Organocatalytic Asymmetric Michael and Cyclization Reactions Involving Electron Deficient Olefins

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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October 2017

Dedicated

to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
Department of Chemistry

Statement

The work comprised in this thesis entitled "***Organocatalytic Asymmetric Michael and Cyclization Reactions Involving Electron Deficient Olefins***" is the outcome of the investigations carried out by me under the supervision of Dr. Subhas C. Pan, Department of Chemistry, Indian Institute of Technology Guwahati, India.

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

Guwahati

October, 2017

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Organocatalytic Asymmetric Michael and Cyclization Reactions Involving Electron Deficient Olefins***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Utpal Nath (Roll No: 11612244) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati — Dr. Subhas Chandra Pan

October, 2017 — Supervisor

Acknowledgements

I sincerely express my wholehearted gratitude to my PhD supervisor Dr. Subhas Chandra Pan for his productive suggestions, constant guidance and insightful advises throughout my entire research work. His inspirational discussions and kind support helped me a lot during my PhD. I find myself privileged to have worked under his guidance and will always be indebted to him.

I would like to acknowledge my sincere gratitude to Dr. Lal Mohan Kundu the chairman of doctoral committee and doctoral committee members Dr. Chandan K. Jana and Dr. A. S. Achalkumar for their valuable suggestions, intellectual inputs and encouragements which helped a lot to improve my research work.

I am thankful to IIT Guwahati for the fellowship. I am thankful to IIT Guwahati, Department of Chemistry and Central Instruments Facilities for providing research facilities and instrumental facilities.

I am delighted to have this opportunity to thank my dear lab mates Keshab Mondal, Rajendra Maity, Soumendra Nath Mukhopadhyay, Buddhadeb Mondal, Subas Chandra Sahoo, Chandan Gharui, Megha Balha and Nimisha Bania for their great support during my PhD period. Their constant help definitely smoothen this journey. I sincerely thank Deepan Chowdhury, Ankush Banerjee, Gobinda Dolai, Bidhan Ghosh and Pratap Mondal for their contribution in my works. I would also like to thank Soumendra and Subas for allowing me to work with them in their projects. I am heartily thankful to my friends specially Samir, Barun and Anindya for being by my side whenever I needed them. I would like to thank all my PhD batch mates, seniors and juniors who helped during my work and for making a friendly environment.

Finally, my PhD endeavor could not have been completed without the endless love, support and blessings from my parents. I thank them for their faith in me, which has always been a

constant source of motivation. I am always thankful to the almighty God for everything in my life.

Sincerely,

Utpal Nath

CONTENTS

Abbreviations

APCI	Atmospheric pressure chemical ionization
Ar	Argon
br.	Broad
Bu	Butyl
CCDC	Cambridge Crystallographic Data Centre
COSY	Correlation spectroscopy
°C	Degrees Celsius
d	Doublet
δ	Chemical shift
DA	Diels-Alder
DCE	Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DIAD	Diisopropyl azo di-carboxylate
DKR	Dynamic kinetic resolution
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenyl phosphoryl azide
dr	Diastereomeric ratio
EA	Ethyl acetate
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
g	Grams
h	Hours
HPLC	High performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i	Iso
J	Coupling Constant
LDA	Lithium diisopropylamide
m	Multiplet
m	*meta*
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Miligram
mL	Millilitre
mol	Mole
mp	Melting point
MS	Molecular sieves
n	Normal
NMM	N-Methyl morpholine
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
o	*ortho*
p	*para*
Ph	Phenyl
PivOH	Pivelic acid
ppm	Parts per million
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
s	Singlet
t	triplet
t	*tert*
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts	*p*-Toluenesulfonyl
UV	Ultra violet
XRD	X-ray diffraction

General Remarks

The present investigations are carried out in Department of Chemistry, Indian Institute of Technology Guwahati, during the period from 26th December, 2011 to 15th October, 2017 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) was freshly distilled from calcium hydride (CaH_2). 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. 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 or neutral alumina (Merck or Fischer Scientific) under gravity. After purifications the solvent was usually removed in Büchi R-114V rotavapour.

MS (ESI or APCI-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).

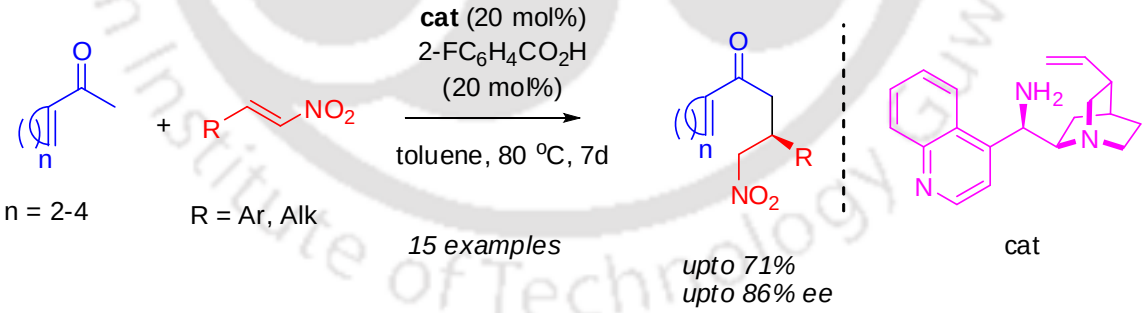
X-RD: X-ray crystallographic data were collected using a Bruker SMART APEX-II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo−Kα radiation (l = 0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods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

Abstract

The contents of this thesis entitled "***Organocatalytic Asymmetric Michael and Cyclization reactions Involving electron Deficient Olefins"*** have been divided into five chapters based on the results of experimental works performed during the complete course of the PhD research period.

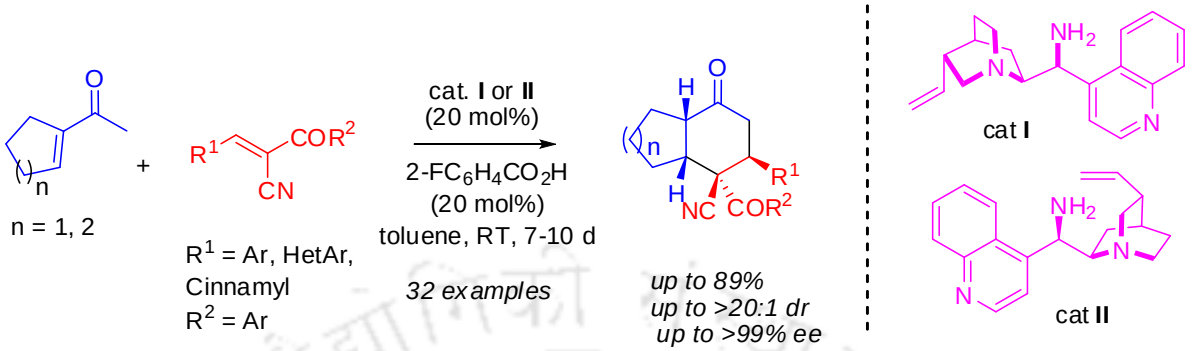
Chapter 1 of the dissertation demonstrates a brief review of organocatalytic Michael and cyclization reactions. Cinchona derived catalysts were highlighted in this context, since these catalysts were primarily utilized in the works presented in this thesis.

Chapter 2 of the thesis documents the asymmetric Michael addition reaction between *α*-branched enones and nitroolefins. 1-Acetylcyclohexene, 1-acetylcyclopentene and 1-acetylcyclobutene have been used in the enantioselective organocatalytic Michael addition reactions to nitroolefins. The enantioselectivity of the products are good to moderate and the nitroolefin scope is broad. The utility of the method has been shown by converting to bicyclized compounds, for which high enantioselectivity could be attained by recrystallization. Despite of the rigorous progress in the field of asymmetric enamine catalysis, *α*-branched enones were almost not investigated and this is the first demonstration that α-branched enones could be activated by amine catalyst for an asymmetric reaction to a Michael acceptor.



Chapter 3 of this thesis describes the catalytic asymmetric [4+2]-cycloaddition reaction of 1-acetylcyclopentene and 1-acetylcyclohexene with electron deficient olefins having simultaneous cyano and keto groups. Easily synthesizable cinchona alkaloid derived primary amines were found to be the best catalysts for this reaction. The bicyclic products having four contiguous stereogenic centres including one quaternary centre are obtained in high diastereo- and enantioselectivities. Valuable synthetic transformations including triazole

synthesis from the products have also been demonstrated. This chapter provides a useful practical route for the synthesis of bicyclic fused carbocycles in a simple and efficient way.



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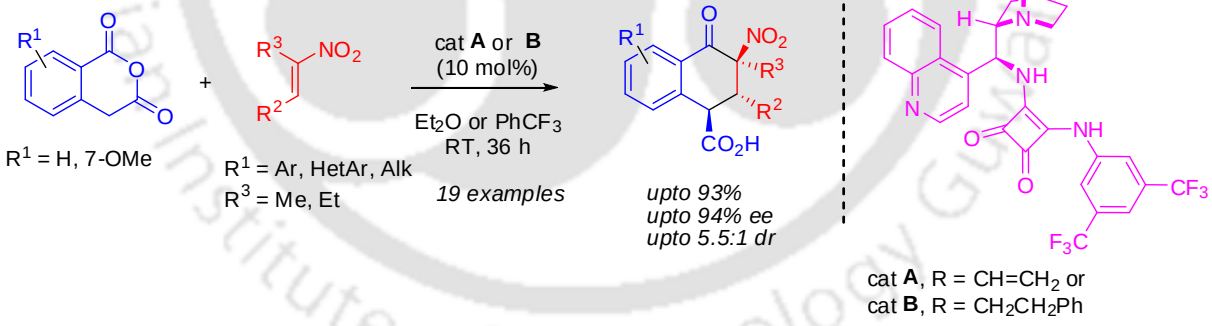
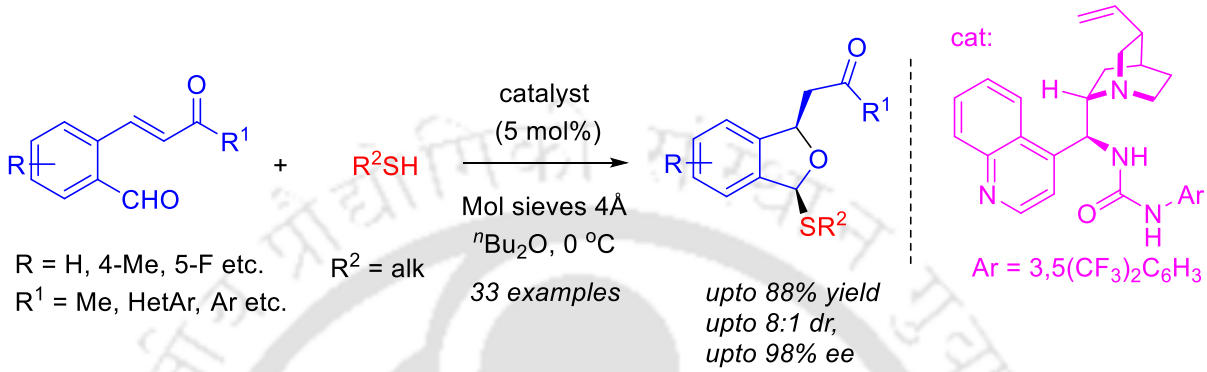
Chapter 4 of the thesis demonstrates the development of a new organocatalytic asymmetric Tamura cycloaddition with nitroolefins. This demonstration of the reaction of α-branched nitroolefins with homophthalic anhydrides delivers highly functionalized 1-tetralone compounds bearing a quaternary center at the α-position. The cinchona derived chiral squramide catalysts can be synthesized easily and using them the tetralone products were obtained in moderate to high diastereo- and with good to excellent enantioselectivities. The usefulness of the method has also been shown by converting the product to a tetrahydronaphthalene derivative and to a trisubstituted tetralone moiety.



Chapter 5 of the thesis reveals the development of the first organocatalytic asymmetric DKR reaction of hemithioacetals. Hemithioacetals were formed *insitu* via thiol addition and subsequently underwent an intramolecular oxa-Michael reaction furnishing sulphur containing 1,3-disubstituted-1,3-dihyroisobenzofurans. Cinchonidine derived urea was the best catalyst for this reaction and the dihyroisobenzofuran products were formed in good yields with high diastereo- and enantioselectivities. The scope of the reaction was quite broad

ranging from aliphatic to aromatic substituents and the products were obtained in moderate to good yields with high diastereo- and enantioselectivities. A few synthetic transformations of the products were also documented in this chapter including a synthesis of dihyroisobenzofuran, a moiety which is present in various biologically active compounds.



Altogether the thesis illustrates some new and efficient asymmetric methodologies based on organocatalytic Michael and cyclization reactions resulting functionalized chiral molecules, especially cyclic ones. The simplicity and efficacy of the presented methodologies may, on later stage, make them applicable in asymmetric synthesis of biologically active molecules and natural products.

Chapter 1: Introduction

1.1. Asymmetric catalysis:

The requirement of enantiopure drugs in pharmaceutical industry intrigued many chemists to develop new methodologies for asymmetric synthesis. Induction of asymmetry by means of catalysis (asymmetric catalysis) is undoubtedly the best among the available techniques of asymmetric synthesis[1] (chiral pool synthesis and chiral auxiliary based synthesis) since it does not require specific chiral starting material and as well delivers highest atom economy by eliminating the stoichiometric addition and removal steps of chiral auxiliaries.

1.2. Asymmetric organocatalysis:

Enzymes[2] and transition metal based complexes[3] have been used as catalysts for asymmetric induction for a long time. Organic molecules acting as catalysts i.e. *Organocatalysis* has now become one of the principle sources of asymmetric induction in numerous reactions.[4] The term "organic catalysis" was first used by Wolfgang Langenbeck in 1928,[5] although the first organocatalytic reaction was reported long back by German chemist Justus von Liebig in 1859.[6] The first report of organocatalytic asymmetric reaction had been documented in 1912 by Bredig and Fiske.[7] Although many asymmetric reactions have been carried out using organic molecules (mainly chiral bases and chiral phase transfer catalysts) in previous millennia, the rapid journey of organocatalysis begun after the discovery of asymmetric enamine[8] and iminium catalysis[9] in the very beginning of this millennium.

Different types of catalysts with various activation modes have been discovered over the years. Several classes of organocatalytic systems were used in asymmetric catalysis namely enamine

catalysis, iminium catalysis, SOMO catalysis, phase-transfer catalysis, chiral Brønsted acids, hydrogen bonding donors and chiral Brønsted and Lewis bases etc. The two key factors controlling the stereochemical outcome of asymmetric organocatalysis is steric congestion and hydrogen bonding. For most of the organocatalytic systems, hydrogen bonding plays a pivotal role in the conformational orientations of reactants in the chiral transition state by forming rigid three dimensional structures. Although the energy contribution of a hydrogen bond is very less to the interactions, it not only plays decisive character in stereoselectivity but also stabilizes the reactive intermediates like it does in enzyme catalysis.

The two main pillars of asymmetric aminocatalysis are HOMO-raising enamine activation and LUMO-lowering iminium activation. Over time, other vinylogous activation modes like dienamine,[10] cross-dienamine,[11] (Figure 1) trienamine,[12] cross-trienamine,[13] tetraenamine,[14] vinylogous iminium ion[15] activations *etc*. have been originated from these two activation modes.

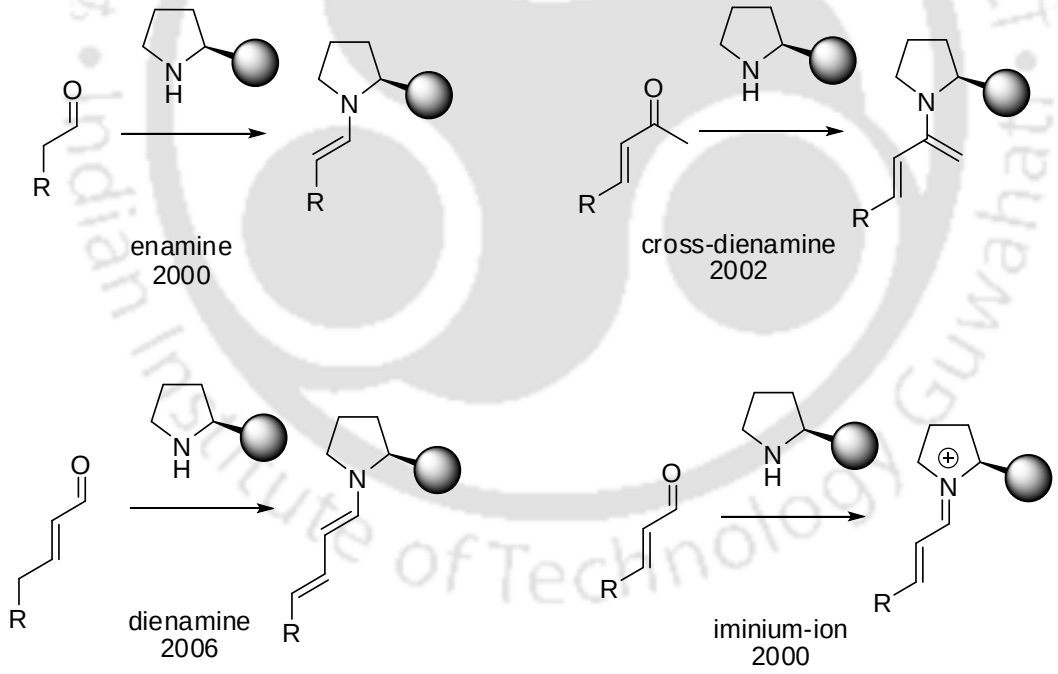


Figure 1: Aminocatalytic activation modes

1.3. Michael Reaction:

The conjugate addition between an electron deficient olefin and a suitable donor molecule is known as Michael reaction after its inventor Arthur Michael.[16] Mild reaction conditions, high functional group tolerance, numerous precursors as well as high conversion rates resulted the Michael addition reaction an important organic transformation[17] and it had emerged as a very important tool for synthesizing natural products and drug molecules.

Asymmetric enamine catalysis progressed with explosive growth since 2000 and the field is still developing. This activation mode has successfully been applied to aldol, Michael, Mannich, α-heterofunctionalization and other reactions.[18] Enamine catalytic methodology has also been applied in performing various cascade reactions.[19] A number of asymmetric total syntheses have been achieved utilizing this mode of amine catalysis. Michael reaction has always been a privileged reaction in this context. Numerous natural products that have been synthesized using enamine mediated conjugate addition reactions, a few of them are given in Figure 2.[20a]

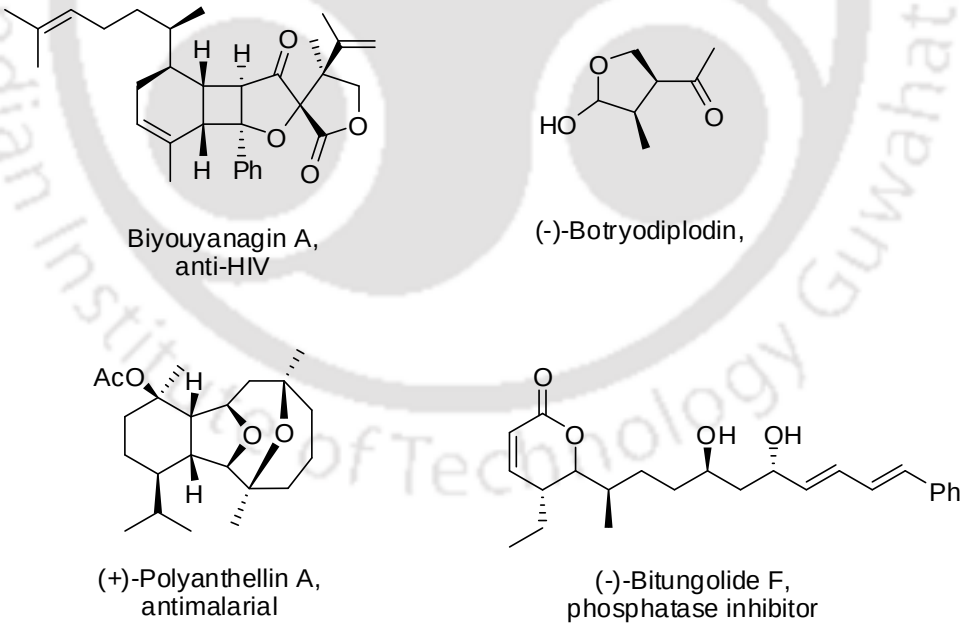
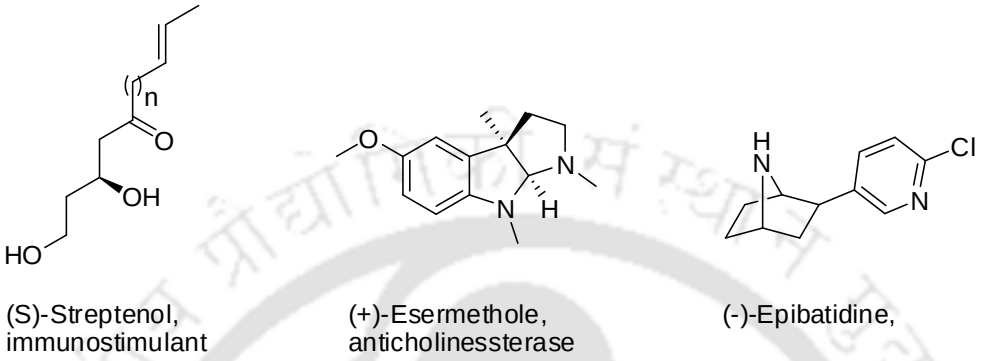


Figure 2: Natural products and drugs by enamine mediated conjugated addition

Bifunctional catalysts having both Lewis base and hydrogenbond donor properties like urea, thiourea and squaramides, derived from chiral amines have also been profoundly used in asymmetric total synthesis of biologicaly active molecules (Figure 3) involving enantioselective Michael addition step.[20b]



(S)-Streptenol, immunostimulant | (+)-Esermethole, anticholinessterase | (-)-Epibatidine,

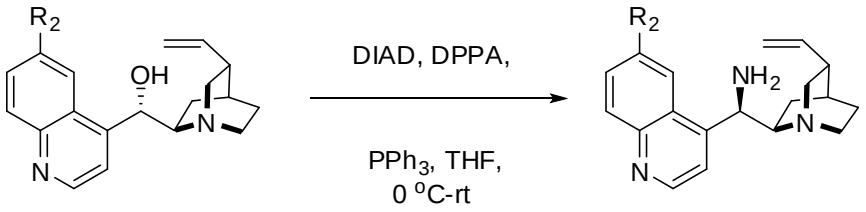
Figure 3: Natural products and drugs by conjugated addition using dual acid-base catalysis

1.4. Organocatalytic asymmetric Michael reactions using Cinchona alkaloids:

Over the years many alkaloids have been screened in different organocatalytic reactions, aiming effective asymmetric induction but majority of them failed to achieve productive result except the cinchona alkaloids. These alkaloids are inexpensive and the two pseudoenantiomeric forms are readily available. Cinchona alkaloids and its derivatives have been extensively used in organocatalytic asymmetric reactions with impressive levels of efficiency.[21] Wynberg used cinchona alkaloids as an organocatalyst in asymmetric Michael addition for the first time.[22] The C9-OH group of cinchona alkaloids were vastly modified to obtain improved enantioselectivity in many reactions. Cinchona alkaloid based amine, urea and squaramide catalysts were used as key catalysts in the works that are presented in this thesis.

1.4.1: Michael reactions using Cinchona alkaloid derived primary amines:

A very useful class of enamine and iminium catalysts were obtained by substituting the C9-OH of the cinchona alkaloids with NH_2 group, simply by Mitsunobu reaction (Scheme 1.4.1.1).[23]



Scheme 1.4.1.1: Preparation of cinchona alkaloid primary amine catalysts

These amines in combination with suitable acid co-catalyst effectively binds with sterically demanding substrates forming chiral enamine or iminium intermediates in the reaction medium resulting in chiral products.[24]

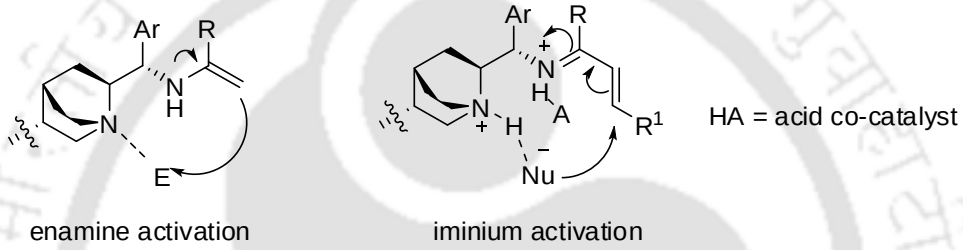
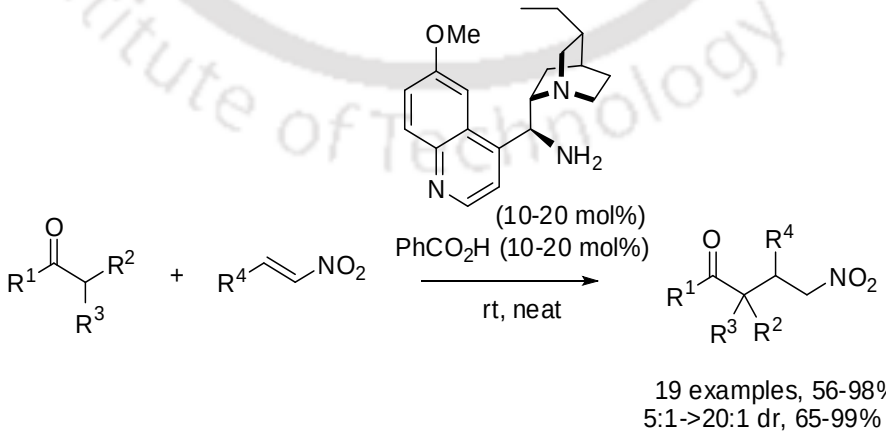


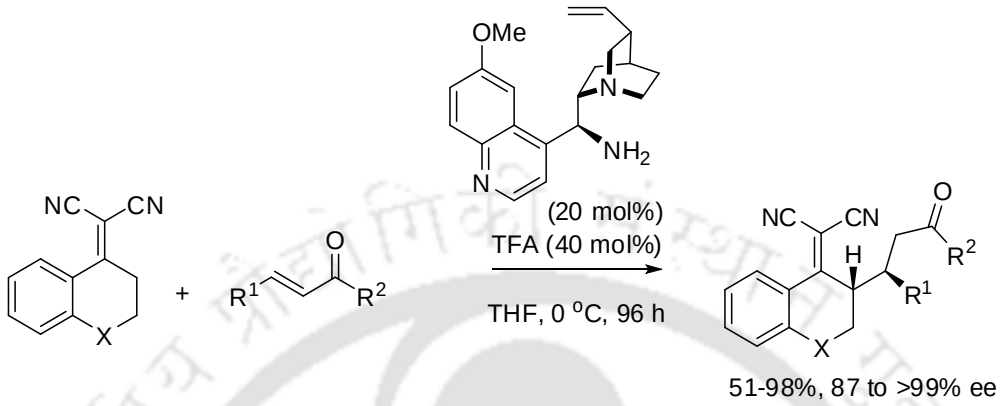
Figure 4: Enamine and iminium activation using cinchona primary amines

McCooey and Connon have reported the first example of asymmetric Michael reaction using cinchona derived primary amine via enamine catalysis. Dihydroquinine derived primary amine catalyst in combination with benzoic acid effectively catalyzed the Michael addition of unmodified aldehydes and ketones to nitrostyrenes. Cyclic ketones and *α,α*-disubstituted aldehydes and ketones were also included in their scope (Scheme 1.4.1.2).[25]



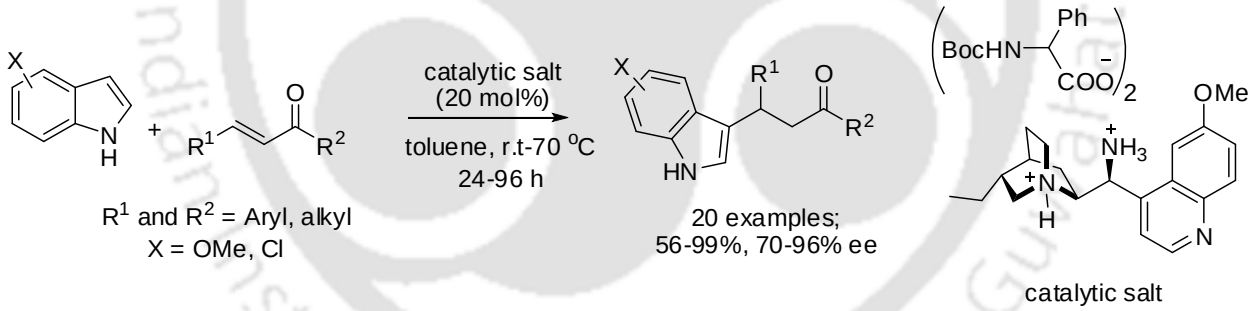
Scheme 1.4.1.2: Cinchona primary amine promoted enantioselective additions to nitroolefins

Deng and co-workers found that the TFA salt of 9-amino-9-deoxyepiquininine amine catalyzes the conjugate addition of enone with *α,α*-dicyanoalkene efficiently, affording the corresponding products with excellent enantioselectivity (Scheme 1.4.1.3).[26]



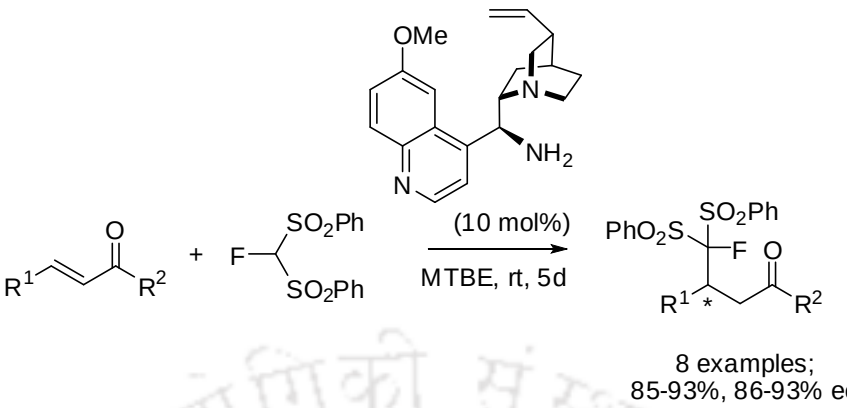
Scheme 1.4.1.3: Addition of dicyanoalkenes to enones

Melchiorre and co-workers reported a conjugate addition of indoles to simple *α,β*-unsaturated ketones utilizing iminium activation mode to furnish the adducts with high yield and enantiomeric excess (Scheme 1.4.1.4).[27]



Scheme 1.4.1.4: Addition of indoles to *α,β* -unsaturated ketones

Later, quinidine derived bifunctional amine catalyzed Michael reaction of fluorobis(phenylsulfonyl)methane with *α,β*-unsaturated ketones was described by Moon *et al.* (Scheme 1.4.1.5).[28]



Scheme 1.4.1.5: Addition of fluorobis(phenylsulfonyl)methane to *α,β*- unsaturated ketones

1.4.2: Michael reactions using Cinchona alkaloid derived hydrogen bonding catalysts:

The usage of urea and thiourea derivatives of chiral amines by utilizing their Lewis basic property was first documented by Takemoto and co-workers,[29] although the hydrogen bond donor property was previously elaborated by Jacobsen and co-workers.[30] Cinchona alkaloids have been used significantly as the chiral scaffold in these type of catalysts.[31]

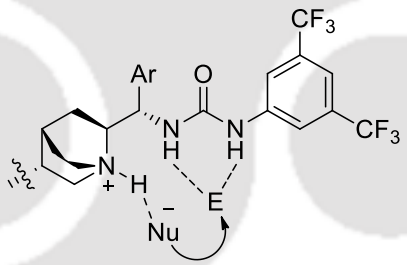
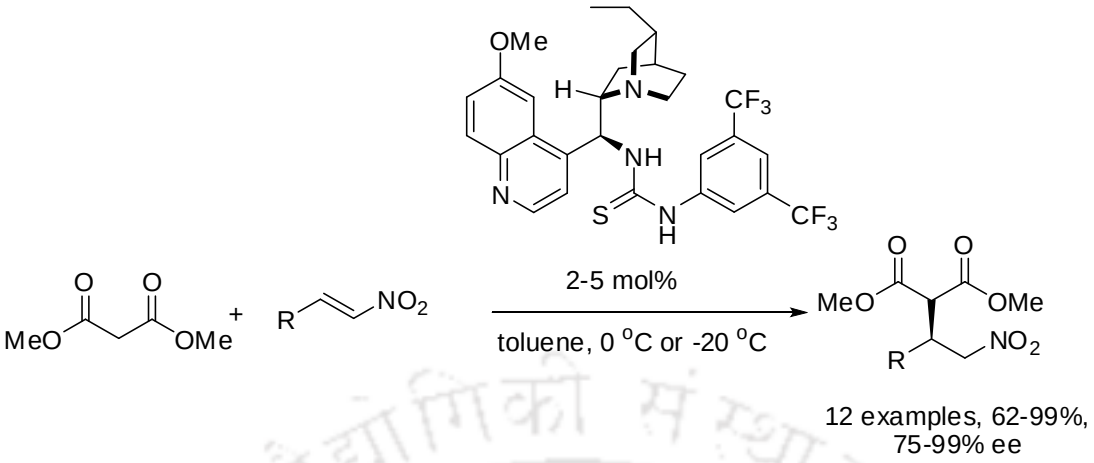


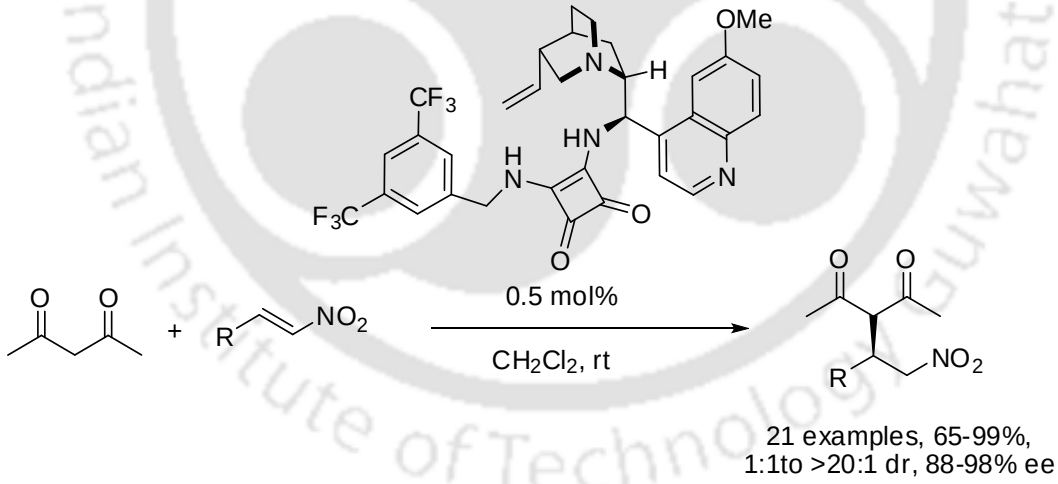
Figure 5: H-bonding activation using cinchona alkaloid derived urea catalyst

The first cinchona alkaloid derived thiourea and urea catalysts have been used by Connon and co-workers to promote the Michael addition reaction of dimethyl malonate to *trans-β*-nitrostyrene (Scheme 1.4.2.1).[32] The excellent results obtained by them triggered further development of organocatalytic asymmetric methodologies utilizing these type of catalysts.



Scheme 1.4.2.1: Bifunctional thiourea catalyzed Michael addition

Rawal group first showed that the squaramide unit could be utilized as an effective scaffold to build chiral H-bond donor catalysts. For the conjugate addition of 2,4-pentanedione to *trans*-β-nitrostyrene (first reaction that had been studied using thiourea catalyst) the authors have successfully obtained excellent yield and stereoselection with submillimolar loading of cinchona alkaloid derived squaramide catalyst (Scheme 1.4.2.2).[33]



Scheme 1.4.2.2: Bifunctional squaramide catalyzed Michael addition

After this discovery in 2008, a great portion of organocatalytic research has been dedicated to chiral squaramide catalysis.[34]

1.5. Organocatalytic asymmetric cyclization reaction:

A significant number of natural products and medicinally as well as biologically important molecules contains chiral mono- and polycyclic systems. Various asymmetric cyclization reactions has been developed and those methodologies were applied in total syntheses. Cyclization reactions could definitively be divided into concerted (cycloaddition) and stepwise counterparts. Among the other mediators, organocatalysis has also been evolved as powerful tool in achieving variety of carbocycles and heterocycles in excellent level of optical purity using cycloaddition and cyclization reactions.[35] Both organocatalytic cycloaddition and domino-cyclization reactions have been utilized in this thesis work to afford functionalized chiral cyclic compounds.

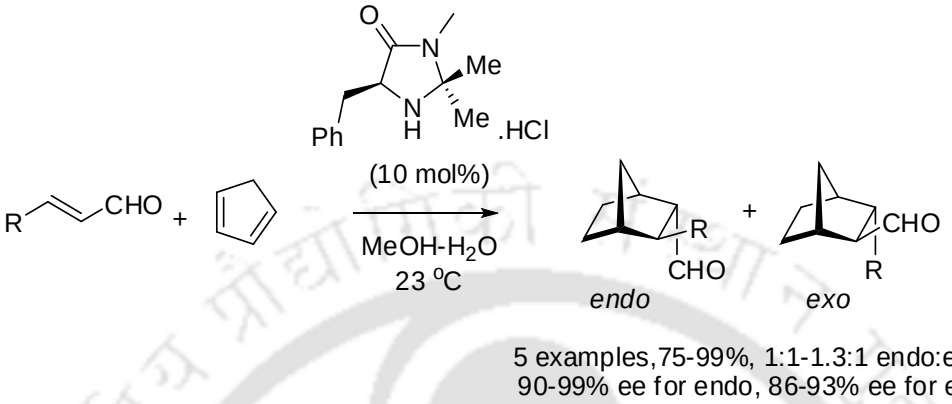
1.5.1. Organocatalytic asymmetric cycloaddition reactions:

The largest milestone in cycloaddition reaction is undoubtedly the Diels-Alder (DA) reaction.[36] It is considered as one of the most commanding, practical, and elegant synthetic approach in organic chemistry, which exhibits plentiful applications in the total synthesis of natural products and drugs. Asymmetric variants of this reaction have also been investigated in depth. Before the discovery of catalytic asymmetric Diels−Alder (DA) reaction chiral auxiliaries have been used extensively to control the stereochemical outcome of this reaction.[37] Since the first asymmetric Diels-Alder reaction, reported by Korolev and Mur in 1948,[38] it has now crossed the horizon of metal containing Lewis acid catalysis to organocatalytic versions.[39a]

Several organocatalytic methodologies for asymmetric DA reaction appeared till date using different catalytic systems like imidazolidinone salts,[39] diarylprolinol silyl ether,[40] chiral hydrazines,[41] diamines,[42] (by iminium activation) secondary amines,[43] primary amines[44] (by dienamine activation) tertiary amine urea and thiourea[45] (bifunctional acid-base activations) etc.

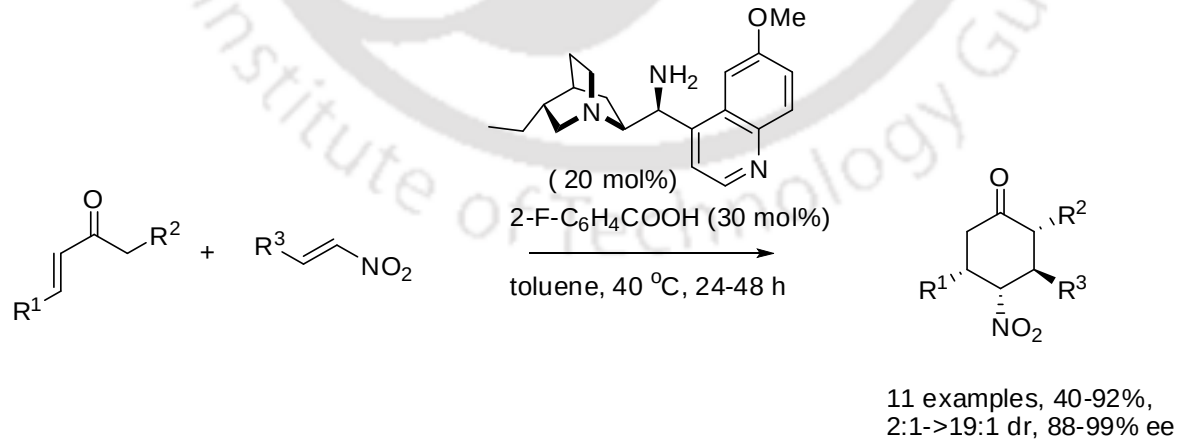
The first asymmetric organocatalytic Diels-Alder reaction was reported by MacMillan and co-workers in 2000 by using iminium activation.[39a] They found that their imidazolidinone organocatalyst could effectively promote the asymmetric Diels–Alder reaction of α,β-unsaturated aldehyde and 1,3-cyclopentadiene providing the cycloadducts in very good yield

and with excellent enantioselectivities (Scheme 1.5.1.1). Dienes other than 1,3-cyclopentadiene have also been successfully employed by the authors in this reaction and excellent endo:exo selectivity and enantioselectivity was obtained.



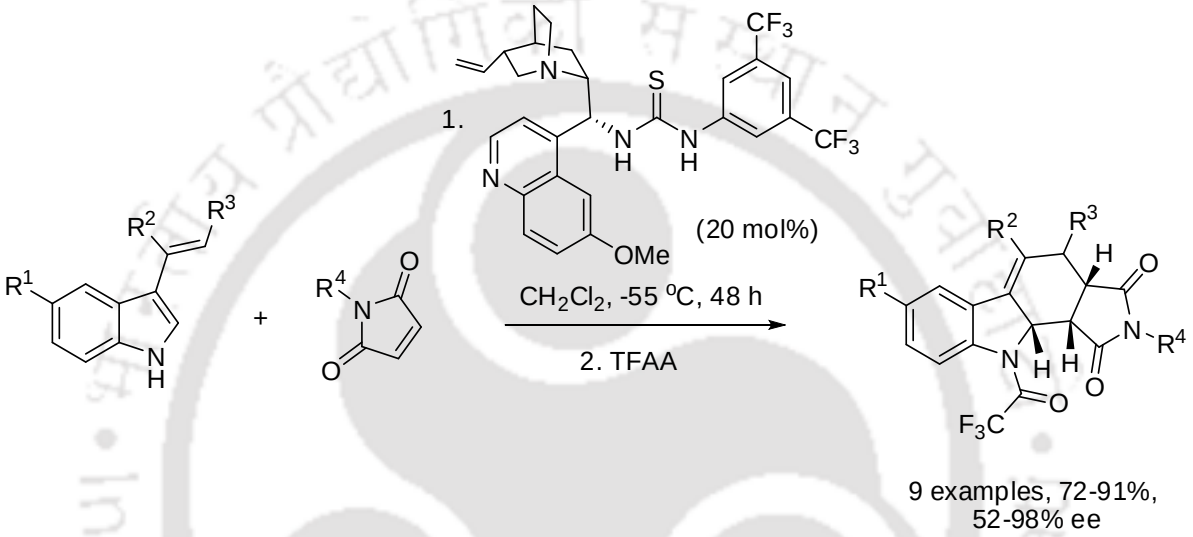
Scheme 1.5.1.1: First asymmetric organocatalytic Diels-Alder reaction (iminium activation)

The field of asymmetric Diels-Alder reaction using cinchona derived primary amines was pioneered by Melchiorre and co-workers.[44] They have activated acyclic enones towards Diels-Alder reaction by an enamine-iminium double Michael pathway using these amine catalysts. The authors have found that the chiral primary amine catalyst derived from natural cinchona alkaloids effectively catalyzes the cycloaddition reaction between acyclic enone and *trans-β*-nitrostyrene forming functionalized cyclohexane derivatives with three contiguous stereogenic centers (Scheme 1.5.1.2).[44a]



Scheme 1.5.1.2: Asymmetric Diels-Alder reaction by dienamine activation

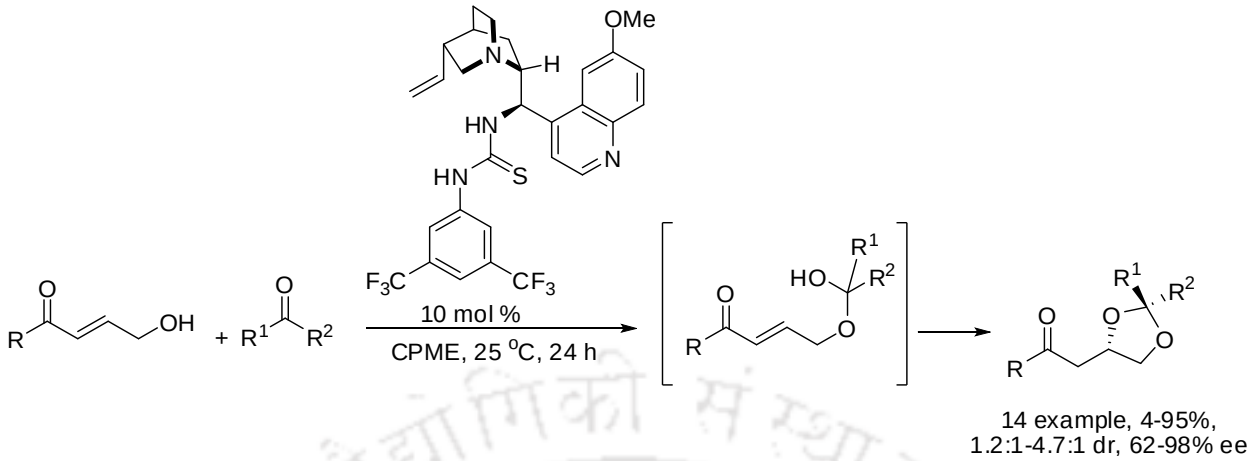
Bifunctional hydrogen bond donor catalysts have also been found to promote asymmetric Diels–Alder reaction quite effectively.[45] Cinchona alkaloid derived thiourea catalyzed asymmetric Diels–Alder reaction between 3-vinylindoles and maleimides has been developed by Ricci *et al.*, furnishing tetrahydrocarbazole derivatives (Scheme 1.5.1.3). The reaction was also carried out with quinones as dienophiles and excellent results were obtained for that case also.[45c]



Scheme 1.5.1.3: Asymmetric Diels-Alder reaction by acid-base activation

The other predominant organocatalytic cycloaddition reaction is [3+2] cycloadditions but examples on formal [2+1], [2+2], [3+2], and [3+3] cycloadditions were also available in literature.[46]

In this context, the organocatalytic asymmetric [3+2] cycloaddition reaction between γ-hydroxy enone and aldehydes/ketones has been reported by Seijiro Matsubara and co-workers. Using cinchona-alkaloid based bifunctional thiourea catalyst the 1,3-dioxolane products were obtained by the authors with moderate diastereoselectivities and good to excellent enantioselectivities (Scheme 1.5.1.4).[47]



Scheme 1.5.1.4: Bifunctional thiourea catalyzed [3+2] cycloaddition reaction

Organocatalytic asymmetric cycloaddition reactions with enolizable anhydrides have also been well documented in literature, after its first development in 2012 by Connon and co-workers (Scetion 4.2.2).

1.5.2. Organocatalytic asymmetric domino cyclizations:

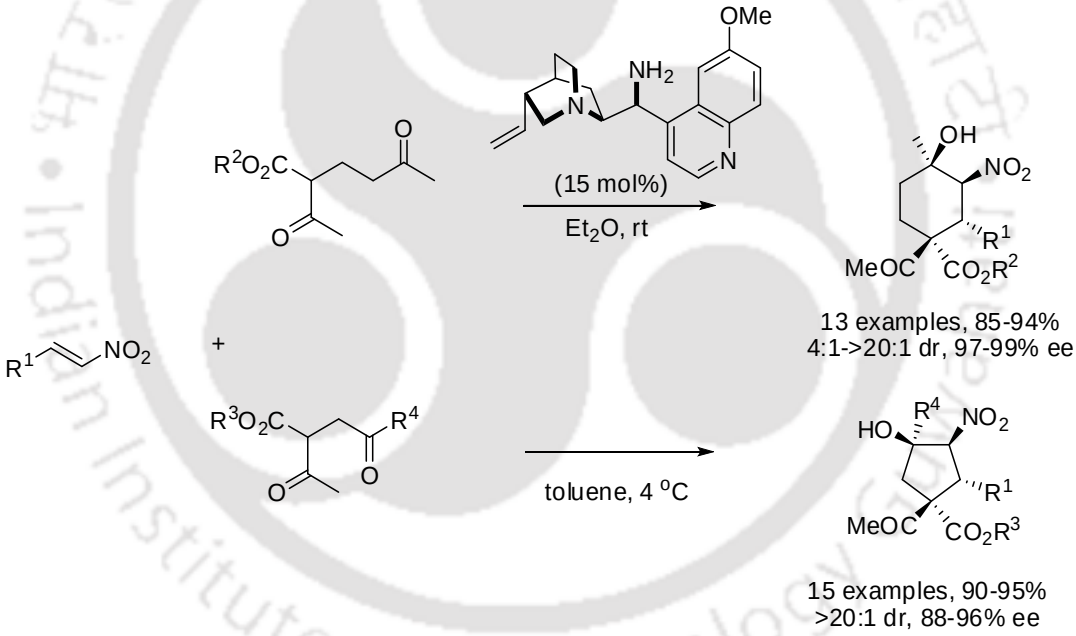
The stepwise organocatalytic cyclization reactions mainly governed by cascade or domino reactions. Over the last decade, organocatalytic domino reactions[48] have been found to be a powerful tool for the synthesis of organic compounds with varied structural frameworks, specially cyclic derivatives having multiple stereocentres. These processes are atom-economical and avoid time, energy and isolation of intermediates and also significant from the green and sustainable chemistry viewpoint. There are wide variety of Michael based domino cyclization reactions. These tandem reactions can be initiated by first a Michael addition step followed by a different reaction to form a cyclic product or can be a domino Michael-Michael reaction resulting a carbocycle or it can be initiated by well-known reaction like aldol, Mannich or an acetal formation *etc.* followed by a Michael addition step to form a heterocycle.

These domino one pot reactions, although generally involve one catalyst, could also be catalyzed by multi catalysts (generally not more than two). In this context achiral bases have also been employed for the cyclization of initially formed acyclic chiral adduct (Section 2.7.4).

1.5.2.1. Cascades start with Michael:

A vast array of cascade reactions have been reported since the last decade which were initiated by Michael addition. Michael/Aldol, Michael/Henry, Michael/Michael, Michael/Alkylation, Michael/Morita−Baylis−Hillman, Michael/Knoevenagel, Michael/Wittig, Michael/Cyclization, Michael/Mannich cascades were widely known in literature.[48]

The reactivity of nitroolefins towards Michael reaction made domino Michael/Henry reaction a thoroughly studied cascade reaction in organocatalysis. Zhong and co-workers have reported a domino Michael/Henry reaction between diketoesters and nitroolefins catalyzed by cinchona alkaloid derivatives. The reaction furnished functionalized cyclohexanes and cyclopentanes having four stereogenic centers with excellent selectivity (Scheme 1.5.2.1).[49]

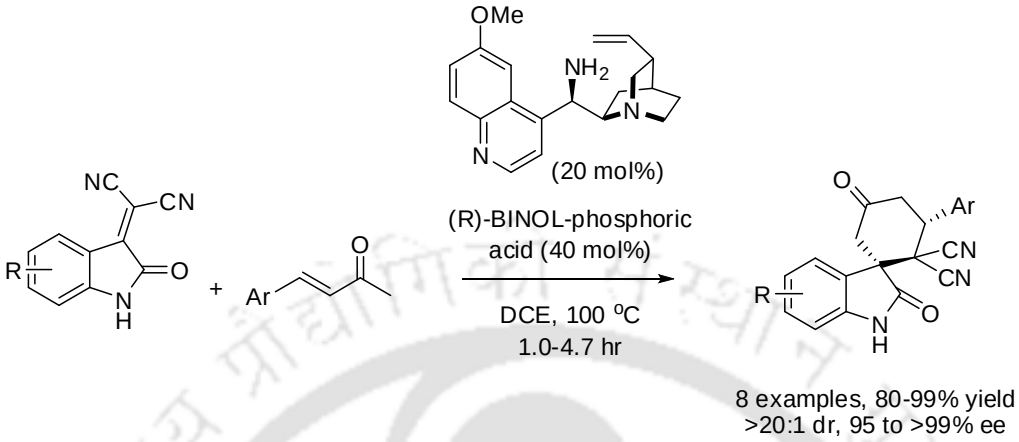


Scheme 1.5.2.1: Primary amine catalyzed domino Michael/Henry reaction

1.5.2.2. Michael-Michael cascade:

Organocatalytic asymmetric Michael-Michael cascade has widely been used for the synthesis of chiral cyclic molecules.[50] Wang and co-workers have reported a double Michael cyclization reaction between methyleneindolinones and α,β-unsaturated ketones to furnish spiro[cyclohexane-1,3′-indoline]-2′3- dione moiety with three contigious stereogenic center.

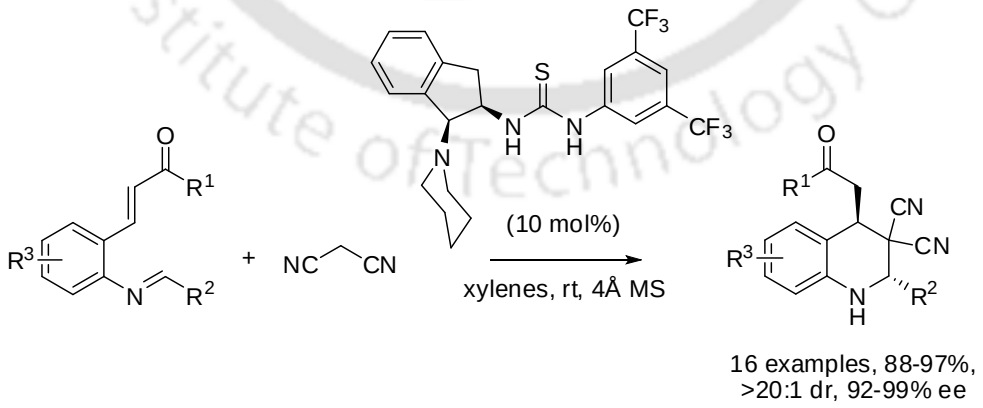
Excellent selectivity has been achieved by them using the synergistic combination of quinidine-based primary amine and BINOL derived phosphoric acid (Scheme 1.5.2.2).[51]



Scheme 1.5.2.2: Double Michael addition of isatylidene malononitriles with *α,β*-unsaturated ketones.

1.5.2.3. Cascades with Michael reaction in last or intermediate step:

Cyclization could also be attained using Michael reaction as the last step or an intermediate step in double or triple cascade reactions.[52] Indane diamine based thiourea catalyst has been utilized in Mannich/Michael cascade reaction of malononitrile with dielectrophiles containing imine and enone moieties by Wang *et al.* Resulting tetrahydroquinoline moieties were formed with excellent level of diastereo- and enantioselectivity. In this reaction malononitrile acted as a dual nucleophile in the initial fast Mannich reaction followed by a relatively slow Michael addition step (Scheme 1.5.2.3).[53]



Scheme 1.5.2.3: Bifunctional thiourea catalyzed domino Mannich/Michael reaction

References:

1. a) P. J. Walsh, M. C. Kozlowski, *Fundamentals of asymmetric catalysis*; University Science Books: Sausalito, Calif., **2009**; b) J. Halpern, B. M. Trost, *Proc Natl Acad Sci U S A* **2004**, *101*, 5347; c) S. V. Malhotra, American Chemical Society. Division of Organic Chemistry.; American Chemical Society. Meeting *Methodologies in asymmetric catalysis*; American Chemical Society : Distributed by Oxford University Press: Washington, D.C., **2004**
2. a) M. Beller, C. Bolm, *Transition metals for organic synthesis: building blocks and fine chemicals*; 2nd rev. and enl. ed.; WILEY-VCH: Weinheim, **2004**; b) R. Noyori, *Angew. Chem., Int. Ed.* **2002**, *41*, 2008; c) T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691-1693; d) D. A. Evans, D. W. C. MacMillan, K. R. Campos, *J. Am. Chem. Soc.* **1997**, *119*, 10859; For the first reports see: e) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. soc.* **1980**, *102*, 7932; f) T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974; g) W. S. Knowles, *Ace. Chem. Res.* **1983**, *16*, 106.
3. a) M. T. Reetz, *Enzyme Functionality* **2004**, 559; b) K. Drauz, H. Waldmann (eds.), *Enzyme Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; c) H. U. Blaser, E. Schmidt (eds.), *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, **2004**.
4. P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, **2004**, *43*, 5138; b) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; c) B. List, J. W. Yang, *Science* **2006**, *313*, 1584; d) T. Mohr, M. R. Krout, B. M. Stoltz, *Nature*, **2008**, *455*, 323; e) D. W. C. MacMillan, *Nature* **2008**, *455*, 304; f) S. Bertelsen, K. A. Jorgensen, *Chem Soc Rev* **2009**, *38*, 2178.
5. W. Langenbeck, *Angew. Chem.* **1932**, *45*, 97.
6. J. von Liebig, *Ann. der Chemie und Pharm.* **1860**, *113*, 246.
7. G. Bredig, P. S. Friske, *Bichem. Z.* **1912**, *46*, 7.
8. B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
9. K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243.

10. a) A. G. Nigmatov, E. P. Serebryakov, *Russ. Chem. Bull.* **1993**, *42*, 213; b) E. P. Serebryakov, A. G. Nigmatov, M. A. Shcherbakov, M. I. Struchkova, *Russ. Chem. Bull.* **1998**, *47*, 82; c) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973.
11. a) R. Thayumanavan, B. Dhevalapally, K. Sakthivel, F. Tanaka, C. F. Barbas, *Tetrahedron Lett.* **2002**, *43*, 3817; b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas, *Tetrahedron Lett.* **2002**, *43*, 6743.
12. a) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053.
13. K. S. Halskov, T. K. Johansen, R. L. Davis, M. Steurer, F. Jensen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2012**, *134*, 12943.
14. a) Q.-Q. Zhou, Y.-C. Xiao, X. Yuan, Y.-C. Chen, *Asian J. Org. Chem.* **2014**, *3*, 545; b) J. Stiller, P. H. Poulsen, D. C. Cruz, J. Dourado, R. L. Davis, K. A. Jørgensen, *Chem. Sci.* **2014**, *5*, 2052.
15. a) K. Lee, H. Kim, J. Hong, *Angew. Chem., Int. Ed.* **2012**, *51*, 5735; b) L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 5200.
16. A. Michael, *J. Prakt. Chem.* **1887**, *35*, 349.
17. For general reviews on Michael additions, see: a) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press: Oxford, U.K. **1992**; b) N. Krause, A. Hoffman-Roder, *Synthesis* **2001**, 101; c) M. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; d) K. Tomioka, Y. Nagaoka, *in Comprehensive Asymmetric Catlaysis*, E. N. Jacobsen, A. Pflatz, H. Yamamoto Eds. Springer: Berlin, **1999**, Vol. 3, Chapt. 31.1.
18. S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471.
19. P. M. Pihko, I. Majander, A. Erkkilä, *Top Curr Chem.* **2010**, *291*, 29.
20. M. Waser, *Progress in the Chemistry of Organic Natural Products*, Vol. 96 *Asymmetric Organocatalysis in Natural Product Syntheses*, Springer, **2012**, a) Scetion 2.4 b) Scetion 7.4.
21. T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *8*, 1229.
22. R. Helder, H. Wynberg, *Tetrahedron Lett.* **1975**, *16*, 4057.

23. H. Brunner, J. Bügler and B. Nuber, *Tetrahedron: Asymmetry*, **1995**, *6*, 1699.
24. a) Y.-C. Chen, *Synlett*, **2008**, *13*, 1919; b) G. Bartoli, P. Melchiorre, *Synlett* **2008**, *12*, 1759; c) P. Melchiorre, *Angew. Chem., Int. Ed.* **2012**, *51*, 9748; c) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol*. **2011**, *1*, 354; d) J. Duan, P. Li, *Catal. Sci. Technol*. **2014**, *4*, 311.
25. S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599.
26. J. W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. C. Chen, Y. Wu, J. Zhu, J. G. Deng, *Angew. Chem., Int. Ed.* **2007**, *46*, 389.
27. G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403.
28. H. W. Moon, M. J. Cho, D. Y. Kim, *Tetrahedron Lett.* **2009**, *50*, 4896.
29. T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc*. **2003**, *125*, 12672.
30. M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.
31. For reviews see: a) S. J. Connon, *Chem. Commun*. **2008**, 2499; b) C. Curti, G. Rassu, V. Zambrano, L. Pinna, *Angew. Chem., Int. Ed.* **2012**, *51*, 6200. For examples: c) B. Vakulya, S. Varga, A. Csa´mpai, T. Soo´s, *Org. Lett*. **2005**, *7*, 1967; d) B. Vakulya, S. Varga, T. Soós, *J. Org. Chem.* **2008**, *73*, 3475.
32. S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525.
33. J. Malerich, K. Hagihara, V. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416.
34. For reviews, see: a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J*. **2011**, *17*, 6890; b) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal*. **2015**, *357*, 253.
35. A. Moyano, R. Rios, *Chem. Rev*. **2011**, *111*, 4703.
36. O. Diels, K. Alder, *Justus Liebigs Annalen der Chemie*. **1928**, *460*, 98.
37. a) W. Oppolzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta*. **1984**, *67*, 1397; b) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **1984**, *106*, 4261; c) W. Oppolzer, D. Dupuis, *Tetrahedron Lett.* **1985**, *26*, 5437; d) G. Helmchen, R. Karge, S. Weetman, *In Modern Synthetic Methods*, R. Scheffold, Ed., Springer: Berlin, **1986**, p 262.
38. A. Korolev, *V. Dokl. Akad. Nauk Mur SSSR* **1948**, *59*, 251.

39. a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2000**, *122*, 4243; b) R. Gordillo, K. N. Houk, *J. Am. Chem. Soc*. **2006**, *128*, 3543; c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2002**, *124*, 2458; d) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2005**, *127*, 11616.
40. a) H. Gotoh, Y. Hayashi, *Org. Lett*. **2007**, *9*, 2859; b) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem., Int. Ed*. **2008**, *47*, 6634.
41. a) M. Lemay, W. W. Ogilvie, *Org. Lett*. **2005**, *7*, 4141; b) M. Lemay, W. W. Ogilvie, *J. Org. Chem.* **2006**, *71*, 4663; c) M. Lemay, L. Aumand, W. W. Ogilvie, *Adv. Synth. Catal*. **2007**, *349*, 441; d) H. He, B. J. Pei, H. H. Chou, T. Tian, W. H. Chan, A. W. M. Lee, *Org. Lett*. **2008**, *10*, 2421.
42. a) Y. Ma, S. Jin, Y. Kan, Y. J. Zhang, W. Zhang, *Tetrahedron* **2010**, *66*, 3849; b) T. Kano, Y. Tanaka, K. Maruoka, *Org. Lett*. **2006**, *8*, 2687.
43. a) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem., Int. Ed.* **2003**, *42*, 4233; b) D. B. Ramachary, Y. V. Reddy, B. V. Prakash, *Org. Biomol. Chem.* **2008**, *6*, 719; c) H. Sundén, R. Rios, Y. Xu, L. Eriksson, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 2549; d) D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu, *Angew. Chem., Int. Ed.* **2009**, *48*, 3821.
44. a) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2009**, *48*, 7196; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.
45. a) A. Zea, G. Valero, A. N. R. Alba, A. Moyano, R. Rios, *Adv. Synth. Catal.* **2010**, *352*, 1102; b) Q. Wei, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 1008; c) C. Goia, A. Hauville, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem., Int. Ed.* **2008**, *47*, 9236.
46. H. Pellissier, *Tetrahedron* **2012**, *68*, 2197.
47. K. Asano, S. Matsubara, *Org. Lett.* **2012**, *14*, 1620.
48. a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem., Int. Ed*. **2007**, *46*, 1570; b) X. Yu, W. Wang, *Org. Biomol. Chem*. **2008**, *6*, 2037; c) A.-N. Alba, X. Companyó, M. Viciano, R. Rios, *Curr. Org. Chem*. **2009**, *13*, 1432; d) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem*. **2010**, *2*, 167; e) L. Albrecht, H. Jiang, K. A. Jorgensen, *Angew. Chem., Int. Ed*. **2011**, *50*, 8492; f) H. Pellissier, *Adv. Synth.*

Catal. **2012**, *354*, 2; g) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev*. **2014**, *114*, 2390.

49. B. Tan, P. J. Chua, Y. Li, G. Zhong, *Org. Lett*. **2008**, *10*, 2437.
50. S. Nayak, P. Panda, S. Bhakta, S. K. Mishra, S. Mohapatra, *RSC Adv.* **2014**, *4*, 31261.
51. Y.-B. Lan,; H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao, X.-W. Wang, *Org. Lett*. **2011**, *13*, 4866.
52. a) W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett*. **2010**, *12*, 3132; b) D. B. Ramachary, C. Venkaiah, P. M. Krishna, *Chem. Commun*. **2012**, *48*, 2252.
53. H. R. Tan, H. F. Ng, J. Chang, J. Wang, *Chem. Eur. J.* **2012**, *18*, 3865.

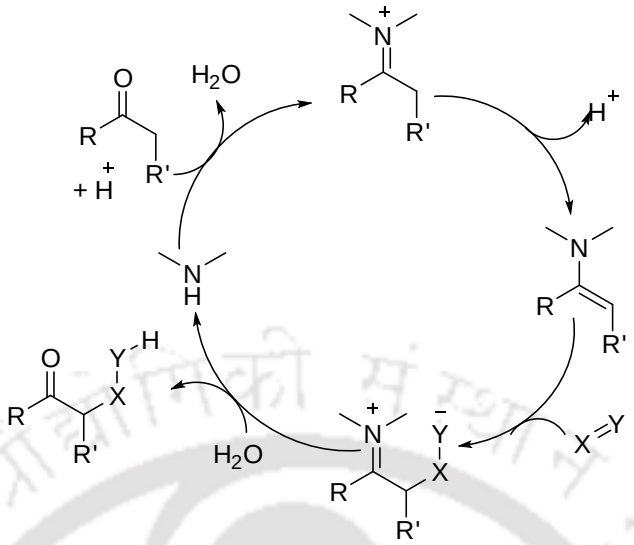
Chapter 2: Organocatalytic asymmetric Michael addition of 1-acetylcyclohexene and 1-acetylcyclopentene to nitroolefins

2.1. Introduction:

Michael donors containing two geminal electron withdrawing groups generate stabilized enolates quite easily before reacting with Michael acceptors. Less reactive substrates like simple ketones and aldehydes usually act as better Michael donors after converting to their enamines. Stork and co-workers first used secondary amines in stoichiometric amounts with ketones under dehydration conditions to form enamines and the preformed enamines were reacted with electron deficient olefins to furnish α-substituted carbonyl compounds.[1] Preformed enamine chemistry has been utilized to synthesize a library of compounds asymmetrically as well as non-asymmetrically.[2] Yamada *et al.* first reported the asymmetric Michael reaction using preformed enamines.[3] Afterwards, Seebach and co-workers extended this scope using various Michael donors and acceptors.[4] The catalytic version of the enamine chemistry using chiral amines has become one of the prime tool for asymmetric Michael reaction.

2.2. Mechanism of enamine mediated catalytic Michael addition reaction:

In these reactions, carbonyl group containing alpha-hydrogen reacted with amine to produce enamine via formation of iminium ion intermediate. Addition of enamine to Michael acceptor resulted in the formation of iminium adduct. Hydrolysis of this charged species furnished the carbonyl adduct with the regeneration of the amine (Scheme 2.2).



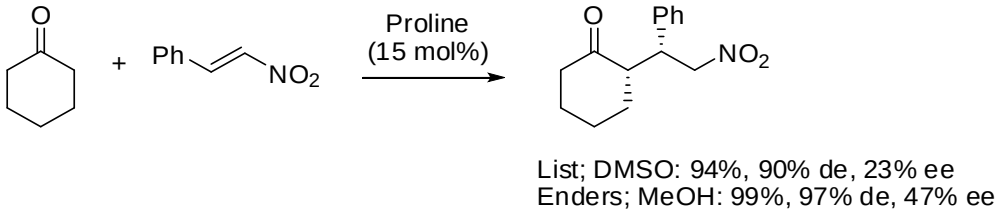
Scheme 2.2: Enamine catalysis in Michael reaction

2.3. Michael addition reactions to nitroolefins:

Nitroolefins are undoubtedly the most widely used Michael acceptors due to the ready availability and high reactivity.[5] The resultant *γ*-nitrocarbonyl adducts can also be converted to useful compounds by Nef reaction,[6] nucleophilic displacement,[7] reduction to an amino group,[8] Meyer reaction,[9] and conversion into a nitrile oxide.[10] Before 2000, asymmetric Michael reactions with nitroolefins using auxiliary control were well known.[11] After the reinvention of asymmetric organocatalysis by List and Barbas[12] the focus shifted towards organocatalysis and many reports of asymmetric Michael reactions with nitroolefins using organocatalysts have been documented since then.

2.3.1. Using proline and its derivatives:

In 2001, List and co-workers reported the first organocatalytic asymmetric intermolecular Michael addition of ketones to nitro-olefins with proline (Scheme 2.3.1).[13] The enantioselectivity was moderate for the reaction between *trans*-*β*-nitrostyrene and cyclohexanone. Shortly after, Enders reported a better enantiomeric excess value for this reaction using methanol as solvent instead of DMSO.[14] This work also demonstrated the effect of solvent on enantiocontrol (Scheme 2.3.1).



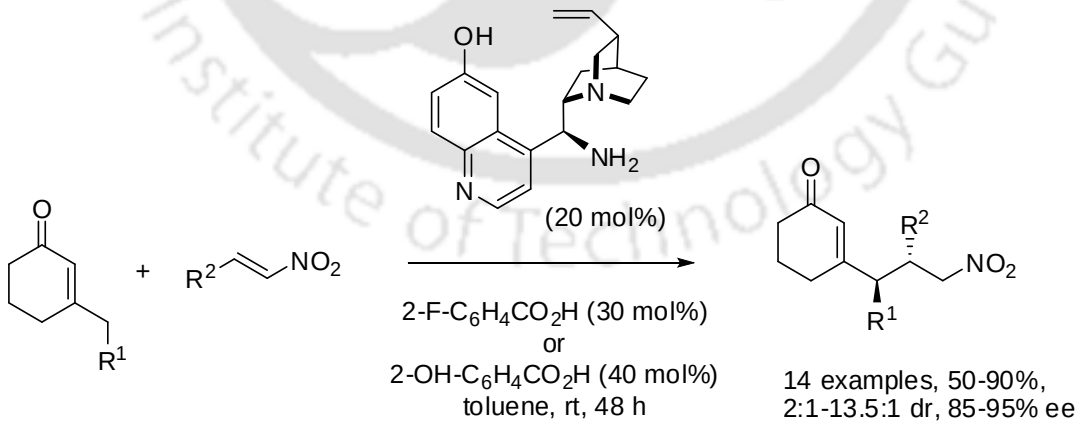
Scheme 2.3.1: Asymmetric Michael addition of ketones to nitroolefins using proline

Till date, a large variety of L-proline derived catalysts were employed in the Michael reaction between ketones and nitroolefins in order to enhance the enantioselection.[15]

2.3.2. Using cinchona alkaloid derived primary amines:

After the first report by McCooey and Connon (Scheme 1.4.1.2)[16] several reports have been published using nitrostyrenes as Michael acceptor with divergent Michael donors using cinchona alkaloids.[17]

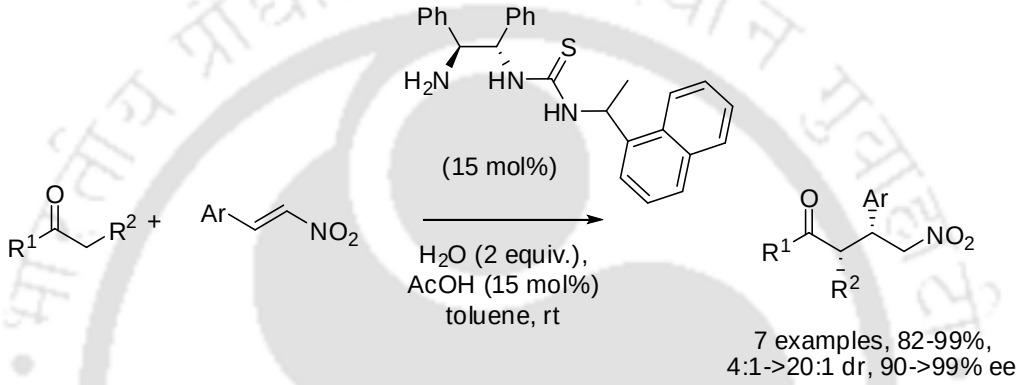
A vinylogous Michael reaction of simple and unmodified *β*-alkyl-substituted enones with nitro alkenes has been reported by Melchiorre and co-workers. Quinine-derived primary amine having a 6′-hydroxy substitution, in combination with 2-fluorobenzoic acid or salicylic acid was found to be the best catalyst for this reaction furnishing *β*-Nitroalkyl substituted cyclohexenones containing two contiguous stereogenic centres with good diastereoselectivity and excellent enantioselectivity (Scheme 2.3.2).



Scheme 2.3.2: Vinylogous Michael reaction using cinchona alkaloid derived primary amine

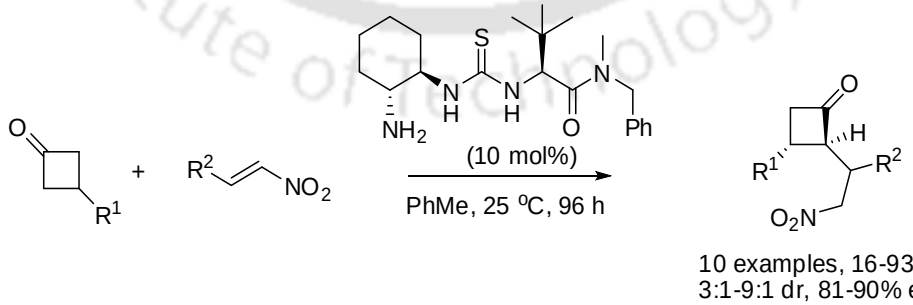
2.3.3. Using primary amine thiourea catalysts:

Primary amine thiourea catalysts have also been enormously employed in Michael reaction with nitroolefins.[18] *Trans*-1,2-1,2-diphenylethane-1,2-diamine derived thiourea catalyst has been used by Tsogoeva and co-workers in the Michael reaction between ketones and nitroolefins. The primary amine moiety of the catalyst forms enamine with ketone and thiourea moiety forms hydrogen bonds with the oxygen atoms of the nitro group and thereby acts as a bifunctional catalyst (Scheme 2.3.3.1).[18b]



Scheme 2.3.3.1: Michael addition using chiral cyclohexane-1,2-diamine-thiourea

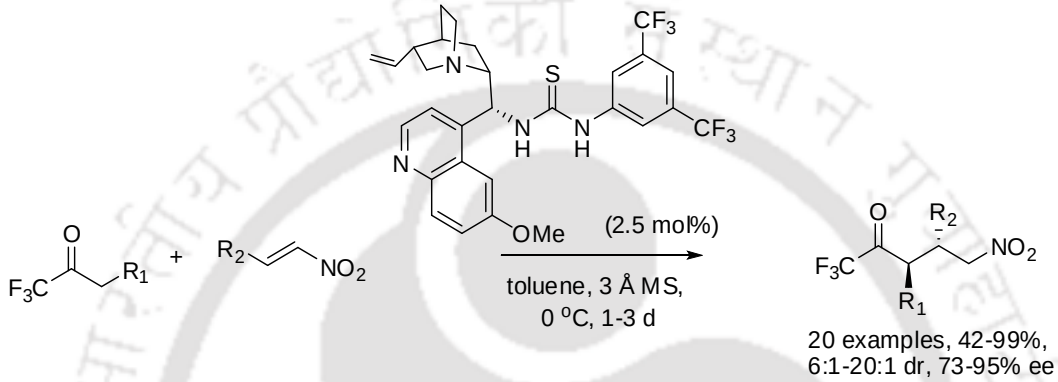
The desymmetrization of prochiral 3-substituted cyclobutanones through organocatalyzed Michael addition to nitroalkenes has been established by Capitta and co-workers. 2-alkyl-3-aryl(alkyl) cyclobutanones with three contiguous stereogenic centers were synthesized with moderate to good diastereoselectivity and high enantioselectivity using thiourea catalyst derived from 1,2-diamino cyclohexane and tert-Leucine (Scheme 2.3.3.2).[19]



Scheme 2.3.3.2: Desymmetrization of 3-substituted cyclobutanones by addition to nitroolefins

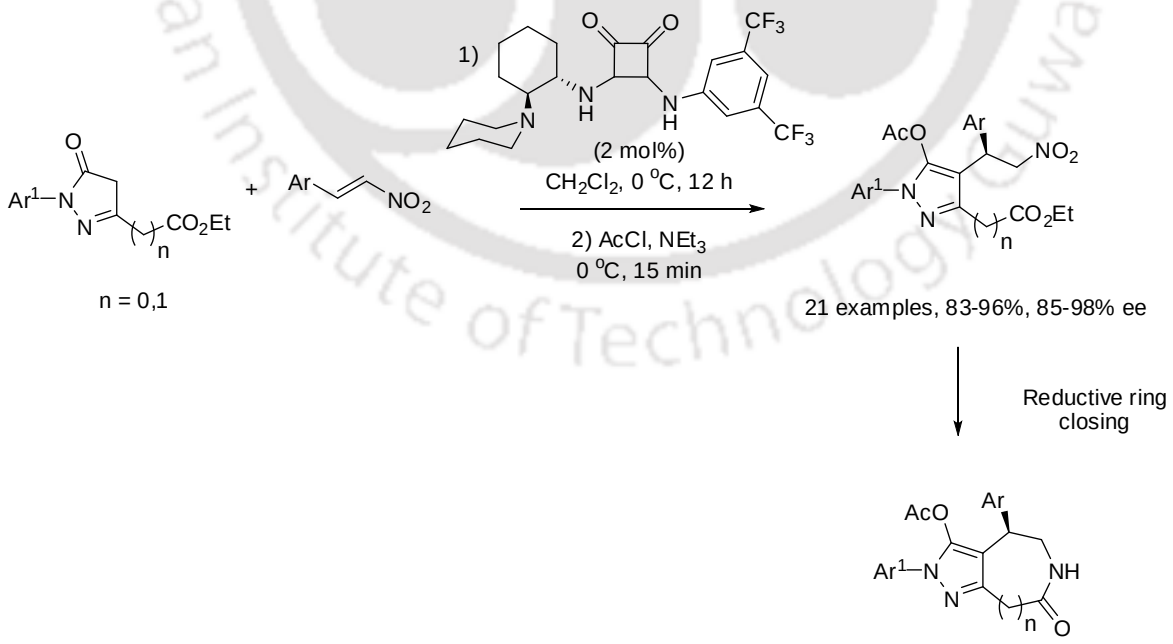
2.3.4. Using tertiary amine thiourea and squaramide catalysts:

Tertiary amine thiourea (bifunctional organocatalysts) were extensively used in Michael addition reaction with nitroolefins.[20] The combination of amines derived from cinchona alkaloids with the thiourea moiety produced a number of useful organocatalysts.[21] For example, Corbett *et al.* has used this type of catalyst in the Michael addition of trifluoromethyl ketones to nitroolefins (Scheme 2.3.4.1).[22]



Scheme 2.3.4.1: Tertiary amine thiourea catalyzed addition of trifluoromethyl ketones to nitroalkenes

Chiral bifunctional squaramides have been proven to be privileged catalysts for the Michael reaction with nitroolefins.[23]

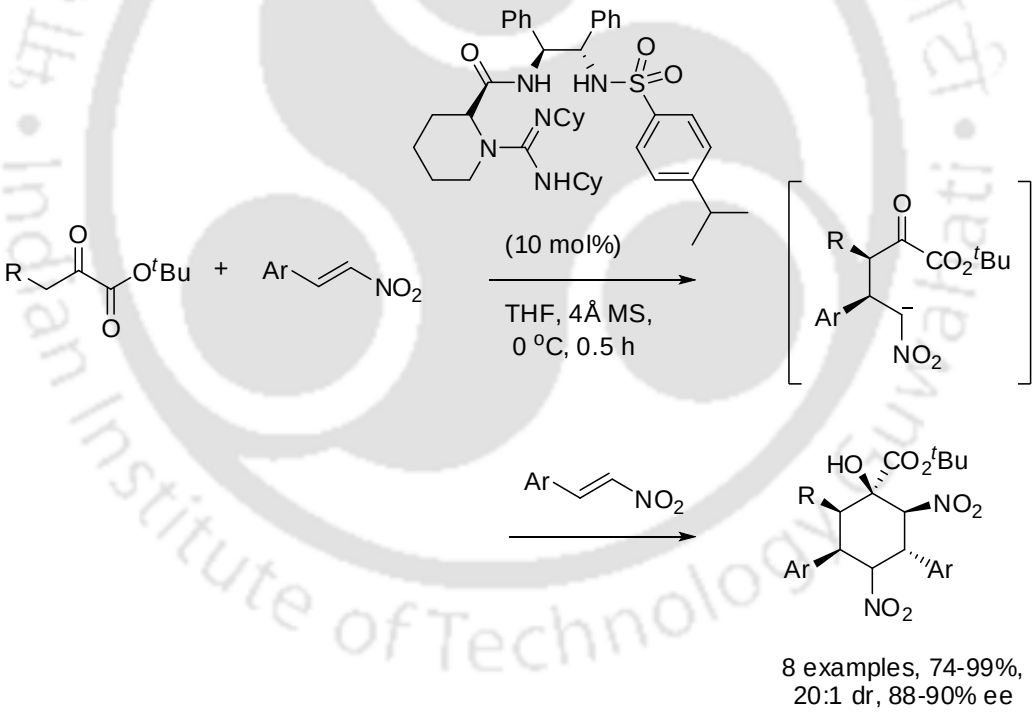


Scheme 2.3.4.2: Michael addition to nitroalkenes catalyzed by squaramide

Shen and co-workers successfully applied chiral bifunctional squaramides in Michael addition reactions of donor-acceptor pyrazolones having an ester functionality with nitroolefins followed by one-pot reductive ring closing to synthesize biologically important chiral pyrazolones with seven-membered lactam frameworks in good yields with excellent enantioselectivities (Scheme 2.3.4.2).[24]

2.3.5. Using guanidine-sulfonamide catalyst:

A triple cascade Michael/Michael/Henry process was reported using guanidine-sulfonamide catalyst. Here, the Brønsted base moiety of the catalyst promoted the deprotonation of α-keto esters and the hydrogen bonding site of the catalyst binds with the two β-nitrostyrene derivatives to form hexa-substituted cyclohexane derivatives having a quaternary stereocenter, in good yields and enantiocontrol (Scheme 2.3.5).[25]



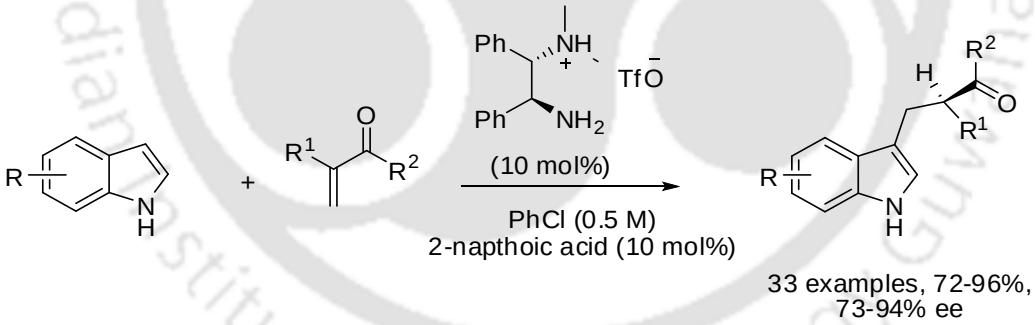
Scheme 2.3.5: Michael/Michael/Henry Sequence with nitroolefins using guanidine-sulfonamide catalyst

2.4. Organocatalytic asymmetric Michael reaction of *α*-branched enones:

Unactivated *α*-branched ketones were very challenging substrates in aminocatalysis because of their inability to form enamine/iminium intermediates due to steric hindrance. Eventually, secondary amines were unable to bind effectively with these kind of substrates, resulting in low enantiomeric ratio of the forming adducts.[26] Luckily, the installation of enantiocontrol in the reaction with these challenging *α*-branched ketones and enones could be achieved by reintroduction of primary amine catalysts. There are two possible ways by which primary amines catalyze the asymmetric Michael reaction: 1) Iminium activation and 2) Enamine activation.

