Organocatalytic Asymmetric Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

…………..Dedicated to My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Organocatalytic Asymmetric Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles***" is the outcome of the research work carried out by me under the supervision of Dr. Subhas Chandra Pan, Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

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

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Organocatalytic Asymmetric Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Buddhadeb Mondal (Roll No: 136122037) 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
January, 2018	Supervisor

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Buddhadeb Mondal

Table of Contents

Abbreviation

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

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

Abstract

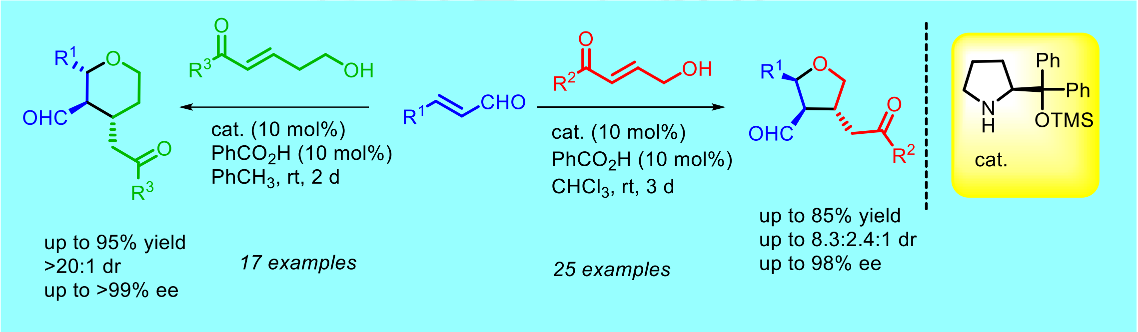
The contents of the present thesis entitled as "***Organocatalytic Asymmetric Synthesis of Oxygen, Nitrogen and Sulfur Heterocycles***" have been divided into six chapters based on the results achieved from the experimental works performed during the entire course of the Ph.D. research programme.

Chapter 1: Overview

Chapter 1 contains a brief discussion on asymmetric organocatalysis particularly, enamine/iminium ion catalysis and also bifunctional thiourea and squaramide catalysis. A brief description of Michael and Mannich reaction are also presented here.

Chapter II: Organocatalytic Asymmetric Synthesis of Highly Substituted Tetrahydrofurans and Tetrahydropyrans *via* Double Michael Addition Strategy

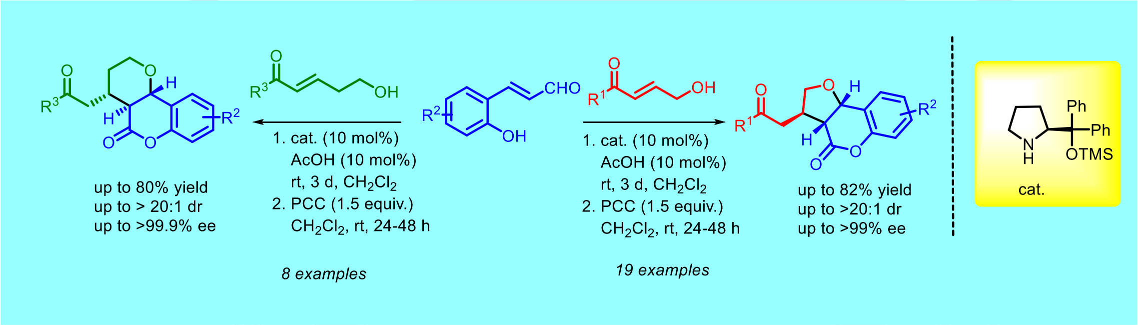
In this chapter, a direct asymmetric double Michael addition reaction between γ/δ-hydroxy-α,β-unsaturated carbonyls and enals has been demonstrated for the synthesis of 2,3,4-trisubstituted tetrahydrofurans and tetrahydropyrans using tandem iminium-enamine catalysis. The formation iminium ion from enals and tendem oxa-Michael/ Michael reaction from γ/δ-hydroxyenones are the key for the success of this reaction. The 2,3,4-trisubstituted tetrahydropyrans are obtained in high yield as well as exelllent enantio- and diasteroselectivities and 2,3,4-trisubstituted tetrahydrofurans are obtained in good to high yield, high enatioselectivities and moderate diasteroselectivities. To illustrate the usefulness of our method, few reactions were envisaged on 2,3,4-trisubstituted tetrahydrofurans/tetrahydropyrans.



Reference: Mondal. B.; Balha. M.; Pan. S. C. *Asian J. Org. Chem.* **2018**, *7*, 1788-1792.

Chapter III: Organocatalytic Asymmetric Cascade Reaction between *o*-Hydroxycinnamaldehydes and *γ*/*δ*-Hydroxyenones: A Route to Tetrahydrofuran/Tetrahydropyran Fused 3,4-Dihydrocoumarins

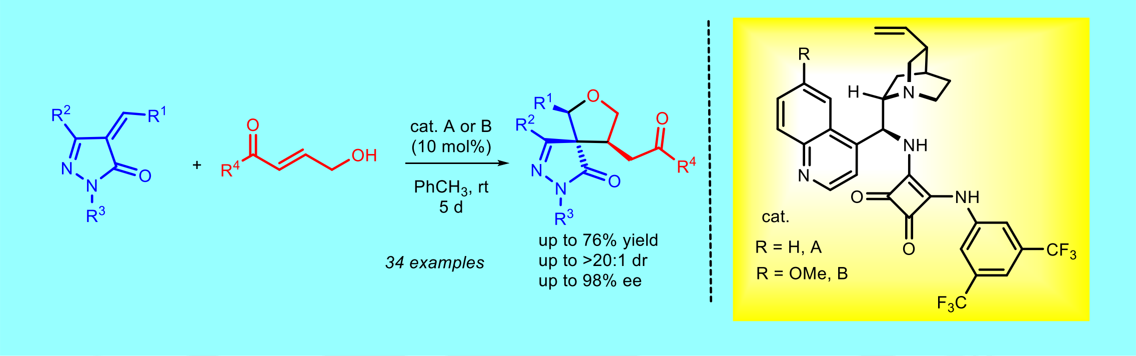
3,4-Dihydrocoumarin is an important structural motif widely distributed in nature and also in pharmaceuticals. In recent years, a number of elegant asymmetric organocatalytic syntheses of 3,4-dihydrocoumarin derivatives have been reported. However the synthesis of fused 3,4-dihydrocoumarin derivatives have been less reported. In this chapter, a mild and operationally simple protocol for the organocatalytic asymmetric synthesis of tetrahydrofuran/tetrahydropyran fused 3,4-dihydrocoumarin has been developed *via* a cascade reaction between 2-hydroxy cinnamaldehydes and *γ*/*δ*-hydroxyenones followed by PCC oxidation. Prolinol TMS ether catalyst in combination with acetic acid was found to be the most effective for the cascade reaction. The desired products were obtained in high yield as well as excellent enantio- and diastereoselectivities. The utility of our method was then demonstrated by converting hemiacetal to a number of useful organic structures.



Reference: Mondal. B.; Pan. S. C. *Adv. Synth. Catal*. **2018**, *360*, 4348-4353.

Chapter IV: Highly Diastereo and Enantioselective Synthesis of Spiro-Tetrahydrofuran-Pyrazolones *via* Organocatalytic Cascade Reaction between *γ*-hydroxyenones and Unsaturated Pyrazolones

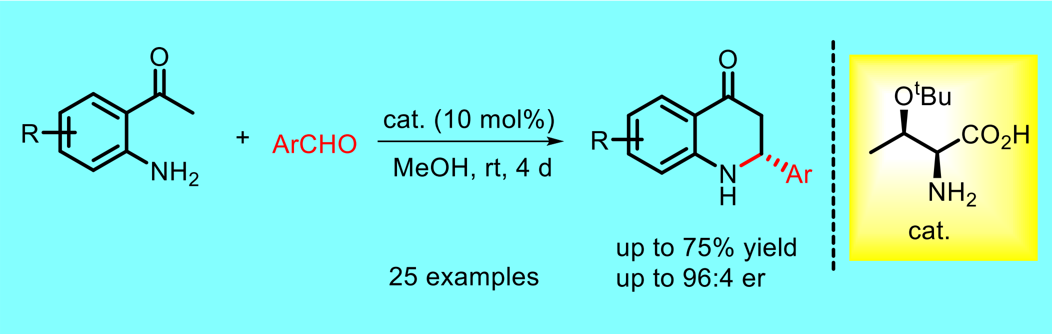
Spiropyrazolones combining stereogenic cycloalkane/cycloalkene heterocycle and pyrazolone motifs, have attracted attention because of their potent bioactivities in medicinal chemistry. However, there is an inherent challenge for the preparation of spiro-motifs, including incorporating heterocycles and attaining high enantioselectivity. Realizing the potential of heterocycle incorporated spiropyrazolones for medicinal chemistry, in this chapter we embarked in a highly diastereo- and enantioselective cascade oxa-Michael/Michael reaction between unsaturated pyrazolones and γ-hydroxyenones with the help of a tertiary amino squaramide bifunctional catalyst. The spiro-tetrahydrofuran-pyrazolones were obtained in high yield as well as excellent enantio- and diastereoselectivities. To exhibit the synthetic utility of our method, few derivatives were also prepared.



Reference: Mondal. B.; R. Maity.; Pan. S. C. *J. Org. Chem.* **2018**, *83*, 8645-8654.

Chapter V: Primary Amino Acid Catalyzed Asymmetric Intramolecular Mannich Reaction for the Synthesis of 2-aryl-2,3-dihydro-4-quinolones

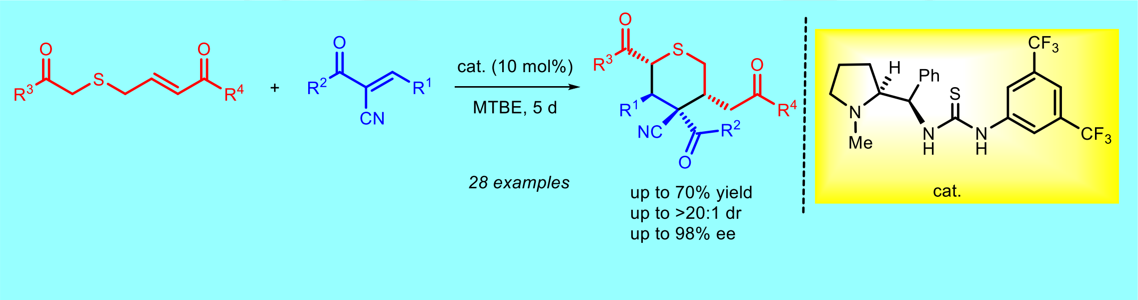
2-Aryl-2,3-dihydro-4-quinolones have attracted considerable attention because of their activities as anticancer, antimalarial as well as antibiotic agents and as potent cross-species micro RNA inhibitors. These important biological properties have stimulated interest for the synthesis of 2-aryl-2,3-dihydro-4-quinolones from different research groups, particularly in enantioselective fashion as two individual stereoisomers behave in totally different ways. In this chapter, we described primary amino acid catalyzed one pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones and also employ a variety of 2-aminoacetophenones for the first time. The products were obtained in moderate yields and with moderate to high enantioselectivities.



Reference: Mondal. B.; Pan. S. C. *Org. Biomol. Chem*. **2014**, *12*, 9789-9792.

Chapter VI: Organocatalytic Asymmetric Synthesis of Pentasubstituted Tetrahydrothiopyrans Bearing a Quaternary Centre through a Double Michael Reaction

Tetrahydrothiopyrans, analogous of tetrahydropyrans, are important structural motifs abundant in a number of bioactive compounds and pharmaceuticals. However, up to now, only *α,β*-unsaturated aldehydes have been successfully used for the synthesis chiral tetrahydrothiopyrans using secondary amine catalysis. Thus it will be really attractive to employ other Michael acceptors for the synthesis of highly substituted tetrahydrothiopyrans. In this chapter, a mild and operationally simple protocol for the asymmetric synthesis of pentasubstituted tetrahydrothiopyrans bearing a quaternary centre using bidentate ketothioether enones and *trans*-*α*-cyano-*α,β*-unsaturated ketones employing proline derived bifunctional tertiary amino thiourea catalyst. This reaction furnished densely functionalized tetrahydrothiopyrans in acceptable yields, moderate diastereomeric ratios as well as good to excellent enantioselectivities.



Reference: Mondal. B.; Pan. S. C. *Synlett* **2018**, *29*, 576-580.

Chapter I

Overview

I. Introduction

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

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

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

Figure 1: The enantiomers of linalool.

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

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

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

Figure 2: The enantiomers of asparagine.

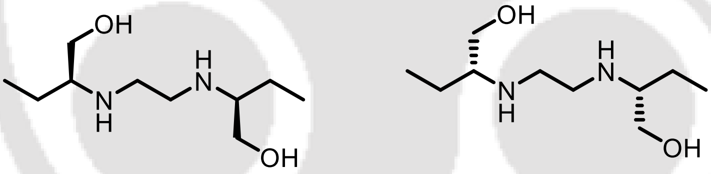
Enzymes in living systems are chiral and mostly exist as single enantiomeric form. Thus they are able to distinguish between enantiomers. One enantiomer of a drug may have a desired valuable effect while the other may cause serious and even harmful side effects. For example, dopamine is an effective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

(*S*)-Dopa
3

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

Figure 3: The enantiomers of Dopa.

Similarly, (*S*,*S*)-ethambutol **4** is effective for the treatment of tuberculosis, whereas the (*R*,*R*)-ethambutol *ent*-4 can cause blindness (Figure 4).[5]



(*S*,*S*)-Ethambutol
4

(*R*,*R*)-Ethambutol
ent-**4**

Figure 4: The enantiomers of ethambutol.

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

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

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

i) Biocatalysis
ii) Metal catalysis and
iii) Organocatalysis

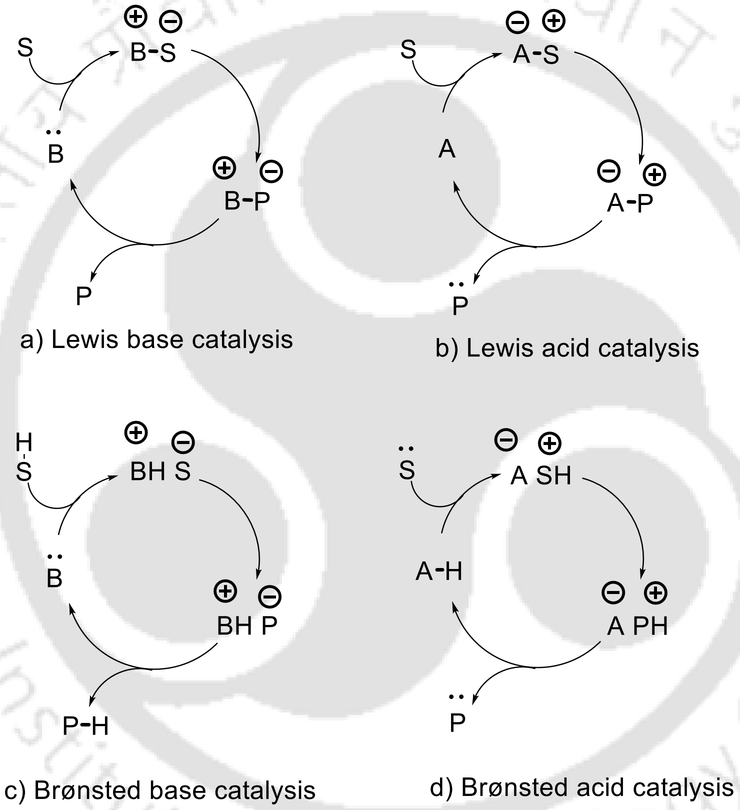
Biocatalysis[6] is the chemical process through which enzymes or other biological catalysts are used as for regio-, chemo- and stereoselective transformations. This process usually requires mild reaction conditions. However there are few disadvantages of biocatalysts such as substrate specificity, sensitivity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

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

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

II. Asymmetric organocatalysis

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



a) Lewis base catalysis

b) Lewis acid catalysis

c) Brønsted base catalysis

d) Brønsted acid catalysis

Scheme 1: Different modes of organocatalysis.

Organocatalysts are broadly classified into four areas according to their mode of action: (i) Lewis base catalysis, (ii) Lewis acid catalysis, (iii) Brønsted base catalysis and (iv) Brønsted acid catalysis. The corresponding simplified catalytic cycles are shown in Scheme 1.[9]

In a Lewis base catalysis, the reaction is initiated by the nucleophilic addition of the catalyst (**B:**) to the substrate (**S**) and the resulting complex undergoes a reaction followed by release of the product (**P**) and catalyst regeneration for further turnover (Scheme 1a). Enamine/iminium catalysis, Morita–Baylis–Hillman reaction, phosphine-catalyzed reactions of allenoates or alkynoates, DMAP-catalyzed acylation, NHC-catalysis etc. are the most common examples of Lewis base catalysis.[10]

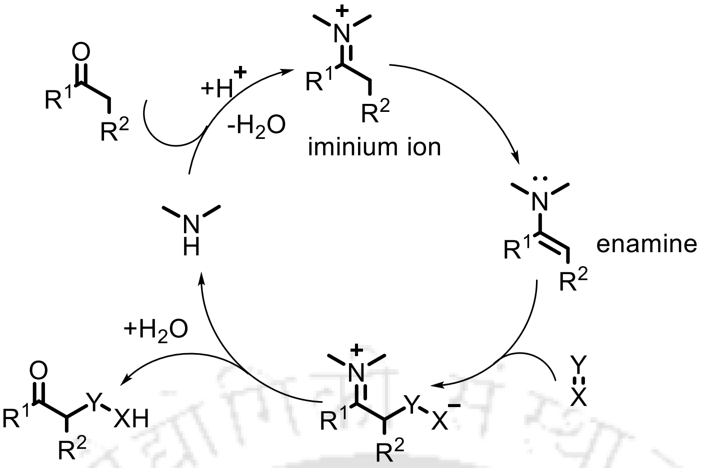
In Lewis acid catalysis, the catalyst (**A**) activates nucleophilic substrates (**S:**) to form an activated complex (Scheme 1b). After the reaction, product (**P:**) is released and catalyst in a similar manner. Baeyer-Villiger oxidation and Shi epoxidation are the representative examples of Lewis acid catalysis.[11]

Brønsted base catalytic cycles are initiated by partial or full deprotonation of the substrate (**S-H**) by the catalyst (**B:**) followed by the chemical transformation to give the product (**P-H**) and regeneration of the catalyst (Scheme 1c). Examples of Brønsted base catalysis are tertiary amine and guanidine catalyzed Strecker, Michael and Henry reactions.[12]

Similarly Brønsted acid catalytic cycles start with partial or full protonation of the substrate (**S:**) by the catalyst (**A-H**) and the resulting ion-pair reacts to give the product (**P:**) followed by the catalyst regeneration (Scheme 1d). TADDOL, phosphoric and carboxylic acids, thiourea derivatives etc. are the most popular examples of Brønsted acid catalysts.[13]

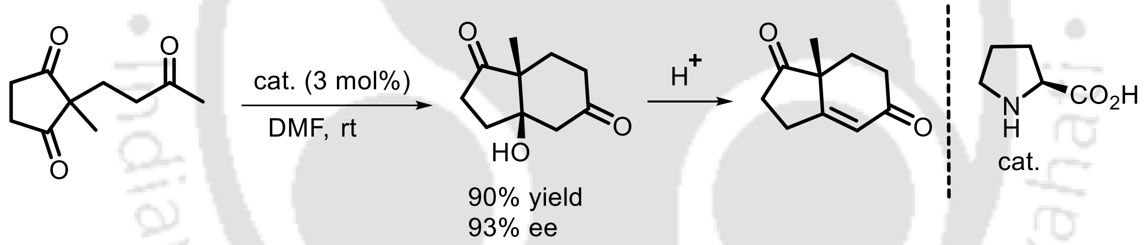
III. Enamine and Iminium catalysis

Enamine catalysis involves catalytic formation of an enamine intermediate. An iminium ion intermediate (Scheme 2)[14] gets reversibly deprotonated to yield the reactive enamine (with elevated HOMO energy).



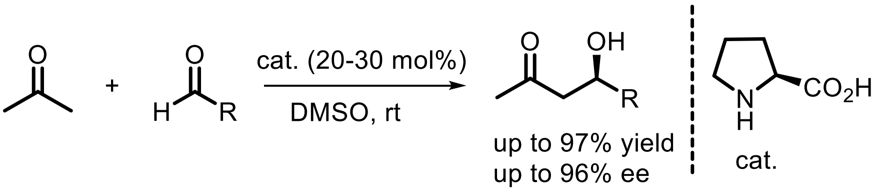
Scheme 2. Enamine catalysis.

Hajos-Parrish-Eder-Sauer-Wiechert[15] reported proline catalysed intramolecular aldol reaction and this is the first example of asymmetric enamine catalysis (Scheme 3).



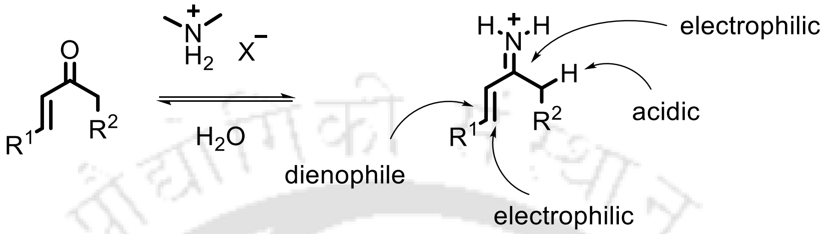
Scheme 3. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

About thirty years later a revival of this chemistry was initiated with the discovery of the proline-catalyzed direct asymmetric intermolecular aldol reaction by List et al. (Scheme 4).[16]



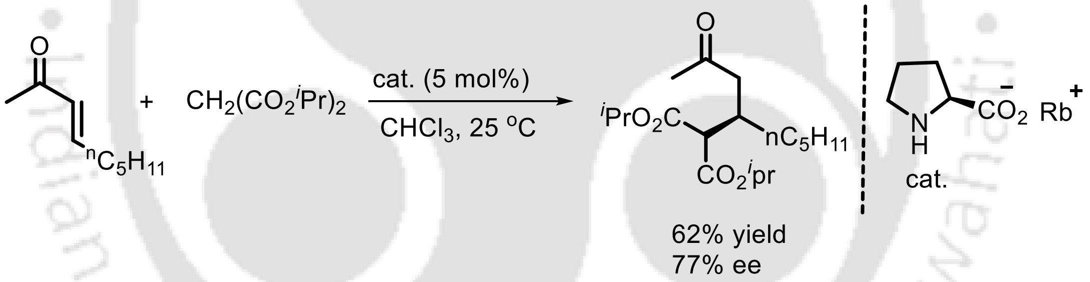
Scheme 4. Proline catalyzed intermolecular aldol reaction with acetone.

Generation of an iminium ion from an unsaturated carbonyl compound lowers the LUMO energy of the system and is thus beneficial to the reactivity of the compound. The iminium ion is reversibly formed by condensation of amine with an enal or an enone (Scheme 5).[17]



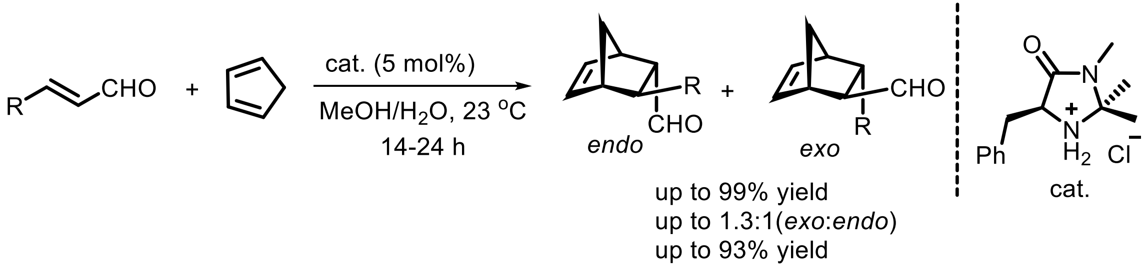
Scheme 5. Iminium catalysis.

In 1993, Yamaguchi and co-workers developed the first asymmetric iminium catalytic conjugate addition reaction using a rubidium salt of proline and good enantioselectivities were achieved (Scheme 6).[18]



Scheme 6. Asymmetric iminium catalytic conjugate addition reaction by Yamaguchi et al.

In 2000, MacMillan and co-workers reported the first highly enantioselective example of iminium catalysis strategy in the asymmetric Diels-Alder reaction (Scheme 7).[19]



Scheme 7. Asymmetric Diels-Alder reaction by Macmillan et al.

IV. Bifunctional (thio)urea catalysis

Activation of a substrate or an intermediate by organocatalysts may not always be restricted to any individual mode. Presence of different functional groups in the same catalyst result in more than one mode of activation which can operate synergistically. Such catalysts are termed as multifunctional organocatalysts.[20] The major domain of multifunctional catalysis is occupied by bifunctional catalysis[21] and used to provide dual activation of nucleophile and electrophile with two activating sites, either through hydrogen bonding or Brønsted acid-Lewis/Brønsted base activation (Figure 5).

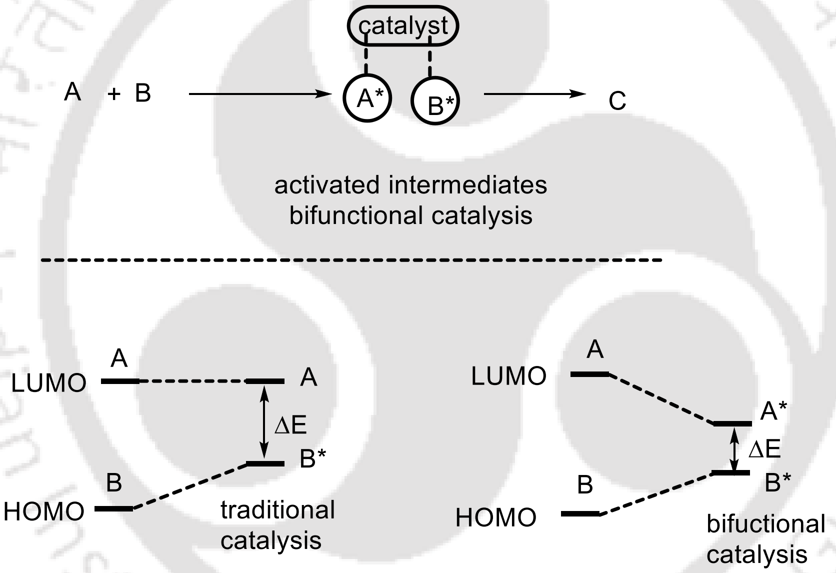
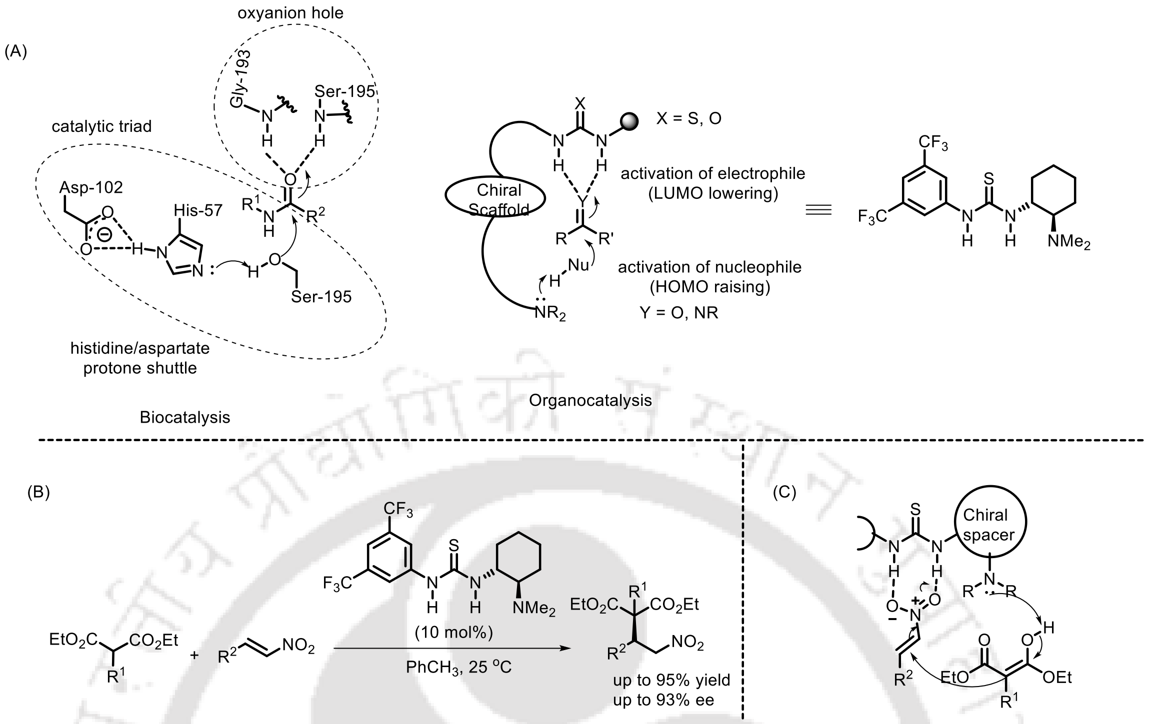


Figure 5. The concept of bifunctional catalysis.

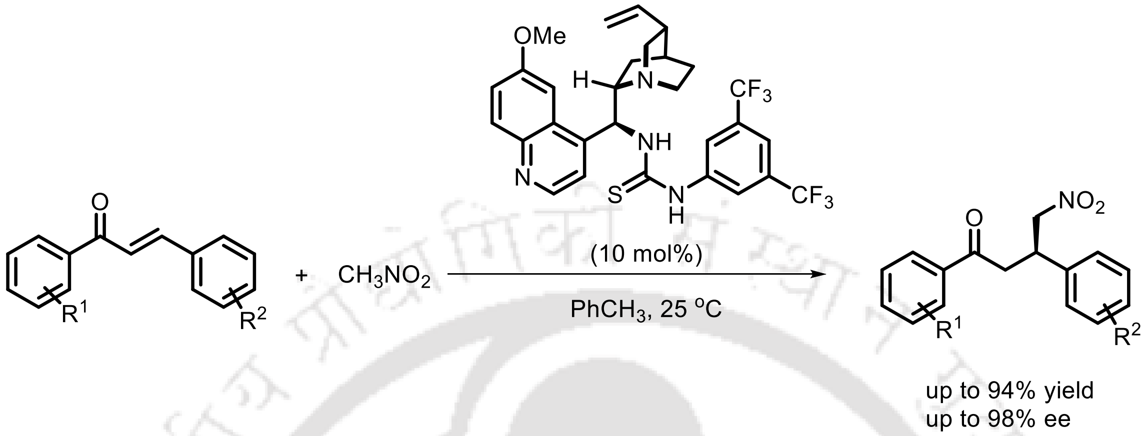
For example, serine protease is an enzyme that accelerate the hydrolysis of peptide bonds by ~10^{10} folds compared to the uncatalyzed reaction. The activation of the serine hydroxyl group is initiated by histidine/aspartate proton shuttle system, known as "catalytic triad", via general base catalysis while the amide carbonyl group is activated by the two H-bond donors in the enzyme active site, known as "oxyanion hole" (Scheme 8A).



Scheme 8: (A) Biomimetic approach towards bifunctional thiourea catalyst. (B) Enantioselective Michael addition of malonates to nitroolefins using bifunctional thiourea catalyst. (C) Proposed transition state model.

In 2003, bifunctional thiourea catalyst was first reported by Takemoto and co-workers,[22] they have developed a tertiary amino thiourea based bifunctional organocatalyst by mimicking the active sites of the serine protease enzyme (Scheme 8B). This bifunctional thiourea catalyst (10 mol%) was used for the Michael addition of malonates to electron deficient nitroolefins and the desired product was obtained with high yields and excellent enantioselectivities. Simultaneous dual activation operates by LUMO lowering of nitroolefin through dual hydrogen bonding with Brønsted acidic protons of thiourea moiety and HOMO raising activation via enolization of malonate by Brønsted basic dimethylamino group.[23] This *trans*-(1*R*,2*R*)-diaminocyclohexane based thiourea derivative (**I**) is now popularly known as Takemoto catalyst.

In 2005, Soós and co-workers have developed cinchona alkaloid derived bifunctional thiourea catalysts and their application in the asymmetric Michael addition of nitromethane to chalcones (Scheme 9).[24] In the same year, similar type of cinchona-derived bifunctional thiourea catalyzed asymmetric Michael addition of malonates to nitroolefins was independently disclosed by Dixon and Connon group.[25]



Scheme 9: Asymmetric Michael addition of nitromethane to chalcones using quinine-derived bifunctional thiourea organocatalyst by Soós et al.

V. Bifunctional squaramides

Squaramide catalysts have emerged as effective alternative to urea/thiourea and guanidine catalysts. Also, squaramide functionality differs significantly from its closest urea or thiourea analogues in several aspects. Squaramide acts as a ditopic binder as it contains two H-bond donor (N-H) and two H-bond acceptor (C=O) functionalities in the same molecular framework (Figure 6A).[21e] The N-H acidity of squaramide is higher than urea/thiourea derivative due to their vinylogous amide nature. The delocalization of nitrogen lone pair occurs through carbon-oxygen double bond thus providing a polarized nitrogen moiety. Hence, the squaramide scaffold is more rigid, which accounts for limited conformational changes (Figure 6B).[26]

In the case of squaramide the distance between the two NH groups (~2.73 Å) is about 0.6 Å longer than that of thiourea (~2.13 Å). The pKa value of squaramide is lower compared to its thiourea and urea analogous. In the case of squaramide further delocalization occurs through cyclobutenedione system and it leads to stronger hydrogen-bonding and increased catalytic activity (Figure 6C and 6D).

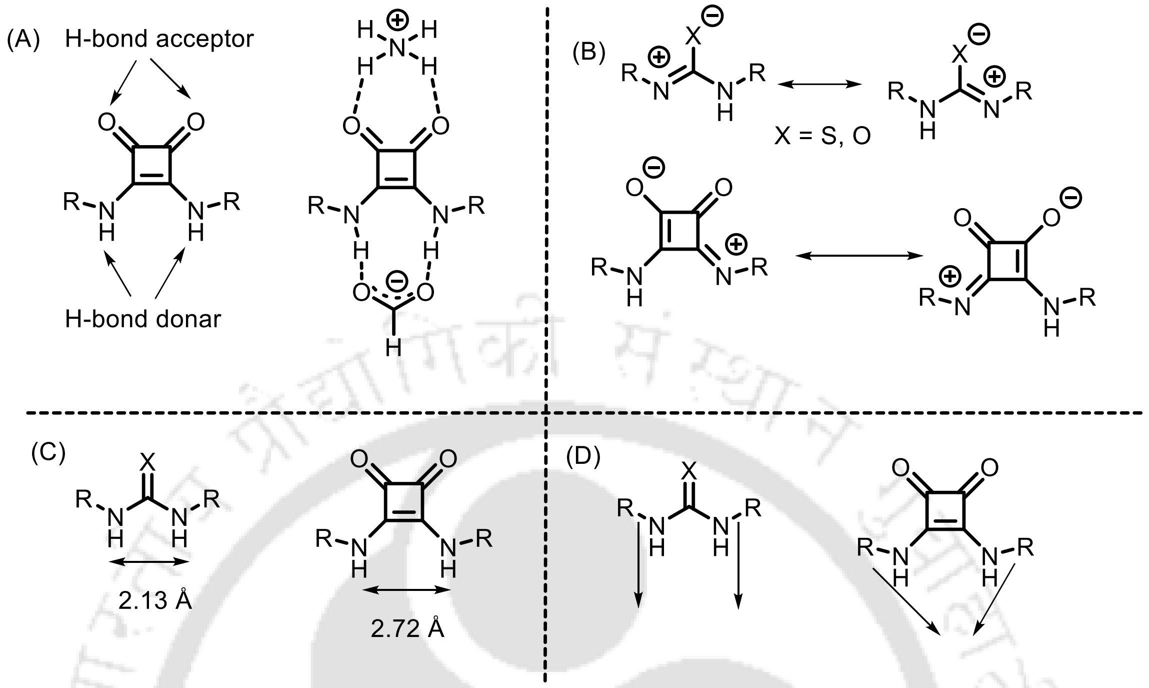
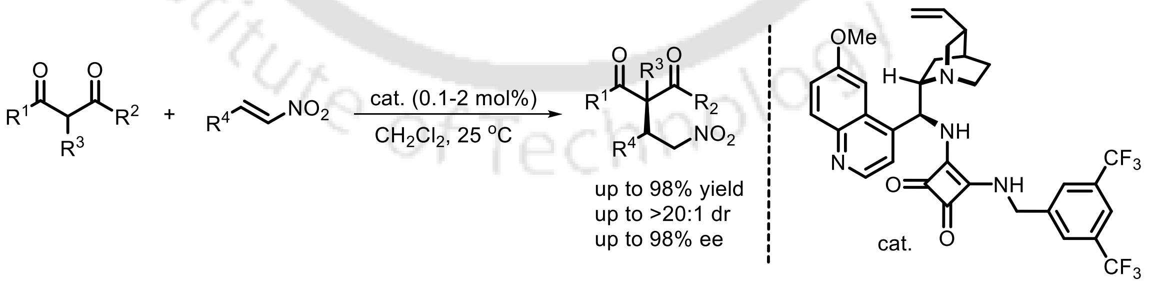


Figure 6: Comparison between squaramide and (thio)urea.

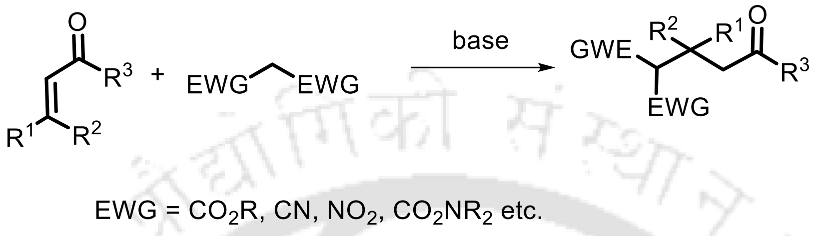
In 2008, Rawal and co-workers first reported cinchona alkaloid derived bifunctional squramide catalyzed enantioselective Michael addition of 1,3-dicarbonyl compounds to nitroolefins. Under the optimized reaction conditions the desired products were obtained in near quantitative yields as well as good to excellent diastereo- and enantioselectivities (Scheme 10).[27]



Scheme 10: The first bifunctional squaramide catalyzed reaction by Rawal et al.

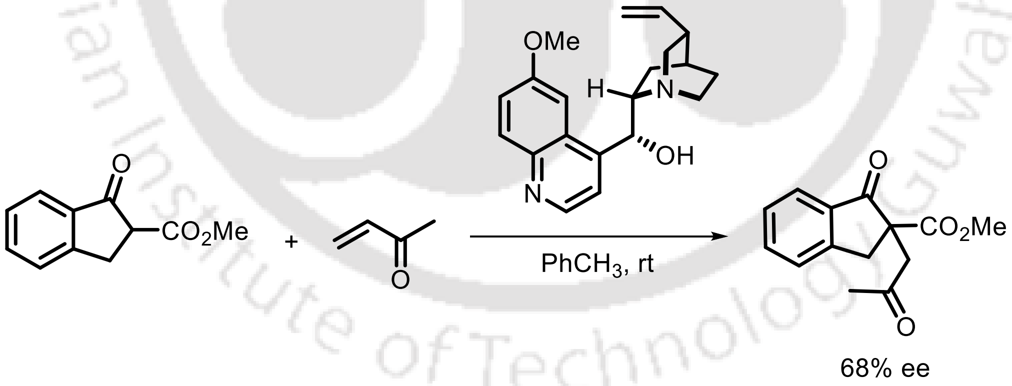
VI. Michael reaction

The Michael reaction is one of the most important reactions in organic chemistry. In 1887 Arthur Michael discovered the addition of carbon nucleophiles to conjugate acceptor systems, which is commonly known as Michael addition (Scheme 11).[28]



Scheme 11: The Michael reaction.

The first example of asymmetric Michael reaction was discovered by Wynberg in 1975. He utilized optically active quinine as catalyst in the Michael addition of 1-oxo-2-indanecarboxylate to methyl vinyl ketone and the desired product was obtained in 68 % ee (Scheme 12).[29]



Scheme 12: The first asymmetric Michael reaction by Wynberg.

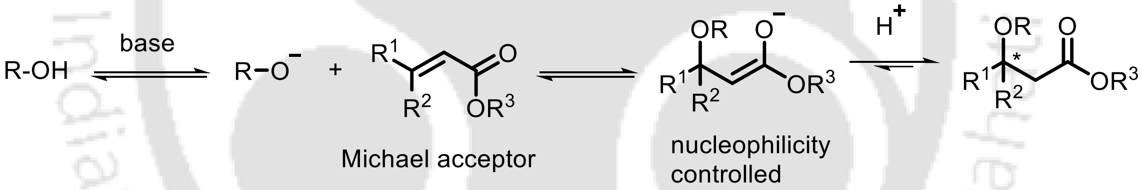
Classification of the Michael addition

Depending on the nature of the nucleophile (Michael donor), Michael addition can be classified into the following types:

- Carba-Michael addition
- Aza-Michael addition
- Oxa-Michael addition
- Phospha-Michael addition
- Thia-Michael addition

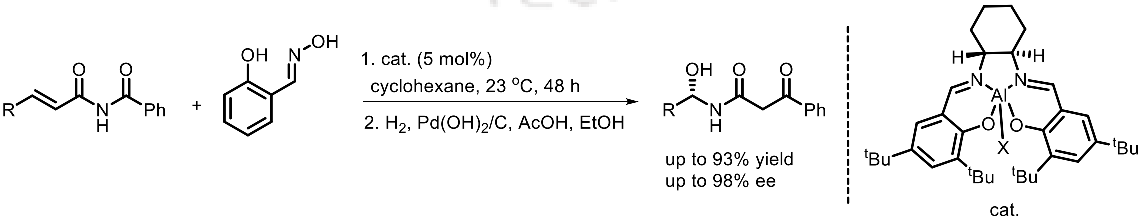
The present thesis is focused on oxa-Michael and thia-Michael addition. The details of other types of Michael additions, namely carba-,[30] aza-[31] and phospha-Michael[32] additions can be found elsewhere.

The first example of an oxa-Michael addition was reported by Loydl in 1878 for the synthesis of malic acid (Scheme 13).[33] Major challenges of oxa-Michael reactions are the reversibility in the alcohol addition step as well as low reactivity of the employed alcohols. Pleasingly, during recent years a variety of approaches have been developed for the enhancement of reactivity and stereoselectivity.



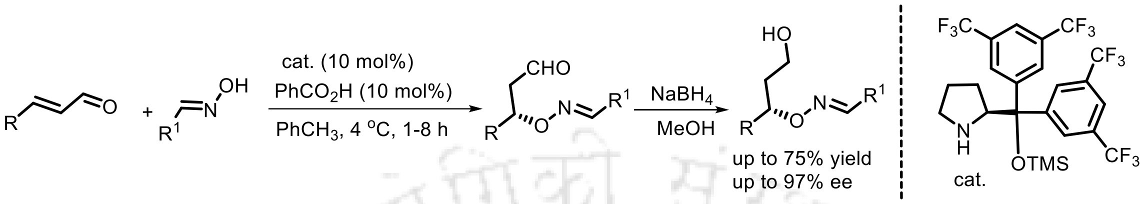
Scheme 13: The oxa-Michael reaction.

In 2005, Jacobsen and co-workers reported aluminium-salen catalyzed enantioselective hydration of *α*,*β*-unsaturated imides. The desired products were obtained in high yields as well as with excellent enantioselectivities (Scheme 14).[34]



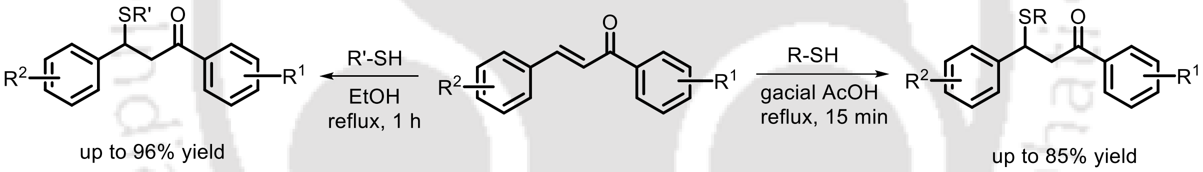
Scheme 14: Enantioselective hydration of *α*,*β*-unsaturated imides by Jacobsen et al.

Jørgensen and his group reported diaryl prolinol ether catalyzed addition of benzaldoxime to *α,β*-unsaturated aldehyde. Under the optimized reaction conditions the desired products were obtained in good yields and excellent enantioselectivities (Scheme 15).[35]



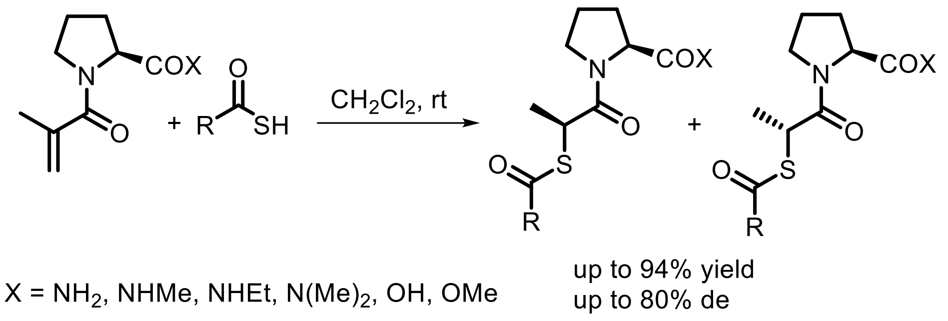
Scheme 15: Enantioselective addition of benzaldoxime to *α,β*-unsaturated aldehyde by Jørgensen et al.

In 1960, Allen and co-workers reported salts of thia-Michael adducts which were formed from the reaction between monosubstituted chalcones and alkylthiols (Scheme 16).[36]



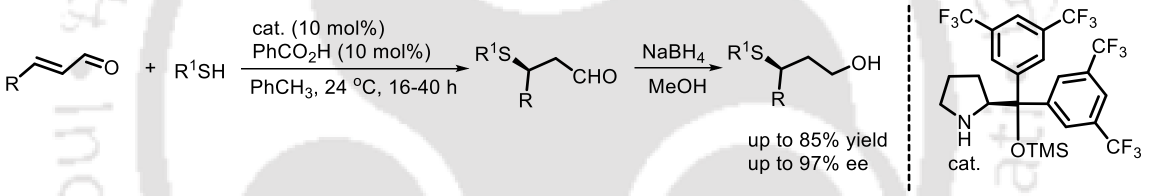
Scheme 16: Reaction between monosubstituted chalcones and alkylthiols by Allen et al.

In 1989, Effenberger et al. used proline and prolinol derived chiral auxiliaries to effect diastereoselective addition of thiocarboxylic acids to auxiliary attached methacryloyl substrates (Scheme 17).[37] The corresponding products were obtained in excellent yields and moderate level of diasteroselectivities.



Scheme 17: The diastereoselective addition of thiocarboxylic acids by Effenberger et al.

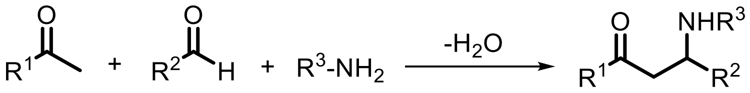
In 2005, Jørgensen and co-workers developed iminium ion promoted sulfa Michael addition between *α*,*β*-unsaturated aldehydes and thiols. Under the optimized reaction conditions the products were obtained in good yields and excellent enantioselectivities (Scheme 18).[38]



Scheme 18: Sulfa Michael addition of *α*,*β*-unsaturated aldehydes and thiols by Jørgensen et al.

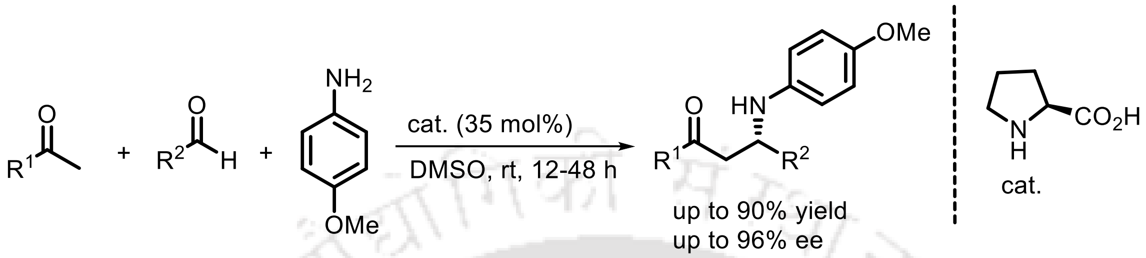
VII. Mannich reaction

Mannich reaction is one of the most fundamental and important C–C bond forming reactions in organic synthesis. In 1912, C. Mannich developed a three-component reaction between an enolizable CH-acidic carbonyl compound, an amine and an aldehyde to produce *β*-amino carbonyl compounds (Scheme 19).[39]



Scheme 19: The Mannich reaction.

List *et al.* reported the first example of a direct organocatalytic asymmetric Mannich reaction using (*S*)-proline as catalyst. This protocol led to efficient syntheses of aminocarbonyl compounds with good yields as well as with excellent enantioselectivities (Scheme 20).[40]



Scheme 20: The first asymmetric Mannich reaction by List et al.

VIII. Conclusion and focal theme of the present work

The focal theme of this thesis is to utilize chiral amine and bifunctional tertiary amine thiourea and squaramide catalysts in various organocascade reactions.

Chiral secondary amine catalyzed enantioselective synthesis of highly substituted tetrahydrofuran/tetrahydropyran and tetrahydrofuran/tetrahydropyran-fused 3,4-dihydrocoumarins by the reaction of *γ*/*δ*-hydroxyenones with substituted *α*,*β*-cinnamaldehydes and *o*-hydroxycinnamaldehydes have been described in the second and third chapters respectively.

In the fourth chapter, bifunctional squaramide catalyzed synthesis of spiro-tetrahydrofuran-pyrazolones has been described.

The Mannich reaction is very useful for the synthesis of nitrogenous molecules. In the fifth chapter, primary amino acid catalyzed asymmetric intramolecular Mannich reaction has been presented for the synthesis of 2-aryl-2,3-dihydro-4-quinolones.

The detailed investigation for the enantioselective synthesis of pentasubstituted tetrahydrothiopyrans by the reaction of bidentate ketothioether enones with *trans*-*α*-cyano-*α*,*β*-unsaturated ketones in the presence of a bifunctional tertiary amine thiourea catalyst is presented in the last chapter of the thesis.

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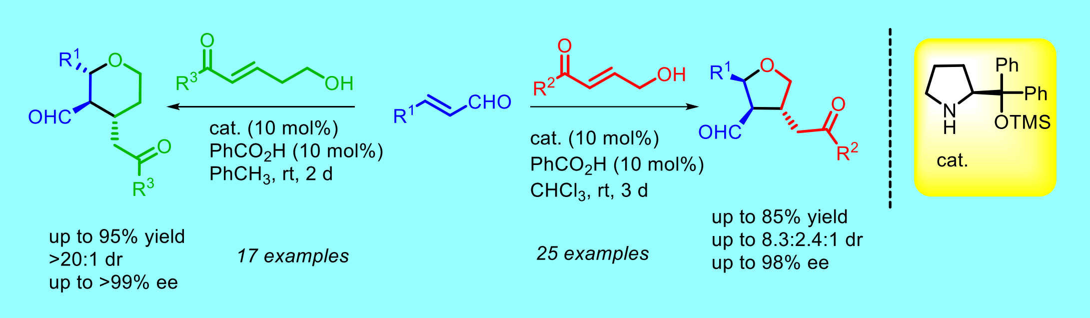
Chapter 2

Organocatalytic Asymmetric Synthesis of Highly Substituted Tetrahydrofurans and Tetrahydropyrans via Double Michael Addition Strategy



Asian J. Org. Chem. **2018**, *7*, 1788-1792.

2.1 Introduction

Carbon - oxygen (C-O) oxacyclic frameworks such as tetrahydrofurans (THF) and tetrahydropyrans (THP) rings in a broad array of natural products and biologically active agents have resulted in the development of a number of methods for their stereoselective synthesis. The tetrahydrofuran and tetrahydropyran rings are important structural motifs present in a diverse range of bioactive compounds such as antibiotics, antitumor, pheromones and marine toxins etc.[1,2] Representative examples having tetrahydrofuran rings include (+)-fragransin A2, lituarin C, leiodelide B, oscillariolide and amphidinolactone B (Figure 1).[3,4]

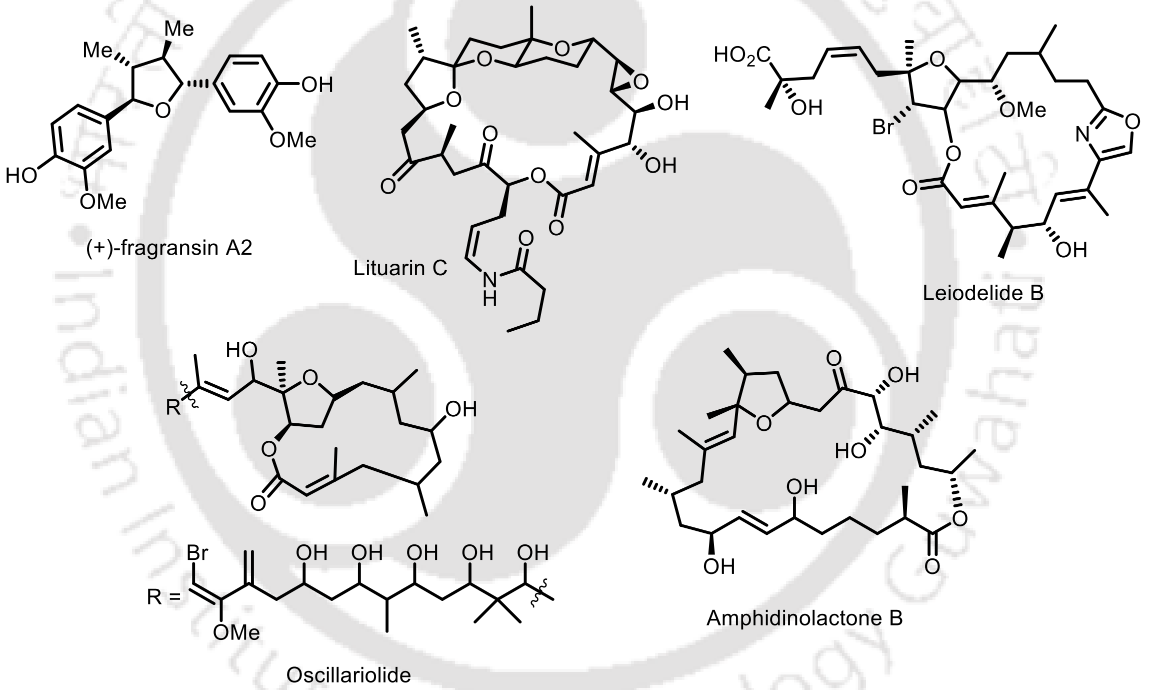


Figure 1. Representative natural products having highly functionalized tetrahydrofuran motifs.

Similarly zincophorin, X-14547A, kendomycin, ratjadone containin tetrahydopyran motif (Figure 2).[5] As a consequence, a variety of approaches were developed for the stereoselective synthesis of tetrahydrofuran[6,7] and tetarhydropyran[8] derivatives.

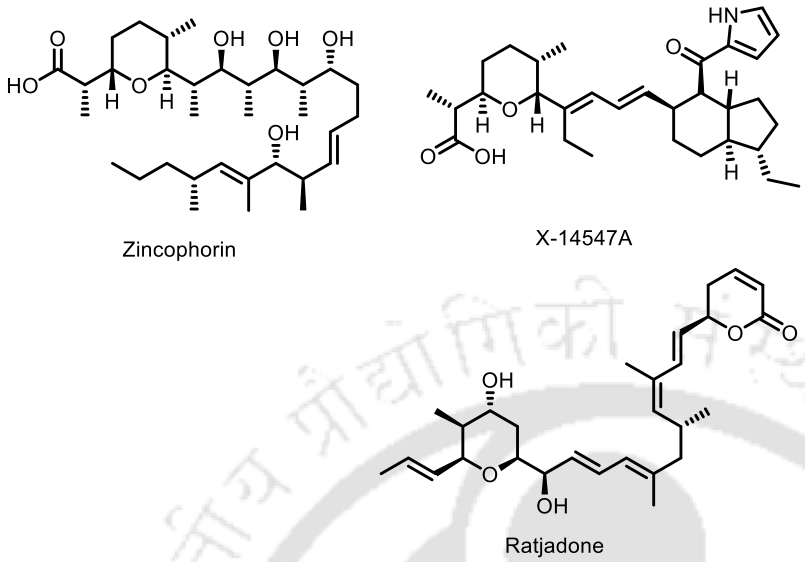
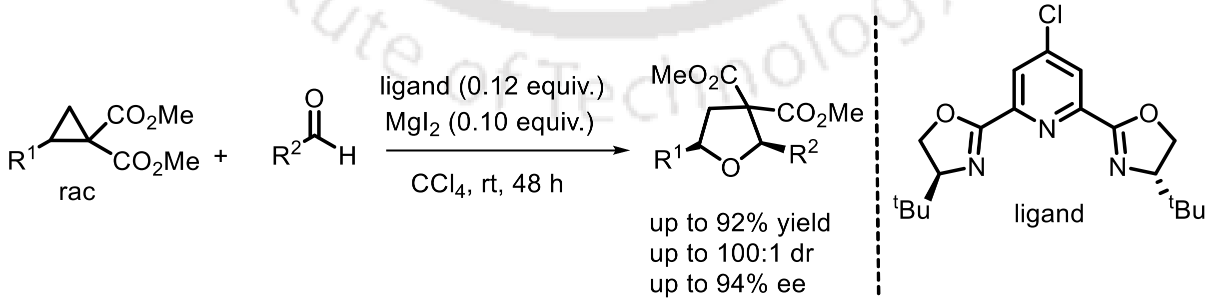


Figure 2. Representative natural products having highly functionalized tetrahydropyran motifs.

2.2 Selected previously reported strategies for the asymmetric synthesis of tetrahydrofuran and tetarhydropyran

2.2.1 Catalytic enantioselective synthesis of tetrahydrofuran

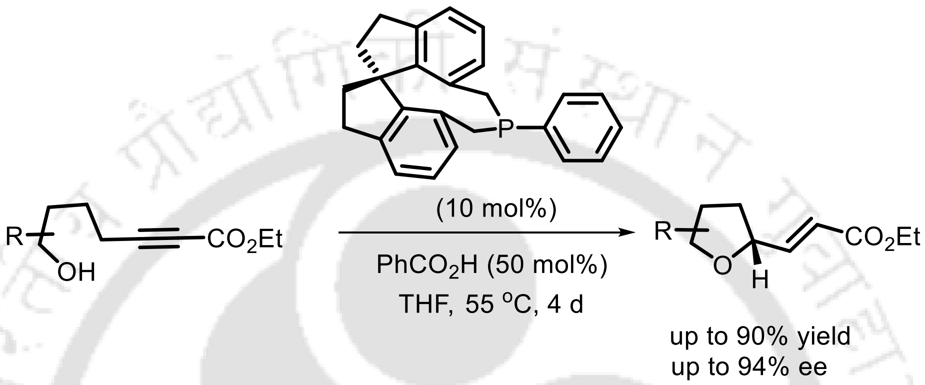
Johnson and co-workers reported organocatalytic enantioselective synthesis of multi-substituted tetrahydrofurans *via* dynamic kinetic asymmetric [3+2] cycloaddition of racemic cyclopropanes with aldehydes using ^{t}Bu-Pybox ligand. The aforementioned protocol provided the desired products in moderate yields with good to excellent diastereoselectivities and enantioselectivities (Scheme 1).[9]



Scheme 1. Organocatalytic enantioselective synthesis of tetrahydrofurans by Johnson et al.

2.2.2 Phosphine-catalyzed enantioselective synthesis of oxygen heterocycles

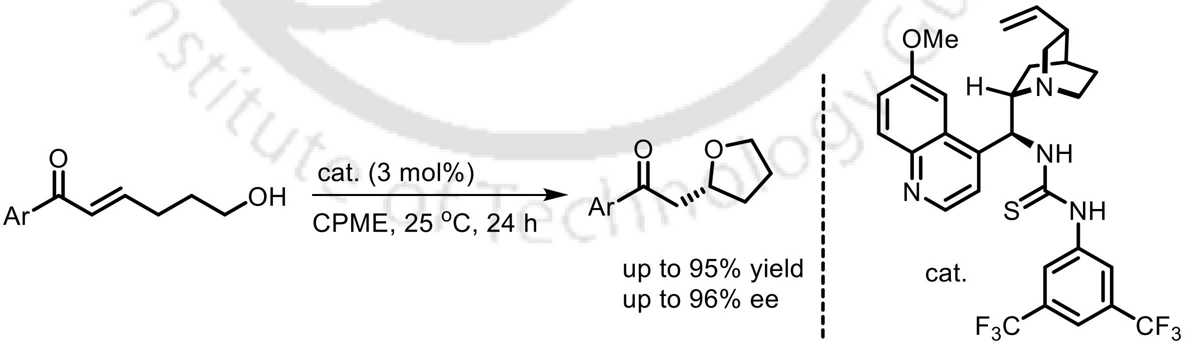
A highly enantioselective synthesis of oxygen heterocycles using chiral phosphine catalyst in high yields and with high levels of enantioselectivities (up to 90% yield and 94% ee respectively) was developed by Fu et al. in 2009 (Scheme 2).[10]



Scheme 2. Phosphine-catalyzed enantioselective synthesis of oxygen heterocycles by Fu et al.

2.2.3 Asymmetric catalytic cycloetherification

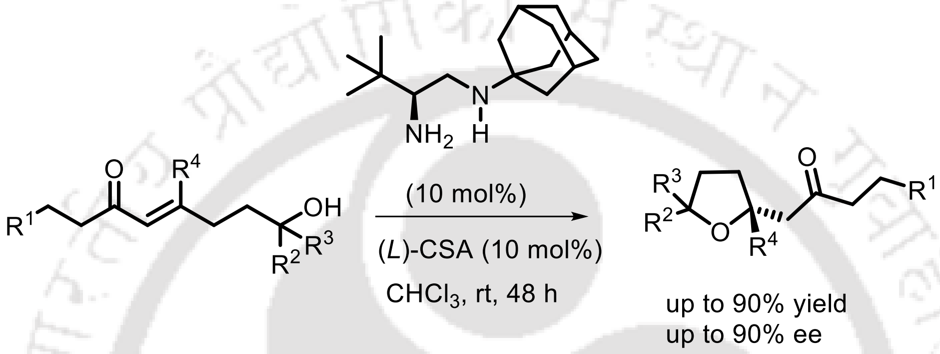
In 2011, the research group of Matsubara developed cinchona-alkaloid-thiourea catalyzed THF synthesis *via* cycloetherification of ε-hydroxy-α,β-unsaturated ketones. The desired products were obtained in excellent yields as well as with excellent enantioselectivities (Scheme 3).[11]



Scheme 3. Cinchona-alkaloid based bifunctional thiourea catalyzed cycloetherification by Matsubara et al.

2.2.4 Asymmetric intramolecular oxa-Michael reaction

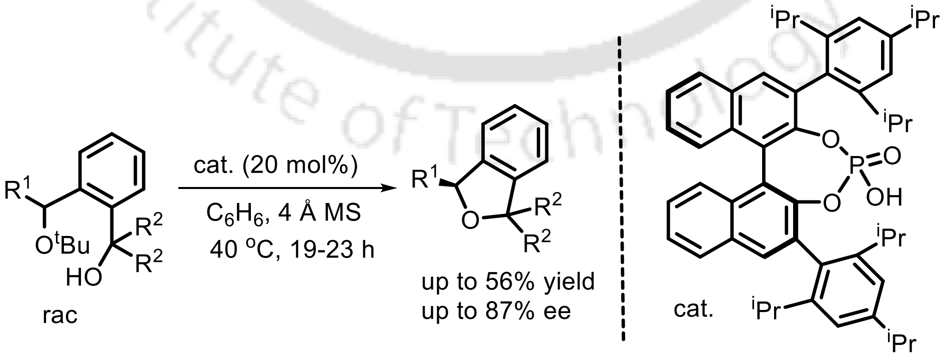
Zhao and co-workers reported an asymmetric intramolecular oxa-Michael reaction of *α,β*-unsaturated ketones for the synthesis of tetrahydrofurans/2H-pyrans catalyzed by primary-secondary diamines (Scheme 4).[12] The aforementioned protocol provided tetrahydrofurans/2H-pyrans in good yields and with high enantioselectivities (up to 96% yield and up to 90% ee respectively).



Scheme 4. Primary-secondary diamines catalyzed enantioselective synthesis of tetrahydrofurans/2H-pyrans by Zhao et al.

2.2.5 Brønsted acid catalyzed asymmetric SN2-type O-alkylations

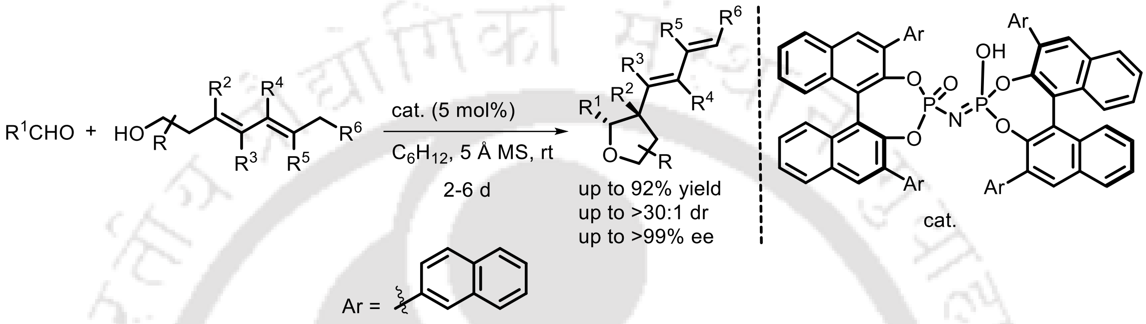
List et al. developed TRIP catalyzed enantioselective intramolecular transetherification reactions of hydroxyl ethers *via* kinetic resolution. This protocol allowed an efficient synthesis 1,3-dihydroisobenzofurans with moderate to excellent enantioselectivities (Scheme 5).[13]



Scheme 5. Chiral phosphoric acid catalyzed asymmetric O-alkylations by List et al.

2.2.6 Asymmetric vinylogous Prins cyclization

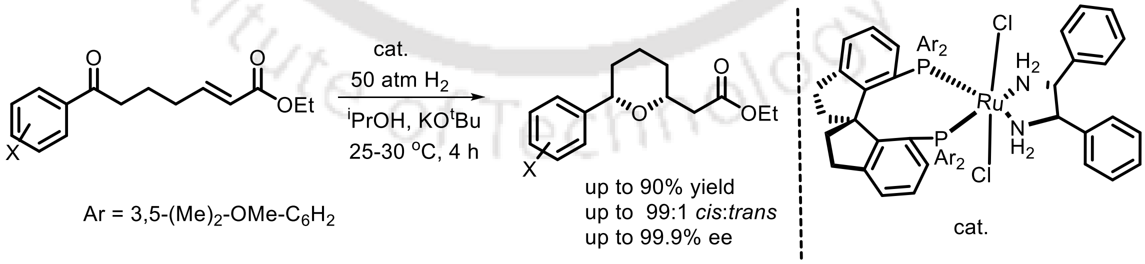
In 2016, the same research group developed chiral imidodiphosphoric acid (IDP) catalyzed asymmetric vinylogous Prins cyclization for an efficient synthesis of 2,3-disubstituted tetrahydrofurans (Scheme 6).[14] The desired products were obtained in high yields as well as with excellent diastereo- and enantioselectities (up to 92% yield, up to >30:1 dr and up to >99% ee respectively).



Scheme 6. Chiral phosphoric acid catalyzed asymmetric vinylogous Prins cyclization by List et al.

2.2.7 Asymmetric synthesis of 2,6-*cis*-disubstituted tetrahydropyrans

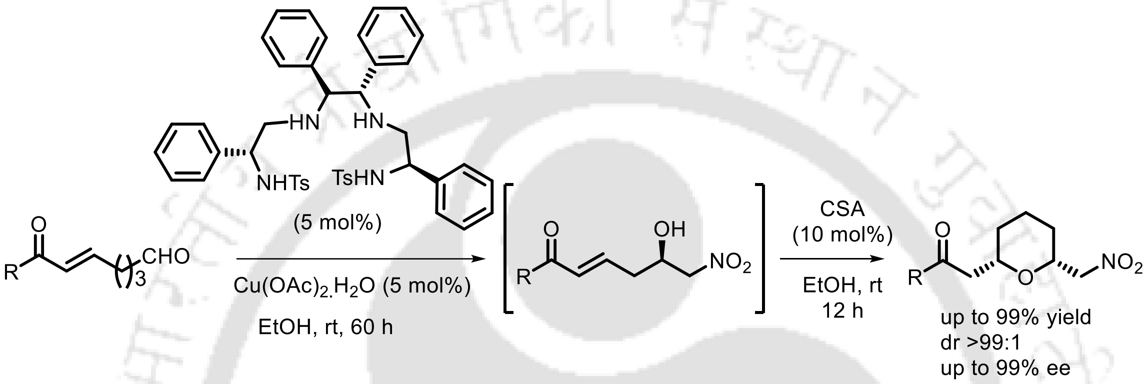
An enantioselective synthesis of chiral 2,6-*cis*-disubstituted tetrahydropyrans was developed by Zhou et al. in 2012. The aforementioned protocol proceeded though asymmetric hydrogenation of acrylate-containing arylketones catalyzed by chiral spiro ruthenium catalysts followed by intramolecular oxa-Michael addition. The desired products were obtained in high yields and excellent enantioselectivities (Scheme 7).[15]



Scheme 7. Chiral ruthenium catalyzed asymmetric hydrogenation of acrylate-containing arylketones by Zhou et al.

2.2.8 2,6-*cis*-substituted tetrahydropyran synthesis using sequential catalysis

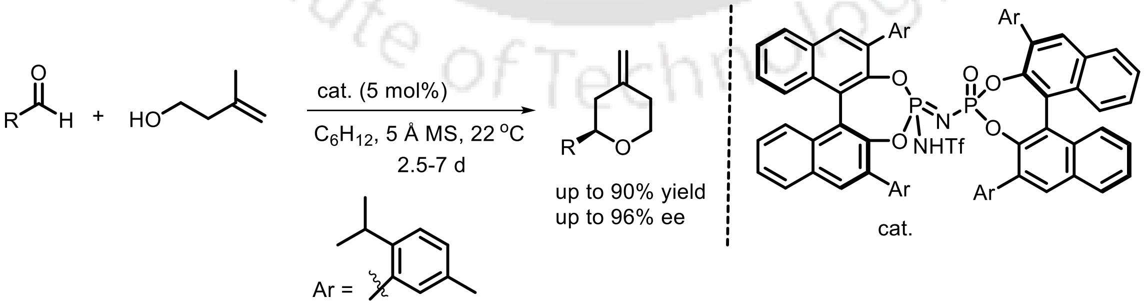
Zhao et al. developed Cu (II) catalyzed highly diastereo- and enantioselective synthesis of 2,6-*cis*-substituted tetrahydropyrans. This reaction proceeded though one-pot sequential catalysis involving Henry and oxa-Michael reactions (Scheme 8).[16] The desired tetrahydropyran products were obtained in high yields (up to 99%) and excellent diastereo- and enantioselectivities (>99:1 dr and up to 99% ee).



Scheme 8. 2,6-*cis*-Substituted tetrahydropyrans using a one-pot sequential catalysis by Zhao et al.

2.2.9 Tetrahydropyran synthesis using catalytic asymmetric Prins cyclization

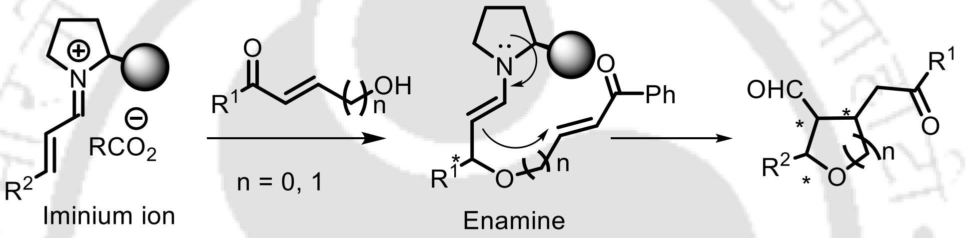
Recently List et al. developed iminoimidodiphosphate (iIDP) brønsted acid catalyzed asymmetric Prins cyclization between aldehyde and homoallylic alcohol for the synthesis of tetrahydropyrans. The desired 4-methylenetetrahydropyrans were obtained in good to excellent yields and with good to excellent regio- and enantioselectivities (Scheme 9).[17]



Scheme 9. Catalytic asymmetric Prins cyclization List et al.

2.3 Concept

Realizing the abundance of highly substituted tetrahydrofuran and tetrahydropyran moieties in natural and non-natural compounds, we embarked in the synthesis of 2,3,4-trisubstituted tetrahydrofurans/tetrahydropyrans using tandem oxa-Michael strategy between γ/δ-hydroxyenones and cinnamaldehydes. It was expected that an iminium ion would generate from cinnamaldehyde and secondary amine catalyst. Then γ/δ-hydroxyenone would attack to iminium ion to deliver an enamine. Finally, catalyst controlled intramolecular Michael addition would deliver the desired tetrahydrofuran/tetrahydropyrans (Scheme 10).



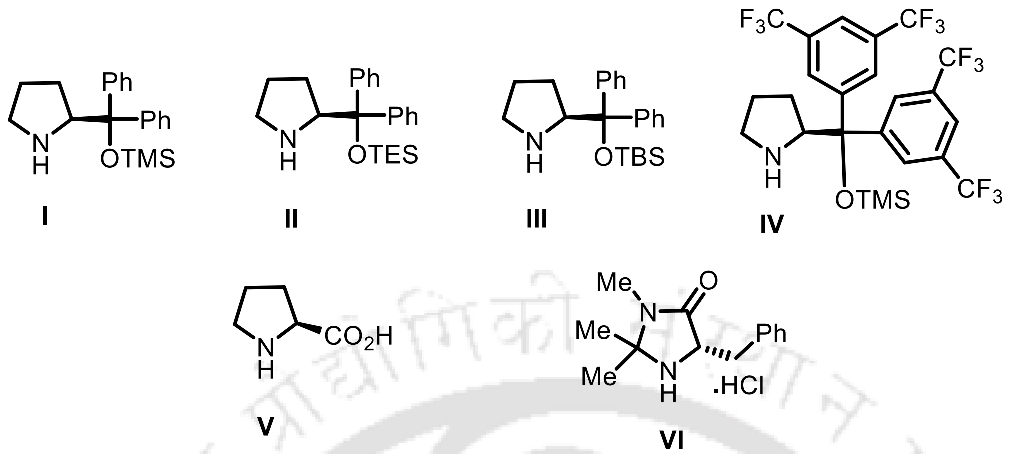
Scheme 10. Double Michael reaction between γ/δ-hydroxyenone and cinnamaldehyde.

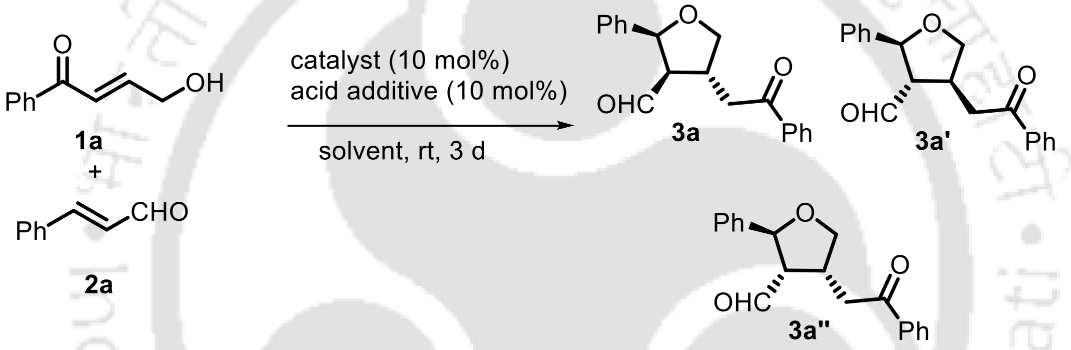
2.4 Results and Discussion

2.4.1 Optimization of catalyst and reaction conditions

We began our exploration by performing a model reaction between (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and cinnamaldehyde (**2a**) with Jørgensen-Hayashi catalyst[18] **I** in combination with benzoic acid additive in chloroform solvent (Table 1, entry 1). Gratifyingly, the desired double Michael reaction took place and the 2,3,4-tetrahydrofuran product was isolated in 85% yield as a mixture of diastereomers in 2.8:1.5:1 ratio with 94% ee for the major diastereomer. Other secondary amine catalysts were also screened in this reaction but found to be inferior to **I** (entries 2-6, Table 1). For example, catalysts **II** and **III** having OTES and OTBS groups respectively provided the product in slightly lower enantioselectivities (90% and 85% respectively) as well as diastereoselectivities (Table 1, entries 2-3).

Table 1. **Catalyst screening and optimization of reaction conditions for THF**





entry[a]	catalyst	additive	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	**$PhCO_2H$**	**$CHCl_3$**	**85**	**2.8:1.5:1**	**94**
2	**II**	$PhCO_2H$	$CHCl_3$	80	2.5:1.5:1	90
3	**III**	$PhCO_2H$	$CHCl_3$	78	2.5:1.5:1	85
4	**IV**	$PhCO_2H$	$CHCl_3$	<5	-	-
5[e]	**V**	$PhCO_2H$	$CHCl_3$	<5	-	-
6	**VI**	$PhCO_2H$	$CHCl_3$	nr	-	-
7	**I**	$PhCO_2H$	$PhCH_3$	60	2.6:1.6:1	32
8	**I**	$PhCO_2H$	$(CH_2Cl)_2$	75	2.2:1.3:1	86

9	**I**	$PhCO_2H$	CH_2Cl_2	68	2.5:1.5:1	92
10	**I**	2-F-$PhCO_2H$	$CHCl_3$	76	2.2:1.3:1	78
11	**I**	3-NO_2-$PhCO_2H$	$CHCl_3$	78	2.5:1.5:1	92
12	**I**	CH_3CO_2H	$CHCl_3$	65	2.1:1.2:1	94
13	**I**	(*L*)-N-BoC-*tert* leucine	$CHCl_3$	70	2.5:1.6:1	90
14[f]	**I**	$PhCO_2H$	$CHCl_3$	80	2.3:1.5:1	80

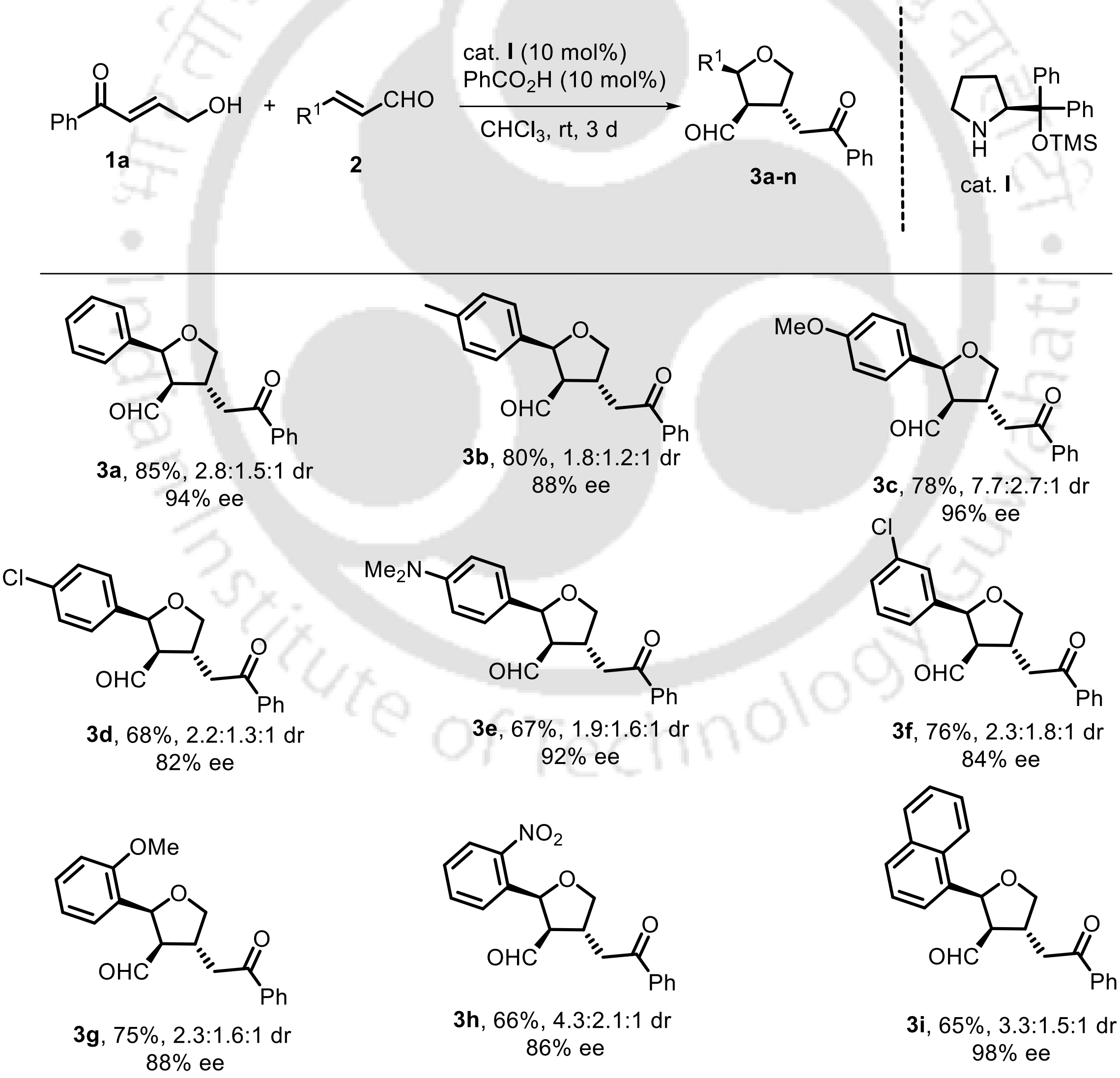
[a]Reaction conditions: 0.1 mmol of **1a** with 0.1 mmol of **2a** in 0.25 mL solvent. [b]Isolated combined yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Enantiomeric excesses of the major diastereomer were determined by chiral HPLC analysis. [e]Without benzoic acid. [f] Reactions was carried at 50 °C.

Surprisingly, almost no reaction took place with catalyst **IV** having bistrifluoromethylphenyl groups, proline (**V**) as well as with MacMillan catalyst **VI** (Table 1, entries 4-6). Then we focused on the screening of other solvents (Table 1, entries 7-9). Much lower enantioselectivity was attained in toluene solvent (32%, Table 1, entry 7) though using 1,2-dichloroethane as solvent moderate enantioselectivity (86%, Table 1, entry 8) of product **3a** was achieved. Then using dichloromethane as solvent excellent enantioselectivity was obtained (92%, Table 1, entry 9). After having the optimum catalyst (**I**) and solvent ($CHCl_3$) in hand, we focused on other reaction parameters. We next turned our attention to investigate the effects of acid additives to improve the result (Table 1, entries 10-13). All other substituted benzoic acids for example, 2-hydroxybenzoic and 3-nitrobenzoic acids provided the product **3a** in lower yields as well as lower enantioselectivities (Table 1, entries 10-11). Using acetic acid as an additive excellent enantioselectivity was obtained, but moderate yield was observed (Table 1, entry 12). We also used Boc protected tertiary leucine as an additive but the yield as well as the enantioselectivity were not improved (Table 1, entry 13). Then the reaction temperature was enhanced to 50 °C and the enantioselectivity got decreased from 94% to 80% ee (Table 1, entry 14).

