanediones are prepared according to reported procedures.[16]

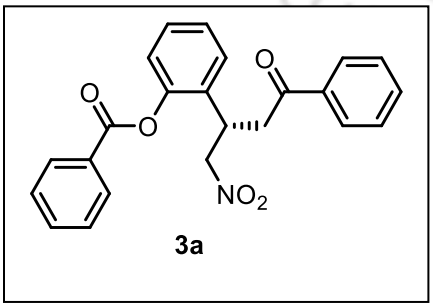
2.6.3. General procedure for the synthesis of catalyst:

The catalyst (**I, II** and **III**) was prepared according to reported procedures.[17]

2.6.4. General procedure for the synthesis of compound 3:

In an oven dried round bottom flask, **1** (8.25 mg, 0.05 mmol), **2** (12.3. mg, 0.055 mmol), 10 mol% of catalyst (**lll**) were taken. 0.2 mL of mesitylene was added to the reaction mixture and stirred at room temperature for 3 days. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10 %) to afford desired product **3a-r.**

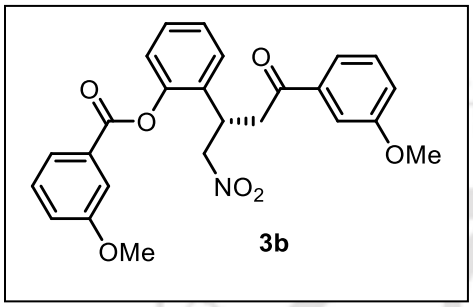
2.6.5. Characterization of the products:



3a

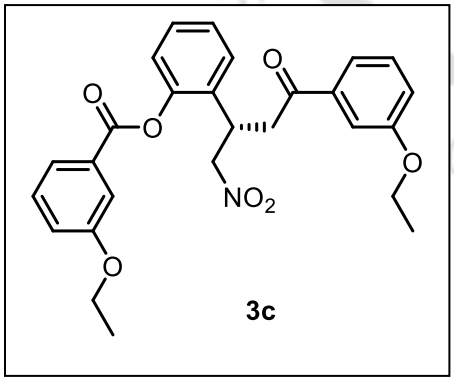
3a. ((S)-2-(1-nitro-4-oxo-4phenylbutan2-yl)phenyl benzoate) was obtained as a brownish yellow sticky compound in 73% yield (28.4 mg) after column chromatography.**^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.23 (d, *J* = 7.1 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 3H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 8.1 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 4.81 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.76 (dd, *J* = 12.7, 7.4 Hz, 1H), 4.50 – 4.44 (m, 1H), 3.49 (dd, *J* = 17.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 17.5, 7.9 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.9, 165.48, 149.0,

136.3, 134.2, 133.7, 131.4, 130.4, 129.1, 129.0, 129.0, 129.0, 128.8, 128.2, 126.9, 123.5, 78.6, 40.9, 33.6, 33.5, 29.8, 29.5.**HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.4 min, t_{minor} = 23.6 min). **ESI HRMS**: calcd. For $C_{23}H_{20}NO_5[M+H]^+$ 390.1336, found 390.1339.



3b

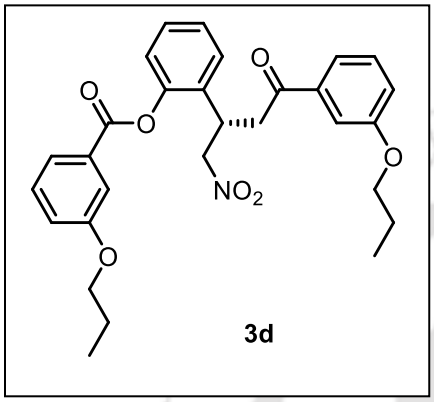
3b. ((S)-2-(4-(3-methoxyphenyl)-1-nitro-4-oxobutan-2-yl)phenyl 3-methoxybenzoate) was obtained as light yellow viscous compound in 75% (33.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.73 (m, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.32 – 7.26 (m, 2H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 4.80 (dd, *J* = 12.7, 6.9 Hz, 1H), 4.75 (dd, *J* = 12.7, 7.5 Hz, 1H), 4.49 – 4.43 (m, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.47 (dd, *J* = 17.5, 6.1 Hz, 1H), 3.40 (dd, *J* = 17.6, 7.8 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.7, 165.3, 160.0, 160.0, 149.0, 137.7, 131.3, 130.3, 130.0, 129.8, 129.1, 128.2, 126.9, 123.6, 122.9, 120.9, 120.8, 120.3, 114.6, 112.3, 78.6, 55.7, 55.6, 41.0, 33.8, 29.9, 14.3. **HPLC Analysis:** ee = 95%, Chiralpak IC Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 34.6 min, t_{minor} = 37.3 min). **ESI HRMS**: calcd. For $C_{25}H_{24}NO_7$ $[M+H]^+$ 450.1547, found 450.1542.



3c

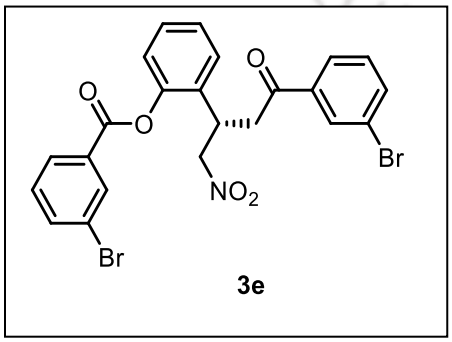
3c. ((S)-2-(4-(3-ethoxyphenyl)-1-nitro-4-oxobutan-2yl)phenyl 3-ethoxybenzoate) was obtained as a light yellow sticky compound in 68% (32.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.75 – 7.73 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.41 – 7.37 (m, 3H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.10 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.83 (dd, *J* = 12.7, 6.9 Hz, 1H), 4.77 (dd, *J* = 12.7, 7.5 Hz, 1H), 4.50 – 4.44 (m, 1H), 4.14 (q, *J* = 7.0 Hz, 2H), 4.05 (tq, *J* = 6.7, 2.1 Hz, 2H), 3.49 (dd, *J* = 17.6, 6.1 Hz, 1H), 3.42 (dd, *J* = 17.6, 7.9 Hz, 1H), 1.48 (t, *J* = 7.0 Hz, 3H), 1 .43 (t, *J* = 7.0 Hz,

3H).**13C NMR (151 MHz, Chloroform-*d*)** δ 196.7, 165.4, 159.3, 149.0, 137.6, 131.3, 130.2, 130.0, 129.8, 129.1, 128.3, 126.9, 123.6, 122.7, 121.4, 120.7, 120.6, 115.2, 112.9, 78.6, 64.0, 63.8, 41.0, 33.7, 14.9, 14.9. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.7 min, t_{minor} = 21.0 min). **ESI HRMS**: calcd. For $C_{27}H_{28}NO_7$ $[M+H]^+$ 478.1860, found 478.1865.



3d

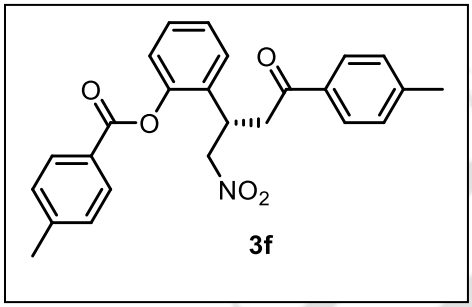
3d. ((S)-2-(1-nitro-4-oxo-4-(3-propoxyphenyl)butan-2-yl)phenyl 3-propoxybenzoate) was obtained as a colorless viscous compound in 66% (33.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 1.7 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.38 – 7.34 (m, 3H), 7.31 – 7.27 (m, 2H), 7.23 – 7.19 (m, 2H), 7.08 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.80 (dd, *J* = 12.7, 6.9 Hz, 1H), 4.75 (dd, *J* = 12.7, 7.4 Hz, 1H), 4.48 – 4.42 (m, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.91 (qd, *J* = 6.1, 2.3 Hz, 2H), 3.47 (dd, *J* = 17.6, 6.1 Hz, 1H), 3.40 (dd, *J* = 17.6, 7.8 Hz, 1H), 1.85 (dt, *J* = 14.1, 7.0 Hz, 2H), 1.79 (dt, *J* = 14.1, 7.2 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H).**^{13}C NMR (151 MHz Chloroform-*d*)** δ 196.7, 165.4, 159.5, 149.0, 137.6, 131.3, 130.2, 130.0, 129.8, 129.1, 128.3, 126.9, 123.6, 122.6, 121.3, 120.7, 120.6, 115.3, 112.9, 78.6, 77.4, 77.2, 77.0, 69.9, 69.8, 41.0, 22.9, 22.7, 22.6, 10.7, 10.7. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 16.7 min, t_{minor} = 15.5 min). **ESI HRMS**: calcd. For $C_{29}H_{32}NO_7$ $[M+H]^+$ 506.2173, found 506.2177.



3e

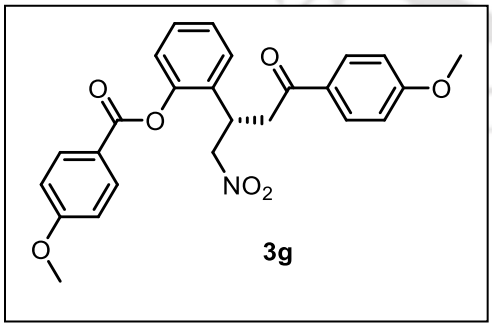
3e. ((S)-2-(4-(3-bromophenyl)-1-nitro-4-oxobutan-2-yl)phenyl 3-bromobenzoate) was obtained as a whitish sticky compound in 78% (42.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.35 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 7.82 – 7.77 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.37 (dd, *J* = 15.3, 7.4 Hz, 2H), 7.31 (dd, *J* = 10.4, 5.3 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 1H), 4.75 (ddd, *J* = 30.7, 12.7, 7.2 Hz, 2H), 4.45 – 4.38 (m, 1H), 3.46

(dd, *J* = 17.7, 6.4 Hz, 1H), 3.38 (dd, *J* = 17.7, 7.4 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 195.4, 164.2, 148.7, 137.9, 137.2, 136.6, 133.4, 131.3, 131.1, 130.9, 130.6, 130.5, 129.3, 129.0, 127.9, 127.2, 126.7, 123.5, 123.3, 123.1, 78.5, 77.4, 77.2, 77.0, 41.1, 33.1, 32.1, 29.9, 29.5, 22.9, 14.3. **HPLC Analysis:** ee = 95%, Chiralpak IC Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 18.4 min, t_{minor} = 17.0 min). **ESI HRMS**: calcd. For $C_{23}H_{18}Br_2NO_5$ $[M+H]^+$545.9546, found 545.9543.



3f

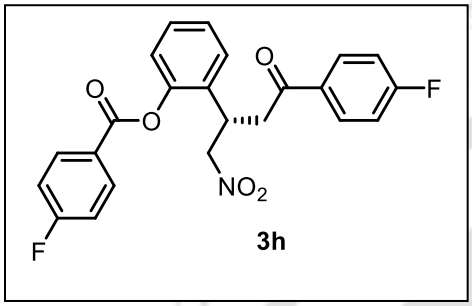
3f. ((S)-2-(1-nitro-4-oxo-4-(p-tolyl)butan-2-yl)phenyl 4-methylbenzoate) was obtained as a yellow sticky compound in 77% (32.2 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.12 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.35 (dd, *J* = 14.3, 7.6 Hz, 4H), 7.26 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.20 (t, *J* = 8.8 Hz, 3H), 4.80 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.75 (dd, *J* = 12.7, 7.5 Hz, 1H), 4.48 – 4.39 (m, 1H), 3.45 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.37 (dd, *J* = 17.4, 8.1 Hz, 1H), 2.47 (s, 3H), 2.38 (s, 3H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.5, 165.5, 149.1, 145.1, 144.6, 133.9, 131.5, 130.5, 129.7, 129.5, 129.0, 128.3, 128.3, 126.7, 126.3, 123.6, 78.6, 77.4, 77.2, 77.0, 40.7, 33.9, 22.0, 21.8. **HPLC Analysis:** ee = 81%, Chiralpak IC Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 47.5 min, t_{minor} = 38.1 min). **ESI HRMS**: calcd. For $C_{25}H_{24}NO_5$ $[M+H]^+$ 418.1649, found 418.1649.



3g

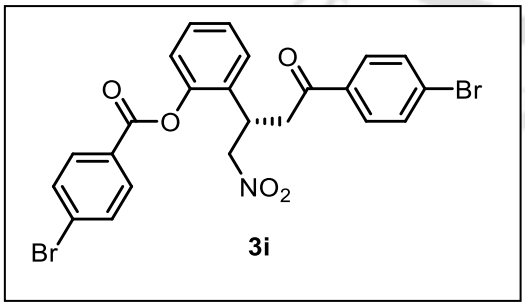
3g. ((S)-2-(4-(4-methoxyphenyl)-1-nitro-4-oxobutan-2-yl)phenyl 4-methoxybenzoate) was obtained as a light yellow sticky compound in 65% (29.2 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.19 (dd, *J* = 9.3, 2.3 Hz, 26H), 7.86 (d, *J* = 8.9 Hz, 27H), 7.54 (s, 1H), 7.51 (s, 1H), 7.37 (t, *J* = 7.1 Hz, 28H), 7.30 – 7.27 (m, 41H), 7.24 – 7.21 (m, 13H), 7.03 (d, *J* = 8.9 Hz, 27H), 6.88 (d, *J* = 8.9 Hz, 26H), 4.84 (dd, *J* = 12.7, 6.7 Hz, 16H), 4.78 (dd, *J* = 12.7, 7.6 Hz, 15H), 4.48 – 4.42 (m, 16H), 3.93 (s, 40H), 3.87 (s, 39H), 3.44 (dd, *J* = 17.1, 5.8

Hz, 15H), 3.36 (dd, *J* = 17.2, 8.2 Hz, 14H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 195.5, 165.2, 164.4, 163.9, 149.1, 132.7, 130.6, 129.0, 12 6.7, 123.7, 114.3, 114.0, 78.6, 77.4, 77.2, 77.0, 55.8, 55.7, 40.5, 33.9.**HPLC Analysis:** ee = 74%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 43.8 min, t_{minor} = 55.7 min). **ESI HRMS:** calcd. For $C_{25}H_{24}NO_7$ $[M+H]^+$ 450.1547, found 450.1552.



3h

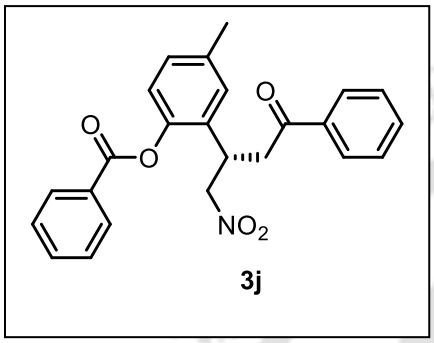
3h. ((S)-2-(4-(4-fluorophenyl)-1-nitro-4-oxobutan-2-yl)phenyl 4-fluorobenzoate) was obtained as a yellow sticky compound in 73% (31.0 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.25 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.91 – 7.87 (m, 2H), 7.36 (dd, *J* = 14.0, 6.6 Hz, 2H), 7.31 – 7.27 (m, 1H), 7.22 (t, *J* = 8.7 Hz, 3H), 7.08 (t, *J* = 8.6 Hz, 2H), 4.79 (dd, *J* = 12.7, 7.0 Hz, 1H), 4.73 (dd, *J* = 12.7, 7.3 Hz, 1H), 4.47 – 4.40 (m, 1H), 3.45 (dd, *J* = 17.4, 6.2 Hz, 1H), 3.37 (dd, *J* = 17.5, 7.7 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 195.2, 164.5, 148.8, 133.2, 133.1, 132.8, 131.3, 130.9, 130.9, 129.2, 127.9, 127.0, 125.3, 125.2, 123.5, 116.3, 116.2, 116.1, 116.0, 78.6, 77.4, 77.2, 77.0, 40.9, 33.3. **HPLC Analysis:** ee = 78%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 26.9 min, t_{minor} = 33.5 min). **ESI HRMS:** calcd. For $C_{23}H_{18}F_2NO_5$ $[M+H]^+$ 426.1148, found 426.1150.



3i

3i. ((S)-2-(4-(4-bromophenyl)-1-nitro-4-oxobutan-2-yl)phenyl 4-bromobenzoate) was obtained as a brownish yellow sticky compound in 76% (41.2 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.74 – 7.67 (m, 4H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 4.77 (dd, *J* = 12.7, 7.1 Hz, 1H), 4.71 (dd, *J* = 12.7, 7.3 Hz, 1H), 4.42 (p, *J* = 7.1 Hz, 1H), 3.42 (dd, *J* = 17.4, 6.4 Hz, 1H), 3.36 (dd, *J* = 17.4, 7.5 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 195.8, 164.8, 148.8, 135.0, 132.4, 132.2,

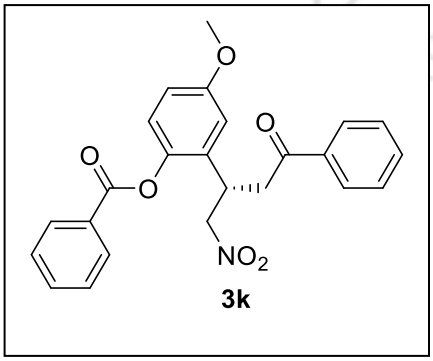
131.9, 131.1, 129.7, 129.2, 129.1, 127.9, 127.8, 127.1, 123.5, 78.6, 77.4, 77.2, 77.0, 41.0, 33.2.**HPLC Analysis:** ee = 86%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 41.5 min, t_{minor} = 56.0 min). **ESI HRMS:** calcd. For $C_{23}H_{18}Br_2NO_5$ $[M+H]^+$ 545.9546, found 545.9549.



3j

3j. ((S)-4-methyl-2-(2-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate) was obtained as a light yellow sticky compound in 75% (30.2 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.24 – 8.19 (m, 2H), 7.89 – 7.85 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (q, *J* = 7.7 Hz, 3H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.17 – 7.13 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 4.77 (ddd, *J* = 31.7, 12.7, 7.2 Hz, 2H), 4.44 – 4.36 (m, 1H), 3.43 (ddd, *J* = 25.6, 17.5, 7.0 Hz, 2H), 2.36 (s, 3H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 197.0, 165.7, 146.7, 136.6, 136.3, 134.1, 133.7, 130.9, 130.5, 129.8, 129.1, 129.0, 128.9, 128.7, 128.2, 123.2, 78.6, 77.4, 77.2, 77.0, 40.9, 33.6, 21.2.

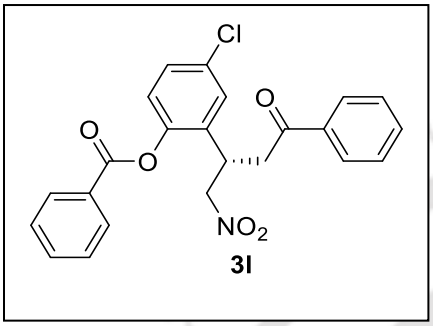
HPLC Analysis: ee = 83%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 29.5 min, t_{minor} = 27.3 min). **ESI HRMS:** calcd. For $C_{24}H_{22}NO_5$ $[M+H]^+$ 404.1492, found 404.1488.



3k

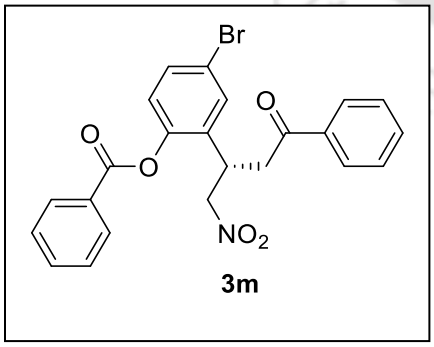
3k. (S)-4-methoxy-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate was obtained as a pale yellow sticky liquid in 75% (31.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.25 – 8.20 (m, 2H), 7.88 – 7.84 (m, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (q, *J* = 7.8 Hz, 3H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.89 – 6.85 (m, 2H), 4.77 (ddd, *J* = 28.8, 12.7, 7.1 Hz, 2H), 4.42 – 4.35 (m, 1H), 3.81 (s, 3H), 3.48 (dd, *J* = 17.6, 5.9 Hz, 1H), 3.39 (dd, *J* = 17.6, 8.0 Hz, 1H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.8, 165.9, 157.8, 142.3, 136.3, 134.1, 133.7, 132.4, 130.4,

129.1, 129.0, 128.9, 128.2, 124.3, 114.0, 113.5, 78.5, 55.8, 40.8, 22.9.**HPLC Analysis:** ee = 86%, Chiralpak IA Column Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 40.5 min, t_{minor} = 37.5 min). **ESI HRMS**: calcd. For $C_{24}H_{22}NO_6$ $[M+H]^+$ 420.1442, found 420.1444.



3l

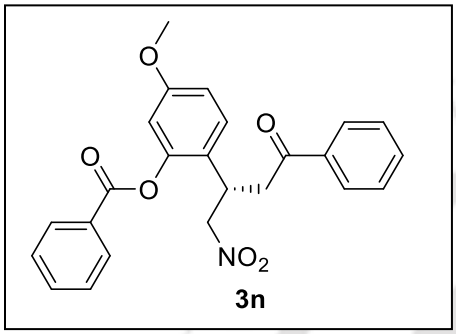
3l. ((S)-4-chloro-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate) was obtained as a brownish sticky compound in 78% (33.0 mg) yield after column chromatography: **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.22 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.89 – 7.86 (m, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (dt, *J* = 11.8, 7.6 Hz, 3H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 4.80 (dd, *J* = 12.9, 6.7 Hz, 1H), 4.73 (dd, *J* = 12.9, 7.6 Hz, 1H), 4.47 – 4.40 (m, 1H), 3.47 (dd, *J* = 17.7, 6.1 Hz, 1H), 3.41 (dd, *J* = 17.8, 7.8 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.4, 165.3, 147.5, 136.2, 134.4, 133.9, 133.4, 132.2, 130.5, 129.2, 129.1, 128.9, 128.7, 128.3, 128.2, 125.0, 78.3, 77.4, 77.2, 77.0, 40.7, 33.4.**HPLC Analysis:** ee = 81%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 26.2 min, t_{minor} = 28.7min). **ESI HRMS:** calcd. For $C_{23}H_{19}ClNO_5$ $[M+H]^+$ 424.0946, found 424.0944.



3m

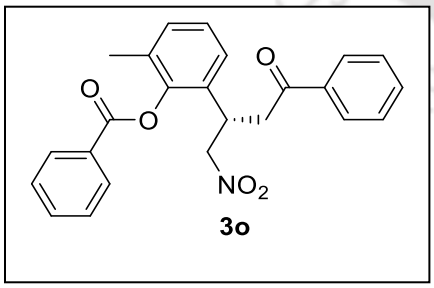
3m. ((S)-4-bromol-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate) was obtained as a yellow sticky compound in 72% (33.6 mg) yield after column chromatography. : **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.22 (d, *J* = 7.3 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (dt, *J* = 12.5, 7.6 Hz, 3H), 7.50 – 7.46 (m, 2H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 1H), 4.80 (dd, *J* = 12.9, 6.7 Hz, 1H), 4.72 (dd, *J* = 12.9, 7.6 Hz, 1H), 4.46 – 4.39 (m, 1H), 3.46 (dd, *J* = 17.7, 6.1 Hz, 1H), 3.40 (dd, *J* = 17.8, 7.8 Hz, 1H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.4, 165.2,

148.1, 136.2, 134.4, 133.9, 132.2, 131.2, 130.5, 129.1, 128.9, 128.7, 128.2, 125.3, 119.9, 78.3, 77.4, 77.2, 77.0, 40.7, 33.4. **HPLC Analysis:** ee = 81%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 31.3 min, t_{minor} = 28.1 min). **ESI HRMS**: calcd. For $C_{23}H_{19}BrNO_5$ $[M+H]^+$ 468.0441, found 468.0446.



3n

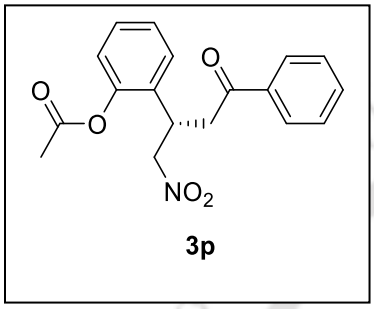
3n. ((S)-5-methoxy-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate) was obtained as a yellow sticky compound in 70% (29.2 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.23 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.89 – 7.86 (m, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 10.9, 4.6 Hz, 3H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 1.5 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 4.78 (dd, *J* = 12.5, 6.9 Hz, 1H), 4.73 (dd, *J* = 12.5, 7.4 Hz, 1H), 4.40 – 4.35 (m, 1H), 3.80 (s, 3H), 3.47 (dd, *J* = 17.4, 6.2 Hz, 1H), 3.40 (dd, *J* = 17.4, 7.9 Hz, 1H). **^{13}C NMR (151 MHz Chloroform-*d*)** δ 197.1, 165.4, 159.9, 149.7, 136.3, 134.2, 133.7, 130.5, 129.0, 128.9, 128.8, 128.7, 128.2, 123.1, 113.1, 108.9, 78.8, 77.4, 77.2, 77.0, 55.7, 41.0, 33.2. **HPLC Analysis:** ee = 92%, Chiralpak IC Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 35.4 min, t_{minor} = 40.5 min). **ESI HRMS**: calcd. For $C_{24}H_{22}NO_6$ $[M+H]^+$ 420.1442, found 420.1446.



3o

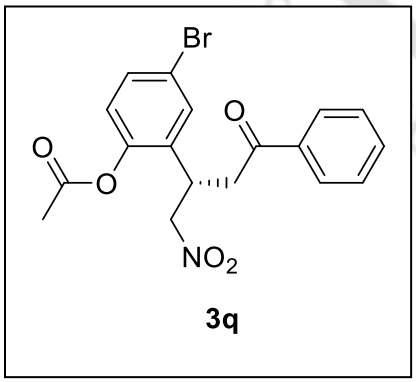
3o. ((S)-2-methyl-6-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl benzoate) was obtained as a brownish sticky compound in 73% (29.4 mg) yield after column **chromatography^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.22 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (q, *J* = 7.6 Hz, 3H), 7.43 – 7.38 (m, 2H), 7.18 – 7.12 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 4.80 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.75 (dd, *J* = 12.7, 7.5 Hz, 1H), 4.43 – 4.37 (m, 1H), 3.47 (dd, *J* = 17.5, 5.9 Hz, 1H), 3.40 (dd, *J* = 17.5, 8.1 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.9, 165.7, 146.7, 136.6, 136.3, 134.1, 133.7,

130.9, 130.5, 129.8, 129.1, 129.0, 128.9, 128.7, 128.2, 123.2, 78.6, 77.4, 77.2, 77.0, 40.9, 33.6, 21.2. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.8 min, t_{minor} = 14.9 min). **ESI HRMS**: calcd. For $C_{24}H_{22}NO_5$ $[M+H]^+$ 404.1492, found 404.1504.



3p

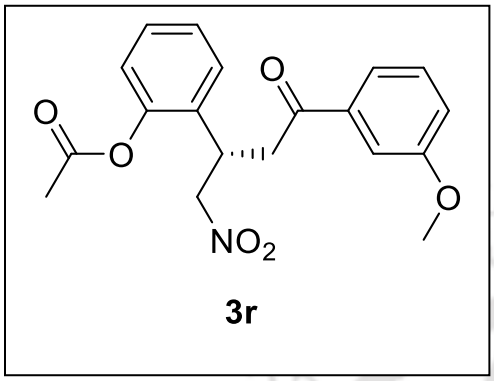
3p. ((S)-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl acetate) was obtained as a yellow sticky liquid 60% (19.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.93 – 7.90 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.21 (m, 1H), 7.13 – 7.10 (m, 1H), 4.77 (dd, *J* = 12.6, 7.2 Hz, 1H), 4.69 (dd, *J* = 12.6, 7.0 Hz, 1H), 4.44 – 4.37 (m, 1H), 3.46 – 3.43 (m, 2H), 2.38 (s, 3H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.8, 196.8, 169.8, 148.7, 136.3, 133.8, 131.3, 129.0, 128.9, 128.8, 128.2, 127.6, 126.8, 123.4, 78.6, 40.9, 33.0, 21.2. **HPLC Analysis:** ee = 80%, Chiralpak IA Column n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 18.6 min, t_{minor} = 26.4 min). **ESI HRMS**: calcd. For $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1179, found 328.1285.



3q

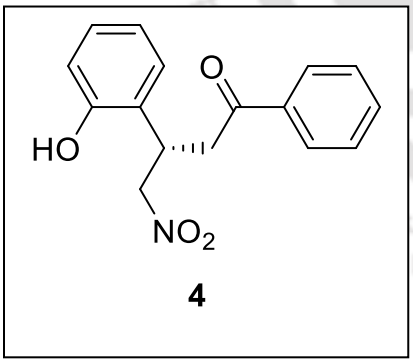
3q. ((S)-4-bromo-2-(1-nitro-4-oxo-4-phenylbutan-2-yl)phenyl acetate) was obtained as a pale yellow sticky compound in 56% (22.6 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.92 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.43 – 7.40 (m, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 4.75 (dd, *J* = 12.8, 7.0 Hz, 1H), 4.65 (dd, *J* = 12.8, 7.2 Hz, 1H), 4.41 – 4.35 (m, 1H), 3.42 (d, *J* = 6.9 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.2, 169.3, 147.6, 135.9, 133.8, 133.5, 131.8, 130.5, 128.8, 128.0, 125.0, 119.7, 78.1, 77.2, 77.0, 76.8, 40.6, 32.5, 20.9. **HPLC Analysis:** ee = 78%, Chiralpak IA

Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 18.6 min, t_{minor} = 17.1 min). **ESI HRMS**: calcd. For $C_{18}H_{17}BrNO_5$ $[M+H]^+$ 406.0285, found 406.0289.



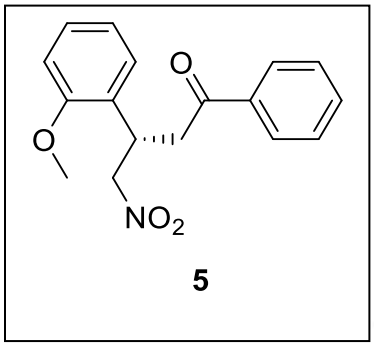
3r

3r. ((S)-2-(1-nitro-4-oxo-4-(m-tolyl)lbutan-2-yl)phenyl acetate) was obtained as a colorless sticky compound in 46% (16.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.49 (d, *J* = 7.7 Hz, 1H), 7.43 (s, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.12 (dd, *J* = 8.0, 4.2 Hz, 1H), 4.76 (dd, *J* = 12.6, 7.3 Hz, 1H), 4.68 (dd, *J* = 12.6, 7.0 Hz, 1H), 4.40 (dt, *J* = 13.9, 7.1 Hz, 1H), 3.84 (s, 2H), 3.43 (qd, *J* = 17.7, 6.9 Hz, 2H), 2.39 (s, 2H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.7, 169.8, 160.0, 148.7, 137.7, 131.2, 129.9, 129.0, 127.6, 126.8, 123.4, 120.8, 120.4, 112.3, 78.6, 55.6, 41.0, 33.1, 21.2. **HPLC Analysis:** ee = 70%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 25.1 min). **ESI HRMS**: calcd. For $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285, found 358.1283.



4

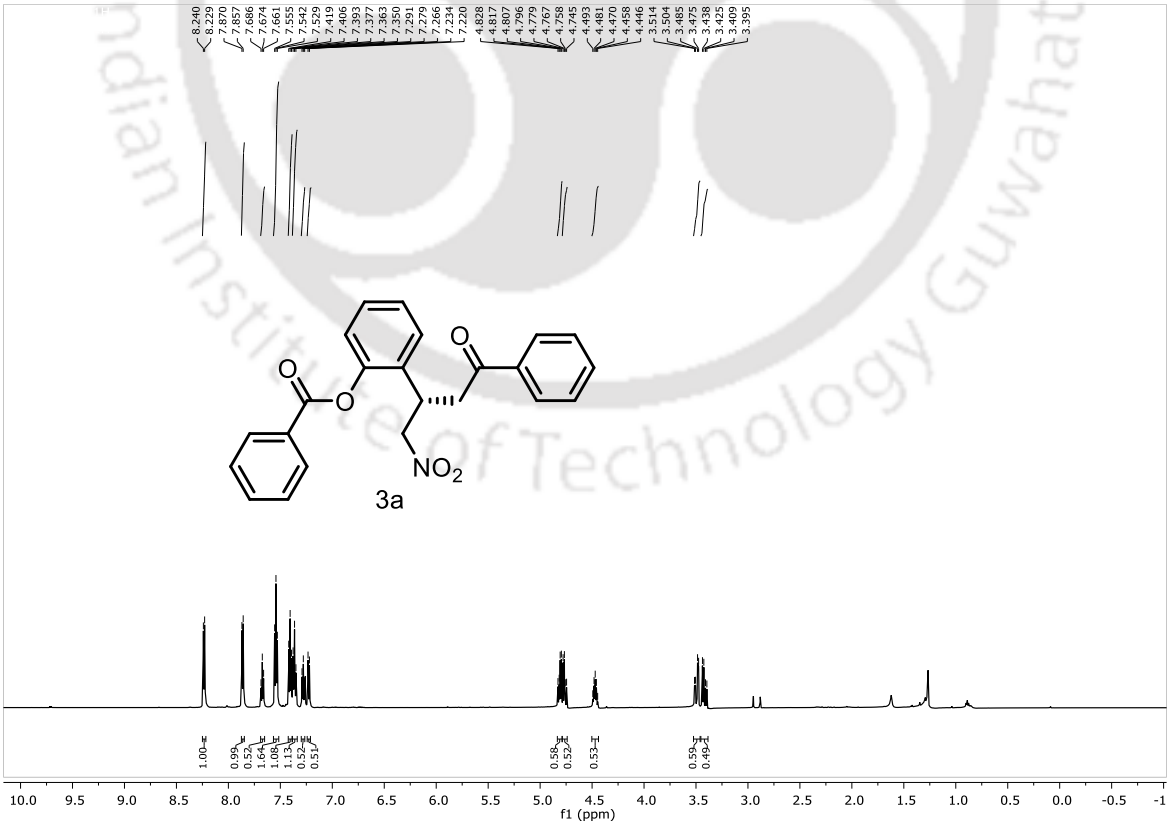
4. ((S)-3-(2-hydroxyphenyl)-4-nitro-1-phenylbutan-1-one) was obtained as a brownish sticky compound in 40% (29.9 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.94 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.16 – 7.11 (m, 2H), 6.90 (td, *J* = 7.6, 0.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.40 (s, 1H), 4.88 (dd, *J* = 12.7, 7.9 Hz, 1H), 4.82 (dd, *J* = 12.7, 6.9 Hz, 1H), 4.47 – 4.41 (m, 1H), 3.61 (dd, *J* = 18.0, 7.9 Hz, 1H), 3.53 (dd, *J* = 18.0, 5.6 Hz, 1H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 198.8, 154.0, 136.2, 134.0, 129.1, 128.9, 128.4, 125.5, 121.4, 117.3, 78.2, 77.4, 77.23, 77.0, 41.1, 34.7.**HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 38.5 min, t_{minor} = 41.2 min). **ESI HRMS**: calcd. For $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1074, found 286.1070.

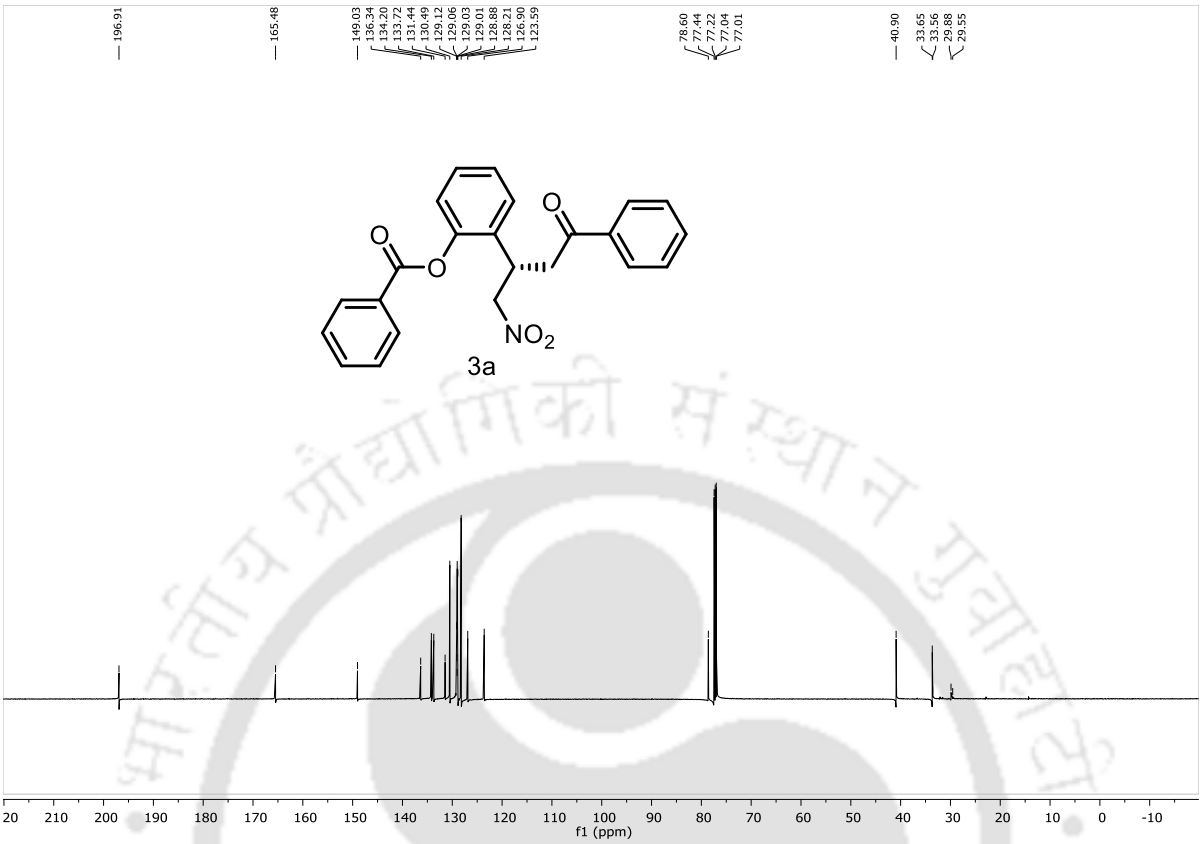


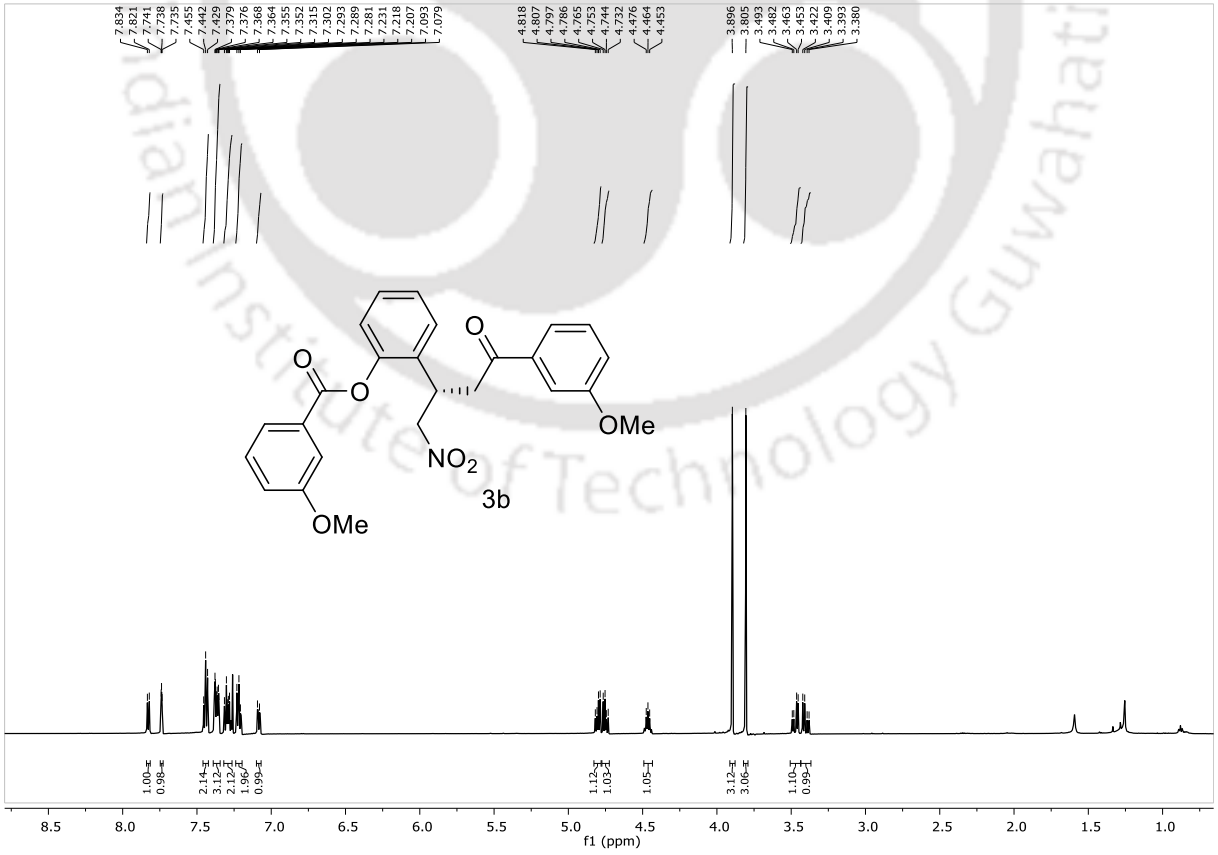
5

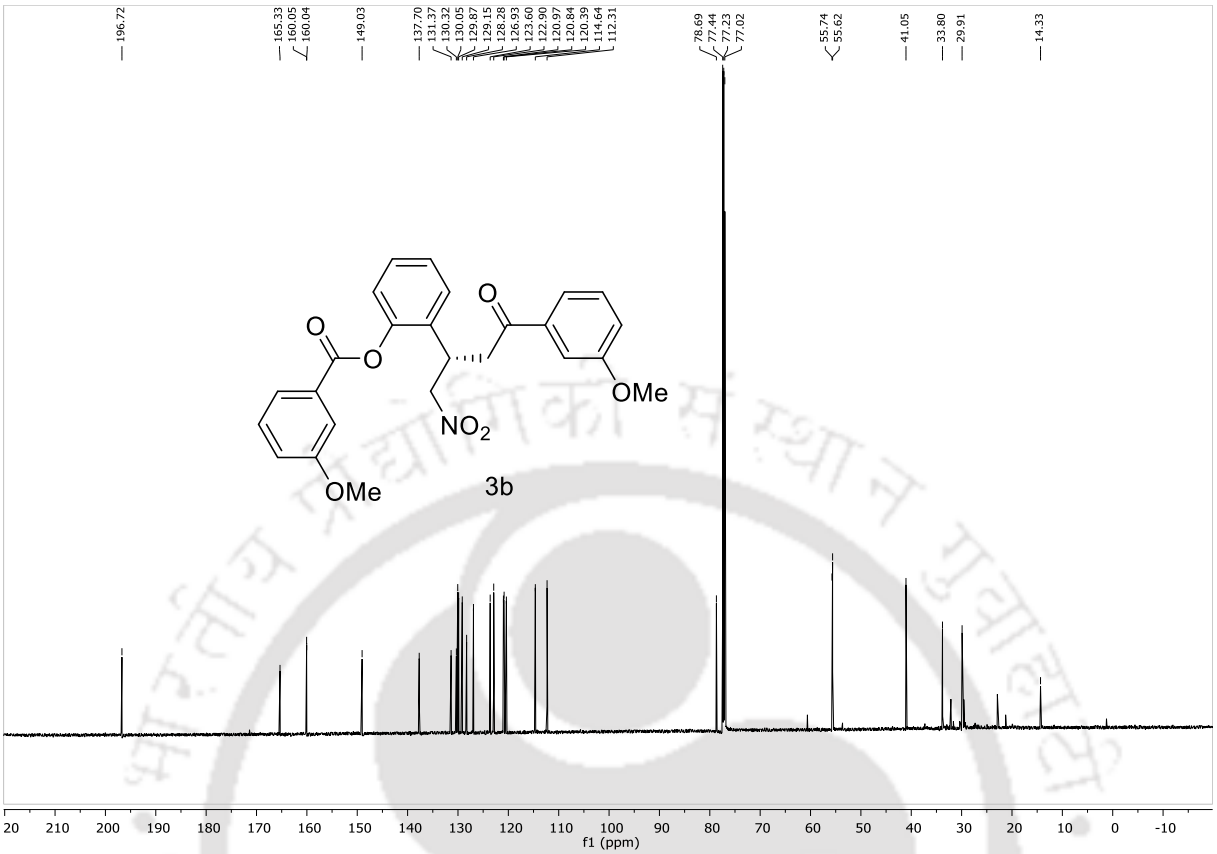
5. ((S)-3-(2-methoxyphenyl)-4-nitro-1-phenylbutan-1-one) was obtained as a colourless sticky compound in 55% (16.4 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.94 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.57 (s, 2H), 7.46 (t, *J* = 7.8 Hz, 3H), 6.92 – 6.87 (m, 3H), 4.86 (dd, *J* = 6.9, 2.3 Hz, 2H), 4.42 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.54 (d, *J* = 7.0 Hz, 2H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 197.8, 157.3, 136.7, 133.6, 129.7, 129.1, 128.8, 128.2, 126.8, 121.1, 111.2, 78.0, 77.4, 77.2, 77.0, 55.5, 39.9, 36.1.**HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 75/25, flow rate 1.0 mL/min, λ = 225 nm (t_{major} = 11.9 min, t_{minor} = 11.1 min). **ESI HRMS**: calcd. For $C_{17}H_{18}NO_4$ $[M+H]^+$ 300.1230, found 300.1242.

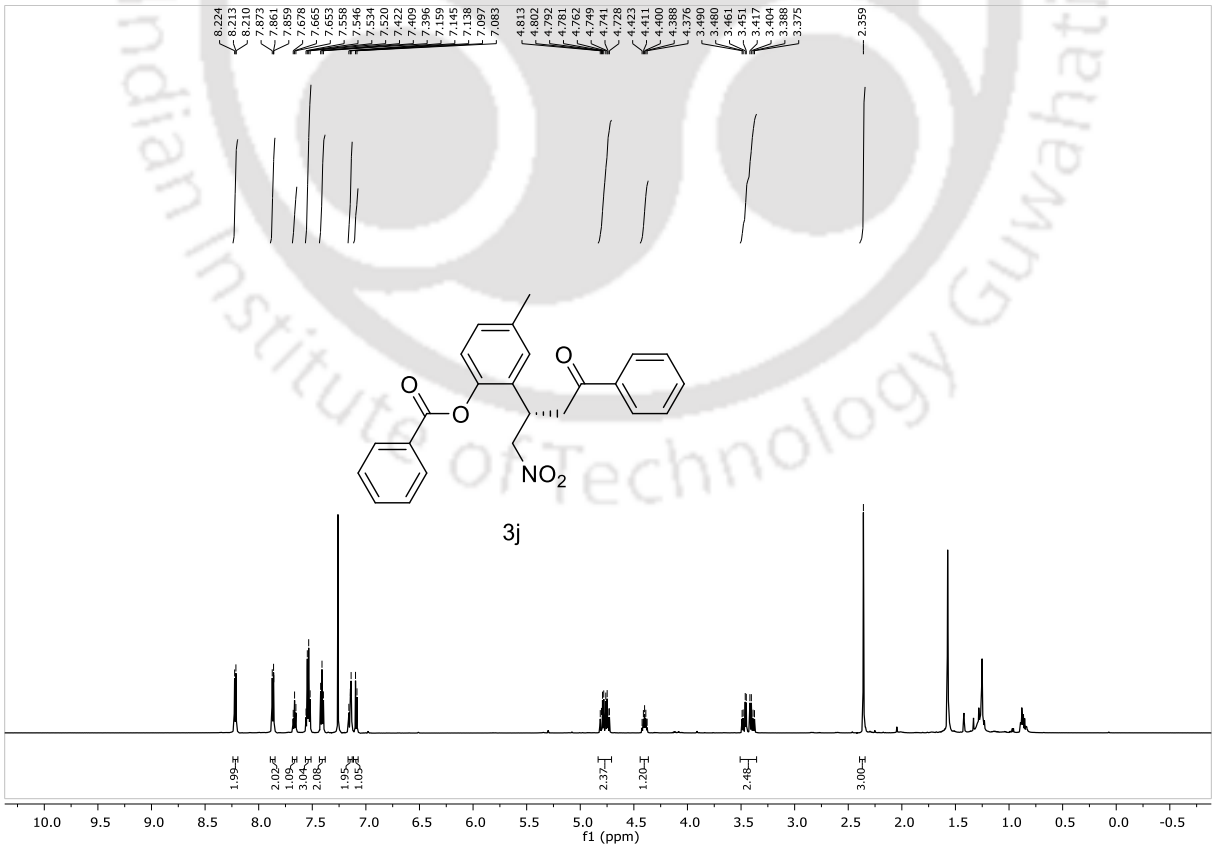
2.6.6. Some selected NMR spectra of the products:

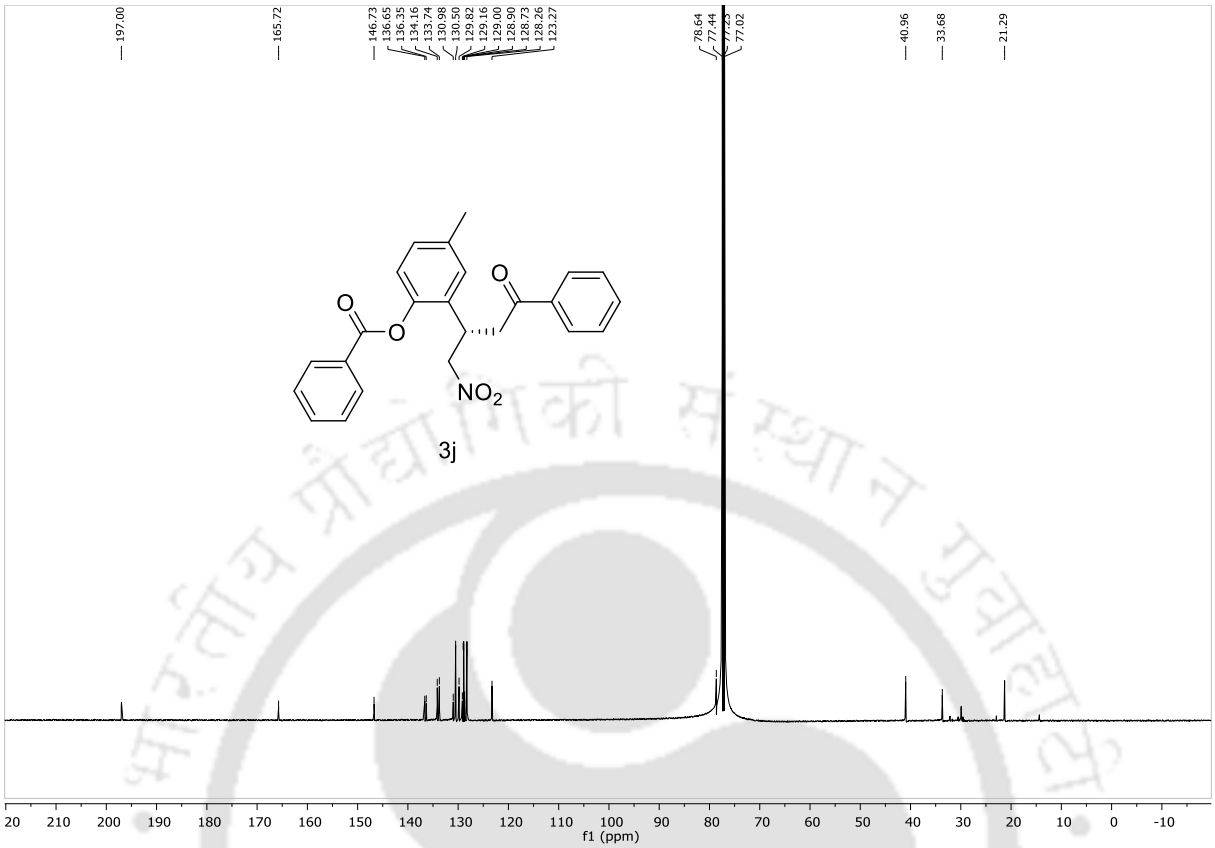


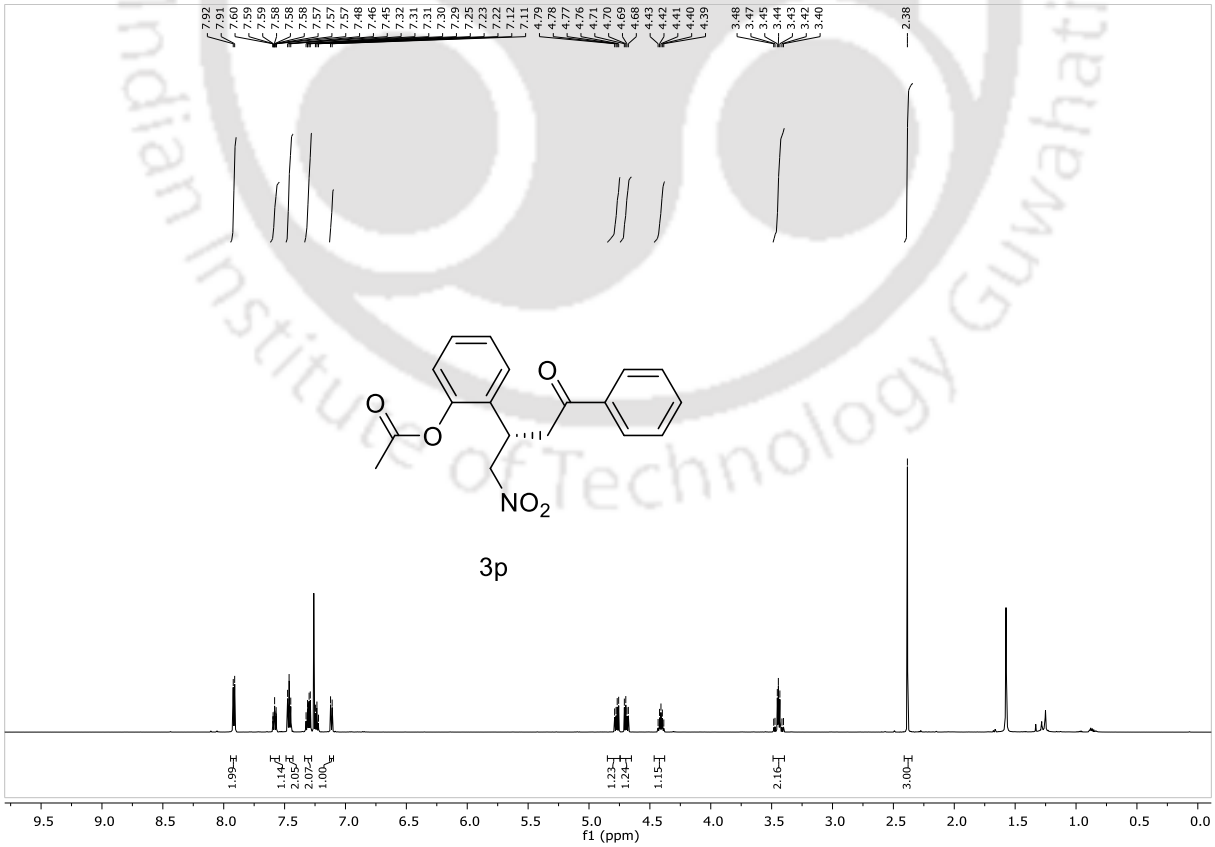


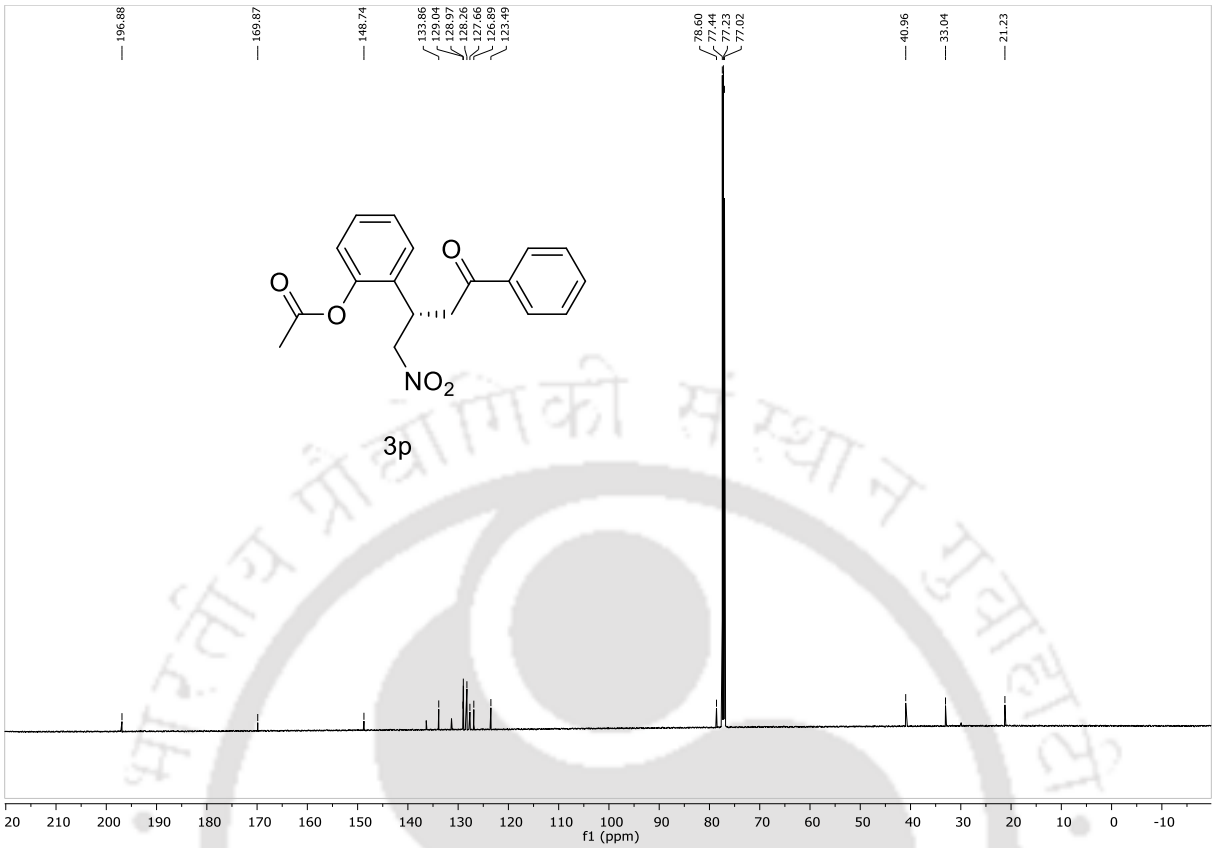


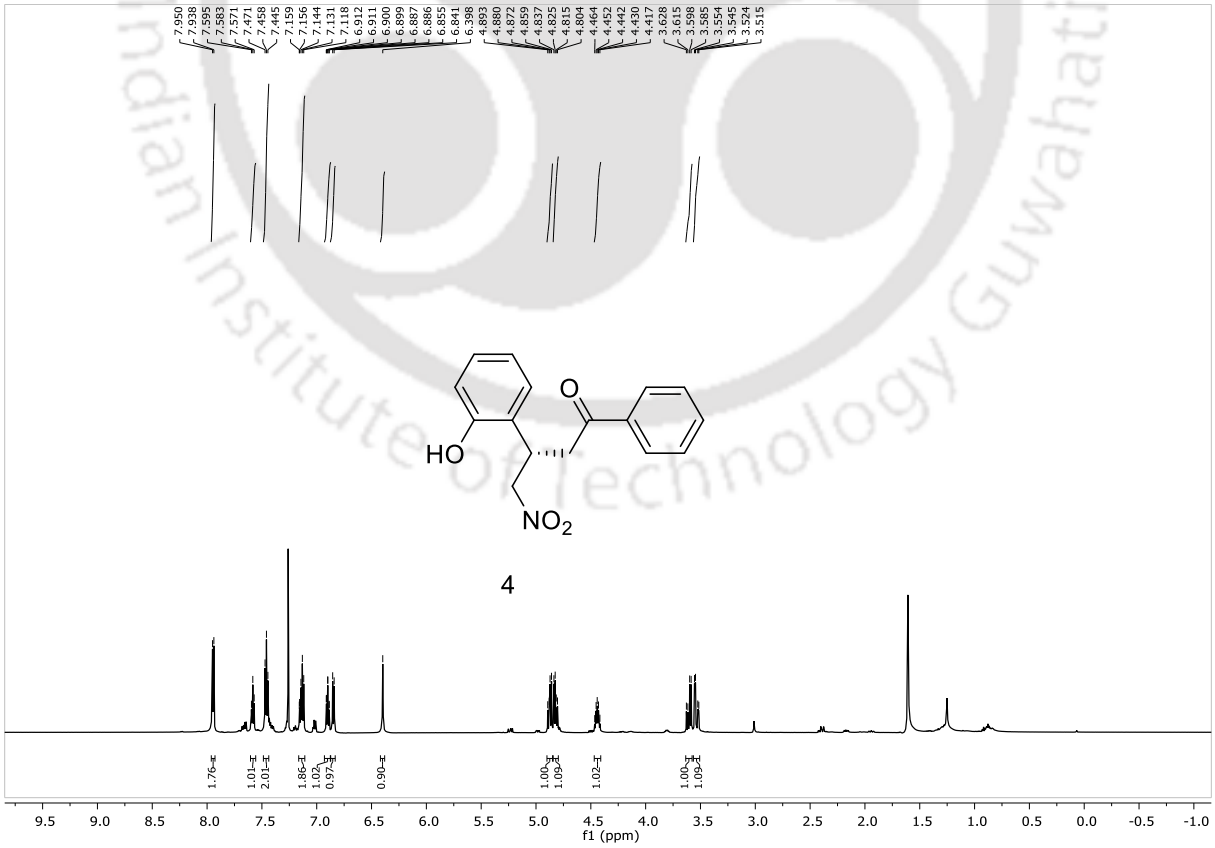


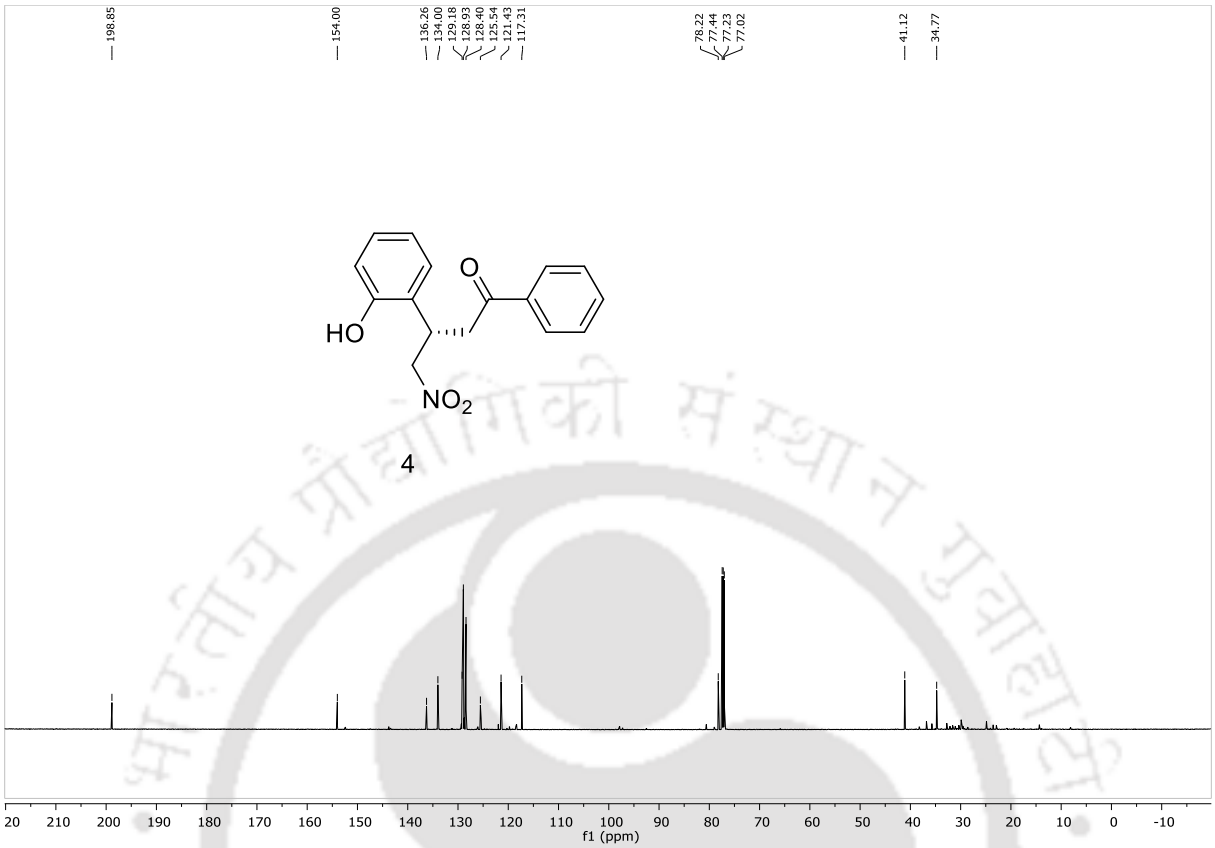


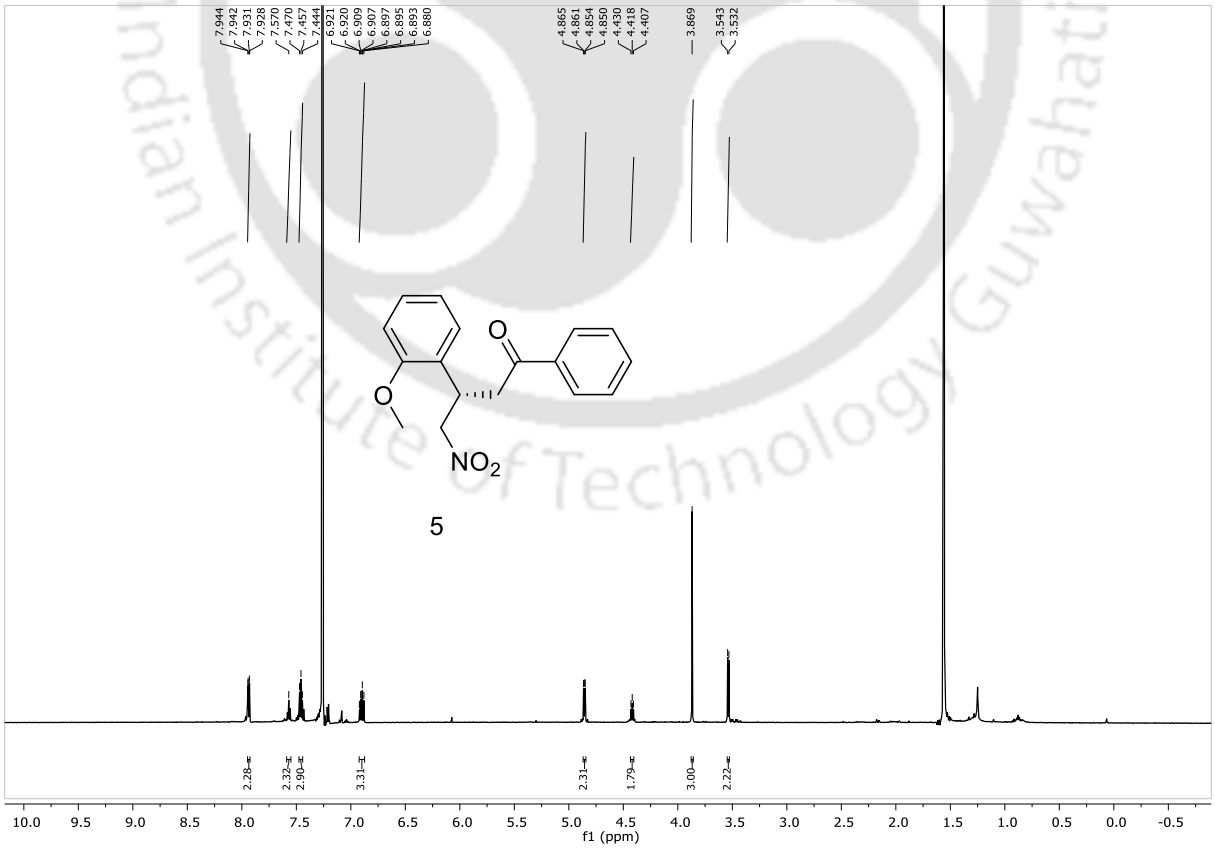


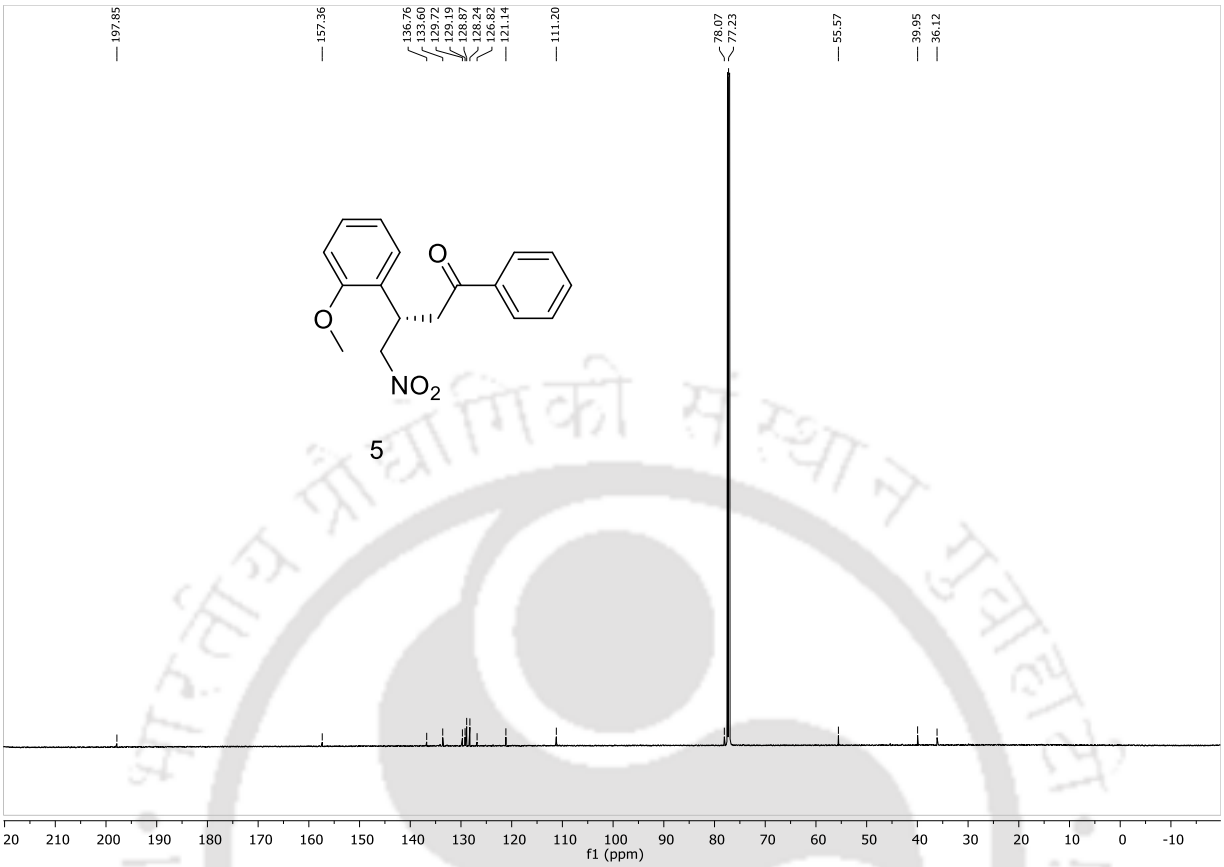






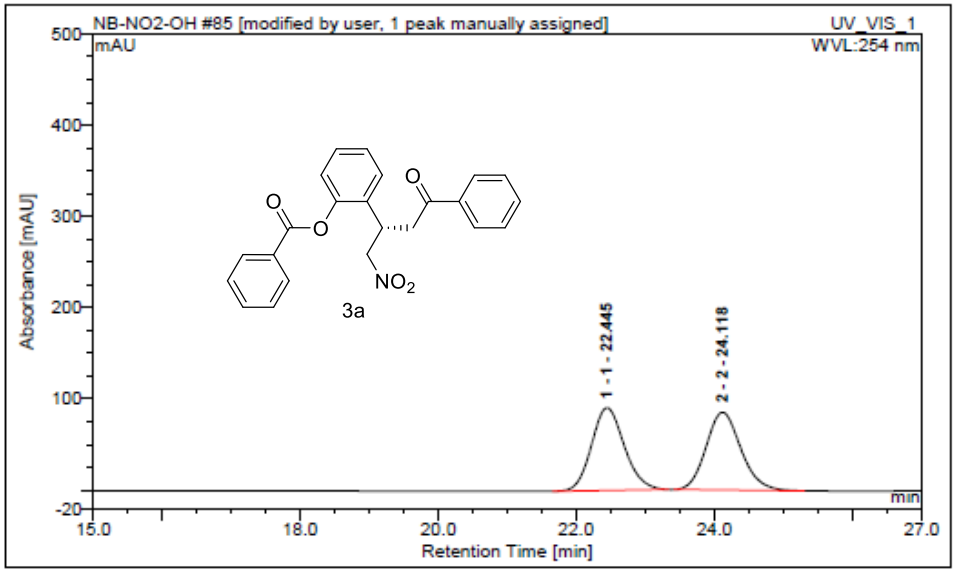






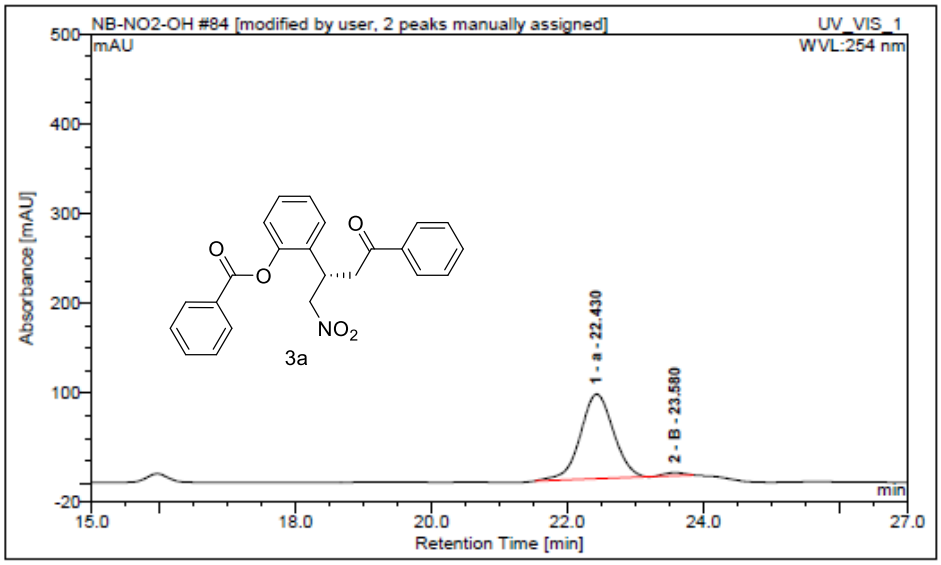
2.6.7. Some selected HPLC spectra of the products:

The HPLC chromatogram of racemic **3a**



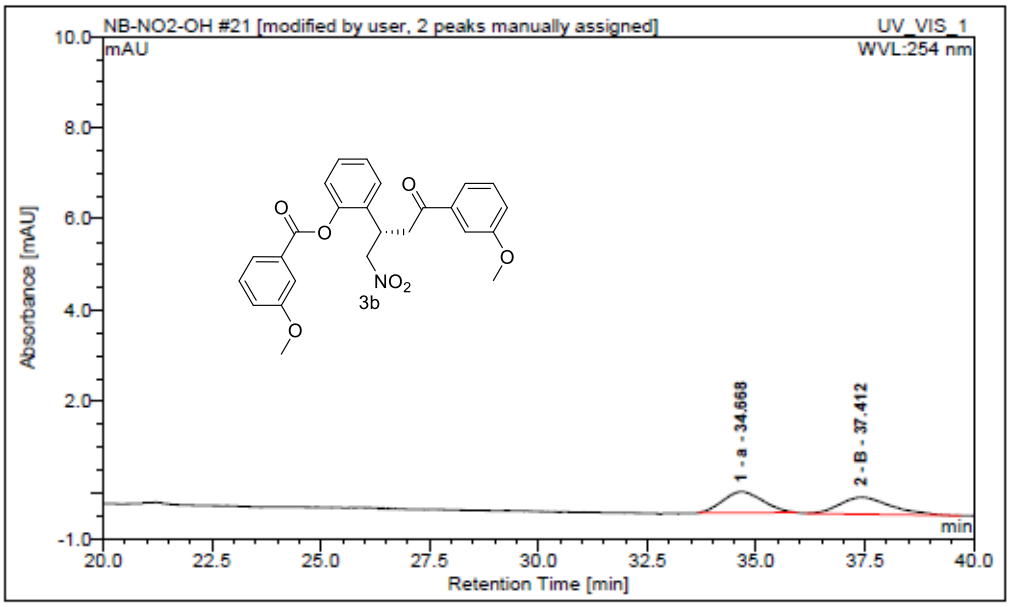
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	22.45	49.9214	49.97441389	90.62098	n.a.
2	2	24.12	49.973	50.02558611	85.225	n.a.

The HPLC chromatogram of chiral **3a**



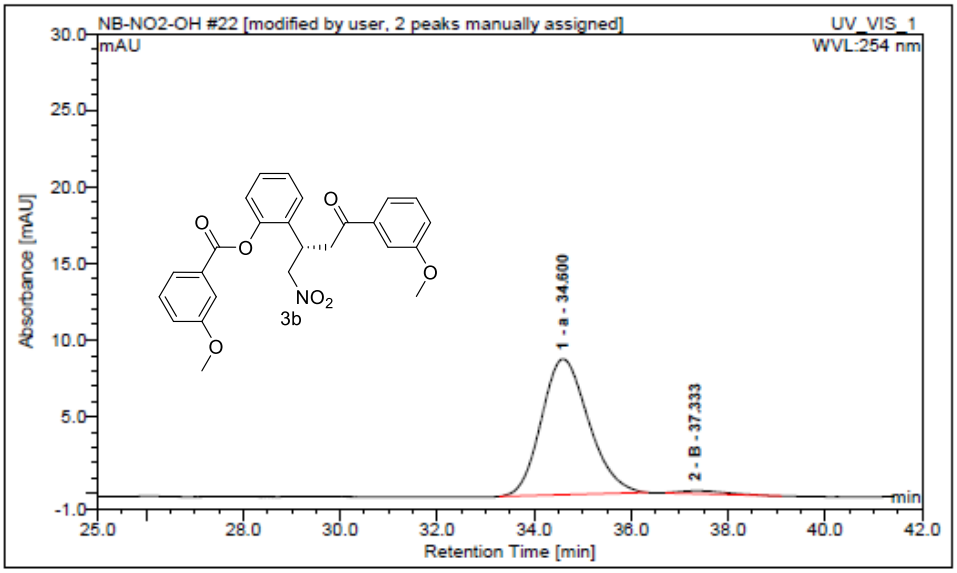
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	22.43	52.96288	97.94421359	93.98245	n.a.
2	B	23.58	1.112	2.055786408	3.381	n.a.

The HPLC chromatogram of racemic **3b**



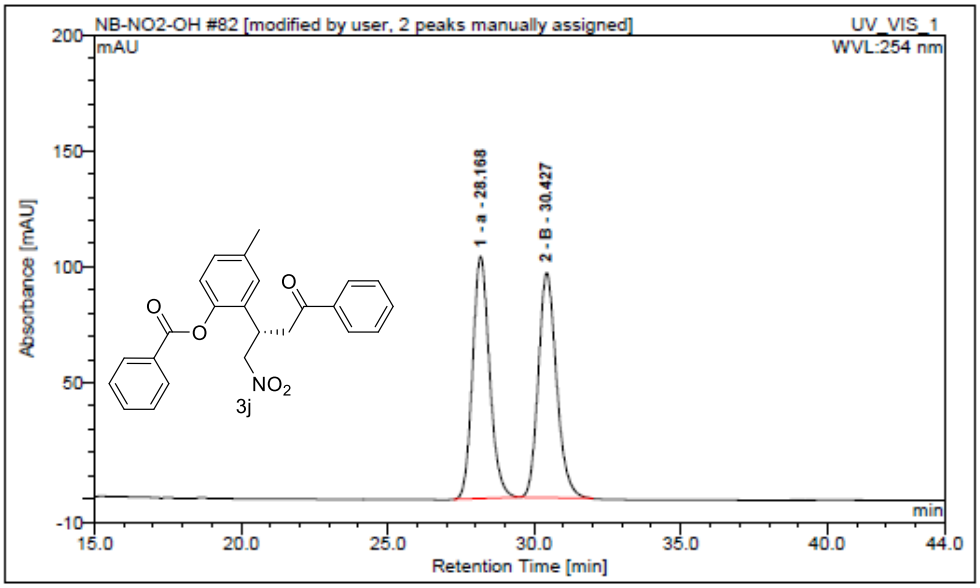
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	34.67	0.48875	49.57814687	0.46271	n.a.
2	B	37.41	0.497	50.42185313	0.367	n.a.

The HPLC chromatogram of chiral **3b**



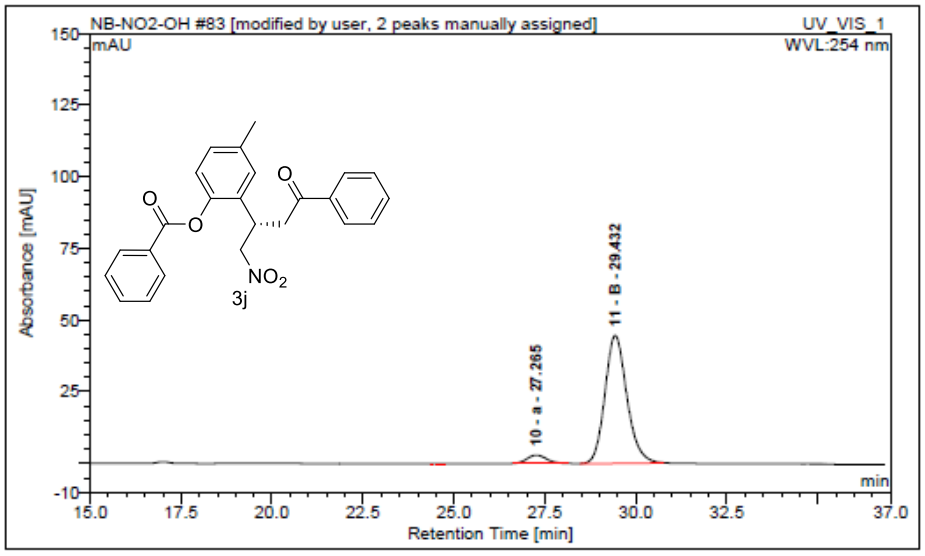
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	34.60	9.998164	97.9753208	8.86157	n.a.
2	B	37.33	0.207	2.024679195	0.200	n.a.

The HPLC chromatogram of racemic **3j**



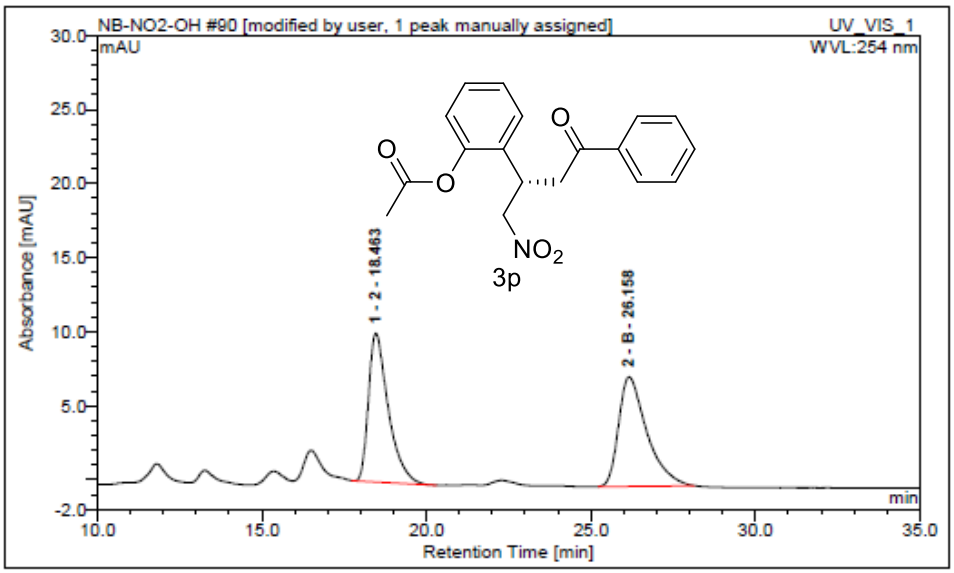
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	28.17	70.00816	49.97447352	104.2762	n.a.
2	B	30.43	70.080	50.02552648	96.936	n.a.

The HPLC chromatogram of chiral **3j**



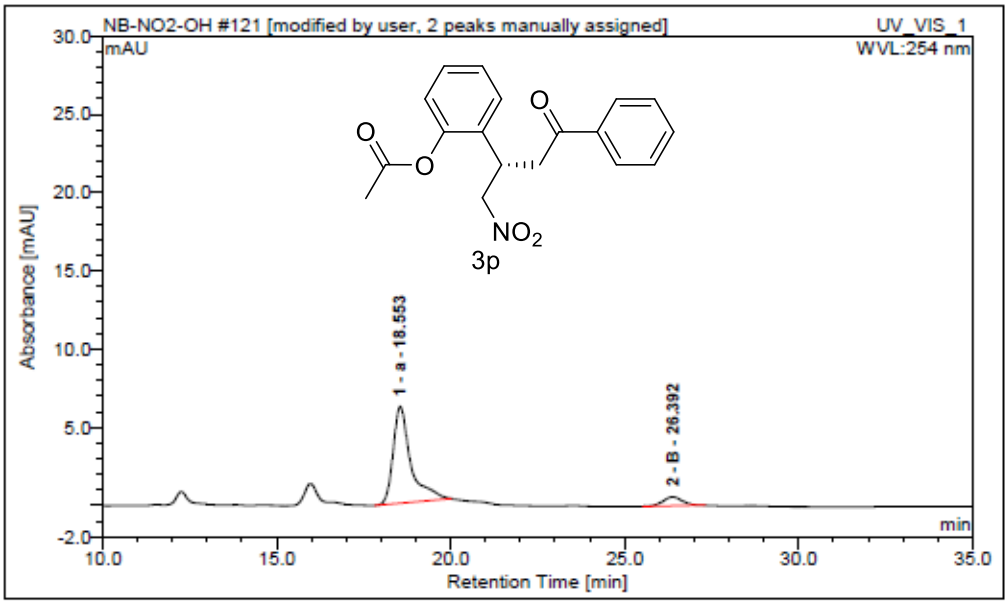
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
10	a	27.27	1.856309	5.621281089	2.98343	n.a.
11	B	29.43	31.167	94.37871891	44.621	n.a.

The HPLC chromatogram of racemic **3p**



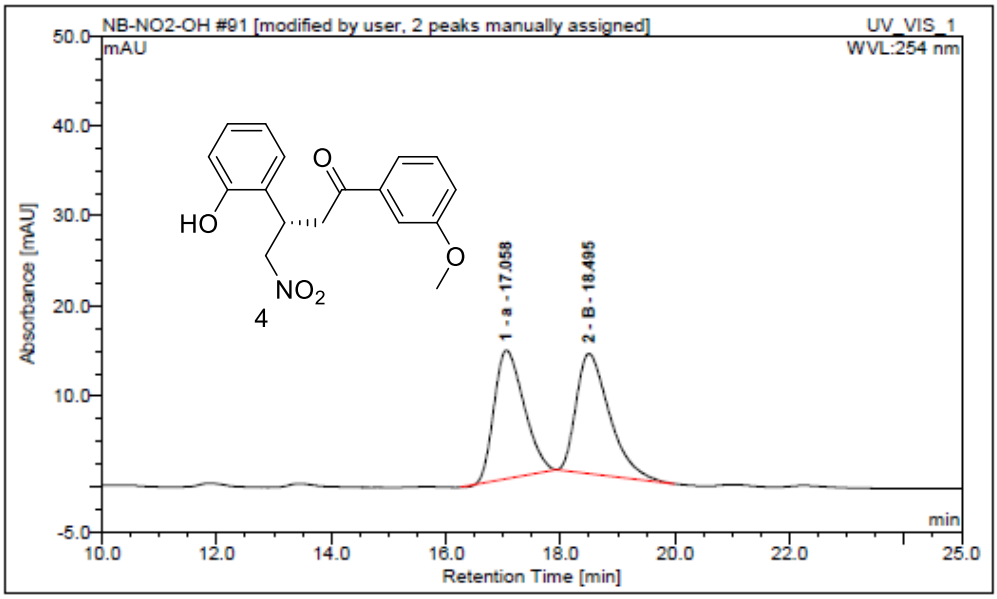
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	2	18.46	7.004031	48.8147866	10.03156	n.a.
2	B	26.16	7.344	51.1852134	7.382	n.a.

The HPLC chromatogram of chiral **3p**



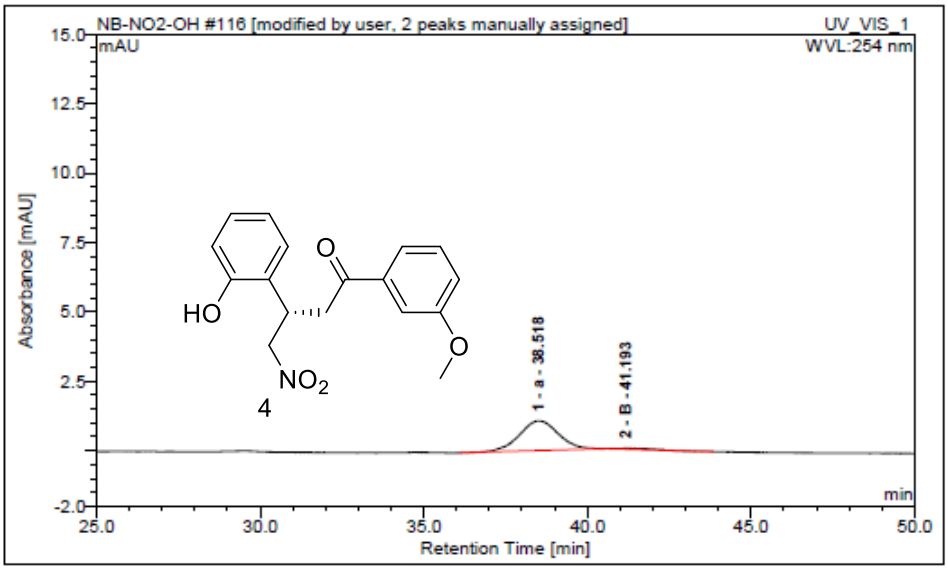
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.55	3.635784	90.88192443	6.16737	n.a.
2	B	26.39	0.365	9.11807557	0.562	n.a.

The HPLC chromatogram of racemic **4**



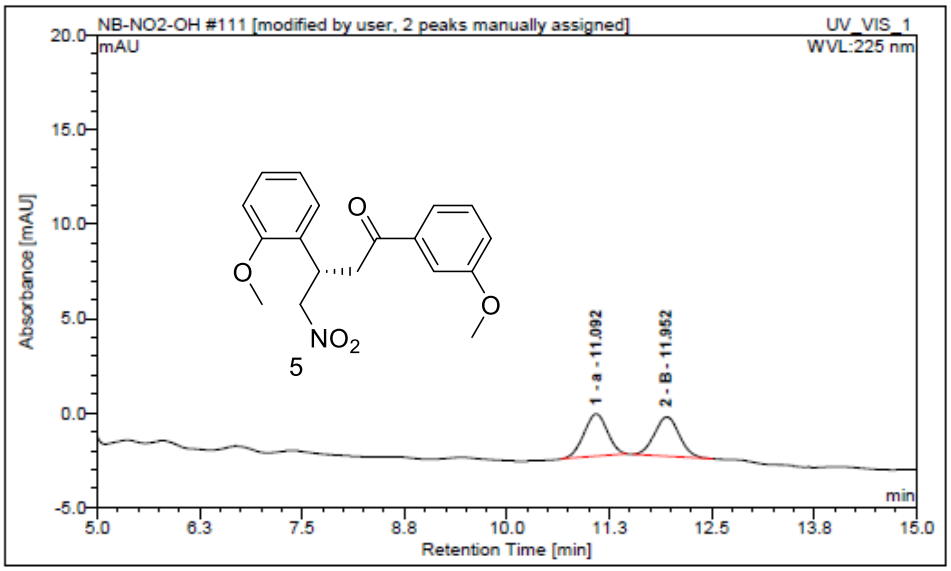
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	17.06	8.620793	48.90465071	14.24302	n.a.
2	B	18.50	9.007	51.09534929	13.309	n.a.

The HPLC chromatogram of chiral **4**



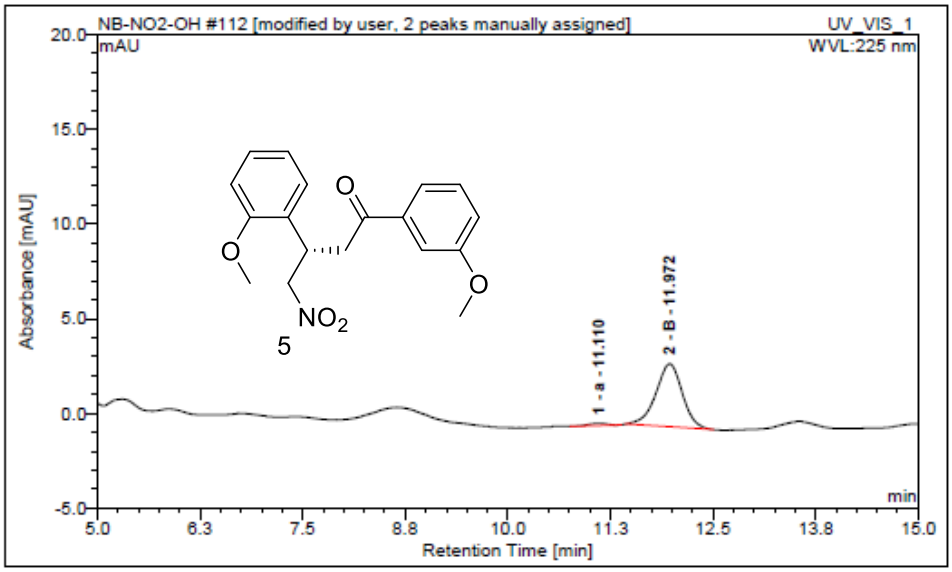
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	38.52	1.505511	96.69194574	1.08123	n.a.
2	B	41.19	0.052	3.308054256	0.041	n.a.

The HPLC chromatogram of racemic **5**



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	11.09	0.744727	50.40907429	2.23649	n.a.
2	B	11.95	0.733	49.59092571	2.084	n.a.

The HPLC chromatogram of chiral **5**

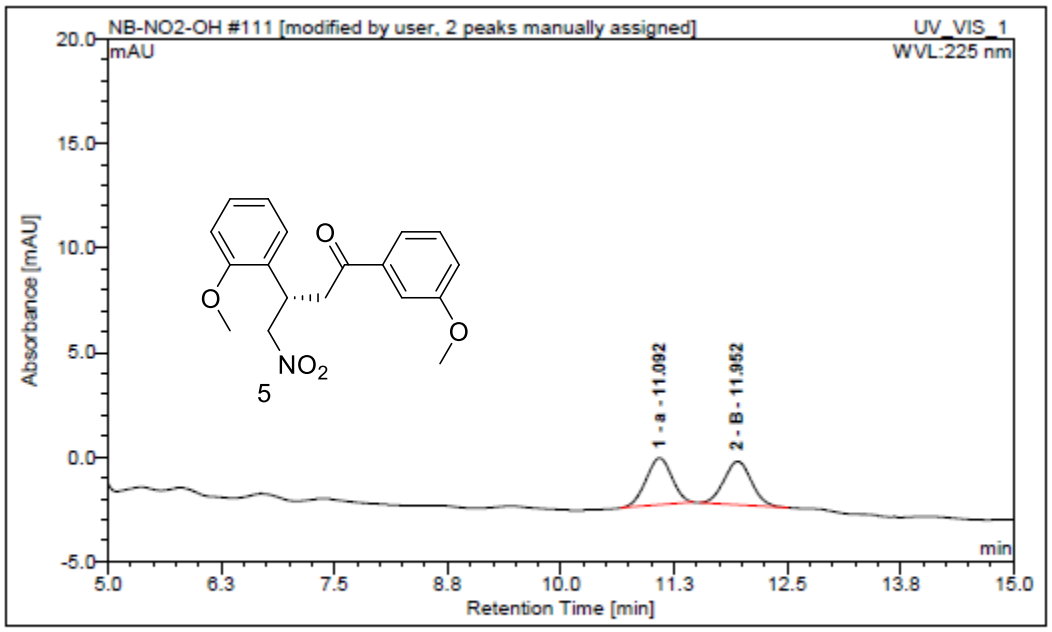


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	11.11	0.028438	2.233624806	0.12235	n.a.
2	B	11.97	1.245	97.76637519	3.330	n.a.

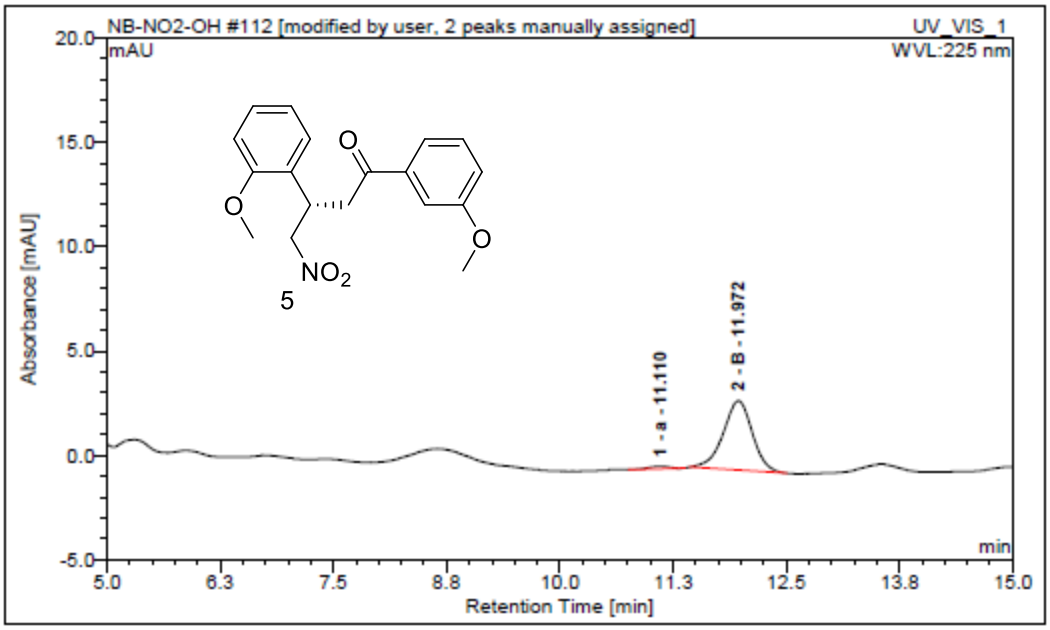
2.6.8. Structure determination:

The stereochemistry has been determined by comparing known compounds.[14] The HPLC of compound 5 was measured according to the reported compound (3e)[14] and the result obtained is the reverse of the reported compound.

HPLC data of compound 5:

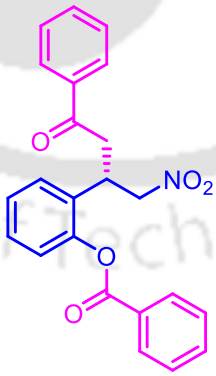


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	11.09	0.744727	50.40907429	2.23649	n.a.
2	B	11.95	0.733	49.59092571	2.084	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	11.11	0.028438	2.233624806	0.12235	n.a.
2	B	11.97	1.245	97.76637519	3.330	n.a.

Hence, the structure is confirmed to be as:



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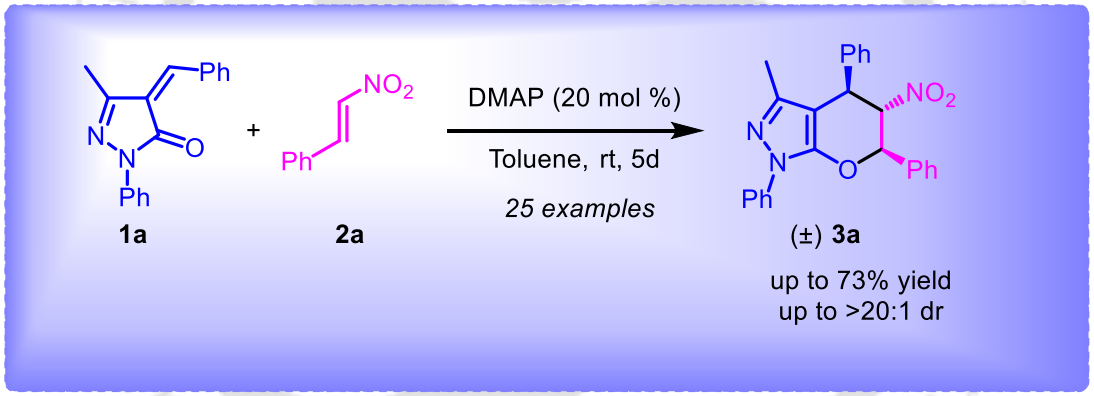
Chapter 3: DMAP Catalyzed Domino Rauhut-Currier Cyclization Reaction between Alkylidene Pyrazolones and Nitro-olefins: Access to Tetrahydropyrano[2,3-c]Pyrazoles



3.1 Introduction:

Pyrano[2,3-*c*]pyrazoles form an important structural heterocyclic motif of fused pyranones and pyrazolones and have attracted the attention of synthetic organic chemists as they are abundant source of biologically active molecules.[1] These motifs possess fungicide,[2] AMPA receptor activity enhancer property,[3] antitubercular,[4] antimicrobial,[5] antibacterial[6] and human Chk1 kinase inhibitory properties[7] (Figure 1). Because of the pharmaceutical importance of pyranopyrazoles, many research groups put their efforts for the synthesis of functionalized pyrano[2,3-c]pyrazoles and a number of useful strategies have been developed in recent years.[1] Both, pyrazolones and alkyidine pyrazolinones were employed for this purpose.

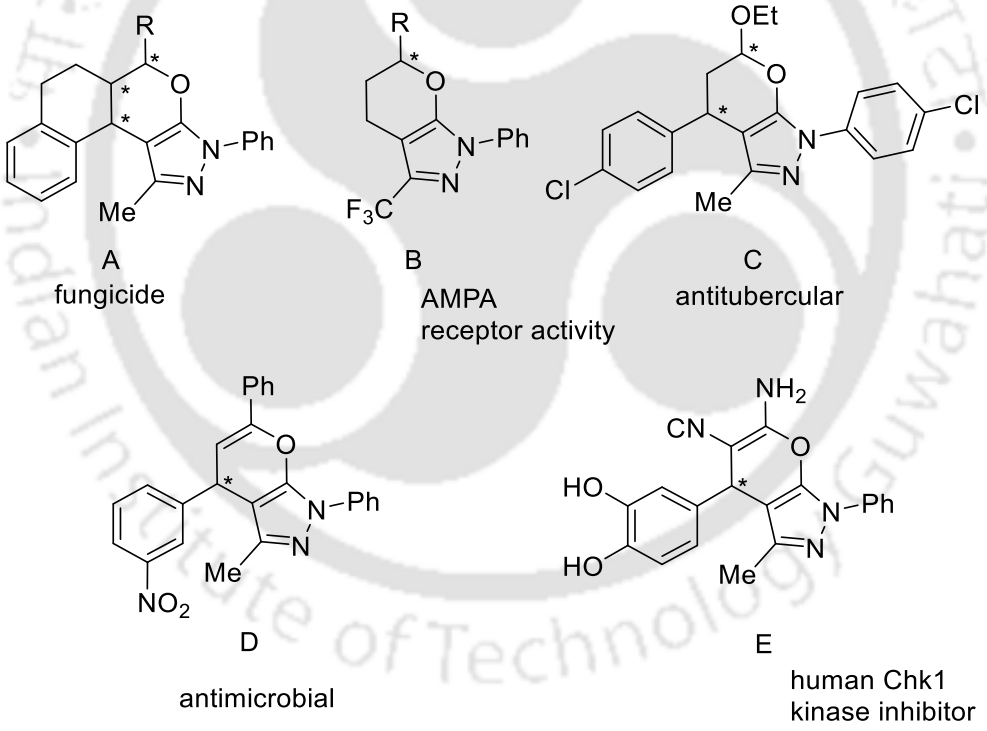
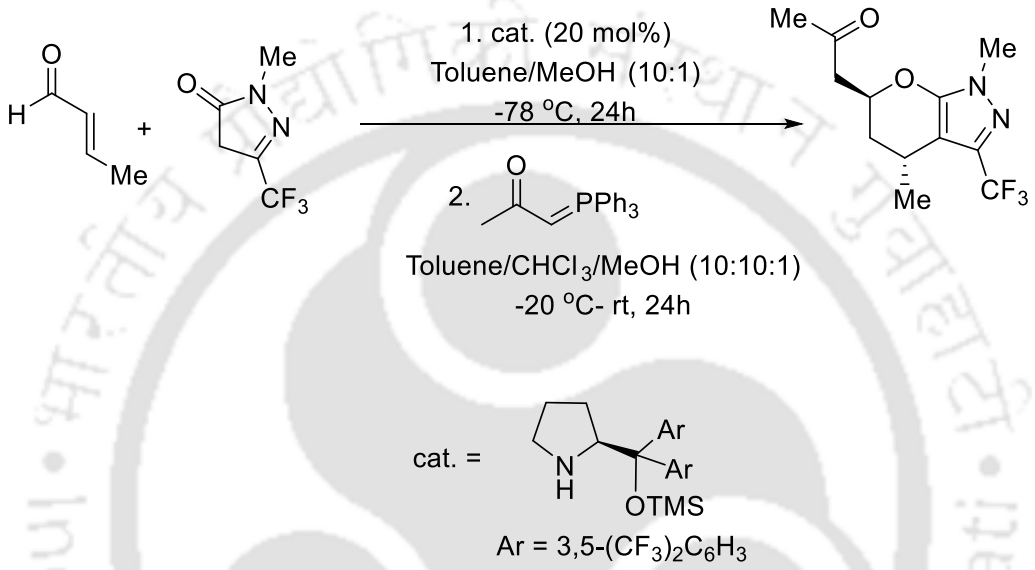


Figure 1. Selected examples of biologically important pyranopyrazoles

3.2 Selected previously reported strategies for the synthesis of Tetrahydropyranopyrazoles (THPPS) from Pyrazolones and unsaturated Pyrazolones

3.2.1 Organocatalytic One-Pot Asymmetric Synthesis:

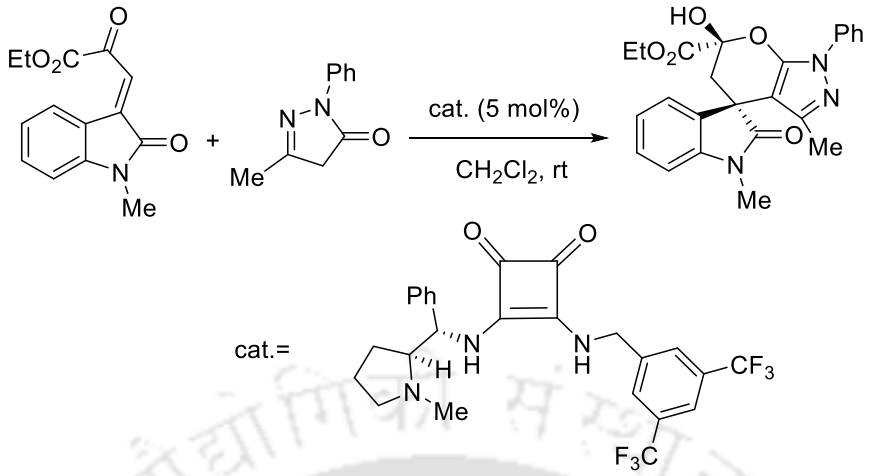
Enders and co-workers, in 2012, developed a one pot asymmetric synthesis of tetrahydropyrano[2,3-c]pyrazoles by a secondary amine catalysed asymmetric Michael/Wittig/oxa-Michael reaction sequence (scheme 1).[8]



Scheme 1: Organocatalytic One-Pot Asymmetric Synthesis tetrahydropyrano[2,3-c]pyrazoles by Enders et al.

3.2.2 Michael/Hemiketalization Reaction catalysed by L-proline mediated bifunctional squaramide organocatalyst:

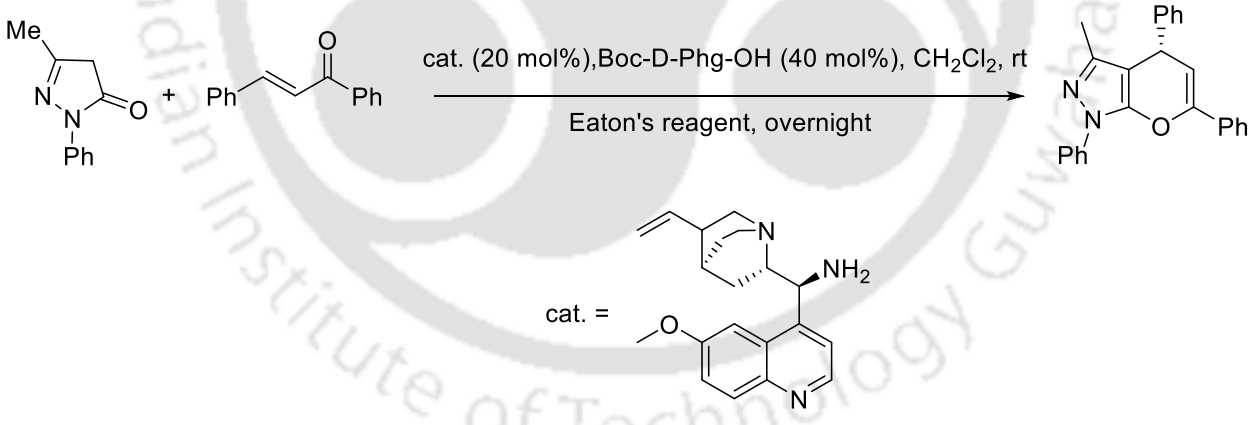
Kesavan and group used L-proline derived bifunctional squaramide organocatalyst to first synthesize dihydrospiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] derivatives, enantioselectively, by reacting pyrazolones with isatylidine β,γ-unsaturated α-ketoester (scheme 2). [9]



Scheme 2: L-proline derived bifunctional squaramide organocatalyzed Michael/Hemiketalization reactions by Kesavan et al.

3.2.3 Enantioselective Michael/cyclodehydration sequential reaction:

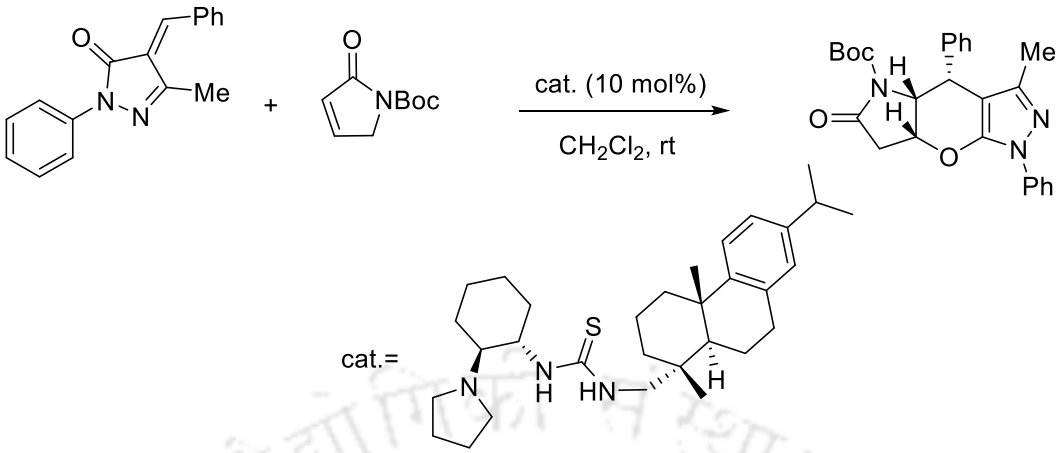
Jeong and co-workers achieved an effective and novel enantioselective Michael/cyclodehydration sequential reaction between pyrazolin-5-one (or 4-hydroxy-2-pyrone) and chalcones, catalyzed by a quininederived primary amine catalyst in the presence of Boc-D-Phg-OH (scheme 3). [10]



Scheme 3: Synthesis of Pyranopyrazoles catalyzed by a quinine-derived primary amine by Jeong et al

3.2.4 Catalytic Asymmetric β, γ Activation of α,β-Unsaturated γ-Butyrolactams:

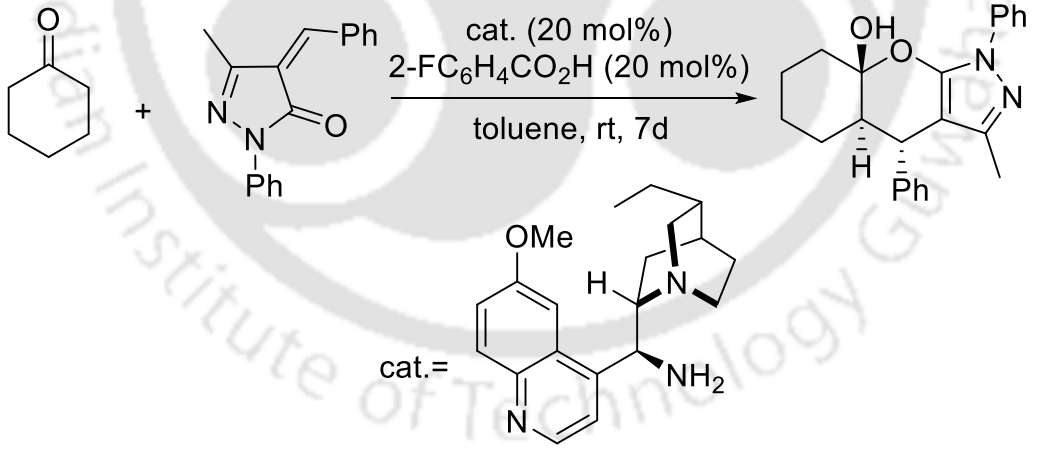
Wang and group formulated selective β, γ activation of α, β -unsaturated **γ** -butyrolactams through in situ formation of a 1,4-unsaturated enolate catalysed by bifunctional organocatalysts (scheme 4). [11]



Scheme 4: Catalytic Asymmetric β, γ Activation of α,β-Unsaturated γ-Butyrolactams by Wang et al.

3.2.5 Domino Michael-Hemiacetalization Reaction:

Pan and co-workers postulated an enantioselective aminocatalytic synthesis of Tetrahydropyrano [2,3-c]Pyrazoles via Domino Michael-Hemiacetalization Reaction with Alkylidene Pyrazolones cyclic ketones (scheme 5). [12]



Scheme 5: Enantioselective Aminocatalytic Synthesis of Tetrahydropyrano[2,3-c]Pyrazoles by Pan et al.

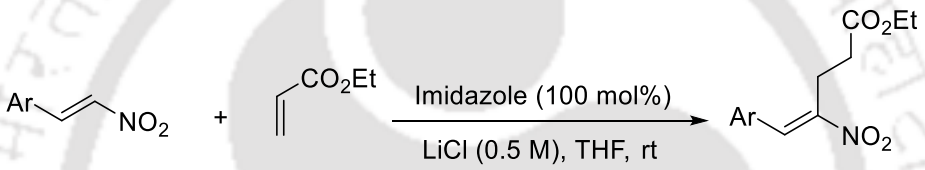
The Rauhut−Currier (RC) reaction, which involves the assembly of two electron-deficient olefins, is a powerful method to construct multi-functional molecules.[13] Due to its efficiency and atom-economical characteristics, a range of organic chemists are actively involved in the development of this reaction and a variety of structural frameworks were prepared. However, the intermolecular RC reaction between two different activated alkenes exhibits a pronounced challenge. Thus, a right

choice of the two reactants with appropriate reactivity would be a direct solution to this challenge.[14] In recent years, domino cyclizations based on intermolecular RC reaction emerged as an elegant strategy when the appropriately structurally modified activated alkenes were chosen as the starting materials.[13c,15] However, to our surprise, though nitrostyrenes are common Michael acceptors in a variety of reactions, their employment in intermolecular RC reaction is rare.

3.3 Selected previously reported strategies for catalytic cross-RC reaction

3.3.1 Rauhut–Currier type reactions involving nitroalkenes:

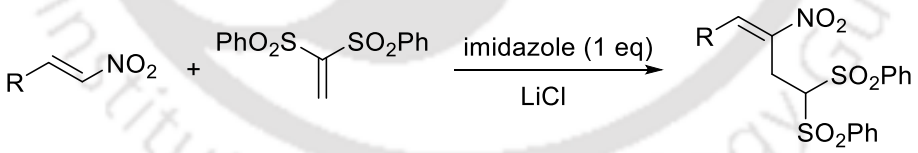
Namboothiri and group developed a reaction of nitroalkenes with acrylate in the presence of the imidazole–LiCl catalyst system to provide Rauhut–Currier adducts (scheme 6). [16]



Scheme 6: Reaction of nitroalkenes with acrylate in the presence of the imidazole‑LiCl catalyst by Namboothiri et al.

3.3.2 Rauhut–Currier Reaction of Nitroalkenes with Vinyl Sulfones:

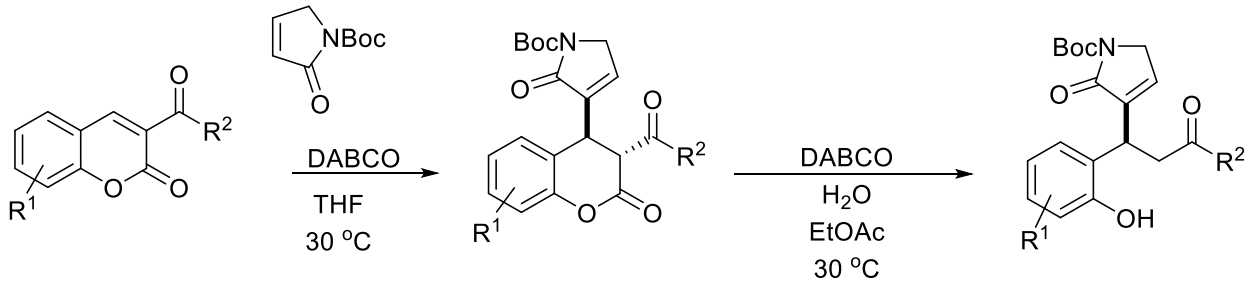
In 2013, Namboothiri and co-workers reported reaction of nitroalkenes with vinyl sulfones in the presence of imidazole–LiCl (Scheme 7).[17]



Scheme 7: Reaction of nitroalkenes with sulphones in the presence of the imidazole‑LiCl catalyst by Namboothiri et al.

3.3.3 α-Functionalization and decarboxylation:

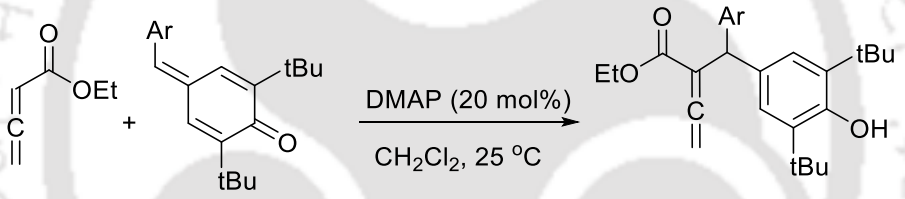
In 2017, Wenwei et al. have reported α-addition of α,β-unsaturated γ-butyrolactams onto the 3-acyl coumarins for to generate RC-type adducts, which were further hydrolysed or decarboxylated (Scheme 8).[18]



Scheme 8: DABCO catalysed α-Functionalization and decarboxylation by Wenwei et al.

3.3.4 Vinylogous RC reaction of 2,3-butadienoates with para-quinone methides:

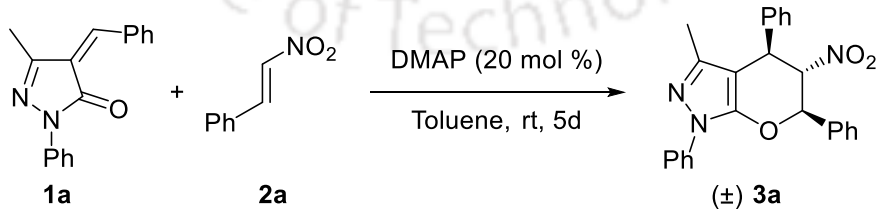
In 2018, Chandra and co-workers, used DMAP to catalyze vinylogous RC reaction of 2,3-butadienoates with para-Quinone methides. para-Quinone methides has a very high reactivity, and in this reaction they act as 1,6-acceptors of the allenoate zwitterionic species, thus making them suitable for the vinylogous RC reaction. (Scheme 9).[19]



Scheme 9: Vinylogous RC reaction of an allenoate and *p*-Quinone methide by Chandra et al.

3.4 Concept

Considering the potential of highly substituted THPPs, we embarked in a domino RC/cyclization reaction and took the challenge to employ nitrostyrenes with unsaturated pyrazolones in the intermolecular Rauhut-Currier cyclization (scheme 10).



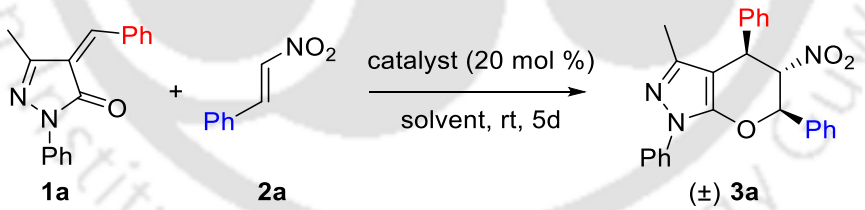
Scheme 10: The present work.