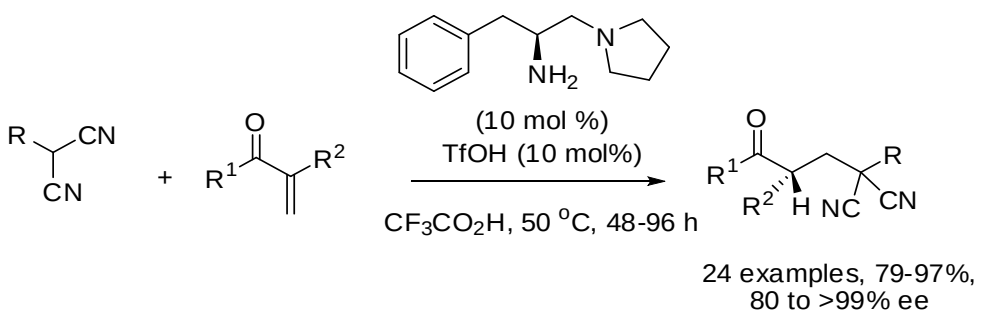
2.4.1. Michael reaction of α-branched *α,β*-unsaturated ketones using iminium activation:

Cheng and co-workers showed that catalyst having primary and tertiary amine moieties can be used as effective promoters in the reactions of *α*-branched vinyl ketones. Satisfactory result has been obtained using acid additive such as 2-napthoic acid in the conjugate addition of indols with *α*-branched vinyl ketones. Both aliphatic and aromatic vinyl ketones were equally active in terms of yield and enantiocontrol (Scheme 2.4.1.1).[27]



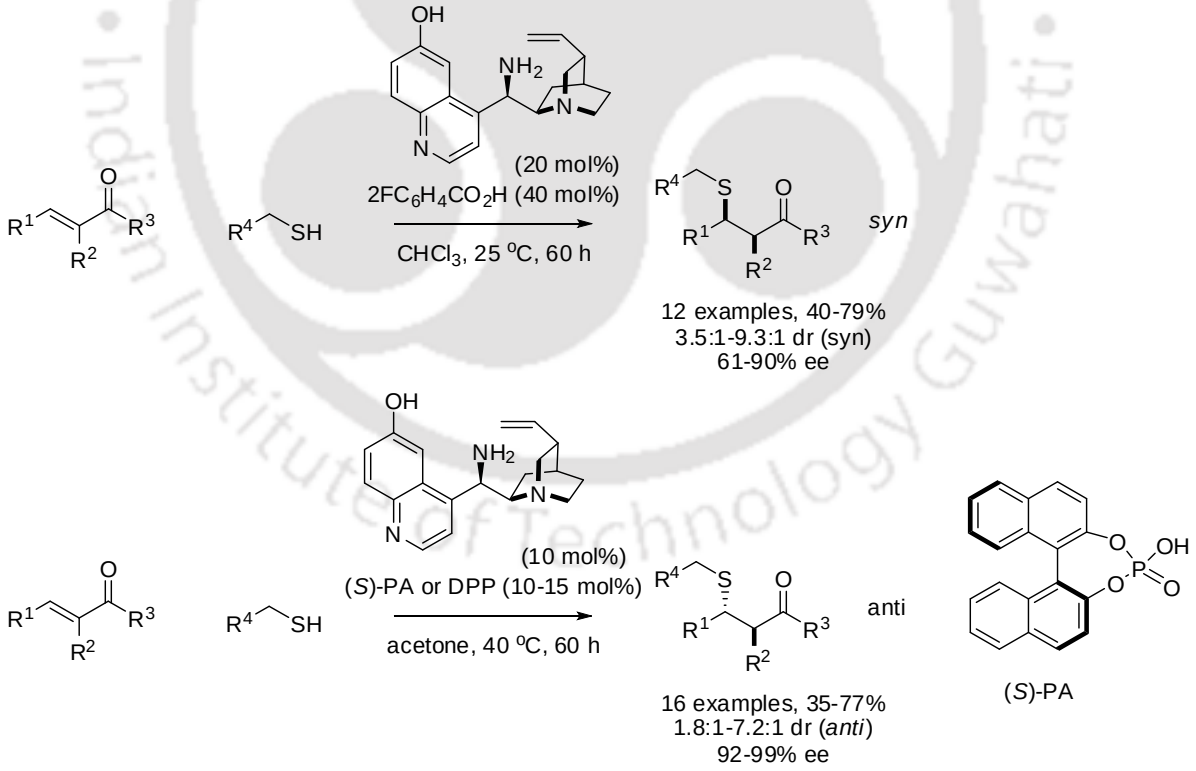
Scheme 2.4.1.1: Primary amine catalyzed addition to *α*-substituted vinyl ketones

Fu *et al.* reported an enantioselective Michael addition-protonation reaction of 2-substituted malononitriles to *α*-branched vinyl ketones using phenyl alanine derived primary amine as an organocatalyst. The Michael adducts were obtained with high yield and good to excellent enantiomeric ratios (Scheme 2.4.1.2).[28]



Scheme 2.4.1.2: Primary amine catalyzed addition of malononitrile to α-substituted vinyl ketone

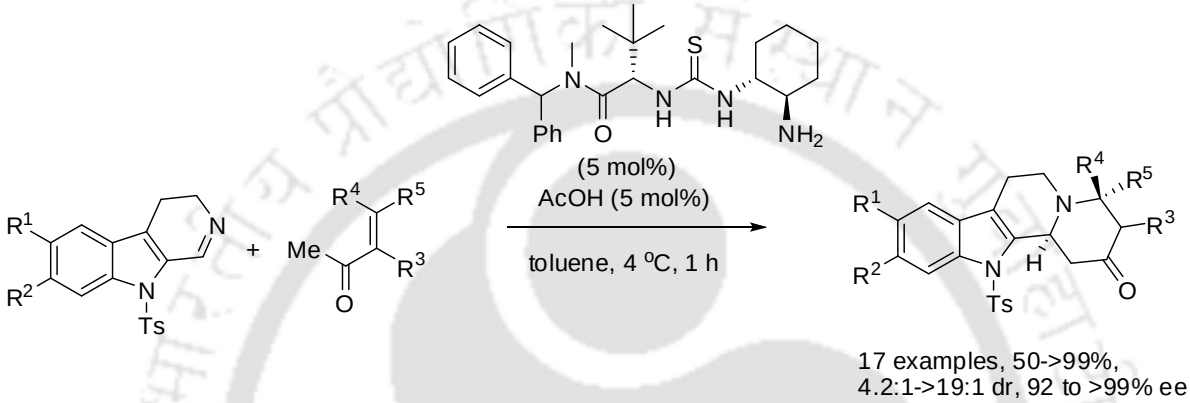
An interesting enantioselective diastereodivergent sulfa-Michael addition to α-branched enones was reported by Melchorrie and co-workers.[29] The authors found that upon changing the acid co-catalyst from a small achiral benzoic acid to large chiral phosphoric acid, the catalyst conformationally changes to furnish the different diastereomers of the Michael adduct. Though for the *syn*-adduct, the enantioselectivity is moderate to good and for the *anti*-isomer, the enantiomeric excess values of the products were excellent (Scheme 2.4.1.3).



Scheme 2.4.1.3: Diastereodivergent asymmetric sulfa-Michael additions of α-branched enones

2.4.2. Michael reaction of α-branched α,β-unsaturated ketones using enamine activation:

However, Michael reaction of α-branched enones using enamine catalysis has rarely been known in literature. Jacobsen and co-workers synthesized indolo- and benzoquinolizidine compounds with moderate to high diastereomeric ratios and excellent enantiomeric excess via formal aza-Diels-Alder reaction of enones with cyclic imines using primary amine thiourea catalyst (Scheme 2.4.2).[30]

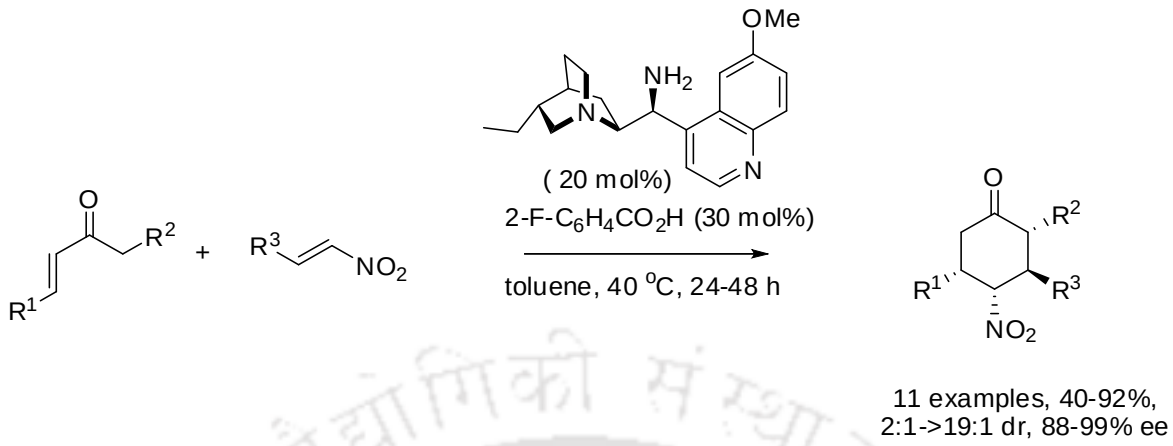


Scheme 2.4.2: Enantioselective formal aza-Diels-Alder reactions of enones with cyclic imines

2.5. Double Michael reaction of enones:

2.5.1. Domino cyclization:

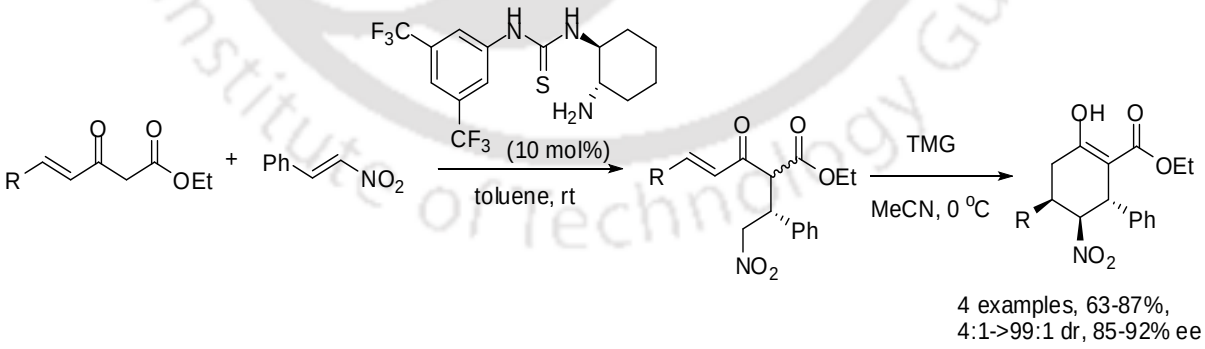
Simple enones have been activated by amine catalysts to generate dienamine[31] and have been utilized for a variety of enamine-iminium cascade reactions.[32] Melchiorre and co-workers pioneered using primary amine catalysts for the activation of acyclic enones towards a enamine–iminium tandem sequence.[32d] They found that chiral primary amine catalyst derived from natural cinchona alkaloids effectively catalyzes the formal cycloaddition by double-Michael reaction between acyclic enone and *trans*-β-nitrostyrene forming functionalized cyclohexane derivatives with three contiguous stereogenic centers (Scheme 2.5.1).



Scheme 2.5.1: Double Michael cyclization of linear enones with nitroolefins

2.5.2. Base catalysed cyclization of chiral single Michael adducts:

There were several reports on synthesis of functionalized carbocycles by an initial Michael addition, catalyzed by chiral catalyst followed by second Michael addition catalyzed by achiral base.[36] Takemoto and co-workers first investigated the double Michael reactions of *γ,δ*-unsaturated-*β*-ketoesters to nitrostyrenes using this methodology (Scheme 2.5.2).[36a] The one pot reaction involved asymmetric Michael reaction using Takemoto catalyst followed by 1,1,3,3-tetramethyl guanidine (TMG) catalyzed intramolecular Michael reaction. High yields of the cyclized products were obtained with good to excellent diastereomeric ratio and enantiomeric excess.



Scheme 2.5.2: Thiourea/TMG-catalyzed enantioselective double Michael reaction of *γ,δ*-unsaturated-*β*-ketoesters to nitroalkene

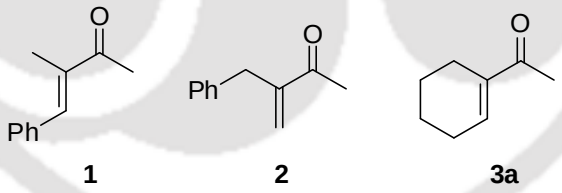
The similar concept has been used by Enders and co-workers to furnish functionalized cyclohexane and spiropyrazolone derivatives moiety using one pot Michael-Michael-1,2-addition sequences.[36c-d]

2.6. Aim of this work:

The aim of this work is to apply α-branched enones in enamine mediated Michael reaction and to find a way to perform asymmetric double Michael reaction of *α*-branched enones using enamine- iminium tandem catalytic sequence as a tool.

2.7. Result and discussion:

Initially, enones **1** and **2** were synthesized (Figure 1) and tried to react with *trans-β*-nitrostyrene. Unfortunately, these enones remained unreacted under various reaction conditions. Some product formation was observed only when 1-acetylcyclohexene **3a** was used. Inspired by this, 1-acetylcyclohexene and *trans-β*-nitrostyrene were chosen as the model substrates in the Michael reaction. Compound **3a** has been previously utilized for tandem cyclization reactions with imines and nitroolefins[33] and recently in the synthesis of cyclopentenone derivatives.[34] Surprisingly, no chiral transformation has been reported using it.[35]



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

Figure 1: various synthesized enones

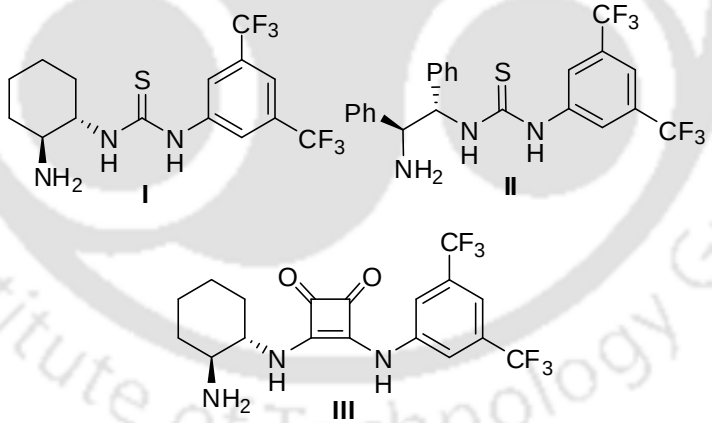
2.7.1. Optimization Studies:

2.7.1.1. Optimization of catalysts:

Initially, primary amine-thiourea **I** was used as a catalyst for the reaction of **3a** with nitrostyrene (**4a**) using toluene as the solvent and 2-fluorobenzoic acid as a co-catalyst as it has been an effective co-catalyst for double Michael reactions. At room temperature, a slight formation of the new spot was observed. After stirring at 80 ^{o}C for seven days, the single

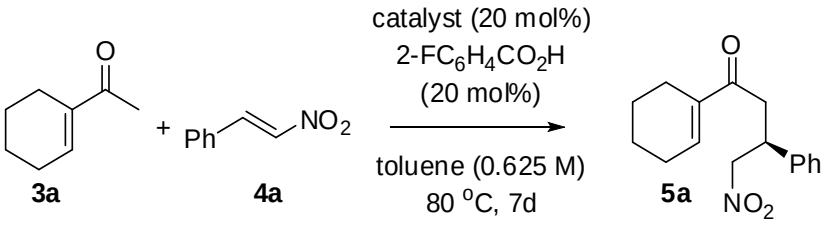
Michael addition product **5a** was formed in poor enantioselectivities and no cyclized product was formed (Table 1, entry 1). For primary amine-thiourea **II**, the enantioselectivity was similar to that obtained with catalyst **I** with lesser yield. Primary amine- squaramide catalyst **III** was also not suitable for this reaction giving the product in poor yield. Then, 9-amino-9-deoxy-*epi*-cinchona alkaloid catalysts (**IV**-**VII**) were employed in the reaction and to our delight, these catalysts were found to be effective for our reaction. Quinidine derived primary amine **IV** furnished the single addition product with 35% yield and 70% ee whereas with quinine derived amine **V,** both yield and enantioselectivity were decreased. Similar results were observed using cinchonine derived amine **VI**. Finally, the *epi*-cinchonidine amine **VII** emerged as the better catalyst providing the product with 75% ee. Further, to improve the results, demethylation of 6'-OMe group of quinine derived amine was done but unfortunately 9-amino-6'-hydroxy-*epi*-cinchonidine catalyst **VIII** failed to increase the enantioselectivity as well as the yield of the reaction. Thus, catalyst **VII** was found to be the best catalyst for this reaction.

Table 1: Catalyst optimization



IV: R^1 = OMe
VI: R^1 = H

V: R^2 = OMe
VII: R^2 = H
VIII: R^2 = OH



3a **4a** **5a**

entry[a]	**catalyst**	**yield**[b] **(%)**	**ee**[c] **(%)**
1	**I**	30	4
2	**II**	20	5
3	**III**	<10	nd
4	**IV**	35	-70
5	**V**	30	68
6	**VI**	40	-70
7	**VII**	55	75
8	**VIII**	52	71

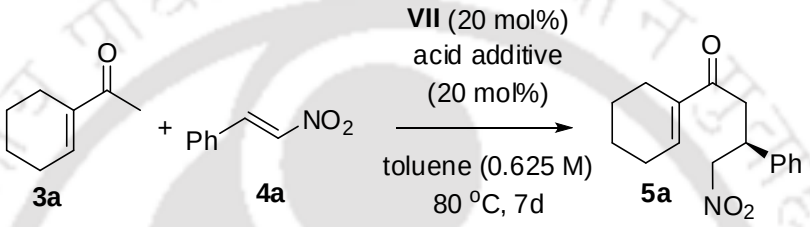
[a]Reactions were carried out in 0.16 mL toluene with 0.12 mmol of **3a** and 0.1 mmol of **4a** in the presence of 20 mol% catalyst and 20 mol% 2-fluorobenzoic acid. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral phase HPLC analysis. nd = not determined

2.7.1.2. Optimization of acid co-catalyst:

The next phase of the screening process involved using different acid additives for the reaction. It was found earlier that the acidity of the additive might play a role to improve the yield as well as enantioselectivity of the reaction and thus different acid co-catalysts were screened with catalyst **VII**. Highly acidic 2,4,5-trifluorobenzoic acid provided poor yield of the reaction with moderate enantioselectivity (entry 2, Table 2). Similar enantioselectivity was also

achieved with 2-nitrobenzoic acid (entry 3). The yield and enantioselectivity did not increase much with 2-bromobenzoic acid (entry 4). Interestingly, 2-methoxybenzoic acid afforded a higher enantioselectivity for the product but with poor yield (entry 5). Camphorsulfonic acid and propionic acid were not suitable co-catalysts for our reaction (entries 6 and 7 respectively). Thus, 2-fluorobenzoic acid was the acid additive of choice. Increasing the mol% of acid additive also could not improve the result (entry 8).

Table 2 Screening of acid-additive:



3a **4a** **5a**

entry	acid-additive	yield[a] (%)	ee[b] (%)
1	2-fluorobenzoic acid	55	75
2	2,4,5-triflurobenzoic acid	20	63
3	3-nitrobenzoic acid	30	64
4	2-bromobenzoic acid	35	64
5	3-methoxybenzoic acid	20	77
6	camphorsulfonic acid	<10	nd
7	propionic acid	<10	nd
8[d]	2-fluorobenzoic acid	56	73

[a]Reactions were carried out in 0.16 mL toluene with 0.12 mmol of **3a** and 0.1 mmol of **4a** in the presence of 20 mol% **VII** and 20 mol% acid. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral phase HPLC analysis. nd = not determined. [d]30 mol% acid-additive was used.

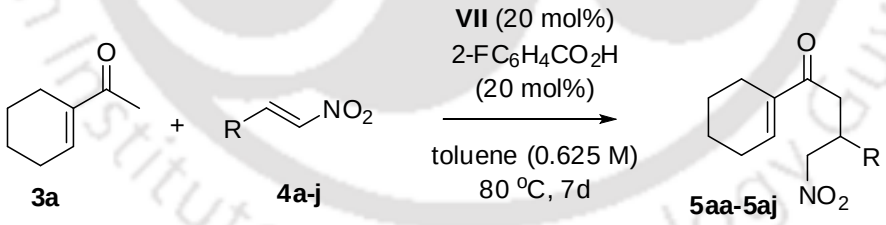
2.7.3. Substrate scope:

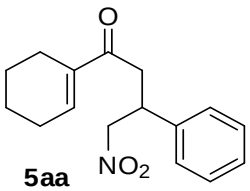
With the optimized conditions in hand, the substrate scope for this reaction was started. 1-Acetyl substituted cyclohexene, cyclopentene and cyclobutene were screened in combination of different nitroolefins.

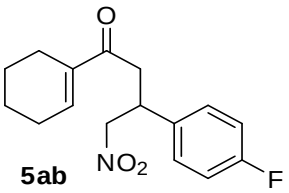
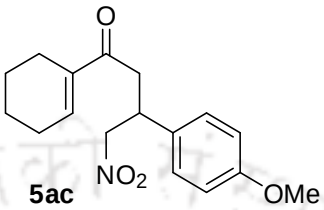
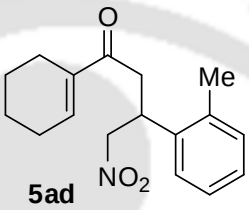
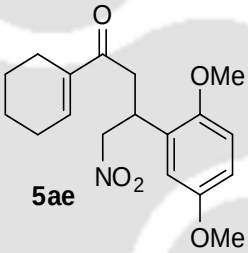
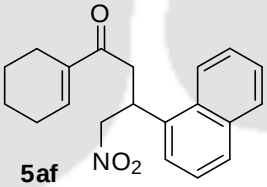
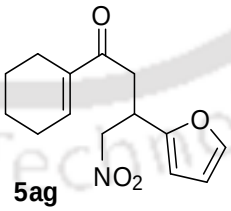
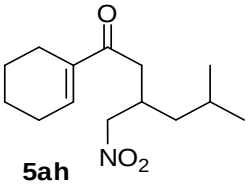
2.7.3.1. Scope with 1-acetylcyclohexene (3a):

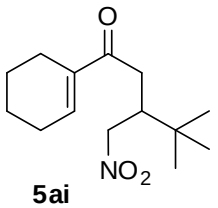
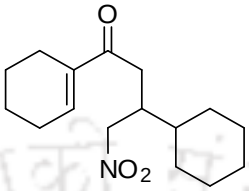
Initially, different aromatic nitroolefins were synthesized and reacted with **3a.** The products were obtained in good yields with varying enantioselectivities (Table 3, entries 1-6). Substituted benzaldehyde derived nitroolefins having electron-donating or electron-withdrawing substitution at 4-position on the aromatic ring were employed and they demonstrated similar reactivity and comparable enantioselectivities were attained (entries 2-3). Surprisingly, 2-substitution on phenyl group showed higher reactivity but the enantioselectivity remained same (entry 4). 2,5-disubstituted nitroolefin **4e** afforded product **5ae** in similar enantioselectivity (entry 5). Higher yield was obtained with 1-naphthyl substituted nitroolefin (**4f**) and moderate enantioselectivity was observed (entry 6). Heteroaromatic nitroolefin also reacted well under the optimized reaction condition with similar enantioselectivity (entry 7).

Table 3: Substrate scope with 1-acetylcyclohexene



entry[a]	R	5	yield[b] (%)	ee[c] (%)
1	Ph	 **5aa**	55	75

2	4-FC_6H_4	 **5ab**	47	54
3	4-$OMeC_6H_4$	 **5ac**	52	54
4	2-MeC_6H_4	 **5ad**	72	58
5	2,5-$(OMe)_2C_6H_3$	 **5ae**	53	60
6	1-naphthyl	 **5af**	74	58
7	2-furyl	 **5ag**	63	62
8	*iso*-butyl	 **5ah**	35	86

9	*tert*-butyl	 **5ai**	37	73
10	*c*-hexyl	 **5aj**	37	72

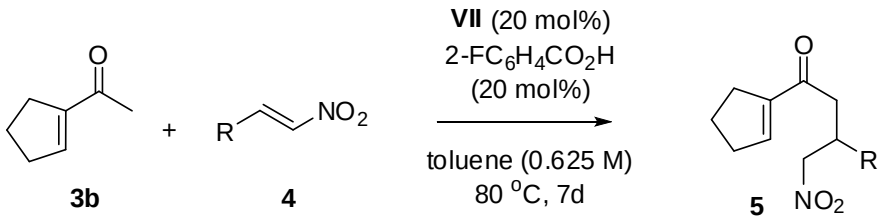
[a]Reactions were carried out in 0.4 ml toluene with 0.3 mmol of **3a** and 0.25 mmol of **4** in the presence of 20 mol% **VII** and 20 mol% 2-fluorobenzoic acid. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral phase HPLC analysis.

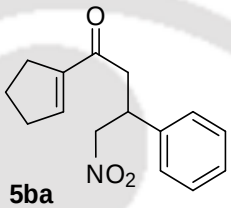
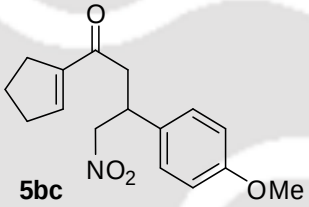
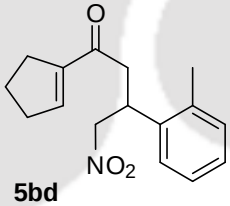
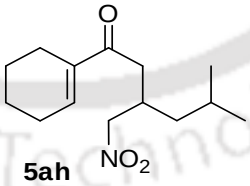
Interestingly, aliphatic nitroolefins were also found to be suitable substrates to obtain products with higher enantioselectivities but with poor yields due to the formation of side products (entries 8-10). The highest enantioselectivity (86% ee) was achieved with isovaleraldehyde derived nitroolefin **4h** (entry 8). Aliphatic α-branched aldehyde derived nitroolefins **4i** and **4j** havig *t*-butyl and cyclohexyl groups respectively, exhibited similar reactivity but slightly lower enantioselectivities were obtained (entries 9-10).

2.7.3.2. Scope with 1-acetylcyclopentene (3b) and 1-acetylcyclobutene (3c):

Further, to expand the scope on the enone side, 1-acetylcyclopentene (**3b**) and 1-acetylcyclobutene (**3c**) were also screened with different nitroolefins (Table 4, entries 1-4 and scheme 2.7.3.2). The yields of the products with 1-acetylcyclopentene were found to be similar to 1-acetylcyclohexene (**3a**); and good enantioselectivities were achieved (Table 4, entries 1-4). Using β-nitrostyrene the product **5ba** was obtained with moderate enantioselectivity (54%) but to our delight 4-Methoxybenzaldehyde derived nitroolefin **4c** provided product **5bc** in 77% enantiomeric excess (entry 2). 2-Methyl substituted nitrostyrene **4d** also furnished the product with good enantiomeric excess (entry 3). Aliphatic nitroolefin **4h** was also employed and good enantioselectivity was attained (entry 4).

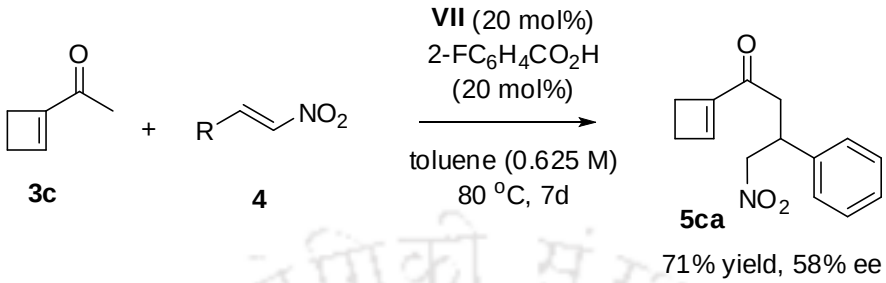
Table 4: Substrate scope with 1-acetylcyclopentene



entry[a]	R	5	yield[b] (%)	ee[c] (%)
1	Ph	 **5ba**	74	54
2	4-OMeC$_6$H$_4$	 **5bc**	53	77
3	2-MeC$_6$H$_4$	 **5bd**	71	70
4	*iso*-butyl	 **5ah**	35	70

[a]Reactions were carried out in 0.4 ml toluene with 0.3 mmol of **3** and 0.25 mmol of **4** in the presence of 20 mol% **VII** and 20 mol% 2-fluorobenzoic acid. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral phase HPLC analysis.

Finally, 1-acetylcyclobutene (**3c**) was prepared and reacted with nitrostyrene (**4a**) to afford product **5ca** in 71% yield and 58% ee (Scheme 2.7.3.2).

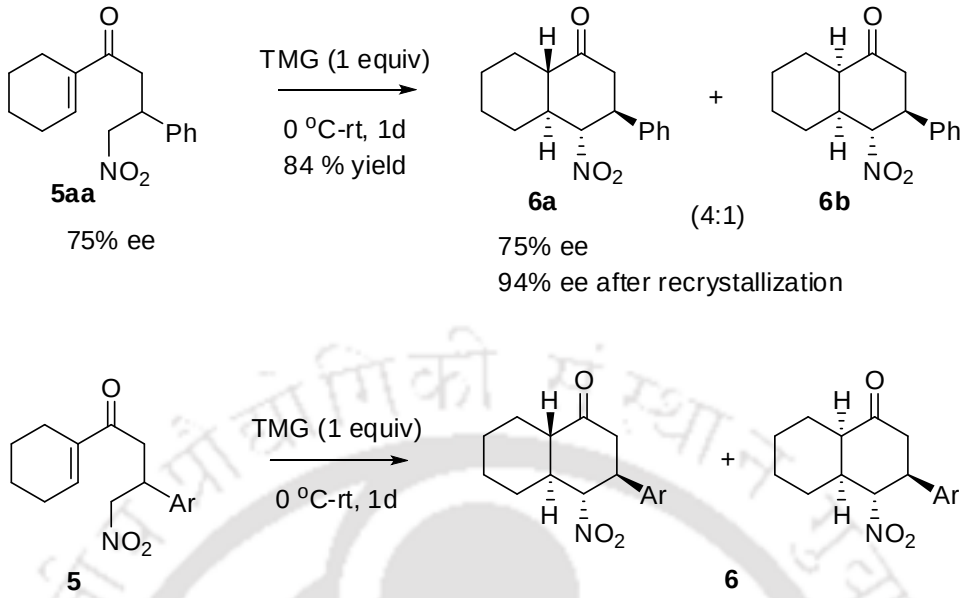


Scheme 2.7.3.2: Reaction with 1-acetylcyclobutene

2.7.4. Base catalysed cyclization by intramolecular Michael addition of chiral single Michael adducts:

Single Michael addition products **5** were converted to cyclized products **6** and **7** by treatment with 1,1,3,3-tetramethylguanidine (TMG) (Scheme 2.7.4). Initially, **5aa** was treated with TMG and to our delight, two diasteromers **6a** and **6b** were formed in 4:1 ratio. The relative structure of the major diastereomer **6a** was unambiguously determined by X-ray crystallography[37] (Figure 2) and it was obtained in 75% ee. Pleasingly, the enantioselectivity was enhanced to 94% ee after single recrystallization. Similarly, the relative structure of the minor isomer **6b** was determined by comparison of the ^{1}H NMR with the known compound.[33d] Similarly, **5ab**, **5af** and **5ag** were converted to their corresponding cyclized products **6** under identical conditions and similar results were obtained. Cyclization of **5ag** afforded major diastereomer **6g** in 81% overall yield with an improvement in enantioselectivity (70% ee) after recrystallization.

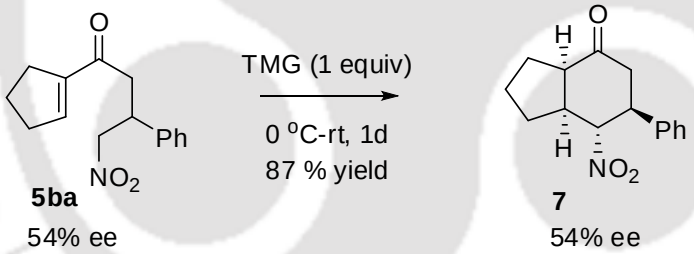
Interestingly, cyclization of **5ba** having cyclopentene moiety provided only single diastereomer **7** with the enantioselectivity being retained. The relative structure of **7** was solved by 2D NMR. However, one-pot reaction of amine catalyzed Michael reaction followed by TMG mediated cyclization did not did not proceed at all.



Ar = 4-FC_6H_4, **5ab**, 54% ee; product 75% yield, dr = 3.3:1, major **6c** 54% ee

Ar = 1-naph, **5af**, 58% ee; product 67% yield, dr = 3.1:1, major **6f** 56% ee

Ar = 2-furyl, **5ag**, 62% ee; product 81% yield, dr = 6.7:1, major **6g** 70% ee after recrystallization



Scheme 2.7.4: TMG mediated cyclization of **5**

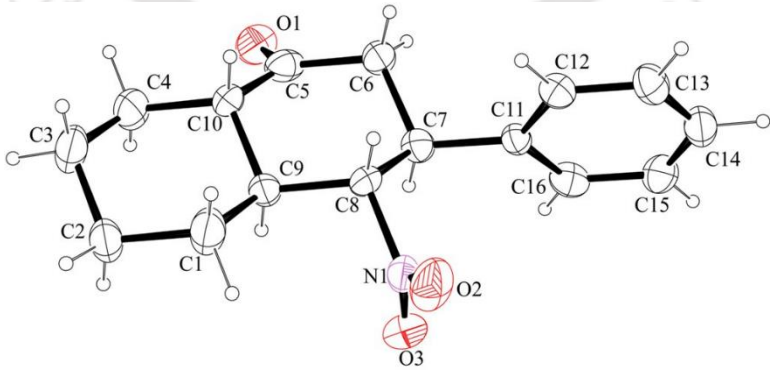
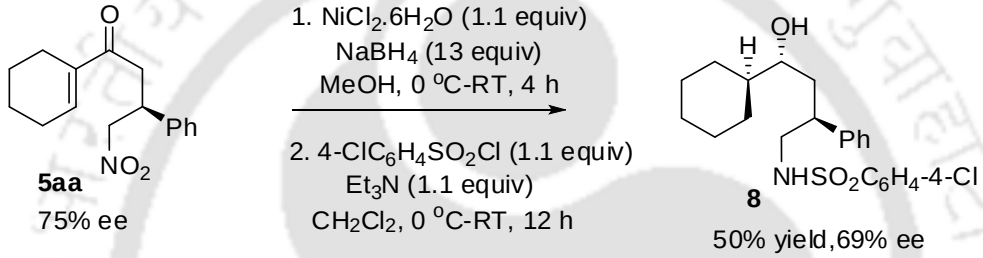


Figure 2: ORTEP diagram of 4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (**6a**):

2.7.5. Synthetic transformation of product:

To demonstrate further application of our method, the reduction of the nitro group in **5aa** was performed with an expectation of the absolute stereochemistry determination (Scheme 2.7.5). After several attempts, it was found that the combination of nickel chloride and sodium borohydride could reduce the nitro group along with simultaneous reduction of enone functionality. After derivatizing the amino group with 4-chlorophenylsulfonyl chloride, compound **8** was obtained as the major diastereomer whose relative configuration was determined by 2D NMR. Unfortunately, compound **8** did not crystallize under various conditions.



Scheme 2.7.5: Reduction of compound **5aa**

2.8. Experimental Procedures and structure determination:

2.8.1. General procedure for the asymmetric Michael reaction:

A 10 mL round bottomed flask was charged with enone **3** (0.3 mmol, 1.2 equiv), nitroolefin **4** (0.25 mmol, 1 equiv), catalyst **VII** (0.05 mmol, 20 mol %) and 2-fluorobenzoic acid (0.05 mmol, 20 mol %) in toluene (0.4 mL). The reaction mixture was stirred at 80 ^{o}C for 7 days. The product **5** was purified by silica gel column chromatography (2-3% EA in hexane).

2.9.2. Preparation of racemic Michael adducts 5:

0.6 mmol (0.085 mL) of diisopropylamine was taken in a 10 mL R.B. flask and dry THF (1 mL) was added to it (under argon atmosphere). The whole container was cooled to -78 ^{o}C and then 0.345 mL of a 1.6 M solution of *n*-BuLi in hexane (0.55 mol) was added to it and the mixture was stirred for 1 min at -78 ^{o}C. Then a solution of **3** (0.5 mmol) in

0.5 mL dry THF was added and the mixture was stirred for 15 min at -78 °C. Next, nitroolefin **4** (0.6 mmol) was added as a solution in 0.5 mL dry THF. The solution was stirred for 15 min at -78 °C and subsequently for 12 hour at 0 °C. The reaction mixture was diluted with 1 M aqueous NH_4Cl and EtOAc. The organic layer was extracted, washed with water, brine and then dried with Na_2SO_4, evaporated under *vacuo* to get the crude product **5** which was purified by silica gel column chromatography.

2.8.3. Procedure for the preparation of catalysts:

Catalysts **I**,[38] **II**,[39] **III**,[40] **IV-VII**[41] and **VIII**[42] were prepared according to the reported procedures.

2.8.4. Procedure for the preparation of nitroolefins:

Nitroolefins **4a-4g**,[43a] **4h**[43b] and **4i-4j**[43c] were synthesized by the reported procedures.

2.8.5. Procedure for base mediated cyclization of compound 5:

1,1,3,3-Tetramethylguanidine (0.095 mmol, 1 equiv) was added to solution of **5** (0.095 mmol, 1 equiv) in dichloromethane at 0 °C. The solution is then allowed to stir for 24 hrs at room temperature. The crude product was subjected to column chromatographic separation (3% ethyl acetate in hexane) to obtain pure cyclized product.

2.8.6. Determination of relative configuration of cyclized product:

Comparing the structure of the product obtained in the tandem double Michael addition of acyclic α, β-unsaturated ketone and *trans*-*β*-nitro styrene in the report published by Melchiorre *et al.*, it can be predicted that cyclized adduct **6** should be among the 8 diastereomers in figure 3. Structure **6a** is confirmed to be the major diastereomer by X-ray crystallographic data. The ^1H NMR spectra of inseparable diastereomeric mixture showed that the peaks corresponding to $C\underline{H}NO_2$ of major and minor diastereomer have same larger coupling constant and different smaller coupling constant indicating phenyl and nitro groups of the two diastereoisomers are in similar orientation (structure **6a4**, **6a5**, **6a6**, **6a7** can be ruled out) and **H-9** and **H-1** of the two diastereoisomers are in opposite orientation (for major diastereomer **H-9** and **H-1** are trans

so for minor diastereomer **H-9** and **H-1** should be cis) leaving only structure **6a1** and **6a3** in count. Pitacco *et al.* synthesized

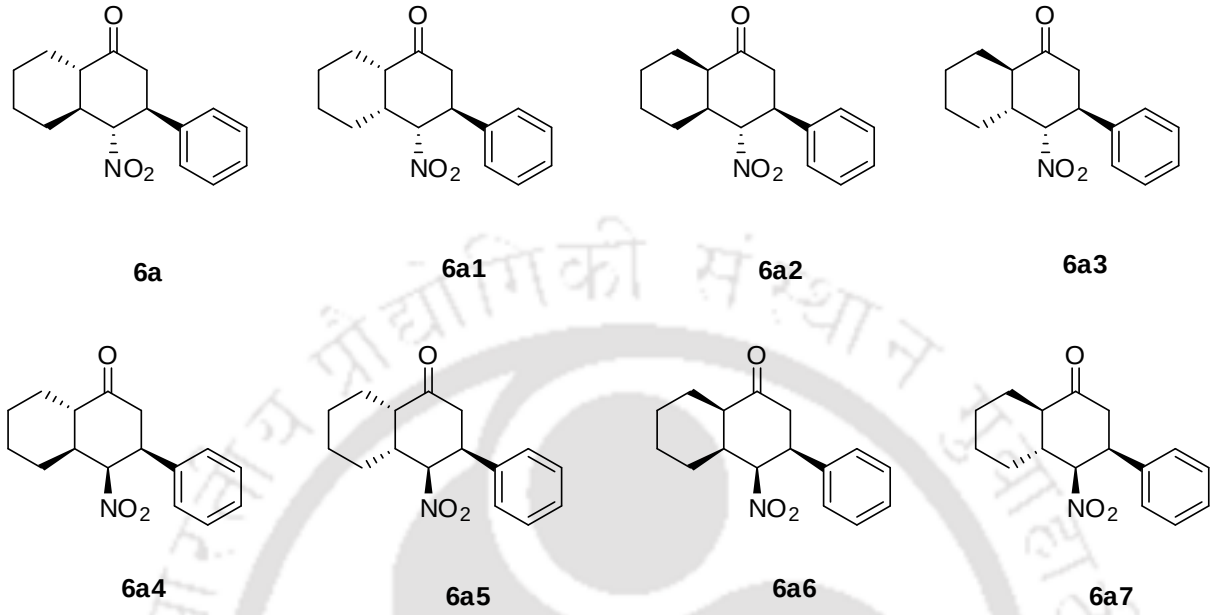


Figure 3

isomers **6a1**, **6a3**, **6a5** and **6a7** by reacting preformed enamine of 1-acetyl-1-cyclohexene and *trans*- *β*-nitrostyrene followed by hydrolysis and interconversion between isomers using different reagents. Compairng the characterization data reported by them the structure of the minor diastereomer was confirmed to be **6a1**.

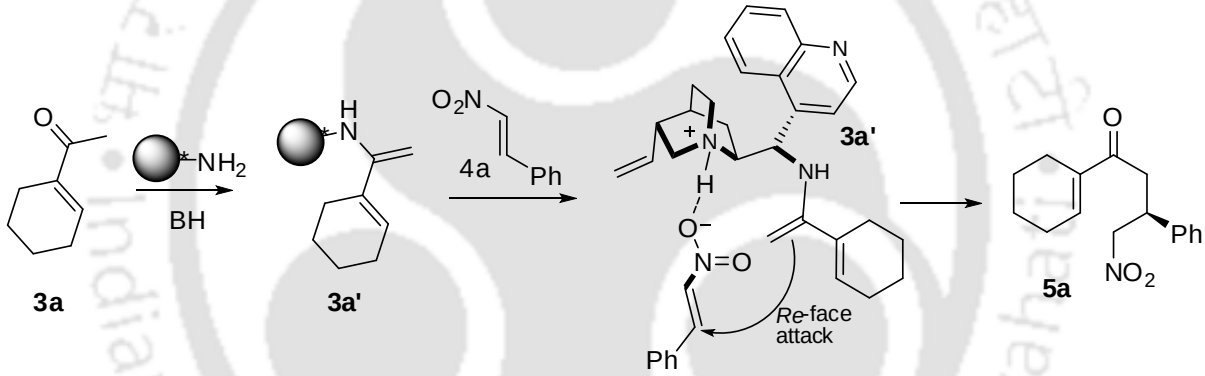
2.8.7. Procedure for reduction of compound 5:

To a stirring solution of compound **5** (0.15 mmols, 1 equiv.) in dry MeOH (0.2 mL) in an oven dried 5 ml RB, $NiCl_2.6H_2O$ (0.165 mmols, 1.1 equiv.) was added at 0 ^oC in Ar atmosphere. To this solution $NaBH_4$ (1.8 mmols, 12 equiv.) was added portion wise at 0 ^oC and the resulting mixture was stirred at room temperature. After the completion of the reaction (4 hours), the solvents were removed in vacuo, DCM and 1 M solution of NH_4Cl was added to it. Organic layer was collected and the aqueous layer was washed twice with DCM. The organic layers were combined and concentrated in vacuo. To the stirring solution of this crude amine in dry DCM at 0 ^oC, Et_3N (0.165 mmols, 1.1 equiv.) followed by 4-chloro benzene sulfonyl chloride

(0.165 mmols, 1.1 equiv.) was added and the resulting mixture was stirred at rt for 12 hours. The crude reaction was then directly subjected to column chromatographic separation using 10% EA in hexane eluent.

2.9. Plausible reaction mechanism:

A plausible mechanism has been shown considering the stereo induction (Scheme 2.9). It seems that the catalyst plays a bifunctional role activating concomitantly enone and nitroolefin.[36d] The enamine **3a'**, generated from the amine and acid catalyst attacks the nitroolefin from *Re*-face. In the enamine **3a'**, the tertiary amino group is protonated and could interact with the nitro functionality and thus assists in the stereocontrol. The configuration of the product is most probably *S* considering the litatature.[32d]



Scheme 2.9: Proposed mechanism

In summary, this chapter describes chiral amine catalyzed asymmetric Michael addition reaction between α-branched enones and nitroolefins. The enantioselectivity of the products are good to moderate and the nitroolefin scope is broad. The utility of our method has been shown by converting to bicyclized compounds and high enantioselectivity could be attained by recrystallization. The α-branched enones are challenging substrates in asymmetric organocatalysis and this is the first demonstration that α-branched enones could be activated by enamine catalysis for an asymmetric reaction to a Michael acceptor.

2.10. Characterization data of the compounds:

1-Cyclohexenyl-4-nitro-3-phenylbutan-1-one (5aa): Yellow thick oil (37.6 mg, 55%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27-7.34 (m, 2H), 7.22-7.27(m, 3H), 6.89 (s, 1H), 4.75 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.62 (dd, *J* = 12.4, 8.4 Hz, 1H), 4.06-4.09 (m, 1H), 3.02-3.16(m, 2H), 2.17-2.23 (broad doublet, 4H), 1.25-1.60 (m , 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.1, 141.2, 139.7, 139.3, 129.1, 127.8, 127.6, 79.8, 40.2, 39.8, 26.3, 23.2, 22.0, 21.6 ppm. **FT-IR** (KBr): 3444(s), 2925(s), 2853(w), 1713(s), 1551(s), 1377(w). **HRMS (ESI^+)**: calculated for [$C_{16}H_{19}NO_3$+H^+]: 274.1438, found: 274.1434. **HPLC:** Chiralpak IB column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{minor} =18.53, τ_{major} =20.08 using hexane: isopropanol= 97:3 as eluent, ee 76%.

1-Cyclohexenyl-3-(4-fluorophenyl)-4-nitrobutan-1-one (5ab): Yellow thick oil (34.4 mg, 47%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.19-7.21 (m, 2H), 6.88-7.18 (m, 2H), 6.87 (s, 1H), 4.72 (dd,*J* = 12.8, 6.4 Hz,1H), 4.56 (dd, *J* = 12.8, 8.4 Hz,1H), 4.06-4.14 (m, 1 H), 3.04-3.08 (m, 2H), 2.15- 2.23 (broad doublet, 4H), 1.23-1.59 (m, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 197.7, 161.0, 141.1, 139.3, 135.3, 129.3, 116.1, 79.8, 40.2, 39.0, 26.3, 23.2, 21.9, 21.5 ppm. **FT-IR** (KBr): 3438(m), 2859(w), 1663(s), 1552(s), 1225(m). **HRMS (ESI^+):** calculated for [$C_{16}H_{18}FNO_3$+H^+]: 293.1343, found: 293.1347. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =16.7, τ_{minor} = 20.3 using hexane: isopropanol= 96:4 as eluent, ee 54%.

1-Cyclohexenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one (5ac): Yellow thick oil (39.5 mg, 52%). **^{1}H NMR(400 MHz, $CDCl_3$):** δ 7.11-7.24 (m , 2H), 6.86 (s, 1H), 6.80-6.82 (m, 2H) , 4.68 (m, 1H), 4.53 (m, 1H), 3.74-4.01 (m, 1H), 3.73 (s, 3H), 3.00 – 3.059 (m, 2H), 2.14-2.19 (broad doublet, 4H), 1.18-1.56 (m, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.1, 159.1, 141.0, 139.3, 131.4, 128.6, 114.4, 80.1, 55.4, 40.3, 39.0, 26.2, 23.1, 21.9, 21.6 ppm. **FT-IR** (KBr): 3441.61(s), 2921(m), 2852(w), 1713(m), 1550(s). **HRMS (ESI^+):** calculated for [$C_{17}H_{21}NO_4$+H^+]: 304.1543, found: 304.1574. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =10.1, τ_{minor} =11.7 using hexane: isopropanol= 96:4 as eluent, ee 54%.

1-Cyclohexenyl-4-nitro-3-*o*-tolylbutan-1-one (5ad): Light yellow thick oil (51.8 mg, 72%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.1-7.22 (m, 4H), 6.87 (s, 1 H), 4.73 (m, 1H), 4.52 (m, 1H), 4.35-4.41 (m, 1H), 3.0-3.15 (m, 2H), 2.44 (s, 3 H), 2.14-2.23 (m, 4H), 1.2-1.5 (m, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 197.7, 141.2, 139.4, 135.3, 129.2, 116.2, 116.0, 79.9, 40.2, 39.0, 29.9, 26.3, 22.8, 22.0, 21.6 ppm. **FT-IR** (KBr): 3443(s), 2925(s), 2854(w), 1660(s), 1551(s), 1377(w). **HRMS (ESI$^+$):** calculated for [$C_{17}H_{21}NO_3$+H^+]: 288.1594, found: 288.1613. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ(major) =11.0, τ(minor) =11.9 using hexane: isopropanol= 96:4 as eluent, ee 58%.

1-Cyclohexenyl-3-(2,5-dimethoxyphenyl)-4-nitrobutan-1-one (5ae): Brown thick oil (44.0 mg, 60%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.89 (s, 1H), 6.71-6.80 (m, 3H), 4.76 (apparent d, *J* = 6.8, 2H), 4.21 (t, *J* = 6.4, 1H), 3.83 (s, 3H), 3.74 (s, 3H), 3.15 (d, *J* = 7.2, 2H), 2.13-2.18 (broad doublet, 4H), 1.58-1.65 (m, 4H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ 198.5, 153.6, 151.4, 140.4, 139.2, 128.2, 115.8, 112.8, 111.9, 77.9, 55.8, 55.7, 38.3, 36.2, 26.1, 23.0, 22.6, 21.8 ppm. **FT-IR** (KBr): 3448(m), 2921(s), 2850(m), 1712(w), 1551(s). **HRMS (ESI$^+$):** calculated for [$C_{18}H_{25}NO_5$ + H^+]: 334.1649, found: 334.1693, **HPLC:** Chiralpak AS-H column. Flow rate 1.2 mL/min. UV detection at 214 nm. τ_{major} =21, τ_{minor} =32 using hexane: isopropanol= 96:4 as eluent, ee 60%.

1-Cyclohexenyl-3-(naphthalen-1-yl)-4-nitrobutan-1-one (5af): Light brown thick oil (60.0 mg, 74%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 8.19 (d, *J* = 12, 1H), 7.88 (d, *J*=12, 1H), 7.78 (d, *J* = 6, 1H), 7.59 (t, *J* = 18, 1H), 7.52 (t, *J* = 12, 1H), 7.42 (t, *J* = 18, 1H), 7.35 (d, *J* = 6, 1H), 6.88 (s, 1H), 4.81-4.88 (m, 2H), 3.48 (q, *J* = 7.2, 1H), 3.25 (d, *J* = 6.6, 2H), 2.19-2.21 (br s, 2H), 2.15-2.18 (br s, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 198.0, 141.1, 139.3, 135.6, 134.3, 131.2, 129.3, 128.4, 127.0, 126.2, 125.4, 122.7, 79.0, 40.2, 32.1, 29.9, 26.3, 23.2, 22.0, 21.6 ppm. **FT-IR** (KBr): 3449(m), 2922(s), 2851(m), 1713(w), 1552(s). **HRMS (ESI$^+$):** calculated for [$C_{20}H_{21}NO_3$+H^+]: 324.1594, found: 324.1597. **HPLC:** Chiralpak AS-H column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =21.9, τ_{minor} = 42.7 using hexane: isopropanol= 96:4 as eluent, ee 58%.

1-Cyclohexenyl-3-(furan-2-yl)-4-nitrobutan-1-one (5ag): Yellow thick oil (51.0 mg, 63%). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.33 (s, 1H), 6.93 (s, 1H), 6.28 (s, 1H), 6.14 (s, 1H), 4.62-4.76

(m, 1H), 4.07-4.23 (m, 1H), 3.03-3.20 (m, 2H), 2.17-2.27 (br d, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$):** δ 197.6, 152.5, 142.3, 141.4, 139.3, 110.6, 107.2, 68.1, 37.7, 33.6, 26.3, 23.2, 22.0, 21.6 ppm. **FT-IR** (KBr): 3441(s), 2921(s), 2852(w), 1713(s), 1551(s), 1020(m). **HRMS (ESI^+)**: Calculated for [$C_{14}H_{17}NO_4$+H^+]:264.1230, found: 264.1241. **HPLC:** Chiralpak AS-H column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =20, τ_{minor} = 32 using hexane: isopropanol = 96:4 as eluent, ee 62%.

1-Cyclohexenyl-5-methyl-3-(nitromethyl)hexan-1-one (5ah): Light yellow thick oil (22.2 mg, 35%). **^{1}H NMR (600 MHz , $CDCl_3$)**: δ 6.87 (s, 1 H), 4.78 (dd, *J* = 12.6, 10.2 Hz, 2H), 4.61 (dd, *J* = 12.6, 4.2 Hz, 2H), 2.72-2.81 (m, 1H), 2.59-2.62 (d, 1H), 2.44-2.50 (m, 2H), 1.90-2.05 (m, 2H), 1.82-1.86 (t, 1H), 1.63-1.67 (q, 4H), 1.19-1.24 (t, 2H), 0.87-0.89 (d, 6H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 200.8, 141.6, 139.6, 87.5, 43.3, 42.7, 26.1, 25.8, 23.3, 22.9, 22.7, 22.5, 22.0 ppm. **HRMS (ESI^+):** Calculated for [$C_{14}H_{23}NO_3$+H^+]: 254.1751, found: 254.1789. **FT-IR** (KBr): 3443(m), 2923(m), 2852(w), 1728(s), 1613(s), 1457(m), 1289(m). **HPLC:** Chiralpack IA column. Flow rate 0.7 mL/min. UV detection at 254 nm. τ_{major} = 34.4, τ_{minor} =37.9 using hexane: isopropanol= 95:5 as eluent, ee 86%.

1-Cyclohexenyl-4,4-dimethyl-3-(nitromethyl)pentan-1-one (5ai): Light yellow thick oil (23.5 mg, 37%). **^{1}H NMR (600 MHz , $CDCl_3$)**: δ 6.91 (s, 1 H), 4.50 (dd, *J* = 12.6, 4.8 Hz,1H), 4.29 (dd, *J* = 12.6, 7.2 Hz,1H), 2.77-2.83 (m, 1H), 2.62-2.70 (m, 2H), 2.29-2.21 (m, 2H), 1.62 (m, 4H), 0.94 (s, 9H) ppm.**^{13}C NMR (151 MHz, $CDCl_3$):** δ 199.2, 140.1, 139.4, 88.8, 42.5, 35.9, 27.6, 27.3, 27.1, 26.3, 23.5, 22.1 ppm. **FT-IR** (KBr): 3442(m), 2925(s), 2856(w), 1715(m), 1552(w), 1374(w). **HRMS (ESI^+):** Calculated for [$C_{14}H_{23}NO_3$+H^+]: 254.1751, found: 254.1756. **HPLC:** Chiralpack IA column. Flow rate 0.7 mL/min. UV detection at 254 nm. τ_{major} =24.2, τ_{minor} =38.7 using hexane: isopropanol= 95:5 as eluent, ee 73%.

1-Cyclohexenyl-3-cyclohexyl-4-nitrobutan-1-one (5aj): Light yellow thick oil (26.0 mg, 37%). **^{1}H NMR (600 MHz , $CDCl_3$)**: δ 6.96 (s, 1H), 4.67 (dd, *J* = 14.4, 2.4 Hz, 1H), 4.43 (dd, *J* = 14.4, 9 Hz, 1H), 2.66-2.68 (m, 1H), 2.20-2.27 (m, 4H), 2.00-2.04 (m, 4H), 1.62-1.65 (m, 4H), 0.94-1.23 (m, 11H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 203.8, 142.1, 141.7, 75.5, 41.2, 38.6, 32.1, 29.9, 26.7, 26.5, 25.1, 23.6, 22.9, 22.1, 21.6 ppm. **FT-IR** (KBr): 3437(m), 2925(m), 2853(m), 1716(w), 1551(s), 1449(w), 1376(s). **HRMS (ESI^+):** Calculated for [$C_{16}H_{25}NO_3$+H^+]: 280.1907, found: 280.2012. **HPLC:** Chiralpack IA column. Flow rate 1

mL/min. UV detection at 254 nm. τ_{major} =7.2, τ_{minor} =13.0 using hexane: isopropanol = 96:4 as eluent, ee 72%.

1-Cyclopentenyl-4-nitro-3-phenylbutan-1-one (5ba): White thick oil (48 mg, 74%). **^{1}H NMR (400 MHz , $CDCl_3$):** δ 7.05-7.39 (m, 5H), 6.7 (s, 1H), 4.79 (m, 1H), 4.61 (m, 1H), 4.02-4.12 (m, 1H), 3.03-3.2 (m, 3H), 2.48-2.58 (m, 4H), 1.84-1.95 (m, 4H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 195.6, 145.6, 144.7, 139.4, 129.2, 127.6, 127.2, 79.7, 42.0, 39.6, 34.2, 30.7, 22.8 ppm. **FT-IR** (KBr): 3439(s), 2923(m), 2853(w), 1710(w), 1548(s), 1377(w). **HRMS (ESI$^+$):** Calculated for [$C_{15}H_{17}NO_3$+H^+]: 260.1281, found: 260.1259. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =15.4, τ_{minor} = 19.9 using hexane: isopropanol = 96:4 as eluent, ee 54%.

1-Cyclopentenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one (5bc): Yellow thick oil (38 mg, 53%). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.14 (d, 2H), 6.85 (d, 2H), 6.73 (s, 1H), 4.72 (m, 1H), 4.56 (m, 1H), 4.00-4.05 (m, 1H), 3.77 (s, 3H), 3.03-3.15 (m, 2H), 2.49-2.55 (m, 4H), 1.89-1.92 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 195.6, 159.2, 144.6, 142.9, 128.7, 114.9, 144.6, 80.0, 55.5, 42.2, 39.0, 34.2, 30.8, 22.9 ppm. **FT-IR** (KBr): 3437(m), 2922(s), 2852(w), 1737(s), 1458(m), 1275(m), 1260(m), **HRMS (ESI$^+$):** Calculated for [$C_{16}H_{19}NO_4$+H^+]: 290.1387, found: 290.1368. HPLC: Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} = 20, τ_{minor} = 32 using hexane: isopropanol = 96:4 as eluent, ee 77%.

1-Cyclopentenyl-4-nitro-3-o-tolylbutan-1-one (5bd): White thick oil (48.4 mg, 71% yield). **^{1}H NMR (600 MHz , $CDCl_3$)** δ 7.10-7.25 (m, 4H), 6.75 (s, 1H), 4.72 (dd, *J* = 12.6, 7.2 Hz,1H), 4.61 (dd, *J* = 12.6, 7.8 Hz, 1H), 4.39-4.42 (m, 1H), 3.9(m, 1H), 3.15-3.22 (m, 1H), 2.5-2.62 (m, 4H), 1.9-2.0 (m, 3H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** δ=195.6, 145.6, 144.6, 137.7, 136.7, 131.4, 127.6, 126.1, 125.6, 79.3, 42.0, 34.2, 29.9, 22.9, 19.8 ppm. **FT-IR** (KBr): 3443(s), 2923(s), 2853(w), 1662(w), 1551(s), 1376(w), **HRMS (ESI$^+$):** calculated for [$C_{16}H_{19}NO_3$+H^+]: 274.1438, found: 274.1411. **HPLC:** Chiralpak AS-H column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} = 17.3, τ_{minor} = 26.3 using hexane: isopropanol= 96:4 as eluent, ee 70%.

1-Cyclopentenyl-5-methyl-3-(nitromethyl)hexan-1-one (5bh): Light yellow thick oil (21 mg, 35%). **^{1}H NMR (600 MHz , $CDCl_3$)**: δ 6.70 (s, 1 H), 4.85 (m, 1H), 4.50 (m, 1H), 2.79-

2.84 (m, 1H), 2.69-2.66 (m, 2H), 2.59-2.61 (m, 2H), 2.54-2.57 (m, 2H), 2.26-2.31 (m, 1H), 1.94-1.98 (m, 2H), 1.20 (t, *J* = 6.6 Hz, 2H), 0.91 (d, *J* = 6.6 Hz, 6H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 192.7, 155.5, 145.5, 142.4, 78.6, 43.9, 40.8, 34.5, 30.7, 25.4, 25.3, 23.3, 23.1, 22.9 ppm. **FT-IR** (KBr): 3448(m), 2924(m), 2854(w), 1660(s), 1551(s), 1377(w). **HRMS (ESI$^+$):** calculated for [$C_{13}H_{21}NO_3$+H^+]: 240.1594, found: 240.1623. **HPLC:** Chiralpack IA column. Flow rate 0.7 mL/min. UV detection at 254 nm. τ_{major} = 19.6, τ_{minor} = 27.5 using hexane: isopropanol = 95:5 as eluent, ee 70%.

1-cyclobutenyl-4-nitro-3-phenylbutan-1-one (5ca): Yellow thick oil (36 mg, 59%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32 -7.27 (m, 5H), 7.17 (s, 1H), 4.91 (dd, *J* = 8, 4.8, 1H), 4.76 (dd, *J* = 8.0, 2.0, 1H), 3.40 – 3.35 (m, 1H), 3.30-3.25 (m, 1H), 2.40 (br d, *J* = 17.2, 1H), 1.43 – 1.35 (m, 4H), **^{13}C NMR (151 MHz, $CDCl_3$)** δ 201.5, 129.6, 129.5, 129.2, 129.0, 127.9, 127.3, 80.6, 43.1, 32.1, 31.9, 29.6, 22.9, 19.5. **FT-IR** (KBr): 2925(s), 2854(w), 1729(s), 1557(s), 1456(m), 1378(m). **HRMS (ESI$^+$):** calculated for [$C_{14}H_{15}NO_3$+H^+]: 246.1125, found: 246.1147. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} =30.7, τ_{minor} = 35.3 using hexane: isopropanol= 99:1 as eluent, ee 58%.

4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (6a + 6b = 4:1): Colorless crystalline solid (22 mg, 84% overall yield). Melting point 166-167 ^{o}C. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.18-7.37 (m, 5H), 5.33 (dd, J = 10.8, 3.6, 0.25 H, C<u>H</u>NO_2), 4.84 (apparent t, *J* = 10.8, 1H), 3.84 (dt, *J* = 12.4, 5.6, 0.25 H, C<u>H</u>Ph), 3.60 (dt, *J* = 12.4, 5.6, 1H), 2.84-2.87 (m, 0.5 H, H10), 2.65-2.75 (m, 2H), 2.49-2.54 (m, 0.25 H, H9), 2.07-2.25 (m, 3H), 1.71-1.93 (m, 3H), 1.18-1.41 (m, 5H) ppm. **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 206.5, 137.9, 129.4, 128.5, 127.1, 95.0, 51.3, 48.1, 46.3, 45.9, 30.3, 25.1, 24.9, 24.7 ppm. **^{1}H NMR (400 MHz, C_6D_6):** δ 6.89-7.07 (m, 7H), 4.8 (dd, *J* = 10.8, 3.6, 0.25 H, C<u>H</u>NO_2), 4.30 (apparent t, *J* = 10.8, 1H), 3.52(dt, *J* = 12.4, 5.6, 0.25 H, C<u>H</u>Ph), 3.20 (dt, *J* = 12.4, 5.6, 1H),2.33 (two psudo AB quartet, 14.8, 2H), 2.21,1.84 (two psudo AB quartet, 13.6, 0.5 H), 1.95-1.98 (d, *J* = 12.4, 1H), 1.73 (q, *J* =10.8, 1H) ppm. **FT-IR** (KBr): 2933(s), 2854(m), 1721(s), 1547(s), 1456(w), 1445(w), 1364(w). **HRMS (ESI$^+$):** Calculated for [$C_{16}H_{19}NO_3$+H^+]: 274.1438, found: 274.1434. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 254 nm. τ_{major} = 18.6, τ_{minor} = 23.1 using hexane: isopropanol= 96:4 as eluent, ee 75%. Recrystallized using chloroform hexane as solvent in 73% yield (from **3aa**). After recrystallization ee was 94 %.

3-(4-fluorophenyl)-4-nitrooctahydronaphthalen-1(2H)-one (6c): Colourless crystalline solid (22 mg, 81% overall yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.25-7.22 (m, 0.5H), 7.20-7.17 (m, 2H), 7.04 – 7.01 (t, *J* = 9, 2H), 5.27 (dd, *J* = 12.4, 4.2, 0.3H), 4.78 (t, *J* = 10.6, 1H), 3.86 – 3.81 (m, 0.3H), 3.61 – 3.56 (m, 1H),2.70 - 2.64 (m, 2H), 2.48 (apparent t, *J* = 14.4, 0.3H), 2.34 (br d, *J* = 12.6, 0.3H), 2.22 (dt, *J* = 10.8, 3.6, 1H), 2.16-2.08 (m, 2H), 1.89 – 1.86 (m, 1H), 1.83 – 1.80 (m, 1H), 1.73 (br d, *J* = 6.6, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 206.2, 133.7, 128.8, 128.8, 116.5, 116.3, 95.1, 51.3, 47.3, 46.3, 45.9, 30.28, 25.1, 24.9, 24.7 ppm. **FT-IR** (KBr): 2927(s), 2852(w), 1719(s), 1561(s). **HRMS (ESI$^+$):** calculated for [$C_{16}H_{18}FNO_3$+H^+]: 292.1343, found: 292.1347. **HPLC:** Chiralpak IA column. Flow rate 0.8 mL/min. UV detection at 214 nm. τ_{major} =30.7, τ_{minor} = 35.3 using hexane: isopropanol= 95:5 as eluent, ee 54%.

1'-nitro-2',3',4'a,5',6',7',8',8'a-octahydro-1,2'-binaphthyl-4'(1'H)-one (6e): White crystalline solid (23 mg, 75% overall yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.4, 0.25 H), 8.05(d, *J* = 8.4, 1H), 7.86 (t, *J* = 8.4, 1H), 7.78 (d, *J* = 8.4, 1H), 7.58 - 7.52 (m, 2H), 7.52 - 7.48(m, 2H), 7.45 (d, *J* = 2.4, 0.24H), 7.43(s, 0.25H), 5.67 (dd, *J* = 12, 4.8, 0.25H), 5.21 (t, *J* = 10.2, 1H), 4.81 (dt, *J* = 12.4, 4.8, 0.25H), 4.63 (dt, *J* = 13.8, 4.8, 1H), 2.87 (d, *J* = 5.4, 0.24H), 2.83 (dd, *J* = 15.0, 4.8, 1H), 2.66 (t, *J* = 13.8, 1H), 2.46 (t, *J* = 14.4, 0.25H), 2.32 -2.25 (m, 2H), 2.15 (br d, *J* = 13.2, 1H), 1.93 - 1.89 (m, 1H), 1.86 – 1.83 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 206.5, 134.4, 130.0, 129.3, 128.8, 128.5, 127.1, 126.3, 125.6, 123.0, 122.9 ppm. **FT-IR** (KBr): 2926 (s), 2856 (w), 1708 (s), 1552(s). **HRMS (ESI$^+$):** calculated for [$C_{20}H_{21}NO_3$+H^+]: 324.1594, found: 324.1589. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{minor} = 22.7, τ_{major} = 31.0 using hexane: isopropanol= 96:4 as eluent, ee 56%.

3-(furan-2-yl)-4-nitrooctahydronaphthalen-1(2H)-one (6g): Colourless crystalline solid (18 mg, 73% overall yield). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36(d, *J* = 1.8, 1H), 7.32(d, *J* = 1.8, 0.16H), 6.28(d, *J* = 1.8, 1H), 6.16(d, *J* = 3, 0.16H), 6.12(d, *J* = 3.0, 1H), 5.28 (dd, *J* = 12, 4.2, 0.16H), 4.83 (t, *J* = 10.8, 1H), 4.01 (dt, *J* = 12, 7.2, 0.16H), 3.73 - 3.79 (m, 1H), 2.85 (dt, *J* = 16.8, 1.2, 1H), 2.74 - 2.68 (m, 1.5H), 2.21 - 2.16 (m, 1H), 2.12 - 2.05 (m, 2H), 1.87 - 1.84 (m, 1H), 1.81 - 1.78 (m, 1H), 1.73 (br d, 1H), 1.36 - 1.27 (m, 2H), 1.23 - 1.19 (m, 2H). **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 206.1, 150.8, 143.0, 110.7, 107.7, 93.3, 51.0, 45.3, 43.3, 41.3, 30.3, 25.0, 24.8, 24.7 ppm. **FT-IR** (KBr): 2922(s), 2855(w), 1722(s), 1551(s). **HRMS (ESI^+):** calculated for [$C_{14}H_{16}NO_4+H^+$]: 263.1158, found: 263.1154. **HPLC:** Chiralpak IA column. Flow rate 0.8 mL/min. UV detection at 214 nm. τ_{minor} = 24.8, τ_{major} = 33.4 using hexane: isopropanol = 95:5 as eluent, ee 70% after crystallisation.

7-Nitro-6-phenylhexahydro-1H-inden-4(2H)-one (7): Colorless solid (21 mg, 87%). **^{1}H NMR ^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.18-7.37 (m, 5H, Ph), 5.00 (t, *J* = 3.6, 1H, C<u>H</u>NO_2), 3.66-3.71 (td, *J* = 12.8, 4.8, 1H, C<u>H</u>Ph), 3.41 (dd, *J* = 2.4, 12.6, 1H), 3.22-3.24 (m, 1H, H9), 2.93 (m, 1H, H8), 2.65 (dd, *J* = 10.6, 4.8, 1H), 2.36-2.39 (m, 1H),1.99-2.02 (m, 1H), 1.75-1.82 (m, 2H), 1.39-1.46 (m, 1H) ppm. **^{13}C NMR (151 MHz, $CDCl_3$):** 206.8, 129.3, 128.5, 127.3, 100.2, 89.4, 49.8, 45.0, 42.7, 40.6, 30.2, 29.9, 25.9, 22.6 ppm. **FT-IR** (KBr): 2923 (s), 2852 (m), 1712 (m), 1629 (m), 1548 (m), 1454 (w), 1384 (w), 1265 (w), 1019 (m). **HRMS (ESI^+):** calculated for [$C_{15}H_{17}NO_3+H^+$]: 260.1281, found: 260.1259. **HPLC:** Chiralpak IA column. Flow rate 1 mL/min. UV detection at 214 nm. τ_{major} = 13.7, τ_{minor} = 18.1 using hexane: isopropanol= 96:5 as eluent, ee 56%.

4-Chloro-N-(4-cyclohexyl-4-hydroxy-2 phenylbutyl)benzenesulfonamide (8): White crystalline solid. 50% overall yield (13 mg, 0.07125 mmol). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.83 (d, *J* = 7.8, 2H), 7.52 (d, *J* = 7.8, 2H), 7.28 (t, *J* = 7.8, 2H), 7.23 (d, *J* = 3.2, 1H), 7.06 (m, *J* = 7.2, 2H), 3.89 (dd, *J* = 12, 6.6, 2H), 3.76 (dd, *J* = 14.4, 7.2, 1H), 3.16(t, *J* = 12, 1H), 2.57 – 2.50 (m, 1H), 2.17 (dd, *J* = 7.8, 3.6 1H), 1.82 (dd, *J* = 11.4, 3.6, 1H), 1.64 - 1.60 (m, 1H), 1.16 – 1.14 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.6, 139.4, 137.8, 129.7, 129.0, 128.9, 127.3, 127.2, 65.6, 55.7, 43.6, 42.6, 35.1, 31.8, 30.3, 26.8, 26.6, 26.4, 26.2 ppm. **FT-IR** (KBr): 2925(s), 2853(w), 1350(s), 1164(s), 1092(s), 1013(s). **HRMS (ESI^+):** calculated for [$C_{22}H_{28}ClNO_3S+H^+$]: 422.1551, found: 422.1579. **HPLC:** Chiralpak OJ column. Flow rate 1 mL/min. UV detection at 254 nm. τ(major) = 18.3, τ(minor) = 27.6 using hexane: isopropanol= 97:3 as eluent, ee 69%.

2.11: Crystal data and structure refinement for chiral compound 6a:

Empirical formula	$C_{16}H_{19}O_3N_1$
Formula weight	273.32

Temperature/K	296K
Space group	P21/c
a/Å	13.9327(12)
b/Å	5.8545(5)
c/Å	18.9127(15)
α/°	90.00
β/°	109.456(5)
γ/°	90.00
Volume/Å^3	1454.6(2)
Z	4
ρ_{calc} mg/mm^3	1.248
m/mm^{-1}	0.086
F(000)	584
Index ranges	$-16 \leq h \leq 16$, $-6 \leq k \leq 6$, $-22 \leq l \leq 22$
Reflections collected	2549
Independent reflections	1946
Data/restraints/parameters	2549/ 0/ 181
Goodness-of-fit on F^2	1.235
Final R indexes [I>=2σ (I)]	$R_1 = 0.0901$, $wR_2 = 0.1455$
Final R indexes [all data]	$R_1 = 0.1735$, $wR_2 = 0.1667$

References:

1. a) G. Stork, R. Terrell, J. Szmuszkovicz, *J. Am. Chem. Soc.* **1954**, *76*, 2029; b) G. Stork, H. K. Landesman, *J. Am. Chem. Soc.* **1956**, *78*, 5128; c) G. Stork, H. K. Landesman, *J. Am. Chem. Soc.* **1956**, *78*, 5129; c) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207.
2. a) J. Barluenga, A. Ballesteros, J. Santamarı´a, R. Bernardo de la Ru´a, E. Rubio, M. Toma´s, *J. Am. Chem. Soc.* **2003**, *125*, 1834; b) G. Bouhalleb, O. Mhasni, G. Poli, F. Rezgui, *Tetrahedron Lett.* **2017**, *58*, 2525; c) M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 214; d) O. Ito, M. Sawamura, K. Kominami, T. Saegusa, *Tetrahedron Lett.* **1985**, *26*, 5303.
3. S.-I. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett*. **1969**, *10*, 4233.

4. a) S. J. Blarer, D. Seebach, *Chem. Ber.* **1983**, *116*, 2250; b) S. J. Blarer, D. Seebach, *Chem. Ber*. **1983**, *116*, 3086; c) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta*. **1982**, *65*, 1637.
5. For reviews see: a) A. G. M. Barrett, *Chem. Soc. Rev.* **1991**, *20*, 95 b) O.M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; b) S. Sulzer-Mosse, A. Alexakis, *Chem. Commun.* **2007**, *43*, 3123; c) R. Somanathan, D. Chavez, F. A. Servin, J. A. Romero, A. Navarrete, M. Parra-Hake, G. Aguirre, D. P. C. Anaya, J. González, *Curr. Org. Chem.* **2012**, *16*, 2440.
6. a) H. W. Pinnick, *Org. React.* **1990**, *38*, 655; b) J. U. Nef, *Justus Liebigs Ann. Chem.* **1894**, *280*, 263.
7. R. Tamura, A. Kamimura, N. Ono, *Synthesis* **1991**, 423.
8. R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1989**, pp. 411; b) A. K. Beck, D. Seebach, *Chem. Ber*. **1991**, *124*, 2897; c) R. E. Maeri, J. Heinzer, D. Seebach, *Liebigs Ann.* **1995**, 1193; d) M. A. Poupart, G. Fazal, S. Goulet, L. T. Mar, *J. Org. Chem.* **1999**, *64*, 1356; e) A. G. M. Barrett, C. D. Spilling, *Tetrahedron Lett.* **1988**, *29*, 5733; f) D. H. Loyd, D. E. Nichols, *J. Org. Chem.* **1986**, *51*, 4294.
9. a) V. Meyer, C. Wurster, *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 1168; b) M. J. Kamlet, L. A. Kaplan, J. C. Dacons, *J. Org. Chem.* **1961**, *26*, 4371.
10. T. Mukayama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339.
11. For a review see: a) D. Enders, J. Adam, D. Klein, *Synlett* **2000**, 1371; for representative works: b) D. Enders, O. M. Berner, N. Vignola, J. W. Bats, *Chem. Commun.* **2001**, 2498; c) R. Ferna´ndez, C. Gasch, J.-M. Lassaletta, J.-M. Llera, *Tetrahedron Lett.* **1994**, *35*, 471; d) D. Enders, R. Syrig, G. Raabe, R. Ferna´ndez, C. Gasch, J.-M. Lassaletta, J.-M. Llera, *Synthesis* **1996**, 48; e) R. Ferna´ndez, C. Gasch, J.-M. Lassaletta, J.-M. Llera, *Synthesis* **1996**, 627; f) H. Uno, K.-I. Kasahara, N. Ono, *Heterocycles* **2000**, *53*, 1011; g) J. d'Angelo, C. Cave´, D. Desmae¨le, A. Gassama, C. Thominiaux, C. Riche, *Heterocycles* **1998**, *47*, 725; h) C. Thominiaux, S. Rousse´, D. Desmae¨le, J. d'Angelo, C. Richie, *Tetrahedron: Asymmetry* **1999**, *10*, 2015; i) U. Schöllkopf, W. Kühnle, E. Egert, M. Dyrbusch, *Angew. Chem.* **1987**, *99*, 480; j) K. Busch, U. M. Groth, W. Kühnle, U. Schöllkopf, *Tetrahedron* **1992**, *48*, 5607; k) M. Brenner, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2365; l) R. B. Silverman, R.

Andruszkiewicz, S. M. Nanavati, C. P. Taylor, M. G. Vartanian, *J. Med. Chem.* **1991**, *34*, 2298; m) G. Calderari, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 1592; n) D. Enders, H. Kipphardt, *Nach. Chem. Tech. Lab.* **1985**, *33*, 882; o) D. Enders, M. Klatt, *Synthesis* **1996**, 1403.

12. B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395.
13. B. List, P. Pojarliev, H. J. Martin, *Org. Lett*. **2001**, *3*, 2423.
14. D. Enders, A. Seki, *Synlett* **2002**, 26.
15. Review: a) B. List, *Chem. Commun.* **2006**, 819; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev*. **2007**, *107*, 5471.
16. S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599.
17. a) V. Rai, S. M. Mobin, I. N. N. Namboothiri, *Tetrahedron: Asymmetry* **2007**, *18*, 2719; b) H. Li, Y. Wang, G. L. Tan, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906; c) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem., Int. Ed*. **2005**, *44*, 105. d) F. Fringuelli, L. Castrica, F. Pizzo, L. Vaccaro, *Lett. Org. Chem.* **2008**, *5*, 602; e) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc*. **2006**, *128*, 3928.
18. For examples: a) D. A. Yalalov, S. B. Tsogoeva; S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826; b) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; c) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; d) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett*. **2007**, *9*, 923; e) M. Durmaz, A. Sirit, *Supramolecular Chemistry* **2013**, *25*, 292. For review see: O. V. Serdyuk, C. M. Heckel, S. B. Tsogoeva, *Org. Biomol. Chem.* **2013**, *11*, 7051.
19. F. Capitta, A. Frongia, J. Ollivier, D.J. Aitken, F. Secci, P.P. Piras, R. Guillot, *Synlett* **2015**, *26*, 123.
20. For the first report see: T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; For more examples: b) P. Vinayagam, M. Vishwanath, V. Kesavan, *Tetrahedron Asymmetry* **2014**, *25*, 568; c) H. Jin, S. T. Kim, G.-S. Hwang, D. H. Ryu, *J. Org. Chem*. **2016**, *81*, 3263; d) H. Jin, S. M. Cho, G.-S. Hwang, D. H. Ryu, *Adv. Synth. Catal*. **2017**, *359*, 163; e) B.-D. Cui, W.-Y. Han, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem*. **2013**, *78*, 8833.

21. a) P. Chauhan, S. Mahajan, D. Enders, *Chem. Commun*. **2015**, *51*, 12890; b) G. Rassu, V. Zambrano, L. Pinna, C. Curti, L. Battistini, A. Sartori, G. Pelosi, G. Casiraghi, F. Zanardi, *Adv. Synth. Catal.* **2014**, *356*, 2330.
22. M. T. Corbett, Q. Xu, J. S. Johnson, *Org. Lett*. **2014**, *16*, 2362.
23. a) H. Y. Bae, C. E. Song, *ACS Catal*. **2015**, *5*, 3613; b) H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Chem. Eur. J.* **2014**, *20*, 8458; c) G. Urbanietz, I. Atodiresei, D. Enders, *Synthesis* **2014**, *46*, 1261; d) E. Kanberoglu, C. Tanyeli, *Asian J. Org. Chem*. **2016**, *5*, 114; e) B.-D. Cui, Y. You, J.-Q. Zhao, J. Zuo, Z.-J. Wu, X.-Y. Xu, X.-M. Zhang, W.-C. Yuan, *Chem. Commun.* **2015**, *51*, 757.
24. Y. Xu, P. Sun, Q. Song, X. Lai, W. Liu, T. Xia, Y. Huang, Y. Shen, *Eur. J. Org. Chem.* **2017**, 2998.
25. Y. Chen, X. Liu, W. Luo, L. Lin, X. Feng, *Synlett.* **2017**, *28*, 966.
26. There is only one example of secondary-amine-catalyzed reaction of α-branched ketones. See: T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett*. **2006**, *8*, 1533.
27. N. Fu, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2013**, *19*, 15669.
28. N. Fu, L. Zhang, S. Luo, *Org. Lett.* **2015**, *17*, 382.
29. X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc*. **2011**, *133*, 17934.
30. M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa, E. N. Jacobsen *J. Am. Chem. Soc.* **2013**, *135*, 1891.
31. For a timely review, see: D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem.* **2012**, 865.
32. For selected examples, see: a) X. Wu, M.-L. Li, D.-F. Chen, S.-S. Chen. *J. Org. Chem.* **2014**,*79*, 4743; b) E. Masalo, M. Benaglia, R. Annunziata, A. Palmieri, G. Celentano, A. Forni, *Adv. Synth. Catal*. **2014**, *356*, 495; c) Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang, L. He. *Org. Lett.* **2013**, *15*, 6090; d) G. Bencinenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2009**, *121*, 7336; e) D.-Q. Xu, A.-B. Xia, S.-P. Luo, J. Tang, S. Zhang, J.-R. Jiang, Z.-Y. Xu, *Angew. Chem., Int. Ed.* **2009**, *48*, 3821; f) H. Yang, R. G. Carter, *J. Org. Chem*. **2009**, *74*, 5151; g) T. Itoh, M.

Yokoya, K. Miyauchi, K. Nagata, A. Ohsawa, *Org. Lett*. **2006**, *8*, 1533; h) H. Sundén, I. Ibrahem, L. Eriksson, A. Córdova, *Angew. Chem. Int. Ed.* **2005**, *44*, 4877; i) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc*. **2004**, *126*, 5962; j) D. B. Ramachary, N. S. Chowdhari, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2003**, *42*, 4233.

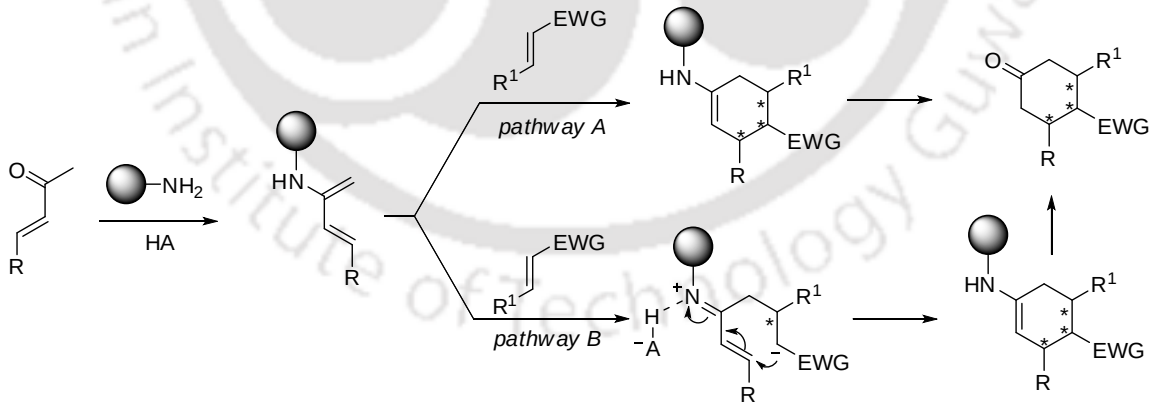
33. a) C. Lin, H. Fang, Z. Tu, J.-T. Liu, C.-F. Yao, *J. Org. Chem.* **2006**, *71*, 6588; b) F. Richter, H.-H. Otto, *Tetrahedron Lett*. **1987**, *28*, 2945; c) C. Veyrat, L. Wartski, J. Seyden-Penne, *Tetrahedron Lett*. **1986**, *27*, 2981; d) G. Pitaco, A. Risaliti, M. L. Trevisan, E. Valentin, *Tetrahedron* **1977**, *33*, 3145.
34. M. Moger, A. K. Pradhan, R. M. Hindupur, H. N. Pati, *Tetrahedron Lett*. **2014**, *55*, 2675.
35. For a different method producing related structures, see: a) P. He, X. Liu, J. Shi, L. Lin, X. Feng, *Org. Lett*. **2011**, *13*, 936; For a recent report on ε-selective asymmetric bisvinylogous Michael addition with 2,5-cyclic dienones, see: b) Z. Zhou, X. Feng, X. Yin, Y.-C. Chen, *Org. Lett*. **2014**, *16*, 2370; For a recent report on δ-regioselective Michael addition with cyclohexenylidene malonitriles, see: c) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc*. **2014**, *136*, 11107.
36. a) Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett*. **2004**, *45*, 9185; b) P. Chauhan, G. Urbanietz, G. Raabe, D. Enders, *Chem. Commun*. **2014**, *50*, 6853; c) P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe, D. Enders *Org. Lett*. **2014**, *16*, 2954; d) P. Sun, C.-Y. Meng, F. Zhou, X.-S. Li, J.-W. Xie, *Tetrahedron* **2014**, *70*, 9330; e) P. Chauhan, S. Mahajan, G. Raabe, D. Enders, *Chem. Commun.* **2015**, *51*, 2270; f) B. Han, W. Huang, W. Ren, G. He, J.-H. Wang, C. Peng, *Adv. Synth. Catal*. **2015**, *357*, 561 and reference 35a.
37. CCDC 1033099 contains the crystallographic data for **6a**. The data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif
38. A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc*. **2010**, *132*, 9286.
39. T. He, J.-Y. Qian, H.-L. Song, X.-Y. Wu, *Synlett* **2009**, 3195.

