Organocatalytic Asymmetric Addition/Cyclization of Carbon/Sulfur Nucleophiles to in situ-Generated ortho-Quinone Methides

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

CHANDAN GHARUI

Roll No. 156122016

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781039

INDIA

March 2021

Dedicated

to

My Parents and Well-wishers

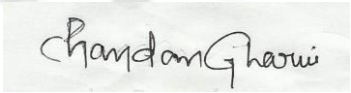
INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I, hereby declared that the work comprised in this thesis entitled "***Organocatalytic Asymmetric Addition/Cyclization of Carbon/Sulfur Nucleophiles to in situ-Generated ortho-Quinone Methides***" is the outcome of the research work carried out by me under the supervision of Prof. Subhas Chandra Pan, Department of Chemistry, Indian Institute of Technology Guwahati, India, for the award of the degree of Doctor of Philosophy.

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



Guwahati

March, 2021

Chandan Gharui
Roll No: 156122016
Department of Chemistry
IIT Guwahati, Assam
India-781039

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

Guwahati – 781039, India

Tel. No.: +91-361-2583304

e-mail: span@iitg.ac.in

Prof. Subhas Chandra Pan

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Organocatalytic Asymmetric Addition/Cyclization of Carbon/Sulfur Nucleophiles to in situ-Generated ortho-Quinone Methides***" which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Chandan Gharui (Roll No: 156122016) 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

March, 2021

Prof. Subhas Chandra Pan

Supervisor

~Acknowledgements~

I would like to appreciate all the people around me who have supported and guided me directly and indirectly throughout my whole academic career. Without their assistances, this thesis would not have been a reality.

First, I would like to express my profound gratitude to my Ph.D. supervisor **Prof. Subhas Chandra Pan** for his continuous guidance, support, motivation, immense knowledge, stimulating scientific discussions and thoughtful advises throughout my research work. I am deeply indebted to him for inspiring me towards scientific research and also greatly thankful for giving me the opportunity to work in his group.

Beside my advisor, I would like to acknowledge my doctoral committee members Prof. Anil Kumar Saikia (Chairman), Dr. Kingsuk Mahata, Dr. Pavan K. Kancharla for their valuable suggestions and encouragement which incented me to widen my thesis work from various perspective.

My sincere thanks also goes to Prof. Benjamin List for providing the TRIP catalyst in one of my project. I am thankful to Dr. Deepak Chopra who helped me with X-ray crystallographic dada recording and analysis. Also, I would like to acknowledge Dr. Sutapa Roy and my M.Sc. project advisor, my teacher Dr. Alakananda Hajra for their motivation and support during my research.

I am thankful to IIT Guwahati for the fellowship and also thankful to IIT Guwahati, Department of Chemistry and Central Instruments Facilities (CIF) for providing research and all sorts of instrumental facilities. I will always remain thankful to the staff members of CIF and the department of chemistry.

I would like to express my sincere gratitude to my dear past lab members Dr. Utpal Nath, Dr. Keshab Mondal, Dr. Rajendra Maity, Dr. Soumendranath Mukhopadhyay, Dr. Buddhadeb Mondal, Dr. Subas Chandra Sahoo for their constant guidance and support throughout my Ph.D. journey. Their continuous help definitely smoothen this journey. Also, I thank to them for their valuable suggestions and advice during thesis writing. I sincerely thank my fellow labmates Dr. Megha Balha, Nimisha Bania, Chandrakanta Parida, Amit Shikari, Subhankar Biswas, Rupkumar Khuntia and Dipankar Barman for their kind cooperation during my work.

Also, I would like to thank CIF operators Dr. Ganesh Chandra Paul, Prasenjit Sarkar, Moumita Dutta and others for their help in data recording and analysis.

I sincerely thank the project students Shreya Singh, Debasmita Behera, Ranajit Mal, and Priyank Sinha for their help in my works. I would also like to thank my B.Sc. and M.Sc. friends. I would like to thank all my Ph.D. batch mates, seniors and juniors who helped me during my work and for creating a friendly environment during my stay at IITG.

Finally, my Ph.D. journey could not have been completed without the endless love, support and blessings from my parents and family members. I thank them for their faith in me, which has always been a constant source of motivation. I am always thankful to the almighty God for everything in my life.

Sincerely,

Chandan Gharui

CONTENTS

Abbreviation

Ar	Aryl group	d	Doublet or day
Alk	Alkyl group	dd	Doublet of doublet
Ac_2O	Acetic anhydride	DCM	Dichloromethane
α	*alpha*	1,2-DCE	1,2-Dichloroethane
AcOH	Acetic acid	DIBAL-H	Diisobutylaluminium hydride
Å	Angstrom	$(Boc)_2O$	Di-*tert*-butyl dicarbonate
CH_3CN	Acetonitrile	dr	Diastereomeric ratio
β	*beta*	DMF	*N,N*-Dimethylformamide
br	Broad	°C	Degree Celsius
^{t}Bu	*tert*-Butyl	Et_2O	Diethyl ether
Cbz	Benzyloxycarbonyl	EWG	Electron withdrawing group
δ	Chemical shift or *delta*	Et	Ethyl
C	Carbon	ee	Enantiomeric excess
cat.	Catalyst	equiv.	Equivalent
CaH_2	Calcium hydride	ESI	Electrospray ionization
CCDC	Cambridge crystallographic data centre	EtOAc	Ethyl acetate
COSY	Correlation spectroscopy	*γ*	*gamma*
J	Coupling constant	HRMS	High resolution mass spectrometry
$CHCl_3$	Chloroform	HPLC	High performance liquid chromatography
CCl_4	Carbon tetrachloride	Hz	Hertz
CH_2Cl_2	Dichloromethane	Halo	Halogen group
$(CH_2Cl)_2$	1,2-Dichloroethane	HCl	Hydrochloric acid

h	Hours	K_2CO_3	Potassium carbonate
^{i}Pr	*iso*-propyl	*p*-TSA	*para*-Toluenesulfonic acid
K	Kelvin	P	Phosphorus
$LiAlH_4$	Lithium aluminium hydride	*p*	*para*
CH_3I	Methyl iodide	Ph	Phenyl
MTPA-Cl	*α*-Methoxy-*α*-(trifluoromethyl)-phenylacetyl chloride	ppm	Parts per million
m	*meta*	*i*-PrOH	*iso*-Propanol
MHz	Mega Hertz	q	Quartet
MS	Molecular sieves	rt	Room temperature
Me	Methyl	NaH	Sodium hydride
m	Multiplet	NaOAc	Sodium acetate
m-CPBA	*meta*-Chloroperoxybenzoic acid	s	Singlet
MP	Melting point	NaOH	Sodium hydroxide
mmol	Milimole	$NaHCO_3$	Sodium bi-carbonate
mL	Mililitre	Na_2CO_3	Sodium carbonate
mg	Miligram	S	Sulfur
N	Nitrogen		
NOESY	Nuclear overhauser enhancement spectroscopy	$PhCH_3$	Toluene
n	Normal	THF	Tetrahydrofuran
NMR	Nuclear magnetic resonance	TsCl	Tosyl chloride
O	Oxygen	$PhCF_3$	*α*,*α*,*α*-trifluorotoluene
o	*ortho*	XRD	X-ray diffraction
o-QMs	*ortho*-Quinone methides		

Abstract

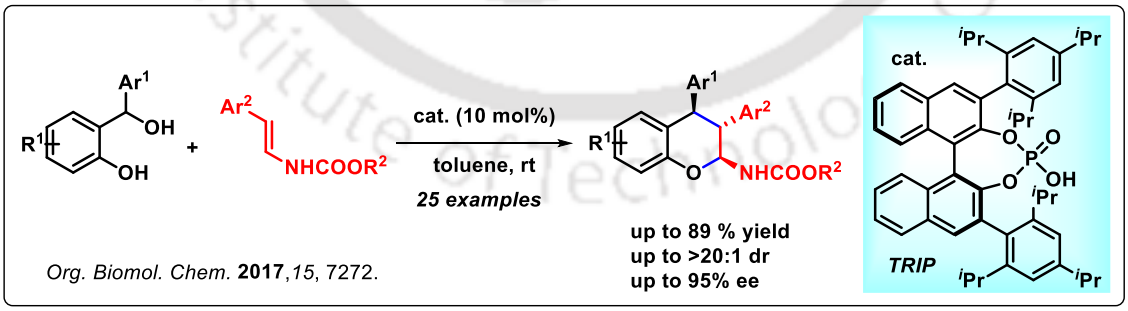
The present thesis, entitled as "***Organocatalytic Asymmetric Addition/Cyclization of Carbon/Sulfur Nucleophiles to in situ-Generated ortho-Quinone Methides***" is divided into five chapters, based on the obtained results of experimental works performed during the complete course of the Ph.D. research period.

ortho-Quinone Methides (*o*-QMs) have been considered as an imperative reactive intermediates in organic and several biological syntheses from long time back. It has wide spectrum of applications in complex natural product synthesis. In recent years, due to its high reactivity *ortho*-quinone Methides were envisaged in a number of asymmetric C-C and C-heteroatom bond formation reactions exclusively.

Chapter I: General Introduction on Asymmetric Organocatalysis and Explorations of *ortho*-Quinone Methides.

This chapter highlights on the basic introduction of asymmetric synthesis, different strategies of asymmetric induction, organocatalysis and its bifunctional applications on *ortho*-quinone methides in a nutshell. Herein, several chiral Brønsted phosphoric acids, thiourea/squaramide catalyzed asymmetric reactions of *ortho*-quinone methides were briefly discussed.

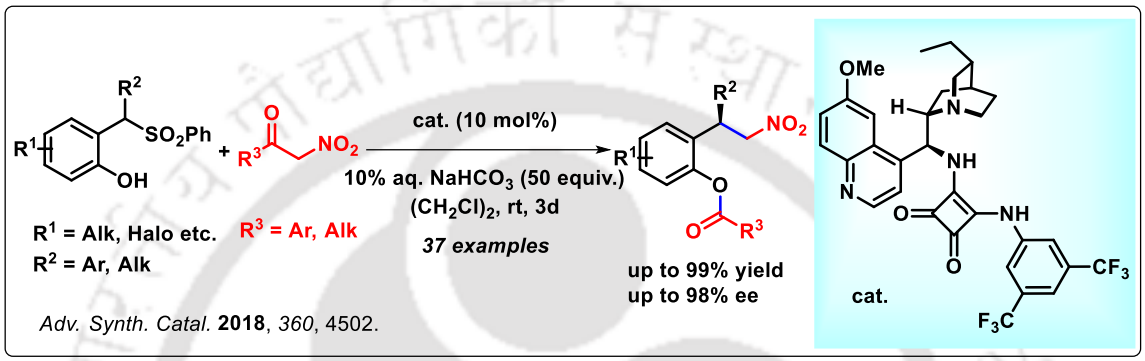
Chapter II: Chiral Phosphoric Acid Catalyzed Enantioselective Annulation of Acyclic Enecarbamates to *in situ*-Generated *ortho*-Quinone Methides.



Chapter II demonstrates highly diastereo- and enantioselective synthesis of tri-substituted chromans having three contiguous stereogenic enters *via* [4+2] cycloaddition of *in situ*-generated *ortho*-quinone methides and acyclic enecarbamates. This was a fascinating catalytic asymmetric reaction where a variety of *ortho*-hydroxybenzyl alcohols and

trans-acyclic enecarbamates were smoothly incorporated in the reaction. The reaction was catalyzed by commercially available chiral TRIP. The mild reaction conditions and operational simplicity are the main feature of this method and which could be applied in natural product synthesis.

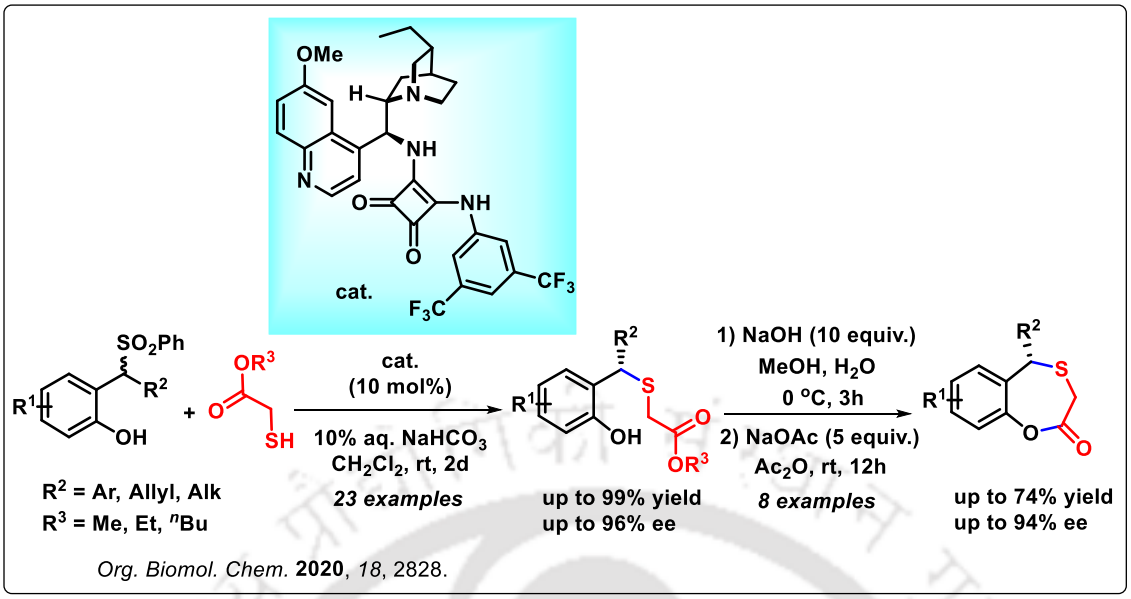
Chapter III: Organocatalytic Asymmetric Domino Michael/acyl Transfer Reaction Between *α*-Nitroketones and *in situ*-Generated *ortho*-Quinone Methides: Route to 2-(1-Arylethyl)phenols.



Chapter III describes first bifunctional squaramide catalyzed an enantioselective acyl transfer sequence for the construction of chiral O-acyl 2-(1-arylethyl)phenols *via* a domino Michael/acyl transfer reaction between *α*-nitroketones and *in situ*-generated *ortho*-quinone methides. Various *ortho*-hydroxybenzyl sulfones and *α*-nitroketones were employed in basic reaction conditions under biphasic medium. Few synthetic transformations were also performed to highlight the potentiality of our method. The reaction conditions are very mild and operationally simple procedure. In general, synthesis of chiral 2-(1-arylethyl)phenols are quite difficult. Thus our methodology would be helpful for chiral 2-(1-arylethyl)phenols synthesis and other natural products.

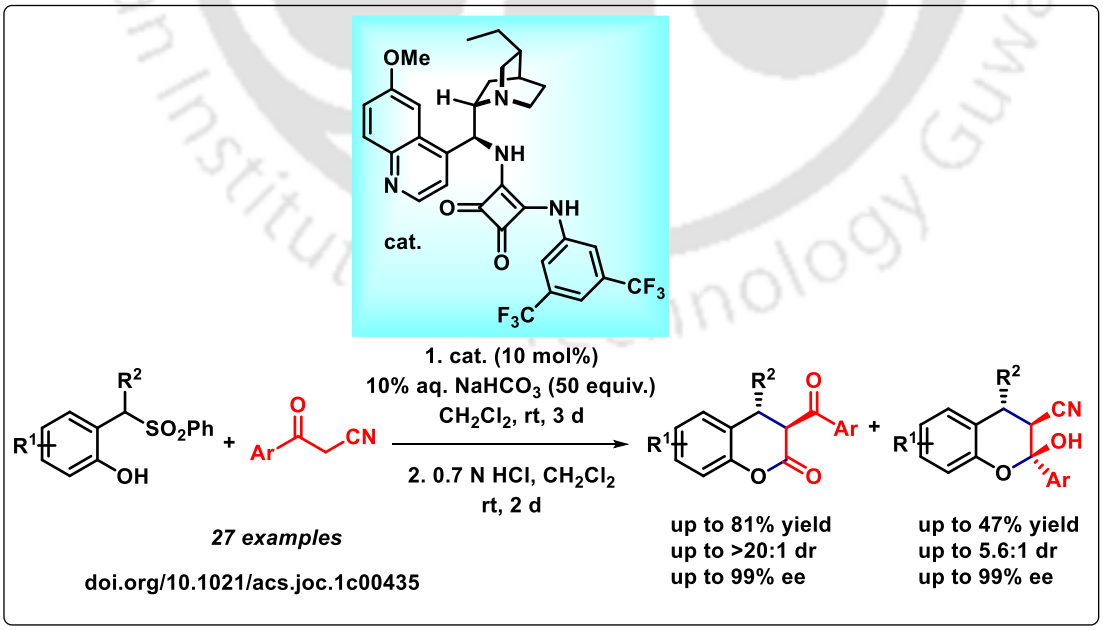
Chapter IV: Organocatalytic Asymmetric Addition of Thioglycolates to *ortho*-Quinone Methides: A Route to 5-Substituted-5*H*-benzoxathiepine-2(3*H*)-ones.

Chapter IV illustrates first enantioselective synthesis of 5-Substituted-5*H*-benzoxathiepine-2(3*H*)-ones *via* cinchona derived squaramide catalyzed asymmetric addition of thioglycolates to *in situ*-generated *ortho*-quinone methides. Various *ortho*-hydroxybenzyl sulfones and alkyl thioglycolates were utilized as the reaction partners to deliver the desired thia-Michael products as well as seven membered heterocyclic benzoxathiepine-2(3*H*)-ones. Wide substrate scope and the important synthetic



applications to diastereo-, enantioselective chiral sulfoxides, sulfone formation are the synthetic potential of this methodology. Although this is an overall three step processes, owing the pharmaceutical significance of benzoxathiepines this might be useful in medicinal industry.

Chapter V: Organocatalytic Asymmetric Addition of Aromatic *α*-Cyanoketones to *ortho*-Quinone Methides: Synthesis of 3,4-Dihydrocoumarins and Tetra-Substituted Chromans.



Chapter V delineates highly diastereo- and enantioselective synthesis of *trans*-3,4-dihydrocoumarins and tetra-substituted chromans *via* an organocatalyzed first asymmetric addition of aromatic *α*-cyanoketones to *in situ*-generated *ortho*-quinone methides. Here also, cinchona derived bifunctional squaramide catalyst was found to be the best catalyst for the activation of substrates under oil/water interface. Broad substrate scope and the reaction scale up are the key features of this methodology. Tetra-substituted chromans were also synthetically transformed to valuable chiral chromenes bearing cyano group. Thus the mild reaction conditions and simple execution might be helpful in biologically significant 3,4-dihydrocoumarins, tetra-substituted chromans and chromenes synthesis.

The individual chapters comprise introduction, previous literature reports, present result and discussion, experimental section, references along with characterization data of products including few selective spectral data. In general, the present thesis depicts organocatalyzed some new and effective asymmetric methodologies for the enantioselective synthesis of various O-acyl 2-(1-arylethyl)phenols and heterocyclic compounds using carbon/sulfur nucleophiles and *in situ*-generated *ortho*-Quinone methides.

General Introduction on Asymmetric Organocatalysis and Explorations of ortho-Quinone Methides

1.1. Brief introduction on asymmetric synthesis:

The term asymmetry means 'lacking of symmetry' in a molecule or an object or anything in nature. There are a lot of examples of chiral objects in nature. They are often not superimposable on their mirror images. Enzymes, proteins, amino acids, carbohydrates, sugars, nucleosides, phospholipids all are chiral. Scientist Louis Pasteur first introduced molecular chirality in nature.[1] Different enantiomers or diastereomers of a molecule often have dissimilar properties i.e. taste, odour, medicinal properties etc. (Figure 1). For example, (*S*)-limonene gives lemon smell whereas its opposite enantiomer (*R*)-limonene provides orange smell. Similarly, (*R*)-thalidomide is an effective drug to calm nervousness however (*S*)-thalidomide shows teratogenic effect during pregnancy. Thus synthesis of simple to complex chiral molecules in pure form and development of various tactics, concepts are highly desirable in pharmaceutical industry as well as in organic synthesis.

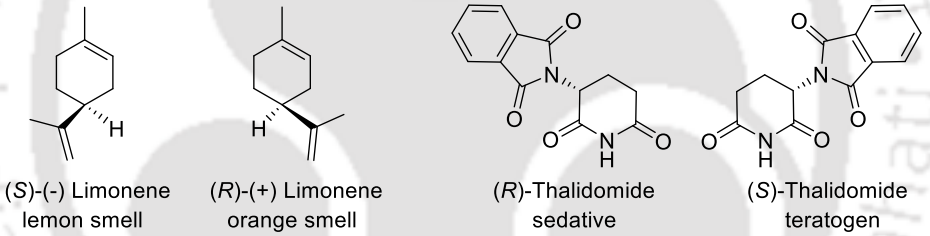


Figure 1. Enantiomeric pairs having different properties.

Asymmetric synthesis is the reaction protocol which introduces chirality on prochiral centres present in a molecule under chiral atmosphere. In this regard, chemists have given special attention in the advancement of multiple asymmetric techniques from long back. Modes of asymmetric synthesis can be classified mainly into four categories: a) substrate controlled approach, b) reagent controlled approach, c) auxiliary controlled and d) catalyst controlled mode. Among them, the first three processes require expensive chiral substrates, reagents in stoichiometric amounts and also involves addition, elimination of chiral auxiliaries. Whereas catalytic asymmetric synthesis is one of the most acceptable, economical and sustainable tool for chirality induction. Again, catalytic asymmetric synthesis is of three types depending upon the catalysts employed i.e. a) Biocatalysis[2] b) Transition metal catalysis[3] and c) Organocatalysis[4].

1.2. Asymmetric organocatalysis:

Organocatalysts are the bench stable organic molecules which have the ability to accelerate several organic transformations. And the field of chemistry with chiral organocatalysts is called asymmetric organocatalysis. In comparison to biocatalysts and transition metal catalysts, use of chiral organocatalysts in catalytic asymmetric synthesis is much advantageous as they are easy to prepare and handle, nontoxic, not too much air sensitive and totally metal free process. Depending upon their mode of activations with the reactants, in general organocatalysis can be classified into three categories: a) Covalent catalysis[5] (Iminium catalysis, Enamine catalysis, SOMO catalysis), b) Non covalent catalysis[6,7] (Hydrogen bonding catalysis, Phase transfer catalysis etc.), c) Cooperative ion pair catalysis[8] (Figure 2).

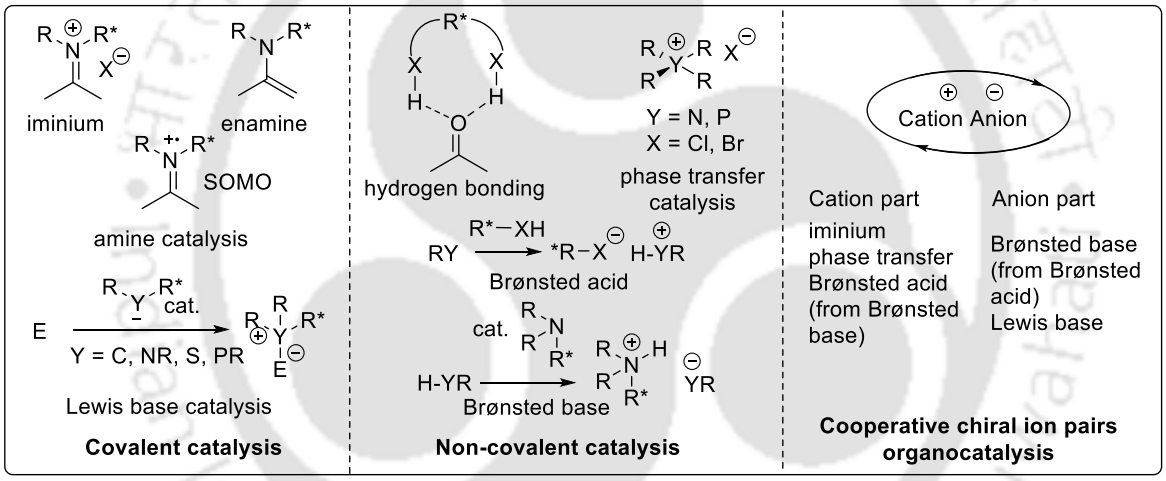


Figure 2. Types of organocatalysis.

1.3. Hydrogen bonding catalysis:

Hydrogen bonding catalysis is one of the important strategies in the area of non-covalent asymmetric organocatalysis. This catalysis has important applications in the molecular recognition and also plays a major part in organocatalytic enantioselective chemical reactions.[6] Thus it became interesting for the synthetic community to make this field more advanced. BINOL-based chiral phosphoric acids,[9] cinchona alkaloids,[10] thiourea,[11] urea[12] and squaramides[13] are the prominent examples of bifunctional hydrogen bonding catalysts having both Brønsted acidic and Lewis basic sites simultaneously within a same molecule (Figure 3). Therefore, synergistic dual activation of electrophile and nucleophile is possible

through hydrogen bond formation to promote a large number of stereoselective transformations.

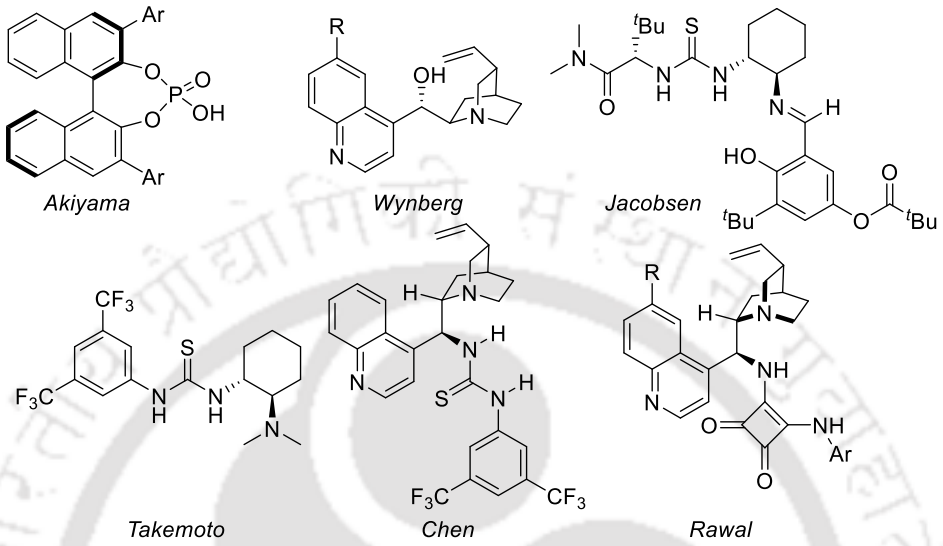
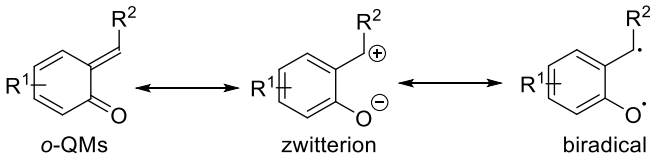


Figure 3. Representative examples of hydrogen bonding chiral organocatalysts.

1.4. Introduction on *ortho*-quinone methides (*o*-QMs):

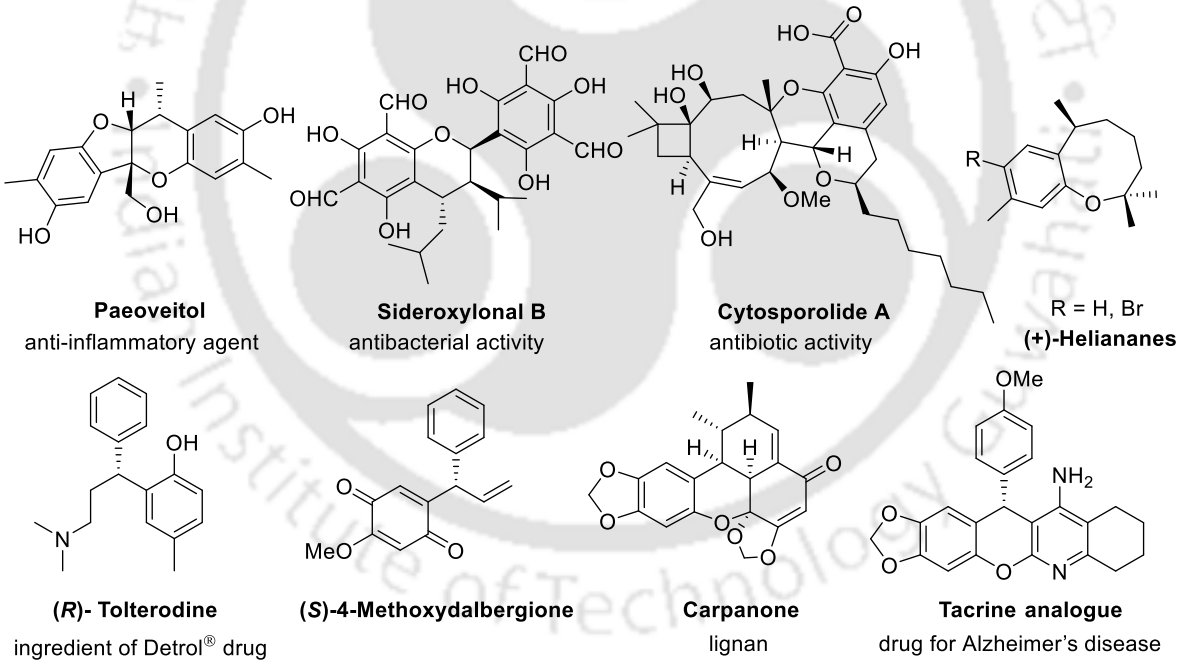
ortho-Quinone methides (*o*-QMs) are highly reactive intermediates and a distinct class of reagents unlike other reactive species such as: carbocation, carbenes, radicals, simple enones etc. It consists of a nonaromatic cyclohexadiene core accompanied by a carbonyl group and a vicinal exocyclic alkylidiene motif (Scheme 1). *o*-QMs are generally neutral species although it can exist in zwitterion and biradical forms. Existence of such short-lived intermediates was characterized for the first time by Vaisserman and co-workers from the crystal structure of *o*-QMs trapped Cp*Ir complex.[14] Instability of this species arises from the thermodynamically disfavoured dearomative system.



Scheme 1. Structural depiction of *ortho*-quinone methides.

1.4.1. Practical significance of *ortho*-quinone methides:

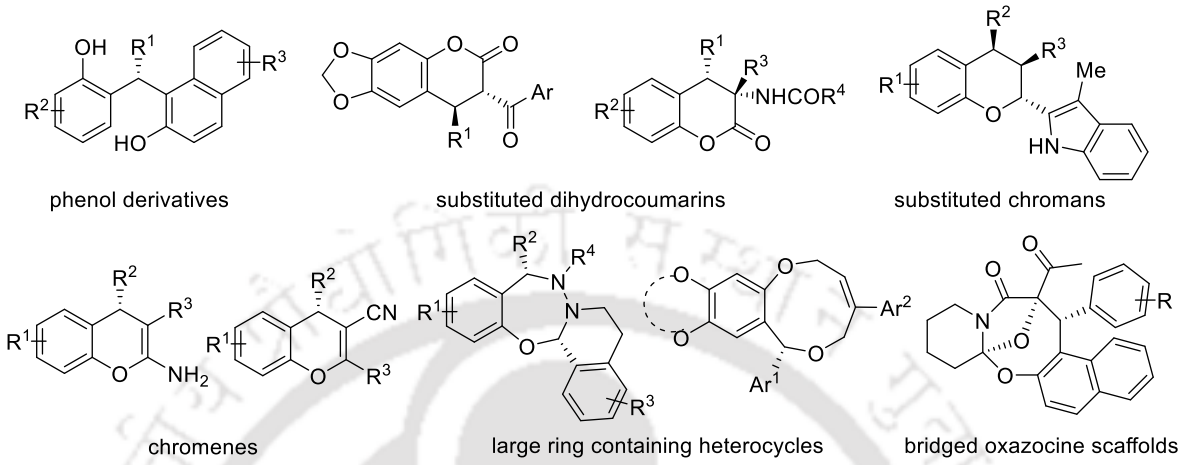
Over the years, *ortho*-quinone methides have established itself as one of the important synthetic intermediates in organic synthesis and material chemistry and also in biological processes.[15] Because of the presence of dearomative 1,4-conjugate system it behaves as an excellent Michael acceptor. It has been envisaged as an intermediate in the synthesis of many useful complex natural products and several drug molecules (Scheme 2).[15c] For example, paeoveitol is an important norditerpene natural product responding anti-inflammation, immunomodulation and hypoglycaemic activities, which could be synthesized in a biomimetic racemic as well as asymmetric [4+2] cycloaddition reaction between benzofuran alcohol and *ortho*-quinone methides.[16] Also, *o*-QMs intermediates have been actively engaged in the total synthesis of other natural products such as: sideroxylonal B,[17] cytosporolides A,[18] (+)-helianes,[19] (*R*)-tolterodine,[20] (*S*)-4-methoxydalbergione,[21] carpanone,[22] tacrine analogue[23] etc.



Scheme 2. Selected natural products and bioactive molecules synthesized from *o*-QMs.

In addition to the natural products and drug candidate synthesis, *ortho*-quinone methides, an impressive class of substrates have been employed in a number of asymmetric and nonasymmetric transformations for the construction of structurally diverse frameworks and building blocks such as: phenol derivatives, substituted dihydrocoumarins, 4-*H*-chromenes,

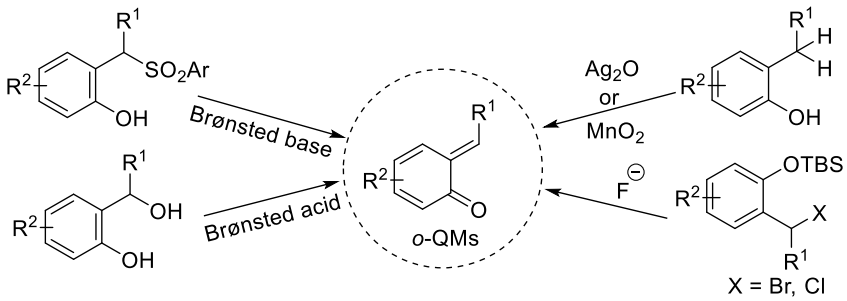
substituted chromans, large ring containing heterocycles[24] and oxa-bridged oxazocine scaffolds[25] synthesis etc. (Scheme 3).



Scheme 3. Diverse applications of *ortho*-quinone methides.

1.4.2. Various precursors of *ortho*-quinone methides for *in situ*-generation:

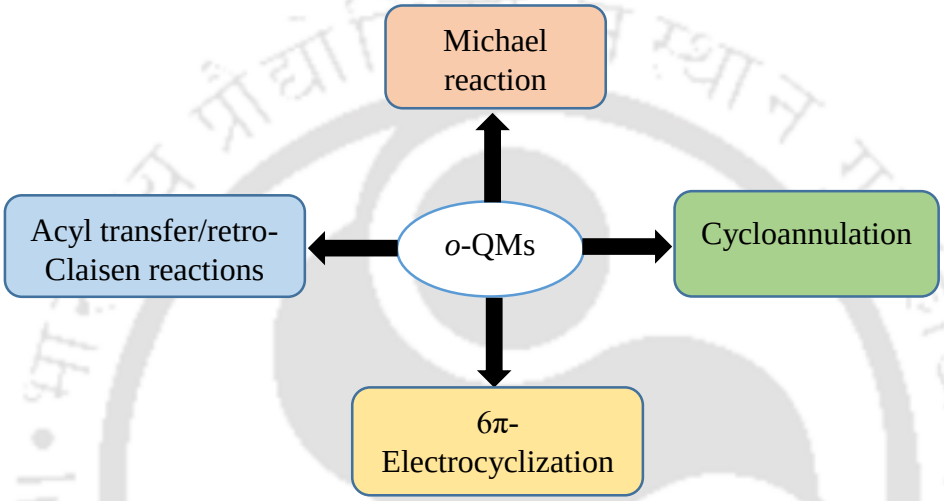
In earlier age, its applications were limited solely to stabilized *ortho*-quinone methides possibly due to transient nature of these intermediates. Despite long history of *ortho*-quinone methides, the catalytic asymmetric versions have only been realized in recent years after innovation of suitable precursors like: *ortho*-hydroxybenzyl alcohols, *ortho*-hydroxybenzyl sulfones, TBS-protected *ortho*-hydroxybenzyl bromide derivatives and others (Scheme 4). For the first two substrates, catalytic amounts of Brønsted acids and Brønsted bases respectively are helpful to generate *o*-QMs *in situ*. Whereas, to initiate the same, stoichiometric amount of fluoride source is necessary for TBS-protected *ortho*-hydroxybenzyl bromides. Also, *o*-QMs can be produced *in situ* through metal mediated benzylic oxidation of 2-alkylphenols.



Scheme 4. Stable precursors of *o*-QMs and theirs *in situ*-generation strategies.

1.4.3. Types of reactions with *ortho*-quinone methides:

ortho-Quinone methides have been effectively engaged in various metal catalyzed and bifunctional organocatalytic asymmetric as well as racemic C-C, C-N, C-S and C-P bond forming reactions. The unique reactivity and high electrophilicity of *ortho*-quinone methides led to a variety of enantioselective Michael reactions, [4+n] cycloannulations, 6π-electrocyclizations and retro-Claisen reaction to accomplish valuable compounds (Scheme 5).



Scheme 5. Different types of reactions with *ortho*-quinone methides.

1.5. Background literature study:

The initial important contributions have been documented by the groups of Sigman,[26] Lectka,[27] Schaus,[28] Ye[29] and Scheidt[30] respectively on enantioselective palladium-, cinchona alkaloid-, BINOL-, and NHC catalysis with *ortho*-quinone methides. Very recently, Guo and co-workers demonstrated palladium-catalyzed another asymmetric methodology using stabilized *ortho*-quinone methides.[31] NHC-catalyzed another important [4+2] cyclization employing *o*-QMs and carboxylic acid derivatives was reported by Yao group.[32] Feng *et al*. described chiral *N*,*N'*-dioxide ligand-Sc(III) metal complex catalyzed enantioselective reaction between *ortho*-hydroxy benzyl alcohols and C3-substituted-*N*-protected indoles.[33] Also, phosphine catalysis with *ortho*-quinone methides have been illustrated independently by Wang,[34] Waser[35] and Shi[36] groups. Furthermore, Hoshino and Honda group disclosed organophotoredox catalyzed [4+2] cycloaddition reaction between

ortho-quinone methides and styrenes.[37]

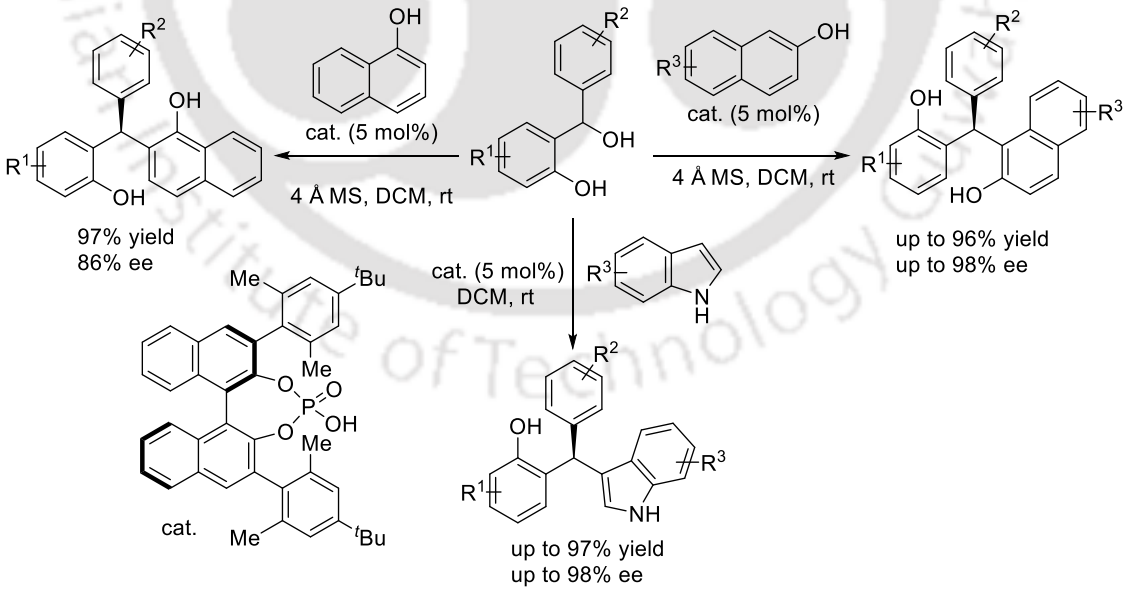
In this particular chapter, the recent explorations of *ortho*-quinone methide intermediates in catalytic asymmetric synthesis using chiral bifunctional organocatalysts have been briefly described.

1.5.1. Chiral phosphoric acid catalyzed asymmetric reactions employing *o*-QMs:

Parallel to the metal-, NHC-, and Lewis acid catalysis, chiral Brønsted acids have emerged applications in organocatalytic enantioselective reactions. In this regard, a plenty of reactions with *o*-QMs had been established using chiral phosphoric acids as the organocatalysts.

1.5.1.1. Enantioselective conjugate addition reactions:

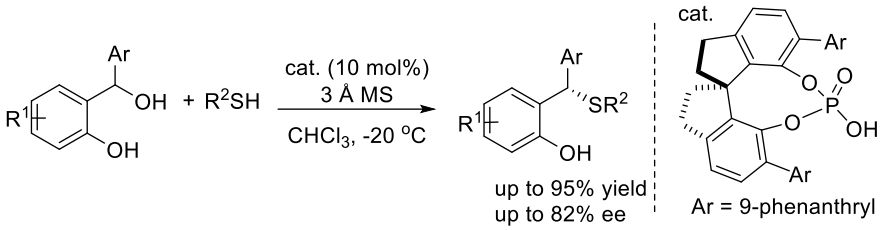
In 2015, Schneider and co-workers reported an asymmetric conjugate addition of electron rich arenes such as: naphthols, indoles to *in situ*-generated *ortho*-quinone methides.[38] Using 5 mol% of phosphoric acid catalyst, a range of chiral phenols were synthesized in high yields and enantioselectivities (Scheme 6).



Scheme 6. Phosphoric acid catalyzed enantioselective C-C bond forming reaction.

In the next year, Sun group disclosed spirophosphoric acid catalyzed conjugate addition reaction between *ortho*-hydroxybenzyl alcohols and thiols at -20 ^{o}C temperature.[39]

Herein, desired products were achieved with moderate enantiomeric excesses (Scheme 7).

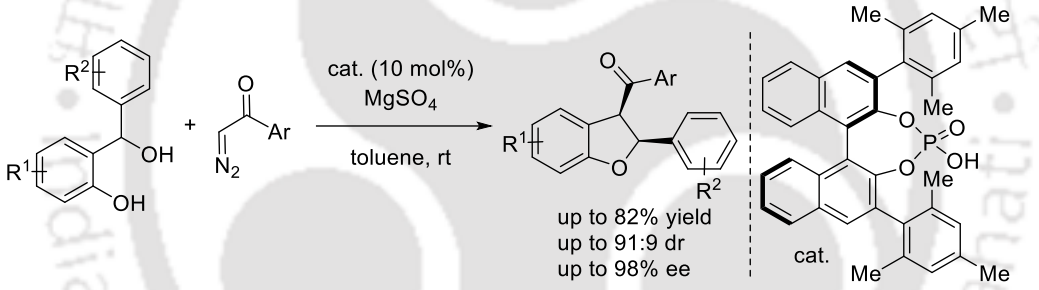


Scheme 7. Phosphoric acid catalyzed enantioselective C-S bond forming reaction.

1.5.1.2. Enantioselective addition/cycloannulation reactions:

1.5.1.2.1. *Enantioselective [4+1] cyclization reaction:*

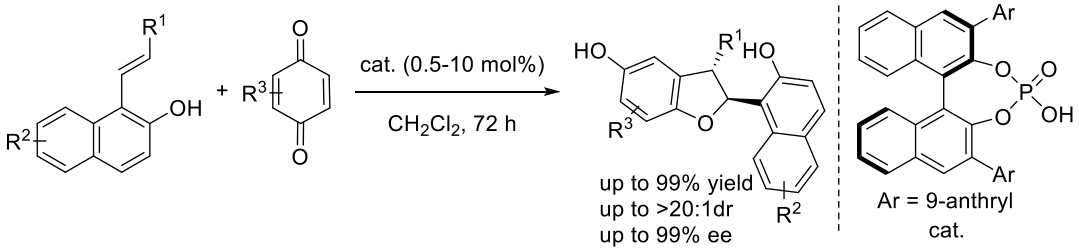
Various *ortho*-hydroxybenzyl alcohols and diazoarylketones were reacted in an enantioselective [4+1] cycloannulation protocol to deliver *cis*-2,3-dihydrobenzofurans by Schneider *et al*. (Scheme 8).[40] With 10 mol% of chiral phosphoric acid catalysts, products were obtained in moderate to good yields and with excellent enantioselectivities.



Scheme 8. Asymmetric [4+1] cycloannulation of diazoarylketones to *in situ*-generated *o*-QMs.

1.5.1.2.2. *Enantioselective [3+2] cyclization reaction:*

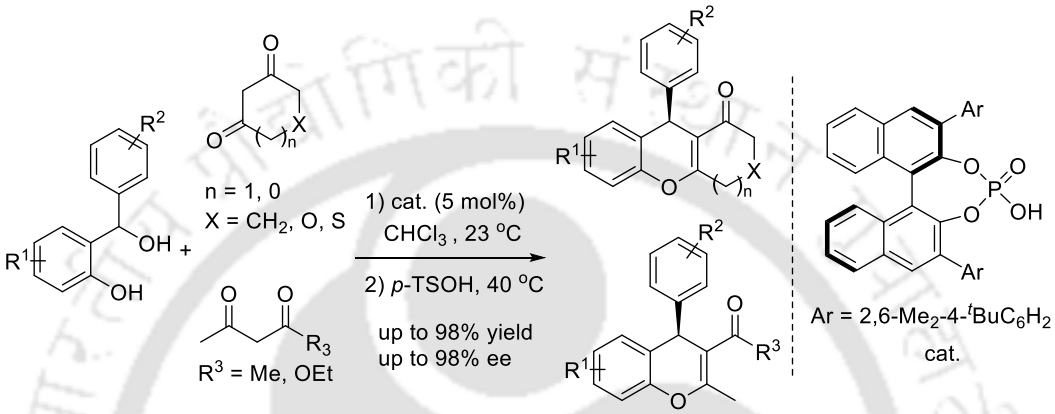
Chen and Zhou and co-workers recently demonstrated chiral phosphoric acid catalyzed an effective asymmetric [3+2] cycloaddition strategy for the synthesis of *trans*-2,3-diarylbenzofurans (Scheme 9).[41] 1-Styrylnaphthols and *para*-quinones were smoothly converted to the products with excellent diastereo- and enantioselectivities.



Scheme 9. Enantioselective [3+2] cyclization using 1-styrylnaphthols and *para*-quinones.

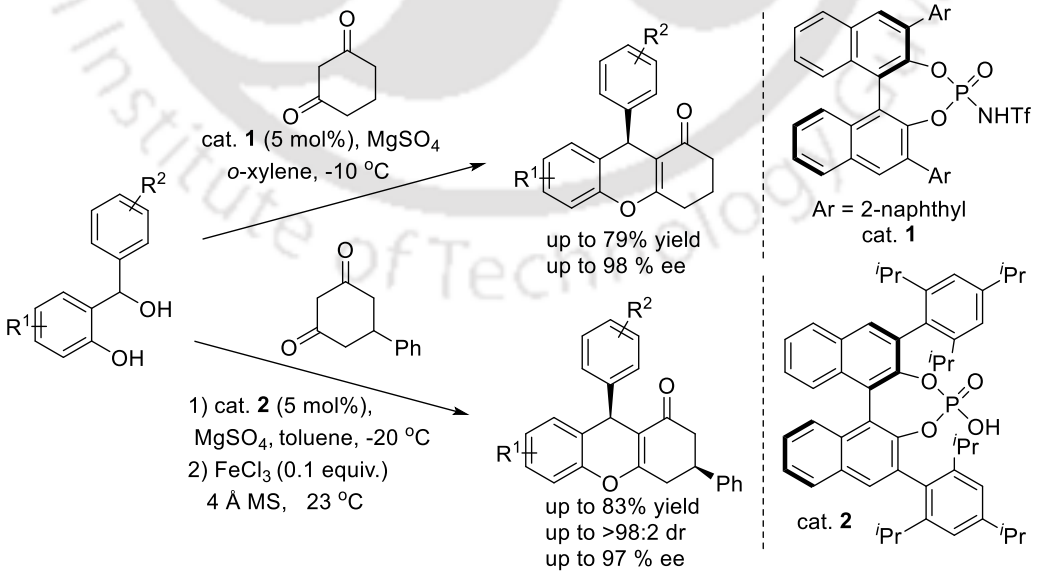
1.5.1.2.3. ***Enantioselective [4+2] cyclization reactions:***

In 2014, Schneider *et al*. successfully anticipated phosphoric acid catalyzed enantioselective [4+2] cyclization reaction between *in situ*-generated *o*-QMs and *β*-dicarbonyl compounds (Scheme 10).[42] Although, it was overall two steps process, varieties of 4-aryl-4*H*-chromenes were achieved in high yields and with high enantiomeric excesses.



Scheme 10. Enantioselective [4+2] cyclization using *in situ*-generated *o*-QMs and *β*-dicarbonyls.

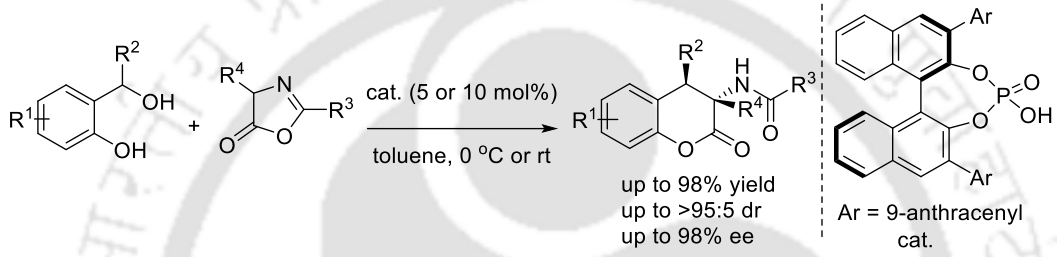
In the same year, Rueping and co-workers independently described an alternative method for one step synthesis of highly enantiopure 4-aryl-4*H*-chromenes bearing one stereo centre using chiral *N*-triflyphosphoramide as a stronger Brønsted acid catalyst (Scheme 11).[43]



Scheme 11. Enantio-, diastereoselective [4+2] cyclization using *in situ*-generated *o*-QMs and 1,3-cyclohexanediones.

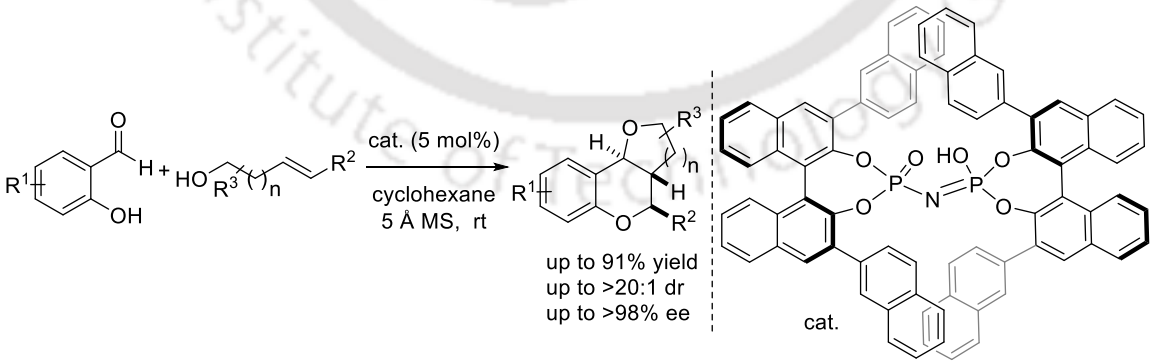
Herein, authors also disclosed TRIP catalyzed exciting desymmetrization reaction between *meso*-5-substituted-1,3-cyclohexadiones and *in situ*-generated *o*-QMs. Chromene products containing two distant stereo centres were obtained in high diastereo- and enantioselectivities (Scheme 11).[43]

Chiral phosphoric acid catalyzed [4+2] cycloaddition of *in situ*-generated *ortho*-quinone methides and azlactones had been published by Chen and co-workers in 2016 (Scheme 12)[44] and fruitful results in terms of diastereomeric ratios and enantiomeric excesses were attained for a variety of highly substituted dihydrocoumarins with contiguous tertiary and quaternary chiral centres.



Scheme 12. Stereoselective [4+2] cycloaddition using *in situ*-generated *o*-QMs and azlactones.

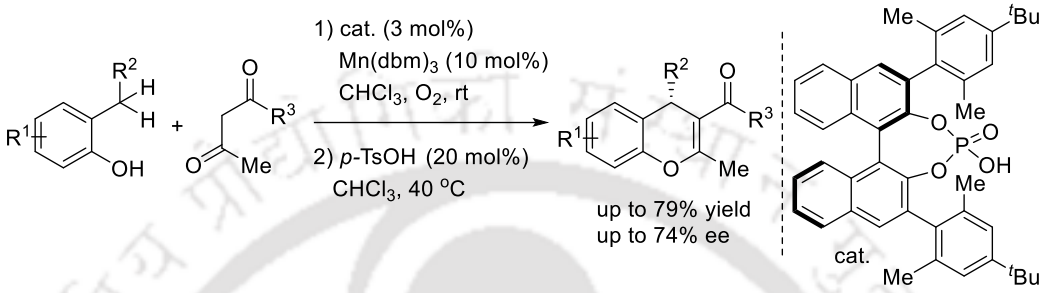
In 2017, imidodiphosphoric acid catalyzed an important intramolecular [4+2] cycloaddition of *in situ*-generated *ortho*-quinone methides had been reported by List *et al*. (Scheme 13).[45] Structurally complex furanochromane and pyranochromane products were synthesized with high level of stereoselectivities starting from salicyldehydes and dienyl alcohols exclusively.



Scheme 13. Asymmetric intramolecular [4+2] cycloaddition of *in situ*-generated *o*-QMs.

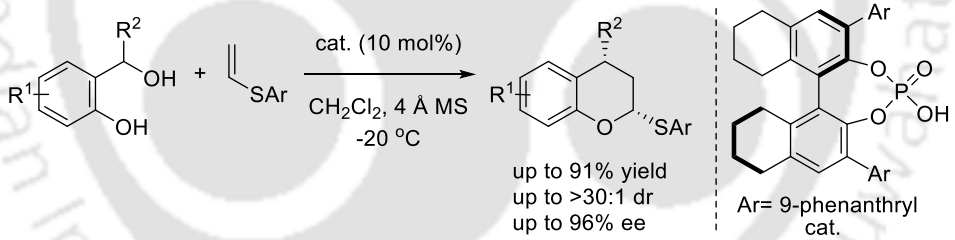
In the same year, Schneider group demonstrated one alternative asymmetric approach for the synthesis of 4*H*-chromenes by reacting 2-alkyl substituted phenols with *β*-dicarbonyls

using relay catalysis and in successive two steps (Scheme 14).[46] Herein, catalytic amount of $Mn(dbm)_3$ and chiral phosphoric acid as a whole were responsible for generation of *ortho*-quinone methide intermediates *in situ* and consequent chirality induction. Although, this methodology provided good yields, enantioselectivities were moderate.



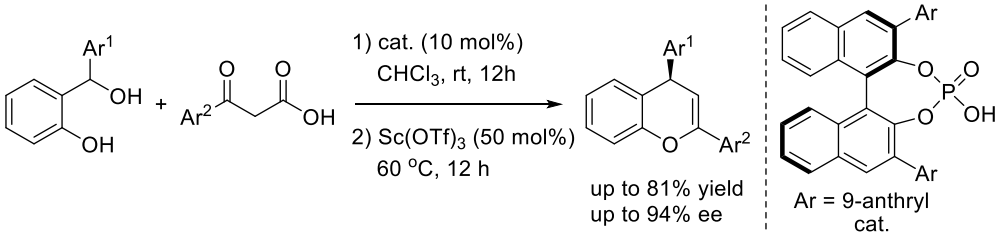
Scheme 14. Mn(III)phosphate catalyzed asymmetric reaction of 2-alkyl substituted-phenols and *β*-dicarbonyls.

Also, Sun group recently presented phosphoric acid catalyzed an effective route for diastereo- as well as enantioselective synthesis of 2,4-disubstituted chromanes from [4+2] cycloaddition of *in situ*-generated *o*-QMs and vinyl sulfides (Scheme 15).[47]



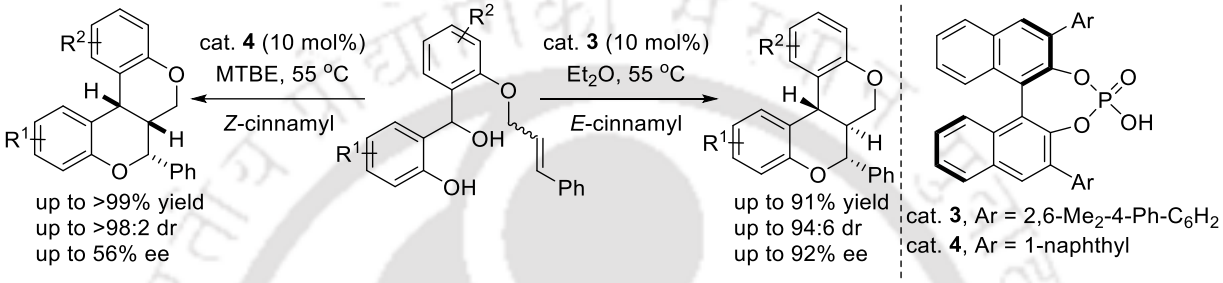
Scheme 15. Stereoselective [4+2] cycloaddition of *in situ*-*o*-QMs and vinyl sulfides.

Chiral phosphoric acid catalyzed another significant contribution was emanated from Kim *et al*. in 2018.[48] *β*-Keto acids were successfully engaged with *in situ*-generated *o*-QMs *via* enantioselective decarboxylative addition/cyclization followed by dehydration to deliver optically active 2,4-diaryl-1-benzopyrans (Scheme 16). Though, it was overall two steps process, reaction outcome was excellent in terms of yields and enantiomeric excesses.



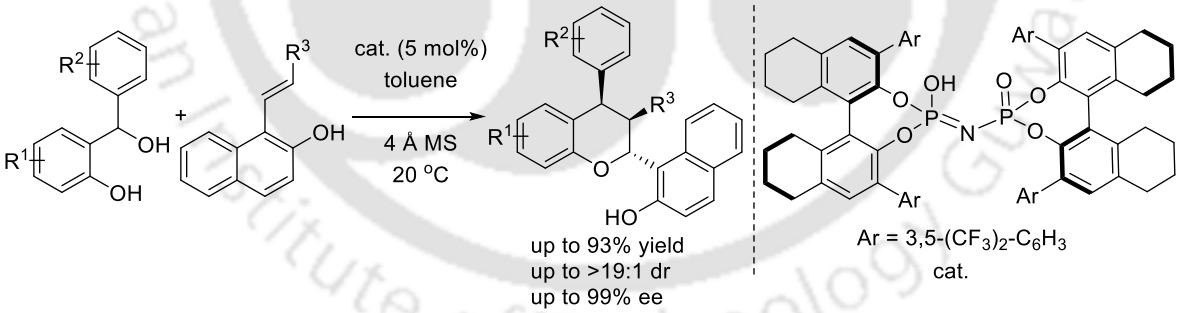
Scheme 16. Enantioselective decarboxylative addition/cyclization/dehydration of *β*-Keto acids with *in situ*-generated *o*-QMs.

Again, Schneider and co-workers narrated an asymmetric intramolecular [4+2] hetero-Diels-Alder reaction of *in situ*-generated *o*-QMs with unactivated (*E*)- and (*Z*)- olefins (Scheme 17).[49] Using suitable chiral phosphoric acid catalyst and solvent, both dihydrochromenochromene products were obtained in high yields and with high diastereomeric ratios along with moderate to excellent enantioselectivities.



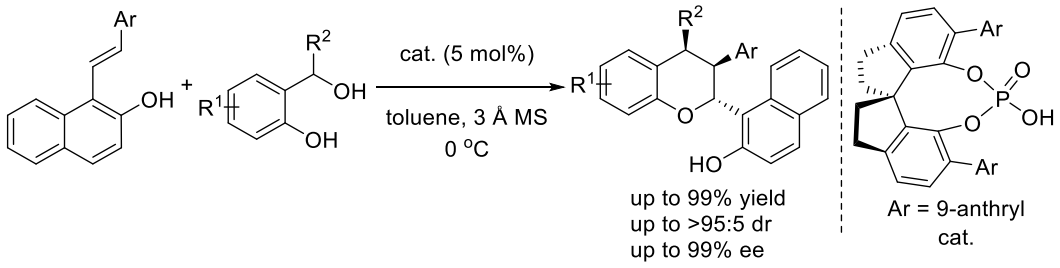
Scheme 17. Asymmetric intramolecular [4+2] hetero- Diels-Alder reaction of *o*-QMs.

H_8-BINOL based imidodiphosphoric acid catalyzed stereoselective [4+2] hetero-Diels-Alder reaction between *in situ*-generated *o*-QMs and (*E*)-1-styrylnaphthols had been developed by Zhang *et al*. in 2019 (Scheme 18).[50] Herein, *trans-cis*- trisubstituted chroman products were achieved in high diastereo- and excellent enantioselectivities.



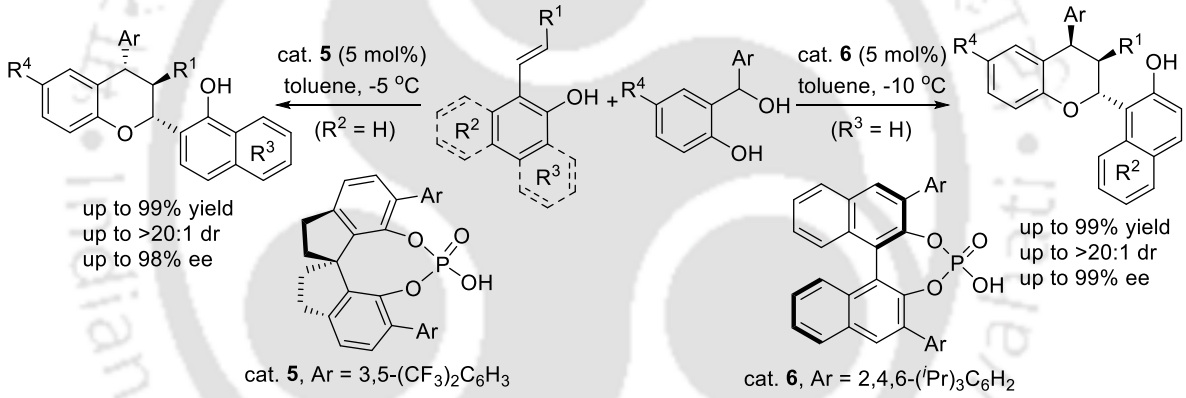
Scheme 18. Stereoselective [4+2] cycloaddition of *o*-QMs and (*E*)-1-styrylnaphthols.

In the next year, You and Yuan and co-workers disclosed the similar reaction earlier stated by Zhang group but the reaction was carried out obvious with different catalyst and different reaction conditions (Scheme 19).[51] Herein, authors have used 9-anthryl based chiral spirocyclicphosphoric acid as the catalyst. *trans-cis*- Trisubstituted chromanes were obtained with high dr and excellent enantiomeric excesses. Also, they extended the scope by performing the reaction with *para*-quinone methides.



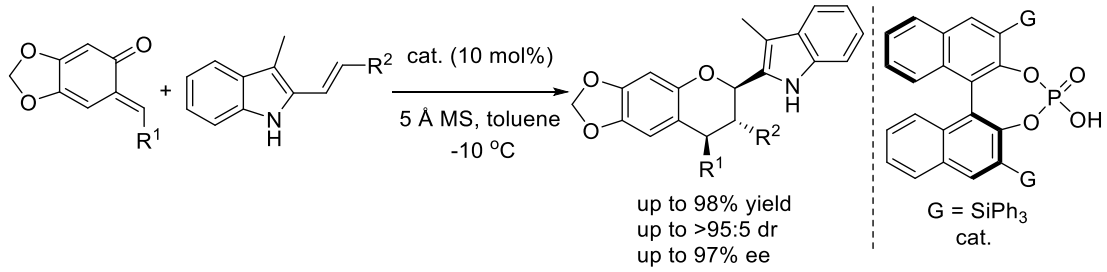
Scheme 19. Stereoselective [4+2] cycloaddition of *in situ*-generated *o*-QMs and 1-((2-aryl)vinyl)-naphthalen-2-ols.

In the same year, Deng and Shao group reported another efficient route for diastereo-enantioselective synthesis of both *trans-cis*- as well as *trans-trans*- 2,3,4-trisubstituted chromanes from a stereoselective [4+2] cycloaddition reaction of *in situ*-generated *o*-QMs and 1-alkenyl-2-naphthols/2-alkenyl-1-naphthols respectively (Scheme 20).[52]



Scheme 20. Stereoselective synthesis of *trans-cis*- and *trans-trans*-2,3,4-trisubstituted chromanes *via* [4+2] cycloaddition.

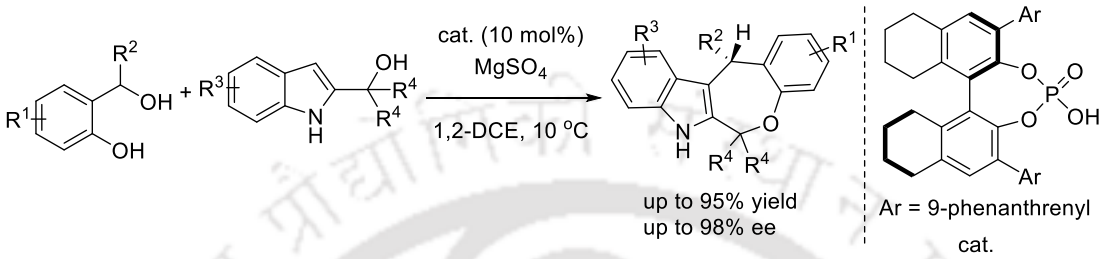
Very recently, Zhang, Zheng and Shi group reported chiral phosphoric acid catalyzed another asymmetric [4+2] cycloaddition reaction using sesamol based stabilized *ortho*-quinone methides and 3-methyl-2-vinylindoles (Scheme 21).[53]



Scheme 21. Asymmetric [4+2] cycloaddition reaction between stabilized *o*-QMs and 3-methyl-2-vinylindoles.

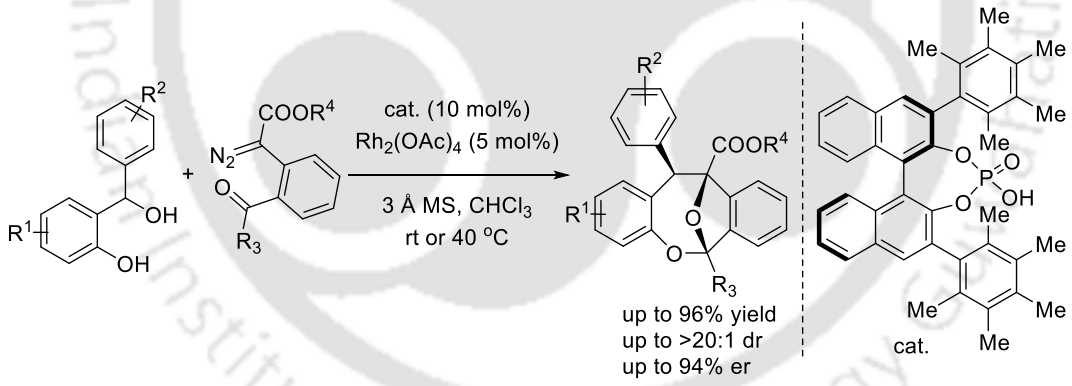
1.5.1.2.4. ***Enantioselective [4+3] cyclization reactions:***

Jiao and Shi and co-workers recently explored a fascinating asymmetric [4+3] cyclization reaction between *in situ*-generated *o*-QMs and 2-indolylmethanols (Scheme 22).[54] With10 mol% of chiral Brønsted acid catalyst loading, a variety of seven membered heterocycles were constructed in excellent enantioselectivities.



Scheme 22. Enantioselective [4+3] cyclization of *o*-QMs with 2-indolylmethanols.

Very recently, Schneider *et al*. anticipated another catalytic asymmetric [4+3] cyclization of *in situ*-generated *o*-QMs and carbonyl ylides (Scheme 23).[55] Cooperative rhodium (II)/phosphoric acid catalysis led to the development of oxa-bridged dibenzooxacines in high diastereo- and enantioselectivities.



Scheme 23. Diastereo-, enantioselective [4+3] cyclization of *o*-QMs with carbonyl ylides.

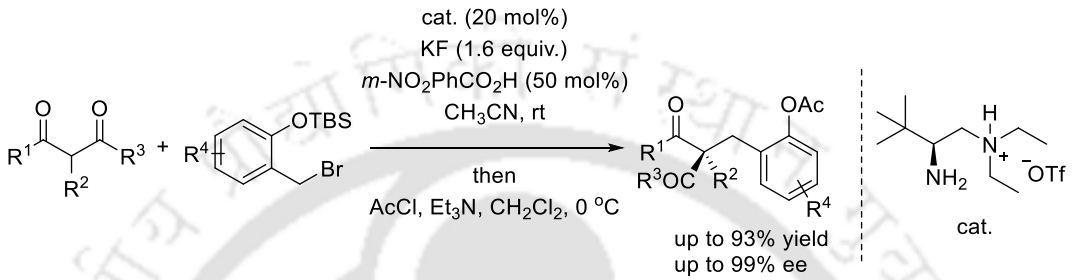
1.5.2. Chiral amine catalyzed asymmetric reactions employing *o*-QMs:

Parallel to the Brønsted acid catalysis, chiral Brønsted base catalysts also have pivotal role in the asymmetric transformations of *ortho*-quinone methides. Various cinchona alkaloids derived bifunctional organocatalysts and other chiral amine catalysts have immense applications in a number of C-C, C-S, C-P bond forming conjugate addition, cycloannulation reactions.

1.5.2.1. Enantioselective conjugate addition reactions:

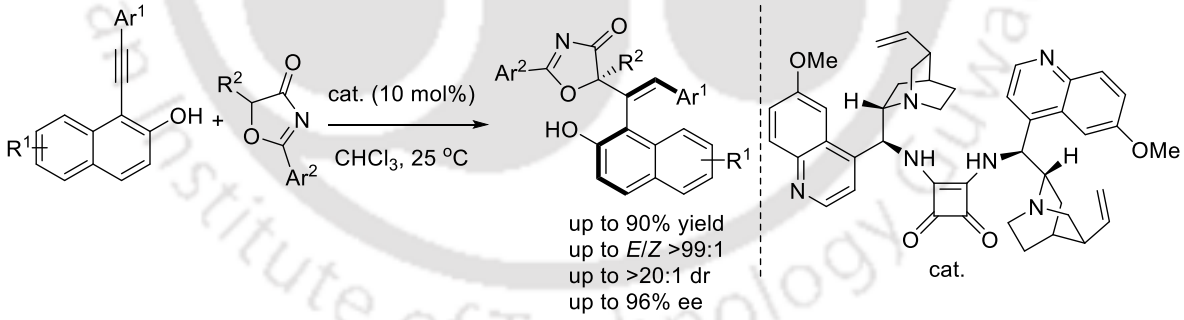
1.5.2.1.1. *Enantioselective carbon-carbon bond forming reactions:*

For example, Luo and co-workers fruitfully engaged *β*-keto carbonyls into *in situ*-generated *o*-QMs in an enantioselective conjugate addition with the help of dual catalytic activations i.e. enamine catalysis and Lewis base activation (Scheme 24).[56]



Scheme 24. Enantioselective addition of *β*-keto carbonyls to *in situ*-generated *o*-QMs.

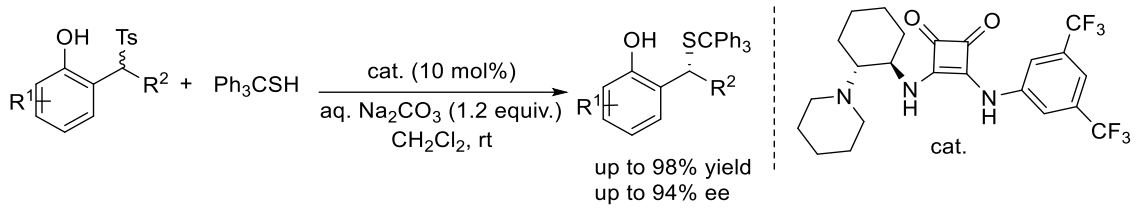
In 2019, Liu, Yan and Li group developed quinine derived bifunctional squaramide catalyzed efficient strategy for the synthesis of axially chiral styrenes (Scheme 25).[57] Here, in the presence of a chiral organocatalyst, racemic 5*H*-oxazol-4-ones smoothly reacted with vinylidene *ortho*-quinone methides to furnish the desired products with high amounts of *E*/*Z*-, diastereo- and enantioselectivities.



Scheme 25. Bifunctional squaramide catalyzed synthesis of axially chiral styrenes.

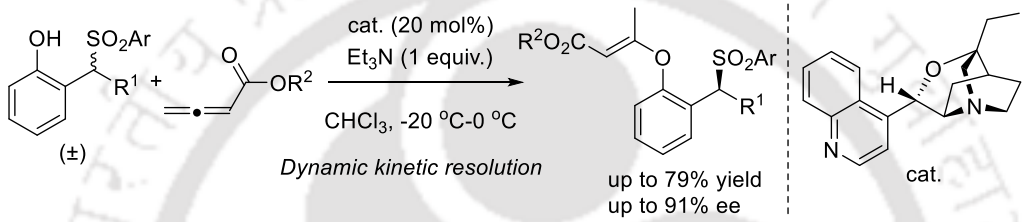
1.5.2.1.2. *Enantioselective carbon-sulfur bond forming reactions:*

Cyclohexyl diamine derived bifunctional squaramide catalyzed asymmetric thiolation of trityl thiol to *in situ*-generated *ortho*-quinone methides had been reported by Li *et al.* (Scheme 26).[58] A range of optically active benzyl mercaptans were synthesized with excellent yields and enantioselectivities.



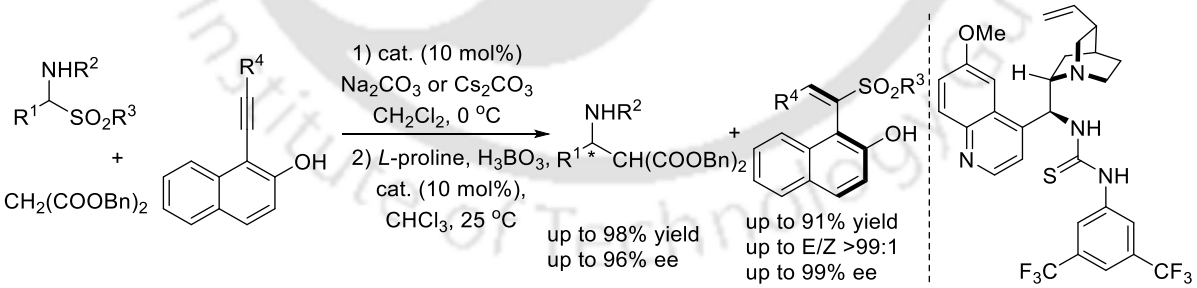
Scheme 26. Enantioselective tritylthiol addition to *in situ*-generated *o*-QMs.

In 2017, Liu and Li group disclosed a dynamic kinetic resolution (DKR) of racemic 2-sulfonylalkyl phenols with allenic esters using 1 equivalent of triethylamine base and catalytic amount cinchona-based catalyst to deliver highly enantiopure benzylic sulfones (Scheme 27).[59]



Scheme 27. DKR of (+/-)-2-sulfonylalkyl phenols with allenic esters.

In the next year, Yan *et al*. described quinine derived thiourea catalyzed enantioselective synthesis of sulfone bearing axially chiral styrenes and *β*-amino diesters from the one pot reactions of *α*-amido sulfones with dibenzyl malonate and waste sulfonate salt with vinylidene *ortho*-quinone methides respectively (Scheme 28).[60] This was totally an atom economical reaction and high selectivities were attained for both products.

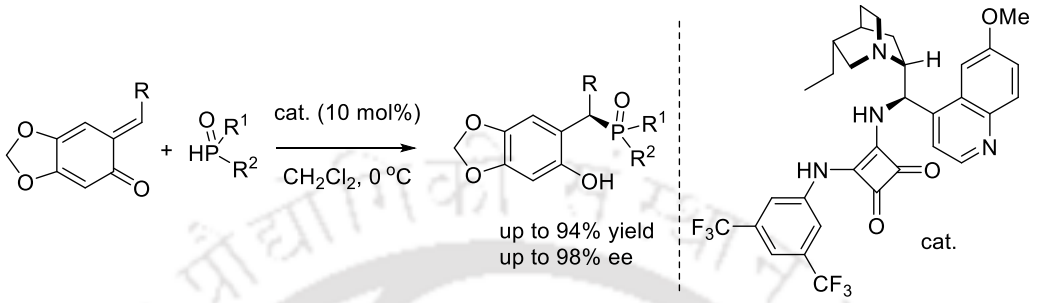


Scheme 28. Asymmetric synthesis of sulfone bearing axially chiral styrenes and *β*-amino diesters.

1.5.2.1.3. *Enantioselective carbon-phosphorus bond forming reaction:*

Hydroquinidine derived bifunctional squaramide catalyzed an enantioselective hydrophosphination reaction between *o*-QMs and H-phosphine oxides had been established

by Jiang and co-workers (Scheme 29).[61] Optically active *α*-arylmethyl phosphine oxides were obtained in high yields and with excellent enantioselectivities. This was only one asymmetric report of *o*-QMs involving carbon-phosphorus bond formation.

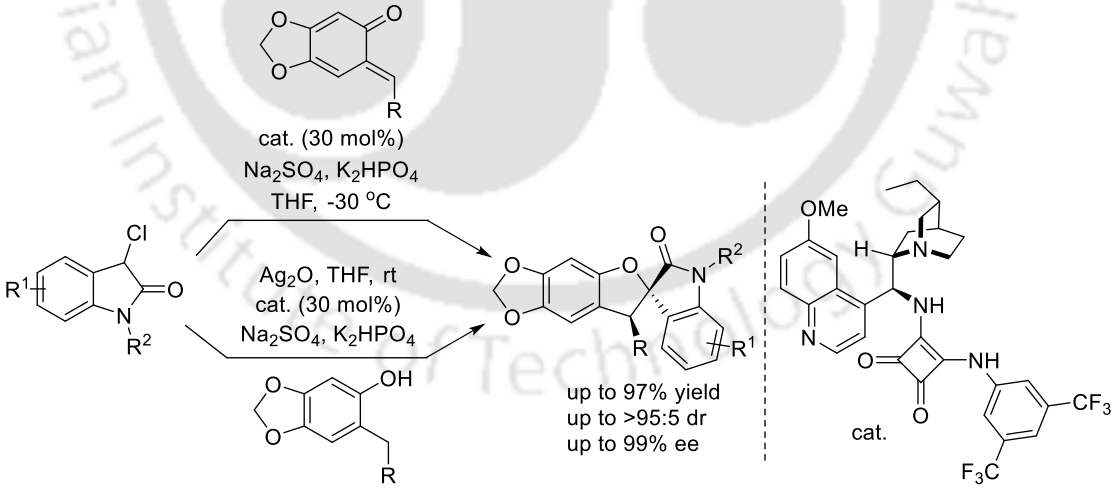


Scheme 29. Enantioselctive hydrophosphination of *o*-QMs.

1.5.2.2. Enantioselective addition/cycloannulation reactions:

1.5.2.2.1. *Enantioselective [4+1] cyclization reactions*:

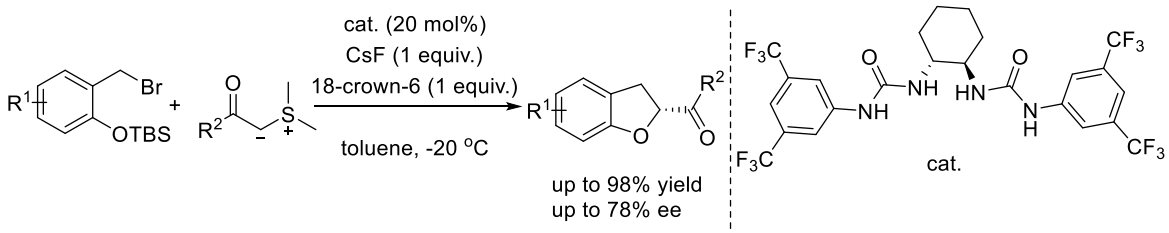
Hydroquinine derived squaramide catalyzed an efficient asymmetric [4+1] cyclization of *ortho*-quinone methides with 3-chlorooxindoles had been manifested by Mei and Shi group (Scheme 30).[62] A variety of spirooxindole bearing 2,3-dihydrobenzofurans were achieved in satisfactory results.



Scheme 30. Diastereo-, enantioselective domino oxidation/[4+1] cyclization of *o*-QMs with 3-chlorooxindoles.

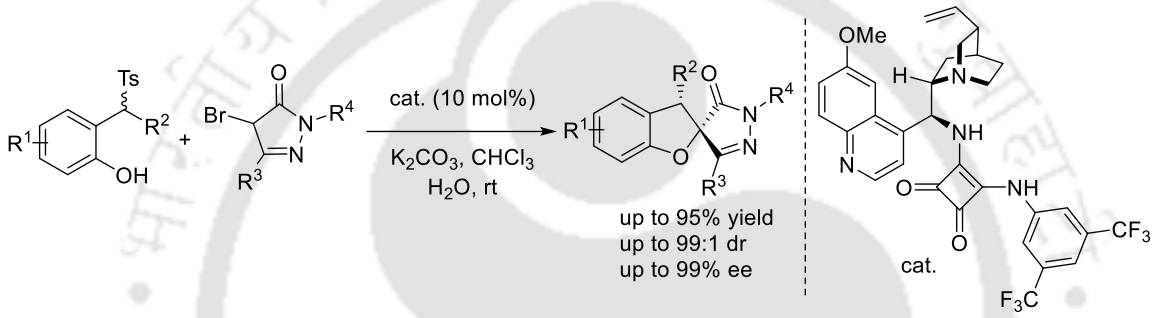
Yang and co-workers described a C2-symmetric chiral bifunctional urea catalyzed another asymmetric [4+1] cycloannulation between *in situ*-generated *o*-QMs and sulfur ylides (Scheme 31).[63] Though 2,3-dihydrobenzofuran products were afforded in excellent yields,

enantioselectivities were moderate.



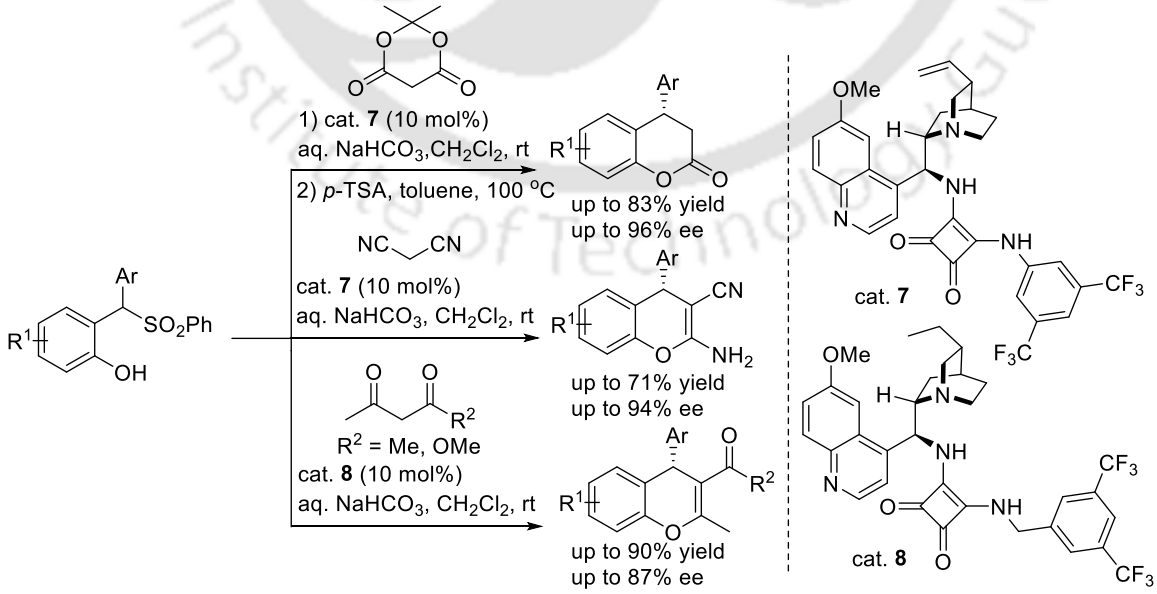
Scheme 31. Asymmetric [4+1] cyclization of *in situ*-generated *o*-QMs with sulfur ylides.

Another significant output also came from Xu group. Recently, they explored quinine derived squaramide catalyzed stereoselective [4+1] cyclization of *in situ*-generated *o*-QMs with 4-halo-pyrazolones (Scheme 32).[64]



Scheme 32. Diastereo-, enantioselective [4+1] cyclization using *in situ*-generated *o*-QMs and 4-halo-pyrazolones.

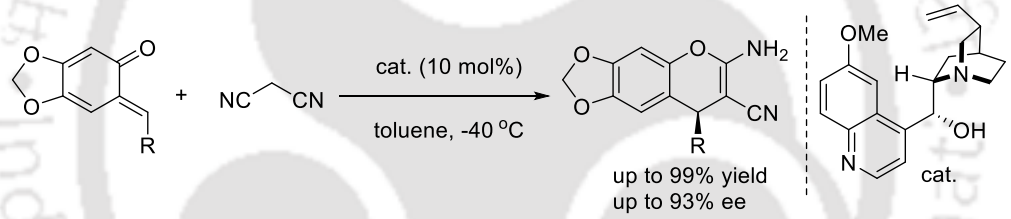
1.5.2.2.2. *Enantioselective [4+2] cyclization reactions:*



Scheme 33. Enantioselective addition/cyclization of Meldrum's acid, malononitrile and 1,3-dicarbonyl compounds to *o*-QMs.

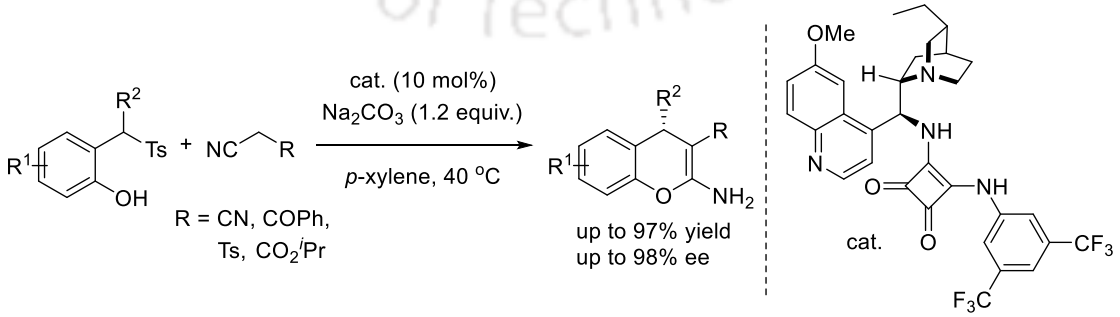
Bernardi *et al*. described cinchona derived bifunctional squaramide catalyzed enantioselective addition/cyclization of Meldrum's acid, malononitrile and 1,3-dicarbonyl compounds to *in situ*-generated *ortho*-quinone methides in 2015 (Scheme 33).[20d] Using catalytic amount organocatalyst under biphasic conditions, structurally important motifs such as dihydrocoumarins, 4*H*-chromenes and xanthenones were afforded in high enantioselectivities.

In the same year, Han group reported quinine catalyzed enantioselective [4+2] cycloannulation of sesamol based stabilized *o*-QMs and malononitrile to deliver chiral 2-amino-3-cyano-4*H*-chromene products in good yields and with high enantiomeric excesses (Scheme 34).[65] Notably, here very low temperature is essential for the better outcome.



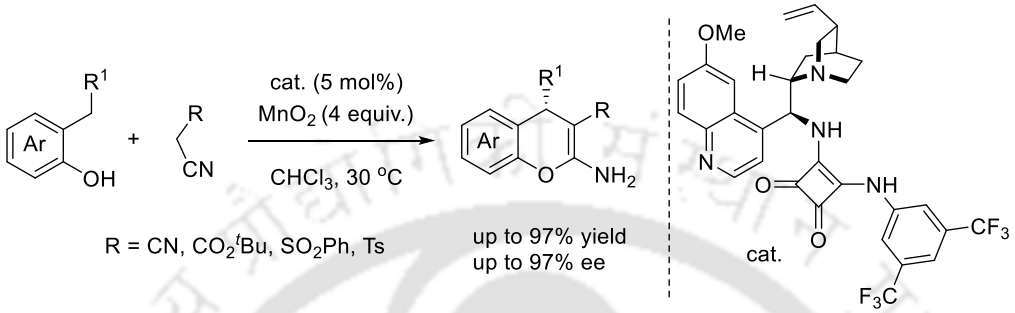
Scheme 34. Enantioselective [4+2] cycloannulation of malononitrile to stabilized *o*-QMs.

After Bernardi and Han's works, an alternative asymmetric methodology regarding 2-amino-4*H*-chromene synthesis had been documented by Zhou and co-workers (Scheme 35).[66] Utilizing hydroquinine derived squaramide catalyst, various active methylene compounds having minimum one cyano group were effectively engaged with *in situ*-generated *ortho*-quinone methides. Interestingly, here biphasic condition was not required.



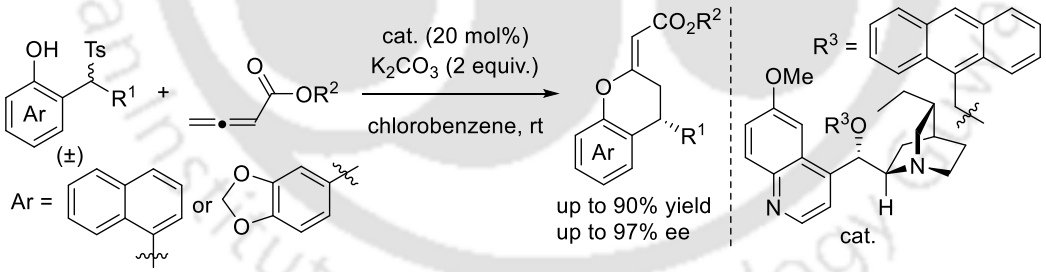
Scheme 35. Enantioselective [4+2] cycloannulation of active methylene compounds with *in situ*-generated *o*-QMs.

One additional contribution on bifunctional squaramide catalyzed chiral 2-amino-4*H*-chromene synthesis was originated from the same group (Scheme 36).[67] Here, 2-alkyl substituted sesamols/naphthols and active methylene compounds having one cyano group were taken as the reactants. Benzylic oxidation followed by conjugate addition/cyclization afforded the expected products in excellent enantioselectivities.



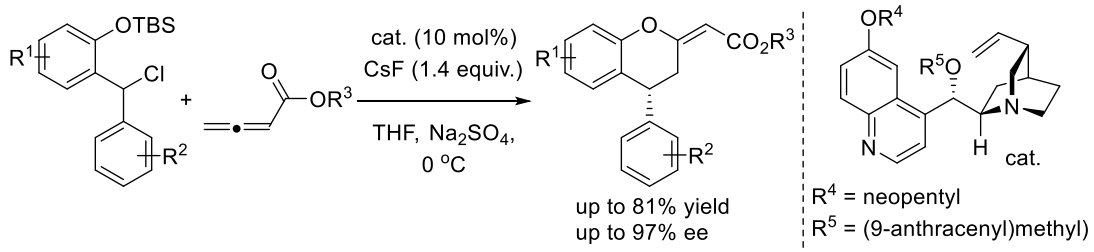
Scheme 36. Chiral 2-amino-4*H*-chromenes synthesis from 2-alkyl-sesamols/naphthols and active methylene compounds.

In 2017, Liu and Li and co-workers demonstrated cinchona alkaloid catalyzed enantioselective synthesis of 4-aryl/alkyl substituted chromans *via* [4+2] cycloaddition of *in situ*-generated *o*-QMs and allenic esters (Scheme 37).[59] Here, 2-(tosylmethyl)sesamols and 2-(tosylmethyl)naphthols were chosen for *o*-QMs generation and the products were obtained in high yields and enantiomeric excesses.



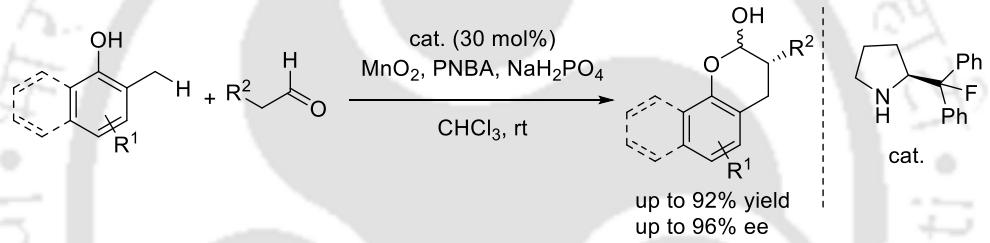
Scheme 37. Enantioselective [4+2] cycloaddition of *in situ*-*o*-QMs with allenic esters.

In the same year, Fan group also described another alternative method for the asymmetric synthesis of 4-aryl substituted chromans in a [4+2] cyclization reaction engaging *in situ*-generated *o*-QMs and allenoates (Scheme 38).[68] Several TBS-protected *ortho*-hydroxybenzyl chloride derivatives, stable precursors of *in situ*-*o*-QMs had been employed in the reactions. Here also, reaction outcomes were excellent in terms of yield and enantiomeric excess.



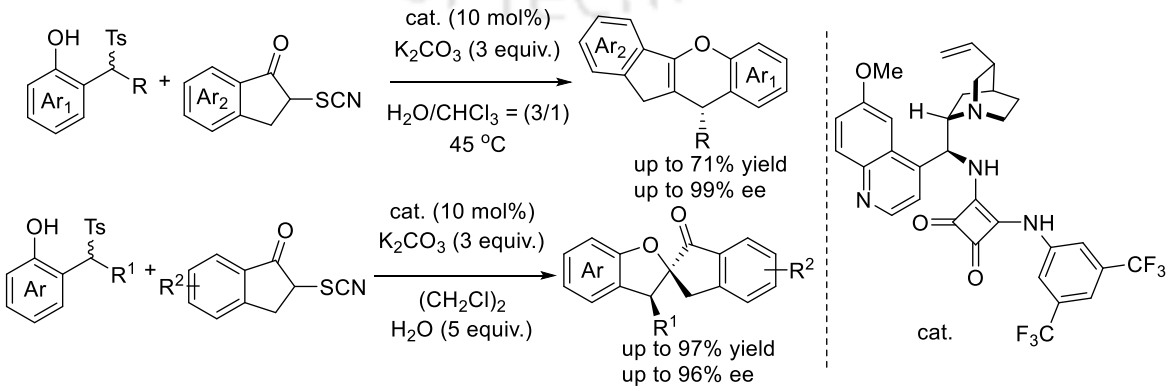
Scheme 38. Enantioselective [4+2] annulation using *in situ*-*o*-QMs and allenoates.

One more asymmetric [4+2] cycloaddition involving *in situ*-generated *o*-QMs had been established recently by Xie *et al*. (Scheme 39).[69] In presence of MnO_2 oxidant and combination of chiral secondary amine/*p*-nitrobenzoic acid (PNBA) catalytic system, various 2-methylphenols/2-methylnaphthols and aldehydes were efficiently reacted to deliver chromanols in high enantioselectivities.



