Organocatalytic Asymmetric Michael and Aza-Henry Reactions for the Synthesis of Nitrogen- & Oxygen-Containing Heterocyclic Compounds

A Dissertation

Submitted in Partial Fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

Rajendra Maity

Roll No. 126122012

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781039

INDIA

February 2018

Dedicated to

My Parents and Brother

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled *"**Organocatalytic Asymmetric Michael and Aza-Henry Reactions for the Synthesis of Nitrogen- & Oxygen-Containing Heterocyclic Compounds**"* is the result of investigations carried out by me under the supervision of Dr. Subhas Chandra Pan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

Guwahati
February 2018

Rajendra Maity
Roll No -126122012

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

Guwahati – 781039, India

Tel. No.: +91-361-2583304

e-mail: span@iitg.ernet.in

Dr. Subhas Chandra Pan

Associate Professor

CERTIFICATE

This is to certify that Rajendra Maity (Roll No - 126122012) has been working under my supervision since July, 2012 as a regular registered Ph. D. student. His thesis entitled "***Organocatalytic Asymmetric Michael and Aza-Henry Reactions for the Synthesis of Nitrogen- & Oxygen-Containing Heterocyclic Compounds***" contains the results obtained from the research work carried out by him in the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding his thesis to submit for the Ph. D. (Science) degree from this institute as he has fulfilled all the requirements according to the rules of this institute and this work has not been submitted elsewhere for a degree.

Guwahati — Dr. Subhas Chandra Pan

February 2018 — Supervisor

Acknowledgement

I would like to express my sincere gratitude to every supportive individual who helped me directly and indirectly during this wonderful journey of my Ph. D. career.

Firstly, I would like to thank my thesis supervisor Dr. Subhas Chandra Pan for his constant support, valuable suggestions and guidance throughout my research tenure. His motivating discussions and kind support helped me a lot. It was indeed a great pleasure working with him.

I would like to thank my thesis examiner Prof. Santanu Mukherjee, department of organic chemistry, IISC Bangalore for valuable correction and suggestion in my thesis.

I take this opportunity to convey my deepest gratitude to the doctoral committee members; Prof. Gopal Das, Prof. Subhendu Sekhar Bag and Dr. A. S. Achalkumar for their valuable suggestions, intellectual inputs and encouragements during the entire period of doctoral studies.

I am thankful to my teachers, Mr Sachinder Nath Dutta and Jhuni madam for their motivation and valuable suggestions. I would like to express sincere gratefulness to my elder brother, Mr Muktipada Giri for his support.

I respectfully acknowledge to Indian Institute Technology Guwahati for providing me the fellowship and to Department of Chemistry and Central Instruments Facilities for providing the research and instrumental facilities.

I would like to express sincere gratefulness to Nibedita Behera for her assistance in solving crystal structures.

I am delighted to have kind cooperation from my dear lab mates, Utpal da, Keshab, Soumendra, Buddhadeb, Subas, Chandan, Megha, Nimisha and Aindrila,

which was a great support during my PhD. I sincerely thank Gobinda and Gaurav for their contribution in my works. I would also like to thank Subas and Buddha for allowing me to work with them in their projects.

My special thanks go to my friends, Raju, Biju, Rajesh, Srikant, Anadi, Muna, Sai, Nibedita, Rabi, Nayan, Priyabrata, Deepan, Bapi and IITG friends for their constant help and support in all aspects. I would like to acknowledge my seniors in IITG, Santosh bhai, Bigyan bhai, Kanhu bhai and Himanshu bhai for their valuable suggestions and guide during my Ph. D. tenure.

Finally, my sincere gratitude goes to my parents and brother for their unflagging love and support throughout my life. I feel deeply indebted to them for whatever I have achieved so far and I dedicate it to them.

Rajendra Maity

Abbreviations

Ar	Aryl group	g	Grams
br	Broad	h	Hours
bs	Broad singlet	HPLC	High performance liquid chromatography
Bu	Butyl	HRMS	High Resolution Mass Spectrometry
CCDC	Cambridge Crystallographic Data Centre	Hz	Hertz
COSY	Correlation spectroscopy	Hex	Hexane
^{o}C	Degrees Celsius	*i*	Iso
CH_2Cl_2	Dichloromethane	i-PrOH	2-propapnol
d	Doublet	*J*	Coupling Constant
dd	Doublet of doublet	KBr	Potassium bromide
ddd	Doublet of doublet of doublet	m	Multiplet
δ	Chemical shift	*m*	*meta*
DCE	1,2-Dichloroethane	*m*CPBA	*meta*-Chloroperoxybenzoic acid
DCM	Dichloromethane	Me	Methyl
de	Diastereomeric excess	mg	Miligram
DMF	N,N-Dimethylformamide	mL	Millilitre
DMSO	Dimethylsulfoxide	mol	Mole
dr	Diastereomeric ratio	mp	Melting point
EA	Ethyl acetate	mg	Milli gram
ee	Enantiomeric excess	mL	Millilitre
eq.	Equivalent	mol	Mole
ESI	Electrospray ionization	mp	Melting point
Et	Ethyl	MS	Molecular sieves

MTBE	Methyl tertiary butyl ether	THF	Tetrahydrofuran
n	Normal	TMS	Tetramethylsilane
NMR	Nuclear magnetic resonance	THPP	Tetrahydropyrano[2,3-*c*]pyrazole
NOESY	Nuclear Overhauser effect spectroscopy	Ts	*p*-Toluenesulfonyl
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program	UV	Ultra violet
TBDPS	Tertiary butyl diphenyl silyl ether	XRD	X-ray diffraction
o	*ortho*		
p	*para*		
Ph	Phenyl		
ppm	Parts per million		
Pr	Propyl		
PTSA	*para*-Toluenesulfonic acid		
$PhCF_3$	Trifluorotoluene		
q	Quartet		
rt	Room temperature		
s	Singlet		
t	triplet		
t	*tert*		
TFA	Trifluoroacetic acid		
TFAA	Trifluoroacetic anhydride		

Contents

General Remarks

The present investigations are carried out in Department of Chemistry, Indian Institute of Technology Guwahati, during the period from July-2012 to February-2018 as a Ph.D. student under the supervision of Dr. Subhas Chandra Pan.

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and diethylether (Et_2O) were freshly distilled from Sodium under argon. Dichloromethane (CH_2Cl_2) and dichloroethane ($ClCH_2CH_2Cl$) were freshly distilled from calcium hydride (CaH_2). Chloroform ($CHCl_3$) was distilled calcium chloride ($CaCl_2$) and store under argon. Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene and toluene were distilled from calcium hydride (CaH_2) before use. Trifluorotoluene ($PhCF_3$) was used as received from Sigma India. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich Acros, Merck and Spectrochem.

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

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

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

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

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

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

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

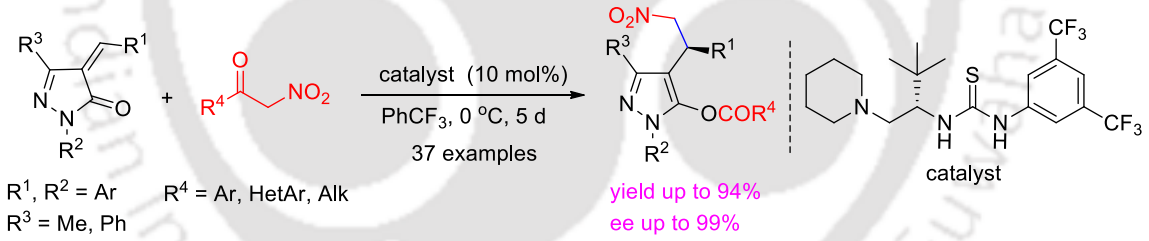
FT-IR: FT-IR spectra were recorded using Perkin Elmer IR spectrometer.

Abstract

The contents of this thesis entitled **"*Organocatalytic Asymmetric Michael and Aza-Henry Reactions for the Synthesis of Nitrogen- and Oxygen- Containing Heterocyclic Compounds*"** have been divided into five chapters based on the results of experimental works performed during the complete course of the PhD research period.

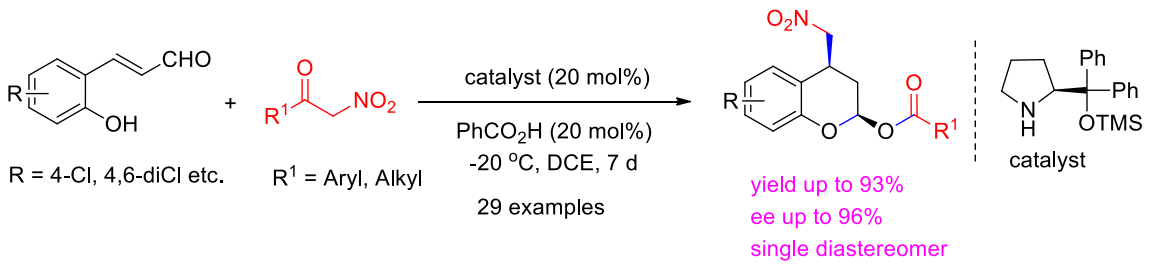
Chapter 1 of the dissertation presents a brief review of organocatalytic Michael and aza-Henry reactions. This chapter mainly highlighted on cinchona alkaloid, prolinol and tertiary leucine derived catalysts, since these catalysts were primarily utilized in the works demonstrated in this thesis.

Chapter 2 describes the bifunctional thiourea catalyzed Michael/hemiketalization/retro-aldol reaction of unsaturated pyrazolones and *α*-nitroketones. Using tertiary leucine derived thiourea catalyst, high yields with excellent enantioselectivities were attained for a variety of 3-acyloxy pyrazoles under mild reaction conditions (Scheme 1). Additionally, few reactions were performed to further extend the synthetic utility of the Michael product and the *N*-protected 3-acyloxy pyrazoles were obtained with excellent enantioselectivities and good yields.



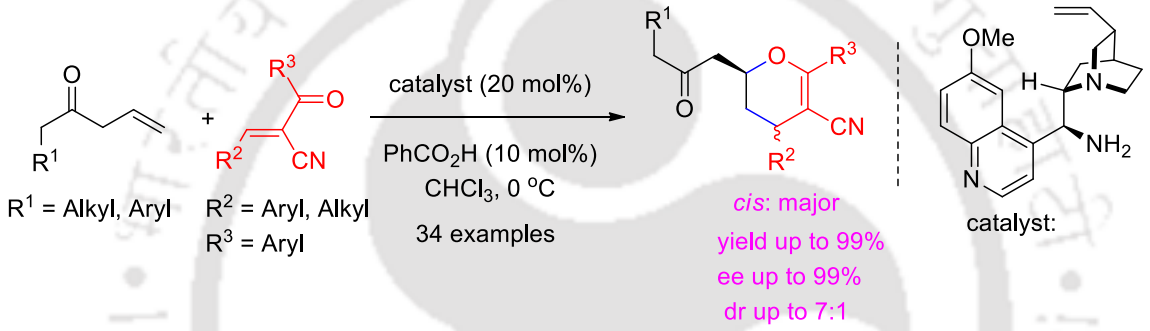
Scheme 1

Chapter 3 demonstrates an organocatalytic asymmetric cascade Michael/hemiacetalization/acyl transfer reaction of *o*-hydroxycinnamaldehydes and *α*-nitroketones. Prolinol TMS ether catalyst in combination with benzoic acid were used for the excellent enantio- and diastereoselective synthesis of 2,4-disubstituted chromans (Scheme 2). This protocol was again extended for the chiral synthesis of 2,4-disubstituted chromans by valuable synthetic transformations such as reduction of nitro to amine and protection of this amine by Boc-anhydride and benzoyl anhydride, reduction of ester to alkane.



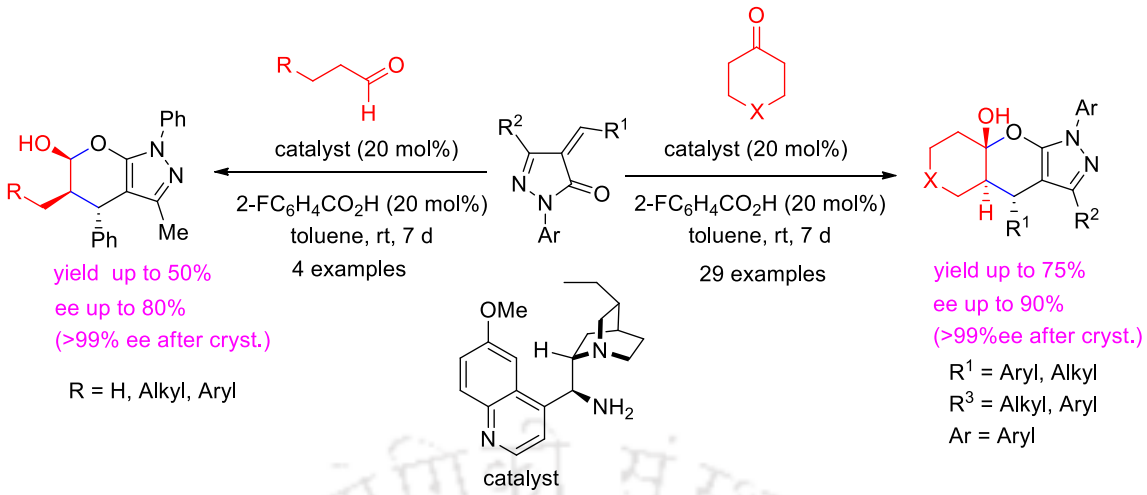
Scheme 2

Chapter 4 discloses the organocatalytic asymmetric Michael-oxa-Michael reaction of linear deconjugated enones having α′-CH groups with electron poor oxadienes. A series of 2,4-stereogenic 3,4-dihydropyrans were synthesised with high yields and excellent enantioselectivities by using the quinine derived primary amine catalyst (Scheme 3).



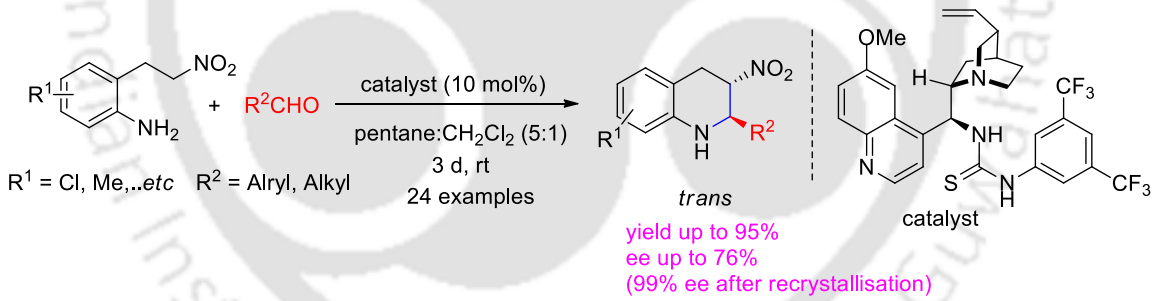
Scheme 3

Chapter 5 describes the hydroquinine amine catalyzed domino Michael-hemiketalization reaction between alkylidene pyrazolones and cyclic ketones/aliphatic aldehydes. Using this standard condition, the fused tetrahydropyrano[2,3-*c*]pyrazole products having three contiguous stereocentres were obtained with moderate to good yields, perfect diastereoselectivities and good to high enantioselectivities (Scheme 4). Also, few synthetic transformations of the product including a spiro derivative formation have been demonstrated.



Scheme 4

Chapter 6 presents an asymmetric synthesis of *trans*-2-aryl/alkyl-3-nitro-tetrahydroquinolines using a direct intramolecular aza-Henry reaction. Using easily available quinine alkaloid derived bifunctional thiourea catalyst, *trans*-2-aryl-3-nitro-tetrahydroquinoline products were achieved in high yields and good enantioselectivities. Interestingly, excellent enantioselectivities were obtained after single recrystallization for some products (Scheme 5).



Scheme 5

Chapter 1

INTRODUCTION

1.1. Asymmetric synthesis:

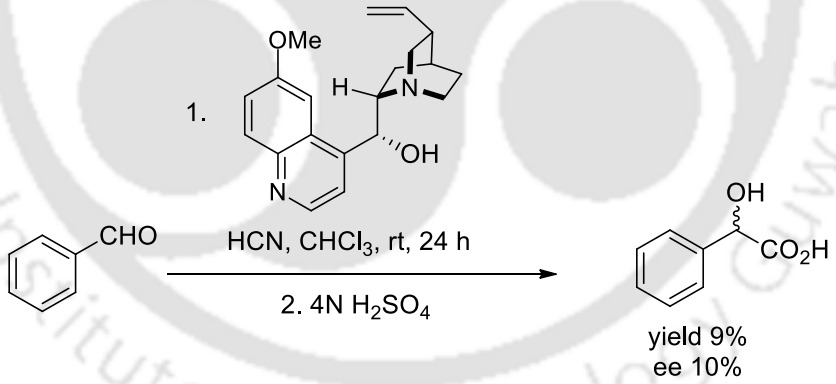
The development of methods for acquiring enantiomerically pure compounds attracts the attention due to the importance in pharmaceutical industry, academics and others. It is well-known that different diastereomers or enantiomers show different biological properties. For example, *S*-Dopa helps to restore nerve function in human body, whereas *R*-Dopa is toxic in nature. In respond to the growing demand of chiral molecules, developments of new asymmetric synthetic methodologies are highly essential. Traditionally, the enantiopure natural products and drugs were synthesized by two synthetic approaches such as chiral pool synthesis or chiral auxiliary approaches. 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. However, considering the step- and atom-economical aspects of synthesis, asymmetric catalysis is the best choice for asymmetric synthesis, because the chiral agents can be used in sub-stoichiometric amount and also for their reusability.

1.2. Organocatalytic asymmetric synthesis:

For long decades, two classes of chiral catalysts such as enzyme and transition metal catalysts were tremendously used in asymmetric synthesis. In 1890, Emil Fischer first established an asymmetric reaction (diastereoselective reaction) of cyanohydrins for the synthesis of sugars by using biocatalysts.[1] In 2001, William S. Knowles and Ryoji Noyori were laureated the Nobel prize for their work on transition metal catalyzed asymmetric hydrogenation reaction. K. Barry Sharpless was also recipient of that honour for his work on transition metal catalyzed asymmetric oxidation reaction in the same year. Though the enzyme and metal catalysts had been enormously employed in asymmetric syntheses to generate enantiopure compounds, their utilizations remained limited for specific reactions. Along with, bio/enzyme catalysts have drawbacks such as less thermostability, narrow substrate scope, and low or wrong stereo- and regioselectivity and metal catalysts may leave the toxic traces in the product and also in general expensive.[2]

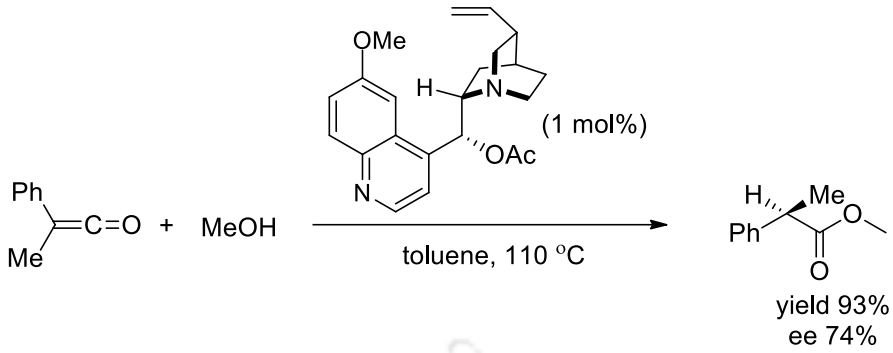
From the last decade, a new asymmetric catalytic method, organocatalysis has emerged as a very powerful strategy for the synthesis of enantiopure compounds. It was first introduced by Bredig and co-workers.[3] Organocatalysts are pure organic (without metals), small molecules (compared to nucleic acids, proteins or polymers) and recycled more efficiently compared to metal/bio-catalysts.[4] Usually, organocatalysts do not require any inert gas, moisture free reagents and solvents as these are unaffected by oxygen or moisture.[3] Moreover, organocatalysts are cheap, stable, easy to handle and can also be synthesized from naturally occurring organic reagents as starting material such as hydroxy acids, amino acids, and carbohydrates *etc*.[5] Especially, the absence of transition metals and non-toxic nature of organocatalyts have great attention of synthetic organic chemists for the preparation of compounds that should not contain metal contamination, e.g. pharmaceutical products or intermediates.

In 1912, Bredig group first reported the organocatalytic asymmetric reaction of aldehydes with HCN by simply using cinchona alkaloid catalyst. Unfortunately, only 9% yield and 10% enantioselectivity were attained for the corresponding product (Scheme 1).[3]



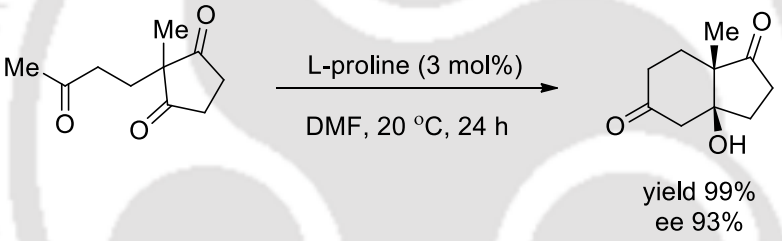
Scheme 1

Remarkably, after almost 50 years Pracejus group (1960) described an organocatalytic asymmetric reaction of phenylmethylketene with methanol by using the acetylquinine as catalyst. The corresponding product was achieved with excellent yield and acceptable level of enantioselectivity (Scheme 2).[6]



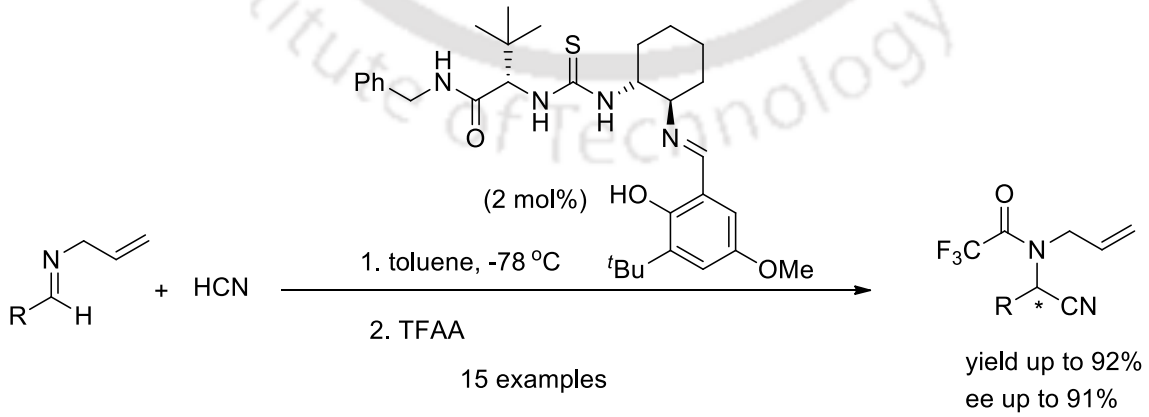
Scheme 2

In the early 1971, Hajosh[7] and Wiechert[8] groups simultaneously pioneered in using proline as effective catalyst for an asymmetric intramolecular aldol cyclization reaction. The reaction used prochiral triketone as substrate through an enamine intermediate and provided the cyclic aldol product with excellent enantioselectivity (93%) and yield (99%, Scheme 3).



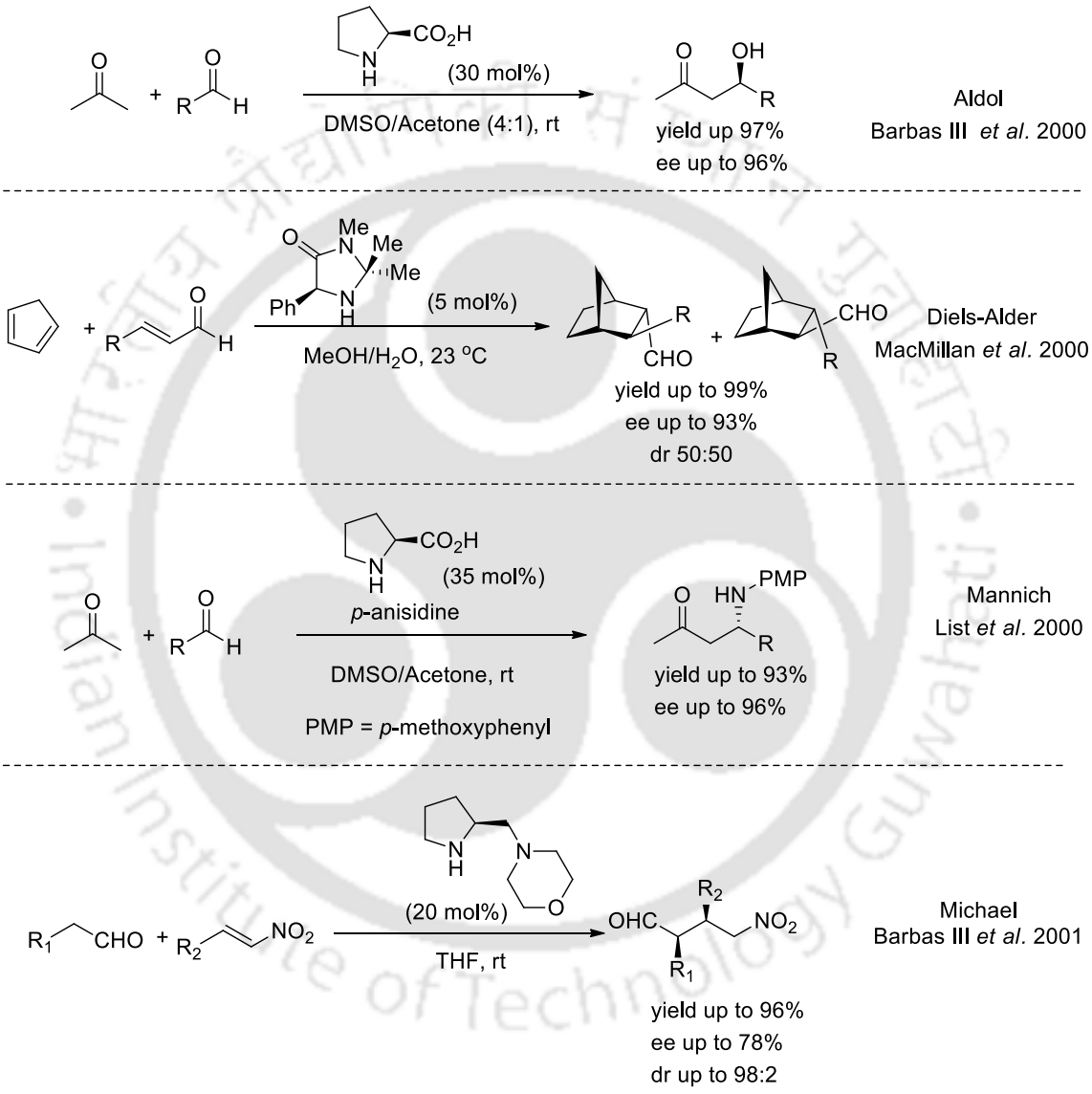
Scheme 3

Later, in 1998, the chiral thiourea was utilized as organocatalyst for the first time. The chiral peptide based thiourea catalyzed Strecker reaction of aldimines and hydrogen cyanide was demonstrated by Jacobsen group (Scheme 4).[9]



Scheme 4

Since 2000, a new era was begun for various organocatalytic asymmetric reactions such as aldol, Mannich, Michael, and Diels-Alder reactions by using proline and its analogues as catalysts, which was developed by List,[10] MacMillan[11] and Barbas III[12] group (Scheme 5). The field of organocatalysis can be classified into four types such as Lewis base, Lewis acid, Brønsted base and Brønsted acid.[13]



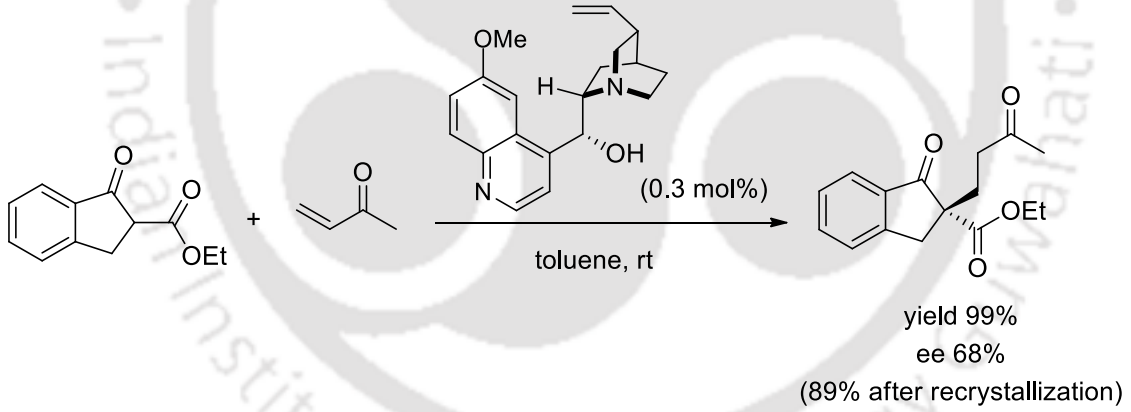
Scheme 5: Illustrates some breakthrough reactions which recognised organocatalysis as efficient asymmetric catalytic system.

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 intermediates.[14]

1.3. Michael Reaction using organocatalysts:

Michael reaction plays a vital role for the formation of C−C bonds in organic chemistry. Michael/conjugate addition reaction defines as the nucleophilic addition of stabilized anions (carbanions, enolates, *etc*) to conjugate enones or α,β-unsaturated carbonyl compounds or similar type of compounds. The first Michael addition reaction was between the ethyl malonates and ethyl esters of cinnamic acids in the presence of sodium acetate base, which was established by Arthur Michael in 1887.[15] After a long time, in the year 1975, the first example of organocatalytic asymmetric Michael addition reaction was demonstrated by Wynberg group. The quinine catalyzed Michael reaction of methyl vinyl ketone and cyclic β-ketoester delivered the corresponding product with 99% yield and 68% enantiomeric excess. Moreover, the enantioselectivity of the product was increased to 89% after recrystallization (Scheme 6).[16]



Scheme 6

Asymmetric organocatalytic Michael reaction has attracted great attention in recent years because of its environmental friendliness and application in natural product synthesis as well as in medicinal chemistry. Since 2000, organocatalytic asymmetric Michael addition reaction was carefully investigated by List,[17] Barbas III,[18] Roder,[19] Enders,[20] and Baro[21] groups. Generally, in the asymmetric Michael addition reaction, chiral organocatalysts activated the reactants by three possible ways, firstly, activate the Michael acceptor *via* formation of an iminium species (**I**, Figure 1), secondly, activation of Michael donors through the formation of an enamine intermediate (**II**, Figure 1) and

thirdly, act as a base forming a complex with Michael donors to react with the acceptor (**III**, Figure 1)[18].

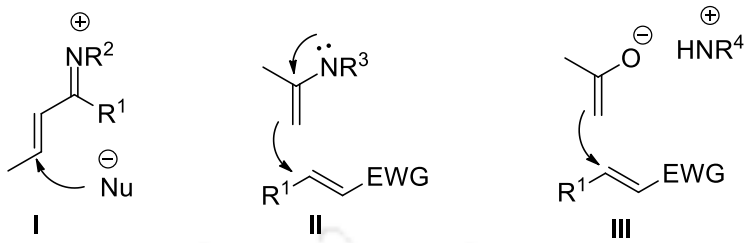
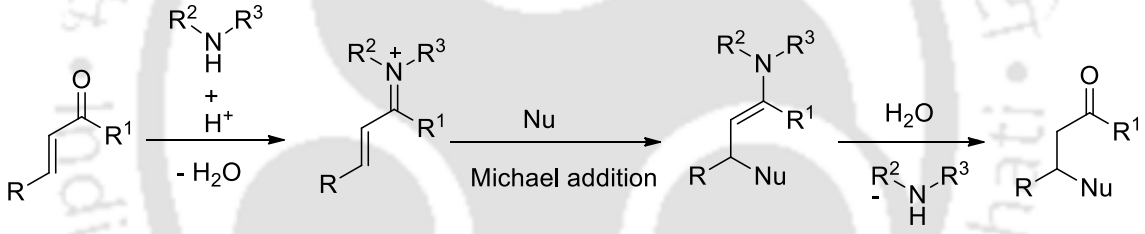


Figure 1. Mechanisms for amine-catalyzed Michael reactions

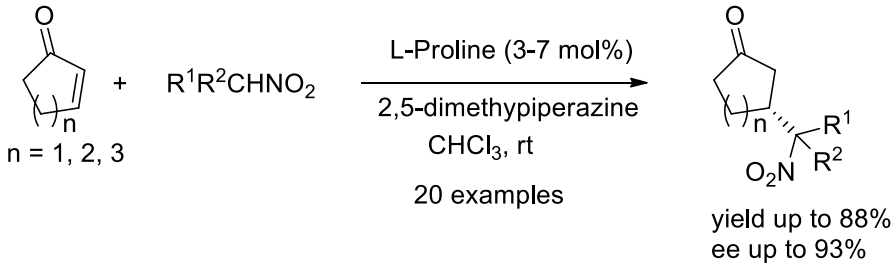
1.3.1. Organocatalysts activate the Michael acceptor *via* formation of an iminium species:

The α,β-unsaturated aldehydes or ketones react with chiral amines, generate iminium ion intermediates, and after reaction with various nucleophiles deliver the Michael addition products (Scheme 7).[10a]



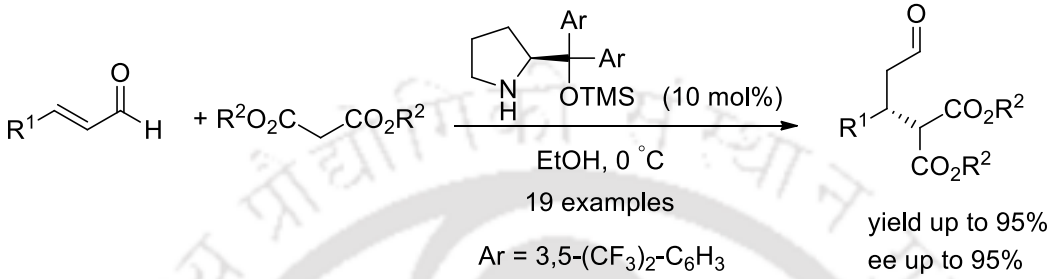
Scheme 7. Activated Michael acceptor by iminium intermediates

Hanessian group reported the first example of iminium catalyzed asymmetric Michael reaction of cyclohexenone with nitroalkanes by using L-proline catalyst in combination with *trans*-2,5-dimethylpiperazine as an additive. A variety of substrates such as cyclopentenone, cycloheptenone, cyclic nitroalkanes and long chain acyclic nitroalkanes were utilized for the reaction and provided the corresponding products with excellent yields and enantiomeric excesses (Scheme 8).[22a]



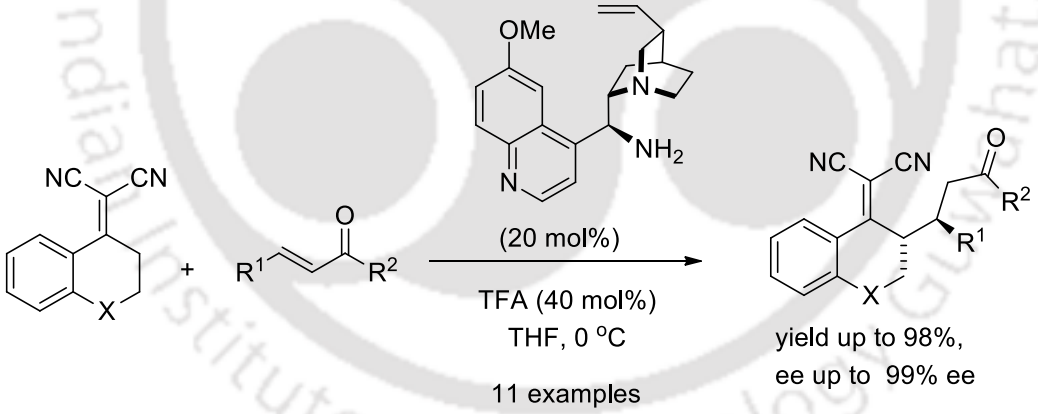
Scheme 8

Recently, α,α-diarylprolinol ether derived catalysts became popular in organocatalytic Michael addition reaction *via* iminium strategy. Jørgensen and co-workers first utilized this type of catalyst in asymmetric organocatalytic Michael addition reaction and performed a reaction between malonates and α,β-unsaturated aldehydes through iminium ion intermediates to achieve highly enantiopure oxo-esters (Scheme 9).[23]



Scheme 9

In 2007, Chen group first introduced the cinchona alkaloid derived primary amine catalyzed Michael addition reaction of α,α-dicyanoalkenes with simple enones through iminium ion intermediates. Using this protocol, a series of Michael addition products were attained with excellent enantioselectivities and yields (Scheme 10).[24]

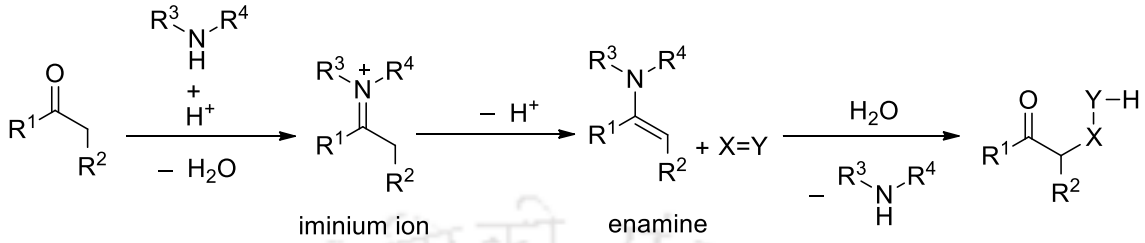


Scheme 10

1.3.2. Activation of ketone or aldehyde donors *via* formation of an enamine intermediate using organocatalysts:

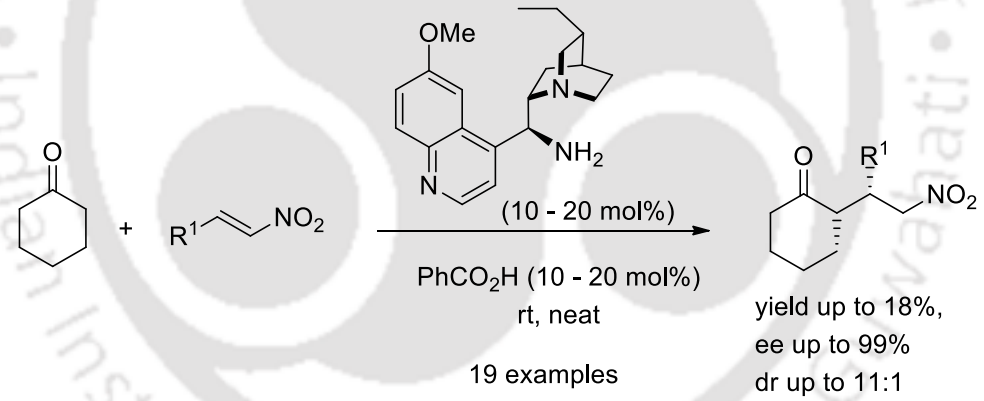
There were many reports on organocatalyzed asymmetric Michael addition to α,β-unsaturated enones or similar types of compounds through enamine intermediates. In enamine catalyzed reactions, chiral amines react with aldehydes or ketones, forming iminium intermediates which subsequently convert into enamine intermediates and consequently react with various electrophiles (Scheme 11).[11] Since 2000, the enamine

catalyzed asymmetric Michael addition reaction was explored by List,[25] Barbas III,[26] Enders,[27]and Andrey[28] group using catalysts such as the L-proline and its derivatives.



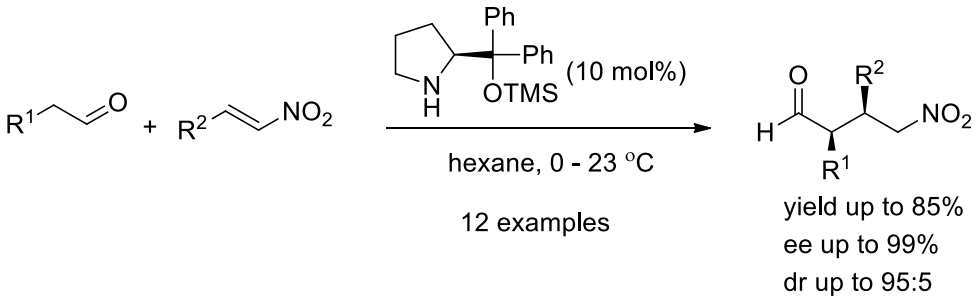
Scheme 11. Activation of Michael donors by formation of enamine intermediates

Connon group presented an asymmetric Michael reaction between cyclic ketones and β-nitrostyrenes *via* enamine intermediates using cinchona alkaloid derived hydroquinine amine catalyst and benzoic acid as an additive. Utilizing this method, other substrates such as linear ketones, linear and α-branched aldehydes also delivered the corresponding Michael products with good yields and diastereoselectivities (Scheme 12).[29]



Scheme 12

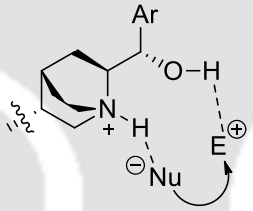
Hayashi *et al.* utilized diphenylprolinol silyl ether catalyst in asymmetric Michael addition reaction of aldehydes with nitroolefins through enamine intermediates and this reaction delivered excellent diastereo- and enantioselective Michael products (Scheme 13).[30]



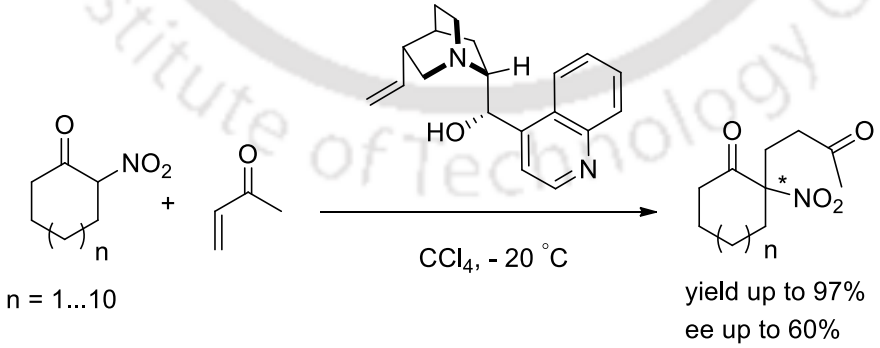
Scheme 13

1.3.3. Organocatalysts forming base complex with Michael donors as well as acceptors:

In 1975, Wynberg group reported quinine catalyzed asymmetric Michael addition reaction through base complex intermediates and illustrated the Bronsted base activity of quinuclidine nitrogen of cinchona alkaloid catalysts (Scheme 14).[31] Later, Hesse group (1993) demonstrated Michael addition of methylvinylketone with 2-nitrocycloalkanes *via* base complex intermediates using the cinchonine catalyst (Scheme 15).[32]



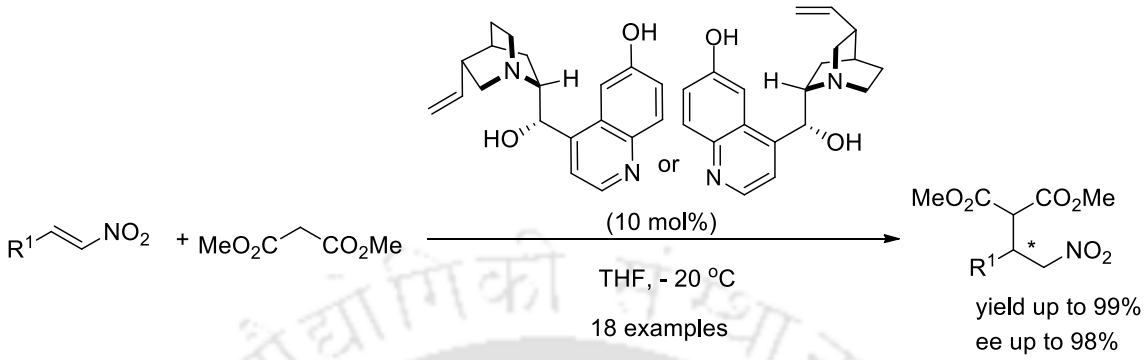
Scheme 14. Formation of base complex intermediates with Michael donors and acceptors.



Scheme 15

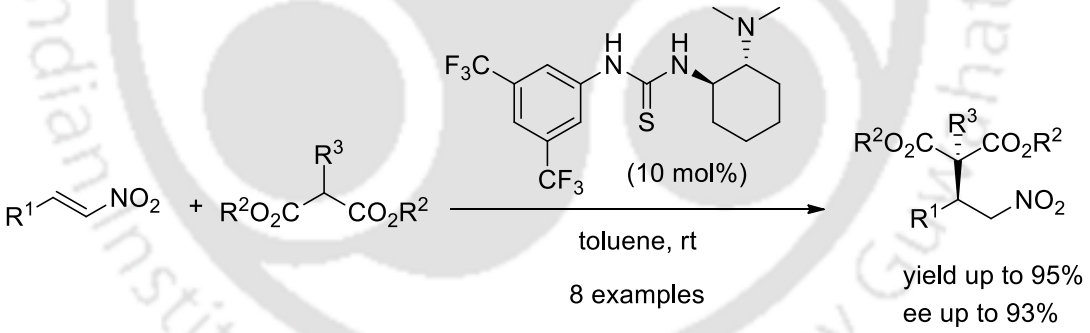
The cinchona alkaloid catalyzed highly enantioselective Michael addition reaction of malonates with nitroalkenes was first demonstrated by Deng group in 2004. The reaction

delivered comparable results using both quinine and quinidine derived catalysts (Scheme 16).[33]

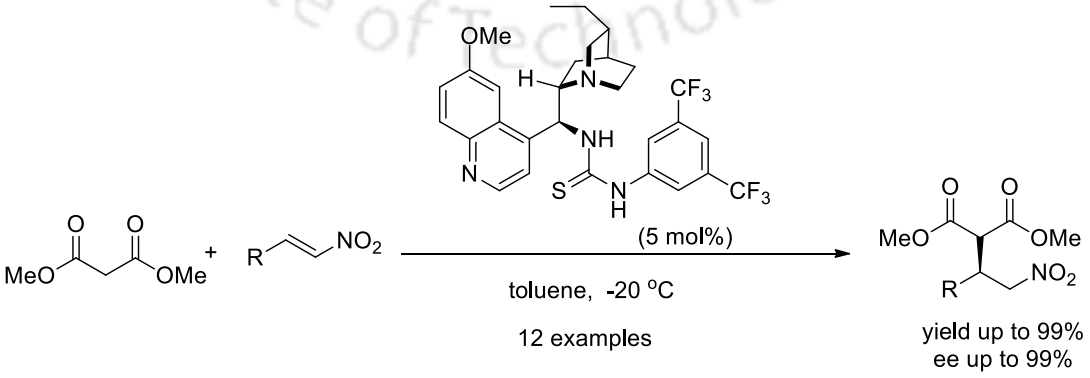


Scheme 16

Recently, bifunctional catalysts were effectively used in asymmetric Michael addition reactions. Takemoto group first introduced cyclohexyl derived bifunctional tertiary amine thiourea catalyst and employed in Michael reaction of malonates with nitroolefins (Scheme 17).[34] Moreover, Connon group also reported similar reaction using cinchona alkaloid bifunctional catalyst to furnish highly enantioenriched Michael adducts (Scheme 18).[35]

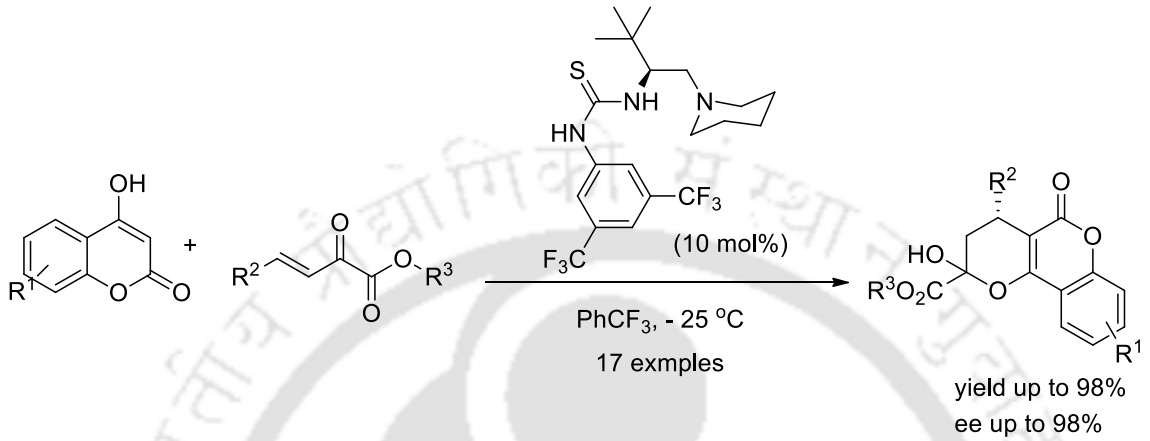


Scheme 17



Scheme 18

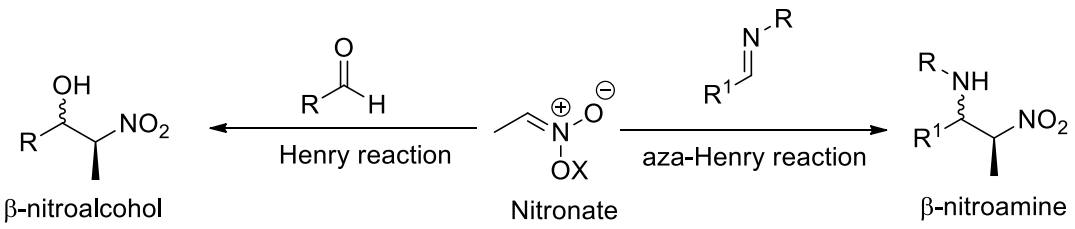
In 2010, the tertiary-leucine derived bifunctional thiourea catalyzed Michael addition reaction was established by Wang and co-workers. The reaction was performed between β,γ-unsaturated-α-keto esters and 4-hydroxycoumarins for the synthesis of coumarin compounds with excellent enantioselectivities (Scheme 19).[36]



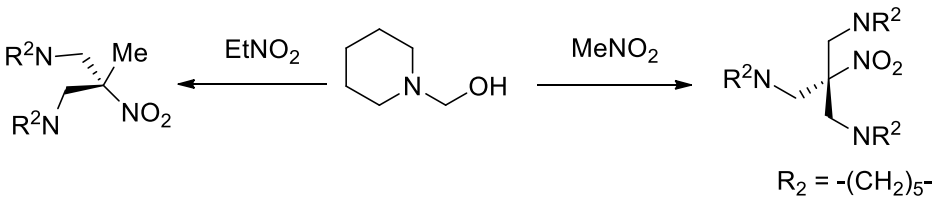
Scheme 19

1.4. Aza-Henry reaction:

The aza-Henry reactions are the nucleophilic addition of nitronate species to imines (Scheme 20).[37] This reaction has been effectively used in the synthesis of chiral intermediates which were eventually converted to different pharmaceutical targets and chiral auxiliaries. This reaction was first introduced by Louis Henry in 1896 and was performed between methanolamine (derived from formaldehyde and piperidine) with nitromethane or nitroethane for the synthesis of tri- and dipiperidine (Scheme 21).[38] In 1912, Mannich reaction has been established by Carl Ulrich Franz Mannich. In this reaction, enolates react with imines to deliver β-amine products.[39] The reaction mechanism is quite similar to the aza-Henry reaction. Thus, it is believed that nitro-Mannich reaction is alternative name of the aza-Henry reaction.

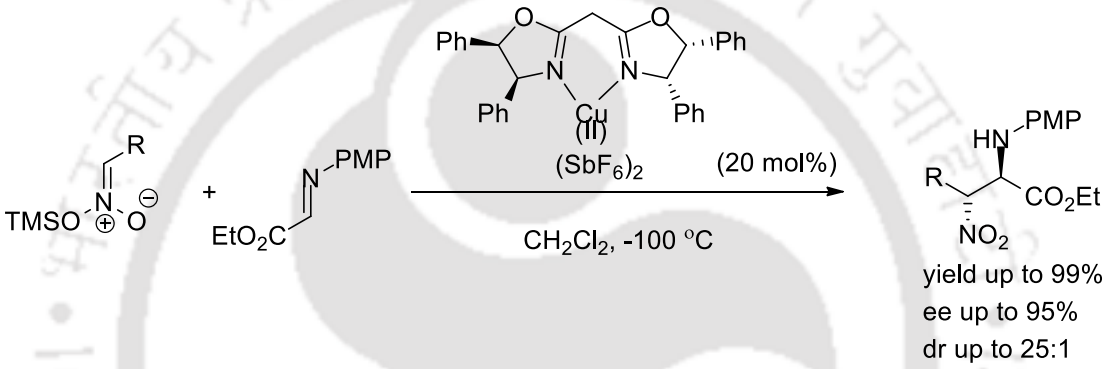


Scheme 20. Mechanism of Henry and aza-Henry reaction



Scheme 21

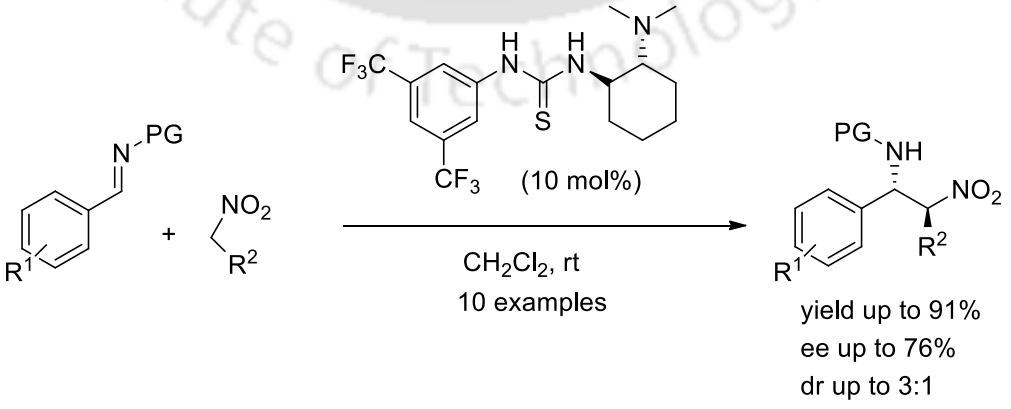
Jørgenson and co-workers demonstrated first asymmetric aza-Henry reaction of TMS-nitronates with ethylglyoxylate-*N*-PMP-imines. The reaction was performed by using Cu(II) catalyst with *cis*-DiPh-BOX ligand, to achieve β-nitroamines with excellent yields, enantio-and diastereoselectivities (Scheme 22).[40]



Scheme 22

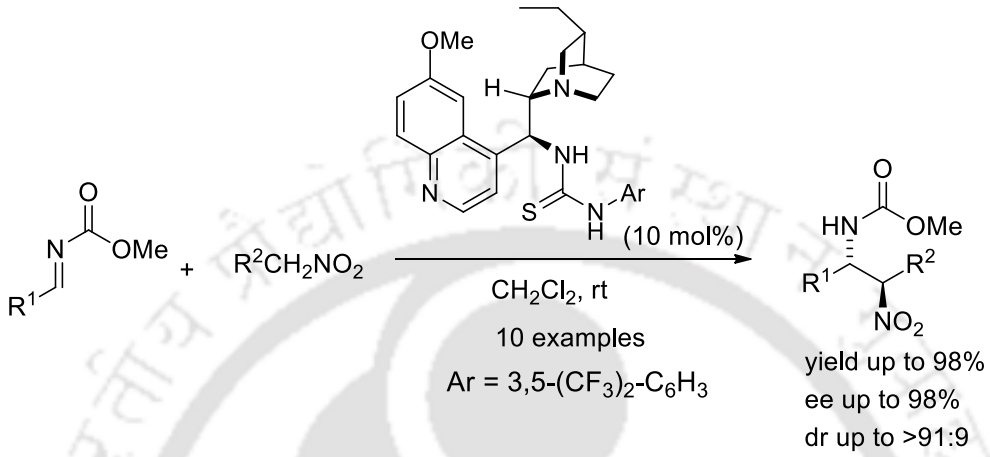
1.4.1. Organocatalytic asymmetric aza-Henry reaction:

The bifunctional thiourea catalyst was first introduced in asymmetric aza-Henry reaction by Takemoto group in 2004. In this reaction nitroalkanes and *N*-phosphinoylaryl imines were utilized for the chiral synthesis of β-nitroamines with good enantio- and diastereoselectivities (Scheme 23).[41]



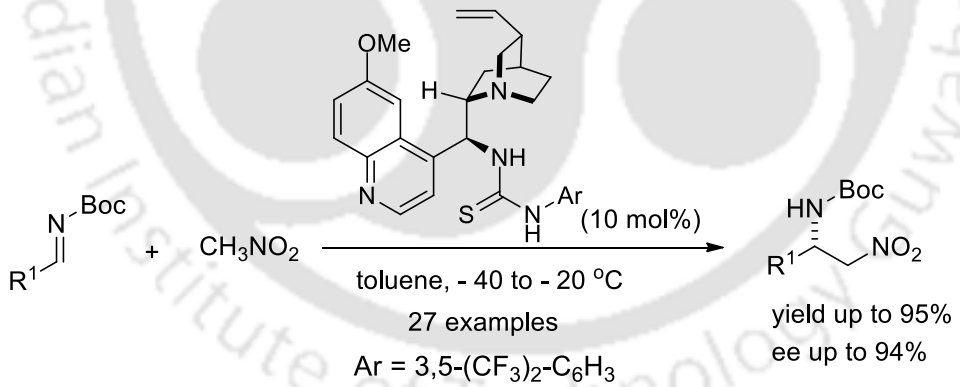
Scheme 23

In 2006, cinchona derived bifunctional thiourea catalyzed asymmetric aza-Henry reaction of methyl carbamate aryl imines with nitroalkanes was first published by Schaus *et al.* A variety of amine compounds with high enantio- and diastereoselectivities were synthesized using this protocol (Scheme 24).[42]



Scheme 24

Later, Ricci *et al.* reported a similar nitro-Mannich reaction using quinine-based thiourea catalyst. The reaction utilized *N*-Boc-aryl imines and nitromethanes to provide β-nitroamines with good to excellent yields and enantioselectivities (Scheme 25).[43]



Scheme 25

1.5. References:

1. (a) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2134. (b) Fischer, E. *Ber.Dtsch. Chem. Ges.* **1890**, *23*, 3684. (c) Lichtenthaler, F. W. *Angew. Chem. Int. Ed.* **1992**, *31*, 1541.
2. Reisinger, C. M.; Pan, S. C.; List, B. *New Concepts for Catalysis* Beilstein-Institut, **2009**, 35.
3. Bredig, G.; Fiske, P. S. *Biochem.* **1912**, *46*, 7.

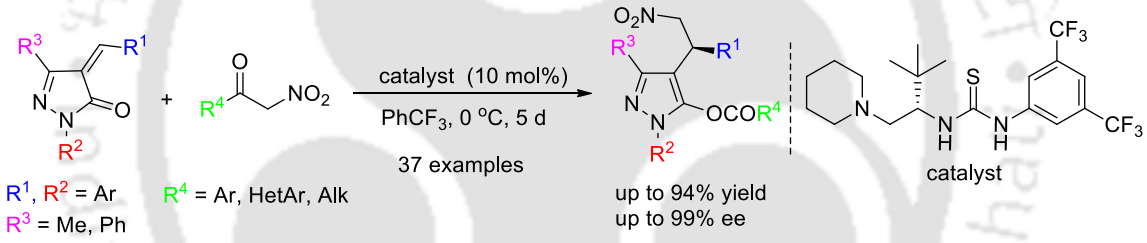
4. (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
5. Lelais, G.; MacMillan, D. W. C. *New Frontier in Asymmetric Catalysis* Wiley-Interscience, **2007**, p-313.
6. (a) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9. (b) Pracejus, H.; mätje, H. *J. Prakt. Chem*. **1964**, *24*, 195.
7. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615.
8. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed*. **1971**, *10*, 496.
9. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
10. (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336.
11. Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.
12. Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.
13. Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
14. Berkessel, A.; Gröger, H. *Asymmetric organocatalysis* John Wiley & Sons, **2006**, p-10.
15. Michael, A. *J. Prak. Chem.* **1887**, *35*, 349.
16. Wynberg, H.; Helder, R. *Tetrahedron lett.* **1975**, *16*, 4057.
17. List, B.; Pojarlier, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
18. (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron lett.* **2001**, *42*, 4441. (b) Barbas, C. F., III. *Angew. Chem. Int. Ed.* **2008**, *47*, 42.
19. Krause, N.; Roder, H. *Synthesis* **2001**, *2*, 171.
20. Berner, O. M.;Tedeschi, L.; Enders, D. *Eur. J. Org. Chem*. **2002**, 1877.
21. Christoffers, J.; Baro, A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1688.
22. (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *32*, 11223.
23. Brandau, S.; Landa, A.; Franzn, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *118*, 4411.
24. Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389.

25. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.
26. (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.*, **2001**, *3*, 3737. (b) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527.
27. Enders, D.; Seki, A. *Synlett* **2001**, 26.
28. Alexakis, A.; Andrey, O. *Org. Lett*. **2002**, *4*, 3611.
29. McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.
30. Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.
31. (a) Wynberg, H.; Helder, R. *Tetrahedron lett.* **1975**, *16*, 4057. (b) Hermannl, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. (c) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc*. **1981**, *103*, 417. (d) Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.
32. Latvala, A.; Stanchev, S.; Linden, A.; Hesse, M. *Tetrahedron: Asymmetric* **1993**, *4*, 173.
33. Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc*. **2004**, *126*, 9906.
34. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672.
35. (a) Connon, S. J. *Chem. Commun*. **2008**, 2499. (b) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 6200. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (d) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475.
36. Gao, Y.; Ren, Q.; Wang, L.; Wang, J. *Chem. Eur. J.* **2010**, *16*, 13068.
37. Noble, A.; Anderson, J. C. *Chem. Rev*. **2013**, *113*, 2887.
38. Henry, L. *Bull. Acad. R. Belg.* **1896**, *32*, 33.
39. Mannich, V. C.; Kröshc, W. *Aratipyrinderivah* **1912**, *9*, 641.
40. Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843.
41. Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto Y. *Org. Lett.* **2004**, *6*, 625.
42. Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499.
43. Bernardi, L.; Fini, F.; Herrera, R. P.; Sgarzania, V.; Riccia, A. *Tetrahedron* **2006**, *62*, 375.

Organocatalytic Asymmetric Michael/Hemiketalization/Retro-aldol Reaction of *α*-Nitroketones with Unsaturated Pyrazolones: Synthesis of 3-Acyloxy Pyrazoles*

Abstract:

An organocatalytic asymmetric cascade Michael/hemiketalization/retro-aldol reaction between unsaturated pyrazolones and *α*-nitroketones is described. Bifunctional thiourea catalyst was found to be efficient for this reaction. With 10 mol% of catalyst, high yields as well as excellent enantioselectivities were attained for a variety of 3-acyloxy pyrazoles under mild reaction conditions.



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

2.1. Introduction:

Pyrazoles and pyrazolones are important nitrogen containing heterocyclic motifs. These motifs are predominant in most of the bioactive compounds having pharmaceutical and agricultural activities.[1] In particular, 3-hydroxypyrazole derivatives are obtained by aromatization of pyrazolones. 3-hydroxypyrazole derivatives have interesting enzyme inhibition[2a-d] and activation[2e] properties, and have been broadly used in antidiabetic,[2a-d] anticancer,[2f-h] anti-inflammatory,[2a] antipsychosis,[2a] insecticidal,[2i] and herbicidal[2j] studies. Phenazone acts as an antipyretic and analgesic drug.[3] Metamizole is a powerful analgesic and antipyretic drug.[4] Few aryl-substituted 3-(3-dimethylaminopropyloxy)-1*H*-pyrazoles display potent activation of soluble guanylate cyclase and the inhibition of platelet aggregation (Figure 1).[2e] Similarly, *o*-pyrazole glucopyranoside and galactopyranoside derivatives such as remogliflozin etabonate (Figure 1)[2d] are the inhibitors of human sodium-glucose co-transporters 1 and 2 (SGLT1 and SGLT2) and may be used for the treatment of diabetes.

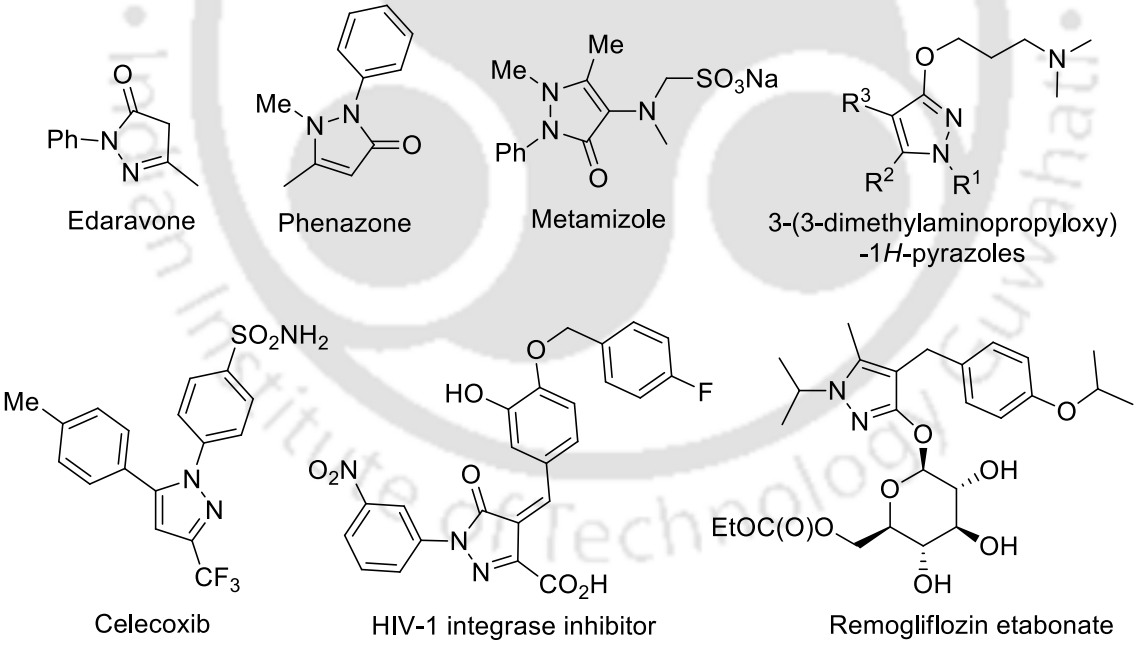


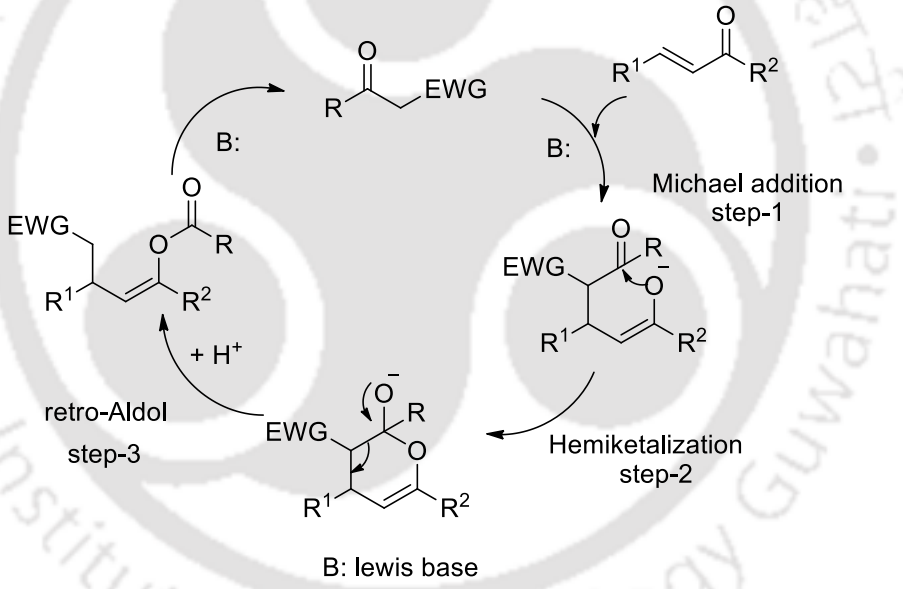
Figure 1. Biologically active pyrazoles and pyrazolones derivatives.

The pyrazole scaffold is present in various drugs such as celecoxib[5] and HIV-1 integrase inhibitor. Integrase inhibitor (HIV-1), an antiretroviral drug, has been designed to stop the action of integrase.[6] Because of the importance of the pyrazole skeleton, the asymmetric synthesis of pyrazoles bearing stereocenters has become an attractive goal,

and many efficient synthetic approaches have been established.[7] Thus, the development of efficient methods for the enantioselective construction of 3-hydroxy as well as 3-acyloxy pyrazoles are important for the discovery of new chiral drugs and other utilities.

2.2. Michael/hemiketalization/retro-aldol reaction:

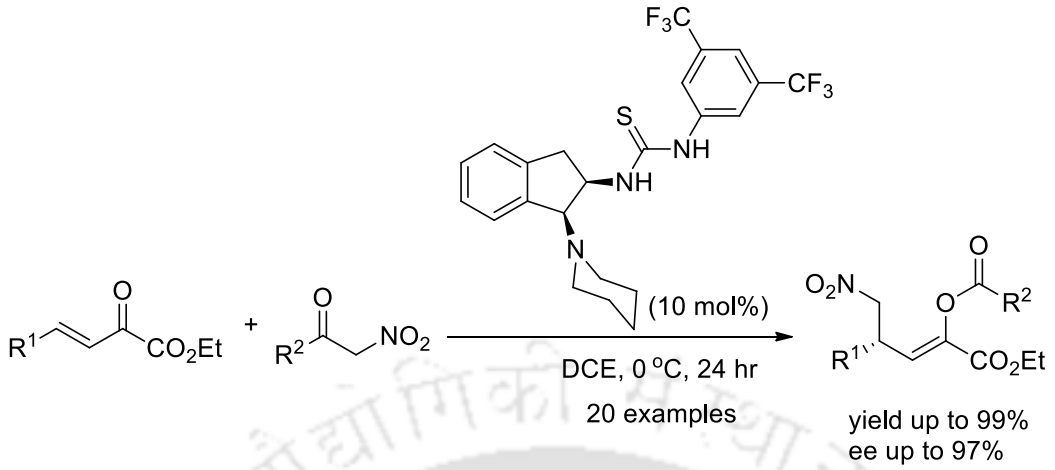
Michael/hemiketalization/retro-aldol reaction was performed employing 1,3-dicarbonyl compounds, nitroketones, or other carbon anions with unsaturated enones in combination with Lewis base catalyst. The final products were obtained by three sequential reaction steps *via* one pot synthesis and intermediates have been proved by NMR studies.[10] In this reaction, first step was Michael addition reaction, then intramolecular hemiketalization reaction was taken place and the final product was obtained followed by retro-aldol reaction (Scheme 1).[8-10]



Scheme 1. Michael/hemiketalization/retro-aldol reaction.

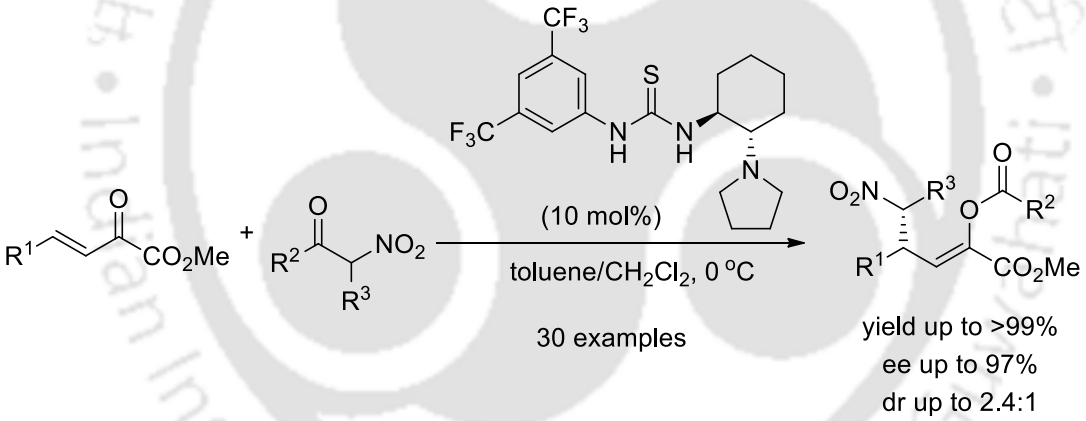
2.2.1. Previous reports on Michael/hemiketalization/retro-aldol reaction:

Wang *et al.* reported asymmetric organocatalytic cascade Michael/hemiketalization/retro-Henry reaction of β,γ-unsaturated ketoesters with α-nitroketones. High enantioselectivity and yield have been obtained in this reaction by using indane based bifunctional tertiary amine thiourea catalyst (Scheme 2).[8]



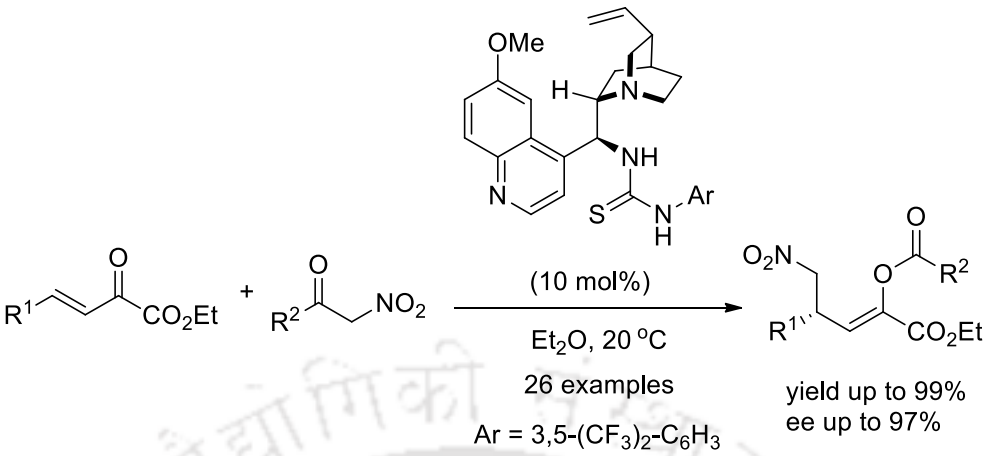
Scheme 2

Yan group utilized similar type of protocol by using pyrrolidine based cyclohexyl thiourea catalyst. Excellent enantioselectivities and moderate diastereoselectivities were achieved using α-substituted α-nitroketones (Scheme 3)[9]



Scheme 3

Chan and co-workers developed highly enantioselective acyl transfer products of β,γ-unsaturated ketoesters with α-nitroketones by using quinine derived thiourea catalyst. High enantioselectivities have been achieved with aromatic as well as aliphatic substituted α-nitroketones. Previously, Wang and Yan groups reported three steps reaction *via* one pot synthesis, but they didn't give any experimental proof. Whereas, Chan group identified those intermediates by NMR studies (Scheme 4).[10]

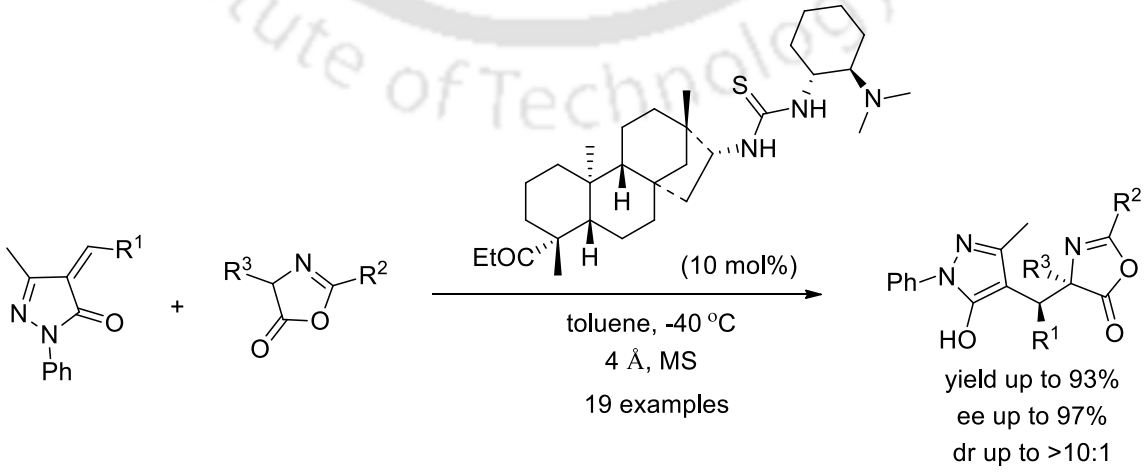


Scheme 4

2.3. Previous reports on the synthesis of asymmetric 3-hydroxy pyrazoles and 3-alkaloxy pyrazoles:

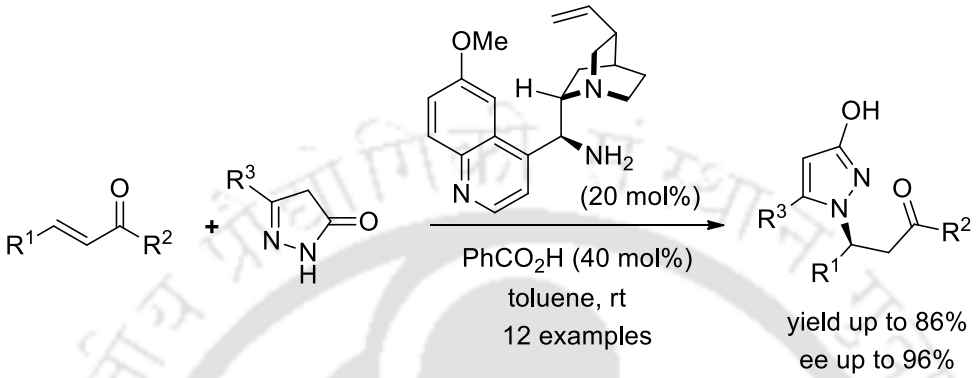
In recent years, unsaturated pyrazolones have been exploited as electrophile in a variety of organocatalytic Michael and cascade reactions. Analogously, pyrazolones have also been found to be suitable nucleophiles in a range of asymmetric reactions. Some examples of asymmetric synthesis of 3-hydroxy and 3-aceloxy pyrazoles have been shown.

Wang *et al.* devised the synthesis of an asymmetric 3-hydroxy pyrazoles through the Michael/aromatization reaction of azlactones with unsaturated pyrazolones by using isosteviol derived amine thiourea as the organocatalyst. These products were obtained in good yields with good diastereoselectivities and moderate to excellent enantioselectivities (Scheme 5).[11]



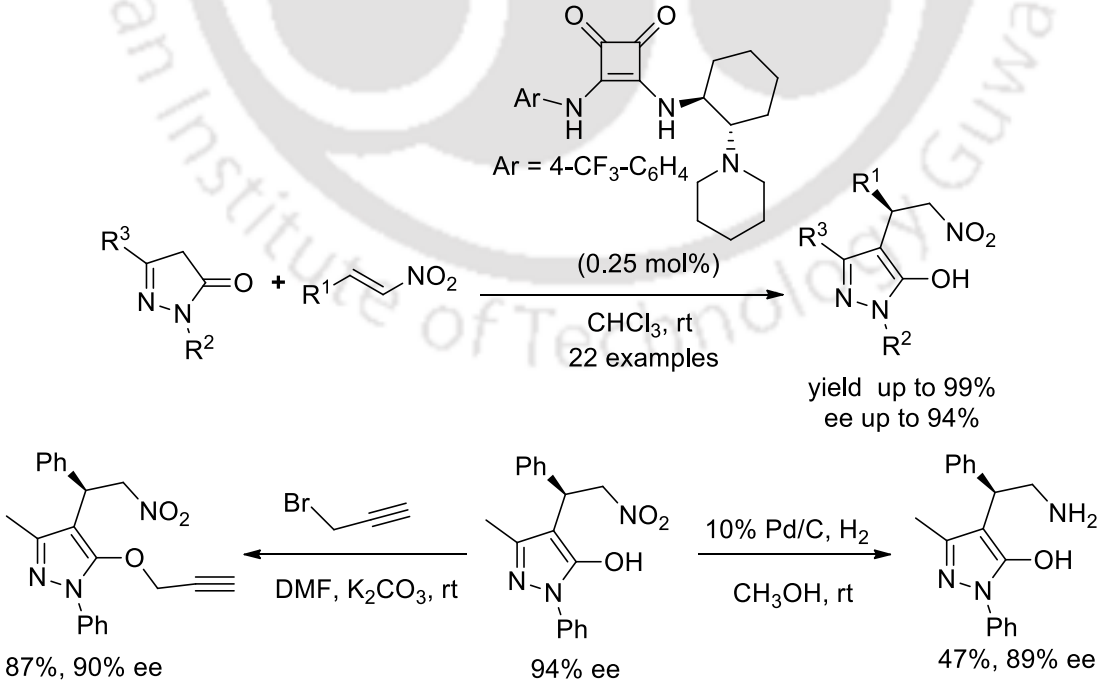
Scheme 5

Zhao and co-workers established an aza-Michael addition reaction for the enantioselective synthesis of β-(3-hydroxypyrazol-1-yl) ketones by using epi-quinine amine catalyst. The 2-pyrazolin-5-one anions were first attempted to react with Michael acceptors *via* aza-Michael addition reaction (Scheme 6).[12]



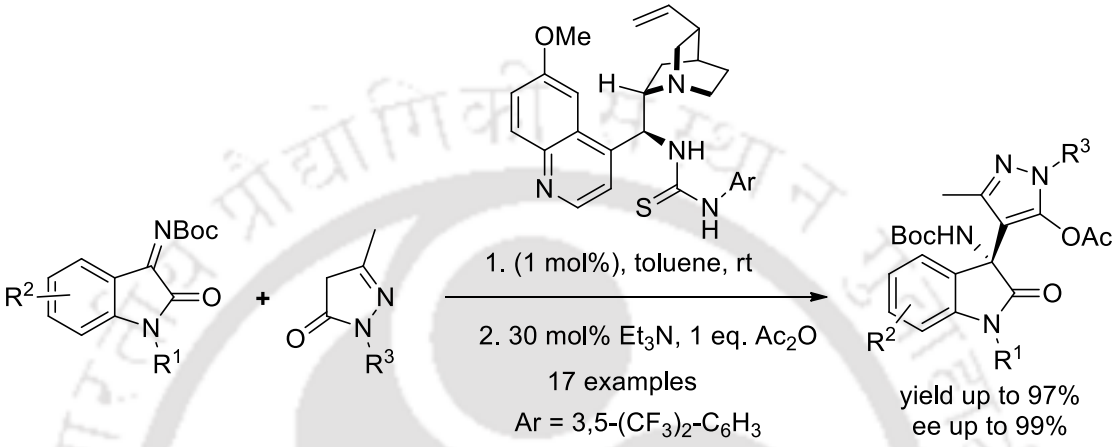
Scheme 6

The squaramide catalyzed Michael reaction of pyrazole and β-nitrostyrene for the highly enantioselective synthesis of 3-hydroxy pyrazoles with high yields has been established by Du and co-workers. They reported the two synthetic transformation of Michael addition product; Pd/C mediated hydrogenation of nitro to amine with 89% ee and synthesis of 3-alkynyl pyrazole with 90% ee (Scheme 7).[13]



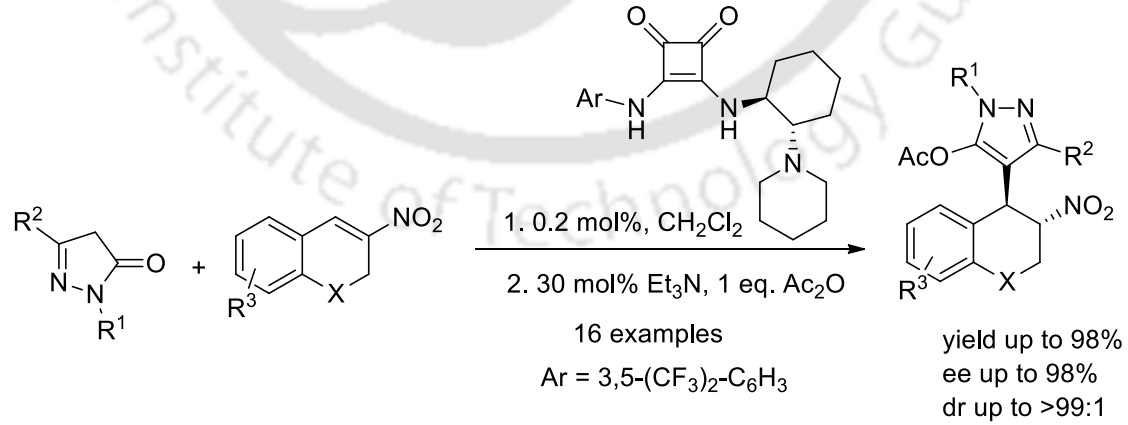
Scheme 7

Pedro group developed a new method for the synthesis of enantiopure 3-acetoxy pyrazoles by using low loading of quinine derived thiourea catalyst. The 3-acetoxy pyrazoles have been synthesized with highly enantioselectivities by adding pyrazolones with isatins derived ketimines and *in situ* treated with Ac_2O-Et_3N high enantioselectivity was achieved (Scheme 8).[5]



Scheme 8

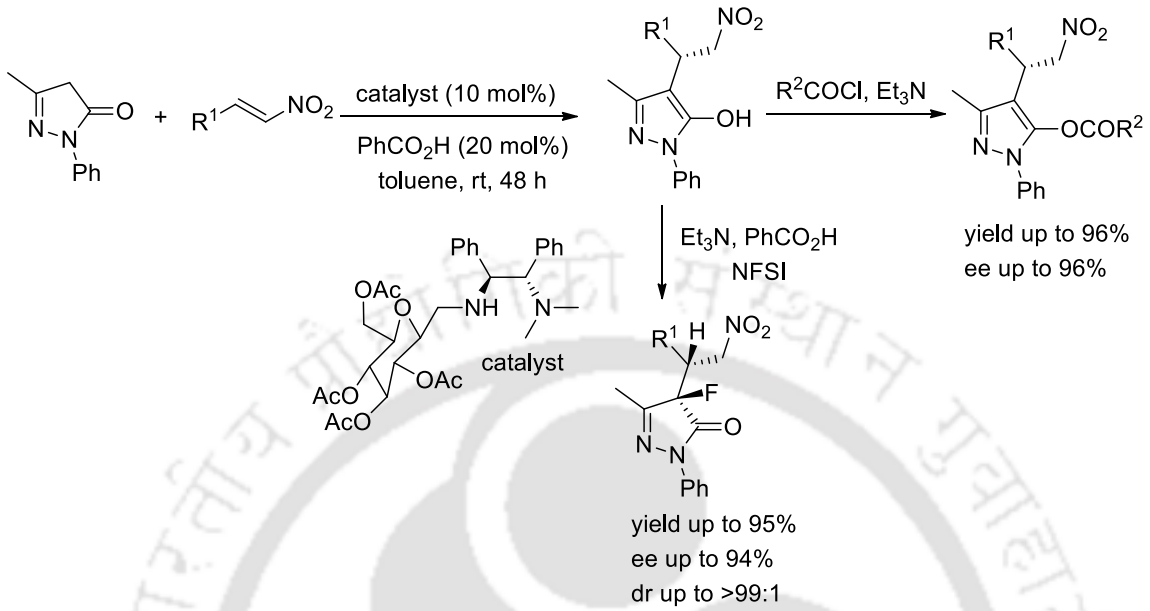
Du group established the chiral synthesis of 3-acetoxy pyrazoles containing both pyrazoles and chroman moieties by using cyclohexyl derived squaramide catalyst. Here they have shown Michal addition reaction of pyrazolin-5-ones with 3-nitro-2*H*-chromenes and *in situ* added Ac_2O-Et_3N for the synthesis of enantioselective 3-acetoxy pyrazoles with excellent diastereoselectivities (Scheme 9).[14]



Scheme 9

An organocatalytic sequential 1,4-addition/dearomative-fluorination reaction of pyrazolones and nitroolefins in the presence of NFSI has been developed by using chiral tertiary amine thiourea catalyst and benzoic acid. The enantioselectivities of 3-

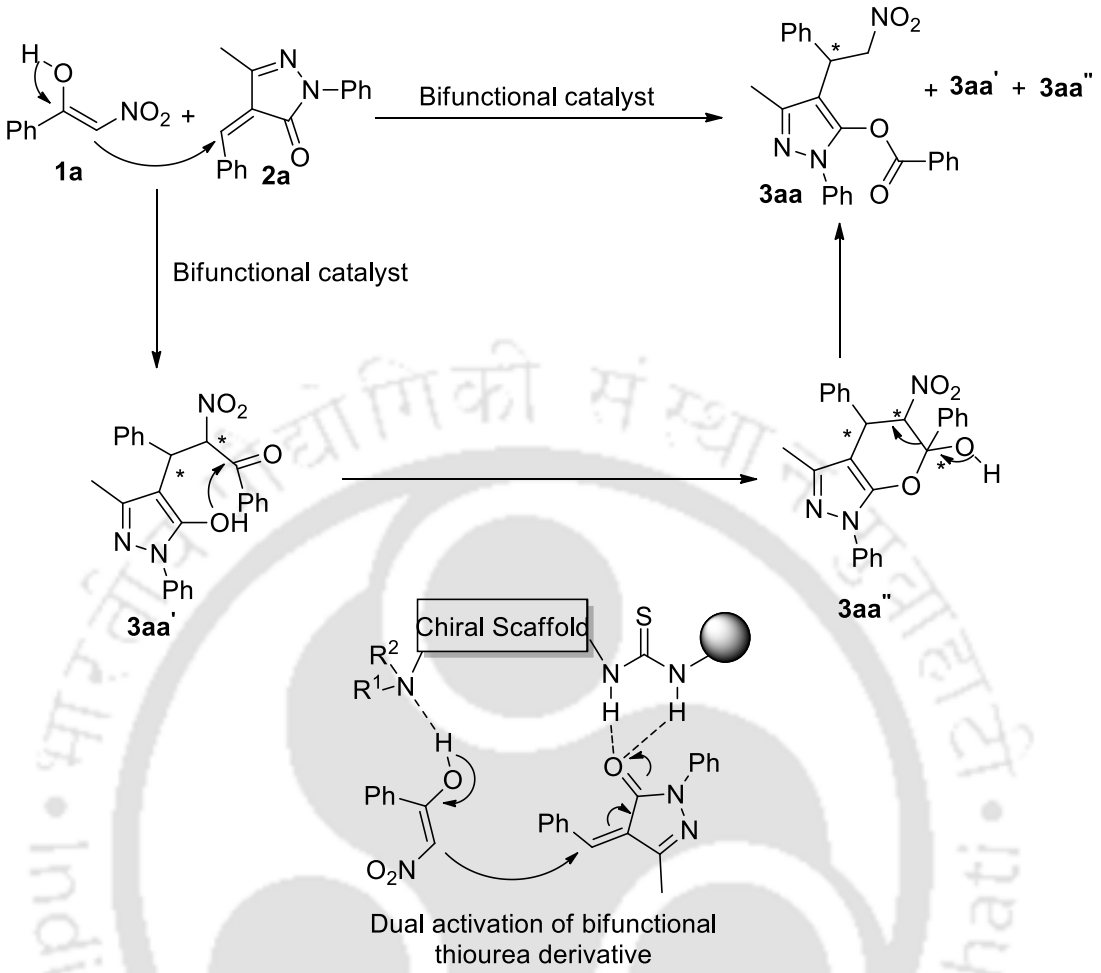
acetoxy/alkoxy pyrazoles were obtained by reacting 3-hydroxy pyrazoles with R_2COCl-Et_3N (Scheme 10).[15,16]



Scheme 10

2.4. Concept:

The use of α-nitroketones is not as widespread and their reactivity has rarely been explored despite their functionality, which offers a useful starting point for Michael addition reaction. From literature study, it was found that chiral 3-acetoxy pyrazole was obtained by two step reactions. Hence, we intended to focus on an organocatalytic asymmetric Michael/hemiketalization/retro-aldol reaction of α-nitroketones with unsaturated pyrazolones for the synthesis of chiral 3-acetoxy pyrazoles by simple one step reaction. We projected that α-nitroketones would be activated *via* enolization by tertiary amine group of the bifunctional thiourea derivative and simultaneously would be activated electrophile unsaturated pyrazolones by hydrogen bonding from the Brønsted acidic protons of the thiourea N-Hs. The reaction may quite challengeable to the synthesis of **3aa**, because three possible products (**3aa**, **3aa′**, **3aa′**) might be formed in the reaction (Scheme 11).

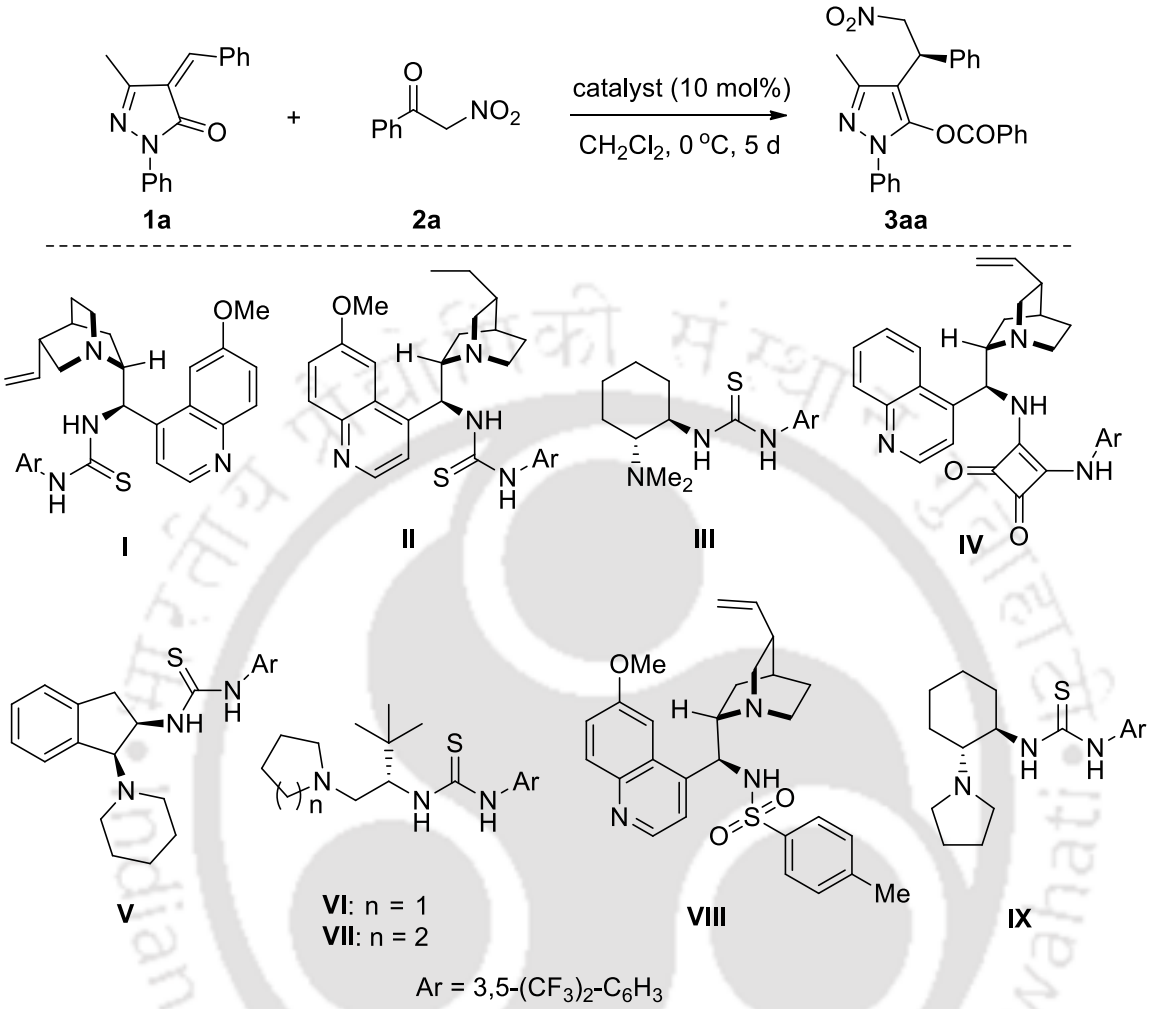


Scheme 11

2.5. Results and discussion:

The investigations were initiated by the reaction between alkylidene pyrazolone **1a** and 2-nitro-1-phenylethanone **2a** with quinidine derived bifunctional thiourea catalyst **I** in CH_2Cl_2 solvent at 0 ^oC (Table 1, entry 1). After 3 d, the desired product **3aa** was isolated with 80% yield and 44% enantiomeric excess. The product **3aa** was confirmed by ^1H and ^{13}C NMR analysis. The enantioselectivity of **3aa** was not improved using hydroquinine derived thiourea catalyst **II** (entry 2). Similar kind of enantioselectivity was achieved with Takemoto catalyst **III** and squaramide catalyst **IV** (entries 3-4). A higher enantioselectivity was achieved with catalyst **V** having indane moiety (entry 5). Then, *tert*-leucine derived bifunctional thiourea catalysts **VI** and **VII** were examined. These catalysts were found to be efficient and in particular catalyst **VII** having piperidine motif provided the product **3aa** in 89% yield with 70% ee (entry 7). Enantioselectivity of product **3aa** was decreased with hydroquinine derived catalyst **VIII** (entry 8).

Table 1. Catalyst optimization



entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	80	44
2	**II**	82	30
3	**III**	84	36
4	**IV**	76	36
5	**V**	85	61
6	**VI**	80	70
7	**VII**	**89**	**70**
8	**VIII**	85	30
9	**IX**	60	61

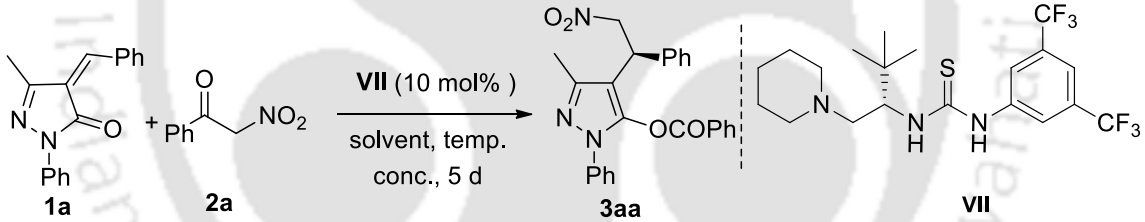
[a]0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL $PhCF_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

Product **3aa** was obtained in 61% ee with 60% yield by pyrrolidine based tertiary amine thiourea catalyst **IX** (entry 9). To improve the enantioselectivity of the desired product **3aa** further optimization was performed.