40. W. Yang, D.-M. Du, *Adv. Synth. Catal*. **2011**, *353*, 1241.
41. B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967.
42. W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2007**, *46*, 7667.
43. a) D. M. Mampreian, A. H. Hoveyda, *Org. Lett.* **2004**, *6*, 2829; b) O. Bassas, J. Huuskonen, K. Rissanen, A. M. P Koskinen, *Eur. J. Org. Chem.* **2009**, 1340; c) B. M. Trost, C. Mueller, *J. Am. Chem. Soc.* **2008**, *130*, 2438.
44. P. Melchiorre, *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.

Chapter 3: Organocatalytic Asymmetric [4 + 2] Cycloaddition of 1-Acetylcyclopentene and 1-Acetyl cyclohexene

3.1. Introduction:

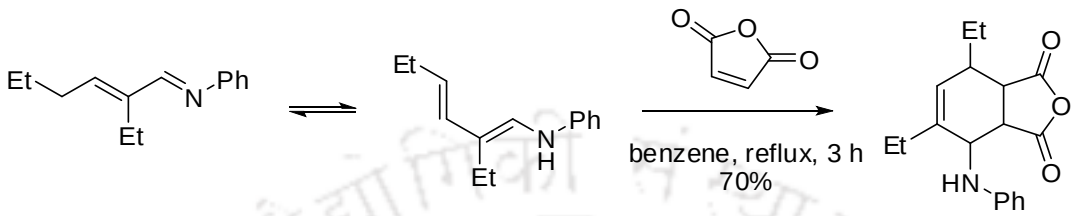
Organocatalytic asymmetric Diels-Alder reactions promoted by both iminium and enamine catalysis have been known extensively in literature.[1] In the organocatalytic DA reaction via enamine activation, generally two reacting partners are *α,β*-unsaturated ketones and electron deficient olefins, first step of which is generation of diene via dienamine formation from the *α,β*-unsaturated ketone. There are two possible route for the formation of Diels-Alder adduct. A) concerted addition of the diene and the dienophile followed by hydrolysis (pathway A) or B) The enamine first attack to the dienophile via a Michael reaction followed by again an intramolecular Michael attack of the formed anion to the iminium ion (pathway B). Both pathways have been accepted depending on the nature of the reaction (Scheme 3.1.1).



Scheme 3.1.1: Concerted and stepwise pathways to get DA adduct

Dienamines were first introduced in organic chemistry by Mannich in 1936.[2] Dienamines can be easily generated from *α,β*-unsaturated aldehydes or ketones having *γ*-CH. The synthetic utility of dienamines are illustrious due to the possibility of three types of reactivity modes i.e.

diene reactivity, vinylogous reactivity and enamine reactivity. These can act also as dienophiles in Diels-Alder reactions by increasing the energy of the olefin HOMO (inverse electron demand Diels-Alder reactions). Snyder *et al.* first used these preformed dienamines as diene source in the Diels-Alder reaction with maleic anhydride (scheme 3.1.2).[3a]



Scheme 3.1.2: First example of dienamines acting as dienes in Diels-Alder reactions

Earlier, various research groups like Snyder,[3] Terada,[4] Oppolzer,[5] Overman,[6] Barluenga[7] and others[8] have been utilized preformed dienamines in developing reaction methodologies as well as in the total synthesis. But the dienamine chemistry has found its pace after the application of in situ generated dienamines in reactions pioneered by Serebryakov[9] and Barbas[10] group. Dienamine chemistry has been utilized to synthesize a number of natural products and drug molecules, a few of them are illustrated in Figure 1.

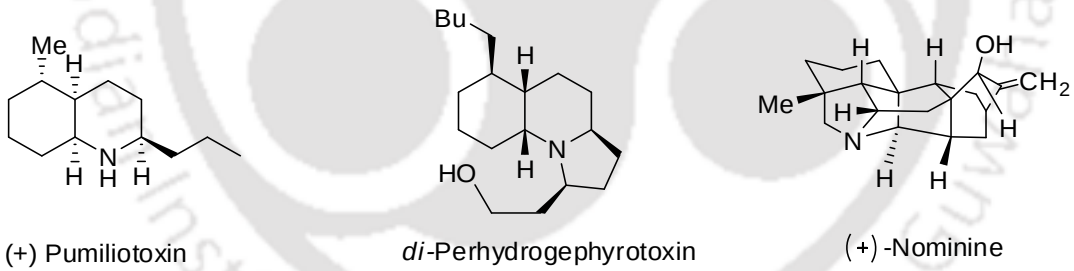


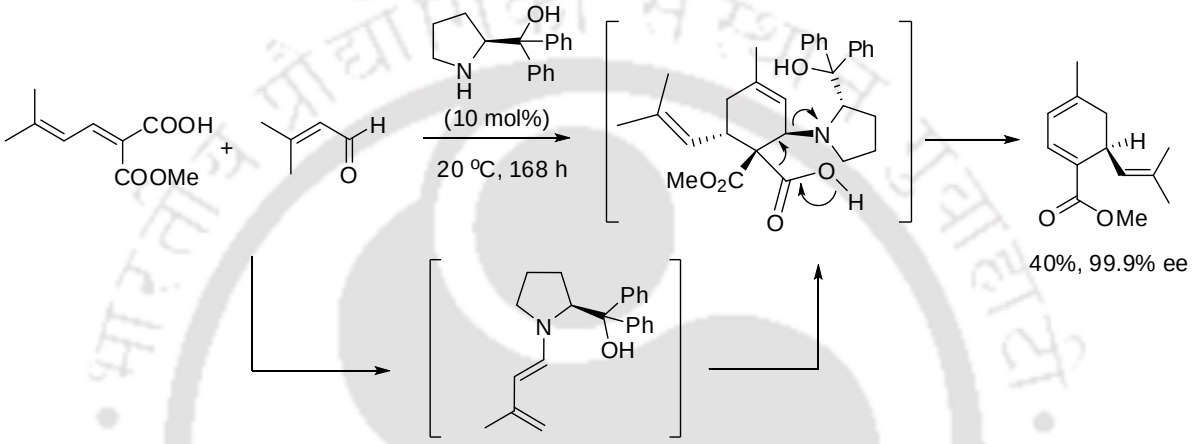
Figure 1: Natural products by dienamine mediated Diels-Alder reaction

3.2. In situ generated dienamines:

Over the years dienamine chemistry has been utilized in Diels-Alder reactions,[11] inverse electron demand Diels-Alder reactions,[12] [2+2] cycloaddition reactions,[13] vinylogous nucleophilic additions[14] etc. In situ generated dienamines acted as the diene component and consequently was reacted with various dienophiles like nitroolefins and other electron deficient olefins, nitrosobenzene, imines, azodicarboxylates etc.

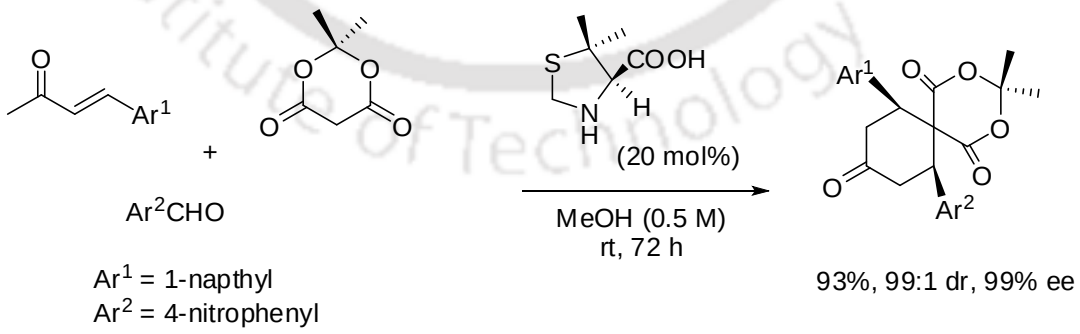
3.2.1. Using proline derived catalysts:

Different proline derived catalysts have been extensively used in Diels Alder reactions utilizing dienamine chemistry by Serebryakov, Barbas, Ramachary and others.[11] In 1998 Serebryakov and co-workers reported the diaryl prolinol catalyzed asymmetric synthesis of the methyl cyclohexa-1,3-dienecarboxylate with high selectivity through a 1-aminobuta- 1,3-diene as the key Diels-Alder reaction intermediate (Scheme 3.2.1.1).[9]



Scheme 3.2.1.1: Diaryl prolinol catalyzed DA reaction of dienamines

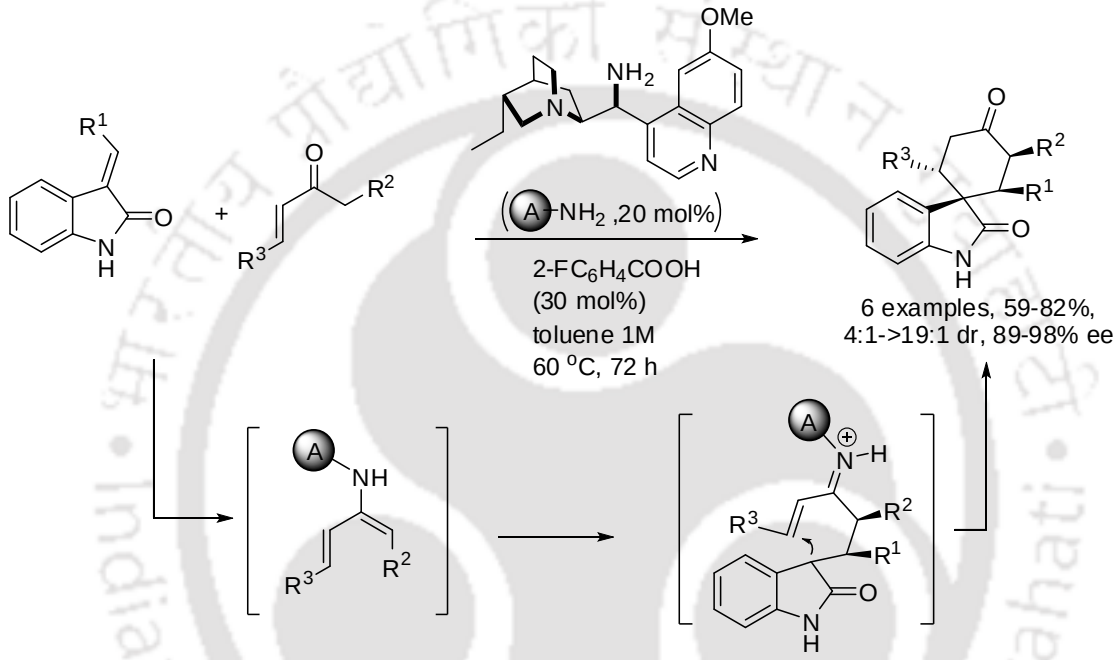
In this context, Barbas and Ramachary have developed an asymmetric three-component Diels–Alder (ATCDA) reaction of aromatic enone, 4-nitrobenzaldehyde and Meldrum's acid, furnishing spirocycles with excellent asymmetric induction using 5,5-dimethylthiazolidinium-4-carboxylic acid as the catalyst (Scheme 3.2.1.2).[10c]



Scheme 3.2.1.2: Dienamine mediated three-component Diels–Alder reaction

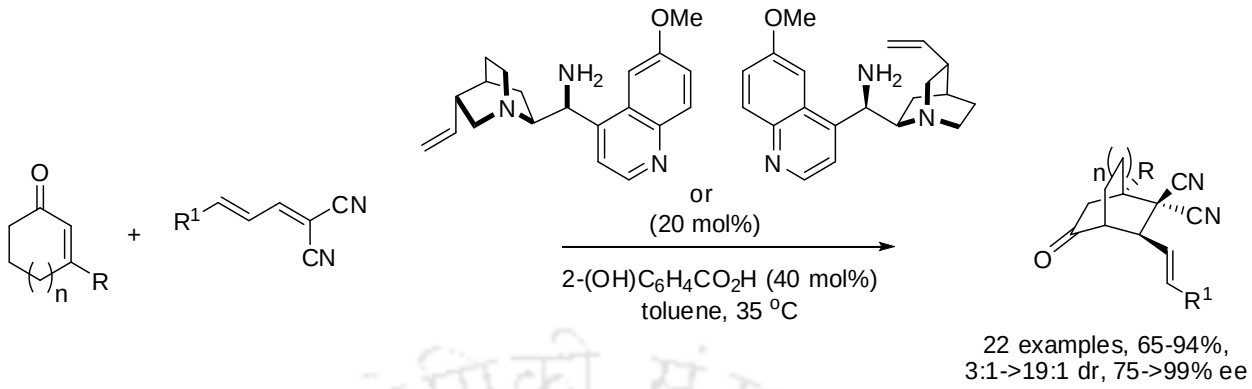
3.2.2. Using cinchona alkaloids:

The large portion of the dienamine chemistry has been driven by primary amine catalysts derived from cinchona alkaloids. In 2009, Melchiorre *et al*. for the first time established the potency of these catalysts in dienamine chemistry in their pioneering works (section 2.5).[15a] Using the same catalytic system a facile synthesis of enantio-enriched spirooxindoles has also been documented by the same group utilizing dienamine strategy (Scheme 3.2.2.1).[15b]



Scheme 3.2.2.1: cinchona derived primary amine catalyzed Diels–Alder reaction

Similarly, Chen and co-workers also developed new methodologies involving dienamine catalysis using cinchona alkaloid derived catalysts.[16] A highly enantioselective and diastereoselective [4 + 2] cycloaddition reaction of cyclic *α,β*-unsaturated ketones with allylidene or alkynylidene malononitriles, affording densely substituted bicyclo[2.2.2]octanes or analogous architectures has been reported by them using quinidine or quinine derived primary amine catalysts (Scheme 3.2.2.2).



Scheme 3.2.2.2: Dienamine mediated Diels–Alder reaction using quinine primary amine

3.3. Synthesis of fused carbocycles: Different approaaches:

Fused organic moieties such as 1-decalone, 1-decalin and octahydro-1*H*-indene are present in a wide range of bioactive compounds[17] such as Rapiculine,[17a] Brasilanes,[17b] Conocephalenols[17c] etc (Figure 2).

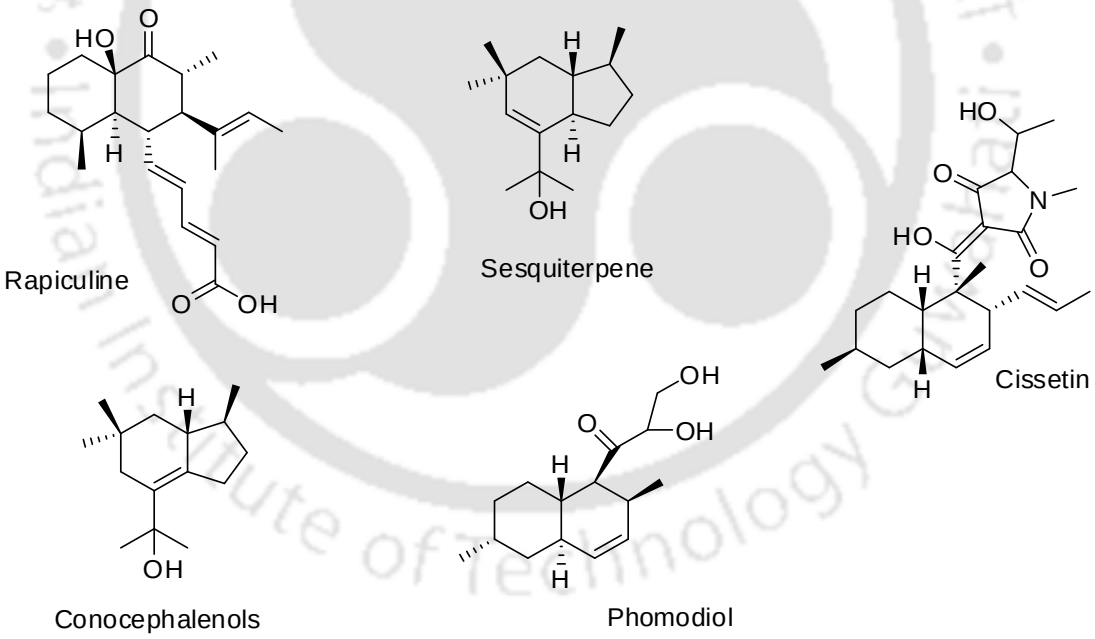


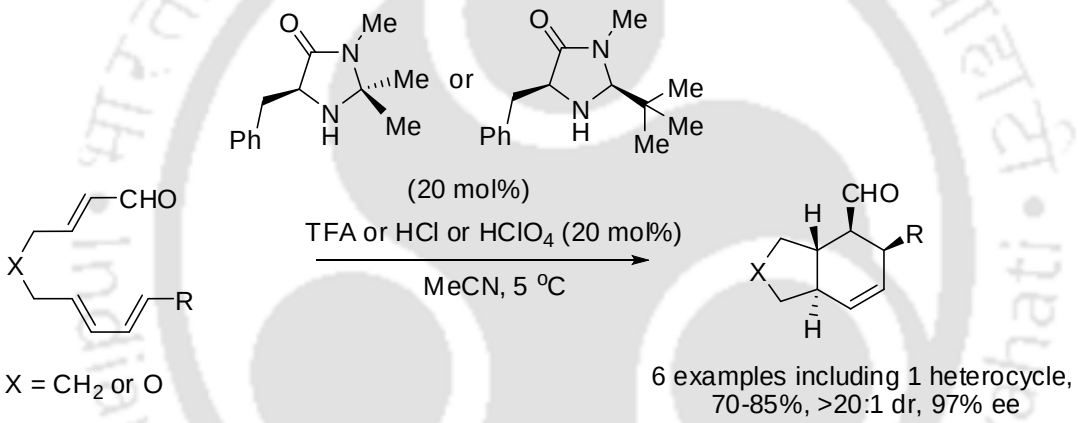
Figure 2: Bioactive compounds having fused bicyclic core

The available organocatalytic synthesis of chiral five and six membered fused carbocycles have been driven by mainly intramolecular approaches such as Hajos-Parrish-Eder-Sauer-Wiechert reaction (and other intramolecular aldol reactions),[18] intramolecular Michael

reaction,[19] intramolecular Diels-Alder reaction,[20] etc. and various domino reaction pathways.[21] Organo-SOMO catalytic bicyclization, developed by MacMillan has also been utilized to synthesize these compounds.[22] Nevertheless, intramolecular Diels-Alder and cascade reactions have been used substantially for the synthesis of fused ring systems that closely resembles our product structure.

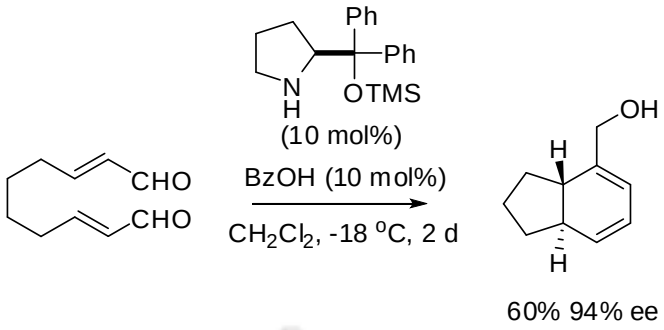
3.3.1 Synthesis of fused carbocycles by Intramolecular Diels-Alder reaction:

In 2005, MacMillan and co-workers developed an iminium catalytic intramolecular Diels-Alder reaction (IMDA) for the synthesis of fused carbocycles and heterocycles. Excellent enantio- and diastereo-selectivity has been obtained for the reaction using two imidazolidinone catalysts invented in the same laboratory (Scheme 3.3.1.1). [20a]



Scheme 3.3.1.1: Fused carbocycles using IMDA reaction

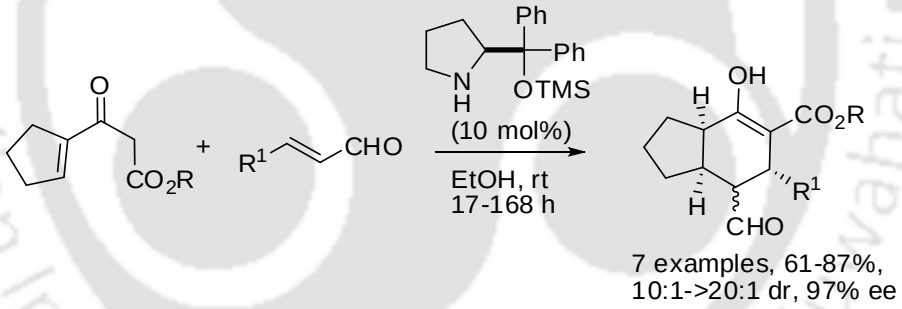
Later in 2008, Christmann *et al.* demonstrated dienamine catalytic intramolecular cyclization of tethered *α,β*-unsaturated aldehydes for the synthesis of fused structures. The intramolecular Diels-Alder reaction of the in situ generated dienamine has been shown to progress well using Jørgensen-Hyashi catalyst furnishing the fused cabocyclic motifs with moderate yield and good enantioselectivity (Scheme 3.3.1.2).[20b]



Scheme 3.3.1.2: Fused carbocycles using IMDA reaction of tethered *α*, *β*-unsaturated aldehydes

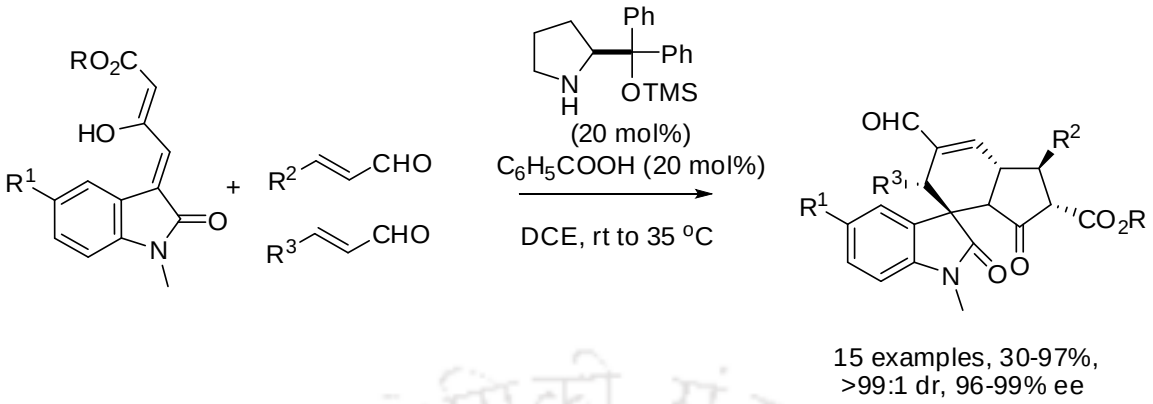
3.3.2. Synthesis of fused carbocycles by domino reactions:

Brenner and McGarraugh reported intermolecular synthesis of hexahydro-1*H*-indene motif *via* double Michael reaction between enals and *β*-ketoesters having cyclopentene moiety. Excellent diastereo- and enantiocontrol have been achieved in this reaction using diaryl prolinol ether catalyst (Scheme 3.3.2.1).[21b]



Scheme 3.3.2.1: Synthesis of fused carbocycles by domino Michael-Michael reaction

Also, Chen and co-workers applied aminocatalytic domino strategy for the synthesis of fused carbocycles with spirooxindole motif. The same catalyst has been successfully applied in a three-component, domino Michael-Michael-Michael-aldol process with two molecules of *α*,*β*-unsaturated aldehydes furnishing the products with excellent diastereo- and enantioselectivities (Scheme 3.3.2.2).[21c]



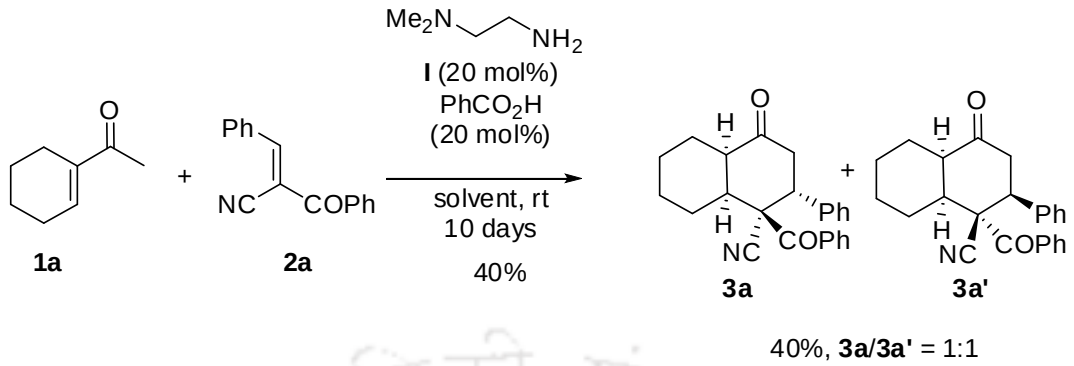
Scheme 3.3.2.2: Synthesis of fused carbocycles by domino Michael-Michael-Michael-aldol reaction

3.4. Our aim:

1-Acetyl cyclohexene has been introduced earlier in preformed dienamine chemistry by Valentin and co-workers.[23] The preformed cross-conjugated dienamine was made from piperidine in presence of $TiCl_4$ and made to react with aliphatic and aromatic nitroolefins furnishing bicyclic and tricyclic fused rings. A stepwise synthesis of 1-decalone and hexahydro-1*H*-inden-4(2*H*)-one structures was reported in previous chapter *via* dienamine catalytic Michael reaction of 1-acetylcyclohexene and 1- acetylcyclopentene with nitroolefins followed by 1,1,3,3-tetramethylguanidine mediated cyclization (Chapter 2). It was anticipated that strong dienophiles could undergo [4+2]-cycloaddition reaction *via* a double Michael cascade, providing fused carbocycles. In this regard, electron poor olefins having cyano and keto group attached to it were used as the dienophile partner with 1-acetylcyclohexene and 1-acetylcyclopentene.

3.5. Result and discussion:

Inspired by these thoughts, the investigation was started by mixing 1-acetylcyclohexene (**1a**, 0.1 mmol), enone **2a** (0.1 mmol), unsymmetrical ethylene diamine **I** (20 mol%) and benzoic acid in toluene as the solvent. After stirring at room temperature for 10 days, the desired fused bicyclic product 1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a)** was obtained in 40% yield with 1:1 diastereomeric ratio (Scheme 3.5).



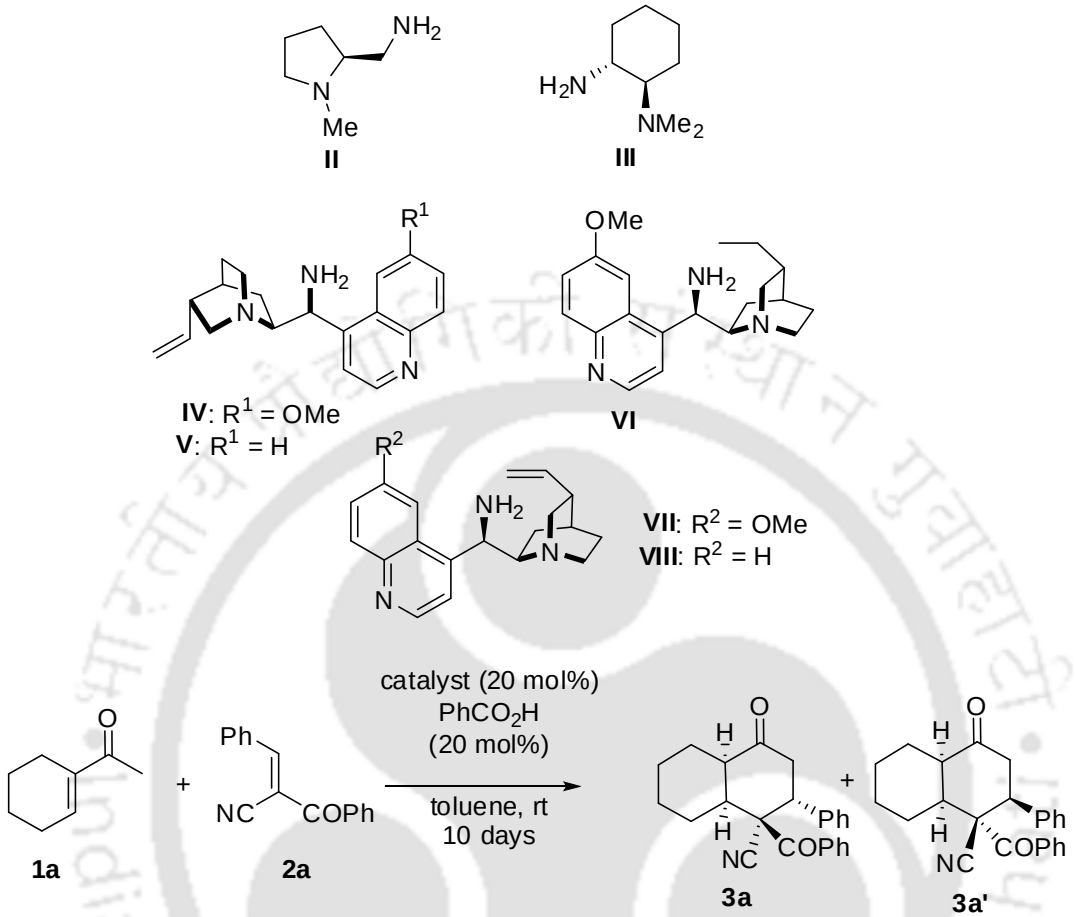
Scheme 3.5. Recemic reaction

3.5.1. Optimization studies:

3.5.1.1. Catalyst screening:

Then the optimization of chiral catalyst for the reaction was started. Initially with proline derived primary amine catalyst **II**, trace amount of product formed (Table 1, entry 1). Cyclohexyl diamine derived primary amine tertiary amine catalyst **III** also failed to produce good result (entry 2). Delightfully, cinchonidine alkaloid derived primary amine catalyst **IV** furnished the products **3a** and **3a'** with 1:1 diastereomeric ratio in 25% overall yield. The enantioselectivity obtained for one diastereomer was good (entry 3). Using cinchonine derived primary amine **V** the enantiomeric excess value obtained for both the diastereomers were very good (92%) and the diastereomeric ratio also increased a bit (entry 4). Other cinchona alkaloid derived primary amines (**VI**, **VII** and **VIII**) were also screened for this reaction with the desire of getting better result (entry 5-7). The yield and diastereoselectivities using catalyst **VI** and **VII** were comparable with the values that obtained using catalyst **V**, although the enantiomeric ratios were lower (entry 4-5). Diastereoselectivity and enantioselectivity of the minor diastereomer were decreased using cinchonidine derived catalyst **VIII** (entry 7). Hence catalyst **V** was identified as the best catalyst for this reaction.

Table 1: Screening of catalysts



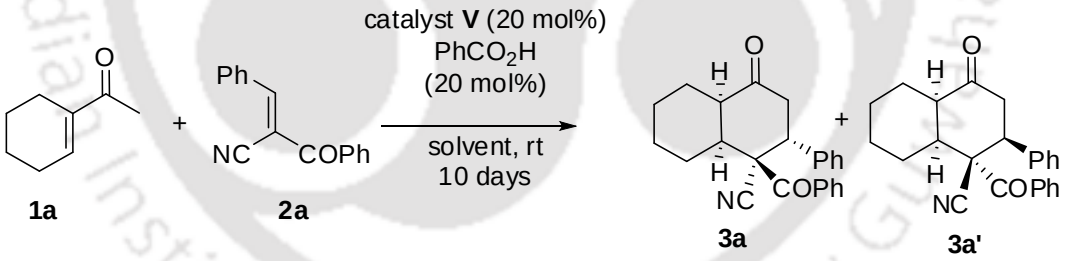
entry[a]	catalyst	yield[b] (%)	dr[c]	ee[d] (%) (major)	ee[d] (%) (minor)
1	**II**	trace	-	-	-
2	**III**	25	2:1	10	-
3	**IV**	25	1:1	80	60
4	**V**	32	1.2:1	92	92
5	**VI**	32	1.2:1	82	66
6	**VII**	30	1.2:1	84	60
7	**VIII**	29	1:1	92	40

[a]Reaction condition: Unless otherwise mentioned, 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 ml toluene using 20 mol% catalyst and 20 mol% benzoic acid co-catalyst at RT for 10 days. [b]Combined yield of the isolated product. [c]Determined ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer.

3.5.1.2. Solvent screening:

With the best catalyst in hand (catalyst **V**) different solvents were screened for this reaction (Table 2). Though diasteroselectivity increased to 1.5:1 using *α,α,α*-trifluorotoluene as the solvent instead of toluene, the enantioselectivity decreased (entry 2). Usage of chloroform as the solvent improved the diastereomeric ratio without having much effect in enantioselectivity but the yield of the reaction decreased (entry 3). Diethyl ether and THF were found to be bad solvents for this reaction as enantioselectivity decreased significantly using these solvents (entries 4 and 5). Albeit, yield was lower using dichloromethane as the solvent, it was found to be the best choice in terms of diastereo- and enantioselectivity (entry 6).

Table 2: Screening of solvent



entry[a]	solvent	yield[b] (%)	dr[c]	ee[d] (%) (major)	ee[d] (%) (minor)
1	$PhCH_3$	33	1.2:1	92	92
2	$PhCF_3$	32	1.5:1	88	89
3	$CHCl_3$	23	3:1	93	88
4	Et_2O	27	5:1	24	92

5	THF	25	5:1	47	89
6	CH_2Cl_2	23	5:1	92	88

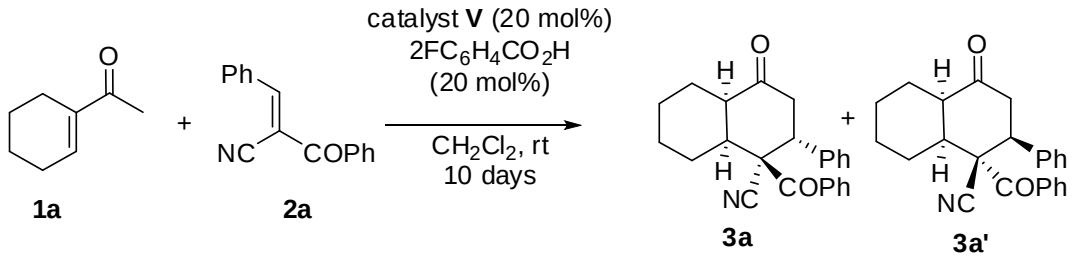
[a]Reaction condition: Unless otherwise mentioned, 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 ml solventusing 20 mol% **V** and 20 mol% benzoic acid co-catalyst at rt for 10 days. [b]Combined yield of the isolated product. [c]Determined ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer.

3.5.1.3. Screening of acid co-catalyst:

After finding the best catalyst and suitable solvent, an inspection for the best acid co-catalyst was started and it was found that 3-nitrobenzoic acid as well as 3-methoxy benzoic acid were not suitable for this reaction. Both diastereoselectivity and enantioselectivity were diminished using these acids (Table 3, entry 1-2). Thankfully, using 2-fluorobenzoic acid satisfactory result was achieved. Excellent 9:1 diastereomeric ratio and 99% enantiomeric excess were obtained using 2-fluorobenzoic acid (entry 3). Acetic acid was also screened but the result was unsatisfactory (entry 4).

It was evident that the yield of the reaction in dichloromethane was less compared to toluene. With the best catalyst (**V**) and the second best catalyst (**VIII**) in combination with 2-fluorobenzoic acid the reaction was repeated in toluene solvent with the hope of getting better yield (Table 3, entry 5-6). Gratifyingly the yield was increased with the expense of little diasteroselectivity. Catalyst **V** was still found to be the best catalyst furnishing product **3a** in 34% yield with 7:1 diastereomeric ratio and 99% enantiomeric excess (entry 6).

Table 3: Screening of acid co catalyst



entry[a]	acid co-catalyst	yield[b] (%)	dr[c]	ee[d] (%) (major)	ee[d] (%) (minor)
1	3-$NO_2C_6H_4CO_2H$	21	3:1	87	95
2	3-$MeOC_6H_4CO_2H$	19	3:1	91	99
3	2-$FC_6H_4CO_2H$	24	9:1	99	-
4	AcOH	15	2.6:1	75	99
6[e]	2-$FC_6H_4CO_2H$	34	7:1	99	-
7[f]	2-$FC_6H_4CO_2H$	33	7:1	96	-

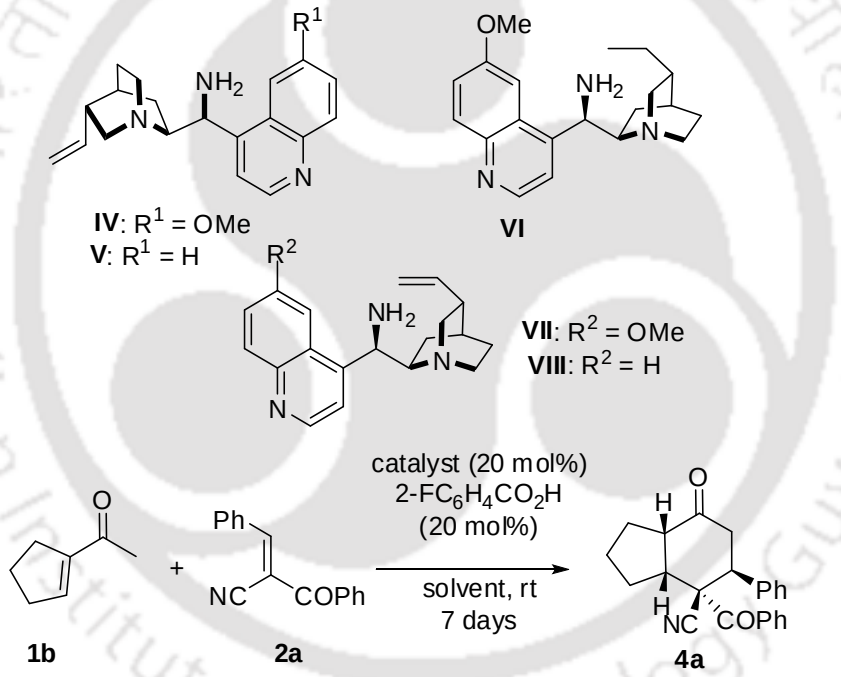
[a]Reaction condition: Unless otherwise mentioned, 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 ml DCM using 20 mol% **V** and 20 mol% benzoic acid co-catalyst at rt for 10 days. [b]Combined yield of the isolated product. [c]Determined ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer. [e]Toluene as solvent. [f]Toluene as solvent and with catalyst **VIII**.

3.5.1.4. Optimization of reaction condition for 1-acetylcyclopentene:

The optimization study for the reaction with 1-acetylcyclopentene was also done. This time catalysts other than cinchona alkaloid derived amines and acids other than 2-fluorobenzoic acid were not screened. Primarily it was found that the rate of conversion for this reaction with **1b** was much faster than with **1a**. That is why the best solvent in terms of diastereoselectivity and enantioselectivity (not in terms of yield) *i.e.* dichloromethane was chosen as the primary solvent for screening of catalysts. When 1-acetylcyclopentene (**1b**, 0.05 mmol) was stirred with enone **2a** (0.05 mmol) in presence of quinidine derived primary amine **IV** (20 mol%) and 2-fluorobenzoic acid (20 mol%) in dichloromethane at room temperature for 7 days, the desired major fused bicyclic product 4-benzoyl-7-oxo-5-phenyloctahydro-1*H*-indene-4-carbonitrile (**4a)** was obtained in 70% yield with 11:1 diastereomeric ratio and 59% ee (Table 4, entry 1). Interestingly, the enantiomeric excess got enhanced to 84% by employing *epi*-cinchonine amine **V**, although the diastereomeric ratio decreased to 7:1 (entry 2). Slightly higher enantioselectivity (89%) and slightly lower diastereomeric ratio were achieved with

hydroquinine derived catalyst **VI** (entry 3). Both the enantioselectivity and diastereoselectivity dropped using quinine derived amine **VII** (entry 4). Pleasingly, cinchonidine derived amine catalyst **VIII** delivered the product **4a** in 6:1 diastereomeric ratio with 94% ee (entry 5). The diastereomeric ratio of 6:1 was unsatisfactory; thus for the further improvements of the diastereo- and enantioselectivity of the reaction, different solvents were again screened (entries 6-8). Gratifyingly an increment of diastereomeric ratio was observed using mesitylene as solvent (entry 6). Enantioselectivity was increased when α,α,α-trifluoro toluene was used as solvent (entry 7) but the diastereoselctivity has droped. Finally, the best solvent turned out to be toluene and the product **4a** was isolated in 87% yield with 13:1 dr and 96% ee (entry 8).

Table 4. Optimization of reaction condition for 1-acetylcyclopentene



entry[a]	catalyst	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**IV**	CH_2Cl_2	70	11:1	59
2	**V**	CH_2Cl_2	75	7:1	84
3	**VI**	CH_2Cl_2	68	6:1	89

4	**VII**	CH_2Cl_2	72	3.2:1	76
5	**VIII**	CH_2Cl_2	72	6:1	94
6	**VIII**	mesitylene	81	9:1	94
7	**VIII**	$PhCF_3$	83	6:1	96
8	**VIII**	$PhCH_3$	87	13:1	96

[a]Reaction condition: 0.05 mmol of **1b** and 0.05 mmol of **2a** in 0.5 mL solvent using 20 mol% catalyst and 20 mol% 2-$FC_6H_4CO_2H$ at rt for 7 days. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

3.5.2. Substrate scope:

Since the overall results obtained with 1-acetylcyclopentene (**1b**) was better compared to 1-acetylcyclohexene (**1a**), **1b** was chosen as the primary substrate in our reaction.

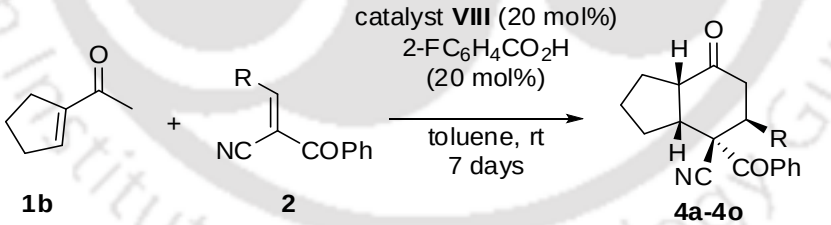
3.5.2.1. With 1-acetyl cyclopentene:

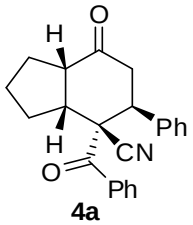
3.5.2.1.1. Scope of enone with varied olefin substituents:

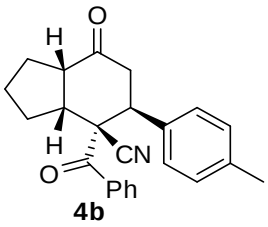
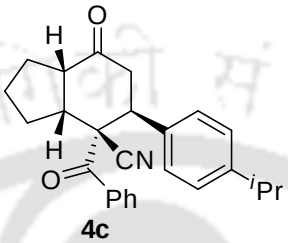
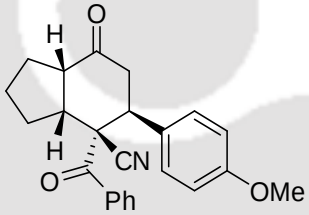
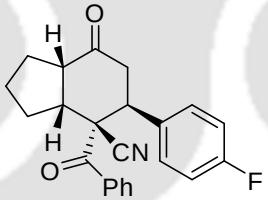
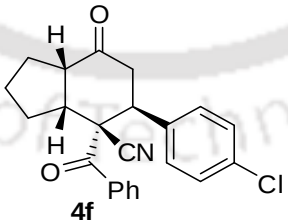
Initially different enones **2** having variations of the substitutions on the aryl group of the double bond was investigated (Table 5). It turned out that a variety of electron donating, electron neutral and electron withdrawing substitutions are well tolerated in our reaction condition. Different *para*-substituted *β*-aryl enones were initially employed in the reaction and excellent results were achieved (entries 2-9). For example, two enones **2b** and **2c** having 4-alkyl substitution on the aromatic ring were screened. The corresponding products **4b** and **4c** having 4-methyl and 4-*iso*propyl substitutions were isolated in high enantioselectivities and interestingly higher diastereomeric ratio was obtained for product **4c** (entries 2-3). 4-alkoxy substituted enaone **2d** furnished the product **4d** with a little less diastereomeric ratio and enantiomeric excess (entry 4). It was found that different 4-halo substituted enones (**2e-2g**) were also good substrates for this reaction. Product **4e** having 4-fluoro substitution was

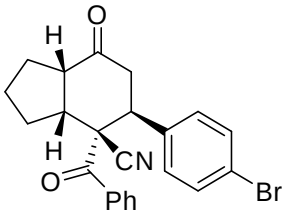
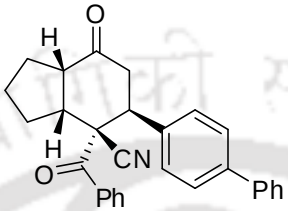
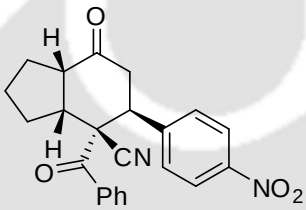
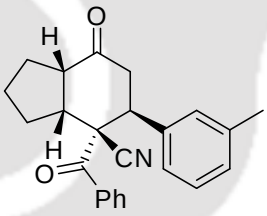
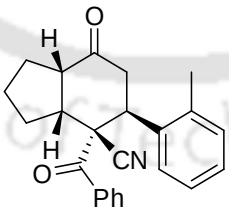
obtained with higher diastere- and enantiomeric ratio compare to the unsubstituted one (entry 5). For the 4-chloro substituted product **4f** the diastereoselectivity was even higher (entry 6). 98% enantiomeric excess and 19:1 diastereomeric ratio was obtained for 4-bromosubstituted product **4g** (entry 7). Biphenyl substituted enone **2h** also participated in the reaction delivering product **4h** in 94% ee and 16:1 dr (entry 8). High diastereo- and enantioselectivity was also observed for product **4i** having *para*-nitro substitution, however the yield was moderate (entry 9). Then *ortho*- and *meta*-substituted enones **2j** and **2k** were employed in the reaction and delightfully the outcome was good (entries 10-11). For the *meta*-substitution the enantio- as well as the diastereocontrol were comparable to that of the unsubstituted one (entry 10) but for the ortho-substitution a decrease in diastereoselectivity observed (entry 11). The reaction also progressed well with enone **2l** having 1-naphthyl group and slight less enenatioselectivity and diastereoselectivity was detected (entry 12). A disubstituted (2,4-dichloro) aryl group containing enone was also tolerated in our reaction displaying good result (entry 13). Importantly, enone **2n** having 2-thienyl moiety could also be a good substrate in the reaction *albeit* slight lesser enantioselectivity was observed (entry 14). Finally, cinnamyl group containing enone was screened and excellent enantioselectivity was attained for product **4o** (entry 15).

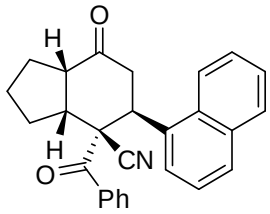
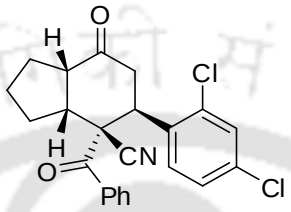
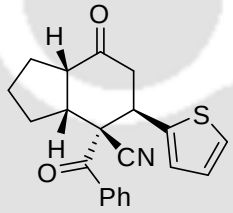
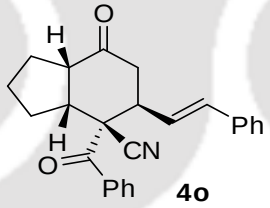
Table 5. Scope of enone with varied olefin substituents



entry[a]	R	Product	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	 4a	87	13:1	96

2	4-MeC_6H_4	 **4b**	72	13:1	96
3	4-$^{i}PrC_6H_4$	 **4c**	67	>20:1	95
4	4-$OMeC_6H_4$	 **4d**	60	10:1	93
5	4-FC_6H_4	 **4e**	89	17:1	98
6	4-ClC_6H_4	 **4f**	69	>20:1	97

7	4-BrC_6H_4	 **4g**	87	19:1	98
8	4-PhC_6H_4	 **4h**	81	16:1	94
9	4-$NO_2C_6H_4$	 **4i**	39	>20:1	94
10	3-MeC_6H_4	 **4j**	83	13:1	94
11	2-MeC_6H_4	 **4k**	65	9:1	92

12	1-napthyl	 **4l**	60	8:1	83
13	2,4-C_6H_3	 **4m**	55	15:1	82
14	2-thienyl	 **4n**	52	6:1	76
15	Cinnamyl	 **4o**	40	5:2:1	>99

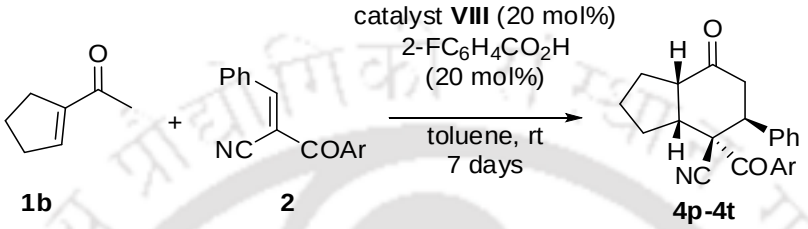
[a]Reaction condition: Unless otherwise mentioned, 0.1 mmol of **1b** and 0.1 mmol of **2** in 1 ml solvent using 20 mol% **VIII** and 20 mol% 2-$FC_6H_4CO_2H$ at rt for 7 days. [b]Combined yield of the isolated product. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC and of the major diastereomer.

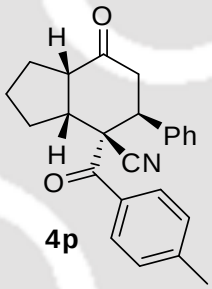
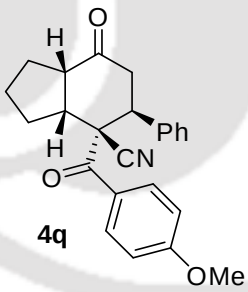
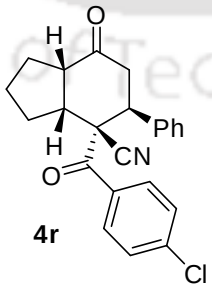
3.5.2.1.2. Scope of enone with varied ketone substituents:

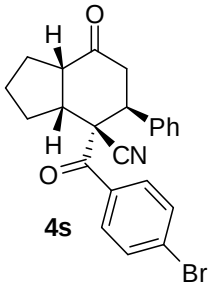
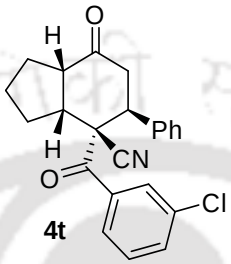
Next, the ketone functionality of the enone was varied and the results are summarized in Table 6. Here also, different substitutions on the phenyl group of ketone were tolerated and excellent results were obtained. Initially, *para*-substituted enones having electron donating groups were screened and higher enantioselectivity and lower diastereoselectivity was detected for alkyl

substituted product **4p** compared to alkoxy substituted product **4q** (entries 1-2). Additionally, the outcome was also excellent with 4-halo substituted enones **2r**-**2s** (entries 3-4). Finally a *meta*-substituted enone was engaged in the reaction and the product **4t** was obtained in high diastereo- and enantioselectivity (entry 5).

Table 6. Scope of enone with varied ketone substituents



entry[a]	Ar	Product	yield[b] (%)	dr[c]	ee[d] (%)
1	4-MeC_6H_4	 **4p**	88	17:1	94
2	4-$OMeC_6H_4$	 **4q**	64	20:1	93
3	4-ClC_6H_4	 **4r**	72	12:1	94

4	4-BrC_6H_4	 **4s**	54	10:1	95
5	3-ClC_6H_4	 **4t**	66	8:1	96

[a]Reaction condition: Unless otherwise mentioned, 0.1 mmol of **1b** 0.1 mmol of **2** in 1 ml solvent using 20 mol% **VIII** and 20 mol% 2-$FC_6H_4CO_2H$ at rt for 7 days. [b]Combined yield of the isolated product. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC and of the major diastereomer.

3.5.2.2. With 1-acetyl cyclohexene:

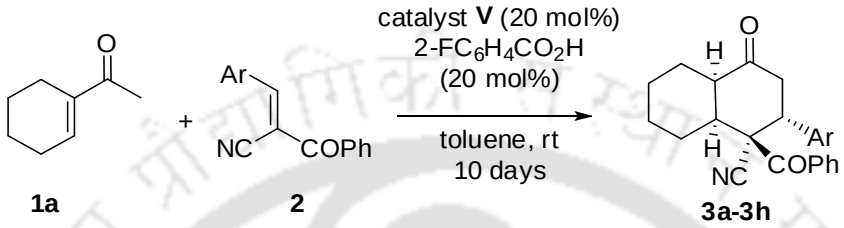
Various enones with electron doneting as well as electron withdrawing substitution on the aromatic ring was reacted with 1-acetylcyclohexene in presence of catalyst **V** and the results were satisfiying.

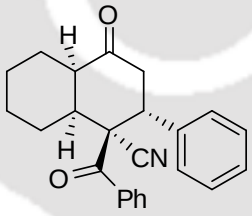
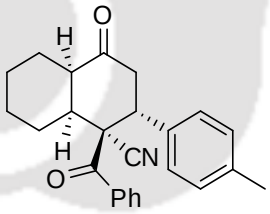
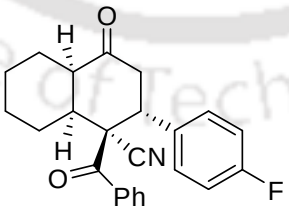
3.5.2.2.1. With varied olefin substituents

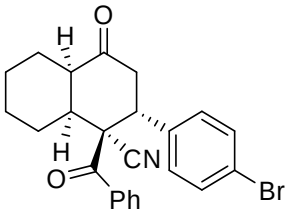
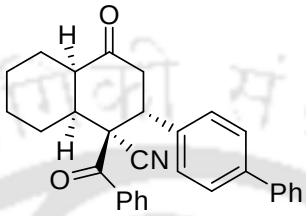
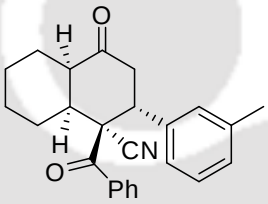
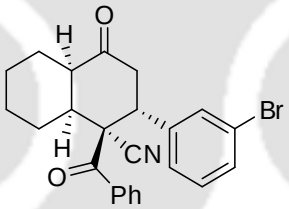
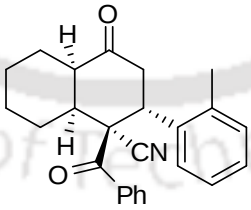
Gratifyingly, as can be seen in Table 7, the decalone products were obtained in high enantioselectivities irrespective of the nature of the substitutions on the aryl group. Initially, different *para*-substitutions were screened and good results were observed. For instance, **1a** on reaction with **3b** furnished the corresponding cyclized product **3b** in 5:1 dr with 90% ee (Table 7, entry 2). Similarly different halo substitutions were tolerated in the reaction providing products **3c-3d** in high enantioselectivities, though for the 4-fluoro substituted product the diastereomeric ratio (5:1) was little bit higher than the 4-bromo substituted derivative (4:1) (entry 3-4). The reaction was sluggish with enone **2h** having biphenyl moiety but the enantiomeric excess of the corresponding product **3e** was excellent (entry 5). Besides *meta*-substituted enones were also found to be good partner in this reaction (entry 6-7). Meta methyl

substituted product **3f** was obtained in 28% yield with 4:1 diastereomeric ratio and 95% ee. The highest diastereoselectivity (9:1 dr) was attained for 3-bromo substituted product **3g**. Finally slight slow reactivity was observed for an *ortho*-substituted enone and the corresponding product **3h** was isolated in 17% yield with 1.6:1 dr and 89% ee.

Table 7. Scope of cyclization of 1a with 2 having varied olefin substituents



entry[a]	Ar	Product	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	 **3a**	34	7:1	99
2	4-MeC_6H_4	 **3b**	25	5:1	96
3	4-FC_6H_4	 **3c**	28	5:1	96

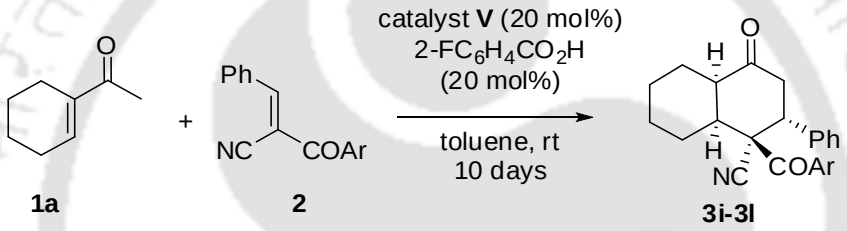
4	4-BrC_6H_4	 **3d**	22	4:1	96
5	4-PhC_6H_4	 **3e**	15	4:1	95
6	3-MeC_6H_4	 **3f**	28	4:1	95
7	3-BrC_6H_4	 **3g**	26	9:1	95
8	2-MeC_6H_4	 **3h**	17	1.6:1	89

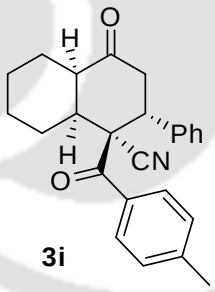
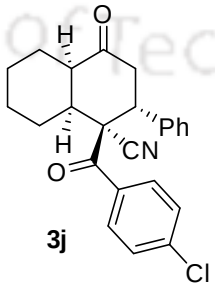
[a]Reaction condition: Unless otherwise mentioned, 0.15 mmol of **1a** and 0.15 mmol of **2** in 1.5 ml solvent using 20 mol% **V** and 20 mol% 2-$FC_6H_4CO_2H$ at rt for 10 days. [b]Combined yield of the isolated product. [c]Determined by ^1H NMR. [d]Measured by chiral HPLC and of the major diastereomer.

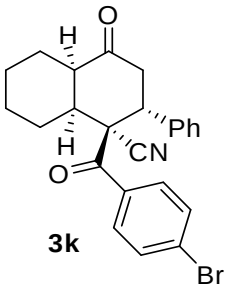
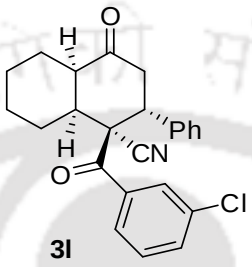
3.5.2.2.2. With varied ketone substituents:

The generality of the reaction was further demonstrated by employing enones with varied keto functionalities (Table 8). Gratifyingly, the reaction condition was also found to be suitable for the enones having different keto functionalities. Good diastereoselectivity was achieved for product **3i**, having a 4-methyl substitution (entry 1). Inferior diastereoselectivity was detected for the products **3j**-**3k** having 4-halo substitution on the aryl group of the ketone moiety (entry 2-3). For 4-Br substitution (product **3k**) excellent enantioselectivity was observed (entry 3). A *meta*-substitutted enone reacted slowly and less yield but high enantioselectivity was observed for the corresponding product **3l**.

Table 8. Scope of cyclization of 1a with 2 having varied ketone substituents



entry[a]	Ar	Product	yield[b] (%)	dr[c]	ee[d] (%)
1	4-MeC_6H_4	 **3i**	22	8:1	94
2	4-ClC_6H_4	 **3j**	26	2:1	90

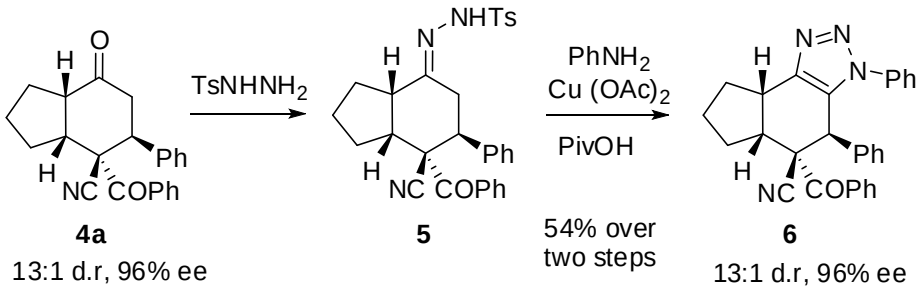
3	4-BrC_6H_4	 **3k**	28	1.6:1	>99
4	3-ClC_6H_4	 **3l**	17	4:1	99

[a]Reaction condition: Unless otherwise mentioned, 0.15 mmol of **1a** and 0.15 mmol of **2** in 1.5 ml solvent using 20 mol% **V** and 20 mol% 2-$FC_6H_4CO_2H$ at RT for 10 days. [b]Combined yield of the isolated product. [c]Determined by ^1H NMR. [d]Measured by chiral HPLC and of the major diastereomer.

3.5.4. Synthetic transformation of products:

3.5.4.1. Copper mediated triazole synthesis:

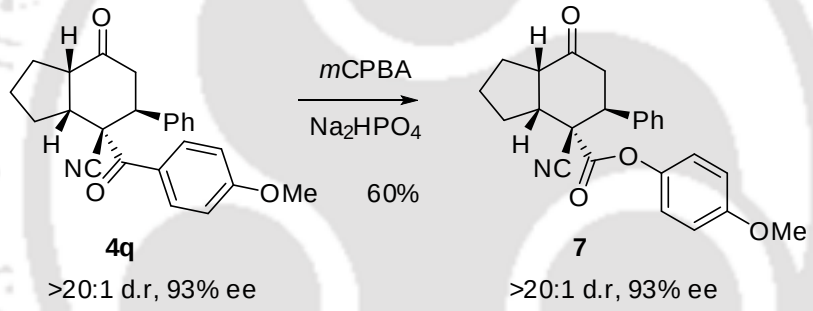
To illustrate the utility of our method, few reactions were carried out on **4a** and **4q.** Initially copper mediated triazole synthesis[24] was envisaged from **4a**. For this, first **4a** was converted to tosylhydrazone **5** which upon treatment with aniline, copper acetate and pivalic acid delivered triazole **6** in 54% overall yield. It is delighting that both the diastereo- and enantiopurity got retained in this process (Scheme 3.5.4.1).



Scheme 3.5.4.1. copper mediated triazole synthesis from **4a**

3.5.4.2. Baeyer Villiger oxidation:

Then a Baeyer Villiger oxidation reaction was performed on **4q** having a 4-anisyl group. The reaction progressed smoothly affording the ester product **7** in 60% yield and here also both diastereo- and enantioselectivity got preserved (scheme 3.5.4.2).



Scheme 3.5.4.2. Baeyer Villiger oxidation of **4q**

In summary, this chapter describes the first catalytic asymmetric double Michael reaction of 1-acetylcyclopentene and 1-acetylcyclohexene providing bicyclic fused frameworks. Electron deficient olefins having simultaneous cyano and keto groups were identified as the most suitable Michael acceptor and cinchona alkaloid derived primary amines were found to be the best catalysts. The bicyclic products having four contiguous stereogenic centres including one quaternary centre are obtained in high diastereo- and enantioselectivities and also valuable synthetic transformations including triazole synthesis has been demonstrated.

3.6. Experimental procedures and structure determination:

3.6.1. General Procedure for the Preparation of starting meterials:

Benzyolacetonitrile (1 mmols) and 4 Å MS (40 mg) is taken in a RB under Ar atmosphere, dry toluene (7.5 mL) was added to it. Corresponding aldehyde (1 mmoles) and piperidine (2 mol%, 0.02 mmoles) was added in the reaction mixture under Ar atmosphere. The reaction mixture was heated at 80 ^{o}C for 8 hours. The concentrated reaction mixture was purified by silica gel column chromatography (4-6% EA in Hexane) to give product **2**.

3.6.2. General procedure for organocatalytic asymmetric Diels-Alder reaction of 1-acetyl cyclohexene with enone 2:

In a 5ml round bottomed flusk enone **2** (0.15 mmols), *epi*-cinchonine amine **V** (20 mol%, 0.03 mmols), 2-fluoro benzoic acid (20 mol%, 0.03 mmoles) was taken and 1-aectyl cyclohexene (**1a**) (0.15 mmols) and 1.5 mL toluene was added and the reaction mixture was stirred at room temperaure for 10 days. The reaction mixture was then directly employed in column chromatographic separation using 3% EA in hexane as eluent to obtain pure product **3**.

3.6.3. General procedure for organocatalytic asymmetric Diels-Alder reaction of 1-acetyl cyclopentene with enone:

In a 5 ml round bottomed flusk enone **2** (0.1 mmols), *epi*-cinchonidine amine **VIII** (20 mol%, 0.02 mmols), 2-fluoro benzoic acid (20 mol%, 0.02 mmols) was taken and 1-aectyl cyclopentene (0.1 mmols) and 1 mL toluene was added and the reaction mixture was stirred at room temperaure for 7 days. The reaction mixture was then directly employed in column chromatographic separation using 4% EA in hexane as eluent to obtain pure product **4**.

3.6.4. Copper-Mediated Synthesis of 1,2,3-Triazole 6 from N-Tosylhydrazone of compound 4a:

Compound **6** was prepared according to a slightly modified literature procedure.[24] A solution of $TsNHNH_2$ (0.05 mmol) and **4a** (0.05 mmol) in methanol (0.1 mL) was stirred and heated to 60 ^{o}C for 5 minutes and the mixture was cooled to room temperature. After 12 hours the crude products was obtained as solid precipitate. The precipitate was washed with petroleum ether,

kept under vacuum to afford pure product **5 (**0.045 mmols). Aniline (0.09 mmol) was added to a mixture of $Cu(OAc)_2$ (0.045 mmol), PivOH (0.09 mmol), N-tosylhydrazone **5** (0.045 mmol) in toluene (0.45 mL). The mixture was stirred at 100 °C in air for 12 h. The reaction mixture was cooled to ambient temperature and purified by column chromatography on silica gel (60-120 mesh, 15% EA in hexane) to afford pure product **6**.

3.6.4. Baeyer Villiger oxidation reaction of compound 4q:

To a stirred solution of **4q** (0.05 mmols) in dichloromethane *m*CPBA (0.1 mmols, 2 equiv.) and disodium hydrogen phosphate (0.2 mmoles, 4 equiv.) were added. The reaction was stirred overnight and then transferred to a separetory funnel, diluted with dichloromethane and extracted with saturated aquous sodium bi-carbonate solution. The organic layer was collected and the aquous layer was again extracted with DCM, the combined organic layer was dried, concentrated and then subjected to column chromatograpic separation using 15% EA in hexane as eluent to obtain pure **7**.

3.6.5. Structure determination of the products:

Compound 4f:

The absolute configuration of product **4f** was assigned to be (3*aR*,4*R*,5*S*,7*aS*) by X-ray crystallography.[25] The absolute structure of other products **4** are expected to be same by analogy. Also, the absolute structure of product **3** can be proposed to be opposite as cinchonine and cinchonidine used to provide enantiomeric products.[26]

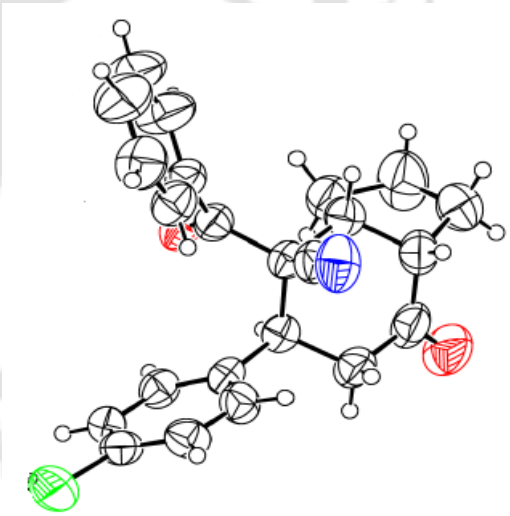
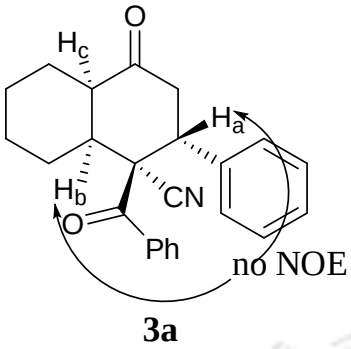


Figure 3: ORTEP diagram of (3aR,4R,5S,7aS)-4-benzoyl-5-(4-chlorophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (**4f**)

Determination of structure of compound 3a:

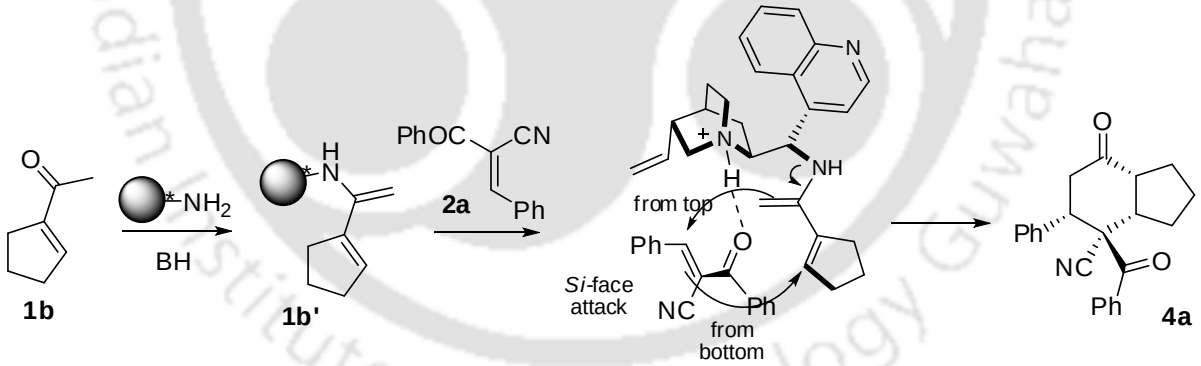


3a

From the coupling constant values of H_c 3.04 (td, J = 11.8, 3.9 Hz, ^{1}H) and H_b 2.29 (td, J = 12.2, 3.3 Hz, ^{1}H) i.e. J = 3.9 and J = 3.3 respectively, it can be predicted that they are *cis* to each other. There is no NOE between H_a and H_b, which predicts that H_a and H_b are *trans* to each other. As here we are using pseudo enantiomer of the best catalyst which furnish **4f**, by analogy it can be said that the above structure is most likely the structure of **3a**.

3.7. Plausible reaction mechanism:

A plausible mechanism has been shown in Scheme 3.7. The catalyst forms a cross dienamine **1b'** from the enone **1b**. **1b'** acts as the diene and reacts with olefin **2a** having cyano and keto group. In absence of the cyano group the reaction doesnot happen at all. The dienamine **2b'**, the olefin from *Si*-face and the second Michael attack to the iminium also happens from the *Si*-face. In the enamine **1b'**, the tertiary amino group is protonated and could interact with the keto functionality and thus assists in the stereocontrol.



Scheme 3.9: Plausible mechanism

3.8. Characterization data for products:

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4a):

Off White sticky compound (29.8 mg, 87%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.95 (dd, J = 8.2, 1.5 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 5.9 Hz, 1H), 4.14 (dd, J = 14.7, 3.7 Hz, 1H), 3.88 – 3.85

(m, 0.08H), 3.36 – 3.28 (m, 2H), 3.20 (dt, *J* = 11.9, 7.1 Hz, 1H), 2.68 (dd, *J* = 14.6, 3.7 Hz, 1H), 2.62 - 2.58 (m, 1H), 1.80 (ddd, *J* = 9.4, 6.3, 3.1 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.58 (d, *J* = 4.1 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.47 – 1.41 (m, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.98, 192.1, 138.0, 135.7, 133.8, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 128.2, 121.0, 55.7, 51.3, 51.0, 44.5, 43.1, 26.2, 23.4, 21.5. **FT-IR** (KBr): 2924(s), 1719(s), 1682(s), 1228(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{22}NO_2^+$ $[M+H]^+$: 344.1645, Found: 344.1626. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IC column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 21.3 min, τ_{major} = 40.9 min), ee 96%.

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-p-tolyloctahydro-1H-indene-4-carbonitrile (**4b**): Off White sticky compound (25.7 mg, 72%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.44 (dd, *J* = 19.4, 8.1 Hz, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.12 (dd, *J* = 14.6, 3.6 Hz, 1H), 3.84 (dd, *J* = 14.2, 4.0 Hz, 0.07H), 3.34 – 3.26 (m, 2H), 3.19 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.66 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.31 (s, 3H), 1.80 (ddd, *J* = 9.3, 6.0, 2.6 Hz, 1H), 1.65 – 1.63 (m, 1H), 1.59 – 1.54 (m, 1H), 1.54 – 1.48 (m, 1H), 1.43 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.1, 192.1, 137.9, 135.7, 135.0, 133.8, 129.3, 129.1, 128.8, 128.7, 121.1, 55.8, 51.3, 51.0, 44.6, 42.8, 26.2, 23.4, 21.5, 21.2. **FT-IR** (KBr): 2924(s), 1719(s), 1687(s), 1230(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_2^+$ $[M+H]^+$:358.1802, Found:358.1877. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.3 min, τ_{major} = 35.2 min), ee 96%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-isopropylphenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4c): Off White sticky compound (25.8 mg, 67%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.93 (d, *J* = 7.9 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.39 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.10 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.79 (dd, *J* = 14.3, 3.7 Hz, 0.05H), 3.33 – 3.24 (m, 2H), 3.16 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.85 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.65 (dd, *J* = 14.5, 3.5 Hz, 1H), 2.58 (t, *J* = 10.1 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.54 (dd, *J* = 16.8, 9.2 Hz, 2H), 1.48 – 1.37 (m, 2H), 1.20 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 207.2, 192.1, 148.7, 135.7, 135.3, 133.8, 129.2, 128.8, 128.7, 126.7, 121.1, 55.8, 51.3, 51.0, 44.5, 42.9, 33.9, 26.2, 24.0, 24.0, 23.4, 21.4. **FT-IR** (KBr): 2924(m), 1718(s), 1685(s), 1229(m). **HRMS (ESI$^+$):** Calcd. for $C_{26}H_{28}NO_2^+$ $[M+H]^+$: 386.2115, Found: 386.2045. The enantiomeric ratio was determined

by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.3 min, $_{\tau major}$ = 17.9 min), ee 95%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-methoxyphenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4d): Yellow sticky compound (22.4 mg, 60%), column chromatography was done using 6% ethyl acetate/hexane. **^{1}H-NMR (600 MHz, $CDCl_3$):** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 4H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.09 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.81 (dd, *J* = 14.2, 4.0 Hz, 0.1H), 3.76 (s, 3H), 3.30 – 3.24 (m, 2H), 3.16 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.62 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.60 – 2.54 (m, 1H), 1.77 (ddd, *J* = 9.3, 5.9, 2.4 Hz, 1H), 1.62 – 1.58 (m, 1H), 1.57 – 1.52 (m, 1H), 1.48 (dd, *J* = 21.5, 12.1 Hz, 1H), 1.40 (dd, *J* = 15.0, 6.3 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.1, 192.2, 159.3, 135.7, 133.8, 130.4, 130.0, 128.8, 128.6, 121.1, 113.9, 56.1, 51.2, 44.6, 42.5, 26.2, 23.3, 21.4. **FT-IR** (KBr): 2925(s), 1716(s), 1686(s), 1259(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_2^+$ $[M+H]^+$:374.1751, Found: 374.1756. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IC column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 44.9 min, τ_{major} = 77.0 min), ee 93%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-fluorophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4e): Off White sticky compound (32.1 mg, 89%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.98 – 7.93 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.44 (t, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 2H), 4.12 (dd, *J* = 14.7, 3.5 Hz, 1H), 3.86 (dd, *J* = 14.3, 4.0 Hz, 0.06H), 3.31 – 3.22 (m, 2H), 3.19 (dt, *J* = 12.4, 7.1 Hz, 1H), 2.62 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.60 – 2.54 (m, 1H), 1.81 – 1.73 (m, 1H), 1.64 (dd, *J* = 8.6, 4.9 Hz, 1H), 1.58 – 1.52 (m, 1H), 1.50 – 1.43 (m, 1H), 1.42 – 1.38 (m, 1H).). **^{13}C NMR (151 MHz, $CDCl_3$)** 206.6, 191.8, 163.3, 161.7, 135.4, 134.0, 133.8, 131.1, 131.0, 128.9, 128.7, 120.9, 115.6, 115.5, 55.8, 51.2, 51.0, 44.5, 42.4, 26.1, 23.4, 21.4. **FT-IR** (KBr): 2924(s), 1715(s), 1685(s), 1223(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{21}FNO_2^+$ $[M+H]^+$: 362.1551, Found: 362.1536. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (96:4 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 15.7 min, τ_{major} = 32.4 min), ee 98%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-chlorophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4f): Off White sticky compound (26 mg, 69%), **^{1}H-NMR (600 MHz, $CDCl_3$):**

δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.37 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.25 (m, 1H), 4.09 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.80 (dd, *J* = 14.1, 4.0 Hz, 0.08H), 3.32 – 3.25 (m, 2H), 3.13 (dt, *J* = 12.4, 7.1 Hz, 1H), 2.66 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.61 – 2.55 (m, 1H), 1.81 – 1.76 (m, 1H), 1.63 (dd, *J* = 6.7, 4.0 Hz, 1H), 1.58 – 1.53 (m, 1H), 1.51 – 1.45 (m, 1H), 1.39 (dd, *J* = 13.1, 6.3 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.6, 191.8, 163.3, 161.7, 135.4, 134.0, 133.8, 131.1, 131.0, 128.9, 128.7, 120.9, 115.6, 115.5, 77.4, 77.2, 77.0, 55.8, 51.2, 51.0, 44.5, 42.4, 26.1, 23.4, 21.4. **FT-IR** (KBr): 2925(s), 1719(s), 1687(m), 1236(m). **HRMS (ESI^+):** Calcd. for $C_{23}H_{21}ClNO_2^+$ $[M+H]^+$: 378.1255, Found: 378.1253. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (95:5 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 15.6min, τ_{major} = 40.9 min), ee 97%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-bromophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4g): Off White sticky compound (36.6 mg, 87%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.62 – 7.56 (m, 1H), 7.48 – 7.39 (m, 6H), 4.09 (dd, *J* = 14.7, 3.6 Hz, 1H), 3.84 (dd, *J* = 14.2, 4.0 Hz, 0.06H), 3.31 – 3.16 (m, 3H), 2.62 (dd, *J* = 14.4, 3.6 Hz, 1H), 2.60 – 2.55 (m, 1H), 1.76 (ddd, *J* = 9.7, 6.4, 3.3 Hz, 1H), 1.66 – 1.60 (m, 1H), 1.55 (dd, *J* = 12.7, 10.9 Hz, 1H), 1.46 – 1.35 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.8, 191.0, 140.5, 137.8, 133.8, 130.2, 129.2, 129.2, 128.7, 128.3, 120.9, 51.3, 51.0, 44.4, 43.2, 26.2, 23.4, 21.5. **FT-IR** (KBr): 2925(s), 1712(s), 1686(s), 1231(m). **HRMS (ESI^+):** Calcd. for $C_{23}H_{21}BrNO_2^+$ $[M+H]^+$: 422.075, Found: 422.0751. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.7 min, τ_{major} = 39.8 min). ee 98%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(biphenyl-4-yl)-7-oxooctahydro-1H-indene-4-carbonitrile (4h): Off White sticky compound (33.9 mg, 81%), **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 9.5, 8.4 Hz, 5H), 7.43 (dt, *J* = 12.2, 8.0 Hz, 4H), 7.33 (t, *J* = 7.4 Hz, 1H), 4.18 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.90 (dd, *J* = 14.0, 3.9 Hz, 0.06H), 3.37 – 3.30 (m, 2H), 3.21 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.70 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.62 – 2.56 (m, 1H), 1.83 – 1.76 (m, 1H), 1.63 – 1.60 (m, 1H), 1.59 – 1.54 (m, 1H), 1.50 (dd, *J* = 11.9, 9.0 Hz, 1H), 1.43 (t, *J* = 4.8 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.0, 191.9, 140.9, 140.6, 137.0, 135.5, 133.9, 129.7, 128.9, 128.9, 128.8, 127.6, 127.3, 127.2, 121.1, 55.7, 51.3, 51.1, 44.5, 42.8, 26.5, 23.4, 21.5. **FT-IR** (KBr): 2924(s), 1721(s), 1687(s), 1228(m).

HRMS (ESI$^+$): Calcd. for $C_{29}H_{26}NO_2^+$ $[M+H]^+$: 420.1958, Found: 420.1952. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (95:5 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 16.8 min, τ_{major} = 19.8 min).

(3aR,4R,5S,7aS)-4-benzoyl-5-(4-nitrophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4i): Yellow sticky compound (15.2 mg, 39%), column chromatography was done using 5% ethyl acetate/hexane. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 8.17 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 4.23 (dd, *J* = 14.7, 3.5 Hz, 1H), 4.03 (dd, *J* = 14.2, 3.9 Hz, 0.04H), 3.35 – 3.23 (m, 3H), 2.64 (dd, *J* = 14.4, 3.5 Hz, 1H), 2.60 – 2.55 (m, 1H), 1.81 – 1.74 (m, 1H), 1.65 (dd, *J* = 6.6, 4.4 Hz, 1H), 1.58 – 1.53 (m, 1H), 1.40 (dd, *J* = 18.6, 8.8 Hz, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 205.8, 190.9, 147.7, 145.2, 134.5, 130.5, 129.1, 129.0, 123.8, 120.5, 55.0, 51.2, 51.1, 44.0, 42.7, 26.0, 23.5, 21.5. **FT-IR** (KBr): 2924(s), 1721 (s), 1689(s), 1349(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{21}N_2O_4^+$ $[M+H]^+$: 389.1496, Found: 389.1496. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (98.5:1.5 *n*-Hexane/EtOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 44.0 min, τ_{major} = 47.1 min), ee 94%.

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-m-tolyloctahydro-1H-indene-4-carbonitrile (4j): Off White sticky compound (29.6 mg, 83%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.96 (d, *J* = 7.9 Hz, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.34 (s, 2H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 4.10 (dd, *J* = 14.5, 2.1 Hz, 1H), 3.82 (dd, *J* = 14.9, 3.4 Hz, 0.08H), 3.36 – 3.26 (m, 2H), 3.24 – 3.15 (m, 1H), 2.67 (dd, *J* = 14.4, 2.3 Hz, 1H), 2.60 (t, *J* = 10.1 Hz, 1H), 2.35 (s, 3H), 1.86 – 1.77 (m, 1H), 1.67 – 1.62 (m, 2H), 1.58 – 1.51 (m, 1H), 1.49 – 1.42 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.1, 192.1, 138.3, 138.0, 135.7, 133.8, 130.0, 128.9, 128.8, 128.7, 128.5, 126.2, 121.1, 55.7, 51.4, 51.0, 44.6, 43.1, 26.2, 23.4, 21.7, 21.5. **FT-IR** (KBr): 2924(s), 1716(s), 1684(s), 1231(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_2^+$ $[M+H]^+$: 358.1802, Found: 358.1792. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IC column (97:3 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.4 min, τ_{major} = 23.3 min), ee 94%.

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-o-tolyloctahydro-1H-indene-4-carbonitrile (4k): Off White sticky compound (23.2 mg, 65%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.94 (d, *J* = 7.9 Hz,

2H), 7.86 (d, *J* = 7.1 Hz, 1H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.15 (dd, *J* = 9.1, 5.5 Hz, 3H), 4.19 (dd, *J* = 14.4, 2.3 Hz, 1H), 4.09 (d, *J* = 10.4 Hz, 0.11H), 3.25 (dt, *J* = 10.3, 7.2 Hz, 2H), 3.15 (t, *J* = 14.8 Hz, 1H), 2.59 (dd, *J* = 20.2, 5.3 Hz, 2H), 2.50 (s, 3H), 1.63 (ddd, *J* = 21.5, 15.2, 8.0 Hz, 3H), 1.52 – 1.43 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ 207.0, 192.6, 137.7, 136.9, 135.9, 133.8, 131.3, 128.8, 128.7, 127.6, 126.8, 125.4, 122.1, 55.2, 51.6, 51.2, 45.5, 37.8, 26.2, 24.1, 22.2, 19.9. **FT-IR** (KBr): 2924(s), 1719(s), 1685(s), 1230(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_2^+$ $[M+H]^+$: 358.1802, Found: 358.1800. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (97:3 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 8.3 min, τ_{minor} = 10.3 min), ee 92%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(naphthalen-1-yl)-7-oxooctahydro-1H-indene-4-carbonitrile (4l): Off White sticky compound (23.6 mg, 60%), **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.22 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.64 – 7.60 (m, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 4.90 (dd, *J* = 14.5, 3.2 Hz, 1H), 4.76 (dd, *J* = 13.9, 3.7 Hz, 0.12H), 3.37 – 3.30 (m, 2H), 3.24 (t, *J* = 14.8 Hz, 1H), 2.84 (dd, *J* = 15.1, 3.3 Hz, 1H), 2.62 (ddd, *J* = 8.9, 8.5, 3.9 Hz, 1H), 1.88 (ddd, *J* = 9.6, 6.2, 2.9 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.56 – 1.49 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.0, 192.1, 135.6, 135.3, 134.3, 133.9, 131.3, 129.3, 128.8, 128.8, 128.6, 126.8, 126.1, 125.4, 123.7, 123.1, 122.1, 55.0, 51.7, 51.3, 46.0, 37.3, 26.4, 23.9, 22.2. **FT-IR** (KBr): 2924(s), 1714(s), 1685(s), 1231(m). **HRMS (ESI$^+$):** Calcd. for $C_{27}H_{24}NO_2^+$ $[M+H]^+$:394.1802, Found:394.1789. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (96:4 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 13.2 min, τ_{minor} = 18.1 min), ee 83%.