3.5 Results and discussion

3.5.1. Reaction optimization:

We started our investigation by performing a model reaction between unsaturated pyrazolone **1a** and nitrostyrene **2a** in toluene at room temperature (Table 1). Initially DABCO was chosen as the catalyst. Delightfully DABCO could promote the desired crossed RC reaction followed by cyclization and product **3a** was obtained as a single diastereomer (>20:1 dr) in 25% yield (Table 1, entry 1). The relative configuration of **3a** was assigned from 1H NMR. The yield of **3a** got slightly improved with imidazole (Table 1, entry 2). However, triphenylphosphine was not suitable for the reaction and very less conversion was detected (Table 1, entry 3). Then we employed DMAP as the catalyst[14] and interestingly, a smooth conversion was observed delivering product **3a** in 76% yield with >20:1 dr (Table 1, entry 4). To improve the yield different solvents were tested with DMAP (Table1, entries 5-8). As can be seen, the yield got decreased in α,α,α-trifluorotoluene (Table 1, entry 5). Then halogenated solvents such as dichloromethane and chloroform were screened and here also better yields were not obtained (Table 1, entries 6-7). The reaction was also sluggish in acetonitrile and less yield was observed (Table 1, entry 8).

Table 1: Reaction optimization:



Entry[a]	Catalyst	Solvent	d.r.[b]	yield(%)[c]
1	DABCO	toluene	>20:1	25
2	Imidazole	toluene	>20:1	40

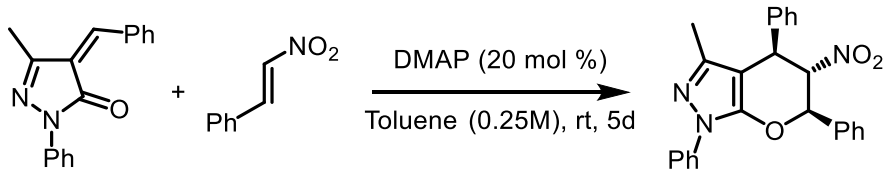
3	PPh_3	toluene	>20:1	<5
4	**DMAP**	**toluene**	**>20:1**	**76**
5	DMAP	$PhCF_3$	>20:1	65
6	DMAP	CH_2Cl_2	>20:1	55
7	DMAP	$CHCl_3$	>20:1	62
8	DMAP	CH_3CN	>20:1	40

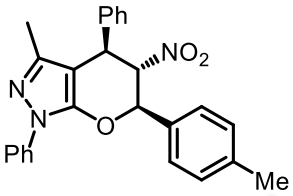
[a]0.05 mmol of **1a** and 0.1 mmol of **2a** were stirred in 0.2 mL solvent at room temperature. [b]Determined by 1H NMR. [c]Isolated yield after silica gel column chromatography.

3.5.2. Substrate scope:

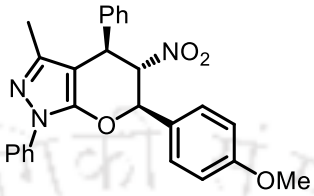
3.5.2.1 Scope of nitro-olefins:

After the optimized conditions were established, the scope and generality of the domino reaction was evaluated. Initially, nitro-olefins having different substituents were screened with unsaturated pyrazolone **1a**. Gratifyingly, in all cases only a single diastereomer was obtained. At the beginning, a variety of *para*-substitutions on the phenyl group of nitro-olefin was checked and the results were moderate to good. For example, nitro-olefin **2c** having *p*-anisole motif delivered product **3c** in 54% yield. Then 4-halo substituted nitro-olefins **2d**-**2f** were engaged in the reaction and the products **3d**-**3f** were attained in moderate yields. The reaction also progressed well with *meta*-substituted nitro-olefins. The product **3g** having *meta*-anisole motif was obtained as a single diastereomer in 45% yield. 3-Fluoro and 3-bromo substituted nitro-olefins **2h** and **2i** also participated in the reaction to deliver products **3h** and **3i** respectively though less yield was observed for product **3i**. 2,4-Disubstitution was also tolerated in the reaction despite less yield was detected. Finally, 2-naphthyl substituted nitro-olefin **2k** was employed in the reaction and product **3k** was isolated in acceptable yield.

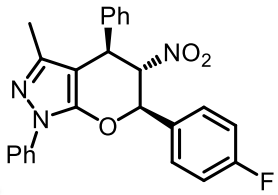




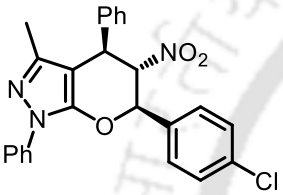
3b,yield = 46%
dr = >20:1



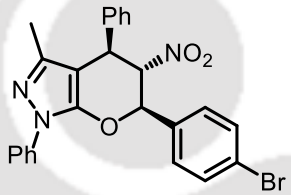
3c, yield = 54%
dr = >20:1



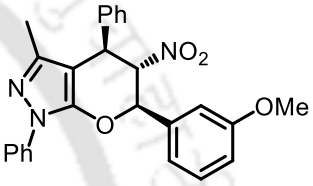
3d, yield = 43%
dr = >20:1



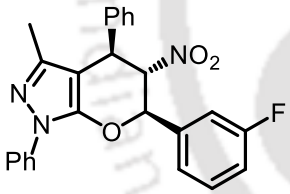
3e, yield = 38%
dr = >20:1



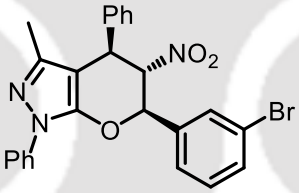
3f, yield = 45%
dr = >20:1



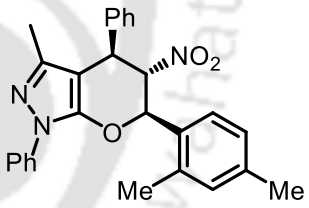
3g, yield = 45%
dr = >20:1



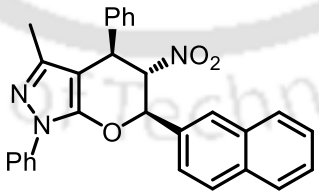
3h, yield = 50%
dr = >20:1



3i, yield = 38%
dr = >20:1



3j, yield = 33%
dr = >20:1

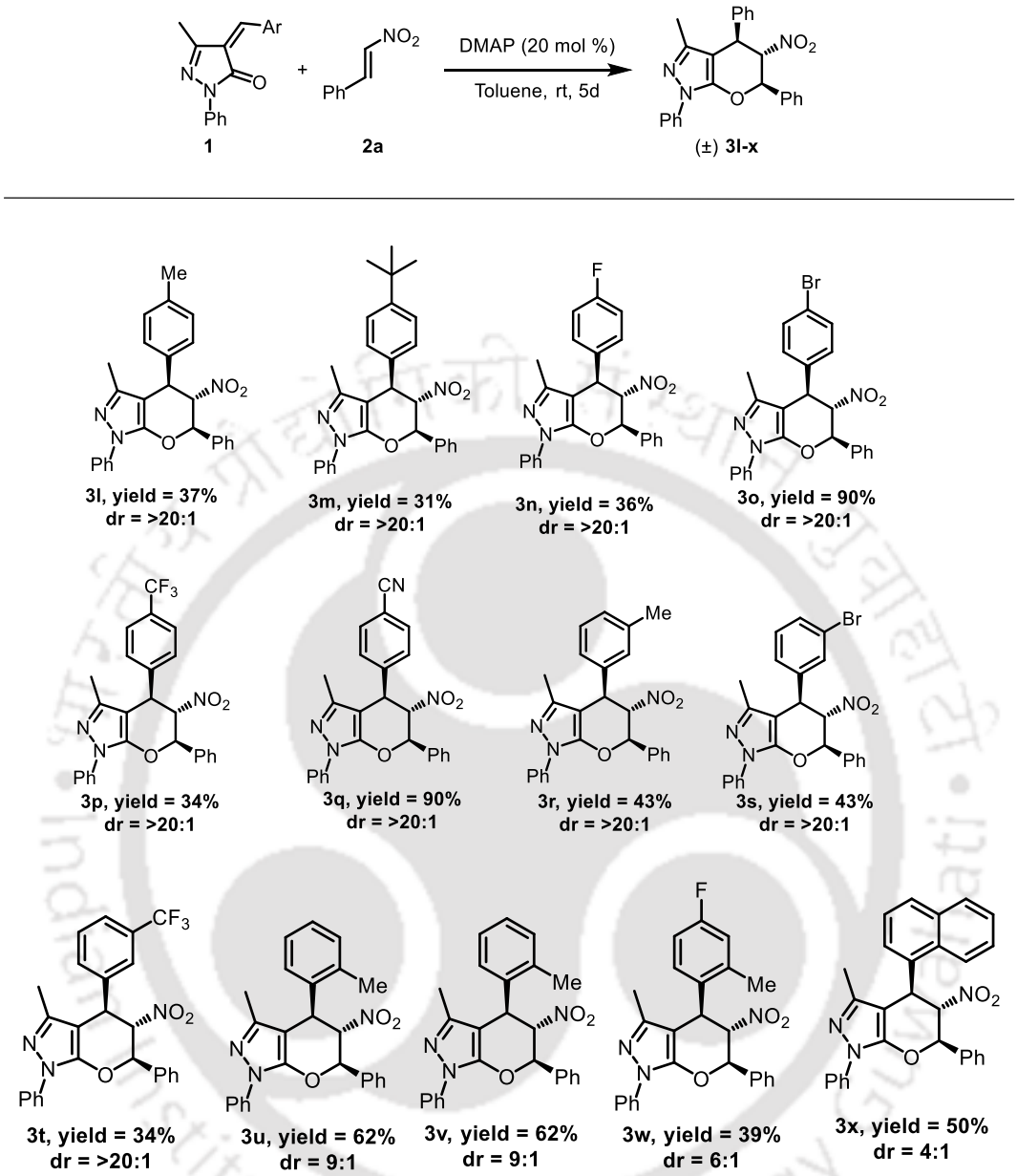


3k, yield = 51%
dr = >20:1

Scheme 11: Scope of olefins

3.5.2.2 Scope of unsaturated pyrazolones:

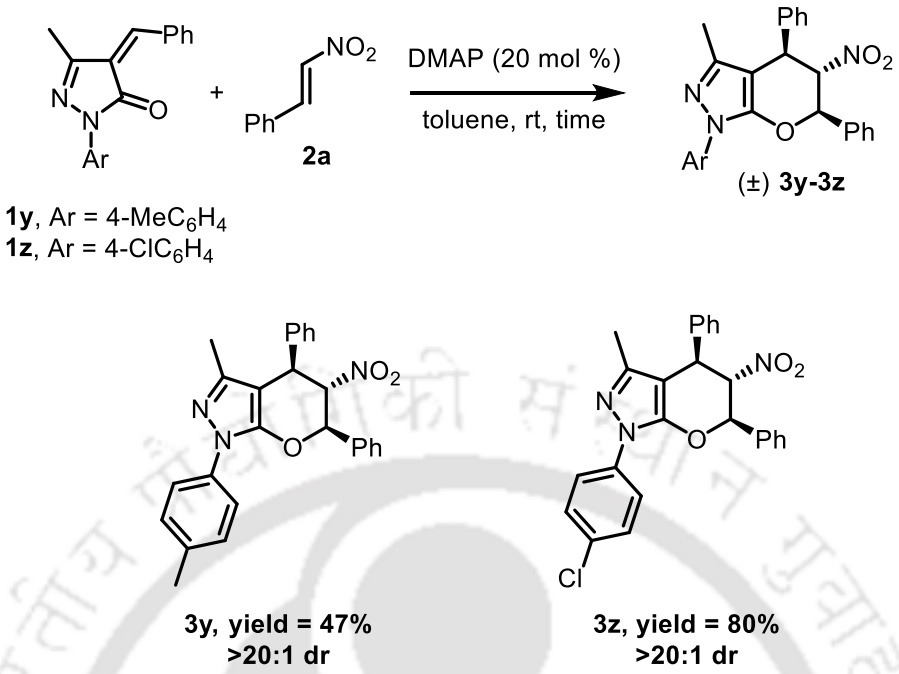
In the next phase the scope of unsaturated pyrazolones **1** was investigated. Here also, excellent diastereoselectivities were attained for almost all cases. Initially, pyrazolones **1** having various benzylidiene substitutents were prepared and reacted with nitrostyrene **2a**. At first, benzylidene pyrazolones **1l-1q** having different *para*-substitutions on the phenyl group were employed in the reaction. Moderate yields were detected for products **3l** and **3m** having 4-alkyl substitutions. Then 4-fluoro and 4-bromo substituted pyrazolones **1n** and **1o** were screened in the reaction. Though product **3n** was obtained in 36% yield, an excellent 90% yield was observed for product **3o** having 4-bromo substitution. An electron poor 4-CF_3 substituent could also be tolerated in the reaction and moderate yield was attained. Then the reaction was performed with *meta*-substituted pyrazolone **1r** having 3-methyl substituent. The reaction progressed smoothly to deliver product **3r** in 43% yield. Other *met*a-substituted pyrazolones **1s** and **1t** having 3-bromo and 3-CF_3 substituents respectively also participated in the reaction and acceptable results were obtained. *ortho*- Substitution could also be tolerated and gratifyingly a decent yield of 62% was observed for product **3u** having 2-methyl substitution and the diastereomeric ratio was 9:1. 2-CF_3 substituted pyrazolone **1v** could also be employed in the reaction though less yield but excellent diastereomeric ratio was detected. 2,4-Disubstituted aryl group containing pyrazolone **1w** also took part in the reaction to provide product **3w** in 39% yield and 6:1 diastereomeric ratio was observed. Finally, 1-naphthyl substituted alkylide pyrazolone **1x** was engaged in the reaction. Though decent yield was obtained for product **3x**, the diastereomeric ratio was 4:1.



Scheme 12: Scope of unsaturated pyrazolones

3.5.2.3. Scope of Unsaturated Pyrazolones having N-Aryl Substituents:

The scope of domino Rauhut-Currier cyclization reaction was further explored on pyrazolones **1** having different *N*-aryl substituents (Scheme 13). Initially, *N*-4-tolyl containing pyrazolone **1x** was screened and the product **3x** was attained as a single diastereomer in 47% yield. Delightfully, a decent yield of 80% was obtained for product **3y** having *N*-4-chloro phenyl substituent.



Scheme 13: Scope of unsaturated pyrazolones having *N*-Aryl Substituents

3.5.3 Determination of product stereochemistry

The relative structure of product **3o** was solved by X-ray crystallography[20]. The configuration of other products are expected to be same by analogy.

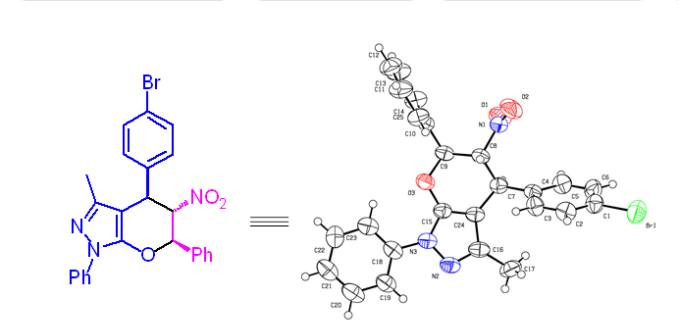
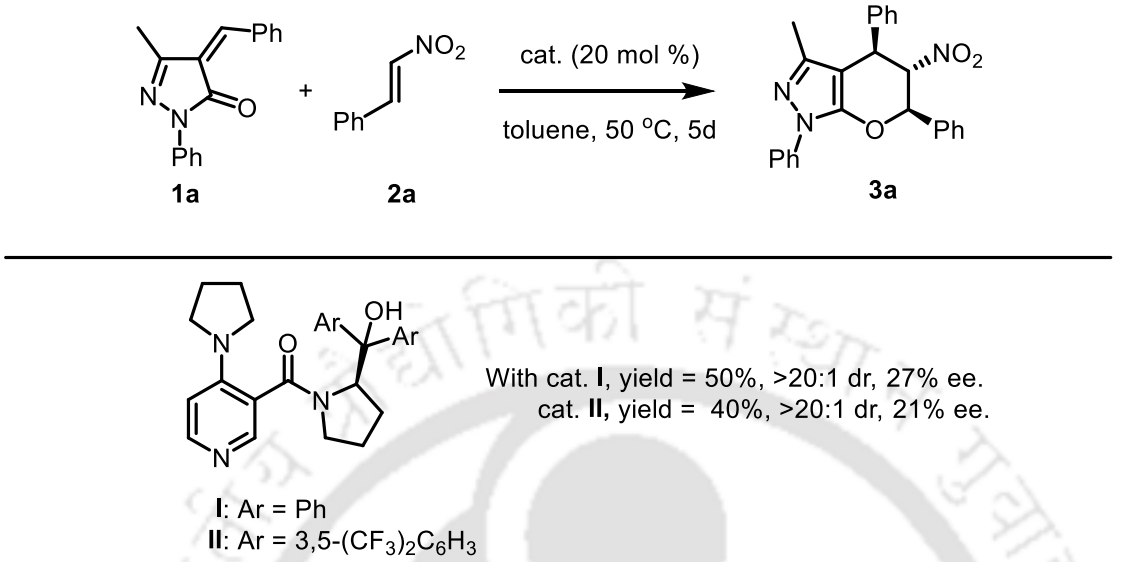


Figure 2. X-ray crystal structure of **3o**.

3.5.4 Preliminary catalytic asymmetric variant

We then decided to develop an enantioselective variant of the reaction. Thus, we synthesized chiral DMAP catalysts **I** and **II** as developed by Connon group.[21] The reaction was sluggish at room temperature with these catalysts but delightfully chiral product **3a**

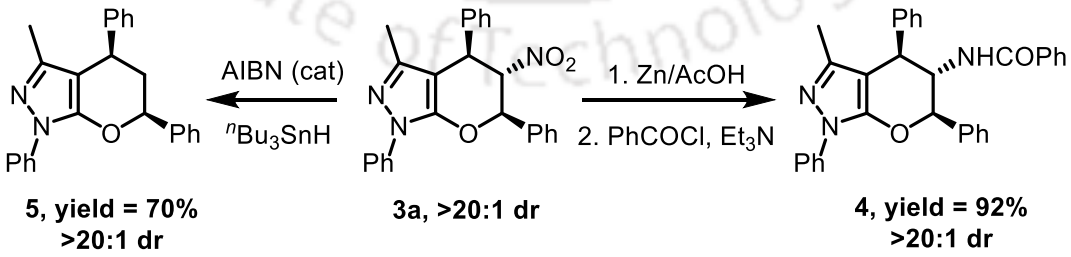


Scheme 14: Preliminary enantioselective variant

obtained on heating at 50 °C (Scheme 4). The maximum enantioselectivity was obtained to be 27% and 50% yield with catalyst **I**.

3.5.5 Synthetic transformation:

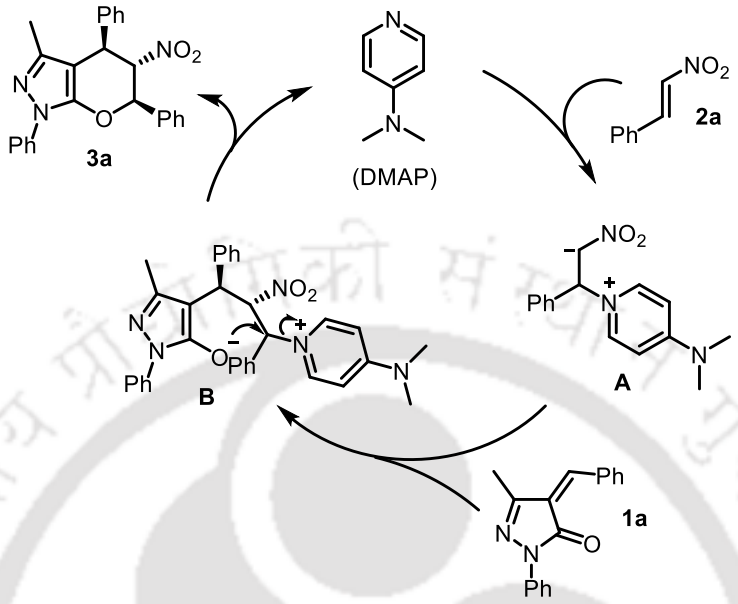
To demonstrate the synthetic potential of our method, few reactions were performed on **3a** (Scheme 5). Initially reduction with Zn/AcOH was carried out. This resulted in the formation of an amine which was protected with benzoyl chloride to provide **4** in 95% yield with preservation of diastereoselectivity. Then **3a** was treated with catalytic 2,2′-azobisisobutyronitrile (AIBN) and 1 equiv of *n*-Bu_3SnH for radical denitration.[22] The disubstituted tetrahydropyrano[2,3-c]pyrazole **5** was obtained in 70% yield and here also no erosion in diastereoselectivity was detected.



Scheme 15: Synthetic transformation

3.5.6. Plausible Reaction Mechanism

A plausible mechanism has been proposed in Scheme 6 for the formation of product **3a**.



Scheme 16: Proposed mechanism

Conjugate addition of DMAP to nitrostyrene **2a** results in theformation of zwitter ion **A,** which was detected by ESI mass spectrometry. Zwitter ion **A** then adds to unsaturated pyrazolone **1a** generating intermediate **B**. Intramolecular S_N2 reaction regenerates DMAP and leads to the formation of **3a**. As formations of **A** and **B** could be reversible, the most stable isomer **3a** is formed. The chiral catalysts would work in the similar way to form the pure diastereomer **3a**.

3.6. Conclusion:

In summary, we have applied unsaturated pyrazolones in the Rauhut-Currier reaction for the first time. This is also the first report for the utilization of nitro-styrenes in Rauhut-Currier cyclization reactions. The tetrahydropyrano[2,3-*c*]pyrazole products were obtained in moderate to high yields with excellent diastereoselectivities under ambient reaction conditions with DMAP catalyst. A preliminary catalytic asymmetric variant was also performed with chiral DMAP catalysts. Synthetic applications such as reduction and denitration have also been shown. Given the

pharmaceutical importance of tetrahydropyrano[2,3-*c*]pyrazoles our methodology might be valuable in drug discovery.

3.7. Experimental section:

3.7.1. General procedure for the synthesis of Unsaturated pyrazolones.

Unsaturated pyrazolones were prepared according to reported procedures. [23]

3.7.2. General procedure for the synthesis of Nitro-olefins.

Nitro-olefins were prepared according to known procedures. [24]

3.7.3. General procedure for the synthesis of chiral DMAP catalysts.

Chiral DMAP catalysts were prepared according reported procedures. [21]

3.7.4. General procedure for the synthesis of Tetrahydropyrano[2,3-*c*]Pyrazoles 3a:

In an oven dried round bottom flask, **1** (26.2 mg, 0.1 mmol), **2** (29.8mg, 0.2 mmol), 20 mol% of DMAP were taken. 0.4 mL of toluene was added to the reaction mixture and stirred at rt for 5 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 (5-10 %) to afford desired product.

3.7.5. General procedure for the synthesis of compound 4:

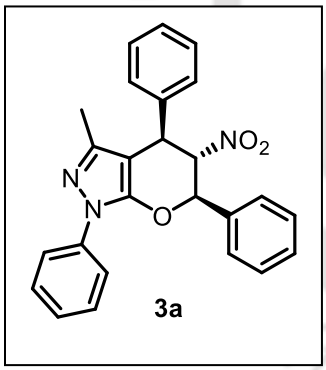
In 1.1 mL of acetic acid compound **3a** (0.12 mmol) was added followed by zinc powder (2.4 mmol) in one portion at 0 °C and the reaction was stirred at RT. After 1 hour, when the reaction was completed, the reaction mixture was passed through celite pad, washed with EtOAc, and solvent was removed under pressure. The residue was then dissolved in aqueous Na_2CO_3 and extracted with EtOAc. The combined organic layer was dried in anhydrous Na_2SO_4 and solvent was removed under pressure. The crude mixture obtained as colourless oil was used further without purification. This crude mixture is then dissolved in 1 mL DCM and Et_3N (0.25 mmol) was added, followed by benzoyl chloride (0.25 mmol) and stirred at 0 °C for 3 hours. The reaction mixture was the purified

by column chromatography (10% EtOAc/Hexane) to obtain the desired product **4** in single diastereomer.

3.7.6. General procedure for the synthesis of compound 5:

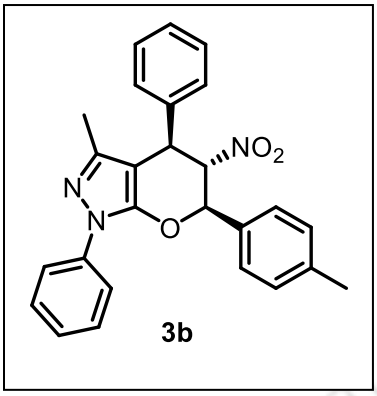
To a solution of **3a** (50mg, 0.12mmol) and azoisobutyronitrile (AIBN) (11mg, 0.067mmol) in toluene, tributyltin hydride was added under Argon atmosphere at room temperature. The reaction was heated for 12 hours at 80 ^{o}C. After completion of reaction, the reaction mixture was cooled and purified through column chromatography (4% EtOAc/hexane) to provide the product **5** in single diastereomer.

3.7.7. Characterization of the Products:

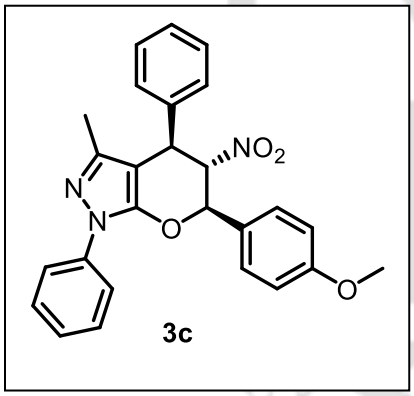


3a

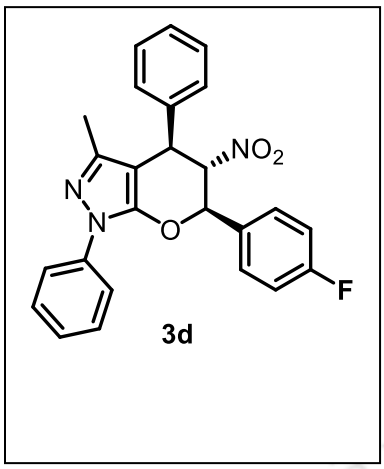
((4R,5S,6R)-3-methyl-5nitro-1,4,6-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3a) was obtained as a yellowish solid in 76% yield (31.2 mg) after column chromatography (10% Ethyl Acetate in Hexane). M.P = 193-198 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.65 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.4 Hz, 2H), 7.34 (d, J = 6.4 Hz, 3H), 7.28 (dt, J = 20.4, 8.2 Hz, 5H), 7.17 (d, J = 6.2 Hz, 2H), 7.13 (t, J = 7.4 Hz, 1H), 5.50 (d, J = 9.7 Hz, 1H), 4.88 (t, J = 9.8 Hz, 1H), 4.69 (d, J = 9.9 Hz, 1H), 1.64 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 149.6, 146.9, 138.4, 137.2, 133.6, 130.4, 129.4, 129.3, 129.2, 129.1, 128.7, 128.0, 127.6, 126.1, 120.3, 97.4, 93.6, 82.4, 45.0, 13.7 **HRMS (ESI) m/z**: $[M+H]^{+}$ Calcd. for $C_{25}H_{22}N_3O_3$ 412.1656; Found 412.1657. **FT-IR (ATR mode)**: 2921, 1551, 1515, 1074, 907, 732cm^{-1}. In case of chiral **3aa**, HPLC Analysis with catalyst **I**, ee = 27%, Chiralpak IB Column, *n*-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.06 min, t_{minor} = 6.5 min). HPLC Analysis with catalyst **II**, ee = 21%, Chiralpak IB Column, *n*-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 7.25 min, t_{minor} = 6.66 min).



((4R,5S,6R)-3-methyl-5nitro-1,4,-diphenyl-6-(p-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3b) was obtained as brownish yellow solid in 46% (19.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 195-200 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.37 (dd, *J* = 12.8, 5.1 Hz, 4H), 7.34 (t, *J* = 4.3 Hz, 3H), 7.26 – 7.18 (m, 5H), 5.55 (d, *J* = 9.7 Hz, 1H), 4.96 (t, *J* = 9.9 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 2.37 (s, 3H), 1.72 (s, 3H).**^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7, 146.9, 140.5, 138.4, 137.3, 130.6, 129.9, 129.4, 129.3, 128.7, 128.0, 127.6, 126.0, 120.3, 97.4, 93.7, 82.4, 45.0, 21.5, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_3$ 426.1812; Found 426.1812. **FT-IR (ATR mode)**: 2922.90, 1553.73, 1517.06, 1073.63, 728.79, 692 cm^{-1}.

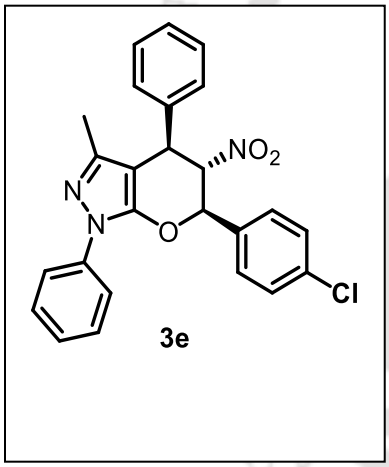


((4R,5S,6R)-6-(4-methoxyphenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3c) was obtained as whitish solid in 54% (23.8 mg) yield after column chromatography (12% Ethyl Acetate in Hexane). M.P = 168-170 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 3.7 Hz, 2H), 7.38 (d, *J* = 2.6 Hz, 2H), 7.36 (s, 2H), 7.34 (dd, *J* = 10.0, 3.3 Hz, 2H), 7.24 (s, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.53 (d, *J* = 9.8 Hz, 1H), 4.95 (t, *J* = 9.9 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.82 (s, 3H), 1.72 (s, 3H).**13C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 160.9, 149.5, 146.7, 137.0, 129.2, 129.1, 128.9, 128.5, 127.7, 125.8, 120.1, 114.4, 97.2, 93.4, 82.0, 55.3, 44.8, 13.5. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_4$ 442.1761; Found 442.1764. **FT-IR (ATR mode)**: 2924, 1597, 1514, 1025, 762, 692 cm $^{-1}$.



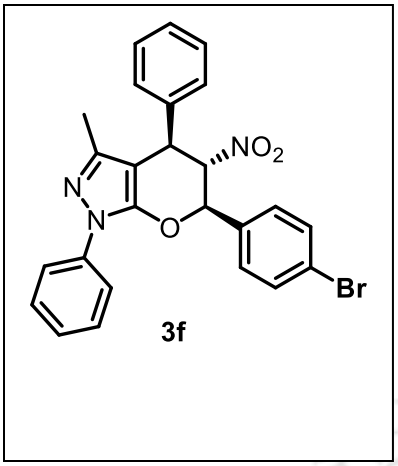
3d

((4R,5S,6R)-6-(4-fluorophenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3d) was obtained as brownish yellow solid in 43% (18.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 178-180 °C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.72 (d, *J* = 7.7 Hz, 2H), 7.45 (dd, *J* = 8.7, 5.2 Hz, 2H), 7.38 (dd, *J* = 15.4, 7.1 Hz, 5H), 7.27 – 7.19 (m, 3H), 7.11 (t, *J* = 8.6 Hz, 2H), 5.57 (d, *J* = 9.7 Hz, 1H), 4.93 (t, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 9.9 Hz, 1H), 1.73 (s, 3H). **^{13}C NMR{^{1}H} (151 MHz, Chloroform-*d*)** δ 164.7, 163.0, 149.4, 146.9, 138.3, 137.0, 129.6, 129.6, 129.5, 129.3, 128.8, 127.9, 126.2, 120.3, 116.5, 116.3, 97.4, 93.6, 81.7, 44.9, 13.7. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -111.03. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}FN_3O_3$ 430.1561; Found 430.1532. **FT-IR (ATR mode)**: 2921, 1556, 1512, 1073, 736 cm^{-1}.

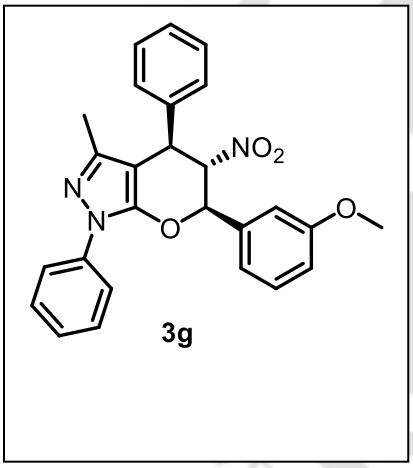


3e

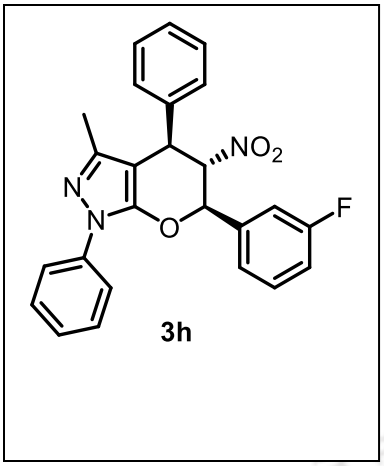
((4R,5S,6R)-6-(4-chlorophenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3e) was obtained as a brownish yellow solid in 38% (16.9 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 165-168 °C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.40 (s, 4H), 7.39 – 7.34 (m, 4H), 7.23 (dd, *J* = 8.6, 6.9 Hz, 4H), 5.57 (d, *J* = 9.7 Hz, 1H), 4.92 (t, *J* = 9.8 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 1.72 (s, 3H).**^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.3, 146.9, 138.2, 136.94, 136.60, 132.06, 129.61, 129.52, 129.37, 129.00, 128.88, 127.9, 126.2, 120.3, 97.4, 93.5, 81.7, 44.9, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}ClN_3O_3$ 446.1266; Found 446.1266. **FT-IR (ATR mode)**: 2922, 1551, 1514, 1073, 731, 693 cm^{-1}.



((4R,5S,6R)-6-(4-bromophenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3f) was obtained as a light brown solid 45% (22.0 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 175-180 °C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.35 (dd, *J* = 12.6, 7.9 Hz, 5H), 7.25 – 7.21 (m, 3H), 5.55 (d, *J* = 9.7 Hz, 1H), 4.91 (t, *J* = 9.8 Hz, 1H), 4.76 (d, *J* = 9.9 Hz, 1H), 1.72 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.3, 146.9, 138.2, 136.9, 132.5, 129.5, 129.3, 129.2, 128.9, 127.9, 126.2, 124.8, 120.3, 97.4, 93.4, 81.7, 44.9, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}BrN_3O_3$ 490.0761; Found 490.0763. **FT-IR (ATR mode)**: 2921, 1553, 1515, 1073, 732, 693cm^{-1}.

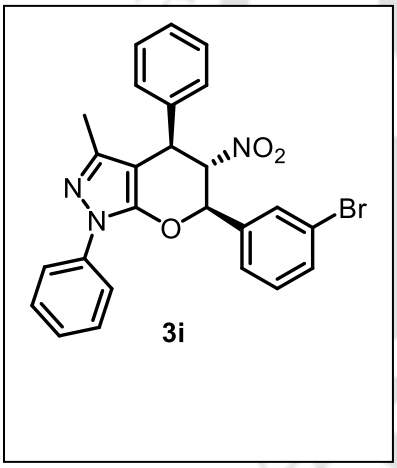


((4R,5S,6R)-6-(3-methoxyphenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3g) was obtained as a light yellow solid in 45% (20.0 mg) yield after column chromatography(10% Ethyl Acetate in Hexane). M.P = 192-195 °C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.37 – 7.31 (m, 4H), 7.25 (d, *J* = 6.4 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 5.3 Hz, 1H), 6.95 (d, *J* = 2.1 Hz, 1H), 5.56 (d, *J* = 9.7 Hz, 1H), 4.95 (t, *J* = 9.8 Hz, 1H), 4.76 (d, *J* = 9.9 Hz, 1H), 3.81 (s, 3H), 1.72 (s, 3H).**^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 160.1, 149.5, 146.9, 138.3, 137.1, 135.0, 130.3, 129.4, 129.3, 129.1, 128.7, 128.0, 126.1, 120.3, 119.8, 119.1, 115.7, 113.3, 97.4, 93.6, 82.3, 55.5, 45.0, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_4$ 442.1761; Found 442.1764. **FT-IR (ATR mode)**: 2921, 1554.38, 1516.10, 1216.02, 1035.91, 732.97, 695 cm^{-1}.



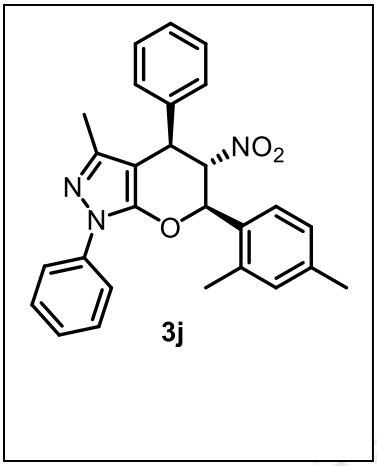
3h

((4R,5S,6R)-6-(3-fluorophenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3h) was obtained as a yellowish solid compound in 50% (21.0 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 165-170 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.36 (d, *J* = 6.5 Hz, 3H), 7.23 (s, 4H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.14 (t, *J* = 8.4 Hz, 1H), 5.58 (d, *J* = 9.6 Hz, 1H), 4.92 (t, *J* = 9.7 Hz, 1H), 4.77 (d, *J* = 9.8 Hz, 1H), 1.73 (s, 3H).**^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 162.2, 149.2, 146.9, 138.2, 136.9, 131.0, 130.9, 129.5, 129.3, 128.8, 127.9, 126.2, 123.4, 120.4, 117.7, 117.5, 114.7, 114.5, 93.5, 81.6, 44.9, 13.7. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -111.95. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}FN_3O_3$ 430.1561; Found 430.1556. **FT-IR (ATR mode)**: 2921.25, 1555.08, 1259.05, 1073.64, 795.07, 691 cm^{-1}.



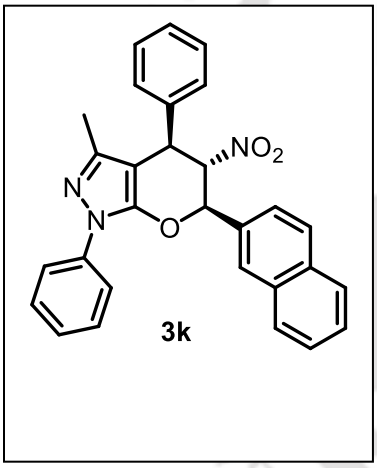
3i

((4R,5S,6R)-6-(3-bromophenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3i) was obtained as a brownish sticky solid in 38% (18.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 185-190 ^{o}C **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.62 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.36 (d, *J* = 6.2 Hz, 3H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.21 (m, 2H), 5.55 (d, *J* = 9.6 Hz, 1H), 4.93 (t, *J* = 9.8 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 1.72 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 149.2, 146.9, 138.2, 136.9, 135.7, 133.7, 130.8, 130.6, 129.5, 129.4, 128.9, 127.9, 126.4, 126.2, 123.3, 120.4, 97.4, 93.4, 81.6, 44.9, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}BrN_3O_3$ 490.0761; Found 490.0749. **FT-IR (ATR mode)**: 2921, 1554, 1457, 1075, 797, 692 cm^{-1}.



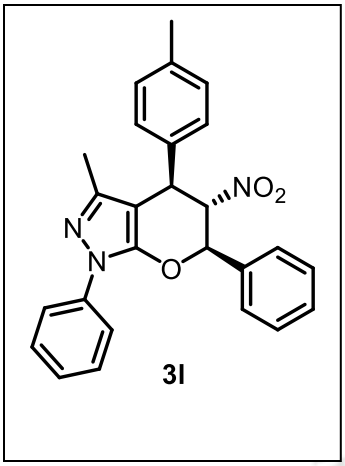
3j

((4R,5S,6R)-6-(2,4-dimethylphenyl)-3-methyl-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3j) was obtained as a brownish sticky solid in 33% (14.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.33 (m, 6H), 7.28 – 7.25 (m, 4H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.03 (s, 1H), 5.85 (d, *J* = 9.9 Hz, 1H), 5.11 (t, *J* = 9.9 Hz, 1H), 4.77 (d, *J* = 10.0 Hz, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 1.72 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.9, 146.9, 140.3, 138.4, 137.3, 137.2, 132.3, 129.4, 129.3, 128.7, 128.0, 127.7, 126.0, 120.2, 97.5, 92.5, 77.2, 45.3, 21.4, 19.4, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_3O_3$ $[M+H]^+$ 440.1969; Found 440.1976. **FT-IR (ATR mode)**: 2921, 1553, 1450, 1070, 738, 697 cm^{-1}.



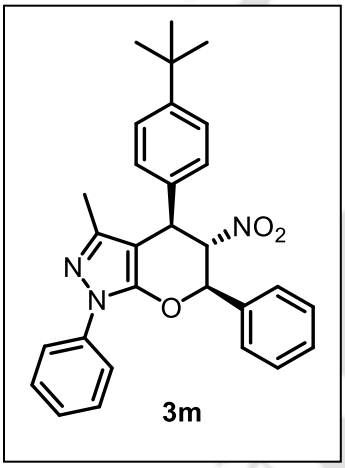
3k

((4R,5S,6R)-3-methyl-6-(naphthalen-2-yl)-5-nitro-1,4-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3k) was obtained as a yellow solid in 51% (23.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 188-190 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.87 (dd, *J* = 6.4, 2.4 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.57 – 7.51 (m, 2H), 7.39 – 7.33 (m, 5H), 7.28 (d, *J* = 6.7 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 5.76 (d, *J* = 9.8 Hz, 1H), 5.11 (t, *J* = 9.9 Hz, 1H), 4.83 (d, *J* = 9.9 Hz, 1H), 1.75 (s, 3H) **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.6, 146.9, 138.3, 137.1, 134.2, 133.0, 130.7, 129.4, 129.4, 129.3, 128.5, 128.2, 128.0, 128.0, 126.0, 123.9, 120.2, 97.4, 93.4, 82.7, 45.0, 13.8. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{29}H_{24}N_3O_3$ 462.1812; Found 462.1819. **FT-IR (ATR mode)**: 2922, 1552, 1517, 1074, 731, 692cm^{-1}.



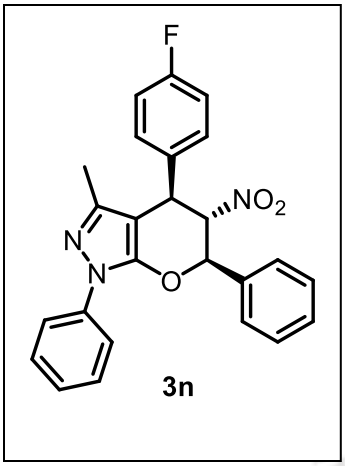
3l

((4R,5S,6R)-3-methyl-5nitro-1,6-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3l) was obtained as a brownish sticky compound in 37% (16.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 180-185 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.44 (qd, *J* = 7.0, 2.0 Hz, 5H), 7.38 (t, *J* = 7.9 Hz, 3H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.18 – 7.09 (m, 3H), 5.57 (d, *J* = 9.7 Hz, 1H), 4.93 (t, *J* = 9.8 Hz, 1H), 4.76 – 4.67 (m, 1H), 2.34 (s, 3H), 1.74 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 149.5, 147.0, 138.5, 138.4, 134.0, 133.6, 130.4, 130.1, 130.1, 129.3, 129.3, 129.2, 129.2, 127.8, 127.6, 127.6, 126.0, 120.3, 120.3, 93.8, 82.4, 44.7, 21.3, 13.8. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_3$ $[M+H]^+$ 426.1812; Found 426.1819. **FT-IR (ATR mode)**: 2925, 1553, 1216, 1076, 758, 693 cm^{-1}.



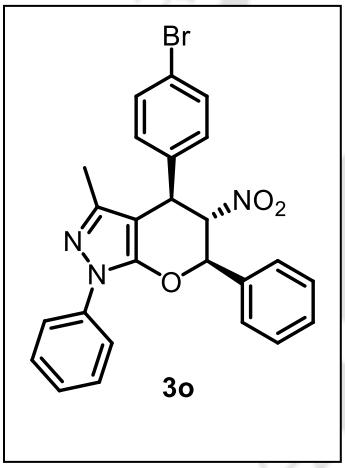
3m

((4R,5S,6R)-4-(4-(tert-butyl)phenyl)-3-methyl-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3m) was obtained as a brown solid compound in 31% (14.5 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 190-195 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.43 (dt, *J* = 12.7, 6.7 Hz, 5H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.57 (d, *J* = 9.7 Hz, 1H), 4.95 (t, *J* = 9.8 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 1.73 (s, 3H), 1.30 (s, 9H). **^{13}C NMR{^{1}H} (150 MHz Chloroform-*d*)**δ 151.6, 149.5, 147.0, 138.3, 133.8, 133.6, 130.4, 129.2, 129.2, 12.6, 127.5, 126.2, 126.0, 120.3, 119.1, 97.6, 93.6, 82.4, 44.4, 34.7, 31.4, 13.8. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{29}H_{30}N_3O_3$ 468.2282; Found 468.2294. **FT-IR (ATR mode)**: 2924, 1553, 1517, 1075, 757, 693 cm^{-1}.



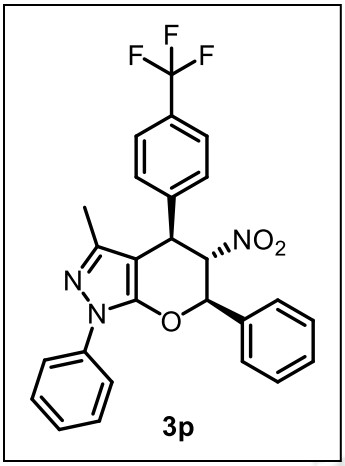
3n

((4R,5S,6R)-4-(4-fluorophenyl)-3-methyl-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3n) was obtained as a yellowish solid sticky compound in 36% (15.0 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 185-190 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.44 (t, *J* = 5.1 Hz, 5H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.26 – 7.20 (m, 3H), 7.06 (t, *J* = 8.5 Hz, 2H), 5.58 (d, *J* = 9.7 Hz, 1H), 4.91 (t, *J* = 9.8 Hz, 1H), 4.78 (d, *J* = 9.9 Hz, 1H), 1.74 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 162.1, 149.5, 146.7, 138.2, 133.4, 130.5, 129.6, 129.6, 129.3, 129.3, 127.5, 126.2, 120.3, 116.6, 116.4, 97.2, 93.7, 82.4, 44.2, 13.8. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -114.04. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}FN_3O_3$ 430.1561; Found 430.1561. **FT-IR (ATR mode)**: 2922, 1555, 1513, 1231, 994, 731, 694 cm^{-1}.



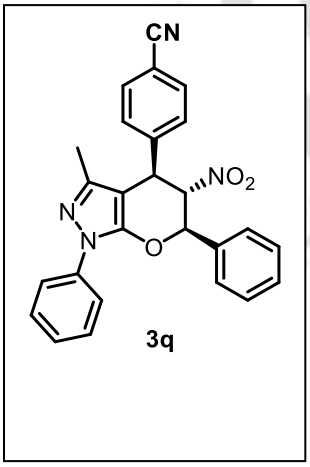
3o

((4R,5S,6R)-4-(4-bromophnyl)-3-methyl-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3o) was obtained as a brownish yellow solid in 90% (45.0 mg) yield after column chromatography (10% Ethyl Acetate in Hexane)**.** M.P = 198 - 204 ^{o}C**. ^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 5H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 15.4, 8.1 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 5.50 (d, *J* = 9.6 Hz, 1H), 4.83 (t, *J* = 9.8 Hz, 1H), 4.68 (d, *J* = 9.9 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.5, 146.6, 138.2, 136.2, 133.3, 132.6, 130.5, 129.6, 129.3, 129.3, 127.5, 126.2, 122.8, 120.3, 96.8, 93.4, 82.3, 44.4, 13.8. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}BrN_3O_3$ $[M+H]^+$ 490.0761; Found 490.0762. **FT-IR (ATR mode)**: 2922, 1553, 1515, 1073, 756, 692 cm^{-1}.



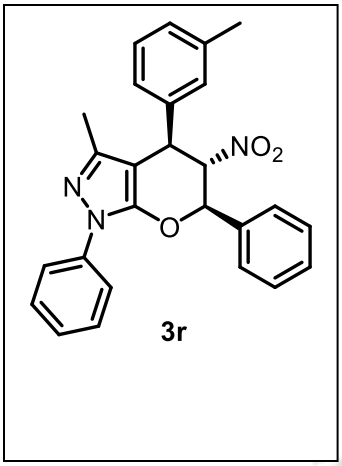
3p

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-4-(4-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3p) was obtained as a brownish yellow solid 34% (16.5 mg) yield after column chromatography (12% Ethyl Acetate in Hexane). M.P = 200-205 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.47 – 7.42 (m, 5H), 7.41 – 7.37 (m, 4H), 7.23 (t, *J* = 7.4 Hz, 1H), 5.60 (d, *J* = 9.5 Hz, 1H), 4.94 (t, *J* = 9.7 Hz, 1H), 4.87 (d, *J* = 9.9 Hz, 1H), 1.73 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 149.6, 146.5, 141.4, 138.2, 133.2, 131.3, 131.0, 130.8 (C-F, $^{2}J_{C\text{-}F}$ = 32.4 Hz), 130.6, 130.6, 130.3, 128.4, 128.4, 126.5, 126.5, 126.5(C-F, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 126.5, 126.4, 125.3, 124.0 (C-F, $^{1}J_{C\text{-}F}$ = 291.8 Hz), 122.6, 119.6, 96.6, 93.3, 82.3, 44.6, 13.8. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -63.79 **HRMS (ESI) m/z**: $[M+H]^{+}$ Calcd. for $C_{26}H_{21}F_3N_3O_3$ 480.1530; Found 480.1530. **FT-IR (ATR mode)**: 2921, 1553, 1516, 1070, 731, 693 cm^{-1}.



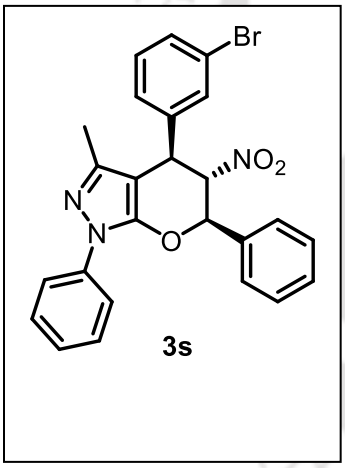
3q

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole-4-yl)benzonitrile) (3q) was obtained as a brown solid in 30% (13.1 mg) yield after column chromatography (15% Ethyl Acetate in Hexane). M.P = 190-200 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 3.5 Hz, 5H), 7.39 (dd, *J* = 7.8, 6.2 Hz, 4H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.60 (d, *J* = 9.2 Hz, 1H), 4.94 – 4.84 (m, 2H), 1.73 (s, 3H).**^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.6, 146.3, 142.8, 138.1, 133.3, 130.7, 129.4, 129.3, 128.8, 127.5, 126.4, 120.4, 112.9, 96.1, 93.0, 82.2, 44.7, 13.8. **HRMS (ESI) m/z**: $[M+H]^{+}$ Calcd. for $C_{26}H_{21}N_4O_3$ 437.1608; Found 437.1614. **FT-IR (ATR mode)**: 2921, 1553, 1514, 1073, 731, 692 cm^{-1}.



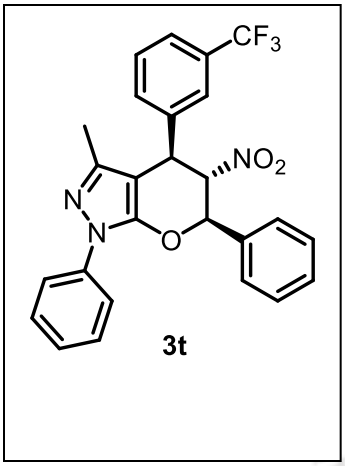
3r

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-4-(*m*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3r) was obtained as a pale yellow solid in 43% (18.3 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 175-180 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.35 (d, *J* = 6.7 Hz, 3H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.15 (dt, *J* = 14.5, 7.6 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 5.2 Hz, 2H), 5.50 (d, *J* = 9.7 Hz, 1H), 4.89 (t, *J* = 9.8 Hz, 1H), 4.65 (d, *J* = 9.9 Hz, 1H), 2.26 (s, 3H), 1.66 (s, 3H) **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.5, 147.0, 139.1, 138.3, 137.0, 133.6, 130.4, 129.5, 129.3, 129.2, 129.2, 128.4, 127.6, 126.0, 125.1, 120.2, 97.5, 93.6, 82.4, 44.9, 21.6, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_3$ $[M+H]^+$ 426.1812; Found 426.1843. **FT-IR (ATR mode)**: 2969, 1552, 1516, 1029, 755, 693 cm^{-1}.



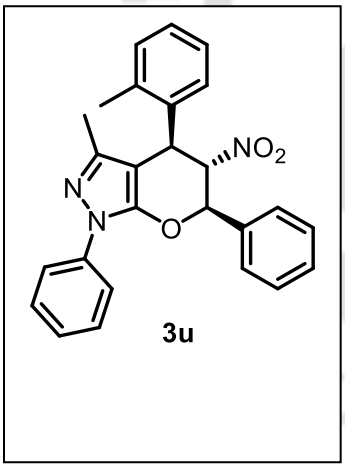
3s

((4R,5S,6R)-4-(3-bromophenyl)-3-methyl-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3s) was obtained as a brownish yellow solid in 41% (20.1 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 178-180 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.66 (d, *J* = 7.9 Hz, 2H), 7.43 – 7.34 (m, 7H), 7.34 – 7.29 (m, 4H), 7.20 – 7.10 (m, 4H), 5.50 (d, *J* = 9.6 Hz, 1H), 4.86 (t, *J* = 9.7 Hz, 1H), 4.68 (d, *J* = 9.8 Hz, 1H), 1.69 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 146.6, 139.6, 132.0, 131.0, 130.7, 130.5, 129.3, 129.3, 127.5, 126.2, 123.5, 120.3, 96.7, 93.3, 82.39, 44.4, 13.8. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{21}BrN_3O_3$ 490.0761; Found 490.0788. **FT-IR (ATR mode)**: 2924, 1551, 1517, 1030, 757, 692 cm^{-1}.



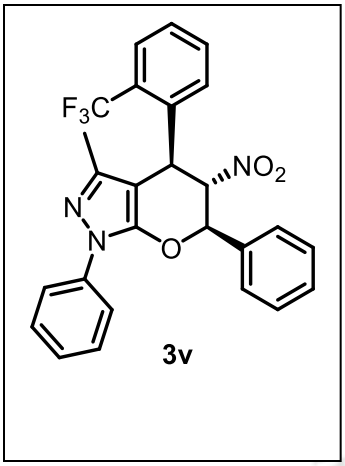
3t

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-4-(3-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3t) was obtained as an orange sticky solid in 34% (16.3 mg) yield after column chromatography (12% Ethyl Acetate in Hexane). **^{1}H NMR (600 MHz, Chloroform-*d*)**δ 7.74 (d, *J* = 7.7 Hz, 6H), 7.62 (d, *J* = 7.6 Hz, 3H), 7.50 (d, *J* = 8.6 Hz, 7H), 7.45 (dd, *J* = 13.1, 4.9 Hz, 19H), 7.39 (t, *J* = 8.0 Hz, 8H), 7.22 (dd, *J* = 14.2, 6.8 Hz, 5H), 5.61 (d, *J* = 9.5 Hz, 3H), 4.95 (t, *J* = 9.7 Hz, 3H), 4.88 (d, *J* = 9.9 Hz, 3H), 1.71 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.6, 146.4, 138.4, 138.1, 133.2, 132.0, 131.6, 130.6, 130.1, 129.3, 129.3, 129.1, 127.5, 126.3, 126.1, 125.8, 125.8, 125.7 (C-F, $^{4}J_{C-F}$ = 4.1 Hz),125.7, 125.7, 124.8, 124.6, 124.5, 124.5(C-F, $^{3}J_{C-F}$ = 14.5 Hz), 124.5, 124.5, 123.0, 120.4, 119.1, 96.5, 93.2, 82.3, 44.6, 13.8. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -63.85.**HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{21}F_3N_3O_3$ 480.1530; found 480.1528. **FT-IR (ATR mode)**: 2923, 1553, 1513, 1071, 754, 701 cm^{-1}.



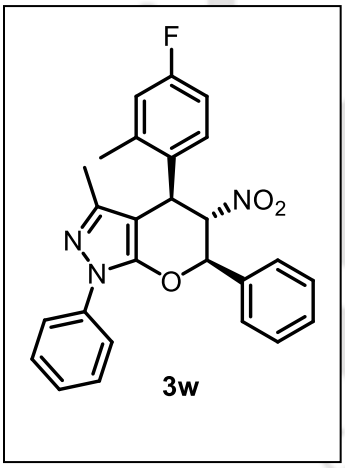
3u

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-4-(*o*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3u) was obtained as a yellow solid in 62% (26.4 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 185-190 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.88 (d, *J* = 7.6 Hz, 0H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.48 (dd, *J* = 6.9, 2.8 Hz, 2H), 7.43 (dd, *J* = 5.3, 1.7 Hz, 3H), 7.41 – 7.35 (m, 2H), 7.20 (d, *J* = 7.2 Hz, 5H), 5.64 (d, *J* = 9.4 Hz, 1H), 5.20 (d, *J* = 8.8 Hz, 1H), 5.08 (d, *J* = 9.3 Hz, 1H), 2.41 (s, 2H), 1.63 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 146.7, 138.3, 133.6, 131.1, 130.4, 129.3, 129.2, 128.2, 127.6, 127.2, 127.0, 126.0, 120.5, 120.2, 92.8, 82.6, 39.6, 19.6, 13.2. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_3$ 426.1812; Found 426.1841. **FT-IR (ATR mode)**: 2922, 1549, 1511, 1070, 755, 698 cm^{-1}.



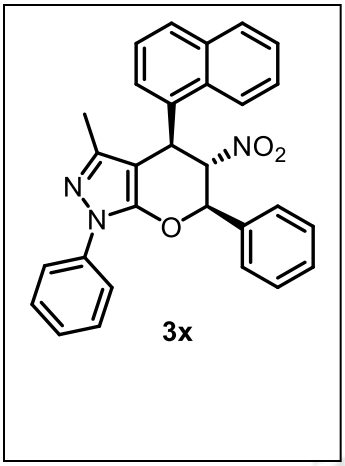
3v

((4R,5S,6R)-3-methyl-5-nitro-1,6-diphenyl-4-(2-(trifluoromethyl)phenyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3v) was obtained as an orange solid 33% (15.8 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 165 °C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.72 (d, *J* = 7.7 Hz, 3H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (ddd, *J* = 9.9, 6.4, 4.0 Hz, 7H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 5.74 (d, *J* = 8.6 Hz, 1H), 5.23 – 5.12 (m, 2H), 1.58 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)**) δ 149.3, 146.6, 138.2, 136.9, 133.6, 132.9, 130.5, 130.4, 130.2, 130.1(C-F, $^{2}J_{C-F}$ = 28.5 Hz), 129.9, 129.6, 128.6, 128.2, 127.8, 126.5, 126.4, 126.4 (C-F, $^{3}J_{C-F}$ = 5.7 Hz), 126.4, 126.3, 126.2, 125.5, 124.1 (C-F, $^{1}J_{C-F}$ = 264.2 Hz),122.8, 119.9, 98.0, 92.2, 82.0, 39.9, 13.0. **^{19}F NMR (376 MHz, $CDCl_3$)** δ -54.01, -58.34. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{21}F_3N_3O_3$ 480.1530; Found 480.1560. **FT-IR (ATR mode)**: 2922, 1553, 1514, 1034, 751, 703cm^{-1}.

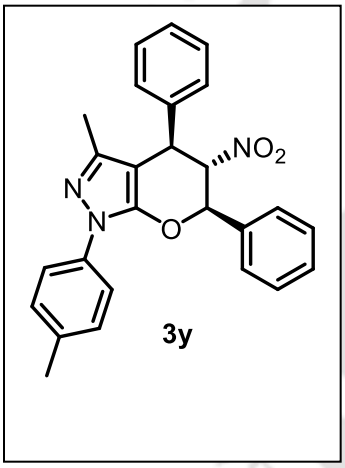


3w

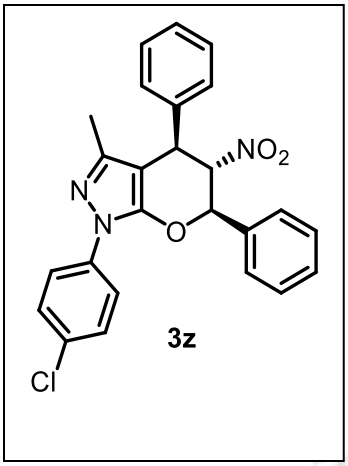
((4R,5S,6R)-4-(4-fluoro-2-methylphenyl)-3-methyl-5nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3w) was obtained as white solid in 39% (17.2 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 190-195 °C. **^{1}H NMR (400 MHz, Chloroform-*d*)** 7.76 – 7.70 (m, 2H), 7.49 – 7.43 (m, 5H), 7.38 (dd, *J* = 10.7, 5.3 Hz, 3H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.90 (dd, *J* = 9.6, 2.2 Hz, 2H), 5.64 (d, *J* = 9.3 Hz, 1H), 5.15 (d, *J* = 9.1 Hz, 1H), 5.01 (t, *J* = 9.2 Hz, 1H), 2.39 (s, 3H), 1.66 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)**δ 146.5, 138.3, 133.5, 130.5, 129.3, 129.3, 129.1, 128.9, 127.6, 126.1, 126.0, 120.5, 120.3, 114.3, 98.2, 92.8, 82.6, 39.2, 19.7, 13.2. **^{19}F NMR (376 MHz, Chloroform-*d*)** δ -115.15. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{23}FN_3O_3$ 444.1718; Found 444.1721. **FT-IR (ATR mode)**: 2923, 1550, 1515, 1075, 760, 694cm^{-1}.