Scheme 39. Enantioselective synthesis of chromanols from *β*-unsubstituted *o*-QMs and aldehydes.

Very recently, Liu and Li group reported quinine derived bifunctional squaramide catalyzed fascinating cascade reaction between *in situ*-generated *o*-QMs and *α*-thiocyanato indanones under biphasic conditions (Scheme 40).[70] Authors also developed an asymmetric spiroannulation route simply by changing the amount of water content. Both fused- and spiro-indanone products were achieved in high enantioselectivities.

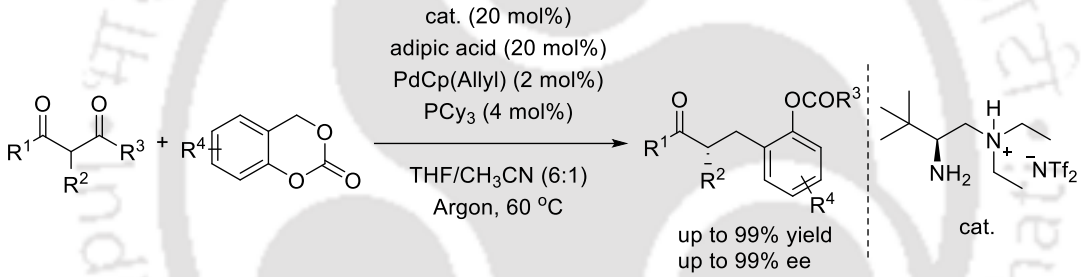


Scheme 40. Enantioselective synthesis of fused- and spiro-indanones employing *in situ*-generated *o*-QMs.

1.5.3. Acyl transfer/asymmetric retro-Claisen reactions:

In 2018, our group utilized hydroquinine based bifunctional squaramide catalyzed asymmetric domino Michael/acyl transfer strategy for a reaction between α-nitroketones and *in situ*-generated *ortho*-quinone methides.[71] Details of it has been discussed in Chapter-3 of this present thesis.

In the next year, another important work related to the acyl group migration in *o*-QMs had been explored by Luo and co-workers (Scheme 41).[72] They presented an interesting enantioselective retro-Claisen reaction between β-diketones and *o*-QMs precursor such as salicylic carbonates by taking the advantage of enamine/Pd-catalysis. Gratifyingly, a variety of α-alkylated ketones were achieved in high yields and high enantiomeric excesses.



Scheme 41. Asymmetric retro-Claisen reaction between β-diketones and salicylic-carbonates.

1.6. References:

1. Pasteur, L. *Ann. Chim. Phys*. **1848**, *24*, 442.
2. Reetz, M. T. *J. Am. Chem. Soc*. **2013**, *135*, 12480.
3. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis, Volume I to III*; Springer: Berlin, Heidelberg, **1999**.
4. (a) List, B. *Chem. Rev*. **2007**, *107*, 5413. (b) Renzi, P.; Bella, M. *Chem. Commun*. **2012**, *48*, 6881.
5. (a) List, B. *Chem. Commun*. **2006**, 819. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471. (c) Mečiarová, M.; Tisovský, P.; Šebesta, R. *New J. Chem.* **2016**, *40*, 4855.

6. (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal*. **2006**, *348*, 999. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 1520. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*. **2007**, *107*, 5713.
7. Maruoka, K. *Org. Process Res. Dev*. **2008**, *12*, 679.
8. Brière, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev*. **2012**, *41*, 1696.
9. (a) Akiyama, T. *Chem. Rev*. **2007**, *107*, 5744. (b) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev*. **2014**, *114*, 9047.
10. (a) Wynberg, H.; Helder, R. *Tetrahedron Lett*. **1975**, *16*, 4057. (b) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc*. **2004**, *126*, 9906. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res*. **2004**, *37*, 621. (d) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem. Int. Ed*. **2005**, *44*, 105.
11. For pioneering work on asymmetric thiourea catalyst, see: (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 4901. Also see: (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed*. **2005**, *117*, 6525. (d) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc*. **2006**, *128*, 6048. (e) Connon, S. J. *Chem. Eur. J*. **2006**, *12*, 5418. (f) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc*. **2007**, *129*, 768. (g) Connon, S. J. *Chem. Commun*. **2008**, 2499. (h) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol*. **2011**, *1*, 1298. For a book chapter, see: (i) Limnios, D.; Kokotos, C. G. *Ureas and Thioureas as Asymmetric Organocatalysts*; Sustainable Catalysis: Without Metals or Other Endangered Elements, Part 2, **2015**, pp. 196.
12. Bifunctional urea catalyzed selected examples, see: (a) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem*. **2010**, *75*, 2089. (b) Liu, Y.-L.; Zhou, J. *Chem. Commun*. **2012**, *48*, 1919. (c) Abbaraju, S.; Zhao, J. C.-G. *Adv. Synth. Catal*. **2014**, *356*, 237. (d) Rong, Z.-Q.; Pan, H.-J.; Yan, H.-L.; Zhao, Y. *Org. Lett*. **2014**, *16*, 208. (e) Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem. Int. Ed*. **2014**, *53*, 8779.
13. (a) For pioneering work on bifunctional squaramide catalyst, see: Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416. For reviews, see: (b) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 6890. (c)

Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev*. **2011**, *40*, 2330. (d) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal*. **2015**, *357*, 253.

14. Amouri, H.; Besace, Y.; Bras, J. L.; Vaissermann, J. *J. Am. Chem. Soc*. **1998**, *120*, 6171.
15. For recent reviews about *o*-QMs, see: (a) *Quinone Methides* (Ed.: Rokita, S. E.), Wiley: Hoboken, **2009**. (b) Pathak, T. P.; Sigman, M. S. *J. Org. Chem*. **2011**, *76*, 9210. (c) Willis, N. J.; Bray, C. D. *Chem. Eur. J.* **2012**, *18*, 9160. (d) Bai, W. J.; David, J. G.; Feng, Z. G.; Weaver, M. G.; Wu, K. L.; Pettus, T. R. *Acc. Chem. Res*. **2014**, *47*, 3655. (e) Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv*. **2014**, *4*, 55924. (f) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015**, *20*, 11733. (g) Wang, Z.; Sun, J. *Synthesis* **2015**, *47*, 3629. (h) Jaworski, A. A.; Scheidt, K. A. *J. Org. Chem*. **2016**, *81*, 10145. (i) Mukhopadhyay, S.; Gharui, C.; Pan, S. C. *Asian J. Org. Chem*. **2019**, *8*, 1970.
16. (a) Xu, L.; Liu, F.; Xu, L.-W.; Gao, Z.; Zhao, Y.-M. *Org. Lett*. **2016**, *18*, 3698. (b) Zhang, Y.; Guo, Y.; Li, Z.; Xie, Z. *Org. Lett*. **2016**, *18*, 4578. (c) Li, T.-Z.; Geng, C.-A.; Yin, X.-J.; Yang, T.-H.; Chen, X.-L.; Huang, X.-Y.; Ma, Y.-B.; Zhang, X.-M.; Chen, J.-J. *Org. Lett*. **2017**, *19*, 429.
17. Tatsuta, K.; Tamura, T.; Mase, T. *Tetrahedron Lett*. **1999**, *40*, 1925.
18. Spence, J. T. J.; George, J. H. *Org. Lett*. **2011**, *13*, 5318.
19. Green, J. C.; Jiménez-Alonso, S.; Brown, E. R.; Pettus, T. R. R. *Org. Lett*. **2011**, *13*, 5500.
20. (a) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285. (b) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem*. **2007**, *72*, 6056. (c) Nilvebrant, L.; Andersson, K.-E.; Gillberg, P.-G.; Stahl, M.; Sparf, B. *Eur. J. Pharmacol.* **1997**, *327*, 195. (d) Caruana, L.; Mondatori, M.; Corti, V.; Morales, S.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Chem. Eur. J*. **2015**, *21*, 6037.
21. Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965.
22. Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc*. **1971**, *93*, 6696.
23. (a) Maalej, E.; Chabchoub, F.; Oset-Gasque, M. J.; Esquivias-Pérez, M.; González, M. P.; Monjas, L.; Pérez, C.; de los Ríos, C.; Rodríguez-Franco, M. I.; Iriepa, I.; Moraleda, I.; Chioua, M.; Romero, A.; Marco-Contelles, J.; Samadi, A. *Eur. J. Med. Chem*. **2012**,

54, 750. (b) Wu, B.; Gao, X.; Yan, Z.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2015**, *17*, 6134.

24. (a) Xu, J.; Yuan, S.; Peng, J.; Miao, M.; Chen, Z.; Ren, H. *Org. Biomol. Chem*. **2017**, *15*, 7513. (b) Du, J.-Y.; Ma, Y.-H.; Meng, F.-X.; Zhang, R.-R.; Wang, R.-N.; Shi, H.-L.; Wang, Q.; Fan, Y.-X.; Huang, H.-L.; Cui, J.-C.; Ma, C.-L. *Org. Lett*. **2019**, *21*, 465. (c) Xia, C.; Wang, D.-C.; Qu, G.-R.; Guo, H.-M. *Org. Chem. Front*. **2020**, *7*, 1474.
25. Lam, H.; Qureshi, Z.; Wegmann, M.; Lautens, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 16185.
26. (a) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 3076. (b) Jensen, K. H.; Pathak, T. P.; Zhang Y.; Sigman, M. S. *J. Am. Chem. Soc*. **2009**, *131*, 17074. (c) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc*. **2010**, *132*, 7870. (d) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471. (e) Jana, R.; Pathak, T. P.; Jensen, K. H.; Sigman, M. S. *Org. Lett*. **2012**, *14*, 4074.
27. Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett.* **2008**, *10*, 4951.
28. Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965.
29. (a) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal*. **2009**, *351*, 2822. (b) Lv, H.; Jia, W. Q.; Sun, L. H.; Ye, S. *Angew. Chem. Int. Ed*. **2013**, *125*, 8769.
30. (a) Mattson, A. E.; Scheidt, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 4508. (b) Izquierdo, J.; Orue, A.; Scheidt, K. A. *J. Am. Chem. Soc*. **2013**, *135*, 10634. (c) Lee, A.; Younai, A.; Price, C. K.; Izquierdo, J.; Mishra, R. K.; Scheidt, K. A. *J. Am. Chem. Soc*. **2014**, *136*, 10589.
31. Xia, C.; Wang, D.-C.; Qu, G.-R.; Guo, H.-M. *Org. Chem. Front*. **2020**, *7*, 1474.
32. Wang, Y.; Pan, J.; Dong, J.; Yu, C.; Li, T.; Wang, X.-S.; Shen, S.; Yao, C. *J. Org. Chem.* **2017**, *82*, 1790.
33. Zheng, J.; Lin, L.; Dai, L.; Yuan, X.; Liu, X.; Feng, X. *Chem. Eur. J*. **2016**, *22*, 18254.
34. Wang, Z.; Wang, T.; Yao, W.; Lu, Y. *Org. Lett*. **2017**, *19*, 4126.
35. Zielke, K.; Waser, M. *Org. Lett*. **2018**, *20*, 768.
36. Jiang, F.; Luo, G.-Z.; Zhu, Z.-Q.; Wang, C.-S.; Mei, G.-J.; Shi, F. *J. Org. Chem*. **2018**, *83*, 10060.

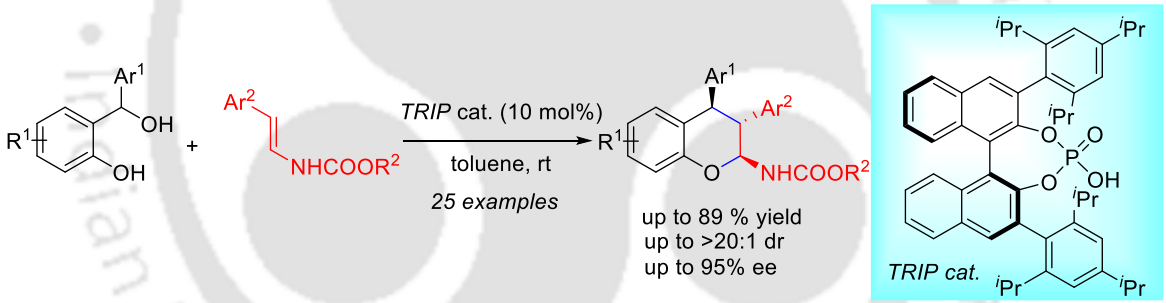
37. Tanaka, K.; Omata, D.; Asada, Y.; Hoshino, Y.; Honda, K. *J. Org. Chem*. **2019**, *84*, 10669.
38. Saha, S.; Alamsetti, S. K.; Schneider, C. *Chem. Commun*. **2015**, *51*, 1461.
39. Lai, Z.; Sun, J.-W. *Synlett* **2016**, *27*, 555.
40. Suneja, A.; Schneider, C. *Org. Lett*. **2018**, *20*, 7576.
41. Feng, W.; Yang, H.; Wang, Z.; Gou, B.-B.; Chen, J.; Zhou, L. *Org. Lett*. **2018**, *20*, 2929.
42. El-Sepelgy, O.; Haseloff, S.; Alamsetti, S. K.; Schneider, C. *Angew. Chem. Int. Ed*. **2014**, *53*, 7923.
43. Hsiao, C.-C.; Liao, H. H.; Rueping, M. *Angew. Chem. Int. Ed*. **2014**, *53*, 13258.
44. Yu, X.-Y.; Chen, J.-R.; Wei, Q.; Cheng, H.-G.; Liu, Z.-C.; Xiao, W.-J. *Chem. Eur. J*. **2016**, *22*, 6774.
45. Xie, Y.; List, B. *Angew. Chem. Int. Ed*. **2017**, *56*, 4936.
46. Gebauer, K.; Reuß, F.; Spanka, M.; Schneider, C. *Org. Lett*. **2017**, *19*, 4588.
47. Wang, Z.; Sun, J. *Org. Lett*. **2017**, *19*, 2334.
48. Jeong, H. J.; Kim, D. Y. *Org. Lett*. **2018**, *20*, 2944.
49. Ukis, R.; Schneider, C. *J. Org. Chem*. **2019**, *84*, 7175.
50. Zhang, H.; Liu, G.; Guan, X.; Gao, J.; Qin, X.; Jiang, G.; Sun, D.; Zhang, G.; Zhang, S. *Eur. J. Org. Chem*. **2019**, 7264.
51. You, Y.; Li, T.-T.; Yuan, S.-P.; Xie, K.-X.; Wang, Z.-H.; Zhao, J.-Q.; Zhou, M.-Q.; Yuan, W.-C. *Chem. Commun*. **2020**, *56*, 439.
52. Feng, S.; Yang, B.; Chen, T.; Wang, R.; Deng, Y.-H.; Shao, Z. *J. Org. Chem*. **2020**, *85*, 5231.
53. Tu, M.-S.; Liu, S.-J.; Zhong, C.; Zhang, S.; Zhang, H.; Zheng, Y.-L.; Shi, F. *J. Org. Chem*. **2020**, *85*, 5403.
54. Sun, M.; Ma, C.; Zhou, S.-J.; Lou, S.-F.; Xiao, J.; Jiao, Y.; Shi, F. *Angew. Chem. Int. Ed*. **2019**, *58*, 8703.
55. Suneja, A.; Loui, H. J.; Schneider, C. *Angew. Chem. Int. Ed*. **2020**, *59*, 5536.
56. Zhu, Y.; Zhang, W.-Z.; Zhang, L.; Luo, S. *Chem. Eur. J*. **2017**, *23*, 1253.
57. Huang, A.; Zhang, L.; Li, D.; Liu, Y.; Yan, H.; Li, W. *Org. Lett*. **2019**, *21*, 95.
58. Guo, W.; Wu, B.; Zhou, X.; Chen, P.; Wang, X.; Zhou, Y.-G.; Liu, Y.; Li, C. *Angew. Chem. Int. Ed*. **2015**, *54*, 4522.

59. Chen, P.; Wang, K.; Guo, W.; Liu, X.; Liu, Y.; Li, C. *Angew. Chem. Int. Ed*. **2017**, *56*, 3689.
60. Li, D.; Tan, Y.; Peng, L.; Li, S.; Zhang, N.; Liu, Y.; Yan, H. *Org. Lett*. **2018**, *20*, 4959.
61. Gu, X.; Yuan, H.; Jiang, J.; Wu, Y.; Bai, W.-J. *Org. Lett.* **2018**, *20*, 7229.
62. Jiang, X.-L.; Liu, S.-J.; Gu, Y.-Q.; Mei, G.-J.; Shi, F. *Adv. Synth. Catal*. **2017**, *359*, 3341.
63. Yang, Q.-Q.; Xiao, W.-J. *Eur. J. Org. Chem.* **2017**, 233.
64. Chu, M.-M.; Qi, S.-S.; Wang, Y.-F.; Wang, B.; Jiang, Z.-H.; Xu, D.-Q.; Xu, Z.-Y. *Org. Chem. Front*. **2019**, *6*, 1977.
65. Adili, A.; Tao, Z.-L.; Chen, D.-F.; Han, Z.-Y. *Org. Biomol. Chem*. **2015**, *13*, 2247.
66. Wu, B.; Gao, X.; Yan, Z.; Huang, W.-X.; Zhou, Y.-G. *Tetrahedron Lett.* **2015**, *56*, 4334.
67. Wu, B.; Gao, X.; Yan, Z.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2015**, *17*, 6134.
68. Deng, Y.-H.; Chu, W.-D.; Zhang, X.-Z.; Yan, X.; Yu, K.-Y.; Yang, L.-L.; Huang, H.; Fan, C.-A. *J. Org. Chem*. **2017**, *82*, 5433.
69. Zhou, D.; Yu, X.; Zhang, J.; Wang, W.; Xie, H. *Org. Lett*. **2018**, *20*, 174.
70. Liu, X.; Wang, K.; Liu, Y.; Li, C. *Chem. Eur. J*. **2021**, *27*, 735.
71. Gharui, C.; Behera, D.; Pan, S. C. *Adv. Synth. Catal.* **2018**, *360*, 4502.
72. Han, Y.; Zhang, L.; Luo, S. *Org. Lett*. **2019**, *21*, 7258.

Chiral Phosphoric Acid Catalyzed Enantioselective Annulation of Acyclic Enecarbamates to in situ-Generated ortho-Quinone Methides[*]

Abstract:

The first organocatalytic asymmetric reaction of acyclic enecarbamates with *in situ*-generated *ortho*-quinone methides is demonstrated. Several BINOL-based phosphoric acid catalysts were found to be effective for such annulation. With 10 mol% of (*S*)-TRIP catalyst, high yields along with good to excellent diastereo- and enantioselectivities were attained for a variety of 2,3,4-trisubstituted chroman products. The reaction conditions were very mild and operationally simple procedure.



[*]Gharui, C.; Singh, S.; Pan, S. C. *Org. Biomol. Chem.* **2017**,*15*, 7272.

2.1. Introduction:

Chromans are the heterocyclic scaffolds comprising a benzene ring fused with a pyran ring. Also it is called benzopyran. Depending on the position of double bond, it can be further categorize to different structural isomers such as *2H*-Chroman and *4H*-chroman (Figure 1). Highly functionalized chromans are the imperative structural frameworks present in many natural products and bioactive molecules.[1]

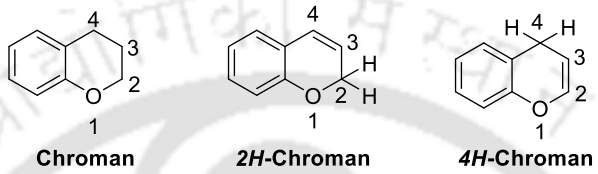
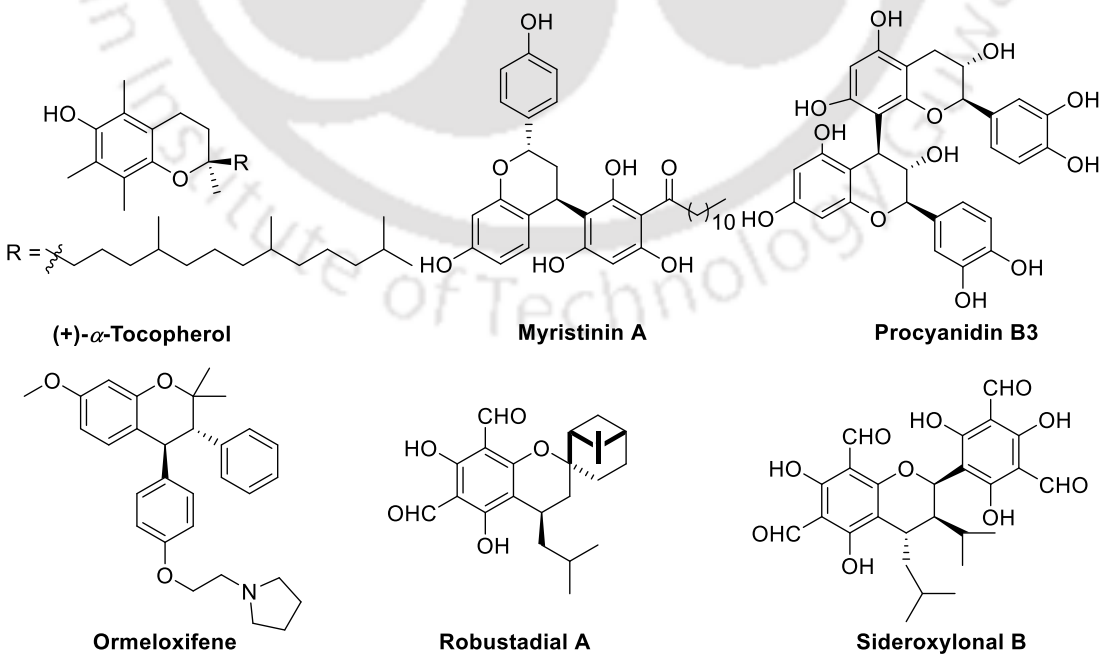


Figure 1. Various types of chromans.

For example, (+)-α-tocopherol is a very common naturally occurring chroman having versatile antioxidant property.[2] It is highly essential in boosting the human immune system and often useful for preventing the cell damage arising from free radical reactions. Myristinin A is an another example of chroman possessing DNA damaging ability and shows potent activity in the inhibition of DNA polymerase β (IC50 2.8 μM), a DNA repair enzyme.[3] Procyanidin B3, a polyphenolic substrate consisting chroman motifs serves as



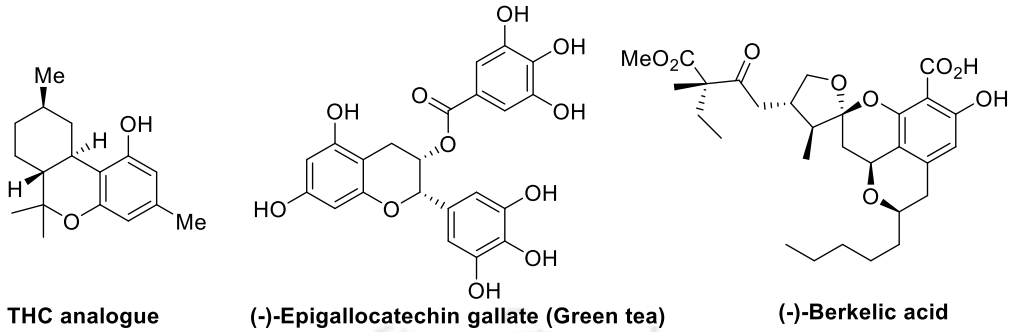


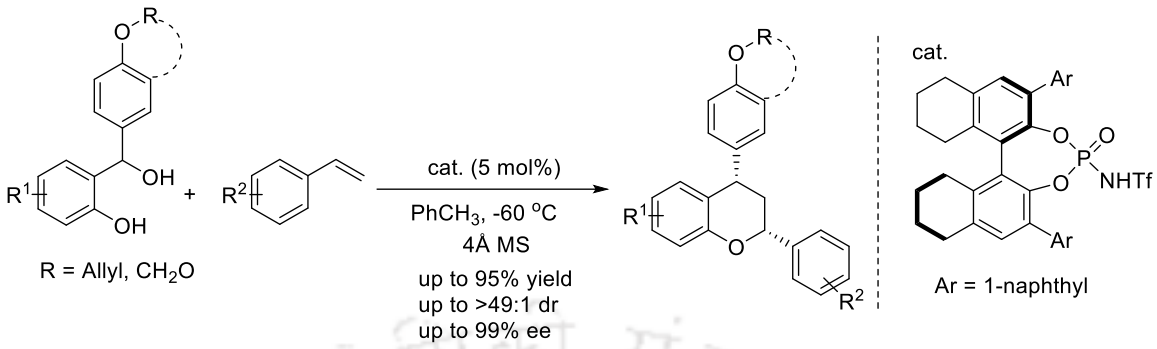
Figure 2. Biologically active chroman molecules.

hair growth stimulant agents.[4] Ormeloxifene is a non-steroidal oral contraceptive drug used as a selective estrogen receptor modulator and also has anticancer properties.[5] Robustadial A acts as an antimalarial agent.[6] Also, Sideroxylonal B,[7] THC analogues[8] are the impressive class of molecules showing numerous activities such as antibacterial, chronic pain relieving properties respectively (Figure 2). In the last few years, many research groups were significantly contributed to the substituted chromans synthesis with the help of asymmetric organocatalysis.[9,10] Despite a range of strategies that have been disclosed, the development of new effective methodologies is exceedingly essential for the construction of multi substituted chiral chromans in an enantio- and diastereoselective fashion to invent many natural products and other hidden activities.

ortho-Quinone methides (*o*-QMs) are often useful synthetic intermediates having versatile applications in complex molecule formation like sideroxylonal B, robustadial A, THC analogue etc.[11] Because of the unique reactivity and high electrophilic nature, it serves as an excellent Michael acceptor in organic synthesis and largely participated in various chiral Brønsted acid catalyzed asymmetric [4+2] cycloannulation reactions.

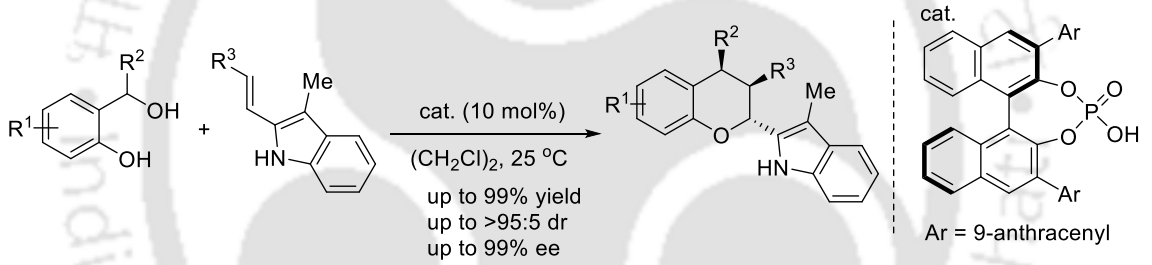
2.2. Reported strategies for the synthesis of substituted chromans employing *o*-QMs:

Rueping and co-workers demonstrated chiral phosphoric acid catalyzed enantioselective synthesis of 2,4-disubstituted chromans using unactivated alkenes and *in situ*-generated *ortho*-quinone methides *via* an oxa-Diels-Alder reaction.[12] Herein, more acidic *N*-triflyphosphoramidate catalyst controlled the enantioselectivity through the monofunctional activation of electrophilic *o*-QMs only (Scheme 1).



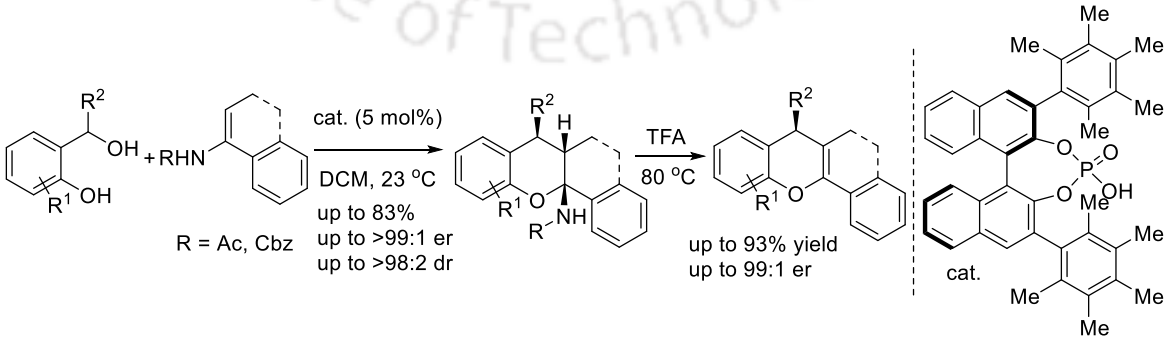
Scheme 1. Enantioselective oxa-Diels-Alder reaction of *o*-QMs with styrenes.

In the same year, Shi *et al*. disclosed Brønsted phosphoric acid catalyzed an inverse electron demand oxa-Diels-Alder reaction of 3-methyl-2-vinyl indoles with *in situ*-generated *ortho*-quinone methides.[13] 2,3,4-trisubstituted chromans have been synthesized with generally high yields, and with excellent diastereo- as well as enantioselectivities (Scheme 2).



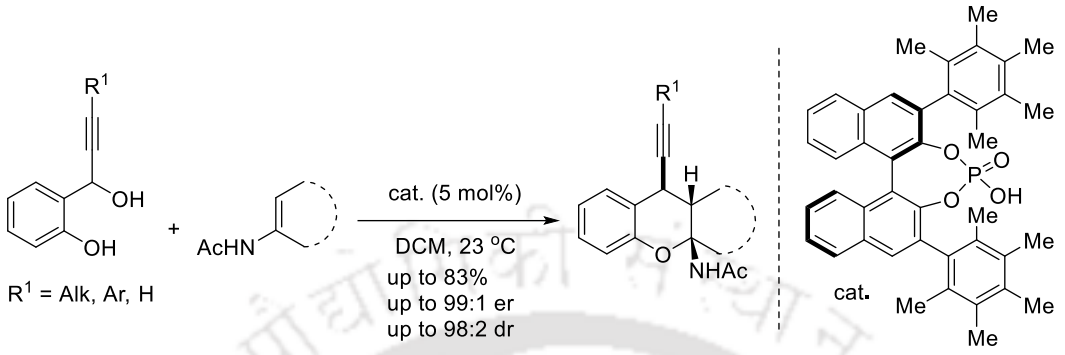
Scheme 2. Trisubstituted chroman synthesis using *in situ*-*o*-QMs and 2-vinylindoles.

Chiral phosphoric acid catalyzed enantioselective synthesis of xanthene based heterocycles from cyclic enamides and *in situ*-generated *ortho*-quinone methides had been described by Schneider and co-workers (Scheme 3).[14a] Herein, the authors have also shown one example of reaction using cyclic *N*-Cbz enecarbamate and *in situ*-generated *ortho*-quinone methide.



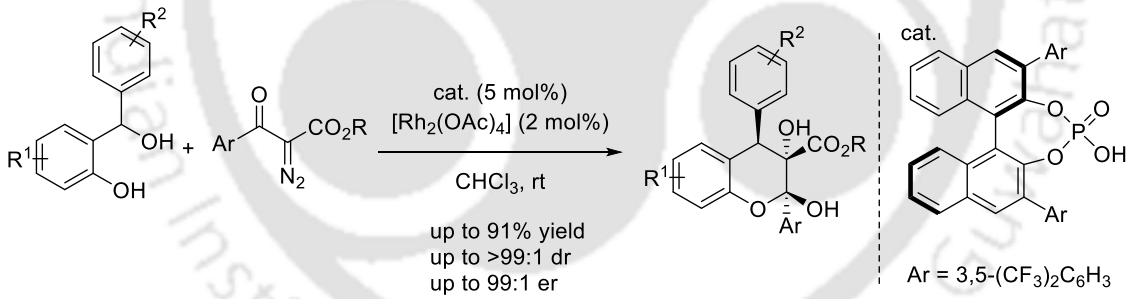
Scheme 3. Enantioselective reaction of cyclic enamides to *in situ*-generated *o*-QMs.

The same group again reported diastereo- and enantioselective synthesis of 7-alkynyl-12a-acetamido-substituted benzo[*c*]xanthenes from the reaction of cyclic enamides and 1-(*o*-hydroxyphenyl)propargylic alcohols (Scheme 4).[14b]



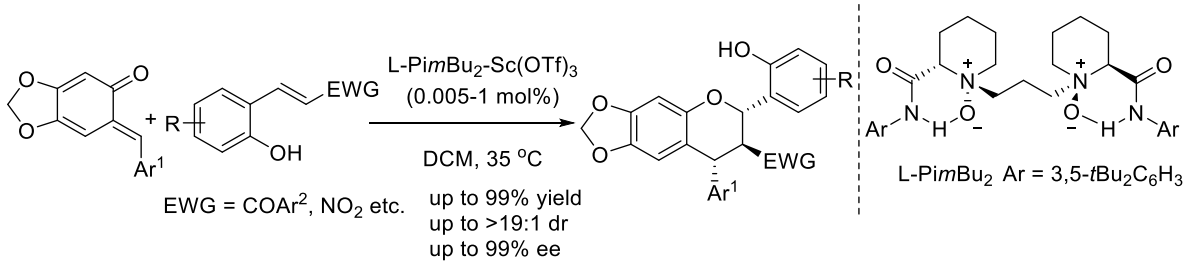
Scheme 4. Synthesis of 7-alkynyl-12a-acetamido-substituted benzo[*c*]xanthenes.

In 2016, the same group manifested an efficient protocol using diazo esters and *in situ*-generated *ortho*-quinone methides as the reactive substrates under rhodium/Brønsted phosphoric acid catalysis.[15] In general, penta-substituted chromans with three contiguous stereogenic centers were synthesized with excellent diastereo- and enantioselectivities (Scheme 5).



Scheme 5. Enantioselective reaction of diazo esters to *in situ*-generated *o*-QMs.

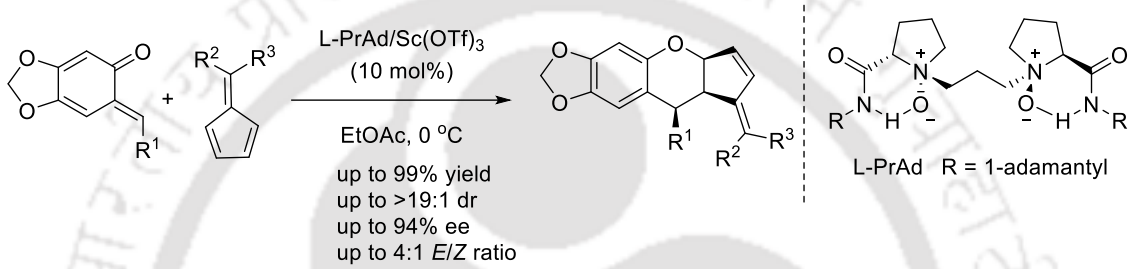
Recently, Feng group described chiral *N*,*N*'-dioxide-Sc(III) catalyzed an enantioselective [4+2] cyclization reaction of *ortho*-quinone methides with various *ortho*-hydroxyaryl-



Scheme 6. Asymmetric cycloannulation of *ortho*-hydroxyaryl *α,β*-unsaturated compounds with *o*-QMs.

α,β-unsaturated compounds.[16] In this reaction, trisubstituted chromans were achieved in high yields and with excellent diastereo- as well as enantioselectivities (Scheme 6).

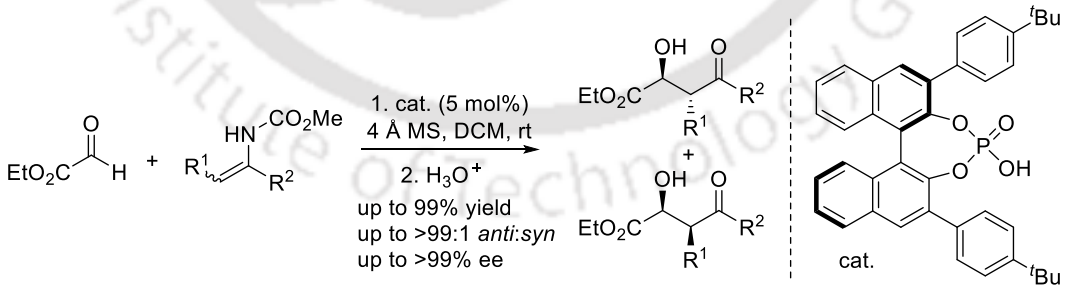
Chiral *N,N'*-dioxide-Sc(III) complex catalyzed another efficient approach using fulvenes and stabilized *ortho*-quinone methides for the diastereo- and enantioselective synthesis of highly substituted chromans was demonstrated by Lin and Feng group (Scheme 7).[17]



Scheme 7. Asymmetric reaction of fulvenes with stabilized *ortho*-quinone methides.

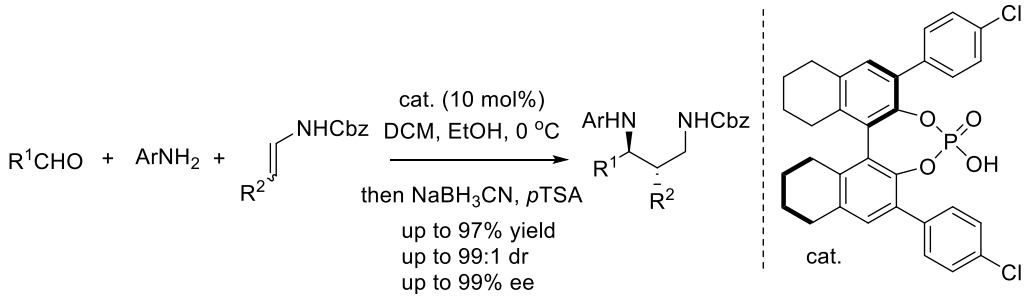
2.3. Chiral phosphoric acid catalyzed selected asymmetric transformations using acyclic enecarbamates:

An enantioselective aza-ene type reaction of glyoxylate and enecarbamates was disclosed by Terada *et al*.[18] Although this was an overall two steps reaction, the desired products were attained with high *anti*- selectivity and with excellent enantioselectivities (Scheme 8).



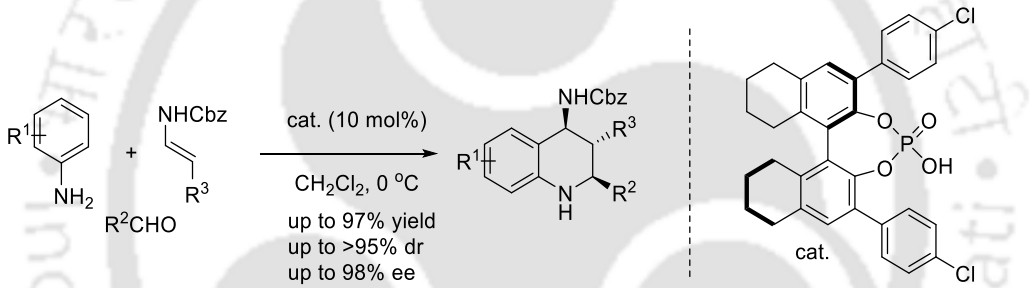
Scheme 8. Enantioselective reaction of glyoxylate and enecarbamates.

Masson and Zhu group described chiral phosphoric acid catalyzed diastereo-, enantioselective synthesis of *anti*-1,3-diamines *via* one pot Mannich reaction using aldehydes, anilines and enecarbamates followed by *in situ* reduction (Scheme 9).[19]



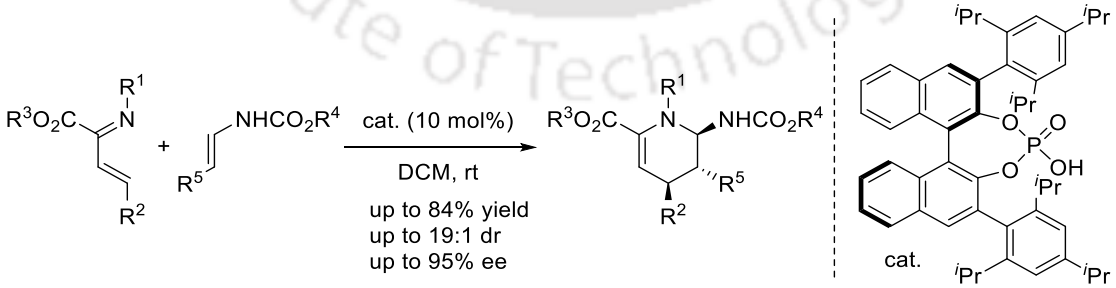
Scheme 9. Asymmetric synthesis of *anti*-1,3-diamines using acyclic enecarbamates.

Again, Zhu and Masson group demonstrated chiral phosphoric acid catalyzed an effective asymmetric route for the preparation of optically active 4-amino tetrahydroquinolines in a multicomponent reaction using aldehydes, anilines and acyclic enecarbamates (Scheme 10).[20] The expected quinolone products were isolated with high dr and excellent enantioselectivities.



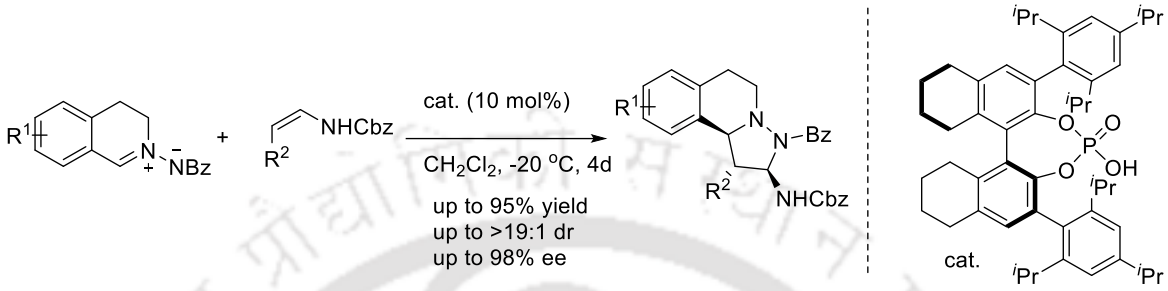
Scheme 10. Asymmetric synthesis of tetrahydroquinolines using acyclic enecarbamates

Masson and co-workers presented an enantioselective aza-Diels-Alder reaction of 1-azadienes and acyclic enecarbamates for the synthesis of 4,5,6-trisubstituted tetrahydropyridines.[21] BINOL-based (*R*)-TRIP catalyst was found to be effective for such asymmetric transformation (Scheme 11).



Scheme 11. Enantioselective aza-Diels-Alder reaction of 1-azadienes and acyclic enecarbamates.

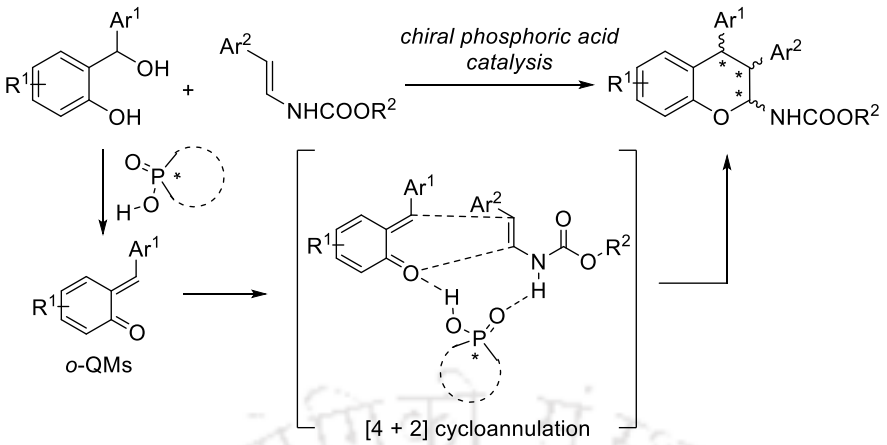
Zhu and co-workers explored [3+2] enantioselective cycloaddition of azomethine imines with acyclic *cis*-enecarbamates for the construction of chiral isoquinoline fused pyrazolidines.[22] Hydrogenated TRIP catalyst was effective in this reaction (Scheme 12).



Scheme 12. Asymmetric reaction of azomethine imines and acyclic enecarbamates.

2.4. Concept:

First, we have realized that densely functionalized chiral chromans are the privileged structural motifs present in many natural products and pharmaceuticals. They have been considered as an important pharmacophore owing to their versatile activities. Hence, searching for new efficient approaches is still demanding to find out the new molecules and its applications. Also, the literature survey revealed that *in situ*-generated *ortho*-quinone methide intermediates are the suitable reaction partner for diverse chroman synthesis. On the other hand, acyclic enecarbamates are the potential nucleophile in organic synthesis. Because of having donor acceptor sites, it was effectively engaged in several chiral Brønsted phosphoric acid catalyzed asymmetric transformations. To the best of our knowledge, asymmetric reaction of acyclic enecarbamates with *in situ*-generated *ortho*-quinone methides was not explored before. Initially, we thought that *ortho*-quinone methide inderemediate can be generated from stable precursor like *ortho*-hydroxybenzyl alcohol derivatives. Then bifunctional chiral phosphoric acid catalysts could activate the *ortho*-quinone methide intermediate as well as acyclic enecarbamates through hydrogen bonding interactions. Then consequent [4+2] cycloannulation may deliver the 2,3,4-trisubstituted chroman products (Scheme 13). Thus, herein we wish to develop an enantioselective [4+2] cycloannulation protocol for the synthesis of functionalized chromans using acyclic enecarbamates and *in situ*-generated *ortho*-quinone methides as the reactive substrates and chiral Brønsted phosphoric acid as the catalyst.

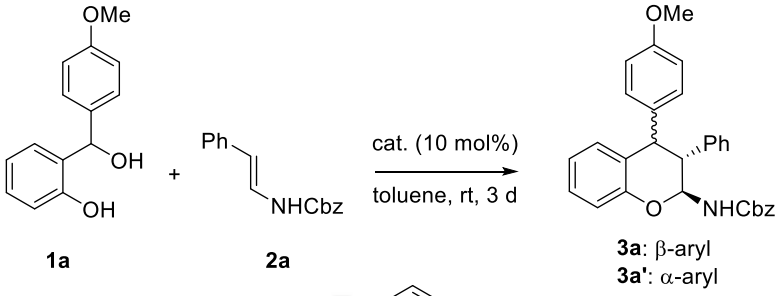


Scheme 13. Proposed strategy for the synthesis of 2,3,4-trisubstituted chromans.

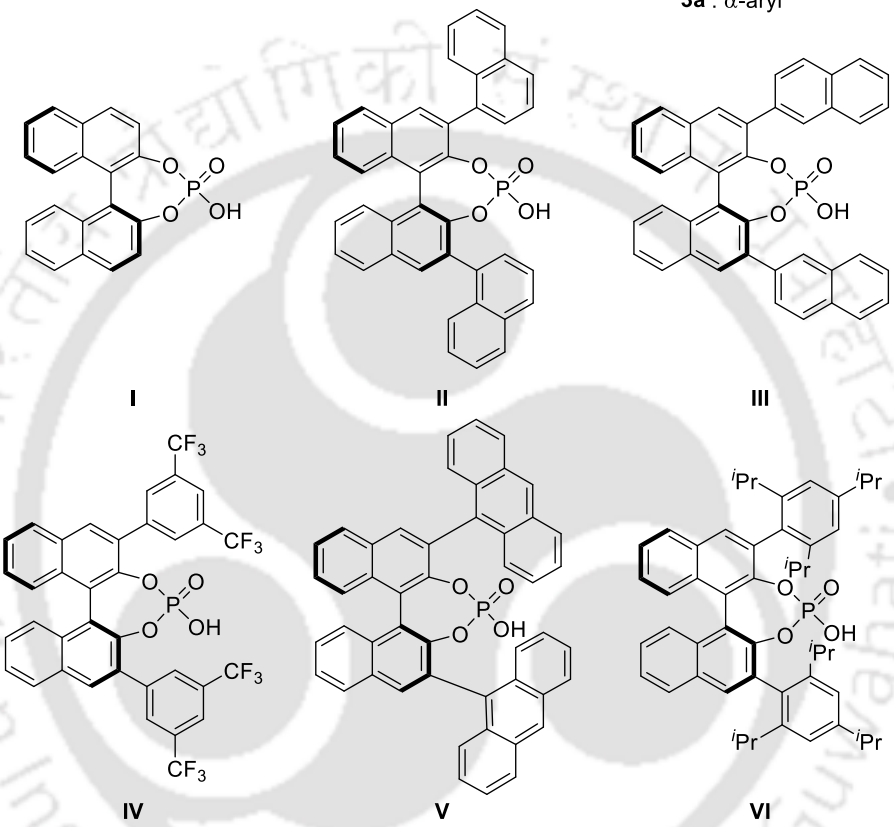
2.5. Result and Discussion:

Initially we started the optimization study by executing a model reaction between *ortho*-hydroxybenzyl alcohol **1a** and *N*-Cbz enecarbamate **2a** using 10 mol% BINOL-based phosphoric acid catalyst **I** in toluene solvent at room temperature (Table 1, entry 1). After three days, the chroman mixture **3a/3a'** was isolated in 77% yield and with 1:2 diastereomeric ratio. Although the diastereoselectivity of the reaction was good, the enantiomeric excess was low. The relative structures of **3a** and **3a'** were solved by NOE experiments. Then different 3,3'-substituted BINOL-phosphoric acid catalysts were screened. For example, catalyst **II** and catalyst **III** having 1-naphthyl and 2-naphthyl substitutions on the 3,3'-positions furnished the products (**3a/3a'**) in good enantioselectivities but diastereoselectivity was moderate (entries 2-3). Sterically demanding catalyst **IV** having bis *meta*-CF_3 groups on the 3,3'-phenyl groups could not change the outcome of the reaction (entry 4). An improvement in enantioselectivity was observed with catalyst **V** having 9-anthryl groups on the 3,3'-positions (entry 5). Interestingly, more sterically demanding catalyst **VI** having 2,4,6-triisopropylated 3,3'-phenyl groups delivered the products in higher enantioselectivities and with higher diastereoselectivity (entry 6). In this case the products **3a**/**3a'** were isolated in 81% yield and with 5.6:1 diastereomeric ratio. The major diastereomer **3a** was obtained in 90% ee.

Table 1. Catalyst screening



1a **2a** **3a**: β-aryl **3a'**: α-aryl



I **II** **III**

IV **V** **VI**

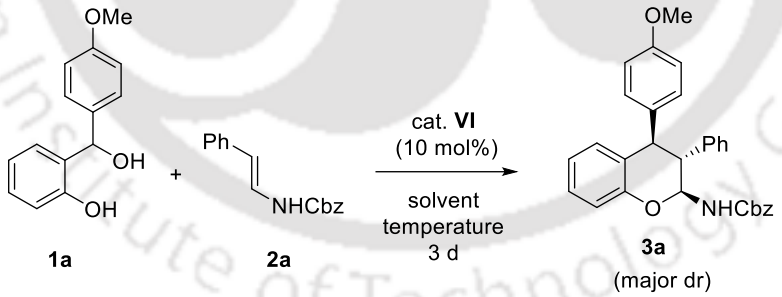
entry[a]	catalyst	yield (%)[b]	dr (**3a**/**3a'**)[c]	ee (**3a**/**3a'**)(%)[d]
1	**I**	77	1:2	20/14
2	**II**	60	1:1.4	78/72
3	**III**	62	1:1	60/80
4	**IV**	65	1:1	54/70
5	**V**	71	1:2	88/74
6	**VI**	**81**	**5.6:1**	**90/82**

[a]Reaction conditions: 0.04 mmol of **1a** and 0.06 mmol of **2a** in 0.2 mL toluene using 10 mol% catalyst at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined using HPLC with a stationary phase chiral column.

2.5.1. Solvent and temperature screening:

After getting the best catalyst i.e. catalyst **VI**, other reaction parameters such as solvent, temperature, use of molecular sieves were also screened (Table 2). Initially, various solvents were varied at room temperature. For example, when dichloromethane was used as the solvent, products **3a**/**3a'** were obtained in 54% yield and with 4.7:1 dr. In addition, the enantioselectivity of the major diastereomer got slightly decreased to 88% (Table 2, entry 2). A significant drop in diastereomeric ratio and enantioselectivity of the major dr were observed when 4 Å molecular sieves was employed (entry 3). Polar solvent like DMF was not suitable for such reaction (entry 4). Other halogenated solvent such as 1,2-dichloroethane afforded the **3a** chroman product with 90% enantiomeric excess although yield and dr value of the reaction were moderate (74% yield, 3.6:1 dr) (entry 5). Furthermore, the enantioselectivity did not improve after lowering the temperature to 0 ^oC (entry 6) and also diastereoselectivity was decreased remarkably. Finally, toluene at room temperature was found to be the best conditions for this reaction.

Table 2. Solvent and temperature screening



entry[a]	solvent	temperature	yield (%)[b]	dr (**3a**/**3a'**)[c]	ee (%)[d]
1	**toluene**	**rt**	**81**	**5.6:1**	**90**
2	DCM	rt	54	4.7:1	88
3[e]	DCM	rt	65	4.4:1	82

4[f]	DMF	rt	n.d	-	-
5	1,2-DCE	rt	74	3.6:1	90
6	toluene	0 ºC	82	2.4:1	88

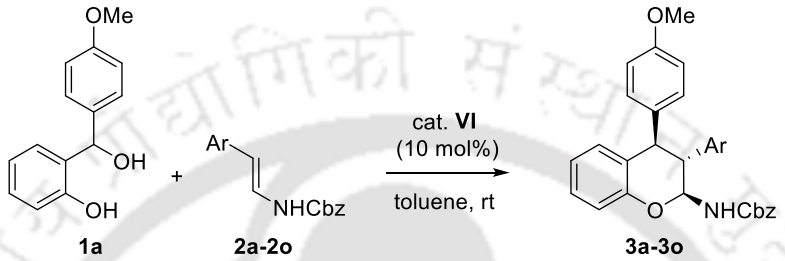
[a]Reaction conditions: 0.04 mmol of **1a** and 0.06 mmol of **2a** in 0.2 mL solvent using 10 mol% (*S*)-TRIP catalyst for 3 days. [b]Isolated yield after silica gel column chromatography. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined using HPLC with a stationary phase chiral column and of the major diastereomer. [e]5 mg 4 Å MS was used. [f]n.d = Not determined.

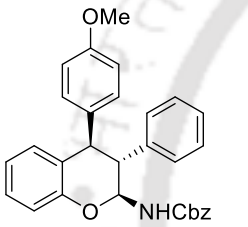
2.5.2. Substrate scope:

After the optimized conditions got established, the scope of the reaction was studied. Initially a variety of enecarbamates **2** having substitutions on the aryl group of the olefin was examined (Table 3). Delightfully, the reactions proceeded well in all cases and typically completed within 3-4 days at room temperature. At the beginning, different *para*-substitutions were screened and the reaction outcome was pleasing. For example, enecarbamate **2b** having *para*-methyl substituent furnished the product **3b** in 84% yield with 5:1 diastereomeric ratio and 92% enantiomeric excess. 4-^{i}Pr substituted *N*-Cbz enecarbamatet **2c** delivered the chroman product **3c** with high yield and excellent diastereoselectivity and enantiomeric excess. Similar results were also observed in case of product **3d** when 4-*tert*-butyl substituted enecarbamate **2d** was engaged in the reaction. To our delight, 4-fluoro substituted enecarbamate **2e** afforded the product **3e** almost as a single diastereomer and with moderate enantiomeric excess (84%). Also, the products **3f**-**3g** having 4-chloro and 4-bromo substitutions were obtained in acceptable yields and with high diastereo- and enantioselectivities. Then different *meta*-substitutions were studied and here also the products were attained in moderate to high yields as well as with high enantioselectivities. *meta*-Methyl substituted enecarbamate **2h** provided the product **3h** with 70% yield and with 10:1 dr and 92% enantiomeric excess. The product **3i** having 3-chloro substituent was isolated in moderate yield (48%) with 5:1 dr and 94% enantiomeric excess. Gratifyingly, the enecarbamate **2j** having 3-bromo substituent supplied the product **3j** with high yield and with excellent diastereo- and enantioselectivity. In the next, *ortho*-substituted enecarbamates were tested by varying different alkyl and halogen substituents

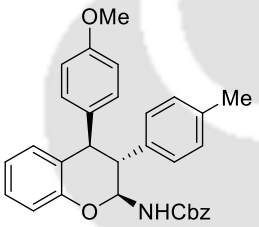
on the aryl ring and here the results were highly promising. 2-Methyl substituted enecarbamate **2k** offered the major product **3k** with 88% enantiomeric excess. Interestingly, the products with halo functionalities **3l-3n** were isolated almost as single diastereomer and with 94% enantiomeric excess. A disubstituted enecarbamate also withstood the reaction condition and delivered the major product **3o** in 92% ee.

Table 3. Scope of *N*-Cbz enecarbamates[a,b,c,d]

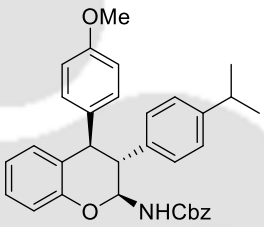




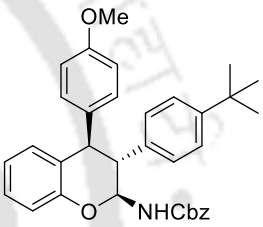
3a, 81%, 5.6:1 dr, 90% ee



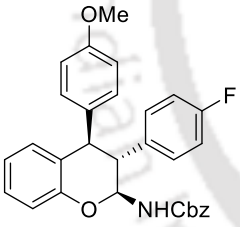
3b, 84%, 5:1 dr, 92% ee



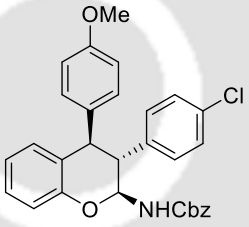
3c, 85%, 8.3:1 dr, 88% ee



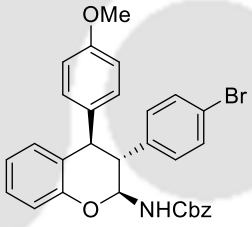
3d, 87%, 9.1:1 dr, 88% ee



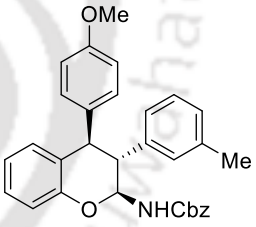
3e, 74%, >20:1 dr, 84% ee



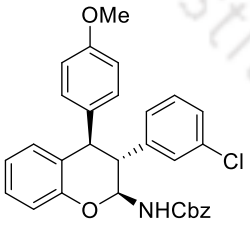
3f, 48%, 8.3:1 dr, 92% ee



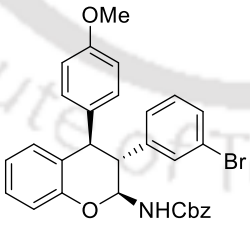
3g, 53%, 9:1 dr, 94% ee



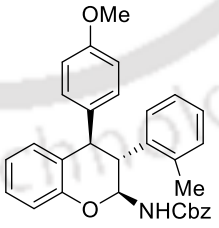
3h, 70%, 10:1 dr, 92% ee



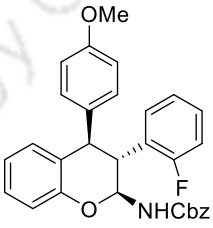
3i, 48%, 5:1 dr, 94% ee



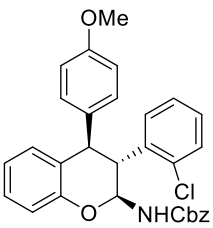
3j, 80%, 20:1 dr, 94% ee



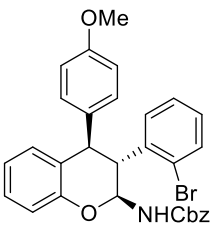
3k, 72%, 4.2:1 dr, 88% ee



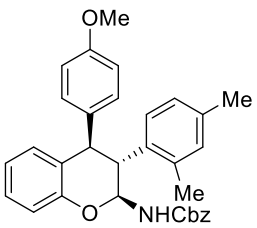
3l, 83%, >20:1 dr, 94% ee



3m, 88%, >20:1 dr, 94% ee



3n, 89%, >20:1 dr, 94% ee

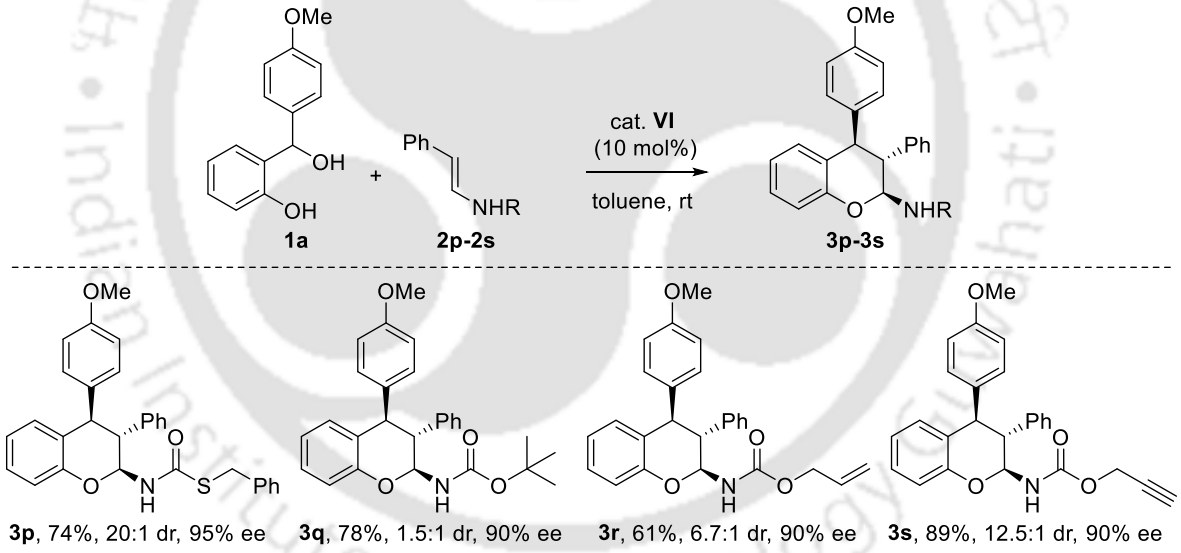


3o, 63%, 4.3:1 dr, 92% ee

[a]Reactions were carried out with catalyst **VI** in toluene at room temperature for 3-4 days. [b]Isolated yield after silica gel column chromatography. [c]Determined using ^{1}H NMR spectroscopy. [d]Determined using HPLC and of the major diastereomer.

The next phase of experiments involved variation of the carbamate moiety and gratifyingly, the fate of the reaction was unaffected (Table 4). Delightfully, *S*-benzyl carbamothioate **2p** delivered the expected chroman product **3p** as almost single diastereomer and with 95% enantiomeric excess. *N*-Boc enecarbamate **2q** participated well in the reaction conditions. Although here the ee of the major product **3q** was excellent, diastereoselectivity was significantly decreased. Other enecarbamates such as **2r** and **2s** having allylic and propargylic substitution respectively were also incorporated in the reaction. In these cases, good to high yields, high dr as well as high enantioselectivities were maintained (Table 4).

Table 4. Scope of other enecarbamates[a,b]

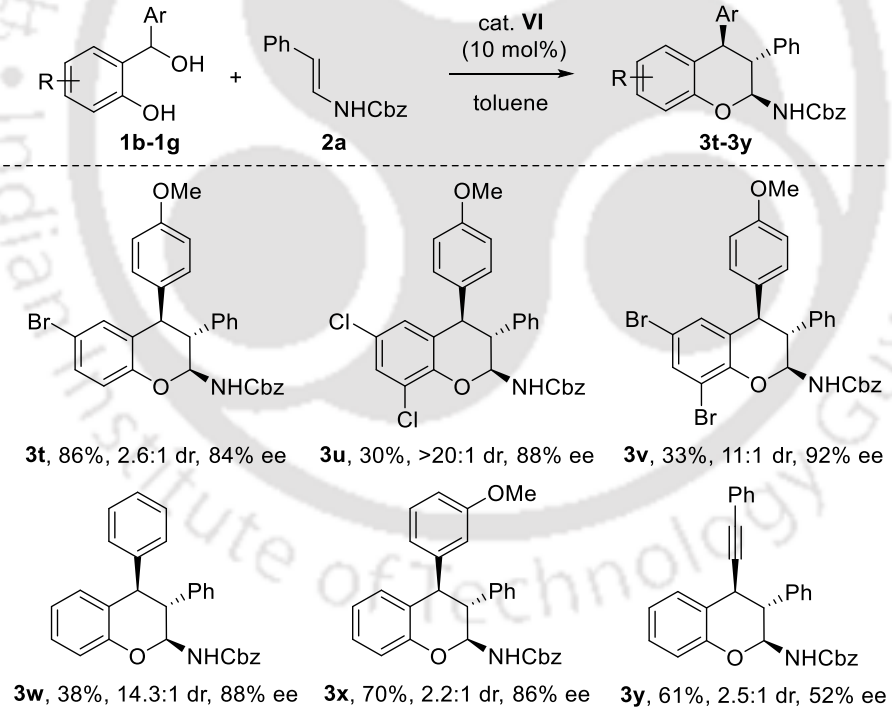


[a]Reaction was carried out with catalyst **VI** in toluene at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography, diastereoselectivity was determined by ^{1}H NMR spectroscopy and enantioselectivity was determined using HPLC with a stationary phase chiral column.

The generality of the reaction was further shown by employing a range of *o*-hydroxybenzyl alcohols (Table 5). Gratifyingly, a range of *o*-hydroxybenzyl alcohols having variations both on the quinone methide fragment and *β*-aryl substituent could be engaged in the reaction and good results were produced. Initially different halo substitutions on the quinone methide component was screened and high enantioselectivities were attained for

products **3t-3v** which can be further functinalized *via* metal catalyzed cross-coupling reactions. The product **3t** was obtained in high yield and with moderate diastereoselectivity. To our delight, excellent diastereoselectivity was observed for products **3u** and **3v**. However, the reactions were sluggish for products **3u** and **3v** and needed to run for 6 days at room temperature and at 50 ^{o}C for 3 days respectively. The enantioselectivity was also high when the *β*-aryl substituents were varied (Table 5). For example, alcohol **1e** having *β*-phenyl motif delivered the product **3w** in 38% yield with 14.3:1 dr and 88% ee. Whereas *β*-3-methoxy phenyl substituted alcohol **1f** furnished the desired product **3x** with high yield (70%) and with high enantiomeric excess (86%) although diastereoselectivity (2.2:1) was less in comparison to **3a** and **3w**. Then we investigated the reaction with different *β*-alkyl substituents and gratifyingly the reaction progressed well with alcohol **1g** having phenyl acetylene motif delivering product **3y** in 61% yield with 2.5:1 dr and 52% ee.

Table 5. Scope of *o*-hydroxybenzyl alcohols[a,b]

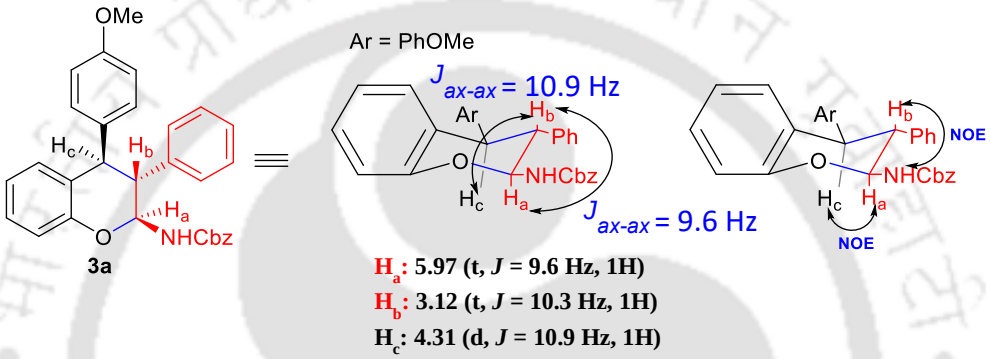


[a]Reaction was carried out with catalyst **VI** in toluene at room temperature for 3 days. [b]Isolated yield after silica gel column chromatography, diastereoselectivity was determined by ^{1}H NMR spectroscopy and enantioselectivity was determined using HPLC with a stationary phase chiral column.

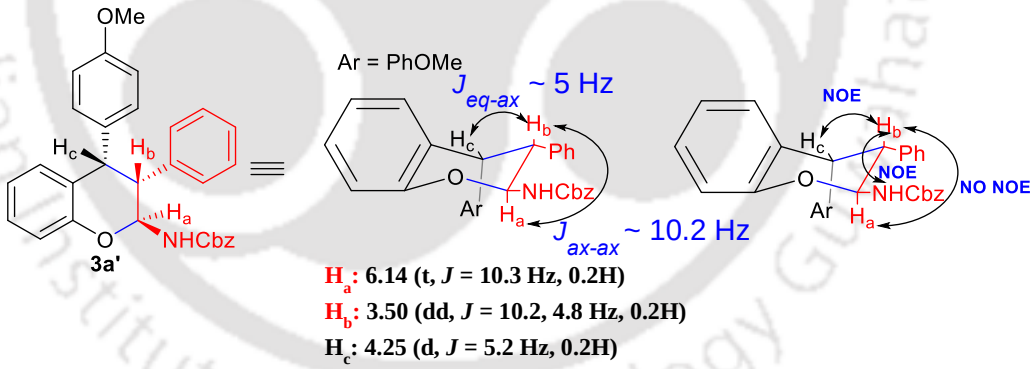
2.5.3. Determination of relative configuration of chroman products 3/3':

The relative stereo chemistry of the products **3a**/**3a'** was confirmed by analyzing the coupling constant value of three characteristic protons H_a, H_b and H_c present in the chroman ring and also by considering the COSY and NOESY interactions in 2D NMR experiments. This has been depicted in Scheme 14 and in the Experimental section. The other products are assumed to have same relative configuration.

Relative configuration of major diastereomer:



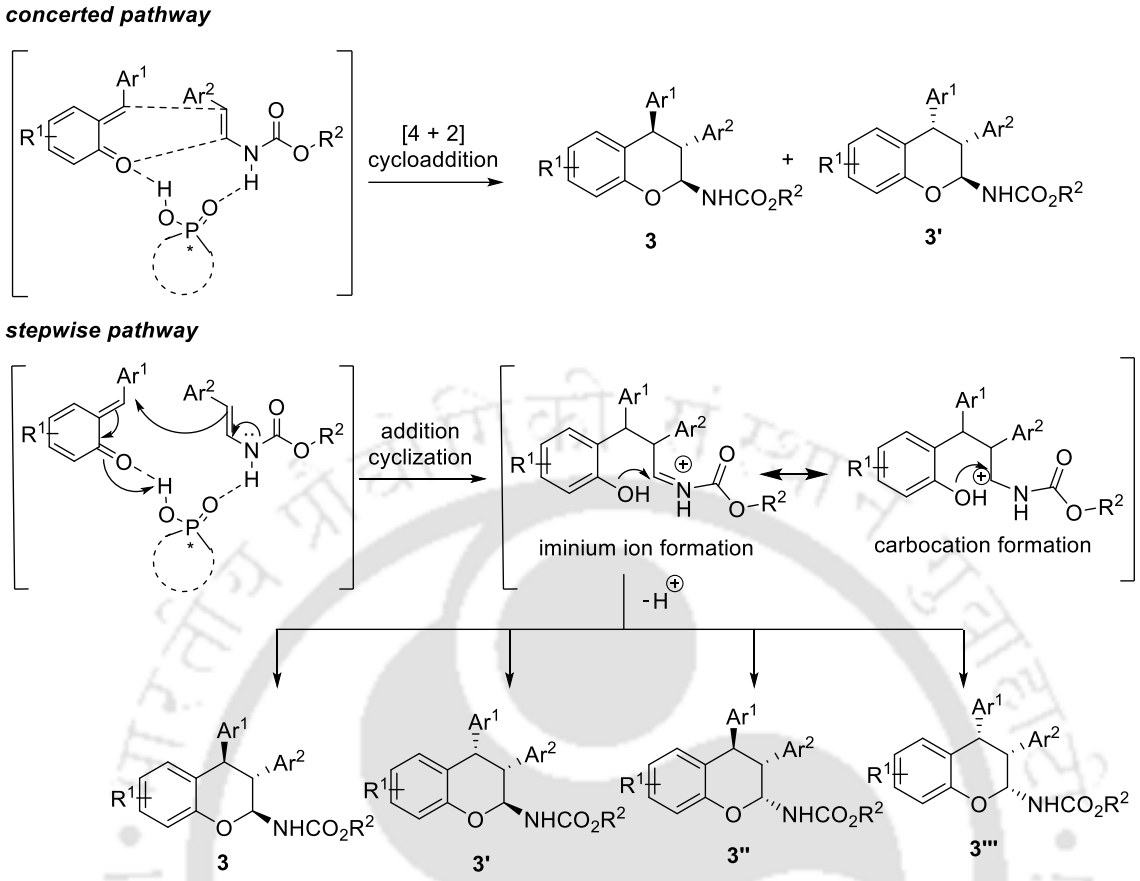
Relative configuration of minor diastereomer:



Scheme 14. Determination of relative configuration of chroman products **3/3'**.

2.5.4. Mechanistic pathway involved in the synthesis of chromans 3/3':

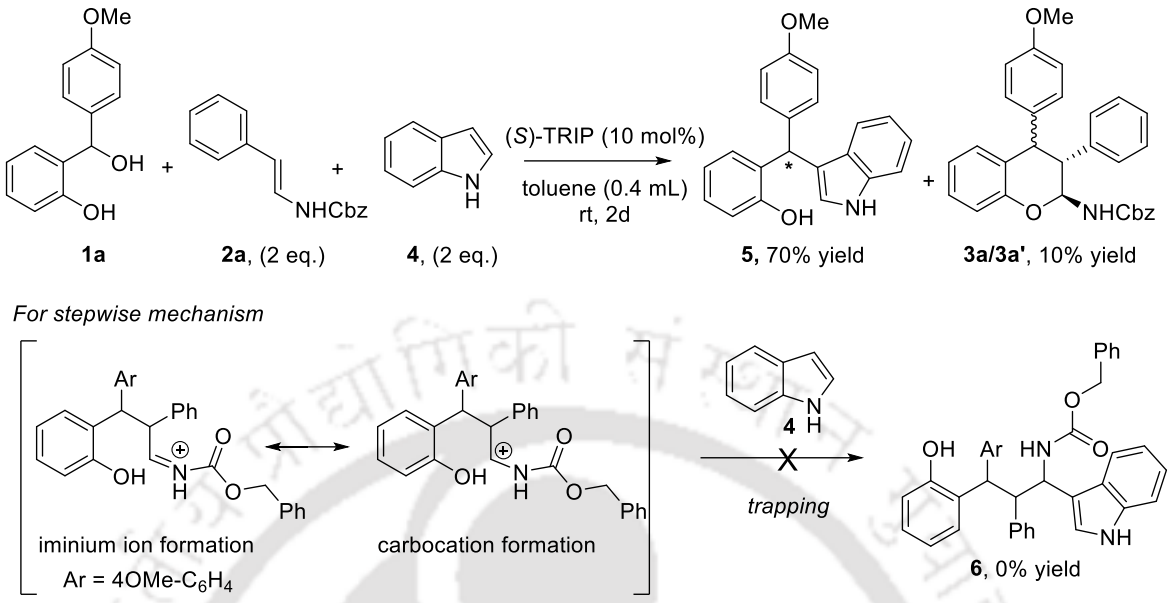
If the reaction proceeds *via* concerted [4+2] mechanism, then maximum two diastereomers formation is possible. Also, *trans*-geometry of enecarbamates **2** will be preserved in the trisubstituted chroman products. Alternatively, if it undergoes *via* stepwise manner then maximum four diastereomers formation is possible. Here, *trans*-geometry of enecarbamates **2** will not essentially be preserved in the final chroman products due to free rotation around C-C bond (Scheme 15).



Scheme 15. Chroman formation based on stepwise and concerted mechanism.

In all of our experiments, we solely observed the presence of two diastereomers **3**/**3'** with generally moderate to high diastereomeric ratio confirmed from ^{1}H NMR experiment and HPLC analysis. Relative stereochemistry of the products **3**/**3'** also suggested the stereo specific *endo*- addition of the enecarbamates **2**. In addition, we did not get any traces of product **3''** & **3'''**. These observations are helpful in supporting the concerted nature of the reaction.

Furthermore, if the reaction proceeded *via* stepwise mechanism, then the iminium ion and carbocation intermediate might be captured by an additional reactive nucleophile like indole for its stability as reported by *Shi et al.*[13] Accordingly, *ortho*-hydroxybenzyl alcohol **1a** (0.086 mmol), *N*-Cbz enecarbamate **2a** (2 eq.) and indole **4** (2 eq.) were reacted under our standard reaction conditions (Scheme 16). Herein, we did not obtain the trapped product **6**. Rather it delivered the indolylphenol product **5** with 70% yield along with trace amount chroman products **3a**/**3a'**. From this experiment it can be concluded that the designed reaction possibly underwent *via* concerted pathway rather than stepwise manner.



Scheme 16. Trapping experiment using indole.

2.5.5. Determination of absolute configuration of chroman product 3:

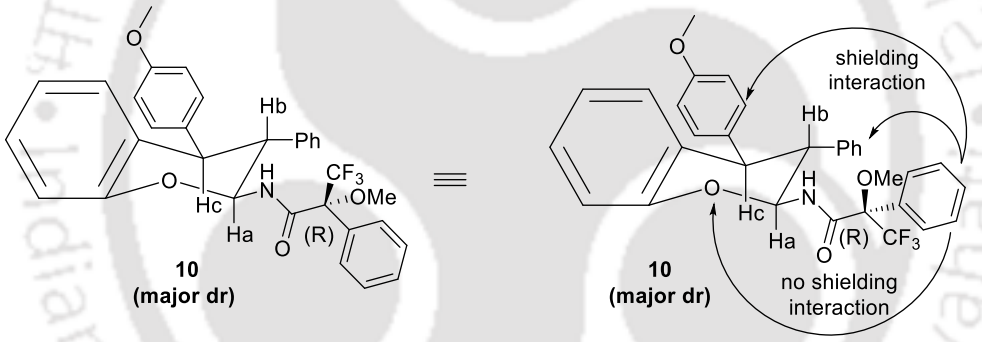
For the determination of absolute configuration, initially recrystallization method was tried using most of the synthesized trisubstituted chroman products. But unfortunately, because of high powder nature of the substrates it was difficult to get the crystal structure. Then an alternative method, i.e. Mosher amide experiment,[23] a procedure for derivatizing and analyzing through the help of ^{1}H NMR of an optically active amine had been performed for the assignment of absolute configuration. For this purpose, chiral product **3q/3q'** had been selected because its conversion into corresponding chiral amine led to no change in configuration at the same time deprotection of Boc group was comparatively easier than Cbz deprotection present in other products.

Accordingly, Boc group of **3q/3q'** was deprotected to chiral amine products **7q/7q'** under formic acid in dichloromethane conditions. After this, amine mixture **7q/7q'** was reacted with (*S*)-(+) MTPA-Cl **8** and (*R*)-(-) MTPA-Cl **9** separately to deliver the corresponding (*R*)-Mosher amide **10/10'** and (*S*)-Mosher amide **11/11'** respectively. Finally, ^{1}H NMR spectra of the products **10** and **11** were analyzed for absolute configuration determination. From the Mosher's methodology,[23] it is known that, in the most stable conformation of the MTPA amide, the trifluoromethyl group remains always *syn*- periplanar situation with

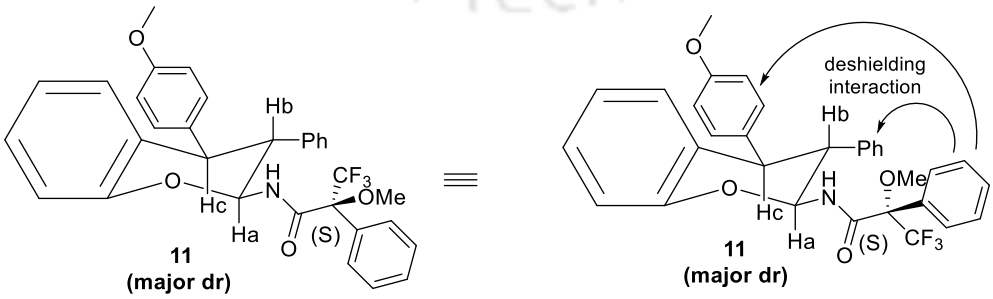
respect to carbonyl group. Furthermore, N-H bond and the carbonyl group prefers *anti*-orientation amongst themselves from minimum energy point of view.

Accordingly, we envisioned the molecular models of our trisubstituted chroman moiety. Analysis of **10** and **11** revealed that H_a, H_b, H_c protons of the major dr were little bit shielded in (*R*)-MTPA-amide **10** compared to (*S*)-MTPA-amide **11** (Scheme 17). Although difference in chemical shift values ($\Delta\delta = (\delta_{11} - \delta_{10})$, ppm) is less for the characteristic protons H_a, H_b and H_c, still it is acceptable as it is common situation in Moser experiments often observed in many other cases also.[23a,24]

	H_a: δ 6.19 (t, *J* = 10.0 Hz, 1H)	shielded
Compound **10**	H_b: δ 3.14 (t, *J* = 10.6 Hz, 1H)	shielded
	H_c: δ 4.35 (d, *J* = 11.0 Hz, 1H)	shielded



	H_a: δ 6.20 (t, *J* = 10.1 Hz, 1H)	deshielded
Compound **11**	H_b: δ 3.15 (d, J = 10.7 Hz, 1H)	deshielded
	H_c: δ 4.36 (d, *J* = 11.2 Hz, 1H)	deshielded



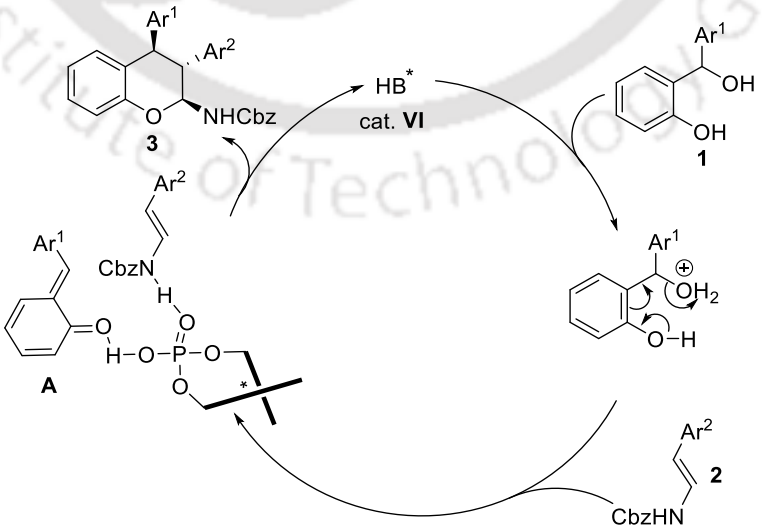
Scheme 17. Mosher amide analysis for absolute configuration determination.

The above results indicated that shielding interaction was present between the phenyl group of the Mosher part and the three adjacent protons. Thus, it could be predicted that the phenyl group adjacent to H_b must be coplanar with the phenyl group of Mosher part. Also, for the concerted mechanism, H_a and H_b must be *trans*- to each other as dienophile enecarbamates having *trans*-geometry. In addition, *J* value, NOESY and COSY analysis (for compound **3a**/**3a'**) had shown that H_b and H_c are also *trans*- to each other for the major diastereomer.

Thus, the absolute configuration for the major diastereomer of compound **3q** was determined as (2*S*,3*R*,4*R*) and the other products are assumed to have same absolute configuration.

2.5.6. Proposed mechanism:

A plausible mechanism has been shown in Scheme 18. In the first step, protonation followed by dehydration of the *ortho*-hydroxybenzyl alcohol **1** catalyzed by phosphoric acid leads to the formation of *ortho*-quinone methide **A**. Then the bifunctional character of phosphoric acid plays the main role in bringing *ortho*-quinone methide **A** and enecarbamate **2** together. Presumably, the catalyst is hydrogen-bonded to the oxygen atom of the *ortho*-quinone methide **A** through its acidic group O-H and simultaneously connected to the enecarbamate N-H moiety through an additional hydrogen bond from the basic phosphoryl oxygen atom. Also, the enecarbamate **2** adjusts in *endo* fashion and consequently the reaction occurs in a concerted pathway that explains the relative *trans*-structure of **3**.



Scheme 18. Plausible mechanism.

2.6. Conclusion:

In conclusion, this report demonstrates the first organocatalytic asymmetric [4+2] cycloannulation reaction between acyclic enecarbamates and *in situ*-generated *ortho*-quinone methides. Commercially available TRIP catalyst was used for our reaction. Reaction conditions are very mild and operationally simple method. Various chiral 2,3,4-trisubstituted chromans were synthesized using this protocol and which could be useful in natural product synthesis.

2.7. Experimental section:

General information:

All the necessary reagents were purchased from commercial suppliers with highest purity grade. They were utilized without further purification unless mentioned. In all cases, oven dried glassware was used during reactions set up. Chiral phosphoric acid catalysts **I**, **IV** and **V** were bought from Sigma Aldrich and other chiral catalysts **II**, **III** and **VI** were made according to the reported procedures.[25] For Grignard reactions, tetrahydrofuran solvent was dried over sodium/benzophenone. Toluene was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Other solvents were purified according to the standard procedures. Progress of the reactions was monitored by performing TLC on silica gel GF-254 using *n*-hexane/ethyl acetate as the solvent system. For column chromatography, 60-120 mesh size silica gel was used.

^{1}H NMR spectra were recorded on 400 MHz and 600 MHz spectrometer using $CDCl_3$ as reference NMR solvent. ^{13}C NMR spectra were recorded on 100 MHz and 150 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) and coupling constants (*J*) were reported in parts per million (ppm) and Hertz (Hz) units respectively. In ^{1}H and ^{13}C NMR, chemical shift values were expressed with reference to $CHCl_3$ (δ(H), 7.26 ppm) and (δ(C), 77.23 ppm, central line of triplet). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet), dt (doublet of triplet).

High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) mode. Melting points were noted with Mel-Tem capillary melting point apparatus. Enantiomeric excesses were determined by HPLC analysis by comparing the

spectra of racemic samples using stationary phase chiral column through the help of Dionex (Ultimate 3000) instrument.

A. General Procedure for the synthesis of *ortho*-hydroxybenzyl alcohols 1a-1g:

Various *ortho*-hydroxybenzyl alcohols were prepared from the reaction of salicyldehyde derivatives and *in situ* Grignard reagents according to the reported procedures.[26]

B. General procedure for the synthesis of various acyclic enecarbamates 2a-2s:

Various acyclic enecarbamates **2a-2s** were synthesized according to the reported procedures.[27] This was overall three steps process. First, substituted *trans*-cinnamic acids were prepared from various benzaldehyde derivatives *via* known procedure.[27a] Next, the *trans*-cinnamic acids were converted to corresponding 3-aryl-acryloyl azides. Finally, 3-aryl-acryloyl azides were transformed to *trans*-acyclic enecarbamates **2a-2s**.[27b,28]

C. General procedure for the synthesis of tri-substituted chromans 3:

To a solution of *ortho*-hydroxybenzyl alcohol (**1**) (0.08 mmol), acyclic enecarbamate (**2**) (0.12 mmol) in 0.4 mL dry toluene, catalyst **VI** (10 mol%) was added. Then the reaction mixture was stirred at room temperature for 3 to 4 days unless otherwise noted. Progress of the reaction was monitored by TLC analysis. After completion of the reaction, the crude mixture was directly subjected to the column chromatography using hexane/ ethyl acetate as eluents to deliver the desired products **3**.

D. General procedure for the Boc group deprotection of substrate 3q/3q':

In a 10 mL Round Bottom Flask under argon atmosphere compound **3q/3q'** (0.37 mmol, 160 mg) was placed. Then 5 mL of 98% formic acid and 1.5 mL dry DCM solvent were added to it. The reaction was continued stirring at room temperature for 3 days. Progress of the reaction was monitored by TLC. After completion of the reaction formic acid was evaporated and then 5 mL water was mixed. pH ~8 was maintained by adding Na_2CO_3 base. The organic phase was extracted with dichloromethane and washed with brine solution. Finally, the crude mixture was purified by column chromatography to deliver the corresponding chiral 4-(4-methoxyphenyl)-3-phenylchroman-2-amine **7q/7q'** with 1.4:1 diastereomeric mixture.

E. General procedure for the preparation of (*S*)-(+) MTPA-Cl and Mosher amide 10/10':

(*S*)-(+) MTPA-Cl **8** was prepared according to the literature procedure.[23b] (*R*)-(+) MTPA, Moshers acid (121 mg, 0.52 mmol) was dissolved in 2.4 mL dry DCM and cooled to 0 ^{o}C. Then oxalyl chloride (0.5 mL, 5.2 mmol) was added followed by the addition of one drop dry DMF. Thereafter, the reaction mixture was continued to stir for 1 hour. Progress of the reaction was then monitored by TLC analysis. The reaction mixture was then concentrated in *vacuo.* After this, residue was suspended in dry hexane and concentrated it again in *vacuo*. Finally, the product (*S*)-(+) MTPA-Cl was dissolved in required amount of dry DCM to prepare 0.21 M solution of corresponding Moshers acid chloride **8**.

In the next step, amine **7q/7q'** (16 mg, 0.048 mmol) was dissolved in 1.2 mL DCM and then previously prepared (*S*)-(+) MTPA-Cl **8** was added followed by the addition of 1.21 mL saturated aqueous Na_2CO_3. The reaction mixture was then stirred overnight. The organic phase was extracted with DCM & concentrated in *vacuo*. Finally purified by column chromatography to afford the Mosher amide **10/10'**.

F. General procedure for the preparation of (*R*)-(-) MTPA-Cl and Mosher amide 11/11':

(*R*)-(-) MTPA-Cl **9** was prepared according to literature procedure.[23b] (*S*)-(-) MTPA, Moshers acid (121 mg, 0.52 mmol) was dissolved in 2.4 mL dry DCM and cooled to 0 ^{o}C. Then oxalyl chloride (0.5 mL, 5.2 mmol) was added followed by the addition of one drop DMF. Thereafter, the reaction mixture was continued to stir for 1 hour. Progress of the reaction was then monitored by TLC analysis. The reaction mixture was concentrated in *vacuo*. After this, residue was suspended in hexane and concentrated it again in *vacuo*. Finally, product (*R*)-(-) MTPA-Cl was dissolved in required amount of dry DCM to prepare 0.21 M solution of corresponding Moshers acid chloride **9**.

In the next step, **7q**/**7q'** amine (16 mg, 0.048 mmol) was dissolved in 1.2 mL DCM and then previously prepared (*R*)-(-) MTPA-Cl **9** was added followed by the addition of 1.21 mL saturated aqueous Na_2CO_3. The reaction mixture was stirred overnight. The organic phase was extracted with DCM & concentrated in *vacuo*. Finally purified by column chromatography to afford the desired Mosher amide product **11/11'**.

2.8. References:

1. For selected examples, see: (a) Breschi, M. C.; Calderone, V.; Martelli, A.; Minutolo, F.; Rapposelli, S.; Testai, L.; Tonelli F.; Balsamo, A. *J. Med. Chem*. **2006**, *49*, 7600. (b) Khelili, S.; Florence, X.; Bouhadja, M.; Abdelaziz, S.; Mechouch, N.; Mohamed, Y.; de Tullio, P. D.; Lebrun P.; Pirotte, B. *Bioorg. Med. Chem*. **2008**, *16*, 6124. (c) Coi, A.; Bianucci, A. M.; Calderone, V.; Tstai, L.; Digiacomo, M.; Rapposelli S.; Balsamo, A. *Bioorg. Med. Chem.* **2009**, *17*, 5565.
2. Brigelius-Flohé, R.; J Kelly, F.; T Salonen, J.; Neuzil, J.; Zingg, J.-M.; Azzi, A. *Am. J. Clin. Nutr*. **2002**, *76*, 703.
3. Sawadjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470.
4. (a) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1764. (b) Ohmori, K.; Ushimaru, N.; Suzuki, K. *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 12002.
5. Umareddy, P.; Veerareddy, A. *J. Chem. Pharm. Res.* **2015**, *7*, 736.
6. Salomon, R. G.; Lal, K.; Mazza, S. M.; Zarate, E. A.; Youngs, W. J. *J. Am. Chem. Soc*. **1988**, *110*, 5213.
7. Tatsuta, K.; Tamura, T.; Mase, T. *Tetrahedron Lett*. **1999**, *40*, 1925.
8. Casiraghi, G.; Cornia, M.; Casnati, G.; Fava, G. G.; Belicchi, M. F. *J. Chem. Soc. Chem. Commun.* **1986**, *3*, 271.
9. For selected recent examples, see: (a) Sunden, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. –Eur. J*. **2007**, *13*, 574. (b) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (c) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776. (d) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, A.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed*. **2010**, *49*, 8379. (e) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 808. (f) Ramachary, D. B.; Shiva Prasad, M. S.; Madhavachary, R. *Org. Biomol. Chem*. **2011**, *9*, 2715. (g) Jia, Z.-X.; Luo, Y.-C.; Cheng, X.-n.; Xu, P.-F.; Gu, Y.-C. *J. Org. Chem*. **2013**, *78*, 6488. (h) Poulsen, P. H.; Feu, K. S.; Paz, B. M.; Jensen, F.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2015**, *54*, 8203. (i) Saha, P.; Biswas, A.; Molletti, N.; Singh, V.

A. *J. Org. Chem*. **2015**, *80*, 11115. (j) Zhu, Y.; Li, X.; Chen, Q.; Su, J.; Jia, F.; Qiu, S.; Ma, M.; Sun, Q.; Yan, W.; Wang, K.; Wang, R. *Org. Lett.* **2015**, *17*, 3826.

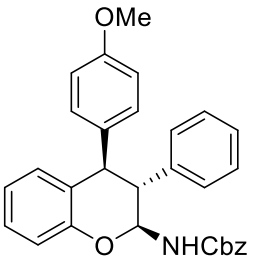
10. For selected reviews on the synthesis of chroman derivatives using organocatalysts, see: (a) Núńez, M. G.; García, P.; Moro, R. F.; Díez, D. *Tetrahedron* **2010**, *66*, 2089. (b) Bhanja, C.; Jena, S.; Nayak S.; Mohapatra, S. *Beilstein J. Org. Chem*. **2012**, *8*, 1668. (c) Nising, C. F.; Brase, S. *Chem. Soc. Rev*. **2012**, *41*, 988.
11. Willis, N. J.; Bray, C. D. *Chem. Eur. J.* **2012**, *18*, 9160.
12. Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed*. **2015**, *54*, 5762.
13. Zhao, J.-J.; Sun, S.-B.; He, S.-H.; Wu, Q.; Shi, F. *Angew. Chem. Int. Ed*. **2015**, *54*, 5460.
14. (a) Saha, S.; Schneider, C. *Chem. Eur. J*. **2015**, *21*, 2348. (b) Saha, S.; Schneider, C. *Org. Lett*. **2015**, *17*, 648.
15. Alamsetti, S. K.; Spanka, M.; Schneider, C. *Angew. Chem. Int. Ed*. **2016**, *55*, 2392.
16. Zhang, J.; Liu, X.; Guo, S.; He, C.; Xiao, W.; Lin, L.; Feng, X. *J. Org. Chem*. **2018**, *83*, 10175.
17. Zhang, J.; Lin, L.; He, C.; Xiong, Q.; Liu, X.; Feng, X. *Chem. Commun*. **2018**, *54*, 74.
18. Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed*. **2008**, *47*, 4122.
19. Dagousset, G.; Drouet, F.; Masson, G.; Zhu, J. *Org. Lett*. **2009**, *11*, 5546.
20. Dagousset, G.; Zhu, J.; Masson, G. *J. Am. Chem. Soc*. **2011**, *133*, 14804.
21. He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. *Angew. Chem. Int. Ed*. **2013**, *52*, 11088.
22. Wang, Y.; Wang, Q.; Zhu, J. *Chem. Eur. J*. **2016**, *22*, 8084.
23. For a review, see: (a) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. Also see: (b) Fox, D. J.; Parris, S.; Pedersen, D. S.; Tyzack, C. R.; Warren, S. *Org. Biomol. Chem.* **2006**, *4*, 3108.
24. (a) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939. (b) Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem*. **1997**, *62*, 7569.
25. (a) Wipf, P.; Jung, J.-K. *J. Org. Chem*. **2000**, *65*, 6319. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed*. **2004**, *43*, 1566. (c) Akiyama, T. PCT Int. Appl. WO 200409675, **2004**. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356. (e) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*,

11804. (f) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett*. **2005**, ***7***, 2583. (g) Akiyama, T.; Saitoh, Y.; Morita, H.; Fuchibe, K. *Adv. Synth. Catal*. **2005**, *347*, 1523. (h) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc*. **2005**, ***127***, 9360. (i) Terada, M.; Uraguchi, D.; Sorimachi, K.; Shimizu, H. PCT Int. Appl. WO 2005070875, **2005**. (j) Seayad, J.; Seayad, A.-M.; List, B. *J. Am. Chem. Soc*. **2006**, *128*, 1086.