(3aR,4R,5S,7aS)-4-benzoyl-5-(2,4-dichlorophenyl)-7-oxooctahydro-1H-indene-4-carbonitrile (4m): Off White sticky compound (22.6 mg, 55%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.12 (d, *J* = 7.9 Hz, 2H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 4.50 (dd, *J* = 14.4, 3.4 Hz, 1H), 4.41 (dd, *J* = 14.0, 4.0 Hz, 0.06H), 3.31 – 3.22 (m, 2H), 2.99 (t, *J* = 14.9 Hz, 1H), 2.70 (dd, *J* = 15.4, 3.4 Hz, 1H), 2.53 (dd, *J* = 9.9, 4.1 Hz, 1H), 1.85 – 1.66 (m, 3H), 1.48 – 1.37 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.0, 190.8, 135.8, 135.6, 134.7, 134.4, 133.9, 130.3, 129.1, 129.1, 127.9, 127.4, 121.5, 53.7, 51.2, 50.9, 44.4, 37.7, 26.0, 24.6, 22.4. **FT-IR** (KBr):

2924(s), 1711(s), 1691(s), 1237(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{20}Cl_2NO_2^+$ $[M+H]^+$: 412.0866, Found: 412.0863. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (94:6 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 9.9 min, τ_{major} = 10.6 min), ee 82%.

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-(thiophen-2-yl)octahydro-1H-indene-4-carbonitrile (4n): Off White sticky compound (18.1 mg, 52%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.19 (d, *J* = 5.2 Hz, 1H), 7.12 (d, *J* = 3.4 Hz, 1H), 6.92 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.46 (dd, *J* = 14.4, 3.8 Hz, 1H), 4.20 (dd, *J* = 14.3, 4.0 Hz, 0.16H), 3.30 – 3.21 (m, 2H), 3.19 – 3.11 (m, 1H), 2.82 (dd, *J* = 14.5, 3.7 Hz, 1H), 2.60 – 2.53 (m, 1H), 1.81 – 1.69 (m, 2H), 1.41 – 1.34 (m, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 205.8, 191.9, 141.0, 134.1, 129.0, 129.0, 128.3, 127.0, 126.8, 125.5, 120.6, 57.2, 50.9, 50.8, 45.2, 39.3, 26.2, 23.4, 21.4. **FT-IR** (KBr): 2924(s), 1721(s), 1689(s), 1235(m). **HRMS (ESI$^+$):** Calcd. for $C_{21}H_{20}NO_2S^+$ $[M+H]^+$: 350.1209, Found: 350.1201. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (97:3 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.9 min, τ_{major} = 19.4 min), ee 76%.

(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-styryloctahydro-1H-indene-4-carbonitrile (4o): Off White sticky compound (14.8 mg, 40%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.18 (d, *J* = 7.5 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 – 7.27 (m, 3H), 6.63 (d, *J* = 15.8 Hz, 1H), 6.17 (dd, *J* = 15.8, 7.7 Hz, 1H), 3.83 – 3.76 (m, 1H), 3.73 – 3.68 (m, 0.2H), 3.51 (ddd, *J* = 13.2, 8.9, 4.3 Hz, 0.4H), 3.18 (ddd, *J* = 18.9, 14.2, 7.2 Hz, 2H), 2.96 (t, *J* = 14.2 Hz, 1H), 2.64 – 2.60 (m, 1H), 2.58 – 2.52 (m, 1H), 1.91 – 1.85 (m, 1H), 1.81 (dd, *J* = 12.2, 6.2 Hz, 1H), 1.75 – 1.66 (m, 2H), 1.51 (dd, *J* = 11.8, 7.7 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.8, 191.2, 136.5, 135.1, 134.7, 134.3, 129.1, 129.1, 128.8, 128.2, 126.8, 126.3, 120.2, 51.0, 50.5, 43.1, 41.4, 32.1, 23.3, 22.9, 21.3. **FT-IR** (KBr): 2924(s), 1721(s), 1685(s), 1231(m). **HRMS (ESI$^+$):** Calcd. for $C_{25}H_{24}NO_2^+$ $[M+H]^+$: 370.1802, Found: 370.1808. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (97:3 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} =19.7 min, τ_{minor} = 35.5 min), ee >99%.

(3aR,4R,5S,7aS)-4-(4-methylbenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4p): Off White sticky compound (31.4 mg, 88%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.23 (m, 3H), 4.14 (dd, *J* = 14.7, 3.5 Hz, 1H), 3.85 (dd, *J* = 14.2, 3.9 Hz, 0.06H), 3.35 – 3.28 (m, 2H), 3.20 (dt, *J* = 12.3, 7.1 Hz, 1H), 2.67 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.40 (s, 3H), 1.82 – 1.77 (m, 1H), 1.63 (d, *J* = 6.6 Hz, 1H), 1.57 (d, *J* = 8.5 Hz, 1H), 1.52 – 1.46 (m, 1H), 1.42 (d, *J* = 6.6 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.1, 191.2, 145.1, 138.1, 132.9, 129.5, 129.3, 129.0, 128.6, 128.1, 121.2, 55.4, 51.4, 51.0, 44.5, 43.1, 26.1, 23.4, 21.9, 21.5. **FT-IR** (KBr): 2924(s), 1717(s), 1683(s), 1236(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_2^+$ $[M+H]^+$: 358.1802, Found: 358.1801. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (94:6 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 21.3 min, τ_{major} = 33.5 min), ee 94%.

(3aR,4R,5S,7aS)-4-(4-methoxybenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4q): Off White sticky compound (23.8 mg, 64%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.12 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.85 (s, 3H), 3.32 – 3.26 (m, 2H), 3.18 (dt, *J* = 12.5, 7.1 Hz, 1H), 2.64 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.60 – 2.54 (m, 1H), 1.78 – 1.73 (m, 1H), 1.62 – 1.58 (m, 1H), 1.55 – 1.51 (m, 1H), 1.47 – 1.41 (m, 1H), 1.39 – 1.35 (m, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 207.2, 189.4, 164.2, 138.3, 131.5, 129.3, 128.6, 128.0, 121.4, 114.1, 55.8, 54.8, 51.5, 51.0, 44.60, 43.0, 26.1, 23.4, 21.5. **FT-IR** (KBr): 2924(s), 1716(s), 1686(s), 1259(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_3^+$ $[M+H]^+$: 374.1751, Found: 374.1764. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (92:8 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 26.2 min, τ_{major} = 42.7 min), ee 93%.

(3aR,4R,5S,7aS)-4-(4-chlorobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4r): Off White sticky compound (27.1 mg, 72%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.00 – 7.97 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 16.2, 8.1 Hz, 4H), 7.30 – 7.25 (m, 2H), 4.10 (dd, *J* = 14.7, 3.6 Hz, 1H), 3.85 (dd, *J* = 14.2, 4.0 Hz, 0.05H), 3.31 – 3.22 (m, 2H), 3.19 (dt, *J* = 12.3, 7.2 Hz, 1H), 2.62 (dd, *J* = 14.5, 3.6 Hz, 1H), 2.57 (ddd, *J* = 8.8, 8.3, 3.8 Hz, 1H), 1.77 (ddd, *J* = 12.9, 6.4, 3.1 Hz, 1H), 1.66 – 1.61 (m, 1H), 1.58 – 1.50 (m, 1H), 1.48 – 1.41 (m, 1H), 1.40 (dd, *J* = 11.7, 4.5 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.5, 191.6, 136.5, 135.2, 134.2, 134.1, 130.7, 128.9, 128.8, 120.8, 55.5, 51.2, 51.0, 44.3, 42.5, 26.1, 23.4, 21.4. **FT-IR** (KBr): 2925(s), 1713(s), 1685(s), 1232(m). **HRMS (ESI$^+$):** $C_{23}H_{21}ClNO_2^+$ $[M+H]^+$: 378.1255, Found: 378.1260. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IC column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 19.6 min, τ_{major} = 32.1 min), ee 94%.

(3aR,4R,5S,7aS)-4-(4-bromobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4s): Off White sticky compound (22.7 mg, 54%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.72 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 12.1, 4.7 Hz, 2H), 7.19 (d, *J* = 3.1 Hz, 1H), 4.02 (dd, *J* = 14.6, 3.5 Hz, 1H), 3.74 – 3.71 (m, 0.1H), 3.25 – 3.18 (m, 2H), 3.09 – 3.03 (m, 1H), 2.59 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.55 – 2.47 (m, 1H), 1.75 – 1.67 (m, 1H), 1.58 – 1.53 (m, 1H), 1.44 – 1.37 (m, 1H), 1.33 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.7, 191.3, 137.8, 134.3, 132.2, 130.2, 129.3, 129.2, 128.7, 128.3, 120.9, 55.7, 51.3, 51.0, 44.4, 43.2, 26.2, 23.4, 21.5. **FT-IR** (KBr): 2924(s), 1712(s), 1686(s), 1232(m). **HRMS (ESI^{+}):** Calcd. for $C_{23}H_{21}BrNO_2^{+}$ $[M+H]^{+}$: 422.075, Found: 422.0749. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (94:6 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 16.0 min, τ_{major} = 29.2 min), ee 95%.

(3aR,4R,5S,7aS)-4-(3-chlorobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (4t): Off White sticky compound (24.9 mg, 66%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.81 (t, *J* = 1.8 Hz, 1H), 7.54 (ddd, *J* = 14.1, 7.6, 4.4 Hz, 3H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.35 (dd, *J* = 14.0, 6.8 Hz, 2H), 7.31 – 7.28 (m, 1H), 4.12 (dd, *J* = 14.6, 3.6 Hz, 1H), 3.82 (dd, *J* = 14.2, 3.9 Hz, 0.12H), 3.32 (dd, *J* = 16.7, 11.9 Hz, 2H), 3.17 (dt, *J* = 12.4, 7.1 Hz, 1H), 2.69 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.64 – 2.58 (m, 1H), 1.84 – 1.79 (m, 1H), 1.67 (dd, *J* = 15.6, 4.8 Hz, 1H), 1.62 – 1.57 (m, 1H), 1.55 – 1.48 (m, 1H), 1.43 (dd, *J* = 9.9, 4.5 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 206.7, 191.2, 137.7, 137.1, 135.3, 133.8, 130.1, 129.2, 128.8, 128.4, 126.3, 120.7, 56.0, 51.2, 51.1, 44.4, 43.2, 26.2, 23.4, 21.5. **FT-IR** (KBr): 2924(s), 1715(s), 1692(s), 1227(m). **HRMS (ESI^{+}):** Calcd. for $C_{23}H_{21}ClNO_2^{+}$ $[M+H]^{+}$: 378.1255, Found: 378.1252. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IE column (94:6 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 16.0 min, τ_{major} = 20.4 min), ee 96%.

(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (3a): Off White sticky compound (18.2 mg, 34%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.39 – 7.35 (m, 3H), 7.25 (d, *J* = 6.5 Hz, 2H), 4.28 (dd, *J* = 6.5, 3.2 Hz, 0.16H), 4.19 (dd, *J* = 9.0, 4.5 Hz, 1H), 3.04 (td, *J* = 11.8, 3.9 Hz, 1H), 2.94 (dd, *J* = 16.6, 9.0 Hz, 1H), 2.70 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.43 – 2.38 (m, 1H), 2.29 (td, *J* = 12.2, 3.3 Hz, 1H), 1.94 (dd, *J* = 12.5, 2.0 Hz, 1H), 1.86 – 1.77 (m, 2H), 1.54 (ddd, *J* = 24.9, 12.6, 3.6 Hz, 2H), 1.33 – 1.30 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 210.0, 197.3, 137.9, 137.0, 133.6, 129.1, 129.1, 129.0, 128.8, 128.7, 121.1, 57.0, 47.8, 47.4, 46.3, 41.1, 29.0, 26.9, 26.3, 25.1. **FT-IR** (KBr): 2924(s), 1717(s), 1681(s), 1226(m). **HRMS (ESI^{+}):** Calcd. for $C_{23}H_{24}NO_2^{+}$ $[M+H]^{+}$: 358.1802, Found: 358.1813. The

enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (99:1 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, , τ_{minor} = 36.2 min, τ_{major} = 39.8 min). τ_{minor} = 34.3 min, τ_{major} = 44.4 min), ee 99%.

(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-p-tolyldecahydronaphthalene-1-carbonitrile (3b): Off White sticky compound (13.9 mg, 25%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.15 (dd, *J* = 24.7, 8.1 Hz, 4H), 4.26 (dd, *J* = 6.6, 2.8 Hz, 1H), 4.16 (dd, *J* = 8.5, 4.7 Hz, 1H), 3.05 (td, *J* = 11.8, 3.8 Hz, 1H), 2.90 (dd, *J* = 16.6, 8.6 Hz, 1H), 2.67 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.43 – 2.37 (m, 1H), 2.34 (s, 3H), 2.28 (dd, *J* = 8.6, 5.3 Hz, 1H), 1.95 (dd, *J* = 12.3, 2.1 Hz, 1H), 1.82 (dd, *J* = 18.4, 15.6 Hz, 2H), 1.57 – 1.52 (m, 2H), 1.36-1.30 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 210.2, 197.2, 138.6, 136.9, 134.8, 133.64, 129.8, 129.1, 128.9, 128.7, 121.2, 57.0, 47.8, 47.1, 45.9, 41.2, 29.6, 26.9, 25.2, 22.9, 14.3. **FT-IR** (KBr): 2924(s), 1716(s), 1685(s), 1227(m). **HRMS (ESI$^+$):** Calcd. for $C_{25}H_{26}NO_2^+$ $[M+H]^+$: 372.1958, Found: 372.1962. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (99:1 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 37.8 min, τ_{minor} = 49.2 min), ee 96%.

(1S,2R,4aR,8aS)-1-benzoyl-2-(4-fluorophenyl)-4-oxodecahydronaphthalene-1-carbonitrile (3c): Off White sticky compound (15.7 mg, 28%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.25 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 4.30 (dd, *J* = 6.5, 3.2 Hz, 0.19H), 4.22 (dd, *J* = 9.4, 4.3 Hz, 1H), 3.03 (td, *J* = 11.9, 3.9 Hz, 1H), 2.94 (dd, *J* = 16.6, 9.5 Hz, 1H), 2.71 (d, *J* = 12.3 Hz, 1H), 2.41 (d, *J* = 12.9 Hz, 1H), 2.32 – 2.27 (m, 1H), 1.97 (d, *J* = 12.3 Hz, 1H), 1.87 – 1.81 (m, 2H), 1.57 – 1.52 (m, 2H), 1.44 – 1.39 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.7, 197.2, 137.1, 133.7, 130.8, 130.8, 129.0, 128.8, 124.1, 121.2, 116.2, 116.0, 57.1, 47.6, 47.4, 45.4, 41.2, 29.2, 26.9, 26.2, 25.1. **FT-IR** (KBr): 2924(s), 1716(s), 1680(s), 1227(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{23}FNO_2^+$ $[M+H]^+$: 376.1707, Found: 376.1708. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98.5:1.5 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 26.1 min, τ_{minor} = 40.5 min), ee 96%.

(1S,2R,4aR,8aS)-1-benzoyl-2-(4-bromopphenyl)-4-oxodecahydronaphthalene-1-carbonitrile (3d): Off White sticky compound (14.3 mg, 22%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.44 (m, 4H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.24 (dd, *J* = 6.6, 3.0 Hz, 0.26H), 4.18 (dd, *J* = 9.4, 4.4 Hz, 1H), 3.00 (td, *J* = 11.9, 3.9 Hz, 1H), 2.91 (dd, *J* = 16.7, 9.4 Hz, 1H), 2.67 (dd, *J* = 16.7, 4.4 Hz, 1H), 2.39 (d, *J* = 10.4 Hz, 1H), 2.26 (td, *J* = 12.3, 3.3 Hz, 1H), 1.95 (dd, *J* = 12.5, 2.1 Hz, 1H), 1.82 (t, *J* = 15.5 Hz, 2H), 1.51 (ddd, *J* = 24.8, 12.5, 3.4 Hz, 2H), 1.21 – 1.15 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.6, 196.9, 136.8, 135.0, 133.8, 132.3, 130.7, 129.0, 128.8,

128.7, 123.0, 56.7, 47.6, 47.3, 45.5, 40.9, 26.9, 26.2, 25.0, 22.9. **FT-IR** (KBr): 2924(s), 1716(s), 1685(s), 1227(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{23}BrNO_2^+$ $[M+H]^+$: 436.0907 Found: 436.0905. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 32.1 min, τ_{minor} = 50.0 min), ee 96%.

(1S,2R,4aR,8aS)-1-benzoyl-2-(biphenyl-4-yl)-4-oxodecahydronaphthalene-1-carbonitrile (3e): Off White sticky compound (9.7 mg, 15%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 7.86 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 8.0 Hz, 5H), 7.45 (dd, *J* = 14.0, 7.7 Hz, 5H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.33 (dd, *J* = 6.5, 3.4 Hz, 0.29H), 4.25 (dd, *J* = 8.8, 4.5 Hz, 1H), 3.07 (td, *J* = 11.7, 3.8 Hz, 1H), 2.97 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.73 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.42 (d, *J* = 13.4 Hz, 1H), 2.32 (td, *J* = 12.2, 3.2 Hz, 1H), 1.97 (d, *J* = 12.2 Hz, 1H), 1.82 (dd, *J* = 35.4, 17.0 Hz, 2H), 1.56 – 1.51 (m, 2H), 1.34 – 1.29 (m, 2H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 210.0, 197.2, 141.6, 140.4, 136.9, 136.8, 133.7, 129.5, 129.1, 129.1, 128.8, 127.8, 127.7, 127.3, 121.2, 56.9, 47.8, 47.3, 45.9, 41.2, 26.9, 26.3, 25.1, 22.9. **FT-IR** (KBr): 2925(s), 1715(s), 1685(s), 1225(m). **HRMS (ESI$^+$):** Calcd. for $C_{30}H_{28}NO_2^+$ $[M+H]^+$: 434.2115, Found: 434.2235. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 34.4 min, τ_{minor} = 44.4 min), ee 95%.

(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-m-tolyldecahydronaphthalene-1-carbonitrile (3f): Off White sticky compound (15.6 mg, 28%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 7.82 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 6.0 Hz, 2H), 4.23 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.17 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.05 (td, *J* = 11.9, 3.9 Hz, 1H), 2.95 (dd, *J* = 16.6, 9.1 Hz, 1H), 2.70 (dd, *J* = 16.6, 4.5 Hz, 1H), 2.43 (d, *J* = 16.0 Hz, 1H), 2.36 (s, 3H), 2.34 – 2.28 (m, 1H), 1.97 (dd, *J* = 12.5, 2.0 Hz, 1H), 1.84 (dd, *J* = 17.7, 15.3 Hz, 2H), 1.59 – 1.52 (m, 2H), 1.35-1.30 (m, 2H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 210.1, 197.5, 138.8, 137.8, 137.1, 133.6, 129.8, 129.5, 129.0, 129.0, 128.7, 126.1, 121.2, 57.1, 47.7, 47.4, 46.1, 41.1, 29.0, 27.0, 26.3, 25.2, 21.7. **FT-IR** (KBr): 2923(s), 1713(s), 1684(s), 1225(m). **HRMS (ESI$^+$):** Calcd. for $C_{25}H_{26}NO_2^+$ $[M+H]^+$: 372.1958, Found: 372.1952. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 32.4 min, τ_{minor} = 35.2 min), ee 95%.

(1S,2R,4aR,8aS)-1-benzoyl-2-(3-bromophenyl)-4-oxodecahydronaphthalene-1-carbonitrile (3g): Off White sticky compound (17 mg, 26%), **^{1}H-NMR (400 MHz, CDCl$_3$):** δ 7.81 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.38 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 4.50 (dd, *J* = 8.8, 5.9 Hz, 0.11H), 4.17 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.00 – 2.89 (m, 2H), 2.68 (dd, *J* = 16.7, 4.3 Hz, 1H), 2.39 (d, *J* = 15.5 Hz, 1H), 2.29 (td, *J* = 12.3, 3.4 Hz, 1H), 1.97 (dd, *J* = 12.6, 1.9

Hz, 1H), 1.86 – 1.77 (m, 2H), 1.50 (ddd, *J* = 24.5, 12.4, 3.3 Hz, 2H), 1.39 – 1.33 (m, 2H) **^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.5, 197.1, 140.0, 137.1, 134.8, 133.8, 132.2, 132.0, 130.6, 129.0, 128.8, 127.5, 123.1, 56.8, 47.5, 45.5, 40.8, 29.2, 26.9, 26.2, 25.0, 22.9. **FT-IR** (KBr): 2924(s), 1716(s), 1682(s), 1225(m). **HRMS (ESI^+):** Calcd. for $C_{24}H_{23}BrNO_2^+$ $[M+H]^+$: 436.0907, Found: 436.0908. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 47.2 min, τ_{major} = 57.4 min), ee 95%.

(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-o-tolyldecahydronaphthalene-1-carbonitrile (3h): Off White sticky compound (9.5 mg, 17%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.85 (d, *J* = 7.6 Hz, 1.3H) (minor), 7.63 (d, *J* = 7.5 Hz, 2H) (major), 7.55 (t, *J* = 7.0 Hz, 1.8H) (minor), 7.41 (dt, *J* = 13.5, 6.6 Hz, 3H), 7.31 (dd, *J* = 6.5, 3.4 Hz, 1H) (major), 7.24 (dd, *J* = 9.5, 3.7 Hz, 0.6H) (minor), 7.17 (t, *J* = 7.2 Hz, 1H) (major), 7.13 – 7.10 (m, 1H) (major), 7.01 – 6.97 (m, 0.6H) (minor), 6.87 – 6.83 (m, 0.6H) (minor), 4.45 (dd, *J* = 6.2, 4.3 Hz, 0.6H) (minor), 4.26 (dd, *J* = 9.3, 4.7 Hz, 1H) (major), 3.24 (dd, *J* = 15.3, 6.3 Hz, 0.6H) (minor), 3.05 – 2.99 (m, 1H) (major), 2.99 – 2.96 (m, 0.6H) (minor), 2.93 (dd, *J* = 16.5, 9.4 Hz, 1H) (major), 2.78 – 2.69 (m, 2H), 2.60 (dd, *J* = 19.4, 7.7 Hz, 1H) (minor), 2.46 – 2.34 (m, 3H), 2.22 (s, 3H), 1.97 (d, *J* = 12.7 Hz, 1H), 1.92 (s, 1.8H) (minor), 1.87 – 1.75 (m, 3H), 1.70 (d, *J* = 14.3 Hz, 1H), 1.53 – 1.46 (m, 2H), 1.45 (s, 1H), 1.33 – 1.29 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ 210.4, 208.6, 198.7, 192.94, 137.7, 136.7, 136.6, 136.6, 136.6, 135.8, 133.7, 133.4, 131.4, 131.3, 129.4, 129.1, 129.0, 128.7, 128.6, 128.6, 128.5, 128.2, 126.9, 126.8, 121.2, 56.7, 56.4, 49.4, 48.3, 47.7, 44.2, 43.9, 43.6, 42.4, 41.3, 27.2, 26.3, 26.0, 25.6, 25.2, 22.9, 20.4, 20.3. **FT-IR** (KBr): 2925(s), 1715(s), 1684(s), 1228(m). **HRMS (ESI^+):** Calcd. for $C_{25}H_{26}NO_2^+$ $[M+H]^+$: 372.1958, Found: 372.1967. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (97:3 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 19.7 min, τ_{minor} = 22.0 min), ee 89%.

(1S,2R,4aR,8aS)-1-(4-methylbenzoyl)-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (3i): Off White sticky compound (12.2 mg, 22%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.38 – 7.33 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 4H), 4.27 (dd, *J* = 6.6, 2.9 Hz, 1H), 4.19 (dd, *J* = 8.6, 4.6 Hz, 1H), 3.06 (td, *J* = 11.8, 3.8 Hz, 1H), 2.92 (dd, *J* = 16.6, 8.7 Hz, 1H), 2.68 (dd, *J* = 16.6, 4.6 Hz, 1H), 2.40 (s, 3H), 2.26 (td, *J* = 12.2, 3.2 Hz, 1H), 1.93 (d, *J* = 12.4 Hz, 1H), 1.81 (dd, *J* = 21.6, 15.5 Hz, 2H), 1.55 (dd, *J* = 12.5, 3.4 Hz, 2H), 1.32 – 1.29 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 210.2, 196.5, 141.2, 138.0, 134.2, 129.4, 129.3, 129.1, 129.1, 128.7, 121.7, 56.67, 47.86, 47.2, 46.3, 41.1, 26.9, 26.3, 25.2, 21.9. **FT-IR** (KBr): 2924(s), 1717(s), 1680(s), 1231(m). **HRMS (ESI^+):** Calcd. for $C_{25}H_{26}NO_2^+$ $[M+H]^+$: 372.1958, Found: 372.1956. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 20.9 min, τ_{minor} = 34.4 min), ee 94%.

(1S,2R,4aR,8aS)-1-(4-chlorobenzoyl)-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (3j): Off White sticky compound (15.2 mg, 26%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.98 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.40 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 4.21 (dd, *J* = 6.3, 3.5 Hz, 0.5H), 4.14 (dd, *J* = 9.7, 4.2 Hz, 1H), 2.97 (dd, *J* = 16.7, 9.7 Hz, 1H), 2.70 – 2.67 (m, 1H), 2.39 (d, *J* = 12.6 Hz, 1H), 2.32 – 2.27 (m, 1H), 1.91 (d, *J* = 12.2 Hz, 1H), 1.86 – 1.78 (m, 2H), 1.71 (d, *J* = 14.3 Hz, 1H), 1.52 – 1.45 (m, 2H), 1.32 – 1.29 (m, 2H).**^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.8, 208.3, 193.6, 190.9, 140.8, 139.5, 137.6, 136.9, 135.4, 134.3, 130.6, 130.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.3, 127.9, 121.1, 120.6, 57.2, 56.9, 49.8, 49.61, 47.5, 46.2, 42.9, 42.4, 32.1, 29.6, 27.3, 26.9, 26.2, 25.8, 25.2, 25.1, 22.9. **FT-IR** (KBr): 2924(s), 1716(s), 1686(s), 1221(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{23}ClNO_2^+$ $[M+H]^+$: 392.1412, Found: 392.1416. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 26.5 min, τ_{minor} = 39.4 min), ee 90%.

(1S,2R,4aR,8aS)-1-(4-bromobenzoyl)-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (3k): Off White sticky compound (18.3 mg, 28%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ .90 – 7.86 (m, 1H), 7.60 (ddd, *J* = 21.0, 14.1, 8.7 Hz, 5H), 7.39 – 7.34 (m, 3H), 7.30 (d, *J* = 4.5 Hz, 2H), 7.22 (dd, *J* = 5.7, 1.9 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.4 Hz, 1H), 4.20 (dd, *J* = 6.3, 3.6 Hz, 0.6H), 4.14 (dd, *J* = 9.7, 4.1 Hz, 1H), 3.35 – 3.30 (m, 1H), 3.01 – 2.94 (m, 2H), 2.87 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.68 (dd, *J* = 16.6, 4.1 Hz, 2H), 2.40 (d, *J* = 11.9 Hz, 2H), 2.30 (td, *J* = 12.3, 3.3 Hz, 1H), 1.91 (d, *J* = 13.0 Hz, 2H), 1.86 – 1.75 (m, 4H), 1.75 – 1.65 (m, 2H), 1.48 (dd, *J* = 12.4, 3.4 Hz, 2H), 1.39 – 1.32 (m, 4H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.7, 196.7, 139.5, 137.6, 136.9, 135.8, 132.1, 130.5, 129.2, 129.0, 121.1, 57.3, 49.6, 47.6, 47.5, 46.2, 41.0, 26.9, 26.2, 25.1, 22.9. **FT-IR** (KBr): 2923(s), 1715(s), 1686(s), 1221(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{23}BrNO_2^+$ $[M+H]^+$: 436.1907, Found: 436.1893. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 29.3 min, τ_{minor} = 44.5 min), ee >99%.

(1S,2R,4aR,8aS)-1-(3-chlorobenzoyl)-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (3l): Off White sticky compound (10 mg, 17%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.51 (m, 1H), 7.37 (dd, *J* = 12.1, 7.4 Hz, 4H), 7.25 – 7.21 (m, 2H), 4.14 (dd, *J* = 9.6, 4.3 Hz, 1H), 4.09 (dd, *J* = 14.3, 4.3 Hz, 0.25H), 3.02 – 2.95 (m, 2H), 2.69 (dd, *J* = 16.8, 4.3 Hz, 1H), 2.41 (d, *J* = 13.2 Hz, 1H), 2.31 (td, *J* = 12.3, 3.3 Hz, 1H), 1.93 (d, *J* = 12.3 Hz, 1H), 1.83 (dd, *J* = 15.2, 13.5 Hz, 2H), 1.49 (dd, *J* = 12.4, 3.2 Hz, 2H), 1.38 – 1.33 (m, 2H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 209.7, 197.0, 136.9, 136.3, 134.8, 133.8, 130.7, 130.4, 129.3, 129.1, 129.0, 128.8, 121.1, 56.8, 47.6, 47.3, 45.4, 41.0, 26.8, 26.2, 25.0, 22.9. **FT-IR** (KBr): 2924(s), 1716(s), 1688(s), 1227(m).

HRMS (ESI$^+$): Calcd. for $C_{24}H_{23}ClNO_2^+$ $[M+H]^+$: 392.1412, Found: 392.1415. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (98:2 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 14.5 min, τ_{minor} = 20.9 min), ee 99%.

Compound 6: Light brown sticky solid (12 mg, 54%), **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.19 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.16 – 7.12 (m, 3H), 7.05 (s, 2H), 6.98 – 6.93 (m, 3H), 5.54 (s, 1H), 4.09 (t, *J* = 6.5 Hz, 1H), 3.25 (dd, *J* = 15.3, 8.8 Hz, 1H), 2.55 (dd, *J* = 11.0, 6.6 Hz, 1H), 2.20 (dt, *J* = 16.6, 7.4 Hz, 1H), 1.75 – 1.71 (m, 1H), 1.66 (dd, *J* = 15.5, 7.7 Hz, 2H), 1.60 (dd, *J* = 10.8, 6.1 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 192.2, 145.5, 136.8, 135.2, 134.0, 133.9, 130.8, 130.3, 129.1, 128.8, 128.7, 128.3, 128.2, 124.5, 119.9, 57.6, 49.1, 40.0, 36.9, 30.4, 24.7, 23.1. **FT-IR** (KBr): 2923(s), 1690(s), 1596(m), 1229(m). **HRMS (ESI$^+$):** Calcd. for $C_{29}H_{25}N_4O^+$ $[M+H]^+$: 445.2023, Found: 445.2023. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 47.2 min, τ_{minor} = 76.4 min), ee 96%.

(3aR,4R,5S,7aS)-4-methoxyphenyl 4-cyano-octahydro-7-oxo-5-phenyl-1H-indene-4-carboxy late (7): Off white amorphous solid (12 mg, 60%), **^{1}H NMR (600 MHz, $CDCl_3$):** ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.0 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 8.1, 7.0 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.22 (s, 1H), 3.99 (d, *J* = 11.8 Hz, 1H), 3.83 (s, 3H), 3.69 (dd, *J* = 14.8, 11.9 Hz, 1H), 2.88 (d, *J* = 14.8 Hz, 1H), 2.74 (dd, *J* = 13.1, 7.4 Hz, 1H), 2.15 (dd, *J* = 12.8, 9.3 Hz, 1H), 2.02 (dt, *J* = 11.2, 5.4 Hz, 1H), 1.86 (ddd, *J* = 11.0, 10.3, 5.1 Hz, 2H), 1.72 (ddd, *J* = 18.2, 12.3, 9.2 Hz, 1H), 1.43 (dt, *J* = 8.4, 6.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 189.5, 172.6, 164.2, 139.9, 131.3, 129.4, 128.6, 128.2, 128.0, 121.6, 114.1, 58.3, 55.8, 52.0, 39.4, 38.6, 32.7, 23.2, 19.2. **FT-IR** (KBr): 2923(s), 1735(s), 1678(s), 1247(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{24}NO_4^+$ $[M+H]^+$: 390.17, Found: 390.1705. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 29.5 min, τ_{minor} = 38.4 min), ee 93%.

3.9: Crystal data and structure refinement for chiral compound 3f

Identification code	1
Empirical formula	$C_{23}H_{15}ClNO_2$
Formula weight	372.81
Temperature/K	296K
Space group	P 21
a/Å	10.4670(4)
b/Å	16.0682(6)
c/Å	12.1224(5)
α/°	90.00
β/°	106.760(2)
γ/°	90.00
Volume/Å^3	1952.21(13)
Z	4
ρ_{calc}mg/mm^3	1.268
m/mm^{-1}	0.212
F(000)	772
Crystal size/mm^3	0.13 x 0.21 x 0.16
2Θ range for data collection	1.75 to 28.45°
Index ranges	$-13 \leq h \leq 13$, $-19 \leq k \leq 21$, $-15 \leq l \leq 16$
Reflections collected	9173
Independent reflections	4484 [R(int) = 0.0576]
Data/restraints/parameters	4484/0/257
Goodness-of-fit on F^2	0.777
Final R indexes [I>=2σ (I)]	R_1 = 0.0436, wR_2 = 0.0936
Final R indexes [all data]	R_1 = 0.0961, wR_2 = 0.1067
Flack parameter	-0.01(4)

References:

1. a) A. Moyano, R. Rios, *Chem. Rev*. **2011**, *111*, 4703; b) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* **2010**, *1*, 0001.
2. C. Mannich, K. Handke, K. Roth, *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 2112.
3. a) H. R. Snyder, R. B. Hasbrouck, J. F. Richardson, *J. Am. Chem. Soc.* **1939**, *61*, 3558; b) H. R. Snyder, J. C. Robinson Jr., *J. Am. Chem. Soc.* **1941**, *63*, 3279.
4. A. Terada, K. Murata, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1644.
5. a) W. Oppolzer, W. Fröstl, *Helv. Chim. Acta* **1975**, *58*, 587; b) W. Oppolzer, W. Fröstl, *Helv. Chim. Acta* **1975**, *58*, 590; c) W. Oppolzer, W. Fröstl, *Helv. Chim. Acta* **1975**, *58*, 593; d) W. Oppolzer, E. Flaskamp, *Helv. Chim. Acta* **1977**, *60*, 204; e) W. Oppolzer, *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10; f) W. Oppolzer, L. Bieber, E. Francotte, *Tetrahedron Lett.* **1979**, *20*, 4537.
6. a) L. E. Overman, L. A. Clizbe, *J. Am. Chem. Soc.* **1976**, *98*, 2352; b) L. E. Overman, G. F. Taylor, P. J. Jessup, *Tetrahedron Lett.* **1976**, *17*, 3089; c) L. E. Overman, P. J. Jessup, *Tetrahedron Lett.* **1977**, *18*, 1253; d) L. E. Overman, P. J. Jessup, *J. Am. Chem. Soc.* **1978**, *100*, 5179; e) L. E. Overman, *Acc. Chem. Res.* **1980**, *13*, 218; f) L. E. Overman, C. Fukaya, *J. Am. Chem. Soc.* **1980**, *102*, 1454.
7. a) J. Barluenga, F. Aznar, R. Liz, M.-P. Cabal, *J. Chem. Soc. Chem. Commun.* **1985**, 1375; b) J. Barluenga, F. Aznar, M.-P. Cabal, F. H. Cano, M. de la C. Foces-Foces, *J. Chem. Soc., Chem. Commun.* **1988**, 1247; c) J. Barluenga, F. Aznar, C. Valdés, C. Ribas, *J. Org. Chem.* **1998**, *63*, 3918; d) J. Barluenga, F. Aznar, C. Ribas, C. Valdés, *J. Org. Chem.* **1998**, *63*, 10052.
8. a) S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252; b) Y. Huang, V. H. Rawal, *Org. Lett.* **2000**, *2*, 3321. c) G. Pitacco, A. Risaliti, M. L. Trevisan, E. Valentin, *Tetrahedron* **1977**, *33*, 3145; d) R. A. Ferri, G. Pitacco, E. Valentin, *Tetrahedron* **1978**, *34*, 2537; e) A. Mezzetti, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1985**, *41*, 1415; f) D. Enders, O. Meyer, G. Raabe, *Synthesis* **1992**, 1242.
9. a) A. G. Nigmatov, E. P. Serebryakov, *Russ. Chem. Bull.* **1993**, *42*, 213; b) A. G. Nigmatov, E. P. Serebryakov, *Russ. Chem. Bull.* **1996**, *45*, 623; c) E. P. Serebryakov,

A. G. Nigmatov, M. A. Shcherbakov, M. I. Struchkova, *Russ. Chem. Bull.* **1998**, *47*, 82.

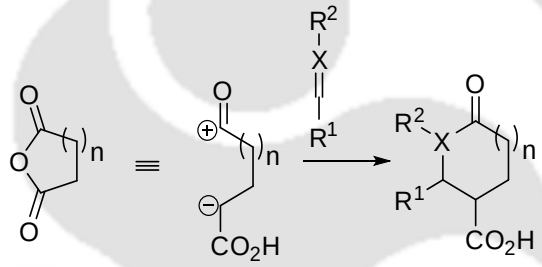
10. a) R. Thayumanavan, D. B. Ramachary, K. Sakthivel, F. Tanaka, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 3817; b) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 6743; c) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Angew. Chem., Int. Ed.* **2003**, *42*, 4233; d) D. B. Ramachary, N. S. Chowdari, C. F. Barbas III, *Synlett* **2003**, 1910; e) D. B. Ramachary, K. Anebouselvy, N. S. Chowdari, C. F. Barbas III, *J. Org. Chem.* **2004**, *69*, 5838; f) D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323.
11. D. B. Ramachary, Y. V. Reddy, *Eur. J. Org. Chem*. **2012**, 865.
12. a) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem., Int. Ed.* **2009**, *48*, 5474; For the same strategy using enamines, see: b) B. Han, J.-L. Li, C. Ma, S.-J. Zhang, Y. C. Chen, *Angew. Chem., Int. Ed*. **2008**, *47*, 9971; c) For the landmark report establishing the potential of transiently generated enamines to engage in inverse electron-demand Diels–Alder reactions, see: K. Juhl, K. A. Jorgensen, *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
13. a) Ł. Albrecht, G. Dickmeiss, F. C. Acosta, C. Rodriguez-Escrich, R. L. Davis, K. A. Jorgensen, *J. Am. Chem. Soc*. **2012**, *134*, 2543; b) G. Talavera, E. Reyes, J. L. Vicario, L. Carrillo, *Angew. Chem., Int. Ed*. **2012**, *51*, 4104.
14. a) G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci.* U. S. A., **2010**, *107*, 20642; b) D. Bastida, Y. Liu, X. Tian, E. Escuder-Ada´n, P. Melchiorre, *Org. Lett*. **2013**, *15*, 220; c) J. Stiller, E. M. Lo´pez, R. P. Herrera, R. Fro¨hlich, C. Strohmann, M. Christmann, *Org. Lett*. **2011**, *13*, 70; d) M. Silvi, C. Cassani, A. Moran, P. Melchiorre, *Helv. Chim. Acta* **2012**, *95*, 1986.
15. a) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2009**, *48*, 7196; b) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.
16. X. Feng, Z. Zhou, R. Zhou, Q-Q. Zhou, L. Dong, Y-C. Chen, *J. Am. Chem. Soc*. **2012**, *134*, 19942.

17. a) K. Nozawa, S. Nakajima, S.-I. Udagawa, K.-I. Kawai, *J. Chem. Soc. Perkin Trans. 1* **1991**, 537; b) M. Tori, K. Nakashima, M. Seike, Y. Asakawa, *Tetrahedron Lett*. **1994**, *35*, 3105; c) M. Tori, K. Nakashima, Y. Asakawa, J. D. Connolly, L. J. Harrison, D. S. Rycroft, J. Singh, N. Woods, *J. Chem. Soc*. *Perkin Trans. 1* **1995**, 593; d) For a review on natural products having decalin motif, see: G. Li, S. Kusari, M. Spiteller, *Nat. Prod. Rep*. **2014**, *31*, 1175; e) For a review on the synthesis of *cis*-decalins, see: V. Singh, S. R. Iyer, S. Pal, *Tetrahedron* **2005**, *61*, 9197.
18. a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, July 29, **1971**; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem*. **1974**, *39*, 1615; c) U. Eder, G. Sauer, R. Wiechert, German Patent DE 2014757, October 7, **1971**; d) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl*. **1971**, *10*, 496; e) K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem., Int. Ed*. **2009**, *48*, 9652; f) J. Hayashi, H. Sekizawa, J. Yamaguchi, H. Gotoh, *J. Org. Chem*. **2007**, *72*, 6493; g) C. L. Chandler, B. List, *J. Am. Chem. Soc*. **2008**, *130*, 6737.
19. Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui, M. Shoji, *J. Am. Chem. Soc*. **2005**, *127*, 16028.
20. a) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2005**, *127*, 11616; b) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem., Int. Ed*. **2008**, *47*, 1450.
21. a) T. Bui, C. F. Barbas III, *Tetrahedron Lett*. **2000**, *41*, 6951; b) P. G. McGarraugh, S. E. Brenner, *Org. Lett*. **2009**, *11*, 5654; c) K. Jiang, Z.-J. Jia, X. Yin, Y.-C. Chen, *Org. Lett*. **2010**, *12*, 2766.
22. S. Rendler, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2010**, *132*, 5027.
23. a) G. Pitacco, A. Risaliti, M. L. Trevisan, E. Valentin, *Tetrahedron* **1977**, *33*, 3145; b) R. A. Ferri, G. Pitacco, E. Valentin, *Tetrahedron* **1978**, *34*, 2537; c) A. Mezzetti, P. Nitti, G. Pitacco, E. Valentin, *Tetrahedron* **1985**, *41*, 1415.
24. Z. Chen, Q. Yan, Z. Liu, Y. Xu and Y. Zhang, *Angew. Chem., Int. Ed*. **2013**, *52*, 13324.
25. CCDC 1546626 contains the crystallographic data of **4f**.
26. For an example of opposite enantiomer formation, see: X. Xu, K. Wang, S. G. Nelson, J. Am. Chem. Soc. **2007**, *129*, 11690

Chapter 4: Organocatalytic Asymmetric Tamura Cycloaddition with α- Branched Nitroolefins

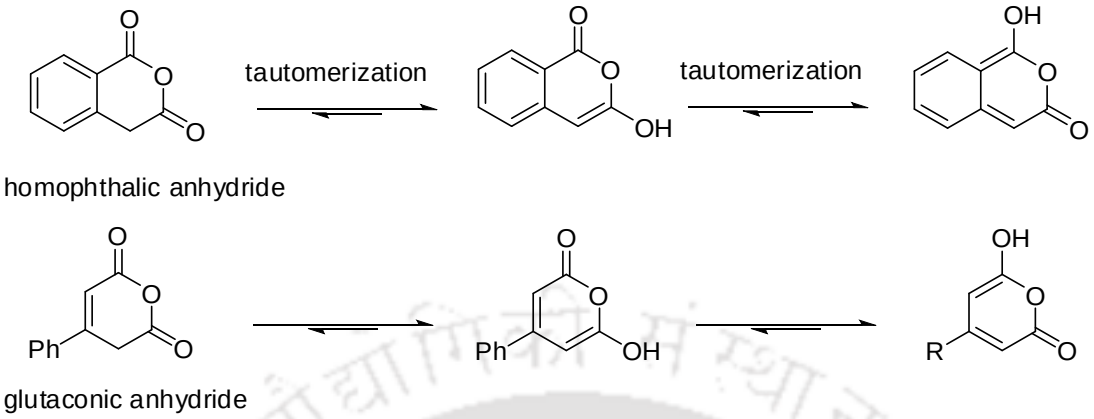
4.1. Introduction:

Anhydrides were previously known to act as mild acylating agents[1] in various transformations. With time, cyclic anhydrides have evolved as the potential substrate for 1,4 dipolar cycloaddition reactions (Scheme 4.1.1).[2]



Scheme 4.1.1: 1,4 dipolar cycloaddition with cyclic anhydrides

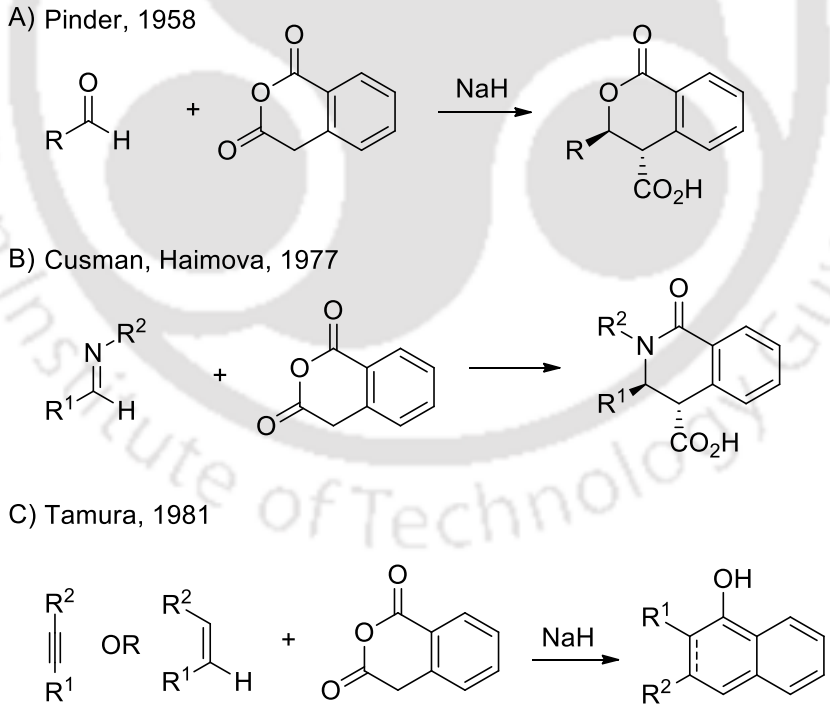
Saturated anhydrides like succinic and glutaric were known to from cycloadducts only at elevated temperatures because of their unstable enol forms. The thermal cycloaddition reaction between imines and non-enolizable succinic anhydrides was first observed by Castagonali in 1969.[3] On the otherhand, the enol form of unsaturated anhydrides like homophthalic and glutaconic anhydride are quite stable due to the conjugation with the phenyl ring or double bond (Scheme 4.1.2). That is why higher temperature is not needed for the desired cycloaddition reaction making these anhydrides suitable substrates for organocatalytic asymmetric reaction.



Scheme 4.1.2: Stabilization of enol form of unsaturated cyclic anhydrides

4.2. Cycloaddition reactions of enolizable anhydrides:

In 1958, Pinder and co-workers synthesized dihydroisocoumarin moiety by condensing homophthalic anhydride and benzaldehyde (Scheme 4.2.A).[4]



Scheme 4.2: First examples of cycloaddition reaction of homophthalic anhydride

Consequently, Cusman[5] and Haimova[6] reported the room temperature cycloaddition reaction between homophthalic anhydride and imines (Scheme 4.2.B).

The cycloaddition reaction between enolizable cyclic anhydrides with activated alkenes and alkynes, i.e Tamura cycloaddition reaction was first developed by Tamura in 1981 (Scheme 4.2.C).[7a] Tamura cycloaddition has found widespread applications in the synthesis of bioactive compounds including natural products and molecules having potential medicinal importance (figure 1).[7b-d]

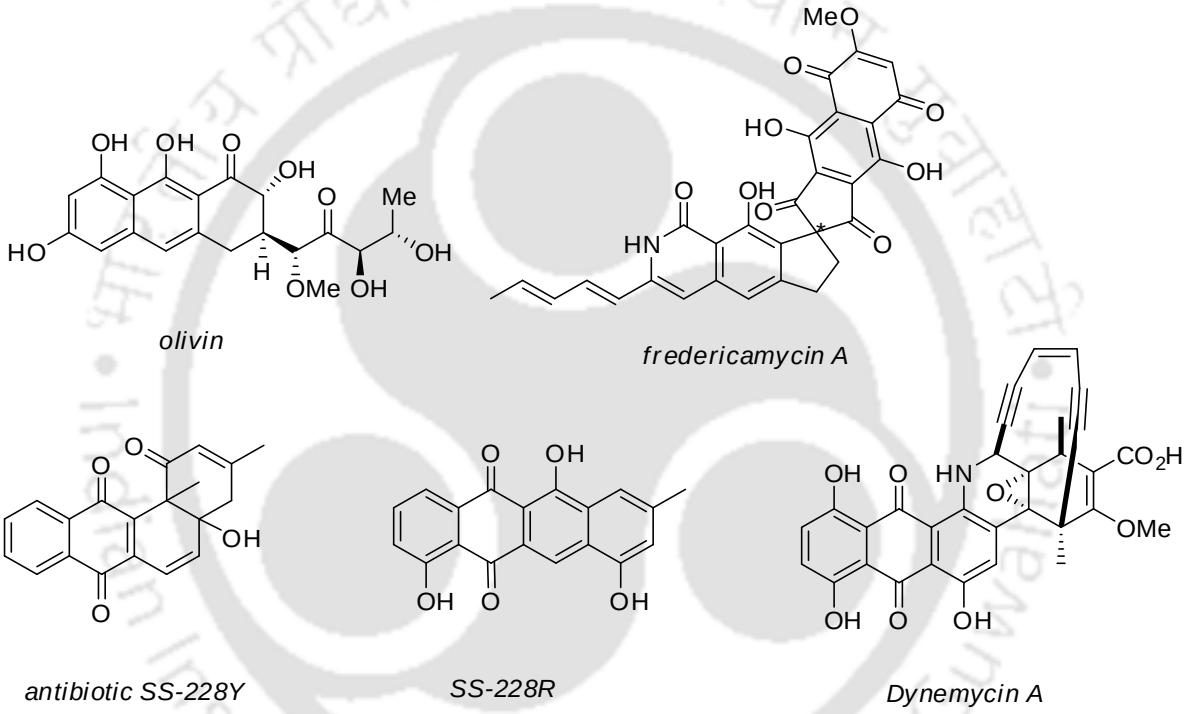
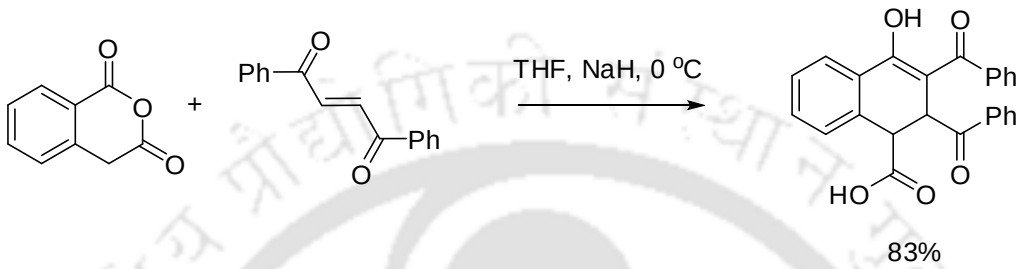


Figure 1: Biologically active molecules synthesized by Tamura cycloaddition reaction

Initially, robust conditions have been used to accomplish the cycloaddition but further research in this area concluded that the usage of stoichiometric amount of base could perform the reaction under milder conditions also.[7c-e,8] There were two difficulties in performing catalytic asymmetric version of Tamura cycloaddition reaction: a) the susceptibility of Tamura cycloaddition products towards aromatization and b) the difficulty associated with the employment of necessary promoters catalytically (as previous methods were reported only with stoichiometric amount of bases).

4.2.1 Tamura cycloaddition without aromatization:

The first cycloaddition reaction without the aromatization step was reported by Tamura and co-workers.[7b] Although the reaction has been carried out in the presence of stoichiometric amount of strong base as it clearly sets the example of generating chiral centers in Tamura cycloaddition (Scheme 4.2.1).

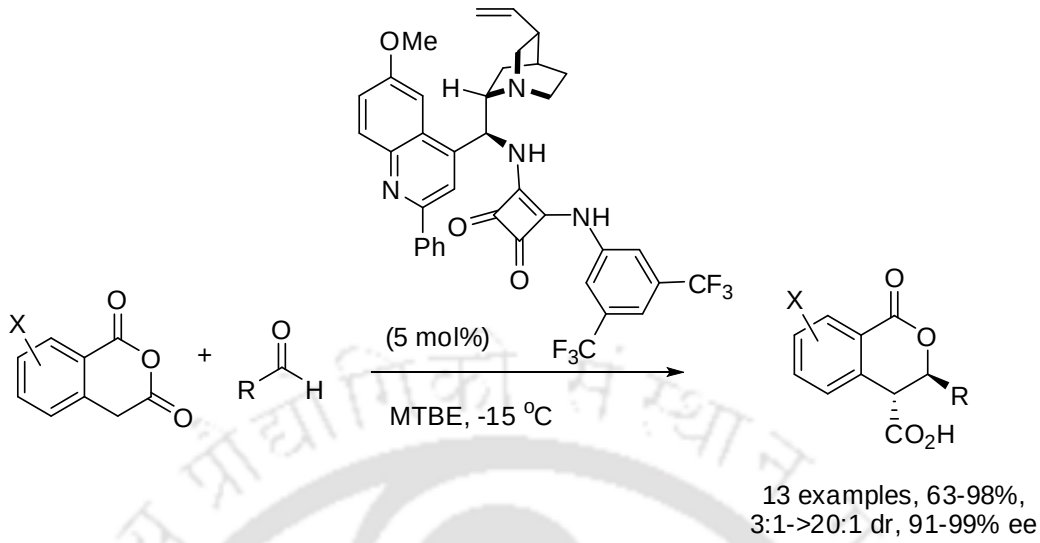


Scheme 4.2.1: Tamura cycloaddition without aromatization

4.2.2. Asymmetric transformations using enolizable anhydrides:

4.2.2.1. With aldehydes and ketones:

The first breakthrough in the organocatalytic asymmetric reaction of enolizable anhydrides was in 2012 by Connon and co-workers (Scheme 4.2.2.1).[9] Cinchona alkaloid derived bifunctional squramide catalysts were employed by them to bring about the activation of homophthalic anhydrides through the equilibrium between the anhydride and its enol form. These type of catalysts have been known to activate anhydrides as electrophiles[10] but the catalytic methodology to convert them into effective nucleophiles have not been known. The strategy enabled the synthesis of a range of stereo-enriched dihydroisocoumarin products using aldehyde and enolizable anhydrides as the reacting partners in Tamura cycloaddition reaction.

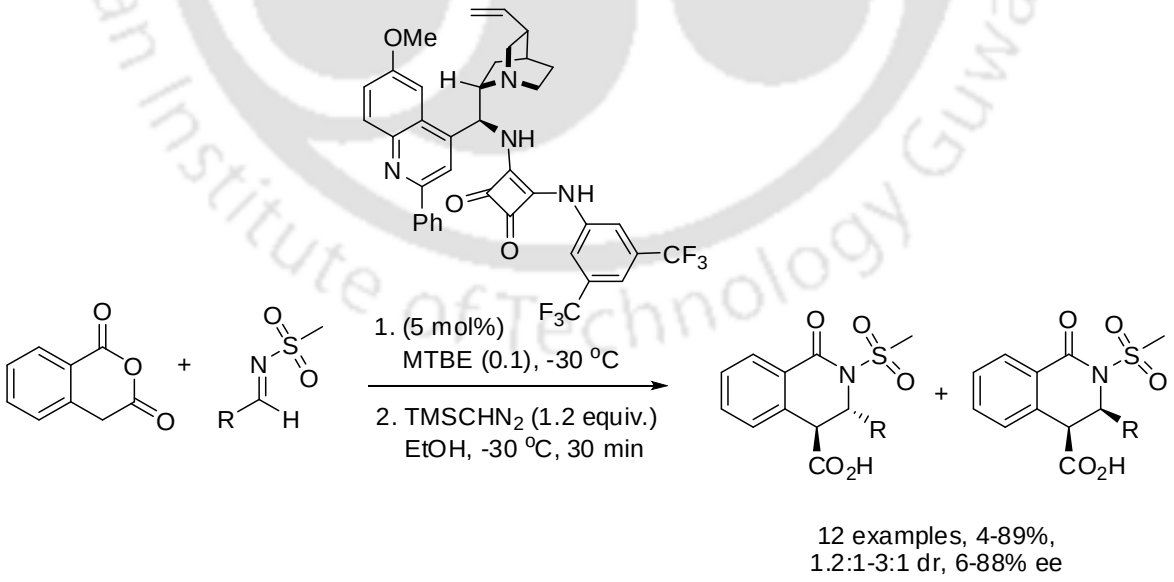


Scheme 4.2.2.1: catalytic asymmetric reaction of enolizable anhydrides and aldehydes

Reaction of aldehydes with enolizable anhydrides other than benzofused anhydrides has also been reported by Connon.[11] The enantioselective reaction of ketones and homophthalic anhydrides have also been documented recently by the same group.[12]

4.2.2.2. With imines:

The first asymmetric cycloaddition reaction between mesyl imine and homophthalic anhydride

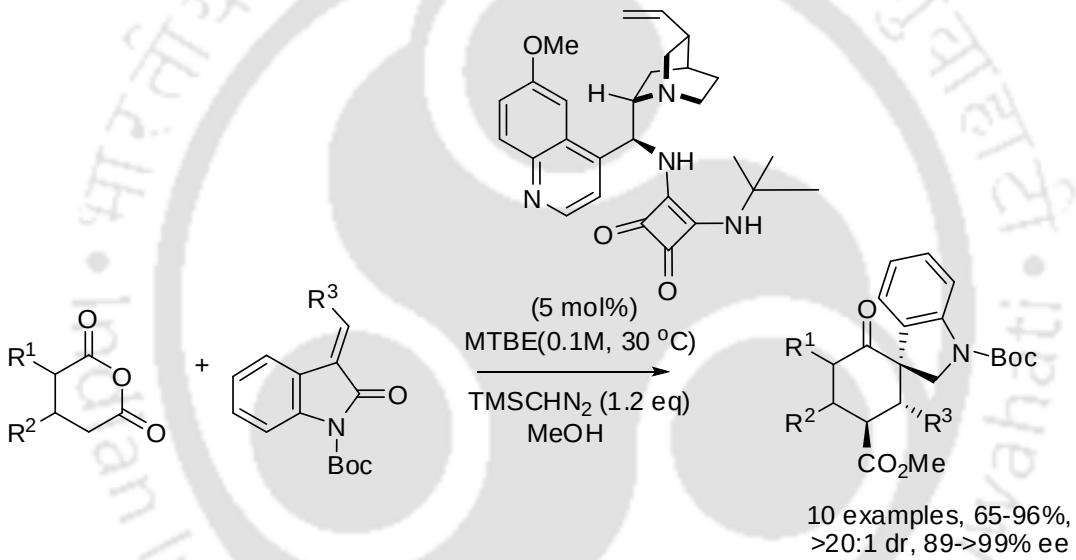


Scheme 4.2.2.2: catalytic asymmetric reaction of enolizable anhydrides and imines

using the same catalyst has been reported recently by Connon *et al.* (Scheme 4.2.2.2).[13] For most of the substrates, the authors obtained the *trans* product as the major diastereomer with moderate to good enantioselectivities.

4.2.2.3. With olefins - Asymmetric Tamura cycloaddition reaction:

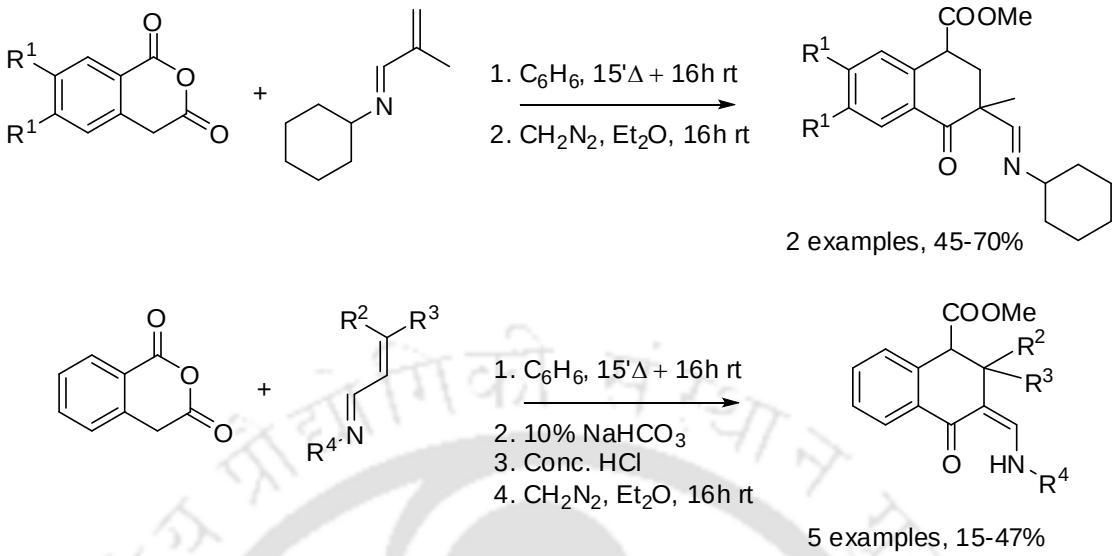
The first asymmetric addition of enolizable anhydrides and olefins activated in both termini was reported by Connon and co-workers in 2014.[14] Doubly activated alkylidene oxindoles were used by them as the reacting partner with homophthalic anhydrides to furnishing highly functionalized spirocyclic Tamura cycloadducts with high diastereoselectivities and good to excellent enantioselectivities (Scheme 4.2.2.3)



Scheme 4.2.2.3: Asymmetric Tamura cycloaddition with doubly activated diene

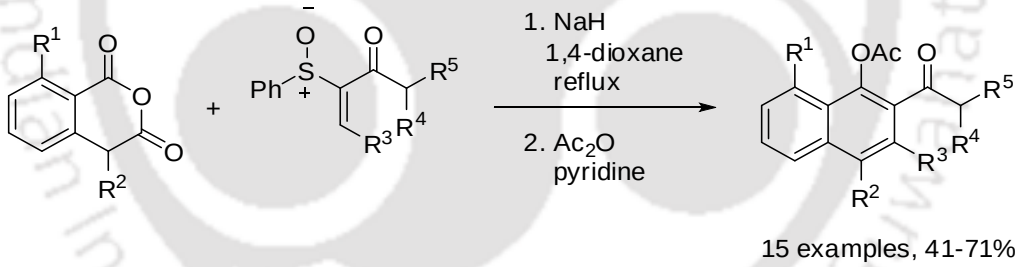
4.2.3. Tamura cycloaddition with monoactivated dienes:

Inspite of having numerous reports on Tamura cycloaddition of doubly activated dieneophiles only few reports using monoactivatead dienophile have been documented. Georgieva and co-workers developed a Tamura cycloaddition reaction between homophthalic anhydride and *α,β*-unsaturated aldimimine and moderate to good results were achieved (Scheme 4.2.3.1).[15]



Scheme 4.2.3.1: Tamura cycloaddition of *α,β*-Unsaturated aldimines

Cycloaddition of homophthalic anhydrides with *α*-sulfinyl-substituted derivatives of enolizable enones has been achieved by Kita *et al.* using sodium hydride as base under reflux condition (Scheme 4.2.3.2).[16]



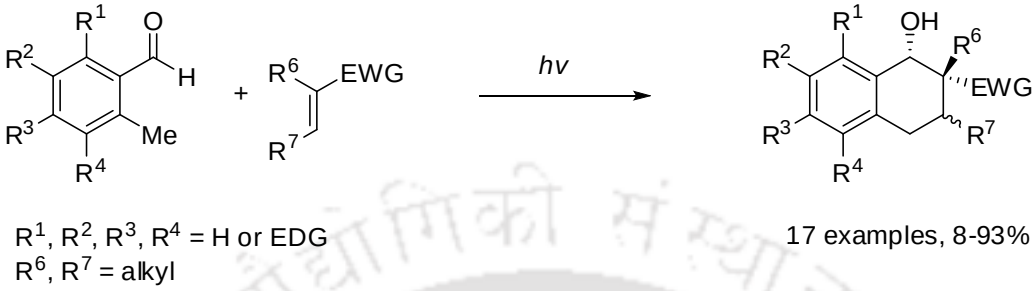
Scheme 4.2.3.2: Tamura cycloaddition of enones

However, the use of singly activated dienophiles in Tamura cycloaddition is still a challenge and in fact methyl acrylate and acrylonitrile were found to be unreactive.[17]

4.3. Methods for the synthesis of *β,γ*-substituted *α*-Tetralones:

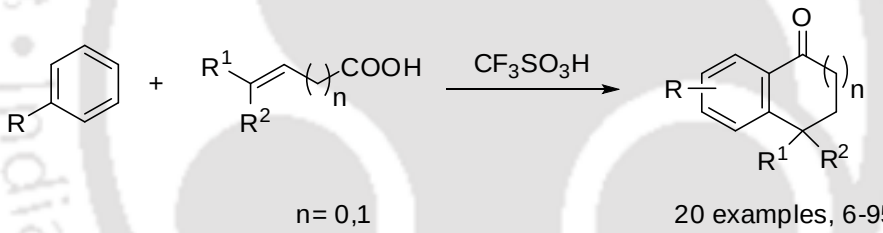
Despite the abundance of *β*-and/or *γ*- substituted 1-tetralone motif in a variety of natural and non-natural compounds,[18] derivatization at the *β*-or *γ*-position of tetralone is difficult as the corresponding enones are unstable and rapidly aromatized.[19] Alternate approaches include Diels-Alder reaction[20] and intramolecular Friedel-Crafts reaction.[21]

Nicolaou *et al.* synthesized *β*-and/or *γ*- substituted *α*-tetralol moieties using Diels-Alder reaction of electron-rich 2-methyl benzaldehydes and various electron deficient olefins (Scheme 4.3.A).[20a]



Scheme 4.3.A: Synthesis of 1-tetralols by Diels-Alder reaction

Olah and co-workers have achieved the synthesis of 1-tetralone derivatives through Friedel–Crafts acylation-alkylation of aromatic moieties with unsaturated carboxylic acids (Scheme 4.3.B).[21c]



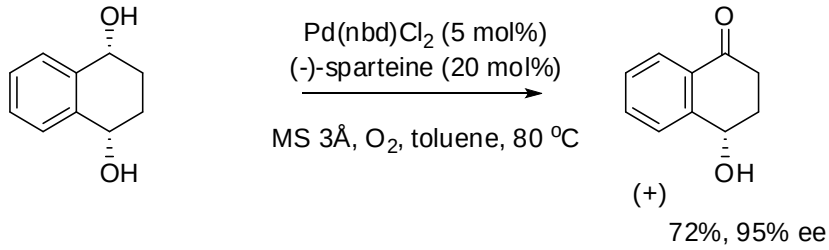
Scheme 4.3.B: Synthesis of 1-tetralones by Friedel–Crafts reaction

4.3.1. Asymmetric synthesis of substituted α-tetralones:

There are very few reports of asymmetric generation of *α*-tetralone moieties. The methods available in this context rely on oxidative kinetic resolution/desymmetrization[22], ring expansion of cyclobutanols[23] and oxidative C-H functionalization.[24]

4.3.1.1. Oxidative kinetic resolution/desymmetrization:

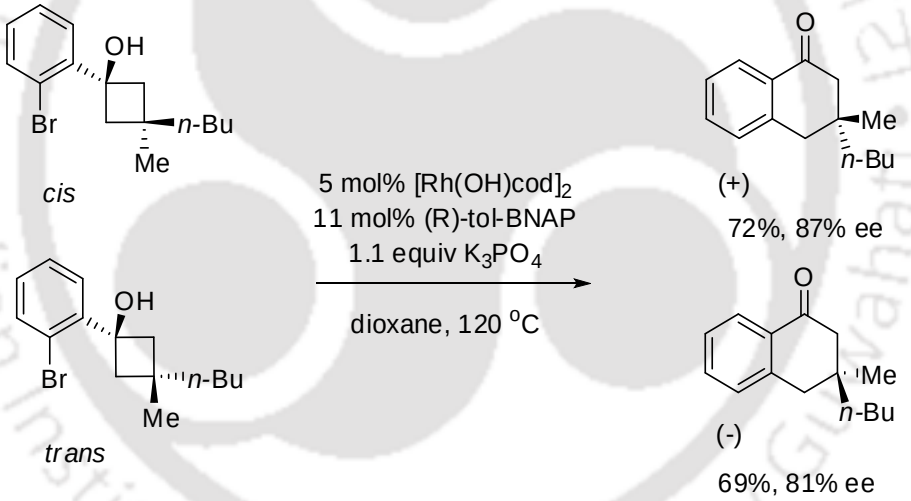
Stoltz and co-workers synthesized 4-hydroxy *α*-tetralone applying palladium-catalyzed oxidative desymmetrization of meso diols.[22] Using naturally occurring diamine (-)-sparteine as a ligand in conjugation with palladium excellent levels of enantio-induction has been achieved by them (Scheme 4.3.1.1).



Scheme 4.3.1.1: Chiral α-tetralones by oxidative kinetic resolution

4.3.1.2. Ring expansion of cyclobutanols:

Ishida *et al.* reported a new technique for the synthesis of α-tetralones by rhodium-catalyzed ring expansion of cyclobutanols. Syntheses of (+) and (-) 3,3-disubstituted α-tetralones with good enantioselectivity have been achieved by them using *cis* and *trans* 1-(2-haloaryl)cyclobutanols respectively (Scheme 4.3.1.2).[23]

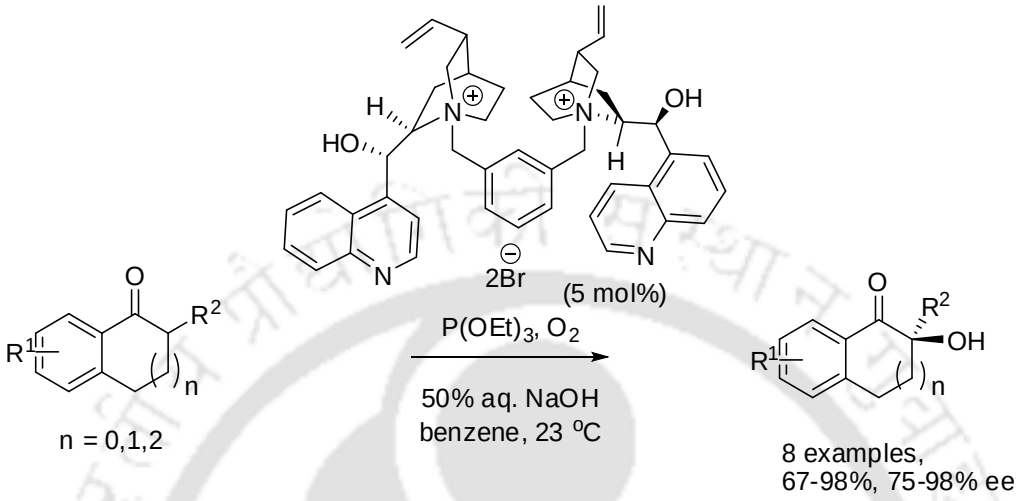


Scheme 4.3.1.2: Chiral α-tetralones by Ring expansion of cyclobutanols

4.3.1.3. Oxidative C-H functionalization:

The most documented syntheses of substituted α-tetralones utilizes oxidative C-H functionalization technique. β or δ-Substituted α-tetralones can be synthesized efficiently using catalytic oxidative C-H functionalization of α-tetralones using metal-ligand catalysts,[24] organocatalysts[25] and enzymes.[26]

Asymmetric phase transfer catalysis has been used by Zhao and co-workers for the synthesis of *β*-substituted *α*-tetralones. Good to excellent enantioselectivities were achieved in this hydroxylation reaction by employing different substituted *α*-tetralones. (Scheme 4.3.1.3).[25b]



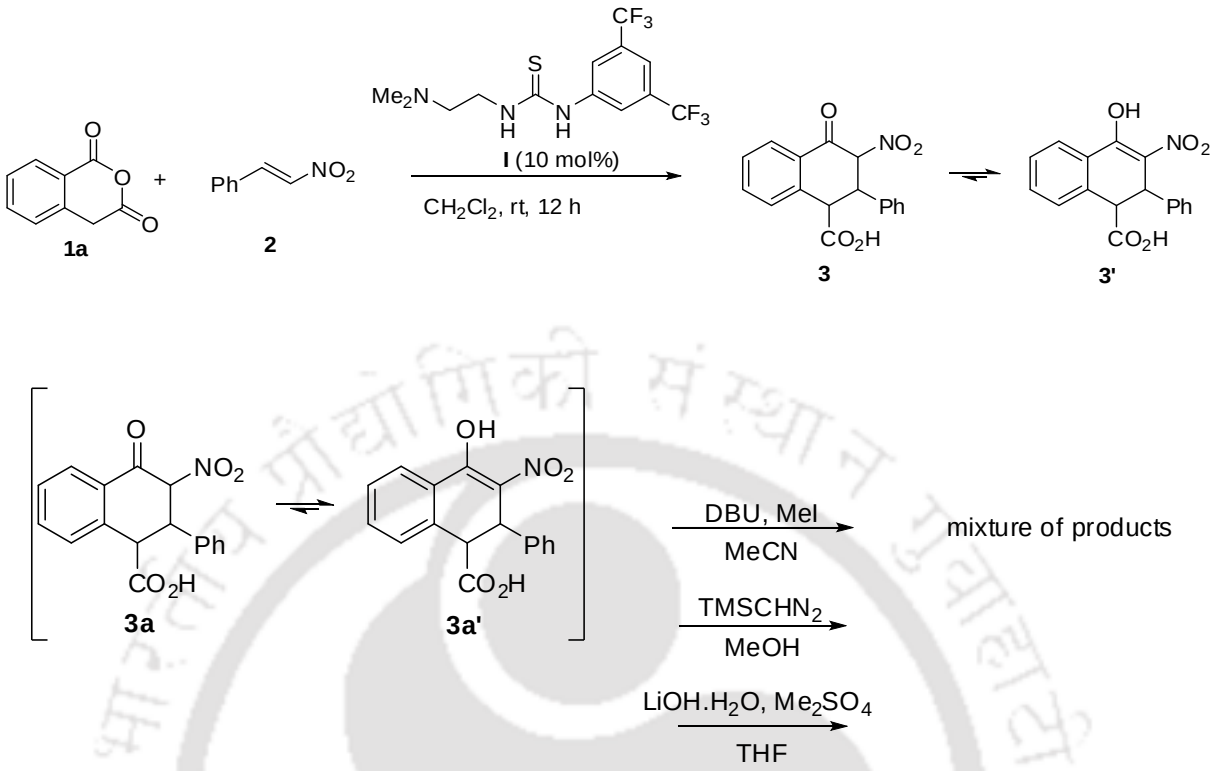
Scheme 4.3.1.3: Synthesis of *α*-tetralones by oxidative C-H functionalization

4.4. Our aim:

The aloofness of monoactivated dienophiles in catalytic asymmetric Tamura cycloaddition reaction has been already mentioned in section 4.2.3. Another captivating fact about this reaction was that it would be able to provide functionalized chiral *α*-tetralone moieties. These assemblage of factors intrigued us upon development of a methodology for catalytic asymmetric Tamura cycloaddition involving monoactivated dienophile.

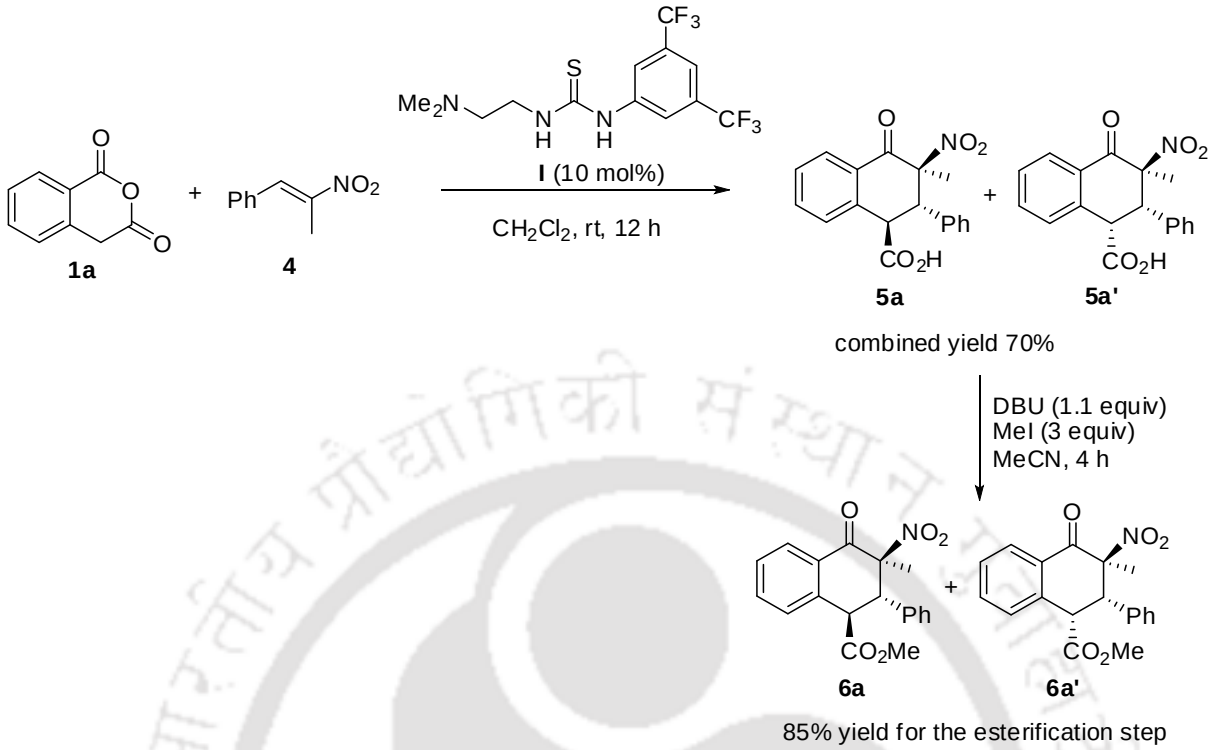
4.5. Result and discussion:

Initially *trans*-*β*-nitrostyrene (**2**) and homophthalic anhydride (**1a**) were chosen as the reacting partner in the presence of racemic tertiary amine thiourea catalyst **I**. The cycloaddition product **3a** was obtained in 65% yield (Scheme 4.5.1). Difficulties arose during esterification of **3a**; a mixture of products were detected due to the presence of acidic hydrogen at the at the *α*-position of the carbonyl group. Both the tautomers **3a** and **3a'** in the presence of either TMS-diazomethane or in DBU/MeI[27] reacted and complex mixture of products were formed. Other esterification techniques were also employed but satisfactory results were not found (Scheme 4.5.1).



Scheme 4.5.1: Reaction with *trans-β*-nitrostyrene

To overcome this problem *trans-β*-Methyl-*β*-nitrostyrene **4a** was used instead of **2**, replacing the forthcoming acidic hydrogen in starting material stage. To our delight the cyclized products 1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxo-2-phenylnaphthalene-1-carboxylic acids (**5a and 5a')** were formed in 70% yield with 1:1 diastereomeric ratio. Upon esterification of **5** with DBU/MeI, the esters **6** were formed in 85% yield (Scheme 4.5.2).



Scheme 4.5.2: Racemic reaction

4.5.1. Optimization of reaction conditions:

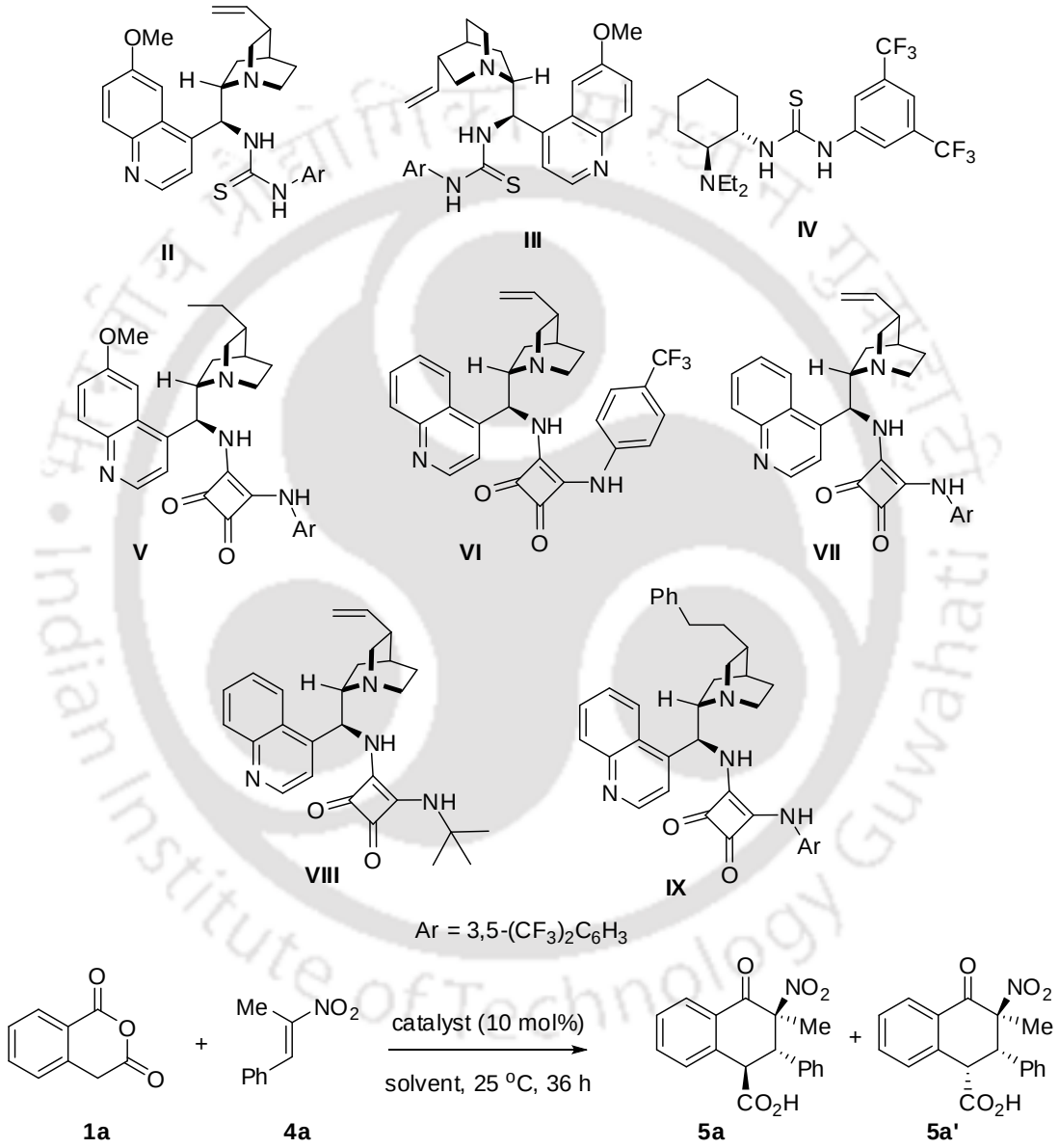
After that the optimization study for the reaction condition was started.

4.5.1.1: Catalyst optimization:

The investigation to find the best chiral catalyst for this reaction was started by screening quinine derived bifunctional thiourea catalyst[28] **II** in toluene. Gratifyingly **5a/5a'** was obtained in 1.5:1 diastereomeric ratio in 72% yield (entry 1, Table 1). The structure of the major diastereomer (*1R, 2S, 3S*) 1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxo-2-phenylnaphthalene-1-carboxylic acid (**5a**) was confirmed unambiguously by X-ray crystallography[29] and the minor diastereomer (*1S, 2S, 3S*) 1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxo-2-phenylnaphthalene-1-carboxylic acid (**5a'**) is epimeric at the carbon attached to the carboxylic acid group. The compound was separated in HPLC after esterification with DBU/CH_3I and the enantiomeric excess (ee) of the major diastereomer was found to be 64% (entry 1). Interestingly, the diastereoselectivity was enhanced to 3:1 in *α,α,α*-trifluorotoluene but ee did not increase (entry

2). This initial screening lead us to continue our catalyst optimization study in *α,α,α*-trifluorotoluene solvent. Quinidine derived thiourea catalyst **III** could not improve the enantioselectivity of this reaction (entry 3).

Table 1: Optimization of catalyst



entry[a]	catalyst	solvent	yield[b] (%)	dr[c] (5a/5a')	ee[d] (%)
1	**II**	toluene	72	1.5:1	64

2	**II**	$PhCF_3$	66	3:1	66
3	**III**	$PhCF_3$	50	3:1	67
4	**IV**	$PhCF_3$	65	2:1	24
5	**V**	$PhCF_3$	80	3:1	74
6	**VI**	$PhCF_3$	75	3:1	80
7	**VII**	$PhCF_3$	85	2.9:1	88
8	**VIII**	$PhCF_3$	84	1.7:1	59

[a]Reaction condition: 0.1 mmol of **1a** with 0.1 mmol of **4a** in 1 ml solvent. [b]Combined yield after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC after converting to methyl ester using CH_3I and DBU.