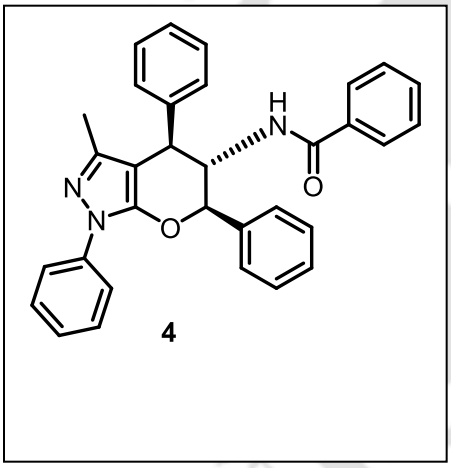
((4R,5S,6R)-3-methyl-4-(naphthalene-1-yl)-5-nitro-1,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3x) was obtained as a white solid in 50% (23.2 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 190-195 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 8.30 (d, *J* = 8.6 Hz, 3H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 4H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.53 (s, 2H), 7.40 (dd, *J* = 19.2, 11.3 Hz, 15H), 7.24 (dd, *J* = 14.8, 7.4 Hz, 3H), 5.85 (t, *J* = 7.5 Hz, 2H), 5.24 (t, *J* = 8.5 Hz, 1H), 1.61 (s, 3H).**^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.6, 146.9, 138.4, 134.0, 133.6, 132.1, 129.3, 129.1, 127.2, 126.1, 125.7, 121.8, 120.5, 120.3, 120.1, 98.2, 92.7, 82.3, 37.8, 13.4. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{29}H_{24}N_3O_3$ 462.1812; Found 462.1831. **FT-IR (ATR mode)**: 2969, 1551, 1024, 753, 696 cm^{-1}.



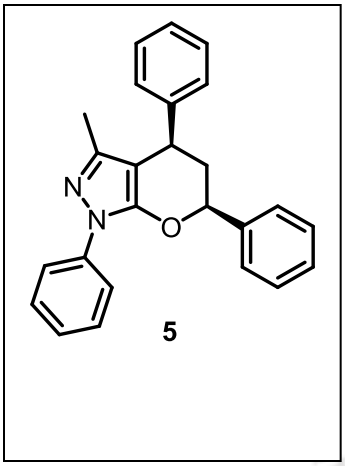
((4R,5S,6R)-3-methyl-5-nitro-4,6-diphenyl-1-(*p*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3y) was obtained as a brownish yellow solid in 47% (20.0 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 165-170 ^{o}C. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.39 (m, 5H), 7.34 (p, *J* = 6.2 Hz, 3H), 7.25 (d, *J* = 7.7 Hz, 3H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.57 (d, *J* = 9.7 Hz, 1H), 4.95 (t, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 10.0 Hz, 1H), 2.33 (s, 3H), 1.72 (s, 3H) **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.4, 146.5, 137.2, 135.9, 135.8, 133.6, 129.8, 129.4, 129.2, 127.9, 127.6, 120.4, 97.1, 93.7, 82.3, 45.0, 21.1, 13.7 **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_3$ 426.1812: Found 426.1829. **FT-IR (ATR mode)**: 2923, 1555, 1522, 1033, 733, 699 cm^{-1}.



((4R,5S,6R)-1-(4-chlorophenyl)-3-methyl-5nitro-4,6-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (3z) was obtained as a brownish yellow solid in 80% (35.6 mg) yield after column chromatography (10% Ethyl Acetate in Hexane). M.P = 188-190 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.62 (d, *J* = 8.9 Hz, 2H), 7.37 (s, 5H), 7.28 (dd, *J* = 8.8, 5.3 Hz, 6H), 7.21 – 7.15 (m, 3H), 5.52 (d, *J* = 9.7 Hz, 1H), 4.89 (t, *J* = 9.8 Hz, 1H), 4.69 (d, *J* = 9.9 Hz, 1H), 1.64 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 149.5, 147.2, 136.9, 133.3, 131.4, 130.6, 129.5, 129.4, 129.4, 129.3, 128.8, 127.9, 127.6, 121.2, 97.7, 93.5, 82.5, 44.9, 13.7. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for For $C_{25}H_{21}ClN_3O_3$ 446.1266; Found 446.1294. **FT-IR (ATR mode)**: 2970, 1554, 1514, 1092, 735, 697cm^{-1}.



(*N*-((4R,5S,6R)-3-methyl-1,4,6-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-5-yl)benzamide) (4) was obtained as a cream colour solid in 92% (11.5 mg) yield after column chromatography (20% Ethyl Acetate in Hexane). M.P = 180 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 8.09 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.41 (dd, *J* = 15.8, 7.8 Hz, 7H), 7.36 – 7.31 (m, 2H), 7.24 (s, 1H), 7.22 – 7.18 (m, 5H), 5.99 (d, *J* = 8.0 Hz, 1H), 5.95 (d, *J* = 8.1 Hz, 1H), 4.68 (d, *J* = 8.0 Hz, 1H), 4.22 (dd, *J* = 16.0, 7.8 Hz, 1H), 1.79 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, Chloroform-*d*)** δ 168.1, 150.6, 147.6, 140.5, 138.8, 137.0, 134.8, 133.6, 131.7, 130.3, 129.8, 129.2, 128.8, 128.7, 128.6, 128.5, 128.4, 127.2, 127.0, 126.8, 125.6, 120.2, 98.9, 82.8, 59.7, 42.1, 13.6. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{32}H_{28}N_3O_2$ 486.2176; Found 486.2166. **FT-IR (ATR mode)**: 2923, 1739, 1368, 1071, 694 cm^{-1}.



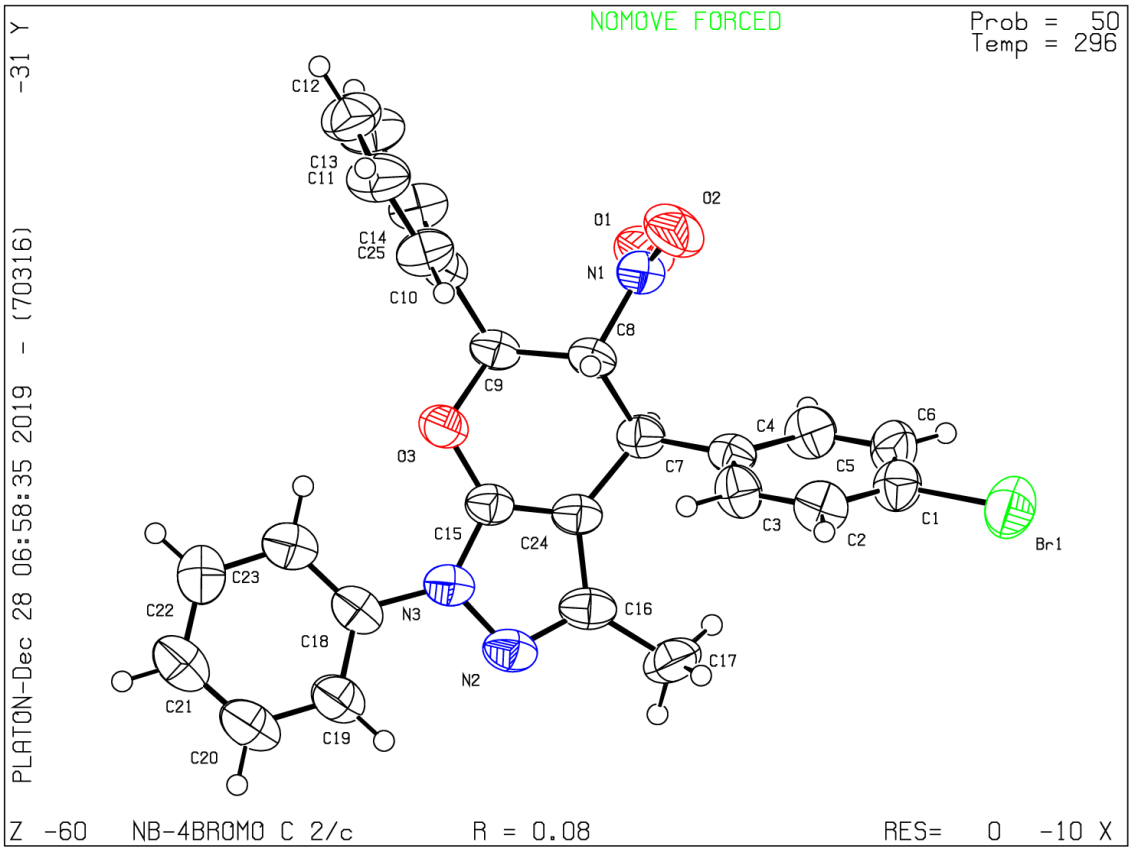
5

((4R,6S)-3-methyl-1,4,6-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole) (5) was obtained as a yellow sticky compound in 70% (25 mg) yield after column chromatography (8% Ethyl Acetate in Hexane). **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.82 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 7.4 Hz, 2H), 7.42 – 7.37 (m, 3H), 7.36 (dd, *J* = 11.1, 3.6 Hz, 2H), 7.34 – 7.30 (m, 3H), 7.26 (s, 7H), 7.18 (t, *J* = 7.4 Hz, 1H), 5.36 (d, *J* = 11.3 Hz, 1H), 4.35 – 4.30 (m, 1H), 2.44 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.12 (dt, *J* = 14.3, 11.4 Hz, 1H), 1.75 (s, 3H). **^{13}C NMR{^{1}H} (150 MHz, Chloroform-*d*)** δ 143.2, 139.0, 129.8, 129.1, 128.8, 128.8, 128.6, 127.8, 127.0, 126.2, 125.4, 120.2, 99.7, 82.4, 42.5, 38.5, 14.3, 13.9. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{25}H_{23}N_2O$ 367.1805; Found 367.1800. **FT-IR (ATR mode)**: 2922, 1074, 733, 694 cm^{-1}.

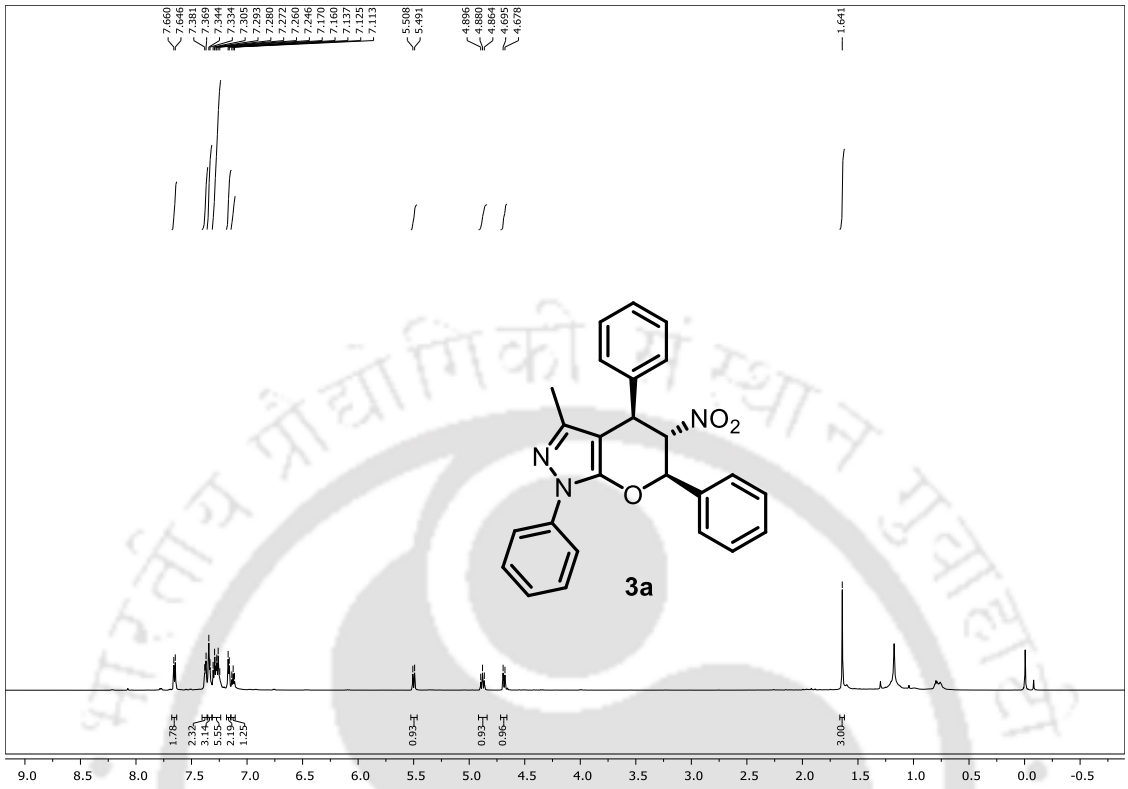
3.7.8. Single crystal X-ray diffraction analysis of 3o:

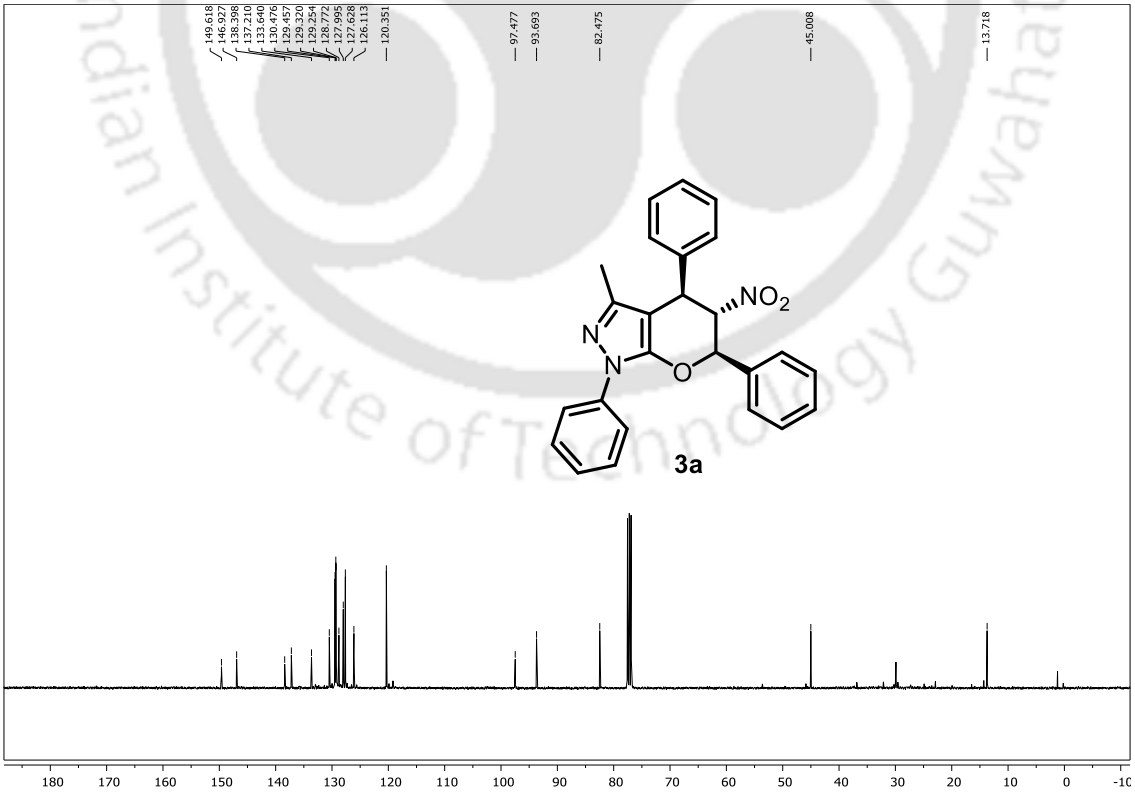
CCDC No.	1975320
Empirical formula	$C_{25}H_{20}N_3O_3Br$
Formula weight	490.35
Crystal habit, colour	block / colourless
Crystal size, mm^3	0.28×0.22×0.15
Temperature, *T*	296 K
Wavelength, λ (Å)	0.71073
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	*a* = 26.833(3) Å
	b = 13.5162(13) Å
	c = 16.602(3) Å
	α = 90°, β = 120.779(13)°, γ = 90°
Volume, *V* ($Å^3$)	5173.1(14)
Z	8

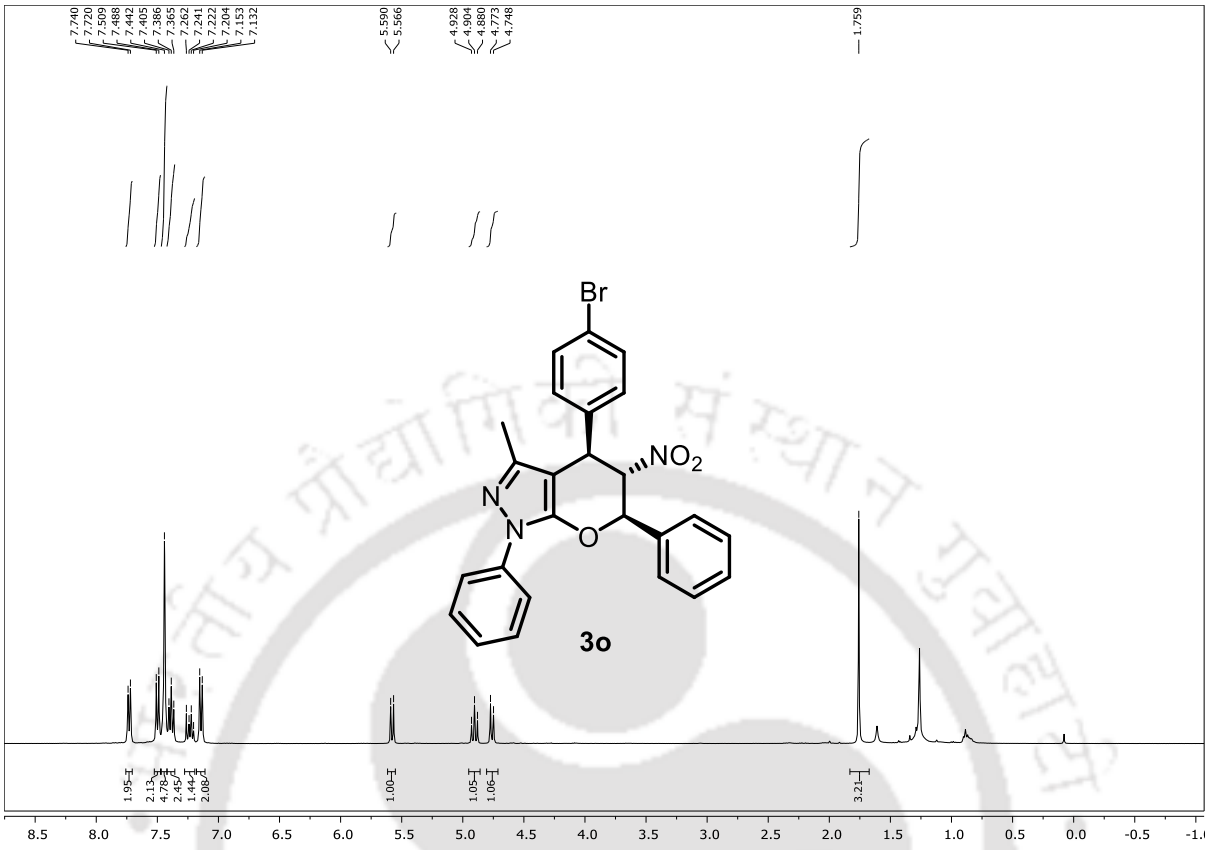
Calculated density, g·cm^{-3}	1.259
Absorption coefficient, μ (mm^{-1})	1.617
F(000)	2000.0
θ range for data collection	2.473° to 25.050°
Limiting indices	$-31 \le h \le 31$, $-16 \le k \le 16$, $-19 \le l \le 19$
Reflection collected/unique	4571/2339
Refinement method	'SHELXL–2014/7 (Sheldrick, 2014)'
Data/restraints/parameters	4571/0/290
Goodness–of–fit on F^2	1.359
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0776, wR2 = 0.2457
R indices (all data)	R1 = 0.1566, wR2 = 0.2806

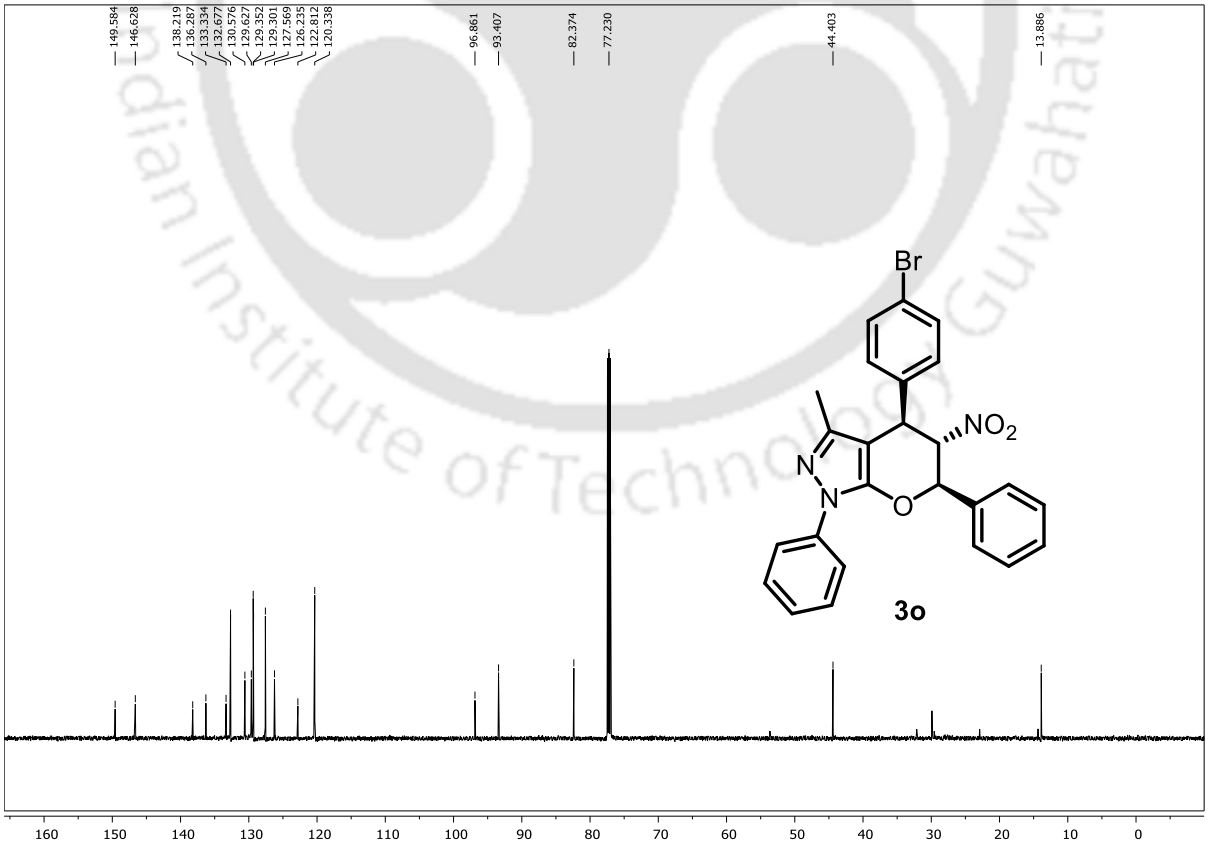


3.7.9. Some selected NMR spectra of the products:

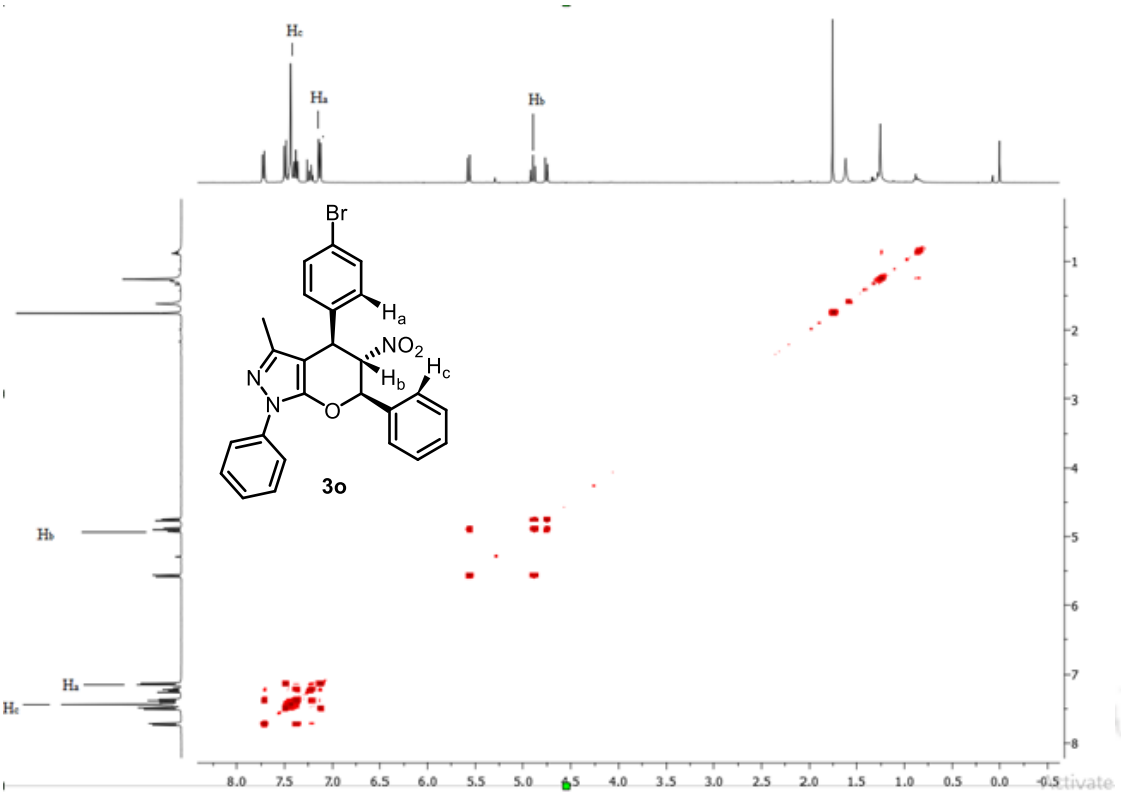




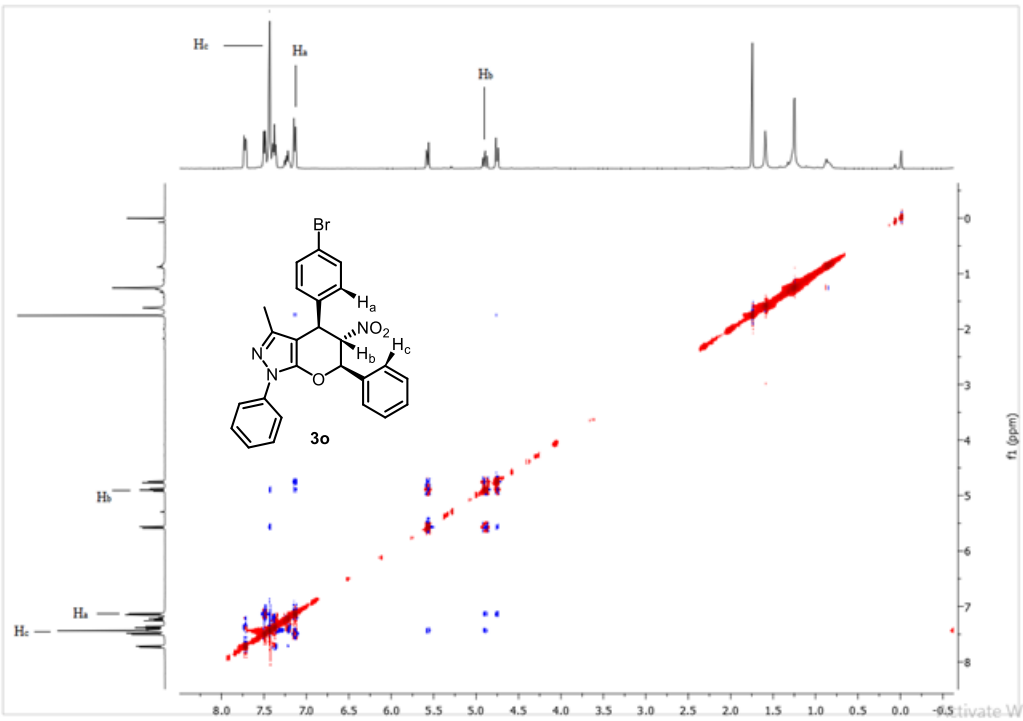




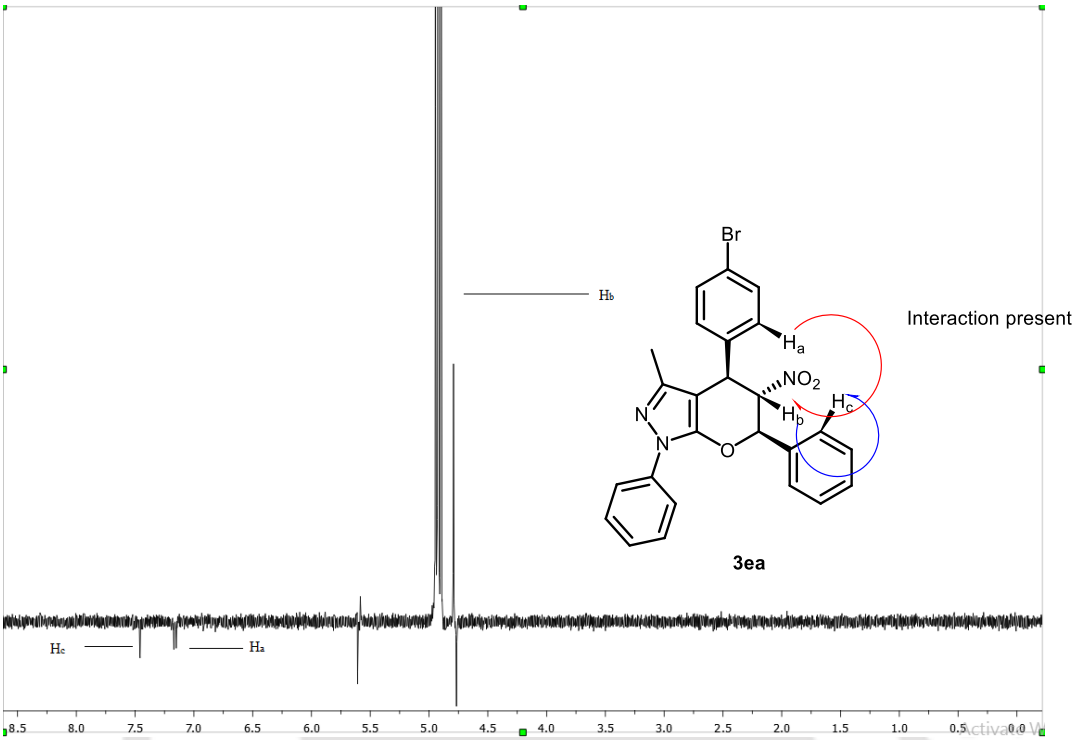
COSY of **3o**:

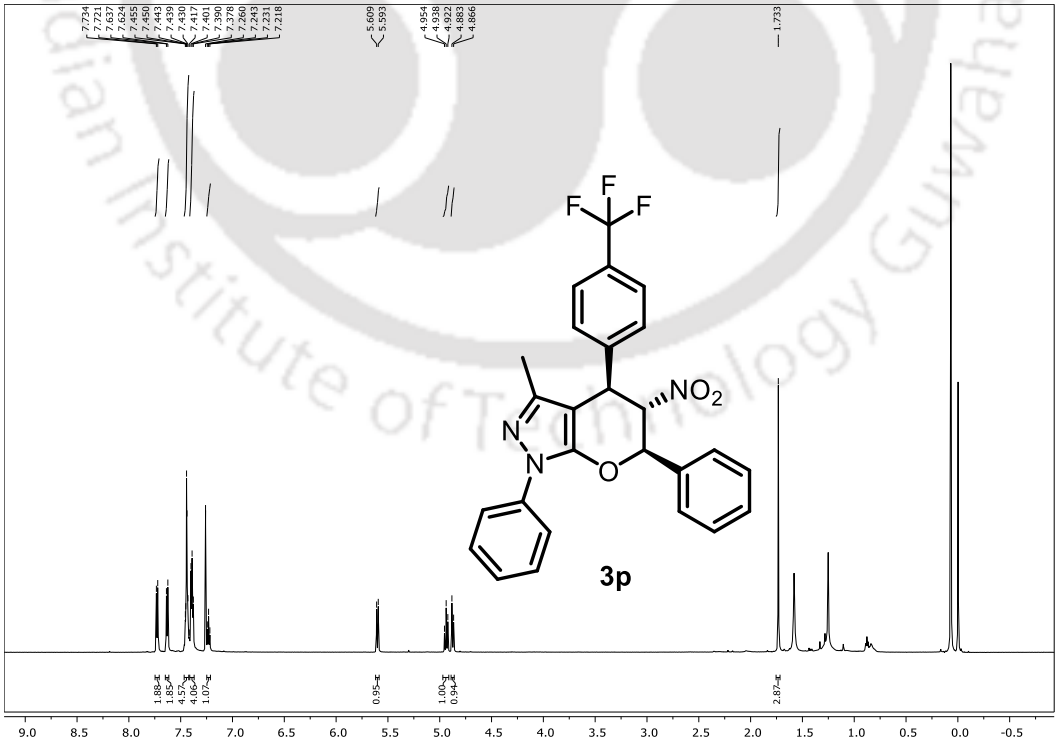


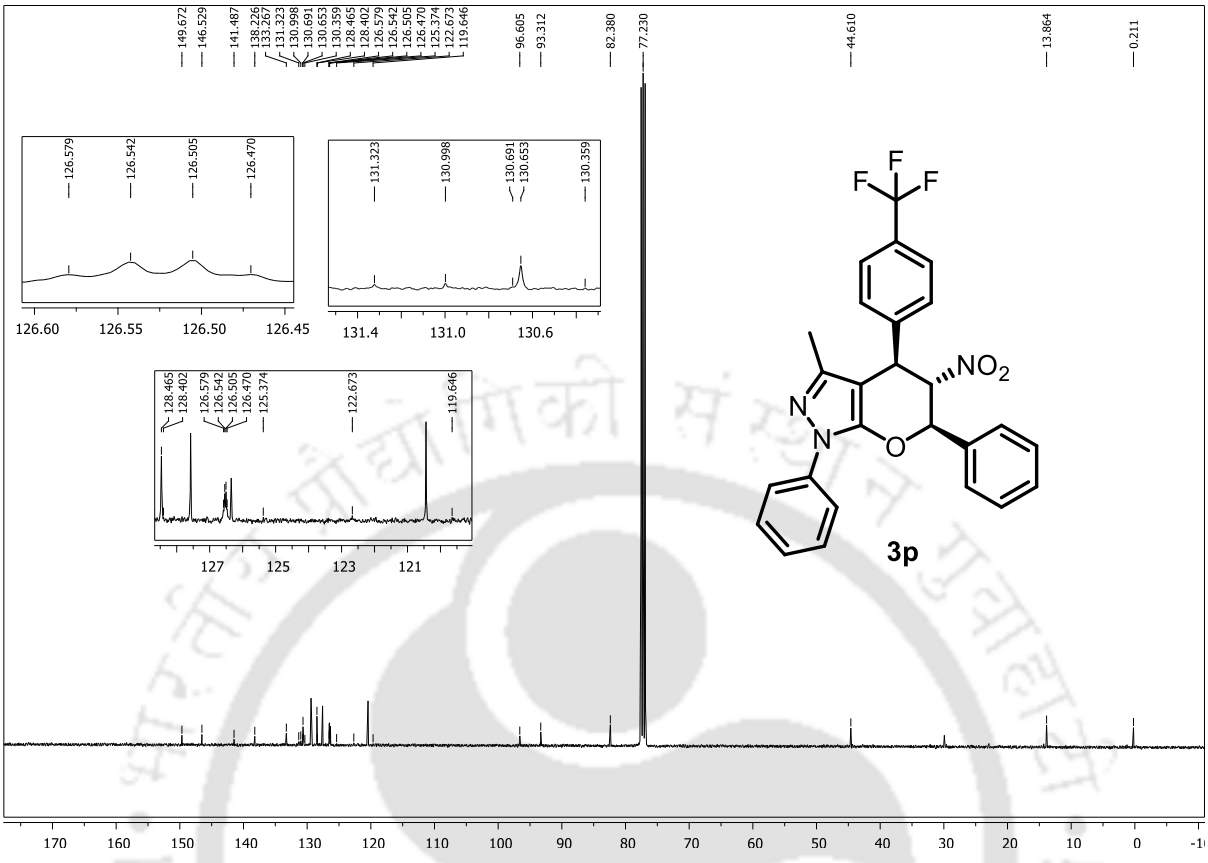
NOESY of **3o**:

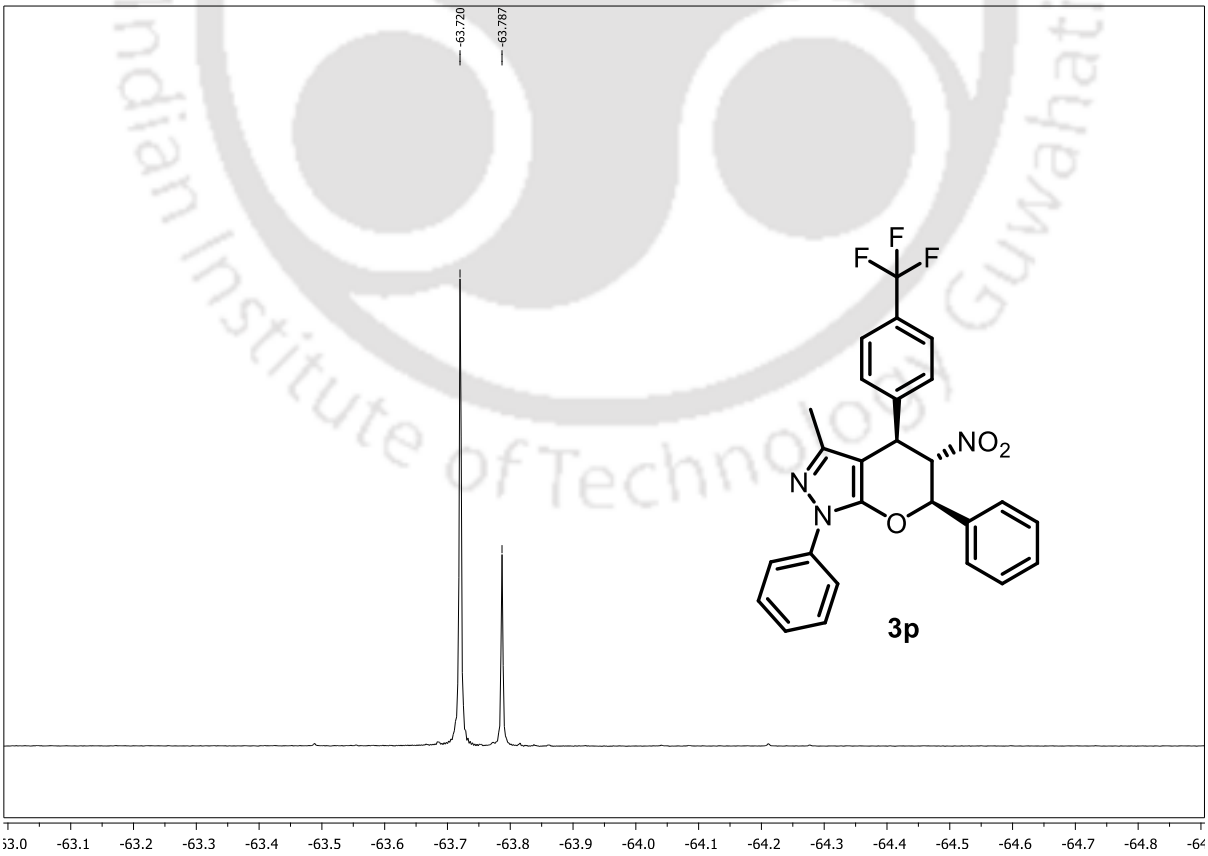


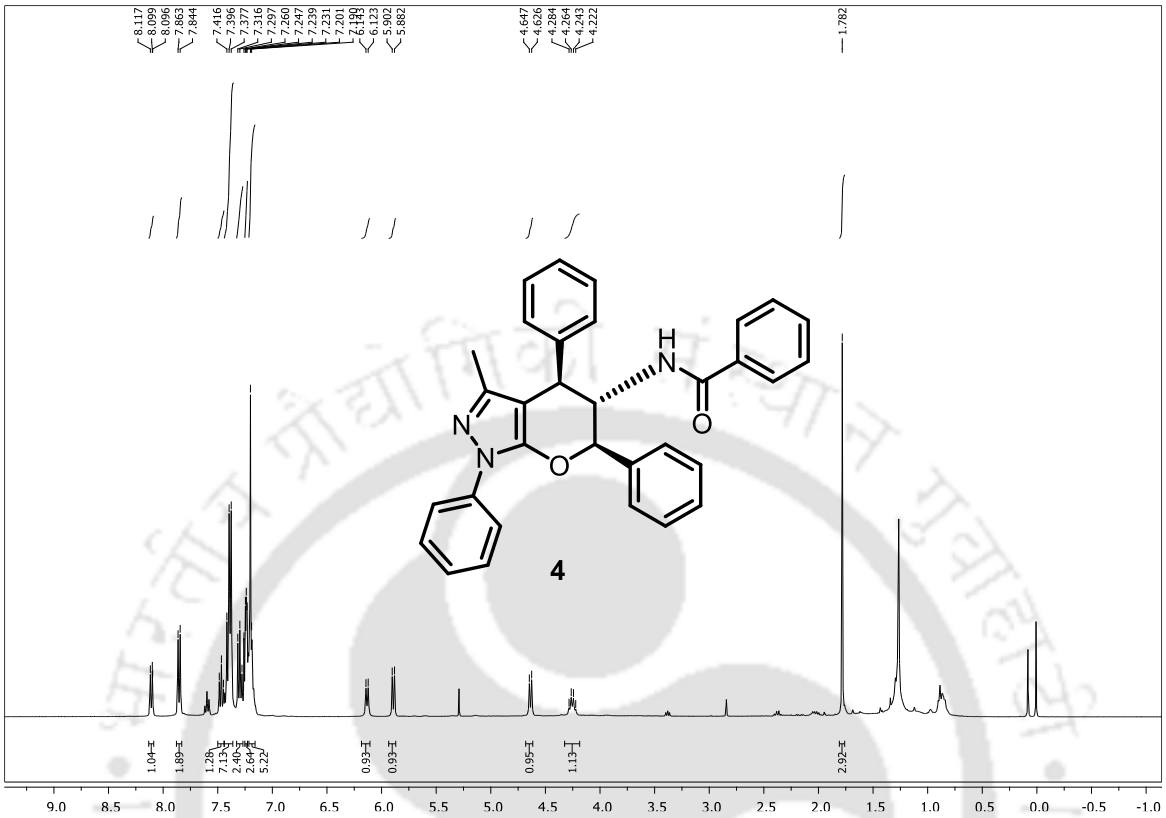
1D NOE of **3o**:

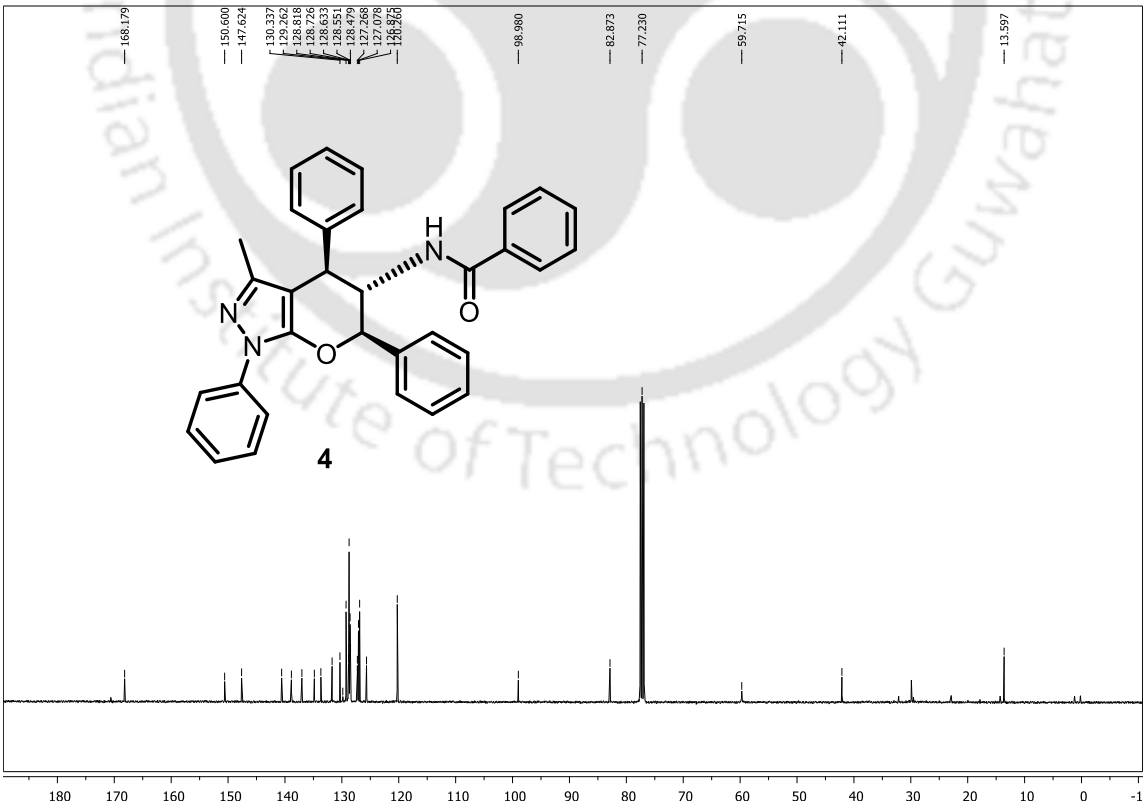


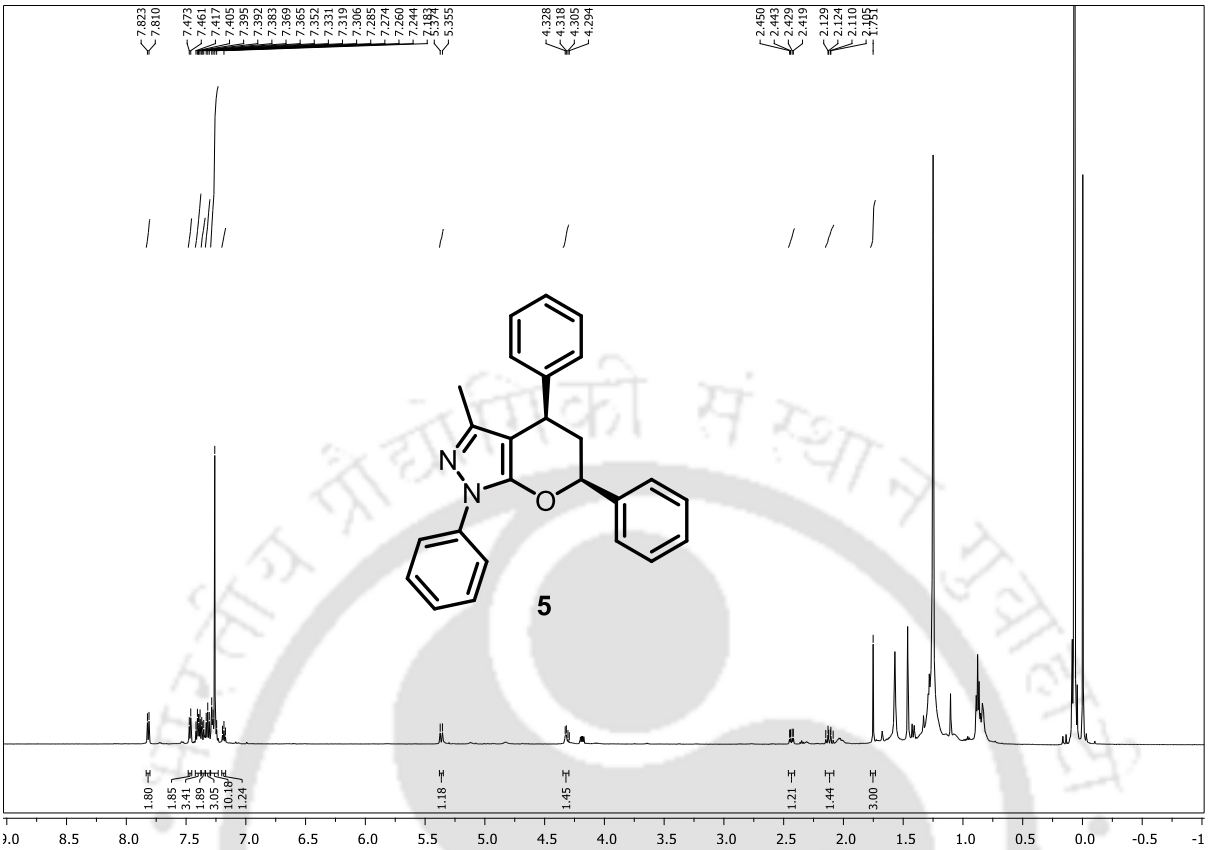


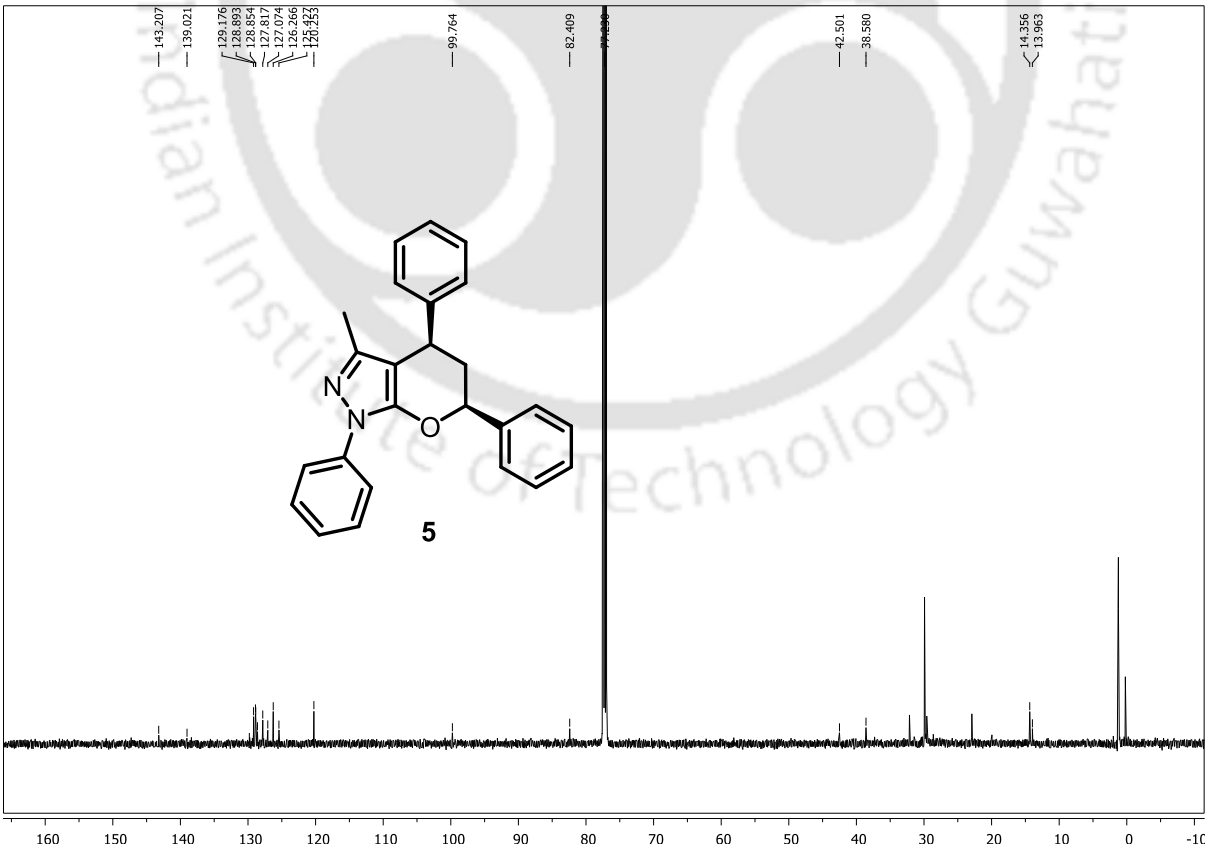






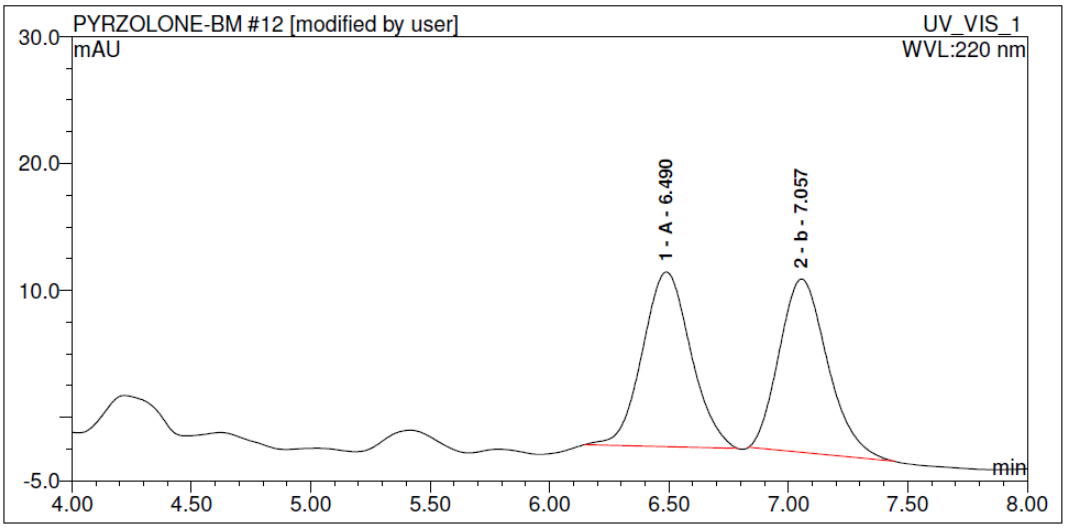






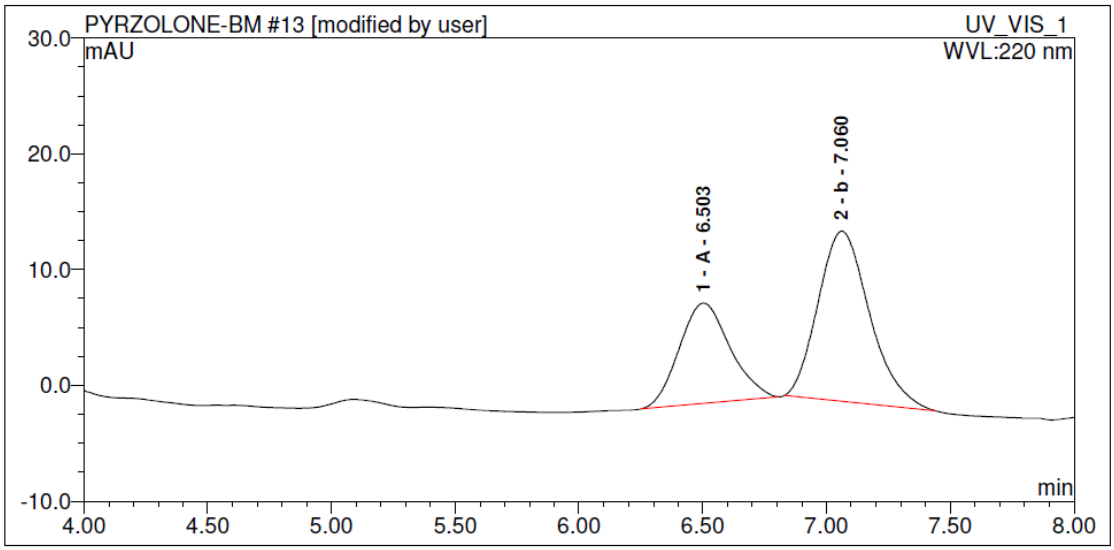
3.7.10. HPLC spectra of compound 3a:

The HPLC chromatogram of racemic **3a** with DMAP is:



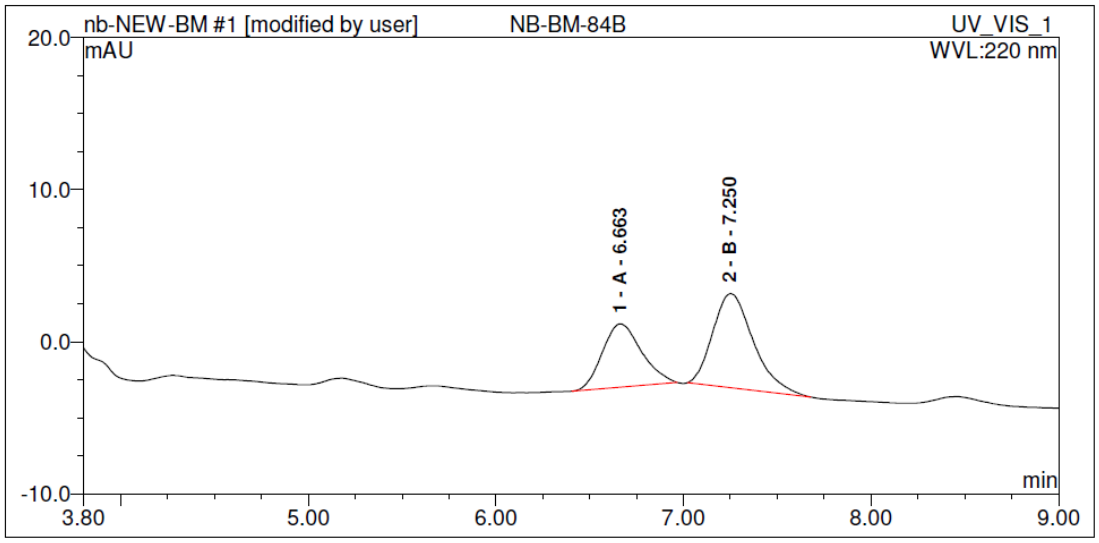
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.49	3.231532	50.13496149	13.76962	n.a.
2	b	7.06	3.214	49.86503851	13.669	n.a.

The HPLC chromatogram of chiral **3a** with catalyst **I** is:



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.50	2.049704	36.61702377	8.64785	n.a.
2	b	7.06	3.548	63.38297623	14.675	n.a.

The HPLC chromatogram of chiral **3a** with catalyst **II** is:



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.66	1.006015	39.32923653	4.1673	n.a.
2	B	7.25	1.552	60.67076347	6.177	n.a.

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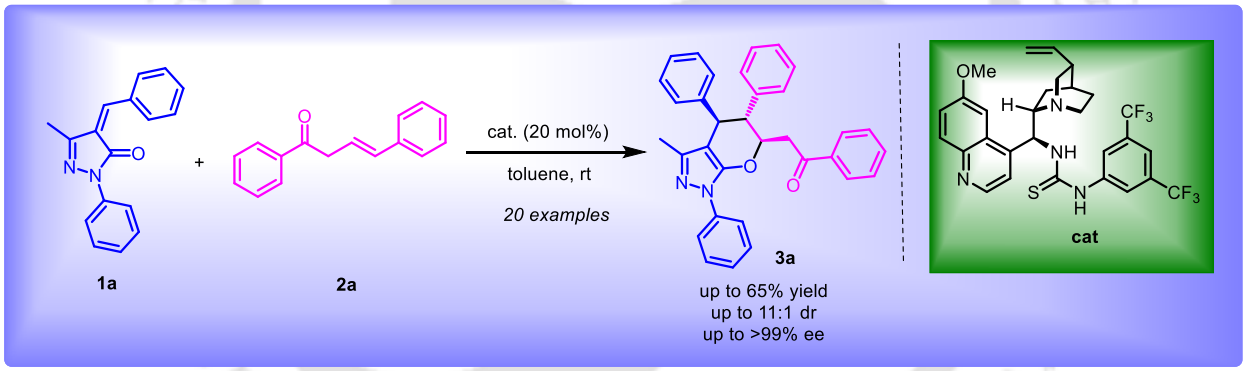
Chapter 4: Organocatalytic Asymmetric Inverse-Electron-Demand Oxa-Diels-Alder Reaction of Allyl Ketones with unsaturated pyrazolones.



4.1 Introduction:

In 1935, Fuson and co-workers formulated the principle of vinylogy which states that the electronic effects of a functional group in a molecule can be transmitted, via interposed conjugated multiple bonds, to a distal position in the molecule.[1] In this context, in recent years, enolates with conjugated C=C double bond (s), that is di(poly)enolates or π-extended enolates, have received special attention.[2] One of the powerful application of these extended enolates to employ them in tandem reaction processes characterized by sequential donor/acceptor reactivity (ambivalent reactivity) and consequently a range of organocatalytic asymmetric cyclization reactions have been reported.[2] β,γ-Unsaturated ketones are an important class of compounds that could be activated either by primary amine or bifunctional tertiary amine-thiourea catalyst depending on the nature of keto substituent.