2.5.1. Solvent, temperature and concentration screening:

The effect of solvent on the yield and enantioselectivity was studied and delightfully promising results were attained (Table 2). For example, enhancement in enantioselectivity was observed using $CHCl_3$ and DCE solvent (entries 2-3). Non polar solvent such as toluene was found to be quite effective and afforded the product **3aa** in 90% ee (entry 4). Comparable results were obtained in $PhCF_3$, xylene and mesitylene (entries 5-7). The best results were obtained in $PhCF_3$ solvent, product **3aa** was isolated in 91% yield with 99% ee (entry 5). Low enantioselectivity was observed by increasing or decreasing temperatures (entries 8-9). Inferior results were obtained by changing the concentration of the reaction (entries 10-11).

Table 2. Optimizations of solvent, temperature and concentration



entry[a]	solvent	temp. (°C)	conc. (M)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	0	0.1	89	70
2	DCE	0	0.1	87	87
3	$CHCl_3$	0	0.1	89	82
4	toluene	0	0.1	88	90
5	**$PhCF_3$**	**0**	**0.1**	**91**	**99**
6	xylene	0	0.1	89	94
7	mesitylene	0	0.1	80	96
8	$PhCF_3$	rt	0.1	95	80
9	$PhCF_3$	–20	0.1	90	96
10	$PhCF_3$	0	0.05	92	96
11	$PhCF_3$	0	0.2	90	95

[a]0.05 mmol of **1a** and 0.05 mmol of **2a** in solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

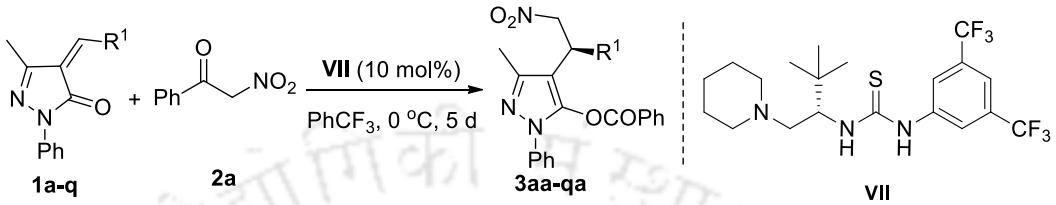
2.5.2. Substrate scope:

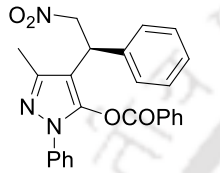
After finding the optimized conditions, the scope of the reactions was attempted. Initially a variety of pyrazolones **1** having different benzylidene substituents were tested (Table 3). Comparable results were obtained using various 4-substituted benzylidene pyrazolones having different electronic natures. 4-Methyl alkylidene pyrazolone **1b** provided product **3ba** with 86% yield and 97% ee. Similar output was found in product **3ca**. Bulky 4-substituted tertiary butyl product **3da** was also achieved good yield with good enantiomeric excess. 4-Halo substituted alkylidene pyrazolones **1e-1g** delivered products **3ea-3ga** with good yields and excellent enantiomeric excesses. Biphenyl benzylidene pyrazolone **1h** participated in the reaction and delivered product **3ha** with 91% yield and 82% ee. The enantioselectivity was decreased in 4-nitro containing unsaturated pyrazolone **1i** due to electron withdrawing effect. Next, *m*-substituted 3-acetoxy pyrazoles **3ja-3la** were obtained with good yields and enantioselectivities. Unsaturated pyrazolones **1m-1n** having 2-methyl and 2-fluoro substitutions were afforded products **3ma-3na** with excellent enantioselectivities. 2,4-Dimethyl substituted 3-acetoxy pyrazole **3oa** was achieved with better enantiomeric excess. While introducing heteroaryl moiety, the pyrazolone product **3pa** was obtained with poor enantioselectivity. After testing with aromatic unsaturated pyrazolones, next aliphatic pyrazolone was also treated with nitroketone **2a**. The cyclohexyl substituted pyrazole **1q** gave 74% enantioselectivity.

The generality of the reaction was further established by engaging pyrazolones **1** with varied *N*-substitutions (Table 4). Accordingly, a variety of pyrazolones **1r-v** with different *N*-substitutions were prepared and employed in the reaction. To our delight, the reactions progressed well irrespective of the electronic nature of the aryl groups and the products were attained in excellent enantioselectivities (Table 4, **3ra-va**). 4-Methyl *N*-substituted alkylidene pyrazolone **1r** provided product **3ra** with excellent enantioselectivity. 4-Halo containing *N*-substituted products **3sa-ta** were achieved with high enantioselectivities. An electron withdrawing aryl group was also incorporated in

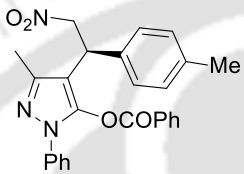
the reaction scope and product **3ua** was obtained in good enantioselectivity. Excellent yield and enantiomeric excess were achieved for the compound **3va** when 2-methyl *N*-substituted alkylidene pyrazolone **1v** was subjected in the reaction conditions.

Table 3. Scope of pyrazolones with varied benzylidene substituents[a,b,c]

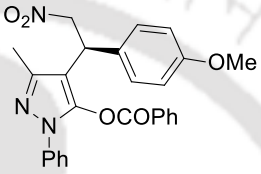




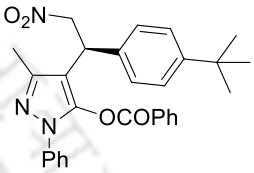
3aa, 91%, 99% ee



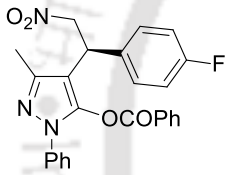
3ba, 86%, 97% ee



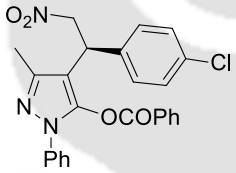
3ca, 85%, 97% ee



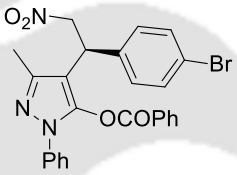
3da, 89%, 85% ee



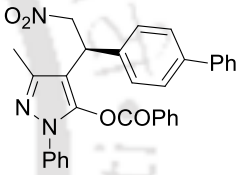
3ea, 65%, 97% ee



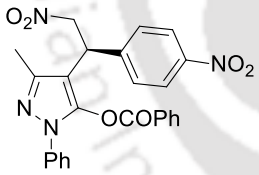
3fa, 93%, 98% ee



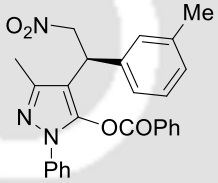
3ga, 93%, 94% ee



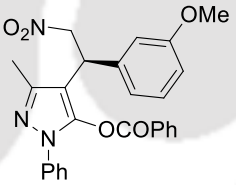
3ha, 91%, 82% ee



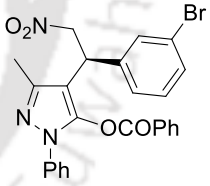
3ia, 85%, 75% ee



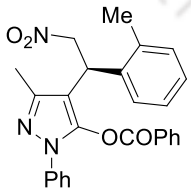
3ja, 88%, 93% ee



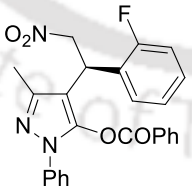
3ka, 83%, 88% ee



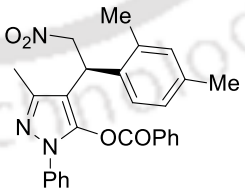
3la, 57%, 88% ee



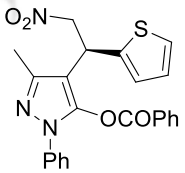
3ma, 93%, 95% ee



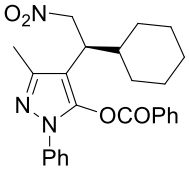
3na, 80%, 89% ee



3oa, 94%, 94% ee



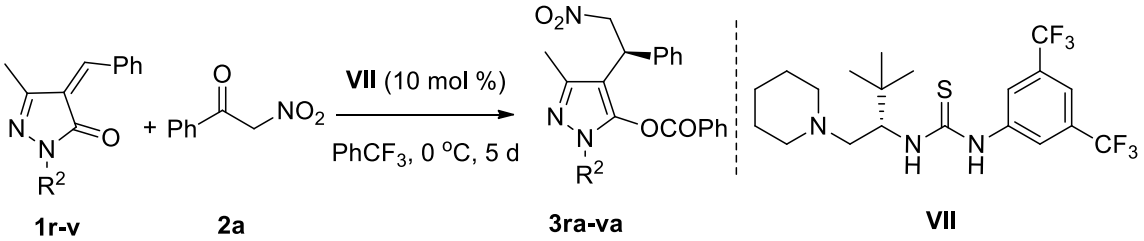
3pa, 70%, 68% ee

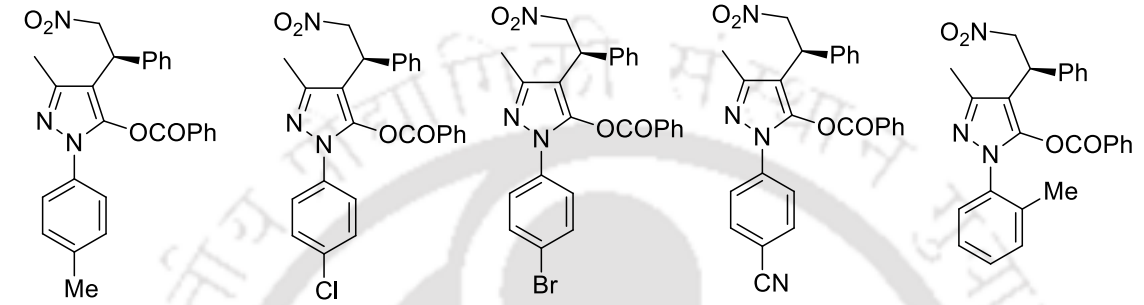


3qa, 65%, 74% ee

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 1mL $PhCF_3$ at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

Table 4. Scope of pyrazolones with varied *N*-substituents[a,b,c]





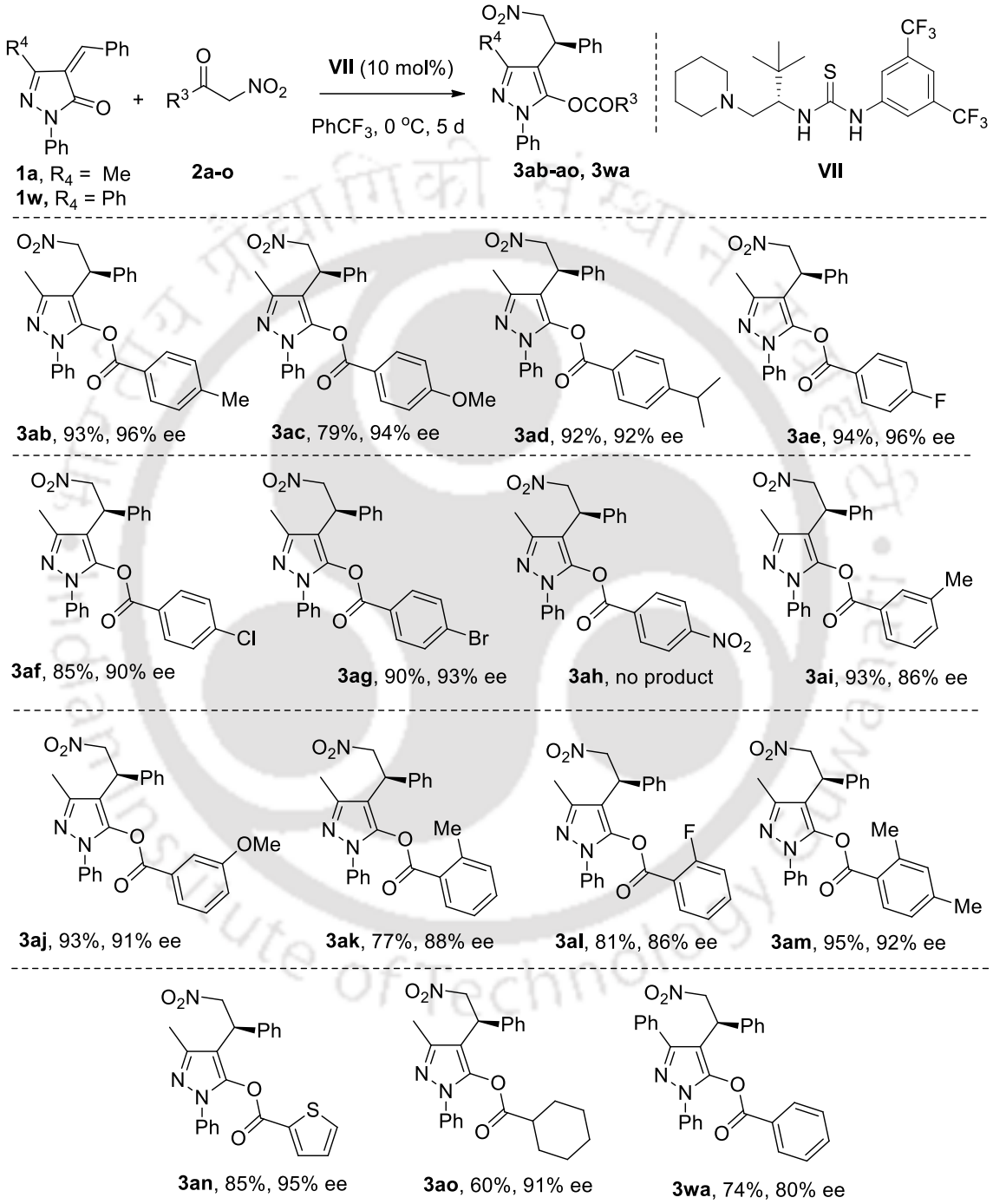
3ra, 82%, 96% ee **3sa**, 87%, 96% ee **3ta**, 81%, 92% ee **3ua**, 77%, 89% ee **3va**, 96%, 99% ee

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 1mL $PhCF_3$ at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC.

The next phase of experiments contained the screening of different α-nitroketones **2** in this method (Table 5). A wide range of aryl group containing α-nitroketones **2** could be employed in the reaction. At first, *para*-substituents were checked. The products **3ab** and **3ac** having 4-methyl and 4-methoxy groups were achieved with excellent enantiomeric excesses and good yields. Pleasing, excellent enantiomeric excess (92%) was also observed for product **3ad**. 4-Halo substituted nitroketones also provided excellent enantioselectivities (**3ae**-**3ag**). Interesting, 4-nitro substituted-α-nitro ketone **2h** did not deliver the product possibly due to the strong withdrawing effect. Then reaction of *meta*-substituted α-nitro ketones **2i** and **2j** containing 3-methyl and 3-methoxy group respectively provided **3ai** and **3aj** with excellent ees and yields. The *ortho*-substituents such as 2-methyl and 2-mthoxy *α*-nitro ketones, (**2k** and **2l**) furnished products **3ak** and **3al** with 88% and 86% ees respectively. 2,4-Dimethyl substituted α-nitro ketone **2m** was prepared and tested for the reaction, better result was obtained for **3am**. Heteroaromatic α-nitro ketone **2n** delivered the product **3an** with 95% enantiomeric excess. α-Nitroketone **2o** having cyclohexyl moiety was screened and gratifyingly excellent enantioselectivity was maintained. Hence, standard condition was highly appreciated for the synthesis of aliphatic substituted product **3ao** with excellent result. Finally, 1,3-

diphenyl-1*H*-pyrazolone **1w** participated in the reaction and delivered the corresponding product **3wa** with good enantiomeric excess.

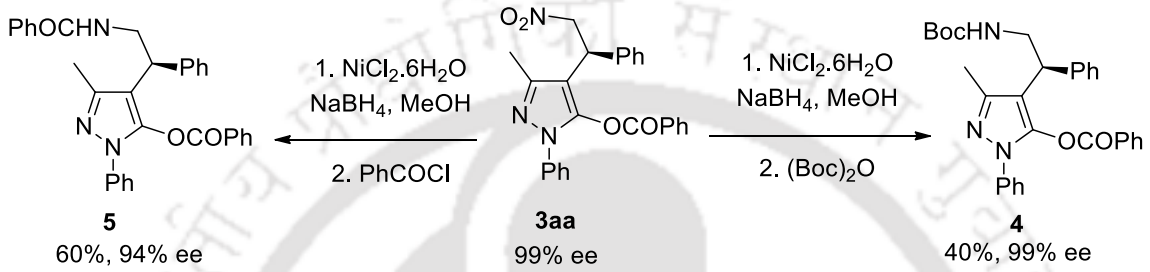
Table 5. Scope of α-nitroketones[a,b]



[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2** in 1mL $PhCF_3$ at 0 °C for 5 days. [b]Isolated yield after silica gel column chromatography and ee was determined by HPLC.

2.5.3. Synthetic transformations of 3aa:

To demonstrate the synthetic utility of our method, few reactions were carried out on **3aa** (Scheme 12). Treatment of nickel chloride-sodium borohydride on **3aa** followed by reaction with Boc anhydride, furnished compound **4** without loss of enantiopurity. Similar reaction with nickel chloride-sodium borohydride and benzoyl chloride provided amide **5** in acceptable yield though slight erosion in enantioselectivity was detected.



5
60%, 94% ee

3aa
99% ee

4
40%, 99% ee

Scheme 12

2.5.4. Absolute configuration:

The absolute configuration of the product **3af** was determined to be (*S*) by X-ray crystallography (Figure 3).[17] The absolute configuration of other products are expected to be same by analogy.

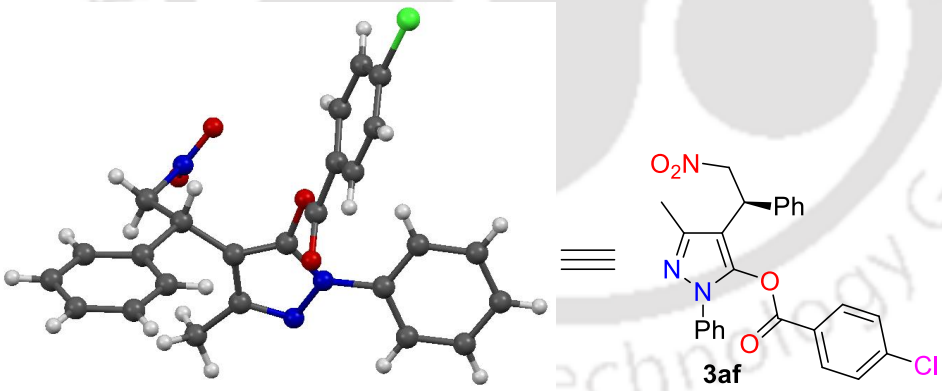
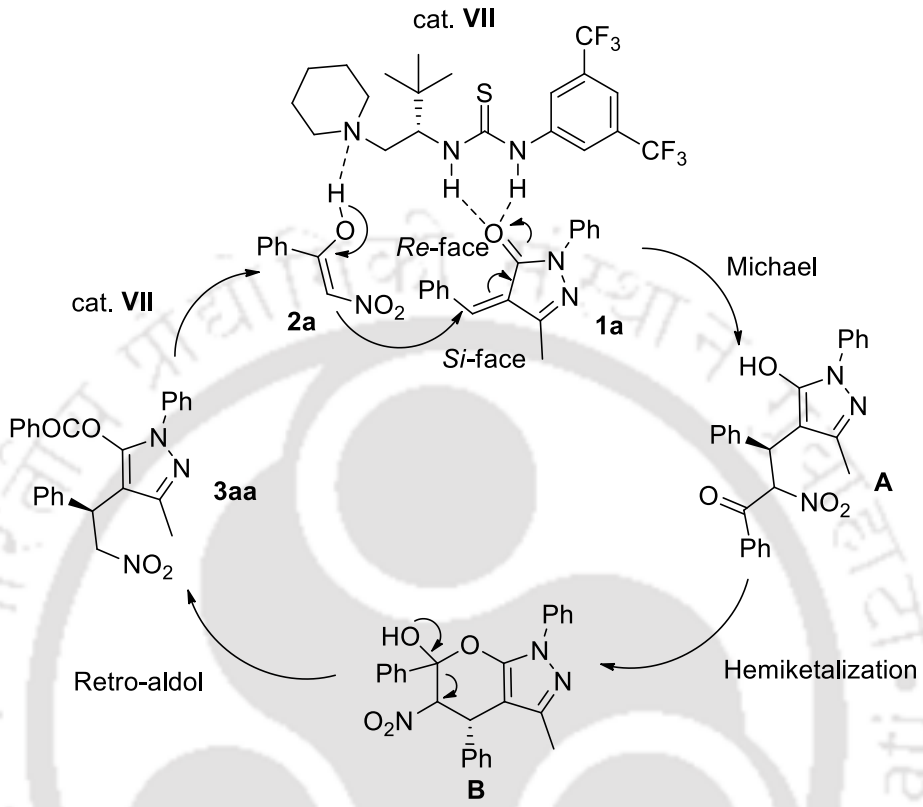


Figure 3. X-ray crystallography structure of compound **3af**.

2.5.5. Proposed mechanism:

Based on the absolute configuration a plausible mechanism has been depicted in Scheme 13. It is expected that *α*-nitroketone **2a** is activated by the piperidine moiety of the catalyst **VII** whereas thiourea motif binds with pyrazolone **1a**. Since the *Re*-face of **1a** is blocked by catalyst **VII**, addition take place from *Si* face to provide intermediate **A**. Then

A is converted to **B** *via* hemi-ketalization. Finally retro-aldol reaction of **C** delivers the product **3aa** (Scheme 13).



Scheme 13. Proposed mechanism.

2.6. Conclusion:

This chapter demonstrated a mild and operationally simple Michael/hemiketalization/retro-aldol reaction between unsaturated pyrazolones and α-nitroketones. This reaction furnished diverse 3-acyloxypyrazoles in good yields and with excellent enantioselectivities. Our method shall be useful for the rapid preparation of pharmaceutically and agriculturally importance 3-alkoxypyrazoles compounds.

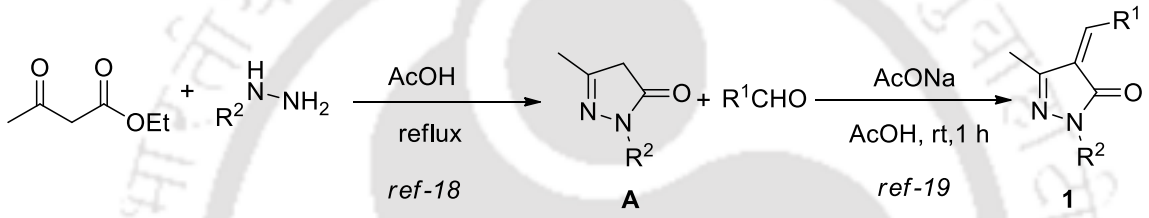
2.7. Experiment section:

2.7.1. General procedure for the synthesis of compound (1):

Ethyl acetoacetate (2.32 mL, 18.4 mmol) and corresponding phenylhydrazine (2.12 mL, 21.5 mmol) in 10 mL of acetic acid were allowed to reflux for 8 h, after which time the solution was cooled to ambient temperature and concentrated in vacuo. The crude

product was purified by silica gel flash chromatography (hexane/EtOAc). The corresponding intermediate compounds pyrazolones **A** were obtained (Scheme 14).

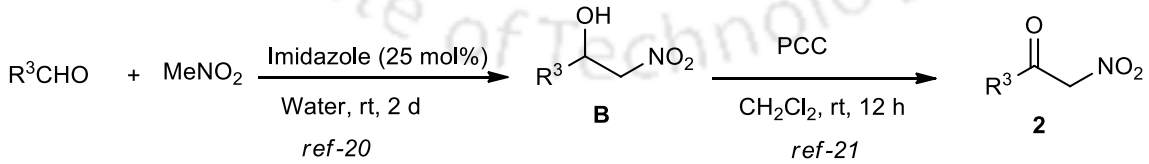
Pyrazolones **A** (5.5 mmol, 1.1 equiv) was slowly added to the mixture of the corresponding aldehyde (5 mmol, 1 equiv) and sodium acetate in glacial acetic acid. The mixture was stirred at room temperature for 1 h. After the reaction was completed, ethyl acetate (50 mL) was added. The precipitate was filtered and the filtrate was washed with water (three times). The combined organic layers were dried over Na_2SO_4 then concentrated in vacuo. The crude product was obtained after quickly purified by flash column chromatography on silica gel (hexane/ethyl acetate). The corresponding products **1** were obtained as red or yellow solid (Scheme 14).



Scheme 14

2.7.2. General procedure for the synthesis of compound (2):

Nitro methane (3 mmol), corresponding aldehyde (1 mmol) and imidazole were mixed in 2 ml of distilled water. The heterogeneous reaction mixture was stirred at ambient temperature for 24 h (Scheme 15). After completion of the reaction, the products were extracted with 10 ml of diethyl ether. The organic layer was dried over Na_2SO_4 then concentrated in vacuo. The intermediate products **B** were purified by flash column chromatography on silica gel (hexane/ethyl acetate).



Scheme 15

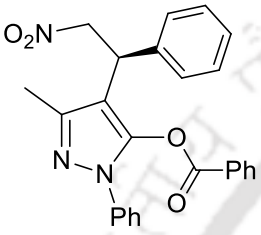
To a stirred solution of intermediate product **B** (1 mmol) in DCM (3 mL) was added PCC (2 mmol) in portions (Scheme 15). The resulting suspension was stirred at room temperature for 12 h. The mixture was passing though short silica gel then concentrated in vacuo. The products **2** were purified by flash column chromatography (hexane/ethyl acetate).

2.7.3. General procedure for the synthesis of compound (3):

To a solution of unsaturated pyrazolones **1** (0.1 mmol), α-nitroketones **2** (0.1 mmol) in 1 mL $PhCF_3$ were added **VII** (10 mol%). The reaction mixture was stirred at 0 °C for 5 days. After completion of reaction, the products were purified by silica gel column chromatography (hexane/ethyl acetate).

2.7.4. Product characterization data:

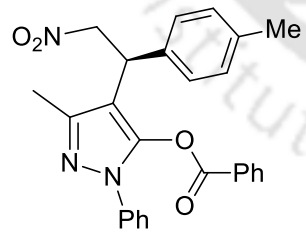
3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3aa

Red colour (41 mg, 91% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 8.4 Hz, 8H), 7.67 (t, *J* = 7.5 Hz, 5H), 7.52 – 7.47 (m, 3H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.25 (bs, 2H), 7.24 (bs, 3H), 7.20 (dd, *J* = 8.6, 4.6 Hz, 1H), 5.03 – 4.85 (m, 3H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.4, 147.7, 142.1, 137.8, 137.7, 134.9, 133.7, 130.7, 130.3, 129.4, 129.1, 129.0, 128.6, 127.7, 127.6, 127.5, 127.2, 123.0, 107.1, 77.4, 38.9, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{22}N_3O_4$ $[M+H]^+$ 428.1605, found 428.1610; **FT-IR (KBr)** 2923, 2850, 1756, 1559, 1555, 1505, 1376, 1235, 1173, 1125, 1006 cm^{-1}; The ee value 99% (t_{minor} = 8.62 min, t_{major} = 11.94 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

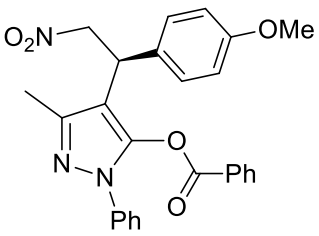
3-Methyl-4-((*S*)-2-nitro-1-*p*-tolylethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3ba

Red colour (38 mg, 86% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 – 7.47 (m, 4H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 4.98 (dd, *J* = 12.9, 8.6 Hz, 1H), 4.90 (dd, *J* = 12.9, 7.5 Hz, 1H), 4.84 (t, *J* = 8.0 Hz, 1H), 2.25 (d, *J* = 4.5 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.4, 147.7, 142.0, 137.9, 137.3, 134.8, 134.6, 130.6, 129.7, 129.3, 129.0, 127.6, 127.4, 127.3, 123.0, 107.2, 77.4, 38.6, 21.1, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1766; **FT-IR (KBr)** 2924, 2859, 1758, 1559, 1554, 1505, 1374, 1235, 1174, 1129, 1006 cm^{-1}; The ee value 97% (t_{minor} = 8.57 min, t_{major} = 12.78 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

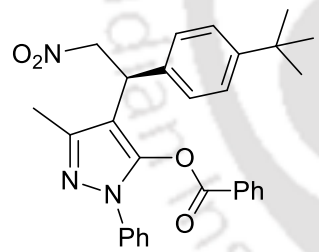
4-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3ca

Red colour (39 mg, 85% yield); R_f value 0.2 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 4.95 (dd, *J* = 12.9, 8.8 Hz, 1H), 4.89 (dd, *J* = 12.8, 7.4 Hz, 1H), 4.82 (t, *J* = 8.0 Hz, 1H), 3.71 (s, 3H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.4, 159.0, 147.7, 142.0, 137.8, 134.8, 130.7, 129.6, 129.3, 129.0, 128.6, 127.6, 127.3, 123.0, 114.4, 107.3, 77.6, 55.3, 38.3, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_5$ $[M+H]^+$ 458.1710, found 458.1711; **FT-IR (KBr)** 2961, 2846, 1762, 1595, 1554, 1509, 1443, 1389, 1239, 1182, 1010 cm^{-1}; The ee value 97% (t_{minor} = 11.54 min, t_{major} = 16.68 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

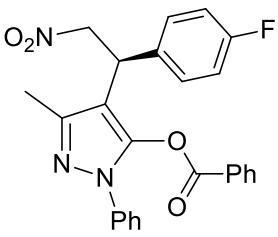
4-((*S*)-1-(4-*tert*-butylphenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3da

Red colour (42 mg, 89% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.51 – 7.47 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 9.5 Hz, 3H), 7.17 (d, *J* = 8.1 Hz, 2H), 5.01 (dd, *J* = 12.8, 8.4 Hz, 1H), 4.91 (dd, *J* = 12.8, 7.6 Hz, 1H), 4.86 (t, *J* = 7.9 Hz, 1H), 2.27 (s, 3H), 1.24 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 150.5, 147.7, 142.0, 137.9, 134.8, 134.5, 130.6, 129.3, 129.0, 127.6, 127.3, 127.1, 125.9, 123.0, 107.3, 38.5, 34.5, 31.3, 13.5; **ESI-MS** m/z calcd. for $C_{29}H_{30}N_3O_4$ $[M+H]^+$ 484.2231, found 484.2234; **FT-IR (KBr)** 2957, 2924, 2867, 1758, 1595, 1554, 509, 1435, 1378, 1247, 1178, 1006 cm^{-1}; The ee value 85% (t_{minor} = 9.68 min, t_{major} = 10.34 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (96:4) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

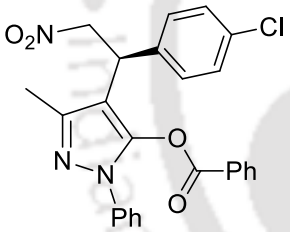
4-((*S*)-1-(4-fluorophenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3ea

Red colour (29 mg, 65% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 14.6, 7.7 Hz, 4H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.23 (dd, *J* = 15.4, 6.6 Hz, 3H), 6.93 (t, *J* = 8.6 Hz, 2H), 4.96 (dd, *J* = 12.8, 8.8 Hz, 1H), 4.90 (dd, *J* = 12.8, 7.2 Hz, 1H), 4.85 (t, *J* = 7.8 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.5, 163.0, 161.3, 147.6, 142.1, 137.8, 135.0, 133.5, 130.6, 129.4, 129.2, 129.2, 129.1, 127.7, 127.2, 123.1, 116.1, 115.9, 106.9, 38.4, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4F$ $[M+H]^+$ 446.1511, found 446.1514; **FT-IR (KBr)** 2961, 2850, 1762, 1595, 1558, 1505, 1443, 1378, 1239, 1010 cm^{-1}; The ee value 97% (t_{minor} = 9.02 min, t_{major} = 12.70 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

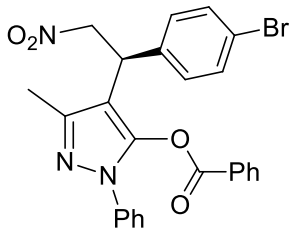
4-((*S*)-1-(4-chlorophenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3fa

Red colour (43 mg, 93% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 16.6, 8.5 Hz, 4H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.17 (m, 4H), 4.96 (dd, *J* = 12.8, 8.7 Hz, 1H), 4.91 – 4.83 (m, 2H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.4, 147.5, 142.1, 137.7, 136.2, 135.0, 133.6, 130.6, 129.4, 129.2, 129.1, 128.9, 127.7, 127.0, 123.0, 106.7, 77.1, 38.4, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Cl$ $[M+H]^+$ 462.1215, found 462.1512; **FT-IR (KBr)** 2924, 2854, 1750, 1595, 1554, 1505, 1488, 1378, 1174, 1014; The ee value 98% (t_{minor} = 9.52 min, t_{major} = 13.60 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

4-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:

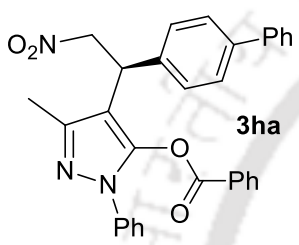


3ga

Red colour (47 mg, 93% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 18.5, 7.9 Hz, 4H), 7.34 (dd, *J* = 13.9, 8.2 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.3 Hz,

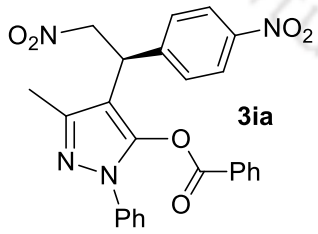
2H), 4.96 (dd, *J* = 13.0, 8.8 Hz, 1H), 4.89 (dd, *J* = 13.0, 7.1 Hz, 1H), 4.83 (t, *J* = 8.4 Hz,1H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.4, 147.5, 142.1, 137.7, 136.7, 135.0, 132.2, 130.6, 129.4, 129.2, 129.1, 127.7, 127.0, 123.0, 121.7, 106.6, 77.0, 38.4, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Br[M+H]^+$ 506.0710, found 506.0707; **FT-IR (KBr**) 2920, 1754, 1591, 1554, 1505, 1488, 1378, 1239, 1182, 1006 cm^{-1}; The ee value 94% (t_{minor} = 9.95 min, t_{major} = 14.06 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

3-Methyl-4-((*S*)-1-(biphenyl)-2-nitroethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



Red colour (46 mg, 91% yield); R_f value 0.25 (10:1 hex/EA); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.01 – 7.96 (m, 2H), 7.64 – 7.60 (m, 1H), 7.46 (ddd, *J* = 15.2, 13.1, 8.1 Hz, 8H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.31 (ddt, *J* = 11.4, 6.7, 2.5 Hz, 5H), 7.24 – 7.19 (m, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.03 (td, *J* = 11.5, 7.4 Hz, 1H), 4.95 – 4.88 (m, 2H), 2.27 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.4, 147.7, 142.1, 140.5, 140.4, 137.8, 136.6, 134.8, 130.6, 129.6, 129.4, 129.0, 128.9, 127.9, 127.7, 127.6, 127.6, 127.2, 127.1, 123.0, 120.8, 114.0, 107.0, 77.3, 38.6, 13.6; **ESI-MS** m/z calcd. for $C_{31}H_{26}N_3O_4$ $[M+H]^+$ 504.1918, found 504.1915; **FT-IR (KBr)** 2922, 2853, 1758, 1591, 1554, 1505, 1450, 1385, 998 cm^{-1}; The ee value 82% (t_{minor} = 13.48 min, t_{major} = 16.16 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

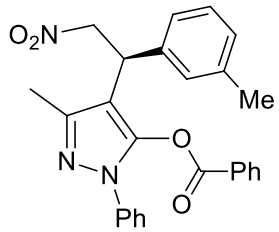
3-Methyl-4-((*S*)-2-nitro-1-(4-nitrophenyl)ethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



Red colour (40 mg, 85% yield); R_f value 0.25 (7:1 hex/EA);**^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.11 – 8.07 (m, 2H), 7.97 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.70 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.53 – 7.44 (m, 6H), 7.35 (dd, *J* = 11.2, 4.6 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.07 (dd, *J* = 12.3, 8.3 Hz, 1H), 5.03 – 4.92 (m, 2H), 2.27 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.4, 147.3, 145.0, 142.2, 137.5, 135.3, 130.62, 129.5, 129.2, 128.6, 128.0, 126.7, 124.3, 123.1, 105.9, 76.5, 38.7, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_4O_6$ $[M+H]^+$ 473.1456, found 473.1455; **FT-IR (KBr)** 2925, 2853, 1758, 1599, 1556, 1510, 1450, 1390, 998 cm^{-1}; The ee value 75%

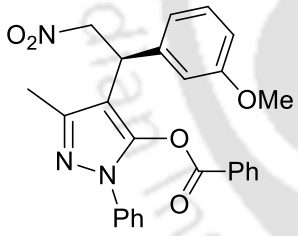
(t_{minor} = 19.51 min, t_{major} = 28.13 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-*m*-tolylethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3ja

Red colour (39 mg, 88% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.06 – 7.01 (m, 2H), 6.98 (d, *J* = 7.5 Hz, 1H), 5.00 (dd, *J* = 12.9, 8.5 Hz, 1H), 4.91 (dd, *J* = 12.9, 7.6 Hz, 1H), 4.85 (t, *J* = 8.0 Hz, 1H), 2.27 (s, 3H), 2.17 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 147.7, 142.1, 138.7, 137.9, 137.5, 134.8, 130.6, 129.3, 129.0, 129.0, 128.4, 128.0, 127.6, 127.3, 124.7, 123.0, 107.2, 77.3, 38.8, 21.4, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1764, found 442.1758; **FT-IR (KBr)** 2928, 2854, 1754, 1595, 1558, 1501, 1374, 1235, 1174, 1014 cm^{-1}; The ee value 93% (t_{minor} = 10.36 min, t_{major} = 11.92 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

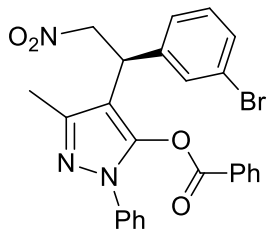


3ka

4-((*S*)-1-(3-methoxyphenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:

Red colour (38 mg, 83% yield); R_f value 0.2 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 11.8, 7.8 Hz, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.78 (bs, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 4.97 (dd, *J* = 13.0, 8.5 Hz, 1H), 4.91 (dd, *J* = 13.0, 7.6 Hz, 1H), 4.84 (t, *J* = 8.0 Hz, 1H), 3.68 (s, 3H), 2.24 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.5, 160.1, 147.8, 142.1, 139.2, 137.8, 134.9, 130.7, 130.1, 129.4, 129.0, 127.6, 127.2, 123.0, 119.8, 113.5, 113.0, 107.0, 77.3, 55.3, 38.9, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_5$ $[M+H]^+$ 458.1710, found 458.1715; **FT-IR (KBr)** 2965, 2846, 1765, 1593, 1550, 1509, 1442, 1389, 1230, 1179, 1010 cm^{-1}; The ee value 88% (t_{minor} = 11.64 min, t_{major} = 16.14 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

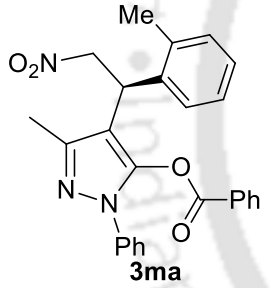
4-((*S*)-1-(3-bromophenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3la

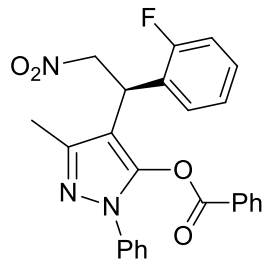
Red colour (29 mg, 57% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.50 (dd, *J* = 16.2, 8.2 Hz, 4H), 7.40 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 3H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 4.97 (dd, *J* = 13.0, 8.6 Hz, 1H), 4.89 (dd, *J* = 13.0, 7.2 Hz, 1H), 4.84 (t, *J* = 7.8 Hz, 1H), 2.26 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.4, 147.5, 142.2, 140.1, 137.8, 135.0, 130.9, 130.7, 130.6, 129.4, 129.1, 127.8, 127.1, 126.3, 123.2, 123.1, 106.6, 38.6, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Br$ $[M+H]^+$ 506.0710, found 506.0708; **FT-IR (KBr)** 2924, 2846, 1758, 1591, 1558, 1497, 1378, 1235, 1006 cm^{-1}; The ee value 88% (t_{minor} = 13.11 min, t_{major} = 15.95 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-*o*-tolylethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3ma

Red colour (41 mg, 93% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 7.4, 4.0 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 5.04 (dd, *J* = 12.5, 8.6 Hz, 1H), 4.99 (t, *J* = 7.2 Hz, 1H), 4.89 (dd, *J* = 12.5, 6.7 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 147.8, 142.2, 137.8, 136.5, 135.1, 134.7, 131.3, 130.6, 129.3, 128.9, 127.6, 127.5, 127.3, 126.3, 125.6, 123.0, 106.0, 76.6, 35.7, 19.5, 13.4; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1768; **FT-IR (KBr)** 2928, 2854, 1758, 1599, 1550, 1505, 1448, 1378, 1239, 1178, 1124, 1055, 1010 cm^{-1}; The ee value 95% (t_{minor} = 13.56 min, t_{major} = 14.99 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.



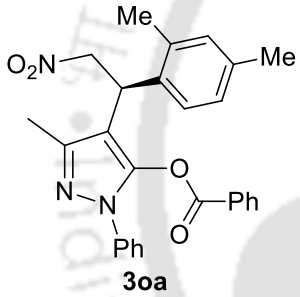
3na

4-((*S*)-1-(2-fluorophenyl)-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:

Red colour (36 mg, 80% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** 8.02 (d, *J* = 8.4 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.49 (dd, *J* = 15.1, 7.7 Hz, 4H), 7.31 (t, *J* = 7.9 Hz,

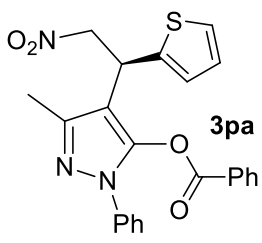
2H), 7.22 (t, *J* = 8.7 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 9.6 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 5.13 (t, *J* = 8.1 Hz, 1H), 5.04 (dd, *J* = 13.3, 8.3 Hz, 1H), 4.95 (dd, *J* = 13.3, 7.9 Hz, 1H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.2, 161.4, 159.8, 147.7, 142.1, 137.8, 134.8, 130.6, 129.5 (d, *J* = 36 Hz), 129.3, 129.0, 128.4 (d, *J* = 12 Hz), 127.6, 127.2, 124.7, 124.6, 124.6, 124.5, 123.0, 116.2 (d, *J* = 90 Hz), 105.7, 75.9, 33.2, 33.2, 13.3.; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4F$ $[M+H]^+$ 446.1511, found 446.1512; **FT-IR (KBr)** 2962, 2853, 1762, 1595, 1552, 1505, 1443, 1373, 1239, 1013 cm^{-1}; The ee value 89% (t_{minor} = 12.30 min, t_{major} = 13.20 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-1-(2,4-dimethylphenyl)-2-nitroethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3oa

Red colour (43 mg, 94% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.44 (m, 4H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.95 (s, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.03 (dd, *J* = 12.8, 8.8 Hz, 1H), 4.95 (t, *J* = 7.2 Hz, 1H), 4.86 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.2, 147.7, 142.2, 137.8, 137.0, 136.3, 134.6, 132.1, 132.0, 130.6, 129.3, 128.8, 127.6, 127.3, 127.0, 125.5, 123.0, 106.1, 76.7, 35.4, 20.9, 19.4, 13.4; **ESI-MS** m/z calcd. for $C_{27}H_{26}N_3O_4$ $[M+H]^+$ 456.1918, found 456.1915; **FT-IR (KBr)** 2920, 2854, 1758, 1591, 1554, 1505, 1448, 1382, 998 cm^{-1}; The ee value 94% (t_{minor} = 13.45 min, t_{major} = 12.44 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.



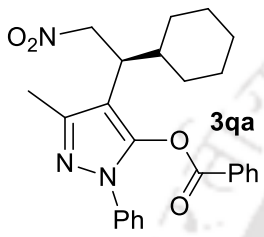
3pa

3-Methyl-4-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)-1-phenyl-1*H*-pyrazol-5-yl benzoate:

Red colour (35 mg, 79% yield); R_f value 0.25 (10:1 hex/EA);**^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.07 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.73 – 7.67 (m, 1H), 7.53 (t, *J* = 7.9 Hz, 4H), 7.37 (dd, *J* = 10.7, 5.1 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.21 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.90 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.86 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.12 (dd, *J* = 11.6, 4.1 Hz, 1H), 5.04 (dd, *J* = 12.9,

8.1 Hz, 1H), 4.95 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.32 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.2, 147.5, 142.1, 141.2, 137.8, 134.9, 130.7, 129.4, 129.1, 127.7, 127.0, 125.3, 125.1, 123.0, 106.9, 77.9, 34.7, 13.5; **ESI-MS** m/z calcd. for $C_{23}H_{20}N_3O_4S$ $[M+H]^+$ 434.1169, found 434.1165; **FT-IR (KBr)** 2926, 2858, 1760, 1599, 1556, 1510, 1450, 1383, 998 cm^{-1}; The ee value 68% (t_{minor} = 10.57 min, t_{major} = 14.61 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

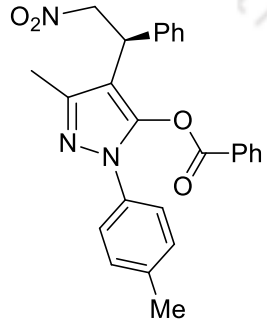
4-((*S*)-1-cyclohexyl-2-nitroethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



3qa

Red colour (28 mg, 65% yield); R_f value 0.25 (13:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.11 (d, *J* = 7.3 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.47 (m, 4H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 4.70 (dd, *J* = 12.4, 6.1 Hz, 1H), 4.61 (dd, *J* = 12.3, 9.5 Hz, 1H), 3.25 (td, *J* = 9.2, 6.2 Hz, 1H), 2.34 (s, 3H), 1.74 (s, 2H), 1.63 (d, *J* = 7.3 Hz, 1H), 1.55 – 1.48 (m, 1H), 1.14 (t, *J* = 9.1 Hz, 3H), 1.04 (t, *J* = 11.7 Hz, 1H), 0.97 – 0.81 (m, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.2, 148.1, 142.2, 138.0, 134.8, 130.6, 129.3, 129.2, 127.5, 127.5, 122.9, 106.4, 77.3, 40.1, 40.0, 31.4, 30.9, 26.3, 26.2, 26.1, 13.9; **ESI-MS** m/z calcd. for $C_{25}H_{28}N_3O_4$ $[M+H]^+$ 434.2074, found 434.2077; **FT-IR (KBr)** 2924, 2854, 1775, 1595, 1554, 1509, 1452, 1374, 1096, 1004 cm^{-1}; The ee value 74% (t_{minor} = 12.10 min, t_{major} = 15.13 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-*p*-tolyl-1*H*-pyrazol-5-yl benzoate:

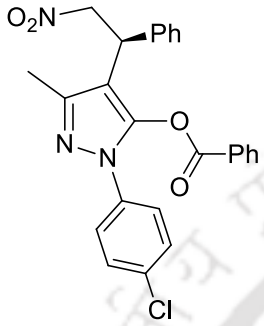


3ra

Red colour (36 mg, 82% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 4.4 Hz, 4H), 7.20 – 7.18 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 4.99 (dd, *J* = 12.8, 8.5 Hz, 1H), 4.93 – 4.85 (m, 2H), 2.28 (s, 3H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.4, 147.4, 142.0, 137.8, 137.6, 135.4, 134.8, 130.7, 129.9, 129.1, 129.0, 127.6, 127.5, 127.3, 122.9, 106.9, 38.9, 21.1, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1766; **FT-IR (KBr)** 2961, 2850, 1754, 1595, 1554, 1531, 1452, 1370, 1239, 1178,

1006 cm^{-1}; The ee value 96% (t_{minor} = 9.74 min, t_{major} = 11.90 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

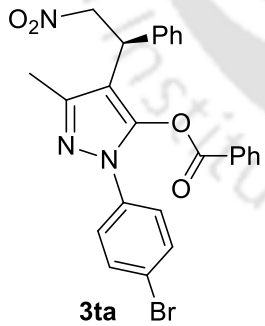
1-(4-Chlorophenyl)-3-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-pyrazol-5-yl benzoate:



3sa

Red colour (40 mg, 87% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.22 (m, 4H), 7.20 (dd, *J* = 8.2, 4.8 Hz, 1H), 4.98 (dd, *J* = 12.8, 8.2 Hz, 1H), 4.92 (dd, *J* = 12.8, 7.8 Hz, 1H), 4.86 (t, *J* = 8.0 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 148.1, 142.1, 137.6, 136.5, 135.1, 133.3, 130.7, 129.6, 129.2, 129.1, 127.8, 127.5, 127.0, 124.0, 107.5, 77.3, 38.9, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Cl$ $[M+H]^+$ 461.1142, found 461.1142; **FT-IR (KBr)** 2924, 1754, 1595, 1554, 1505, 1452, 1370, 1239, 1174, 1010 cm^{-1}; The ee value 96% (t_{minor} = 9.36 min, t_{major} = 10.80 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

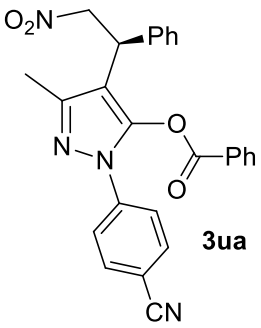
1-(4-Bromophenyl)-3-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-pyrazol-5-yl benzoate:



3ta

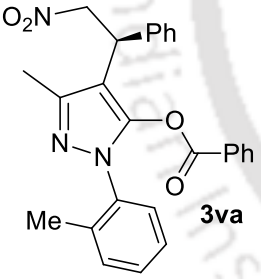
Red colour (41 mg, 81% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 2H), 7.44 (d, *J* = 9.5 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.25 – 7.22 (m, 4H), 7.22 – 7.18 (m, 1H), 4.98 (dd, *J* = 12.8, 8.2 Hz, 1H), 4.92 (dd, *J* = 12.8, 7.8 Hz, 1H), 4.86 (t, *J* = 8.0 Hz, 1H), 2.21 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 148.2, 142.1, 137.5, 137.0, 135.1, 132.5, 130.7, 129.2, 129.1, 127.7, 127.5, 127.0, 124.2, 121.2, 107.5, 77.2, 38.9, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Br$ $[M+H]^+$ 506.0710, found 506.0710; **FT-IR (KBr)** 2924, 2854, 1758, 1599, 1554, 1493, 1452, 1382, 1239, 1006 cm^{-1}; The ee value 92% (t_{minor} = 15.68 min, t_{major} = 19.46 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

1-(4-Cyanophenyl)-3-methyl-4-((*S*)-2-nitro-1-phenylethyl)-1*H*-pyrazol-5-yl benzoate:

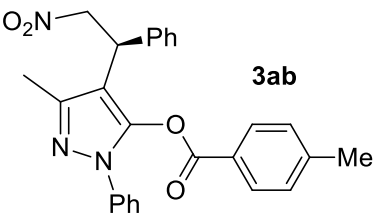


Red colour (34 mg, 77% yield); R_f value 0.2 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 7.6 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.23 – 7.19 (m, 4H), 4.98 (dd, *J* = 12.9, 8.0 Hz, 1H), 4.92 (dd, *J* = 12.9, 8.1 Hz, 1H), 4.87 (t, *J* = 8.0 Hz, 1H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.2, 149.4, 142.5, 141.4, 137.2, 135.4, 133.5, 130.7, 130.3, 129.3, 129.2, 128.6, 127.9, 127.4, 122.2, 118.3, 110.6, 108.6, 38.8, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{21}N_4O_4$ $[M+H]^+$ 453.1557, found 453.1561; **FT-IR (KBr)** 2920, 2850, 2229, 1758, 1607, 1554, 1509, 1448, 1378, 1205, 1006 cm^{-1}; The ee value 89% (t_{minor} = 17.10 min, t_{major} = 19.90 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-*o*-tolyl-1*H*-pyrazol-5-yl benzoate:



Red colour (42 mg, 96% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 4.4 Hz, 5H), 7.21 (d, *J* = 3.4 Hz, 3H), 7.17 – 7.13 (m, 1H), 4.98 – 4.94 (m, 2H), 4.88 (t, *J* = 8.1 Hz, 1H), 2.21 (s, 3H), 2.19 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 147.4, 142.9, 138.0, 136.2, 136.1, 134.6, 131.1, 130.4, 129.4, 129.1, 128.9, 127.7, 127.7, 127.5, 127.2, 126.5, 105.5, 77.7, 39.1, 17.6, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1756; **FT-IR (KBr)** 2920, 2854, 1758, 1591, 1558, 1505, 1452, 1374, 1239, 1178, 1043, 1014 cm^{-1}; The ee value 99% (t_{minor} = 7.41 min, t_{major} = 9.90 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

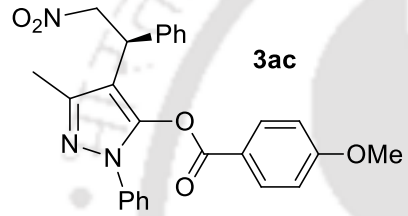


4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-methylbenzoate:

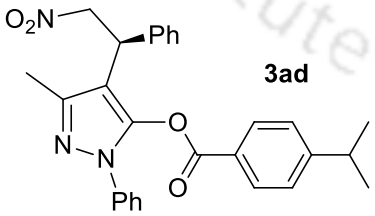
Red colour (41 mg, 93% yield); R_f value 0.3 (10:1

hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.33 (dd, *J* = 14.3, 7.7 Hz, 4H), 7.28 (d, *J* = 4.1 Hz, 4H), 7.26 – 7.20 (m, 2H), 5.05 – 4.86 (m, 3H), 2.46 (s, 3H), 2.24 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.4, 147.7, 146.1, 142.1, 137.8, 137.8, 130.7, 130.1, 129.8, 129.3, 129.0, 128.5, 127.6, 127.5, 122.9, 107.1, 77.4, 39.0, 22.0, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1763; **FT-IR (KBr)** 2919, 2850, 1753, 1591, 1553, 1505, 1452, 1379, 1235, 1178, 1045, 1014 cm^{-1}; The ee value 96% (t_{minor} = 8.30 min, t_{major} = 11.22 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-methoxybenzoate:



Red colour (36 mg, 79% yield); R_f value 0.2 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.26 (bs, 1H), 7.25 (bs, 2H), 7.25 – 7.17 (m, 3H), 6.96 (d, *J* = 9.0 Hz, 2H), 5.01 – 4.84 (m, 3H), 3.89 (s, 3H), 2.21 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 164.9, 163.1, 147.7, 142.2, 137.9, 137.9, 133.0, 129.3, 129.1, 127.6, 127.6, 127.5, 122.9, 119.4, 114.4, 107.1, 77.4, 55.8, 39.0, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_5$ $[M+H]^+$ 458.1710, found 458.1706; **FT-IR (KBr)** 2984, 2850, 1742, 1603, 1550, 1505, 1370, 1243, 1169, 993 cm^{-1}; The ee value 94% (t_{minor} = 11.63 min, t_{major} = 16.54 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

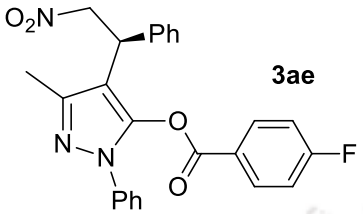


3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-isopropylbenzoate:

Red colour (42 mg, 92% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.34 (dd, *J* = 15.9, 8.2 Hz, 4H), 7.25 (s, 3H), 7.25 – 7.14 (m, 3H), 5.00 – 4.91 (m, 2H), 4.86 (t, *J* = 8.0 Hz, 1H), 3.00 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.21 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.5, 156.7, 147.7, 142.2, 137.9, 137.9, 130.9, 129.3, 129.1, 127.7, 127.5, 127.2, 124.7, 123.0, 107.1, 77.4, 39.0, 34.6, 23.7, 13.6; **ESI-MS** m/z calcd. for $C_{28}H_{28}N_3O_4$ $[M+H]^+$ 470.2070, found 470.2080; **FT-IR (KBr)** 2961, 2924, 2850, 1754,

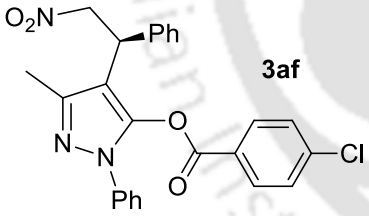
1599, 1558, 1505, 1374, 1239, 1178, 1059, 1002 cm^{-1}; The ee value 92% (t_{minor} = 6.62 min, t_{major} = 8.02 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-fluorobenzoate:

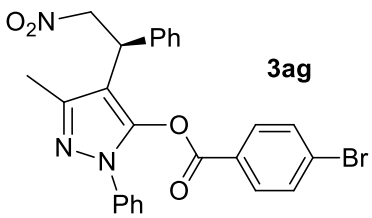


Red colour (42 mg, 94% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.06 – 8.00 (m, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.26 – 7.22 (m, 5H), 7.22 – 7.18 (m, 1H), 7.16 (t, *J* = 8.5 Hz, 2H), 4.99 (dd, *J* = 12.1, 7.5 Hz, 1H), 4.89 (dq, *J* = 15.7, 7.7 Hz, 2H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 167.8, 166.1, 162.4, 147.8, 141.9, 137.8, 137.6, 133.5, 133.4, 129.4, 129.1, 127.7, 127.7, 127.5, 123.5, 123.0, 116.5, 116.3, 107.1, 77.3, 38.8, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4F$ $[M+H]^+$ 446.1511, found 446.1512; **FT-IR (KBr)** 2828, 2859, 1754, 1595, 1554, 1501, 1435, 1374, 1239, 1153, 1063 cm^{-1}; The ee value 96% (t_{minor} = 8.99 min, t_{major} = 11.45 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-chlorobenzoate:



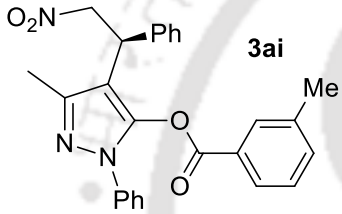
Red colour (39 mg, 85% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.46 (dd, *J* = 7.9, 5.5 Hz, 4H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.24 (q, *J* = 4.1 Hz, 5H), 7.22 – 7.18 (m, 1H), 4.98 (dt, *J* = 15.0, 7.5 Hz, 1H), 4.92 – 4.85 (m, 2H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 162.6, 147.8, 141.8, 141.6, 137.7, 137.6, 132.0, 129.5, 129.4, 129.1, 127.7, 127.7, 127.5, 125.6, 123.0, 107.1, 77.3, 38.8, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Cl$ $[M+H]^+$ 462.1215, found 462.1214; **FT-IR (KBr)** 2924, 2854, 1754, 1591, 1558, 1488, 1443, 1384, 1239, 1169, 1088, 1006 cm^{-1}; The ee value 90% (t_{minor} = 9.16 min, t_{major} = 11.55 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.



3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 4-bromobenzoate:

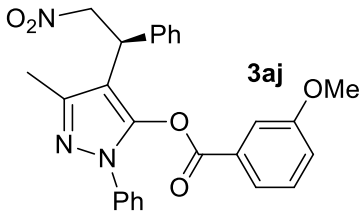
Red colour (45 mg, 90% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.26 – 7.23 (m, 4H), 7.20 (dd, *J* = 13.7, 6.8 Hz, 2H), 4.98 (dt, *J* = 15.1, 7.5 Hz, 1H), 4.92 – 4.85 (m, 2H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 162.8, 147.8, 141.9, 137.8, 137.6, 132.5, 132.0, 130.5, 129.4, 129.1, 127.8, 127.7, 127.5, 126.1, 123.1, 107.1, 77.3, 38.9, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4Br$ $[M+H]^+$ 506.0710, found 506.0709; **FT-IR (KBr)** 2924, 2850, 1758, 1582, 1550, 1492, 1382, 1239, 1063, 1006 cm^{-1}; The ee value 93% (t_{minor} = 9.32 min, t_{major} = 12.11 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 3-methylbenzoate:



Red colour (41 mg, 93% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 – 7.82 (m, 2H), 7.50 (dd, *J* = 12.4, 8.1 Hz, 3H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 4.3 Hz, 4H), 7.25 – 7.15 (m, 2H), 5.00 (dd, *J* = 12.8, 8.5 Hz, 1H), 4.94 (dd, *J* = 12.9, 7.5 Hz, 1H), 4.89 (t, *J* = 8.0 Hz, 1H), 2.43 (s, 3H), 2.24 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.6, 147.7, 142.2, 139.0, 137.9, 137.8, 135.7, 131.2, 129.3,129.1, 128.9, 127.8, 127.6, 127.6, 127.5, 127.1, 123.0, 107.1, 39.0, 21.4, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1761; **FT-IR (KBr)** 2920, 2859, 1750,1559, 1550, 1501, 1374, 1268, 1178, 1071 cm^{-1}; The ee value 86% (t_{minor} = 7.04 min, t_{major} = 7.76 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

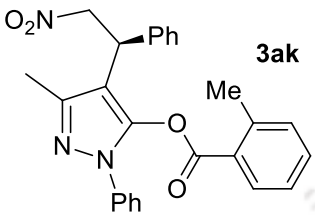
4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 3-methoxybenzoat:



Red colour (42.5 mg, 93% yield); R_f value 0.2 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 3H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.26 (s, 1H), 7.25 (s, 3H), 7.24 - 7.12 (m, 3H), 5.02 – 4.85 (m, 3H), 3.85 (s, 3H), 2.22 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.3, 159.9, 147.7, 142.0, 137.8, 137.7, 130.1, 129.4, 129.1, 128.4, 127.7, 127.6, 127.5, 123.0, 122.9, 121.5, 114.9, 107.0, 77.4, 55.7, 38.9, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_5$ $[M+H]^+$ 458.1710, found 458.1710; **FT-IR (KBr)** 2928, 2850,

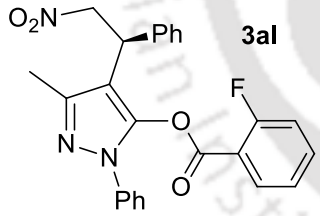
1750, 1599, 1550, 1484, 1435, 1321, 1268, 1210, 1063; The ee value 91% (t_{minor} = 8.82 min, t_{major} = 9.61 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 2-methylbenzoate:



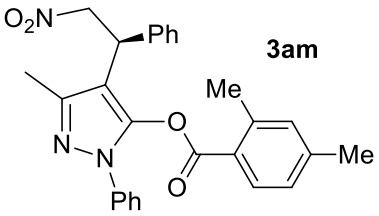
Red colour (34 mg, 77% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 3H), 7.33 (dt, *J* = 15.6, 7.6 Hz, 3H), 7.28 (bs, 1H), 7.25 (bs, 4H), 7.24 – 7.17 (m, 2H), 5.01 (dd, *J* = 12.9, 8.5 Hz, 1H), 4.94 (dd, *J* = 12.9, 7.5 Hz, 1H), 4.87 (t, *J* = 8.0 Hz, 1H), 2.41 (s, 3H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.3, 147.7, 142.6, 142.3, 138.0, 137.9, 134.0, 132.3, 131.4, 129.3, 129.1, 127.7, 127.7, 127.5, 126.4, 126.1, 123.3, 107.1, 77.5, 38.9, 21.8, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ 442.1761, found 442.1763; **FT-IR (KBr)** 2924, 1767,1595, 1542, 1501, 1452, 1386, 1223, 1129, 989 cm^{-1}; The ee value 88% (t_{minor} = 6.90 min, t_{major} = 7.53 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 2-fluorobenzoate:



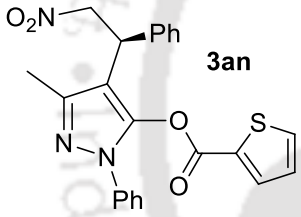
Red colour (36 mg, 81% yield); R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.83 (t, *J* = 6.6 Hz, 1H), 7.63 (dd, *J* = 12.2, 6.7 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.27 (bs, 1H), 7.26 (d, *J* = 1.8 Hz, 2H), 7.25 – 7.21 (m, 3H), 7.20 – 7.10 (m, 2H), 5.03 (dd, *J* = 12.9, 8.7 Hz, 1H), 4.94 (dd, *J* = 12.9, 7.3 Hz, 1H), 4.90 – 4.87 (t, *J* = 8.4 Hz, 1H), 2.23 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 163.3, 161.6, 160.8, 160.8, 147.7, 141.6, 137.8, 137.7, 136.7, 136.6, 132.9, 129.4, 129.1, 127.7, 127.7, 127.5, 124.6, 124.6, 123.1, 117.6, 117.5, 107.1, 77.3, 38.9, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{21}N_3O_4F$ $[M+H]^+$ 446.1511, found 446.1511; **FT-IR (KBr)** 2928, 2854, 1767, 1599, 1550, 1488, 1456, 1374, 1276, 1227, 1014 cm^{-1}; The ee value 86% (t_{minor} = 9.48 min, t_{major} = 10.41 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl 2,4-dimethylbenzoate:



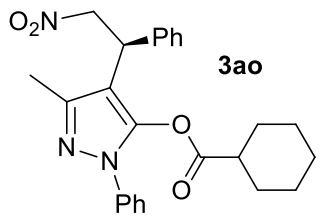
Red colour (43 mg, 95% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.25 (bs, 3H), 7.24 – 7.07 (m, 5H), 5.03 – 4.91 (m, 2H), 4.89 – 4.83 (m, 1H), 2.38 (s, 6H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.2, 147.6, 145.0, 142.8, 142.4, 138.0, 129.3, 129.2, 129.0, 128.4, 127.6, 127.6, 127.5, 127.1, 125.4, 123.1, 107.1, 77.5, 38.9, 21.8, 21.7, 13.6; **ESI-MS** m/z calcd. for $C_{27}H_{26}N_3O_4$ $[M+H]^+$ 456.1918, found 456.1921; **FT-IR (KBr)** 2920, 2854, 1771, 1599, 1550, 1505, 1374, 1227, 1141, 981 cm^{-1}; The ee value 92% (t_{minor} = 6.58 min, t_{major} = 7.45 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl thiophene-2-carboxylate:



Red colour (37 mg, 85% yield); R_f value 0.3 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 3.6 Hz, 1H), 7.71 (d, *J* = 4.9 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.25 (bs, 3H), 7.25 – 7.17 (m, 3H), 7.17 – 7.15 (m, 1H), 5.01 (dd, *J* = 12.9, 8.7 Hz, 1H), 4.92 (dd, *J* = 12.9, 7.3 Hz, 1H), 4.87 (t, *J* = 7.8 Hz, 1H), 2.21 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 158.5, 147.7, 141.6, 137.8, 137.7, 136.5, 135.5, 130.0, 129.4, 129.1, 128.7, 127.7, 127.6, 127.5, 123.0, 107.3, 77.4, 39.0, 13.5; **ESI-MS** m/z calcd. for $C_{23}H_{20}N_3O_4S$ $[M+H]^+$ 434.1169, found 434.1171; **FT-IR (KBr)** 2924, 1738, 1595, 1554, 1501, 1411, 1378, 1349, 1239, 1055 cm^{-1}; The ee value 95% (t_{minor} = 10.62 min, t_{major} = 12.76 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C

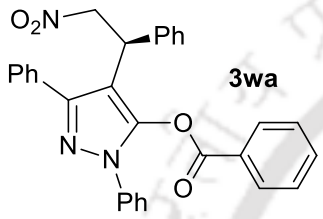
3-Methyl-4-((*S*)-2-nitro-1-phenylethyl)-1-phenyl-1*H*-pyrazol-5-yl cyclohexanecarboxylate:



Red colour (26 mg, 60% yield); R_f value 0.3 (15:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.42 – 7.37 (m, 4H), 7.34 – 7.29 (m, 3H), 7.25 – 7.22 (m, 3H), 4.98 (dd, *J* = 12.9, 8.6 Hz, 1H), 4.84 (dd, *J* = 12.9, 7.3 Hz, 1H), 4.78 (t, *J* = 7.9 Hz, 1H), 2.90 (d, *J* = 42.1 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.13 (s, 3H), 1.82 (dd, *J* = 28.4, 12.0 Hz, 2H), 1.74 – 1.66 (m, 3H),

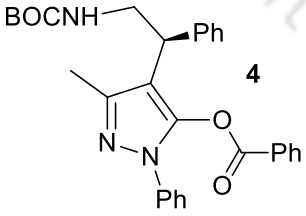
1.61 (d, *J* = 8.9 Hz, 1H), 1.34 (dd, *J* = 15.7, 11.4 Hz, 2H), 1.20 – 1.14 (m, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 172.6, 147.6, 142.2, 138.0, 137.7, 129.2, 129.1, 127.9, 127.7, 127.5, 123.8, 106.8, 77.5, 42.8, 38.8, 28.7, 28.6, 25.5, 25.2, 25.2, 13.6; **ESI-MS** m/z calcd. for $C_{25}H_{28}N_3O_4$ $[M+H]^+$ 434.2074, found 434.2076; **FT-IR (KBr)** 2924, 2854, 1775, 1595, 1554, 1509, 1452, 1374, 1096, 1004 cm^{-1}; The ee value 91% (t_{minor} = 11.08 min, t_{major} = 12.75 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

4-((*S*)-2-nitro-1-phenylethyl)-1,3-diphenyl-1*H*-pyrazol-5-yl benzoate:



Red colour (36 mg, 74% yield); R_f value 0.5 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.06 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.75 – 7.70 (m, 1H), 7.63 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.58 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.55 (t, *J* = 7.9 Hz, 2H), 7.49 – 7.45 (m, 3H), 7.40 (dd, *J* = 10.8, 5.0 Hz, 2H), 7.33 – 7.30 (m, 1H), 7.25 – 7.23 (m, 1H), 5.16 (t, *J* = 8.1 Hz, 1H), 5.01 – 4.94 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.2, 151.1, 142.7, 138.1, 137.9, 134.9, 132.9, 130.7, 129.4, 129.1, 129.1, 128.8, 128.8, 128.0, 127.7, 127.6, 127.2, 123.2, 106.8, 77.6, 39.1; **ESI-MS** m/z calcd. for $C_{25}H_{28}N_3O_4$ $[M+H]^+$ 434.2074, found 434.2076; **FT-IR (KBr)** 2924, 2854, 1770, 1595, 1554, 1510, 1455, 1375, 1096, 1004 cm^{-1}; The ee value 80% (t_{minor} = 9.11 min, t_{major} = 13.03 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

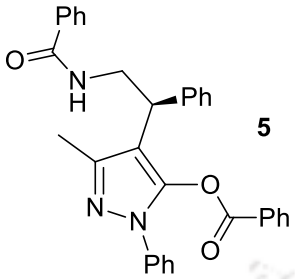
***tert*-Butyl (*S*)-2-(5-(benzoyloxy)-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-phenylethylcarbamate:**



Colourless (20 mg, 40% yield); R_f value 0.2 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.48 – 7.42 (m, 3H), 7.41 – 7.29 (m, 8H), 6.66 (s, 1H), 4.27 (td, *J* = 12.9, 6.4 Hz, 2H), 3.80 – 3.75 (m, 1H), 2.16 (s, 3H), 1.31 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 167.6, 150.2, 148.7, 142.3, 140.8, 138.1, 134.6, 131.6, 129.4, 128.9, 128.7, 128.0, 127.5, 127.2, 127.1, 123.1, 108.5, 86.3, 43.3, 40.8, 27.4, 13.6; **ESI-MS** m/z calcd. for $C_{30}H_{32}N_3O_4$ $[M+H]^+$ 498.2387, found 498.2385; **FT-IR (KBr)** 2924, 2850, 1775, 1644, 15599, 1501, 1452, 1374, 1141 cm^{-1}; The ee value 99% (t_{minor} = 18.39 min, t_{major} = 14.59 min) was determined by HPLC

using Daicel Chiralpak IA with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

4-((*S*)-2-(benzamido)-1-phenylethyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl benzoate:



5

Colourless (30 mg, 60% yield); R_f value 0.2 (5:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 7.3 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.48 (q, *J* = 7.3 Hz, 3H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 4H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 13.9, 6.8 Hz, 2H), 6.66 (s, 1H), 4.29 (dd, *J* = 10.1, 6.3 Hz, 1H), 4.21 (dt, *J* = 13.0, 6.4 Hz, 1H), 3.84 – 3.78 (m, 1H), 2.22 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 167.7, 164.6, 148.8, 142.0, 140.5, 138.0, 135.0, 134.5, 131.6, 130.7, 129.4, 129.1, 128.9, 128.7, 127.9, 127.5, 127.2, 127.1, 123.0, 109.1, 43.0, 40.2, 13.9; **ESI-MS** m/z calcd. for $C_{32}H_{28}N_3O_3$ $[M+H]^+$ 502.2125, found 502.2122; **FT-IR (KBr)** 2924, 2850, 1758, 1640, 1599, 1443, 1386, 1239, 1047, 1014 cm^{-1}; The ee value 94% (t_{minor} = 22.05 min, t_{major} = 30.49 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

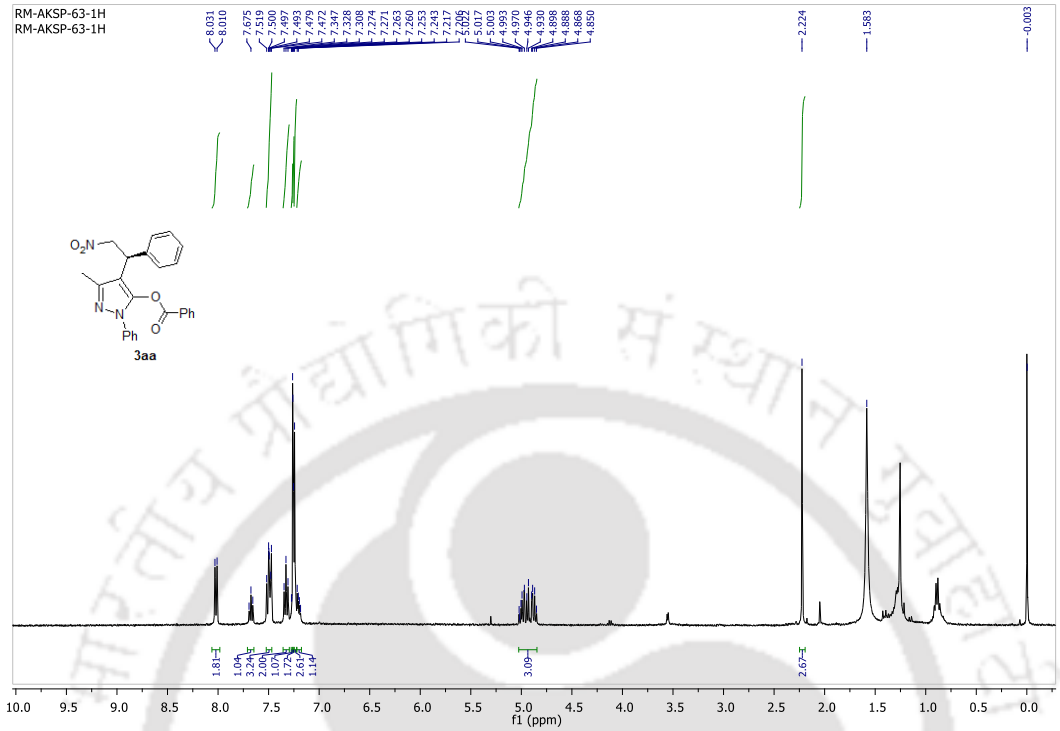
2.7.5. Crystal information:

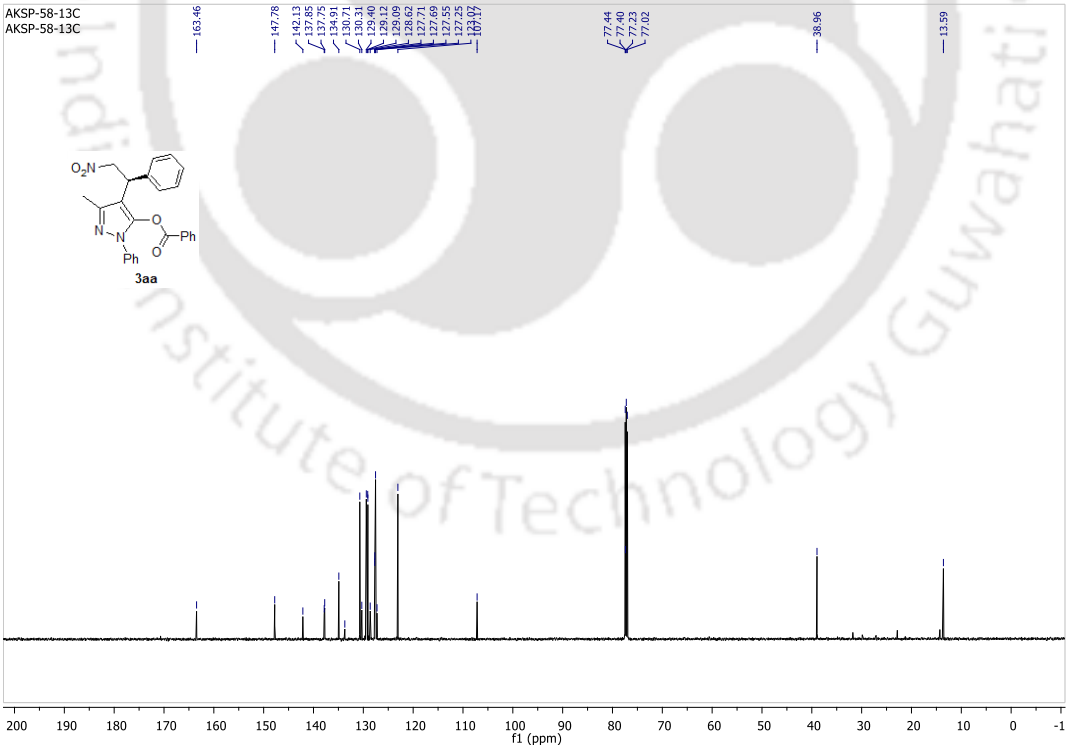
Crystal data and structure refinement for chiral compound **3af** (CCDC 1523176):

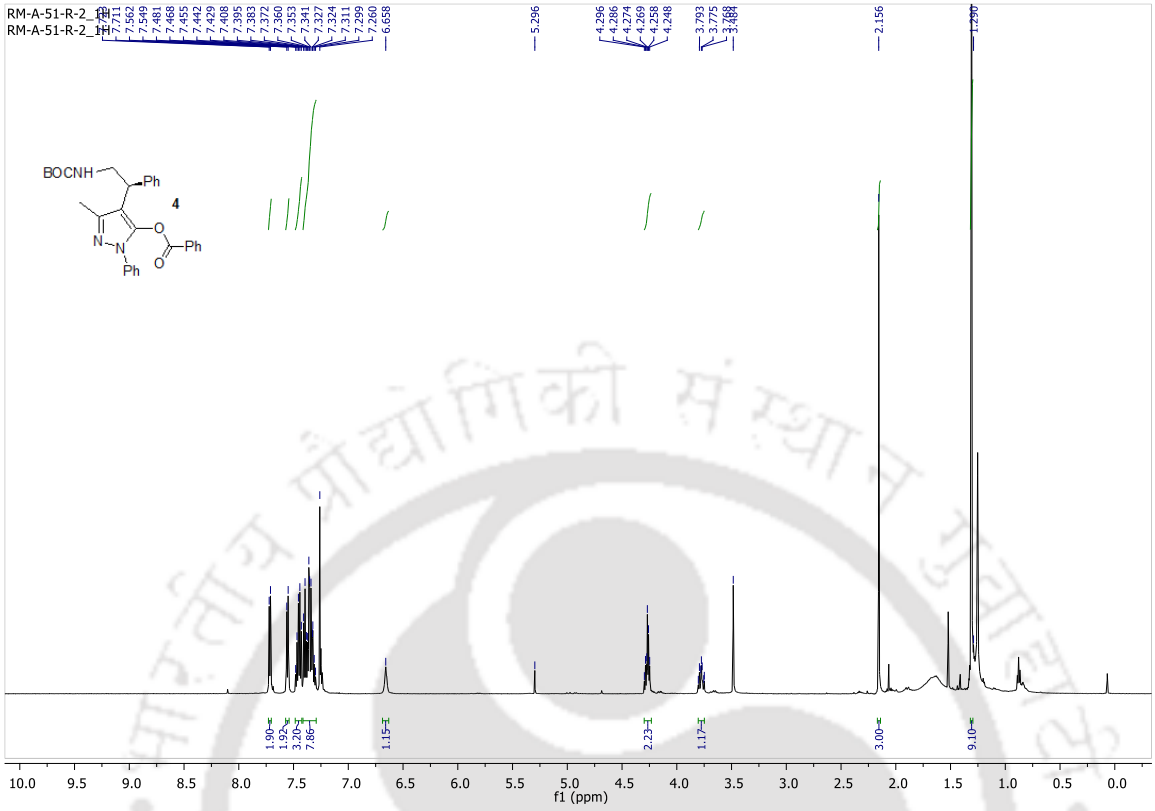
Identification code	**compound 3af**
Empirical formula	$C_{25}H_{20}ClN_3O_4$
Formula weight	461.89
Temperature/K	296K
Crystal system	monoclinic
Space group	'P 21 21 21'
a/Å	9.2043(12)
b/Å	19.510(3)
c/Å	12.5785(17)
α/°	90.00

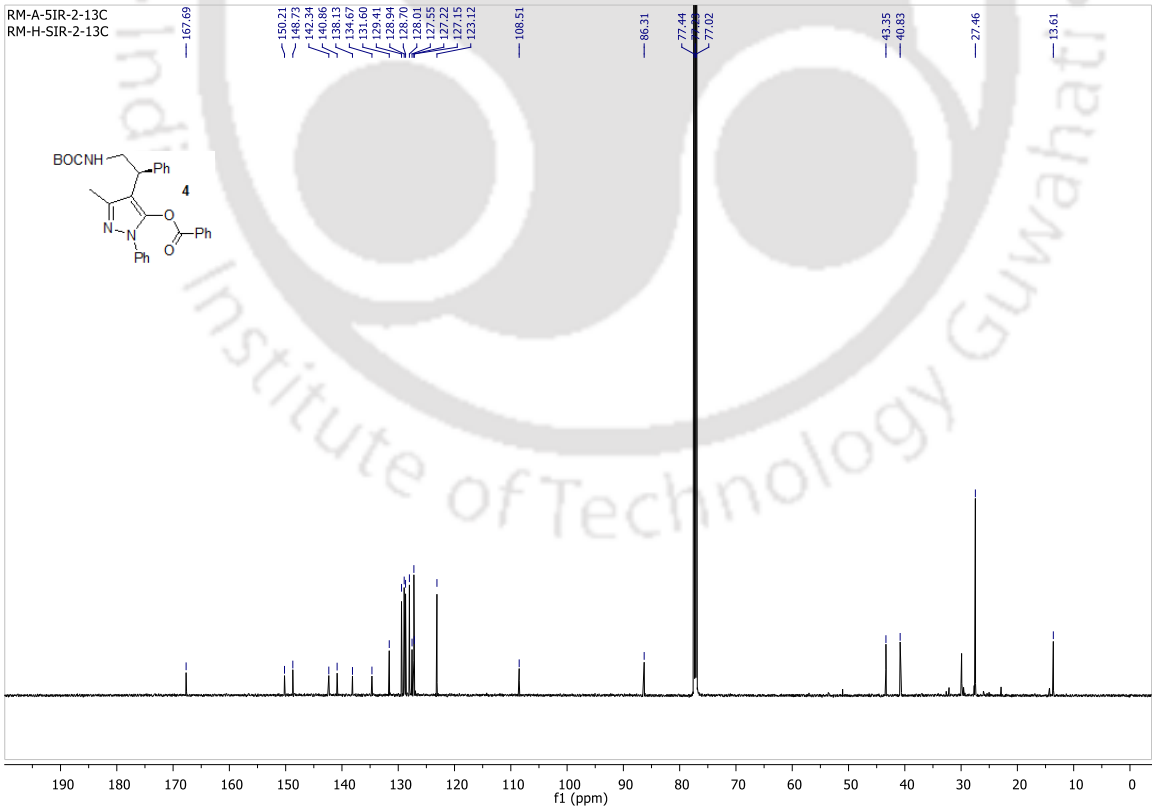
β/°	101.112(3)
γ/°	90.00
Volume/Å^3	2216.5(5)
Z	4
ρ_{calc}mg/mm^3	1.384
m/mm^{-1}	0.221
F(000)	960.0
Crystal size/mm^3	0.28 × 0.24 × 0.21
2Θ range for data collection	2.48 to 52.54°
Index ranges	-7 ≤ h ≤ 7, -8 ≤ k ≤ 7, -36 ≤ l ≤ 40
Reflections collected	13277
Independent reflections	2607[R(int) = 0.0576]
Data/restraints/parameters	2607/0/181
Goodness-of-fit on F^2	1.080
Final R indexes [I>=2σ (I)]	R_1 = 0.0643, wR_2 = 0.1987
Final R indexes [all data]	R_1 = 0.0870, wR_2 = 0.1446
Largest diff. peak/hole / e Å^{-3}	0.51/-0.51
Flack parameter	-0.06(5)

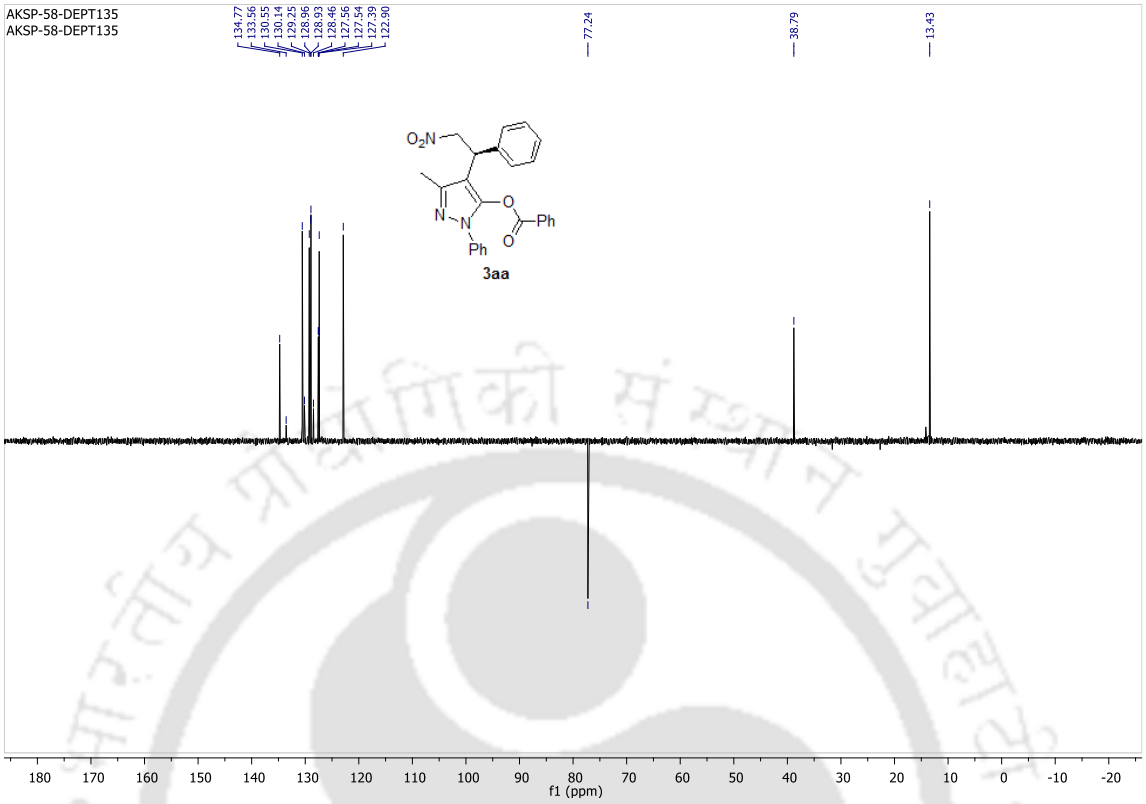
2.8. Selected spectra of NMR, DEPT and HPLC:

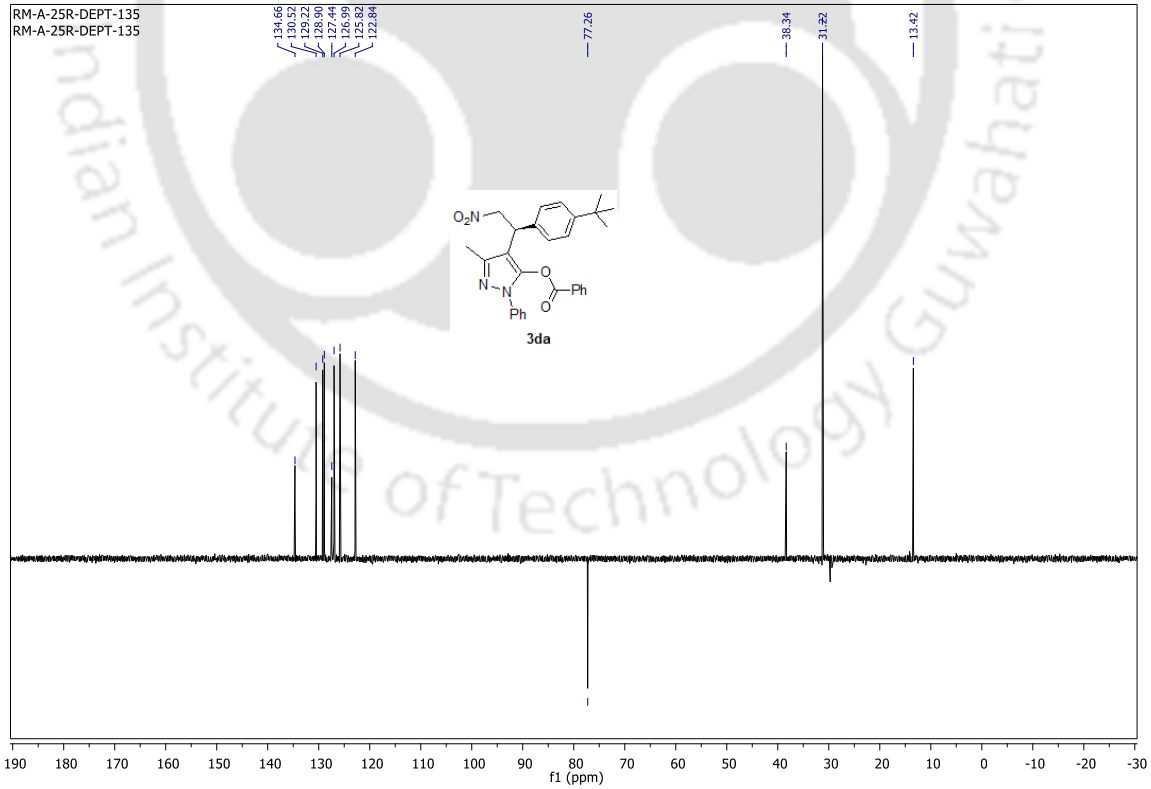




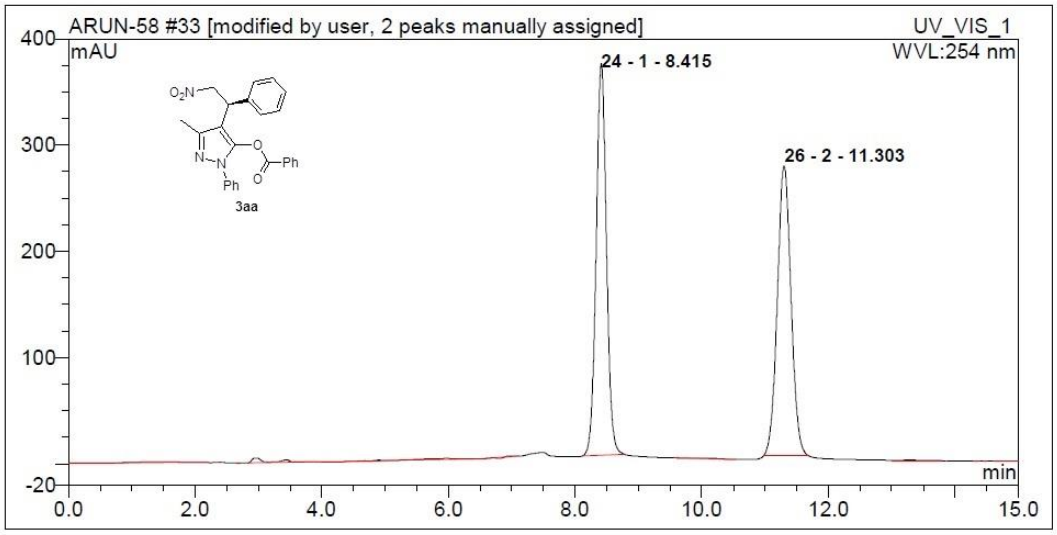






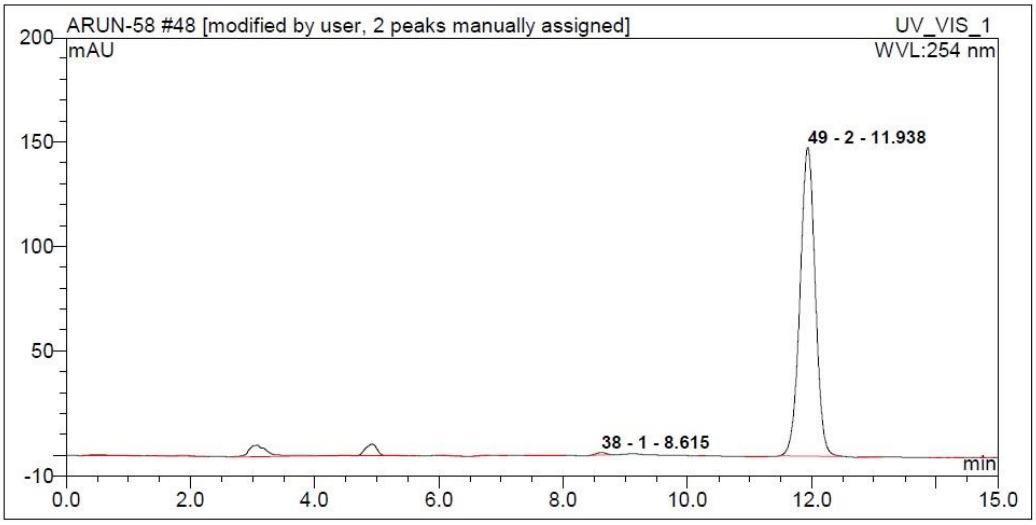


RM-A-1R



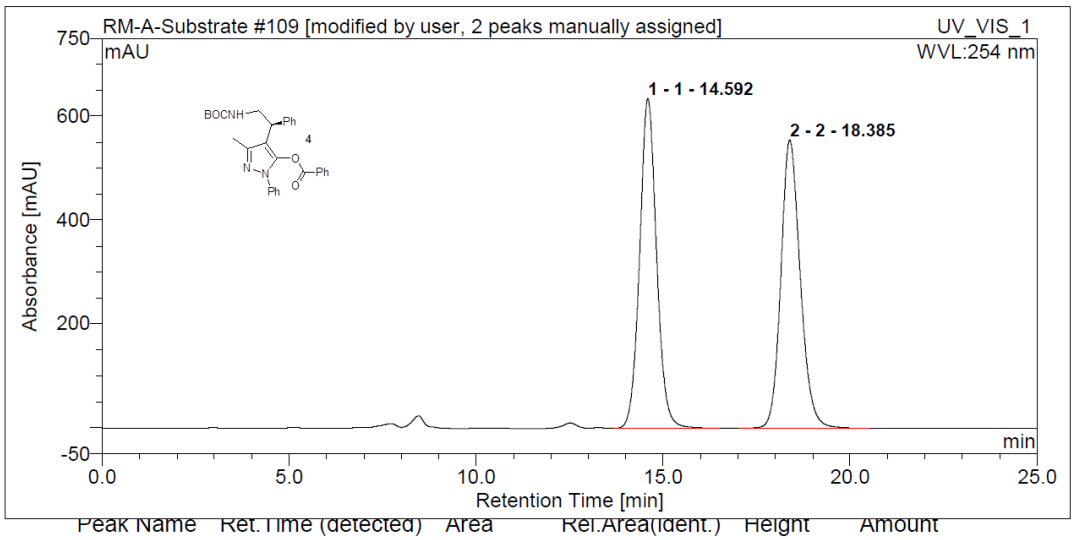
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
24	1	8.42	69.32186	50.31991654	368.6073	n.a.
26	2	11.30	68.440	49.68008346	272.868	n.a.

RM-A-1C



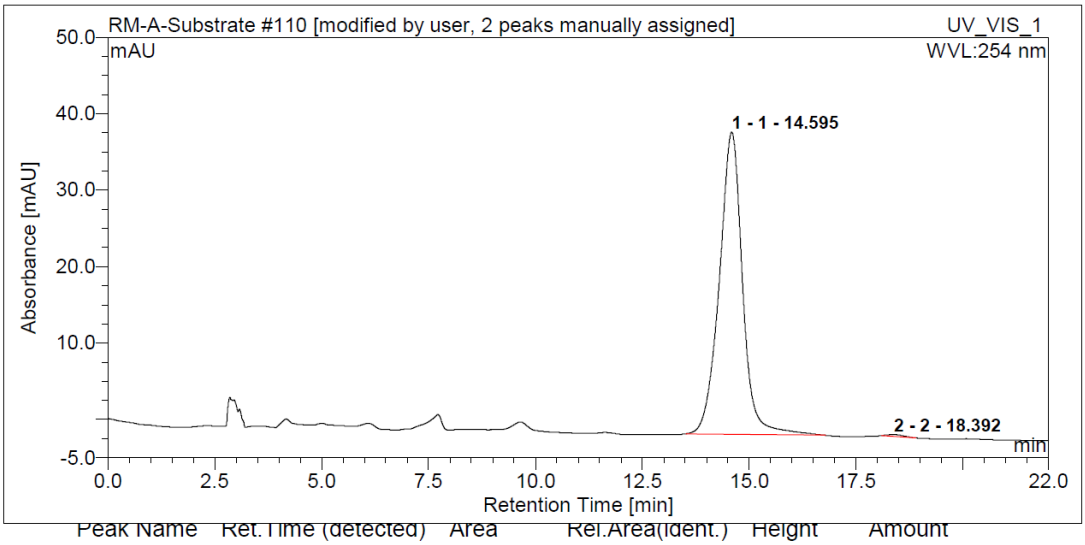
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
38	1	8.62	0.225035	0.5328755442	1.22187	n.a.
49	2	11.94	42.005	99.46712446	147.895	n.a.