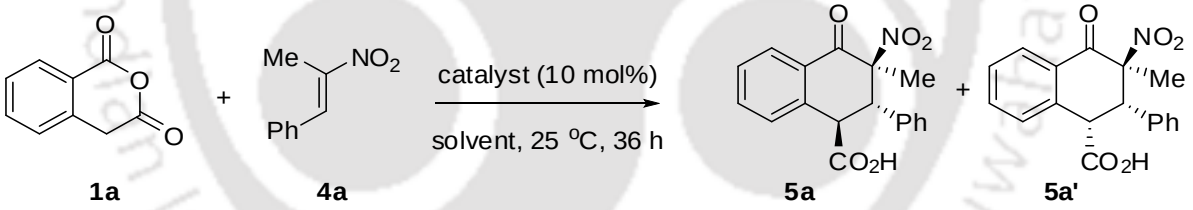
Also *trans*-cyclohexyl diamine based thiourea catalyst **IV** furnished the product with very low stereoselectivity (entry 4). Then the investigation was switched from thiourea to squaramide catalyst motif. A variety of squaramide catalysts[30] were employed for this reaction and the outcome was encouraging for us. Compound **5a** was obtained in 80% combined yield with 74% ee for the major diastereomer using the hydroquinine derived squaramide catalyst **V** (entry 5). The enantioselectivity was further improved to 80% ee with cinchonidine derived squaramide **VI** having *p*-trifluoromethyl phenyl group (entry 6). Then a better catalyst turned out to be cinchonidine derived squramide **VII** which afforded 88% ee for the product **5a** that was obtained in 2.9:1 dr (entry 7). With the hope of getting improved result the bis-trifluoromethyl phenyl moiety of the squaramide catalyst was replaced with a tertiary butyl group (catalyst **VIII**), since same type of catalyst has been used effectively in the reaction with homophthalic anhydride earlier.[14] Unfortunately catalyst **VIII** was not suitable for our reaction (entry 8).

4.5.1.1: Optimization of solvent and additive:

Using catalyst **VII** the solvent optimization for the reaction was started. Employing MTBE as a solvent could not improve the enantioselectivity (Table 1, entry 1) and the

diastereoselectivity also decreased a bit. To our delight, higher enantioselectivity (92% ee) and yield (91%) were observed by switching the solvent to diethyl ether though diastereoselectivity decreased to 2:1 (entry 2). Other ethers were also employed as solvents for the reaction. Diphenyl ether and di-*n*-butyl ether were screened, but for each case selectivity decreased (entries 3-4). Decreasing the concentration of reactants also could not improve the enantioselectivity; moreover the diastereoselectivity got reduced (entry 5). Interestingly, addition of 4Å molecular sieves showed beneficial effect by improving the diastereomeric ratio to 4:1 (entry 6). In an expectation for improvement in enantioselectivity, a new catalyst **IX** was prepared where ethenyl group has been replaced by homobenzyl group.[31] Though a similar enantiomeric ratio (90%) was detected but diastereomeric ratio got reduced to 1.7:1 without MS 4Å (entry 7). Employing catalyst **IX** in presence of MS 4Å enantioselectivity was dropped (entry 8). Nevertheless, we planned to screen both catalysts **VII** and **IX** in the substrate scope as during screening of substrates it was found that catalyst **IX** was beneficial for some cases despite of its poor performance compared to catalyst **VII** for **4a**.

Table 2: Optimization of solvent and additive



entry[a]	catalyst	solvent	yield[b] (%)	dr[c] (5a/5a')	ee[d] (%)
1	**VII**	MTBE	84	2.5:1	88
2	**VII**	Et_2O	91	2:1	92
3	**VII**	Ph_2O	67	1.7:1	90
4	**VII**	$^nBu_2O$	74	1.8:1	85
5[e]	**VII**	Et_2O	89	1.8:1	92

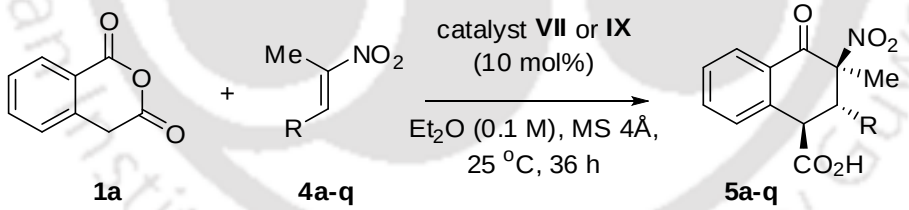
6[f]	**VII**	Et_2O	91	4:1	91
7	**IX**	Et_2O	91	1.7:1	90
8[f]	**IX**	Et_2O	90	4:1	82

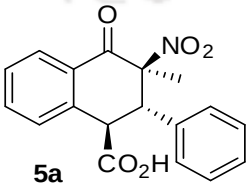
[a]Reaction condition: 0.1 mmol of **1a** with 0.1 mmol of **4a** in 1 ml solvent. [b]Combined yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC after converting to methyl ester using CH_3I and DBU. [e]2 ml solvent was used (0.05 M) [f]With molecular sieves 4Å.

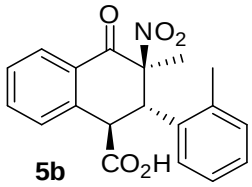
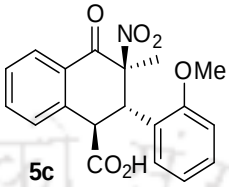
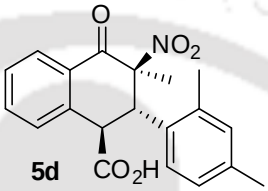
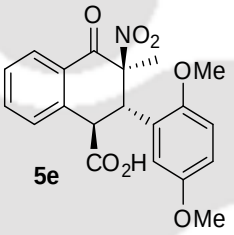
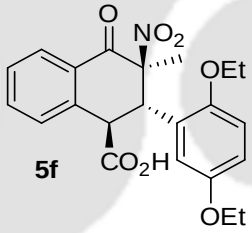
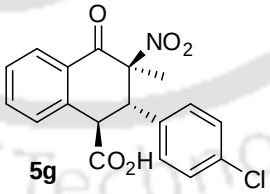
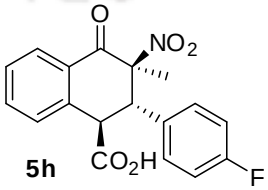
4.5.2. Substrate scope:

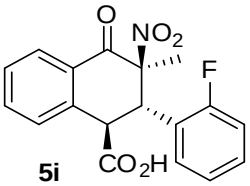
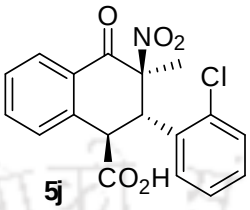
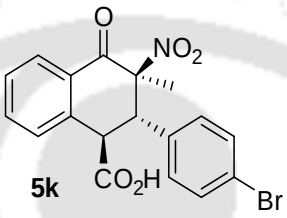
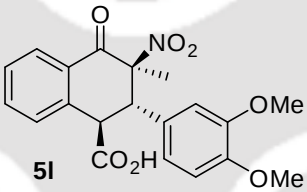
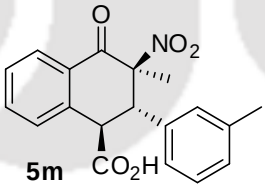
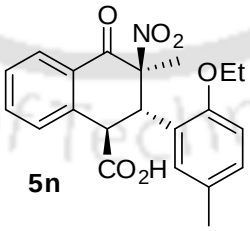
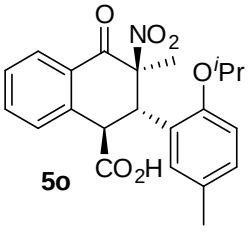
With the optimized conditions in hand, the scope and generality of the reaction was investigated (Table 3). Different electron-rich, neutral, electron-poor and hindered aromatic substituents on the nitrostyrene were studied and good to excellent enantiomeric excesses with high yields and good to high diastereoselectivities were observed (entries 1-15). Aliphatic nitroolefins as well as differently *α*-substituted nitroolefin were also screened and moderate results were obtained. The substrate scope for the reaction also encompass a 7′-methoxy substituted homophthalic anhydride derivative.

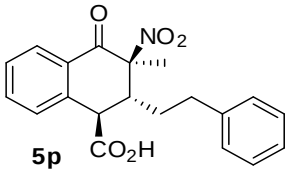
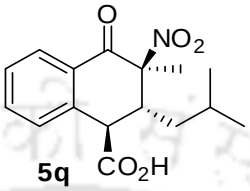
Table 3. Substrate Scope: *α*-methyl nitroolefin



entry[a]	R	catalyst	product	yield[b] (%)	dr[c] (5/5′)	ee[d] (%)
1	Ph	**VII**	 **5a**	91	4:1	91

2[e]	2-MeC$_6$H$_4$	**VII**	 **5b**	92	2:1	97
3	2-OMeC$_6$H$_4$	**VII**	 **5c**	91	2:1	90
4[e]	2,4-(Me)$_2$C$_6$H$_3$	**VII**	 **5d**	90	1.6:1	94
5[e]	2,5-(OMe)$_2$C$_6$H$_3$	**VII**	 **5e**	85	3:1	90
6	2,5-(OEt)$_2$C$_6$H$_3$	**VII**	 **5f**	72	2.6:1	84
7[e]	4-ClC$_6$H$_4$	**IX**	 **5g**	88	2.5:1	92
8[e]	4-FC$_6$H$_4$	**IX**	 **5h**	90	2.2:1	86

9	2-FC_6H_4	**IX**	 **5i**	92	4.5:1	77
10[f]	2-ClC_6H_4	**VII**	 **5j**	79	2:1	76
11[e,f]	4-BrC_6H_4	**VII**	 **5k**	88	2:1	80
12	3,4-$(OMe)_2C_6H_3$	**VII**	 **5l**	89	3:1	76
13	3-MeC_6H_6	**VII**	 **5m**	93	5:1	70
14[e]	2-OEt,5-MeC_6H_3	**VII**	 **5n**	82	2.1:1	84
15[e]	2-O^{i}Pr,5-MeC_6H_3	**VII**	 **5o**	70	2:1	72

16[e,g]	$PhCH_2CH_2$	**VII**	 **5p**	76	3.5:1	62
17[e,g]	^{i}Butyl	**VII**	 **5q**	72	5.5:1	58

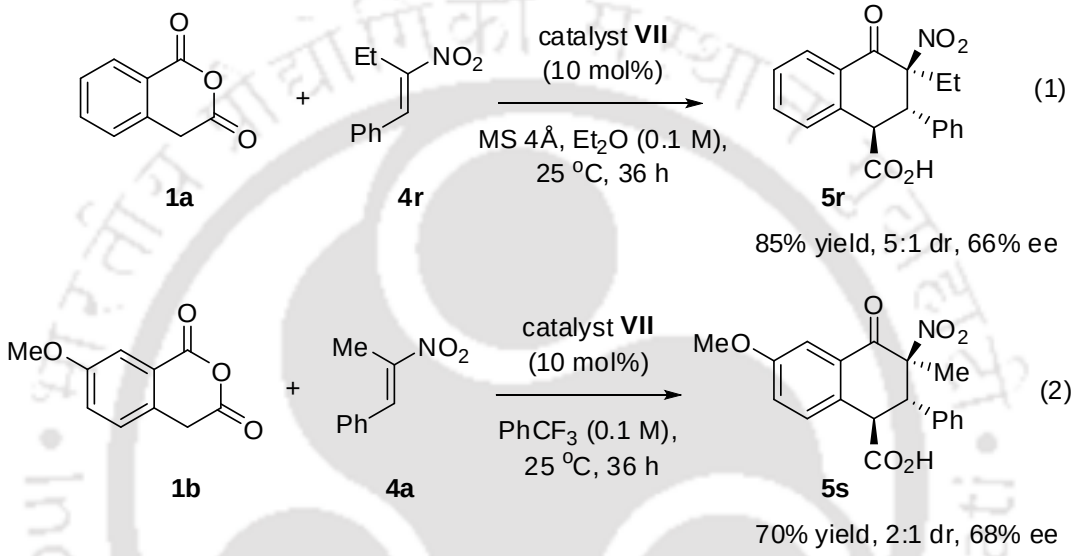
[a]Unless otherwise mentioned, reactions were carried out with 0.15 mmol of **1a** with 0.15 mmol of **4** in 1.5 mL Et_2O with 150 mg molecular sieves 4Å . [b]Combined yield after silica gel column chromatography. [c]Determined by 1H NMR. [d]Determined by chiral HPLC after converting **5** to it's methyl ester using CH_3I and DBU. [e]Without molecular sieves 4Å. [f]$PhCF_3$ as the solvent. [g]Reaction time 2 days.

As mentioned earlier (Section 4.5.1.1), absence of molecular sieves 4Å had positive effects in some substrates, for example nitroolefin **2b** having *o*-tolyl substitution afforded product **5b** in 96% ee and 2:1 diastereomeric ratio without molecular sieves (entry 2), but upon using 4Å MS the enantiomeric excess of product **5b** got reduced to 88% while the diastereoselectivity remained almost similar (2.2:1). On the other hand using molecular sieves, the enantiomeric excess of **5c** got enhanced from 68% to 90% ee (entry 3). An excellent enantiomeric excess of 94% was achieved using nitroolefin **4d** having *m*-xylyl group (entry 4) in the absence of 4Å MS, although the diastereoselectivity was less. Similarly, 2,5-dimethoxyphenyl substituted nitroolefin **2e** afforded product **5e** in 85% yield with 90% ee and 3:1 diastereomeric ratio (entry 5). Gratifyingly, the enantiomeric excess of product **5f** having 2,5-diethoxyphenyl substituent could be increased to 84% ee from 66% ee using MS 4Å (entry 6). Halo substitutions on the aryl group were also tolerated though catalyst **IX** was found to be better in some cases (entries 7-9). For instance, a smooth reaction was observed with *p*-chlorophenyl containing nitroolefin **4g** in the presence of catalyst **IX** providing product **5g** in 2.5:1 diastereomeric ratio with 92%

ee (entry 7) and the enantiomeric excess was less (83%) using molecular sieves. Lower enantiomeric excesses (62%) was observed for *p*-fluoro substitution when catalyst **VII** was used, but luckily higher enantioselectivity (86%) was detected for product **5h** using catalyst **IX** (entry 8). The best result for *o*-fluoro substituted nitrostyrene was achieved with MS 4Å and product **5i** was obtained with 4.5:1 diastereomeric ratio, although the enantioselectivity could not be increased above 77% (entry 9). On the other hand, catalyst **VII** was found to be the best catalyst for substrates **4j** and **4k** having *o*-chloro and *p*-bromo substitutions on the aryl group. A moderate diastereoselectivity (2:1) and enantioselectivity (76%) ware observed for product **5j** (entry 10). Triflurotoluene was found to be the better solvent for nitroolefin **4k**, providing **5k** in high yields (88%) with acceptable enantiomeric excess (80%) and diasteromeric ratio (2:1) (entry 11). With diethyl ether less enantioselectivity (76%) was observed for **4k**. It was found that for 3,4-dimethoxy substituted nitroolefin usage of MS 4Å produced better diastereoselectivity (3:1) and enantioselectivity (76%, wihout MS 4Å 70%) of the product **5l** (entry 12). Then nitroolefin **4m** having *m*-methyl substitution was screened and moderate enantioselectivity (70% ee) was obtained with MS 4Å (entry 13). Interestingly, good diastereomeric ratio (5:1) was achieved in this case (entry 13). Then screening of different nitroolefins having both alkoxy and alkyl substituted aryl groups were started and **4n** and **4o** were prepared. Though product **5n** with 2-ethoxy 5-methyl substitution on aromatic ring was obtained in 84% ee (entry 14), lower enantioselectivity (72%) was attained for product **5o** having an isopropoxy group in place of ethoxy group (entry 15). The reaction condition was also suitable for aliphatic nitroolefins and best results were obtained without molecular sieves (entries 16-17). Thus **4p** and **4q** were prepared and pleasingly the corresponding products **5p** and **5q** were obtained in acceptable yields with moderate enantioselectivities and with a high diastereomeric ratio for **5q** (entry 17).

After that nitroolefin **4r** was prepared where methyl group has been replaced by an ethyl group. Delightfully, the desired major tetralone product **5r** was attained in 5:1 diastereomeric ratio in good yield and moderate enantioselectivity was achieved with MS 4Å (Scheme 4.5.2, eq 1). The next part of substrate scope involved the use of substituted homopthalic anhydrides. Thus different hompthalic anhydrides were prepared and it was found that only 7-methoxy substituted anhydride **1b** could provide major product **5s** in moderate enantioselectivity with

catalyst **VII** (Scheme 4.5.2, eq 2). Nitrooalkene having an ester group at the α-position was also studied but the reaction was unclean. Furthermore, alkenes containing other electron-withdrawing groups like cyano, ester and ketone were also employed in the reaction with homopthalic anhydride. Unfortunately, the desired product either did not form or obtained with very low enantioselectivity. Other aliphatic nitroolefins like having cyclohexyl group did not provide any product.



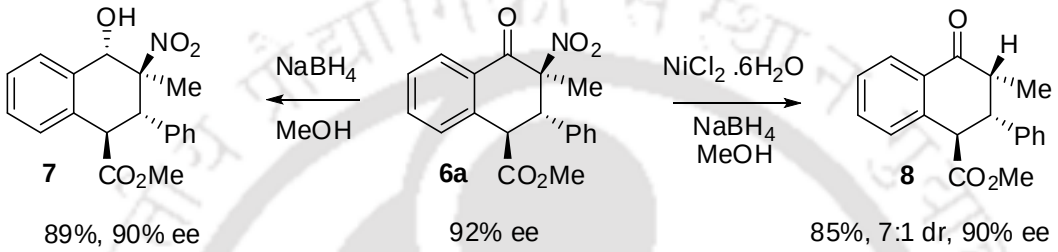
Scheme 4.5.2. Substrate scope: Employment of nitroolefin **4r** and anhydride **1b**

4.5.3. Synthetic transformations of product:

To further demonstrate the utility of our methodology, a few reactions on ester product **6a** were carried out (Scheme 4.5.3). On treatment of **6a** with sodium borohydride, the tetrahydronaphthalene derivative **7** was isolated in 89% yield as a single diastereomer with preservation of enantiopurity. The structure of **7** was determined by 2D NMR studies.

Then the reduction of the nitro group in pure diastereomer **6a** was tried. The reaction of zinc dust and acetic acid with compound **6a** was not clean. Interestingly, when **6a** was reacted with nickel chloride and sodium borohydride, a departure of nitro group was observed and trisubstituted tetralone **8** was obtained in 78% yield with 90% ee and in 7:1 diasteromeric ratio. The structure of the major diastereomer **8** was solved by 2D NMR studies and it was found that the hydrogen came from the same face of the nitro group. Though, a variety of

denitrohydrogenation of α-nitrocarbonyl compounds has been reported previously,[32] only few diastereoselective report[32a] have been documented. To understand the mechanism of the reaction, the reduction reaction in the presence of radical scavengers like TEMPO, BHT were performed. However, the reaction progressed well suggesting a non-radical intermediate. Most likely the nitro group after being converted to amino derivative generates a carbocation at the alpha position to the carbonyl moiety.[33] The hydride ion comes from the less sterically hindered face opposite to that of the bulky phenyl group and thus **8** was formed.



Scheme 4.5.3. Synthetic transformations of methyl ester **6a**.

In summary, this chapter describes a new organocatalytic asymmetric Tamura cycloaddition with nitroolefins to construct highly functionalized 1-tetralone compounds bearing a quaternary center at the α-position. The reaction is catalyzed by easily synthesized chiral squramide catalysts and the tetralone products are attained in moderate to high diastereo- and with good to excellent enantioselectivities. The usefulness of the method has also been shown by converting to a tetrahydronaphthalene derivative and to a trisubstituted tetralone moiety.

4.6. Experimental section:

4.6.1. Preparation of starting meterials:

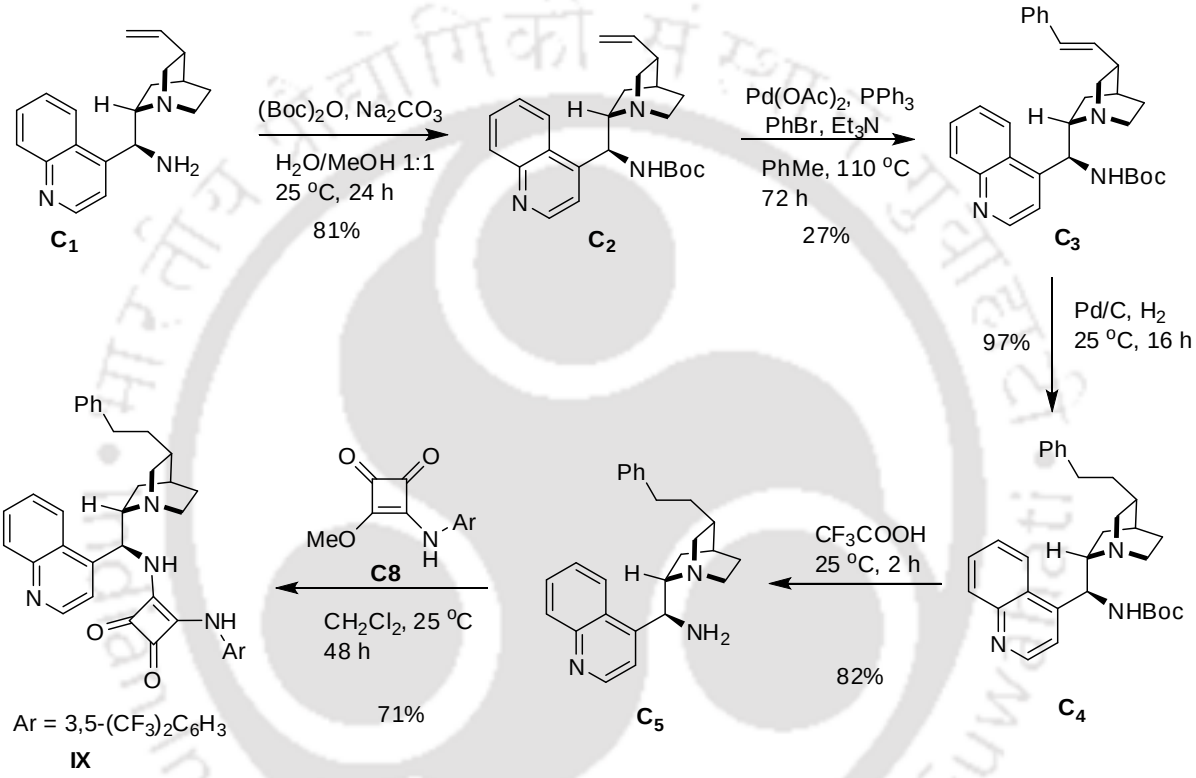
Aromatic nitroolefins **4a-o** and aliphatic nitroolefins **4p-q** were prepared following literature procedures.[34] Homopthalic anhydride derivative **1b** was prepared according to literature procedure.[9]

4.6.2. Catalyst preparation and characterization:

All other catalysts except catalyst **IX** were prepared by following literature procedure.[35]

Synthesis of new catalyst IX:

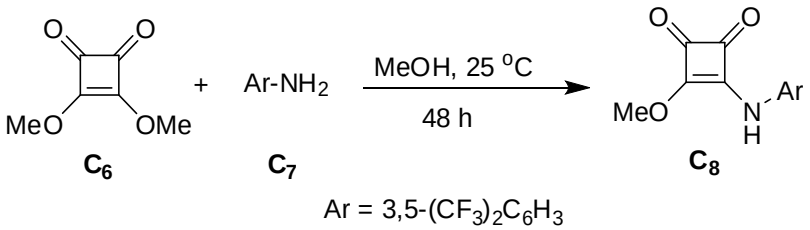
The compounds **C₂-C₅** were prepared from 9-amino(9-deoxy)epicinchonidine **C₁** following previously reported procedure.[31] The characterization data were found to be in accord with the literature values.



Scheme 4.6.2.A: Synthesis of catalyst **IX**

Bis(trifluoromethyl)phenylamino)-4-methoxycyclo but-3-ene-1,2-dione **C₈** was synthesized from 3,4-dimethoxycyclobut-3-ene-1,2-dione **C₆** according to literature procedure (Scheme 4.6.2).[35d]

To a solution of **C₅** (1.0 mmol) in 5 mL dry CH_2Cl_2, **C₈** (1.0 mmol) was added. The reaction mixture was stirred for 48 h at room temperature. Catalyst **IX** was obtained by silica gel column chromatography (100-200 mesh), using 4% methanol in dichloromethane as eluent.



Scheme 4.6.2.B: Synthesis of catalyst **IX**

IX: Off-white solid, (561 mg, 78% yield). **^{1}H NMR (600 MHz, $CDCl_3$):** δ ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.97 (s, 1H), 7.81 – 7.70 (m, 3H), 7.32 (s, 1H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 2H), 3.96 - 3.91 (m, 1H), 3.55 - 3.48 (m, 1H), 3.12 (br s, 1H), 2.99 – 2.94 (m, 1H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.83 (d, *J* = 15.3 Hz, 1H), 1.74 – 1.55 (m, 5H), 1.38 – 1.35 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 184.6, 181.1, 169.2, 164.6, 150.6, 148.8, 141.0, 139.5, 132.7(q, *J* = 32.3 Hz), 132.27, 130.9, 130.2, 126.4, 124.0, 122.2, 118.3, 116.3, 115.3, 114.3, 56.8, 41.5, 35.7, 34.0, 31.8, 29.6, 24.9, 22.9, 14.3. **HRMS (ESI+):** Calcd for $C_{37}H_{33}F_6N_4O_2$ ($[M+H]^+$): 679.2502, Found: 679.2505.

4.6.3. Experimental procedures and structure determinations:

4.6.3.1. General procedure for the catalytic enantioselective Tamura cycloaddition of homopthalic anhydride with α-branched nitroolefins:

In an oven dried round bottomed flask homopthalic anhydride (1 eq), *α*-branched nitroolefin (1 eq) and catalyst **VII** or **IX** (10 mol %) were added under argon. Diethyl ether (or *α,α,α*-trifluorotoluene) (0.1 M) was added to that round bottomed flask via a syringe and it was stirred under argon atmosphere for 36 hours at room temperature. The reaction mixture was diluted with dichloromethane and transferred into a separating funnel, extracted with sodium bicarbonate and the organic layer was discarded. The aqueous layer was acidified with 10% HCL and extracted two times with dichloromethane. The combined organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography using 50% ethyl acetate in hexane as eluent or using 4% methanol in DCM as eluent. The major diastereomer was precipitated in 1:1 hexane in dichloromethane

while the minor stayed in solution. The precipitate was collected and washed with 1:1 hexane in DCM before proceeding for characterization.

For the reaction with 4Å molecular sieves, 100 mg of MS 4Å was added in the reaction vessel for 0.1 mmols of **1a** keeping the other conditions intact.

4.6.3.2. Structure determination of 5a and 5a':

The absolute configuration of the major product 1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxo-2-phenylnaphthalene-1-carboxylic acid (**5a**) was determined by (*1R, 2S, 3S*) by X-ray crystallography (Section 3.7).

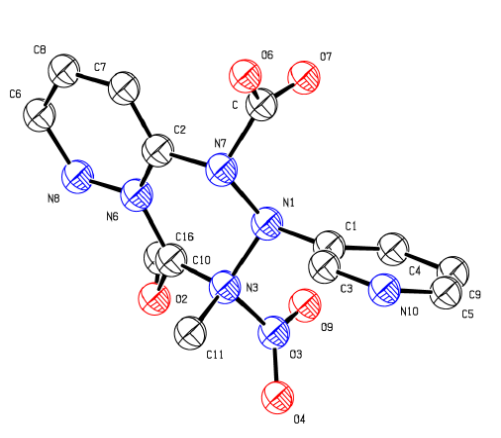
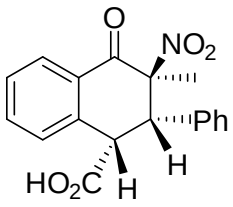


Figure 2: ORTEP diagram of (*1R, 2S, 3S*)-1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxo-2-phenylnaphtha lene-1-carboxylic acid (**5a**)

Structure of minor diastereomer (**5a'**) was determined by comparing the coupling constant values.



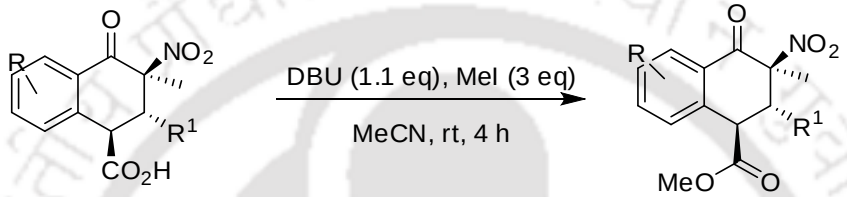
5a'

For the major diastereomer the coupling constant values of hydrogen attached with phenyl and carboxylic acid group (J =12 Hz) shows that those two hydrogen were *trans* to each other. For the minor diastereomer the coupling constant values of those two hydrogen (J = 6 Hz) confirms *cis* orientation.

4.6.3.3. General procedure for esterification of Tamura Cycloadducts:

Esterification of product acids were done using DBU/MeI following previously reported procedure.[27]

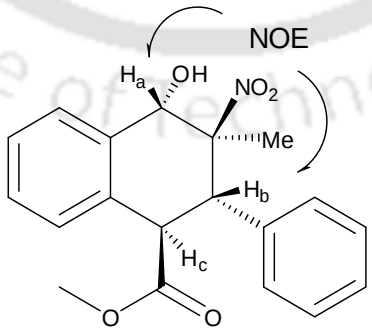
To a solution of compound **5** (1 eq) in dry MeCN in an oven dried round bottomed flask dry DBU (1.1 eq) was added at once. After 10 minutes stirring iodomethane (3 eq) was added dropwise. After 4 hours the methyl ester **6** was obtained by column chromatography or by preparative TLC.



5 **6**

4.6.3.4. Sodium borohydride reduction of compound 6a:

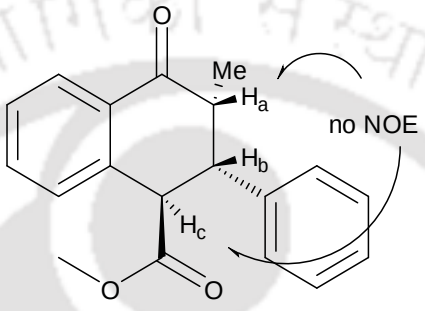
To a solution of the methyl ester **6a** of Tamura cycloadduct **5a** (1 eq) in dry methanol, sodium borohydride (1.05 eq) was added portion wise. After completion of reaction dichloromethane and water were added to the reaction mixture, the organic layer was collected and the aqueous layer was extracted two times with dichloromethane. The combined organic layer was washed with brine and dried over anhydrous sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography to obtain reduced product **7**. Relative structure of compound **7** was determined by using ^{1}H and NOESY experiment.



7

4.6.3.5. Denitrohydrogenation of compound 6a by $NiCl_2.6H_2O$ and $NaBH_4$:

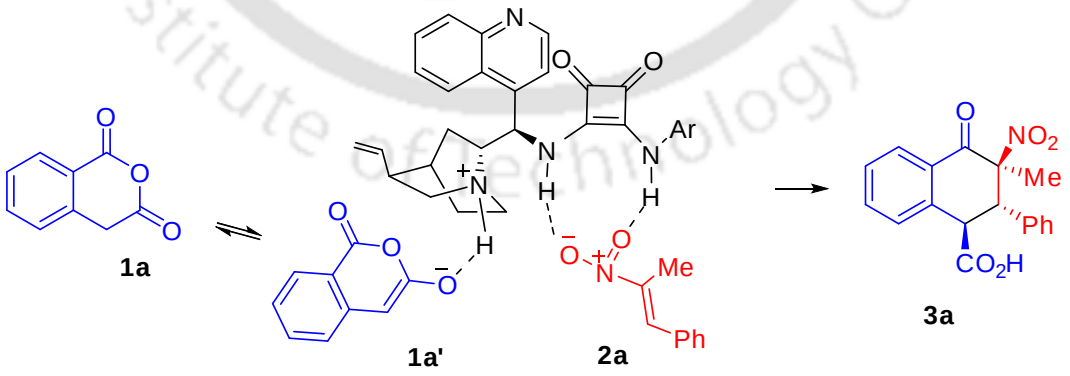
To a solution of compound **6a** (0.1 mmol) and $NiCl_2.6H_2O$ (1.1 eq) in methanol, sodium borohydride was added (12 eq) at 0 ^oC and allowed to stir at room temperature overnight. After complete conversion to a less polar product (monitored by TLC) the reaction mixture was directly subjected to column chromatographic separation. Relative structure of compound **8** was determined by using ^1H and NOESY experiment.



8

4.7. Plausible reaction mechanism:

Based on the absolute configuration a plausible TS has been drawn in Scheme 4.7. It describes that chiral squramide catalyst activates both the compounds, presumably binds with nitroolefin from the *Re* face and the enolate **1a'** binds with the catalyst through hydrogen bonding. Thus the *Si* face of nitroolefin is exposed for the cycloaddition reaction and the desired stereoselectivity was achieved.



Scheme 4.7: Proposed TS

4.8. Characterization data of products:

(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5a): This compound was prepared according to the general procedure. Combined yield 91%. White solid (31 mg, 64 %), **m.p**. 182-183 °C. **^{1}H-NMR (600 MHz, CDCl3):** δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 6.8 Hz, 1H), 7.49 (t, *J* = 6.0 Hz, 2H), 7.25 – 7.32 (m, 5H), 4.78 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 12.2 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** 190.4, 172.7, 139.3, 135.7, 133.5, 129.3, 129.2, 128.8, 128.6, 127.5, 127.5, 97.20, 50.3, 16.1. **FT-IR (KBr):** 1714, 1700, 1548, 1295, 972, 749, 704 cm^{-1}. **HRMS (APCI$^-$):** Calcd. for $C_{18}H_{14}NO_5^-$ ($[M]^-$): 324.0877, Found: 324.0876. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5a** using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.7 min, τ_{major} = 13.7 min), ee 91%.

(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-o-tolyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5b): This compound was prepared according to the general procedure. Combined yield 92%. White solid (26 mg, 52 %), **m.p**. 167-168 °C. **^{1}H-NMR (400 MHz, CD_3OD):** δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 6.0 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.17 (m, 3H), 5.01 (d, *J* = 11.9, 1H), 4.62 (d, *J* = 11.9 Hz, 1H), 2.29 (s, 3H), 1.80 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** δ 192.2, 174.3, 141.8, 139.7, 136.8, 134.1, 132.6, 130.2, 130.1, 130.0, 129.9, 129.5, 128.8, 127.0, 97.7, 51.7, 46.6, 19.7, 17.9. **FT-IR (KBr):** 1719, 1695, 1553, 1383, 1293, 757. **HRMS (APCI$^-$):** Calcd. for $C_{19}H_{16}NO_5^-$ ($[M]^-$): 338.1034, Found: 338.1034. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5b** using Merck OD column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.8 min, τ_{major} = 13.8 min), ee 97%.

(1R,2S,3S)-2-(2-methoxyphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5c): This compound was prepared according to the general procedure. Combined yield 91%. White solid (28 mg, 53 %), **m.p**. 173-144 °C. **^{1}H-NMR (400 MHz, CD_3OD):** 8.15 (d, *J* = 7.9 Hz, 1H), 7.73 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.28 (m, 2H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.94 (s, 1H), 4.97 (m, 2H), 3.76 (s, 3H), 1.70 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 190.8, 173.2, 154.5, 141.9, 135.1, 129.6, 128.9, 128.4, 128.1, 127.2, 124.4, 122.7, 120.0, 111.4, 54.6, 50.9,

16.7. **FT-IR (KBr):** 1718, 1684, 1554, 1298, 757. **HRMS (APCI$^-$):** Calcd. for $C_{19}H_{16}NO_6^-$ ([M]$^-$): 354.0983, Found: 354.0984. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5c** using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, (τ_{minor} = 17.2 min, τ_{major} = 17.9 min), ee 90%.

(1R,2S,3S)-2-(2,4-dimethylphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5d): This compound was prepared according to the general procedure. White solid (47.5 mg, 90%), **m.p**. 174-176 °C. **^{1}H-NMR (400 MHz, CD$_3$OD):** 8.22 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.01 – 6.93 (m, 2H), 5.08 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 2.28 (s, 6H), 1.82 (s, 3H). **^{13}C NMR (100 MHz, CD$_3$OD):** 190.1, 174.3, 138.6, 138.5, 138.4, 135.5, 132.8, 129.7, 129.4, 129.3, 129.2, 128.0, 127.6, 126.9, 95.8, 50.4, 44.7, 21.2, 19.4, 17.6. **FT-IR (KBr):** 1715, 1700, 1548, 1453, 1387, 1295. **HRMS (APCI$^-$):** Calcd. for $C_{20}H_{18}NO_5^-$ ([M]$^-$): 352.1190, Found: 352.1178 The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5d** using Merck Chiralpak OD column (95:5 *n*-Hexane/2PrOH, 0.7 mL/min, 25 °C, 254 nm, , τ_{minor} = 18.26 min, τ_{major} = 19.53 min), ee 94%.

(1R,2S,3S)-2-(2,5-dimethoxyphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5e): This compound was prepared according to the general procedure. Combined yield 85%. Purified by silica gel column chromatography (60-120 mesh, 60% EtOAc in hexane). White solid (33 mg, 57 %), **m.p**. 186-187 °C. **^{1}H-NMR (400 MHz, CD$_3$OD):** δ 8.15 (d, *J* = 7.9 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 6.99 – 6.80 (m, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 1.71 (s, 3H). **^{13}C NMR (100 MHz, CD$_3$OD):** 192.3, 174.6, 154.8, 153.9, 142.1, 136.7, 136.7, 130.4, 129.9, 129.7, 128.7, 115.4, 114.0, 56.7, 56.3, 49.8, 18.3. **FT-IR (KBr):** 1750, 1670, 1551, 1233, 1151. **HRMS (APCI$^-$):** Calcd. for $C_{20}H_{18}NO_7^-$ ([M]$^-$): 384.1089, Found: 384.1077. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5e** using Merck OD column (85:15 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.6 min, τ_{major} = 12.2 min), ee 94%.

(1R,2S,3S)-2-(2,5-diethoxyphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5f): This compound was prepared according to the general procedure. Combined yield 72%. Purified by silica gel column chromatography (60-120 mesh, 60%

EtOAc in hexane). Off white sticky solid (26 mg, 42%), **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 8.20 (d, *J* = 7.9 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 6.77 (br s, 3H), 4.32 (d, *J* = 6.5 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 1H), 3.90 (dd, *J* = 13.8, 6.9 Hz, 4H), 1.75 (s, 3H), 1.37 – 1.32 (m, 6H). **^{13}C NMR (125 MHz, $CDCl_3$):** 190.4, 174.0, 152.7, 151.8, 143.9, 135.4, 129.9, 129.7, 129.5, 128.8, 128.4, 127.8, 127.6, 115.5, 113.4, 64.3, 51.1, 44.5, 22.9, 18.1, 15.0. **FT-IR (KBr):** 1738, 1696, 1556, 1296. **HRMS (APCI$^-$):** Calcd. for $C_{22}H_{22}NO_7^-$ ([M]$^-$): 412.1402, Found: 412.1406. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5f** using Daicel Chiralpak OD column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, *τ*minor = 8.0 min, *τ*major = 10.1 min), ee 84%.

(1R,2S,3S)-2-(4-chlorophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5g): This compound was prepared according to the general procedure. Combined yield 88 %. White solid (28 mg, 52%), **m.p**. 168-170 °C. **^{1}H-NMR (400 MHz, CD_3OD):** δ 8.15 (d, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 6.4 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.11 (t, *J* = 8.5 Hz, 2H), 4.76 (d, *J* = 12.4 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 1.70 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 191.7, 174.1, 141.2, 137.0, 135.9, 134.1, 132.4, 130.1, 130.0, 129.9, 129.8, 128.8, 98.6, 51.5, 49.7, 16.7. **FT-IR (KBr):** 1722, 1700, 1553, 1292, 760. **HRMS (APCI$^-$):** Calcd. for $C_{18}H_{13}ClNO_5$ ([M]$^-$): 358.0488, Found: 358.0479. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5g** using Merck OD column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, *τ*minor = 19.0 min, *τ*major = 21.7 min), ee 92%.

(1R,2S,3S)-2-(4-fluorophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5h): This compound was prepared according to the general procedure. Combined yield 90%. White solid (27 mg, 53%), **m.p**. 167-169 °C. **^{1}H-NMR (400 MHz, CD_3OD:** 8.16 (d, *J* = 8.2 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.37 (q, *J* = 8.7 Hz, 4H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.69 (d, *J* = 12.3 Hz, 1H), 1.70 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 191.8, 174.1, 165.2, 163.6, 141.3, 137.0, 132.8, 132.7, 131.4, 130.1, 129.9, 128.8, 116.7, 116.5, 98.7, 51.4, 50.0, 16.7. **FT-IR (KBr):** 1722, 1708, 1549, 1290, 766. **HRMS (APCI$^-$):** Calcd. for $C_{18}H_{13}FNO_5^-$ ([M]$^-$): 342.0783, Found: 342.0790. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5h** using Merck OD column (88:12 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, *τ*minor = 12.3 min, *τ*major = 16.4 min), ee 86%.

(1R,2S,3S)-2-(2-fluorophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5i): This compound was prepared according to the general procedure. Combined yield 92%. White solid (32 mg, 62%), **m.p**. 165-166 °C. **^{1}H-NMR (400 MHz, CD_3OD:** 8.17 (d, *J* = 6.9 Hz, 1H), 7.75 (s, 1H), 7.53 (m, 3H), 7.38 (s, 1H), 7.21 (s, 1H), 7.12 (t, *J* = 9.2 Hz, 1H), 5.01 (s, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 1.77 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 191.6, 174.0, 163.9, 161.5, 141.4, 136.9, 132.0, 131.9, 130.1, 129.9, 128.7, 125.6, 122.7, 122.6, 117.4, 117.2, 97.9, 49.8, 49.6, 49.5, 49.1, 48.9, 48.7, 48.5, 46.7, 17.6, 17.6. **FT-IR (KBr):** 1721, 1709, 1548, 1289, 970, 768. **HRMS (APCI$^-$):** Calcd. for $C_{18}H_{13}FNO_5$ ($[M]^-$): 342.0783, Found: 342.0788. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5i** using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 8.8 min, τ_{major} = 12.2min), ee 77%.

(1R,2S,3S)-2-(2-chlorophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5j): This compound was prepared according to the general procedure. Combined yield 79%. White solid (24 mg, 45%), **m.p**. 166-167 °C. **^{1}H-NMR (400 MHz, CD_3OD):** 8.17 (d, *J* = 7.9 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.43 – 7.28 (m, 3H), 5.40 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 1.80 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 191.7, 174.0, 141.5, 136.9, 136.8, 133.9, 131.7, 131.7, 131.0, 130.4, 130.0, 129.9, 128.9, 128.1, 96.6, 51.0, 47.2, 18.1. **FT-IR (KBr):** 1721, 1700, 1552, 1291, 759. **HRMS (APCI$^-$):** Calcd. for $C_{18}H_{13}ClNO_5$ ($[M]^-$): 358.0488, Found: 358.0496. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5j** using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.1 min, τ_{major} = 17.3 min), ee 76%.

(1R,2S,3S)-2-(4-bromophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5k): This compound was prepared according to the general procedure. Combined yield 88%. White solid (33 mg, 55%), **m.p**. 172-173 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** 8.20 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.45 (m, 3H), 7.15 (d, *J* = 8.4 Hz, 2H), 4.76 (d, *J* = 12.3 Hz, 1H), 4.48 (d, *J* = 12.2 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** 189.6, 173.6, 138.2, 135.9, 132.5, 132.3, 130.9, 129.7, 129.2, 128.7, 127.4, 123.4, 96.7, 49.7, 48.5, 16.2. **FT-IR (KBr):** 1718, 1700, 1553, 1292, 974,

739. **HRMS (APCI⁻):** Calcd. for $C_{18}H_{13}BrNO_5^-$ ([M]⁻): 401.9983, Found: 401.9974. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5k** using Merck OD column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.8 min, τ_{major} = 19.7 min), ee 80%.

(1R,2S,3S)-2-(3,4-dimethoxyphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphtha lene-1-carboxylic acid (5l): This compound was prepared according to the general procedure. Combined yield 89%. White solid (35 mg, 61%), **m.p**. 186-187 °C. **^{1}H-NMR (400 MHz, CD_3OD):** 8.15 (d, *J* = 7.9 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 6.99 – 6.80 (m, 3H), 5.15 (d, *J* = 11.7, 1H), 4.81 (d, *J* = 11.7, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 1.71 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** 192.1, 174.4, 150.4, 141.6, 136.9, 130.0, 129.9, 128.8, 127.8, 123.4, 114.7, 112.9, 99.0, 56.7, 56.5, 51.8, 49.9, 16.9. **FT-IR (KBr):** 1723, 1694, 1546, 1260, 1016. **HRMS (APCI⁻):** Calcd. for $C_{20}H_{18}NO_7^-$ ([M⁻): 384.1089, Found: 384.1094. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5l** using Merck OD column (94:6 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τminor = 38.3 min, τmajor = 42.6 min), ee 76%.

(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-m-tolyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5m): This compound was prepared according to the general procedure. Combined yield 93%. White solid (37 mg, 73%), **m.p**. 178-179 °C. **^{1}H-NMR (400 MHz, CD_3OD):** δ 8.14 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.55 (m, 2H), 7.23 (t, *J* = 7.1 Hz, 1H), 7.19 – 7.09 (m, 3H), 4.76 (d, *J* = 12.2 Hz, 1H), 4.64 (d, *J* = 12.3 Hz, 1H), 2.32 (s, 3H), 1.69 (s, 3H). **^{13}C NMR (100 MHz, CD_3OD):** δ 192.2, 174.3, 141.8, 139.7, 136.8, 134.1, 132.6, 130.2, 130.1, 130.0, 129.9, 129.5, 128.8, 127.0, 97.7, 51.7, 46.6, 19.7, 17.9. **FT-IR (KBr):** 1706, 1599, 1557, 1293, 974. **HRMS (APCI⁻):** Calcd. for $C_{19}H_{16}NO_5^-$([M⁻): 338.1034, Found: 338.1038. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5m** using Daicel Chiralpak IA column (95:5 *n*-Hexane/2PrOH, 0.6 mL/min, 25 °C, 254 nm, τ_{minor} = 25.0 min, τ_{major} = 26.3 min), ee 70%.

(1R,2S,3S)-2-(2-ethoxy-5-methylphenyl)-1,2,3,4-tetrahydro-3-methyl-3-nitro-4-oxonaphtha lene-1-carboxylic acid (5n): This compound was prepared according to the general procedure. Combined yield 82%. Purified by silica gel column chromatography (60-120 mesh, 60% EtOAc in hexane). Off white sticky solid (26 mg, 45%), **^{1}H-NMR (400 MHz,**

$CDCl_3$): δ 8.22 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 4.63 (d, *J* = 12.4, 1H), 4.10 – 3.86 (m, 3H), 2.23 (s, 3H), 1.75 (s, 3H), 1.39 (t, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.8, 173.9, 157.0, 137.7, 135.4, 134.9, 132.4, 130.6, 129.7, 129.6, 128.7, 127.0, 125.5, 112.3, 104.1, 64.1, 50.1, 49.9, 20.7, 18.0, 14.8. **FT-IR (KBr):** 1723, 1684, 1551, 1312, 1260, 1066, 732. **HRMS (APCI$^-$):** Calcd. for $C_{21}H_{20}NO_6^-$([M$^-$): 382.1296, Found 382.1284. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5n** using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 7.2 min, τ_{major} = 8.1 min), ee 84%.

(1R,2S,3S)-1,2,3,4-tetrahydro-2-(2-isopropoxy-5-methylphenyl)-3-methyl-3-nitro-4-oxo naphthalene-1-carboxylic acid (5o): This compound was prepared according to the general procedure. Combined yield 70%. Purified by silica gel column chromatography (60-120 mesh, 60% EtOAc in hexane). Off white sticky solid (22 mg, 36%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.21 (d, *J* = 7.9 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.41 (d, *J* = 12.4, 1H), 4.63 (d, *J* = 12.4, 1H), 4.50-4.38 (m, 1H), 2.21 (s, 3H), 1.73 (s, 3H), 1.34 (d, *J* = , 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.8, 173.9, 157.0, 137.7, 135.4, 134.9, 132.4, 130.6, 129.7, 129.6, 128.7, 127.0, 125.5, 112.3, 104.1, 64.1, 50.1, 49.9, 20.7, 18.0, 14.8. **FT-IR (KBr):** 1717, 1699, 1556, 1498, 1253, 1113. **HRMS (APCI$^-$):** Calcd. for $C_{22}H_{22}NO_6^-$([M$^-$): 396.1453, Found 396.1445. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5o** using Merck OD column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 7.3 min, τ_{major} = 8.1 min), ee 72%.

(1R,2R,3S)-3-methyl-3-nitro-4-oxo-2-phenethyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5p): This compound was prepared according to the general procedure. Reaction was completed after 48 h. Combined yield 76%. White solid (28 mg, 53%), **m.p**. 152-153 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.07 (d, *J* = 7.1 Hz, 1H), 7.64 (t, 1H), 7.53 – 7.37 (m, 2H), 7.33 – 7.20 (m, 2H), 7.20 – 7.02 (m, 3H), 3.87 (d, *J* = 10.9 Hz, 1H), 3.45 (d, *J* = 12.2 Hz, 1H), 2.66 (dd, *J* = 76.8, 6.3 Hz, 6H), 1.89 – 1.62 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 190.4, 174.1, 141.1, 139.0, 135.5, 128.9, 128.9, 128.7, 128.6, 128.6, 128.3, 128.3, 128.0,

126.3, 96.8, 50.8, 43.5, 34.3, 32.9, 16.0. **FT-IR (KBr):** 1700, 1695, 1557, 1295. **HRMS (APCI$^-$):** Calcd. for $C_{20}H_{18}NO_5$ ([M]$^-$): 352.1190, Found 352.1201. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5p** using Daicel Chiralpak OD column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.3 min, τ_{minor} = 17.8 min), ee 62%.

(1R,2R,3S)-2-isobutyl-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5q): This compound was prepared according to the general procedure. Reaction was completed after 48 h. Combined yield 72%. White solid (26 mg, 57%), **m.p**. 125-127 °C. **^{1}H-NMR (400 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 3.85 (d, *J* = 8.9 Hz, 1H), 3.67 (dd, *J* = 7.8, 5.4 Hz, 1H), 1.69 (s, 1H), 1.47 – 1.41 (m, 1H), 1.21 (t, 6 Hz), 0.88 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 189.9, 177.0, 138.0, 135.4, 129.5, 129.0, 128.9, 128.5, 96.0, 41.4, 39.6, 25.8, 23.6, 21.6, 16.9. **FT-IR (KBr):** 1700, 1695, 1560, 1299. **HRMS (APCI$^-$):** Calcd. for $C_{16}H_{18}NO_5^-$ ([M]$^-$): 304.1190, Found. 304.1183. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5q** using Daicel Chiralpak OD column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 6.8 min, τ_{minor} = 7.3 min), ee 58%.

(1R,2S,3S)-3-ethyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5r): This compound was prepared according to the general procedure. Combined yield 85%. White solid (31 mg, 63%), **m.p**. 171-172 °C. **^{1}H-NMR (400 MHz, CD_3OD):** δ 8.19 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.25 (m, 2H), 4.76 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 2.39 (dt, *J* = 14.5, 7.2 Hz, 1H), 1.94 (dt, *J* = 14.7, 7.3 Hz, 1H), 0.90 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, CD_3OD):** δ 191.1, 172.8, 136.5, 135.8, 131.1, 130.9, 129.7, 129.5, 129.4, 129.2, 102.3, 53.5, 49.8, 23.2, 8.9. **FT-IR (KBr):** 1731, 1684, 1556, 1286, 729. **HRMS (APCI$^-$):** Calcd. for $C_{19}H_{16}NO_5^-$ ([M]$^-$): 338.1034, Found. 338.1026. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5r** using Merck OD column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.0 min, τ_{major} =13.4 min), ee 66%.

(1R,2S,3S)-6-methoxy-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (5s): This compound was prepared according to the general procedure. Combined yield 70%. Off white sticky solid (20 mg, 38%), **^{1}H-NMR (400 MHz, $CDCl_3$):** δ

7.67 (s, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.48 – 7.36 (m, 4H), 7.08 (d, *J* = 8.1 Hz, 1H), 4.70 (d, *J* = 12.5 Hz, 1H), 3.67 (d, *J* = 12.5, 1H), 3.81 (s, 3H), 1.62 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 192.1, 174.7, 153.6, 140.4, 134.8, 134.6, 129.0, 128.9, 127.4, 126.0, 123.9, 112.0, 99.9, 56.8, 51.7, 50.0, 17.0. **FT-IR (KBr):** 1718, 1696, 1554, 1292, 756. **HRMS (APCI$^-$):** Calcd. for $C_{19}H_{16}NO_6^-$ ([M$^-$): 354.0983, Found 354.0977. The enantiomeric ratio was determined by HPLC analysis of methyl ester of **5s** using Merck OD column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 20.4 min, τ_{major} =22.6 min), ee 68%.

(1R,2S,3S,4S)-methyl 1,2,3,4-tetrahydro-4-hydroxy-3-methyl-3-nitro-2-phenylnaphthalene-1-carboxylate (7): Purified by silica gel column chromatography (60-120 mesh, 15% EtOAc in hexane). White solid (30.5 mg, 90%), **m.p**. 208-210 °C. **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.35 – 7.29 (m, 5H), 7.25 (d, *J* = 1.5 Hz, 2H), 5.89 (s, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 11.8 Hz, 1H), 3.57 (s, 3H), 2.62 (s, 1H), 1.49 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** 172.4, 136.5, 134.5, 131.0, 129.2, 129.0, 128.9, 128.6, 128.6, 127.1, 126.6, 96.0, 75.0, 52.8, 50.6, 50.1, 10.8. **FT-IR (KBr):** 3488, 1719, 1547, 1332, 1229, 1066, 752, 708. **HRMS (ESI$^+$):** Calcd. for $C_{19}H_{19}NO_5^+$ ([M+H]$^+$): 341.1263, Found 341.1252. The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (90:10 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 10.5 min, τ_{minor} = 13.4 min), ee 90%.

(1R,2S,3R)-methyl 1,2,3,4-tetrahydro-3-methyl-4-oxo-2-phenylnaphthalene-1-carboxylate (8): Purified by silica gel column chromatography (60-120 mesh, 7% EtOAc in hexane). White sticky solid (26 mg, 89%), **^{1}H-NMR (600 MHz, $CDCl_3$):** δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.32 (m, 3H), 7.17 (d, *J* = 7.8 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 3.70 (s, 0.5H), 3.53 (s, 3H), 3.41(t, *J* = 12.6, 1H), 2.88 (tt, *J* = 17.7, 8.9 Hz, 1H), 1.60 (s, 3H), 1.11 (d, *J* = 7.0 Hz, 0.5H), 1.03 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$):** δ 198.6, 172.9, 140.1, 139.7, 134.1, 131.9, 129.0, 128.1, 127.7, 127.1, 54.2, 52.2, 51.2, 46.8, 29.9, 13.1. **FT-IR (KBr):** 1738, 1675, 1599, 1453, 1156, 968, 771, 707 **HRMS (ESI$^+$):** Calcd. for $C_{19}H_{19}O_3^+$ ([M+H]$^+$): 295.1329, Found 295.1339. The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak

IA column (93:7 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 17.1, τ_{major} = 17.8 min), ee 90%.

4.9. Crystal data and structure refinement for chiral compound (CCDC 1512677) 5a:

Identification code	ud-195
Empirical formula	$C_{20}H_{21}NO_6S$
Formula weight	403.44
Temperature/K	298K
Crystal system	orthorhombic
Space group	'P 21 21 21'
a/Å	20.392(2)
b/Å	10.2856(10)
c/Å	9.7344(15)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	2041.8(4)
Z	4
ρ_{calc}mg/mm^3	1.312
m/mm^{-1}	2.957
F(000)	848.0
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	6516
Independent reflections	3388[R(int) = 0.0576]
Data/restraints/parameters	3388/0/257
Goodness-of-fit on F^2	1.093
Final R indexes [I>=2σ (I)]	R_1 = 0921, wR_2 = 0.1632
Final R indexes [all data]	R_1 = 0.1372, wR_2 = 0.1863
Largest diff. peak/hole / e Å^{-3}	0.51/-0.51
Flack parameter	0.07(11)

References:

1. J. March, *Advanced Organic Chemistry*, 4th ed, Wiley, New York, **1992**.
2. For a review of cyclic anhydrides in formal cycloaddition reactions, see: M. González-López, J. T. Shaw, *Chem. Rev*. **2009**, *109*, 164.
3. N. Castagnoli, Jr., *J. Org. Chem.* **1969**, *34*, 3187.
4. J. B. Jones, A. R. Pinder, *J. Chem. Soc.* **1958**, 2612.
5. M. Cushman, J. Gentry, F. W. Dekow, *J. Org. Chem.* **1977**, *42*, 1111.
6. M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, V. I. Ognyanov, *Tetrahedron* **1977**, *33*, 331.
7. a) Y. Tamura, A. Wada, M. Sasho, Y. Kita, *Tetrahedron Lett*. **1981**, *22*, 4283; b) Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi, Y. Kita, *J. Org. Chem.* **1984**, *49*, 473; c) Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, Y. Kita, *J. Org. Chem*. **1982**, *47*, 4376; d) Y. Kita, R. Okunaka, M. Sasho, M. Taniguchi, T. Honda, Y. Tamura, *Tetrahedron Lett.* **1988**, *29*, 5943; e) Y. Kita, R. Okunaka, T. Honda, M. Shindo, M. Taniguchi, M. Kondo, M. Sasho, *J. Org. Chem.* **1991**, *56*, 119.
8. a) Y. Kita, S.-I. Mohri, T. Tsugoshi, H. Maeda, Y. Tamura, *Chem. Pharm. Bull.* **1985**, *33*, 4723; b) For an example of the reaction of homophthalic anhydrides with an alkyne in the presence of catalytic NEt_3, see: F. T. Smith, R. V. Atigadda, *J. Heterocycl. Chem*. **1991**, *28*, 1813.
9. C. Cornaggia, F. Manoni, E. Torrente, S. Tallon, S. J. Connon, *Org. Lett*. **2012**, *14*, 1850.
10. a) A. Peschiulli, Y. Gun'ko, S. J. Connon, *J. Org. Chem*. **2008**, *73*, 2454; b) A. Peschiulli, C. Quigley, S. Tallon, Y. Gun'ko, S. J. Connon, *J. Org. Chem*. **2008**, *73*, 6409; c) A. Peschiulli, B. Procuranti, C. J. O' Connor, S. J. Connon, *Nat. Chem*. **2010**, *2*, 380.
11. F. Manoni, C. Cornaggia, J. Murray, S. Tallon, S. J. Connon, *Chem. Commun.* **2012**, *48*, 6502.
12. C. Cornaggia, S. Gundela, F. Manoni, N. Gopalasetty, S. J. Connon, *Org. Biomol. Chem*. **2016**, *14*, 3040.

13. S. A. Cronin, A. G. Collar, S. Gundela, C. Cornaggia, E. Torrente, F. Manoni, A. Botte, B. Twamley, S. J. Connon, *Org. Biomol. Chem*. **2016**, *14*, 6955.
14. F. Manoni, S. J. Connon, *Angew. Chem., Int. Ed*. **2014**, *53*, 2628.
15. a) A. Georgieva, E. Stanoeva, S. Spassov, M. Haimova, N. De Kimpe, M. Boeleus, M. Keppens, A. Kemme, A. Mishnev, *Tetrahedron* **1995**, *51*, 6099; b) A. Georgieva, S. Spassov, E. Stanoeva, I. Topalova, C. Tchanev, *J. Chem. Res. Synop*. **1997**,148.
16. K. Iio, N. G. Ramesh, A. Okajima, K. Higuchi, H. Fujioka, S. Akai, Y. Kita, *J. Org. Chem*. **2000**, *65*, 89.
17. G.-D. Roiban, R. Agudo, A. Ilie, R. Lonsdale, M. T. Reetz, *Chem. Commun*. **2014**, *50*, 14310.
18. Representative natural products having *β*- and/or *γ*-substituted 1-tetralone core: a) K. W. Wang, J. S. Mao, Y. P. Tai, Y. J. Pan, *Bioorg. Med. Chem. Lett*. **2006**, *16*, 2274; b) J. P. Cueva, A. G. Godoy, J. I. Juncosa, P. A. Vidi, M. A. Lill, V. J. Watts, D. E. Nichols, *J. Med. Chem*. **2011**, *54*, 5508; c) K. P. Devkota, D. Covell, T. Ransom, J. B. McMahon, J. A. Beutler, *J. Nat. Prod*. **2013**, *76*, 710; d) M. Izawa, S. Kimata, A. Maeda, T. Kawasaki, Y. Hayakawa, *J. Antibiot*. **2014**, *67*, 159.
19. a) A. C. Vargass, I. P. Martin, B. Q. Sire, S. Z. Zard, *Org. Biomol. Chem*. **2004**, *2*, 3018; b) T. F. Yang, K. Y. Wang, H. W. Li, Y. C. Tseng, T. C. Lien, *Tetrahedron Lett*. **2012**, *53*, 585.
20. For selected examples, see: a) K. C. Nicolaou, D. L. Gray, J. Tae, *J. Am. Chem. Soc*. **2004**, *126*, 613; b) C. P. Ting, T. J. Maimone, *Angew. Chem., Int. Ed.* **2014**, *53*, 3115.
21. For selected recent examples, see: a) B. Pita, C. F. Masaguer, E. Ravian, *Tetrahedron Lett.* **2002**, *43*, 7929; b) D. M. Cui, M. Kawamura, S. Shimada, T. Hayashi, M. Tanaka, *Tetrahedron Lett*. **2003**, *44*, 4007; c) G. K. S. Prakash, P. Yan, B. Torok, G.A. Olah, *Catal. Lett*. **2003**, *87*, 109; d) L. Zhang, S.A. Kozmin, *J. Am. Chem. Soc*. **2004**, *126*, 10204; e) E. Fillion, D. Fishlock, A. Wilsily, J. M. Goll, *J. Org. Chem*. **2005**, *70*, 1316.
22. a) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc*. **2001**, *123*, 7725; b) M. Odagi, K. Furukori, Y. Yamamoto, M. Sato, K. Iida, M. Yamanaka, K. Nagasawa, *J. Am. Chem. Soc*. **2015**, *137*, 1909.

23. N. Ishida, S. Sawano, M. Murakami, *Chem. Commun*. **2012**, *48*, 1973.

24. a) K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa, S. Iwasa, *J. Am. Chem. Soc*. **2012**, *134*, 9836; b) C. Yin, W. Cao, L. Lin, X. Liu, X. Feng, *Adv. Synth. Catal*. **2013**, *355*, 1924.

25. a) M. Odagi, K. Furukori, T. Watanabe, K. Nagasawa, *Chem. Eur. J*. **2013**, *19*, 16740; b) S.-B. Derek Sim, M. Wang, Y. Zhao, *ACS Catal*. **2015**, *5*, 3609.

26. G.-D. Roiban, R. Agudo, A. Ilie, R. Lonsdale, M. T. Reetz, *Chem. Commun*. **2014**, *50*, 14310.

27. D. Mal, A. Jana, S. Ray, S. Bhattacharya, A. Patra, S. R. De, *Synth. Commun*. **2008**, *38*, 3937.

28. For selected recent reviews, see: a) W. –Y. Sian, J. Wang, *Catal. Sci. Technol*. **2011**, *1*, 1298; b) S. J. Connon, *Chem. Commun*. **2008**, 2499.

29. CCDC 1512677 contains the crystallographic data for **3a.**

30. a) J. Malerich, K. Hagihara, V. Rawal, *J. Am. Chem. Soc*. **2008**, *130*, 14416. For reviews, see: b) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J*. **2011**, *17*, 6890; c) P. Chauhan, S. Mahajan, U. Kaya, D. Hack, D. Enders, *Adv. Synth. Catal*. **2015**, *357*, 253.

31. For a related thiourea catalyst, see: C. B. Tripathi, S. Mukherjee, *Org. Lett*. **2015**, *17*, 4424.

32. a) M. V. Gil, E. Román, J. A. Serrano, M. B. Hursthouse, M. E. Light, *Tetrahedron: Asymmetry*, **2001**, *12*, 1673; b) A. Kamimura, K. Murata, N. Ono, *Tetrahedron Lett*. **1989**, *30*, 4819 and references cited there in.

33. For represntative examples involving α-carbonyl cation, see: a) M. Röck, M. Schmittel, *J. Chem. Soc. Chem. Commun.* **1993**, 1739; b) S. A. Hewlins, J. A. Murphy, J. Lin, *J. Chem. Soc. Chem. Commun*. **1995**, 559; c) X. Creary, *Chem. Rev.* **1991**, *91*, 1625.

34. a) G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem., Int. Ed*. **2013***, 52,* 4235; b) L. F. Fieser, M. Gates, *J. Am. Chem. Soc.* **1946**, *68*, 2249.

35. a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett*. **2005**, *7*, 1967; b) M. S. Manna, V. Kumar, S. Mukherjee, *Chem. Commun*. **2012**, *48*, 5193; c) C. B. Tripathi, S. Kayal, S. Mukherjee, *Org. Lett*. **2012**, *14*, 3296; d) W. Yang, D. M. Du, *Org. Lett.* **2010**, *12*, 5450.

36. F. Manoni, U. Farid, C. Trujillo, S. J. Connon, *Org. Biomol. Chem*. **2017**, *15*, 1463.

Chapter 5: Organocatalytic Asymmetric Hemithioacetalization/Oxa-Michael Cascade Reaction of *Ortho*-Formyl Chalcone

5.1. Introduction:

Kinetic resolution is a process where two enantiomers of a racemate react at different rates towards the formation of products. The invention of dynamic kinetic resolution (DKR) prevailed particularly due to the limitation of classical kinetic resolutions to produce more than 50% theoretical yield. In DKR, an in situ fast racemization process of the chirally-labile substrate is accompanied with the slow resolution process (figure 1). The rate of racemization should be very higher than the rate of the reaction of the slow reacting enantiomer ($k_{rac} \gg k_{slow}$) for an effective dynamic kinetic resolution to occur. The trivial condition for any kinetic resolution process is $k_{fast} \gg k_{slow}$.

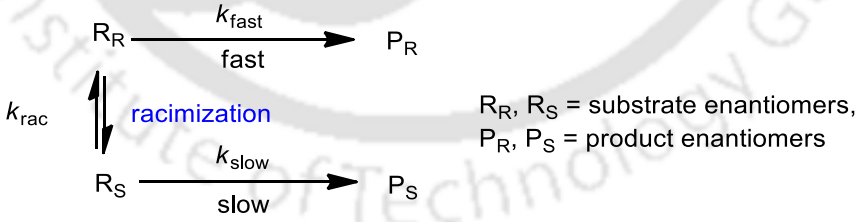
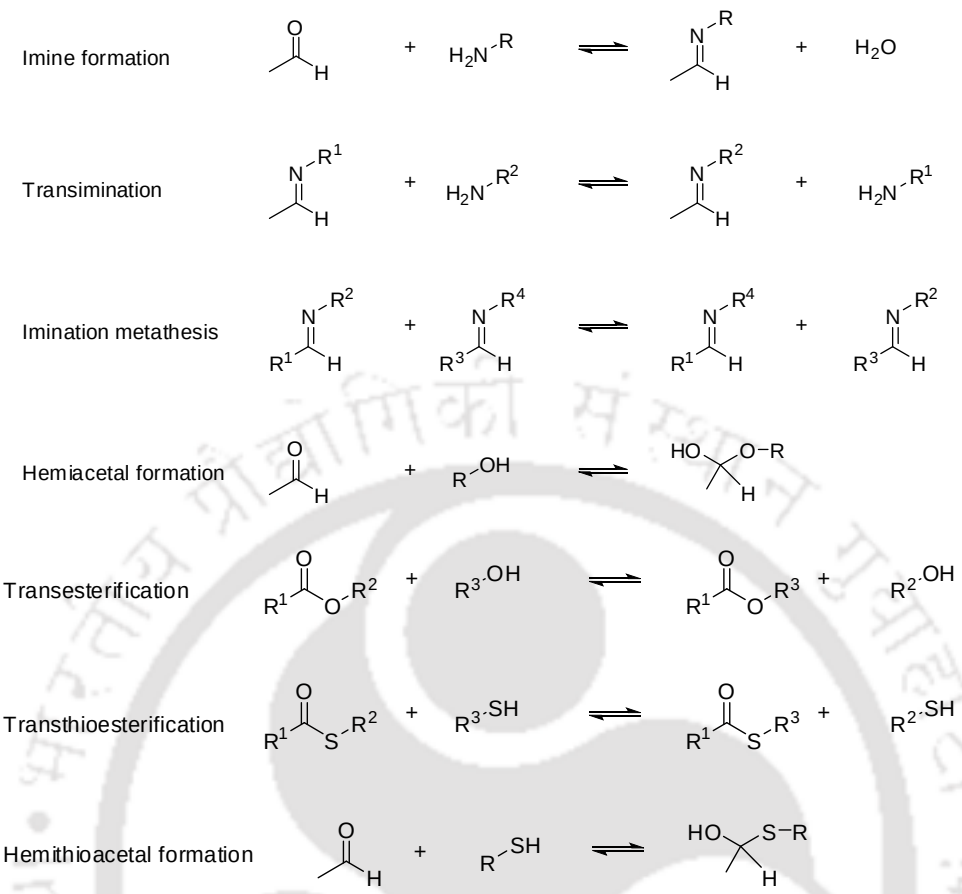


Fig 1: Dynamic kinetic resolution

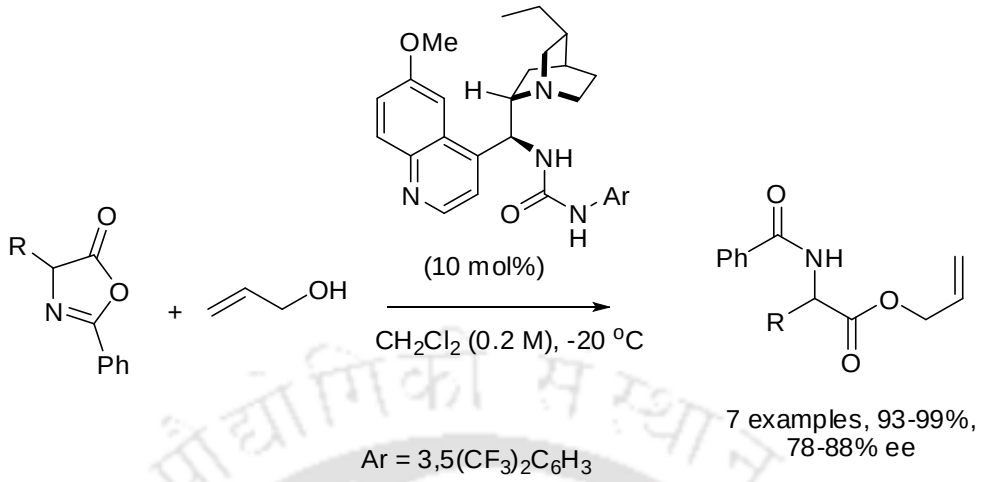
Mainly four types of reactions have been investigated in DKR studies. 1. Carbon-carbon bond formation. 2. Carbon-heteroatom bond formation. 3. Heteroatom-heteroatom bond formation. 4. Non-covalent bond formation. Scheme 5.1.1 summarizes the list of carbon-heteroatom bond formation reactions that utilized DKR technique.



Scheme 5.1.1: carbon-heteroatom bond formations using DKR

Enzyme catalysis[1] and asymmetric ligand-metal catalysis[2] had been the principle promoters for DKR processes in the previous millennia. Since its invention, organocatalysis has become the main mediators of these processes. Catalysts utilized in these studies were predominantly derived from cinchona alkaloids and amino acids, although other catalysts were also found to be effective in this context.[3] Several organocatalytic DKR process have been developed since the first report by Deng and co-workers in 2002.[4]

The first example of cinchona alkaloid derived bifunctional urea catalyzed DKR reaction was documented by S. J. Connon and co-workers in 2008. Alanine-, methionine-, and phenylalanine-derived azlactones have been shown to undergo alcohol and thiol addition reaction furnishing orthogonally protected amino acid esters and thio-esters with excellent level of enantiocontrol (Scheme 5.1.2).[5a]



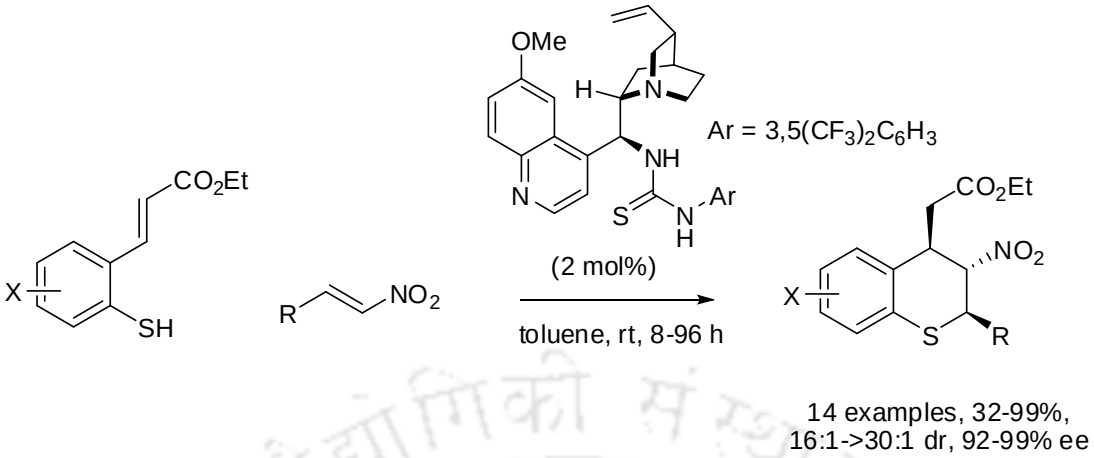
Scheme 5.1.2: Bifunctional urea catalyzed ring opening of azlactones

Athough thiourea catalyzed version has been reported earlier by Berkessel *et al*.,[5b-c] this was the first reaction where cinchona alkaloid derived catalyst was used.

5.2. Organocatalytic cascade reactions using DKR:

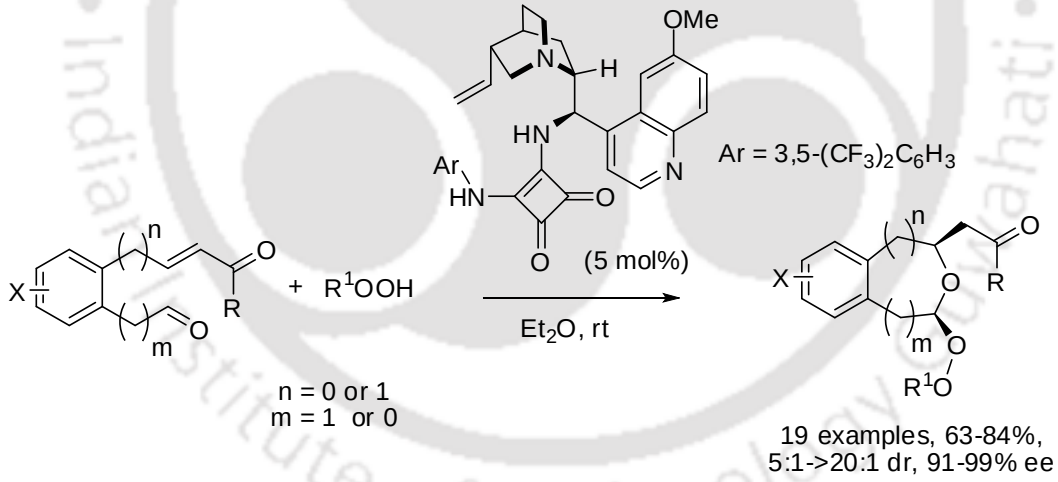
In these type of organocascades the racemic pronucleophile generated in the first step undergoes catalytic DKR in the second step forming mainly cyclic adducts. A variety of these kind of reactions like Michael-Michael,[6] Michael-aldol,[7] imination-redution (reductive amination),[8] Michael-Michael-Wittig,[9] hemiacetylation-aldol[10] has been documented over the last ten years.

Wang *et al.* have reported an asymmetric *thia*-Michael/Michael cascade reaction between trans-3-(2-mercaptophenyl)-2-propenoic acid ethyl ester and nitroalkenes. The product thiochromanes with three contagious stereogenic centers were obtained in high yield and stereoselectivity using cinchona alkaloid amine thiourea catalyst (Scheme 5.2.1).[6a]



Scheme 5.2.1: Bifunctional thiourea catalyzed Michael-Michael cascade involving DKR

Ghorai and co-workers have reported a Peroxyhemiacetalization/oxa-Michael Addition cascade reaction of *ortho*-formyl homchalcones furnishing exo-peroxyacetals, a new class of organic peroxides. Good yields and excellent enantio- and diastereoselectivities have been achieved by the authors using cinchona derived squaramide catalyst (Scheme 5.2.2).[11]



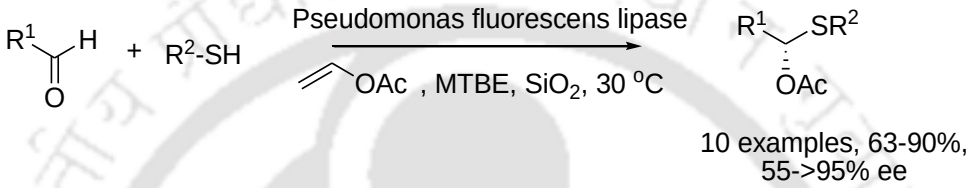
Scheme 5.2.2: Bifunctional squramide catalyzed Peroxyhemiacetalization/oxa-Michael reaction

5.3. DKR processes involving hemithioacetalyzation:

Aromatic and aliphatic thiols reacts with aldehydes forming racemic hemithioacetal intermediates which then undergo different catalytic intramolecular or intermolecular DKR processes like lactonization,[12] acetylation,[13] addition across a double bond[14] *etc*. to furnish

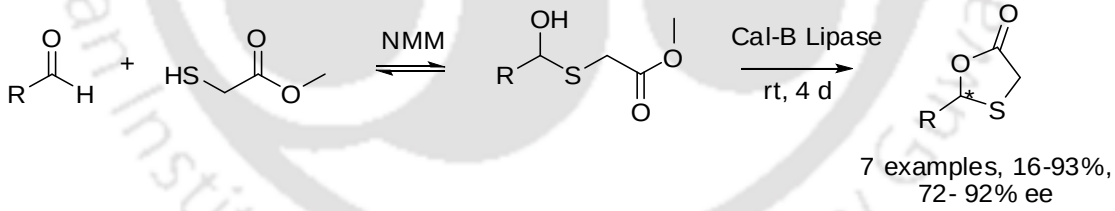
enantio-enriched adducts. Most DKR processes involving hemithioacetal formation were promoted by enzymes.

Lipase could be regarded as the most promising enzyme in this context. The first dynamic kinetic resolution by enantioselective acetylation of hemithioacetals has been documented by Rayner and co-workers. In their study, pseudomonas fluorescens lipase has been reported to catalyze the acetylation reaction of racemic hemithioacetals of glyoxalates and benzoyl- or acetyl- protected glycolaldehydes quite effeciently (Scheme 5.3.1).[13]



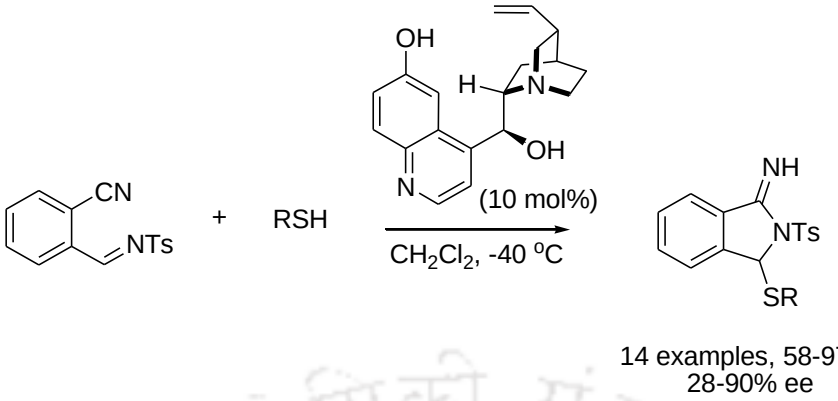
Scheme 5.3.1: Lipase catalyzed acetylation of hemithioacetals involving DKR

Lipase catalyzed dynamic kinetic resolution of *in situ* generated recemic hemithioacetals *via* lactonization was reported by Ramström group. The one pot base catalyzed hemithioacetal formation followed by Cal-B lipase catalyzed lactonization rection produced 1,3-oxathiolan-5-one derivatives in good yield with moderate to good enantiomeric excess (Scheme 5.3.2).[12]



Scheme 5.3.2: Lipase catalyzed lactonization of hemithioacetals involving DKR

Very recently an organocatalytic asymmetric DKR study of *N*-tosylprotected *N*,*S*-acetals has been reported by Capaccio *et al.* The first step of this cascade reaction involved formation of racemic *N*,*S*-acetals from thiols and 2-cyano-*N*-tosylbenzylidenimine. The next DKR step was a highly stereo-selective heterocyclization leading to a new class of multi-heteroatomic cyclic compound by using trifunctional cinchona alkaloid-based organocatalysts (Scheme 5.3.3).[14]



Scheme 5.3.3: Organocatalytic cyclization of *N*,*S*-acetals involving DKR

5.4. Synthesis of Phthalans:

Chiral 1,3-dihydroisobenzofurans (phthalans) are important structural motifs that are present in a range of natural products having impressive pharmacological activities such as antidepressive, antimycotic, anti-HIV, anticancer, antioxidant, antifungal, antibaceterial, antitumor and cardiovascular disease etc.[15] Besides a few industrial applications of them are also known[16] and they also serve as important building blocks in organic synthesis.[17] Some representative 1,3-dihydroisobenzofurans have been shown in Figure 2.

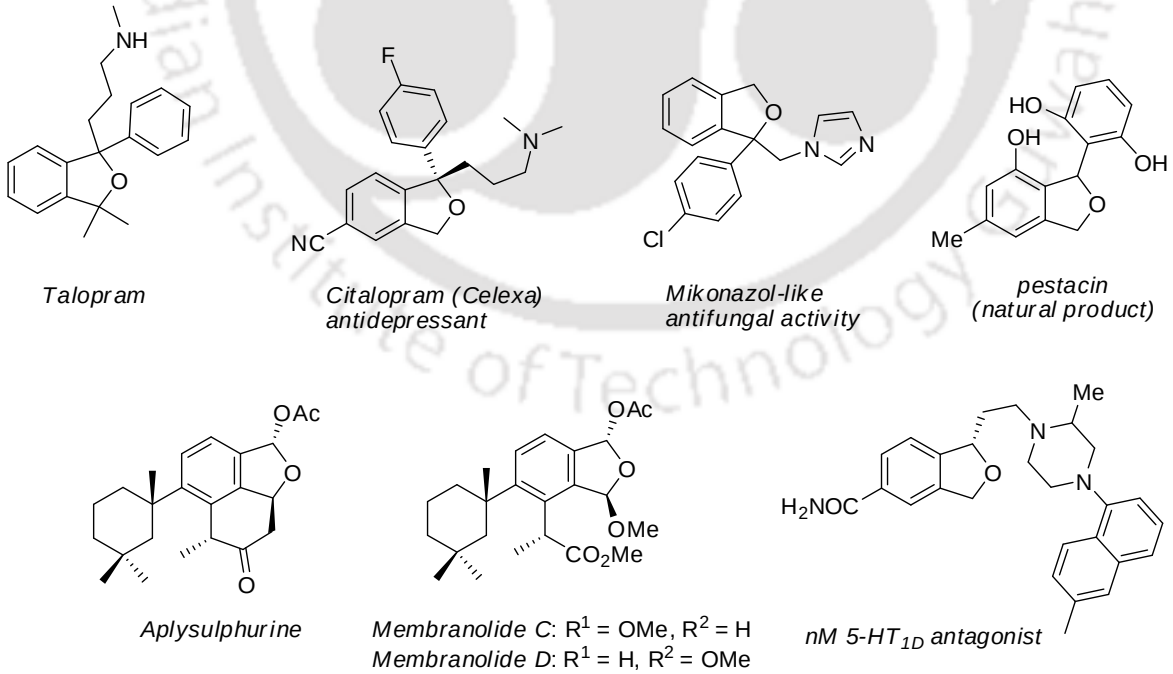
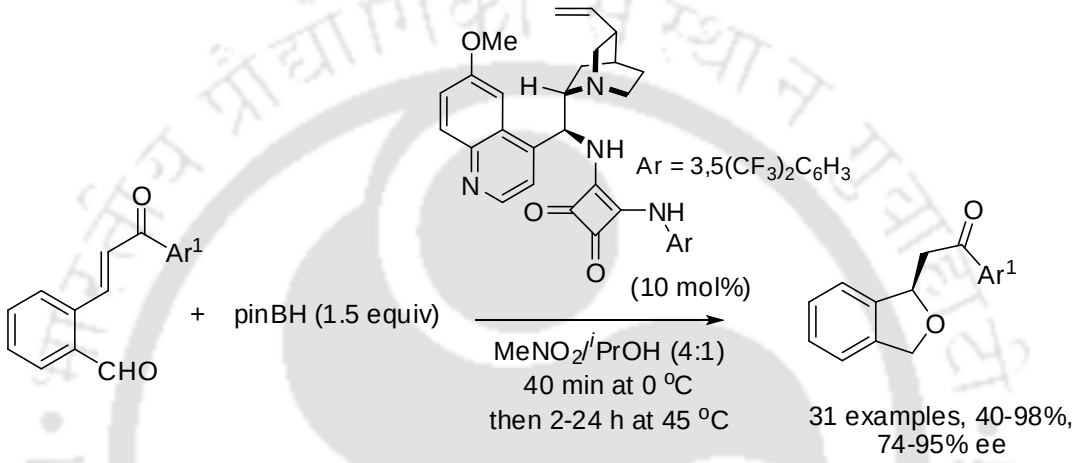


Figure 2: Biologically active phthalans

Fascinated by their impressive activities, a variety of groups are engaged in the synthesis of 1,3-diyhroisobenzofurans[18] but asymmetric reports were only few.