2.4.2 Substrate scope

After establishment of the optimized conditions, the substrate scope of the reaction was studied. Initially, differently substituted enals were investigated and it turned out that electron neutral, electron poor as well as electron rich substituents were tolerated in the reaction (Scheme 11). At the beginning, different *para*-substituted phenyl group containing enals were employed and excellent results were achieved. Previously, Johnson and co-workers observed formation of tetrahydrofurans having *cis*-configuration similar to us.[19] In some cases, the minor diastereomer was isolated with the major diaste-

Scheme 11. **Scope of enals in the tetrahydrofuran synthesis**[a]



3a, 85%, 2.8:1.5:1 dr
94% ee

3b, 80%, 1.8:1.2:1 dr
88% ee

3c, 78%, 7.7:2.7:1 dr
96% ee

3d, 68%, 2.2:1.3:1 dr
82% ee

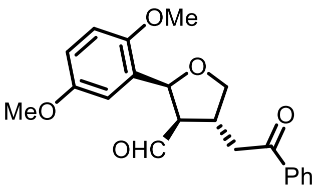
3e, 67%, 1.9:1.6:1 dr
92% ee

3f, 76%, 2.3:1.8:1 dr
84% ee

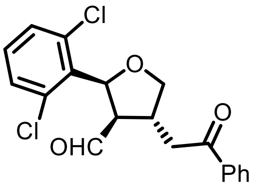
3g, 75%, 2.3:1.6:1 dr
88% ee

3h, 66%, 4.3:2.1:1 dr
86% ee

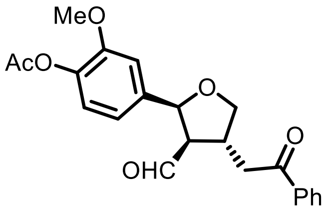
3i, 65%, 3.3:1.5:1 dr
98% ee



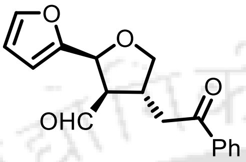
3j, 72%, 4:1.7:1 dr
90% ee



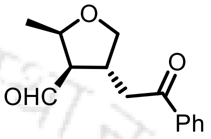
3k, 68%, 5.8:2.4:1 dr
98% ee



3l, 69%, 2.8:2.2:1 dr
88% ee



3m, 60%, 8.3:2.6:1 dr
92% ee



3n, 64%, 3.1:1.8:1 dr
57% ee

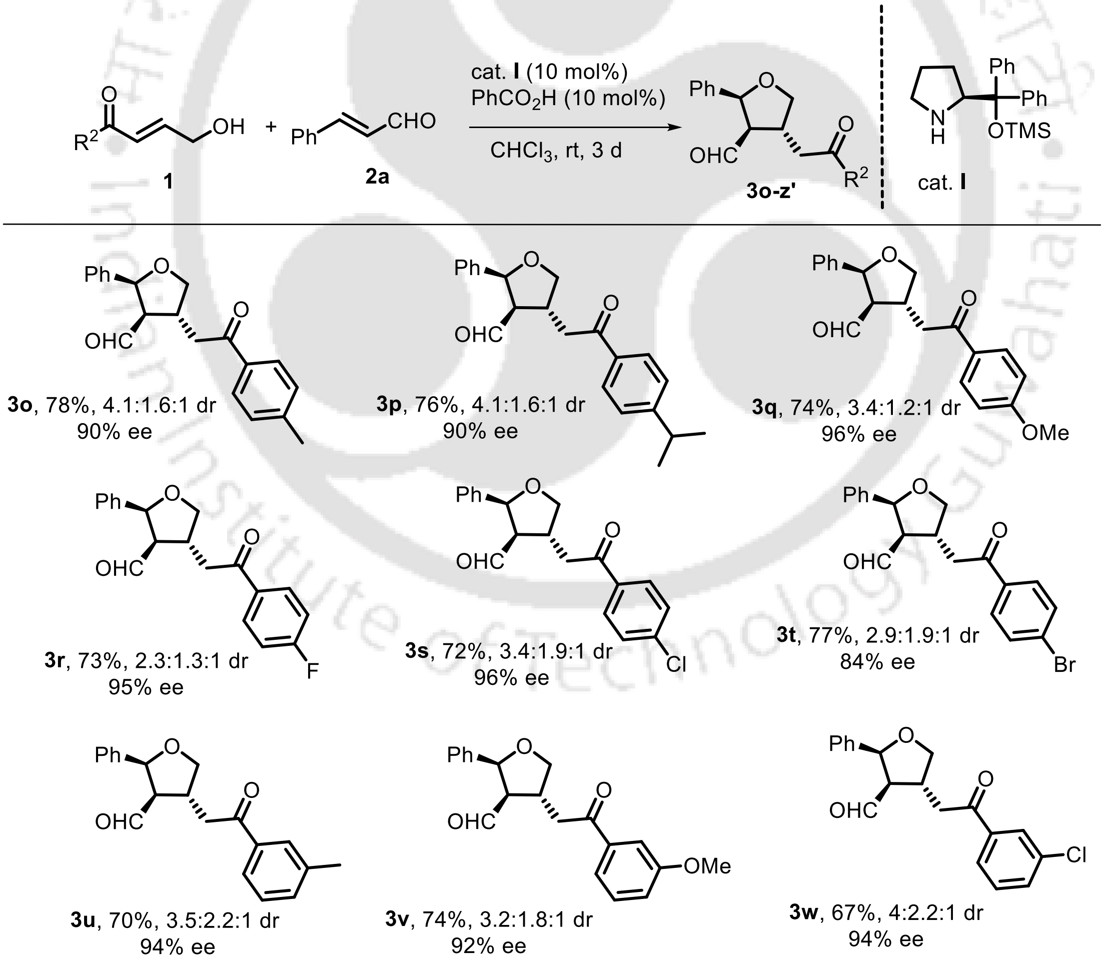
[a] Reaction condition: 0.2 mmol of **1a** with 0.2 mmol of **2** in 0.8 mL $CHCl_3$. Isolated combined yield after silica gel column chromatography.The diastereomeric ratio was determined by ^{1}H NMR. Enantiomeric excess of the major diastereomer was determined by chiral HPLC analysis.

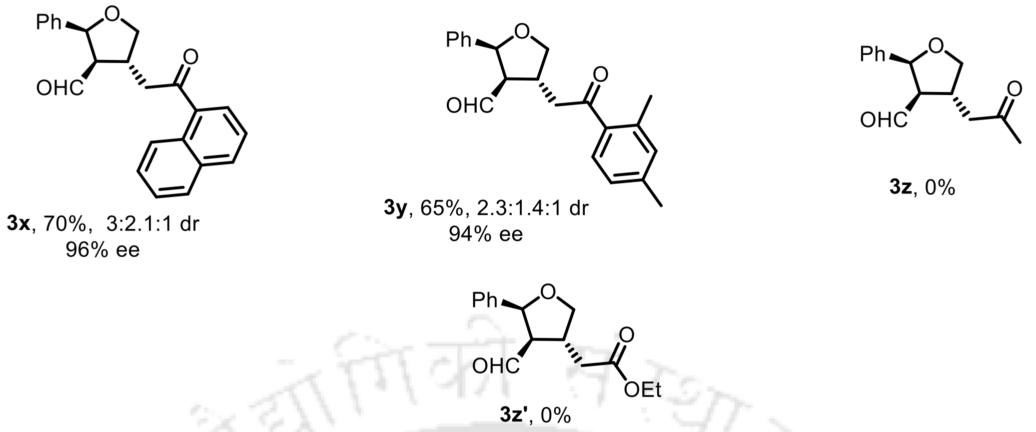
reomer as a mixture and the diastereomeric ratio was determined by ^{1}H NMR. For example, enal **1b** having 4-methyl group delivered products **3b/3b'/3b″** as a mixture of diastereomers in 1.8:1.2:1 ratio with 80% yield and 88% ee of the major diastereomer (Scheme 11). 4-Methoxy enal **2c** provided products **3c/3c'/3c″** as a mixture of diastereomers in 7.7:2.7:1 ratio and the enantiomeric excess of the major diastereomer was 96%. Similarly diastereomeric products **3d/3d'/3d″** were isolated in 2.2:1.3:1 ratio and the major diastereomer **3d** was obtained in 82% ee. Also, the scope was extended to *meta*- and *ortho*- substituted enals and high enantioselectivities were attained (Scheme 11). Interestingly, smooth conversion was observed for 3-chloro enal delivering the products **3f/3f'/3f″** as a mixture of diastereomers in 2.3:1.8:1 ratio and 84% ee of the major diastereomer (Scheme 11). The *ortho* substituted enals **3g** and **3h** delivered products **3g/3g'/3g″** and **3h/3h'/3h″** as a mixture of diastereomers in 2.3:1.6:1 and 4.3:2.1:1 ratio; and 88% and 86% ees were detected for the major diastereomers respectively. Then 1-naphthyl group containing enal **2i** took part in the reaction and provided products **3i/3i'/3i″** as a mixture of diastereomers in 3.3:1.5:1 ratio and the enantiomeric excess of the major diastereomer was 98%. Moreover, disubstituted phenyl groups can also be tolerated under our reaction condition and the outcome was excellent.

The methodology also worked with heteroaryl substituted enal such as **2m** delivering the major product **3m** in 92% ee. Finally, an aliphatic enal **2n** was employed but the product **3n** was obtained with moderate enantioselectivity.

Then the scope of γ-hydroxyenone **1** was studied and the results are shown in scheme 12. It turned out that a variety of substitutions on the aryl group could be incorporated and excellent outcome was observed. For example, enones **1b** having 4-methyl group delivered products **3o/3o'/3o″** as a mixture of diastereomers in 4.1:1.6:1 ratio with 78% yield and 90% ee of the major diastereomer (Scheme 12). 4-Isopropyl and 4-methoxy enones **1c** and **1d** provided products **3p/3p'/3p″** and **3q/3q'/3q″** as a mixture of diastereomers in 4.1:1.6:1 and 3.4:1.2:1 ratios with 90% and 96% enantiomeric excesses

Scheme 12. Scope of γ-hydroxyenones in the tetrahydrofuran synthesis[a]





3x, 70%, 3:2.1:1 dr
96% ee

3y, 65%, 2.3:1.4:1 dr
94% ee

3z, 0%

3z', 0%

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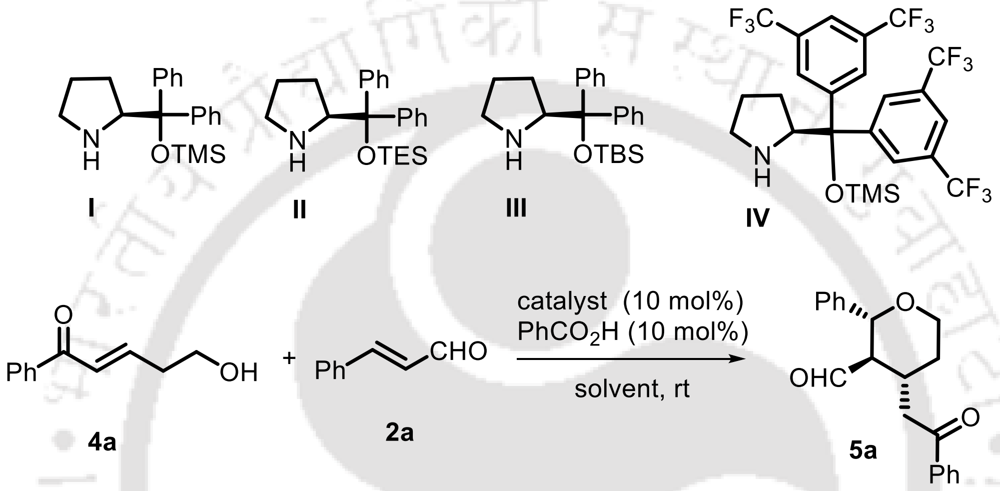
[a]Reaction condition: 0.2 mmol of **1** with 0.2 mmol of **2a** in 0.8 mL $CHCl_3$. Isolated combined yield after silica gel column chromatography. The diastereomeric ratio was determined by ^1H NMR. Enantiomeric excess of the major diastereomer was determined by chiral HPLC analysis.

of the major diastereomers respectively (Scheme 12). Then, enones **1e-1g** having 4-halosubstituted aryl groups were subjected to the reaction conditions. To our delight, the desired products **3r-3s** were isolated in acceptable yields after 3 days and excellent enantiomeric excesses were detected (Scheme 12). 4-Fluoro substituted enone **1e** produced products **3r/3r'/3r″** as a mixture of diastereomers in 3.5:2.2:1 ratio with 73% yield and 95% ee of the major diastereomer. Other 4-halosubstituted enones **1f** and **1g** executed products **3s/3s'/3s″** and **3t/3t'/3t″** as a mixture of diastereomers in 3.4:1.9:1 and 2.9:1.9:1 ratio with 96% and 84% enantiomeric excesses of the major diastereomers respectively (Scheme 12). Then different *meta* substituted aryl enones were screend under the reaction conditions. Interestingly, smooth conversions were observed and the products were isolated with good yields as well as excellent enantioselectivites (Scheme 12). 1-Naphthyl group containing enone **1k** underwent the reaction smoothly delivering the product **3x** in 96% ee of the major diastereomer. Finally, a disubstituted aryl group containing enone **1l** was engaged in the reaction and 94% ee was obtained for product **3y**. Unfortunately no reaction took place with methyl ketone **1m** and also with ester **1n**.

The next phase of attention was to employ different *δ*-hydroxyenones for the synthesis of trisubstituted tertahydropyrans. Initially, (*E*)-5-hydroxy-1-phenylpent-2-en-1-one (**4a**) and cinnamaldehyde (**2a**) were reacted with catalyst **I** in combination with benzoic acid in chloroform at room temperature. Pleasingly, the desired tetrahydropyran **5a** was formed as a single diastereomer in good yield but the enantiomeric excess was only 78% (Table 2). Other secondary amine catalysts were also screened in this reaction but found to be inferior to **I** (entries 2-3, Table 2). Also the reaction provided only traces of **5a** when performed with catalyst **IV** (entry 4, Table 2).

Table 2. **Catalyst screening and optimization of reaction conditions for THP**

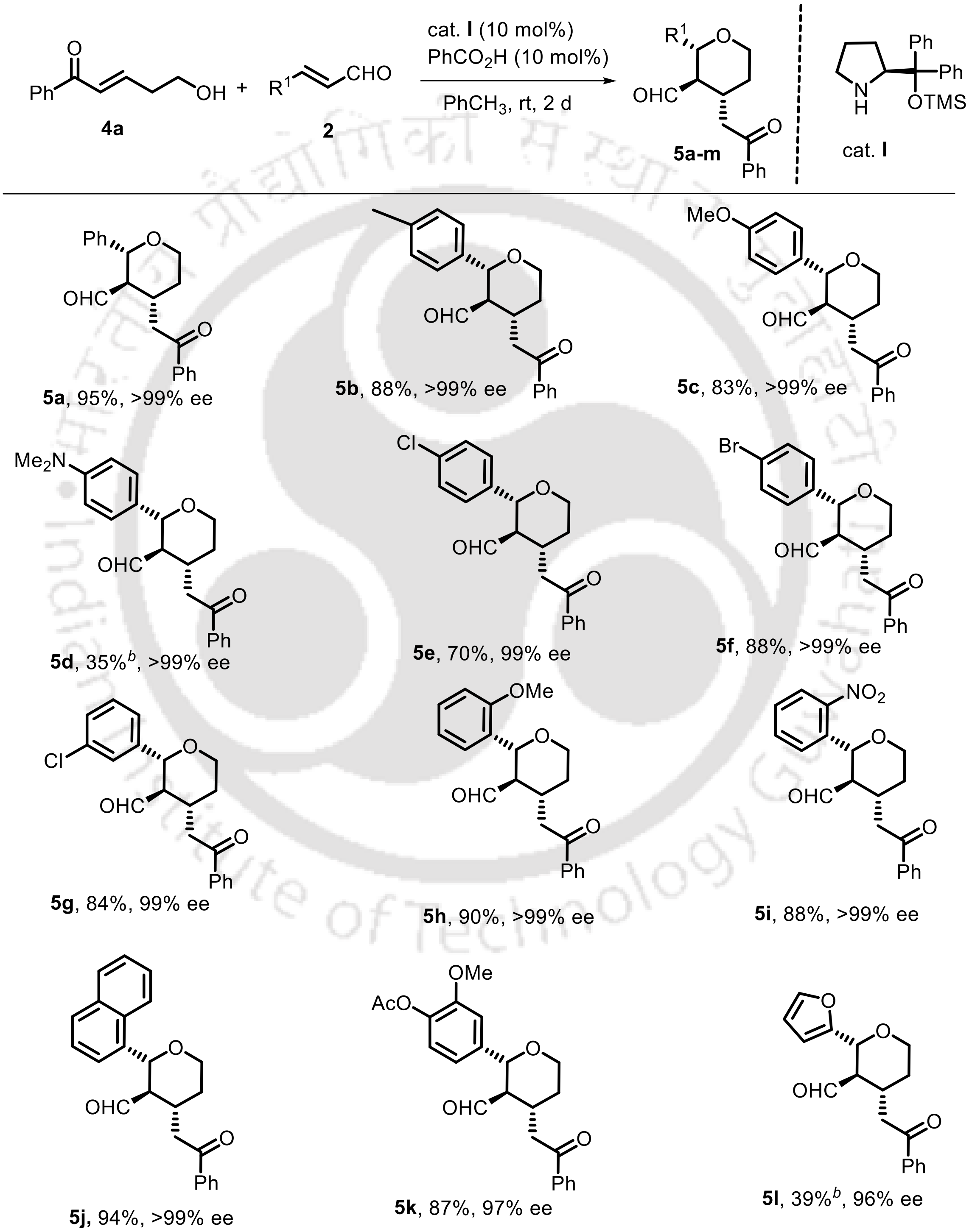


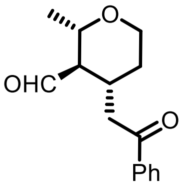
entry[a]	catalyst	solvent	additive	time(d)	yield (%)[b]	ee (%)[c]
1	**I**	$CHCl_3$	$PhCO_2H$	2	90	78
2	**II**	$CHCl_3$	$PhCO_2H$	2	88	54
3	**III**	$CHCl_3$	$PhCO_2H$	2	90	76
4	**IV**	$CHCl_3$	$PhCO_2H$	2	<5	nd
5	**I**	CH_2Cl_2	$PhCO_2H$	2	82	80
6	**I**	$(CH_2Cl)_2$	$PhCO_2H$	2	86	79
7	**I**	$PhCF_3$	$PhCO_2H$	2	90	93
5	**I**	**$PhCH_3$**	**$PhCO_2H$**	**2**	**95**	**>99**

[a]All reactions were carried out with 0.1 mmol of **4a** with 0.1 mmol of **2a** in 0.4 mL solvent. [b]Isolated yield of the pure diastereomer after silica gel column chromatography. [c] Determined by chiral HPLC.

A rapid solvent screening indicated that CH_2Cl_2 and $(CH_2Cl)_2$ resulted in comparable results (entries 6-7, Table 2). After some optimization, it was found that an enhancement in enantioselectivity (>99%) as well as in yield (90%) could be achieved by using toluene as solvent.

Scheme 13. Scope of enals in the tetrahydropyran synthesis[a]





5m, 90%, >99% ee

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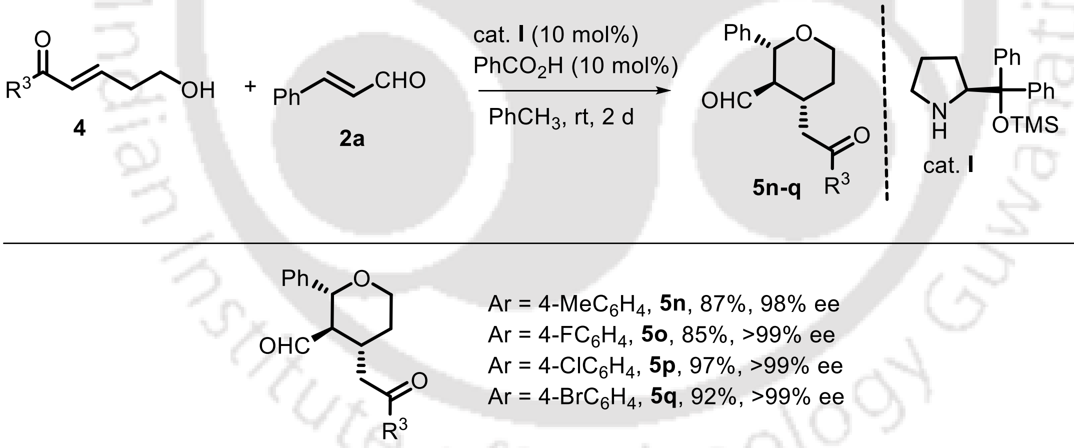
[a]Reaction condition: 0.2 mmol of **4a** with 0.2 mmol of **2** in 0.8 mL $PhCH_3$. Isolated yield after silica gel column chromatography. Enantiomeric excess was determined by chiral HPLC. [b]Reaction was stirred for 7 days.

After obtaining the suitable conditions, we decided to screen a variety of enals for the reaction (Scheme 13). As can be seen the reaction is quite general and applicable to both aromatic as well as aliphatic enals. Gratifyingly, the enantiomeric excess is excellent irrespective of the nature and position of the functional groups in the phenyl ring (Scheme 13). 1-Napthaldehyde derived enal **2i** also participated in the reaction without a change of the outcome of the reaction.

Scheme 14. **Scope of *δ*-hydroxyenones in the tetrahydropyran synthesis**[a]



Ar = 4-MeC_6H_4, **5n**, 87%, 98% ee
Ar = 4-FC_6H_4, **5o**, 85%, >99% ee
Ar = 4-ClC_6H_4, **5p**, 97%, >99% ee
Ar = 4-BrC_6H_4, **5q**, 92%, >99% ee

---

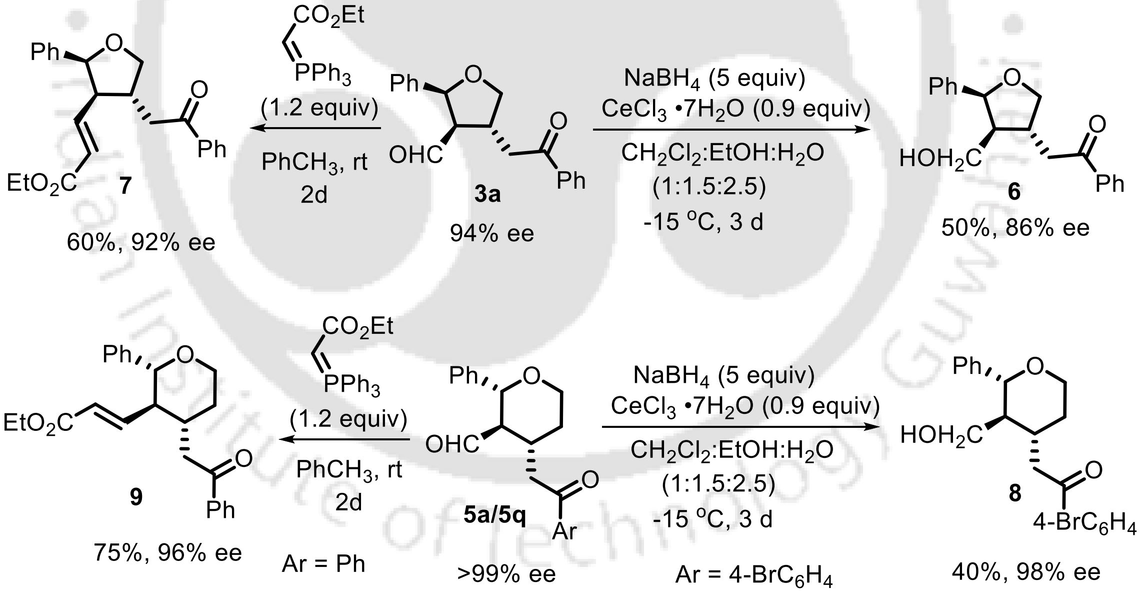
[a]Reaction condition: 0.2 mmol of **4** with 0.2 mmol of **2a** in 0.8 mL $PhCH_3$. Isolated yield after silica gel column chromatography. Enantiomeric excess was determined by chiral HPLC.

The reaction was quite slow for heteroaromatic enal **2m** though high enantioselectivity was observed for product **5l**. Moreover, crotonaldehyde **2n** can also be employed and delivered product **5m** in 90% yield with 99% ee.

Then we turned our attention to investigate the scope of *δ*-hydroxyenones **4** in the reaction (Scheme 14). Thus, different *para*-substituted *δ*-hydroxyenones **4** were prepared and subjected in the reaction. Delightfully, the reactions progressed well and excellent enantioselectivities were achieved for all cases.

2.4.3 Synthetic transformations

To illustrate the usefulness of our method, few reactions were envisaged on **3a** and **5a/5q** (Scheme 15). Sodium borohydride reaction of **3a** in the presence of cerium chloride heptahydrate resulted in the selective reduction of aldehyde group producing **6** in 50% yield with 86% ee. Slight drop in enanantiomeric purity of compound **6** might be due to higher rate of reactivity of the minor enantiomer. Similarly Wittig reaction with (carbethoxymethylene) triphenylphosphorane was carried out on **3a** to furnish **7** in 92% ee. The sodium borohydride reaction was repeated with tetrahydropyran **5q** to provide **8** in 40% yield with 98% ee. Wittig reaction of **5a** delivered **9** in good yield though slight erosion in enantioselectivity was observed.



Scheme 15. Synthetic transformations.

2.4.4 Determination of product stereochemistry

The absolute structure of product **3k** was determined to be (2*S*, 3*R*, 4*R*) by single crystal X-ray crystallography (Figure 3) and it is assumed that other tetrahydrofurans have the same configuration.

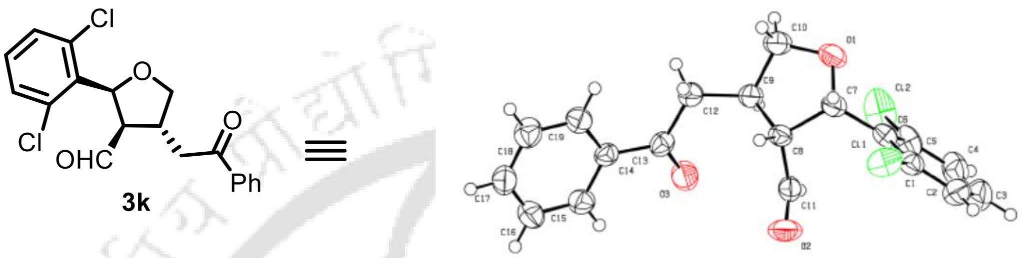


Figure 3. X-ray crystal structure of **3k**.

Similarly, the absolute configuration of product **5i** was determined to (2*R*, 3*R*, 4*R*) by single crystal X-ray crystallography (Figure 4). The absolute configurations of other products are assumed to be same by analogy.

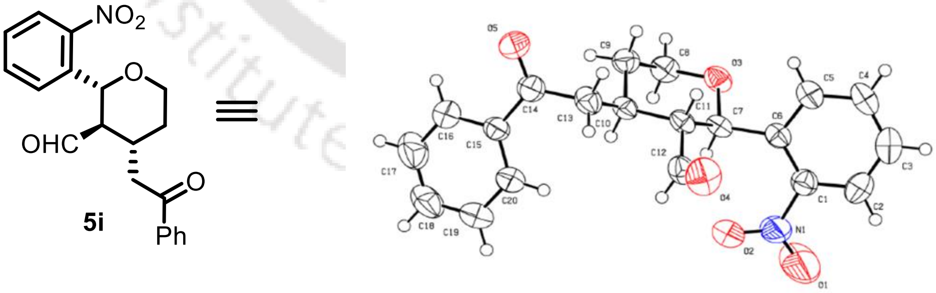
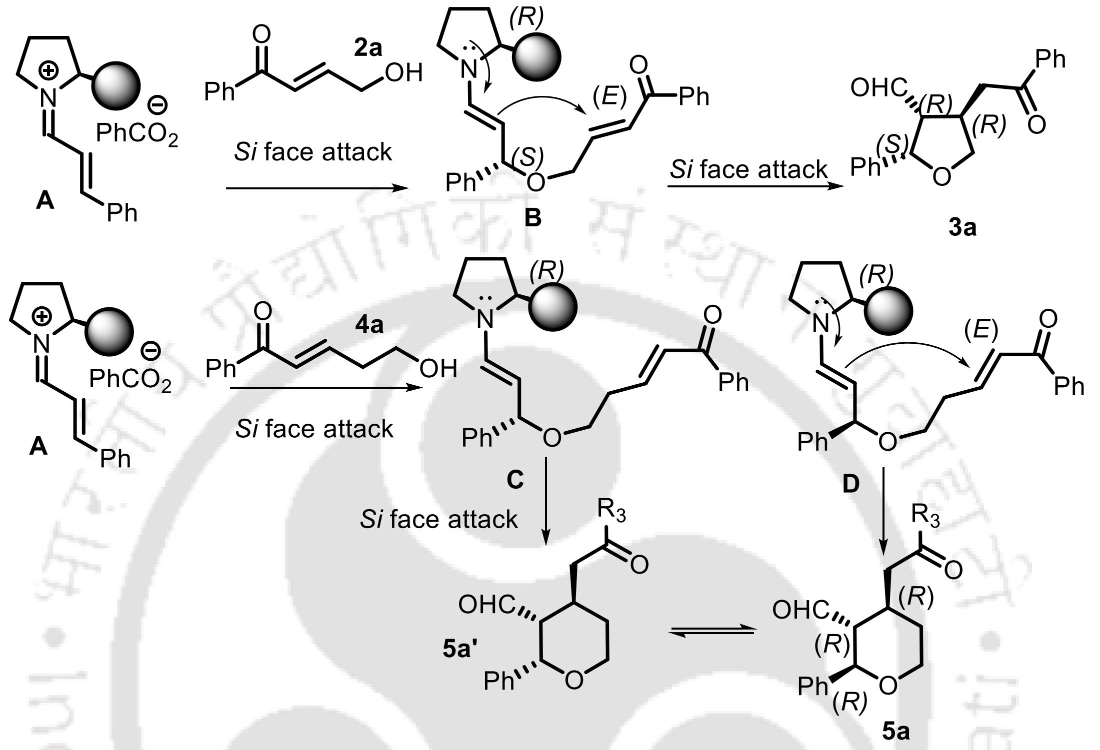


Figure 4. X-ray crystal structure of **5i**.

2.4.5 The proposed mechanism



Scheme 16. The proposed mechanism.

A plausible mechanism has been shown in Scheme 16 for the formation of **3a** and **5a**. Iminium ion **A** is first generated from **1a** and catalyst. Then attack of enone **2a** on the *Si* face of **A** provides enamine **B**. Finally, catalyst controlled intramolecular Michael addition to the *Si* face of enone delivers tetrahydrofuran **3a**. Also, MM2 calculation energies of **3** follows the order **3a<3a'<3a″**. The formation of 2,3-*cis* fused tetrahydrofuran was earlier demonstarted by Johnson and co-workers[19] and the low diastereoselectivity obtained here is possibly due to slight energy differences between kinetically and thermodynamically controlled products. Similarly, δ-hydroxyenone **4a** reacts from the *Si* face of **A** to deliver enamine **C**. Enamine **C** then cyclizes to provide diastereomeric tetrahydropyran **5a'** which transforms into more stable all equatorial **5a** via reversible oxa-Michael reaction.[20] Alternatively, enamine **C** can be converted to enamine **D** via reversible oxa-Michael reaction which on further cyclization generates **5a**.

2.5 Conclusion

In summary, we have developed a mild and simple procedure for the asymmetric synthesis of trisubstituted tetrahydrofurans and tetrahydropyrans *via* double Michael strategy for the first time. The reaction is catalyzed by commercially available TMS-prolinol catalyst. The synthesis of highly substituted tetrahydrofurans and tetrahydropyrans *via* organocatalysis is rare and our methodology could find application in the synthesis of complex natural products. Also, the demonstration of the selective functionalization reactions is appealing. Further related cyclization reactions are in progress in our laboratory.

2.6 Experimental Section

2.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, and Daicel Chiralpak ID Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

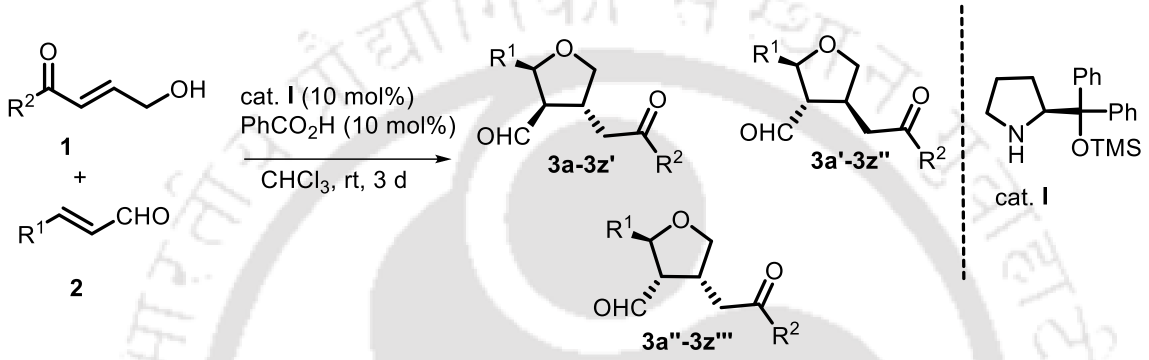
Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

2.6.2 General procedure for the synthesis of *trans-γ*-hydroxyenones and and *trans-δ*-hydroxyenones

Trans-γ-hydroxyenones (**1a-1l**)[22] and *trans-δ*-hydroxyenones (**4**)[23] were synthesized according to reported procedure.

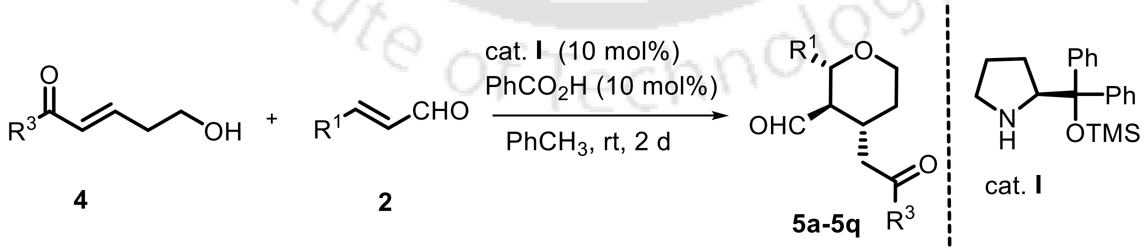
Trans-cinnamaldehydes were prepared according to reported procedures.[24]

2.6.3 General procedure for the synthesis of compound 3a-3z'



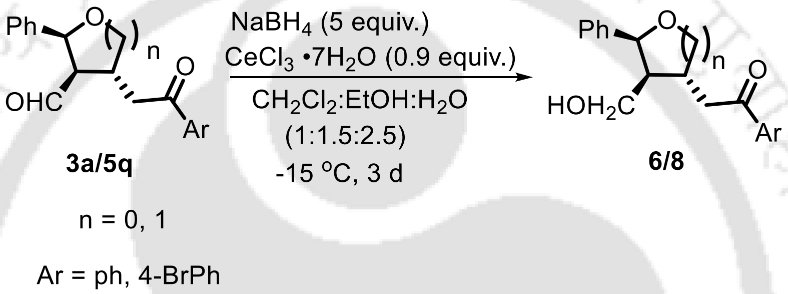
In an oven dried R.B flask, catalyst **I** (10 mol%), PhCO$_2$H (10 mol%) and *trans-γ*-hydroxyenones **1** (0.2 mmol) were taken with 0.8 mL dry CHCl$_3$. Then cinnamaldehyde **2** (0.2 mmol) was added. The reaction mixture was stirred for 3 days at room temperature. After 3 days, the crude reaction mixture was subjected to column chromatography on silica gel (60-120 mesh) using 10-15 % ethyl acetate in hexane as eluent to afford the corresponding compounds **3a-3z'**.

2.6.4 General procedure for the synthesis of compound 5a-5q



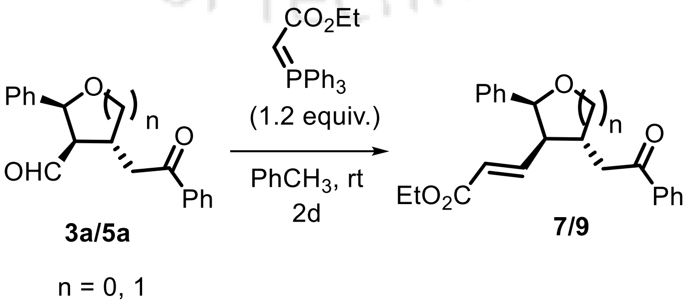
In an oven dried R.B flask, catalyst **I** (10 mol%), $PhCO_2H$ (10 mol%) and *trans-δ-*hydroxyenones **4** (0.2 mmol) were taken with 0.8 mL dry $PhCH_3$, Then cinnamaldehyde **2** (0.2 mmol) was added. The reaction mixture was stirred for 2 days at room temperature. After 2 days, the crude reaction mixture was subjected to column chromatography on silica gel (60-120 mesh) using 10-15 % ethyl acetate in hexane as eluent to afford the corresponding compounds **5a-5q**.

2.6.5 General procedure for selective reduction of aldehyde in presence of ketone of 3a and 5q



In an oven dried R.B flask, aldehyde (**3a** or **5q**) (0.1 mmol) and 32.0 mg $CeCl_3.7H_2O$ (0.9 equiv.) were dissolved in 0.2 mL DCM. Then 0.3 mL of EtOH and 0.5 mL of H_2O were added. The mixture was cooled to -15 °C, and then 20.0 mg of $NaBH_4$ (5 equiv.) was added in one portion and stirred for 3 days. After 3 days, the crude reaction mixture was diluted with aqueous saturated NaCl and extracted with diethyl ether and subjected to column chromatography on silica gel (60-120 mesh) using 25-30 % ethyl acetate in hexane as eluent to afford the corresponding compounds **6** or **8**.

2.6.6 General procedure for Wittig reaction of 3a and 5a[25]



In an oven dried R.B flask, aldehyde (**3a** or **5a**) (0.1 mmol) and (carbethoxymethylene)triphenylphosphorane (0.12 mmol) were taken under positive pressure of argon. Then 1 mL dry toluene was added. The reaction mixture was stirred for 2 days at room temperature. After 2 days, the crude reaction mixture was subjected to column chromatography on silica gel (60-120 mesh) using 10-15 % ethyl acetate in hexane as eluent to afford the corresponding compounds **7** or **9**.

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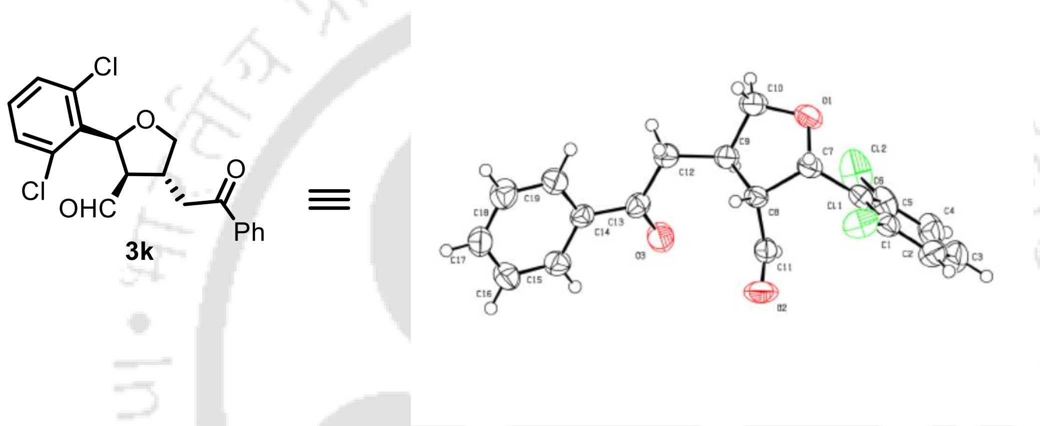
2.6.7 Crystal structure of compound 3k[26]



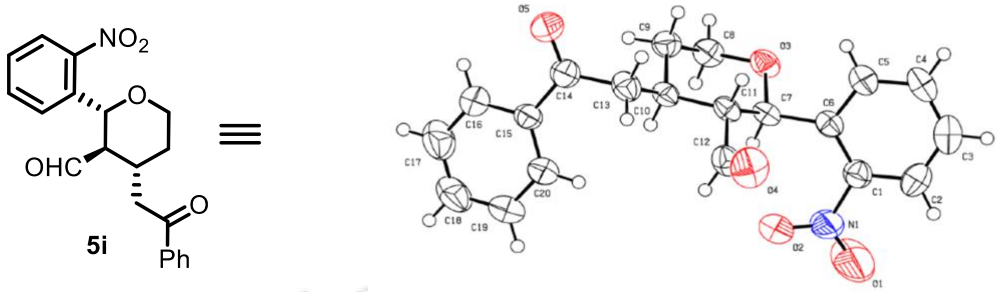
ORTEP crystal structure

Table 3. Crystal data and structure refinement for compound 3k

Parameters	3k
CCDC No.	1531840
Empirical formula	$C_{19}H_{16}O_3Cl_2$
Formula weight	363.22
Crystal habit, colour	needle/white
Crystal size, mm^3	0.30 × 0.22 × 0.18
Temperature, *T*	293(2) K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic

Space group	*' P 21/c'*
Unit cell dimensions	a = 20.2870(18) Å b = 7.4051(7) Å c = 11.2507(14) Å α = 90.00°, β = 103.784(9)°, γ = 90.00°
Volume, V (Å^3)	1641.5(4)
Z	4
Calculated density, Mg/m^3	1.470
Absorption coefficient, μ (mm^{-1})	0.410
F(000)	752.0
θ range for data collection	2.9390° to 28.7298°
Limiting indices	$-27 \leq h \leq 26$, $-9 \leq k \leq 7$, $-14 \leq l \leq 15$
Reflection collected/unique	2876/2016 [R(int) = 0.0535]
Completeness to θ	99.75 % (θ = 26.32°)
Max. and min. transmission	0.960/ 0.929
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	2876/0/271
Goodness of fit on F^2	1.065
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0757, wR2 = 0.2217
R indices (all data)	R1 = 0.1036, wR2 = 0.2344
Ellipsoid contour % probability	40%

2.6.8 Crystal structure of compound 5i[27]



5i

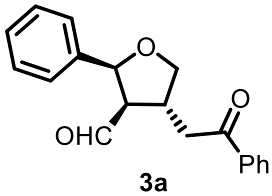
ORTEP crystal structure

Table 4. Crystal data and structure refinement for compound 5i

Parameters	**5i**
CCDC No.	1531841
Empirical formula	$C_{20}H_{18}N_1O_5$
Formula weight	353.36
Crystal habit, colour	needle/white
Crystal size, mm^3	0.30× 0.22 × 0.18
Temperature, *T*	293(2) K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	*' P 21'*
Unit cell dimensions	a = 8.3473(7) Å b = 8.3650(8) Å c = 12.5450(12) Å α = 90.00°, β = 91.857(9)°, γ = 90.00°
Volume, *V* (Å^3)	875.49(14)

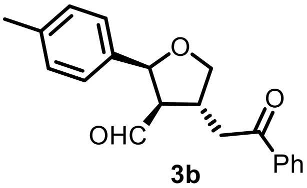
Z	2
Calculated density, Mg/m^3	1.340
Absorption coefficient, μ (mm^{-1})	0.097
F(000)	372.0
θ range for data collection	2.9273° to 28.9677°
Limiting indices	$-7 \leq h \leq 11$, $-11 \leq k \leq 11$, $-16 \leq l \leq 16$
Reflection collected/unique	2625/2077 [R(int) = 0.0245]
Completeness to θ	99.69 % (θ = 26.32°)
Max. and min. transmission	0.989/ 0.982
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	2625/1/235
Goodness of fit on F^2	1.052
Final *R* indices [$I > 2\sigma(I)$]	R1 = 0.0540, wR2 = 0.1336
R indices (all data)	R1 = 0.0677, wR2 = 0.1501
Ellipsoid contour % probability	40%

2.7 Characterization Data of Products



3a

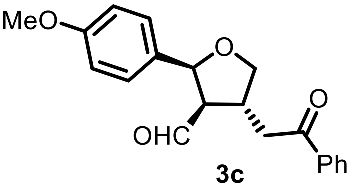
(2S,3R,4R)-4-(2-oxo-2-phenylethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3a): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 85% yield (50.0 mg). Diastereomeric ratio 2.8:1.5:1 (**3a**:**3a′**:**3a″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.13 (d, *J* = 3.5 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.34-7.31 (m, 4H), 5.29 (d, *J* = 8.1 Hz, 1H), 4.67 (t, *J* = 8.0 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.30 (dd, *J* = 22.3, 6.1 Hz, 2H), 3.18 (dd, *J* = 18.1, 8.2 Hz, 1H), 3.08-3.00 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 200.9, 198.0, 137.5, 136.4, 133.7, 128.9, 128.9, 128.2, 128.2, 126.2, 125.7, 81.8, 74.0, 61.2 41.0, 35.9. **FT-IR (thin film)** 3062, 2850, 1719, 1683, 1597, 1450, 1217, 757 cm^{-1}. **HPLC analysis**: 94% ee of major diastereomer; Determined using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 44.5 min, t_{minor} = 38.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{29}H_{19}O_3$ $[M+H]^+$ 295.1334 found: 295.1346.



3b

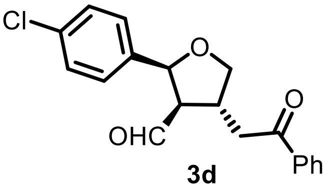
(2S,3R,4R)-4-(2-oxo-2-phenylethyl)-2-(p-tolyl) tetrahydrofuran-3-carbaldehyde (3b): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 80% yield (49.6 mg). Diastereomeric ratio 1.8:1.2:1 (**3b**:**3b′**:**3b″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.14 (d, *J* = 3.7 Hz, 1H), 7.95 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 11.9 Hz, 3H), 5.26 (d, *J* = 8.3 Hz, 1H), 4.69-4.62 (m, 1H), 3.62 (t, *J* = 8.5 Hz, 1H), 3.35-3.25 (m, 2H), 3.18 (dd, *J* = 13.0, 6.0 Hz, 1H), 3.05-2.98 (m, 1H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 201.1, 198.0, 137.9, 136.4, 134.4, 133.6, 129.5, 128.9, 128.2, 126.1, 81.7, 73.9, 61.2, 41.0, 35.9, 21.3. **FT-IR (thin film)** 3060, 2852, 1715, 1680, 1599, 1453, 1212, 755 cm^{-1}. **HPLC analysis**: 88% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 34.7

min, t_{minor} = 65.1 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_3$ $[M+H]^+$ 309.1491, found 309.1485.



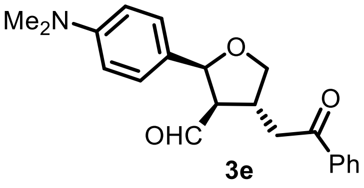
3c

(2S,3R,4R)-2-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3c): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 78% yield (51.0 mg). Diastereomeric ratio 7.7:2.7:1 (**3c**:**3c′**:**3c″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.16 (d, *J* = 3.6 Hz, 1H), 7.96-7.94 (m, 3H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 3H), 7.25 (d, *J* = 6.1 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 3H), 5.24 (d, *J* = 8.3 Hz, 1H), 4.65 (dd, *J* = 17.3, 8.7 Hz, 1H), 3.79 (d, *J* = 2.7 Hz, 4H), 3.61 (t, *J* = 8.6 Hz, 1H), 3.34 (d, *J* = 7.7 Hz, 1H), 3.28 (t, *J* = 11.7 Hz, 2H), 3.22-3.15 (m, 1H), 3.05-2.95 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 201.2, 198.0, 159.4, 136.4, 133.6, 129.5, 128.9, 128.2, 127.5, 114.2, 81.6, 81.5, 73.8, 61.2, 55.4, 55.4, 41.0, 35.9. **FT-IR (thin film)** 3058, 2848, 1710, 1685, 1590, 1450, 1218, 765 cm^{-1}. **HPLC analysis**: 96% ee of the major diastereomer; Determined using a Daicel Chiralpak IB column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 37.2 min. t_{minor} = 31.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{20}NaO_4$ $[M+Na]^+$ 347.1254, found 347.1249.



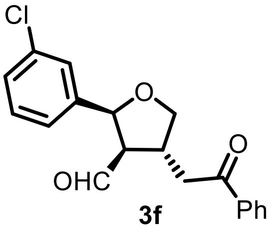
3d

(2S,3R,4R)-2-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3d): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 68% yield (44.8 mg). Diastereomeric ratio 2.2:1.3:1 (**3d**:**3d′**:**3d″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.12 (d, *J* = 3.6 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.36-7.28 (m, 5H), 5.29 (d, *J* = 8.3 Hz, 1H), 4.68-4.63 (m, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.35-3.21 (m, 2H), 3.14 (dd, *J* = 17.3, 7.5 Hz, 1H), 3.03 (ddd, *J* = 8.3, 6.6, 3.6 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ200.9, 196.8, 140.2, 137.4, 134.7, 129.6, 129.2, 128.9, 128.3, 126.2, 81.7, 73.9, 61.1, 40.9, 35.8. **FT-IR (thin film)** 2925, 2855, 1719, 1682, 1585, 1490, 1217, 754 cm^{-1}. **HPLC analysis**: 82% ee of the major diastereomer: Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 26.7 min, t_{minor} = 40.8 min. **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{17}ClNaO_3$ [M+Na]$^+$ 351.0758, found 351.0754.



3e

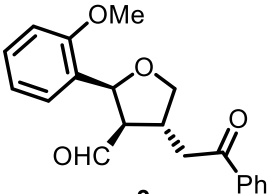
(2S,3R,4R)-2-(4-(dimethylamino)phenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3e): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 67% yield (45.2 mg). Diastereomeric ratio 1.9:1.6:1 (**3e**:**3e′**:**3e″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.18 (d, *J* = 3.5 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 3H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 3H), 7.20-7.24 (m, 1H), 7.19-7.14 (m, 3H), 6.69 (t, *J* = 7.1 Hz, 3H), 5.21 (d, *J* = 8.3 Hz, 1H), 4.67-4.59 (m, 1H), 3.58 (t, *J* = 8.5 Hz, 1H), 3.29 (dd, *J* = 24.1, 8.6 Hz, 3H), 3.14 (dd, *J* = 17.2, 7.6 Hz, 1H), 3.00-2.95 (m, 1H), 2.93 (s, 9H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 201.5, 198.2, 150.5, 136.5, 133.6, 133.6, 128.9, 128.2, 127.3, 127.1, 127.0, 125.0, 112.7, 112.6, 81.8, 73.8, 61.3, 41.1, 40.8, 40.7, 40.7, 35.9. **FT-IR (thin film)** 2930, 2852, 1717, 1680, 1578, 1486, 1220, 758 cm^{-1}. **HPLC analysis**: 92% ee of the major diastereomer; Determined using a Daicel Chiralpak ID column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 ^{o}C λ = 254 nm (t_{major} = 125.9 min. t_{minor} = 117.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{24}NO_3$ [M+H]$^+$ 338.1756, found 338.1758.



3f

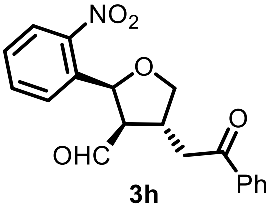
(2S,3R,4R)-2-(3-chlorophenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyd (3f): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 70% yield (46.0 mg). Diastereomeric ratio 2.3:1.8:1 (**3f**:**3f′**:**3f″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.15 (d, *J* = 3.8 Hz, 1H), 7.97-7.92 (m, 2H), 7.59 (m, 1H), 7.51-7.44 (m, 2H), 7.36 (t, *J* = 1.7 Hz, 1H), 7.30-7.24 (m, 2H), 7.21-7.16 (m, 1H), 5.25 (d, *J* = 8.3 Hz, 1H), 4.66 (dd, *J* = 8.8, 7.1 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.35-3.14 (m, 3H), 3.05

(ddd, *J* = 8.3, 6.2, 3.8 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 200.4, 197.9, 139.7, 136.3, 135.0, 133.7, 130.2, 128.9, 128.4, 128.2, 126.4, 124.4, 81.1, 74.0, 61.0, 40.8, 36.0. **FT-IR (thin film)** 2923, 2860, 1720, 1680, 1588, 1460, 1221, 752 cm^{-1}. **HPLC analysis**: 84% ee of the major diastereomer; Determined using a Lux cellulose-4 column (hexane/2-propanol = 80:20), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.6 min, t_{minor} = 40.0 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}ClO_3$ $[M+H]^+$ 329.0944, found: 329.0949.



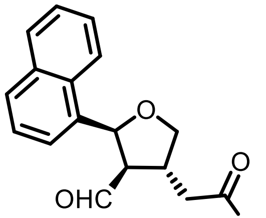
3g

(2S,3R,4R)-2-(2-methoxyphenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3g): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; Brown oil; 75% yield (49.0 mg). Diastereomeric ratio 2.3:1.6:1 (**3g**:**3g′**:**3g″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.08 (d, *J* = 3.7 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.58 (t, *J* = 6.8 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 3H), 7.26 (s, 1H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.69-4.62 (m, 1H), 3.82 (s, 3H), 3.60 (t, *J* = 8.3 Hz, 1H), 3.31 (dd, *J* = 15.8, 4.0 Hz, 1H), 3.23-3.11 (m, 4H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 201.1, 198.2, 155.3, 141.3, 136.5, 133.6, 129.0, 128.9, 128.2, 128.1, 126.6, 126.2, 121.7, 110.0, 73.6, 59.4, 55.3, 41.0, 36.0. **FT-IR (thin film)** 2928, 2857, 1722, 1688, 1593, 1450, 1220, 760 cm^{-1}. **HPLC analysis**: 88% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 33.2 min, t_{minor} = 57.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_4$ $[M+H]^+$ 325.1434, found: 325.1437.



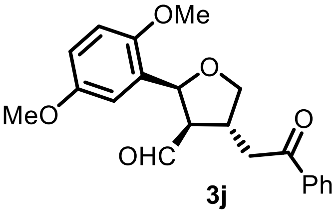
3h

(2S,3R,4R)-2-(2-nitrophenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3h): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; yellow sticky solid; 66% yield (45.5 mg). Diastereomeric ratio 4.3:2.1:1 (**3h**:**3h′**:**3h″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 10.05 (d, *J* = 2.3 Hz, 1H), 8.14 (s, 1H), 7.93-7.86 (m, 3H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 4H), 5.92 (d, *J* = 2.8 Hz, 1H), 4.56 (t, *J* = 7.4 Hz, 1H), 3.85-3.79 (m, 1H), 3.42 (d, *J* = 8.1 Hz, 1H), 3.33 (dd, *J* = 18.2, 7.2 Hz, 1H), 3.19 (dd, *J* = 18.7, 6.7 Hz, 2H), 3.13 – 3.03 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: 202.2, 198.0, 139.2, 134.3, 133.8, 128.9, 128.7, 128.2, 128.1, 128.1, 125.4, 78.2, 73.8, 60.0, 37.1, 36.1. **FT-IR (thin film)** 3060, 2928, 2847, 1720, 1683, 1595, 1496, 1218, 755 cm^{-1}. **HPLC analysis**: 86% ee of the major diastereomer; Determined using a Daicel Chiralpak IE column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.5 min t_{minor} = 19.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}NO_5$ [M+H]$^+$ 340.1185, found 340.1188.



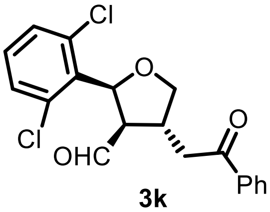
3i

(2S,3R,4R)-2-(naphthalen-1-yl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3i): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; Light yellow sticky solid, 76% yield (52.6 mg). Diastereomeric ratio 3.3:1.5:1 (**3i**:**3i′**:**3i″**). **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 9.22 (d, *J* = 2.9 Hz, 1H), 8.09 (d, *J* = 6.9 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 3H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.73-7.55 (m, 3H), 7.48 (t, *J* = 7.7 Hz, 4H), 5.67 (d, *J* = 8.5 Hz, 1H), 4.74-4.64 (m, 1H), 3.63 (t, *J* = 8.8 Hz, 1H), 3.54 (dd, *J* = 11.1, 4.3 Hz, 1H), 3.39-3.29 (m, 2H), 3.18 (dd, *J* = 16.2, 7.0 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: 200.1, 198.0, 137.0, 136.4, 136.3, 133.9, 133.6, 132.9, 129.7, 129.2, 128.8, 128.5, 128.1, 128.1, 126.6, 125.9, 125.7, 123.7, 122.5, 78.7, 73.5, 64.4, 60.1, 40.8, 36.2. **FT-IR (thin film)** 3056, 2923, 2843, 1715, 1680, 1475, 1213, 765 cm^{-1}. **HPLC analysis**: 98% ee of the major diastereomer: Determined using a Daicel Chiralpak AS-H column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 59.2 min, t_{minor} = 41.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{21}O_3$ [M+H]$^+$ 345.4175, found 345.4180.



3j

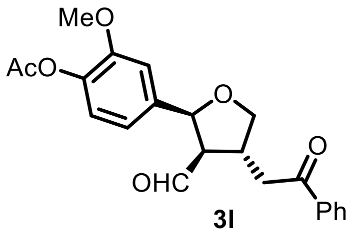
(2S,3R,4R)-2-(2,5-dimethoxyphenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3j): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; brown sticky solid; 72% yield (51.2 mg). Diastereomeric ratio 4:1.7:1 (**3j**:**3j′**:**3j″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.27 (d, *J* = 3.7 Hz, 1H), 8.12 (d, *J* = 7.3 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 3H), 6.94 (s, 2H), 5.57 (d, *J* = 7.7 Hz, 1H), 4.82 (dd, *J* = 8.5, 6.9 Hz, 1H), 3.95 (s, 6H), 3.76 (t, *J* = 8.3 Hz, 1H), 3.48 (d, *J* = 12.0 Hz, 1H), 3.32 (dd, *J* = 26.4, 10.3 Hz, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: 200.9, 198.1 154.0, 149.5, 136.5, 129.0, 128.7, 128.2, 128.1, 127.2, 113.5, 110.9, 73.6, 59.3, 56.0, 55.8, 55.6, 41.0, 35.9. **FT-IR (thin film)** 2961, 2928, 2823, 1721, 1680, 1455, 1225, 792 cm^{-1}. **HPLC analysis**: 90% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 70:30), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 19.2 min, t_{minor} = 47.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{22}NaO_5$ [M+Na]$^+$ 377.1365, found 377.1365.



3k

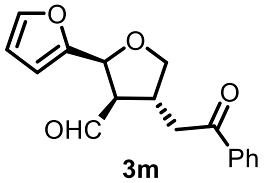
(2S,3R,4R)-2-(2,6-dichlorophenyl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3k): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; Light yellow semi solid; 68% yield (49.3 mg). Diastereomeric ratio 5.8:2.4:1 (**3k**:**3k′**:**3k″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.47 (d, *J* = 3.0 Hz, 1H), 7.96 (d, *J* = 9.4 Hz, 3H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.48 (s, 2H), 7.30 (d, *J* = 8.2 Hz, 3H), 7.15-7.20 (m, 2H), 5.95 (d, *J* = 10.1 Hz, 1H), 4.72-4.64 (m, 1H), 3.62 (t, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 15.1, 7.9 Hz, 1H), 3.26 (dd, *J* = 28.9, 6.8 Hz, 3H), 3.08 (ddd, *J* = 10.4, 7.8, 3.0 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: 199.9, 198.1, 136.4, 135.2, 135.1, 133.7, 133.1, 130.0, 129.7, 128.9, 128.2, 78.6, 73.9, 60.0 41.0, 37.2. **FT-IR (thin film)** 2923, 2820, 1713, 1686, 1465, 1210, 778 cm^{-1}. **HPLC analysis**: 98% ee of the major diastereomer; Determined using a Daicel Chiralpak IB column (hexane/2-propanol = 90:10), flow rate

= 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 18.6 min, t_{minor} = 21.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{17}Cl_2O_3$ $[M+H]^+$ 363.0555, found 363.0554.



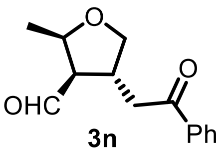
3l

4-((2S,3R,4R)-3-formyl-4-(2-oxo-2-phenylethyl) tetrahydrofuran-2-yl)-2-methoxyphenylacetate (3l): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 69% yield (52.7 mg). Diastereomeric ratio 2.8:2.2:1 (**3l**:**3l′**:**3l″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.17 (d, *J* = 3.6 Hz, 1H), 7.97-7.92 (m, 3H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.49-7.45 (m, 3H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.95-6.88 (m, 2H), 5.25 (d, *J* = 8.1 Hz, 1H), 4.68-4.62 (m, 1H), 3.82 (s, 3H), 3.62 (s, 1H), 3.41-3.15 (m, 5H), 3.05 (ddd, *J* = 9.5, 6.1, 3.6 Hz, 1H), 2.30 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 200.7, 198.0, 169.0, 151.5, 140.5, 139.4, 139.2, 136.3, 130.2, 128.8, 128.1, 118.3, 117.7, 110.2, 81.3, 81.2, 73.9, 61.0, 56.0, 41.0, 37.8, 20.9. **FT-IR (thin film)** 3063, 2928, 2854, 1763, 1719, 1684, 1453, 1204, 790 cm^{-1}. **HPLC analysis**: 88% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 80:20), flow rate = 1.00 mL/min, 25 °C; λ = 254 nm (t_{major}) = 16.2 min, t_{minor} = 25.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{22}H_{22}NaO_6$ $[M+Na]^+$ 405.1309, found 405.1305.



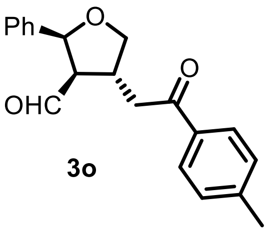
3m

(2S,3R,4R)-2-(furan-2-yl)-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3m): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; Yellow oil; 60% yield (34.0 mg). Diastereomeric ratio 8.3:2.6:1 (**3m**:**3m′**:**3m″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.39 (d, *J* = 3.4 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 3H), 7.59 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 3H), 7.29-7.23 (m, 1H), 6.34 (d, *J* = 1.6 Hz, 2H), 5.31 (d, *J* = 8.4 Hz, 1H), 4.59 (t, *J* = 8.1 Hz, 1H), 3.63 (t, *J* = 8.4 Hz, 1H), 3.52-3.40 (m, 2H), 3.36-3.30 (m, 1H), 3.14 (dd, *J* = 17.7, 7.9 Hz, 2H), 3.03-2.98 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 199.7, 198.1, 151.3, 143.1, 136.4, 133.7, 133.7, 129.2, 128.9, 128.4, 128.2, 110.6, 109.3, 75.1, 73.8, 61.5, 60.7, 41.2, 37.5, 36.0. **FT-IR (thin film)** 2924, 2830, 1720, 1680, 1449, 1221, 752 cm^{-1}. **HPLC analysis**: 92% ee of the major diastereomer; Determined using a Daicel Chiralpak ID column (hexane/2-propanol = 93:7), flow rate = 1.00 mL/min, 25 °C; λ = 254 nm (t_{major} = 47.5 min, t_{minor} = 39.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{17}H_{16}NaO_4$ $[M+Na]^+$ 305.0941, found 305.0942.



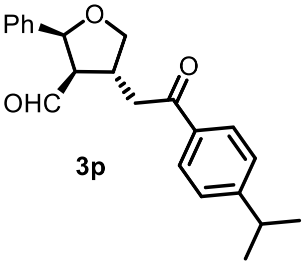
3n

(2R,3R,4R)-2-methyl-4-(2-oxo-2-phenylethyl)tetrahydrofuran-3-carbaldehyde (3n): Purified by silica-gel column chromatography using 10% ethyl acetate/hexane; colourless oil; 64% yield (30.5 mg). Diastereomeric ratio 3.1:1.8:1 (**3n**:**3n′**:**3n″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.76 (d, *J* = 4.0 Hz, 1H), 7.94-7.93 (m, 2H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 4.44-4.38 (m, 1H), 4.34-4.25 (m, 1H), 3.45 (t, *J* = 8.3 Hz, 1H), 3.18 (ddd, *J* = 21.6, 13.0, 6.9 Hz, 3H), 2.68 (ddd, *J* = 7.7, 5.7, 4.1 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.2, 198.3, 136.6, 133.6, 133.6, 128.9, 128.2, 76.0, 72.9, 60.4, 41.4, 36.1, 17.0. **FT-IR (thin film)** 2974, 2929, 1724, 1683, 1598, 1449, 1217, 756 cm^{-1}. **HPLC analysis**: 57% ee of the major diastereomer; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 35.8 min, t_{minor} = 42.1 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{17}H_{17}O_3$ $[M+H]^+$ 233.1178, found 233.1178.



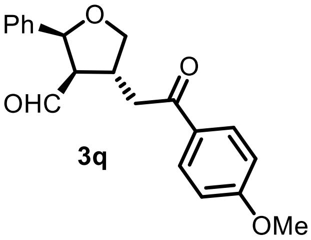
3o

(2S,3R,4R)-4-(2-oxo-2-(p-tolyl)ethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3o): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless oil; 78% yield (48.4 mg). Diastereomeric ratio 4.1:1.6:1 (**3o**:**3o′**:**3o″**). **^{1}H NMR (600 MHz, CDCl$_3$):** δ 9.12 (d, *J* = 3.7 Hz, 1H), 7.84 (t, *J* = 7.3 Hz, 3H), 7.34 (t, *J* = 8.0 Hz, 7H), 7.27 (d, *J* = 7.7 Hz, 4H), 5.29 (d, *J* = 8.2 Hz, 1H), 4.68-4.65-4.63 (m, 1H), 3.63 (t, *J* = 8.6 Hz, 1H), 3.33-3.24 (m, 3H), 3.19-3.11 (m, 2H), 3.07-3.00 (m, 1H), 2.41 (s, 5H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.0, 197.7, 144.5, 137.6, 134.0, 129.6, 128.9, 128.3, 128.2, 126.2, 125.7, 81.8, 74.0, 61.2, 40.8, 36.0, 21.8. **FT-IR (thin film)** 2927, 2848, 1725, 1686, 1440, 1220, 758 cm^{-1}. **HPLC analysis**: 90% ee of the major diastereomer; Determined using a Daicel Chiralpak ID column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 87.1 min, t_{minor} = 105.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_3$ $[M+H]^+$ 309.1491, found 309.1498.



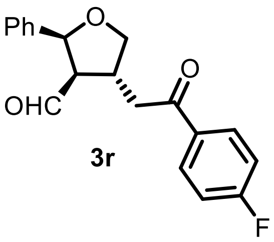
3p

(2S,3R,4R)-4-(2-(4-isopropylphenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3p): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless oil; 76 % yield (51.0 mg). Diastereomeric ratio 4.1:1.6:1 (**3p**:**3p′**:**3p″**). **^{1}H NMR (600 MHz, CDCl$_3$):** δ 9.12 (d, *J* = 3.7 Hz, 1H), 7.88 (s, 1H), 7.38-7.33 (m, 8H), 5.29 (d, *J* = 8.2 Hz, 1H), 4.68-4.64 (m, 1H), 3.63 (t, *J* = 8.6 Hz, 1H), 3.32-3.25 (m, 2H), 3.17-3.13 (m, 1H), 3.06-3.02 (m, 1H), 2.98 (d, *J* = 6.9 Hz, 1H), 1.28 (s, 6H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.0, 197.7, 155.3, 143.2, 137.6, 128.9, 128.5, 128.2, 127.0, 126.3, 125.7, 81.8, 74.0, 61.2, 40.9, 36.0, 34.4, 23.8. **FT-IR (thin film)** 2928, 2840, 1715, 1687, 1455, 1213, 760 cm^{-1}. **HPLC analysis**: 90% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C; λ = 254 nm (t_{major} = 34.2 min, t_{minor} = 52.3 min). **HRMS (+ESI-TOF**) *m/z*: calcd. for $C_{22}H_{25}O_3$ $[M+H]^+$ 337.1804, found 337.1808.



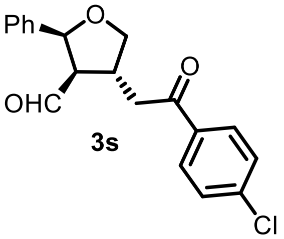
3q

(2S,3R,4R)-4-(2-(4-methoxyphenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3q): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 74% yield (48.2 mg). Diastereomeric ratio 3.4:1.2:1 (**3q**:**3q′**:**3q″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.12 (d, *J* = 3.7 Hz, 1H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.40-7.29 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.28 (d, *J* = 8.3 Hz, 1H), 4.68-4.63 (m, 1H), 3.87 (s, 3H), 3.63 (s, 1H), 3.32-3.27 (m, 1H), 3.23 (dd, *J* = 17.2, 6.1 Hz, 1H), 3.12 (dd, *J* = 17.3, 7.8 Hz, 1H), 3.03 (ddd, *J* = 8.2, 6.9, 3.8 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.0, 196.5, 163.9, 137.6, 130.5, 129.6, 128.8, 128.2, 126.2, 114.0, 81.8, 74.0, 61.2, 55.7, 40.6, 36.1. **FT-IR (thin film)** 2922, 2847, 1712, 1690, 1458, 1216, 767 cm^{-1}. **HPLC analysis**: 96% ee of the major diastereomer; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 43.9 min, t_{minor} = 38.0 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_4$ [M+H]$^+$ 325.1440, found 325.1443.



3r

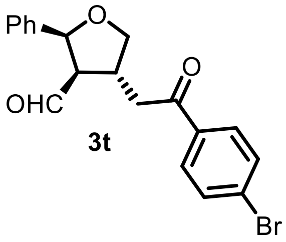
(2S,3R,4R)-4-(2-(4-fluorophenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3r): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 73% yield (46.0 mg). Diastereomeric ratio 2.3:1.3:1 (**3r**:**3r′**:**3r″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.12 (d, *J* = 3.6 Hz, 1H), 7.98-7.96 (m, 2H), 7.30-7.36 (m, 7H), 7.14 (t, *J* = 9 Hz, 2H), 5.29 (d, *J* = 8.3 Hz, 1H), 4.69-4.61 (m, 1H), 3.63 (t, *J* = 8.6 Hz, 1H), 3.27 (m, 3H), 3.14 (dd, *J* = 17.3, 7.6 Hz, 1H), 3.03 (ddd, *J* = 8.3, 6.8, 3.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 200.8, 196.4, 166.9, 165.3, 137.5, 130.9, 128.9, 128.2, 126.2, 125.7, 116.1, 116.0, 81.7, 73.9, 61.1, 40.9, 35.9. **FT-IR (thin film)** 2928, 2850, 1708, 1695, 1460, 1210, 775 cm^{-1}. **HPLC analysis**: 95% ee of the major diastereomer; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 29.6 min, t_{minor} = 49.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}FO_3$ [M+H]$^+$ 313.1240, found 313.1238.



3s

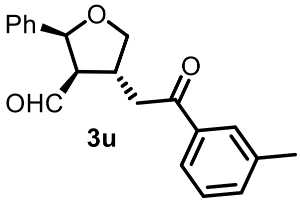
(2S,3R,4R)-4-(2-(4-chlorophenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3s): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; Light brown oil; 72% yield (47.4 mg). Diastereomeric ratio 3.4:1.9:1 (**3s**:**3s′**:**3s″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.12 (d, *J* = 3.6 Hz, 1H), 7.89-7.87 (m, 3H), 7.45-7.43 (m, 3H), 7.33 (t, *J* = 10.5 Hz, 6H), 5.29 (d, *J* = 8.3 Hz, 1H), 4.69-4.62 (m, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.25 (dd, *J* = 17.0, 6.6 Hz, 4H), 3.18-3.11 (m, 2H), 3.03 (ddd, *J*

= 8.3, 6.9, 3.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 200.8, 196.8, 140.2, 137.4, 129.6, 129.6, 129.2, 128.9, 128.3, 126.2, 81.7, 73.9, 61.1, 40.9, 35.8. **FT-IR (thin film)** 2924, 2848, 1710, 1688, 1462, 1212, 770 cm^{-1}. **HPLC analysis**: 96% ee of the major diastereomer; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 32.6 min, t_{minor} = 35.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}ClO_3$ [M+H]$^+$ 329.0944, found 329.0949.



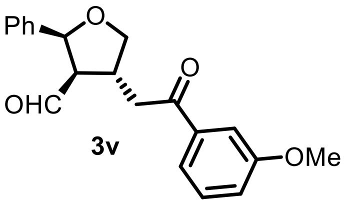
3t

(2S,3R,4R)-4-(2-(4-bromophenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3t): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; yellow sticky solid; 77% yield (58.0 mg). Diastereomeric ratio 2.9:1.9:1 (**3s**:**3s′**:**3s″**). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.21 (d, *J* = 3.6 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 7.47-7.37 (m, 6H), 5.38 (d, *J* = 7.8 Hz, 1H), 4.86-4.62 (m, 1H), 3.70 (d, *J* = 8.5 Hz, 1H), 3.41-3.24 (m, 3H), 3.12 (ddd, *J* = 8.3, 6.6, 3.6 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 200.7, 197.0, 137.4, 135.1, 131.9, 130.1, 129.3, 128.5, 126.6, 125.8, 82.1, 81.4, 61.4, 60.7, 35.7. **FT-IR (thin film)** 2921, 2853, 1705, 1690, 1465, 1215, 778 cm^{-1}. **HPLC analysis**: 84% ee of the major diastereomer; Determined using a Daicel Chiralpak IE column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ^{o}C, λ = 254 nm (t_{major}) = 75.9 min, t_{minor} = 48.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}BrO_3$ [M+H]$^+$ 373.0439, found 373.0443.



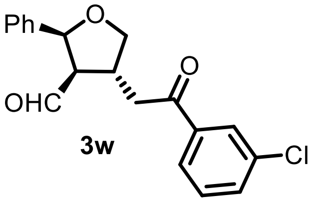
3u

(2S,3R,4R)-4-(2-oxo-2-(m-tolyl)ethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3u): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless oil; 70% yield (44.0 mg). Diastereomeric ratio 3.5:2.2:1 (**3u**:**3u′**:**3u″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.13 (d, *J* = 3.7 Hz, 1H), 7.76-7.73 (m, 3H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.37-7.32 (m, 8H), 5.29 (d, *J* = 8.3 Hz, 1H), 4.69- 4.64 (m, 1H), 3.63 (t, *J* = 8.6 Hz, 1H), 3.32-3.25 (m, 3H), 3.22-3.14 (m, 2H), 3.07-3.00 (m, 1H), 2.41 (s, 4H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.0, 198.2, 138.7, 134.4, 128.9, 128.8, 128.2, 126.3, 125.7, 125.4, 81.8, 74.0, 61.2, 41.0, 36.0, 21.5. **FT-IR (thin film)** 2960, 2927, 1720, 1685, 1458, 1225, 780 cm^{-1}. **HPLC analysis**: 94% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, λ = 254 nm (t_{major} = 31.9 min, t_{minor} = 54.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_3$ $[M+H]^+$ 309.1491, found 309.1497.



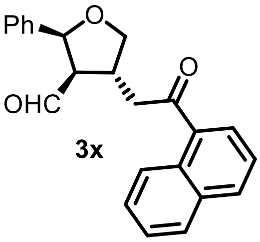
3v

(2S,3R,4R)-4-(2-(3-methoxyphenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3v): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 74% yield (48.7 mg). Diastereomeric ratio 3.2:1.8:1 (**3v**:**3v′**:**3v″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.30 (d, *J* = 3.7 Hz, 1H), 7.72-7.68 (m, 2H), 7.55-7.51 (m, 7H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.32-7.35 (m, 2H), 5.46 (d, *J* = 8.3 Hz, 1H), 4.86-4.80 (m, 1H), 4.03 (s, 4H), 3.81 (t, *J* = 8.6 Hz, 1H), 3.50-3.43 (m, 3H), 3.39-3.30 (m, 2H), 3.21 (ddd, *J* = 8.2, 6.6, 3.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 200.9, 197.9, 160.1, 137.5, 129.9, 128.9, 128.8, 128.2, 126.2, 125.7, 120.8, 120.2, 112.4, 81.8, 73.9, 61.2, 55.6, 41.1, 36.0. **FT-IR (thin film)** 2958, 2929, 1718, 1682, 1465, 1228, 785 cm^{-1}. **HPLC analysis**: 92% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 48.8 min, t_{minor} = 86.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_4$ $[M+H]^+$ 325.1440, found 325.1448.



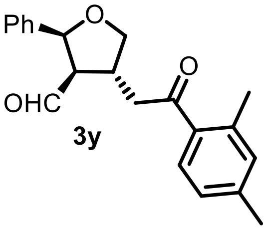
3w

(2S,3R,4R)-4-(2-(3-chlorophenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3w): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 67% yield (45.0 mg). Diastereomeric ratio 4:2.2:1 (**3w**:**3w′**:**3w″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.12 (d, *J* = 3.6 Hz, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 2H), 7.33-7.30 (m, 6H), 5.29 (d, *J* = 8.4 Hz, 1H), 4.69-4.61 (m, 1H), 3.62 (t, *J* = 8.6 Hz, 1H), 3.35-3.23 (m, 3H), 3.15 (dd, *J* = 17.6, 7.6 Hz, 2H), 3.06-2.99 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ. 200.8, 196.8, 141.4, 135.3, 133.6, 130.2, 128.9, 128.8, 128.3, 128.3, 126.2, 125.7, 81.7, 73.8, 61.1, 41.1, 35.7. **FT-IR (thin film)** 2925, 2853, 1725, 1684, 1452, 1265, 1121, 765 cm^{-1}. **HPLC analysis**: 94% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 29.4 min, t_{minor} = 80.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{18}ClO_3$ [M+H]$^+$ 329.0944, found 329.0943.



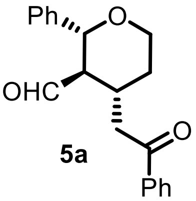
3x

(2S,3R,4R)-4-(2-(naphthalen-1-yl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3x): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 70% yield (49.0 mg). Diastereomeric ratio 3:2.1:1 (**3x**:**3x′**:**3x″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.16 (d, *J* = 3.6 Hz, 1H), 8.62 (d, *J* = 8.6 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 8.2 Hz, 2H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.52-7.49 (m, 1H), 7.37-7.34 (m, 4H), 7.29 (t, *J* = 7.0 Hz, 1H), 5.31 (d, *J* = 8.3 Hz, 1H), 4.74-4.67 (m, 1H), 3.70 (t, *J* = 8.5 Hz, 1H), 3.42-3.36 (m, 2H), 3.31-3.24 (m, 1H), 3.08 (ddd, *J* = 8.2, 6.5, 3.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ. 202.0, 200.9, 137.5, 135.0, 134.2, 133.5, 130.2, 128.9, 128.7, 128.4, 128.2, 128.1, 126.8, 126.3, 125.8, 125.7, 124.5, 81.8, 74.0, 61.2, 44.1, 36.4. **FT-IR (thin film)** 2930, 2849, 1716, 1680, 1450, 1255, 1116, 769 cm^{-1}. **HPLC analysis**: 96% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 24.5 min, t_{minor} = 17.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{23}H_{21}O_3$ [M+H]$^+$ 345.1491, found 345.1490.



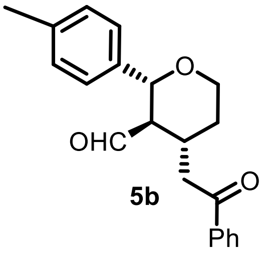
3y

(2S,3R,4R)-4-(2-(2,4-dimethylphenyl)-2-oxoethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (3y): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; yellow oil; 65% yield (42.6 mg). Diastereomeric ratio 2.3:1.4:1 (**3y**:**3y′**:**3y″**). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.11 (d, *J* = 3.8 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.37-7.32 (m, 6H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.07 (s, 2H), 5.28 (d, *J* = 8.3 Hz, 1H), 4.68-4.62 (m, 1H), 3.63 (t, *J* = 8.7 Hz, 1H), 3.30-3.18 (m, 3H), 3.15-3.06 (m, 2H), 3.04-2.98 (m, 1H), 2.48 (s, 4H), 2.36 (s, 4H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ. 201.0, 200.9, 142.7, 139.3, 137.6, 133.3, 129.4, 128.9, 128.7, 128.2, 126.6, 126.2, 125.7, 81.8, 74.1, 61.2, 43.3, 36.3, 21.9, 21.5. **FT-IR (thin film)** 2922, 2855, 1710, 1686, 1448, 1255, 1110, 775 cm^{-1}. **HPLC analysis**: 94% ee of the major diastereomer; Determined using a Daicel Chiralpak IC column (hexane/2-propanol = 95:5), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 44.4 min, t_{minor} = 86.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{23}O_3$ [M+H]$^+$ 323.1647, found 323.1646.



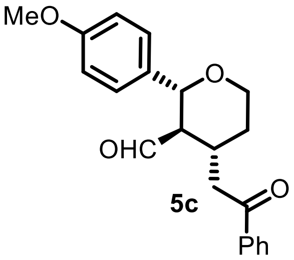
5a

(2R,3R,4R)-4-(2-oxo-2-phenylethyl)-2-phenyltetrahydro-2H-pyran-3-carbaldehyde (5a): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 95% yield (58.2 mg). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.42 (d, *J* = 3.5 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 2H), 7.59-7.54 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.37-7.30 (m, 5H), 4.45 (d, *J* = 9.9 Hz, 1H), 4.13 (dd, *J* = 12.4, 5.7 Hz, 1H), 3.69 (td, *J* = 12.3, 2.2 Hz, 1H), 3.11 (q, *J* = 7.4 Hz, 1H), 2.81 (td, *J* = 8.3, 4.8 Hz, 2H), 2.70 (td, *J* = 10.3, 3.6 Hz, 1H), 1.95-1.87 (m, 1H), 1.62-1.49 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 202.6, 198.5, 139.3, 136.8, 133.4, 128.9, 128.8, 128.8, 128.2, 127.1, 80.4, 68.2, 61.1, 42.8, 31.9, 30.9. **FT-IR (thin film)** 3061, 2922, 2850, 1718, 1681, 1597, 1450, 1286, 1115, 756 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 9.4 min, t_{minor} = 10.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{21}O_3$ [M+H]$^+$ 309.1491, found 309.1487.