RM-A-51R



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(Ident.) %	Height mAU	Amount
1	1	14.59	334.1361	50.03660034	635.1529	n.a.
2	2	18.39	333.647	49.96339966	555.262	n.a.

RM-A-51C



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(Ident.) %	Height mAU	Amount
1	1	14.60	24.94148	99.56793267	39.53263	n.a.
2	2	18.39	0.108	0.4320673341	0.249	n.a.

2.9. References:

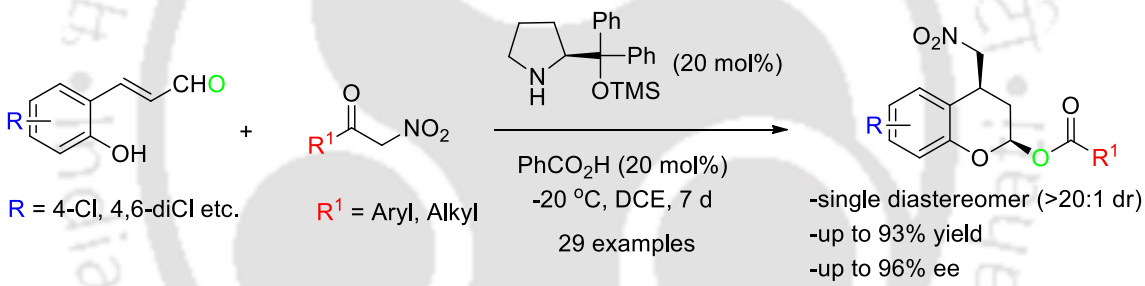
1. For selected reviews, see: (a) Sondhi, S. M.; Dinodia, M.; Singh, J.; Rani, R. *Curr. Bioact. Comp*. **2007**, *3*, 91. (b) Varvounis, G. *Adv. Heterocycl. Chem*. **2009**, *98*, 143. (c) Schmidt, A.; Dreger, A. *Curr. Org. Chem*. **2011**, *15*, 1423. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev*. **2011**, *111*, 6984.
2. (a) Cuberes-Altisent, R.; Holenz, J. PCT Int. Appl. WO2007098953, 2007; *Chem. Abstr*. **2007**, *147*, 301168. (b) Teranishi, H.; Fushimi, N.; Yonekubo, S.; Shimizu, K.; Shibazaki, T.; Isaji, M. PCT Int. Appl. WO2004014932, 2004; *Chem. Abstr*. **2004**, *140*, 199632. (c) Washburn, W. N. Pct Int. Appl. WO2003020737, 2003; *Chem. Abstr.* **2003**, *138*, 221784. (d) Shiohara, H.; Fujikura, H.; Fushimi, N.; Ito, F.; Isaji, M. PCT Int. Appl. WO 2002098893, 2002; *Chem. Abstr*. **2003**, *138*, 24917. (e) Selwood, D. L.; Brummell, D. G.; Budworth, J. *J. Med. Chem*. **2001**, *44*, 78. (f) Barladi, P. G.; Nunez, M. D. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Estevez, F.; Romagnoli, R. *J. Med. Chem*. **2004**, *47*, 2877. (g) Brana, M. F.; Gradillas, A.; Ovalles, A. G.; Lopez, B.; Acero, N.; Llinares, F.; Mingarro, D. M. *Bioorg. Med. Chem*. **2006**, *14*, 9. (h) Alterico, D.; Jereczek-Fossa, B. A.; Fiore, M. R.; Piperno, G.; Ansarin, M.; Orecchia, R. *Anticancer Res*. **2007**, *27*, 1105. (i) Hughes, K. A.; Lahm, G. P.; Selby, T. P. PCT Int. Appl. WO2004046129, **2009**; *Chem. Abstr.* **2004**, *141*, 23526. (j) Ohno, R.; Watanabe, A.; Matsukawa, T.; Ueda, T.; Sakurai, H.; Hori, M.; Hirai, K. *J. Pesticide Sci.* **2004**, *29*, 15. For a review, see: Washburn, W. N. *J. Med. Chem*. **2009**, *52*, 1785.
3. Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett.* **2015**, *17*, 1417.
4. (a) Janin, Y. L. *Bioorg. Med. Chem.* **2007**, *15*, 2479. (b) Gutierrez-Lugo, M. T.; Bewley, C. *J. Med. Chem.* **2008**, *51*, 2606. (c) Matthews, I. R. PCT Int.Appl. WO 46679, **2005**. (d) Kimata, A.; Nakagawa, H.; Ohyama, R.; Fukuuchi, T.; Ohta, S.; Suzuki, T.; Miyata, N. *J. Med. Chem.* **2007**, *50*, 5053.
5. Vila, C.; Amr, F. I.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Chem. Asian J.* **2016**, *11*, 1532
6. Šimek, M.; Remeš, M.; Veselý, J.; Rios, R. *Asian J. Org. Chem.* **2013**, *2*, 64.
7. (a) Hu, X.; Gao, B.; Chu, Y.; Li, W.; Liu, X.; Lin, L.; Feng, X. *Chem. Eur. J.* **2012**, *18*, 3473. (b) Pérez-Aguilar, M. C.; Valdés, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13729; *Angew. Chem. Int. Ed* **2015**, *127*, 13933.

8. Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819.
9. Lu, R.-J.; Yan, Y.-Y.; Wang, J.-J.; Du, Q.-S.; Nie, S.-Z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230.
10. Li, P.; Chan, S. H.; Chan, A. S. C.; Kwong, F. Y. *Org. Biomol. Chem.* **2011**, *9*, 7997.
11. Geng, Z.-C.; Chen, X.; Zhang, J.-X.; Li, N.; Chen, J.; Huang, X.-F.; Zhang, S.-Y.; Tao, J.-C.; Wang, X.-W. *Eur. J. Org. Chem.* **2013**, 4738.
12. Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249.
13. Li, J.-H.; Du, D.-M. *Org. Biomol. Chem.* **2013**, *11*, 6215.
14. Li, J.-H.; Du, D.-M. *Org. Biomol. Chem.* **2015**, *13*, 5636.
15. Li, F.; Sun, L.; Teng, Y.; Yu, P.; Zhao, J. C.-G.; Ma, J.-A. *Chem. Eur. J.* **2012**, *18*, 14255.
16. Hack, D.; Chauhan, P.; Deckers, K.; Mizutani,Y.; Raabea, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 2266.
17. CCDC 1523176 contains the crystallographic data for **3af**.
18. Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2014**, *356*, 2330.
19. Yang, W.; Zhang, Y.; Qiu, S.; Zhao, C.; Zhang, L.; Liu, H.; Zhou, L.; Xiao, Y.; Guo, H. *RSC Adv.* **2015**, *5*, 62343.
20. Phukan, M.; Jyoti, K.; Borah, Borah, R. *Synthetic Communications* **2008**, *38*, 3068.
21. Zhou, M.; Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. *Org. Lett.* **2013**, *15*, 5524.

Organocatalytic Asymmetric Michael/Hemiacetalization/Acyl Transfer Reaction of α-Nitroketones with *o*-Hydroxycinnamaldehydes: Synthesis of 2,4-Disubstituted Chromans*

Abstract:

An organocatalytic asymmetric cascade Michael/hemiacetalization/acyl transfer reaction between *o*-hydroxycinnamaldehydes and α-nitroketones was developed. Prolinol TMS ether catalyst in combination with benzoic acid was found to be the most effective for this reaction which proceeded through an equilibrium of lactols to provide a single diastereomer of enantioenriched 2,4-disubstituted chromans.



*Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2018**, *16*, 1598.

3.1. Introduction of chroman:

Chroman is the heterocyclic motif consisting of a benzene ring fused to a pyran ring and also known as benzopyran. Chromans have two structural isomers such as 2*H*-chroman and 4*H*-chroman (Figure 1). Chiral chroman is one of the privileged medicinal pharmacophores which appears as an important structural component in several natural compounds and achieved great attention because of their interesting biological activities.[1] For example, (*S*)-Equol, a metabolite of the soy isoflavone daidzein, demonstrated higher estrogenic activity than daidzein, and may enhance the propagation

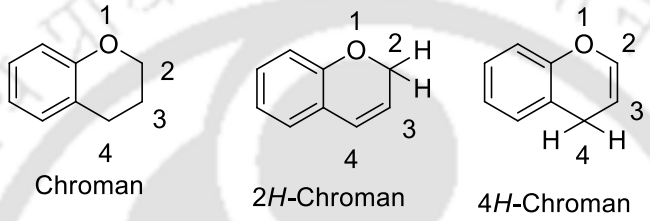


Figure 1. Types of chromans.

of breast cancer cells.[2] (+)-Myristinin A is a naturally occurring DNA polymerase β inhibitor and effective DNA damaging agent.[3] Cromakalim is found to have vasodilatory or anti-hypertensive effects.[4] Sorbinil acts as an aldolase reductase inhibitor and has been shown to recover nerve conduction velocity in diabetic patients.[5] Catechin prevents

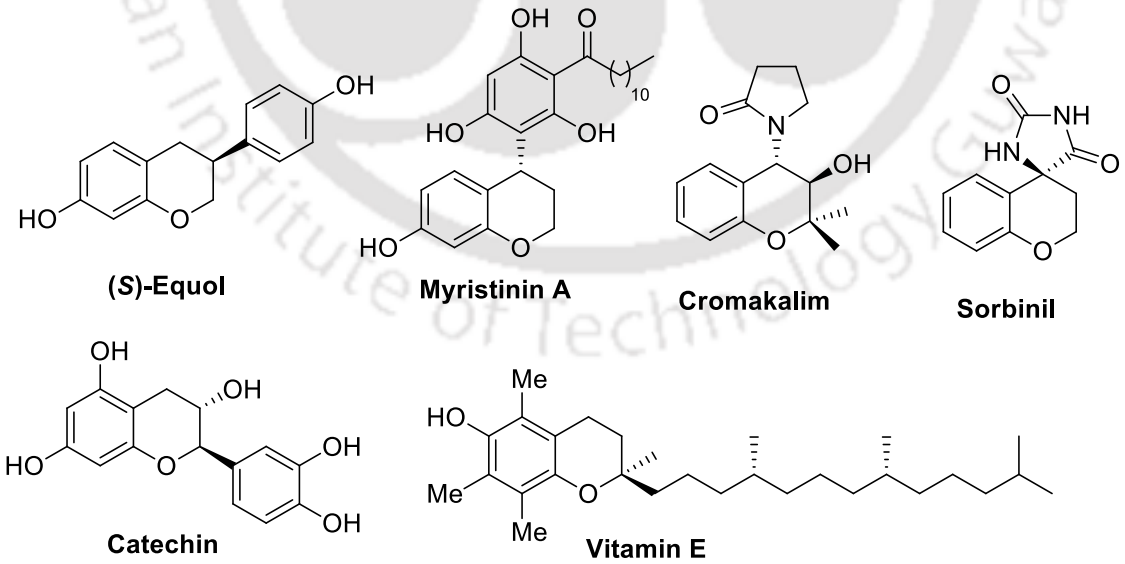


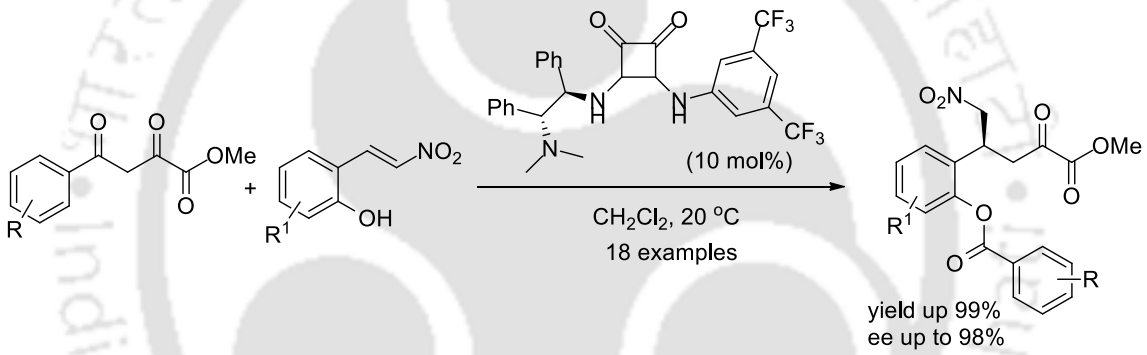
Figure 2. Biologically active chroman derivatives.

intestinal tumor formation and suppresses focal adhesion kinase activation in the min/+mouse.[6] Vitamine E is the naturally occurring chroman, which has antioxidant

activity (Figure 2).[7] Though a variety of organocatalytic routes have been reported in the last decade, the development of efficient methods for the enantioselective construction of chroman rings having diverse substitutions is important to find of new chiral drugs and other utilities.

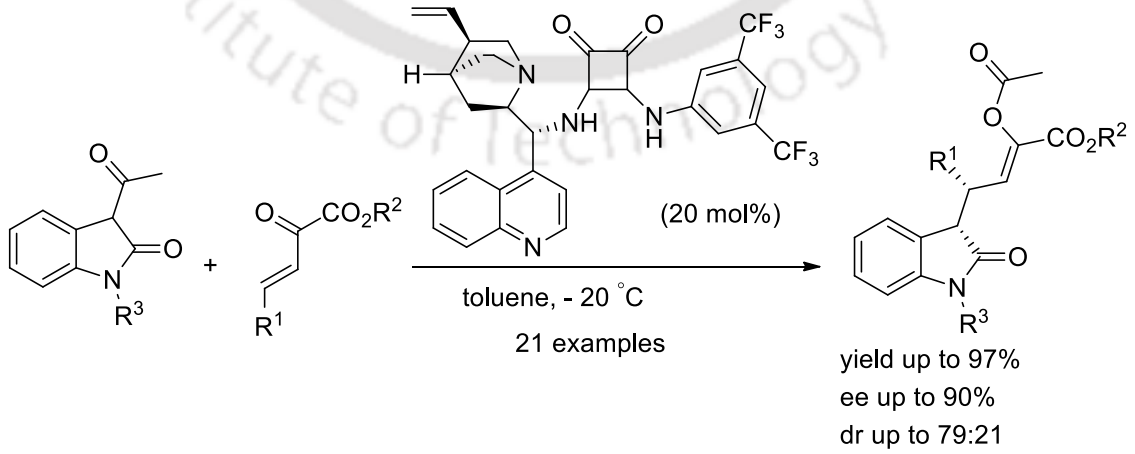
3.2. Michael/hemiketalization/acyl or alkyl transfer reaction:

An organocatalytic asymmetric cascade Michael/hemiketalization/retro-aldol reaction has been established for the chiral synthesis of α-keto esters by Wang *et al*. Acyl transfer reaction of 2-[(*E*)-2-nitrovinyl]phenols and 2,4-dioxo-4-arylbutanoates furnished α-keto esters with moderate to excellent enantioselectivities by using bifunctional tertiary amine squaramide catalyst having (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine moiety (Scheme 1).[8]



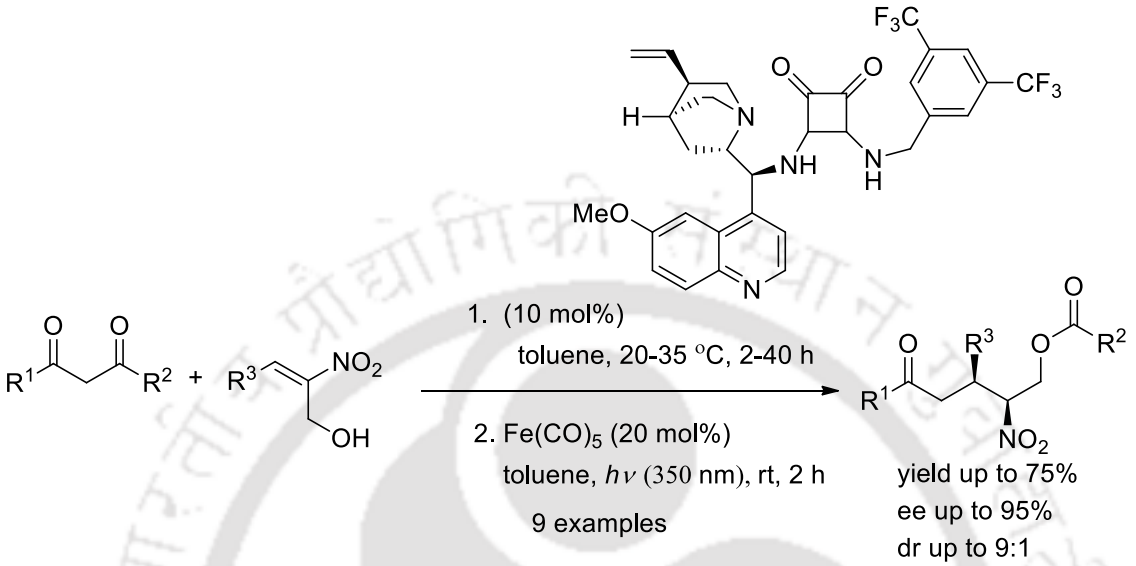
Scheme 1

Wang group developed Michael/hemiketalization/alkyl reaction of 3-acetyl-oxindoles with α,β-unsaturated ketoesters by using cinchonine amino bifunctional squaramide catalyst (Scheme 2).[9]



Scheme 2

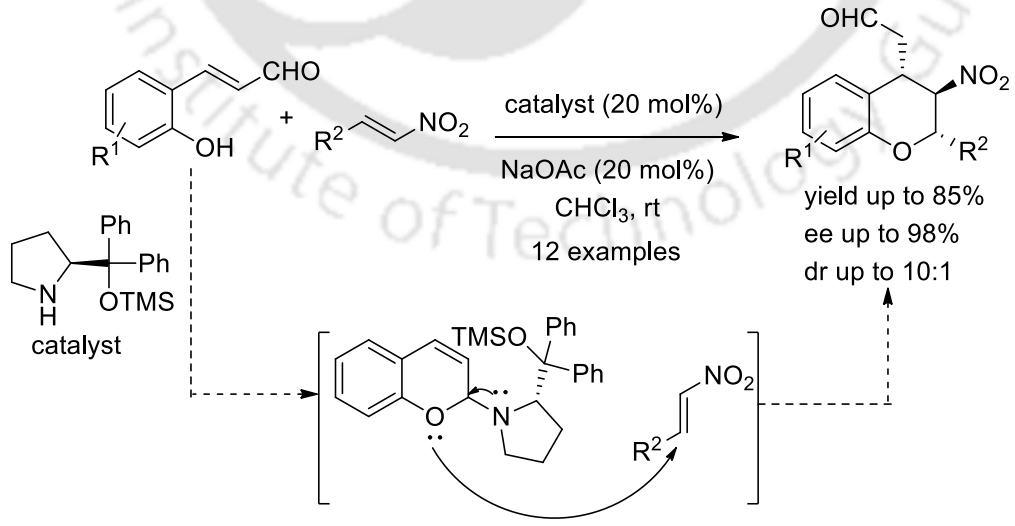
A bi-catalytic method based on Michael/hemiketalization/acyl transfer reaction of 1,3-diketones with α-hydroxynitroolefins for the chiral synthesis of nitro ketoesters has been developed by Rodriguez *et al*. (Scheme 3).[10]



Scheme 3

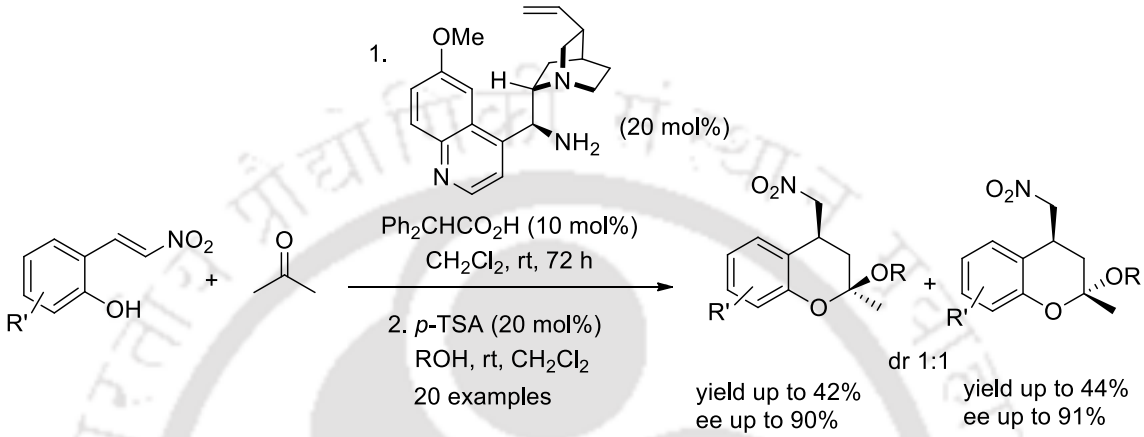
3.3. Previous reports on synthesis of chiral chromans:

Chromans containing three stereogenic centers have been achieved with excellent enantio- and diastereoselectivities by reacting 2-hydroxycinnamaldehydes with α,β-unsaturated nitroolefins under the catalytic condition of diphenylprolinol TMS ether *via.* enantioselective cascade oxa-Michael-Michael mechanistic pathway (Scheme 4).[11]



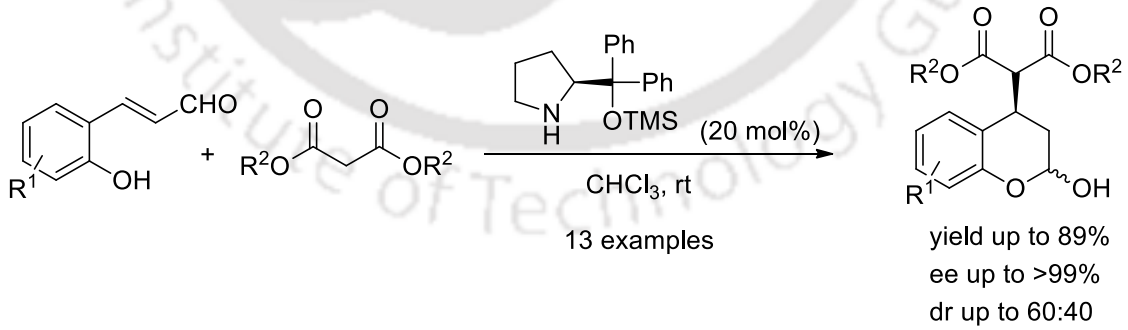
Scheme 4

Ramachary and co-workers disclosed asymmetric Michael/acetalization reactions of acetones with 2-hydroxy-β-nitrostyrenes in presence of epi-quinine amine catalyst and additive Ph_2CHCO_2H followed by *p*-TSA and alcohol. Substituted chromans have been synthesized with 1:1 diastereoselectivities and moderate to good enantiomeric excesses (Scheme 5).[12]

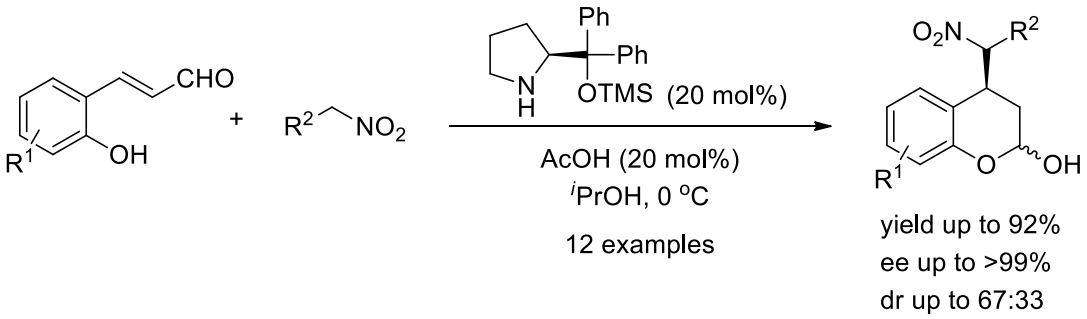


Scheme 5

The asymmetric organocatalytic Michael/cyclization reaction of malonates with *o*-hydroxycinnamaldehydes has been developed by Kim *et al*. Chromans with excellent enantioselectivities and poor diastereoselectivities were obtained by using the diphenylprolinol trimethylsilyl (TMS) ether catalyst (Scheme 6).[13] This group utilized a similar protocol for the synthesis of substituted chromans by using nitroalkanes as the nucleophiles in place of malonates (Scheme 7).[14]



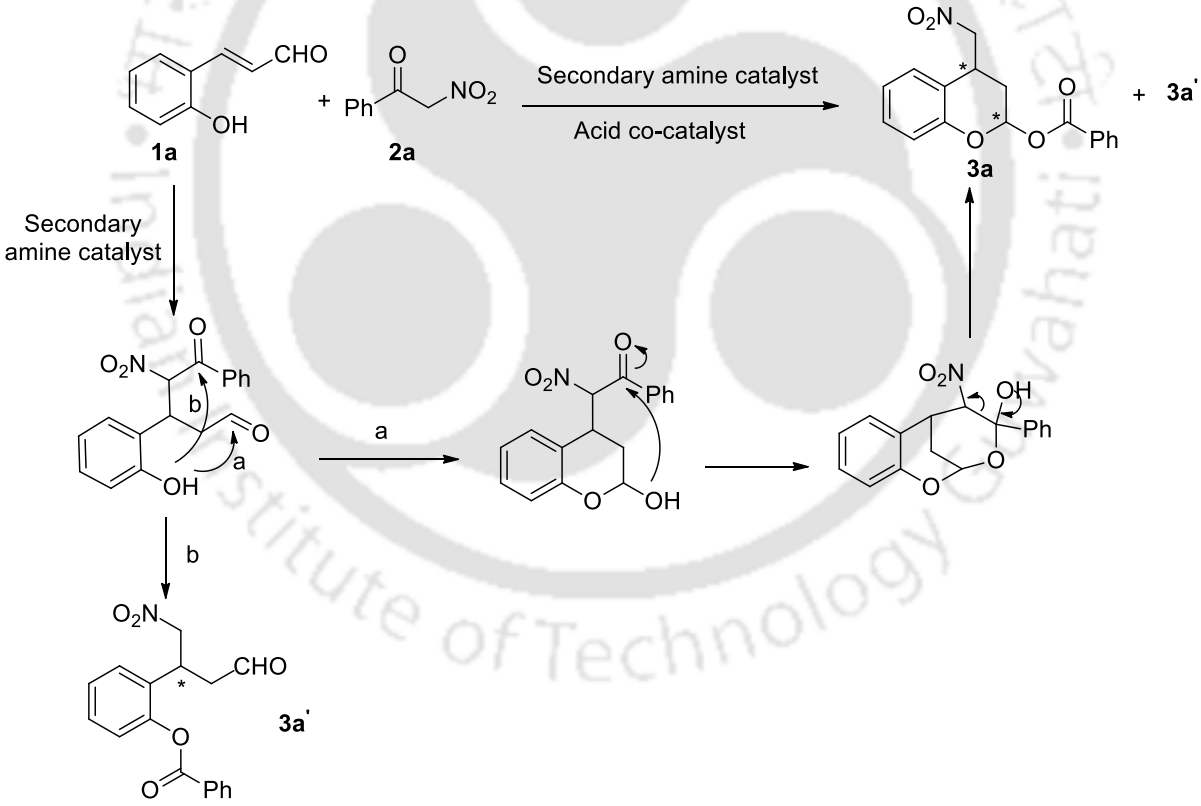
Scheme 6



Scheme 7

3.4. Concept

From the literature studies, most of the classical methods suffer from lack of diastereoselectivity synthesis of chromans. Realizing the significance of chiral chromans, the development of new divergent synthetic strategies for enantiomerically enriched



Scheme 8

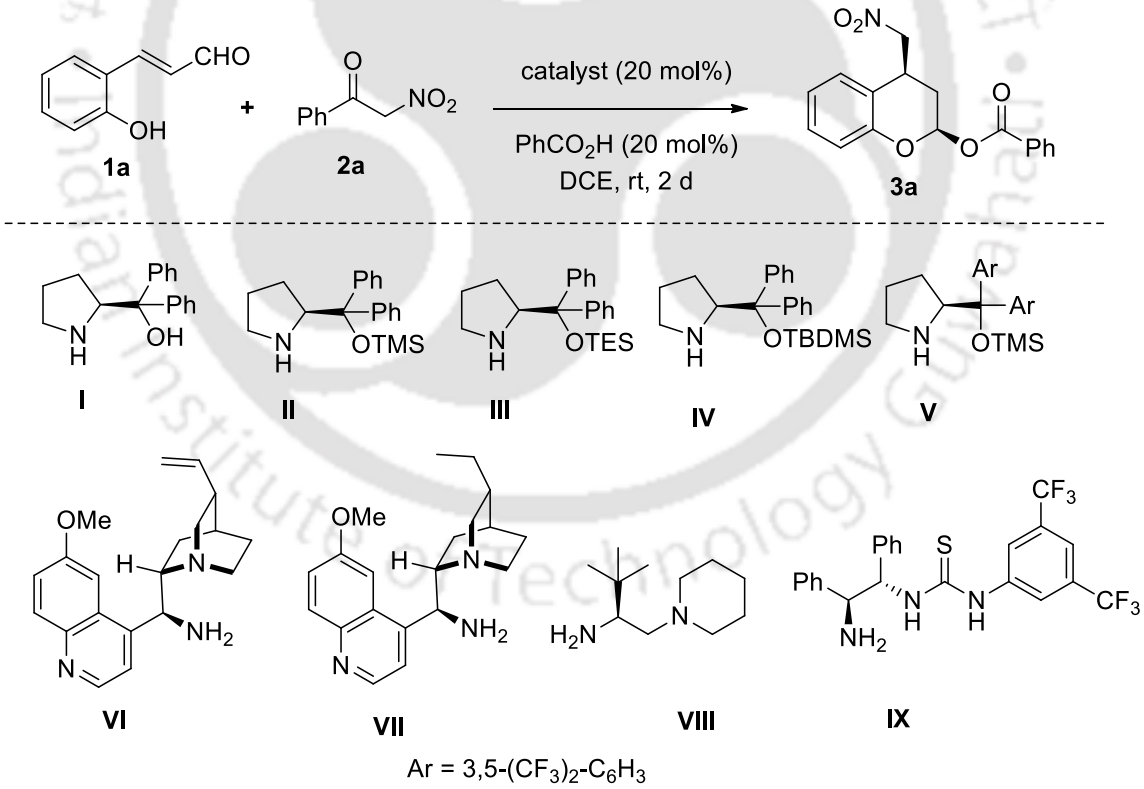
chroman derivatives are still in high demand. Inspired by the reported literatures[15] on chiral chroman synthesis, we thought of an alternative approach for asymmetric Michael/hemiacetalization/acyl transfer reaction between α-nitroketones and *o*-hydroxycinnamaldehydes and envisioned to utilize secondary amine catalyst prolinol

ethers derivative which would activate the electrophilic aldehyde by forming enamine intermediate. In our designed protocol, there might be possibility of formation of two products **3a** and **3a′**, but our interest was on diastereoselective synthesis of **3a** with an enantioenriched form (Scheme 8).

3.5. Results and discussion:

Initially, a model reaction between *o*-hydroxycinnamaldehyde (**1a**) and 2-nitro-1-phenylethanone (**2a**) was studied with α,α-diphenyl-2-pyrrolidinemethanol (**I**) and benzoic acid in DCE solvent at room temperature (Table 1, entry 1). The product **3a** was isolated in 80% yield and with 56% ee, and the structure was determined to be chroman **3a** by ^{1}H NMR. The relative stereochemistry of pure single diastereomer **3a** was solved by 2D NMR analysis. Gratifyingly, in presence of prolinol TMS ether catalyst **II**, a considerable increase in enantioselectivity was observed (entry 2).[16]

Table 1. Catalyst optimization



entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	80	56
2	**II**	**85**	**78**

3	**III**	84	72
4	**IV**	82	78
5	**V**	complex mixture	-
6	**VI**	75	52
7	**VII**	70	65
8	**VII**	60	30
9	**IX**	85	-

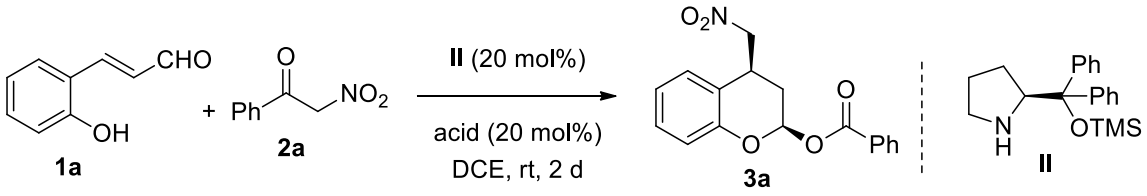
[a]Reactions were carried out with 0.25 mmol of **1a** and 0.05 mmol of **2a** in DCE (0.5 mL) at room temperature for 2 days. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]ee was determined by HPLC.

To further improve the enantioselectivity, other silyl ether catalysts **III** and **IV** were prepared but they failed to enhance the enantiomeric excess of the product (entries 3-4). Then catalyst **V** having aryl groups with bis-3,5-trifluoromethyl substituent was engaged in the reaction, however, only a complex mixture was attained (entry 5). Cinchona alkaloid derived catalysts such as **VI** and **VII** were checked in the reaction but provided only moderate enantioselectivity of the product **3a** (entries 6-7). Then, *tert*-leucine derived catalyst **VIII** was employed in the reaction, delivering the desired product **3a** with only 30% ee (entry 8). Unfortunately, the catalyst **IX** derived from (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine furnished a racemic product **3a** (entry 9). Therefore, catalyst **II** provided the best result compared to the other catalysts (entry 2).

3.5.1. Acid screening:

After screening a variety of catalysts, the reaction was further studied to improve the enantioselectivity of product **3a** by changing different types of acids such as aromatic and aliphatic acids in the presence of catalyst **II** (Table 2, entries 1-5). Initially, aromatic acids such as 2-$FC_6H_4CO_2H$ and 3-$NO_2C_6H_4CO_2H$ were screened, but enantioselectivity of the product **3a** did not improve (entries 2-3). Aliphatic acid such as AcOH provided similar result of $PhCO_2H$ (entries 1 and 4). Besides, inorganic base like NaOAc in combination with catalyst **II** was also examined for the reaction, but surprisingly the reaction did not deliver any product (entry 5).

Table 2. Acid optimization



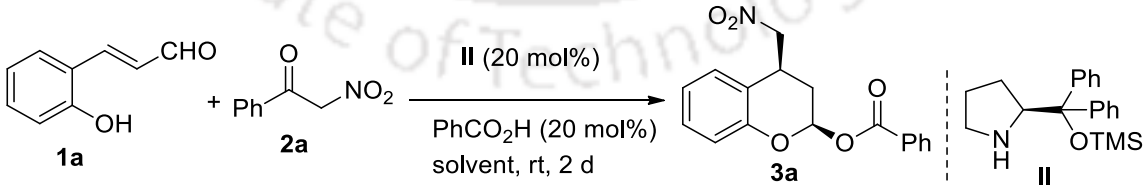
entry[a]	acid	yield (%)[b]	ee (%)[c]
1	**$PhCO_2H$**	**85**	**78**
2	$2\text{-}FC_6H_4CO_2H$	77	76
3	$3\text{-}NO_2C_6H_4CO_2H$	75	70
4	AcOH	80	78
5[d]	NaOAc	0	-

[a]Reactions were carried out with 0.25 mmol of **1a** and 0.05 mmol of **2a** in DCE (0.5 mL) at room temperature for 2 days. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]ee was determined by HPLC. [d]Inorganic base.

3.5.2. Solvent screening:

Furthermore, the effect of solvents was examined for the reaction by using different types of solvents such as polar, non-polar, etherate variants (Table 3, entries 1-4). Interestingly, comparable results were observed using polar solvents such as CH_2Cl_2 and DCE (entries 1-2). Toluene was also tested under the reaction condition and only 68% enantioselectivity was observed (entry 3). In addition, 1,4-dioxane afforded product **3a** in good yield but with lesser enantioselectivity (entry 4).

Table 3. Solvent optimization



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	85	72
2	**DCE**	**87**	**78**
3	$PhCH_3$	80	68

4	1,4-dioxane	70	45

[a]Reactions were carried out with 0.25 mmol of **1a** and 0.05 mmol of **2a** in solvent (0.5 mL) at room temperature for 2 days. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]ee was determined by HPLC.

3.5.3. Optimization of temperature and concentration:

In the next phase of screening, we turned our attention to the reaction temperature and it proved to be beneficial (Table 4). Lowering the temperature to 0 °C and −20 °C improved the enantiomeric excess significantly (entries 2-3), but the yield dropped. Pleasingly, a good yield of 85% was achieved by running the reaction for 7 days at −20 °C without loss of enantiomeric excess (entry 4). Further decrease in temperature to −40 °C did not provide any product of the reaction (entry 5). The enantioselectivity of **3a** was slightly decreased by varying the concentrations of the reaction (entries 6-7). Then, inferior results were observed by increasing or decreasing the equivalent of aldehyde **1a** (entries 8-9). As a result, the best optimized reaction conditions was detected by using catalyst **II** (20 mol%) and additive benzoic acid (20 mol%) in DCE at −20 °C (entry 4).

Table 4. Temperature and concentration optimization

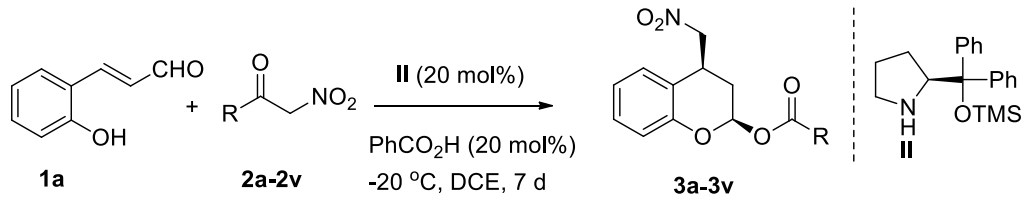
entry[a]	temp (°C)	conc. (M)	time (day)	yield (%)[b]	ee (%)[c]
1	25	0.1	2	85	78
2	0	0.1	2	50	90
3	−20	0.1	2	40	94
4	**−20**	**0.1**	**7**	**85**	**94**
5	−40	0.1	7	0	-
6	−20	0.2	7	85	93
7	−20	0.05	7	85	92
8[d]	−20	0.1	7	85	90
9[e]	−20	0.1	7	85	89

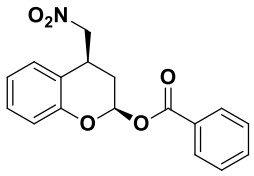
[a]Reactions were carried out with 0.25 mmol of **1a** and 0.05 mmol of **2a** in solvent. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]ee was determined by HPLC. [d]4 eq. of **1a**. [e]6 eq. of **1a**.

3.5.4. Substrate scope:

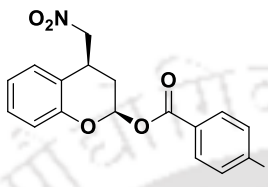
With the optimized reaction condition, the scope and generality of the reaction was investigated. Initially, a variety of α-nitroketones **1** having different aryl groups were tested (Table 5). It was found that a range of substituents can be incorporated in the *ortho*-, *meta*- and *para*- position of the aryl group and the corresponding products were achieved in high yields and enantioselectivities. At first, 4-alkyl substituted aryl nitroketones were studied; such as **2b** and **2c** having 4-methyl and 4-isopropyl groups respectively delivered products **3b** and **3c** with excellent enantioselectivities as well as in good yields. 4-*tert*-Butyl substituted product **3d** was also obtained in good enantioselectivity. Then, nitroketone **2e** with 4-anisyl group was employed in the reaction and the desired product **3e** was obtained in 92% ee. Inspired by this result, 4-alkoxy substituted nitroketones were checked in the reaction and excellent results were observed. Nitroketones **2f** and **2g** having 4-ethoxy and 4-^{n}propoxy substitutions respectively furnished products **3f** and **3g** with good yields and in excellent level of enantioselectivities. Other 4-alkoxy substituted α-nitroketones **2h**-**2k** were synthesized and engaged in the reaction. Interestingly, the reactions were effective enough to provide the corresponding products **3h**-**3k** with promising results (88-96% ees). 4-Halo substituted aryl nitroketones also participated in the reaction and delivered the products **3l**-**3n** in good yields with acceptable enantioselectivities. The *meta*-substituted products **3o** and **3p** were found to have slight effect on the enantioselectivities, but in good yields. Delightfully, *ortho*-substituted product **3q** having 2-methyl group was achieved in excellent enantioselectivity with good yield. Additionally, the other *ortho*-substituented nitroketones such as with 2-methoxy and 2-fluoro namely **2r** and **2s** furnished the products **3r** and **3s** with 86% and 84% enantiomeric excesses respectively. Then, 2,4-disubstituted nitroketone **2t** was checked and provided the product **3t** in 94% ee. Heteroaryl substituted nitroketone **2u** was also well tolerated in the optimized reaction condition and delivered the corresponding product **3u** with good yield and enantioselectivity. Nitroketone **2v** containing a cyclohexyl moiety was then screened and delightfully afforded the product **3v** with excellent enantioselectivity and moderate yield.

Table 5. Scope of α-nitroketones[a,b,c]

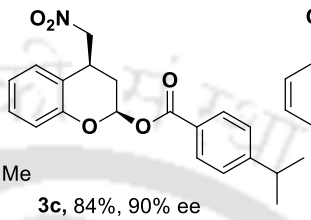




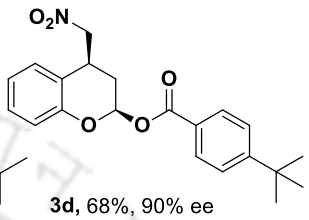
3a, 85%, 94% ee



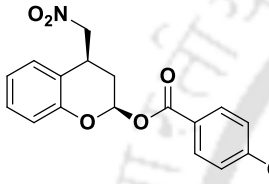
3b, 76%, 92% ee



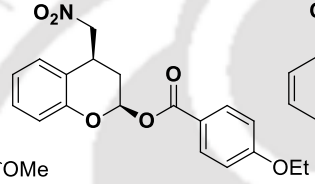
3c, 84%, 90% ee



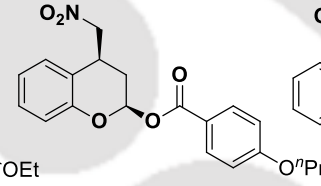
3d, 68%, 90% ee



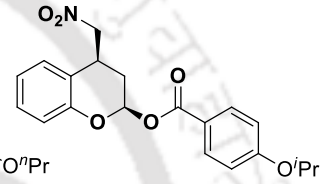
3e, 90%, 92% ee



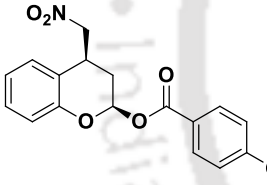
3f, 70%, 90% ee



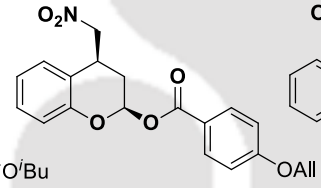
3g, 84%, 96% ee



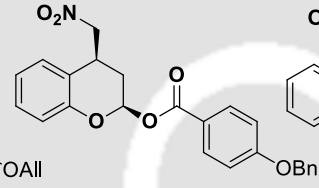
3h, 78%, 96% ee



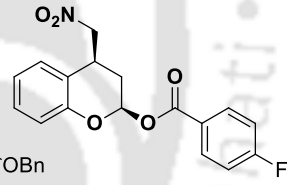
3i, 86%, 96% ee



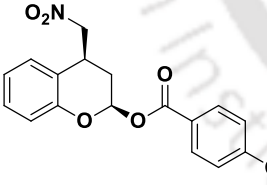
3j, 60%, 88% ee



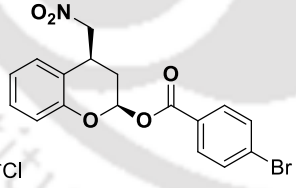
3k, 84%, 96% ee



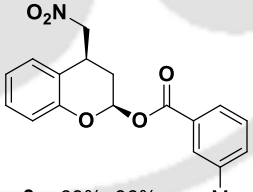
3l, 76%, 84% ee



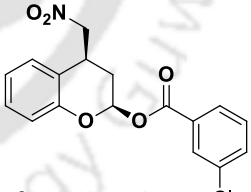
3m, 72%, 82% ee



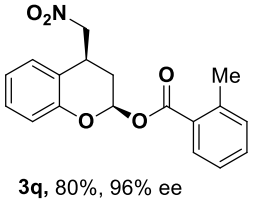
3n, 70%, 88% ee



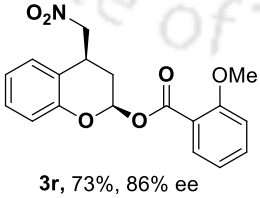
3o, 69%, 86% ee



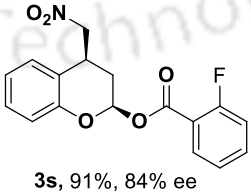
3p, 78%, 86% ee



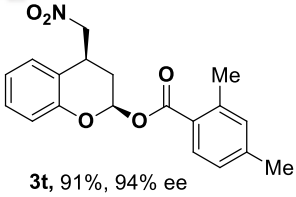
3q, 80%, 96% ee



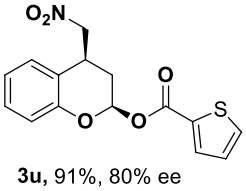
3r, 73%, 86% ee



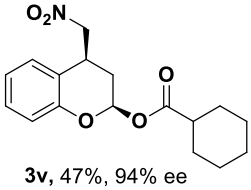
3s, 91%, 84% ee



3t, 91%, 94% ee



3u, 91%, 80% ee



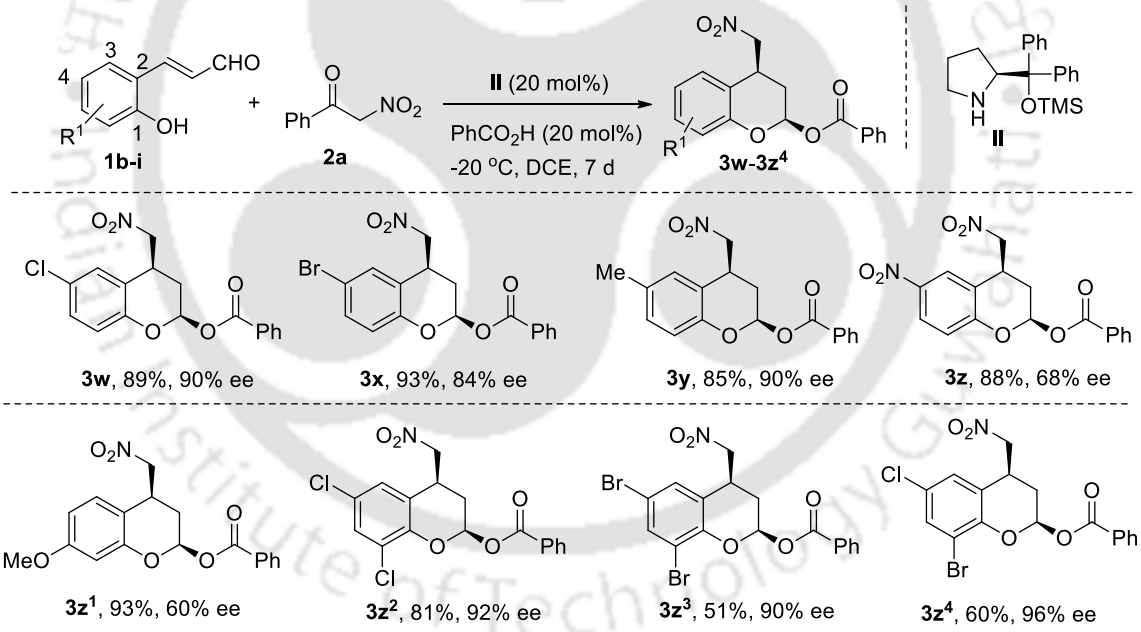
3v, 47%, 94% ee

[a]Reactions were carried out with 0.5 mmol of **1a** and 0.1 mmol of **2** with 20 mol% catalyst **II** and 20 mol%

$PhCO_2H$ in 1 mL DCE at −20 °C for 7 days. [b]Isolated yield after silica gel column chromatography of the single diastereomer (>20:1 dr). [c]Determined by HPLC.

The next stage of experiments involved screening of different *o*-hydroxyaromatic α,β-unsaturated aldehydes in this method (Table 6). Thus different substituted α,β-unsaturated aldehydes **1b-i** were prepared and employed in the reaction with nitroketone **2a**. The reaction progressed smoothly by delivering the corresponding products **3w-3z^4** in moderate to high yields with high enantioselectivities. For examples, *para*-substituted α,β-unsaturated aldehydes **1b** and **1c** having 4-chloro and 4-bromo substituents furnished products **3w** and **3x** respectively with moderate to good enantiomeric excesses. In addition, 4-methyl substituted *o*-hydroxycinnamaldehyde **1d** delivered the product **3y** with excellent enantiomeric excess. When 4-nitro substituted *o*-hydroxycinnamaldehyde **1e** was introduced in the reaction, enantioselectivity of the product **3z** got decreased.

Table 6. Scope of o-hydroxycinnamaldehyde[a,b,c]



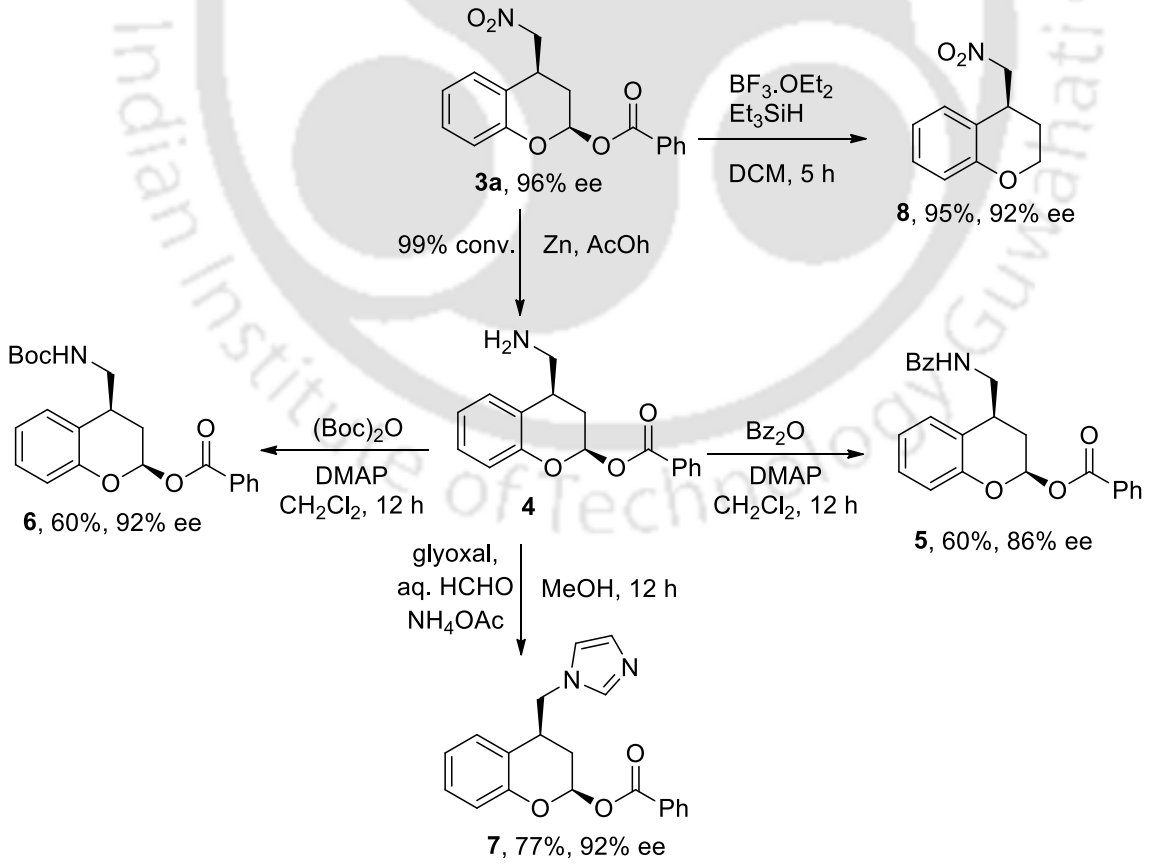
[a]Reactions were carried out with 0.5 mmol of **1** and 0.1 mmol of **2a** with 20 mol% catalyst **II** and 20 mol% $PhCO_2H$ in 1 mL DCE at −20 °C for 7 days. [b]Isolated yield after silica gel column chromatography of the single diastereomer (> 20:1 dr). [c]Determined by HPLC.

Unfortunately, the enantioselectivity dropped to 60% ee for 5-methoxy substituted product **3z^1** although excellent yield was observed. The products **3z^2** and **3z^3** containing 4,6-dichloro and 4,6-dibromo substitutions respectively were achieved with excellent enantioselectivities. Interestingly, the highest 96% ee was obtained for product **3z^4**

having 4-chloro-6-bromo substitutions with moderate yield. These halo group containing products are important as they can be converted to other derivatives *via* cross-coupling reactions.

3.5.5. Synthetic transformations:

The synthetic utility of our method was further demonstrated by carrying out few reactions on **3a** (Scheme 9). Initially the reduction of **3a** using zinc and acetic acid was performed to provide amino group containing chroman **4** in 99% conversion. Chroman **4** was then subjected to a range of reactions. Protection of the amino group with benzoic anhydride led to the formation of **5** with the slight reduction in enantiopurity. Gratifyingly, the enantiomeric excess was almost preserved for **6** having *N*-Boc protection. Then imidazole containing chroman **7** was synthesized by the reaction of **4** with glyoxal, aqueous formaldehyde and ammonium acetate[17] and here also the enantiomeric excess was nearly retained. Finally, 4-substituted chroman **8** was prepared in high yield and enantiopurity after treatment of **3a** with $BF_3 \cdot OEt_2$ and triethylsilane.



Scheme 9. Synthetic transformations of **3a**

3.5.6. Absolute configuration:

The absolute configuration of the product **3p** was elucidated to be (2*R*,4*S*) by X-ray crystallography (Figure 3).[18] The absolute structure of other products is expected to be the same by analogy.

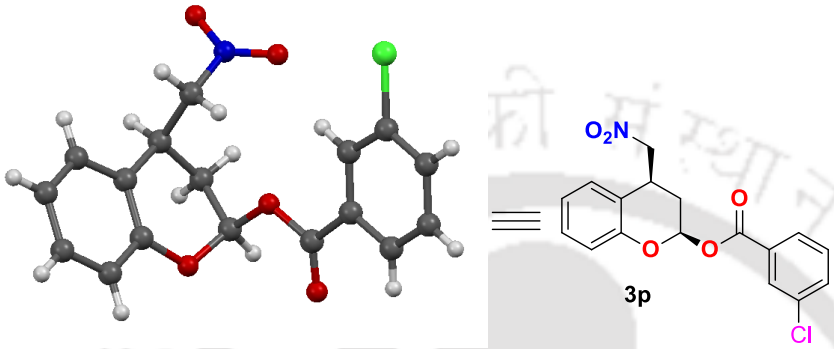
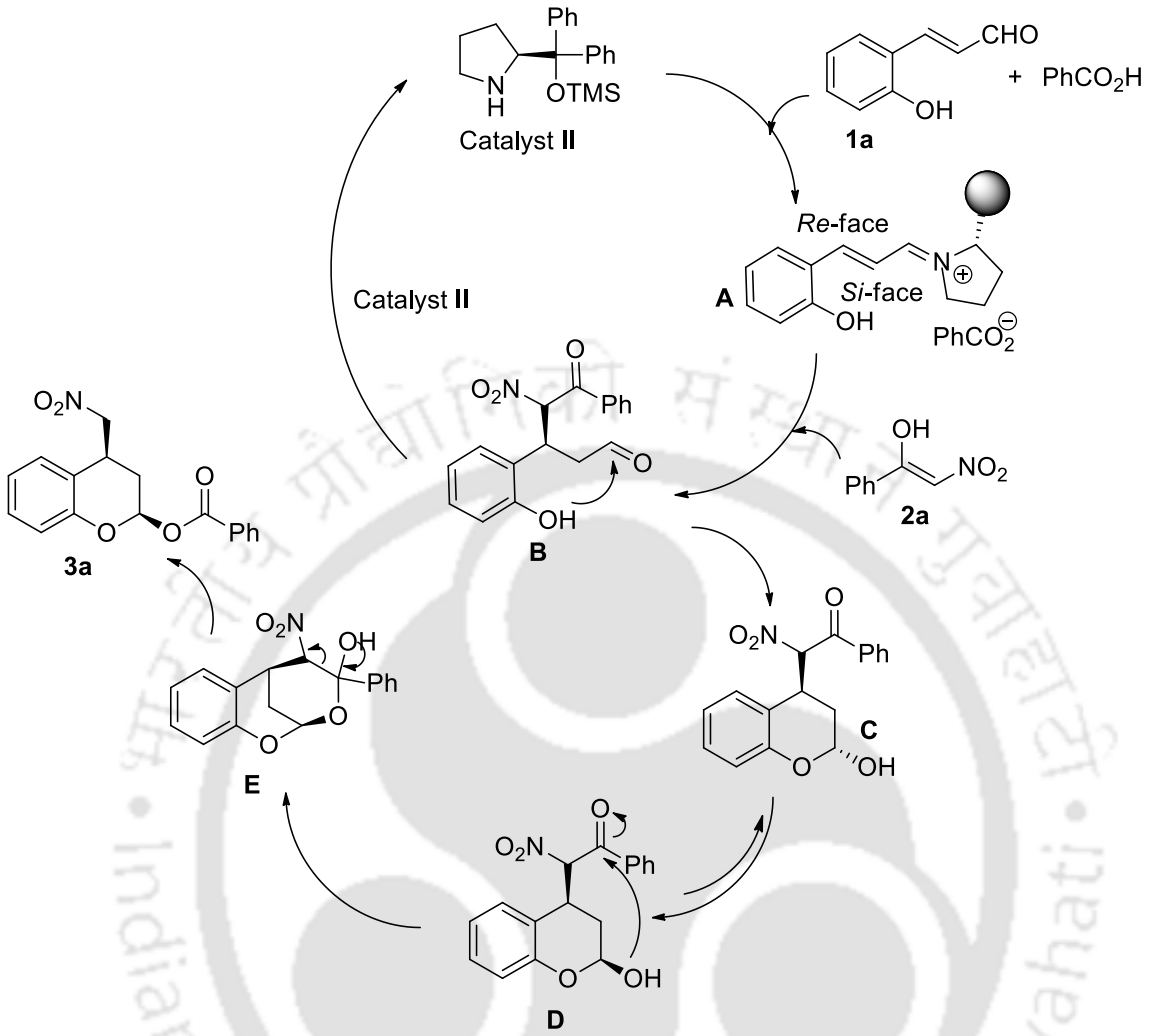


Figure 3. X-ray crystal structure of **3p**

3.5.7. Proposed mechanism:

It was believed that at first *o*-hydroxycinnamaldehyde **1a** reacted with catalyst **II** to provide iminium ion **A** (Scheme 10). Since the *Si*-face of the chiral iminium ion was blocked by bulky diphenylsiloxymethyl group, the additions of nitroketone **2a** occurred only from the *Re*-face to generate intermediate **B** after hydrolysis. Intramolecular hemiacetalization provided two diastereomeric hemiacetals **C** and **D**. Since in **C**, further ketalization reaction could not take place due to *trans*-orientation, only **D** participated in the ketalization step; and thus only **E** was obtained in good yield. Finally retro-Henry reaction of **E** generated chroman **3a**.



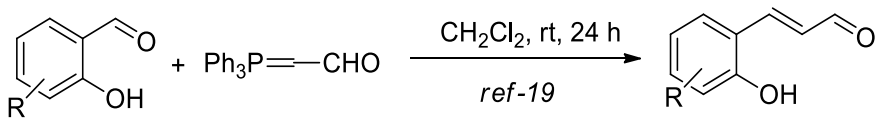
Scheme 10. Proposed mechanism

3.6. Conclusion:

This chapter presented an efficient Michael-hemiacetalization-acyl transfer reaction between α-nitroketones and *o*-hydroxycinnamaldehydes. This reaction delivered single diastereomer of 2,4-disubstituted chroman compounds in good to high yields and with excellent enantioselectivities. Also, selective functionalizations for the synthesis of different di-substituted as well as mono-substituted chromans are appealing. Given the high pharmaceutical significance of chroman compounds our method might be beneficial to synthesize these compounds in a convenient way.

3.7. Experimental section:

3.7.1. General procedure for the synthesis of compound (1):



Scheme 11

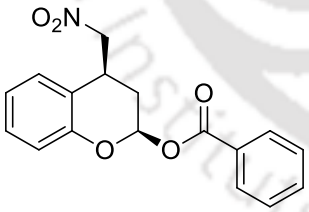
To the stirred solution of salicylaldehyde in CH_2Cl_2 was added (triphenylphosphoranylidene) acetaldehyde at 0 °C, and the resulting mixture was warmed to room temperature (Scheme 11). After 24 h, the products **1** were purified by flash column chromatography on silica gel (Hexane/Ethyl acetate).

3.7.2. General procedure for the synthesis of compound (3):

To a solution of o-hydroxycinnamaldehyde **1** (0.5 mmol) in 1 mL DCE were added **II** (20 mol%) and $PhCO_2H$ (20 mol%) at −20 °C and after 2 h, *α*-nitroketones **2** (0.1 mmol) was added. The reaction mixture was stirred at −20 °C for 7 days. After completion of the reaction, the products were purified by silica gel column chromatography (hexane/ethyl acetate).

3.7.3. Product characterization data:

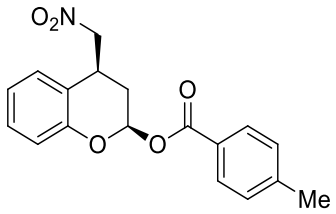
(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3a):



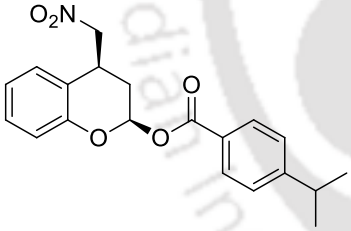
White solid (85%, 27 mg); mp-115 °C; R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 6.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.84 (t, *J* = 2.5 Hz, 1H), 5.04 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.78 (dd, *J* = 12.5, 5.8 Hz, 1H), 3.93 – 3.85 (m, 1H), 2.45 (ddd, *J* = 15.2, 6.6, 3.2 Hz, 1H), 2.37 (dt, *J* = 15.3, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.5, 151.3, 133.9, 130.0, 129.8, 129.4, 129.2, 128.9, 122.6, 118.8, 118.3, 90.4, 80.3, 30.7, 27.1; **ESI-MS** m/z calcd. for $C_{17}H_{19}N_2O_5^+$ $[M+NH_4^+]^+$ 331.1288, found 331.1291; **FT-IR (KBr)** 3437, 2925, 1731, 1604, 1584, 1547, 1491, 1451, 1424, 1374, 1270, 1215, 1176, 1137, 1055 cm^{-1}; The ee value 94% (t_{major} = 20.52 min, t_{minor} = 23.40 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the

eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{24.2}$ = + 177.29 (c 0.775, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-methylbenzoate (3b):



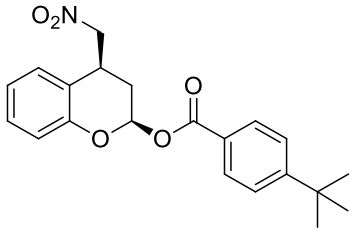
White solid (76%, 25 mg); mp-146 °C; R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.27 (s, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.84 (t, *J* = 2.3 Hz, 1H), 5.05 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.79 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.92 – 3.86 (m, 1H), 2.45 (ddd, *J* = 15.3, 6.6, 3.2 Hz, 1H), 2.42 (s, 3H), 2.37 (dt, *J* = 15.2, 1.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.5, 151.4, 144.8, 130.0, 129.8, 129.6, 129.2, 126.7, 122.5, 118.8, 118.4, 90.3, 80.3, 30.7, 27.2, 21.9; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_5^+$ $[M+NH_4^+]^+$ 345.1445, found 345.1442; **FT-IR (KBr)** 3436, 2924, 2853, 1730, 1610, 1582, 1548, 1490, 1426, 1375, 1331, 1274, 1215, 1175, 1091, 1074 cm^{-1}; The ee value 92% (t_{major} = 29.78 min, t_{minor} = 37.72 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.7}$ = + 133.92 (c 0.790, $CHCl_3$).



(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-isopropylbenzoate (3c):

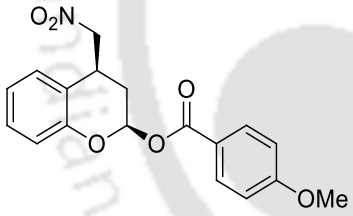
Colourless sticky oil (84%, 30 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 2.3 Hz, 1H), 5.06 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.78 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.92 – 3.86 (m, 1H), 2.95 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.44 (ddd, *J* = 15.2, 6.6, 3.2 Hz, 1H), 2.36 (dt, *J* = 15.2, 1.9 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.5, 155.5, 151.3, 130.2, 129.8, 129.2, 127.0, 127.0, 122.5, 118.8, 118.4, 90.2, 80.3, 34.5, 30.7, 27.2, 23.8, 23.8; **ESI-MS** m/z calcd. for $C_{20}H_{25}N_2O_5^+$ $[M+NH_4^+]^+$ 373.1758, found 373.1762; **FT-IR (KBr)** 3458, 2963, 2927, 2871, 1730, 1610, 1586, 1552, 1490, 1458, 1421, 1379, 1268, 1216, 1180, 1075 cm^{-1}; The ee value 90% (t_{major} = 28.01 min, t_{minor} = 33.01 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-*tert*-butylbenzoate (3d):

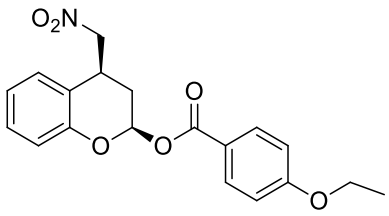


White semisolid (68%, 25 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.23 (t, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.83 (s, 1H), 5.07 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.78 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.94 – 3.84 (m, 1H), 2.44 (ddd, *J* = 15.2, 6.6, 3.1 Hz, 1H), 2.36 (d, *J* = 15.2 Hz, 1H), 1.32 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.4, 157.7, 151.3, 129.9, 129.8, 129.2, 126.6, 125.9, 122.5, 118.8, 118.4, 90.1, 80.4, 35.4, 31.3, 30.7, 27.2; **ESI-MS** m/z calcd. for $C_{21}H_{27}N_2O_5^+$ $[M+NH_4^+]^+$ 387.1914, found 387.1918; **FT-IR (KBr)** 3438, 2960, 2925, 1732, 1607, 1587, 1489, 1458, 1435, 1407, 1379, 1267, 1184, 1214, 1184, 1131 cm^{-1}; The ee value 90% (t_{major} = 22.39 min, t_{minor} = 24.75 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{23.5}$ = + 105.00 (c 1.25, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-methoxybenzoate (3e):



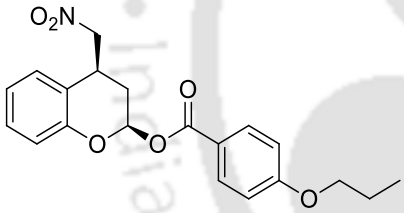
White solid (90%, 31 mg); mp-120 °C; R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 6.8 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.81 (t, *J* = 2.3 Hz, 1H), 5.04 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.78 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.89 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.86 (s, 3H), 2.43 (ddd, *J* = 15.2, 6.5, 3.2 Hz, 1H), 2.35 (dt, *J* = 15.2, 1.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.1, 164.1, 151.4, 132.1, 129.8, 129.1, 122.5, 121.6, 118.9, 118.4, 114.1, 90.1, 80.3, 55.7, 30.7, 27.2; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_6^+$ $[M+NH_4^+]^+$ 361.1394, found 361.1399; **FT-IR (KBr)** 2924, 2851, 1727, 1605, 1548, 1512, 1491, 1452, 1425, 1377, 1326, 1214, 1185, 1165, 1134, 1091 cm^{-1}; The ee value 92% (t_{major} = 38.43 min, t_{minor} = 47.84 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.



(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-ethoxybenzoate (3f):

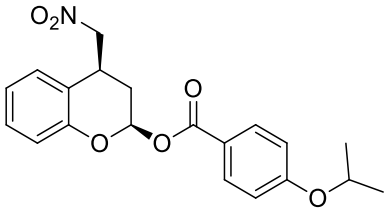
White semisolid (70%, 25 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.81 (t, *J* = 2.3 Hz, 1H), 5.04 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.78 (dd, *J* = 12.6, 5.8 Hz, 1H), 4.08 (q, *J* = 7.0 Hz, 2H), 3.88 (dt, *J* = 11.0, 6.1 Hz, 1H), 2.43 (ddd, *J* = 15.1, 6.6, 3.2 Hz, 1H), 2.37 – 2.32 (m, 1H), 1.43 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.1, 163.5, 151.4, 132.1, 129.8, 129.1, 122.5, 121.4, 118.8, 118.4, 114.6, 90.1, 80.3, 64.0, 30.7, 27.3, 14.8; **ESI-MS** m/z calcd. for $C_{19}H_{23}N_2O_6^+$ $[M+NH_4^+]^+$ 375.1551, found 375.1548; **FT-IR (KBr)** 2984, 2925, 2854, 1724, 1606, 1583, 1549, 1511, 1491, 1455, 1423, 1378, 1378, 1324, 1258, 1214, 1168, 1135, 1113, 1075 cm^{-1}; The ee value 90% (t_{major} = 33.46 min, t_{minor} = 44.58 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC; **Optical Rotation**: $[\alpha]_D^{27}$ = + 120.00 (c 0.765, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-propoxybenzoate (3g):



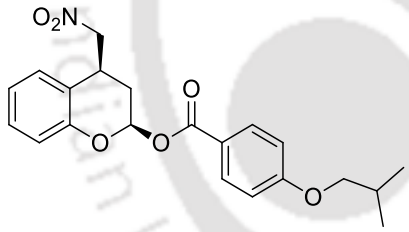
Yellow semisolid (84%, 31 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.24 (t, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.81 (t, *J* = 2.2 Hz, 1H), 5.04 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.77 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.91 – 3.85 (m, 1H), 2.43 (ddd, *J* = 15.1, 6.4, 3.1 Hz, 1H), 2.35 (d, *J* = 15.2 Hz, 1H), 1.85 – 1.79 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.2, 163.7, 151.4, 132.1, 129.8, 129.1, 122.4, 121.3, 118.8, 118.4, 114.6, 90.1, 80.3, 70.0, 30.7, 27.3, 22.6, 10.6; **ESI-MS** m/z calcd. for $C_{20}H_{25}N_2O_6^+$ $[M+NH_4^+]^+$ 389.1707, found 389.1703; **FT-IR (KBr)** 3418, 2966, 2876, 1723, 1604, 1548, 1510, 1492, 1456, 1422, 1377, 1314, 1259, 1214, 1165, 1056 cm^{-1}; The ee value 96% (t_{major} = 28.97 min, t_{minor} = 39.23 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC; **Optical Rotation**: $[\alpha]_D^{28.7}$ = + 107.76 (c 0.850, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-isopropoxybenzoate (3h):



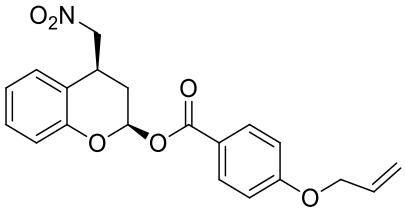
Colorless sticky oil (78%, 29 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.81 (s, 1H), 5.04 (dd, *J* = 12.3, 10.5 Hz, 1H), 4.78 (dd, *J* = 12.6, 5.8 Hz, 1H), 4.63 (dt, *J* = 12.0, 6.0 Hz, 1H), 3.88 (dd, *J* = 13.2, 8.6 Hz, 1H), 2.43 (ddd, *J* = 15.1, 6.5, 3.1 Hz, 1H), 2.34 (d, *J* = 15.2 Hz, 1H), 1.35 (dd, *J* = 5.9, 3.1 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.1, 162.6, 151.4, 132.1, 129.8, 129.1, 122.4, 121.1, 118.7, 118.4, 115.5, 90.1, 80.3, 70.4, 30.7, 27.3, 22.1, 22.0; **ESI-MS** m/z calcd. for $C_{20}H_{25}N_2O_6^+$ $[M+NH_4^+]^+$ 389.1707, found 389.1709; **FT-IR (KBr)** 3444, 2924, 2854, 1875, 1725, 1606, 1551, 1508, 1489, 1457, 1426, 1380, 1313, 1256, 1165, 1110, 1072 cm^{-1}; The ee value 96% (t_{major} = 28.68 min, t_{minor} = 36.92 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-isobutoxybenzoate (3i):



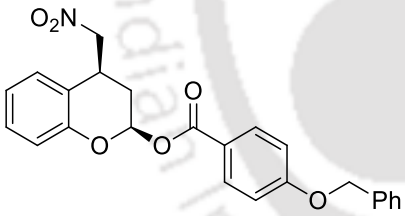
White semisolid (86%, 33 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 8.8 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.81 (t, *J* = 2.3 Hz, 1H), 5.04 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.77 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.76 (d, *J* = 7.8 Hz, 2H), 2.43 (ddd, *J* = 15.1, 6.5, 3.2 Hz, 1H), 2.37 – 2.32 (m, 1H), 2.09 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.2, 163.9, 151.4, 132.1, 129.8, 129.1, 122.5, 121.3, 118.9, 118.4, 114.6, 90.1, 80.3, 74.8, 30.7, 28.4, 27.3, 19.4; **ESI-MS** m/z calcd. for $C_{21}H_{27}N_2O_6^+$ $[M+NH_4^+]^+$ 403.1864, found 403.1862; **FT-IR (KBr)** 3421, 2923, 2854, 1722, 1605, 1549, 1511, 1492, 1465, 1377, 1259, 1215, 1165, 1113, 1090 cm^{-1}; The ee value 96% (t_{major} = 22.37 min, t_{minor} = 29.95 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC; **Optical Rotation**: $[\alpha]_D^{26.6}$ = + 111.27 (c 0.985, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-(allyloxy)benzoate (3j):



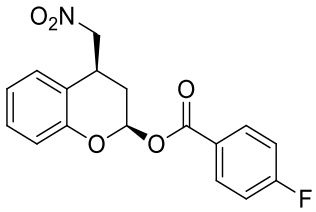
White semisolid (60%, 22 mg); R_f value 0.35 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.9 Hz, 2H), 7.23 (t, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.81 (t, *J* = 2.4 Hz, 1H), 6.03 (ddd, *J* = 22.5, 10.5, 5.3 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.31 (d, *J* = 9.3 Hz, 1H), 5.04 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.77 (dd, *J* = 12.6, 5.8 Hz, 1H), 4.59 (d, *J* = 5.3 Hz, 2H), 3.91 – 3.85 (m, 1H), 2.43 (ddd, *J* = 15.2, 6.6, 3.3 Hz, 1H), 2.34 (dt, *J* = 15.2, 1.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.1, 163.1, 151.4, 132.6, 132.1, 129.8, 129.2, 122.5, 121.8, 118.8, 118.5, 118.4, 114.9, 90.2, 80.3, 69.1, 30.8, 27.2; **ESI-MS** m/z calcd. for $C_{20}H_{23}N_2O_6^+$ $[M+NH_4^+]^+$ 387.1551, found 387.1550; **FT-IR (KBr)** 3074, 2924, 2854, 1724, 1606, 1582, 1549, 1510, 1489, 1456, 1424, 1379, 1258, 1214, 1133, 1073 cm^{-1}; The ee value 88% (t_{major} = 35.34 min, t_{minor} = 47.62 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{27.6}$ = + 109.03 (c 0.620, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-(benzyloxy)benzoate (3k):



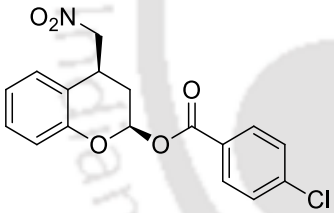
Yellow semisolid (84%, 35 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.38 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.1 Hz, 3H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.81 (s, 1H), 5.12 (s, 2H), 5.03 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.77 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.91 – 3.85 (m, 1H), 2.43 (ddd, *J* = 15.1, 6.5, 3.2 Hz, 1H), 2.34 (d, *J* = 15.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.0, 163.2, 151.4, 136.2, 132.1, 129.8, 129.1, 128.9, 128.5, 127.6, 122.5, 121.9, 118.8, 118.4, 115.0, 90.2, 80.3, 70.4, 30.7, 27.2; **ESI-MS** m/z calcd. for $C_{24}H_{25}N_2O_6^+$ $[M+NH_4^+]^+$ 437.1707, found 437.1703; **FT-IR (KBr)** 3484, 2923, 1724, 1605, 1547, 1510, 1455, 1378, 1260, 1215, 1169, 1087, 999, 946 cm^{-1}; The ee value 96% (t_{major} = 55.84 min, t_{minor} = 75.63 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.6}$ = + 95.82 (c 1.125, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-fluorobenzoate (3l):



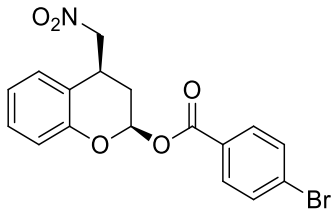
Yellow semisolid (76%, 25 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 7.02 (t, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.81 (t, *J* = 2.5 Hz, 1H), 5.00 (dd, *J* = 12.5, 10.7 Hz, 1H), 4.76 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.92 – 3.85 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.6, 3.2 Hz, 1H), 2.35 (dt, *J* = 15.3, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 167.2, 165.5, 164.5, 151.3, 132.7, 132.6, 129.9, 129.2, 125.7, 125.7, 122.6, 118.7, 118.4, 116.2, 116.1, 90.6, 80.2, 30.7, 27.1; **ESI-MS** m/z calcd. for $C_{17}H_{18}FN_2O_5^+$ $[M+NH_4^+]^+$ 349.1194, found 349.1193; **FT-IR (KBr)** 3436, 2924, 2853, 1731, 1603, 1550, 1507, 1490, 1453, 1426, 1375, 1272, 1237, 1154, 1055 cm^{-1}; The ee value 84% (t_{major} = 26.13 min, t_{minor} = 31.26 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.5}$ = + 126.88 (c 0.785, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-chlorobenzoate (3m):



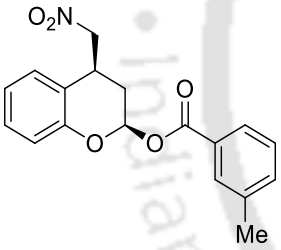
White solid (72%, 25 mg); mp-125 °C; R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 2.1 Hz, 1H), 4.98 (dd, *J* = 12.4, 10.7 Hz, 1H), 4.76 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.92 – 3.85 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.5, 3.2 Hz, 1H), 2.35 (dt, *J* = 15.3, 1.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.7, 151.2, 140.4, 131.3, 129.9, 129.3, 129.2, 127.9, 122.7, 118.6, 118.4, 90.7, 80.2, 30.7, 27.0; **ESI-MS** m/z calcd. for $C_{17}H_{18}ClN_2O_5^+$ $[M+NH_4^+]^+$ 365.0899, found 365.0898; **FT-IR (KBr)** 3436, 2973, 2924, 1729, 1590, 1548, 1488, 1452, 1400, 1375, 1329, 1274, 1215, 1170, 1136, 1095, 1057, 1008 cm^{-1}; The ee value 82% (t_{major} = 27.65 min, t_{minor} = 32.06 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{27.9}$ = + 138.02 (c 1.365, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 4-bromobenzoate (3n):

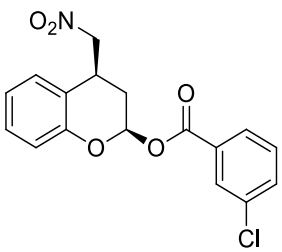


White solid (70%, 27 mg); mp-157 °C; R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 6.9 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.81 (t, *J* = 2.4 Hz, 1H), 4.98 (dd, *J* = 12.4, 10.7 Hz, 1H), 4.75 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.92 – 3.85 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.5, 3.2 Hz, 1H), 2.35 (dt, *J* = 15.3, 1.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.8, 151.2, 132.3, 131.4, 129.9, 129.2, 129.1, 128.3, 122.7, 118.6, 118.4, 90.8, 80.2, 30.7, 27.0; **ESI-MS** m/z calcd. for $C_{17}H_{18}BrN_2O_5^+$ $[M+NH_4^+]^+$ 409.0394, found 409.0394; **FT-IR (KBr)** 3436, 2922, 2847, 1729, 1588, 1543, 1488, 1429, 1377, 1332, 1271, 1217, 1134, 1071, 1010, 934 cm^{-1}; The ee value 88% (t_{major} = 30.48 min, t_{minor} = 34.88 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 3-methylbenzoate (3o):



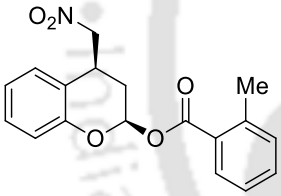
Yellow semisolid (69%, 23 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85 (s, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 2.3 Hz, 1H), 5.06 (dd, *J* = 12.6, 10.4 Hz, 1H), 4.77 (dd, *J* = 12.7, 5.8 Hz, 1H), 3.92 – 3.86 (m, 1H), 2.44 (ddd, *J* = 15.2, 6.5, 3.2 Hz, 1H), 2.40 (s, 3H), 2.36 (dt, *J* = 15.2, 1.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.6, 151.4, 138.8, 134.6, 130.6, 129.8, 129.3, 129.2, 128.8, 127.1, 122.5, 118.8, 118.4, 90.4, 80.2, 30.7, 27.2, 21.4; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_5^+$ $[M+NH_4^+]^+$ 345.1445, found 345.1449; **FT-IR(KBr)** 3059, 2918, 2855, 1731, 1608, 1548, 1487, 1457, 1434, 1382, 1329, 1298, 1276, 1217, 1188, 1130, 1112, 1070, 1051 cm^{-1}; The ee value 86% (t_{major} = 23.69 min, t_{minor} = 27.79 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.6}$ = + 139.64 (c 0.825, $CHCl_3$).



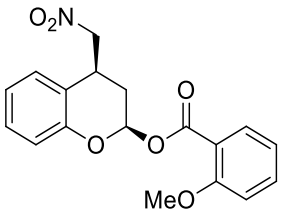
(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 3-chlorobenzoate (3p):

White solid (78%, 27 mg); mp-127 °C, R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (t, *J* = 1.6 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 2.3 Hz, 1H), 4.99 (dd, *J* = 12.4, 10.8 Hz, 1H), 4.77 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.92 – 3.86 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.5, 3.2 Hz, 1H), 2.36 (dt, *J* = 15.3, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.4, 151.2, 135.1, 133.9, 131.2, 130.2, 130.1, 129.9, 129.2, 128.0, 122.7, 118.6, 118.4, 90.9, 80.2, 30.7, 27.0; **ESI-MS** m/z calcd. for $C_{17}H_{18}ClN_2O_5^+$ $[M+NH_4^+]^+$ 365.0899, found 365.0894; **FT-IR (KBr)** 2920, 2844, 1734, 1579, 1548, 1488, 1461, 1435, 1382, 1330, 1287, 1254, 1209, 1136, 1117, 1069, 1051 cm^{-1}; The ee value 86% (t_{major} = 25.81 min, t_{minor} = 28.60 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{24.8}$ = + 152.14 (c 0.280, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 2-methylbenzoate (3q):



Yellow semisolid (80%, 26 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 – 7.22 (m, 4H), 7.17 (t, *J* = 9.8 Hz, 1H), 7.00 (dd, *J* = 17.5, 7.9 Hz, 2H), 6.81 (t, *J* = 2.5 Hz, 1H), 4.98 (dd, *J* = 12.4, 10.4 Hz, 1H), 4.72 (dd, *J* = 12.5, 5.6 Hz, 1H), 3.89 – 3.83 (m, 1H), 2.60 (s, 3H), 2.44 (ddd, *J* = 15.2, 6.6, 3.1 Hz, 1H), 2.37 (dt, *J* = 15.2, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.8, 151.4, 141.2, 132.8, 132.1, 130.3, 129.8, 129.2, 128.8, 126.1, 122.5, 118.9, 118.3, 90.0, 80.3, 30.8, 27.2, 21.7; **ESI-MS** m/z calcd. for $C_{17}H_{21}N_2O_5^+$ $[M+NH_4^+]^+$ 345.1445, found 345.144; **FT-IR (KBr)** 2923, 2853, 1726, 1587, 1550, 1488, 1454, 1432, 1377, 1331, 1249, 1214, 1191, 1128, 1065, 1037 cm^{-1}; The ee value 96% (t_{major} = 19.05 min, t_{minor} = 32.28 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{27.2}$ = + 130.93 (c 0.805, $CHCl_3$).

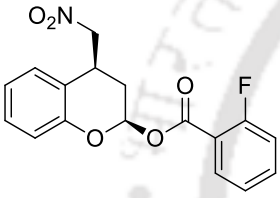


(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 2-methoxybenzoate (3r):

Colorless sticky oil (73%, 25 mg); R_f value 0.3 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (t, *J* = 8.7 Hz, 1H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.01 – 6.96

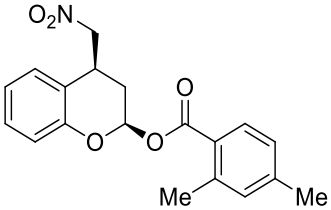
(m, 3H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.85 (t, *J* = 2.2 Hz, 1H), 5.09 (dd, *J* = 13.0, 9.2 Hz, 1H), 4.79 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.85 (dd, *J* = 14.7, 6.8 Hz, 1H), 3.72 (s, 3H), 2.45 (ddd, *J* = 15.1, 6.8, 3.1 Hz, 1H), 2.38 (d, *J* = 15.1 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.4, 159.2, 151.4, 134.5, 132.4, 129.6, 129.2, 122.4, 120.6, 119.4, 119.3, 118.4, 112.2, 89.7, 80.3, 55.9, 30.5, 27.5; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_6^+$ $[M+NH_4^+]^+$ 361.1394, found 361.1390; **FT-IR (KBr)** 2923, 2852, 1726, 1603, 1550, 1490, 1462, 1436, 1380, 1297, 1251, 1212, 1185, 1037, 946 cm^{-1}; The ee value 86% (t_{major} = 41.06 min, t_{minor} = 33.79 min) was determined by HPLC using Daicel Phenomenex Lux Amalyse-A2 with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.9}$ = + 102.40 (c 0.750, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 2-fluorobenzoate (3s):



White semisolid (91%, 30 mg); R_f value 0.5 (5:95 EA in hex**); ^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98 (t, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 12.6, 6.3 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.15 – 7.10 (m, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.87 (s, 1H), 5.14 – 5.05 (m, 1H), 4.75 (dd, *J* = 12.9, 5.8 Hz, 1H), 3.86 (dd, *J* = 15.0, 6.3 Hz, 1H), 2.46 (ddd, *J* = 15.2, 6.6, 3.1 Hz, 1H), 2.40 (d, *J* = 15.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.3, 162.8, 161.1, 151.1, 135.6, 135.5, 132.8, 129.7, 129.3, 124.6, 124.6, 122.7, 119.2, 118.3, 118.1, 118.0, 117.4, 117.3, 90.3, 80.2, 80.1, 30.4, 27.4; **ESI-MS** m/z calcd. for $C_{17}H_{18}FN_2O_5^+$ $[M+NH_4^+]^+$ 349.1194, found 349.1199; **FT-IR (KBr)** 3463, 2925, 2853, 1744, 1723, 1612, 1583, 1547, 1489, 1454, 1374, 1330, 1292, 1252, 1161, 1138 cm^{-1}; The ee value 84% (t_{major} = 26.44 min, t_{minor} = 35.42 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.8}$ = + 120.00 (c 1.070, $CHCl_3$).

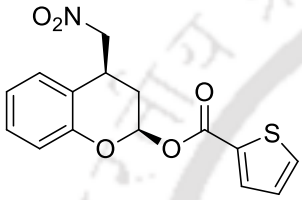
(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl 2,4-dimethylbenzoate (3t):



White solid (91%, 31 mg); mp-112 °C, R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.08 – 6.97 (m, 4H), 6.79 (t, *J* = 2.4 Hz, 1H), 4.98 (dd, *J* = 12.5, 10.3 Hz, 1H), 4.72 (dd, *J* = 12.5, 5.7 Hz, 1H), 3.89 – 3.83 (m, 1H), 2.57 (s, 3H), 2.43 (ddd, *J* = 15.1, 6.7, 3.1 Hz, 1H), 2.37 (t, *J* = 1.9 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR (150**

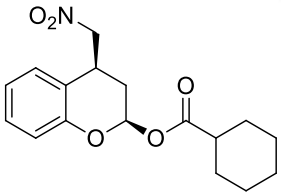
MHz, $CDCl_3$) δ 165.7, 151.5, 143.5, 141.5, 132.9, 130.5, 129.7, 129.2, 126.9, 125.8, 122.5, 119.0, 118.3, 89.8, 80.3, 30.8, 27.3, 21.7, 21.6; **ESI-MS** m/z calcd. for $C_{19}H_{23}N_2O_5^+$ $[M+NH_4^+]^+$ 359.1601, found 359.1601; **FT-IR (KBr)** 2961, 2931, 1726, 1610, 1582, 1548, 1457, 1429, 1337, 1256, 1217, 1151, 1070, 1044 cm^{-1}; The ee value 94% (t_{major} = 17.84 min, t_{minor} = 28.59 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 274 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{28.8}$ = + 130.29 (c 0.700, $CHCl_3$).

(2R,4S)-3,4-dihydro-4-(nitromethyl)-2H-chromen-2-yl thiophene-2-carboxylate (3u):



^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 3.6 Hz, 1H), 7.61 (d, *J* = 4.8 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.15 – 7.11 (m, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.79 (s, 1H), 5.08 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.80 (dd, *J* = 12.8, 5.9 Hz, 1H), 3.91 – 3.85 (m, 1H), 2.43 (ddd, *J* = 15.2, 6.6, 3.1 Hz, 1H), 2.35 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.6, 151.1, 134.8, 133.6, 132.6, 129.8, 129.2, 128.4, 122.6, 118.9, 118.3, 90.3, 80.3, 30.5, 27.2; **ESI-MS**: m/z calcd. for $C_{15}H_{17}N_2O_5S^+$ $[M+NH_4^+]^+$ 337.0853, found 337.0855; **FT-IR(KBr)**: 3059, 2918, 2855, 1731, 1608, 1548, 1487, 1457, 1434, 1382, 1329, 1298, 1276, 1217, 1188, 1130, 1112, 1070, 1051 cm^{-1}; The ee value 82% (t_{major} = 32.96 min, t_{minor} = 39.66 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{27.5}$ = + 105.60 (c 1.25, $CHCl_3$).

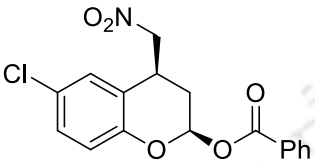
(2*R*,4*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl cyclohexanecarboxylate (3v):



Colorless sticky oil (47%, 15 mg); R_f value 0.55 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.23 (t, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.61 (t, *J* = 2.3 Hz, 1H), 4.92 (dd, *J* = 12.6, 10.3 Hz, 1H), 4.69 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.84 – 3.77 (m, 1H), 2.34 – 2.28 (m, 2H), 2.19 (dt, *J* = 15.2, 1.9 Hz, 1H), 1.95 – 1.89 (m, *J* = 7.5, 3.5, 1.8 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.77 – 1.70 (m, 2H), 1.65 – 1.61 (m, 1H), 1.46 – 1.39 (m, 2H), 1.30 – 1.27 (m, 1H), 1.24 – 1.18 (m, 2H); **^{13}C NMR (150 MHz, CDCl3)** δ 174.5, 151.3, 129.7, 129.2, 122.4, 118.9, 118.3, 89.2, 80.3, 43.4, 30.7,

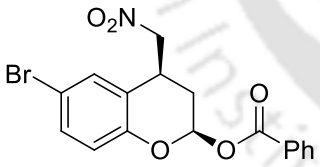
29.00, 28.9, 27.1, 25.8, 25.5; **ESI-MS** m/z calcd. for $C_{17}H_{25}N_2O_5^+$ $[M+NH_4^+]^+$ 337.1758, found 337.1757; **FT-IR (KBr)** 3445, 2931, 2855, 1748, 1586, 1552, 1490, 1454, 1379, 1221, 1158, 1116, 1076 cm^{-1}; The ee value 94% (t_{major} = 13.69 min, t_{minor} = 15.63 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-6-chloro-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3w):



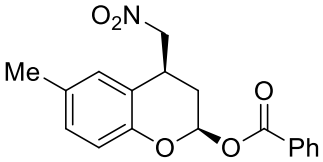
White solid (89%, 31 mg); mp-110 °C, R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 6.9 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.19 (dd, *J* = 16.4, 2.4 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.83 (t, *J* = 2.3 Hz, 1H), 5.04 (dd, *J* = 12.7, 10.4 Hz, 1H), 4.76 (dd, *J* = 12.7, 5.7 Hz, 1H), 3.91 – 3.83 (m, 1H), 2.42 (ddd, *J* = 15.3, 6.5, 3.1 Hz, 1H), 2.36 (dt, *J* = 15.3, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.3, 149.9, 134.0, 130.0, 129.9, 129.2, 128.9, 128.8, 127.4, 120.4, 119.8, 90.2, 79.9, 30.5, 26.9; **ESI-MS** m/z calcd. for $C_{17}H_{14}ClNaNO_5$ [M+Na] 370.0458, found 370.0446; **FT-IR (KBr)** 3438, 3046, 2922, 1732, 1582, 1549, 1482, 1549, 1485, 1452, 1411, 1379, 1266, 1215, 1179, 1137, 1056 cm^{-1}; The ee value 90% (t_{major} = 26.43 min, t_{minor} = 34.29 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-6-bromo-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3x):



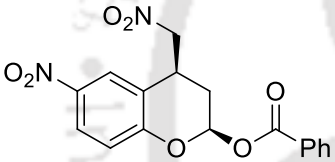
White solid (93%, 36 mg); mp-125 °C, R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.35 – 7.31 (m, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.83 (s, 1H), 5.04 (dd, *J* = 12.7, 10.4 Hz, 1H), 4.76 (dd, *J* = 12.7, 5.6 Hz, 1H), 3.90 – 3.84 (m, 1H), 2.42 (ddd, *J* = 15.3, 6.5, 3.2 Hz, 1H), 2.36 (dt, *J* = 15.3, 2.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.3, 150.5, 134.0, 132.8, 131.7, 130.0, 129.2, 129.0, 120.9, 120.2, 114.6, 90.2, 79.9, 30.5, 26.9; **ESI-MS** m/z calcd. for $C_{17}H_{18}BrN_2O_5^+$ $[M+NH_4^+]^+$ 409.0394, found 409.0386; **FT-IR (KBr)** 3436, 2923, 2853, 1731, 1579, 1549, 1481, 1451, 1429, 1379, 1265, 1213, 1178, 1137, 1053 cm^{-1}; The ee value 84% (t_{major} = 34.03 min, t_{minor} = 32.45 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{27.8}$ = + 131.73 (c 0.665, $CHCl_3$).