26. (a) Meier, B.; Dumez, J.-N.; Stevanato, G.; Hill-Cousins, J. T.; Roy, S. S.; Håkansson, P.; Mamone, S.; Brown, R. C. D.; Pileio, G.; Levitt, M. H. *J. Am. Chem. Soc.* **2013**, *135*, 18746. (b) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun*. **2013**, *49*, 1660. (c) Saha, S.; Schneider, C. *Org. Lett*. **2015**, *17*, 648.
27. (a) Li, X.; Sheng, J.; Huang, G.; Yin, F.; Sang, D. *Eur. J. Med. Chem*. **2015**, *97*, 32. (b) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett*. **2014**, *16*, 1240.
28. Gharui, C.; Singh, S.; Pan, S. C. *Org. Biomol. Chem.* **2017**,*15*, 7272.

2.9. Characterization Data of Products:

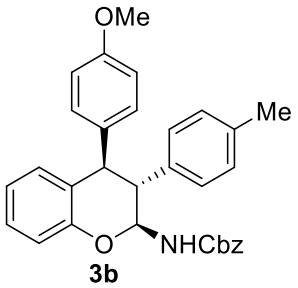
Benzyl 3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3a/3a')



3a

Compound **(3a/3a')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (30.2 mg, 81% yield); **mp**: 114-116 ^{o}C; **Diastereomeric ratio:** 5.6:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 3H), 7.23 – 7.13 (m, 7H), 7.03 (d, *J* = 8.2 Hz, 0.3H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 5.6 Hz, 2H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 0.5H), 6.51 (d, *J* = 8.6 Hz, 0.4H), 6.14 (t, *J* = 10.3 Hz, 0.2H), 5.97 (t, *J* = 9.6 Hz, 1H), 5.42 (d, *J* = 8.9 Hz, 1H), 5.03 (dd, *J* = 30.8, 11.1 Hz, 2.2H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.25 (d, *J* = 5.2 Hz, 0.2H), 3.73 (s, 0.5H), 3.72 (s, 3H), 3.50 (dd, *J* = 10.2, 4.8 Hz, 0.2H), 3.12 (t, *J* = 10.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.4, 155.5, 154.0, 138.8, 136.1, 134.6, 130.1, 128.9, 128.7, 128.4, 128.3, 128.1, 127.3, 126.2, 121.4, 117.2, 113.9, 82.1, 67.2, 55.3, 53.0, 50.8; **HRMS (+ESI):** Calc for $C_{30}H_{28}NO_4$ $[M+H]^+$ 466.2013; found: 466.2016; The ee value of the major diastereomer 90% (t_{major} = 20.1 min, t_{minor} = 15.0 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

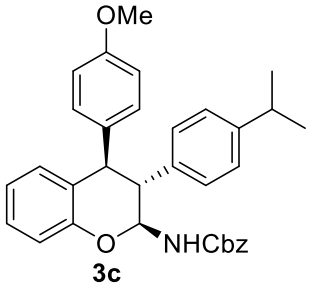
Benzyl 3,4-dihydro-4-(4-methoxyphenyl)-3-p-tolyl-2H-chromen-2-ylcarbamate (3b/3b')



3b

Compound **(3b/3b')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (32.2 mg, 84% yield); **mp**: 53-55 ^{o}C; **Diastereomeric ratio:** 5:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.30 (brs, 3H), 7.20 (brs, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.97 (dd, *J* = 15.2, 7.8 Hz, 4H), 6.84 – 6.75 (m, 5H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 0.4H), 6.52 (d, *J* = 8.4 Hz, 0.4H), 6.10 (t, *J* = 10.2 Hz, 0.2H), 5.93 (brs, 1H), 5.34 (brs, 1H), 5.04 (d, *J* = 19.8 Hz, 2.4H), 4.29 (d, *J* = 11.0 Hz, 1H), 4.22 (d, *J* = 5.3 Hz, 0.2H), 3.73 (s, 3.6H), 3.07 (t, *J* = 9.6 Hz, 1H), 2.29 (s, 0.5H), 2.27 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.4, 155.5, 154.0, 136.8, 136.2, 135.7, 134.8, 131.4, 130.2, 130.1, 129.6, 129.0, 129.0, 128.7, 128.3, 128.2, 128.0, 126.3, 124.7, 121.3, 121.1, 117.2, 117.0, 113.8, 113.3, 82.2, 82.2, 67.2, 67.2, 55.4, 55.3, 52.5, 50.7, 48.6, 48.4, 21.3; **HRMS (+ESI):** Calc for $C_{31}H_{30}NO_4$ $[M+H]^+$ 480.2169; found: 480.2172; The ee value of the major diastereomer 92% (t_{major} = 33.6 min, t_{minor} = 58.2 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Benzyl 3,4-dihydro-3-(4-isopropylphenyl)-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3c/3c')

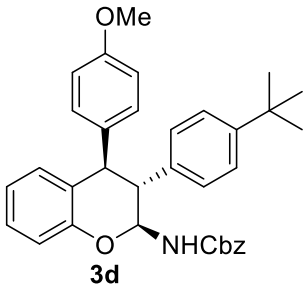


3c

Compound **(3c/3c')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; Pale yellow solid (34.5 mg, 85% yield); **mp**: 48-50 ^{o}C; **Diastereomeric ratio:** 8.3:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.30 (brs, 3H), 7.22 (brs, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.82 (dd, *J* = 12.8, 6.2 Hz, 3H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 0.5H), 6.48 (d, *J* = 8.5 Hz, 0.3H), 6.11 (t, *J* = 10.2 Hz, 0.1H), 5.94 (brs, 1H), 5.35 (d, *J* = 7.5 Hz, 1H), 5.04 (d, *J* = 19.8 Hz, 2.1H), 4.29 (d, *J* = 10.9 Hz, 1H), 4.23 (d, *J* = 5.3 Hz, 0.12H), 3.73 (s, 3.4H), 3.08 (t, *J* = 9.8 Hz, 1H), 2.83 (dt, *J* = 13.8, 6.9 Hz, 1.1H), 1.20 (dd, *J* = 6.9, 3.1 Hz, 6.7H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.4, 155.56, 154.0, 147.7, 136.0, 134.9, 131.4, 130.2,

129.0, 128.7, 128.3, 128.2, 128.0, 126.8, 126.3, 121.3, 117.2, 113.8, 113.2, 82.2, 67.2, 55.3, 52.5, 50.7, 33.8, 24.1, 24.1; **HRMS (+ESI):** Calc for $C_{33}H_{34}NO_4$ $[M+H]^+$ 508.2482; found: 508.2483; The ee value of the major diastereomer 88% (t_{major} = 24.8 min, t_{minor} = 20.0 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (93:7) up to 30.0 min thereafter, with *n*-hexane/*i*-PrOH (86:14) as the eluent, flow: 1.0 mL/min, 274 nm, 25 ^oC.

Benzyl 3-(4-tert-butylphenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3d/3d')

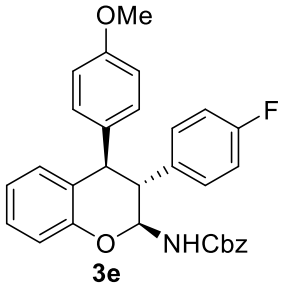


3d

Compound **(3d/3d')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (36.3 mg, 87% yield); **mp**: 56-58 ^oC; **Diastereomeric ratio:** 9.1:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 4H), 7.23 (brs, 2H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 6.82 (dd, *J* = 16.1, 8.0 Hz, 3H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 0.3H), 6.47 (d, *J* = 8.5 Hz, 0.2H), 6.10 (t, *J* = 10.3 Hz, 0.1H), 5.93 (brs, 1H), 5.34 (brs, 1H), 5.04 (d, *J* = 20.0 Hz, 2H), 4.29 (d, *J* = 10.8 Hz, 1H), 4.23 (d, *J* = 5.2 Hz, 0.11H), 3.73 (s, 3.4H), 3.10 (t, *J* = 7.2 Hz, 1H), 1.26 (s, 10H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.4, 155.6, 154.0, 150.1, 136.2, 135.6, 135.0, 131.4, 130.2, 128.7, 128.3, 128.1, 128.0, 127.9, 126.3, 125.7, 125.1, 121.3, 117.2, 113.8, 113.1, 82.2, 67.2, 55.3, 52.4, 50.6, 34.6, 31.5; **HRMS (+ESI):** Calc for $C_{34}H_{36}NO_4$ $[M+H]^+$ 522.2639; found: 522.2639; The ee value of the major diastereomer 88% (t_{major} = 23.9 min, t_{minor} = 19.9 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (93:7) up to 55.1 min thereafter, with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 274 nm, 25 ^oC.

Benzyl 3-(4-fluorophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3e/3e')

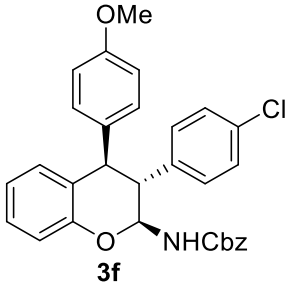
Compound **(3e/3e')** was purified by silica gel column chromatography using 7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (28.6 mg, 74% yield); **mp**: 53-55 ^oC; **Diastereomeric ratio: >20:1**; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs,



3e

3.2H), 7.19 (brs, 2H), 7.16 (t, *J* = 7.8 Hz, 1.3H), 6.95 (d, *J* = 8.2 Hz, 1.1H), 6.87 (d, *J* = 6.5 Hz, 4.3H), 6.82 (t, *J* = 7.4 Hz, 1.5H), 6.76 (d, *J* = 8.4 Hz, 2.3H), 6.72 (d, *J* = 7.7 Hz, 1.1H), 6.69 (d, *J* = 8.6 Hz, 2.2H), 6.08 (t, *J* = 10.3 Hz, 0.05H), 5.93 (t, *J* = 9.9 Hz, 1H), 5.35 (brs, 1.1H), 5.04 (s, 2.1H), 4.25 (d, *J* = 11.1 Hz, 1.1H), 3.73 (s, 3.3H), 3.10 (t, *J* = 10.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 162.8, 161.2, 158.5, 155.5, 154.0, 136.0, 134.6, 134.3, 130.1, 129.8, 129.8, 128.7, 128.4, 128.2, 128.1, 125.9, 121.4, 117.2, 115.8, 115.7, 113.9, 82.0, 67.3, 55.3, 52.4, 50.9; **HRMS (+ESI):** Calc for $C_{30}H_{30}FN_2O_4$ $[M+NH_4]^+$ 501.2184; found: 501.2178; The ee value of the major diastereomer 84% (t_{major} = 14.7 min, t_{minor} = 12.9 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

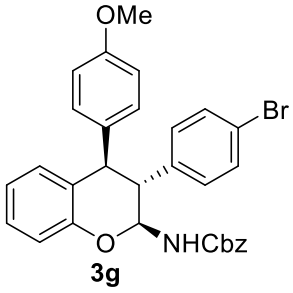
Benzyl 3-(4-chlorophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3f/3f')



3f

Compound **(3f/3f')** was purified by silica gel column chromatography using 6-7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (19.2 mg, 48% yield); **mp**: 56-58 °C; **Diastereomeric ratio:** 8.3:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.32 (d, *J* = 6.8 Hz, 3.3H), 7.20 (d, *J* = 5.8 Hz, 1.9H), 7.15 (t, *J* = 7.1 Hz, 3.4H), 6.95 (d, *J* = 8.2 Hz, 1.2H), 6.85 (d, *J* = 7.7 Hz, 1.9H), 6.82 (t, *J* = 7.5 Hz, 1.5H), 6.76 (d, *J* = 8.4 Hz, 2.3H), 6.71 (d, *J* = 7.8 Hz, 1.3H), 6.69 (d, *J* = 8.6 Hz, 2.2H), 6.65 (d, *J* = 8.6 Hz, 0.3H), 6.51 (d, J = 8.6 Hz, 0.2H), 6.07 (t, *J* = 10.4 Hz, 0.12H), 5.93 (t, *J* = 10.0 Hz, 1H), 5.28 (d, *J* = 9.3 Hz, 1H), 5.05 (s, 2.2H), 4.25 (d, *J* = 11.1 Hz, 1.2H), 3.74 (s, 3.4H), 3.10 (t, *J* = 10.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**:δ 158.6, 155.4, 153.9, 137.5, 136.0, 134.2, 133.1, 130.1, 130.1, 129.7, 129.1, 128.8, 128.5, 128.2, 128.1, 125.9, 121.5, 117.2, 114.0, 81.9, 67.3, 55.4, 52.6, 50.8; **HRMS (+ESI):** Calc for $C_{30}H_{30}ClN_2O_4$ $[M+NH_4]^+$ 517.1889; found: 517.1895; The ee value of the major diastereomer 92% (t_{major} = 50.8 min, t_{minor} = 109.5 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

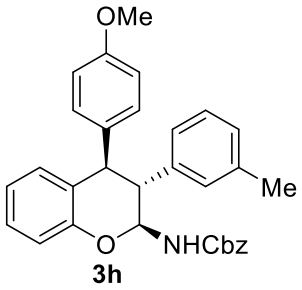
Benzyl 3-(4-bromophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3g/3g')



3g

Compound **(3g/3g')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White amorphous solid (23.1 mg, 53% yield); **Diastereomeric ratio:** 9:1; **^{1}H NMR (600 MHz, CDCl3)**: δ 7.30 (d, J = 4.9 Hz, 1H), 7.24 (d, J = 8.4 Hz, 4H), 7.19 (s, 1H), 7.13 (d, J = 6.0 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.74 – 6.71 (m, 2H), 6.69 (d, J = 8.5 Hz, 2H), 6.63 (t, J = 9.6 Hz, 3H), 6.58 (d, J = 8.7 Hz, 1H), 6.45 (d, J = 8.6 Hz, 1H), 6.00 (t, J = 10.5 Hz, 0.11H), 5.86 (t, J = 9.9 Hz, 1H), 5.25 (d, J = 9.9 Hz, 1H), 4.98 (s, 2.2H), 4.17 (d, J = 11.1 Hz, 1.1H), 3.67 (s, 3.4H), 3.02 (t, J = 10.5 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.6, 155.4, 153.9, 138.0, 136.0, 134.2, 132.0, 130.1, 130.1, 130.0, 128.8, 128.5, 128.2, 128.1, 125.9, 121.5, 121.3, 117.2, 114.0, 81.8, 67.3, 55.4, 52.6, 50.8; **HRMS (+ESI):** Calc for $C_{30}H_{30}BrN_2O_4$ $[M+NH_4]^+$ 561.1383; found: 561.1377; The ee value of the major diastereomer 94% (t_{major} = 57.1 min, t_{minor} = 108.3 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (92:8) up to 45.1 min thereafter, with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1 mL/min, 220 nm, 25 ^oC.

Benzyl 3,4-dihydro-4-(4-methoxyphenyl)-3-m-tolyl-2H-chromen-2-ylcarbamate (3h/3h')

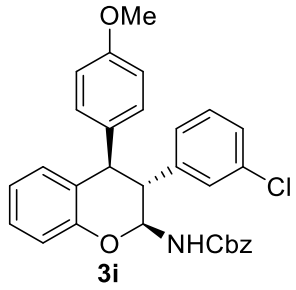


3h

Compound **(3h/3h')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; Pale yellow solid (26.9 mg, 70% yield); **mp**: 52–54 ^oC; **Diastereomeric ratio:** 10:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 3H), 7.20 (brs, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 0.3H), 6.97 (t, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 0.2H), 6.82 (t, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 7.6 Hz, 3H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 0.3H), 6.50 (d, *J* = 8.6 Hz, 0.3H), 6.10 (t, *J* = 10.3 Hz, 0.1H), 5.93 (t, *J* = 9.3 Hz, 1H), 5.34 (d, *J* = 8.9 Hz, 1H), 5.04 (dd, *J* = 24.5, 11.5 Hz, 2H), 4.31 (d, *J* =

11.1 Hz, 1H), 4.23 (d, *J* = 5.3 Hz, 0.1H), 3.73 (s, 3.3H), 3.06 (t, *J* = 10.2 Hz, 1H), 2.23 (s, 3H), 2.19 (s, 0.3H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.4, 155.5, 154.0, 138.7, 138.3, 136.1, 134.8, 131.4, 130.1, 129.0, 128.7, 128.3, 128.1, 128.0, 126.3, 125.4, 124.6, 121.4, 117.2, 113.8, 82.1, 67.2, 55.3, 52.9, 50.6, 21.6; **HRMS (+ESI):** Calc for $C_{31}H_{30}NO_4$ $[M+H]^+$ 480.2169; found: 480.2170; The ee value of the major diastereomer 92% (t_{major} = 19.0 min, t_{minor} = 14.3 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 274 nm, 25 °C.

Benzyl 3-(3-chlorophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3i/3i')

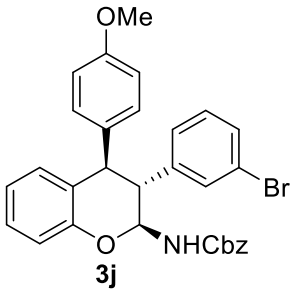


3i

Compound **(3i/3i')** was purified by silica gel column chromatography using 6-7% EtOAc in hexane; **Reaction time**: 4 days at room temperature; White semi solid (19.2 mg, 48% yield); **Diastereomeric ratio:** 5:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.32 (d, *J* = 6.9 Hz, 4H), 7.22 (d, *J* = 6.4 Hz, 2H), 7.18 – 7.10 (m, 4H), 7.01 (d, *J* = 8.1 Hz, 0.3H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.82 (dd, *J* = 11.0, 3.9 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.71 (dd, *J* = 12.7, 8.3 Hz, 3H), 6.65 (d, *J* = 8.6 Hz, 0.4H), 6.52 (d, *J* = 8.5 Hz, 0.3H), 6.07 (t, *J* = 10.3 Hz, 0.2H), 5.92 (t, *J* = 9.8 Hz, 1H), 5.31 (d, *J* = 9.9 Hz, 1H), 5.06 (brs, 2.1H), 4.28 (d, *J* = 11.0 Hz, 1H), 4.24 (d, *J* = 5.3 Hz, 0.2H), 3.74 (s, 3.6H), 3.10 (t, *J* = 10.4 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.6, 155.4, 153.9, 141.0, 136.0, 134.6, 134.1, 131.4, 130.1, 130.1, 129.5, 128.7, 128.4, 128.2, 128.2, 127.7, 126.5, 125.8, 121.5, 117.2, 114.0, 81.8, 67.4, 55.4, 52.8, 50.6; **HRMS (+ESI):** Calc for $C_{30}H_{30}ClN_2O_4$ $[M+NH_4]^+$ 517.1889; found: 517.1907; The ee value of the major diastereomer 94% (t_{major} = 29.3 min, t_{minor} = 48.7 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

Benzyl 3-(3-bromophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3j/3j')

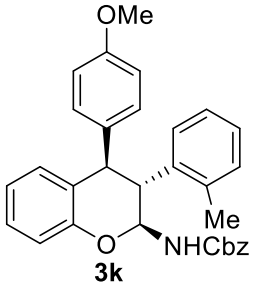
Compound **(3j/3j')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 4 days at room temperature; Yellow white solid (34.8 mg, 80% yield); **mp**: 64-66 °C; **Diastereomeric ratio:** 20:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.31 (t, *J* = 6.9 Hz, 4H), 7.22 (brs, 2H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.09 – 7.02 (m, 2H), 6.95 (d, *J*



3j

= 8.1 Hz, 1H), 6.87 (d, *J* = 6.8 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.71 (dd, *J* = 11.7, 8.5 Hz, 3H), 6.08 (t, *J* = 10.3 Hz, 0.03H), 5.92 (t, *J* = 9.7 Hz, 1H), 5.41 (d, *J* = 9.2 Hz, 1H), 5.05 (d, *J* = 6.1 Hz, 2H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.21 (d, *J* = 5.3 Hz, 0.05H), 3.74 (s, 3.1H), 3.09 (t, *J* = 10.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.6, 155.5, 153.9, 141.3, 136.0, 134.1, 131.5, 130.5, 130.4, 130.1, 130.1, 128.7, 128.4, 128.2, 128.1, 126.9, 125.8, 122.8, 121.5, 117.2, 114.0, 81.8, 67.3, 55.4, 52.7, 50.6; **HRMS (+ESI):** Calc for $C_{30}H_{30}BrN_2O_4$ $[M+NH_4]^+$ 561.1383; found: 561.1428; The ee value of the major diastereomer 94% (t_{major} = 30.1 min, t_{minor} = 48.0 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

Benzyl 3,4-dihydro-4-(4-methoxyphenyl)-3-o-tolyl-2H-chromen-2-ylcarbamate (3k/3k')

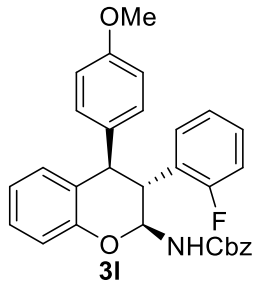


3k

Compound **(3k/3k')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White amorphous solid (27.6 mg, 72% yield); **mp**: 71-73 °C; **Diastereomeric ratio:** 4.2:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 4H), 7.25 – 7.15 (m, 5H), 7.08 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.3 Hz, 0.3H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 0.3H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 0.5H), 6.45 (d, *J* = 8.3 Hz, 0.5H), 6.14 (t, *J* = 10.1 Hz, 0.2H), 5.93 (brs, 1H), 5.24 (d, *J* = 7.3 Hz, 1H), 5.01 (dd, *J* = 31.1, 16.0 Hz, 2.4H), 4.34 (d, *J* = 10.6 Hz, 1H), 4.27 (d, *J* = 4.9 Hz, 0.24H), 3.73 (s, 3H), 3.72 (s, 0.6H), 3.45 (t, *J* = 9.7 Hz, 1H), 2.42 (s, 0.7H), 1.73 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 158.5, 158.5, 155.7, 155.5, 154.3, 153.9, 137.5, 136.9, 136.1, 134.7, 132.9, 131.3, 130.4, 130.3, 130.2, 130.1, 128.7, 128.5, 128.3, 128.1, 126.9, 126.8, 126.3, 125.7, 124.6, 121.4, 121.2, 117.3, 117.1, 113.7, 113.1, 82.7, 78.5, 67.2, 55.3, 51.2, 47.5, 45.9, 44.0, 19.8, 19.7; **HRMS (+ESI):** Calc for $C_{31}H_{30}NO_4$ $[M+H]^+$ 480.2169; found: 480.2189; The ee value of the major diastereomer 88% (t_{major} = 38.0 min, t_{minor} = 73.6 min) was determined by HPLC analysis using

Chiralpak IA column with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

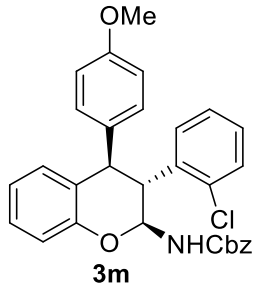
Benzyl 3-(2-fluorophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3l)



3l

Compound **(3l)** was purified by silica gel column chromatography using 7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (32.1 mg, 83% yield); **mp**: 60-62 ^{o}C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.31 (d, *J* = 6.0 Hz, 3H), 7.21 (d, *J* = 5.9 Hz, 2H), 7.15 (dd, *J* = 14.6, 7.7 Hz, 2H), 7.09 (brs, 1H), 7.03 (t, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 9.3 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.01 (t, *J* = 9.9 Hz, 1H), 5.47 (d, *J* = 8.8 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 5.01 (d, *J* = 12.3 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 3.73 (s, 3H), 3.58 (t, *J* = 10.6 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 161.9, 160.3, 158.5, 155.5, 153.9, 136.1, 134.1, 130.0, 130.0, 128.9, 128.9, 128.7, 128.3, 128.2, 128.1, 125.89, 124.7, 121.4, 117.2, 115.7, 115.6, 113.9, 81.7, 67.2, 55.3, 48.7, 32.1; **HRMS (+ESI):** Calc for $C_{30}H_{30}FN_2O_4$ $[M+NH_4]^+$ 501.2184; found: 501.2187; The ee value of the major diastereomer 94% (t_{major} = 28.4 min, t_{minor} = 56.7 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Benzyl 3-(2-chlorophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3m)

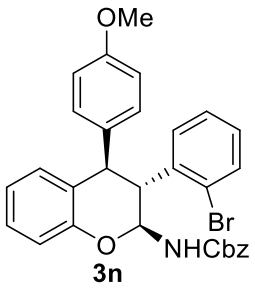


3m

Compound **(3m)** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (35.2 mg, 88% yield); **mp**: 70-72 ^{o}C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.31 (d, *J* = 6.5 Hz, 5H), 7.21 (d, *J* = 5.3 Hz, 3H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.5 Hz, 2H), 5.89 (brs, 1H), 5.50 (d, *J* = 8.4 Hz, 1H), 5.03 (dd, *J* = 41.7, 12.3 Hz, 2H), 4.40 (brs, 1H), 4.03 (brs, 1H), 3.73 (s, 3H); **^{13}C NMR (150 MHz,**

$CDCl_3$): δ 158.6, 155.5, 153.8, 136.5, 136.1, 133.4, 130.2, 129.9, 129.7, 128.7, 128.4, 128.3, 128.2, 128.1, 127.7, 126.0, 121.4, 117.2, 113.9, 82.7, 67.2, 55.3, 49.5, 46.6; **HRMS (+ESI):** Calc for $C_{30}H_{27}ClNO_4$ $[M+H]^+$ 500.1623; found: 500.1604; The ee value of the major diastereomer 94% (t_{major} = 19.6 min, t_{minor} = 65.3 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Benzyl 3-(2-bromophenyl)-3,4-dihydro-4-(4-methoxyphenyl)-2H-chromen-2-ylcarbamate (3n)

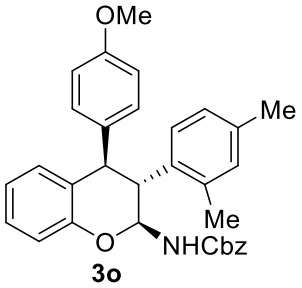


3n

Compound **(3n)** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (38.8 mg, 89% yield); **mp**: 72-74 °C; **Diastereomeric ratio:**>20:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.29 (m, 5H), 7.21 (d, *J* = 5.7 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 5.88 (t, *J* = 9.4 Hz, 1H), 5.54 (d, *J* = 9.6 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 4.99 (d, *J* = 12.3 Hz, 1H), 4.40 (d, *J* = 10.7 Hz, 1H), 4.04 (t, *J* = 10.0 Hz, 1H), 3.73 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.6, 155.5, 153.7, 138.2, 136.1, 133.2, 133.0, 130.3, 129.9, 128.7, 128.7, 128.4, 128.3, 128.2, 128.1, 126.4, 126.0, 121.4, 117.1, 113.9, 82.8, 67.2, 55.3, 49.7, 49.3; **HRMS (+ESI):** Calc for $C_{30}H_{27}BrNO_4$ $[M+H]^+$ 544.1118; found: 544.1148; The ee value of the major diastereomer 94% (t_{major} = 10.6 min, t_{minor} = 16.8 min) was determined by HPLC analysis using Chiralpak IB column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Benzyl 3,4-dihydro-4-(4-methoxyphenyl)-3-(2,4-dimethylphenyl)-2H-chromen-2-ylcarbamate (3o/3o')

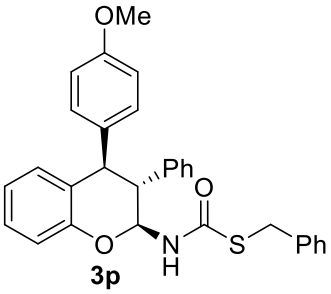
Compound **(3o/3o')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (24.9 mg, 63% yield); **mp**: 95-97 °C; **Diastereomeric ratio:** 4.3:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 4H), 7.24 – 7.19 (m, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.10 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H),



3o

7.00 – 6.96 (m, 2H), 6.88 (t, *J* = 7.3 Hz, 0.3H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 3H), 6.66 (d, *J* = 8.6 Hz, 2H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.46 (d, *J* = 8.4 Hz, 0.5H), 6.11 (t, *J* = 10.1 Hz, 0.2H), 5.89 (brs, 1H), 5.21 (brs, 1H), 5.03 (dd, *J* = 46.0, 9.0 Hz, 2.5H), 4.31 (d, *J* = 10.4 Hz, 1H), 4.25 (d, *J* = 4.9 Hz, 0.23H), 3.73 (s, 3.7H), 3.40 (t, *J* = 9.7 Hz, 1H), 2.37 (s, 0.6H), 2.25 (s, 3.7H), 1.69 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.5, 158.5, 155.5, 154.3, 154.0, 136.6, 136.2, 134.9, 134.4, 133.0, 131.4, 131.1, 130.2, 130.2, 128.7, 128.4, 128.3, 128.0, 127.7, 126.4, 124.7, 121.4, 121.1, 117.3, 117.1, 113.7, 113.2, 82.7, 78.6, 67.2, 60.6, 55.3, 51.2, 46.0, 43.8, 21.2, 21.1, 19.7, 19.6; **HRMS (+ESI):** Calc for $C_{32}H_{32}NO_4$ $[M+H]^+$ 494.2326; found: 494.2324; The ee value of the major diastereomer 92% (t_{major} = 24.1 min, t_{minor} = 22.5 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

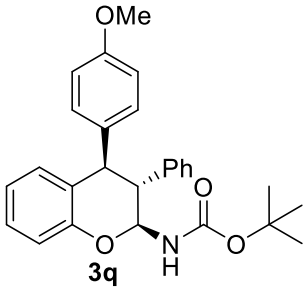
S-benzyl N-3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamothioate (3p/3p')



3p

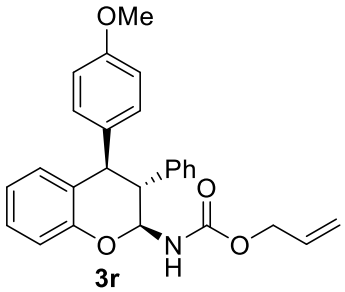
Compound **(3p/3p')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (28.5 mg, 74% yield); **mp**: 79-81 ^{o}C; **Diastereomeric ratio:** 20:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.27 (d, *J* = 7.0 Hz, 1H), 7.25 (brs, 1H), 7.24 – 7.14 (m, 7H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 6.1 Hz, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 6.13 (brs, 1H), 5.88 (d, *J* = 8.8 Hz, 1H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 0.1H), 4.10 (brs, 2.1H), 3.73 (s, 3.2H), 3.12 (t, *J* = 10.4 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$)**: δ 168.1, 158.4, 153.8, 138.4, 137.7, 134.5, 131.3, 130.1, 129.0, 128.8, 128.7, 128.3, 128.1, 127.4, 126.0, 121.5, 117.2, 113.9, 113.3, 80.8, 55.3, 52.8, 50.4, 34.3, 29.9; **HRMS (+ESI):** Calc for $C_{30}H_{28}NO_3S$ $[M+H]^+$ 482.1784; found: 482.1780; The ee value of the major diastereomer 95% (t_{major} = 32.4 min, t_{minor} = 57.1 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

tert-butyl 3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3q/3q')



Compound **((3q/3q')** was purified by silica gel column chromatography using 6-7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White amorphous solid (26.9 mg, 78% yield); **mp**: 55-57 ^{o}C; **Diastereomeric ratio:** 1.5:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.21 – 7.13 (m, 7H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 3H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 6.9 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.09 (t, *J* = 10.4 Hz, 0.7H), 5.90 (brs, 1H), 5.07 (dd, *J* = 17.9, 9.1 Hz, 2H), 4.30 (d, *J* = 11.1 Hz, 1H), 4.24 (d, *J* = 5.3 Hz, 0.7H), 3.73 (s, 3H), 3.72 (s, 2H), 3.47 (t, *J* = 4.8 Hz, 0.7H), 3.08 (t, *J* = 9.9 Hz, 1H), 1.36 (s, 6H), 1.33 (s, 9H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.5, 158.4, 155.0, 154.6, 154.2, 154.0, 139.0, 138.1, 134.8, 132.7, 131.3, 130.2, 130.1, 130.0, 129.2, 128.7, 128.5, 128.4, 128.2, 128.0, 127.2, 127.1, 126.2, 124.6, 121.2, 121.0, 117.2, 117.1, 113.8, 113.3, 81.9, 80.6, 77.8, 55.3, 55.3, 53.2, 53.2, 50.8, 48.8, 28.4, 28.3; **HRMS (+ESI):** Calc for $C_{27}H_{30}NO_4$ $[M+H]^+$ 432.2169; found: 432.2167; The ee value of the major diastereomer 90% (t_{major} = 17.4 min, t_{minor} = 27.6 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

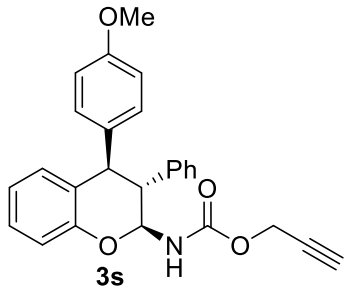
Allyl 3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3r/3r')



Compound **(3r/3r')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White semi solid (20.3 mg, 61% yield); **Diastereomeric ratio:** 6.7:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.24 – 7.12 (m, 5H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 2H), 6.81 (t, *J* = 7.1 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 7.7 Hz, 0.3H), 6.49 (d, *J* = 7.8 Hz, 0.3H), 6.11 (t, *J* = 9.7 Hz, 0.1H), 5.94 (brs, 1H), 5.80 (brs, 1H), 5.27 (brs, 1H), 5.13 (d,

J = 12.3 Hz, 2H), 4.50 (d, *J* = 23.1 Hz, 2H), 4.31 (d, *J* = 11.0 Hz, 1H), 4.25 (d, *J* = 4.5 Hz, 0.2H), 3.73 (s, 3.3H), 3.10 (t, *J* = 9.2 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.4, 155.4, 154.0, 138.8, 134.6, 132.5, 131.4, 130.1, 129.2, 128.9, 128.3, 128.1, 127.3, 126.2, 121.4, 118.0, 117.2, 113.9, 113.3, 82.0, 66.1, 55.3, 53.0, 50.8; **HRMS (+ESI):** Calc for $C_{26}H_{26}NO_4$ $[M+H]^+$ 416.1856; found: 416.1890; The ee value of the major diastereomer 90% (t_{major} = 28.6 min, t_{minor} = 22.1 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Prop-2-ynyl 3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate(3s/3s')

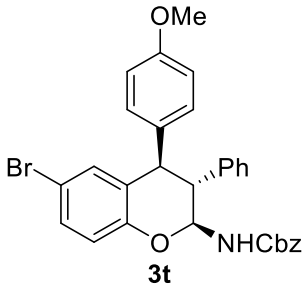


3s

Compound **(3s/3s')** was purified by silica gel column chromatography using 7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White semi solid (29.4 mg, 89% yield); **Diastereomeric ratio:** 12.5:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.23 – 7.12 (m, 4H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 2H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 6.09 (t, *J* = 10.3 Hz, 0.1H), 5.92 (t, *J* = 9.8 Hz, 1H), 5.41 (brs, 1H), 4.60 (dd, *J* = 57.5, 15.5 Hz, 2.1H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.24 (d, *J* = 5.3 Hz, 0.1H), 3.72 (s, 3.2H), 3.11 (t, *J* = 10.4 Hz, 1H), 2.42 (s, 1H); **^{13}C NMR (150 MHz, CDCl$_3$)**: δ 158.5, 154.7, 153.9, 138.7, 134.6, 131.4, 130.1, 128.9, 128.3, 128.1, 127.4, 126.1, 121.4, 117.2, 113.9, 113.3, 82.0, 77.8, 75.2, 55.3, 53.1, 52.9, 50.7; **HRMS (+ESI):** Calc for $C_{26}H_{24}NO_4$ $[M+H]^+$ 414.170; found: 414.1693; The ee value of the major diastereomer 90% (t_{major} =17.4 min, t_{minor} = 12.7 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Benzyl 6-bromo-3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3t/3t')

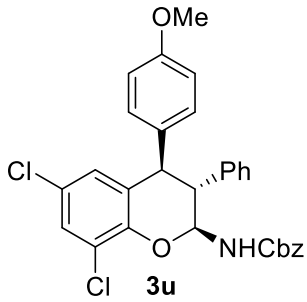
Compound **(3t/3t')** was purified by silica gel column chromatography using 6-7% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White semi solid (37.5 mg, 86% yield); **Diastereomeric ratio:** 2.6:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.29 (brs, 5H), 7.26 – 7.11 (m, 8H), 7.08 (s, 0.4H), 6.90 (brs, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 8.5 Hz, 1H), 6.11 (t, *J*



3t

= 10.1 Hz, 0.3H), 5.93 (t, *J* = 8.6 Hz, 1H), 5.34 (brs, 1.1H), 5.03 (d, *J* = 20.1 Hz, 2.6H), 4.25 (d, *J* = 11.0 Hz, 1H), 4.19 (d, *J* = 5.2 Hz, 0.4H), 3.74 (s, 4.1H), 3.08 (t, *J* = 10.1 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.8, 158.7, 155.5, 155.4, 153.2, 153.0, 138.4, 136.1, 133.7, 132.6, 131.9, 131.5, 131.3, 131.1, 130.1, 129.1, 128.9, 128.7, 128.4, 128.4, 128.3, 128.1, 127.5, 127.4, 126.7, 119.1, 118.9, 114.2, 113.6, 113.5, 113.3, 82.4, 67.4, 67.3, 55.4, 55.3, 52.6, 50.6, 48.5, 48.4; **HRMS (+ESI):** Calc for $C_{30}H_{27}BrNO_4$ $[M+H]^+$ 544.1118; found: 544.1101; The ee value of the major diastereomer 84% (t_{major} = 41.7 min, t_{minor} = 62.4 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ºC.

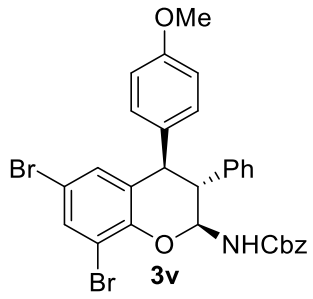
Benzyl 6,8-dichloro-3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3u/3u')



3u

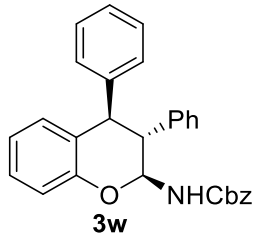
Compound **(3u/3u')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 6 days at room temperature; White semi solid (12.8 mg, 30% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.29 (brs, 3H), 7.24 (d, *J* = 1.8 Hz, 1H), 7.18 (brs, 5H), 6.89 (brs, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.5 Hz, 2H), 6.61 (s, 1H), 6.18 (brs, 0.03H), 6.00 (t, *J* = 8.9 Hz, 1H), 5.36 (d, *J* = 8.5 Hz, 1H), 5.05 (s, 2H), 4.27 (d, *J* = 11.1 Hz, 1H), 3.74 (s, 3H), 3.12 (t, *J* = 10.1 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.8, 155.4, 148.8, 139.5, 137.9, 136.0, 133.1, 130.1, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.0, 127.6, 125.9, 122.9, 114.2, 83.1, 67.4, 55.4, 52.4, 51.0; **HRMS (+ESI):** Calc for $C_{30}H_{26}Cl_2NO_4$ $[M+H]^+$ 534.1233; found: 534.1232; The ee value of the major diastereomer 88% (t_{major} = 40.4 min, t_{minor} = 70.8 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ºC.

Benzyl 6,8-dibromo-3,4-dihydro-4-(4-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3v/3v')



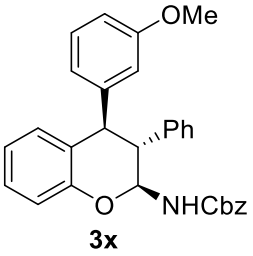
Compound **(3v/3v')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at 50 °C temperature; White solid (16.5 mg, 33% yield); **mp**: 66-68 °C; **Diastereomeric ratio:** 11:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.54 (d, *J* = 1.8 Hz, 1H), 7.29 (brs, 3H), 7.18 (brs, 5H), 6.89 (brs, 2H), 6.79 (s, 1H), 6.73 (d, *J* = 8.5 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 6.18 (t, *J* = 10.8 Hz, 0.1H), 5.99 (brs, 1H), 5.34 (brs, 1H), 5.07 (d, *J* = 11.9 Hz, 2H), 4.28 (d, *J* = 10.7 Hz, 1H), 4.21 (d, *J* = 5.1 Hz, 0.1H), 3.74 (s, 3.1H), 3.11 (t, *J* = 9.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 158.9, 155.3, 150.2, 139.5, 137.9, 136.1, 134.1, 133.2, 131.9, 131.3, 130.1, 129.7, 129.0, 128.7, 128.4, 128.3, 128.0, 127.7, 114.3, 113.6, 113.4, 112.2, 83.4, 67.4, 55.4, 52.6, 50.9; **HRMS (+ESI):** Calc for $C_{30}H_{26}Br_2NO_4$ $[M+H]^+$ 622.0223; found: 622.0226; The ee value of the major diastereomer 92% (t_{major} = 19.9 min, t_{minor} = 48.6 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Benzyl 3,4-dihydro-3,4-diphenyl-2H-chromen-2-ylcarbamate (3w/3w')



Compound **(3w/3w')** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (13.2 mg, 38% yield); **mp**: 95-97 °C; **Diastereomeric ratio:** 14.3:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.30 (brs, 3H), 7.18 (brs, 5H), 7.14 (d, *J* = 4.1 Hz, 4H), 7.08 (t, *J* = 7.4 Hz, 0.2H), 7.03 (d, *J* = 8.2 Hz, 0.1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 4.9 Hz, 2H), 6.86 (d, *J* = 3.9 Hz, 2H), 6.82 (t, *J* = 7.4 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 6.9 Hz, 0.1H), 6.60 (d, *J* = 7.5 Hz, 0.2H), 6.16 (t, *J* = 10.2 Hz, 0.1H), 5.98 (t, *J* = 9.4 Hz, 1H), 5.33 (d, *J* = 8.7 Hz, 1H), 5.04 (dd, *J* = 29.0, 12.0 Hz, 2H), 4.37 (d, *J* = 11.0 Hz, 1H), 4.30 (d, *J* = 5.4 Hz, 0.07H), 3.15 (t, *J* = 10.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 155.5, 154.1, 142.6, 139.5, 138.6, 136.1, 130.4, 130.2, 129.2, 128.9, 128.7, 128.5, 128.3, 128.2, 128.1, 127.4, 126.9, 125.9, 121.4, 117.2, 114.3, 82.1, 67.2, 53.0, 51.6; **HRMS (+ESI):** Calc for $C_{29}H_{26}NO_3$ $[M+H]^+$ 436.1907; found: 436.1909; The ee value of the major diastereomer 88% (t_{major} = 17.0 min, t_{minor} = 14.6 min) was determined by HPLC analysis using Chiralpak IC column with *n*-hexane/*i*-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

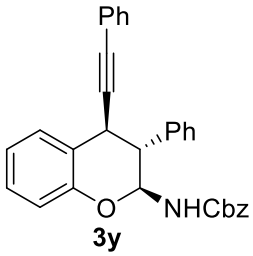
Benzyl 3,4-dihydro-4-(3-methoxyphenyl)-3-phenyl-2H-chromen-2-ylcarbamate (3x/3x')



3x

Compound **(3x/3x')** was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time**: 3 days at room temperature; White solid (26.1 mg, 70% yield); **mp**: 48-50 ^{o}C; **Diastereomeric ratio:** 2.2:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.30 (brs, 4H), 7.23 – 7.14 (m, 8H), 7.06 (t, *J* = 7.9 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.97 (d, *J* = 9.1 Hz, 2H), 6.94 (d, *J* = 6.1 Hz, 2H), 6.88 (t, *J* = 7.4 Hz, 0.6H), 6.83 (t, *J* = 7.1 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.1 Hz, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.67 (d, *J* = 2.6 Hz, 1H), 6.47 (d, *J* = 7.5 Hz, 1H), 6.39 (s, 1H), 6.26 (d, *J* = 7.5 Hz, 0.5H), 6.17 (t, *J* = 10.3 Hz, 0.4H), 6.02 (s, 0.5H), 5.96 (t, *J* = 9.8 Hz, 1H), 5.36 (d, *J* = 9.7 Hz, 1.2H), 5.03 (dd, *J* = 29.0, 10.1 Hz, 2.7H), 4.34 (d, *J* = 11.0 Hz, 1H), 4.27 (d, *J* = 5.5 Hz, 0.46H), 3.63 (s, 3H), 3.51 (s, 1.5H), 3.15 (t, *J* = 10.4 Hz, 1H); **^{13}C NMR (150MHz, CDCl$_3$)**: δ 159.6, 159.0, 155.7, 155.5, 154.0, 153.8, 144.2, 142.0, 139.5, 138.7, 137.7, 136.1, 130.1, 129.4, 129.1, 128.9, 128.7, 128.3, 128.3, 128.2, 128.1, 127.4, 127.2, 125.6, 124.0, 122.8, 121.6, 121.4, 121.2, 117.2, 117.1, 115.9, 115.0, 114.3, 112.9, 112.3, 82.0, 78.1, 67.3, 67.2, 55.3, 55.2, 52.8, 51.6, 49.4, 48.6; **HRMS (+ESI):** Calc for $C_{30}H_{28}NO_4$ $[M+H]^+$ 466.2013; found: 466.2014; The ee value of the major diastereomer 86% (t_{major} = 66.0 min, t_{minor} = 45.6 min) was determined by HPLC analysis using Chiralpak IA column with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Benzyl (3-phenyl-4-(phenylethynyl)chroman-2-yl)carbamate (3y/3y')

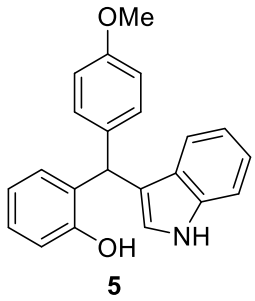


3y

Compound **(3y/3y')** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time**: 2 days at room temperature; White solid (22.4 mg, 61% yield); **mp**: 176-178 ^{o}C; **Diastereomeric ratio:** 2.5:1; **^{1}H NMR (600 MHz, CDCl$_3$)**: δ 7.58 (d, *J* = 7.6 Hz, 1.1H), 7.36 (d, *J* = 6.5 Hz, 4.2H), 7.32 (brs, 6.3H), 7.28 (d, *J* = 7.6 Hz, 5.2H), 7.23 (dd, *J* = 14.7, 8.1 Hz, 7H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.42 (t, *J* = 9.8 Hz, 0.3H), 5.97 (t, *J* = 9.4 Hz, 1H), 5.69 (d, *J* = 9.8 Hz, 1H), 5.42 (d, *J* = 9.7 Hz, 0.4H), 5.09 (d, *J* = 28.8 Hz, 2.8H), 4.38 (d, *J* = 9.9 Hz, 1H), 4.21 (d, *J* = 4.5 Hz, 0.4H), 3.39 (dd, *J* = 8.9, 4.3 Hz,

0.4H), 3.24 (t, *J* = 9.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 155.5, 152.7, 152.6, 138.7, 136.1, 131.8, 131.7, 129.3, 129.3, 129.2, 129.1, 129.0, 128.7, 128.6, 128.4, 128.3, 128.2, 127.9, 127.9, 123.2, 123.1, 122.0, 121.7, 121.4, 121.4, 117.5, 117.4, 84.0, 81.5, 67.4, 49.6, 47.0, 37.3, 36.9; **HRMS (+ESI):** Calc for $C_{31}H_{26}NO_3$ $[M+H]^+$ 460.1907; found: 460.1912; The ee value of the major diastereomer 52% (t_{major} = 89.4 min, t_{minor} = 70.7 min) was determined by HPLC analysis using Chiralpak ID column with *n*-hexane/*i*-PrOH (95:5) up to 50.1 min thereafter, with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

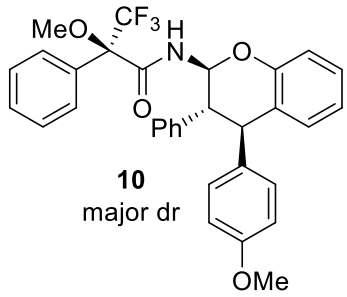
2-((1H-indol-3-yl)(4-methoxyphenyl)methyl)phenol (5)



5

Compound (**5**) was obtained from the trapping experiment; Purified by silica gel column chromatography using 6 to 8% EtOAc in hexane; (19.8 mg, 70% yield); **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 8.04 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.21 – 7.15 (m, 4H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 6.9 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 4H), 6.68 (d, *J* = 1.4 Hz, 1H), 5.77 (s, 1H), 5.02 (s, 1H), 3.79 (s, 3H); **^{13}C NMR (100 MHz, CDCl3)**: δ 158.5, 154.1, 137.1, 134.5, 130.2, 130.1, 129.2, 128.1, 127.0, 124.1, 122.7, 121.0, 120.1, 119.9, 118.1, 116.5, 114.2, 111.4, 55.4, 42.7; **HRMS (-ESI):** Calc for $(C_{22}H_{19}NO_2\text{-}H)^-$ $[M-H]^-$ 328.1343; found: 328.1345.

(R)-3,3,3-trifluoro-2-methoxy-N-(4-(4-methoxyphenyl)-3 phenylchroman-2-yl)-2-phenylpropanamide (10/10')

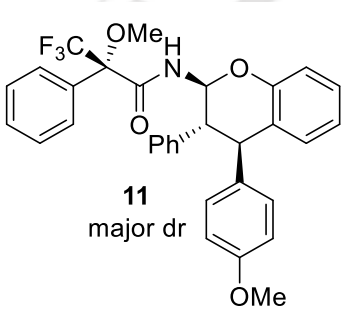


10
major dr

Compound **10/10'** was purified by silica gel column chromatography using 10% EtOAc in hexane; **Reaction time**: 12 hours at room temperature; Colorless sticky type (10 mg, 38% yield); **Diastereomeric ratio:** 1.4:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.55 – 7.51 (m, 2H), 7.42 – 7.40 (m, 3H), 7.37 (d, *J* = 6.4 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 3H), 7.15 (dt, *J* = 15.2, 7.5 Hz, 4H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.99 – 6.95 (m, 4H), 6.94 – 6.91 (m, 3H), 6.90 – 6.86 (m, 2H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.59 (s, 0.3H), 6.19 (t, *J* = 10.0 Hz, 1H), 6.08 (dd, *J* = 9.9, 3.1 Hz, 0.7H),

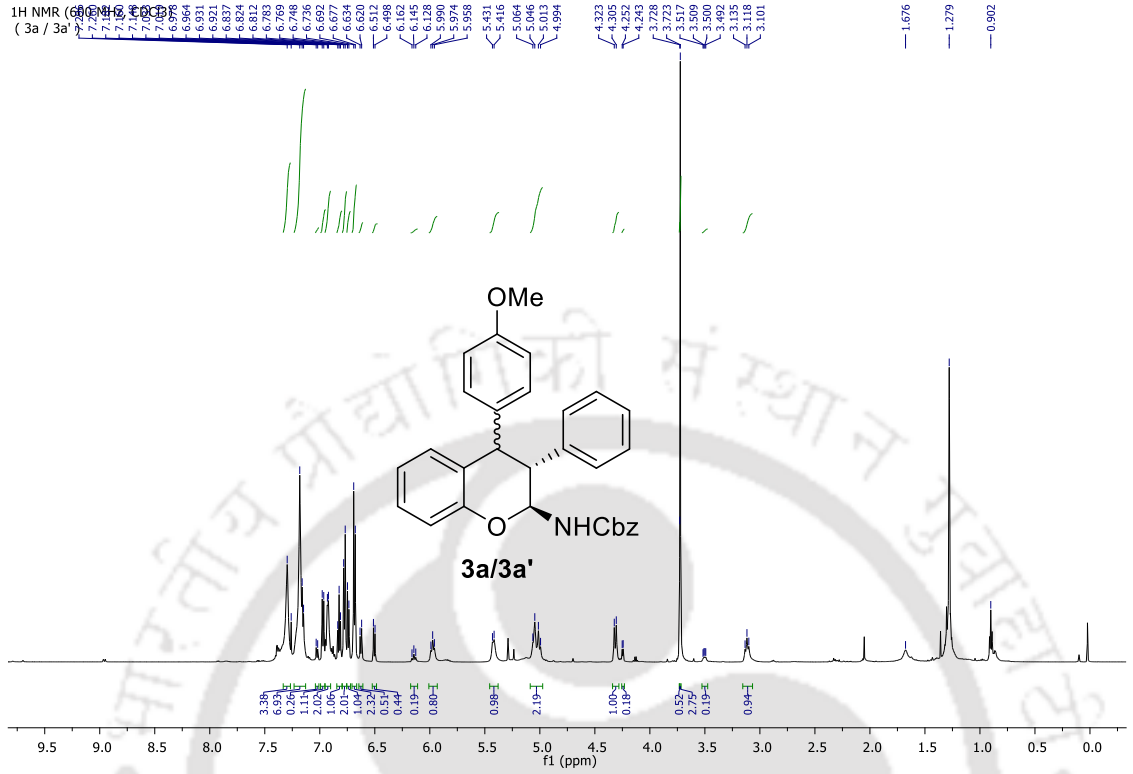
4.35 (d, *J* = 11.0 Hz, 1H), 4.31 (d, *J* = 5.0 Hz, 0.7H), 3.75 (s, 1.9H), 3.72 (s, 3H), 3.32 (s, 1.88H), 3.27 (dd, *J* = 4.8, 3.3 Hz, 0.7H), 3.14 (t, *J* = 10.6 Hz, 1H), 2.88 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**: 166.5, 166.4, 158.6, 158.5, 153.9, 153.5, 138.6, 137.7, 137.1, 134.5, 132.9, 132.7, 130.9, 130.2, 130.1, 129.8, 129.8, 129.7, 129.0, 128.95, 128.9, 128.7, 128.66, 128.6, 128.4, 128.1, 127.8, 127.76, 127.5, 126.0, 123.3, 122.1, 121.9, 121.5, 121.3, 117.6, 117.3, 114.3, 113.9, 113.8, 79.0, 75.0, 55.4, 55.3, 54.9, 54.85, 52.8, 50.6, 50.4, 45.1; **HRMS (+ESI):** Calc for $C_{32}H_{29}F_3NO_4$ $[M+H]^+$ 548.2043; found: 548.2021.

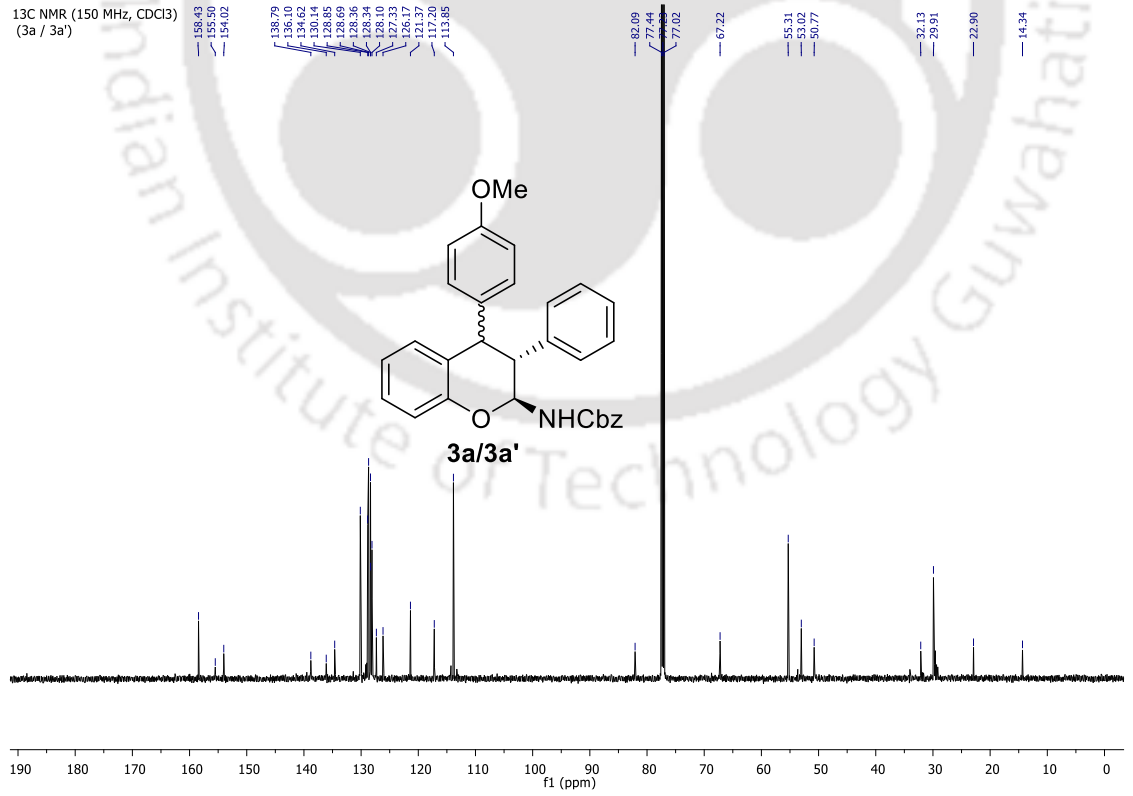
(S)-3,3,3-trifluoro-2-methoxy-N-(4-(4-methoxyphenyl)-3-phenylchroman-2-yl)-2-phenylpropanamide (11/11')



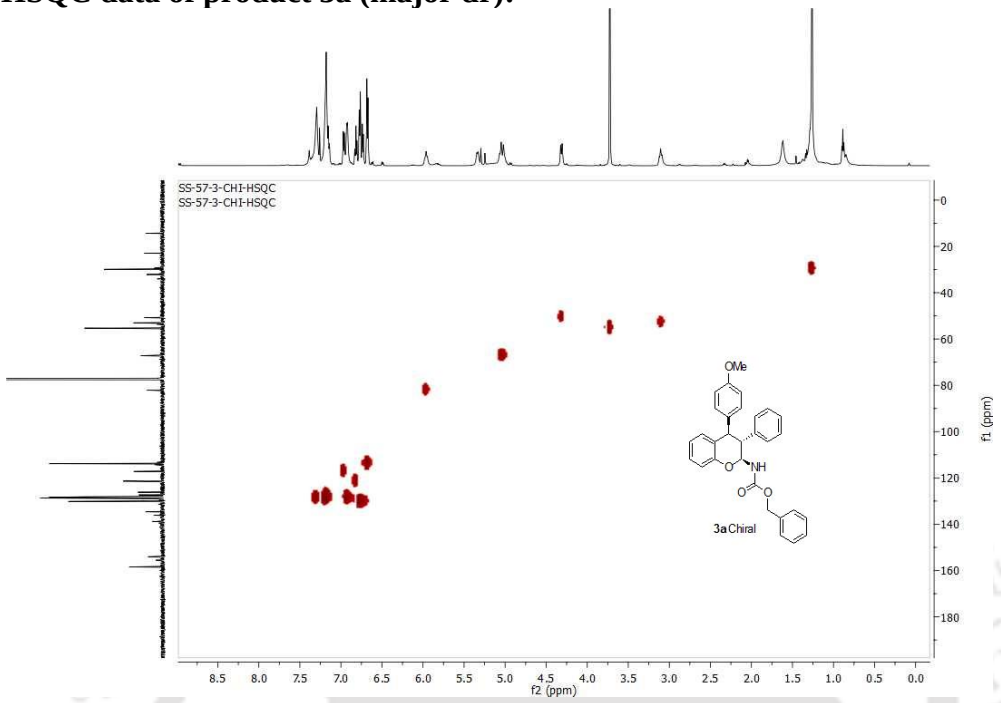
Compound **11**/**11'** was purified by silica gel column chromatography using 10% EtOAc in hexane; **Reaction time**: 12 hours at room temperature; Colorless sticky type (11 mg, 42% yield); **Diastereomeric ratio:** 2:1; **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.48 – 7.44 (m, 1H), 7.37 (d, *J* = 5.3 Hz, 1H), 7.33 (d, *J* = 10.2 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.20 – 7.17 (m, 2H), 7.15 (d, *J* = 6.9 Hz, 2H), 7.09 (t, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.98 – 6.94 (m, 4H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.84 – 6.80 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 7.7 Hz, 3H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.59 (s, 0.4H), 6.20 (t, *J* = 10.1 Hz, 1H), 6.08 (dd, *J* = 9.8, 3.0 Hz, 0.5H), 4.38 (d, *J* = 3.5 Hz, 0.4H), 4.36 (d, *J* = 11.2 Hz, 1H), 3.77 (s, 1.2H), 3.72 (s, 3H), 3.33 (t, *J* = 3.3 Hz, 0.5H), 3.23 (s, 3H), 3.18 (s, 1.5H), 3.15 (d, *J* = 10.7 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ**: 166.4, 166.3, 158.7, 158.5, 154.0, 153.9, 138.7, 138.0, 137.7, 134.4, 132.2, 131.9, 131.8, 131.0, 130.1, 129.8, 129.3, 129.1, 129.07, 129.0, 128.8, 128.7, 128.66, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.69, 127.4, 126.0, 123.1, 122.1, 121.5, 117.4, 117.3, 114.4, 114.3, 113.9, 79.0, 74.7, 55.5, 55.3, 55.1, 55.0, 53.2, 50.6, 50.4, 45.8; **HRMS (+ESI):** Calc for $C_{32}H_{29}F_3NO_4$ $[M+H]^+$ 548.2043; found: 548.2036.

2.10. Selected NMR spectra and HPLC chromatogram:

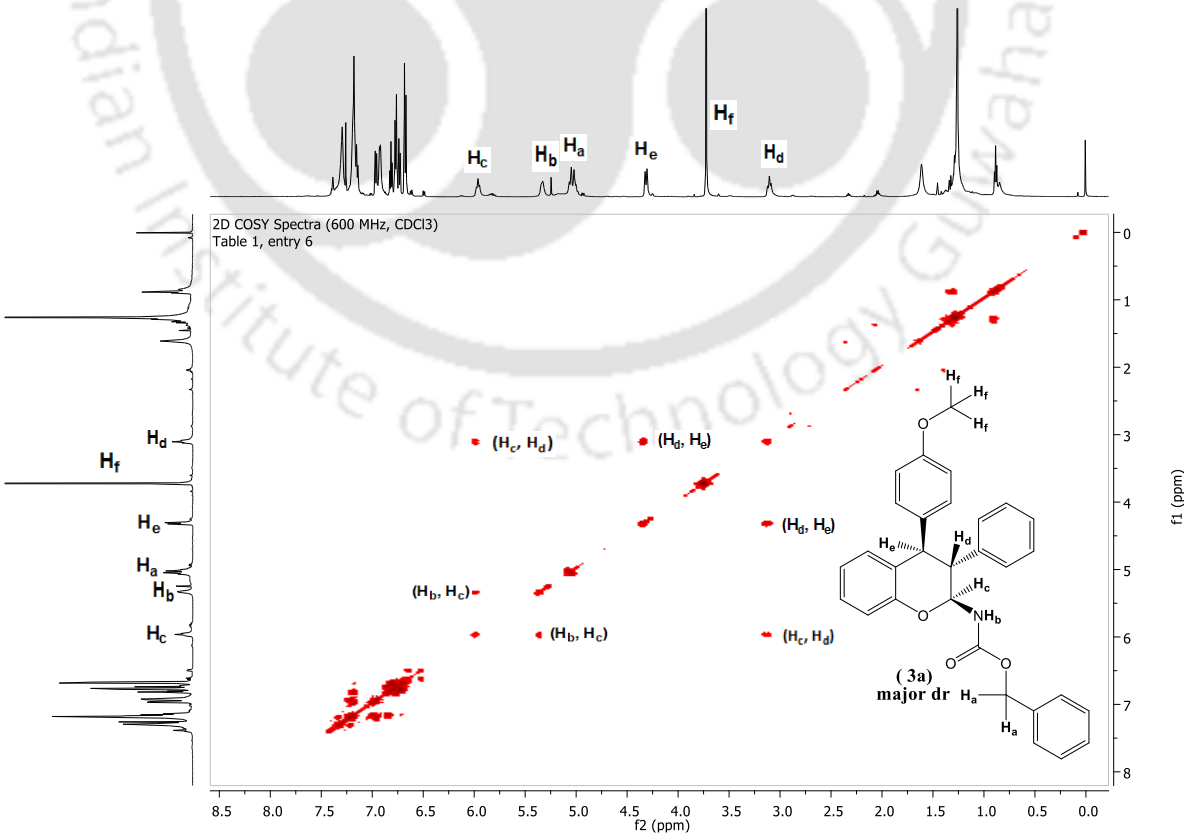


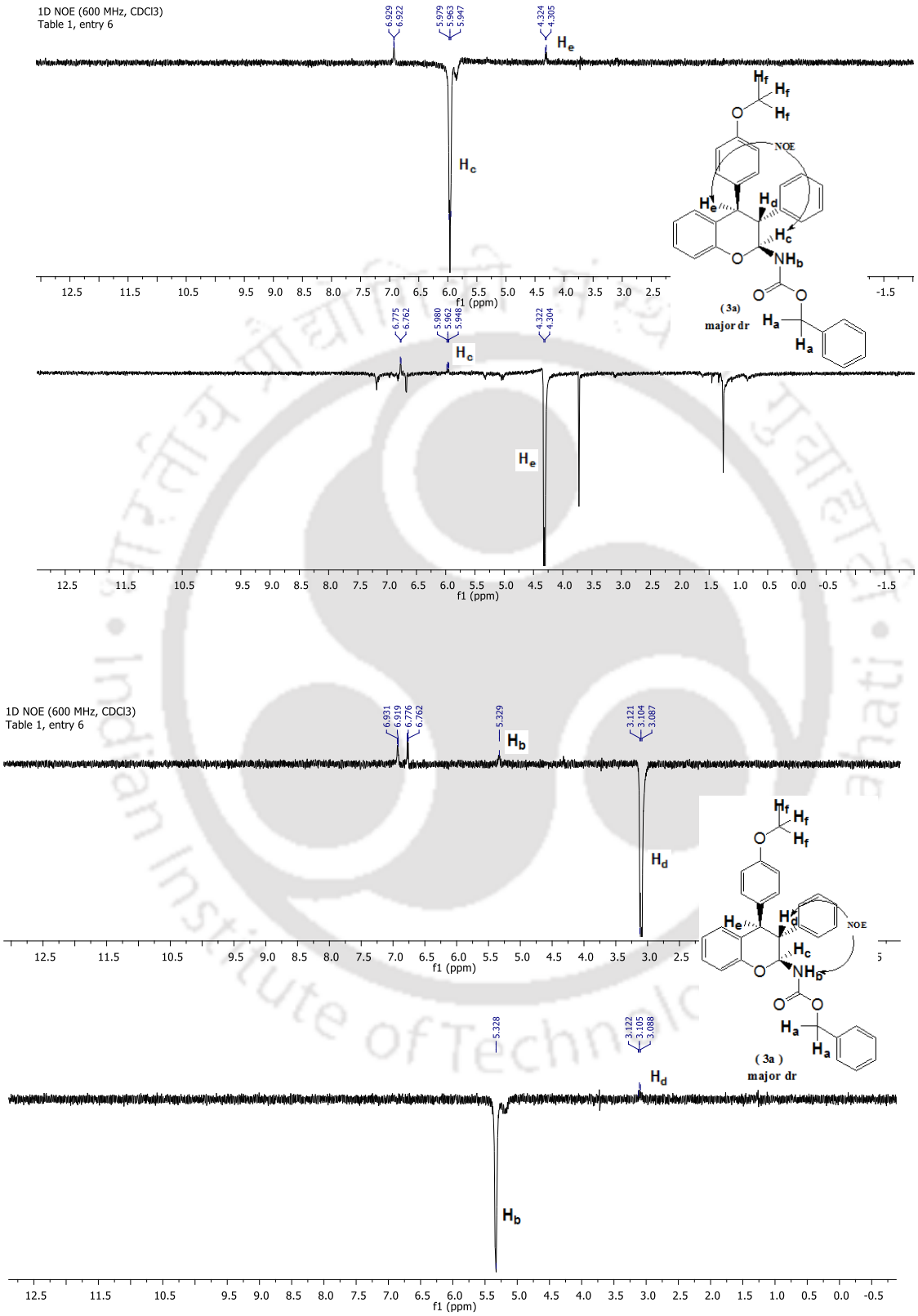


HSQC data of product 3a (major dr):

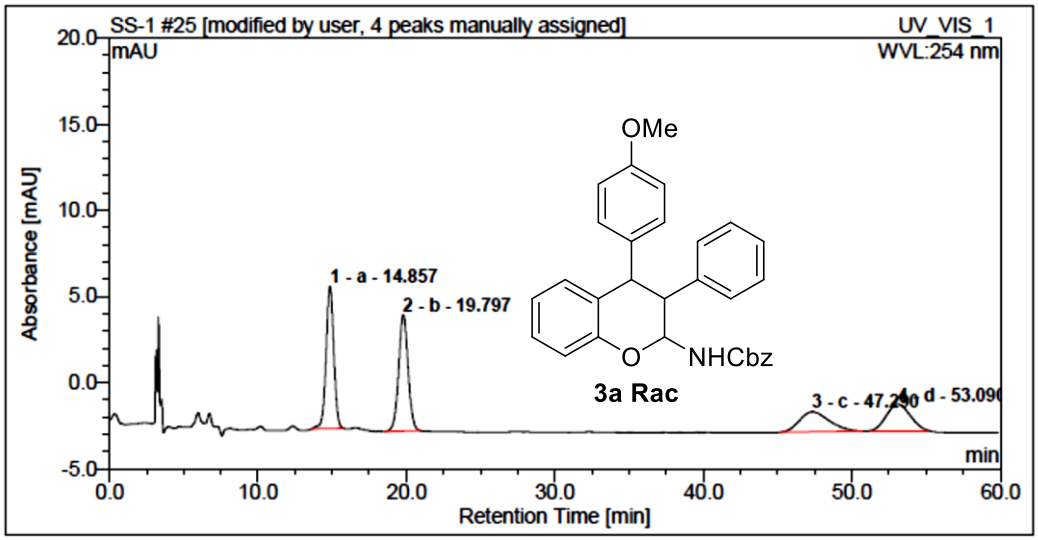


COSY and 1D NOE spectra for the relative stereo chemistry of 3a (major dr), (Table 1, entry 6):



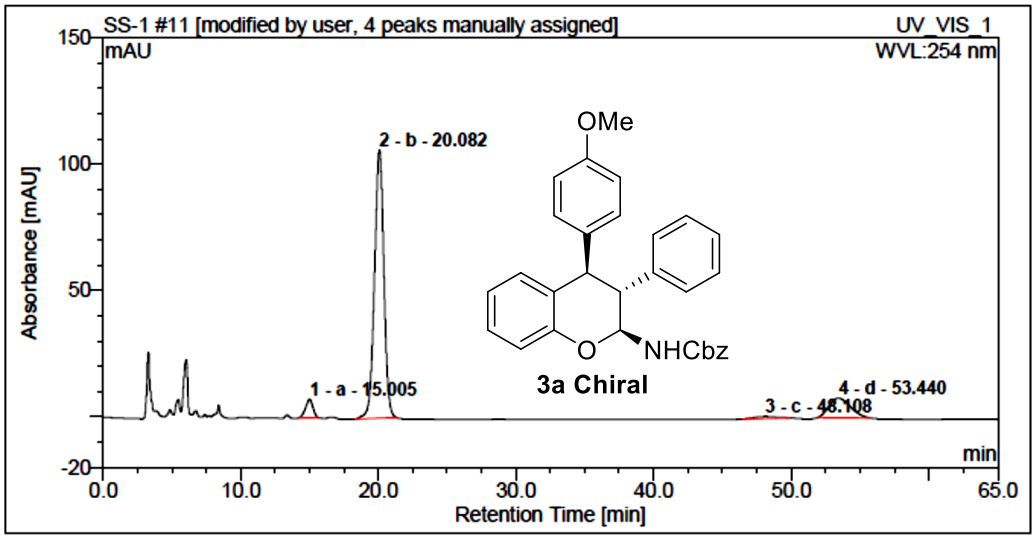


SS-57-RAC-IC

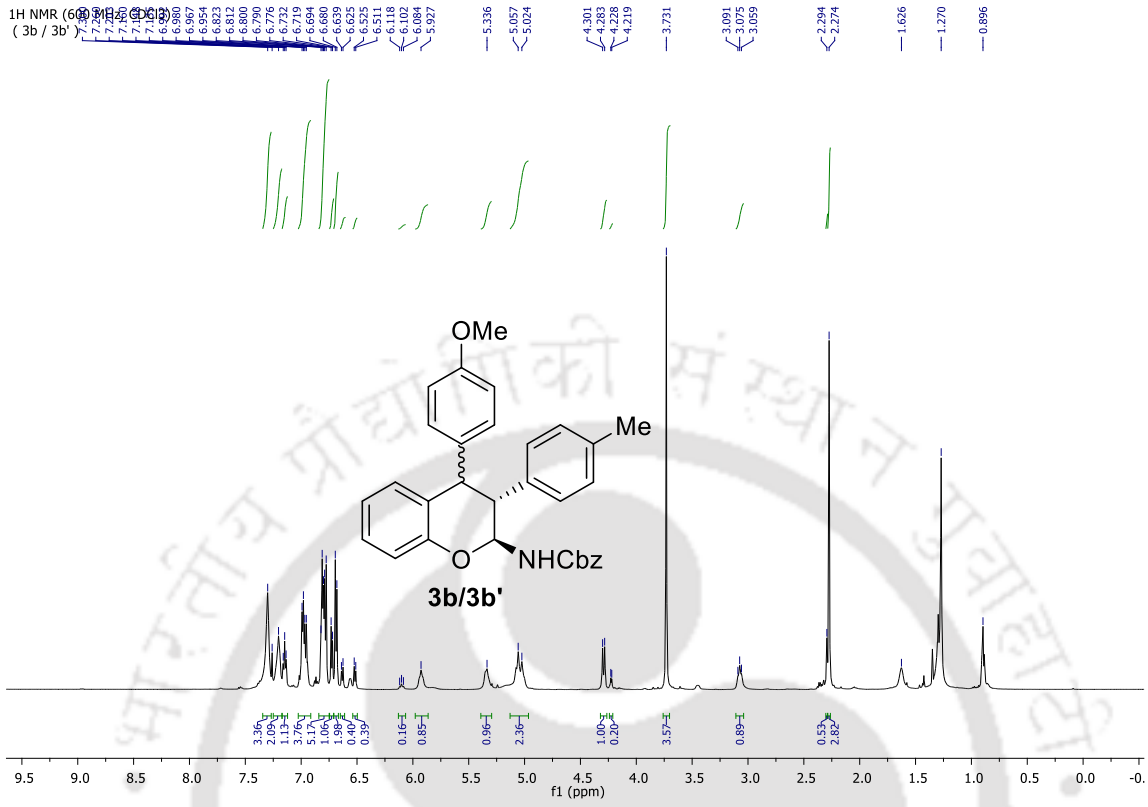


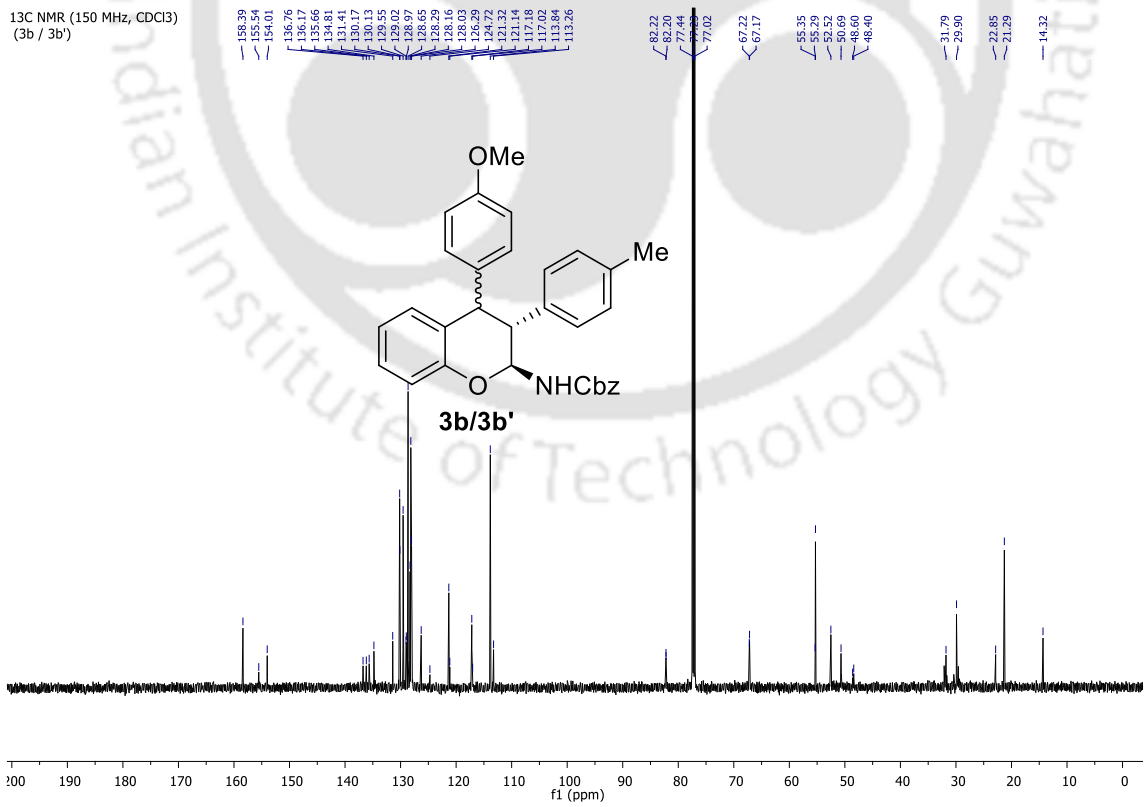
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	14.86	4.923752	32.0145676	8.24147	n.a.
2	b	19.80	4.9754	32.35038778	6.75735	n.a.
3	c	47.29	2.682175	17.43967992	1.16426	n.a.
4	d	53.09	2.798	18.19536471	1.524	n.a.

SS-57-CHI-IC

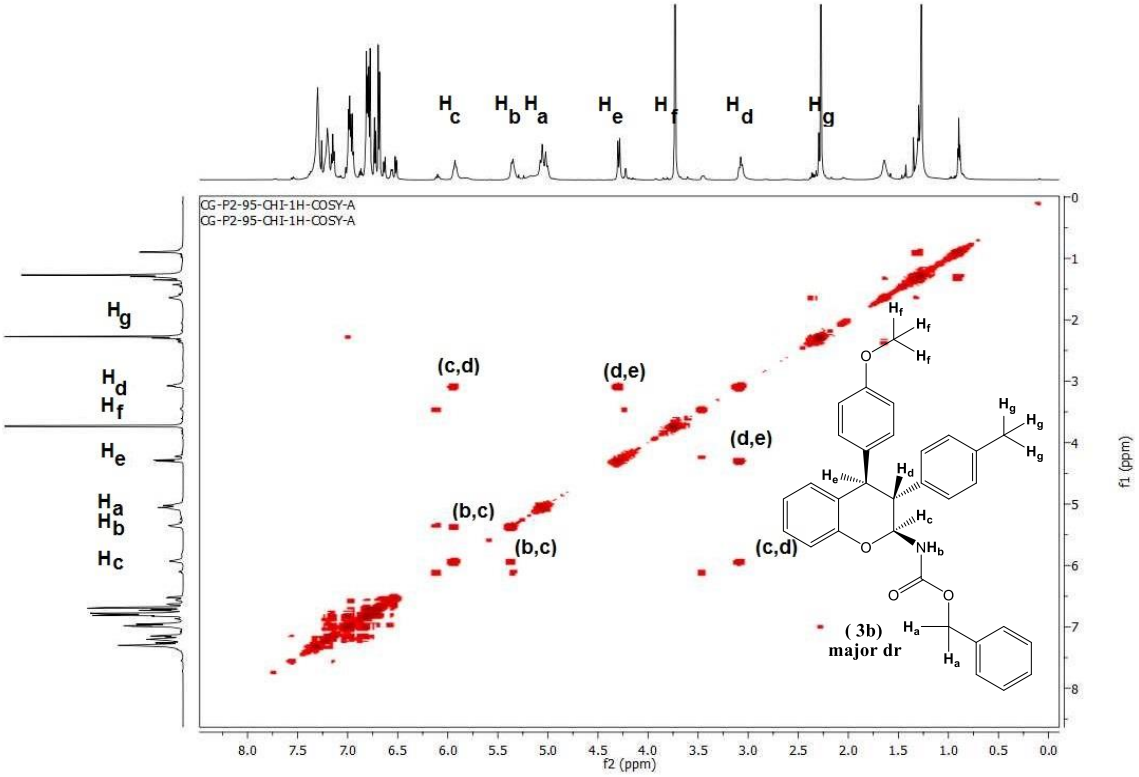


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	15.01	4.623583	4.472750321	7.364	n.a.
2	b	20.08	83.6376	80.90914224	106.2197	n.a.
3	c	48.11	1.329568	1.286194158	0.75086	n.a.
4	d	53.44	13.781	13.33191328	7.645	n.a.

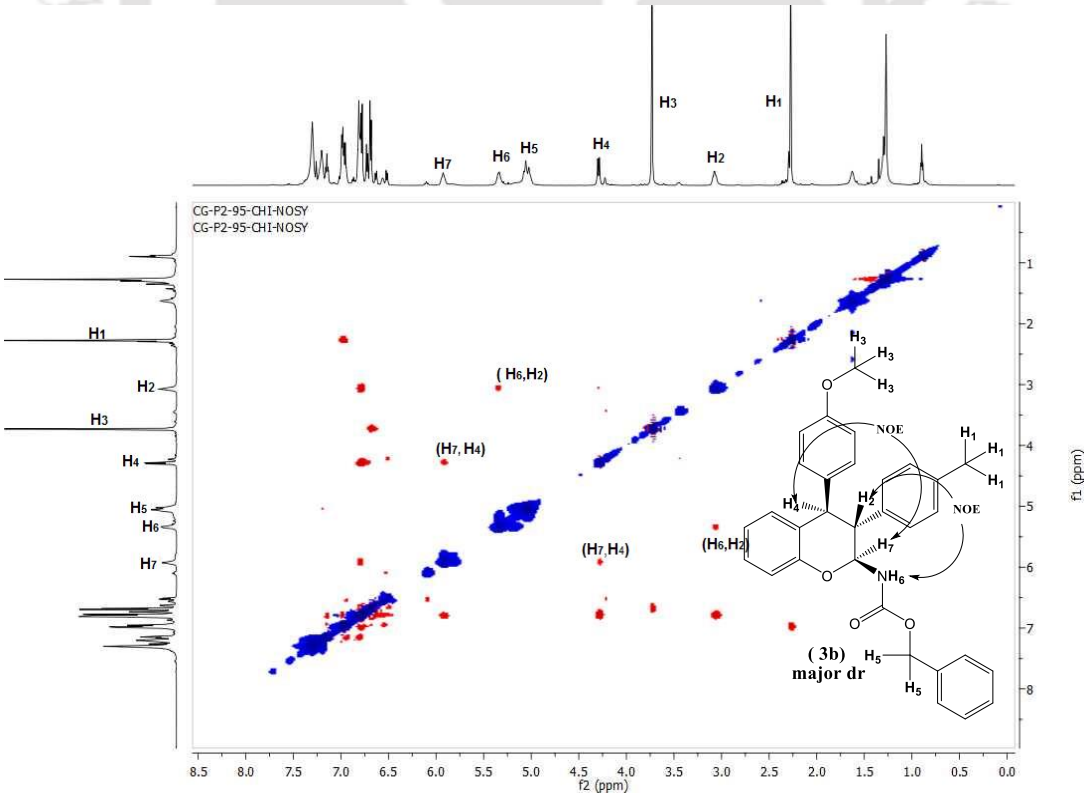




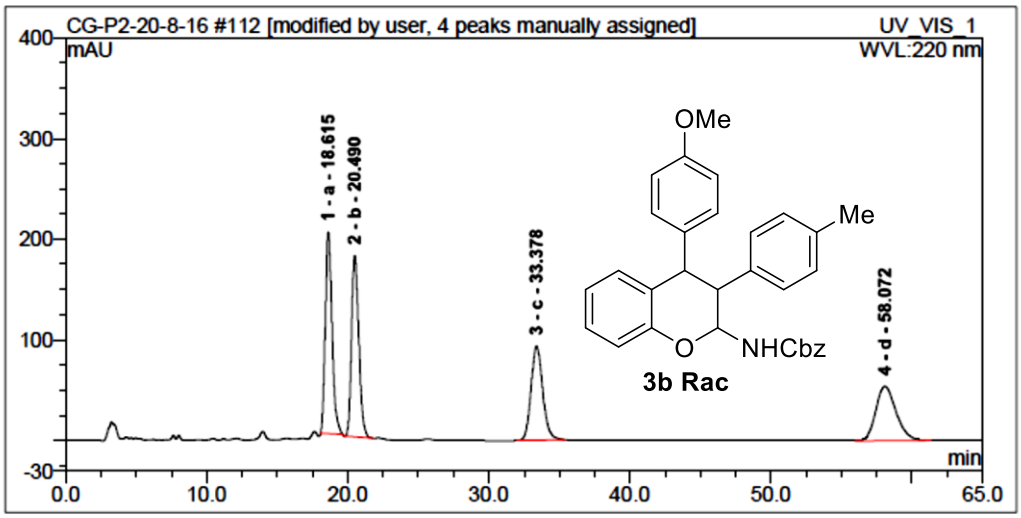
COSY spectra for the relative stereo chemistry of product 3b (major dr):



NOESY spectra for the relative stereo chemistry of product 3b (major dr):

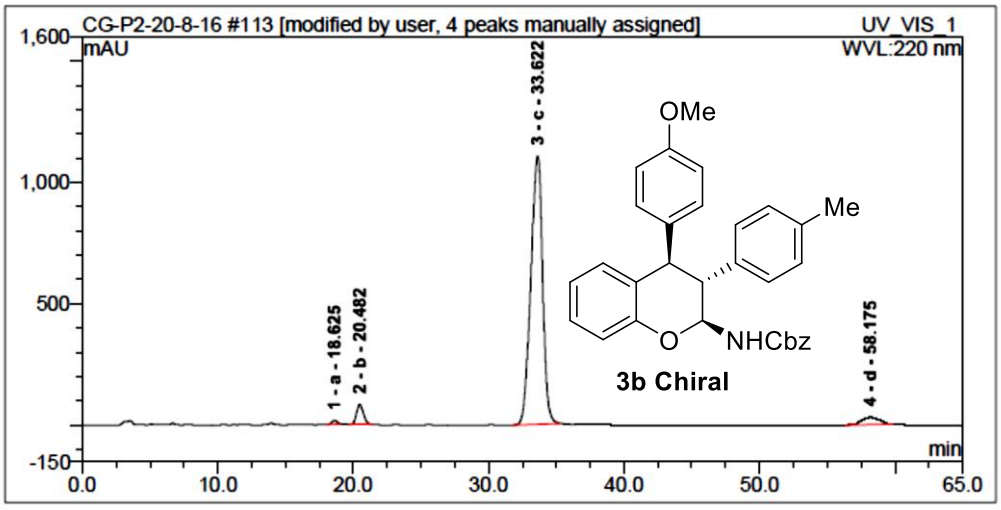


P2-90-RAC-IA



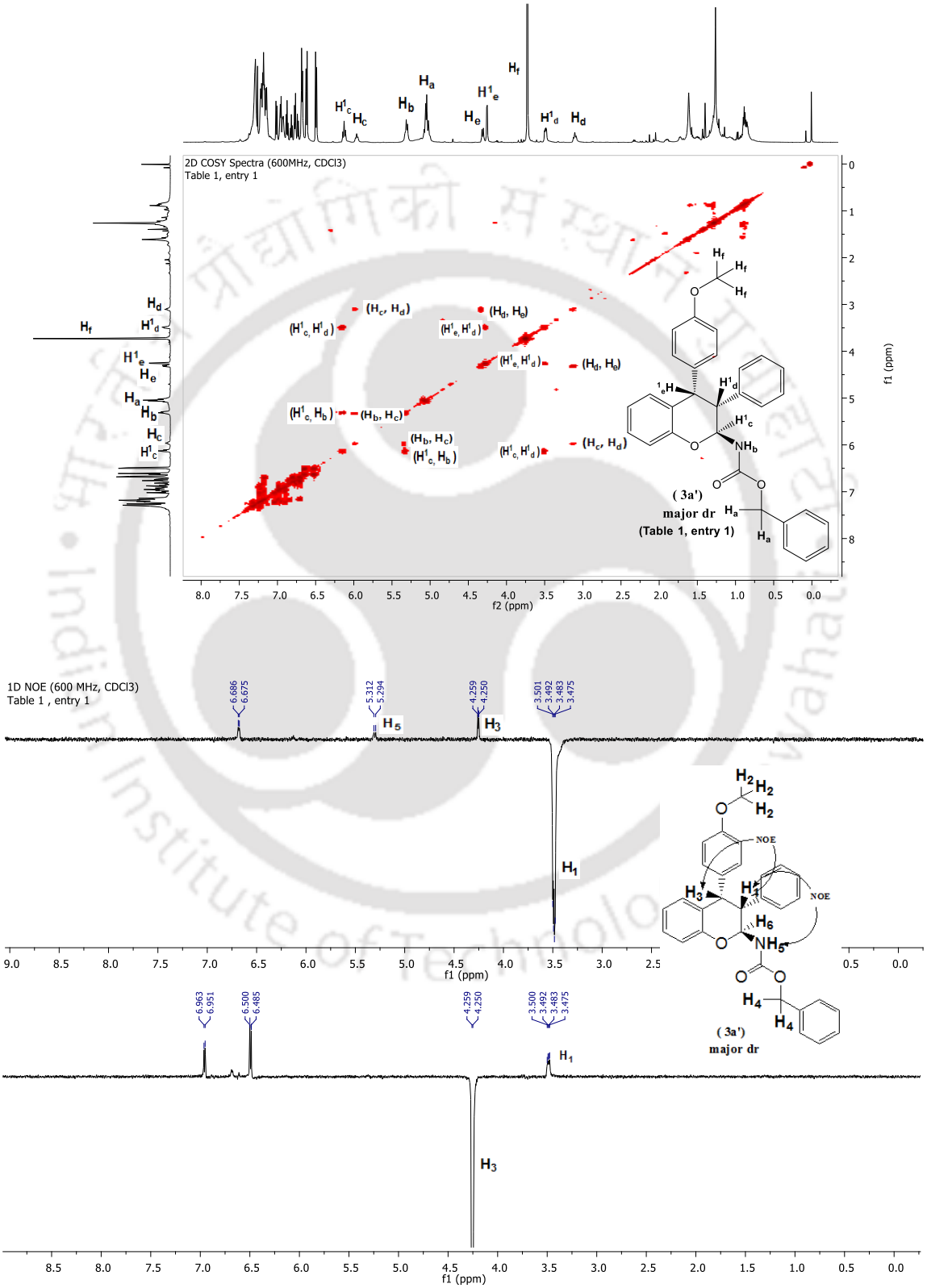
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.62	111.2762	27.86351322	200.5874	n.a.
2	b	20.49	107.369	26.88515748	180.3395	n.a.
3	c	33.38	90.33453	22.6197375	93.59877	n.a.
4	d	58.07	90.382	22.6315918	54.159	n.a.