Ghorai and co-workers disclosed an enantioselective synthesis of 1-substituted phthalans. Reaction of pinacol borane with *ortho*-formyl chalcone in the presence of bifunctional squramide catalyst furnished the phthalan products with excellent enantioselectivities (scheme 5.4.1).[19]



Scheme 5.4.1: Synthesis of chiral phthalans

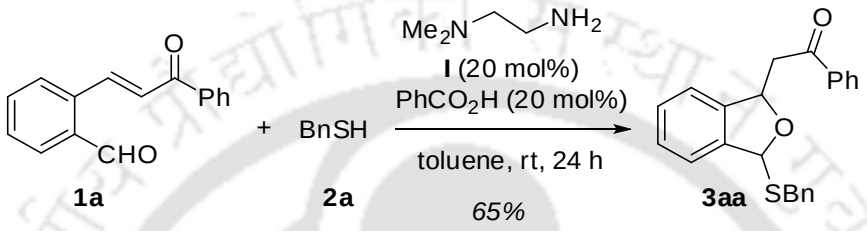
1,3-Disubstituted-phthalan system has drawn our attention as they act as extended scaffold analogous to the more structurally abbreviated 1,3-disubstituted- 2,5-dihydrofurans such as 2',3'-benzo-fused didehydronucleoside analogs.[20]

5.5. Our aim:

The organocatalytic approach for the DKR of hemithioacetals is still not known. Thus we envisage to develop the first organocatalytic DKR reaction involving hemithioacetal intermediates. Using *o*-formyl chalcone and benzyl mercaptan as reacting partners a diastereo- and enantioselective synthesis of 1,3-disubstituted phthalans was focused involving thia-DKR followed by intramolecular oxa-Michael addition.[21]

5.6. Result and Discussion:

When *o*-formyl chalcone (**1a**, 0.05 mmol) and benzyl mercaptan (**2a**, 0.05 mmol) was stirred in the presence of unsymmetrical ethylene diamine **I** (20 mol%) and benzoic acid (20 mol%) in toluene at room temperature, after 24 hours the tandem thiol addition followed by oxa-Michael addition proceeded smoothly to deliver 1,3-disubstituted phthalan **3aa** in 65% yield (Scheme 5.6.1).



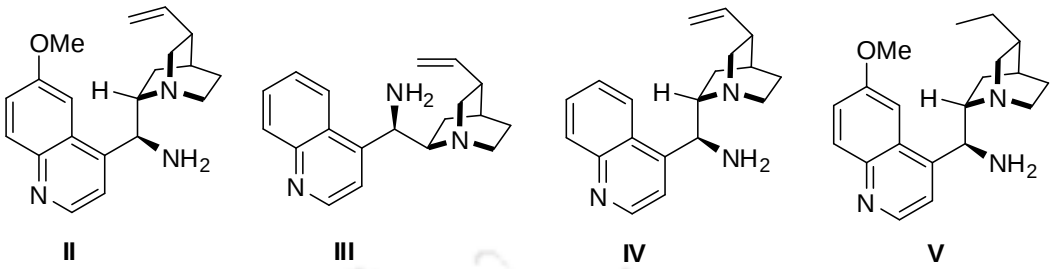
Scheme 5.6.1: Recemic reaction

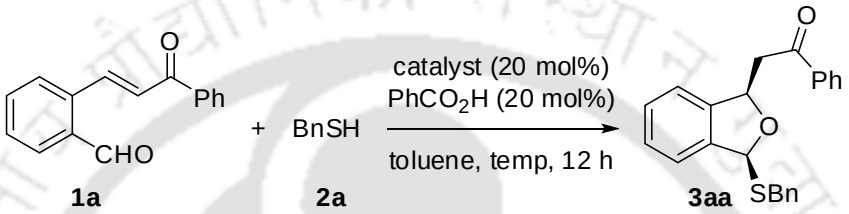
5.6.1. Optimization studies:

5.6.1.1. Catalyst screening:

After that different primary amine catalyst in combination with benzoic acid in toluene solvent were tried in this reaction. Initial screening with quinine derived primary amine **II** failed to produce any diastereoselectivity but the product **3aa** was obtained with 70% enantiomeric excess (Table 1, entry 1). Primary amine derived from cinchonine furnished the product with 1.2:1 diastereomeric ratio but the enantioselectivity decreased to 33% (entry 2). Better result compared to catalyst **II** was obtained with cinchonidine derived primary amine catalyst **IV** in terms of diasteroselectivity (entry 3). Finally the best catalyst was found to be hydroquinine derived primary amine **V**, furnishing the product phthalan with 1.6:1 diastereomeric ratio and 75% enantiomeric excess for the major diastereomer (entry 4). Since the reaction was quite fast at room temperature, the temperature was lowered to 0 ^{o}C and it proved to be beneficial (entry 5). The structure of the major diastereomer 2-((*1R,3S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**) was confirmed unambiguously by X-ray crystallography[22]

Table 1: Catalyst screening





entry[a]	catalyst	temperature	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	**II**	rt	71	1:1	70
2	**III**	rt	68	1.2:1	33
3	**IV**	rt	65	1.5:1	66
4	**V**	rt	70	1.6:1	75
5[e]	**V**	0 °C	67	1.9:1	81

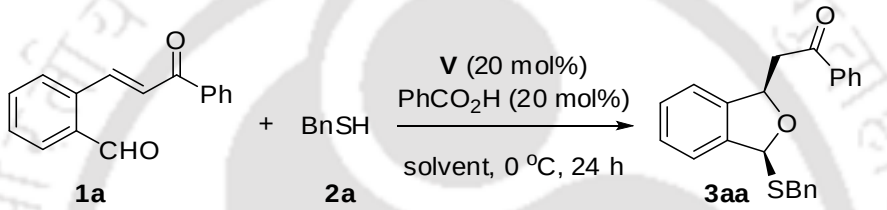
[a]Reaction condition: 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL toluene using 20 mol% catalyst and 20 mol% benzoic acid. [b]Combined yield of the isolated product. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer. [e]Reaction time 24 h.

5.6.1.2. Solvent screening:

Different solvents for this reaction were screened with 9-amino(9-deoxy)epi hydroquinine amine in combination with benzoic acid co-catalyst at 0 °C. Xylene and *α,α,α*-trifluorotoluene, when applied as solvents in this reaction, enantioselectivity was decreased compared to that of toluene, although the diastereoselectivity remained unchanged (Table 2, entry 1-2). Using mesitylene as solvent comparable result to that of toluene was observed (entry 3).

Tetrahydrofuran was found to be unsuitable for this reaction (entry 4). Enantioselectivity as well as diastereoselectivity were increased using diethyl ether as the solvent (entry 5). Inspired by this result, various ethers were screened for this reaction. As can be seen, comparable diastereoselectivity as well as yield was observed using these solvents (entries 6-9). But for saturated ethers *i.e*. di-*n*-butyl ether and diisopropyl ether (entries 6-7) the enantioselectivity was higher compared to the unsaturated ethers *i.e* butyl-vinyl ether and butyl-phenyl ether (entries 8-9). The best solvent was found to be di-*n*-butyl ether (entry 7) furnishing the product **3aa** with 88% ee.

Table 2: Solvent screening



entry[a]	solvent	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	xylene	68	1.9:1	72
2	$PhCF_3$	70	1.9:1	70
3	mesitylene	68	1.9:1	82
4	THF	61	2:1	71
5	Et_2O	66	2.3:1	84
6	$^{i}Pr_2O$	69	2.5:1	87
7	$^{n}Bu_2O$	68	2.5:1	88
8	Butyl-vinyl ether	65	2.5:1	80
9	Butyl-phenyl ether	66	2.5:1	78

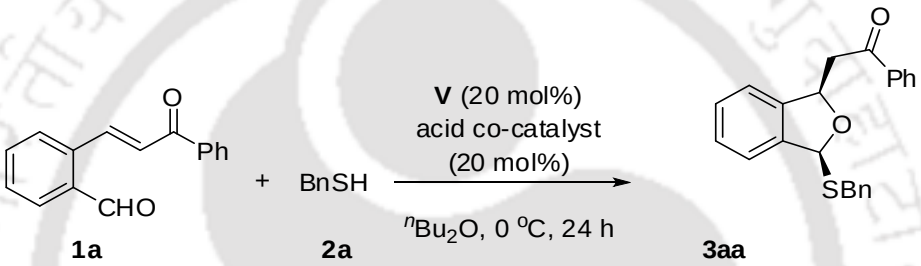
[a]Reaction condition: 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL solvent using 20 mol% catalyst **V** and 20 mol% benzoic acid. [b]Combined yield of the isolated product. [c]Determined by ^{1}H NMR.

[d]Determined by chiral HPLC and of the major diastereomer.

5.6.1.3. Screening of acid co-catalyst:

Different acid co-catalysts were also screened in this reaction with the hope of obtaining better stereoselectivity (Table 3). Both electron-rich and electron-poor benzoic acids substituted at the different positions were screened but better results were not observed (entry 1-3). Di-chloro substituted benzoic acid was also ineffective in improving the selectivity of the reaction (entry 4).

Table 3: Screening of acid co-catalyst



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

entry[a]	acid co-catalyst	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	2-$FC_6H_4CO_2H$	70	2.2:1	81
2	3-$NO_2C_6H_4CO_2H$	62	2.1:1	80
3	3-$MeOC_6H_4CO_2H$	65	2.3:1	79
4	2,4-$Cl_2C_6H_3CO_2H$	61	2:1	79

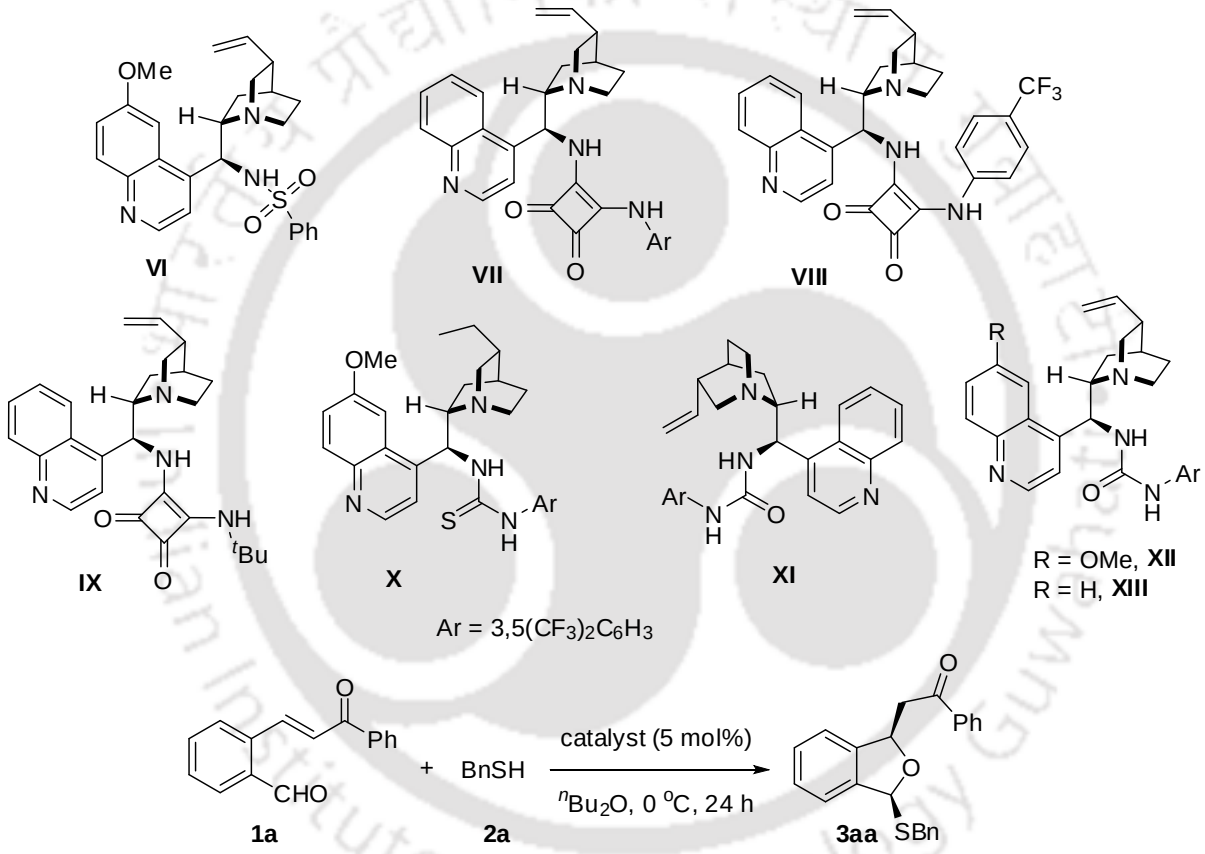
[a]Reaction condition: 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL *n*-butyl ether using 20 mol% catalyst **V** and 20 mol% acid co-catalyst. [b]Combined yield of the isolated product. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer.

5.6.1.4. Catalyst screening using hydrogen-bonding bifunctional catalysts:

Unfortunately the enantiomeric excess value obtained after all these optimization was less than 90%. That is why, hydrogen-bonding bifunctional catalysts were also employed in place of the primary amine (iminium activation) catalysts. Although very poor results were obtained using

quinine derived sulfonamide catalyst **VI** (Table 4, entry 1), better enantioselectivity was observed when squramide catalysts were employed (entry 2-4). Squaramide catalysts **VII** and **VIII**, synthesized from bis- and mono-trifluoromethyl substituted aniline produced 90% enantiomeric excess but the diastereoselectivity decreased. Higher enantio- and diastereo-control were observed using squramide catalyst **IX** containing a tertiary butyl group. The diastereoselectivity further increased upon using 4Å molecular sieves as additive (entry 5).

Table 4: Catalyst screening using bifunctional catalysts



entry[a]	catalyst	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	**VI**	56	1:1	41
2	**VII**	72	1.2:1	90
3	**VIII**	69	1:1	90

4	**IX**	74	1.3:1	96
5[e]	**IX**	73	1.4:1	96
6[e]	**X**	70	1.1:1	81
7[e]	**XI**	75	3:1	81
8[e]	**XII**	74	3:1	96
9[e]	**XIII**	75	3:1	98

[a]Reaction condition: 0.05 mmol of **1a** and 0.05 mmol of **2a** in 0.5 mL solvent using 5 mol% catalyst. [b]Combined yield of the isolated product. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer. [e]Using 4 Å MS.

Bifunctional thiourea catalyst **X** was found to be inferior catalyst compared to squramides in this reaction (entry 6). Interestingly, diastereoselectivity got increased when cinchonine derived urea catalyst **XI** was employed in this reaction in the presence of 4Å MS but enantioselectivity decreased (entry 7). Inspired by this result, other cinchona alkaloid derived urea catalysts **XII** and **XIII** were screened and fortunately higher enantioselectivity was obtained without any change of diastereocontrol (entries 8-9). Cinchonidine derived urea catalyst **XIII** in the presence of 4Å MS was found to be the best catalyst furnishing the product **3aa** in 3:1 diastereomeric ratio with 98% ee of the major diastereomer (entry 9).

5.6.2. Substrate scope:

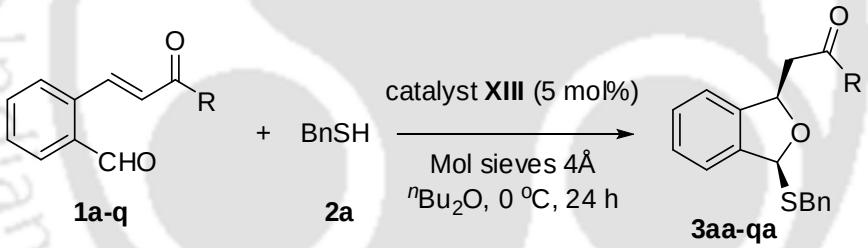
After fixing the optimized conditions the scope and generality of the DKR reaction were investigated.

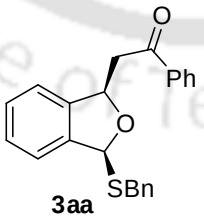
5.6.2.1. Scope of enones:

Intially the aryl group on the carbonyl functionality was varied and it turned out that the reaction outcome is indifferent to the elctronic nature of the aryl group. At first, different *para*-substitutions on the aryl group were checked and excellent results were achieved (Table 5, entries 2-9). For example, products **3ba** and **3ca** having 4-methyl and 4-methoxy substitutions

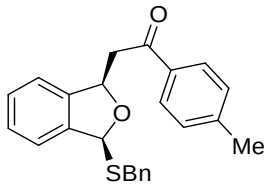
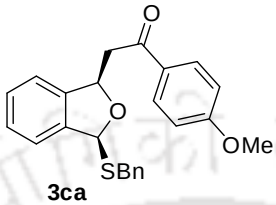
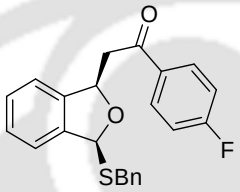
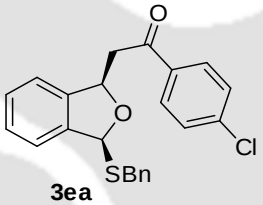
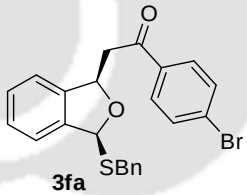
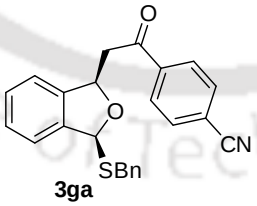
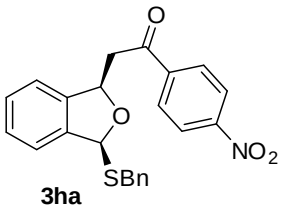
were isolated in good diastereo- and high enantioselectivities (entries 2-3). Also, high diastereo- and enantioselectivities were achieved for products **3da-3fa** having different 4-halo substitutions (entries 4-6). However, for enones **1g-1h** having 4-cyano and 4-nitrogroups, the enantioselectivities were moderate for the corresponding products with catalyst **XIII** (entries 7-8). Delightfully, the enantioselectivities got enahanced with catalyst **IX** in the expence of little amount of diastereoselectivity (the data in parenthesis). Biphenyl substituted enone **1i** also took part in the reaction delivering product **3ia** in acceptable yield with 98% ee (entry 9). Then *ortho*- and *meta*-substituted enones **1j-n** were engaged in the reaction and delightfully here also the outcome was also very good (entries 10-14). Although 2-methyl substituted enone **2j** furnished the product with lesser enantioselctivity and diastereoselectivity (entry 10), with 2-fluoro substituted enone better results were obtained (entry 11). *meta*-Bromo substituted enone **2l** furnished the corresponding product with 3:1 diastereoselectivity and 95% ee. Slight lower diastereo- and enantioselectivity was observed with 3-nitro substitution (entry 13).

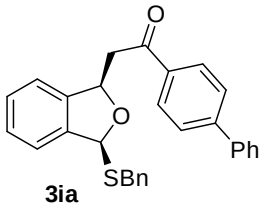
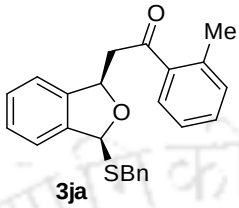
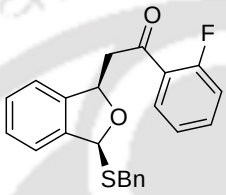
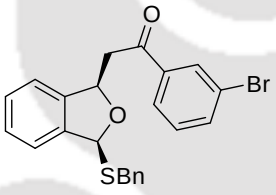
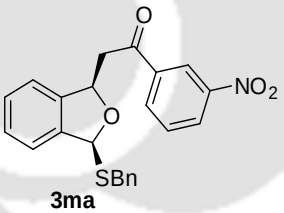
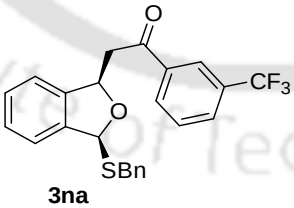
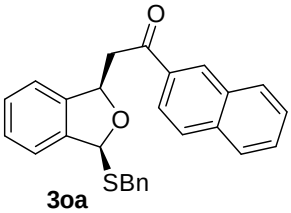
Table 5: Scope of enone with varied ketone substitutents

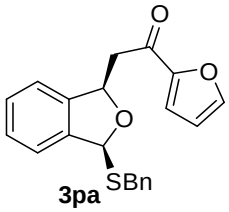
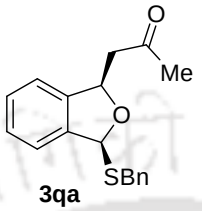


entry[a]	R	product	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	Ph		77	3:1	98

3aa

2	4-MeC_6H_4	 **3ba**	80	2.2:1	95
3	4-$MeOC_6H_4$	 **3ca**	65	2.7:1	95
4	4-FC_6H_4	 **3da**	63	3:1	96
5	4-ClC_6H_4	 **3ea**	64	2.5:1	96
6	4-BrC_6H_4	 **3fa**	91	2.5:1	88
7	4-CNC_6H_4	 **3ga**	53(52)	2:1(1.5:1)	75(82)
8	4-$NO_2C_6H_4$	 **3ha**	41(43)	2.2:1(2:1)	74(90)

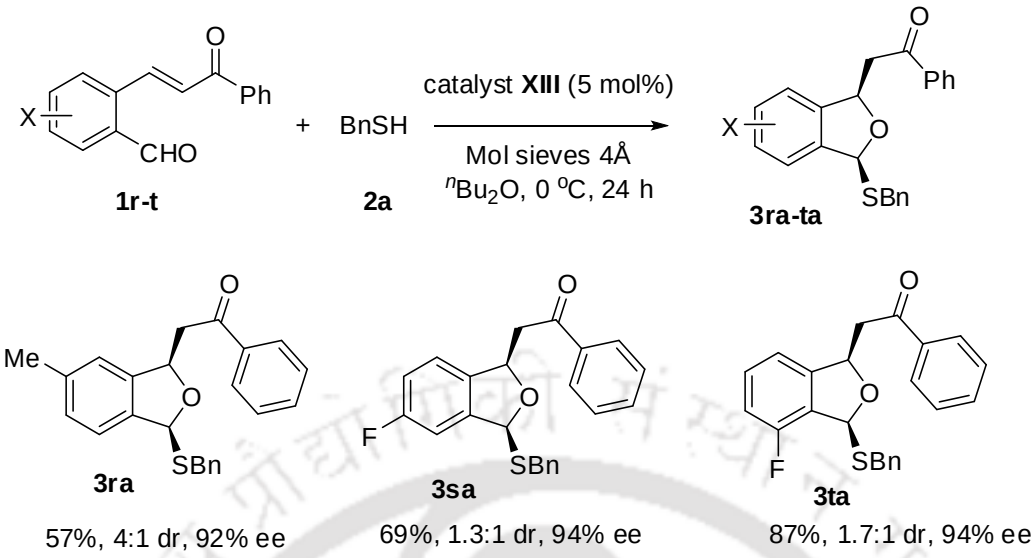
9	4-PhC_6H_4	 **3ia**	50	3:1	98
10	2-MeC_6H_4	 **3ja**	48	2:1	85
11	2-FC_6H_4	 **3ka**	88	2.5:1	90
12	3-BrC_6H_4	 **3la**	58	3:1	95
13	3-$NO_2C_6H_4$	 **3ma**	43	2:1	86
14	3-$CF_3C_6H_4$	 **3na**	62	2.8:1	95
15	2-Naphthyl	 **3oa**	69	4:1	86

16	2-Furyl	 **3pa**	70	5:1	96
17	Me	 **3qa**	55	3.2:1	88

[a]Reaction condition: Unless otherwise mentioned, 0.1 mmol of **1** and 0.1 mmol of **2a** in 1 mL solvent using 5 mol% **XIII** at 0 °C for 1 day. [b]Yield of the isolated product. [c]Determined ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer. [e]The data in parenthesis is with catalyst **IX**.

Product **3na** having 3-trifluoromethyl substitution was obtained with moderate diastereoseletivity and good enantioselectivity (entry 14). Then better diastereoselectivity (4:1 dr) and enantioselectivity (99% ee) was obtained for product **3oa** having 2-naphthyl group (entry 15). A heteraromatic furyl containing enone **1p** can also be employed and gratifyingly highest diastereoselectivity (5:1) as well as excellent enantioselectivity was attained for the product **3pa** (entry 16). Our methodology also worked with aliphatic enone **1q** and the corresponding product **3qa** was achieved in 55% yield with 88% ee (entry 17).

Then different substitutions on the phenyl group attached to the aldehyde functionality were also screened and the results are shown in Scheme 5.6.2. As can be seen, the outcome did not change with the substitutions and excellent results were maintained. For example, substrate **1r** having 4-methyl substitution provided product **3ra** in 57% yield with 4:1 diastereomeric ratio and a high 92% ee was detected (Scheme 5.6.2). Similarly excellent enantioselectivities were obtained for products **3sa** and **3ta** having 5-F and 6-F substitutions respectively albeit with lesser diastereoselectivity.



Scheme 5.6.2: Scope of enone with varied olefin substitutents[a,b]

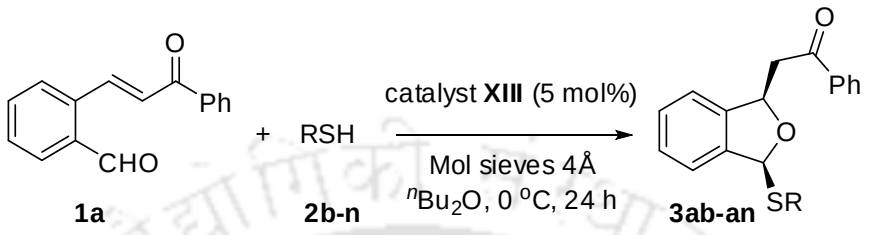
[a]Reaction condition: 0.1 mmol of **1** and 0.1 mmol of **2a** in 1ml solvent using 5 mol% **XIII** at 0 °C for 1 day. [b]Combined yield of the isolated product, dr was determined by ^{1}H NMR and ee was measured by chiral HPLC and of the major diastereomer.

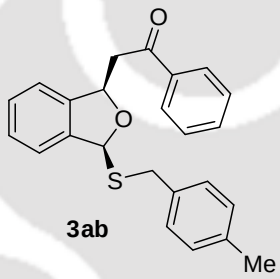
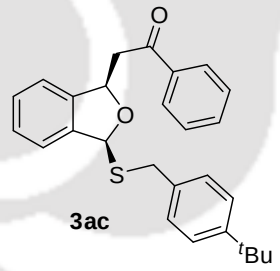
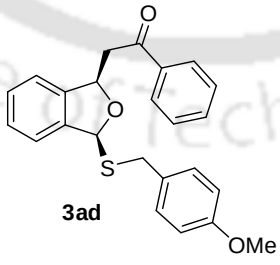
5.6.2.2. Scope of thiols:

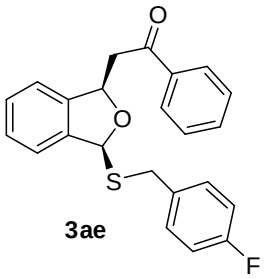
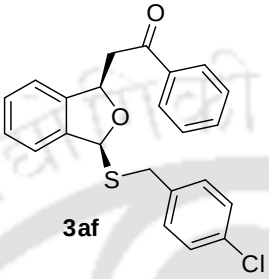
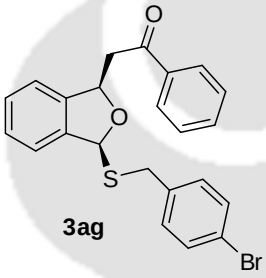
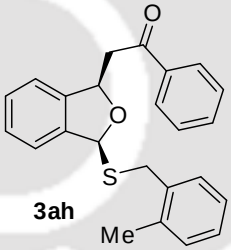
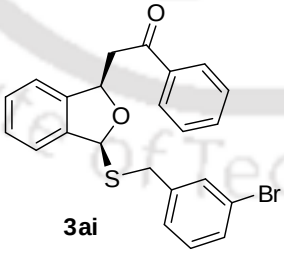
Next, the generality of the reaction was further demonstrated by employing a variety of thiols and the results were summarized in Table 6. Here also, different substitutions on the phenyl group of benzyl mercaptan as well as other thiols were tolerated and excellent results were achieved. Initially, *para*-substituted benzyl mercaptans having electron-neutral and donating groups were subjected in the reaction conditions (entries 1-6). High enantioselectivities were obtained for both alkyl and alkoxy substituted benzyl mercaptans. Higher diastereoselcetivities compare to unsubstituted benzyl mercaptan were also observed for 4-methyl and 4-methoxy substitution. Similarly, excellent enantioselectivities were achieved with 4-halo substituted mercaptans **3af-3ag** (entries 5-6). A little less enantiocontrol and better diastereocontrol was observed for 4-fluoro substituted mercaptan compared to 4-chloro and 4-bromo substituted enones (entry 4). Moreover, *ortho*- and *meta*-substituted benzyl mercaptans **2h** and **2i** also participated in the reaction delivering products **3ah** and **3ai** in high enantioselectivities (entries 7-8). 2,4-Disubstituted benzyl mercaptan **2j** could also be

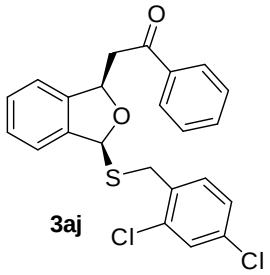
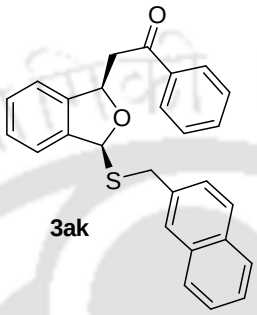
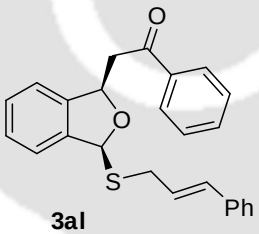
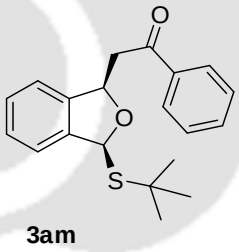
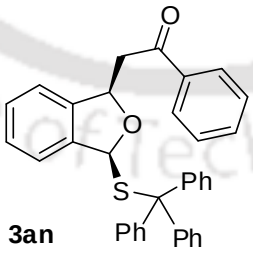
employed in the reaction and high enantioselectivity (94% ee) was detected for product **3aj** (entry 9).

Table 6: Scope of thiols



entry[a]	R	Product	yield (%)[b]	dr[c]	ee(major) (%)[d]
1	4-$MeC_6H_4CH_2$	 **3ab**	53	4.2.:1	96
2	4-$^tBuC_6H_4CH_2$	 **3ac**	62	2.7:1	96
3	4-$MeOC_6H_4CH_2$	 **3ad**	78	4.7:1	96

4	4-$FC_6H_4CH_2$	 **3ae**	56	4.3:1	89
5	4-$ClC_6H_4CH_2$	 **3af**	59	3:1	94
6	4-$BrC_6H_4CH_2$	 **3ag**	62	3.5:1	94
7	2-$MeC_6H_4CH_2$	 **3ah**	57	3.3:1	92
8	3-$BrC_6H_4CH_2$	 **3ai**	57	3:1	93

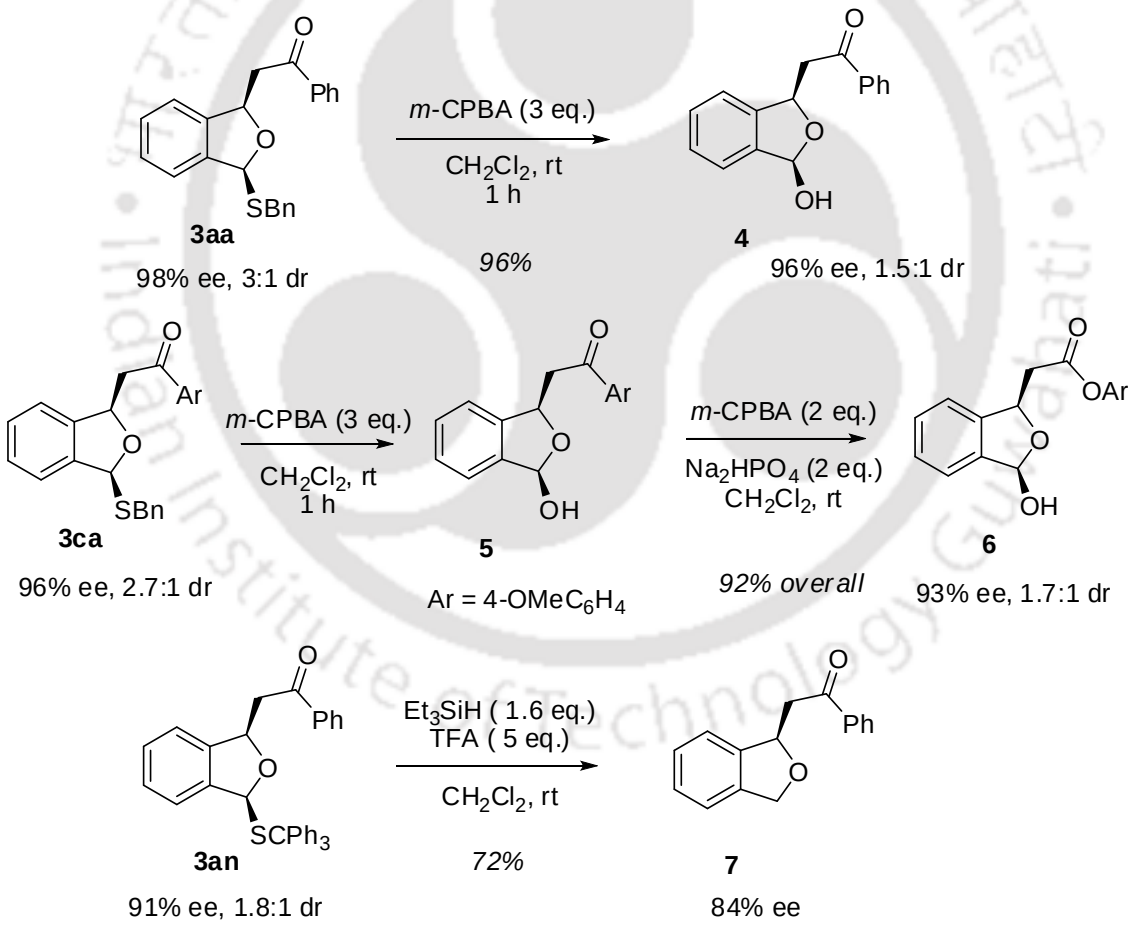
9	2,4-$Cl_2C_6H_3CH_2$	 **3aj**	59	3.6:1	94
10	2-Naphthyl	 **3ak**	62	4:1	98
11	Cinnamyl	 **3al**	39	1.9:1	97
12	^{t}Bu	 **3am**	65	9:1	98
13[e]	Ph_3C	 **3an**	25	1.8:1	91

[a]Reaction condition: 0.1 mmol of **1a** and 0.1 mmol of **2** in 1 mLsolvent using 5 mol% **VII** at 0 °C for 1 day. [b]Yield of the isolated product. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC and of the major diastereomer. [e]Reaction time 7 days.

Excellent enantioselectivity was also obtained for product **3ak** having 2-naphthylmethylthio group (entry 10). Then different aromatic and aliphatic thiols were screened and pleasingly the results were excellent (entries 11-13). (*E*)-2 Phenylethenethiol (**2l**) on reaction with **1a** provided product **3al** in 97% ee *albeit* the yield was less (entry 11). Gratifyingly, the highest diastereo- and excellent enantioselectivity was observed for product **3am** having an aliphatic ^{t}butyl thiol moiety (entry 12). Finally, triphenylmethanethiol (**2n**) was engaged in the reaction; though the rate of conversion was slow but high enantioselectivity was detected (entry 13).

5.6.3. Synthetic transformations of product:

The synthetic utilities of our reaction were demonstrated by performing few reactions on the products (Scheme 5.6.3).



Scheme 5.6.3: Synthetic transformations of products

Initially oxidation of **3aa** was carried out in the presence of 3 equivalents of *m*-CPBA. Instead of the desired sulfone hemiacetal **4** was formed in 96% yield and 1.5:1 diastereomeric ratio with 96% enantiomeric excess of the major diastereomer. Then compound **3ca** was first converted to hemiacetal **5** by the same mechanism, on which a Baeyer Villiger oxidation reaction was performed. This resulted in the formation of ester **6** in 92% overall yield with 93% ee. Then triethylsilane mediated selective removal of trityl group[23] was envisaged in compound **3an**. However, under the acidic conditions, the complete removal of triphenylmethanethiol motif was noticed and *mono*-substituted phthalan **7** was formed in 72% yield with slight erosion in enantioselectivity (Scheme 5.6.3).

In summary, this chapter describes the first organocatalytic DKR of *insitu* generated hemithioacetals leading to the synthesis of 1,3-disubstituted-1,3-dihydroisobenzofurans. Cinchonidine derived urea was the best catalyst for this reaction and the dihydroisobenzofuran products were formed in good yields with high diastereo- and enantioselectivities. Also few synthetic transformations including mono-substituted dihydroisobenzofuran synthesis has been demonstrated. This methodology would be useful for the synthesis of different derivatives of biologically active 1,3-disubstituted dihydroisobenzofurans.

5.7. Experimental procedures and structure determination:

5.7.1. General procedure for cascade hemithioacetalization/oxa-Michael reaction:

A 5 mL round bottomed flask was charged with *ortho*-formyl chalcone **1** (0.1 mmols), catalyst **XIII** (5 mol%) and 100 mg of 4Å molecular sieves. Benzyl mercaptan **2** (0.1 mmols) and 1 mL *n*-butyl ether was then added to it. The reaction vessel was closed by means of a stopper and the reaction was stirred at 0 ^{o}C for 24 hours. The solvent from the crude reaction mixture was then evaporated and it was directly subjected to column chromatographic separation using 3% EtOAc in hexaane as eluent.

5.7.2. Structure determination for compound 3aa:

The absolute configuration of the major product 2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**) was determined to be (1*R*,3*S*) by X-ray crystallography (Section 5.9).

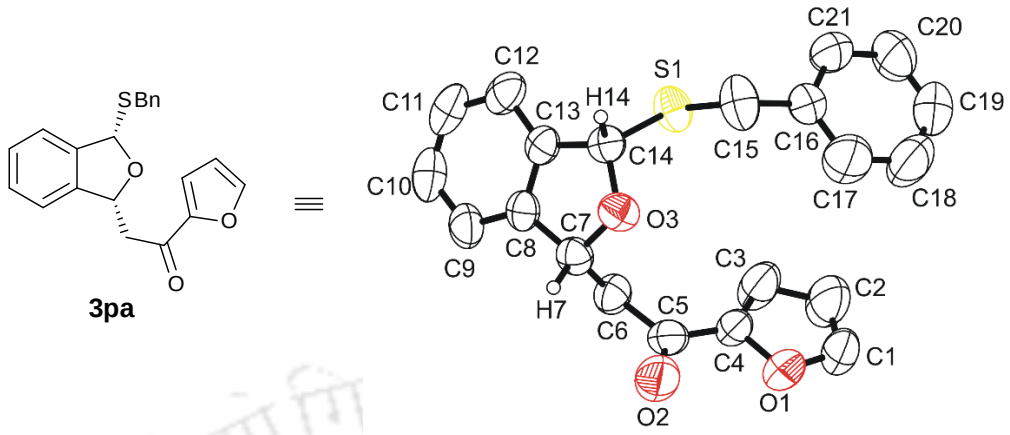


Figure 2: ORTEP diagram of 2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**)

5.7.3. Procedure for formation of hemiacetal 4 from 3aa:

To a stirring solution of compound **3aa** (0.05 mmoles) in dry dichloromethane (0.1 mL) at room temperature *m*-CPBA (0.3 mmoles) was added and the reaction mixture was stirred for 1 hour at argon environment. The crude reaction mixture was diluted with dichloromethane and washed with saturated solution of sodium bicarbonate. The organic layer was dried with anhydrous sodium sulphate and concentrated. The crude product was purified by silica gel column chromatography using 20% EA in hexane as eluent to obtain pure cyclic hemiacetal **4**.

5.7.4. Baeyer Villiger oxidation on hemiacetal of compound 3ca:

To the hemiacetal **5** (0.05 mmloes) formed from **3ca** following the previously mentioned procedure, dry dichloromethane (0.1 mL) was added and it was stirred at room temperature in argon atmosphere. To this stirring solution 2 equiv. of *m*CPBA and 4 equiv. Of disodium hydrogen phosphate was added The reaction was stirred overnight and then transferred to a separetory funnel, diluted with dichloromethane and extracted with saturated aquous sodium bi-carbonate solution. The organic layer was collected and the aquous layer was again extracted with DCM, the combined organic layer was dried, concentrated and then subjected to column chromatograpic separation using 25% EA in hexane as eluent to obtain pure **6**.

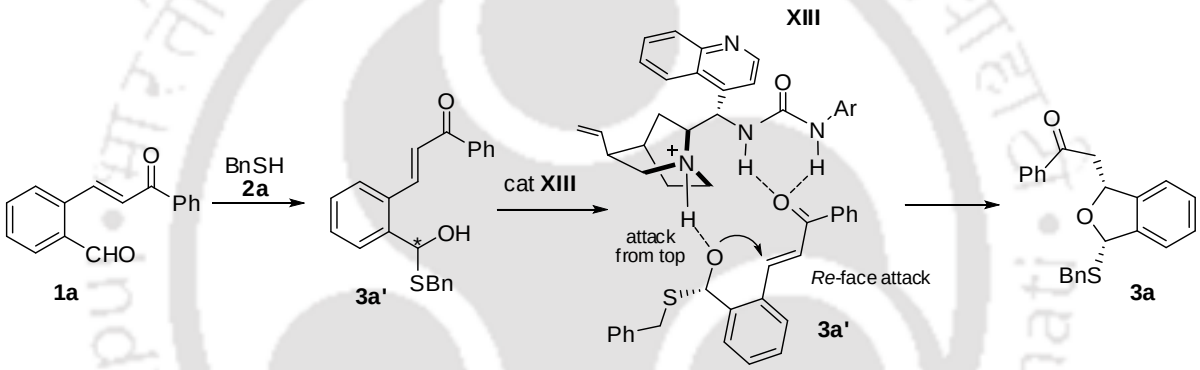
5.7.5. Synthesis of *mono*-substituted phthalan 7 from 3an:

To a solution of **3an** (0.05 mmol) in CH_2Cl_2 (0.1 mL) at 0 ^oC under Ar atmosphere, pyridine

(0.1mmol) and Tf_2O (0.06 mmol) was added and the resulting mixture was stirred at room temperature for 12 hours. The solvent was removed in vacuo, the residue was subjected to coulmn chromatographic separation (SiO_2) using 4% EA in hexane as eluent to obtain pure phthalan **7**.

5.8. Plausible reaction mechanism:

The first step of the tandem reaction was formation of racemic hemithioacetal **3a'** from **1a** and **2a**. It seems the quiniclidine moiety activates the hemiacetal to attack from the *Re*-face of the enone moiety of **3a'** while the enone oxygen binds with the urea moiety of the catalyst by means of hydrogen bonding.



Scheme 5.8: Plausible reaction mechanism

5.9. Characterization data for products:

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3aa): Off White sticky liquid (27 mg, 77%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.21 (dd, *J* = 7.6, 4.2 Hz, 8H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.36 (s, 0.34H), 6.31 (s, 1H), 5.92 – 5.89 (m, 1H), 3.85 (d, *J* = 13.2 Hz, 1H), 3.74 – 3.68 (m, 2H), 3.23 (dd, *J* = 16.7, 5.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 198.1, 141.9, 138.8, 138.3, 137.3, 133.5, 129.3, 128.8, 128.7, 128.7, 128.6, 128.4, 127.2, 122.6, 121.9, 87.9, 80.9, 46.5, 35.5. **FT-IR** (KBr): 1682(s), 1449(m), 1016(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{24}NO_2S^+$ $[M+NH_4]^+$: 378.1522, Found: 378.1524. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 17.9 min, τ_{major} = 27.7 min), ee 98%.

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-p-tolylethanone (3ba): Off white sticky liquid (30 mg, 80%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.31 – 7.27 (m, 11H), 6.44 (d, *J* = 2.0 Hz, 0.49H), 6.39 (s, 1H), 5.98 (t, *J* = 6.4 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.81 – 3.74 (m, 2H), 3.28 (dd, *J* = 16.6, 5.5 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 197.7, 144.4, 142.0, 138.8, 138.3, 134.9, 129.5, 129.3, 128.9, 128.8, 128.7, 128.3, 127.2, 122.6, 121.9, 87.9, 81.0, 46.4, 35.5, 21.9. **FT-IR** (KBr): 1679(s), 1606(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1682. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (98:2 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.5 min, τ_{major} = 24.5min), ee 95%.

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-(4-methoxyphenyl)ethanone (3ca):

Yellow sticky liquid (25 mg, 65%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 9H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 2.0 Hz, 0.4H), 6.39 (s, 1H), 5.98 – 5.95 (m, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.88 (s, 3H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.24 (dd, *J* = 16.4, 5.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.6, 163.9, 142.1, 138.7, 138.3, 131.0, 129.3, 128.9, 128.7, 128.6, 128.3, 127.2, 122.6, 121.9, 114.0, 87.9, 55.7, 46.1, 35.5. **FT-IR** (KBr): 1673(s), 1462(w), 1026(s). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{26}NO_3S^+$ $[M+NH_4]^+$: 408.1628, Found: 408.1623. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (90:10 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 16.1 min, τ_{major} = 69.6 min), ee 95%.

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-(4-fluorophenyl)ethanone (3da): Off White sticky liquid (30 mg, 80%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.08 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.32 – 7.27 (m, 8H), 7.16 (t, *J* = 7.4 Hz, 3H), 6.44 (d, *J* = 2.1 Hz, 0.43H), 6.41 (s, 1H), 5.99 – 5.96 (m, 1H), 3.95 (d, *J* = 13.3 Hz, 1H), 3.83 – 3.79 (m, 1H), 3.79 – 3.75 (m, 1H), 3.28 (dd, *J* = 16.5, 5.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.6, 141.8, 138.7, 138.2, 131.4, 131.3, 129.2, 129.0, 128.7, 128.4, 127.2, 122.7, 121.8, 116.0, 115.8, 88.0, 81.0, 46.4, 35.6. **FT-IR** (KBr): 1684(s), 1454(m), 1011(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2FS^+$ $[M+NH_4]^+$: 396.1428, Found: 396.1429. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (99:1 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 26.0 min, τ_{major} = 34.9 min), ee 96%.

2-((1*R*,3*S*)-2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-(4-chlorophenyl)ethanone (3ea): Off White sticky liquid (25.2 mg, 64%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.45 (s, 2H), 7.31 (d, *J* = 2.9 Hz, 3H), 7.29 – 7.27 (m, 5H), 7.23 – 7.21 (m, 1H), 6.42 (d, *J* = 2.1 Hz, 0.33H), 6.39 (s, 1H), 5.95 (dd, *J* = 7.7, 5.3 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.74 (dd, *J* = 16.5, 7.7 Hz, 1H), 3.25 (dd, *J* = 16.5, 5.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 197.0, 141.5, 139.8, 138.0, 135.4, 130.0, 129.8, 129.0, 128.9, 128.8, 128.5, 128.2, 127.0, 122.5, 121.6, 87.8, 80.7, 46.2, 35.4. **FT-IR** (KBr): 1684(s), 1400(m), 1013(m). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2ClS^+$ $[M+NH_4]^+$: 412.1133, Found: 412.1142. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.0 min, τ_{major} = 30.2 min), ee 96%.

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-(4-bromophenyl)ethanone (3fa): Off White sticky liquid (39.8 mg, 91%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.28 (dd, *J* = 6.4, 3.7 Hz, 5H), 7.24 (s, 2H), 6.41 (d, *J* = 2.1 Hz, 0.12H), 6.39 (s, 1H), 5.94 (dd, *J* = 7.5, 5.2 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.73 (d, *J* = 8.9 Hz, 1H), 3.23 (dd, *J* = 16.5, 5.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 197.0, 141.5, 138.5, 138.0, 135.8, 131.9, 130.0, 129.4, 129.0, 128.8, 128.6, 128.6, 128.25, 122.5, 121.6, 87.8, 80.7, 46.2, 35.4. **FT-IR** (KBr): 1681(s), 1584(m), 1015(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2BrS^+$ $[M+NH_4]^+$: 456.0627, Found: 456.0633. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.7 min, τ_{major} = 24.2 min), ee 88%.

4-(2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)acetyl)benzonitrile (3ga): yellow sticky liquid (20 mg, 52%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.33 – 7.31 (m, 2H), 7.27 (d, *J* = 6.7 Hz, 6H), 7.22 (d, *J* = 4.5 Hz, 1H), 6.40 (d, *J* = 2.1 Hz, 0.55H), 6.39 (s, 1H), 5.93 (dd, *J* = 7.8, 5.1 Hz, 1H), 3.91 (d, *J* = 13.3 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.28 (dd, *J* = 16.6, 5.0 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$):** δ 196.9, 141.4, 140.2, 138.7, 138.2, 132.7, 129.2, 129.1, 129.0, 128.7, 128.7, 128.6, 127.3, 122.8, 121.7, 88.3, 80.8, 46.7, 35.8. **FT-IR** (KBr): 1691(s), 1454(m), 1014(m). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{23}N_2O_2S^+$ $[M+NH_4]^+$: 403.1475, Found: 403.1475. The enantiomeric ratio was

determined by HPLC analysis using Chiralpak IB column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.7 min, τ_{major} = 24.2 min), ee 82%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(4-nitrophenyl)ethanone (3ha) (major diastereomer): Light brown sticky liquid (17.4 mg, 43%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.24 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.26 (td, *J* = 5.9, 3.1 Hz, 3H), 7.21 (d, *J* = 4.1 Hz, 4H), 7.19 (s, 2H), 6.33 (s, 1H), 5.88 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.85 (d, *J* = 13.3 Hz, 1H), 3.75 – 3.68 (m, 2H), 3.33 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.23 (dd, *J* = 16.5, 4.9 Hz, 1H). **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.8, 150.7, 141.6, 141.3, 138.7, 138.1, 129.8, 129.2, 128.7, 128.7, 127.3, 124.1, 124.0, 122.8, 121.7, 88.3, 80.8, 47.0, 35.8, 32.1. **FT-IR** (KBr): 1682(s), 1455(m), 1026(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}N_2O_4S^+$ $[M+NH_4]^+$: 423.1373, Found: 423.1397. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (80:20 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 32.0 min, τ_{major} = 50.7 min), ee 90%.

Compound 3ia: Off White sticky liquid (21.8 mg, 50%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 3H), 7.45 (s, 1H), 7.34 – 7.30 (m, 5H), 7.22 (t, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 0.36H), 6.39 (s, 1H), 6.00 – 5.97 (m, 1H), 3.87 (d, *J* = 13.5 Hz, 1H), 3.78 – 3.71 (m, 2H), 3.31 (dd, *J* = 16.7, 5.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 197.5, 146.0, 141.7, 140.0, 138.6, 138.1, 135.8, 129.1, 129.1, 129.0, 128.8, 128.5, 128.3, 128.2, 127.3, 127.0, 126.9, 122.4, 121.6. **FT-IR** (KBr): 1675(s), 1455(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{29}H_{28}NO_2S^+$ $[M+NH_4]^+$: 454.1835, Found: 454.1836. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (98:2 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 56.6 min, τ_{major} = 42.1 min), ee 98%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-o-tolylethanone (3ja): Off White sticky liquid (18 mg, 48%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.1 Hz, 2H), 7.29 (td, *J* = 6.6, 2.2 Hz, 11H), 6.38 (s, 1H), 5.96 (dd, *J* = 7.9, 5.1 Hz, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.76 (d, *J* = 13.2 Hz, 1H), 3.73 – 3.69 (m, 1H), 3.45 (dd, *J* = 16.3, 7.0 Hz, 0.55H), 3.27 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.60 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 201.9, 141.9, 138.8, 138.6, 138.2, 138.1, 132.2, 131.7, 129.3, 128.9, 128.7, 128.3, 127.2, 125.9, 122.6, 121.7, 87.8, 81.1, 49.4, 35.4, 21.6. **FT-IR** (KBr): 1680(s), 1454(m), 1015(s). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1707.

The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.6 min, τ_{major} = 18.4 min), ee 85%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(2-fluorophenyl)ethanone (3ka): Off White sticky liquid (33.2 mg, 88%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.97 (td, *J* = 7.6, 1.8 Hz, 2H), 7.56 – 7.52 (m, 2H), 7.31 – 7.28 (m, 7H), 7.13 (dd, *J* = 11.1, 2.6 Hz, 2H), 6.63 – 6.57 (m, 1H), 6.43 (d, *J* = 2.1 Hz, 0.34H), 6.38 (s, 1H), 5.99 – 5.95 (m, 1H), 3.91 (d, *J* = 13.1 Hz, 1H), 3.75 (d, *J* = 12.9 Hz, 1H), 3.72 – 3.68 (m, 1H), 3.46 (dd, *J* = 5.0, 1.9 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 196.1, 143.9, 141.8, 138.8, 138.3, 135.0, 130.9, 130.2, 129.2, 128.6, 128.3, 127.1, 124.8, 122.6, 121.8, 117.0, 116.8, 87.9, 80.2, 51.4, 43.5. **FT-IR** (KBr): 1686(s), 1453(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2FS^+$ $[M+NH_4]^+$: 396.1428,, Found: 396.1432. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (90:10 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 20.9 min, τ_{major} = 35.2 min), ee 90%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(3-bromophenyl)ethanone (3la): Off White sticky liquid (25.4 mg, 58%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 3H), 7.33 – 7.30 (m, 4H), 7.27 (d, *J* = 5.3 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.12 (dd, *J* = 13.6, 5.8 Hz, 1H), 6.43 (d, *J* = 1.9 Hz, 0.37H), 6.39 (s, 1H), 6.00 – 5.97 (m, 1H), 3.87 (d, *J* = 13.5 Hz, 1H), 3.78 – 3.71 (m, 2H), 3.31 (dd, *J* = 16.7, 5.5 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 196.7, 141.4, 138.8, 138.5, 138.1, 136.2, 131.6, 130.2, 129.0, 128.8, 128.5, 128.3, 127.0, 126.9, 123.0, 122.5, 121.6, 87.7, 80.6, 46.3, 35.4. **FT-IR** (KBr): 1685(s), 1421(m), 1024(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2BrS^+$ $[M+NH_4]^+$: 456.0627, Found: 456.0622. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (98:2 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.7 min, τ_{major} = 17.0 min), ee 95%.

2-((1*R*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-(3-nitrophenyl)ethanone (3ma) (major diastereomer): yellow sticky liquid (17.4 mg, 43%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.84 (t, *J* = 1.8 Hz, 1H), 8.44 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.34 – 7.32 (m, 2H), 7.29 (d, *J* = 6.9 Hz, 4H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 6.39 (s, 1H), 5.95 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.90 (d, *J* = 13.4 Hz, 1H),

3.80 – 3.75 (m, 2H), 3.31 (dd, *J* = 16.6, 4.9 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 196.1, 141.4, 138.7, 138.5, 138.3, 134.3, 130.1, 129.6, 129.2, 129.1, 128.7, 128.6, 127.8, 127.2, 123.6, 122.8, 121.8, 88.2, 80.7, 46.7, 35.7. **FT-IR** (KBr): 1686(s), 1454(m), 1025(s). **HRMS (ESI^+):** Calcd. for $C_{23}H_{23}N_2O_4S^+$ $[M+NH_4]^+$: 423.1373, Found: 423.1370. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (92:8 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 19.1 min, τ_{major} = 17.8 min), ee 86%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(3-(trifluoromethyl)phenyl) ethanone (3na): Light yellow sticky liquid (26.5 mg, 62%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.26 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 3.7 Hz, 2H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 4H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 0.35H), 6.37 (s, 1H), 5.94 (dd, *J* = 7.6, 5.3 Hz, 1H), 3.88 (d, *J* = 13.4 Hz, 1H), 3.78 – 3.73 (m, 2H), 3.27 (dd, *J* = 16.7, 5.1 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)**: δ 196.9, 141.6, 138.8, 138.3, 131.9, 129.9, 129.9, 129.5, 129.2, 129.0, 128.7, 128.5, 127.2, 125.5, 125.5, 122.7, 121.8, 88.0, 80.8, 46.6, 35.5. **FT-IR** (KBr): 1672(s), 1465(m), 1124(s). **HRMS (ESI^+):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1707. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.6 min, τ_{major} = 18.4 min), ee 95%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(naphthalen-3-yl)ethanone (3oa): Off White sticky liquid (28.3 mg, 69%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.55 (s, 1H), 8.12 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.91 (dd, *J* = 16.3, 8.4 Hz, 4H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.56 (dd, *J* = 15.1, 7.3 Hz, 2H), 7.33 (d, *J* = 2.2 Hz, 3H), 7.30 (d, *J* = 3.3 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 3H), 6.45 (d, *J* = 2.0 Hz, 0.67H), 6.41 (s, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.75 (d, *J* = 13.4 Hz, 1H), 3.71 (dd, *J* = 9.8, 3.2 Hz, 1H), 3.39 (dd, *J* = 16.4, 5.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)**: δ 198.1, 141.9, 138.8, 138.2, 135.9, 134.7, 132.7, 130.8, 129.9, 129.3, 129.0, 128.8, 128.7, 128.6, 128.4, 128.0, 127.1, 127.0, 124.2, 122.6, 121.9, 87.9, 81.2, 46.5, 35.6. **FT-IR** (KBr): 1674(s), 1468(m), 1017(s). **HRMS (ESI^+):** Calcd. for $C_{27}H_{26}NO_2S^+$ $[M+NH_4]^+$: 428.1679, Found: 428.1683. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (98:2 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 59.2 min, τ_{major} = 40.5 min), ee 86%.

2-((1*R*,3*S*)-1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (3pa):

Off White sticky liquid (24.5 mg, 70%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.65 (d, *J* = 0.7 Hz, 1H), 7.35 – 7.27 (m, 10H), 6.58 (dd, *J* = 3.6, 1.6 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 0.2H), 6.39 (s, 1H), 5.95 (dd, *J* = 8.1, 5.1 Hz, 1H), 3.96 (d, *J* = 13.2 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.63 (dd, *J* = 15.9, 8.2 Hz, 1H), 3.21 (dd, *J* = 15.9, 5.0 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 186.6, 153.0, 147.1, 141.6, 138.7, 138.2, 129.3, 128.9, 128.7, 128.4, 127.2, 122.6, 121.7, 118.7, 112.5, 87.9, 80.7, 46.5, 35.4. **FT-IR** (KBr): 1672(s), 1467(m), 1018(s). **HRMS (ESI^+):** Calcd. for $C_{21}H_{22}NO_3S^+$ $[M+NH_4]^+$: 368.1315, Found: 368.1311. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (98:2 n-Hexane/2PrOH, 0.7 mL/min, 25 °C, 254 nm, τ_{minor} = 60.0 min, τ_{major} = 71.7 min), ee 96%.

1-((1*S*,3*S*)-3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)propan-2-one (3qa):

Off White sticky liquid (16.4 mg, 55%). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.35 (d, *J* = 7.5 Hz, 2H), 7.31 – 7.29 (m, 3H), 7.24 (d, *J* = 5.5 Hz, 2H), 7.21 – 7.18 (m, 1H), 6.42 (s, 0.27H), 6.37 (s, 1H), 5.73 (dd, *J* = 7.7, 5.4 Hz, 1H), 3.98 (d, *J* = 13.3 Hz, 1H), 3.82 (d, *J* = 13.3 Hz, 1H), 3.11 (dd, *J* = 16.5, 8.1 Hz, 1H), 2.87 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.24 (s, 4H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 206.8, 141.6, 138.6, 138.3, 129.3, 128.9, 128.7, 128.4, 127.2, 122.7, 121.6, 88.0, 80.4, 51.3, 35.5, 29.9. **FT-IR** (KBr): 1715(s), 1360(m), 1012(s). **HRMS (ESI^+):** Calcd. for $C_{18}H_{22}NO_2S^+$ $[M+NH_4]^+$: 316.1366, Found: 316.1377. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (97:3 n-Hexane/2PrOH, 1 mL/min, 25 °C, 254 nm, τ_{minor} = 18.7 min, τ_{major} = 20.4 min), ee 88%.

2-((1*R*,3*S*)-3-(benzylthio)-6-methyl-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ra): Off White sticky liquid (21.4 mg, 57%) **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 2H), 7.09 (s, 1H), 6.40 (d, *J* = 1.6 Hz, 0.23H), 6.36 (s, 1H), 5.96 – 5.92 (m, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.81 – 3.75 (m, 2H), 3.30 (dd, *J* = 16.7, 5.4 Hz, 1H), 2.36 (s, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.2, 142.2, 139.0, 138.4, 137.3, 135.9, 133.5, 129.3, 129.3, 129.2, 128.8, 128.7, 127.1, 122.4, 122.3, 87.9, 80.8, 46.6, 35.5, 21.6. **FT-IR** (KBr): 1678(s), 1449(m), 1019(s). **HRMS (ESI^+):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1684. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (97.5:2.5 n-Hexane/2PrOH, 1 mL/min, 25 °C, 254 nm, τ_{minor} = 43.1 min, τ_{major} = 21.0 min), ee 92%.

2-((1*R*,3*S*)-3-(Benzylthio)-5-fluoro-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3sa): (mixture of diastereomer): Off White sticky liquid (26.1 mg, 69%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.3 Hz, 1.8H), 7.99 (d, *J* = 7.3 Hz, 2.5H), 7.60 (t, *J* = 7.0 Hz, 2H), 7.51 – 7.47 (m, 4H), 7.29 – 7.27 (m, 4H), 7.23 (d, *J* = 7.1 Hz, 2H), 6.99 (dd, *J* = 8.7, 2.2 Hz, 2H), 6.93 – 6.90 (m, 1.7H), 6.37 (s, 1H), 6.32 (s, 0.78H), 5.93 (t, *J* = 6.3 Hz, 1.7H), 3.93 (d, *J* = 13.3 Hz, 0.8H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.79 (d, *J* = 12.9 Hz, 1H), 3.73 (s, 0.8H), 3.60 – 3.56 (m, 8H), 3.34 (dd, *J* = 11.5, 6.2 Hz, 1H), 3.32 – 3.29 (m, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.0, 197.6, 164.1, 164.0, 141.3, 141.0, 138.1, 138.0, 137.4, 137.1, 133.6, 133.5, 130.8, 130.7, 129.3, 129.2, 128.9, 128.7, 128.6, 128.5, 127.3, 127.2, 123.5, 123.3, 118.6, 118.5, 116.4, 116.2, 115.7, 115.5, 109.8, 109.6, 88.2, 87.4, 80.5, 79.3, 46.5, 45.3, 35.5, 34.7. **FT-IR** (KBr): 1683(s), 1477(m), 990(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2FS^+$ $[M+NH_4]^+$: 396.1428, Found: 396.1431. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (98.5:1.5 n-Hexane/2PrOH, 1 mL/min, 25 °C, 254 nm, τ_{minor} = 13.5 min, τ_{major} = 20.0 min), ee 94%.

2-((1*R*,3*S*)-3-(Benzylthio)-4-fluoro-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ta): Off White sticky liquid (32.9 mg, 87%). **^{1}H NMR (600 MHz, $CDCl_3$)**: *δ* 8.02 (d, *J* = 7.2 Hz, 2H), 7.62 – 7.59 (m, 1H), 7.50 – 7.48 (m, 2H), 7.31 (s, 2H), 7.30 (d, *J* = 4.1 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 4.7 Hz, 1H), 6.49 (d, *J* = 1.7 Hz, 0.6H), 6.46 (s, 1H), 6.00 – 5.98 (m, 1H), 3.99 (d, *J* = 13.3 Hz, 1H), 3.89 – 3.83 (m, 2H), 3.35 (dd, *J* = 16.9, 5.7 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 197.9, 155.7, 155.6, 145.5 (AB q), 137.9, 137.1, 133.7, 131.5, 129.3, 128.9, 128.7, 128.6, 128.5, 127.2, 117.9, 117.8, 115.4, 81.3, 79.6, 46.3, 35.9. **FT-IR** (KBr): 1683(s), 1476(m), 1001(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2FS^+$ $[M+NH_4]^+$: 396.1428, Found: 396.1429. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (97:3 n-Hexane/2PrOH, 1 mL/min, 25 °C, 254 nm, τ_{minor} = 16.2 min, τ_{major} = 36.5 min), ee 94%.

2-((1*R*,3*S*)-3-(4-methylbenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ab): Off White sticky liquid (14.6 mg, 53%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.06 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 3.2 Hz, 3H), 7.29 (t, *J* = 4.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.46 (d, *J* = 2.0 Hz, 0.22H), 6.42 (s, 1H), 6.01 (dd, *J* = 7.0, 5.8 Hz, 1H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.83 (dd, *J* = 16.7, 7.5 Hz, 1H), 3.78 (d, *J* = 13.2 Hz, 1H), 3.33 (dd, *J* = 16.7, 5.4 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR**

(151 MHz, $CDCl_3$): δ 198.2, 142.0, 138.9, 137.3, 136.8, 135.2, 133.5, 129.4, 129.2, 128.9, 128.8, 128.7, 128.3, 122.6, 121.9, 87.9, 80.9, 46.5, 35.2, 21.3. **FT-IR** (KBr): 1678(s), 1448(m), 1019(s). **HRMS (ESI^+):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1685. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.3 min, τ_{major} = 29.0 min), ee 96%.

2-((1*R*,3*S*)-3-(4-tert-butylbenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ac): Off White sticky liquid (25.8 mg, 62%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.48 (dd, *J* = 10.8, 4.6 Hz, 3H), 7.30 (t, *J* = 4.0 Hz, 5H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.45 (d, *J* = 2.1 Hz, 0.37H), 6.41 (s, 1H), 5.99 (dd, *J* = 7.2, 5.5 Hz, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 3.83 (dd, *J* = 16.7, 7.5 Hz, 1H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.34 (dd, *J* = 16.7, 5.5 Hz, 1H), 1.29 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 198.2, 150.1, 141.9, 138.9, 137.3, 133.5, 129.3, 128.9, 128.8, 128.7, 128.5, 128.3, 125.6, 122.6, 121.9, 88.0, 80.9, 46.6, 35.1, 31.5. **FT-IR** (KBr): 1684(s), 1449(m), 1365(m), 1017(s). **HRMS (ESI^+):** Calcd. for $C_{27}H_{32}NO_2S^+$ $[M+NH_4]^+$: 434.2148, Found: 434.2155. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (94:6 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 9.9 min, τ_{major} = 10.7 min), ee 96%.

2-((1*R*,3*S*)-3-(4-methoxybenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ad): Light yellow sticky liquid (30.5 mg, 78%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 3.6 Hz, 3H), 7.26 (t, *J* = 4.3 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.43 (d, *J* = 1.8 Hz, 0.21H), 6.39 (s, 1H), 5.98 (dd, *J* = 6.9, 5.9 Hz, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.78 (d, *J* = 5.9 Hz, 1H), 3.77 (s, 3H), 3.74 (d, *J* = 13.2 Hz, 1H), 3.30 (dd, *J* = 16.7, 5.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 198.2, 158.8, 141.9, 138.8, 137.3, 133.5, 130.3, 130.2, 128.9, 128.8, 128.7, 128.3, 122.6, 121.9, 114.1, 87.9, 80.9, 55.5, 46.5. **FT-IR** (KBr): 1680(s), 1511(m), 1013(s). **HRMS (ESI^+):** Calcd. for $C_{24}H_{26}NO_3S^+$ $[M+NH_4]^+$: 408.1628, Found: 408.1622. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-4 column (94:6 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 19.4 min, τ_{major} = 30.3 min), ee 96%.

2-((1*R*,3*S*)-3-(4-fluorobenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ae): Off White sticky liquid (21.2 mg, 56%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.94 (d, *J* =

7.3 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 3H), 7.24 (d, *J* = 4.1 Hz, 2H), 7.19 – 7.17 (m, 3H), 6.85 (t, *J* = 8.7 Hz, 2H), 6.34 (d, *J* = 2.1 Hz, 0.23H), 6.30 (s, 1H), 5.91 (dd, *J* = 7.4, 5.4 Hz, 1H), 3.82 (d, *J* = 13.4 Hz, 1H), 3.73 – 3.65 (m, 2H), 3.22 (dd, *J* = 16.7, 5.3 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)**: δ 197.8, 141.7, 138.4, 137.0, 133.8, 133.4, 130.6, 130.5, 128.8, 128.7, 128.4, 128.2, 122.4, 121.7, 121.5, 115.4, 115.2, 87.7, 80.7, 46.2, 34.6. **FT-IR** (KBr): 1682(s), 1450(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2FS^+$ $[M+NH_4]^+$: 396.1428, Found: 396.1425. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (97:3 n-Hexane/2PrOH, 1 mL/min, 25 °C, 254 nm, τ_{minor} = 33.7 min, τ_{major} = 20.0 min), ee 89%.

2-((1*R*,3*S*)-3-(4-Chlorobenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3af): Off White sticky liquid (23.3 mg, 59%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.33 – 7.29 (m, 3H), 7.26 – 7.24 (m, 1H), 7.22 (s, 4H), 6.41 (d, *J* = 2.0 Hz, 0.33H), 6.37 (s, 1H), 5.98 (d, *J* = 5.6 Hz, 1H), 3.88 (d, *J* = 13.5 Hz, 1H), 3.79 – 3.72 (m, 2H), 3.29 (dd, *J* = 16.7, 5.3 Hz, 1H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 197.9, 141.9, 138.6, 137.2, 136.9, 133.6, 130.6, 129.0, 128.9, 128.9, 128.8, 128.6, 128.4, 122.6, 121.9, 87.9, 80.9, 46.4, 34.8. **FT-IR** (KBr): 1677(s), 1489(m), 1015(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2ClS^+$ $[M+NH_4]^+$: 412.1133, Found: 412.1136. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (98:2 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 44.1 min, τ_{major} = 26.0 min), ee 94%.

2-((1*R*,3*S*)-3-(4-Bromobenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ag): Off White sticky liquid (27.2 mg, 62%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.32 – 7.30 (m, 2H), 7.28 (d, *J* = 7.5 Hz, 6H), 7.22 (d, *J* = 6.6 Hz, 1H), 6.41 (d, *J* = 2.0 Hz, 0.23H), 6.39 (s, 1H), 5.95 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.24 (dd, *J* = 16.5, 5.2 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 197.9, 141.9, 138.5, 137.5, 137.2, 133.6, 131.7, 131.0, 129.0, 128.9, 128.6, 128.4, 122.6, 121.9, 121.0, 87.9, 80.9, 46.4, 34.9. **FT-IR** (KBr): 1679(s), 1486(m), 1012(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2BrS^+$ $[M+NH_4]^+$: 456.0627, Found: 456.0636. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IB column (95:5 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.2 min, τ_{major} = 10.1 min), ee 94%.

2-((1*R*,3*S*)-3-(2-Methylbenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ah): Off White sticky liquid (15.7 mg, 57%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 4.0 Hz, 3H), 7.26 (d, *J* = 4.4 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 4.2 Hz, 2H), 7.10 (dd, *J* = 7.6, 4.1 Hz, 1H), 6.45 (d, *J* = 2.0 Hz, 0.29H), 6.42 (s, 1H), 6.02 – 5.98 (m, 1H), 3.94 (d, *J* = 12.7 Hz, 1H), 3.82 (dd, *J* = 16.7, 7.5 Hz, 1H), 3.78 (d, *J* = 12.7 Hz, 1H), 3.35 (dd, *J* = 16.7, 5.4 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 198.1, 141.9, 138.8, 137.3, 136.9, 135.9, 133.5, 130.7, 130.2, 128.9, 128.8, 128.6, 128.3, 127.5, 126.1, 122.6, 121.9, 88.0, 80.9, 46.6, 33.4, 19.4. **FT-IR** (KBr): 1688(s), 1448(m), 1017(s). **HRMS (ESI$^+$):** Calcd. for $C_{24}H_{26}NO_2S^+$ $[M+NH_4]^+$: 392.1679, Found: 392.1680. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (94:6 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.2 min, τ_{major} = 33.6 min), ee 92%.

2-((1*R*,3*S*)-3-(3-bromobenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ai): Off White sticky liquid (25 mg, 57%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 4H), 6.45 (d, *J* = 2.0 Hz, 0.37H), 6.41 (s, 1H), 6.00 (d, *J* = 5.8 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.33 (dd, *J* = 16.5, 5.4 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.0, 141.9, 140.8, 138.5, 137.2, 133.6, 132.2, 130.3, 130.2, 129.1, 128.9, 128.6, 128.4, 127.9, 122.6, 122.6, 122.0, 87.9, 81.0, 46.4, 34.9. **FT-IR** (KBr): 1677(s), 1461(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{23}NO_2BrS^+$ $[M+NH_4]^+$: 456.0627, Found: 456.0641. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 17.8 min, τ_{major} = 19.6 min), ee 93%.

2-((1*R*,3*S*)-3-(2,4-dichlorobenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3aj): Off White sticky liquid (25.3 mg, 59%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.32 – 7.29 (m, 4H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.08 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.46 (d, *J* = 1.9 Hz, 1H), 6.45 (s, 1H), 5.99 (dd, *J* = 7.5, 5.4 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.86 (d, *J* = 13.5 Hz, 1H), 3.77 (dd, *J* = 16.9, 7.7 Hz, 1H), 3.30 (dd, *J* = 16.9, 5.2 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 197.83, 141.91, 138.42, 137.14, 134.92, 133.61, 133.59, 132.01, 129.68, 129.12, 128.87, 128.56, 128.53,

128.42, 127.19, 122.63, 121.93, 88.23, 80.91, 77.48, 77.23, 76.98, 46.39, 32.84. **FT-IR** (KBr): 1686(s), 1469(m), 1023(s). **HRMS (ESI$^+$):** Calcd. for $C_{23}H_{22}NO_2Cl_2S^+$ $[M+NH_4]^+$: 446.0743, Found: 446.0741. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (95:5 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.9 min, τ_{major} = 16.7 min), ee 94%.

2-((1*R*,3*S*)-3-(naphthalen-2-ylmethylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3ak): Off White sticky liquid (25.5 mg, 62%). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 8.01 – 7.98 (m, 2H), 7.80 – 7.74 (m, 3H), 7.70 (s, 1H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.44 (m, 5H), 7.31 – 7.29 (m, 2H), 6.45 (d, *J* = 2.1 Hz, 0.25H), 6.42 (s, 1H), 6.02 – 5.96 (m, 1H), 4.10 (d, *J* = 13.3 Hz, 1H), 3.93 (d, *J* = 13.4 Hz, 1H), 3.78 (dd, *J* = 16.8, 7.4 Hz, 1H), 3.29 (dd, *J* = 16.8, 5.4 Hz, 1H). **^{13}C NMR (125 MHz, CDCl$_3$):** δ 198.14, 141.96, 138.68, 137.23, 135.69, 133.51, 133.46, 132.68, 128.96, 128.84, 128.63, 128.53, 128.36, 127.89, 127.85, 127.74, 127.50, 126.36, 125.97, 122.62, 121.92, 87.82, 80.91, 77.48, 77.23, 76.98, 46.46, 35.75. **FT-IR** (KBr): 1678(s), 1447(m), 1018(s). **HRMS (ESI$^+$):** Calcd. for $C_{27}H_{26}NO_2S^+$ $[M+NH_4]^+$: 428.1679, Found: 428.1683. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 31.5 min, τ_{major} = 84.6 min), ee 98%.

2-((1*R*,3*S*)-3-(cinnamylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3al): Light brown sticky liquid (15.1 mg, 39%). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 8.02 (d, *J* = 7.4 Hz, 4H), 7.58 (d, *J* = 6.9 Hz, 3H), 7.47 (d, *J* = 7.8 Hz, 6H), 7.32 (d, *J* = 6.0 Hz, 12H), 7.22 (t, *J* = 7.2 Hz, 4H), 6.54 (d, *J* = 2.1 Hz, 0.52H), 6.51 (s, 2H), 6.45 (d, *J* = 15.7 Hz, 2H), 6.27 – 6.22 (m, 2H), 5.99 – 5.96 (m, 2H), 3.83 (dd, *J* = 16.7, 7.5 Hz, 2H), 3.59 – 3.54 (m, 3H), 3.33 (dd, *J* = 16.7, 5.3 Hz, 4H). **^{13}C NMR (126 MHz, CDCl$_3$)** δ 198.2, 141.9, 138.7, 138.3, 137.3, 133.5, 129.3, 128.9, 128.8, 128.7, 128.7, 128.5, 128.4, 127.2, 126.5, 122.6, 121.9, 87.9, 80.9, 46.5, 35.5. **FT-IR** (KBr): 1681(s), 1448(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{25}H_{26}NO_2S^+$ $[M+NH_4]^+$: 404.1679, Found:. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 18.5 min, τ_{major} = 86.0 min), ee 97%.

2-((1*R*,3*S*)-3-(tert-butylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (3am): Off White sticky liquid (21.2 mg, 65%). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 8.03 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.28 (m, 4H), 6.71 (s, 0.11H),

6.68 (s, 1H), 5.97 (dd, *J* = 7.3, 5.6 Hz, 1H), 3.84 (dd, *J* = 16.7, 7.5 Hz, 1H), 3.31 (dd, *J* = 16.7, 5.5 Hz, 1H), 1.42 (s, 9H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ 198.4, 141.9, 133.4, 129.3, 128.8, 128.7, 128.7, 128.2, 127.1, 122.9, 121.8, 86.9, 80.9, 47.0, 35.5, 32.0. **FT-IR** (KBr): 1685(s), 1460(m), 1016(s). **HRMS (ESI$^+$):** Calcd. for $C_{20}H_{26}NO_2S^+$ $[M+NH_4]^+$: 344.1679, Found: 344.1680. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (97:3 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 8.5 min, τ_{major} = 7.0 min), ee 98%.

1-phenyl-2-((1*R*,3*S*)-3-(tritylthio)-1,3-dihydroisobenzofuran-1-yl)ethanone (3an): Off White sticky liquid (12.9 mg, 25%). **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.10 (d, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 7H), 7.30 – 7.27 (m, 9H), 7.23 (d, *J* = 7.9 Hz, 6H), 5.91 – 5.88 (m, 1H), 5.76 (s, 1H), 3.90 (dd, *J* = 16.8, 7.4 Hz, 1H), 3.41 (dd, *J* = 16.8, 5.5 Hz, 1H), 2.81 (s, 1H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 197.9, 147.0, 145.3, 141.6, 139.1, 137.1, 133.6, 130.4, 128.9, 128.7, 128.1, 128.1, 128.0, 127.5, 127.0, 123.4, 121.6, 89.8, 80.8, 70.04, 46.83. **FT-IR** (KBr): 1678(s), 1638(m), 1449(m), 1015(s). **HRMS (ESI$^+$):** Calcd. for $C_{35}H_{32}NO_2S^+$ $[M+NH_4]^+$: 530.2148, Found: 530.2147. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 16.8 min, τ_{major} = 15.1 min), ee 91%.

2-((1*R*,3*S*)-3-hydroxy-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (4): White amorphous solid (12.2 mg, 96%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.58 – 7.55 (m, 1H), 7.46 (d, *J* = 7.9 Hz, 4H), 7.38 – 7.34 (m, 2H), 6.47 (s, 1H), 6.07 (t, *J* = 5.6 Hz, 0.59H), 5.74 (t, *J* = 5.5 Hz, 1H), 3.68 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.55 – 3.50 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.9, 141.8, 137.1, 133.7, 129.6, 128.8, 128.5, 128.5, 128.4, 123.3, 121.4, 101.6, 79.1, 45.70. **FT-IR** (KBr): 1678(m), 1464(s), 1377(w), 1011(m). **HRMS (ESI$^+$):** Calcd. for $C_{16}H_{14}O_3^+$ $[M]^+$: 254.0943, Found: 254.1180. The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux cellulose-1 column (85:15 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 15.1 min, τ_{major} = 13.1 min), ee 96%.

4-Methoxyphenyl 2-((*1R,3R*)-3-hydroxy-1,3-dihydroisobenzofuran-1-yl)acetate (6): White amorphous solid (13.8 mg, 92%)**. ^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.45 (d, *J* = 4.9 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.25 – 7.22 (m, 1H), 6.90 (d, *J* = 8.8 Hz,

2H), 6.45 (s, 1H), 6.04 (t, *J* = 5.6, 0.63H), 5.71 (t, *J* = 5.5 Hz, 1H), 3.85 (s, 3H), 3.61 (dd, *J* = 17.1, 6.0 Hz, 1H), 3.47 – 3.44 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 170.4, 157.5, 143.7, 140.3, 140.0, 129.7, 128.8, 123.5, 122.4, 121.2, 114.6, 101.9, 78.8, 55.77, 41.23. **FT-IR** (KBr): 1750(s), 1507(m), 1196(m), 1002(s). **HRMS (ESI$^+$):** Calcd. for $C_{17}H_{16}O_5^+$ $[M]^+$: 300.0998, Found: 300.1223. The enantiomeric ratio was determined by HPLC analysis using Chiralpak IA column (85:15 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 19.7 min, τ_{major} = 21.4 min), ee 93%.

(*S*)-2-(1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (7): Off white sticky solid (8.6 mg, 72%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 1H), 5.91 (t, *J* = 6.0 Hz, 1H), 5.16 (dd, *J* = 12.2, 2.3 Hz, 1H), 5.10 (d, *J* = 12.2 Hz, 1H), 3.55 (dd, *J* = 16.7, 7.4 Hz, 1H), 3.36 (dd, *J* = 16.7, 5.0 Hz, 1H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 198.1, 141.6, 139.5, 137.3, 133.5, 128.8, 128.5, 128.0, 127.7, 121.7, 121.2, 80.4, 72.8, 45.8. **FT-IR** (KBr): 1633(s), 1384(m), 1025(s). **HRMS (ESI$^+$):** Calcd. for $C_{16}H_{14}O_2^+$ $[M]^+$: 239.1067, Found: 239.1066. The enantiomeric ratio was determined by HPLC analysis using Chiralpak ID column (96:4 n-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 30.8 min, τ_{major} = 32.3 min), ee 84%.

5.10. Crystal data and structure refinement for chiral compound (CCDC 1581645) 3pa:

Empirical formula	$C_{21}H_{18}O_3S$
Formula weight	350.44
Temperature/K	298K
Crystal system	orthorhombic
Space group	'P 21 21 21'
a/Å	4.6966(2)
b/Å	12.0477(6)
c/Å	31.218(2)
α/°	90.00
β/°	90.00
γ/°	90.00
Volume/Å^3	1766.43(17)
Z	4

ρ_{calc}mg/mm^3	1.3176
m/mm^{-1}	0.200
F(000)	736.8
Crystal size/mm^3	0.35 × 0.22 × 0.14
2Θ range for data collection	6.22 to 50°
Index ranges	-6 ≤ h ≤ 4, -15 ≤ k ≤ 8, -23 ≤ l ≤ 41
Reflections collected	5085
Independent reflections	2843 [R_{int}=0.0193, R_{sigma} = 0.0449]
Data/restraints/parameters	2843/0/225
Goodness-of-fit on F^2	1.432
Final R indexes [I>=2σ (I)]	R_1 = 0.0504, wR_2 = 0.0987
Final R indexes [all data]	R_1 = 0.0629, wR_2 = 0.1038
Largest diff. peak/hole / e Å^{-3}	0.21/-0.24
Flack parameter	0.02(17)

References:

1. a) N. J. Turner, *Curr. Opin. Biotechnol*. **2003**, *14*, 401; b) N. J. Turner, Trends *Biotechnol*. **2003**, *21*, 474; c) M. Alexeeva, R. Carr, N. J. Turner, *Org. Biomol. Chem.* 2003, 1, 4133; d) N. J. Turner, *Curr. Opin. Chem. Biol.* **2004**, *8*, 114; e) B. Schnell, K. Faber, W. Kroutil, *Adv. Synth. Catal*. **2003**, *345*, 653; f) U. T. Bornscheuer, *Adv. Biochem. Eng./Biotechnol.* **2005**, *100*, 181; g) P. Gadler, S. M. Glueck, W. Kroutil, B. M. Nestl, B. Larissegger-Schnell, B. T. Ueberbacher, S. R. Wallner, K. Faber, *Biochem. Soc. Trans*. **2006**, *34*, 296.
2. D. E. J. E. Robinson, S. D. Bull, *Tetrahedron: Asymmetry* **2003**, *14*, 1407.
3. a) J. W. Evans, M. B. Fierman, S. J. Miller, J. A. Ellman, *J. Am. Chem. Soc.* **2004**, *126*, 8134; b) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251; c) A. Berkessel, F. Cleemann, S. Mukherjee, T. N. Müller, J. Lex, *Angew. Chem., Int. Ed*. **2005**, *44*, 807; d) X. Yang, G. Lu, V. B. Birman, *Org. Lett*. **2010**, *12*, 892; e) S. Yamada, K. Yamashita, *Tetrahedron Lett.* **2008**, *49*, 32; f) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 13074.
4. L. Tang, L. Deng, *J. Am. Chem. Soc*. **2002**, *124*, 2870.