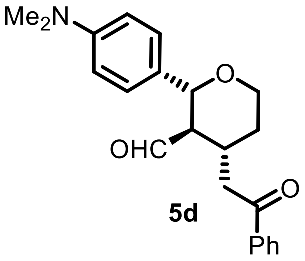
5b

(2R,3R,4R)-4-(2-oxo-2-phenylethyl)-2-(p-tolyl)tetrahydro-2H-pyran-3-carbaldehyde (5b): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 88% yield (57.0 mg). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 9.41 (d, *J* = 3.6 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.61-7.54 (m, 1H), 7.48 (d, *J* = 7.8 Hz, 2H), 7.24 (s, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H), 3.68 (t, *J* = 12.1 Hz, 1H), 3.18-3.06 (m, 1H), 2.88-2.76 (m, 2H), 2.69 (td, *J* = 10.4, 3.6 Hz, 1H), 2.33 (s, 3H), 1.91 (d, *J* = 13.5 Hz, 1H), 1.55 (ddd, *J* = 24.4, 13.1, 4.7 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 202.7, 198.5, 138.6, 136.8, 136.3, 133.4, 129.6, 128.8, 128.3, 128.2, 127.0, 80.2, 68.2, 61.0, 42.9, 31.9, 31.0, 21.3. **FT-IR (thin film)** 3056, 2923, 2848, 1710, 1685, 1590, 1450, 1280, 766 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 8.6 min, t_{minor} = 9.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{23}O_3$ [M+H]$^+$ 323.1647, found 323.1649.



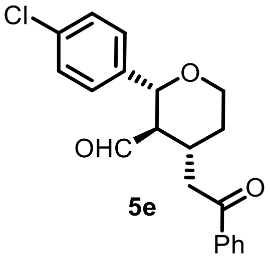
5c

(2R,3R,4R)-2-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5c): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 83% yield (56.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.32 (d, *J* = 3.6 Hz, 1H), 7.86 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.06-3.99 (m, 1H), 3.70 (s, 3H), 3.60 (td, *J* = 12.2, 1.9 Hz, 1H), 3.03 (q, *J* = 7.6 Hz, 1H), 2.76-2.70 (m, 2H), 2.60 (td, *J* = 10.3, 3.6 Hz, 1H), 1.86-1.76 (m, 1H), 1.46 (ddd, *J* = 24.8, 12.9, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.7, 198.5, 159.9, 136.9, 133.4, 131.5, 129.1, 128.8, 128.4, 128.3, 128.2, 114.3, 79.9, 68.2, 61.0, 55.4, 42.9, 32.0, 31.0. **FT-IR (thin film)** 3063, 2925, 2850, 1716, 1682, 1600, 1452, 1240, 754 cm^{-1}. **HPLC analysis**: : >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.4 min, t_{minor} = 15.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{22}NaO_4$ [M+Na]$^+$ 361.1416, found 361.1441.



5d

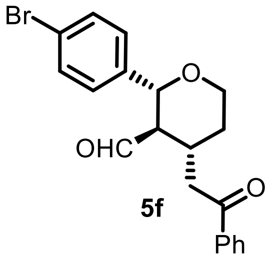
(2R,3R,4R)-2-(4-(dimethylamino)phenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5d): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown oil; 35% yield (24.6 mg). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 9.40 (d, *J* = 3.4 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 4.34 (d, *J* = 9.8 Hz, 1H), 4.18-4.08 (m, 1H), 3.67 (t, *J* = 11.1 Hz, 1H), 3.18-3.09 (m, 1H), 2.93 (s, 5H), 2.79 (dd, *J* = 17.1, 6.4 Hz, 2H), 2.72 (td, *J* = 10.2, 3.4 Hz, 1H), 1.89 (d, *J* = 13.5 Hz, 1H), 1.53 (ddd, *J* = 24.1, 13.1, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 203.0, 198.8, 151.0, 133.4, 128.8, 128.3, 128.2, 126.9, 112.7, 80.3, 68.3, 60.8, 43.1, 40.6, 32.2, 31.1. **FT-IR (thin film)** 3056, 2921, 2855, 1710, 1688, 1608, 1450, 1200, 765 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 16.4 min, t_{minor} = 17.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{22}H_{26}NO_3$ $[M+H]^+$ 352.1913, found 352.1927.



5e

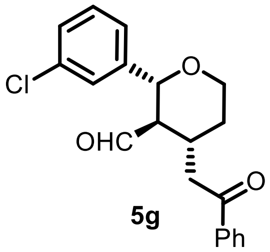
(2R,3R,4R)-2-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5e): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 70% yield (48.0 mg). **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 9.44 (d, *J* = 3.6 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.69 (t, *J* = 11.9 Hz, 1H), 3.09 (d, *J* = 13.0 Hz, 1H), 2.87-2.77 (m, 2H), 2.70-2.59 (m, 1H), 1.92 (d, *J* = 13.3 Hz, 1H), 1.61-1.50 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 202.3, 198.4, 138.0, 134.6, 133.5, 129.1, 128.8, 128.5, 128.2, 79.6, 68.3, 61.2, 42.8, 32.1, 31.0. **FT-IR (thin film)** 3049, 2927, 2855, 1713, 1680, 1598, 1460, 1230, 778 cm^{-1}. **HPLC analysis**: 99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate

= 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 11.7 min, t_{minor} = 13.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{20}ClO_3$ $[M+H]^+$ 343.1101, found 343.1103.



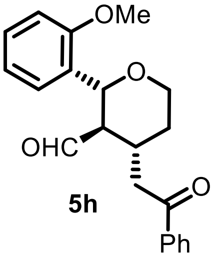
5f

(2R,3R,4R)-2-(4-bromophenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5f): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 88% yield (68.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.43 (d, *J* = 3.7 Hz, 1H), 7.95 – 7.91 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.52-7.44 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.44 (d, *J* = 10.0 Hz, 1H), 4.16-4.08 (m, 1H), 3.69 (t, *J* = 11.0 Hz, 1H), 3.09 (q, *J* = 7.5 Hz, 1H), 2.89-2.76 (m, 2H), 2.63 (td, *J* = 10.4, 3.6 Hz, 1H), 1.92 (d, *J* = 13.5 Hz, 1H), 1.55 (ddd, *J* = 24.8, 13.0, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.3, 198.4, 138.5, 136.8, 133.5, 132.1, 128.9, 128.8, 128.2, 122.8, 79.7, 68.3, 61.2, 42.83, 32.0, 30.9. **FT-IR (thin film)** 3040, 2923, 2849, 1708, 1682, 1610, 1468, 1209, 770 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 14.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{19}BrNaO_3$ $[M+Na]^+$ 409.0415, found 409.0406.



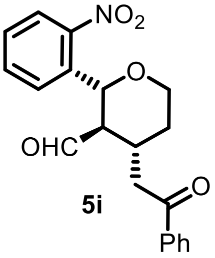
5g

(2R,3R,4R)-2-(3-chlorophenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5g): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 84% yield (57.5 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.46 (d, *J* = 3.5 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.38 (s, 1H), 7.28 (d, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 5.9 Hz, 1H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.13 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.69 (dd, *J* = 17.4, 6.7 Hz, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 2.87-2.77 (m, 2H), 2.65 (t, J = 12.0 Hz, 1H), 1.92 (d, *J* = 13.3 Hz, 1H), 1.56 (ddd, *J* = 25.2, 12.8, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.3, 198.4, 141.5, 136.8, 135.0, 133.5, 130.2, 129.0, 128.9, 128.2, 127.3, 125.3, 79.7, 68.3, 61.1, 42.8, 32.0, 30.9. **FT-IR (thin film)** 3032, 2921, 2850, 1716, 1680, 1625, 1455, 1228, 775 cm^{-1}. **HPLC analysis**: 99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 95:5), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 9.9 min, t_{minor} = 11.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{20}ClO_3$ [M+H]$^+$ 343.1101, found 343.1102.



5h

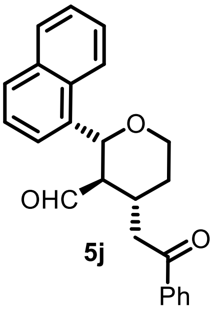
(2R,3R,4R)-2-(2-methoxyphenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5h): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 90% yield (60.5 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.39 (d, *J* = 4.0 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.51-7.45 (m, 3H), 7.29-7.26 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 4.18-4.08 (m, 1H), 3.79 (s, 3H), 3.74-3.63 (m, 1H), 3.11 (dd, *J* = 16.5, 3.5 Hz, 1H), 2.91-2.82 (m, 1H), 2.77 (dd, *J* = 16.5, 8.9 Hz, 1H), 2.50 (td, *J* = 10.5, 4.0 Hz, 1H), 1.96-1.88 (m, 1H), 1.53 (ddd, *J* = 25.4, 12.6, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.1, 198.7, 155.6, 137.0, 133.4, 129.4, 129.1, 128.8, 128.3, 128.2, 128.1, 127.6, 125.4, 121.3, 110.6, 72.8, 68.3, 62.1, 55.4, 43.1, 31.4, 31.0. **FT-IR (thin film)** 3055, 2923, 2843, 1718, 1682, 1597, 1459, 1247, 1102, 754 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 8.5 min, t_{minor} = 12.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{23}O_4$ [M+H]$^+$ 339.1596, found 339.1593.



5i

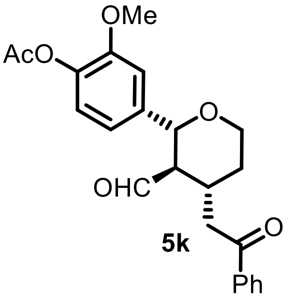
(2R,3R,4R)-2-(2-nitrophenyl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5i): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; yellow semi solid; 84% yield (59.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.55 (d, *J* = 4.1 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.87-7.83 (m, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.49-7-44 (m, 3H), 5.20 (d, *J*

= 9.9 Hz, 1H), 4.10 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.69 (t, *J* = 12.1 Hz, 1H), 3.15-3.09 (m, 1H), 2.99-2.83 (m, 2H), 2.65 (td, *J* = 10.4, 4.2 Hz, 1H), 1.96 (dd, *J* = 13.5, 1.7 Hz, 1H), 1.63-1.50 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.3, 198.1, 148.5, 136.8, 134.6, 133.7, 133.5, 129.5, 129.3, 128.8, 128.2, 124.4, 74.5, 68.4, 62.1, 42.9, 31.7, 30.8. **FT-IR (thin film)** 3060, 2925, 2851, 1716, 1683, 1602, 1460, 1238, 756 cm^{-1}. **HPLC analysis**: 97% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.5 min, t_{minor} = 15.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{20}NO_5$ $[M+H]^+$ 354.1341, found 354.1343.



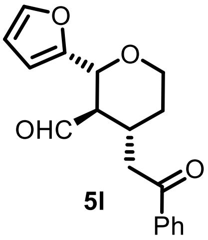
5j

(2R,3R,4R)-2-(naphthalen-1-yl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5j): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; yellow semi solid; 94% yield (67.2 mg,). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.34 (d, J = 3.6 Hz, 1H), 8.02-7.94 (m, 2H), 7.90-7.86 (m, 2H), 7.62-7.43 (m, 7H), 7.28-7.16 (m, 1H), 5.18 (d, J = 10.1 Hz, 1H), 4.28-4.19 (m, 1H), 3.84 (t, J = 12.0 Hz, 1H), 3.23-3.08 (m, 2H), 3.01-2.82 (m, 2H), 2.01 (d, J = 13.4 Hz, 1H), 1.74-1.61 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.2, 198.6, 136.9, 134.7, 134.3, 133.5, 131.0, 129.6, 129.2, 129.1, 128.8, 128.4, 128.3, 126.6, 126.0, 125.7, 125.4, 125.4, 68.6, 59.7, 42.9, 32.2, 31.1. **FT-IR (thin film)** 3048, 2931, 2849, 1712, 1680, 1598, 1446, 1225, 776 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 11.1 min, t_{minor} = 19.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{24}H_{23}O_3$ $[M+H]^+$ 359.1647, found 359.1652.



5k

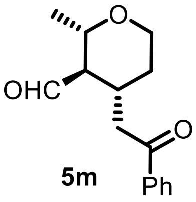
4-((2R,3R,4R)-3-formyl-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-2-yl)-2-methoxyphenyl acetate (5k): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 87% yield (68.5 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.45 (d, *J* = 3.1 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.59-7.54 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.03-6.96 (m, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.11 (dd, *J* = 12.3, 5.1 Hz, 2H), 3.83 (s, 3H), 3.66 (t, *J* = 12.0 Hz, 1H), 3.10 (q, *J* = 7.4 Hz, 1H), 2.80 (dd, *J* = 17.4, 6.4 Hz, 2H), 2.69 (td, *J* = 10.0, 3.1 Hz, 1H), 2.28 (s, 3H), 2.04 (d, *J* = 14.7 Hz, 2H), 1.90 (d, *J* = 13.0 Hz, 1H), 1.59-1.53 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.6, 198.5, 168.9, 151.6, 140.0, 138.3, 136.8, 133.4, 129.1, 128.8, 128.3, 128.2, 123.0, 119.3, 111.1, 80.1, 68.2, 60.9, 56.0, 42.8, 32.1, 30.9, 20.7. **FT-IR (thin film)** 3063, 2925, 2852, 1764, 1719, 1682, 1602, 1510, 1205, 754 cm^{-1}. **HPLC analysis**: 97% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 ºC, λ = 254 nm (t_{major} = 22.0 min, t_{minor} = 26.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{23}H_{25}O_6$ [M+H]$^+$ 397.1658, found 397.1658.



5l

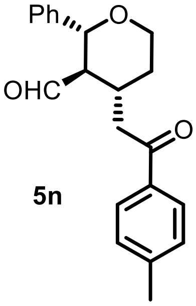
(2R,3R,4R)-2-(furan-2-yl)-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5l): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 39% yield (23.3 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.48 (d, *J* = 3.7 Hz, 1H), 7.97-7.91 (m, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.41 (s, 1H), 6.34 (d, *J* = 0.9 Hz, 2H), 4.60 (d, *J* = 10.4 Hz, 1H), 4.10 (d, *J* = 11.6 Hz, 1H), 3.69 (t, *J* = 11.0 Hz, 1H), 3.15 (dd, *J* = 16.8, 3.7 Hz, 1H), 2.90-2.82 (m, 2H), 2.77 (ddd, *J* = 11.6, 7.8, 3.7 Hz, 1H), 1.91 (d, *J* = 13.5 Hz, 1H), 1.52 (ddd, *J* = 25.3, 12.4, 4.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 201.4, 198.4, 143.3, 133.5, 128.9, 128.2, 110.6, 109.1, 72.4, 68.0, 57.5, 42.8, 31.6, 30.8. **FT-IR (thin film)** 3050, 2922, 2847, 1715, 1685, 1610, 1496, 1225, 774 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol

= 85:15), flow rate = 1.00 mL/min, 25 ºC, λ = 254 nm (t_{major} = 7.9 min, t_{minor} = 12.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{18}H_{19}O_4$ $[M+H]^+$ 299.1283, found 299.1282.



5m

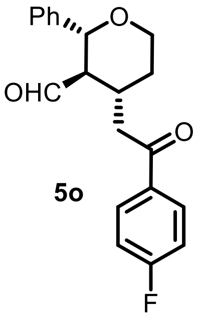
(2S,3R,4R)-2-methyl-4-(2-oxo-2-phenylethyl)tetrahydro-2H-pyran-3-carbaldehyde (5m): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 90 % yield (44.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.59 (d, *J* = 4.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 3H), 3.97 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.65 (dq, *J* = 12.3, 6.1 Hz, 1H), 3.54 (t, *J* = 13.0 Hz, 1H), 2.99 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.81 (dd, *J* = 17.0, 8.4 Hz, 1H), 2.72-2.64 (m, 1H), 2.18-2.06 (m, 1H), 1.82 (d, *J* = 13.4 Hz, 2H), 1.42-1.31 (m, 2H), 1.22 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 203.1, 198.5, 136.8, 133.5, 128.8, 128.1, 72.4, 67.5, 62.0, 43.0, 31.0, 30.8, 20.7. **FT-IR (thin film)** 3054, 2927, 2843, 1720, 1688, 1606, 1499, 1230, 770 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 ºC, λ = 254 nm (t_{major} = 7.4 min, t_{minor} = 8.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1334, found 247.1347.



5n

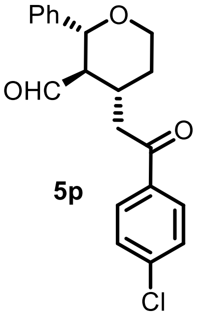
(2R,3R,4R)-4-(2-oxo-2-(p-tolyl)ethyl)-2-phenyltetrahydro-2H-pyran-3-carbaldehyde (5n): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 87% yield (56.4 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.42 (d, *J* = 3.6 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.37-7.31 (m, 5H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.13 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.69 (t, *J* = 11.1 Hz, 1H), 3.08 (d, *J* = 12.8 Hz, 1H), 2.83-2.76 (m, 2H), 2.70 (td, *J* = 10.3, 3.6 Hz, 1H), 2.41 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.7, 198.2, 144.3, 139.4, 134.4, 129.5, 129.0, 128.9, 128.4, 127.1, 80.5, 68.3, 61.2, 42.8, 32.1, 31.0, 21.8. **FT-IR (thin film)** 3033, 2921, 2850, 1719, 1678, 1605, 1452, 1289, 1115, 760 cm^{-1}. **HPLC analysis**: 98% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 ºC, λ =

254 nm (t_{major} = 25.7 min, t_{minor} = 32.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{21}H_{23}O_3$ $[M+H]^+$ 323.1647, found 323.1642.



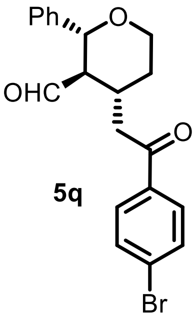
5o

(2R,3R,4R)-4-(2-(4-fluorophenyl)-2-oxoethyl)-2-phenyltetrahydro-2H-pyran-3-carbaldehyde (5o): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky semi solid; 85% yield (55.5 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.41 (d, *J* = 3.4 Hz, 1H), 7.99-7.95 (m, 2H), 7.38-7.31 (m, 5H), 7.14 (t, *J* = 8.6 Hz, 2H), 4.44 (d, *J* = 9.9 Hz, 1H), 4.14 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.69 (td, *J* = 12.2, 2.1 Hz, 1H), 3.10 (dd, *J* = 15.9, 3.1 Hz, 1H), 2.81-2.67 (m, 3H), 1.91 (d, *J* = 13.4 Hz, 1H), 1.56 (dt, *J* = 16.8, 10.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.7, 196.9, 166.9, 165.2, 139.3, 133.3, 131.0, 130.97, 129.0, 128.9, 127.1, 116.0, 115.9, 80.6, 68.3, 61.1, 42.9, 32.0, 31.0. **FT-IR (thin film)** 3030, 2924, 2853, 1720, 1682, 1597, 1450, 1221, 1149, 751 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 95:5), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 17.4 min, t_{minor} = 21.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{20}FO_3$ $[M+H]^+$ 327.1396, found 327.1413.



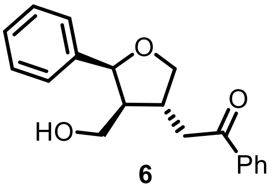
5p

(2R,3R,4R)-4-(2-(4-chlorophenyl)-2-oxoethyl)-2-phenyltetrahydro-2H-pyran-3-carbaldehyde (5p): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 97% yield (67.6 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.40 (d, *J* = 3.4 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.37-7.31 (m, 5H), 4.43 (d, *J* = 9.9 Hz, 1H), 4.14 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.69 (t, *J* = 12.1 Hz, 1H), 3.09 (dd, *J* = 15.9, 3.0 Hz, 1H), 2.74 (tdd, *J* = 20.7, 14.2, 10.9 Hz, 3H), 1.90 (d, *J* = 13.5 Hz, 1H), 1.59-1.52 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.7, 197.3, 140.0, 139.2, 135.1, 129.7, 129.2, 129.0, 128.9, 127.1, 80.5, 68.2, 61.1, 42.9, 31.9, 31.0. **FT-IR (thin film)** 3038, 2922, 2858, 1716, 1686, 1594, 1455, 1230, 1140, 758 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 11.0 min, t_{minor} = 13.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{19}ClNaO_3[M+Na]^+$ 365.0920, found 365.0946.



5q

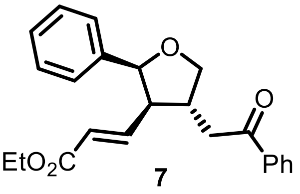
(2R,3R,4R)-4-(2-(4-bromophenyl)-2-oxoethyl)-2-phenyltetrahydro-2H-pyran-3-carbaldehyde (5q): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 92% yield (82.4 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 9.40 (d, *J* = 3.4 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.39-7.29 (m, 5H), 4.43 (d, *J* = 9.9 Hz, 1H), 4.16-4.10 (m, 1H), 3.69 (t, J = 11.1 Hz, 1H), 3.08 (dd, *J* = 15.9, 3.0 Hz, 1H), 2.82-2.67 (m, 3H), 1.89 (d, *J* = 15.2 Hz, 1H), 1.55 (ddd, *J* = 16.8, 12.8, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 202.7, 197.5, 139.2, 135.5, 132.1, 129.8, 129.0, 128.9, 128.7, 127.1, 80.5, 68.2, 61.0, 42.9, 31.9, 30.9. **FT-IR (thin film)** 3045, 2927, 2850, 1710, 1683, 1592, 1447, 1225, 1135, 778 cm^{-1}. **HPLC analysis**: >99% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 85:15), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 12.2 min, t_{minor} = 15.1 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{19}BrNaO_3$ $[M+Na]^+$ 409.0415, found 409.0406.



6

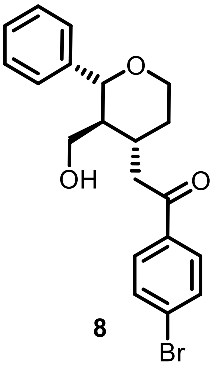
2-((3R,4S,5S)-4-(hydroxymethyl)-5-phenyltetrahydrofuran-3-yl)-1-phenylethanone (6): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; colourless sticky compound; 50% yield (14.8 mg). **^{1}H NMR (400 MHz, CDCl$_3$)**: δ 7.99 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 5H), 5.06 (d, *J* = 7.1 Hz, 1H), 4.56 (t, *J* = 8.4 Hz, 1H), 3.59 (t, *J* = 8.2 Hz, 1H), 3.41 (dd, *J* = 17.9, 6.8 Hz, 1H), 3.30 (d, J = 6.8 Hz, 2H), 3.18 (dd, J = 17.8, 7.1 Hz, 1H), 2.89 (dd, J = 12.7, 7.1 Hz, 1H), 2.42-2.33 (m, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 199.5, 138.9, 136.7, 133.6, 128.9, 128.7, 128.5, 128.2, 127.7, 126.1, 125.8, 81.8, 73.4, 62.9, 51.5, 42.6, 37.6. **FT-IR (thin film)** 3320, 2925, 2848, 1680, 1458, 1228, 1125, 1045, 770 cm^{-1}. **HPLC analysis**: 86% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 70:30), flow rate = 1.00

mL/min, 25 °C, λ = 254 nm (t_{major} = 8.9 min, t_{minor} = 8.0 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1491, found 297.1524.



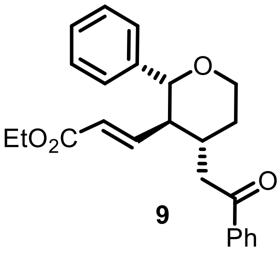
7

(E)-ethyl-3-((2S,3R,4R)-4-(2-oxo-2-phenylethyl)-2-phenyltetrahydrofuran-3-yl)acrylate (7): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 60% yield (21.8 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.96 (d, *J* = 7.2 Hz, 4H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.31-7.22 (m, 7H), 6.30 (dd, *J* = 15.5, 10.1 Hz, 2H), 5.80 (d, *J* = 15.5 Hz, 2H), 5.22 (d, *J* = 7.6 Hz, 2H), 4.76 (dd, *J* = 8.5, 7.6 Hz, 2H), 4.11 (dd, *J* = 9.5, 7.1 Hz, 4H), 3.66 (t, *J* = 8.6 Hz, 2H), 3.28 (dd, *J* = 17.4, 4.2 Hz, 2H), 3.01 (dt, *J* = 17.9, 8.9 Hz, 4H), 2.91-2.83 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 198.3, 165.8, 146.7, 139.2, 136.7, 133.6, 128.9, 128.4, 128.2, 127.7, 126.4, 123.4, 83.1, 74.3, 60.4, 53.3, 40.9, 39.9, 14.3. **FT-IR (thin film)** 2922, 2851, 1714, 1679, 1647, 1450, 1226, 1110, 1038, 758 cm^{-1}. **HPLC analysis**: 92% ee; Determined using a Daicel Chiralpak ID column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 254 nm (t_{major} = 41.0 min, t_{minor} = 31.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{23}H_{25}O_4$ $[M+H]^+$ 365.1753, found 365.1752.



8

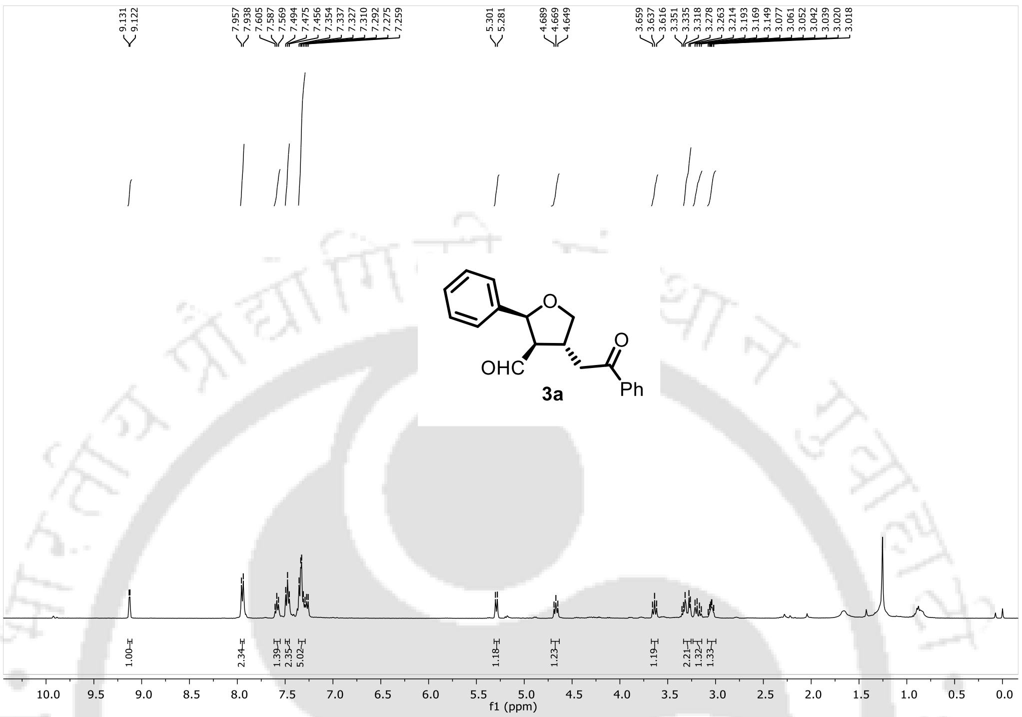
1-(4-bromophenyl)-2-((2R,3S,4R)-3-(hydroxymethyl)-2-phenyltetrahydro-2H-pyran-4-yl)ethanone (8): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; colourless oil; 40% yield (15.6 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 4.3 Hz, 3H), 7.33-7.29 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.92 (t, *J* = 5.4 Hz, 1H), 4.26 (d, *J* = 10.1 Hz, 1H), 3.99 (dd, *J* = 11.4, 4.1 Hz, 1H), 3.68 (d, *J* = 11.7 Hz, 1H), 3.47 (t, *J* = 12.0 Hz, 1H), 3.23 (d, *J* = 11.9 Hz, 1H), 1.79-1.72 (m, 2H), 1.62 (dd, *J* = 12.4, 3.4 Hz, 2H), 1.54 (t, *J* = 10.6 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 199.5, 138.9, 136.7, 133.7, 128.9, 128.6, 128.2, 127.7, 126.1, 125.8, 81.9, 73.4, 63.0, 51.6, 42.6, 37.6, 32.1. **FT-IR (thin film)** 3330, 2920, 2856, 1686, 1448, 1235, 1130, 1058, 780 cm^{-1}. **HPLC analysis**: 98% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 70:30), flow rate = 1.00 mL/min, 25 °C, λ = 220 nm (t_{major} = 8.9 min, t_{minor} = 10.5 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{20}H_{22}BrO_3$ [M+H]$^+$ 389.0747, found 389.0712.

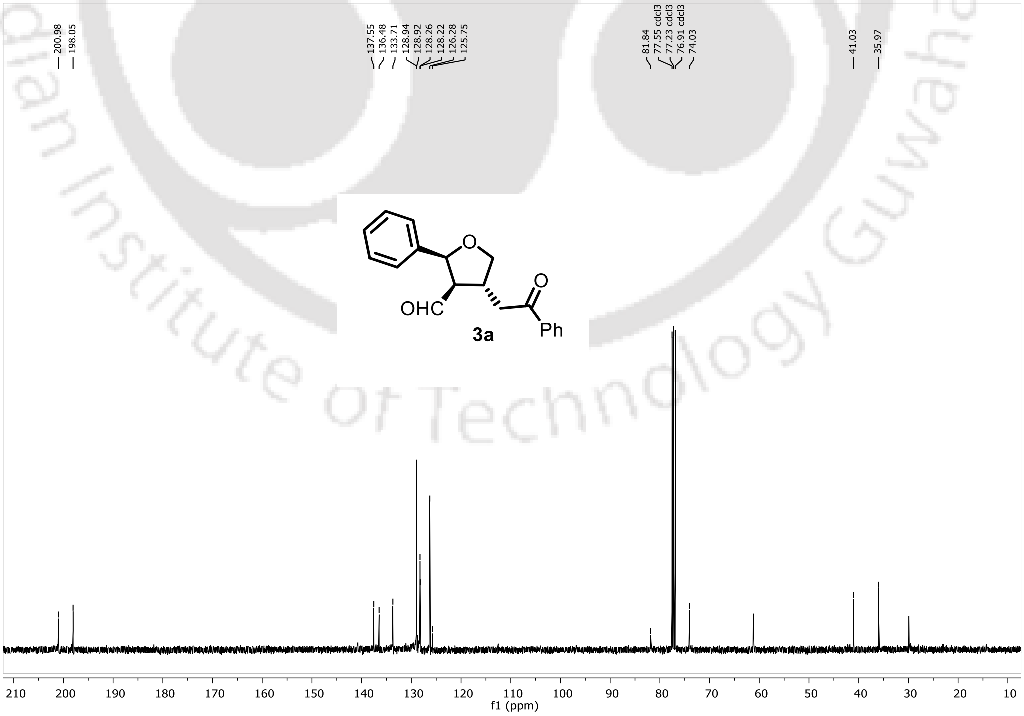


9

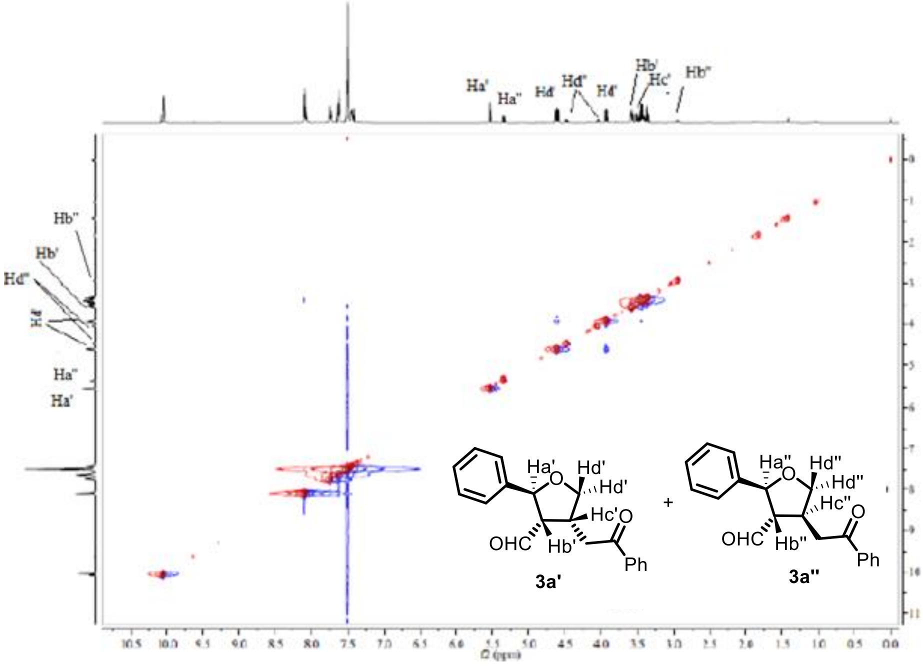
(E)-ethyl 3-((2R,3S,4R)-4-(2-oxo-2-phenylethyl)-2-phenyltetrahydro-2H-pyran-3-yl)acrylate (9): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; colourless sticky solid; 75% yield (23.3 mg). **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.94 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.35-7.25 (m, 6H), 6.60 (dd, *J* = 15.7, 10.1 Hz, 1H), 5.49 (d, *J* = 15.7 Hz, 1H), 4.26 (d, *J* = 9.6 Hz, 1H), 4.16 (dd, *J* = 11.0, 3.8 Hz, 1H), 4.11-4.04 (m, 2H), 3.74 (t, *J* = 12.0 Hz, 1H), 3.09 (dd, *J* = 16.8, 3.3 Hz, 1H), 2.82 (dd, *J* = 16.8, 9.3 Hz, 1H), 2.50 (dd, *J* = 20.6, 11.1 Hz, 1H), 2.38 (dd, *J* = 20.3, 10.2 Hz, 1H), 1.95 (d, *J* = 13.4 Hz, 1H), 1.57 (ddd, *J* = 25.3, 12.5, 4.6 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)**: δ 199.0, 165.7, 146.6, 140.4, 137.2, 133.4, 128.8, 128.5, 128.2, 128.2, 127.2, 124.9, 83.6, 68.3, 60.4, 52.5, 43.0, 36.0, 14.3. **FT-IR (thin film)** 2928, 2847, 1710, 1675, 1657, 1456, 1220, 1116, 1028, 765 cm^{-1}. **HPLC analysis**: 96% ee; Determined using a Daicel Chiralpak IA column (hexane/2-propanol = 90:10), flow rate = 1.00 mL/min, 25 °C, λ = 220 nm (t_{major} = 9.8 min, t_{minor} = 13.0 min). **HRMS (+ESI-TOF)** *m/z*: calcd. for $C_{24}H_{27}O_4$ [M+H]$^+$ 379.1909, found 379.1915.

2.8 Selected NMR and HPLC spectra of products

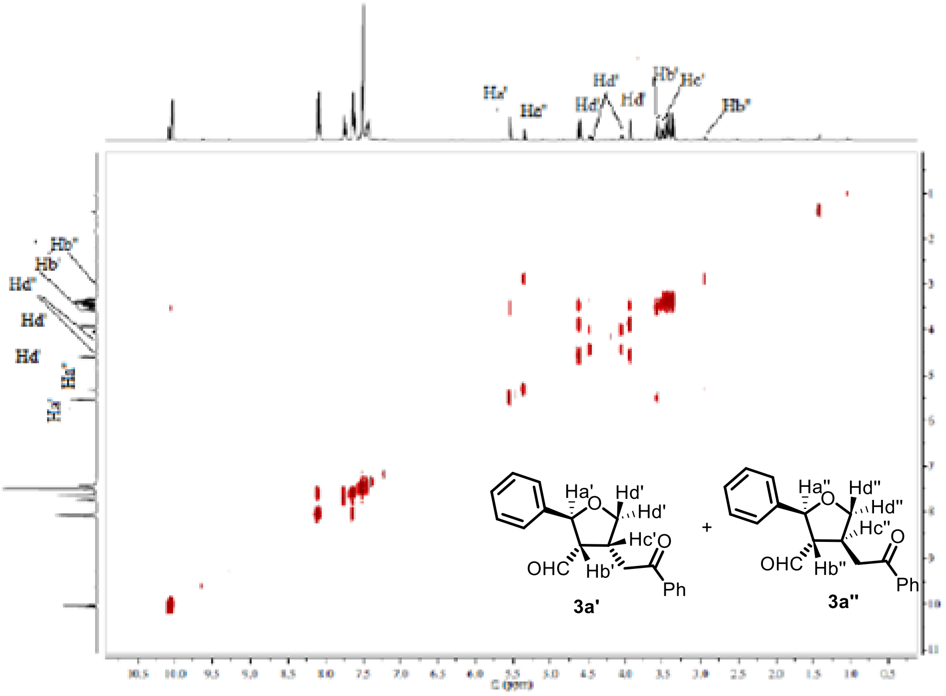




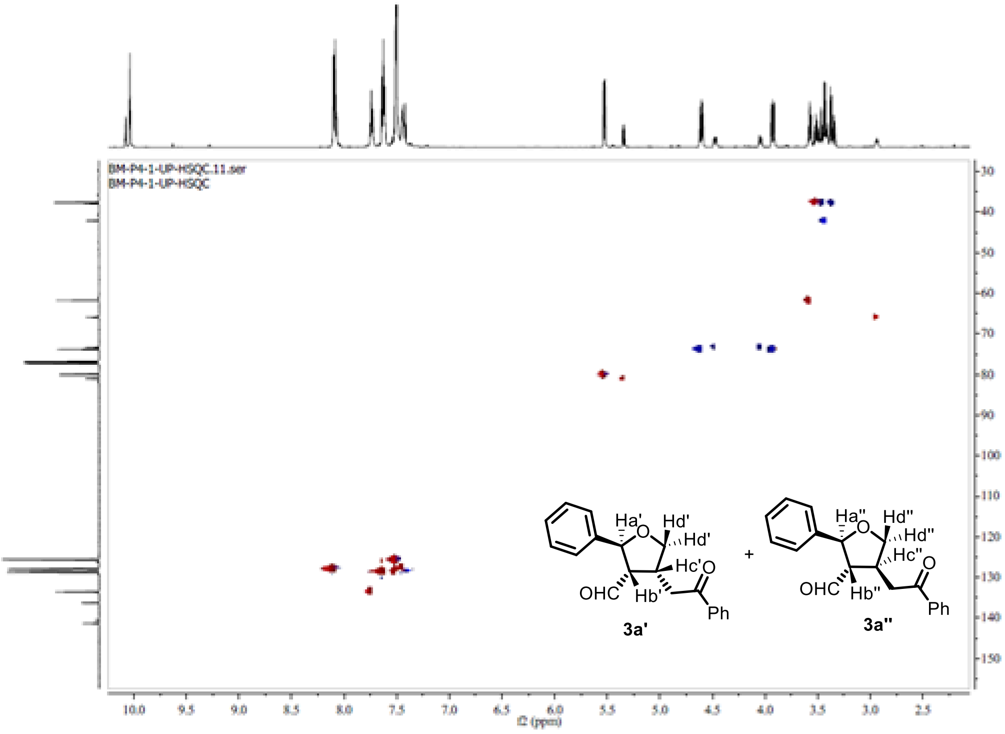
NOESY spectra of compound **3a'+3a"**



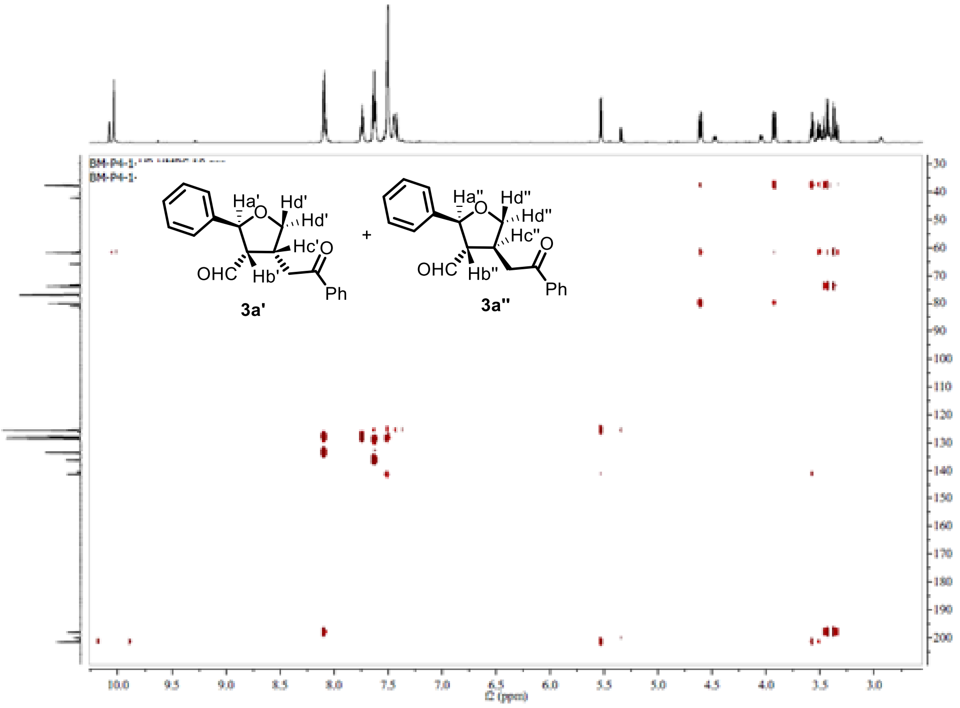
COSY spectra of compound **3a'+3a"**

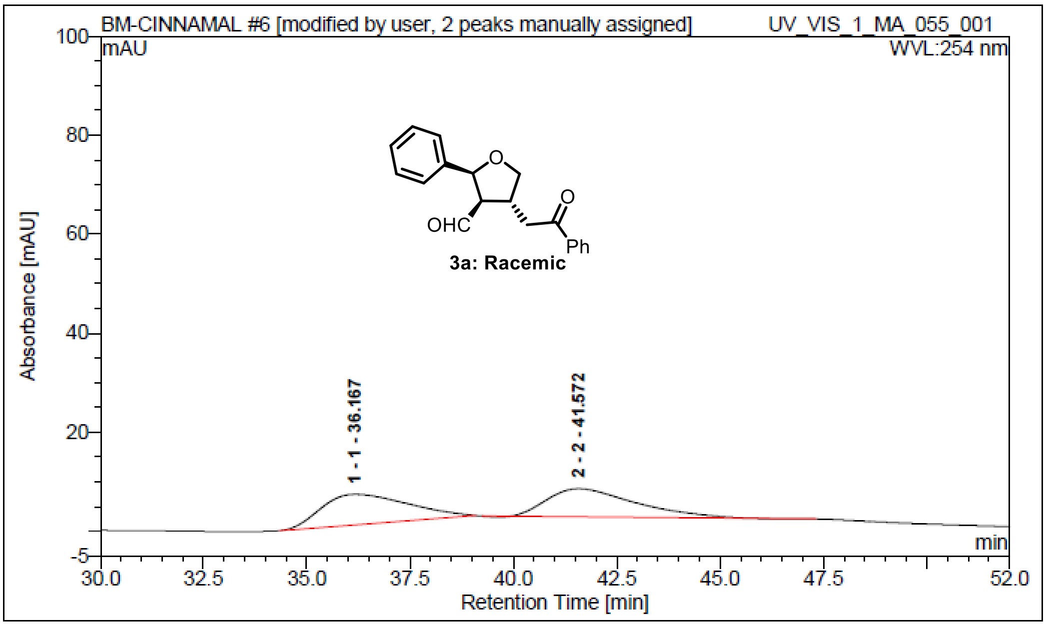


HSQC spectra of compound **3a'+3a"**

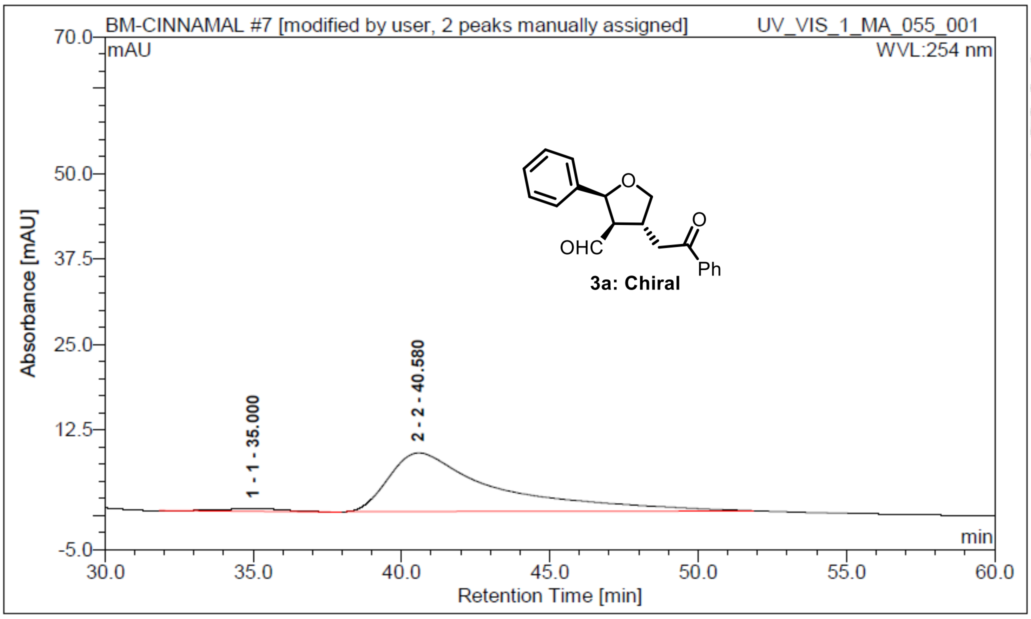


HMBC spectra of compound **3a'+3a"**

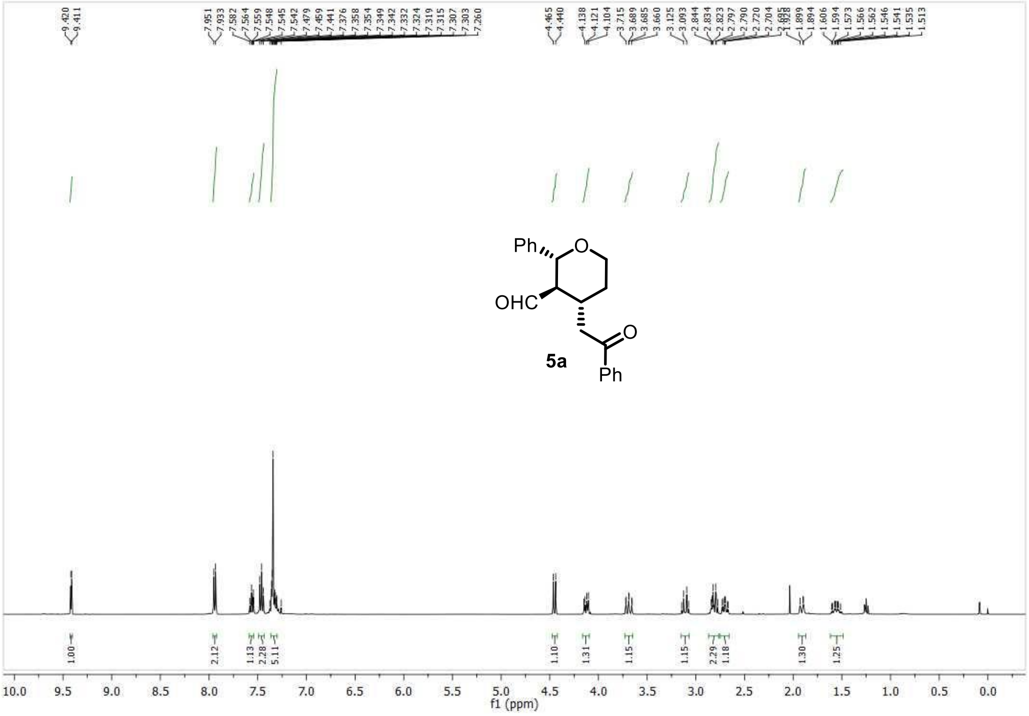




No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	36.17	14.89133	51.17779502	6.17613	n.a.
2	2	41.57	14.206	48.82220498	5.677	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	35.00	1.169473	3.170653919	0.43642	n.a.
2	2	40.58	35.715	96.82934608	8.581	n.a.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7.582
7.564
7.559
7.548
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7.307
7.303
7.260
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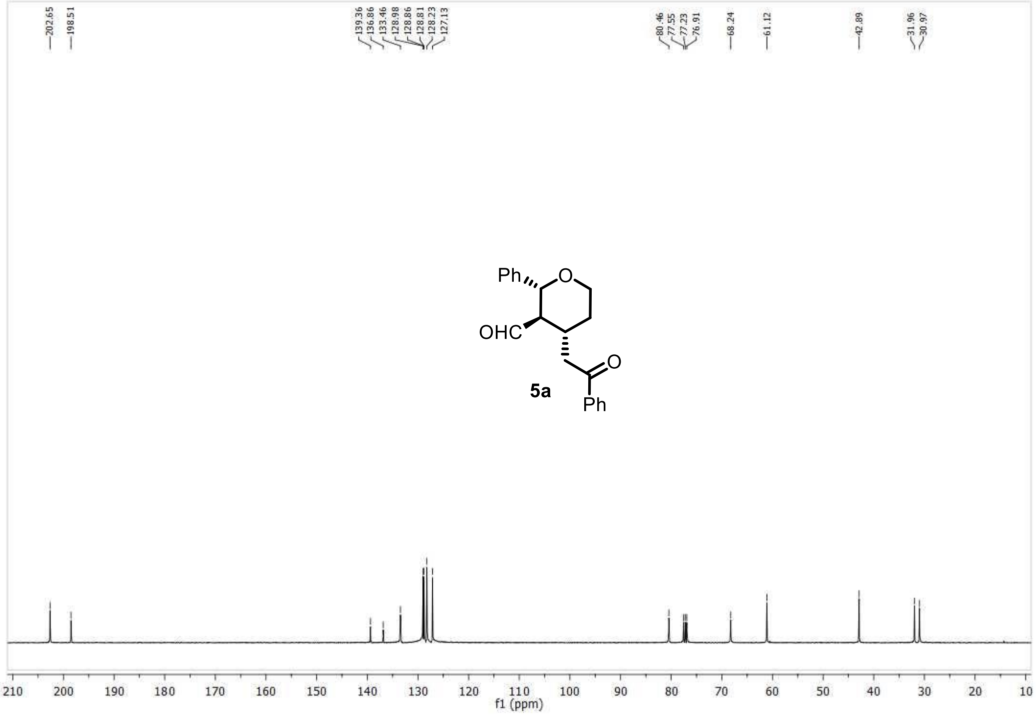
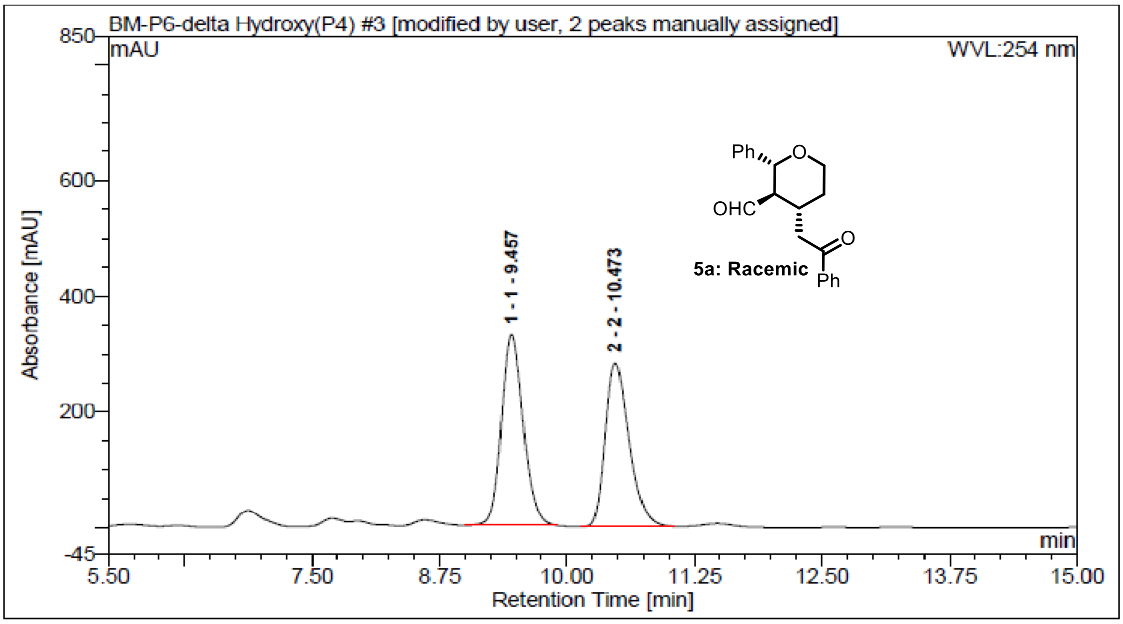
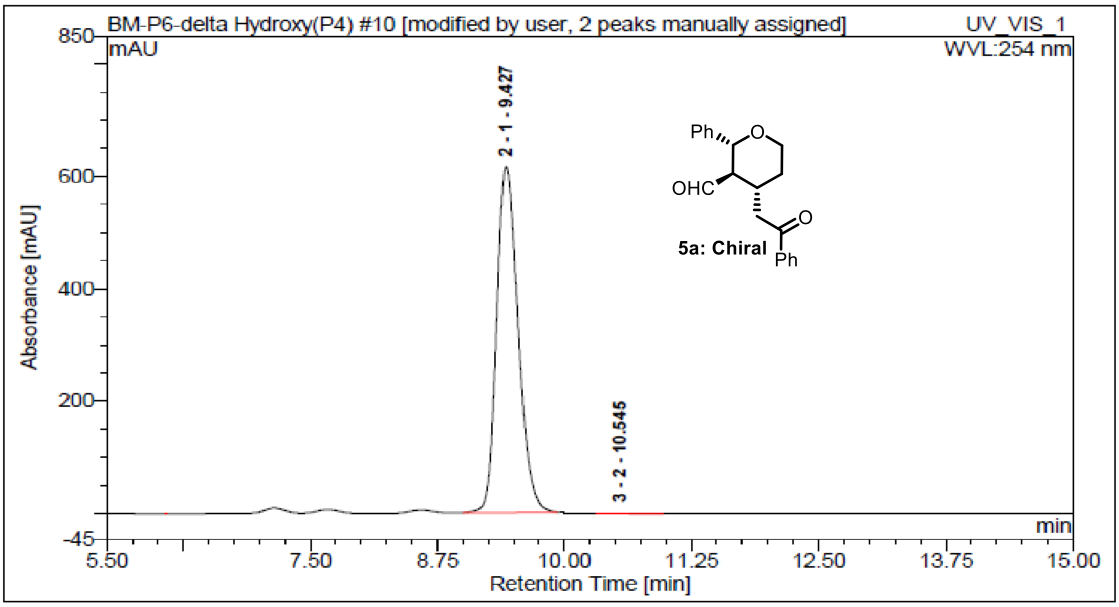
4.138
4.121
4.104
3.715
3.689
3.685
3.660
3.125
3.093
2.844
2.834
2.823
2.797
2.790
2.720
2.704
2.695
1.928
1.899
1.894
1.606
1.594
1.573
1.566
1.562
1.546
1.541
1.535
1.513
Ph
O
OHC
O
5a
Ph
1.00
2.12
1.13
2.28
5.11
1.10
1.31
1.15
1.15
2.29
1.18
1.30
1.25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


202.65
198.51
139.36
136.86
133.46
128.98
128.86
128.81
128.23
127.13
80.46
77.55
77.23
76.91
68.24
61.12
42.89
31.96
30.97
Ph
O
OHC
O
5a
Ph
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	9.46	82.08235	51.72694528	329.2854	n.a.
2	2	10.47	76.602	48.27305472	282.333	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
2	1	9.43	150.5204	99.85913425	614.6259	n.a.
3	2	10.55	0.212	0.1408657464	0.745	n.a.

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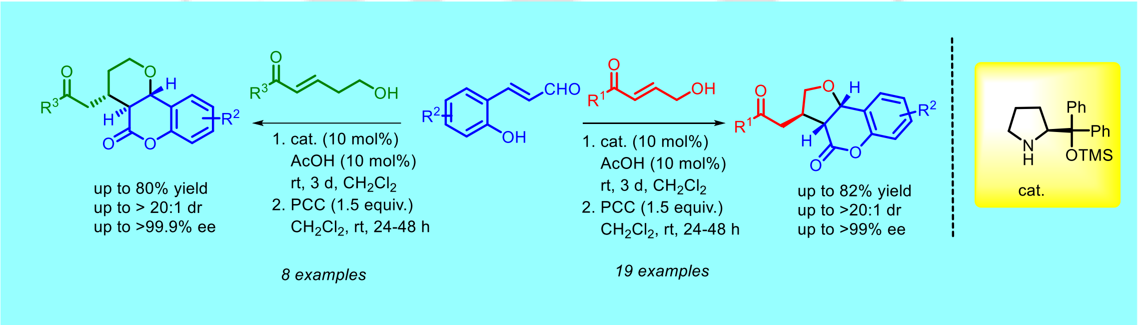
26. CCDC 1531840 (**3k**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request /cif.
27. CCDC 1531841 (**5i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.

Chapter 3

Organocatalytic Asymmetric Cascade Reaction between o-Hydroxycinnamaldehydes and γ/δ-Hydroxyenones: A Route to Tetrahydrofuran/Tetrahydropyran-Fused 3,4-Dihydrocoumarins



Adv. Synth. Catal. **2018**, *360*, 4348-4353.

3.1 Introduction

Dihydrocoumarins, chromans and chromenes are important classes of benzopyran derivatives which are very important structural motifs and exist in a number of natural products and pharmaceuticals. Compounds incorporating chiral dihydrocoumarin core structure have been found to exhibit a wide spectrum of biological activity, such as antioxidation, antitumor, and anti-inflammatory properties. Representative examples include Calomelanol A, Herbertenolide, Ammodoremin, Aloe dihydrocoumarin and Cinchonain Ib (Figure 1).[1]

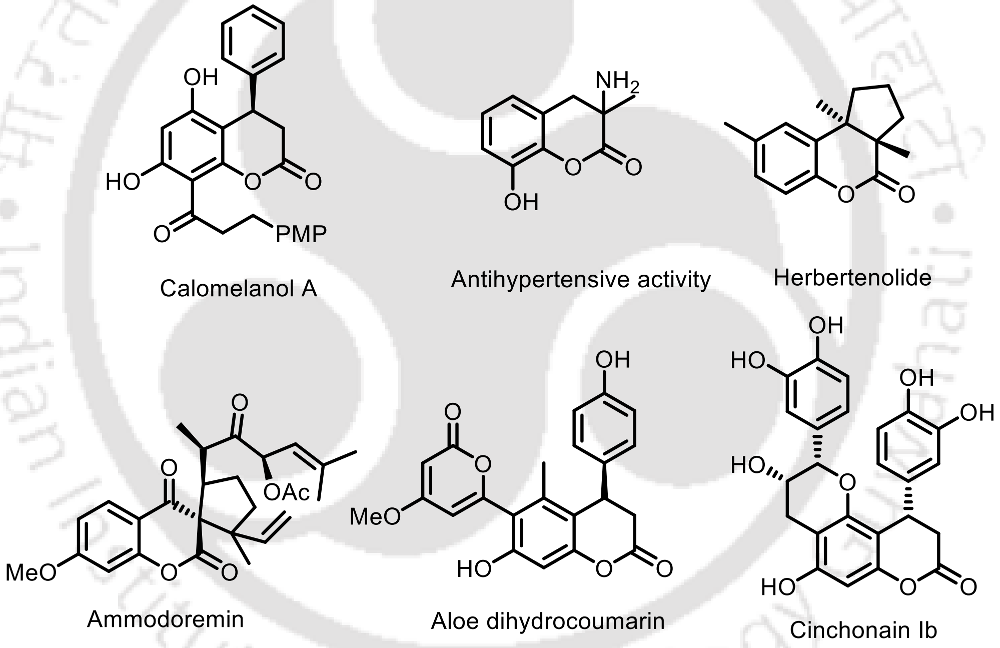


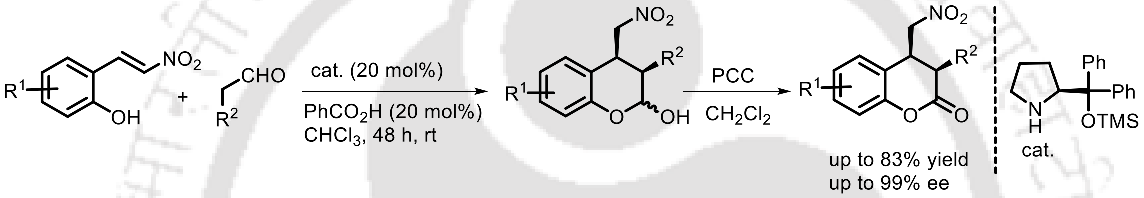
Figure 1. Biologically active dihydrocoumarins, chromans, and chromene derivatives.

Due to the importance of benzopyran framework, it has received considerable attention. As a consequence, a variety of approaches were developed such as cyclization of diols,[2] Friedel-Crafts reactions,[3] cycloadditions,[4] ring-closing metathesis (RCM)[5] and domino reactions.[6] Chiral benzopyran represents a powerful structural motif that is ubiquitous in a range of natural products and drug candidates with broad biological implications. Thus, it is crucial to develop asymmetric strategies to construct optically active dihydrocoumarins, chromans and chromenes.[7]

3.2 Known strategies for the synthesis of chiral dihydrocoumarins, chromanes, and 4H-chromenes

3.2.1 Synthesis of chiral dihydrocoumarins, chromones, and 4H-chromenes

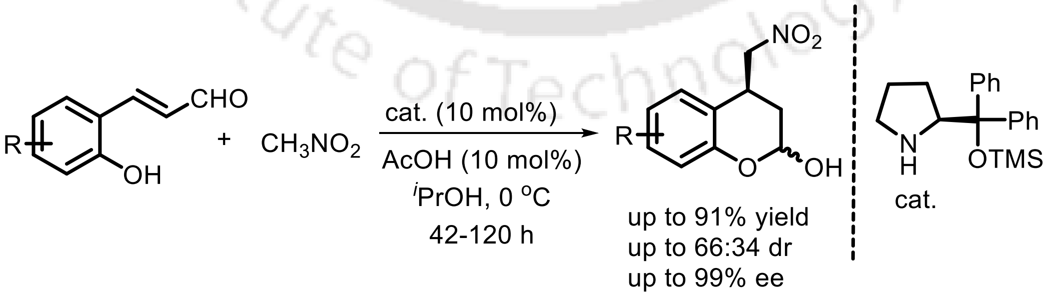
In 2010, Gong et al. reported organocatalytic asymmetric tandem Michael addition-hemiacetalization for an efficient synthesis of chiral dihydrocoumarins, chromones, and 4H-chromenes using prolinol derived catalyst with high yields and enatioselectivities (Scheme 1).[8]



Scheme 1. Organocatalytic asymmetric tandem Michael addition-hemiacetalization by Gong et al.

3.2.2 Organocatalytic asymmetric synthesis of 4-substituted chroman-2-ols

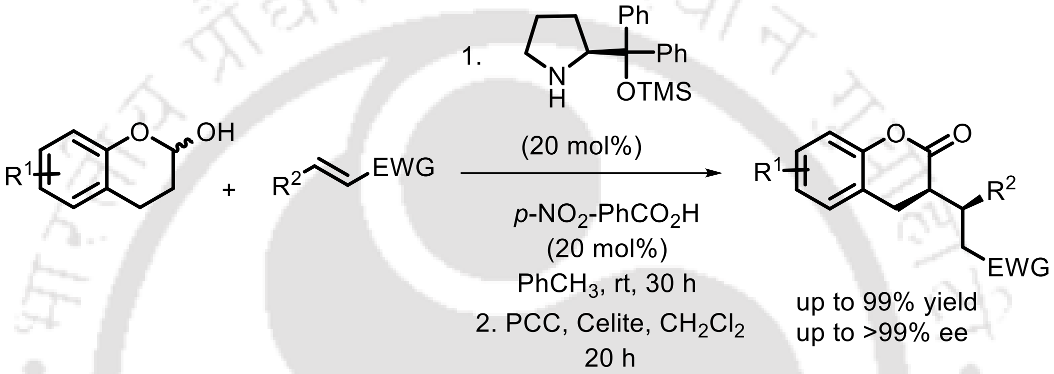
Kim and co-workers reported asymmetric organocatalytic Michael addition-cyclization cascade reaction of nitroalkanes with *o*-hydroxycinnamaldehydes using prolinol derived catalyst. This protocol allowed efficient synthesis of 4-substituted chroman-2-ols with high yields and with moderate diastereo- and excellent enantioselectivities (Scheme 2).[9]



Scheme 2. Asymmetric organocatalytic Michael addition-cyclization cascade reaction by Kim et al.

3.2.3 *α*-Functionalization of lactone *via* enamine catalysis under mild conditions

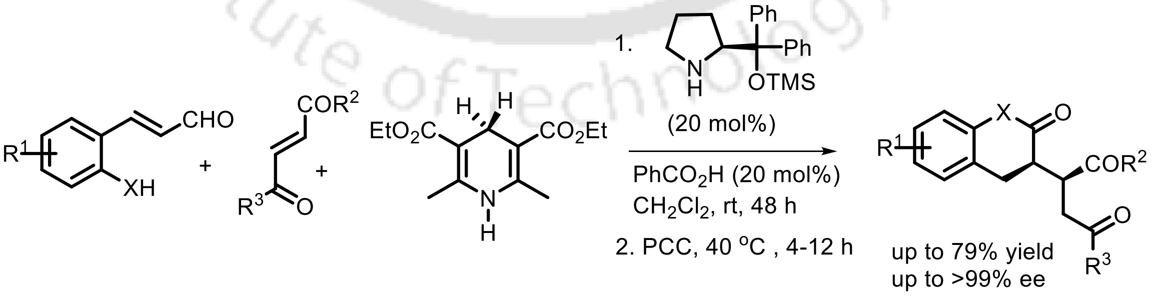
Liu and co-workers have reported an efficient one-pot method for the *α*-functionalization of lactone *via* enamine catalysis under mild conditions. By using 20 mol% of prolinol catalyst, this reaction delivered *α*-functionalized chroman-2-ones in near quantitative yields with outstanding enatioselectivities (Scheme 3).[10]



Scheme 3. An efficient one-pot method for *α*-functionalization of lactone by Liu et al.

3.2.4 Substrate-controlled synthesis of chiral chroman-2-one and polycyclic derivatives

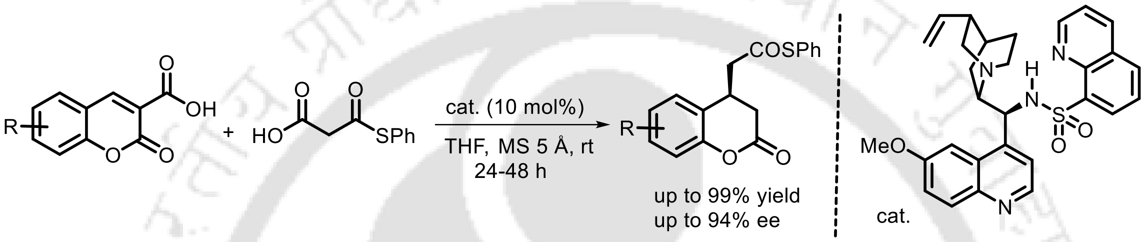
Recently, the same group developed substrate-controlled, one-pot synthesis of chiral chroman-2-one and polycyclic derivatives obtained in good yields with excellent enantioselectivities using prolinol derived catalyst (Scheme 4).[11]



Scheme 4. Substrate-controlled synthesis of chiral chroman-2-one and polycyclic derivatives by Liu et al.

3.2.5 The efficient synthesis of 4-substituted 3,4-dihydrocoumarin

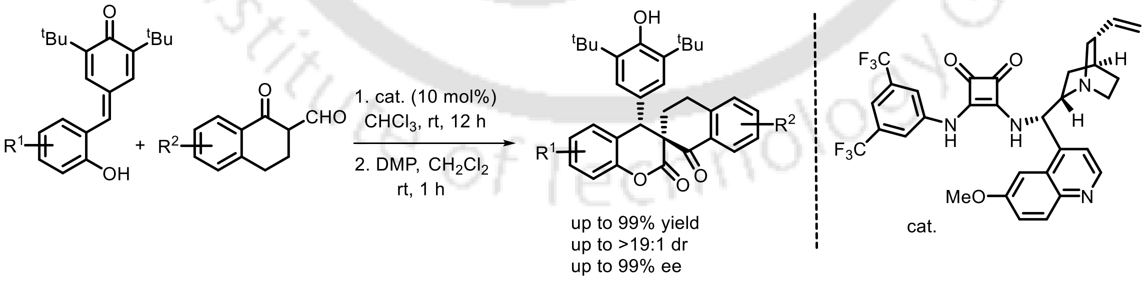
N-heteroarenesulfonyl cinchona alkaloid amides have recently been utilized by Nakamura and co-workers for the synthesis of 4-substituted 3,4-dihydrocoumarins in high yields and enantioselectivities. This reaction involved conjugate addition of malonic acid half thioesters to coumarin-3-carboxylic acids (Scheme 5).[12]



Scheme 5. Synthesis of 4-substituted 3,4-dihydrocoumarins by Nakamura et al.

3.2.6 Organocatalytic synthesis of spiro-3,4-dihydrocoumarins

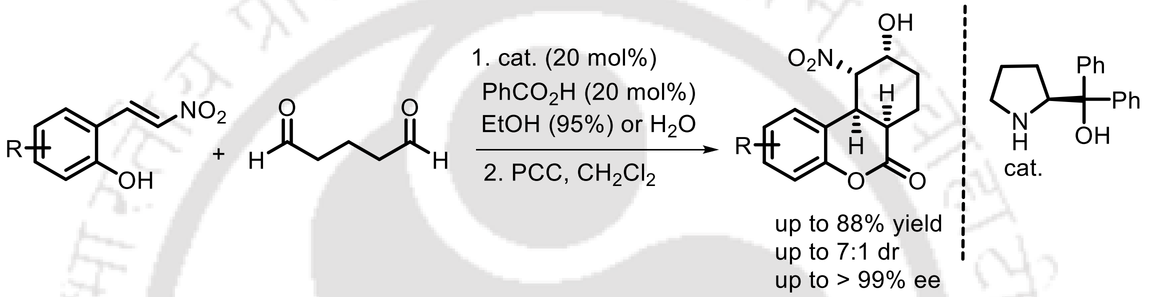
Very recently Li group developed an organocatalytic asymmetric sequential 1,6 addition/acetalization of 1-oxotetralin-2-carbaldehyde to *ortho*-hydroxyphenyl-substituted *para*-quinone methides for the synthesis of spiro-3,4-dihydrocoumarins with excellent yields as well as excellent diastero- and enantioselectivities using bifunctional squaramide catalyst (Scheme 6).[13]



Scheme 6. 1,6 Addition/acetalization of 1-oxotetralin-2-carbaldehyde to *ortho*-hydroxyphenyl-substituted *para*-quinone methides by Li et al.

3.2.7 Enantioselective synthesis of tetrahydro-6H-benzo[c]chromenones

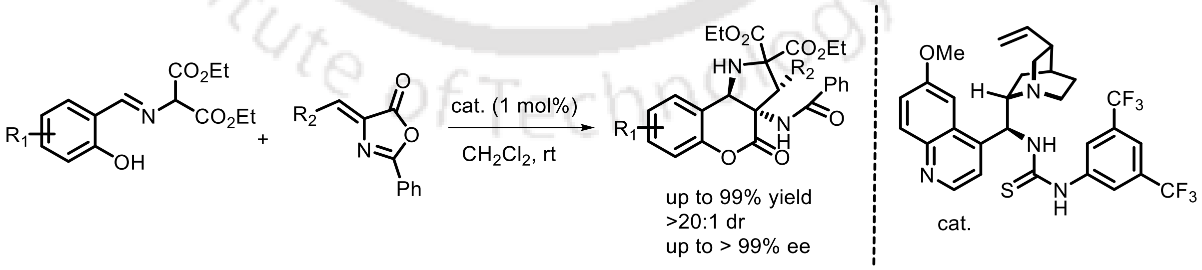
In 2010, Hong and co-workers demonstrated an enantioselective organocatalytic domino Michael-acetalization-Henry reaction between hydroxynitrostyrenes and pentanedial for the synthesis of tetrahydro-6H-benzo[c]chromenones in high yields, moderate diastereoselectivities as well as excellent enatioselectivities using prolinol derived catalyst (Scheme 7).[14]



Scheme 7. Enantioselective organocatalytic domino Michael–acetalization–Henry reaction of 2-hydroxynitrostyrene and pentanedial by Hong et al.

3.2.8 Enantioselective the synthesis of polysubstituted chromeno[4,3-b]pyrrolidine derivatives

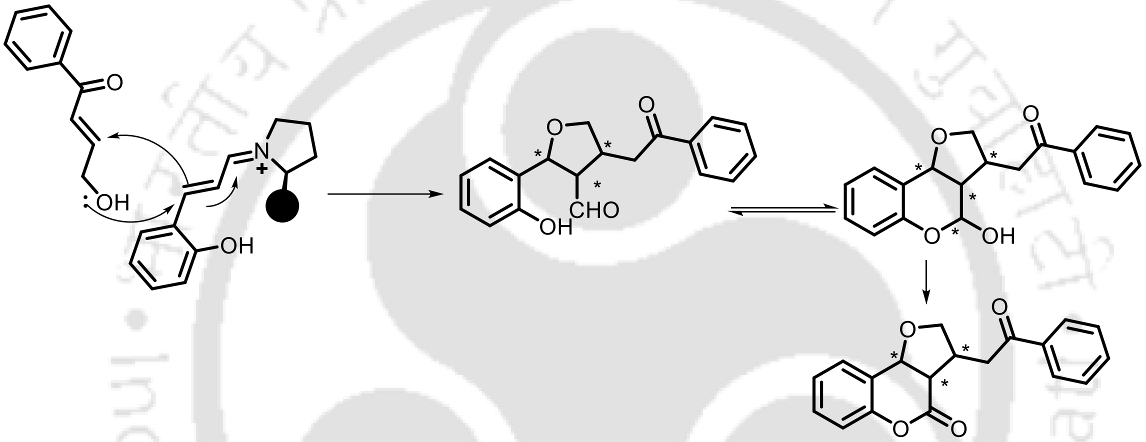
In 2014, a powerful cascade reaction was developed by Xu group for the synthesis of chromeno[4,3-*b*]pyrrolidines with high yields and excellent stereoselectivities (Scheme 8).[15]



Scheme 8. Enantioselective synthesis of polysubstituted chromeno[4,3-b]pyrrolidines by Xu et al.

3.3 Concept

Based on the previously reported literature survey, we examined that the synthesis of tetrahydrofuran/tetrahydropyran-fused 3,4-dihydrocoumarins is still not reported. Realizing the synthetic potential of chiral dihydrocoumarin moieties in natural compounds, we became interested to synthesize via catalytic asymmetric oxa-Michael strategy. Thus the reaction between *γ*/*δ*-hydroxyenone and 2-hydroxycinnamaldehyde was studied and it has been reported in this chapter (Scheme 9).



Scheme 9. Catalytic asymmetric oxa-Michael strategy: Reaction between *γ*/*δ*-hydroxyenones and 2-hydroxycinnamaldehyde.

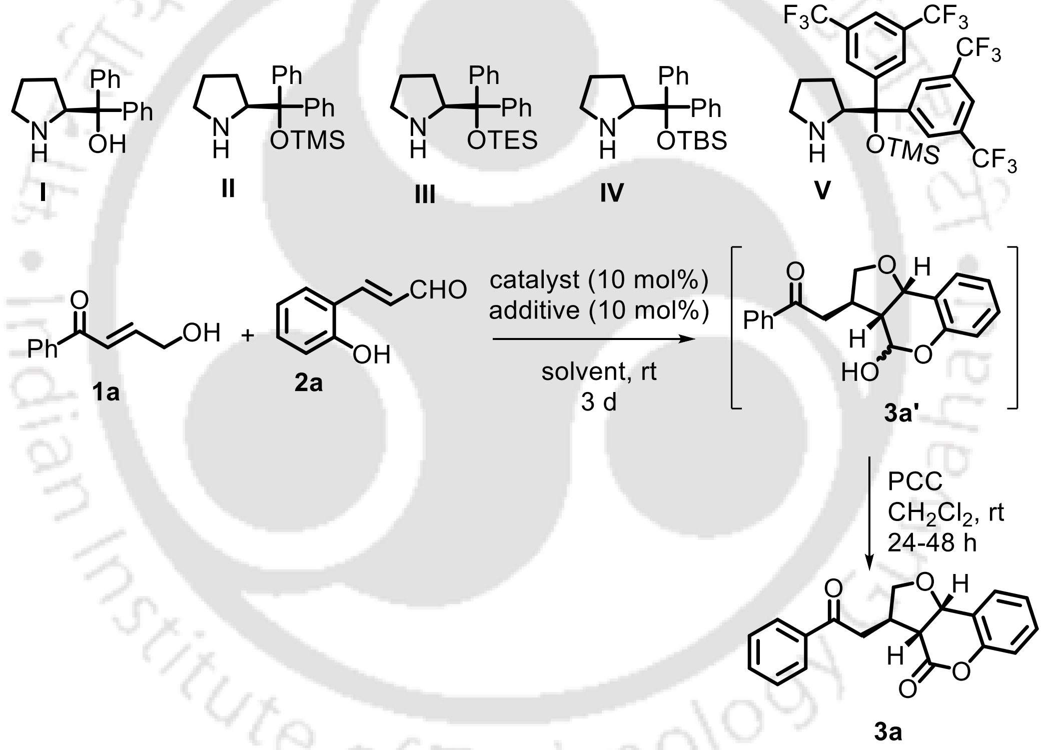
3.4 Results and discussion

3.4.1 Optimization of catalyst and reaction conditions

We started our investigation by performing a model reaction between 3-benzoyl prop-2-en-1-ol (**1a**)[16] and *o*-hydroxy cinnamaldehyde (**2a**)[17] in the presence of catalyst **I** and benzoic acid in toluene at room temperature. Gratifyingly, after stirring for 3 days, the desired cascade reaction occurred to provide a hemiacetal **3a'** which was oxidized to dihydrocoumarin **3a** by pyridinium chlorochromate (Table 1). Though the diastereomeric ratio of **3a** was excellent (>20:1 dr), the enantiomeric excess was 65% (Table 1, entry 1).

In the presence of Jørgensen-Hayashi catalyst **II**,[18] the desired product **3a** was obtained in 60% yield, >20:1 diastereoselectivity and 80% ee. To improve the enantiomeric excess, other silyl ether catalysts **III** and **IV** were screened but they failed to enhance the enantioselectivity (Table 1, entries 3-4). Then catalyst **V** having bis trifluoromethyl aryl group was employed, surprisingly however poor conversion was detected (entry 5).

Table 1. Catalyst screening and optimization of reaction conditions



entry[a]	catalyst	additive	solvent	yield(%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCO_2H$	$PhCH_3$	50	>20:1	65
2	**II**	$PhCO_2H$	$PhCH_3$	60	>20:1	80
3	**III**	$PhCO_2H$	$PhCH_3$	54	>20:1	76

4	**IV**	$PhCO_2H$	$PhCH_3$	48	>20:1	66
5	**V**	$PhCO_2H$	$PhCH_3$	-	-	-
6	**II**	$PhCO_2H$	CH_2Cl_2	72	>20:1	92
7	**II**	$PhCO_2H$	$CHCl_3$	67	>20:1	90
8	**II**	$PhCO_2H$	$(CH_2Cl)_2$	65	>20:1	80
9	**II**	$3\text{-}NO_2\text{-}PhCO_2H$	CH_2Cl_2	70	>20:1	94
10	**II**	$2\text{-}OH\text{-}PhCO_2H$	CH_2Cl_2	73	>20:1	94
11	**II**	**CH_3CO_2H**	**CH_2Cl_2**	**80**	**>20:1**	**98**

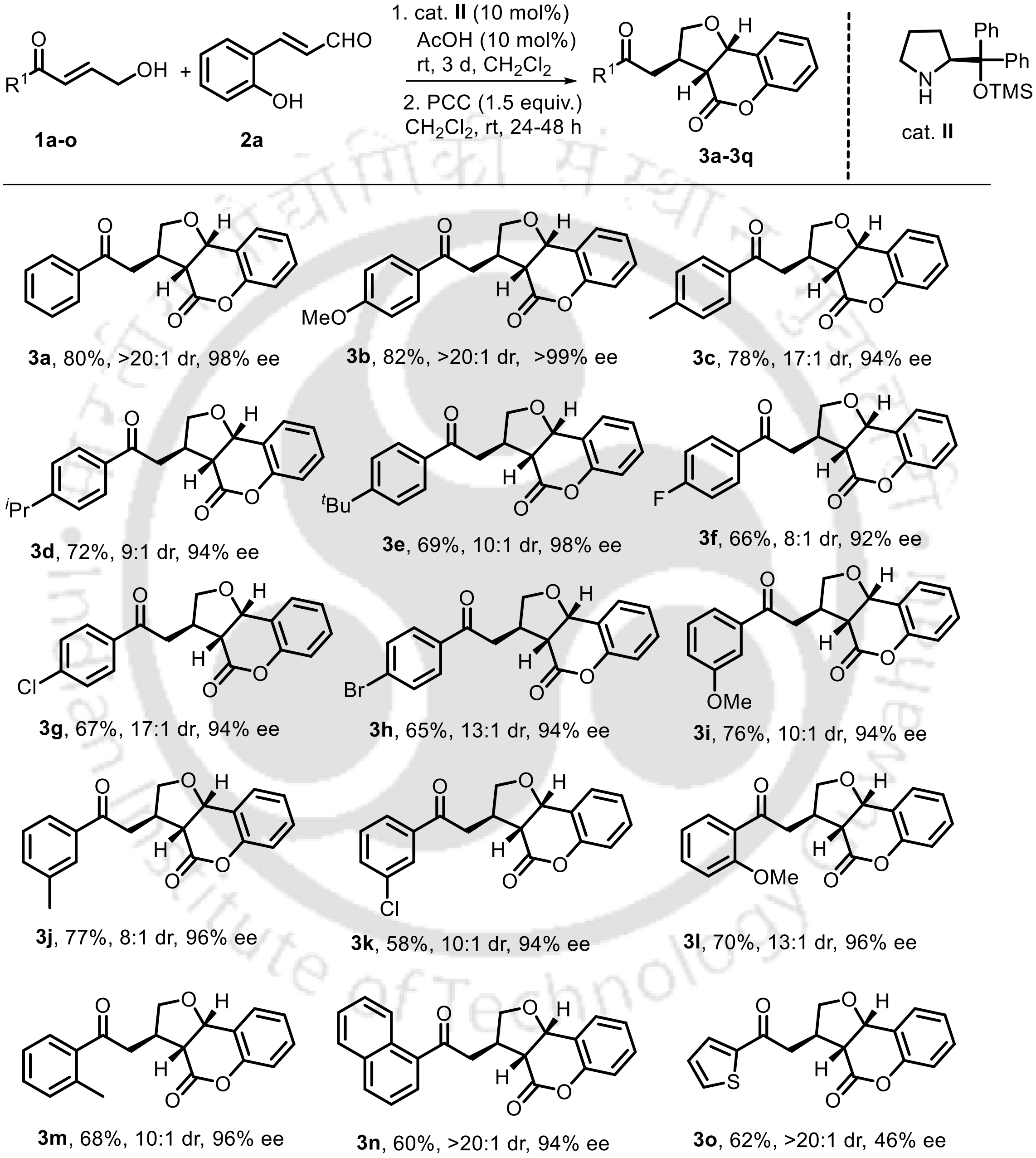
[a]Unless otherwise mentioned, reactions were carried out with 0.1 mmol of **1a** with 0.1 mmol of **2a** in 0.4 mL of solvent. [b]Isolated yield by two steps after silica gel column chromatography. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC.