(2*R*,4*S*)-3,4-dihydro-6-methyl-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3y):



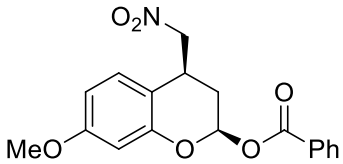
White semisolid (85%, 27 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.97 (s, 1H), 6.90 – 6.78 (m, 2H), 5.03 (dd, *J* = 12.4, 10.5 Hz, 1H), 4.77 (dd, *J* = 12.5, 5.6 Hz, 1H), 3.90 – 3.77 (m, 1H), 2.48 – 2.31 (m, 2H), 2.29 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.5, 149.1, 133.8, 132.0, 130.5, 130.0, 129.5, 129.3, 128.9, 118.4, 118.1, 90.5, 80.4, 30.7, 27.2, 20.7; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_5^+$ $[M+NH_4^+]^+$ 345.1445, found 345.1443; **FT-IR (KBr)** 2925, 2853, 1727, 1551, 1500, 1450, 1378, 1318, 1272, 1172, 1142, 1026 cm^{-1}; The ee value 90% (t_{major} = 23.82 min, t_{minor} = 21.75 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(2*R*,4*S*)-3,4-dihydro-6-nitro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3z):



Yellow semisolid (88%, 31 mg); R_f value 0.5 (7:93 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.19 – 8.11 (m, 2H), 8.01 (d, *J* = 7.4 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.91 (t, *J* = 2.5 Hz, 1H), 5.08 (dd, *J* = 12.8, 10.5 Hz, 1H), 4.84 (dd, *J* = 12.9, 5.7 Hz, 1H), 4.00 (dd, *J* = 6.6, 3.5 Hz, 1H), 2.51 – 2.42 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.0, 156.6, 142.7, 134.3, 130.0, 129.0, 128.8, 125.6, 125.5, 119.7, 119.3, 90.3, 79.4, 30.6, 26.8; **ESI-MS** m/z calcd. for $C_{17}H_{18}N_3O_7^+$ $[M+NH_4^+]^+$ 376.1139, found 376.1140; **FT-IR (KBr)** 2922, 2855, 1727, 1623, 1586, 1545, 1481, 1446, 1419, 1345, 1270, 1227, 1086, 1022 cm^{-1}; The ee value 68% (t_{major} = 93.50 min, t_{minor} = 90.17 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97.5:2.5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

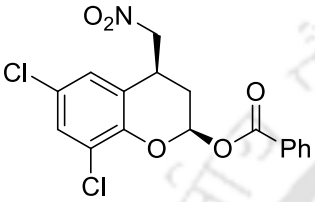
(2*R*,4*S*)-7-methoxy-4-(nitromethyl)chroman-2-yl benzoate (3z^1):



White sticky solid (93%, 33 mg); R_f value 0.5 (5:95 EA in hex) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.81 (s, 1H), 6.59 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.51 (d, *J* = 2.4 Hz, 1H), 5.00 (dd, *J* = 12.3, 10.3 Hz, 1H), 4.74 (dd, *J* = 12.4, 5.8 Hz, 1H), 3.81 (d, *J* = 8.7 Hz, 1H), 3.75 (s, 3H), 2.42 (ddd, *J* = 15.2, 6.6, 3.1 Hz, 1H), 2.34 (d, *J* =

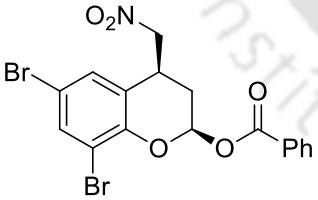
15.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 165.5, 160.7, 152.1, 133.9, 129.9, 129.8, 129.4, 128.9, 110.7, 109.9, 102.6, 90.4, 80.4, 55.6, 30.2, 27.2; **ESI-MS** m/z calcd. for $C_{18}H_{21}N_2O_6^+$ $[M+NH_4^+]^+$ 361.1394, found 361.1390; **FT-IR (KBr)** 2923, 2852, 1726, 1603, 1550, 1490, 1462, 1436, 1380, 1297, 1251, 1212, 1185, 1037, 946 cm^{-1}; The ee value 60% (t_{major} = 26.01 min, t_{minor} = 33.49 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-6,8-dichloro-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3z^2):



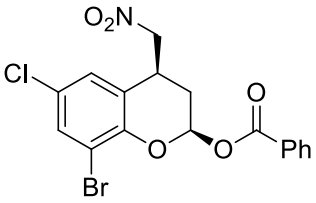
White solid (81%, 31 mg); MP-130 °C, R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 2.3 Hz, 1H), 6.94 (t, *J* = 2.4 Hz, 1H), 5.00 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.76 (dd, *J* = 12.8, 5.9 Hz, 1H), 3.93 – 3.87 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.3, 3.1 Hz, 1H), 2.39 (dt, *J* = 15.3, 2.1 Hz, 1H); **^{13}C NMR (151 MHz, $CDCl_3$)** δ 164.8, 146.3, 134.1, 130.3, 130.0, 129.0, 129.0, 127.3, 127.1, 124.3, 121.8, 90.3, 79.7, 30.7, 27.1; **ESI-MS** m/z calcd. for $C_{17}H_1Cl_2N_2O_5^+$ $[M+NH_4^+]^+$ 399.0509, found 399.0504; **FT-IR (KBr)** 3446, 3070, 2925, 1737, 1646, 1552, 1458, 1376, 1319, 1266, 1181, 1128, 1070, 1020 cm^{-1}; The ee value 92% (t_{major} = 41.38 min, t_{minor} = 46.01 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(2*R*,4*S*)-6,8-dibromo-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3z^3):



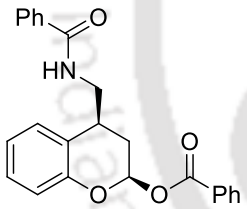
Yellow semisolid (51%, 24 mg); R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.64 (s, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.28 (s, 1H), 6.93 (s, 1H), 5.00 (dd, *J* = 12.6, 10.2 Hz, 1H), 4.75 (dd, *J* = 12.8, 5.8 Hz, 1H), 3.95 – 3.83 (m, 1H), 2.43 (ddd, *J* = 15.2, 6.1, 3.1 Hz, 1H), 2.38 (d, *J* = 15.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.8, 147.7, 135.9, 134.1, 130.9, 130.0, 129.0, 129.0, 122.2, 114.5, 113.5, 90.5, 79.7, 30.7, 27.1; **ESI-MS** m/z calcd. for $C_{17}H_{17}Br_2N_2O_5^+$ $[M+NH_4^+]^+$ 486.9484, found 486.9469; **FT-IR (KBr)** 3438, 2923, 2853, 1731, 1635, 1549, 1450, 1374, 1314, 1266, 1224, 1162, 1128, 1071, 1046 cm^{-1}; The ee value 90% (t_{major} = 76.60 min, t_{minor} = 53.67 min) was determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{25.5}$ = + 51.05 (c 0.286, $CHCl_3$).

(2*R*,4*S*)-8-bromo-6-chloro-3,4-dihydro-4-(nitromethyl)-2*H*-chromen-2-yl benzoate (3z[4]):



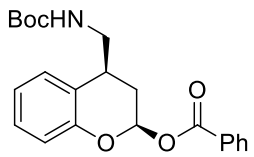
White solid (60%, 25 mg); mp-130 ^{o}C; R_f value 0.5 (5:95 EA in hex); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.01 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 16.5, 8.8 Hz, 3H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.93 (s, 1H), 5.00 (dd, *J* = 12.8, 10.0 Hz, 1H), 4.76 (dd, *J* = 12.8, 5.9 Hz, 1H), 3.94 – 3.84 (m, 1H), 2.44 (ddd, *J* = 15.3, 6.3, 3.1 Hz, 1H), 2.39 (d, *J* = 15.3 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 164.8, 147.2, 134.1, 133.2, 130.0, 129.0, 129.0, 128.0, 127.6, 121.7, 113.1, 90.5, 79.7, 30.8, 27.1; **ESI-MS** m/z calcd. for $C_{17}H_{17}BrClN_2O_5^+$ $[M+NH_4^+]^+$ 443.0004, found 443.0001; **FT-IR (KBr)** 3444, 2920, 2853, 1732, 1601, 1549, 1454, 1375, 1314, 1268, 1224, 1206, 1171, 1122, 1084, 1066 cm^{-1}; The ee value 96% (t_{major} = 126.00 min, t_{minor} = 106.66 min) was determined by HPLC using Daicel Chiralpak I8 with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(2*R*,4*S*)-4-((benzamido)methyl)-3,4-dihydro-2*H*-chromen-2-yl benzoate (5):



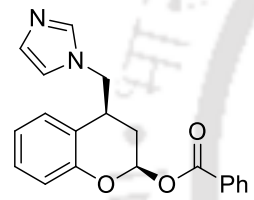
White semisolid (60%, 23 mg); R_f value 0.3 (10:90 EA in hex); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 6.9 Hz, 1H), 7.44 (dd, *J* = 13.9, 7.5 Hz, 4H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 8.4 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 3.1 Hz, 1H), 6.42 (t, *J* = 5.4 Hz, 1H), 4.01 (dt, *J* = 13.4, 6.6 Hz, 1H), 3.92 (dt, *J* = 13.7, 7.0 Hz, 1H), 3.43 – 3.37 (m, 1H), 2.40 – 2.37 (m, 2H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 167.9, 165.6, 151.5, 134.5, 133.8, 131.9, 130.0, 129.7, 129.3, 128.9, 128.8, 128.8, 127.0, 122.7, 122.1, 117.9, 91.5, 45.4, 31.8, 28.3; **ESI-MS** m/z calcd. for $C_{17}H_{14}NaNO_5$ [M+Na] 410.1368, found 410.1364; **FT-IR (KBr)** 3336, 2922, 2851, 1732, 1639, 1580, 1487, 1380, 1451, 1311, 1270, 1214, 1187, 1073 cm^{-1}; The ee value 86% (t_{major} = 25.92 min, t_{minor} = 29.42 min) was determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

***tert*-butyl((2*R*,4*S*)-2-(benzoyloxy)-3,4-dihydro-2*H*-chromen-4-yl)methylcarbamate (6):**



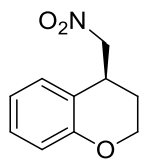
Yellow semisolid (60%, 23 mg); R_f value 0.5 (10:90 EA in hex); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.98 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.24 (s, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 4.83 (s, 1H), 3.71 (dt, *J* = 13.5, 6.5 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.23 (s, 1H), 2.37 – 2.29 (m, 2H), 1.46 (s, 9H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.6, 156.2, 151.5, 133.7, 130.0, 129.7, 129.3, 128.8, 128.6, 122.7, 122.0, 117.7, 91.4, 79.7, 46.1, 32.1, 28.6, 27.8; **ESI-MS** m/z calcd. for $C_{17}H_{15}BrNO_5^+$ $[M+H^+]^+$ 384.1805, found 384.1810; **FT-IR (KBr)** 3389, 2977, 2926, 1735, 1692, 1528, 1488, 1450, 1371, 1274, 1218, 1174, 1073, 1030 cm^{-1}; The ee value 92% (t_{major} = 25.82 min, t_{minor} = 31.04 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(2*R*,4*S*)-4-((1H-imidazol-1-yl)methyl)-3,4-dihydro-2*H*-chromen-2-yl benzoate (7)[19]:



Colorless sticky oil (77%, 26 mg); R_f value 0.5 (50:50 EA in hex); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 7.42 (s, 1H), 7.22 (t, *J* = 8.5 Hz, 1H), 7.11 (s, 1H), 6.98-6.95 (m, 3H), 6.86 (t, *J* = 2.7 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 4.47 – 4.40 (m, 2H), 3.33 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.31 (ddd, *J* = 15.0, 6.9, 3.2 Hz, 1H), 2.16 (dt, *J* = 15.0, 2.4 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 165.4, 151.1, 137.8, 134.0, 130.2, 129.9, 129.5, 129.3, 129.3, 129.0, 122.3, 120.6, 119.2, 90.8, 52.6, 34.1, 29.9, 27.2; **ESI-MS** m/z calcd. for $C_{20}H_{19}N_2O_3^+$ $[M+H^+]^+$ 335.1390, found 335.1388; **FT-IR (KBr)** 3419, 2923, 2853, 1723, 1583, 1489, 1451, 1366, 1266, 1214, 1133, 1050, 995, 936 cm^{-1}; The ee value 92% (t_{major} = 47.05 min, t_{minor} = 38.38 min) was determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (70:30) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(*S*)-3,4-dihydro-4-(nitromethyl)-2*H*-chromene (8)[17]:



Colorless sticky oil (95%, 18 mg); R_f value 0.5 (3:97 EA in hex); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.18 (t, *J* = 7.1 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.71 (dd, *J* = 12.3, 4.7 Hz, 1H), 4.55 (dd, *J* = 12.2, 10.8 Hz, 1H), 4.27 (dt, *J* = 11.4, 4.3 Hz, 1H), 4.20 – 4.13 (m, 1H), 3.72 (td, *J* = 9.9, 4.7 Hz, 1H), 2.24 – 2.16 (m, 1H), 1.96-1.92 (m, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 155.1, 129.2, 129.0, 121.1, 119.6, 117.9, 80.1, 62.5, 33.0, 25.1; **ESI-MS** m/z calcd. for $C_{10}H_{11}NaNO_3$ [M+Na] 216.0637, found 216.1251; **FT-IR**

(KBr) 3445, 2923, 2853, 1740, 1582, 1551, 1490, 1456, 1379, 1263, 1226, 1118, 1038 cm^{-1}; The ee value 92% (t_{major} = 11.57 min, t_{minor} = 22.38 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

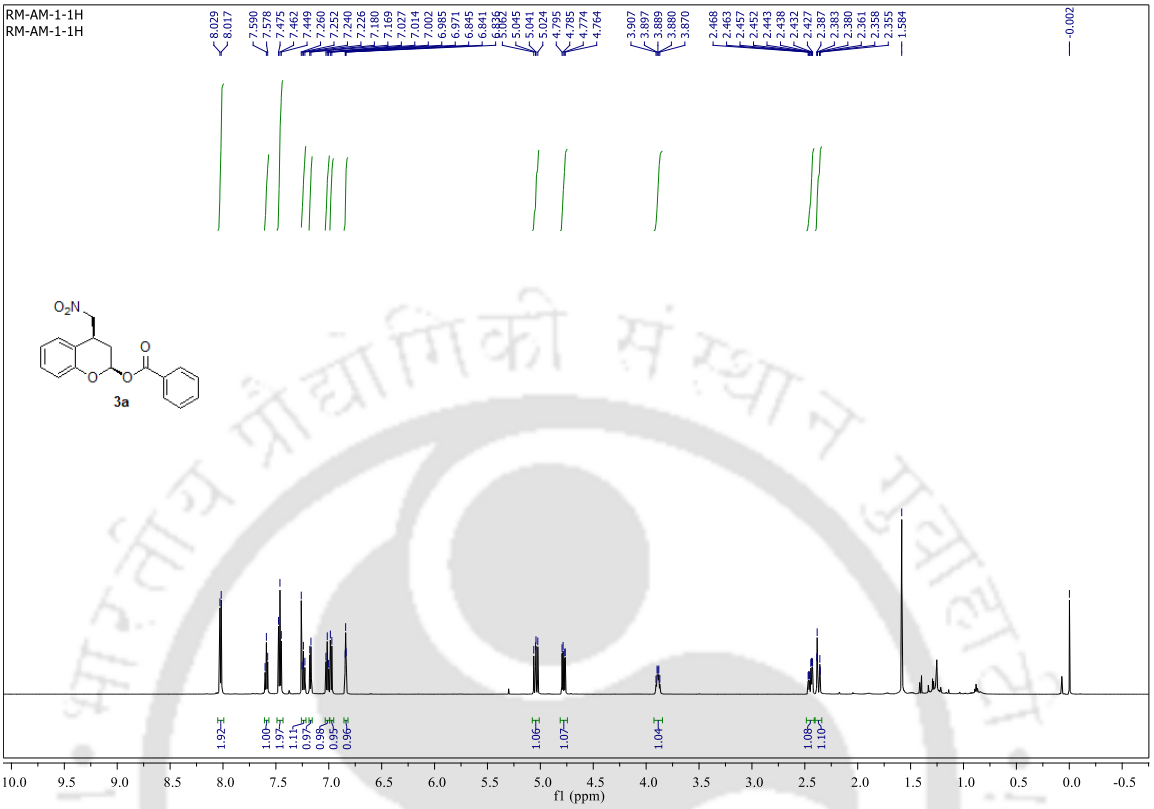
3.7.5. Crystal information:

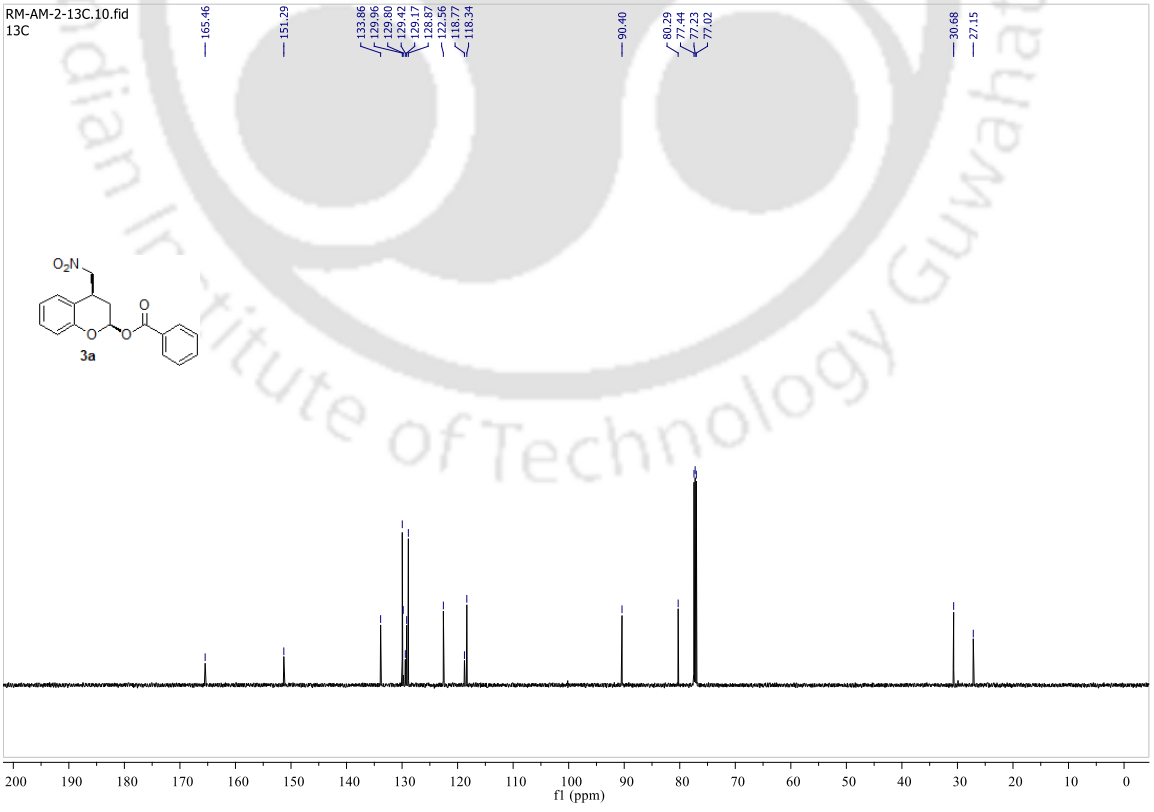
Crystal data and structure refinement for **3p**

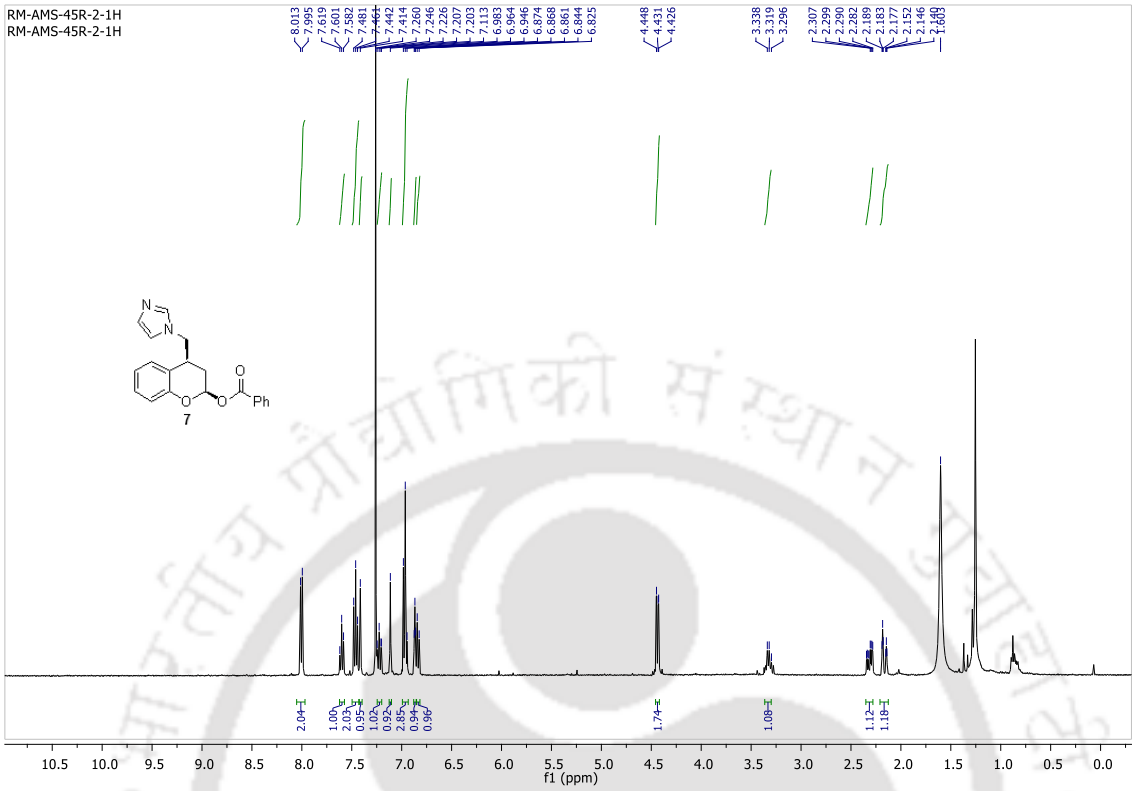
Identification code	**3p** (CCDC 1581364)
Empirical formula	$C_{17}H_{14}ClNO_5$
Formula weight	347.74
Temperature/K	569(2)
Crystal system	orthorhombic
Space group	P 21 21 21
a/Å	7.5946(3)
b/Å	13.4938(6)
c/Å	15.8269(7)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/$Å^3$	1621.94(12)
Z	4
$\rho_{calc}mg/mm^3$	1.424
m/mm^{-1}	0.262
F(000)	720.0
Crystal size/mm^3	0.28 × 0.24 × 0.21
2Θ range for data collection	5.94 to 50°
Index ranges	$-9 \leq h \leq 8$, $-7 \leq k \leq 16$, $-18 \leq l \leq 14$
Reflections collected	4970
Independent reflections	2760[R(int) = 0.0211]
Data/restraints/parameters	2760/0/217

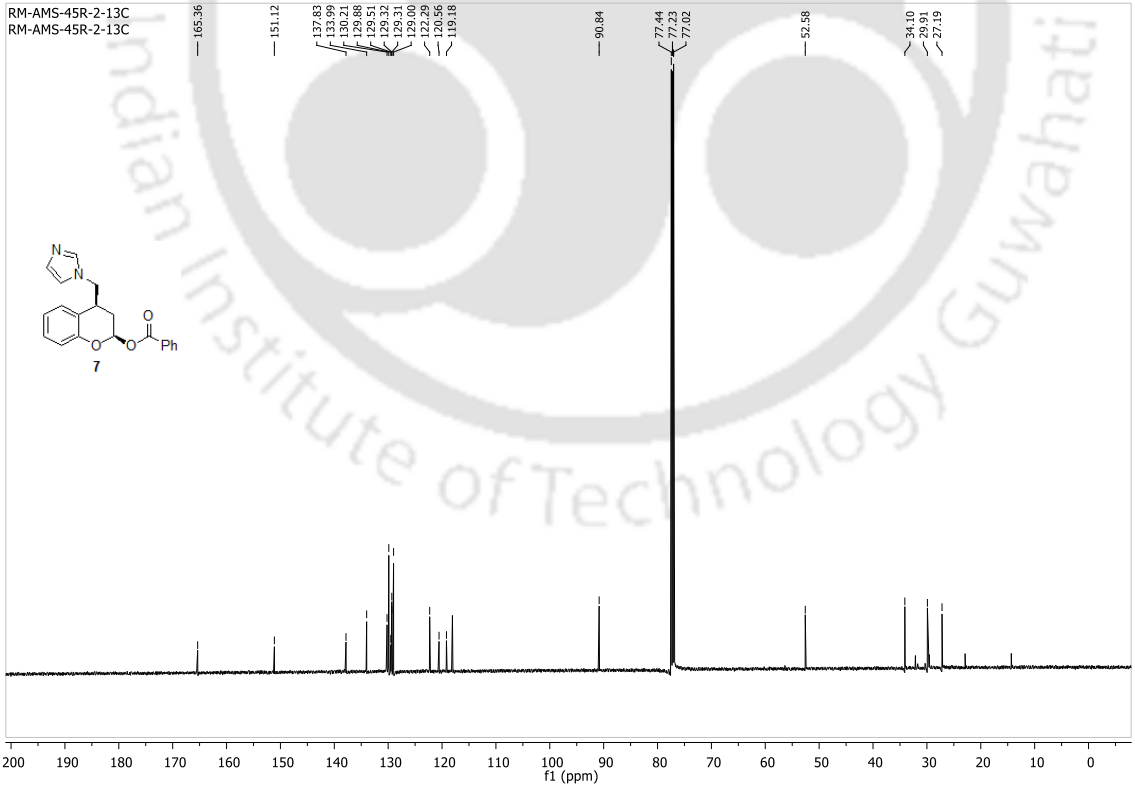
Goodness-of-fit on F^2	0.991
Final R indexes [I>=2σ (I)]	R_1 = 0.0433, wR_2 = 0.1073
Final R indexes [all data]	R_1 = 0.0577, wR_2 = 0.1193
Largest diff. peak/hole / e $Å^{-3}$	0.18/-0.16
Flack parameter	0.04(10)

3.8. Selected spectra of NMR and HPLC:

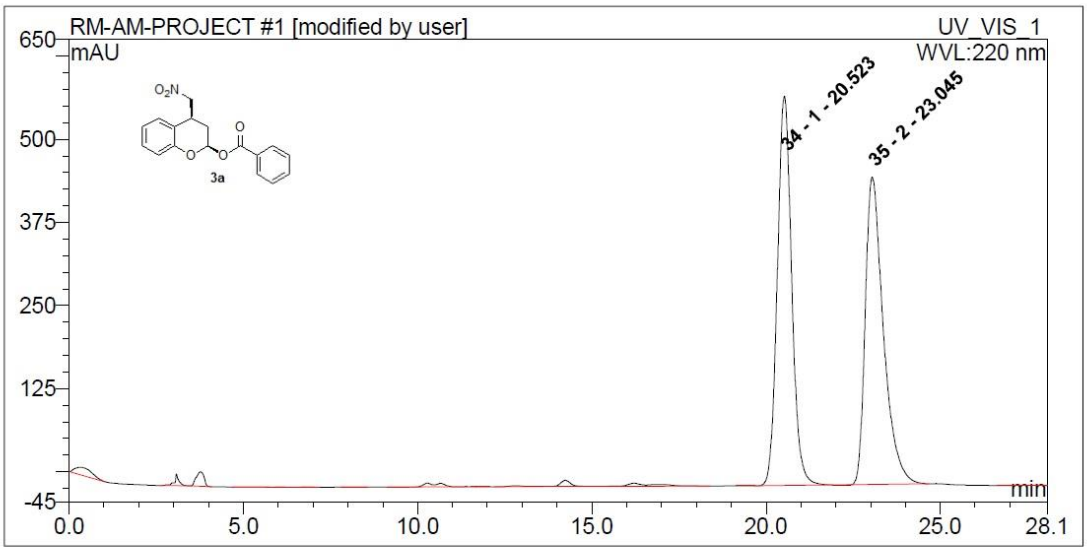






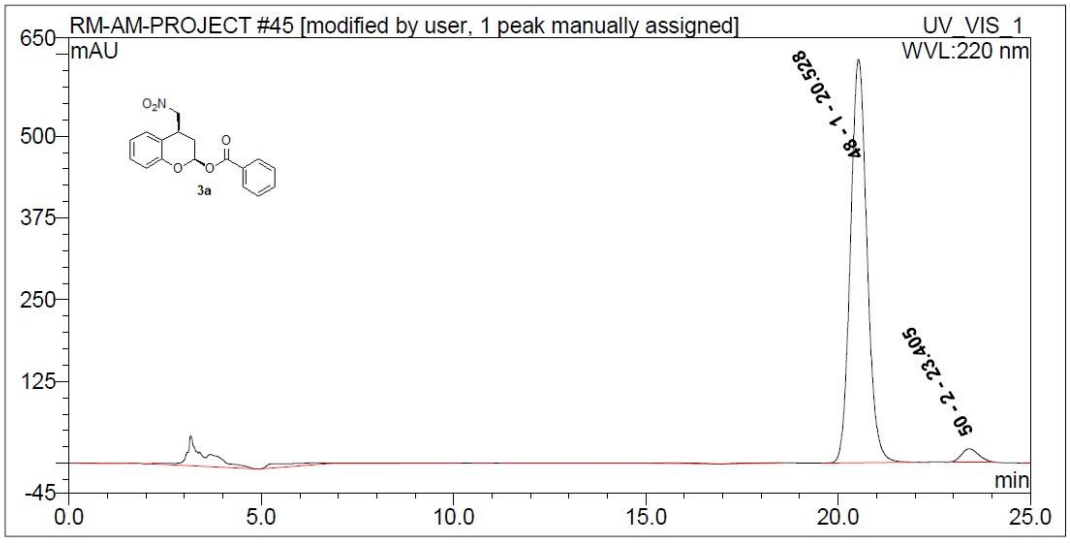


RM-AMS-1R



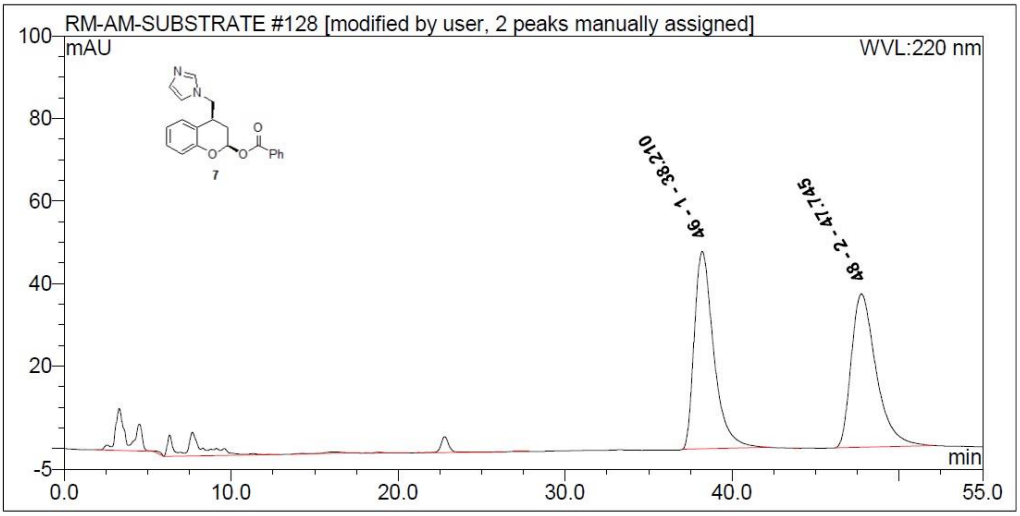
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
34	1	20.52	279.4747	50.1472899	585.2813	n.a.
35	2	23.05	277.833	49.8527101	462.042	n.a.

RM-AMS-1C



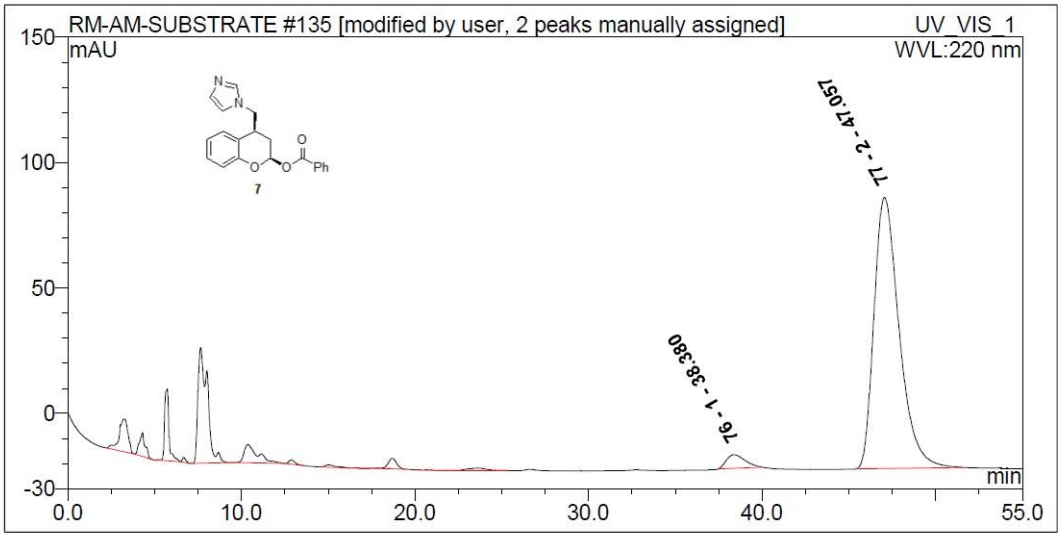
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
48	1	20.53	306.9522	96.73848084	616.5783	n.a.
50	2	23.41	10.349	3.261519156	20.201	n.a.

RM-AMS-45R-IM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
46	1	38.21	64.57679	50.16603231	47.83468	n.a.
48	2	47.75	64.149	49.83396769	37.116	n.a.

RM-AMS-45C-IM



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
76	1	38.38	6.684822	3.553845847	5.40461	n.a.
77	2	47.06	181.416	96.44615415	108.107	n.a.

3.9. References:

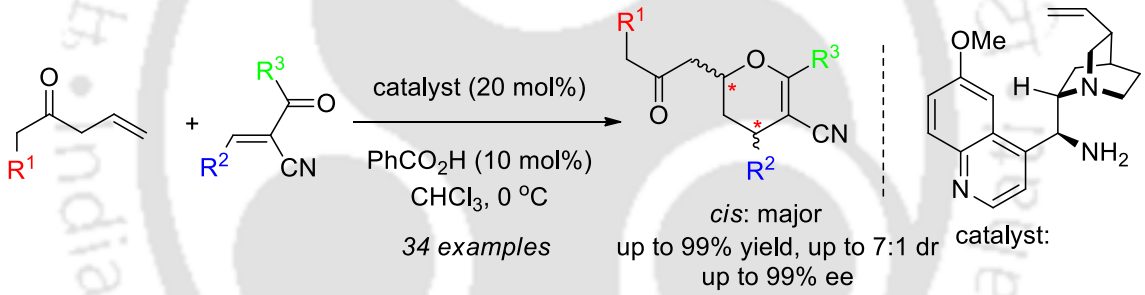
1. (a) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059. (b) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli, F.; Balsamo, A. *J. Med. Chem*. **2006**, *49*, 7600. (c) Khelili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; de Tullio, P. D.; Lebrun, P.; Pirotte, B. *Bioorg. Med. Chem*. **2008**, *16*, 6124. (d) Coi, A.; Bianucci, A. M.; Calderone, V.; Tstai, L.; Digiacomo, M.; Rapposelli, S.; Balsamo, A. *Bioorg. Med. Chem.* **2009**, *17*, 5565.
2. Muthyala, R. S.; Ju, Y. H.; Sheng, S.; Williams, L. D.; Doerge, D. R.; Katzenellenbogen, B. S.; Helferich, W. G.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2004**, *12*, 1559.
3. Maloney, D. J.; Deng, J.-Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140.
4. Van de Water, A.; Janssen, W.; Van Nueten, J.; Xhonneux, R.; de Cree, J.; Verhaegen, H.; Reneman, R. S.; Janssen, P. A. J. J. *Cardiovasc. Pharmacol.* **1988**, *11*, 552.
5. Judzewitsch, R. G.; Jaspan, J. B.; Polonsky, K. S.; Weinberg, C. R.; Halter, J. B.; Halar, E.; Pfeifer, M. A.; Vukadinovic, C.; Bernstein, L.; Schneider, M.; Liang, K. Y.; Gabbay, K. H.; Rubenstein, A. H.; Porte, D. N. *Engl. J. Med.* **1983**, *308*, 119.
6. Weyant, M. J.; Carothers, A. M.; Dannenberg, A. J.; Bertagnolli, M. M. *Cancer Res.* **2001**, *61*, 118.
7. Jain, N.; Xu, J.; Ramesh, M. K.; Du, F.; Jian-Zhong, G.; Pacia, E. *J. Med. Chem.* **2009**, *52*, 7544.
8. Liu, Y.; Wang, Y.; Song, H.; Zhou, Z.; Tanga, C. *Adv. Synth. Catal.* **2013**, *355*, 2544.
9. Zhou, J.; Jia, L.-N.; Wang, Q.-L.; Peng, L.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Tetrahedron* **2014**, *70*, 8665.
10. (a)Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. *Org. Lett.* **2014**, *16*, 2802. (b) Quintard, A.; Rodriguez, J. *Adv. Synth. Catal*. **2016**, *358*, 3362.
11. Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *7*, 1627.
12. Ramachary, D. B.; Sakthidevi, R. *Org. Biomol. Chem.* **2010**, *8*, 4259.
13. Lee, Y.; Seo, S. W.; Kim, S.-G. *Adv. Synth. Catal*. **2011**, *353*, 2671.

14. Choi, K.-S.; Kim, S.-G. *Eur. J. Org. Chem.* **2012**, 1119.
15. Selected examples synthesis of chiral chromans; (a) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2007**, *13*, 574. (b) Feng, Y.-H.; Luo, R.-S.; Nie, L.; Wenga, J.; Lu, G. *Tetrahedron: Asymmetry* **2014**, 25, 523. (c) Li, H.; Wang, J.; Nunu, T. -E.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun*. **2007**, 507. (d) Xu, D. Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xua, Z.-Y. *Adv. Synth. Catal.* **2008**, *350*, 2610. (e) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem. Int. Ed.* **2010**, *49*, 1481. (f) Enders, D.; Urbanietz, G.; Raabe, G. *synthesis* **2011**, *12*, 1905. (g) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (h) Saha, P.; Biswas, A.; Molleti, N.; Singh, V. K. *J. Org. Chem.* **2015**, *80*, 11115.
16. For reviews on diarylprolinol ethers as organocatalysts, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem. Asian. J.* **2008**, *3*, 922. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.
17. Blay, G.; Domingo, L. R.; Hernández-Olmos, V. Pedro. J. R. *Chem. Eur. J.* **2008**, *14*, 4725.
18. CCDC 1581364 contains the crystallographic data for **3p**.
19. Padhi, B.; Reddy, D. S.; Mohapatra, D. K. *Eur. J. Org. Chem.* **2015**, 542.

Dienamine-Mediated Asymmetric Michael-Oxa-Michael Reaction of Linear Deconjugated Enones: Synthesis of 3,4-Dihydropyrans*

Abstract:

The first organocatalytic asymmetric Michael-oxa-Michael reaction of linear deconjugated enones having α′-CH groups is disclosed. Electron poor oxadienes having cyano group were found to be suitable for this reaction. With 20 mol% of quinine derived primary amine catalyst, high yields as well as excellent enantioselectivities were attained for a variety of 2,4-stereogenic 3,4-dihydropyran products under mild reaction conditions.



*Maity, R.; Pan, S. C. *Eur. J. Org. Chem.* **2017**, *4*, 871.

4.1. Introduction:

Stereogenic dihydropyrans are important structural motifs mostly present in natural products and biologically active synthetic compounds.[1] In addition, dihydropyrans undergo a variety of chemical transformations and can be converted to biologically important tetrahydropyrans by reduction of the double bond.[2] Herein, some examples of biologically active compounds having dihydropyran motif are depicted in Figure 1. PI3Ka inhibitor is an anti-tumar drug.[3] Scytophycin C and Laulimalide act as potent microtubule stabilizing anti-cancer agents.[4,5] Phospono-zanamivir helps in inhibitory activity against neuraminidases of the influenza viruses.[6] Halichondrin B is one of the most cytotoxic member of poly ether macrolides.[7]

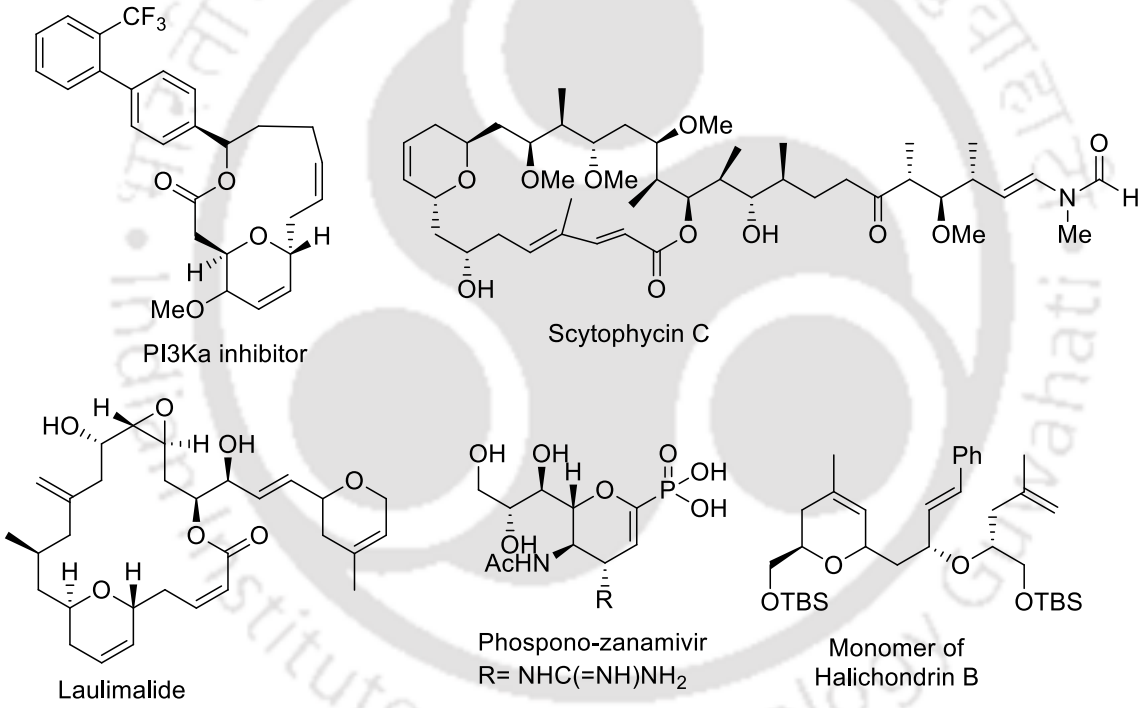
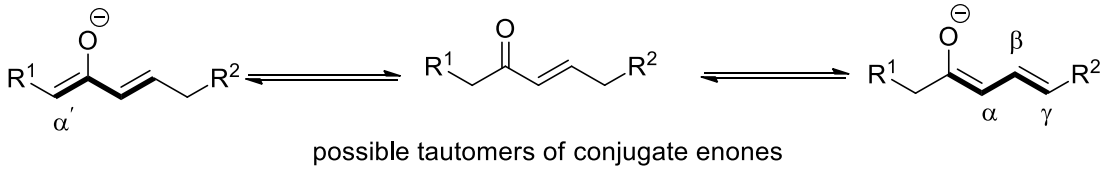


Figure 1. Some biologically active compounds containing dihydropyran moiety.

4.2. Asymmetric direct vinylogous Michael addition reaction:

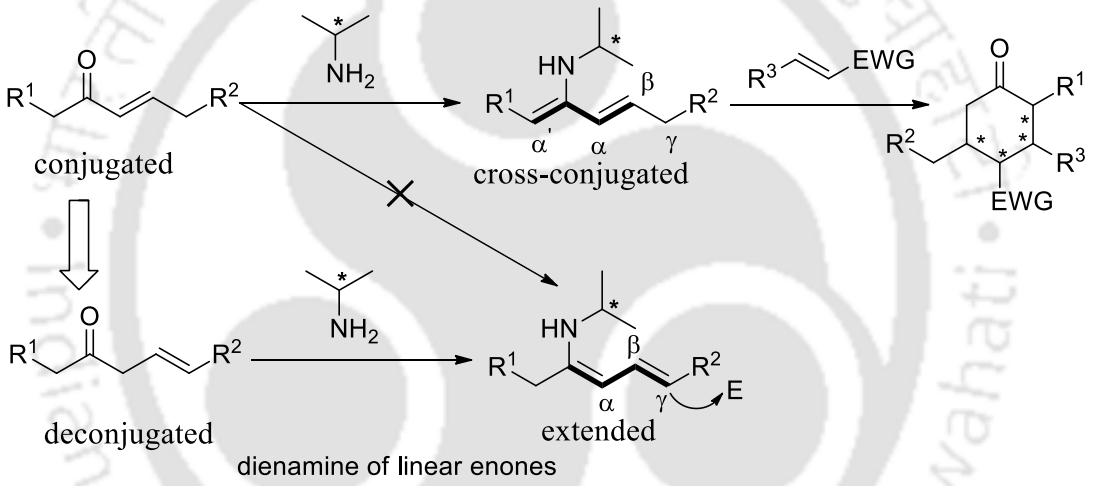
Unsaturated enols *via* vinylogous addition reactions deliver extended carbon skeleton products in comparison with other simple addition reactions of enolates; thus, efforts have been gradually increased in this field over the last few years.[8] Moreover, α,β-unsaturated ketones with an α′-CH group can have two potential pathways of enolization and three potential nucleophilic sites, thus regio- and stereoselectivity of vinylogous addition reactions are quite challenging problems (Scheme 1).[9]



Scheme 1

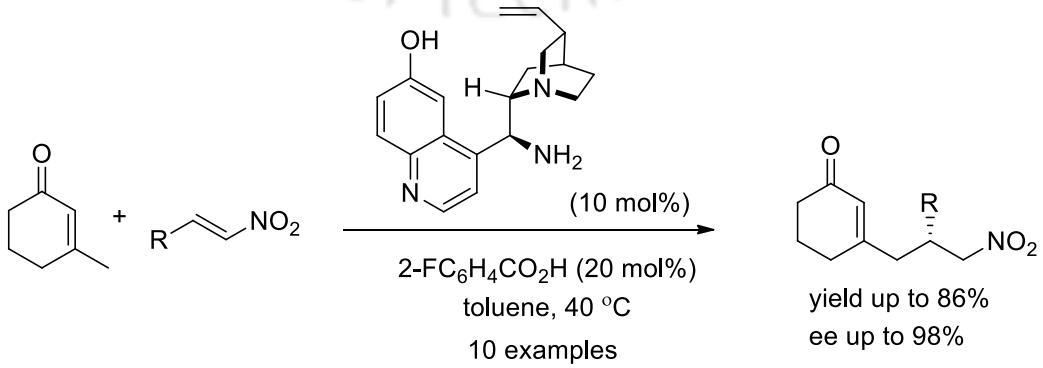
4.2.1. Vinylogous Michael addition reaction utilizing deconjugated enones:

Generally, the conjugated enones having α′-CH allow the formation of cross-conjugated dienamines which lead to a variety of cyclization reactions (Scheme 2).[10] On the other hand, the deconjugated enones may able to form extended conjugated species or dienamine intermediates with a specific geometry for the subsequent high stereo- and enantioselective reactions (Scheme 2).[11]



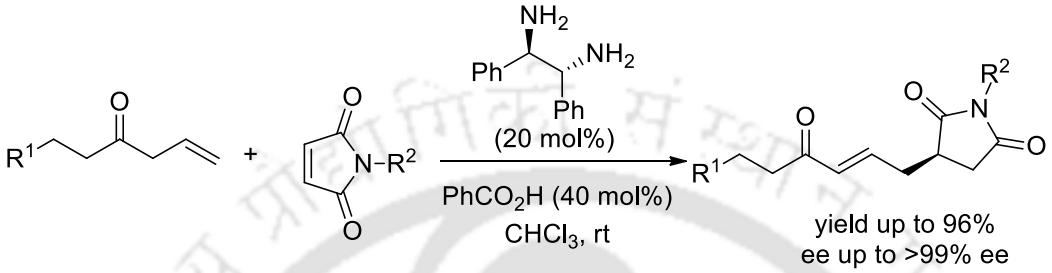
Scheme 2. Possible tautomer of conjugate and deconjugate enones.

Melchiorre group first developed primary amine catalyzed asymmetric vinylogous addition reaction of β-substituted 2-cyclohexenones with nitrostyrenes *via* extended dienamine (Scheme 3).[12]

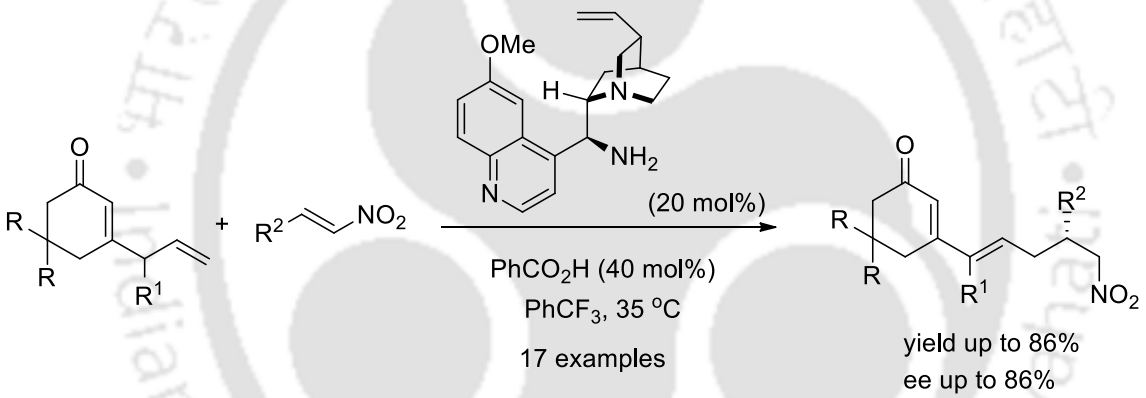


Scheme 3

Chen and co-workers reported an alternate method for the generation of extended dienamines from the deconjugated linear ketones having α′-CH groups and utilized it in asymmetric vinylogous Michael addition reaction to maleimides (Scheme 4).[13] They developed another Michael reaction of cyclic-2,5-dienones with nitroalkenes to achieve high enantioselective bisvinylogous 1,4-adducts (Scheme 5).[14]

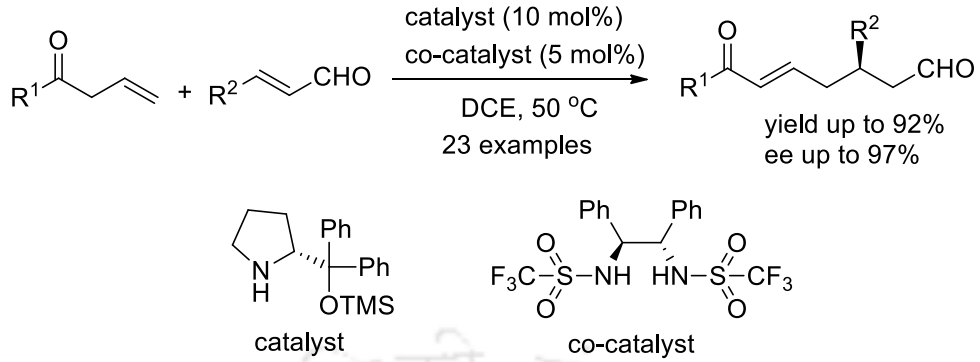


Scheme 4



Scheme 5

Deconjugated linear ketones having non-enolizable aryl or *tert*-butyl groups were employed in vinylogous addition reactions using a variety of organocatalysts.[15] Xu group first introduced vinylogous Michael addition reaction of deconjugated linear ketones having non-enolizable aryl ring system with α,β-unsaturated aldehydes for the synthesis of chiral 1,7-dioxo compounds with good yields as well as excellent enantioselectivities (Scheme 6).[15b]

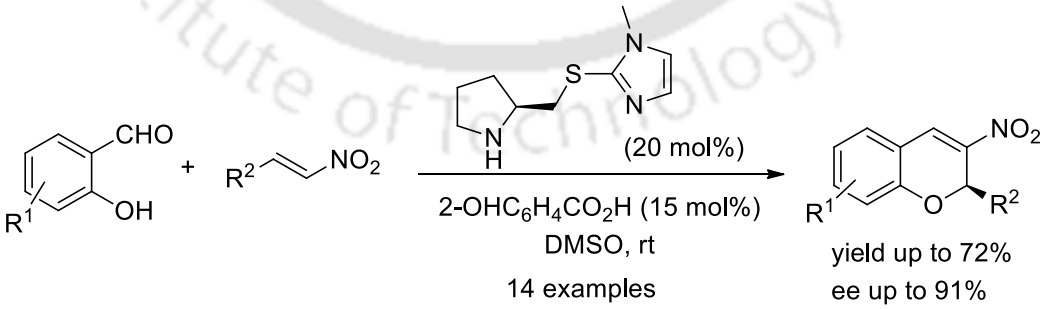


Scheme 6

4.3. Asymmetric oxa-Michael reaction:

Oxa-Michael reaction is an addition reaction of oxygen nucleophiles to conjugate systems. Because of its less reactivity and selectivity compared to other Michael addition reactions, this method has traditionally received less importance from scientific community.[16] Despite this, Oxa-Michael reaction has remarkable synthetic potential and the products are valuable intermediates in organic synthesis. Additionally, it can be applied for the synthesis of oxygen-containing heterocyclic compounds such as tetrahydropyrans, chromenes, xanthones etc. which are often be found in many natural products.[17]

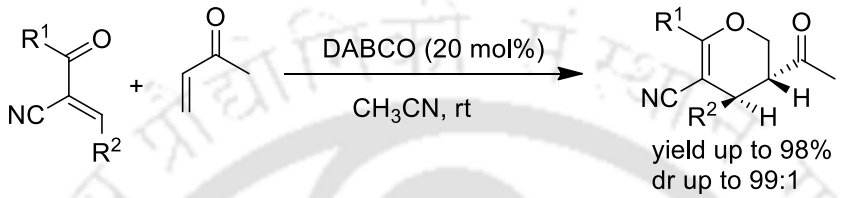
The oxa-Michael reaction has been used for the enantiopure synthesis of chromans by employing pyrrolidine thio-imidazole catalyst. The reactions between salicylaldehydes and nitroolefins afforded 3-nitro-2*H*-chromenes with good enantioselectivities (Scheme 7).[18]



Scheme 7

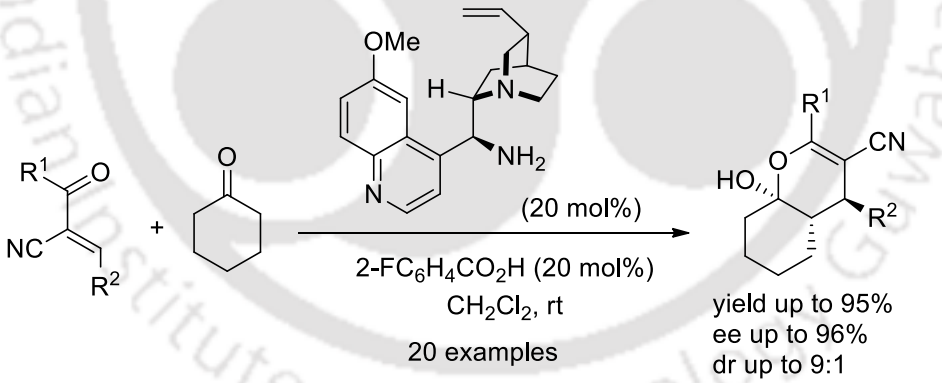
4.4. Literature study for the synthesis of dihydropyrans:

In this context, DABCO catalyzed reaction of methyl vinyl ketones with (*E*)-2-benzoyl-3-phenylacrylonitriles *via* tandem cross Rauhut-Currier/cyclization reaction has been developed by Zhao and co-workers. Using this protocol, highly functionalized 3,4-dihydropyrans were obtained with excellent diastereoselectivities and yields (Scheme 8).[19]



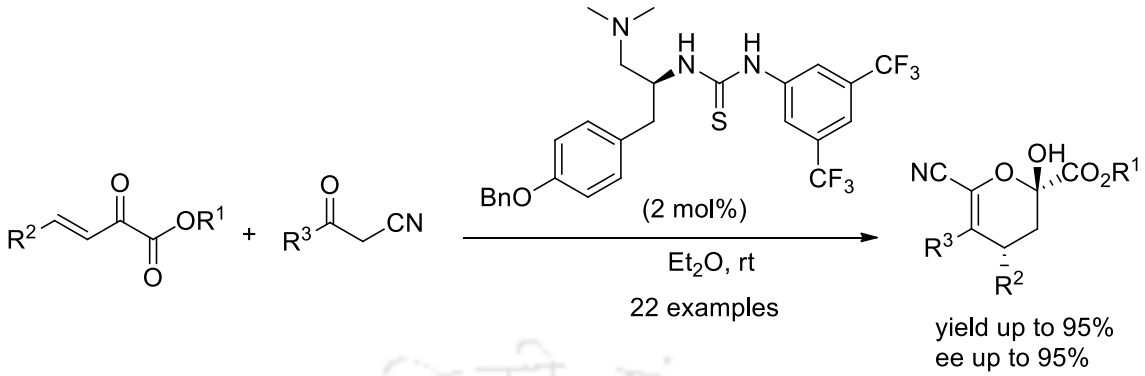
Scheme 8

Lin *et al*. exposed an organocatalytic asymmetric reaction for the facile synthesis of dihydropyrans *via* amine-catalyzed Michael addition and subsequent enolization/cyclisation reactions. As a result, the dihydropyrans having three contiguous chiral centers were generated with excellent enantioselectivities and in moderate to good diastereoselectivities (Scheme 9).[20]



Scheme 9

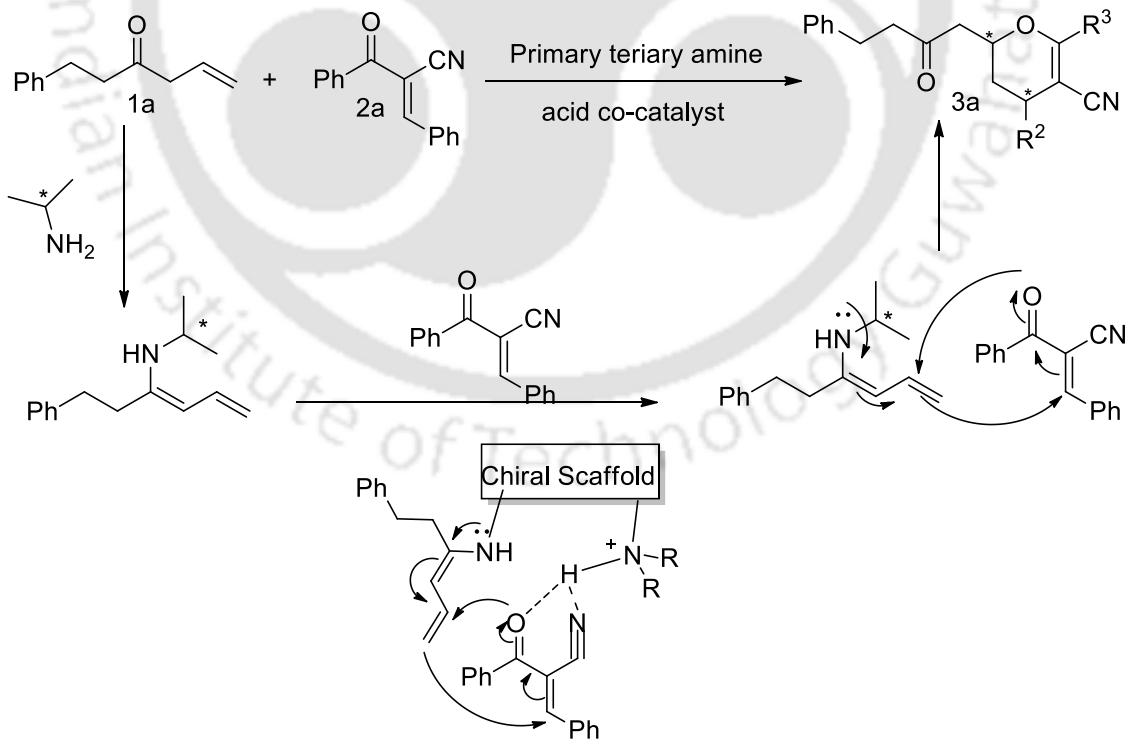
Tyrosine derived thiourea catalyzed reaction of α-substituted cyano ketones with β,γ-unsaturated α-keto esters has been established by Zhao group for the enantiopure synthesis of dihydropyrans *via* Michael/hemiketalization reaction and high yields and high enantioselectivities were achieved (Scheme 10).[21]



Scheme 10

4.5. Concept

From the overview of literature, the direct synthesis of chiral dihydropyrans with different substituents and stereogenic divergence are still a difficult task. The deconjugated β,γ-C-C bond is crucial for formation of the desired dienamine species since the conjugated enone substrates were not responsive under the same catalytic conditions.[22] Hence, we interested to design a new synthetic strategy for the development of the asymmetric Michael-oxa-Michael reaction of deconjugated enones bearing α′-CH



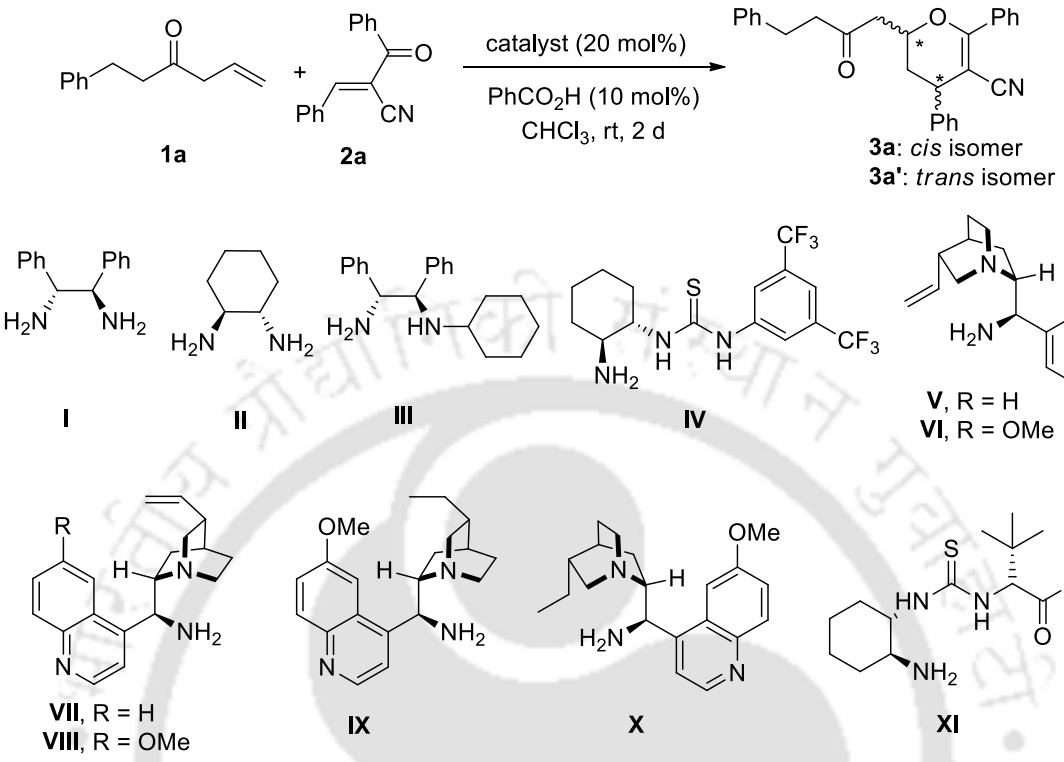
Scheme 11

groups with oxodienes (Scheme 11). We expected that chiral primary and tertiary amine catalysts could be utilized for the simultaneous dual activation of deconjugated enones (*via* dienamine intermediate) and oxadienes (activation of tertiary amine group with help of hydrogen bonding).

4.6. Results and discussion:

Taking the inspiration from the literatures, the investigation was initiated by performing a model reaction between the deconjuagated enone **1a** and readily accessible oxodiene **2a** with a commercially available catalyst, (*R*,*R*)-1,2-diphenylethanediamine (**I**) in combination with benzoic acid in $CHCl_3$ (Table 1). Pleasingly, the desired Michael-oxa-Michael products **3a**/**3a'** were formed in 80% yield with 1.3:1 diastereomeric ratio, although moderate enantiomeric excesses were obtained (major 59% ee, minor 68% ee). The structure of the major product *cis* diastereomer **3a** was confirmed by X-ray crystallography.[23] Catalyst (*S*,*S*)-1,2-cyclohexyldiamine **II** did not help to improve the enantioselectivity of the products (entry 2). Interestingly, catalyst **III** having secondary amine moiety delivered the products with higher enantioselectivities though similar diastereoselectivity were obtained (entry 3). Bifunctional thiourea catalyst **IV** also provided the products with similar enantioselectivities (entry 4). Then we turned our attention on the use of cinchona alkaloid derived primary amine catalysts **V-X** (entries 5-10). In presence of catalysts **V** and **VI**, slightly higher diastereoselectivities without loss of enantioselectivities were observed. Gratifyingly, catalysts **VII** and **VIII** were found to be efficient and in particular, 9-amino-9-deoxyepiquinine **VIII** provided excellent enantioselectivities (95% and 93% ee) for both the diastereomers (entries 7-8). Also, other chinchona alkaloid derived catalysts such as dihydroquinine amine catalyst **IX** and dihydroquinidine amine catalyst **X** were prepared and examined in the reaction but inferior results were found in terms of enantioselectivities (entries 9-10). Additionally, tertiary leucine derived thioamide catalyst **XI** was also tested for the reaction, here also low enantioselectivities and diastereoselectivity were obtained (entries 11). Thus, among all catalysts screened, catalyst **VIII** provided the best catalytic activity (entry 8).

Table 1. Catalyst optimization



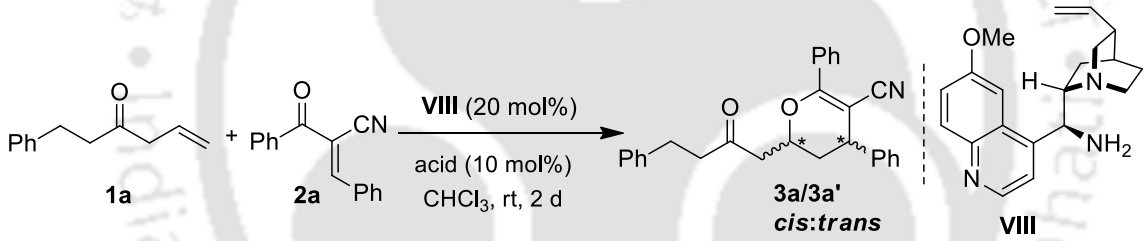
entry[a]	catalyst	yield (%) [b]	dr[c]	ee (%)[d]
1	**I**	80	1.3:1	59/68
2	**II**	80	1.2:1	55/50
3	**III**	90	1.5:1	82/91
4	**IV**	60	1.2:1	80/82
5	**V**	92	1.8:1	79/84
6	**VI**	90	2:1	81/82
7	**VII**	98	1.2:1	90/88
8	**VIII**	**98**	**2:1**	**95/93**
9	**IX**	93	1.8:1	92/92
10	**X**	90	2:1	80/82
11	**XI**	60	1.2:1	80/82

[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2a** in 1 mL $CHCl_3$. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

4.6.1. Acid screening:

To further optimize the reaction conditions, the reaction was surveyed in different acids as co-catalysts with catalyst **VIII** (Table 2). It is believed that, acids might change the enantioselectivity as well as diastereoselectivity of the reaction, so different acids were tested for the reaction. Initially, substituted benzoic acids such as 2-$FC_6H_4CO_2H$, 3-$NO_2C_6H_4CO_2H$ and 3-$MeC_6H_4CO_2H$ were engaged in the reaction. However, the enantioselectivities as well as the diastereoselectivity did not improve (entries 2-4). Similarly, the reaction was studied with chiral acid (*N*-Boc *tert*-luicene) and aliphatic acid (AcOH) co-catalyst but both diastereoselectivities and enantioselectivities got diminished (entries 5-6). In contrast, the reaction did not proceed with strong acid such as TFA (entry 7). As a result, it was concluded that benzoic acid was the best to provide the highest diastereoselectivity and enantioselectivities with excellent yield (entry 1).

Table 2. Acid optimization



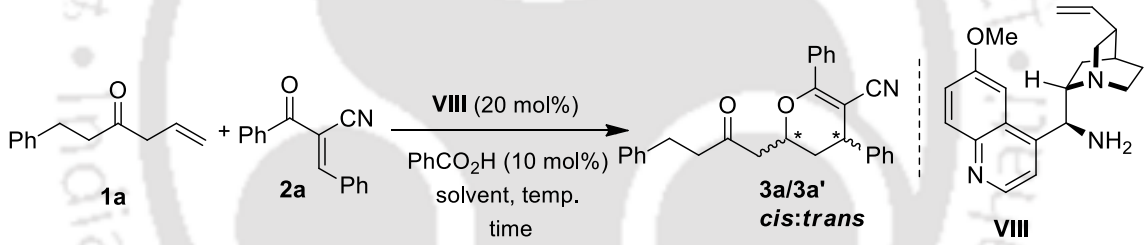
entry[a]	acid	yield (%)[b]	dr[c]	ee (%)[d]
1	**$PhCO_2H$**	**98**	**2:1**	**95/93**
2	2-$FC_6H_4CO_2H$	95	1.8:1	87/84
3	3-$NO_2C_6H_4CO_2H$	95	1.7:1	92/92
4	3-$MeC_6H_4CO_2H$	92	1.5:1	94/90
5	*N*-Boc *tert*-luicene	94	1.9:1	88/74
6	AcOH	94	1.8:1	90/91
7	TFA	ND	-	-

[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2a** in 1 mL $CHCl_3$. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

4.6.2. Solvent and temperature screening:

The reaction was also studied in different solvents and at various temperatures to examine the further enhancement of the diastereoselectivity (Table 3). Gratifyingly, slightly better diastereoselectivity was observed in toluene, whereas enantioselectivity got diminished to 78% for the minor diastereomer (**3a′**, entry 2). Inferior result was obtained using Et_2O as solvent (entry 3). Delightfully, the diastereoselectivity of the reaction was enhanced when performed at 0 ^oC in $CHCl_3$ (entry 4). Further decrease in temperature did not display any significant improvement of enantioselectivities and diastereoselectivity (entry 5). Interestingly, increase in the reaction temperature gave inferior result (entry 6). From all the above optimization conditions, it was concluded that, catalyst V**III** (20 mol%), and benzoic acid (10 mol%) in $CHCl_3$ at 0 ^oC would be the standard condition for the respective transformation.

Table 3. Solvent and temperature optimization



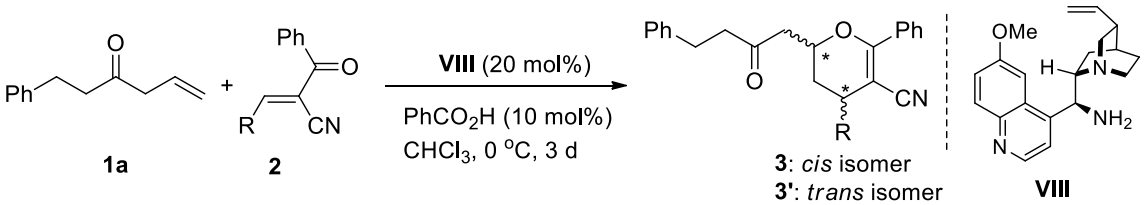
entry[a]	solvent	temp. (^oC)	time (days)	yield (%)[b]	dr[c]	ee (%)[d]
1	$CHCl_3$	rt	2	98	2:1	95/93
2	toluene	rt	2	95	2.3:1	95/78
3	Et_2O	rt	2	40	1.9:1	86/68
4	**$CHCl_3$**	**0**	**3**	**98**	**2.6:1**	**96/93**
5	$CHCl_3$	-10	3	80	2.6:1	95/93
6	$CHCl_3$	55	2	95	1:1	90/87

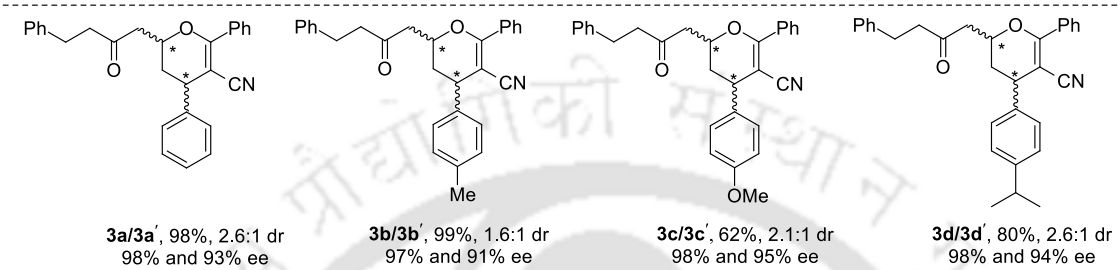
[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2a** in 1 mL solvent. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

4.6.3. Substrate scope:

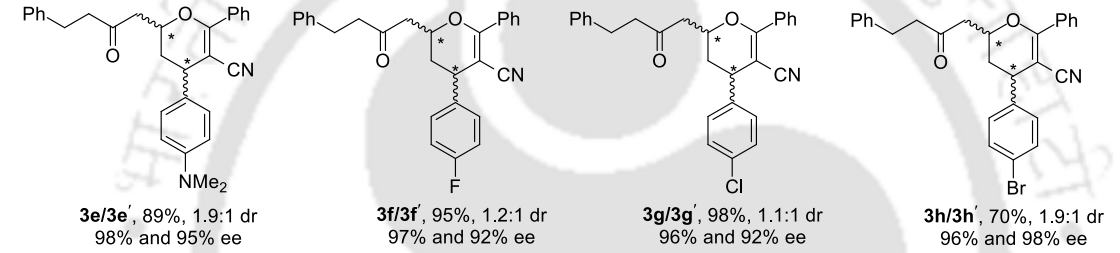
With the establised optimized conditions the scope of the reaction was explored with respect to both the electrophiles and nucleophiles. Initially, a variety of oxadienes **2**

Table 4. Scope of oxadiene with varied double bond substituents[a,b,c,d]

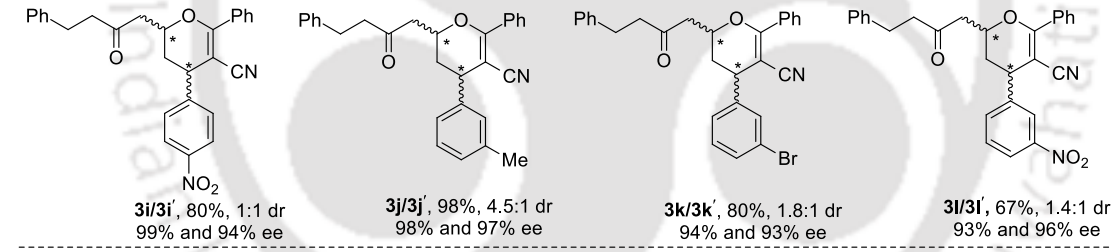




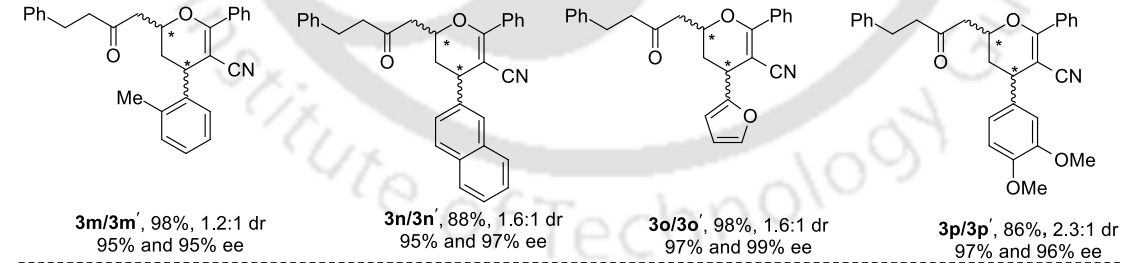
3a/3a′, 98%, 2.6:1 dr, 98% and 93% ee; **3b/3b′**, 99%, 1.6:1 dr, 97% and 91% ee; **3c/3c′**, 62%, 2.1:1 dr, 98% and 95% ee; **3d/3d′**, 80%, 2.6:1 dr, 98% and 94% ee



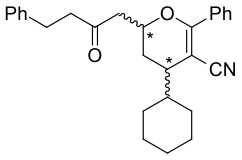
3e/3e′, 89%, 1.9:1 dr, 98% and 95% ee; **3f/3f′**, 95%, 1.2:1 dr, 97% and 92% ee; **3g/3g′**, 98%, 1.1:1 dr, 96% and 92% ee; **3h/3h′**, 70%, 1.9:1 dr, 96% and 98% ee



3i/3i′, 80%, 1:1 dr, 99% and 94% ee; **3j/3j′**, 98%, 4.5:1 dr, 98% and 97% ee; **3k/3k′**, 80%, 1.8:1 dr, 94% and 93% ee; **3l/3l′**, 67%, 1.4:1 dr, 93% and 96% ee



3m/3m′, 98%, 1.2:1 dr, 95% and 95% ee; **3n/3n′**, 88%, 1.6:1 dr, 95% and 97% ee; **3o/3o′**, 98%, 1.6:1 dr, 97% and 99% ee; **3p/3p′**, 86%, 2.3:1 dr, 97% and 96% ee



3q/3q′, 85%, 7:1 dr, 94% ee

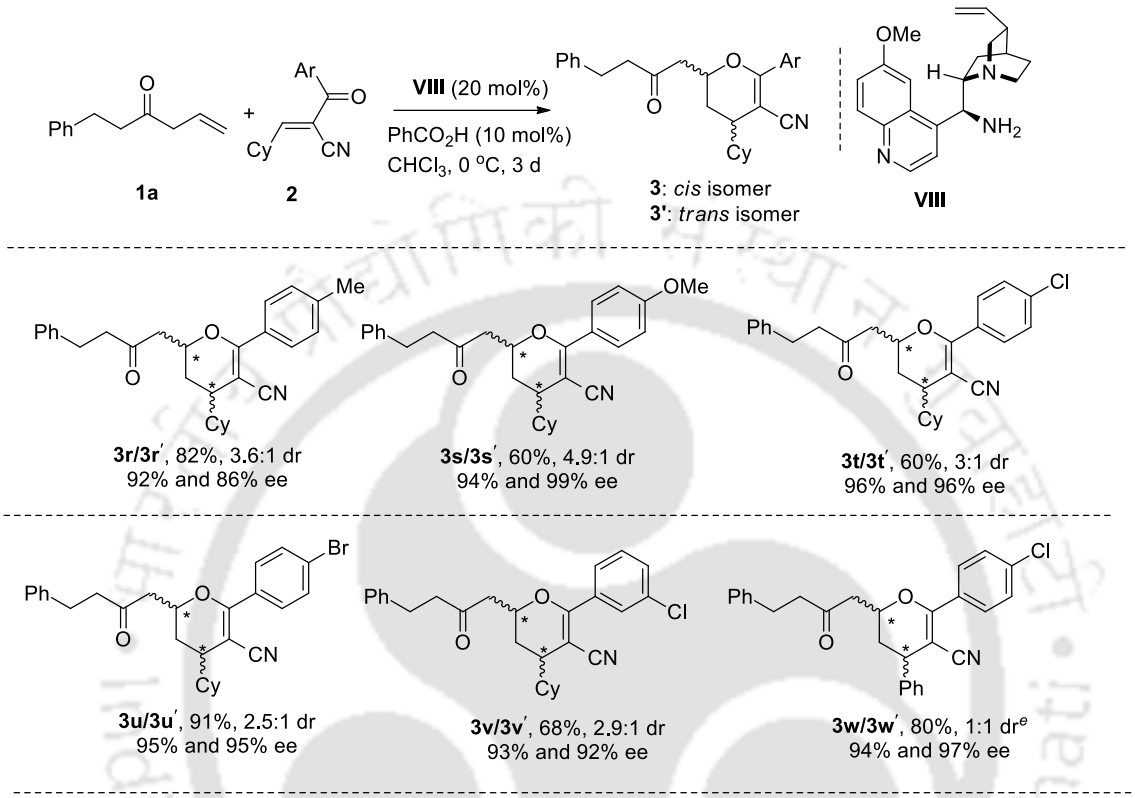
[a]All reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 mL $CHCl_3$. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

having substitutions on the aryl group of the olefin was screened and the results were summarized in Table 4. It turned out that a variety of electron-withdrawing and electron-donating groups incorporated in the *ortho*-, *meta*- and *para*-positions of the aryl group gave excellent enantioselectivities. For example, oxadienes **2b** and **2c** having 4-methyl and 4-methoxy moiety provided products **3b/3b'** and **3c/3c'** with good diastereoselectivities and excellent enantioselectivities. Additionally, the products **3d/3d'** and **3e/3e'** having 4-isopropyl and 4-*N*,*N*-dimethyl group were isolated with excellent enantioselectivities of both diastereomers. The products **3f/3f'** having 4-phenyl substitution was obtained 97% and 92% ees of the both diastereomers respectively. Similarly, 4-halo substituted oxadienes **2g**-**2h** and 4-nitro substituted oxadiene **2i** furnished the corresponding Michael-oxa-Michael products **3g/3g'**-**3h/3h'** and **3i/3i'** respectively with excellent enantioselectivities. Next, *meta*-substituted enones **2j**-**2l** provided the products **3j/3j'**-**3l/3l'** with high enantioselectivities. Among *meta*-substituted enones, *m*-tolylsubstituted enone **2j** gave the highest value of diastereomeric ratio (4.5:1). Then *ortho*-substituted aryl enone **2m** reacted smoothly to provide the products **3m/3m'** with 98% yield. Moreover, 2-naphthyl and 2-furyl containing enones (**2n** and **2o)** could also be employed in the reaction, and high enantioselectivities were preserved. 3,4-Disubstituted aryl enone **2p** exhibited similar high reactivity and the corresponding Michael products **3p**/**3p'** were obtained in 97% and 96% ees respectively. Gratifyingly, this methodology was also appropriate for aliphatic enone such as cyclohexyl substituted enone **2q**, and the desired products **3q**/**3q'** were obtained in a decent 7:1 dr with 94% ee for the major diastereomer.

The generality of the reaction was further demonstrated by applying oxadienes **2** with various ketone functionalties (Table 5). Accordingly, a variety of cyclohexyl substituted oxadienes **2r-w** were prepared and subjected in the reaction. To our delight, the reaction was in general irrespective of the electronic nature of the aryl group and the enantiomeric excess was up to 99% with fair diastereomeric ratio. The reaction of 4-substituted oxadienes **2r**-**2u** proceeded smoothly under the established optimized conditions and the desired products **3r/3r'**-**3u**/**3u'** were isolated in excellent enantioselectivities with good diastereoselectivities. Moreover, excellent enantioselectivities (93% and 92% respectively) were achieved for *meta*-substituted products **3v**/**3v'** with good combined yield (68%). In contrast to these results, less diastereoselectivity (1:1) was observed for

the products **3w**/**3w'** having phenyl group, while maintaining the excellent enantioselectivities and yield.

Table 5. Scope of oxadiene with varied ketone substituents[a,b,c,d]

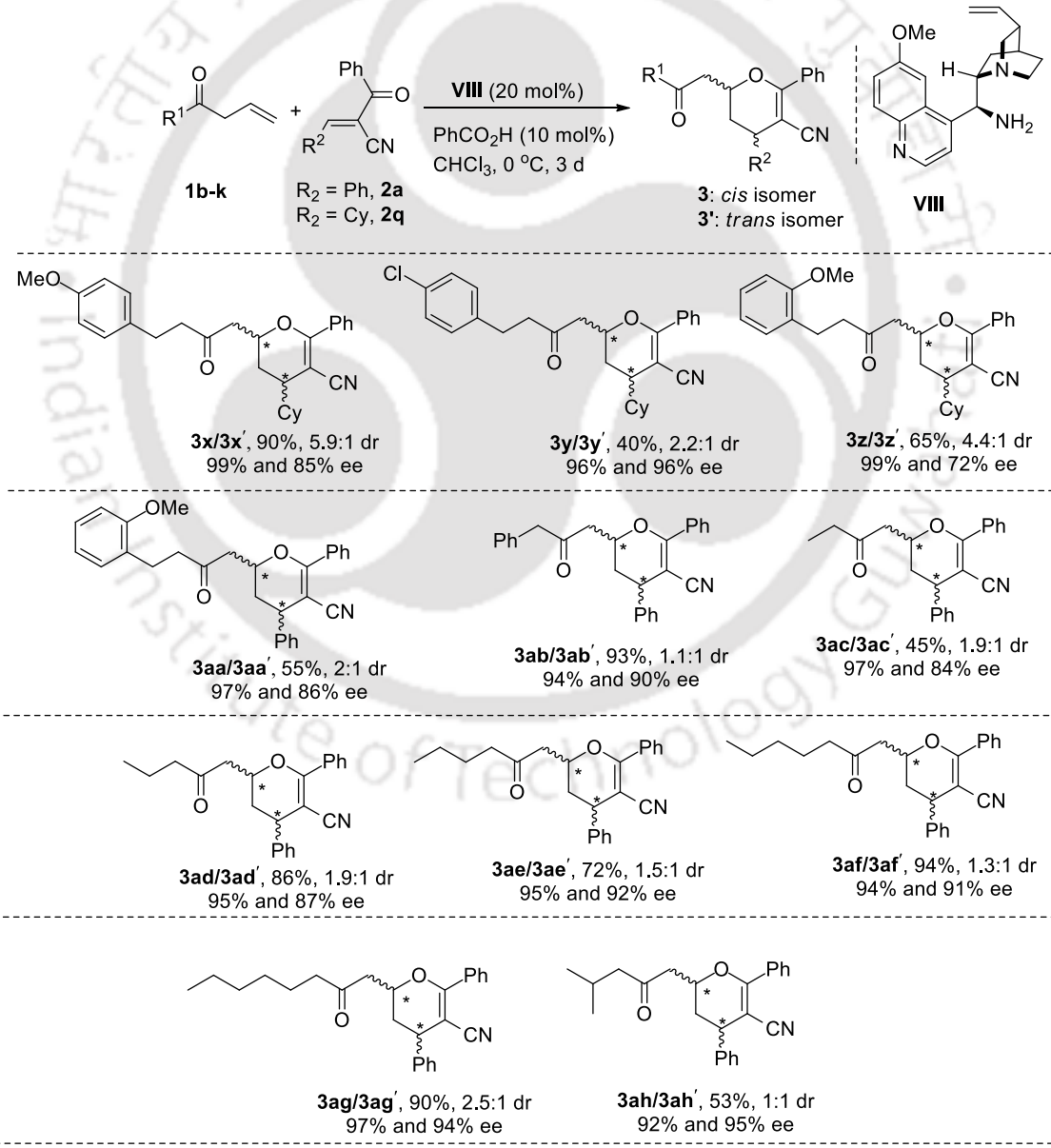


[a]All reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2** in 1 mL $CHCl_3$. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]The cyclohexyl (Cy) in **2** was substituted for a phenyl (Ph) group.

The next phase of experiments involved screening of different deconjugated enones **1** in this method (Table 6). It turns out that a wide range of alkyl groups could be employed in the reaction and excellent enantioselectivities were attained with moderate to good diastereomeric ratios. Initially, different substitutions on the phenyl moiety of hydrocinnamyl group were studied and delightfully excellent results were obtained (**3x**/**3x'**-**3aa**/**3aa'**). For example, deconjugated enone **1b** having 4-methoxy group provided the corresponding products **3x**/**3x'** with 90% yield and 5.9:1 diastereomeric ratio. In addition 4-chloro substituted products **3y**/**3y'** also achieved excellent enantioselectivities of both diastereomers. Interestingly, enones **1d** on reaction with **2q** and **2a** delivered the products **3z**/**3z'** and **3aa**/**3aa'** with similar enatioselectivities, and to our delight higher diasteremeric ratio (4.4:1) was obtained for the products **3z**/**3z'**. Then

enone **1e** having benzyl moiety was employed and the products **3ab**/**3ab'** were attained with high enantioselectivities. Then we focussed on the investigation of different branched (**1k**) and unbranched (**1f-1j**) alkyl group substituted enones with different chain length. Gratifyingly, linear deconjugated enones **1f-1j** having ethyl, propyl, butyl, pentyl and hexyl groups could be well tolerated and delivered the corresponding dihydropyran products **3ac**/**3ac'**-**3ag**/**3ag'** with excellent enantioselectivies of both diastereomers. Additionally, the branched enones **1k** having isobutyl group delivered the products **3ah**/**3ah'** with good result.

Table 6. Scope of deconjugated enones[a,b,c,d]



[a]All reactions were carried out with 0.1 mmol of **1** with 0.1 mmol of **2a/2q** in 1 ml solvent. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC.

4.6.4. Crystal Structure:

The crystal structure of product **3a** was unambiguously confirmed by X-ray crystallography (Figure 2).

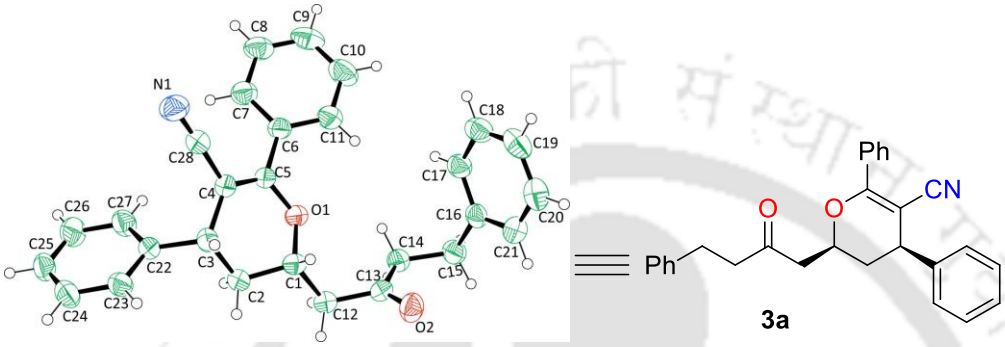


Figure 2. X-ray crystallography structure of compound **3a**.

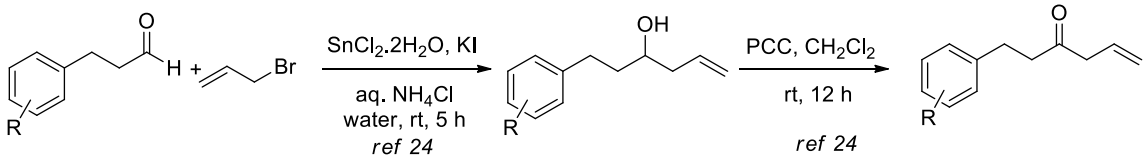
4.7. Conclusion:

This chapter documented a fascinating Michael-oxa-Michael reaction of linear deconjugated enones with oxadienes by using easily available quinine derived primary amine and benzoic acid. Easily available starting materials derived from aldehydes were utilized in this reaction. The dihydropyran products having two stereogenic centres are important frameworks and could be applied in the synthesis of pharmaceuticals and for natural product synthesis.

4.8. Experimental section:

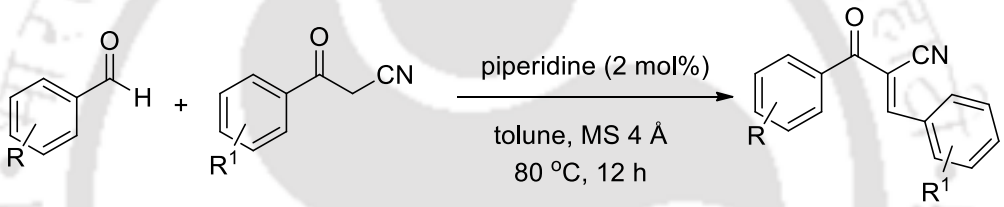
4.8.1. General procedure for preparation of allylic ketone (1): The corresponding aldehyde (1 eq.) was added to solution of water containing potassium iodide (3 eq.), $SnCl_2.2H_2O$ (3 eq.) and allyl bromide (1.5 eq.). After 15 min saturated ammonium chloride was added, than orange solution turns white. The stirring was continued 5-6 h at room temperature. After end of the reaction, the reaction mixture was extracted with DCM (2 times), wash with water and brine, dried with sodium sulphate, concentration under reduced pressure and continuing the next step. The obtained residue was dissolved into CH_2Cl_2. Then PCC (1.5 eq.) was added to the solution in several times at 0 ^oC. The reaction was stirring 12 h at room temperature. Then mixture was diluted with CH_2Cl_2

and passed though the short silica gel column. Then compound was purified column chromatography (Scheme 12)[24].



Scheme 12

4.8.2. General procedure for preparation compound (2): The solution benzyolacetonitril (1eq.), 4 Å MS in toluene was added corresponding aldehyde (1 eq.) and piperidine (2 mol%) under argon atmosphere. The reaction mixture was heated at 80 ^{o}C for 8 h. After reaction was over reduced the toluene and purified the compound by flash chromatography (Scheme 13).

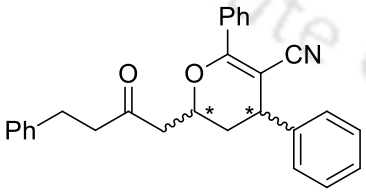


Scheme 13

4.8.3. General procedure for preparation compound (3): The solution of allylketone **1** (0.1 mmol), **2** (0.1 mmol), **VIII** (20 mol%) in $CHCl_3$ (1 mL) were stirring at 0 ^{o}C for 3 days. Purification by silica gel column chromatography (EA in Hexane) gave products **3**.

4.8.4. Product characterisation:

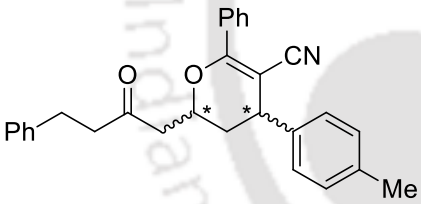
5,6-Dihydro-6-(2-oxo-4-phenylbutyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile(3a/3a'):



Colourless oil (40 mg, 98% yield), 2.6:1 dr; R_f value 0.25 (10:1 hex/EA); **A**. *cis* product: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.48 – 7.35 (m, 5H), 7.29 (dd, *J* = 14.9, 6.7 Hz, 4H), 7.26 – 7.20 (m, 2H), 7.17 (t, *J* = 6.8 Hz, 2H), 4.78 – 4.69 (m, 1H), 3.85 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.02 – 2.90 (m, 3H), 2.84 – 2.78 (m, 2H), 2.64 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.30 (dd, *J* = 13.8, 6.6 Hz, 1H), 1.77 (dd, *J* = 25.1, 11.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.3, 166.2, 141.3, 140.7, 133.0, 131.1, 129.2, 128.7, 128.5, 128.4, 128.4, 127.8, 127.7, 126.4, 119.5, 88.7, 74.20 47.6, 45.4, 41.4, 37.3, 29.6; **B**. Mixture of *cis* and *trans* :**^{1}H NMR (400**

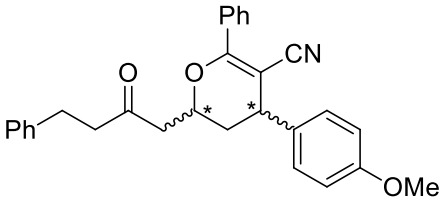
MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 0.73H), 7.75 (d, *J* = 6.6 Hz, 2H), 7.50 – 7.38 (m, 7H), 7.31 (dd, *J* = 17.3, 10.1 Hz, 6H), 7.25 – 7.14 (m, 4H), 4.78 – 4.69 (m, 1H), 4.64 – 4.56 (m, 0.35H), 3.90 (d, *J* = 3.6 Hz, .37H), 3.85 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.00-2.89 (m, 4H), 2.80-2.76 (m, 3H), 2.64 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.52 (dd, *J* = 16.6, 4.1 Hz, 0.42H), 2.30 (dd, *J* = 13.0, 7.5 Hz, 1H), 2.13 – 2.07 (m, 0.32H), 1.99 (dt, *J* = 13.8, 2.4 Hz, 0.42H), 1.78 (dd, *J* = 25.3, 11.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.3, 206.1, 166.1, 165.9, 142.1, 141.3, 140.7, 140.7, 133.1, 133.0, 131.1, 131.0, 129.1, 129.0, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.1, 127.7, 127.7, 127.5, 126.4, 120.2, 119.5, 88.6, 85.1, 74.1, 69.9, 47.5, 47.2, 45.3, 41.4, 39.4, 37.2, 34.8; **ESI-MS** m/z calcd. for $C_{28}H_{25}NO_2$ $[M+H]^+$ 408.1958, found 408.1959; **FT-IR (KBr)** 2949, 2910, 2179, 1717, 1608, 1573, 1491, 1368, 1280, 1154, 1122, 1067 cm^{-1}; The ee (98% ee_{major}, 93% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (65:35) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 13.66 min, t_{minor} = 16.40 min; major diastereoisomer t_{major} = 31.71 min, t_{minor} = 92.27 min.

5,6-Dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4-p-tolyl-4*H*-pyran-3-carbonitrile



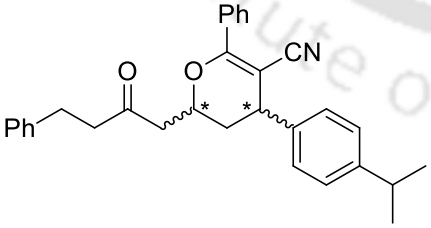
(3b/3b'): Colourless oil (42 mg, 99% yield), 1.6:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.0 Hz, 1.15H), 7.72 (d, *J* = 7.1 Hz, 2H), 7.45-7.40 (m, 5H), 7.27 (s, 2H), 7.22 – 7.16 (m, 11H), 7.14 (d, *J* = 7.2 Hz, 1.58H), 4.72 (bs, 2H), 4.58 (bs, 0.6H), 3.86 (s, 0.6H), 3.83 – 3.78 (m, 1H), 2.99 – 2.87 (m, 5H), 2.84-2.80 (s, 2H), 2.79 – 2.75 (m, 2H), 2.63 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.52 (d, *J* = 16.6 Hz, 1H), 2.35 (bs, 5.9H), 2.25 (dd, *J* = 18.0, 5.2 Hz, 1H), 2.05 (dd, *J* = 17.4, 12.5 Hz, 1H), 1.96 (d, *J* = 13.3 Hz, 1H), 1.77 (dd, *J* = 24.4, 12.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.3, 206.2, 165.9, 165.8, 140.7, 140.75 139.2, 138.3, 137.4, 137.2, 133.1, 133.0, 131.1, 131.0, 129.8, 129.7, 129.2, 128.7, 128.7, 128.5, 128.5, 128.4, 128.3, 128.0, 127.5, 126.4, 126.3, 125.4, 120.2, 119.6, 88.9, 85.4, 74.2, 69.9, 47.6, 47.3, 45.4, 41.0, 39.1, 37.3, 35.0, 29.8, 29.6, 21.3, 21.2; **ESI-MS** m/z calcd. for $C_{29}H_{27}NO_2$ $[M+H]^+$ 422.2115, found 422.2113; **FT-IR (KBr)** 2923, 2851, 2203, 1723,1610, 1493, 1364, 1283, 1154, 1081 cm^{-1}; The ee (97% ee_{major}, 91% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 19.52 min, t_{minor} = 24.33 min; major diastereoisomer t_{major} = 42.91 min, t_{minor} = 89.20 min.