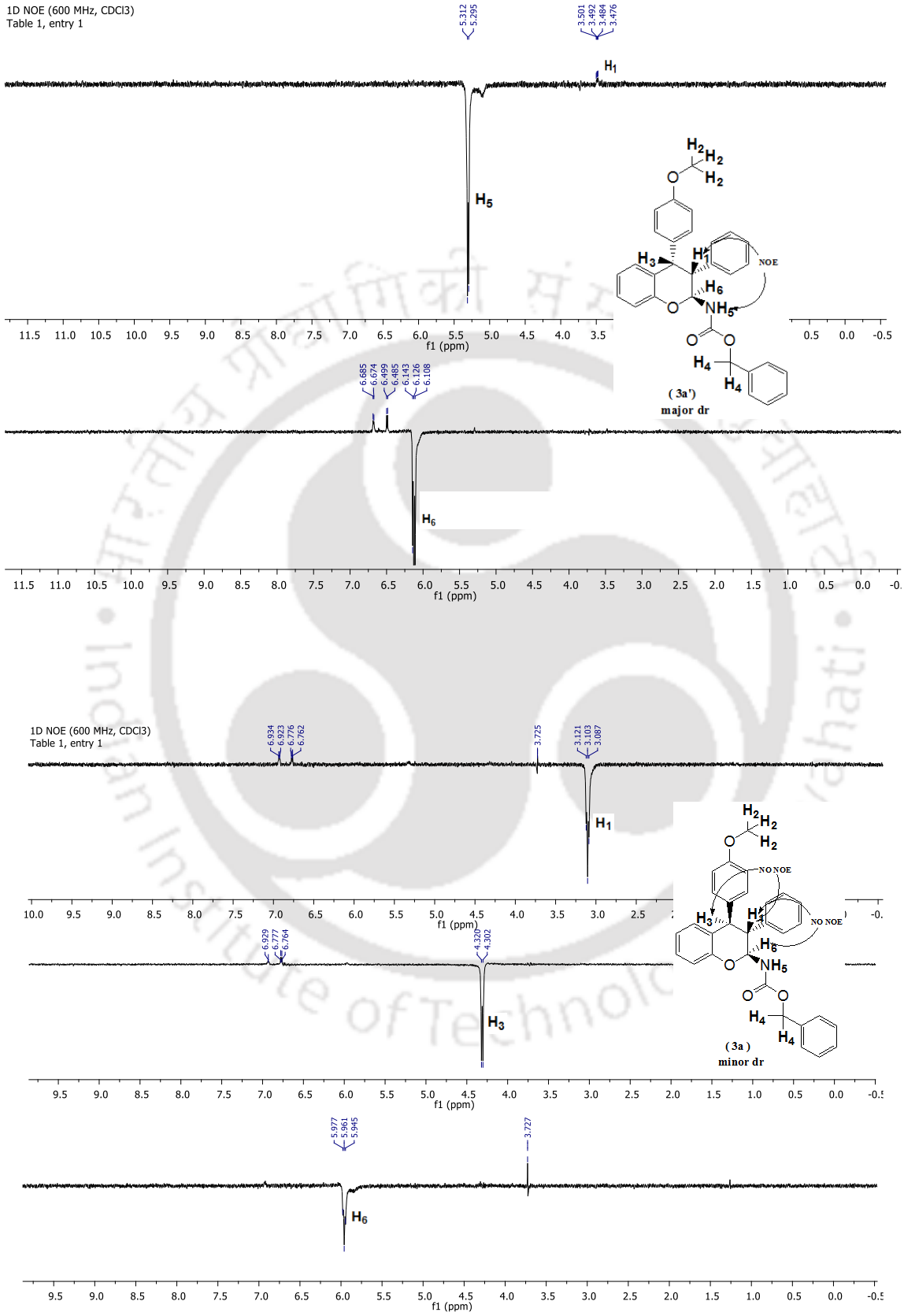
P2-90-CHI-IA

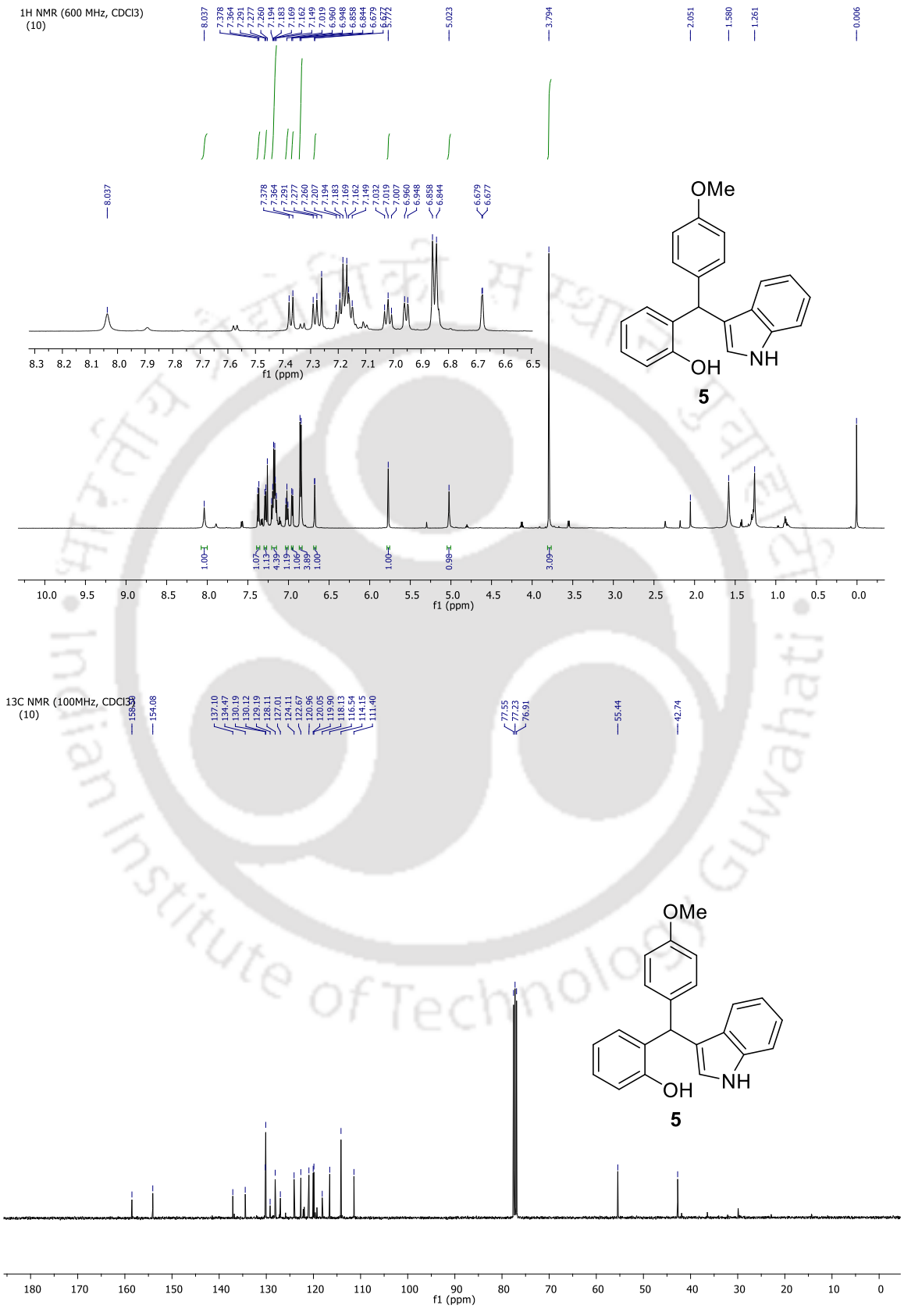


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	18.63	7.463579	0.614450587	15.95955	n.a.
2	b	20.48	49.41242	4.067953051	84.40162	n.a.
3	c	33.62	1111.585	91.51293701	1105.709	n.a.
4	d	58.18	46.214	3.80465935	30.689	n.a.

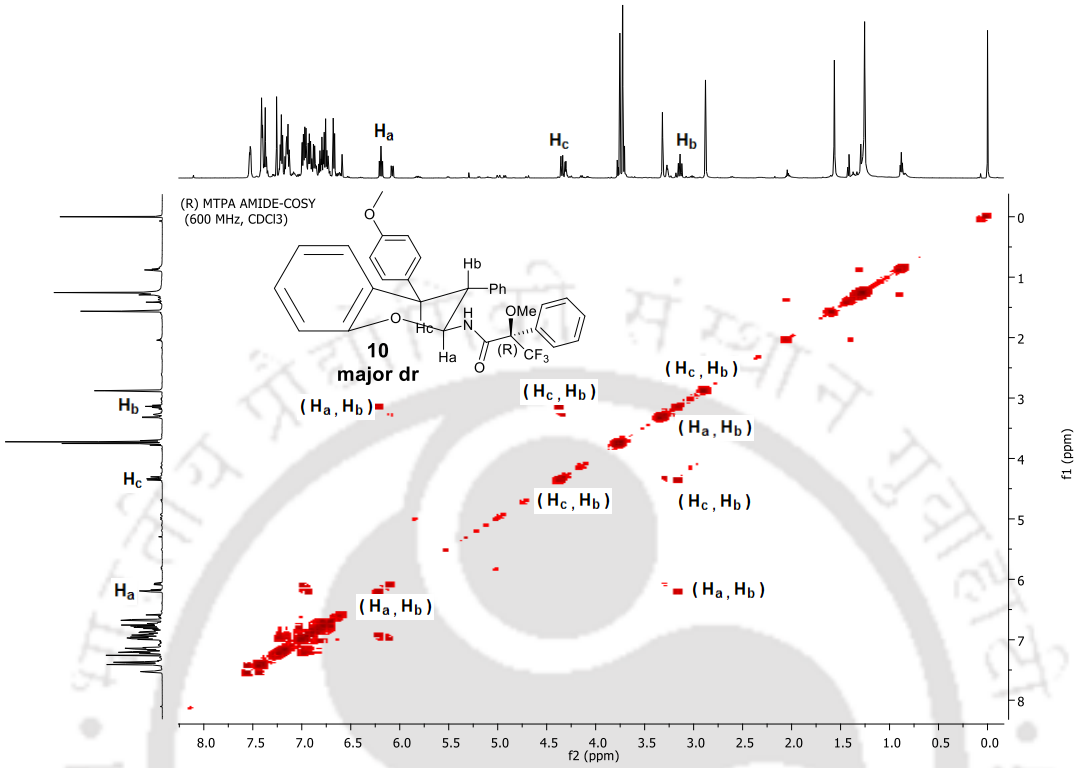
COSY and 1D NOE spectra for the relative stereo chemistry of product 3a'(major dr) of (Table 1, entry 1) [which is equivalent to 3a'{(minor dr) of (Table 1, entry 6)]



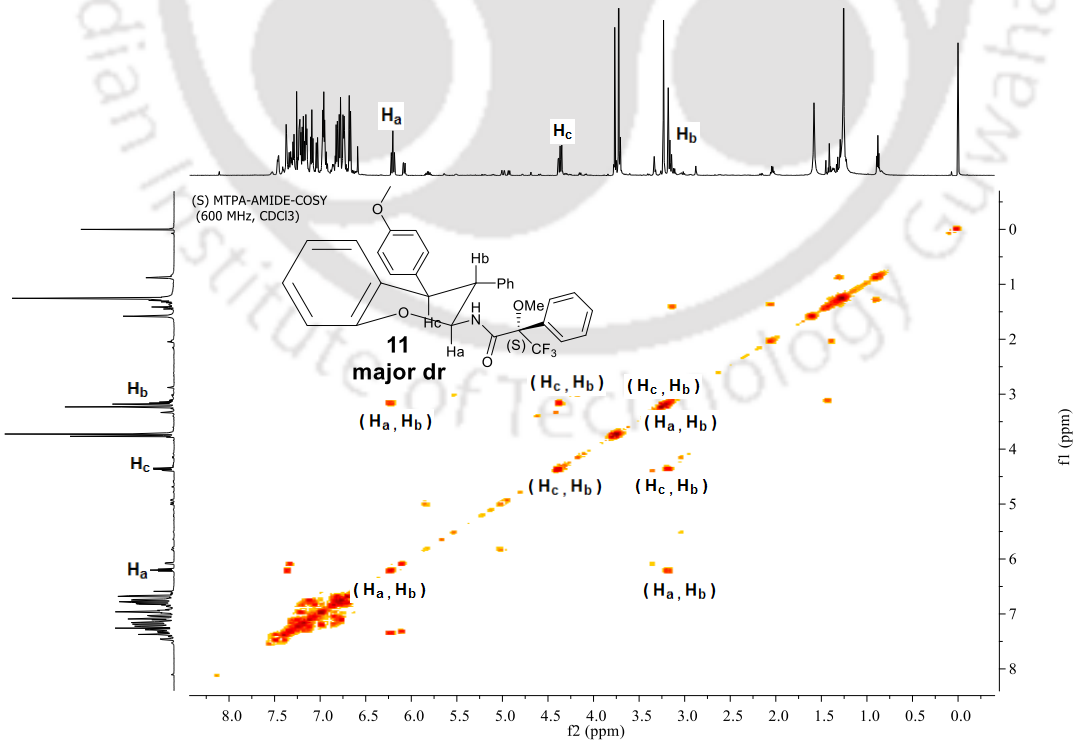




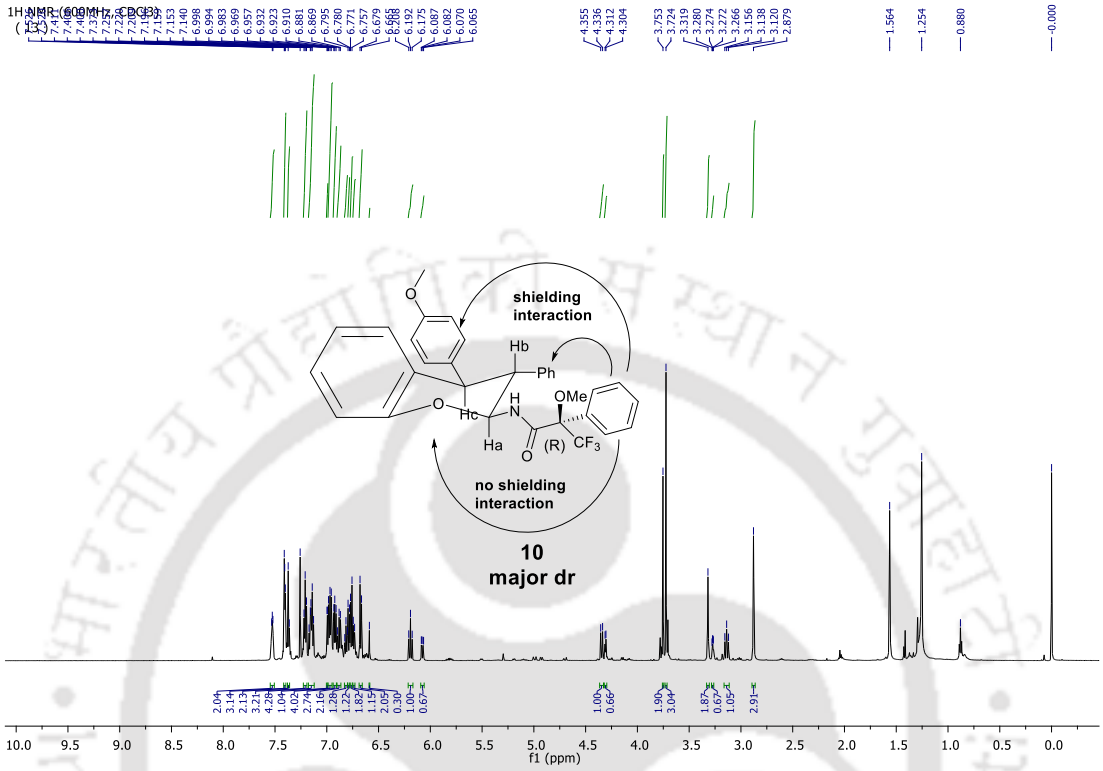
COSY spectra of (*R*)-Mosher amide 10/10' derived from (*S*)-(+) MTPA-Cl & 7q/7q'



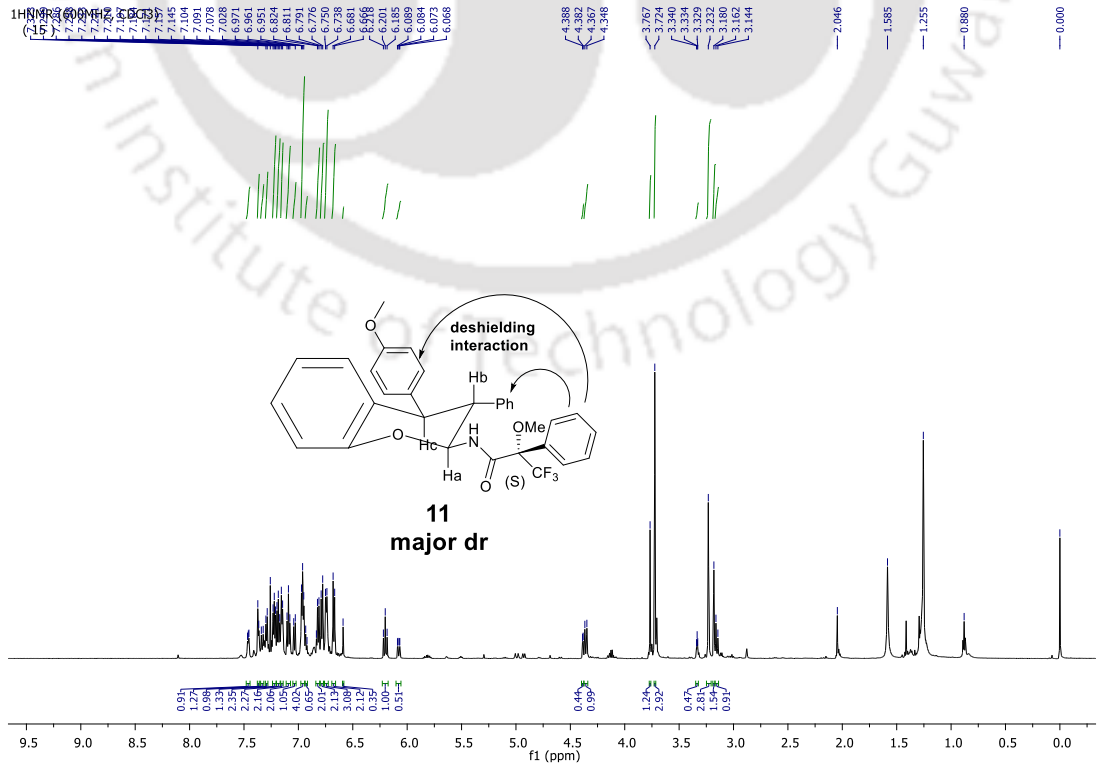
COSY spectra of (*S*)-Mosher amide 11/11' derived from (*R*)-(-) MTPA-Cl & 7q/7q'



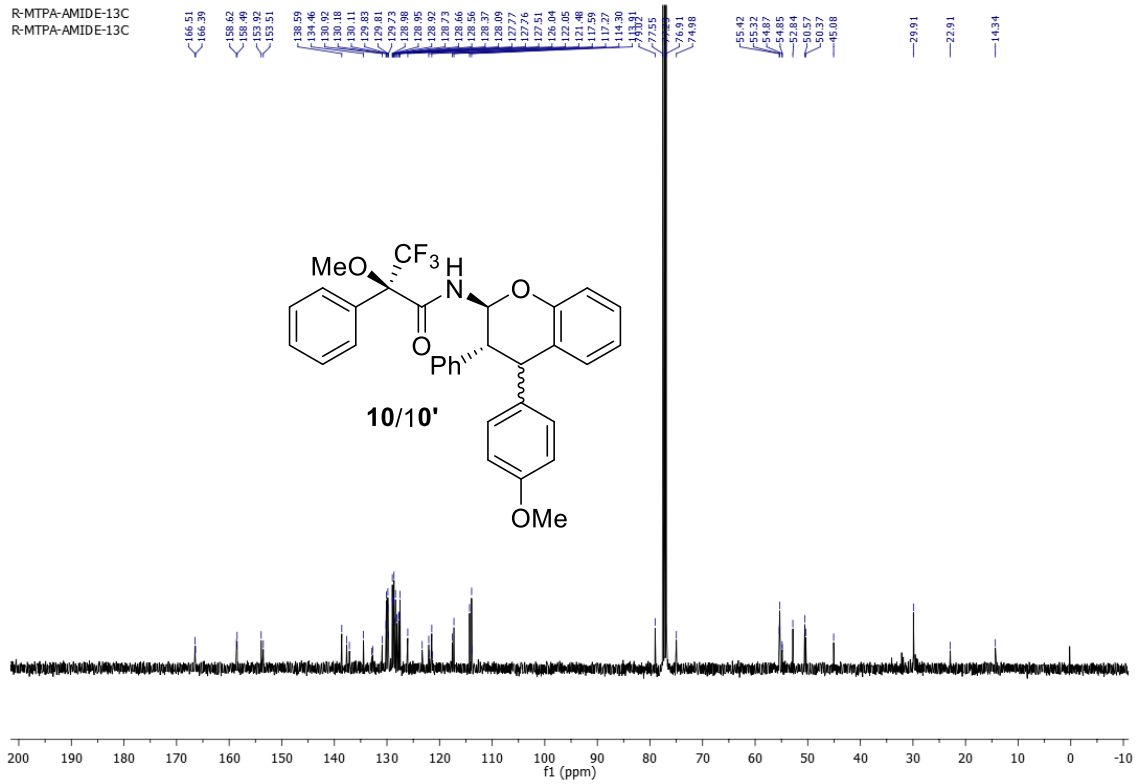
NMR spectra of (*R*)-Mosher amide 10/10' derived from (*S*)-(+) MTPA-Cl & 7q/7q'



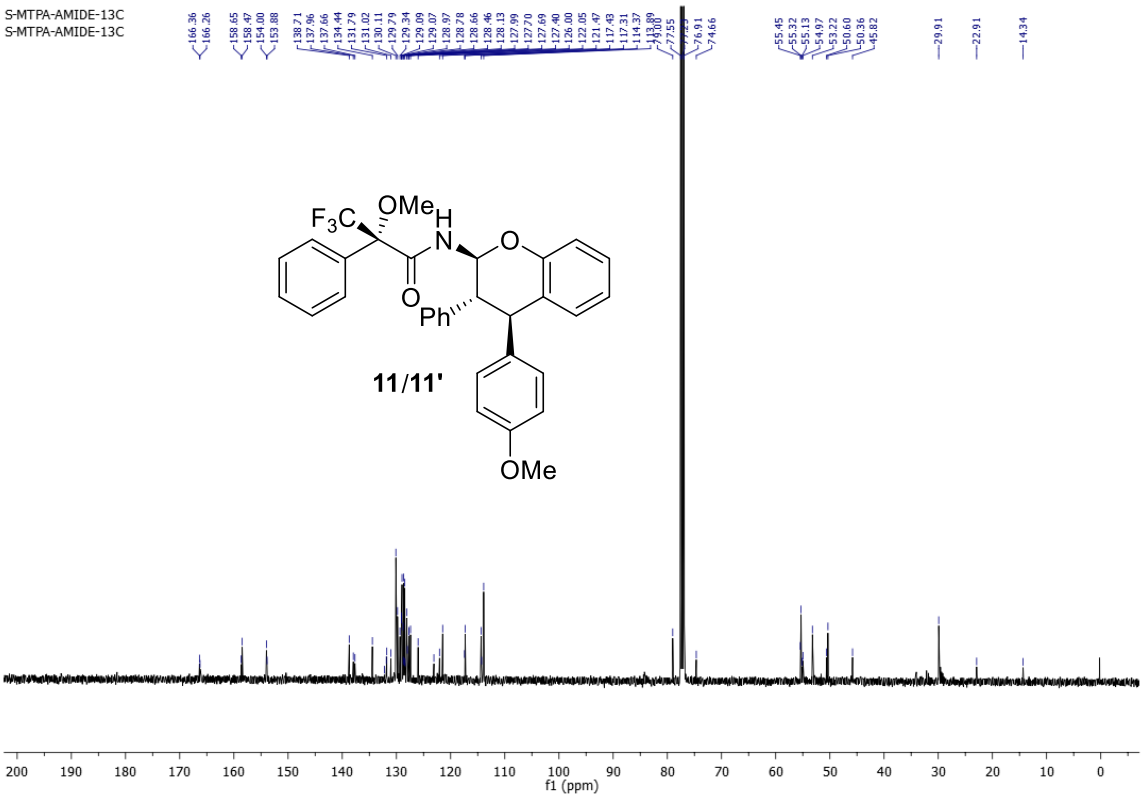
NMR spectra of (*S*)-Mosher amide 11/11' derived from (*R*)-(-) MTPA-Cl & 7q/7q'



^{13}C NMR spectra of (*R*)-Mosher amide 10/10'



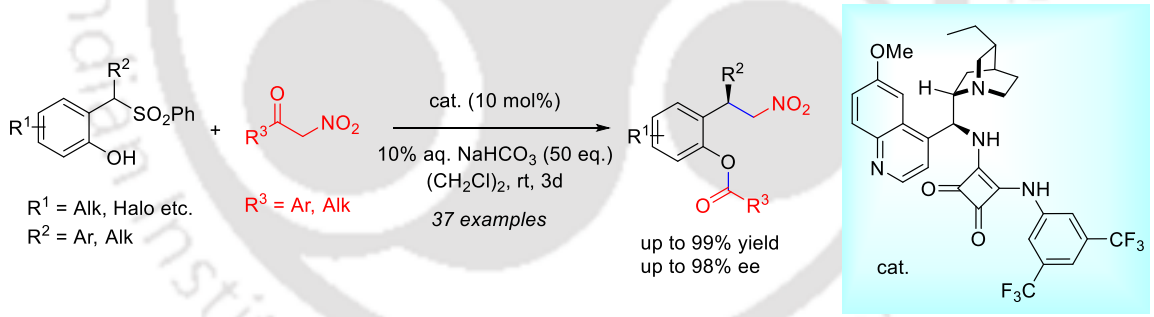
^{13}C NMR spectra of (*S*)-Mosher amide 11/11'



Organocatalytic Asymmetric Domino Michael/Acyl Transfer Reaction Between α-Nitroketones and in situ-Generated ortho-Quinone Methides: Route to 2-(1-Arylethyl)phenols[*]

Abstract:

An organocatalytic asymmetric domino Michael/acyl transfer reaction between *α*-nitroketones and *in situ*-generated *ortho*-quinone methides is developed. *ortho*-Quinone methide intermediates were prepared from stable precursors 2-sulfonylmethylphenols under aqueous sodium bicarbonate medium. Bifunctional squaramide catalyst with 10 mol% catalyst loading furnished a variety of *O*-acyl 2-(1-arylethyl)phenols in oil/water interface with excellent enantioselectivities and high yields. The reaction conditions were very mild and operationally simple procedure. Few potential synthetic transformations were also carried out.



[*]Gharui, C.; Behera, D.; Pan, S. C. *Adv. Synth. Catal.* **2018**, *360*, 4502.

3.1. Introduction:

Phenolics and polyphenolics are important structural frameworks and building blocks frequently found in nature in various forms. They have wide spectrum of applications in secondary metabolites, in protection against harmful pathogens as well as in chemical and pharmaceutical industry. Chiral 2-(1-arylethyl)phenols are the significant pharmacophores present in many natural products and bioactive molecules (Figure 1).[1] For example, (*R*)-tolterodine (trade name Detrol drug) is a powerful muscarinic receptor antagonist for the treatment of urinary incontinence and other symptoms related to an overactive bladder.[1c] (*R*)-Latifolin and (*S*)-4-methoxydalbergione are the another examples of natural products having chiral 2-(1-arylethyl)phenol motif.[1e] Both the neoflavonoids exhibit antitermite and antifungal activities. Similarly, 6-benzyl-1,3-benzodioxole had shown the activity against P388 murine lymphocytic leukemia.[1f] Again the tacrine analogues are the useful drug candidates used in the treatment of Alzheimer's disease.[1g,1h] (-)-Simulanol, a lignan type natural product having 2-(1-alkylethyl)phenol scaffold found in the stem of Formosan *Zanthoxylum simulans*.[1i] Also, procyanidin B3 and several other oligomers[1j] derived from (+)-catechins are capable in displaying versatile activities (Figure 1).

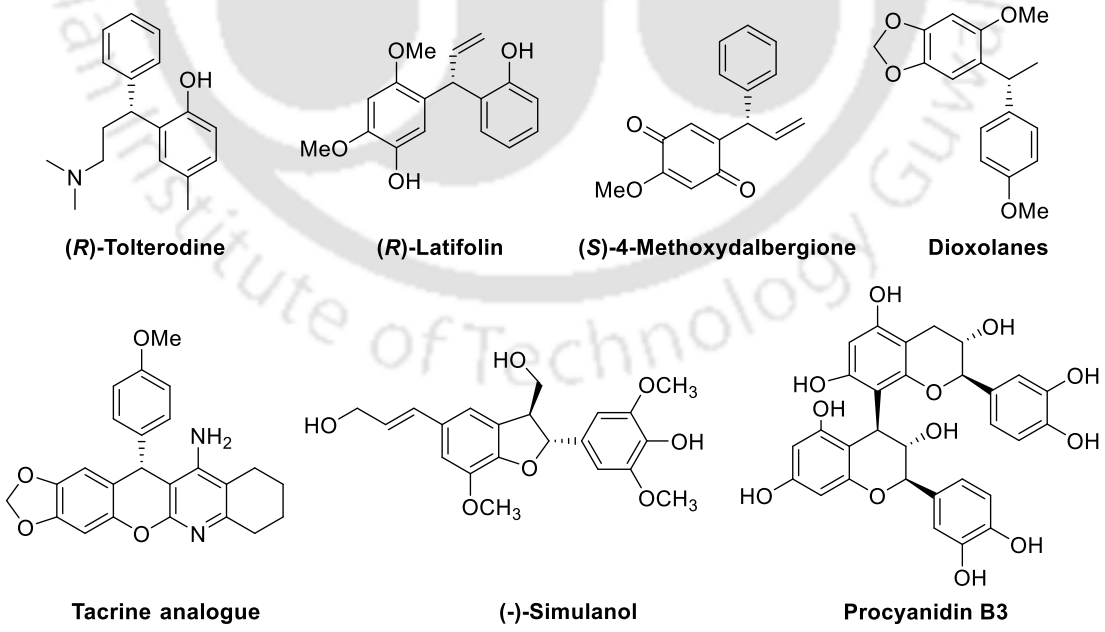


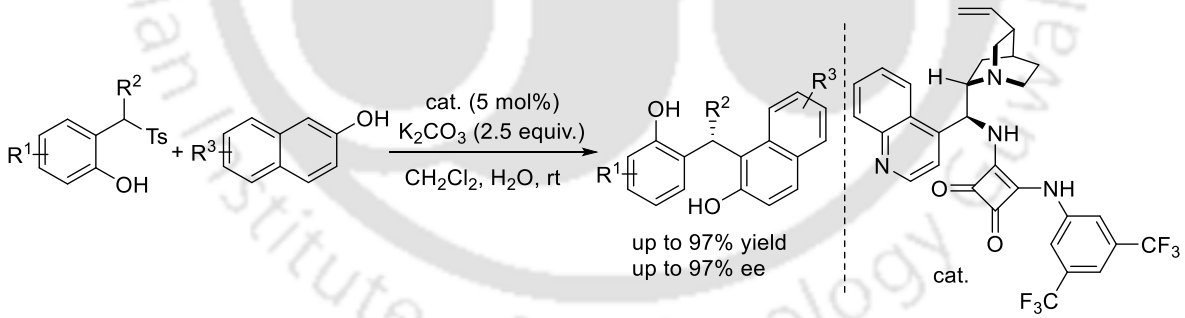
Figure 1. Selective examples of bioactive phenol derivatives.

Realizing the diverse applications of chiral phenols, recently, the asymmetric version of phenolics has become an attractive target. In recent years, various methodologies have been elucidated for the synthesis of chiral phenol derivatives *via* organocatalytic asymmetric 1,4-Friedel-Crafts alkylation/cascade strategy.[2] Still devolopment of new other efficient approaches are highly desirable for the synthesis of complex drug molecules and for other benefits.

in situ-Generated *ortho*-quinone methides (*o*-QMs) have been identified as valuable Michael acceptors in organic synthesis. 2-Sulfonylmethylphenols are the stable precursors of *ortho*-quinone methide intermediates which could be generated *in situ* under basic conditions. In the last decades *in situ*-generated *o*-QM intermediates have been employed in several organocatalytic enantioselective conjugate addition reactions for the construction of chiral phenols in effective ways.

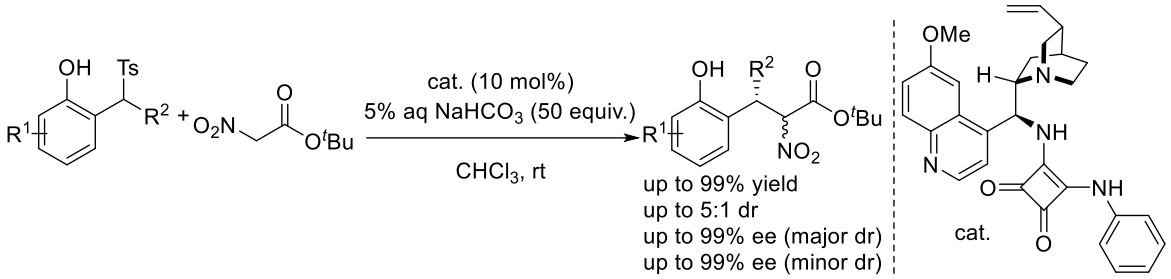
3.2.1. Selected previous reports for the synthesis of chiral phenols employing *o*-QMs:

Xu and co-workers demonstrated cinchonidine amine based bifunctional squaramide catalyzed enantioselective Friedel-Crafts alkylation of *β*-naphthols with *in situ*-generated *ortho*-quinone methides (Scheme 1).[3] Several triarylmethane derivatives were obtained with good yields and in moderate to excellent enantioselectivities.



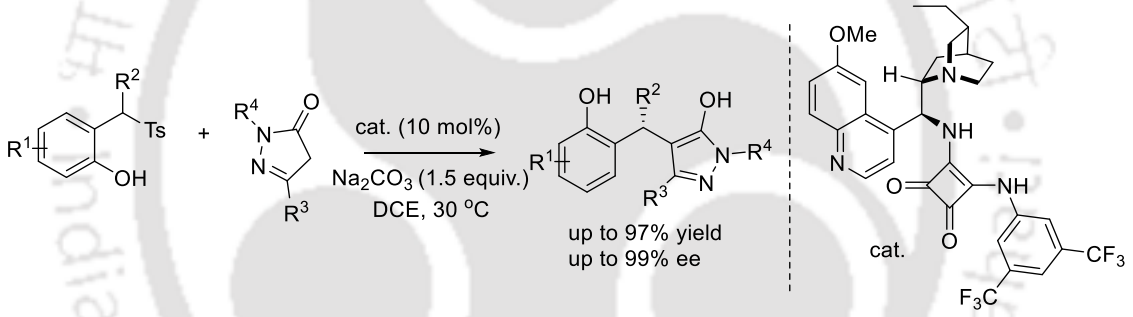
Scheme 1. Enantioselective Friedel-Crafts alkylation of *β*-naphthols to *o*-QMs.

Quinine amine derived squaramide catalyzed enantioselective conjugate addition reaction of *tert*-butyl nitroacetate with *in situ*-generated *ortho*-quinone methides had been depicted by Yan *et al.* (Scheme 2).[4] Herein, *α*-nitro-*β*,*β*-diaryl-propionate derivatives were achieved with high enantiomeric excesses and moderate to good diastereoselectivities. Surprisingly, other alkyl-nitroacetates were not suitable in this reaction.



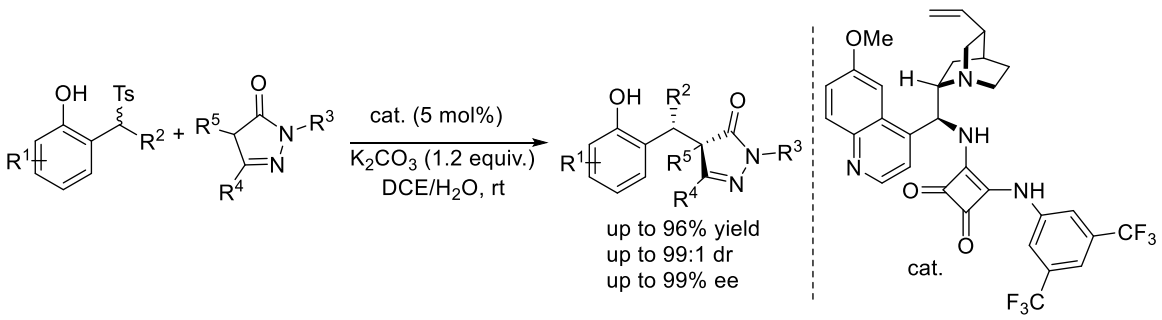
Scheme 2. Enantioselective conjugate addition of *tert*-butyl nitroacetate to *o*-QMs.

Jiang group successfully disclosed hydroquinine amine derived squaramide catalyzed efficient route for the synthesis of enantiopure 5-hydroxy-pyrazoles containing triarylmethane derivatives from the reaction of 2-(1-tosylalkyl)phenols and pyrazolin-5-ones (Scheme 3).[5] The desired products were obtained in general with high yields and in high enantiomeric excesses.



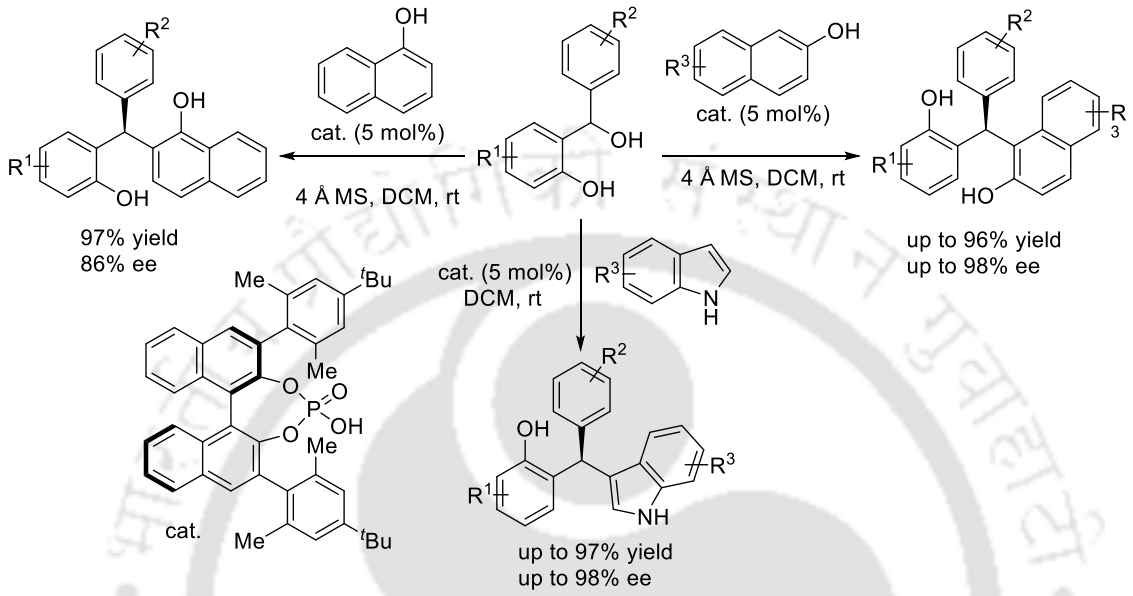
Scheme 3. Synthesis of triarylmethanes having pyrazole-5-ol motifs.

Bifunctional squaramide catalyzed another enantioselective asymmetric reaction between 2-(1-tosylalkyl)phenol and pyrazolin-5-one was explored by Xu and co-workers (Scheme 4).[6] Optically active tetrasubstituted pyrazolin-5-ones having adjacent tertiary and quaternary stereo ccenters were synthesized with high yields and excellent diastereo- and enantioselectivities.



Scheme 4. Synthesis of tetrasubstituted pyrazolin-5-ones from *in situ*-generated *o*-QMs.

Also, Schneider group anticipated chiral phosphoric acid catalyzed enantioselective Friedel-Crafts alkylation reactions of electron rich arenes such as naphthols, indoles with *in situ*-generated *ortho*-quinone methides (Scheme 5).[7] Various diarylindolylmethanes and triarylmethanes were obtained with high yields and excellent enantioselectivities.



Scheme 5. Enantioselective synthesis of various phenols from *in situ*-generated *o*-QMs.

On the other hand, *α*-nitroketones are the useful reactive nucleophiles in organic synthesis having both nitro and keto functionalities. In the last few decades, this has been utilized in several metal- and organocatalyzed C-C, C-O and C-N bond forming reactions.[8] *α*-Nitroketones are one of the useful substrates which have delivered different types

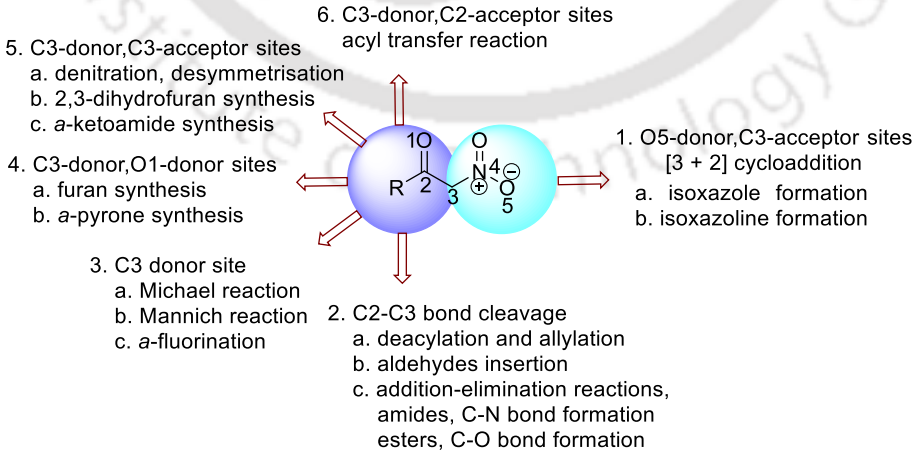
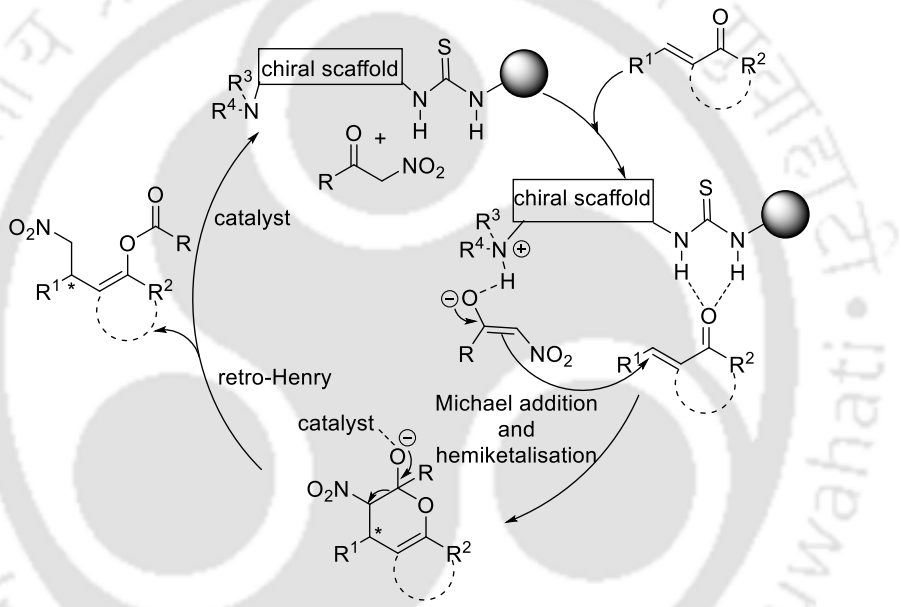


Figure 2. Reactive sites of *α*-nitroketones.

of reactions such as: Michael, domino-Michael, denitration, desymmetrisation, Mannich, nucleophilic addition/elimination, cycloaddition etc. under different reaction conditions (Figure 2). Interestingly, because of having C3-donor, C2-acceptor sites in *α*-nitroketones, it is highly facile in enantioselective acyl transfer type reaction.

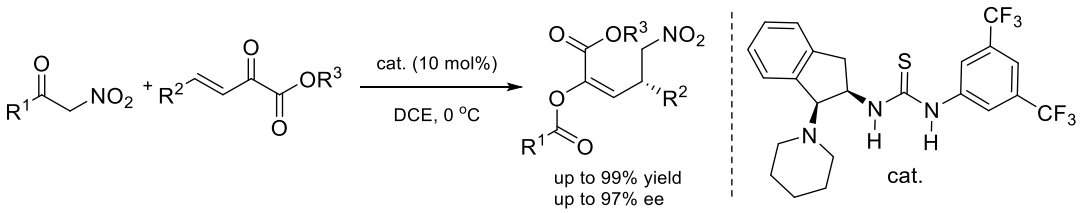
Acyl transfer reaction sequence of *α*-nitroketones with various Michael acceptors is usually promoted by bifunctional organocatalysts *via* successive one pot three steps reaction i.e. i) Michael addition ii) hemiketalisation reaction and iii) retro-Henry reaction as depicted in Scheme 6.



Scheme 6. Acyl transfer reaction sequence using *α*-nitroketones.

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

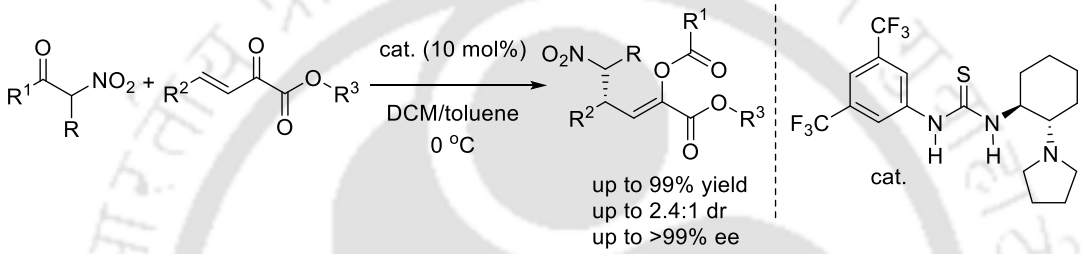
For the first time Wang group successfully reported an indane derived thiourea catalyzed enantioselective acyl transfer reaction between *α*-nitroketones and *β*,*γ*-unsaturated ketoesters (Scheme 7).[9]



Scheme 7. Indane derived thiourea catalyzed acyl transfer reaction of α-nitroketones with β,γ-unsaturated ketoesters.

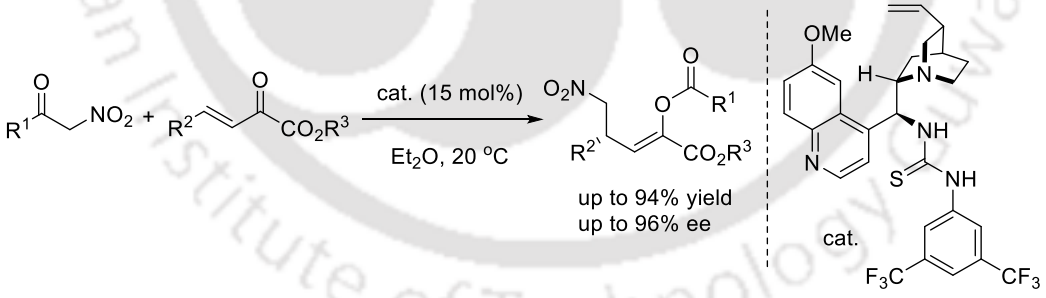
The expected products (*S*, *E*)-5-nitro-pent-2-enoates, were achieved in high yields and with excellent enantiomeric excesses.

In the same year, pyrrolidine based tertiary amine thiourea catalyzed similar enantioselective acyl transfer reaction had been explored by Yan and co-workers (Scheme 8).[10] Herein, (*R*, *Z*)-selective 5-nitro-2-acyloxypent-2-enoate products were obtained with excellent results. However, diastereoselectivity was moderate in case of α-alkyl-α-nitroketones.



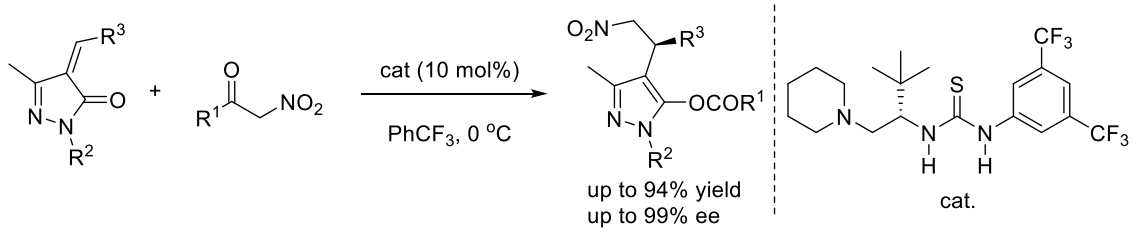
Scheme 8. Pyrrolidine based tertiary amine thiourea catalyzed acyl transfer sequence with α-nitroketones.

Chan and Kwong group anticipated another approach for the above identical reaction using quinine amine derived bifunctional thiourea catalyst (Scheme 9).[11]



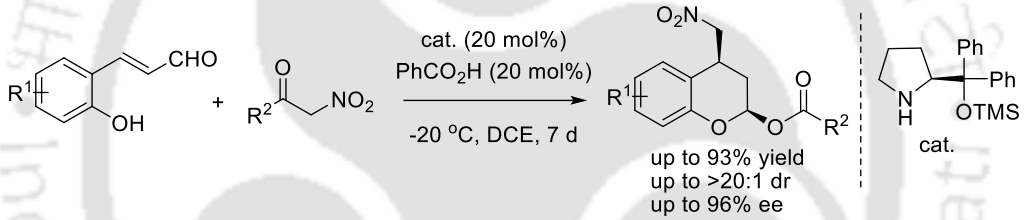
Scheme 9. Quinine amine derived thiourea catalyzed acyl transfer sequence with α-nitroketones.

Recently, our group disclosed various organocatalytic enantioselective acyl transfer protocols using α-nitroketones as the reaction partners. For example, *tert*-leucine derived thiourea catalyzed enantioselective acyl transfer sequence with α-nitroketones and α,β-unsaturated pyrazolones was described by Maity *et al*. (Scheme 10).[12] 3-Acyloxy pyrazole products were attained with high yields and with excellent enantiomeric excesses.



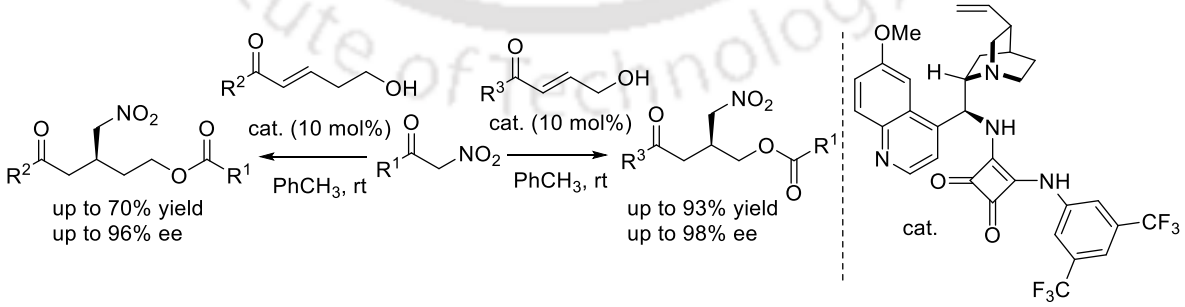
Scheme 10. Enantioselective acyl transfer between *α,β*-unsaturated pyrazolones and *α*-nitroketones.

Another acyl transfer strategy for the synthesis of 2,4-disubstituted chromans from 2-hydroxycinnamaldehydes and *α*-nitroketones had been successfully reported by our group (Scheme 11).[13] Prolinol-TMS-ether catalyst in combination with benzoic acid additive afforded the desired products in good to high yields and with high diastereomeric ratio and enantioselectivities.



Scheme 11. Prolinol-TMS-ether catalyzed acyl transfer sequence with *α*-nitroketones.

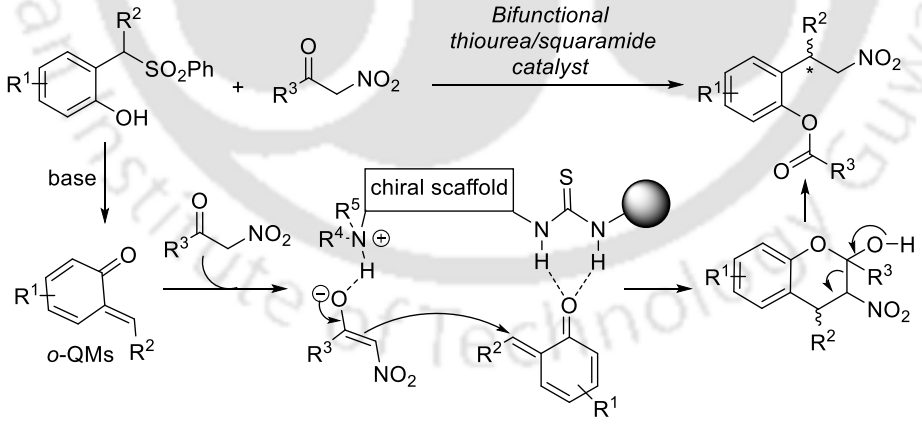
In addition, *γ/δ*-hydroxyenones and *α*-nitroketones were effectively engaged in another acyl transfer reaction and was developed by Mondal *et al*. (Scheme 12).[14] Quinine amine derived squaramide catalyst was suitable for such reaction and delivered the products with very satisfactory results.



Scheme 12. Enantioselective acyl transfer reaction between *γ/δ*-hydroxyenones and *α*-nitroketones.

3.3. Concept:

Literature survey revealed that chiral 2-(1-arylethyl)phenols use to have significant medicinal and other applications in pharmaceuticals as well as in total synthesis. Particularly in this regard, synthesis of (*R*)-Tolterodine and Dioxolanes molecules from easygoing efficient methods are quiet appealing. Also, the reports using *ortho*-quinone methide intermediates related to chiral phenols synthesis are limited. Beside, less reactive nitroalkanes usually do not participate in1,4-conjugate addition reactions. Thus expansion of new strategy for nitroalkane containing phenols is highly necessary. In addition, *α*-nitroketones have been identified as potent acylating reagent. To the best of our knowledge, the asymmetric reaction of *in situ*-generated *ortho*-quinone methides and *α*-nitroketones was not established before. Thus our interest was to develop an efficient method for 2-(1-phenylnitroethyl)-*O*-acyloxyphenols *via* conjugate addition followed by acyl transfer reaction between *α*-nitroketones and *in situ*-generated *o*-QMs. Initially, we thought that *ortho*-quinone methide intermediates could be generated *via in situ* from stable precursor like 2-(aryllsulfonyl)methyl phenols under basic medium. Then enol form of *α*-nitroketone and *ortho*-quinone methide might be activated by the bifunctional thiourea/squaramide catalysts. After this, domino Michael/acyl transfer reaction will provide the desired products in an enantioselective fashion (Scheme 13).



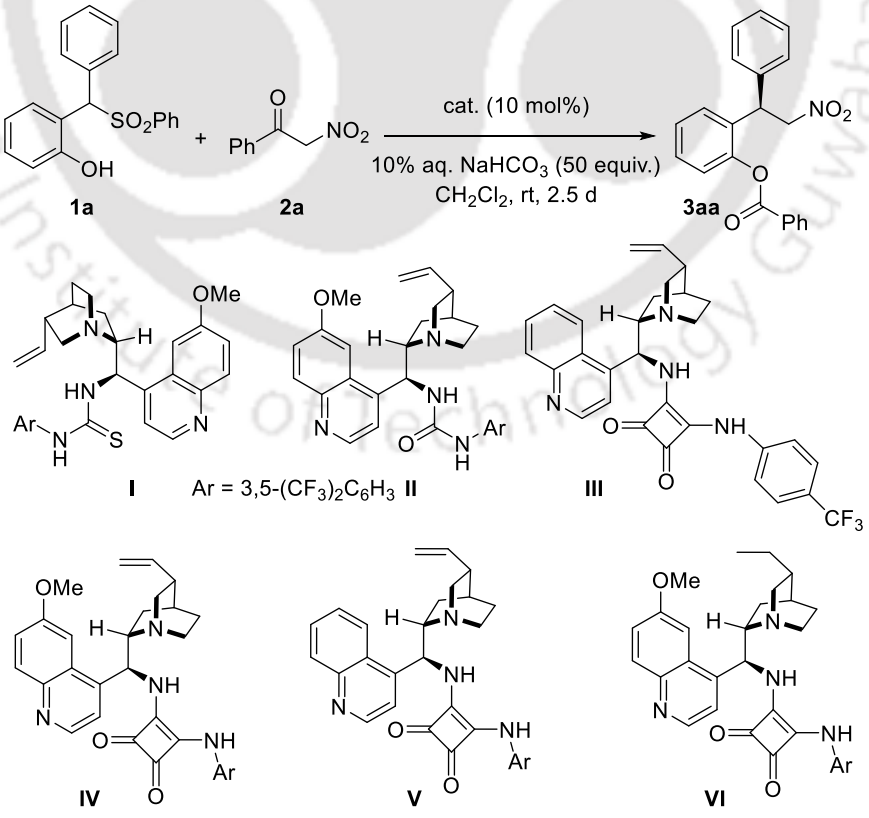
Scheme 13. Proposed route to chiral 2-(1-arylethyl)phenol derivatives.

3.4. Result and Discussion:

Thus a model reaction was performed between 2-(phenylsulfonyl)methyl phenol **1a** and nitroketone **2a** with bifunctional thiourea/squaramide catalysts and aq. $NaHCO_3$ (50 equiv.)

in dichloromethane solvent (Table 1). After stirring at room temperature for 2.5 days with quinidine derived thiourea catalyst **I** (10 mol%), the desired nitroketone addition followed by acyl transfer reaction took place and the product **3aa** was isolated in 81% yield with 42% ee (entry 1). The enantioselectivity was further improved to 74% with bifunctional urea catalyst **II** (entry 2). Then different bifunctional squaramide catalysts were screened and the results were encouraging. For example, cinchonidine derived catalyst **III** having 4-trifluoromethylphenyl group provided the product **3aa** in 81% yield with 94% ee (Table 1, entry 3). The enantioselectivity was further improved by employing quinine derived squaramide catalyst **IV** having bis(trifluromethyl)phenyl group (entry 4). Here, the product **3aa** was obtained in 87% yield and with 96% ee. Then cinchonidine and hydroquinine derived squaramide catalysts **V** and **VI** were investigated and identical enantioselectivities (96% ee) were attained but slight less yield was detected with **V** (entries 5-6). Finally, 10 mol% hydroquinine derived squaramide catalyst **VI** was found to be the best catalyst and provided the product **3aa** in 93% yield and with 96% ee (Table 1, entry 6).

Table 1. Catalyst screening



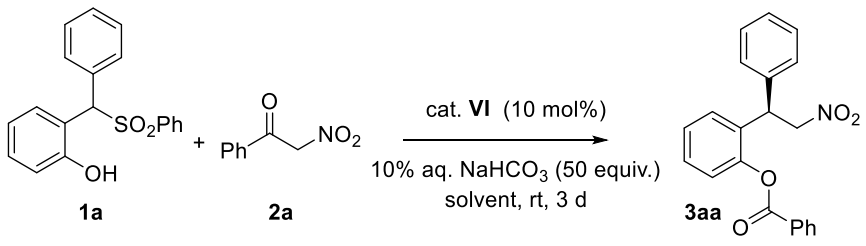
entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	81	42
2	**II**	78	74
3	**III**	81	94
4	**IV**	87	96
5	**V**	90	96
6	**VI**	**93**	**96**

[a]Reaction conditions: 0.05 mmol of **1a** and 0.25 mmol of **2a** in 0.6 mL solvent using 10 mol% catalyst and 10% aq. $NaHCO_3$ at room temperature for 2.5 days followed by acidification using 10% aq. HCl. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

3.4.1. Solvent screening:

For further improvement in enantioselectivity of the product **3aa**, another set of reactions were studied with catalyst **VI** and in various solvents (Table 2). The enantioselectivity was slightly enhanced to 97% in chloroform solvent (entry 2). Other halogenated solvent such as 1,2-dichloroethane delivered the product with 98% ee (entry 3). Enantioselectivity got significantly decreased to 78% in trifluorotoluene solvent (entry 4). Next, the effect of non-halogenated solvents was examined. For example, similar enantioselectivity (76%) was observed in xylene (entry 5). Decent results (88% yield, 92% ee) were obtained in case of toluene (entry 6). The ethereal solvent provided the expected product with less ee (entry 7). Although, more polar solvent like DMF afforded the product in high yield (91%), enantioselectivity was almost null (entry 8). In addition, when the reaction was performed using 2.5 equivalents of α-nitroketone **2a** instead of 5 equivalents, both the yield and enantiomeric excess of the reaction got reduced in substantial amount (entry 9).

Table 2. Solvent screening



entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	93	96
2	$CHCl_3$	94	97
3	**$(CH_2Cl)_2$**	**93**	**98**
4	$PhCF_3$	91	78
5	xylene	86	76
6	$PhCH_3$	88	92
7	Et_2O	84	30
8	DMF	91	2
9[d]	$(CH_2Cl)_2$	63	95

[a]Reaction conditions: 0.05 mmol of **1a** with 0.25 mmol of **2a** in 0.6 mL solvent using 10 mol% catalyst **VI** and 10% aq. $NaHCO_3$ at rt for 3 days followed by acidification using 10% aq. HCl. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column. [d]0.125 mmol of **2a** was used.

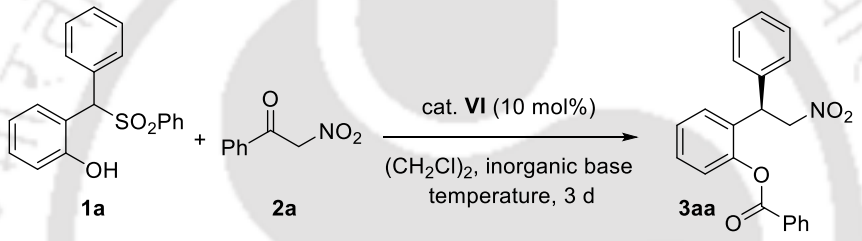
Thus the best solvent was 1,2-dichloroethane in terms of yield and ee of the reaction.

3.4.2. Inorganic base and temperature screening:

In order to improve the yield and enantiomeric excess of the reaction, other reaction parameters such as effect of inorganic base and temperature were thoroughly screened (Table 3). First, the effect of inorganic base was optimized by performing the reactions at room temperature (entries 1-9). When K_2CO_3 was used in 1,2-dichloroethane solvent and in the absence of aqueous medium, no desired product was obtained (entry 1). Very low conversion and low to moderate level of enantioselectivities were detected in the cases of Na_2CO_3, and $NaHCO_3$ conditions respectively (entries 2-3). Interestingly, when the reactions were carried out under oil/water interface both the yield and enantiomeric excess of the reactions were significantly high (entries 4-10). For instance, 89% yield and 78% ee were attained when 50 equivalents of 5% aqueous $NaHCO_3$ solution was applied (entry 4). Amount of water was also varied for getting better results. 50 equivalents of 10% aqueous

$NaHCO_3$ solution furnished the product **3aa** in 93% yield and with 98% ee (Table 3, entry 5). Then, other inorganic bases like K_2CO_3, Na_2CO_3 in oil/water medium were also employed. But, in these cases moderate yields as well as moderate enantioselectivities were observed for the product **3aa** (entries 6-7). Moreover, when the amount of 10% aqueous $NaHCO_3$ was reduced, slightly less enantioselectivity was detected (entries 8-9). Further optimization was done by setting up the reaction under slightly elevated temperature (entry 10). Here, the yield of the reaction got enhanced to 95% but enantioselectivity got decreased to 92%. Finally, the catalyst **VI** and 50 equivalents of 10% aqueous $NaHCO_3$ in 1,2-dichloroethane solvent at ambient temperature were found to be the best optimized conditions for this acyl transfer reaction (Table 3, entry 5).

Table 3. Inorganic base and temperature screening



entry[a]	inorganic base[equiv.]	yield (%)[b]	ee (%)[c]
1	K_2CO_3 [50]	no reaction	-
2	Na_2CO_3 [50]	25	20
3	$NaHCO_3$ [50]	27	64
4	5% aq. $NaHCO_3$ [50]	89	78
5	**10% aq. $NaHCO_3$ [50]**	**93**	**98**
6	10% aq. K_2CO_3 [50]	78	54
7	10% aq. Na_2CO_3 [50]	87	68
8	10% aq. $NaHCO_3$ [10]	91	95
9	10% aq. $NaHCO_3$ [25]	93	94
10[d]	10% aq. $NaHCO_3$ [50]	95	92

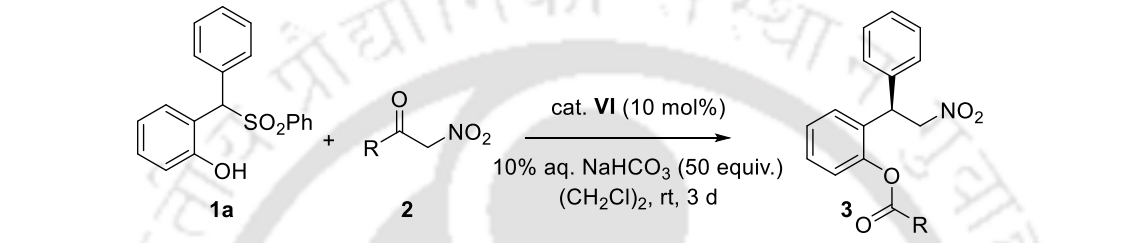
[a]Reaction conditions: 0.05 mmol of **1a** with 0.25 mmol of **2a** in 0.6 mL 1,2-dichloroethane using 10 mol% catalyst **VI** and required amount inorganic base at rt for 3 days followed by acidification using 10% aq. HCl. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column. [d]Reaction was performed at 50 °C for 27 hours.

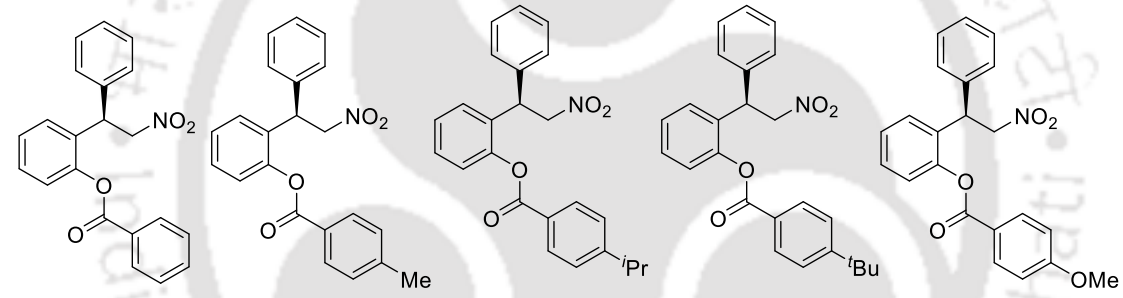
3.4.3. Substrate scope:

After the optimized conditions got established, the scope and generality of the reaction was investigated. Initially, a variety of nitroketones **2** with different electronic and steric properties was examined (Table 4). Delightfully, the reaction outcome was excellent in almost all the cases. At the beginning, different *para*-substitutions were screened and high to excellent enantioselectivities were obtained (**3ab**-**3ai**). For example, nitroketone **2b** having *p*-tolyl motif provided the product **3ab** in 94% yield and with 92% ee. Similarly, high enantioselectivities (i.e. 86% and 94% ees) were achieved for products **3ac** and **3ad** having 4-*iso*-propyl and 4-*tert*-butyl substitutions respectively. Interestingly, the yields were found to decrease monotonically with the increase of bulkiness of the *para*-alkyl substituents (**3ab**-**3ad**). 4-Alkoxy substituted nitroketone **2e** well participated in the reaction conditions and smooth conversion along with excellent enantiomeric excess (96%) were detected for **3ae**. Then nitroketones **2f**-**2h** having 4-halo substitutions were employed in the reaction and the corresponding products were isolated in high yields with excellent enantioselectivities. Here, an increase in both yield and ee was observed in the following order 4-F<4-Cl<4-Br. In particular, almost quantitative yield was attained for product **3ah** with 98% ee. Biphenyl nitroketone **2i** was also tolerated in the reaction and furnished the product **3ai** in 96% ee. Then different *meta*-substitutions were studied and here also the products were obtained in acceptable yields as well as with high enantioselectivities. For instance, nitroketone **2j** having *m*-tolyl substitution provided the product **3aj** with 83% yield and 86% ee. *meta*-Methoxy substituted nitroketone **2k** supplied the product in 74% yield with 90% ee. In addition, nitroketones **2l** and **2m** having 3-halo substitutions were efficiently employed and the products were isolated with 96% and 94% enantiomeric excesses respectively. Interestingly, *ortho*-substitutions in the nitroketone had no pronounced effect on the enantioselectivitity. Satisfactory results (77% yield, 90% ee) were obtained for product **3an** having *o*-tolyl motif. Noticeable drop on the yield was observed for products **3ao**-**3ap** though excellent enantioselectivities (92%) were maintained. A

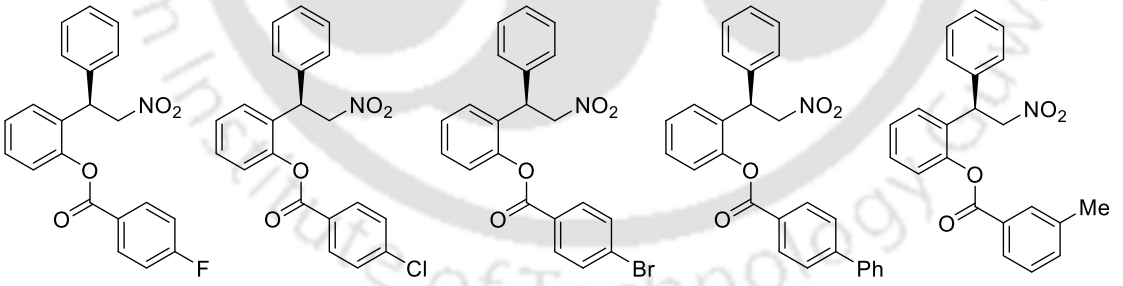
disubstituted aryl group containing nitroketone **2q** also withstood the reaction conditions and delivered product **3aq** in 90% ee. High enantioselectivity was also detected for product **3ar** with 1-naphthyl group. Then heteroarmoatic 2-thienyl nitroketone **2s** was engaged in the reaction and gratifyingly high ee of 92% was perceived for product **3as**. Moreover, an aliphatic nitroketone **2t** could also participate in the reaction and good results were achieved.

Table 4: Scope of *α*-nitroketones[a,b,c]

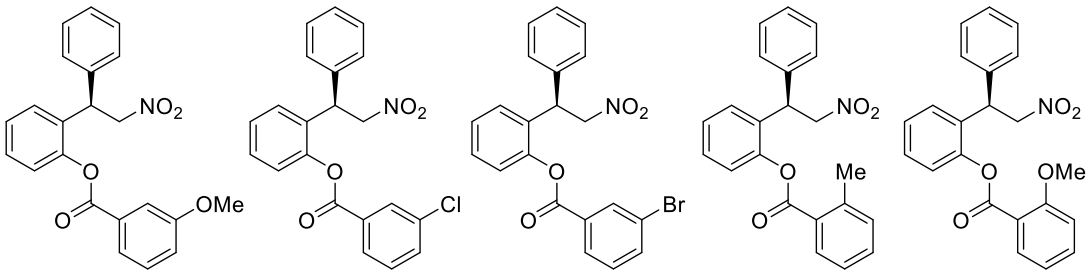




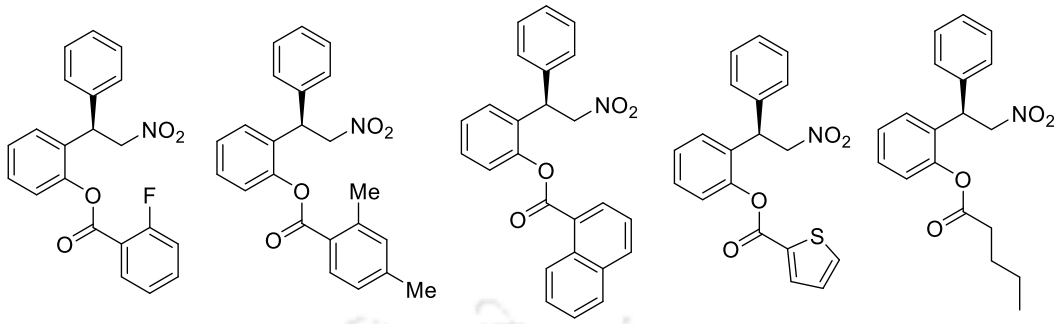
3aa, 93%, 98% ee **3ab**, 94%, 92% ee **3ac**, 85%, 86% ee **3ad**, 74%, 94% ee **3ae**, 90%, 96% ee



3af, 82%, 94% ee **3ag**, 89%, 95% ee **3ah**, 99%, 98% ee **3ai**, 83%, 96% ee **3aj**, 83%, 86% ee



3ak, 74%, 90% ee **3al**, 73%, 96% ee **3am**, 70%, 94% ee **3an**, 77%, 90% ee **3ao**, 53%, 92% ee

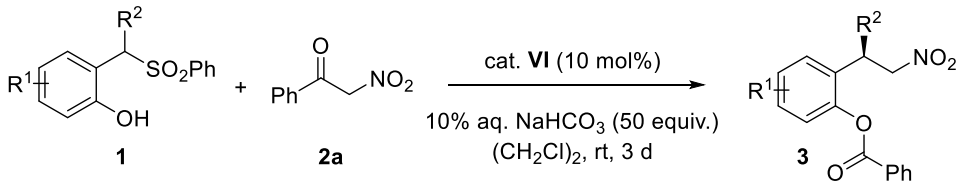


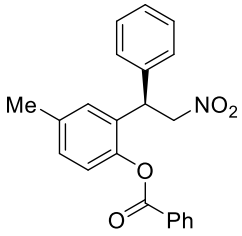
3ap, 60%, 92% ee **3aq**, 96%, 90% ee **3ar**, 86%, 96% ee **3as**, 96%, 92% ee **3at**, 79%, 88% ee

[a]Reactions were carried out with catalyst **VI** in 1,2-dichloroethane at room temperature for 3 days followed by acidification using 10% aq. HCl. [b]Isolated yield after silica gel column chromatography. [c]Enantioselectivity was determined by HPLC using stationary phase chiral column.

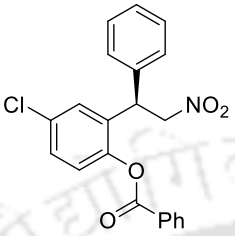
In the next phase, the scope of 2-sulfonylmethylphenols was studied and gratifyingly, a range of phenols having variations both on the phenolic fragment and *β*-aryl substituent could be employed in the reaction and good results were accomplished (Table 5). For example, 4-methylsubstituted 2-tosylmethylphenol **1b** on reaction with nitroketone **2a** provided the product **3ba** in high yield with 94% ee. Also, the reactions progressed effectively with different halo substitutions on the phenol part of 2-sulfonylmethylphenols **1c**-**1g**. Good to high yields as well as same enantioselectivity (i.e. 94% ee) were almost maintained for the products **3ca**-**3ea**. 4,6-Dibromo substituted phenol **1f** delivered the product **3fa** with 87% yield and 90% ee. Whereas slight higher enantioselectivity (94%) was identified for product **3ga**. Phenol **1h** having ethoxy substitution at 6- position was also studied and provided 92% ee for product **3ha**. Interestingly, in this case, higher isolated yield (91%) was observed after doing aqueous work up instead of aqueous hydrochloric acid due to the removal of unreacted nitroketone in the aqueous phase. Similar technique was also followed in the synthesis of **3ia**. The product **3ia** having sesamol motif was obtained in high enantioselectivity (96%) along with high yield (84%). Then we turned our attention to check variations on the *β*-aryl group and here also different substitutions were tolerated. Initially, different *para*-substitutions were checked and excellent results were obtained. Product **3ja** having *p*-tolyl moiety was isolated in 94% yield with 96% ee. Similar result was also achieved with 4-^{t}butylaryl group containing 2-sulfonylmethylphenol **1k**. Then *para*-anisyl substituted phenol **1l** was employed in the reaction, excellent yield as well as enantiomeric excess were detected for product **3la**.

Table 5: Scope of 2-sulfonylmethylphenols[a,b]

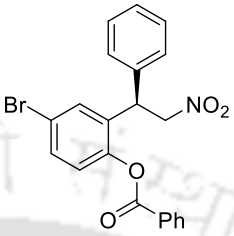




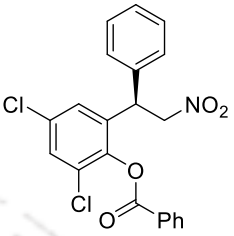
3ba, 97%, 94% ee



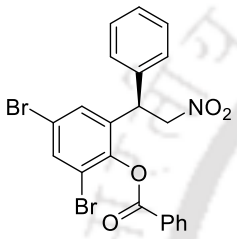
3ca, 92%, 94% ee



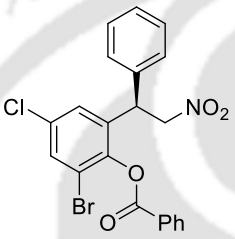
3da, 94%, 94% ee



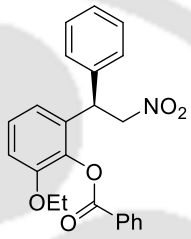
3ea, 77%, 94% ee



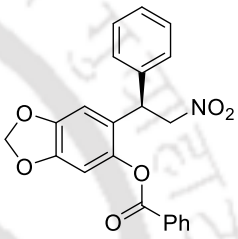
3fa, 87%, 90% ee



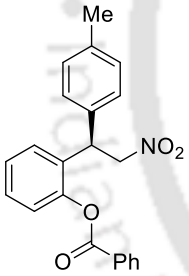
3ga, 85%, 94% ee



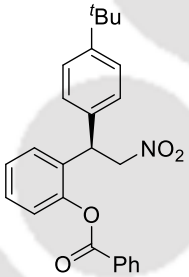
[c]**3ha**, 91%, 92% ee



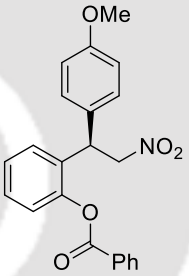
[c]**3ia**, 84%, 96% ee



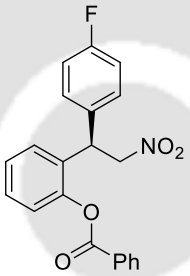
3ja, 94%, 96% ee



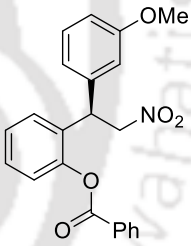
3ka, 89%, 96% ee



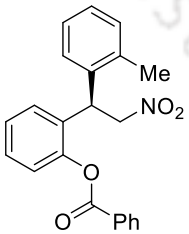
[c]**3la**, 90%, 96% ee



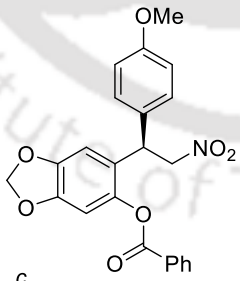
[c]**3ma**, 77%, 90% ee



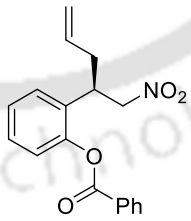
[c]**3na**, 87%, 96% ee



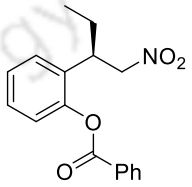
3oa, 88%, 98% ee



[c]**3pa**, 88%, 96% ee



3qa, 39%, 68% ee



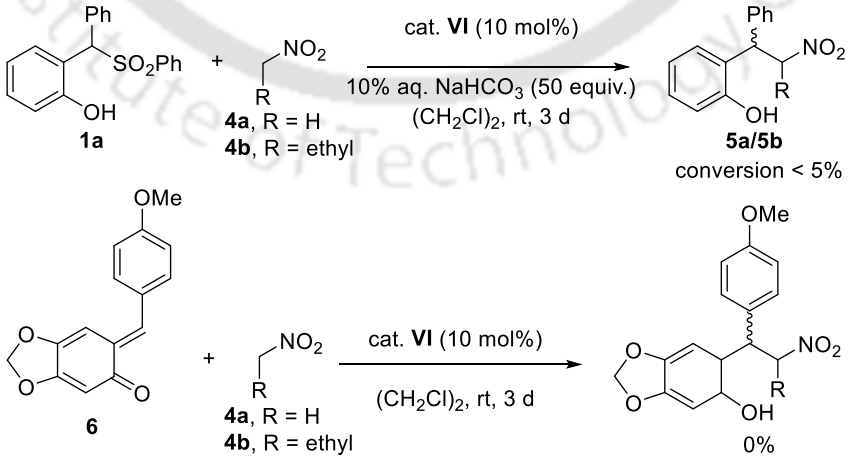
3ra, 54%, 60% ee

[a]Unless otherwise mentioned reaction was carried out with catalyst **VI** in 1,2-dichloroethane at room temperature for 3 days followed by acidification using 10% aq. HCl. [b]Isolated yield after silica gel column chromatography and enantioselectivity was determined by HPLC using stationary phase chiral column. [c]Performed aqueous work up without using HCl.

Electron withdrawing functionality present at the *para*- position of *β*-aryl part of the phenol **1m** also gave promising result in terms of yield and ee. Phenol **1n** having *meta*-methoxy substitution on the *β*-aryl group also took part in the reaction providing excellent result (87% yield, 96% ee). Almost similar reaction outcome (88% yield, 98% ee) was noticed for **3oa** having *ortho*-alkylated *β*-aryl motif. Then sesamol motif containing phenol **1p** having *β-para*-anisyl group was engaged in the reaction which resulted in the formation of **3pa** in 88% yield with 96% ee. Then *β*-allyl and *β*-ethyl group containing phenols **1q**-**1r** were prepared and employed in the reaction. To our delight, the reactions progressed well to deliver the corresponding products in moderate yields and enantioselectivities.

3.4.4. Reactions of nitroalkanes with *ortho*-quinone methides:

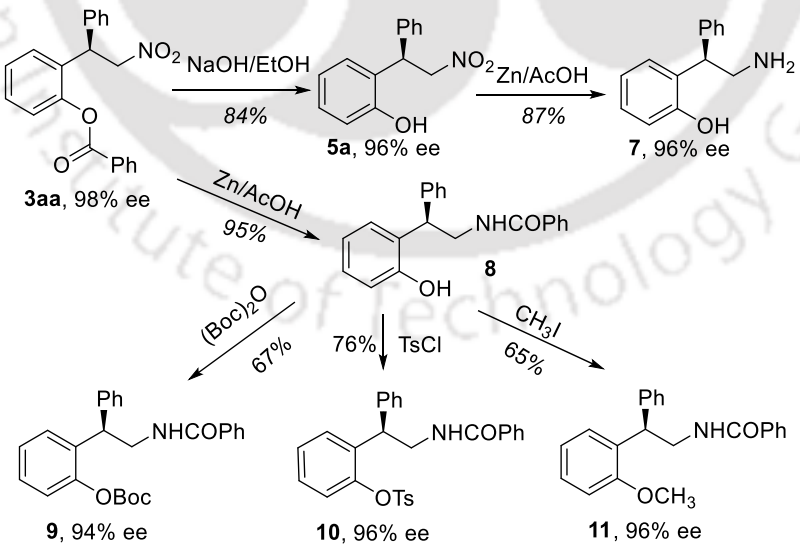
The reaction of 2-sulfonylmethylphenol **1a** with nitromethane **4a** as well as 1-nitropropane **4b** had been performed under the optimized reaction conditions (Scheme 14). However, negligible conversion (<5%) was detected for products **5a/5b**. Furthermore, to understand the barrier in such nitroalkane addition reactions, another set of reactions using preformed stabilized *ortho*-quinone methide **6**[15] and nitroalkanes were carried out (Scheme 14). But here also, no desired products were found to produce. This experiment suggests that there is no problem in the *in situ*-generation of *ortho*-quinone methide intermediate *via* desulfonylation of **1a**, rather possibly the less reactivity of nitroalkanes did not facilitate the normal conjugate addition to *in situ*-generated *ortho*-quinone methide.



Scheme 14. Reactions of nitroalkanes with *in situ*-generated and preformed *o*-QMs.

3.4.5. Synthetic applications of 3aa:

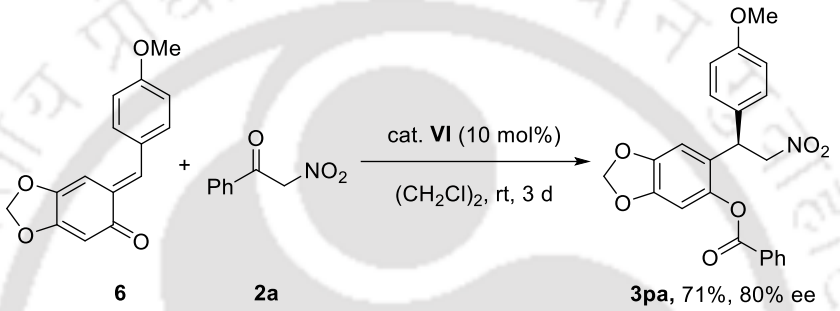
To demonstrate the synthetic utilities of our method, few reactions were carried out on **3aa** (Scheme 15). Initially the basic hydrolysis of **3aa** using sodium hydroxide in ethanol was accomplished to provide phenol **5a** in 84% yield and the enantiopurity was retained. Further reduction of nitro group of **5a** with zinc-acetic acid delivered the (*R*)-2-(2-amino-1-phenylethyl)phenol **7** with high yield (87%) and excellent enantioselectivity (96%). Although, this was an overall two steps process, reaction outcome was outstanding in terms of yield and enantiomeric excess. However, treatment of excess $LiAlH_4$ in anhydrous THF on chiral substrate **3aa** did not provide any (*R*)-2-(2-amino-1- phenylethyl)phenol **7**. Instead of that, compound **5a** was obtained in 40% yield and with 96% enantiomeric excess. Then reduction of nitro group of our main product **3aa** with zinc-acetic acid was carried out. Interestingly, in this reaction concomitant reduction to amine followed by acyl transfer reaction took place to deliver amide **8** in 95% yield. Amide **8** was then subjected to different protection reactions. Protection of the phenolic OH with Boc-anhydride led to the formation of **9** with slight reduction in enantiomeric excess. Similarly, tosyl and methyl protections were performed to obtain **10** and **11** respectively. Also, the amide **8** was attempted to hydrolyze into corresponding aminophenol **7** by using 6 N HCl as well as by 6 N NaOH under reflux conditions. But, the reactions were very sluggish.



Scheme 15. Synthetic applications of **3aa**.

3.4.6. Evidence of *in situ*-generation of *ortho*-quinone methides:

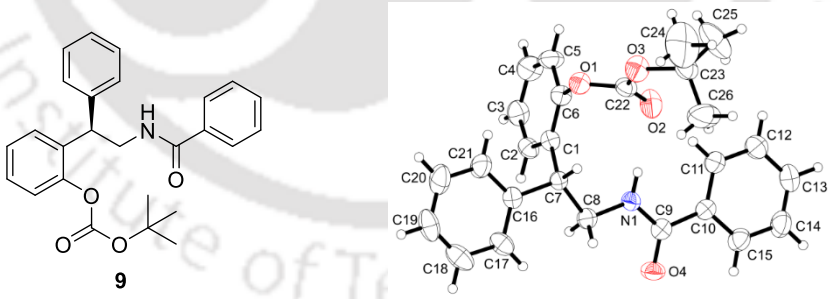
An additional experiment was performed to understand the mechanism of the reaction. First, preformed stabilized *ortho*-quinone methide **6** was prepared according to the known literature procedure.[15] Then it was reacted with nitroketone **2a** under the standard reaction conditions and in absence of aqueous $NaHCO_3$ medium (Scheme 16). Herein, the desired product **3pa** was achieved with moderate yield and high enantioselectivity (Scheme 16). This confirms the intermediacy of *ortho*-quinone methide in the proposed reaction.



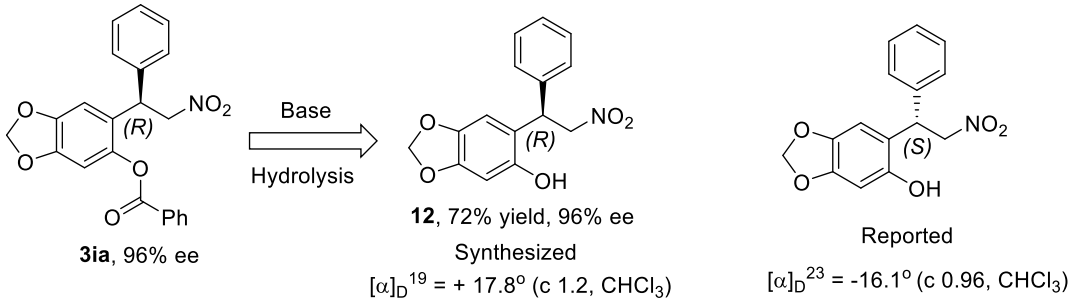
Scheme 16. Reaction of α-nitroketone with preformed *ortho*-quinone methide.

3.4.7. Absolute configuration of 9 and 3ia:

The absolute configuration of product **9** was determined to be (*R*) by X-ray crystallography.[16]



In addition, the chiral substrate **3ia** was also converted to compound **12** with retention of enantioselectivity *via* sodium hydroxide mediated ester hydrolysis (Scheme 17). Beside the crystal structure of compound **9**, optical rotation data of synthesized compound **12** was highly helpful in the determination of absolute stereochemistry of the products **3**. Absolute configuration of **3ia** was determined as (*R)* by comparing the optical rotation data provided earlier by Nagasawa *et al*.[2e]

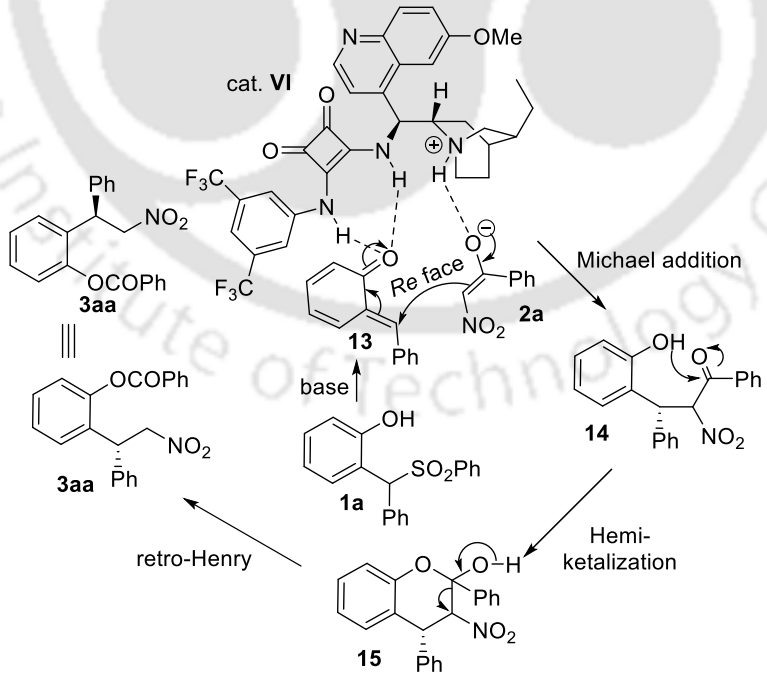


Scheme 17. Absolute stereochemistry determination.

Thus it is expected that products **3** should have same absolute structure by analogy.

3.4.8. Proposed mechanism:

Based on the above mechanistic evidence and the absolute configuration, a plausible mechanism for the formation of **3** has been shown in Scheme 18. In the first step, base mediated desulfonylation of **1a** leads to the formation of *ortho*-quinone methide **13**. Then the bifunctional character of squaramide catalyst **VI** allowed to fetch *ortho*-quinone methide **13** and nitroketone **2a** together and the desired Michael reaction takes place from the *Re* face of **13** to provide **14** (Scheme 18). Hemiketalization of **14** generates cyclic intermediate**15** which upon retro-Henry reaction delivers product **3aa**.



Scheme 18. The proposed mechanism.

3.5. Conclusion:

In summary, a fascinating catalytic asymmetric domino Michael/acyl transfer reaction has been developed using *ortho*-quinone methides and *α*-nitroketones as the reactants. The reaction is catalyzed by easily available hydroquinine derived squaramide catalyst. The reaction conditions are very mild and operationally simple method. Broad range of substrate scope is possible. Also, few derivatization reactions have been carried out to highlight the synthetic potential of the method. The synthesis of 2-(1-phenylethyl)phenol products in general is difficult and thus current methodology is important for the preparation of 2-(1-phenylethyl)phenols in an efficient way and the products could be applied in natural product (i.e. Dioxolane) and drug molecule (i.e. (*R*)-Tolterodine) syntheses.

3.6. Experimental section:

General Information:

All the necessary reagents were purchased from commercial suppliers with highest purity grade. They were utilized directly without further any purification. In all cases, oven dried glassware was used during reactions set up. For Grignard reactions in the preparation of *ortho*-hydroxybenzyl alcohols, tetrahydrofuran solvent was super dried over sodium/benzophenone. Dichloromethane solvent required for 2-sulfonylmethylphenols synthesis, was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Other solvents such as ethanol, methanol were purified according to the standard procedures. Progress of the reactions was monitored by performing TLC on silica gel GF-254 using *n*-hexane/ethyl acetate as the solvent system. For column chromatography, 60-120 mesh size silica gel was used unless mentioned.

^1H NMR spectra were recorded on 600 MHz spectrometer using $CDCl_3$ as reference NMR solvent. ^{13}C NMR spectra were recorded on150 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) and coupling constants (*J*) were reported in parts per million (ppm) and Hertz (Hz) units respectively. In ^1H and ^{13}C NMR, chemical shift values were expressed with reference to $CHCl_3$ (δ(H), 7.26 ppm) and (δ(C), 77.23 ppm, central line of triplet).

Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet), dt (doublet of triplet).

High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) mode. Enantiomeric excesses were determined by HPLC analysis by comparing the spectra of racemic samples using stationary phase chiral column through the help of Dionex (Ultimate 3000) instrument.

Single-crystal X-ray diffraction data were collected on a Super Nova, Single source at offset/far, Eos diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The data refinement and cell reductions were carried out by CrysAlisPro[17] at 293 K. Structures were solved by direct methods using SHELXS-97 and refined by the full matrix least squares method using SHELXL-97.[18]

A. General procedure for the synthesis of 2-sulfonylmethylphenols 1a-1r:

2-Sulfonylmethylphenols **1a-1r** were prepared according to the reported procedure in successive two steps.[19,20] Initially, various salicyldehyde derivatives were engaged in C-C coupling reaction with *in situ*-generated Grignard reagents to furnish *ortho*-hydroxybenzyl alcohol derivatives.[19] Thereafter, sulfonylation reaction was performed on *ortho*-hydroxybenzyl alcohols to deliver the final 2-sulfonylmethylphenols **1a-1r**.[20]

B. General procedure for the synthesis of *α*-nitroketones 2a-2t:

α-Nitroketones were prepared according to the known reported procedure.[21]

C. General procedure for the preparation of thiourea, urea and squaramide catalysts (I-VI):

Thiourea catalyst[22] (**I**), urea catalyst[23] (**II**) and squaramide catalysts[24] (**III-VI**) were prepared by following the previous reported procedures.

D. General procedure for the synthesis of domino Michael/Acyl transfer products 3:

To a stirrer solution of compound 2-sulfonylmethylphenol **1** (0.05 mmol) and *α*-nitroketone **2** (0.25 mmol) in 1,2-DCE solvent (0.6 mL), catalyst **VI** (10 mol%) and 10% aq. $NaHCO_3$ solution (50 eq.) were added. Then the resulting reaction mixture was stirred at ambient temperature for 3 days. Progress of the reaction was then monitored by TLC analysis. After completion of the reaction, resulting mixture was acidified using 10% HCl solution and extracted with DCM (2 times). Finally, organic parts were concentrated in *vacuo* and

subjected to the silica gel column chromatography to obtain the desired domino Michael/Acyl transfer products **3**.

Compounds (*R*)-2-ethoxy-6-(2-nitro-1-phenylethyl)phenyl benzoate **3ha**, (*R*)-6-(2-nitro-1-phenylethyl)benzo[*d*][1,3]dioxol-5-yl benzoate **3ia**, (*R*)-2-(1-(4-methoxyphenyl)-2-nitroethyl)phenyl benzoate **3la**, (*R*)-2-(1-(4-fluorophenyl)-2-nitroethyl)phenyl benzoate **3ma**, (*R*)-2-(1-(3-methoxyphenyl)-2-nitroethyl)phenyl benzoate **3na** and (*R*)-6-(1-(4-methoxyphenyl)-2 nitroethyl)benzo[*d*][1,3]dioxol-5-yl benzoate **3pa** were prepared according to the general procedure **3.5.D.** where aqueous work up was performed without using HCl to avoid the purification problem.

E. General procedure for the synthesis of (*R*)-2-(2-nitro-1-phenylethyl)phenol 5a:[25]

To a stirrer solution of (*R*)-2-(2-nitro-1-phenylethyl)phenyl benzoate **3aa** (0.05 mmol) in EtOH (0.5 mL), NaOH (6 mg) and H_2O (0.008 mL) were added at 0 ^oC. Then stirring was continued for 1 hour at the same temperature. After completion of the reaction, the resulting mixture was evaporated in *vacuo* to remove EtOH solvent. Thereafter, crude product was dissolved in DCM and acidification was done by using 10% HCl solution. Organic parts were collected and concentrated. Finally, it was purified by silica gel column chromatography using EtOAc in hexane to afford the pure product (*R*)-2-(2-nitro-1-phenylethyl)phenol **5a**.

F. General procedure for the synthesis of (*R*)-2-(2-amino-1-phenylethyl)phenol 7:

To a stirrer solution of (*R*)-2-(2-nitro-1-phenylethyl)phenol **5a** (0.2 mmol) in 1.5 mL acetic acid, activated Zn powder (200 mg) was added. The resulting reaction mixture was stirred for 1 day at room temperature. After completion of the reaction, it was filtered through Celite pad and concentrated in *vacuo*. Then the residue was dissolved in aqueous sodium carbonate and extracted with DCM (2 times). After that the DCM layer was acidified properly using 10% HCl. The aqueous phase was washed with DCM (3 times). At the end the aqueous phase was made alkaline with excess cc. aqueous ammonia and was washed with DCM (2 times). Finally, organic parts were concentrated in *vacuo* to obtain (*R*)-2-(2-amino-1-phenylethyl)phenol **7** with high yield and high enantiomeric excess. Further column chromatography was not required for purification.