After having the optimum catalyst **II** in hand, we focused on other reaction parameters. We checked different solvents in this reaction (Table 1, entries 6-8). Product **3a** was obtained with 72% yield and 92% enantioselectivity in CH_2Cl_2 solvent (Table 1, entry 6). Other halogenated solvents such as $CHCl_3$ and $(CH_2Cl)_2$ were also checked, but the yield and enantioselectivity of product **3a** got decreased (Table1, entries 7-8). We next turned our attention to investigate acid additives (Table 1, entries 9-11). Substituted benzoic acids such as 3-nitrobenzoic acid and 2-hydroxybenzoic acid provided the product **3a** in slightly higher enantioselectivities (Table 1, entries 9-10). Surprisingly, when acetic acid was used as an additive, the enantioselectivity got increased to 98% and yield to 80% however the diastereoselectivity remained same (>20:1).

3.4.2 Substrate scope

After establishment of the optimized conditions, the substrate scope of the reaction was studied. Initially, differently *γ*-hydroxyenones were investigated and it turned out that electron neutral, electron poor as well as electron rich substituents were tolerated in the

Scheme 10. Scope of γ-hydroxyenones[a]



3a, 80%, >20:1 dr, 98% ee

3b, 82%, >20:1 dr, >99% ee

3c, 78%, 17:1 dr, 94% ee

3d, 72%, 9:1 dr, 94% ee

3e, 69%, 10:1 dr, 98% ee

3f, 66%, 8:1 dr, 92% ee

3g, 67%, 17:1 dr, 94% ee

3h, 65%, 13:1 dr, 94% ee

3i, 76%, 10:1 dr, 94% ee

3j, 77%, 8:1 dr, 96% ee

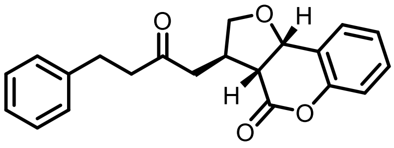
3k, 58%, 10:1 dr, 94% ee

3l, 70%, 13:1 dr, 96% ee

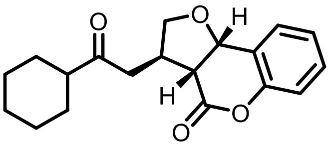
3m, 68%, 10:1 dr, 96% ee

3n, 60%, >20:1 dr, 94% ee

3o, 62%, >20:1 dr, 46% ee



3p, 0%



3q, 0%

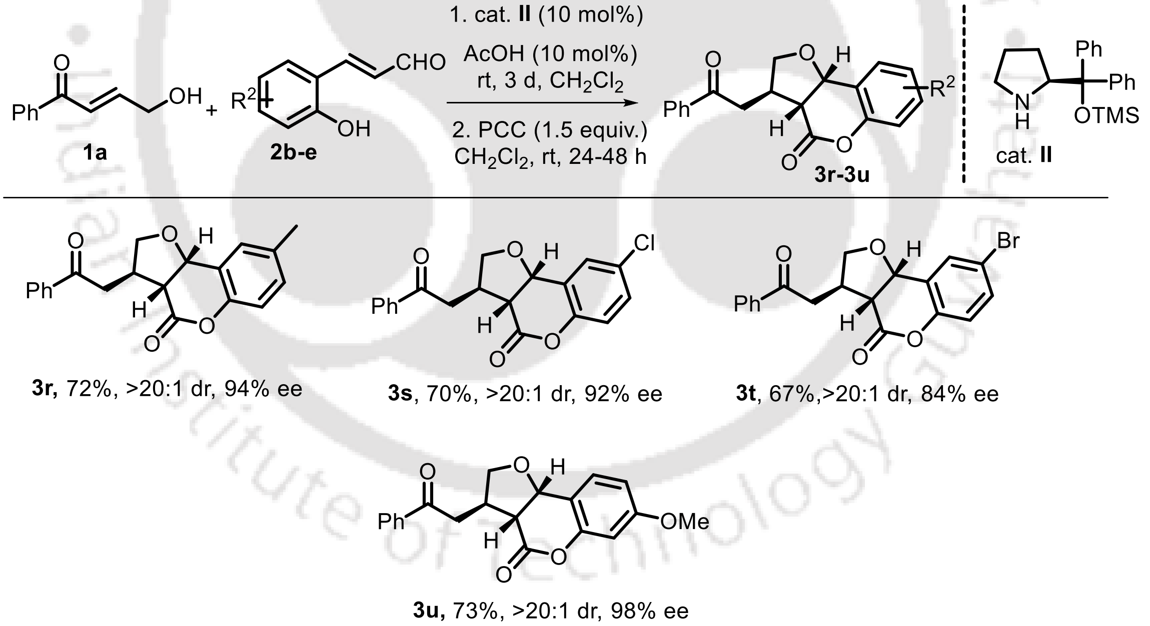
[a] Reaction condition: 0.2 mmol of **1** with 0.2 mmol of **2a** in 0.8 mL CH_2Cl_2. Isolated combined yield by two steps after silica gel column chromatography. The diastereomeric ratio was determined by ^1H NMR. Enantiomeric excess was determined by chiral HPLC analysis.

reaction (Scheme 10). At the beginning, different *para*-substituted phenyl group containing *γ*-hydroxyenones were employed and excellent results were achieved. For example, enones **1b**-**1e** having electron donating groups delivered products **3b**-**3e** in good yields and with good to excellent diastereoselectivities, as well as with excellent enantioselectivities. In particular high enantioselectivity (>99% ee) was achieved for product **3b**. Then, enones **1f**-**1h** having 4-halosubstituted aryl groups were subjected to the reaction conditions. To our delight, the desired products **3e**-**3g** were isolated in acceptable yields after 3 days and excellent enantiomeric excesses and with moderate to excellent diastereoselectivities were detected (Scheme 10). Then different *meta*-substituted aryl enones were screened under the reaction conditions. Interestingly, smooth conversions were observed for 3-methyl (**1i**) and 3-methoxy (**1j**) substituted enones delivering products **3h** and **3i** with high enantioselectivities. Interestingly, slightly less conversion was observed with 3-chloro substituted enone **1k**. The reaction outcome also did not change much with *ortho*-substituted aryl enone **1l**-**1m** and the corresponding products **3l**-**3m** were obtained with excellent enantiomeric excesses and with good diastereoselectivities. 1-Naphthyl group containing enone **1n** underwent the reaction smoothly delivering product **3n** in 94% ee and >20:1 dr. Finally, thiophene containing enone **1o** was engaged in the reaction; though the diastereomeric excess of the product **3o** was excellent, only moderate enantioselectivity was observed. Unfortunately no reaction took place with aliphatic *γ*-hydroxy enone **1p** and also with **1q**.

The next stage of experiments involved screening of different substituted (*E*)-3-(2-hydroxyphenyl)acrylaldehyde in this method (Scheme 11). Thus different substituted

(*E*)-3-(2-hydroxyphenyl)acrylaldehyde **2b-2e** were prepared and employed in the reaction with *γ*-hydroxyenone **1a**. The reaction progressed smoothly by delivering the corresponding products **3p-3s** in good yields and with excellent diastereoselectivities as well as with high enantioselectivities. For example, 5-substituted 2-hydroxy acrylaldehydes **2b**, **2c** and **2d** having 4-bromo, 4-chloro and 4-methyl substituents furnished products **3p**, **3q** and **3r** respectively with acceptable yields, high diastereoselectivities (>20:1 dr.); and also excellent enantiomeric excesses was achieved for all of the cases. In addition, 4-methoxy substituted 2-hydroxy acrylaldehyde **2e** delivered product **3s** with 73% yield and >20:1 dr and with 98% enantiomeric excess.

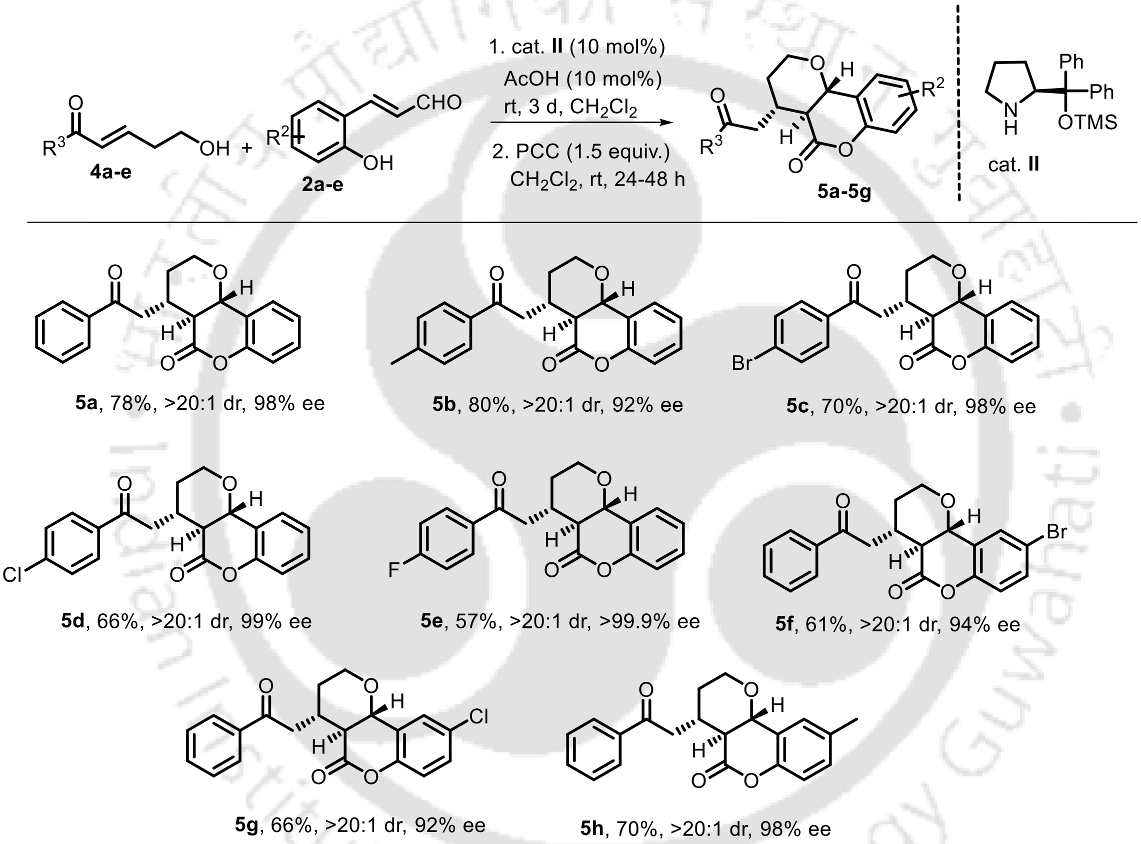
Scheme 11. **Scope of *o*-hydroxycinnamaldehydes**[a]



[a]Reaction condition: 0.2 mmol of **1a** with 0.2 mmol of **2** in 0.8 mL CH_2Cl_2. Isolated combined yield by two steps after silica gel column chromatography. The diastereomeric ratio was determined by ^{1}H NMR. Enantiomeric excess was determined by chiral HPLC analysis.

Then we became interested to expand the scope by employing δ-hydroxyenones in the reaction. Gratifyingly, when the reaction of enone **4a** and *ortho*-hydroxy cinnamaldehyde **2a** was carried out with catalyst **II** under similar conditions, the desired reaction progressed smoothly to provide a single diastereomer of tetrahydropyran fused dihydrocoumarin **5a** in 78% yield with 98% ee (Scheme 12).

Scheme 12. **Scope of δ-Hydroxyenones and *o*-hydroxycinnamaldehydes**[a]



5a, 78%, >20:1 dr, 98% ee

5b, 80%, >20:1 dr, 92% ee

5c, 70%, >20:1 dr, 98% ee

5d, 66%, >20:1 dr, 99% ee

5e, 57%, >20:1 dr, >99.9% ee

5f, 61%, >20:1 dr, 94% ee

5g, 66%, >20:1 dr, 92% ee

5h, 70%, >20:1 dr, 98% ee

[a] Reaction condition: 0.2 mmol of **4** with 0.2 mmol of **2** in 0.8 mL CH_2Cl_2. Isolated combined yield by two steps after silica gel column chromatography. The diastereomeric ratio was determined by ^{1}H NMR. Enantiomeric excess was determined by chiral HPLC analysis.

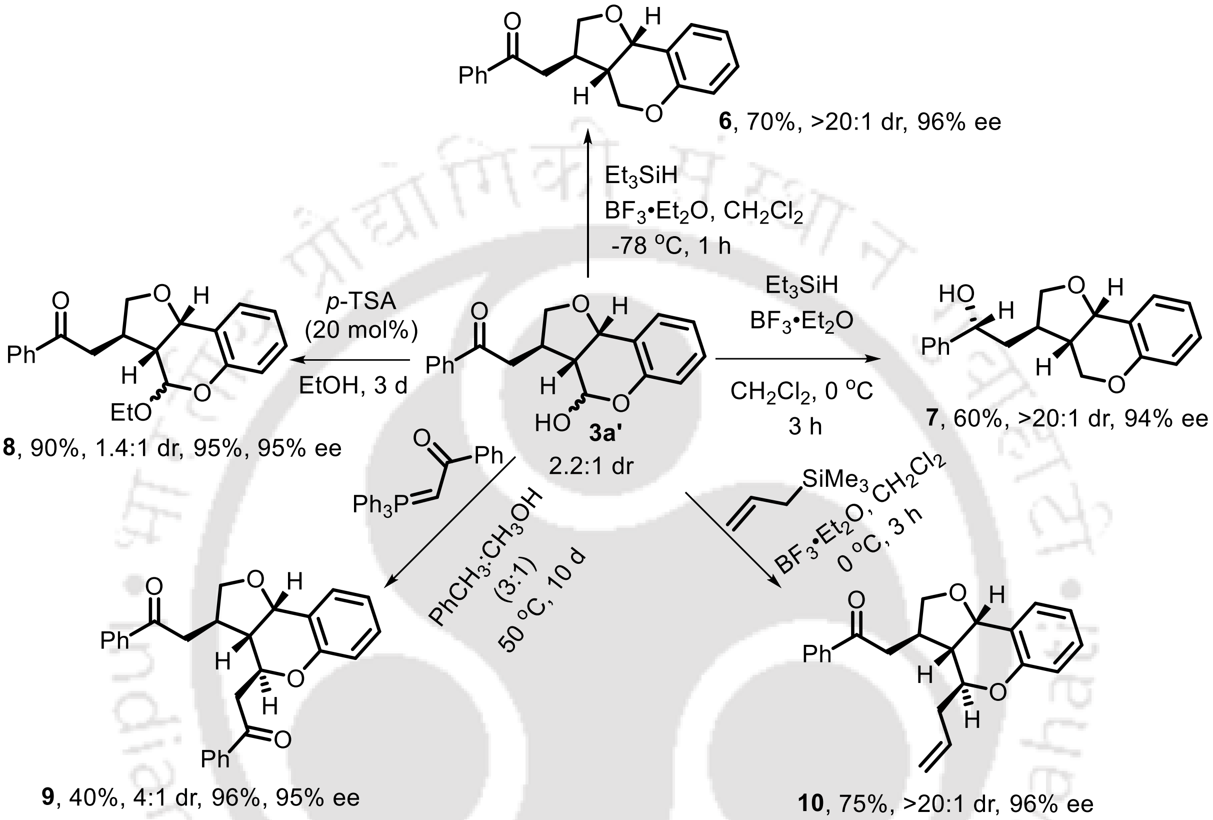
dihydrocoumarin **5a** in 78% yield with 98% ee (Scheme 12). Inspired by this result, other δ-hydroxyenones were employed in the reaction. Then different 4-substituted aryl group containing δ-hydroxyenones were prepared and engaged in the reaction. Pleasingly, the corresponding products **5b**-**5e** were obtained in acceptable yields and with high enantioselectivities (Scheme 12). For example, 4-methyl substituted *δ*-hydroxyenones **4b** delivered the product **5b** with 80% yield and slightly less enantioselectivity was observed as compared to **5a**. In addition, different 4-halosubstituted enones were introduced and similar enantiomeric excess were obtained for the products **5c** and **5d** bearing 4-bromo and 4-chloro moieties. Nevertheless, the diastereo- and enantioselectivity remained impervious to the electronic nature of the aryl substituents. Noteworthy, the highest enantioselectivity (>99.9% ee) was achieved for the 4-fluoro substituted product **5e**.

The next phase of attention was to screen different (*E*)-3-(2-hydroxyphenyl)acrylaldehydes in this method (Scheme 12). For example, 5-substituted (*E*)-3-(2-hydroxyphenyl)acrylaldehydes **2f**, **2g** and **2h** having 5-bromo, 5-chloro and 5-methyl substituents respectively furnished products **5f**, **5g** and **5h** respectively with good yields, excellent diastereo- and enantiomeric excesses.

3.4.3 Synthetic transformations of 3a'

The utility of our method was demonstrated by converting hemiacetal **3a'** to a number of useful organic structures (Scheme 13). Initially, **3a'** was treated with triethyl silane and $BF_3.OEt_2$ at -78 ^{o}C to furnish tetrahydrofuran fused chroman **6** in good yield with retention of diastereo- and enantioselectivity. Interestingly, when the same reaction was performed at 0 ^{o}C, concomitant reduction of the keto group was observed and product **7** was isolated in high diastereo- and enantioselectivity. The relative structure of **7** was determined by 2D NMR studies. The hemiacetal **3a'** was also converted to acetal **8** by treatment with catalytic amount of *p*-TSA in ethanol and enantioselectivity was preserved. Then a tandem Wittig-Michael reaction was performed on **3a'** to provide **9** in moderate diastereoselectivity without any loss of enantiopurity. Finally an allyl group was incorporated when **3a'** was reacted with allyl trimethyl silane in the presence of

$BF_3.OEt_2$ at 0 °C. Thus **10** was formed as a single diastereomer in high enantioselectivity and the structure was solved by 2D NMR studies.



Scheme 13. Synthetic transformations.

3.4.4 Determination of product stereochemistry

The absolute structure of the product **3f** was determined to be (7*S*, 8*R*, 11*R*) by single crystal X-ray crystallography (Figure 2). By analogy, it is predicted that other products will also have similar absolute configuration.

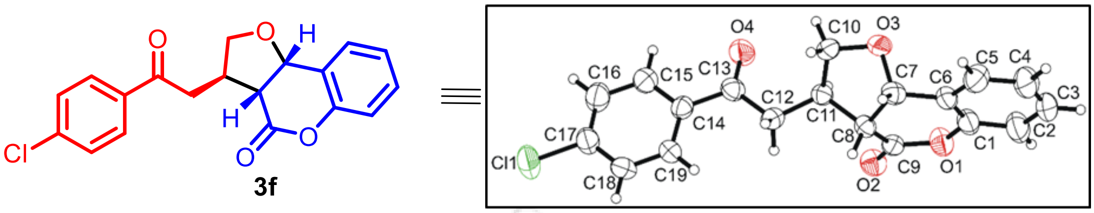


Figure 2. X-ray crystal structure of **3f**.

Similarly, the absolute configuration of the product **5c** was determined to be (7*S*, 8*S*, 12*R*) by single crystal X-ray crystallography (Figure 3). The absolute configuration of other products are assumed to be same by analogy.

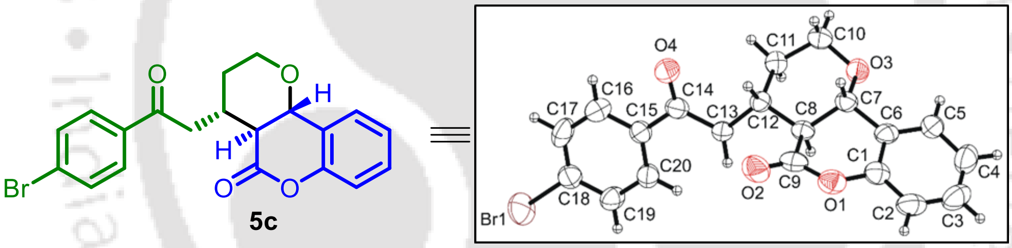


Figure 3. X-ray crystal structure of **5c**.

3.4.5 The proposed mechanism

A proposed mechanism has been drawn in Scheme 6 to rationalize the absolute structure of the products. At first it is expected that iminium ion **A** will formed and the conjugate addition of **1a** from *Re* face will provide enamine **B**. Then catalyst controlled cyclization *via* attack on the *Si* face of enone will generate tetrahydrofuran **C** having the respective stereochemistry. Pyridinium chlorochromate oxidation of hemiacetal **3a'** then delivers dihydrocumarin **3a**. In a similar way **4a** reacts with iminium ion **A** to afford enamine **D** which takes a chair like TS for the cyclization. Thus tetrahydropyran **E** is formed having all equatorial substituents in the chair form. Finally oxidation with pyridinium chlorochromate generates **5a**.

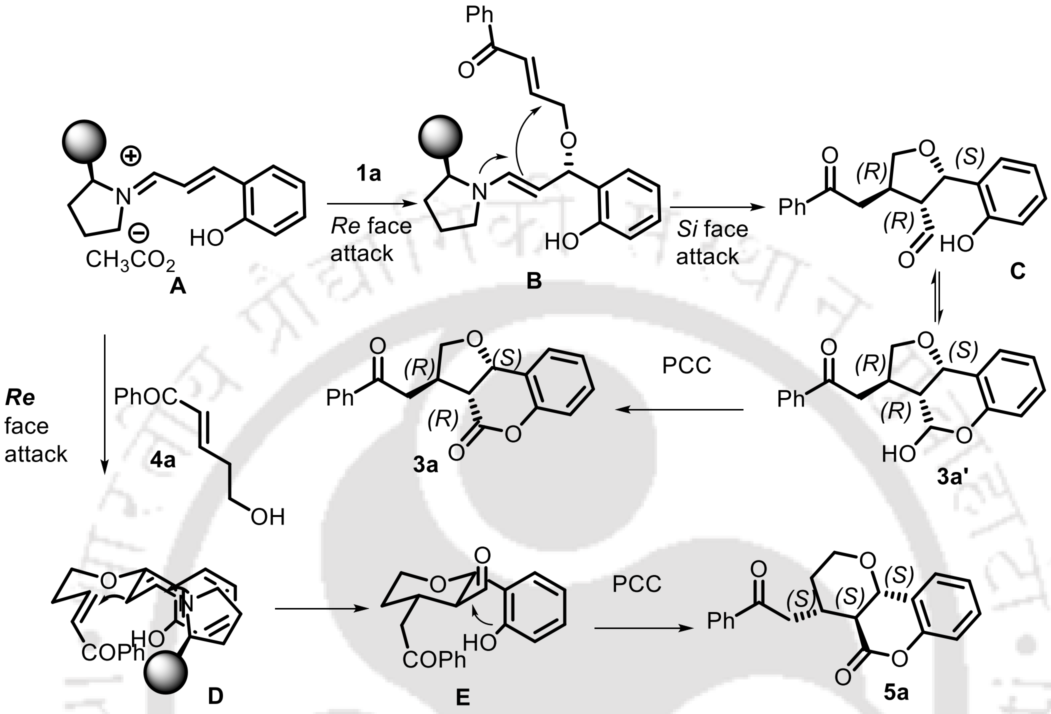


Figure 4. The proposed mechanism.

3.5 Conclusion

In summary this report demonstrates a convenient asymmetric synthesis of tetrahydrofuran/tetrahydropyran-fused 3,4-dihydrocoumarins *via* cascade strategy. The reactants and the catalyst of this reaction are easily available. Also our methodology provides a range of tetrahydrofuran-fused chroman derivatives after single synthetic transformation. Thus, this attractive methodology might be applied in the synthesis of biologically important fused dihyrocoumarins and chromans.

3.6 Experimental Section

3.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, Daicel Chiralpak ID Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

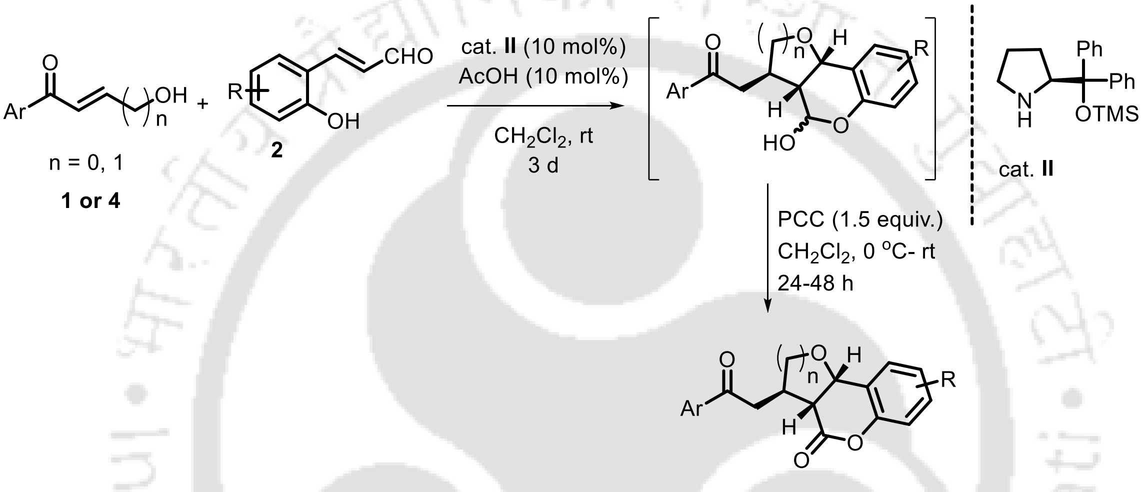
Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

3.6.2 General procedure for the synthesis of *trans*-*γ*-hydroxyenones and and *trans*-*δ*-hydroxyenones

Trans-*γ*-hydroxyenones (**1a-1l**)[20] and *trans*-*δ*-hydroxyenones (**4**)[21] were synthesized according to reported procedure.

o-Hydroxycinnamaldehydes were prepared according to reported procedures.[22]

3.6.3 General procedure for the synthesis of products 3a-5h

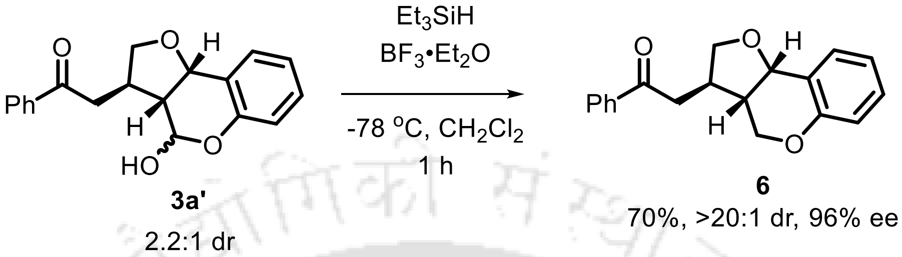


3a-5h

In an oven dried round bottom flask, **1** (0.2 mmol), **2** (0.2 mmol), 10 mol% of catalyst **II** and 10 mol% of glacial acetic acid were taken. Then 0.8 mL of CH_2Cl_2 was added to the reaction mixture and stirred at rt for 3 days. Completion of the reaction was checked by TLC. After completion, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (25-30%) to afford desired hemicaetal product.

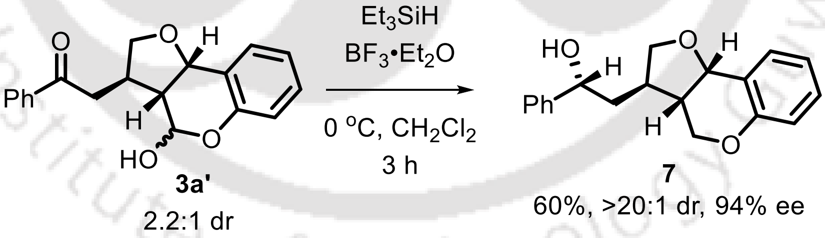
The hemicaetal product was placed in a round bottom flask in CH_2Cl_2 (2.0 mL) and cooled to 0 °C. PCC (1.5 eq.) was added to it. Then the reaction mixture was shifted to room temperature and stirred for 24-48 h. After the reaction was completed monitored by TLC, the solvent was evaporated and the crude reaction mixture was subjected to column chromatography on silica gel using 15-20% ethyl acetate in hexane to afford the corresponding products **3a-5h**.

3.6.4 General procedure for the preparation of compound 6



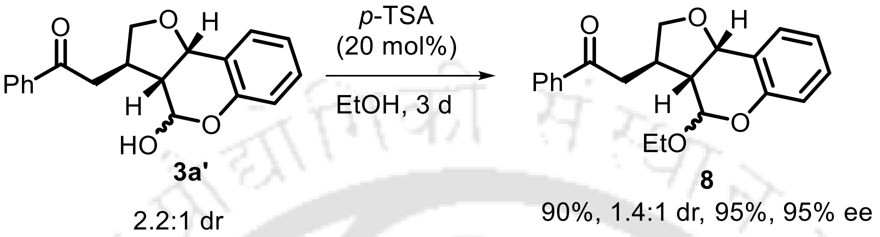
To a dry DCM solution (2 mL) of compound **3a'** (31.0 mg, 0.1 mmol) and triethylsilane (48 μL, 0.3 mmol) in an oven dried flask was added $BF_3.Et_2O$ (25 μL, 0.2 mmol) at -78 °C. Progress of the reaction was monitored by TLC. After 1 h, the reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM (3 X 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (85/15) to afford the desired product **6**.

3.6.5 General procedure for the preparation of compound 7



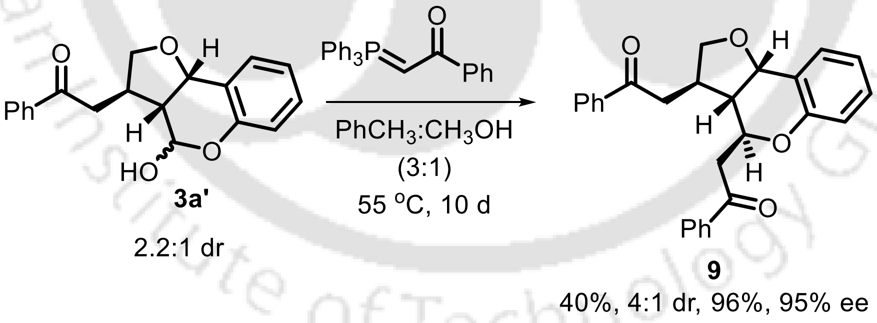
To a dry DCM solution (2.5 mL) of compound **3a'** (31.0 mg, 0.1 mmol) and triethylsilane (48 μL, 0.3 mmol) in an oven dried flask was added $BF_3.Et_2O$ (37 μL, 0.3 mmol) at 0 °C. Progress of the reaction was monitored by TLC. After 3 h, the reaction was quenched with aqueous $NaHCO_3$ and extracted with DCM (3 X 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (80/20) to afford desired product **7**.

3.5.6 General procedure for the synthesis of compound 8



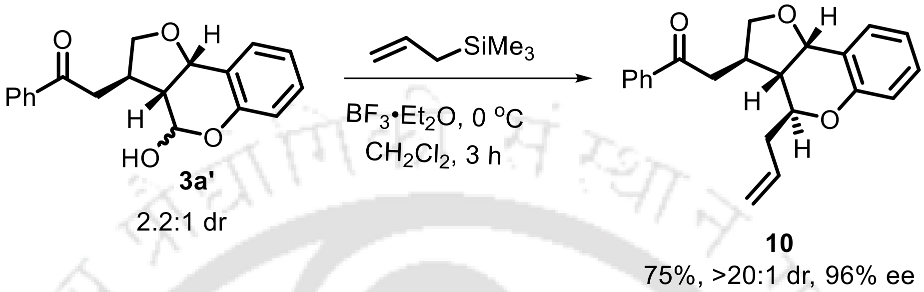
In an oven dried round bottom flask, to a solution of compound **3a'** (31.0 mg, 0.1 mmol) in 0.3 mL of EtOH was added *p*-toluenesulfonic acid (3.4 mg, 0.02 mmol) and stirred for 3 days at rt. The solvent was concentrated under vacuum and the residue was purified by column chromatography on silica gel with hexane/ethyl acetate (90/10) to afford the desired product **8**.

3.5.7 General procedure for the preparation of compound 9



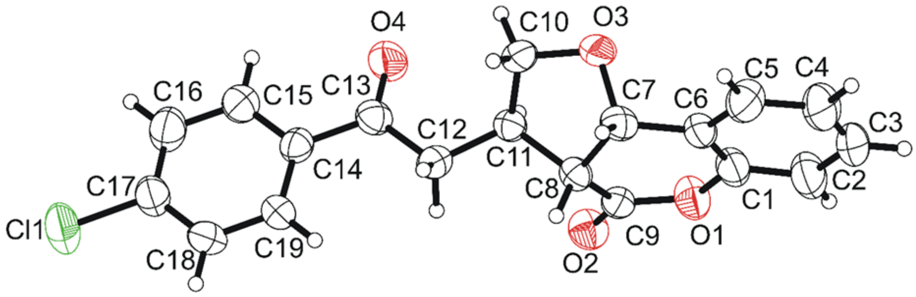
In an oven dried round bottom flask, compound **3a'** (46.5 mg, 0.15 mmol) and 1-phenyl-2-(triphenyl-λ^5-phosphaneylidene)ethan-1-one (171.0 mg, 0.45 mmol) were taken in dry toluene/methanol (3:1) solution (1.5 mL) and stirred for 10 days at 55 °C. The solvent was concentrated under vacuum. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (75/25) to afford desired product **9**.

3.5.8 General procedure for the preparation of compound 10



In an oven dried round bottom flask, to a solution of **3a'**(31.0 mg, 0.1 mmol) in dry DCM (1.3 mL), 3 equivalents of allyl trimethyl silane (48 μL, 0.3 mmol) were added *via* syringe and the reaction mixture was cooled to 0 °C. Then, 3 equivalents of the $BF_3.Et_2O$ (37 μL, 0.3 mmol) were also added via syringe and the reaction mixture was allowed to stir for 3 h. Water (2 ml/mmol) was added to the reaction mixture and extracted with DCM (3 X 3 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (85/15) to afford desired product **10**.

3.5.9 Crystal structure of compound 3g[23]



ORTEP crystal structure

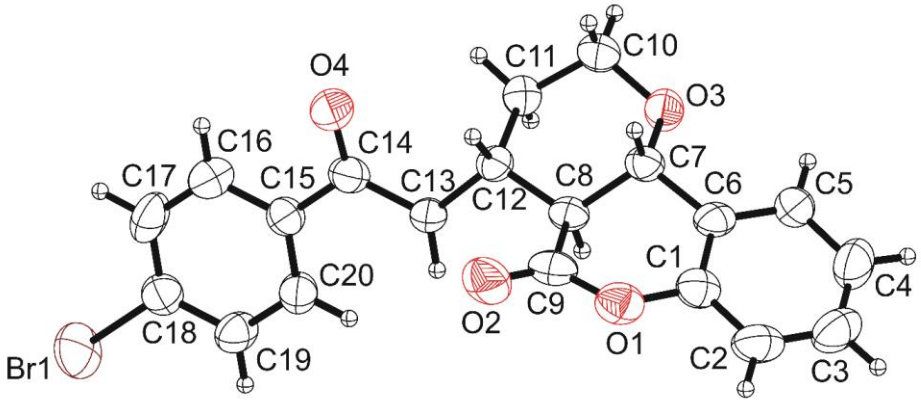
Table 1. Crystal data and structure refinement for compound 3g

Parameters	3g
CCDC No.	1849827
Empirical formula	$C_{19}H_{15}O_4Cl$
Formula weight	342.76
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.26× 0.22 × 0.20
Temperature, *T*	293 K
Wavelength, λ (Å)	0.71073
Crystal system	monoclinic
Space group	′ I 2′

Unit cell dimensions	a = 32.433 (2) Å b = 4.7591 (3) Å c = 21.8528 (15) Å α = 90 (1)°, β = 104.582 (6)°, γ = 90 (1)°
Volume, V (Å^3)	3264.4 (4)
Z	8
Calculated density, Mg/m^3	1.395
Absorption coefficient, μ (mm^{-1})	0.254
F(000)	1424
θ range for data collection	3.05° to 24.99°
Limiting indices	$-38 \leq h \leq 38, -5 \leq k \leq 5, -15 \leq l \leq 25$
Reflection collected/unique	4985/2502[R(int) = 0.0262]
Completeness to θ	99.7 % (θ = 24.990°)
Max. and min. transmission	0.950/ 0.936
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	4985/1/433
Goodness of fit on F^2	1.018
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0638, wR2 = 0.0852

R indices (all data)	R1 = 0.1404, wR2 = 0.1174
Ellipsoid contour % probability	40

3.5.10 Crystal structure of compound 5e[24]



ORTEP crystal structure

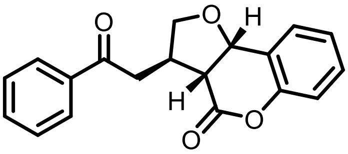
Table 2. Crystal data and structure refinement for compound 5e

Parameters	**5e**
CCDC No.	1849828
Empirical formula	$C_{20}H_{16}O_4Br$
Formula weight	400.23
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.24× 0.20 × 0.16
Temperature, *T*	293 K
Wavelength, λ (Å)	0.71073

Crystal system	orthorhombic
Space group	'P 21 21 21'
Unit cell dimensions	a = 4.6107 (3) Å b = 14.6436 (11) Å c = 25.5248 (14) Å α = 90 (1)°, β = 90 (1)°, γ = 90 (1)°
Volume, V (Å^3)	1723.4(2)
Z	4
Calculated density, Mg/m^3	1.543
Absorption coefficient, μ (mm^{-1})	2.407
F(000)	812.0
θ range for data collection	3.19° to 24.99°
Limiting indices	$-5 \le h \le 4$, $-17 \le k \le 16$, $-30 \le l \le 15$
Reflection collected/unique	2892/1921[R(int) = 0.0366]
Completeness to θ	99.7 % (θ = 24.990°)
Max. and min. transmission	0.680/ 0.567
Refinement method	'SHELXL-97 (Sheldrick, 1997)'

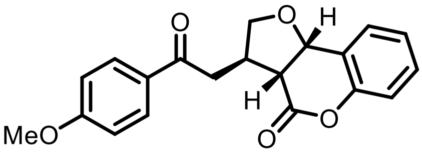
Data/restraints/parameters	2892/0/226
Goodness of fit on F^2	1.026
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0494, wR2 = 0.0954
R indices (all data)	R1 = 0.0855, wR2 = 0.1169
Ellipsoid contour % probability	40

3.6 Characterization data of products



3a

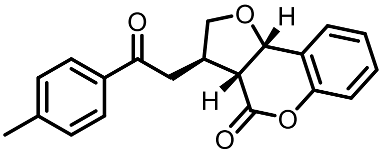
(3R,3aR,9bS)-3-(2-oxo-2-phenylethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3a): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white semi solid; 80% yield (49.3 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53-7.45 (m, 3H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 5.25 (d, *J* = 6.4 Hz, 1H), 4.37-4.28 (m, 1H), 3.65 (q, *J* = 7.7 Hz, 1H), 3.59 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.26-3.16 (m, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 198.0, 168.3, 149.9, 136.3, 133.7, 130.6, 128.9, 128.9, 128.2, 125.3, 120.4, 117.1, 74.5, 72.5, 48.4, 42.0, 39.9. **FT-IR (thin film)** 2889, 1762, 1683, 1594, 1456, 1222, 1002, 759 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 34.3 min, t_{minor} = 43.6 min). $[\alpha]_D^{27}$= +60.0 (c 0.235, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{17}O_4$ [M+H]$^+$ 309.1121, found 309.1121.



3b

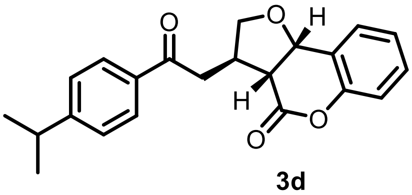
(3R,3aR,9bS)-3-(2-(4-methoxyphenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4- one (3b): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 82% yield (55.5 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.24 (d, *J* = 6.0 Hz, 1H), 4.34-4.26 (m, 1H), 3.87 (s, 3H), 3.58 (dd, *J* = 10.2, 3.6 Hz, 2H), 3.23-3.11 (m, 3H). **^{13}C NMR**

(150 MHz, $CDCl_3$) δ 196.4, 168.3, 164.0, 149.8, 130.5, 129.5, 128.90, 125.3, 120.5, 117.1, 114.0, 74.4, 72.5, 55.7, 48.4, 41.6, 40.0. **FT-IR (thin film)** 2924, 1760, 1677, 1459, 1224, 1187, 1002, 774 cm^{-1}. **HPLC Analysis**: >99% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 9.9 min, t_{minor} = 28.6 min. $[\alpha]_D^{25}$= +136.3 (c 0.55, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_5$ $[M+H]^+$ 339.1227, found 339.1226.



3c

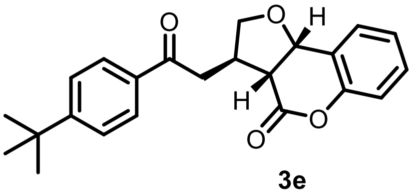
(3R,3aR,9bS)-3-(2-oxo-2-(p-tolyl)ethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3c): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 78% yield (50.2 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 5.26 (d, *J*= 6.5 Hz, 1H), 4.33 (dd, *J* = 8.7, 7.3 Hz, 1H), 3.66-3.59 (m, 2H), 3.24-3.18 (m, 3H), 2.44 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.6, 168.3, 149.9, 144.6, 133.9, 130.5, 129.6, 128.9, 128.3, 125.3, 120.5, 117.1, 74.4, 72.5, 48.4, 41.9, 39.9, 21.9. **FT-IR (thin film)** 2890, 1762, 1672, 1455, 1220, 1193, 1008, 770 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 46.0 min, t_{minor} = 59.0 min). $[\alpha]_D^{28}$= +60.7 (c 0.145, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_4$ $[M+H]^+$ 323.1278, found 323.1284.



3d

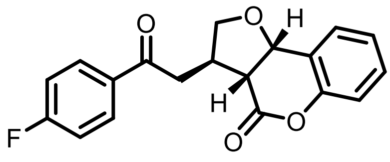
(3R,3aR,9bS)-3-(2-(4-isopropylphenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3d): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white sticky solid; 72% yield (50.4

mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 16.0, 7.8 Hz, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 5.24 (d, *J* = 5.8 Hz, 1H), 4.36-4.26 (m, 1H), 3.68-3.54 (m, 2H), 3.25-3.14 (m, 3H), 2.96 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.6, 168.3, 155.3, 149.8, 134.2, 130.5, 128.9, 128.5, 127.0, 125.3, 120.5, 117.0, 74.4, 72.5, 48.4, 41.9, 39.9, 34.4, 23.8. **FT-IR (thin film)** 2927, 1756, 1678, 1627, 1448, 1265, 1157, 1030, 756 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 34.6 min, t_{minor} = 45.7 min). $[\alpha]_D^{24}$ = +131.4 (c 0.68, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{22}H_{23}O_4$ $[M+H]^+$ 351.1591, found 351.1593.



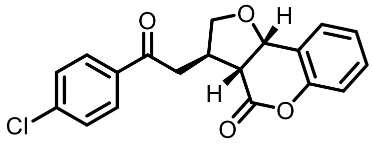
3e

3R,3aR,9bS)-3-(2-(4-(tert-butyl)phenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4- one (3e): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white sticky solid; 69% yield (50.2 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.49 (t, *J* = 8.8 Hz, 3H), 7.35 (t, *J* = 8.5 Hz, 1H), 7.21 (t, *J* = 7.0 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 6.6 Hz, 1H), 5.22-5.21 (m, 1H), 4.30 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.64-3.56 (m, 2H), 3.23-3.15 (m, 3H), 1.34 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.6, 168.3, 157.6, 149.9, 130.5, 128.9, 128.2, 125.8, 125.34, 120.4, 117.0, 74.4, 72.5, 48.4, 41.9, 39.9, 35.3, 31.2. **FT-IR (thin film)** 2923, 1758, 1680, 1620, 1444, 1159, 1003, 758 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 32.7 min, t_{minor} = 59.0 min). $[\alpha]_D^{24}$ = +47.0 (c 0.155, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{23}H_{25}O_4$ $[M+H]^+$ 365.1747, found 365.1752.



3f

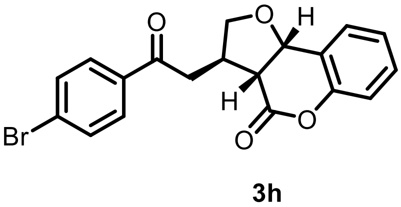
3R,3aR,9bS)-3-(2-(4-fluorophenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3f): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white semi solid; 66% yield (43.0 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.99 (d, J = 5.8 Hz, 2H), 7.50 (d, J = 7.4 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 8.4 Hz, 2H), 7.07 (d, J = 8.2 Hz, 1H), 5.25 (d, J = 5.3 Hz, 1H), 4.37-4.25 (m, 1H), 3.68-3.54 (m, 2H), 3.18 (d, J = 11.3 Hz, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.3, 168.2, 149.8, 130.9, 130.9, 130.6, 128.9, 125.4, 120.4, 117.1, 116.1, 116.0, 74.4, 72.4, 48.4, 41.9, 39.9. **FT-IR (thin film)** 2920, 1765, 1682, 1628, 1449, 1162, 1013, 768 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t$_{major}$ = 31.7 min, t$_{minor}$ = 40.1 min). $[\alpha]_D^{24}$ = +68.3 (c 0.31, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}FO_4$ $[M+H]^+$ 327.1027, found 327.1030.



3g

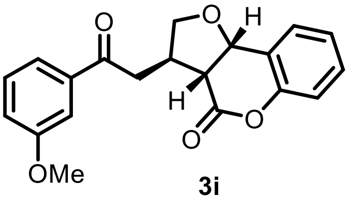
3R,3aR,9bS)-3-(2-(4-chlorophenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3g): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white semi solid; 67% yield (45.8 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.81 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.6 Hz, 2H), 7.51-7.48 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 5.23 (d, J = 6.3 Hz, 1H), 5.18 (d, J = 6.7 Hz, 1H), 4.29 (dd, J = 8.8, 7.2 Hz, 1H), 3.62-3.54 (m, 2H), 3.22-3.14 (m, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.9, 168.2, 149.8, 135.0, 132.2, 130.6, 129.7, 129.0, 128.9, 125.3, 120.3, 117.1, 74.4, 72.4, 48.3, 41.9, 39.8. **FT-IR (thin film)** 2927, 1759, 1683, 1626, 1440, 1156, 1008, 758 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t$_{major}$ = 33.2 min,

t_{minor} = 42.9 min). $[\alpha]_D^{27}$= +66.9 (c 0.415, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}ClO_4$ $[M+H]^+$ 343.0732, found 343.0748.



3h

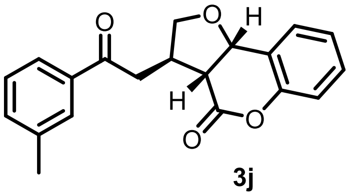
(3R,3aR,9bS)-3-(2-(4-bromophenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3h): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 65% yield (50.2 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 6.5 Hz, 1H), 4.30 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.63-3.54 (m, 2H), 3.23-3.12 (m, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.7, 168.2, 149.8, 140.2, 134.6, 130.6, 129.6, 129.2, 128.9, 125.4, 120.3, 117.1, 74.4, 72.4, 48.3, 41.9, 39.8. **FT-IR (thin film)** 2923, 1761, 1688, 1620, 1479, 1221, 1180, 756 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 35.8 min, t_{minor} = 46.5 min). $[\alpha]_D^{27}$= +80.0 (c 0.355, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}BrO_4$ $[M+H]^+$ 387.0226, found 387.0236.



3i

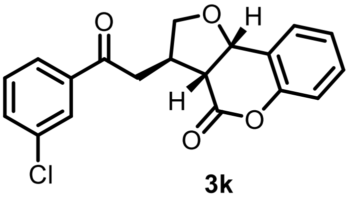
(3R,3aR,9bS)-3-(2-(3-methoxyphenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3i): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless sticky solid; 76% yield (51.4 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 6.2 Hz, 1H), 4.34-4.27 (m, 1H), 3.62-3.54 (m, 2H), 3.21-3.13 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 197.8, 168.2, 160.1, 149.9, 137.7, 130.6, 129.9, 128.9, 125.3, 120.9, 120.4, 120.2, 117.1, 112.3, 74.4, 72.4, 55.6, 48.3, 42.1, 39.9. **FT-IR (thin film)** 2920, 1766, 1683, 1475, 1215, 1185, 766 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 55.7 min, t_{minor} = 68.2 min). $[\alpha]_D^{27}$= +80.7 (c 0.280, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_5$ M+H]$^+$ 339.1227, found 339.1234.



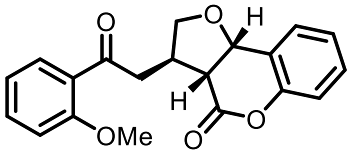
3j

(3R,3aR,9bS)-3-(2-oxo-2-(m-tolyl)ethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3j): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 77% yield (49.6 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.75 (m, 2H), 7.50 (m, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.24-7.20 (m, 1H), 7.06 (m, 1H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.33-4.29 (m, 1H), 3.66-3.56 (m, 2H), 3.24-3.15 (m, 3H), 2.41 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.1, 168.3, 149.8, 138.7, 136.4, 134.5, 130.5, 128.9, 128.8, 128.7, 125.4, 125.3, 120.5, 117.1, 74.4, 72.5, 48.4, 42.1, 39.9, 21.5. **FT-IR (thin film)** 2927, 1756, 1682, 1627, 1593, 1277, 1158, 756 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 36.0 min, t_{minor} = 45.1 min). $[\alpha]_D^{27}$= +104.4 (c 0.205, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_4$ [M+H]$^+$ 323.1278, found 323.1282.



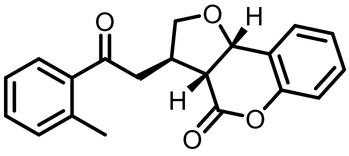
3k

(3R,3aR,9bS)-3-(2-(3-chlorophenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3k): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless gummy solid; 58% yield (39.7 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.92 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 5.25 (d, *J* = 5.8 Hz, 1H), 4.37-4.27 (m, 1H), 3.59 (dd, *J* = 18.9, 12.0 Hz, 2H), 3.29-3.10 (m, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.7, 168.2, 149.8, 137.8, 135.3, 133.7, 130.6, 130.3, 128.9, 128.3, 126.3, 125.4, 120.3, 117.1, 74.4, 72.4, 48.3, 42.1, 39.8. **FT-IR (thin film)** 2923, 1758, 1680, 1625, 1590, 1444, 1160, 765 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 31.9 min, t_{minor} = 38.7 min). $[\alpha]_D^{25}$= +146.4 (c 0.265, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}ClO_4$ [M+H]$^+$ 343.0732, found 343.0735.



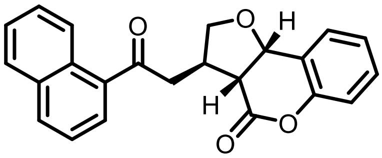
3l

(3R,3aR,9bS)-3-(2-(2-methoxyphenyl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3l): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless semi solid; 70% yield (47.3 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.71 (m, 1H), 7.50-7.46 (m, 2H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 7.00-9.68 (m, 2H), 5.21 (d, *J* = 6.8 Hz, 1H), 4.27-4.22 (m, 1H), 3.93 (s, 3H), 3.65-3.59 (m, 2H), 3.25-3.11 (m, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 199.8, 168.3, 159.1, 149.9, 134.3, 130.7, 130.5, 128.9, 127.3, 125.2, 120.9, 120.6, 117.0, 111.7, 74.5, 72.6, 55.7, 48.4, 47.2, 40.1. **FT-IR (thin film)** 2925, 1768, 1685, 1500, 1479, 1175, 769 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 85:15), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 18.5 min, t_{minor} = 17.1 min). $[\alpha]_D^{28}$= +75.1 (c 0.535, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_5$ [M+H]$^+$ 339.1227, found 339.1225.



3m

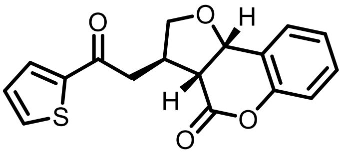
(3R,3aR,9bS)-3-(2-oxo-2-(o-tolyl)ethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3m): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless gummy solid; 68% yield (43.8 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.70 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 1H), 7.30-7.24 (m, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 5.23 (d, *J* = 6.9 Hz, 1H), 4.34-4.28 (m, 1H), 3.63-3.52 (m, 2H), 3.23-3.13 (m, 3H), 2.48 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 201.5, 168.2, 149.9, 138.8, 136.8, 132.4, 132.1, 130.5, 129.0, 128.9, 126.0, 125.3, 120.4, 117.1, 74.5, 72.5, 48.3, 44.6, 40.0, 21.7. **FT-IR (thin film)** 2923, 1764, 1683, 1486, 1221, 1185, 756 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, ee = 96%, λ = 254 nm (t_{major} = 9.9 min, t_{minor} = 7.5 min). $[\alpha]_D^{28}$= +36.7 (c 0.310, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_4$ $[M+H]^+$ 323.1278, found 323.1283.



3n

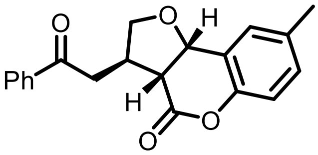
(3R,3aR,9bS)-3-(2-(naphthalen-1-yl)-2-oxoethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3n): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 60% yield (43.0 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.62 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.95 (d, *J* = 7.1 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.62-7.49 (m, 4H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.23 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 5.24 (d, *J* = 6.9 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.78-3.64 (m, 2H), 3.37-3.27 (m, 2H), 3.19 (t, *J* = 7.0 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 201.8, 168.2, 149.9, 134.7, 134.1, 133.6, 130.6, 130.2, 128.9, 128.7, 128.4, 128.4, 126.8, 125.8, 125.3, 124.5, 120.4, 117.1, 74.5, 72.5, 48.3, 45.0, 40.2. **FT-IR (thin film)** 2920, 1757, 1680, 1478, 1226, 1188, 766 cm^{-1}.

HPLC Analysis: 94% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 45.2 min, t_{minor} = 59.6 min). $[\alpha]_D^{24}$ = +95.4 (c 0.620, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{23}H_{19}O_4$ $[M+H]^+$ 359.1278, found 359.1278.



3o

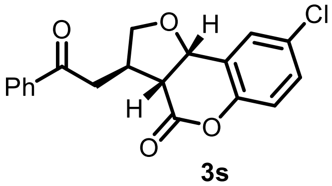
(3R,3aR,9bS)-3-(2-oxo-2-(thiophen-2-yl)ethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3o): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 62% yield (39.0 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.75 (d, *J* = 3.8 Hz, 1H), 7.66 (d, *J* = 4.9 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.17-7.13 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 5.22 (d, *J* = 6.2 Hz, 1H), 4.27 (dd, *J* = 8.8, 7.3 Hz, 1H), 3.68-3.60 (m, 1H), 3.55 (dd, *J* = 16.1, 2.7 Hz, 1H), 3.24-3.13 (m, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 190.8, 168.2, 149.9, 143.5, 134.4, 132.5, 130.6, 129.0, 128.5, 125.3, 120.3, 117.1, 74.4, 72.3, 48.2, 42.3, 40.1. **FT-IR (thin film)** 2922, 1760, 1684, 1586, 1458, 1397, 1222, 1190, 761 cm^{-1}. **HPLC Analysis**: 46% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 85:15), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 22.7 min, t_{minor} = 18.4 min). $[\alpha]_D^{24}$ = +96.9 (c 0.365, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{17}H_{15}O_4S$ $[M+H]^+$ 315.0686, found 315.0692.



3r

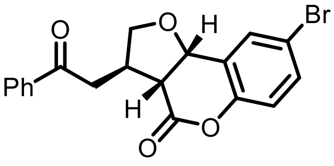
(3R,3aR,9bS)-8-methyl-3-(2-oxo-2-phenylethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3r): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 72% yield (46.4 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 7.2

Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.29 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.20 (d, *J* = 6.4 Hz, 1H), 4.36 – 4.29 (m, 1H), 3.70-3.55 (m, 2H), 3.26-3.12 (m, 3H), 2.35 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 198.0, 168.5, 147.7, 136.3, 135.0, 133.7, 131.1, 129.0, 128.9, 128.2, 120.0, 116.8, 74.5, 72.5, 48.3, 42.0, 39.9, 20.9. **FT-IR (thin film)** 2924, 1760, 1682, 1599, 1457, 1225, 1189, 792 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 21.5 min, t_{minor} = 15.3 min). $[\alpha]_D^{28}$= +215.0 (c 0.160, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_4$ $[M+H]^+$ 323.1278, found 323.1279.



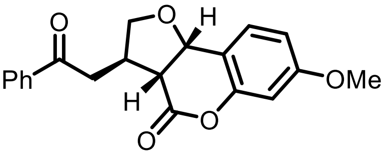
3s

(3R,3aR,9bS)-8-chloro-3-(2-oxo-2-phenylethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3s): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 70% yield (47.9 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.95 (d, *J* = 7.4 Hz, 2H), 7.59 (m, 1H), 7.52-7.44 (m, 3H), 7.31 (d, *J* = 8.7 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 5.23 (d, *J* = 6.5 Hz, 1H), 4.32 (t, *J* = 8.1 Hz, 1H), 3.61 (dd, *J* = 17.5, 11.0 Hz, 2H), 3.26-3.11 (m, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 197.8, 167.6, 148.2, 136.3, 133.8, 130.6, 128.9, 128.6, 128.2, 122.4, 118.5, 74.1, 72.5, 48.1, 41.8, 39.7. **FT-IR (thin film)** 2928, 1765, 1685, 1589, 1459, 1228, 1188, 762 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 25.7 min, t_{minor} = 23.1 min). $[\alpha]_D^{26}$= +35.0 (c 0.490, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}ClO_4$ $[M+H]^+$ 343.0732, found 343.0733.



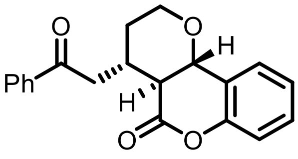
3t

(3R,3aR,9bS)-8-bromo-3-(2-oxo-2-phenylethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3t): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 67% yield (51.7 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.97-7.93 (m, 2H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51-7.44 (m, 3H), 6.95 (d, *J* = 8.7 Hz, 1H), 5.23 (d, J = 6.7 Hz, 1H), 4.35-4.30 (m, 1H), 3.66-3.57 (m, 2H), 3.24-3.12 (m, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 197.8, 167.5, 148.7, 136.3, 133.8, 133.5, 131.6, 128.9, 128.2, 122.8, 118.9, 118.0, 74.0, 72.5, 48.1, 41.8, 39.7. **FT-IR (thin film)** 2926, 1763, 1688, 1592, 1454, 1225, 1187, 768 cm^{-1}. **HPLC Analysis**: 84% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 23.8 min, t_{minor} = 26.2 min). $[\alpha]_D^{26}$= +46.0 (c 0.50, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{16}BrO_4$ [M+H]$^+$ 387.0226, found 387.0237.



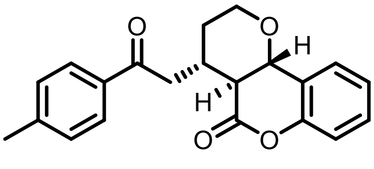
3u

(3R,3aR,9bS)-7-methoxy-3-(2-oxo-2-phenylethyl)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-4-one (3u): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless semi solid; 73% yield (49.4 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.98-7.94 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 1H), 6.76 (m, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 6.9 Hz, 1H), 4.34-4.27 (m, 1H), 3.81 (s, 3H), 3.64-3.54 (m, 2H), 3.29-3.11 (m, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 198.0, 168.5, 161.4, 151.0, 136.4, 133.7, 129.8, 128.9, 128.2, 112.2, 111.8, 102.1, 74.3, 72.4, 55.8, 48.3, 42.1, 40.1. **FT-IR (thin film)** 2921, 1767, 1687, 1562, 1465, 1228, 1178, 767 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 85:15), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 23.9 min, t_{minor} = 18.6 min). $[\alpha]_D^{26}$= +28.0 (c 0.435, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_5$ $[M+H]^+$ 339.1227, found 339.1244.



5a

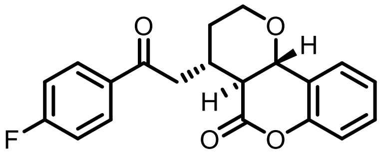
(4S,4aS,10bS)-4-(2-oxo-2-phenylethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5a): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 78% yield (50.3 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.17 (dd, *J* = 11.7, 3.5 Hz, 1H), 4.02 (s, 1H), 3.67 (t, *J* = 12.1 Hz, 1H), 2.76 (ddd, *J* = 14.6, 13.5, 6.9 Hz, 2H), 2.59-2.53 (m, 1H), 2.03-1.96 (m, 1H), 1.53 (ddd, *J* = 25.9, 12.8, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.0, 169.0, 149.08, 137.0, 133.4, 129.4, 128.8, 128.4, 125.9, 124.9, 124.4, 116.4, 72.7, 67.7, 47.0, 43.7, 31.9, 31.6. **FT-IR (thin film)** 2922, 1763, 1681, 1565, 1454, 1227, 1145, 791 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 16.7 min, t_{minor} = 11.7min). $[\alpha]_D^{26}$= -17.3 (c 0.115, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{19}O_4$ $[M+H]^+$ 323.1278, found 323.1289.



5b

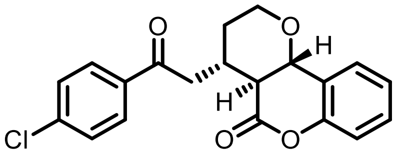
(4S,4aS,10bS)-4-(2-oxo-2-(p-tolyl)ethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5b): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 80% yield (53.8 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.17 (dd, *J* = 10.9, 5.4 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.66 (td, *J* = 12.5, 2.1 Hz, 1H), 2.73

(ddd, *J* = 24.3, 17.6, 9.8 Hz, 2H), 2.56 (dd, *J* = 12.0, 10.7 Hz, 1H), 2.42 (s, 3H), 2.01-1.95 (m, 1H), 1.53 (ddd, *J* = 18.4, 13.2, 4.7 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.6, 168.9, 149.1, 144.2, 134.6, 129.5, 129.4, 128.6, 126.0, 124.9, 124.4, 116.4, 72.8, 67.7, 47.1, 43.7, 32.0, 31.6, 21.8. **FT-IR (thin film)** 2923, 1765, 1683, 1562, 1457, 1237, 1141, 783 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 19.5 min, t_{minor} = 14.1 min). $[\alpha]_D^{27}$= +13.6 (c 0.235, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{21}H_{21}O_4$ $[M+H]^+$ 337.1434, found 337.1429.



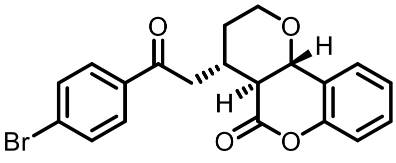
5c

(4S,4aS,10bS)-4-(2-(4-fluorophenyl)-2-oxoethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5c): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 57% yield (38.8 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.09 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.21 – 4.14 (m, 1H), 3.98 (d, *J* = 13.7 Hz, 1H), 3.67 (td, *J* = 12.5, 2.0 Hz, 1H), 2.72 (ddd, *J* = 16.2, 12.9, 6.9 Hz, 2H), 2.59-2.52 (m, 1H), 2.01-1.95 (m, 1H), 1.57 – 1.50 (m, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.3, 169.0, 166.8, 165.1, 149.0, 133.4, 133.38, 131.2, 131.1, 129.4, 125.9, 125.0, 124.4, 116.4, 116.0, 115.9, 72.7, 67.6, 47.0, 43.7, 31.9, 31.6. **FT-IR (thin film)** 2928, 1768, 1680, 1559, 1463, 1242, 1147, 765 cm^{-1}. **HPLC Analysis**: >99% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 18.6 min, t_{minor} = 22.2 min). $[\alpha]_D^{27}$= -5.0 (c 0.120, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{18}FO_4$ $[M+H]^+$ 341.1184, found 341.1183.



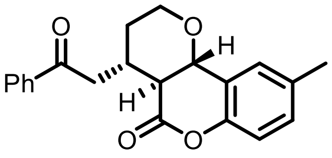
5d

(4S,4aS,10bS)-4-(2-(4-chlorophenyl)-2-oxoethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5d): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 66% yield (47.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.99 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.18 (dd, *J* = 11.7, 4.6 Hz, 1H), 3.97 (d, *J* = 13.7 Hz, 1H), 3.67 (t, *J* = 12.2 Hz, 1H), 2.79-2.66 (m, 2H), 2.59-2.52 (m, 1H), 2.00-1.94 (m, 1H), 1.58-1.49 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.7, 169.0, 149.0, 139.8, 135.3, 129.9, 129.4, 129.2, 125.9, 125.0, 124.5, 116.4, 72.7, 67.6, 47.0, 43.7, 31.9, 31.7. **FT-IR (thin film)** 2923, 1765, 1678, 1560, 1468, 1238, 1143, 760 cm^{-1}. **HPLC Analysis**: 99% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.4 min, t_{minor} = 26.2 min). $[\alpha]_D^{25}$= -12.3 (c 0.325, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{18}ClO_4$ $[M+H]^+$ 357.0888, found 357.0895.



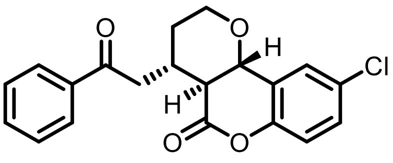
5e

(4S,4aS,10bS)-4-(2-(4-bromophenyl)-2-oxoethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5e): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 70% yield (56.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.15 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.93 (d, *J* = 13.6 Hz, 1H), 3.68-3.60 (m, 1H), 2.73-2.62 (m, 2H), 2.56-2.48 (m, 1H), 1.98-1.90 (m, 1H), 1.54-1.46 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.9, 169.0, 149.0, 135.7, 132.2, 130.0, 129.5, 128.6, 125.9, 125.0, 124.5, 116.4, 72.7, 67.6, 47.0, 43.7, 31.9, 31.7. **FT-IR (thin film)** 2923, 1762, 1680, 1553, 1467, 1240, 1149, 761 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IC Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.9 min, t_{minor} = 11.0 min). $[\alpha]_D^{26}$= -39.0 (c 1.07, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{18}BrO_4$ $[M+H]^+$ 401.0383, found 401.0378.



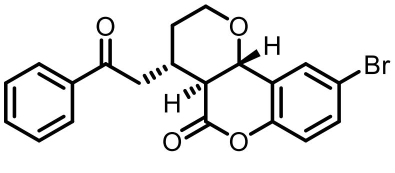
5f

(4S,4aS,10bS)-9-methyl-4-(2-oxo-2-phenylethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5f): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 70% yield (47.0 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.29 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.20 (d, *J* = 6.4 Hz, 1H), 4.36-4.29 (m, 1H), 3.70-3.55 (m, 2H), 3.26-3.12 (m, 3H), 2.35 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 198.0, 168.5, 147.7, 136.3, 135.0, 133.7, 131.1, 129.0, 128.9, 128.2, 120.0, 116.8, 74.5, 72.5, 48.3, 42.0, 39.9, 20.9. **FT-IR (thin film)** 2924, 1766, 1682, 1560, 1466, 1240, 1149, 765 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 9.4 min, t_{minor} = 10.6 min). $[\alpha]_D^{28}$= -50.5 (c 0.150, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{21}H_{21}O_4$ $[M+H]^+$ 337.1434, found 337.1432.



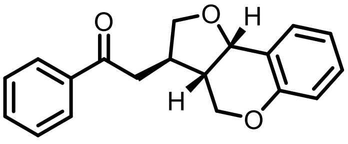
5g

(4S,4aS,10bS)-9-chloro-4-(2-oxo-2-phenylethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5g)**:** Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless semi solid; 66% yield (47.0 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 3H), 7.28 (m, 1H), 7.00 (d, J = 8.6 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.20-4.15 (m, 1H), 3.96 (dd, J = 16.2, 2.3 Hz, 1H), 3.66 (t, J = 12.2 Hz, 1H), 2.83 (dd, J = 16.2, 9.7 Hz, 1H), 2.77-2.68 (m, 1H), 2.61-2.53 (m, 1H), 2.03-1.97 (m, 1H), 1.56-1.50 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 198.8, 168.4, 147.5, 136.9, 133.4, 130.4, 129.4, 128.9, 128.4, 127.5, 124.8, 117.8, 72.3, 67.7, 46.6, 43.5, 31.8, 31.6. **FT-IR (thin film)** 2924, 1768, 1681, 1557, 1465, 1242, 1144, 770 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.4 min, t_{minor} = 15.5 min). $[\alpha]_D^{28}$= -55.3 (c 0.170, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{18}ClO_4$ [M+H]$^+$ 357.0888, found 357.0893.



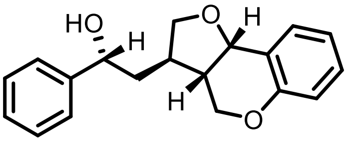
5h

(4S,4aS,10bS)-9-bromo-4-(2-oxo-2-phenylethyl)-3,4,4a,10b-tetrahydro-2H,5H-pyrano[3,2-c]chromen-5-one (5h): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 61% yield (48.8 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.03 (d, J = 7.1 Hz, 2H), 7.55-7.62 (m, 2H), 7.52-7.37 (m, 3H), 6.94 (d, J = 8.6 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.22-4.11 (m, 1H), 3.95 (d, J = 16.1 Hz, 1H), 3.66 (t, J = 12.2 Hz, 1H), 2.83 (dd, J = 16.1, 9.6 Hz, 1H), 2.72 (d, J = 9.1 Hz, 1H), 2.56 (t, J = 11.4 Hz, 1H), 1.99 (d, J = 13.8 Hz, 1H), 1.56-1.46 (m, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 198.8, 168.3, 148.1, 137.0, 133.4, 132.4, 128.9, 128.4, 127.9, 127.7, 118.2, 117.8, 72.3, 67.7, 46.6, 43.5, 31.8, 31.6. **FT-IR (thin film)** 2925, 1768, 1688, 1549, 1458, 1238, 1157, 775 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 14.4 min, t_{minor} = 16.4 min). $[\alpha]_D^{28}$= -33.7 (c 0.160, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{20}H_{18}BrO_4$ [M+H]$^+$ 401.0383, found 401.0392.



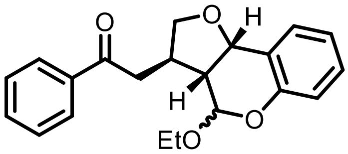
6

1-phenyl-2-((3R,3aS,9bS)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-3-yl)ethan-1-one (6): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless gummy liquid; 70% yield (20.6 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 4.74 (d, *J* = 5.7 Hz, 1H), 4.36-4.29 (m, 2H), 3.74 (t, *J* = 10.8 Hz, 1H), 3.53 (dd, *J* = 9.1, 6.7 Hz, 1H), 3.35 (dd, *J* = 17.7, 7.2 Hz, 1H), 3.23 (dd, *J* = 17.7, 7.3 Hz, 1H), 2.69-2.61 (m, 1H), 2.35-2.28 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 198.6, 155.3, 136.7, 133.6, 131.1, 129.6, 128.9, 128.1, 121.4, 117.1, 73.1, 72.4, 66.0, 42.7, 42.6, 37.0. **FT-IR (thin film)** 2923, 2854, 1681, 1487, 1454, 1222, 1017, 755 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 12.8 min, t_{minor} = 18.3 min). $[\alpha]_D^{26}$= -18.7 (c 0.260, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{19}O_3$ [M+H]$^+$ 295.1329, found 295.1337.



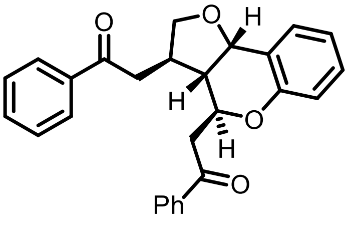
7

R)-1-phenyl-2-((3R,3aS,9bS)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-3-yl)ethan-1-ol (7): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless sticky liquid; 60% yield (17.8 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.27 (d, *J* = 7.6 Hz, 2H), 7.20-7.13 (m, 3H), 7.05 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.81 (t, *J* = 6.9 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.30-4.25 (m, 1H), 3.91-3.85 (m, 1H), 3.73 (m, 2H), 2.82-2.57 (m, 4H), 2.24-2.14 (m, 1H), 1.8-1.71 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 154.8, 142.2, 130.1, 128.6, 128.5, 127.4, 126.1, 122.0, 120.5, 116.6, 69.5, 62.7, 41.4, 33.8, 33.7, 30.4, 28.8. **FT-IR (thin film)** 2923, 2855, 1490, 1455, 1229, 1032, 753 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 14.0 min, t_{minor} = 10.5 min). $[\alpha]_D^{26}$ = -8.7 (c 0.160, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{21}O_3$ $[M+H]^+$ 297.1485, found 297.1491.



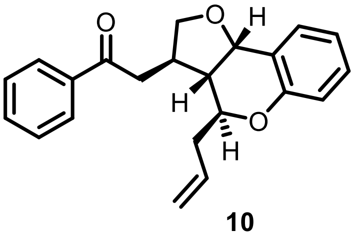
8

2-((3R,3aR,9bS)-4-ethoxy-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-3-yl)-1-phenylethan-1-one (8): Purified by silica-gel column chromatography using 10% ethyl acetate/hexane; colourless sticky liquid; 90% yield (30.4 mg).The dr value was found to be 1.4:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98 (m, 4H), 7.58 (m, 2H), 7.48 (m, 4H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.22 (q, *J* = 7.4 Hz, 2H), 7.00 (t, *J* = 7.5 Hz, 2H), 6.89 (t, *J* = 8.4 Hz, 2H), 5.29 (d, *J* = 3.3 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 4.98 (d, *J* = 6.9 Hz, 1H), 4.95 (d, *J* = 5.8 Hz, 1H), 4.26-4.22 (m, 1H), 4.21-4.17 (m, 1H), 4.00-3.90 (m, 2H), 3.64 (m, 2H), 3.56 (dd, *J* = 8.7, 5.5 Hz, 2H), 3.52-3.43 (m, 3H), 3.19 (dd, *J* = 17.5, 9.5 Hz, 1H), 3.16-3.10 (m, 2H), 2.53 (dd, *J* = 7.7, 3.4 Hz, 1H), 2.33 (dd, *J* = 12.6, 5.8 Hz, 1H), 1.20 (m, 6H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2, 198.8, 152.0, 151.6, 136.8, 136.6, 133.5, 133.4, 129.9, 129.8, 129.6, 129.5, 128.9, 128.8, 128.2, 128.2, 123.0, 122.5, 122.2, 122.0, 117.6, 117.4, 100.3, 98.7, 73.8, 73.5, 73.0, 72.6, 65.1, 65.1, 48.0, 47.6, 43.6, 43.2, 37.2, 35.7, 15.2, 15.2. **FT-IR (thin film)** 2924, 2854, 1681, 1633, 1559, 1456, 1215, 757 cm^{-1}. **HPLC Analysis**: ee = 95%, (t_{major} = 17.1 min, t_{minor} = 11.5 min) and ee = 95%, (t_{major} = 16.6 min, t_{minor} = 14.7 min), Chiralpak OD Column, n-Hexane/i-PrOH = 94/6, flow rate 1.0 mL/min, 25 °C, λ = 254 nm. **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{21}H_{23}O_4$ $[M+H]^+$ 339.1596, found 339.1591.



9

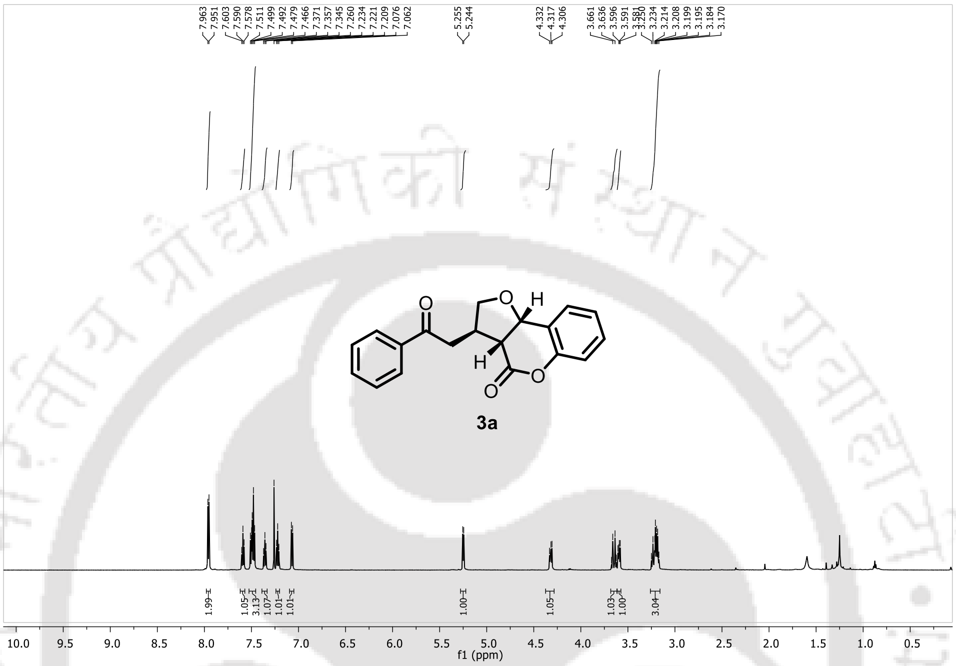
2,2'-((3R,3aS,4S,9bS)-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromene-3,4-diyl)bis(1-phenylethan-1-one) (9): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; brown sticky liquid; 40% yield (25.8 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.06-8.02 (m, 2H), 8.01-7.98 (m, 2H), 7.62-7.57 (m, 3H), 7.52-7.47 (m, 4H), 7.20-7.16 (m, 1H), 6.99-6.64 (m, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 4.79 (d, *J* = 5.7 Hz, 1H), 4.47-4.42 (m, 1H), 4.39-4.35 (m, 1H), 3.59-3.53 (m, 2H), 3.52-3.43 (m, 2H), 3.22 (dd, *J* = 17.6, 7.5 Hz, 1H), 2.29 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 198.7, 198.1, 154.3, 137.4, 136.7, 133.7, 133.4, 130.7, 129.6, 128.9, 128.8, 128.8, 128.6, 128.2, 121.5, 121.1, 117.2, 73.1, 72.4, 72.2, 47.0, 43.0, 41.9, 37.7. **FT-IR (thin film)** 2923, 2855, 1681, 1599, 1454, 1229, 1021, 757 cm^{-1}. **HPLC Analysis**: ee = 96%, (t_{major} = 96.5 min, t_{minor} = 76.2 min) and ee = 95%, (t_{major} = 50.7 min, t_{minor} = 44.9 min), Chiralpak OD Column, n-Hexane/i-PrOH = 94/6, flow rate 1.0 mL/min, 25 °C, λ = 254 nm. **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{25}O_4$ $[M+H]^+$ 413.1753, found 413.1759.

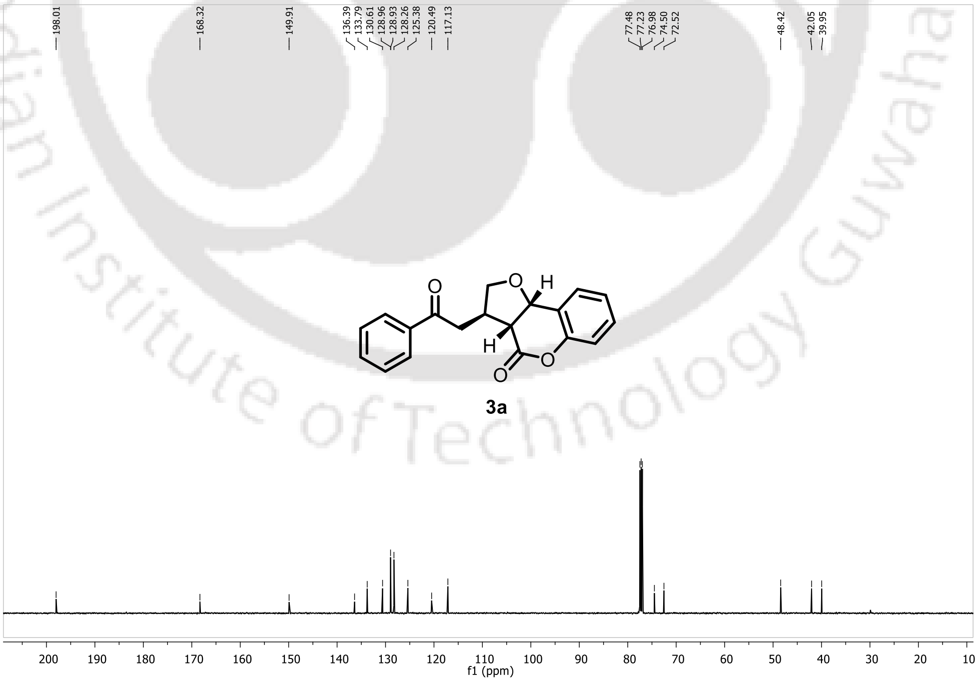


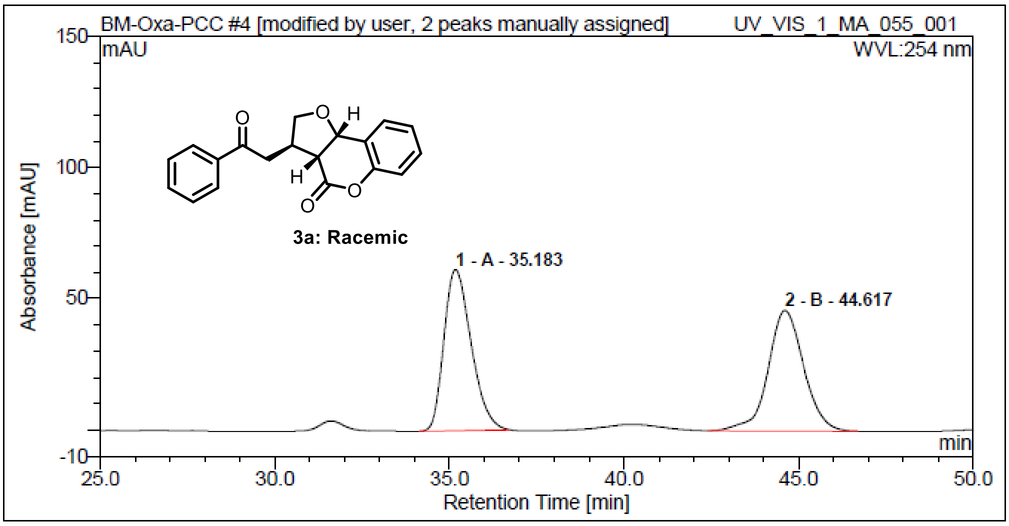
10

2-((3R,3aS,4S,9bS)-4-allyl-2,3,3a,9b-tetrahydro-4H-furo[3,2-c]chromen-3-yl)-1-phenylethan-1-one (10): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless gummy liquid; 75% yield (25.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.00-7.97 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.06-5.97 (m, 1H), 5.15 (t, *J* = 13.8 Hz, 2H), 4.72 (d, *J* = 5.8 Hz, 1H), 4.36 (dd, *J* = 9.1, 7.7 Hz, 1H), 3.80-3.73 (m, 1H), 3.47 (dd, *J* = 9.2, 6.3 Hz, 1H), 3.39 (dd, *J* = 17.6, 5.0 Hz, 1H), 3.23 (dd, *J* = 17.6, 9.4 Hz, 1H), 2.83-2.73 (m, 1H), 2.72-2.64 (m, 1H), 2.47 (dt, *J* = 14.9, 7.3 Hz, 1H), 2.17-2.10 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 198.6, 154.7, 136.7, 134.3, 133.6, 130.7, 129.6, 128.9, 128.2, 121.3, 117.8, 117.1, 75.2, 73.2, 72.7, 46.5, 43.0, 37.8, 36.9. **FT-IR (thin film)** 2924, 2855, 1683, 1589, 1486, 1235, 756 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 10.6 min, t_{minor} = 7.5 min). $[\alpha]_D^{27}$= -20.0 (c 0.35, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{22}H_{23}O_3$ $[M+H]^+$ 335.1642, found 335.1637.