5,6-Dihydro-4-(4-methoxyphenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile(3c/3c'):



Colourless oil (28 mg, 62% yield), 2.1:1 dr; R_f value 0.25 (12:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 – 7.74 (m, 1.54H), 7.73 – 7.69 (m, 2H), 7.48 – 7.37 (m, 4H), 7.28 (d, *J* = 6.9 Hz, 1H), 7.25 (s, 1H), 7.24 – 7.12 (m, 7H), 6.93 – 6.90 (m, 3H), 4.77 – 4.69 (m, 1H), 4.60 – 4.54 (m, 0.45H), 3.85 – 3.82 (m, 1H), 3.81 (bs, 3H), 3.81 (bs, 1.21H), 3.79 (d, *J* = 6.6 Hz, 0.45H), 3.00 – 2.86 (m, 4H), 2.84 – 2.75 (m, 3H), 2.64 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.53 (dd, *J* = 16.6, 4.2 Hz, 0.43H), 2.27 (ddd, *J* = 13.8, 6.6, 1.6 Hz, 1H), 2.05 – 2.00 (m, 0.51H), 1.97 – 1.93 (m, 0.45H), 1.75 (dt, *J* = 13.7, 11.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.4, 206.2, 165.9, 165.7, 159.1, 159.0, 140.8, 140.7, 134.3, 133.3, 133.2, 133.1, 131.1, 131.0, 129.1, 128.7, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 126.4, 126.4, 120.2, 119.6, 114.6, 114.5, 89.1, 85.6, 74.2, 70.0, 55.4, 47.7, 47.4, 45.4, 45.4, 40.7, 38.7, 37.3, 35.1, 29.7, 29.6; **ESI-MS** m/z calcd. for $C_{29}H_{27}NO_3$ $[M+H]^+$ 438.2064, found 438.2066; **FT-IR (KBr)** 2927, 2855, 2205, 1712, 1608, 1509, 1448, 1356, 1251, 1161, 1031 cm^{-1}; The ee (98% ee_{major}, 95% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 41.05 min, t_{minor} = 48.81 min; major diastereoisomer t_{major} = 56.05 min, t_{minor} = 75.95 min.

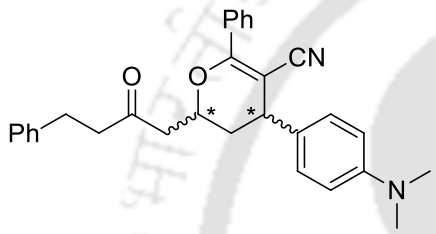
5,6-Dihydro-4-(4-isopropylphenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3d/3d'):



Colourless oil (36 mg, 80% yield), 2.6:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 6.6 Hz, 1H), 7.73 (d, *J* = 6.7 Hz, 2H), 7.50 – 7.38 (m, 4H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.24 – 7.13 (m, 8H), 4.74 (dt, *J* = 11.3, 5.6 Hz, 1H), 4.63 – 4.54 (m, 0.41H), 3.87 (dd, *J* = 5.9, 2.2 Hz, 0.39H), 3.82 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.02 – 2.87 (m, 5H), 2.83-2.76 (m, 3H), 2.64 (dd, *J* = 16.9, 5.2 Hz, 1H), 2.52 (dd, *J* = 16.6, 3.8 Hz, 0.39H), 2.29 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.12 – 2.02 (m, 0.51H), 1.97 (dt, *J* = 13.7, 2.3 Hz, 0.45H), 1.77 (dd, *J* = 25.3, 11.5 Hz, 1H), 1.27 (d, *J* = 2.5 Hz, 6H), 1.25 (d, *J* = 2.7 Hz, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.4, 206.3, 166.0, 165.8, 148.2, 148.0,

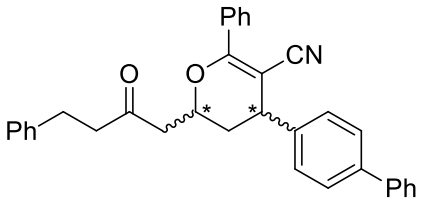
140.7, 140.7, 139.4, 138.5, 133.1, 133.0, 131.1, 131.0, 128.7, 128.7, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.0, 127.6, 127.2, 127.1, 126.4, 126.3, 120.3, 119.7, 88.9, 85.3, 74.2, 69.9, 47.6, 47.3, 45.5, 45.4, 41.0, 39.1, 37.3, 34.9, 33.9, 33.8, 29.6, 29.5, 24.1; **ESI-MS** m/z calcd. for $C_{31}H_{31}NO_2$ $[M+H]^+$ 450.2428, found 450.2434; **FT-IR (KBr)** 2923, 2851, 2205, 1723,1610, 1615, 1493, 1369, 1283, 1154, 1039 cm^{-1}; The ee (98% ee_{major}, 94% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 17.93 min, t_{minor} = 19.05 min; major diastereoisomer t_{major} = 25.93 min, t_{minor} = 27.61 min.

4-(4-(Dimethylamino)phenyl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3e/3e'):



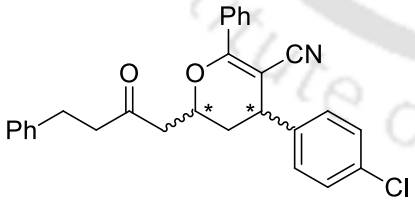
Red colourless oil (40 mg, 89% yield), 1.9:1 dr; R_f value 0.25 (13:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 – 7.75 (m, 0.79H), 7.72 (dd, *J* = 6.7, 1.5 Hz, 2H), 7.49 – 7.38 (m, 4H), 7.32 – 7.27 (m, 1H), 7.25 – 7.20 (m, 1H), 7.20 – 7.11 (m, 6H), 6.74 (dd, *J* = 8.2, 2.8 Hz, 2H), 4.78 – 4.67 (m, 1H), 4.60 (t, *J* = 9.6 Hz, 0.52H), 3.81 (d, *J* = 3.8 Hz, 0.42H), 3.76 (dd, *J* = 11.3, 6.6 Hz, 1H), 2.99 (d, *J* = 7.7 Hz, 1H), 2.95 (d, *J* = 1.3 Hz, 4H), 2.95 (d, *J* = 1.3 Hz, 3H), 2.88 (dd, *J* = 15.6, 11.9 Hz, 3H), 2.84 – 2.75 (m, 3H), 2.63 (dd, *J* = 16.8, 5.1 Hz, 1H), 2.52 (dd, *J* = 16.5, 3.8 Hz, 0.52H), 2.25 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.04 – 1.98 (m, 0.42H), 1.94 (d, *J* = 14.5 Hz, 0.52H), 1.77 (dd, *J* = 24.7, 11.9 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.5, 206.3, 165.5, 165.4, 150.1, 149.9, 140.8, 140.7, 133.2, 133.1, 130.9, 130.9, 129.9, 128.7, 128.7, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 126.4, 126.3, 120.4, 119.8, 113.1, 113.0, 89.5, 85.8, 74.2, 70.0, 47.6, 47.4, 45.4, 45.4, 40.8, 40.5, 38.6, 37.3, 36.7, 35.2, 31.7, 29.8, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{30}H_{30}N_2O_2$ $[M+H]^+$ 451.2380, found 451.2390; **FT-IR (KBr)** 2921, 2851, 2203, 1725,1610, 1659, 1493, 1364, 1283, 1157, 1088 cm^{-1};The ee (98% ee_{major}, 95% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (65:35 up to 54 min then 64:40) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 16.00 min, t_{minor} = 21.54 min; major diastereoisomer t_{major} = 64.73 min, t_{minor} = 56.79 min.

5,6-Dihydro-4-(4-biphenylphenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile(3f/3f'):



Colourless oil (43 mg, 95% yield), 1.2:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.81 (dd, *J* = 8.0, 1.5 Hz, 1.5H), 7.79 – 7.75 (m, 2H), 7.61 (dt, *J* = 7.0, 4.8 Hz, 7H), 7.46 (dd, *J* = 12.5, 4.8 Hz, 8H), 7.40 – 7.36 (m, 5H), 7.30 – 7.27 (m, 3H), 7.23 (d, *J* = 1.3 Hz, 1H), 7.22 – 7.14 (m, 7H), 4.77 (dt, *J* = 9.0, 6.2 Hz, 1H), 4.63 (td, *J* = 10.8, 2.5 Hz, 0.87H), 3.94 (dd, *J* = 5.9, 2.2 Hz, 0.76H), 3.90 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.03 – 2.88 (m, 6H), 2.85 – 2.76 (m, 4H), 2.65 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.54 (dd, *J* = 16.7, 4.0 Hz, 1H), 2.33 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.11 (dd, *J* = 17.7, 6.8 Hz, 1H), 2.05 – 1.99 (m, 1H), 1.81 (dd, *J* = 25.3, 11.5 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.3, 206.2, 166.3, 166.0, 141.2, 140.8, 140.7, 140.7, 140.7, 140.6, 140.4, 140.3, 133.0, 132.9, 131.2, 131.1, 129.1, 128.9, 128.9, 128.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.1, 127.9, 127.8, 127.5, 127.4, 127.2, 127.2, 126.4, 126.3, 125.4, 120.2, 119.7, 88.5, 85.0, 74.1, 69.9, 60.5, 47.5, 47.2, 45.4, 41.0, 39.1, 37.2, 34.8, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{34}H_{29}NO_2$ $[M+H]^+$ 484.2271, found 484.2273; **FT-IR (KBr)** 2926, 2853, 2203, 1717,1610, 1515, 1493, 1364, 1285, 1081 cm^{-1};The ee (97% ee_{major}, 92% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (96:4 up to 119 min then 80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 71.43 min, t_{minor} = 88.68 min; major diastereoisomer t_{major} = 98.68 min, t_{minor} = 129.92 min.

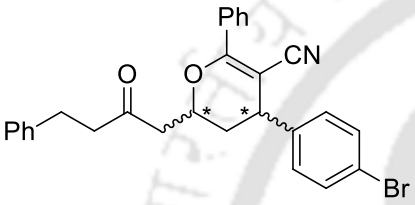
4-(4-Chlorophenyl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3g/3g'):



Colourless oil (44 mg, 98% yield), 1.1:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.80 – 7.76 (m, 2H), 7.75 – 7.71 (m, 2H), 7.46 (dt, *J* = 23.8, 7.4 Hz, 5H), 7.37 (d, *J* = 8.4 Hz, 3H), 7.32 – 7.27 (m, 3H), 7.24 (dd, *J* = 9.1, 4.5 Hz, 4H), 7.22 – 7.14 (m, 7H), 4.74 (dt, *J* = 12.8, 6.3 Hz, 1H), 4.58 – 4.48 (m, 1H), 3.90 – 3.86 (m, 1H), 3.84 (dd, *J* = 11.4, 6.5 Hz, 1H), 3.03 – 2.88 (m, 6H), 2.86 – 2.77 (m, 4H), 2.65 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.54 (dd, *J* = 16.8, 4.4 Hz, 1H), 2.31 (dd, *J* = 10.5, 6.6 Hz, 1H), 2.08 (dd, *J* = 20.7, 10.1 Hz, 1H), 1.96 (dt, *J* = 13.8, 2.3 Hz, 1H), 1.75 – 1.70 (m, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.2, 206.0, 166.4, 166.2, 140.7, 140.7, 140.6, 139.8, 133.5, 133.4, 132.8, 132.8, 131.30, 131.2, 129.4, 129.3, 129.2, 129.2, 129.1, 128.7, 128.7,

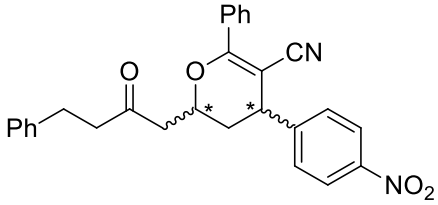
128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 126.45, 126.4, 125.4, 120.0, 119.4, 88.1, 84.6, 74.1, 69.8, 47.5, 47.2, 45.4, 40.9, 38.5, 37.1, 34.7, 32.1, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{28}H_{24}ClNO_2$ $[M+H]^+$ 442.1568, found 442.1569; **FT-IR (KBr)** 2921, 2855, 2201, 1719, 1608, 1579, 1493, 1280, 1161, 1095 cm^{-1}; The ee (96% ee_{major}, 92% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 25.75 min, t_{minor} = 28.70 min; major diastereoisomer t_{major} = 50.97 min, t_{minor} = 75.45 min.

4-(4-Bromophenyl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3h/3h'):



Colourless oil (34 mg, 70% yield), 1.9:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.75 (dd, *J* = 6.7, 1.7 Hz, 1H), 7.72 – 7.68 (m, 2H), 7.52 – 7.49 (m, 3H), 7.47 – 7.41 (m, 4H), 7.28 (dd, *J* = 6.5, 1.4 Hz, 1H), 7.24 (t, *J* = 3.6 Hz, 1H), 7.21 – 7.11 (m, 7H), 4.73 (dt, *J* = 11.5, 5.9 Hz, 1H), 4.56 – 4.49 (m, 0.56H), 3.87 – 3.83 (m, 0.72H), 3.83 – 3.79 (m, 1H), 3.02 – 2.87 (m, 5H), 2.84 – 2.75 (m, 3H), 2.64 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.53 (dd, *J* = 16.8, 4.5 Hz, 0.63H), 2.28 (ddd, *J* = 13.8, 6.6, 1.7 Hz, 1H), 2.11 – 2.05 (m, 0.51H), 1.95 (dt, *J* = 13.9, 2.3 Hz, 0.66H), 1.71 (dt, *J* = 13.8, 11.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.2, 206.0, 166.4, 166.2, 141.2, 140.6, 140.6, 140.3, 132.8, 132.7, 132.3, 132.2, 131.3, 131.2, 129.8, 129.4, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 126.4, 126.4, 121.1, 121.5, 120.0, 119.4, 87.9, 84.5, 74.0, 69.8, 47.4, 47.1, 45.3, 40.9, 39.0, 37.0, 34.6, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{28}H_{24}BrNO_2$ $[M+H]^+$ 486.1063, found 486.1066; **FT-IR (KBr)** 2921, 2855, 2201, 1716, 1608, 1579, 1493, 1280, 1161, 1084 cm^{-1}; The ee (96% ee_{major}, 98% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 27.58 min, t_{minor} = 30.75 min; major diastereoisomer t_{major} = 56.17 min, t_{minor} = 84.27 min.

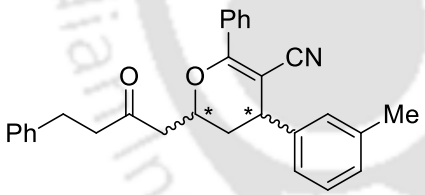
5,6-Dihydro-4-(4-nitrophenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3i/3i'):



Colourless oil (36 mg, 80% yield), 1:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ

8.26 (d, *J* = 8.6 Hz, 4H), 7.77 (dd, *J* = 8.1, 1.2 Hz, 2H), 7.72 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.52 – 7.40 (m, 10H), 7.27 (s, 1H), 7.25 (s, 1H), 7.24 (d, *J* = 1.4 Hz, 1H), 7.21 (s, 1H), 7.19 – 7.16 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 2H), 4.81 – 4.72 (m, 1H), 4.51 (ddd, *J* = 9.9, 6.5, 3.3 Hz, 1H), 4.04 – 3.98 (m, 2H), 3.06 – 2.87 (m, 6H), 2.85 – 2.76 (m, 4H), 2.68 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.57 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.32 (dd, *J* = 6.6, 1.5 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.05 – 1.99 (m, 1H), 1.74 (d, *J* = 13.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.1, 205.9, 167.1, 166.9, 149.5, 148.9, 147.5, 147.4, 140.6, 132.5, 132.5, 131.5, 131.5, 129.2, 129.1, 128.7, 128.7, 128.7, 128.6, 128.4, 128.4, 128.4, 126.5, 126.4, 125.4, 124.5, 124.4, 119.7, 119.2, 86.9, 83.8, 74.0, 69.8, 47.4, 47.0, 45.3, 41.3, 39.4, 36.7, 34.3, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{28}H_{24}N_2O_2$ $[M+H]^+$ 453.1809, found 453.1807; **FT-IR (KBr)** 2921, 2855, 2203, 1717, 1595, 1573, 1518, 1491, 1345, 1280, 1157, 1109 1074 cm^{-1}; The ee (99% ee_{major}, 94% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (92:8 up to 112 min then 80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 73.64 min, t_{minor} = 100.87 min; major diastereoisomer t_{major} = 94.44 min, t_{minor} = 119.50 min.

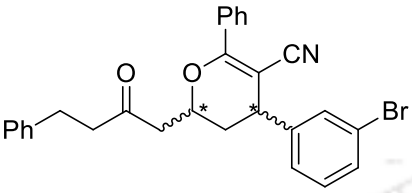
5,6-Dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4-*m*-tolyl-4*H*-pyran-3-carbonitrile (3j/3j'):



Colourless oil (42 mg, 98% yield), 4.5:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 8.1, 1.6 Hz, 0.33H), 7.75 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.50 – 7.40 (m, 4H), 7.29 (dd, *J* = 11.3, 4.5 Hz, 4H), 7.24 – 7.17 (m, 4H), 7.16 – 7.09 (m, 4H), 4.79 – 4.70 (m, 1H), 4.60 (dd, *J* = 10.8, 6.9 Hz, 0.23H), 3.90 – 3.85 (m, 0.24H), 3.81 (dd, *J* = 11.4, 6.6 Hz, 1H), 3.02 – 2.86 (m, 4H), 2.85 – 2.76 (m, 3H), 2.64 (dd, *J* = 16.9, 5.3 Hz, 1H), 2.53 (dd, *J* = 16.6, 4.0 Hz, 0.32H), 2.39 (s, 3H), 2.37 (s, 1H), 2.32 – 2.25 (m, 1H), 2.12 – 2.04 (m, 0.25H), 1.99 (dt, *J* = 13.8, 2.5 Hz, 0.25H), 1.78 (dd, *J* = 25.3, 11.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.3, 166.0, 141.2, 140.7, 138.7, 133.0, 131.1, 129.2, 129.0, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 126.4, 124.7, 119.6, 88.8, 74.2, 47.6, 45.4, 41.4, 37.3, 29.6; **ESI-MS** m/z calcd. for $C_{29}H_{27}NO_2$ $[M+H]^+$ 422.2115, found 422.2116; **FT-IR (KBr)** 2927, 2846, 2201, 1717, 1608, 1577, 1446, 1489, 1325, 1278, 1171, 1148, 1083 cm^{-1}; The ee (98% ee_{major}, 97% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer

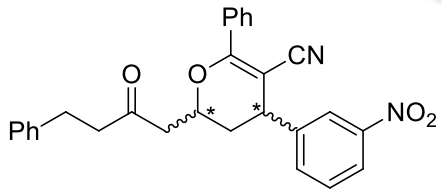
t_{major} = 19.58 min, t_{minor} = 21.96 min; major diastereoisomer t_{major} = 47.17 min, t_{minor} = 122.67 min.

4-(3-Bromophenyl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3k/3k'):



Colourless oil (39 mg, 80% yield), 1.8:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.51 – 7.40 (m, 7H), 7.31 – 7.27 (m, 3H), 7.24 (d, *J* = 3.5 Hz, 1H), 7.22 – 7.14 (m, 4H), 4.77 – 4.68 (m, 1H), 4.59 – 4.51 (m, 0.60H), 3.86 (d, *J* = 6.1 Hz, 0.55H), 3.83 (dd, *J* = 11.5, 6.6 Hz, 0.91H), 3.03 – 2.88 (m, 5H), 2.86 – 2.77 (m, 3H), 2.66 (dd, *J* = 17.0, 5.4 Hz, 1H), 2.56 (dd, *J* = 16.8, 4.4 Hz, 0.57H), 2.29 (dd, *J* = 13.0, 7.4 Hz, 1H), 2.11 (dd, *J* = 10.0, 7.0 Hz, 0.45H), 2.02 – 1.96 (m, 0.50H), 1.74 (dd, *J* = 25.3, 11.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.2, 206.0, 166.6, 166.4, 144.5, 143.7, 140.7, 140.6, 132.8, 132.8, 131.3, 131.2, 131.1, 131.0, 130.8, 130.8, 130.7, 130.6, 129.2, 128.7, 128.7, 128.6, 128.6, 128.4, 128.4, 128.4, 126.8, 126.5, 126.4, 126.4, 125.4, 123.2, 123.1, 119.9, 119.3, 87.8, 84.4, 74.1, 69.8, 47.5, 47.2, 45.4, 41.1, 39.2, 37.1, 34.6, 29.6, 29.6; **ESI-MS** m/z calcd. for $C_{28}H_{24}BrNO_2$ $[M+H]^+$ 486.1063, found 486.1064; **FT-IR (KBr)** 2921, 2853, 2199, 1717, 1616, 1571, 1495, 1475, 1362, 1280, 1159, 1074 cm^{-1}; The ee (94% ee_{major}, 93% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (70:30 up to 96 min then 60:40) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 29.44 min, t_{minor} = 35.31 min; major diastereoisomer t_{major} = 62.36 min, t_{minor} = 157.22 min.

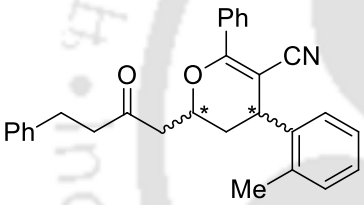
5,6-Dihydro-4-(3-nitrophenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile(3l/3l'):



Colourless oil (31 mg, 67% yield), 1.4:1 dr; R_f value 0.25 (15:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.21 – 8.16 (m, 3H), 7.78 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.75 – 7.71 (m, 2H), 7.67 (t, *J* = 7.0 Hz, 2H), 7.59 (td, *J* = 8.1, 3.5 Hz, 2H), 7.54 – 7.39 (m, 5H), 7.30 – 7.27 (m, 1H), 7.26 – 7.23 (m, 2H), 7.22 – 7.12 (m, 6H), 4.77 (dt, *J* = 12.2, 6.2 Hz, 1H), 4.53 (dd, *J* = 11.8, 3.8 Hz, 0.74H), 4.00 (dd, *J* = 11.6, 6.4 Hz, 2H), 3.06 – 2.87 (m, 5H), 2.86 – 2.76 (m, 3H), 2.68 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.58 (dd, *J* = 17.0, 4.9 Hz, 0.76H), 2.33 (d, *J* = 7.5 Hz,

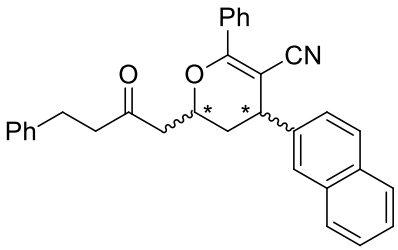
0.65H), 2.19 – 2.11 (m, 1H), 2.08 – 2.05 (m, 0.52H), 1.77 (dd, *J* = 25.2, 11.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.1, 205.9, 167.1, 166.9, 148.9, 144.3, 143.5, 140.6, 138.0, 134.2, 134.1, 132.6, 132.5, 131.5, 131.5, 130.3, 130.2, 129.2, 128.7, 128.7, 128.7, 128.6, 128.4, 128.4, 128.4, 123.1, 123.0, 122.8, 122.7, 119.7, 119.2, 87.1, 83.8, 74.0, 69.8, 47.4, 47.0, 45.4, 41.2, 39.2, 36.8, 34.5, 29.7, 29.6; **ESI-MS** m/z calcd. for $C_{28}H_{24}N_2O_2$ $[M+H]^+$ 453.1809, found 453.1808; **FT-IR (KBr)** 2921, 2853, 2205, 1741, 1614, 1520, 1448, 1343, 1159, 1083, 1029 cm^{-1}; The ee (93% ee_{major}, 96% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (90:10 up to 135 min then 80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 58.66 min, t_{minor} = 68.72 min; major diastereoisomer t_{major} = 96.81 min, t_{minor} = 123.35 min.

5,6-Dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4-*o*-tolyl-4*H*-pyran-3-carbonitrile (3m/3m'):



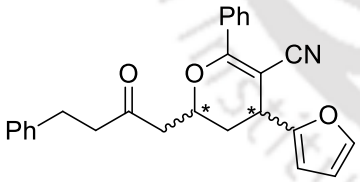
Colourless oil (42 mg, 98% yield), 1.2:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 6.9 Hz, 2H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.52 – 7.40 (m, 6H), 7.28 (s, 5H), 7.24 (d, *J* = 16.3 Hz, 5H), 7.20 (d, *J* = 4.5 Hz, 6H), 7.15 (d, *J* = 6.9 Hz, 2H), 4.77 (bs, 1H), 4.59 (bs, 1H), 4.14 (bs, 1H), 4.09 (d, *J* = 4.8 Hz, 1H), 3.02 – 2.86 (m, 6H), 2.85 – 2.75 (m, 4H), 2.65 (d, *J* = 16.7 Hz, 1H), 2.51 (d, *J* = 16.2 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H), 2.30 (s, 1H), 2.24 (s, 1H), 2.10 – 2.05 (m, 1H), 1.85 (d, *J* = 13.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.3, 206.1, 166.1, 165.7, 140.7, 140.7, 139.8, 135.9, 135.5, 133.1, 133.0, 131.2, 131.1, 131.0, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 127.5, 127.5, 127.0, 126.5, 126.4, 126.3, 120.2, 119.6, 88.9, 85.4, 74.3, 69.7, 47.6, 47.3, 45.4, 36.4, 33.0, 29.6, 29.5, 19.5, 19.2; **ESI-MS** m/z calcd. for $C_{29}H_{27}NO_2$ $[M+H]^+$ 422.2115, found 422.2114; **FT-IR (KBr)** 2921, 2851, 2203, 1719, 1610, 1600, 1573, 1491, 1448, 1362, 1282, 1157, 1031 cm^{-1}; The ee (95% ee_{major}, 95% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (90:10 up to 65 min then 60:40) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 86.08 min, t_{minor} = 133.13 min; major diastereoisomer t_{major} = 51.65 min, t_{minor} = 47.84 min.

5,6-Dihydro-4-(naphthalen-2-yl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3n/3n'):



Colourless oil (40 mg, 88% yield), 1.6:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.93 (t, *J* = 8.6 Hz, 2H), 7.87 – 7.80 (m, 5H), 7.63 – 7.45 (m, 12H), 7.27 (bs, 1H), 7.25 (bs, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 4H), 7.12 (d, *J* = 6.8 Hz, 2H), 4.89 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.84 – 4.76 (m, 0.69H), 4.72 (d, *J* = 5.6 Hz, 1H), 4.54 (ddd, *J* = 11.1, 5.4, 2.1 Hz, 1H), 2.97 (dd, *J* = 12.8, 5.9 Hz, 3H), 2.91 – 2.79 (m, 2H), 2.77 – 2.72 (m, 1H), 2.46 – 2.39 (m, 1H), 2.36 – 2.31 (m, 1H), 2.29 –2.17 (m, 2H), 2.09 (s, 1H), 2.06 (s, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.4, 166.6, 140.7, 140.7, 137.1, 134.4, 133.1, 131.2, 131.1, 130.6, 129.5, 128.7, 128.6, 128.6, 128.4, 128.4, 126.7, 126.6, 126.4, 126.3, 126.0, 125.6, 122.4, 120.3, 84.8, 70.2, 47.2, 45.4, 36.1, 33.3, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{32}H_{27}NO_2$ $[M+H]^+$ 458.2115, found 458.2114; **FT-IR (KBr)** 2921, 2853, 2203, 1712, 1610, 1571, 1493, 1368, 1278, 1169, 1072 cm^{-1}; The ee (95% ee_{major}, 97% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (97.5:2.5) as the eluent; flow: 0.8 mL/min; 272 nm; minor diastereoisomer t_{major} = 128.18 min, t_{minor} = 121.54 min; major diastereoisomer t_{major} = 94.71 min, t_{minor} = 111.15 min.

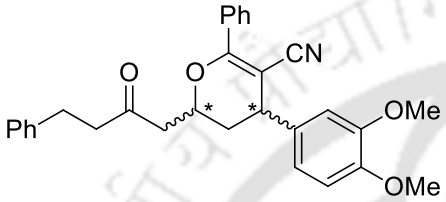
4-(Furan-2-yl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3o/3o'):



Colourless oil (39 mg, 98% yield), 1.6:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.72 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.71 – 7.66 (m, 1.30H), 7.48 – 7.39 (m, 6H), 7.30 – 7.26 (m, 2H), 7.25 (s, 1H), 7.21 (d, *J* = 1.6 Hz, 1H), 7.19 (dd, *J* = 5.4, 1.9 Hz, 2H), 7.16 (d, *J* = 6.8 Hz, 2.5H), 6.36 (ddd, *J* = 8.3, 3.2, 1.9 Hz, 1.54H), 6.30 (dd, *J* = 17.0, 3.6 Hz, 1.51H), 4.76 – 4.69 (m, 0.74H), 4.68 – 4.60 (m, 1H), 3.99 (dd, *J* = 11.2, 6.5 Hz, 0.74H), 3.91 (d, *J* = 5.0 Hz, 1H), 3.04 – 2.90 (m, 5.3H), 2.84 – 2.78 (m, 3.2H), 2.71 – 2.58 (m, 2H), 2.32 – 2.25 (m, 1H), 2.21 (d, *J* = 13.8 Hz, 1H), 2.03 (dt, *J* = 11.2, 2.7 Hz, 1H), 1.97 – 1.86 (m, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.3, 206.2, 166.1, 166.0, 154.2, 152.9, 142.5, 142.4, 140.7, 140.7, 132.9, 132.9, 131.2, 131.1, 129.2, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.3, 126.4, 126.4, 125.4, 120.0, 119.2, 110.7, 110.6, 108.1, 107.4, 86.2, 83.6, 73.8, 70.9, 47.4, 47.3, 45.4, 34.6, 33.7, 31.3, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{27}H_{23}NO_2$ $[M+H]^+$ 398.1751, found

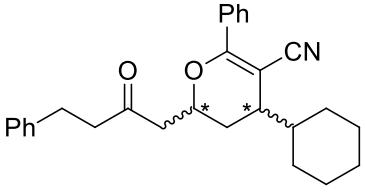
398.1752; **FT-IR (KBr)** 2921, 2853, 2201, 1717, 1612, 1577, 1450, 1489, 1325, 1278, 1154, 1148, 1083 cm^{-1}; The ee (97% ee_{major}, 99% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (93:7) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 27.27 min, t_{minor} = 26.03 min; major diastereoisomer t_{major} = 17.54 min, t_{minor} = 18.73 min.

5,6-Dihydro-4-(3,4-dimethoxyphenyl)-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3p/3p'):



Colourless oil (40 mg, 86% yield), 2.3:1 dr; R_f value 0.25 (15:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.1 Hz, 0.89H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.50 – 7.40 (m, 5H), 7.28 (d, *J* = 7.2 Hz, H), 7.25 (bs, 1H), 7.22 – 7.13 (m, 5H), 6.87 (bs, 2H), 6.78 (bs, 1H), 4.73 (bs, 1H), 4.60 (bs, 0.45H), 3.91 (bs, 4H), 3.88 (bs, 4H), 3.83 (bs, 0.50H), 3.82 – 3.77 (m, 1H), 2.95 (ddd, *J* = 32.9, 21.4, 7.0 Hz, 5H), 2.81 (dd, *J* = 16.5, 7.5 Hz, 3H), 2.64 (d, *J* = 17.3 Hz, 1H), 2.55 (d, *J* = 16.5 Hz, 0.58H), 2.37 – 2.30 (m, 1H), 2.19 (d, *J* = 13.9 Hz, 0.36H), 1.99 (d, *J* = 13.4 Hz, 0.50H), 1.77 (dd, *J* = 24.4, 12.1 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.4, 206.2, 165.9, 165.8, 149.4, 149.4, 148.5, 148.5, 140.7, 140.7, 134.7, 133.7, 133.1, 133.0, 131.1, 131.0, 130.5, 130.2, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 126.4, 126.3, 120.2, 119.8, 119.6, 111.7, 111.4, 111.2, 110.7, 88.9, 85.4, 74.2, 70.0, 56.1, 56.1, 56.0, 47.6, 47.3, 45.4, 41.1, 39.1, 37.3, 34.9, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{30}H_{29}NO_4$ $[M+H]^+$ 468.2169, found 468.2168; **FT-IR (KBr)** 2921, 2846, 2207, 1720, 1610, 1577, 1450, 1489, 1325, 1278, 1171, 1148, 1083 cm^{-1}; The ee (97% ee_{major}, 96% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (92:8) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 46.79 min, t_{minor} = 62.07 min; major diastereoisomer t_{major} = 59.41 min, t_{minor} = 70.92 min.

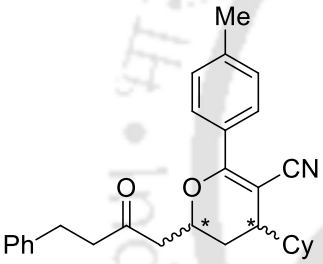
4-Cyclohexyl-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3q/3q'):



Colourless oil (35 mg, 85% yield), 7:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.66 – 7.64 (m, 1H), 7.63 (t, *J* = 2.0 Hz, 1H), 7.43 – 7.37 (m, 3H), 7.28 (d, *J* = 6.9 Hz, 1H), 7.26 (s, 1H), 7.19 (dd, *J* = 14.4, 7.0 Hz, 3H), 4.68 – 4.63 (m, 0.15H), 4.54 (dt, *J* = 12.7, 6.2 Hz, 1H), 2.94 (dt, *J* = 7.5, 6.1

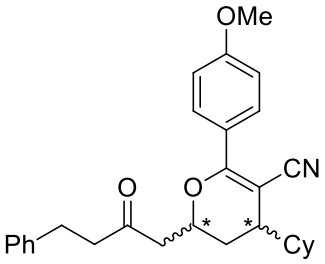
Hz, 3H), 2.81 (dd, *J* = 11.2, 4.6 Hz, 2H), 2.62 (dt, *J* = 10.2, 5.1 Hz, 2H), 2.02 – 1.92 (m, 1H), 1.90 – 1.85 (m, 1H), 1.83 – 1.58 (m, 7H), 1.53 – 1.43 (m, 1H), 1.36 (dd, *J* = 12.9, 2.3 Hz, 2H), 1.23 – 1.10 (m, 2H), 1.08 – 0.97 (m, 1H), 0.88 (t, *J* = 6.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.6, 166.4, 140.8, 133.3, 130.9, 128.7, 128.5, 128.4, 128.4, 128.3, 126.4, 119.7, 88.8, 74.2, 48.0, 45.5, 40.2, 38.9, 31.3, 29.6, 28.1, 26.9, 26.7, 26.5, 26.3; **ESI-MS** m/z calcd. for $C_{28}H_{31}NO_2$ $[M+H]^+$ 414.2428, found 414.2438; **FT-IR (KBr)** 2923, 2857, 2205, 1714, 1610, 1577, 1493, 1454, 1370, 1286, 1157, 1079 cm^{-1}; The ee 94% value was determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (85:15) as the eluent; flow: 1.0 mL/min; 272 nm; major diastereoisomer t_{major} = 19.45 min, t_{minor} = 23.17 min.

4-Cyclohexyl-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-2-p-tolyl-4*H*-pyran-3-carbonitrile (3r/3r'):



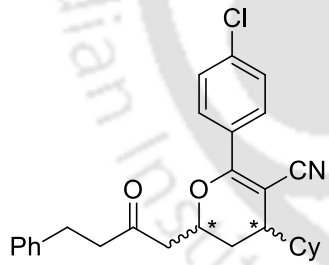
Colourless oil (35 mg, 82% yield), 3.6:1 dr ; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.23 – 7.15 (m, 6H), 4.64 (dd, *J* = 11.7, 9.1 Hz, 0.25H), 4.56 – 4.48 (m, 1H), 2.94 (dt, *J* = 13.6, 4.3 Hz, 4H), 2.82 (d, *J* = 7.3 Hz, 2H), 2.62 (dd, *J* = 16.8, 5.2 Hz, 2H), 2.37 (bs, 3H), 1.96 (td, *J* = 14.8, 5.5 Hz, 1H), 1.87 (dd, *J* = 12.7, 7.3 Hz, 1H), 1.79 (d, *J* = 10.7 Hz, 3H), 1.71 (t, *J* = 12.2 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.38 – 1.22 (m, 5H), 1.16 (ddd, *J* = 13.0, 11.2, 3.5 Hz, 2H), 1.08 – 0.95 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.7, 166.5, 141.2, 140.8, 130.5, 129.1, 128.7, 128.5, 128.3, 128.2, 126.4, 119.9, 88.1, 74.1, 48.0, 45.4, 40.2, 38.9, 31.3, 29.6, 28.2, 26.9, 26.7, 26.5, 26.3, 21.6; **ESI-MS** m/z calcd. for $C_{29}H_{33}NO_2$ $[M+H]^+$ 428.2584, found 428.2584; **FT-IR (KBr)** 2925, 2857, 2201, 1714, 1610, 1577, 1493, 1454, 1370, 1286, 1157, 1079 cm^{-1}; The ee (92% ee_{major}, 86% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (96:4) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 41.12 min, t_{minor} = 30.48 min; major diastereoisomer t_{major} = 56.66 min, t_{minor} = 46.45 min.

4-Cyclohexyl-5,6-dihydro-2-(4-methoxyphenyl)-6-(2-oxo-4-phenylbutyl)-4*H*-pyran-3-carbonitrile (3s/3s'):



Colourless oil (27 mg, 60% yield), 4.9:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, cdcl$_3$)** δ 7.60 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.19 (dd, *J* = 13.3, 7.2 Hz, 3H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.63 (dd, *J* = 10.1, 5.1 Hz, 0.23H), 4.55 – 4.42 (m, 1H), 3.83 (bs, 3H), 2.93 (dd, *J* = 16.1, 8.1 Hz, 3H), 2.84 – 2.78 (m, 2H), 2.65 – 2.55 (m, 2H), 1.92 (ddd, *J* = 18.3, 14.9, 4.5 Hz, 2H), 1.82 – 1.51 (m, 8H), 1.52 – 1.28 (m, 4H), 1.21 – 1.04 (m, 3H), 1.00 (d, *J* = 12.5 Hz, 1H), 0.90 – 0.77 (m, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 206.6, 166.1, 161.6, 140.8, 130.0, 128.7, 128.5, 126.4, 125.7, 120.2, 113.8, 87.2, 74.0, 71.5, 55.5, 48.0, 45.4, 40.3, 39.0, 31.3, 29.7, 28.2, 26.9, 26.8, 26.6, 26.3; **ESI-MS** m/z calcd. for $C_{29}H_{33}NO_3$ $[M+H]^+$ 444.2533, found 444.2532; **FT-IR (KBr)** 2927, 2853, 2201, 1714, 1610, 1511, 1452, 1306, 1253, 1177, 1113, 1029 cm^{-1}; The ee (94% ee_{major}, 99% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (65:35) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 26.74 min, t_{minor} = 37.29 min; major diastereoisomer t_{major} = 20.94 min, t_{minor} = 17.64 min.

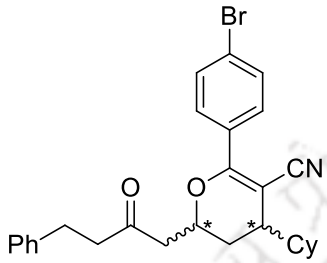
2-(4-Chlorophenyl)-4-cyclohexyl-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-4*H*-pyran-3-carbonitrile (3t/3t'):



Colourless oil (27 mg, 60% yield), 3:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.58 (dd, *J* = 8.4, 3.4 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.19 (dd, *J* = 16.4, 7.1 Hz, 4H), 4.68 – 4.60 (m, 0.35H), 4.58 – 4.49 (m, 1H), 2.93 (dd, *J* = 15.8, 8.6 Hz, 4H), 2.81 (t, *J* = 7.4 Hz, 3H), 2.67 – 2.56 (m, 2H), 1.96 (dd, *J* = 22.2, 11.3 Hz, 1H), 1.87 (dd, *J* = 13.4, 6.7 Hz, 1H), 1.82 – 1.67 (m, 5H), 1.60 – 1.54 (m, 1H), 1.47 (dd, *J* = 23.4, 10.4 Hz, 2H), 1.39 – 1.22 (m, 5H), 1.16 (dd, *J* = 27.5, 12.5 Hz, 2H), 1.02 (dd, *J* = 12.4, 3.2 Hz, 1H), 0.88 (t, *J* = 6.7 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.5, 206.4, 165.1, 163.9, 140.7, 140.7, 136.9, 136.6, 132.0, 131.7, 129.7, 129.6, 128.7, 128.7, 128.4, 128.4, 126.4, 120.6, 119.4, 89.2, 87.5, 74.2, 71.6, 47.9, 47.4, 45.4, 45.4, 41.8, 40.2, 38.9, 37.9, 31.3, 31.2, 29.6, 29.4, 28.0, 27.7, 27.0, 26.9, 26.7, 26.6, 26.5, 26.5, 26.3; **ESI-MS** m/z calcd. for $C_{28}H_{30}ClNO_2$ $[M+H]^+$ 448.2038, found 448.2039; **FT-IR (KBr)** 2921, 2849, 2203, 1717, 1614, 1495, 1452, 1401, 1290, 1161, 1095 cm^{-1}; The ee (96% ee_{major}, 96% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (97:3 up

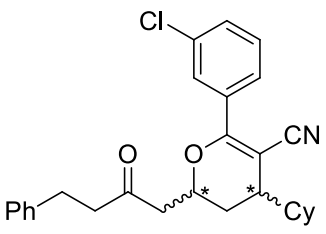
to 120 min then 75:25) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 21.33 min, t_{minor} = 26.47 min; major diastereoisomer t_{major} = 54.37 min, t_{minor} = 77.42 min.

2-(4-Bromophenyl)-4-cyclohexyl-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-4*H*-pyran-3-carbonitrile (3u/3u'):



Colourless oil (45 mg, 91% yield), 2.5:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.52 (d, *J* = 0.8 Hz, 1H), 7.51 (d, *J* = 0.8 Hz, 3H), 7.29 (d, *J* = 6.9 Hz, 2H), 7.21 (d, *J* = 7.1 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 3H), 4.67 – 4.60 (m, 0.41H), 4.57 – 4.49 (m, 1H), 2.93 (t, *J* = 7.9 Hz, 3H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.65 (d, *J* = 5.1 Hz, 1H), 2.63 – 2.59 (m, 1H), 2.01 – 1.91 (m, 1H), 1.87 (dd, *J* = 12.9, 6.0 Hz, 1H), 1.80 (d, *J* = 12.7 Hz, 3H), 1.76 – 1.66 (m, 3H), 1.60 – 1.54 (m, 1H), 1.52 – 1.44 (m, 1H), 1.42 (d, *J* = 3.6 Hz, 1H), 1.39 – 1.33 (m, 2H), 1.32 – 1.28 (m, 2H), 1.22 – 1.06 (m, 3H), 1.02 (dd, *J* = 12.5, 3.4 Hz, 1H), 0.88 (t, *J* = 6.1 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 206.5, 206.4, 165.2, 163.9, 140.7, 140.7, 132.4, 132.2, 131.7, 131.7, 129.9, 129.8, 129.2, 128.7, 128.4, 128.4, 128.4, 126.4, 125.3, 125.0, 120.6, 119.4, 89.2, 87.6, 74.2, 71.6, 47.9, 47.4, 45.4, 45.3, 41.8, 40.2, 38.9, 37.9, 31.3, 31.2, 29.6, 29.4, 28.0, 27.7, 27.0, 26.9, 26.7, 26.6, 26.5, 26.4, 26.3; **FT-IR (KBr)** 2923, 2855, 2203, 1719, 1606, 1587, 1491, 1392, 1288, 1165, 1068 cm^{-1}; **ESI-MS** m/z calcd. for $C_{28}H_{30}BrNO_2$ $[M+H]^+$ 492.1533, found 492.1523; The ee (95% ee_{major}, 95% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (90:10) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 41.13 min, t_{minor} = 76.00 min; major diastereoisomer t_{major} = 29.51 min, t_{minor} = 37.62 min.

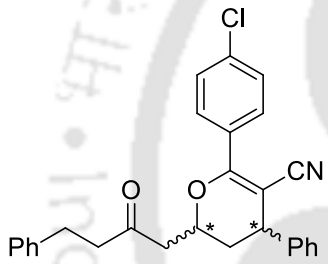
2-(3-Chlorophenyl)-4-cyclohexyl-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-4*H*-pyran-3-carbonitrile (3v/3v'):



Colourless oil (31 mg, 68% yield), 2.9:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.58 (d, *J* = 7.0 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 4.4 Hz, 1H), 7.28 (s, 29H), 7.19 (dd, *J* = 12.5, 7.0 Hz, 3H), 4.67 – 4.60 (m, 0.33H), 4.56 – 4.49 (m, 1H), 2.98 – 2.90 (m, 4H), 2.83 – 2.78 (m, 2H), 2.68 – 2.58 (m, 2H), 2.04 – 1.94 (m, 1H), 1.90 (dd, *J* = 13.0, 6.2 Hz, 1H), 1.80 (d, *J* = 12.4 Hz, 3H), 1.76 – 1.67 (m, 2H), 1.59 (bs, 1H), 1.53 –

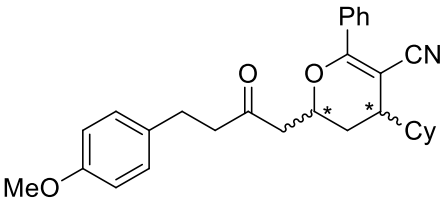
1.44 (m, 1H), 1.42 (d, *J* = 5.4 Hz, 1H), 1.36 (d, *J* = 16.2 Hz, 2H), 1.32 – 1.28 (m, 2H), 1.21-0.96 (m, 5H), 0.88 (t, *J* = 6.7 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 206.4, 164.7, 140.7, 135.0, 134.2, 130.9, 129.7, 128.7, 128.5, 128.4, 128.3, 128.2, 126.7, 126.6, 126.4, 119.1, 89.8, 74.4, 48.0, 45.5, 40.2, 38.9, 31.30, 29.7, 28.0, 26.9, 26.7, 26.5, 26.3; **ESI-MS** m/z calcd. for $C_{28}H_{30}ClNO_2$ $[M+H]^+$ 448.2038, found 448.2037; **FT-IR (KBr)** 2927, 2853, 2201, 1712, 1614, 1563, 11452, 1299, 1284, 1299, 1261, 1167, 1077 cm^{-1}; The ee (93% ee_{major}, 92% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (97:3) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 33.10 min, t_{minor} = 27.13 min; major diastereoisomer t_{major} = 37.12 min, t_{minor} = 43.96 min.

2-(4-Chlorophenyl)-5,6-dihydro-6-(2-oxo-4-phenylbutyl)-4-phenyl-4*H*-pyran-3-carbonitrile(3w/3w'):



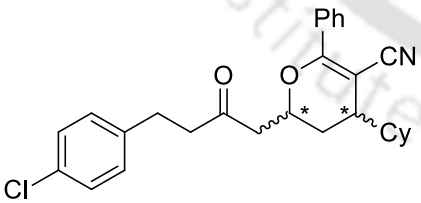
Colourless oil (36 mg, 80% yield), 1:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 10.9, 8.0 Hz, 6H), 7.30 (dd, *J* = 13.8, 6.6 Hz, 6H), 7.22 (dd, *J* = 12.2, 5.8 Hz, 2H), 7.16 (dd, *J* = 13.3, 7.5 Hz, 4H), 4.79 – 4.69 (m, 1H), 4.61 – 4.52 (m, 0.92H), 3.90 – 3.87 (m, 0.76H), 3.83 (dd, *J* = 11.4, 6.6 Hz, 1H), 2.94 (ddd, *J* = 21.6, 13.8, 7.1 Hz, 5H), 2.80 (dt, *J* = 14.9, 8.8 Hz, 4H), 2.64 (dd, *J* = 17.1, 5.1 Hz, 1H), 2.52 (dd, *J* = 16.8, 3.8 Hz, 1H), 2.29 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.10 (d, *J* = 13.7 Hz, 0.56H), 2.05 (t, *J* = 5.4 Hz, 0.78H), 1.98 (d, *J* = 13.7 Hz, 1H), 1.77 (dd, *J* = 25.2, 11.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.2, 206.0, 164.9, 164.8, 141.9, 141.0, 140.7, 140.6, 137.1, 137.1, 131.4, 131.4, 129.8, 129.7, 129.2, 129.1, 128.8, 128.8, 128.7, 128.7, 128.4, 128.4, 128.0, 127.9, 127.7, 127.6, 126.4, 126.4, 119.9, 119.3, 89.1, 85.5, 74.2, 69.9, 47.5, 47.2, 45.3, 41.4, 39.4, 37.1, 34.8, 29.6, 29.5; **ESI-MS** m/z calcd. for $C_{28}H_{24}ClNO_2$ $[M+H]^+$ 442.1568, found 442.1567; **FT-IR (KBr)** 2925, 2853, 2199, 1712, 1608, 1493, 1456, 1362, 1290, 1150, 1089 cm^{-1}; The ee (94% ee_{major}, 97% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (85:15 up to 52 min then 75:25) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 38.18 min, t_{minor} = 46.15 min; major diastereoisomer t_{major} = 76.37 min, t_{minor} = 136.59 min.

4-Cyclohexyl-5,6-dihydro-6-(4-(4-methoxyphenyl)-2-oxobutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3x/3x'):



Colourless oil (40 mg, 90% yield), 5.9:1 dr; R_f value 0.25 (12:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.64 (d, *J* = 6.6 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.68 – 4.61 (m, 0.16H), 4.57 – 4.48 (m, 1H), 3.77 (bs, 3H), 2.97 – 2.90 (m, 1H), 2.90 – 2.86 (m, 2H), 2.77 (dd, *J* = 10.9, 4.4 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.02 – 1.90 (m, 1H), 1.87 (dd, *J* = 14.2, 7.3 Hz, 1H), 1.80 (d, *J* = 12.6 Hz, 3H), 1.75 – 1.66 (m, 3H), 1.61 (d, *J* = 12.0 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.42 (d, *J* = 3.0 Hz, 1H), 1.36 (d, *J* = 15.3 Hz, 2H), 1.30 (d, *J* = 10.1 Hz, 1H), 1.25 – 1.09 (m, 3H), 1.07-0.98 (m, 2H), 0.88 (t, *J* = 6.6 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 206.7, 166.3, 158.2, 133.3, 132.7, 130.9, 130.6, 129.4, 128.4, 128.3, 119.7, 114.1, 88.7, 77.0, 74.2, 55.4, 48.0, 45.7, 40.2, 38.9, 31.3, 28.8, 28.1, 26.9, 26.7, 26.5, 26.3; **ESI-MS** m/z calcd. for $C_{29}H_{33}NO_3$ $[M+H]^+$ 444.2533, found 444.2534; **FT-IR (KBr)** 2923, 2855, 2207, 1712, 1608, 1511, 1445, 1356, 1251, 1161, 1031 cm^{-1}; The ee (99% ee_{major}, 85% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (95:5) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 58.05 min, t_{minor} = 47.89 min; major diastereoisomer t_{major} = 65.95 min, t_{minor} = 69.77 min.

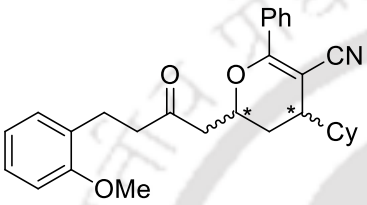
6-(4-(4-Chlorophenyl)-2-oxobutyl)-4-cyclohexyl-5,6-dihydro-2-phenyl-4*H*-pyran-3-carbonitrile (3y/3y'):



Colourless oil (18 mg, 40% yield), 2.2:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.64 (d, *J* = 7.0 Hz, 2H), 7.40 (dt, *J* = 14.2, 7.2 Hz, 4H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 14.2, 7.0 Hz, 4H), 4.65 (dd, *J* = 14.6, 8.7 Hz, 0.47H), 4.58 – 4.50 (m, 1H), 2.95 (dd, *J* = 12.6, 6.8 Hz, 4H), 2.82 (t, *J* = 7.5 Hz, 3H), 2.66 – 2.58 (m, 2H), 2.06 – 1.92 (m, 2H), 1.88 (d, *J* = 19.9 Hz, 1H), 1.80 (d, *J* = 10.3 Hz, 3H), 1.72 (t, *J* = 12.9 Hz, 3H), 1.63 (s, 1H), 1.53 – 1.43 (m, 1H), 1.43 – 1.31 (m, 3H), 1.26 (bs, 2H), 1.16 (dd, *J* = 27.5, 14.5 Hz, 2H), 1.09 – 0.97 (m, 2H), 0.88 (t, *J* = 5.7 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 206.7, 206.6, 166.4, 165.1, 140.8, 140.7, 133.6, 133.3, 130.9, 130.7, 128.7, 128.5, 128.4, 128.4, 128.3, 126.4, 120.9, 119.7, 88.8, 87.1, 74.2, 71.6, 48.0, 47.5, 45.5, 41.9, 40.2, 38.9, 37.9, 31.3,

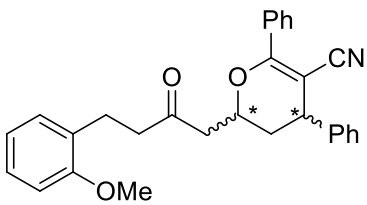
31.3, 29.7, 29.5, 28.1, 27.8, 26.9, 26.7, 26.7, 26.6, 26.5, 26.5, 26.3; **ESI-MS** m/z calcd. for $C_{28}H_{30}ClNO_2$ $[M+H]^+$ 448.2038, found 444.2039; **FT-IR (KBr)** 2929, 2857, 2205, 1721, 1614, 1573, 1495, 1452, 1384, 1284, 1159, 1079 cm^{-1}; The ee (96% ee_{major}, 96% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (98:2) as the eluent; flow: 0.8 mL/min; 272 nm; minor diastereoisomer t_{major} = 129.09 min, t_{minor} = 137.71 min; major diastereoisomer t_{major} = 103.54 min, t_{minor} = 137.71 min.

4-Cyclohexyl-5,6-dihydro-6-(4-(2-methoxyphenyl)-2-oxobutyl)-2-phenyl-4*H*-pyran-3-carbonitrile (3z/3z'):



Colourless oil (29 mg, 65% yield), 4.4:1 dr; R_f value 0.25 (12:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.66 (d, *J* = 7.3 Hz, 3H), 7.41 (dd, *J* = 15.5, 6.9 Hz, 4H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.86 (dd, *J* = 20.3, 7.6 Hz, 3H), 4.67 (bs, 0.23H), 4.55 (bs, 1H), 3.79 (bs, 4H), 2.92 (t, *J* = 7.8 Hz, 3H), 2.79 (d, *J* = 7.1 Hz, 2H), 2.63 (d, *J* = 5.9 Hz, 2H), 2.08 – 1.85 (m, 3H), 1.81 (d, *J* = 12.4 Hz, 3H), 1.72 (t, *J* = 14.5 Hz, 3H), 1.62 (d, *J* = 13.2 Hz, 2H), 1.53 – 1.46 (m, 1H), 1.37 (d, *J* = 12.9 Hz, 3H), 1.22 (d, *J* = 12.3 Hz, 1H), 1.16 (dd, *J* = 24.8, 12.3 Hz, 2H), 1.03 (dd, *J* = 26.1, 13.8 Hz, 2H), 0.90 (d, *J* = 5.8 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 207.2, 166.4, 157.5, 133.4, 130.8, 130.2, 129.0, 128.4, 128.4, 128.3, 127.7, 120.6, 110.4, 88.7, 74.3, 55.3, 47.9, 43.8, 40.2, 38.9, 31.3, 28.2, 26.9, 26.7, 26.8, 26.3, 25.0; **ESI-MS** m/z calcd. for $C_{29}H_{33}NO_3$ $[M+H]^+$ 444.2533, found 444.2532; **FT-IR (KBr)** 2927, 2855, 2207, 1712, 1608, 1511, 1448, 1356, 1251, 1165, 1031 cm^{-1}; The ee (99% ee_{major}, 72% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (96:3.5) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 58.05 min, t_{minor} = 47.89 min; major diastereoisomer t_{major} = 65.95 min, t_{minor} = 69.77 min.

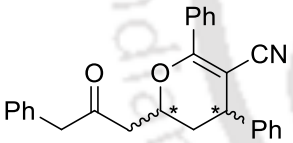
5,6-Dihydro-6-(4-(2-methoxyphenyl)-2-oxobutyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3aa/3aa'):



Colourless oil (24 mg, 55% yield), 2:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.36 (m, 9H), 7.32 (t, *J* = 8.0 Hz, 5H), 7.21 (dd, *J* = 15.0, 6.7 Hz, 2H), 7.14 – 7.10 (m, 1H), 6.89 – 6.79 (m, 3H), 4.75 (dt, *J* = 17.0, 6.4 Hz, 1H), 4.60

(dd, *J* = 7.4, 3.3 Hz, 0.50H), 3.97 – 3.89 (m, 1H), 3.85 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.78 (t, *J* = 3.1 Hz, 3H), 3.75 (d, *J* = 1.1 Hz, 1H), 3.03 – 2.85 (m, 4H), 2.81 – 2.72 (m, 3H), 2.70 – 2.66 (m, 1H), 2.64 (d, *J* = 5.5 Hz, 1H), 2.54 (dd, *J* = 16.7, 4.1 Hz, 0.58H), 2.38 – 2.31 (m, 1H), 2.29 (t, *J* = 6.9 Hz, 0.69H), 2.00 (d, *J* = 13.7 Hz, 0.58H), 1.77 (dd, *J* = 25.2, 11.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.0, 206.8, 166.3, 166.1, 157.5, 142.2, 141.4, 133.1, 133.0, 131.1, 131.0, 131.0, 130.8, 130.2, 130.1, 129.1, 129.1, 128.9, 128.8, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 127.8, 127.7, 127.7, 127.7, 127.5, 120.6, 119.6, 110.6, 110.3, 93.8, 88.6, 74.2, 70.0, 55.3, 55.3, 47.4, 47.1, 43.8, 41.4, 37.3, 34.9, 32.1, 29.8, 25.0, 24.9; **ESI-MS** m/z calcd. for $C_{29}H_{27}NO_3$ $[M+H]^+$ 438.2064, found 438.2065; **FT-IR (KBr)** 2921, 2854, 2205, 1711, 1610, 1511, 1450, 1356, 1251, 1161, 1031 cm^{-1}; The ee (97% ee_{major}, 86% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 25.69 min, t_{minor} = 22.34 min; major diastereoisomer t_{major} = 32.40 min, t_{minor} = 37.25 min.

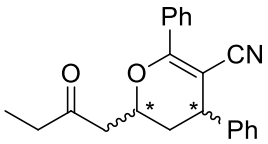
5,6-Dihydro-6-(2-oxo-3-phenylpropyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3ab/3ab'):



Colourless oil (37 mg, 93% yield), 1.1:1 dr; R_f value 0.25 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.1 Hz, 2H), 7.74 (d, *J* = 7.2 Hz, 2H), 7.45 (ddd, *J* = 23.7, 13.4, 7.1 Hz, 6H), 7.38 (dd, *J* = 7.1, 4.3 Hz, 4H), 7.33 (dd, *J* = 14.0, 6.6 Hz, 4H), 7.32 – 7.27 (m, 9H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.16 (d, *J* = 7.1 Hz, 2H), 4.74 (dt, *J* = 11.5, 5.8 Hz, 1H), 4.60 – 4.55 (m, 0.87H), 3.87 (dd, *J* = 5.9, 2.0 Hz, 0.82H), 3.84 (dd, *J* = 11.4, 6.7 Hz, 1H), 3.76 (bs, 2H), 3.72 (bs, 2H), 3.03 (dd, *J* = 17.3, 7.3 Hz, 1H), 2.97 (dd, *J* = 16.9, 8.2 Hz, 1H), 2.70 (dd, *J* = 17.3, 5.4 Hz, 1H), 2.58 (dd, *J* = 16.9, 4.3 Hz, 1H), 2.31 (d, *J* = 4.2 Hz, 1H), 2.28 (d, *J* = 6.4 Hz, 1H), 1.97 (d, *J* = 13.8 Hz, 1H), 1.75 (dd, *J* = 25.2, 11.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 204.7, 204.5, 166.1, 165.9, 142.1, 141.3, 133.5, 133.4, 133.1, 133.0, 131.1, 131.0, 129.5, 129.1, 129.0, 129.0, 128.5, 128.5, 128.4, 128.3, 128.1, 127.7, 127.7, 127.5, 127.5, 127.4, 120.1, 119.5, 88.6, 85.1, 74.1, 69.9, 51.1, 51.0, 46.4, 46.1, 41.4, 39.4, 37.1, 34.7; **ESI-MS** m/z calcd. for $C_{27}H_{23}NO_2$ $[M+H]^+$ 394.1802, found 394.1802; ; **FT-IR (KBr)** 2922, 2855, 2205, 1712, 1619, 1573, 1495, 1348, 1282, 1159, 1115 cm^{-1}; The ee (94% ee_{major}, 90% ee_{minor}) values were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272

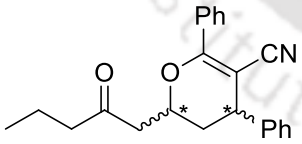
nm; minor diastereoisomer t_{major} = 18.07 min, t_{minor} = 20.68 min; major diastereoisomer t_{major} = 42.95 min, t_{minor} = 52.06 min.

5,6-Dihydro-6-(2-oxobutyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3ac/3ac'):



Colourless oil (15 mg, 45% yield), 1.9:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.92 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 10.5 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.67 (t, *J* = 6.5 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 3H), 7.38 (d, *J* = 7.0 Hz, 2H), 7.32 (bs, 3H), 4.82 – 4.72 (m, 1H), 4.63 – 4.54 (m, 0.55H), 3.92 – 3.89 (m, 0.45H), 3.87 (dd, *J* = 11.5, 6.7 Hz, 1H), 3.01 (dd, *J* = 16.9, 7.4 Hz, 1H), 2.93 (dd, *J* = 16.7, 8.3 Hz, 1H), 2.68 (dd, *J* = 16.9, 5.4 Hz, 1H), 2.58 (d, *J* = 4.0 Hz, 0.31H), 2.54-2.45 (m, 3H), 2.35 (dd, *J* = 12.7, 6.2 Hz, 1H), 2.14 – 2.08 (m, 0.48H), 2.05 – 1.99 (m, 1H), 1.81 (dd, *J* = 25.3, 11.6 Hz, 1H), 1.13 – 1.03 (m, 4H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 207.8, 207.6, 166.3, 166.0, 142.2, 141.4, 133.2, 133.1, 131.1, 131.1, 129.3, 129.2, 128.6, 128.5, 128.5 128.4, 128.1, 127.8, 127.7, 127.6, 120.2, 119.6, 88.7, 85.2, , 74.3, 70.1, 47.0, 46.8, 41.5, 39.5, 37.4, 37.3, 32.1, 31.6, 7.8, 7.7; **ESI-MS** m/z calcd. for $C_{22}H_{21}NO_2$ $[M+H]^+$ 332.1645, found 332.1645; **FT-IR (KBr)** 2923, 2853, 2205, 1712, 1616, 1573, 1491, 1348, 1282, 1159, 1115 cm^{-1}; The ee (97% ee_{major}, 84% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (85:15) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 18.17 min, t_{minor} = 20.68 min; major diastereoisomer t_{major} = 42.95 min, t_{minor} = 52.06 min.

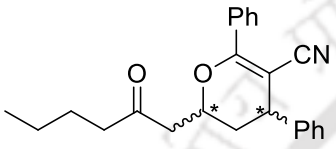
5,6-Dihydro-6-(2-oxopentyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile(3ad/3ad'):



Colourless oil (30 mg, 86% yield), 1.9:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.79 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 3H), 7.41 – 7.35 (m, 4H), 7.31 (d, *J* = 10.7 Hz, 4H), 4.81 – 4.73 (m, 1H), 4.63 – 4.55 (m, 0.54H), 3.90 (d, *J* = 5.9 Hz, 0.45H), 3.89 – 3.83 (m, 1H), 3.00 (dd, *J* = 16.5, 7.9 Hz, 1H), 2.92 (dd, *J* = 17.2, 8.9 Hz, 0.6H), 2.66 (dd, *J* = 17.0, 5.4 Hz, 1H), 2.53 (dd, *J* = 17.2, 4.7 Hz, 0.67H), 2.49 – 2.39 (m, 3H), 2.34 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.15 – 2.06 (m, 0.63H), 2.00 (dd, *J* = 9.6, 6.4 Hz, 0.65H), 1.80 (dd, *J* = 24.0, 11.6 Hz, 1H), 1.62 (tq, *J* = 15.6, 7.6 Hz, 5H), 1.42 (d, *J* = 5.0 Hz, 1H), 1.29 (d, *J* = 3.4 Hz, 2H), 0.91 (dt, *J* = 14.5, 7.4 Hz, 5H); **^{13}C NMR (151 MHz, CDCl$_3$)** δ 207.4, 207.2, 166.3, 166.0, 142.2, 141.4, 133.1, 133.1, 131.1, 131.0, 129.2, 129.1, 128.5, 128.5, 128.4, 128.1, 127.8, 127.7, 127.5, 124.2,

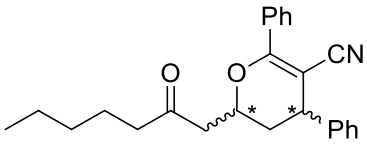
123.6, 120.2, 119.6, 88.7, 85.1, 74.3, 70.0, 47.3, 47.1, 45.9, 41.5, 39.5, 37.4, 35.0, 31.8, 17.2, 17.1, 13.8, 13.8; **ESI-MS** m/z calcd. for $C_{23}H_{23}NO_2$ $[M+H]^+$ 346.1802, found 346.1805; **FT-IR (KBr)** 2925, 2869, 2205, 1714, 1610, 1575, 1493, 1450, 1284, 1181, 1154,1079 cm^{-1}; The ee (95% ee_{major}, 87% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 10.27 min, t_{minor} = 8.73 min; major diastereoisomer t_{major} = 20.44 min, t_{minor} = 37.93 min.

5,6-Dihydro-6-(2-oxohexyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3ae/3ae'):



Colourless oil (26 mg, 72% yield), 1.5:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 6.7 Hz, 2H), 7.47 – 7.36 (m, 7H), 7.31 (dd, *J* = 8.8, 5.0 Hz, 5H), 4.76 (dt, *J* = 12.3, 6.2 Hz, 1H), 4.64 – 4.54 (m, 0.69H), 3.92 – 3.90 (m, 0.48H), 3.87 (dd, *J* = 11.6, 6.8 Hz, 1H), 3.00 (dd, *J* = 17.0, 7.4 Hz, 1H), 2.93 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.66 (dd, *J* = 17.0, 5.4 Hz, 1H), 2.54 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.48 (dd, *J* = 7.4, 2.9 Hz, 1H), 2.46 – 2.40 (m, 2H), 2.34 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.11 (ddd, *J* = 13.8, 10.9, 6.0 Hz, 1H), 2.02 (dt, *J* = 13.7, 2.3 Hz, 1H), 1.80 (dd, *J* = 25.2, 11.5 Hz, 1H), 1.63 – 1.50 (m, 4H), 1.35 – 1.24 (m, 7H), 0.89 (dt, *J* = 11.1, 7.3 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.6, 207.4, 166.3, 166.0, 142.2, 141.4, 133.1, 133.0, 131.1, 131.0, 129.2, 129.1, 128.6, 128.5, 128.5, 128.5, 128.4, 128.1, 127.8, 127.7, 127.5, 120.3, 119.6, 88.7, 85.1, 74.3, 70.0, 47.3, 47.0, 43.7, 43.7, 41.5, 39.5, 37.42, 34.9, 29.9, 29.8, 25.3, 25.7, 22.4, 22.4, 14.3, 14.0; **ESI-MS** m/z calcd. for $C_{24}H_{25}NO_2$ $[M+H]^+$ 360.1958, found 360.1958; **FT-IR (KBr)** 2929, 2873, 2205, 1712, 1608, 1575, 1493, 1362, 1278, 1159, 1077 cm^{-1}; The ee (95% ee_{major}, 92% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (95:5 up to 40 min then 80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 21.33 min, t_{minor} = 26.47 min; major diastereoisomer t_{major} = 54.37 min, t_{minor} = 77.42 min.

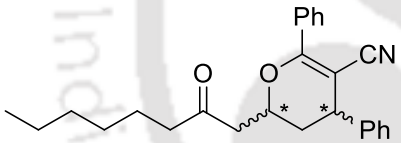
5,6-Dihydro-6-(2-oxoheptyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3af/3af'):



Colourless oil (35 mg, 94% yield), 1.3:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.41 (ddt, *J* = 13.1, 8.8, 5.1 Hz, 8H), 7.34 – 7.28 (m, 5H), 4.80 – 4.72 (m, 1H), 4.63 – 4.55 (m, 0.75H), 3.92 – 3.89 (m,

0.60H), 3.87 (dd, *J* = 11.5, 6.6 Hz, 1H), 3.00 (dd, *J* = 17.0, 7.4 Hz, 1H), 2.92 (dd, *J* = 16.6, 8.3 Hz, 1H), 2.66 (dd, *J* = 17.0, 5.4 Hz, 1H), 2.53 (dd, *J* = 16.6, 4.2 Hz, 1H), 2.49 – 2.41 (m, 3H), 2.34 (ddd, *J* = 13.8, 6.6, 1.7 Hz, 1H), 2.11 (ddd, *J* = 13.7, 10.8, 6.0 Hz, 1H), 2.01 (dt, *J* = 13.7, 2.5 Hz, 1H), 1.80 (dt, *J* = 13.8, 11.5 Hz, 1H), 1.65 – 1.51 (m, 4H), 1.34 – 1.20 (m, 8H), 0.87 (q, *J* = 7.1 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 207.5, 207.4, 166.3, 166.0, 142.2, 141.4, 133.1, 133.1, 131.1, 131.0, 129.2, 129.1, 128.5, 128.5, 128.5, 128.4, 128.1, 127.8, 127.7, 127.5, 120.2, 119.6, 88.7, 85.1, 74.3, 70.0, 47.3, 47.0, 44.0, 44.0, 41.5, 39.5, 37.4, 34.9, 31.4, 31.4, 29.8, 23.4, 23.3, 22.6, 14.3, 14.0; **ESI-MS** m/z calcd. for $C_{25}H_{27}NO_2$ $[M+H]^+$ 374.2115, found 374.2114; **FT-IR (KBr)** 2927, 2853, 2199, 1717, 1602,1511, 1495, 1450, 1378, 1290, 1157, 1111 cm^{-1}; The ee (94% ee_{major}, 91% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (93:7 up to 45 min then 75:25) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 17.06 min, t_{minor} = 20.78 min; major diastereoisomer t_{major} = 41.48 min, t_{minor} = 62.01 min.

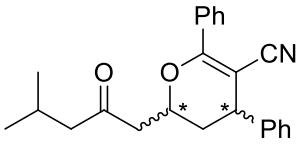
5,6-Dihydro-6-(2-oxooctyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3ag/3ag'):



Colourless oil (35 mg, 90% yield), 2.5:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.4 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 9.1 Hz, 2H), 7.41 – 7.35 (m, 4H), 7.31 (d, *J* = 6.9 Hz, 4H), 4.81 – 4.71 (m, 1H), 4.62 – 4.55 (m, 0.39H), 3.90 (d, *J* = 3.9 Hz, 0.30H), 3.87 (dd, *J* = 11.5, 6.7 Hz, 1H), 3.00 (dd, *J* = 16.9, 7.4 Hz, 1H), 2.92 (dd, *J* = 17.0, 8.3 Hz, 0.44H), 2.66 (dd, *J* = 17.0, 5.3 Hz, 1H), 2.53 (dd, *J* = 16.5, 3.8 Hz, 0.49H), 2.48 (d, *J* = 2.5 Hz, 0.47H), 2.46 (d, *J* = 2.8 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.34 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.16 – 2.07 (m, 0.47H), 2.01 (dt, *J* = 13.7, 2.3 Hz, 0.48H), 1.80 (dd, *J* = 25.2, 11.5 Hz, 1H), 1.57 (dd, *J* = 16.0, 8.0 Hz, 4H), 1.27 (bs, 8H), 0.91 – 0.82 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 207.5, 207.4, 166.2, 166.0, 142.2, 141.4, 133.1, 133.0, 131.1, 131.0, 129.2, 129.1, 128.5, 128.5, 128.4, 128.1, 127.7, 127.7, 127.5, 120.2, 119.6, 88.6, 85.1, 74.3, 70.0, 47.3, 47.0, 44.0, 41.5, 39.5, 37.4, 34.9, 31.7, 28.9, 23.7, 22.6, 14.2; **ESI-MS** m/z calcd. for $C_{26}H_{29}NO_2$ $[M+H]^+$ 388.2271, found 388.2277; **FT-IR (KBr)** 2925, 2853, 2209, 1717, 1612, 1577, 1493, 1452, 1254, 1161, 1029 cm^{-1}; The ee (97% ee_{major}, 94% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (65:35) as the eluent; flow: 1.0

mL/min; 272 nm; minor diastereoisomer t_{major} = 5.75 min, t_{minor} = 6.64 min; major diastereoisomer t_{major} = 11.95 min, t_{minor} = 26.11 min.

5,6-Dihydro-6-(4-methyl-2-oxopentyl)-2,4-diphenyl-4*H*-pyran-3-carbonitrile (3ah/3ah'):



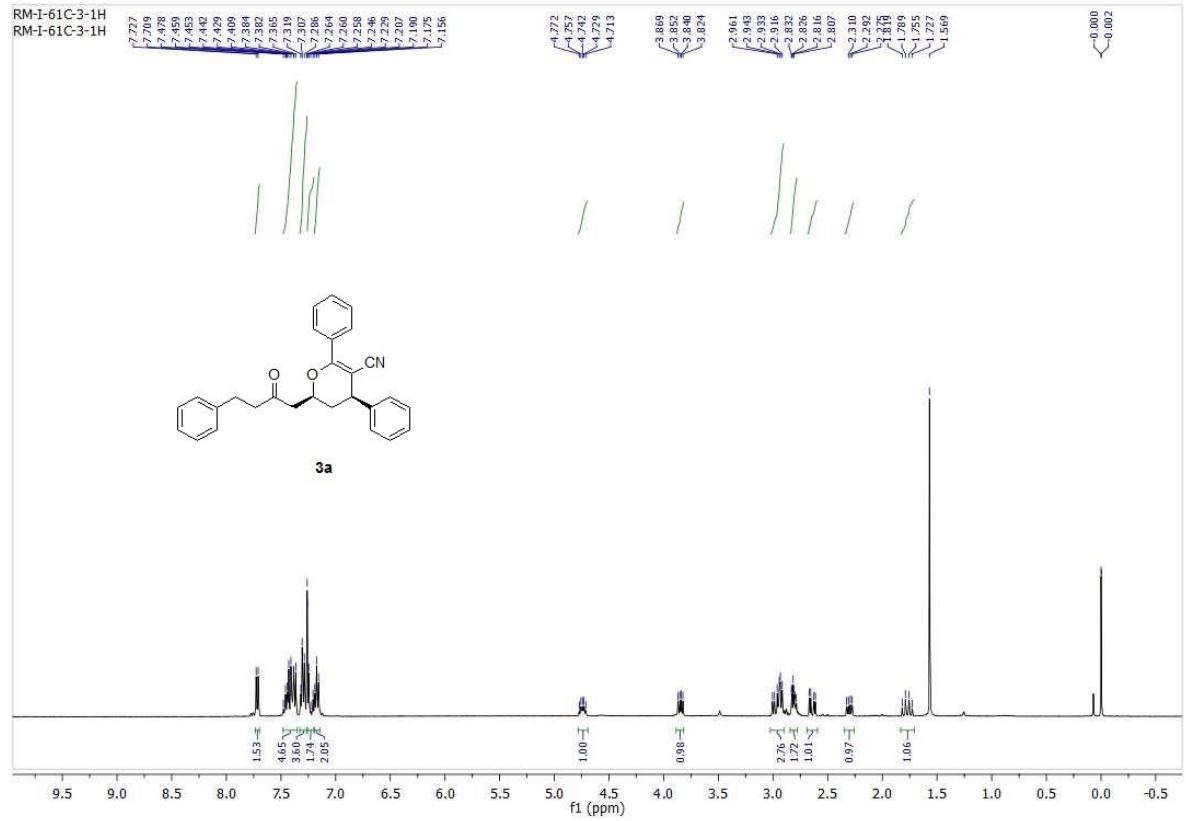
Colourless oil (19 mg, 53% yield), .11:1 dr; R_f value 0.25 (8:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 6.4 Hz, 2H), 7.75 (d, *J* = 6.6 Hz, 2H), 7.49 – 7.36 (m, 9H), 7.33 – 7.28 (m, 5H), 4.81 – 4.72 (m, 1H), 4.64 – 4.55 (m, 0.98H), 3.93 – 3.90 (m, 0.75H), 3.87 (dd, *J* = 11.7, 6.8 Hz, 1H), 2.99 (dd, *J* = 17.1, 7.4 Hz, 1H), 2.91 (dd, *J* = 16.7, 8.4 Hz, 1H), 2.64 (dd, *J* = 17.1, 5.4 Hz, 1H), 2.51 (dd, *J* = 16.7, 4.2 Hz, 1H), 2.33 (ddd, *J* = 8.6, 6.8, 2.9 Hz, 5H), 2.21 – 2.06 (m, 3H), 2.01 (dt, *J* = 13.7, 2.4 Hz, 1H), 1.80 (dd, *J* = 25.2, 11.5 Hz, 1H), 0.95 – 0.87 (m, 12H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 207.1, 206.9, 166.3, 166.1, 142.2, 141.4, 133.1, 133.0, 131.1, 131.0, 129.2, 129.1, 128.5, 128.5, 128.5, 128.4, 128.1, 127.8, 127.7, 127.5, 120.3, 119.6, 88.6, 85.0, 74.2, 69.9, 52.9, 47.7, 47.5, 41.5, 39.5, 37.4, 34.9, 24.7, 24.5, 22.7, 22.7, 22.6, 22.6; **ESI-MS** m/z calcd. for $C_{24}H_{25}NO_2$ $[M+H]^+$ 360.1958, found 360.1956; **FT-IR (KBr)** 2922, 2853, 2205, 1712, 1618, 1573, 1495, 1348, 1282, 1159, 1115 cm^{-1}; The ee (92% ee_{major}, 95% ee_{minor}) values were determined by HPLC using Chiralpak OD-H with hexane/i-PrOH (80:20) as the eluent; flow: 1.0 mL/min; 272 nm; minor diastereoisomer t_{major} = 7.26 min, t_{minor} = 9.03 min; major diastereoisomer t_{major} = 18.17 min, t_{minor} = 36.02 min.

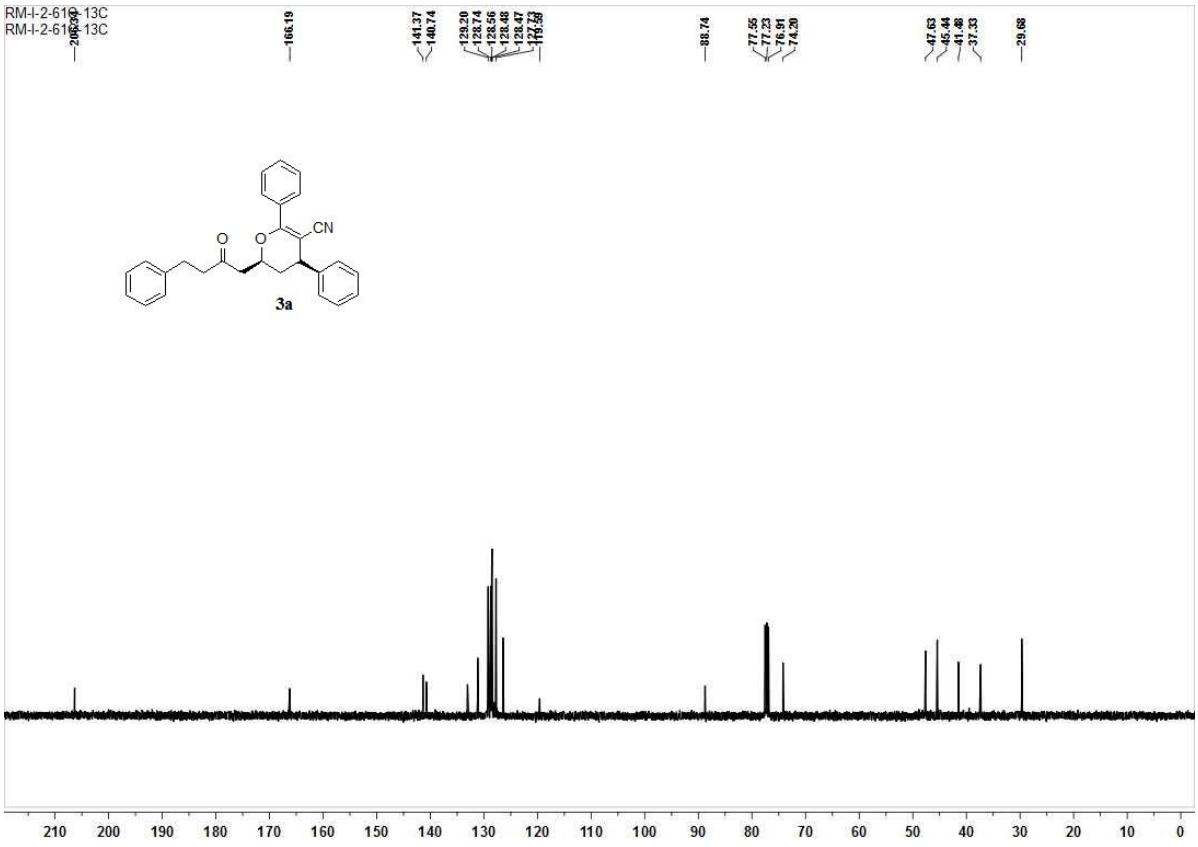
4.8.5. Crystal information:

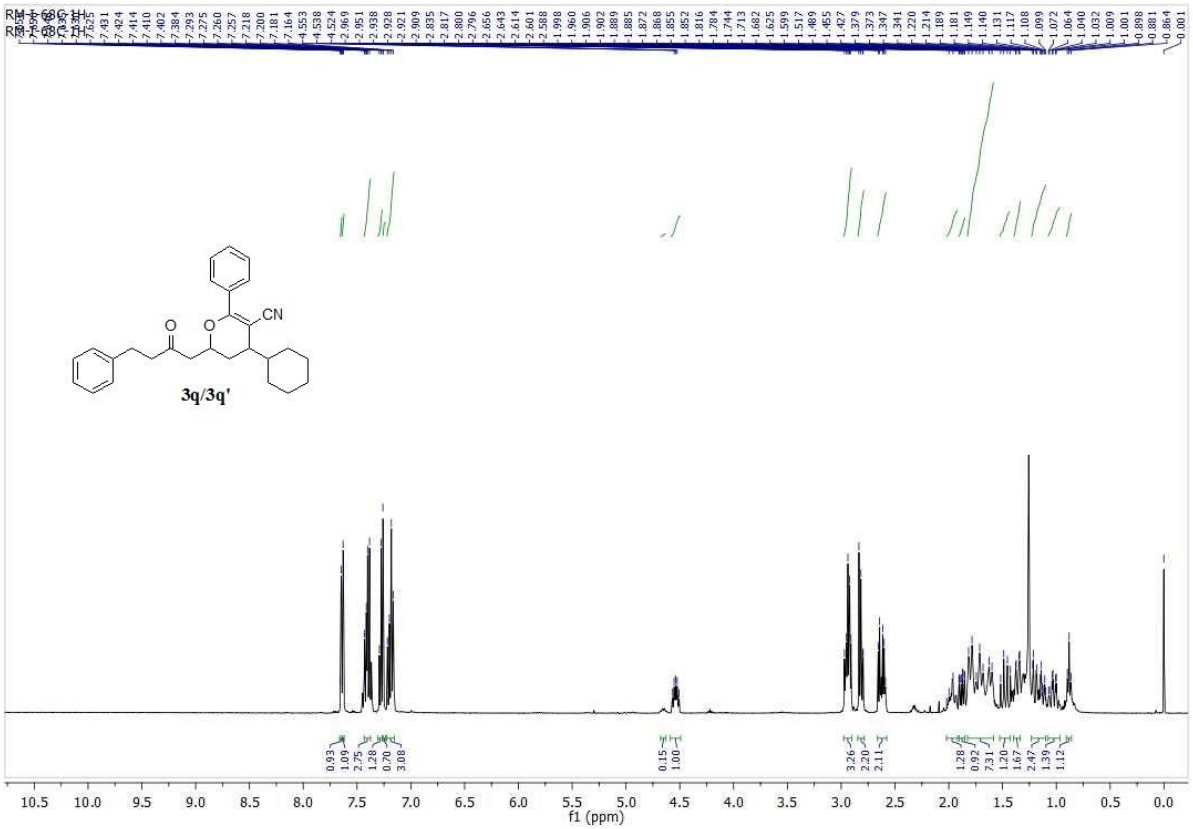
Identification code	**3a**
Empirical formula	$C_{28}H_{25}NO_2$
Formula weight	407.49
Temperature/K	298K
Crystal system	orthorhombic
Space group	'P 21 21 21'
a/Å	10.6310(3)
b/Å	12.0184(4)
c/Å	17.2054(6)
α/°	90.00
β/°	90.00

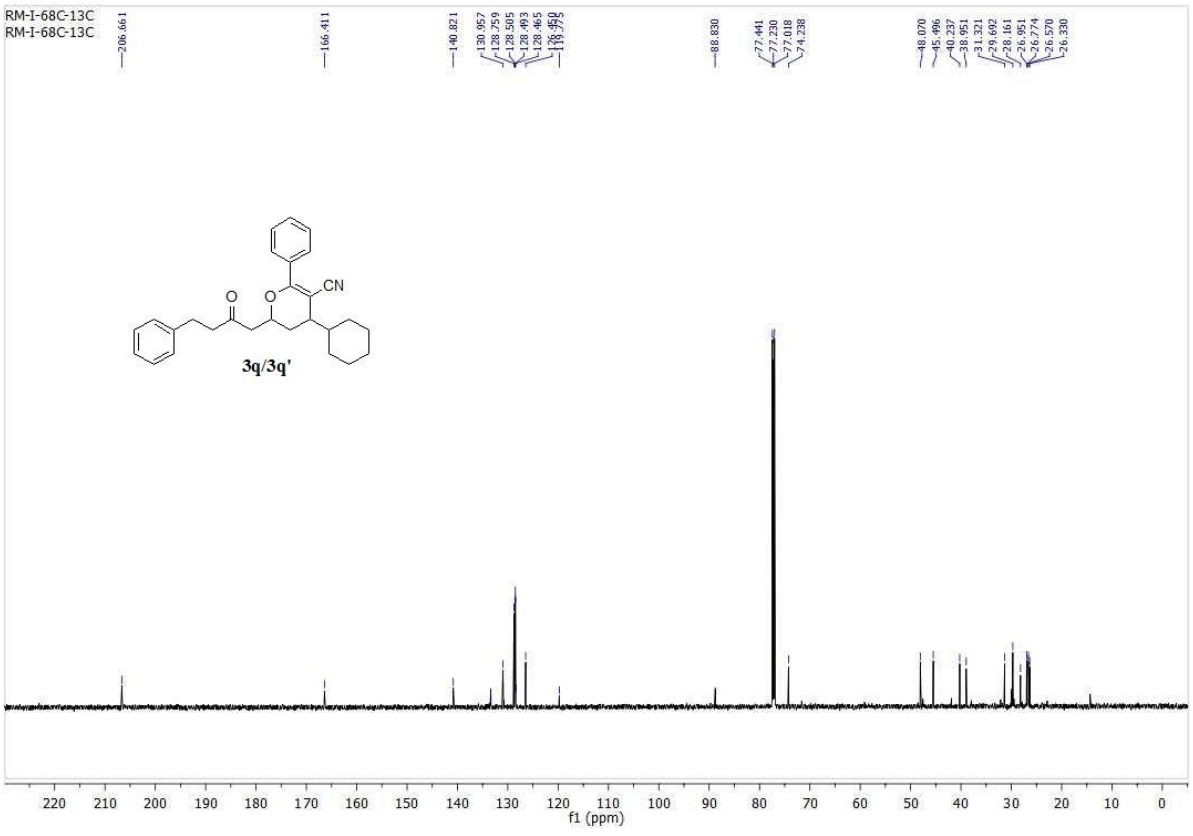
γ/°	90.00
Volume/Å^3	2198.29(12)
Z	4
ρ_{calc}mg/mm^3	1.591
m/mm^{-1}	2.957
F(000)	672.0
Crystal size/mm^3	0.35 × 0.22 × 0.14
2Θ range for data collection	2.48 to 52.54°
Index ranges	$-7 \leq h \leq 7, -8 \leq k \leq 7, -36 \leq l \leq 40$
Reflections collected	13277
Independent reflections	2607[R(int) = 0.0576]
Data/restraints/parameters	2607/0/181
Goodness-of-fit on F^2	0.903
Final R indexes [I>=2σ (I)]	R_1 = 0.0416, wR_2 = 0.1129
Final R indexes [all data]	R_1 = 0.0824, wR_2 = 0.1446
Largest diff. peak/hole / e Å^{-3}	0.51/-0.51
Flack parameter	0.2(5)

4.9. Selected spectra of NMR, COSY, NOESY and HPLC:



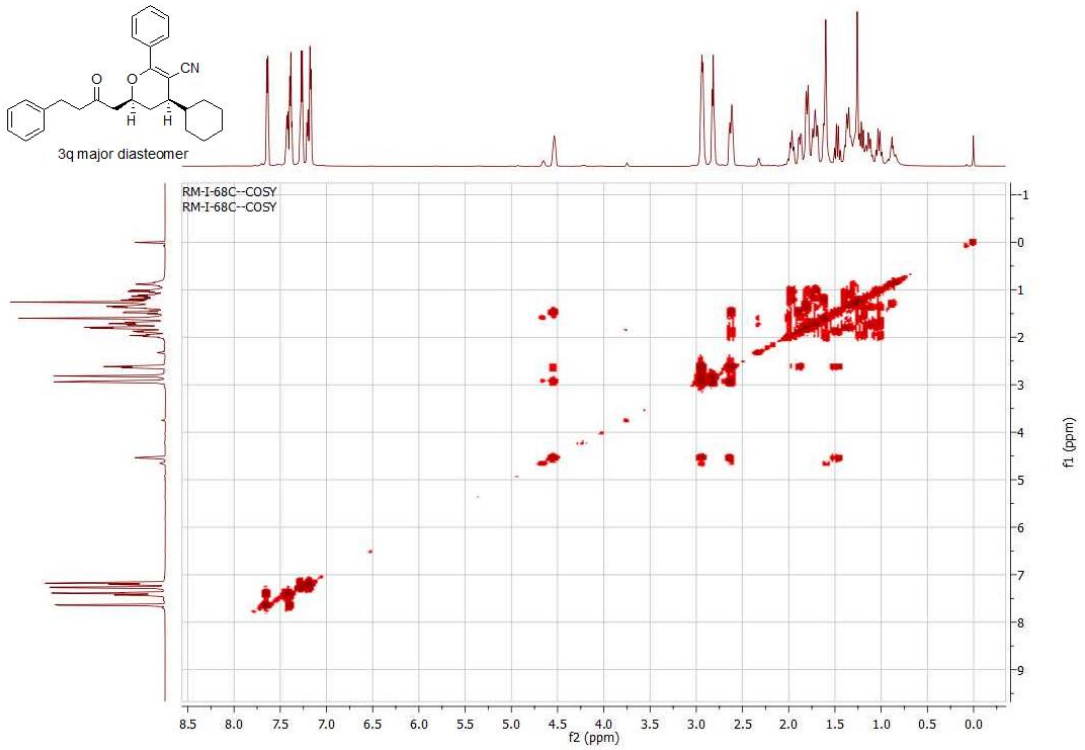




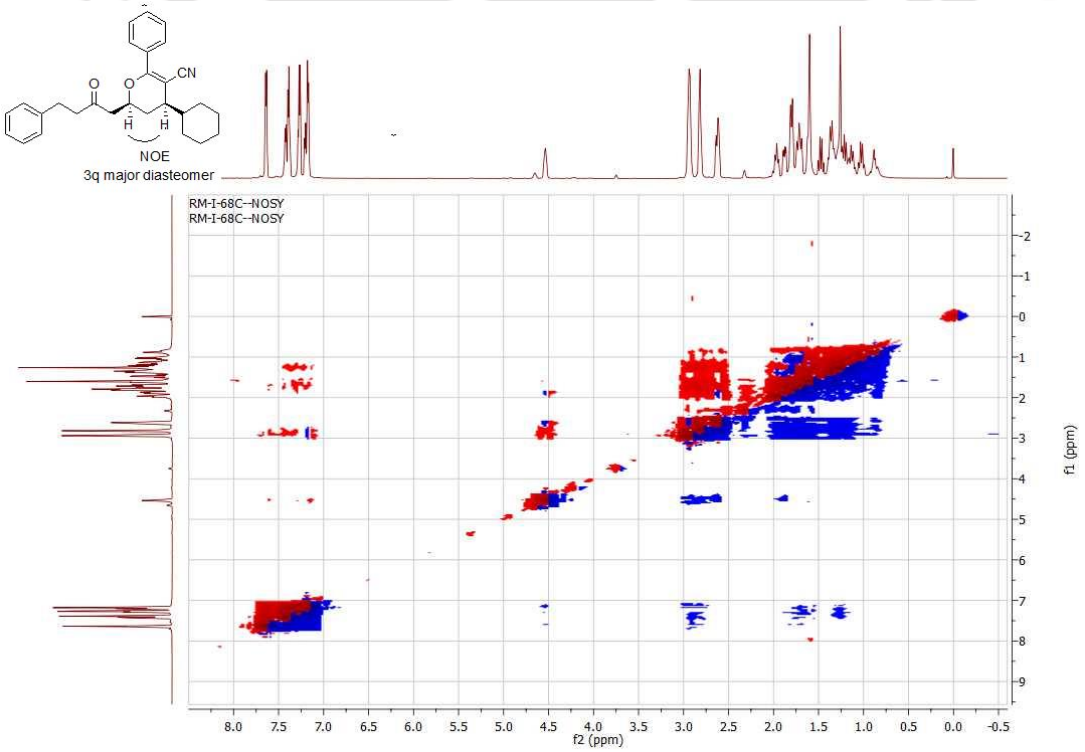


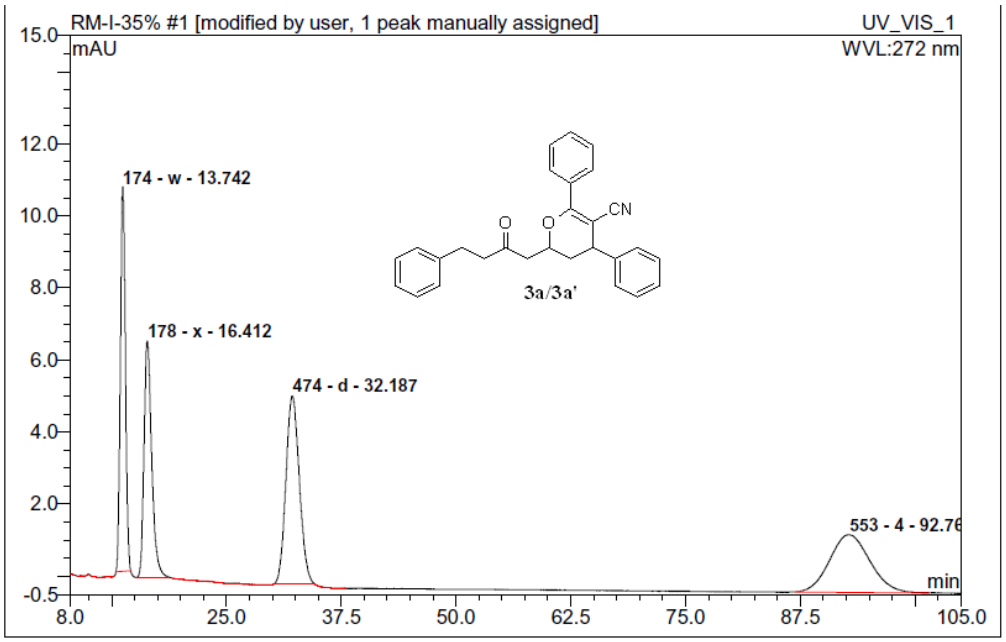
COSY and NOESY data of compound 3q/3q′:

COSY spectra

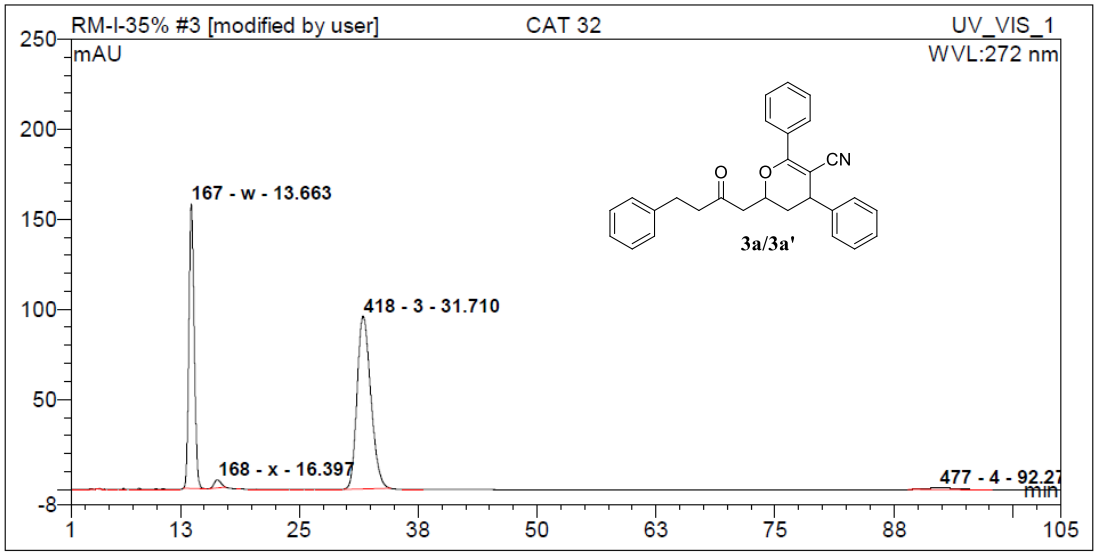


NOESY spectra



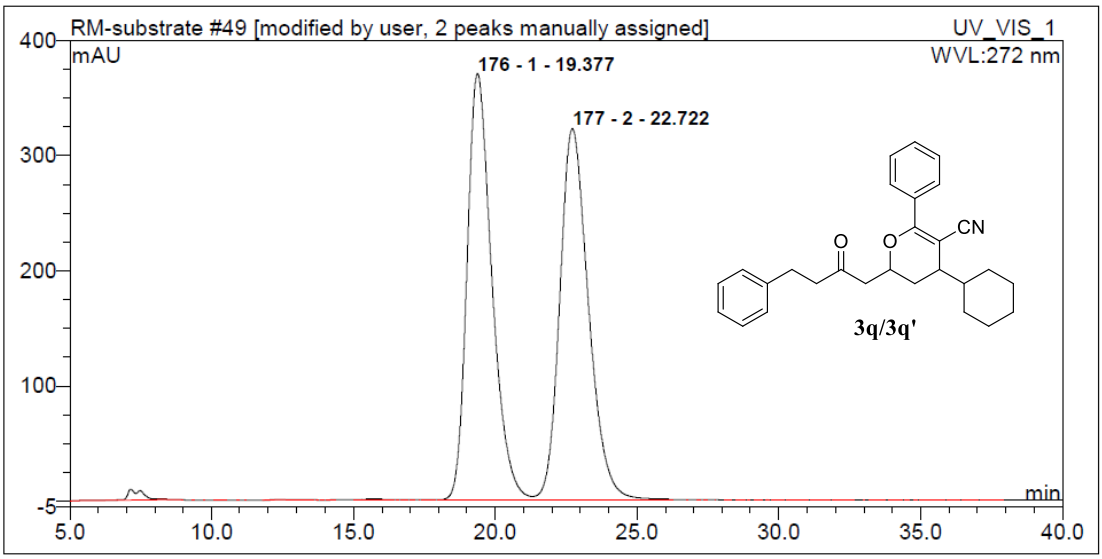


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(id %	Height mAU	Amount
	w	13.74166667	6.793329	22.66756	10.65101	n.a.
	x	16.41166667	6.328388	21.11617	6.54594	n.a.
	d	32.18666667	8.760463	29.23137	5.19839	n.a.
	4	92.765	8.08721	26.9849	1.60244	n.a.