G. General procedure for the synthesis of (*R*)-*N*-(2-(2-hydroxyphenyl)-phenylethyl)benzamide 8:[26]

To a stirrer solution of (*R*)-2-(2-nitro-1-phenylethyl)phenyl benzoate (**3aa**) (0.1 mmol) in 1 mL acetic acid, activated Zn powder (134 mg) was added. The resulting reaction mixture was stirred for 1 day at room temperature. After completion of the reaction, mixture was filtered through Celite pad and concentrated in *vacuo.* Then the residue was dissolved in aqueous sodium carbonate and extracted with DCM. At the end it was purified by silica gel column chromatography using 15% Hexane/EtOAc to obtain the pure product (*R*)-N-(2-(2-hydroxyphenyl)-phenylethyl)benzamide **8**.

H. General procedure for the synthesis of (*R*)-2-(2-benzamido-1-phenylethyl)phenyl *tert*-butyl carbonate 9:[27]

(*R*)-*N*-(2-(2-Hydroxyphenyl)-phenylethyl)benzamide intermediate **8** (0.05 mmol) was dissolved in 3.5 mL dry DCM under an ice bath. Inert condition was maintained throughout the reaction using argon balloon. Thereafter, triethylamine (0.055 mmol) was added in a portion. A solution of $(Boc)_2O$ (0.055 mmol) in 1 mL DCM was added dropwise. Reaction mixture was stirred under ice bath for 30 minutes thereafter it was shifted to room temperature for 20 hours. Progress of the reaction was monitored by TLC analysis. The mixture was then diluted in DCM and added water. Organic parts were concentrated in *vacuo*. Lastly, crude mixture was subjected to the silica gel column chromatography using 15% Hexane/EtOAc for to afford pure product (*R*)-2-(2-benzamido-1-phenylethyl)phenyl *tert*-butyl carbonate **9**.

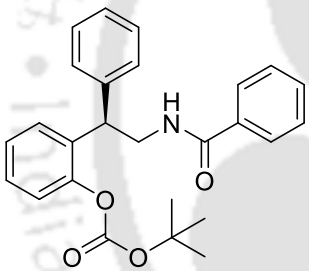
I. General procedure for the synthesis of (*R*)-2-(2-benzamido-1-phenylethyl)phenyl 4-methylbenzenesulfonate 10:[28]

(*R*)-*N*-(2-(2-Hydroxyphenyl)-phenylethyl)benzamide intermediate **8** (0.05 mmol), *p*-toluene sulphonyl chloride (0.06 mmol) and triethylamine (0.06 mmol) were dissolved in 1 mL dry DCM under dry condition. Then the reaction mixture was stirred at 45 ^oC for 12 hours. Workup was done using DCM/H_2O. Finally, the concentrated crude mixture was purified by silica gen column chromatography with 15% Hexane/EtOAc to obtain (*R*)-2-(2-benzamido-1-phenylethyl)phenyl 4-methylbenzenesulfonate **10**.

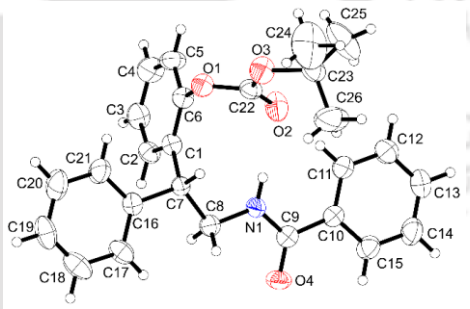
J. General procedure for the synthesis of (*R*)-*N*-(2-(2-methoxyphenyl)-2-phenylethyl)benzamide 11:[29]

To a solution of (*R*)-*N*-(2-(2-hydroxyphenyl)-phenylethyl)benzamide intermediate **8** (0.05 mmol) in dry THF (1 mL), NaH (0.12 mmol) and methyl iodide (0.3 mmol) were added successively under an ice bath. Resulting mixture was stirred at 0 °C for 0.5 hour then the reaction mixture was shifted to room temperature for 4.5 hours. The mixture was quenched by aqueous NH_4Cl and extracted with EtOAc twice. Crude mixture was further purified by column chromatography using 230-400 mesh size silica gel and 15 % Hexane/ EtOAc solvent system to provide the product (*R*)-*N*-(2-(2-methoxyphenyl)-2-phenylethyl)benzamide **11**.

Crystal structure of compound (*R*)-2-(2-benzamido-1-phenylethyl)phenyl *tert*-butyl carbonate 9:



9



Empirical Formula	C_{26} H_{27} NO_4
Formula weight, Fw	417.49
Crystal system	tetragonal
Space group	P 41 21 2
Unit cell dimensions	a = 8.5863(3)Å b = 8.5863(3)Å c = 60.748(3)Å α = 90.00° , β = 90.00 ° γ = 90.00°
Volume, V/Å^3	4478.6(3)
Z	8
Calculated density, D_c/g cm^{-3}	1.238
μ Mo K_α/mm^{-1}	0.083
F000	1776.0
Temperature, T/K	293 K
θ max.	24.990

Total no. of reflections	3932
Independent reflections	2689
Parameters refined	284
R_1, $I > 2\sigma(I)$	0.0719
wR_2, $I > 2\sigma(I)$	0.1271
GOF (F^2)	1.078
CCDC No.	**1834655**

3.7. References:

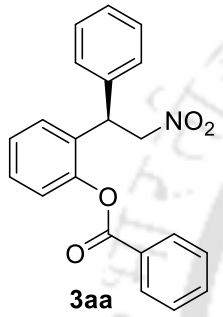
1. (a) Tyman, J. H. P. *Synthetic and Natural Phenols*, Elsevier, New York, **1996**. (b) Batra, J. K.; Jurd, L.; Chu, P. S.; Lin, C. M.; Hamel, E. *Mol. Pharm*. **1985**, *27*, 94. (c) Nilvebrant, L.; Andersson, K.-E.; Gillberg, P.-G.; Stahl, M.; Sparf, B. *Eur. J. Pharmacol*. **1997**, *327*, 195. (d) Sawadjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470. (e) Sekine, N.; Ashitani, T.; Murayama, T.; Shibutani, S.; Hattori, S.; Takahashi, K. *J. Agric. Food Chem*. **2009**, *57*, 5707. (f) Jurd, L.; Narayanan, V. L.; Paull, K. D. *J. Med. Chem*. **1987**, *30*, 1752. (g) Maalej, E.; Chabchoub, F.; Oset-Gasque, M. J.; Esquivias-Pérez, M.; González, M. P.; Monjas, L.; Pérez, C.; C. de los Ríos, M. I. Rodríguez-Franco, I. Iriepa, I. Moraleda, M. Chioua, A. Romero, J. Marco-Contelles, A. Samadi, *Eur. J. Med. Chem.* **2012**, *54*, 750. (h) Wu, B.; Gao, X.; Yan, Z.; Chen, M.-W.; Zhou, Y.-G. *Org. Lett.* **2015**, *17*, 6134. (i) Yanga, Y.-P.; Chenga, M.-J.; Tengb, C.-M.; Changb, Y.-L.; Tsaia, I.-L.; Chena, I.-S. *Phytochemistry* **2002**, *61*, 567. (j) Ohmori, K.; Ushimaru, N.; Suzuki, K.; *Proc. Natl. Acad. Sci. USA*, **2004**, *101*, 12002.
2. (a) Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2006**, *45*, 1147. (b) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun*. **2007**, 2228. (c) Wang, X.-S.; Zheng, C.-W.; Zhao, S.-Li.; Chai, Z.; Zhao, G.; Yang, G.-S. *Tetrahedron: Asymmetry* **2008**, *19*, 2699. (d) Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881. (e) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem. Int. Ed*. **2010**, *49*, 7299. (f) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett*. **2010**, *12*, 1096. (g) Liu, G.; Zhang, S.; Li, H.; Zhang, T.; Wang, W. *Org. Lett.* **2011**, *13*, 828.

3. Wang,Y.; Zhang, C.; Wang, H.; Jiang, Y.; Du, X.; Xu, D. *Adv. Synth. Catal*. **2017**, *359*, 791.
4. Liu,R.-l.; Tang, X.-z.; Zhang, X.-j.; Yan, M.; Chan, A. S. C. *RSC Adv*. **2017**, *7*, 6660.
5. Zhou, J.; Huang, W.-J.; Jiang, G.-F. *Org. Lett.* **2018**, *20*, 1158.
6. Chu, M.-M.; Qi, S.-S.; Ju, W.-Z.; Wang, Y.-F.; Chen, X.-Y.; Xu, D.-Q.; Xu, Z.-Y. *Org. Chem. Front*. **2019**, *6*, 1140.
7. Saha, S.; Alamsetti, S. K.; Schneider, C. *Chem. Commun*. **2015**, *51*, 1461.
8. Gharui, C.; Pan, S. C. *Org. Biomol. Chem.* **2019,** *17*, 5190.
9. Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819.
10. Lu, R.-J.; Yan, Y.-Y.; Wang, J.-J.; Du, Q.-S.; Nie, S.-Z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230.
11. Li, P.; Chan, S. H.; Chan, A. S. C.; Kwong, F. Y. *Org. Biomol. Chem.* **2011**, *9*, 7997.
12. Maity, R.; Gharui, C.; Sil, A. K.; Pan, S. C. *Org. Lett.* **2017**, *19*, 662.
13. Maity, R.; Pan, S. C. *Org. Biomol. Chem.* **2018**, *16*, 1598.
14. Mondal, K.; Pan, S. C. *J. Org. Chem.* **2018**, *83*, 5301.
15. Jurd, L. *Tetrahedron*, **1977**, *33*, 163.
16. CCDC 1834655 contains the crystallographic data for product **9**.
17. CrysAlisPro, Oxford Diffraction Ltd. Version 1.171.40.23a (Rigaku OD, **2018**).
18. G. M. Sheldrick, SHELXL-97, Program for crystal structure refinement; University of Göttingen: Göttingen, Germany, **1997**.
19. Meier, B.; Dumez, J.-N.; Stevanato, G.; Hill-Cousins, J. T.; Roy, S. S.; Håkansson, P.; Mamone, S.; Brown, R. C. D.; Pileio, G.; Levitt, M. H. *J. Am. Chem. Soc.* **2013**, *135*, 18746.
20. Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun*. **2013**, *49*, 1660.
21. (a) Phukan, M.; Jyoti, K.; Borah, R. *Synth. Commun.* **2008**, *38*, 3068. (b) Zhou, M.; Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. *Org. Lett.* **2013**, *15*, 5524.
22. (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967. (b) Tripathi, C. B.; Kayal, S.; Mukherjee, S. *Org. Lett*. **2012**, *14*, 3296.
23. McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367.

24. Yang, W.; Du, D. M. *Org. Lett*. **2010**, *12*, 5450.
25. Cires, L.; Ofenberg, H.; Craita, C. *OPPl BRIEFS* **2001**, *33*, 361.
26. Liu, J.-Y.; Zhao, J.; Zhang, J.-L.; Xu, P.-F. *Org. Lett.* **2017**, *19*, 1846.
27. Liu, R.-l.; Tang, X.-z.; Zhang, X.-j.; Yan, M.; Chan, A. S. C. *RSC Adv*. **2017**, *7*, 6660.
28. Laha, J. K.; Jethava, K. P.; Dayal, N. *J. Org. Chem.* **2014**, *79*, 8010.
29. Ramachary, D. B.; Sakthidevi, R. *Org. Biomol. Chem.* **2010**, *8*, 4259.

3.8. Characterization Data of Products:

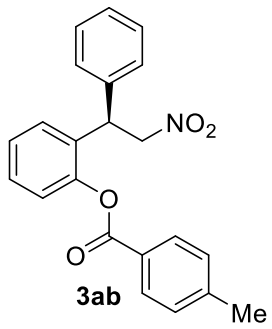
(R)-2-(2-nitro-1-phenylethyl)phenyl benzoate (3aa)



3aa

Compound **3aa** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (16.2 mg, 93% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.14 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.30 – 7.28 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 4H), 7.15 (d, *J* = 6.4 Hz, 2H), 5.16 (t, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.9, 148.9, 138.3, 134.1, 131.8, 130.4, 129.1, 129.0, 128.9, 128.3, 127.9, 127.8, 126.8, 123.7, 78.4, 43.1; **HRMS (+ESI):** Calc for $C_{21}H_{21}N_2O_4$ $[M+NH_4]^+$ 365.1501; found: 365.1507; The ee value 98% (t_{minor} = 10.9 min, t_{major} = 12.0 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 4-methylbenzoate (3ab)

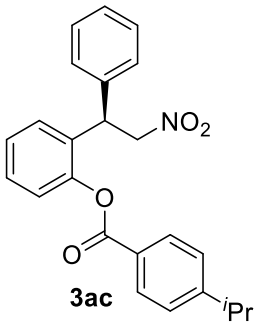


3ab

Compound **3ab** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; White gummy mass (17.0 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.39 – 7.36 (m, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.29 (m, 1H), 7.29 – 7.28 (m, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.25 (t, *J* = 1.8 Hz, 1H), 7.24 (brs, 1H), 7.23 (d, *J* = 1.0 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.3 Hz, 2H), 5.18 (t, *J* = 8.0 Hz, 1H), 5.01 (dd, *J* = 8.0, 1.7 Hz, 2H), 2.50 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.0, 149.0, 145.0, 138.3, 131.8,

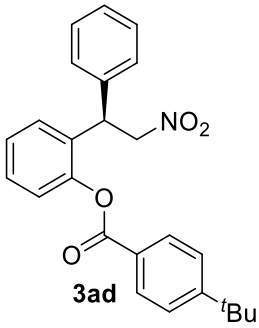
130.5, 129.6, 129.1, 129.0, 128.3, 127.9, 127.8, 126.6, 126.4, 123.8, 78.4, 43.1, 22.0; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1652; found: 379.1651; The ee value 92% (t_{minor} = 12.0 min, t_{major} = 12.8 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(R)-2-(2-nitro-1-phenylethyl)phenyl 4-isopropylbenzoate(3ac)



Compound **3ac** was purified by silica gel column chromatography using 1- 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (16.6 mg, 85% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.31 – 7.27 (m, 5H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.22 – 7.20 (m, 2H), 5.20 (t, *J* = 8.0 Hz, 1H), 5.06 – 5.00 (m, 2H), 3.09 – 3.04 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.0, 155.8, 149.0, 138.3, 131.8, 130.7, 129.1, 129.0, 128.3, 127.9, 127.8, 127.1, 126.7, 126.7, 123.7, 78.4, 43.1, 34.6, 23.9; **HRMS (+ESI):** Calc for $C_{24}H_{27}N_2O_4$ $[M+NH_4]^+$ 407.1965; found: 407.1966; The ee value 86% (t_{minor} = 11.1 min, t_{major} = 11.7 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

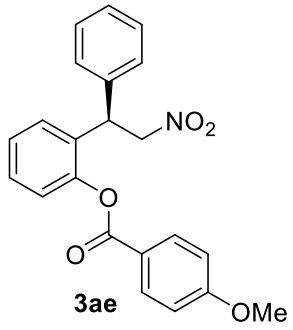
(R)-2-(2-nitro-1-phenylethyl)phenyl 4-(tert-butyl)benzoate (3ad)



Compound **3ad** was purified by silica gel column chromatography using 1% EtOAc in hexane; **Reaction time:** 3 days at room temperature; White gummy mass (14.9 mg, 74% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.31 – 7.28 (m, 4H), 7.27 – 7.26 (m, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.22 – 7.21 (m, 2H), 5.20 (t, *J* = 8.0 Hz, 1H), 5.06 – 5.00 (m, 2H), 1.43 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.0, 158.0, 149.0, 138.3, 131.8, 130.4, 129.1, 129.0, 128.3, 127.9, 127.8, 126.6, 126.3, 125.9, 123.7, 78.4, 43.1, 35.5, 31.3; **HRMS (+ESI):** Calc for $C_{25}H_{29}N_2O_4$ $[M+NH_4]^+$ 421.2122; found: 421.2121; The ee value 94% (t_{minor} = 9.0 min, t_{major} = 9.9 min) was determined by HPLC analysis using Daicel

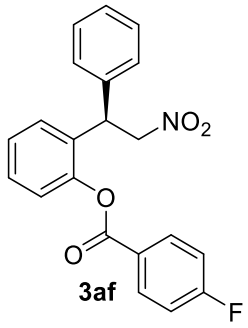
Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 4-methoxybenzoate (3ae)



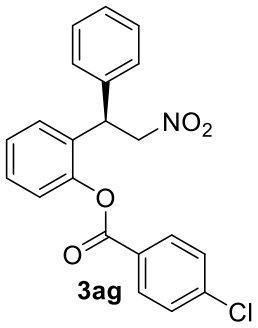
Compound **3ae** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (17.0 mg, 90% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.13 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.38 (m, 1H), 7.30 – 7.29 (m, 3H), 7.28 (brs, 1H), 7.27 (t, *J* = 1.5 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.21 – 7.20 (m, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 5.20 (t, *J* = 8.0 Hz, 1H), 5.03 (dd, *J* = 8.0, 3.5 Hz, 2H), 3.96 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.7, 164.4, 149.0, 138.3, 132.6, 131.8, 129.1, 129.0, 128.3, 127.9, 127.8, 126.6, 123.8, 121.4, 114.2, 78.4, 55.8, 43.2; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_5$ $[M+NH_4]^+$ 395.1601; found: 395.1600; The ee value 96% (t_{minor} = 17.2 min, t_{major} = 19.1 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 4-fluorobenzoate (3af)



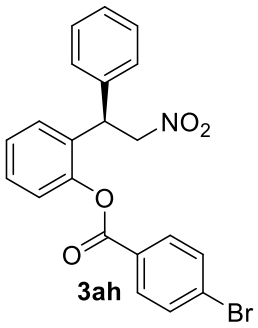
Compound **3af** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (15.0 mg, 82% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.19 – 8.16 (m, 2H), 7.42 – 7.39 (m, 1H), 7.33 – 7.32 (m, 2H), 7.30 – 7.29 (m, 1H), 7.28 – 7.27 (m, 1H), 7.27 (t, *J* = 1.6 Hz, 1H), 7.25 – 7.24 (m, 1H), 7.23 (brs, 1H), 7.22 (t, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 7.6, 1.6 Hz, 2H), 5.17 (t, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.4, 165.7, 164.0, 148.8, 138.2, 133.1, 133.1, 131.7, 129.1, 129.1, 128.3, 127.9, 126.9, 125.4, 125.4, 123.7, 116.2, 116.1, 78.5, 43.2; **HRMS (+ESI):** Calc for $C_{21}H_{20}FN_2O_4$ $[M+NH_4]^+$ 383.1402; found: 383.1403; The ee value 94% (t_{minor} = 14.2 min, t_{major} = 15.3 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 4-chlorobenzoate (3ag)



Compound **3ag** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (17.0 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.05 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.36 (m, 1H), 7.31 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.5, 1.6 Hz, 2H), 5.13 (t, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.1, 148.8, 140.7, 138.2, 131.8, 131.7, 129.3, 129.2, 129.1, 128.2, 127.9, 127.9, 127.6, 126.9, 123.7, 78.5, 43.2; **HRMS (+ESI):** Calc for $C_{21}H_{20}ClN_2O_4$ $[M+NH_4]^+$ 399.1106; found: 399.1105; The ee value 95% (t_{minor} = 12.2 min, t_{major} = 13.9 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

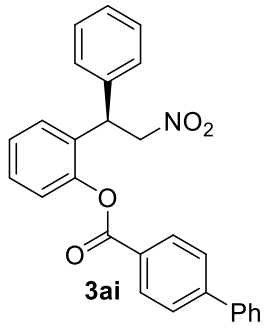
(R)-2-(2-nitro-1-phenylethyl)phenyl 4-bromobenzoate (3ah)



Compound **3ah** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (21.1 mg, 99% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.39 – 7.36 (m, 1H), 7.31 – 7.28 (m, 2H), 7.24 – 7.20 (m, 4H), 7.12 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.12 (t, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.1 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.2, 148.8, 138.2, 132.3, 131.9, 131.7, 129.4, 129.2, 129.1, 128.2, 128.0, 127.9, 127.8, 126.9, 123.6, 78.4, 43.2; **HRMS (+ESI):** Calc for $C_{21}H_{20}BrN_2O_4$ $[M+NH_4]^+$ 443.0601; found: 443.0598; The ee value 98% (t_{minor} = 13.3 min, t_{major} = 15.4 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

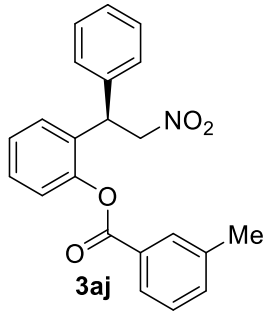
(R)-2-(2-nitro-1-phenylethyl)phenyl [1,1'-biphenyl]-4-carboxylate (3ai)

Compound **3ai** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (17.6mg, 83% yield);



^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.70 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.31 – 7.29 (m, 2H), 7.28 – 7.27 (m, 2H), 7.25 (dd, *J* = 9.7, 4.5 Hz, 2H), 7.20 – 7.19 (m, 2H), 5.21 (t, *J* = 8.0 Hz, 1H), 5.03 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.8, 149.0, 146.9, 140.0, 138.3, 131.8, 131.0, 129.2, 129.1, 129.0, 128.6, 128.3, 127.9, 127.9, 127.8, 127.6, 126.8, 123.8, 78.4, 43.2; **HRMS (+ESI):** Calc for $C_{27}H_{25}N_2O_4$ $[M+NH_4]^+$ 441.1809; found: 441.1807; The ee value 96% (t_{minor} = 25.3 min, t_{major} = 40.8 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 274 nm, 25 ^{o}C.

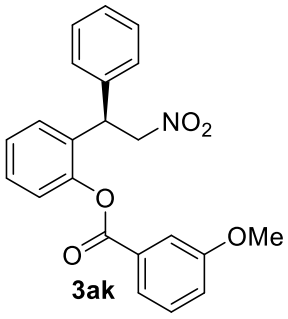
(R)-2-(2-nitro-1-phenylethyl)phenyl 3-methylbenzoate (3aj)



Compound **3aj** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (15.0 mg, 83% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (d, *J* = 9.1 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.31 (s, 1H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 1.6 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.20 – 7.19 (m, 2H), 5.19 (t, *J* = 8.0 Hz, 1H), 5.02 (d, *J* = 8.0 Hz, 2H), 2.48 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.1, 149.0, 138.8, 138.3, 134.9, 131.8, 131.0, 129.1, 129.1, 129.0, 128.8, 128.3, 127.9, 127.8, 127.6, 126.7, 123.7, 78.4, 43.2, 21.5; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1652; found: 379.1645; The ee value 86% (t_{minor} = 9.6 min, t_{major} = 12.1 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 3-methoxybenzoate (3ak)

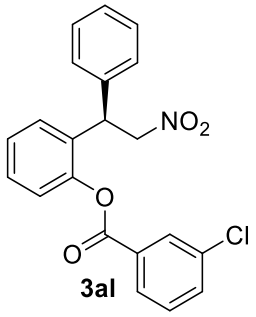
Compound **3ak** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (14.0 mg, 74% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.66 (dd, *J* = 2.5, 1.6 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.32 – 7.30 (m, 2H), 7.28 (s, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.26 – 7.25 (m, 1H), 7.24 – 7.22 (m, 2H), 7.19 – 7.17 (m, 2H), 5.18 (t,



3ak

J = 8.0 Hz, 1H), 5.02 (d, *J* = 8.0 Hz, 2H), 3.91 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 164.9, 160.0, 148.9, 138.3, 131.8, 130.4, 129.9, 129.1, 129.0, 128.3, 127.9, 127.8, 126.8, 123.7, 122.9, 120.8, 114.7, 78.5, 55.8, 43.1; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_5$ $[M+NH_4]^+$ 395.1601; found: 395.1602; The ee value 90% (t_{minor} = 13.6 min, t_{major} = 26.3 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

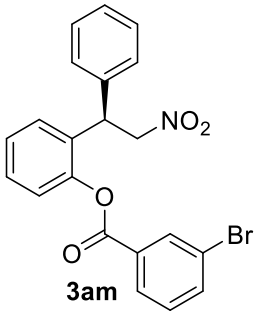
(R)-2-(2-nitro-1-phenylethyl)phenyl 3-chlorobenzoate (3al)



3al

Compound **3al** was purified by silica gel column chromatography using 2-4% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (13.9 mg, 73% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.08 (t, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.65 (m, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.34 – 7.31 (m, 2H), 7.29 – 7.25 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.6 Hz, 2H), 5.15 (t, *J* = 8.0 Hz, 1H), 5.01 (dd, *J* = 8.0, 1.3 Hz, 2H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 163.7, 148.7, 138.2, 135.1, 134.1, 131.6, 130.9, 130.4, 130.2, 129.2, 129.1, 128.5, 128.2, 127.9, 127.9, 127.0, 123.6, 78.4, 43.2; **HRMS (+ESI):** Calc for $C_{21}H_{20}ClN_2O_4$ $[M+NH_4]^+$ 399.1106; found: 399.1105; The ee value 96% (t_{minor} = 10.5 min, t_{major} = 12.0 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(R)-2-(2-nitro-1-phenylethyl)phenyl 3-bromobenzoate (3am)

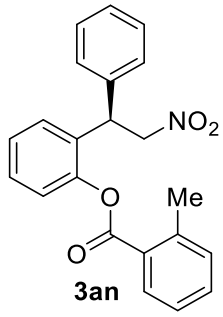


3am

Compound **3am** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (14.9 mg, 70% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.23 (t, *J* = 1.7 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.80 (m, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.34 – 7.32 (m, 2H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.27 (s, 1H), 7.26 – 7.25 (m, 1H), 7.22 (d, *J* = 7.7 Hz,

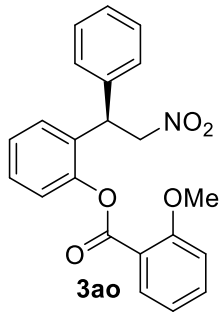
1H), 7.15 (dd, *J* = 7.6, 1.5 Hz, 2H), 5.14 (t, *J* = 8.0 Hz, 1H), 5.00 (dd, *J* = 8.0, 1.9 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 163.6, 148.7, 138.2, 137.1, 133.3, 131.6, 131.1, 130.5, 129.2, 129.1, 129.0, 128.1, 128.0, 127.9, 127.0, 123.6, 123.0, 78.4, 43.2; **HRMS (+ESI):** Calc for $C_{21}H_{20}BrN_2O_4$ $[M+NH_4]^+$ 443.0601; found: 443.0603; The ee value 94% (t_{minor} = 16.2 min, t_{major} = 33.4 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(R)-2-(2-nitro-1-phenylethyl)phenyl 2-methylbenzoate (3an)



Compound **3an** was purified by silica gel column chromatography using 1.5% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (13.9 mg, 77% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.13 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.38 – 7.35 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.25 – 7.20 (m, 4H), 7.14 (dd, *J* = 7.4, 1.8 Hz, 2H), 5.16 (t, *J* = 8.0 Hz, 1H), 4.99 (d, *J* = 8.0 Hz, 2H), 2.56 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 149.0, 142.0, 138.3, 133.3, 132.3, 131.9, 131.3, 129.1, 129.0, 128.3, 128.0, 127.9, 127.8, 126.7, 126.2, 123.9, 78.4, 43.2, 22.1; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1652; found: 379.1665; The ee value 90% (t_{minor} = 8.7 min, t_{major} = 9.4 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

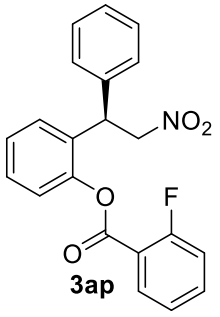
(R)-2-(2-nitro-1-phenylethyl)phenyl 2-methoxybenzoate (3ao)



Compound **3ao** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (10.0 mg, 53% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.95 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.36 – 7.34 (m, 1H), 7.28 – 7.27 (m, 3H), 7.25 – 7.23 (m, 5H), 7.07 (dd, *J* = 11.3, 4.4 Hz, 2H), 5.31 (dd, *J* = 9.6, 6.5 Hz, 1H), 5.10 – 5.00 (m, 2H), 3.97 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.8, 159.9, 148.9, 138.4, 134.8, 132.7, 131.7, 129.1, 128.9, 128.8, 127.9, 127.7, 126.6, 123.8, 120.6, 118.9, 112.4, 78.0, 56.2, 42.9; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_5$ $[M+NH_4]^+$ 395.1601; found: 395.1603; The ee value 92% (t_{minor} = 17.9 min, t_{major} = 25.1 min) was determined by

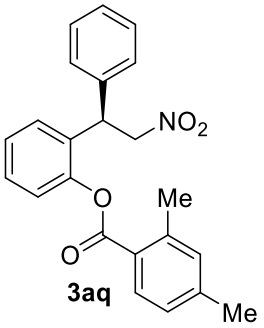
HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ºC.

(R)-2-(2-nitro-1-phenylethyl)phenyl 2-fluorobenzoate (3ap)



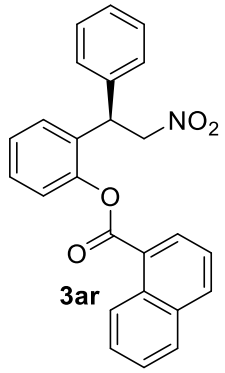
Compound **3ap** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (11.0 mg, 60% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.04 – 8.01 (m, 1H), 7.66 – 7.63 (m, 1H), 7.39 – 7.36 (m, 1H), 7.30 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.28 – 7.28 (m, 1H), 7.27 (brs, 2H), 7.26 – 7.24 (m, 3H), 7.23 – 7.22 (m, 1H), 7.20 – 7.18 (m, 2H), 5.22 (t, *J* = 8.0 Hz, 1H), 5.03 (dd, *J* = 8.0, 1.5 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 163.3, 162.6, 162.6, 161.6, 148.6, 138.1, 135.8, 135.8, 132.9, 131.6, 129.1, 129.0, 128.6, 127.9, 127.8, 126.9, 124.5, 124.5, 123.7, 117.7, 117.6, 117.6, 117.4, 78.1, 43.1; **HRMS (+ESI):** Calc for $C_{21}H_{20}FN_2O_4$ $[M+NH_4]^+$ 383.1402; found: 383.1417; The ee value 92% (t_{minor} = 12.3 min, t_{major} = 13.3 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ºC.

(R)-2-(2-nitro-1-phenylethyl)phenyl 2,4-dimethylbenzoate (3aq)



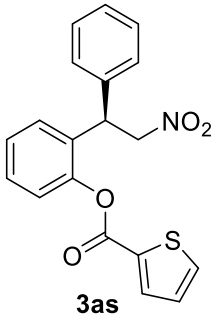
Compound **3aq** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (18.0 mg, 96% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.28 (dd, *J* = 3.0, 1.7 Hz, 1H), 7.27 (s, 1H), 7.26 – 7.25 (m, 1H), 7.23 (dd, *J* = 6.1, 1.9 Hz, 2H), 7.20 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.16 (dd, *J* = 7.9, 2.1 Hz, 4H), 5.16 (t, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 8.0 Hz, 2H), 2.54 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 149.0, 144.0, 142.2, 138.3, 133.1, 131.9, 131.5, 129.1, 128.9, 128.3, 127.9, 127.7, 127.0, 126.6, 125.1, 123.9, 78.3, 43.2, 22.1, 21.8; **HRMS (+ESI):** Calc for $C_{23}H_{25}N_2O_4$ $[M+NH_4]^+$ 393.1809; found: 393.1808; The ee value 90% (t_{minor} = 9.0 min, t_{major} = 9.8 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ºC.

(R)-2-(2-nitro-1-phenylethyl)phenyl 1-naphthoate (3ar)



Compound **3ar** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (17.1 mg, 86% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.84 (d, *J* = 8.6 Hz, 1H), 8.43 (dd, *J* = 7.3, 1.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.57 (m, 3H), 7.43 – 7.40 (m, 1H), 7.35 – 7.30 (m, 3H), 7.20 – 7.19 (m, 3H), 7.15 – 7.14 (m, 2H), 5.22 (t, *J* = 8.0 Hz, 1H), 5.06 – 4.98 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.4, 149.0, 138.3, 134.9, 134.1, 131.9, 131.9, 131.5, 129.2, 129.0, 128.9, 128.5, 128.3, 127.9, 127.8, 126.8, 126.7, 126.0, 125.4, 124.8, 123.9, 78.4, 43.3; **HRMS (+ESI):** Calc for $C_{25}H_{23}N_2O_4$ $[M+NH_4]^+$ 415.1652; found: 415.1639; The ee value 96% (t_{minor} = 17.3 min, t_{major} = 28.0 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

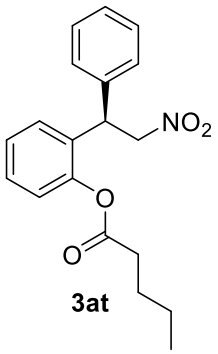
(R)-2-(2-nitro-1-phenylethyl)phenyl thiophene-2-carboxylate (3as)



Compound **3as** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (17.0 mg, 96% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.97 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.72 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.39 – 7.36 (m, 1H), 7.29 – 7.27 (m, 5H), 7.25 – 7.20 (m, 4H), 5.20 (t, *J* = 8.0 Hz, 1H), 5.03 (dd, *J* = 8.0, 2.7 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 160.2, 148.5, 138.1, 135.3, 134.1, 132.3, 131.7, 129.1, 129.0, 128.4, 128.4, 127.9, 127.9, 126.8, 123.7, 78.3, 43.2; **HRMS (+ESI):** Calc for $C_{19}H_{19}N_2O_4S$ $[M+NH_4]^+$ 371.1060; found: 371.1061; The ee value 92% (t_{minor} = 17.7 min, t_{major} = 24.2 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 274 nm, 25 ^{o}C.

(R)-2-(2-nitro-1-phenylethyl)phenyl pentanoate (3at)

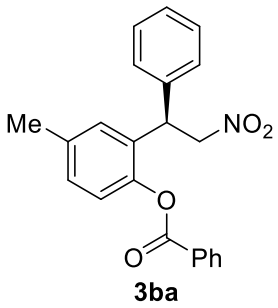
Compound **3at** was purified by silica gel column chromatography using 1% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (12.9 mg, 79% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.35 – 7.30 (m, 3H), 7.28 – 7.27 (m, 1H), 7.23 – 7.21 (m,



3at

3H), 7.19 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.11 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.11 (dd, *J* = 9.0, 6.9 Hz, 1H), 5.01 (dd, *J* = 13.0, 9.1 Hz, 1H), 4.91 (dd, *J* = 13.0, 6.8 Hz, 1H), 2.58 – 2.55 (m, 2H), 1.74 – 1.69 (m, 2H), 1.48 – 1.41 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 172.1, 148.7, 138.3, 131.4, 129.2, 128.9, 128.5, 127.9, 127.8, 126.6, 123.6, 78.3, 43.0, 34.1, 27.1, 22.5, 13.9; **HRMS (+ESI):** Calc for $C_{19}H_{25}N_2O_4$ $[M+NH_4]^+$ 345.1809; found: 345.1803; The ee value 88% (t_{minor} = 8.8 min, t_{major} = 9.7 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (96:4) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

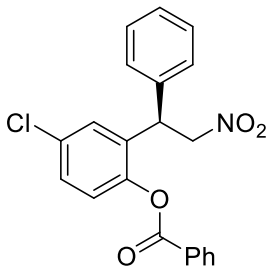
(R)-4-methyl-2-(2-nitro-1-phenylethyl)phenyl benzoate (3ba)



3ba

Compound **3ba** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; White gummy mass (17.5 mg, 97% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.13 (d, *J* = 7.1 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.26 – 7.20 (m, 3H), 7.18 – 7.13 (m, 3H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.06 (s, 1H), 5.11 (t, *J* = 8.0 Hz, 1H), 4.98 (dd, *J* = 8.0, 3.2 Hz, 2H), 2.35 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.1, 146.6, 138.3, 136.5, 134.0, 131.3, 130.4, 129.6, 129.2, 129.1, 128.9, 128.7, 127.9, 127.8, 123.4, 78.4, 43.1, 21.3; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1658; found: 379.1646; The ee value 94% (t_{minor} = 21.3 min, t_{major} = 22.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(R)-4-chloro-2-(2-nitro-1-phenylethyl)phenyl benzoate (3ca)

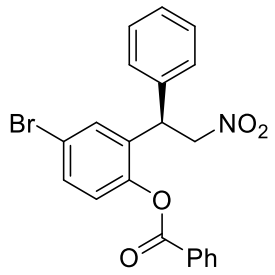


3ca

Compound **3ca** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (17.6 mg, 92% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.15 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.9 Hz, 2H), 7.36 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.31 – 7.26 (m, 4H), 7.20 (d, *J* = 8.6 Hz,

1H), 7.17 (dd, *J* = 7.5, 1.7 Hz, 2H), 5.15 (t, *J* = 8.0 Hz, 1H), 5.03 – 4.97 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.8, 147.4, 137.5, 134.3, 133.7, 132.2, 130.5, 129.3, 129.1, 129.0, 128.8, 128.4, 128.2, 127.9, 125.1, 78.1, 43.1; **HRMS (+ESI):** Calc for $C_{21}H_{20}ClN_2O_4$ $[M+NH_4]^+$ 399.1106; found: 399.1097; The ee value 94% (t_{minor} = 12.6 min, t_{major} = 15.1 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

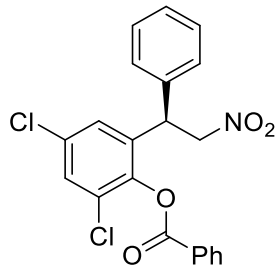
(R)-4-bromo-2-(2-nitro-1-phenylethyl)phenyl benzoate (3da)



3da

Compound **3da** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (20.0 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.15 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.51 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.17 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 1H), 5.15 (t, *J* = 8.0 Hz, 1H), 5.00 (dd, *J* = 8.0, 5.7 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.7, 148.0, 137.5, 134.3, 134.1, 132.1, 131.3, 130.5, 129.3, 129.0, 128.8, 128.2, 127.8, 125.5, 119.9, 78.1, 43.0; **HRMS (+ESI):** Calc for $C_{21}H_{20}BrN_2O_4$ $[M+NH_4]^+$ 443.0601; found: 443.0607; The ee value 94% (t_{minor} = 15.4 min, t_{major} = 53.8 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2,4-dichloro-6-(2-nitro-1-phenylethyl)phenyl benzoate (3ea)

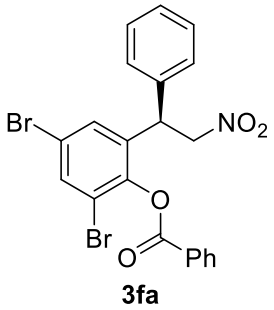


3ea

Compound **3ea** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (16.0 mg, 77% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.16 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.70 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.26 (s, 3H), 7.15 – 7.11 (m, 3H), 5.10 – 4.98 (m, 1H), 4.94 (d, *J* = 6.6 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 163.9, 163.4, 144.6, 144.5, 137.2, 136.6, 135.9, 134.6, 132.6, 130.7, 129.8, 129.7, 129.4, 129.0, 128.4, 128.0, 127.7, 127.1, 126.8, 78.1, 43.5, 43.4; **HRMS (+ESI):** Calc for $C_{21}H_{19}Cl_2N_2O_4$ $[M+NH_4]^+$ 433.0716; found: 433.0717; The ee value 94% (t_{minor} = 8.1 min, t_{major} = 9.6 min)

was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

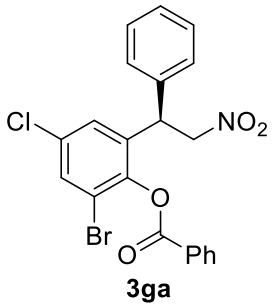
(R)-2,4-dibromo-6-(2-nitro-1-phenylethyl)phenyl benzoate (3fa)



3fa

Compound **3fa** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; oil type (22.0 mg, 87% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.16 (d, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 2.2 Hz, 1H), 7.70 (brs, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.26 (m, 4H), 7.13 (d, *J* = 25.1 Hz, 2H), 5.10 – 4.99 (m, 2H), 4.93 (d, *J* = 5.4 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 163.9, 163.5, 146.4, 146.2, 137.3, 136.6, 136.3, 135.4, 134.6, 134.5, 130.8, 130.7, 130.4, 129.4, 129.1, 128.4, 128.3, 128.0, 127.7, 120.3, 119.4, 78.2, 43.6, 43.5; **HRMS (+ESI):** Calc for $C_{21}H_{19}Br_2N_2O_4$ $[M+NH_4]^+$ 520.9706; found: 520.9704; The ee value 90% (t_{minor} = 9.4 min, t_{major} = 10.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

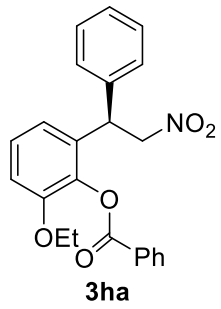
(R)-2-bromo-4-chloro-6-(2-nitro-1-phenylethyl)phenyl benzoate (3ga)



3ga

Compound **3ga** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (19.6 mg, 85% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 8.22 (d, *J* = 7.8 Hz, 2H), 7.75 (brs, 1H), 7.64 – 7.63 (m, 1H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.31 (brs, 4H), 7.18 (d, *J* = 25.2 Hz, 2H), 5.15 – 5.03 (m, 2H), 4.98 (d, *J* = 6.0 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 164.0, 163.5, 145.9, 145.6, 137.3, 136.6, 135.9, 134.6, 134.5, 132.9, 132.6, 130.8, 130.7, 129.4, 129.3, 129.1, 128.8, 128.8, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 119.1, 78.1, 43.6, 43.5; **HRMS (+ESI):** Calc for $C_{21}H_{19}BrClN_2O_4$ $[M+NH_4]^+$ 477.0211; found: 477.0207; The ee value 94% (t_{minor} = 8.7 min, t_{major} = 10.1 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

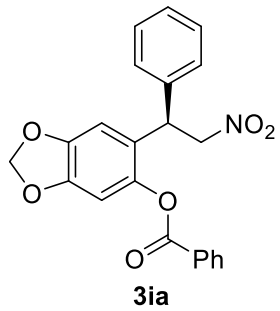
(R)-2-ethoxy-6-(2-nitro-1-phenylethyl)phenyl benzoate (3ha)



3ha

Compound **3ha** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 3 days at room temperature; colorless gummy mass (17.8 mg, 91% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.15 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.30 – 7.11 (m, 6H), 6.92 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 5.13 (brs, 1H), 4.98 (brs, 2H), 4.01 (dd, *J* = 13.8, 6.8 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.3, 151.4, 138.6, 133.8, 133.2, 130.4, 129.3, 129.0, 128.8, 127.9, 127.7, 127.0, 119.3, 112.9, 78.3, 64.7, 43.2, 14.8; **HRMS (+ESI):** Calc for $C_{23}H_{25}N_2O_5$ $[M+NH_4]^+$ 409.1758; found: 409.1770; The ee value 92% (t_{minor} = 18.4 min, t_{major} = 25.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

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

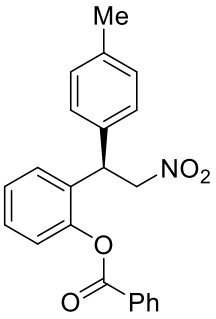


3ia

Compound **3ia** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (16.4 mg, 84% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.15 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.16 – 7.14 (m, 2H), 6.71 (s, 1H), 6.66 (s, 1H), 6.00 (d, *J* = 1.4 Hz, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.07 (t, *J* = 8.0 Hz, 1H), 4.98 – 4.88 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 147.6, 146.3, 142.9, 138.4, 134.2, 130.4, 129.2, 129.0, 128.9, 127.9, 127.7, 124.4, 107.3, 105.0, 102.2, 78.4, 42.8; **HRMS (+ESI):** Calc for $C_{22}H_{21}N_2O_6$ $[M+NH_4]^+$ 409.1394; found: 409.1382; The ee value 96% (t_{minor} = 31.8 min, t_{major} = 41.1 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(R)-2-(2-nitro-1-(p-tolyl)ethyl)phenyl benzoate (3ja)

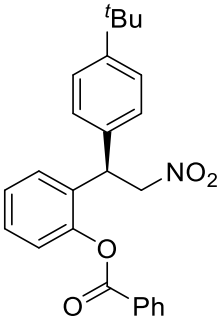
Compound **3ja** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (17.0 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.16 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.68 (t, *J* = 7.5 Hz,



3ja

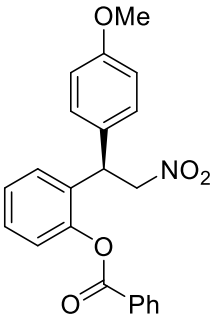
1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.29 – 7.26 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.05 (brs, 4H), 5.13 (t, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.0 Hz, 2H), 2.29 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.0, 148.89, 137.5, 135.2, 134.1, 131.9, 130.4, 129.8, 129.2, 128.9, 128.3, 127.8, 126.7, 123.7, 78.5, 42.8, 21.2; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1652; found: 379.1651; The ee value 96% (t_{minor} = 11.6 min, t_{major} = 12.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(1-(4-(tert-butyl)phenyl)-2-nitroethyl)phenyl benzoate (3ka)



3ka

Compound **3ka** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (18.0 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.12 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 6.4 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 8.1 Hz, 3H), 7.06 (d, *J* = 8.3 Hz, 2H), 5.14 (t, *J* = 8.0 Hz, 1H), 4.99 (d, *J* = 8.0 Hz, 2H), 1.26 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.9, 150.6, 148.9, 135.1, 134.0, 132.0, 130.4, 129.2, 128.9, 128.9, 128.4, 127.5, 126.7, 126.0, 123.7, 78.5, 42.8, 34.6, 31.4; **HRMS (+ESI):** Calc for $C_{25}H_{29}N_2O_4$ $[M+NH_4]^+$ 421.2122; found: 421.2118; The ee value 96% (t_{minor} = 8.1 min, t_{major} = 8.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.



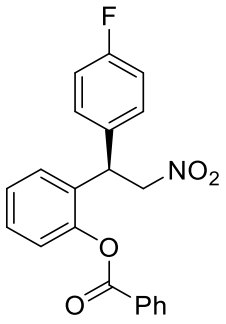
3la

(R)-2-(1-(4-methoxyphenyl)-2-nitroethyl)phenyl benzoate (3la)

Compound **3la** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (17.0 mg, 90% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.16 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.37 – 7.35 (m, 1H), 7.28 (brs, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H),

5.11 (t, *J* = 8.0 Hz, 1H), 4.96 (dd, *J* = 8.0, 2.9 Hz, 2H), 3.74 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 164.9, 159.1, 148.9, 134.1, 132.0, 130.4, 130.2, 129.2, 129.0, 128.9, 128.1, 126.7, 123.7, 114.5, 78.6, 55.4, 42.5; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_5$ $[M+NH_4]^+$ 395.1601; found: 395.1606; The ee value 96% (t_{minor} = 15.6 min, t_{major} = 17.3 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

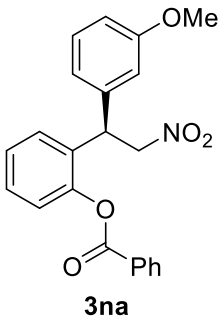
(R)-2-(1-(4-fluorophenyl)-2-nitroethyl)phenyl benzoate (3ma)



3ma

Compound **3ma** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless oil (14.1 mg, 77% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.13 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.22 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.11 (dd, *J* = 8.6, 5.2 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 5.13 (t, *J* = 8.1 Hz, 1H), 5.01 – 4.93 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.9, 163.1, 161.4, 148.9, 134.2, 134.0, 134.0, 131.5, 130.4, 129.6, 129.5, 129.2, 129.0, 129.0, 128.0, 126.9, 123.9, 116.1, 116.0, 78.5, 42.5; **HRMS (+ESI):** Calc for $C_{21}H_{20}FN_2O_4$ $[M+NH_4]^+$ 383.1402; found: 383.1406; The ee value 90% (t_{minor} = 21.2 min, t_{major} = 48.8 min) was determined by HPLC analysis using Daicel Chiralpak Lux C1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(1-(3-methoxyphenyl)-2-nitroethyl)phenyl benzoate (3na)

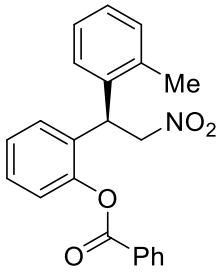


3na

Compound **3na** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (16.4 mg, 87% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.15 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.35 (m, 1H), 7.30 – 7.27 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.76 – 6.73 (m, 2H), 6.67 (t, *J* = 2.1 Hz, 1H), 5.13 (t, *J* = 8.0 Hz, 1H), 4.98 (d, *J* = 8.0 Hz, 2H), 3.64 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 164.9, 160.0, 148.9, 139.8, 134.1, 131.7, 130.4, 130.1, 129.2, 129.0, 128.9,

128.2, 126.8, 123.7, 120.0, 113.9, 113.2, 78.3, 55.3, 43.2; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_5$ $[M+NH_4]^+$ 395.1601; found: 395.1603; The ee value 96% (t_{minor} = 20.9 min, t_{major} = 18.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

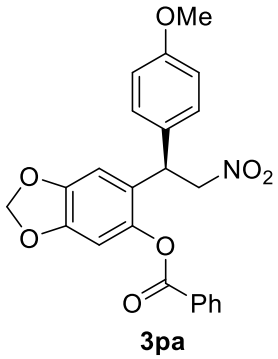
(R)-2-(2-nitro-1-(o-tolyl)ethyl)phenyl benzoate (3oa)



3oa

Compound **3oa** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (15.9 mg, 88% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.17 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.34 (m, 1H), 7.23 (dd, *J* = 11.9, 5.5 Hz, 3H), 7.20 – 7.15 (m, 3H), 7.10 – 7.09 (m, 1H), 5.36 (t, *J* = 8.1 Hz, 1H), 4.98 – 4.91 (m, 2H), 2.16 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.1, 149.0, 136.9, 136.2, 134.2, 131.5, 131.0, 130.4, 129.1, 129.0, 128.9, 127.8, 126.8, 126.6, 126.2, 123.5, 77.4, 39.5, 19.6; **HRMS (+ESI):** Calc for $C_{22}H_{23}N_2O_4$ $[M+NH_4]^+$ 379.1652; found: 379.1654; The ee value 98% (t_{minor} = 13.9 min, t_{major} = 15.0 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

(R)-6-(1-(4-methoxyphenyl)-2-nitroethyl)benzo[d][1,3]dioxol-5-yl benzoate (3pa)

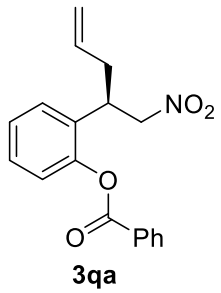


3pa

Compound **3pa** was purified by silica gel column chromatography using 4-5% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Yellow gummy mass (18.5 mg, 88% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.16 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.70 (s, 1H), 6.65 (s, 1H), 6.00 (d, *J* = 1.3 Hz, 1H), 5.98 (d, *J* = 1.3 Hz, 1H), 5.01 (t, *J* = 8.1 Hz, 1H), 4.93 – 4.85 (m, 2H), 3.75 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 159.1, 147.5, 146.2, 142.7, 134.2, 130.4, 130.2, 129.0, 128.9, 128.8, 124.7, 114.5, 107.2, 105.0, 102.2, 78.6, 55.5, 42.1; **HRMS (+ESI):** Calc for $C_{23}H_{23}N_2O_7$ $[M+NH_4]^+$ 439.1500; found: 439.1492; The ee value 96% (t_{minor} = 52.6 min, t_{major} = 60.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH

(90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

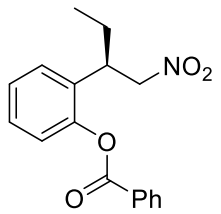
(R)-2-(1-nitropent-4-en-2-yl)phenyl benzoate (3qa)



3qa

Compound **3qa** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature; Colorless gummy mass (6.1 mg, 39% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.24 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.34 (m, 1H), 7.29 (d, *J* = 4.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 5.66 – 5.59 (m, 1H), 5.05 – 5.02 (m, 2H), 4.65 – 4.59 (m, 2H), 3.85 (q, *J* = 7.4 Hz, 1H), 2.53 – 2.41 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)**: δ 165.3, 149.2, 134.2, 134.1, 131.5, 130.5, 129.2, 129.0, 128.9, 128.0, 126.8, 123.5, 118.6, 79.1, 37.7, 36.9; **HRMS (+ESI):** Calc for $C_{18}H_{21}N_2O_4$ $[M+NH_4]^+$ 329.1496; found: 329.1499; The ee value 68% (t_{minor} = 13.2 min, t_{major} = 14.4 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(1-nitrobutan-2-yl)phenyl benzoate (3ra)

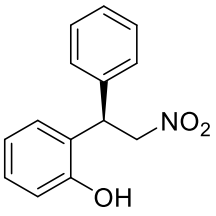


3ra

Compound **3ra** was purified by silica gel column chromatography using 2% EtOAc in hexane; **Reaction time:** 3 days at room temperature ; Oil type (8.1 mg, 54% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.24 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.34 (m, 1H), 7.31 – 7.26 (m, 2H), 7.22 – 7.21 (m, 1H), 4.63 – 4.53 (m, 2H), 3.70 – 3.65 (m, 1H), 1.78 – 1.70 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 149.6, 134.2, 131.6, 130.5, 129.2, 129.0, 128.8, 128.0, 126.8, 123.5, 80.1, 39.7, 25.6, 11.8; **HRMS (+ESI):** Calc for $C_{17}H_{21}N_2O_4$ $[M+NH_4]^+$ 317.1496; found: 317.1498; The ee value 60% (t_{minor} = 10.2 min, t_{major} = 11.0 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(2-nitro-1-phenylethyl)phenol (5a)

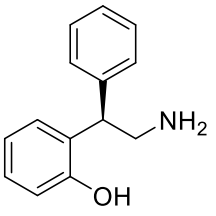
Compound **5a** was prepared from **3aa** and was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time:** 1 hour at 0 °C; Pale yellow oil type (10.2 mg, 84% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.35 – 7.29 (m, 4H), 7.28



5a

– 7.26 (m, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.22 (t, *J* = 8.1 Hz, 1H), 5.12 (dd, *J* = 13.0, 7.4 Hz, 1H), 5.07 (s, 1H), 5.00 (dd, *J* = 13.0, 8.7 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 153.2, 138.8, 129.1, 129.0, 129.0, 128.1, 127.7, 126.0, 121.5, 116.3, 78.1, 43.8; **HRMS (+ESI):** Calc for $C_{14}H_{13}NNaO_3$ $[M+Na]^+$ 266.0788; found: 266.0791; The ee value 96% (t_{minor} = 17.1 min, t_{major} = 13.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

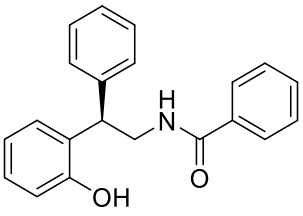
(R)-2-(2-amino-1-phenylethyl)phenol (7)



7

Compound **7** was prepared from the reduction of compound **5a** under Zn/AcOH condition; **Reaction time:** 1 day at room temperature; White solid (37.1 mg, 87% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 16.8, 6.5 Hz, 3H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.76 (t, *J* = 7.3 Hz, 1H), 5.29 (brs, 2H), 4.36 (d, *J* = 5.4 Hz, 1H), 3.56 (dd, *J* = 12.4, 6.2 Hz, 1H), 3.32 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 156.9, 140.6, 131.7, 128.9, 128.6, 128.3, 126.8, 119.2, 118.4, 51.1, 45.4; **HRMS (+ESI):** Calc for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1226; found: 214.1239; The ee value 96% (t_{minor} = 22.5 min, t_{major} = 13.6 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(R)-N-(2-(2-hydroxyphenyl)-2-phenylethyl)benzamide (8)

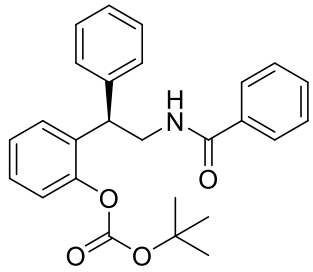


8

Compound **8** was purified by silica gel column chromatography using 15% EtOAc in hexane; **Reaction time:** 1 day at room temperature; Semisolid type (30.2 mg, 95% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.68 (d, *J* = 7.2 Hz, 2H), 7.56 (s, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.40 – 7.34 (m, 6H), 7.31 – 7.27 (m, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 6.94 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.90 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.56 (s, 1H), 4.70 (dd, *J* = 8.9, 5.2 Hz, 1H), 4.18 – 4.11 (m, 1H), 3.93 – 3.88 (m, 1H); **^{13}C NMR (150**

MHz, $CDCl_3$): δ 169.0, 154.8, 140.5, 133.9, 132.0, 129.0, 129.0, 128.8, 128.5, 128.3, 128.0, 127.3, 127.2, 120.5, 116.8, 44.8, 44.6; **HRMS (+ESI):** Calc for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489; found: 318.1490.

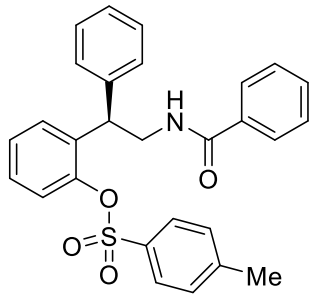
(R)-2-(2-benzamido-1-phenylethyl)phenyl tert-butyl carbonate (9)



9

Compound **9** was purified by silica gel column chromatography using 15% EtOAc in hexane; **Reaction time:** 30 minutes at 0 °C thereafter 20 hours at room temperature; Semisolid (14.0 mg, 67% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.67 (d, *J* = 7.1 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.39 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.26 (m, 5H), 7.25 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.14 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.43 (s, 1H), 4.50 (t, *J* = 8.1 Hz, 1H), 4.15 – 4.12 (m, 2H), 1.48 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.7, 152.5, 149.5, 141.3, 134.6, 134.2, 131.5, 128.9, 128.7, 128.6, 128.4, 128.0, 127.2, 127.2, 127.0, 122.9, 84.2, 44.0, 43.5, 27.8; **HRMS (+ESI):** Calc for $C_{26}H_{28}NO_4$ $[M+H]^+$ 418.2013; found: 418.2024; The ee value 94% (t_{minor} = 18.2 min, t_{major} = 10.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (75:25) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(R)-2-(2-benzamido-1-phenylethyl)phenyl 4-methylbenzenesulfonate (10)

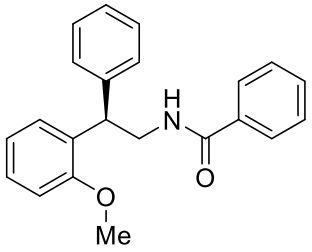


10

Compound **10** was purified by silica gel column chromatography using 15% EtOAc in hexane; **Reaction time:** 12 hours at 45 °C temperature; Colorless gummy mass (17.9 mg, 76% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 7.1 Hz, 2H), 7.46 – 7.43 (m, 2H), 7.39 – 7.32 (m, 4H), 7.30 – 7.26 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 3H), 7.23 – 7.19 (m, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.81 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.52 (s, 1H), 4.81 (dd, *J* = 10.5, 6.2 Hz, 1H), 4.32 – 4.27 (m, 1H), 3.96 – 3.92 (m, 1H), 2.45 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.7, 148.0, 146.1, 140.9, 135.7, 134.6, 132.8, 131.5, 130.3, 129.0, 129.0, 128.7, 128.6, 128.2, 128.0, 128.0, 127.3, 127.1, 122.6, 43.8, 43.1, 22.0; **HRMS (+ESI):** Calc for $C_{28}H_{26}NO_4S$ $[M+H]^+$ 472.1577; found: 472.1579; The ee value 96% (t_{minor} = 31.7

min, t_{major} = 28.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (75:25) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

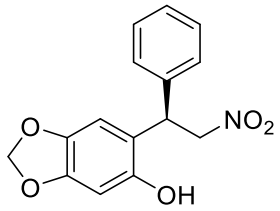
(R)-N-(2-(2-methoxyphenyl)-2-phenylethyl)benzamide (11)



11

Compound **11** was purified by using 230-400 mesh size silica gel column chromatography with 15% EtOAc in hexane; **Reaction time:** 30 minutes at 0 °C thereafter 4.5 hours at room temperature; Colorless gummy mass (10.8 mg, 65% yield);**^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.60 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.32 (d, *J* = 4.3 Hz, 4H), 7.24 – 7.20 (m, 2H), 7.18 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.26 (s, 1H), 4.76 (t, *J* = 7.9 Hz, 1H), 4.12 – 4.03 (m, 2H), 3.80 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.7, 157.2, 142.0, 135.0, 131.5, 130.6, 128.7, 128.7, 128.5, 128.2, 127.0, 126.8, 121.1, 111.0, 55.7, 43.9, 43.3; **HRMS (+ESI):** Calc for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645; found: 332.1642; The ee value 96% (t_{minor} = 38.4 min, t_{major} = 29.5 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

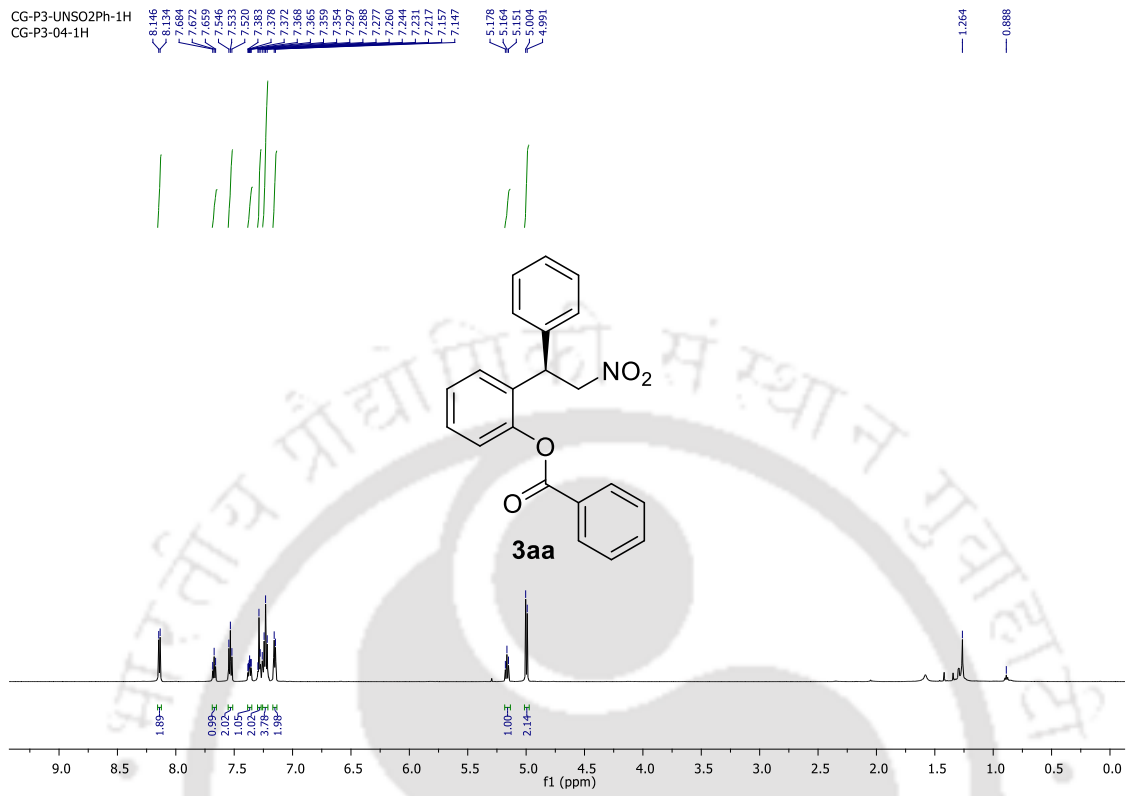
(R)-6-(2-nitro-1-phenylethyl)benzo[d][1,3]dioxol-5-ol (12)

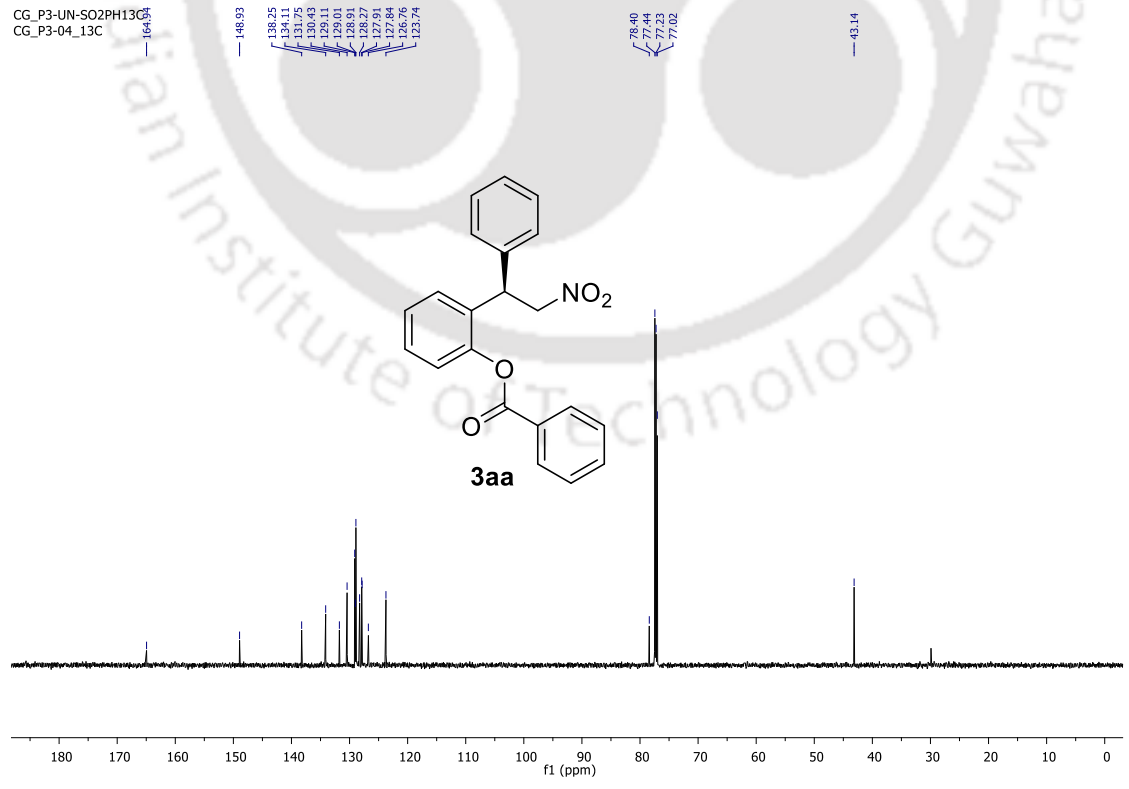


12

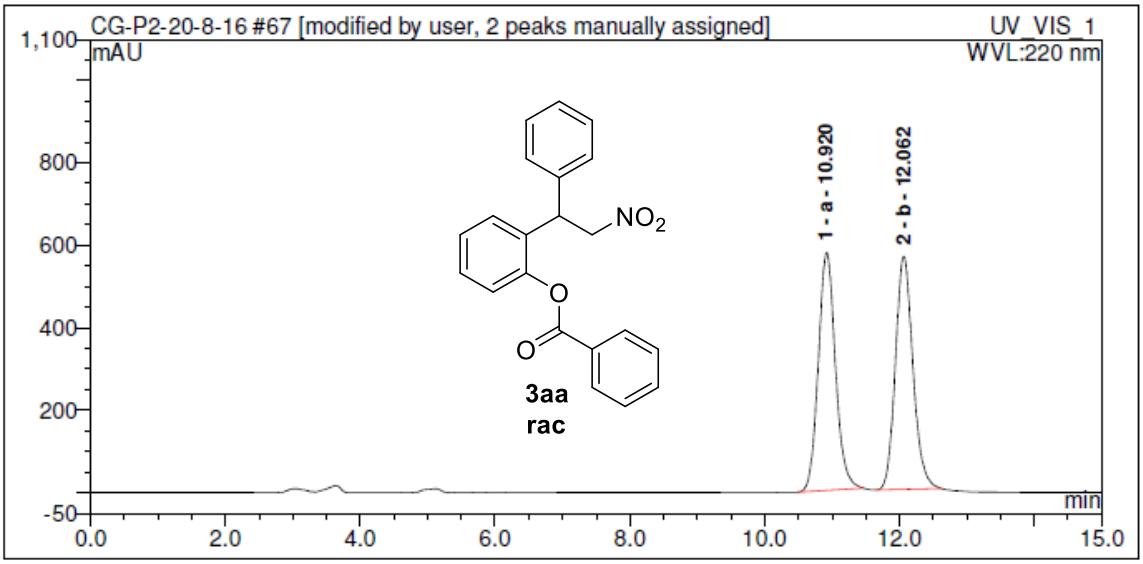
Compound **12** was prepared according to the general procedure **3.6.E.** and it was purified by silica gel column chromatography using 6% EtOAc in hexane; **Reaction time:** 1 hour at 0 °C; Red violet gummy type (72% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.36 – 7.32 (m, 2H), 7.28 – 7.26 (m, 3H), 6.54 (s, 1H), 6.36 (s, 1H), 5.89 (d, *J* = 1.3 Hz, 1H), 5.88 (d, *J* = 1.3 Hz, 1H), 5.16 (t, *J* = 8.1 Hz, 1H), 5.02 (dd, *J* = 12.9, 7.8 Hz, 1H), 4.95 (dd, *J* = 12.9, 8.4 Hz, 1H), 4.70 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 147.8, 147.5, 142.3, 139.0, 129.2, 127.9, 127.8, 118.0, 108.2, 101.6, 99.1, 78.1, 43.3; **HRMS (+ESI):** Calc for $C_{15}H_{13}NNaO_5$ $[M+Na]^+$ 310.0686; found: 310.0698; The ee value 96% (t_{minor} = 17.2 min, t_{major} = 13.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

3.9. Selected NMR spectra and HPLC chromatogram:



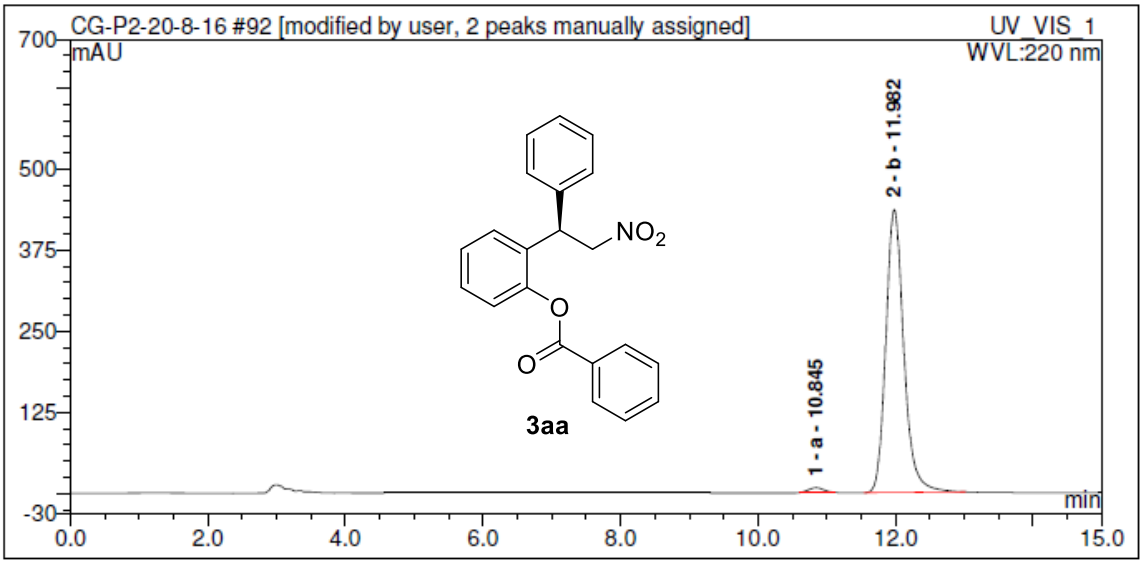


SO2PH-PH-RAC-DCE-IA

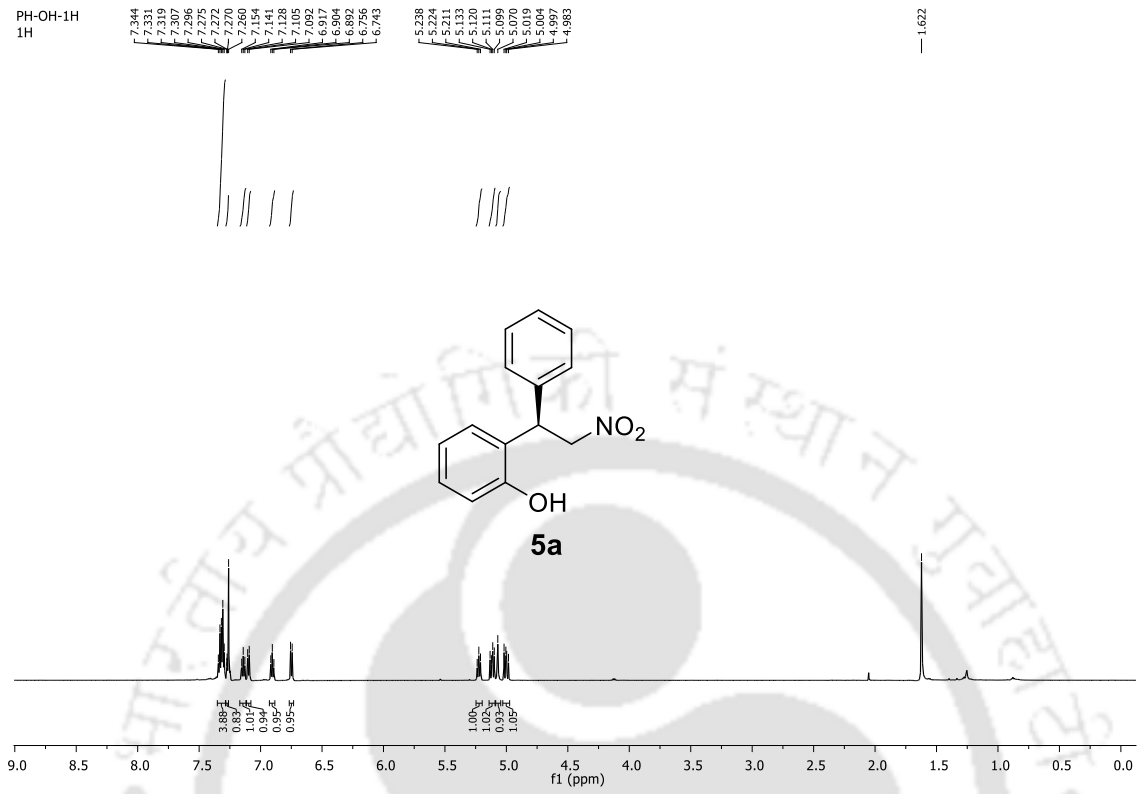


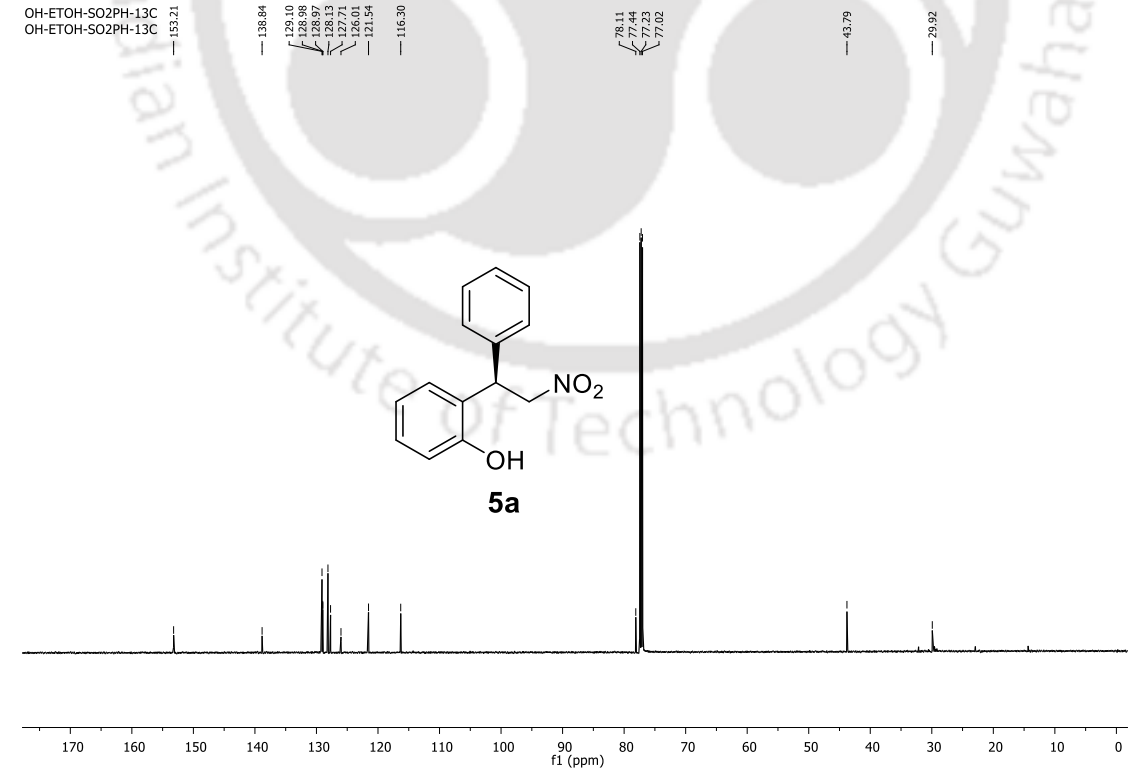
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	10.92	169.3618	49.85920355	577.0425	n.a.
2	b	12.06	170.318	50.14079645	565.236	n.a.

SO2PH-CAT 5-DCE-IA

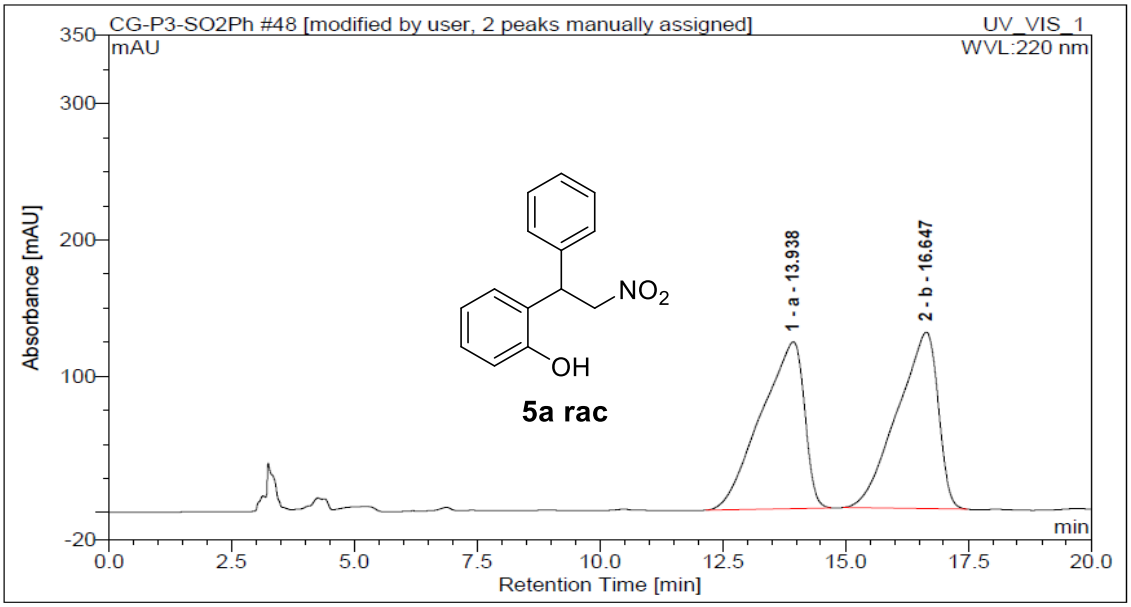


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	10.85	1.815933	1.351956926	7.35398	n.a.
2	b	11.98	132.503	98.64804307	436.040	n.a.



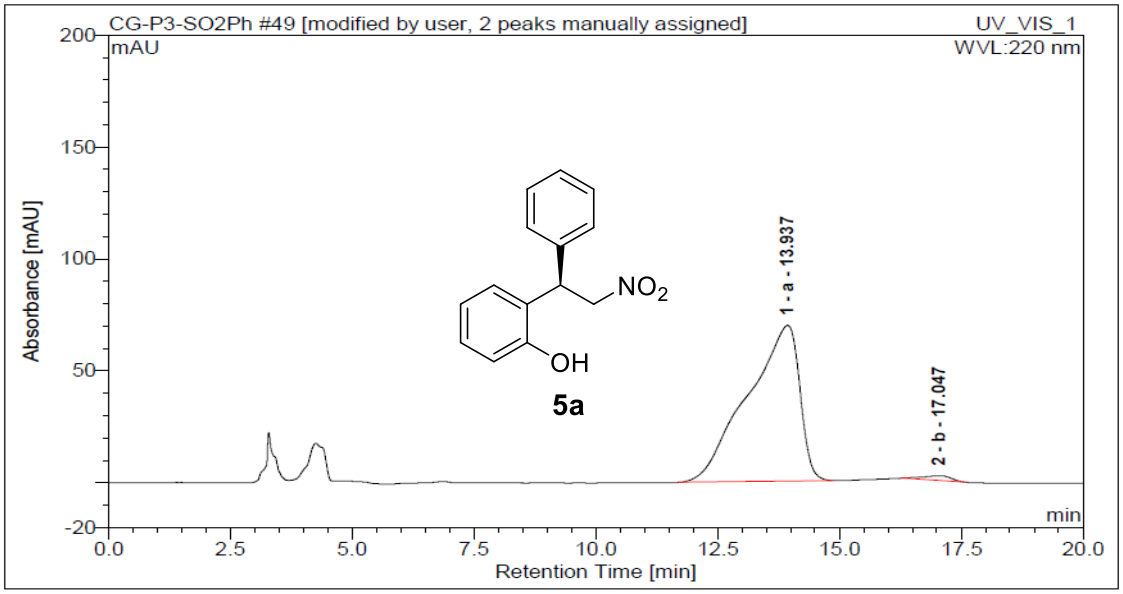


OH-UNSO2PH-RAC-ID

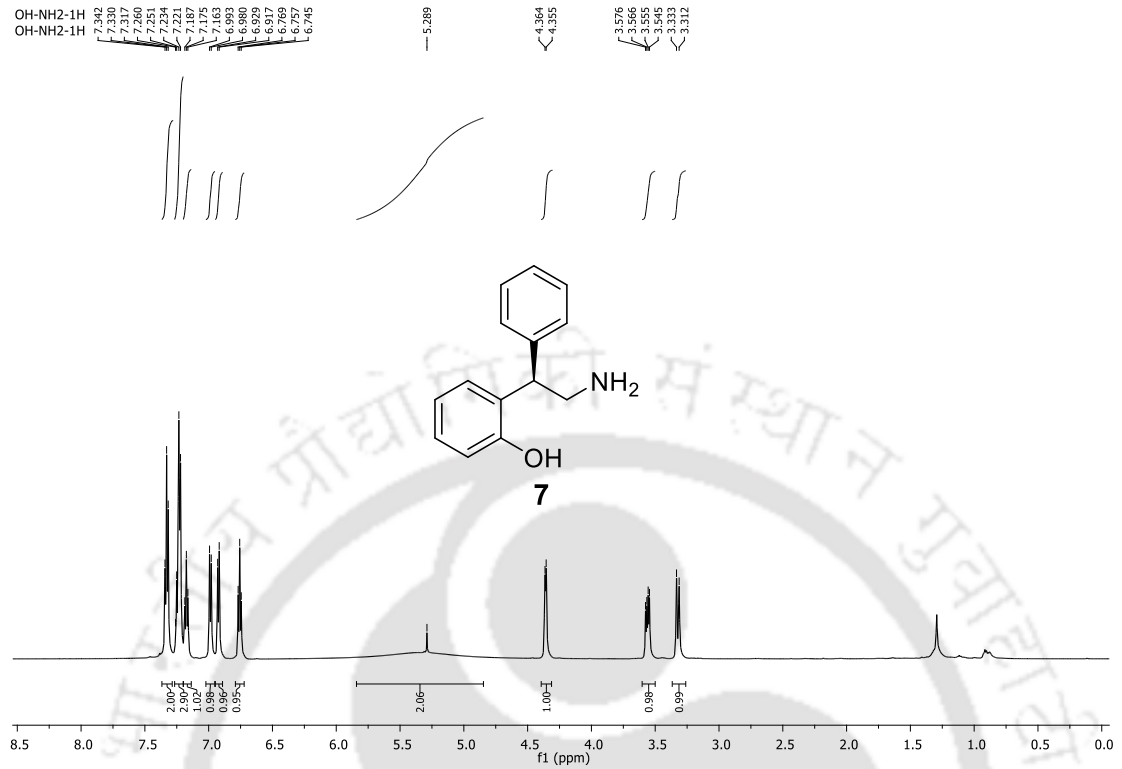


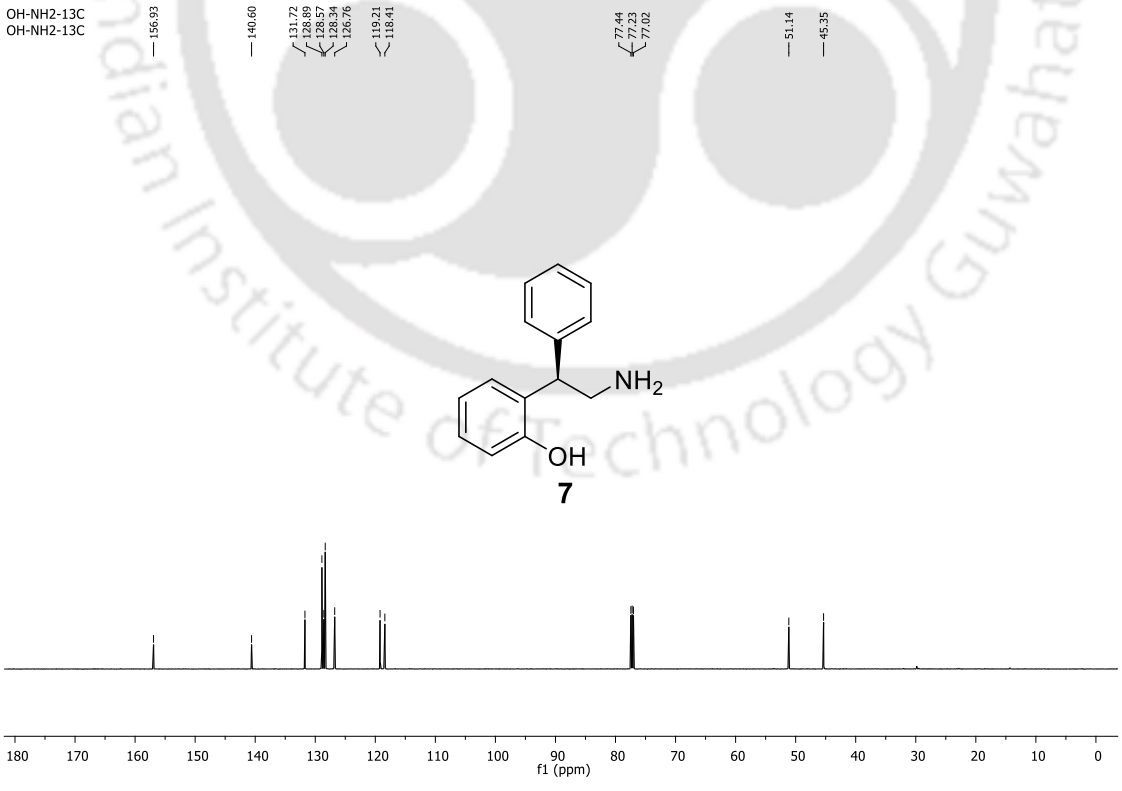
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	13.94	125.6674	50.15858385	122.3372	n.a.
2	b	16.65	124.873	49.84141615	129.550	n.a.

OH-UNSO2PH-CHI-ID

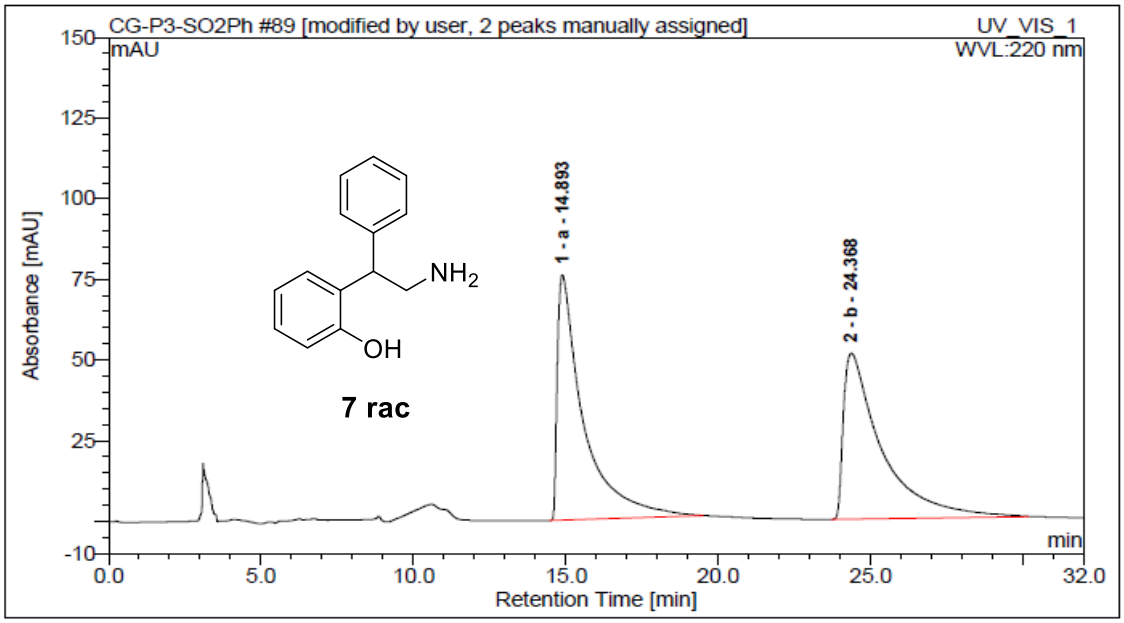


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	13.94	86.17286	98.36357206	69.55911	n.a.
2	b	17.05	1.434	1.636427938	2.149	n.a.



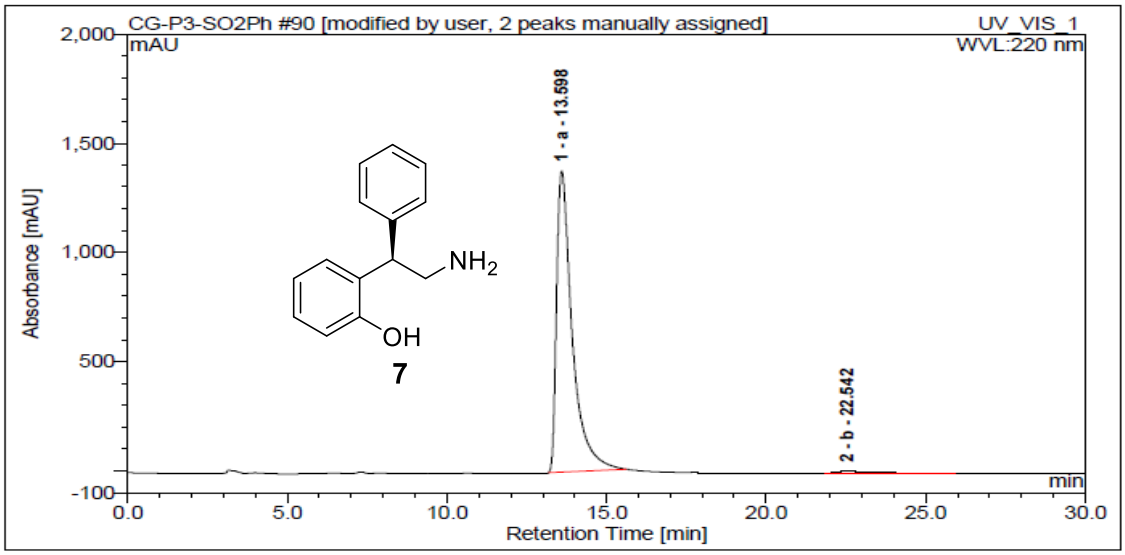


SO2PH-OH-NH2-RAC-ID

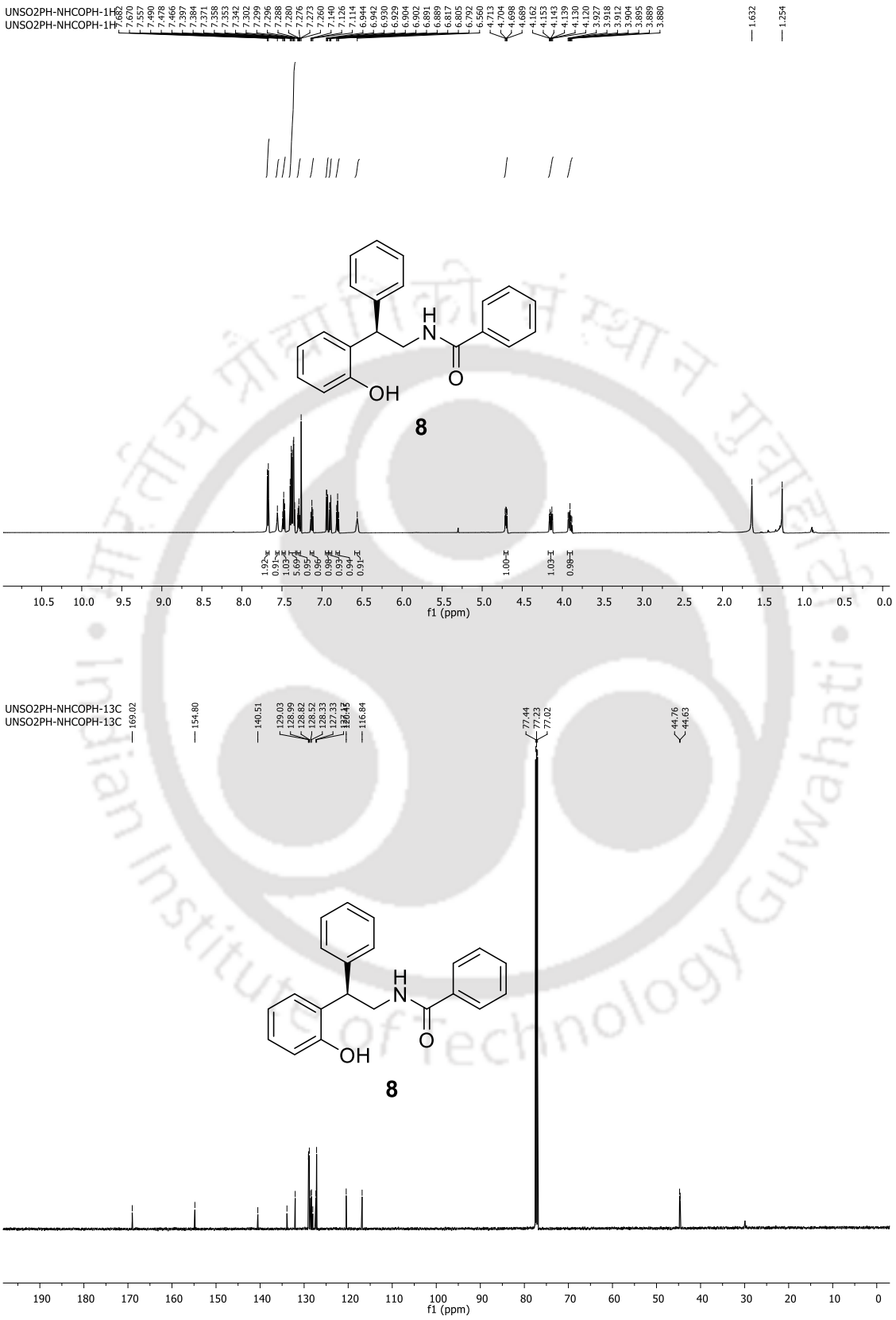


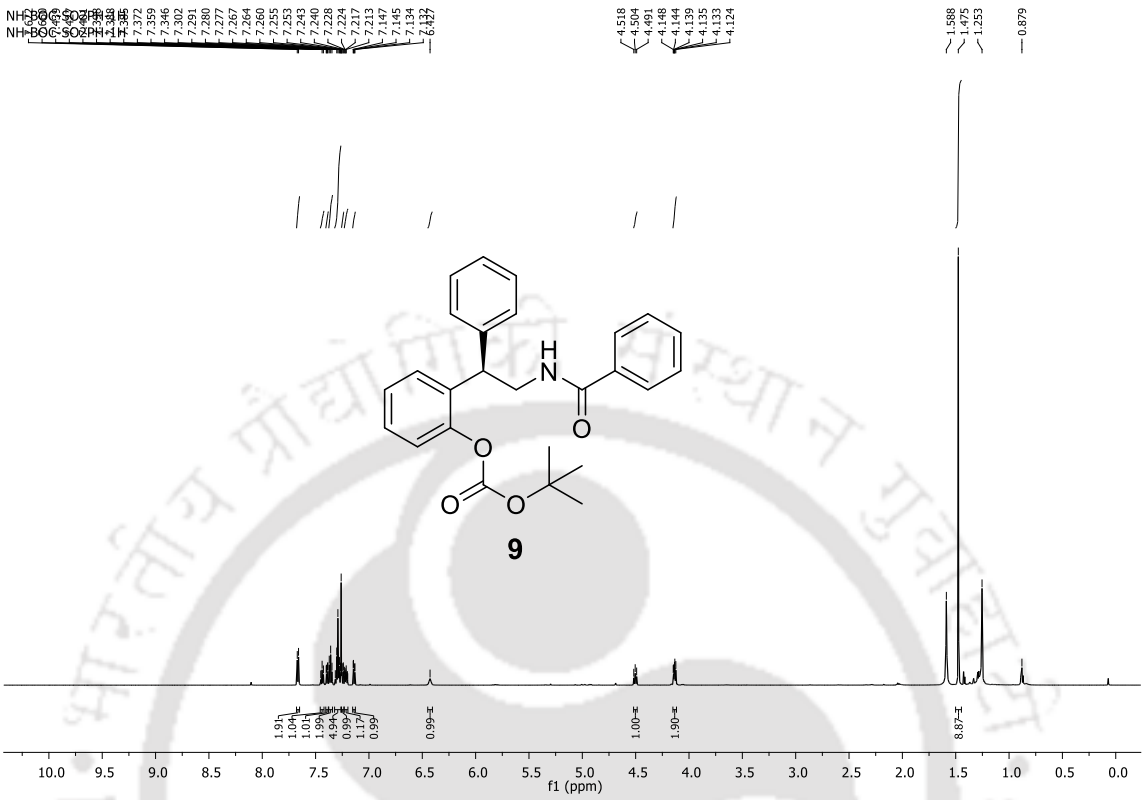
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	14.89	75.52479	50.38313674	76.08587	n.a.
2	b	24.37	74.376	49.61686326	51.364	n.a.