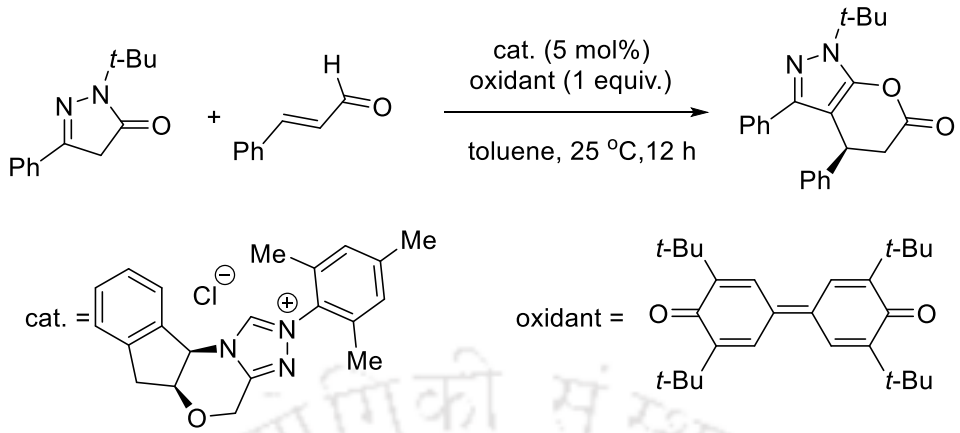
Inverse-electron-demand hetero-Diels-Alder cycloaddition (IEDHDA cycloaddition) plays a special role in the synthesis of tetrahydropyranopyrazolones.[3] This type of annulation is considered as a one of the most powerful tools for construction of six-membered rings from readily available starting materials under mild reaction conditions.

The groups of Enders, Jeong, Ye, Biju, Kesavan, Zhou and others reported the preparation of various tetrahydropyranopyrazoles (THPPs) by employing pyrazolones.[4] Interestingly, the syntheses of chiral tetrahydropyranopyrazoles (THPPs) utilizing alkylidene pyrazolones are less. Only Wang, Pericàs and our group engaged unsaturated pyrazolones in the synthesis of THPPs. [5] However, the preparation of different functionalized tetrahydropyranopyrazoles are still required as they demonstate different activities.

4.2 Selected examples of previous reports of use of pyrazolones for the synthesis of tetrahydropyranopyrazoles

4.2.1 Enantioselective Synthesis of Functionalized Pyrazoles by NHC Catalyzed Reaction of Pyrazolones with α,β-Unsaturated Aldehydes

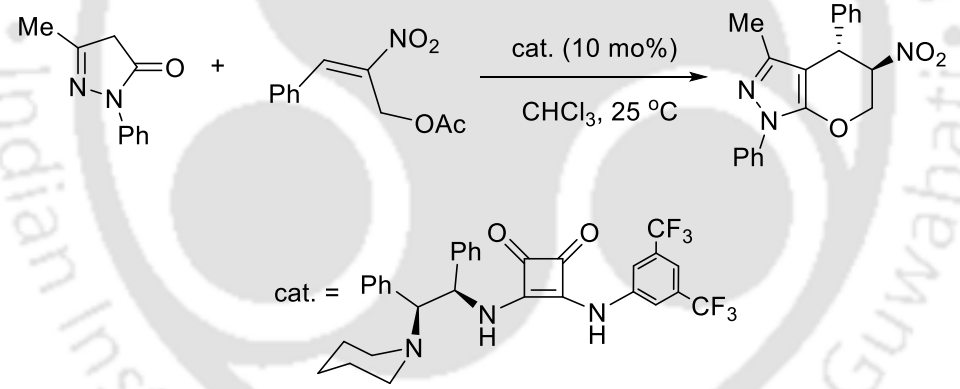
Biju and group, in 2015, reported N-heterocyclic carbene (NHC)-organocatalyzed enantioselective annulation reaction of pyrazolones with α,β-unsaturated aldehydes via the chiral α,β-unsaturated acyl azolium intermediates under oxidative conditions (scheme 1).[4d]



Scheme 1: Enantioselective Synthesis of Functionalized Pyrazoles by NHC Catalyzed Reaction of Pyrazolones with α,β-Unsaturated Aldehydes by Biju et al.

4.2.2 Stereocontrolled Construction of Tetrahydropyrano[2,3-c]pyrazole Scaffold via an Organocatalyzed Formal [3 + 3] Annulation

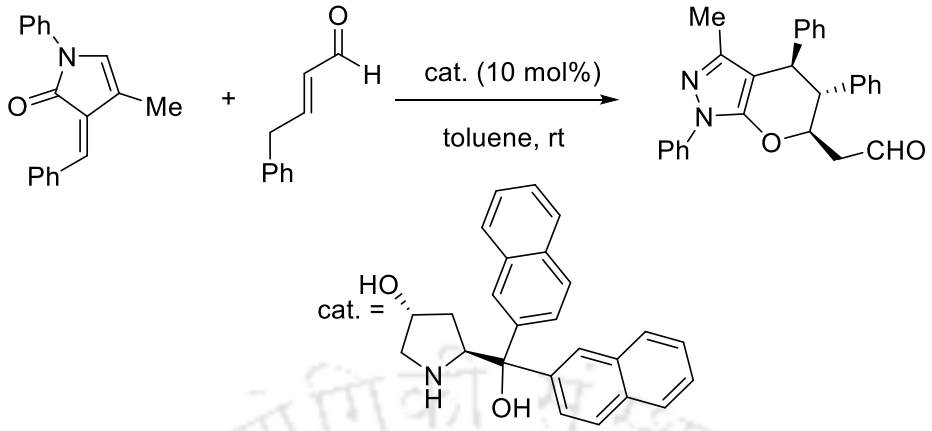
A bifunctional squaramide catalyzed enantioselective formal [3 + 3] annulation reaction with pyrazolin-5-ones and nitroallylic acetates was developed by Zhou group (scheme 2).[4f]



Scheme 2: Stereocontrolled Construction of Tetrahydropyrano[2,3- c]pyrazole Scaffold via an Organocatalyzed Formal [3 + 3] Annulation by Zhou et al.

4.2.3 H-Bond-Directing Organocatalyst for Enantioselective [4 + 2] Cycloadditions via Dienamine Catalysis

An efficient, highly regio- and stereoselective [4+ 2] cycloaddition reaction via dinaphthylprolinol type aminocatalyst to generate tetrahydropyranopyrazole frameworks was developed by Pericus et al (scheme 3).[5b]

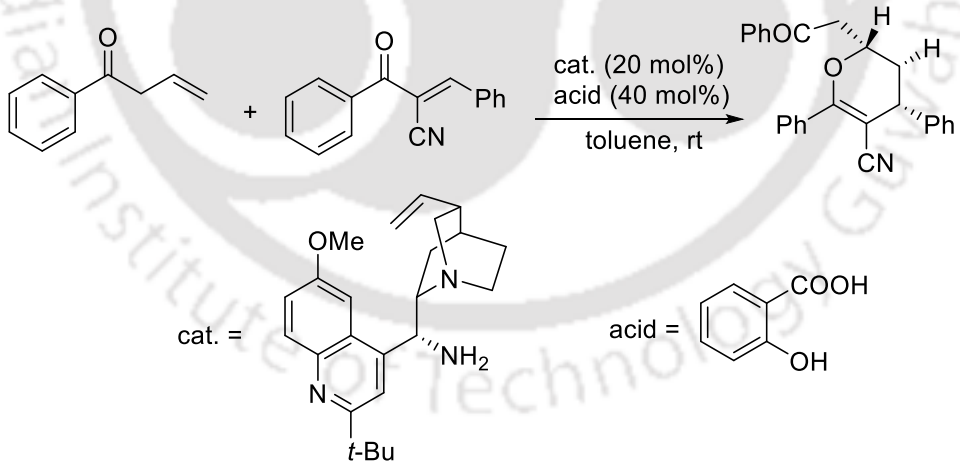


Scheme 3: H-Bond-Directing Organocatalyst for Enantioselective [4 + 2] Cycloadditions via Dienamine Catalysis by Pericas et al.

4.3 Selected examples of previous reports Direct Employment of (E)-1,4-diphenyl but-3-ene-1-one in [4+2] IEDHDA reaction

4.3.1 Asymmetric Inverse-Electron-Demand Oxa-Diels−Alder Reaction of Allylic Ketones through Dienamine Catalysis

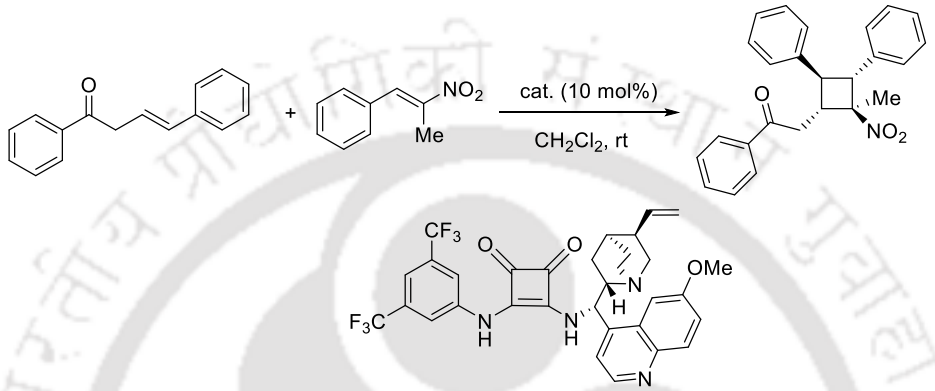
Chen and co-workers, developed a remote β,γ-regioselective asymmetric inverse electron-demand oxa-Diels−Alder reaction between allylic ketones and α-cyano-α,β-unsaturated ketones in presence of a cinchona-derived primary amine (scheme 4).[6]



Scheme 4: Asymmetric Inverse-Electron-Demand Oxa-Diels−Alder Reaction of Allylic Ketones through Dienamine Catalysis by Chen et al.

4.3.2 Catalyst- and Substituent-Controlled Switching of Chemoselectivity for the Enantioselective Synthesis of Fully Substituted Cyclobutane Derivatives via 2 + 2 Annulation of Vinylogous Ketone Enolates and Nitroalkene

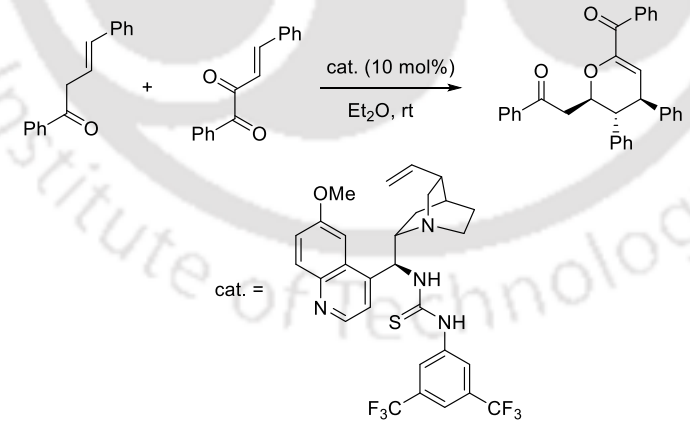
Lee et al. reported the first regioselective, diastereoselective, and enantioselective organocatalyzed Michael−Michael cascade of vinylogous ketone enolates and nitroalkenes for the construction of fully substituted cyclobutanes via chiral squaramide catalyst (scheme 5).[7]



Scheme 5: Enantioselective Synthesis of Fully Substituted Cyclobutane Derivatives by Lee et al.

4.3.3 Bifunctional Thiourea-Catalyzed Asymmetric Inverse-Electron-Demand Diels−Alder Reaction of Allyl Ketones and Vinyl 1,2-Diketones via Dienolate Intermediate

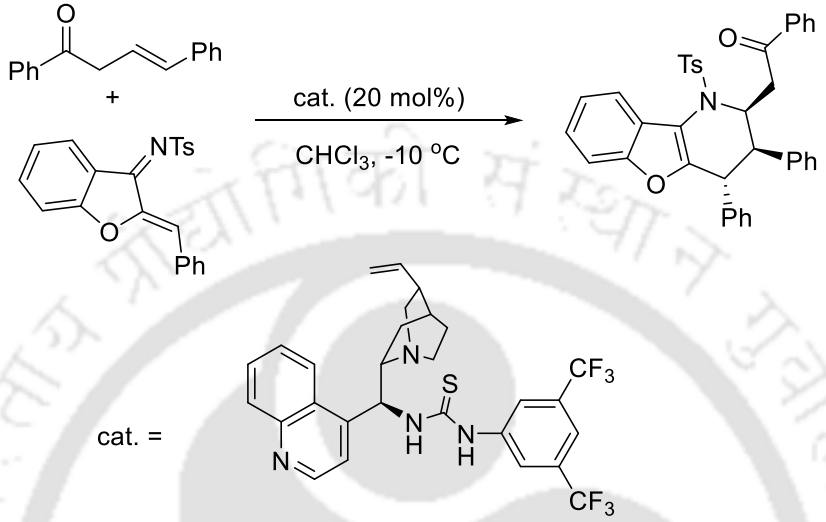
Fang and group, reported the asymmetric inverse-electron-demand oxa-Diels−Alder reaction between allyl ketones and alkenyl 1,2-diketones using a bifunctional thiourea catalyst (scheme 6).[8]



Scheme 6: Inverse-Electron-Demand Diels−Alder Reaction of Allyl Ketones and Vinyl 1,2-Diketones by Fang et al.

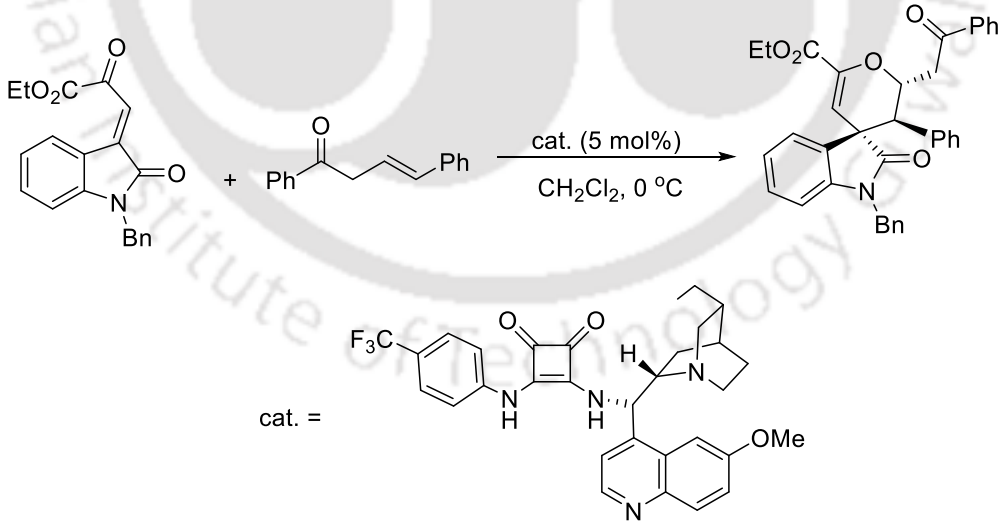
4.3.4 Deconjugated-Ketone-Derived Dienolates in Remote, Stereocontrolled, Aromative aza-Diels-Alder Cycloaddition

Albrecht et al. describes the application of β,γ-unsaturated ketones as precursors of electron-rich dienophiles in the organocatalytic, aromative inverse-electron-demand hetero-Diels-Alder cycloaddition leading to the formation of biologically relevant benzofuran derivatives bearing additional tetrahydropyridine ring (scheme 7).[9]



Scheme 7: Deconjugated-Ketone-Derived Dienolates in Remote, Stereocontrolled, Aromative aza-Diels-Alder Cycloaddition by Albrecht et al.

4.3.5 Organocatalytic Remote Asymmetric Inverse-Electron-Demand Oxa-Diels-Alder Reaction of Allyl Ketones with Isatin-Derived Unsaturated Keto Esters

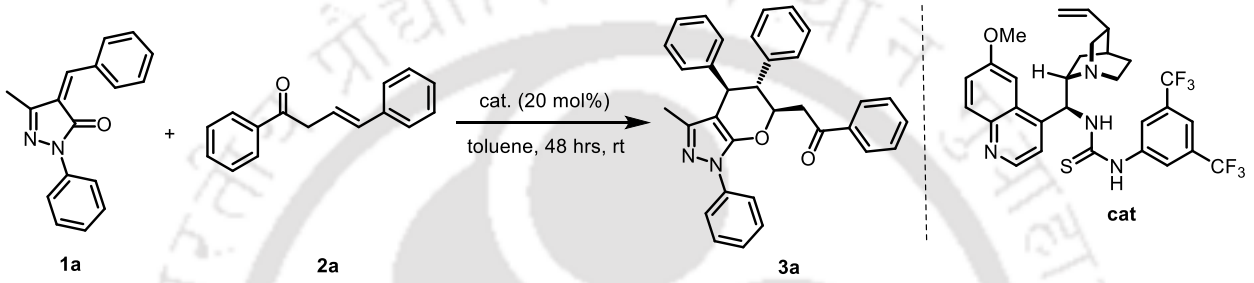


Scheme 8: Inverse-Electron-Demand Oxa-Diels-Alder Reaction of Allyl Ketones with Isatin-Derived Unsaturated Keto Esters by Du et al.

Du and group developed a remote cascade asymmetric inverse-electron-demand oxa-Diels-Alder reaction of allyl ketones with isatin-derived β,γ-unsaturated α-keto esters catalysed by chiral bifunctional squaramide catalyst (scheme 8).[10]

4.3 Concept:

Realising the potential β,γ-unsaturated ketones as precursors of electron-rich dienophiles, we decided to utilise this substrate with unsaturated pyrazolones to obtain, tetrahydropyranopyrazolones using organcatalysts.



Scheme 9: The present work.

4.4 Results and discussion:

4.4.1 Reaction optimization:

We began our study by checking a model reaction benzylidene pyrazolone 1a and (*E*)-1,4-diphenyl but-3-ene-1-one (2a) in dichloromethane at room temperature (Table 1). Initially ^{t}leucine derived bifunctional squaramide I was employed as the catalyst. Delightfully the proposed IEDHDA reaction progressed well in 2 days to provide the desired product 3a in 35% yield with 2:1 dr and 65% ee (Table 1, entry 1). The relative configuration of 3a was assigned from 1H NMR. The diastereoselectivity of 3a got slightly improved with quinine derived bifunctional squramide catalyst II though enantioselectivity remained same (Table 1, entry 2). Cyclohexyl diamine derived bifunctional thiourea catalyst III was also not suitable for the reaction (Table 1, entry 3). Then we employed quinine derived bifunctional urea catalyst IV in the reaction and gratifyingly both diastereo- and enantioselectivity got improved (Table 1, entry 4). Better enantioselectivity was attained with hydroquinine derived bifunctional thiourea catalyst V but the diastereoselecitivity got decreased (Table1, entry 5). Finally, the best catalyst turned out to be quinine derived bifunctional thiourea VI and product 3a was attained in 65% yield with 7:1 dr and 93% ee (Table

1, entry 6). To further improve the diastereo- and enantioselectivity, different solvents were screened (Table 1, entries 7-9). Similar results were observed in chloroform and 1,2-dichloroethane though diastereoselectivity got decreased in 1,2-dichloroethane (Table 1, entries 7-8). Then toluene emerged as the best solvent and delivered product 3a in 70% yield with 8:1 dr and 93% ee (Table 1, entry 9).

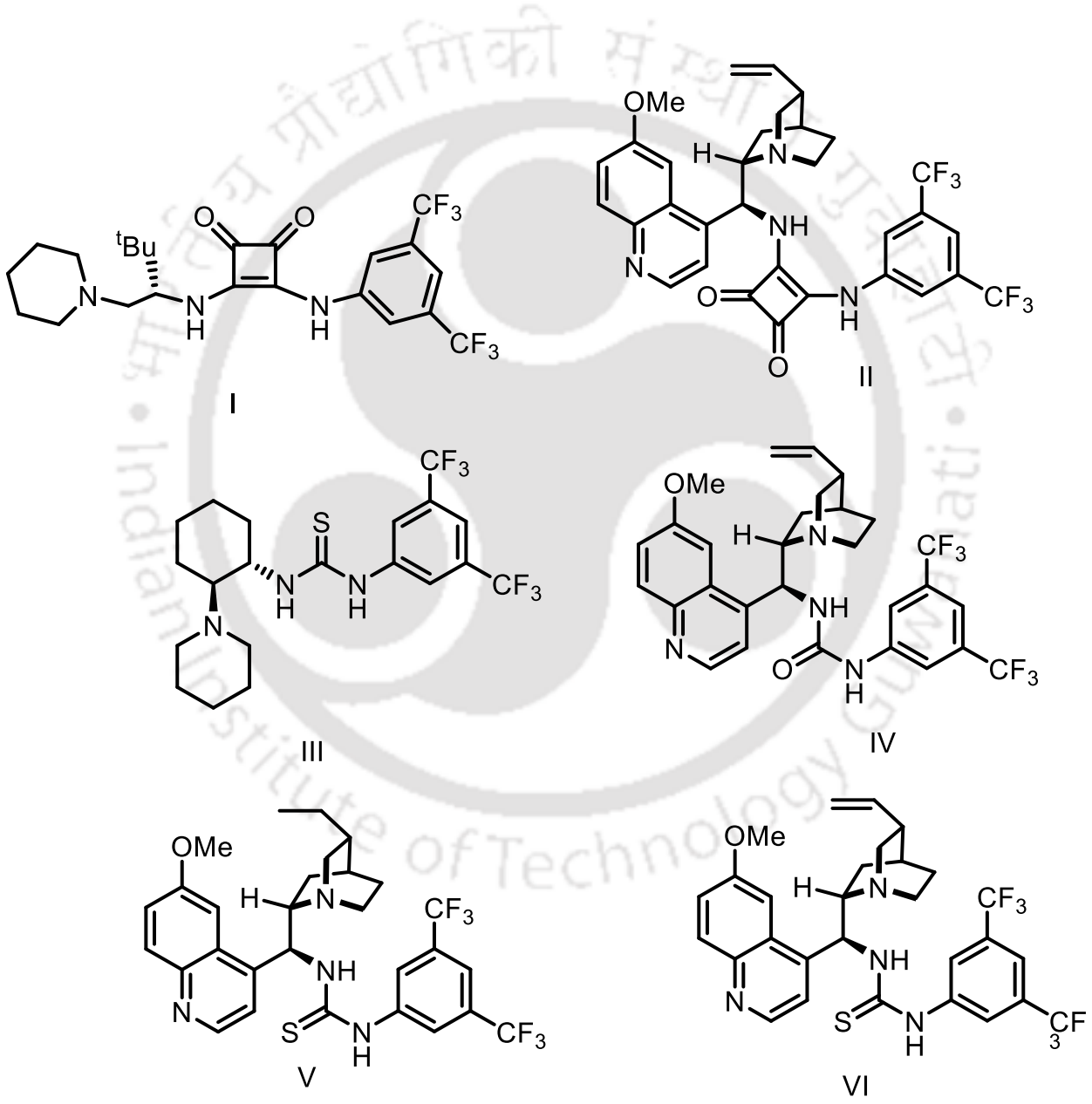
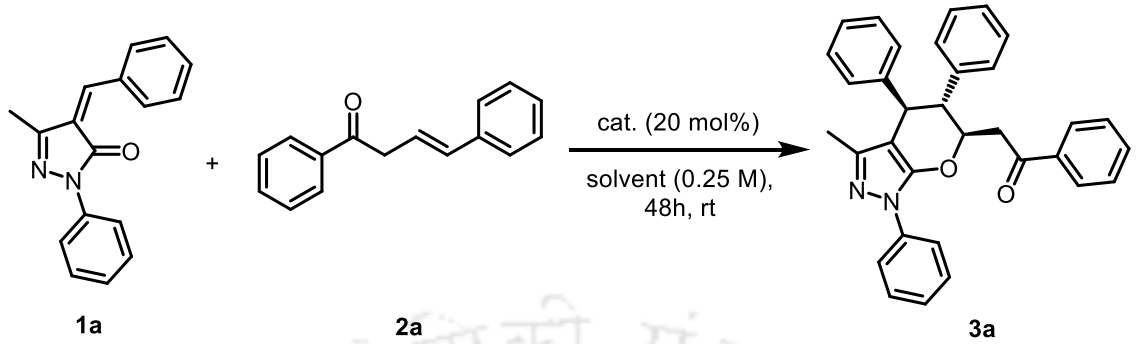


Figure 1: Catalysts screened

Table 1: Catalyst and solvent screening



1a **2a** **3a**

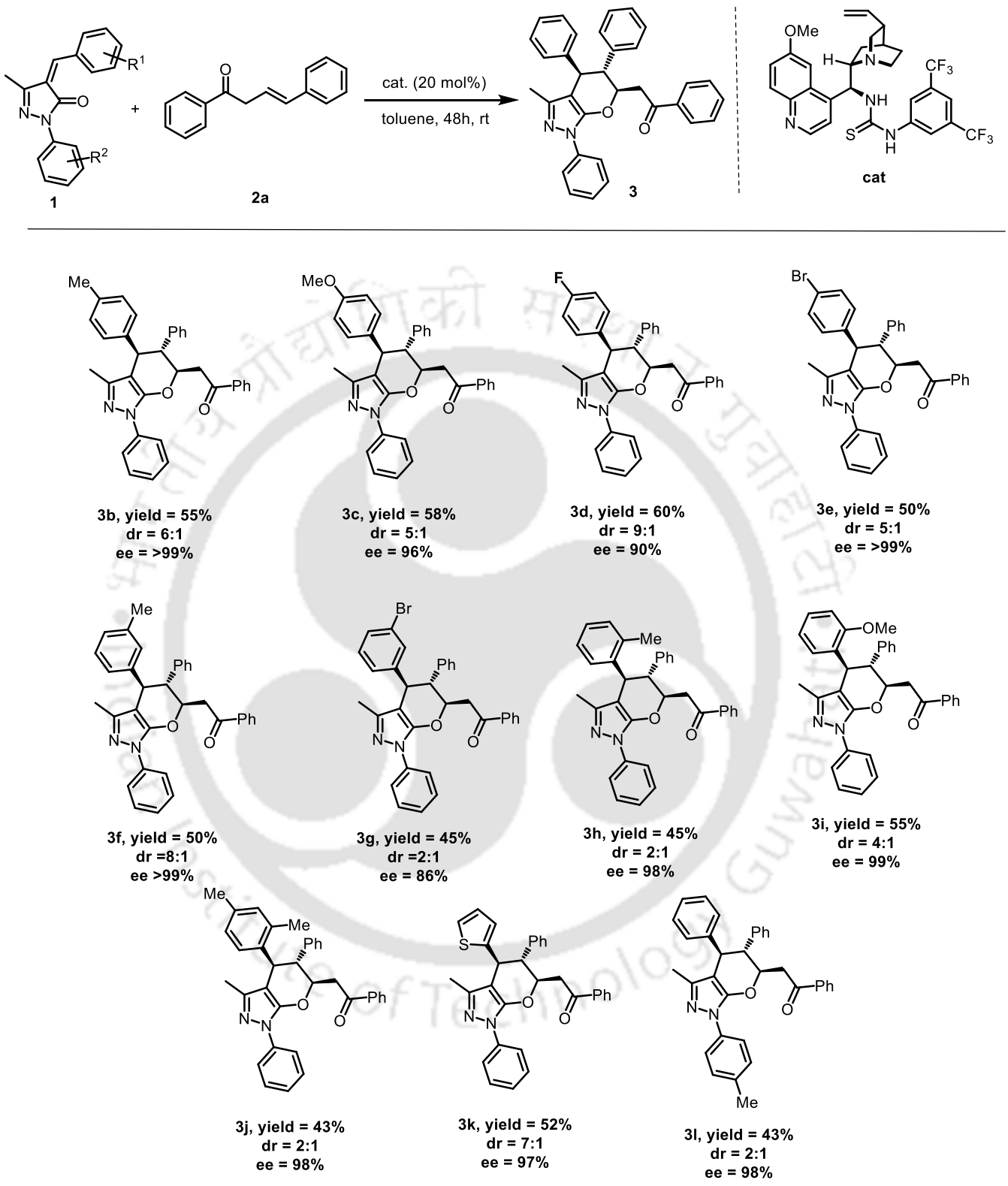
Entry[a]	Catalyst	Solvent	Yield(%)[b]	dr[c]	ee(%)[d]
1	I	DCM	40	4:1	64
2	II	DCM	20	2:1	35
3	III	DCM	45	5:1	82
4	IV	DCM	40	2:1	89
5	V	DCM	30	2:1	65
6	VI	DCM	60	7:1	93
7	VI	$CHCl_3$	60	9:1	92
8	VI	DCE	55	4:1	93
9	**VI**	**Toluene**	**65**	**14:1**	**93**

[a]0.05 mmol of **1a** and 0.06 mmol of **2a** were stirred in 0.2 mL solvent at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by 1H NMR. [d]Determined by HPLC.

4.4.1 Substrate scope:

4.4.1.2 Scope of unsaturated pyrazolones:

After the optimized conditions were established, the scope of this inverse-electron-demand-Diels-Alder reaction was checked. Initially, pyrazolones **1** having different benzylidiene substitutents were prepared and reacted with (*E*)-1,4-diphenyl but-3-ene-1-one **(2a)**. Gratifyingly, in almost all cases excellent enantioselectivity was attained. At first, different *para*-substitutions were tested on



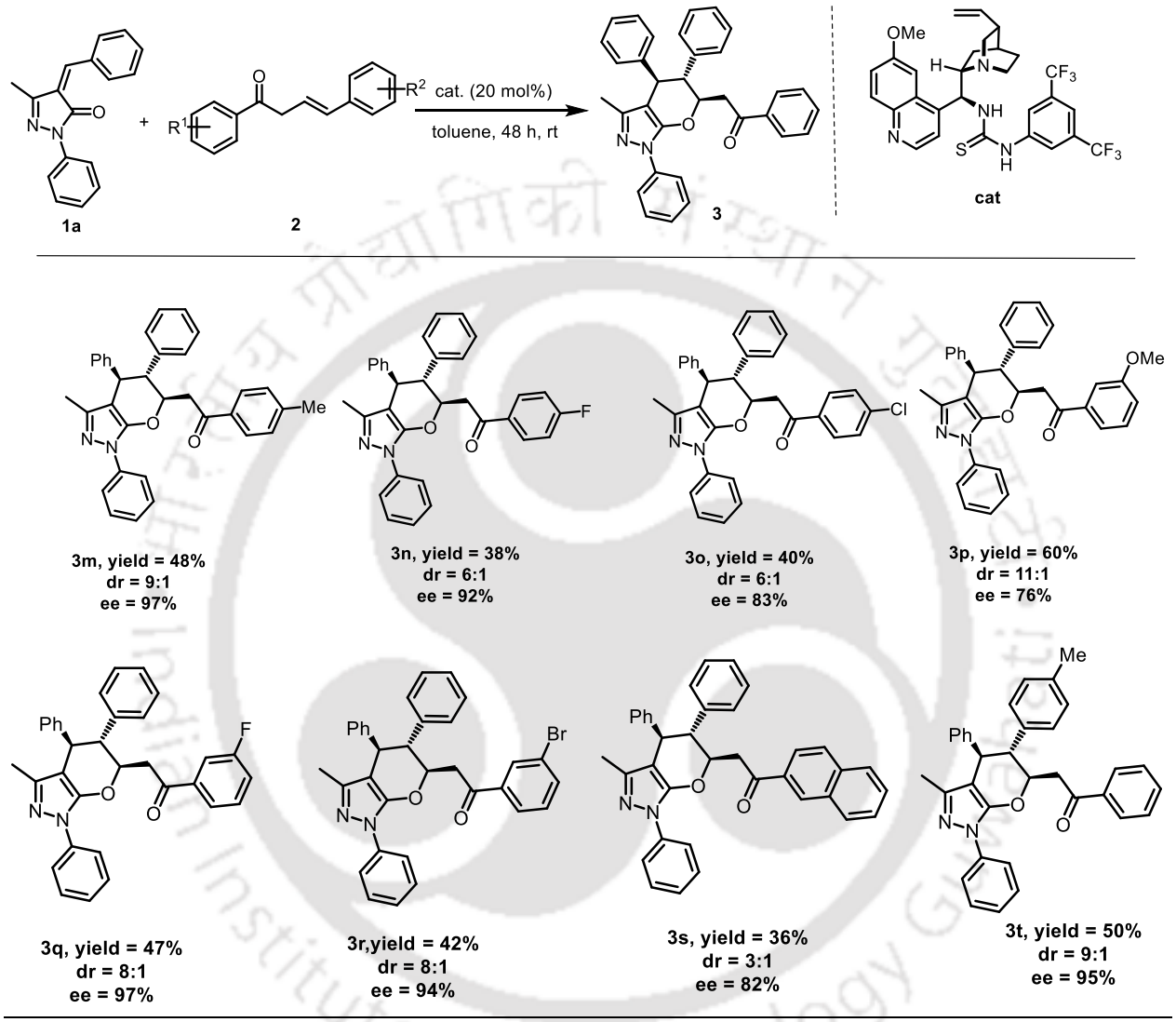
Scheme 10: Scope of unsaturated pyrazolones

the benzylidene group of pyrazolones and the reactions progressed efficiently. For example, *p*-tolyl substituted unsaturated pyrazolone **1b** delivered the cyclized product **3b** in 55% yield with 6:1 dr and in perfect enantiopurity. Similar result was also detected with *p*-anisyl substituted unsatuarated pyrazolone **1c** and product **3c** was isolated in 96% ee. Then different halo substitutions were checked and gratifyingly good results were obtained. In particular, product **3e** having 4-bromophenyl substituent was obtained as single enantiomer. Then different *meta*-substitutions were checked and here also good results were achieved. The product **3f** having *meta*-tolyl motif was obtained in 50% yield with 8:1 dr and 99% ee. Then 3-anisyl and 3-bromo phenyl substituted unsaturated pyrazolones **1g** and **1h** were engaged in the reaction and the products **3g**-**3h** were isolated in moderate yields. Although product **3g** was attained in 6:1 dr and 96% ee, slight less diastereo- and enantioselectivity was detected for **3h**. *ortho*-Substitution could also be tolerated and gratifyingly smooth conversion was detected for unsaturated pyrazolone **1h** with *ortho*-tolyl substituent (Table 2, entry 9). Though the diastereoselectivity was less, a high enantiomeric excess (98% ee) was achieved for product **3h**. Similar enantioselectivity was also detected for product 3i with 2-anisyl substituent . Then 2,4-disubstituted phenyl group containing pyrazolone **1j** was employed in the reaction and good result was observed. A heteroaromatic such as 2-thienyl group containing pyrazolone **1k** also participated in the reaction to deliver product **3k** in 52% yield with 9:1 dr and 97% ee. Then we turned our attention to vary *N*-substitution on the pyrazolone motif. Thus, *N*-4-toyl substituted pyrazolone **1l** was prepared and employed in the reaction. This resulted in the formation of product **3l** in 5:1 dr and 98% ee.

4.4.1.3 Scope of allyl ketones:

In the next phase the scope of de-conjugated allyl ketone **2** was studied. Here also, good results were obtained in almost all cases. Initially, allyl ketones **2** having various aryl groups on the ketone part were prepared and reacted with unsaturated pyrazolone **1a**. At first, different *para*-substitutions on the phenyl group were screened. Product **3m** having para-tolyl substituent was isolated in 9:1 dr with 97% ee. Then 4-fluoro and 4-chloro substituted allyl ketones **2c** and **2d** were employed in the reaction. Though diastereomeric ratios for products **3n** and **3o** are same, the enantiomeric excesses are different. A higher enantioselectivity of 92% was achieved with 4-fluoro substitution. Then different *meta*-substitutions were checked in the reaction and gratifyingly here

also the reaction progressed efficiently. Allyl ketone **2e** with 3-anisyl substituted reacted well to deliver product **3p** in 60% yield though the enantioselectivity was moderate. Then 3-fluoro and 3-



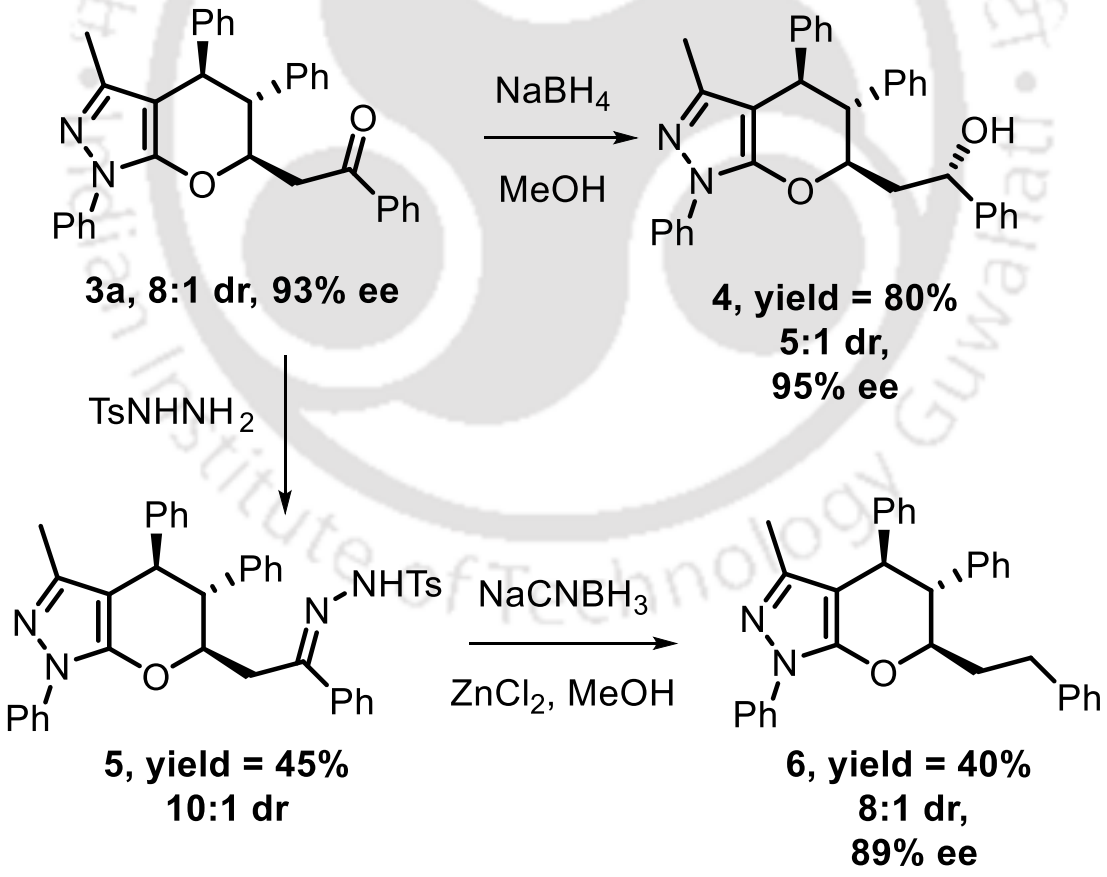
Scheme 11: Scope of allyl ketones

bromo containing allyl ketones **2f** and **2g** were engaged in the reaction. Gratifyingly, in both cases acceptable yields and excellent enantioselectivities were obtained for the desired products **3q** and **3r**. Naphthyl group can also be tolerated in the reaction and product **3s** was isolated in slightly lower enantioselectivity. Then we turned our attention to vary the aryl group in the olefin part of allyl ketone. Thus, we prepared allyl ketone **2i** with 4-tolyl group on the olefin part and employed

in the reaction. This resulted in the formation of product **3t** which was obtained in 9:1 dr and 95% ee.

4.4.2. Synthetic transformations:

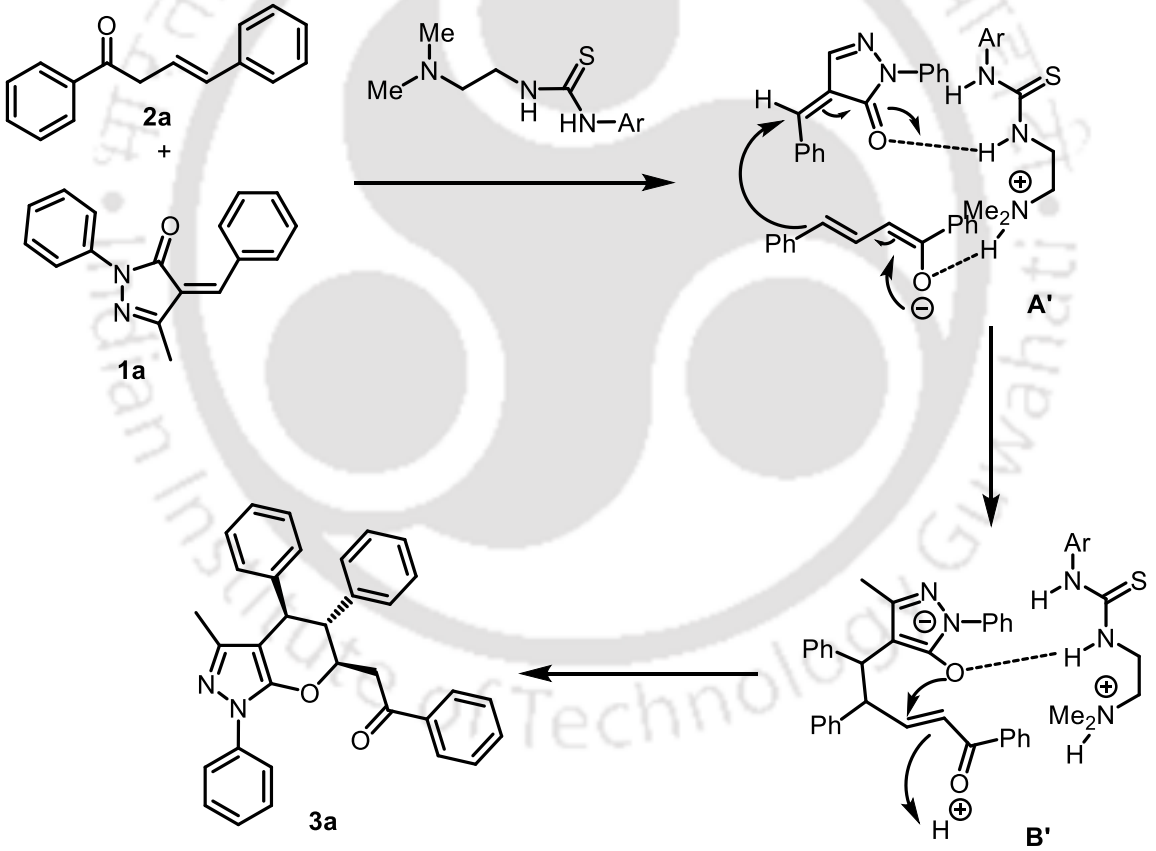
The synthetic potential of our method was demonstrated by performing few reactions on **3a** (Scheme 2). Initially sodium borohydride mediated reduction of carbonyl group was carried out. The corresponding alcohol **4** was formed in 5:1 diastereomeric mixture and the enantioselectivity got slightly decreased. Then **3a** was subjected to hydrazone formation with tosylhydrazine. Thus, hydrazone **5** was formed in 45% yield whose enantioselectivity could not be measured. It was then treated with sodium cyanoborohydride and zinc chloride to get decarbonylated product **6** in 40% yield and slight erosion in enantioselectivity was observed. However, the diastereoselectivity was maintained in this process.



Scheme 11: Synthetic transformations

4.4.3. Plausible mechanism:

Based on the relative structure, a plausible mechanism has been described. At first, catalyst deprotonates the β,γ-unsaturated ketone in the α-position leading to the formation of dienolate **A′**. Subsequently, it participates in the inverse-electron hetero-Diels-Alder reaction proceeding via step-wise mechanism. It is postulated that the protonated nitrogen atom of catalyst acts as H-bond donor, thus catalyst places both reactants in the strictly defined position in space. As a consequence, the initial doubly vinylogous Michael addition of **A** ′to benzylidene group of unsaturated pyrazolone **1a** takes place at the distal double bond of the dienolate. The subsequent cyclization via the oxa-Michael reaction and protonation releases the desired product **3a**(Scheme 12).



Scheme 12: Plausible mechanistic pathway

4.5. Conclusion

In summary, we have reported the first inverse electron demand Diels-Alder reaction of unsaturated pyrazolones with deconjugated ketones. The tetrahydropyrano[2,3-c]pyrazole products were obtained in moderate to good yields with high diastereo- and enantioselectivities under ambient reaction conditions with easily available bifunctional thiourea catalyst. Synthetic applications such as reduction and decarbonylation have also been shown. Given the high medicinal importance of tetrahydropyrano[2,3-c]pyrazoles our methodology might be useful in pharmaceutical industry.

4.6. Experimental section:

4.6.1. General procedure for the synthesis of Unsaturated pyrazolones:

Unsaturated pyrazolones are prepared according to reported procedure.[11]

4.6.2. General procedure for the synthesis of Allyl ketones:

Allyl ketones are prepared according to reported procedures.[12]

4.6.3. General procedure for the synthesis of compound 3a:

In an oven dried round bottom flask, **1** (26.2 mg, 0.1 mmol), **2** (26.7mg, 0.12 mmol), 20 mol% of Catalsyt **VI** were taken. 0.4 mL of toluene was added to the reaction mixture and stirred at rt for 1 day. 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 **3a.**

4.6.4. General procedure for the synthesis of compound 4:

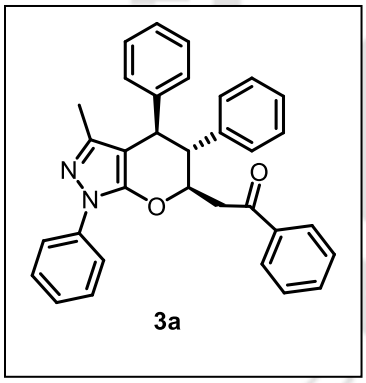
In 1.0 mL of Methanol, compound **3a** (0.1 mmol) was added followed by Sodium borohydride (2 mmol) in one portion at 0 °C and the reaction was stirred for 10 mins. The TLC was checked and the reaction shows full conversion. This was followed by a work up with EtOAc. The combined organic layer was dried in anhydrous Na_2SO_4 and solvent was removed under pressure. After purification by column chromatography (10% EtOAc)/Hexane) compound **4**, a white solid, was obtained in 5:1 dr and 95% ee.

4.6.5. General procedure for the synthesis of compound 5 and 6:

To an oven dried round-bottom flask previously equipped with a magnetic stir bar, was charged with tosylhydrazide (0.1 mmol) in dry methanol (0.5 mL) at 60 °C, **3a** was added. After the completion of reaction, the product began to precipitate. The crude product was filtered and purified by silica gel column chromatography with hexane/ethyl acetate (20-25) % and dried to afford the pure hydrazone, **5** with 45% yield and 10:1 dr value.

To a stirred solution of tosylhydrazone, **5** (48 mg, 0.07mmol) in methanol (3 mL) at room temperature was added a solution of sodium cyanoborohydride (0.3 mmol) and zinc chloride (0.2 mmol) in methanol (1 mL). The reaction mixture was refluxed at 65 ^{o}C for 3 h and after completion taken up in 0.1 N NaOH (10 mL), and extracted with hexane (10 mL X 3). The combined extracts were washed with water and brine, dried, and evaporated to dryness. Pure product, **6** was obtained by column chromatography (5% ethyl acetate in hexane) in 45% yield, 7:1 dr and 89% ee.

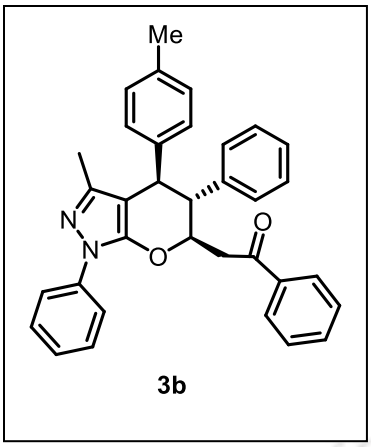
4.6.6. Characterization of the products:



3a

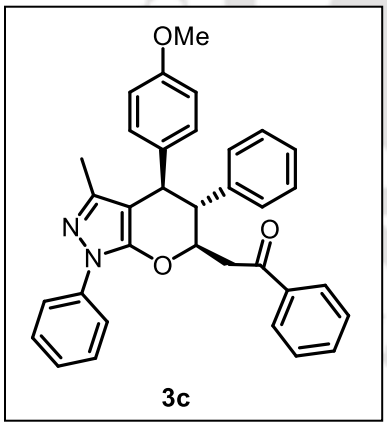
3a. 2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky solid in 70% yield (34.0 mg) after column chromatography. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.9 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.59 – 7.53 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 3H), 7.35 – 7.31 (m, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 9.4 Hz, 1H), 7.20 (t, *J* = 8.0 Hz, 3H), 7.16 – 7.12 (m, 2H), 7.11 – 7.06 (m, 3H), 6.75 (d, *J* = 7.5 Hz, 2H), 5.40 (ddd, *J* = 11.4, 9.3, 2.6 Hz, 1H), 4.14 (d, *J* = 5.6 Hz, 1H), 3.58 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.42 (dd, *J* = 16.0, 9.3 Hz, 1H), 2.84 (dd, *J* = 15.9, 2.6 Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.9, 150.4, 146.9, 140.0, 138.9, 138.3, 137.4, 133.5, 130.0, 129.9, 128.9, 128.8, 128.8, 128.5, 128.4, 127.9, 127.3, 126.9, 126.6, 125.1, 119.8, 99.4, 76.1, 50.2, 42.5, 42.1, 12.7.

HPLC Analysis: ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.29 min, t_{minor} = 10.18 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{29}N_2O_2$ 485.2224; Found 485.2221.



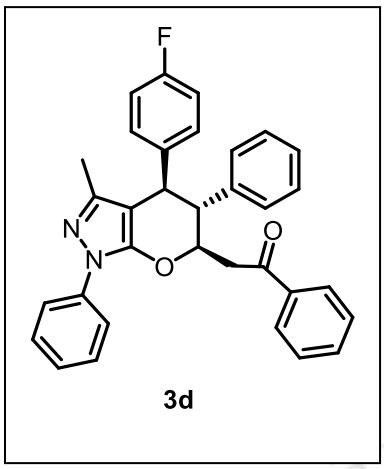
3b

3b. 2-((4R,5R,6R)-3-methyl-1,5-diphenyl-4-(*p*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as brownish yellow sticky solid in 55% (27.5 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.88 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.59 – 7.54 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 3H), 7.22 – 7.17 (m, 3H), 7.15 (d, *J* = 6.5 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 2H), 6.62 (d, *J* = 7.3 Hz, 2H), 5.43 – 5.36 (m, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 3.56 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.40 (dd, *J* = 15.9, 9.2 Hz, 1H), 2.85 (dd, *J* = 15.9, 2.6 Hz, 1H), 2.28 (s, 3H), 1.92 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.9, 150.4, 146.9, 138.9, 138.5, 137.5, 137.4, 136.9, 136.7, 136.5, 133.6, 133.4, 133.4, 129.9, 129.1, 129.1, 129.0, 128.9, 128.9, 128.8, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 127.6, 127.2, 127.1, 125.5, 125.2, 125.1, 120.3, 119.9, 119.8, 99.7, 76.2, 50.3, 42.2, 42.2, 31.8, 21.2, 12.7 . **HPLC Analysis:** ee = >99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.64 min, t_{minor} = 9.52 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_2$ 499.2380; Found 499.2377.



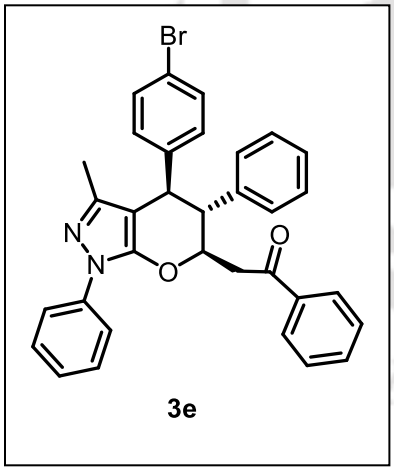
3c

3c. 2-((4R,5R,6R)-4-(4-methoxyphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as reddish brown sticky solid in 58% (29.8 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.91 – 7.87 (m, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 3H), 7.20 (t, *J* = 7.8 Hz, 3H), 7.15 (d, *J* = 6.0 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.65 (s, 4H), 5.39 – 5.34 (m, 1H), 4.10 (d, *J* = 5.7 Hz, 1H), 3.76 (s, 3H), 3.55 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.41 (dd, *J* = 15.9, 9.4 Hz, 1H), 2.85 (dd, *J* = 15.9, 2.6 Hz, 1H), 1.92 (s, 3H). **13C NMR (126 MHz, Chloroform-*d***) δ 197.9, 158.7, 150.3, 146.9, 138.9, 138.5, 137.4, 133.5, 132.1, 131.0, 129.0, 129.0, 128.8, 128.5, 128.4, 127.3, 125.1, 119.9, 119.8, 113.3, 99.7, 76.2, 55.4, 50.4, 42.1, 41.8, 12.7. **HPLC Analysis:** ee = 97%, Chiralpak IC Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.6 min, t_{minor} = 14.30 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_3$ 513.2329; Found 515.2326.



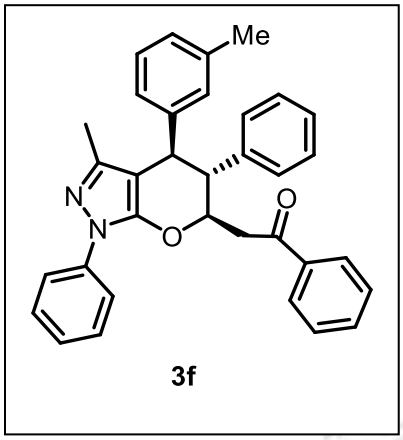
3d

3d. 2-((4R,5R,6R)-4-(4-fluorophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as brownish sticky solid in 60% (30.2 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.91 – 7.87 (m, 2H), 7.65 – 7.62 (m, 2H), 7.60 – 7.53 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.16 (d, *J* = 6.4 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.81 (t, *J* = 8.8 Hz, 2H), 6.75 – 6.66 (m, 2H), 5.36 (ddd, *J* = 11.4, 9.3, 2.6 Hz, 1H), 4.14 (d, *J* = 5.9 Hz, 1H), 3.58 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.42 (dd, *J* = 16.0, 9.3 Hz, 1H), 2.87 (dd, *J* = 16.0, 2.6 Hz, 1H), 1.91 (s, 3H).**^{13}C NMR (151 MHz, Chloroform-*d*)** δ 197.8, 162.8, 161.2, 150.3, 146.8, 138.8, 138.22, 137.3, 133.6, 129.0, 128.8, 128.49, 127.4, 125.2, 119.8, 114.8, 114.6, 99.3, 75.9, 50.0, 42.0, 41.8, 12.7. **^{19}F NMR (377 MHz, Chloroform-*d*)** δ -117.12. **HPLC Analysis:** ee = 90%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.6 min, t_{minor} = 12.1 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}FN_2O_2$ 503.2129; Found 503.2128.



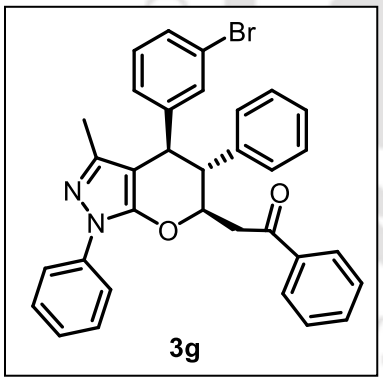
3e

3e. 2-((4R,5R,6R)-4-(4-bromophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky solid in 50% (28.2 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)**δ 7.90 – 7.86 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 3H), 7.25 (s, 2H), 7.23 (d, *J* = 4.0 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 5.8 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.62 (d, *J* = 7.9 Hz, 2H), 5.35 (ddd, *J* = 11.4, 9.2, 2.6 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 3.59 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.45 – 3.38 (m, 1H), 2.89 (dd, *J* = 16.1, 2.7 Hz, 1H), 1.91 (s, 3H).**^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.4, 150.2, 146.5, 139.0, 138.5, 137.8, 137.1, 133.3, 131.4, 130.81, 128.8, 128.6, 128.4, 128.2, 128.1, 127.3, 125.5, 125.1, 120.9, 120.2, 119.74, 98.7, 75.7, 49.7, 41.9, 41.8, 12.4. **HPLC Analysis:** ee = >99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.8 min, t_{minor} = 12.7 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}BrN_2O_2$ 563.1329; Found 563.1321.



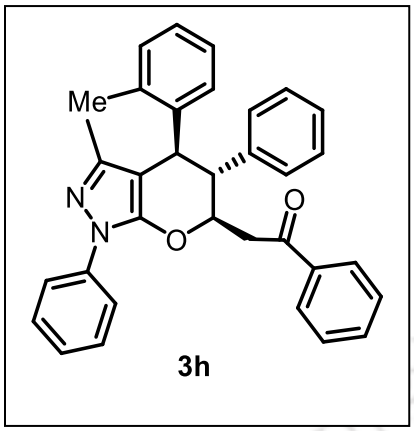
3f

3f. 2-((4R,5R,6R)-3-methyl-1,5-diphenyl-4-(m-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a light brownish sticky solid 50% (25.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** 7.93 – 7.87 (m, 2H), 7.67 – 7.62 (m, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 3H), 7.16 – 7.12 (m, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 7.03 – 6.94 (m, 2H), 6.55 (d, *J* = 7.2 Hz, 1H), 6.48 (s, 1H), 5.38 (ddd, *J* = 11.4, 9.3, 2.6 Hz, 1H), 4.10 (d, *J* = 5.8 Hz, 1H), 3.57 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.42 (dd, *J* = 15.9, 9.3 Hz, 1H), 2.89 – 2.82 (m, 1H), 2.16 (s, 3H), 1.93 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.9, 150.4, 147.0, 139.8, 139.0, 138.4, 137.5, 137.3, 133.5, 130.9, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.4, 128.2, 127.7, 127.7, 127.3, 127.1, 125.1, 119.8, 99.5, 76.2, 50.3, 42.5, 42.2, 22.9, 21.5, 14.3, 12.7. **HPLC Analysis:** ee = >99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.9 min, t_{minor} = 9.7 min). **ESI HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_2$ 499.2380; Found 499.2381.

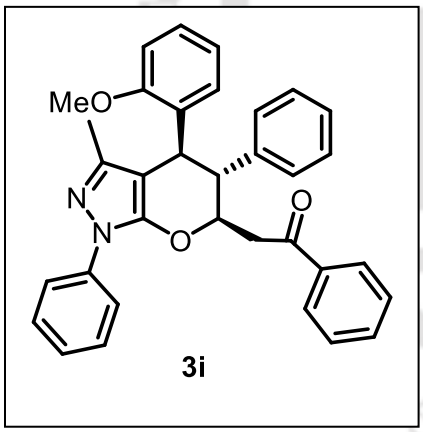


3g

3g. 2-((4R,5R,6R)-4-(3-bromophenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a reddish brown sticky solid solid compound in 45% (25.3 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 3H), 7.23 – 7.17 (m, 5H), 7.13 – 7.08 (m, 2H), 7.01 (t, *J* = 7.7 Hz, 2H), 6.79 – 6.71 (m, 2H), 5.37 – 5.31 (m, 1H), 5.11 (dd, *J* = 26.8, 17.8 Hz, 1H), 4.11 (d, *J* = 5.4 Hz, 1H), 3.60 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.42 (dd, *J* = 16.1, 9.2 Hz, 1H), 2.90 (dd, *J* = 16.1, 2.7 Hz, 1H), 1.93 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.6, 150.4, 146.80 142.6, 138.8, 137.9, 137.4, 133.5, 130.1, 129.4, 129.25, 129.0, 128.8, 128.8, 128.5, 128.4, 127.7, 125.3, 120.02, 119.9, 98.6, 76.0, 50.01, 42.3, 42.0, 12.7. **HPLC Analysis:** ee = 86%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 15.5 min, t_{minor} = 13.5 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}BrN_2O_2$ 563.1329; Found 563.1325.

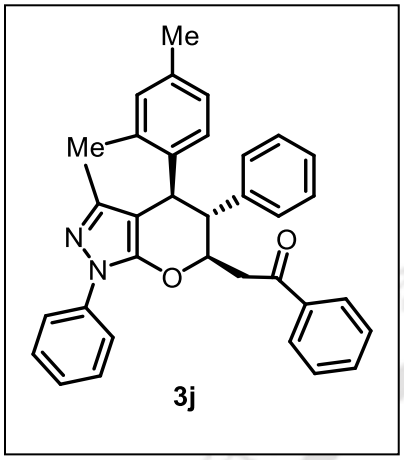


3h. 2-((4R,5R,6R)-3-methyl-1,5-diphenyl-4-(o-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky solid in 45% (22.5 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.89 – 7.85 (m, 2H), 7.66 – 7.62 (m, 2H), 7.44 (t, *J* = 7.8 Hz, 3H), 7.24 – 7.18 (m, 5H), 7.18 – 7.14 (m, 3H), 7.12 – 7.07 (m, 3H), 6.88 (d, *J* = 7.6 Hz, 1H), 5.46 (ddd, *J* = 11.5, 9.2, 2.8 Hz, 1H), 4.52 (d, *J* = 5.7 Hz, 1H), 3.58 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.35 (dd, *J* = 15.8, 9.2 Hz, 1H), 2.74 (dd, *J* = 15.8, 2.8 Hz, 1H), 1.88 (s, 3H), 1.56 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 196.9, 149.5, 145.68, 137.9, 137.7, 137.1, 137.0, 136.4, 132.4, 129.0, 128.7, 127.9, 127.8, 127.4, 127.4, 126.5, 125.9, 125.0, 124.1, 118.83, 99.3, 75.3, 49.3, 41.1, 35.8, 35.7, 18.2, 11.5. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 13.3 min, t_{minor} = 9.7 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_2$ 499.2380; Found 499.2380.