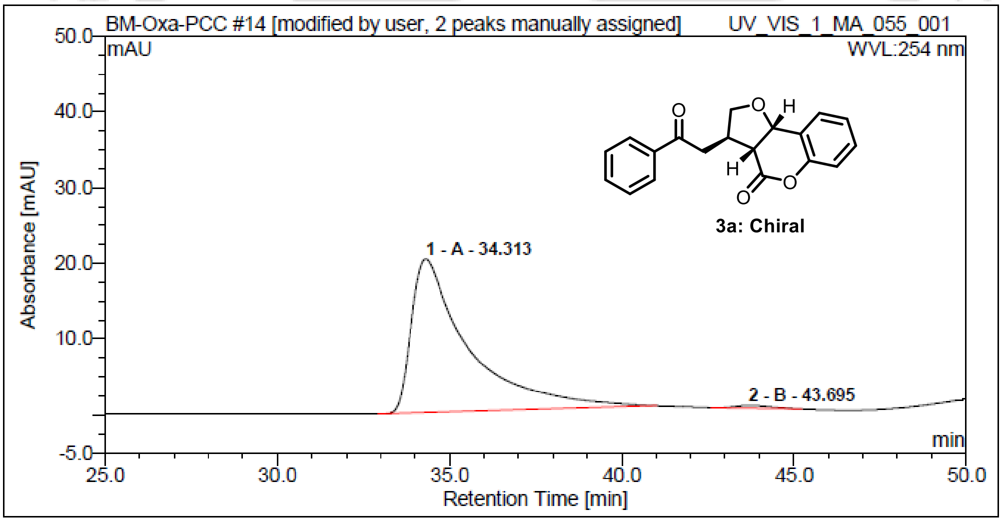
3.7 Selected NMR and HPLC spectra of products



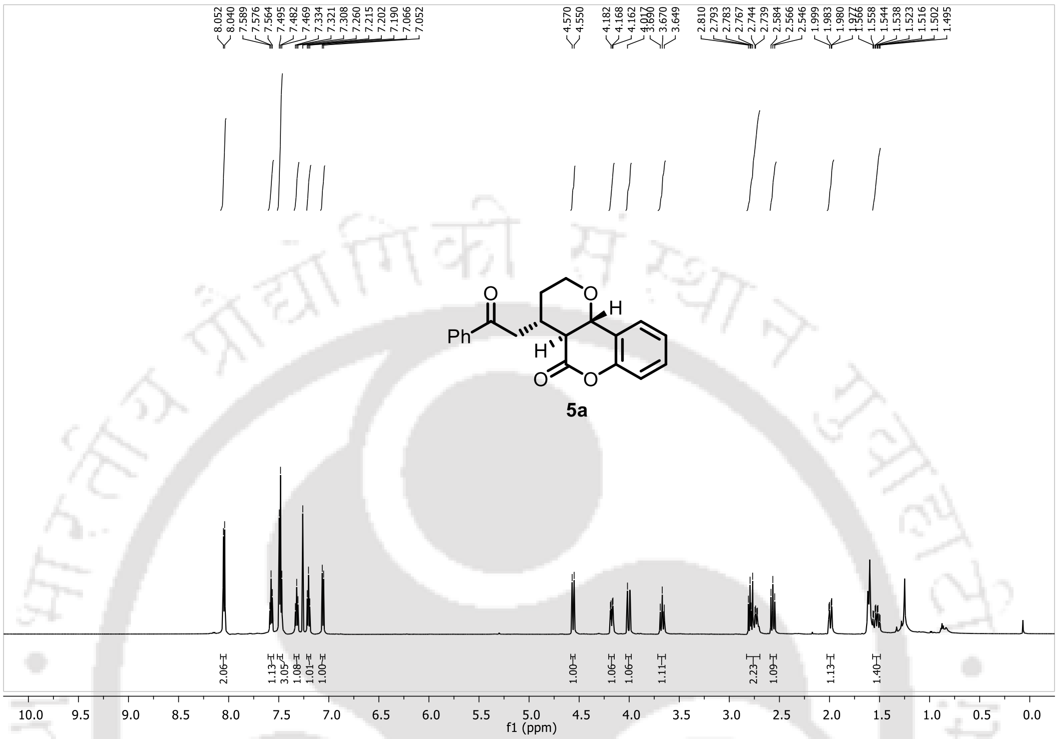


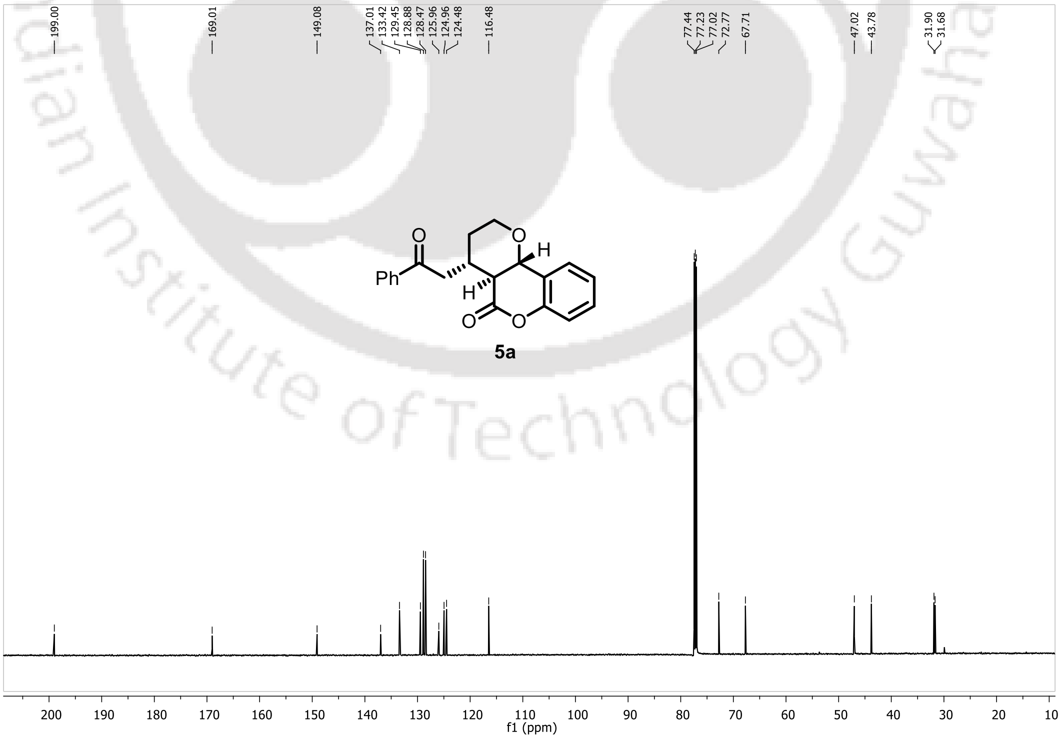


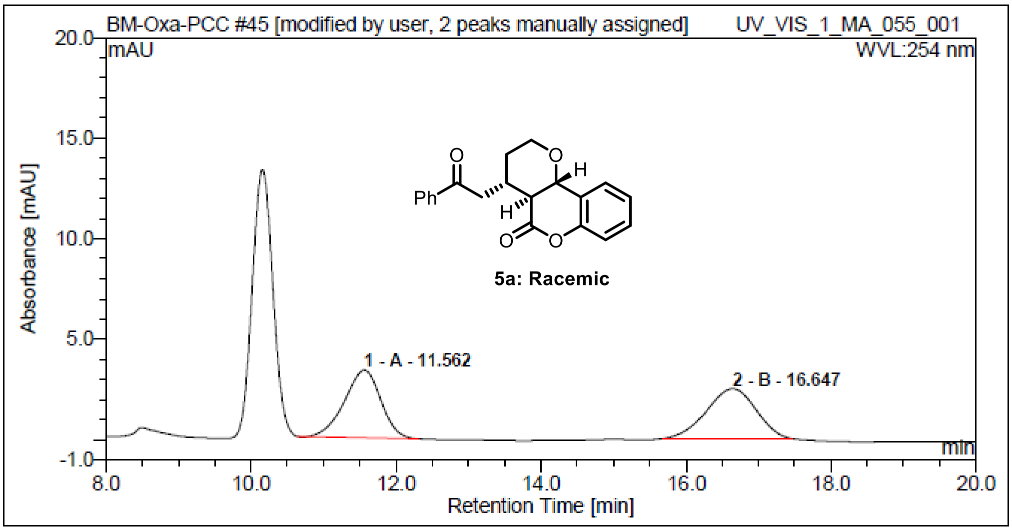
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	35.18	55.14083	50.37682463	61.39832	n.a.
2	B	44.62	54.316	49.62317537	45.906	n.a.



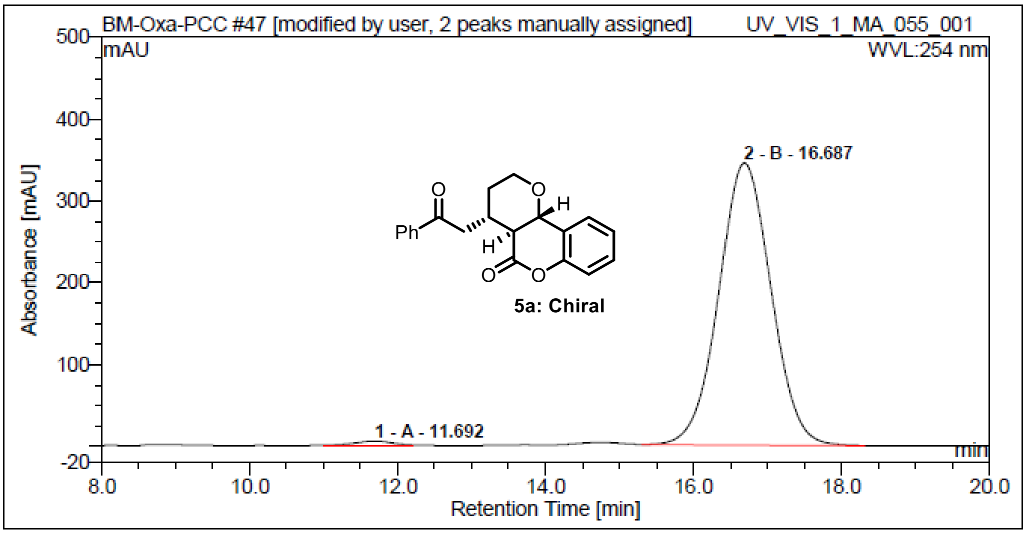
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	34.31	38.99997	98.87647566	20.21964	n.a.
2	B	43.70	0.443	1.123524339	0.365	n.a.


5a
8.052
8.040
7.589
7.576
7.564
7.495
7.482
7.469
7.334
7.321
7.308
7.260
7.215
7.202
7.190
7.066
7.052
4.570
4.550
4.182
4.168
4.162
4.017
3.690
3.670
3.649
2.810
2.793
2.783
2.767
2.744
2.739
2.584
2.566
2.546
1.999
1.983
1.980
1.977
1.566
1.558
1.544
1.538
1.523
1.516
1.502
1.495
O
O
H
Ph
H
O
O
2.06
1.13
3.05
1.08
1.01
1.00
1.00
1.06
1.06
1.11
2.23
1.09
1.13
1.40
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


5a
199.00
169.01
149.08
137.01
133.42
129.45
128.88
128.47
125.96
124.96
124.48
116.48
77.44
77.23
77.02
72.77
67.71
47.02
43.78
31.90
31.68
O
O
H
Ph
H
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

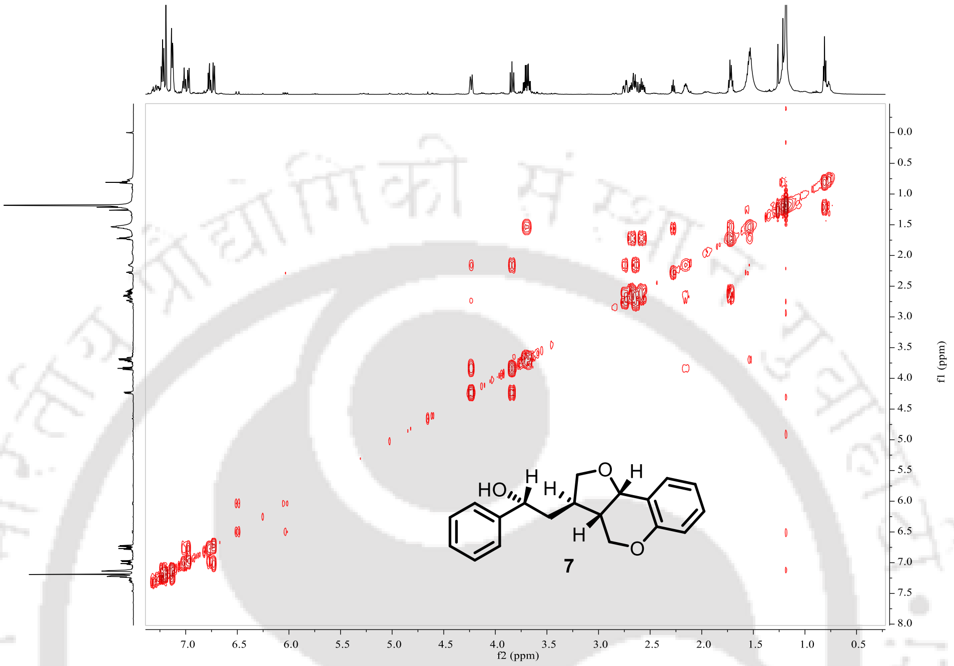


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	11.56	1.983626	50.09703039	3.38297	n.a.
2	B	16.65	1.976	49.90296961	2.497	n.a.

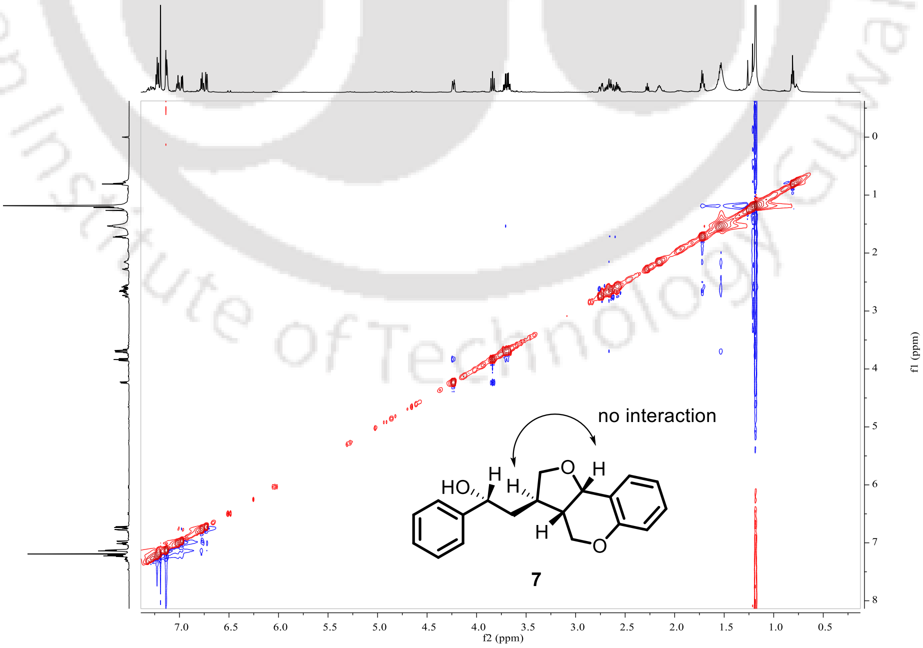


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	11.69	2.540586	0.89022008	4.73812	n.a.
2	B	16.69	282.848	99.10977992	344.898	n.a.

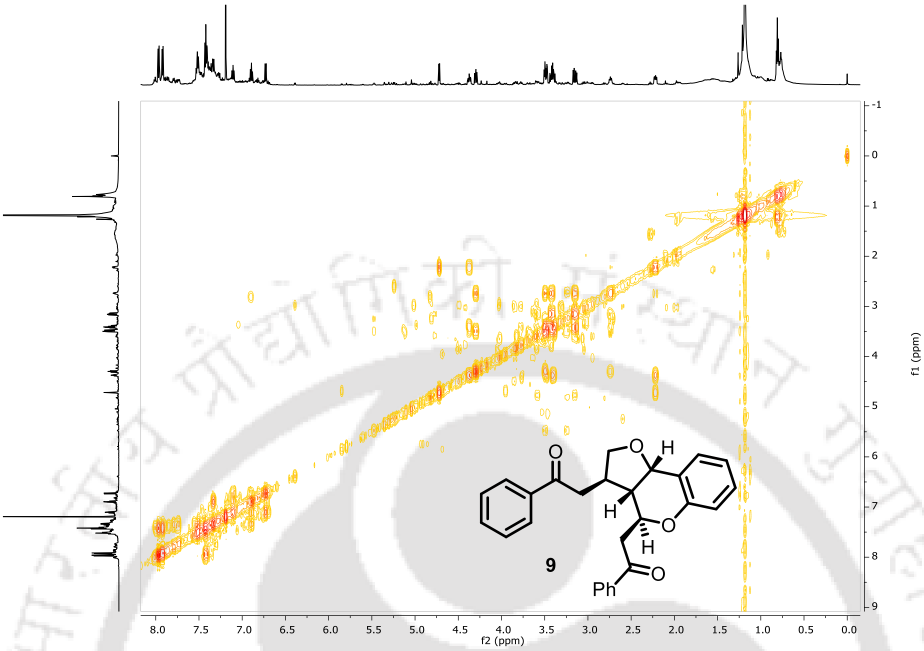
COSY spectra of 7



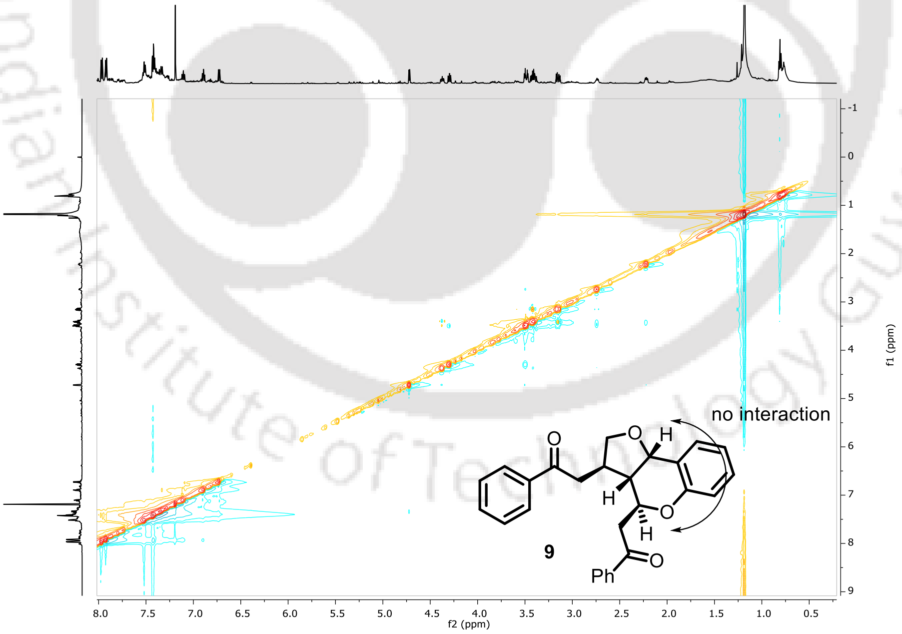
NOESY spectra of 7



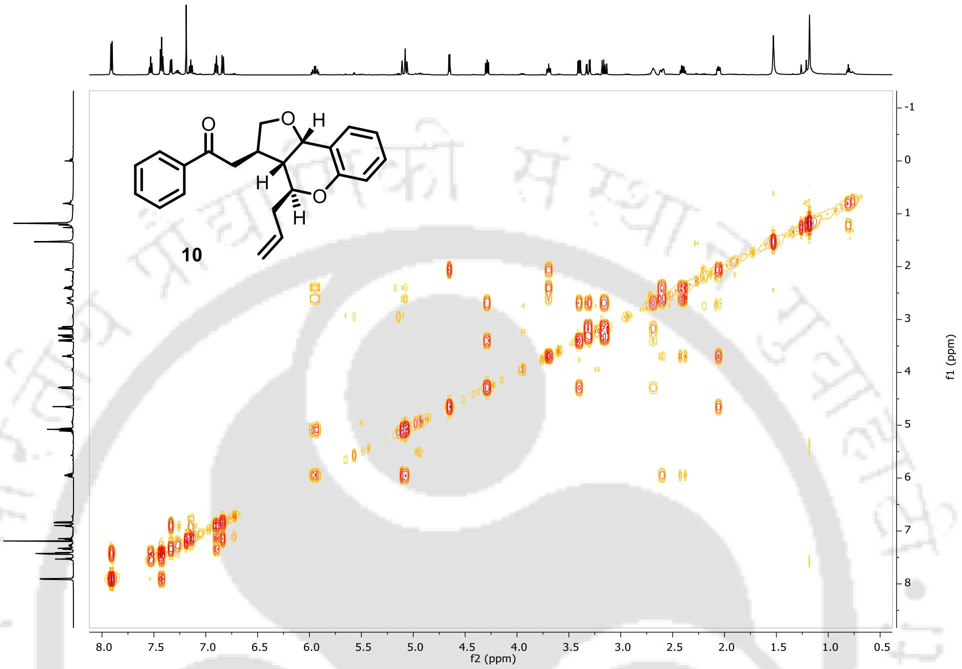
COSY spectra of 9



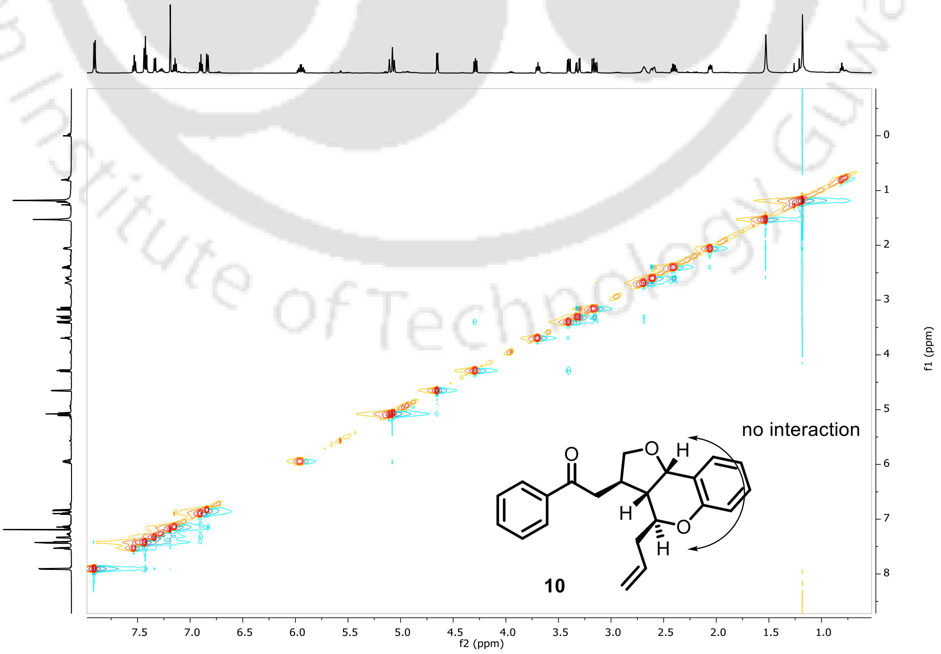
NOESY spectra of 9



COSY spectra of 10



NOESY spectra of 10



3.8 References

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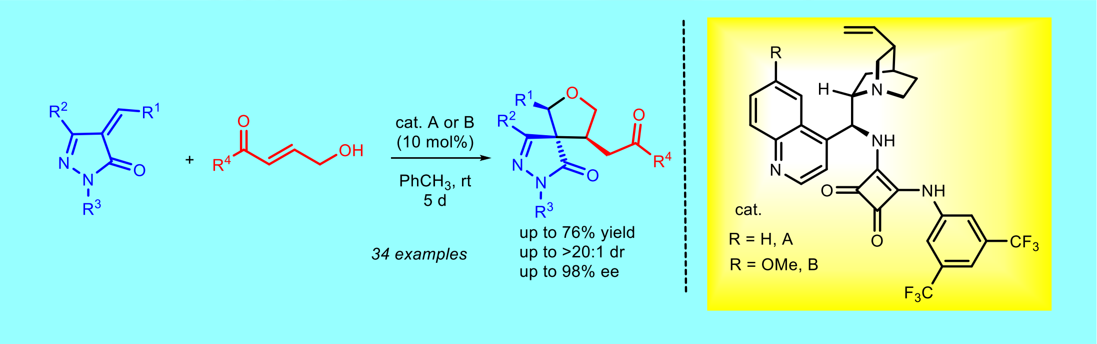
23. CCDC 1849827 (**3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.

24. CCDC 1849828 (**5e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.

Chapter 4

Highly Diastereo- and Enantioselective Synthesis of Spiro-Tetrahydrofuran-Pyrazolones via Organocatalytic Cascade Reaction between γ-Hydroxyenones and Unsaturated Pyrazolones



J. Org. Chem. **2018**, *83*, 8645-8654.

4.1 Introduction

Over the last decade, pyrazole and pyrazolone derivatives have been extensively studied due to their diverse applications as potential pharmaceutical agents, synthetic scaffolds, photographic couplers, and chelating agents etc.[1] In particular, spiropyrazolones combining stereogenic cycloalkane/cycloalkane heterocycle and pyrazolone motifs, have attracted attention because of their potent bioactivities in medicinal chemistry.[2a] For instance, pyrazolone related spirocyclic derivatives can act as neuroprotective agent, effective analgesic and antipyretic agent, antibacterial agent and also as type-4-phosphodiesterase inhibitor.[2b,c]

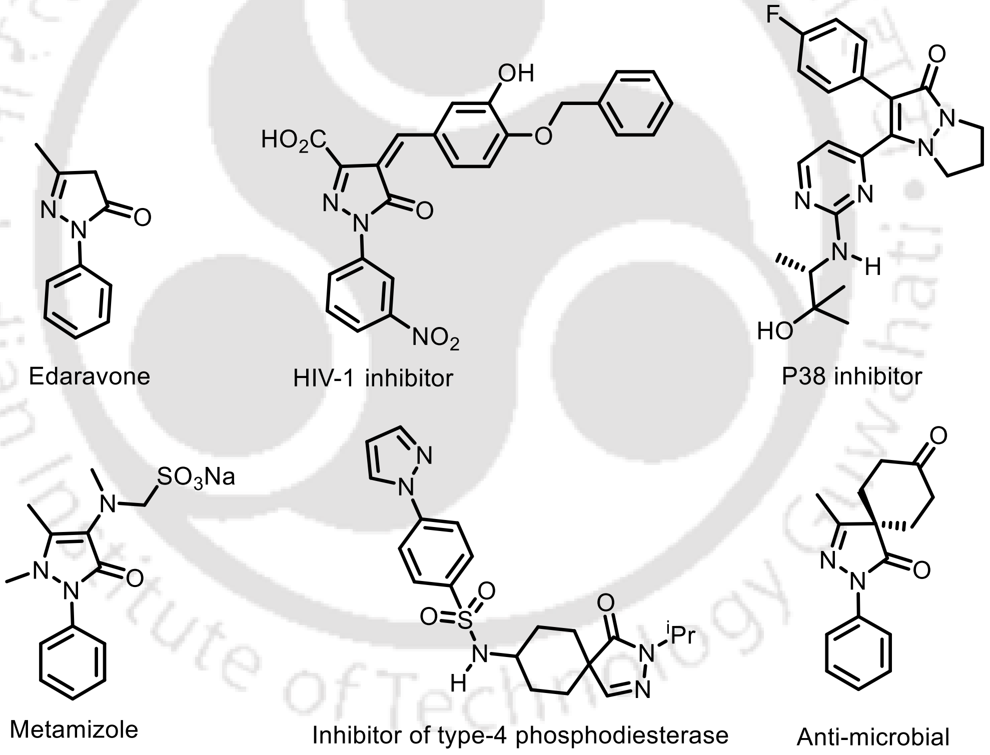


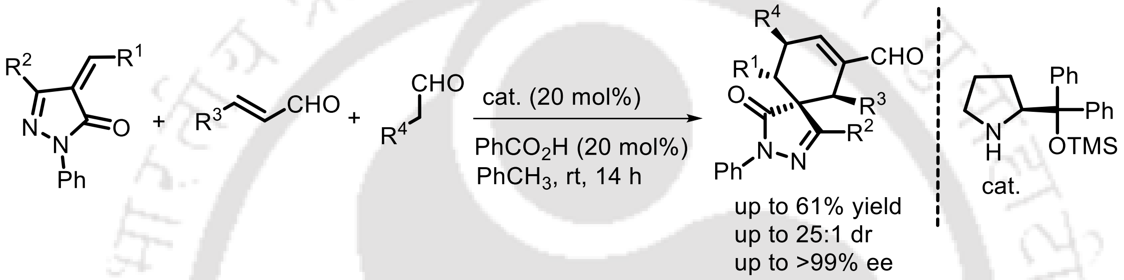
Figure 1. Biologically active spiropyrazolone derivatives.

Thus, the development of highly efficient methods to prepare optically active spiro-pyrazolones,[3] in particular unprecedented O-heterocycle embedded spiropyrazones, would be of great utility for the discovery of new chiral drugs.

4.2 Known strategies for organocatalytic asymmetric synthesis of spiropyrazolones from unsaturated pyrazolones

4.2.1 Organocatalytic asymmetric synthesis of spiropyrazolones

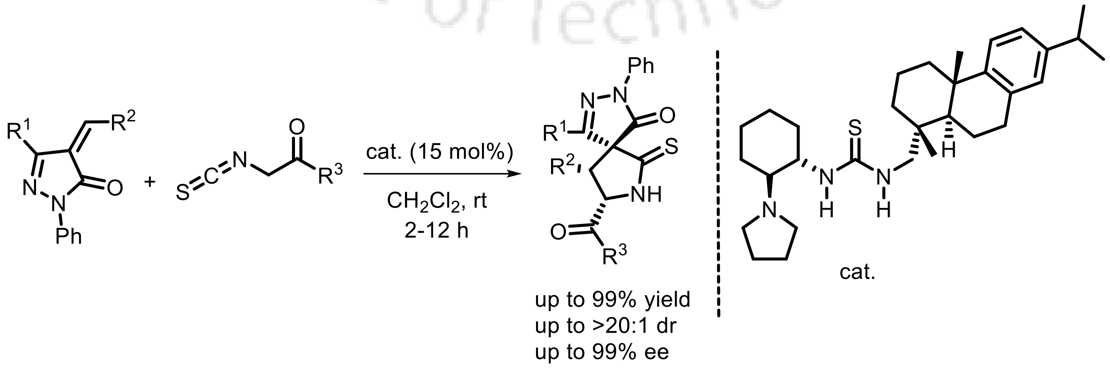
Rios and co-workers first reported organocatalytic asymmetric synthesis of spiropyrazolones from unsaturated pyrazolones *via* a three component reaction with aldehydes and unsaturated aldehydes using prolinol derived seecondary amine catalyst. The aforementioned protocol provided the desired product in moderate yields with good to excellent diastereo- and enantioselectivities (Scheme 1).[4]



Scheme 1. The first organocatalytic asymmetric synthesis of spiropyrazolones by Rios et al.

4.2.2 Rosin-derived tertiary amine-thiourea catalyzed enantioselective [3+2] cycloaddition of *α*-isothiocyanato imides with unsaturated pyrazolones

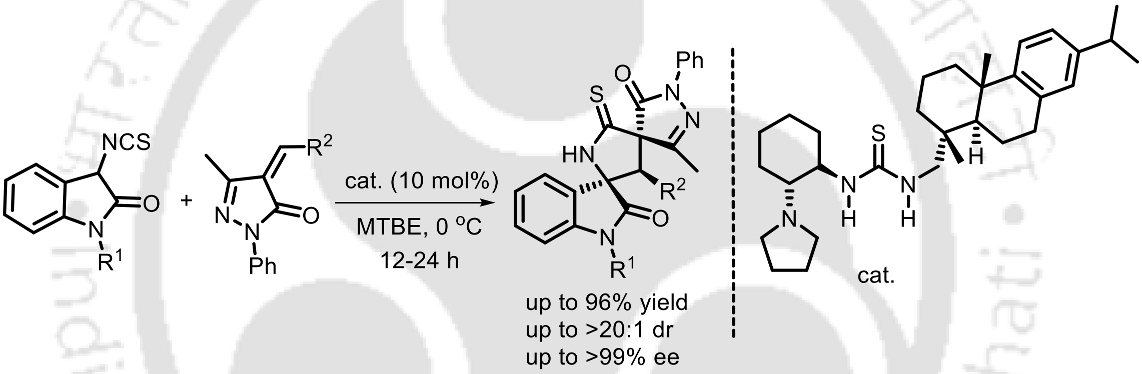
A highly enantioselective [3+2] cycloaddition of *α*-isothiocyanato imides with unsaturated pyrazolones by using rosin-derived tertiary amine-thiourea to form functionalized spiropyrazolones bearing three contiguous stereogenic centers in high yields and with high levels of enantio- and diastereoselectivities (up to 99% yield, up to >20:1 dr and 99% ee respectively) was developed by Wang et al. in 2012 (Scheme 2).[5]



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

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

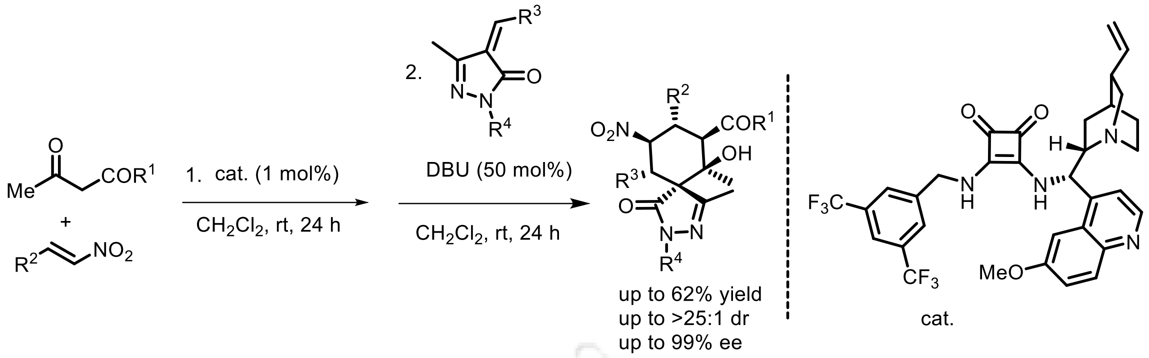
After one year the same group reported an organocatalytic asymmetric Michael-cyclization sequence of 3-isothiocyanato oxindoles and unsaturated pyrazolones with rosin-derived bifunctional tertiary amine thiourea as catalyst, providing polycyclic spiro[oxindole/thiobutyrolactam/pyrazolone] core structures in high yields, excellent diastereo- and enantioselectivities (Scheme 3).[6]



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

4.2.4 The synthesis of densely functionalized spirocyclohexanepyrazolone

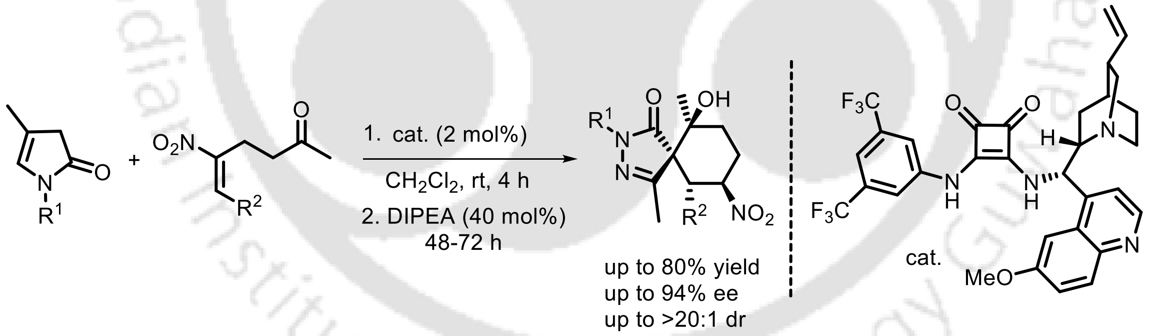
In 2014, Enders et al. also shown the synthesis of a variety of spirocyclohexanepyrazolone derivatives bearing six stereocentres *via* sequential organocatalytic reactions. The strategy allowed the synthesis of densely functionalized spirocyclohexanepyrazolones in moderate to good yields, excellent diastereoselectivities and with outstanding enatioselectivities (Scheme 4).[7]



Scheme 4. The synthesis of a variety of spirocyclohexanepyrazolone derivatives bearing six stereocentres *via* sequential organocatalytic reactions by Ender et al.

4.2.5 Chiral cinchona derived squaramide catalyzed synthesis spirocyclohexane pyrazolone

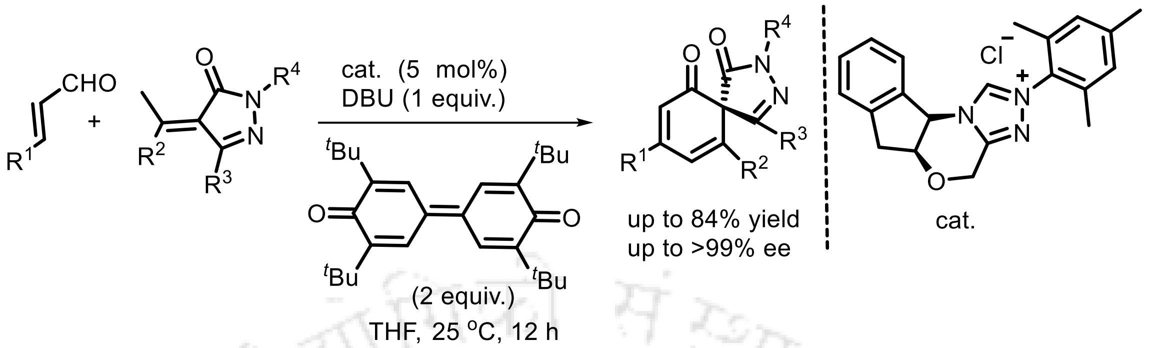
The synthesis of spirocyclohexane pyrazolones containing four continuous stereogenic centres *via* the reaction of 3-methyl-1-aryl-2-pyrazolin-5-one with (*E*)-5-nitro-6-aryl-hex-5-en-2-one and catalyzed by chiral cinchona derived squaramide catalyst was reported by Chen et al. in 2016. The desired spirocyclohexane compounds were formed in high yields with excellent diastereo- and enatioselectivities. (Scheme 5).[8]



Scheme 5. Chiral cinchona derived squaramide catalyzed synthesis of spirocyclohexane pyrazolones containing four continuous stereogenic centres by Chen et al.

4.2.6 Enantioselective synthesis of spirocyclohexadienones catalyzed by NHC

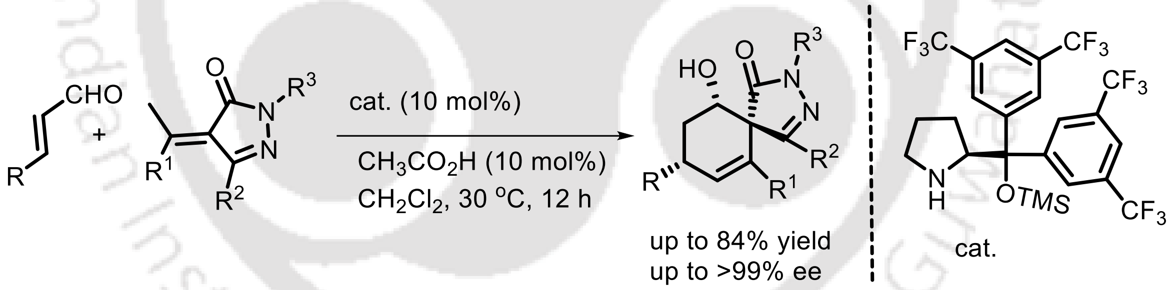
Recently, Biju et al. reported formal [3+3] annulation reaction of enals with α-arylidene pyrazolinones for the enantioselective synthesis of spirocyclohexadienones catalyzed by NHC. Under the optimized reaction conditions, the desired products were obtained in acceptable yields up to 84% and with excellent enatioselectivities >99% ee (Scheme 6).[9]



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

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

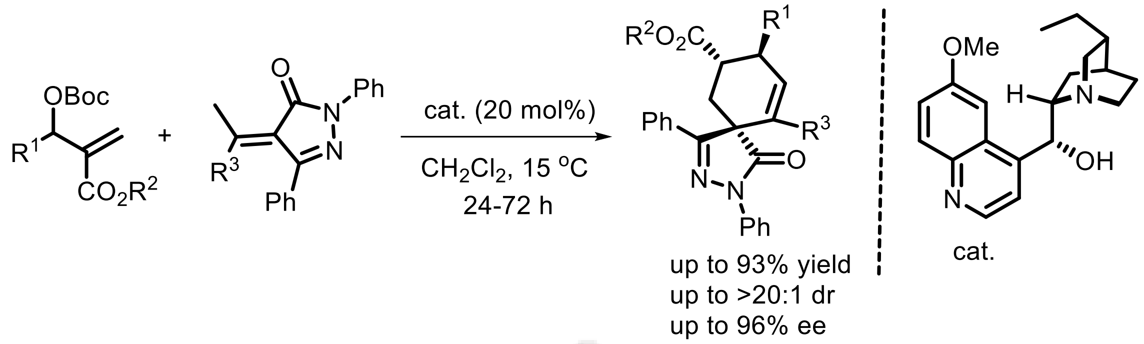
Very recently, Biju et al. reported the secondary amine-catalyzed cascade reaction of *α*,*β*-unsaturated aldehydes with *α*-arylidene pyrazolinones for the synthesis of pyrazolone-fused spirocyclohexenols (Scheme 7).[10]



Scheme 7. Secondary amine-catalyzed cascade reaction of *α*,*β*-unsaturated aldehydes with *α*-arylidene pyrazolinones by Biju et al.

4.2.8 Enantioselective Synthesis of Spirocyclohexenes

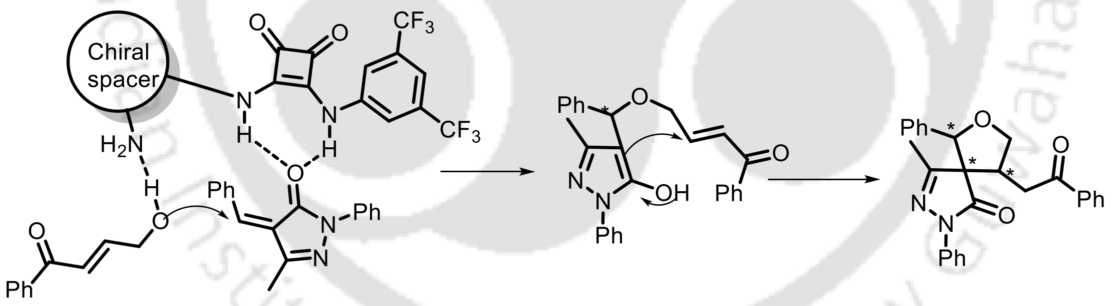
In 2017, Guo et al. reported Lewis-base-catalyzed enantioselective [3+3] annulation reaction of Morita-Baylis-Hillman (MBH) carbonates with *α*-arylidene pyrazolinones for the synthesis of the pyrazolone-fused spirocyclohexenes bearing an all-carbon quaternary stereocenter in high yields with good to excellent diastereoselectivities and excellent enantioselectivities (Scheme 8).[11]



Scheme 8. Lewis-base-catalyzed enantioselective [3+3] annulation reaction of Morita-Baylis-Hillman (MBH) carbonates by Guo et al.

4.3 Concept

Realizing the potential of heterocycle incorporated spiropyrazolones for medicinal chemistry, we embarked in a highly diastereo- and enantioselective double Michael reaction between unsaturated pyrazolones and γ-hydroxyenones. We envisioned that chiral bifunctional catalyst can be used as organocatalyst for the simultaneous dual activation of γ-hydroxyenones and pyrazolones (Scheme 9).



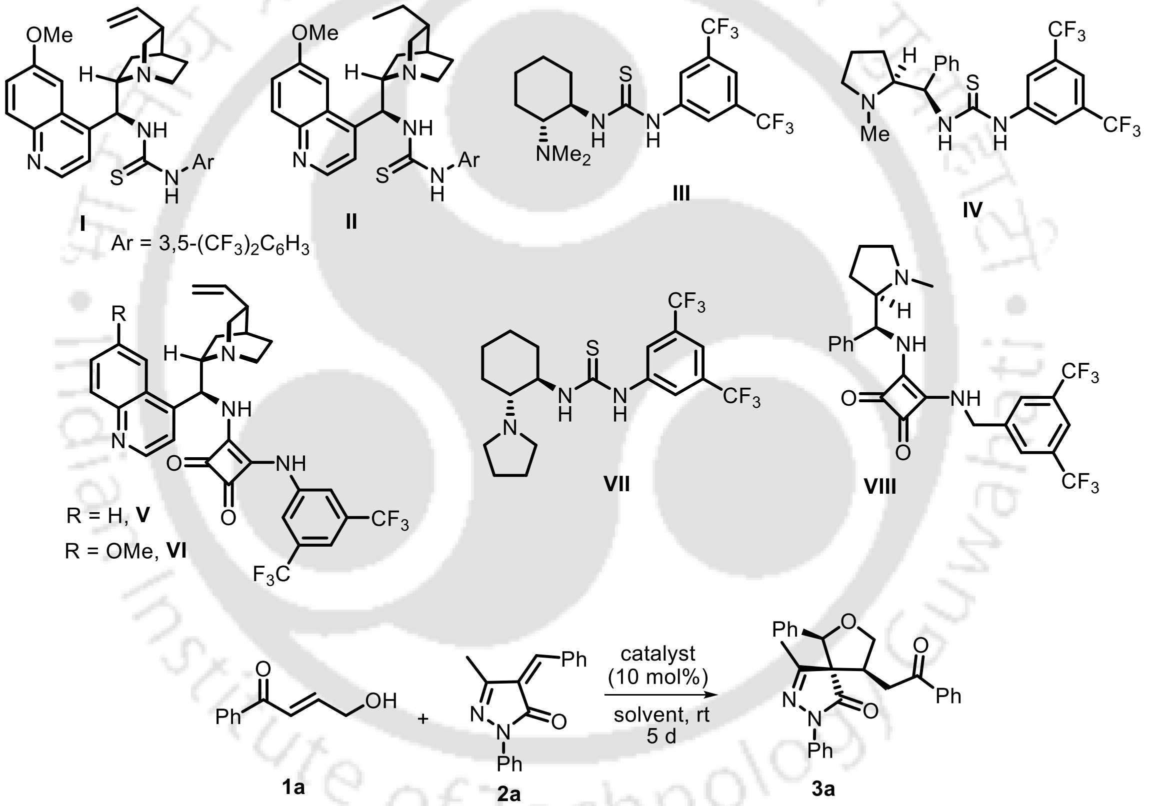
Scheme 9. Double Michael reaction between unsaturated pyrazolones and γ-hydroxyenone.

4.4 Results and discussion

4.4.1 Optimization of catalyst and reaction conditions

We began our investigation by performing a model reaction between (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**)[12] and alkylidene pyrazolone **2a** with quinine derived bifunctional thiourea catalyst **I** in toluene solvent at room temperature (Table 1).

Table 1. Catalyst screening and optimization of reaction conditions



entry[a]	catalyst	solvent	time (d)	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCH_3$	5	62	18:1	28
2	**II**	$PhCH_3$	5	56	18:1	36
3	**III**	$PhCH_3$	5	60	14:1	40

4	**IV**	$PhCH_3$	5	52	15:1	32
5	**V**	**$PhCH_3$**	**5**	**70**	**>20:1**	**96**
6	**VI**	**$PhCH_3$**	**5**	**68**	**>20:1**	**96**
7	**VII**	$PhCH_3$	5	50	14:1	30
8	**VIII**	$PhCH_3$	5	58	16:1	44
9	**V**	CH_2Cl_2	5	50	17:1	90
10	**V**	$(CH_2Cl)_2$	5	40	17:1	95
11	**V**	MTBE	5	55	18:1	94
12	**V**	$PhCF_3$	5	60	>20:1	94
13	**V**	Mesitylene	5	62	>20:1	92

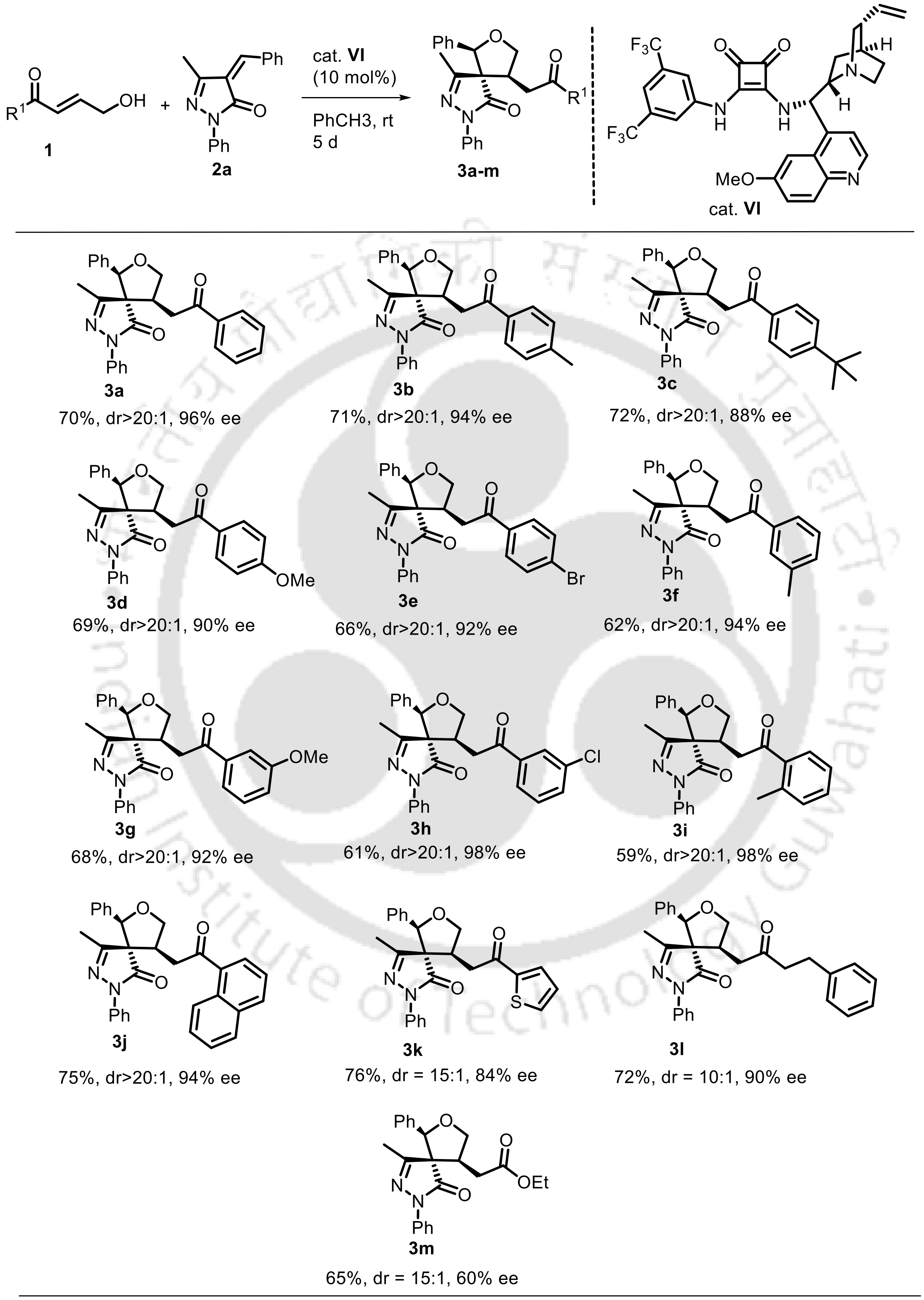
[a] Reaction condion: 0.12 mmol of **1a** with 0.1 mmol of **2a** in 0.4 mL solvent using 10 mol% catalyst. [b] Isolated yield after silica gel column chromatography. [c] Determined by 1H NMR. [d] Determined by chiral HPLC.

Pleasingly, after stirring for 5 days, the desired spiropyrazolone **3a** having tetrahaydrofuran motif was isolated in 62% yield with 18:1 dr but the enantioselectivity was less (entry 1). Hydroquinine derived thiourea **II** also could not improve the enantioselectivity of the reaction (entry 2). Then Takemoto catalyst **III** and proline derived bifunctional thiourea **IV** were employed in the reaction (entries 3-4). Though the yields and diastereomeric ratios of **3a** with these catalysts were good but the enantiomeric excesses were low. Then we turned our attention to screen squaramide catalysts[13] **V** and **VI** and the results were promising for us (entries 5-6). Gratifyingly, an excellent enantioselectivity of 96% and diastereoselectivity of >20:1 were achieved with both catalysts and also acceptable yields were detected. However, catalysts **VII** and **VIII** were not suitable and low level of enantioselectivities were obtained (entries 7 and 8). After having the optimum catalysts **V** and **VI** in hand, we screened different solvents in this reaction. Interestingly, the outcome did not alter so much in terms of enantioseletivities. Halogenated solvents such as DCM and DCE were screened and slightly less enantiomeric excesses were obtained (Table 2, entries 9-10). Moderate conversion was also observed in an ether solvent like MTBE providing 50% yield, 94% ee and 17:1 dr (Table 2, entry 11). Then product **3a** was obtained with 94% and 92% ee respectively in $PhCF_3$ and mesitylene solvents (Table 2, entries 13-14). Thus, both catalysts **V** and **VI** in $PhCH_3$ solvent was found to be the best choice in terms of yield and enantioselectivity (Table 2, entry 5-6).

4.4.2 Substrate scope

With the best optimized conditions established, the scope and generality of the cascade reaction was studied. At the beginning, a variety of *γ*-hydroxyenones **1** having different keto substitutents were investigated (Scheme 10). Interestingly, catalyst **VI** was the best catalyst for *γ*-hydroxyenones. As can be seen in Scheme 10, a wide range of aryl group containing *γ*-hydroxyenones were tested and delightfully excellent enantioselectivities were obtained. For example, *p*-tolyl containing enone **1b** delivered product **3b** in 71% yield with 94% ee. 4-tert-Butyl enone **1c** provided product **3c** with 72% yield and in slightly less enantiomeric excess. A smooth conversion was also detected with enone **1d** having 4-anisyl motif. Enone **1e** with 4-bromoaryl group also took part in the reaction and high enantioselectivity was attained for **3e**. Then different *m*-substituted aryl enones were employed in the reaction and excellent results were detected. An *o*-substituted aryl enone **1i** also underwent smooth reaction with pyrazolone **2a** delivering product **3i** in excellent enantioselectivity as well as with high diastereoselectivity. The reaction outcome was not much different with 1-naphthyl substituted enone **1j** and product **3j** was isolated in 75% yield and 94% ee. A heteroaromatic group was also tolerated in the reaction; though acceptable yield was obtained for **3k**, slight less enantioselectivity of 84% was observed. Then an aliphatic enone **1l** was prepared and engaged in the reaction. To our delight, the desired product **3l** was obtained in high yield, 10:1 dr and 90% ee.

Scheme 10. Scope of γ-hydroxyenones^{a}



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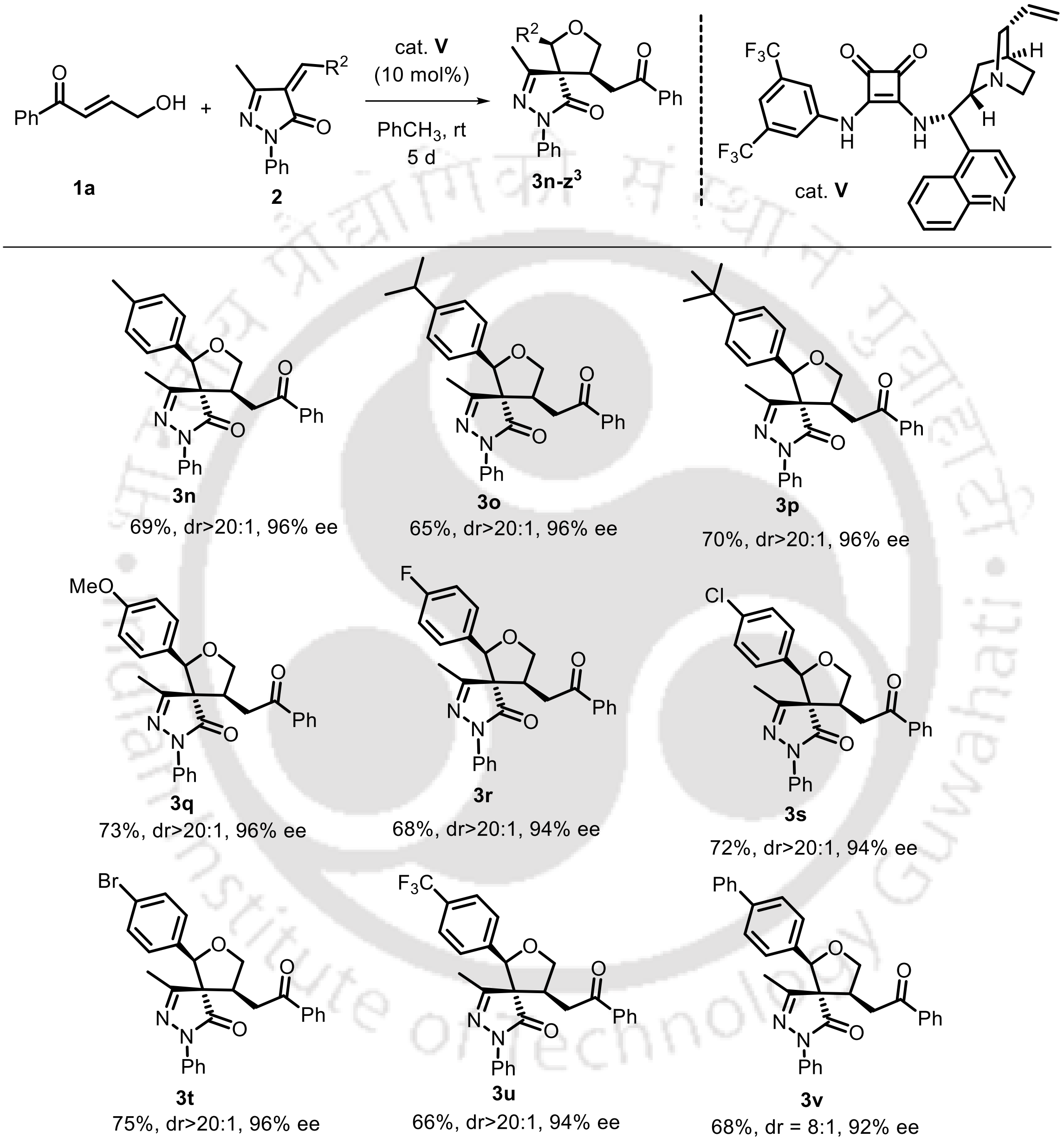
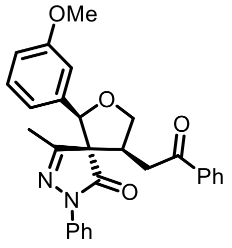
[a]Reactions were carried out with 0.2 mmol of **1** with 0.24 mmol of **2a** in 0.8 mL $PhCH_3$ using 10% **VI** at rt for 5 days. Yields correspond to isolated yields after silica gel column chromatography. Diastereoselectivity was determined by ^1H NMR. ees were determined by chiral HPLC.

Interestingly, an ester **1m** can also participate in the reaction to provide **3m**; though the obtained diastereoselectivity was high, enantioselectivity was moderate.

In the next phase, screening of a variety of pyrazolones **2** having different benzylidene substitutents were investigated with catalyst **V** (Scheme 11). It turned out that a range of electron-withdrawing and electron-donating groups can be incorporated in the *ortho*-, *meta*- and *para*-position of the aryl group without having much pronounced effects on the yields and enantioselectivities. Here also, excellent diastereoselectivity was maintained. For example, pyrazolone **2n** having *p*-tolyl group provided the single disastereomeric product **3n** in 96% ee. The reaction outcome was also not changed with other 4-alkylphenyl substituents (**3o**-**3p**). Product **3q** having 4-anisyl group was isolated in slightly higher yield of 73% and in 96% ee. Then 4-halosubstituted pyrazolones **2r**-**2t** were screened in the reaction and excellent results were achieved. In particular high yield was obtained for product **3t** having 4-bromophenyl group. Pyrazolone **2u** having 4-trifluromethyl substituent also participated in the reaction delivering the product **3u** in 66% yields with 94% ee. Pyrazolone **2v** having biphenyl motif was also tolerated in the reaction and provided product **3v** in 68% yield and 92% ee albeit slight lower diastereoselectivity (8:1 dr) was attained. Smooth conversions were also observed with *meta*-substituted pyrazolones **2w**-**2y** and the corresponding products **3w**-**3y** were obtained in acceptable yields with excellent diastereo- and enantioselectivities. The reaction also progressed well with *o*-substituted pyrazolone **2z** and acceptable enantioslectivity was detected. A disubstituted aryl group containing pyrazolone **2z^1** also took part in the reaction and product **3z^1** was obtained in high enantioselectivity. Then a heteroaryl 2-thienyl group was incorporated in the pyrazolone motif and gratifyingly the corresponding product **3z^2** was isolated in an acceptable yield with high enantioselectivity though the diastereoselectivity got reduced slightly. Finally, an aliphatic cyclohexyl substituted pyrazolone **2z**^{3} was employed in the reaction and pleasingly product **3z**^{3} also exhibited similar results.

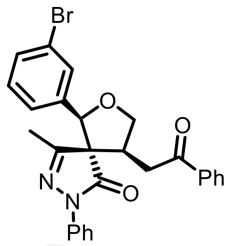
Scheme 11. **Scope of pyrazolones with varied benzylidene substituent**[a]





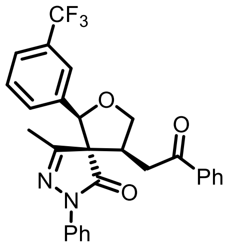
3w

58%, dr>20:1, 96% ee



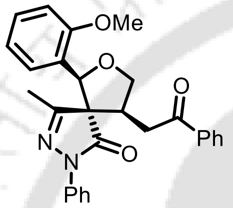
3x

55%, dr>20:1, 94% ee



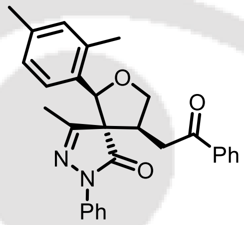
3y

57%, dr>20:1, 96% ee



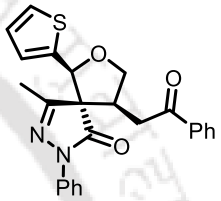
3z

62%, dr>20:1, 88% ee



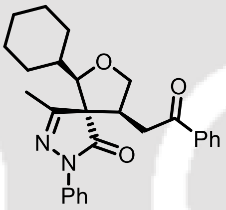
3z^1

64%, dr>20:1, 96% ee



3z^2

57%, dr = 9:1, 90% ee



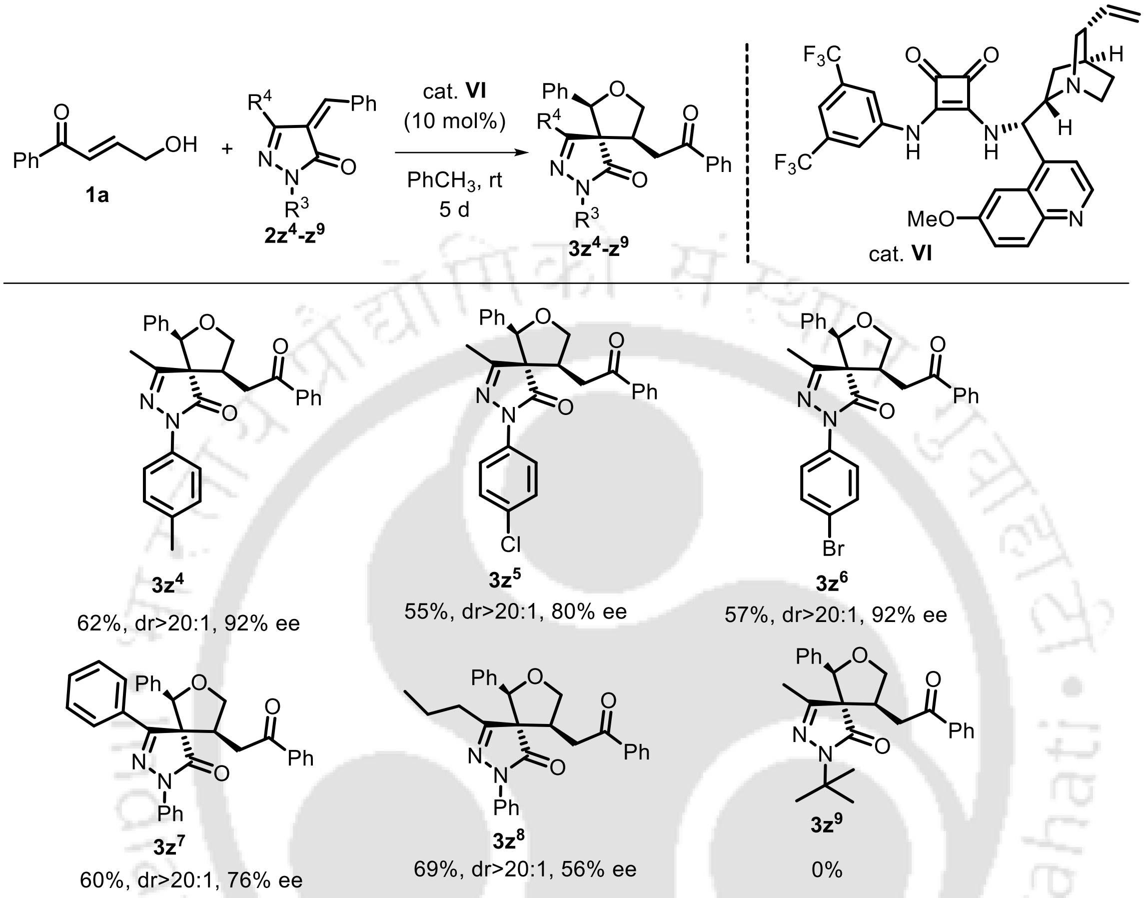
3z^3

50%, dr = 9:1, 90% ee

[a]Reactions were carried out with 0.2 mmol of **1a** with 0.24 mmol of **2** in 0.8 mL $PhCH_3$ using 10% **V** at rt for 5 days. Yields correspond to isolated yields after silica gel column chromatography. Diastereoselectivity was determined by ^{1}H NMR. ees were determined by chiral HPLC.

The generality of the reaction was further extended by incorporating pyrazolones **2** with varied *N*-substitutions and hydrazone carbon substitutions (Scheme 12). Accordingly, a variety pyrazolones **2z^4-2z^6** with different *N*-substitutions and **2z^7-2z^8** with different *N*-substitutions and **2z^7-2z^8** with different hydrazone carbon substitutions were prepared and employed in the reaction. To our delight, the reactions progressed well and the products **2z^4**-2z**^{8}** were attained in moderate to excellent enantioselectivities. Then pyrazolones with *N*-aliphatic substitutions (**2z^9**) were employed in the reaction but unfortunately no product formation was observed.

Scheme 12. Scope of pyrazolones with varied *N*-substituents and hydrazone C-substituents[a]



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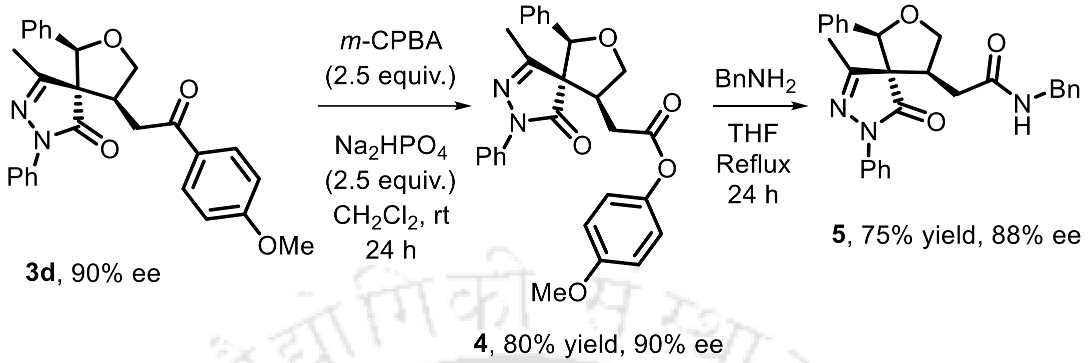
[a]Reactions were carried out with 0.2 mmol of **1a** with 0.24 mmol of **2z^4-z^9** in 0.8 mL $PhCH_3$ using 10% **VI** at rt for 5 days. Yields correspond to isolated yields after silica gel column chromatography. Diastereoselectivity was determined by ^{1}H NMR. ees were determined by chiral HPLC.

4.4.3 Synthetic transformations of 3d

To exhibit the synthetic utility of our method, few derivatives were prepared from **3d** (Scheme 13). Bayer-Villiger oxidation of **3d** selectively provided ester **4** in 80% yield and the enantioselectivity was retained. Then a substitution reaction of **4** with benzylamine was performed. The reaction resulted in the formation of amide **5** with moderate yield and here also the enantioselectivity got almost preserved.



Scheme 13. Synthetic transformations.

4.4.4 Determination of product stereochemistry

The absolute structure of the product **3s** was determined to be (2*R*, 3*S*, 4*S*) by single crystal X-ray crystallography. By analaogy, it is predicted that other products will also have similar absolute configuration.

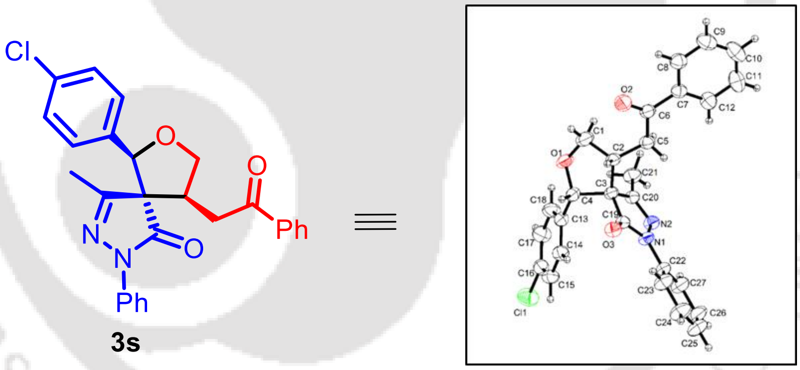


Figure 2. X-ray crystal structure of **3s**.

4.4.5 Proposed TS

Based on the absolute configuration a proposed TS has been drawn in Figure 3. It seems a bifunctional mode of catalysis operates and pyrazolone **2a** is activated by the squaramide motif of the catalyst from the *Si* face. Thus the Michael addition takes place form the *Re* face to generate intermediate **6**. A second Michael cyclization from the *Re* face of the enone then provides **3a**.

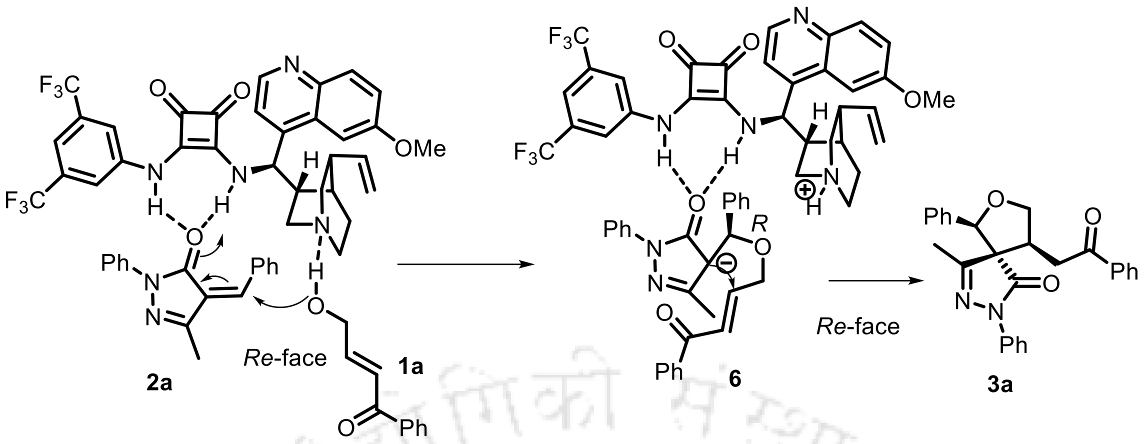


Figure 3. Proposed TS.

4.5 Conclusion

In summary, we have developed the first diastereo- and enantioselective synthesis of spiro-tetrahydrofuran-pyrazolones *via* a mild and operationally simple oxa-Michael/Michael reaction between unsaturated pyrazolones and γ-hydroxyenones. This reaction furnished diverse multi-substituted spiropyrazolones in good yields and with excellent diastero- and enantioselectivities.

4.6 Experimental section

4.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, Daicel Chiralpak ID Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

4.6.2 General procedure for the synthesis of *trans*-γ-hydroxyenones and unsaturated pyrazolones

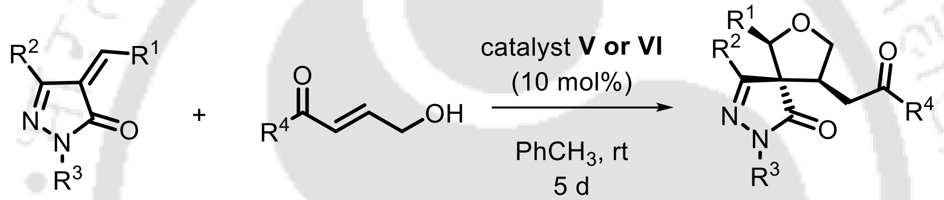
Trans-γ-hydroxyenones were prepared according to reported procedure.[14]

Unsaturated pyrazolones were prepared according to reported procedures.[15]

4.6.3 General procedure for the synthesis of catalyst

The catalysts **I**, **II**, **III** and **VII** were prepared according to reported procedures.[16] The catalyst **IV** was prepared according to reported procedure.[17] The catalysts **V** and **VI** were prepared according to reported procedures.[18] The catalyst **VIII** was prepared according to reported procedure.[19]

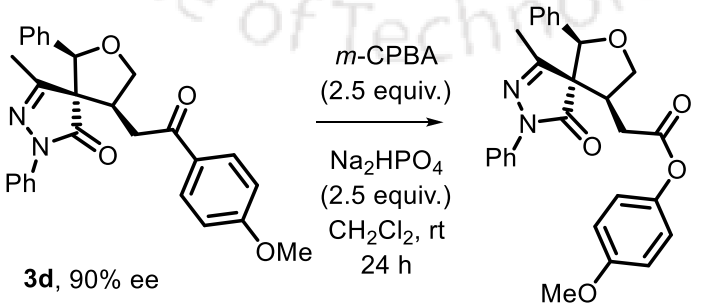
4.6.4 General procedure for the synthesis of compound 3a-3z[8]



1 **2** **3a-3z[8]**

In an oven dried round bottom flask, **1** (0.2 mmol), **2** (0.24 mmol), 10 mol% of catalyst **V** or **VI** were taken, then 0.8 mL of toluene was added to the reaction mixture and stirred at rt for 5 days. Completion of the reaction was checked by TLC. After the completion of the reaction, solvent was concentrated and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10-15%) to afford the desired products **3a-3z[6]**.

4.6.5 General procedure for the preparation of derivatives 4[20]

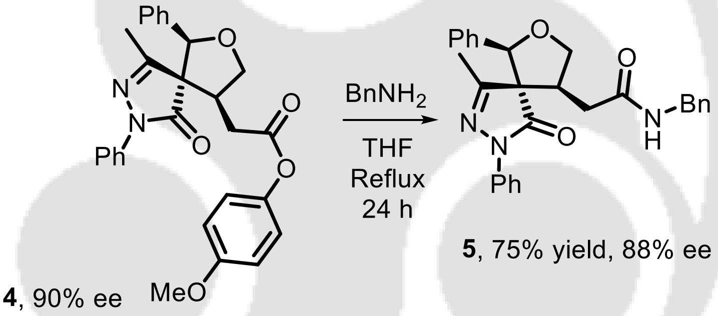


3d, 90% ee

4, 80% yield, 90% ee

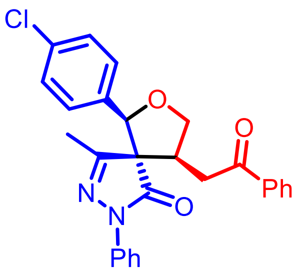
In an oven dried round bottom flask, compound **3d** (45.2 mg, 0.1 mmol) in CH_2Cl_2 (3.3 mL) was taken. Then *m*-CPBA (56.0 mg, 0.25 mmol) and Na_2HPO_4 (36.0 mg, 0.25 mmol) were added and the solution was stirred at room temperature overnight. The mixture was poured into water (2 mL) and saturated aq. $NaHCO_3$ (2 mL), the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layer was washed with water (5 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product which was purified by silica gel column chromatography using EtOAc-Hexane (15-20%) as eluent to afford compound **4**.

4.6.6 General procedure for the preparation of derivatives 5[21]



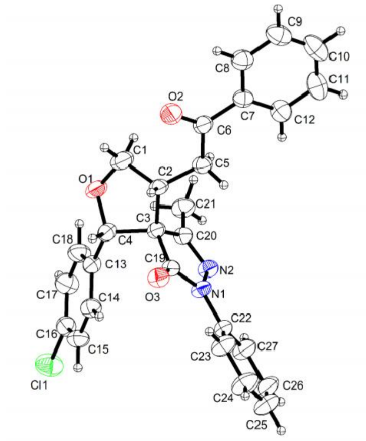
To a solution of compound **4** (47.0 mg, 0.1 mmol) in THF (1 mL) was added benzylamine (23 μL, 0.2 mmol) and the mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (3 mL), the organic layer was washed with 1 N HCl (2 × 2 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using EtOAc-Hexane (30-50%) as eluent to afford amide **5**.

4.6.7 Crystal structure of compound 3s[22]



3s

≡



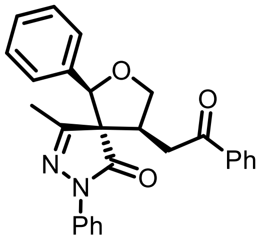
ORTEP crystal structure

Table 2. **Crystal data and structure refinement for compound 3s**

Parameters	**3s**
CCDC No.	1824042
Empirical formula	$C_{27}H_{23}N_2O_3Cl$
Formula weight	458.92
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.36× 0.33 × 0.33
Temperature, *T*	293 K
Wavelength, λ (Å)	0.71073
Crystal system	Triclinic
Space group	*'P -1'*
Unit cell dimensions	*a* = 10.0751(6) Å *b* = 10.5272(5) Å *c* = 12.2309(9) Å

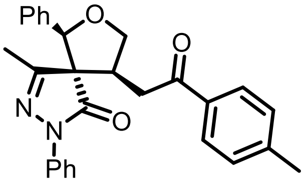
	α = 107.851(5)°, β = 98.524(5)°, γ = 103.443(5)°
Volume, V (Å^3)	1166.70(12)
Z	2
Calculated density, Mg/m^3	1.306
Absorption coefficient, μ (mm^{-1})	0.195
F(000)	480
θ range for data collection	3.4170° to 27.5150°
Limiting indices	$-13 \le h \le 13$, $-14 \le k \le 13$, $-16 \le l \le 16$
Reflection collected/unique	4107/3047[R(int) = 0.0195]
Completeness to θ	99.83% (θ = 26.320°)
Max. and min. transmission	0.943/ 0.932
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data/restraints/parameters	4100/0/299
Goodness of fit on F^2	1.054
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0460, wR2 = 0.1055
R indices (all data)	R1 = 0.0646, wR2 = 0.1212
Ellipsoid contour % probability	40%

4.7 Characterization data of products



3a

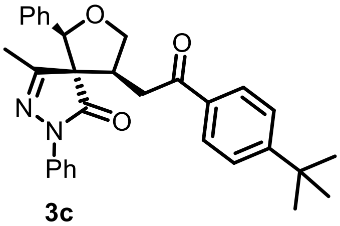
(5R,6R,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3a): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 70% yield (59.4 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.90-7.84 (m, 4H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44-7.40 (m, 4H), 7.26-7.21 (m, 6H), 5.41 (s, 1H), 4.88 (t, *J* = 9.2 Hz, 1H), 4.03 (t, *J* = 9.0 Hz, 1H), 3.85-3.74 (m, 1H), 3.17 (dd, *J* = 17.7, 4.8 Hz, 1H), 3.01 (dd, *J* = 17.7, 10.0 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.7, 171.8, 159.2, 137.9, 136.0, 135.9, 133.7, 129.0, 128.9, 128.6, 128.2, 128.1, 125.5, 124.4, 119.2, 86.3, 72.6, 68.1, 45.1, 38.2, 17.6. **FT-IR (thin film)** 3057, 2910, 1704, 1678, 1596, 1496, 792 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 21.2 min, t_{minor} = 18.2 min). $[\alpha]_D^{24}$ = -60.0 (c 0.35, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{25}N_2O_3$ $[M+H]^+$ 425.1865, found 425.1861.



3b

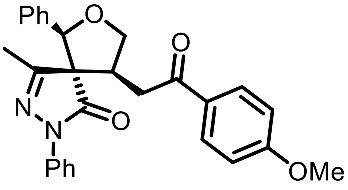
(5R,6R,9S)-4-methyl-9-(2-oxo-2-(p-tolyl)ethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3b): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; off white solid; 71% yield (62.3 mg). m.p. = 135-138 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 8H), 5.39 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.82-3.72 (m, 1H), 3.14 (dd, *J* = 17.5, 4.7 Hz, 1H), 2.96 (dd, *J* = 17.5, 10.1 Hz, 1H), 2.39 (s, 3H), 2.02 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.4, 171.9, 159.3, 144.7, 138.0, 136.0, 133.6, 129.6, 129.1, 128.6, 128.3, 128.2, 125.5, 124.4, 119.2, 86.3, 72.7, 68.1, 45.2, 38.1, 21.8, 17.7. **FT-IR (thin film)** 3060, 2954, 1706, 1685, 1597, 1492, 789 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 220 nm (t_{major} = 29.9 min,

t_{minor} = 20.1 min). $[\alpha]_D^{26}$ = -36.9 (c 0.13, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_3$ $[M+H]^+$ 439.2022, found 439.2023.