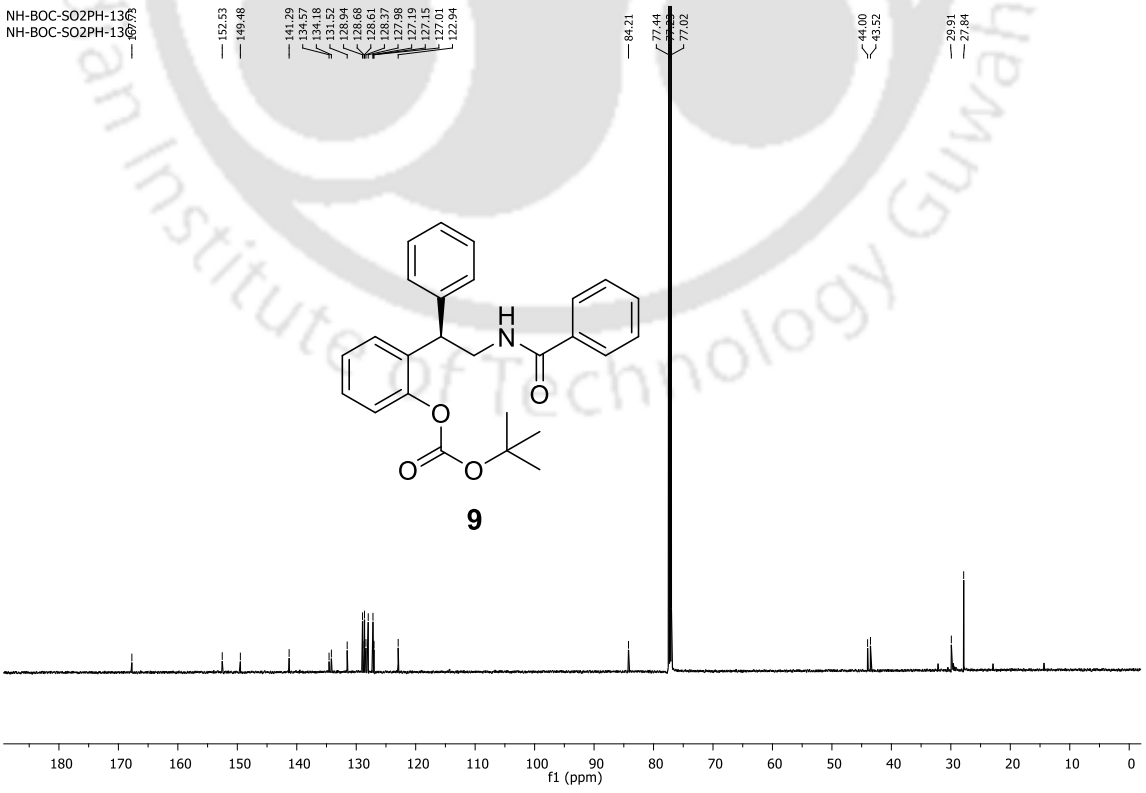
SO2PH-OH-NH2-CHI-ID



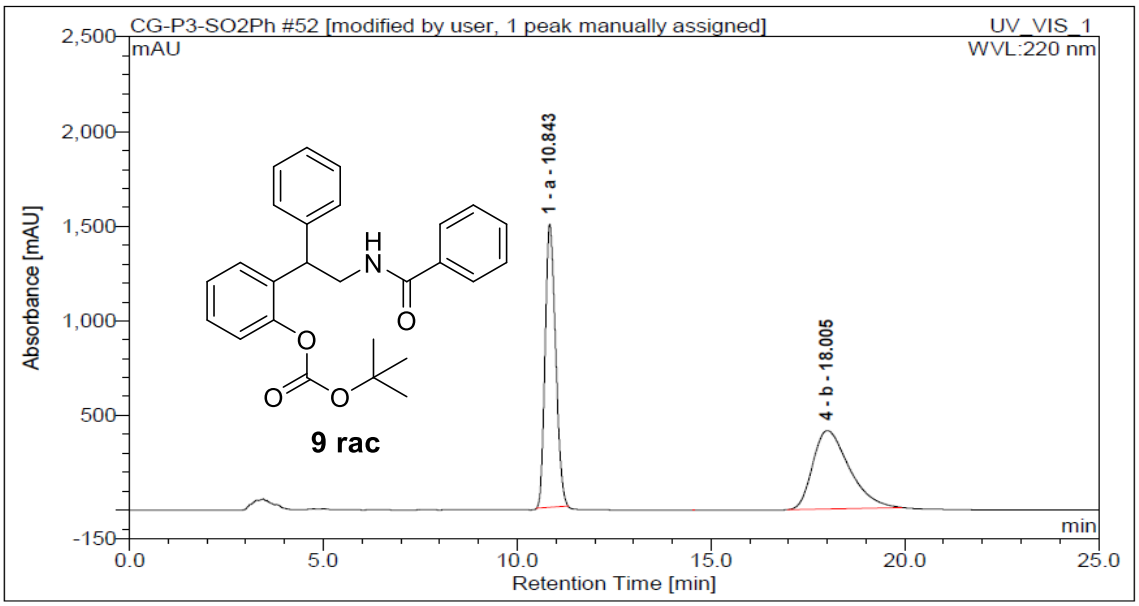
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	13.60	783.3106	97.98112455	1377.744	n.a.
2	b	22.54	16.140	2.018875447	10.453	n.a.





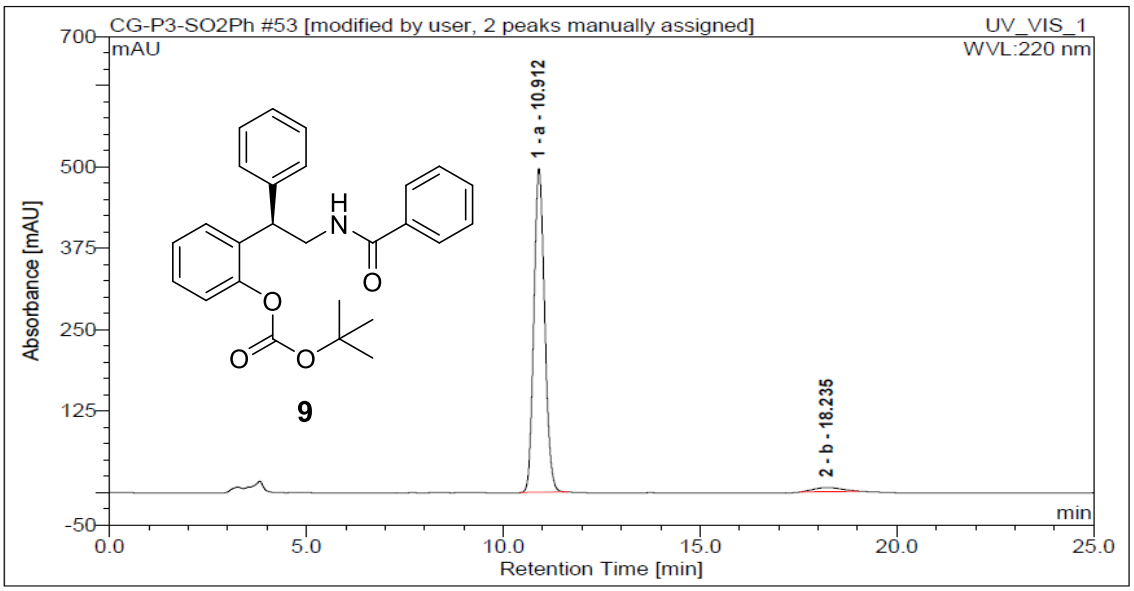


O-BOC-RAC-ID

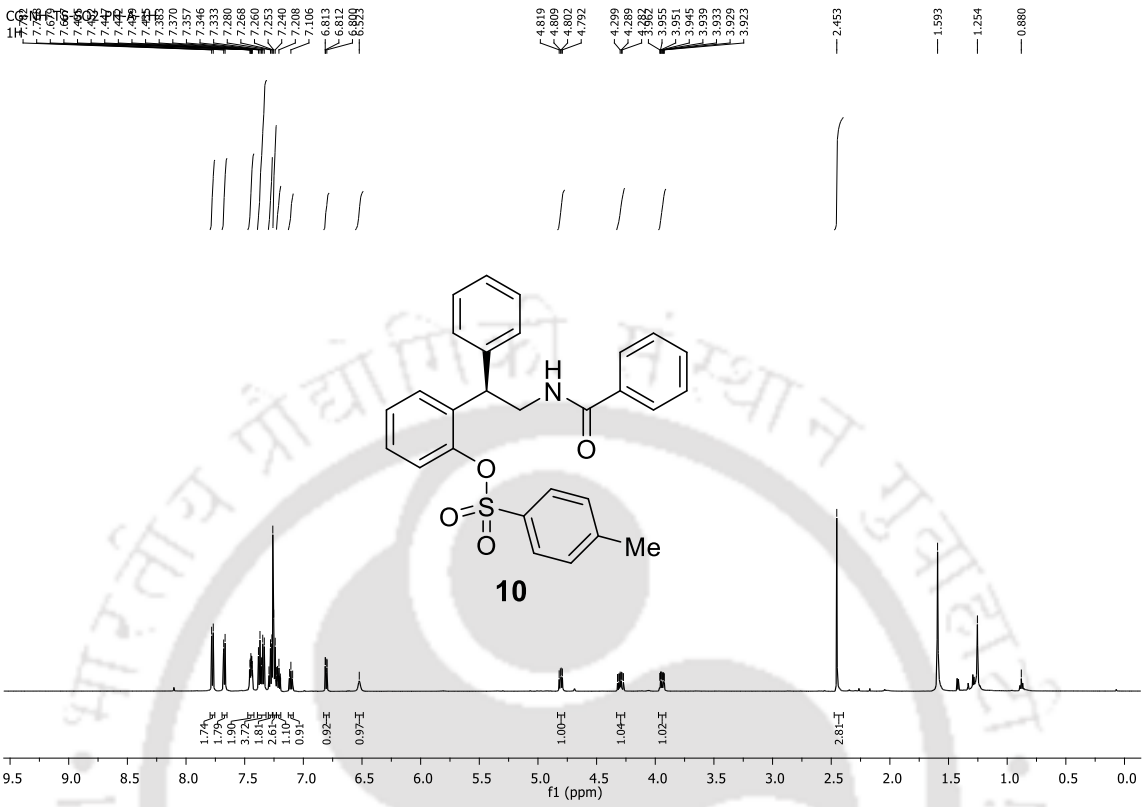


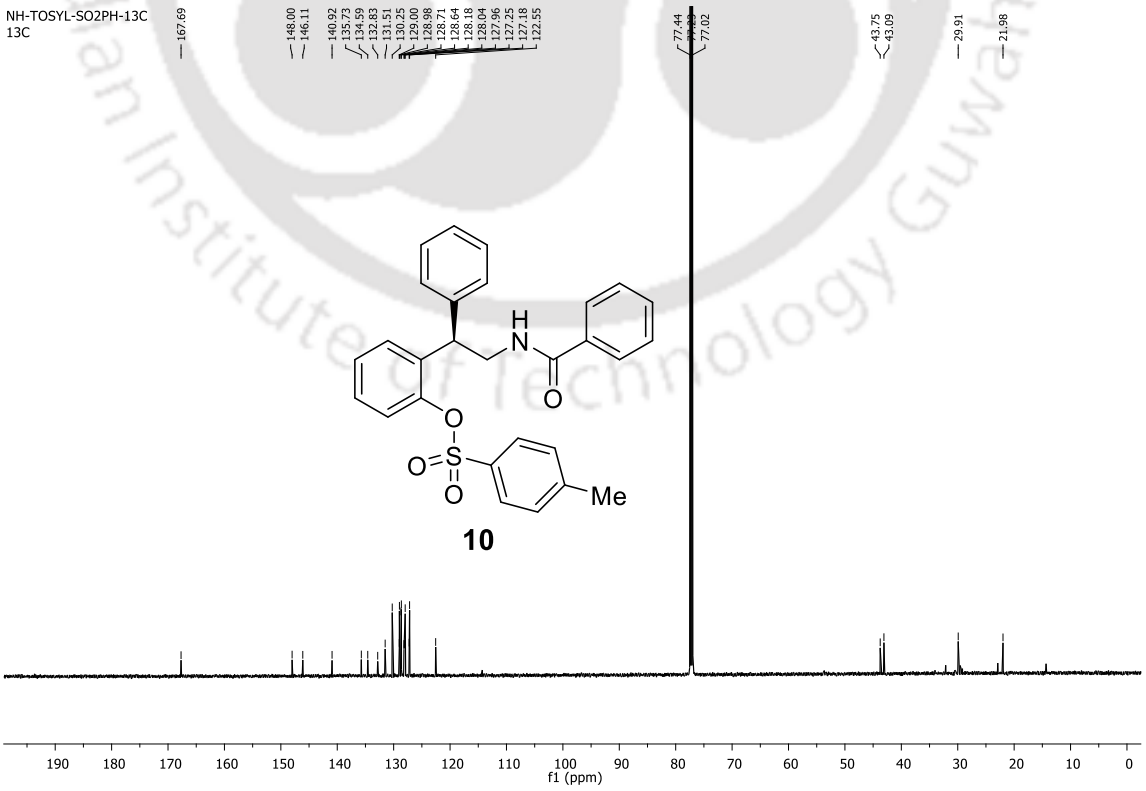
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	10.84	472.1345	51.131771	1497.472	n.a.
4	b	18.01	451.234	48.868229	415.016	n.a.

O-BOC-CHI-ID

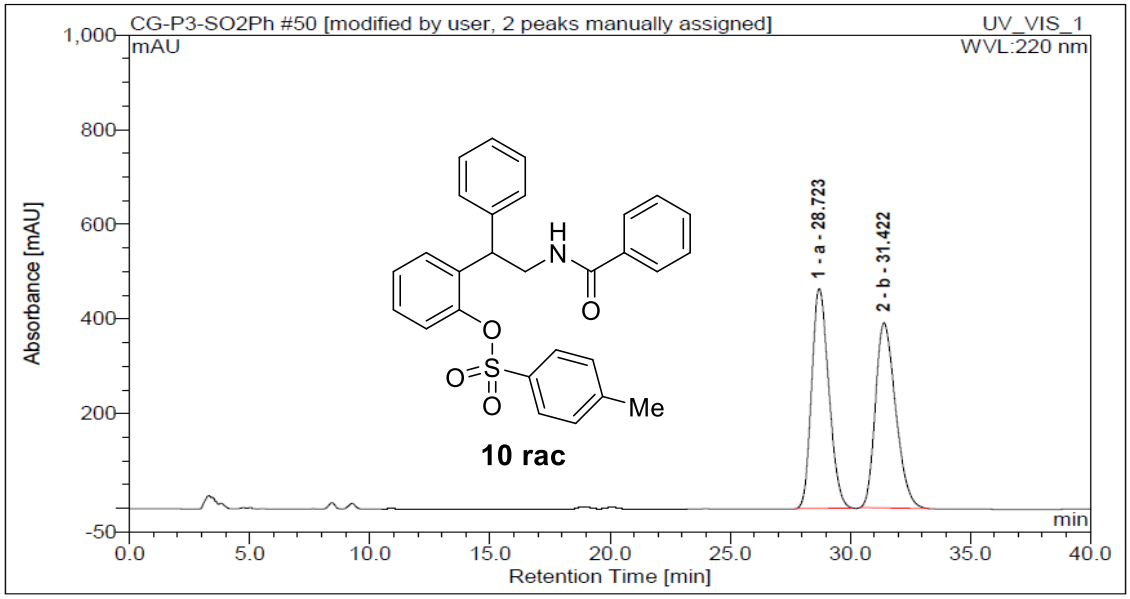


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	10.91	158.3993	96.94411837	497.3423	n.a.
2	b	18.24	4.993	3.055881626	6.021	n.a.



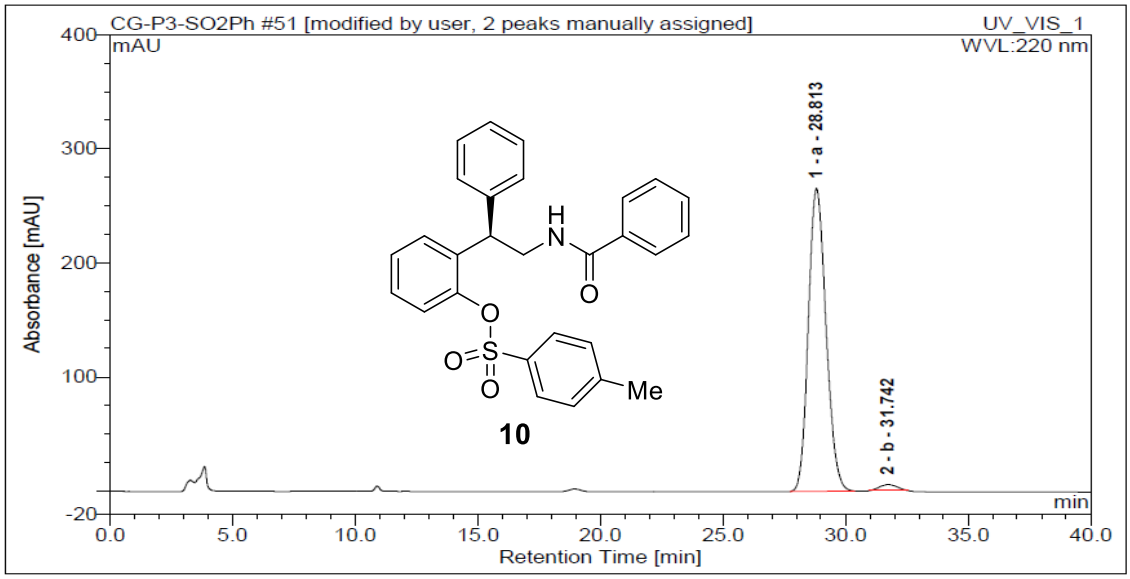


O-Ts-RAC-ID

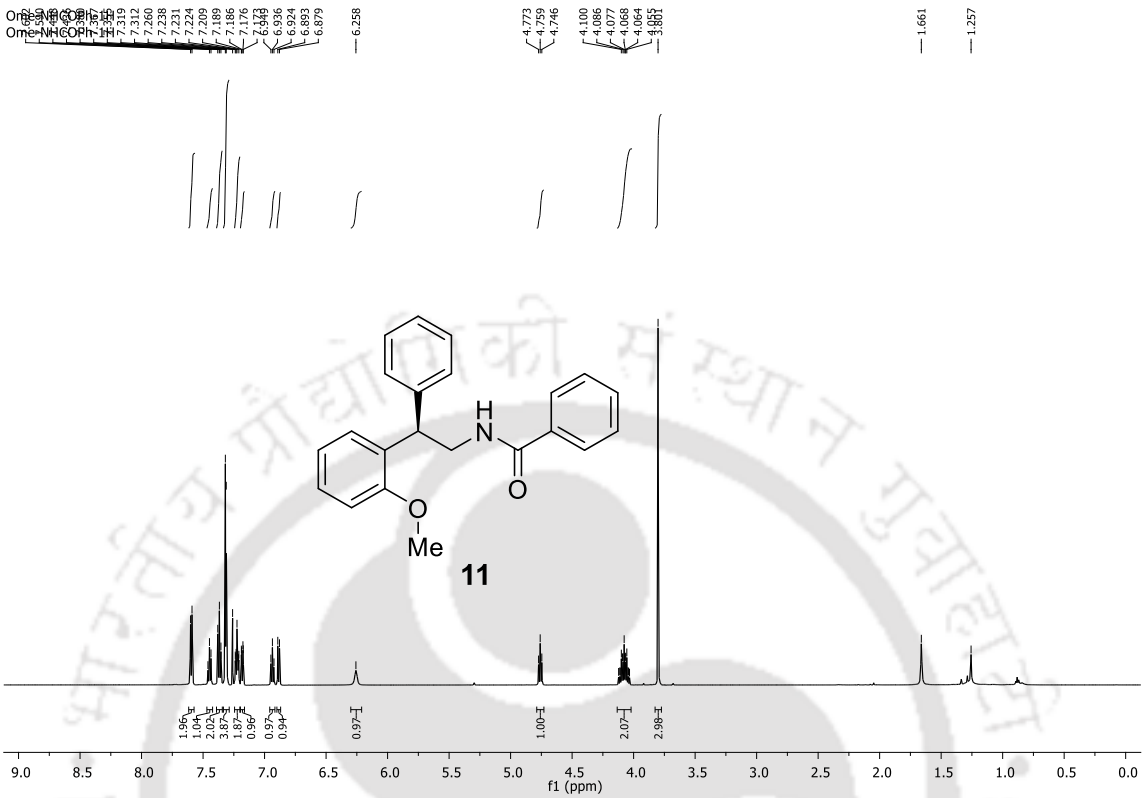


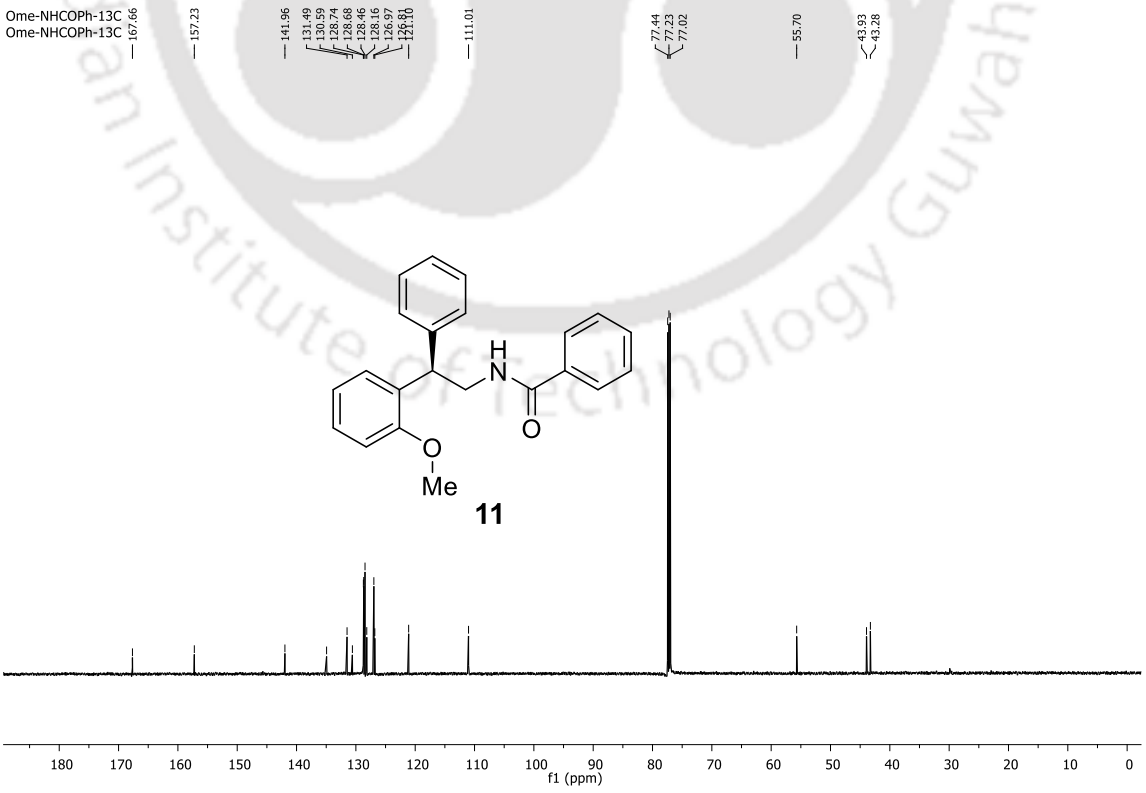
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	28.72	384.8009	50.1418549	464.4684	n.a.
2	b	31.42	382.624	49.8581451	391.378	n.a.

O-Ts-CHI-ID

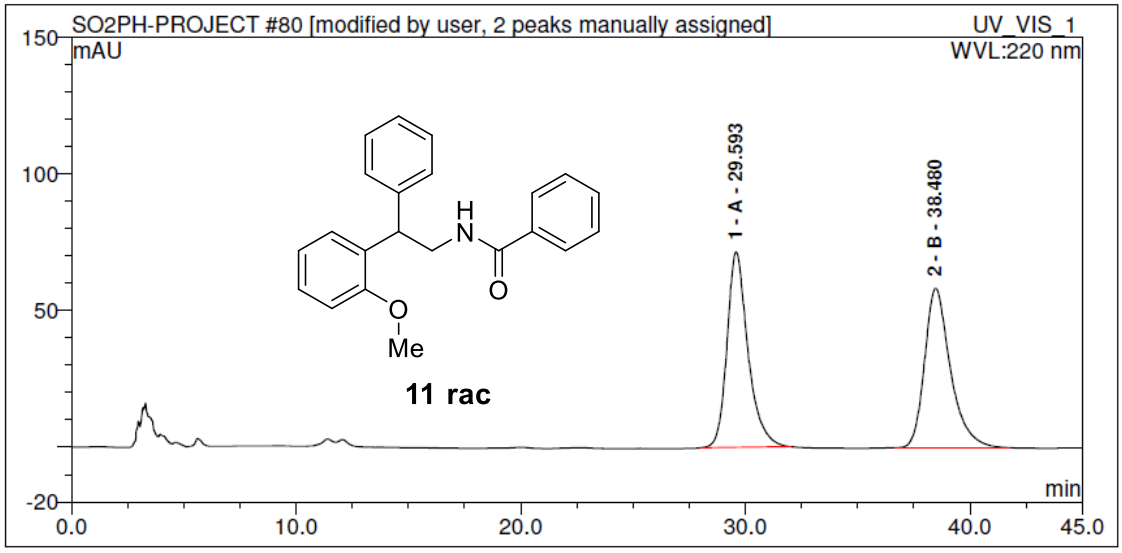


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	28.81	221.0955	98.04812259	265.4243	n.a.
2	b	31.74	4.401	1.95187741	5.257	n.a.



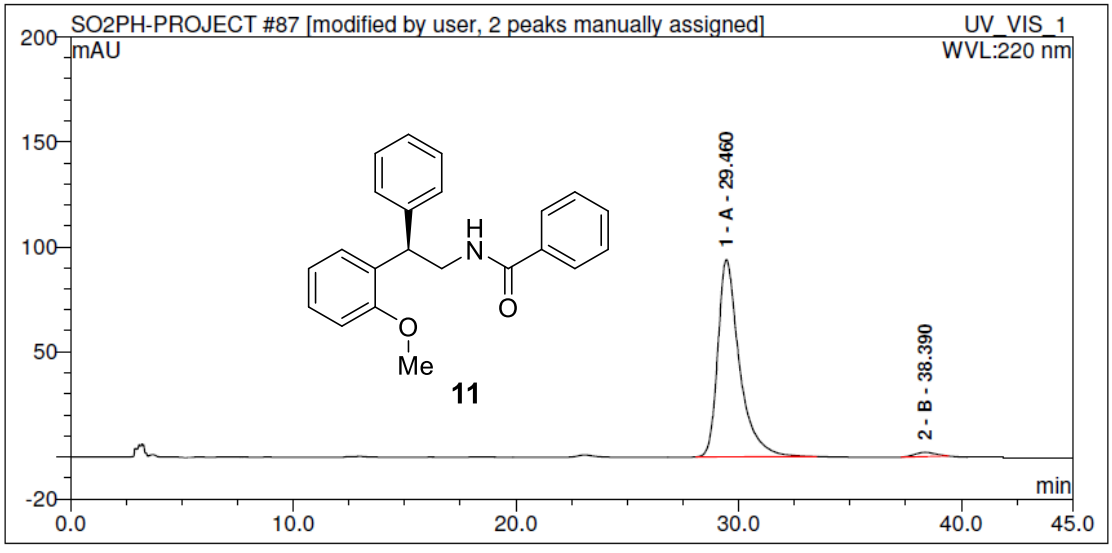


PH-OMe-NHCOPH-R-IA



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	29.59	77.61835	49.92276644	71.52753	n.a.
2	B	38.48	77.859	50.07723356	58.327	n.a.

PH-OMe-NHCOPH-CHI-IA

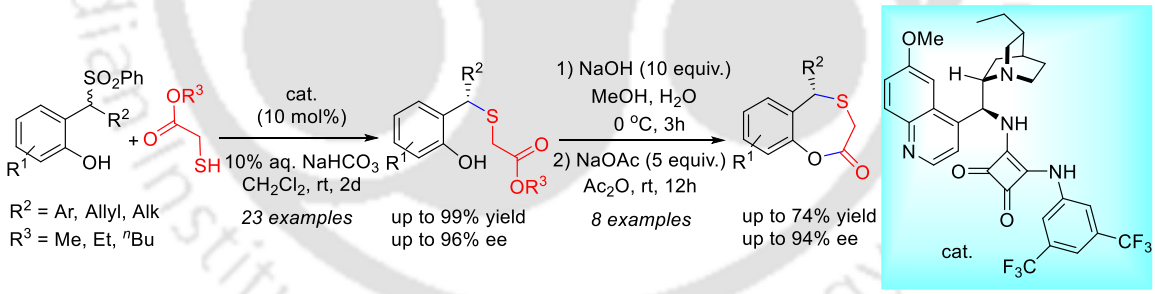


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	29.46	105.8125	98.0429051	93.94966	n.a.
2	B	38.39	2.112	1.957094903	2.017	n.a.

Organocatalytic Asymmetric Addition of Thioglycolates to ortho-Quinone Methides: A Route to 5-Substituted-5H-benzoxathiepine-2(3H)-ones[*]

Abstract:

The first enantioselective synthesis of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones have been described. Herein, 2-sulfonylmethyl phenols and thioglycolates were engaged as the reaction partners. The desired thia Michael products were obtained *via* bifunctional squaramide catalyzed conjugate addition reaction to *in situ*-generated *ortho*-quinone methides under oil/water biphasic conditions. Then basic hydrolysis followed by cyclization of thia Michael adducts led to the formation of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones. Broad scope and moderate to high enantioselectivities were observed for both products. In addition, few important synthetic transformations have been illustrated to show the potential of this method.

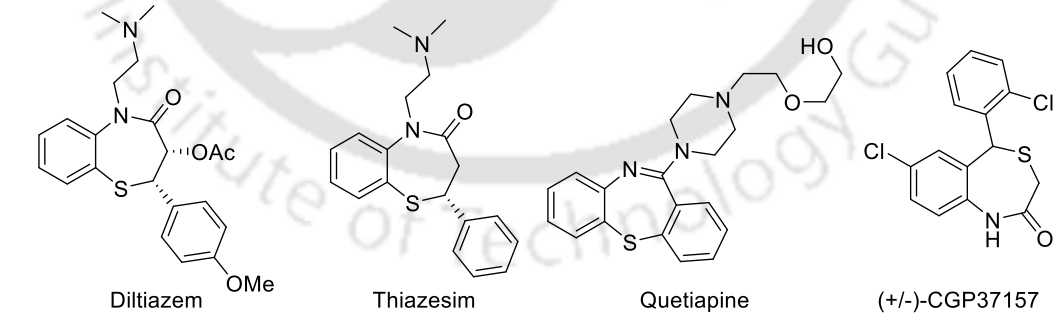


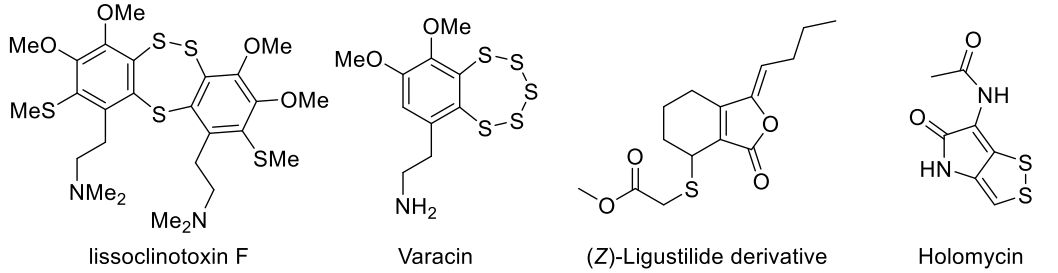
[*]Gharui, C.; Prakash, S.; Chopra, D.; Pan, S. C. *Org. Biomol. Chem.* **2020**, *18*, 2828.

4.1. Introduction:

Small heterocyclic scaffolds are responsible in showing important functions in the living processes.[1] Sometimes, they have been identified as new therapeutic and drug candidates.[2] Also, it has been observed that more than 80% of top small molecule drugs contain minimum one heterocyclic motif in their structures.[2c] Thus in modern era, synthesis of heterocycles has become an attractive goal to the chemists.

1,5-Benzothiazepinones[3a] are the imperative class of molecules having significant biological[3b-3e] and medicinal activities (Figure 1). For example, diltiazem[4] is a well-known drug for angina-relieving calcium channel blocker and coronary vasodilator. Thiazesim[5] is an another representative 1,5-benzothiazepinone drug used as an antidepressant agent. Quetiapine[6] is responsive towards antipsychotic activity. Generally, it is highly beneficial in the treatment of bipolar disorder, schizophrenia and other depressive disorders. (+/-)-CGP37157 is one of the 1,4-benzothiazepin-2-one class of molecule which have been testified to inhibit the mitochondrial sodium-calcium exchanger activity.[7] Also, sulphur containing large ring heterocycles widely exist in many natural products (Figure 1). For instance, lissoclinotoxin F is a cytotoxic alkaloid shows action against the Chinese hamster V79 and HL-60 cell lines.[8] One more natural product, varacin[9] exhibits antifungal, antibacterial and antitumor activities.





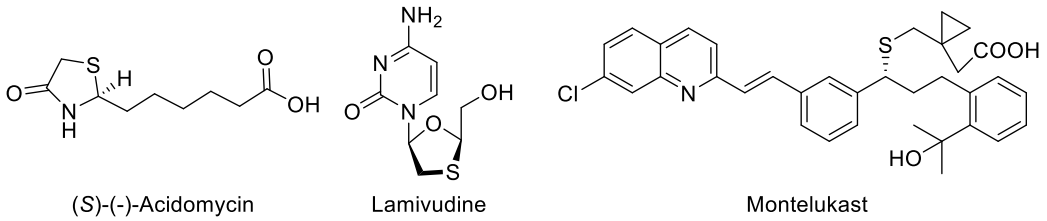


Figure 1. Sulfur containing representative 1,5-benzothiazepine drugs and bioactive natural products.

Besides, alkyl thioglycolates are the potent nucleophiles and have been successfully incorporated in many bioactive natural products and drug molecule synthesis (Figure 1). Such as, (*Z*)-Ligustilide having methyl thioglycolate motif shows antiviral and antimicrobial activities.[10] Similarly, holomycin is an antibiotic which could be constructed from simple precursors like 4-methoxy acetophenone and methyl thioglycolate by Ellis's method.[11] Furthermore, (*S*)-acidomycin is another sulfur containing natural product possessing versatile antimicobacterial property.[12] Lamivudine is a renowned drug commonly used in the medication of HIV.[13] Also, montelukast, a popular anti allergic drug possess chiral carbon-sulfur (C-S) motif in their structural entity.[14]

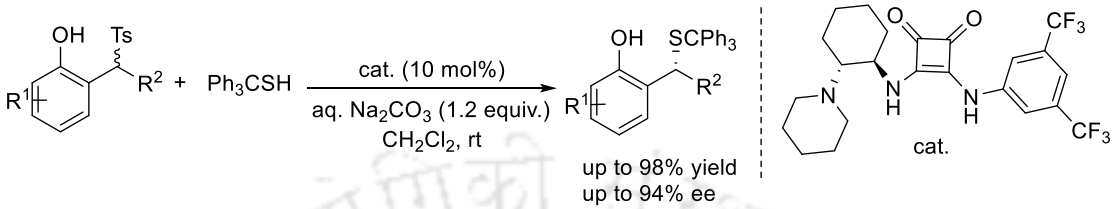
Thus owing to divergent applications of sulfur based natural products and drug molecules, many scientists enthusiastically indulged their interest in sulfur heterocyclic framework syntheses. In particular, construction of sulfur containing seven membered chiral heterocycles are quite challenging. Therefore, it is highly essential to develop synthetic methodologies for the efficient synthesis of natural product like or active drug like small molecules.

ortho-Quinone methides (*o*-QMs) are the essential reactive intermediates in organic synthesis. In addition to the hetero Diels-Alder, electrocyclization, domino/acyl transfer type reactions, *in situ*-generated *o*-QMs were elegantly employed in many bifunctional organocatalyst mediated enantioselective 1,4-conjugate addition reactions. Among them, catalytic asymmetric thiolation reactions are quite interesting.

4.2.1. Previous reports on asymmetric thiolation employing *o*-QMs:

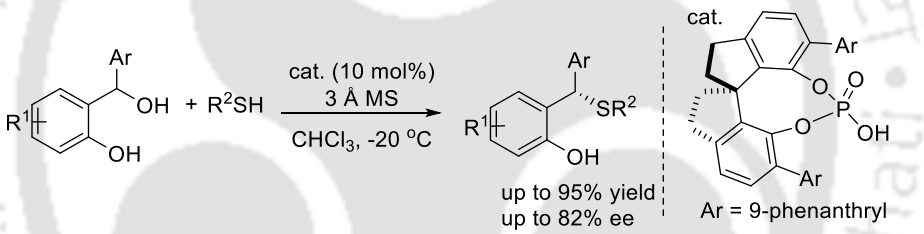
Li and co-workers described cyclohexyl diamine derived squaramide catalyzed enantioselective thiolation of trityl thiol to *in situ*-generated *ortho*-quinone methides

(Scheme 1).[15] Optically active benzyl mercaptan derivatives were furnished with high yields and excellent enantioselectivities. Surprisingly, linear thiols other than trityl one delivered the expected products with less enantiomeric excesses.



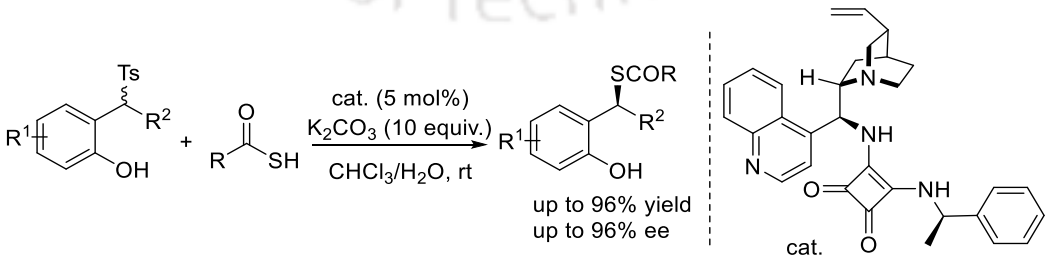
Scheme 1. Bifunctional squaramide catalyzed thiolation to *in situ*-generated *o*-QMs.

Chiral phosphoric acid catalyzed another enantioselective thiolation reaction with *in situ*-generated *ortho*-quinone methides at low temperature had been explored by Sun *et al*. (Scheme 2).[16] Although yields of the reactions were high, enantioselectivities were moderate.



Scheme 2. Chiral phosphoric acid catalyzed thiolation to *in situ*-generated *o*-QMs.

Recently, Xu group reported 1-phenylethan-1-amine and cinchonidine amine derived bifunctional squaramide catalyzed enantioselective conjugate addition of thiocarboxylic acids to *in situ*-generated *ortho*-quinone methides (Scheme 3).[17] With 5 mol% catalyst loading, optically active benzyl mercaptans were obtained with satisfactory results in terms of yield and ee.



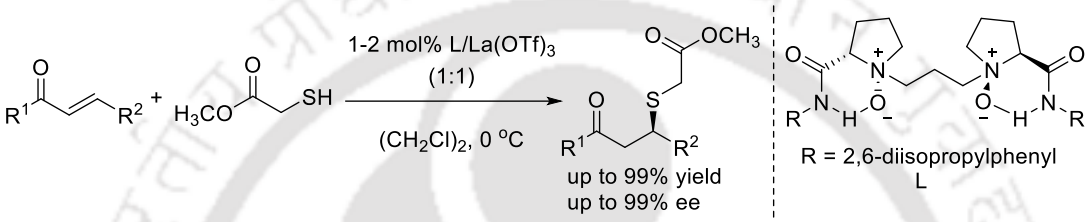
Scheme 3. Enantioselective thiocarboxylic acid addition to *in situ*-generated *o*-QMs.

In this regard, sulfur bearing other reactants such as alkyl thioglycolates were significantly

engaged in several metal-ligand catalyzed, enzyme-catalyzed and bifunctional organocatalyzed asymmetric conjugate addition/cyclization reactions which have been shown in Section 4.2.2.

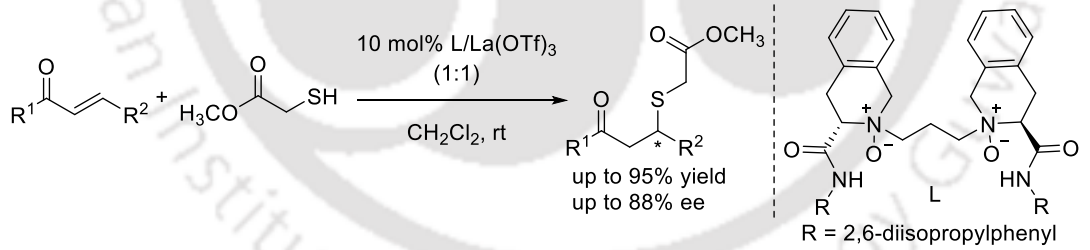
4.2.2. Previous reports on asymmetric thiolation employing alkyl thioglycolates:

Feng group demonstrated chiral *N*,*N*′-dioxide-La(III) complex catalyzed efficient enantioselective thiolation reactions between thioglycolates and various chalcones (Scheme 4).[18] With very low catalyst loading at 0 °C temperature, the conjugate addition products were achieved in high yields and excellent enantioselectivities.



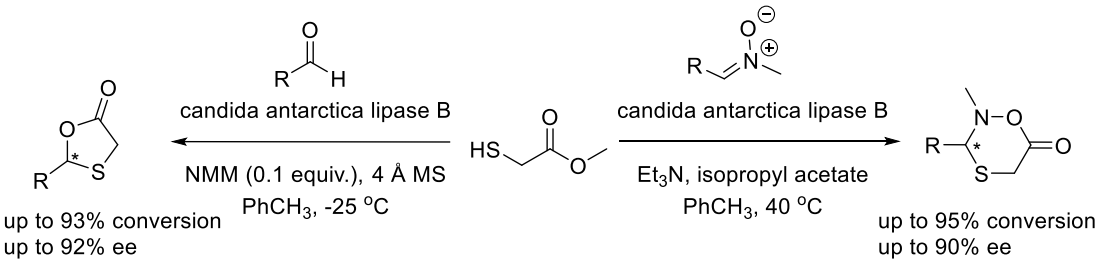
Scheme 4. Metal-ligand catalyzed asymmetric thiolation of thioglycolates to chalcones.

Later, the same chiral reaction was further extended by Kruger and Govender *et al*. under different reaction conditions using chiral tetrahydroisoquinoline *N*,*N*′-dioxide-La(III) complex (Scheme 5).[19] Herein, products were obtained in high yields and with moderate ees. Also, substrate scope was limited.



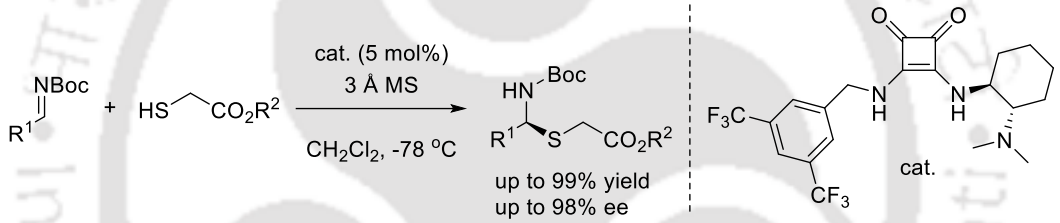
Scheme 5. Tetrahydroisoquinoline *N*,*N*′-dioxide-La(III) catalyzed reactions of thioglycolates and chalcones.

Enzyme catalyzed enantioselective reaction of methyl thioglycolate and nitrone *via* dynamic kinetic resolution was elucidated by Ramström and co-workers (Scheme 6).[20a] A variety of oxathiazinanone products were attained with moderate to good enantioselectivities. Also, the same group reported another enantioselective route for the synthesis of 1,3-oxathiolan-5-ones using methyl thioglycolate and aldehydes as the reacting components (Scheme 6).[20b]



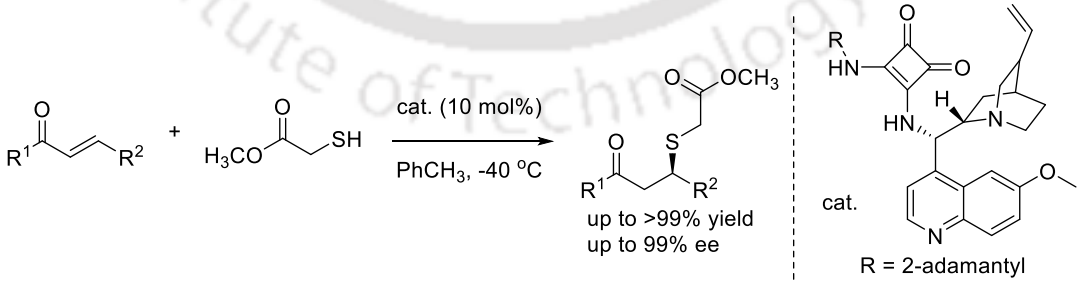
Scheme 6. Enzyme catalyzed asymmetric reactions of thioglycolate with nitrones and various aldehydes.

Wang and Li group disclosed bifunctional tertiary amine derived squaramide catalyzed an effective asymmetric approach for the synthesis of optically active *N*,*S*-acetals (Scheme 7).[21] With the aid of 5 mol% catalyst, *N*-Boc aldimines and thioglycolates reacted smoothly to deliver the desired products with moderate to high enantiomeric excesses.



Scheme 7. Bifunctional squaramide catalyzed chiral *N*,*S*-acetals synthesis.

Quinine amine derived squaramide catalyzed asymmetric addition of thioglycolate to chalcone derivatives had been described by Tanyeli *et al*. (Scheme 8).[22] With 10 mol% catalyst loading at very low temperature, the products were furnished with excellent yields as well as enantiomeric excesses.



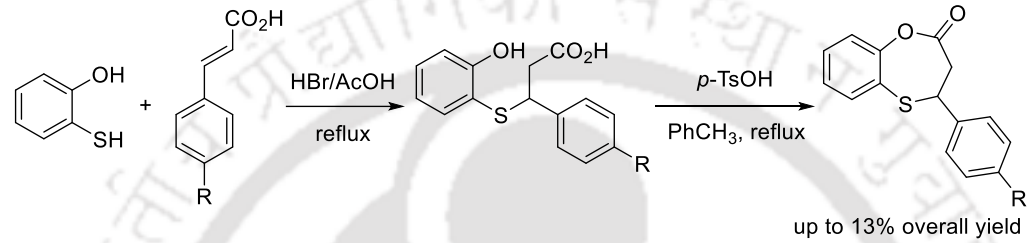
Scheme 8. Bifunctional squaramide catalyzed asymmetric thiolation of thioglycolate to chalcones.

On the other hand, 1,4-benzoxathiepin-5-ones have been recognized as interesting structural frameworks in chemical synthesis. After surveying literatures, it turned out that

there were only two reports on the achiral synthesis of 1,4-benzoxathiepin-5-one derivatives that have been discussed in Section 4.2.3.

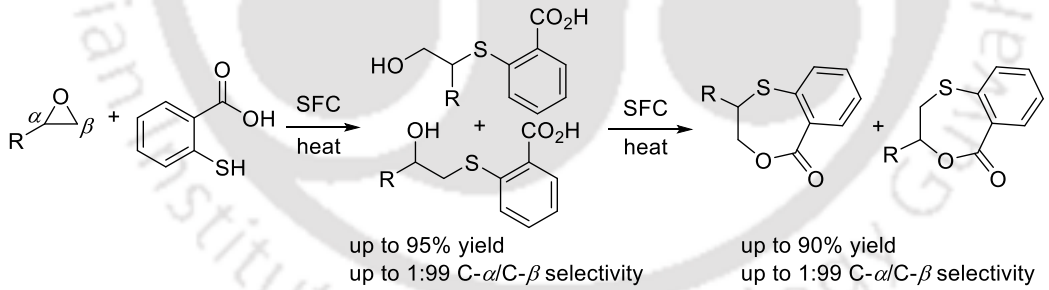
4.2.3. Previous reports on achiral synthesis of 1,4-benzoxathiepin-5-ones:

Gelebe and co-workers reported a methodology for the synthesis of benzoxathiepine analogues starting from 2-mercaptophenol and cinnamic acid derivatives (Scheme 9).[23] This is overall two steps process. The scope of the reaction was narrow and also overall yield of the reaction was very less.



Scheme 9. Synthesis of benzoxathiepines from 2-mercaptophenol and cinnamic acids.

Fringuelli group manifested an efficient strategy for the synthesis of achiral 1,4-benzoxathiepin-5-one entities from the reactions of 1,2-epoxides and thiosalicylic acid under solvent free conditions *via* thiolysis and lactonization pathway (Scheme 10).[24] Both products were achieved with high yields and having excellent C-β selectivity.

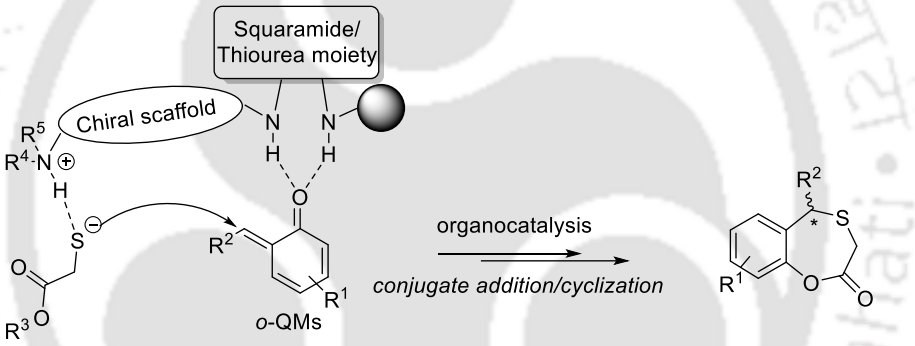


Scheme 10. Synthesis of achiral 1,4-benzoxathiepin-5-ones from 1,2-epoxides and thiosalicylic acid.

4.3. Concept:

From the literature study it has been comprehended that 1,5-benzothiazepinones have expressed numerous activities in medications as well as in natural products synthesis. On the contrary, the pharmacological properties of the isosterically related oxathiepinones was not checked, possibly because of the lack of their efficient preparation. Surprisingly, no asymmetric report was known in the synthesis of 1,4-benzoxathiepin-5-ones.

In addition, previous reports on asymmetric thiolation employing *in situ*-generated *ortho*-quinone methides were less explored. Thus realizing the potential of benzoxathiepinones in drug development, herein we like to develop the first organocatalytic asymmetric synthesis of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones utilizing thioglycolates and *in situ*-generated *ortho*-quinone methides as the suitable reaction partners. At the beginning, we assumed that *o*-QMs intermediates could be initiated *via in situ* from 2-(aryllsulfonyl)methyl phenol derivatives under basic conditions. In the next step, bifunctional thiourea/squaramide catalysts might activate the *o*-QMs intermediates and thioglycolates through the hydrogen bonding interactions. Then stereo selective thia-Michael addition followed by cyclization will deliver the desired 5-substituted-5*H*-benzoxathiepine-2(3*H*)-one products (Scheme 11).



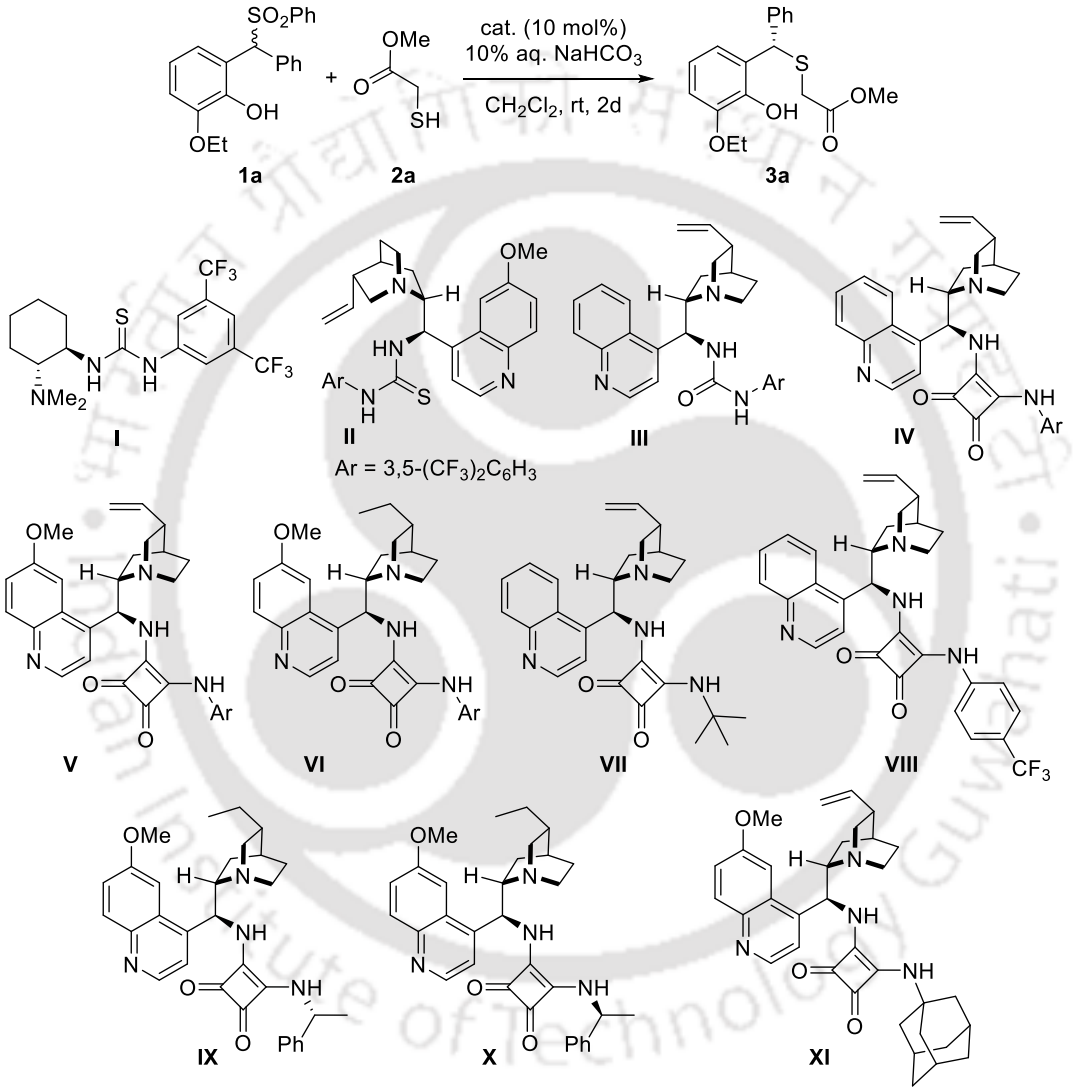
Scheme 11. Proposed route to chiral 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones.

4.4. Result and Discussion:

Accordingly, we initiated our exploration by performing a model reaction between 2-ethoxy-6-(phenyl(phenylsulfonyl)methyl)phenol **1a** and methyl 2-mercaptoacetate **2a** with Takemoto catalyst **I** and 10 % aq. sodium bi-carbonate in dichloromethane solvent at room temperature (Table 1). After stirring for two days, the desired addition product **3a** was formed in 86% yield though the enantioselectivity was less (48% ee, entry 1). Then quinidine derived bifunctional thiourea catalyst **II** was screened and the enantioselectivity got improved slightly to 61% (entry 2). Cinchonidine derived bifunctional urea catalyst was unable to alter the enantioselectivity of **3a** (entry 3). For further improvement in enantioselectivity, several cinchona alkaloids derived bifunctional squaramide catalysts were examined (Table 1, entry 4-11). Gratifyingly, cinchonidine derived bifunctional squaramide catalyst **IV** having 3,5-bistrifluoromethylphenyl group promoted the reaction

efficiently to form **3a** in 95% yield with 93% ee (entry 4). Slight higher enantioselectivity (95% ee) was achieved with catalyst **V** having quinine motif (entry 5). Interestingly, hydroquinine derived squaramide catalyst **VI** delivered the product **3a** with the same enantioselectivity (95%) and along with a slight higher yield i.e. 96% (entry 6).

Table 1. Catalyst screening



entry[a]	catalyst	yield (%)[b]	ee (%)[c]
1	**I**	86	48
2	**II**	90	61
3	**III**	84	60

4	**IV**	95	93
5	**V**	94	95
6	**VI**	**96**	**95**
7	**VII**	90	74
8	**VIII**	95	91
9	**IX**	88	78
10	**X**	86	79
11	**XI**	82	79

[a]All reactions were carried out with 0.05 mmol of **1a** with 0.125 mmol of **2a** in 1 mL CH_2Cl_2 with 25 equivalents of 10% aq. $NaHCO_3$ and 10 mol% catalyst at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

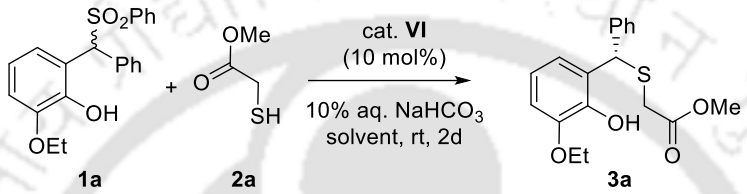
Other squaramide catalysts (**VII** to **XI**) were also screened but enantioselectivities were less compared to the catalyst **VI** (Table 1, entry 7-11). For example, cinchonidine derived catalyst **VII** having *tert*-butyl group furnished the product in 90% yield with 74% ee (entry 7). 95% yield and 91% ee were obtained when catalyst **VIII** having 4-trifluoromethylphenyl group was employed (entry 8). Hydroquinine derived catalyst **IX** bearing (*R*)-1-phenylethan-1-amine motif supplied the product with 78% ee (entry 9). Similar reaction outcome (86% yield, 79% ee) was detected for catalyst **X** having (*S*)-1-phenylethan-1-amine group (entry 10). Also, 1-adamantyl amine based squaramide catalyst **XI** provided the product with same enantioselectivity (entry 11). Finally, hydroquinine derived catalyst **VI** was turned out to be the best catalyst in terms of yield and ee (Table 1, entry 6).

4.4.1. Solvent screening:

In the next, to augment the enantioselectivity of the product **3a**, other solvents were screened but it became unfruitful (Table 2, entries 2-10). First, the effect of halogenated solvents was examined. For example, 94% and 93% ees were obtained in chloroform and 1,2-dichloroethane respectively (entries 2-3). The enantioselectivity was further decreased

to 92% in *α,α,α*-trifluorotoluene solvent (entry 4). Also, significant drop in ee (i.e. 87%) was observed in the case of carbon tetrachloride (entry 5). Then different non-halogenated solvents were tested. For instance, toluene and xylene both provided identical results (92% yield, 90% ee) (entries 6-7). Though diethyl ether gave 92% ee but lesser yield (85%) was detected (entry 8). Ethyl acetate solvent was also checked but little lower enantioselectivity (90%) was attained (entry 9). More polar solvent acetonitrile afforded the expected product with high yield (98%) and with racemization (entry 10).

Table 2. Solvent screening



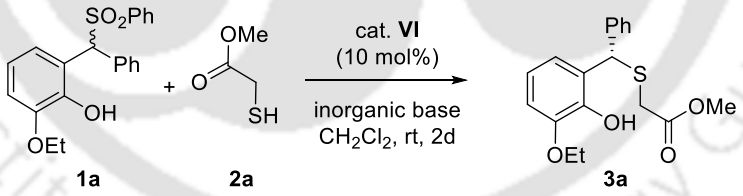
entry[a]	solvent	yield (%)[b]	ee (%)[c]
1	**CH_2Cl_2**	**96**	**95**
2	$CHCl_3$	96	94
3	$(CH_2Cl)_2$	94	93
4	$PhCF_3$	92	92
5	CCl_4	93	87
6	$PhCH_3$	92	90
7	xylene	92	90
8	Et_2O	85	92
9	EtOAc	85	90
10	CH_3CN	98	0

[a]All reactions were carried out with 0.05 mmol of **1a** with 0.125 mmol of **2a** in 1 mL solvent with 25 equivalents of 10% aq. $NaHCO_3$ and 10 mol% catalyst **VI** at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

4.4.2. Inorganic base screening:

For further enhancement in yield as well as enantiomeric excess of the reaction, other reaction parameter such as choice of inorganic base was optimized (Table 3). When the reaction was carried out using 25 equivalents of $NaHCO_3$ in absence of aqueous medium, surprisingly very less yield (20%) and moderate ee (72%) were achieved for the product **3a** (entry 1). However, promising results in terms of yield and ee were obtained when reactions were performed under oil/water biphasic medium (entries 2-7). For example, 25 equivalents of 10% aq. $NaHCO_3$ delivered the expected product with 96% yield and 95% enantiomeric excess (entry 2). Other inorganic bases like Na_2CO_3 and K_2CO_3 furnished the product with slightly lower enantiomeric excess (i.e. 94%) (entries 3-4). After finding the best inorganic base as 10% aq. $NaHCO_3$, the quantity of the base was also varied (entries 5-7). When 50 equivalents of $NaHCO_3$ was treated, the yield of the reaction remained unchanged although enantioselectivity was littlebit dropped to 92% (entry 5). Similarly, 10 equivalents of $NaHCO_3$ offered the product in 94% yield and with 94% ee (entry 6). Greater influence on yield rather than ee was observed when base quantity was reduced to 2 equivalents (entry 7).

Table 3. Inorganic base screening



entry[a]	inorganic base (equiv.)	yield (%)[b]	ee (%)[c]
1	$NaHCO_3$ (25)	20	72
2	**10% aq. $NaHCO_3$ (25)**	**96**	**95**
3	10% aq. Na_2CO_3 (25)	94	94
4	10% aq. K_2CO_3 (25)	96	94
5	10% aq. $NaHCO_3$ (50)	96	92

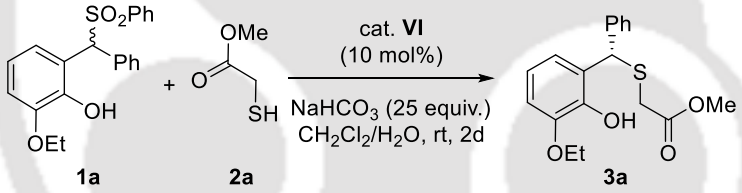
6	10% aq. $NaHCO_3$ (10)	94	94
7	10% aq. $NaHCO_3$ (2)	84	94

[a]All reactions were carried out with 0.05 mmol of **1a** with 0.125 mmol of **2a** in 1 mL CH_2Cl_2 and 10 mol% catalyst **VI** at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

4.4.3. Concentration screening:

After catalyst, solvent and inorganic base optimization, other parameter such as effect of concentration of the starting materials was thoroughly screened by changing the amount of dichloromethane and water content at different ratio (Table 4, entries 1-6). Herein, concentration had no pronounced effect on the enantioselectivity of the reaction although yield was slightly effected. The best optimum result (96% yield, 95% ee) was found when ~ 0.025 M concentration of **1a** was maintained using 1:1 mixture of dichloromethane and water (entry 3).

Table 4. Concentration screening



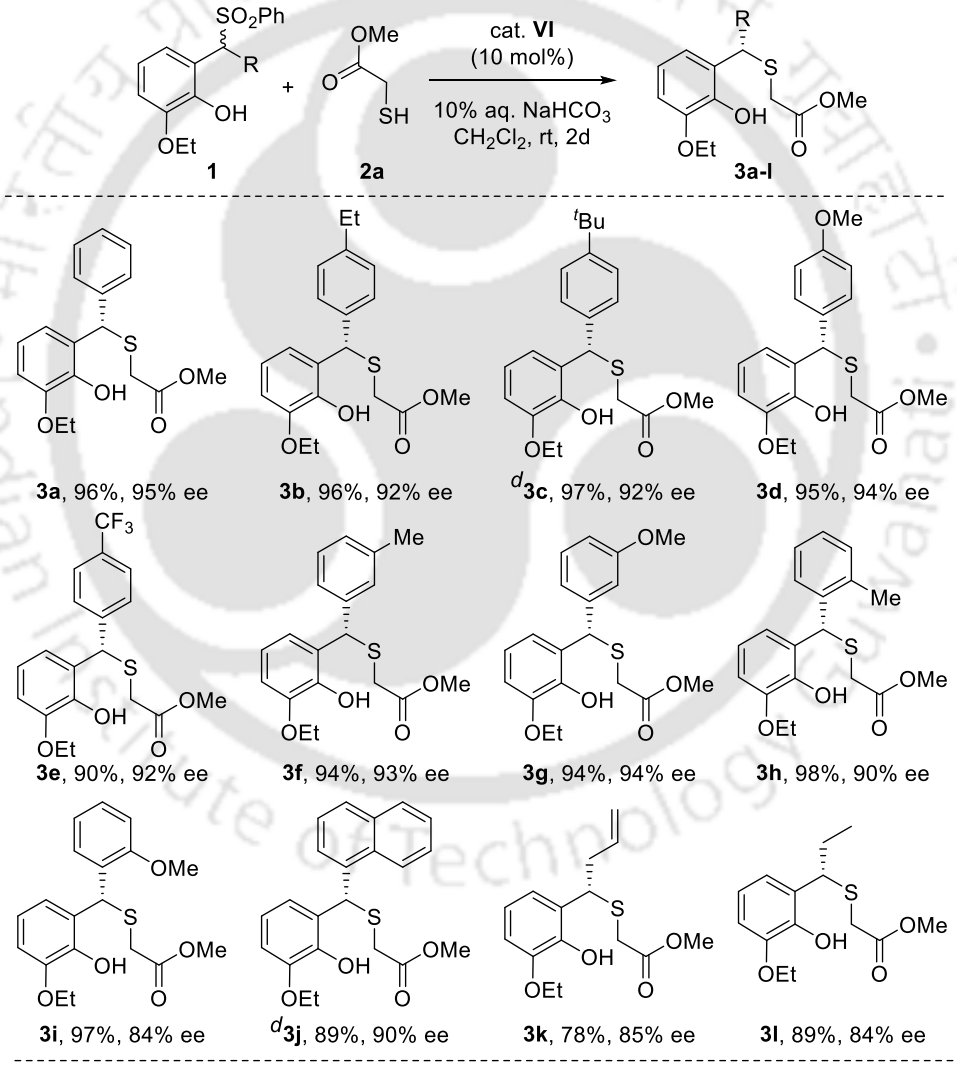
entry[a]	CH_2Cl_2/H_2O (mL)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2/H_2O (0.25/0.25)	89	95
2	CH_2Cl_2/H_2O (0.5/0.5)	94	95
3	**CH_2Cl_2/H_2O (1/1.05)**	**96**	**95**
4	CH_2Cl_2/H_2O (1/0.5)	92	95
5	CH_2Cl_2/H_2O (1/0.25)	88	95
6	CH_2Cl_2/H_2O (0.25/1)	92	94

[a]All reactions were carried out with 0.05 mmol of **1a** with 0.125 mmol of **2a** under biphasic conditions using 10 mol% catalyst **VI** and 25 equivalents of $NaHCO_3$ at room temperature. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

4.4.4. Substrate scope:

After finding the optimized conditions, the generality and scope of the reaction was investigated. At the beginning, the scope of 2-ethoxy-6-sulfonylmethylphenols with different *β*-aryl substituents was studied and gratifyingly, good to excellent results were obtained (Table 5). Initially, different *para*-substitutions on the aryl group were investigated and delightfully excellent results were achieved. For example, same 92% ee

Table 5. Scope of 2-ethoxy-6-sulfonylmethylphenols with different *β*-substituents[a,b,c]

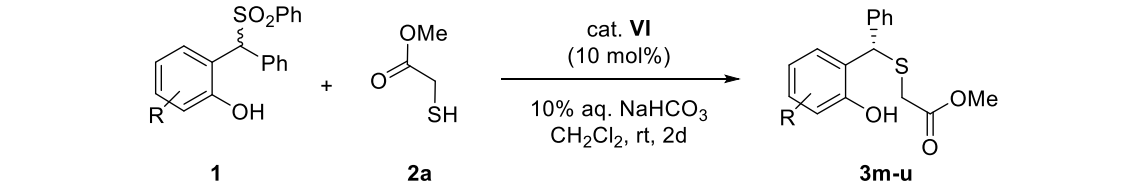


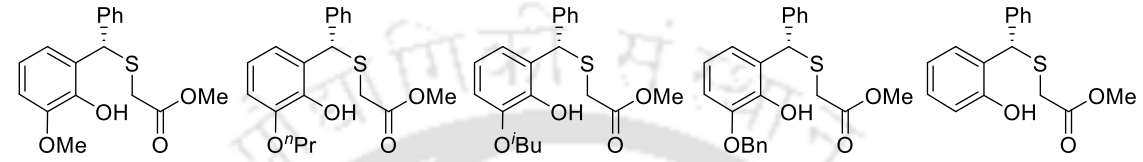
[a]All reactions were carried out with 0.1 mmol of **1** with 0.25 mmol of **2a** and 25 equivalents of 10% aq. $NaHCO_3$ in 2 mL dichloromethane. [b]Isolated yield after silica gel column chromatography. [c]Determined by chiral HPLC using stationary phase chiral column. [d]1.5 equivalents methyl 2-mercaptoacetate was used for to ease the purification.

was obtained for products **3b** and **3c** having 4-methyl and 4-^{t}butyl substitutions respectively. Slight better result was detected with *para*-anisyl substituted phenol **1d** and the product **3d** was isolated in 95% yield and with 94% ee. Phenol **1e** having 4-CF_3 group could also be employed in the reaction, and delivered product **3e** in excellent yield (90%) as well as enantiomeric excess (92%). Then *meta*-substitutions on the *β*-aryl group was checked and here also excellents results were observed in terms of yield and ee. For instance, product **3f** having 3-tolyl motif was isolated with 94% yield and 93% ee. The same yield with littel higher ee (94%) was detected for **3g** having *meta*-methoxy phenyl group. Also, *ortho*-substitutions on *β*-aryl fragment of the phenols **1h**-**1i** were well tolerated. Product **3h** having 2-methyl substitution was obtained in 98% yield and 90% ee. However significant decrease in enantioselecitivity was observed for **3i** having 2-anisyl substitution. Phenol **1j** having 1-naphthyl group also participated in the reaction delivering product **3j** in satisfactory enantioselectivity (90%). Finally, aliphatic such as *β*-allyl and *β*-ethyl group containing phenols **1k**-**1l** were prepared and employed in the reaction. To our delight, the reactions progressed efficiently to deliver the corresponding products **3k** and **3l** in acceptable yields and enantioselectivities.

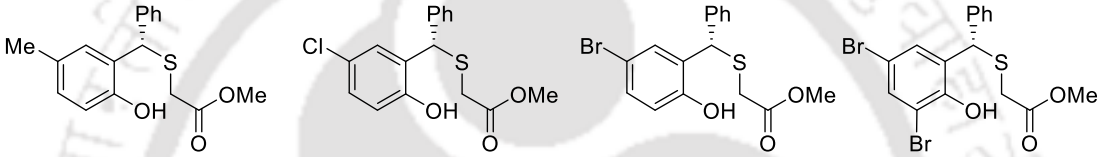
Next, the scope of the reaction was further extended by varying the phenolic component of 2-sulfonylmethyl phenols (Table 6). Initially the alkoxy group at the 2-position was varied. Gratifyingly, excellent enantioselectivity (i.e. 96%) was obtained when ethoxy group was replaced with methoxy group. Also similar enantioselectivity was achieved with *n*-propoxy group. Then isobutoxy and benzyloxy groups were screened. Interestingly, in both cases, the same enantioselectivity (90%) was obtained. Then we have employed sulfonylmethylphenol **1q** without alkoxy group. In this case, the product **3q** was obtained in 95% yield with 88% ee (Table 6). Inspired by this result, other substitutions were also checked and good results were obtained. In fact, product **3r** having 4-methyl substitution was isolated in high enantioselectivity (90% ee). 4-Halo substitutions were also tolerated though slight less enantioselectivities were obtained for product **3s** and **3t**. Finally, 4,6-dibromo sulfonylmethylphenol **1u** was prepared and then employed in the reaction (Table 6). Though high yield (99%) was observed for product **3u** but moderate enantioselectivity (62%) was detected.

Table 6. Scope of 2-sulfonylmethylphenols with different phenolic substitutions[a,b]





3m, 94%, 96% ee **3n**, 83%, 94% ee **3o**, 86%, 90% ee **3p**, 81%, 90% ee **3q**, 95%, 88% ee

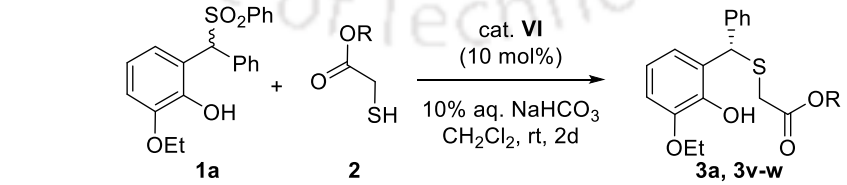


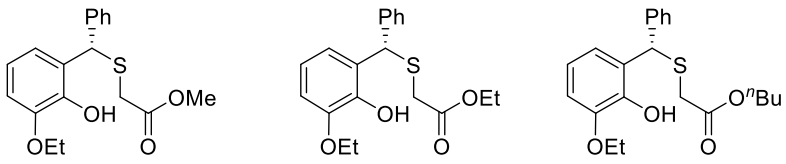
3r, 89%, 90% ee **3s**, 98%, 84% ee **3t**, 98%, 82% ee [c]**3u**, 99%, 62% ee

[a]All reactions were carried out with 0.1 mmol of **1** with 0.25 mmol of **2a** and 25 equivalents of 10% aq. $NaHCO_3$ in 2 mL dichloromethane. [b]Isolated yield after silica gel column chromatography and enantioselectivity was determined by chiral HPLC using stationary phase chiral column. [c]1.5 equivalents methyl 2-mercaptoacetate was used to ease the purification.

Then the ester group in alkyl thioglycolate **2** was varied (Table 7). Product **3v** was obtained by mixing ethylthioglycolate **2b** with **1a** under the standard reaction conditions. In this case, 92% yield and 92% enantioselectivity were attained. Same enantioselectivity but higher yield (98%) was obtained when *n*-butyl thioglycolate **2c** was employed.

Table 7. Scope of thioglycolates[a,b]

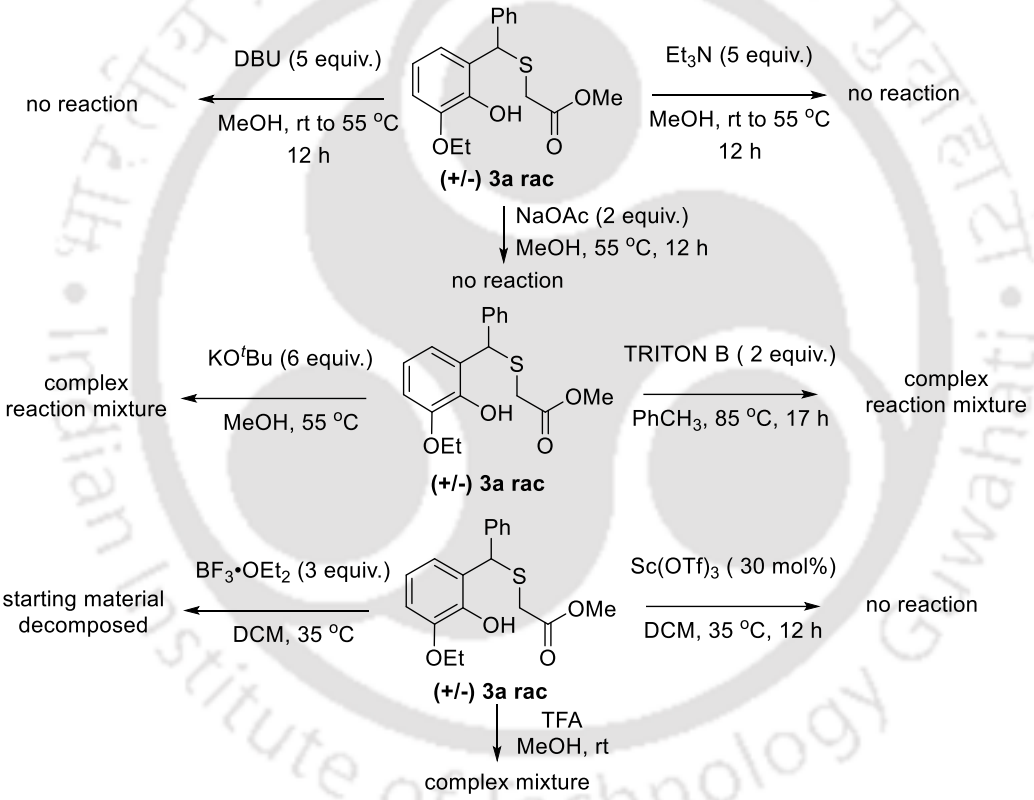




3a, 96%, 95% ee **3v**, 92%, 92% ee **3w**, 98%, 92% ee

[a]All reactions were carried out with 0.1 mmol of **1a** with 0.25 mmol of **2** and 25 equivalents of 10% aq. $NaHCO_3$ in 2 mL dichloromethane. [b]Isolated yield after silica gel column chromatography and enantioselectivity was determined by chiral HPLC using stationary phase chiral column.

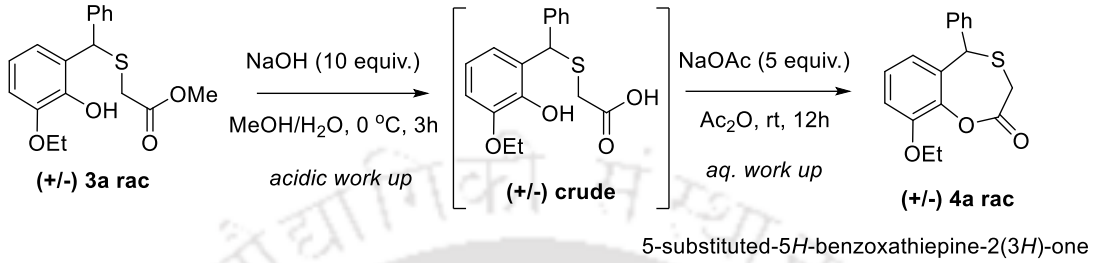
After surveying the potential application of benzoxathiepine-2(3*H*)-one derivatives, next attention was to cyclize the products **3** to corresponding 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones **4**. In this regard, several attempts were taken for lactonization by choosing achiral **(+/-)-3a** as the starting material (Scheme 12). Organic bases like Et_3N, TRITON B and DBU were not helpful for such transformation. Other inorganic bases like NaOAc, KO^{t}Bu were not able to cyclize the racemic substrate **3a**. Treatment of TFA was also unfruitful.



Scheme 12. Unsuccessful attempts for cyclization.

Interestingly, when **(+/-)-3a** was treated with sodium hydroxide in methanol with a slight amount of water, an acid was formed which was directly reacted with sodium acetate/acetic anhydride to afford the cyclized product (+/-)-5-phenyl-5*H*-benzoxathiepine-2(3*H*)-one **4a** (Scheme 13). For better conversion of **(+/-)-4a**, amount of NaOH, effect of water and reaction time in the ester hydrolysis step was examined. When 3 equivalents of base were

used, reaction conversion was low even after 3 hours. The best optimum result (overall 51% yield) was obtained when 10 equivalents of NaOH in methanol/water at 0 ^{o}C for 3 hours was employed (Scheme 13).

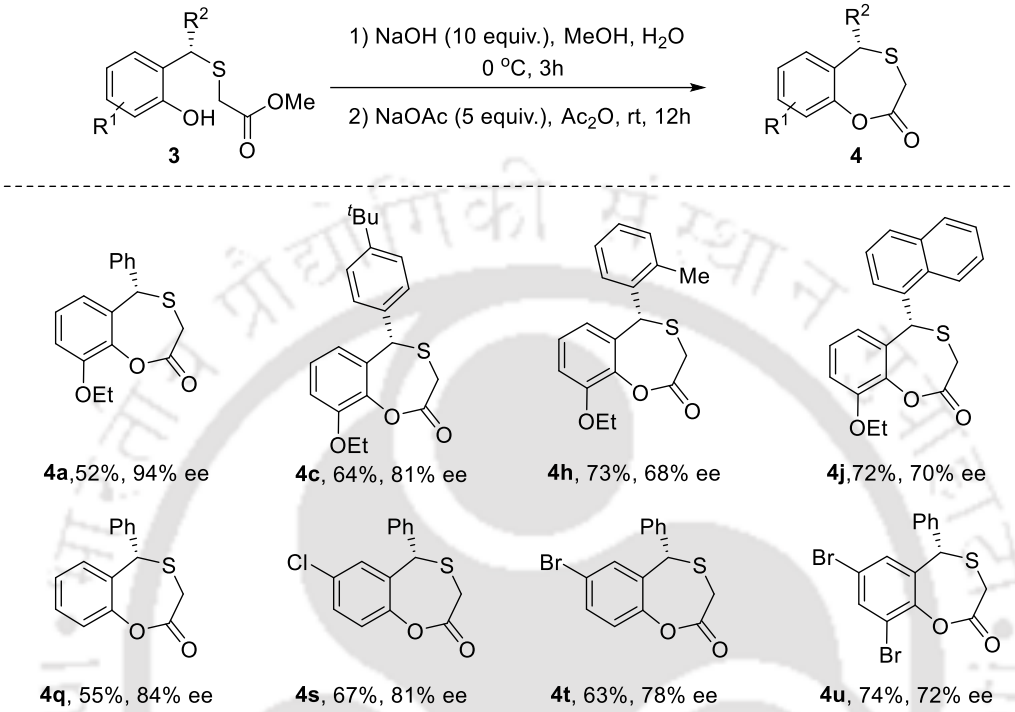


Scheme 13. Cyclization of **(+/-)-3a** to **(+/-)**-5-substituted-5*H*-benzoxathiepine-2(3*H*)-one.

Once the conditions got established, chiral products **3** were converted to the corresponding 5-substituted-5*H*-benzoxathiepine-2(3*H*)-one products **4** (Table 8). For example, product **4a** was isolated in 52% yield and with retention of enantiomeric excess. Remarkably, the yield got improved to 75% when **3w** was converted to **4a** under same conditions. Gratifyingly, here also the enantioselectivity for **4a** was preserved. Similarly, **3c** was converted to **4c** and here the enantioselectivity dropped to 81% ee from 92% ee. Then **3h** and **3j** were converted to **4h** and **4j** (Table 8). Though acceptable yields were observed, the enantioselectivities were moderate i.e. 68% ee and 70% ee respectively. However, in such cases a decrease in enantioselectivity was observed possibly due to partial racemization *via* retro Michael decomposition of thia-Michael products **3** during basic hydrolysis. Erosion in optical purity was higher for **4h** and **4j** compared to **4c** may be because of enhanced leaving ability of thioglycolate favored by +R effect as well as the steric interaction between *ortho*-substituted *β*-aryl motif and sulfur atom. Then the compounds having variations on the phenolic ring were checked and here also similar observations were detected. For example, compound **4q** was obtained in 55% yield and 84% ee. In this case, a drop of 4% ee from that of **3q** was observed. To examine the yield and enantioselectivity of **4q**, compound **3q** was treated with 2 equivalents of base (instead of 10 equivalents) but conversion of ester to acid was less although ee was similar. Then, different halo substituted products were converted to 5-substituted-5*H*-benzoxathiepine-2(3*H*)-one **4s**-**4u** (Table 8). For instance, product **4s** having chloro substituent was obtained in 67% yield and 81% ee. However, slight lower yield (i.e. 63%) and moderate enantioselectivity (78%) was detected

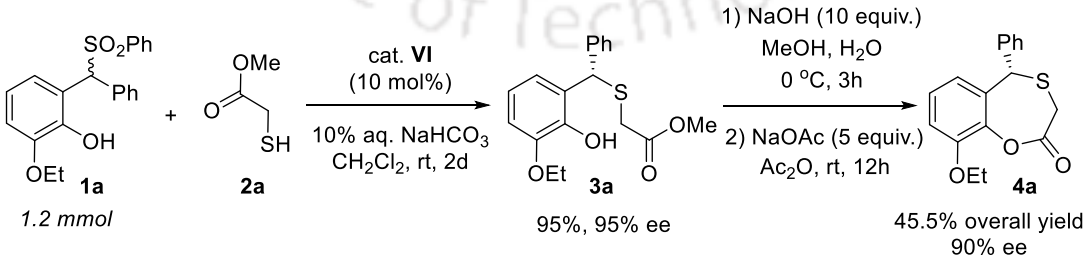
for the product **4t** containing bromo substituent. Also, dibromo substituted product **4u** was isolated in 74% yield and 72% ee.

Table 8. Scope of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones.



4.4.5. Scale-up experiment:

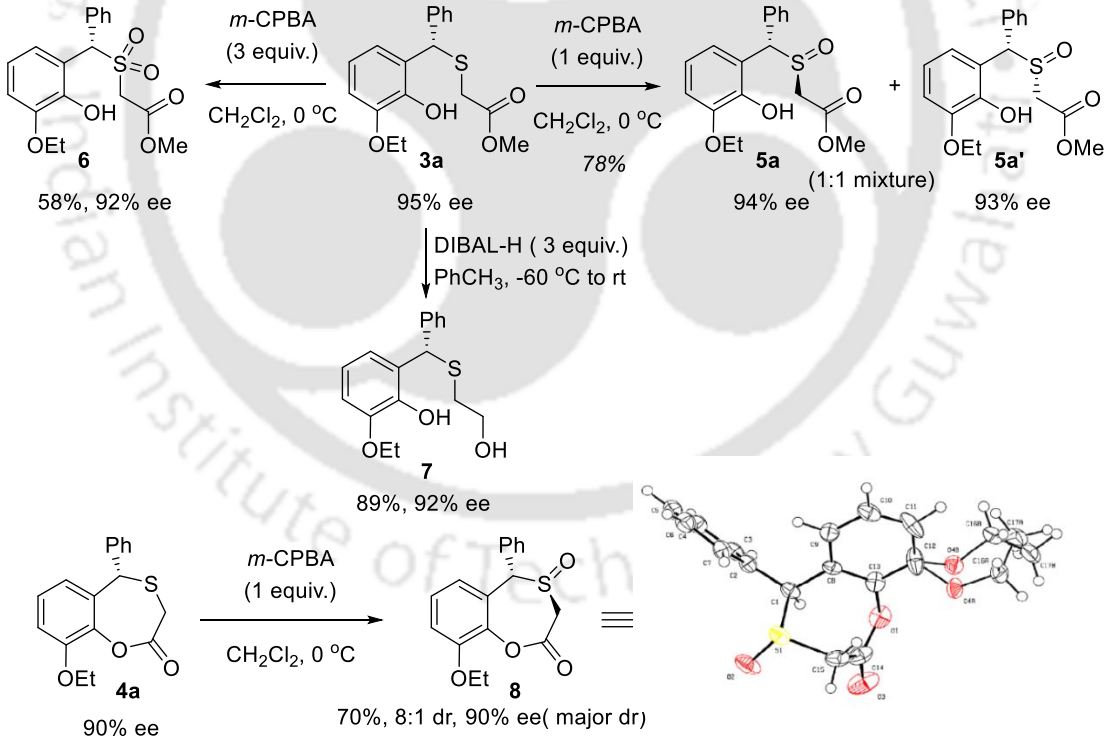
Then a scale-up experiment was carried out with 1.2 mmol of **1a** and 3 mmol of **2a** (Scheme 14). Gratifyingly, under the same reaction conditions and after stirring for 2 days with catalyst **VI**, the desired product **3a** was obtained in 95% yield with 95% ee. After this, the isolated **3a** (1.14 mmol) was further cyclized to deliver **4a** in 45.5% overall yield and 90% ee.



Scheme 14. Scale-up experiment.

4.4.6. Synthetic applications:

The synthetic potential of this method was demonstrated by performing few reactions on **3a** and **4a** (Scheme 15). Thus first **3a** was oxidized with 1 equivalent of *m*-CPBA. This led to the formation of diastereomeric sulfoxides **5a** and **5a'** as 1:1 mixture and gratifyingly the enantiomeric excesses were preserved. On the other hand, sulfone **6** was formed in 58% yield when **3a** was treated with 3 equivalents of *m*-CPBA. Here also, the enantioselectivity did not alter much. Then **3a** was reduced with DIBAL-H. This resulted in the formation of alcohol **7** in 89% yield with almost no erosion in enantioselectivity. 5-Phenyl-5*H*-benzoxathiepine-2(3*H*)-one **4a** was also converted to sulfoxide **8** *via* treatment with 1 equivalent *m*-CPBA. Delightfully, the diastereoselectivity was high and preservation of enantiopurity was observed in the major diastereomer. Also, the structure of **8** was unambiguously confirmed by X-ray crystallography.[25]

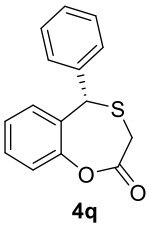


Scheme 15. Synthetic applications.

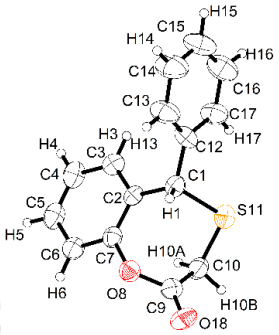
4.4.7. Absolute configuration of 4q:

The absolute structure of product **4q** was determined by X-ray crystallography[26] and was

determined to be (*S*). The configuration of other products is expected to be same by analogy.

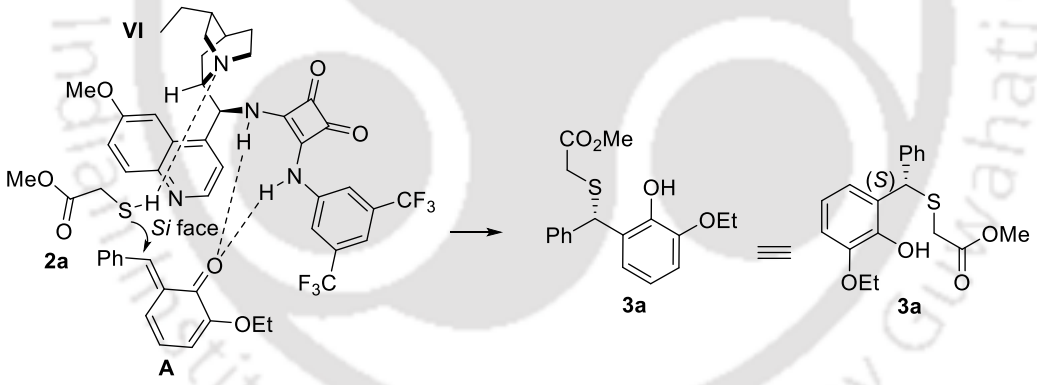


4q



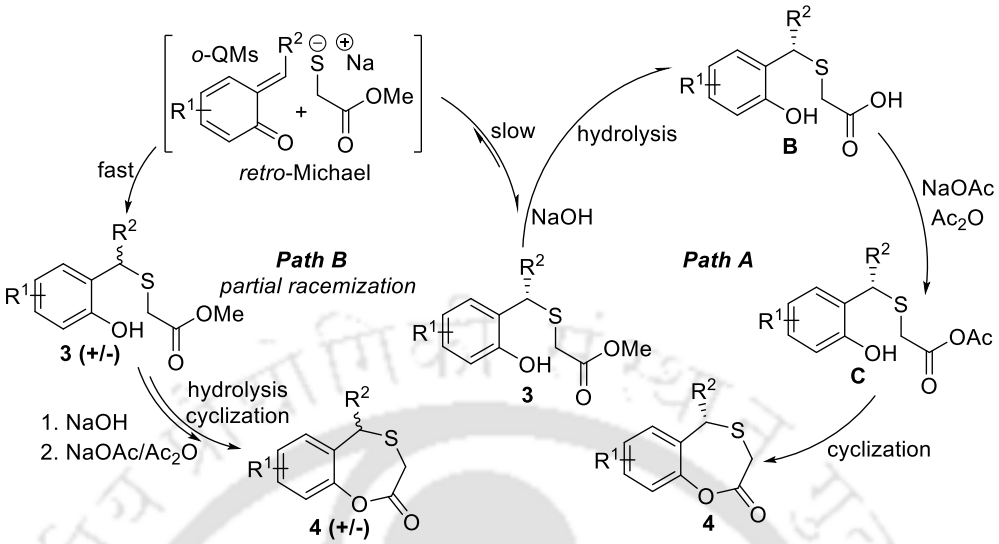
4.4.8. Proposed mechanism:

A plausible TS has been drawn in Scheme 16 to explain the stereochemistry of the product. It is expected that *ortho*-quinone methide **A** will be formed from **1a** after treatment with 10% aq. $NaHCO_3$. The catalyst **VI** activates both **A** and thioglycolate **2a**. Since the *Re* face of *ortho*-quinone methide **A** is blocked by the squaramide motif of the catalyst, the addition of **2a** takes place from the *Si* face to deliver the product **3a** (Scheme 16).