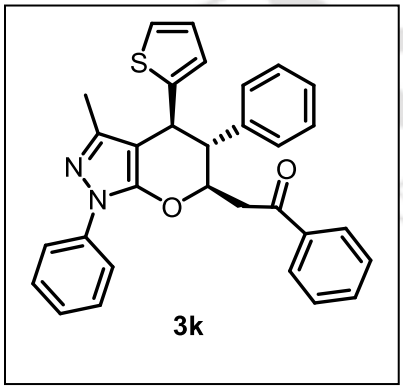


3i. 2-((4R,5R,6R)-4-(2-methoxyphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky solid in 55% (28.3 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 – 7.85 (m, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 3H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.19 – 7.13 (m, 3H), 7.08 (t, *J* = 7.4 Hz, 4H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 5.37 – 5.31 (m, 1H), 4.83 (d, *J* = 5.9 Hz, 1H), 3.54 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.37 (dd, *J* = 15.8, 9.4 Hz, 1H), 3.06 (s, 3H), 2.76 (dd, *J* = 15.9, 2.7 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 198.0, 157.78, 150.8, 146.9, 139.0, 137.5, 133.4, 130.3, 129.0, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.4, 128.4, 128.1, 127.8, 126.9, 125.00, 120.3, 120.2, 119.76, 109.9, 99.4, 76.4, 54.7, 49.9, 42.2, 42.1, 12.6. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.7

min, t_{minor} = 9.4 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_3$ 515.2329; Found 515.2337.

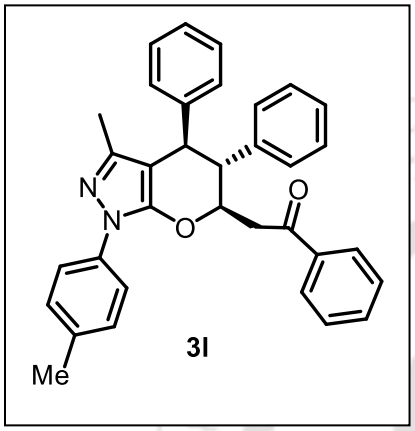


3j. 2-((4R,5R,6R)-4-(2,4-dimethylphenyl)-3-methyl-1,5-diphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a reddish brown sticky solid in 43% (22.1 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.92 – 7.88 (m, 2H), 7.68 – 7.63 (m, 2H), 7.59 (td, *J* = 7.1, 1.4 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 3H), 7.25 – 7.20 (m, 3H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 3H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 5.50 – 5.44 (m, 1H), 4.48 (d, *J* = 5.6 Hz, 1H), 3.57 (dd, *J* = 10.9, 5.6 Hz, 1H), 3.38 (dd, *J* = 15.8, 9.3 Hz, 1H), 2.78 – 2.72 (m, 1H), 2.30 (s, 3H), 1.91 (s, 3H), 1.51 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 150.4, 146.6, 138.9, 138.2, 137.8, 137.4, 136.3, 135.5, 133.5, 133.4, 130.75, 129.7, 129.1, 128.9, 128.9, 128.8, 128.8, 128.8, 128.4, 128.4, 127.4, 126.7, 125.0, 119.8, 119.7, 100.4, 76.3, 50.4, 42.1, 36.4, 21.1, 19.1, 12.5. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 274 nm (t_{major} = 12.9 min, t_{minor} = 9.6 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{35}H_{33}N_2O_2$ 513.2537; Found 513.2545.



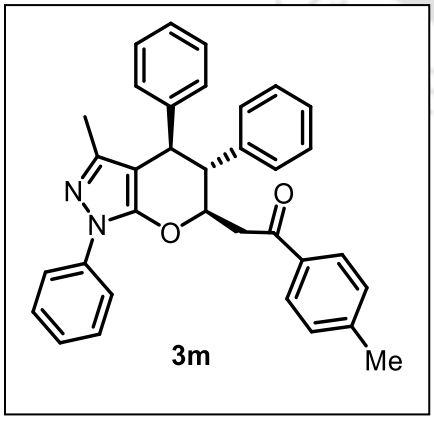
3k. 2-((4R,5R,6R)-3-methyl-1,5-diphenyl-4-(thiophen-2-yl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky compound in 52% (25.5 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.91 – 7.88 (m, 2H), 7.61 (dd, *J* = 8.7, 1.3 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 3H), 7.22 – 7.17 (m, 4H), 7.12 – 7.08 (m, 2H), 6.81 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.32 (d, *J* = 3.5 Hz, 1H), 5.52 (ddd, *J* = 11.2, 9.1, 2.6 Hz, 1H), 4.39 (d, *J* = 5.6 Hz, 1H), 3.56 (dd, *J* = 10.9, 5.5 Hz, 1H), 3.43 (dd, *J* = 16.0, 9.1 Hz, 1H), 2.94 (dd, *J* = 16.0, 2.7 Hz, 1H), 2.00 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.7, 149.8, 146.9, 144.4, 138.8, 138.3, 137.4, 133.5, 129.1, 129.0, 128.8,

128.5, 128.5, 128.4, 127.56, 127.0, 126.1, 125.2, 124.88, 120.0, 119.9, 100.3, 76.3, 50.2, 42.1, 38.0, 12.6. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.1 min, t_{minor} = 12.5 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{31}H_{27}N_2O_2S$ 491.1788; Found 491.1788.



3l

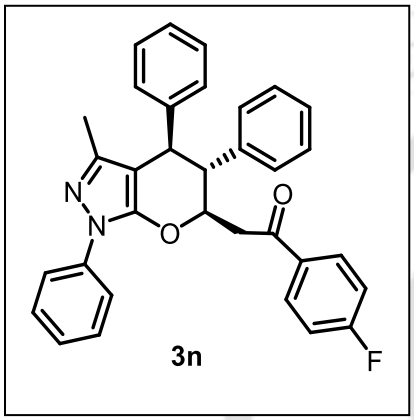
3l. 2-((4R,5R,6R)-3-methyl-4,5-diphenyl-1-(*p*-tolyl)-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-phenylethan-1-one was obtained as a brownish sticky solid compound in 55% (27.5 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.87 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 3H), 7.13 (dd, *J* = 17.4, 7.4 Hz, 7H), 7.01 (d, *J* = 8.1 Hz, 3H), 6.75 (d, *J* = 7.5 Hz, 2H), 5.39 (ddd, *J* = 11.4, 9.3, 2.6 Hz, 1H), 4.14 (d, *J* = 5.7 Hz, 1H), 3.58 (dd, *J* = 10.8, 5.8 Hz, 1H), 3.39 (dd, *J* = 16.1, 9.2 Hz, 1H), 2.86 (dd, *J* = 16.1, 2.6 Hz, 1H), 2.29 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (151 MHz Chloroform-*d*)** δ 197.6, 150.0, 146.3, 139.9, 138.2, 137.1, 136.30, 134.5, 133.2, 129.8, 129.5, 129.3, 128.8, 128.80, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 127.6, 127.0, 126.7, 120.2, 119.7, 119.6, 99.0, 75.7, 50.0, 42.4, 42.0, 20.9, 12.5. **HPLC Analysis:** ee = >99 %, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.8 min, t_{minor} = 10.5 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{28}N_2O_2$ 499.2380; Found 499.2378.



3m

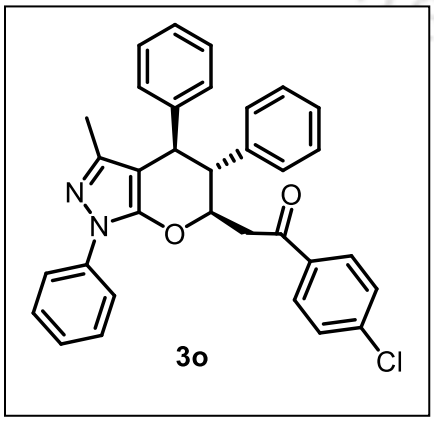
3m. 2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-(*p*-tolyl)ethan-1-one was obtained as a brownish sticky compound in 48% (24.0 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.9 Hz, 3H), 7.15 (d, *J* = 6.7 Hz, 2H), 7.10 (q, *J* = 7.4 Hz, 4H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.39 (ddd, *J* = 11.2, 9.4, 2.6 Hz, 1H), 4.14 (d, *J* = 5.7 Hz, 1H), 3.58 (dd, *J* = 10.8, 5.8 Hz, 1H), 3.39 (dd, *J* = 15.9, 9.4 Hz, 1H), 2.82 (dd, *J* = 15.9,

2.6 Hz, 1H), 2.41 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.4, 150.4, 146.9, 144.3, 140.1, 138.9, 138.4, 134.9, 130.0, 129.5, 128.9, 128.6, 128.6, 128.4, 128.3, 127.8, 127.2, 126.9, 125.0, 119.8, 99.4, 76.2, 50.2, 42.6, 42.0, 21.8, 12.7. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 16.4 min, t_{minor} = 14.6 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_2$ 499.2380; Found 499.2381.



3n

3n. 1-(4-fluorophenyl)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-ethan-1-one was obtained as a brownish yellow sticky solid in 38% (19.1 mg) yield after column chromatography**. ^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.93 – 7.87 (m, 2H), 7.64 – 7.59 (m, 2H), 7.23 – 7.19 (m, 3H), 7.17 – 7.05 (m, 10H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.41 – 5.34 (m, 1H), 4.15 (d, *J* = 5.8 Hz, 1H), 3.57 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.37 (dd, *J* = 15.9, 9.3 Hz, 1H), 2.82 (dd, *J* = 15.9, 2.6 Hz, 1H), 1.91 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 167.1, 165.0, 150.3, 146.9, 140.0, 138.8, 138.3, 131.2, 131.1, 130.0, 128.9, 127.9, 127.3, 127.0, 125.2, 119.9, 116.0, 115.8, 99.4, 76.1, 50.2, 42.5, 42.0, 12.7. **^{19}F NMR (377 MHz, Chloroform-*d*)** ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.67.**HPLC Analysis:** ee = 92%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.1 min, t_{minor} = 13.1 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}FN_2O_2$ 503. 2129; Found 503.2149.

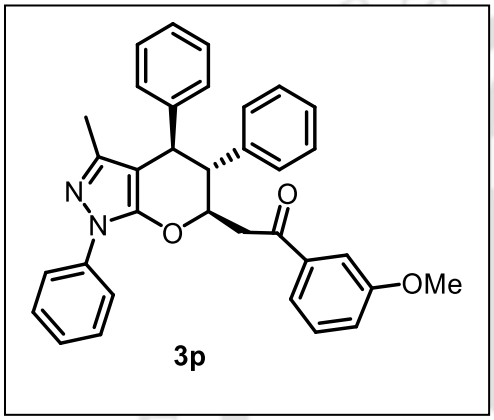


3o

3o. 1-(4-chlorophenyl)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-ethan-1-one was obtained as a Yellowish sticky solid 40% (20.8 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.84 – 7.79 (m, 2H), 7.63 – 7.58 (m, 2H), 7.43 – 7.38 (m, 4H), 7.24 – 7.19 (m, 3H), 7.13 (ddd, *J* = 19.0, 9.2, 6.4 Hz, 7H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.36 (ddd, *J* =

11.4, 9.2, 2.7 Hz, 1H), 4.14 (d, *J* = 5.7 Hz, 1H), 3.57 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.36 (dd, *J* = 15.9, 9.3 Hz, 1H), 2.82 (dd, *J* = 15.9, 2.7 Hz, 1H), 1.91 (s, 3H).

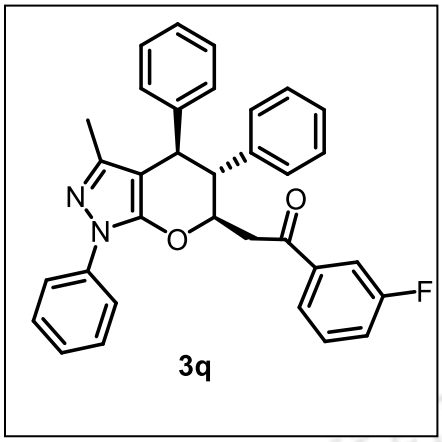
^{13}C NMR (126 MHz, Chloroform-*d*) δ 196.7, 150.3, 146.9, 140.0, 140.0, 138.8, 138.2, 135.7, 130.0, 129.9, 129.8, 129.1, 129.1, 129.1, 128.9, 128.4, 127.9, 127.8, 127.4, 127.2, 127.0, 125.3, 120.4, 120.0, 119.9, 99.4, 76.2, 50.2, 42.5, 42.1, 12.7. **HPLC Analysis:** ee = 83%, Chiralpak IF Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.4 min, t_{minor} = 10.3 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}ClN_2O_2$ 519.1834; Found 519.1813.



3p

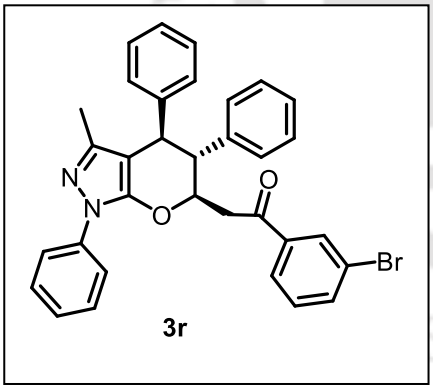
3p. 1-(3-methoxyphenyl)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-ethan-1-one was obtained as a pale brownish sticky solid in 60% (30.9 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.64 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.46 – 7.42 (m, 2H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 2H), 7.19 – 7.14 (m, 2H), 7.11 (td, *J* = 7.9, 3.2 Hz, 5H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.39 (ddd, *J* = 11.3, 9.4, 2.6 Hz, 1H), 4.15 (d, *J* = 5.7 Hz, 1H), 3.82 (s, 3H), 3.59 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.39 (dd, *J* = 15.9, 9.3 Hz, 1H), 2.85 (dd, *J* = 15.9, 2.6 Hz, 1H), 1.92 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 197.79, 160.04, 150.40, 146.91, 140.07, 138.91, 138.80, 138.34, 130.0, 129.8, 129.1, 128.9, 128.3, 127.8, 127.3, 126.96, 125.1, 121.1, 120.0, 119.8, 112.6, 112.6, 99.4, 76.2, 55.6, 50.1, 42.5, 42.3, 12.7. **HPLC Analysis:** ee =76%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 12.7 min, t_{minor} = 15.1 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_3$ 515.2329; Found 515.2339.



3q

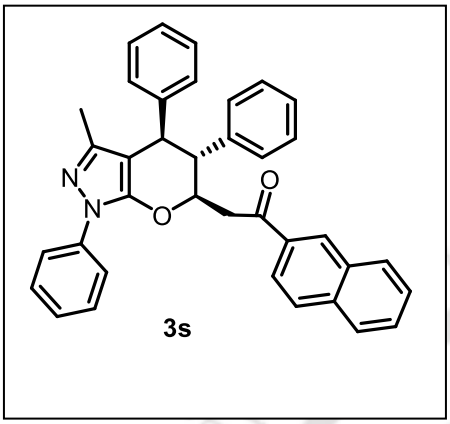
3q. 1-(3-fluorophenyl)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-ethan-1-one was obtained as a brownish sticky solid in 47% (23.7 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.63 (d, *J* = 8.2 Hz, 3H), 7.56 (dt, *J* = 9.4, 2.1 Hz, 1H), 7.41 (td, *J* = 7.8, 5.1 Hz, 2H), 7.26 (s, 3H), 7.23 (t, *J* = 7.8 Hz, 3H), 7.13 (dt, *J* = 19.4, 7.2 Hz, 7H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.38 (ddd, *J* = 11.4, 9.3, 2.7 Hz, 1H), 4.15 (d, *J* = 5.7 Hz, 1H), 3.58 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.36 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.85 (dd, *J* = 16.0, 2.7 Hz, 1H), 1.91 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 196.72, 196.71, 163.86, 162.21, 150.30, 146.96, 139.99, 139.48, 139.44, 138.85, 138.21, 130.54, 130.49, 130.06, 129.01, 127.92, 127.41, 127.03, 125.30, 124.26, 124.24, 120.64, 120.50, 119.95, 115.27, 115.12, 99.47, 76.02, 50.20, 42.55, 42.32, 12.73. **^{19}F NMR (377 MHz, Chloroform-*d*)** -112.90. **HPLC Analysis:** ee = 97%, Chiralpak ID Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 11.9 min, t_{minor} = 14.1 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}FN_2O_2$ 503. 2129; Found 503.2133.



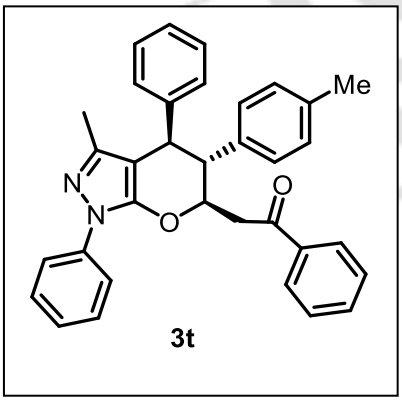
3r

3r. 1-(3-bromophenyl)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-*c*]pyrazol-6-yl)-1-ethan-1-one was obtained as an reddish brown sticky solid in 42% (23.65 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.99 (d, *J* = 1.9 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.68 (dd, *J* = 7.9, 2.0 Hz, 2H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.17 – 7.13 (m, 3H), 7.13 – 7.09 (m, 4H), 6.75 (d, *J* = 7.3 Hz, 2H), 5.40 – 5.34 (m, 1H), 4.15 (d, *J* = 5.7 Hz, 1H), 3.58 (dd, *J* = 10.8, 5.7 Hz, 1H), 3.35 (dd, *J* = 16.0, 9.2 Hz, 1H), 2.84 (dd, *J* = 15.9, 2.7 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 196.6, 150.3, 146.9, 140.0, 139.2, 138.8, 138.2, 136.3, 131.5, 130.4, 130.07, 129.0, 127.9, 127.4, 127.0, 126.9, 125.3, 123.2, 123.2, 120.0, 99.4, 76.1, 50.2, 42.6, 42.2, 12.7. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major}

= 8.3 min, t_{minor} = 7.7 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{28}BrN_2O_2$ 563.1329; Found 563.1329.

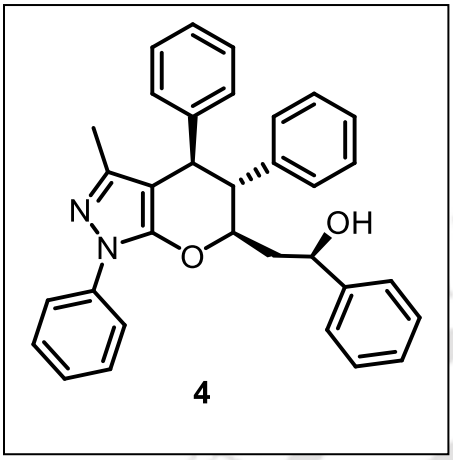


3s. 2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(naphthalen-2-yl)ethan-1-one was obtained as a yellow sticky solid in 36% (19.3 mg) yield after column chromatography. M.P = 185-190 ^{O}C. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 8.37 (d, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 4H), 7.62 – 7.55 (m, 5H), 7.17 – 7.09 (m, 6H), 7.04 – 6.98 (m, 3H), 6.76 (d, *J* = 7.4 Hz, 2H), 5.44 (ddd, *J* = 11.3, 9.2, 2.6 Hz, 1H), 4.17 (d, *J* = 5.8 Hz, 1H), 3.65 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.57 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.96 (dd, *J* = 15.8, 2.6 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.9, 150.4, 146.9, 140.1, 138.8, 138.4, 135.9, 134.8, 132.6, 130.4, 130.0, 129.8, 128.91, 128.8, 128.7, 128.4, 127.9, 127.9, 127.3, 127.1, 127.0, 125.1, 124.0, 119.8, 99.4, 76.4, 50.3, 42.6, 42.1, 12.7. **HPLC Analysis:** ee = 82%, Chiralpak IF Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 14.9 min, t_{minor} = 12.8 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{37}H_{31}N_2O_2$ 535.2380; Found 535.2365.



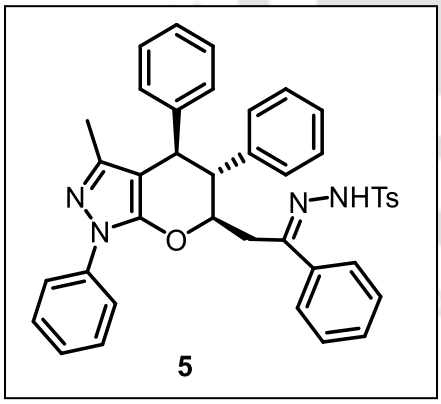
3t. 2-((4R,5R,6R)-3-methyl-1,4-diphenyl-5-(p-tolyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-phenylethan-1-one was obtained as an brownish sticky solid 50% (25.0 mg) yield after column chromatography. M.P = 165 ^{O}C. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.91 – 7.85 (m, 2H), 7.63 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 2H), 7.17 – 7.05 (m, 5H), 6.95 – 6.85 (m, 2H), 6.77 (d, *J* = 7.0 Hz, 2H), 5.36 (ddd, *J* = 11.3, 9.3, 2.4 Hz, 1H), 4.12 (d, *J* = 5.8 Hz, 1H), 3.53 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.39 (dd, *J* = 15.9, 9.3 Hz, 1H), 2.83 (dd, *J* = 15.9, 2.6 Hz, 1H), 2.25 (s, 3H), 1.91 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 197.9, 150.4, 146.9, 133.4, 130.1, 129.0, 128.9, 128.8, 128.4, 127.8, 126.9, 125.1, 119.8, 99.5, 77.2, 76.3, 49.9, 42. 42.2, 31. 21.2, 12.7.**HPLC Analysis:** ee = 95%, Chiralpak IC Column, n-Hexane/i-PrOH

= 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 8.2 min, t_{minor} = 7.1 min **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_2$ 499.2380; Found 499.2390.



4

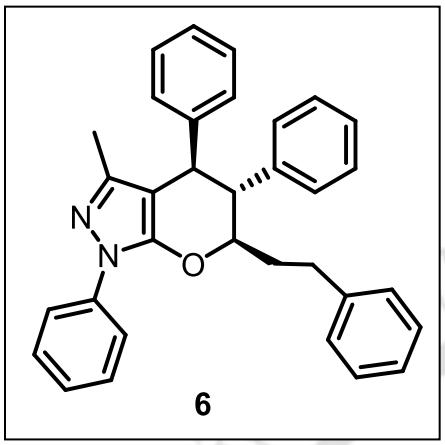
4. (S)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-phenylethan-1-ol was obtained as white solid in 80% (39.0 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.92 – 7.88 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.24 – 7.20 (m, 3H), 7.16 – 7.12 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 4H), 6.71 (d, *J* = 7.4 Hz, 2H), 5.17 (d, *J* = 9.9 Hz, 1H), 5.11 – 5.06 (m, 1H), 4.11 (d, *J* = 5.7 Hz, 1H), 3.44 (dd, *J* = 10.6, 5.6 Hz, 1H), 1.93 (s, 3H), 1.91 – 1.87 (m, 1H).**^{13}C NMR (126 MHz, Chloroform-*d*)** δ 150.6, 147.1, 144.6, 140.3, 138.6, 130.0, 129.2, 128.7, 128.1, 127.7, 127.0, 126.85, 125.59, 125.5, 120.2, 99.6, 76.0, 70.5, 50.4, 50.4, 43.01, 42.7, 42.4, 12.7.**HPLC Analysis:** ee = 95%, Chiralpak AD-H Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 8.6 min, t_{minor} = 6.3 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{31}N_2O_2$ 487.2380; Found 487.2383.



5

5. 4-methyl-N'-((Z)-2-((4R,5R,6R)-3-methyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-phenylethylidene)benzenesulfonohydrazide was obtained as a yellow solid in 45% (29.4 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.53 (m, 3H), 7.50 – 7.47 (m, 2H), 7.38 – 7.33 (m, 2H), 7.28 (d, *J* = 7.7 Hz, 3H), 7.21 (td, *J* = 8.1, 2.1 Hz, 6H), 7.17 – 7.11 (m, 3H), 7.08 (q, *J* = 7.4, 6.5 Hz, 3H), 6.68 – 6.59 (m, 2H), 4.88 (td, *J* = 10.2, 2.7 Hz, 1H), 4.09 (d, *J* = 6.1 Hz, 1H), 3.45 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.03 (dd, *J* = 15.2, 9.8 Hz, 1H), 2.67 (dd, *J* = 15.2, 2.8 Hz, 1H), 2.39 (s, 3H), 1.85 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 154.6, 149.7, 146.9, 144.2, 139.9, 138.6, 138.0, 136.4, 135.56, 130.0, 129.7, 129.3, 128.6, 128.3, 128.0, 127.7, 127.1, 126.8, 125.4, 119.75, 99.6,

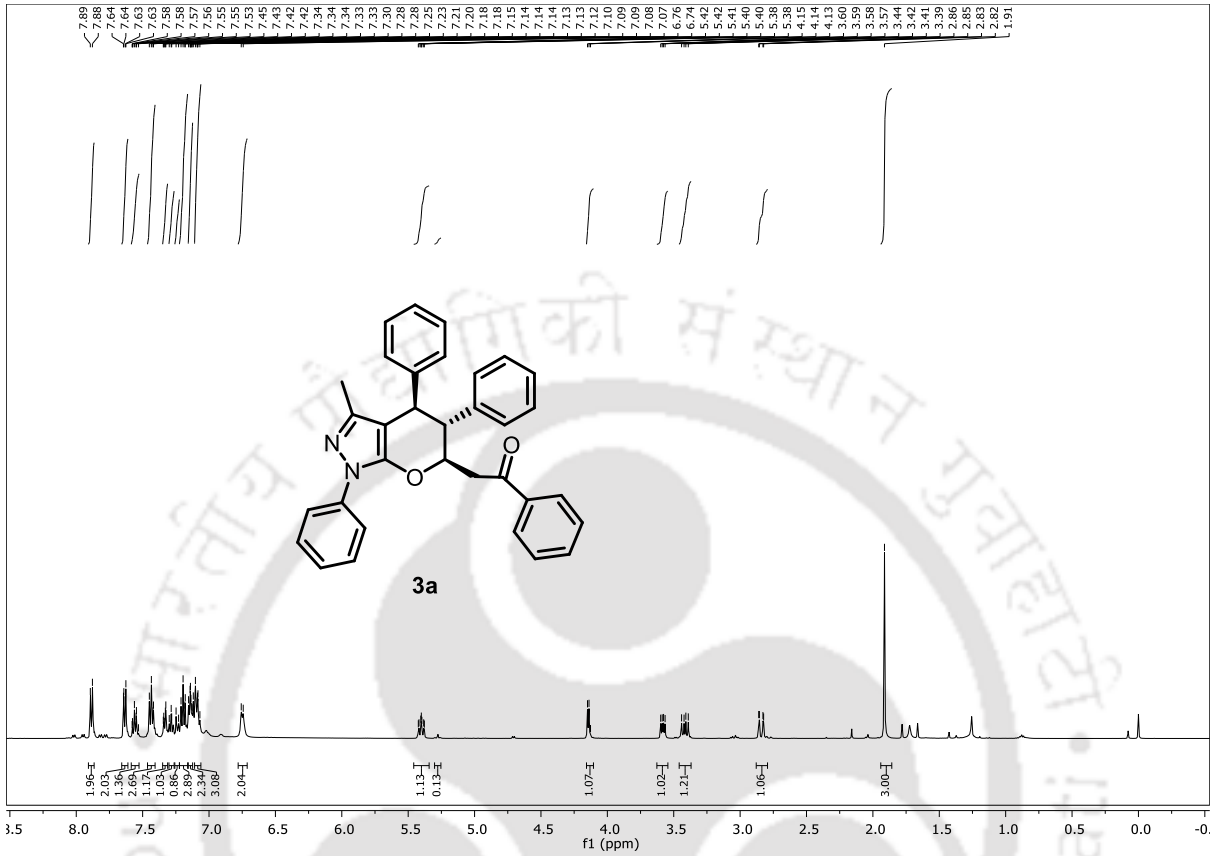
76.6, 50.82, 42.2, 31.8, 21.8, 12.6. **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{40}H_{37}N_4O_3S$ 653.2581; Found 653.2587.

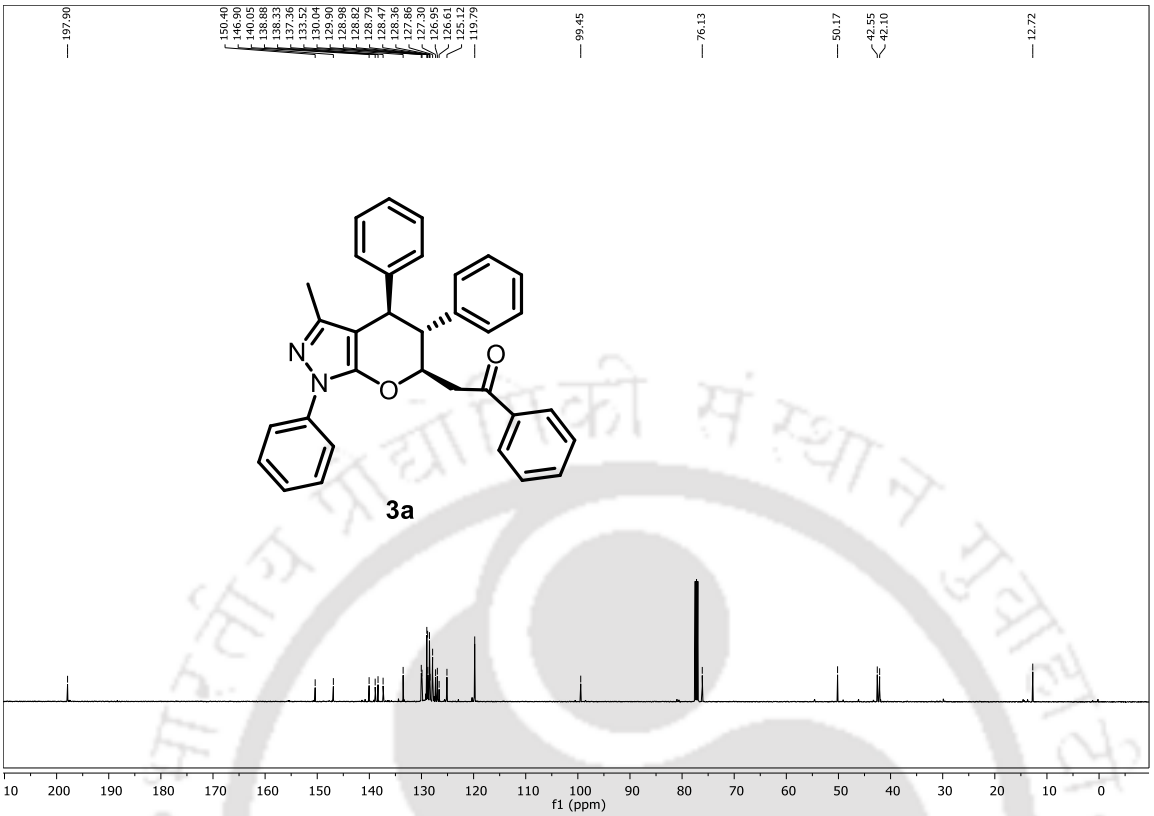


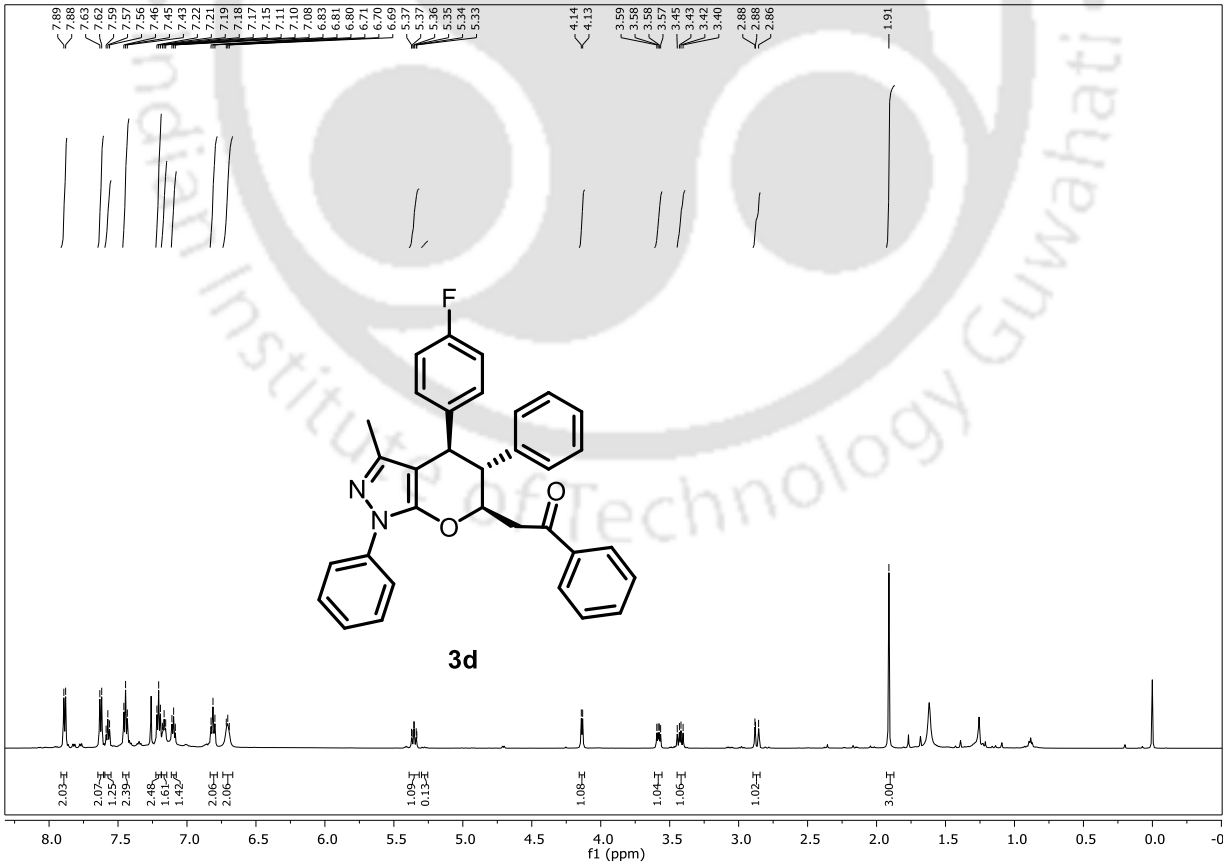
6

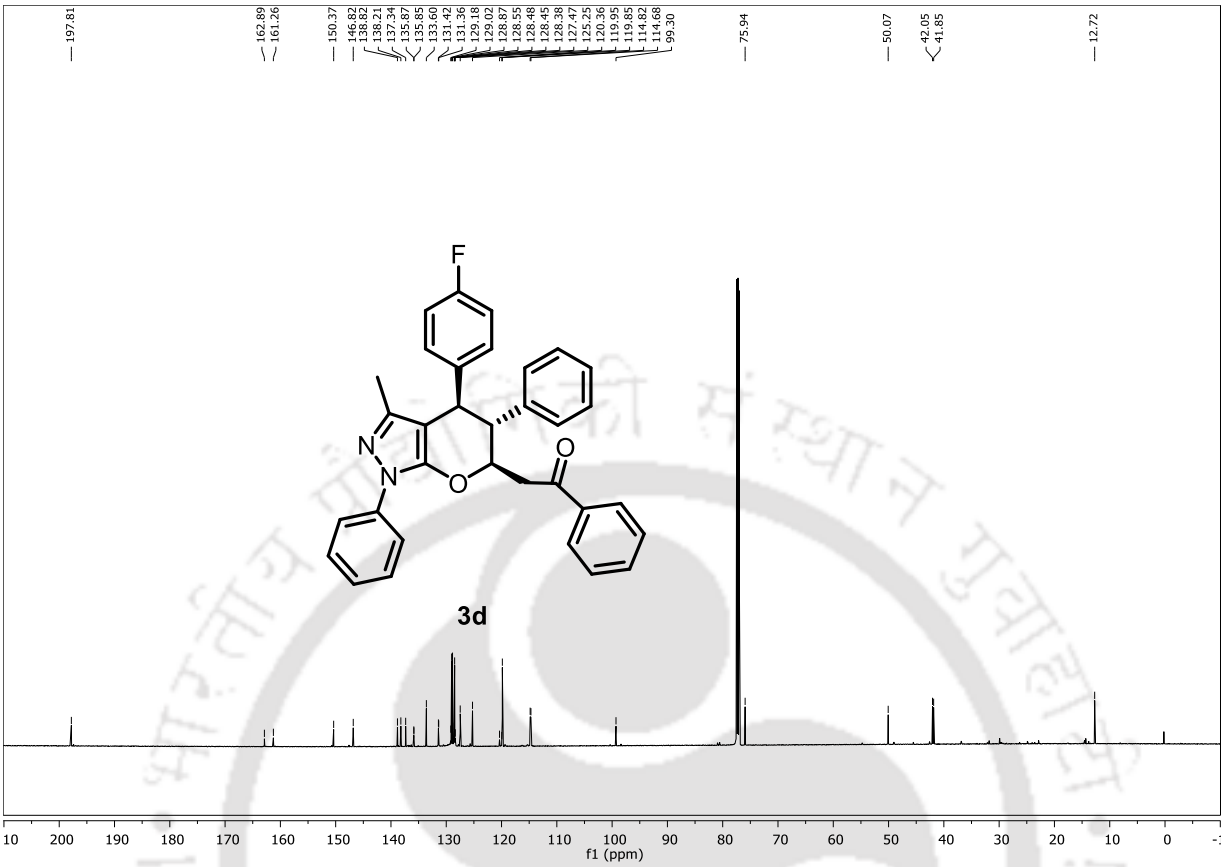
6. (4R,5R,6R)-3-methyl-6-phenethyl-1,4,5-triphenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole was obtained as a white solid d in 40% (13.2 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.95 – 7.89 (m, 2H), 7.47 (t, *J* = 7.9 Hz, 2H), 7.22 (dd, *J* = 16.8, 7.7 Hz, 3H), 7.13 (td, *J* = 7.5, 3.5 Hz, 3H), 7.10 – 7.01 (m, 5H), 6.67 (d, *J* = 7.4 Hz, 2H), 4.69 (td, *J* = 8.2, 4.2 Hz, 1H), 4.08 (d, *J* = 5.7 Hz, 1H), 3.44 (dd, *J* = 10.5, 5.7 Hz, 1H), 2.94 (ddd, *J* = 14.7, 9.9, 5.2 Hz, 1H), 2.76 (ddd, *J* = 13.7, 9.7, 6.9 Hz, 1H), 1.92 (s, 3H), 1.85 (qd, *J* = 9.4, 9.0, 5.9 Hz, 2H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 151.0, 147.0, 141.5, 140.4, 139.2, 138.8, 130.0, 129.2, 128.5, 128.5, 128.3, 128.0, 127.71, 127.0, 126.8, 126.1, 125.37, 120.04, 99.5, 77.9, 50.1, 42.6, 34.9, 12.7. **HPLC Analysis:** ee = 89%, Chiralpak IB Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220nm (t_{major} = 11.7min, t_{minor} = 14.1min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{33}H_{31}N_2O$ 471.2431; Found 471.2427.

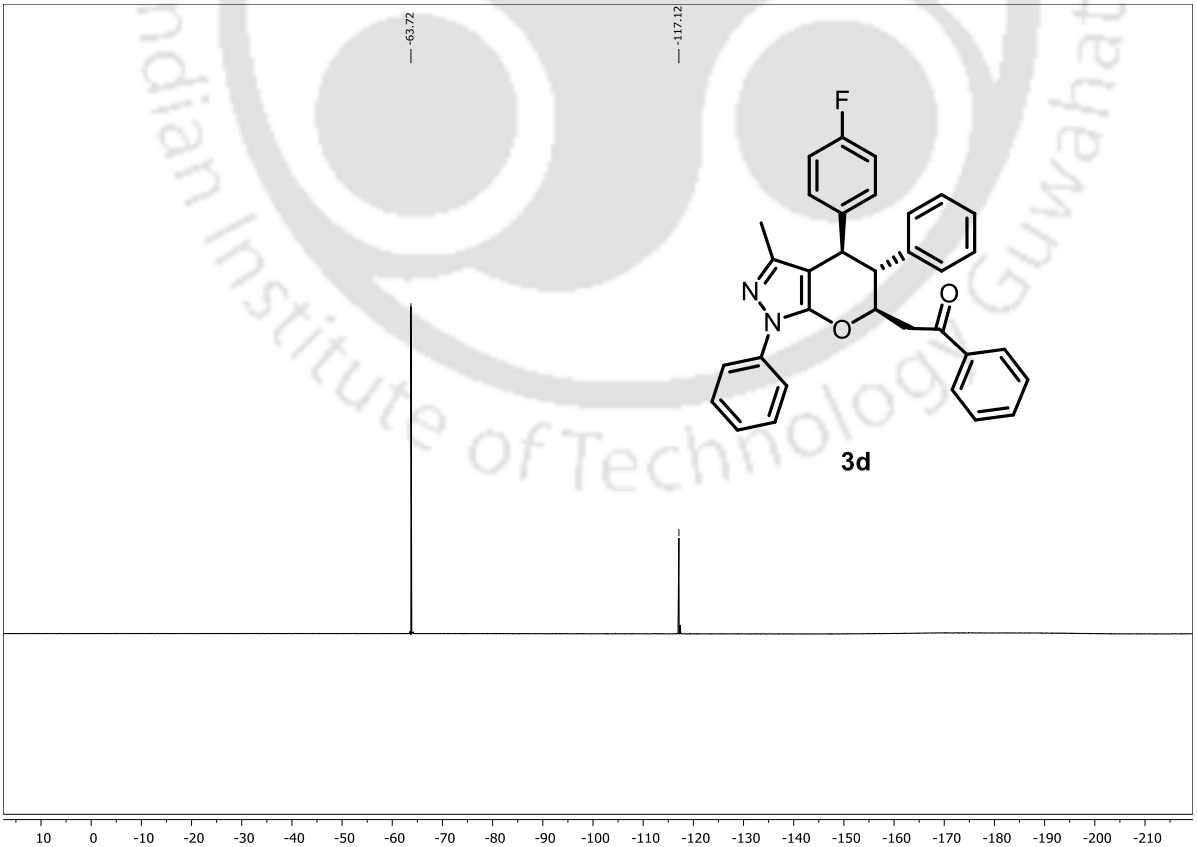
4.6.7. Some selected NMR spectra of the products:

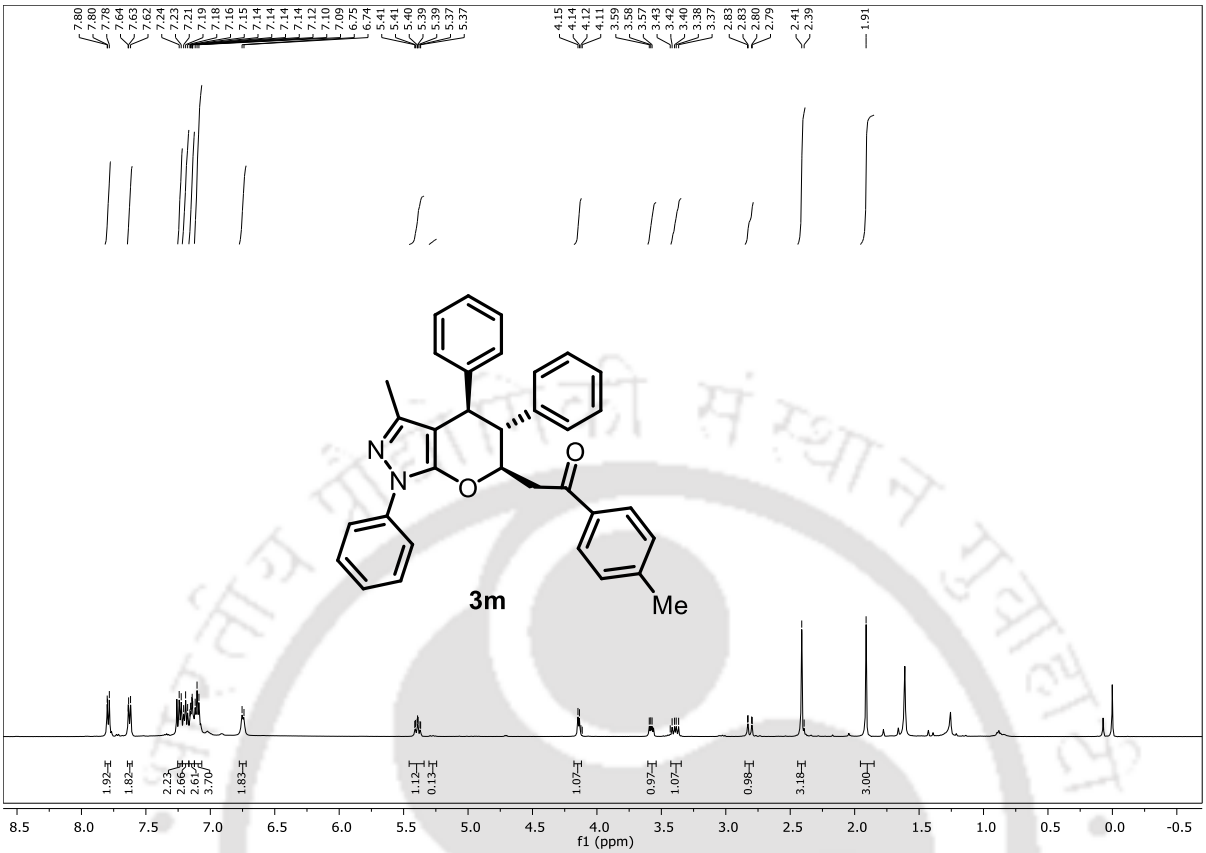


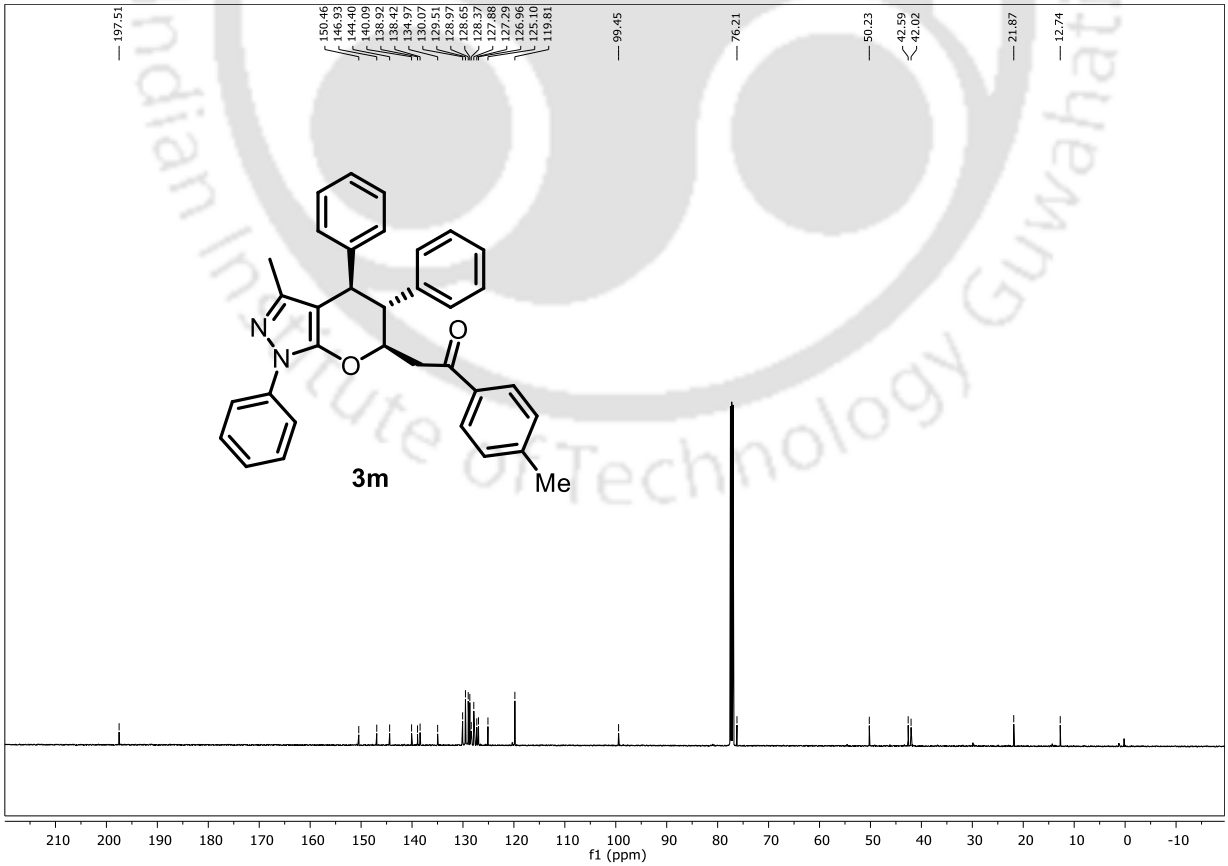


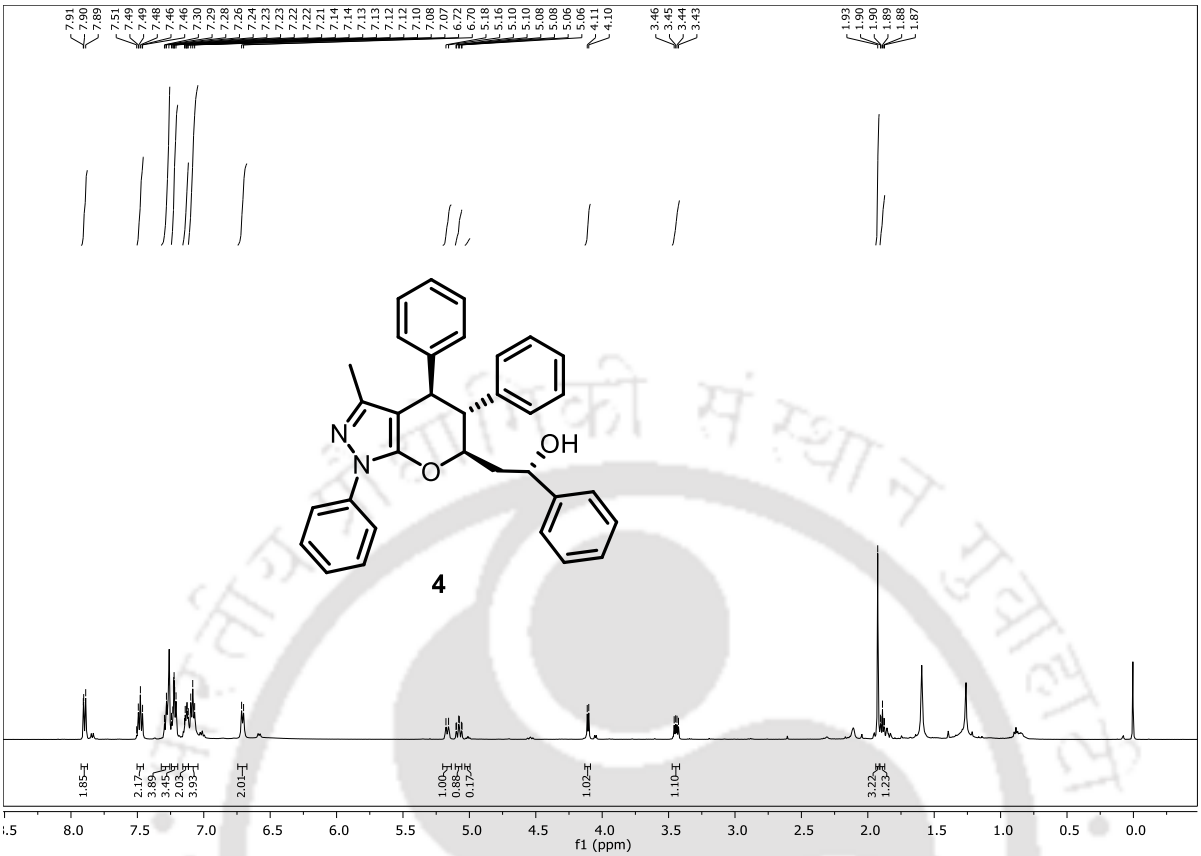


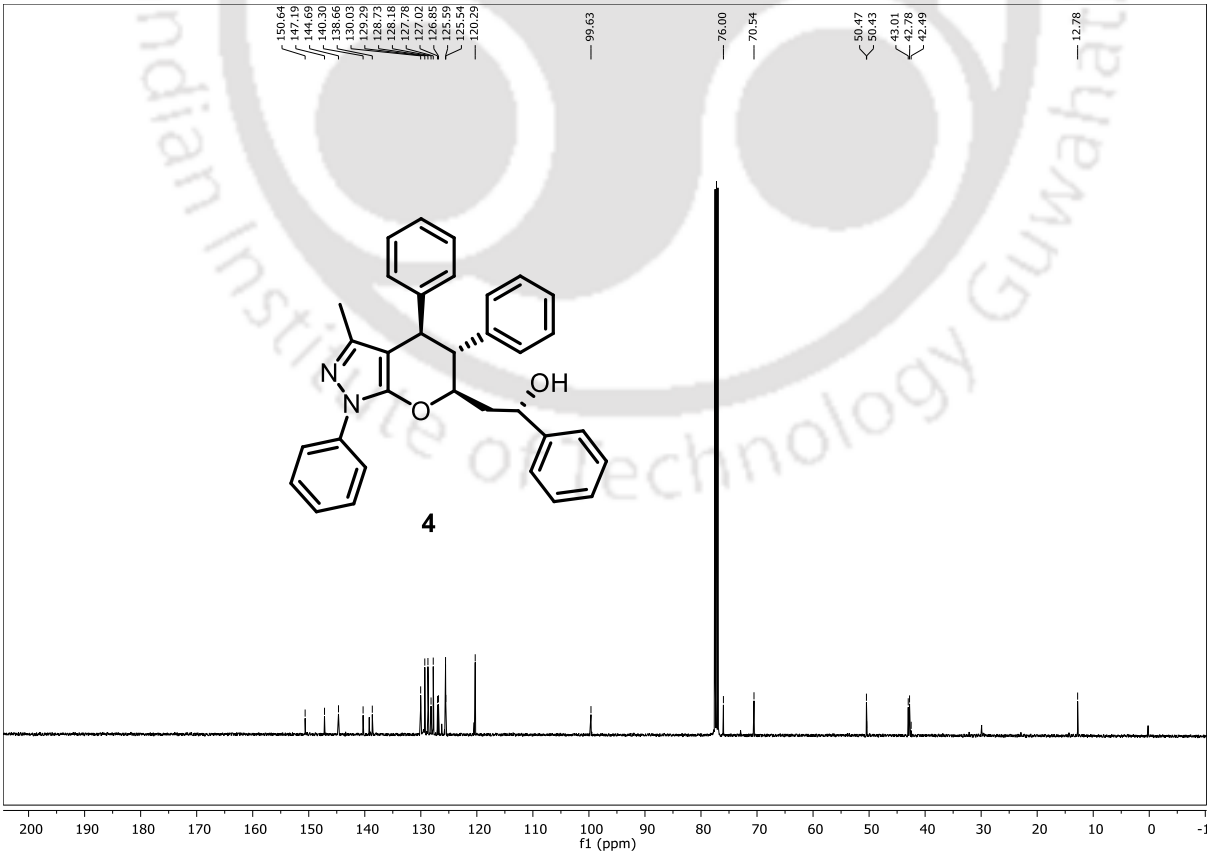












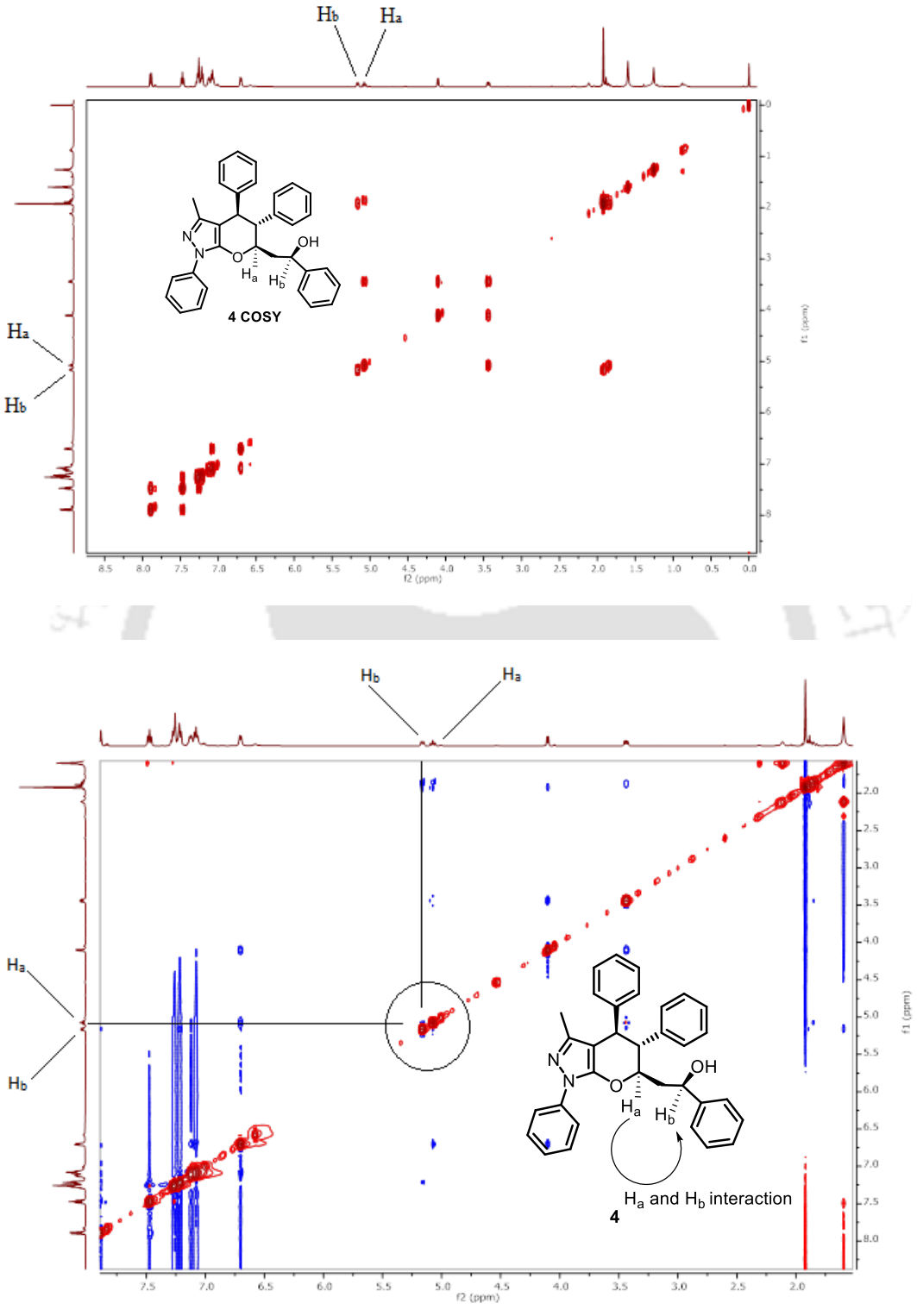


Figure1: NOESY spectra of compound 4 exhibiting the interaction between the protons (marked as Ha and Hb).