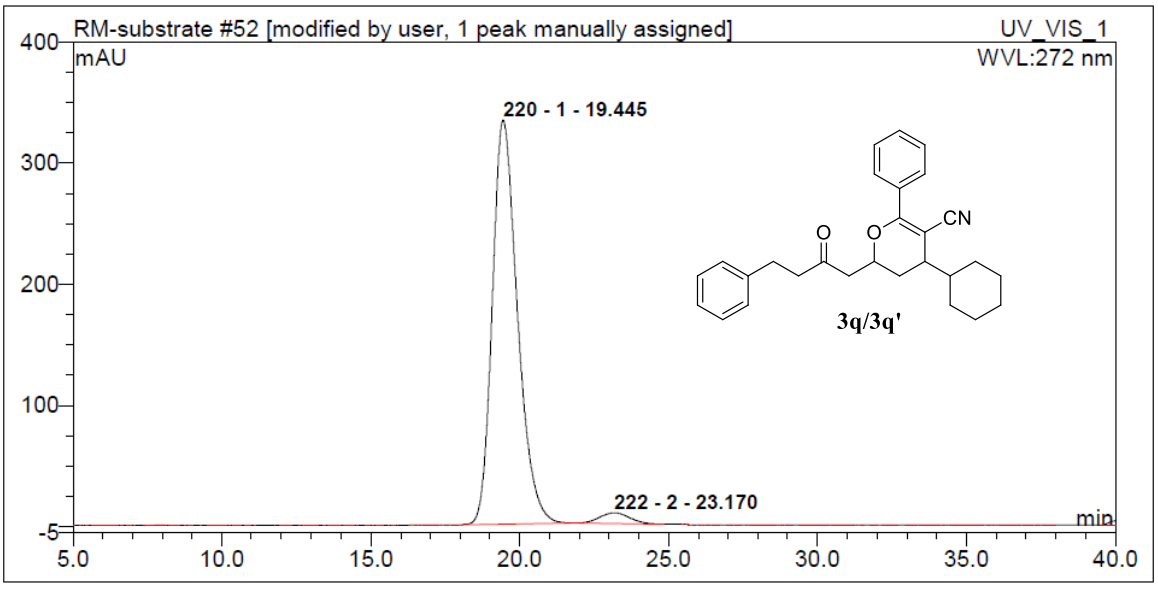
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
167	w	13.66	101.5785	37.60360236	157.8572	n.a.
168	x	16.40	3.733255	1.382023361	4.5721	n.a.
418	3	31.71	160.3863	59.37383822	95.8084	n.a.
477	4	92.27	4.432	1.640531759	1.033	n.a.

RM-I-68R



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
176	1	19.38	374.1623	49.85746806	370.2584	n.a.
177	2	22.72	376.301	50.1425216	322.163	n.a.

RM-I-68C



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
220	1	19.45	326.5679	96.85156579	333.4457	n.a.
222	2	23.17	10.616	3.148434209	8.967	n.a.

4.10. References:

1. (a) Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. *J. Nat. Prod*. **2001**, *64*, 640. (b) Yeung, K.-S.; Paterson, I. *Chem. Rev*. **2005**, *105*, 4237. (c) Kang, E. J.; Lee, E. *Chem. Rev*. **2005**, *105*, 4348.
2. (a) Atta-ur-Rahman, N. A.; Akhtar, F.; Shekhani, M. S.; Clardy, J.; Parvez, M.; Choudhary, M. I. *J. Nat. Prod*. **1997**, *60*, 472. (b) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2001**, *123*, 10772. (c) Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem*. **2005**, *70*, 8533. (d) Smith, A. B.; Sperry, J. B.; Han, Q. *J. Org. Chem*. **2007**, *72*, 6891. (e) Kumar, S.; Malachowski, W. P.; Duhadaway, J. B.; LaLonde, J. M. P.; Carroll, J.; Jaller, D.; Metz, R.; Prendergast, G. C.; Muller, A. J. *J. Med. Chem*. **2008**, *51*, 1706. (f) Laurent, M. Y.; Stocker, V.; Temgona, V. M.; Dujardin, G.; Dhal, R. *Tetrahedron Lett*. **2011**, *52*, 1608. (g) Zhu, X.-B.; Wang, M.; Wang, S.; Yao, Z.-J. *Tetrahedron* **2012**, *68*, 2041.
3. Lambu, M. R.; Kumar, S.; Yousuf, S. K.; Sharma, D. K.; Hussain, A.; Kumar, A.; Malik, F.; Mukherjee, D. *J. Med. Chem.* **2013**, *56*, 6122.
4. Paterson, I.; Savi, C. D.; Tudge, M. *Org. Lett.* **2001**, *3*, 3149
5. Norcrosst, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041.
6. (a) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (b) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5788. (c) Shie, J.-J.; Fang, J.-M.; Lai, P.-T.; Wen, W.-H.; Wang, S.-Y.; Cheng, Y.-S. E.; Tsai, K.-C.; Yang, A.-S.; Wong, C.-H. *J. Am. Chem. Soc*. **2011**, *133*, 17959.
7. Burke, S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem.* **1998,** *63*, 8626.
8. (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev*. **2011**, *111*, 3076.
9. (a) Devasagayaraj, A.; Schwink, L.; Knochel, P. *J. Org. Chem*. **1995**, *60*, 3311. (b) Van Orden, L. J.; Patterson, B. D.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 5784. (c) Denmark, S. E.; Heemstra, J. R. *J. Org. Chem.* **2007**, *72*, 5668. (d) Frings, M.; Atodiresei, I.; Wang, Y.; Runsink, J.; Raabe, G.; Bolm, C. *Chem. Eur. J.* **2010**, *16*, 4577.

10. For selected examples, see: (a) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem. Int. Ed*. **2003**, *42*, 4233. (b) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 5962. (c) Sundén, H.; Ibrahem, I.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 4877. (d) Xu, D.-Q.; Xia, A.-B.; Luo, S.-P.; Tang, J.; Zhang, S.; Jiang, J.-R.; Xu, Z.-Y. *Angew. Chem. Int. Ed*. **2009**, *48*, 3821. (e) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2009**, *48*, 7196. (f) Feng, X.; Zhou, Z.; Zhou, R.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *J. Am. Chem. Soc*. **2012**, *134*, 19942. (g) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2013**, *135*, 1891. (h) Wu, X.; Li, M.-L.; Chen, D.-F.; Chen, S.-S. *J. Org. Chem*. **2014**, *79*, 4743. (i) Masalo, E.; Benaglia, M.; Annunziata, R.; Palmieri, A.; Celentano, G.; Forni, A. *Adv. Synth. Catal*. **2014**, *356*, 493. (j) Fei, J.; Qian, Q.; Sun, X.; Gu, X.; Zou, C.; Ye, J. *Org. Lett*. **2015**, *17*, 5296.

11. (a) Feng, X.; Zhou, Z.; Ma, C.; Yin, X.; Li, R.; Dong, L.; Chen, Y.-C. *Angew. Chem. Int. Ed*. **2013**, *52*, 14173. (b) Chen, P.-Q.; Xiao, Y.-C.; Yue, C.-Z.; Chen, Y.-C. *Org. Chem. Front*. **2014**, *1*, 490. (c) Feng, X.; Zhou, Z.; Yin, X.; Li, R.; Chen, Y.-C. *Eur. J. Org. Chem*. **2014**, 5906. (d) Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J*. **2014**, *20*, 2145.

12. (a) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642. (b) Gupta, V.; Sudhir, S.V.; Mandal, T.; Schneider, C. *Angew. Chem. Int. Ed*. **2012**, 12609. (c) Basu, S.; Gupta, V.; Nickel, J.; Schneider, C. *Org. Lett*. **2014**, *16*, 274. (d) Abels, F.; Schneider, C. *Org. Biomol. Chem*. **2012**, *12*, 3531.

13. Zhan, G.; He, Q.; Yuan, X.; Chen, Y.-C. *Org. Lett*. **2014**, *16*, 6000.

14. Zhou, Z.; Feng, X.; Yin, X.; Chen, Y.-C. *Org. Lett*. **2014**, *16*, 2370.

15. (a) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem. Int. Ed*. **2013**, *52*, 6666. (b) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. *Angew. Chem. Int. Ed*. **2014**, *53*, 14128. (c) Jing, Z.; Bai, X.; Chen, W.; Zhang, G.; Zhu, B.; Jiang, Z. *Org. Lett.* **2016**, *18*, 260. For related recent organocatalytic vinylogous additions, see: (d) Zheng, C.; Wang, H.-f.; Chen, W.-Q.; Chen, W.-X.; Chen, F. E. *Asian. J. Org. Chem.* **2015**, *4*, 619. (e) Zhao, S.; Zhao, Y.-Y.; Lin, J.-B.; Xie, T.; Liang, Y.-M.; Xu, P.-F. *Org. Lett.* **2015**, *17*, 3206. (f) Li, T.

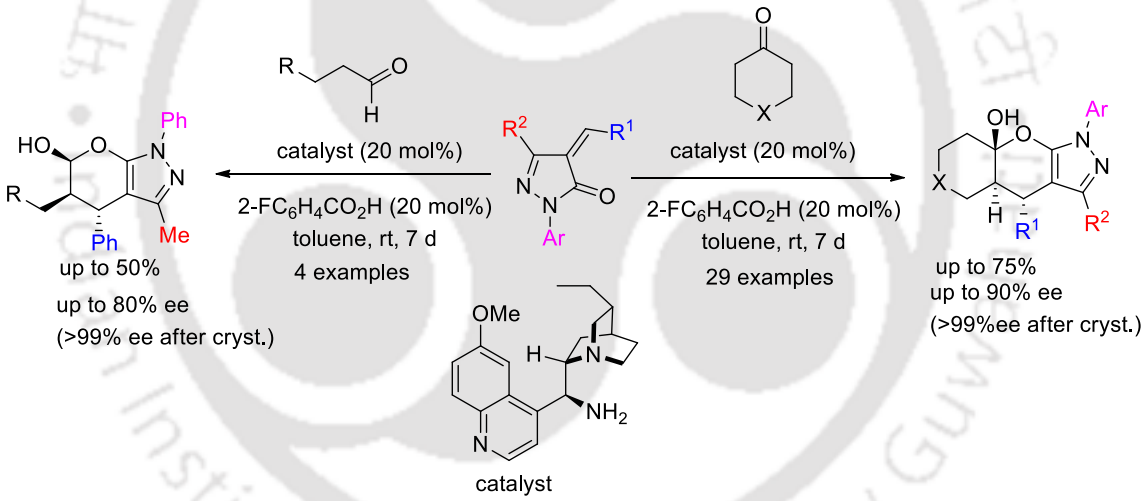
Z.; Xie, J.; Jiang, Y.; Sha, F.; Wu, X.-Y. *Adv. Synth. Catal*. **2015**, *357*, 3507. (g) Iorio, N. D.; Righi, P.; Ranieri, S.; Mazzanti, A.; Margutta, R. G.; Bencivenni, G. *J. Org. Chem.* **2015**, *80*, 7158. (h) Han, J.-L.; Chang, C.-H. *Chem. Commun.* **2016**, *52*, 2322.

16. Nising, C. F.; Bröse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.
17. Tang, Y.; Oppenheimer, J.; Song, Z.-L.; You, L.-F.; Zhang, X.-J. Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785.
18. Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y.; *Adv. Synth. Catal*. **2008**, *350*, 2610.
19. Liu, W.; Zhou, J.; Zheng, C.; Chen, X.; Xiao, H.; Yang, Y.; Guo, Y.; Zhao, G. *Tetrahedron* **2011**, *67*, 1768.
20. Das, U.; Huang, C.-H.; Lin, W. *Chem. Commun.* **2012**, *48*, 5590.
21. Zhao, S.-L.; Zheng, C.-W.; Wang, H.-F.; Zhaoa, G. *Adv. Synth. Catal.* **2009**, *351*, 2811.
22. Shi, M.-L. Zhan, G. Zhou, S.-L. Du, W. Chen, Y.-C. *Org. Lett*. **2016**, *18*, 6480.
23. CCDC 1486531 contains the crystallographic data for **3a**.
24. (a) Sada, M.; Ueno, S.; Asano, K.; Nomura, K.; Matsubara, S. *Synlett* **2009**, 724. (b) Silva, F. P. L.; Cirqueira, M. L.; Martins, F. T.; Vasconcellos, M. L. A. A. *J. Mater. Chem*. **2013**, *1052*, 189.

Enantioselective Aminocatalytic Synthesis of Tetrahydropyrano[2,3-*c*]Pyrazoles via Domino Michael-Hemiketalization Reaction with Alkylidene Pyrazolones*

Abstract:

An enantioselective organocatalytic domino Michael-hemiketalization reaction between alkylidene pyrazolones and cyclic ketones/aliphatic aldehydes has been disclosed. The fused tetrahydropyranopyrazole products having three contiguous stereocentres were obtained in perfect diastereoselectivities and in moderate to good yields with good to high enantioselectivities. Also, few synthetic transformations of the product including a spiro derivative formation have been demonstrated.



*Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2017**, *15*, 8032.

5.1. Introduction of pyranopyrazole:

Pyran, a six membered non-aromatic heterocyclic ring, consists of five carbon atoms with one oxygen atom and two double bonds. Whereas, pyrano[2,3-*c*]pyrazole has fused ring of pyran 2,3 positions with c-side of pyrazole. Pyrano[2,3-*c*]pyrazole is of two types, dihydropyrano[2,3-*c*]pyrazole (pyran ring contains one double bond, Figure 1) and tetrahydropyrano[2,3-c]pyrazole (no double bond in pyran ring, Figure 1).

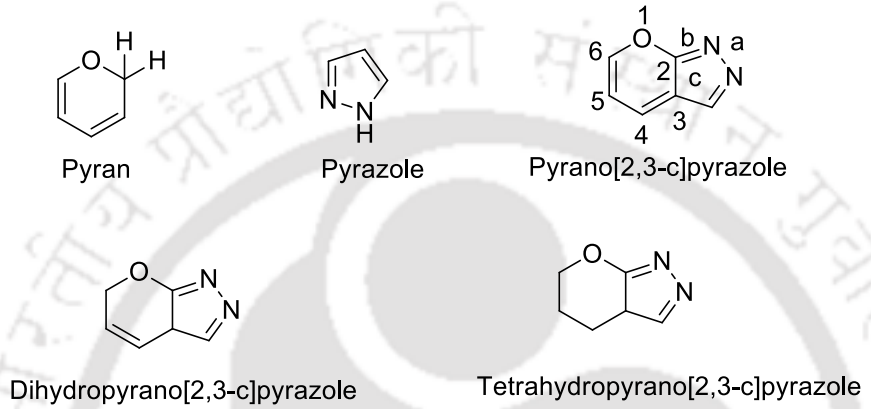


Figure 1. Structures of pyran, pyrazole and pyranopyrazole.

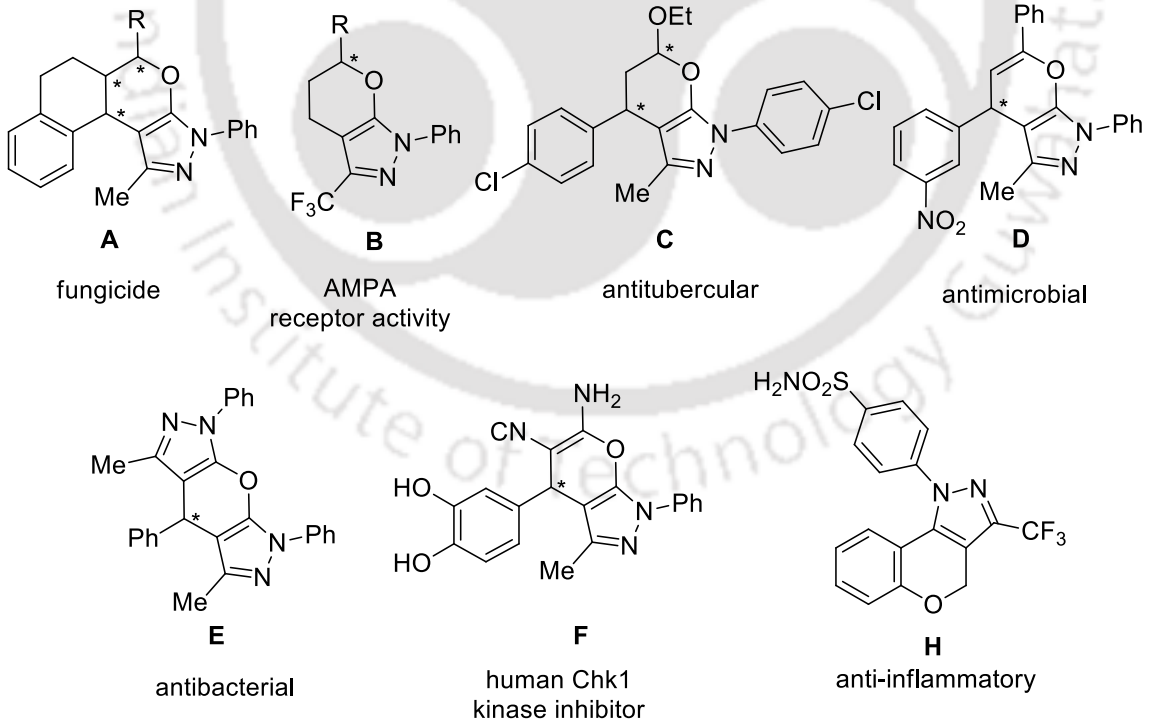


Figure 2. Selected examples of biologically important pyranopyrazoles.

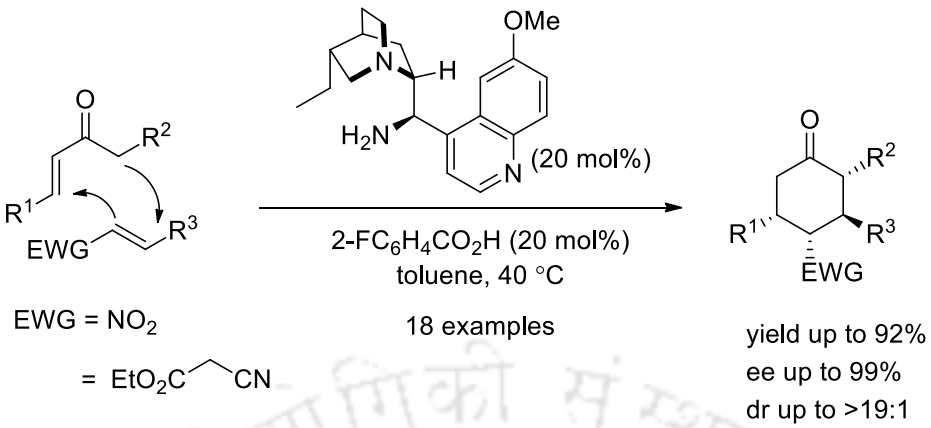
These heterocyclic pyrano[2,3-*c*]pyrazole motif is an important structural core which resides in numerous bioactive reagents and natural products Figure 2.[1] For example, pyranopyrazole of type **A** displays fungiside activity[2] whereas trifluoromethylated analogue **B** has AMPA receptor activity and enhancer property.[3] Also the pyranopyrazole acetal derivative **C** is known to show antitubercular activity.[4] Moreover, other chiral pyrano-fused pyrazoles **D**, **E** and **F** possess impressive bioactivities like antimicrobial,[5] antibacterial[6] and human Chk1 kinase inhibitor properties[7] respectively and compound **H** shows anti-inflammatory property.[8] Considering the various biological activities of pyrano-annulated pyrazole scaffolds, featured with multiple stereogenic centers, the developments of pyrano-annulated pyrazole have emerged as appealing synthetic targets in recent years.

5.2. Domino reaction:

Domino reactions prefer less reaction time, avoid costly protection/deprotection and purification of intermediates. The reactions often display excellent stereoselectivities for ecologically and economically favourable products. The efficiencies of asymmetric domino reactions are correlated firstly, to the number of bonds formed, secondly, to the number of newly created stereocenters, and thirdly, to the increase in structural complexity.[9,10]

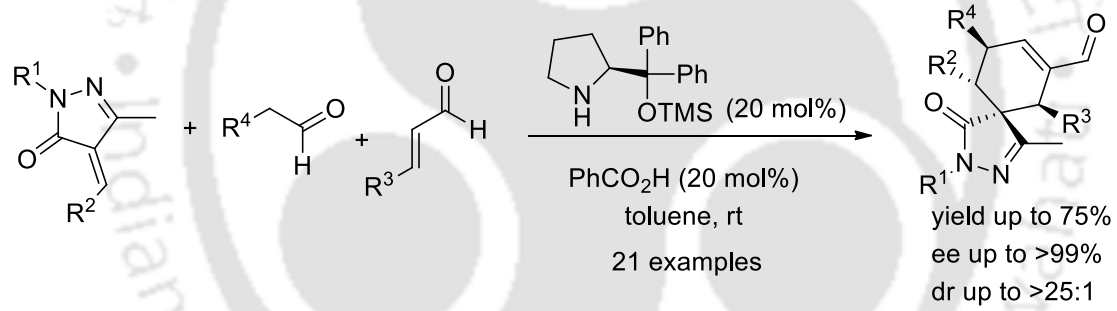
5.2.1. Domino Michael reaction:

The domino double Michael reaction of substituted benzylidene acetones with electron deficient olefins under hydroquinidine derived catalyst has been published by Melchiorre and co-workers. The Michael products, the substituted cyclohexanones with four stereogenic centres provided excellent enantio- and diastereoselectivities. (Scheme 1).[11]



Scheme 1

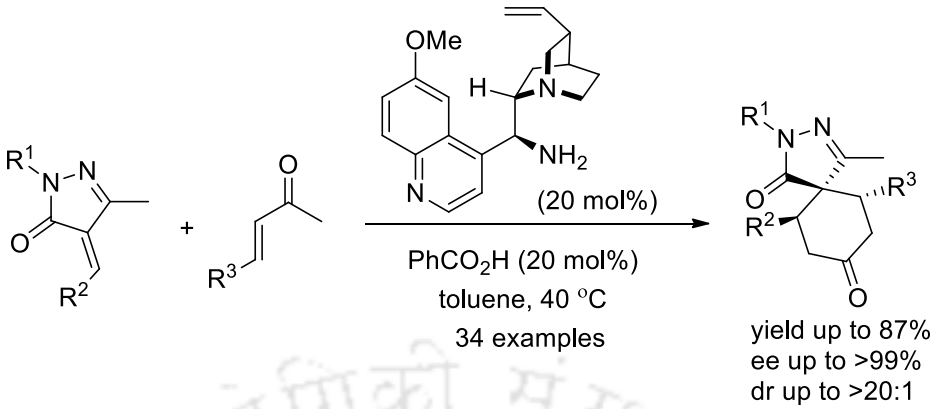
A domino Michael reaction of enals, unsaturated pyrazolones and enolizable aldehydes *via* iminium-enamine ion intermediate has been established by Rios *et al*. The final spiro products bearing four stereogenic centres were afforded with excellent enantio- and diastereoselectivities (Scheme 2).[12]



Scheme 2

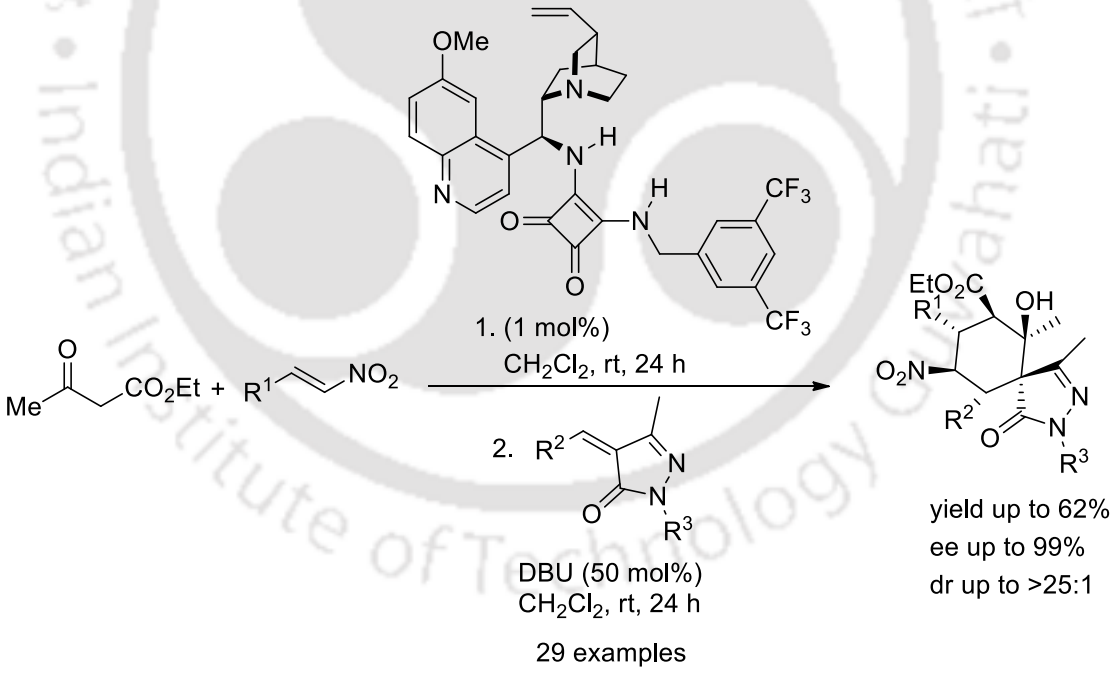
5.3. Organocatalytic asymmetric Michael addition reactions using unsaturated pyrazolones:

Wang group disclosed efficient protocol for asymmetric organocatalytic reaction of unsaturated pyrazolones with benzylidene acetones in the presence of quinine derived primary amine catalyst. This method tolerated a wide range of substrates and excellent diastereo- and enantioselectivities of cyclic products were achieved (Scheme 3).[13]



Scheme 3

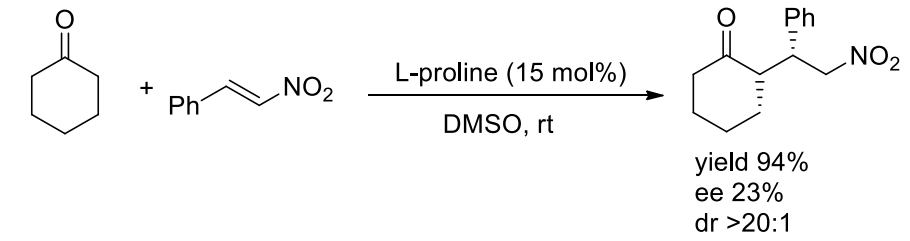
An organocatalytic one-pot sequential Michael/Michael/1,2-additon reaction of β-dicarbonyl compounds, β-nitrostyrenes and α,β-unsaturated pyrazolones was reported by Enders group. A series of diversely functionalized spiro cyclohexanepyrazolones bearing six stereocenters were synthesised with excellent diastereo- and enantioselectivities by using mild reaction conditions (Scheme 4).[14]



Scheme 4

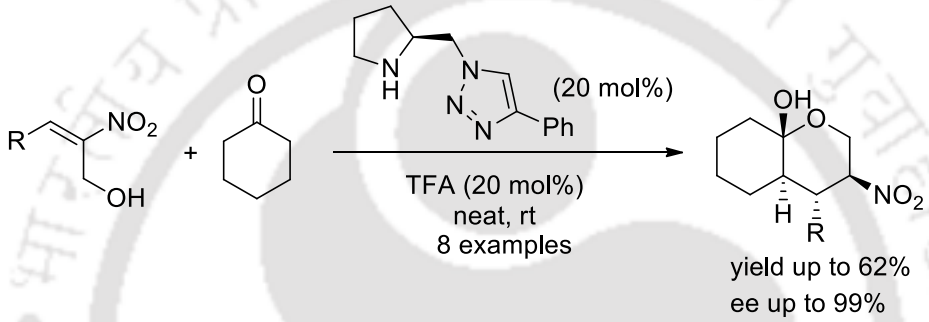
5.4. Asymmetric organocatalytic Michael addition reactions using cyclohexanones:

List group first pioneered an organocatalytic asymmetric Michael addition reaction of cyclohexanones with nitroolefines *via* iminium-enamine ion intermediates by using L-proline as a catalyst (Scheme 5).[15]



Scheme 5

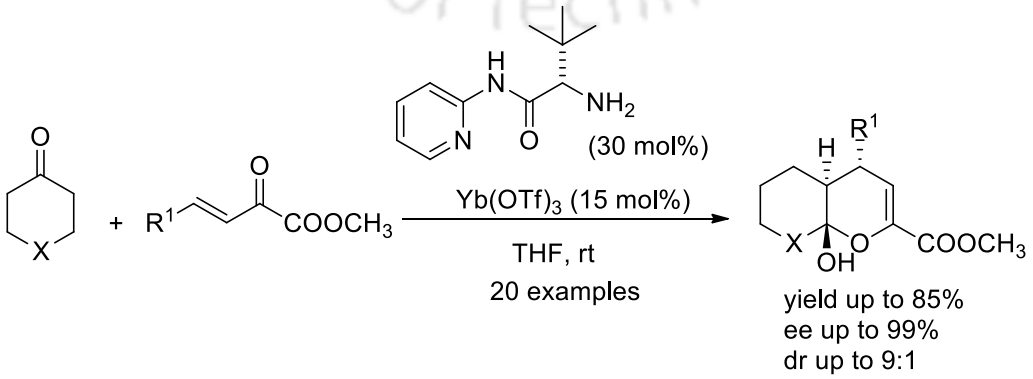
Jagadeesh and co-workers reported a secondary amine catalyzed Michael/ketalization reaction of cyclohexanones and 2,3-disubstituted nitro olefins to furnish the enantiopure fused tetrahydropyrans (Scheme 6).[16a,17]



Scheme 6

5.5. Asymmetric cyclization reaction of cyclohexanones using organo-metal catalysis:

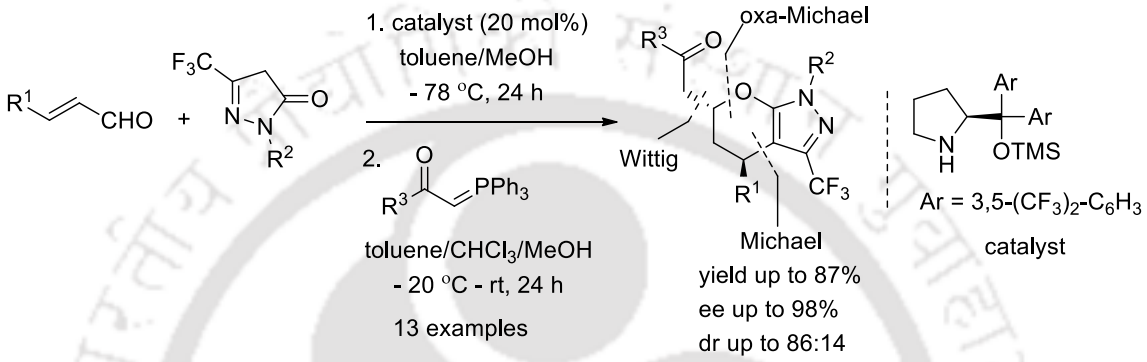
Wang group developed new efficient protocol for the enantioselective synthesis of dihydropyrans, which was synthesized from the reaction between cyclohexanones and α,β-unsaturated enones employing the combination of organic and metal catalysts. The dihydropyran products consisting of three stereogenic centers including a quaternary carbon centre were achieved with good yields and excellent enantioselectivities (Scheme 7).[18]



Scheme 7

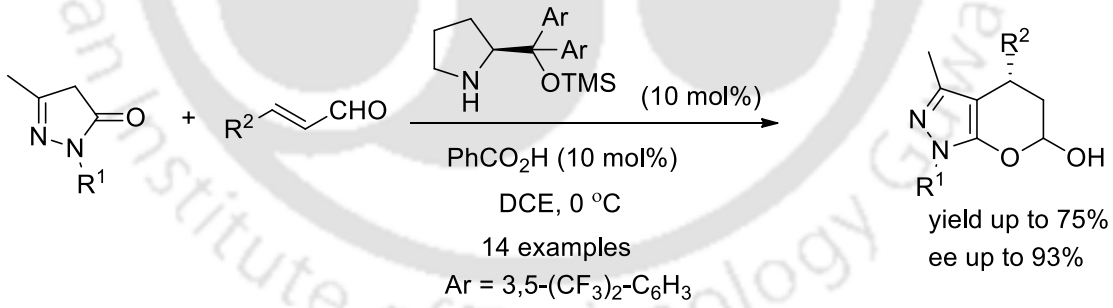
5.6. Previous reports on asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazole (THPP):

Prolinol TMS ether catalyzed highly enantioselective Michael/Wittig/oxa-Michael reactions of pyrazolones, α,β-unsaturated aldehydes and Wittig reagents for the preparation of tetrahydropyrano[2,3-*c*]pyrazoles have been decorated by Enders and co-workers (Scheme 8).[19]



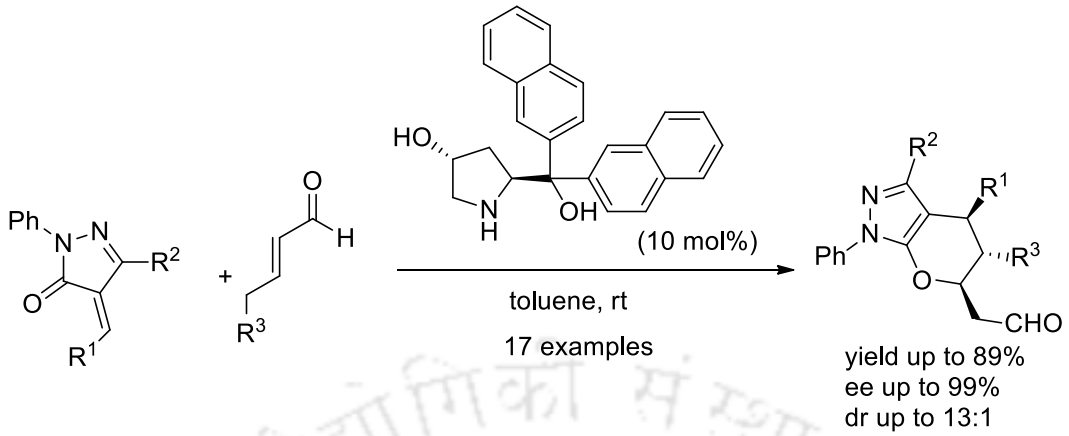
Scheme 8

Wang *et al.* presented an organocatalytic asymmetric Michael addition reaction of pyrazolones with cinnamaldehydes for the enantiopure synthesis of tetrahydropyrano[2,3-*c*]pyrazoles with excellent yields (Scheme 9).[20]



Scheme 9

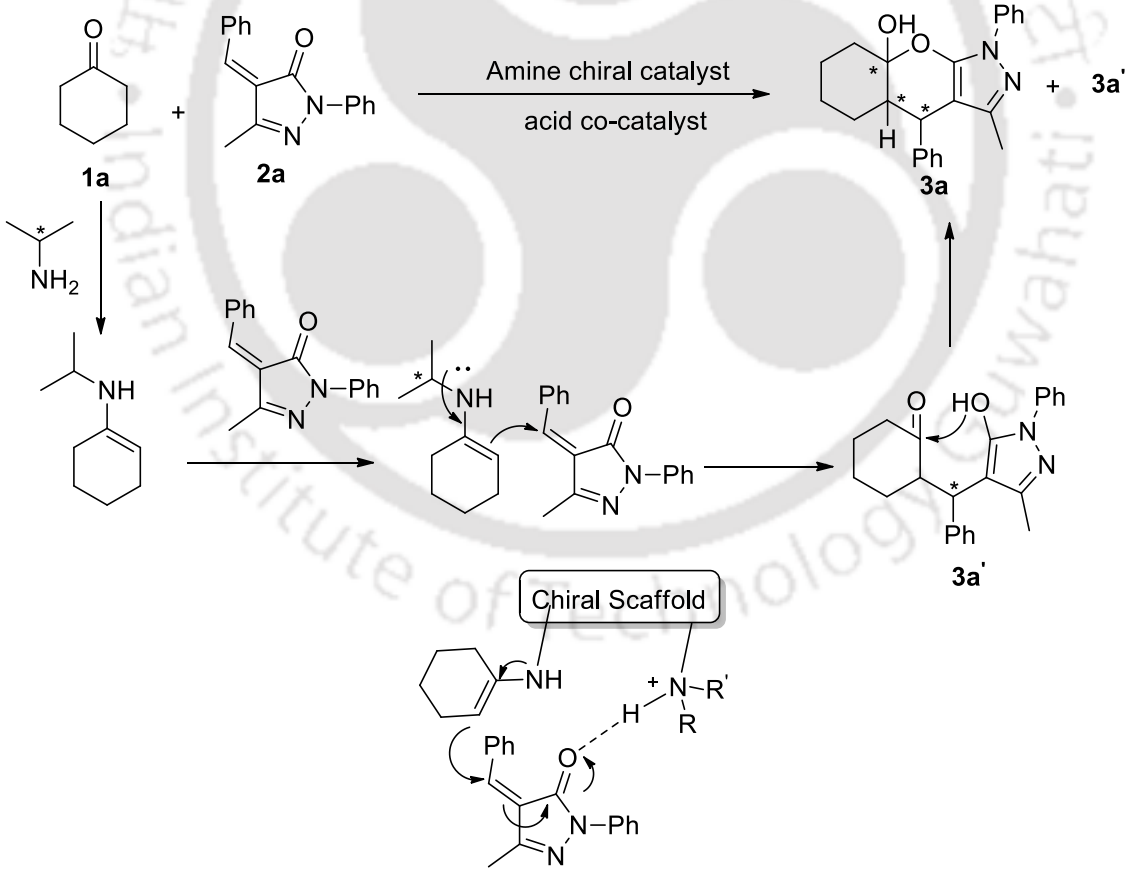
Pericàs *et al.* disclosed the [4+2] cycloaddition reaction of unsaturated pyrazoles with enals using prolinol derived catalyst and obtained excellent enantio- and diastereoselectivities of tetrahydropyrano[2,3-*c*]pyrazoles bearing three contiguous stereocenters (Scheme 10).[21]



Scheme 10

5.7. Concept:

From literature studies, we observed that the cyclic ketones have never been employed for the synthesis of THPP despite many enamine catalytic reactions with known cyclic



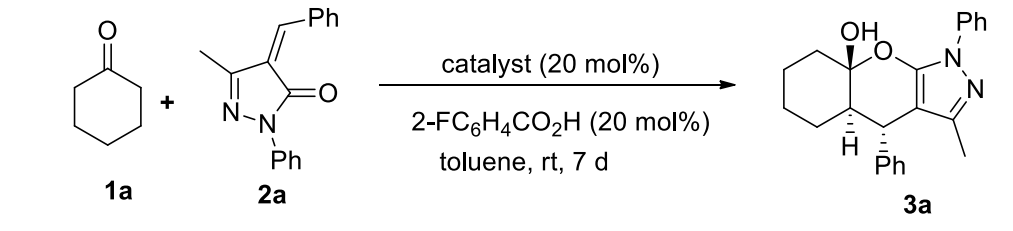
Scheme 11

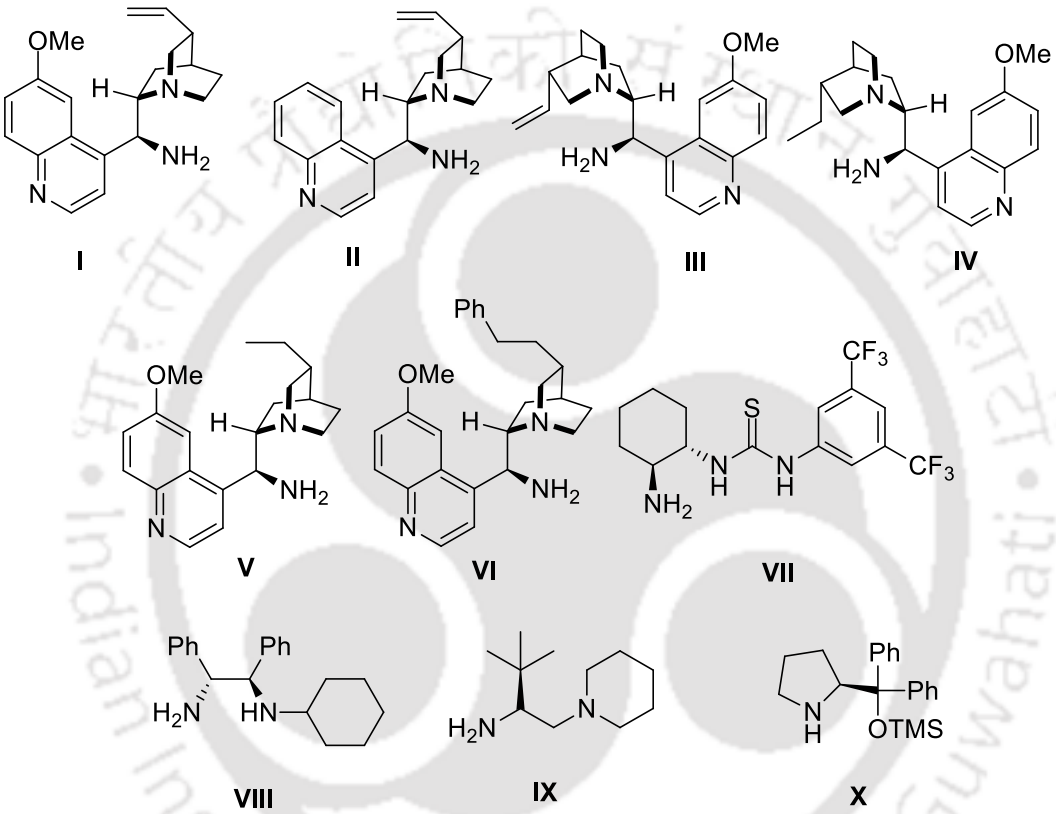
ketones. So based on our interest in the synthesis of chiral pyrazoles, organocatalytic enantioselective domino Michael-hemiketalization reaction between cyclic ketones and unsaturated pyrazolones would be demonstrated (Scheme 11). We envisioned that chiral primary and tertiary amine catalyst may control the enantioselective addition of cyclohexanone and unsaturated pyrazolone using the concept of simultaneous dual activation of cyclohexanones (*via* enamine intermediate) and unsaturated pyrazolones (activation by tertiary amine group through the hydrogen bonding). The chiral scaffold present in the primary tertiary amine derivatives would control the regio- and stereoselectivity in the reaction.

5.8. Results and discussion:

The investigation was commenced by performing a model reaction between cyclohexanone **1a** and unsaturated pyrazolone **2a** in toluene at room temperature in the presence of catalyst **I** and 2-$FC_6H_4CO_2H$ as additive (Table 1, entry 1). The expected Michael-hemiketalization product **3a** was obtained in 80% yield with 72%ee, and only single diastereomer was detected by 2D NMR analysis. The relative configuration of **3a** was assigned by X-ray crystal structure.[22] Cinchonidine derived primary amine catalyst **II** and quinidine derived primary amine catalyst **III** afforded the product **3a** with poor enantioselectivity (entries 2-3). Remarkably, an enhancement in enantioselectivity (85%) was detected with hydroquinidine derived primary amine catalyst **IV** and the product **3a** was isolated in 52% yield (entry 4). Slight improvement in enantioselectivity was observed using hydroquinine derived amine catalyst **V** and as always only a single diastereomer was detected (entry 5). However, with substituted hydroquinine derived catalyst **VI**, a reduced enantioselectivity of 74% (entry 6) and with bifunctional thiourea catalyst **VII** further lower enantioselectivity was attained (entry 7). Primary-tertiary amine catalyst **VIII** displayed similar results (entry 8). Unfortunately, the tertiary leucine derived amine catalyst **IX** provided a racemic product (entry 9). When reaction was performed under catalytic condition of prolinol TMS ether **X**, it failed to provide the corresponding product (entry 10).

Table 1: Catalyst optimization





entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	53	72
2	**II**	52	62
3	**III**	50	50
4	**IV**	52	85
5	**V**	**56**	**87**
6	**VI**	55	74
7	**VII**	45	34
8	**VIII**	57	34
9	**IX**	52	00

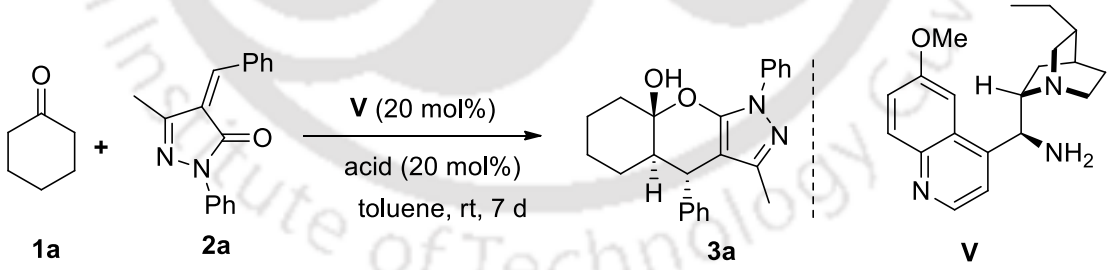
10	**X**	ND	-

[a]0.2 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL toluene using 20 mol% catalyst and 20 mol% acid co-catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column. ND - not determine.

5.8.1. Acid screening:

An additive might influence and sometimes greatly improves enantioselectivity of asymmetric organocatalytic reactions. Thus, the next phase of optimization was progressed by involving different types of acid additives such as substituted benzoic acids, chiral amino acid and aliphatic acids (Table 2). Using $PhCO_2H$, low enantioselectivity was obtained (entry 1). Other substituted benzoic acids such as 3-methoxy, 2,4-dichloro, 3-nitro group containing acids were tested in the reaction, but inferior results in terms of enantioselectivity and yield were observed (entries 2-4). Gratifyingly, 2-$FC_6H_4CO_2H$ gave the highest enantiomeric excess of value 87% (entries 2-5). Also, *N*-Boc-L-leucine chiral acid was screened and diminished enantioselectivity of desired product **3a** was observed (entry 6). Interestingly, with strong acid such as TFA, no product was attained (entry 7). Besides, an aliphatic acid was also checked for the reaction, but lesser yield with similar enantioselectivity to that obtained with 2-$FC_6H_4CO_2H$ was observed (entries 5 and 8).

Table 2: Acid optimization



1a 2a 3a V

entry[a]	acid	yield (%)[b]	ee(%)[c]
1	$PhCO_2H$	50	56
2	3-$OMeC_6H_4CO_2H$	43	76
3	2,4-di$ClC_6H_4CO_2H$	40	82
4	3-$NO_2C_6H_4CO_2H$	47	48
5	**2-$FC_6H_4CO_2H$**	**56**	**87**
6	*N*-Boc-L-leucine	50	76

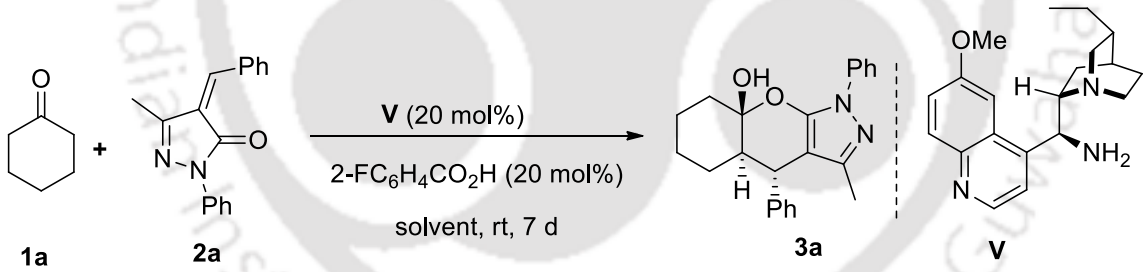
7	TFA	ND	00
8	AcOH	45	86

[a]0.2 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL toluene using 20 mol% catalyst and 20 mol% acid co-catalyst. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]Determined by HPLC using stationary phase chiral column. ND-not determine.

5.8.2. Solvent screening:

The reaction was also optimized using various polar, polar aprotic, non-polar and chlorinated solvents with catalyst **V** and 2-$FC_6H_4CO_2H$ (Table 3). Firstly, non-polar solvents such as toluene, benzene, trifluorotoluene, mesitylene, *o*-xylene, *p*-xylene were examined in the reaction and comparable enantioselectivity was obtained (entries 1-6). Moreover, both the yield and enantioselectivity was decreased using 1,4-dioxane and MTBE compared to non-polar solvents (entries 7-8). Also, satisfactory results were not observed with chlorinated solvents (entries 9-10). After scrutinizing various solvents, it was realized that toluene should be the optimum solvent since it afforded the desired product **3a** in 56% yield and 87% ee (entry 1).

Table 3: Solvent optimization



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	**Toluene**	**56**	**87**
2	Benzene	52	86
3	Trifluorotoluene	50	70
4	Mesitylene	47	76
5	*o*-Xylene	42	78
6	*p*-Xylene	45	80
7	1,4-Dioxane	52	74
8	MTBE	35	69
9	CH_2Cl_2	30	40

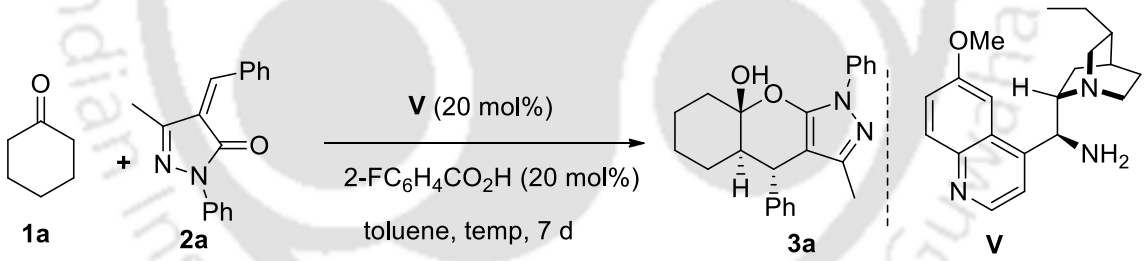
10	DCE	35	34

[a]0.2 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL solvent using 20 mol% catalyst and 20 mol% acid co-catalyst. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]Determined by HPLC using stationary phase chiral column.

5.8.3. Screening of temperature and equivalents of cyclohexanone (1a):

Initially, the reaction was performed using 4 equivalents of cyclohexanone **1a** with 1 equivalent of unsaturated pyrazolone **2a** (Table 4, entry 1). When the reaction was performed by altering equivalents of cyclohexanone (**1a**), the product **3a** was observed with less yields and enantioselectivities (entries 2-5). The yield also got diminished without affecting the enantioselectivity at low temperature (0 ^{o}C), but at high temperature (60 ^{o}C), poor enantioselectivity was identified with minute change in the yield (entries 6-7). Interestingly, the enantioselectivity of **3a** got enhanced to 98% ee by recrystallizing with ethanol. Thus, after detailed investigations, the combination of catalyst **V** and additive 2-$FC_6H_4CO_2H$ with toluene as solvent at room temperature, was the best optimized conditions.

Table 4: Temperature and equivalent of cyclohexanone (**1a**)



entry[a]	**1a** (eq.)	temp.(^{o}C)	yield (%)[b]	ee (%)[c]
1	**4**	**rt**	**56**	**87(98)[d]**
2	5	rt	52	82
3	6	rt	45	78
4	7	rt	42	78
5	2	rt	40	66
6	4	0	35	87
7	4	60	60	60

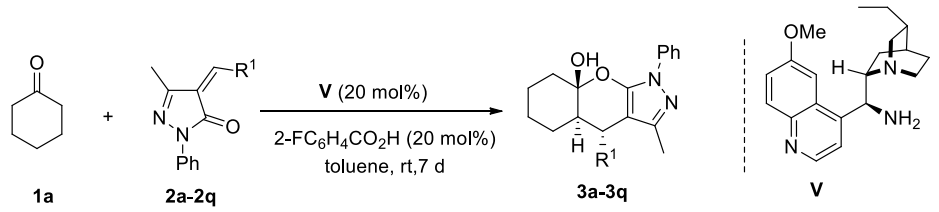
[a]0.2 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL solvent using 20 mol% catalyst and 20 mol% acid co-catalyst. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]Determined by HPLC using stationary phase chiral column. [d]After recrystallization.

5.8.4. Substrate scope:

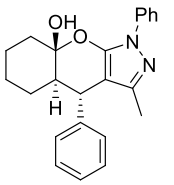
With an effective protocol for the enantioselective synthesis of tetrahydropyrano[2,3-*c*]pyrazole in hand, the scope of the cascade reaction was evaluated by using various benzylidene substitutents of the unsaturated pyrazolones (Table 5). At first, benzylidene pyrazolones, **2b**-**2n** having different *para*-substitutions on the phenyl groups were subjected into the optimized reaction conditions. The result of the reaction was not changed by varying the electronic nature of the *para*-substitutents of the phenyl group. For example, product **3b** having *para*-tolyl group was isolated with 45% yield and 80% ee. The enantioselectivity can be improved to >99% ee after single recrystallization. Interestingly, other 4-alkyl substituted pyrazolones **2c**-**2d** also provided the crystalline products **3c**-**3d** in moderate yields; and excellent enantioselectivities were achieved after recrystallization. Pyrazolone **2e** having 4-anisyl group also participated in the reaction and good result was obtained. The enantioselectivity of **3e** was further enhanced to 96% ee after recrystallization. Inspired by this outcome, other 4-alkoxysubstituted pyrazolones **2f**-**2j** were employed in the reaction. Here also the products **3f**-**3j** were obtained in good enantioselectivities and except product **3g**, other products could also be recrystallized and excellent enantioselectivities were detected. Then different 4-halo substituted aryl group containing pyrazolones **2k**-**2m** were checked and the corresponding products **3k**-**3m** were obtained in good enantioselectivities. As usual, enhancements in enantioselectivities were observed after recrystallization for **3l** and **3m** though compound **3k** was not crystalline. Biphenyl group containing pyrazolone **2n** also took part in the reaction and delivered the product **3n** in 80% ee (98% ee after recrystallization). Pyrazolones **2o** and **2p** having *meta*- and *ortho*-substituions were also well tolerated in the reaction, displaying good results. Finally, a disubstituted aryl group containing pyrazole **2q** was engaged in the reaction and 82% enantioselectivity was obtained for the product **3q**.

The scope of Michael-hemiketalization reaction was further explored on pyrazolones **2** having different *N*- and olefin substitutions (Table 6). Initially, a variety of *para*-substitutions on the phenyl group of nitrogen atom was screened and the results were pleasing. Delightfully, higher yield for the product **3r** having 4-tolyl substitution was realized and enhancement in enantioselectivity was observed after recrystallization.

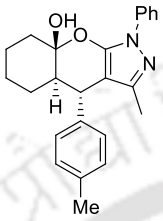
Table 5: Scope of pyrazolones with varied benzylidene substitutents[a,b,c]



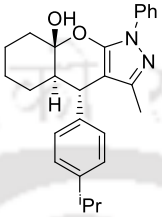
1a 2a-2q 3a-3q V



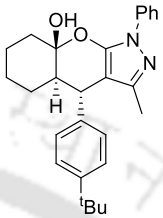
3a
57%, 87%(98%)[c] ee



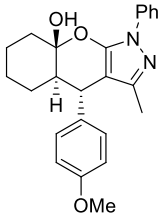
3b
45%, 80%(>99%)[c] ee



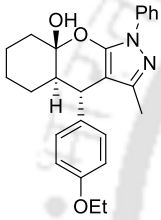
3c
62%, 84%(>99%)[c] ee



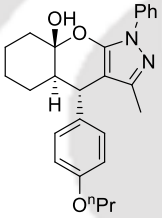
3d
61%, 86%(>99%)[c] ee



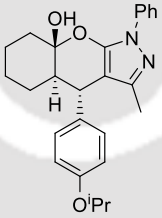
3e
52%, 82%(96%)[c] ee



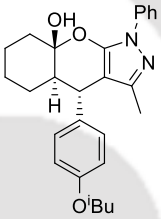
3f
41%, 88%(98%)[c] ee



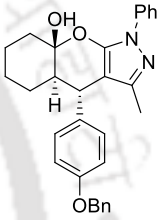
3g
42%, 82% ee



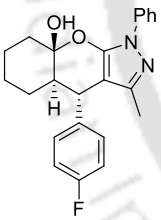
3h
35%, 84%(96%)[c] ee



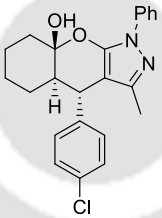
3i
42%, 82%(>99%)[c] ee



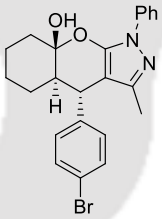
3j
54%, 84%(>99%)[c] ee



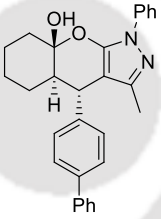
3k
53%, 84% ee



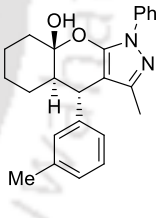
3l
44%, 82%(>99%)[c] ee



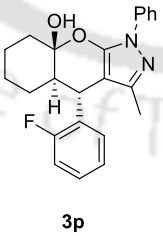
3m
47%, 78%(>99%)[c] ee



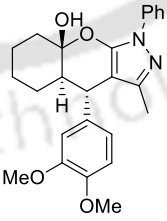
3n
62%, 80%(98%)[c] ee



3o
65%,80%(96%)[c] ee



3p
57%, 78%(99%)[c] ee

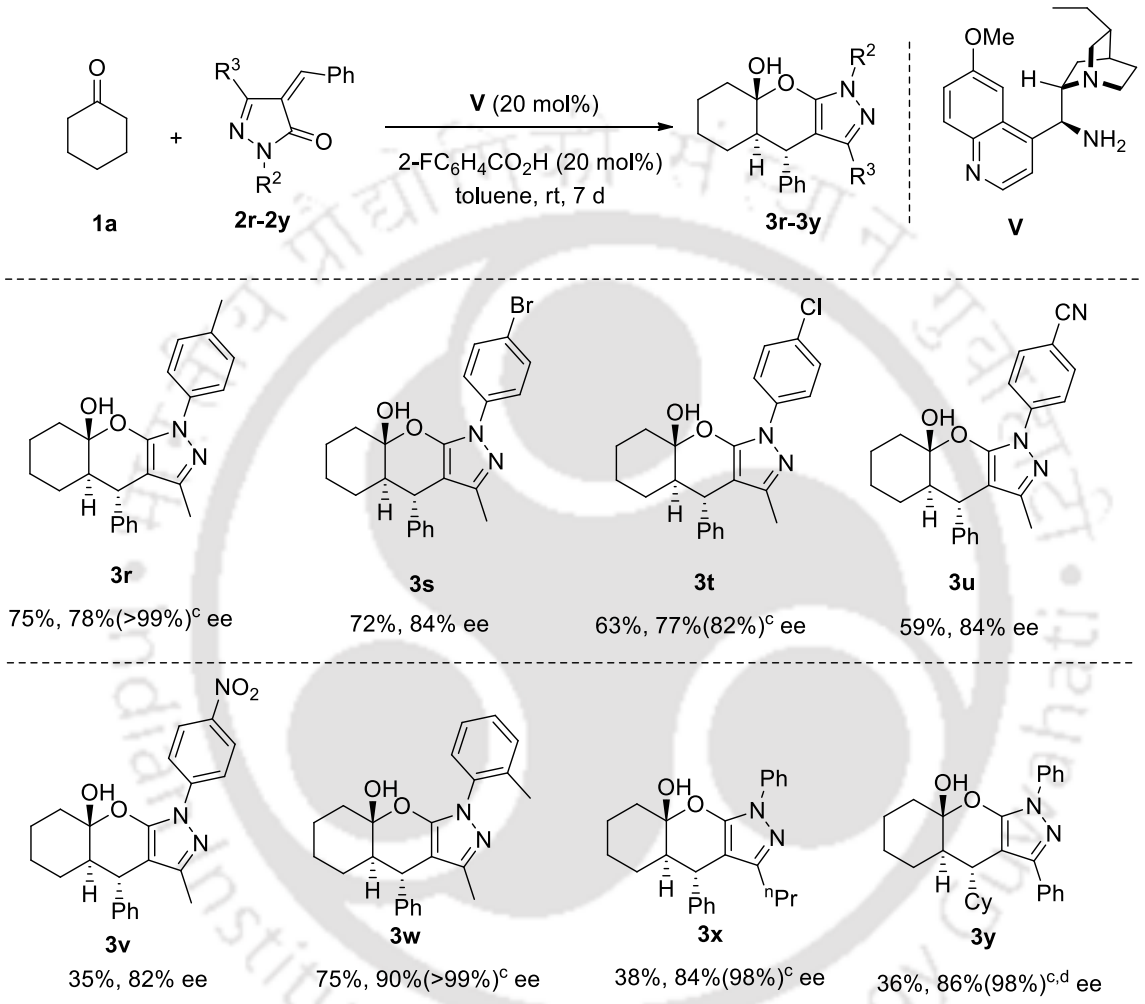


3q
42%, 82%(>99%)[c] ee

[a]Reaction conditions: Unless otherwise mentioned, 0.8 mmol of **1a** and 0.2 mmol of **2** were stirred with 20 mol% catalyst and 20 mol% 2-$FC_6H_4CO_2H$ in 2 mL toluene. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]Determined by HPLC and ee in parenthesis are after recrystallization.

Then 4-halo *N*-substituted unsaturated pyrazolones **2s-2t** were prepared and examined in the reaction; and good enantioselectivities were obtained for products **3s-3t**. Recrystallization of product **3t** has increased the enantioselectivity to 82% ee.

Table 6: Scope of pyrazolones with varied nitrogen substitutions[a,b,c,d]



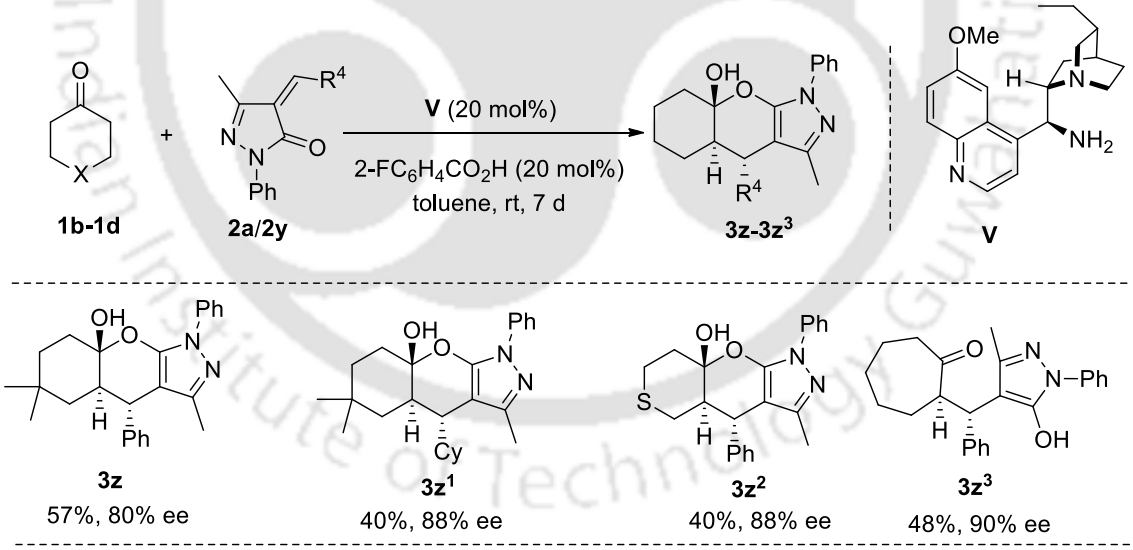
[a]Reaction conditions: Unless otherwise mentioned, 0.8 mmol of **1a** and 0.2 mmol of **2** were stirred with 20 mol% catalyst and 20 mol% 2-$FC_6H_4CO_2H$ in 2 mL toluene. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr). [c]Determined by HPLC and ee in parenthesis are after recrystallization. [d]Instead of benzylidene pyrazolone cyclohexylidene pyrazolone.

Moreover, electron poor *para*-substituted **2u** and **2v** having 4-cyano and 4-nitro groups provided good enantioselectivities with moderate yields. Then pyrazolone **2w** having 2-tolyl *N*-substitution was prepared and employed in the reaction. Gratifyingly, the desired tetrahydropyranopyrazole product **3w** was formed with 75% yield and 90% ee. Recrystallization of **3w** improved the enantioselectivity to >99% ee. Besides these, the olefin substituents in pyrazolones **2** were varied and smooth conversions were detected.

For example, pyrazolone **2x** having *n*-propyl substituent delivered the product **3x** in 84% ee and significant increase in the enantioselectivity was observed after recrystallization. Finally, a phenyl substituted cyclohexylidene pyrazolone **2y** was prepared and treated under the reaction condition. The desired product **3y** was isolated in 36% yield with 86% ee which can be augmented to 98% ee after recrystallization.

In the next phase, the scope of cyclic ketones was investigated. As shown in Table 7, different cyclohexanones **1b-1f** provided the corresponding products **3z-3z**^{5} with good enantiomeric excesses. 4,4-Dimethylcyclohexanone (**1b)** provided the products **3z** and **3z**^{1} after reacting with pyrazolones **2a** and **2y** in acceptable yields with good enantioselectivities. Interestingly, the enantioselectivity of **3z**^{1} was higher than **3z**. Similarly, on treatment of tetrahydrothiopyran-4-one **1c** with pyrazolone **2a**, product **3z**^{2} was formed in 40% yield with 88% ee. Moreover, cycloheptanone **1d** also participated in the reaction but only single Michael adduct **3z**^{3} was detected with 90% enantiomeric excess.

Table 7: Scope of Ketone[a,b,c]

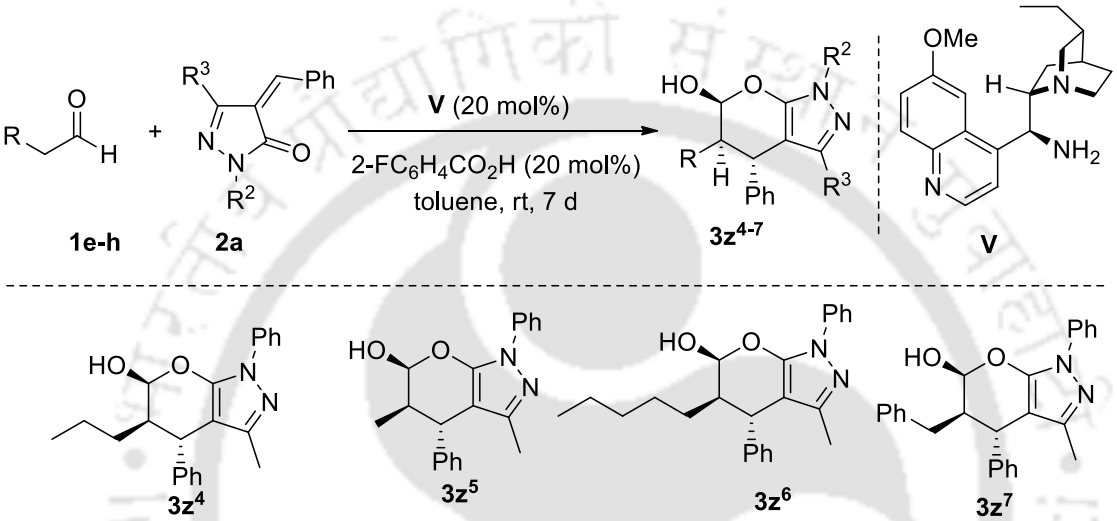


[a]Reaction conditions: 0.8 mmol of **1** and 0.2 mmol of **2** were stirred with 20 mol% catalyst **V** and 20 mol% 2-$FC_6H_4CO_2H$ in 2 mL toluene. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr) and ee was determined by chiral HPLC.

In addition, the scope of aldehydes was inspected (Table 8). Aldehydes **1e-1h** were tested for this reaction; delightfully their corresponding THPP products were obtained with goods to moderate enantiomeric excesses. Pentanal **1e** provided THPP product **3z**^{4} in 40% yield and 80% ee. Remarkably, the enantioselectivity of **3z**^{4} was further

improved to >99% ee after crystallization. Similarly, propionaldehyde **1f** also furnished product **3z**[5] with 72% ee and 45% yield. Taking inspiration from these results, other aldehydes such as heptanal **1g** and hydrocinnamaldehyde **1h** were also empolyed under the reaction condition. Unfortunately, the derised products **3z**[6] and **3z**[7] were attained in moderate yields with low level of enantiomeric excesses.

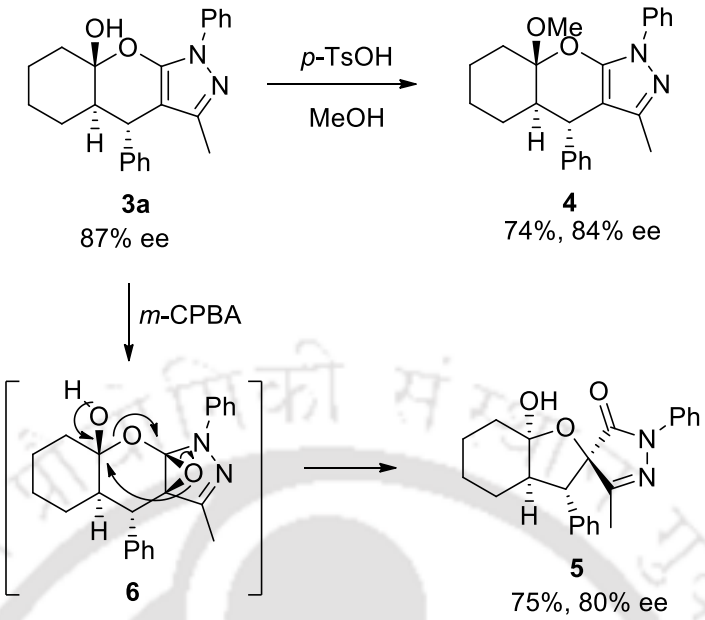
Table 8: Scope of aldehyde[a,b,c]



[a]Reaction conditions: 0.8 mmol of **1** and 0.2 mmol of **2** were stirred with 20 mol% catalyst **V** and 20 mol% 2-$FC_6H_4CO_2H$ in 2 mL toluene. [b]Isolated yield after silica gel column chromatography and obtained as single diastereomer (>20:1 dr) and ee was determined by chiral HPLC. [c]Determined by HPLC and ee in parenthesis are after recrystallization.

5.8.5. Synthetic transformations of product 3a:

The synthetic utility of our method was shown by performing few reactions on **3a** (Scheme 12). Initially, the hemiacetal group of **3a** was converted to acetal **4** by treatment with MeOH and *p*-TsOH[23a] and the enantioselectivity was almost retained. Then **3a** was stirred with *m*-CPBA in dichloromethane. This resulted in the unexpected formation of spiro derivative **5**[24] in good yield with 80% ee, and excellent diastereoselectivity was maintained. The structure of **5** was confirmed by X-ray crystallography.[25] The formation of **5** can be explained that at first epoxide **6** is formed which then underwent ring-opening reaction followed by diastereoselective hemiacetal formation (Scheme 12).



Scheme 12

5.8.6. Absolute configuration:

The absolute structure of **3l** was determined to be (4*S*, 4*aR*, 8*aS*) by X-ray crystallography (Figure 3).[26] The other products are assumed to possess the same absolute configuration.

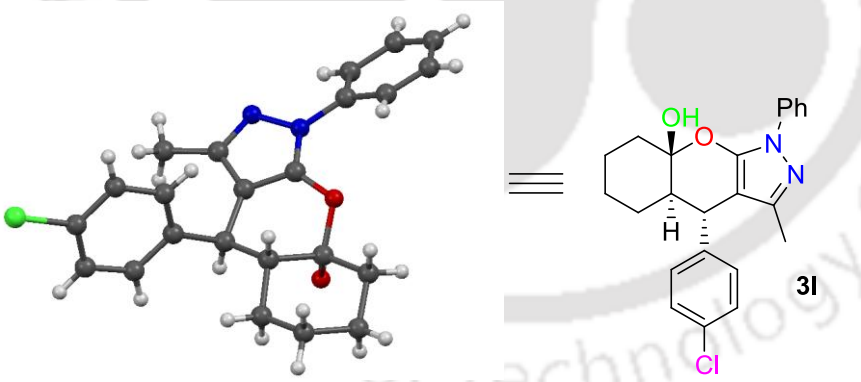
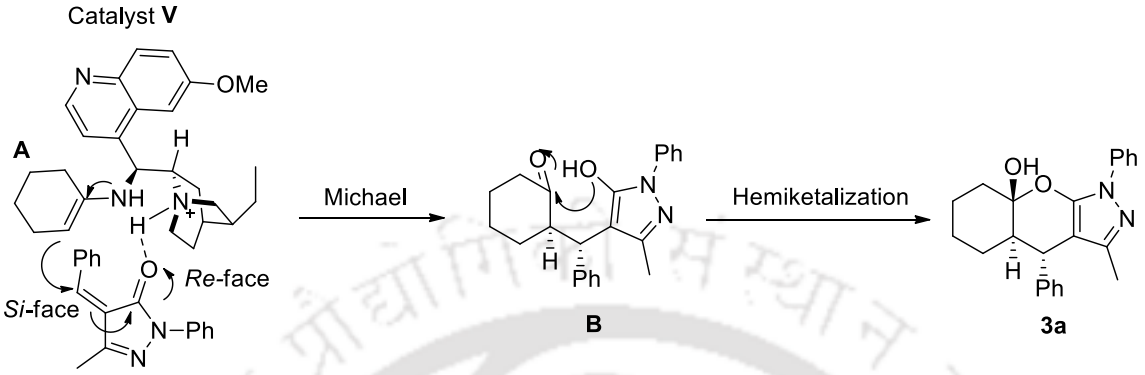


Figure 3. Ortep daigram of compound **3l**.

5.8.6. Possible mechanism:

After conforming the absolute structure of the compound **3**, a possible transition state **A** has been drawn (Scheme 13). It is believed that first cyclohexanone **1a** reacts with catalyst **V** and provide enamine intermediate, and simultaneous unsaturated pyrazolone **2a** is activated by the protonated tertiary amino group of catalyst **V** from *Re*-face. Thus, attack of cyclohexanone takes place from *Si*-face of the unsaturated pyrazolone, because

Re-face was block by catalyst **V**, generate intermediate **B**. Then, final product **3a** is obtained followed by the hemiketalization reaction.



Scheme 13. Possible mechanism

5.9. Conclusion:

This chapter reported a convenient diastereo- and enantioselective synthesis of tetrahydropyrano[2,3-*c*]pyrazoles by the reaction between alkylidene pyrazolones and cyclic ketones. Linear aldehydes were also employed in the reaction. The reaction is catalyzed by easily available hydroquinine derived primary amine and 2-flurobenzoic acid. The tetrahydro[2,3-*c*]pyranopyrazole products having three contiguous stereogenic centers are significant use in pharmaceuticals and for natural products syntheses.

5.10. Experiment section:

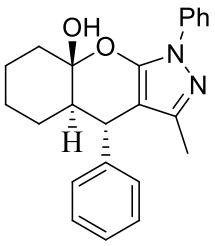
5.10.1. General procedure for the synthesis of compound 3:

To a solution of unsaturated pyrazolones **1** (0.2 mmol), ketones or aldehydes **2** (0.8 mmol) in 2 mL of toluene were added **V** (20 mol%) and 2-$FC_6H_4CO_2H$ (20 mol%). The reaction mixture was stirred at room temperature for 7 days. After completion of reaction, the products were purified by silica gel column chromatography (hexane/ethyl acetate).

5.10.2. Products characterizing:

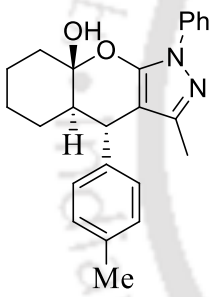
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1,4-diphenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3a):

Yellow solid (41 mg, 57% yield); mp- 205-206 ^oC; R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.31 (dd, *J*



= 16.1, 9.0 Hz, 3H), 7.21 (dd, *J* = 14.9, 7.3 Hz, 3H), 3.59 (d, *J* = 10.7 Hz, 1H), 2.72 (s, 1H), 2.12 (d, *J* = 17.1 Hz, 1H), 1.93 (td, *J* = 12.9, 3.8 Hz, 2H), 1.85 – 1.63 (m, 4H), 1.61 (s, 3H), 1.33 (dd, *J* = 21.7, 8.8 Hz, 2H), 1.17 – 1.11 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 147.2, 142.0, 138.9, 129.0, 128.6, 126.9, 125.4, 120.5, 103.3, 100.1, 47.9, 40.5, 38.5, 26.9, 25.6, 23.2, 13.5; **ESI-MS** m/z calcd. for $C_{23}H_{25}N_2O_2^+$ $[M+H]^+$ 361.1911, found 361.1918; **FT-IR (KBr)** 3440, 2928, 2855, 1701, 1599, 1515, 1499, 1455, 1387, 1215, 1130, 1051, 1020, 923 cm $^{-1}$; The ee values 87% (t_{major} = 7.18 min, t_{minor} = 9.15 min) and after recrystallization 98% were determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{28.2}$ = + 16.34 (c 0.355, $CHCl_3$).

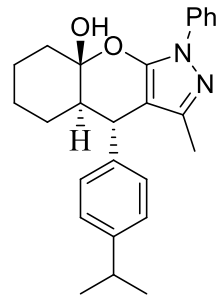
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenyl-4-p-tolylchromeno[2,3-*c*]pyrazol-8*a*-ol (3b):



White semi solid (34 mg, 45% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.11 (q, *J* = 8.2 Hz, 4H), 3.54 (d, *J* = 10.7 Hz, 1H), 2.94 (s, 1H), 2.35 (s, 3H), 2.06 (dd, *J* = 44.0, 15.7 Hz, 2H), 1.90 (t, *J* = 11.6 Hz, 1H), 1.75 (dd, *J* = 23.4, 11.6 Hz, 3H), 1.62 (s, 3H), 1.57 (d, *J* = 14.4 Hz, 1H), 1.31 (dd, *J* = 24.2, 11.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 147.4, 138.8, 136.4, 129.3, 129.1, 128.8, 125.4, 120.5, 119.5, 103.3, 102.0, 47.9, 40.1, 38.7, 34.6, 26.9, 25.7, 23.2, 21.3, 13.6; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2069; **FT-IR (KBr)** 3440, 2924, 2853, 1701, 1599, 1515, 1496, 1452, 1387, 1215, 1125, 1051, 1020, 921 cm $^{-1}$; The ee values 80% (t_{major} = 6.45 min, t_{minor} = 26.70 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{29}$ = + 35.18 (c 0.520, $CHCl_3$).

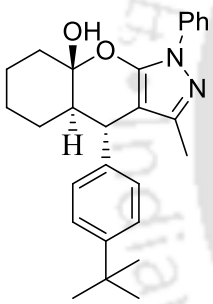
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-4-(4-isopropylphenyl)-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3c):

Yellow sticky (50 mg, 62% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 20.2, 8.0 Hz, 4H), 3.72 (q, *J* = 7.0 Hz, 1H), 3.55 (d, *J* = 10.7 Hz, 1H), 2.88 (ddd,



J = 22.4, 14.7, 5.9 Hz, 2H), 2.11 (d, *J* = 13.5 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.81 – 1.75 (m, 2H), 1.74 – 1.68 (m, 2H), 1.60 (s, 3H), 1.35 – 1.28 (m, 2H), 1.25 (d, *J* = 6.5 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 147.5, 139.0, 129.2, 128.9, 127.6, 127.4, 126.9, 126.6, 125.5, 125.3, 120.5, 119.7, 103.3, 100.3, 47.8, 42.1, 40.1, 38.5, 33.9, 26.9, 25.7, 24.2, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{31}N_2O_2^+$ $[M+H]^+$ 403.2380, found 403.2379; **FT-IR (KBr)** 3434, 2920, 2853, 2357, 1725, 1630, 1599, 1511, 1502, 1444, 1380, 1127, 925 cm^{-1}; The ee values 84% (t_{major} = 5.86 min, t_{minor} = 23.50 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC; **Optical Rotation**: $[\alpha]_D^{29.5}$ = + 40.38 (c 0.520, $CHCl_3$).

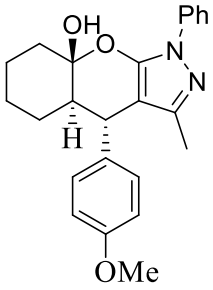
(4*S*,4*aR*,8*aS*)-4-(4-*tert*-butylphenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3d):



White solid (51 mg, 61% yield); mp- 210-211 ^oC; R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 2H), 3.55 (d, *J* = 10.8 Hz, 1H), 2.89 (s, 1H), 2.10 (d, *J* = 15.1 Hz, 1H), 1.91 (td, *J* = 13.7, 4.2 Hz, 1H), 1.82 – 1.67 (m, 4H), 1.59 (s, 3H), 1.32 (s, 9H), 1.27 (d, *J* = 10.7 Hz, 1H), 1.24 (d, *J* = 16.2 Hz, 1H), 1.15 (dt, *J* = 13.2, 3.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.8, 148.4, 139.0, 138.6, 129.0, 128.9, 125.7, 125.4, 120.5, 119.7, 103.3, 100.3, 49.8, 47.7, 44.1, 39.9, 38.5, 34.6, 31.6, 23.2, 13.5; **ESI-MS** m/z calcd. for $C_{27}H_{33}N_2O_2^+$ $[M+H]^+$ 417.2537, found 417.2542; **FT-IR (KBr)** 3440, 2926, 2855, 2357, 1725, 1625, 1599, 1511, 1509, 1452, 1380, 1127, 921 cm^{-1}; The ee values 86% (t_{major} = 7.24 min, t_{minor} = 36.64 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC; **Optical Rotation**: $[\alpha]_D^{29.2}$ = + 45.22 (c 0.575, $CHCl_3$).

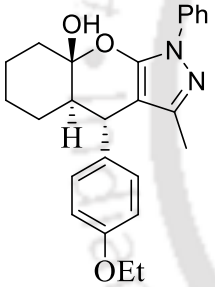
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-4-(4-methoxyphenyl)-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3e):

White semi solid (41 mg, 52% yield); R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.54 (d, *J* = 10.7 Hz, 1H), 2.89



(d, *J* = 15.9 Hz, 1H), 2.10 (d, *J* = 13.6 Hz, 1H), 1.91 (td, *J* = 13.7, 4.1 Hz, 1H), 1.77 – 1.70 (m, 3H), 1.63 (s, 3H), 1.57 (d, *J* = 13.9 Hz, 2H), 1.31 (dd, *J* = 12.8, 3.1 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 158.6, 148.4, 147.3, 138.9, 133.9, 129.0, 125.4, 120.5, 119.5, 113.9, 103.3, 100.3, 55.4, 47.9, 39.6, 38.5, 26.9, 25.7, 23.2, 13.6; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_3^+$ $[M+H]^+$ 391.2016, found 391.2016; **FT-IR (KBr)** 3439, 2923, 2853, 2357, 1723, 1651, 1590, 1517, 1502, 1455, 1390, 1127, 925 cm^{-1}; The ee values 82% (t_{major} = 6.31 min, t_{minor} = 20.88 min) and after recrystallization 96% were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.3}$ = + 40.62 (c 0.650, $CHCl_3$).

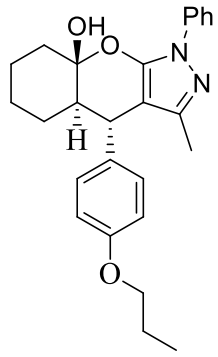
(4*S*,4*aR*,8*aS*)-4-(4-ethoxyphenyl)-1,4,4a,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3f):



White semi solid (33 mg, 41% yield); R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.03 (dd, *J* = 14.0, 7.0 Hz, 2H), 3.53 (d, *J* = 10.7 Hz, 1H), 2.73 (s, 1H), 2.11 (d, *J* = 13.5 Hz, 1H), 1.91 (td, *J* = 13.6, 3.5 Hz, 1H), 1.79 – 1.66 (m, 4H), 1.64 (s, 3H), 1.42 (t, *J* = 6.9 Hz, 3H), 1.35 – 1.28 (m, 2H), 1.17 – 1.13 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.0, 147.4, 138.8, 133.7, 129.9, 129.1, 125.7, 125.6, 120.6, 119.1, 114.6, 114.3, 63.6, 47.9, 39.7, 32.2, 32.0, 25.7, 22.9, 15.1, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{29}N_2O_3^+$ $[M+H]^+$ 405.2173, found 405.2185; **FT-IR (KBr)** 3443, 2929, 2855, 1597, 1514, 1498, 1454, 1381, 1244, 1123, 1050, 1018, 923 cm^{-1}; The ee values 88% (t_{major} = 42.70 min, t_{minor} = 51.46 min) and after recrystallization 98% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (99:1) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{29.6}$ = + 28.57 (c 0.210, $CHCl_3$).

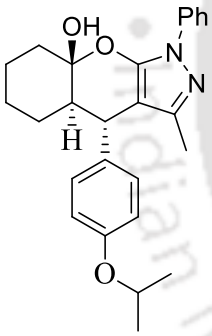
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenyl-4-(4-propoxyphenyl)chromeno[2,3-*c*]pyrazol-8*a*-ol (3g):

White solid (35 mg, 42% yield); mp- 200-201°C; R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.92 (t, *J* = 6.6 Hz, 2H), 3.53



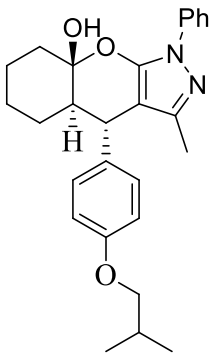
(d, *J* = 10.7 Hz, 1H), 2.81 (s, 1H), 2.10 (d, *J* = 16.8 Hz, 1H), 1.91 (td, *J* = 13.7, 4.2 Hz, 1H), 1.81 (dd, *J* = 14.0, 6.9 Hz, 2H), 1.74 (ddd, *J* = 23.0, 20.4, 13.3 Hz, 4H), 1.64 (s, 3H), 1.57 (s, 1H), 1.34 – 1.27 (m, 1H), 1.14 (ddd, *J* = 16.7, 13.1, 9.7 Hz, 1H), 1.05 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.1, 148.4, 147.4, 138.9, 133.7, 129.7, 129.0, 125.4, 120.5, 114.5, 103.3, 100.4, 69.6, 47.9, 39.6, 38.5, 26.9, 25.7, 23.2, 22.8, 13.5, 10.8; **ESI-MS** m/z calcd. for $C_{26}H_{31}N_2O_3^+$ $[M+H]^+$ 419.2329, found 419.2319; **FT-IR (KBr)** 3115, 2922, 2853, 1705, 1602, 1520, 1500, 1453, 1389, 1260, 1217, 1124, 1051, 925 cm $^{-1}$; The ee values 82% (t_{major} = 7.09 min, t_{minor} = 8.30 min) was determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; ; **Optical Rotation**: $[\alpha]_D^{29.8}$ = + 42.26 (c 0.530, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4a,5,6,7,8,8*a*-octahydro-4-(4-isopropoxyphenyl)-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3h):



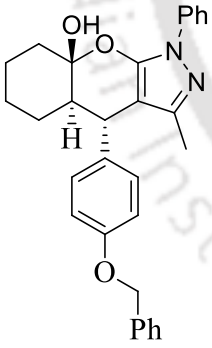
White semi solid (29 mg, 35% yield); R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.18 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 4.56 – 4.52 (m, 1H), 3.52 (d, *J* = 10.7 Hz, 1H), 2.34 – 2.31 (m, 1H), 2.11 (dd, *J* = 26.1, 9.4 Hz, 2H), 2.02 (t, *J* = 9.4 Hz, 1H), 1.92 (dd, *J* = 24.8, 11.9 Hz, 2H), 1.87 – 1.80 (m, 2H), 1.64 (s, 3H), 1.33 (d, *J* = 3.4 Hz, 6H), 1.15 (d, *J* = 10.8 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 156.9, 148.3, 133.6, 129.9, 129.1, 129.0, 125.4, 120.5, 119.1, 116.0, 103.2, 100.3, 70.0, 47.9, 39.7, 38.6, 32.1, 26.9, 25.7, 22.3, 13.6; **ESI-MS** m/z calcd. for $C_{26}H_{31}N_2O_2^+$ $[M+H]^+$ 419.2329, found 419.2328; **FT-IR (KBr)** 3443, 2925, 2852, 1715, 1603, 1508, 1454, 1384, 1266, 1238, 1028, 955 cm $^{-1}$; The ee values 84% (t_{major} = 10.70 min, t_{minor} = 13.59 min) and after recrystallization 96% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (97:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{29.4}$ = + 22.86 (c 0.210, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4a,5,6,7,8,8*a*-octahydro-4-(4-isobutoxyphenyl)-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3i):



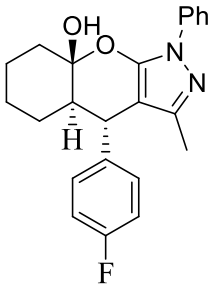
White solid (36 mg, 42% yield); mp- 199-200°C; R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 3.74 (d, *J* = 6.5 Hz, 2H), 3.55 (d, *J* = 10.7 Hz, 1H), 2.87 (s, 1H), 2.11 (dt, *J* = 13.1, 10.1 Hz, 2H), 1.93 (td, *J* = 13.6, 4.0 Hz, 1H), 1.80 – 1.73 (m, 3H), 1.67 (s, 3H), 1.60 (dd, *J* = 13.0, 2.3 Hz, 1H), 1.35 (dd, *J* = 12.6, 3.4 Hz, 1H), 1.31 (d, *J* = 4.3 Hz, 1H), 1.18 – 1.14 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.3, 148.4, 147.3, 139.0, 133.6, 129.8, 129.0, 125.3, 120.5, 114.6, 103.3, 100.4, 74.6, 48.0, 39.5, 38.5, 28.5, 26.9, 25.7, 23.2, 19.5, 13.7; **ESI-MS** m/z calcd. for $C_{27}H_{33}N_2O_3^+$ $[M+H]^+$ 433.2484, found 433.2484; **FT-IR (KBr)** 3424, 2924, 2855, 1693, 1603, 1570, 1521, 1489, 1458, 1384, 1275, 1069, 1025 cm^{-1}; The ee values 82% (t_{major} = 15.12 min, t_{minor} = 20.09 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (98:2) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.2}$ = + 34.69 (c 0.490, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-4-(4-(benzyloxy)phenyl)-1,4,4a,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3j):



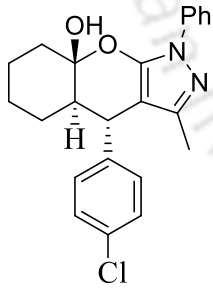
White solid (50 mg, 54% yield); mp- 190-191°C; R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 4.3 Hz, 2H), 7.39 (t, *J* = 7.1 Hz, 4H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 5.05 (s, 2H), 3.54 (d, *J* = 10.8 Hz, 1H), 2.82 (s, 1H), 2.14 – 2.11 (m, 1H), 1.91 (t, *J* = 13.6 Hz, 1H), 1.76 – 1.69 (m, 3H), 1.64 (s, 1H), 1.58 (d, *J* = 13.9 Hz, 2H), 1.33 – 1.28 (m, 1H), 1.14 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.8, 137.2, 129.0, 128.7, 128.2, 127.8, 125.4, 120.5, 118.9, 114.9, 103.3, 100.3, 70.2, 47.9, 39.6, 38.5, 29.9, 25.6, 23.2, 13.6; **ESI-MS** m/z calcd. for $C_{30}H_{31}N_2O_3^+$ $[M+H]^+$ 467.2329, found 467.2329; **FT-IR (KBr)** 3429, 2924, 2855, 1693, 1609, 1575, 1521, 1489, 1458, 1388, 1275, 1069, 1025 cm^{-1}; The ee values 84% (t_{major} = 10.08 min, t_{minor} = 14.38 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm; **Optical Rotation**: $[\alpha]_D^{30.9}$ = + 33.09 (c 0.810, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-4-(4-fluorophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3k):



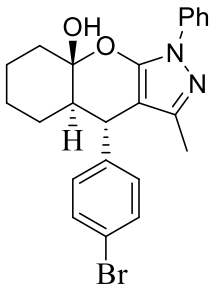
White semi solid (40 mg, 53% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.22 – 7.16 (m, 3H), 7.01 (t, *J* = 8.5 Hz, 2H), 3.58 (d, *J* = 10.7 Hz, 1H), 2.95 (s, 1H), 2.10 (d, *J* = 11.7 Hz, 1H), 1.91 (td, *J* = 13.7, 4.1 Hz, 1H), 1.79 – 1.65 (m, 4H), 1.61 (s, 3H), 1.53 (d, *J* = 12.7 Hz, 1H), 1.32 (dd, *J* = 27.2, 14.5 Hz, 1H), 1.14 (dd, *J* = 24.7, 11.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 163.2, 160.7, 147.3, 139.0, 137.8, 135.1, 132.9, 130.5, 129.1, 128.9, 125.6, 120.7, 119.5, 115.6, 115.4, 103.2, 99.9, 48.2, 43.9, 39.9, 26.9, 25.5, 23.2, 13.1; **ESI-MS** m/z calcd. for $C_{23}H_{24}FN_2O_2^+$ $[M+H]^+$ 379.1816, found 379.1816; **FT-IR (KBr)** 3121, 2923, 2853, 1700, 1610, 1520, 1496, 1456, 1389, 1260, 1217, 1124, 1051, 948 cm $^{-1}$; The ee values 84% (t_{major} = 39.727 min, t_{minor} = 54.54 min) .was determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (99:1) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.0}$ = + 21.29 (c 0.565, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-4-(4-chlorophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3l):



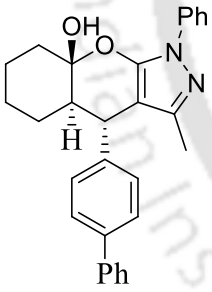
White semi solid (35 mg, 44% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.15 (m, 2H), 3.58 (d, *J* = 10.5 Hz, 1H), 2.19 – 2.11 (m, 1H), 1.95 – 1.84 (m, 1H), 1.75 (s, 2H), 1.62 (s, 3H), 1.52 (d, *J* = 11.4 Hz, 1H), 1.16 – 1.03 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 148.4, 146.9, 140.7, 132.7, 131.6, 129.1, 128.8, 125.6, 120.6, 119.5, 103.2, 99.8, 47.9, 40.1, 38.6, 32.1, 26.9, 22.9, 14.3; **ESI-MS** m/z calcd. for $C_{23}H_{24}ClN_2O_2^+$ $[M+H]^+$ 395.1521, found 395.1520; **FT-IR (KBr)** 3464, 2922, 2855, 1708, 1597, 1517, 1492, 1451, 1390, 1273, 1216, 1120, 1095, 917 cm $^{-1}$; The ee values 82% (t_{major} = 6.38 min, t_{minor} = 20.04 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(4*S*,4*aR*,8*aS*)-4-(4-bromophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-c]pyrazol-8*a*-ol (3m):



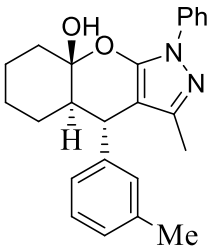
White solid (42 mg, 47% yield); mp- 205-206 °C; R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.57 (d, *J* = 10.7 Hz, 1H), 2.87 (s, 1H), 2.12 – 2.07 (m, 1H), 1.91 (td, *J* = 13.7, 4.2 Hz, 1H), 1.77 – 1.69 (m, 3H), 1.63 (s, 3H), 1.52 (d, *J* = 11.8 Hz, 1H), 1.38 – 1.22 (m, 2H), 1.13 (dt, *J* = 13.2, 3.6 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** 148.7, 147.0, 141.2, 138.9, 131.8, 130.6, 129.1, 125.6, 120.7, 120.5, 103.2, 99.7, 47.8, 40.1, 38.6, 26.9, 25.6, 23.1, 13.7; **ESI-MS** m/z calcd. for $C_{23}H_{24}BrN_2O_2^+$ $[M+H]^+$ 439.1016, found 439.1016; **FT-IR (KBr)** 3439, 2929, 2855, 1603, 1521, 1483, 1454, 1387, 1371, 1273, 1212, 1123, 1069, 923 cm $^{-1}$; The ee values 78% (t_{major} = 8.40 min, t_{minor} = 9.95 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.4}$ = + 71.95 (c 0.397, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-4-(biphenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3n):



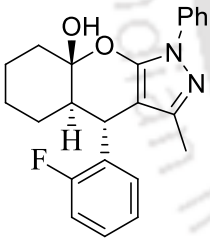
White semi solid (54 mg, 62% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.77 (t, *J* = 8.6 Hz, 3H), 7.41 (dt, *J* = 15.8, 7.8 Hz, 4H), 7.20 (dd, *J* = 16.5, 9.2 Hz, 2H), 7.04 – 7.00 (m, 1H), 6.99 (s, 2H), 6.96 (s, 1H), 6.92 (dd, *J* = 17.3, 10.2 Hz, 1H), 3.94 (d, *J* = 10.8 Hz, 1H), 2.85 (s, 1H), 2.11 (d, *J* = 13.3 Hz, 2H), 1.92 (td, *J* = 13.8, 4.0 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.75 (d, *J* = 14.3 Hz, 1H), 1.57 (s, 3H), 1.39 – 1.36 (m, 1H), 1.16 – 1.13 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.4, 147.3, 141.1, 140.9, 139.8, 139.0, 129.0, 128.9, 127.4, 127.3, 127.2, 125.4, 120.5, 119.5, 103.2, 100.2, 47.9, 40.2, 38.7, 27.0, 25.7, 23.2, 13.7; **ESI-MS** m/z calcd. for $C_{29}H_{29}N_2O_2^+$ $[M+H]^+$ 437.2224, found 437.2216; **FT-IR (KBr)** 3455, 2933, 2851, 1601, 1518, 1497, 1454, 1391, 1274, 1211, 1024, 919 cm^{-1}; The ee values 80% (t_{major} = 8.55 min, t_{minor} = 11.25 min) and after recrystallization 98% were determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.8}$ = + 39.05 (c 0.210, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4a,5,6,7,8,8*a*-octahydro-3-methyl-1-phenyl-4-*m*-tolylchromeno[2,3-*c*]pyrazol-8*a*-ol (3o):



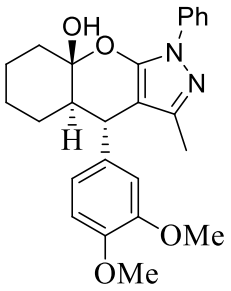
White semi solid (51 mg, 65% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.01 (s, 2H), 3.53 (d, *J* = 10.7 Hz, 1H), 3.22 (s, 1H), 2.33 (s, 3H), 2.09 (d, *J* = 13.4 Hz, 1H), 1.89 (td, *J* = 13.6, 3.9 Hz, 1H), 1.81 – 1.73 (m, 2H), 1.69 (d, *J* = 17.0 Hz, 2H), 1.60 (s, 3H), 1.56 (d, *J* = 13.2 Hz, 1H), 1.31 (dd, *J* = 12.8, 3.1 Hz, 1H), 1.15 – 1.11 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 147.4, 141.9, 138.9, 138.1, 129.0, 128.9, 128.4, 127.7, 125.4, 120.5, 119.6, 103.3, 100.2, 47.8, 40.4, 38.5, 26.9, 25.6, 24.9, 23.2, 13.5; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2060; **FT-IR (KBr)** 3431, 2929, 2852, 1711, 1597, 1514, 1492, 1463, 1394, 1371, 1273, 1209, 1022, 917 cm $^{-1}$; The ee values 80% (t_{major} = 9.17 min, t_{minor} = 13.64 min) and after recrystallization 96% were determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.8}$ = + 22.79 (c 0.825, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-4-(3-fluorophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3p):



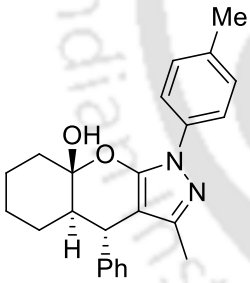
White semi solid (43 mg, 57% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.21 (td, *J* = 12.3, 6.5 Hz, 3H), 7.10 (t, *J* = 7.5 Hz, 2H), 4.17 (d, *J* = 10.4 Hz, 1H), 2.85 (s, 1H), 2.13 – 2.08 (m, 1H), 1.96 – 1.88 (m, 1H), 1.74 (t, *J* = 15.8 Hz, 3H), 1.61 (s, 3H), 1.55 (s, 2H), 1.49 – 1.41 (m, 1H), 1.18 – 1.14 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.9, 146.8, 139.0, 129.1, 128.3, 125.5, 124.7, 124.3, 120.6, 120.4, 119.7, 115.8, 115.6, 115.4, 115.3, 103.3, 99.3, 49.5, 38.5, 29.5, 27.9, 26.9, 25.6, 23.1, 13.1; **ESI-MS** m/z calcd. for $C_{23}H_{24}FN_2O_2^+$ $[M+H]^+$ 379.1816, found 379.1816; **FT-IR (KBr)** 3119, 2923, 2853, 1700, 1602, 1520, 1496, 1453, 1389, 1265, 1217, 1124, 1051, 948 cm $^{-1}$; The ee values 78% (t_{major} = 4.99 min, t_{minor} = 7.20 min) and after recrystallization 99% were determined by HPLC using Daicel Chiralpak IC with hexane/EtOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.0}$ = + 30.98 (c 0.510, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-4-(3,4-dimethoxyphenyl)-3-methyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3q):



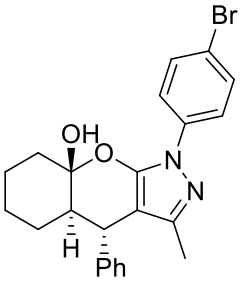
Yellow semi solid (35 mg, 42% yield); R_f value 0.20 (5:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.7 Hz, 2H), 7.39 (t, *J* = 8.0 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.69 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.53 (d, *J* = 10.8 Hz, 1H), 2.91 (s, 1H), 2.13 – 2.08 (m, 1H), 1.92 (td, *J* = 13.7, 4.1 Hz, 1H), 1.78 – 1.68 (m, 4H), 1.66 (s, 3H), 1.58 (d, *J* = 12.5 Hz, 1H), 1.31 (ddd, *J* = 16.0, 13.2, 3.4 Hz, 1H), 1.15 (dt, *J* = 13.3, 3.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.2, 148.5, 147.9, 147.4, 138.9, 134.4, 129.0, 125.3, 120.4, 119.0, 114.2, 110.9, 103.4, 100.2, 56.1, 55.9, 47.8, 42.1, 27.1, 25.7, 25.1, 23.2, 13.5; **ESI-MS** m/z calcd. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 421.2122, found 421.2113; **FT-IR (KBr)** 3464, 2925, 2852, 1702, 1594, 1514, 1454, 1387, 1263, 1235, 1142, 1025, 914 cm^{-1}; The ee values 82% (t_{major} = 7.70 min, t_{minor} = 10.07 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{31.1}$ = + 37.60 (c 0.250, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4a,5,6,7,8,8*a*-octahydro-3-methyl-4-phenyl-1-*p*-tolylchromeno[2,3-*c*]pyrazol-8*a*-ol (3r):



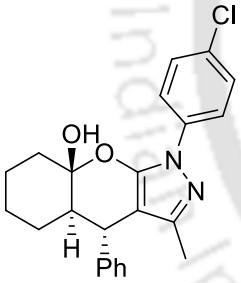
White solid (56 mg, 75%); mp- 188-189 °C; R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 3.58 (d, *J* = 10.8 Hz, 1H), 2.78 (s, 1H), 2.36 (s, 3H), 2.10 (d, *J* = 13.5 Hz, 1H), 1.91 (td, *J* = 13.7, 4.2 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.72 (dd, *J* = 27.1, 13.2 Hz, 3H), 1.60 (s, 3H), 1.56 (s, 1H), 1.33 (dd, *J* = 24.0, 11.2 Hz, 1H), 1.13 (dd, *J* = 26.3, 13.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.1, 135.2, 135.1, 132.8, 129.6, 128.9, 128.6, 126.9, 124.1, 120.8, 119.6, 117.1, 49.5, 42.9, 40.6, 34.5, 25.6, 22.8, 21.1, 13.4; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2067; **FT-IR (KBr)** 3435, 2925, 2850, 1721, 1705, 1599, 1518, 1505, 1455, 1388, 1129, 923 cm^{-1}; The ee values 78% (t_{major} = 6.96 min, t_{minor} = 11.63 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.5}$ = + 14.63 (c 0.410, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1-(4-bromophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-4-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3s):



White solid (63 mg, 72% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 (s, 1H), 7.21 (d, *J* = 7.1 Hz, 2H), 3.57 (d, *J* = 10.7 Hz, 1H), 2.91 (s, 1H), 2.14 – 2.07 (m, 1H), 1.92 (td, *J* = 13.7, 4.0 Hz, 1H), 1.83 – 1.66 (m, 4H), 1.64 (d, *J* = 3.6 Hz, 1H), 1.58 (s, 3H), 1.33 (dd, *J* = 25.5, 12.9 Hz, 1H), 1.17 – 1.12 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.9, 141.7, 137.8, 135.5, 132.9, 132.2, 128.7, 127.1, 124.3, 121.8, 120.7, 117.2, 49.8, 40.5, 34.4, 32.1, 25.9, 25.6, 13.5; **ESI-MS** m/z calcd. for $C_{23}H_{24}BrN_2O_2^+$ $[M+H]^+$ 439.1016, found 439.1016; **FT-IR (KBr)** 3439, 2925, 2855, 1605, 1525, 1483, 1453, 1386, 1371, 1272, 1212, 1123, 1069, 923 cm^{-1}; The ee values 84% (t_{major} = 6.48 min, t_{minor} = 7.31 min) was determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm; **Optical Rotation**: $[\alpha]_D^{31.0}$ = + 19.88 (c 0.835, $CHCl_3$).