Scheme 16. The proposed TS.

In the second step, at first base hydrolysis of **3** provides acid **B**. Then cyclization with sodium acetate/acetic anhydride generates 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones **4** *via* the intermediacy of **C** (path A, Scheme 17). Beside this, stronger hydroxide base also competes to form *o*-QMs *via* retro-Michael reaction and hence the chiral product **3** is partially racemized (path B, Scheme 17). Thus, in few cases, a drop in the overall enantioselectivity was observed for the final product **4**.



Scheme 17. Proposed mechanism for product **4**.

4.5. Conclusion:

In summary, an organocatalytic asymmetric addition of thioglycolates to *ortho*-quinone methides leading to the first asymmetric synthesis of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones has been illustrated. The methodology involves bifunctional squaramide catalyzed conjugate addition to *in situ*-generated *ortho*-quinone methides followed by basic hydrolysis of ester motif with sodium hydroxide and then cyclization reaction with NaOAc/Ac_2O. The conjugated addition products were obtained in high yields with excellent enantioselectivities whereas there is slight erosion in enantioselectivities found in 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones. Also, the formations of sulfoxides and sulfone have been demonstrated from the conjugate addition products. Given the high medicinal significance of benzoxathiepines our products might be important in pharmaceutical industry.

4.6. Experimental section:

General Information:

All the necessary reagents were purchased from commercial suppliers with highest purity grade. They were utilized directly without further any purification. Thioglycolates **2a-c** were purchased from Sigma Aldrich and Alfa Aesar chemicals. In all cases, oven dried

glassware was used during reactions set up. For Grignard reactions in the preparation of *ortho*-hydroxybenzyl alcohols, tetrahydrofuran solvent was super dried over sodium/benzophenone. Dichloromethane solvent (required for 2-sulfonylmethylphenols preparation and *m*-CPBA oxidation reactions) was distilled over CaH_2 under argon and stored over 4 Å molecular sieves. Other solvent such as toluene was purified according to the standard procedure. Progress of the reactions was monitored by performing TLC on silica gel GF-254 using *n*-hexane/ethyl acetate as the solvent system. Every time, 60-120 mesh size silica gel was used during products purification through column chromatography. ^{1}H NMR spectra were recorded on 600 MHz spectrometer using $CDCl_3$ as reference NMR solvent. ^{13}C NMR spectra were recorded on 150 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) and coupling constants (*J*) were reported in parts per million (ppm) and Hertz (Hz) units respectively. In ^{1}H and ^{13}C NMR, chemical shift values were expressed with reference to $CHCl_3$ (δ(H), 7.26 ppm) and (δ(C), 77.23 ppm, central line of triplet). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet), dt (doublet of triplet).

High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) mode. Enantiomeric excesses were determined by HPLC analysis by comparing the spectra of racemic samples using stationary phase chiral column through the help of Dionex (Ultimate 3000) instrument.

Single-crystal X-ray diffraction data of compound **4q** were collected on a Super Nova, Single source at offset/far, Eos diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The data refinement and cell reductions were carried out by CrysAlisPro[27] at 293 K. Structure was solved by direct methods using SHELXS-97 and refined by the full matrix least squares method using SHELXL-97.[28]

Single-crystal X-ray diffraction data of compound **8** were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data collection was carried out at 100 K. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell refinement and data reduction were performed using the program SAINT.[29] The data were scaled and absorption correction performed using SADABS.[29] The structure was solved by direct methods using SHELXS-18[30] and refined by full-matrix least-squares methods based on F^2 using SHELXL-2018.[30] Melting points were noted on a Büchi Melting Point B-540 apparatus.

A. General procedure for the synthesis of 2-sulfonylmethylphenols 1a-1u:

2-Sulfonylmethylphenols **1a-1u** were prepared according to the previous known procedure.[31]

B. General procedure for the preparation of thiourea, urea and squaramide catalysts (I-XI):

Thiourea catalyst[32] (**I-II**), urea catalyst[33] (**III**) and squaramide catalysts[34] (**IV-XI**) were prepared by following the previous reported procedures.

C. General procedure for the synthesis of sulfa-Michael products 3a-3w:

In a 5 mL round bottom flask, 2-sulfonylmethylphenol **1** (0.1 mmol), alkyl thioglycolate **2** (0.25 mmol) and the catalyst **VI** (10 mol%) were mixed in 2 mL DCM solvent. Then 10% aq. $NaHCO_3$ solution (25 equivalents) was added to the reaction mixture and continued stirring for 2 days at room temperature. After completion of the reaction, it was extracted with DCM (3 times). Finally, the organic parts were concentrated in *vacuo* and the crude was purified by silica gel column chromatography using hexane/EtOAc as eluting solvent to deliver the sulfa-Michael products **3a-3w**.

D. General procedure for the synthesis of 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones 4 from sulfa-Michael products 3:

5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones **4** were synthesized from sulfa-Michael products **3** in successive two steps.

In the first step, sodium hydroxide (1 mmol) and water (60 μL) were added to a stirrer solution of compound **3** (0.1 mmol) in 1 mL MeOH at 0 ^{o}C. Then the reaction mixture was allowed to stir for 3 hours. After completion of the reaction, it was diluted with DCM and acidified with 10% aq. HCl. Thereafter, the reaction mixture was extracted with DCM (3 times) and concentrated in *vacuo*. Finally, the crude mixture was dried properly and subjected to the next step without purification.

In the second step, the crude mixture was dissolved in 0.8 mL Ac_2O. Then NaOAc (0.5 mmol) was added and continued stirring for 12 hours at room temperature. Finally, the reaction mixture was extracted with DCM, concentrated and purified by silica gel column

chromatography to obtain the desired 5-substituted-5*H*-benzoxathiepine-2(3*H*)-ones **4**.

E. General procedure for the synthesis of sulfoxides 5a/5a':[35]

To a stirred solution of compound **3a** (0.1 mmol) in 1 mL dry DCM at 0 ºC, *m*-CPBA (0.1 mmol) was added. After 1.5 hours, the reaction mixture was quenched with saturated K_2CO_3 solution. Then work up was performed using DCM. Organic parts were concentrated in *vacuo* and finally purified by silica gel column chromatography to furnish the desired sulfoxides **5a** and **5a'**.

F. General procedure for the synthesis of sulfone 6:[35]

To a stirred solution of compound **3a** (0.1 mmol) in 1 mL dry DCM at 0 ºC, *m*-CPBA (0.3 mmol) was added. Then progress of the reaction was monitored by TLC analysis. After reaction completion, the mixture was quenched with saturated K_2CO_3 solution and work up was performed using DCM. Then organic parts were concentrated in *vacuo*. Finally, it was purified by silica gel column chromatography to obtain the desired sulfone **6**.

G. General procedure for the synthesis of alcohol 7:[36]

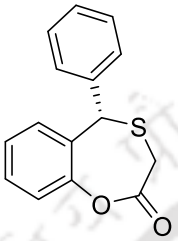
First, the compound **3a** (0.1 mmol) was dissolved in 2.5 mL dry toluene under argon. Then the whole set up was cooled to -60 ºC. After this, 0.3 mL 1 (M) DIBAL-H in cyclohexane was added dropwise to the stirring solution of **3a**. After completion of addition, the reaction was shifted to room temperature and allowed stirring for additional 2.5 hours. Thereafter, it was quenched with 0.5 mL methanol and diluted with diethyl ether. Next, the crude was extracted with diethyl ether and finally was purified by silica gel column chromatography to get the alcohol product **7**.

H. General procedure for the synthesis of sulfoxides 8:

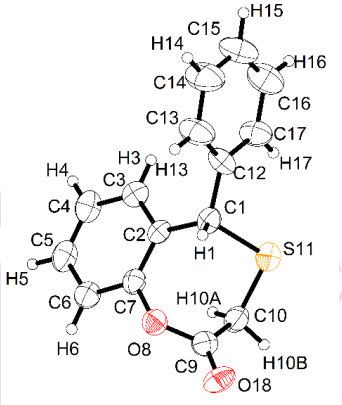
To a stirred solution of product **4a** (0.1 mmol) in 1 mL dry DCM at 0 ºC, *m*-CPBA (0.1 mmol) was added. After1.5 hours, the reaction mixture was quenched with saturated K_2CO_3 solution. Then it was extracted using DCM (3 times). The organic parts were concentrated in *vacuo* and provided diastereomeric sulfoxides **8** as white solid in pure form. Further purification by column chromatography was not required for such case. Interestingly, when

crude sulfoxides **8** was washed with cold *n*-pentane (3 mL X 2 times) diastereoselectivity of the products got significantly improved from 3:1 ratio to 8:1.

Crystal structure of compound (*S*)-5-phenyl-5*H*-benzo[*f*][1,4]oxathiepin-2(3*H*)-one, 4q:

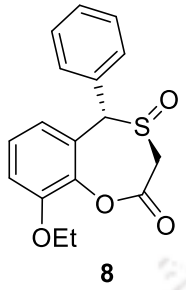


4q

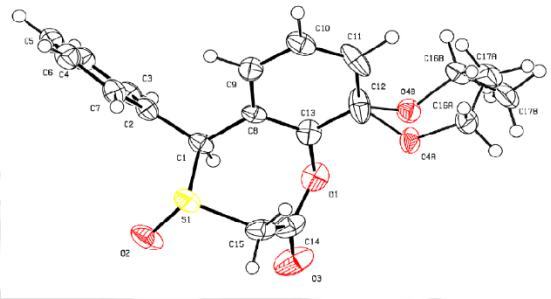


Empirical Formula	C_{15} H_{12} O_2 S
Formula weight, Fw	256.31
Crystal system	orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 7.5756(8)Å b = 8.7063(6)Å c =19.340(3)Å α = 90º , β = 90º γ = 90º
Volume, V/Å^3	1275.6(2)
Z	4
Dx, g cm-3	1.335
Mu (mm-1)	0.244
F000	536.0
Temperature, T/K	293 K
Theta(max)	25.000
Total no. of reflections	2140
Independent reflections	1132
Parameters refined	163
R (reflections)	0.0683(1132)
wR2 (reflections)	0.1308(2140)
GOF (F^2)	1.006
CCDC No.	**1969971**

Crystal structure of compound (4*S*,5*S*)-9-ethoxy-5-phenyl-5*H*-benzo[*f*][1,4]oxathiepin-2(3*H*)-one 4-oxide, 8:



8



Empirical Formula	$C_{17}\ H_{16}\ O_4\ S$
Formula weight, Fw	316.36
Crystal system	orthorhombic
Space group	$P2_12_12$
Unit cell dimensions	a = 7.969(3)Å
	b = 34.663(14)Å
	c = 5.361(2)Å
	$\alpha = 90^o$, $\beta = 90^o$
	$\gamma = 90^o$
Volume, V/Å^3	1480.9(10)
Z	4
Dx, g cm-3	1.419
Mu (mm-1)	0.234
F000	664.0
Crystal size/mm^3	0.234 × 0.204 × 0.086
2Θ range for data collection/°	9.164 to 59.394
Index ranges	-11 ≤ h ≤ 11, -48 ≤ k ≤ 47, -6 ≤ l ≤ 7
Temperature, T/K	100 K
Theta(max)	29.697
Reflections collected	12986
Independent reflections	3818 [Rint = 0.1470, Rsigma = 0.1607]
Parameters refined	265
R (reflections)	0.0762(2003)
wR2 (reflections)	0.1915(3818)
Largest diff. peak/hole / e Å-3	0.32/-0.54
GOF (F^2)	0.959
CCDC No.	**1984977**

4.7. References:

1. For reviews, see: (a) Hung, D. T.; Jamison, T. F.; Schreiber, S. L. *Chem. Biol.* **1996**, *3*, 623. (b) Hinterding, K.; Alonso-Dı´az, D.; Waldmann, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 688.
2. For selected reviews, see: (a) Shu, Y.-Z. *J. Nat. Prod.* **1998**, *61*, 1053. (b) Couladouros, E. A.; Strongilos, A. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 3677. (c) Gomtsyan, A. *Chem. Heterocycl. Compd.* **2012**, *48*, 7.
3. For synthesis of 1,5-benzothiazepines, see: (a) Asano, K.; Matsubara, S.; *ACS Catal.* **2018**, *8*, 6273. For selected examples, see: (b) Yanagisawa, H.; Ishihara, S.; Ando, A.; Kanazaki, T.; Miyamoto, S.; Koike, H.; Iijima, Y.; Oizumi, K.; Matsushita, Y.; Hata, T. *J. Med. Chem.* **1987**, *30*, 1984. (c) Pieper, G. M.; Siebeneich, W. *Eur. J. Pharmacol.* **2000**, *403*, 129. (d) Arakawa, M.; Sasaki, M.; Ohmori, M.; Harada K.; Fujimura, A. *Eur. J. Clin. Pharmacol.* **2001**, *56*, 775. (e) Lesuisse, D.; Deprez, P.; Albert, E.; Duc, T. T.; Sortais, B.; Gofflo, D.; Jean-Baptiste, V.; Marquette, J. P.; Schoot, B.; Sarubbi, E.; Lange, G.; Broto, P.; Mandine, E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2127.
4. Phippen, C. B. W.; McErlean, C. S. P. *Tetrahedron Lett.* **2011**, *52*, 1490.
5. Micheli, F.; Degiorgis, F.; Feriani, A.; Paio, A.; Pozzan, A.; Zarantonello, P.; Seneci, P. *J. Comb. Chem.* **2001**, *3*, 224.
6. Akbarzadeh, R.; Amanpour, T.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2014**, *70*, 169.
7. Cox, D. A.; Matlib, M. A. *Trends Pharmacol. Sci.* **1993**, *14*, 408.
8. Davis, R. A.; Sandoval, I. T.; Concepcion, G. P.; da Rocha, R. M.; Ireland, C. M. *Tetrahedron* **2003**, *59*, 2855.
9. Makarieva, T. N.; Stonik, V. A.; Dmitrenok, A. S.; Grebnev, B. B.; Isakov, V. V.; Rebachyk, N. M.; Rashkes, Y. W. *J. Nat. Prod.* **1995**, *58*, 254.
10. Beck, J. J.; Stermitz, F. R. *J. Nat. Prod.* **1995**, *58*, 1047.
11. Ellis, J. E.; Fried, J. H.; Harrison, I. T.; Rapp, E.; Ross, C. H. *J. Org. Chem.* **1977**, *42*, 2891.
12. Bockman, M. R.; Engelhart, C. A.; Cramer, J. D.; Howe, M. D.; Mishra, N. K.; Zimmerman, M.; Larson, P.; Alvarez-Cabrera, N.; Park, S. W.; Boshoff, H. I. M.; Bean, J. M.; Jr., V. G. Y.; Ferguson, D. M.; Dartois, V.; Jarrett, J. T.; Schnappinger, D.;

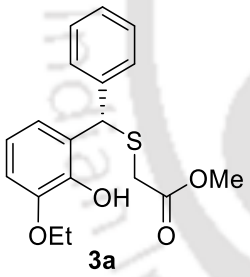
Aldrich, C. C. *ACS Infect. Dis*. **2019**, *5*, 598.

13. Huang, J. J.; Rideout, J. L.; Martin, G. E. *Nucleosides Nucleotides* **1995**, *14*, 195.
14. Halama, A.; Jirman, J.; Bouškova, O.; Gibala, P.; Jarrah, K. *Org. Process Res. Dev*. **2010**, *14*, 425.
15. Guo, W.; Wu, B.; Zhou, X.; Chen, P.; Wang, X.; Zhou, Y.-G.; Liu, Y.; Li, C. *Angew. Chem. Int. Ed*. **2015**, *54*, 4522.
16. Lai, Z.; Sun, J.-W. *Synlett* **2016**, *27*, 555.
17. Wang, Y.; Chu, M.; Zhang, C.; Shao, J.; Qi, S.; Wang, B.; Du, X.; Xu, D. *Adv. Synth. Catal.* **2017**, *359*, 4170.
18. Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Cai, Y.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed*. **2010**, *49*, 4290.
19. Chakka, S. K.; Cele, Z. E. D.; Sosibo, S. C.; Francis, V.; Arvidsson, P. I.; Kruger, H. G.; Maguire, G. E. M.; Govender, T. *Tetrahedron: Asymmetry* **2012**, *23*, 616.
20. (a) Hu, L.; Zhang, Y.; Ramström, O. *Org. Biomol. Chem.* **2014**, *12*, 3572. (b) Zhang, Y.; Schaufelberger, F.; Sakulsombat, M.; Liu, C.; Ramström, O. *Tetrahedron* **2014**, *70*, 3826.
21. Feng, B.-X.; Wang, B.; Li, X. *Org. Biomol. Chem*. **2016**,*14*, 9206.
22. Hasılcıoğulları, D.; Tanyeli, C. *Tetrahedron Lett*. **2018**, *59*, 1414.
23. Gelebe, A. C.; Kaye, P. T. *Synth. Commun.* **1996**, *26*, 4459.
24. Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem*. **2004**, *69*, 8780.
25. CCDC 1984977 contains the crystallographic data for **8**.
26. CCDC 1969971 contains the crystallographic data for **4q**.
27. CrysAlisPro, Oxford Diffraction Ltd., Version 1.171.40.23a (Rigaku OD, **2018**).
28. G. M. Sheldrick, SHELXL-97, Program for crystal structure refinement; University of Göttingen: Göttingen, Germany, **1997**.
29. APEX 2, SAINT, SADABS Bruker AXS Inc., Madison, WI, USA, **2012**.
30. G. M. Sheldrick, **2015**, Acta Cryst. C71, 3-8.
31. (a) Meier, B.; Dumez, J.-N.; Stevanato, G.; Hill-Cousins, J. T.; Roy, S. S.; Håkansson, P.; Mamone, S.; Brown, R. C. D.; Pileio, G.; Levitt, M. H. *J. Am. Chem. Soc.* **2013**, *135*, 18746. (b) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun*. **2013**, *49*, 1660.

32. (a) Berkessel, A.; Mukherjee, S.; Muller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudorfl, J.-M.; Lex, J. *Org. Biomol. Chem*. **2006**, *4*, 4319. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967. (c) Tripathi, C. B.; Kayal, S.; Mukherjee, S. *Org. Lett*. **2012**, *14*, 3296.
33. McCooey, S. H.; Connon, S. J. *Angew. Chem*. **2005**, *117*, 6525.
34. (a) Yang, W.; Du, D. M. *Org. Lett*. **2010**, *12*, 5450. (b) Manoni, F.; Connon, S. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 2628. (c) Berkes, B.; Ozsváth, K.; Molnár, L.; Gáti, T.; Holczbauer, T.; Kardos, G.; Soós, T. *Chem. Eur. J*. **2016**, *22*, 18101. (d) Kanberoğlu, E.; Tanyeli, C. *Asian J. Org. Chem*. **2016**, *5*, 114.
35. Mondal, B.; Pan, S. C. *Synlett* **2018**, *29*, 576.
36. Rice, J. E.; He, Z.-M. *J. Org. Chem.* **1990**, *55*, 5490.

4.8. Characterization Data of Products:

Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3a)

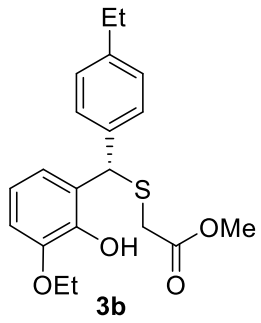


3a

Product **3a** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (31.9 mg, 96% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.3 Hz, 1H), 5.99 (s, 1H), 5.82 (s, 1H), 4.07 (dd, *J* = 9.5, 7.1 Hz, 2H), 3.67 (s, 3H), 3.17 (q, *J* = 14.9 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.9, 145.9, 143.5, 140.4, 128.7, 128.6, 127.4, 126.3, 120.8, 119.8, 110.5, 64.7, 52.5, 47.1, 34.1, 15.1; **HRMS (+ESI):** Calc for $C_{18}H_{24}NO_4S$ $[M+NH_4]^+$ 350.1421; found: 350.1434; The ee value 95% (t_{minor} = 22.9 min, t_{major} = 25.2 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (98:2) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(4-ethylphenyl)methyl)thio)acetate (3b)

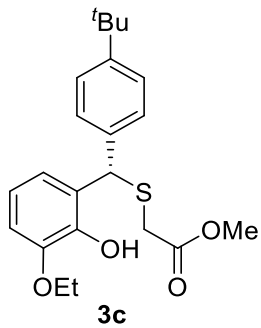
Product **3b** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (34.6 mg, 96% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 3H), 6.81 (t,



3b

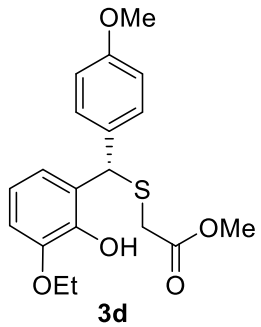
J = 8.0 Hz, 1H), 6.73 (d, *J* = 7.1 Hz, 1H), 5.98 (s, 1H), 5.79 (s, 1H), 4.07 (dd, *J* = 11.3, 7.0 Hz, 2H), 3.66 (s, 3H), 3.16 (q, *J* = 14.9 Hz, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.0, 145.9, 143.5, 143.4, 137.5, 128.6, 128.1, 126.5, 120.8, 119.8, 110.5, 64.7, 52.6, 46.9, 34.1, 28.7, 15.6, 15.1; **HRMS (+ESI):** Calc for $C_{20}H_{28}NO_4S$ $[M+NH_4]^+$ 378.1734; found: 378.1731; The ee value 92% (t_{minor} = 12.2 min, t_{major} = 20.9 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-(((4-(tert-butyl)phenyl)(3-ethoxy-2-hydroxyphenyl)methyl)thio)acetate (3c)



3c

Product **3c** was purified by silica gel column chromatography using 4-5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (37.7mg, 97% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.00 (s, 1H), 5.80 (s, 1H), 4.07 (dd, *J* = 10.7, 7.0 Hz, 2H), 3.66 (s, 3H), 3.21 – 3.13 (m, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.28 (s, 9H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.0, 150.2, 145.9, 143.5, 137.3, 128.3, 126.5, 125.6, 120.9, 119.8, 110.5, 64.7, 52.5, 46.8, 34.6, 34.1, 31.5, 15.1; **HRMS (+ESI):** Calc for $C_{22}H_{32}NO_4S$ $[M+NH_4]^+$ 406.2047; found: 406.2045; The ee value 92% (t_{minor} = 12.0 min, t_{major} = 22.0 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.



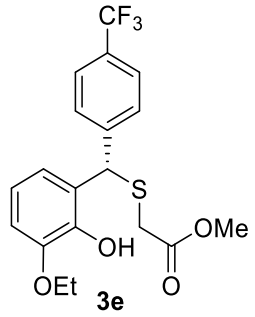
3d

Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(4-methoxyphenyl) methyl)thio)acetate (3d)

Product **3d** was purified by silica gel column chromatography using 6-8% EtOAc in hexane; **Reaction time:** 2 days at room temperature; pale yellow gummy mass (34.4 mg, 95% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 1H),

6.74 (d, *J* = 7.9 Hz, 1H), 5.98 (s, 1H), 5.77 (s, 1H), 4.07 (dd, *J* = 10.3, 7.0 Hz, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 3.15 (q, *J* = 14.9 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.0, 158.9, 146.0, 143.5, 132.4, 129.8, 126.5, 120.7, 119.8, 114.0, 110.5, 64.7, 55.4, 52.5, 46.6, 34.1, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_5S$ $[M+NH_4]^+$ 380.1526; found: 380.1517; The ee value 94% (t_{minor} = 13.2 min, t_{major} = 23.8 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

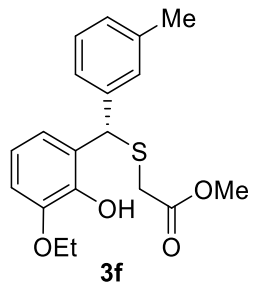
Methyl(S)-2-(((3-ethoxy-2hydroxyphenyl)(4(trifluoromethyl)phenyl)methyl)thio)acetate (3e)



3e

Product **3e** was purified by silica gel column chromatography using 6-8% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless oil type (36.0 mg, 90% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.2 Hz, 1H), 5.96 (s, 1H), 5.85 (s, 1H), 4.08 (dd, *J* = 8.1, 7.2 Hz, 2H), 3.67 (s, 3H), 3.17 (dd, *J* = 39.6, 14.9 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.7, 146.0, 144.7, 143.5, 129.0, 125.6, 125.6, 125.6, 125.5, 120.5, 120.1, 110.8, 64.8, 52.6, 46.8, 34.0, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{23}F_3NO_4S$ $[M+NH_4]^+$ 418.1294; found: 418.1290; The ee value 92% (t_{minor} = 11.0 min, t_{major} = 21.2 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(m-tolyl)methyl)thio)acetate (3f)

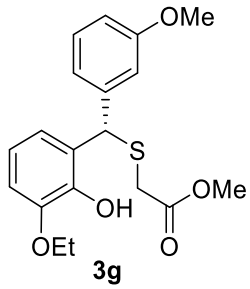


3f

Product **3f** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (32.6 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.29 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.00 (s, 1H), 5.79 (s, 1H), 4.07 (dd, *J* = 10.3, 7.0 Hz, 2H), 3.67 (s, 3H), 3.17 (q, *J* = 14.9 Hz, 2H), 2.32 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz,**

$CDCl_3$): δ 171.0, 145.9, 143.5, 140.2, 138.2, 129.3, 128.5, 128.3, 126.3, 125.7, 120.8, 119.8, 110.5, 64.7, 52.5, 47.1, 34.1, 21.7, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{22}NaO_4S$ $[M+Na]^+$ 369.1131; found: 369.1157; The ee value 93% (t_{minor} = 10.6 min, t_{major} = 13.6 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

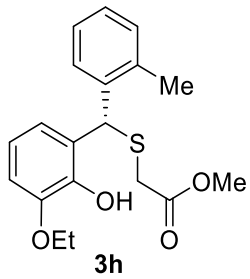
Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(3-methoxyphenyl)methyl)thio)acetate (3g)



3g

Product **3g** was purified by silica gel column chromatography using 6-8% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (34.1 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.21 (t, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 6.81 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.00 (s, 1H), 5.80 (s, 1H), 4.07 (dd, *J* = 8.7, 7.2 Hz, 2H), 3.78 (s, 3H), 3.67 (s, 3H), 3.17 (d, *J* = 6.2 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.9, 159.8, 145.9, 143.5, 142.0, 129.6, 126.3, 121.1, 120.8, 119.9, 114.4, 112.8, 110.6, 64.7, 55.4, 52.5, 47.1, 34.1, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_5S$ $[M+NH_4]^+$ 380.1526; found: 380.1522; The ee value 94% (t_{minor} = 18.6 min, t_{major} = 24.4 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(o-tolyl)methyl)thio)acetate (3h)

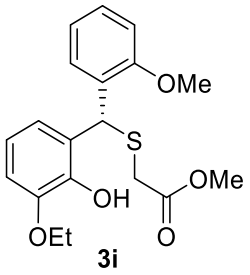


3h

Product **3h** was purified by silica gel column chromatography using 3-5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; pale orange gummy mass (34.0 mg, 98% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.56 (d, *J* = 7.5 Hz, 1H), 7.20 – 7.12 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.81 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.01 (s, 2H), 4.08 (dd, *J* = 6.9, 4.9 Hz, 2H), 3.67 (s, 3H), 3.18 (q, *J* = 14.8 Hz, 2H), 2.42 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.1, 145.9, 143.7, 138.2, 137.0, 130.6, 128.2, 127.4, 126.3, 125.7, 121.3, 119.8, 110.5, 64.7, 52.5, 43.7, 34.2, 19.4, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_4S$ $[M+NH_4]^+$ 364.1577; found: 364.1576; The ee value 90% (t_{minor} = 12.8 min, t_{major} = 26.8 min) was determined by HPLC analysis using Lux® 5 µm-

Amylose-1 with *n*-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

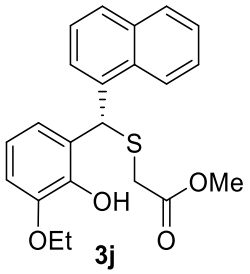
Methyl (R)-2-(((3-ethoxy-2-hydroxyphenyl)(2-methoxyphenyl)methyl)thio)acetate (3i)



3i

Product **3i** was purified by silica gel column chromatography using 6-8% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (35.2 mg, 97% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.79 (t, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 7.1 Hz, 1H), 6.16 (s, 1H), 4.07 (dd, *J* = 6.9, 4.1 Hz, 2H), 3.83 (s, 3H), 3.64 (s, 3H), 3.23 (d, *J* = 2.9 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.9, 157.1, 146.0, 143.8, 129.5, 128.6, 126.3, 121.3, 120.8, 119.5, 111.2, 110.7, 64.7, 56.1, 52.4, 41.1, 34.6, 15.1; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_5S$ $[M+NH_4]^+$ 380.1526; found: 380.1519; The ee value 84% (t_{minor} = 16.3 min, t_{major} = 30.8 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

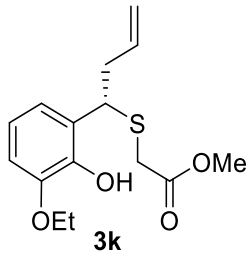
Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(naphthalen-1-yl)methyl)thio)acetate (3j)



3j

Product **3j** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (34.0 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 8.27 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.53 – 7.42 (m, 3H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.76 – 6.71 (m, 2H), 6.65 (s, 1H), 6.17 (s, 1H), 4.09 (dd, *J* = 7.0, 2.4 Hz, 2H), 3.65 (s, 3H), 3.26 (q, *J* = 15.0 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.0, 146.0, 143.3, 135.9, 134.2, 131.9, 128.9, 128.3, 126.6, 126.2, 126.2, 125.9, 125.5, 123.8, 121.5, 120.0, 110.7, 64.8, 52.5, 43.4, 34.5, 15.1; The ee value 90% (t_{minor} = 16.5 min, t_{major} = 27.2 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

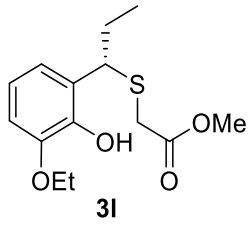
Methyl (S)-2-((1-(3-ethoxy-2-hydroxyphenyl)but-3-en-1-yl)thio)acetate (3k)



3k

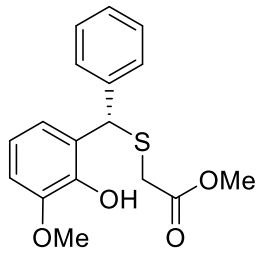
Product **3k** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless oil type (23.1 mg, 78% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.95 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.93 (s, 1H), 5.77 - 5.71 (m, 1H), 5.06 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.99 (dd, *J* = 10.2, 0.7 Hz, 1H), 4.54 (t, *J* = 7.6 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.12 (d, *J* = 3.7 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.1, 145.9, 143.9, 135.4, 126.5, 120.5, 119.9, 117.2, 110.3, 64.7, 52.5, 42.8, 39.3, 33.1, 15.1; **HRMS (+ESI):** Calc for $C_{15}H_{24}NO_4S$ $[M+NH_4]^+$ 314.1421; found: 314.1430; The ee value 85% (t_{minor} = 9.9 min, t_{major} = 8.3 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-((1-(3-ethoxy-2-hydroxyphenyl)propyl)thio)acetate (3l)



3l

Product **3l** was purified by silica gel column chromatography using 4% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless oil type (25.3 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 6.94 (d, *J* = 7.9 Hz, 1H), 6.81 (t, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.92 (s, 1H), 4.39 (dd, *J* = 8.6, 6.6 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.11 (d, *J* = 2.0 Hz, 2H), 1.98 - 1.86 (m, 2H), 1.45 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.3, 145.8, 144.1, 127.0, 120.4, 119.9, 110.1, 64.7, 52.5, 44.8, 33.1, 28.3, 15.1, 12.4; **HRMS (+ESI):** Calc for $C_{14}H_{24}NO_4S$ $[M+NH_4]^+$ 302.1421; found: 302.1437; The ee value 84% (t_{minor} = 8.3 min, t_{major} = 7.4 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.



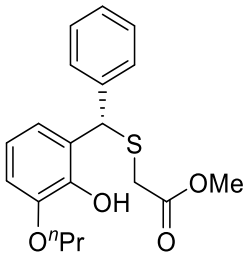
3m

Methyl (S)-2-(((2-hydroxy-3-methoxyphenyl)(phenyl)methyl) thio)acetate (3m)

Product **3m** was purified by silica gel column chromatography using 3% EtOAc in hexane; **Reaction time:** 2 days at room temperature; pale yellow gummy mass (29.9 mg, 94% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* =

7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 1H), 5.81 (s, 1H), 3.86 (s, 3H), 3.67 (s, 3H), 3.17 (q, *J* = 14.9 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.9, 146.8, 143.5, 140.4, 128.7, 128.6, 127.5, 126.4, 121.0, 119.9, 109.8, 56.3, 52.5, 47.2, 34.1; **HRMS (+ESI):** Calc for $C_{17}H_{22}NO_4S$ $[M+NH_4]^+$ 336.1264; found: 336.1258; The ee value 96% (t_{minor} = 15.3 min, t_{major} = 26.2 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with *n*-hexane/*i*-PrOH (88:12) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

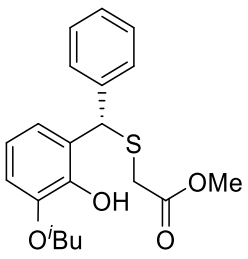
Methyl (S)-2-(((2-hydroxy-3-propoxyphenyl)(phenyl)methyl)thio)acetate (3n)



3n

Product **3n** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (28.8 mg, 83% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.1 Hz, 1H), 5.97 (s, 1H), 5.83 (s, 1H), 4.01 – 3.92 (m, 2H), 3.67 (s, 3H), 3.17 (q, *J* = 14.9 Hz, 2H), 1.85 – 1.78 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.9, 146.0, 143.5, 140.4, 128.7, 128.6, 127.4, 126.3, 120.7, 119.8, 110.5, 70.6, 52.5, 47.1, 34.1, 22.8, 10.7; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_4S$ $[M+NH_4]^+$ 364.1577; found: 364.1578; The ee value 94% (t_{minor} = 8.9 min, t_{major} = 13.1 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-(((2-hydroxy-3-isobutoxyphenyl)(phenyl)methyl)thio)acetate (3o)

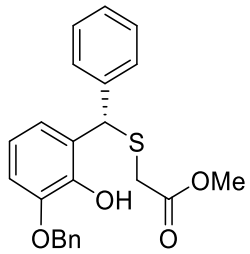


3o

Product **3o** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (31.0 mg, 86% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.2 Hz, 1H), 5.94 (s, 1H), 5.83 (s, 1H), 3.77 (dd, *J* = 11.3, 6.6 Hz, 2H), 3.67 (s, 3H), 3.17 (q, *J* = 14.9 Hz, 2H), 2.14 – 2.07 (m, 1H), 1.03 (d, *J* = 2.5 Hz, 3H), 1.02 (d, *J* = 2.4 Hz, 3H); **^{13}C NMR**

(150 MHz, $CDCl_3$): δ 170.9, 146.1, 143.5, 140.4, 128.7, 128.6, 127.4, 126.3, 120.7, 119.9, 110.5, 75.4, 52.5, 47.1, 34.1, 28.4, 19.4; **HRMS (+ESI):** Calc for $C_{20}H_{28}NO_4S$ $[M+NH_4]^+$ 378.1734; found: 378.1733; The ee value 90% (t_{minor} = 7.3 min, t_{major} = 8.5 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

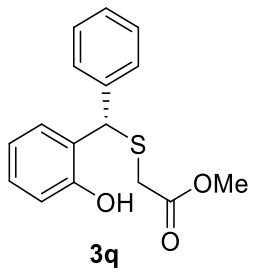
Methyl (S)-2-(((3-(benzyloxy)-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3p)



3p

Product **3p** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (32.0 mg, 81% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 7.4 Hz, 2H), 7.42 – 7.34 (m, 5H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.16 (t, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 4.4 Hz, 2H), 6.01 (s, 1H), 5.83 (s, 1H), 5.08 (d, *J* = 5.1 Hz, 2H), 3.66 (s, 3H), 3.18 (q, *J* = 14.9 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 170.9, 145.9, 143.6, 140.3, 136.4, 128.9, 128.7, 128.6, 128.6, 128.0, 127.5, 126.6, 121.3, 119.9, 111.2, 71.4, 52.5, 47.1, 34.1; **HRMS (+ESI):** Calc for $C_{23}H_{26}NO_4S$ $[M+NH_4]^+$ 412.1577; found: 412.1576; The ee value 90% (t_{minor} = 20.5 min, t_{major} = 17.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

Methyl (S)-2-(((2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3q)

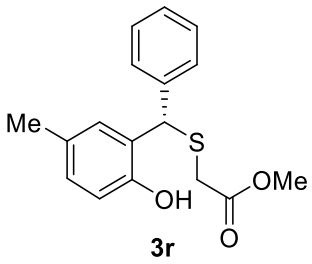


3q

Product **3q** was purified by silica gel column chromatography using 5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; pale yellow gummy mass (27.4 mg, 95% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 5.53 (s, 1H), 3.76 (s, 3H), 3.21 (d, *J* = 1.8 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.8, 155.0, 139.5, 138.3, 129.5, 129.5, 129.2, 128.9, 128.0, 125.6, 120.8, 117.6, 114.3, 53.2, 49.8, 33.6; **HRMS (+ESI):** Calc for $C_{16}H_{16}NaO_3S$ $[M+Na]^+$ 311.0712; found: 311.0713; The ee value 88% (t_{minor} = 22.2 min, t_{major} = 24.1 min) was determined by HPLC analysis using Lux® 5 μm Amylose-1 with

n-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

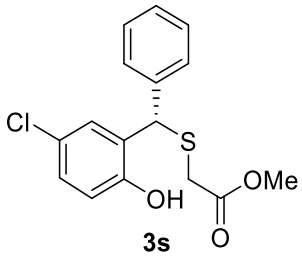
Methyl (S)-2-(((2-hydroxy-5-methylphenyl)(phenyl)methyl)thio)acetate (3r)



3r

Product **3r** was purified by silica gel column chromatography using 3-5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (26.9 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.75 (s, 1H), 5.53 (s, 1H), 3.75 (s, 3H), 3.19 (d, *J* = 2.1 Hz, 2H), 2.18 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.6, 152.6, 138.6, 130.0, 130.0, 130.0, 129.2, 128.9, 127.9, 125.3, 117.5, 53.0, 49.9, 33.7, 20.8; **HRMS (+ESI):** Calc for $C_{17}H_{18}NaO_3S$ $[M+Na]^+$ 325.0869; found: 325.0881; The ee value 90% (t_{minor} = 10.9 min, t_{major} = 12.2 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Methyl (S)-2-(((5-chloro-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3s)

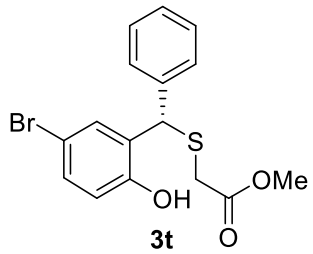


3s

Product **3s** was purified by silica gel column chromatography using 8-10% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (31.6 mg, 98% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (s, 1H), 7.47 (s, 1H), 7.39 (t, *J* = 7.4 Hz, 3H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.89 (dd, *J* = 7.5, 5.6 Hz, 2H), 5.47 (s, 1H), 3.77 (s, 3H), 3.21 (d, *J* = 3.9 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.9, 153.6, 137.6, 129.3, 129.2, 129.1, 129.0, 128.3, 127.6, 125.5, 118.9, 53.3, 49.2, 33.6; **HRMS (+ESI):** Calc for $C_{16}H_{15}ClNaO_3S$ $[M+Na]^+$ 345.0323; found: 345.0297; The ee value 84% (t_{minor} = 12.8 min, t_{major} = 15.5 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Methyl (S)-2-(((5-bromo-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3t)

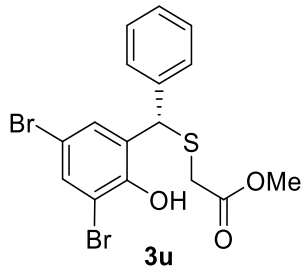
Product **3t** was purified by silica gel column chromatography using 8-10% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (36.0 mg, 98%



3t

yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.44 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 2.2 Hz, 1H), 7.02 (d, *J* = 1.9 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 5.47 (s, 1H), 3.77 (s, 3H), 3.21 (d, *J* = 4.1 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.9, 154.1, 137.6, 132.2, 131.9, 129.1, 129.1, 128.3, 128.1, 119.4, 112.7, 53.3, 49.2, 33.6; **HRMS (+ESI):** Calc for $C_{16}H_{15}BrNaO_3S$ $[M+Na]^+$ 388.9817; found: 388.9821; The ee value 82% (t_{minor} = 13.0 min, t_{major} = 16.5 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

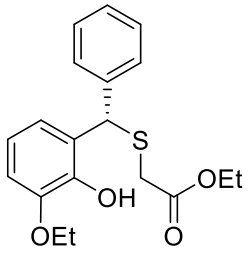
Methyl (S)-2-(((3,5-dibromo-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3u)



3u

Product **3u** was purified by silica gel column chromatography using 6-8% EtOAc in hexane; **Reaction time:** 2 days at room temperature; colorless gummy mass (44.2 mg, 99% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.53 (d, *J* = 2.2 Hz, 1H), 7.45 (s, 1H), 7.43 (s, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 2.1 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 5.63 (s, 1H), 3.73 (s, 3H), 3.18 (d, *J* = 6.9 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 171.2, 150.0, 138.3, 133.9, 131.4, 129.8, 129.0, 128.9, 128.2, 112.8, 112.0, 53.0, 48.4, 33.8; **HRMS (+ESI):** Calc for $C_{16}H_{18}Br_2NO_3S$ $[M+NH_4]^+$ 461.9369; found: 461.9381; The ee value 62% (t_{minor} = 13.8 min, t_{major} = 17.9 min) was determined by HPLC analysis using Daicel Chiralpak IB with *n*-hexane/*i*-PrOH (97:3) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

Ethyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3v)

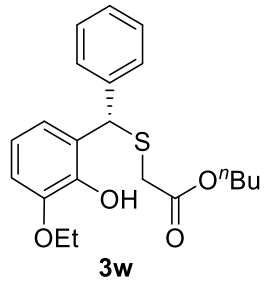


3v

Product **3v** was purified by silica gel column chromatography using 3-5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; pale yellow gummy mass (31.9 mg, 92% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.3 Hz, 1H), 5.99 (s, 1H), 5.85 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.11 – 4.04 (m, 2H),

3.14 (q, *J* = 14.8 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.5, 146.0, 143.6, 140.5, 128.7, 128.6, 127.4, 126.4, 120.9, 119.8, 110.6, 64.8, 61.5, 47.1, 34.3, 15.1, 14.3; **HRMS (+ESI):** Calc for $C_{19}H_{26}NO_4S$ $[M+NH_4]^+$ 364.1577; found: 364.1572; The ee value 92% (t_{minor} = 7.8 min, t_{major} = 11.9 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

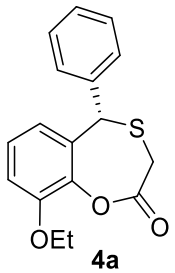
Butyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)thio)acetate (3w)



3w

Product **3w** was purified by silica gel column chromatography using 3-5% EtOAc in hexane; **Reaction time:** 2 days at room temperature; yellow oil type (36.7 mg, 98% yield); **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.98 (s, 1H), 5.85 (s, 1H), 4.08 (dd, *J* = 11.8, 5.2 Hz, 4H), 3.15 (q, *J* = 14.9 Hz, 2H), 1.62 (dd, *J* = 14.7, 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.38 (t, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 170.6, 146.0, 143.6, 140.5, 128.7, 128.6, 127.4, 126.4, 120.9, 119.8, 110.6, 65.4, 64.8, 47.1, 34.3, 30.8, 19.3, 15.1, 13.9; **HRMS (+ESI):** Calc for $C_{21}H_{30}NO_4S$ $[M+NH_4]^+$ 392.1890; found: 392.1883; The ee value 92% (t_{minor} = 7.1 min, t_{major} = 12.5 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(S)-9-ethoxy-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4a)

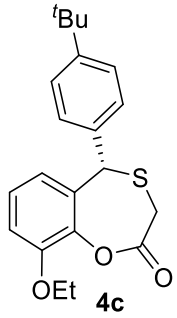


4a

Product **4a** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; white solid (15.6 mg, 52% yield); **M.P.** = 93-94 °C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.49 (s, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 1H), 5.73 (s, 1H), 4.09 (dd, *J* = 7.0, 2.4 Hz, 2H), 3.36 (d, *J* = 12.0 Hz, 1H), 3.14 (d, *J* = 12.0 Hz, 1H), 1.43 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 167.4, 149.8, 139.4, 136.0, 131.1, 129.6, 129.0, 128.7, 127.5, 119.3, 113.7, 65.2, 46.6, 30.4, 15.0; **HRMS (+ESI):** Calc for $C_{17}H_{20}NO_3S$ $[M+NH_4]^+$ 318.1158; found: 318.1175; The ee value

94% (t_{minor} = 14.2 min, t_{major} = 13.3 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

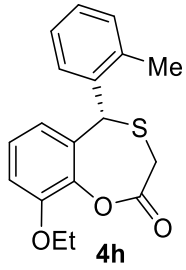
(S)-5-(4-(tert-butyl)phenyl)-9-ethoxy-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4c)



4c

Product **4c** was purified by silica gel column chromatography using 2% EtOAc in hexane; white solid (22.8 mg, 64% yield); **M.P.** = 204-205 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.41 (d, *J* = 5.1 Hz, 4H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 5.71 (s, 1H), 4.09 (dd, *J* = 7.0, 2.4 Hz, 2H), 3.35 (d, *J* = 12.0 Hz, 1H), 3.12 (d, *J* = 12.0 Hz, 1H), 1.43 (t, *J* = 7.0 Hz, 3H), 1.34 (s, 9H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 167.5, 151.7, 149.7, 139.3, 132.8, 131.2, 129.3, 127.5, 125.9, 119.3, 113.5, 65.1, 46.2, 34.9, 31.5, 30.5, 15.0; **HRMS (+ESI):** Calc for $C_{21}H_{28}NO_3S$ $[M+NH_4]^+$ 374.1784; found: 374.1789; The ee value 81% (t_{minor} = 22.7 min, t_{major} = 16.3 min) was determined by HPLC analysis using Daicel Chiralpak IE with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(S)-9-ethoxy-5-(o-tolyl)-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4h)

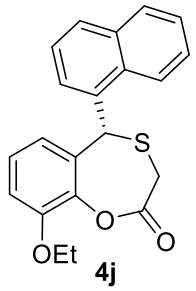


4h

Product **4h** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; white solid (23.0 mg, 73% yield); **M.P.** = 156-157 ^{o}C; **^{1}H NMR (600 MHz, CDCl$_3$):** δ 7.68 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 6.8 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.25 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 4.10 (dd, *J* = 6.9, 5.3 Hz, 2H), 3.36 (d, *J* = 12.0 Hz, 1H), 3.16 (d, *J* = 12.0 Hz, 1H), 2.13 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, CDCl$_3$):** δ 167.6, 149.5, 139.5, 137.0, 134.2, 131.2, 130.5, 129.2, 128.5, 127.6, 126.4, 118.7, 113.5, 65.0, 42.7, 30.4, 19.6, 15.0; **HRMS (+ESI):** Calc for $C_{18}H_{22}NO_3S$ $[M+NH_4]^+$ 332.1315; found: 332.1302; The ee value 68% (t_{minor} = 22.0 min, t_{major} = 15.1 min) was determined by HPLC analysis using Daicel Chiralpak IE with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(S)-9-ethoxy-5-(naphthalen-1-yl)-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4j)

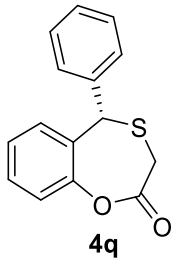
Product **4j** was purified by silica gel column chromatography using 3% EtOAc in hexane;



4j

white solid (25.2 mg, 72% yield); **M.P.** = 207-208 °C; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.88 (dd, *J* = 17.0, 7.4 Hz, 3H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 1H), 6.96 (t, *J* = 8.1 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.55 (s, 1H), 6.21 (d, *J* = 7.6 Hz, 1H), 4.11 (dd, *J* = 6.9, 4.4 Hz, 2H), 3.43 (d, *J* = 11.9 Hz, 1H), 3.25 (d, *J* = 11.9 Hz, 1H), 1.47 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 167.6, 149.5, 139.1, 134.1, 131.7, 131.3, 131.0, 129.3, 129.1, 127.8, 127.3, 126.9, 126.2, 125.3, 123.5, 118.9, 113.4, 65.0, 42.4, 30.5, 15.0; **HRMS (+ESI):** Calc for $C_{21}H_{22}NO_3S$ $[M+NH_4]^+$ 368.1315; found: 368.1311; The ee value 70% (t_{minor} = 20.3 min, t_{major} = 18.6 min) was determined by HPLC analysis using Daicel Chiralpak IE with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

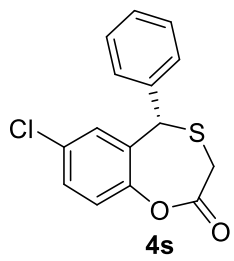
(S)-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4q)



4q

Product **4q** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; colorless solid (14.1 mg, 55% yield); **M.P.** = 157-158 °C; **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.50 (d, *J* = 6.8 Hz, 2H), 7.46 – 7.36 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 5.75 (s, 1H), 3.34 (d, *J* = 12.1 Hz, 1H), 3.15 (d, *J* = 12.1 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 167.3, 150.3, 135.9, 129.9, 129.6, 129.1, 128.8, 128.4, 127.5, 120.3, 46.4, 30.3; **HRMS (+ESI):** Calc for $C_{15}H_{16}NO_2S$ $[M+NH_4]^+$ 274.0896; found: 274.0899; The ee value 84% (t_{minor} = 15.0 min, t_{major} = 7.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(S)-7-chloro-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4s)

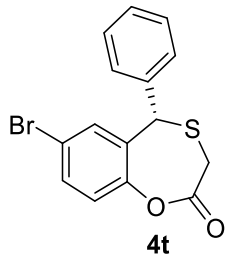


4s

Product **4s** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; colorless gummy mass (19.5 mg, 67% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.50 – 7.40 (m, 5H), 7.29 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 2.2 Hz, 1H), 5.70 (s, 1H), 3.36 (d, *J* = 12.1 Hz, 1H), 3.17 (d, *J* = 12.2

Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 166.7, 148.7, 135.0, 132.9, 131.6, 129.6, 129.5, 129.3, 129.2, 128.3, 121.7, 46.1, 30.3; **HRMS (+ESI):** Calc for $C_{15}H_{15}ClNO_2S$ $[M+NH_4]^+$ 308.0507; found: 308.0524; The ee value 81% (t_{minor} = 16.3 min, t_{major} = 10.2 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

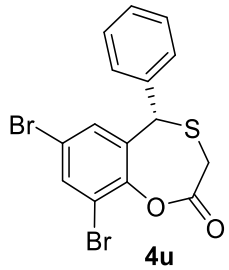
(S)-7-bromo-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4t)



4t

Product **4t** was purified by silica gel column chromatography using 1-2% EtOAc in hexane; colorless gummy mass (21.1 mg, 63% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.47 (t, *J* = 6.5 Hz, 3H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 2.2 Hz, 1H), 5.69 (s, 1H), 3.35 (d, *J* = 12.2 Hz, 1H), 3.17 (d, *J* = 12.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 166.5, 149.3, 135.0, 132.6, 132.0, 131.3, 129.5, 129.3, 129.2, 122.1, 120.5, 46.1, 30.3; **HRMS (+ESI):** Calc for $C_{15}H_{15}BrNO_2S$ $[M+NH_4]^+$ 352.0001; found: 352.0016; The ee value 78% (t_{minor} = 15.6 min, t_{major} = 10.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

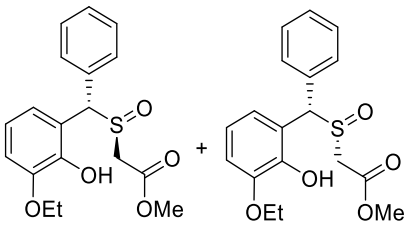
(S)-7,9-dibromo-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one (4u)



4u

Product **4u** was purified by silica gel column chromatography using 2-3% EtOAc in hexane; colorless gummy mass (30.6 mg, 74% yield); **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.71 (d, *J* = 2.2 Hz, 1H), 7.48 – 7.41 (m, 5H), 6.96 (d, *J* = 2.1 Hz, 1H), 5.70 (s, 1H), 3.30 (d, *J* = 12.3 Hz, 1H), 3.20 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 165.3, 146.5, 135.5, 134.5, 133.3, 130.3, 129.5, 129.4, 120.6, 116.1, 46.4, 30.3; **HRMS (+ESI):** Calc for $C_{15}H_{14}Br_2NO_2S$ $[M+NH_4]^+$ 429.9107; found: 429.9109; The ee value 72% (t_{minor} = 9.6 min, t_{major} = 7.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (93:7) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

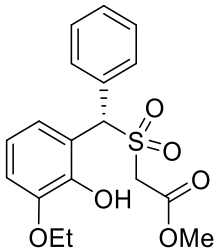
Methyl 2-((S)-((S)-(3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)sulfinyl)acetate (5a) & methyl 2-((R)-((S)-(3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)sulfinyl)acetate (5a')



5a **5a'**

Products **5a and 5a'** were inseparable in silica gel column chromatography, purified by using 40% EtOAc in hexane; **Reaction time:** 1.5 h at 0 °C; pale orange gummy mass (27.2 mg, 78% yield); **Diastereomeric ratio:** 1:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.56 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.40 – 7.34 (m, 4H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.69 (s, 1H), 5.64 (s, 1H), 4.09 (dd, *J* = 14.4, 7.3 Hz, 4H), 3.74 (s, 3H), 3.72 (s, 3H), 3.64 (d, *J* = 14.5 Hz, 1H), 3.60 (s, 2H), 3.48 (d, *J* = 14.5 Hz, 1H), 1.45 – 1.42 (m, 6H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 166.3, 166.3, 146.7, 146.3, 144.6, 143.5, 135.7, 134.4, 129.9, 129.3, 129.1, 128.9, 128.5, 128.5, 122.1, 121.6, 120.9, 120.4, 120.3, 120.3, 111.9, 111.5, 65.5, 65.0, 64.8, 64.8, 55.2, 54.6, 53.0, 52.95, 15.04, 15.0; **HRMS (+ESI):** Calc for $C_{18}H_{20}NaO_5S$ $[M+Na]^+$ 371.0924; found: 371.0927; The ee value of one diastereomer 94% (t_{minor} = 67.7 min, t_{major} = 38.5 min) and ee value of other diastereomer 93% (t_{minor} = 148.7 min, t_{major} = 42.5 min) were determined by HPLC analysis using Lux® 5 μm Amylose-2 with *n*-hexane/EtOH (85:15) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

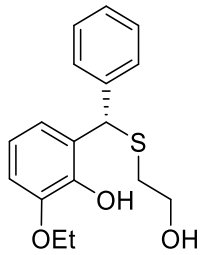
Methyl (S)-2-(((3-ethoxy-2-hydroxyphenyl)(phenyl)methyl)sulfonyl)acetate (6)



6

Product **6** was purified by silica gel column chromatography using 25-30% EtOAc in hexane; **Reaction time:** 1.5 h at 0 °C; pale orange gummy mass (21.1 mg, 58% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.69 (d, *J* = 7.0 Hz, 2H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.40 – 7.34 (m, 3H), 6.91 (t, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 7.3 Hz, 1H), 6.49 (s, 1H), 6.08 (s, 1H), 4.09 (dd, *J* = 10.6, 7.0 Hz, 2H), 3.92 (s, 2H), 3.80 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 163.6, 146.1, 144.4, 132.1, 130.6, 129.2, 129.1, 121.2, 120.3, 118.6, 111.9, 65.1, 64.8, 55.8, 53.4, 15.0; **HRMS (+ESI):** Calc for $C_{18}H_{24}NO_6S$ $[M+NH_4]^+$ 382.1319; found: 382.1325; The ee value 92% (t_{minor} = 25.7 min, t_{major} = 31.5 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min,220 nm, 25 °C.

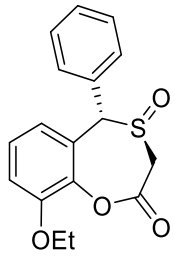
(S)-2-ethoxy-6-(((2-hydroxyethyl)thio)(phenyl)methyl)phenol (7)



7

Product **7** was purified by silica gel column chromatography using 15-20% EtOAc in hexane; **Reaction time:** 2.5 h at -60°C to room temperature; pale orange gummy mass (27.1 mg, 89% yield); **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.51 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.80 (t, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.06 (s, 1H), 5.69 (s, 1H), 4.11 – 4.05 (m, 2H), 3.76 – 3.69 (m, 2H), 2.66 (t, *J* = 4.7 Hz, 2H), 1.43 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 145.8, 143.1, 141.0, 128.7, 128.6, 127.3, 127.2, 120.9, 120.0, 110.3, 64.7, 60.4, 45.8, 35.6, 15.1; **HRMS (+ESI):** Calc for $C_{17}H_{20}NaO_3S$ $[M+Na]^+$ 327.1025; found: 327.1028; The ee value 92% (t_{minor} = 8.9 min, t_{major} = 9.4 min) was determined by HPLC analysis using Lux® 5 µm Amylose-1 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

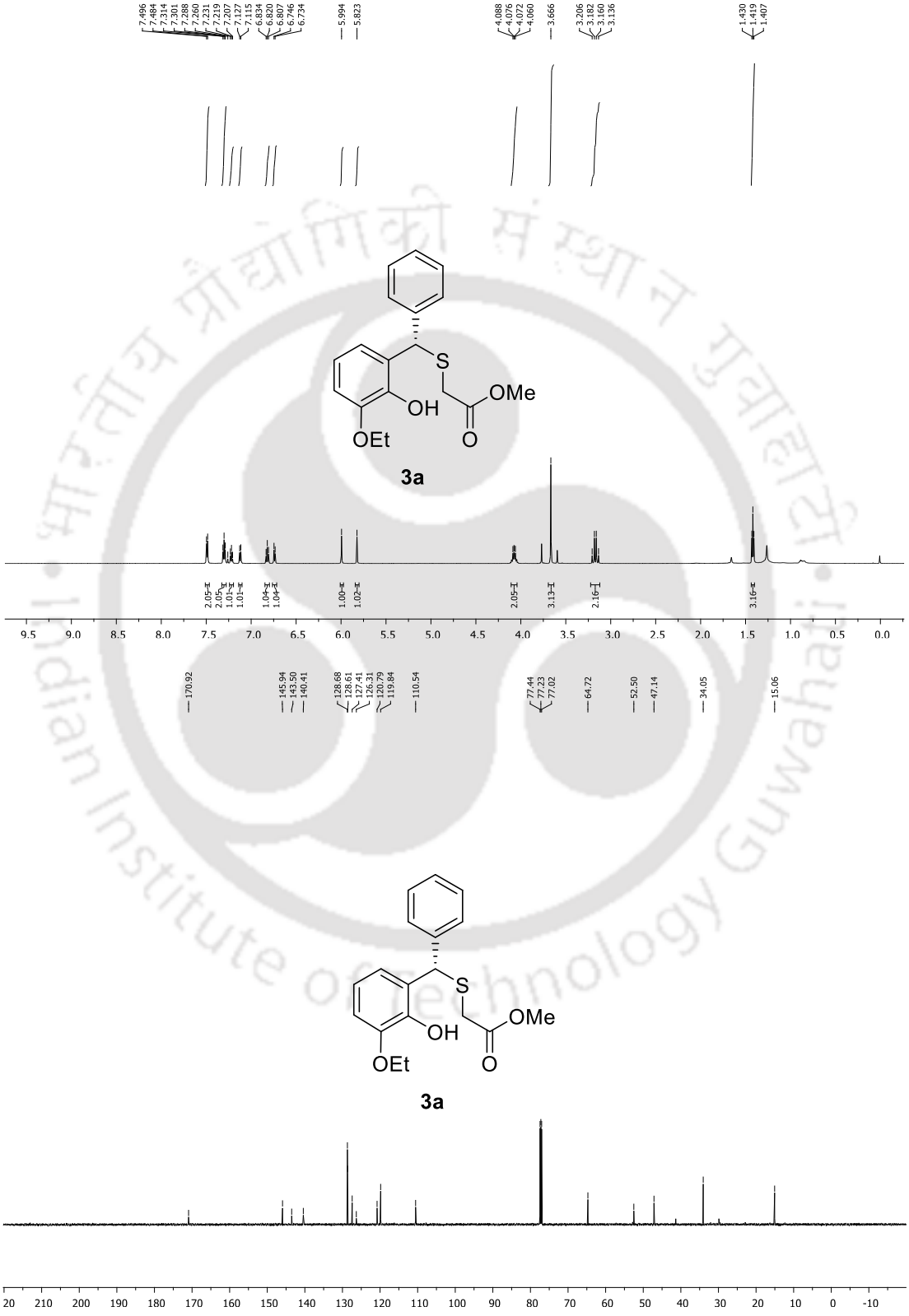
(4S,5S)-9-ethoxy-5-phenyl-5H-benzo[f][1,4]oxathiepin-2(3H)-one 4-oxide (8)



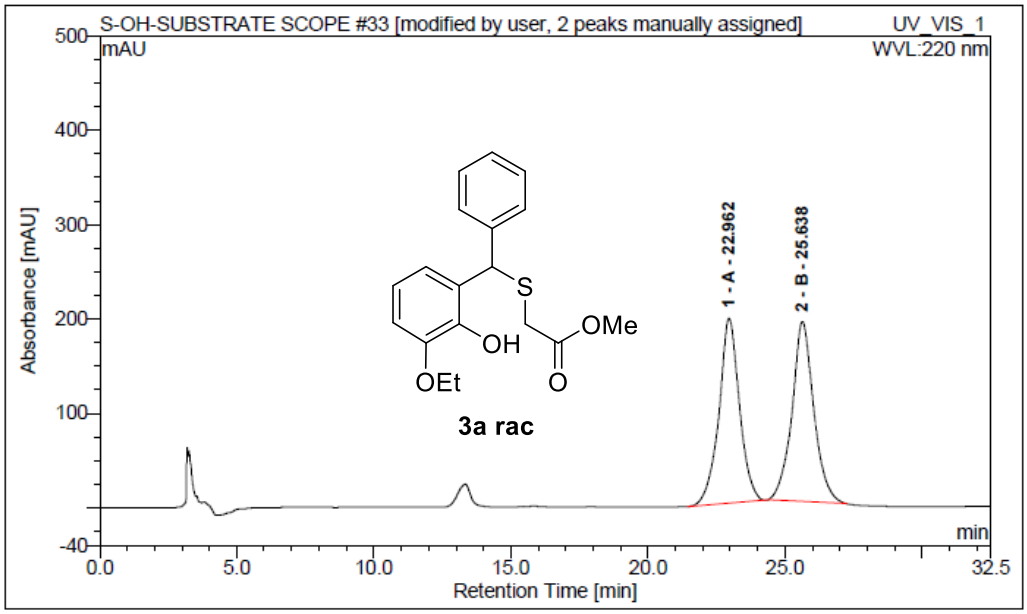
8

Reaction time: 1.5 h at 0 °C; white solid (22.2 mg, 70% yield); **M.P.** = 161-162 °C; **Diastereomeric ratio:** 8:1; **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.52 – 7.42 (m, 5H), 7.10 (t, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.48 (s, 1H), 4.10 (dd, *J* = 6.9, 1.4 Hz, 2H), 3.84 (d, *J* = 12.9 Hz, 1H), 3.68 (d, *J* = 12.9 Hz, 1H), 1.45 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$):** δ 161.5, 150.2, 140.1, 131.8, 130.5, 130.1, 129.7, 129.4, 127.0, 121.0, 115.1, 70.5, 65.2, 51.6, 14.9; **HRMS (+ESI):** Calc for $C_{17}H_{17}O_4S$ $[M+H]^+$ 317.0842; found: 317.0844; The ee value of major diastereomer 90% (t_{minor} = 67.0 min, t_{major} = 36.4 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (70:30) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

4.9. Selected NMR spectra and HPLC chromatogram:

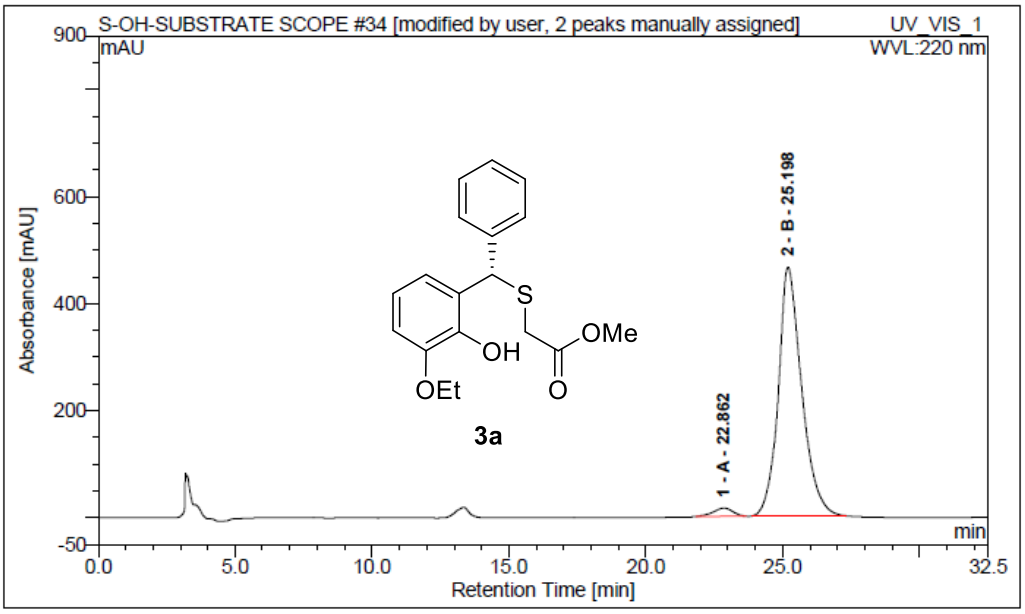


3-OEt-SALI-S-OH-IB-R

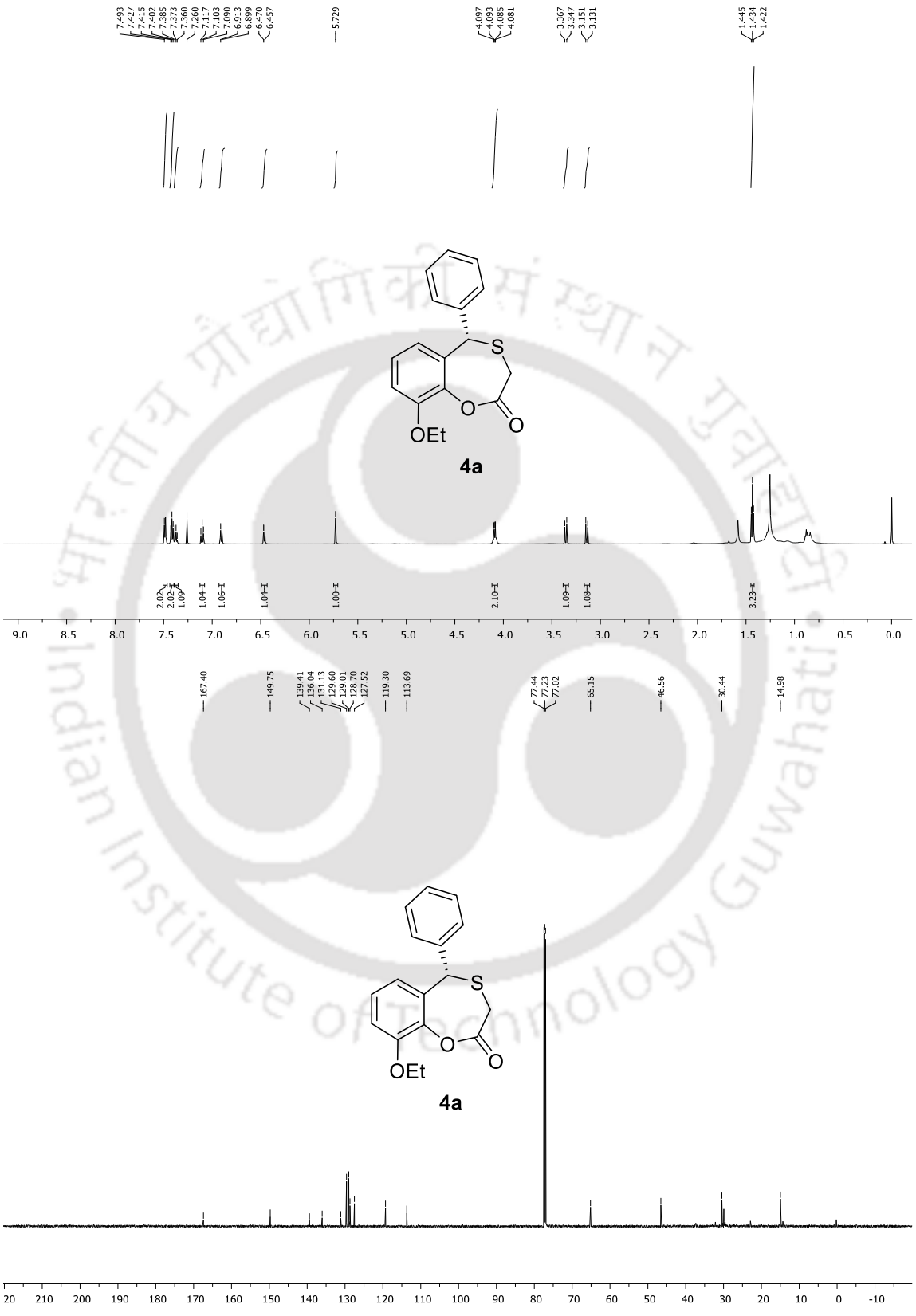


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	22.96	169.7495	49.09824003	195.8707	n.a.
2	B	25.64	175.985	50.90175997	190.556	n.a.

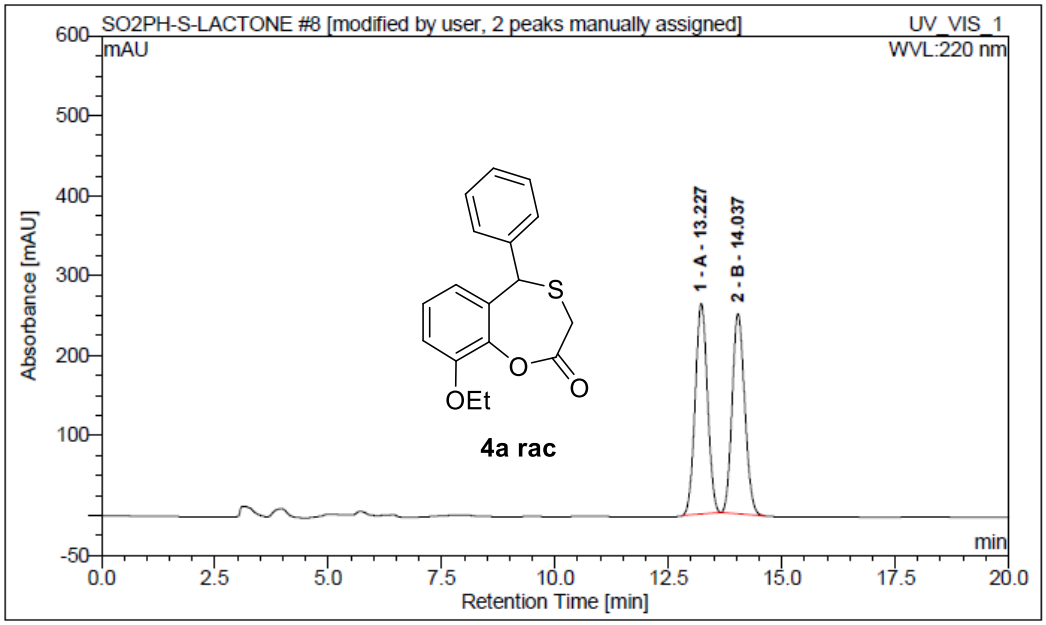
3-OEt-SALI-S-OH-IB-CHI



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	22.86	12.62895	2.670508594	15.43966	n.a.
2	B	25.20	460.276	97.32949141	464.828	n.a.

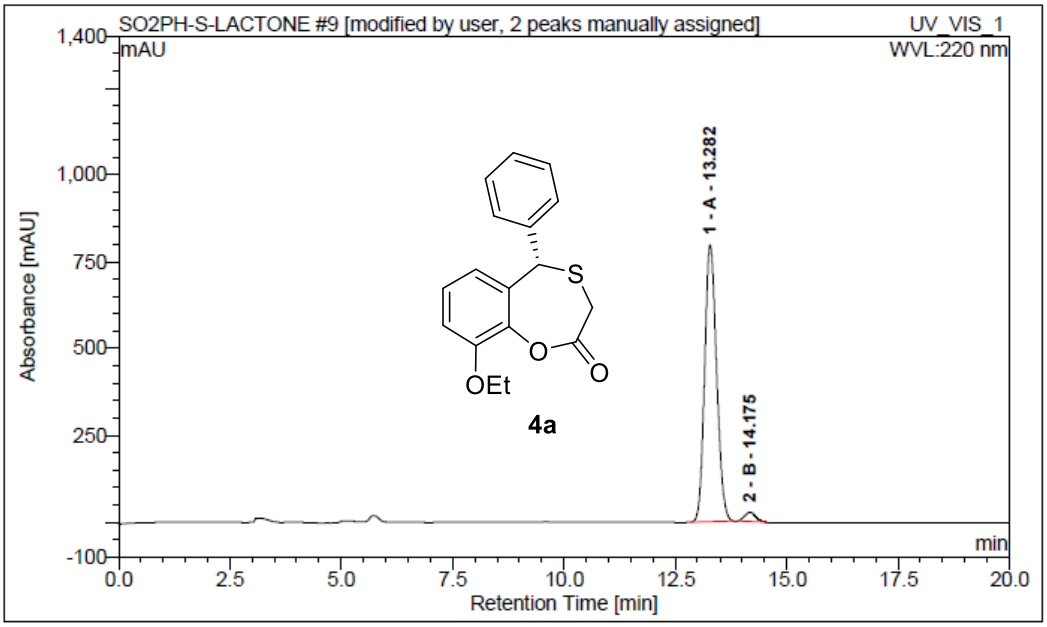


3-OEt-SALI-Me-GLYCO-ID-RAC

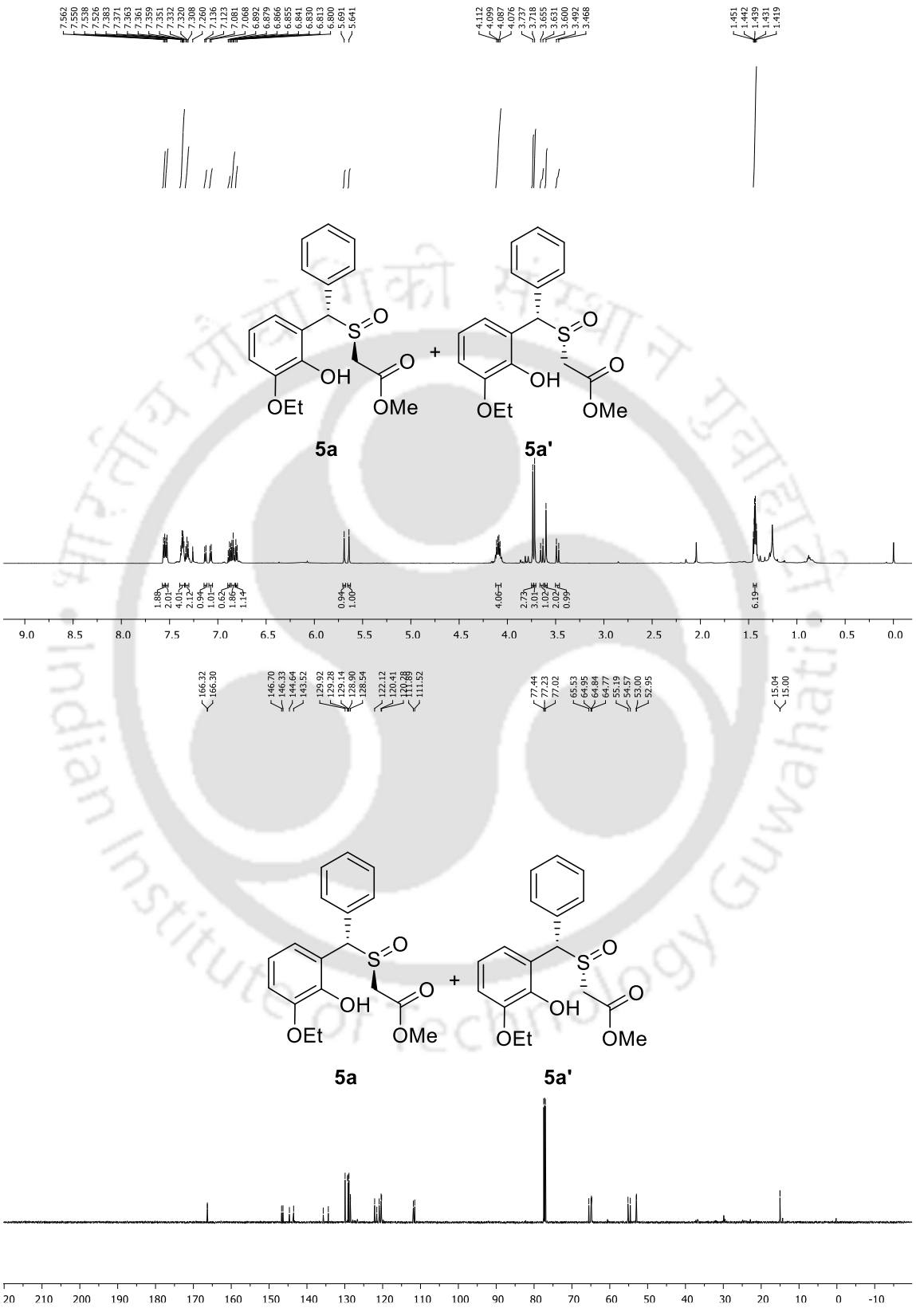


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.23	82.48868	50.55503914	263.279	n.a.
2	B	14.04	80.677	49.44496086	250.268	n.a.

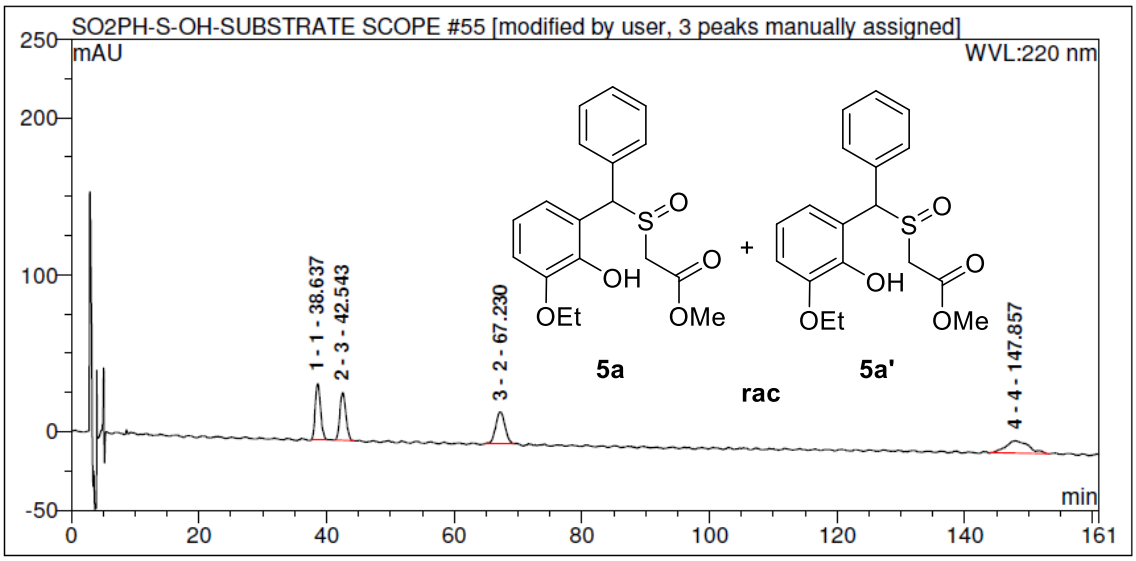
3-OEt-SALI-Me-GLYCO-LACTONE-ID-CHI



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.28	247.9938	97.04532561	797.3713	n.a.
2	B	14.18	7.551	2.954674385	26.158	n.a.

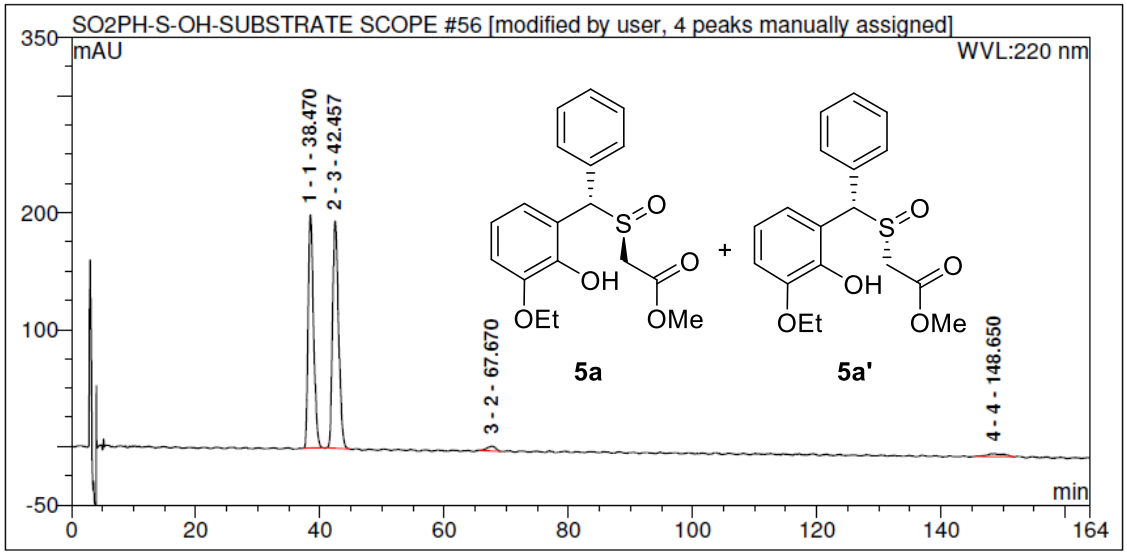


1eq-MCPBA-S-OH-RC-AMYLOSE-2

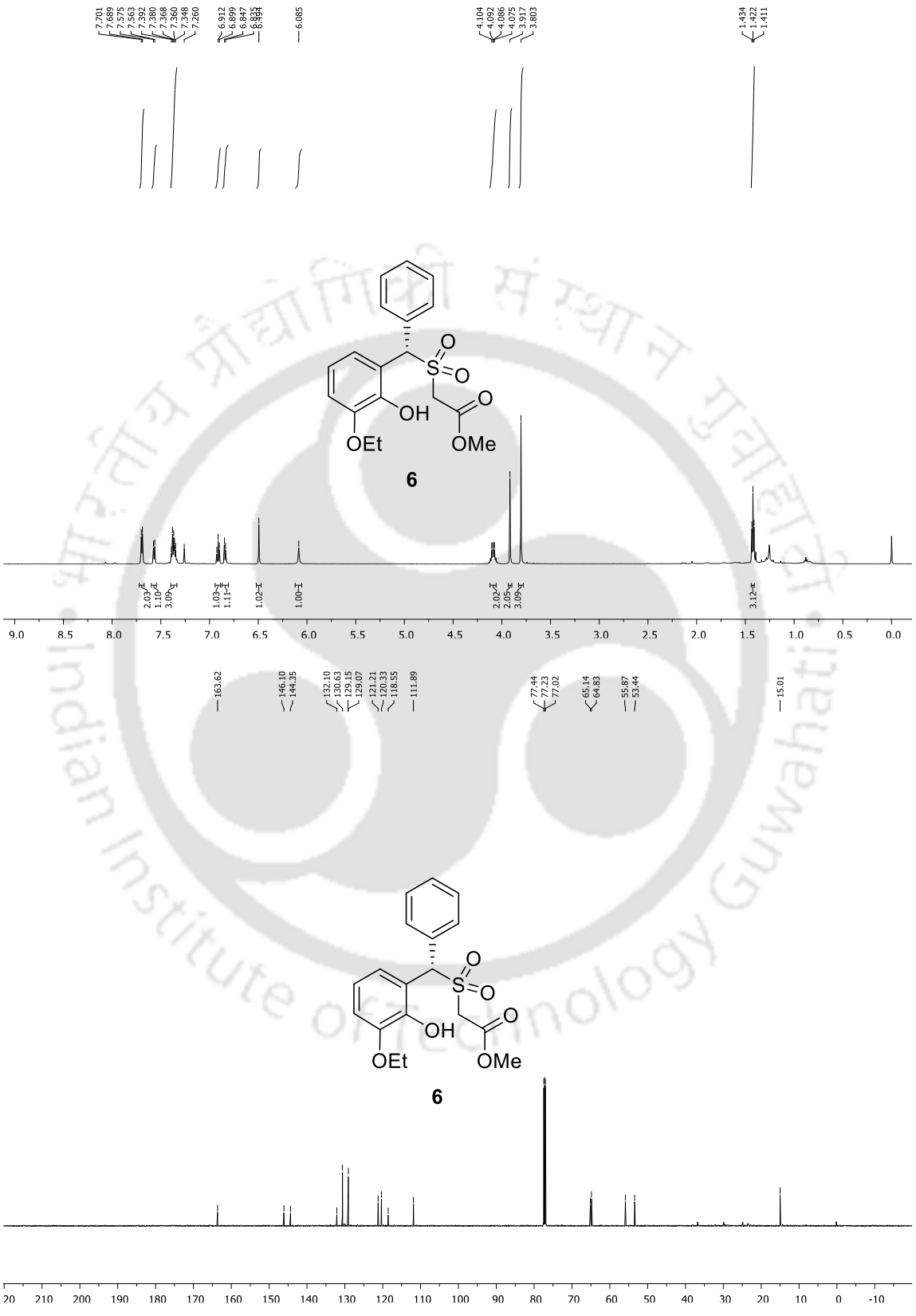


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	38.64	34.18475	25.37008557	35.51991	n.a.
2	3	42.54	33.16501	24.6132947	30.35997	n.a.
3	2	67.23	34.35309	25.49502512	20.26102	n.a.
4	4	147.86	33.041	24.5215946	7.937	n.a.

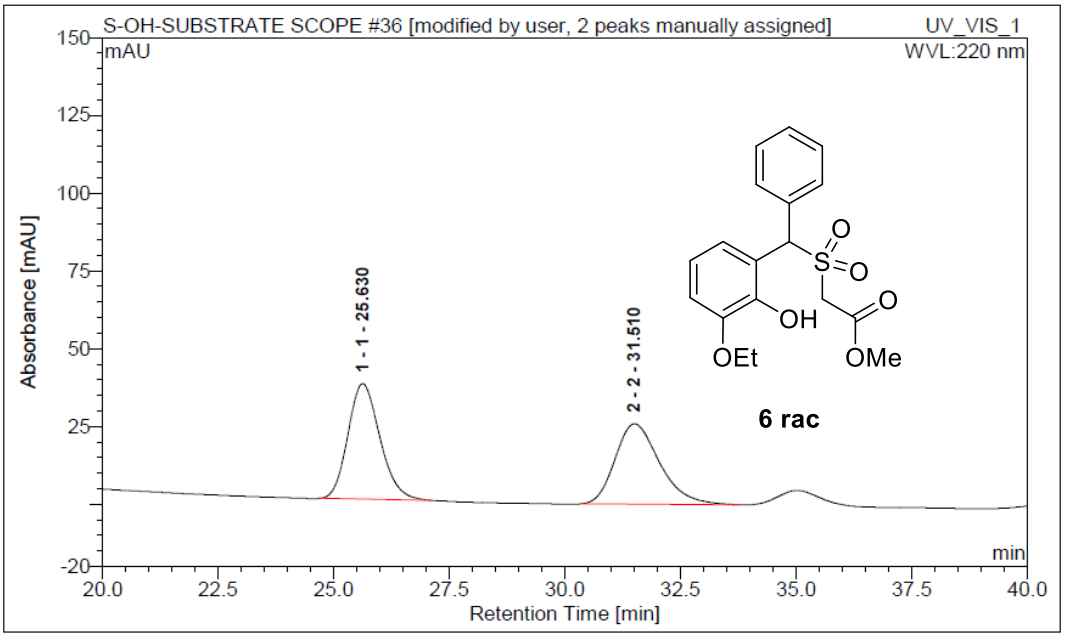
1eq-MCPBA-S-OH-CHI-AMYLOSE-2



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	38.47	200.6097	46.27754155	199.549	n.a.
2	3	42.46	218.5642	50.41936268	194.3258	n.a.
3	2	67.67	6.329706	1.460164505	3.94943	n.a.
4	4	148.65	7.989	1.842931271	2.424	n.a.

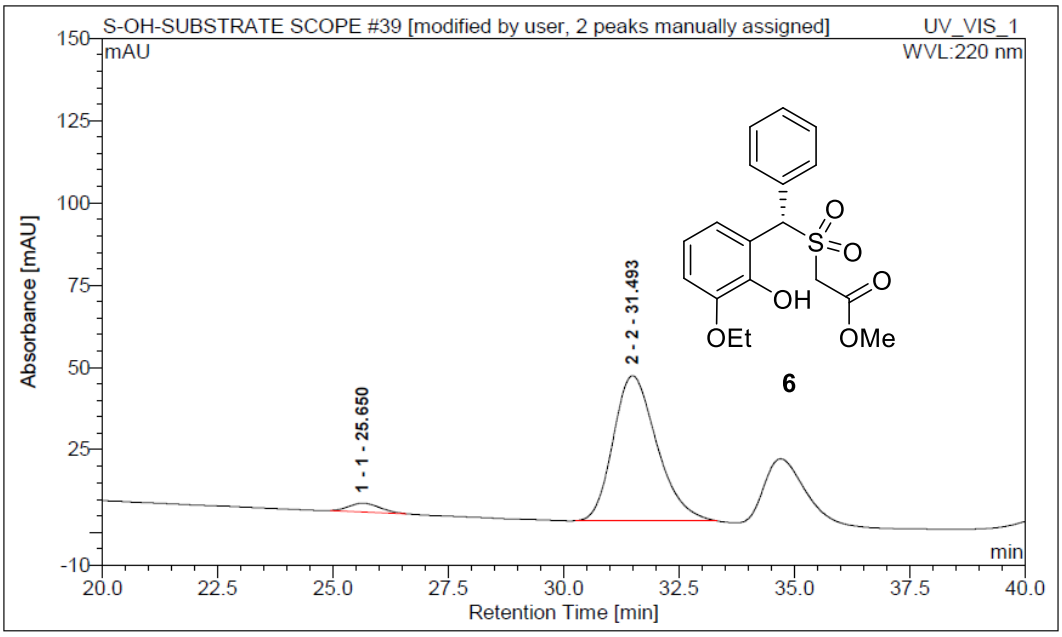


3-EQ-MCPBA-SO2-OH-RAC-ID

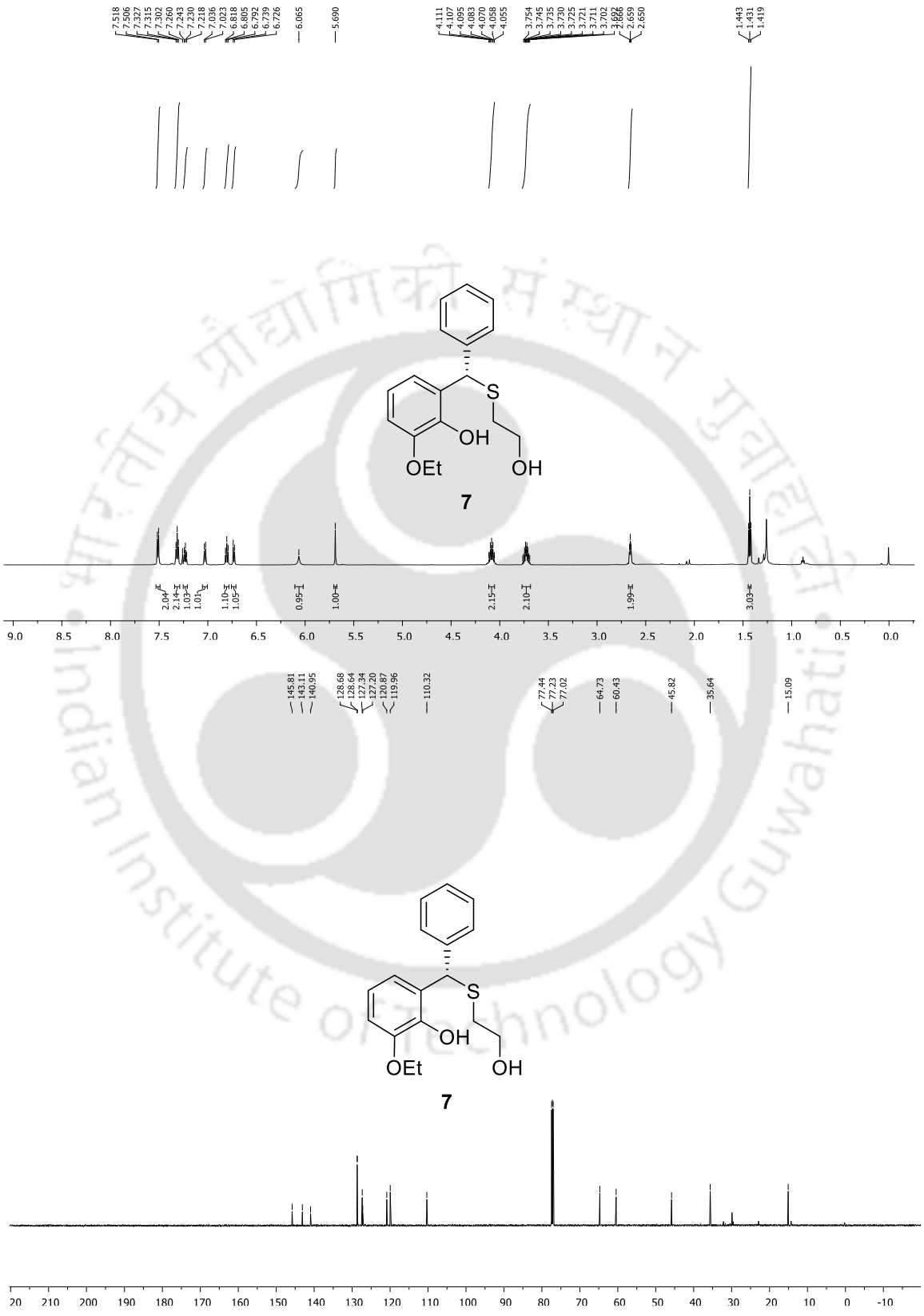


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	25.63	29.8455	50.83162131	37.14589	n.a.
2	2	31.51	28.869	49.16837869	25.836	n.a.