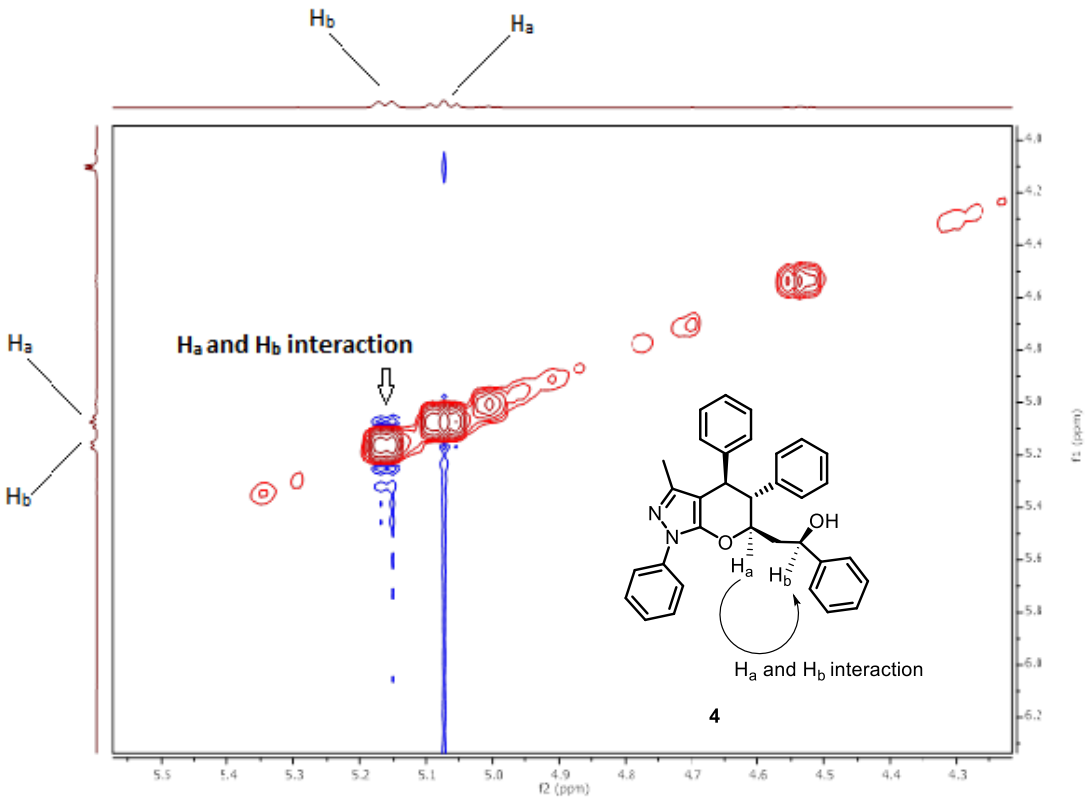
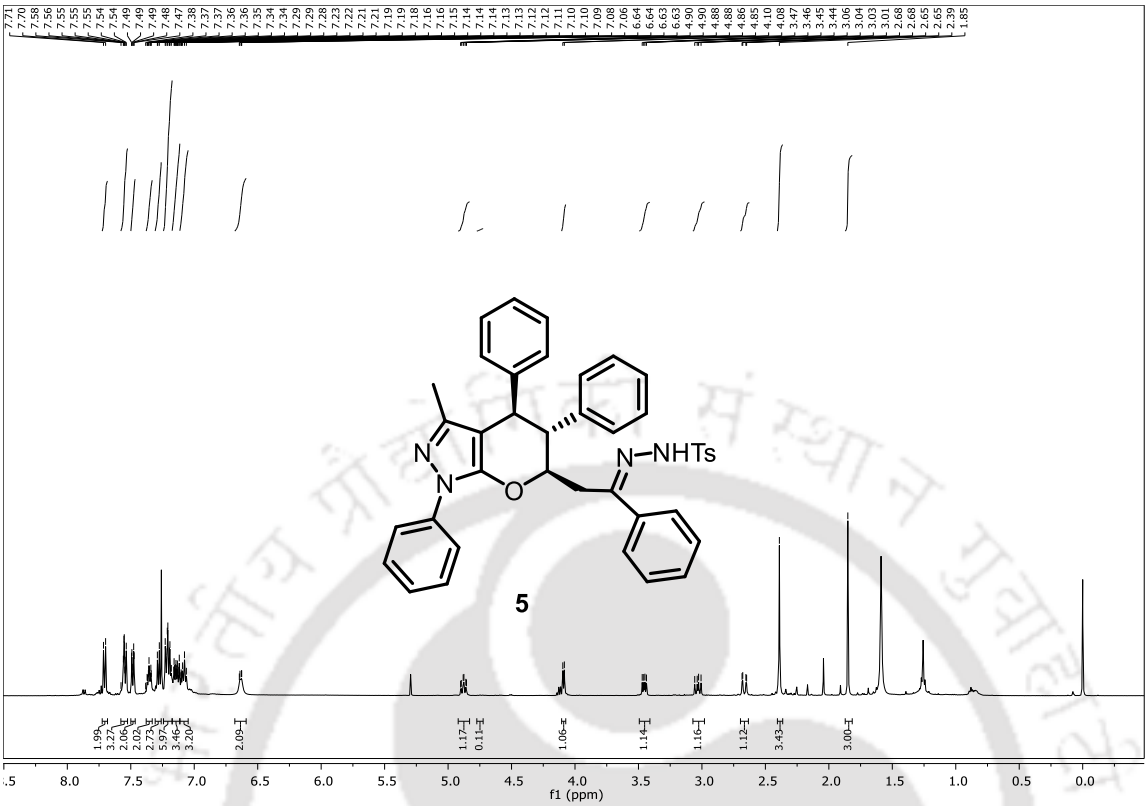
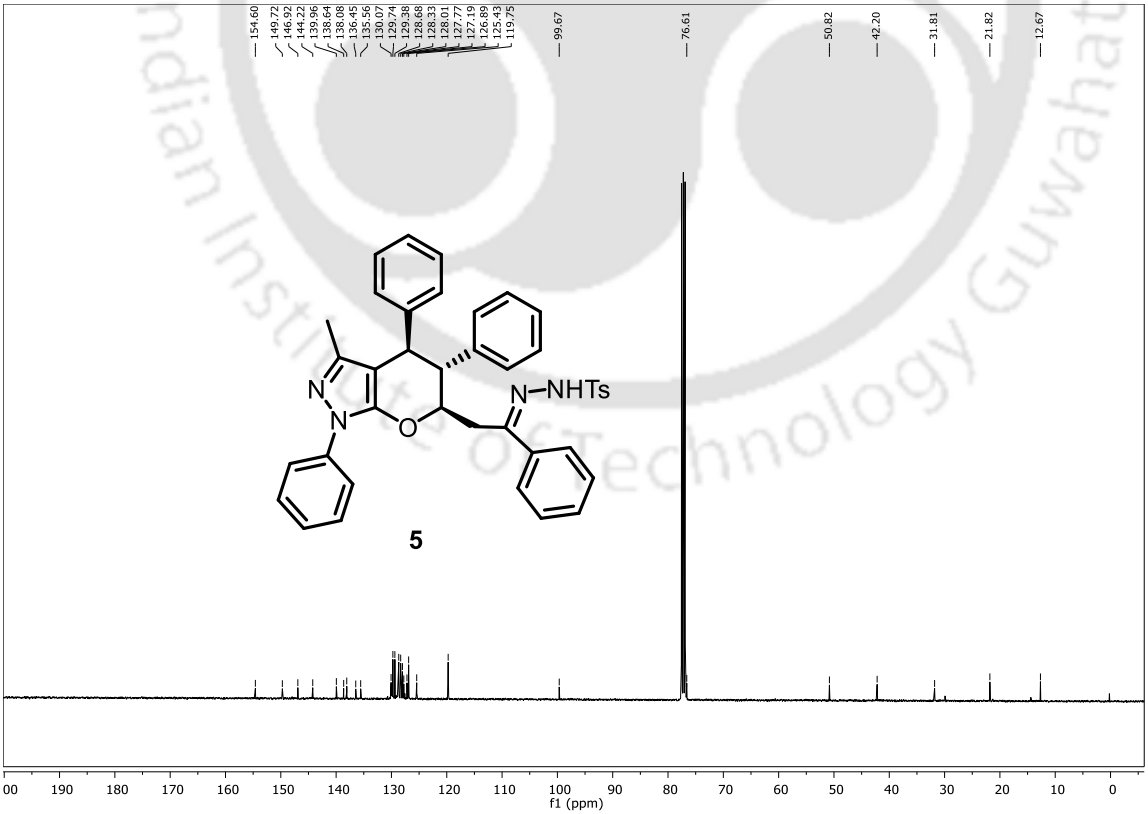
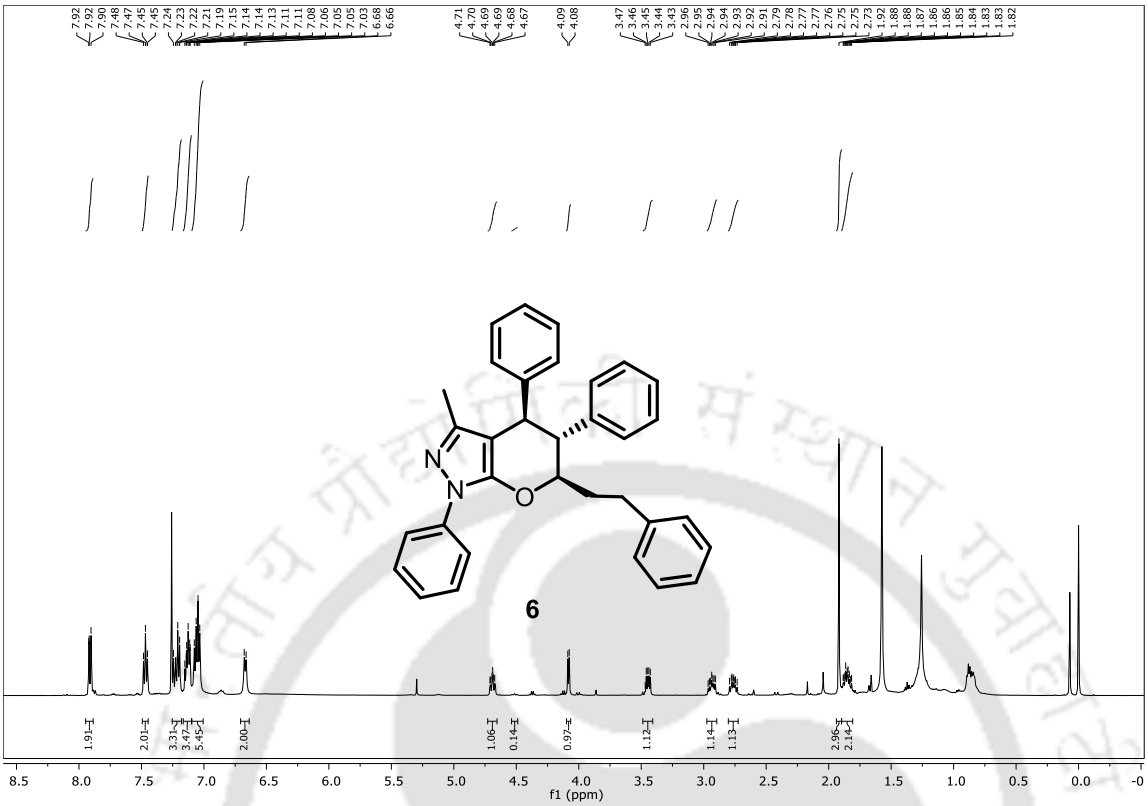


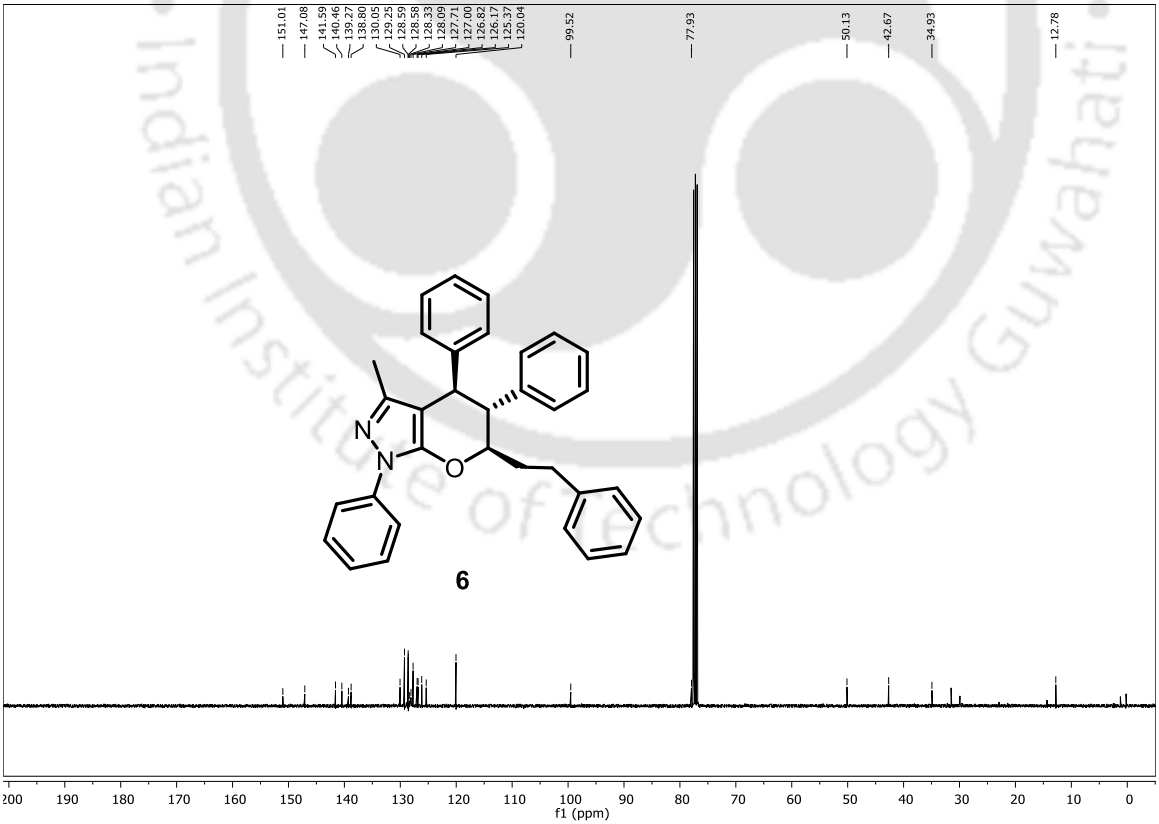
Figure2: zoomed NOESY spectra of compound 4 exhibiting the interaction between the protons (marked as Ha and Hb).

NOESY spectra of compound 4 exhibits the interaction between the protons (marked as Ha and Hb), so we can conclude that both the Ha and Hb are in the same plane.



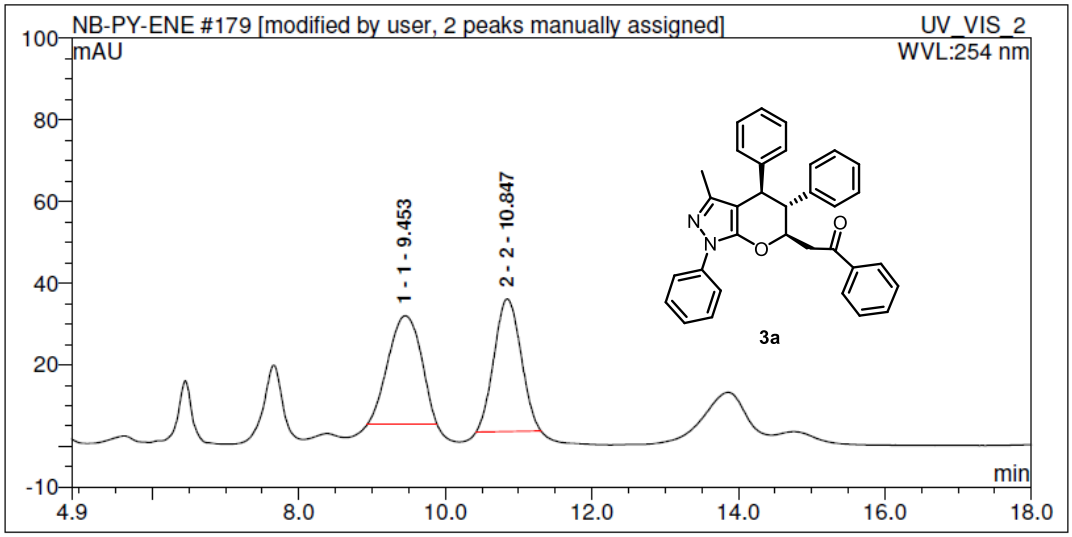






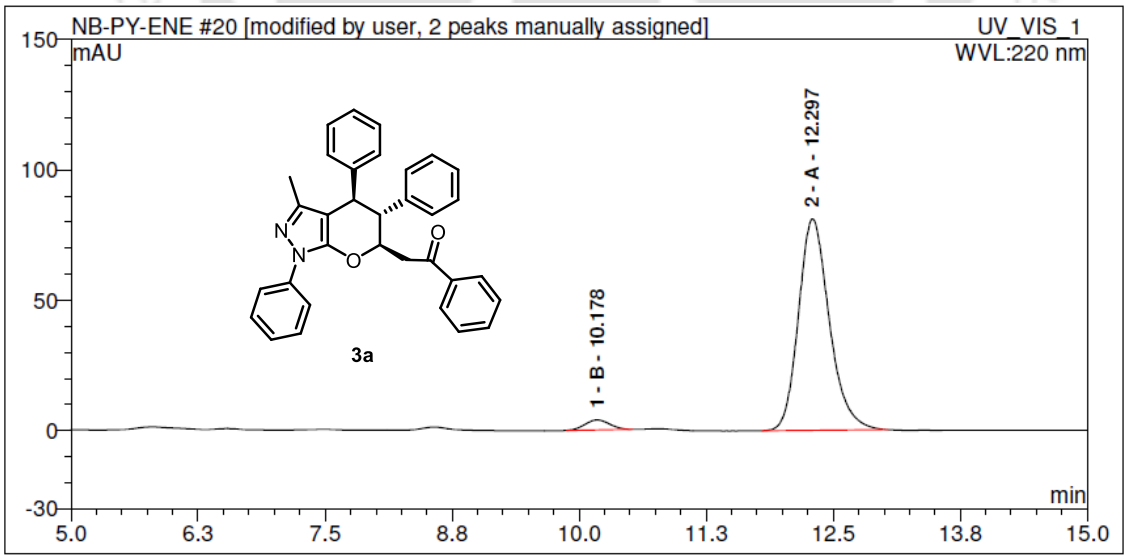
4.6.8. Some selected HPLC chromatogram of the compounds:

The HPLC chromatogram of racemic **3a.**



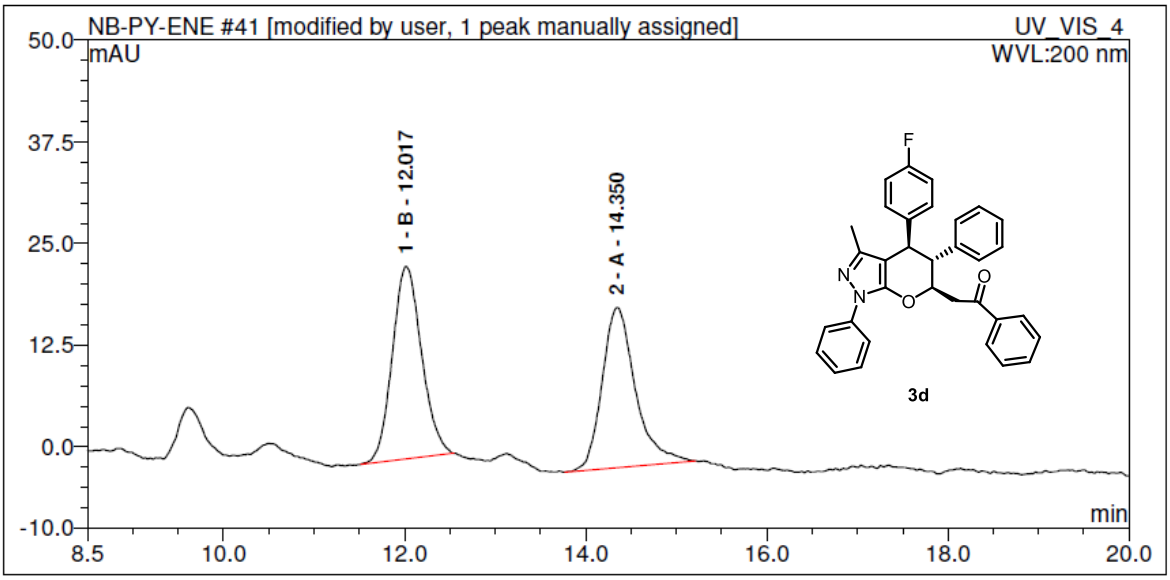
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.45	13.80675	49.99852018	26.59311	n.a.
2	2	10.85	13.808	50.00147982	32.482	n.a.

The HPLC chromatogram of chiral **3a.**



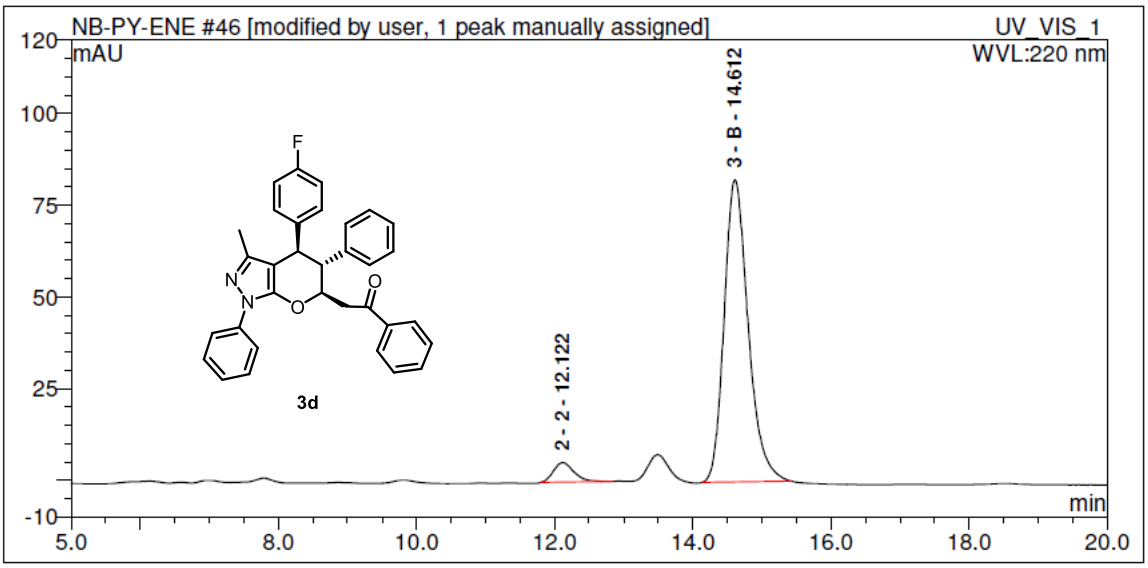
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	B	10.18	1.084438	3.65370541	3.82987	n.a.
2	A	12.30	28.596	96.34629459	81.057	n.a.

The HPLC chromatogram of racemic **3d.**



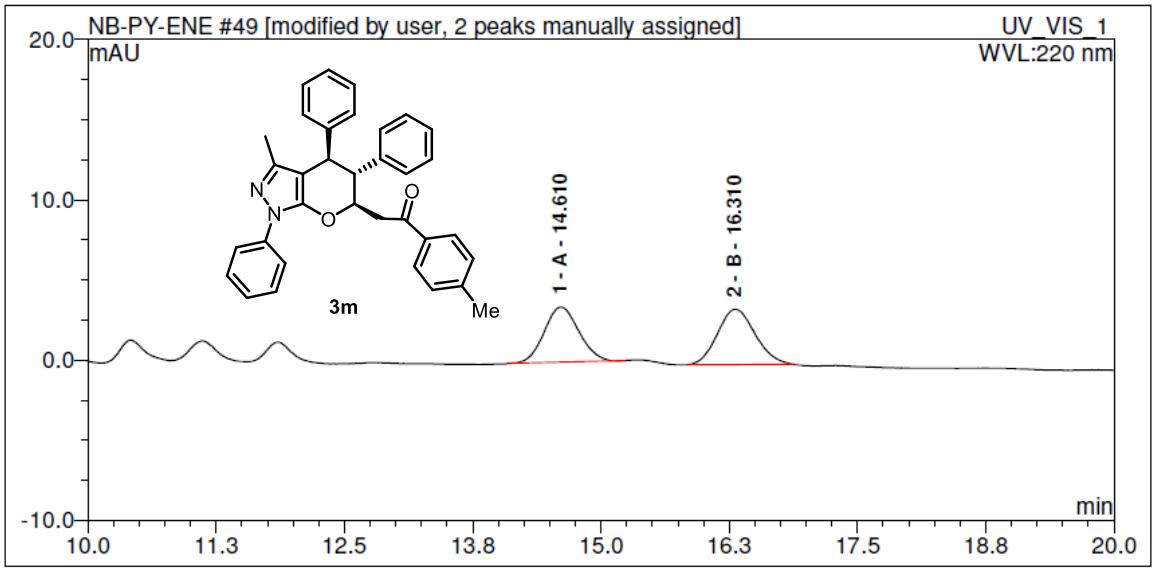
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	B	12.02	8.86016	51.46768705	23.67409	n.a.
2	A	14.35	8.355	48.53231295	19.668	n.a.

The HPLC chromatogram of chiral **3d.**



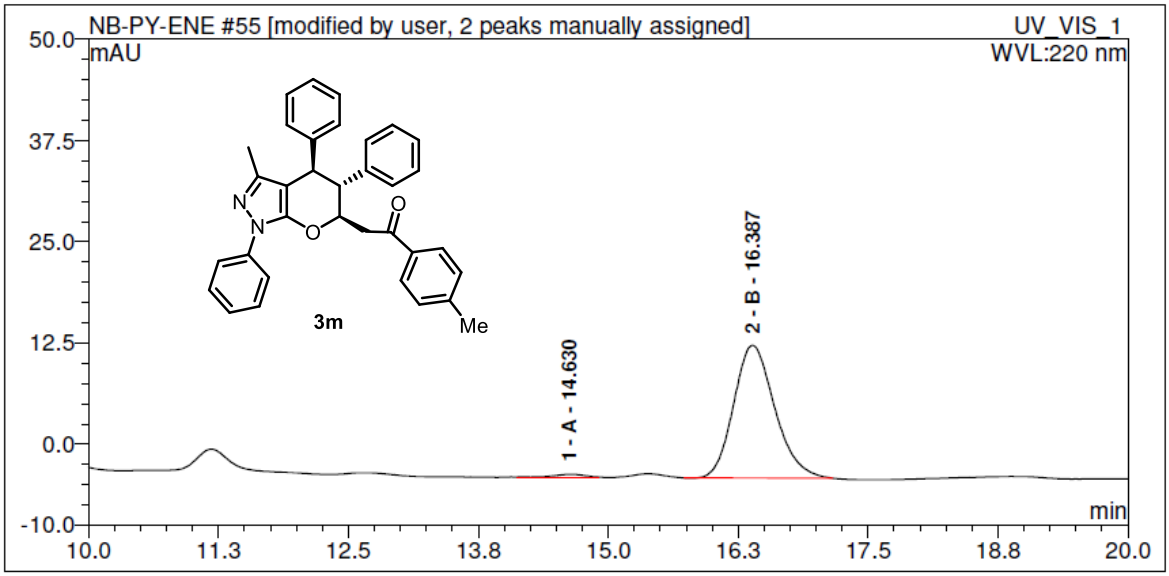
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
2	2	12.12	1.817628	5.19192433	5.28184	n.a.
3	B	14.61	33.191	94.80807567	82.292	n.a.

The HPLC chromatogram of racemic **3m.**



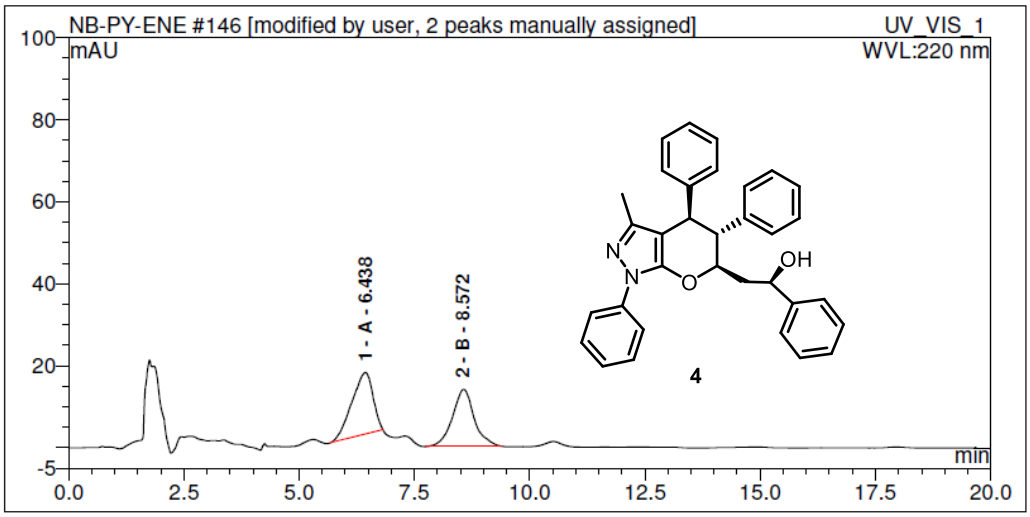
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	14.61	1.335401	47.64684372	3.421	n.a.
2	B	16.31	1.467	52.35315628	3.451	n.a.

The HPLC chromatogram of chiral **3m.**



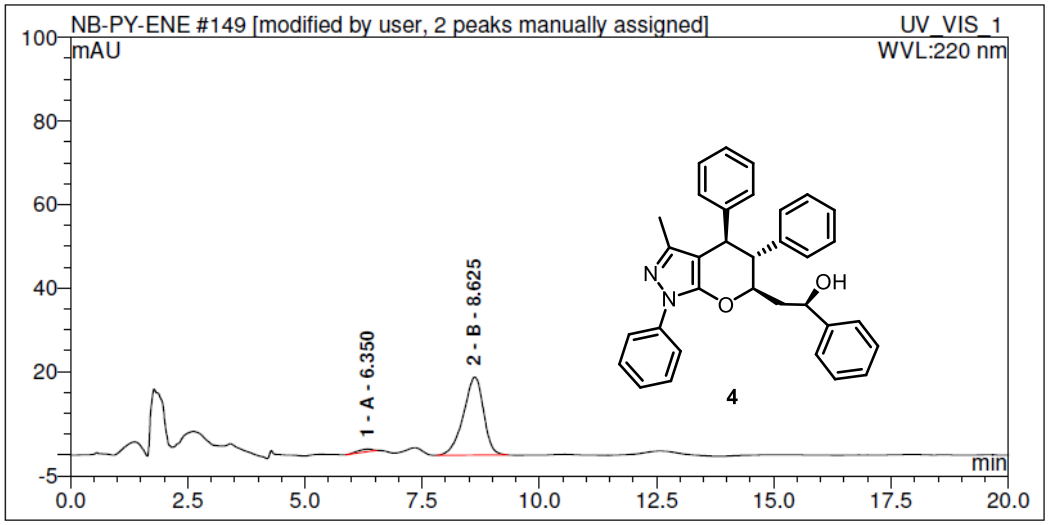
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	14.63	0.112874	1.47816655	0.34539	n.a.
2	B	16.39	7.523	98.52183345	16.398	n.a.

The HPLC chromatogram of racemic **4.**



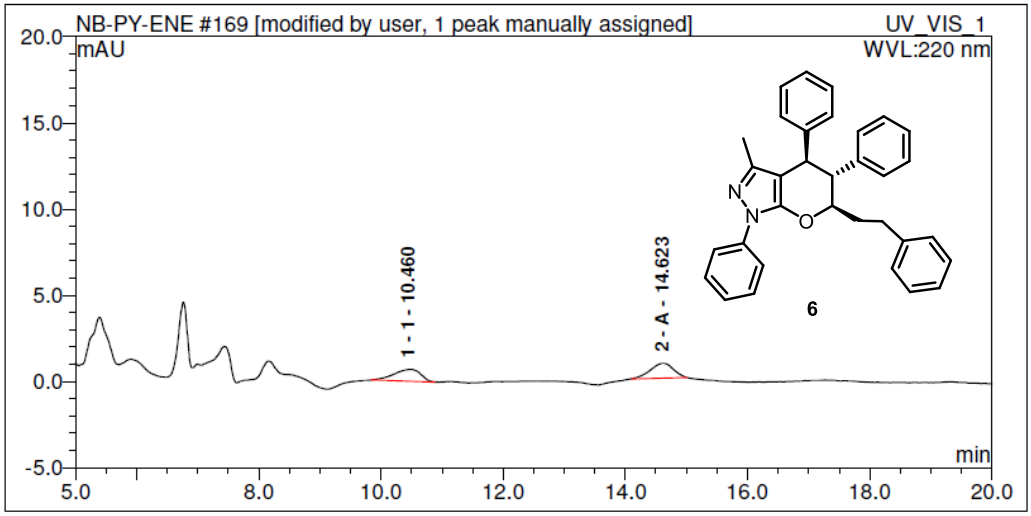
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.44	7.99675	51.26616696	15.01731	n.a.
2	B	8.57	7.602	48.73383304	13.891	n.a.

The HPLC chromatogram of chiral **4.**



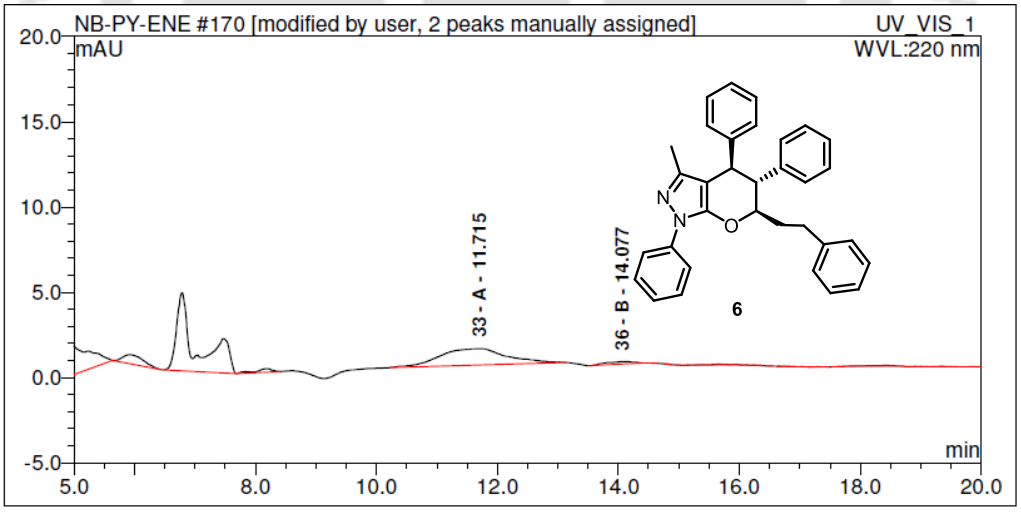
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.35	0.218097	2.28824585	0.56711	n.a.
2	B	8.63	9.313	97.71175415	18.694	n.a.

The HPLC chromatogram of racemic **6.**



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	10.46	0.345542	47.71317992	0.68424	n.a.
2	A	14.62	0.379	52.28682008	0.866	n.a.

The HPLC chromatogram of chiral **6.**



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	Peak 1	0.10	0.001493	0.1141384506	0.02094	n.a.
33	A	11.72	1.2355	94.47445743	0.96279	n.a.
36	B	14.08	0.071	5.411404121	0.141	n.a.

4.7. References:

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2. For selected reviews, see: (a) Jiang, H.; Albrecht, Ł.; Jorgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287. (b) Jurberg, I. D.; Chatterjee, I.; Tannerta, R.; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869. (c) Marcos, V.; Aleman, J. *Chem. Soc. Rev.* **2016**, *45*, 6812. (d) Curti, C.; Battistini, L.; Sartori, A.; Zanardi, F. *Chem. Rev*. **2020**, *120*, 2448. (e) Oiarbide, M.; Palomo, C. *Chem. Eur. J.* **2021**, *27*, 10226.
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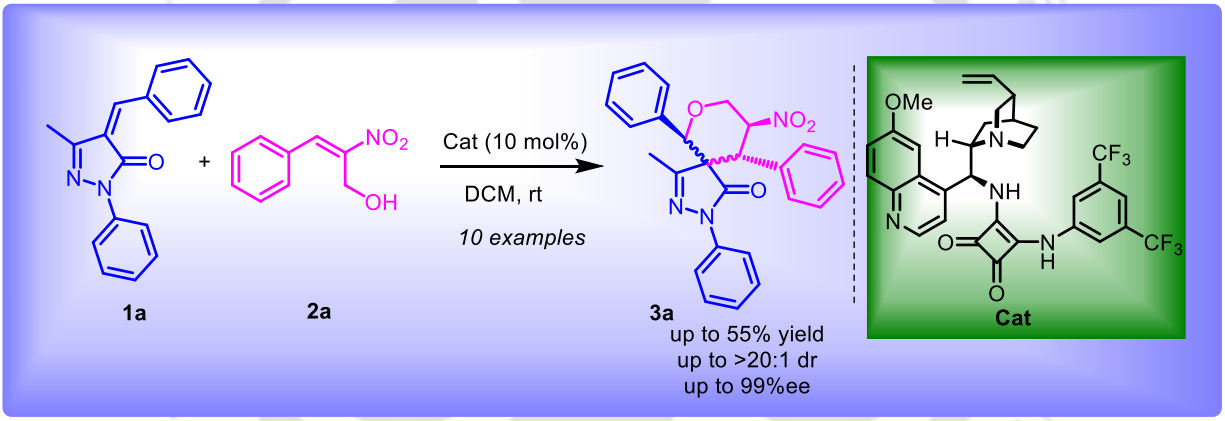
Chapter 5: Organocatalytic asymmetric oxa-Michael-Michael reaction between 3-aryl-2-nitroprop-2-enols and unsaturated pyrazolones: Synthesis of spiro-tetrahydropyran-pyrazolones.



5.1 Introduction:

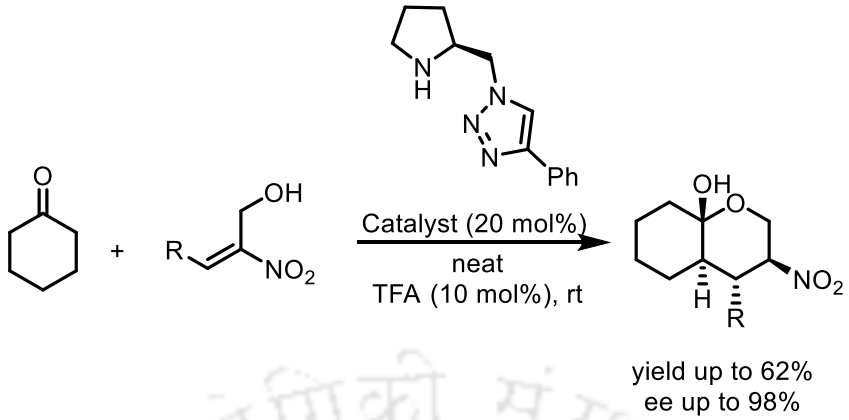
The conjugate addition of oxygen-centered nucleophiles to Michael acceptors, namely the oxa-Michael reaction (OMR), is one of the versatile and powerful organic transformations for the preparation of oxygen–carbon bonds.[1] Also, oxa-Michael addition triggered organocatalytic cascade reactions represent one of the most efficient methods for the synthesis of oxygen-containing heterocycles.[2] Though phenol derivatives have been used successfully in organocatalytic oxa-Micahel cascade reactions,[3] the challenge is to employ alcohols because of the the poor nucleophilicity and reactivity of the hydroxyl group. In recent years, bidentate compounds having alcohol groups such as gamma/delta-hydroxy enones,[4] omega-hydroxy enals,[5] *p*-hydroxyl cycloenones[6] and hydroxypyranones[7] etc were utilized in organocatalytic cascade reactions. Despite these discoveries, the employment of various bidentate alcohol compounds is still required to prepare a diverse range of oxygen heterocycles.

Here in we like to employ 3-aryl-2-nitroprop-2-enols in oxa-Michael-Michael reactions. Previously, 3-aryl-2-nitroprop-2-enols were used as Michael acceptor followed by acetalization/ketalization reaction to obtain enantiopure cyclic compounds.[8]

5.2 Selected examples of previous reports of use of 3-aryl-2-nitroprop-2-enols as Michael acceptor followed by acetalization/ketalization reaction

5.2.1. Domino Michael ketalization reaction between cyclohexanone and 3-aryl-2-nitroprop-2-enols

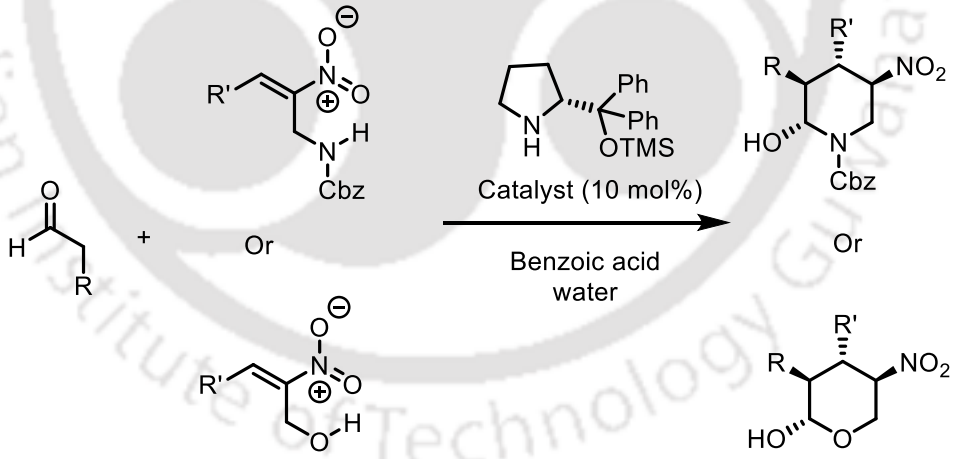
Chandrasekhar et al. in 2009, reported organocatalytic enantiopure cycloalkane fused tetrahydropyrans through domino Michael–ketalizations using cyclohexanone and 3-aryl-2-nitroprop-2-enols (Scheme 1).[8a]



Scheme 1: Domino Michael ketalization reaction between cyclohexanone and 3-aryl-2-nitroprop-2-enols by Chandrashekhar et al.

5.2.1. Domino Michael ketalization reaction between cyclohexanone and 3-aryl-2-nitroprop-2-enols

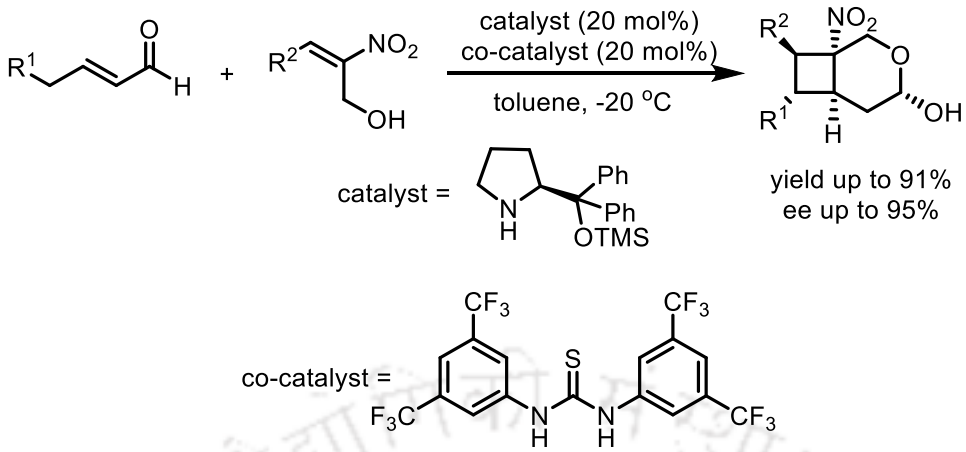
In 2011, Ma and co-workers reported synthesis of tetrahydropyrans or piperidines via domino Michael- aminalization or acetalization reaction of n-pentanal and Cbz-protected 1-aminomethyl Nitroolefins or 3-aryl-2-nitroprop-2-enols catalysed by O-TMS protected diphenylprolinol (Scheme 2).[8b]



Scheme 2: domino Michael- aminalization or acetalization reaction by Ma et al.

5.2.2. Enantioselective Formal [2+2] Cycloaddition of Enals with Nitroalkenes

In 2012, Vicario et al. reported formation of cyclobutane fused bicyclic hemiacetal compounds from the dienamine mediated reaction of enals and 3-aryl-2-nitroprop-2-enols. (Scheme 3).[8c]



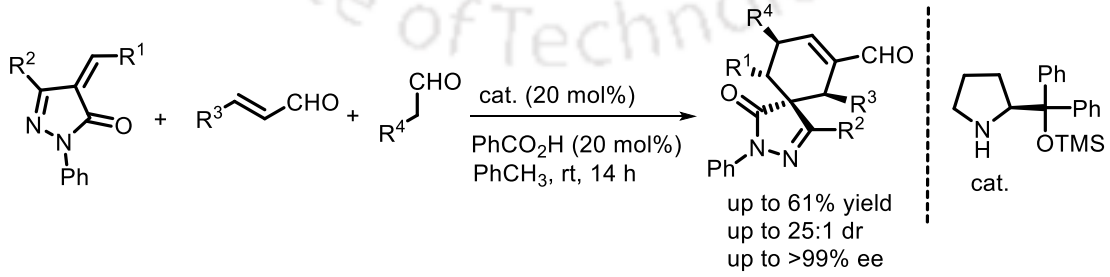
Scheme 3: Cooperative Dienamine/Hydrogen-Bonding Catalysis by Vicario et al

The groups of Hong, Jørgensen, Enders and Zhao reported Michael-hemiketalization reaction with different nucleophiles. However, there is no report on the utlization of 3-aryl-2-nitroprop-2-enol as O-nucleophile in organocatalytic asymmetric Michael reactions.[9] Spiropyrazolones having stereogenic cycloalkane/heterocycle and pyrazolone motifs have engrossed attention because of their useful bioactivities in medicinal chemistry.[10] Accordingly, several organocatalytic methods to access structurally diverse spiropyrazolone derivatives have been developed.[11]

5.3 Previously reported strategies for organocatalytic asymmetric synthesis of spiropyrazolones from unsaturated pyrazolones

5.3.1 Synthesis of spiropyrazolones *via* a three component reaction

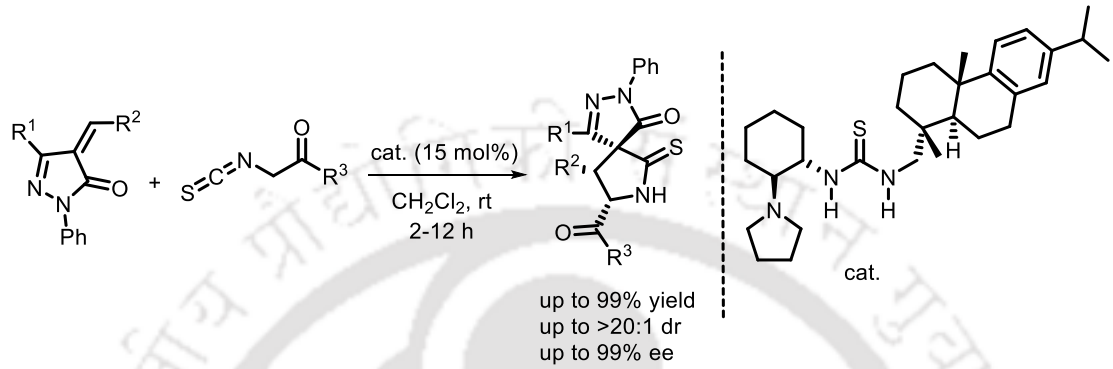
Organocatalytic asymmetric synthesis of spiropyrazolones from unsaturated pyrazolones *via* a three-component reaction with aldehydes and unsaturated aldehydes using prolinol derived secondary amine catalyst was first reported by Rios and co-workers. (Scheme 4).[12]



Scheme 4. The first organocatalytic asymmetric synthesis of spiropyrazolones by Rios et al.

5.3.2 Rosin-derived tertiary amine-thiourea catalyzed enantioselective [3+2] cycloaddition

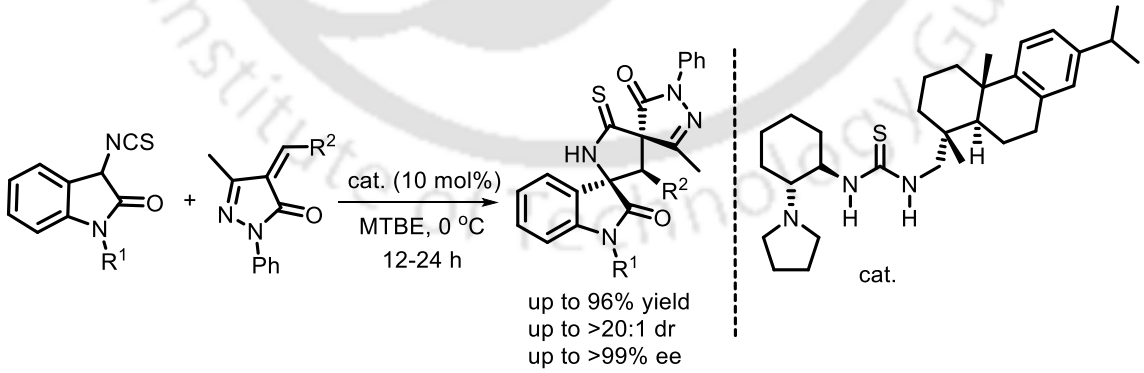
In 2012, Wang et al. developed a highly enantioselective [3+2] cycloaddition of α-isothiocyanato imides with unsaturated pyrazolones by using rosin-derived tertiary amine-thiourea to form functionalized spiropyrazolones bearing three contiguous stereogenic centers. (Scheme 5).[13]



Scheme 5. Enantioselective [3+2] cycloaddition of α-isothiocyanato imides with unsaturated pyrazolones by Wang et al.

5.3.3 Asymmetric Michael-cyclization sequence of 3-isothiocyanato oxindoles and unsaturated pyrazolones

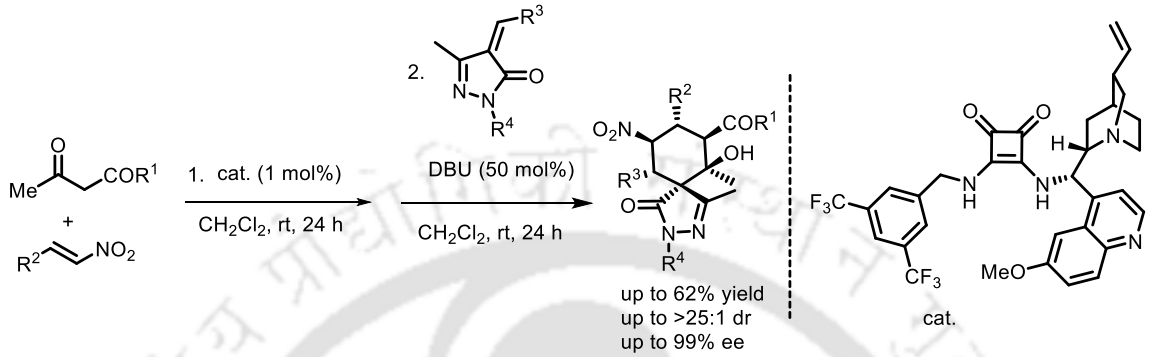
In 2013, the Wang group also reported the synthesis of polycyclic spiro[oxindole/thiobutyrolactam/pyrazolone] core structures by an organocatalytic asymmetric Michael-cyclization sequence of 3-isothiocyanato oxindoles and unsaturated pyrazolones catalyzed by rosin-derived bifunctional tertiary amine thiourea . (Scheme 6).[14]



Scheme 6. The first organocatalytic asymmetric Michael-cyclization sequence of 3-isothiocyanato oxindoles and unsaturated pyrazolones by Wang et al.

5.3.4 The synthesis of densely functionalized spirocyclohexanepyrazolone

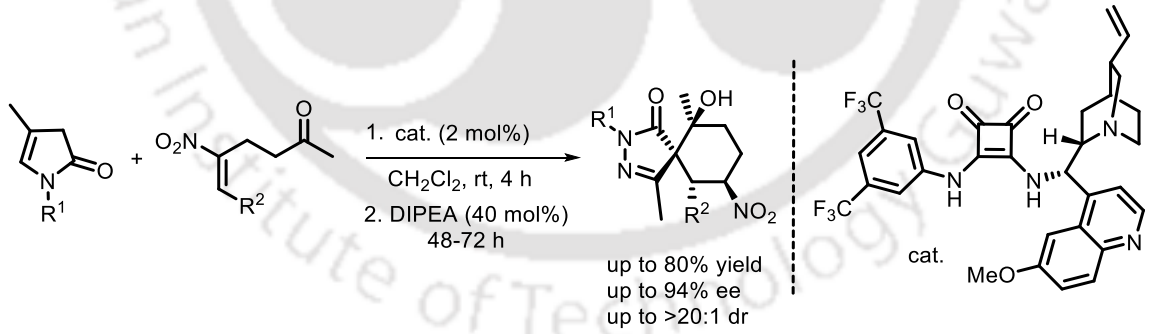
In 2014, Enders et al. reported the synthesis of a variety of spirocyclohexanepyrazolone derivatives bearing six stereocentres *via* sequential organocatalytic reactions. The strategy allowed the synthesis of densely functionalized spirocyclohexanepyrazolones (Scheme 7).[15]



Scheme 7. The synthesis of a variety of spirocyclohexanepyrazolone derivatives bearing six stereocentres *via* sequential organocatalytic reactions by Enders et al.

5.3.5 Synthesis of spirocyclohexane Pyrazolone catalyzed by Chiral cinchona derived squaramide

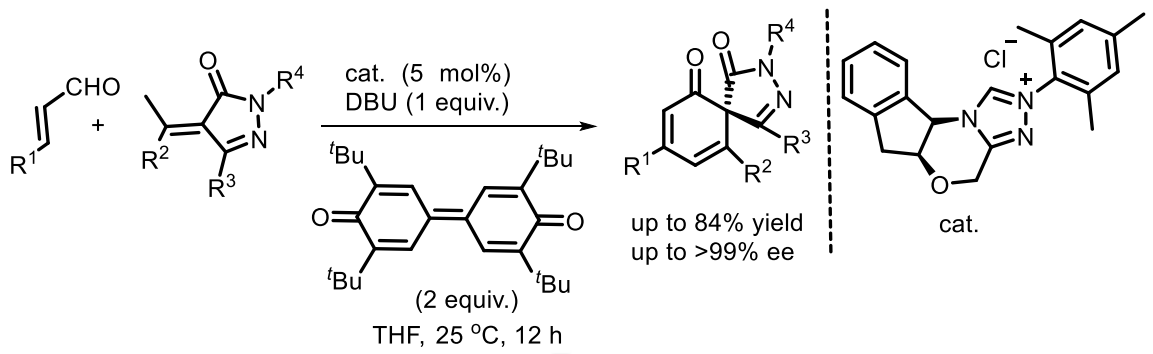
In 2016, Chen et al. synthesized spirocyclohexane pyrazolones containing four contiguous stereogenic centres *via* the reaction of 3-methyl-1-aryl-2-pyrazolin-5-one with (*E*)-5-nitro-6-aryl-hex-5-en-2-one and catalyzed by chiral cinchona derived squaramide catalyst. (Scheme 8).[16]



Scheme 8. Chiral cinchona derived squaramide catalyzed synthesis of spirocyclohexane pyrazolones containing four continuous stereogenic centres by Chen et al.

5.3.6. NHC catalyzed enantioselective synthesis of spirocyclohexadienones

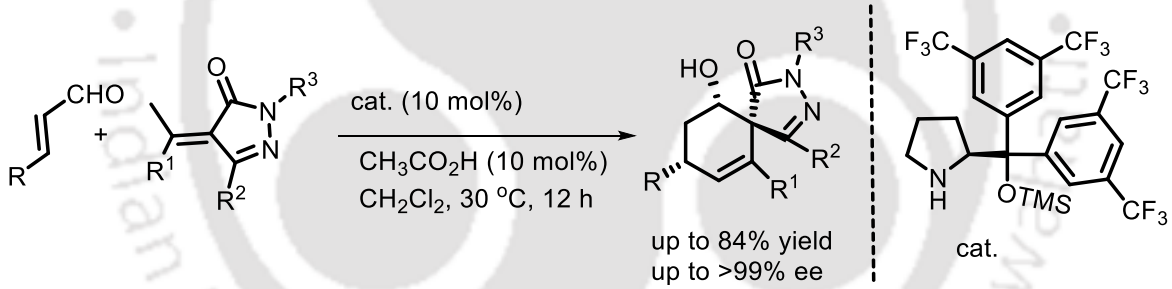
Biju et al. reported NHC catalyzed formal [3+3] annulation reaction of enals with α-arylidene pyrazolinones for the enantioselective synthesis of spirocyclohexadienones. (Scheme 9).[17]



Scheme 6. Formal [3+3] annulation reaction of enals with *α*-arylidene pyrazolinone catalyzed by NHC by Biju et al.

5.3.7. Enantioselective synthesis of pyrazolone-fused spirocyclohexenols by the secondary amine-catalyzed

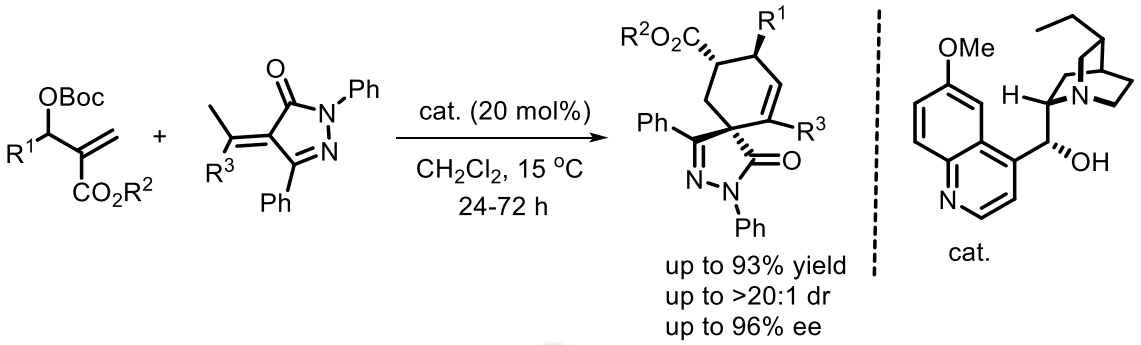
In 2016, Biju et al. also reported the synthesis of pyrazolone-fused spirocyclohexenols via secondary amine-catalyzed cascade reaction of *α,β*-unsaturated aldehydes with *α*-arylidene pyrazolinones (Scheme 10).[18]



Scheme 10. Secondary amine-catalyzed cascade reaction of *α,β*-unsaturated aldehydes with *α*-arylidene pyrazolinones by Biju et al.

5.3.8. Lewis base catalyzed enantioselective synthesis of Spirocyclohexenes

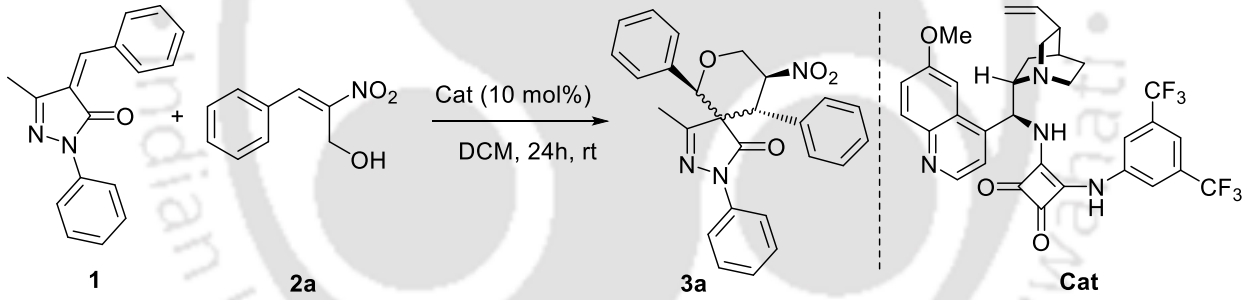
In 2017, Guo et al. reported enantioselective [3+3] annulation reaction of Morita-Baylis-Hillman (MBH) carbonates with *α*-arylidene pyrazolinones for the synthesis of the pyrazolone-fused spirocyclohexenes bearing an all-carbon quaternary stereocenter and catalyzed Lewis-base (Scheme 11).[19]



Scheme 11. Lewis-base-catalyzed enantioselective [3+3] annulation reaction of Morita-Baylis-Hillman (MBH) carbonates by Guo et al.

5.4 Concept

As there is an intrinsic challenge for the preparation of O-heterocycle embedded spiropyrazolones, and attaining high enantioselectivity, we envisaged 3-aryl-2-nitroprop-2-enol to be a reaction partner with unsaturated pyrazolones for the formation of novel spiro-tetrahydropyran-pyrazolones.



Scheme 12: The present work.

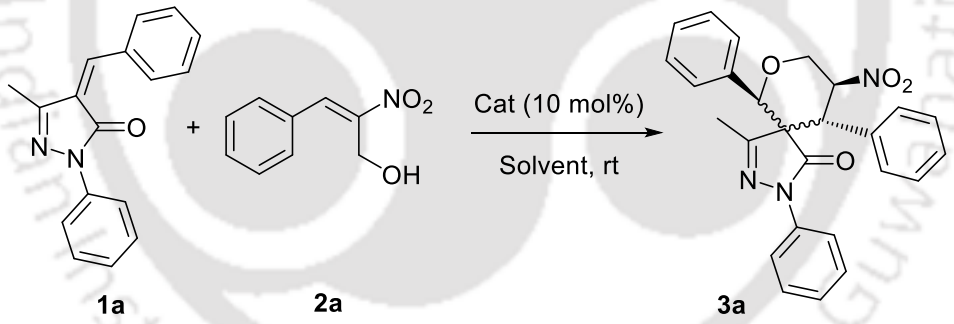
5.5 Results and discussion

5.5.1. Reaction optimization:

We started our investigation by performing a model reaction between alkylidene pyrazolone **1a** and 3-aryl-2-nitroprop-2-enol (**2a**) in the presence of quinine derived bifunctional thiourea catalyst **I** in toluene at room temperature (Table 1). To our delight, after 1 day, the oxa-Michael-Michael reaction progressed well to provide spiro-tetrahydropyran-pyrazolone **3a** in 45% yield with 4:1 diastereomeric ratio and 85% ee of the major diastereomer (entry 1). To improve the diastereo- and enantioselectivity, other bifunctional thiourea catalysts **II-III** were screened. However, the enantioselectivity was not enhanced though slight improvement in

diastereoselectivity was observed with catalyst **II** (entries 2-3). Then we turned our attention to employ bifunctional squaramide catalysts[20] **IV-VI** in the reaction (entries 4-6). To our delight, quinine derived squaramide catalyst **IV** provided the product **3a** as a single distereomer however the enantioselectivity was moderate (entry 4). Higher enantioselectivity amd moderate diastereoselectivity was detected with catalyst **V** (entry 5). Cinchonidine derived squaramide catalyst **VI** was also not effective for the reaction (entry 6). Then we speculated that solvent could have an effect on the enatioselectivity. Gratifyingly, the enantioselectivity got improved in dichloromethane solvent with both catalysts **I** and **V** but the diastereoselectivity remained same (entries 7-8). Finally, the best result was obtained with catalyst **IV** and the product **3a** was isolated as single diastereomer in 55% yield with 98% ee (entry 9). Other solvents were also screened but better result was not achieved.