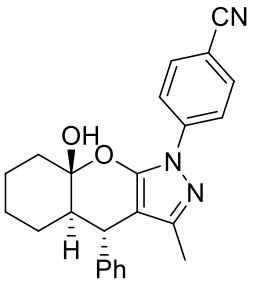
(4*S*,4*aR*,8*aS*)-1-(4-chlorophenyl)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-4-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3t):



White solid (50 mg, 63% yield); Rf value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.29 (m, 5H), 7.21 (d, *J* = 6.6 Hz, 2H), 3.58 (d, *J* = 10.7 Hz, 1H), 2.90 (s, 1H), 2.14 – 2.07 (m, 1H), 1.92 (t, *J* = 13.7 Hz, 1H), 1.83 – 1.67 (m, 4H), 1.63 (d, *J* = 13.4 Hz, 2H), 1.59 (s, 3H), 1.33 (dd, *J* = 19.1, 6.7 Hz, 1H), 1.16 – 1.09 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.8, 141.7, 137.3, 135.3, 132.9, 130.7, 129.1, 128.7, 127.0, 124.2, 121.6, 117.1, 44.7, 40.5, 32.1, 25.6, 22.9, 13.4; **ESI-MS** m/z calcd. for $C_{23}H_{24}ClN_2O_2^+$ $[M+H]^+$ 395.1521, found 395.1520; **FT-IR (KBr)** 3464, 2922, 2855, 1708, 1597, 1517, 1492, 1451, 1390, 1273, 1216, 1120, 1095, 917 cm^{-1};The ee values 77% (t_{major} = 11.40 min, t_{minor} = 15.40 min,) and after recrystallization 82% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (98:2) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

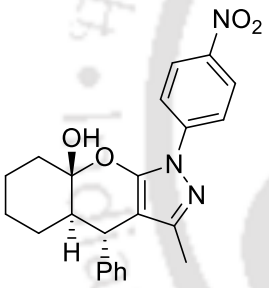
4-((4*S*,4*aR*,8*aS*)-4*a*,5,6,7,8,8*a*-hexahydro-8*a*-hydroxy-3-methyl-4-phenylchromeno[2,3-*c*]pyrazol-1(4*H*)-yl)benzonitrile (3u):

Yellow solid (45 mg, 59% yield); mp- 195-200 ^oC; R_f value 0.20 (8:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 6.6 Hz, 2H), 7.27 (d, *J* = 6.8 Hz, 1H), 7.21 (d, *J* = 5.4 Hz, 2H), 3.58 (d, *J* = 10.4 Hz, 1H),

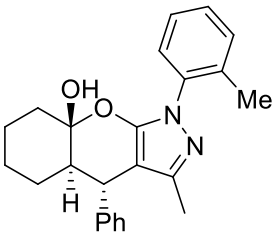


3.02 (s, 1H), 2.16 (d, *J* = 12.4 Hz, 1H), 1.97 (dd, *J* = 22.8, 12.5 Hz, 1H), 1.79 (d, *J* = 14.7 Hz, 3H), 1.70 (dd, *J* = 23.1, 15.9 Hz, 2H), 1.61 (s, 3H), 1.34 (dd, *J* = 24.8, 12.8 Hz, 1H), 1.19 – 1.12 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.4, 149.2, 142.4, 141.4, 133.2, 128.7, 127.1, 119.5, 119.1, 118.5, 107.6, 104.1, 101.5, 47.7, 40.3, 38.5, 26.9, 25.6, 23.2, 13.6; **ESI-MS** m/z calcd. for $C_{24}H_{24}N_3O_3^+$ $[M+H]^+$ 386.1863, found 386.1863; **FT-IR (KBr)** 3453, 2922, 2855, 2229, 1603, 1517, 1495, 1444, 1409, 1394, 1270, 1123, 1098, 917 cm^{-1}; The ee values 84% (t_{major} = 11.14 min, t_{minor} = 13.17 min) was determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.6}$ = + 39.74 (c 0.765, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1-(4-nitrophenyl)-4-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3v):



Yellow solid (26 mg, 35% yield); R_f value 0.20 (6:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.27 (d, *J* = 9.2 Hz, 3H), 8.03 (d, *J* = 9.1 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 7.1 Hz, 2H), 3.60 (d, *J* = 10.8 Hz, 1H), 2.85 (s, 1H), 2.38 – 2.32 (m, 1H), 2.02 – 1.96 (m, 2H), 1.82 – 1.76 (m, 2H), 1.75 – 1.69 (m, 2H), 1.61 (s, 3H), 1.36 – 1.34 (m, 1H), 1.16 (dd, *J* = 10.7, 6.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.6, 144.1, 134.0, 133.9, 129.1, 128.8, 125.1, 125.0, 119.1, 118.0, 104.2, 101.7, 47.7, 40.3, 38.7, 26.9, 25.5, 22.9, 14.4; **ESI-MS** m/z calcd. for $C_{23}H_{24}N_3O_4^+$ $[M+H]^+$ 406.1761, found 406.1761; **FT-IR (KBr)** 3453, 2923, 1701, 1614, 1599, 1567, 1521, 1339, 1110, 1092, 916 cm^{-1}; The ee values 82% (t_{major} = 10.44 min, t_{minor} = 11.86 min) was determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.3}$ = + 51.43 (c 0.105, $CHCl_3$).

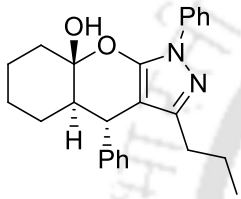


(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-4-phenyl-1-*o*-tolylchromeno[2,3-*c*]pyrazol-8*a*-ol (3w):

White solid (56 mg, 75% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.33 (t, *J* = 7.4 Hz, 4H), 7.28 (s, 2H), 7.24 (d, *J* = 7.2 Hz, 3H), 3.61 (d, *J* = 10.7 Hz, 1H), 2.83 (s, 1H), 2.24 (s, 2H), 1.95 (d, *J* = 13.4 Hz, 1H), 1.79 – 1.73 (m, 3H), 1.67 (d, *J* = 11.2 Hz,

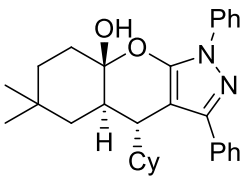
3H), 1.59 (s, 3H), 1.31 (dd, *J* = 19.2, 9.1 Hz, 1H), 1.10 (d, *J* = 13.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.3, 135.6, 134.8, 132.7, 130.9, 128.6, 127.8, 126.9, 126.4, 124.0, 117.2, 116.9, 49.6, 42.1, 40.6, 29.9, 25.6, 25.1, 18.1, 13.2; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2067; **FT-IR (KBr)** 3439, 2923, 2853, 1723, 1701, 1599, 1515, 1500, 1451, 1388, 1127, 923 cm $^{-1}$; The ee values 90% (t_{major} = 19.26 min, t_{minor} = 21.46 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IC with hexane/EtOH (98:2) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.9}$ = + 54.13 (c 0.248, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-1,4-diphenyl-3-propylchromeno[2,3-*c*]pyrazol-8*a*-ol (3x):



White sticky (30 mg, 38% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.45 (dd, *J* = 14.8, 7.2 Hz, 3H), 7.35 (d, *J* = 4.4 Hz, 2H), 7.09 (t, *J* = 7.9 Hz, 2H), 7.03 (s, 1H), 3.89 (d, *J* = 10.6 Hz, 1H), 3.72 (dd, *J* = 14.1, 7.0 Hz, 1H), 2.86 (s, 1H), 2.16 (d, *J* = 13.8 Hz, 2H), 1.95 (d, *J* = 13.8 Hz, 1H), 1.78 – 1.70 (m, 4H), 1.60 (s, 4H), 1.40 (dd, *J* = 23.6, 10.9 Hz, 2H), 1.13 (dd, *J* = 24.6, 14.1 Hz, 2H), 0.88 (t, *J* = 6 Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.4, 141.9, 139.0, 133.4, 129.1, 128.0, 127.8, 127.5, 125.9, 121.0, 102.9, 99.4, 48.4, 42.9, 41.4, 38.6, 32.1, 27.2, 25.6, 23.2, 14.3; **ESI-MS** m/z calcd. for $C_{25}H_{29}N_2O_4^+$ $[M+H]^+$ 389.2224, found 389.2219; **FT-IR (KBr)** 3424, 2925, 2855, 1699, 1600, 1575, 1511, 1489, 1457, 1384, 1276, 1069, 1025 cm $^{-1}$; The ee values 84% (t_{major} = 7.52 min, t_{minor} = 11.52 min) and after recrystallization 98% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.2}$ = + 27.83 (c 0.115, $CHCl_3$).

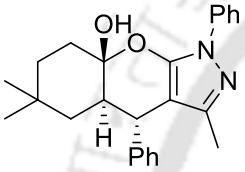
(4*R*,4*aR*,8*aS*)-4-cyclohexyl-1,4,4*a*,5,6,7,8,8*a*-octahydro-1,3-diphenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3y):



White semi solid (31 mg, 36% yield); R_f value 0.20 (12:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.76 (d, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 3H), 7.29 (d, *J* = 6.9 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.18 (s, 1H), 7.15 (t, *J* = 7.4 Hz, 2H), 3.75 – 3.69 (m, 1H), 3.51 (d, *J* = 11.0 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.03 (dd, *J* = 14.3, 6.7 Hz, 1H), 1.69 – 1.62 (m, 5H), 1.58 (s, 5H), 1.08 – 1.01 (m, 2H), 0.88 (t, *J* = 6.9 Hz, 2H), 0.84 – 0.78 (m, 2H), 0.66 (dd,

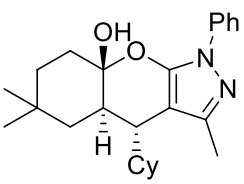
J = 22.0, 9.1 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 150.5, 139.4, 137.4, 128.9, 128.8, 128.6, 127.3, 126.3, 121.5, 119.0, 114.3, 91.0, 42.2, 36.9, 36.1, 34.0, 32.7, 32.1, 29.6, 27.2, 26.6, 25.2, 22.9, 14.3; **ESI-MS** m/z calcd. for $C_{28}H_{33}N_2O_2^+$ $[M+H]^+$ 429.2537, found 429.2537; **FT-IR (KBr)** 3506, 2924, 2853, 1699, 1600, 1515, 1448, 1392, 1364, 1275, 1123, 1020, 916 cm $^{-1}$; The ee values 86% (t_{major} = 8.84 min, t_{minor} = 11.54 min) and after recrystallization 98% were determined by HPLC using Daicel Chiralpak IB with hexane/EtOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.2}$ = + 6.00 (c 0.100, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4a,5,6,7,8,8*a*-octahydro-3,6,6-trimethyl-1,4-diphenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3z):



Yellow sticky (44 mg, 57% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 2.69 (s, 1H), 2.61 (d, *J* = 12.0 Hz, 1H), 2.39 – 2.34 (m, 1H), 2.28 (d, *J* = 12.0 Hz, 1H), 2.19 – 2.16 (m, 1H), 1.69 – 1.65 (m, 2H), 1.59 (s, 3H), 1.47 (s, 1H), 1.44 (dd, *J* = 4.5, 1.3 Hz, 2H), 1.25 (s, 6H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.9, 138.0, 129.0, 128.9, 128.9, 128.7, 127.8, 125.3, 119.5, 114.3, 102.1, 86.6, 55.9, 48.8, 44.5, 38.6, 32.1, 25.0, 22.9, 15.9, 14.3; **ESI-MS** m/z calcd. for $C_{25}H_{29}N_2O_2^+$ $[M+H]^+$ 389.2224, found 389.2223; **FT-IR (KBr)** 3428, 2922, 2852, 1702, 1597, 1502, 1454, 1368, 1400, 1308, 1127, 1028, 910 cm $^{-1}$; The ee values 80% (t_{major} = 9.31 min, t_{minor} = 14.24 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 254 nm; **Optical Rotation**: $[\alpha]_D^{30.1}$ = + 110.81 (c 0.675, $CHCl_3$).

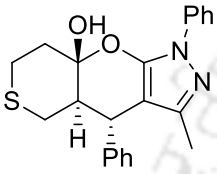
(4*R*,4*aR*,8*aS*)-4-cyclohexyl-1,4,4*a*,5,6,7,8,8*a*-octahydro-3,6,6-trimethyl-1-phenylchromeno[2,3-*c*]pyrazol-8*a*-ol (3z^1):



Yellow semi solid (32 mg, 40% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.21 – 7.16 (m, 1H), 2.78 (s, 1H), 2.37 – 2.29 (m, 1H), 2.31 – 2.25 (m, 1H), 1.87 – 1.77 (m, 3H), 1.77 (d, *J* = 17.0 Hz, 2H), 1.66 (d, *J* = 9.9 Hz, 4H), 1.58 (s, 3H), 1.46 (d, *J* = 6.5 Hz, 1H), 1.38 (d, *J* = 18.6 Hz, 2H), 1.25 (s, 6H), 0.97 (d, *J* = 4.7 Hz, 2H),

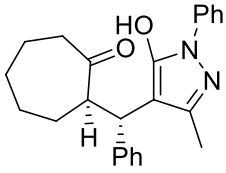
0.87 (d, *J* = 5.4 Hz, 5H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 137.8, 129.2, 128.9, 126.4, 125.5, 121.5, 121.2, 119.4, 72.2, 68.9, 55.1, 37.7, 35.2, 32.1, 29.6, 26.7, 25.7, 22.9, 21.5, 14.4, 12.4; **ESI-MS** m/z calcd. for $C_{25}H_{35}N_2O_2^+$ $[M+H]^+$ 395.2693, found 395.2698; **FT-IR (KBr)** 3434, 2922, 2852, 1708, 1629, 1597, 1559, 1495, 1457, 1371, 1298, 1028, 901 cm $^{-1}$; The ee values 88% (t_{major} = 9.76 min, t_{minor} = 16.88 min) was determined by HPLC using Daicel Chiralpak IC with hexane/EtOH (94:6) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C; **Optical Rotation**: $[\alpha]_D^{30.1}$ = + 15.79 (c 0.380, $CHCl_3$).

(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-1,4-diphenylthiochromeno[2,3-*c*]pyrazol-8*a*-ol (3z^2):



Yellow semi solid (30 mg, 40% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.23 (dd, *J* = 18.4, 7.3 Hz, 3H), 3.62 (d, *J* = 10.7 Hz, 1H), 3.05 (d, *J* = 11.0 Hz, 1H), 2.99 – 2.94 (m, 1H), 2.86 (s, 1H), 2.79 – 2.72 (m, 1H), 2.72 – 2.67 (m, 1H), 2.41 (dd, *J* = 28.7, 15.4 Hz, 2H), 2.18 (t, *J* = 11.1 Hz, 1H), 1.60 (s, 3H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ 147.4, 147.3, 140.9, 138.8, 129.2, 128.9, 127.5, 125.7, 120.6, 120.6, 101.9, 99.7, 49.3, 40.7, 40.4, 29.1, 25.8, 13.5; **ESI-MS** m/z calcd. for $C_{22}H_{23}N_2O_2S^+$ $[M+H]^+$ 379.1475, found 379.1469; **FT-IR (KBr)** 3439, 2925, 2860, 1708, 1629, 1600, 1555, 1490, 1457, 1371, 1298, 1028, 910 cm $^{-1}$; The ee values 88% (t_{major} = 16.13 min, t_{minor} = 26.48 min) was determined by HPLC using Daicel Chiralpak IB with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

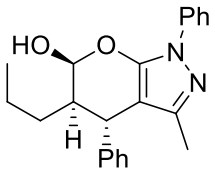
(R)-2-((S)-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)(phenyl)methyl)cycloheptanone (3z^3):



Yellow sticky (36 mg, 48% yield); R_f value 0.25 (5:1 hex/EA); **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.43 – 7.38 (m, 3H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.22 – 7.18 (m, 3H), 4.12 (t, *J* = 10.5 Hz, 1H), 3.81 (d, *J* = 5.1 Hz, 1H), 3.57 (t, *J* = 12.5 Hz, 1H), 3.07 (d, *J* = 16.4 Hz, 1H), 2.54 (s, 3H), 2.10 (s, 3H), 1.93 (s, 2H), 1.76 (s, 4H), 1.13 (d, *J* = 13.9 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ 217.0, 173.0, 159.8, 138.2, 137.9, 129.0, 128.9, 128.2, 127.9, 125.4, 119.6, 53.8, 50.4, 45.7, 44.3, 44.1, 27.8, 24.5, 22.9, 15.9; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2070; **FT-IR (KBr)** 3440, 2924, 2850, 1804, 1723, 1650, 1599, 1545, 1520, 1451, 1396, 1302, 1154, 1074, 906 cm^{-1}; The ee values

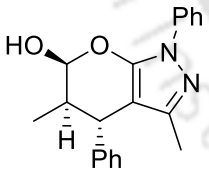
90% (t_{major} = 30.55 min, t_{minor} = 58.55 min) was determined by HPLC using phenomenex cellulose-4 with hexane/i-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(4*S*,5*R*,6*S*)-1,4,5,6-tetrahydro-3-methyl-1,4-diphenyl-5-propylpyrano[2,3-*c*]pyrazol-6-ol (3z^4):



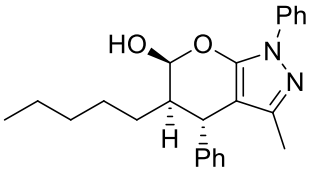
Yellow semi solid (28 mg, 40% yield); R_f value 0.20 (15:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.21 (dt, *J* = 15.0, 7.8 Hz, 4H), 5.73 (s, 1H), 3.70 (d, *J* = 9.9 Hz, 1H), 1.99 (s, 1H), 1.86 (s, 1H), 1.60 (s, 3H), 1.51 – 1.43 (m, 2H), 1.39 – 1.33 (m, 1H), 1.29 (dd, *J* = 16.9, 6.4 Hz, 1H), 0.79 (t, *J* = 7.2 Hz, 8H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.4, 142.3, 138.7, 129.4, 128.0, 127.0, 125.6, 120.7, 119.4, 100.8, 99.8, 53.4, 45.1, 39.7, 30.2, 20.5, 14.3, 13.3; **ESI-MS** m/z calcd. for $C_{22}H_{25}N_2O_2^+$ $[M+H]^+$ 349.1911, found 349.1916; **FT-IR (KBr)** 3440, 2924, 2853, 1804, 1723, 1599, 1549, 1518, 1451, 1396, 1302, 1154, 1074, 906 cm^{-1}; The ee values 80% (t_{major} = 18.07 min, t_{minor} = 14.83 min) and after recrystallization >99% were determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{30.4}$ = + 41.40 (c 0.570, $CHCl_3$).

(4*S*,5*R*,6*S*)-1,4,5,6-tetrahydro-3,5-dimethyl-1,4-diphenylpyrano[2,3-*c*]pyrazol-6-ol (3z^5):



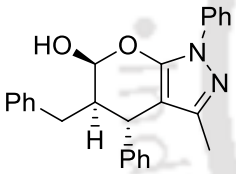
Yellow semi solid (29 mg, 45% yield); R_f value 0.20 (15:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.42 – 7.37 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 3H), 7.24 (dd, *J* = 6.1, 4.9 Hz, 2H), 7.21 (d, *J* = 7.3 Hz, 1H), 5.62 (s, 1H), 3.67 (d, *J* = 10.1 Hz, 1H), 2.17 – 2.04 (m, 2H), 1.64 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 148.1, 142.1, 138.8, 129.2, 128.9, 128.5, 127.0, 125.7, 120.7, 102.2, 98.9, 43.4, 40.7, 40.2, 13.9, 13.5; **ESI-MS** m/z calcd. for $C_{20}H_{21}N_2O_2^+$ $[M+H]^+$ 320.1598, found 320.1600; **FT-IR (KBr)** 3440, 2924, 2853, 1804, 1723, 1599, 1549, 1518, 1451, 1396, 1302, 1154, 1074, 906 cm^{-1}; The ee values 72% (t_{major} = 15.26 min, t_{minor} = 11.84 min) was determined by HPLC using Daicel Chiralpak ID with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(4*S*,5*R*,6*S*)-1,4,5,6-tetrahydro-3-methyl-5-pentyl-1,4-diphenylpyrano[2,3-*c*]pyrazol-6-ol (3z^6):



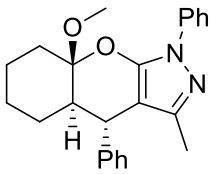
Yellow semi solid (32 mg, 42% yield); R_f value 0.20 (15:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$** 7.74 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.14 (m, 4H), 5.75 (s, 1H), 3.70 (d, *J* = 9.9 Hz, 1H), 1.98 (s, 1H), 1.87 (s, 1H), 1.62 (s, 3H), 1.51 – 1.43 (m, 2H), 1.31 (dd, *J* = 19.1, 9.6 Hz, 3H), 1.17 (s, 2H), 0.81 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 148.0, 147.4, 142.4, 138.7, 129.12, 128.7, 128.07, 127.0, 125.6, 120.6, 107.6, 97.1, 50.7, 45.3, 39.2, 32.0, 27.9, 27.1, 22.7, 14.2, 13.4; **ESI-MS** m/z calcd. for $C_{24}H_{29}N_2O_2^+$ $[M+H]^+$ 376.2224, found 376.2226; **FT-IR (KBr)** 3440, 2924, 2855, 1806, 1725, 1599, 1550, 1519, 1451, 1396, 1302, 1154, 1074, 906 cm^{-1}; The ee values 30% (t_{major} = 9.16 min, t_{minor} = 16.87 min) was determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(4*S*,5*R*,6*S*)-5-benzyl-1,4,5,6-tetrahydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazol-6-ol (3z[7]):



Yellow semi solid (39 mg, 50% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 8.4 Hz, 14H), 7.39 – 7.35 (m, 28H), 7.29 (ddd, *J* = 7.6, 4.8, 3.1 Hz, 40H), 7.20 – 7.18 (m, 24H), 7.08 (t, *J* = 7.9 Hz, 18H), 5.42 (s, 7H), 3.83 (d, *J* = 10.0 Hz, 8H), 2.89 (t, *J* = 7.7 Hz, 6H), 2.72 – 2.67 (m, 17H), 2.60 – 2.55 (m, 7H), 1.66 (s, 23H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 147.4, 142.0, 139.5, 138.8, 129.1, 128.9, 128.8, 128.7, 128.7, 127.3, 126.6, 125.6, 120.7, 99.9, 96.3, 47.8, 39.1, 29.9, 13.5; **ESI-MS** m/z calcd. for $C_{26}H_{25}N_2O_2^+$ $[M+H]^+$ 396.1911, found 396.1916; **FT-IR (KBr)** 3445, 2925, 2850, 1806, 1722, 1599, 1550, 1520, 1453, 1396, 1302, 1154, 1074, 906 cm^{-1}; The ee values 40% (t_{major} = 19.04 min, t_{minor} = 26.34 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

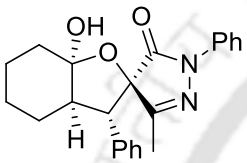
(4*S*,4*aR*,8*aS*)-1,4,4*a*,5,6,7,8,8*a*-octahydro-8*a*-methoxy-3-methyl-1,4-diphenylchromeno[2,3-*c*]pyrazole (4):



Colour less sticky (56 mg, 74% yield); R_f value 0.20 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.82 (d, J = 7.7 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.30 (t, J = 7.4 Hz, 2H), 7.20 (dd, J = 14.5, 7.2 Hz, 4H), 3.60 (d, J = 10.7 Hz, 1H), 3.30 (s, 3H), 2.48 (d, J = 14.0 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.69 (t, J = 11.7 Hz, 3H), 1.60 (s, 3H), 1.44 – 1.41 (m, 1H), 1.40 – 1.34 (m,

2H), 1.14 (dd, J = 9.3, 4.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.2, 147.2, 142.3, 139.2, 129.1, 128.6, 126.9, 125.2, 120.0, 105.6, 100.9, 49.0, 48.7, 40.4, 31.8, 26.9, 25.6, 22.8, 13.6; **ESI-MS** m/z calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067, found 375.2069; **FT-IR (KBr)** 3431, 2925, 2852, 1600, 1514, 1489, 1444, 1397, 1273, 1254, 1209, 1149, 1076, 993 cm^{-1}; The ee values 84% (t_{major} = 5.40 min, t_{minor} = 4.50 min) was determined by HPLC using Daicel Chiralpak IA with hexane/i-PrOH (98:3) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(3*S*,3*aR*,7*aR*)-(octahydro-3-phenylbenzofuran-7*a*-ol) 3-methyl-1-phenyl-1*H*-pyrazol-5-one (5):



Yellow sticky oil (57 mg, 75% yield); R_f value 0.30 (10:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 (dd, *J* = 7.3, 3.1 Hz, 4H), 7.23 (t, *J* = 6.3 Hz, 3H), 7.13 (t, *J* = 7.3 Hz, 1H), 3.56 (d, *J* = 12.4 Hz, 1H), 3.35 – 3.28 (m, 1H), 2.32 (s, 3H), 2.17 (dt, *J* = 13.6, 4.7 Hz, 1H), 2.06 (dd, *J* = 14.6, 6.9 Hz, 1H), 1.93 – 1.83 (m, 3H), 1.74 (dd, *J* = 12.5, 6.9 Hz, 2H), 1.69 (dd, *J* = 17.5, 7.0 Hz, 2H), 1.56 (d, *J* = 4.3 Hz, 1H), 1.51 – 1.47 (m, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.1, 159.7, 136.9, 132.2, 128.9, 128.8, 128.2, 125.8, 119.7, 108.7, 89.2, 55.2, 45.6, 42.1, 34.7, 27.2, 23.2, 19.3, 12.9; **ESI-MS** m/z calcd. for $C_{23}H_{23}N_2O_2^+$ $[M-OH]^+$ 359.1754, found 359.1757; **FT-IR (KBr)** 3439, 2929, 2860, 1710, 1640, 1629, 1600, 1555, 1490, 1457, 1375, 1298, 1028, 911 cm^{-1}; The ee values 80% (t_{major} = 25.92 min, t_{minor} = 23.79 min) was determined by HPLC using Daicel Chiralpak IC with hexane/i-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C; **Optical Rotation**: $[\alpha]_D^{31.0}$ = + 154.17 (c 0.515, $CHCl_3$).

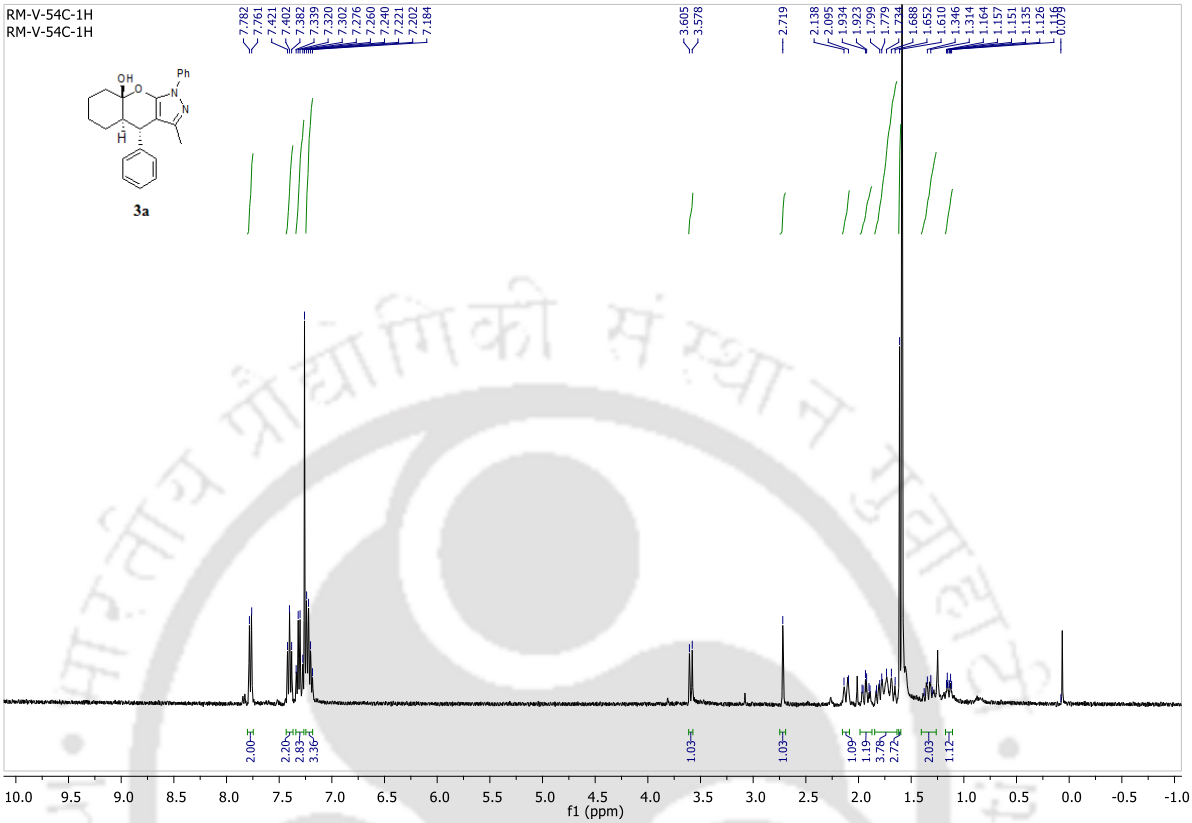
5.10.3. Crystal Information:

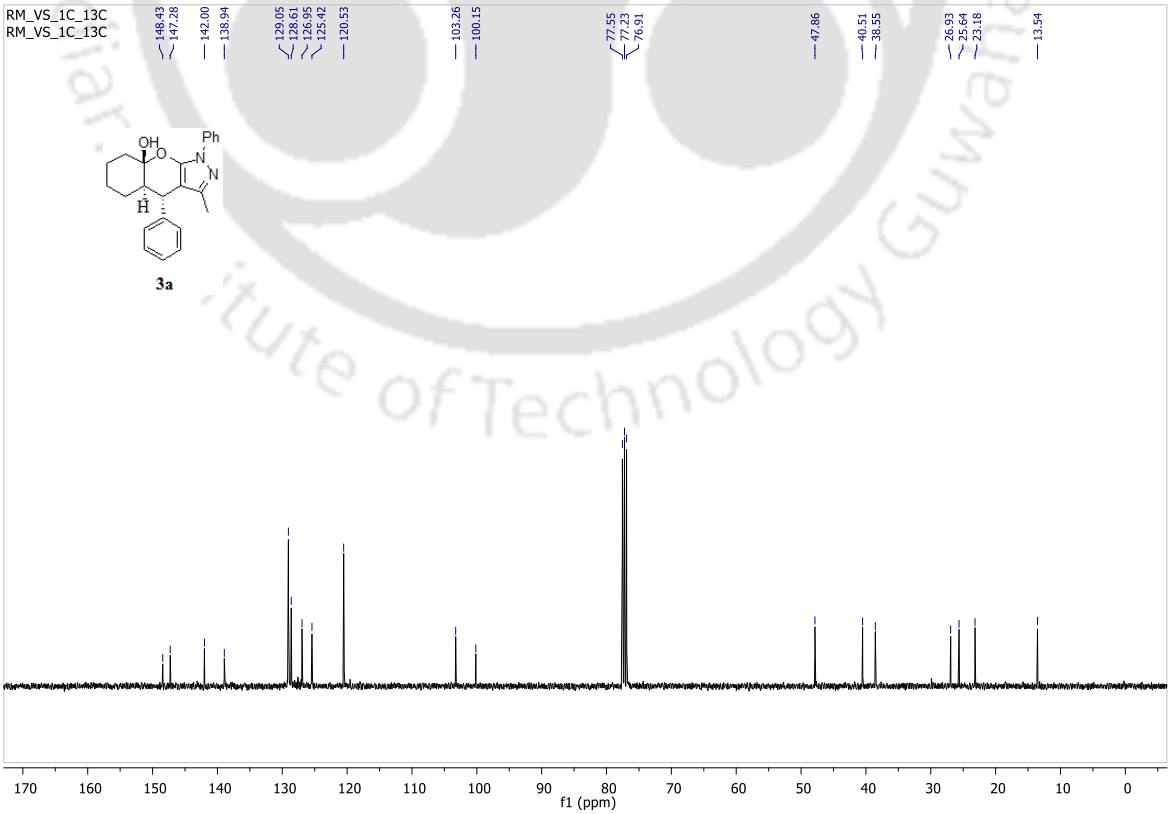
Identification code	**3l**	**3a**	**5**
CCDC No	CCDC156055	CCDC1556054	CCDC1556056
Empirical formula	$C_{23}H_{23}ClN_2O_2$	$C_{23}H_{24}N_2O_2$	$C_{23}H_{24}N_2O_3$
Formula weight	394.88	360.44	376.44
Temperature/K	296(2)	296(2)	373.1(2)
Crystal system	orthorhombic	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P22_12_1$	$P2_1/c$
a/Å	5.9545(7)	5.7189(11)	12.6633(19)

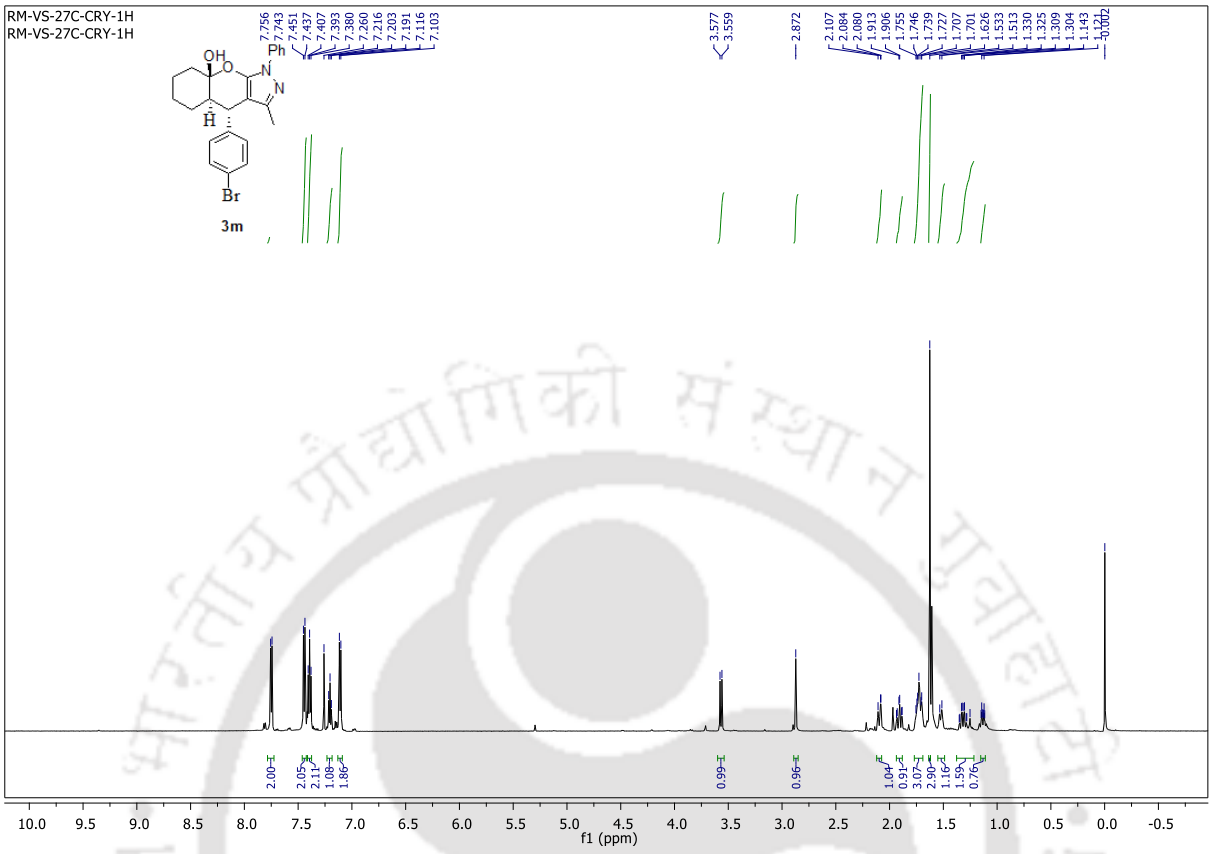
b/Å	12.1404(9)	12.5306(17)	16.796(2)
c/Å	28.388(2)	26.957(3)	9.3590(15)
α/°	90	90	90
β/°	90	90	104.449(16)
γ/°	90	90	90
V/Å^3	2052.2(3)	1931.7(5)	1927.6(5)
Z	4	4	4
D_{calcd} (g m^{-3})	1.278	1.239	1.297
μ (mm^{-1})	0.207	0.079	0.086
F(000)	832.0	768.0	800.0
Reflections collected	4400	4405	22212
Independent reflections	2939[R(int) = 0.1165]	2871[R(int) = 0.0928]	6770[R(int) = 0.0906]
Goodness-of-fit (GOF)[a] on F^2	1.081	1.149	1.017
R_1[b], wR_2[c] ($I \geq 2\sigma(I)$)	0.1216, 0.2518	0.1268, 0.2270	0.0698, 0.1432
R_1[b], wR_2[c] (all data)	0.2029, 0.3503	0.2183, 0.3032	0.1554, 0.1859
Flack parameter	-0.09(13)		

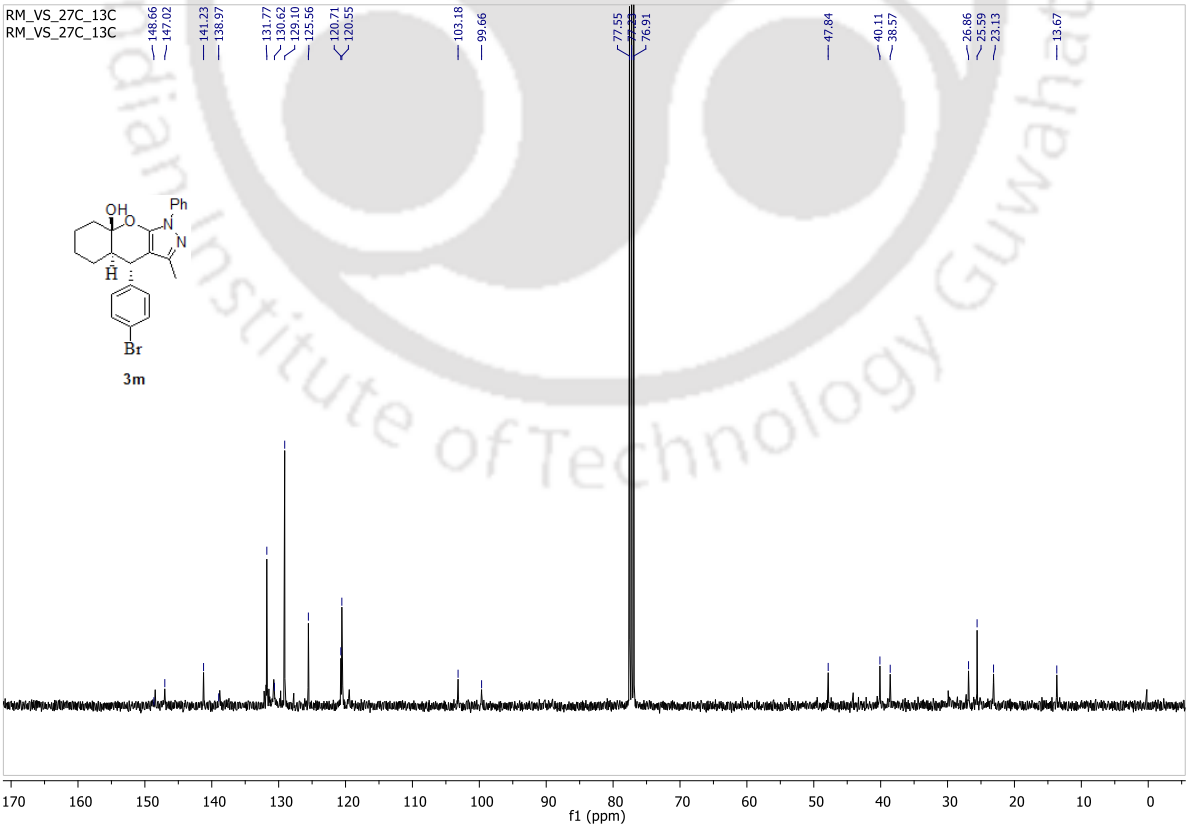
[a]GOF = $[\sum[w(F_0^2 - F_c^2)^2] / M - N]^{1/2}$ (M =number of reflections, N = number of parameters refined). [b]$R_1 = \sum \| F_0 | - | Fc \| / \sum | F_0$, [c]$wR_2 = [\sum[w(F_0^2 - F_c^2)^2] / \sum[w(F_0^2)^2]]^{½}$

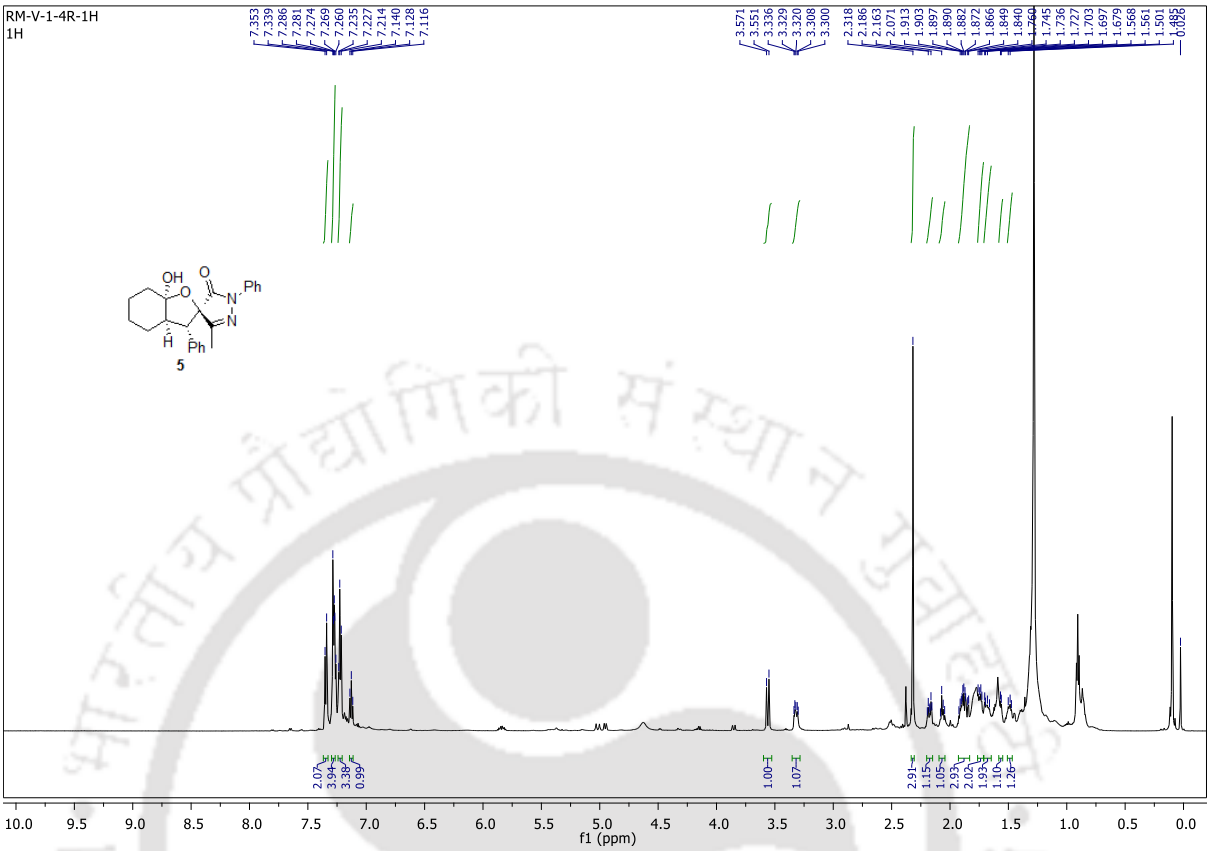
5.11. Selected spectra of NMR and HPLC:

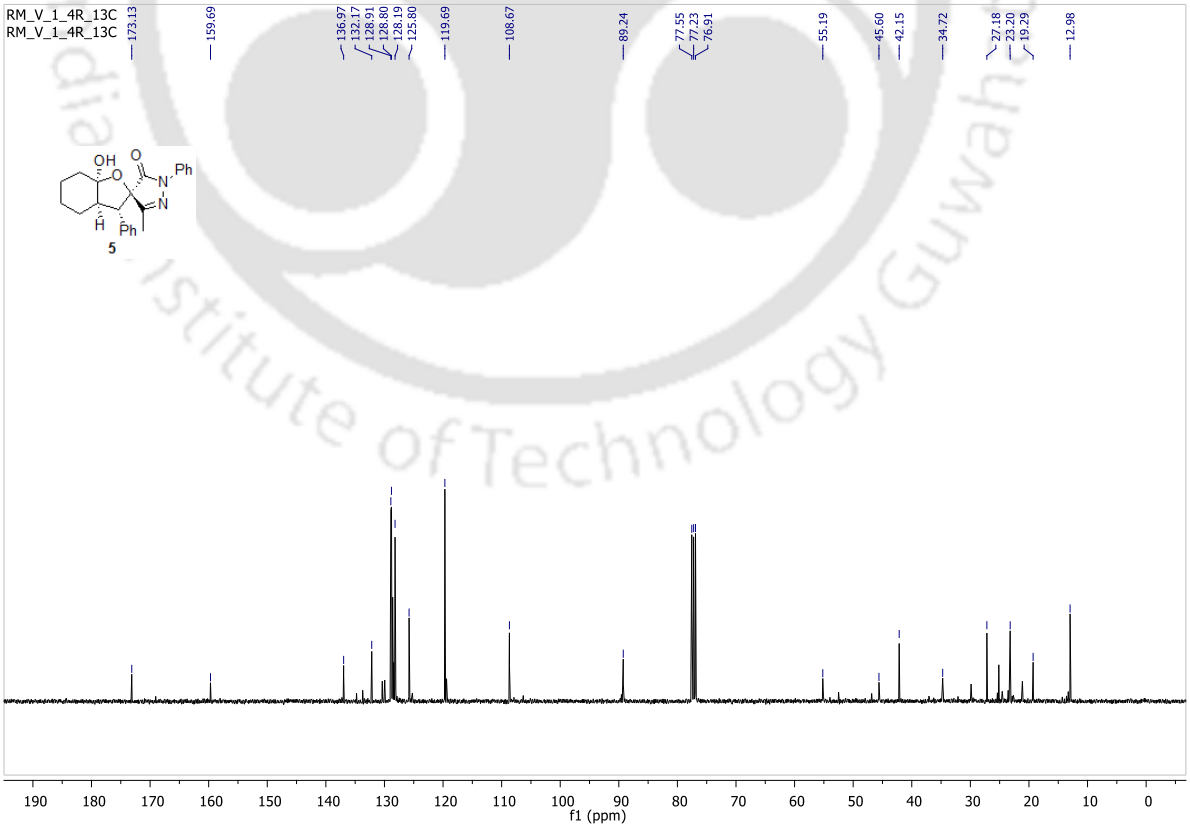


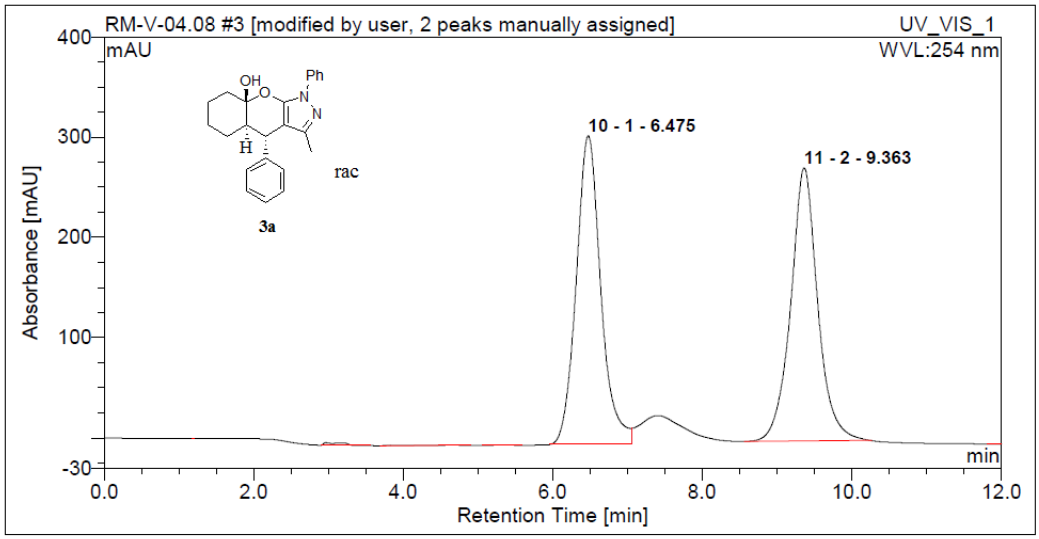




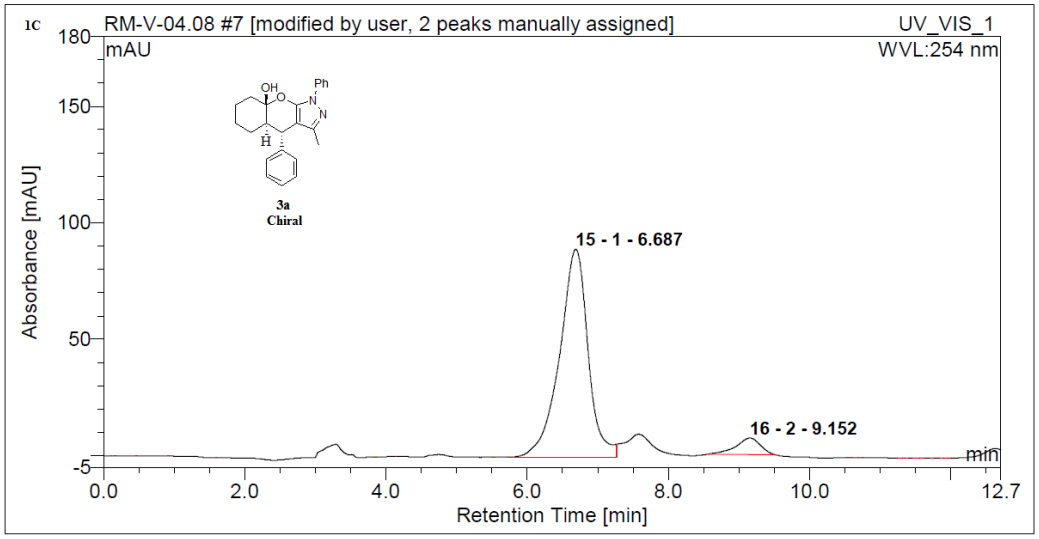




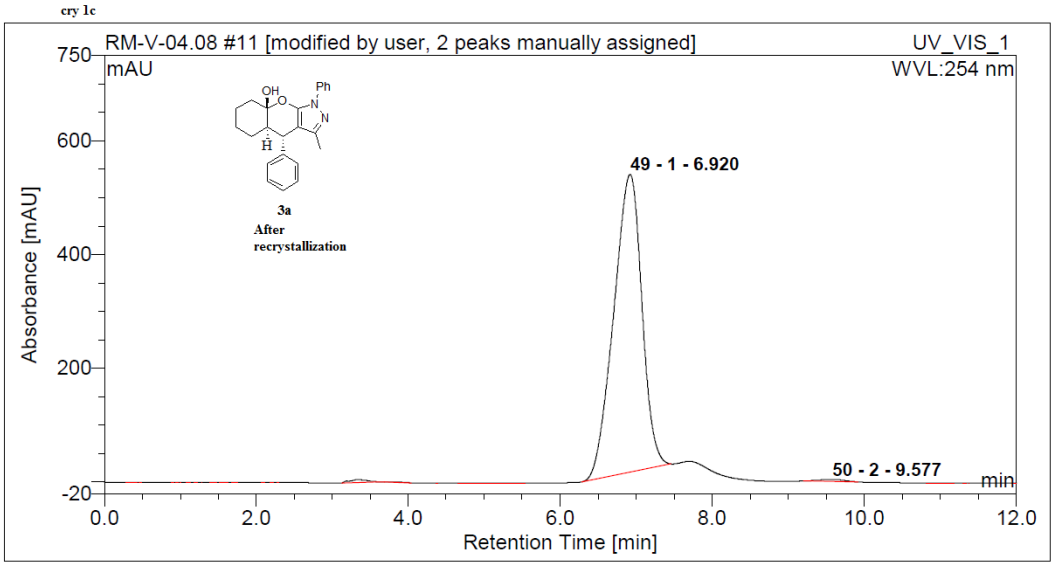




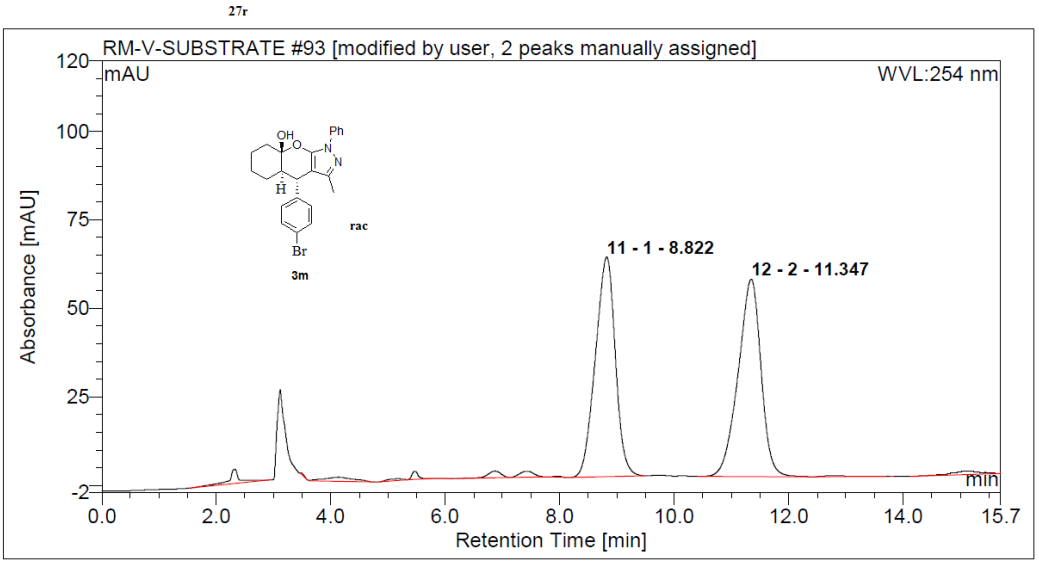
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
10	1	6.48	117.5589	50.7342853	308.0702	n.a.
11	2	9.36	114.156	49.2657147	272.572	n.a.



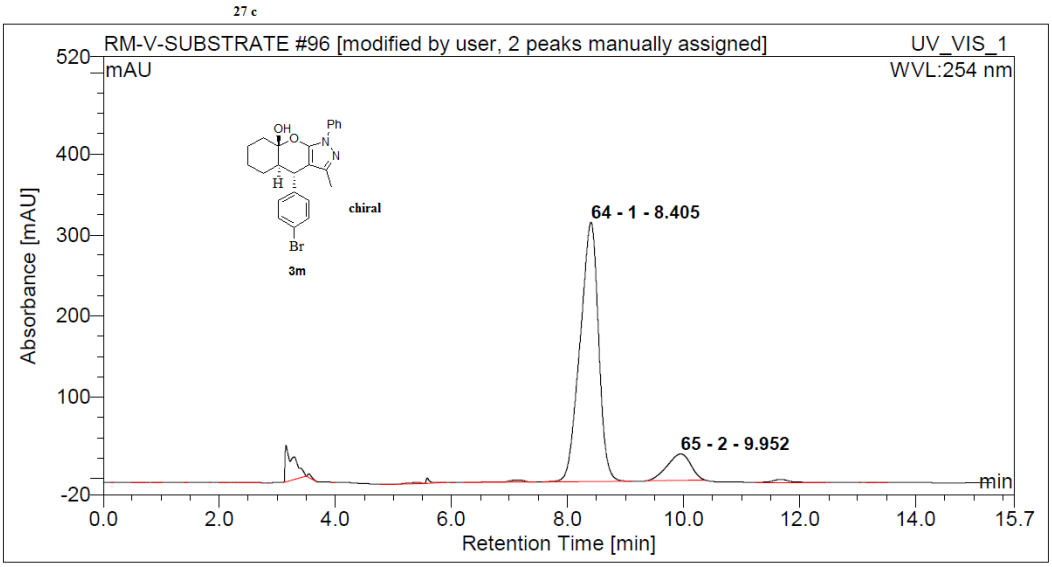
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
15	1	6.69	41.65523	93.51426841	89.29235	n.a.
16	2	9.15	2.889	6.485731593	7.100	n.a.



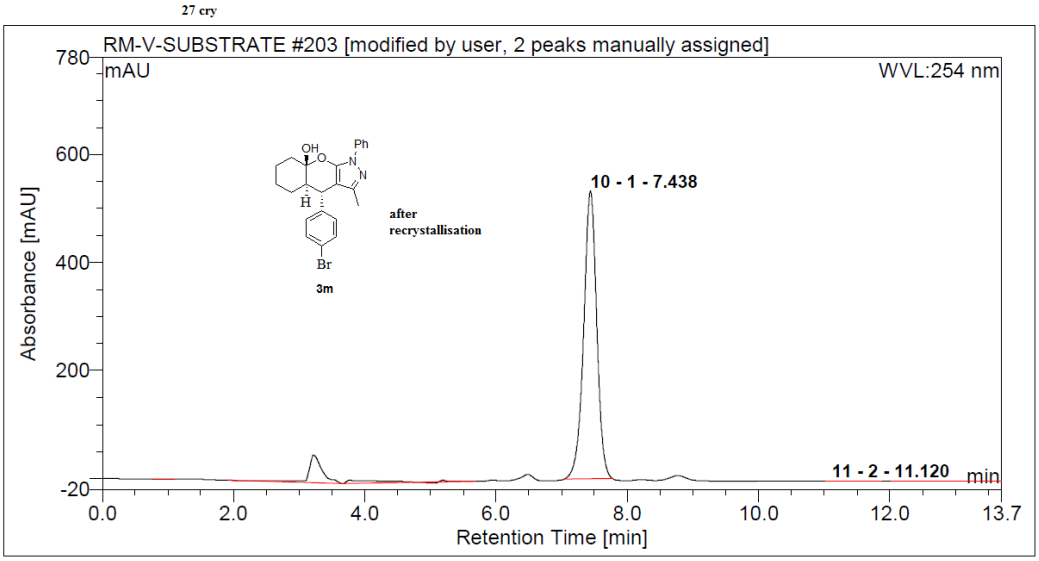
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
49	1	6.92	224.6229	99.40378003	523.4093	n.a.
50	2	9.58	1.347	0.5962199704	3.419	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
11	1	8.82	25.12067	49.26859273	62.09706	n.a.
12	2	11.35	25.867	50.73140727	55.838	n.a.

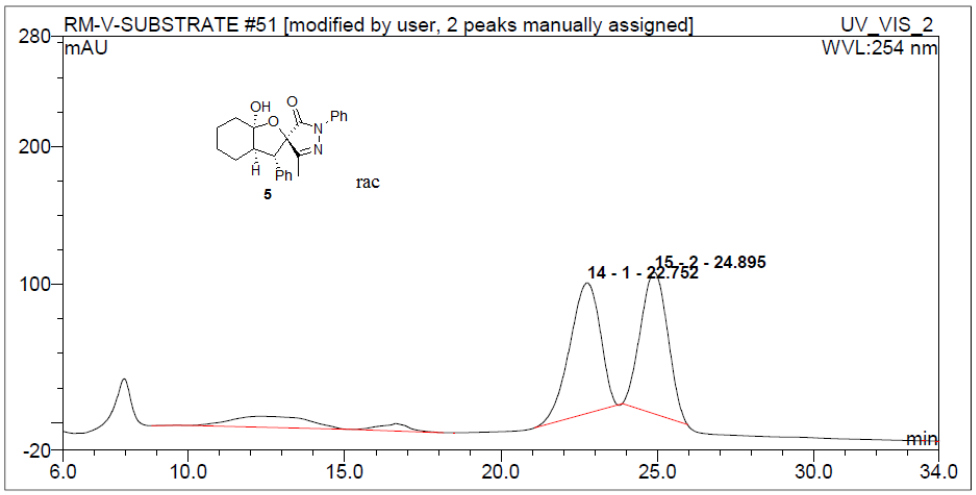


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
64	1	8.41	118.148	88.5557724	319.5478	n.a.
65	2	9.95	15.268	11.4442276	32.521	n.a.



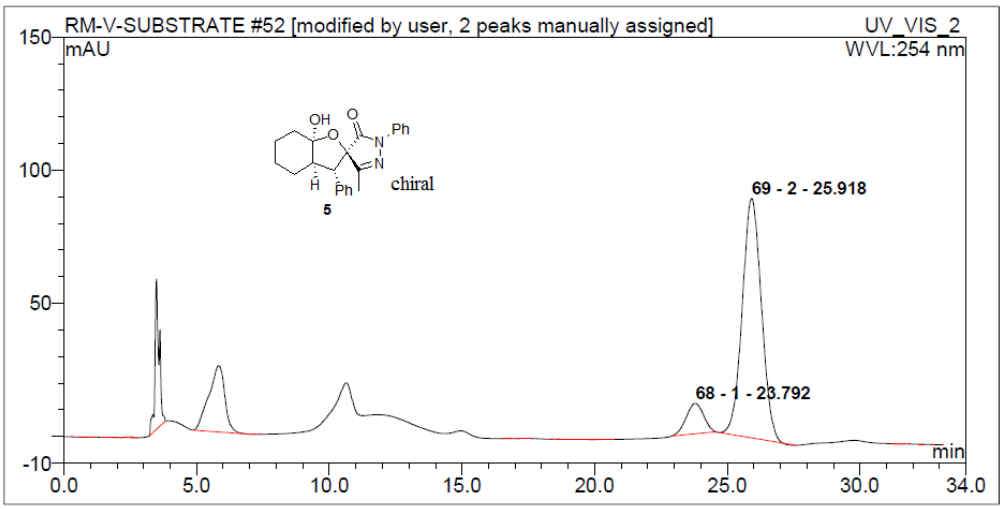
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
10	1	7.44	123.0126	99.92915816	532.6069	n.a.
11	2	11.12	0.087	0.07084184129	0.096	n.a.

RM-V-1-4C



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
14	1	22.75	106.7035	50.7354729	94.36267	n.a.
15	2	24.90	103.610	49.2645271	102.453	n.a.

RM-V-1-4C



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
68	1	23.79	8.674532	10.33547803	11.40714	n.a.
69	2	25.92	75.255	89.66452197	89.898	n.a.

5.12. References:

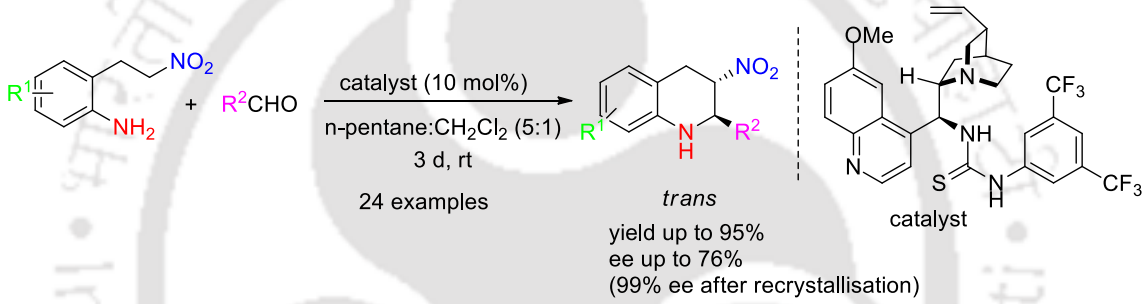
1. (a) Varvounis, G.; *Adv. Heterocycl. Chem.* **2009**, *98*, 143. (b) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (c) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 1423.
2. Hartmut, S.; Wilhelm, B. Ger. Offen. DE 3243714A1, May 30, **1984**.
3. Bradley, D. M.; Chan, W. N.; Thewlis, K. M.; Ward, S. E. PCT/EP2007/061794; WO2008053031A1.
4. Radi, M.; Bernardo, V.; Bechi, B.; Castagnolo, D.; Pagano, M.; Botta, M. *Tetrahedron Lett.* **2009**, *50*, 6572.
5. Koohshari, M.; Dabiri, M.; Salehi, P. *RSC Adv*. **2014**, *4*, 10669.
6. Bertheleme, N.; Bradley, D. M.; Cardullo, F. Glaxo Group Limited. PCT/EP2007/061794; WO2008053031A1, **2008**.
7. Sapkal, S. B.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, *50*, 1754.
8. (a) Pégurier, C.; Collart, P.; Danhaive, P.; Defays, S.; Gillard, M.; Gilson, F.; Kogej, T.; Pasau, P.; Van Houtvin, N.; Van Thuyne, M.; Van Keulen, B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4228. (b) Bondock, S.; Rabie, R.; Etman, H. A.; Fadda, A. A.; *Eur. J. Med. Chem.* **2008**, *43*, 2122.
9. (a) Azzam, S. H. S.; Pasha, M. A. *Tetrahedron Lett.* **2012**, *53*, 6834.
10. (a) Tietze, L. F. *Chem. Rev.* **1996**, 96, 115. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570.
11. Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196.
12. Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2011**, *9*, 6519.
13. Liang, J.; Chen, Q.; Liu, L.; Jianga, X.; Wang, R. *Org. Biomol. Chem.* **2013**, *11*, 1441.
14. Chauhan, P.; Mahajan, S.; Loh, C. C. J.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 2954.
15. List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

16. (a) Chandrasekhar, S.; Mallikarjun, K.; Pavankumarreddy, G.; Rao, K. V.; Jagadeesh, B. *Chem. Commun.* **2009**, 4985. (b) Ramachary, D. B.; Sakthidevi, R.; Shruthi, K. S. *Chem. Eur. J.* **2012**, *18*, 8008.
17. Das, U.; Huang, C.-H.; Lin, W. *Chem. Commun.* **2012**, *48*, 5590.
18. Xu, Z.; Liu, L.; Wheeler, K.; Wang, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 3484.
19. Enders, D.; Grossmann, A.; Gieraths, B.; Düzdemir, M.; Merkens, C. *Org. Lett.* **2012**, *14*, 4254.
20. (a) Zhang, Y.; Wu, S.; Wang, S.; Fang, K.; Dong, G.; Liu, N.; Miao, Z.; Yao, J.; Li, J.; Zhang, W.; Sheng, C.; Wang, W. *Eur. J. Org. Chem.* **2015**, 2030. (b) Yang, S.; Shen, L.-L.; Kim, Y.-J.; Jeong, J.-H. *Org. Biomol. Chem.* **2016**, *14*, 623.
21. Wang, S.; Rodriguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2016**, *18*, 556.
22. CCDC 1556054 contains the crystallographic data for **3a**.
23. (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Pihko, P. M.; Majander, I.; ErkkilaÌ, A.; *Top. Curr. Chem.* **2009**, *291*, 145.
24. (a) Li, J.-H.; Du, D.-M. *Chem. Asian J.* **2014**, *9*, 3278. (b) Li, J.-H.; Feng, T.-F.; Du, D.-M. *J. Org. Chem.* **2015**, *80*, 11369. (c) Han, B.; Huang, W.; Ren, W.; He, G.; Wang, J.-H.; Peng, C. *Adv. Synth. Catal.* **2015**, *357*, 561. (d) Sun, J.; Jiang, C.-P.; Zhou, Z.-H. *Eur. J. Org. Chem.*, **2016**, 1165. (f) Wang, L.; Li, S.; Chauhan, P.; Hack, D.; Phillips, A. R.; Puttreddy, R.; Rissanen, K.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2016**, *22*, 5123. (g) Hack, D.; Dürr, A. B.; Deckers, K.; Chauhan, P.; Seling, N.; Rübennach, L.; Mertens, L.; Raabe, G.; Schoenebeck, F.; Enders, D. *Angew. Chem. Int. Ed.*, **2016**, *55*, 1797. (h) Zhang, X.-L.; Tang, C.-K.; Xia, A.-B.; Feng, K.-X.; Du, X.-H.; Xu, D.-Q. *Eur. J. Org. Chem.* **2017**, 3152.
25. CCDC 1556056 contains the crystallographic data for **5**.
26. CCDC 1556055 contains the crystallographic data for **3l**.

Organocatalytic asymmetric intramolecular aza-Henry reaction: Facile synthesis of *trans*-2,3-disubstituted tetrahydroquinolines*

Abstract:

An enantio- and diastereoselective organocatalytic intramolecular aza-Henry (nitro-Mannich) reaction has been developed. The *trans*-2-aryl-3-nitro-tetrahydroquinoline products were obtained in high yields and good enantioselectivities using a bifunctional tertiary amine thiourea catalyst. Excellent enantioselectivities were obtained after single recrystallization for some products.



*Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2015**, *13*, 6825.

6.1. Introduction:

The tetrahydroquinoline motifs are present in several biologically active and medicinal compounds.[1-3] The basic skeleton having tetrahydroquinoline ring resides in a significant number of the pharmaceutical drugs and biologically active molecules as shown in the Figure 1. Angustureine, Cuspareine and Galipinine have been reported to exhibit anti-malarial and cytotoxic activities.[4] 2-Substituted quinoline alkaloids were used in folk medicine as a bitter tonic in dyspepsia, dysentery and chronic diarrhoea and for the treatment of fever.[5] (-)-Isoschizogaline[6] and Helquinone[7] display antibiotic activities. The other drug molecules, Viratmycin[8] displays antiviral, antibiotic and antifungal activities and the racemic tetrahydroquinoline[9] containing imidazole ring is treated as an antimalarial drug (Figure 1).

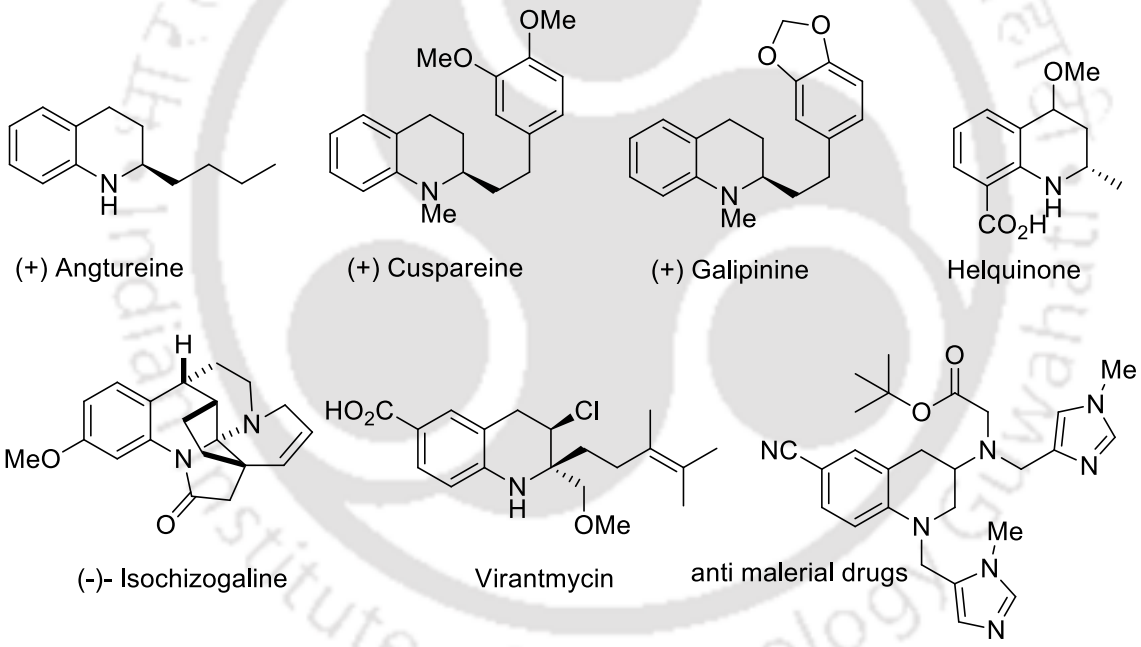


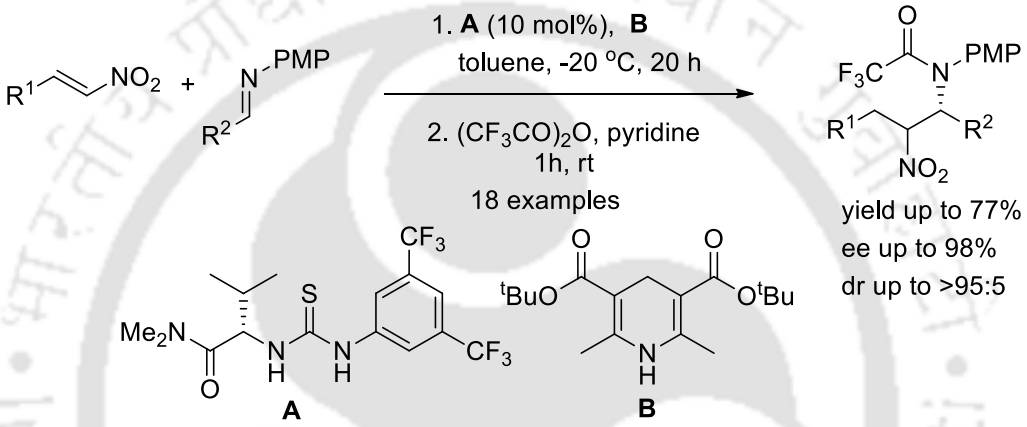
Figure 1. Pharmaceutical drugs and biologically active tetrahydroquinolines.

Thus, the development of new strategies and protocols for the synthesis of tetrahydroquinoline derivatives in enantiomerically pure form is an important task for synthetic chemists.[10a-d] In addition, the interest for the synthesis of nitrogen heterocycles is persistent due to their importance in medicinal chemistry and presence in various natural products. Enantiopure nitro substituted compounds are multipurpose building blocks in organic synthesis because they can easily be transformed into a vast array of

important chiral compounds, such as amines, aldehydes, acids or de-nitrated compounds.[10e-g]

6.2. Previous reports nitro-Mannich reaction (aza-Herny reaction):

Anderson group developed asymmetric tandem reduction nitro-Mannich reaction of β-nitrostyrene and PMP-imine using thio urea catalyst and a Hantzsch ester as hydride source. The anti-β-nitroamines was protected by trifluoroacetic anhydrides and the trifluoroacetamides products were reported in good yields, high diastereomeric ratios and excellent enantioselectivity (Scheme 1).[11]



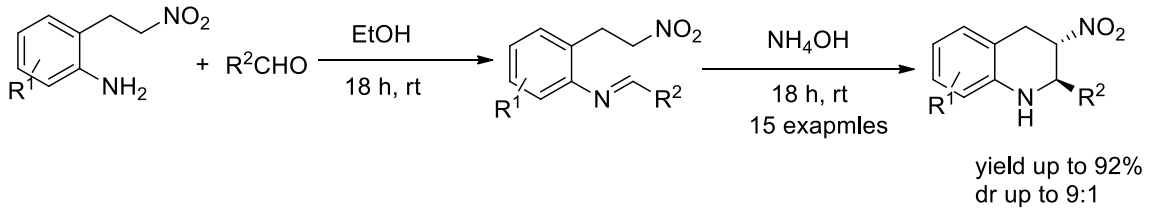
Scheme 1

6.3. Previous reports on synthesis of tetrahydroquinoline:

General synthetic methods for the synthesis of tetrahydroquinolines include the asymmetric Povarov reaction,[12] double Michael reaction, inverse electron-demand aza-Diels-Alder, aza-Michael addition,[13] nitro-Mannich cyclization,[14] aza-Henry reaction,[15] internal redox processes[16] and various reductions of quinolones.[17]

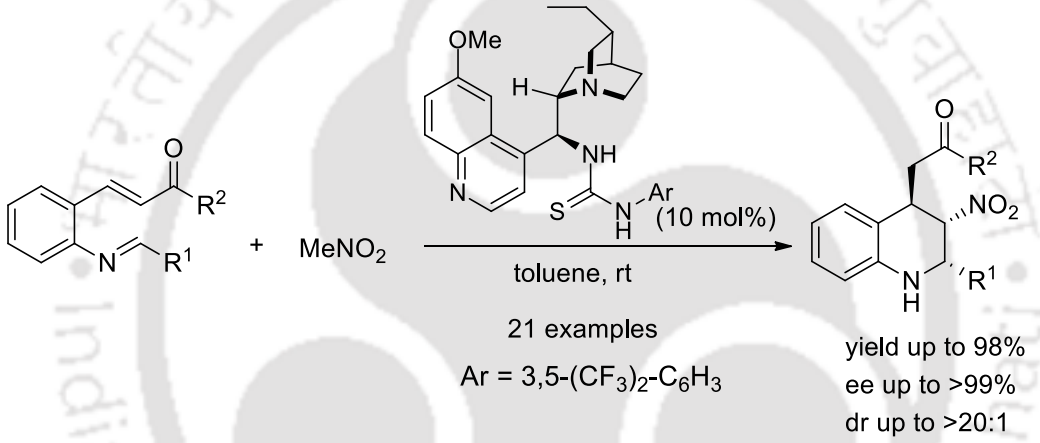
6.3.1. Synthesis of tetrahydroquinolines *via* aza-Henry reaction:

Anderson *et al.* established a simple protocol for the synthesis of substituted 3-nitrotetrahydroquinolines with high diastereoselectivities by intramolecular aza-Henry reaction. The reaction was performed between 2-(2-nitroethyl)arylamines and an aldehydes, in EtOH, followed by the addition of NH_4OH to synthesize *trans*-3-nitrotetrahydroquinolines in high yields (Scheme 2).[18]



Scheme 2

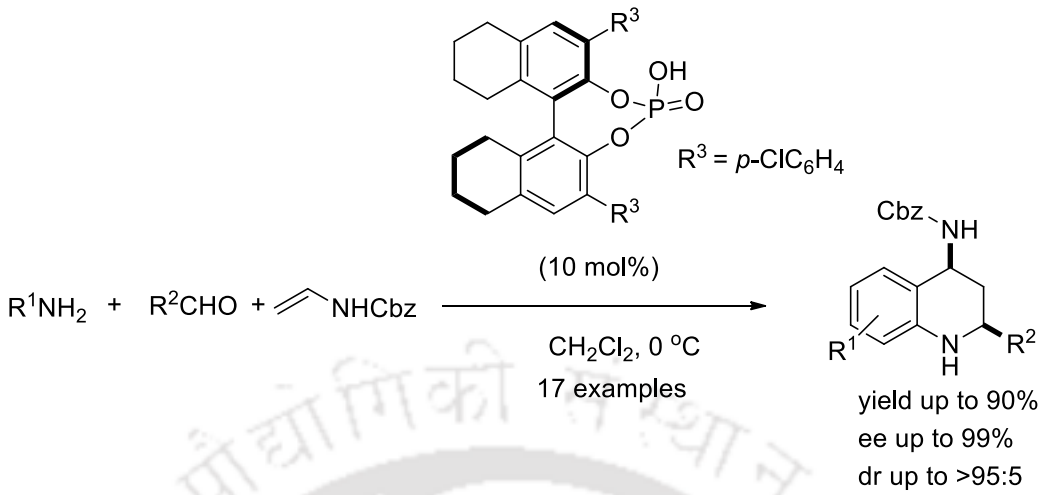
An organocatalytic enantioselective Michael/aza-Henry tandem reaction of chalcone derived imines and nitromethane was described by Xu *et al*. Using hydroquinine derived tertiary amine thiourea catalyst, a variety of trisubstituted tetrahydroquinolines were synthesized with excellent enantio- and diastereoselectivities (Scheme 3).[15]



Scheme 3

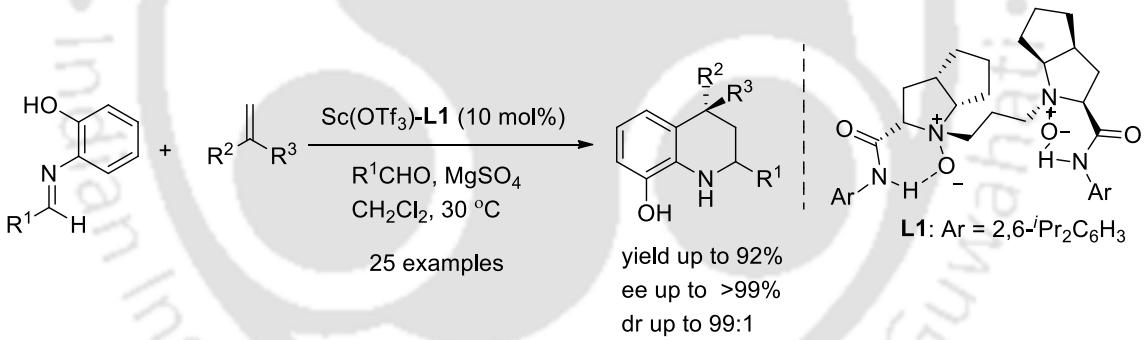
6.3.2. Synthesis of tetrahydroquinoline *via* Povarov reaction:

Povarov reaction is a three component reaction between suitable arylamine, aldehyde, and a dienophile. This reaction allows the formation of three bonds in a single operation.[19] For example, Zhu and co-workers achieved a phosphoric acid catalyzed Povarov reaction between anilines, aldehydes and benzyl *N*-vinylcarbamates to furnish the disubstituted tetrahydroquinolines with excellent enantio- and diastereoselectivities (Scheme 4).[20]



Scheme 4

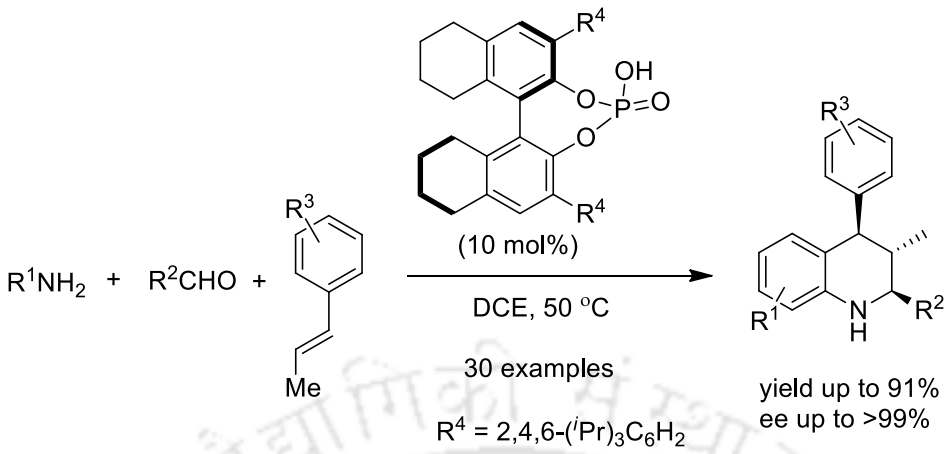
The *N*,*N*′-dioxide **L1**-Sc(OTf)$_3$ complex catalyzed Povarov reaction of *N*-aryl aldimines and α-alkyl styrenes was demonstrated by Feng group. Using *N*,*N*′-dioxide **L1**-Sc(OTf)$_3$ complex, a series of tetrahydroquinolines bearing a quaternary stereocenter at the C4 position was achieved with excellent diastereo- and enantioselectivities (Scheme 5).[21]



Scheme 5

6.3.3. Synthesis of tetrahydroquinoline *via* inverse electron demand aza-Diels-Alder reaction:

The chiral phosphoric acid catalyzed inverse electron demand aza-Diels-Alder reaction of aldehydes, derivatives of anilines and isoeugenol derivatives has been described to give high range of enantio- and diastereoselectivities of substituted tetrahydroquinolines by Masson *et al.* (Scheme 6). [22]

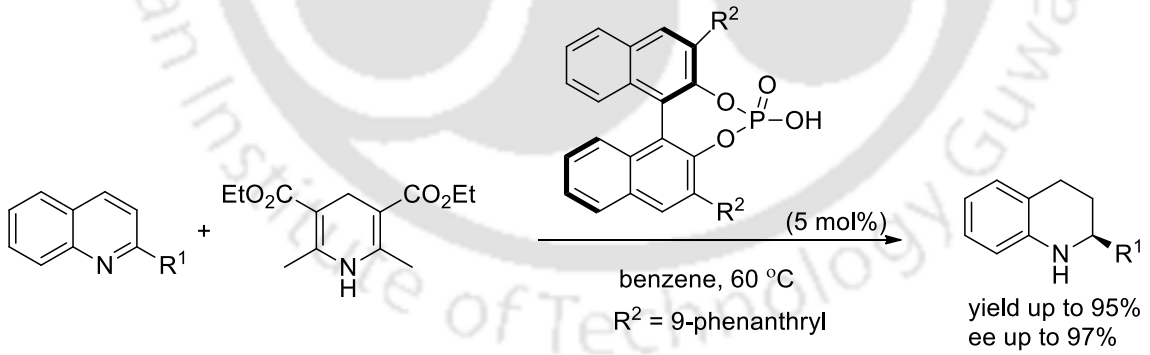


Scheme 6

6.3.4. Asymmetric synthesis of tetrahydroquinoline *via* hydrogenation reaction:

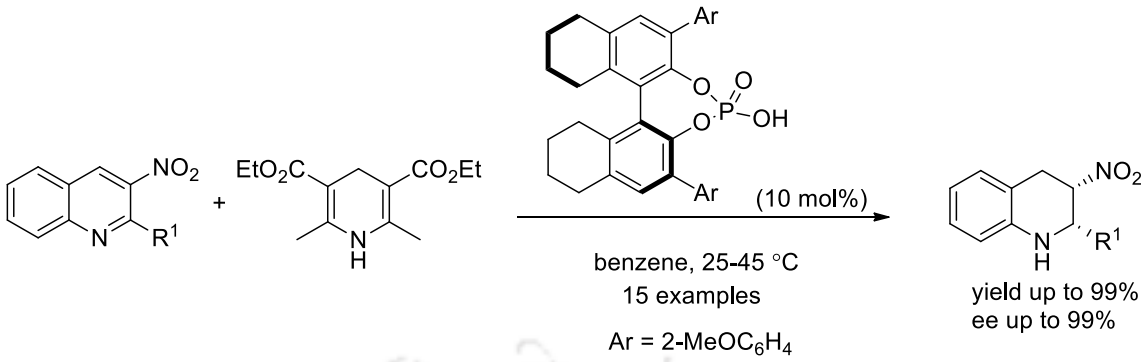
Asymmetric hydrogenation reaction was applied for the synthesis of enantiopure tetrahydroquinolines, which is the best and easiest way to synthesize tetrahydroquinolines from quinoline derivatives.

The first chiral Brønsted acid catalysed asymmetric hydrogenation reaction was demonstrated by Rueping group. Using a chiral phosphoric acid catalyst, a variety of 2-arylquinolines were reacted with Hantzsch esters to provide the corresponding 2-aryl-tetrahydroquinolines in high yields and excellent enantioselectivities (Scheme 7).[23]



Scheme 7

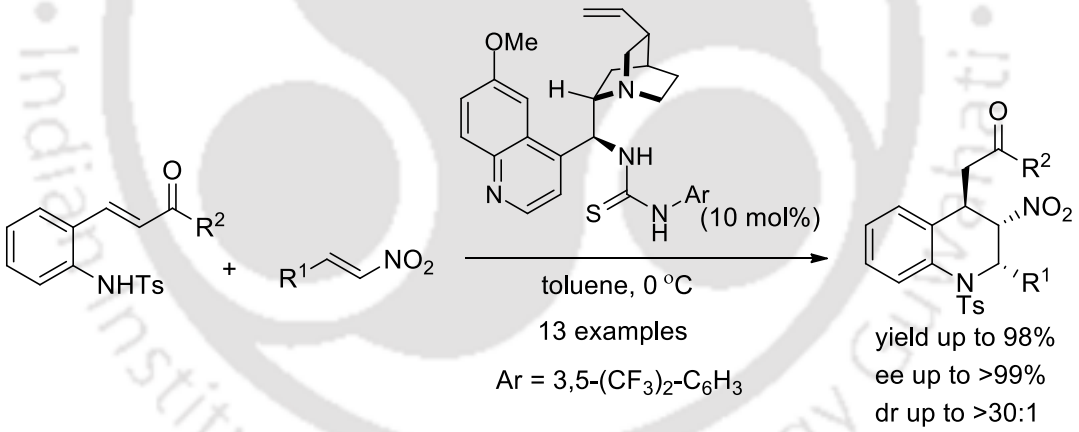
Zhou group established a chiral phosphoric acid catalyzed asymmetric hydrogenation reaction of 2-aryl-3-nitroquinolines with Hantzsch esters to generate highly optically pure *cis*-3-nitrotetrahydroquinolines by using the chiral phosphoric acid catalyst. Generally *cis*-products were observed, however, when the reaction was performed between DBU and *cis*-3-nitrotetrahydroquinolines, the diastereoselectivity got switched in favour of the *trans*-3-nitrotetrahydroquinolines (Scheme 8).[24]



Scheme 8

6.3.5. Synthesis of tetrahydroquinoline *via* double Michael reaction:

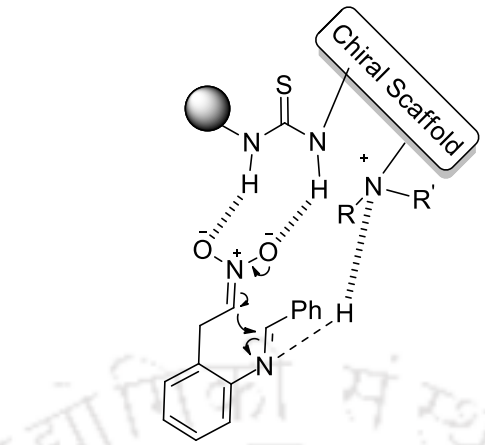
Kim group reported a highly efficient double Michael reaction of *ortho*-*N*-tosylaminophenyl-α,β-unsaturated ketones with nitrostyrenes. In this method, quinine derived tertiary amine thiourea catalyst was employed to afford a series of 2,3,4-trisubstituted tetrahydroquinolines with high diastereo- and enantioselectivities (Scheme 9).[25]



Scheme 9

6.4. Concept:

By taking the inspiration from literature, we interested to synthesize enantiopure *trans*-3-nitrotetrahydroquinolines since the achiral version of the same reaction was previously reported by Anderson and co-workers.[18] We estimated that chiral bifunctional thiourea derivative would be used for simultaneous dual activation of nitro- and imine group of the substrates. The thiourea moiety would activate the nitronate moiety by dual hydrogen bonding. Simultaneously the imine would be activated by the protonated tertiary amino group of thiourea derivative (Scheme 10).