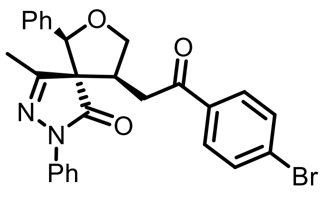
3c

(5R,6R,9S)-9-(2-(4-(tert-butyl)phenyl)-2-oxoethyl)-4-methyl-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3c): Purified by silica-gel column chromatography using 10% ethyl acetate/hexane; brown sticky solid; 72% yield (69.3 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.47-7.38 (m, 4H), 7.23 (d, *J* = 7.3 Hz, 6H), 5.40 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.84-3.73 (m, 1H), 3.15 (dd, *J* = 17.5, 4.8 Hz, 1H), 2.97 (dd, *J* = 17.5, 10.1 Hz, 1H), 2.02 (s, 3H), 1.31 (s, 9H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.4, 171.9, 157.7, 138.0, 136.1, 133.5, 129.2, 129.0, 128.2, 128.0, 126.0, 125.7, 124.6, 119.4, 119.2, 86.5, 86.3, 68.2, 45.4, 45.1, 35.3, 31.3, 31.1, 17.8. **FT-IR (thin film)** 3055, 2915, 1708, 1672, 1590, 1493, 790 cm^{-1}. **HPLC Analysis**: 88% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 18.4 min, t_{minor} = 13.6 min). $[\alpha]_D^{25}$ = -60.0 (c 0.170, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{31}H_{33}N_2O_3$ $[M+H]^+$ 481.2491, found 481.2487.



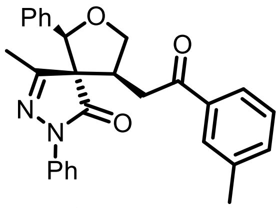
3d

(5R,6R,9S)-9-(2-(4-methoxyphenyl)-2-oxoethyl)-4-methyl-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3d): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 69% yield (62.7 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.26-7.18 (m, 6H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.39 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.02 (t, *J* = 8.9 Hz, 1H), 3.83 (s, 3H), 3.78 (dd, *J* = 9.3, 4.8 Hz, 1H), 3.12 (dd, *J* = 17.3, 4.7 Hz, 1H), 2.93 (dd, *J* = 17.1, 10.1 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.2, 171.9, 164.0, 159.4, 138.0, 136.0, 130.5, 129.1, 129.0, 128.6, 128.2, 125.5, 124.4, 119.2, 114.0, 86.3, 72.7, 68.2, 55.6, 45.3, 37.8, 17.7. **FT-IR (thin film)** 3063, 2962, 1700, 1668, 1595, 1491, 757 cm^{-1}. **HPLC Analysis**: 90% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 220 nm (t_{major} = 38.5 min, t_{minor} = 31.8 min). $[\alpha]_D^{25}$ = -48.8 (c 0.40, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1971, found 455.1969.



3e

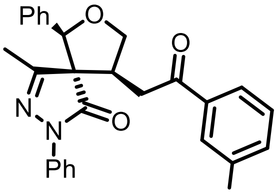
(5R,6R,9S)-9-(2-(4-bromophenyl)-2-oxoethyl)-4-methyl-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3e): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 66% yield (66.3 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 6H), 5.39 (s, 1H), 4.85 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.77 (qd, *J* = 9.3, 5.0 Hz, 1H), 3.12 (dd, *J* = 17.7, 4.9 Hz, 1H), 2.96 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 195.8, 171.8, 159.2, 138.0, 135.9, 134.8, 132.3, 129.7, 129.1, 128.6, 128.3, 125.6, 124.5, 119.2, 86.5, 72.6, 68.1, 45.1, 38.2, 17.7. **FT-IR (thin film)** 3060, 2965, 1703, 1680, 1595, 1490, 765 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 26.6 min, t_{minor} = 24.1 min). $[\alpha]_D^{23}$ = -34.6 (c 0.455, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}BrN_2O_3$ $[M+H]^+$ 503.0970, found 503.0972.



3f

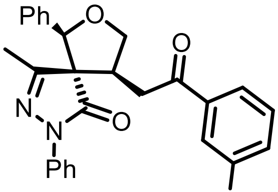
(5R,6R,9S)-4-methyl-9-(2-oxo-2-(m-tolyl)ethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3f): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 62% yield (54.4 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.91 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.29-7.23 (m, 6H), 5.42 (s, 1H), 4.90 (t, *J* = 9.2 Hz, 1H), 4.04 (t, *J* = 9.0 Hz, 1H), 3.87-3.77 (m, 1H), 3.17 (dd, *J* =

17.6, 4.8 Hz, 1H), 3.01 (dd, *J* = 17.6, 10.1 Hz, 1H), 2.40 (s, 3H), 2.05 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 197.0, 171.8, 159.3, 138.8, 138.0, 136.1, 136.0, 134.5, 129.1, 128.8, 128.6, 128.2, 125.5, 125.4, 124.4, 119.2, 86.4, 72.7, 68.1, 45.2, 38.3, 21.4, 17.7. **FT-IR (thin film)** 3061, 2925, 1702, 1678, 1596, 1495, 791 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 220 nm (t_{major} = 16.0 min, t_{minor} = 15.1 min). $[\alpha]_D^{28}$ = -72.8 (c 0.390, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_3$ [M+H]$^+$ 439.2022, found 439.2022.

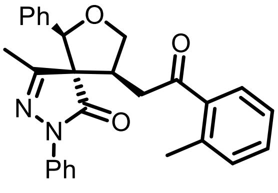


3g

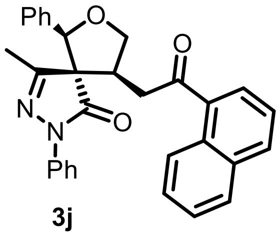
(5R,6R,9S)-9-(2-(3-methoxyphenyl)-2-oxoethyl)-4-methyl-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3g): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 68% yield (62.0 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 3H), 7.37 (s, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.26-7.21 (m, 6H), 7.12-7.10 (m, 1H), 5.40 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.80 (s, 3H), 3.78 (dd, *J* = 9.7, 4.2 Hz, 1H), 3.14 (dd, *J* = 17.6, 4.9 Hz, 1H), 2.99 (dd, *J* = 17.6, 9.9 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 196.7, 171.9, 160.1, 159.2, 138.1, 137.5, 136.0, 129.9, 129.1, 128.9, 128.6, 128.3, 125.5, 124.5, 120.8, 120.2, 119.6, 119.3, 112.5, 86.5, 72.7, 68.1, 55.6, 45.3, 38.4, 17.7. **FT-IR (thin film)** 3063, 2923, 1710, 1685, 1589, 1496, 792 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.7 min, t_{minor} = 12.2 min). $[\alpha]_D^{24}$ = -42.4 (c 0.50, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_4$ [M+H]$^+$ 455.1971, found 455.1962.


3h

(5R,6R,9S)-9-(2-(3-chlorophenyl)-2-oxoethyl)-4-methyl-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3h): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 61% yield (58.8 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.80 (d, *J* = 7.7 Hz, 2H), 7.74 (t, *J* = 1.6 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.37-7.32 (m, 4H), 7.19-7.14 (m, 5H), 5.32 (s, 1H), 4.79 (t, *J* = 9.2 Hz, 1H), 3.93 (t, *J* = 9.0 Hz, 1H), 3.71 (dt, *J* = 14.1, 6.8 Hz, 1H), 3.05 (dd, *J* = 17.8, 5.0 Hz, 1H), 2.91 (dd, *J* = 17.8, 9.9 Hz, 1H), 1.95 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 195.6, 171.8, 159.1, 138.0, 137.6, 135.9, 135.4, 133.7, 130.3, 129.1, 128.6, 128.3, 128.3, 126.3, 125.6, 124.5, 119.3, 86.5, 72.6, 68.1, 45.1, 38.4, 17.7. **FT-IR (thin film)** 3061, 2926, 1699, 1686, 1610, 1491, 753 cm^{-1}. **HPLC Analysis**: 99% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 19.0 min, t_{minor} = 14.2 min). $[\alpha]_D^{23}$ = -25.3 (c 0.205, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}ClN_2O_3$ [M+H]$^+$ 459.1475, found 459.1472.

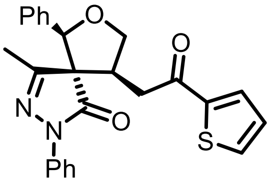

3i

(5R,6R,9S)-4-methyl-9-(2-oxo-2-(o-tolyl)ethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3i): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light brown sticky solid; 59% yield (51.7 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.34-7.30 (m, 3H), 7.18-7.11 (m, 8H), 5.32 (s, 1H), 4.77 (t, *J* = 9.1 Hz, 1H), 3.95 (t, *J* = 9.0 Hz, 1H), 3.75-3.62 (m, 1H), 2.96 (td, *J* = 17.6, 10.2 Hz, 2H), 2.34 (s, 3H), 1.92 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 200.2, 172.0, 159.2, 139.0, 138.0, 136.4, 136.0, 132.5, 132.2, 129.0, 128.8, 128.6, 128.3, 126.0, 125.5, 124.5, 119.2, 86.5, 72.7, 68.1, 45.4, 40.8, 21.7, 17.7. **FT-IR (thin film)** 3058, 2928, 1715, 1685, 1596, 1498, 765 cm^{-1}. **HPLC Analysis**: 98% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 65.8 min, t_{minor} = 18.7 min). $[\alpha]_D^{26}$ = -7.7 (c 0.08, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_3$ [M+H]$^+$ 439.2022, found 439.2021.



3j

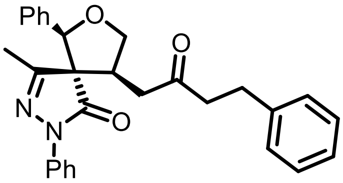
(5R,6R,9S)-4-methyl-9-(2-(naphthalen-1-yl)-2-oxoethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3j): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 75% yield (70.8 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.51 (d, *J* = 6.8 Hz, 1H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.54-7.39 (m, 5H), 7.30-7.22 (m, 6H), 5.43 (s, 1H), 4.90 (t, *J* = 9.0 Hz, 1H), 4.10 (t, *J* = 9.0 Hz, 1H), 3.88 (dt, *J* = 9.7, 6.6 Hz, 1H), 3.19 (ddd, *J* = 24.0, 17.6, 10.1 Hz, 2H), 2.01 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 200.5, 172.0, 159.2, 138.1, 136.0, 134.4, 134.1, 133.7, 130.2, 129.1, 128.6, 128.5, 128.3, 128.2, 126.8, 125.8, 125.5, 124.5, 124.4, 119.2, 86.6, 72.7, 68.1, 45.6, 41.4, 29.9, 17.7. **FT-IR (thin film)** 3060, 2922, 1706, 1596, 1497, 756 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 30.2 min, t_{minor} = 25.7 min). $[\alpha]_D^{26}$ = -2.4 (c 0.075, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{31}H_{27}N_2O_3$ $[M+H]^+$ 475.2022, found 475.2022.



3k

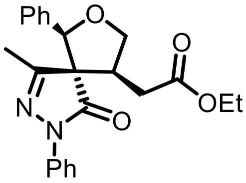
(5R,6R,9S)-4-methyl-9-(2-oxo-2-(thiophen-2-yl)ethyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3k): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; off white semisolid; 76% yield (73.2 mg). The dr value was found to be 15:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.65-7.62 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.26-7.20 (m, 6H), 7.12-7.08 (m, 1H), 5.39 (s, 1H), 4.83 (t, *J* = 9.2 Hz, 1H), 4.05 (t, *J* = 9.1 Hz, 1H), 3.77 (td, *J* = 14.0, 9.3 Hz, 1H), 3.09 (dd, *J* = 17.0, 4.7 Hz, 1H), 2.92 (dd, *J* = 17.0, 10.3 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 189.6, 171.7, 143.1, 138.0, 135.9, 134.5, 132.5, 129.1, 128.6, 128.4, 128.3, 125.6, 124.5, 119.3, 86.4, 72.5, 68.1, 45.2, 38.7, 17.7. **FT-IR (thin film)** 3065, 2923, 1703, 1592, 1499, 770 cm^{-1}. **HPLC Analysis**: 84% ee; Determined using a

Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.5 min, t_{minor} = 13.5 min). $[\alpha]_D^{24}$ = -60.3 (c 0.58, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{25}H_{23}N_2O_3S$ $[M+H]^+$ 431.1429, found 431.1425.



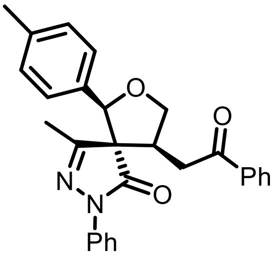
3l

(5R,6R,9S)-4-methyl-9-(2-oxo-4-phenylbutyl)-2,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3l): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 63% yield (65.2 mg). The dr value was found to be 10:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 7.7 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.29-7.25 (m, 6H), 7.27-7.24 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 5.36 (s, 1H), 4.75 (t, *J* = 9.2 Hz, 1H), 3.86 (t, *J* = 9.1 Hz, 1H), 3.60 (qd, *J* = 9.4, 5.0 Hz, 1H), 2.86 (t, *J* = 7.5 Hz, 2H), 2.70 (dt, *J* = 12.6, 6.2 Hz, 2H), 2.51 (dd, *J* = 17.9, 4.9 Hz, 1H), 2.43-2.34 (m, 2H), 1.93 (s, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 206.8, 171.7, 159.2, 140.5, 137.9, 135.9, 129.1, 128.7, 128.6, 128.4, 128.2, 126.4, 125.5, 124.4, 119.1, 86.2, 72.4, 67.9, 44.7, 44.2, 42.5, 30.0, 17.5. **FT-IR (thin film)** 3050, 2920, 1701, 1592, 1490, 762 cm^{-1}. **HPLC Analysis**: 90% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 220 nm (t_{major} = 17.9 min, t_{minor} = 20.5 min). $[\alpha]_D^{24}$ = -82.6 (c 0.230, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2173, found 453.2170.



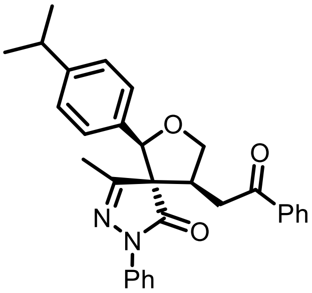
3m

Ethyl 2-((5R,6R,9S)-1-methyl-4-oxo-3,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-1-en-9-yl)acetate (3m): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 65% yield (51.0 mg). The dr value was found to be 15:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.24-7.22 (m, 3H), 7.20 (d, *J* = 7.8 Hz, 3H), 5.36 (s, 1H), 4.70 (t, *J* = 9.2 Hz, 1H), 4.08-4.00 (m, 3H), 3.62 (dd, *J* = 9.1, 6.8 Hz, 1H), 2.41 (dd, *J* = 7.8, 4.3 Hz, 2H), 1.98 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 171.7, 170.6, 158.9, 138.0, 135.9, 129.1, 128.6, 128.3, 125.5, 124.4, 119.2, 86.7, 72.4, 68.0, 61.3, 45.5, 34.0, 17.6, 14.2. **FT-IR (thin film)** 3064, 2928, 1680, 1587, 1482, 1290, 762 cm^{-1}. **HPLC Analysis**: 60% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.5 min, t_{minor} = 14.5 min). $[\alpha]_D^{24}$ = -40.5 (c 0.218, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{23}H_{25}N_2O_4$ [M+H]$^+$ 393.1814, found 393.1812.



3n

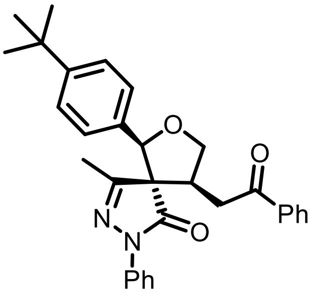
(5R,6R,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-6-(p-tolyl)-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3n): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; off white solid; 69% yield (60.5 mg). m.p. = 151-154 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.89-7.84 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44-7.39 (m, 4H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.37 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.79 (td, *J* = 9.6, 4.7 Hz, 1H), 3.16 (dd, *J* = 17.7, 4.7 Hz, 1H), 3.00 (dd, *J* = 17.6, 10.1 Hz, 1H), 2.28 (s, 3H), 2.04 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.8, 171.9, 159.4, 138.0, 137.9, 136.1, 133.8, 132.9, 129.3, 129.1, 128.9, 128.1, 125.5, 124.3, 119.2, 86.5, 72.6, 68.2, 45.1, 38.3, 21.3, 17.7. **FT-IR (thin film)** 3055, 2926, 1710, 1595, 1486, 765 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 22.8 min, t_{minor} = 15.7 min). $[\alpha]_D^{28}$ = -71.8 (c 0.805, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_3$ [M+H]$^+$ 439.2022, found 439.2020.



3o

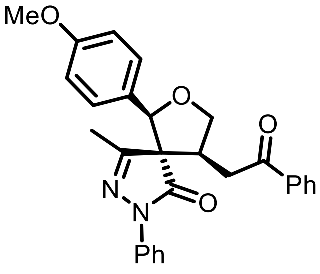
(5R,6R,9S)-6-(4-isopropylphenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3o): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 65% yield (60.6 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.89-7.84 (m, 4H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.44-7.41 (m, 4H), 7.26-

7.20 (m, 1H), 7.15-7.08 (m, 4H), 5.38 (s, 1H), 4.86 (t, *J* = 9.1 Hz, 1H), 4.00 (t, *J* = 8.9 Hz, 1H), 3.78 (td, *J* = 13.7, 9.2 Hz, 1H), 3.16 (dd, *J* = 17.6, 4.4 Hz, 1H), 3.00 (dd, *J* = 17.7, 10.2 Hz, 1H), 2.88-2.76 (m, 1H), 2.04 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 196.8, 172.0, 159.5, 148.8, 138.1, 136.1, 133.8, 133.3, 129.1, 128.9, 128.2, 126.6, 125.5, 124.5, 119.3, 86.4, 72.6, 68.1, 45.3, 38.3, 33.9, 24.0, 24.0, 17.7. **FT-IR (thin film)** 3049, 2926, 1694, 1594, 1493, 768 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t$_{major}$ = 21.4 min, t$_{minor}$ = 17.2 min). $[\alpha]_D^{28}$ = -66.2 (c 0.160, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{30}H_{31}N_2O_3$ [M+H]$^+$ 467.2335, found 467.2336.



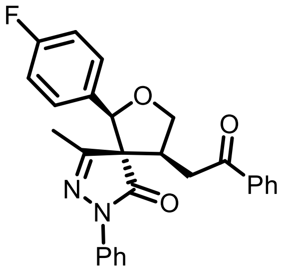
3p

(5R,6R,9S)-6-(4-(tert-butyl)phenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3p): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 70% yield (67.3 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.82-7.78 (m, 4H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.37-7.33 (m, 4H), 7.19-7.15 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 2H), 5.30 (s, 1H), 4.79 (t, *J* = 9.2 Hz, 1H), 3.93 (t, *J* = 9.0 Hz, 1H), 3.70 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.09 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.92 (dd, *J* = 17.7, 10.1 Hz, 1H), 1.96 (s, 3H), 1.18 (s, 9H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 196.8, 172.0, 159.6, 151.1, 138.1, 136.1, 133.8, 132.9, 129.1, 128.9, 128.2, 128.2, 125.5, 125.5, 124.4, 124.2, 119.3, 86.3, 72.6, 68.0, 45.3, 38.3, 31.4, 17.7. **FT-IR (thin film)** 3049, 2926, 1694, 1594, 1493, 768 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t$_{major}$ = 19.4 min, t$_{minor}$ = 13.7 min). $[\alpha]_D^{27}$ = -83.6 (c 0.495, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{31}H_{33}N_2O_3$ [M+H]$^+$ 481.2491, found 481.2491.



3q

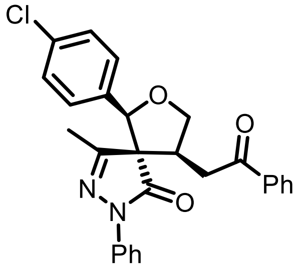
(5R,6R,9S)-6-(4-methoxyphenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3q): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; off white solid; 73% yield (66.3 mg). m.p. = 159-162 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.89-7.83 (m, 4H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.44-7.39 (m, 4H), 7.21 (t, *J* = 7.1 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.77 (d, *J* = 8.2 Hz, 2H), 5.35 (s, 1H), 4.86 (t, *J* = 9.1 Hz, 1H), 4.00 (t, *J* = 8.9 Hz, 1H), 3.75 (s, 4H), 3.16 (dd, *J* = 17.6, 4.3 Hz, 1H), 3.00 (dd, *J* = 17.6, 10.0 Hz, 1H), 2.04 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.8, 171.9, 159.5, 138.1, 133.8, 129.1, 128.9, 128.2, 125.7, 125.5, 119.2, 114.0, 86.4, 72.6, 68.3, 55.3, 45.1, 38.3, 17.7. **FT-IR (thin film)** 3059, 2930, 1706, 1598, 1499, 757 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 29.3 min, t_{minor} = 22.3 min). $[\alpha]_D^{28}$ = -37.0 (c 0.60, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1971, found 455.1979.



3r

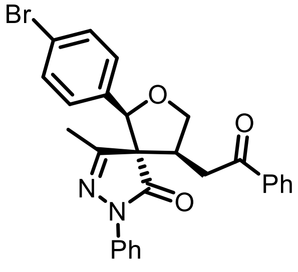
(5R,6R,9S)-6-(4-fluorophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3r): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 68% yield (60.2 mg). m.p. = 124-127 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.88-7.83 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49-7.40 (m, 4H), 7.26-7.19 (m, 3H), 6.94 (t, *J* = 8.6 Hz, 2H), 5.35 (s, 1H), 4.87 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.87-3.72 (m, 1H), 3.16 (dd, *J* = 17.8, 5.0 Hz, 1H), 3.01 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.7, 171.7, 162.5 (d, $J_{C\text{-}F}$ = 246.6 Hz), 159.1, 137.9, 136.0, 133.9, 129.1, 128.9, 128.1, 126.2, (d, $J_{C\text{-}F}$ = 8.1 Hz), 125.6, 119.2, 115.6 (d, $J_{C\text{-}F}$ = 21.6 Hz), 85.9, 72.7, 68.1, 45.0, 38.2, 17.7. **FT-IR (thin film)** 3059, 2928, 1707, 1596, 1497, 758 cm^{-1}. **HPLC Analysis**: 94%

ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 22.7 min, t_{minor} = 15.4 min). $[\alpha]_D^{25}$ = -43.2 (c 0.685, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{27}FN_2O_3$ $[M+H]^+$ 443.1771, found 443.1774.



3s

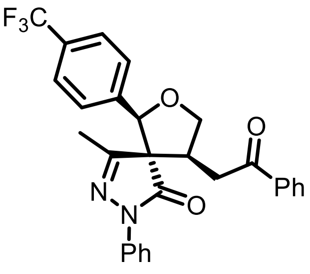
(5R,6R,9S)-6-(4-chlorophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3s): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 72% yield (66.0 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88-7.83 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44-7.40 (m, 4H), 7.23 (d, *J* = 8.6 Hz, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.34 (s, 1H), 4.87 (t, *J* = 9.1 Hz, 1H), 4.01 (t, *J* = 9.1 Hz, 1H), 3.78 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.16 (dd, *J* = 17.7, 4.9 Hz, 1H), 3.00 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.7, 171.6, 159.0, 137.9, 136.0, 134.6, 134.1, 133.8, 129.1, 128.9, 128.9, 128.2, 125.9, 125.7, 119.2, 85.8, 72.7, 68.0, 45.1, 38.2, 17.7. **FT-IR (thin film)** 3061, 2927, 1699, 1596, 1492, 762 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 24.1 min, t_{minor} = 15.8 min). $[\alpha]_D^{29}$ = -86.8 (c 0.70, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}ClN_2O_3$ $[M+H]^+$ 459.1475, found 459.1475.



3t

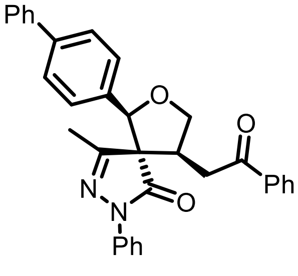
(5R,6R,9S)-6-(4-bromophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3t): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 75% yield (75.4 mg). m.p. = 172-175 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.89-7.83 (m, 4H), 7.56 (t, *J* = 7.1 Hz, 1H), 7.47-7.36 (m, 6H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.32 (s, 1H), 4.87 (t, *J* = 9.1 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.83-3.71 (m, 1H), 3.16 (dd, *J* = 17.7, 4.5 Hz, 1H), 3.00 (dd, *J* = 17.7, 9.9 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR**

(150 MHz, CDCl$_3$) δ 196.7, 171.6, 158.9, 137.9, 136.0, 135.1, 133.8, 131.8, 129.1, 128.9, 128.2, 126.3, 125.7, 122.2, 119.2, 85.8, 72.7, 68.0, 45.2, 38.2, 17.7. **FT-IR (thin film)** 3060, 2924, 1698, 1592, 1490, 760 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 26.7 min, t_{minor} = 16.7 min). $[\alpha]_D^{28}$ = -79.6 (c 0.60, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}BrN_2O_3$ $[M+H]^+$ 503.0970, found 503.0968.



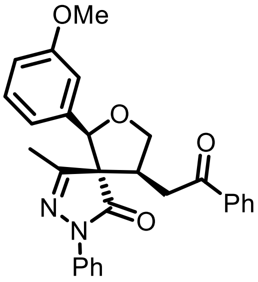
3u

(5R,6R,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-6-(4-(trifluoromethyl)phenyl)-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3u): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; red semi solid; 66% yield (65.0 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.81-7.75 (m, 4H), 7.50-7.43 (m, 3H), 7.35 (t, *J* = 8.1 Hz, 4H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.19-7.13 (m, 1H), 5.33 (s, 1H), 4.81 (t, *J* = 9.2 Hz, 1H), 3.96 (t, *J* = 9.1 Hz, 1H), 3.73 (qd, *J* = 9.3, 5.0 Hz, 1H), 3.09 (dd, *J* = 17.7, 4.9 Hz, 1H), 2.93 (dd, *J* = 17.7, 9.9 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.6, 171.5, 158.8, 140.1, 137.8, 135.9, 133.9, 130.4 (q, $J_{C\text{-}F}$ = 31.5 Hz), 129.2, 128.9, 128.1, 125.80, 125.6 (q, $J_{C\text{-}F}$ = 3.0 Hz), 124.97, 124.1 (q, $J_{C\text{-}F}$ = 286.5 Hz), 119.1, 85.6, 72.8, 67.9, 45.2, 38.1, 17.6. **FT-IR (thin film)** 3047, 2920, 1702, 1600, 1505, 780 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 22.8 min, t_{minor} = 15.0 min). $[\alpha]_D^{24}$ = -67.0 (c 0.480, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{24}F_3N_2O_3$ $[M+H]^+$ 493.1739, found 493.1745.



3v

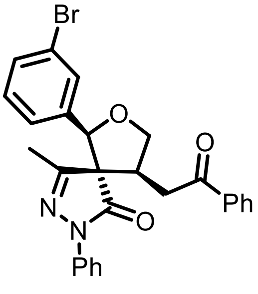
(5R,6R,9S)-6-([1,1'-biphenyl]-4-yl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3v): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow semi solid; 68% yield (68.2 mg). The dr value was found to be 8:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.85-7.76 (m, 4H), 7.45 (d, J = 7.0 Hz, 3H), 7.40 (d, J = 8.0 Hz, 2H), 7.36-7.29 (m, 6H), 7.23 (t, J = 8.1 Hz, 3H), 7.16-7.12 (m, 1H), 5.36 (s, 1H), 4.81 (t, J = 9.1 Hz, 1H), 3.96 (t, J = 8.9 Hz, 1H), 3.73 (dd, J = 9.0, 4.4 Hz, 1H), 3.08 (dd, J = 16.2, 11.7 Hz, 1H), 2.94 (dd, J = 17.6, 10.0 Hz, 1H), 1.98 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.8, 171.9, 159.3, 141.0, 140.6, 138.0, 136.1, 135.0, 133.8, 129.1, 129.0, 128.9, 128.2, 128.2, 127.6, 127.3, 127.2, 125.6, 125.0, 119.3, 86.3, 72.7, 68.2, 45.2, 38.3, 17.7. **FT-IR (thin film)** 3053, 2928, 1705, 1599, 1488, 778 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 25.7 min, t_{minor} = 21.4 min). $[\alpha]_D^{29}$ = -86.4 (c 0.90, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{33}H_{29}N_2O_3$ $[M+H]^+$ 501.2178, found 501.2178.



3w

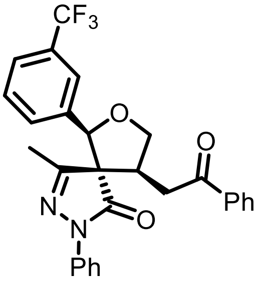
(5R,6R,9S)-6-(3-methoxyphenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3w): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light brown semi solid; 58% yield (52.7 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.90-7.83 (m, 4H), 7.56 (t, J = 7.4 Hz, 1H), 7.44-7.39 (m, 4H), 7.22-7.13 (m, 2H), 6.80-6.75 (m, 3H), 5.37 (s, 1H), 4.87 (t, J = 9.1 Hz, 1H), 4.01 (t, J = 9.0 Hz, 1H), 3.82-3.74 (m, 1H), 3.60 (s, 3H), 3.17 (dd, J = 17.7, 4.7 Hz, 1H), 3.00 (dd, J = 17.7, 10.0 Hz, 1H), 2.04 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.8, 171.9, 159.8, 159.3, 138.0, 137.6, 136.1, 133.8, 129.7, 129.1, 128.9, 128.2, 128.2, 125.5, 119.1, 116.7, 114.5, 109.4, 86.3, 72.7, 68.1, 55.2, 45.1, 38.2, 17.7. **FT-IR (thin film)** 3057, 2919, 1608, 1597, 1500, 775 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate

1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 26.8 min, t_{minor} = 22.4 min). $[\alpha]_D^{24}$ = -51.3 (c 0.755, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1971, found 455.1963.



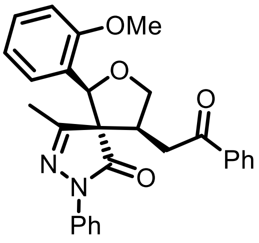
3x

(5R,6R,9S)-6-(3-bromophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3x): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 55% yield (55.3 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88-7.82 (m, 4H), 7.58-7.54 (m, 2H), 7.45-7.36 (m, 4H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 5.34 (s, 1H), 4.87 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.78 (tt, *J* = 13.9, 7.0 Hz, 1H), 3.17 (dd, *J* = 17.8, 4.9 Hz, 1H), 3.01 (dd, *J* = 17.7, 9.8 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.7, 171.6, 158.9, 138.4, 137.9, 136.1, 133.8, 131.4, 130.3, 129.1, 128.9, 128.2, 127.8, 125.8, 123.1, 122.96, 119.5, 85.6, 72.8, 68.0, 45.1, 38.1, 17.7. **FT-IR (thin film)** 3060, 2923, 1701, 1590, 1497, 770 cm^{-1}. **HPLC Analysis**: 94% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 24.7 min, t_{minor} = 18.9 min). $[\alpha]_D^{27}$ = -58.7 (c 0.695, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}BrN_2O_3$ $[M+H]^+$ 503.0970, found 503.0974.



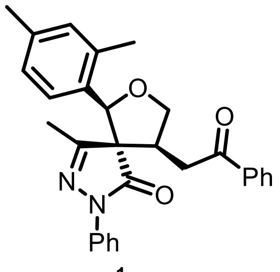
3y

(5R,6R,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-6-(3-(trifluoromethyl)phenyl)-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3y): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 57% yield (56.2 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 7.7 Hz, 4H), 7.57 (s, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.38-7.33 (m, 4H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.22-7.14 (m, 2H), 5.34 (s, 1H), 4.83 (t, *J* = 9.2 Hz, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.74 (td, *J* = 14.1, 9.2 Hz, 1H), 3.11 (dd, *J* = 17.7, 4.7 Hz, 1H), 2.95 (dd, *J* = 17.7, 9.8 Hz, 1H), 1.92 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.67, 171.52, 158.78, 137.75, 137.18, 135.96, 133.94, 131.0 (q, $J_{C\text{-}F}$ = 33.0 Hz), 129.23, 129.17, 128.98, 128.20, 127.86, 125.85, 125.2 (q, $J_{C\text{-}F}$ = 4.5 Hz), 123.7 (q, $J_{C\text{-}F}$ = 270.0 Hz), 121.6 (q, $J_{C\text{-}F}$ = 3.0 Hz), 119.3, 85.8, 72.8, 68.0, 45.0, 38.1, 17.6. **FT-IR (thin film)** 3053, 2922, 1706, 1602, 1496, 778 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 21.9 min, t_{minor} = 17.5 min). $[\alpha]_D^{25}$ = -53.2 (c 0.50, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{24}F_3N_2O_3$ $[M+H]^+$ 493.1739, found 493.1735.



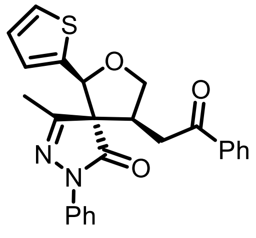
3z

(5R,6R,9S)-6-(2-methoxyphenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow semi solid; 62% yield (56.3 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.99 (d, *J* = 7.7 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.59-7.53 (m, 1H), 7.38-7.44 (m, 4H), 7.25-7.13 (m, 2H), 6.96 (s, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 5.50 (s, 1H), 4.83 (t, *J* = 8.7 Hz, 1H), 3.97 (t, *J* = 9.2 Hz, 1H), 3.79-3.65 (m, 1H), 3.36 (s, 3H), 3.09 (dd, *J* = 17.6, 3.6 Hz, 1H), 2.98-2.82 (m, 1H), 1.80 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 196.9, 173.2, 159.2, 156.1, 138.7, 136.2, 133.7, 129.1, 129.0, 128.9, 128.2, 128.2, 126.7, 124.7, 120.3, 118.2, 109.7, 82.7, 72.8, 67.0, 54.8, 46.9, 37.5, 17.7. **FT-IR (thin film)** 3025, 2923, 1711, 1597, 1498, 768 cm^{-1}. **HPLC Analysis**: 88% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 19.7 min, t_{minor} = 17.2 min). $[\alpha]_D^{26}$ = +6.4 (c 0.340, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_4$ $[M+H]^+$ 455.1971, found 455.1978.



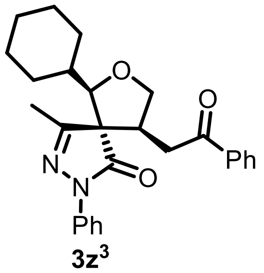
3z^1

(5R,6R,9S)-6-(2,4-dimethylphenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^1): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 64% yield (57.9 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.88-7.83 (m, 4H), 7.59-7.48 (m, 2H), 7.45-7.36 (m, 4H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.85 (s, 1H), 5.57 (s, 1H), 4.82 (t, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 9.0 Hz, 1H), 3.78 (dt, *J* = 13.5, 9.2 Hz, 1H), 3.12 (dd, *J* = 17.5, 4.5 Hz, 1H), 2.99 (dd, *J* = 17.5, 10.2 Hz, 1H), 2.25 (s, 3H), 2.07 (d, *J* = 5.1 Hz, 6H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 196.8, 172.3, 159.7, 138.1, 137.9, 136.1, 135.3, 133.8, 132.0, 131.5, 129.1, 128.9, 128.2, 126.3, 126.2, 125.4, 118.9, 84.9, 72.7, 67.8, 46.6, 37.9, 21.1, 19.3, 18.4. **FT-IR (thin film)** 3023, 2928, 1705, 1599, 1497, 788 cm^{-1}. **HPLC Analysis**: 96% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 21.4 min, t_{minor} = 16.6 min). $[\alpha]_D^{26}$ = -68.9 (c 0.925, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178, found 453.2174.



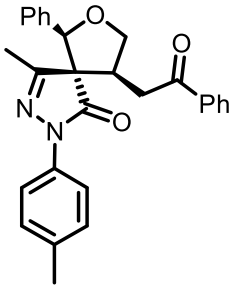
3z^2

(5R,6S,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-6-(thiophen-2-yl)-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^2): Purified by silica-gel column chromatography using 10% ethyl acetate/hexane; brown sticky solid; 57% yield (49.0 mg). The dr value was found to be 9:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.99 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.47-7.42 (m, 5H), 7.19 (d, *J* = 5.0 Hz, 1H), 6.93-6.87 (m, 1H), 6.80 (s, 1H), 5.54 (s, 1H), 4.86 (t, *J* = 9.1 Hz, 1H), 4.01 (t, *J* = 9.1 Hz, 1H), 3.74 (m, 1H), 3.34 (t, *J* = 6.2 Hz, 1H), 3.23-3.13 (m, 1H), 3.02 (dd, *J* = 17.7, 10.0 Hz, 1H), 2.16 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.7, 171.0, 159.1, 138.1, 136.1, 133.8, 129.1, 128.9, 128.2, 128.2, 127.2, 125.6, 124.8, 123.4, 119.2, 84.2, 72.9, 68.1, 44.9, 38.1, 17.9. **FT-IR (thin film)** 3047, 2926, 1701, 1590, 1491, 759 cm^{-1}. **HPLC Analysis**: 90% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.7 min, t_{minor} = 23.3 min). $[\alpha]_D^{28}$ = -21.4 (c 0.215, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{25}H_{23}N_2O_3S$ $[M+H]^+$ 431.1429, found 431.1427.



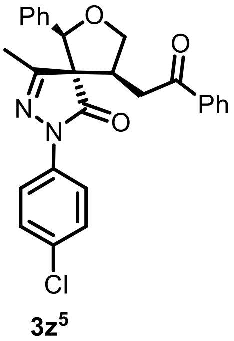
3z^3

(5R,6R,9S)-6-cyclohexyl-4-methyl-9-(2-oxo-2-phenylethyl)-2-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^3): Purified by silica-gel column chromatography using 10% ethyl acetate/hexane; brown sticky solid; 50% yield (43.0 mg). The dr value was found to be 9:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 4H), 7.30-7.26 (m, 1H), 4.66 (t, *J* = 9.2 Hz, 1H), 3.94 (d, *J* = 10.1 Hz, 1H), 3.76 (t, *J* = 9.0 Hz, 1H), 3.62-3.54 (m, 1H), 3.08 (dd, *J* = 17.5, 4.0 Hz, 1H), 2.88 (dd, *J* = 17.5, 10.6 Hz, 1H), 2.41-2.31 (m, 4H), 1.74 (d, *J* = 12.6 Hz, 2H), 1.63-1.54 (m, 3H), 1.09 (dd, *J* = 37.5, 9.8 Hz, 4H), 0.93-0.85 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.9, 172.2, 160.12, 138.2, 136.1, 133.7, 129.1, 128.9, 128.1, 125.4, 119.1, 90.1, 71.7, 65.4, 46.4, 39.9, 37.8, 31.36, 27.9, 26.1, 25.8, 25.5, 17.9. **FT-IR (thin film)** 3050, 2925, 1711, 1597, 1499, 758 cm^{-1}. **HPLC Analysis**: 90% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.6 min, t_{minor} = 10.6 min). $[\alpha]_D^{28}$ = +39.2 (c 0.530, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{31}N_2O_3$ $[M+NH_4]^+$ 431.2335, found 431.2339.



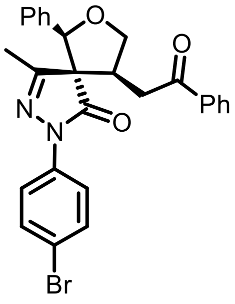
3z^4

(5R,6R,9S)-4-methyl-9-(2-oxo-2-phenylethyl)-6-phenyl-2-(p-tolyl)-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^4): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 62% yield (54.0 mg). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.21– 7.24 (m, 7H), 5.39 (s, 1H), 4.87 (t, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 9.0 Hz, 1H), 3.82-3.74 (m, 1H), 3.16 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.99 (dd, *J* = 17.7, 10.2 Hz, 1H), 2.36 (s, 3H), 2.01 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.8, 171.6, 159.2, 136.0, 136.0, 135.5, 135.3, 133.8, 129.6, 128.9, 128.6, 128.2, 128.2, 124.4, 119.3, 86.3, 72.7, 68.0, 45.1, 38.2, 21.2, 17.7. **FT-IR (thin film)** 3058, 2930, 1710, 1594, 1496, 770 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 43.6 min, t_{minor} = 28.3 min). $[\alpha]_D^{28}$ = -41.8 (c 0.530, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_3$ $[M+H]^+$ 439.2022, found 439.2026.



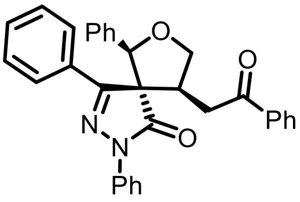
3z^5

(5R,6R,9S)-2-(4-chlorophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-6-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^5): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 55% yield (50.5 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.89-7.83 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.26-7.22 (m, 3H), 7.22-7.19 (m, 2H), 5.38 (s, 1H), 4.86 (t, *J* = 9.2 Hz, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.78 (qd, *J* = 9.3, 5.4 Hz, 1H), 3.15 (dd, *J* = 17.7, 5.3 Hz, 1H), 3.03 (dd, *J* = 17.7, 9.6 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR (125 MHz, CDCl$_3$)** δ 196.7, 171.9, 159.5, 136.5, 136.0, 135.8, 133.9, 130.6, 129.1, 128.9, 128.6, 128.4, 128.1, 124.4, 120.2, 86.6, 72.7, 68.1, 45.0, 38.3, 17.7. **FT-IR (thin film)** 3060, 2927, 1704, 1600, 1500, 780 cm^{-1}. **HPLC Analysis**: 80% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 36.3 min, t_{minor} = 23.2 min). $[\alpha]_D^{28}$ = -37.8 (c 0.465, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}ClN_2O_3$ $[M+H]^+$ 459.1475, found 459.1476.



3z⁶

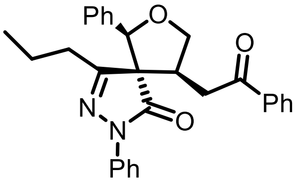
(5R,6R,9S)-2-(4-bromophenyl)-4-methyl-9-(2-oxo-2-phenylethyl)-6-phenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^6): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 57% yield (57.4 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.84-7.79 (m, 4H), 7.58-7.50 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.25-7.18 (m, 5H), 5.38 (s, 1H), 4.85 (t, *J* = 9.2 Hz, 1H), 4.02 (t, *J* = 9.0 Hz, 1H), 3.78 (td, *J* = 14.6, 9.1 Hz, 1H), 3.14 (dd, *J* = 17.6, 5.4 Hz, 1H), 3.02 (dd, *J* = 17.7, 9.5 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.7, 172.0, 159.5, 137.1, 136.0, 135.8, 133.9, 132.1, 128.9, 128.6, 128.4, 128.1, 124.4, 120.5, 118.4, 86.6, 72.7, 68.2, 45.1, 38.3, 17.7. **FT-IR (thin film)** 3049, 2920, 1700, 1600, 1495, 782 cm^{-1}. **HPLC Analysis**: 92% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 43.8 min, t_{minor} = 26.3 min). $[\alpha]_D^{28}$ = -43.4 (c 0.290, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{27}H_{24}BrN_2O_3$ [M+H]$^+$ 503.0970, found 503.0977.



3z⁷

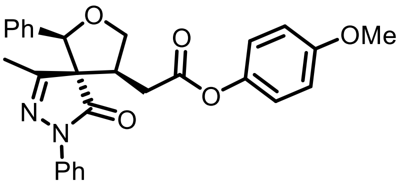
(5R,6R,9S)-9-(2-oxo-2-phenylethyl)-2,4,6-triphenyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z^7): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 60% yield (58.4 mg). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.94-7.92 (m, 2H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 8.0 Hz, 3H), 7.38-7.27 (m, 6H), 7.19-7.17 (m, 2H), 7.13-7.08 (m, 3H), 5.54 (s, 1H), 4.85 (t, *J* = 9.5 Hz, 1H), 4.17 (dd, *J* = 9.0, 7.6 Hz, 1H), 3.88 (dd, *J* = 9.6, 7.8 Hz, 1H), 3.08 (dd, *J* = 18.2, 7.4 Hz, 1H), 2.93 (dd, *J* = 18.2, 8.1 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 197.2, 173.3, 158.1, 138.2, 136.2, 135.5, 133.5, 132.3, 130.2, 129.1, 128.7, 128.7, 128.4, 128.1, 127.9, 127.8, 125.8, 124.7, 119.8, 89.1, 72.7, 68.3, 45.6, 39.2. **FT-IR (thin film)** 3055, 2925, 1706, 1660, 1598, 1493, 790 cm^{-1}. **HPLC Analysis**: 76% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 31.9 min, t_{minor} = 27.4 min). $[\alpha]_D^{24}$ = -55.8 (c

0.265, CHCl3). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{32}H_{27}N_2O_3$ $[M+H]^+$ 487.2022, found 487.2030.



3z8

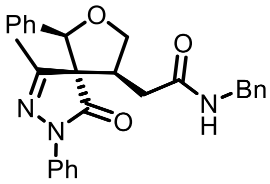
(5R,6R,9S)-9-(2-oxo-2-phenylethyl)-2,6-diphenyl-4-propyl-7-oxa-2,3-diazaspiro[4.4]non-3-en-1-one (3z8): Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 69% yield (62.4 mg). **^{1}H NMR (400 MHz, CDCl3)** δ 7.95-7.90 (m, 2H), 7.87-7.82 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45-7.41 (m, 4H), 7.25-7.18 (m, 6H), 5.40 (s, 1H), 4.86 (t, *J* = 9.1 Hz, 1H), 3.99 (t, *J* = 9.0 Hz, 1H), 3.77 (qd, *J* = 9.3, 4.6 Hz, 1H), 3.15 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.98 (dd, *J* = 17.6, 10.1 Hz, 1H), 2.37-2.18 (m, 2H), 1.35-1.24 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR (100 MHz, CDCl3)** δ 196.8, 171.9, 162.3, 138.2, 136.2, 136.1, 133.8, 129.0, 128.9, 128.6, 128.1, 125.4, 124.4, 119.2, 86.3, 72.8, 68.1, 45.4, 38.3, 33.1, 17.9, 13.8. **FT-IR (thin film)** 3063, 2925, 1705, 1598, 1498, 792 cm^{-1}. **HPLC Analysis**: 56% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.7 min, t_{minor} = 14.8 min). $[\alpha]_D^{29}$ = + 5.3 (c 0.150, CHCl3). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{29}H_{29}N_2O_3$ $[M+H]^+$ 453.2178, found 453.2186.



4

4-methoxyphenyl 2-((5R,6R,9S)-1-methyl-4-oxo-3,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-1-en-9-yl)acetate (4): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless sticky solid; 80% yield (37.6 mg). **^{1}H NMR (600 MHz, CDCl3)** δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.34-7.30 (m, 2H), 7.19-7.12 (m, 6H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 9.1 Hz, 2H), 5.32 (s, 1H), 4.69 (t, *J* = 9.2 Hz, 1H), 4.59-4.55 (m, 1H), 4.04 (t, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.67 (dd, *J* = 9.5, 6.6 Hz, 1H), 2.60-2.55 (m, 2H). **^{13}C NMR (150 MHz,**

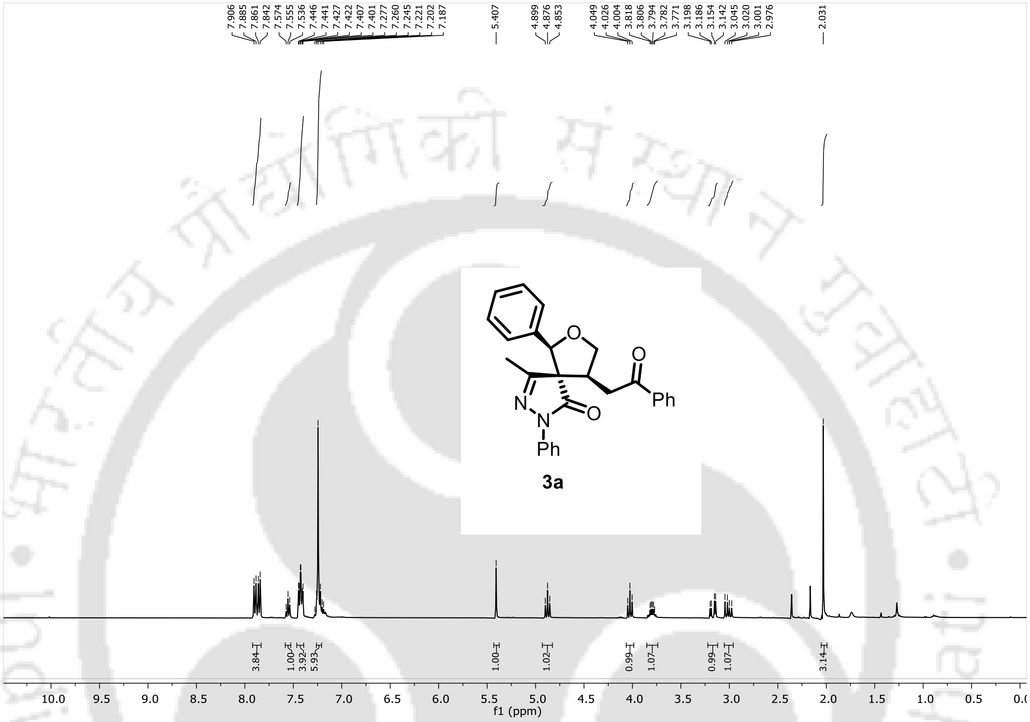
$CDCl_3$) δ 171.6, 169.6, 158.8, 157.5, 143.8, 137.9, 135.7, 129.0, 128.7, 128.4, 125.6, 124.4, 122.2, 119.3, 114.6, 86.80, 72.3, 68.0, 55.7, 45.5, 34.0, 17.6. **FT-IR (thin film)** 3059, 2923, 1698, 1588, 1490, 1290, 783 cm^{-1}. **HPLC Analysis:** ee = 90% ee; Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 22.1 min, t_{minor} = 37.9 min). $[\alpha]_D^{28}$ = -38.9 (c 0.320, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{27}N_2O_5$ $[M+H]^+$ 471.1920, found 471.1926.

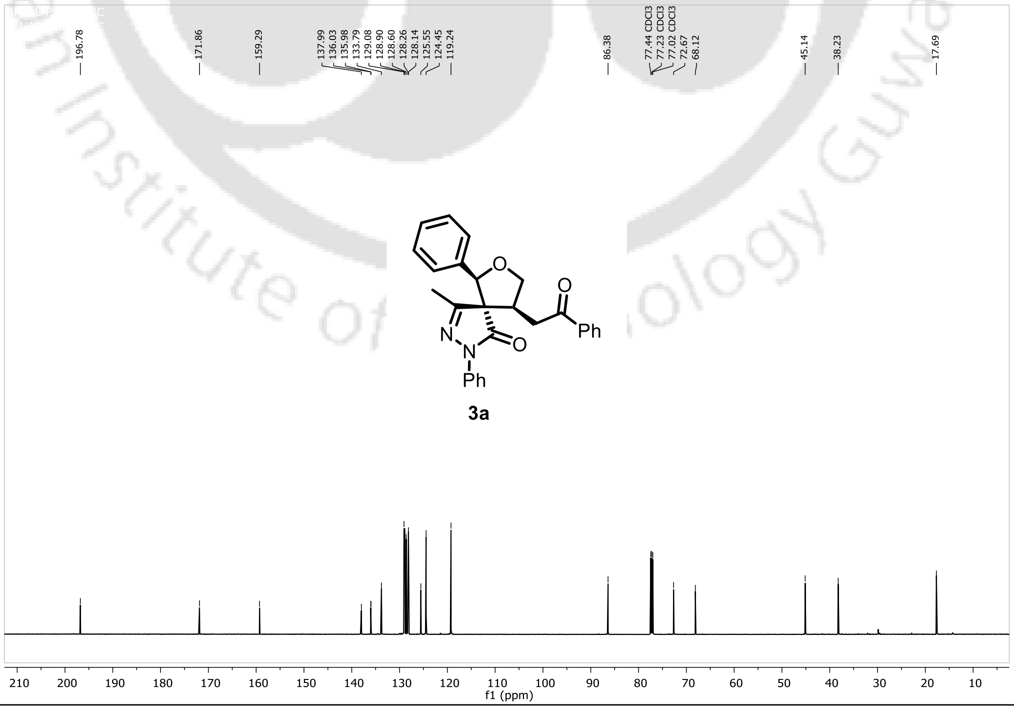


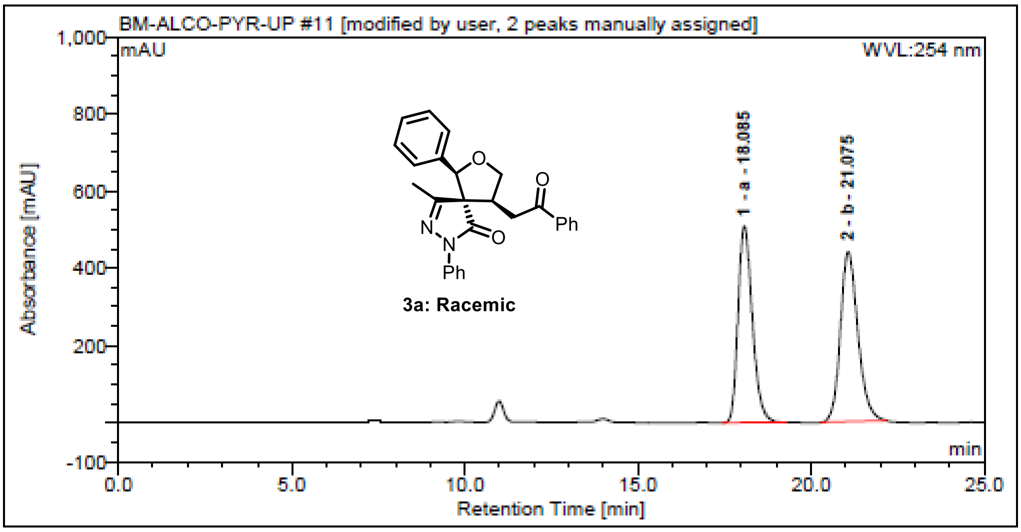
5

N-benzyl-2-((5R,6R,9S)-1-methyl-4-oxo-3,6-diphenyl-7-oxa-2,3-diazaspiro[4.4]non-1-en-9-yl)acetamide (5): Purified by silica-gel column chromatography using 50% ethyl acetate/hexane; brown oil; 75% yield (34.2 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.31-7.27 (m, 3H), 7.24-7.18 (m, 8H), 5.68 (s, 1H), 5.36 (s, 1H), 4.75 (t, *J* = 9.2 Hz, 1H), 4.31 (ddd, *J* = 43.5, 14.5, 5.6 Hz, 2H), 4.15-4.11 (m, 1H), 3.62 (m, 1H), 2.32 (dd, J = 15.0, 10.3 Hz, 1H), 2.21 (dd, J = 15.0, 5.3 Hz, 1H), 1.97 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 171.7, 169.2, 159.3, 137.9, 137.8, 136.0, 129.1, 128.9, 128.6, 128.3, 128.1, 127.9, 125.6, 124.4, 119.1, 86.2, 72.5, 68.2, 46.4, 44.0, 35.6, 17.6. **FT-IR (thin film)** 3278, 3071, 2924, 1665, 1630, 1596, 759 cm^{-1}. **HPLC Analysis:** ee = 88% ee; Determined using a Daicel Chiralpak ID Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 86.4 min, t_{minor} = 65.3 min). $[\alpha]_D^{28}$ = -25.5 (c 0.395, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{28}H_{28}N_3O_3$ $[M+H]^+$ 454.2131, found 454.2122.

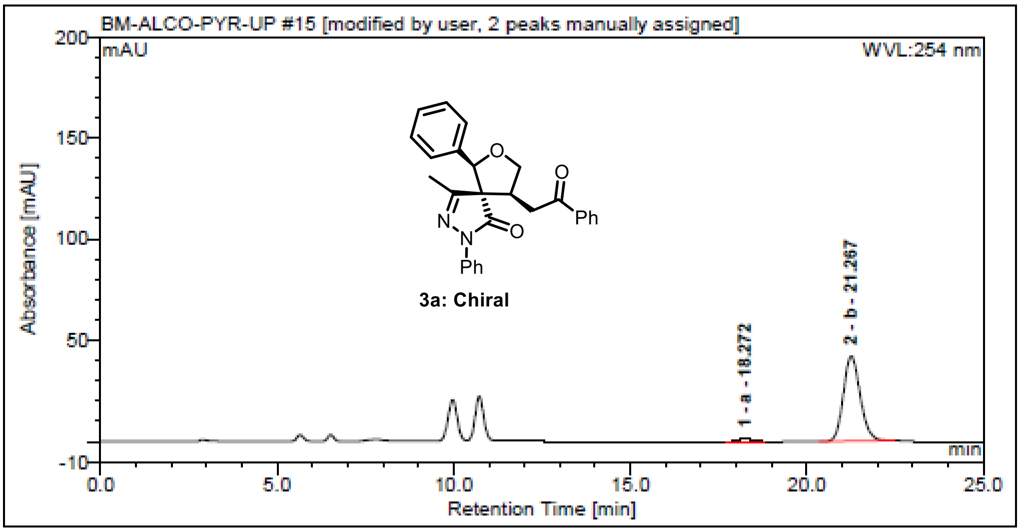
4.8 Selected NMR and HPLC spectra of products







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.09	243.1191	48.45760418	507.5409	n.a.
2	b	21.08	258.596	51.54239582	438.795	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.27	0.544021	2.283395724	1.20219	n.a.
2	b	21.27	23.281	97.71660428	42.031	n.a.

4.9 References

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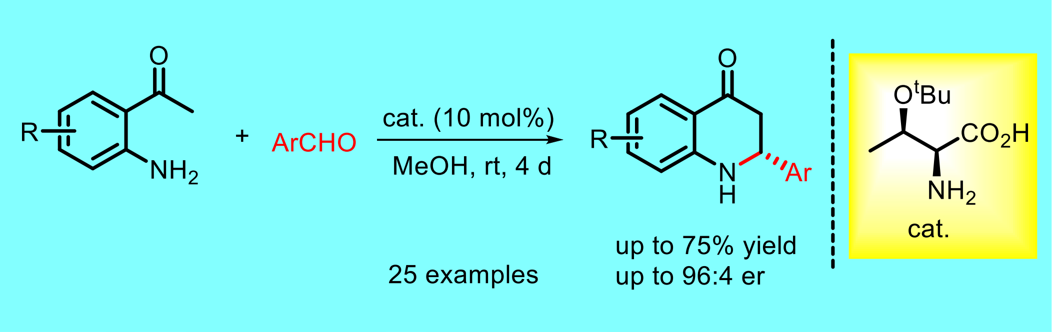
22. CCDC 1824042 (**3s**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.

Chapter 5

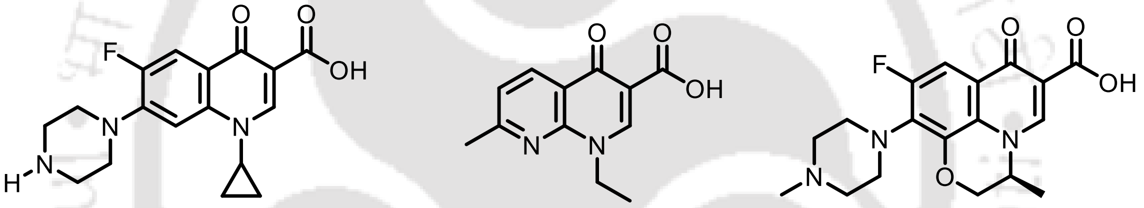
Primary Amino Acid Catalyzed Asymmetric Intramolecular Mannich Reaction for the Synthesis of 2-Aryl-2,3-Dihydro-4-Quinolones



Org. Biomol. Chem. **2014**, *12*, 9789-9792.

5.1 Introduction

Quinolones, the aza-analogues of flavanones, have wide spectrum antibacterial properties and they have been used in pharmaceutical chemistry not only because of their availability orally and parentally but also for their favourable pharmacokinetics.[1] In particular, 2-aryl-2,3-dihydro-4-quinolones have attracted attention because of their activities as anticancer, antimalarial as well as antibiotic agents[2] and as potent cross-species micro RNA inhibitors.[3] Additionally, they illustrate a new class of antimitotic antitumor agents for the treatment of a panel of human tumor cell lines. These important biological properties have stimulated interest for the synthesis of 2-aryl-2,3-dihydro-4-quinolones from different research groups, particularly in enantioselective fashion as two individual stereoisomers behave in totally different ways.



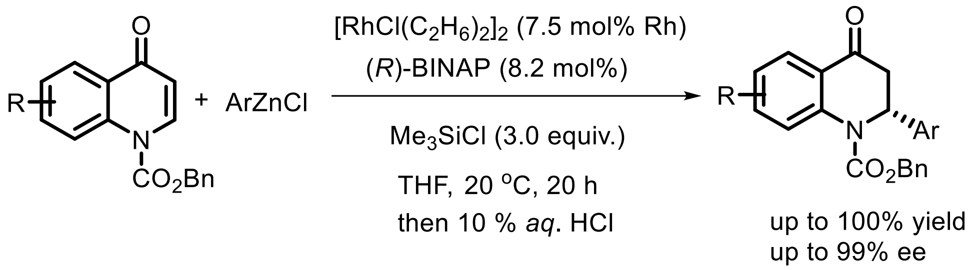
Ciprofloxacin Nalidixic acid Levofloxacin

Figure 1. Biologically active derivatives.

5.2 Known strategies for synthesis of 2-aryl-2,3-dihydro-4-quinolones

5.2.1 Asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones by rhodium-catalyzed 1,4-addition of arylzinc

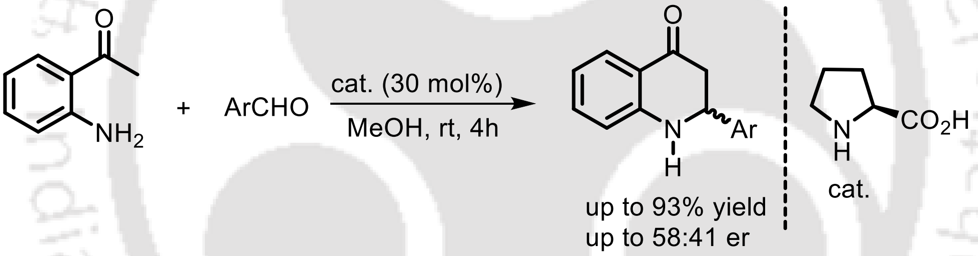
In 2005, the research group of Hayashi established the first catalytic asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones by a rhodium-catalyzed asymmetric 1,4-addition of arylzinc to 4-quinolones, and obtained the 2-aryl-2,3-dihydro-4-quinolones derivatives with excellent yields as well as enatioselectivities (Scheme 1).[4]



Scheme 1. The first catalytic asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones by Hayashi et al.

5.2.2 *L*-Proline-catalyzed one-pot synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)

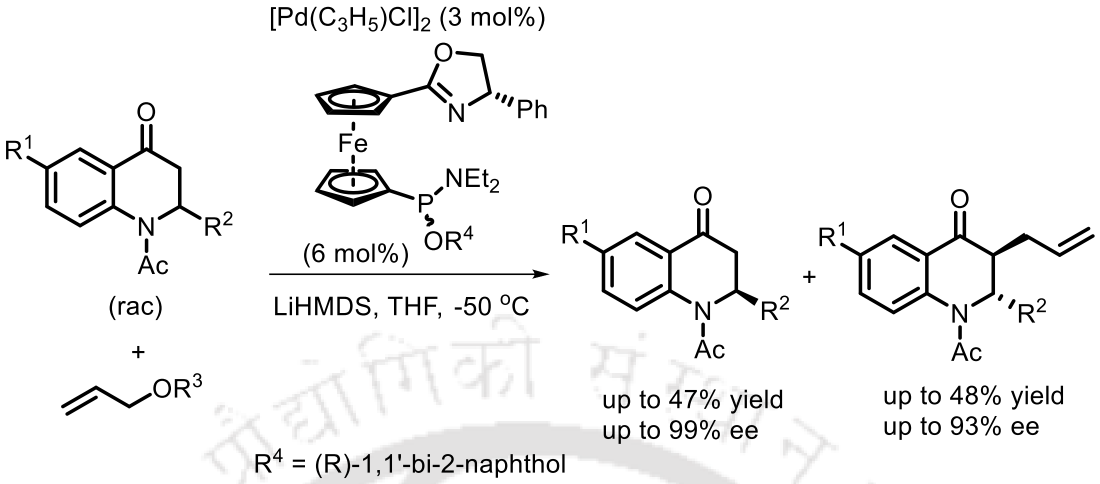
Chandrasekhar and co-workers reported *L*-proline catalyzed one pot synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones. Although the product was obtained with good yields but enantioselectivities were less (Scheme 2).[5]



Scheme 2. *L*-proline catalyzed one-pot synthesis of 2-aryl-2,3-dihydroquinolin-4(1H)-ones by Chandrasekhar et al.

5.2.3 Kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones

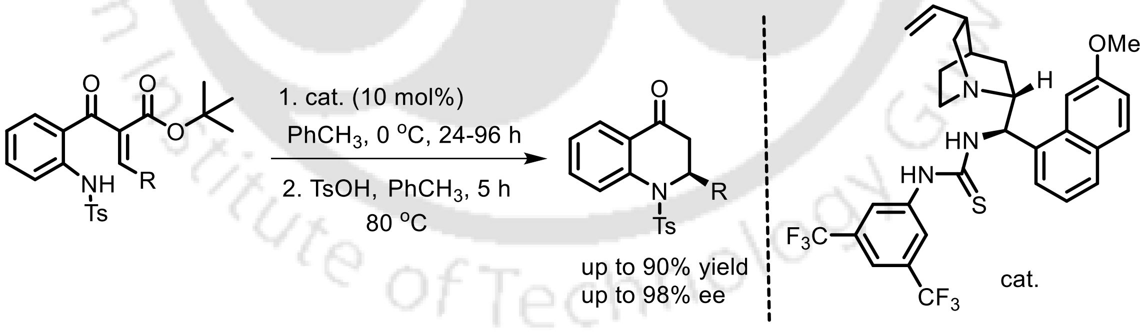
In 2009, Hou and co-workers demonstrated a highly enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones from kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones which involved Pd-catalyzed asymmetric allylic alkylation. The desired products were obtained in moderate yields up to 47% and with excellent enatioselectivities up to 99% (Scheme 3).[6]



Scheme 3. Kinetic resolution of 2,3-dihydro-2-substituted 4-quinolones by Hou et al.

5.2.4 Bifunctional thiourea catalyzed synthesis of 2-aryl-2,3-dihydro-4-quinolones

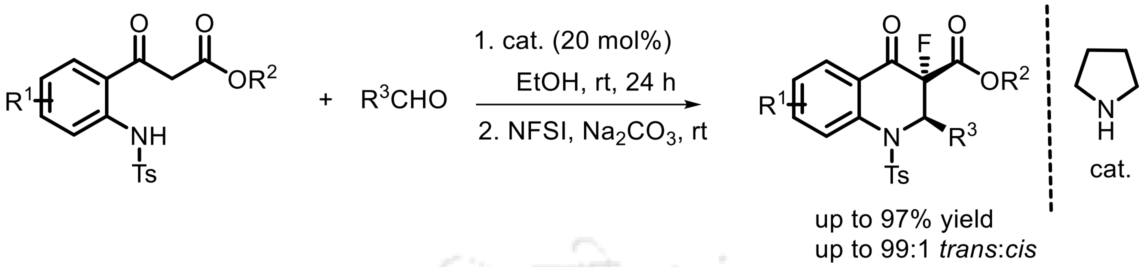
One year later, Lu and co-workers established an enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones *via* 6-*endo*-trig cyclization of amino alkylidene β-keto esters in the presence of a bifunctional thiourea catalyst. The aforementioned protocol provided the desired products in excellent yields with good to excellent enantioselectivities (Scheme 4).[7]



Scheme 4. 6-*endo*-trig Cyclization of amino alkylidene β-keto esters by Lu et al.

5.2.5 Synthesis of fluorinated 2,3-dihydroquinolin-4(1H)-ones

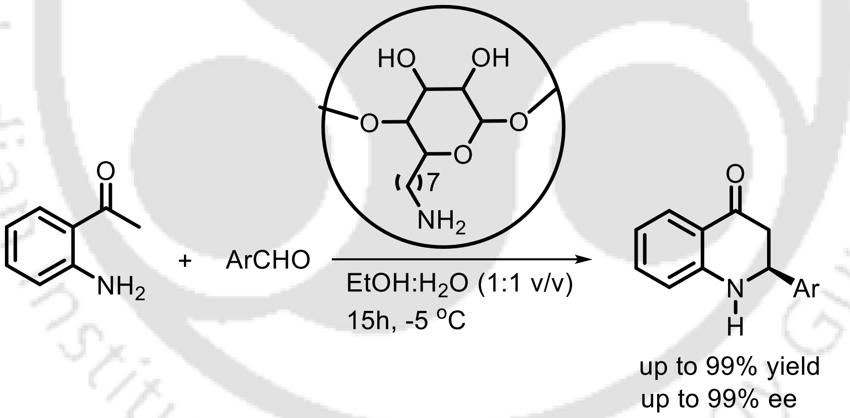
The research group of Ma developed an organocatalytic one-pot synthesis of 2-aryl-2,3-dihydro-4-quinolones *via* Knoevenagel condensation/aza-Michael addition/ electrophilic fluorination. This method provided the desired product in excellent yields as well as excellent diastereoselectivities (Scheme 5).[8]



Scheme 5. Fluorinated 2,3-dihydroquinolin-4(1H)-ones by Ma et al.

5.2.6 Per-6-amino-*β*-cyclodextrin catalyze synthesis of 2-aryl-2,3-dihydro-4-quinolones

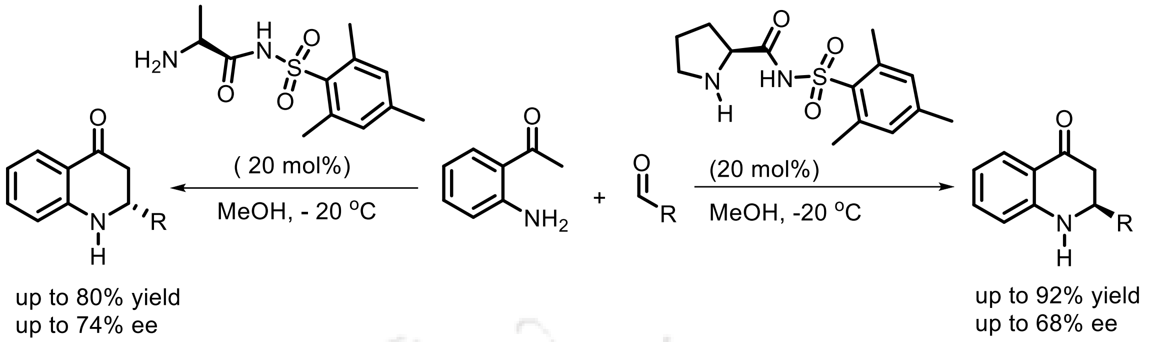
For the first time, per-6-ABCD catalyzed synthesis of enantiomerically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones was developed by Pitumani and co-workers in 2013. The desired 2-aryl-2,3-dihydro-4-quinolones were formed in excellent yields as well as excellent enantioselectivities (Scheme 6).[9]



Scheme 6. Per-6-ABCD catalyzed synthesis of 2-aryl-2,3-dihydro-4-quinolones Pitumani et al.

5.2.7 Amino-acid derived sulfonamide catalyzed synthesis of 2-aryl-2,3-dihydro-4-quinolones

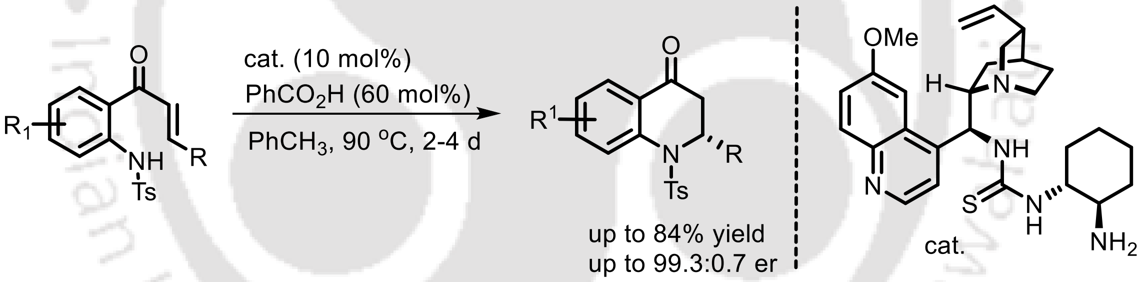
Amino-acid derived sulfonamide catalyzed asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones was demonstrated by Luo and co-works (Scheme 7).[10] This protocol provided the desired products in excellent yields (up to 92%) and with moderate to good enatioselectivities (up to 74% ee).



Scheme 7. Amino-acid derived sulfonamide catalyzed synthesis of 2-aryl-2,3-dihydro-4-quinolones by Luo et al.

5.2.8 Organocatalytic 6-*endo*-trig aza-Michael addition

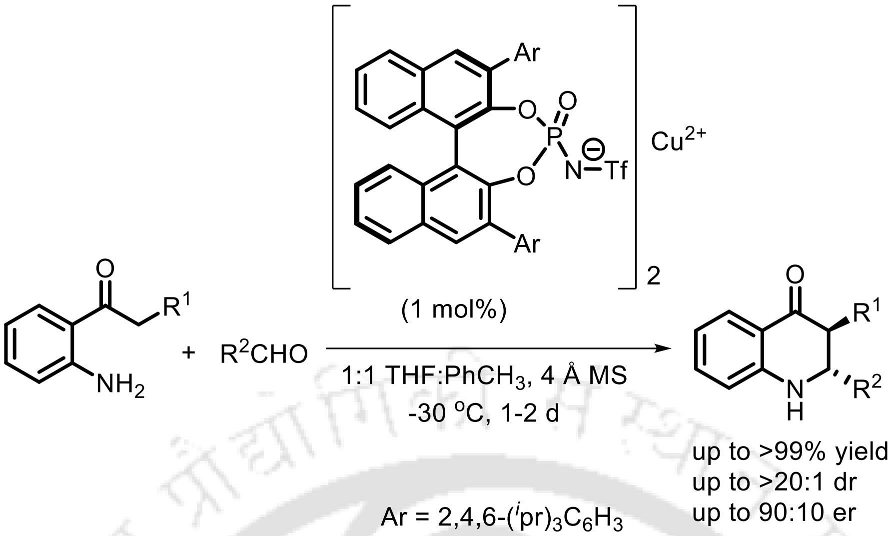
Yu and co-works developed a highly enantioselective 6-*endo*-trig aza-Michael addition of aminochalcones for the synthesis of 2-aryl-2,3-dihydro-4-quinolones using a trifunctional organocatalyst (Scheme 8).[11] This method provided the desired products in good yields (up to 84%) and with excellent enatioselectivities (99.3:0.7 er).



Scheme 8. Organocatalytic 6-*endo*-trig aza-Michael addition by Yu et al.

5.2.9 BINOL-derived Lewis acid catalyzed enantioselective synthesis of dihydroquinolones

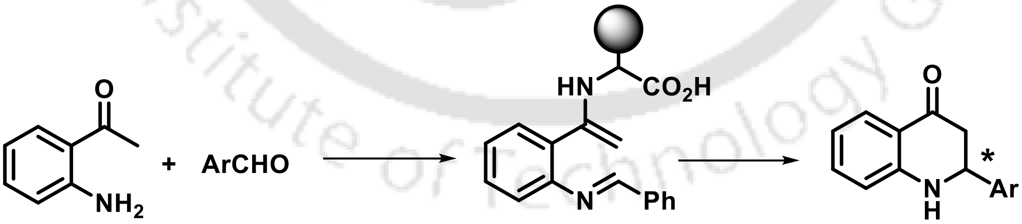
Smith and co-works reported the enantioselective one-pot synthesis of dihydroquinolones using a novel Lewis acid BINOL-derived copper(II) catalyst. This protocol allowed an efficient synthesis of dihydroquinolones with excellent yields and excellent diastereoselectivities but only with modest enatioselectivities (Scheme 9).[12]



Scheme 9. BINOL-derived Lewis acid catalyzed enantioselective synthesis of dihydroquinolones by Smith et al.

5.3 Concept

Taking all these facts into account and realizing the importance of 2-aryl-2,3-dihydro-4-quinolones we thought that a highly enantioselective synthesis by intramolecular Mannich reaction[13] using simple organocatalysts is well desirable. Herein, we describe primary amino acid[14] catalyzed one pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones and also employ a variety of 2-aminoacetophenones for the first time (Scheme 10).



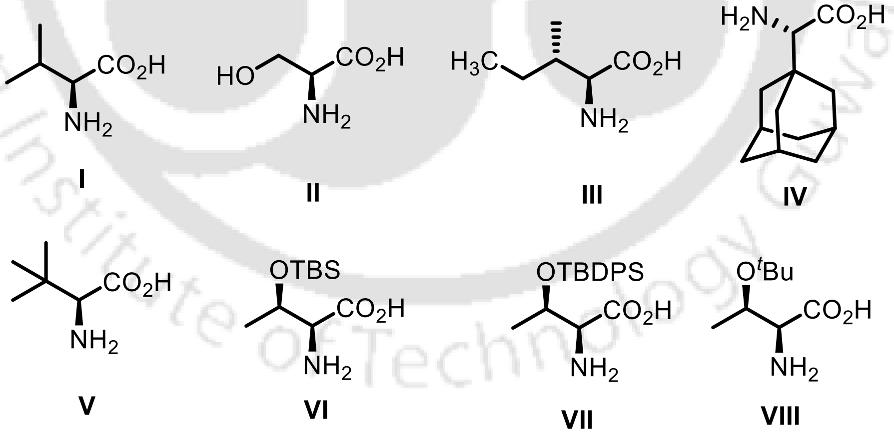
Scheme 10. Primary amino acid catalyzed one pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones.

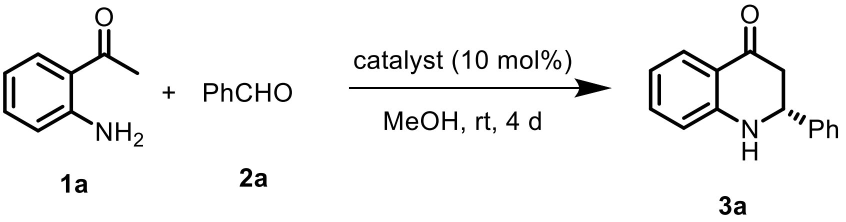
5.4 Results and discussion

5.4.1 Optimization of catalyst and reaction conditions

We started our investigation by screening different primary amino acids **I-VIII** for the reaction between 2-aminoacetophenone (**1a**) and benzaldehyde (**2a**). The reactions were performed in the presence of 10 mol% of catalyst in methanol solvent at room temperature. After stirring for 4 days with valine (**I**) catalyst, the product **3a** was obtained in 40% yield with 77:23 er (Table 1, entry 1). A little less enantioselectivity was observed with *L*-serine (**II**) (Table 1, entry 2). *L*-isoleucine (**III**) could not change the enantioselectivity much and the product was obtained in similar yield (Table 1, entry 3). A higher enantioselectivity was achieved with 1-adamantyl(amino)acetic acid (**IV**) albeit in less yield (Table 1, entry 4). *L-tert*-leucine (**V**) provided the product in similar enantioselectivity but a higher yield of 50% was obtained (Table 1, entry 5). Then we found that O-protected *L*-threonine derivatives (**VI-VIII**)[15] are quite effective for our reaction. Though TBS protected *L*-threonine (**VI**) and TBDPS protected *L*-threonine (**VII**) could not change much the enantioselectivity of the reaction (Table 1, entries 6-7),

Table 1. **Catalyst screening and solvent optimization**





entry[a]	**catalyst**	**solvent**	**yield (%)**[b]	**er**[c]
1	**I**	MeOH	40	77:23
2	**II**	MeOH	46	67:33
3	**III**	MeOH	44	76:24
4	**IV**	MeOH	35	85:15
5	**V**	MeOH	50	85:15
6	**VI**	MeOH	45	81.5:18.5
7	**VII**	MeOH	42	79:21
8	**VIII**	**MeOH**	**55**	**87:13**
9	**VIII**	TFE	50	85:13
10	**VIII**	EtOH	46	86:14
11	**VIII**	*n*-Propanol	44	83:17
12	**VIII**	*n*-Butanol	43	81:19
13	**VIII**	^{t}Butanol	35	70:30
14	**VIII**	CH_2Cl_2	-	-
15	**VIII**	$CHCl_3$	-	-
16[d]	**VIII**	MeOH	48	79:21
17[e]	**VIII**	MeOH	-	-

[a] Reaction condion: 0.1 mmol of **1a** with 0.15 mmol of **2a** in 0.1 mL solvent using 10 mol% catalyst. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral HPLC. [d] At 50 °C. [e] At 0 °C.

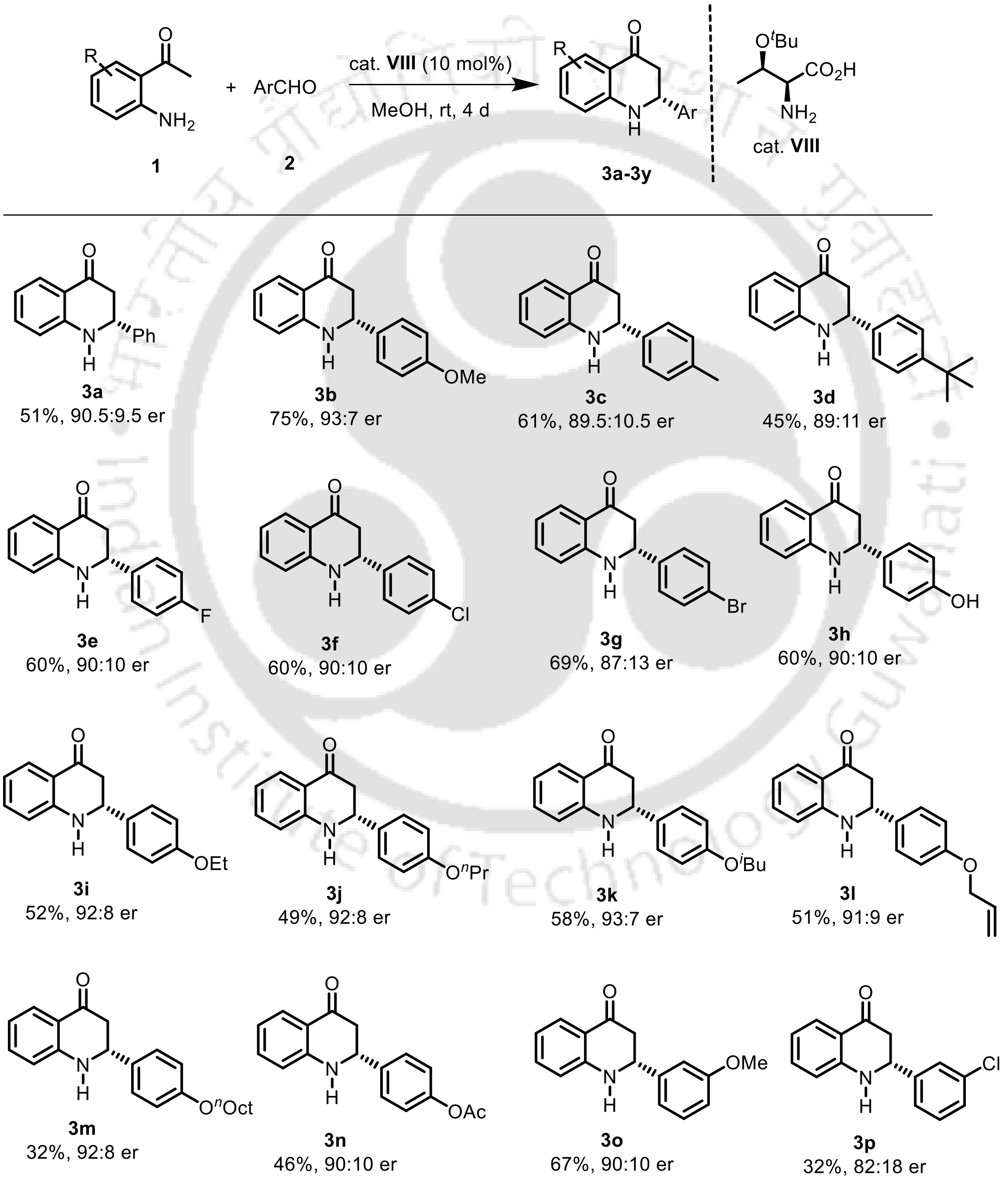
After having the optimum catalyst **VIII** in hand, we focused on the optimization of other reaction parameters. We checked the influence of different solvents in this reaction (Table 1, entries 9-15). A change of the solvent from methanol to other alcohols did not alter the enantioselectivity (Table 1, entries 9-13). Unfortunately no reaction took place with halogenated solvents such as CH_2Cl_2 and $CHCl_3$ (Table 1, entries 14-15). Surprisingly, when we increased the reaction temperature from rt to 50 ^oC, enantioselectivity got decreased to 58% (Table 1, entry 16). A sluggish reaction was observed after lowering the reaction temperature to 0 ^oC (Table 1, entry 17).