Table 1: Reaction optimization:



Entry[a]	Catalyst	Solvent	time	Yield[b]	dr[c]	ee[d]
1	**I**	toluene	24 h	45	4:1	85
2	**II**	toluene	24 h	40	7:1	80
3	**III**	toluene	24 h	35	3:1	60
4	**IV**	toluene	24 h	50	20:1	66

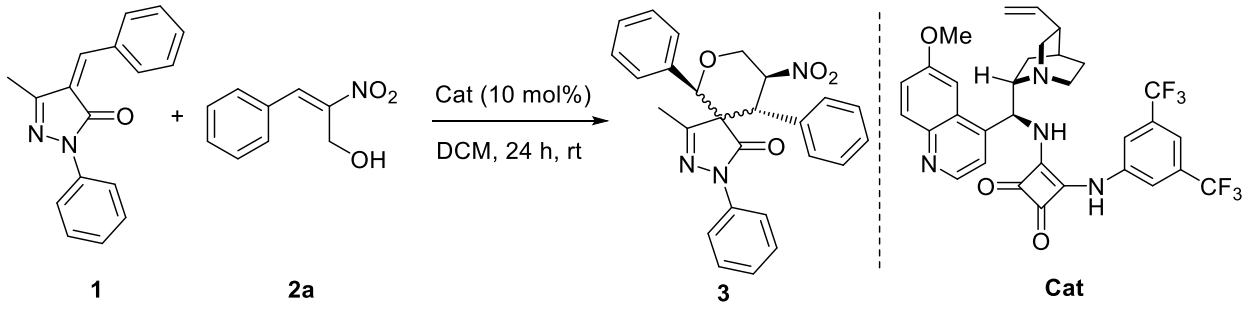
5	**V**	toluene	24 h	40	3:1	85
6	**VI**	toluene	24 h	40	4:1	61
7	**I**	CH_2Cl_2	24 h	50	4:1	98
8	**V**	CH_2Cl_2	24 h	45	3:1	94
9	**IV**	CH_2Cl_2	24 h	55	>20:1	98

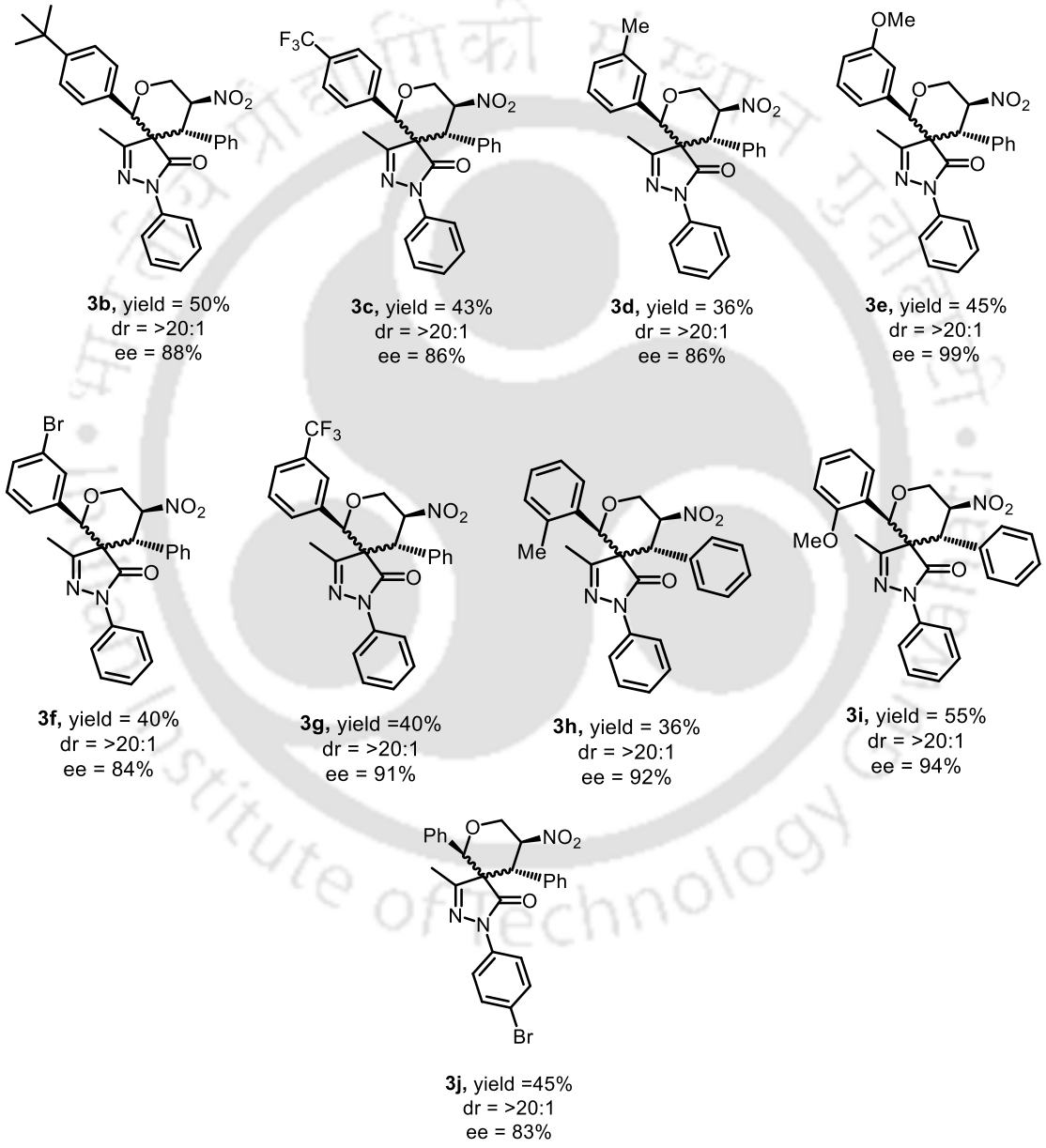
[a] Reaction condition: 0.11 mmol of **1a** and 0.1 mmol of **2a** in 0.4 mL solvent using 10 mol% catalyst. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR. [d] Determined by HPLC and of the major diastereomer.

5.5.2. Substrate scope:

5.5.2.1. Scope of unsaturated pyrazolones:

After the best catalyst and reaction conditions were found, the scope and generality of the reaction was checked. Pleasantly, in all cases a single diastereomer was formed. Initially, the alkylidene group of pyrazolone **1** was varied. Delightfully, a range of electron-withdrawing and electron-donating groups can be incorporated in the *ortho*-, *meta*- and *para*-position of the aryl group and good results were attained. At the beginning, different *para*-substitutions were checked and the products **3b**-**3c** having 4-^{t}Bu and 4-CF_3 groups were isolated in good yields and high enantioselectivities. Then different *meta*-substituted aryl group containing pyrazolones **1d**-**1g** were employed and the outcome was very satisfactory. To our delight, *meta*-OMe group containing pyrazolone **1e** delivered the corresponding product **3e** in 45% yield and 99% ee. A halo-substitution was also tolerated and product **3f** were obtained in 86% ee. Pyrazolone **1g** having 3-CF_3 group also reacted smoothly to deliver product **3g** in 40% yield with 91% ee. Our methodology was also suitable for *ortho*-substituted aryl group containing pyrazolones. Gratifyingly, high enantioselectivities were obtained for products **3h** and **3i** having *ortho*-tolyl and *ortho*-anisyl groups respectively. Then we turned our attention to check N-aryl substitution of the pyrazolone motif. Thus, pyrazolone **1j** having 4-bromophenyl substitution was prepared and employed in the reaction. A smooth conversion was detected and product **3j** was isolated in 45% yield with 83% ee.





Scheme 13: Scope of 1,3-propandiones

5.5.2.2. Scope of 3-aryl-2-nitroprop-2-enols:

Unfortunately, the reaction was not clean when phenyl group in nitrolefin **2a** was replaced by other aryl groups and only complex mixtures were obtained.

5.5.3. Proposed mechanistic pathway:

Based on the relative configuration (which is determined by 2D NMR) a proposed mechanism has been drawn in Figure 1. A bifunctional mode of catalysis operates and pyrazolone **2a** is activated by the squaramide motif of the catalyst. Thus the Michael addition takes place to generate intermediate **A**. A second Michael cyclization of the enone then provides **3a**.

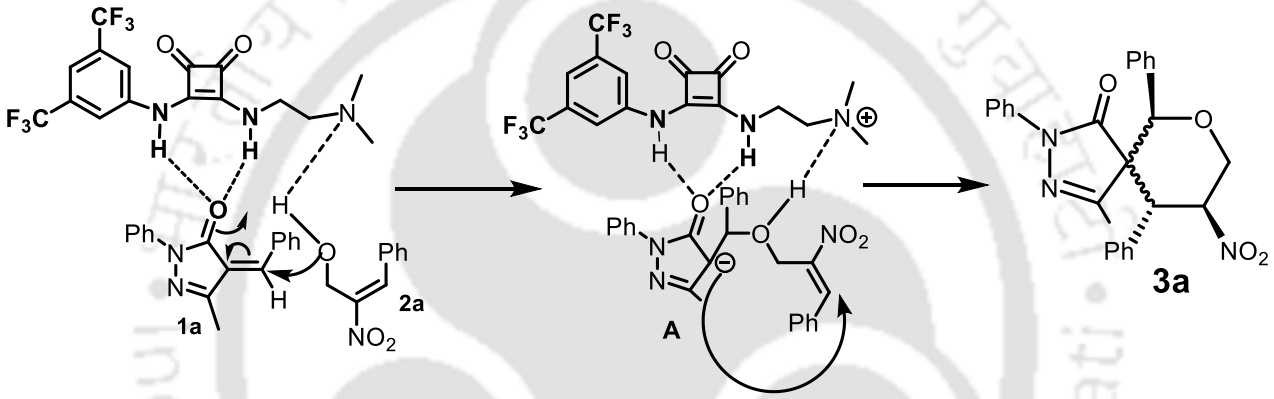


Figure 1: Proposed TS

5.6. Conclusion:

Thus, we summarize that, we have developed an efficient organocatalytic cascade oxa-Michael-Michael reaction for the first catalytic asymmetric synthesis of spiro-tetrahydropyran-pyrazolones. Our method also reports the first utilization of 3-aryl-2-nitroprop-2-enol as O-nucleophile in enantioselective catalysis. The reaction furnished the products in acceptable yields; and perfect diastereomeric ratios as well as good to excellent enantioselectivities were observed. Given the high pharmaceutical importance of spiro-pyrazolones our method might be applicable to prepare these compounds in a short way.

5.7. Experimental section:

5.7.1. General procedure for the synthesis of Unsaturated pyrazolones:

Unsaturated pyrazolones are prepared according to reported procedure.[21]

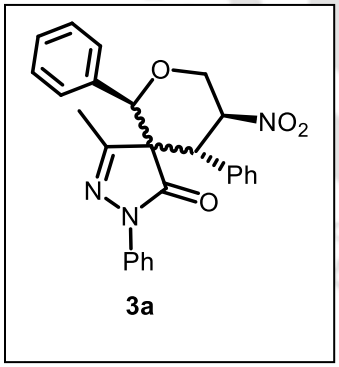
5.7.2. General procedure for the synthesis of 3-aryl-2-nitroprop-2-enols:

3-aryl-2-nitroprop-2-enols are prepared according to reported procedures.[22]

5.7.3. General procedure for the synthesis of compound 3a:

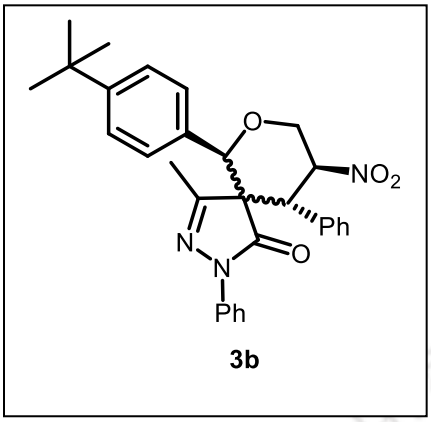
In an oven dried round bottom flask, **1** (17.9 mg, 0.1 mmol), **2** (28.8mg, 0.11 mmol), 10 mol% of Catalsyt **IV** were taken. 0.4 mL of DCM was added to the reaction mixture and stirred at rt for 1 day. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (8 %) to afford desired product **3a.**

5.7.4. Characterisation of the products:



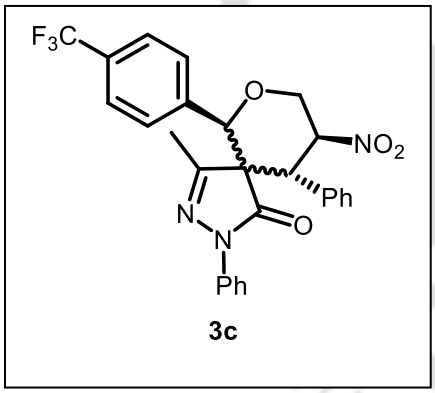
3a

3a 4-methyl-9-nitro-2,6,10-triphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a Yellowish sticky solid in 55% yield (24.3 mg) after column chromatography. **1H NMR (500 MHz, Chloroform-*d*)** δ 7.27 (t, *J* = 4.6 Hz, 4H), 7.26 – 7.22 (m, 5H), 7.19 (t, *J* = 8.0 Hz, 3H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 5.68 (dt, *J* = 12.3, 7.2 Hz, 1H), 4.77 (s, 1H), 4.69 – 4.60 (m, 3H), 2.33 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 171.7, 156.5, 136.9, 135.0, 133.0, 129.3, 129.0, 128.9, 128.7, 128.4, 127.6, 126.2, 125.8, 120.1, 81.7, 78.7, 68.4, 64.1, 45.9, 16.96.**HPLC Analysis:** ee = 98%, Chiralpak IF Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.99 min, t_{minor} = 17.90 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{24}N_3O_4$ 442.1761; Found 442.1750.



3b

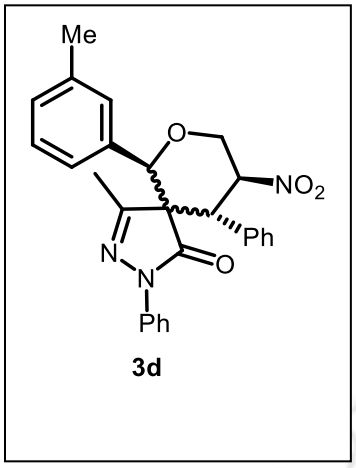
3b 6-(4-(tert-butyl)phenyl)-4-methyl-9-nitro-2,10-diphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as white sticky solid in 50% (25.0 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.23 (m, 3H), 7.23 – 7.19 (m, 4H), 7.17 (t, *J* = 7.8 Hz, 2H), 7.09 – 7.04 (m, 1H), 7.04 – 7.00 (m, 1H), 5.71 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.73 (s, 1H), 4.69 (d, *J* = 12.6 Hz, 1H), 4.65 – 4.60 (m, 2H), 2.31 (s, 3H), 1.20 (s, 9H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 171.8, 156.5, 152.1, 136.7, 133.2, 131.5, 129.2, 128.8, 128.6, 127.5, 126.0, 125.9, 125.2, 120.4, 81.6, 78.7, 68.3, 64.4, 45.4, 34.7, 31.3, 16.9. **HPLC Analysis:** ee = 88%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 21.40 min, t_{minor} = 15.46 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{30}H_{32}N_3O_4$ 498.2387; Found 498.2393.



3c

3c 4-methyl-9-nitro-2,10-diphenyl-6-(4-(trifluoromethyl)phenyl)-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as yellowish sticky solid in 43% (22.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.45 (dd, *J* = 8.7, 3.5 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 2.5 Hz, 3H), 7.22 (d, *J* = 3.2 Hz, 2H), 7.19 (dd, *J* = 8.6, 2.2 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.06 – 7.01 (m, 2H), 5.68 (dt, *J* = 12.4, 7.1 Hz, 1H), 4.81 (s, 1H), 4.73 – 4.60 (m, 3H), 2.35 (s, 3H). **13C NMR (126 MHz, Chloroform-*d*)** ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 156.4, 139.1, 136.6, 132.6, 131.3, 131.0, 130.8, 129.3, 129.1, 129.0 (C-F, $^{1}J_{C\text{-}F}$ = 203.3 Hz), 128.8, 127.7, 127.6, 126.6, 126.2, 125.9, 125.4, 125.4(C-F, $^{4}J_{C\text{-}F}$ = 3.8 Hz), 125.41, 125.3, 124.1, 122.8 (C-F, $^{1}J_{C\text{-}F}$ = 168.8 Hz), 121.3, 120.1, 120.0, 81.6, 78.02, 68.4, 63.8, 45.9, 16.9. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -63.86.

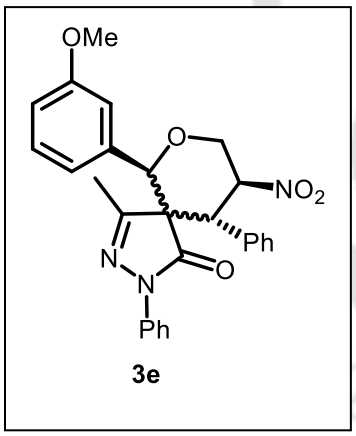
HPLC Analysis: ee = 86%, Chiralpak ID Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 43.95 min, t_{minor} = 38.69 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{23}F_3N_3O_4$ 510.1635; Found 510.1639.



3d

3d 4-methyl-9-nitro-2,10-diphenyl-6-(m-tolyl)-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as pale yellow sticky solid in 36% (16.4 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.25 – 7.21 (m, 5H), 7.21 – 7.17 (m, 2H), 7.16 – 7.12 (m, 3H), 7.12 – 7.07 (m, 2H), 7.04 (t, *J* = 7.9 Hz, 2H), 5.65 (ddd, *J* = 12.2, 7.7, 6.4 Hz, 1H), 4.74 (s, 1H), 4.71 – 4.59 (m, 3H), 2.30 (s, 3H), 2.26 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 171.8, 156.7, 138.2, 134.9, 133.1, 129.7, 129.3, 128.9, 128.7, 128.3, 127.7, 126.8, 125.8, 123.2, 120.0, 81.7, 78.7, 68.3, 64.0, 45.9, 21.6, 16.9.

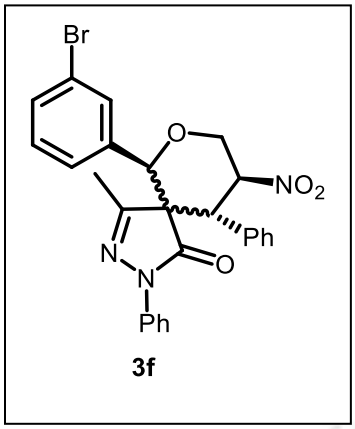
HPLC Analysis: ee = 86%, Chiralpak IA Column, n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 274 nm (t_{major} = 12.30 min, t_{minor} = 17.08 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_3O_4$ 456.1918; Found 456.1910.



3e

3e 6-(3-methoxyphenyl)-4-methyl-9-nitro-2,10-diphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a yellow sticky solid in 45% (21.2 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** 7.24 (q, *J* = 2.9 Hz, 3H), 7.21 (dd, *J* = 7.4, 2.6 Hz, 3H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.16 (dt, *J* = 6.4, 1.5 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.90 (t, *J* = 2.1 Hz, 1H), 6.79 – 6.73 (m, 2H), 5.65 (ddd, *J* = 12.2, 7.8, 6.4 Hz, 1H), 4.75 (s, 1H), 4.72 – 4.60 (m, 3H), 3.73 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (126 MHz, Chloroform-*d*)** δ 171.8, 159.7, 156.6, 129.3, 128.8, 127.7, 120.0, 81.7, 78.5, 68.4, 63.9, 55.5, 46.0, 16.9.

HPLC Analysis: ee = 99%, Chiralpak IC Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 18.92 min, t_{minor} = 23.33 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_3O_5$ 472.1867; Found 472.1867.

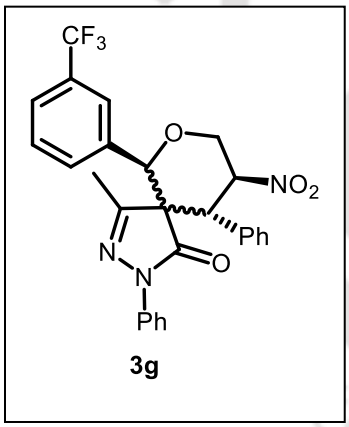


3f

3f 6-(3-bromophenyl)-4-methyl-9-nitro-2,10-diphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a white sticky solid 40% (21.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.45 (s, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.25 (s, 3H), 7.22 (d, *J* = 6.9 Hz, 4H), 7.19 – 7.15 (m, 3H), 7.14 – 7.08 (m, 2H), 5.64 (dt, *J* = 13.4, 6.8 Hz, 1H), 4.73 (s, 1H), 4.69 – 4.58 (m, 3H), 2.31 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.5, 156.4, 137.4, 136.7, 132.8, 132.1, 129.3, 128.8, 127.7, 126.0, 124.6, 122.6, 120.0, 81.6, 77.7, 68.3, 63.7, 45.9, 16.9.

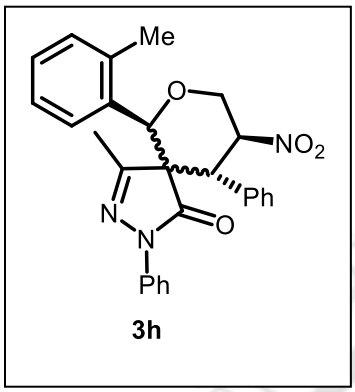
HPLC Analysis: ee = 84%, Chiralpak IA Column, n-Hexane/i-PrOH =85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.20 min, t_{minor} = 19.26 min). **ESI HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{26}H_{23}BrN_3O_4$ 520.0866; Found 520.0867.



3g

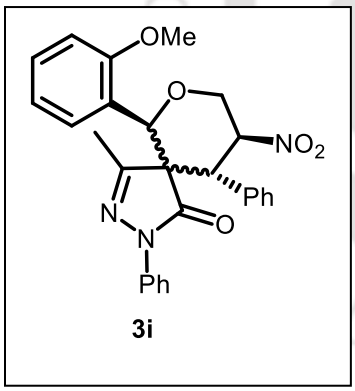
3g 4-methyl-9-nitro-2,10-diphenyl-6-(3-(trifluoromethyl)phenyl)-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a pale yellow sticky compound in 40% (20.4 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.52 (s, 1H), 7.50 – 7.44 (m, 3H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.25 (d, *J* = 1.7 Hz, 2H), 7.22 (dd, *J* = 7.3, 2.6 Hz, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.15 – 7.11 (m, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 5.70 – 5.62 (m, 1H), 4.82 (s, 1H), 4.71 (dd, *J* = 12.2, 6.2 Hz, 1H), 4.64 (dd, *J* = 12.1, 8.8 Hz, 2H), 2.33 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 171.4, 156.3, 136.8, 136.6, 136.2, 135.8, 133.9 (C-F, $^{1}J_{C\text{-}F}$ = 393.1 Hz), 132.7, 131.2, 131.0, 130.8 (C-F, $^{2}J_{C\text{-}F}$ = 34.2 Hz), 130.5, 130.3, 129.83, 129.7, 129.4, 129.4, 129.1, 128.9, 128.9, 128.8, 127.7, 126.0, 125.8, 125.8 (C-F, $^{4}J_{C\text{-}F}$ = 4.0 Hz), 125.7, 125.7, 124.8, 123.1, 123.1, 123.1(C-F, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 123.0, 119.7, 119.5, 81.53, 77.9, 68.4, 63.8, 45.8, 16.9. **^{19}F NMR (471 MHz, Chloroform-*d*)** δ -63.7.

HPLC Analysis: ee = 91%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 15.63 min, t_{minor} = 19.32 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{23}F_3N_3O_4$ 510.1635 Found 510.1630.



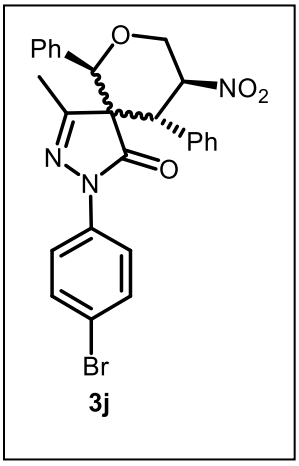
3h

3h 4-methyl-9-nitro-2,10-diphenyl-6-(o-tolyl)-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a white sticky solid in 36% (16.4 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.81 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.28 (s, 1H), 7.22 – 7.20 (m, 4H), 7.19 – 7.15 (m, 3H), 7.09 – 7.06 (m, 2H), 7.06 – 7.02 (m, 2H), 5.62 (ddd, *J* = 12.5, 7.5, 4.9 Hz, 1H), 5.03 (s, 1H), 4.92 – 4.87 (m, 1H), 4.67 – 4.60 (m, 2H), 2.51 (s, 3H), 2.18 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)** δ 170.9, 157.5, 136.8, 134.1, 133.9, 132.2, 130.6, 129.1, 129.0, 128.8, 128.7, 128.3, 125.8, 125.8, 120.0, 82.9, 68.1, 62.7, 45.9, 19.73, 17.7. **HPLC Analysis:** ee = 92%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 20.58 min, t_{minor} = 10.58 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{27}H_{26}N_3O_4$ 456.1918; Found 456.1913.



3i

3i 6-(2-methoxyphenyl)-4-methyl-9-nitro-2,10-diphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a yellowish sticky solid in 55% (26.0 mg) yield after column chromatography. **^{1}H NMR (500 MHz, Chloroform-*d*)** δ 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.13 (m, 6H), 7.13 – 7.09 (m, 2H), 7.09 – 7.02 (m, 2H), 6.67 (d, *J* = 8.2 Hz, 1H), 5.65 (ddd, *J* = 12.7, 7.9, 4.9 Hz, 1H), 5.14 (s, 1H), 4.64 (dd, *J* = 12.6, 4.9 Hz, 1H), 4.57 – 4.50 (m, 2H), 3.54 (s, 3H), 2.42 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*)**) δ 171.5, 157.9, 154.9, 137.1, 132.2, 129.5, 128.9, 128.84, 128.7, 128.1, 128.1, 125.4, 124.7, 120.8, 119.7, 109.59, 82.9, 74.3, 68.9, 62.9, 54.8, 46.4, 17.0. **HPLC Analysis:** ee = 94%, Chiralpak IF Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 32.44 min, t_{minor} = 30.10 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{34}H_{31}N_2O_3$ 472.1867; Found 472.1869.

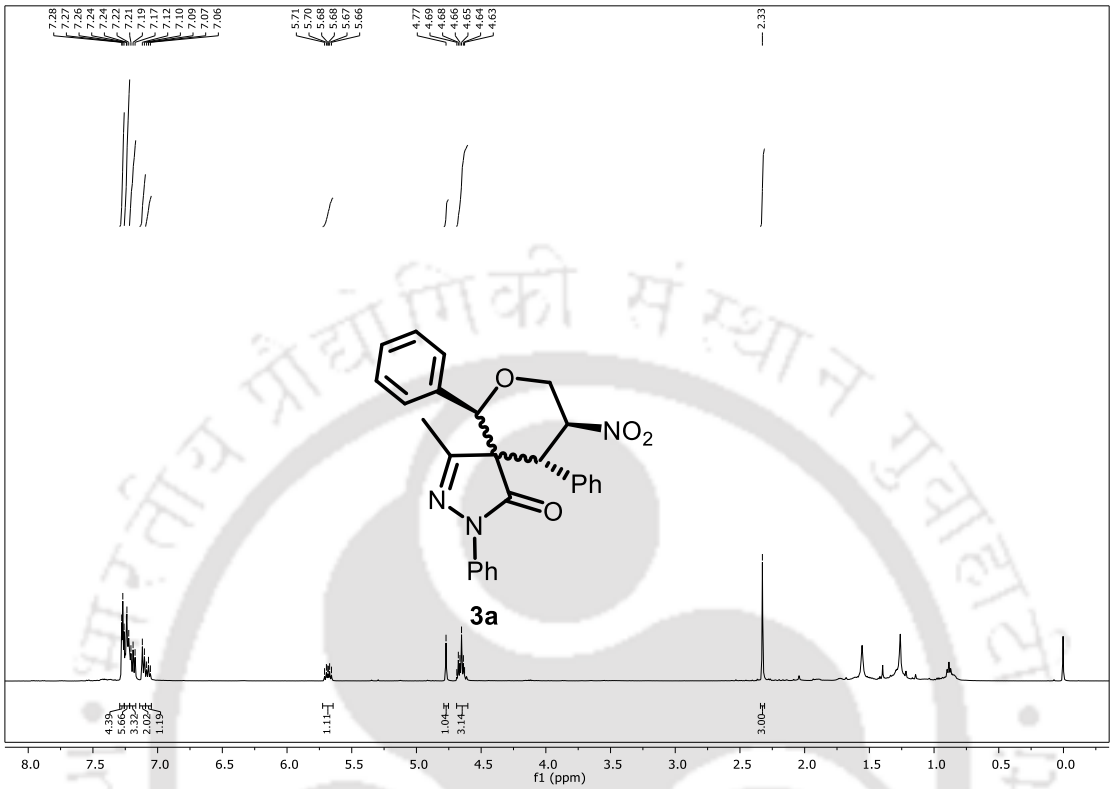


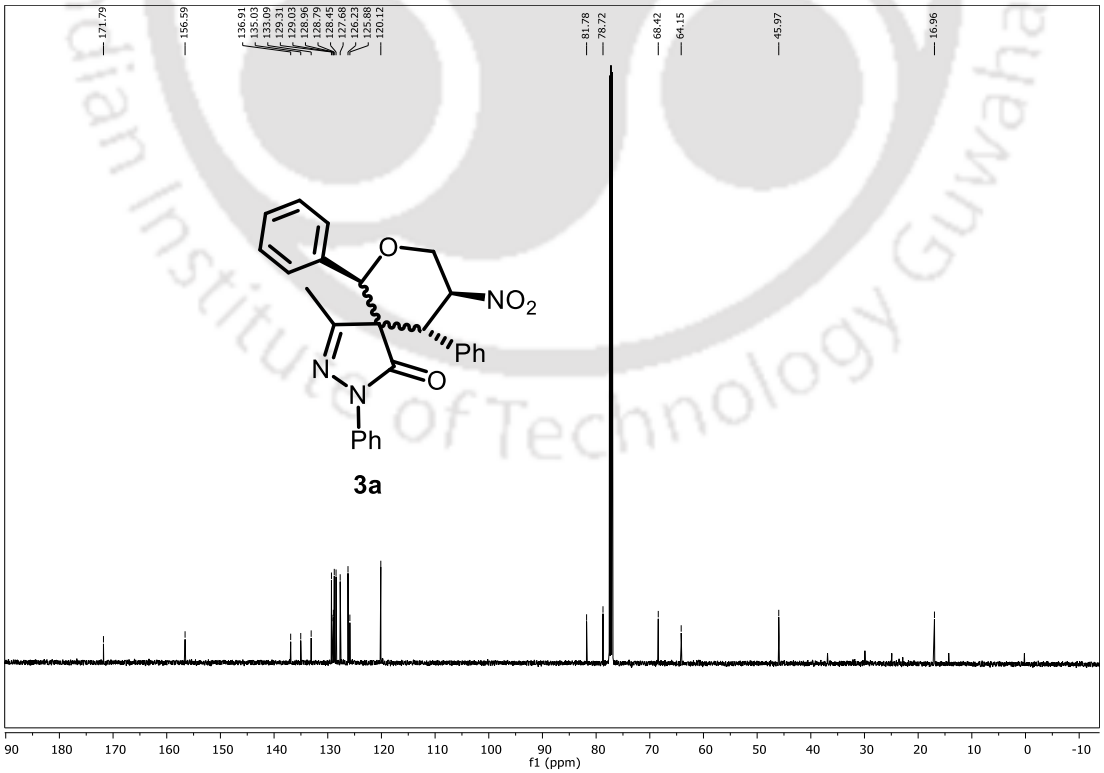
3j

3j 2-(4-bromophenyl)-4-methyl-9-nitro-6,10-diphenyl-7-oxa-2,3-diazaspiro[4.5]dec-3-en-1-one was obtained as a white sticky solid in 45% (23.3 mg) yield after column chromatography. **^{1}H NMR (600 MHz, Chloroform-*d*)** δ 7.52 – 7.39 (m, 2H), 7.35 – 7.32 (m, 2H), 7.28 – 7.24 (m, 6H), 7.22 (dd, *J* = 6.9, 2.9 Hz, 2H), 7.14 – 7.10 (m, 2H), 5.68 (ddd, *J* = 12.2, 7.7, 6.4 Hz, 1H), 4.79 (s, 1H), 4.73 – 4.63 (m, 3H), 2.34 (s, 3H). **^{13}C NMR (151 MHz, Chloroform-*d*)** δ 171.7, 157.0, 135.9, 134.8, 132.9, 131.8, 129.3, 129.1, 129.0, 128.4, 127.5, 126.0, 121.0, 118.7, 81.5, 78.6, 68.3, 64.2, 45.8, 16.9.

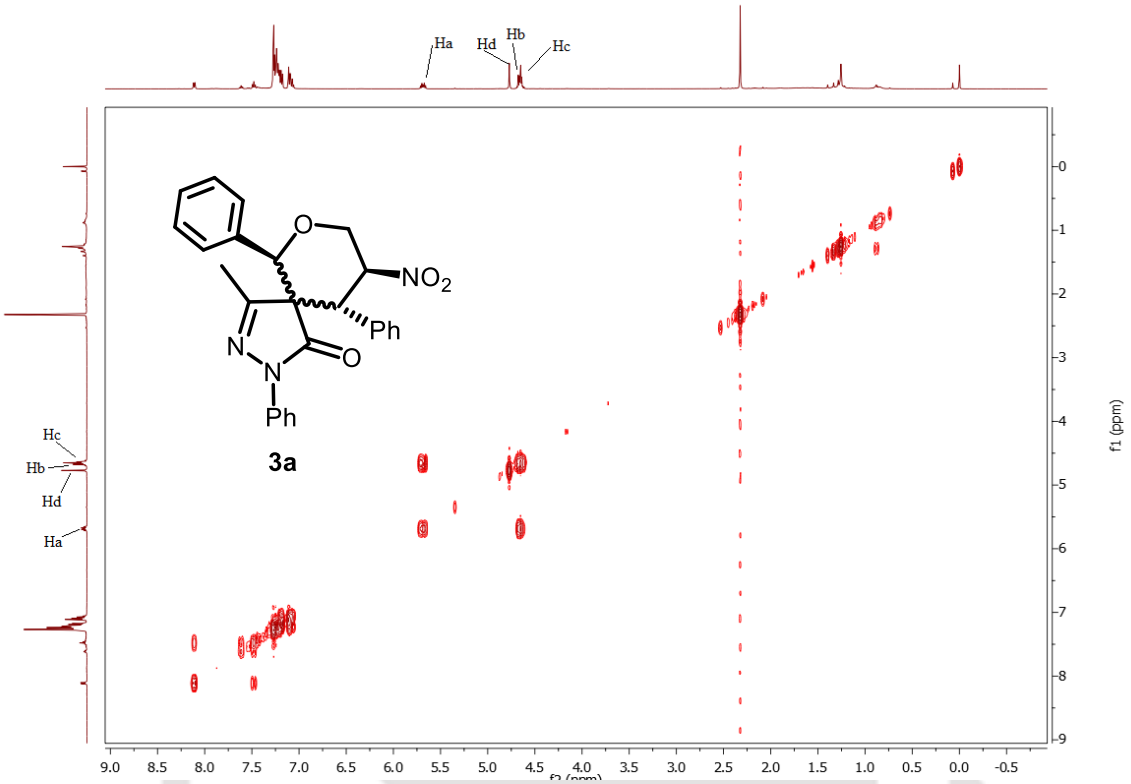
HPLC Analysis: ee = 83%, Chiralpak IF Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 220 nm (t_{major} = 31.30 min, t_{minor} = 43.16 min). **HRMS (ESI) m/z**: $[M+H]^+$ Calcd. for $C_{35}H_{33}N_2O_2$ 520.0866; Found 520.0862.

5.7.5. Some selective NMR spectra of products:

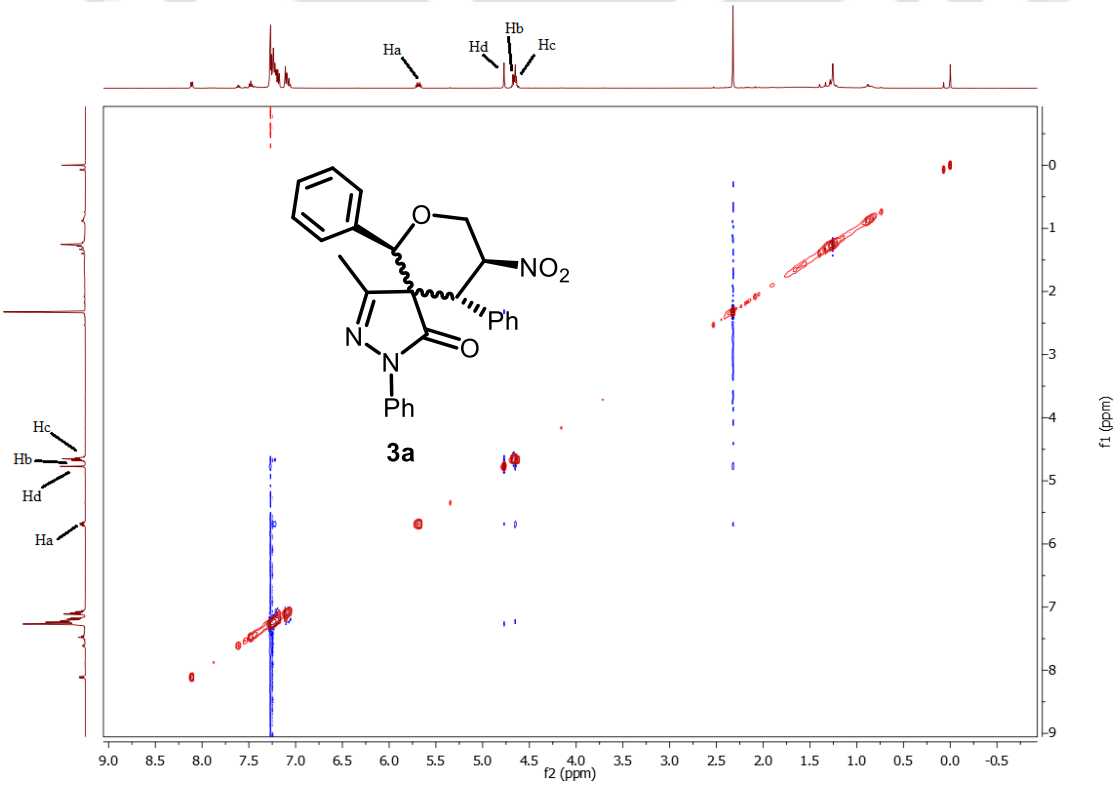




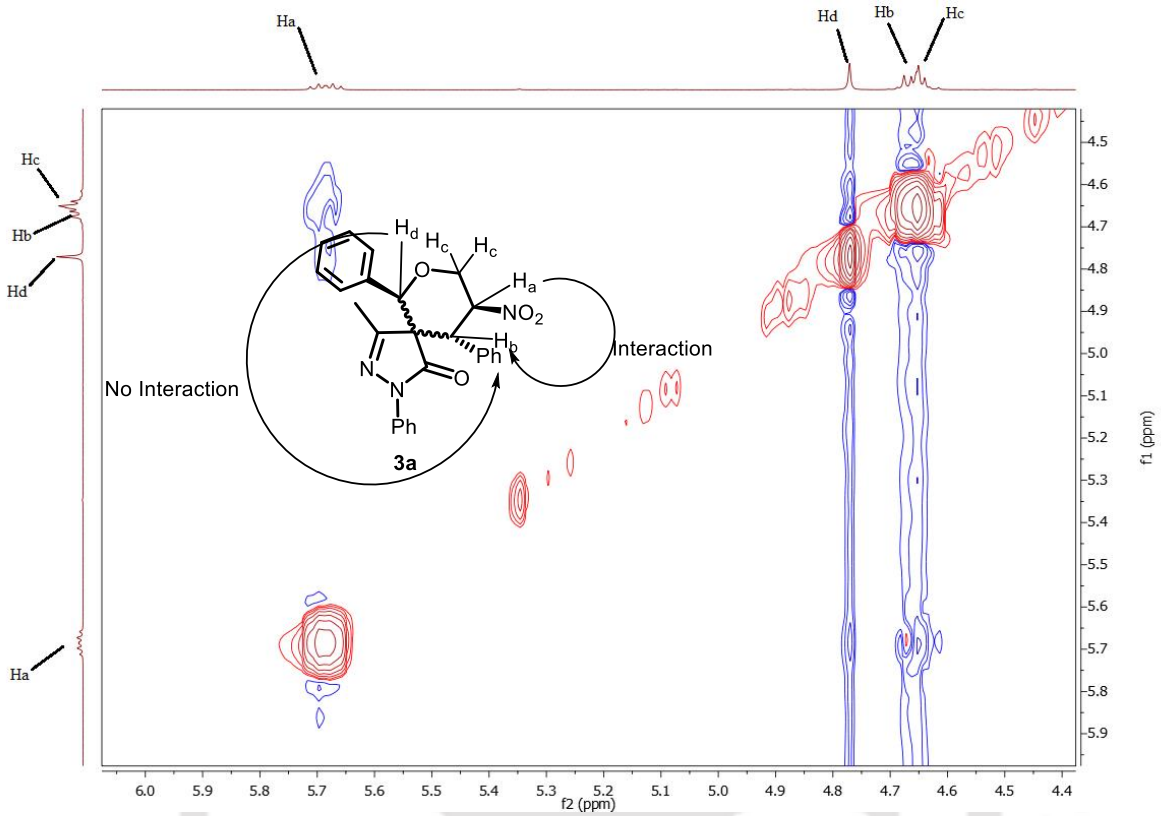
COSY of 3a



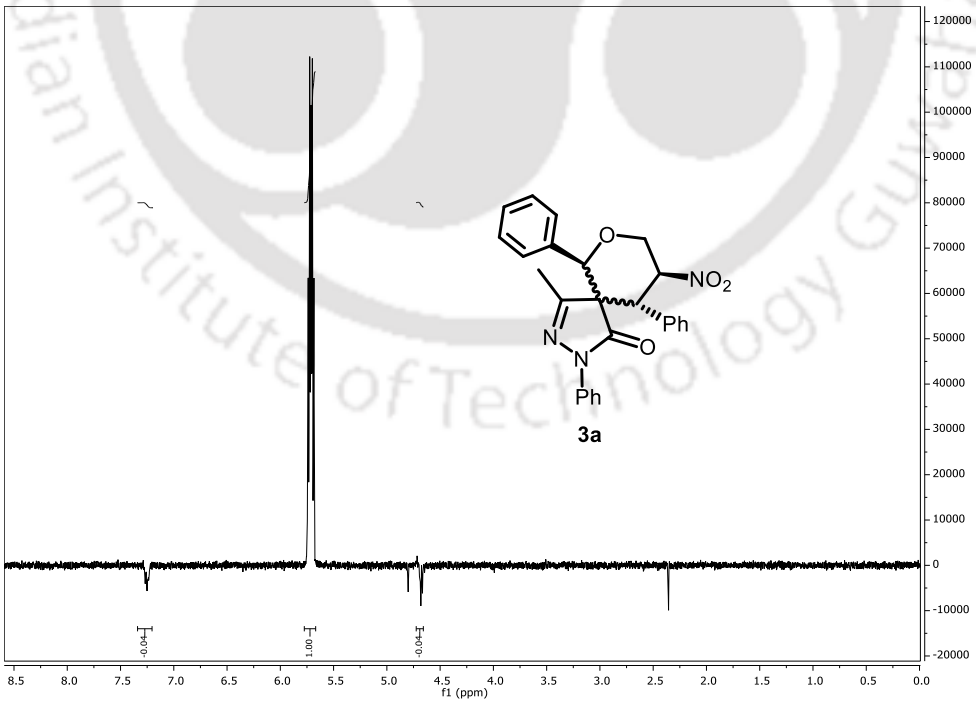
NOESY of 3a

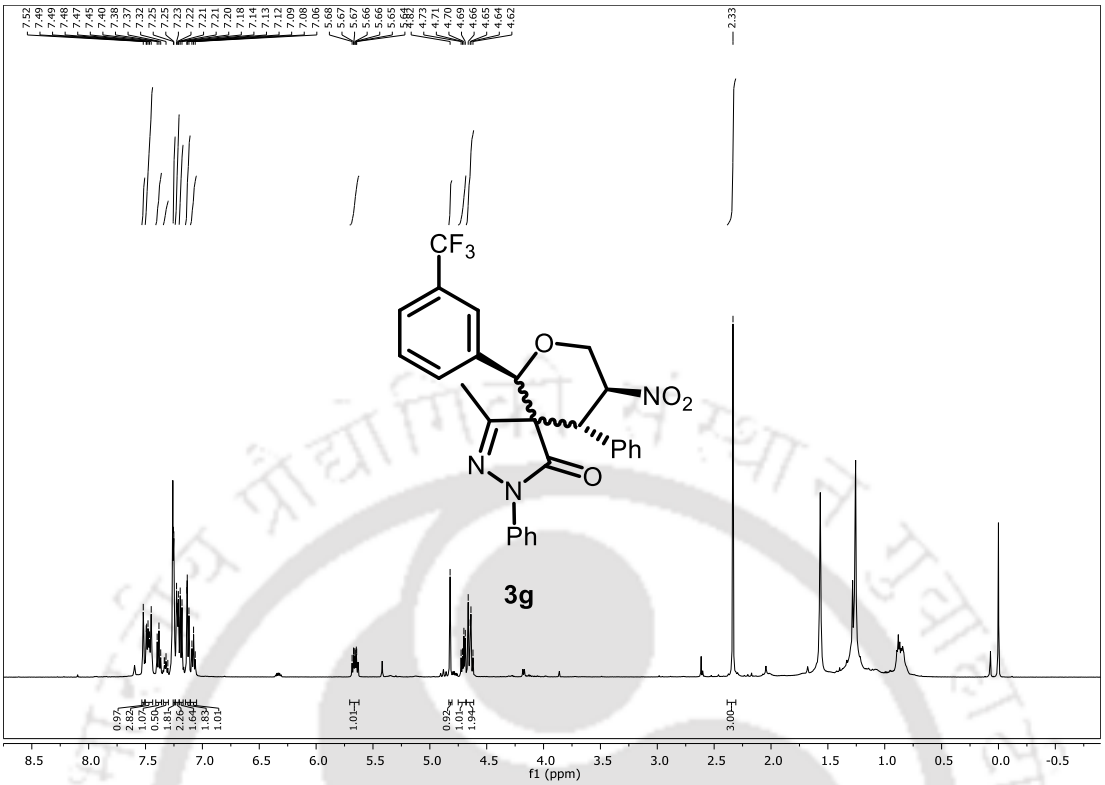


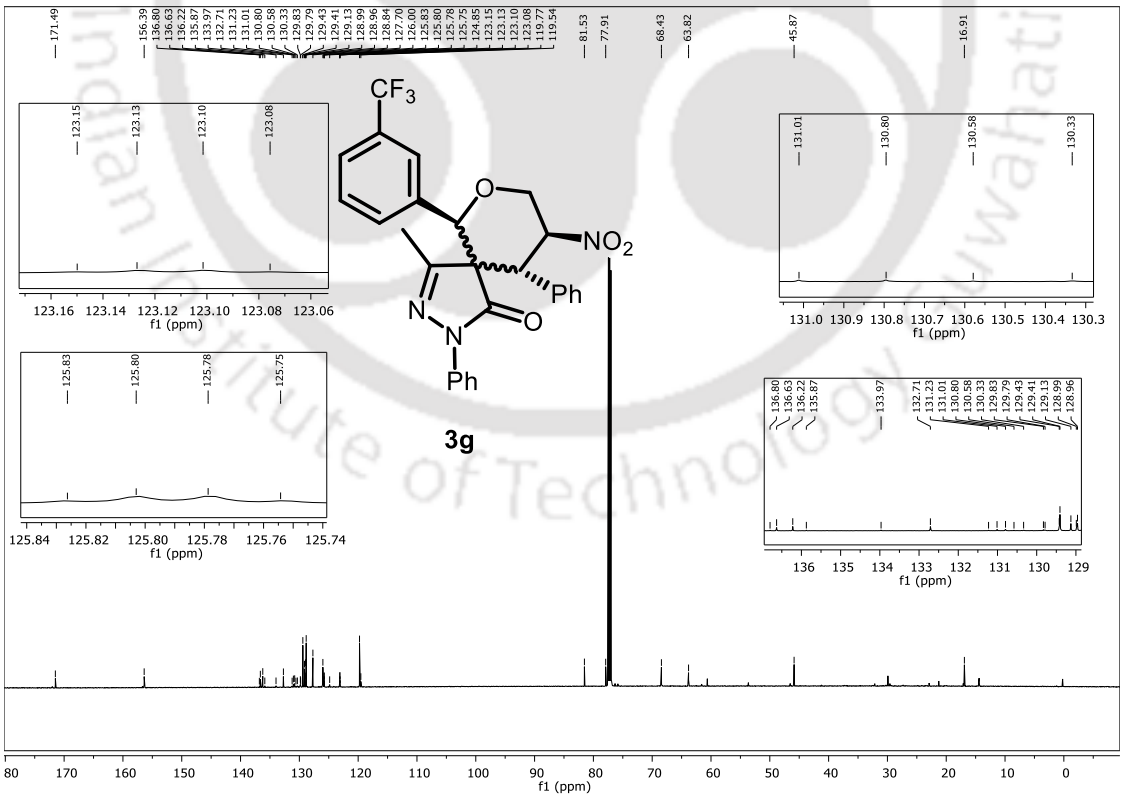
NOESY of 3a (zoomed out figure)

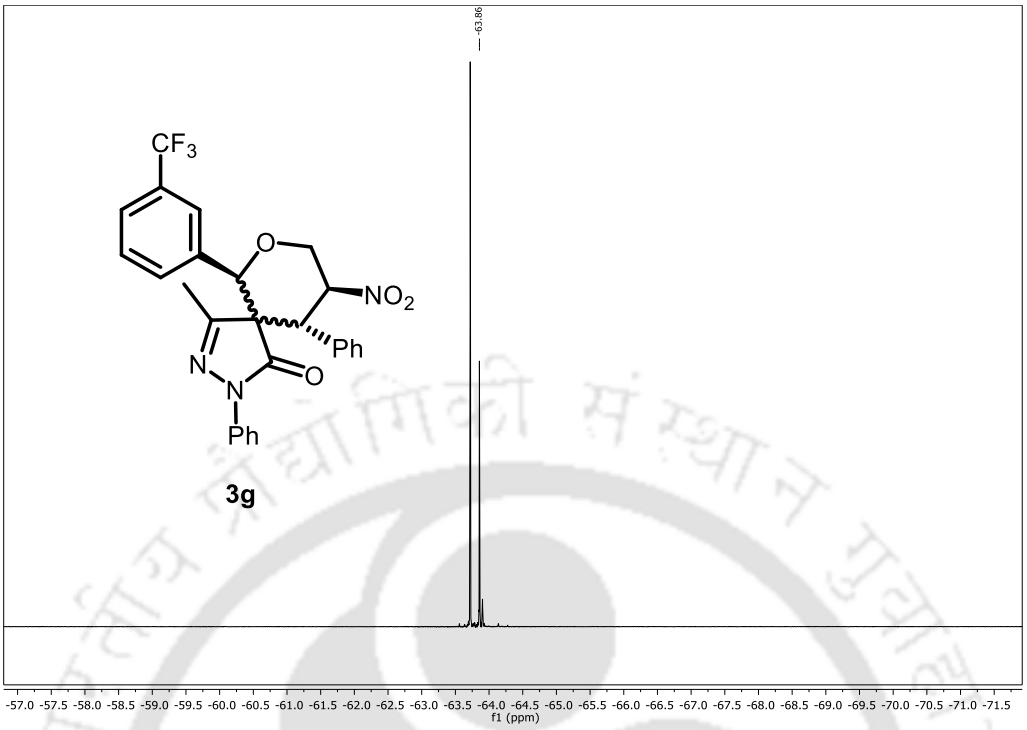


1D NOE of 3a, irradiation at 5.6 (H_a) ppm



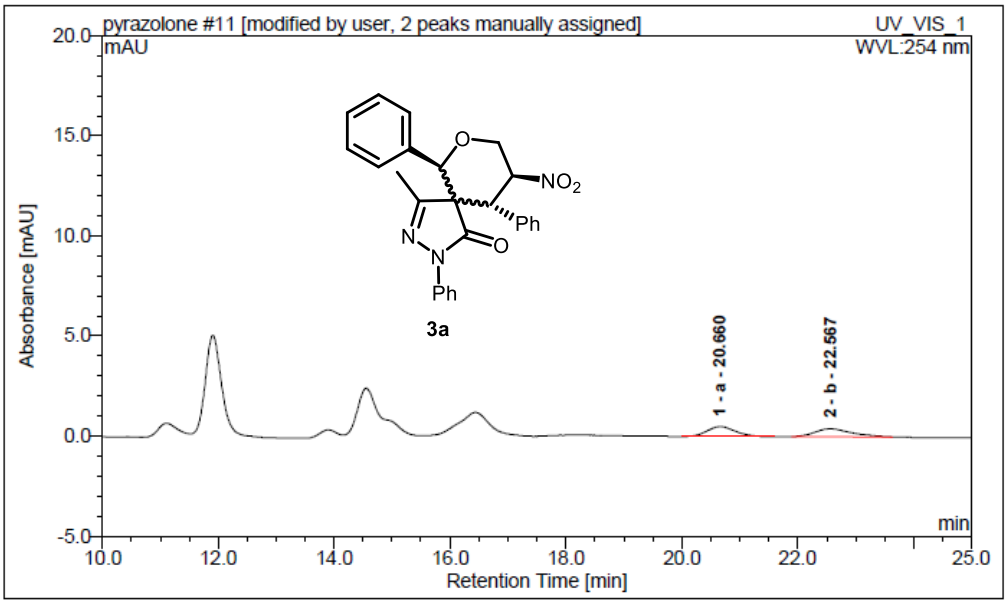






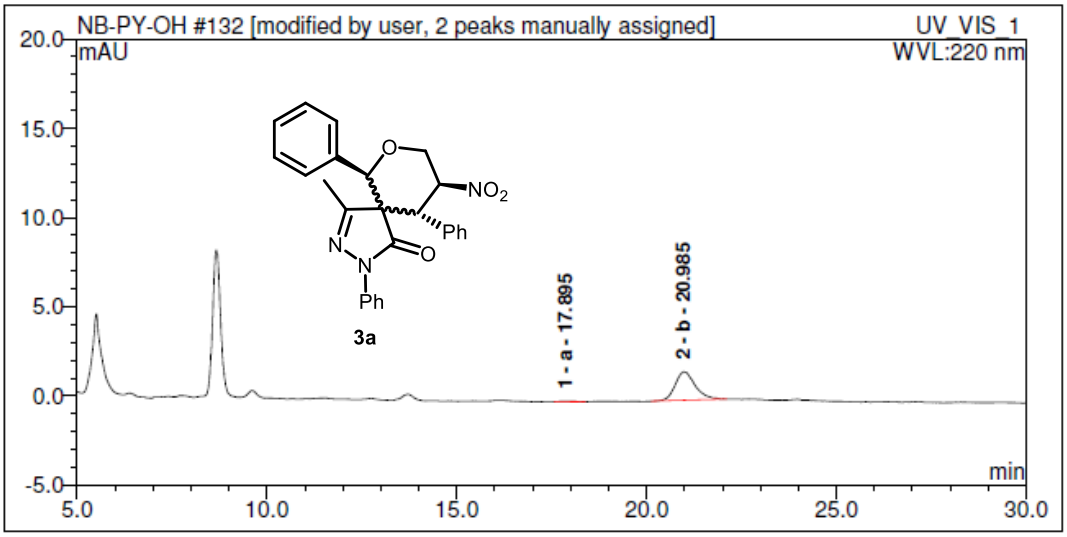
5.7.9. Some selective HPLC chromatogram of compounds:

The HPLC chromatogram of racemic **3a**



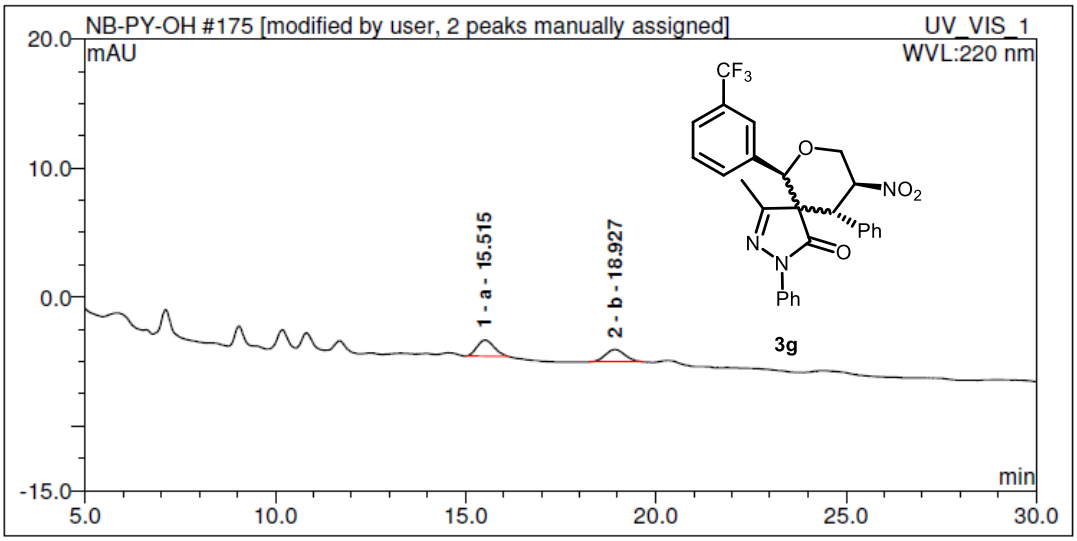
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	20.66	0.27875	49.12926523	0.49442	n.a.
2	b	22.57	0.289	50.87073477	0.401	n.a.

The HPLC chromatogram of chiral **3a**



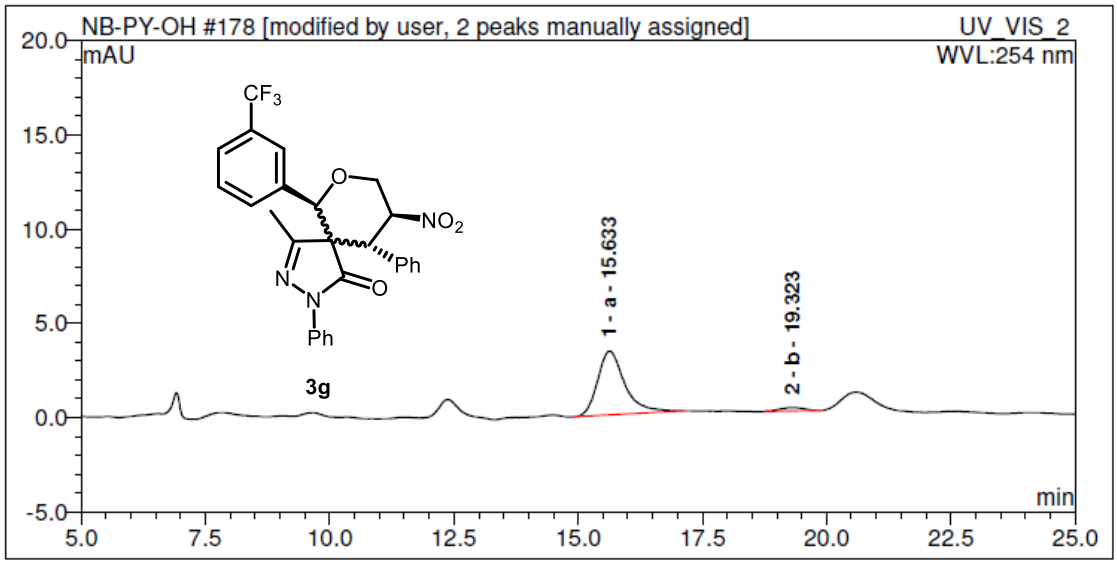
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	17.90	0.012298	1.237926277	0.03261	n.a.
2	b	20.99	0.981	98.76207372	1.600	n.a.

The HPLC chromatogram of racemic **3g**



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	15.52	0.648559	52.89226109	1.24346	n.a.
2	b	18.93	0.578	47.10773891	0.962	n.a.

The HPLC chromatogram of chiral **3g**



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	15.63	2.151036	95.46003802	3.38842	n.a.
2	b	19.32	0.102	4.539961983	0.187	n.a.

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PUBLICATIONS

Published:

1. **Nimisha Bania** and Subhas Chandra Pan. **"Organocatalytic asymmetric Michael/ hemiketalization/acyl transfer reaction of 1, 3-propanediones with (E)-2-(2-nitrovinyl) phenols"** *Org. Biomol. Chem.*, **2019**,*17,* 1718.

2. **Nimisha Bania**, B. Mondal, S. Ghosh and Subhas Chandra Pan. **"DMAP Catalyzed Domino Rauhut–Currier Cyclization Reaction between Alkylidene Pyrazolones and Nitro-olefins: Access to Tetrahydropyrano [2, 3-c] pyrazoles".** *J. Org. Chem.* **2021**, *86*, 5, 4304.

3. **Nimisha Bania**, D. Barman and Subhas Chandra Pan. **"Organocatalytic asymmetric oxa-Michael-Michael reaction between 3-aryl-2-nitroprop-2-enols and unsaturated pyrazolones: Synthesis of spiro-tetrahydropyran-pyrazolones". *Synlett,* 2022,** *33,* A-D.

In process:

1. **Nimisha Bania**, D. Barman and Subhas Chandra Pan. **"Organocatalytic Asymmetric Inverse-Electron-Demand-Diels-Alder Reaction between Alkylidene Pyrazolones and Allyl Ketones: Access to Tetrahydropyrano[2,3-c] Pyrazoles"** manuscript under revision.in JOC.

CONFERENCES

1. Presented a poster entitled "**Organocatalytic asymmetric Michael/ hemiketalization/acyl transfer reaction of 1, 3-propanediones with (E)-2-(2-nitrovinyl) phenols**" at the international conference Frontiers in Chemical Science (FICS-2018) held at IIT Guwahati.

2. Presented a poster entitled "**Organocatalytic asymmetric Michael/ hemiketalization/acyl transfer reaction of 1, 3-propanediones with (E)-2-(2-nitrovinyl) phenols**" at the international conference Organix-2018 held at Tezpur University.