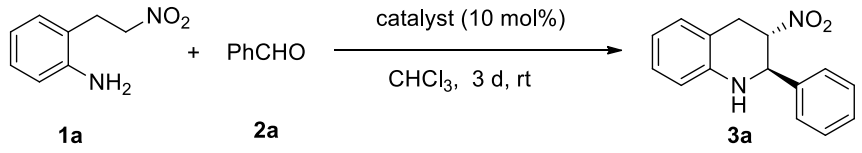
Proposed simultaneous dual activation
by bifunctional thiourea derivative

Scheme 10

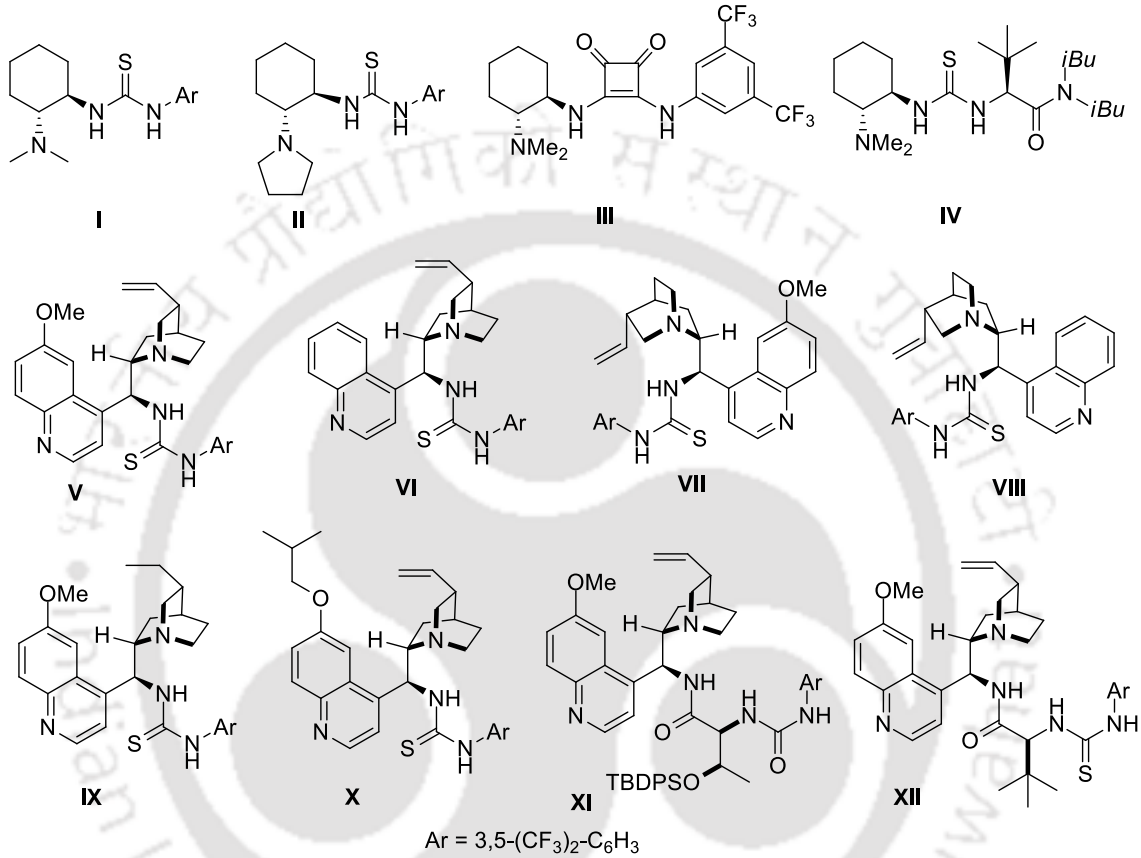
6.5. Result and discussion:

Initially, the optimization of the reaction was investigated with different organocatalysts (Table 1). The model reaction was performed with nitroalkane **1a** and benzaldehyde **2a** using Takemoto catalyst **I** in $CHCl_3$ at room temperature. After stirring for three days, the desired intramolecular aza-Henry product **3a** was isolated in 65% yield with 40% ee as a single diastereomer (entry 1). However, a racemic product was obtained with catalyst **II** having pyrrolidine moiety (entry 2). Then the bifunctional tertiary amine squaramide catalyst **III** was screened and no product was obtained. Further, the reaction was checked with catalyst **IV** with an extra chiral centre. Though the desired product **3a** was obtained with catalyst **IV**, the enantioselectivity was poor (entry 4). Pleasantly, both the yield and enantioselectivity were improved with quinine derived bifunctional thiourea catalyst **V** (entry 5).[26] Despite these catalysts, other cinchona alkaloids derived tertiary amine thiourea catalysts **VI-IX** were also tested (entries 6-8). Unfortunately, the enantioselectivity did not improve with these catalysts. In addition, the catalyst screening was extended using quinine derived catalysts **X-XII**, but better results were not obtained (entries 10-12). As a result, catalyst **V** was selected as the best catalyst for further optimizations.

Table 1: Catalyst optimization



1a 2a 3a



entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	65	40
2	**II**	50	0
3	**III**	-	-
4	**IV**	50	5
5	**V**	**75**	**66**
6	**VI**	68	54
7	**VII**	65	60
8	**VIII**	70	60
9	**IX**	68	42
10	**X**	55	60

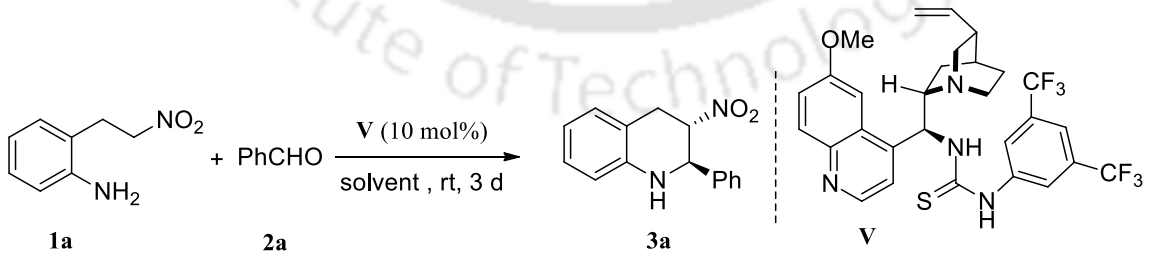
11	**XI**	40	37
12	**XII**	45	33

[a]Reaction condition: 0.12 mmol of **1a** with 0.16 mmol of **2a** in 0.6 mL $CHCl_3$ using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

6.5.1. Solvent and temperature screening:

The reaction optimization was further continued with various solvents in presence of catalyst **V** (Table 2). Initially, the racemic tetrahydroquinoline product **3a** was obtained with ethanol (entry 1). Comparable results were observed employing aromatic solvents such as toluene, benzene, trifluorotoluene and xylene (entries 2-5). Moreover, chlorinated solvents were also used in the reaction, but moderate enantioselectivities were attained (entries 6-10). Slight high enantioselectivities were achieved in etharate solvents such as diethyl ether and MTBE (entries 11-12). Interestingly, solvent blends such as n-pentane:CH_2Cl_2 (5:1), n-hexane:CH_2Cl_2 (5:1) and n-heptane:CH_2Cl_2 (5:1), were found to be slightly effective to improve the enantioselectivity of the product (entries 13-15). From the solvent examinations, the highest enantioselectivity (74%) and yield (85%) were attained with n-pentane:CH_2Cl_2 (entry 14). After performing the reaction at low temperature (0 ^oC), enantioselectivity was slightly improved, but equal amounts of *cis* and *trans* isomers of **3a** were obtained (entry 16). To our delight, the enantioselectivity of product **3a** got improved to 98% ee after recrystallization of the product in ethanol at room temperature (entry 14)

Table 2: Solvents and temperature optimization



1a 2a 3a V

entry[a]	solvent	yield (%)[b]	ee[c]
1	Ethanol	70	-
2	Toluene	70	48
3	Benzene	80	67

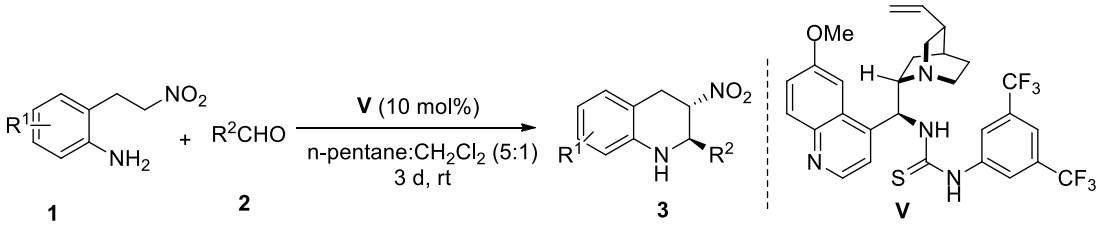
4	$PhCF_3$	78	60
5	Xylene	50	50
6	Chlorobenzene	75	60
7	CH_3Cl	75	66
8	CH_2Cl_2	78	58
9	CCl_4	80	57
10	DCE	70	52
11	Diethyl ether	80	70
12	MTBE	70	70
13	n-Hexane:CH_2Cl_2(5:1)	80	72
14	**n-Pentane:CH_2Cl_2(5:1)**	**85**	**74(98)[d]**
15	n-Heptane:CH_2Cl_2(5:1)	78	69
16[e]	n-Pentane:CH_2Cl_2(5:1)	85	80

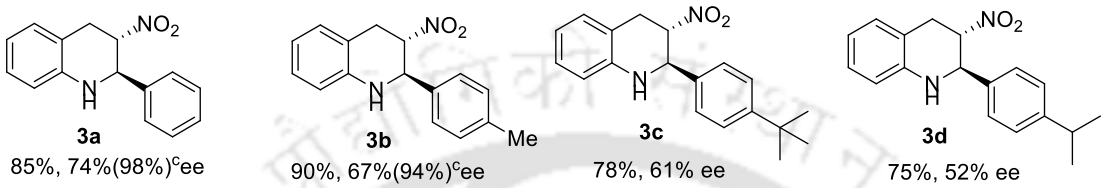
[a]Reaction condition: 0.12 mmol of **1a** with 0.16 mmol of **2a** in 0.6 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column. [d]After recrystallization. [e]Reaction run at 0 °C.

6.5.2. Substrate scope:

The scope of the reaction was ventured using the standard optimized conditions. Initially, different aldehydes were reacted with nitroalkane **1a** and the standard reaction conditions were found to be suitable for a variety of aryl and aliphatic aldehydes affording only *trans*-isomer (Table 3). Firstly, different *para*-substituted benzaldehydes were found to provide the products in high yields and good enantioselectivities. For example, 4-methylbenzaldehyde **2b** afforded the product **3b** in 67% ee and pleasingly, it was improved to 94% ee after recrystallization. However, other 4-alkyl substituted products **3c** and **3d**, which were obtained with moderate enantioselectivities, were sticky liquids and did not recrystallize under various conditions. Anisaldehyde (**2e)** delivered a sticky liquid product **3e** in moderate yield and enantioselectivity. Interestingly, solid crystalline products (**3f**-**3h**) were obtained from 4-halo substituted benzaldehydes in high yields with good optical purities. Excellent enantioselectivities could be attained after single recrystallization for these products. In addition, a solid product **3i** having 4-phenyl moiety was attained in excellent yield (95%) with 61% enantioselectivity which could be

Table 3. Substrate scope for the aza-Henry reaction[a,b,c]



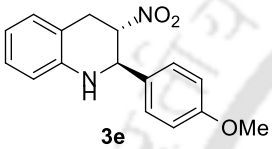


3a 85%, 74%(98%)[c]ee

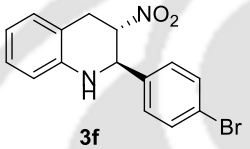
3b 90%, 67%(94%)[c]ee

3c 78%, 61% ee

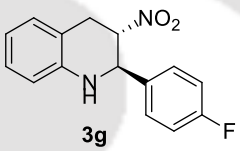
3d 75%, 52% ee



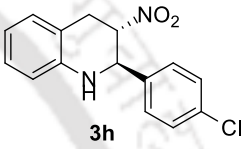
3e 60%, 60% ee



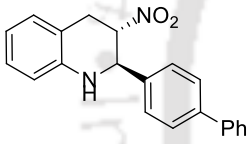
3f 80%, 58%(94%)[c] ee



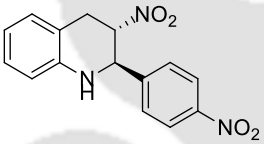
3g 80%, 68%(99%)[c] ee



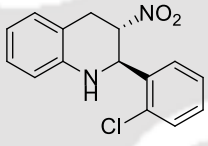
3h 83%, 70%(96%)[c]ee



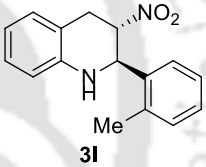
3i 95%, 61%(78%)[c]ee



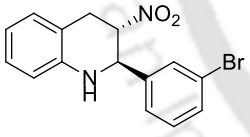
3j 95%, 14% ee



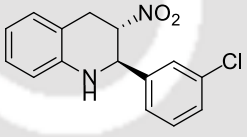
3k 75%, 40%(99%)[c] ee



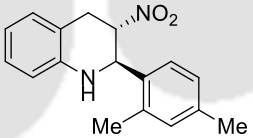
3l 70%, 48%ee



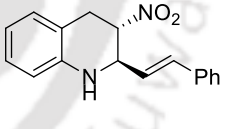
3m 85%, 47% ee



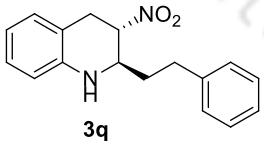
3n 80%, 20% ee



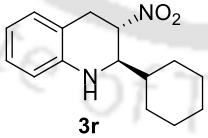
3o 91%, 70%(95%)[c] ee



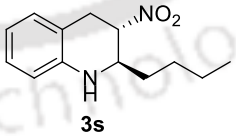
3p 75%, 28% ee



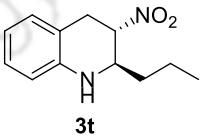
3q 75%, 41% ee



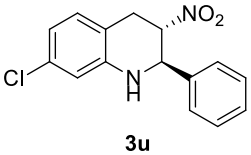
3r 83%, 40% ee



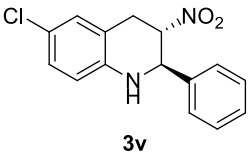
3s 82%, 68% ee



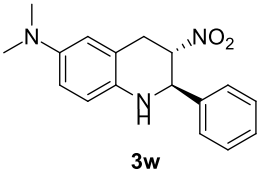
3t 81%, 63% ee



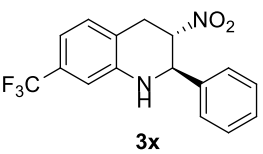
3u 70%, 75%(88%)[c] ee



3v 72%, 62%(74%)[c] ee



3w 80%, 64%(76%)[c] ee



3x 69%, 76%(82%)[c] ee

[a]Reaction condition: 0.12 mmol of **1** with 0.16 mmol of **2** in 0.6 mL n-pantane:CH_2Cl_2 (5:1) using 10

mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column, ees in parenthesis are after recrystallization.

enhanced to 78% ee after recrystallization. When 4-nitrobenzaldehyde **2j** was tested in the reaction, the product **3j** was isolated with excellent yield but having lowest value enantioselectivity possibly due to strong electron drawing effect. Next, *ortho*-substituted benzaldehydes **2k** and **2l** having 2-chloro and 2-methyl group were employed in the reaction. The corresponding products **3k** and **3l** were isolated with low level of enantioselectivities and in good yields. However, the enantioselectivity of product **3k** could be improved to an excellent 99% ee after single crystallization. Under the reaction conditions, *meta*-substituted products **3m** and **3n** were achieved in excellent yields with good ees. Whereas the product **3o**, synthesized from 2,4-dimethyl substituted benzaldehyde, was obtained with excellent yield (91%) and good enantioselectivity (70%) and also the enantioselectivity could be improved to 95% ee after recrystallization. Meanwhile, cinnamaldehyde was employed in the reaction, but poor enantioselectivity was attained for the product **3p**. Aliphatic aldehydes are challenging substrates for this kind of reaction due to imine-enamine tautomerization. Gratifyingly, aliphatic aldehydes were successfully engaged in the reaction and moderate enantioselectivities with good yields were obtained for the products **3q**-**3t**. Moreover, different nitroalkanes (**1b**-**1d**) having substitutions on the aryl group were prepared and reacted with benzaldehyde **2a** under the reaction conditions. 4-Chloro substituted nitroalkane **1b** provided the product **3u** in 70% yield with 75% ee which can be boosted up to 88% ee after crystallization. Similarly, 5-chloro substituted nitroalkane **1c** resulted in the formation of the product **3v** in 72% yield and with slightly lower enantioselectivity (62% ee). The enantioselectivity can be augmented to 74% ee after crystallization. The chloro functionalities in the products **3u** and **3v** could be exploited in Pd catalyzed cross-coupling reactions. Then nitroalkane **1d** having dimethylamino functionality was prepared and it was found to be tolerant under the reaction condition providing product **3w** in 80% yield and 64% ee. Here also crystallization helps to improve the enantioselectivity (up to 76% ee). Finally, CF_3 substituted product **3x** was obtained from nitroalkane **1e** in moderate yield (69%) and enantioselectivity (76% ee) that can be increased to 82% ee after crystallization.

6.5.3. Absolute configuration:

The absolute configuration of the product **3f** was determined to be (2*R*, 3*S*) by single X-ray crystallography[27] (Figure 3) as well as by comparison with the optical rotation with literature value[24]

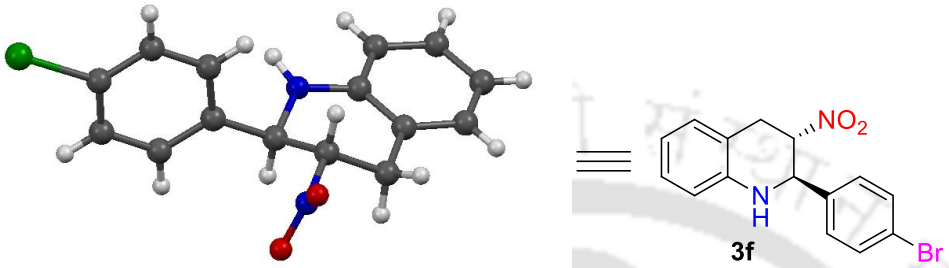
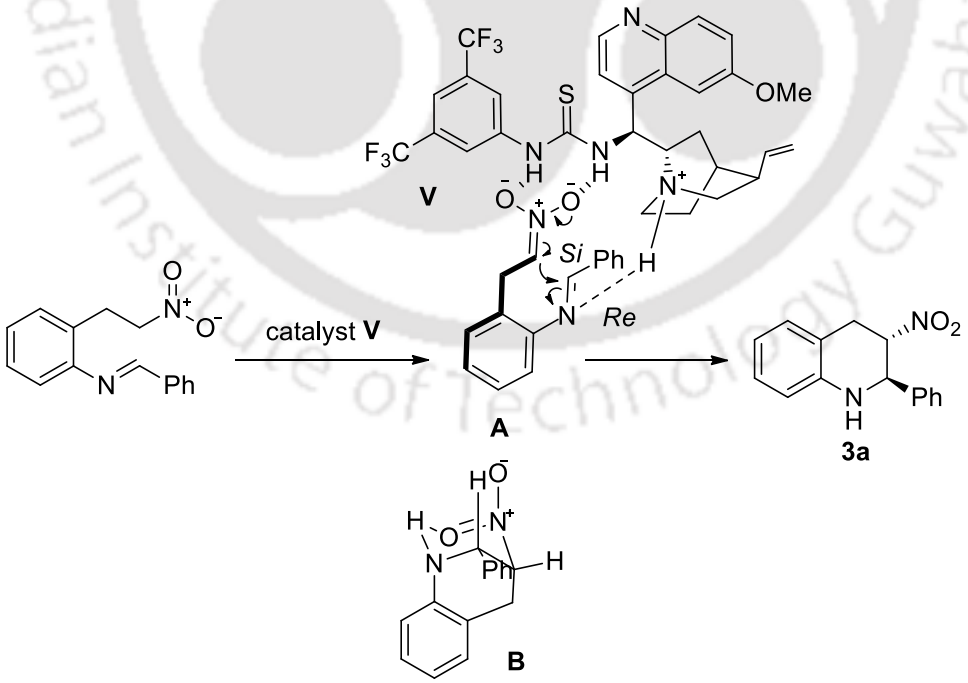


Figure 3. X-ray crystallographic structure of **3f**

6.5.4. Transition state of the aza-Henry reaction of product 3a:

On the basis of the absolute configuration, a plausible transition state (**A**) has been drawn in Scheme 10. It dictates that the quinine derived thiourea catalyst **V** binds in bifunctional mode with the substrate.[28] The thiourea moiety presumably activates the nitronate moiety[14] that is generated from the nitroalkane by deprotonation.



Scheme 10. Plausible TS and explanation for diastereoselectivity

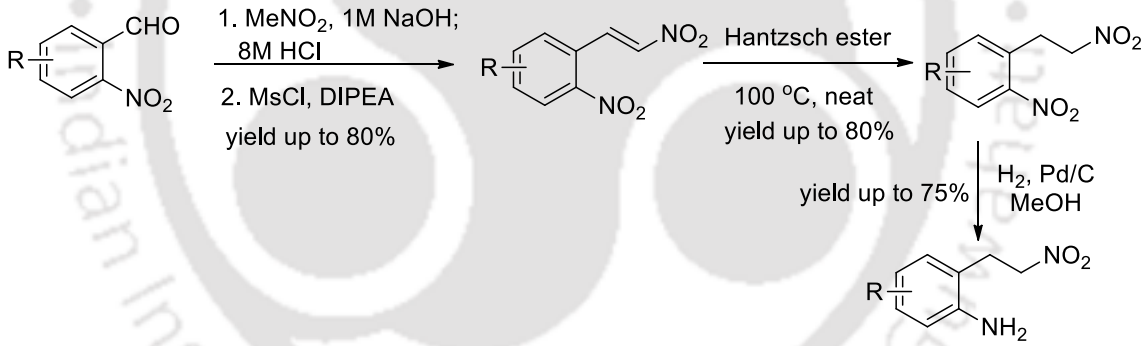
Then the attack of the nitronate group takes place from the *Si* face of the imine. Simultaneous activation of the imine by the protonated tertiary amino group takes place from the *Re* face and the desired product **3a** is formed. The extra stability of the *trans*-product could be explained by the model (**B**) where the nitro group and amino group are connected through intramolecular H-bond and the phenyl group takes the equatorial position.[5b]

6.6. Conclusions:

In this chapter was demonstrated asymmetric synthesis of *trans*-2-aryl/alkyl-3-nitro-tetrahydroquinolines using a direct intramolecular aza-Henry reaction. Easily available quinine alkaloid derived bifunctional thiourea catalyst and straight forwardly synthesized amino nitroalkanes were utilized for this purpose.

6.7. Experiment section:

6.7.1. General procedure for the synthesis of nitroamine (1):[5b]



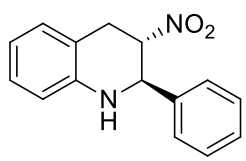
Scheme 11

6.7.2. General procedure for the intramolecular aza-Henry reaction (3):

A solution of nitro-amine **1 (**0.12 mmol, 1 eq.) and aldehyde **2 (**0.156 mmol, 1.3 eq.) in 0.6 mL pentane:CH_2Cl_2 (5:1) was stirred at room temperature for 2-3 h. Then **V** (10 mol%) was added to the mixture and stirred for 3 days. After 3 days the crude reaction mixture subjected to column chromatography on silica gel using mixtures of hexanes and ethyl acetate as eluent to afford the corresponding product. Recrystallization was done in ethanol at room temperature.

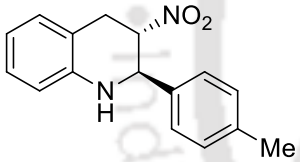
6.7.3. Characterization of the products:

(2*R*,3*S*)-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3a):



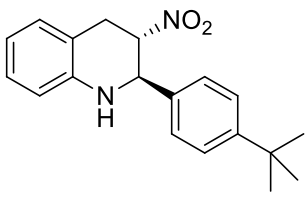
Yellow solid (26 mg, 85% yield); mp- 100-101 °C (lit.[18] mp 98-99° C); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.25 (dd, *J* = 4.4, 15.2 Hz, 1H), 3.57 (dd, *J* = 8.6, 15.8 Hz, 1H), 4.14 (bs, 1H), 4.87 (d, *J* = 7.6 Hz, 1H), 4.90-4.96 (m, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 7.05-7.11 (m, 2H), 7.34-7.40 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.4, 59.0, 85.3, 114.2, 116.7, 118.6, 127.3, 128.1, 129.2, 129.5, 138.7, 142.7; **ESI-MS** m/z calcd. for $C_{15}H_{14}N_2O_2$ $[M+H]^+$ 255.1128, found 255.1123; **FT-IR (KBr)** 3407, 3030, 1604, 1547, 1493, 1371 cm^{-1}; The ee value 74% (t_{minor} = 10.62 min, t_{major} = 16.82 min) and after recrystallization ee value 98% were measured by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-propanol = 80:20, flow rate = 1mL/min; **Optical rotation** $[\alpha]_D^{23}$ = +42.0 (c 0.17, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-3-nitro-2-*p*-tolylquinoline (3b):



White solid (29 mg, 90% yield); mp- 105-106 °C (lit.[18] mp 107-109 °C); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.25 (dd, *J* = 4.8, 16 Hz, 1H), 3.57 (dd, *J* = 8.8, 16.2 Hz, 1H), 4.11 (bs, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 4.88-4.93 (m, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 8.4 Hz, 1H), 7.05-7.10 (m, 2H), 7.16-7.18 (m, 2H), 7.26-7.28 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 21.3, 31.6, 58.9, 85.5, 114.2, 116.7, 118.5, 127.2, 128.1, 129.5, 129.9, 135.5, 139.1, 142.8; **ESI-MS** m/z calcd for $C_{16}H_{16}N_2O_2$ $[M+H]^+$ 269.1285, found 269.1283; **FT-IR (KBr)** 3390, 2920, 2850, 1603, 1546, 1454, 1366, 1204 cm^{-1}; The ee value 67% (t_{minor} = 9.76 min, t_{major} = 13.14 min) and after recrystallization ee value 94% were determined by HPLC analysis using Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{23}$ = +41.0 (c 0.15, $CHCl_3$)

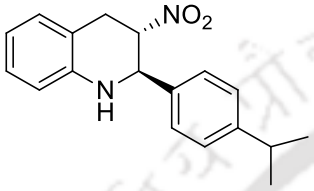
(2*R*,3*S*)-2-(4-*tert*-butylphenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3c):



Yellow oil (23.8 mg, 78% yield); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 1.30 (s, 9H), 3.26 (dd, *J* = 4.8, 16 Hz, 1H), 3.56 (dd, *J* = 9.2, 16 Hz, 1H), 4.12 (bs, 1H), 4.84 (d, *J* = 9.2 Hz, 1H), 4.90-4.96 (m, 1H), 6.58 (d, *J* = 8, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 7.06-7.11 (m, 2H), 7.31-7.32 (m, 2H), 7.37-7.39 (m, 2H);

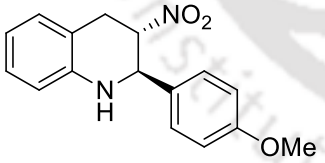
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 31.4, 31.6, 58.7, 85.2, 114.2, 116.7, 118.5, 126.1, 127.1, 128.1, 129.5, 135.5, 142.8, 152.2; **ESI-MS** m/z calcd for $C_{19}H_{22}N_2O_2$ $[M+H]^+$ 311.1754, found 311.1753; **FT-IR (KBr)** 3374, 2964, 2924, 1607, 1546, 1370 cm^{-1}; The ee value 61% (t_{minor} = 12.24 min, t_{major} = 14.36 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 99.5:0.5, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{23}$ = +20.0 (c 0.75, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-2-(4-isopropylphenyl)-3-nitro-quinoline (3d):



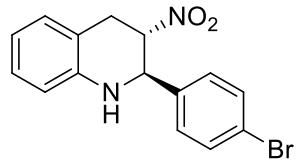
Yellow oil (26.7 mg, 75% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 1.23 (d, *J* = 6.4 Hz, 6H), 2.86-2.93 (m, 1H), 3.26 (dd, *J* = 5.2, 16.28 Hz, 1H), 3.56 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.12 (bs, 1H), 4.83 (d, *J* = 8 Hz, 1H), 4.91-4.95 (m, 1H), 6.58 (d, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 7.05-7.10 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 24.0, 24.1, 31.6, 34.0, 58.8, 85.3, 114.2, 116.7, 118.5, 127.3, 127.3, 128.1, 129.5, 135.9, 142.8, 150.0; **ESI-MS** m/z calcd for $C_{18}H_{20}N_2O_2$ $[M+H]^+$ 297.1598, found 297.1595; **FT-IR (KBr)** 3427, 2965, 2928, 1726, 1607, 1550, 1493, 1370 cm^{-1}; The ee value 52% (t_{minor} = 12.53 min, t_{major} = 17.15 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 99.5:0.5, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{24}$ = +25.0 (c 0.27, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-2-(4-methoxyphenyl)-3-nitro-quinoline (3e):



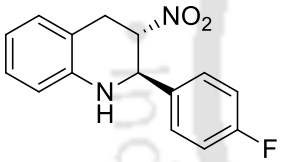
Brown oil (20.5 mg, 60% yield); R_f value 0.25 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.27 (dd, *J* = 4.8, 16 Hz, 1H), 3.57 (dd, *J* = 9.6, 16 Hz, 1H), 3.80 (s, 3H), 4.09 (bs, 1H), 4.77 (d, *J* = 8.4 Hz, 1H), 4.87-4.92 (m, 1H), 6.59 (d, *J* = 8 Hz,1H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.06-7.10 (m, 2H),7.31 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.9, 55.5, 58.8, 85.7, 114.2, 114.6, 116.8, 118.6, 128.1, 128.6, 129.5, 130.3, 142.9, 160.3; **ESI-MS** m/z calcd for $C_{16}H_{16}N_2O_2$ $[M+H]^+$ 285.1234, found 285.1237; **FT-IR (KBr)** 3382, 3345, 2924, 2854, 1730, 1603, 1546, 1509, 1374, 1337 cm^{-1}; The ee value 60% (t_{minor} = 26.31 min, t_{major} = 31.05 min) was determined by HPLC analysis using AS-H Chiralpak column, 254 nm, 25 °C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{27}$ = +33.0 (c 0.15, $CHCl_3$).

(2*R*,3*S*)-2-(4-bromophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3f):



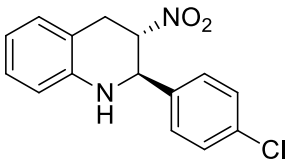
Yellow solid (31.9 mg, 80% yield); mp- 128-129 ^{o}C (lit.[18] mp 125-127^{o} C); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.56 (dd, *J* = 8.4, 16 Hz, 1H), 4.12 (bs, 1H), 4.84-4.91 (m, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.76(t, *J* = 7.6 Hz, 1H), 7.06-7.12 (m, 2H), 7.26-7.29(m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.2, 58.4, 85.1, 114.4, 116.6, 118.9, 123.2, 128.2, 129.0, 129.5, 132.4, 137.7, 142.4; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Br$ $[M+H]^+$ 333.0233, found 333.0231; **FT-IR (KBr)** 3398, 2924, 2854, 1607, 1550, 1488, 1374 cm^{-1}; The ee value 58% (t_{minor} = 20.09 min, t_{major} = 25.19 min) and after recrystallization ee value 96% were determined by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min; **Optical rotation** was $[\alpha]_D^{25}$ = +14.0 (c 0.25, $CHCl_3$).

(2*R*,3*S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-3-nitro- quinoline (3g):



Pale yellow solid (26 mg, 80% yield), mp- 130-131 ^{o}C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.26 (dd, *J* = 4.8, 16 Hz, 1H), 3.58 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.11 (bs, 1H), 4.82-4.91 (m, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 7.04-7.11 (m, 4H), 7.37-7.40 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.6, 58.5, 85.5, 114.4, 116.2 (d, *J* = 22 Hz), 116.7, 118.9, 128.2, 129.2 (d, *J* = 9 Hz), 129.5, 134.5, 134.3, 142.6, 162.0, 164.4; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2F$ $[M+H]^+$ 273.1034, found 273.1030; **FT-IR (KBr)** 3407, 2920, 2850, 1730, 1546, 1370, 1337 cm^{-1}; The ee value 68% (t_{minor} = 14.7 min, t_{major} = 22.73 min) and after recrystallization ee value 99% were determined by HPLC analysis using chiralpak IA column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 95:5, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{26}$ = +57.0 (c 0.27, $CHCl_3$).

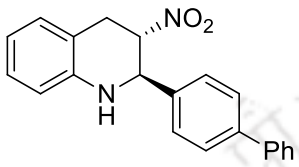
(2*R*,3*S*)-2-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3h):



Pale yellow solid (28.7 mg, 83% yield); mp- 119-120 ^{o}C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (dd, *J* = 4.8, 17 Hz, 1H), 3.57 (dd, *J* = 8.4, 16.4 Hz, 1H), 4.11 (bs, 1H), 4.85(d, *J* = 7.6 Hz, 1H), 4.88-4.91 (m, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.76 (t, *J* = 6.8 Hz, 1H), 7.06-7.12 (m, 2H), 7.32-7.35 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.3, 58.4, 85.2, 114.4, 116.6, 119.0, 128.2, 128.8, 129.5, 129.5, 135.1, 137.2,

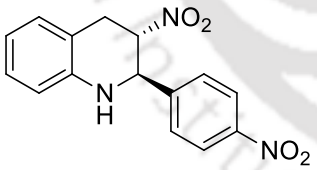
142.5; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Cl$ $[M+H]^+$ 289.0738, found 289.0736; **FT-IR (KBr)** 3398, 2924, 2850, 1607, 1548, 1484, 1370, 1337 cm^{-1}; The ee value 70% (t_{minor} = 9.07 min, t_{major} = 11.52 min) and after recrystallization ee value 96% were determined by HPLC analysis using a chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-propanol = 70:30, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{25}$ = +44.0 (c 0.25, $CHCl_3$).

(2*R*,3*S*)-2-(Biphenyl)-1,2,3,4-tetrahydro-3-nitroquinoline (3i):



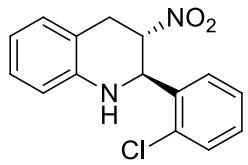
Yellow solid (37.6 mg, 95% yield); mp- 187-189 °C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.29 (dd, *J* = 4.8, 16 Hz, 1H), 3.59 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.18 (bs,1H), 4.92-5.00 (m, 2H), 6.63 (d, *J* = 8 Hz,1H), 6.76 (t, *J* = 7.2 Hz, 1H), 7.07-7.12 (m, 2H), 7.34-7.38 (m, 1H), 7.42-7.48 (m, 4H), 7.56-7.60 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 31.4, 58.7, 85.2, 114.3, 116.7, 118.7, 127.3, 127.8, 127.9, 128.1, 129.0, 129.5, 137.6, 140.5, 142.1, 142.7; **ESI-MS** m/z calcd for $C_{21}H_{18}N_2O_2$ $[M+H]^+$ 331.1441, found 331.1441; **FT-IR (KBr)** 3411, 2924, 2854, 1734, 1611, 1546, 1480, 1370, 1333 cm^{-1}; The ee value 61% (t_{minor} = 20.57 min, t_{major} = 23.57 min) and recrystallization ee 78% were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 98:2, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{27}$ = +51.0 (c 0.30, $CHCl_3$).

(2R,3S)-1,2,3,4-tetrahydro-3-nitro-2-(4-nitrophenyl)quinolone (3j):



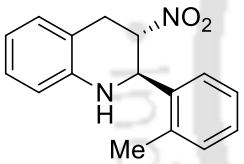
Yellow oil (34 mg, 95% yield); R_f value 0.3 (15:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.16 – 7.06 (m, 2H), 6.80 (t, *J* = 7.4 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.07 (d, *J* = 7.3 Hz, 1H), 4.92 (dd, *J* = 13.0, 7.9 Hz, 1H), 4.20 (s, 1H), 3.60 (dd, *J* = 16.3, 8.4 Hz, 1H), 3.22 (dd, *J* = 16.4, 5.0 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 30.7, 58.2, 84.7, 114.7, 116.5, 119.5, 124.5, 128.5, 129.7, 142.0, 146.0, 148.5; **ESI-MS** m/z calcd for $C_{15}H_{14}N_3O_4^+$ $[M+H]^+$ 300.0979, found 300.0978; **FT-IR (KBr)** 3402, 2925, 2854, 1622, 1594, 1568, 1548, 1489, 1370, 1337 cm^{-1}; The ee value 14% (t_{major} = 41.49 min, t_{minor} = 49.25 min) was determined by HPLC analysis using Daicel Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-propanol = 80:20, flow rate = 1 ml/min.

(2*R*,3*S*)-2-(2-chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3k):



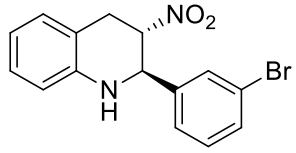
Pale yellow solid (25.9 mg, 75% yield); mp- 129-130 °C (lit.[1] mp 126-128° C); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 2.99 (dd, *J* = 4.8, 17 Hz, 1H), 3.51 (dd, *J* = 4.6, 17.2 Hz, 1H), 4.27 (bs, 1H), 5.03-5.06 (m, 1H), 5.64-5.66 (m, 1H), 6.68 (d, J = 8 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.22-7.29 (m, 2H), 7.38- 7.45 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 28.1, 54.3, 80.5, 114.1, 115.6, 118.6, 127.8, 128.3, 128.7, 129.6, 129.9, 130.2, 132.3, 137.7, 142.0; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Cl$ $[M+H]^+$ 289.0738, found 289.0737; **FT-IR (KBr)** 3398, 2924, 2854, 1726, 1607, 1546, 1464, 1484, 1362, 1259 cm^{-1}; The ee value 40% (t_{minor} = 7.55 min, t_{major} = 10.05 min) and recrystallization ee value 99% (t_{minor} = 7.55 min, t_{major} = 10.09 min) were determined by HPLC analysis using Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{30}$ = +04.0 (c 0.15, $CHCl_3$).

(2R,3S)-1,2,3,4-tetrahydro-3-nitro-2-*o*-tolylquinoline (3l):



Yellow oil (22 mg, 70% yield); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 6.7 Hz, 1H), 7.21 (d, *J* = 12.5 Hz, 3H), 7.09 (t, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 5.22 (d, *J* = 7.1 Hz, 1H), 4.97 (q, *J* = 8.0 Hz, 1H), 4.05 (s, 1H), 3.57 (dd, *J* = 16.1, 8.4 Hz, 1H), 3.24 (dd, *J* = 23.5, 2.9 Hz, 1H), 2.44 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 19.3, 31.0, 54.9, 83.4, 114.1, 116.5, 118.5, 127.0, 127.0, 128.2, 128.8, 129.5, 131.3, 136.2, 137.0, 142.8; **ESI-MS** m/z calcd for $C_{16}H_{16}N_2O_2$ $[M+H]^+$ 269.1285, found 269.1283; **FT-IR (KBr)** 3390, 2920, 2850, 1603, 1546, 1454, 1366, 1204 cm^{-1}; The ee value 48% (t_{minor} = 8.09 min, t_{major} = 10.23 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 98:2, flow rate = 1 mL/min.

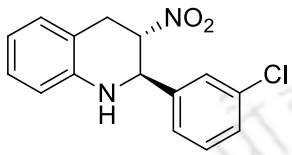
(2*R*,3*S*)-2-(3-bromophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3m):



Yellow solid (33.8 mg, 85% yield); mp- 108-110 °C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (d, *J* = 16 Hz, 1H), 3.56 (dd, *J* = 8.4, 17.2 Hz, 1H), 4.14 (bs, 1H), 4.88 (bs, 2H), 6.62 (d, *J* = 8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 7.08(t, *J* = 8.4 Hz, 2H), 7.22-7.25 (m.1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.57 (bs, 1H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 31.2, 58.3, 85.0, 114.4, 116.5, 119.0, 123.3, 126.2,

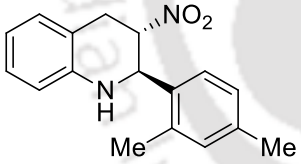
128.2, 129.5, 130.4, 130.8, 132.4, 141.1, 142.3; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Br$ $[M+H]^+$ 333.0233, found 333.0233; **FT-IR (KBr)** 3407, 2924, 2854, 1607, 1546, 1468, 1362 cm^{-1}; The ee value 47% (t_{minor} = 29.71 min, t_{major} = 37.24 min) was determined by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 95:5, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{28}$ = +06.0 (c 0.28, $CHCl_3$).

(2R,3S)-2-(3-chlorophenyl)-1,2,3,4-tetrahydro-3-nitroquinoline (3n):



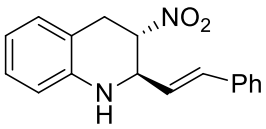
Yellow oil (28 mg, 80% yield); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.42 (s, 1H), 7.36 – 7.27 (m, 3H), 7.09 (dd, *J* = 16.7, 8.0 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.95 – 4.85 (m, 2H), 4.14 (s, 1H), 3.57 (dd, *J* = 16.3, 8.5 Hz, 1H), 3.24 (dd, *J* = 15.7, 3.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 31.2, 58.4, 58.0, 114.4, 116.5, 119.0, 125.7, 127.5, 128.3, 129.5, 129.6, 130.5, 135.2, 140.9, 142.4; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Cl$ $[M+H]^+$ 289.0738, found 289.0736; **FT-IR (KBr)** 3398, 2924, 2850, 1607, 1548, 1484, 1370, 1337 cm^{-1}; The ee value 20% (t_{minor} = 14.00 min, t_{major} = 16.94 min) was determined by HPLC analysis using a chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-propanol = 98:2, flow rate = 1 mL/min.

(2*R*,3*S*)-1,2,3,4-tetrahydro-2-(2,4-dimethylphenyl)-3-nitro-quinoline (3o):



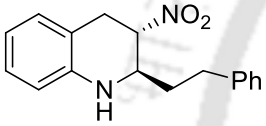
White solid (31 mg, 91% yield); mp 126-128 °C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 2.29 (s, 3H), 2.39 (s, 3H), 3.25 (dd, *J* = 4.8, 16.4 Hz,1H), 3.56 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.99 (bs, 1H), 4.92-4.97 (m, 1H), 5.14 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.99-7.03 (m, 2H), 7.06-7.10 (m, 2H), 7.27-7.29 (m, 1H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 19.2, 21.2, 31.3, 54.8, 83.6, 114.1, 116.5, 118.4, 126.9, 127.7, 128.1, 129.5, 132.0, 133.8, 136.1, 138.6, 142.9; **ESI-MS** m/z cacld for $C_{17}H_{18}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1443; **FT-IR (KBr)** 3374, 3345, 2924, 1607, 1546, 1337 cm^{-1}; The ee value 70% (t_{minor} = 7.59 min, t_{major} = 8.58 min) and recrystallization ee value 95% were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/ i-Propanol = 98.5:1.5, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{30}$ = +18.0 (c 0.05, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-3-nitro-2-styrylquinoline (3p):



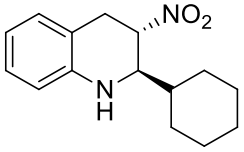
Yellow oil (25.2 mg 75% yield); R_f value 0.35 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.28 (dd, *J* = 5.2, 16.2 Hz, 1H), 3.54 (dd, *J* = 8.4, 16.2 Hz, 1H), 4.02 (bs, 1H), 4.46-4.50 (m ,1H), 4.76-4.81 (m, 1H), 6.16 (dd, *J* = 7.6, 15.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 6.70-6.76 (m ,2H), 7.04-7.10 (m, 2H), 7.35-7.38 (m, 5H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 30.7, 57.4, 83.8, 114.5, 116.7, 118.7, 125.5, 126.9, 128.1, 128.6, 128.8, 129.5, 135.4, 135.7, 142.0; **ESI-MS** m/z calcd for $C_{17}H_{16}N_2O_2$ $[M+H]^+$ 281.1285, found 281.1276; **FT-IR (KBr)** 3411, 2928, 2850, 1544, 1484, 1452, 1372 cm^{-1}; The ee value 28% (t_{major} = 18.04 min, t_{minor} = 37.99 min) was determined by HPLC analisis using Daicel Chiralpak OD-H column, 254 nm, 25 ^oC, n-Hexane/i-Propanol = 70:30, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{28}$ = +16.0 (c 0.23, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-3-nitro-2-phenethylquinoline (3q):



Yellow oil (25 mg, 75% yield); R_f value 0.35 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.21 (dd, *J* = 17.8, 7.3 Hz, 4H), 7.04 (t, *J* = 7.6 Hz, 2H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 4.70 (q, *J* = 6.4 Hz, 1H), 4.19 (dt, *J* = 13.1, 6.3 Hz, 1H), 3.87 (dd, *J* = 12.2, 7.0 Hz, 2H), 3.50 (dd, *J* = 16.7, 7.2 Hz, 1H), 3.20 (dd, *J* = 16.6, 5.2 Hz, 1H), 2.80 (ddd, *J* = 21.8, 14.0, 6.5 Hz, 2H), 1.93 – 1.83 (m, 2H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 30.0, 31.9, 34.6, 53.8, 83.3, 114.9, 116.8, 118.7, 126.6, 127.9, 128.5, 128.9, 129.4, 140.7, 141.9; **ESI-MS** m/z calcd for $C_{17}H_{19}N_2O_2^+$ $[M+H]^+$ 283.1441, found 283.1441; **FT-IR (KBr)** 3411, 2928, 2850, 1544, 1488, 1453, 1372 cm^{-1}; The ee value 41% (t_{major} = 47.75 min, t_{minor} = 35.80 min) was determined by HPLC analisis using Daicel Chiralpak OD-H column, 254 nm, 25 ^oC, n-Hexane/i-Propanol = 93:7, flow rate = 1 mL/min.

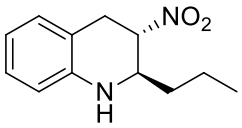
(2*R*,3*S*)-2-cyclohexyl-1,2,3,4-tetrahydro-3-nitroquinoline (3r):



Yellow oil (26 mg, 83% yield); R_f value 0.35 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.05 (t, *J* = 7.7 Hz, 2H), 6.75 (t, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 5.15 (s, 1H), 3.93 (s, 1H), 3.36 (d, *J* = 17.0 Hz, 1H), 3.21 (dd, *J* = 20.2, 6.7 Hz, 2H), 2.20 – 2.11 (m, 1H), 1.99 (d, *J* = 12.2 Hz, 1H), 1.79 (s, 2H), 1.72 (d, *J* = 12.9 Hz, 1H), 1.26 (ddd, *J* = 35.9, 24.5, 14.1 Hz, 4H), 1.04 (dd, *J* = 23.2, 11.9 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 25.8, 25.9, 26.3, 29.3, 30.3, 31.1, 38.6, 59.3, 78.6, 115.3, 117.8, 119.1, 127.5, 129.2, 143.3; **ESI-MS** m/z calcd

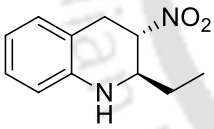
for $C_{15}H_{21}N_2O_2^+$ $[M+H]^+$ 261.1591, found 261.1595; **FT-IR (KBr)** 3418, 2957, 2927, 1725, 1603, 1546, 1489, 1375, 1268 cm^{-1}; The ee value 40% (t_{minor} = 8.79 min, t_{major} = 18.78 min) was determined by HPLC analysis using Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 95:5, flow rate = 1 mL/min.

(2*R*,3*S*)-2-butyl-1,2,3,4-tetrahydro-3-nitroquinoline (3s):



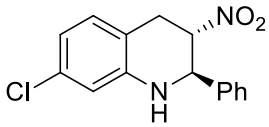
Yellow oil (23 mg, 82% yield); R_f value 0.35 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 0.92 (t, *J* = 7.2 Hz, 3H), 1.32-141 (m, 3H), 1.47-1.56 (m, 3H), 3.20 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.49 (dd, *J* = 7.6, 16.4 Hz, 1H), 3.76-3.81 (m, 1H), 3.89 (bs, 1H), 4.63-4.68 (m, 1H), 6.55 (d, *J* = 8 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 7.02-7.06 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 14.1, 22.7, 27.4, 30.4, 32.7, 54.1, 83.6, 114.7, 116.9, 118.4, 127.9, 129.4, 142.2; **ESI-MS** m/z calcd for $C_{13}H_{18}N_2O_2$ $[M+H]^+$ 235.1441, found 235.1443; **FT-IR (KBr)** 3415, 2957, 2928, 1726, 1603, 1546, 1488, 1378, 1268 cm^{-1}; The ee value 68% (t_{minor} = 14.43 min, t_{major} = 16.48 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 99:1, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{28}$ = +27.0 (c 0.78, $CHCl_3$).

(2*R*,3*S*)-1,2,3,4-tetrahydro-3-nitro-2-propylquinoline (3t):



Yellow oil (21.4 mg, 81% yield); R_f value 0.35 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 0.87-0.98 (m, 5H), 1.56 (m, 2H), 3.22 (dd, *J* = 6.4, 17 Hz, 1H), 3.38 (dd, *J* = 6.4, 17.4 Hz, 1H), 3.71 (bs, 1H), 3.92 (bs, 1H), 4.93-4.97 (m, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 7.02-7.07 (m , 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ (ppm) 14.0, 19.2, 29.1, 32.8, 53.3, 81.2, 115.1, 117.3, 118.9, 127.6, 129.5, 142.4; **ESI-MS** m/z calcd for $C_{12}H_{16}N_2O_2$ $[M+H]^+$ 221.1285, found 221.1283; **FT-IR (KBr)** 3415, 2957, 2928, 1726, 1603, 1546, 1488, 1378, 1268 cm^{-1}; The ee value 63% (t_{major} = 33.06 min, t_{minor} = 55.86 min) was determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 93:7, flow rate 1 mL/min; **Optical rotation** $[\alpha]_D^{28}$ = +28.0 (c 1.05, $CHCl_3$).

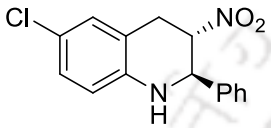
(2*R*,3*S*)-6-chloro-1,2,3,4-tetrahydro-3-nitro-2-phenyl-quinoline (3u):



Yellow oil (24 mg, 70% yield); R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ (ppm) 3.16 (dd, *J* = 4.8, 16.8 Hz,

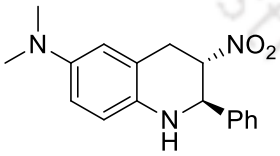
1H), 3.51(dd, *J* = 7.8, 16.5 Hz, 1H), 4.18-4.22 (m, 1H), 4.88-4.94 (m, 2H), 6.53-6.55 (m, 1H), 7.03-7.39 (m, 5H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ (ppm) 32.1, 58.7, 94.5, 115.2, 118.1, 123.2, 127.5, 128.1, 129.1, 129.3, 129.3, 138.6, 141.2; **ESI-MS** m/z calcd for $C_{15}H_{13}ClN_2O_2$ $[M+H]^+$ 289.0733, found 289.0737; **FT-IR (KBr)** 3398, 2924, 2850, 1607, 1548, 1484, 1370, 1337 cm^{-1}; The ee value 75% (t_{major} = 13.43 min, t_{minor} = 18.90 min) and recrystalliszation ee 88% were determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 70:30, flow rate = 1 mL/min; **Optical rotation** $[\alpha]_D^{28}$ = +46.0 (c 0.10, $CHCl_3$).

(2*R*,3*S*)-5-chloro-1,2,3,4-tetrahydro-3-nitro-2-phenyl-quinoline (3v):



Yellow solid (25 mg, 72% yield); mp 165-166 °C; R_f value 0.3 (20:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ (ppm) 3.31 (dd, *J* = 5.8, 16.8 Hz, 1H), 3.52 (dd, *J* = 7.8, 17.1 Hz, 1H), 4.27 (bs, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.93-4.96 (m, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.36-7.39 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 28.8, 58.3, 85.0, 112.6, 115.1, 119.2, 127.2, 128.5, 129.3, 134.8, 138.2, 144.2; **ESI-MS** m/z calcd for $C_{15}H_{13}ClN_2O_2$ $[M+H]^+$ 289.0733, found 289.0735; **FT-IR (KBr)** 3393, 2923, 1599, 1545, 1493, 1475, 1334, 1316 cm^{-1}; The ee value 62% (t_{major} = 15.77 min, t_{minor} = 22.52 min) and after recrystallization 74% were determined by HPLC analysis using Daicel Chiralpak OD-H column , 254 nm, 25 °C, n-Hexane/i-propanol = 80:20, flow rate = 1 mL/min; **Optical rotation** was $[\alpha]_D^{29}$ = +31.0 (c 0.25, $CHCl_3$).

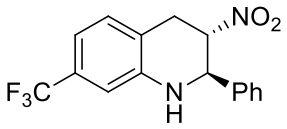
(2*R*,3*S*)-1,2,3,4-tetrahydro-*N*,*N*-dimethyl-3-nitro-2-phenyl-quinolin-7-amine (3w):



Red solid (29 mg, 80% yield); mp 109-111 °C; R_f value 0.25 (20:1 hex/EA); **^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm)** 3.19 (dd, *J* = 4.8, 15.6 Hz, 1H), 3.48 (dd, *J* = 9.6, 15.6 Hz, 1H), 4.07 (bs, 1H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.88-4.93 (m, 1H), 5.95 (d, *J* = 2.4 Hz, 1H), 6.23 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.33-7.41 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.0, 40.8, 59.2, 86.0, 97.8, 104.4, 105.3, 127.4, 129.1, 129.1, 129.9, 138.8, 143.3, 150.9; **ESI-MS** m/z calcd for $C_{17}H_{19}N_3O_2$ $[M+H]^+$ 298.1550, found 298.1551; **FT-IR (KBr)** 3316, 2871, 1579, 1619, 1553,1520, 1479, 1451, 1336, 1372 cm^{-1}; The ee value 64% (t_{minor} = 33.56 min, t_{major} = 40.16 min) and recrystallization 76% were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-

Hexane/i-propanol = 80:2, flow rate = 0.8 mL/min; **Optical rotation** $[\alpha]_D^{29}$ = +04.0 (c 0.75, $CHCl_3$).

(2*R*,3*S*)-6-(trifluoromethyl)-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3x):



White solid (27 mg, 69% yield); mp 125-127 °C; R_f value 0.25 (20:1 hex/EA); **^{1}H NMR (600 MHz, $CDCl_3$)** δ (ppm) 3.22 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.57 (dd, *J* = 8.4, 16.8 Hz, 1H), 4.38 (bs, 1H), 4.90-4.93 (m, 2H), 6.84 (bs, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.35-7.40 (m, 5H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ (ppm) 30.3, 56.5, 84.2, 110.7, 114.9, 115.0, 120.0, 123.3, 125.1, 127.0, 127.0, 129.4 (d, *J* = 36 Hz), 130.1, 138.5, 142.7; **ESI-MS** m/z calcd for $C_{16}H_{13}F_3N_2O_2^+$ $[M+H]^+$ 323.1002, found 323.1005; **FT-IR (KBr)** 3401, 2923, 2853, 1622, 1595, 1563, 1549, 1487, 1369, 1337 cm^{-1};The ee value 76% (t_{major} = 8.45 min, t_{minor} = 9.91 min) and recrystallization ee 82% were determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-propanol = 70:30, flow rate = 1 ml/min; **Optical rotation** [α]D29 = +25.0 (c 0.40, CHCl3).

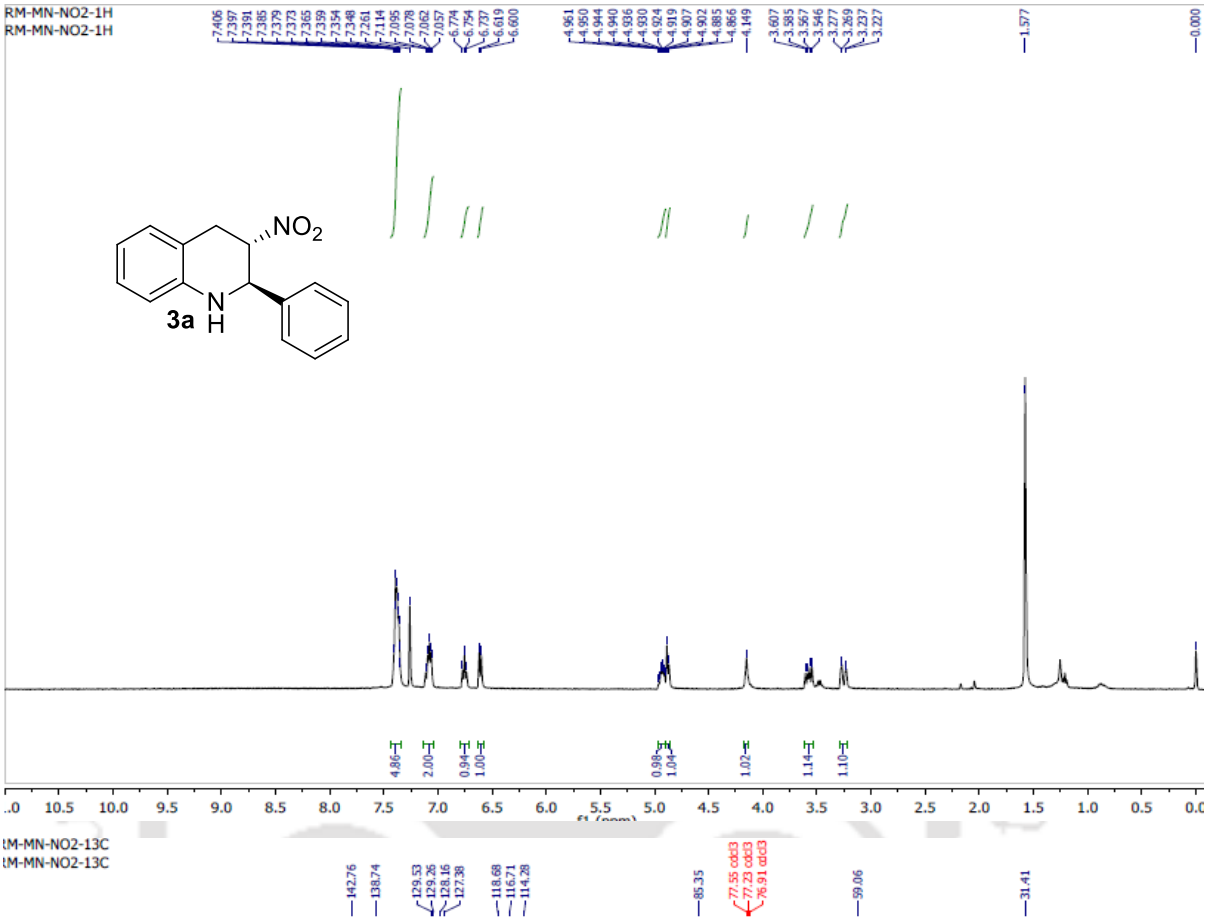
6.8. Crystal information:

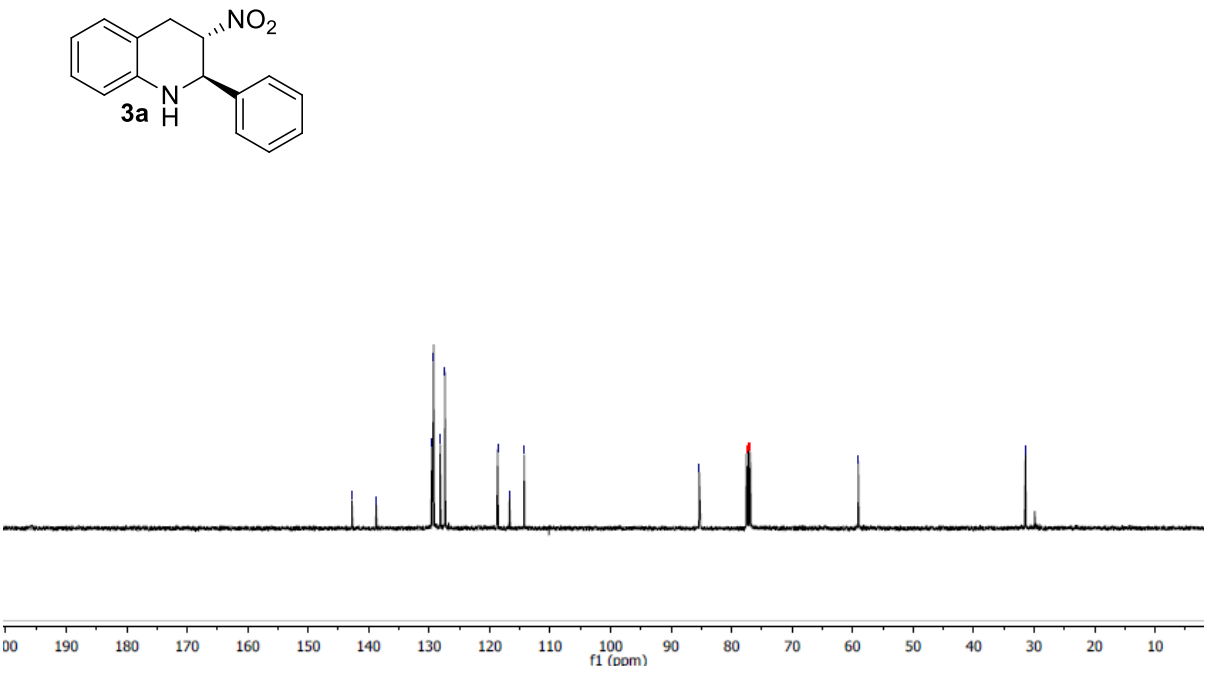
Crystal data and structure refinement for chiral compound 3f (CCDC 1048919):

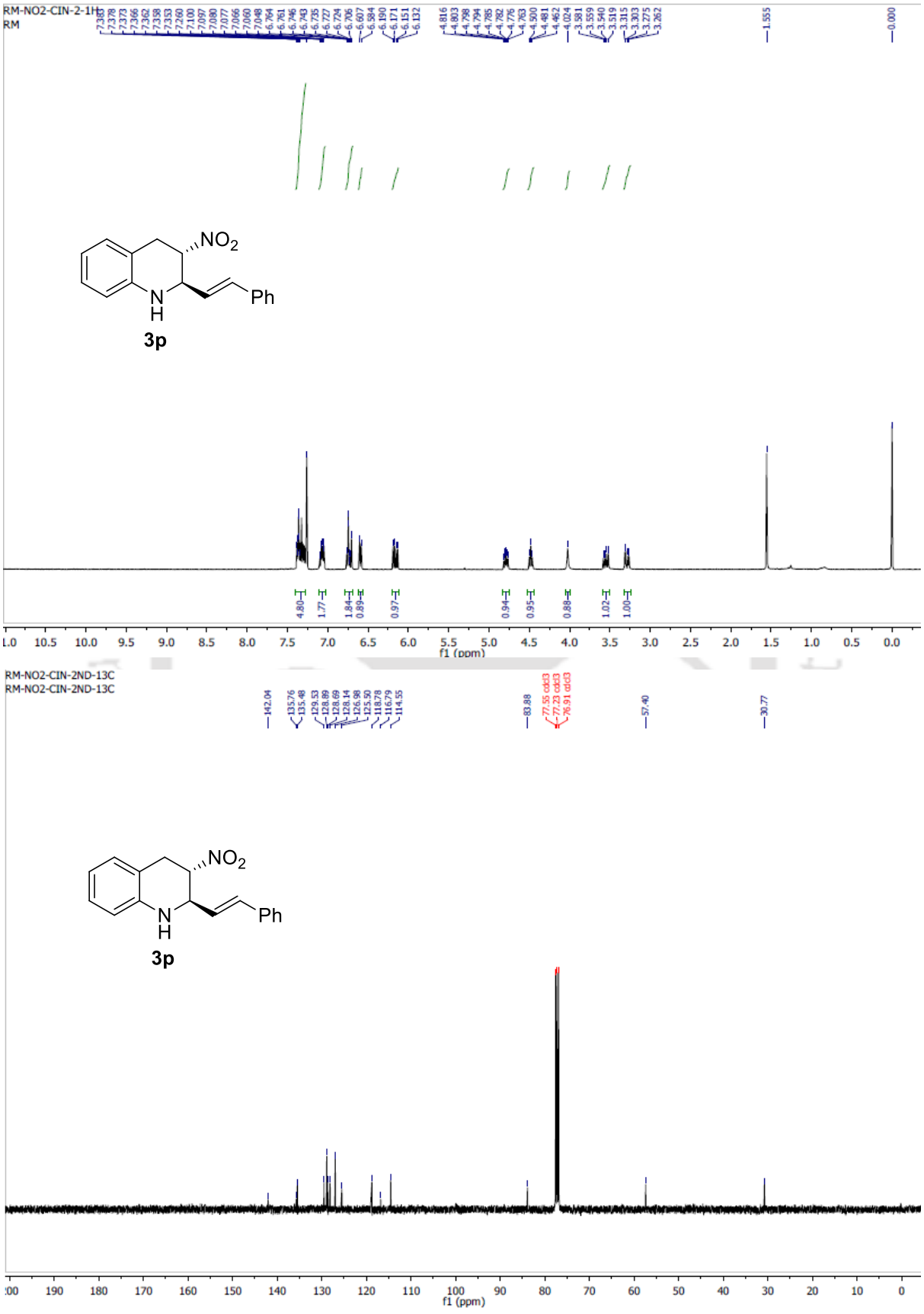
Identification code	**3f**
Empirical formula	$C_{15}H_{13}BrN_2O_2$
Formula weight	333.18
Temperature/K	296(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	5.947(3)
b/Å	7.118(3)
c/Å	32.870(11)
α/°	90.00
β/°	90.00

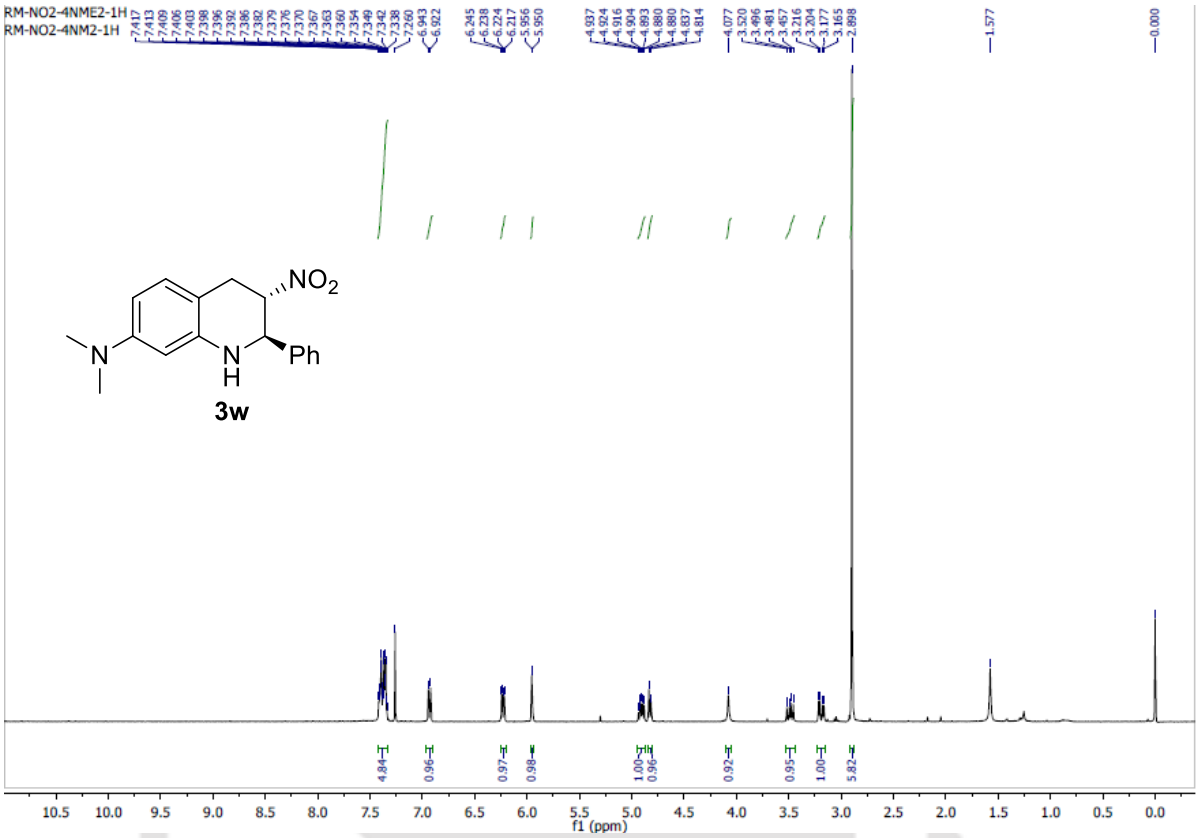
γ/°	90.00
Volume/Å^3	1391.4(10)
Z	4
ρ_{calc}mg/mm^3	1.591
m/mm^{-1}	2.957
F(000)	672.0
Crystal size/mm^3	0.32 × 0.28 × 0.20
2Θ range for data collection	2.48 to 52.54°
Index ranges	$-7 \leq h \leq 7$, $-8 \leq k \leq 7$, $-36 \leq l \leq 40$
Reflections collected	13277
Independent reflections	2607[R(int) = 0.0576]
Data/restraints/parameters	2607/0/181
Goodness-of-fit on F^2	0.903
Final R indexes [I>=2σ (I)]	R_1 = 0.0416, wR_2 = 0.1129
Final R indexes [all data]	R_1 = 0.0824, wR_2 = 0.1446
Largest diff. peak/hole / e Å^{-3}	0.51/-0.51
Flack parameter	-0.011(19)

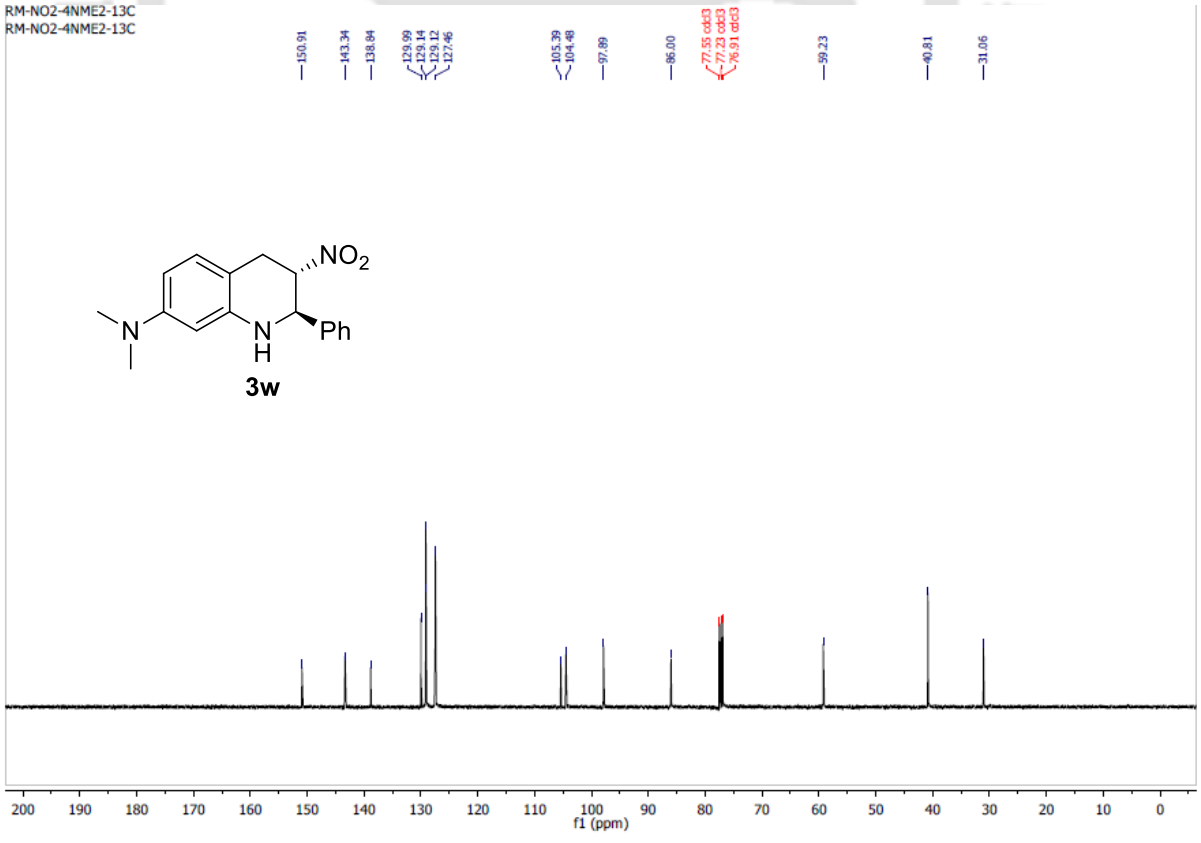
6.9. Selected spectra of NMR and HPLC:



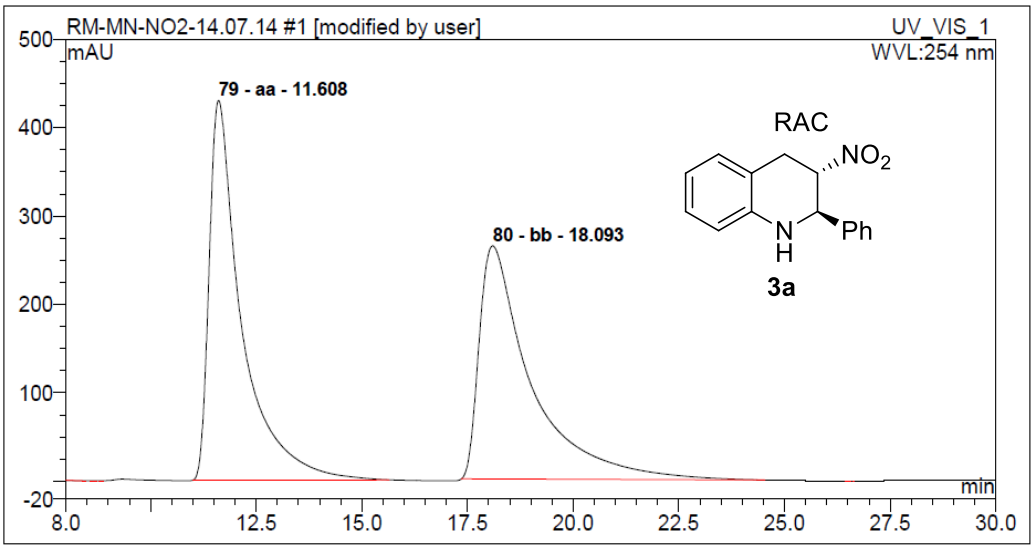






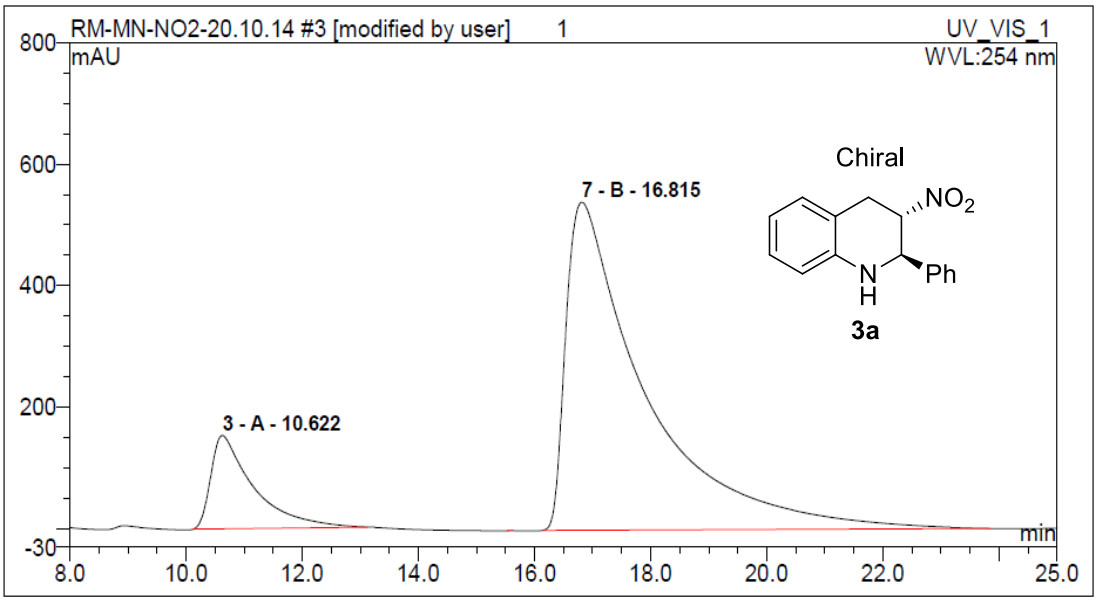


RM-NO2--rac



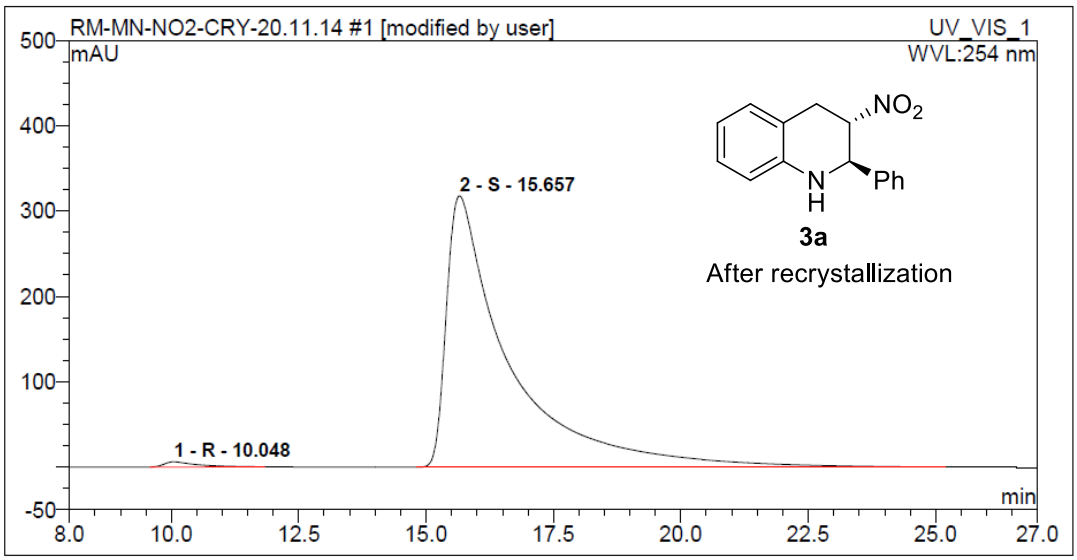
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
79	aa	11.61	381.3727	50.37396303	429.3288	n.a.
80	bb	18.09	375.710	49.62603697	263.659	n.a.

RM-NO2--63-chi-final



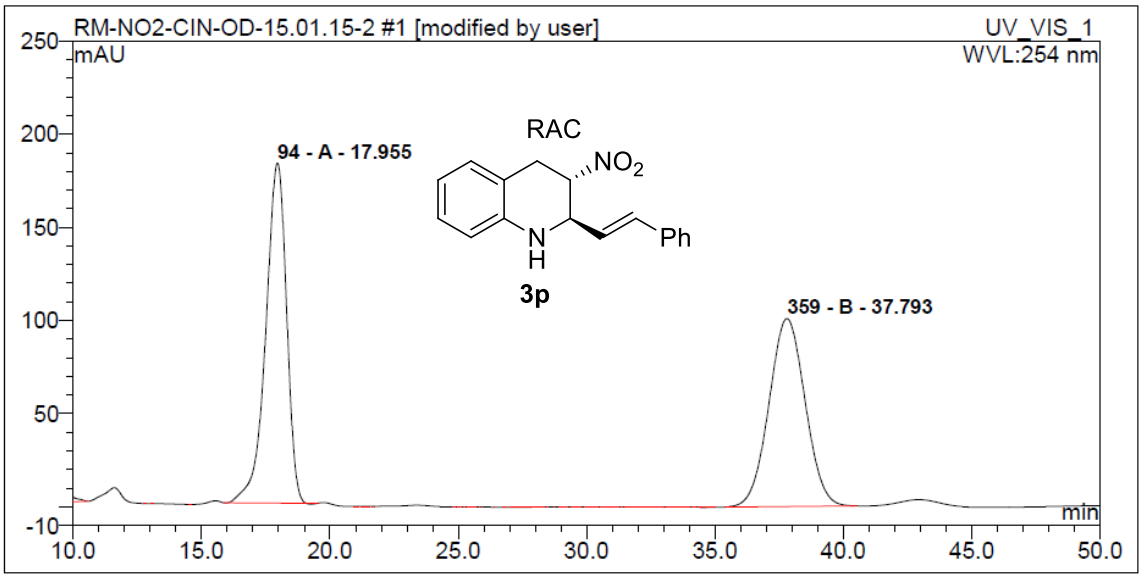
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
3	A	10.62	130.149	13.26822863	153.5928	n.a.
7	B	16.82	850.758	86.73177137	539.395	n.a.

RM-PURE-CRY-2ND



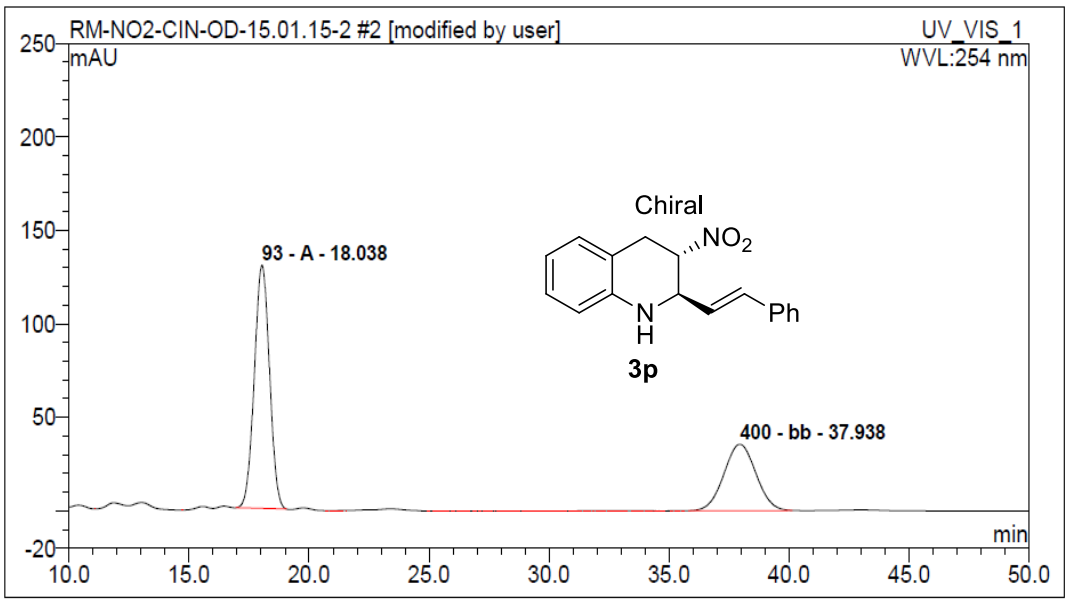
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	R	10.05	4.555784	0.9905253208	6.17194	n.a.
2	S	15.66	455.380	99.00947468	318.035	n.a.

RM-NO2--cin-rac

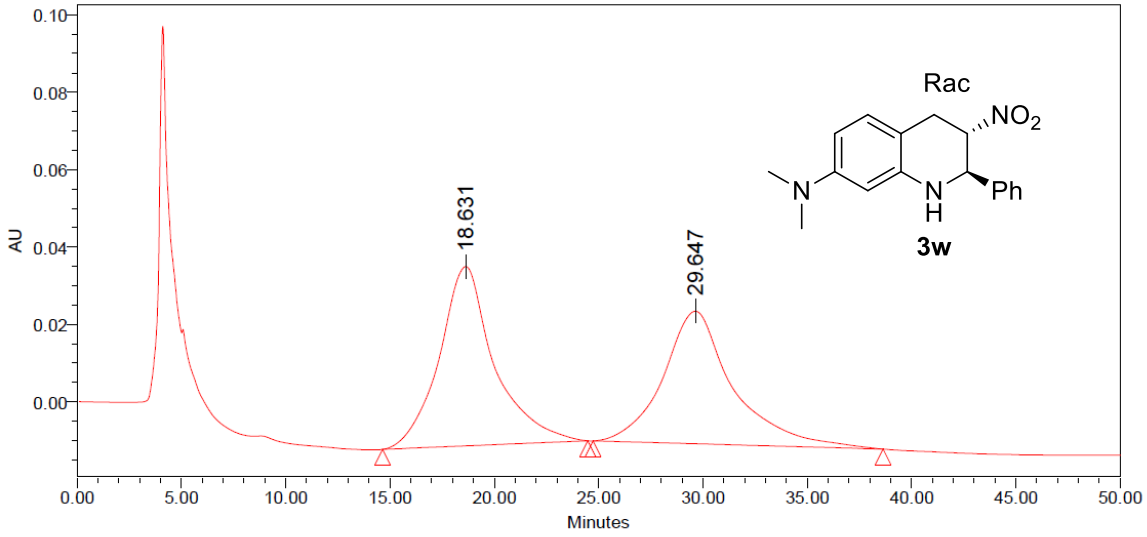


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
94	A	17.96	171.384	50.99830055	182.3699	n.a.
359	B	37.79	164.674	49.00169945	100.750	n.a.

RM-NO2--cin-chi

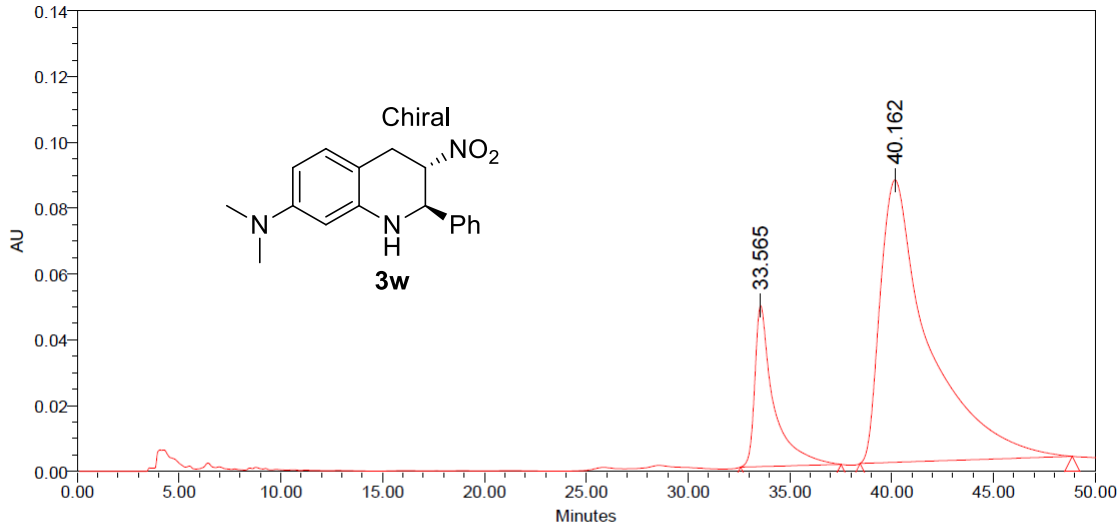


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
93	A	18.04	95.76953	63.51579761	130.0774	n.a.
400	bb	37.94	55.011	36.48420239	35.552	n.a.



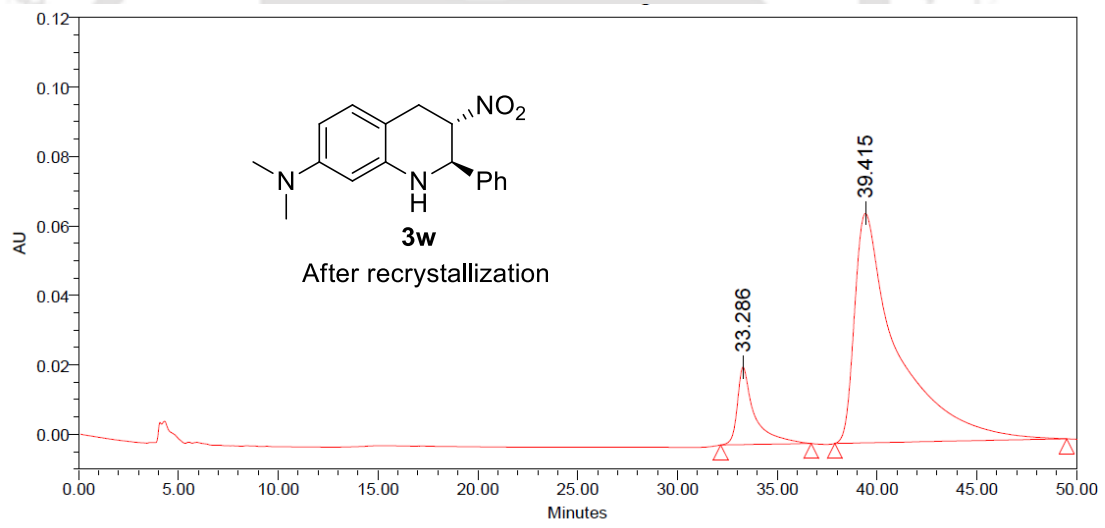
Peak Results

	Name	RT	Area	Height	% Area
1		18.631	8507685	46345	51.65
2		29.647	7963601	34246	48.35



Peak Results

	Name	RT	Area	Height	% Area
1		33.565	3143133	48904	17.98
2		40.162	14341553	85825	82.02



Peak Results

	Name	RT	Area	Height	% Area
1		33.286	1347850	22310	11.95
2		39.415	9934682	66035	88.05

6.10. Reference:

1. Tan, H. R.; Ng, H. F.; Chang, J.; Wang, J. *Chem. Eur. J*. **2012**, *18*, 3865.
2. Kim, S.; Kang, K. T.; Kim, S. G. *Tetrahedron* **2014**, *70*, 5114.
3. Lopez, E. M.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.
4. Jacquemond-Collet, I.; Benoit-Vical, F.; Mustofa; Valentin, A.; Stanislas, E.; Mallié, M. *Planta Med.* **2002**, *68*, 68.
5. Mester, I. *Fitoterapia* **1973**, *44*, 123.
6. Asolkar, R. N.; Schröder, D.; Heckmann, R.; Lang, S.; Wagner-Döbler, I.; Laatsch, H. J. *Antibiot.* **2004**, *57*, 17.
7. Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509.
8. Keck, D.; Vanderheiden, S.; Brase, S. A. *Eur. J. Org. Chem.* **2006**, *2006*, 4916. (b) Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Tetrahedron* **2005**, 61, 2075. (c) Steinhagen, H.; Corey, E. J. *Org. Lett.* **1999**, *1*, 823. (d) Back, T. G.; Wulff, J. E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6493.
9. Nallan, L.; Bauer, K. D.; Bendale, P.; Rivas, K.; Yokoyama, K.; Horney, C. P.; Rao, P. P. *J. Med. Chem.* **2005**, *48*, 3704.
10. (a) Sridharan, V.; Suryavanshi, P. A.; Menédez, J. C. *Chem. Rev*. **2011**, *111*, 7157. (b) Mitchinson, A.; Nadin, A. *J. Chem. Soc. Perkin Trans 1* **2000**, *17*, 2862. (c) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem*. **1998**, *35*, 761. (d) Katrizky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (e) Zhang, W.; Wang, Y.; Bai, C.; Wen, J.; Wang, N. *Chin. J. Chem.* **2015**, *33*, 401. (f) Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703. (g) Kang, K. T.; Kim, S. G. *Synthesis* **2014**, *46*.
11. Anderson, J. C.; Koovits, P. J. *Chem. Sci*. **2013**, 4, 2897.
12. Ishitani, S.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.
13. Jia, X.; Han, B.; Zhang, W.; Jin, X.; Yang, L.; Liu, Z.-L. *Synthesis* **2006**, *17*, 2831.
14. Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887.
15. Jia, Z.-X.; Luo, Y.-C.; Xu, P.-F. *Org. Lett*. **2011**, 13, 832.
16. Kang, Y. K. S.; Kim, M.; Kim, D. Y. *J. Am. Chem. Soc*. **2010**, *132*, 11847. (b) Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T.; *J. Am. Chem. Soc*. **2011**, *133*, 6166.
17. Kadyrov, R.; Riermeier, T. H. *Angew. Chem. Int. Ed*. **2003**, *42*, 5472.
18. Noble, A.; Torres, P. R.; Anderson, J. C.; *Tetrahedron Lett.* **2012**, *53*, 5707.

19. (a) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656. (b) Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137. (c) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721. (d) Bello, D.; Ramón, R.; Lavilla, R. *Curr. Org. Chem*. **2010**, *14*, 332.
20. Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598.
21. Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. *Chem. Eur. J.* **2011**, *17*, 13800.
22. He, L.; Bekkaye, M.; Retailleau, P.; Masson, G. *Org. Lett.* **2012**, *14*, 3158.
23. (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683. (b) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal*. **2008**, *350*, 1001.
24. Cai, X.-F.; Chen, M.-W.; Ye, Z.-S.; Guo, R.-N.; Shi, L.; Li, Y.-Q.; Zhou, Y.-G. *Chem. Asian J.* **2013**, *8*, 1381.
25. Kim, S.; Kang, K.-T.; Kim, S.-G. *Tetrahedron* **2014**, *70*, 5114.
26. For a review on bifunctional cinchona alkaloid-based urea and thiourea organocatalysts, see: Connon, S. J. *Chem. Commun.* **2008**, 2499.
27. CCDC 1048919 contains the crystallographic data for **3f.**
28. For a theoretical study, see: Zhu, J.-L.; Zhang, Y.; Liu, C.; Zhang, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813.

Conclusion

The thesis describes the synthesis of nitrogen- and oxygen-containing heterocyclic compounds based on the Michael and aza-Henry reactions. In the chapter 2, a series of highly enantioselective 3-acyloxypyrazoles are presented. Concerned method was established for the Michael/hemiketalization/retro-aldol reaction of α-nitroketones and unsaturated pyrazolones. Chapter 3 demonstrates an alternative appreach for the Michael/acetalization/acyl transfer reaction to provide enantiopure 2,4-disubstituted chromans with single diastereomeric ratio by using a wide range of 2-hydroxycinnamaldehydes instead of unsaturated pyrazolones. Chapter 4 represents Michael-oxa-Michael reaction of deconjugated enones having α′-CH groups with electron poor oxadienes bearing cyano group. The following reaction was performed using quinine derived primary amine catalyst and benzoic acid as an additive for the synthesis of oxygen-containing heterocyclic compounds (3,4-dihydropyrans) with excellent enantioselectivities. Penultimately, chapter 5 depicts both nitrogen and oxygen-containing heterocyclic compounds (tetrahydropyrano[2,3-*c*]pyrazolones) which have been synthesized from alkylidene pyrazolones and cyclic ketones *via* domino Michael-hemiketalization reaction with high enantioselectivities and diastereoselectivities. Lastly, in chapter 6 aza-Henry reaction was illustrated to construct a series of tetrahydroquinolines where the nitroalkanes and aldehydes in the presence of quinine derived thiourea catalyst were employed to provide enantiomerically pure tetrahydroquinolines with moderate to good yields *via* intra molecular cyclization.

List of publications

1. Organocatalytic asymmetric intramolecular aza-Henry reaction: Facile synthesis of *trans*-2,3-disubstituted tetrahydroquinolines.

Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2015**, *13*, 6825.

2. Dienamine-Mediated Asymmetric Inverse-Electron-Demand Hetero-Diels–Alder Reaction of Linear Deconjugated Enones: Diversity-Oriented Synthesis of 3,4-Dihydropyrans.

Maity, R.; Pan, S. C. *Eur. J. Org. Chem.* **2017**, *4*, 871.

3. Organocatalytic Asymmetric Michael/Hemiketalization/Retro-aldol Reaction of α-Nitroketones with Unsaturated Pyrazolones: Synthesis of 3-Acyloxy Pyrazoles.

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

4. Enantioselective aminocatalytic synthesis of tetrahydropyrano[2,3-c]pyrazoles via a domino Michael-hemiacetalization reaction with alkylidene pyrazolones.

Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2017**, *15*, 8032.

5. Organocatalytic asymmetric Michael/hemiacetalization/acyl transfer reaction of α-nitroketones with o-hydroxycinnamaldehydes: synthesis of 2,4-disubstituted chromans.

Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2018**, *16*, 1598.

6. Organocatalytic asymmetric Michael/hemiacetalization/acyl transfer reaction of α-nitroketones with o-hydroxy benzylideneacetone synthesis of 2,4-disubstituted chromans.

Maity, R.; Pan, S. C. Manuscript to be submitted.

7. Highly Diastereo and Enantioselective Synthesis of Spiro-Tetrahydrofuran-Pyrazolones via Organocatalytic Cascade Reaction between γ-hydroxyenones and Unsaturated Pyrazolones.

Mondal, B.; **Maity, R.**; Pan, S. C. Manuscript submitted.

Conferences

1. Organocatalytic asymmetric intramolecular aza-Henry reaction: Facile synthesis of *trans*-2,3-disubstituted tetrahydroquinolines.

ChemCovene-2015, April 8, 2015, department of chemistry, IIT Guwahati.

2. Dienamine-Mediated Asymmetric Inverse-Electron-Demand Hetero-Diels–Alder Reaction of Linear Deconjugated Enones: Diversity-Oriented Synthesis of 3,4-Dihydropyrans.

XIIth J-NOST Conference for research scholars (**J-NOST-2016**), November 24-27, 2016, CSIR-Central Drug Research Institute, Lucknow, India.

3. Organocatalytic Asymmetric Michael/Hemiketalization/Retro-aldol Reaction of α-Nitroketones with Unsaturated Pyrazolones: Synthesis of 3-Acyloxy Pyrazoles.

ChemConvene-2017, July 25, 2017, department of chemistry, IIT Guwahati.