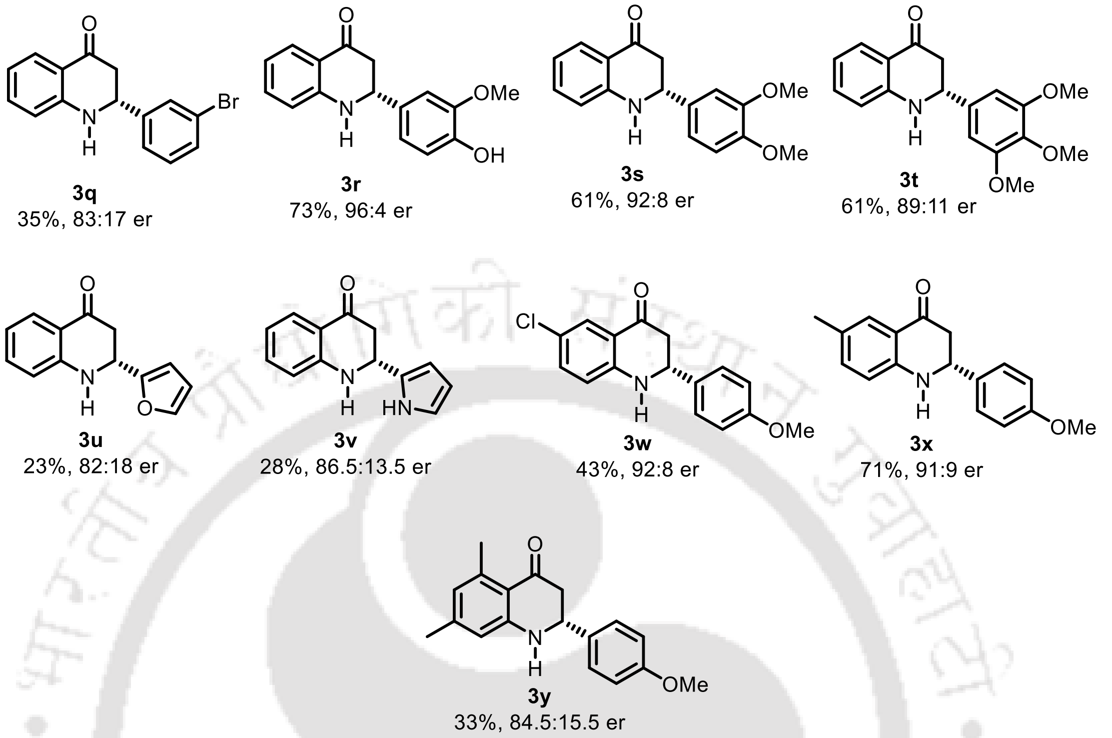
5.4.2 Substrate scope

With the optimized reaction conditions in hand we ventured in the scope of the reaction (Scheme 11). Initially a variety of 4-substituted benzaldehydes was employed in our reaction and incorporation of electron withdrawing or electron rich groups did not affect the outcome of the reaction. For example, *p*-anisaldehyde provided product **3b** in 75% yield with 93:7 er. 4-Alkyl substituted benzaldehydes were also tolerated. For example, 4-methyl and 4-tert-butyl group containing aryl aldehydes delivered product **3c** in 61% yield with 89.5:10.5 er and product **3d** in 45% yield with 89:11 er respectively (Scheme 11). Different halo-substitutions at the 4-position of benzaldehyde were also tolerated and the products (**3e**, **3f** and **3g**) were obtained in similar enantioselectivities (Scheme 11). 4-Hydroxybenzaldehyde can also be employed and product **3h** was observed in satisfactory yield with 92:8 er. Then we screened different 4-alkoxybenzaldydes (**1i-1m**) for our reaction and the corresponding products (**3i-3m**) were obtained acceptable yields with high enantioselectivities (>90:10 er) in all cases (Scheme 11). 4-Acetoxybezaldehyde provided the product **3n** with 46% yield and 90:10 er. Then different 3-substituted benzaldehydes (**1o-1q**) were screened. Though, *m*-anisaldehyde afforded product **3o** in good enantioselectivity, diminished yields and enantioselectivities were observed for products **3p** and **3q** (Scheme 11). Pleasingly, our reaction condition is suitable for the employment of different di and tri-substituted benzaldehydes (**1r-1t**) and vanillin (**1r**) proved to be the best aldehyde with 73% yield and 96:4 er. Different heteroaromatic aldehydes (**1u-1v**) can also be engaged in our reaction albeit the products **3u** and **3v** were obtained in poor yields as well as with moderate enatioselectivities.

Additionally, different substituted 2-amino acetophenones were also employed for the first time in this reaction (Scheme 11). 5-Chloro-2-aminoacetophenone (**1b**) provided product **3w** in moderate yield with 92:8 er but a higher yield was attained for product **3x** in similar enantioselectivity.

Scheme 11. Substrate scope^a





3q 35%, 83:17 er

3r 73%, 96:4 er

3s 61%, 92:8 er

3t 61%, 89:11 er

3u 23%, 82:18 er

3v 28%, 86.5:13.5 er

3w 43%, 92:8 er

3x 71%, 91:9 er

3y 33%, 84.5:15.5 er

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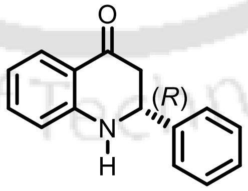
[a]Reactions were carried out with 0.2 mmol of **1** with 0.3 mmol of **2** in 0.2 mL MeOH using 10% **VIII** at rt for 4 days. Yields correspond to isolated yields after silica gel column chromatography. Enantiomeric ratio were determined by chiral HPLC.

5.4.3 Determination of product stereochemistry

Absolute configuration was determined as '*R'* by comparison of optical rotation with literature value.[6]



Literature optical rotation: $[\alpha]_D^{20} = + 27.1$ (c = 0.42, $CHCl_3$) for the (*S*)-enantiomer.

Observed optical rotation: $[\alpha]_D^{25} = - 23.4$ (c = 0.7, $CHCl_3$).

5.4.4 Proposed TS

A proposed transition state model has been shown in Figure 3 and it dictates that the primary amino group of the catalyst generates an enamine intermediate. Also only *Re* face of the newly generated imine double bond is exposed for enamine addition. We also assume that the carboxylic acid group of catalyst simultaneously activates the imine from the *Si* face for the addition. The absolute configuration of the product could be envisaged as "*R*" by this model and it was also confirmed by the comparison of the optical rotation with literature value.

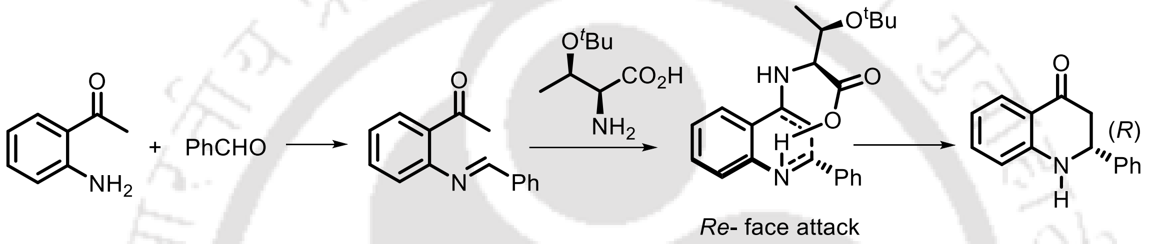


Figure 3. Proposed TS.

5.5 Conclusion

In summary, we have developed primary *α*-amino acid catalyzed asymmetric intramolecular Mannich reaction between 2-aminoacetophenones and aryl aldehydes. This report shows that primary *α*-amino acids are better catalysts than secondary *α*-amino acid such as proline for this particular reaction.

5.6 Experimental section

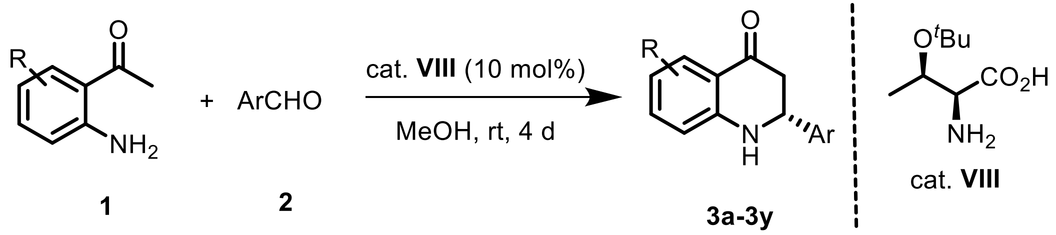
5.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak OD Column, Daicel Chiralpak AS-H Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

5.6.2 General procedure for the synthesis of 2-aminoacetophenones 2b-2d

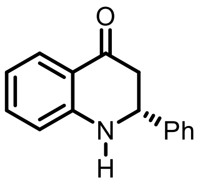
Substituted 2-aminoacetophenones were prepared according to the literature procedures.[16,17]

5.6.3 General procedure for the synthesis of compound 3a-3y



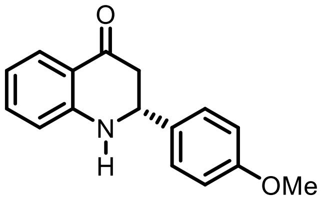
In an oven dried round bottom flask, **1** (0.2 mmol) and **2** (0.3 mmol) were taken. Then 0.2 mL dry methanol was added and the mixture was stirred at room temperature for 30 minutes. After 30 minutes, catalyst **VIII** (10 mol%) was added to the reaction mixture and stirred for 4 days at room temperature. After 4 days, the crude reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (20-25%) to afford the desired products **3a-3y**.

5.7 Characterization data of products



3a

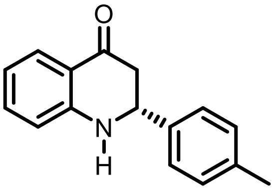
(R)-2-phenyl-2,3-dihydroquinolin-4(1H)-one (3a): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; yellow solid; 55% yield (24.7 mg); m.p. 150-151 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 7.61 Hz, 1H), 7.47-7.38 (m, 2H), 7.37-7.31 (m, 4H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.76 (dd, *J* = 4 13.6 Hz, 1H), 4.52 (br s, 1H), 2.89 (dd, *J* = 13.6, 16.2 Hz, 1H), 2.77 (dd, *J* = 2.4, 15.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 193.4, 151.7, 141.2, 135.6, 129.2, 128.7, 127.8, 126.8, 119.3, 118.7, 116.1, 58.7, 46.6. **FT-IR (thin film)** 3320, 3070, 1650, 1610, 1513, 1390, 1247, 1116, 1022, 735 cm^{-1}. **HPLC Analysis**: 87:13 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 10.2 min, t_{minor} = 7.9 min). $[\alpha]_D^{25}$ = -23.4 (c 0.7, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{15}H_{13}NO$ $[M+H]^+$ 224.1076, found 224.1119.



3b

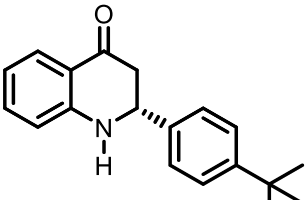
(R)-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3b): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; pale yellow solid; 75% yield (38 mg); m.p. 145-147 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.38-7.32 (m, 2H), 7.33-7.32 (m, 1H), 6.92 (d, *J* = 9.0, 2H), 6.78 (t, *J* = 6.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H),), 4.70 (dd, *J* = 3.6 , 13.8, Hz, 1H), 4.45 (br s,1H), 3.82 (s, 3H), 2.87 (dd, *J* = 13.8, 16.2 Hz, 1H), 2.74

(dd, *J* = 4.8, 16.2 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 193.7, 159.8, 151.8, 135.5, 133.2, 128.0, 127.7, 119.1, 118.5, 116.0, 114.4, 58.0, 55.5, 46.7. **FT-IR (thin film)** 3310, 3050, 1640, 1605, 1510, 1395, 1248, 1112, 1025, 740 cm^{-1}. **HPLC Analysis**: 93:7 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 13.4 min, t_{minor} = 7.8 min). $[\alpha]_D^{25}$ = -32.4 (c 0.4, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{15}NO_2$ $[M+H]^+$ 254.1176, found 254.1178.



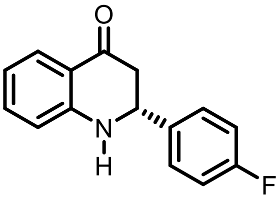
3c

(R)-2-(p-tolyl)-2,3-dihydroquinolin-4(1H)-one (3c): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; yellow solid; 61% yield (29.0 mg); m.p. 148-150 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.36-7.33 (m, 3H), 7.20-7.22 (m, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.70 (d, J = 8.0 Hz 1H), 4.72 (dd, J = 4.0, 13.8 Hz, 1H), 4.48 (br s, 1H), 2.88 (dd, *J* = 13.6, 16.4 Hz, 1H), 2.75 (dd, *J* = 3.6, 16.4 Hz, 1H), 2.37 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 193.6, 151.8, 138.3, 138.1, 135.5, 129.7, 127.6, 126.6, 119.0, 118.3, 116.0, 58.2, 46.5, 21.2. **FT-IR (thin film)** 3320, 3050, 1650, 1510, 1330, 1240, 1150, 1025, 760 cm^{-1}. **HPLC Analysis**: 89.5:10.5 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 12.8 min, t_{minor} = 6.5 min). $[\alpha]_D^{25}$ = -25.2 (c 0.5, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{15}NO$ $[M+H]^+$ 238.1226, found 238.1240.



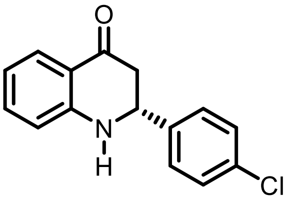
3d

(R)-2-(4-tert-butyl)phenyl)-2,3-dihydroquinolin-4(1H)-one (3d): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; yellow solid; 45% yield (25.2 mg); m.p. 135-137 °C. **^{1}H NMR** (**600 MHz, CDCl$_3$**) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.43-7.38 (m, 4H), 7.34-7.32 (m, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 4.73 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.48 (br s, 1H), 2.90 (dd, *J* = 13.8, 16.2 Hz, 1H), 2.79 (dd, *J* = 1.2, 3.6 Hz, 1H), 1.33 (s, 9H). **^{13}C NMR** (**150 MHz, CDCl$_3$**) δ 193.6, 151.8, 151.7, 138.1, 135.5, 127.8, 126.5, 126.0, 119.2, 118.5, 116.6, 58.3, 46.5, 34.8, 31.5. **FT-IR (thin film)** 3330, 3055, 1660, 1525, 1325, 1245, 1153, 1028, 763 cm^{-1}. **HPLC Analysis**: 89:11 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 ^{o}C, λ = 365 nm (t_{major} = 14.6 min, t_{minor} = 10.3 min). $[\alpha]_D^{25}$ = -21.6 (c 0.3, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{21}NO$ $[M+H]^+$ 280.1696, found 280.1666.



3e

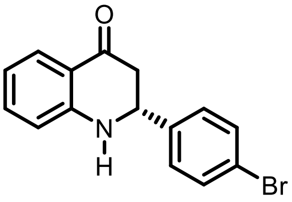
(R)-2-(4-fluorophenyl)-2,3-dihydroquinolin-4(1H)-one (3e): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; yellow solid; 62% yield (30.0 mg); m.p. 135-137 ^{o}C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.46-7.42 (m, 2H), 7.41-7.34 (m, 1H), 7.32-7.05 (m, 2H), 6.80 (t, *J* = 8 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H) 4.74 (dd, *J* = 4, 13.6 Hz, 1H), 4.48 (br s, 1H), 2.88-2.72 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 193.6, 163.5, 161.9, 151.6, 137.0, 135.6, 128.4, 127.7, 119.2, 118.7, 115.9, 46.7, 58.0. **FT-IR (thin film)** 3310, 3075, 1648, 1516, 1328, 1219, 1120, 1010, 760 cm^{-1}. **HPLC Analysis**: 89:11 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 ^{o}C, λ = 365 nm (t_{major} = 9.0 min, t_{minor} = 5.7 min). $[\alpha]_D^{25}$ = +3.6 (c 0.3, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{15}H_{12}FNO$ $[M+H]^+$ 242.0976, found 242.0992.



3f

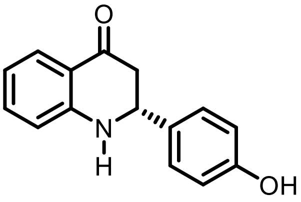
(R)-2-(4-chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (3f): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; Pale yellow solid; 60% yield (30.8 mg); m.p. 169-171 ^{o}C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.46-7.42 (m, 2H), 7.42-7.33 (m, 5H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 4.74 (dd, *J* = 4, 13.2 Hz, 1H), 4.46 (br s, 1H), 2.88-2.73 (m, 2H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 193.0, 151.5, 139.7, 135.6, 134.3, 129.3, 128.1, 127.7, 119.2, 118.8, 116.1, 58.0, 46.5. **FT-IR (thin film)** 3310, 2910, 1652, 1328, 1120, 1010, 760 cm^{-1}. **HPLC Analysis**: 90:10 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-

propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 11.9 min, t_{minor} = 6.5 min). $[\alpha]_D^{25}$ = +3.6 (c 0.3, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{15}H_{12}ClNO$ $[M+H]^+$ 258.0680, found 258.0680.



3g

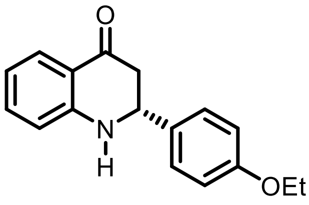
(R)-2-(4-bromophenyl)-2,3-dihydroquinolin-4(1H)-one (3g): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; yellow solid; 69% yield; (41.7 mg); m.p. 159-161. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.86-7.52 (m, 2H), 7.51-7.33 (m, 3H), 6.83-6.81 (m, 1H), 6.79-6.71 (m, 1H), 4.73 (dd, *J* = 4.4, 13.4 Hz, 1H) 4.46 (br s, 1H), 2.87-2.73 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.0, 151.5, 140.2, 135.7, 132.3, 128.5, 127.8, 122.4, 119.2, 118.9, 116.1, 58.1, 46.5. **FT-IR (thin film)** 3326, 2930, 1650, 1333, 1127, 1030, 819, 763 cm^{-1}. **HPLC Analysis**: 87:13 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 13.6 min, t_{minor} = 7.2 min). $[\alpha]_D^{25}$ = -25.8 (c 0.5, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{15}H_{12}BrNO$ $[M+H]^+$ 302.0175, found 302.0143.



3h

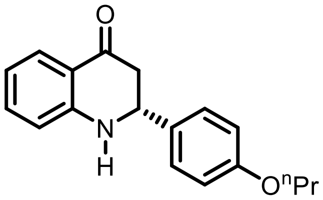
(R)-2-(4-hydroxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3h): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; brownish yellow solid; 70% yield; (33.5 mg); m.p. 159-161 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8.4 Hz, 1H) 7.36-7.31 (m, 3H), 6.86 (d, *J* = 8.4Hz, 2H), 6.78 (t, *J* = 8 Hz, 1H), 6.69 (d, *J* = 8.4 Hz 1H), 4.64 (dd, *J* = 3.6, 14.0 Hz, 1H), 4.46 (br s, 1H), 2.87 (dd, *J* = 14, 16.4 Hz, 1H), 2.74 (dd, *J* = 2.8, 16 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 193.6, 156.3, 151.8, 135.6, 133.0, 128.2, 127.8, 119.1, 118.5, 116.1, 116.0, 58.1, 46.7. **FT-IR (thin film)** 3555, 3065, 1650, 1530, 1490, 1270, 1110, 950, 900, 760 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 8.5 min, t_{minor} = 6.2 min). $[\alpha]_D^{25}$ = +23.5 (c

0.2, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{15}H_{13}NO_2$ $[M+H]^+$ 240.1019, found 240.1046.



3i

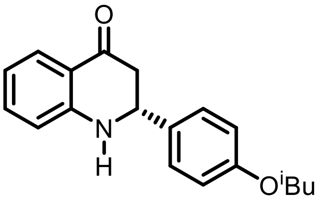
(R)-2-(4-ethoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3i): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; light yellow solid; 52% yield; (27.8 mg); m.p. 112-114 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.37-7.31 (m, 3H), 6.91 (d, *J* = 6.8 Hz, 2H), 6.78 (t, *J* = 8.4 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 4.69 (dd, *J* = 3.6, 15.2 Hz, 1H), 4.46 (br s, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.87 (dd, *J* = 16, 16.2 Hz, 1H), 2.73 (dd, *J* = 6, 15.2 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.7, 159.1, 151.8, 135.5, 133.0, 127.9, 127.7, 119.1, 118.4, 116.0, 114.9, 63.7, 58.0, 46.6, 14.0. **FT-IR (thin film)** 3308, 2935, 1657, 1610, 1515, 1480, 1263, 1115, 920, 747 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 10.9 min, t_{minor} = 6.7 min). $[\alpha]_D^{25}$ = -35.1 (c 0.6, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{17}H_{17}NO_2$ $[M+H]^+$ 268.1332, found 268.1316.



3j

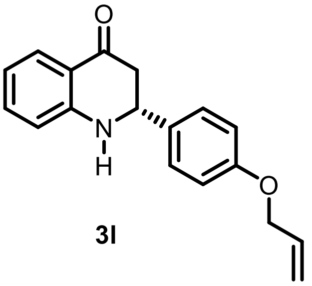
(R)-2-(4-propoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3j): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; pale yellow solid; 49% yield; (27.5 mg); m.p. 118-120 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.37-7.31 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.78 (t, J = 6.8 Hz, 1H), 6.69 (d, J = 8.4 Hz 1H), 4.69 (dd, *J* = 4, 13.8 Hz, 1H), 4.45 (br s, 1H), 3.93 (t, *J* = 6.8 Hz, 2H), 2.87 (dd, *J* = 14, 16.4 Hz, 1H), 2.73 (dd, *J* = 3.6, 16.4 Hz, 1H), 1.86-1.77 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 193.7, 159.4, 151.8, 135.5, 133.0, 127.9, 127.8, 119.2, 118.5, 116.0, 115.0, 69.8, 58.1, 46.7, 22.7, 10.7. **FT-IR (thin film)** 3325, 2948, 1665, 1635, 1525, 1485, 1258, 1111, 930, 741 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 8.9 min, t_{minor} = 6.0 min). $[\alpha]_D^{25}$ = -21.1 (c

0.35, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{18}H_{19}NO_2$ $[M+H]^+$ 282.1489, found 282.1518.



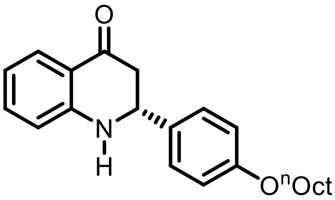
3k

(R)-2-(4-isobutyloxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3k): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; Pale yellow solid; 58% yield (34.2 mg); m.p. 155-157 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8 Hz, 1H), 7.37-7.31 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.69 (dd, *J* = 3.6, 14.2 Hz, 1H), 4.45 (br s, 1H), 3.73 (d, *J* = 6.4 Hz, 2H), 3.93 (t, *J* = 6.8 Hz, 2H), 2.87 (dd, *J* = 14, 16.4 Hz, 1H), 2.73 (dd, *J* = 3.6, 16.4 Hz, 1H), 2.04 – 2.14 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 193.7, 159.5, 151.8, 135.5, 132.9, 127.9, 127.7, 119.1, 118.4, 116.0, 115.0, 74.7, 58.1, 46.7, 28.4, 19.4. **FT-IR (thin film)** 3322, 2895, 1656, 1613, 1508, 1268, 1130,747, 630 cm^{-1}. **HPLC Analysis**: 93:7 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 7.2 min, t_{minor} = 5.5 min). $[\alpha]_D^{25}$ = -15.3 (c 0.22, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{19}H_{21}NO_2$ $[M+H]^+$ 296.1645, found 296.1635.



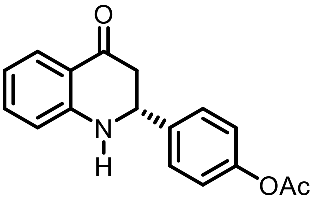
3l

(R)-2-(4-(allyloxy)phenyl)-2,3-dihydroquinolin-4(1H)-one (3l): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; yellow solid; 55% yield (30.7 mg); m.p. 108-110 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 9 Hz, 1H), 7.38-7.35 (m, 2H), 7.37-7.31 (m, 1H), 6.95-6.92 (m, 2H), 6.78 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.8 Hz 1H), 6.09-6.02 (m, 1H), 5.40-5.44 (m, 1H), 5.30 (dd, *J* = 1.2, 10.8 Hz, 1H), 4.69 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.45 (br s, 1H), 4.56-4.55 (m, 2H), 2.87 (dd, *J* = 13.8, 16.5 Hz, 1H), 2.74 (dd, *J* = 3.8, 16.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 193.7, 158.7, 151.8, 135.5, 133.3, 133.2, 127.9, 127.7, 119.1, 118.4, 117.9, 116.0, 115.2, 69.0, 58.0, 46.6. **FT-IR (thin film)** 3325, 2945, 1670, 1620, 1532, 1492, 1253, 1122, 910, 757 cm^{-1}. **HPLC Analysis**: 91:9 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 11.8 min, t_{minor} = 7.4 min). $[\alpha]_D^{25}$ = -18.6 (c 0.3, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{18}H_{17}NO_2$ $[M+H]^+$ 280.1332, found 280.1333.



3m

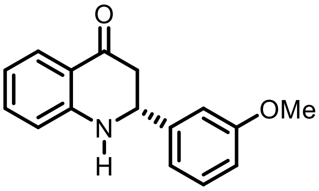
(R)-2-(4-(octyloxy)phenyl)-2,3-dihydroquinolin-4(1H)-one (3m): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; pale yellow solid; 32% yield; (22.5 mg); m.p. 120-122 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.37-7.31 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 1H), 4.69 (dd, *J* = 1.6, 14.6 Hz, 1H), 4.45 (br s, 1H), 3.96 (t, *J* = 6.4 Hz, 2H), 2.87 (dd, *J* = 15.6, 15.8 Hz, 1H), 2.73 (dd, *J* = 3.6, 16.2 Hz, 1H), 1.82-1.75 (m, 2H), 1.28-1.49 (m, 10H), 0.88 (t, *J* = 1.6 Hz, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 193.7, 159.4, 151.8, 135.5, 133.0, 128.0, 127.8, 119.2, 118.5, 116.0, 115.0, 68.3, 58.1, 46.7, 30.0, 29.9, 29.5, 29.4, 26.2, 22.8, 14.3. **FT-IR (thin film)** 3300, 2925, 1665, 1600, 1535, 1478, 1272, 1105, 913, 732 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 7.5 min, t_{minor} = 5.3 min). $[\alpha]_D^{25}$ = -30.2 (c 0.5, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{23}H_{29}NO_2$ $[M+H]^+$ 352.2271, found 352.2264.



3n

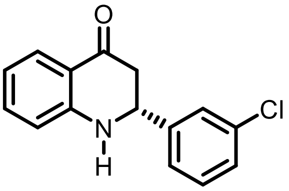
(R)-4-(4-oxo-1,2,3,4-tetrahydroquinoline-2-yl)phenyl acetate (3n): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; brownish solid; 46% yield; (25.9 mg); m.p. 147-149 °C. **^{1}H NMR** (**600 MHz, $CDCl_3$**) δ 7.88-7.87 (m, 1H), 7.49-7.47 (m, 2H), 7.36-7.33 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.76 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.48 (br s, 1H), 2.87 (dd, *J* = 13.8, 16.2 Hz, 1H), 2.77 (dd, *J* = 3.6, 16.5 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR** (**150 MHz, $CDCl_3$**) δ 193.3, 169.6, 151.6, 150.8, 138.7, 135.6, 127.9, 127.8, 122.3, 119.2, 118.7, 116.1, 58.1, 46.6, 21.3. **FT-IR (thin film)** 3312, 2942, 1662, 1623, 1532, 1492, 1268, 1130, 737 cm$^-$

^{1}. **HPLC Analysis**: 90:10 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 14.2 min, t_{minor} = 9.1 min). $[\alpha]_D^{25}$ = -20.3 (c 0.45, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{17}H_{15}NO_3$ $[M+H]^+$ 282.1125, found 282.1124.



3o

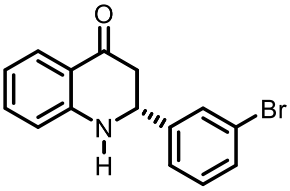
(R)-2-(3-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3o): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; brownish yellow solid; 67% yield; (33.8 mg); m.p. 128-130 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.2 Hz, 1H), 7.35-7.29 (m, 2H), 7.03-7.01 (m, 2H), 6.89-6.87 (m, 1H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 4.72 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.52 (br s, 1H), 3.82 (s, 3H), 2.89-2.76 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 193.4, 160.2, 151.8, 142.8, 135.6, 130.2, 127.7, 119.2, 119.0, 118.5, 116.1, 113.8, 112.4, 58.6, 55.5, 46.6. **FT-IR (thin film)** 3338, 2929, 1651, 1400, 1248, 1180, 1078, 840 cm^{-1}. **HPLC Analysis**: 90:10 er; Determined using a Daicel Chiralpak AS-H Column (hexane/2-propanol = 90:10), flow rate 1.2 mL/min, 25 °C, λ = 365 nm (t_{major} = 37.4 min, t_{minor} = 32.4 min). $[\alpha]_D^{25}$ = -30.3 (c 0.5, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{15}NO_2$ $[M+H]^+$ 254.1176, found 254.1166.



3p

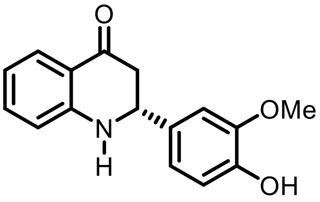
(R)-2-(3-chlorophenyl)-2,3-dihydroquinolin-4(1H)-one (3p): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; pale yellow solid; 38% yield; (19.5 mg); m.p. 145-147 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.37-7.32 (m, 4H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.73 (dd, *J* = 3.6, 13.5 Hz, 1H), 4.50 (br s, 1H), 2.87-2.75 (m, 2H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 192.9, 151.5, 143.3, 135.7, 135.0, 130.4, 128.7, 127.7, 126.9, 125.0, 119.2, 118.9, 116.2, 58.1, 46.6. **ESI-MS** m/z calcd. for $C_{15}H_{12}ClNO$ $[M+H]^+$ 258.0680, found: 258.0661. **FT-IR (thin film)** 3318, 2932, 1657, 1613, 1446, 1279, 1112, 767 cm^{-1}. **HPLC Analysis**: 82:18 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ =

365 nm (t_{major} = 9.6 min, t_{minor} = 7.3 min). $[\alpha]_D^{25}$ = -18.3 (c 0.5, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{12}ClNO$ $[M+H]^+$ 258.0680, found 258.0661.



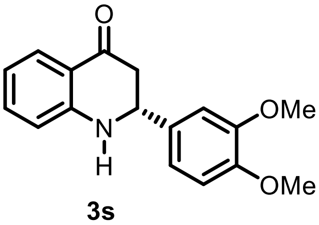
3q

(R)-2-(3-bromophenyl)-2,3-dihydroquinolin-4(1H)-one (3q): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; orange solid; 35% yield; (21.6 mg); m.p. 104-106 °C. **^{1}H NMR** (**400 MHz, $CDCl_3$**) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.37-7.33 (m, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 4.70 (dd, *J* = 4.4, 13.2 Hz, 1H), 4.54 (br s, 1H), 2.86-2.72 (m, 2H). **^{13}C NMR** (**100 MHz, $CDCl_3$**) δ 192.9, 151.5, 143.5, 135.7, 131.6, 130.7, 129.8, 127.7, 125.4, 123.1, 119.0, 118.8, 116.2, 58.0, 46.6. **FT-IR (thin film)** 3327, 2936, 1655, 1478, 1267, 1125, 765 cm^{-1}. **HPLC Analysis**: 83:17 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 10.7 min, t_{minor} = 8.1 min). $[\alpha]_D^{25}$ = -15.7 (c 0.45, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{12}BrNO$ $[M+H]^+$ 302.0175, found 302.0165.



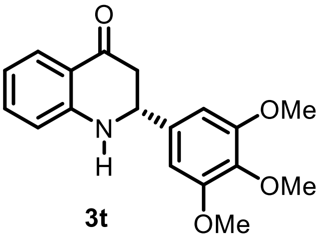
3r

(R)-2-(4-hydroxy-3-methoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3r): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; brown solid; 73% yield (39.3 mg); m.p. 143-145 °C. **^{1}H NMR** (**400 MHz, $CDCl_3$**): δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.00-6.91 (m, 3H), 6.79 (t, *J* = 6.8 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.67 (br s, 1H), 4.67 (dd, *J* = 4, 13.8 Hz, 1H), 4.46 (br s, 1H), 3.91 (s, 3H), 2.90-2.72 (m, 2H). **^{13}C NMR** (**150 MHz, $CDCl_3$**) δ 193.4, 151.5, 146.7, 145.6, 135.3, 132.8, 127.5, 119.5, 118.9, 118.3, 115.8, 114.5, 108.7, 58.3, 55.8, 46.6. **FT-IR (thin film)** 3538, 3318, 2843, 1649, 1617, 1512, 1276, 1128, 739 cm^{-1}. **HPLC Analysis**: 96:4 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 17.5 min, t_{minor} = 11.7 min). $[\alpha]_D^{25}$ = -40.4 (c 0.7, $CHCl_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{16}H_{15}NO_3$ $[M+H]^+$ 270.1125, found 270.1135.



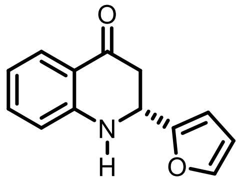
3s

(R)-2-(3,4-dimethoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3s): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; brown solid; 61% yield; (34.6 mg); m.p. 129-131 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 7.00-6.96 (m, 2H), 6.86 (d, *J* = 8 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 4.68 (dd, *J* = 3.6, 14.2 Hz, 1H), 4.51 (br s, 1H), 3.98 (s, 6H), 2.91-2.72 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 193.6, 151.8, 149.4, 149.1, 135.5, 133.7, 127.6, 119.0, 118.4, 116.1, 111.4, 109.6, 58.3, 56.0, 46.7. **FT-IR (thin film)** 3338, 2895, 1658, 1622, 1518, 1268, 1122, 746 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 23.4 min, t_{minor} = 13.0 min). $[\alpha]_D^{25}$ = -29.8 (c 0.3, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{17}H_{17}NO_3$ [M+H]$^+$ 284.1281, found 284.1279.



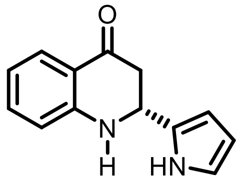
3t

(R)-2-(3,4,5-trimethoxyphenyl)-2,3-dihydroquinolin-4(1H)-one (3t): Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; brown solid; 61% yield (38.5 mg); m.p. 131-133 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 9.6 Hz, 1H), 7.36-7.33 (m, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.67 (s, 2H), 4.67 (dd, *J* = 3.8, 14.0 Hz, 1H), 4.54 (br s, 1H), 3.87 (s, 6H), 3.85 (s, 3H), 2.90-2.74 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 193.6, 153.6, 151.8, 137.9, 137.0, 135.6, 127.7, 124.9, 119.1, 118.6, 116.1, 103.6, 60.9, 59.0, 56.3, 46.8. **FT-IR (thin film)** 3318, 2930, 1643, 1609, 1510, 1259, 1111, 743 cm^{-1}. **HPLC Analysis**: 89:11 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 28.3 min, t_{minor} = 13.2 min). $[\alpha]_D^{25}$ = +13.5 (c 0.3, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{18}H_{19}NO_4$ [M+H]$^+$ 314.1387, found 314.1373.



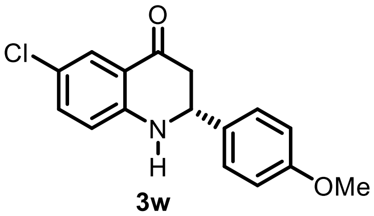
3u

(R)-2-(furan-2-yl)-2,3-dihydroquinolin-4(1H)-one (3u): Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; brown sticky solid; 23% yield; (9.8 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.39 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.33 (s, 1H), 6.26 (s, 1H), 4.83 (dd, *J* = 4.8, 9.6 Hz, 1H), 4.68 (br s, 1H), 3.03-2.94 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 192.8, 153.5, 150.6, 142.6, 135.6, 127.6, 118.8, 116.2, 115.9, 110.5, 107.0, 51.0, 42.1. **FT-IR (thin film)** 3316, 2915, 1651, 1482, 1330, 1135, 1006, 747 cm^{-1}. **HPLC Analysis**: 82:18 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 ^{o}C, λ = 365 nm (t_{major} = 30.6 min, t_{minor} = 28.7 min). $[\alpha]_D^{25}$ = -10.6 (c 0.3, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{13}H_{11}NO_2$ $[M+H]^+$ 214.0863, found 214.0866.



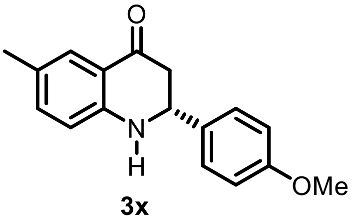
3v

(R)-2-(1H-pyrrol-2-yl)-2,3-dihydroquinolin-4(1H)-one (3v): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; brown sticky solid; 28% yield (12 mg). **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 6.8 Hz, 1H), 6.80 (t, *J* = 6.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.19-6.18 (m, 2H), 4.82 (dd, *J* = 4.8, 12.2 Hz, 1H), 4.55 (br s, 1H), 2.93-2.80 (m, 2H). **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 193.5, 151.4, 135.7, 130.9, 127.7, 119.3, 118.9, 118.4, 116.2, 108.7, 106.8, 52.0, 45.5. **FT-IR (thin film)** 3323, 2916, 1653, 1475, 1333, 1140, 1115, 1022, 769 cm^{-1}. **HPLC Analysis**: 86.5:13.5 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 ^{o}C, λ = 365 nm (t_{major} = 7.3 min, t_{minor} = 6.5 min). $[\alpha]_D^{25}$ = -12.1 (c 0.6, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{13}H_{12}N_2O_2$ $[M+H]^+$ 213.1022, found 213.1032.



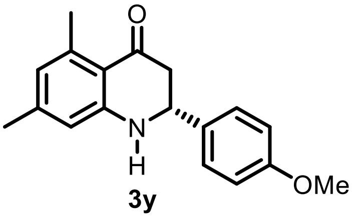
3w

***(R)*-6-chloro-2-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (3w)**: Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; yellow solid; 43% yield; (24.7 mg); m.p. 128-130 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.82 (d, *J* = 2.4 Hz, 1H), 7.37-7.35 (m, 2H), 7.27-7.25 (m, 1H), 6.92 (q, *J* = 3.0 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 1H), 4.68 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.48 (br s, 1H), 3.82 (s, 3H), 2.85 (dd, *J* = 13.8, 16.5 Hz, 1H), 2.74 (dd, *J* = 3.6, 16.5 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 192.5, 159.9, 150.1, 135.4, 132.7, 127.9, 127.0, 123.8, 119.8, 117.6, 114.5, 57.9, 55.5, 46.2. **FT-IR (thin film)** 3435, 3329, 2930, 1650, 1612, 1487, 1400, 1203, 860, 757 cm^{-1}. **HPLC Analysis**: 92:8 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 80:20), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 25.4 min, t_{minor} = 14.4 min). $[\alpha]_D^{25}$ = -28.7 (c 0.6, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{13}H_{12}ClNO_2$ [M+H]$^+$ 288.0786, found 288.0871.



3x

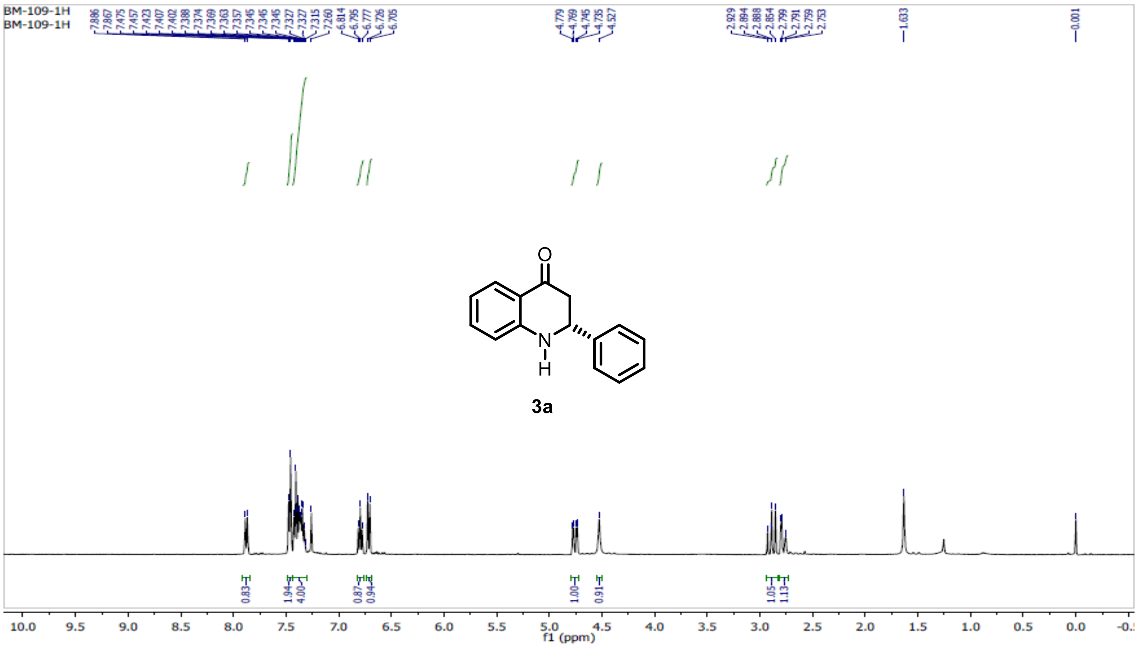
***(R)*-2-(4-methoxyphenyl)-6-methyl-2,3-dihydroquinolin-4(1*H*)-one (3x)**: Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; light yellow solid; 71% yield (38 mg) m.p. 135-137 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.67 (d, *J* = 1.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16 (q, *J* = 1.8 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.66 (dd, *J* = 3.6, 13.8 Hz, 1H), 4.34 (br s, 1H), 3.82 (s, 3H), 2.84 (dd, *J* = 13.8, 16.5 Hz, 1H), 2.72 (dd, *J* = 3.6, 16.2 Hz, 1H), 2.26 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 193.9, 159.6, 149.9, 136.7, 134.4, 127.9, 127.7, 127.1, 118.9, 116.1, 114.3, 58.2, 55.4, 46.7, 20.4. **FT-IR (thin film)** 3338, 3069, 2999, 1652, 1610, 1468, 1261, 1100, 758 cm^{-1}. **HPLC Analysis**: 91:9 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 12.7 min, t_{minor} = 7.4 min). $[\alpha]_D^{25}$ = -33.0 (c 0.5, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{17}H_{17}NO_2$ [M+H]$^+$ 268.1332, found 268.1332.

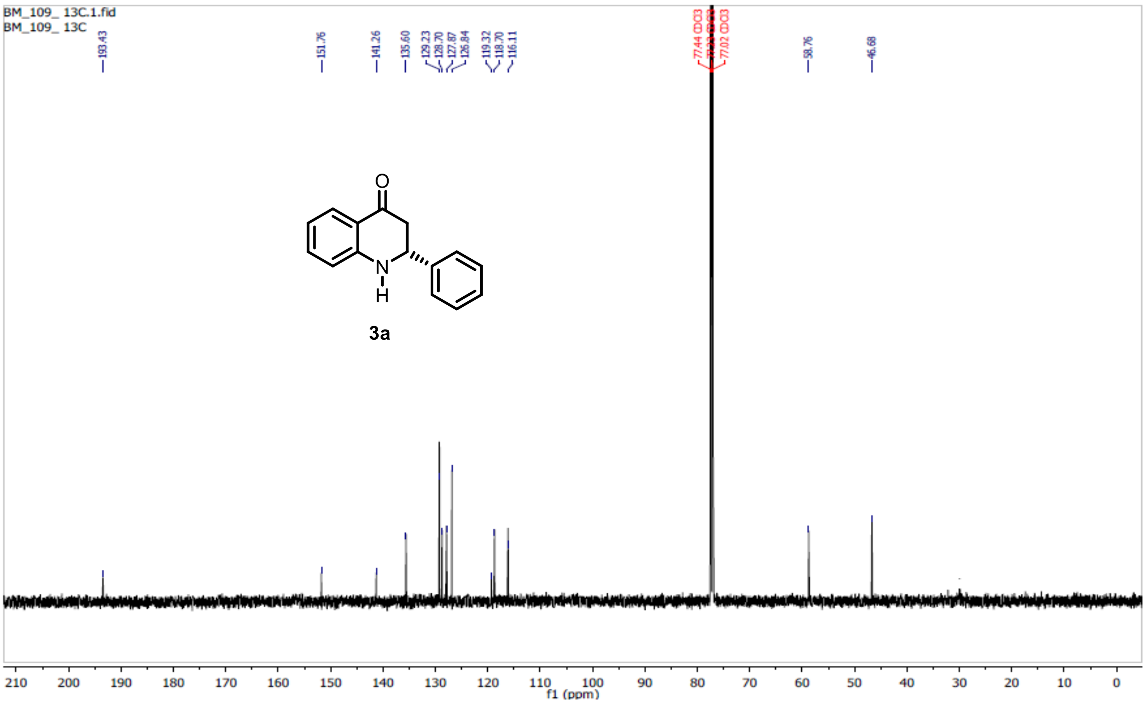


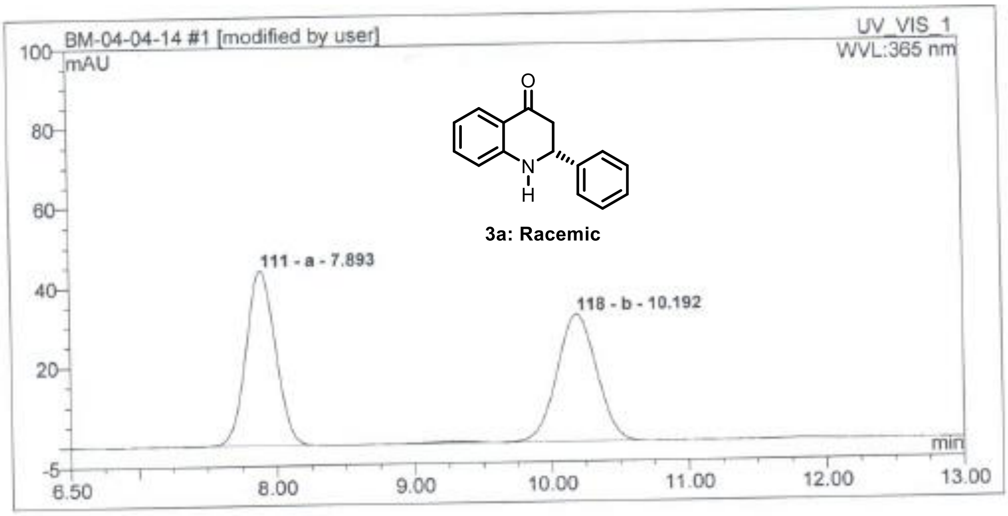
3y

(R)-2-(4-methoxyphenyl)-6,8-dimethyl-2,3-dihydroquinolin-4(1H)-one (3y): Purified by silica-gel column chromatography using 25% ethyl acetate/hexane; light yellow solid; 33% yield; (18.5 mg); m.p. 103-105 °C. **^{1}H NMR** (**600 MHz, CDCl$_3$**) δ 7.59 (s, 1H), 7.72-7.39 (m, 2H), 7.08 (s, 1H), 6.95-6.92 (m, 2H), 4.66 (dd, *J* = 3.8, 14.4 Hz, 1H), 4.22 (br s, 1H), 3.76 (s, 3H), 2.86 (dd, *J* = 14.4, 15.9 Hz, 1H), 2.72 (dd, *J* = 3.6, 16.2 Hz, 1H), 2.13 (s, 3H), 2.24 (s, 3H). **^{13}C-NMR** (**100 MHz, CDCl$_3$**): δ 194.1, 159.8, 148.2, 137.5, 136.6, 128.0, 127.1, 125.1, 123.1, 118.8, 114.4, 58.1, 55.5, 46.5, 20.4, 17.1. **FT-IR (thin film)** 3340, 2968, 1655, 1603, 1463, 1264, 1099, 750 cm^{-1}. **HPLC Analysis**: 84.5:15.5 er; Determined using a Daicel Chiralpak OD-H Column (hexane/2-propanol = 70:30), flow rate 1.0 mL/min, 25 °C, λ = 365 nm (t_{major} = 9.5 min, t_{minor} = 6.5 min). $[\alpha]_D^{25}$ = -20.2 (c 0.4, CHCl$_3$). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{18}H_{19}NO_2$ $[M+H]^+$ 282.1489, found 282.1487.

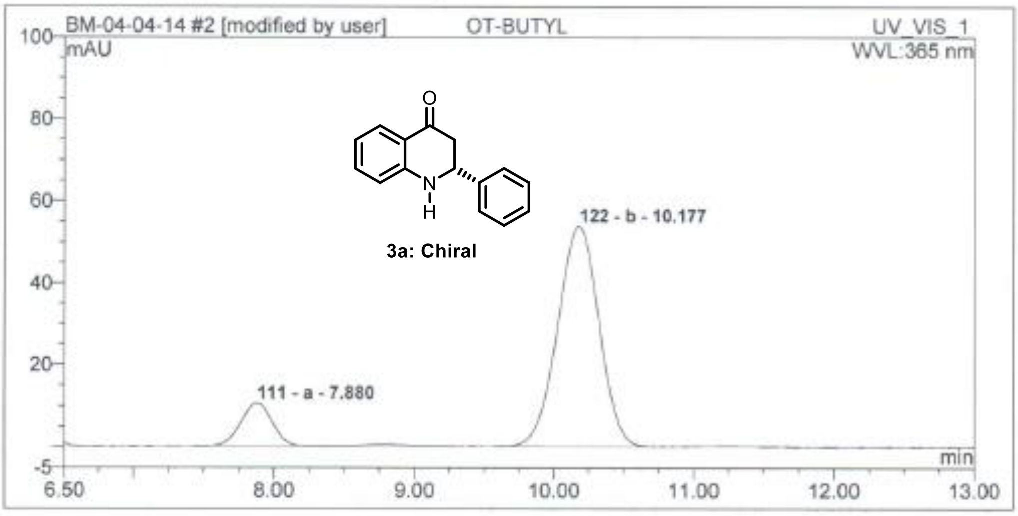
5.8 Selected NMR and HPLC spectra of products



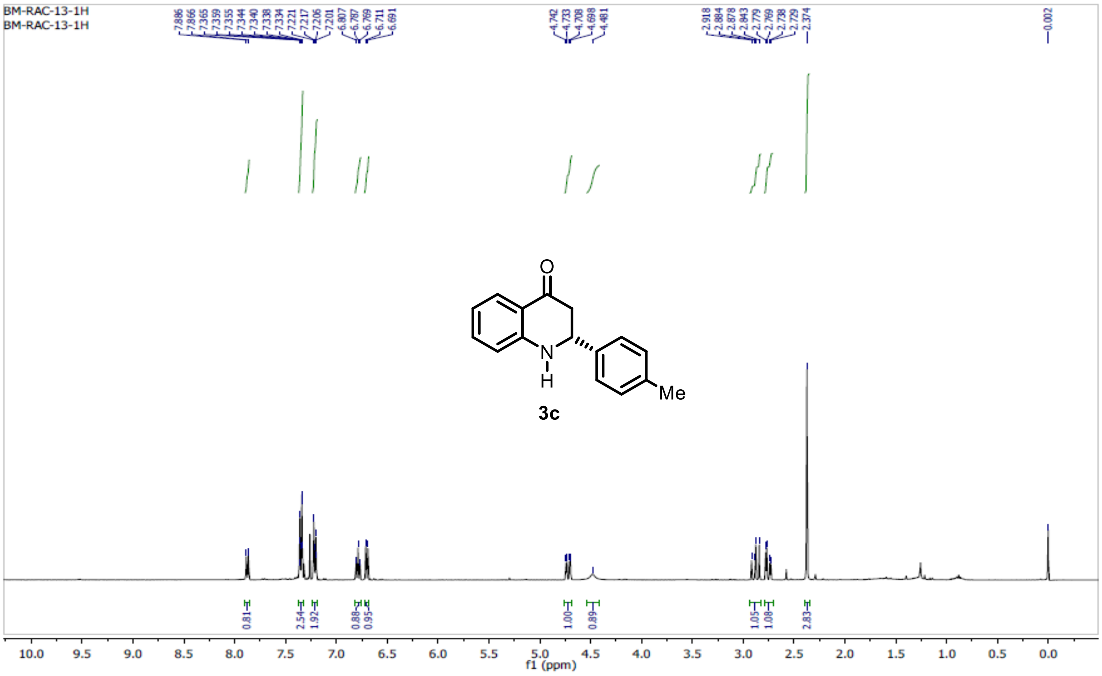


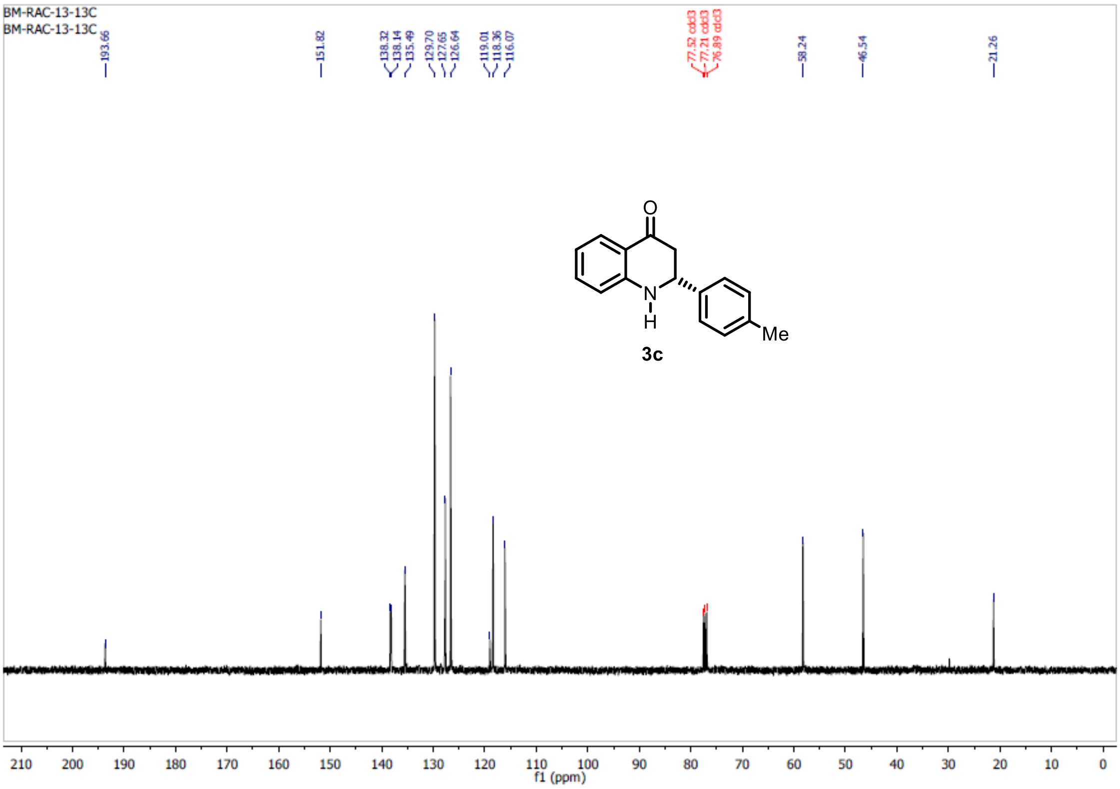


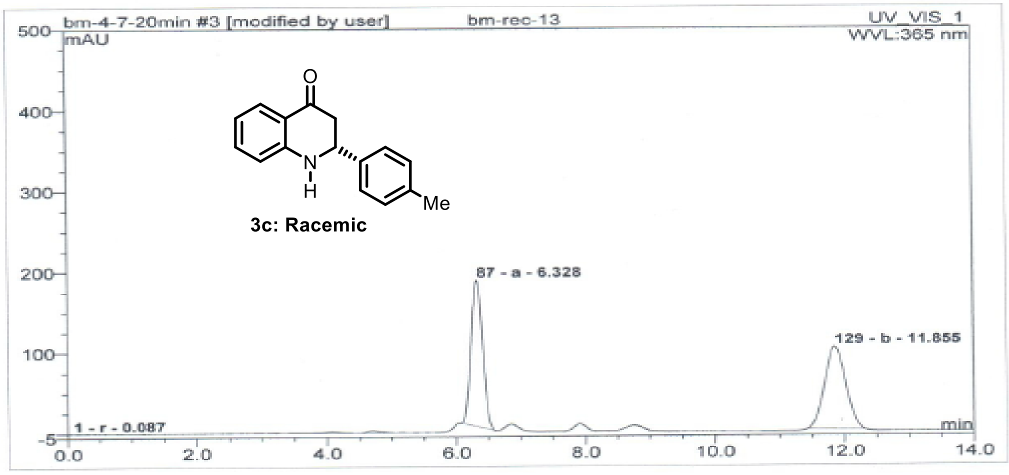
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
111	a	7.893333333	10.75095	50.30924259	43.82358	n.a.
118	b	10.19	10.619	49.69	31.739	n.a.



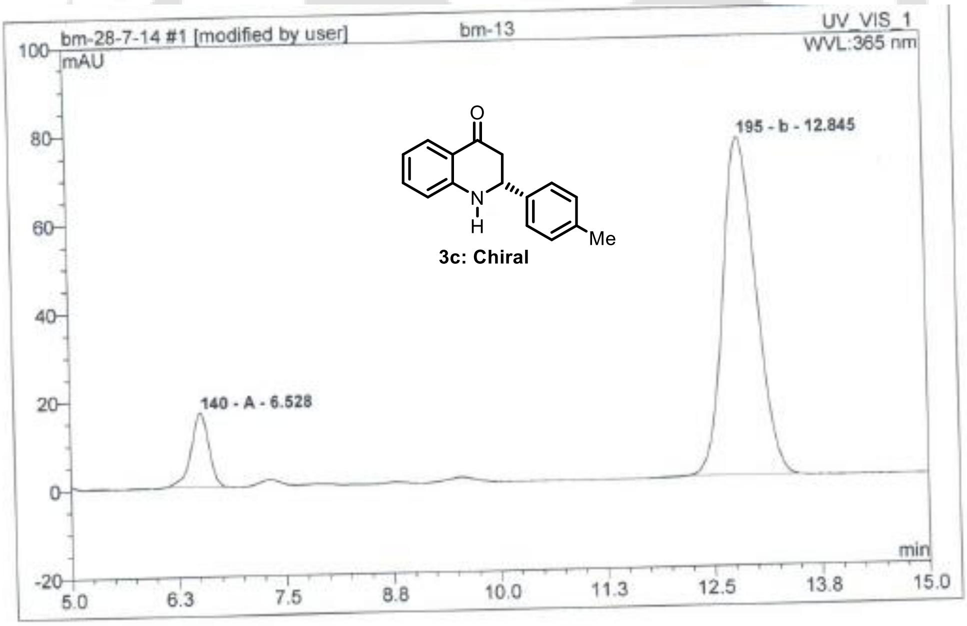
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
111	a	7.88	2.667351	12.61789534	10.44292	n.a.
122	b	10.18	18.472	87.38	53.789	n.a.


BM-RAC-13-1H
BM-RAC-13-1H
7.886
7.866
7.365
7.359
7.355
7.344
7.340
7.338
7.334
7.221
7.217
7.206
7.201
6.807
6.787
6.769
6.711
6.691
4.742
4.733
4.708
4.698
4.481
2.918
2.884
2.878
2.843
2.779
2.769
2.738
2.729
2.374
0.002
O
N
H
Me
3c
0.81
2.54
1.92
0.88
0.95
1.00
0.89
1.05
1.08
2.83
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


BM-RAC-13-13C
BM-RAC-13-13C
193.66
151.82
138.32
138.14
135.49
129.70
127.65
126.64
119.01
118.36
116.07
77.52 cdcl3
77.21 cdcl3
76.89 cdcl3
58.24
46.54
21.26
O
N
H
Me
3c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ic %	Height mAU	Amount
	a	6.328333333	37.4135	49.05074	181.3718	
	b	11.855	38.86158	50.94924	101.9761	



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(id %	Height mAU	Amount
	A	6.528333333	3.96432	10.44635	16.67707	
	b	12.845	33.98488	89.55333	76.40701	

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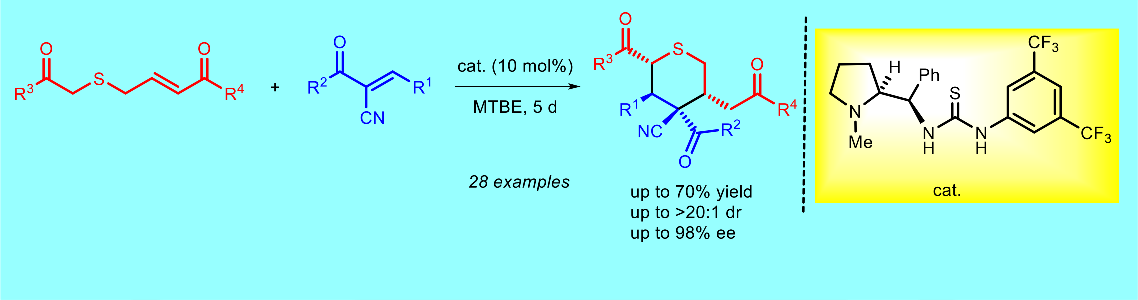
Chapter 6

Organocatalytic Asymmetric Synthesis of Pentasubstituted Tetrahydrothiopyrans Bearing a Quaternary Centre through a Double Michael Reaction



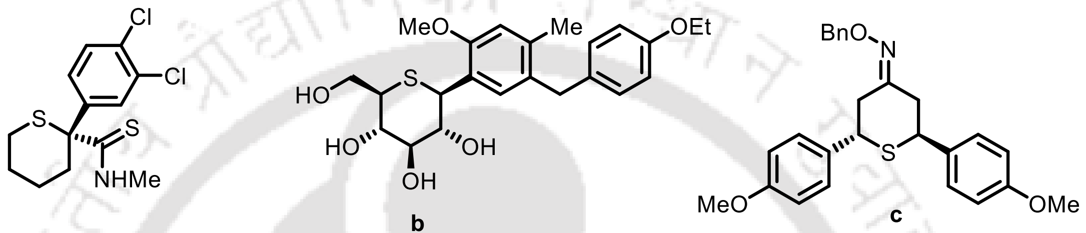
28 examples

up to 70% yield
up to >20:1 dr
up to 98% ee

Synlett **2018**, *29*, 576-580.

6.1 Introduction

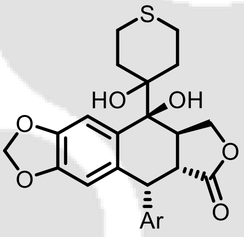
Tetrahydrothiopyrans, analogous of tetrahydropyrans has been less explored due to its lesser abundance in nature. Tetrahydrothiopyrans are important structural motifs abundant in a number of bioactive compounds and pharmaceuticals.[1] Representative activities include antihypersensitive (a),[2] antidiabetes (b),[3] antimicrobial (c)[4] and antimiotic (d)[5] properties (Figure 1).



a
antihypersensitive activity

b
antidiabetics
(SGLT2 inhibitor)

c
antimicrobial activity



d
antimitotic activity
(tubulin polymerization inhibitor)

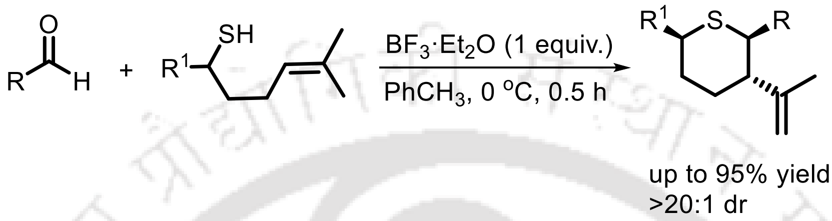
Figure 1. Biologically active derivatives.

In addition, tetrahydrothiopyrans can also be converted into a variety of useful structures.[6] Though a number of diastereoselective approaches are reported in the literature,[7] asymmetric reports are few[8,9] and mainly relied on the employment of chiral substrates.[8]

6.2 Known strategies for the synthesis of tetrahydrothiopyrans

6.2.1 Diastereoselective synthesis of tetrahydrothiopyrans

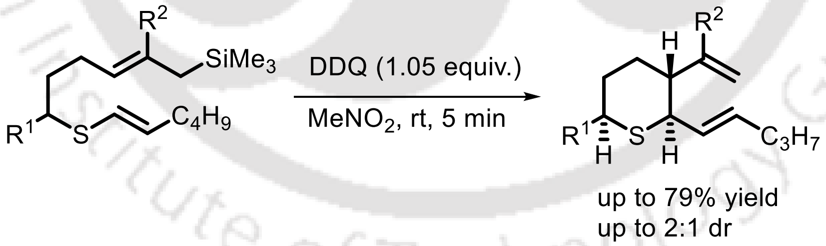
In 2011, Saikia co-workers reported boron trifluoride etherate mediated diastereoselective synthesis of substituted tetrahydrothiopyrans *via* (3,5)-thionium-ene cyclization reaction. Under the optimized reaction conditions, the desired products were obtained in high yields as well as with excellent diastereoselectivities (Scheme 1).[10]



Scheme 1. Diastereoselective synthesis of tetrahydrothiopyrans by Saikia et al.

6.2.2 Synthesis of tetrahydrothiopyrans by the oxidation of unsaturated sulfides with DDQ

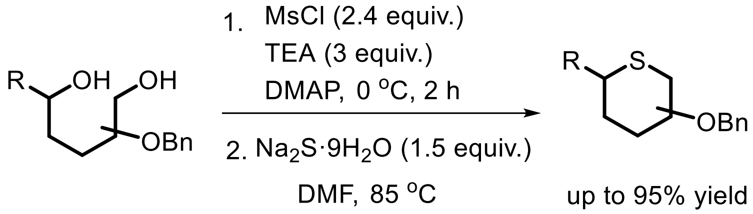
Floreancig and co-workers have reported 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) mediated oxidation of unsaturated sulfides for the preparation of tetrahydrothiopyrans *via* stabilized thiocarbenium ions intermediate. The desired tetrahydrothiopyrans were formed in high yields and with low diasteroselectivities (Scheme 2).[11]



Scheme 2. Oxidation of unsaturated sulfides with DDQ by Floreancig et al.

6.2.3 Convenient synthesis of polyoxygenated tetrahydrothiopyrans

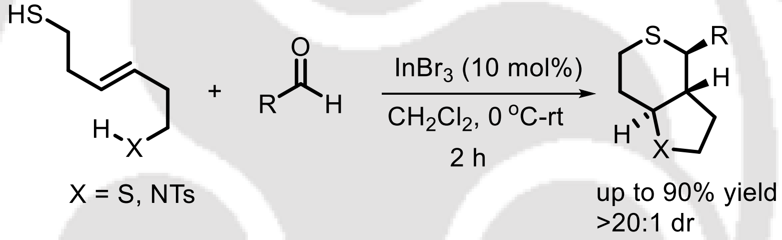
A convenient synthesis of polyoxygenated tetrahydrothiopyrans from alditols was reported by Ye and co-workers in 2012. Under the optimized reaction conditions, the desired tetrahydrothiopyrans were formed in good yields (Scheme 3).[12]



Scheme 3. Convenient synthesis of polyoxygenated tetrahydrothiopyrans by Ye et al.

6.2.4 Stereoselective synthesis of dithia- and azathia-bicycles

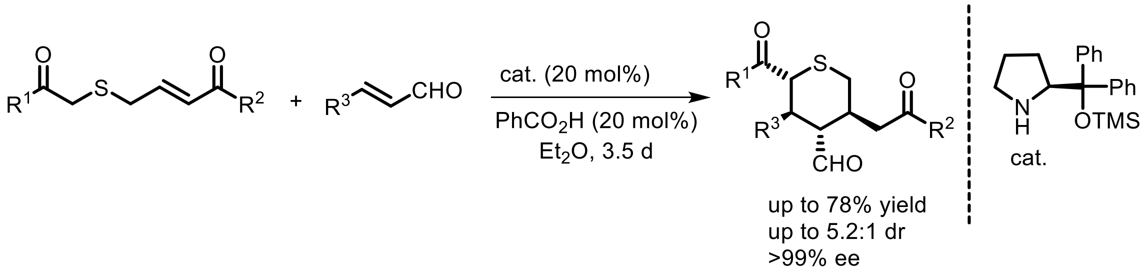
In 2013, Sridhar and co-workers have developed a novel thia-Prins bicyclization reaction of hex-3-ene-1,6-dithiol with various aldehydes, catalyzed by 10 mol% of $InBr_3$. This protocol provided a concise access to dithia- and azathia-bicycles in high yields as well as with excellent diasteroselectivities (Scheme 4).[13]



Scheme 4. Stereoselective synthesis of dithia- and azathia-bicycles by Sridhar et al.

6.2.5 Organocatalytic enantioselective synthesis of chiral tetrahydrothiopyrans

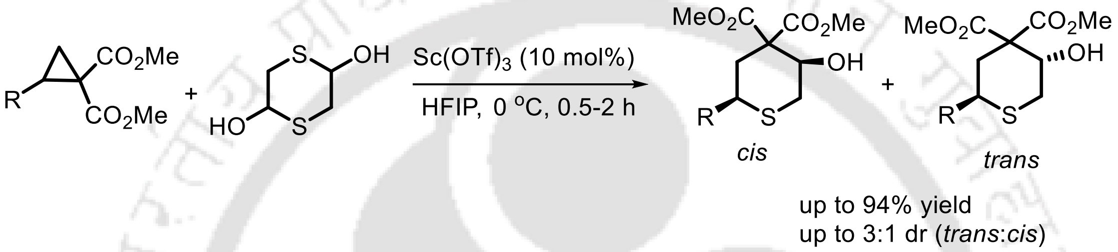
In 2014, Wang and co-workers reported an organocatalytic enantioselective Michael-Michael cascade reaction of ketothioether enones and *trans*-cinnamaldehydes in the presence of commercially available diphenylprolinol silyl ether catalyst. The aforementioned protocol provided the desired products in good yields with moderate diasteroselectivities and with excellent enantioselectivities (Scheme 5).[14]



Scheme 5. Enantioselective synthesis of chiral tetrahydrothiopyrans by Wang et al.

6.2.6 Synthesis of polyfunctionalized tetrahydrothiopyrans

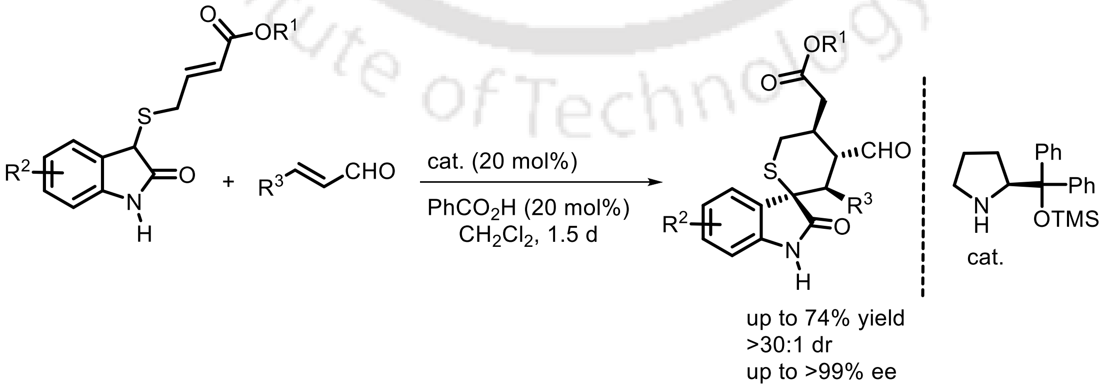
A catalytic [3+3] cycloaddition reaction between cyclopropane 1,1-diesters and in situ generated mercaptoacetaldehyde for the construction of polyfunctionalized tetrahydrothiopyran derivatives was developed by Zhang et al. in 2015. By using $Sc(OTf)_3$ as Lewis acid catalyst, this methodology provided the desired products in high yields with excellent diasteroselectivities (Scheme 6).[15]



Scheme 6. Synthesis of polyfunctionalized tetrahydrothiopyrans by Zhang et al.

6.2.7 Asymmetric synthesis of oxindole-spiro-tetrahydrothiopyrans

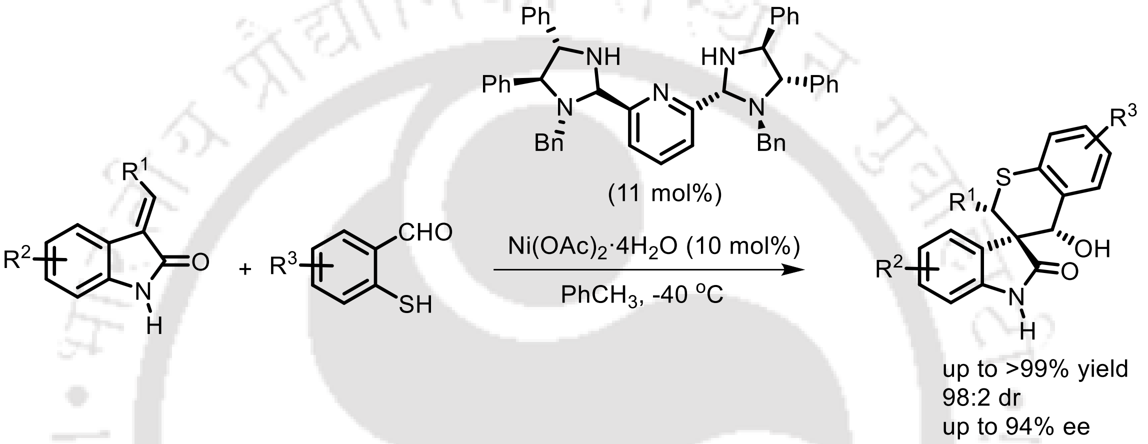
Enantioselective Michael-Michael cascade reaction for the synthesis of highly functionalized chiral spirotetrahydrothiopyrans using commercially available diphenylprolinol silyl ether catalyst was developed by Sheng and co-workers in 2016. Under the optimized reaction conditions, the desired spirotetrahydrothiopyrans were formed in good yields as well as with outstanding diastereo- and enatioselectivities (Scheme 7).[16]



Scheme 7. Asymmetric synthesis of oxindole-spiro-tetrahydrothiopyrans by Sheng et al.

6.2.8 Asymmetric Michael/aldol reaction for the synthesis of thiochromanyl-spirooxindoles

In the same year, Arai and co-workers were reported PyBidine-Ni(OAc)$_2$ catalyzed Michael/aldol reaction for the direct construction of thiochromanyl-spirooxindoles. The aforementioned protocol provided the desired products in excellent yields high diasteroselectivities and moderate to excellent enatioselectivities (Scheme 8).[17]

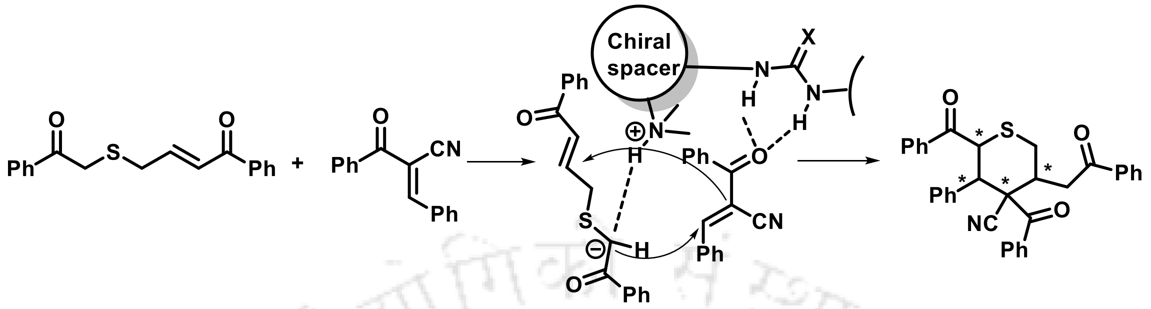


Scheme 8. Asymmetric Michael/aldol reaction synthesis of thiochromanyl-spirooxindoles by Arai et al.

6.3 Concept

However, up to now, only α,β-unsaturated aldehydes and thiosalicylaldehydes have been successfully used for the synthesis of chiral tetrahydrothiopyrans using secondary amine or chiral metal catalysis. Thus it will be really attractive to employ other Michael acceptors for the synthesis of highly substituted tetrahydrothiopyrans.

Our plan was to accomplish a catalytic asymmetric cascade Michael addition/cyclization reaction of bifunctional ketothioether enones with *trans*-α-cyano-α,β-unsaturated ketones. Bifunctional tertiary amino-(thio)urea derivatives were selected as the potential catalyst candidates. We envisioned that Brønsted acidic thio(urea) moiety would enhance the electrophilicity of *trans*-α-cyano-α,β-unsaturated ketone through dual H-bonding by lowering the lowest unoccupied molecular orbital (LUMO), additionally Brønsted basic tertiary amine group would enhance the nucleophilicity of bifunctional ketothioether enone through general base catalysis by raising its highest occupied molecular orbital (HOMO) (Scheme 9).



Scheme 9. Plausible role of the bifunctional thio(urea) catalyst in the Michael addition-cyclization reaction.

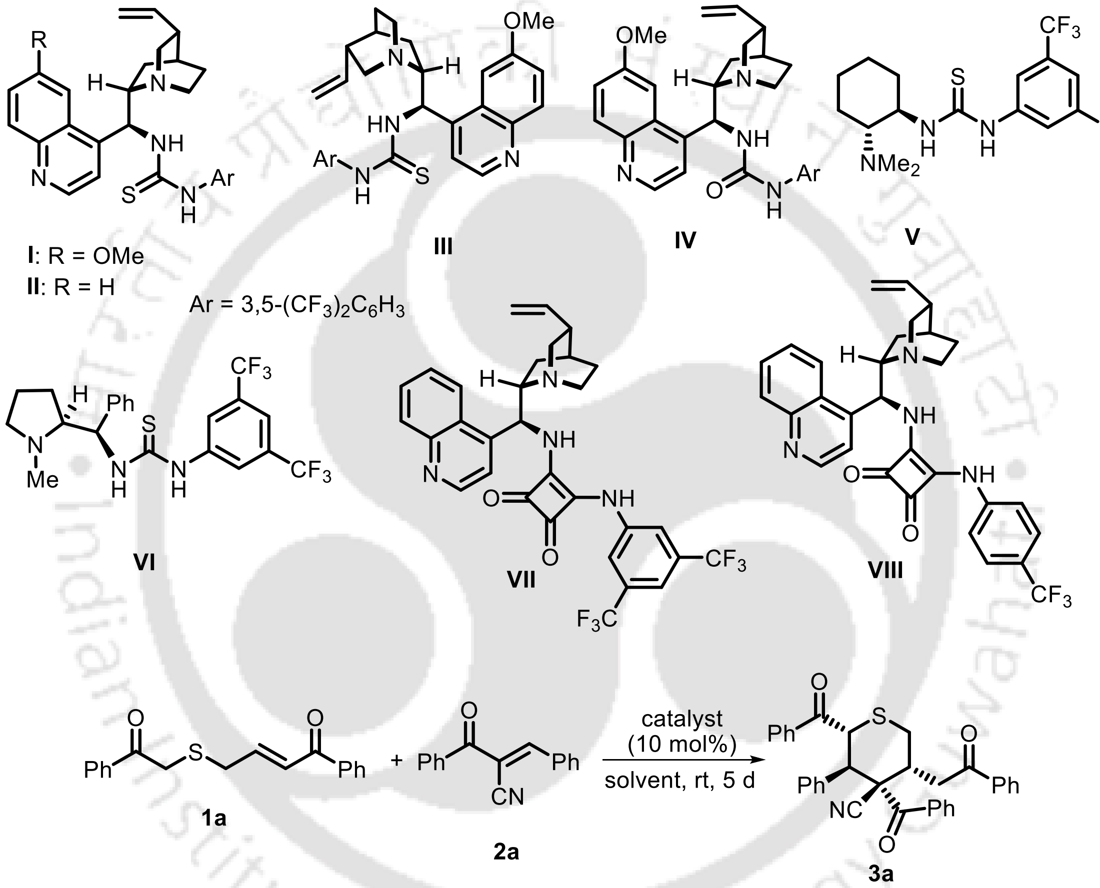
6.4 Results and discussion

6.4.1 Optimization of catalyst and reaction conditions

At the outset of our investigation, bifunctional ketothioether enone **1a** and *trans-α*-cyano-*α,β*-unsaturated ketone **2a**[18] were reacted with a range of bifunctional catalysts in toluene at room temperature (Table 1). Pleasingly quinine derived bifunctional thiourea catalyst **I** provided the desired tetrahydrothiopyran product **3a** in 5:1 diastereomeric ratio with moderate yield and enantioselectivity (Table 1, entry 1). Slightly higher enantioselectivity was achieved with cinchonidine derived thiourea **II** (Table 1, entry 2). The outcome was not much different with quinidine derive thiourea **III** (Table 1, entry 3) but less enantioselectivity was observed with quinine derived urea catalyst **IV** (Table 1, entry 4). Takemoto catalyst (**V**) also failed to enhance the enantioselectivity and the outcome was similar to catalyst **IV** (Table 1, entry 5). Then we screened proline derived bifunctional catalyst **VI**[19] in our reaction and gratifyingly the enantioselectivity increased to 84% ee (Table 1, entry 6). Then, the investigation was switched to screen different bifunctional squaramide catalysts (**VII**, **VIII**) but very less (<5%) conversion was observed (Table 1, entries 7 and 8). With the best catalyst (**VI**) in hand, we next turned our attention on solvent screening. The reaction was quite efficient in trifluorotoluene providing the product in 88% ee, 65% yield and 5.5:1 dr (Table 1, entry 9). Smooth conversions were also achieved in ether solvents. Et_2O afforded the product **3a** with 90%

ee, 60% yield and 5.5:1 dr and MTBE provided the product with slightly higher yield as well as diastereoselectivity (70% yield, 6:1 dr) maintaining the same ee value (Table 1, entries 10 and 11). Halogenated solvents such as CH_2Cl_2 and $CHCl_3$ were screened though very less conversions were detected.