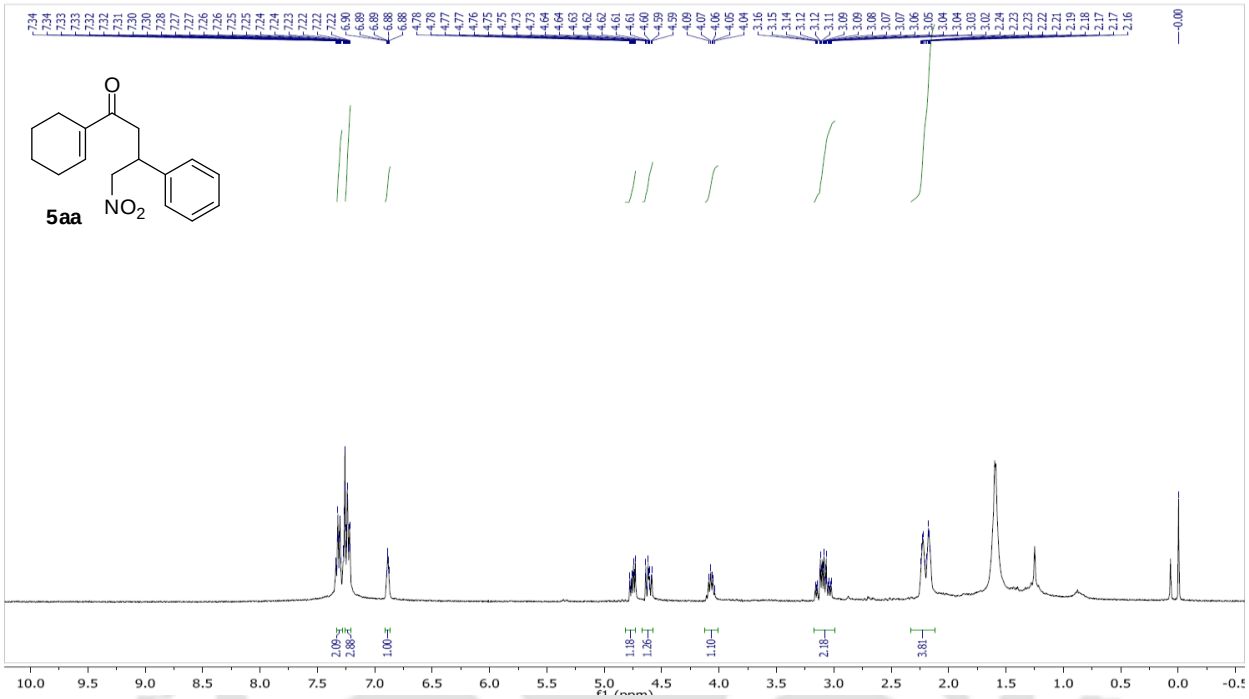
5. a) A. Peschiulli, C. Quigley, S. Tallon, Y. K. Gun'ko, S. J. Connon, *J. Org. Chem*. **2008**, *73*, 6409.
6. a) J. Wang, H. Xie, H. Li, L. Zu, W. Wang, *Angew. Chem., Int. Ed.* **2008**, *47*, 4177; b) S. Meninno, G. Croce, A. Lattanzi, *Org. Lett*. **2013**, *15*, 3436; c) C. Yu, Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* **2011**, *17*, 770; d) W. Yang, Y. Yang, D.-M. Du, *Org. Lett*. **2013**, *15*, 11.
7. L. Zu, H. Xie, H. Li, J. Wang, W. Jiang, W. Wang, *Adv. Synth. Catal*. **2007**, *349*, 1882.
8. a) V. N. Wakchaure, J. Zhou, S. Hoffmann, B. List, *Angew. Chem., Int. Ed.* **2010**, *49*, 4612; b) S. Hoffmann, M. Nicoletti, B. List, *J. Am. Chem. Soc*. **2006**, *128*, 13074.
9. B.-C. Hong, R.-H. Jan, C.-W. Tsai, R. Y. Nimje, J.-H. Liao, G.-H. Lee, *Org. Lett*. **2009**, *11*, 5246.
10. a) E. Reyes, A. Cordova, *Tetrahedron Lett*. **2005**, *46*, 6605; b) A. Cordova, I. Ibrahem, J. Casas, H. Sunden, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772.
11. S. Maity, B. Parhi, P. Ghorai, *Angew. Chem., Int. Ed.* **2016**, *55*, 7723.
12. a) M. Sakulsombat, Y. Zhang, O. Ramström, *Chem. Eur. J.* **2012**, *18*, 6129; b) Y. Zhang, L. Hu, O. Ramström, *Chem. Commun.* **2013**, *49*, 1805; c) Y. Zhang, F. Schaufelberger, M. Sakulsombat, C. Liu, O. Ramström, *Tetrahedron* **2014**, *70*, 3826.
13. S. Brand, M. F. Jones, C. M. Rayner, *Tetrahedron Lett*. **1995**, *36*, 8493.
14. V. Capaccio, A. Capobianco, A. Stanzione, G. Pierri, C. Tedesco, A. D. Mola, A. Massa, L. Palombi, *Adv. Synth. Catal*. **2017**, *359***,** 2874.
15. For selected examples and reviews, see: a) R. Karmakar, P. Pahari, D. Mal, *Chem. Rev*. **2014**, *114*, 6213; b) L. Dorell, M. A. Cohen, S. S. Hupriker, J. M. Gorman, M. Jones, *Psychosomatics* **2005**, *46*, 91; c) J. K. Harper, A. M. Arif, E. J. Ford, G. A. Strobel, J. A. Porco Jr., D. P. Tomer, K. L. Oneill, E. M. Heider, D. M. Grant, *Tetrahedron* **2003**, *59*, 2471; d) U. Holler, J. B. Gloer, D. T. Wicklow, *J. Nat. Prod*. **2002**, *65*, 876; e) B. Gozler, T. Gozler, M. Shamma, *Tetrahedron* **1983**, *39*, 577.
16. a) J. F. DeBernardis, D. L. Arendsen, J. J. Kynel, D. J. Kerkman, *J. Med. Chem*. **1987**, *30*, 178.
17. For selected examples, see: a) D. Garcia, F. Foubelo, M. Yus, *Tetrahedron* **2008**, *64*, 4275; b) T.-Y. Yuen, S.-H. Yang, M. A. Brimble, *Angew. Chem. Int. Ed.* **2011**, *50*, 8350; c) S. E. Denmark, C. S. Regens, Kobayashi, *J. Am. Chem. Soc*. **2007**, *129*, 2774.

18. M. Ghosh, R. Singha, S. Dhara, J. K. Ray, *RSC Adv.* **2015**, *5*, 85911 and referenes cited there in.
19. B. Ravindra, B. G. Das, P. Ghorai, *Org. Lett.* **2014**, *16*, 5580.
20. D. F. Ewing, C. Len, G. Mackenzie, G. Ronco, P. Villa, *Tetrahedron: Asymmetry*, **2000**, *11*, 4995.
21. For selected examples on organocatalytic oxa-Michael additions, see: a) R. R. Reddy, S. S. Gudup, P. Ghorai, *Angew. Chem., Int. Ed.* **2016**, *55*, 15115; b) P. Saha, A. Biswas, N. Moleleti, V. K. Singh, *J. Org. Chem*. **2015**, *80*, 11115; c) Y. Zhu, X. Li, Q. Chen, J. Su, F. Jia, Q. Qiu, M. Ma, Q. Sun, W. Yan, K. Wang, R. Wang, *Org. Lett*. **2015**, *17*, 3826; d) Z.-C. Geng, S.-Y. Zhang, N.-K. Li, N. Li, J. Chen, H.-Y. Li, X.-W. Wang, *J. Org. Chem*. **2014**, *79*, 10722; e) T. Azuma, A. Murata, Y. Kobayashi, T. Inokuma, Y. Takemoto, *Org. Lett*. **2014**, *16*, 4256; f) R. Miyaji, K. Asano, S. Matsubara, *Org. Biomol. Chem*. **2014**, *12*, 119; g) Y. Lu, G. Zou, G. Zhao, *ACS Catal*. **2013**, *3*, 1356; h) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma, Y. Takemoto, *Angew. Chem. Int. Ed*. **2013**, *52*, 11114; i) M. T. Corbett, J. S. Johnson, *Chem. Sci*. **2013**, *4*, 2828. (j) Hou, W.; Zheng, B. B.; Chen, J.; Peng, Y. *Org. Lett*. **2012**, *14*, 2378.
22. CCDC 1581645 contains the crystallographic data for **3pa**.
23. W. Guo, B. Wu, X. Zhou, P. Chen, X. Wang, Y.-G. Zhou, Y. Liu, C. Li, *Angew. Chem., Int. Ed*. **2015**, *54*, 4522.

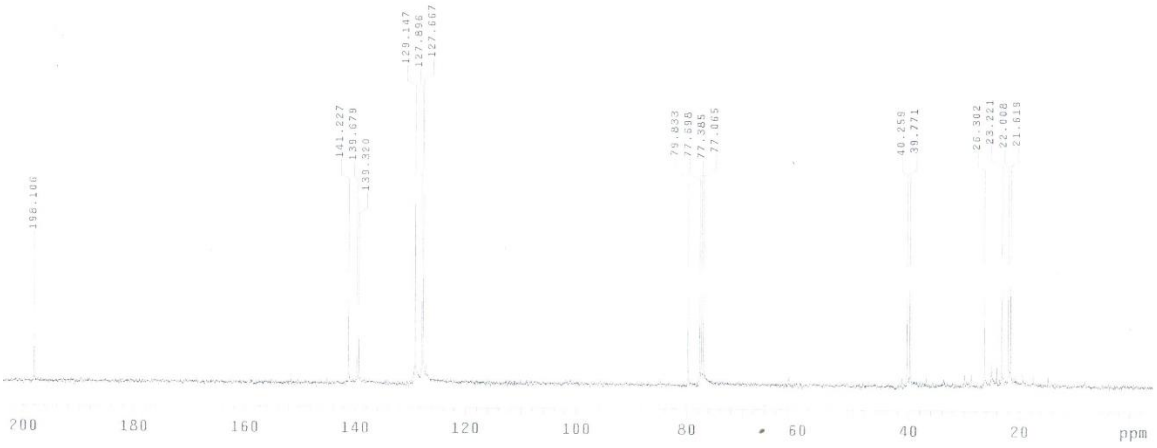
Selected NMR Spectra and HPLC Chromatograms

Chapter 2

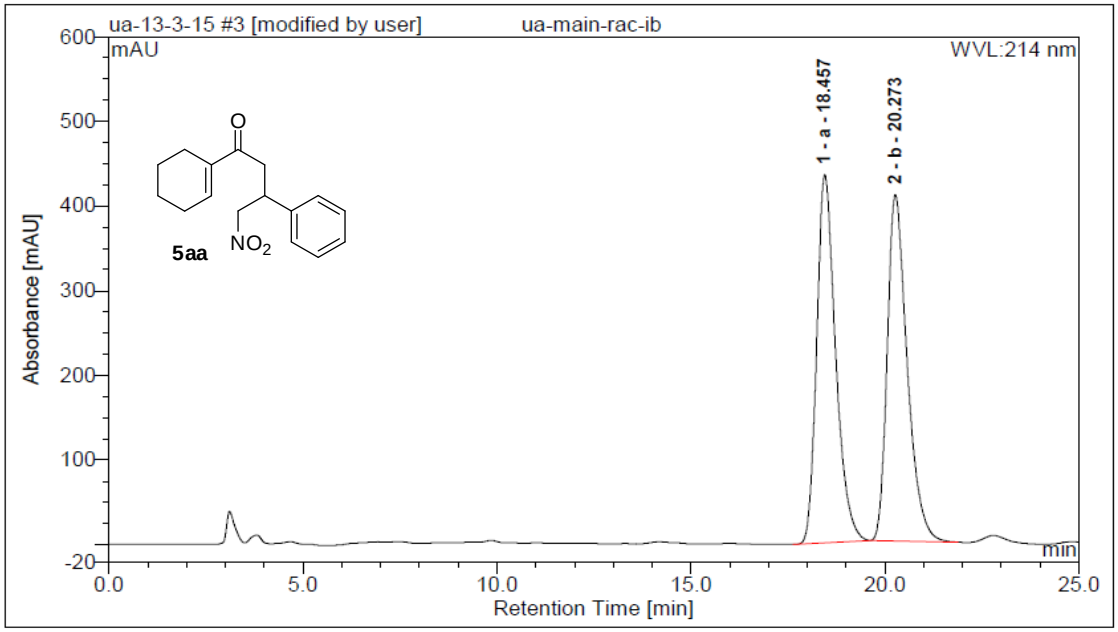
^{1}H-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclohexenyl-4-nitro-3-phenylbutan-1-one (**5aa**):*



^{13}C-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclohexenyl-4-nitro-3-phenylbutan-1-one (**5aa**):*

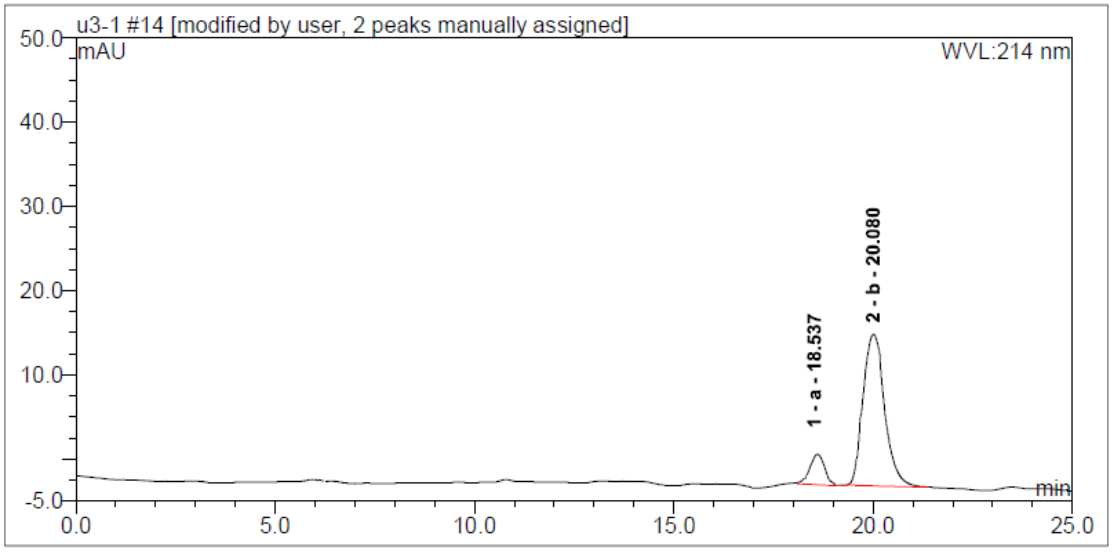


HPLC Chromatogram (racemic): *1-Cyclohexenyl-4-nitro-3-phenylbutan-1-one (**5aa**):*



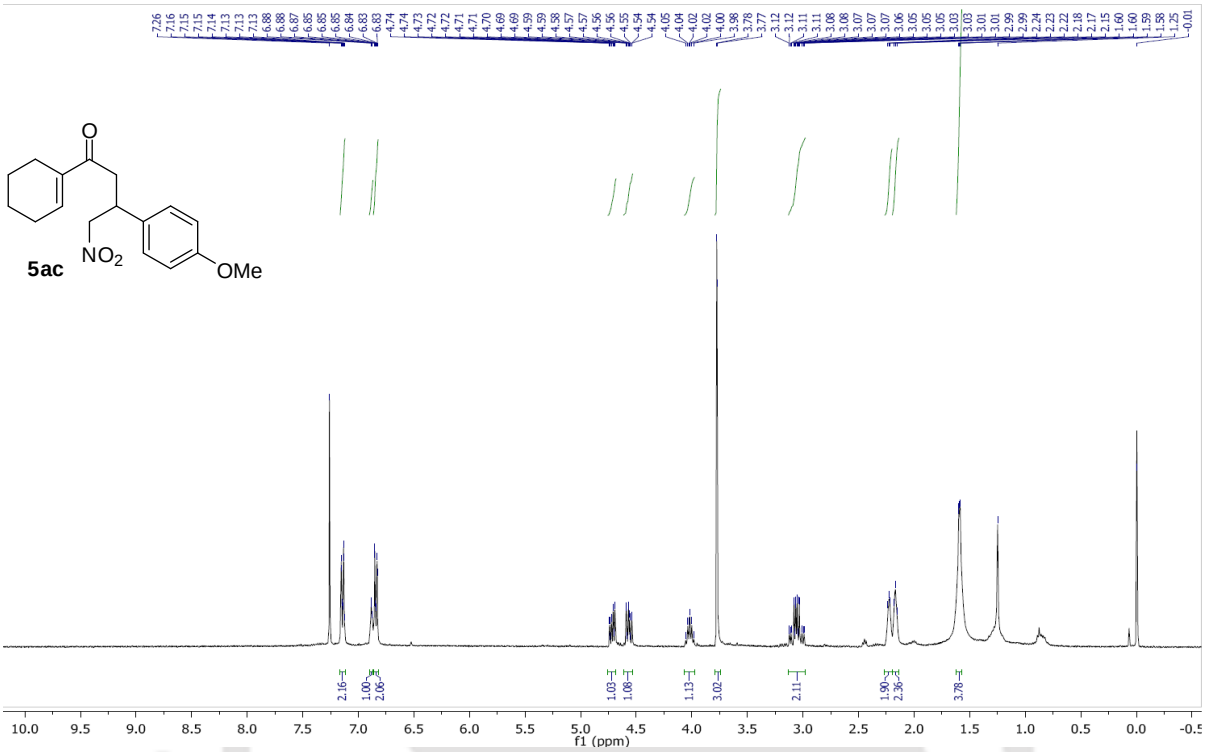
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.46	245.2792	50.19423007	434.6023	n.a.
2	b	20.27	243.381	49.80576993	408.903	n.a.

HPLC Chromatogram (chiral): *1-Cyclohexenyl-4-nitro-3-phenylbutan-1-one (**5aa**):*

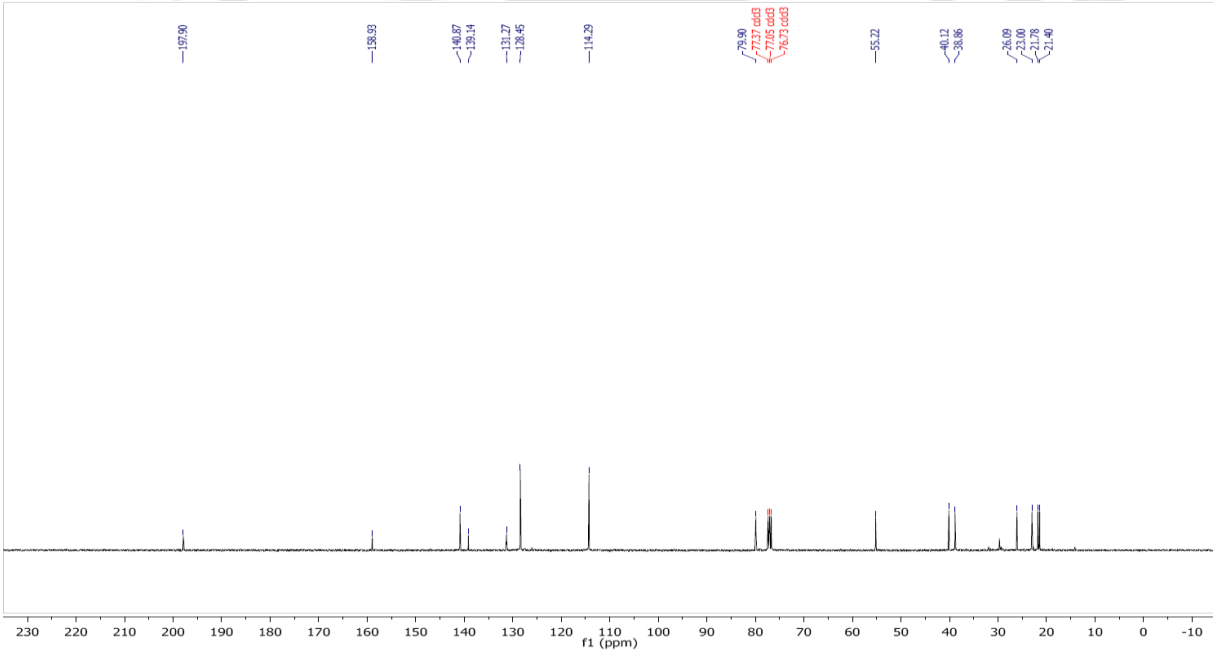


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.54	0.805026	12.06188408	2.56125	n.a.
2	b	20.08	5.869	87.93811592	10.268	n.a.

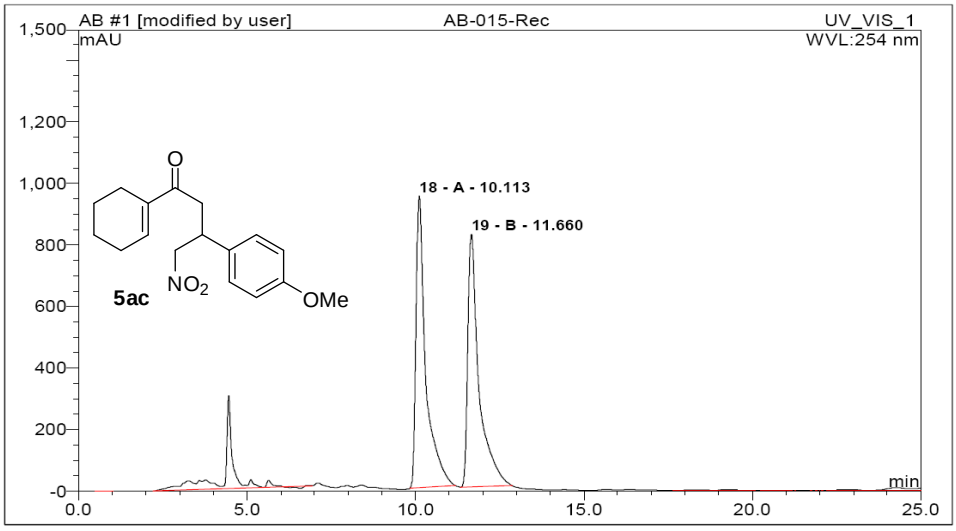
^{1}H-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclohexenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one* ***(5ac)****:*



^{13}C-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclohexenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one* ***(5ac)****:*

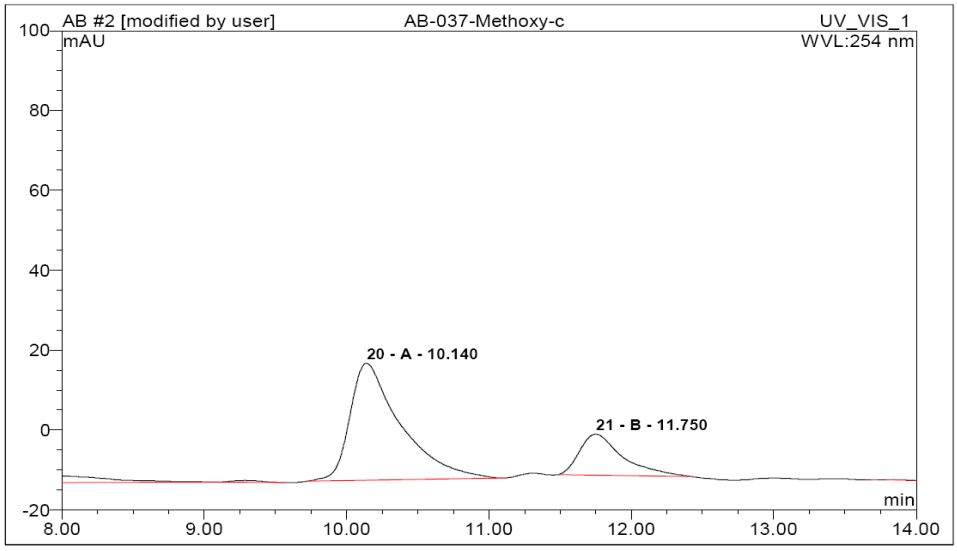


HPLC Chromatogram (racemic): *1-Cyclohexenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one* ***(5ac)****:*



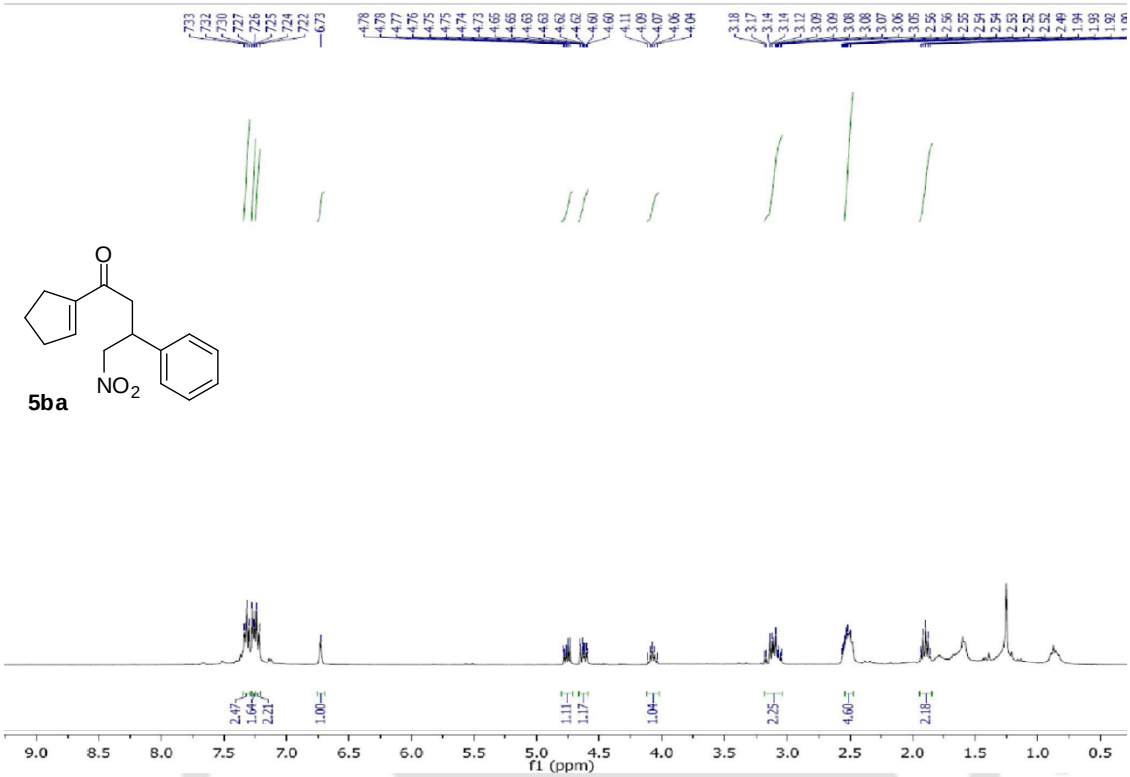
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(id %	Height mAU	Amount
	A	10.11333333	320.5163	50.28589	949.1114	
	B	11.66	316.8718	49.71411	821.532	

HPLC Chromatogram (chiral): *1-Cyclohexenyl-3-(4-methoxyphenyl)-4-nitrobutan-1-one* ***(5ac)****:*

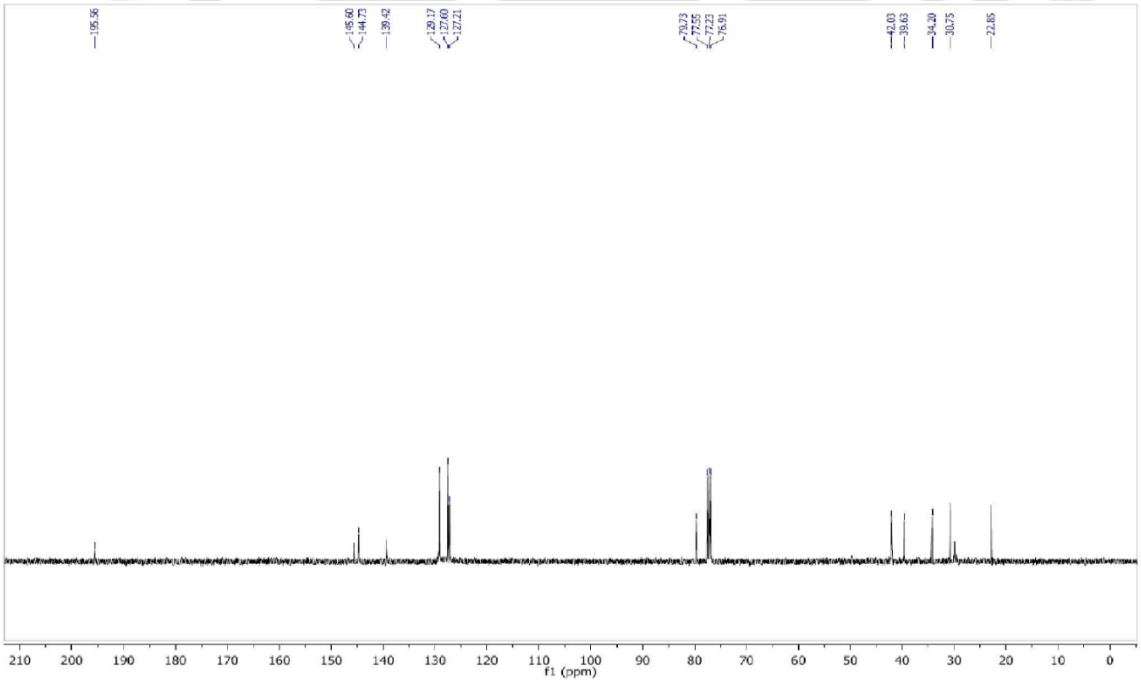


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(id %	Height mAU	Amount
	A	10.14	12.03725	77.14042	29.28104	
	B	11.75	3.567085	22.85958	10.24287	

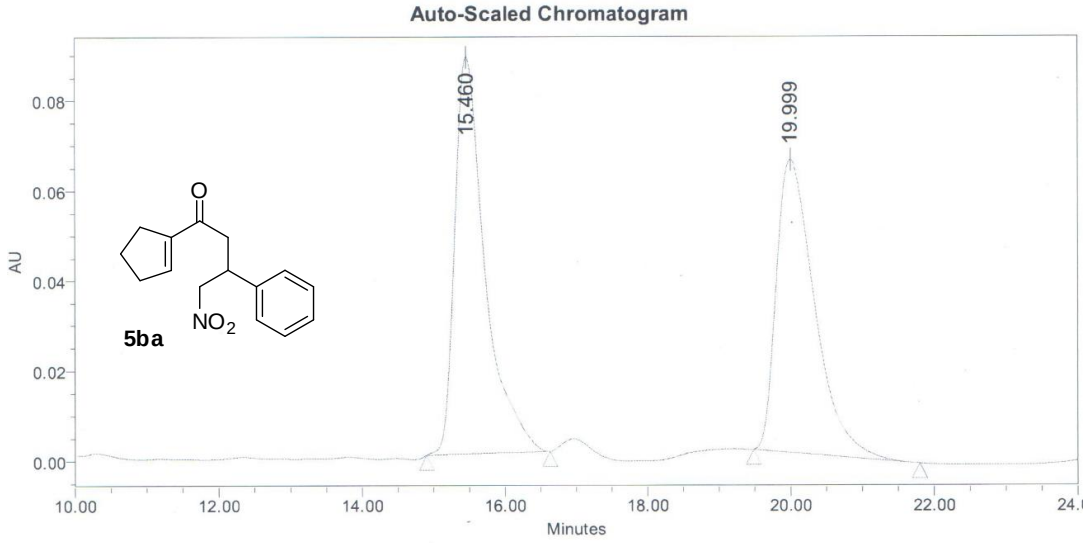
^{1}H-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclopentenyl-4-nitro-3-phenylbutan-1-one* ***(5ba)****:*



^{13}C-NMR Spectra (400 MHz, $CDCl_3$): *1-Cyclopentenyl-4-nitro-3-phenylbutan-1-one* ***(5ba)****:*



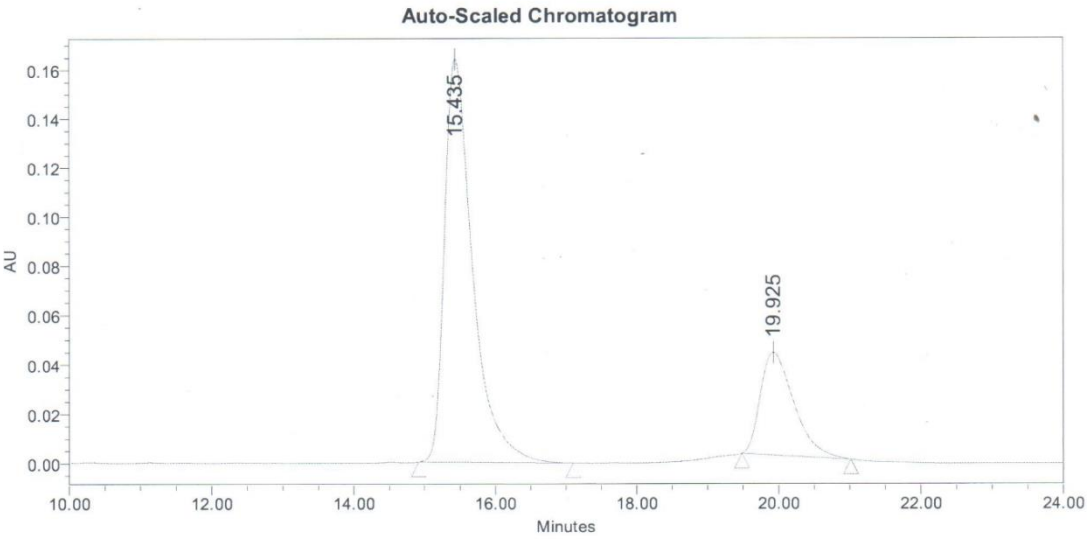
HPLC Chromatogram (racemic): *1-Cyclopentenyl-4-nitro-3-phenylbutan-1-one* ***(5ba)****:*



Peak Results

	Name	RT	Area	Height	% Area
1		15.460	2589944	88068	51.71
2		19.999	2418635	64978	48.29

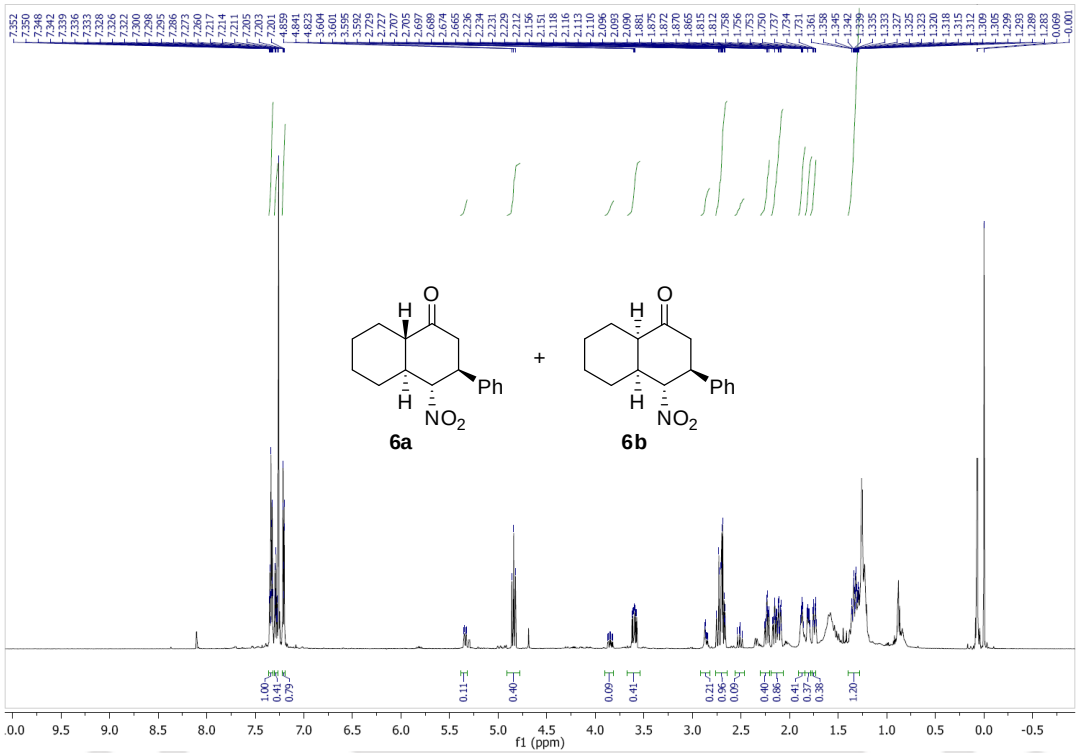
HPLC Chromatogram (chiral): *1-Cyclopentenyl-4-nitro-3-phenylbutan-1-one* ***(5ba)****:*



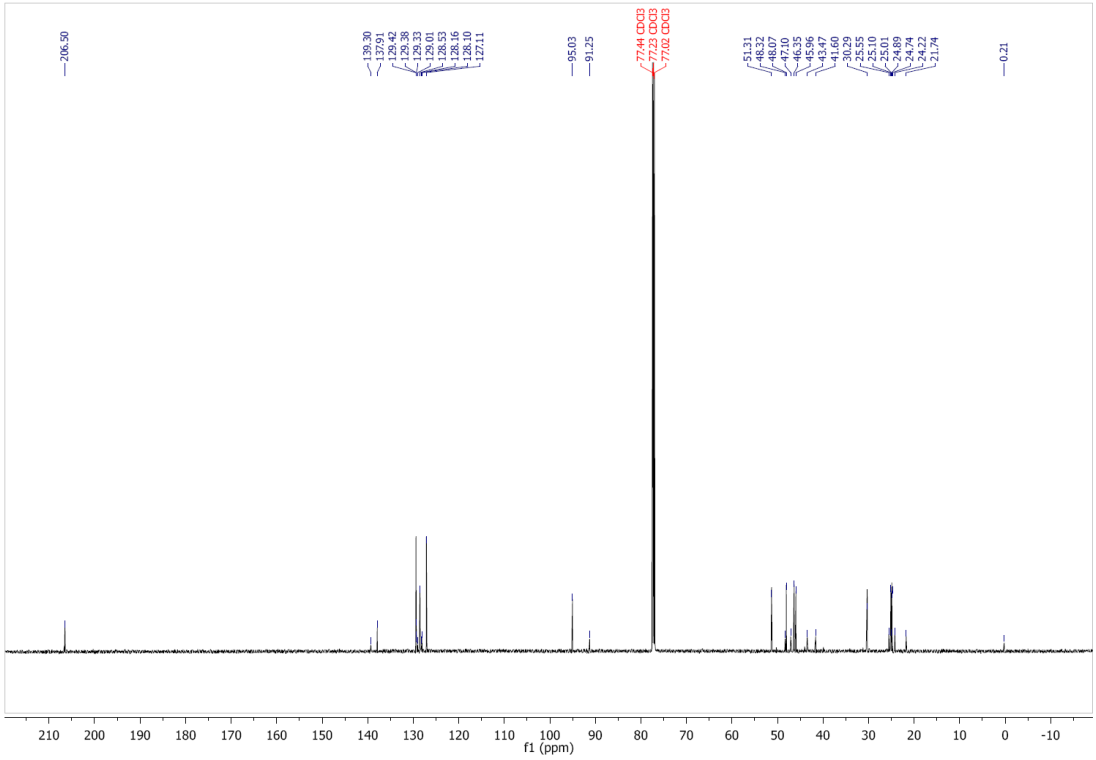
Peak Results

	Name	RT	Area	Height	% Area
1		15.435	4535657	164027	76.88
2		19.925	1364039	41618	23.12

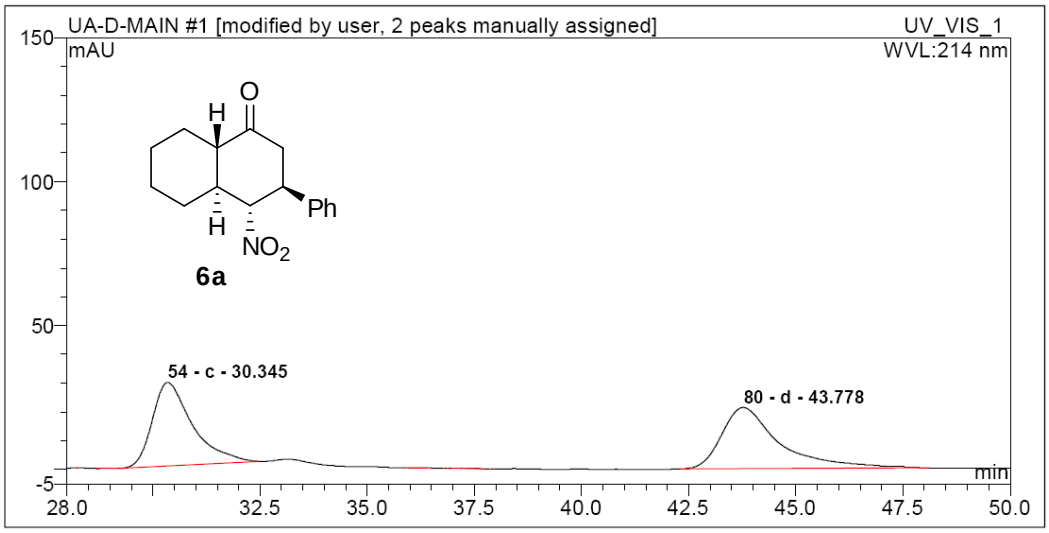
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (**6a** + **6b** = 4:1):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (**6a** + **6b** = 4:1):*

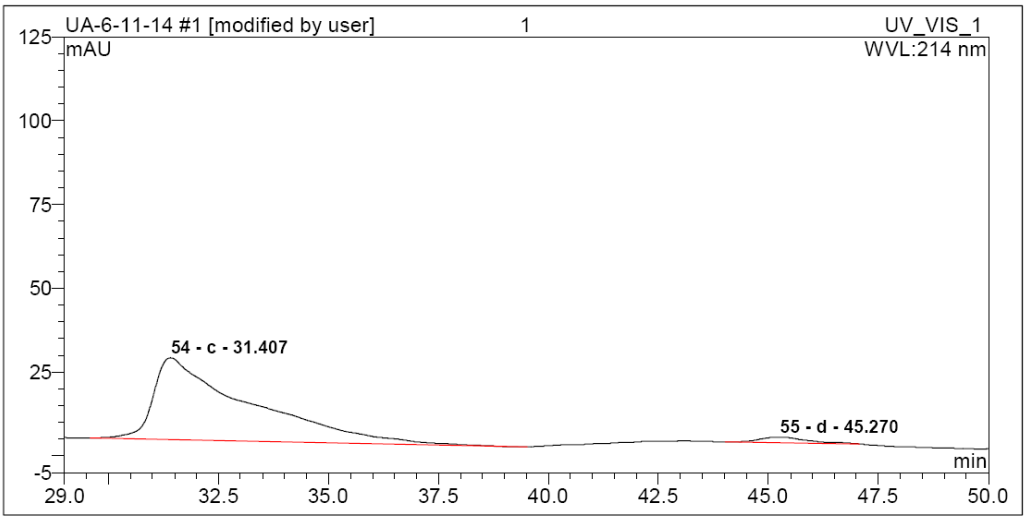


HPLC Chromatogram (racemic): *4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (**6a**):*



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
54	c	30.345	31.38767	48.67968264	28.98986	n.a.
80	d	43.78	33.090	51.32	21.268	n.a.

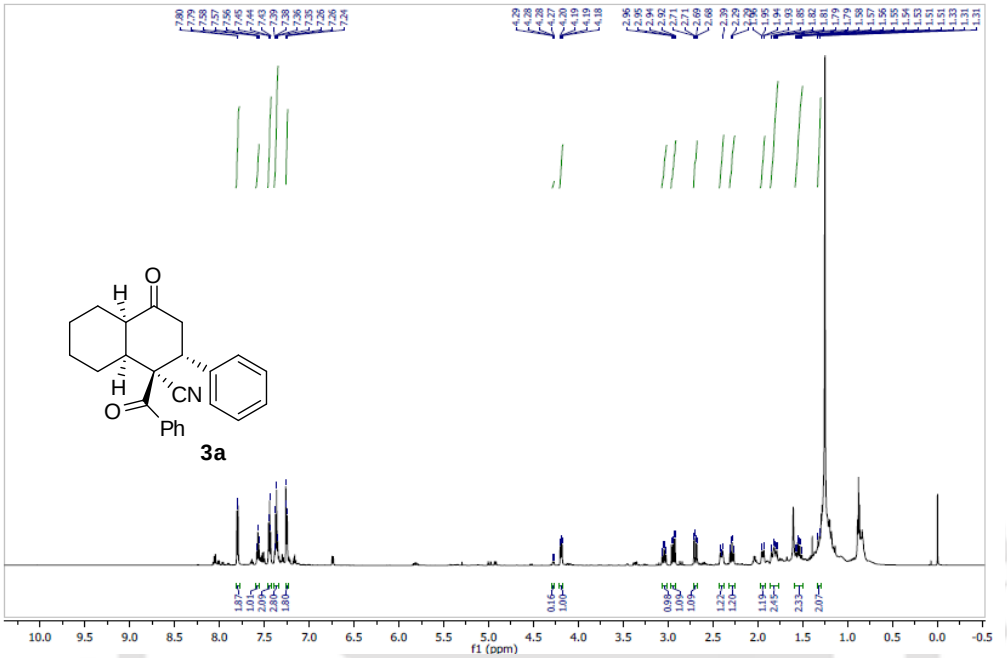
HPLC Chromatogram (chiral): *4-Nitro-3-phenyloctahydronaphthalen-1(2H)-one (**6a**):*



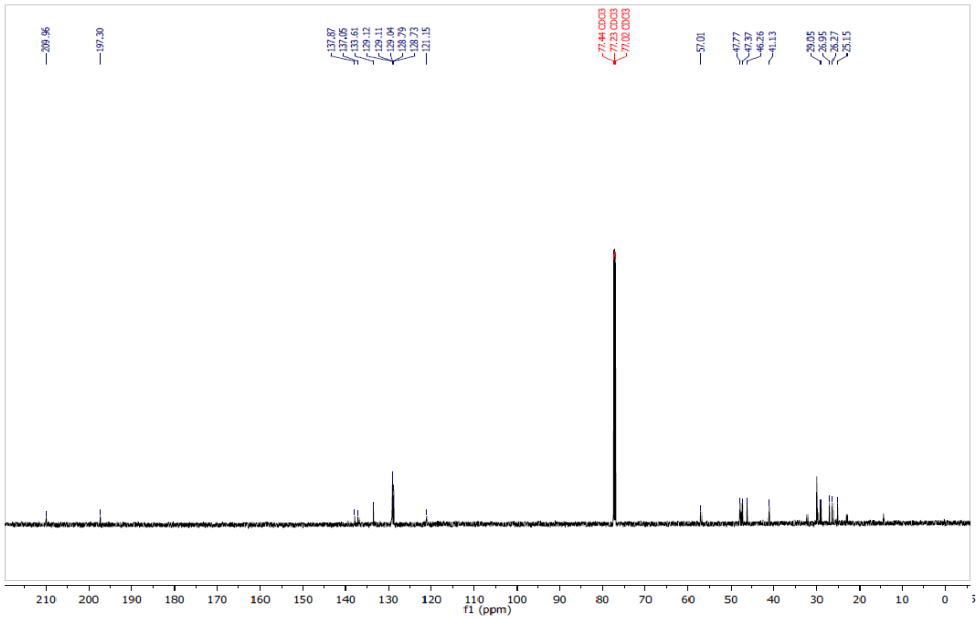
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
54	c	31.40666667	63.14059	96.74638753	24.38137	n.a.
55	d	45.27	2.123	3.25	1.677	n.a.

Chapter 3

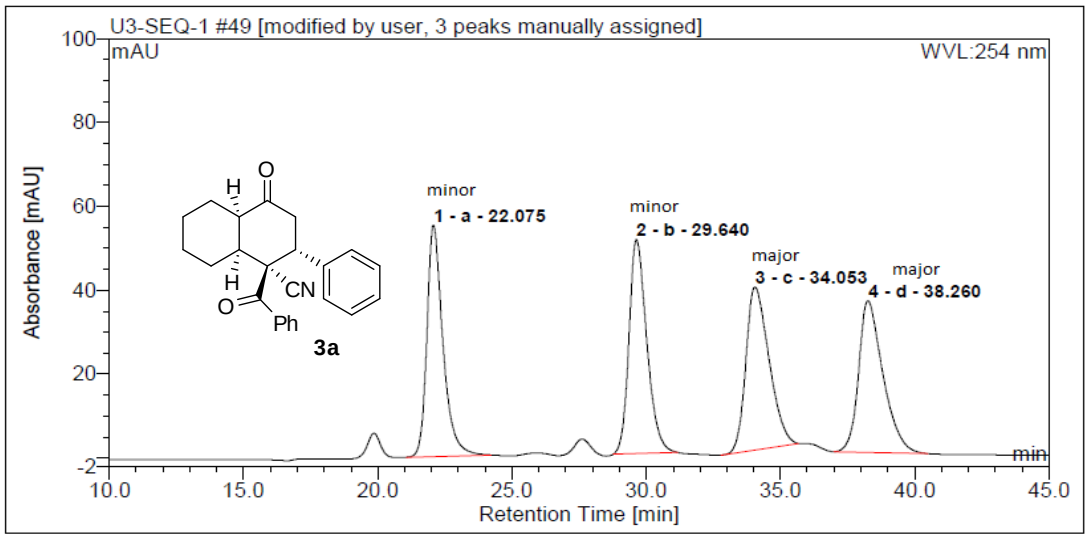
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*

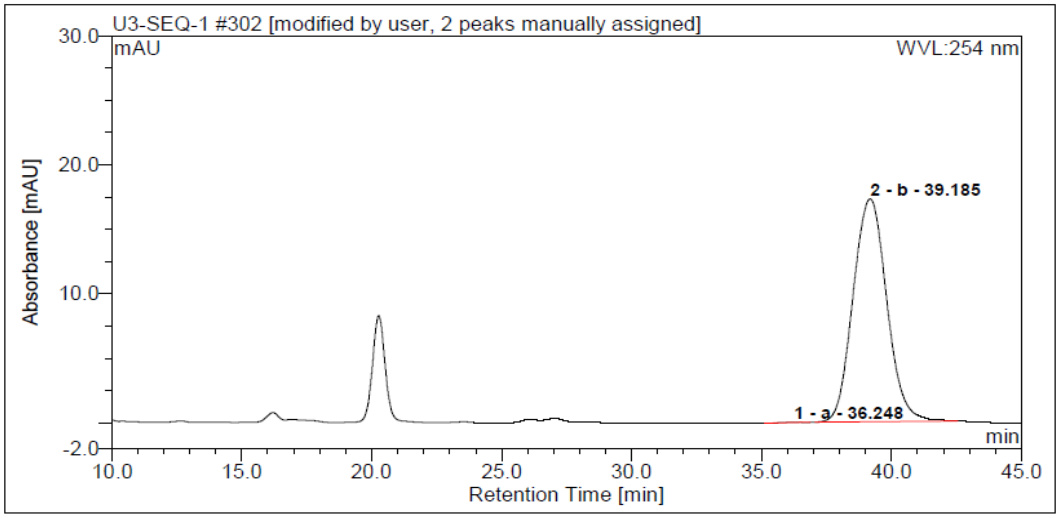


HPLC Chromatogram (racemic): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*



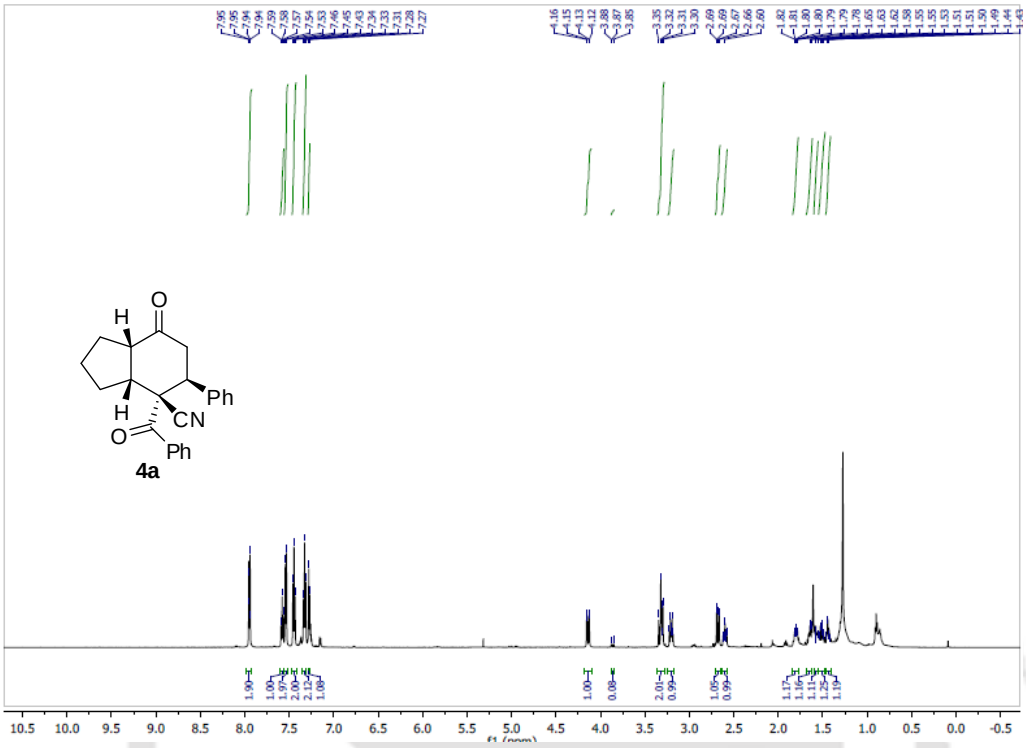
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	22.08	38.07304	24.71068371	55.14261	n.a.
2	b	29.64	39.1212	25.39097525	50.96912	n.a.
3	c	34.05	38.8119	25.19023005	38.85762	n.a.
4	d	38.26	38.069	24.70811099	36.163	n.a.

HPLC Chromatogram (chiral): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*

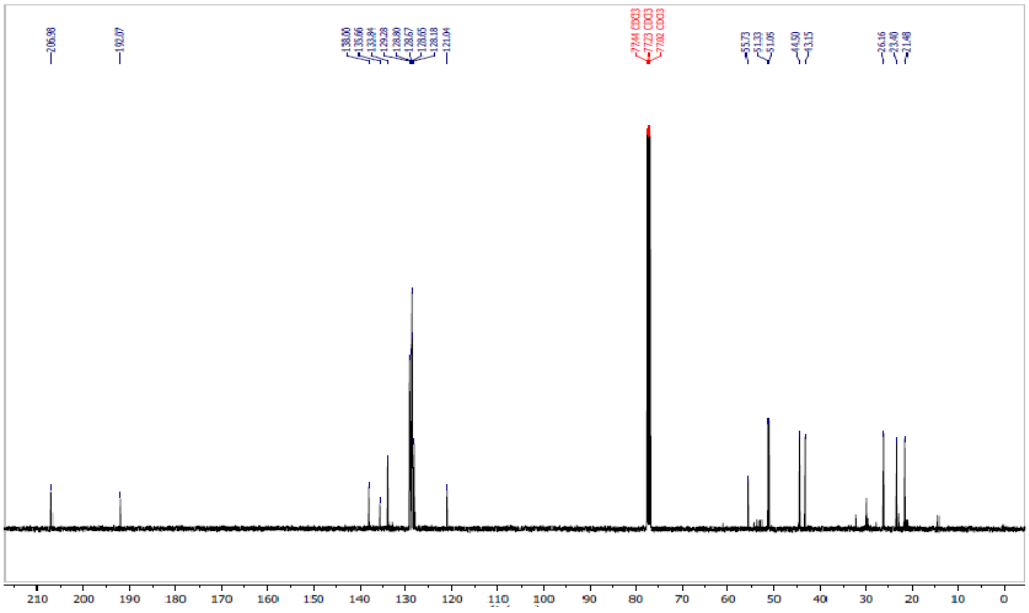


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	36.25	0.030687	0.1181443211	0.03988	n.a.
2	b	39.19	25.943	99.88185568	17.256	n.a.

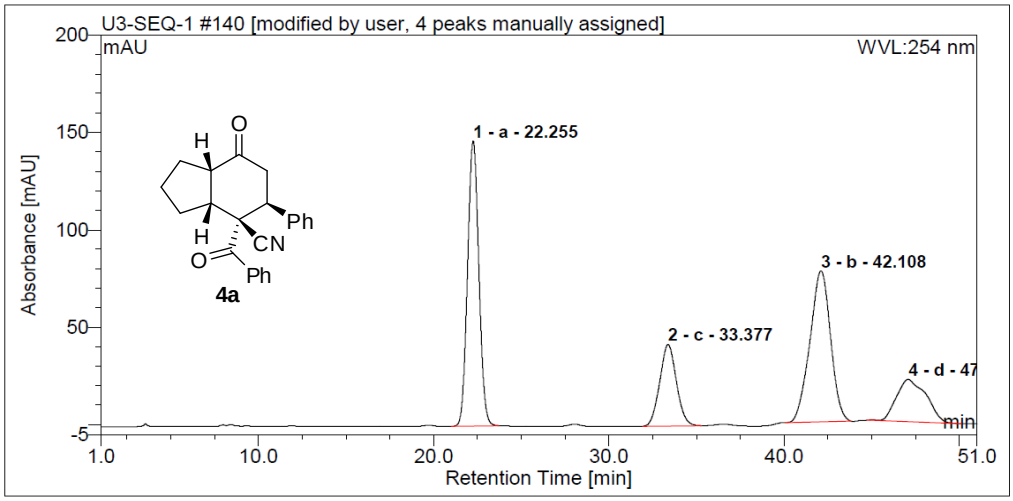
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (**4a**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *(3aR,4R,5S,7aS)-4-benzoyl-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (**4a**):*

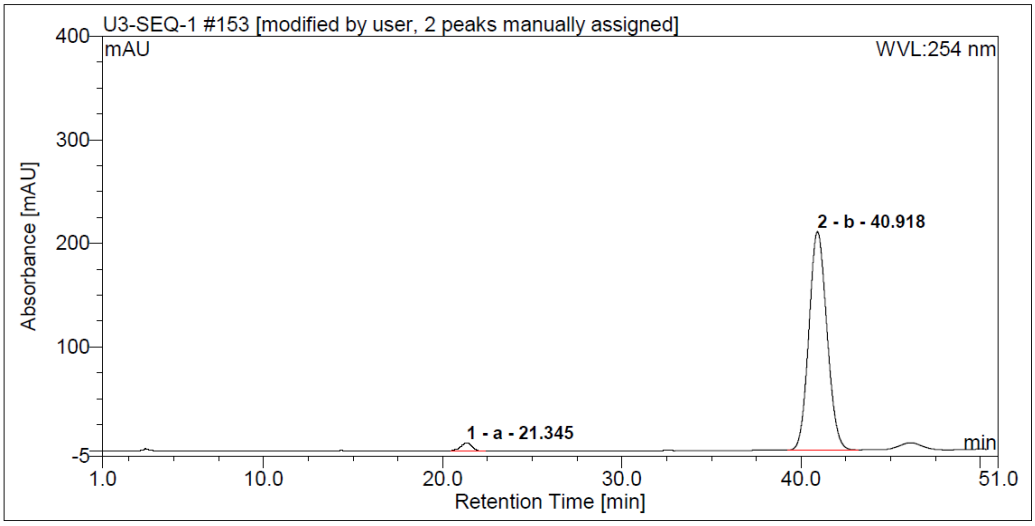


HPLC Chromatogram (racemic): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*



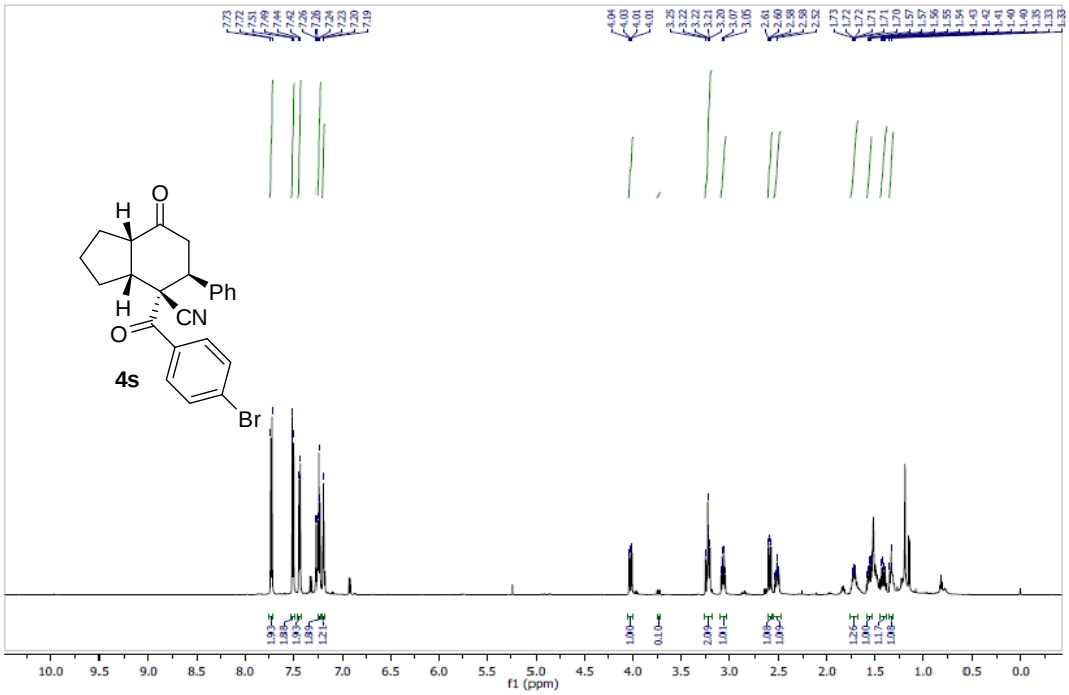
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	22.26	109.1742	35.90516359	146.4262	n.a.
2	c	33.38	45.99549	15.12697248	41.90148	n.a.
3	b	42.11	105.9129	34.83257914	77.55427	n.a.
4	d	47.08	42.980	14.1352848	21.756	n.a.

HPLC Chromatogram (chiral): *(1S,2R,4aR,8aS)-1-benzoyl-4-oxo-2-phenyldecahydronaphthalene-1-carbonitrile (**3a**):*

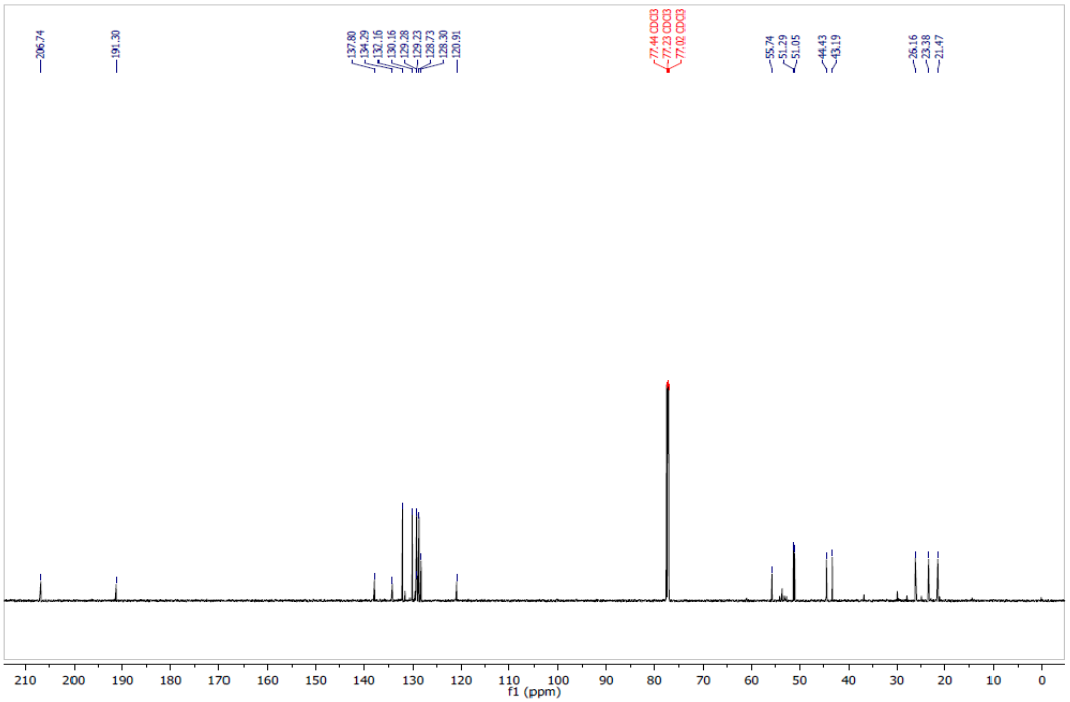


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	21.35	5.142219	2.048418589	7.57209	n.a.
2	b	40.92	245.891	97.95158141	210.935	n.a.

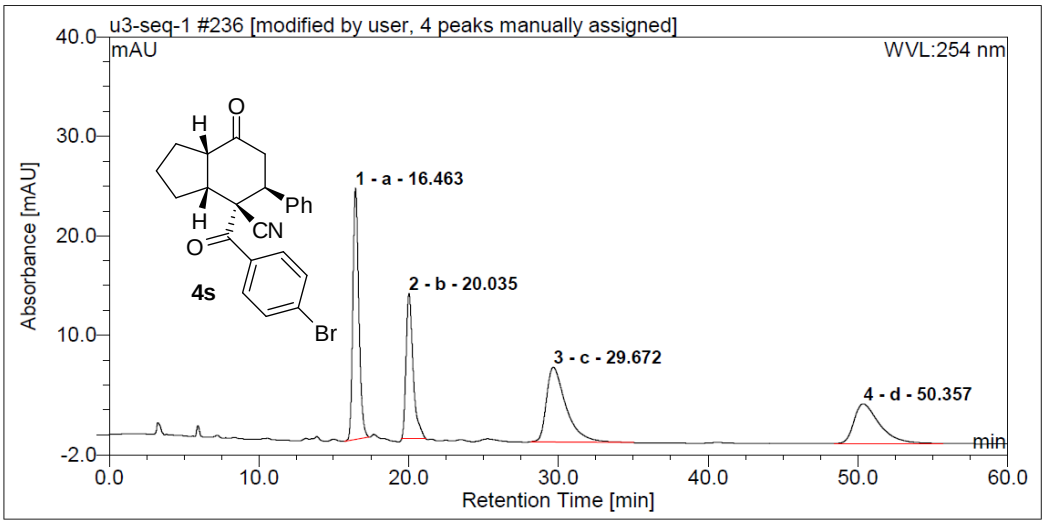
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): ***(****3aR,4R,5S,7aS)-4-(4-bromobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (****4s****):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): ***(****3aR,4R,5S,7aS)-4-(4-bromobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (****4s****):*

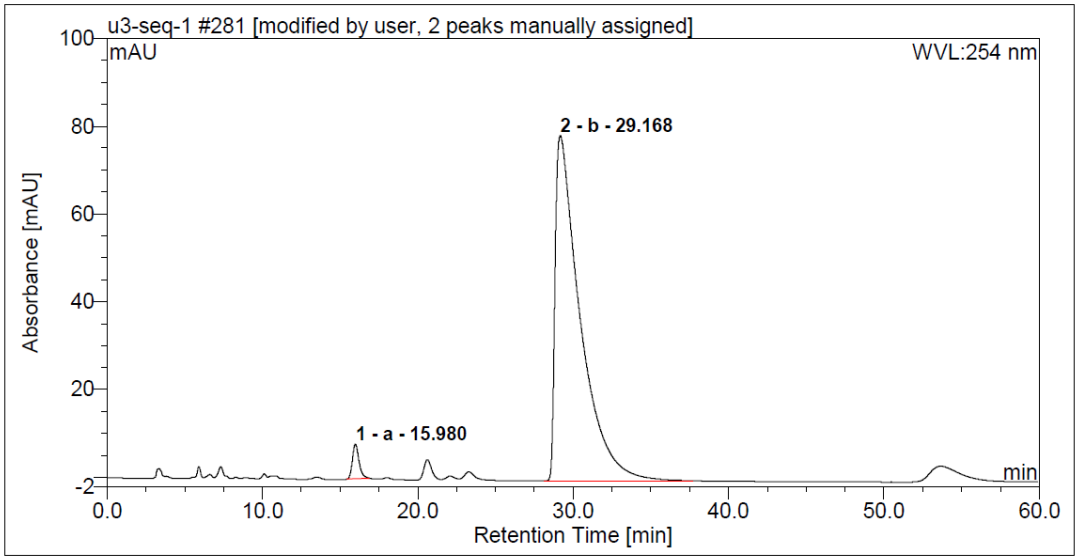


HPLC Chromatogram (racemic): ***(****3aR,4R,5S,7aS)-4-(4-bromobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (****4s****):***



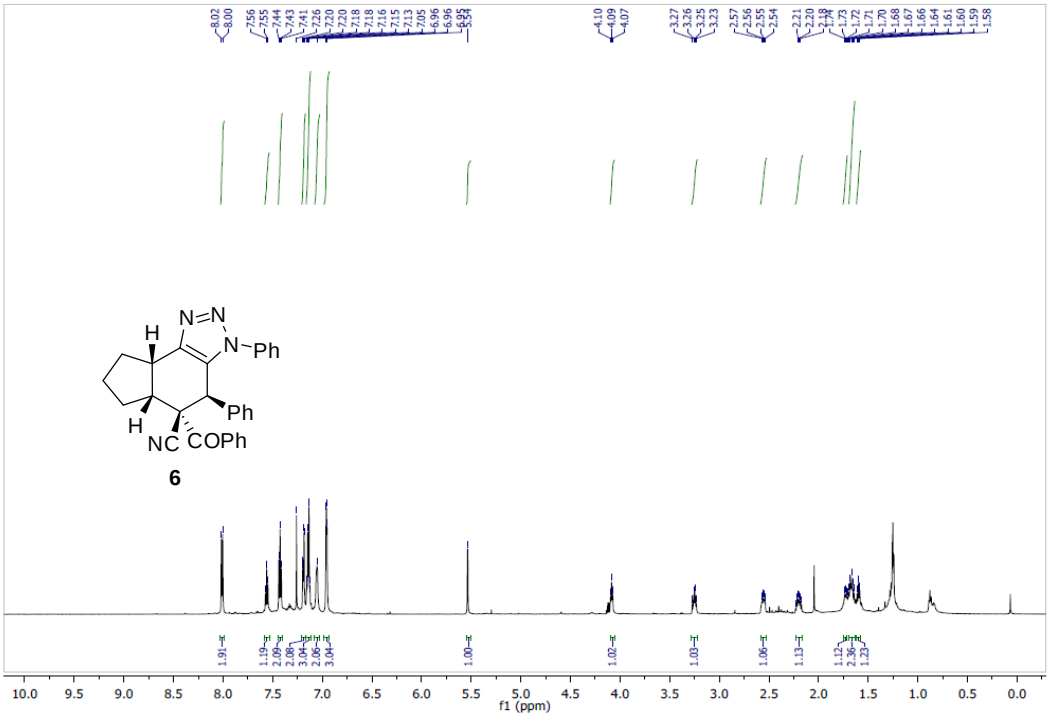
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	16.46	11.68795	29.99221208	25.26869	n.a.
2	b	20.04	7.994483	20.51447846	14.61507	n.a.
3	c	29.67	11.43552	29.34445386	7.51095	n.a.
4	d	50.36	7.852	20.14885559	3.993	n.a.

HPLC Chromatogram (chiral): ***(****3aR,4R,5S,7aS)-4-(4-bromobenzoyl)-7-oxo-5-phenyloctahydro-1H-indene-4-carbonitrile (****4s****):***

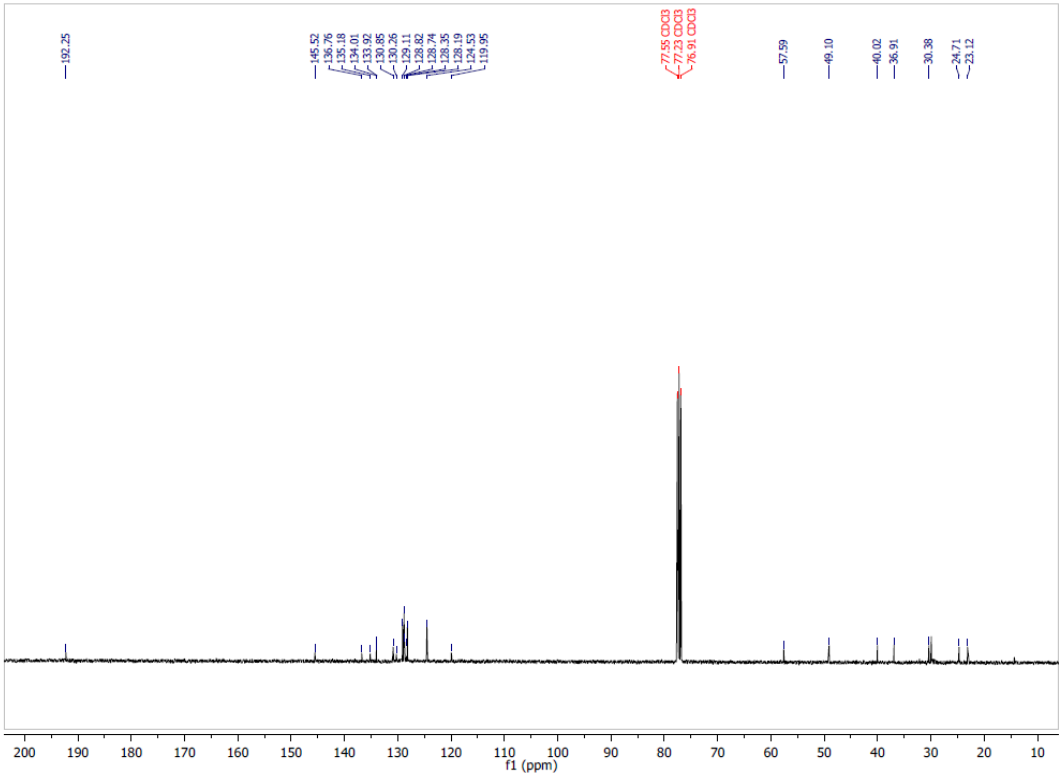


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	15.98	3.866118	2.582524511	7.91411	n.a.
2	b	29.17	145.837	97.41747549	78.659	n.a.

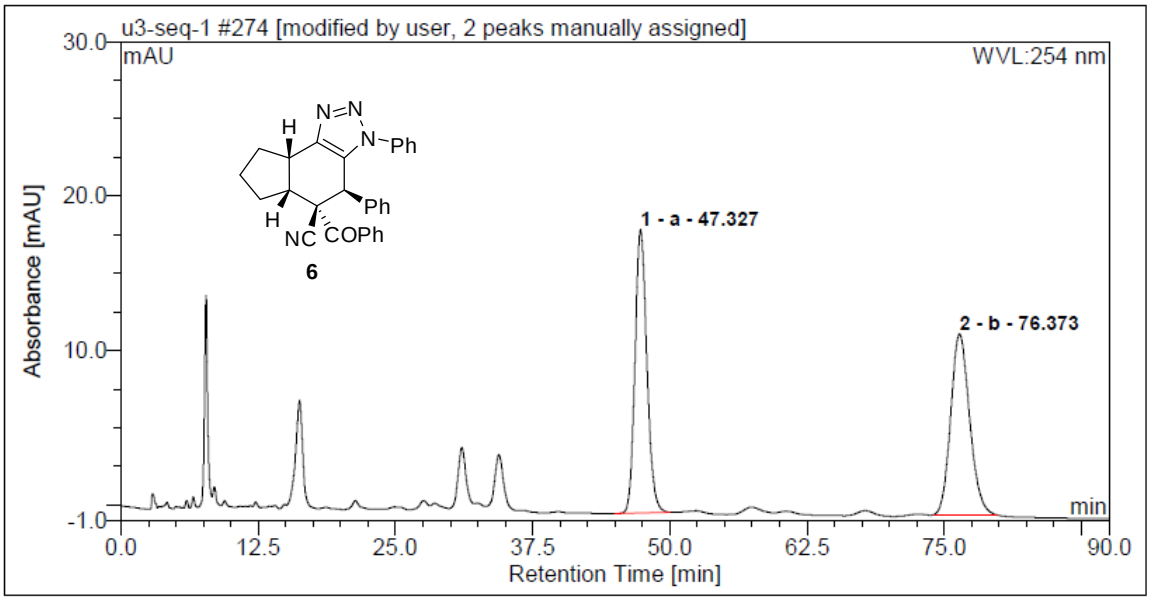
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *Compound **6***



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *Compound **6***

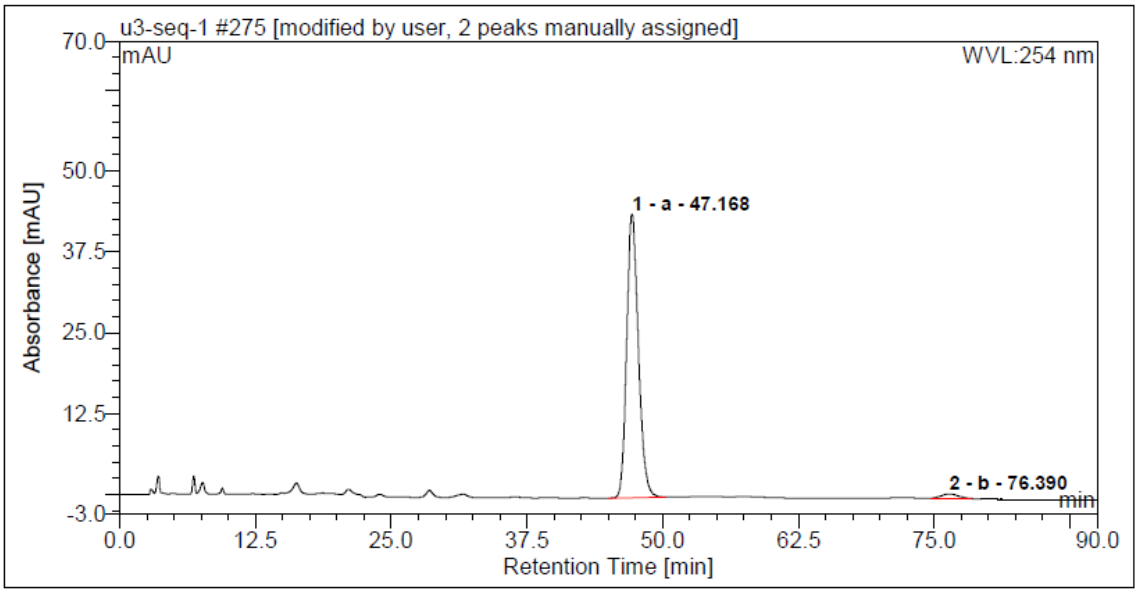


HPLC Chromatogram (racemic): *Compound **6***



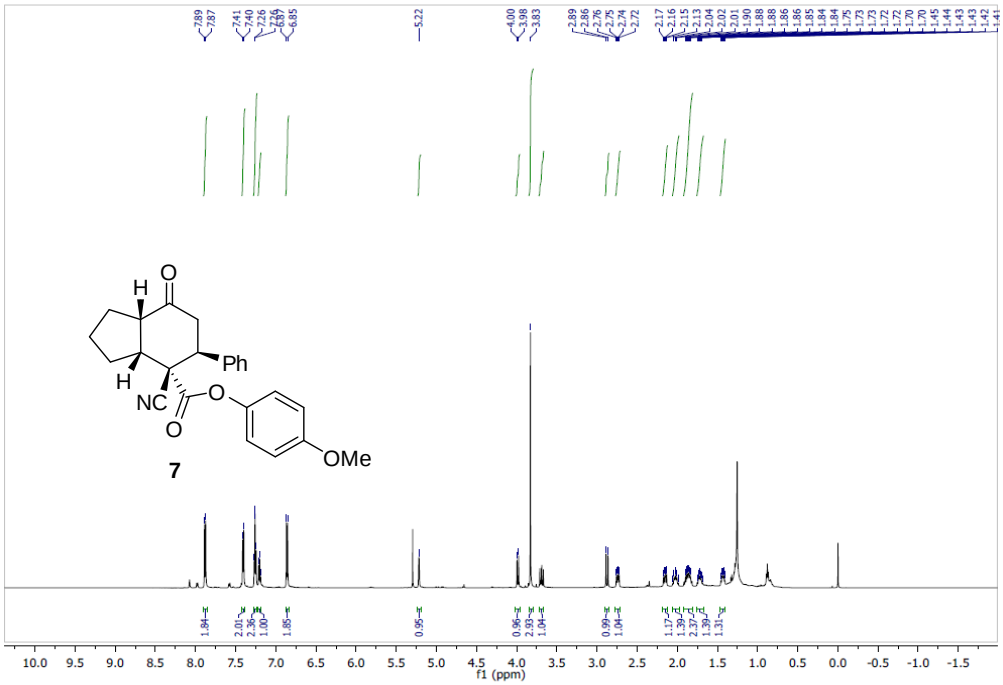
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	47.33	23.00779	49.65787837	18.34028	n.a.
2	b	76.37	23.325	50.34212163	11.698	n.a.

HPLC Chromatogram (chiral): *Compound **6***

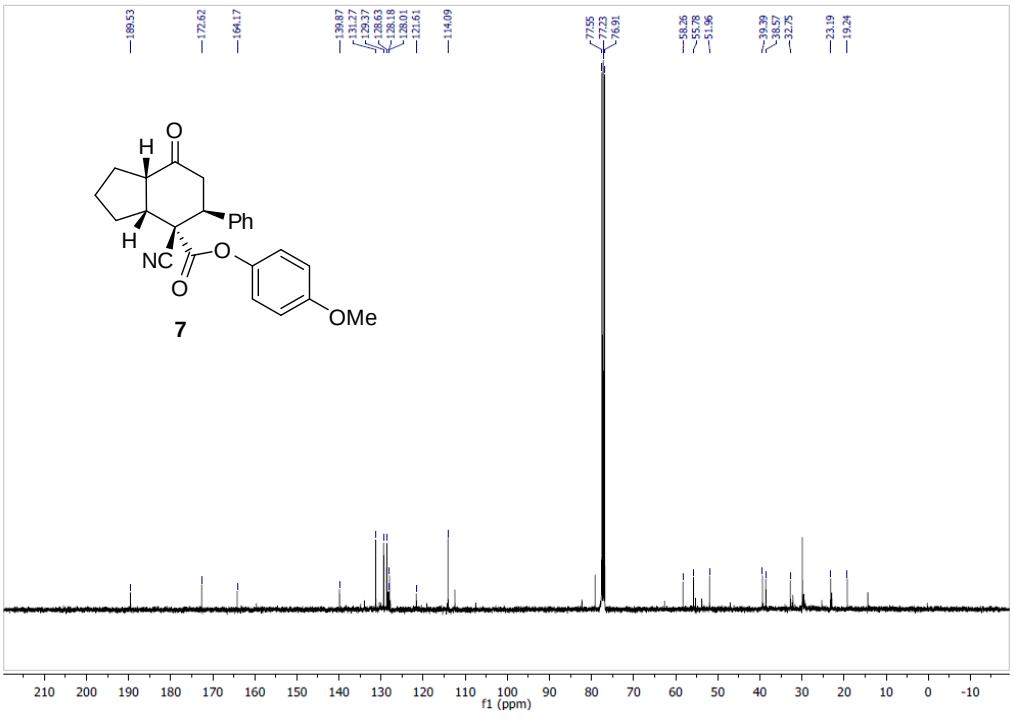


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	47.17	54.58033	97.80142877	43.77959	n.a.
2	b	76.39	1.227	2.198571226	0.681	n.a.