Table 1. **Catalyst screening and solvent optimization**



entry[a]	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	$PhCH_3$	65	5:1	50
2	**II**	$PhCH_3$	58	5:1	56
3	**III**	$PhCH_3$	63	5:1	-60
4	**IV**	$PhCH_3$	50	5:1	24

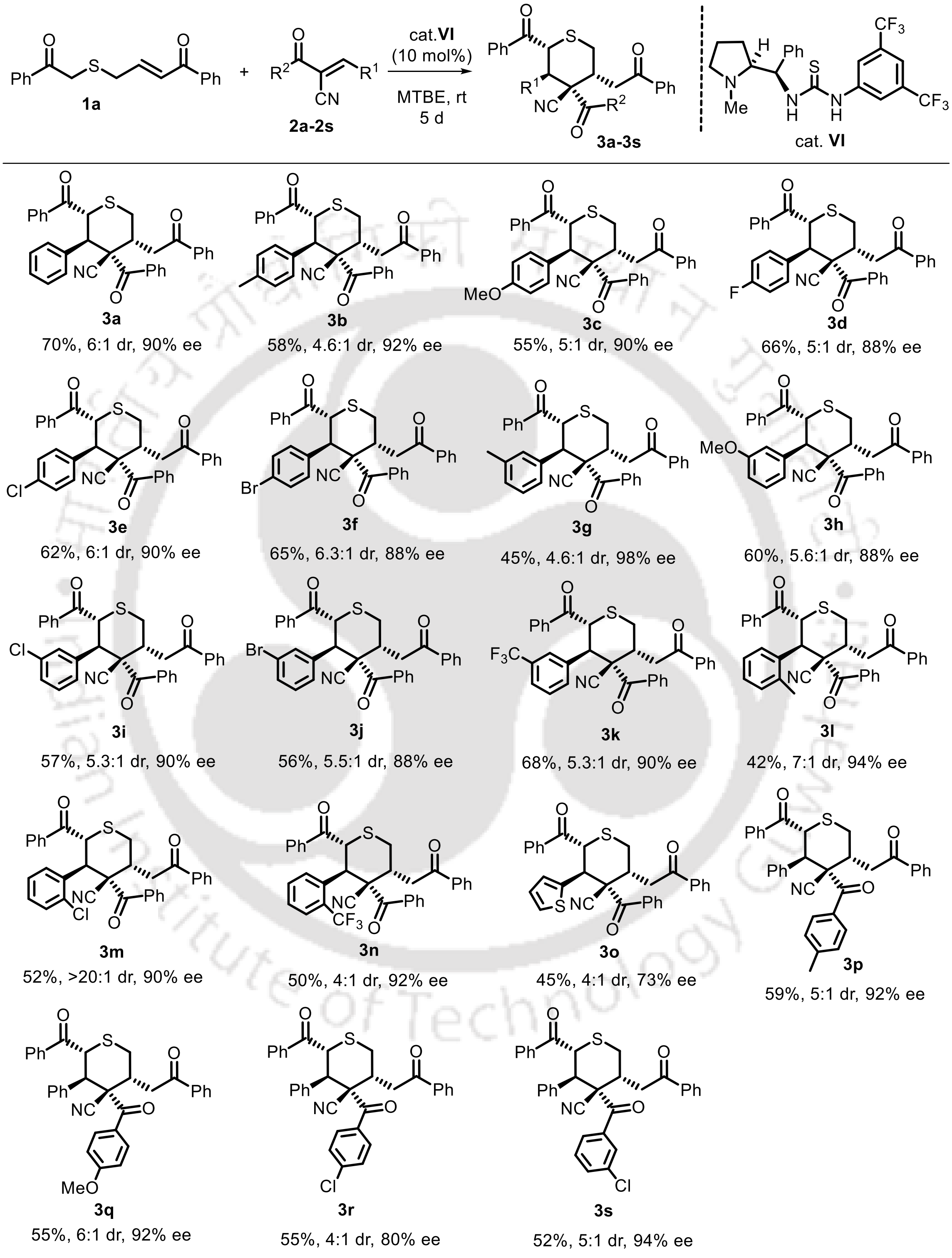
5	**V**	$PhCH_3$	60	4.5:1	27
6	**VI**	$PhCH_3$	65	5:1	84
7	**VII**	$PhCH_3$	<5	-	-
8	**VIII**	$PhCH_3$	<5	-	-
9	**VI**	$PhCF_3$	65	5.5:1	88
10	**VI**	Et_2O	60	5.5:1	90
11	**VI**	**MTBE**	**70**	**6:1**	**90**
12	**VI**	CH_2Cl_2	-	-	-
13	**VI**	$CHCl_3$	-	-	-

[a]Reaction condition: 0.05 mmol of **1a** and 0.06 mmol of **2a** in 0.2 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by HPLC.

6.4.2 Substrate scope

After identifying the best catalyst and the optimized reaction conditions, the scope and generality of the reaction was investigated. Initially the *β*-aryl group of *α*-cyano-*α*,*β*-unsaturated ketones was varied and the results are shown in Scheme 10. Pleasingly, a range of electron withdrawing and electron donating groups can be tolerated in the *ortho*-,*meta*- and *para*-position of the aryl group. At the beginning, different *para*- substitutions were tested and the products **3a**-**3f** were isolated in good yields and high to excellent enantioselectivities. For example, unsaturated ketones **2b** having 4-methyl group delivered product **3b** with 58% yield, 4.6:1 dr and 92% ee (Scheme 10). 4-methoxy unsaturated ketones **2c** provided the product **3c** with 55% yield and similar enantio- and diasteroselectivities. Then, *α*-cyano-*α*,*β*-unsaturated ketones **2d**-**2f** having 4-halosubstituted aryl groups were subjected to the reaction conditions. To our delight, the desired products **3d**-**3f** were isolated in acceptable yields, moderate diasteroselectivities and high enatioselectivities were detected (Scheme 10). Then different *meta*-substituted

Scheme 10. **Scope of *trans-α*-cyano-*α,β*-unsaturated ketones**[a]



3a 70%, 6:1 dr, 90% ee

3b 58%, 4.6:1 dr, 92% ee

3c 55%, 5:1 dr, 90% ee

3d 66%, 5:1 dr, 88% ee

3e 62%, 6:1 dr, 90% ee

3f 65%, 6.3:1 dr, 88% ee

3g 45%, 4.6:1 dr, 98% ee

3h 60%, 5.6:1 dr, 88% ee

3i 57%, 5.3:1 dr, 90% ee

3j 56%, 5.5:1 dr, 88% ee

3k 68%, 5.3:1 dr, 90% ee

3l 42%, 7:1 dr, 94% ee

3m 52%, >20:1 dr, 90% ee

3n 50%, 4:1 dr, 92% ee

3o 45%, 4:1 dr, 73% ee

3p 59%, 5:1 dr, 92% ee

3q 55%, 6:1 dr, 92% ee

3r 55%, 4:1 dr, 80% ee

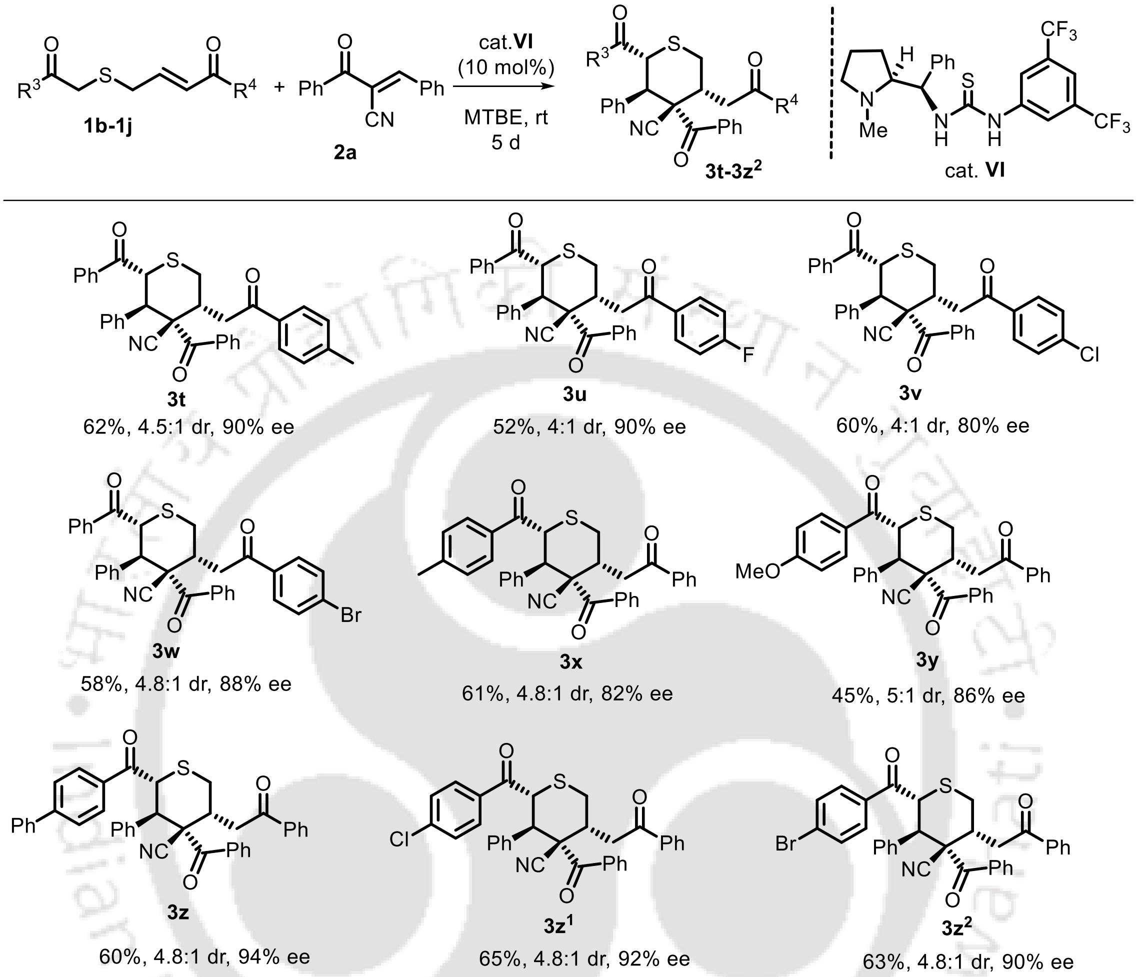
3s 52%, 5:1 dr, 94% ee

[a]Reaction condition: 0.1 mmol of **1a** with 0.12 mmol of **2** in 0.4 mL MTBE. Yields correspond to isolated yields after silica gel column chromatography. Diastereoselectivity was determined by ^{1}H NMR. Enantioselectivity was determined by chiral HPLC of the major diastereomer.

α-cyano-α,β-unsaturated ketones (**2g-2k**) were screend under the reaction conditions. Interestingly, smooth conversions were observed for products **3g**- **3k** with acceptable yields, high enatioselectivities as well as moderate diasteroselectivities. Gratifyingly, the highest diastereoselctivity was obtained for product **3m** (Scheme 10). Heteroaromatic enone **2o** also participated in the reaction, however the desired product **3o** was isolated with moderate enantioselectivity (Scheme 10). Then we turned our attention to check different substitutions on the aryl group of the carbonyl functionality in α-cyano-α,β-unsaturated ketone **2**. Thus enones **2p**-**2s** having variations in the *para*- and *meta*-substititions were prepared and engaged in the reaction. Here also, good to excellent results were obtained and in particular, product **3q** was attained in 6:1 dr and with 92% ee (Scheme 10).

The generality of the reaction was further recognized by employing different thioethers **1** in the reaction (Scheme 11). Initially, the aryl group of the enone part in thioether **1** was varied. Thus thioethers **1b**-**1e** having different *para*-substitutions were prepared and subjected in the reaction. To our delight, the reactions progressed well providing the products **3t**-**3w** in good diastereoselectivities and with high to excellent enantioselectivities (Scheme 11). Noteworthy, slightly drop in enantioselectivity was observed for 4-chloro substituted product **3v** compared to other 4-halosubstituted products (Scheme 11). Similarly, different *para*-substitutions on the phenyl group of ketone moiety in thioether **1** were incorporated and the outcome was excellent for products **3x**-**3z^2** irrespective of the electronic nature of the aryl group. For example, product **3z** having a biphenyl moiety was isolated in 4.8:1 diastereomeric ratio and the enantiomeric excess of the major diastereomer was 94%. It was found that the enantioselectivity was slightly lower for *para*-electron-donating group compared to *para*-electron-withdrawing group present in the thioether **1** (Scheme 11).

Scheme 11. **Scope of ketothioether enones**[a]



3t
62%, 4.5:1 dr, 90% ee

3u
52%, 4:1 dr, 90% ee

3v
60%, 4:1 dr, 80% ee

3w
58%, 4.8:1 dr, 88% ee

3x
61%, 4.8:1 dr, 82% ee

3y
45%, 5:1 dr, 86% ee

3z
60%, 4.8:1 dr, 94% ee

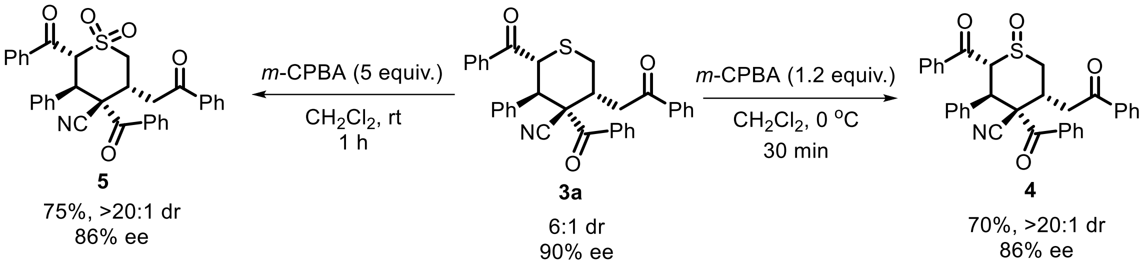
3z¹
65%, 4.8:1 dr, 92% ee

3z²
63%, 4.8:1 dr, 90% ee

[a]Reaction condition: 0.1 mmol of **1** with 0.12 mmol of **2a** in 0.4 mL MTBE. Yields correspond to isolated yields after silica gel column chromatography. Diastereoselectivity was determined by ^{1}H NMR. Enantioselectivity was determined by chiral HPLC of the major diastereomer.

6.4.3 Synthetic transformations of 3a

To demonstrate the synthetic utility of our method, few reactions were performed on **3a** (Scheme 12). Selective mono oxidation of **3a** in the presence of *m*-CPBA (1.2 equiv.) at 0 °C for 30 minutes produced sulfoxide **4** in 70% yield with 86% ee and in high dr >20:1. Similarly oxidation of **3a** in the presence of *m*-CPBA (5 equiv.) at room temperature delivered sulfone **5** in 75% yield with 86% ee, and here also high diastereoselectivity was detected (>20:1).



Scheme 12. Synthetic transformation of **3a**.

6.4.4 Determination of product stereochemistry

The relative structure of the product **3a** was determined by single crystal X-ray crystallography. The relative configurations of other products are thought to be similar by correlation.

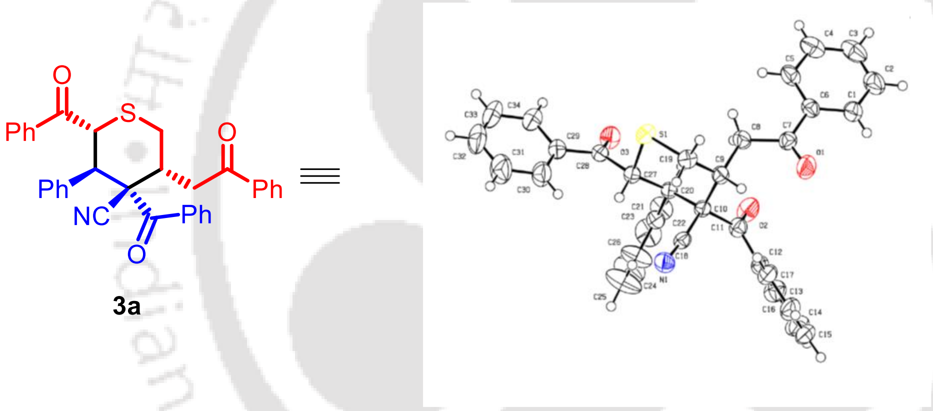


Figure 2. X-ray crystal structure of **3a**.

6.4.5 Proposed mechanism

A plausible mechanism for the reaction is shown in Figure 3. The *trans*-*α*-cyano-*α,β*-unsaturated ketone **2a** is activated by the thiourea moiety of catalyst **VI**. Simultaneously, **1a** is activated by the tertiary amine functionality of the catalyst, and consequently intermediate **6** is formed. The diastereoselective intramolecular Michael addition of **6** then delivers product **3a**.

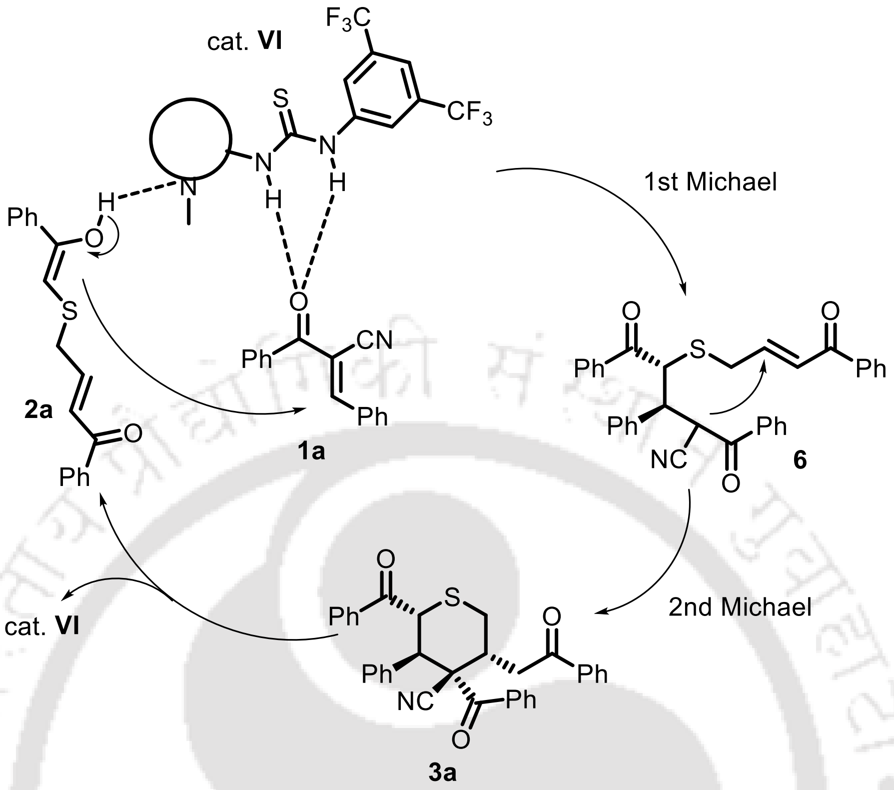


Figure 3. Proposed mechanism.

6.5 Conclusion

In summary, we have developed an efficient organocatalytic cascade double Michael reaction for the synthesis of pentasubstituted tetrahydrothiopyrans. This reaction furnished densely functionalized tetrahydrothiopyrans in acceptable yields and with moderate to good diastereomeric ratios as well as good to excellent enantioselectivities. Particularly, one all carbon quaternary centre is formed in this reaction which is a familiar synthetic challenge in organic chemistry. Given the high pharmaceutical importance of substituted tetrahydrothiopyrans our method might be applicable to prepare these compounds in a short way.

6.6 Experimental Section

6.6.1 General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz, 125 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants (*J*) were reported in Hertz (Hz). High-resolution mass spectra (HRMS) were recorded in Q-TOF electron spray ionization (ESI). Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns using a Daicel Chiralpak IA Column, Daicel Chiralpak IB Column, Daicel Chiralpak IC Column, Daicel Chiralpak ID Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Polarimetry: Rudolph research analytical autoplo II. IR spectra were recorded on an FT-IR Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. DCM was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

6.6.2 General procedure for the synthesis of ketothioether enone

Ketothioether enone were prepared according to reported procedures.[14]

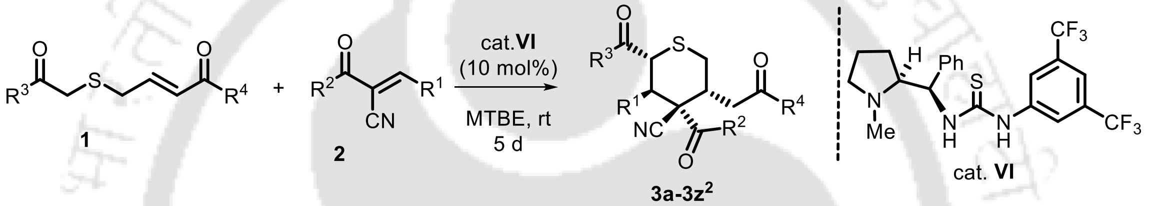
6.6.3 General procedure for the synthesis *trans-α*-cyano-*α,β*-unsaturated ketones

Trans-α-cyano-*α,β*-unsaturated ketones were prepared according to reported procedures.[20]

6.6.4 General procedure for the synthesis of catalyst

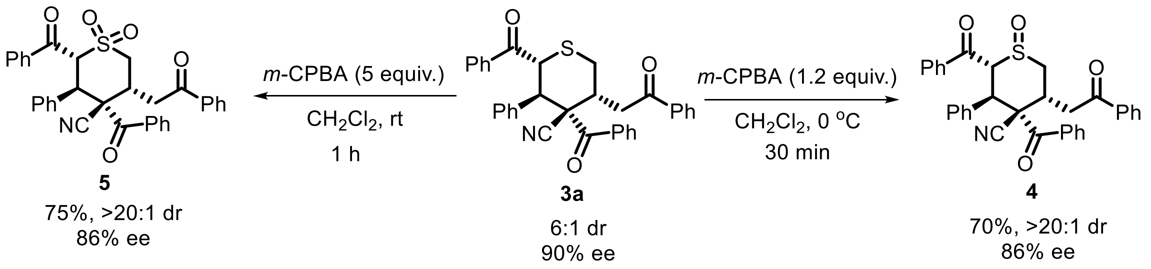
The catalysts (**I**, **II**, **III**, **IV** and **V**) were prepared according to reported procedures.[21] The catalysts (**VII** and **VIII**) were prepared according to reported procedures.[22]

6.6.5 General procedure for the synthesis of compound 3a-3z^2



In an oven dried round bottom flask, **1** (0.1 mmol), **2** (0.12 mmol) and 10 mol% of catalyst **VI** were taken. Then 0.4 mL of MTBE was added to the reaction mixture and was stirred at rt for 5 days. Completion of the reaction was checked by TLC. After the completion of the reaction, solvent was concentrated and the reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10-15 %) to afford desired products **3a-3z^2**.

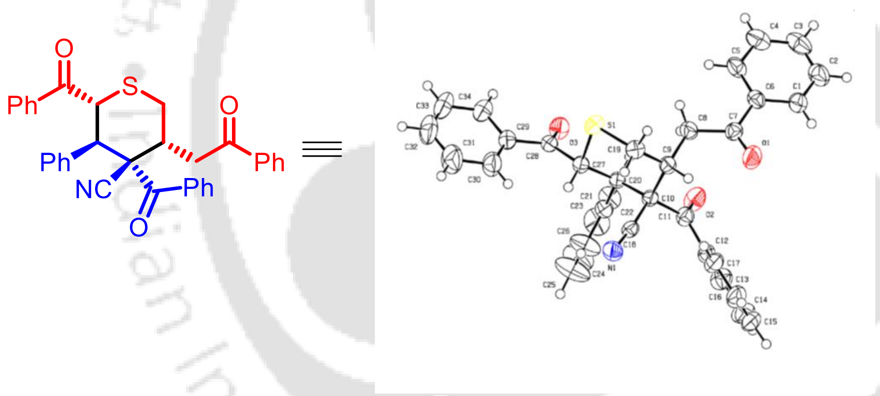
6.6.5 General procedure for the preparation of derivatives 4 and 5



Preparation of derivatives 4: In an oven dried round bottom flask, compound **3a** (37.0 mg, 0.07 mmol) in DCM (3 mL), *m*-CPBA (16 mg, 0.084 mmol) were added and the solution was stirred at 0 °C for 30 min. After reaction, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: EtOAc = 70:30) to give compound **4** as white solid 26.7 mg (70% yield).

Preparation of derivatives 5: In an oven dried round bottom flask, compound **3a** (37.0 mg, 0.07 mmol) in DCM (3 mL), *m*-CPBA (65 mg, 0.35 mmol) were added and the solution was stirred at rt for 1 h. After reaction, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane: EtOAc = 70:30) to give compound **5** as white solid 29.5 mg (yield: 75%).

6.6.7 Crystal structure of compound 3a[22]



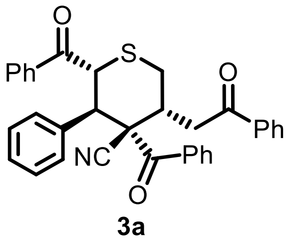
ORTEP crystal structure

Table 1. Crystal data and structure refinement for compound 3a

Parameters	3a
CCDC No.	1562510
Formula	$C_{34}H_{27}NO_3S$
Formula weight	529.17
Crystal habit, colour	block/colourless
Crystal size, mm^3	0.30×0.22×0.18

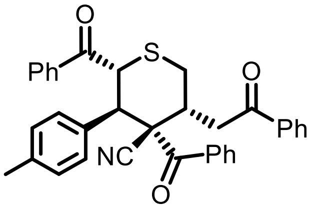
Temperature, T	293(2) K
Wavelength, λ (Å)	0.71073
Crystal system	*triclinic*
Space group	*'P -1'*
Unit cell dimensions	a = 11.1473(11) Å b = 11.5982(11) Å c = 11.8885(8) Å α = 73.859(7)°, β = 70.252(8)°, γ = 88.577(8)°
Volume, V (Å^3)	1385.6(2)
Z	2
Calculated density, Mg·m^{-3}	1.269
Absorption coefficient, μ (mm^{-1})	0.153
F(000)	556.0
T/K	293(2)
θ range for data collection	2.9951° to 28.8095°
Limiting indices	$-13 \leq h \leq 15$, $-15 \leq k \leq 15$, $-14 \leq l \leq 15$
Reflection collected/unique	4882/3806 [R(int) = 0.0325]
Completeness to θ	99.82% (θ = 26.32°)
Max. and min. transmission	0.973/ 0.964
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data/restraints/parameters	4882/0/352
Goodness–of–fit on F^2	1.060
Final R indices [$I > \sigma 2(I)$]	$R1 = 0.0502$, $wR2 = 0.1333$
R indices (all data)	$R1 = 0.0666$, $wR2 = 0.1333$
Ellipsoid contour % probability	40%

6.7 Characterization data of products



3a

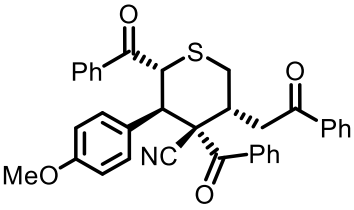
3a: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 70% yield (37.0 mg). The dr value was found to be 6:1 by ^{1}H NMR analysis. m.p. = 65-67 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 3H), 7.54 (s, 1H), 7.50-7.47 (m, 5H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.14-7.05 (m, 3H), 5.54 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 14.4 Hz, 1H), 3.93 (dd, *J* = 18.7, 7.4 Hz, 1H), 3.85-3.80 (m, 1H), 3.62 (dd, *J* = 18.6, 2.5 Hz, 1H), 2.90 (dd, *J* = 14.6, 3.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 194.9, 194.0, 137.0, 136.5, 136.4, 135.7, 134.0, 133.8, 133.2, 128.9, 128.8, 128.7, 128.4, 128.4, 128.1, 120.9, 58.4, 46.8, 44.4, 36.6, 36.4, 32.2. **FT-IR (thin film)** 3061, 2924, 1684, 1595, 1492, 1268, 694 cm^{-1}. **HPLC Analysis**: ee = 90%, Determined using a Daicel Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.6 min, t_{minor} = 16.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{31}N_2O_3S$ [M+NH$_4$]$^+$ 547.2055, found 547.2055.



3b

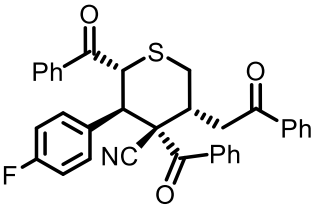
3b: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 58% yield (31.5 mg). The dr value was found to be 4.6:1 by ^{1}H NMR analysis. m.p. = 192-194 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 3H), 7.49-7.43 (m, 4H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 3H), 6.92 (d, *J* = 8.1 Hz, 2H), 5.52 (d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.12 (d, *J* = 14.5 Hz, 1H), 3.93 (dd, *J* = 18.6, 7.5 Hz, 1H), 3.85-3.78 (m, 1H), 3.60 (dd, *J* = 18.7, 3.4 Hz, 1H), 2.89 (dd, *J* = 14.8, 3.3 Hz, 1H), 2.15 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 194.9, 193.9, 137.6, 136.5, 136.4, 135.7, 134.0, 133.9, 133.8, 133.2, 129.1, 129.0, 128.9, 128.8, 128.8, 128.5, 128.4, 128.3, 128.2, 121.0, 58.5, 46.8, 43.9, 36.6, 36.4, 32.2, 21.1. **FT-IR (thin film)** 2927, 1690, 1593, 1496, 1361, 1258, 689 cm^{-1}. **HPLC Analysis**: ee = 92%, Chiralpak IA Column (hexane/2-propanol =

90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.2 min, t_{minor} = 16.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{30}NO_3S$ $[M+H]^+$ 544.1946, found 544.1945.



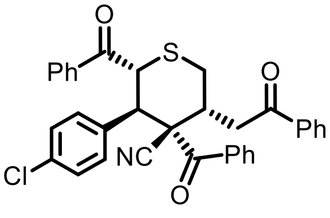
3c

3c: Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; white solid; 55% yield (30.8 mg). The dr value was found to be 5:1 by ^{1}H NMR analysis. m.p. = 145-147 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 3H), 7.43-7.39 (m, 4H), 7.35 (t, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 3H), 7.17 (d, *J* = 7.1 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 5.50 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.11 (d, *J* = 14.4 Hz, 1H), 3.92 (dd, *J* = 18.6, 7.3 Hz, 1H), 3.89 (brs, 1H), 3.65 (s, 3H), 3.59 (d, *J* = 18.8 Hz, 1H), 2.90 (d, *J* = 14.5 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 195.0, 194.0, 159.0, 136.5, 136.4, 135.8, 133.9, 133.8, 133.3, 128.9, 128.9, 128.7, 128.1, 128.4, 128.1, 121.0, 113.7, 58.6, 55.2, 46.8, 43.5, 36.8, 36.6, 36.4, 32.1. **FT-IR (thin film)** 2920, 1696, 1590, 1492, 1447, 1360, 1248, 695 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IB Column (hexane/2-propanol = 98:2), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 31.3 min, t_{minor} = 14.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_4S$ $[M+NH_4]^+$ 577.2161, found 577.2150.



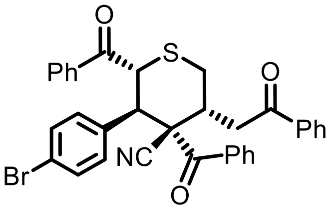
3d

3d: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 66% yield (36.2 mg). The dr value was found to be 5:1 by ^{1}H NMR analysis. m.p. = 178-180 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.90 (d, *J* = 7.4 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 7.51-7.45 (m, 6H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 3H), 6.81 (t, *J* = 8.6 Hz, 2H), 5.48 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 7.3 Hz, 1H), 3.93 (dd, *J* = 18.6, 7.6 Hz, 1H), 3.85 (dd, *J* = 7.2, 3.4 Hz, 1H), 3.59 – 3.51 (m, 1H), 2.91 (dd, *J* = 14.6, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.9, 194.8, 193.6, 163.4, 160.9, 136.4, 136.0, 135.6, 134.1, 133.9, 133.6, 132.9, 132.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 120.8, 115.4, 115.2, 58.3, 46.9, 43.6, 36.6, 36.3, 32.1. **FT-IR (thin film)** 2928, 1685, 1593, 1498, 1442, 1368, 1248, 690 cm^{-1}. **HPLC Analysis**: ee = 88%, Chiralpak IA Column Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 14.3 min, t_{minor} = 23.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}FN_2O_3S$ $[M+NH_4]^+$ 565.1961, found 565.1959.



3e

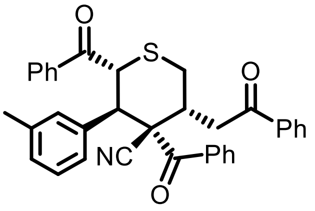
3e: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 62% yield (35.0 mg). The dr value was found to be 6:1 by ^{1}H NMR analysis. m.p. = 176-178 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 2H), 7.59-7.54 (m, 2H), 7.50-7.42 (m, 6H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 5.48 (d, *J* = 11.3 Hz, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 14.0 Hz, 1H), 3.94 (dd, *J* = 18.6, 7.7 Hz, 1H), 3.88-3.82 (m, 1H), 3.50 (dd, *J* = 18.6, 2.0 Hz, 1H), 2.92 (dd, *J* = 14.7, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.9, 194.6, 193.3, 136.4, 135.8, 135.7, 135.5, 134.2, 133.9, 133.9, 133.7, 131.6, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 120.7, 58.2, 46.8, 43.7, 36.6, 36.2, 32.0. **FT-IR (thin film)** 2927, 1684, 1596, 1447, 1328, 1258, 1126, 683 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 14.5 min, t_{minor} = 22.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{27}ClNO_3S$ $[M+H]^+$ 564.1400, found 564.1395.



3f

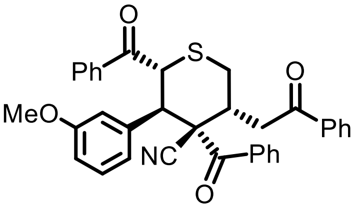
3f: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white sticky solid; 65% yield (39.4 mg). The dr value was found to be 6.3:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.03-7.99 (m, 2H), 7.93 (d, *J* = 7.3 Hz, 2H), 7.69 (d, *J* = 7.8 Hz, 2H), 7.64-7.55 (m, 3H), 7.54-7.42 (m, 6H), 7.43-7.37 (m, 4H), 7.28 (d, *J* = 1.7 Hz, 2H), 5.48 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.14 (d, *J* = 14.6 Hz, 1H), 3.95 (dd, *J* = 18.5, 7.7 Hz, 1H), 3.85 (dd, *J* = 7.2, 3.6 Hz, 1H), 3.50 (d, *J* =

18.6 Hz, 1H), 2.93 (dd, *J* = 14.6, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.8, 194.6, 193.2, 136.4, 136.3, 135.8, 135.5, 134.2, 133.9, 133.7, 131.5, 129.0, 128.9, 128.8, 128.6, 128.4, 128.4, 122.2, 120.7, 58.1, 46.7, 43.7, 36.6, 36.2, 32.0. **FT-IR (thin film)** 2923, 1689, 1587, 1440, 1326, 1260, 1123, 690 cm^{-1}. **HPLC Analysis**: ee = 88%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 15.2 min, t_{minor} = 23.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}BrN_2O_3S$ $[M+NH_4]^+$ 625.1161, found 625.1162.



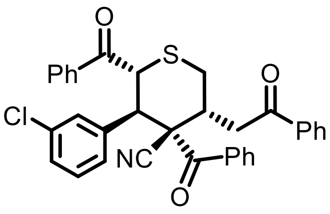
3g

3g: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; colourless sticky solid; 45% yield (24.5 mg). The dr value was found to be 4.6:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 4H), 7.53-7.38 (m, 7H), 7.34 (t, *J* = 7.6 Hz, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 5.53 (d, *J* = 11.2 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 14.4 Hz, 1H), 3.91 (dd, *J* = 18.5, 7.2 Hz, 1H), 3.83 (brs, 1H), 3.64 (d, *J* = 18.5 Hz, 1H), 2.94-2.84 (m, 1H), 2.17 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 195.0, 193.0, 144.9, 137.2, 135.9, 133.9, 133.8, 133.6, 130.4, 130.2, 129.7, 129.4, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 127.9, 121.1, 58.19, 47.0, 44.4, 36.8, 36.5, 36.4, 32.1, 21.8. **FT-IR (thin film)** 2922, 1680, 1602, 1449, 1248, 1140, 693 cm^{-1}. **HPLC Analysis**: ee = 98%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 ^{o}C, λ = 254 nm (t_{major} = 10.9 min, t_{minor} = 12.1 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{30}NO_3S$ $[M+H]^+$ 544.1946, found 544.1948.



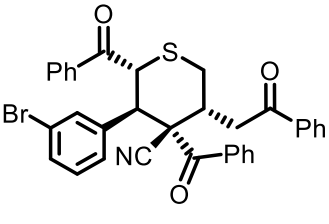
3h

3h: Purified by silica-gel column chromatography using 20% ethyl acetate/hexane; colourless stick solid; 60% yield (33.6 mg). The dr value was found to be 5.6:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.92 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 17.0 Hz, 4H), 7.56-7.38 (m, 7H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.02 (t, *J* = 7.9 Hz, 2H), 6.61 (d, *J* = 7.1 Hz, 1H), 5.52 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 14.3 Hz, 1H), 3.93 (dd, *J* = 18.6, 7.4 Hz, 1H), 3.83 (brs, 1H), 3.66 (s, 3H), 3.57 (d, *J* = 13.7 Hz, 1H), 2.95-2.85 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 197.0, 194.9, 193.8, 159.2, 138.4, 136.5, 136.4, 135.8, 133.9, 133.8, 133.3, 129.3, 129.0, 128.9, 128.8, 128.8, 128.7, 128.4, 128.4, 128.3, 128.1, 121.0, 114.0, 58.4, 55.2, 46.8, 44.4, 36.6, 36.4, 32.1. **FT-IR (thin film)** 2927, 1682, 1598, 1452, 1245, 1180, 686 cm^{-1}. **HPLC Analysis**: ee = 88%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.6 min, t_{minor} = 17.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_4S$ $[M+NH_4]^+$ 577.2161, found 577.2156.



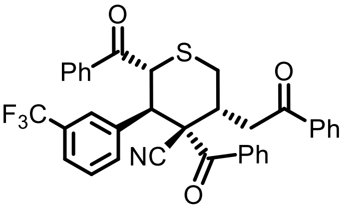
3i

3i: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 57% yield (32.0 mg). The dr value was found to be 5.3:1 by ^{1}H NMR analysis. m.p. = 148-150 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.00 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.63-7.52 (m, 3H), 7.53-7.33 (m, 10H), 7.05 (d, *J* = 6.3 Hz, 2H), 5.48 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 14.6 Hz, 1H), 3.93 (dd, *J* = 18.4, 7.6 Hz, 1H), 3.85 (d, *J* = 2.5 Hz, 1H), 3.51 (d, *J* = 18.4 Hz, 1H), 2.92 (dd, *J* = 14.6, 2.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.9, 194.6, 193.2, 139.1, 136.4, 135.9, 135.6, 134.2, 133.9, 133.7, 129.5, 128.9, 128.8, 128.6, 128.4, 128.4, 128.3, 120.6, 58.1, 46.8, 44.0, 36.6, 36.2, 32.0. **FT-IR (thin film)** 2925, 1693, 1597, 1459, 1243, 1178, 698 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 11.7 min, t_{minor} = 13.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{27}ClNO_3S$ $[M+H]^+$ 564.1400, found 564.1393.



3j

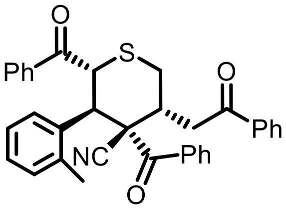
3j: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 56% yield (33.9 mg). The dr value was found to be 5.5:1 by ^{1}H NMR analysis. m.p. = 202-204 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 7.99 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 2H), 7.70 (d, *J* = 7.5 Hz, 2H), 7.66 (s, 1H), 7.59-7.53 (m, 2H), 7.52-7.48 (m, 3H), 7.45-7.41 (m, 4H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 5.47 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 14.2 Hz, 1H), 3.93 (dd, *J* = 18.6, 7.7 Hz, 1H), 3.85 (dd, *J* = 7.3, 3.3 Hz, 1H), 3.50 (dd, *J* = 18.6, 2.0 Hz, 1H), 2.92 (dd, *J* = 14.7, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.9, 194.6, 193.2, 139.4, 136.4, 135.8, 135.6, 134.2, 133.9, 133.7, 131.2, 129.8, 128.9, 128.7, 128.6, 128.4, 128.4, 122.3, 120.6, 58.1, 46.8, 44.0, 36.6, 36.2, 32.0. **FT-IR (thin film)** 2924, 1682, 1597, 1446, 1246, 978, 691 cm^{-1}. **HPLC Analysis**: ee = 88%, Chiralpak IB Column (hexane/2-propanol = 94:6), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 16.7 min, t_{minor} = 12.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}BrN_2O_3S$ $[M+NH_4]^+$ 625.1161, found 625.1157.



3k

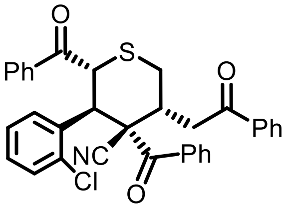
3k: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 68% yield (40.6 mg). The dr value was found to be 5.3:1 by ^{1}H NMR analysis. m.p. = 160-162 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02-7.97 (m, 2H), 7.90-7.85 (m, 2H), 7.78 (s, 1H), 7.72-7.69 (m, 3H), 7.63-7.45 (m, 6H), 7.45-7.32 (m, 6H), 7.23 (t, *J* = 7.9 Hz, 1H), 5.52 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.14 (d, *J* = 14.2 Hz, 1H), 3.98 (dd, *J* = 18.6, 7.9 Hz, 1H), 3.86 (dd, *J* = 7.8, 3.2 Hz, 1H), 3.46 (d, *J* = 18.6 Hz, 1H), 2.94 (dd, *J* = 14.8, 3.2 Hz, 1H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 196.8, 194.7, 193.0, 138.2, 136.4, 135.5, 134.2, 133.9, 133.9, 128.9, 128.8, 128.7, 128.5, 128.4, 124.9, 120.5, 58.1, 46.9, 44.2, 36.6, 36.1, 32.0. **FT-IR (thin film)** 2929, 1686, 1593, 1446, 1245, 1361, 980, 692 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} =

10.2 min, t_{minor} = 11.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{30}F_3N_2O_3S$ $[M+NH_4]^+$ 615.1929, found 615.1928.



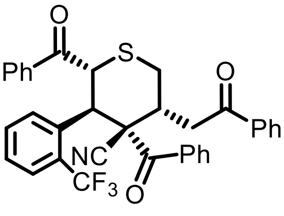
3l

3l: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 42% yield (22.8 mg). The dr value was found to be 7:1 by ^{1}H NMR analysis. m.p. = 130-132 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.83 (d, *J* = 7.6 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.45 (m, 6H), 7.44-7.28 (m, 4H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 5.53 (d, *J* = 10.9 Hz, 1H), 4.50 (d, *J* = 10.9 Hz, 1H), 4.16 (d, *J* = 14.5 Hz, 1H), 3.95 (dd, *J* = 18.4, 7.2 Hz, 1H), 3.84 (brs, 1H), 3.70 (d, *J* = 18.4 Hz, 1H), 2.89 (d, *J* = 2.4 Hz, 1H), 2.72 (s, 3H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.0, 195.4, 194.8, 139.4, 136.7, 136.6, 136.1, 136.0, 133.8, 133.0, 131.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.9, 127.8, 126.1, 126.0, 121.5, 58.9, 48.3, 39.7, 37.5, 36.2, 32.3, 20.4. **FT-IR (thin film)** 2922, 1684, 1596, 1504, 1447, 1237, 976, 695 cm^{-1}. **HPLC Analysis**: ee = 94%, Chiralpak IB Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.6 min, t_{minor} = 12.3 min). **HRMS (+ESI-TOF)** *m/z:* calcd. For $C_{35}H_{30}NO_3S$ $[M+H]^+$ 544.1946, found 544.1942.



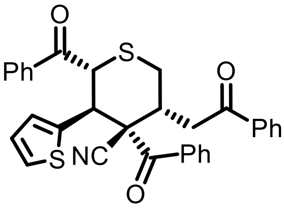
3m

3m: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 52% yield (29.3 mg). The dr value was found to be >20:1 by ^{1}H NMR analysis. m.p. = 169-171 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93-7.89 (m, 2H), 7.78 (d, *J* = 7.4 Hz, 2H), 7.70 – 7.68 (m, 1H), 7.63-7.59 (m, 2H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.44-7.38 (m, 4H), 7.32-7.24 (m, 5H), 6.92 (t, *J* = 6.9 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 5.42 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 10.9 Hz, 1H), 4.08 (d, *J* = 14.1 Hz, 1H), 3.95 (dd, *J* = 18.6, 8.1 Hz, 1H), 3.81 (dd, *J* = 7.9, 3.0 Hz, 1H), 3.45 (d, *J* = 18.6 Hz, 1H), 2.83 (dd, *J* = 14.7, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 196.9, 194.4, 192.8, 137.3, 136.4, 135.8, 135.8, 135.7, 133.9, 133.5, 130.6, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.2, 127.0, 121.1, 58.5, 48.4, 40.1, 37.6, 35.8, 32.0. **FT-IR (thin film)** 2922, 1686, 1595, 1500, 1445, 1239, 791, 693 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 94:6), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 18.9 min, t_{minor} = 19.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}ClN_2O_3S$ $[M+NH_4]^+$ 581.1666, found 581.1668.



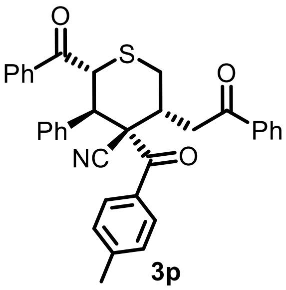
3n

3n: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; a light yellow semi solid; 50% yield (29.9 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.86 (d, *J* = 7.5 Hz, 3H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.59-7.57 (m, 2H), 7.52-7.47 (m, 4H), 7.39-7.35 (m, 3H), 7.21-7.17 (m, 2H), 5.56 (d, *J* = 10.6 Hz, 1H), 5.13 (dd, *J* = 10.5, 3.4 Hz, 1H), 4.18 (d, *J* = 14.8 Hz, 1H), 4.07 (dd, *J* = 18.7, 9.0 Hz, 1H), 3.93-3.84 (m, 1H), 3.32 (d, *J* = 18.3 Hz, 1H), 2.93 (dd, *J* = 14.7, 3.3 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.6, 194.4, 192.3, 136.3, 135.7, 135.2, 134.0, 133.9, 133.8, 131.6, 129.3, 129.0, 128.8, 128.7, 128.7, 128.7, 128.3, 128.0, 126.4, 121.0, 58.4, 48.7, 39.3, 37.7, 35.4, 31.6. **FT-IR (thin film)** 2922, 1686, 1595, 1500, 1445, 1239, 791, 693 cm^{-1}. **HPLC Analysis**: ee = 92%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 13.3 min, t_{minor} = 33.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{30}F_3N_2O_3S$ $[M+NH_4]^+$ 615.1929, found 615.1930.



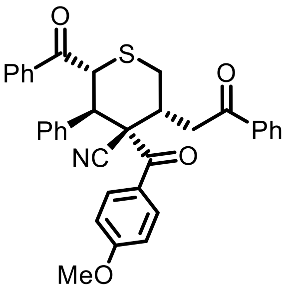
3o

3o: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 45% yield (24.0 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.00-7.95 (m, 4H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.62-7.52 (m, 3H), 7.49-7.39 (m, 6H), 7.09-7.05 (m, 2H), 6.75-6.69 (m, 1H), 5.44 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.10 (d, *J* = 14.9 Hz, 1H), 3.95 (dd, *J* = 18.5, 7.9 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.45 (d, *J* = 18.6 Hz, 1H), 2.91 (dd, *J* = 14.5, 3.2 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.9, 194.5, 193.2, 139.2, 136.4, 135.8, 135.5, 134.1, 133.9, 133.7, 129.0, 128.9, 128.8, 128.6, 128.6, 128.4, 128.3, 128.2, 126.4, 125.9, 120.6, 59.0, 47.8, 40.1, 36.6, 36.1, 31.7. **FT-IR (thin film)** 2925, 1685, 1597, 1490, 1447, 1266, 1183, 735, 690 cm^{-1}. **HPLC Analysis**: ee = 73%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 17.2 min, t_{minor} = 18.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{32}H_{29}N_2O_3S_2$ $[M+NH_4]^+$ 553.1620, found 553.1621.



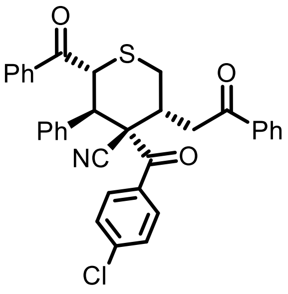
3p

3p: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 59% yield (32.0 mg). The dr value was found to be 5:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.04-7.98 (m, 2H), 7.93-7.87 (m, 2H), 7.61-7.56 (m, 3H), 7.49-7.46 (m, 5H), 7.40 (t, *J* = 7.7 Hz, 3H), 7.18-7.03 (m, 6H), 5.54 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.14 (d, *J* = 14.4 Hz, 1H), 3.95 (dd, *J* = 18.7, 7.7 Hz, 1H), 3.82 (dd, *J* = 7.5, 3.3 Hz, 1H), 3.54 (dd, *J* = 18.7, 2.0 Hz, 1H), 2.91 (dd, *J* = 14.7, 3.3 Hz, 1H), 2.33 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 195.0, 192.9, 144.5, 137.1, 136.5, 136.2, 135.8, 134.01, 133.9, 133.9, 133.8, 133.5, 130.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.7, 128.5, 128.5, 128.4, 128.3, 127.9, 121.1, 58.1, 46.9, 44.3, 36.7, 36.3, 32.0, 21.8. **FT-IR (thin film)** 2930, 1690, 1599, 1493, 1438, 1260, 1178, 694 cm^{-1}. **HPLC Analysis**: ee = 92%, Chiralpak IC Column (hexane/2-propanol = 98:2), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 19.8 min, t_{minor} = 30.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_3S$ $[M+NH_4]^+$ 561.2212, found 561.2211.



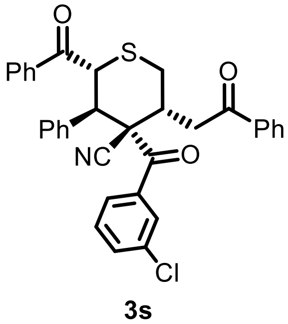
3q

3q: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; brown sticky solid; 55% yield (30.8 mg). The dr value was found to be 6:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.89 (s, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.53-7.48 (m, 10H), 7.13-7.03 (m, 3H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.54 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.14 (d, *J* = 14.7 Hz, 1H), 3.99 (dd, *J* = 18.8, 8.1 Hz, 1H), 3.85-3.76 (m, 5H), 3.43 (d, *J* = 17.8 Hz, 1H), 2.92 (dd, *J* = 14.5, 3.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.1, 195.1, 190.8, 164.0, 137.3, 136.6, 135.9, 133.9, 133.8, 131.3, 128.9, 128.8, 128.7, 128.4, 128.2, 127.8, 113.8, 57.6, 55.7, 47.0, 44.3, 36.9, 36.2, 31.8. **FT-IR (thin film)** 2923, 1682, 1596, 1489, 1447, 1361, 1268, 753, 690 cm^{-1}. **HPLC Analysis**: ee = 92%, Chiralpak IA Column (hexane/2-propanol = 97:3), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 24.8 min, t_{minor} = 40.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_4S$ $[M+NH_4]^+$ 577.2161, found 577.2166.



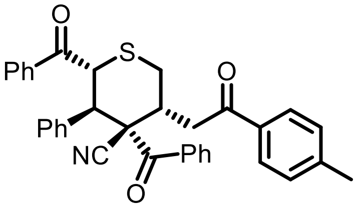
3r

3r: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 55% yield (31.0 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. m.p. = 176-178 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.63-7.48 (m, 7H), 7.43 (t, *J* = 7.4 Hz, 5H), 7.31 (s, 2H), 7.12-7.07 (m, 4H), 5.52 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 14.7 Hz, 1H), 3.81 (dd, *J* = 13.5, 6.8 Hz, 2H), 3.75-3.65 (m, 1H), 2.88 (dd, *J* = 14.6, 3.0 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.8, 194.6, 193.0, 139.6, 136.6, 136.2, 135.5, 134.5, 133.8, 133.7, 130.1, 129.6, 129.4, 129.1, 128.8, 128.7, 128.7, 128.6, 128.5, 128.2, 128.2, 128.1, 127.9, 120.7, 58.2, 46.6, 44.3, 36.6, 36.4, 32.3. **FT-IR (thin film)** 2927, 1693, 1597, 1484, 1450, 1365, 1270, 686 cm^{-1}. **HPLC Analysis**: ee = 80%, Chiralpak ID Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, Chiralpak ID Column, n-Hexane/i-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 30.8 min, t_{minor} = 46.1 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{27}ClNO_3S$ $[M+H]^+$ 564.1400, found 564.1398.



3s

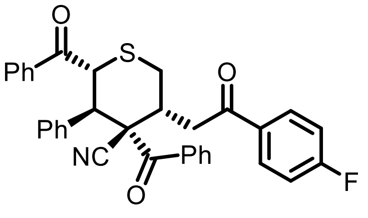
3s: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 52% yield (29.3 mg). The dr value was found to be 5:1 by ^{1}H NMR analysis. m.p. = 145-147 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.06-7.99 (m, 2H), 7.93 – 7.89 (m, 2H), 7.64-7.38 (m, 11H), 7.35 (t, *J* = 1.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.18-7.07 (m, 4H), 5.52 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 14.8 Hz, 1H), 3.83 (dt, *J* = 10.1, 6.3 Hz, 2H), 3.76-3.67 (m, 1H), 2.89 (dd, *J* = 14.6, 2.9 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.0, 194.7, 193.4, 138.1, 136.8, 135.8, 134.0, 133.9, 133.1, 129.7, 128.9, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 125.8, 120.7, 58.7, 46.8, 44.6, 36.8, 36.6, 32.5. **FT-IR (thin film)** 2924, 1685, 1598, 1500, 1449, 1238, 752, 689 cm^{-1}. **HPLC Analysis**: ee = 94%, Chiralpak IA Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 20.9 min, t_{minor} = 23.6 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{27}ClNO_3S$ $[M+H]^+$ 564.1400, found 564.1399.



3t

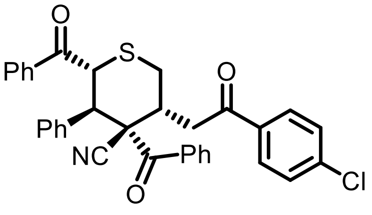
3t: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 62% yield (34.0 mg).The dr value was found to be 4.5:1 by ^{1}H NMR analysis. m.p. = 169-171 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.92-7.89 (m, 3H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.26-7.23 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 5.53 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.12 (d, *J* = 13.8 Hz, 1H), 3.90 (dd, *J* = 18.5, 7.5 Hz, 1H), 3.82 (dd, *J* = 7.1, 3.3 Hz, 1H), 3.56 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.89 (dd, *J* = 14.6, 3.4 Hz, 1H), 2.42 (s, 3H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.6, 195.0, 193.9, 144.9, 144.7, 137.1, 136.4, 135.8, 134.1, 134.0, 133.2, 129.6, 128.8, 128.7, 128.5, 128.5, 128.4, 128.1, 128.0, 121.0, 58.5, 46.9, 44.4, 36.7, 36.2, 32.2, 21.9. **FT-IR (thin film)** 2926, 1684, 1596, 1510, 1444, 1235, 750, 662 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.3 min, t_{minor} =

17.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{30}NO_3S$ $[M+H]^+$ 544.1946, found 544.1944.



3u

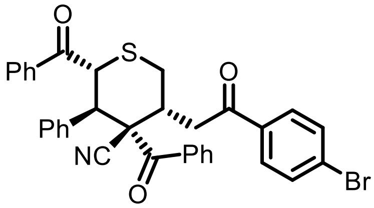
3u: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 52% yield (28.5 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. m.p. = 175-177 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.08-8.06 (m, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 3H), 7.48-7.38 (m, 5H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.19-7.04 (m, 6H), 5.54 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.13 (d, *J* = 14.5 Hz, 1H), 3.91-3.79 (m, 2H), 3.62 (d, *J* = 16.8 Hz, 1H), 2.89 (d, *J* = 12.5 Hz, 1H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 195.5, 194.9, 194.20, 136.9, 136.5, 135.7, 134.0, 133.3, 131.2, 131.1, 130.3, 128.9, 128.7, 128.5, 128.4, 128.0, 120.9, 116.2, 115.9, 58.4, 46.8, 44.4, 36.6, 36.4, 32.3. **FT-IR (thin film)** 2924, 1684, 1596, 1447, 1263, 957, 790, 691 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IA Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 28.2 min, t_{minor} = 31.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{27}FNO_3S$ $[M+H]^+$ 548.1690, found 548.1704.



3v

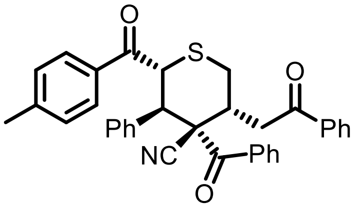
3v: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; white solid; 60% yield (33.8 mg). The dr value was found to be 4:1 by ^{1}H NMR analysis. m.p. = 180-182 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.49-7.38 (m, 7H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.15-7.04 (m, 3H), 5.54 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 14.8 Hz, 1H), 3.84 (q, *J* = 6.8 Hz, 2H), 3.64 (dd, *J* = 21.5, 7.2 Hz, 1H), 2.88 (dd, *J* = 14.3, 2.1 Hz, 1H). **^{13}C NMR (151 MHz, CDCl$_3$)** δ 195.9, 194.9, 194.2, 140.3, 136.9, 136.4, 135.7, 134.8, 134.0, 133.3, 129.8, 129.2, 128.9, 128.7, 128.4, 128.4, 128.1, 128.0, 120.9, 58.4, 46.8, 44.4, 36.6, 36.6, 32.3. **FT-IR (thin film)** 2920, 1688, 1592, 1441, 1269, 973, 793, 693 cm^{-1}. **HPLC Analysis**: ee = 80%, Chiralpak ID

Column (hexane/2-propanol = 93:7), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 27.1 min, t_{minor} = 48.0 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}ClN_2O_3S$ $[M+NH_4]^+$ 581.1666, found 581.1665.



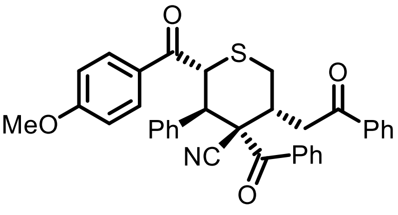
3w

3w: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 58% yield (35.2 mg). The dr value was found to be 4.8:1 by ^{1}H NMR analysis. m.p. = 185-187 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.89 (t, *J* = 7.6 Hz, 3H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 3H), 7.49-7.38 (m, 5H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.16-7.04 (m, 3H), 5.53 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.13 (d, *J* = 14.7 Hz, 1H), 3.88-3.77 (m, 2H), 3.70-3.59 (m, 1H), 2.93-2.83 (m, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.1, 194.9, 194.2, 136.9, 136.5, 135.7, 135.2, 134.0, 133.3, 132.2, 129.9, 129.8, 129.1, 128.9, 128.7, 128.5, 128.4, 128.1, 128.0, 120.9, 58.4, 46.8, 44.5, 36.6, 36.5, 32.3. **FT-IR (thin film)** 2923, 1683, 1640, 1585, 1448, 1244, 977, 753, 689 cm^{-1}. **HPLC Analysis**: ee = 88%, Chiralpak ID Column (hexane/2-propanol = 93:7), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 31.0 min, t_{minor} = 55.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}BrN_2O_3S$ $[M+NH_4]^+$ 625.1161, found 625.1161.



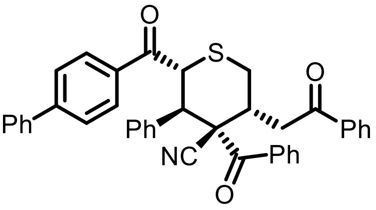
3x

3x: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow sticky solid; 61% yield (33.1 mg). The dr value was found to be 4.8:1 by ^{1}H NMR analysis. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.61-7.55 (m, 3H), 7.50-7.46 (m, 5H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 5.52 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H), 3.92 (dd, *J* = 18.7, 7.4 Hz, 1H), 3.82 (dd, *J* = 7.1, 3.5 Hz, 1H), 3.62 (dd, *J* = 18.7, 2.5 Hz, 1H), 2.89 (dd, *J* = 14.6, 3.3 Hz, 1H), 2.38 (s, 3H). **^{13}C NMR (100 MHz, CDCl$_3$)** δ 196.6, 194.9, 193.9, 144.7, 137.1, 136.4, 135.7, 134.0, 133.9, 133.2, 129.5, 128.8, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 120.9, 58.4, 46.9, 44.4, 36.6, 36.2, 32.2, 21.9. **FT-IR (thin film)** 2926, 1683, 1600, 1490, 1267, 979, 761, 696 cm^{-1}. **HPLC Analysis**: ee = 82%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 14.3 min, t_{minor} = 20.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_3S$ $[M+NH_4]^+$ 561.2212, found 561.2212.



3y

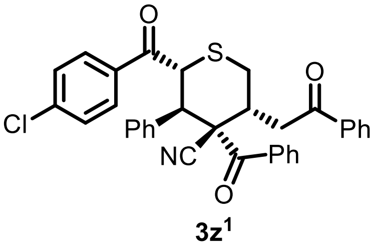
3y: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light brown sticky solid; 45% yield (25.2 mg). The dr value was found to be 5:1 by ^{1}H NMR analysis. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.61-7.52 (m, 3H), 7.50-7.45 (m, 5H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.49 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.20-4.05 (m, 2H), 4.01-3.77 (m, 6H), 3.62 (dd, *J* = 18.7, 2.7 Hz, 1H), 2.88 (dd, *J* = 14.5, 3.3 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.2, 194.1, 193.0, 164.3, 137.2, 136.5, 136.5, 133.8, 133.25, 131.3, 131.3, 128.9, 128.6, 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 121.0, 114.1, 114.1, 58.5, 55.7, 46.3, 44.4, 36.6, 36.5, 32.2. **FT-IR (thin film)** 2922, 1681, 1597, 1448, 1249, 1173, 975, 753, 688 cm^{-1}. **HPLC Analysis**: ee = 86%, Chiralpak IA Column (hexane/2-propanol = 90:10), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 30.9 min, t_{minor} = 38.2 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{35}H_{33}N_2O_4S$ $[M+NH_4]^+$ 577.2161, found 577.2166.



3z

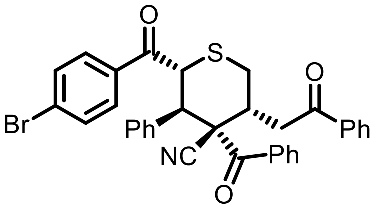
3z: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 60% yield (36.3 mg). The dr value was found to be 4.8:1 by ^{1}H NMR analysis. m.p. = 114-116 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.03-7.99 (m, 4H), 7.67-7.55 (m, 7H), 7.54 – 7.43 (m, 7H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.19-7.06 (m, 3H), 5.58 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.16 (d, *J* =

13.8 Hz, 1H), 3.94 (dd, *J* = 18.3, 7.4 Hz, 1H), 3.89-3.82 (m, 1H), 3.64 (dd, *J* = 18.6, 3.4 Hz, 1H), 2.92 (dd, *J* = 14.4, 3.2 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.1, 194.3, 194.0, 146.7, 139.8, 137.1, 136.5, 136.5, 134.3, 133.8, 133.3, 129.4, 129.1, 128.9, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.5, 127.4, 121.0, 58.5, 53.6, 46.8, 44.4, 36.6, 36.5, 32.3. **FT-IR (thin film)** 2920, 1686, 1599, 1450, 1243, 1169, 970, 765, 698 cm^{-1}. **HPLC Analysis**: ee = 94%, Chiralpak IC Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 15.8 min, t_{minor} = 24.4 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{40}H_{35}N_2O_3S$ $[M+NH_4]^+$ 623.2368, found 623.2369.



3z^1

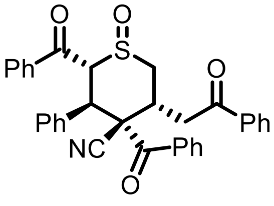
3z^1: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 65% yield (36.6 mg). The dr value was found to be 4.8:1 by ^{1}H NMR analysis. m.p. = 95-97 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.61-7.55 (m, 3H), 7.49-7.45 (m, 5H), 7.40-7.30 (m, 4H), 7.16-7.06 (m, 4H), 5.46 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.13 (d, *J* = 14.8 Hz, 1H), 3.92 (dd, *J* = 18.5, 7.3 Hz, 1H), 3.83 (dd, *J* = 7.2, 3.2 Hz, 1H), 3.60 (dd, *J* = 19.0, 3.2 Hz, 1H), 2.91 (dd, *J* = 14.8, 3.1 Hz, 1H). **^{13}C NMR (150 MHz, $CDCl_3$)** δ 197.0, 193.8, 193.8, 140.6, 136.9, 136.5, 136.3, 134.0, 133.9, 133.3, 130.2, 130.1, 129.2, 128.9, 128.5, 128.4, 128.4, 128.1, 128.1, 120.9, 58.4, 46.9, 44.4, 36.6, 36.4, 32.2. **FT-IR (thin film)** 2921, 1684, 1596, 1447, 1362, 1267, 754, 690 cm^{-1}. **HPLC Analysis**: ee = 92%, Chiralpak IC Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 8.9 min, t_{minor} = 11.8 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}ClN_2O_3S$ $[M+NH_4]^+$ 581.1666, found 581.1667.



3z^2

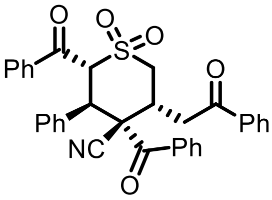
3z^2: Purified by silica-gel column chromatography using 15% ethyl acetate/hexane; light yellow solid; 63% yield (38.3 mg). The dr value was found to be 4.8:1 by ^{1}H NMR analysis. m.p. = 142-144 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.61-7.53 (m, 5H), 7.52-7.43

(m, 5H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.15-7.06 (m, 3H), 5.45 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.13 (d, *J* = 14.7 Hz, 1H), 3.91 (dd, *J* = 18.4, 7.5 Hz, 1H), 3.83 (dd, *J* = 7.0, 3.6 Hz, 1H), 3.60 (dd, *J* = 18.4, 2.6 Hz, 1H), 2.91 (dd, *J* = 14.6, 3.1 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 197.0, 194.7, 193.4, 138.1, 136.8, 135.8, 134.0, 133.9, 133.1, 129.7, 128.9, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 125.8, 120.7, 58.7, 46.8, 44.6, 36.8, 36.6, 32.5. **FT-IR (thin film)** 2923, 1684, 1590, 1491, 1441, 1264, 792, 698 cm^{-1}. **HPLC Analysis**: ee = 90%, Chiralpak IC Column (hexane/2-propanol = 95:5), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 9.4 min, t_{minor} = 12.3 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{30}BrN_2O_3S$ $[M+NH_4]^+$ 625.1161, found 625.1175.



4

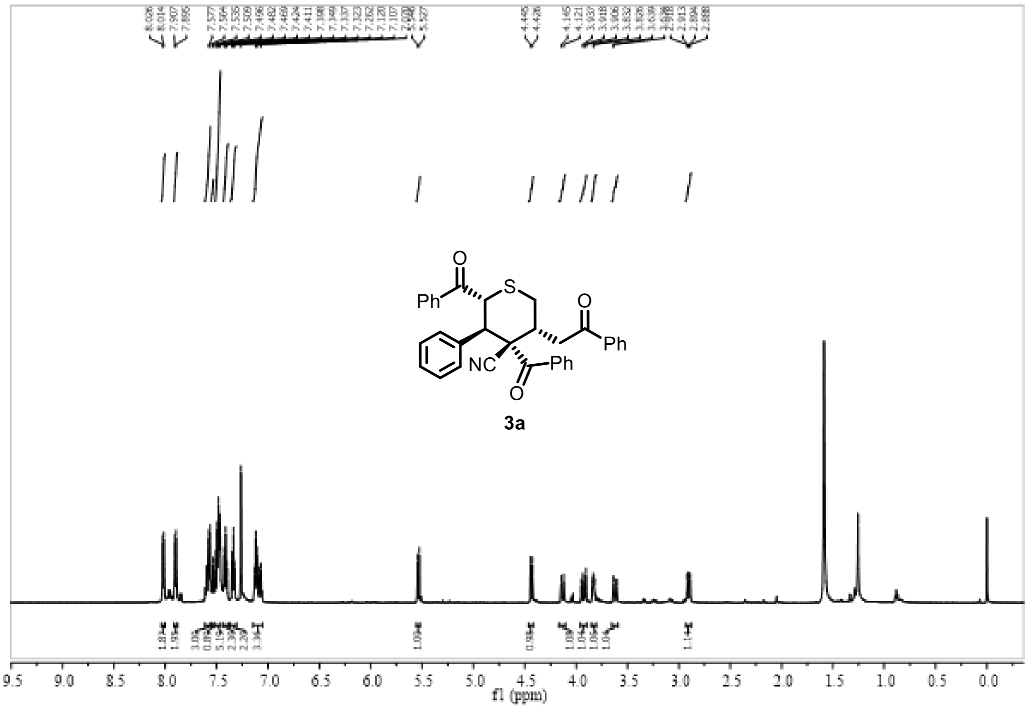
4: Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; white solid; 70% yield (26.7 mg). The dr value was found to be >20:1 by ^{1}H NMR analysis. m.p. = 175-177 °C. **^{1}H NMR (400 MHz, CDCl$_3$)** δ 8.06 (d, *J* = 1.6 Hz, 1H), 7.96-7.92 (m, 2H), 7.79 (d, *J* = 7.4 Hz, 2H), 7.51-7.48 (m, 6H), 7.40-7.31 (m, 6H), 7.07-7.02 (m, 3H), 5.63 (d, *J* = 12.3 Hz, 1H), 4.42 (d, *J* = 12.3 Hz, 1H), 4.18 (s, 1H), 4.03 (dd, *J* = 13.3, 3.1 Hz, 1H), 3.85-3.73 (m, 2H), 3.41 (dd, *J* = 18.6, 5.6 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 195.8, 195.2, 193.7, 137.8, 136.1, 135.7, 134.6, 134.0, 133.6, 133.6, 133.4, 131.1, 130.2, 129.8, 128.9, 128.5, 128.4, 128.3, 128.2, 128.2, 128.2, 127.9, 120.2, 69.8, 57.0, 53.8, 45.5, 37.6, 37.5. **FT-IR (thin film)** 2930, 1690, 1588, 1395, 1260, 780, 685 cm^{-1}. **HPLC Analysis**: ee = 86%, Chiralpak IB Column (hexane/2-propanol = 80:20), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 58.2 min, t_{minor} = 35.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{26}NO_4S$ $[M-H]^-$ 544.1588, found 544.1582.

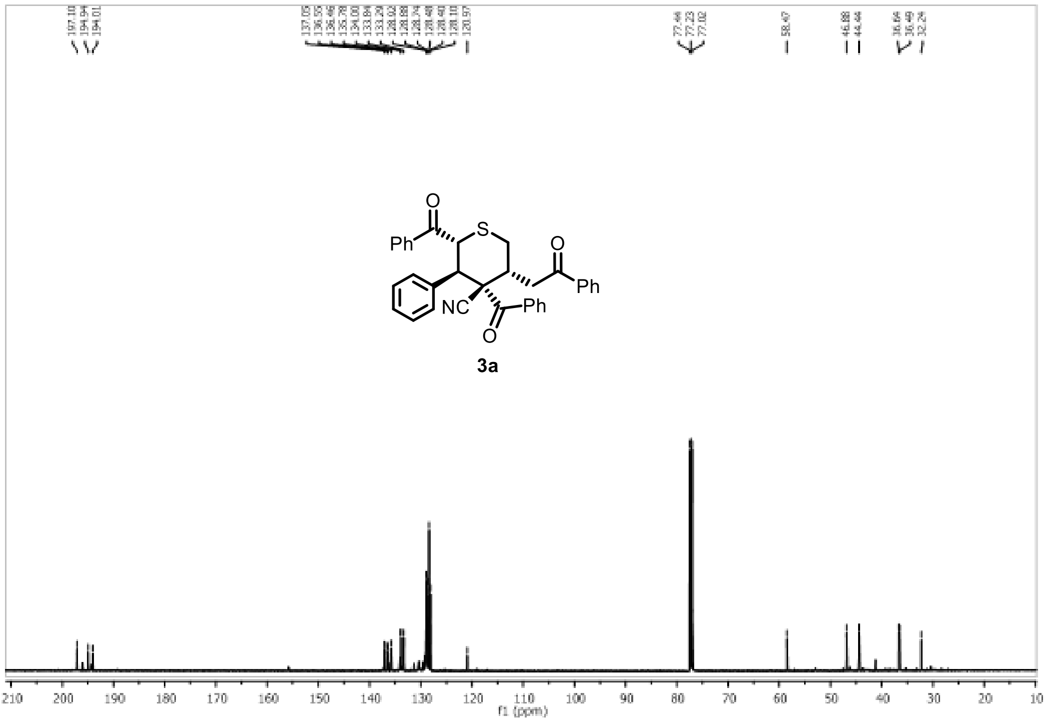


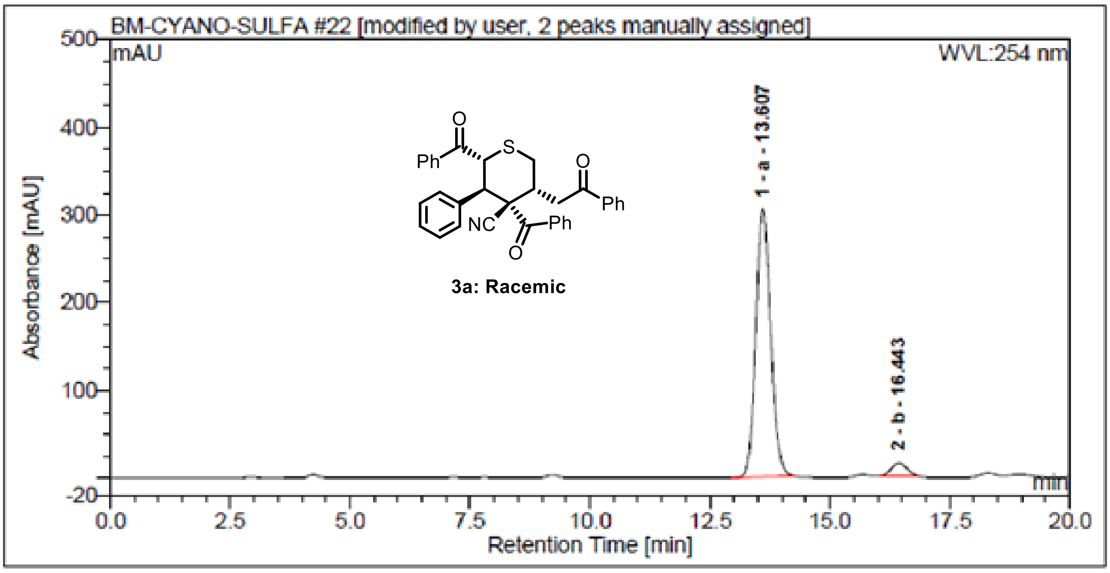
5

5: Purified by silica-gel column chromatography using 30% ethyl acetate/hexane; white solid; 75% yield (29.5 mg). The dr value was found to be >20:1 by ^{1}H NMR analysis. m.p. = 206-208 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ 8.09 (s, 1H), 8.00 (d, *J* = 7.4 Hz, 3H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.60-7.55 (m, 3H), 7.50-7.47 (m, 4H), 7.44-7.40 (m, 4H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 6.5 Hz, 2H), 5.98 (d, *J* = 12.3 Hz, 1H), 5.00 (d, *J* = 12.3 Hz, 1H), 4.31-4.25 (m, 1H), 4.17 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.96 – 3.85 (m, 2H), 3.57 (dd, *J* = 15.2, 3.2 Hz, 1H). **^{13}C NMR (150 MHz, CDCl$_3$)** δ 196.4, 193.1, 186.9, 137.0, 136.2, 135.8, 134.7, 134.4, 133.9, 133.8, 133.8, 133.4, 130.2, 129.8, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.1, 127.7, 120.0, 67.0, 56.9, 53.4, 45.8, 37.0, 36.5. **FT-IR (thin film)** 2928, 1695, 1587, 1350, 1262, 790, 693 cm^{-1}. **HPLC Analysis**: ee = 86%, Chiralpak IA Column (hexane/2-propanol = 80:20), flow rate 1.0 mL/min, 25 °C, λ = 254 nm (t_{major} = 17.4 min, t_{minor} = 22.7 min). **HRMS (+ESI-TOF)** *m/z*: calcd. For $C_{34}H_{26}NO_4S$ [M-H]$^-$ 560.1537, found 560.1534.

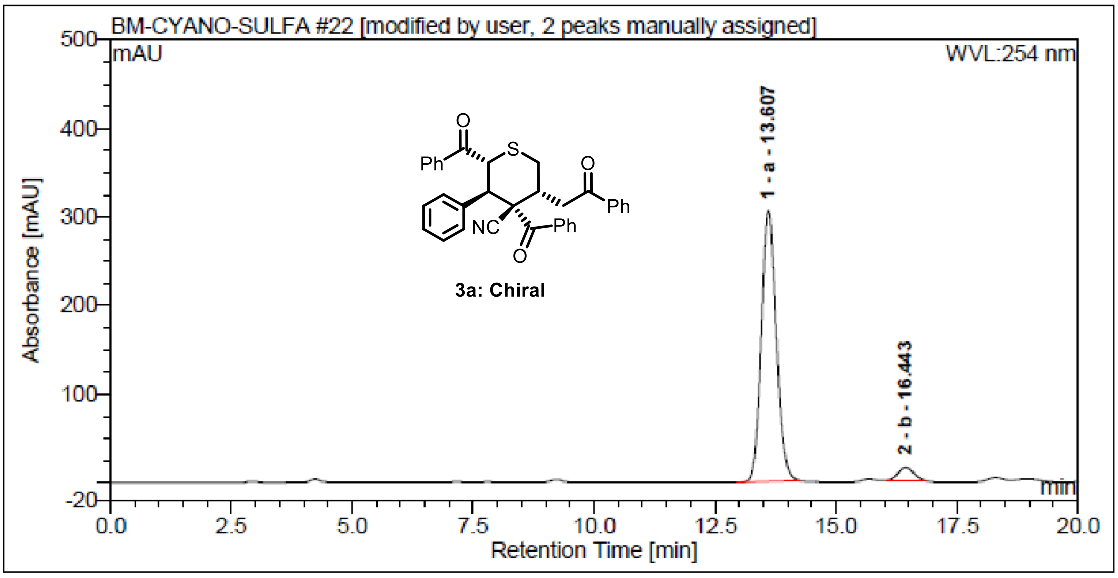
6.8 Selected NMR and HPLC spectra of products







No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	13.61	109.633	95.10583415	305.9735	n.a.
2	b	16.44	5.642	4.894165852	14.837	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	13.61	109.633	95.10583415	305.9735	n.a.
2	b	16.44	5.642	4.894165852	14.837	n.a.

6.9 References

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23. CCDC 1562510 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request /cif.


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List of publications

1. "Primary Amino acid Catalyzed Asymmetric Intramolecular Mannich Reaction for the Synthesis of 2-aryl-2,3-dihydro-4-quinolones", **Mondal**. **B**.; Pan. S. C. *Org. Biomol. Chem.* **2014**, *12*, 9789-9792.
2. "*n*Bu$_4$NI-Catalyzed *α*-Benzoxylation of Ketones with Terminal Aryl Alkenes", **Mondal**. **B**.; Shaoo. S. C.; Pan. S. C. *Eur. J. Org. Com.* **2015**, 3135-3140.
3. "Organocatalytic Redox Isomerization of Electron- Deficient Allylic Alcohols: Synthesis of 1,4-ketoaldehydes", Mondal. K.; **Mondal**. **B**.; Pan. S. C. *J. Org. Chem.* **2016**, *81*, 4835-4840.
4. "Organocatalytic Asymmetric Michael-Hemiacetalization Reaction Between 2-Hydroxyacetophenones and Enals: A Route to Chiral *β,γ*-Disubstituted *γ*-Butyrolactones", Balha. M.; **Mondal**. **B**.; Pan. S. C. *J. Org. Chem.* **2017**, *82*, 6409-6416.
5. "Organocatalytic Asymmetric Synthesis of Tetrahydrothiophenes and Tetrahydrothiopyrans", **Mondal**. **B**.; Nandi. S.; Pan. S. C. *Eur. J. Org. Com.* **2017**, 4666-4677.
6. "Organocatalytic Asymmetric Dimerization of *γ*-Hydroxyenones to Acetals and Theoretical Investigations into the Diastereoselection", **Mondal**. **B**.; Mondal. K.; Satpati. P.; Pan. S. C. *Eur. J. Org. Com.* **2017**, 7101-7106.
7. "Organocatalytic Asymmetric Synthesis of Pentasubstituted Tetrahydrothiopyrans Bearing a Quaternary Centre through a Double Michael Reaction", **Mondal**. **B**.; Pan. S. C. *Synlett*. **2018**, *29*, 576-580.
8. "Highly Diastereo- and Enantioselective Synthesis of Spiro-tetrahydrofuran-pyrazolones *via* Organocatalytic Cascade Reaction between *γ*- Hydroxyenones and Unsaturated Pyrazolones", **Mondal**. **B**.; Maity. R.; Pan. S. C. *J. Org. Chem.* **2018**, *83*, 8645-8654.
9. "Organocatalytic Asymmetric Synthesis of Highly Substituted Tetrahydrofurans and Tetrahydropyrans *via* Double Michael Addition Strategy", **Mondal**. **B**.; Balha. M.; Pan. S. C. *Asian J. Org. Chem.* **2018**, *7*, 1788-1792.

10. “Organocatalytic Asymmetric Cascade Reaction between *o*-Hydroxycinnamaldehydes and *γ*/*δ*-Hydroxyenones: A Route to Tetrahydrofuran/Tetrahydropyran-Fused 3,4-Dihydrocoumarins”, **Mondal**. **B**.; Pan. S. C. *Adv. Synth. Catal*. **2018**, *360*, 4348-4353.
11. “Organocatalytic Asymmetric Spirocyclization Reactions of Cyclic 2,4-dienones with Cyanoketones”, **Mondal**. **B**.; Pan. S. C. *Manuscript under preparation*.

Conferences Attended

1. Presented a poster in **Frontiers in Chemical Sciences** (**FICS-2014**) held at Institute of Technology, Guwahati, India.
2. Presented a poster in **CRSI National Symposium in Chemistry-2017** held at Gauhati University, Guwahati, India.
3. Presented a poster in **International Conference on Chemistry for Human Development (ICCHD-2018)** held at Heritage Institute of Technology, Kolkata, India.
4. Presented a poster in **National Organic Symposium Trust (JNOST-2018)** held at CSIR- Indian Institute of Chemical Technology Hyderabad, India.