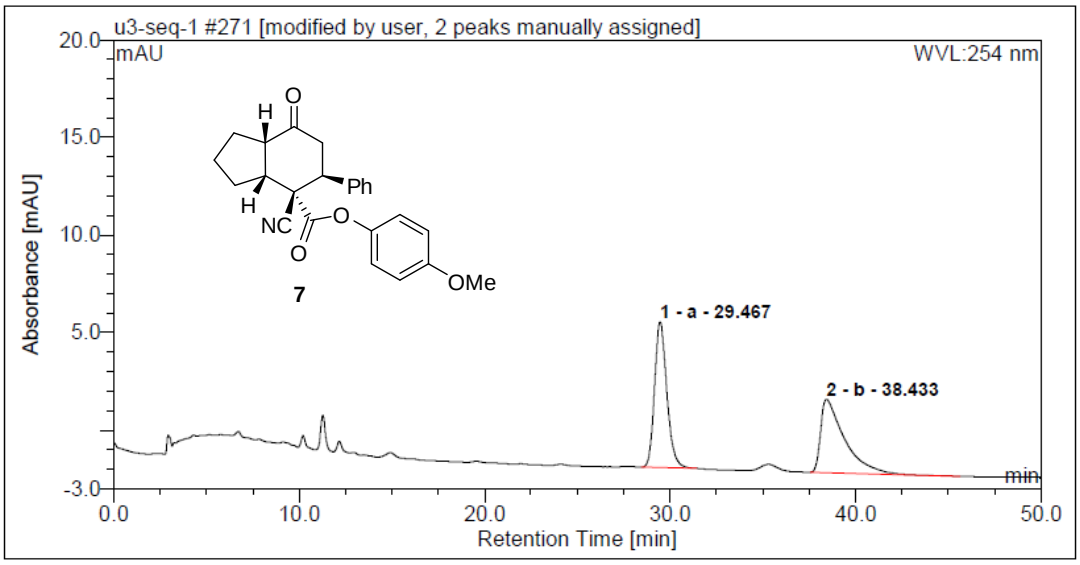
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *(3aR,4R,5S,7aS)-4-methoxyphenyl 4-cyano-octahydro-7-oxo-5-phenyl-1H-indene-4-carboxy late (**7**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *(3aR,4R,5S,7aS)-4-methoxyphenyl 4-cyano-octahydro-7-oxo-5-phenyl-1H-indene-4-carboxy late (**7**):*

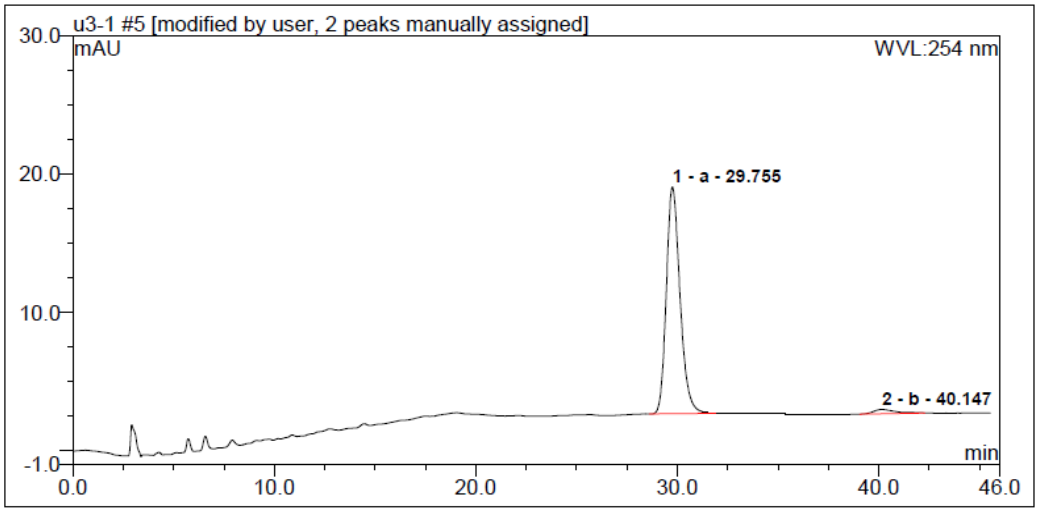


HPLC Chromatogram (racemic): *(3aR,4R,5S,7aS)-4-methoxyphenyl 4-cyano-octahydro-7-oxo-5-phenyl-1H-indene-4-carboxy late (**7**):*



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	29.47	5.748548	50.84508151	7.45953	n.a.
2	b	38.43	5.557	49.15491849	3.750	n.a.

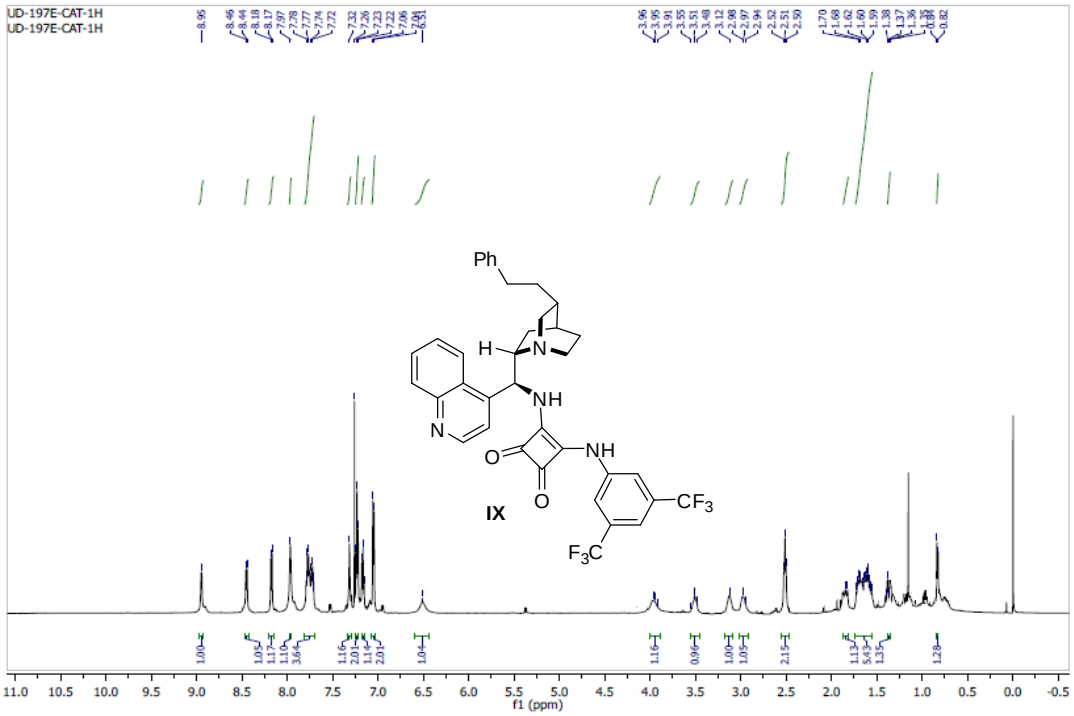
HPLC Chromatogram (chiral): *(3aR,4R,5S,7aS)-4-methoxyphenyl 4-cyano-octahydro-7-oxo-5-phenyl-1H-indene-4-carboxy late (**7**):*



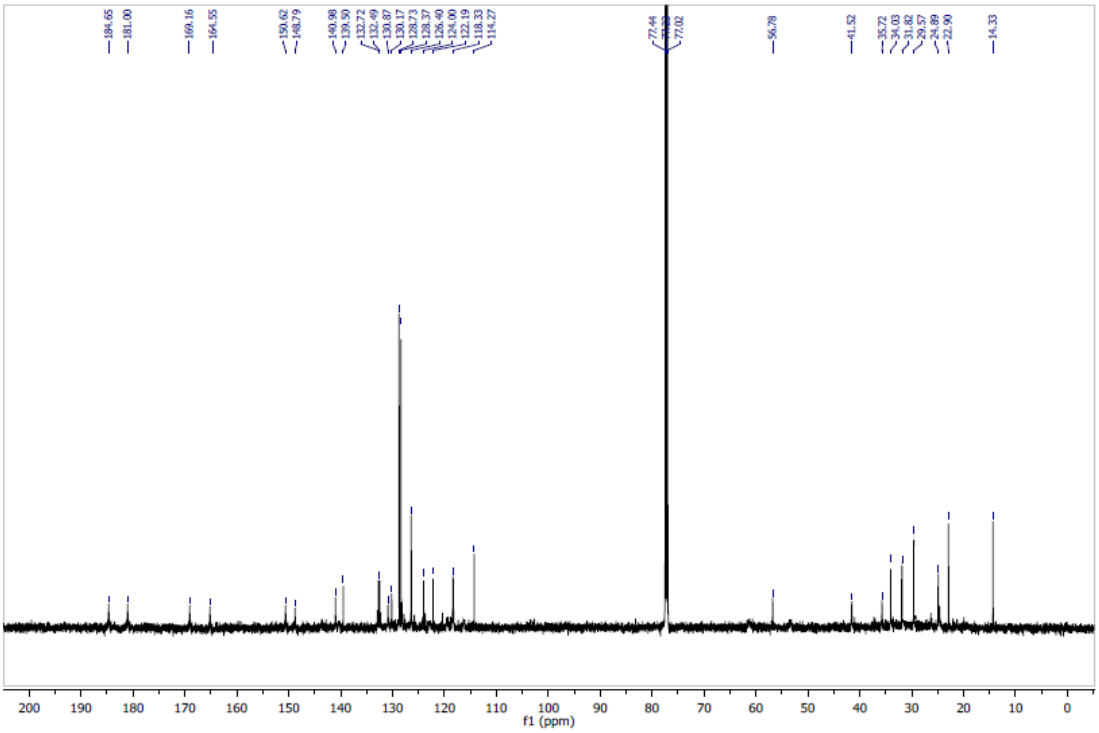
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	29.76	12.92171	97.15314325	16.39449	n.a.
2	b	40.15	0.379	2.846856746	0.305	n.a.

Chapter 4

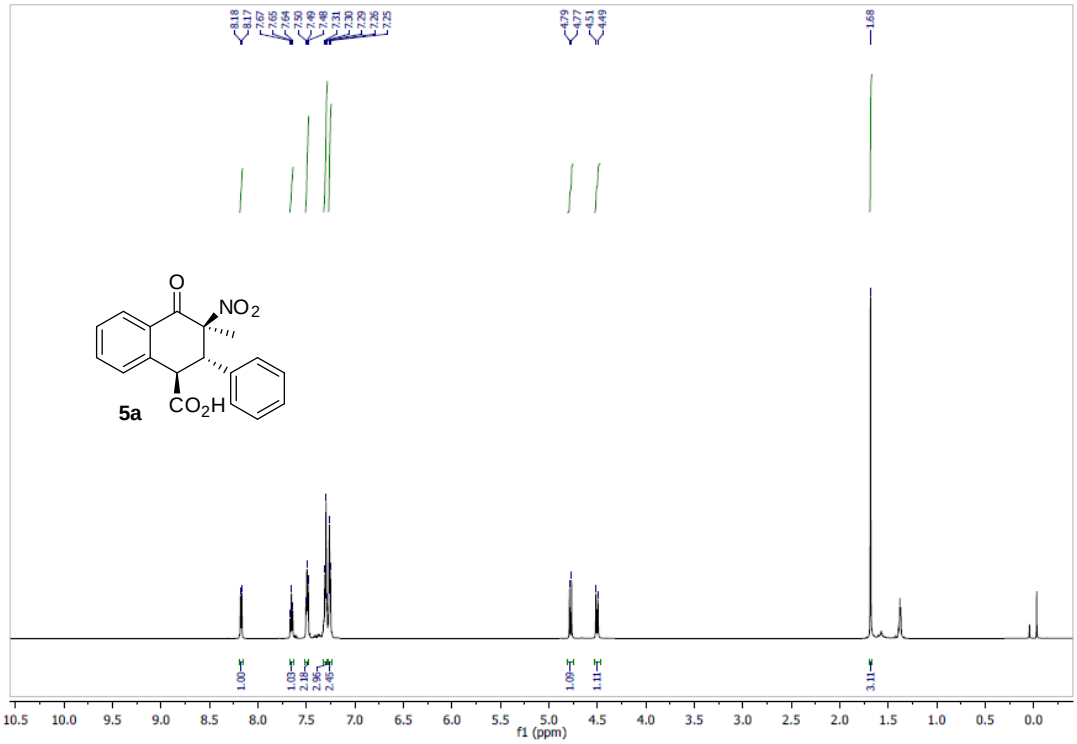
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *catalyst **IX***



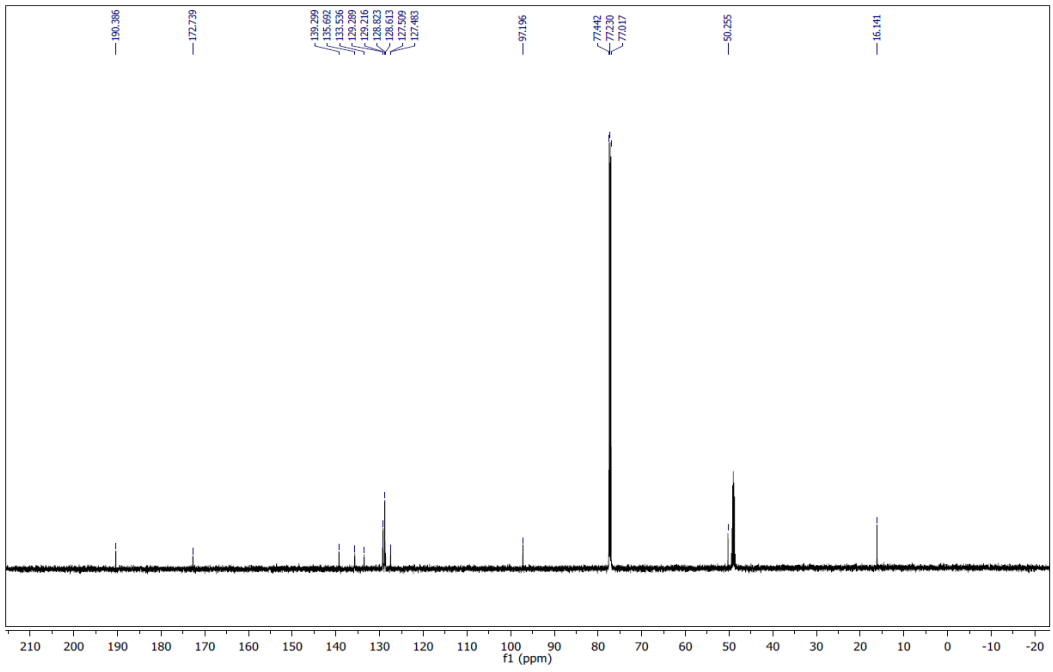
^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *catalyst **IX***



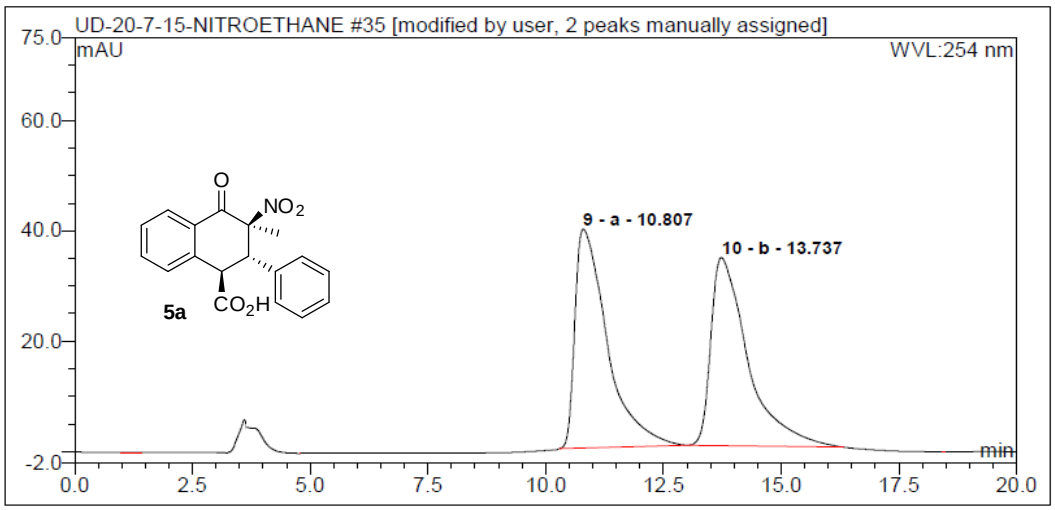
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5a**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5a**):*

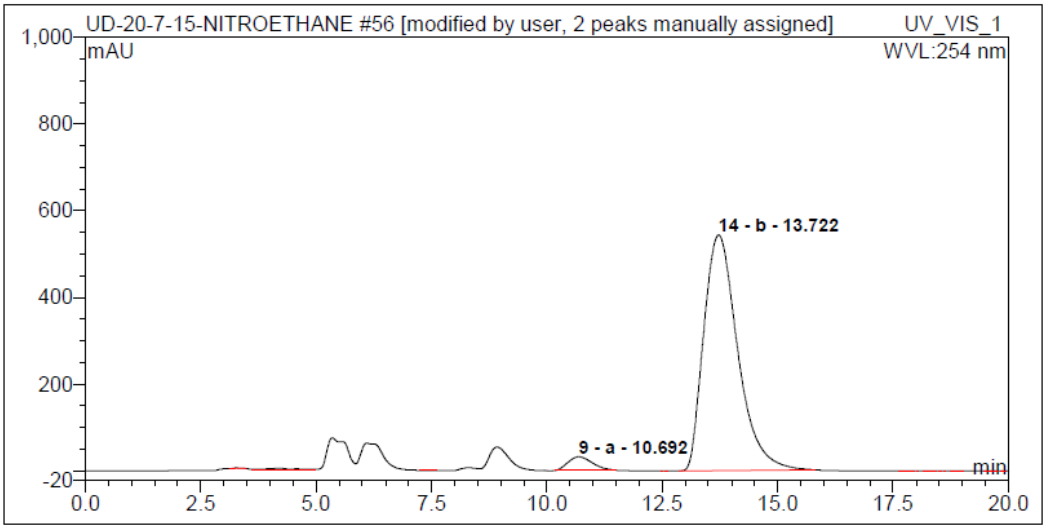


HPLC Chromatogram (racemic): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5a**) –Methyl ester:*



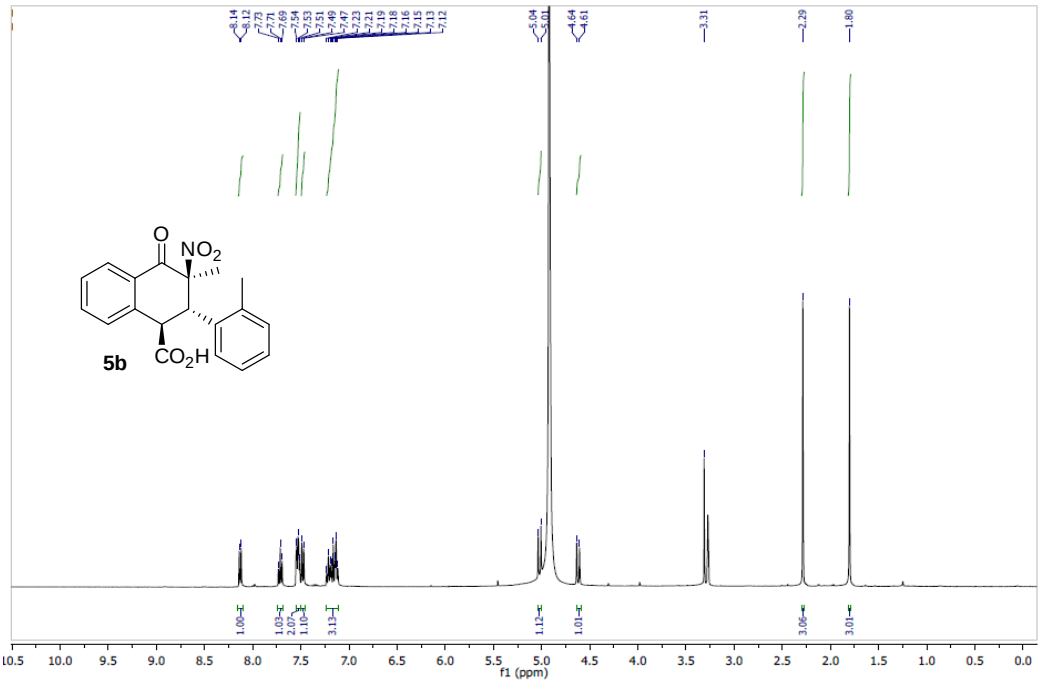
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
9	a	10.81	31.41891	50.26196061	39.64371	n.a.
10	b	13.74	31.091	49.73803939	34.097	n.a.

HPLC Chromatogram (chiral): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5a**)-Methyl ester:*

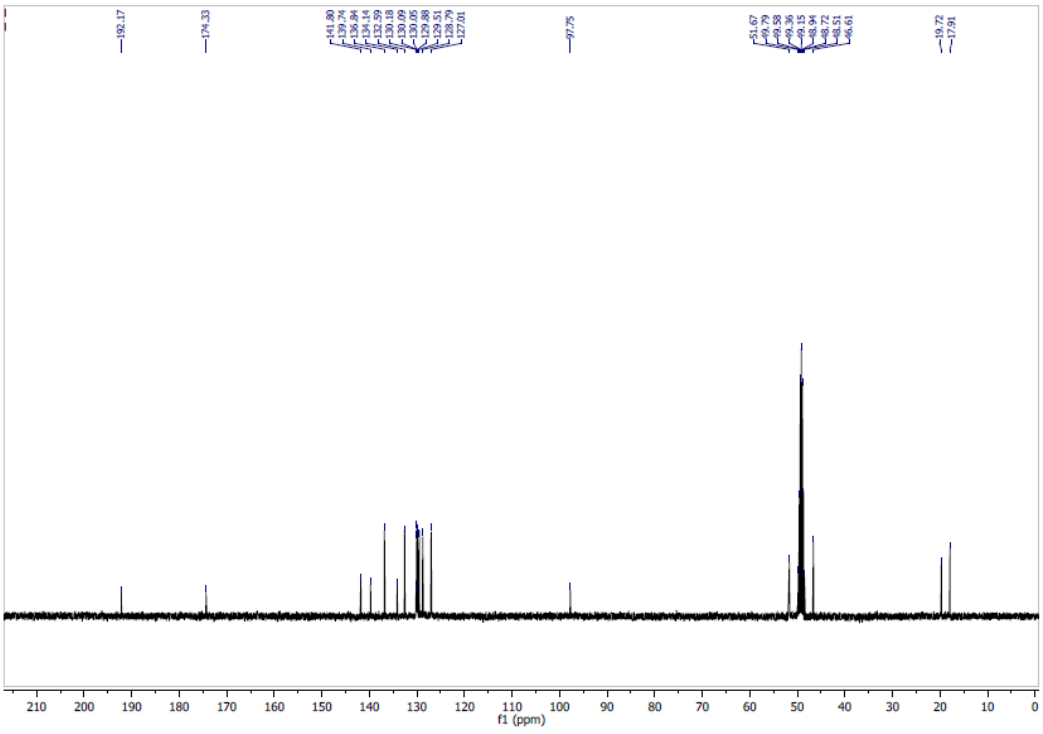


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
9	a	10.69	18.89506	3.917955065	31.04009	n.a.
14	b	13.72	463.373	96.08204494	542.830	n.a.

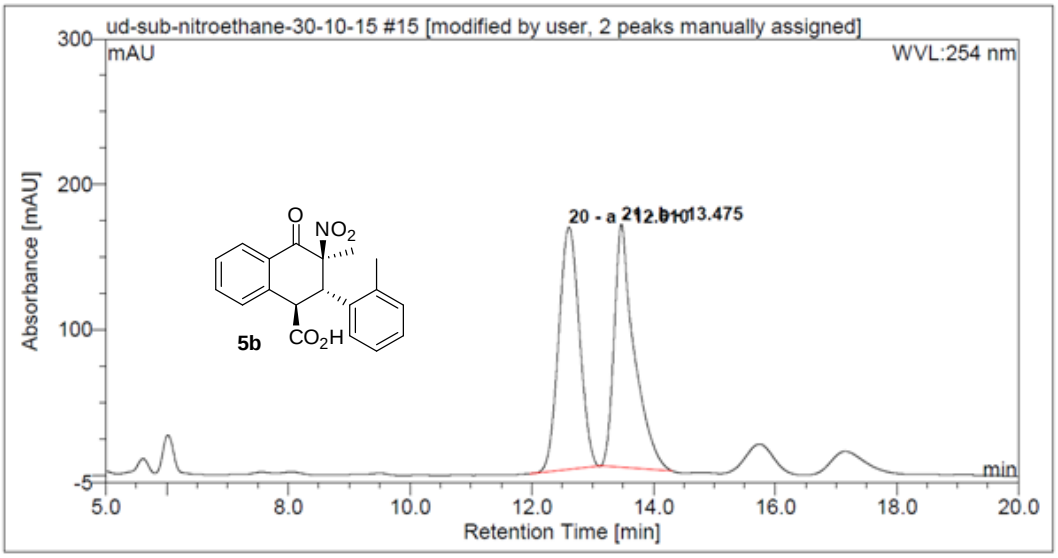
^{1}H-NMR Spectra (400 MHz, CD_3OD): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-o-tolyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5b**)*



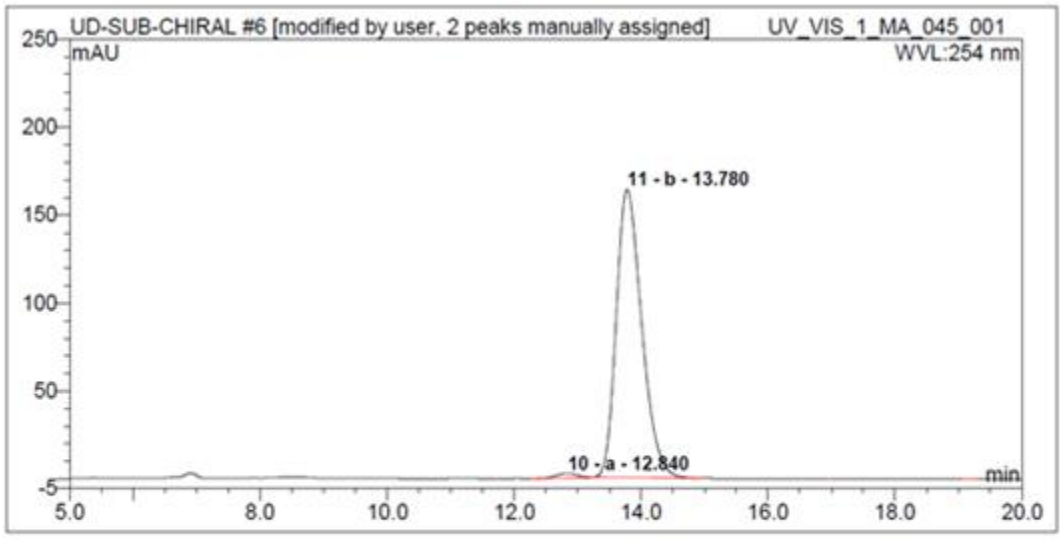
^{13}C-NMR Spectra (400 MHz, CD_3OD): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-o-tolyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5b**)*



HPLC Chromatogram (racemic): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-o-tolyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5b**)-Methyl ester:*

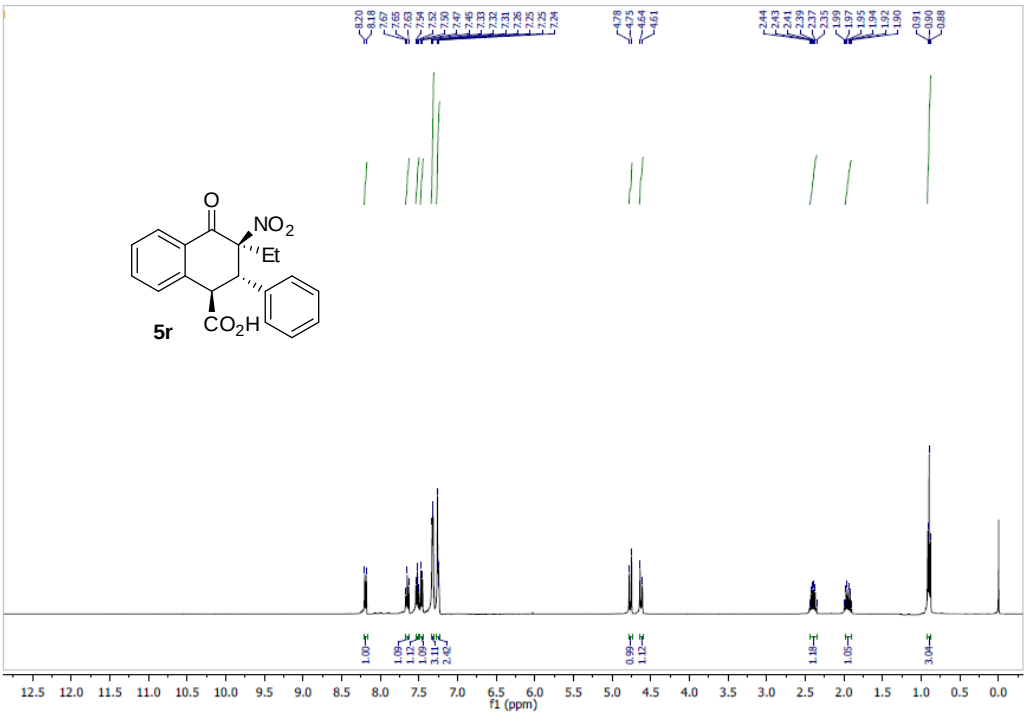


HPLC Chromatogram (chiral): *(1R,2S,3S)-3-methyl-3-nitro-4-oxo-2-o-tolyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5b**)-Methyl ester:*

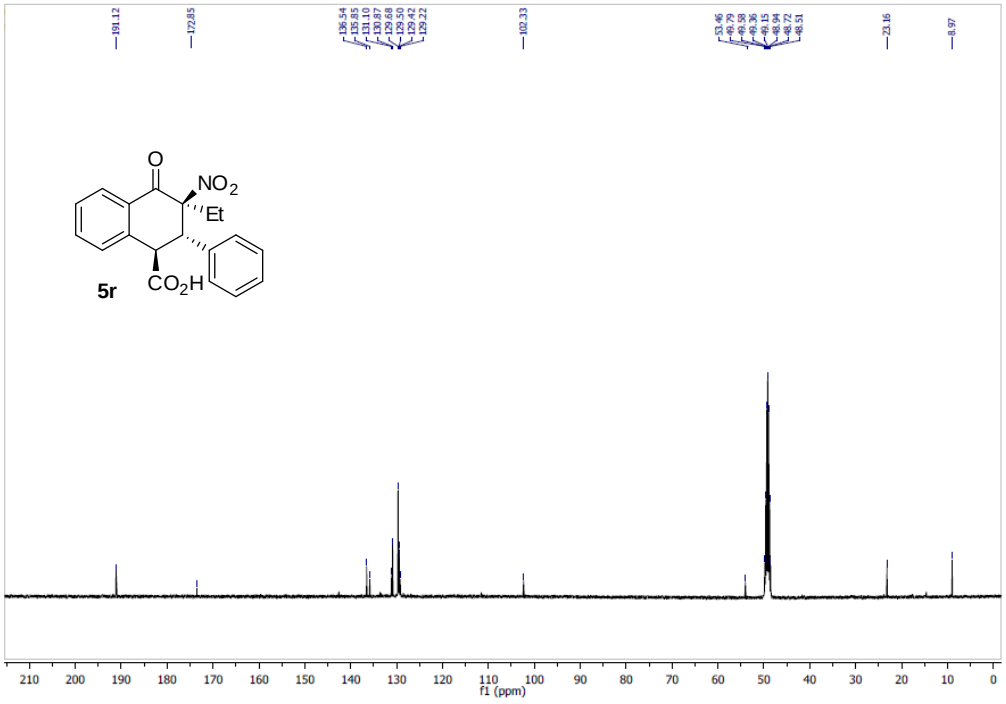


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
10	a	12.84	0.959421	1.242924762	2.54836	n.a.
11	b	13.78	76.231	98.75700109	163.836	n.a.

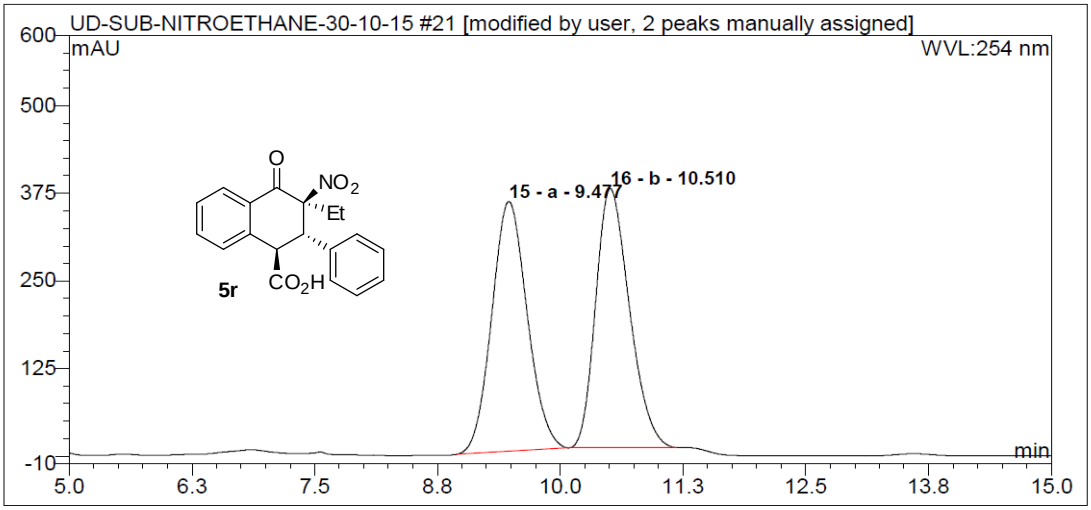
^{1}H-NMR Spectra (400 MHz, $CDCl_3$): *(1R,2S,3S)-3-ethyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5r**):*



^{13}C-NMR Spectra (400 MHz, CD_3OD): *(1R,2S,3S)-3-ethyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5r**):*

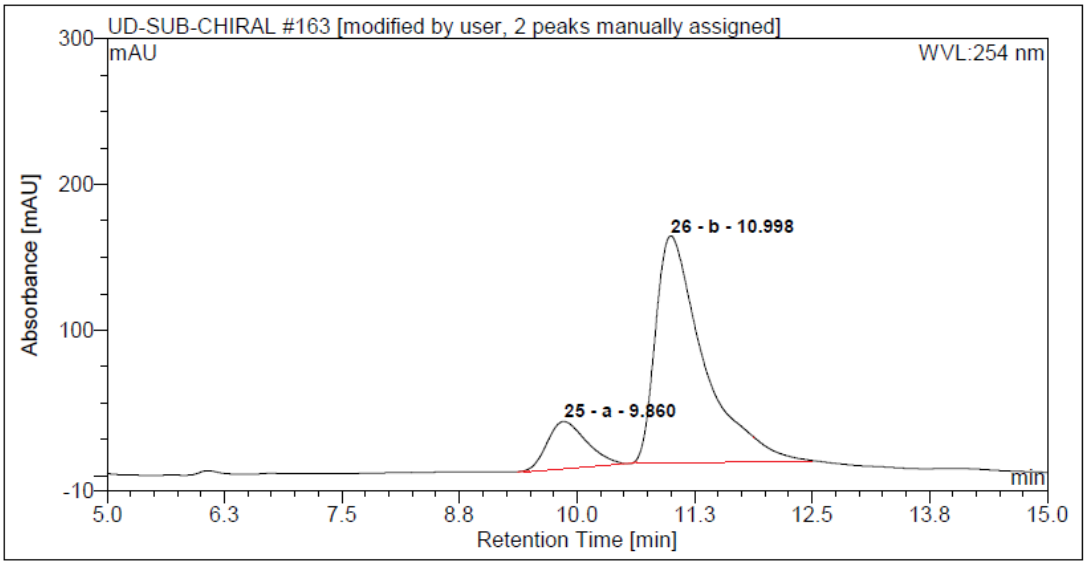


HPLC Chromatogram (racemic): *(1R,2S,3S)-3-ethyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydro naphthalene-1-carboxylic acid (**5r**)-Methyl ester:*



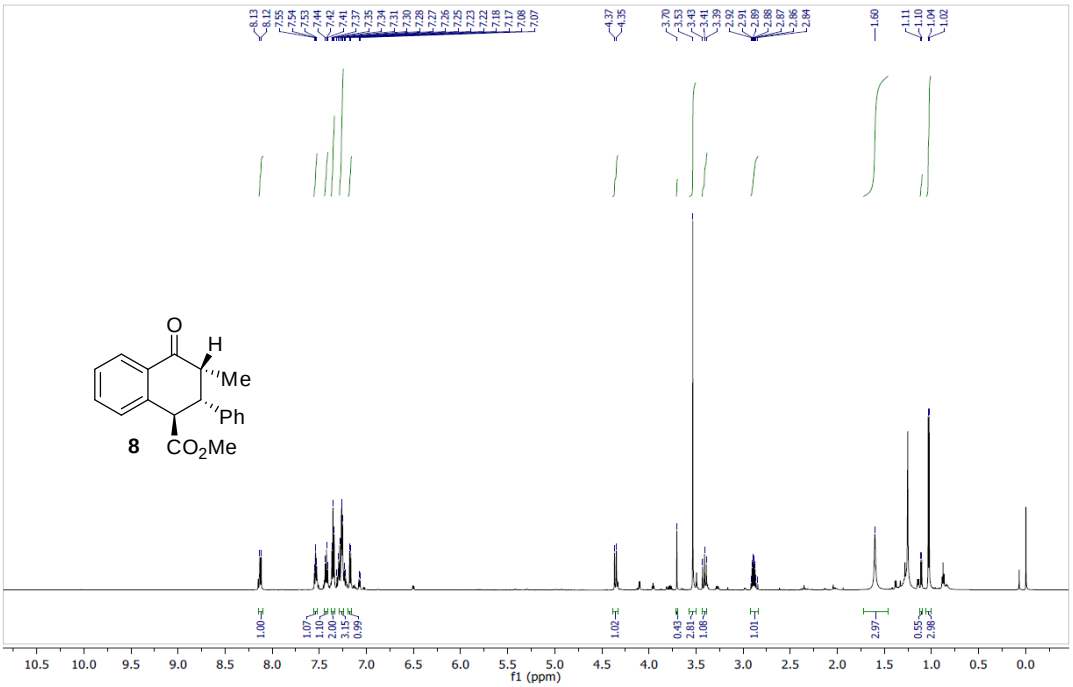
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
15	a	9.48	148.5684	50.3034846	356.1859	n.a.
16	b	10.51	146.776	49.69643622	369.355	n.a.

HPLC Chromatogram (chiral): *(1R,2S,3S)-3-ethyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (**5r**)-Methyl ester:*

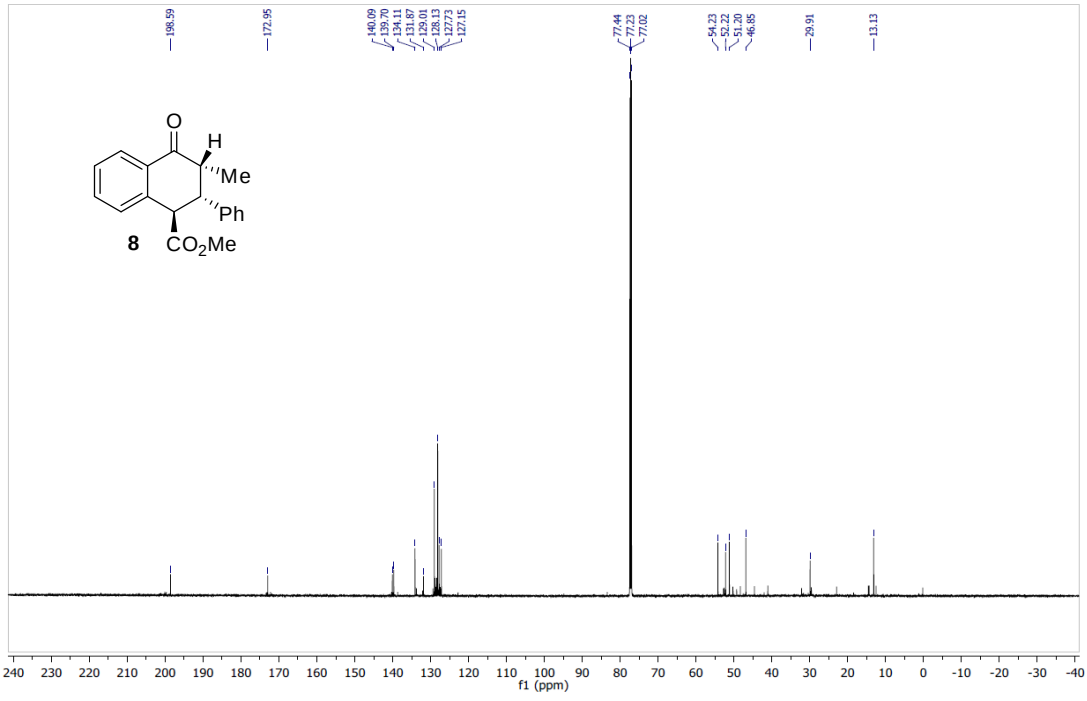


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
25	a	9.86	15.51713	16.64702974	32.16638	n.a.
26	b	11.00	77.695	83.35297026	150.398	n.a.

^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *(1R,2S,3R)-methyl 1,2,3,4-tetrahydro-3-methyl-4-oxo-2-phenylnaphthalene-1-carboxylate (**8**):*

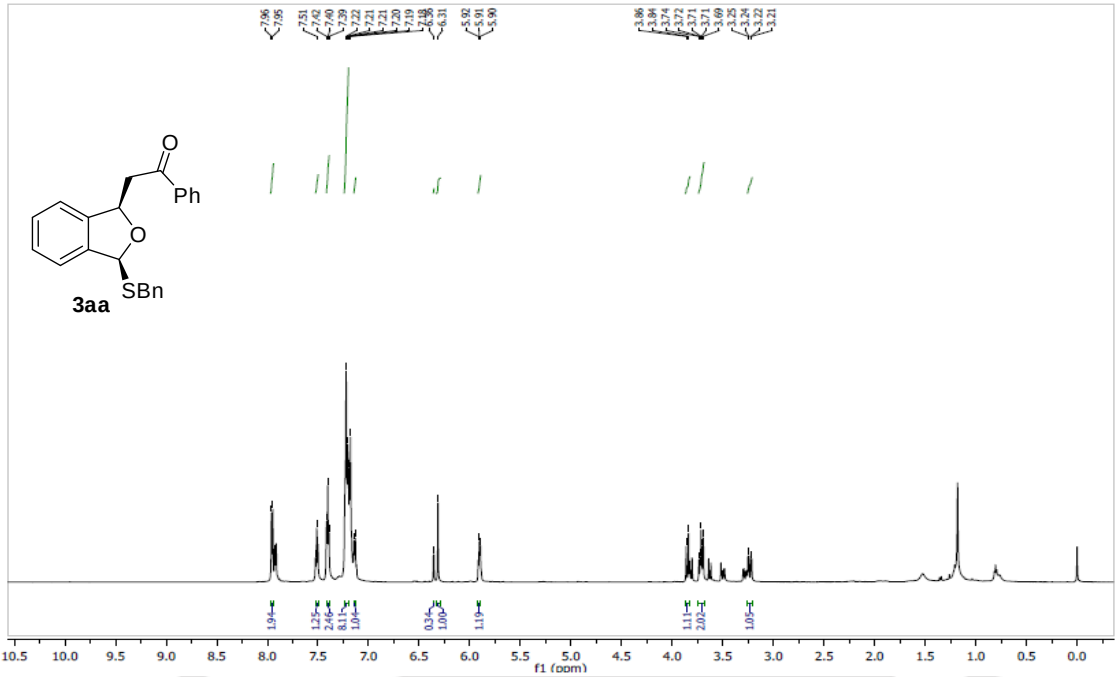


^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *(1R,2S,3R)-methyl 1,2,3,4-tetrahydro-3-methyl-4-oxo-2-phenylnaphthalene-1-carboxylate (**8**):*

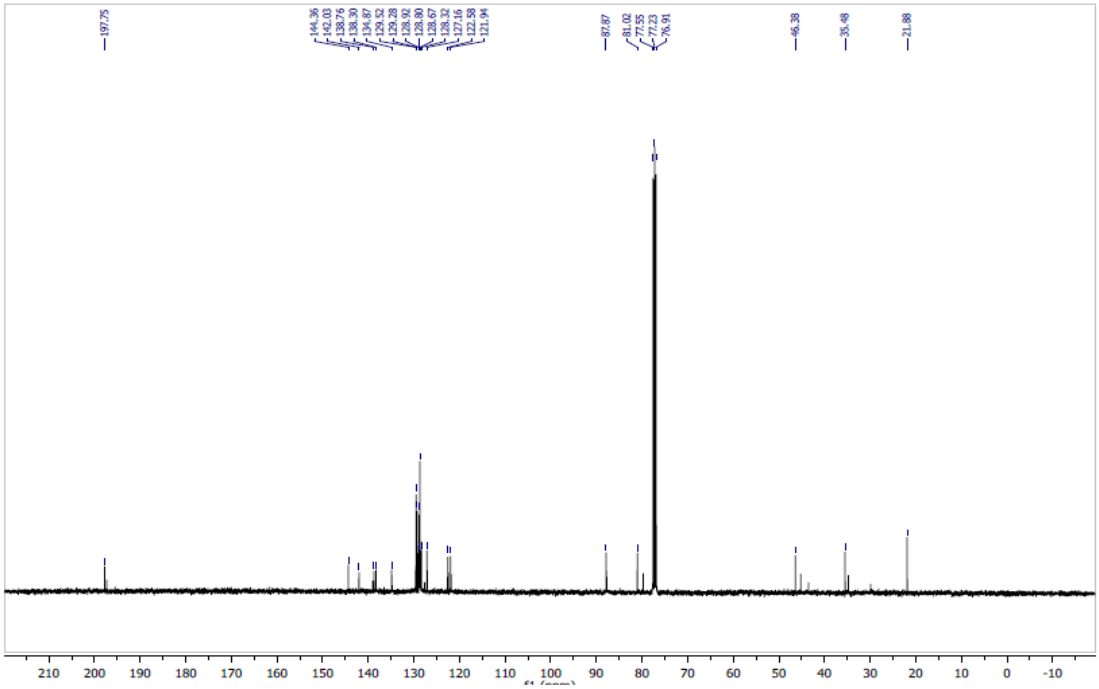


Chapter 5

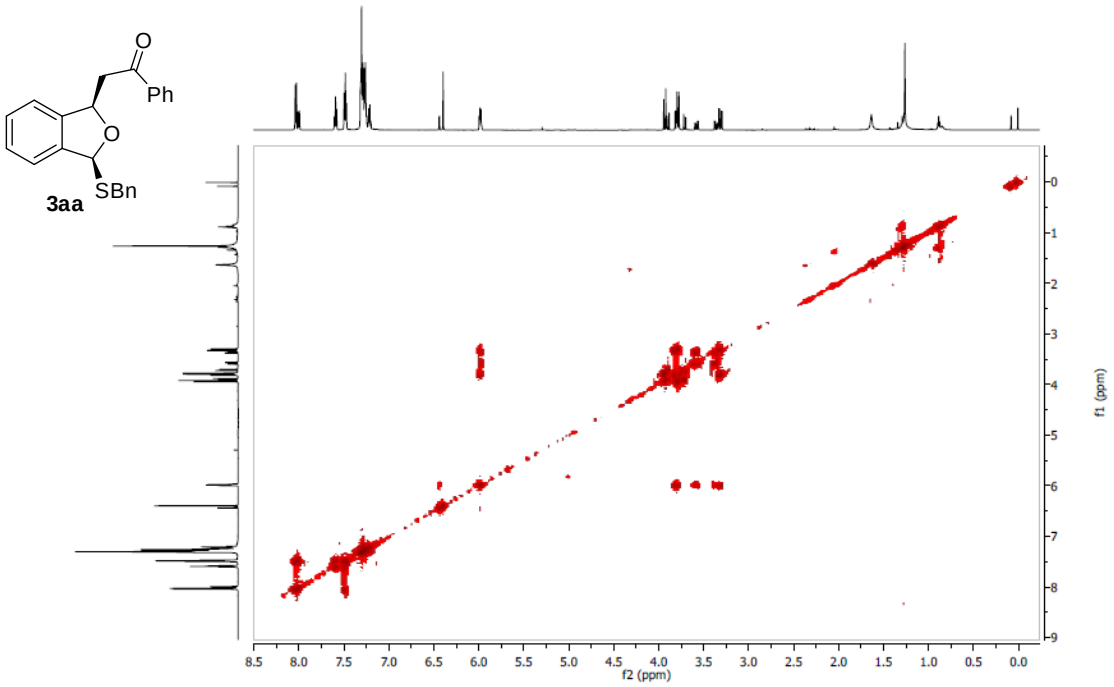
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*



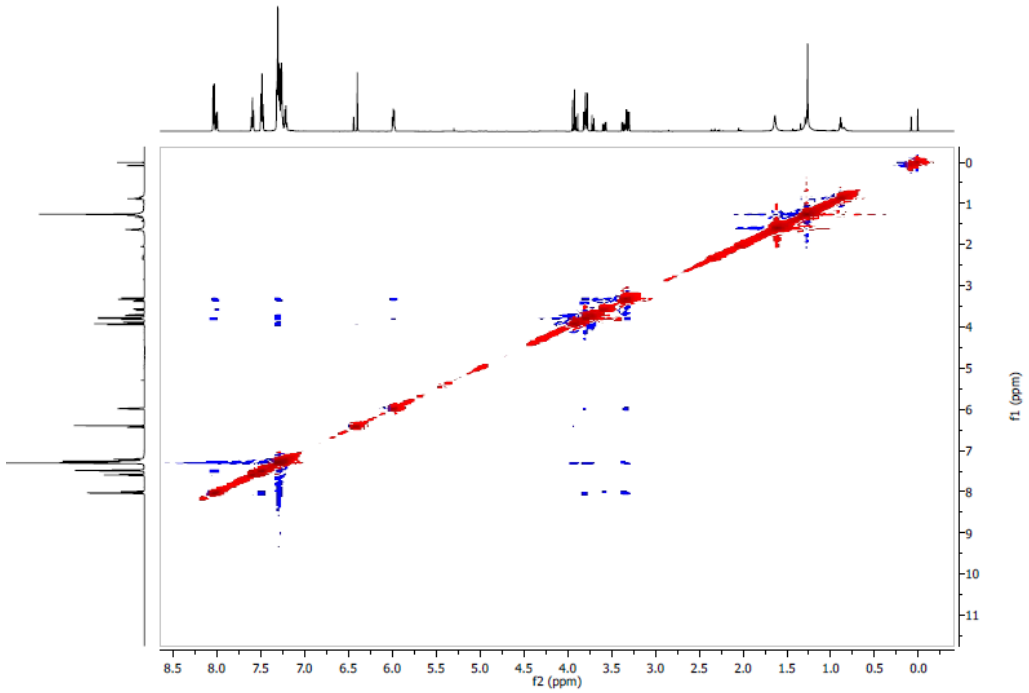
^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*



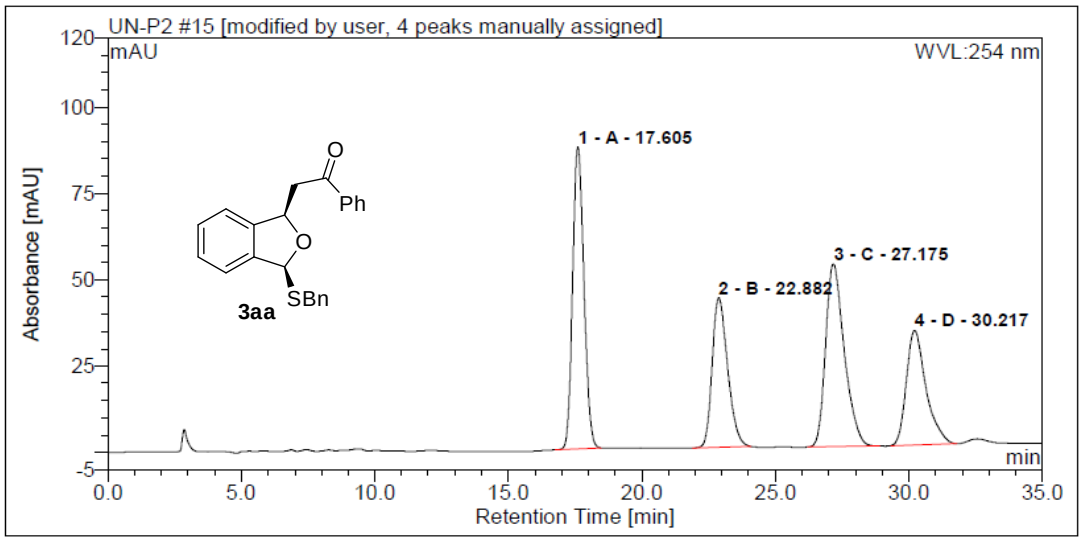
^{1}H-COSY Spectra (600 MHz, $CDCl_3$): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*



NOESY-NMR Spectra (600 MHz, $CDCl_3$): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*

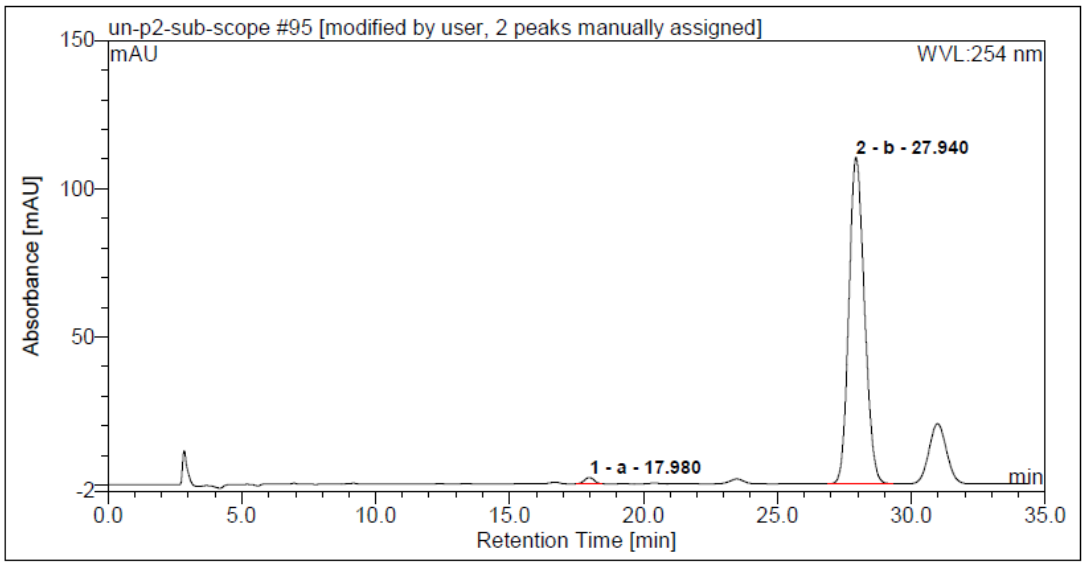


HPLC Chromatogram (racemic): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*



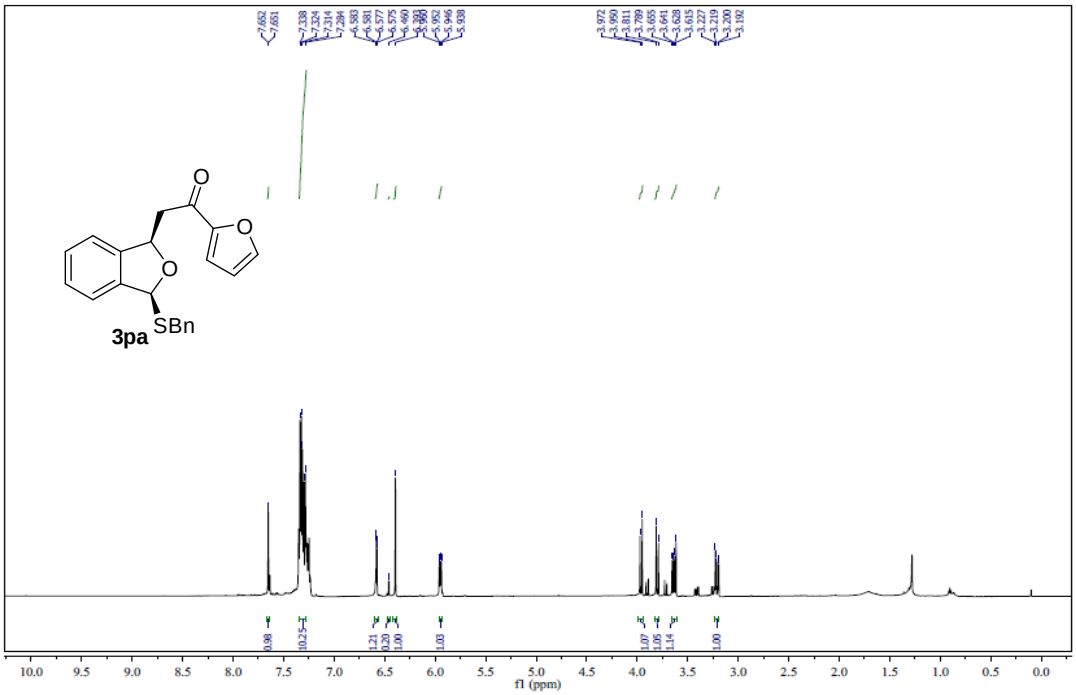
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	17.61	42.81887	29.90411947	87.41527	n.a.
2	B	22.88	29.05389	20.29084198	43.31854	n.a.
3	C	27.18	42.99303	30.02574979	52.96168	n.a.
4	D	30.22	28.321	19.77928875	33.198	n.a.

HPLC Chromatogram (chiral): *2-(3-(benzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3aa**):*

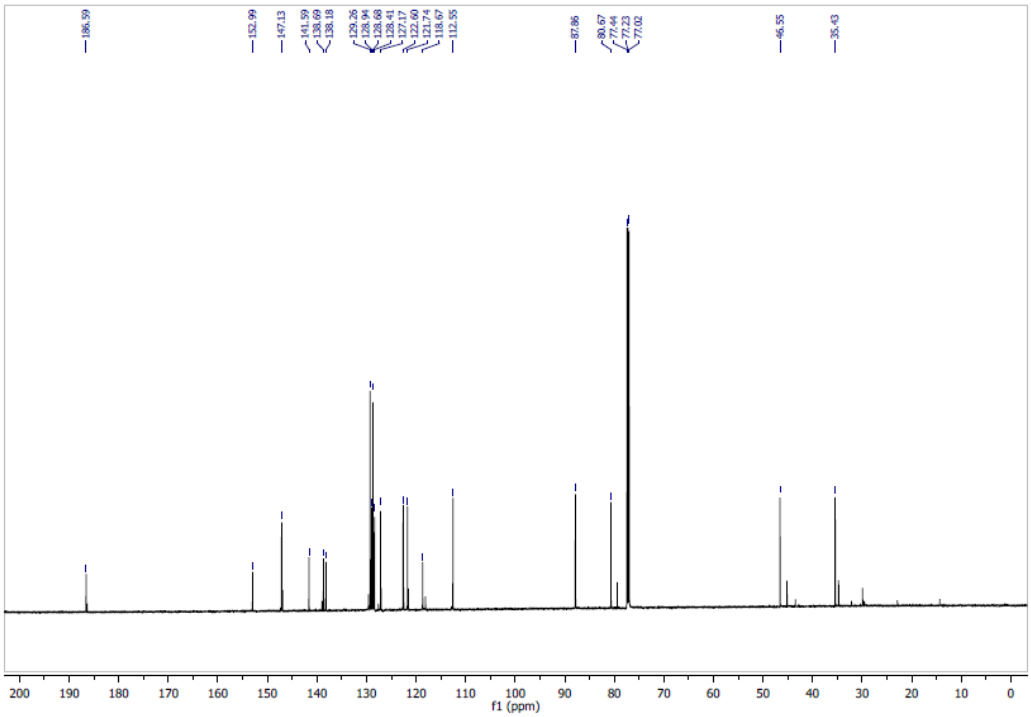


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	17.98	0.845945	1.125248694	2.0991	n.a.
2	b	27.94	74.333	98.87475131	110.159	n.a.

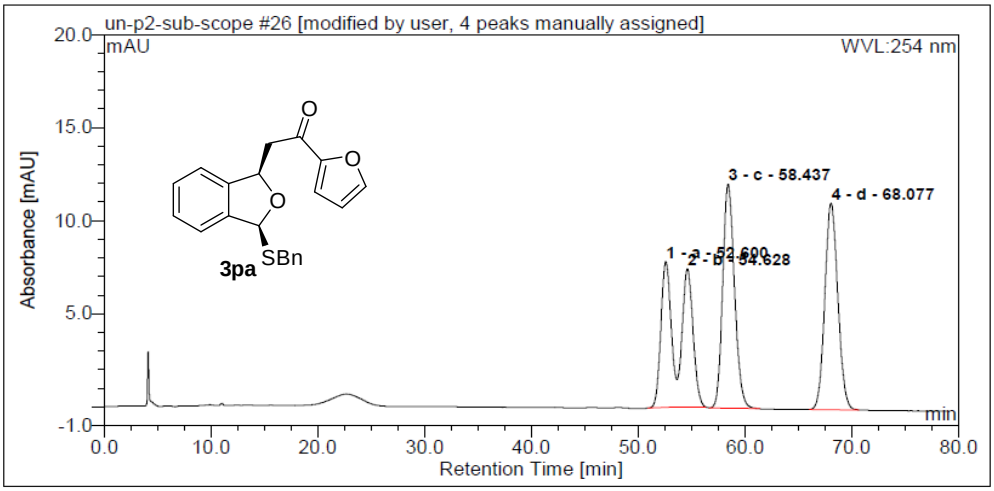
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *2-(1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *2-(1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**):*

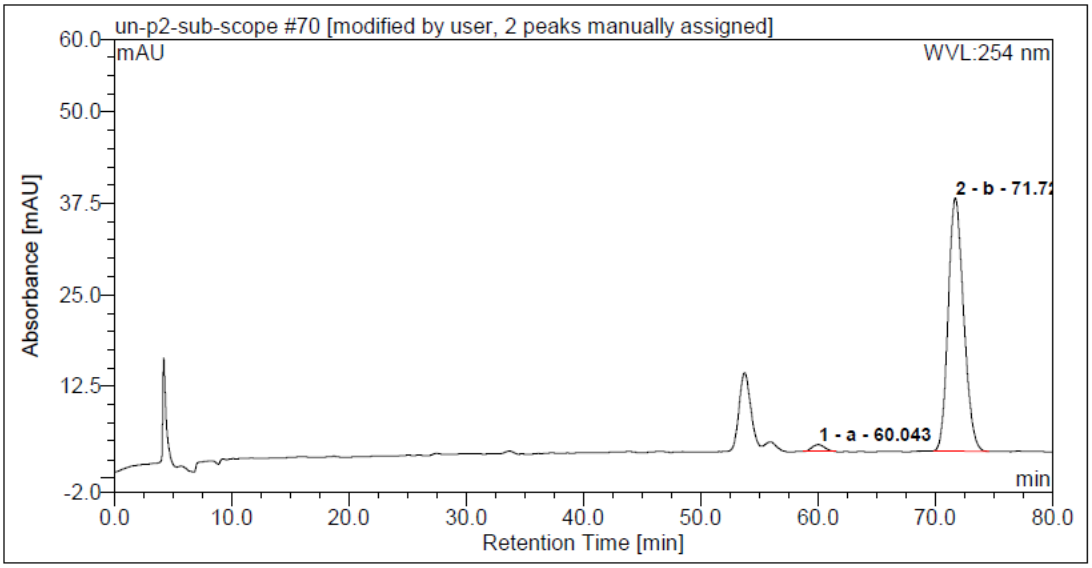


HPLC Chromatogram (racemic): *2-(1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**):*



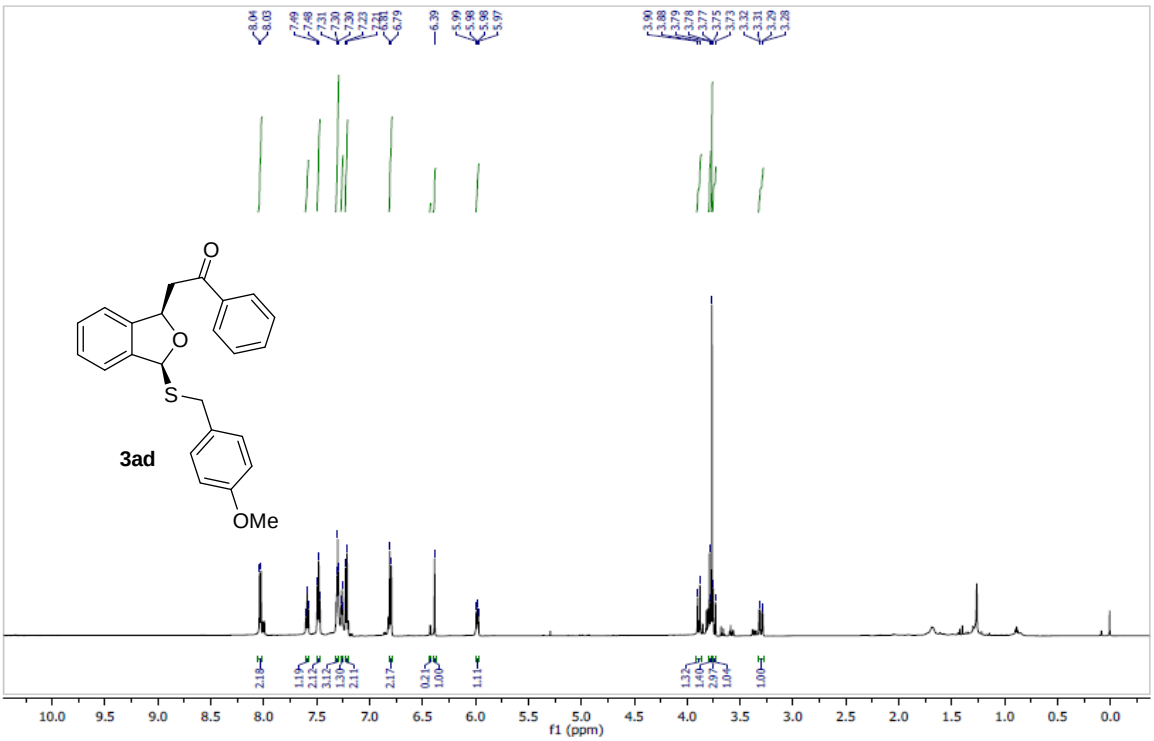
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	52.60	8.688981	17.84330094	7.8386	n.a.
2	b	54.63	8.883264	18.24227147	7.40776	n.a.
3	c	58.44	15.42855	31.68337391	12.02899	n.a.
4	d	68.08	15.695	32.23105367	11.084	n.a.

HPLC Chromatogram (chiral): *2-(1-(benzylthio)-1,3-dihydroisobenzofuran-3-yl)-1-(furan-2-yl)ethanone (**3pa**):*

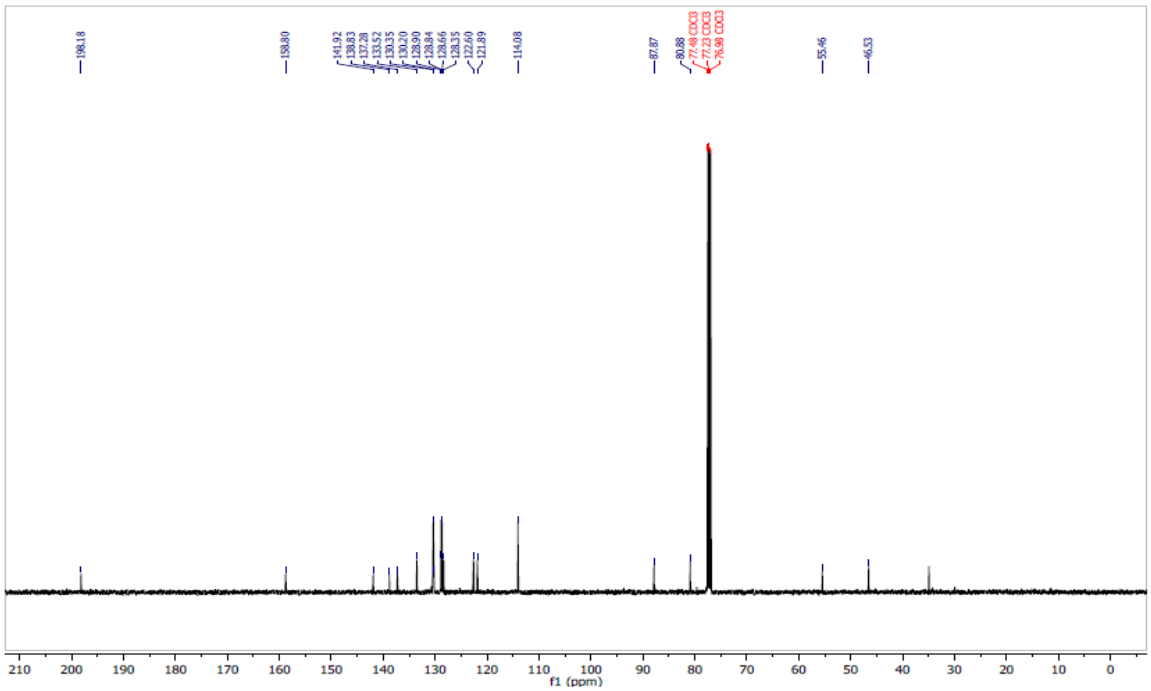


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	60.04	1.218709	2.25762592	0.94514	n.a.
2	b	71.72	52.763	97.74237408	34.577	n.a.

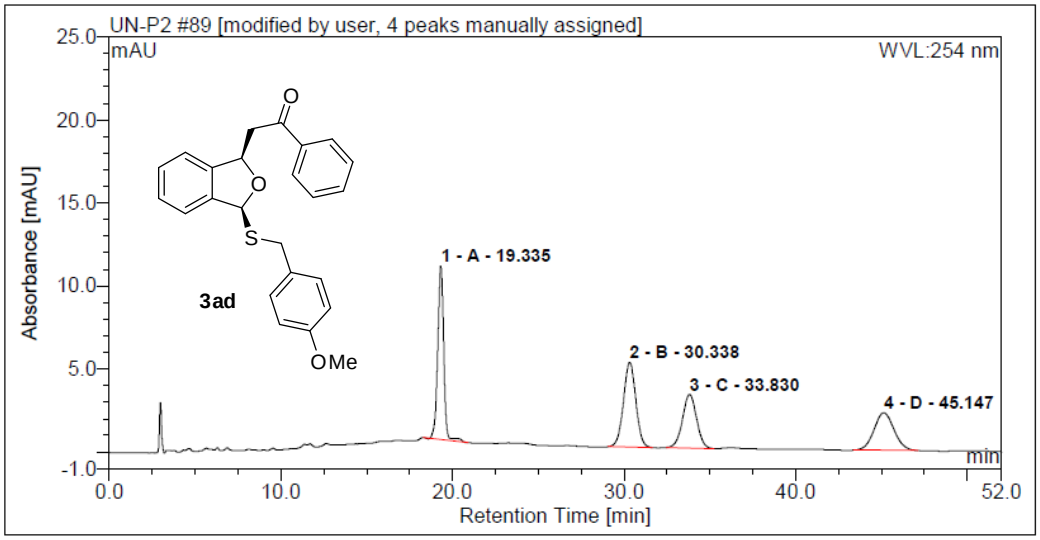
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *2-(3-(4-methoxybenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3ad**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *2-(3-(4-methoxybenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3ad**):*

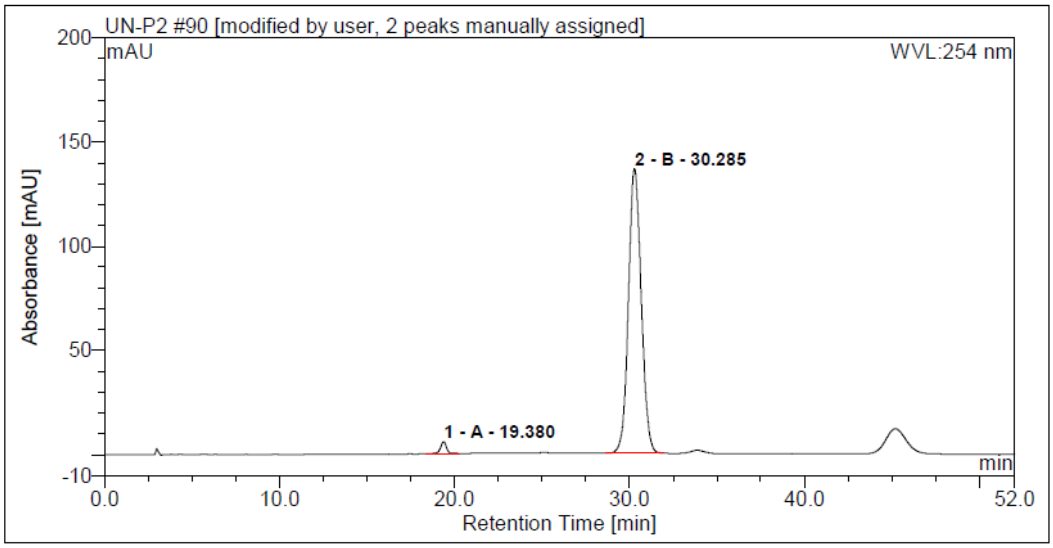


HPLC Chromatogram (racemic): *2-(3-(4-methoxybenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3ad**):*



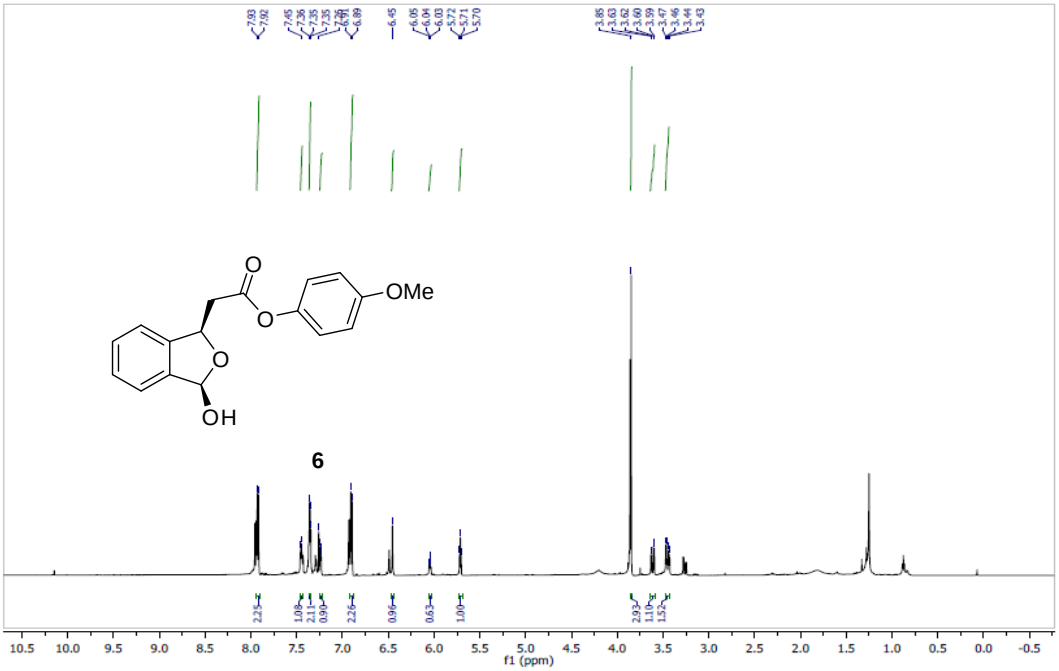
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	19.34	4.223216	28.88354965	10.44464	n.a.
2	B	30.34	4.280274	29.27378186	5.10776	n.a.
3	C	33.83	3.058983	20.92109225	3.23277	n.a.
4	D	45.15	3.059	20.92157624	2.261	n.a.

HPLC Chromatogram (chiral): *2-(3-(4-methoxybenzylthio)-1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**3ad**):*

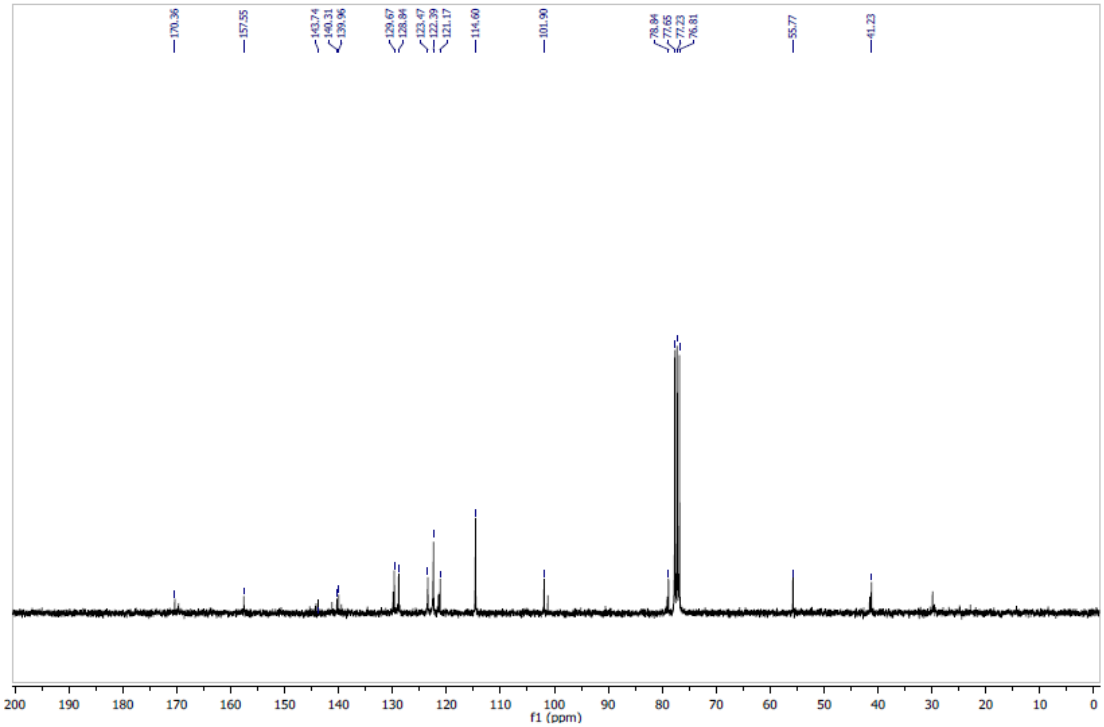


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	19.38	2.389712	2.025357766	5.76866	n.a.
2	B	30.29	115.600	97.97464223	136.465	n.a.

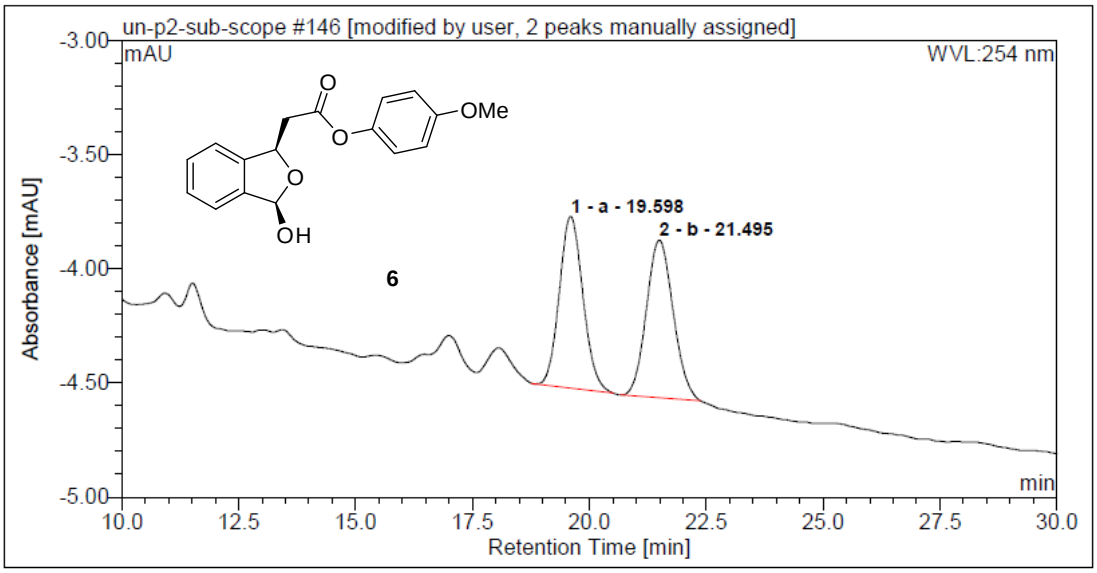
^{1}H-NMR Spectra (600 MHz, $CDCl_3$): *4-Methoxyphenyl 2-(3-hydroxy-1,3-dihydroisobenzofuran-1-yl)acetate (**6**):*



^{13}C-NMR Spectra (600 MHz, $CDCl_3$): *4-Methoxyphenyl 2-(3-hydroxy-1,3-dihydroisobenzofuran-1-yl)acetate (**6**):*

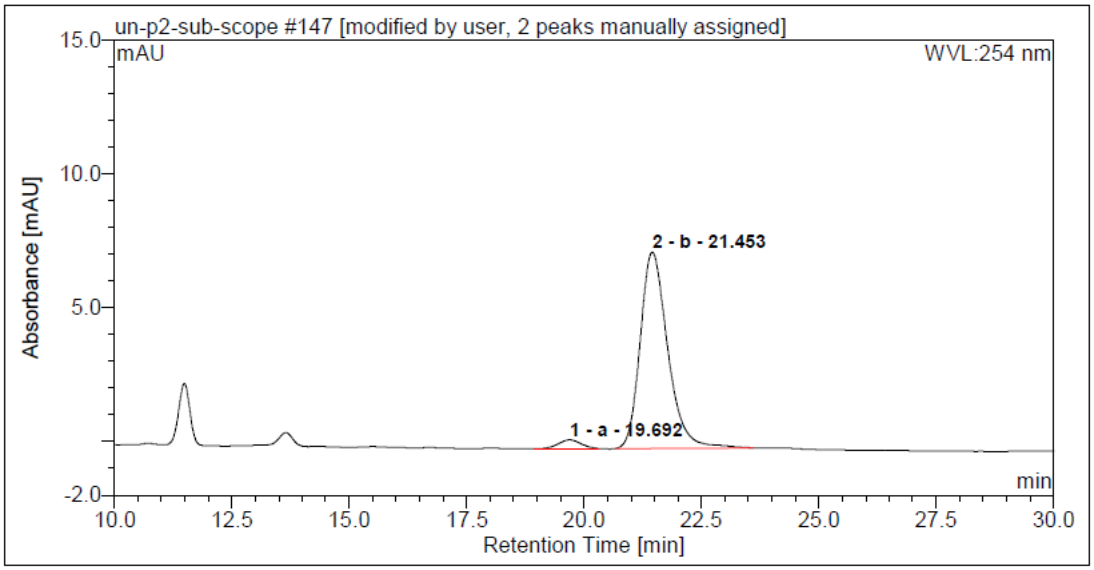


HPLC Chromatogram (racemic): *4-Methoxyphenyl 2-(3-hydroxy-1,3-dihydroisobenzofuran-1-yl)acetate (**6**):*



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	19.60	0.442097	49.13103762	0.75218	n.a.
2	b	21.50	0.458	50.86896238	0.690	n.a.

HPLC Chromatogram (chiral): *4-Methoxyphenyl 2-(3-hydroxy-1,3-dihydroisobenzofuran-1-yl)acetate (**6**):*



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	19.69	0.183047	3.538535344	0.32372	n.a.
2	b	21.45	4.990	96.46146466	7.337	n.a.

Publications:

1) **Organocatalytic asymmetric Michal addition of 1-acetylcyclohexene and 1-acetylcyclopentene to nitroolefins,** Utpal Nath, Ankush Banerjee, Bidhan Ghosh, Subhas Chandra Pan, *Organic & Biomolecular Chemistry*, **2015,** *13*, 7076.

2) **Organocatalytic Asymmetric Tamura Cycloaddition with alpha- Branched Nitroolefins: Synthesis of Functionalized 1- Tetralones,** Utpal Nath, Subhas Chandra Pan, *The Journal of Organic Chemistry*, **2017,** *82(6*), 3262.

3) **Direct Aerobic Oxidative Reactions of 2-Hydroxyacetophenones**, Subas Chandra Sahoo, Utpal Nath, Subhas Chandra Pan, *European Journal of Organic Chemistry*, **2017**, 4434.

4) **Organocatalytic Asymmetric Synthesis of 3,3-Disubstituted-3,4-dihydro-2-quinolones,** Soumendranath Mukhopadhyay, Utpal Nath, and Subhas Chandra Pan *Advanced Synthesis & Catalysis*, **2017**, *359(22)*, 3911.

5) **Organocatalytic Asymmetric [4 + 2] cycloaddition of 1-Acetylcyclohexene and 1-Acetylcyclopentene for the Synthesis of Fused Carbocycles**, Utpal Nath, Subhas Chandra Pan, *European Journal of Organic Chemistry*, **2017**, 6457.

6) **Nonenzymatic Dynamic Kinetic Resolution of in situ Generated Hemithioacetals: Access to 1,3-Disubstituted Phthalans**, Utpal Nath, Deepan Chowdhury, Subhas Chandra Pan (Accepted manuscript in *Advanced Synthesis & Catalysis*, DOI: 10.2002/adsc.201701518).

Conferences attended:

- National Conference on Frontiers in Chemical Sciences (**FICS-2012**), December 2-3, 2012, Indian Institute of Technology Guwahati, Guwahati, India (poster presented).
- XIIth J-NOST Conference for research scholars (**J-NOST-2016**), November 24-27, 2016, CSIR-Central Drug Research Institute, Lucknow, India (poster presented).
- International Conference on Chemistry for Human Development (**ICCHD-2018**), January 8-10, 2018, Heritage Institute of Technology, Kolkata, India (poster presented).