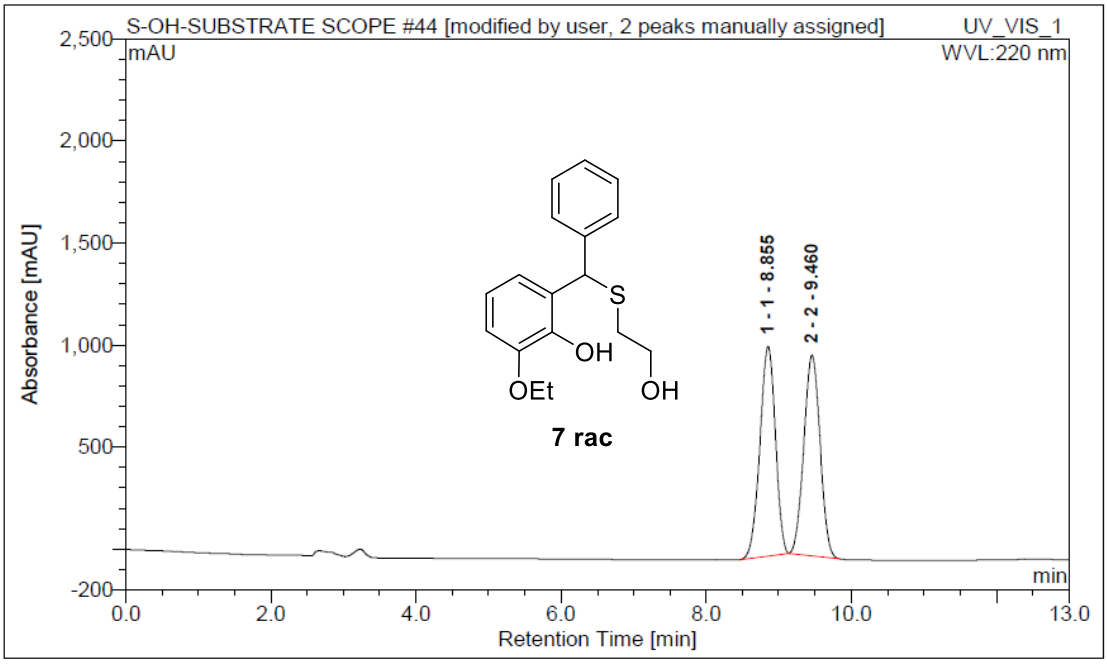
3-EQ-MCPBA-SO2-OH-CHI-ID-0oC



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	25.65	2.031334	4.027698549	2.64921	n.a.
2	2	31.49	48.403	95.97230145	44.046	n.a.

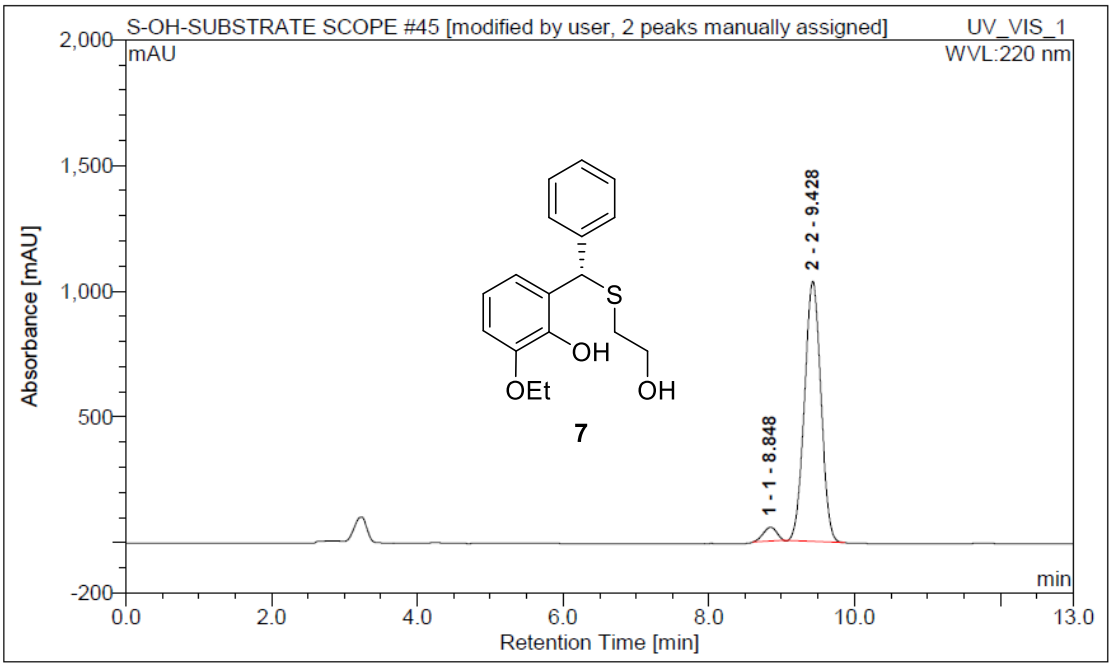


3-EQ-DIBALH-S-OH-OH-RAC-AMYLOSE-1

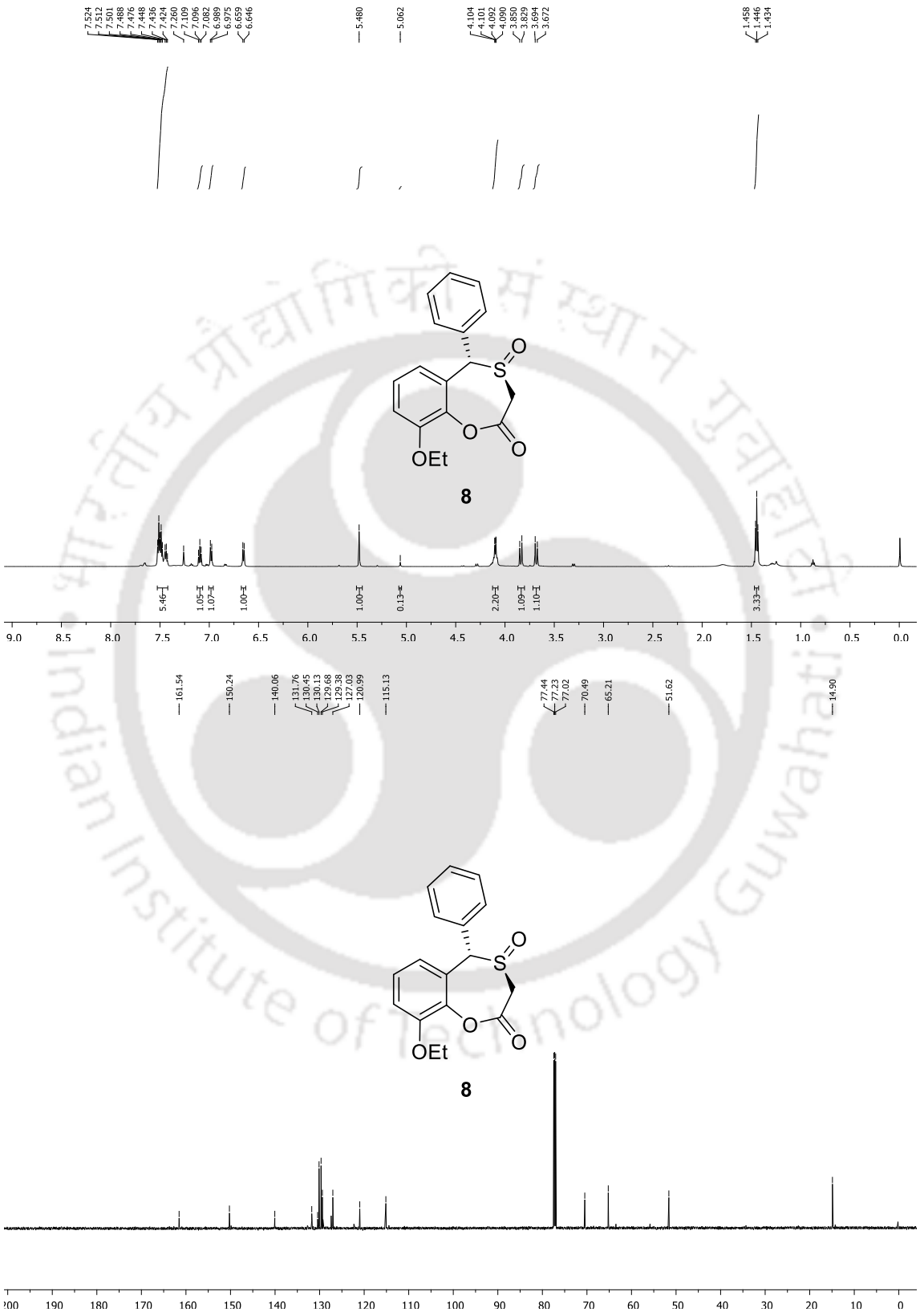


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.86	254.2293	49.95951217	1027.939	n.a.
2	2	9.46	254.641	50.04048783	983.925	n.a.

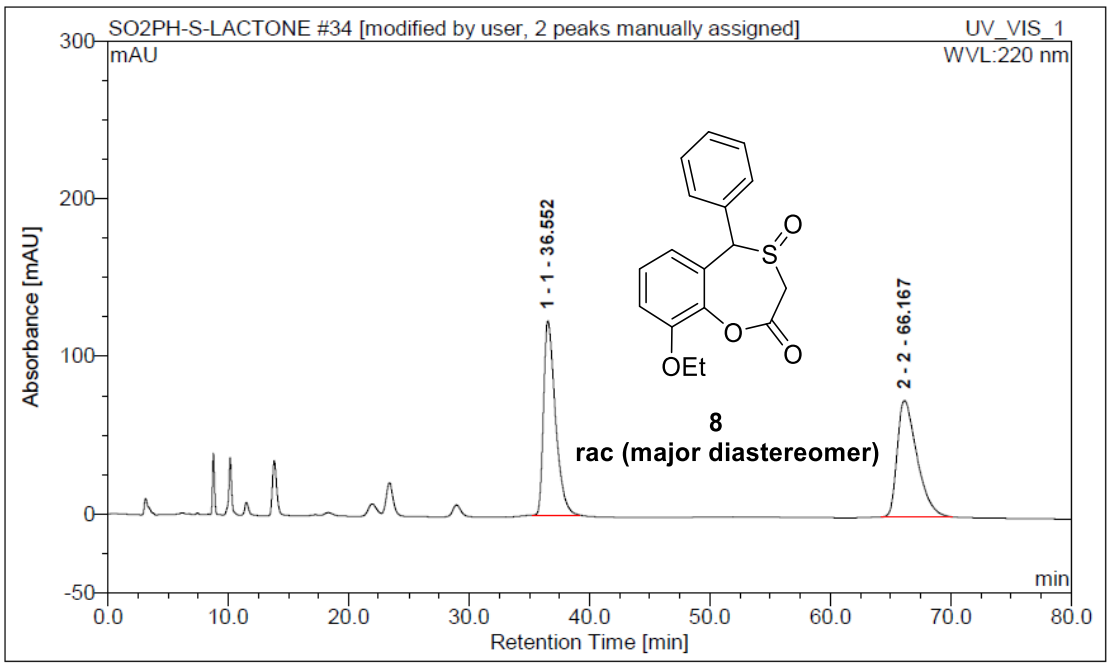
3-EQ-DIBALH-S-OH-OH-CHI-AMYLOSE-1



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	8.85	11.54384	4.084998356	54.0741	n.a.
2	2	9.43	271.047	95.91500164	1034.756	n.a.

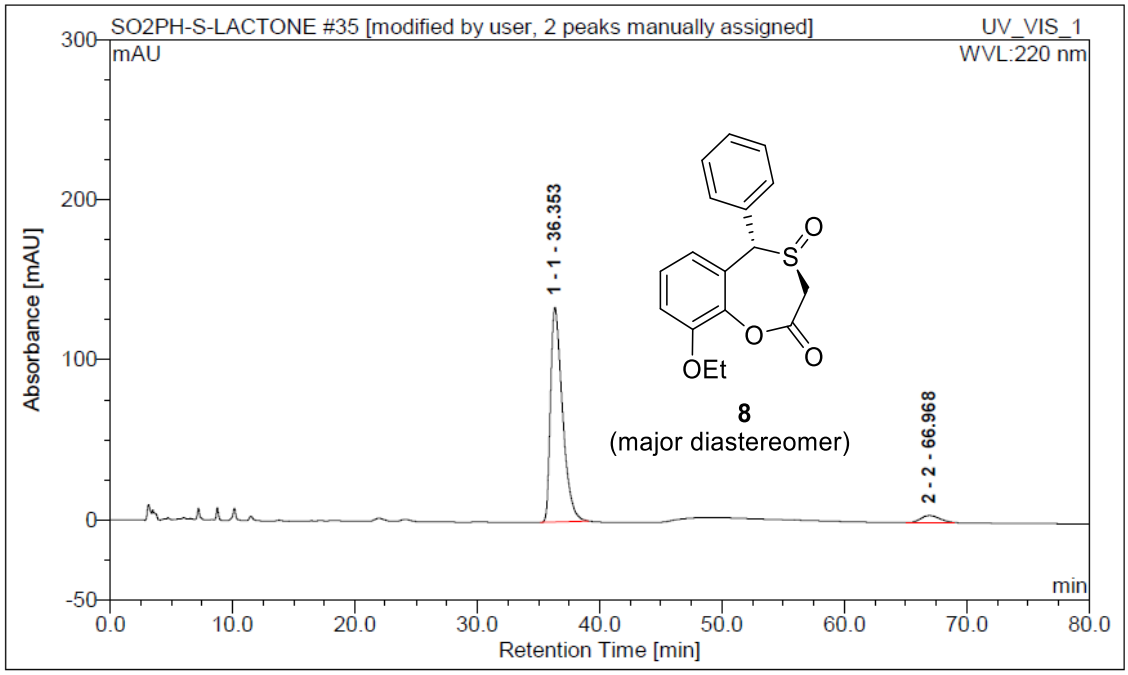


1-eq-MCPBA-SO2-lac-ID-rac



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	36.55	140.4331	49.97981856	123.2565	n.a.
2	2	66.17	140.547	50.02018144	73.775	n.a.

1-eq-MCPBA-SO2-lac-ID-chi

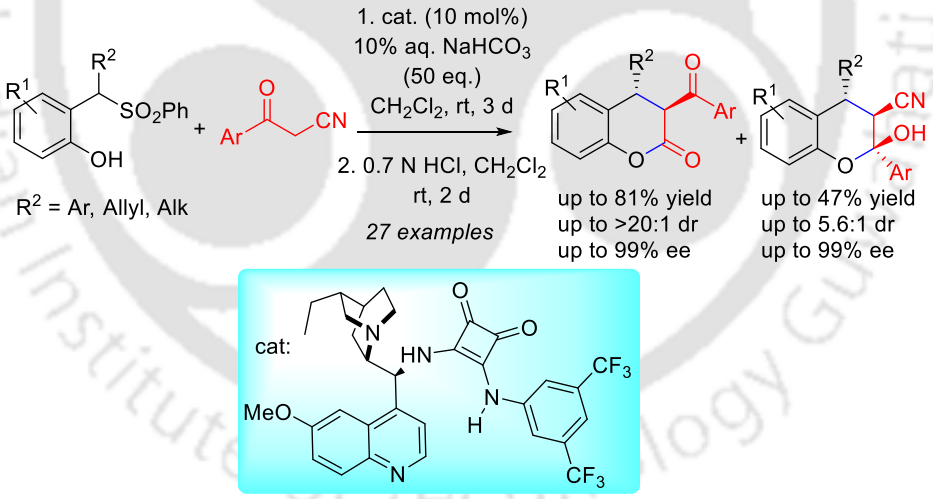


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	36.35	152.1167	95.25926947	134.3095	n.a.
2	2	66.97	7.570	4.740730526	4.376	n.a.

Organocatalytic Asymmetric Addition of Aromatic α-Cyanoketones to ortho-Quinone Methides: Synthesis of 3,4-Dihydrocoumarins and Tetra-Substituted Chromans[*]

Abstract:

The first organocatalytic asymmetric addition of aromatic *α*-cyanoketones to *in situ*-generated *ortho*-quinone methides have been described. The products namely 3,4-dihydrocoumarins and tetra-substituted chromans were obtained *via* bifunctional squaramide catalyzed conjugate addition reaction to *in situ*-generated *ortho*-quinone methides followed by treatment with 0.7 N HCl. With 10 mol% of the catalyst loading, the desired products were achieved in high enantio- and diastereoselectivities. Expansive scope and the reaction scale-up delineated the uniqueness of this method. Also, a route to chiral chromenes has been elucidated.



[*]Gharui, C.; Parida, C.; Pan, S. C. doi.org/10.1021/acs.joc.1c00435.

5.1. Introduction:

3,4-Dihydrocoumarin is an important structural motif widely present in nature and also in biologically active molecules (Figure 1).[1] For example, calomelanol was isolated from the plant pityrogramma calomelanos and it demonstrates antihypertensive, analgesic, antihemorrhagic, and antipyretic activities.[1a] Herbertenolide, a fused 3,4-dihydrocumarin, was isolated from liverwort Herberta adunca and it has useful biological properties such as growth inhibiting and antilipid peroxidation activities.[1b] Also, soulamarin, found in the stem bark of calophyllum soulattri, exhibits a range of biological activities.[1c] Aloe dihydrocoumarin (compound **A**) is another example of natural product possessing antioxidant and other useful medicinal properties.[1d] Dimeric 4-aryl-coumarin (compound **B**) shows potential estrogenic behaviour.[1e] In addition, safficinolide[1f] and ammodoremin[1g] having chroman-2-one moiety display antiviral and haemorrhagic activities respectively.

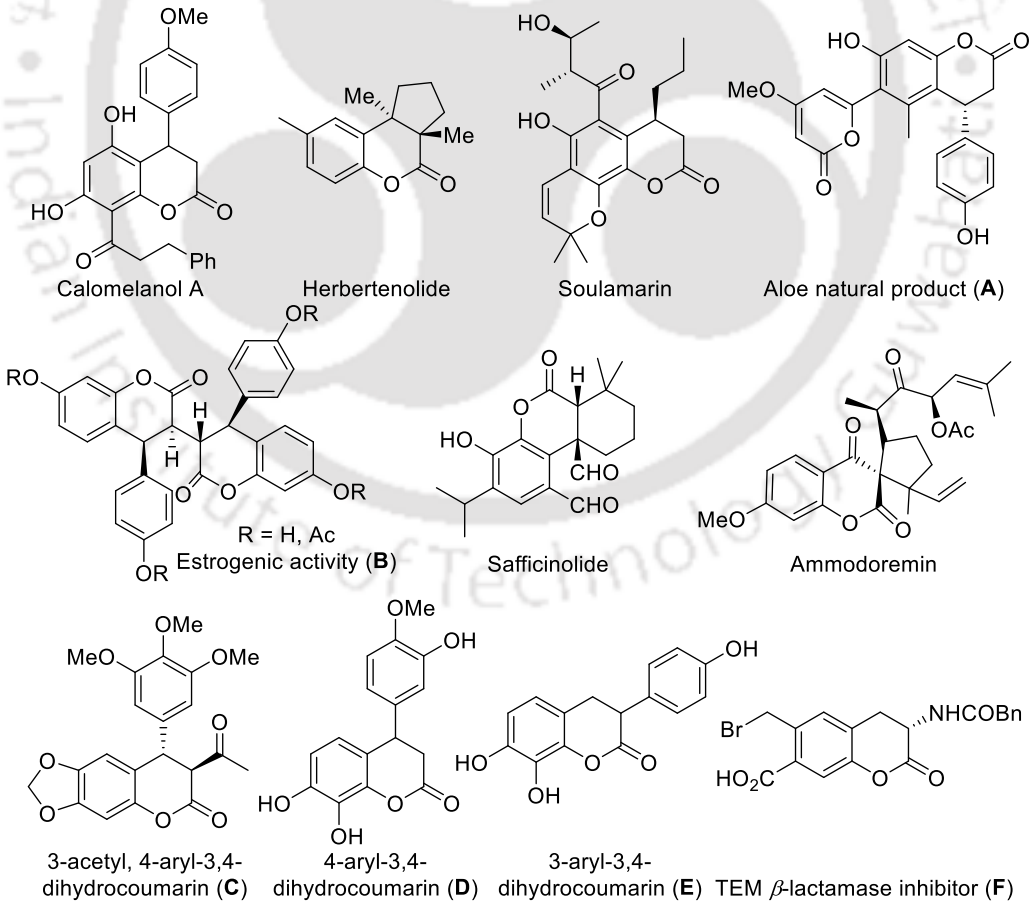


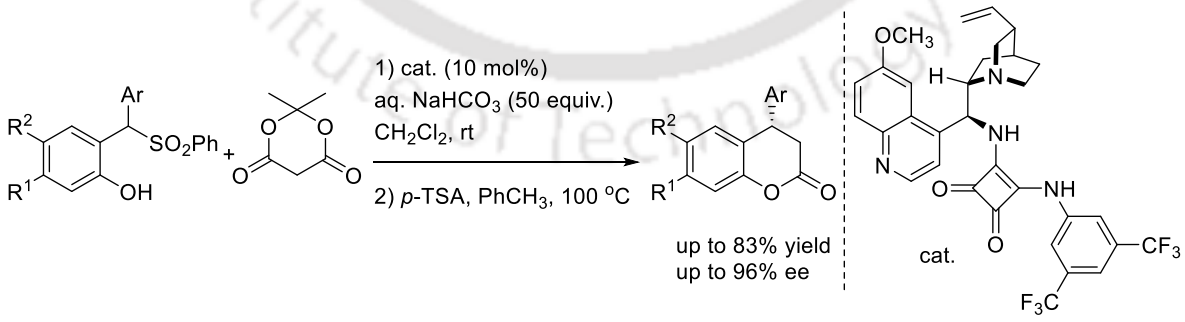
Figure 1. Biologically active 3,4-dihydrocoumarins.

Also synthetic 3,4-dihydrocoumarin derivatives display interesting biological activities such as antimitotic (compound **C**),[1h] antitumor (compound **D**),[1i] antioxidation (compound **E**)[1j] and TEM-*β*-lactamase inhibition (compound **F**).[1k] Besides, dihydrocoumarins are utilized as important building block in organic chemistry.[2] Therefore, it is highly desirable to develop efficient routes for the preparation of 3,4-dihydrocoumarins having different substitutions in an enantioselective manner.

In fact, in recent years, significant efforts have been devoted to the asymmetric synthesis of 3,4-dihydrocoumarin derivatives, and a number of elegant asymmetric organocatalytic syntheses have been developed.[3,4] Among these methods, asymmetric formal [4+2] annulation between *ortho*-quinone methides (*o*-QMs) and a variety of two-carbon reaction partners represents a convenient approach for the facile construction of 3,4-dihydrocoumarins (Figure 1).[4] On the other hand, *α*-cyanoketones are the reactive small molecules having keto and nitrile functionality and thus they had been engaged in many racemic and asymmetric transformations. Although, asymmetric reports[5] are very limited.

5.2.1. Previous strategies on chiral dihydrocoumarins synthesis employing *o*-QMs:

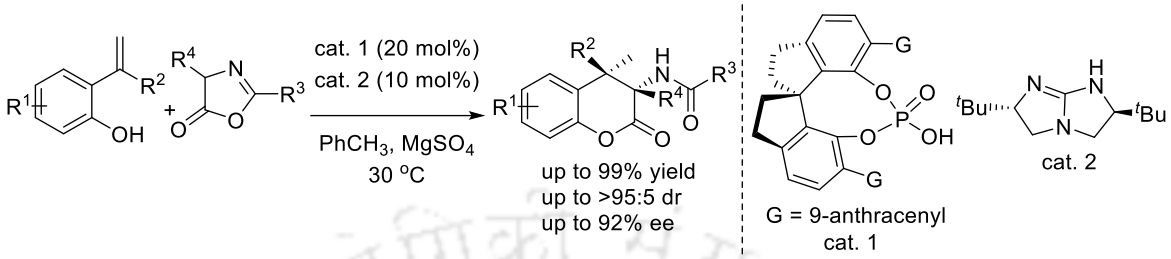
Bernardi and co-workers developed an organocatalytic enantioselective route for the synthesis of 4-aryl substituted dihydrocoumarins using Meldrum's acid and *in situ*-generated *ortho*-quinone methides (Scheme 1).[4d] With 10 mol% quinine derived squaramide catalyst and *p*-TSA, desired products were obtained in high yields and excellent enantioselectivities. Also, the reaction of malononitrile under similar conditions provided 4*H*-chromene products.



Scheme 1. Enantioselective addition/cyclization of Meldrum's acid to *in situ*-*o*-QMs.

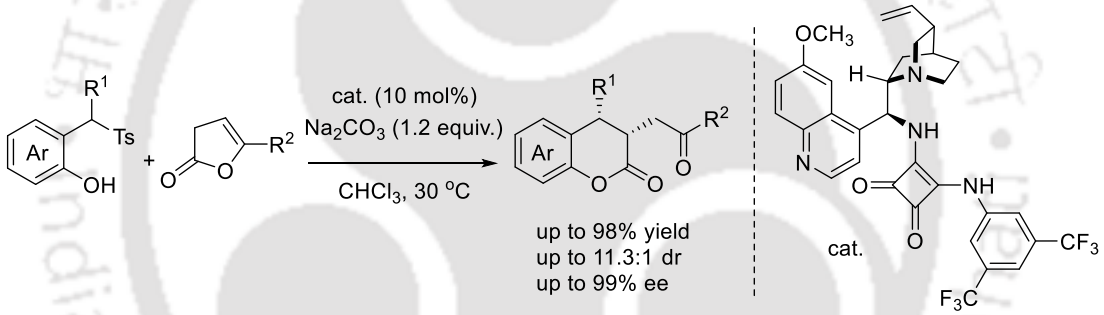
Another organocatalytic asymmetric [4+2] cycloaddition reaction between *ortho*-hydroxystyrenes and azlactones had been disclosed by Shi *et al*. (Scheme 2).[4f] Herein,

chiral phosphoric acid catalyst in combination with cooperative guanidine catalyst delivered 3,3,4,4-tetrasubstituted dihydrocoumarins with excellent reaction outcome.



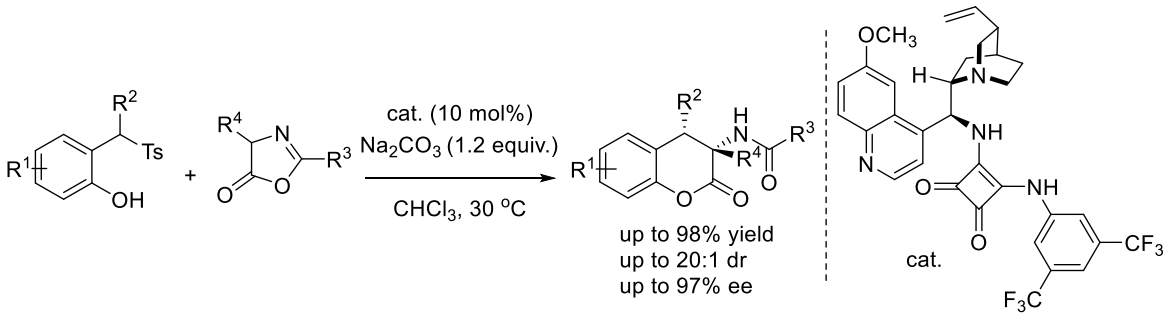
Scheme 2. Asymmetric [4+2] cycloaddition of azlactones to *in situ*-*o*-QMs.

In 2017, Lan and Zhou and co-workers established bifunctional squaramide catalyzed enantioselective *α*-addition/cyclization of deconjugated butenolides to *in situ*-generated *o*-QMs to provide *cis*-3,4-disubstituted dihydrocoumarin derivatives (Scheme 3).[4g]



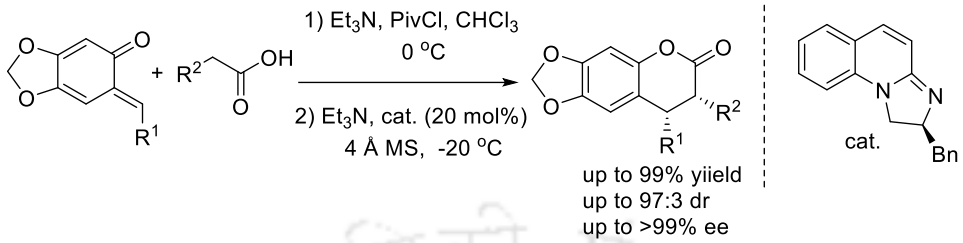
Scheme 3. Asymmetric addition/cyclization of deconjugated butenolides to *in situ*-*o*-QMs.

In the same year, again Zhou group independently described diastereo- and enantioselective addition/cyclization of azlactones to *in situ*-generated *o*-QMs under same reaction conditions (Scheme 4).[4h] 2-(Aryl(tosyl)methyl)phenols under basic medium furnished trisubstituted chroman-2-ones containing contiguous quaternary and tertiary stereogenic centres at C-3 and C-4 positions respectively with good results.



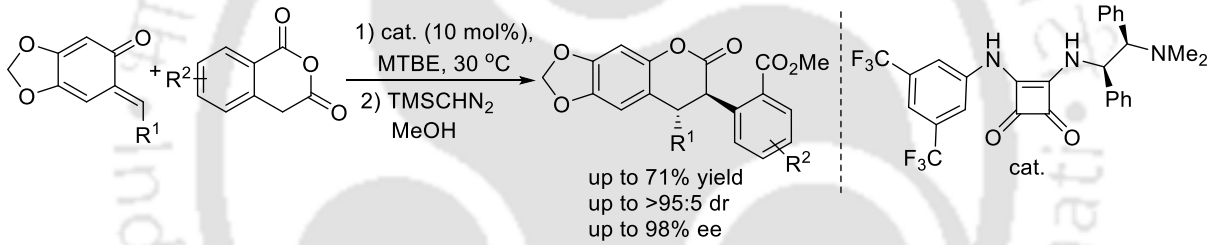
Scheme 4. Squaramide catalyzed asymmetric reaction of azlactones to *in situ*-*o*-QMs.

Also, Deng and co-workers reported a chiral amidine catalyzed domino Michael addition/ lactonization of carboxylic acids with stabilized *o*-QMs for the synthesis of *cis* 3,4-disubstituted dihydrocoumarins in an enantioselective manner (Scheme 5).[4i]



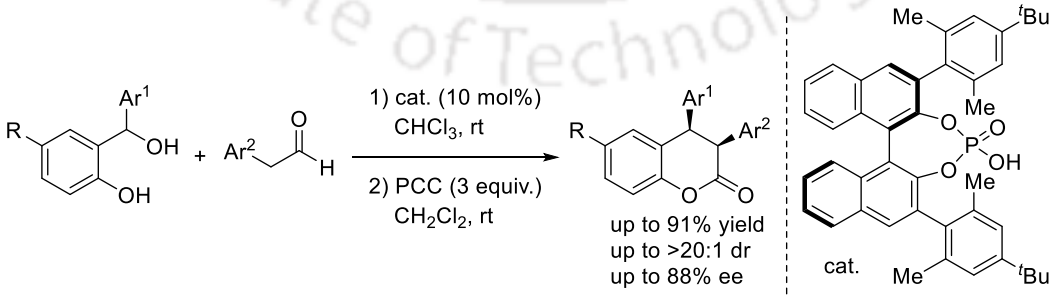
Scheme 5. Chiral amidine catalyzed asymmetric reaction of carboxylic acids to *o*-QMs.

In 2018, Shi *et al*. demonstrated chiral bifunctional squaramide catalyzed another [4+2] cyclization reaction employing stabilized *o*-QMs and homophthalic anhydrides (Scheme 6).[4k] With 10 mol% of catalyst the expected *trans*-dihydrocoumarins were achieved in high diastereomeric ratio and enantiomeric excesses.



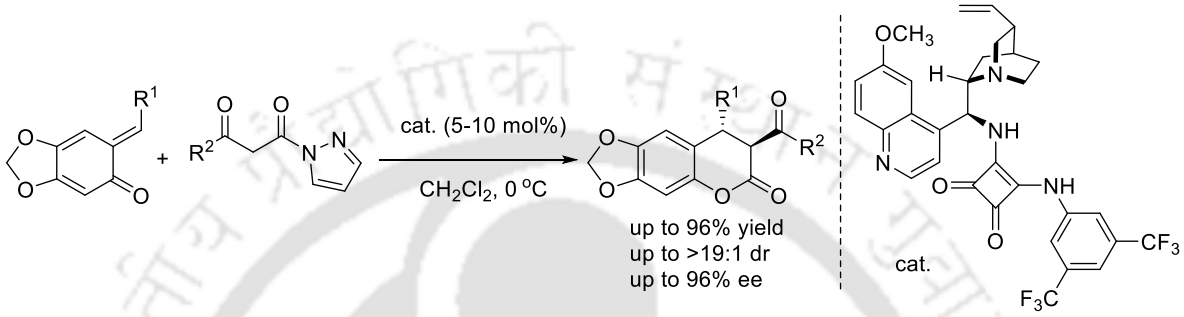
Scheme 6. Asymmetric [4+2] cyclization of homophthalic anhydrides and *o*-QMs.

In the same year, Schneider group successfully anticipated chiral phosphoric acid catalyzed addition of aryl acetaldehydes to *in situ*-generated *o*-QMs to generate *cis*-3,4-diaryl dihydrocoumarins (Scheme 7).[4l] Herein, moderate to good diastereo- and enantioselectivities were observed for the products.



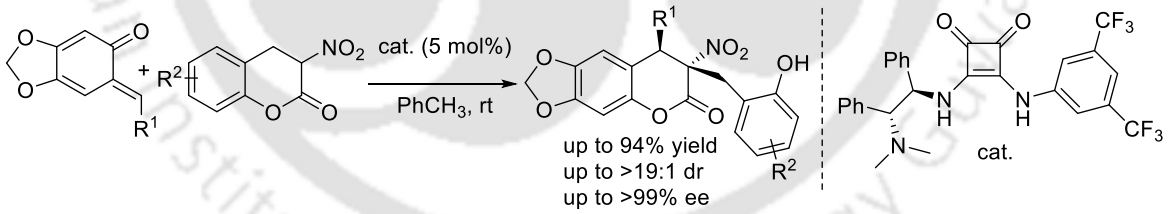
Scheme 7. Enantioselective addition of aryl acetaldehydes to *in situ*-*o*-QMs.

Zhou group recently described an organocatalytic [4+2] cyclization of *β*-keto acylpyrazoles and stabilized *o*-QMs for the synthesis of chiral *trans*-3,4-dihydrocoumarins (Scheme 8).[4m] Although, high yields and enantiomeric excesses were attained in case of stabilized *o*-QMs, surprisingly a decrease in enantioselectivity was observed when *in situ*-generated *o*-QMs were employed.



Scheme 8. Asymmetric [4+2] annulation of *β*-keto acylpyrazoles to stabilized *o*-QMs.

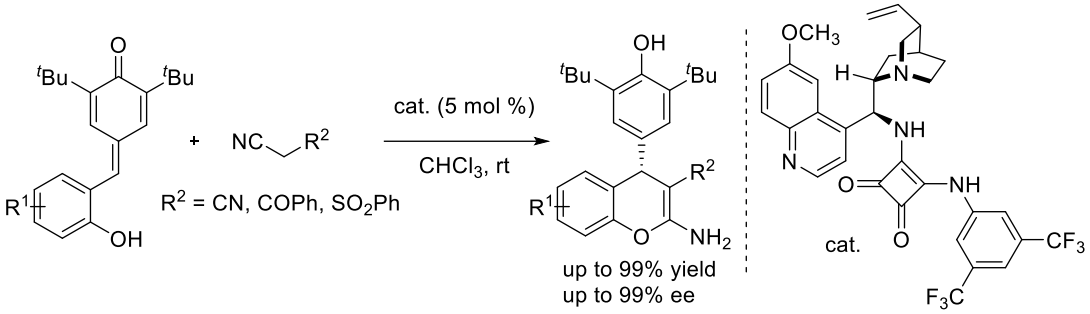
Another organocatalytic asymmetric [4+2] cyclization reaction between stabilized *o*-QMs and 3-nitro-3,4-dihydrocoumarins had been illustrated by the same group in 2019 (Scheme 9).[4n] With 5 mol% of squaramide catalyst loading, a variety of dihydrocoumarin products had been synthesized with high level of diastereomeric ratios and moderate to high enantioselectivities.



Scheme 9. Asymmetric [4+2] annulation of 3-nitro-3,4-dihydrocoumarins to stabilized *o*-QMs.

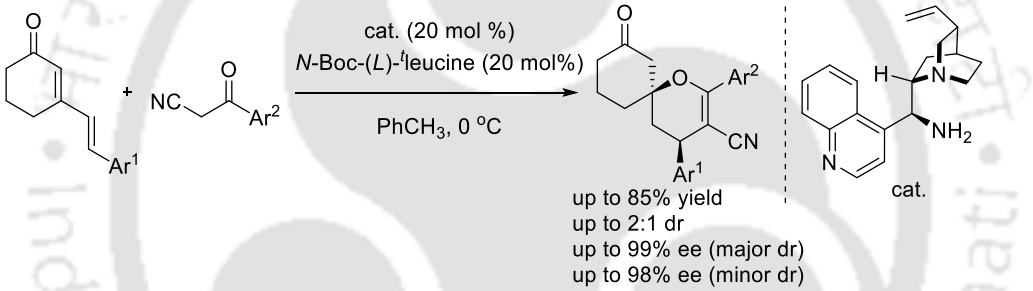
5.2.2. Previous asymmetric reports on *α*-cyanoketones:

Li and co-workers demonstrated quinine derived squaramide catalyzed enantioselective 1,6-conjugate addition/cyclization reaction between *ortho*-hydroxylated *para*-quinone methides (*p*-QMs) and malononitrile/benzoylacetonitrile/(phenylsulfonyl)acetonitrile (Scheme 10).[5a] Using 5 mol% chiral catalyst, a range of 2-amino-4aryl-4*H*-chromene derivatives were achieved in high yields and with excellent enantioselectivities.



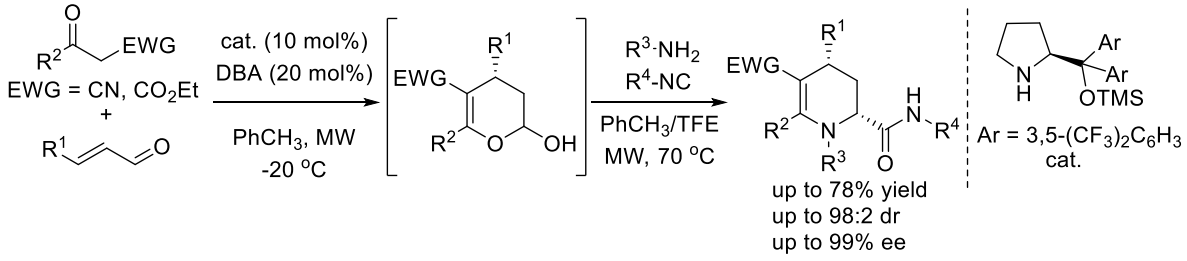
Scheme 10. Enantioselective synthesis of 2-amino-4aryl-4*H*-chromenes from substituted-acetonitriles and *p*-QMs.

Recently, our group reported cinchonidine amine catalyzed asymmetric approach for the construction of spiro-dihydropyrano-cyclohexanones from the reaction of α-cyanoketones and cyclic 2,4-dienones (Scheme 11).[5b] Though enantiomeric excesses of these products were high, diastereoselectivities and yields of the reactions were moderate.



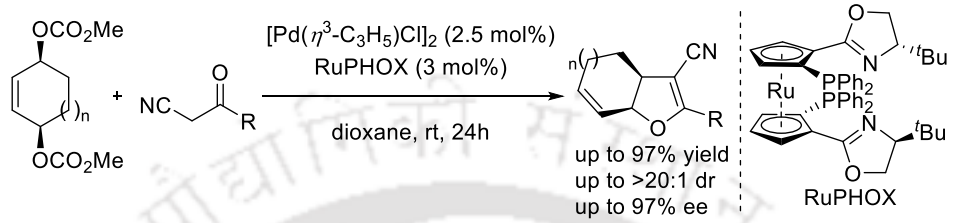
Scheme 11. Asymmetric synthesis of spiro-dihydropyrano-cyclohexanones using cyclic 2,4-dienones and α-cyanoketones.

Microwave assisted organocatalytic asymmetric one pot multicomponent reaction (MCR) using α,β-unsaturated aldehydes, α-cyanoketones, primary amine and alkyl isocyanides had been explored by Paixão *et al*. (Scheme 12).[5c] Herein, the desired tetrahydropyridine products were obtained in moderate to good yields with high diastereomeric ratios and in high enantiomeric excesses.



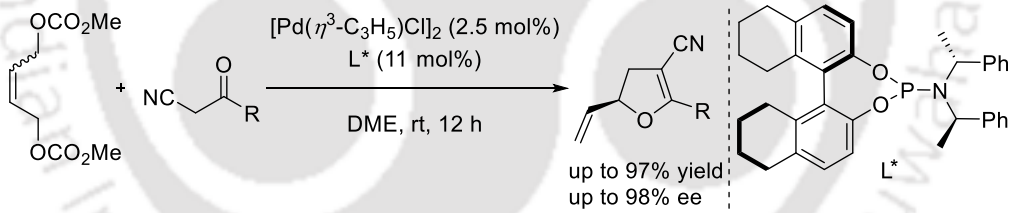
Scheme 12. Synthesis of chiral tetrahydropyridines *via* organocascade/MCR sequence.

In addition, allylic *meso*-dicarbonates and binucleophilic *α*-cyanoketones were efficiently engaged in an asymmetric allylic substitution/ring closing reaction by Shen and Liu group in 2019 (Scheme 13).[5d] A variety of bicyclic dihydrofuran products were achieved with excellent diastereo- and enantioselectivities using catalytic amount Pd/RuPHOX complex.



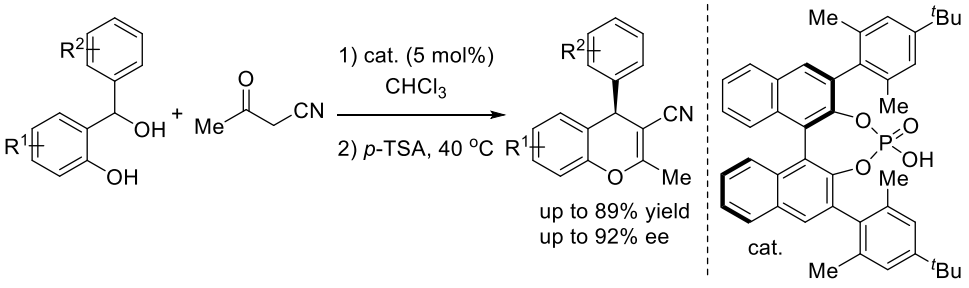
Scheme 13. Pd/RuPHOX catalyzed reaction of allylic *meso*-dicarbonates with *α*-cyanoketones.

In the next year, again Liu group independently disclosed another asymmetric methodology employing both geometric isomers of but-2-ene-1,4-diyl dimethyl carbonates and *α*-cyanoketones separately to deliver 2,3-dihydrofurans with same absolute configuration (Scheme 14).[5e] Interestingly, here Pd/hydrogenated phosphoramidite metal-ligand combination was found to be effective in terms of yield and ee of the reaction.



Scheme 14. Pd/hydrogenated phosphoramidite catalyzed reaction of (*Z*)/(*E*)-but-2-ene-1,4-diyl dimethyl carbonates and *α*-cyanoketones.

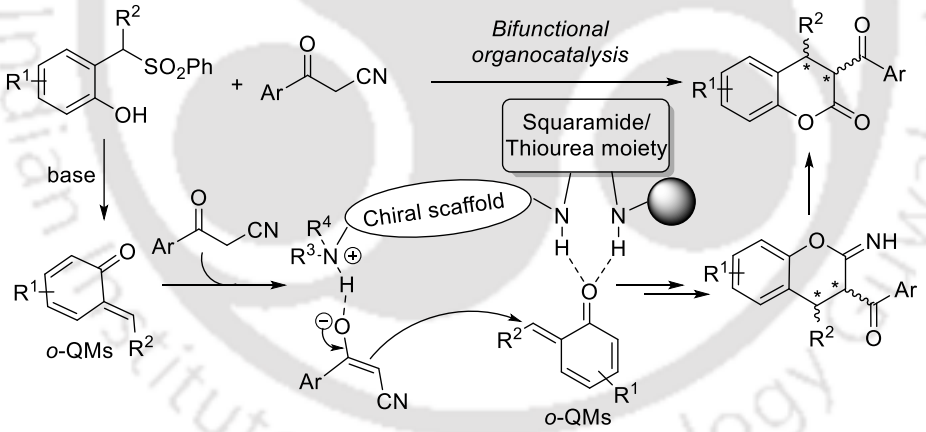
Very recently, Schneider and co-workers reported chiral phosphoric acid catalyzed enantioselective addition of aliphatic 3-oxobutanenitrile to *in situ*-generated *o*-QMs for the synthesis of 4*H*-chromenes in successive two steps (Scheme 15).[5f]



Scheme 15. Chiral phosphoric acid catalyzed reaction of 3-oxobutanenitrile to *o*-QMs.

5.3. Concept:

From the literature survey it has been identified that chiral 3,4-dihydrocoumarins are the significant class of molecules having broad spectrum of applications in biological as well as in medicinal chemistry. Thus in this regard, various methodologies have been developed for the preparation of enantiopure substituted dihydrocoumarins. However, most of the methods are focused on the development of mono-substituted or tri-substituted 3,4-dihydrocoumarins and the syntheses of 3,4-disubstituted dihydrocoumarins are less known. Also, to the best of our knowledge, aromatic *α*-cyanoketones were never applied in the asymmetric reaction with *o*-QMs. Therefore, we envisioned that chiral bifunctional (thio)urea/squaramide catalyzed reaction of aromatic *α*-cyanoketones and *in situ*-generated *o*-QMs could lead to the formation of 3,4-disubstituted dihydrocoumarins. Initially, we expected that basic quinuclidine motif of the catalyst will activate the enol form of *α*-cyanoketone and the (thio)urea/squaramide part will activate *o*-QM intermediate. Then conjugate addition followed by oxa-nucleophilic cyclization may deliver the desired products in an enantioselective fashion (Scheme 16).

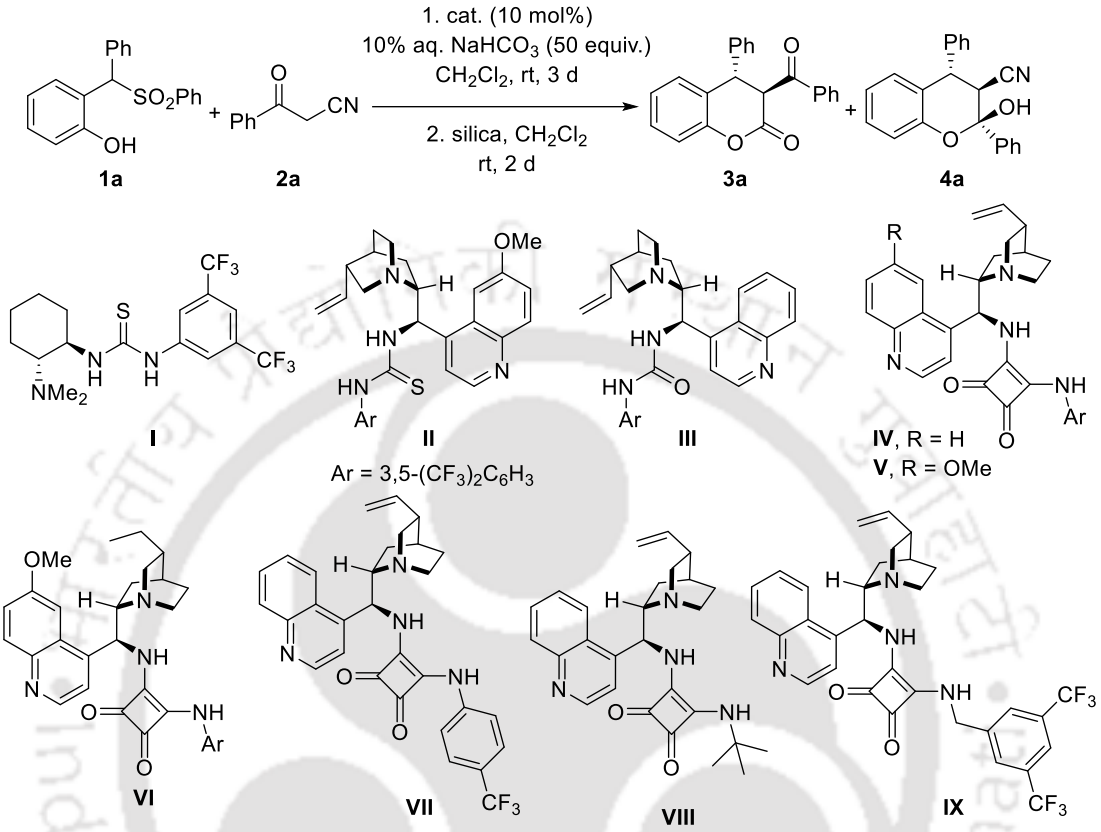


Scheme 16. Proposed route to 3,4-disubstituted dihydrocoumarins.

5.4. Result and Discussion:

We started our investigation by performing a model reaction between 2-(phenyl(phenylsulfonyl)methyl)phenol (**1a)** and *α*-cyanoacetophenone (**2a**) with Takemoto catalyst (**I**) and 50 equivalents of 10% aq. sodium bi-carbonate in dichloromethane at room temperature (Table 1). Gratifyingly, after stirring for 3 days, the desired dihydrocoumarin **3a** was formed along with chroman **4a** in 1:1 ratio in overall 80% yield.

Table 1. Catalyst screening



entry[a]	catalyst	**3a**/**4a**[b]	yield (**3a**)[c]	dr (**3a**)[d]	ee (**3a**)[e]
1	**I**	2.2:1	59	>20:1	72
2	**II**	1.9:1	58	>20:1	76
3	**III**	1.5:1	54	>20:1	74
4	**IV**	1.6:1	52	>20:1	94
5	**V**	1.2:1	48	>20:1	96
6	**VI**	**1.7:1**	**57**	**>20:1**	**96**
7	**VII**	1.2:1	52	>20:1	92
8	**VIII**	0.2:1	12	>20:1	90
9	**IX**	2.1:1	41	>20:1	92

[a]Reaction conditions: Unless otherwise mentioned, 0.05 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL CH_2Cl_2 using 10 mol% catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then work up using 1 N HCl/CH_2Cl_2 and and then 100 mg silica (60-120 mesh) in 1 mL CH_2Cl_2 at room temperature for 2 days. [b]Determined by ^{1}H NMR. [c]Isolated yield of **3a** after silica gel column chromatography. [d]Determined by ^{1}H NMR. [e]Determined by HPLC using stationary phase chiral column.

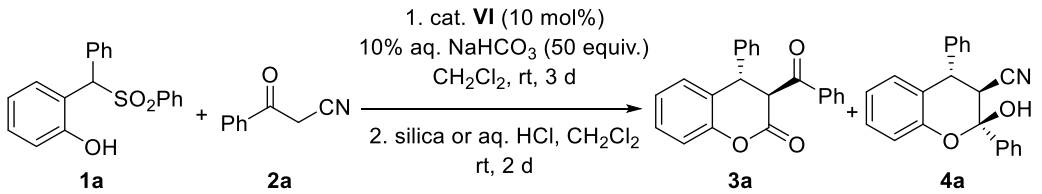
We realized that an acidic treatment could change the product ratio and thus the reaction mixture after work up was mixed with 100 mg of silica (60-120 mesh) in dichloromethane and stirred for another 2 days. Delightfully, the product ratio improved to 2.2:1 and the dihydrocoumarin **3a** was isolated as single diastereomer in 59% yield with 72% enantiomeric excess (entry 1). To improve the enantiomeric excess, different bifunctional thiourea and squaramide catalysts were screened. Quinidine derived thiourea **II** also provided the product **3a** in similar product ratio (i.e. 1.9:1) and with similar enantioselectivity (76% ee) (entry 2). The outcome did not change much with cinchonine derived urea catalyst **III** (entry 3). Then various bifunctional squaramide catalysts were employed and interestingly better results were obtained. For example, catalyst **IV** having cinchonidine motif and 3,5-bistrifluoromethylphenyl group provided dihydrocoumarin **3a** in 52% yield with 94% ee and 1.6:1 product ratio was detected. The enantioselectivity got slightly improved to 96% ee with quinine derived squaramide catalyst **V** although product ratio was decreased to 1.2:1 (entry 5). Next, hydroquinine derived squaramide catalyst **VI** was employed and provided the product **3a** in 57% yield with 96% ee and in 1.7:1 product ratio (entry 6). Cinchonidine based squaramide catalyst **VII** having 4-trifluoromethylphenyl group was also engaged but the product ratio (i.e. 1.2:1) and the enantioselectivity of **3a** (92% ee) were found to decrease significantly (entry 7). Surprisingly, very less conversion and further drop in enantioselectivity of **3a** (i.e. 90% ee) were detected in case of catalyst **VIII** having *tert*-butyl amine motif (entry 8). Also, catalyst **IX** having 3,5-bistrifluoromethylbenzyl group promoted the reaction with 2.1:1 product ratio and with 92% enantiomeric excess (entry 9). Finally, the best catalyst turned out to be hydroquinine derived squaramide catalyst **VI** in terms of yield as well as enantiomeric excess of the product **3a** (entry 6).

5.4.1. Acidic condition and catalyst loading optimization:

In order to further improve the product ratio as well as the enantiomeric excess of product

3a, other reaction parameters such as effects of acidic conditions in the second step and catalyst loading optimization were carefully performed (Table 2). Interestingly, in all cases product **3a** was isolated in a single diastereomer. Aqueous work up followed by stirring with 100 mg silica (for 0.05 mmol of **1a**) delivered the desired product **3a** in 46% yield with 92% ee and 0.8:1 product ratio (Table 2, entry 1). To our delight, product ratio (1.7:1) and enantioselectivity (96% ee) were enhanced when acidic work up was performed using 1 N HCl (entry 2). Then the effect of silica contents on ee and product ratio was checked. With the increase of silica amount (i.e. 300 mg or 500 mg instead of 100 mg), product ratio got suddenly dropped and low conversions were noticed although excellent enantioselectivities were maintained (entries 3-4). After this, further optimization was executed by treating hydrochloric acid in different concentrations (entries 5-11). When 0.3 N HCl was used, decent result was obtained for product **3a** (i.e. 56% yield, 95% ee, **3a**/**4a** =1.3:1) (entry 5). Further enhancements in both the product ratio and the enantioselectivity were observed with 0.5 N hydrochloric acid (entry 6). Then the best condition was found to be 0.7 N hydrochloric acid which afforded the product **3a** in 78% yield with 98% ee and in 3.9:1 product ratio (entry 7). Under these conditions, chroman[6] **4a** was isolated in 18% yield with 5.6:1 dr and 94% ee. However, in case of 1 N HCl treatment, ee of **3a** got slightly dropped to 97% and the product ratio was 2.1:1 (entry 8). Similar reaction outcome (i.e. 98% ee and 2:1 product ratio) was achieved for 3 N HCl (entry 9). With the addition of more concentrated acids (such as 6 N and 9 N), enantioselectivities of product **3a** got decreased in significant amounts although product ratios were almost similar (entries 10-11). After the acidic conditions got optimized, the reaction with low catalyst loading was also tested. A little decline in yield (i.e. 69%) of **3a** was perceived with 5 mol% of catalyst though enantioselectivity was maintained (98% ee) (Table 2, entry 12).

Table 2. Acidic condition and catalyst loading optimization



1a **2a** **3a** **4a**

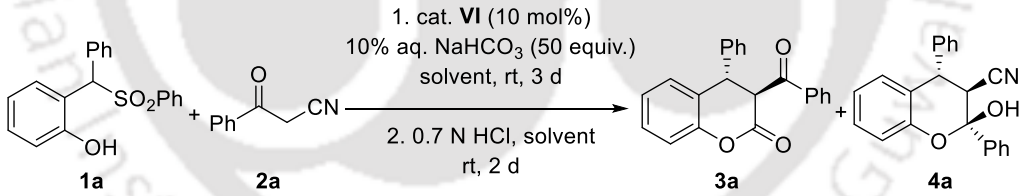
entry[a]	acidic conditions	**3a**/**4a**[b]	yield (**3a**)[c]	dr (**3a**)[d]	ee (**3a**)[e]
1	aq. work up then stirring with 100 mg silica	0.8:1	46	>20:1	92
2	1 N HCl work up then stirring with 100 mg silica	1.7:1	57	>20:1	96
3	1 N HCl work up then stirring with 300 mg silica	0.8:1	25	>20:1	96
4	1 N HCl work up then stirring with 500 mg silica	0.6:1	21	>20:1	97
5	0.3 N HCl work up then stirring with 1 mL 0.3 N HCl	1.3:1	56	>20:1	95
6	0.5 N HCl work up then stirring with 1 mL 0.5 N HCl	2.8:1	70	>20:1	98
7	**0.7 N HCl work up then stirring with 1 mL 0.7 N HCl**	**3.9:1**	**78**	**>20:1**	**98**
8	1 N HCl work up then stirring with 1 mL 1 N HCl	2.1:1	67	>20:1	97
9	3 N HCl work up then stirring with 1 mL 3 N HCl	2:1	63	>20:1	98
10	6 N HCl work up then stirring with 1 mL 6 N HCl	2:1	63	>20:1	92
11	9 N HCl work up then stirring with 1 mL 9 N HCl	1.9:1	61	>20:1	87
12[f]	0.7 N HCl work up then stirring with 1 mL 0.7 N HCl	2.7:1	69	>20:1	98

[a]Reaction conditions: 0.05 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL CH_2Cl_2 using 10 mol% **VI** catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then work up and then stirring under acidic conditions using 1 mL CH_2Cl_2 at room temperature for 2 days. [b]Determined by ^{1}H NMR. [c]Isolated yield of **3a**. [d]Determined by ^{1}H NMR. [e]Determined by HPLC using stationary phase chiral column. [f]5 mol% catalyst **VI** was used instead of 10 mol%.

5.4.2. Solvent screening:

In the next phase, effects of various solvents on the enantioselectivity of the dihydrocoumarin product were thoroughly checked (Table 3). First, different halogenated solvents other than dichloromethane were investigated. For example, chloroform solvent provided the expected product **3a** in 75% yield with enantiomeric excess (98%) and with slight less product ratio (i.e. 3.3:1) (Table 3, entry 2). A significant drop in the enantioselectivity (86% ee) along with 2.5:1 product ratio were observed in the case of 1,2-dichloroethane (entry 3). Interestingly, *α,α,α*-trifluorotoluene solvent afforded the product **3a** in highest 80% yield and with maximum 4.3:1 ratio. However, the ee got decreased in little amount (entry 4). Ethereal solvent like diethylether gave the dihydrocoumarin product only with 17% yield and 66% enantiomeric excess (entry 5). Herein, tetra-substituted chroman **4a** was found to form as the major product. In addition, non-halogenated solvent like toluene furnished the product **3a** in acceptable results (64% yield, 90% ee and 2.3:1 product ratio) (entry 6). Thus finally, dichloromethane was found to be the best solvent in terms of yield, ee and product ratio (entry 1).

Table 3. Solvent screening



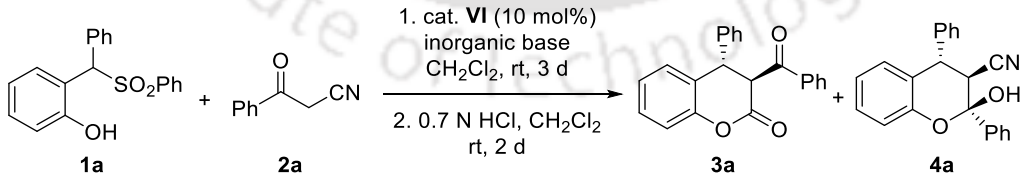
entry[a]	solvent	**3a**/**4a**[b]	yield (**3a**)[c]	dr (**3a**)[d]	ee (**3a**)[e]
1	**CH_2Cl_2**	**3.9:1**	**78**	**>20:1**	**98**
2	$CHCl_3$	3.3:1	75	>20:1	98
3	$(CH_2Cl)_2$	2.5:1	67	>20:1	86
4	$PhCF_3$	4.3:1	80	>20:1	94
5	Et_2O	0.2:1	17	>20:1	66
6	toluene	2.3:1	64	>20:1	90

[a]Reaction conditions: 0.05 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL solvent using 10 mol% **VI** catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then acidic work up followed by stirring with 0.7 N HCl in 1 mL same solvent at room temperature for 2 days. [b]Determined by ^1H NMR. [c]Isolated yield of **3a**. [d]Determined by ^1H NMR. [e]Determined by HPLC using stationary phase chiral column.

5.4.3. Inorganic base screening:

After getting the best catalyst, acidic condition and solvent optimization; the effects of various inorganic bases were exclusively examined (Table 4). To our delight, **3a** was isolated always as a sole diastereomer in all cases. For instance, 50 equivalents of 10% aq. Na_2CO_3 supplied the product **3a** in 80% yield with 89% ee and 4.3:1 product ratio (Table 4, entry1). Other inorganic base like K_2CO_3 under the same conditions delivered the expected product with less enantiomeric excess (i.e. 70%) and in 3.3:1 ratio (entry 2). Gratifyingly, excellent results (78% yield, 98% ee and 3.9:1 product ratio) were achieved with 50 equivalents of 10% aq. $NaHCO_3$ (entry 3). After finding the best inorganic base i.e. $NaHCO_3$, the impact of the quantity of base on the yield and ee of the reaction was then studied (entries 4-6). With gradual decrease in the base amount, product ratio and consequently the yield of **3a** were found to fall though enantioselectivities were remained almost unaltered. For example, when 25 equivalents of aq. $NaHCO_3$ was treated, **3a** was attained in 68% yield and 97% ee (entry 4). Similar results (70% yield and 96% ee) were obtained when 10 equivalents of $NaHCO_3$ base were utilized (entry 5). Also, employment of 2 equivalents of base delivered the product with 46% yield and 99% enantiomeric excess (entry 6). Finally, 50 equivalents of 10% aq. Na_2CO_3 had been identified as the best condition for this reaction (entry 3).

Table 4. Inorganic base optimization



entry[a]	inorganic base [eq.]	**3a**/**4a**[b]	yield (**3a**)[c]	dr (**3a**)[d]	ee (**3a**)[e]
1	10% aq. Na_2CO_3 [50]	4.3:1	80	>20:1	89
2	10% aq. K_2CO_3 [50]	3.3:1	72	>20:1	70

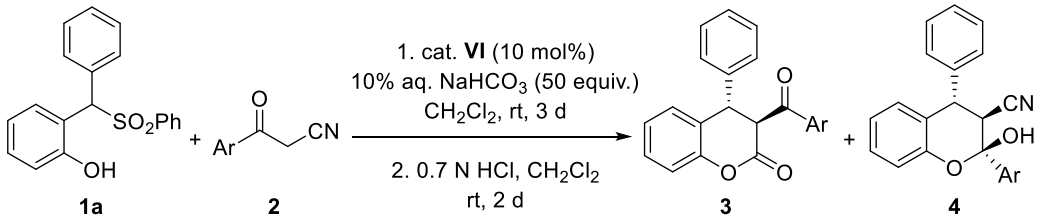
3	**10% aq. $NaHCO_3$ [50]**	**3.9:1**	**78**	**>20:1**	**98**
4	10% aq. $NaHCO_3$ [25]	2.8:1	68	>20:1	97
5	10% aq. $NaHCO_3$ [10]	2.9:1	70	>20:1	96
6	10% aq. $NaHCO_3$ [2]	0.9:1	46	>20:1	99

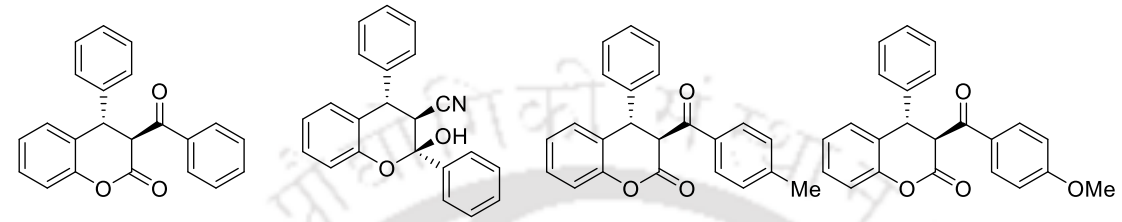
[a]Reaction conditions: 0.05 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL CH_2Cl_2 using 10 mol% **VI** catalyst and 10% aq. inorganic base at room temperature for 3 days and then acidic work up followed by stirring with 0.7 N HCl and 1 mL CH_2Cl_2 at room temperature for 2 days. [b]Determined by ^{1}H NMR. [c]Isolated yield of **3a**. [d]Determined by ^{1}H NMR. [e]Determined by HPLC using stationary phase chiral column.

5.4.4. Substrate scope:

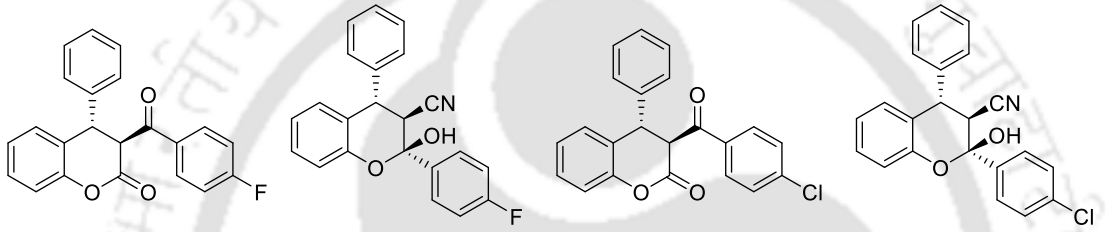
After the optimized conditions got established, the scope and generality of the reaction have been investigated. Initially, different *α*-cyanoketones were tested under the reaction conditions with **1a** (Table 5) and gratifyingly good results were attained. At first, different *para*-substituted aryl group containing *α*-cyanoketones **2b**-**2f** were employed (Table 5). On reaction between *p*-tolyl containing cyanoketone **2b** and 2-(phenyl(phenylsulfonyl)methyl)phenol **1a**, product **3b** was obtained in 5.2:1 ratio with perfect diastereoselectivity (>20:1 dr) and excellent enantioselectivity (98% ee). Then anisole containing *α*-cyanoketone **2c** was screened and here also the reaction proceeded efficiently to provide product **3c** as a single diastereomer in 4.9:1 ratio with high enantiomeric excess (96% ee). The reaction outcome was also excellent for 4-halo substituted *α*-cyanoketones **2d**-**2f** though in few cases the chroman product was isolated in significant amounts (Table 5). For example, 4-fluoro substituted aryl ketone **2d** delivered the dihydrocoumarin product **3d** in 4.8:1 ratio with 76% yield, >20:1 dr and 95% ee. The chroman product **4d** was isolated in 10% yield with 3.2:1 dr and 91% ee. 4-Chloro and 4-bromo aryl group containing dihydrocoumarins **3e** and **3f** were obtained in 1.5:1 and 1.3:1 ratios respectively indicating substantial amount of formations of chromans **4e** and **4f**. The dihydrocoumarin product **3e** was achieved in 43% yield with >20:1 dr and 92% ee. Similar yield, dr (i.e. 41% yield, >20:1 dr) along with high ee (97%) were detected for product **3f**. Excellent enantioselectivity (99% ee) was observed for chroman **4e**. Also, similar enantioselectivity (98% ee) was identified for chroman **4f** (Table 5).

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

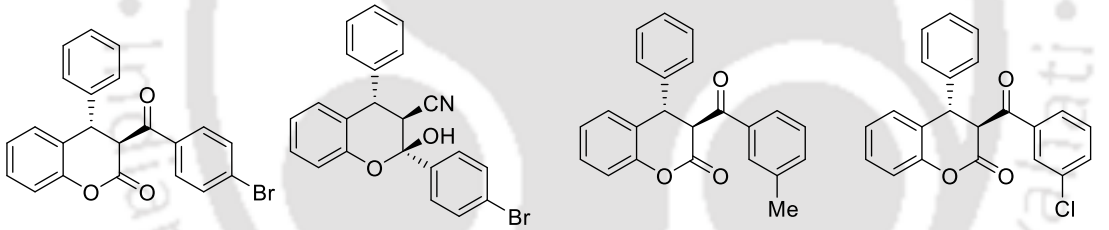




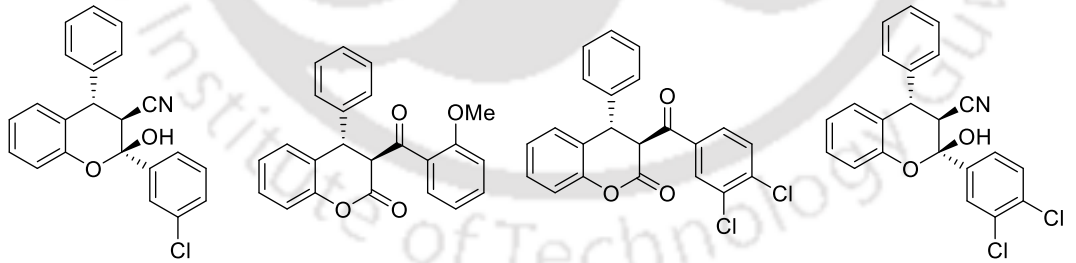
3a, 78%, >20:1 dr, 98% ee **4a**, 18%, 5.6:1 dr, 94% ee **3b**, 81%, >20:1 dr, 98% ee **3c**, 78%, >20:1 dr, 96% ee



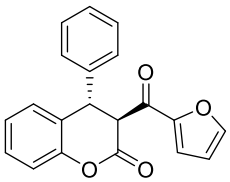
3d, 76%, >20:1 dr, 95% ee **4d**, 10%, 3.2:1 dr, 91% ee **3e**, 43%, >20:1 dr, 92% ee **4e**, 26%, 4.8:1 dr, 99% ee



3f, 41%, >20:1 dr, 97% ee **4f**, 32%, 4.5:1 dr, 98% ee **3g**, 79%, >20:1 dr, 97% ee **3h**, 21%, >20:1 dr, 97% ee



4h, 43%, 3.2:1 dr, 93% ee **3i**, 15%, >20:1 dr, 96% ee **3j**, 22%, >20:1 dr, 99% ee **4j**, 47%, 4.1:1 dr, 90% ee



[d]**3k**, 41%, >20:1 dr, 78% ee

[a]Reaction conditions: 0.1 mmol of **1a** and 0.2 mmol of **2** in 1.2 mL CH_2Cl_2 using 10 mol% catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then work up and then 2 mL 0.7 N HCl in 2 mL CH_2Cl_2 at

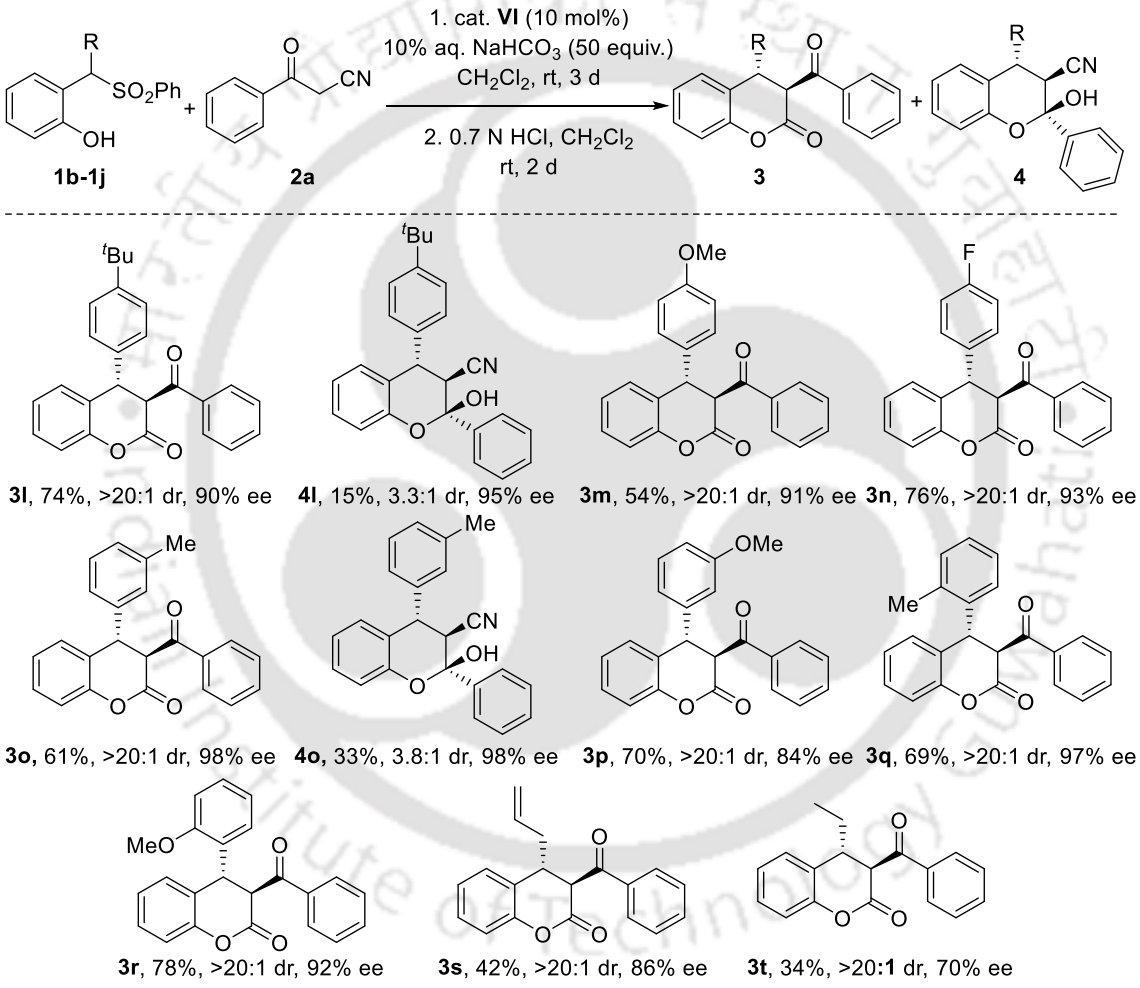
room temperature for 2 days. [b]Isolated yield in two steps after silica gel column chromatography. [c]The diastereomeric ratio was determined by ^{1}H NMR and the enantiomeric excess was determined by chiral HPLC analysis. [d]0.1 mmol of **2k** was used.

The reaction conditions were also suitable for *meta*-substituted aryl ketones **2g** and **2h**. Product **3g** was obtained in 5.3:1 ratio with >20:1 dr and 97% ee. Interestingly, for ketone **2h**, the chroman **4h** was found to be the major product (1:0.4 ratio) and was isolated in 43% yield with 3.2:1 dr and 93% ee (Table 5). High enantioselectivity (97% ee) was also seen for dihydrocoumarin **3h**. *ortho*-Substitution was also tolerated in the reaction and gratifyingly high enantiomeric excess (96% ee) was attained for product **3i** (Table 5). A di-substituted cyanoketone **2j** also took part in the reaction, delivering chroman **4j** as the major product which was isolated in 47% yield with 4.1:1 dr and 90% ee and dihydrocoumarin **3j** as the minor product in 22% yield with >20:1 dr and 99% ee. In addition, heteroaromatic cyanoketone **2k** having 2-furyl motif well participated in the reaction delivering only one product **3k** in moderate yield (41%) with >20:1 dr and good enantioselectivity (78% ee).

In the next, the scope of 2-sulfonylmethylphenols was studied and initially different *β*-aryl substituents were checked in the reaction (Table 6). Gratifyingly, here also good results were obtained and in all cases a single diastereomer was detected for **3**. At first, different *para*-substituted aryl group containing sulfones were reacted with *α*-cyanoketone **2a** and smooth conversions were noticed. Product **3l** having 4-^{t}butyl substituent was produced in 3.7:1 ratio and was isolated in 74% yield with 90% ee. The corresponding chroman product **4l** was obtained in 15% yield with 3.3:1 dr and 95% ee. The sulfone **1c** having electron rich *p*-anisyl group also smoothly engaged in the reaction to deliver the product **3m** in 1.7:1 product ratio and with 54% isolated yield and 91% ee. Halo substitution on the *β*-aryl part can also be incorporated. Interestingly, sulfone **1d** with 4-fluoro substituent furnished the dihydrocoumarin **3n** in 8.3:1 ratio and was isolated in 76% yield and 93% ee. The reaction outcome did not change much with *meta*-substitution. The reaction progressed efficiently with *m*-tolyl sulfone **1e** to provide **3o** and **4o** in 61% and 33% yields respectively with same 98% ee. In the case of *m*-anisyl substituent, the desired product **3p** was attained in 3.3:1 ratio and was isolated in 70% yield and with slightly lower ee (84%). *ortho*-Substituted aryl group containing sulfones also elegantly participated in the reaction. In this regard, *o*-tolyl and *o*-anisyl groups were screened, and afforded the desired products **3q** and **3r** in 6:1

and 6.1:1 ratios respectively. Gratifyingly, high enantioselectivities (97% ee and 92% ee respectively) were achieved for both of the products. Moreover, aliphatic groups can also be employed in the reaction conditions. For example, allyl group containing sulfone **1i** reacted smoothly to provide product **3s** in 42% yield with 86% ee and the product ratio was 1:1. An ethyl group containing sulfone **1j** delivered the product **3t** in 3:1 ratio despite the yield (34%) and enantioselectivity (70% ee) got decreased.

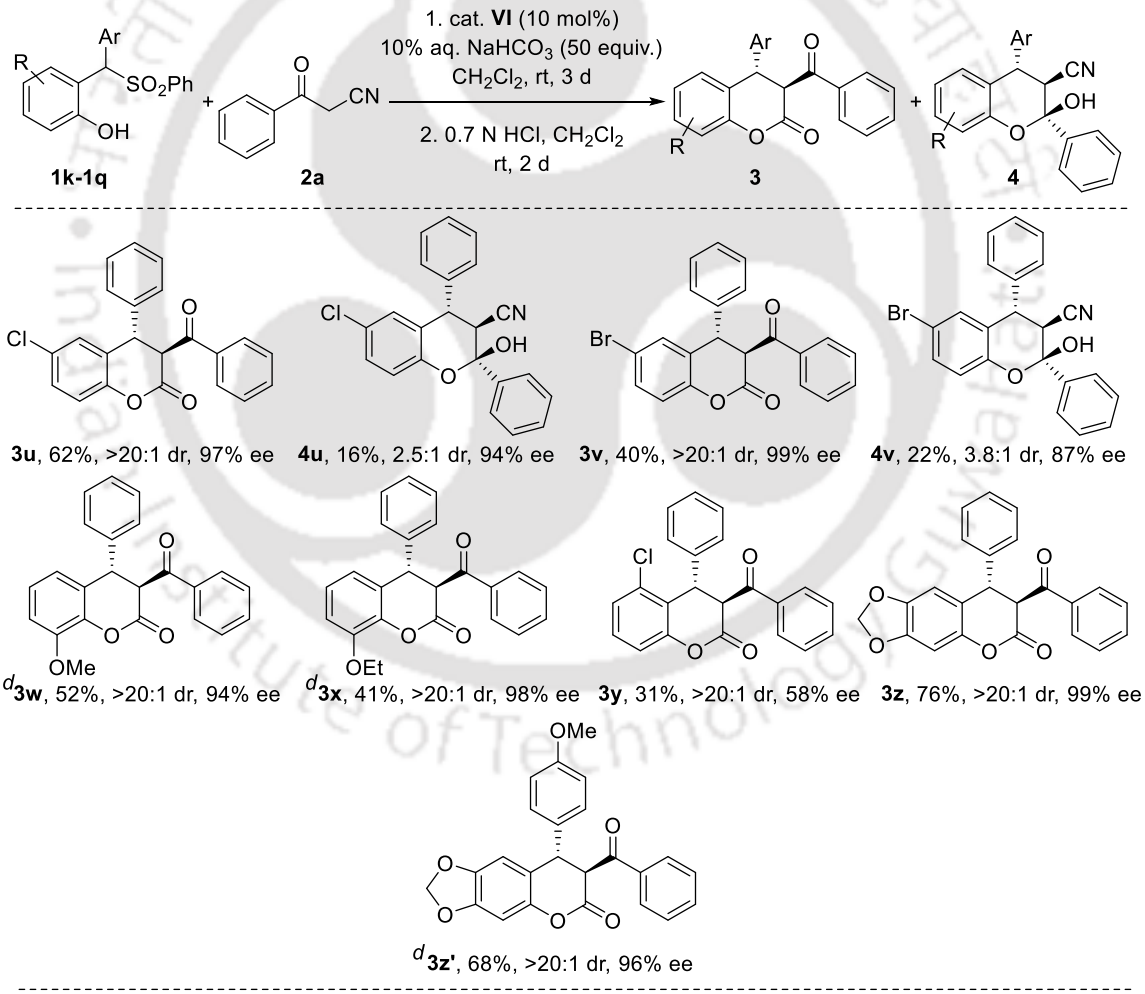
Table 6. Scope of sulfones with different *β*-substituents[a,b,c]



[a]Reaction conditions: 0.1 mmol of **1** and 0.2 mmol of **2a** in 1.2 mL CH_2Cl_2 using 10 mol% catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then work up and then 2 mL 0.7 N HCl in 2 mL CH_2Cl_2 at room temperature for 2 days. [b]Isolated yield in two steps after silica gel column chromatography. [c]The diastereomeric ratio was determined by ^1H NMR and the enantiomeric excess was determined by chiral HPLC analysis.

Then the phenolic component of the sulfone **1** was varied in the reaction and delightfully different substitutions were tolerated (Table 7). Here also, in all cases dihydrocoumarins **3** were obtained as a single diastereomer. At the begining, 4-halo substituted sulfones **1k** and **1l** were employed and good results were detected. The dihydrocoumarin **3u** was isolated in 62% yield with 97% ee and the chroman **4u** was isolated in 16% yield with 2.5:1 dr and 94% ee. The enantioselectivity got slightly enhanced for product **3v** (99% ee) though **4v** was obtained in slight less ee (87% ee). Here, **3v** and **4v** were isolated in 40% yield and 22% yield with 3.8:1 dr respectively.

Table 7. Scope of sulfones with different phenolic components[a,b,c]



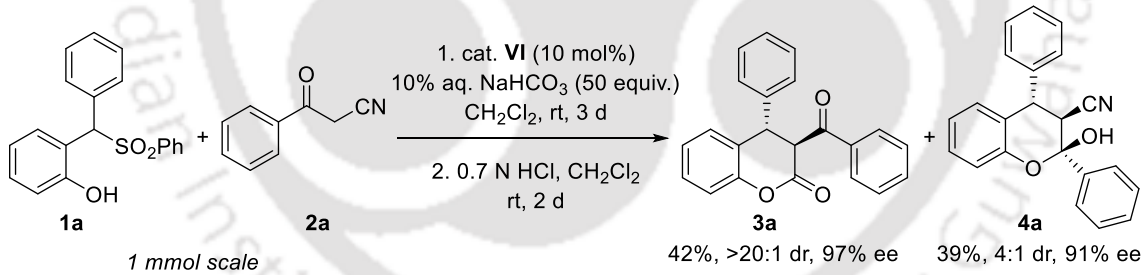
[a]Reaction conditions: 0.1 mmol of **1** and 0.2 mmol of **2a** in 1.2 mL CH_2Cl_2 using 10 mol% catalyst and 10% aq. $NaHCO_3$ at room temperature for 3 days and then work up and then 2 mL 0.7 N HCl in 2 mL CH_2Cl_2 at room temperature for 2 days. [b]Isolated yield in two steps after silica gel column chromatography. [c]The

diastereomeric ratio was determined by ^{1}H NMR and the enantiomeric excess was determined by chiral HPLC analysis. [d]0.1 mmol of **2a** was used.

Then 6-alkoxy substituted sulfones **1m** and **1n** were tested and good conversions along with >20:1 product ratio were observed. For example, product **3w** with 6-methoxy substituent was attained in 52% yield with 94% ee whereas product **3x** having 6-ethoxy group was isolated in 41% yield with 98% ee. Then 3-chloro substituted sulfone **1o** was employed in the reaction though lower enantioselectivity (58% ee) and less yield (31%) were detected for **3y**. Here also, no chroman product was found to form. Finally, sesamol based two sulfones **1p** and **1q** having phenyl and *p*-anisyl substituents respectively were prepared and engaged in the reaction. Both dihydrocoumarin/chroman products for **1p** and **1q** were produced in 4.9:1 and 3.4:1 ratios correspondingly. Gratifyingly, the reactions progressed efficiently to provide the products **3z** and **3z'** in 99% and 96% ees respectively.

5.4.5. Scale-up experiment:

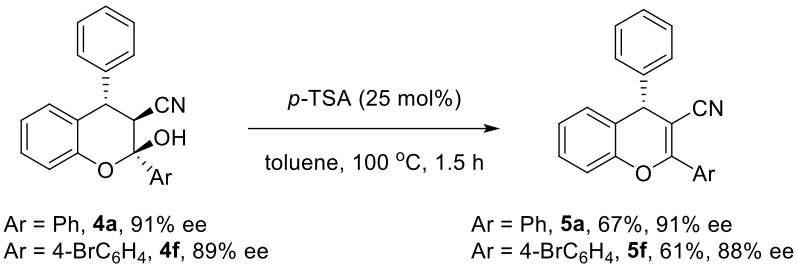
To highlight the potential of this method, a scale-up reaction was carried out in 1 mmol scale between **1a** and **2a** under standard optimized conditions. Gratifyingly, the enantioselectivities of both **3a** and **4a** got retained (Scheme 17).



Scheme 17. Scale-up experiment.

5.4.6. Synthetic transformation:

To further demonstrate the synthetic utility of our reaction, chroman hemiketals **4a** and **4f** were converted to chromenes **5a** and **5f** (Scheme 18). Thus with catalytic amount of *p*-TSA at 100 ^{o}C in toluene, chromenes **5a** and **5f** were isolated in 67% and 61% yields respectively with retention in enantioselectivities.



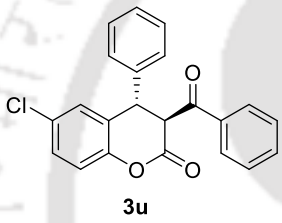
Ar = Ph, **4a**, 91% ee
Ar = 4-BrC_6H_4, **4f**, 89% ee

Ar = Ph, **5a**, 67%, 91% ee
Ar = 4-BrC_6H_4, **5f**, 61%, 88% ee

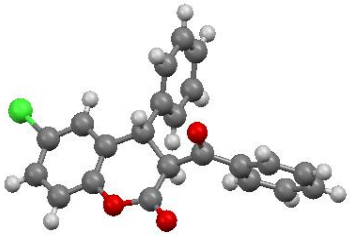
Scheme 18. Synthetic transformation.

5.4.7. Absolute configuration of 3u and 4j:

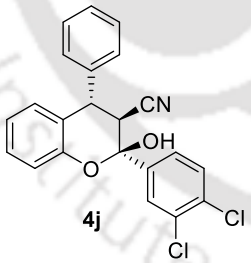
The absolute configuration of **3u** was confirmed (3*S*,4*S*) by X-ray crystallography.[7] Thus other products **3** are expected to have same absolute structure by analogy.



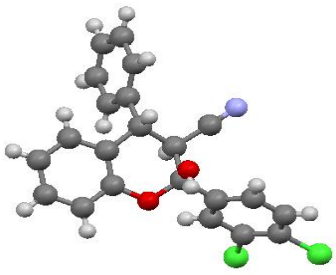
3u



Similarly, the relative and absolute structure of **4j** was identified to be (2*R*,3*S*,4*S*) by X-ray crystallography[8] and other compounds **4** are considered to have same configuration.



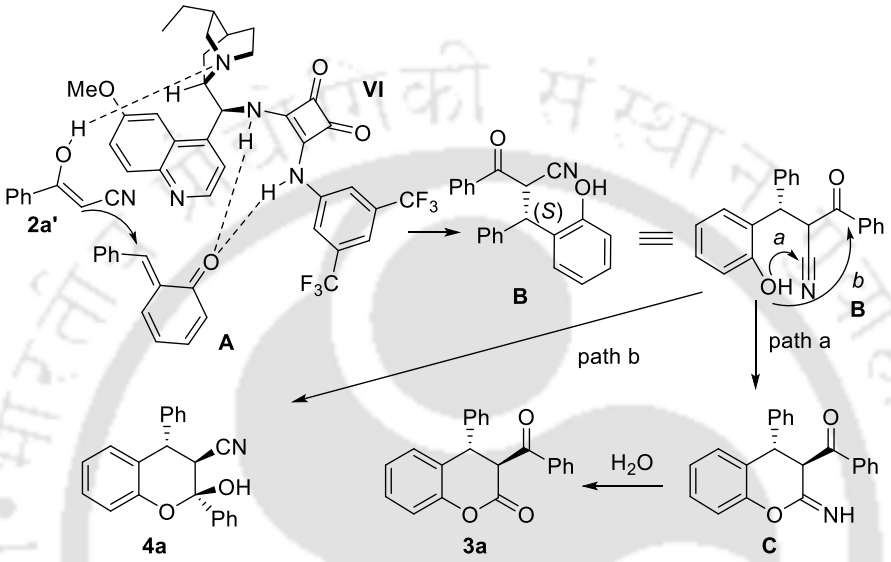
4j



5.4.8. Proposed mechanism:

A proposed mechanism has been shown in Scheme 19 to explain the absolute structure of the products. At first, it is expected that *ortho*-quinone methide **A** will be formed from **1a** after treatment with 10% aq. $NaHCO_3$. Then the catalyst **VI** activates both **A** and enol form of cyanoketone **2a'**. Since the *Re* face of *ortho*-quinone methide **A** is blocked by the squaramide motif of the catalyst, the addition of **2a'** takes place from the *Si* face to afford intermediate **B** with (*S*) configuration. The phenolic OH of intermediate **B** then either reacts

with cyano group (path a) or with the ketone group (path b). Path a provides intermediate **C** which on hydrolysis delivers 3,4-dihydrocoumarin **3a**. On the other hand, path b leads to the formation of chroman **4a**. Here, path a and path b could be reversible. Also, it is expected that dilute HCl will activate the cyano group and thus favored the formation of **3a** over the formation of **4a**. In both cases, stable *trans* isomers are obtained as the major products.



Scheme 19. The proposed mechanism.

5.5. Conclusion:

In summary, the first asymmetric addition of aromatic *α*-cyanoketones to *in situ*-generated *o*-QMs have been demonstrated. This methodology leads to the formation of 3,4-dihydrocoumarins and tetra-substituted chromans in a diastereo- as well as enantioselective manner. The reactants and the catalyst of this reaction are easily available. Also, chromenes with cyano substituent were obtained after single synthetic transformation. Thus, this attractive methodology might be useful in the synthesis of biologically important dihydrocoumarins and chromans.

5.6. Experimental section:

General Information:

All the required chemicals and reagents were purchased from commercial providers with highest purity grade and which were utilized directly without further purification. Starting

materials *α*-cyanoketones **2** were purchased from Sigma-Aldrich and Alfa Aesar. In all cases, oven dried glassware was used during reactions set up. Solvents were dried instantly using common techniques and drying agents wherever proper dryness was essential. Progress of the reactions was monitored by performing TLC on silica gel GF-254 using *n*-hexane/ethyl acetate as the solvent system. All 2-sulfonylmethylphenols **1** were prepared and purified by silica gel (60-120 mesh size) column chromatography. In case of 3,4-dihydrocoumarins and tetra-substituted chromans purification, 100-200 mesh silica was used. ^{1}H NMR spectra were recorded on Bruker 400 MHz and 600 MHz spectrometer using $CDCl_3$ as reference NMR solvent. ^{13}C NMR spectra were recorded on 100 MHz and 150 MHz spectrometer in $CDCl_3$. Chemical shifts (δ) and coupling constants (*J*) were reported in parts per million (ppm) and Hertz (Hz) units respectively. In ^{1}H and ^{13}C NMR, chemical shift values were expressed with reference to $CHCl_3$ (δ(H), 7.26 ppm) and (δ(C), 77.23 ppm, central line of triplet). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet), dt (doublet of triplet). High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) mode. Enantiomeric excesses were determined by HPLC analysis by comparing the spectra of racemic samples using stationary phase chiral column through the help of Dionex (Ultimate 3000) instrument. Melting points were noted on Büchi Melting Point B-540 apparatus.

Single-crystal X-ray diffraction data of compound **3u** and **4j** were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). Data collection was carried out at 100 K. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell refinement and data reduction were performed using the program SAINT.[9] The structure was solved by direct methods and refined by full-matrix least-squares methods based on F^2 using SHELXL-2013.[10]

A. General procedure for the synthesis of 2-sulfonylmethylphenols 1a-1q:

2-Sulfonylmethylphenols **1a-1q** were prepared according to the previous known procedure.[11] This was overall two steps process i.e. synthesis of various *ortho*-hydroxybenzyl alcohols from 2-hydroxy salicyldehydes and *in situ*-Grignard reagents and then sulfonation reactions.

B. General procedure for the preparation of thiourea, urea and squaramide catalysts (I-IX):

Thiourea catalyst[12] (**I-II**), urea catalyst[13] (**III**) and squaramide catalysts[14] (**IV-IX**) were prepared by following the previous reported procedures.

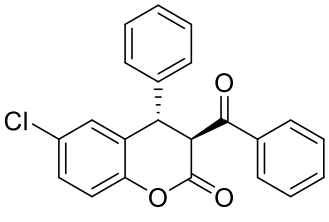
C. General procedure for the synthesis of 3,4-dihydrocoumarins 3 and tetra-substituted chromans 4:

To a stirred solution of 2-sulfonylmethylphenol **1** (0.1 mmol) and aromatic α-cyanoketone **2** (0.2 mmol) in DCM solvent (1.2 mL), catalyst **VI** (10 mol%) and 10% aq. $NaHCO_3$ solution (50 eq.) were added. Then the reaction mixture was allowed to stir for three days at room temperature. After this, an acidic work up was performed using 0.7 N HCl/DCM and the organic parts were concentrated in *vacuo*. Next, the crude mixture was dissolved in 4 mL 1:1 mixture of DCM and 0.7 N HCl solution and then continued stirring for another two days. After completion of the reaction, the resulting mixture was extracted with DCM (3 times) and concentrated in *vacuo*. Finally, the crude was subjected to silica gel column chromatography to obtain the desired 3,4-dihydrocoumarin **3** along with a little amount of tetra-substituted chroman **4**.

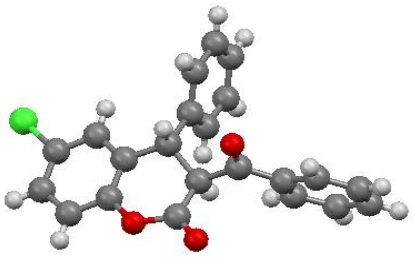
D. General procedure for the synthesis of 4*H*-chromenes 5:

To a stirred solution of tetra-substituted chroman **4** (0.07 mmol) in dry toluene (0.5 mL), catalytic amount of *para*-toluene sulfonic acid monohydrate (25 mol%) was added and heated to 100 ^oC temperature for 1.5 hours. After completion of the reaction, it was cooled down to room temperature. Then toluene was evaporated in rotary evaporator and finally the crude mixture was subjected to normal silica gel column chromatography to obtain the enantiopure 4*H*-chromene product **5**.

Crystal structure of compound (3*S*,4*S*)-3-benzoyl-6-chloro-4-phenylchroman-2-one, 3u:

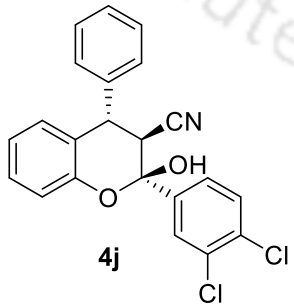


3u

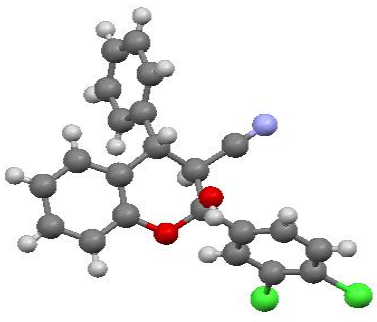


Moiety Formula	C_{22} H_{15} Cl O_3
Sum Formula	C3.14 H2.14 Cl0.14 O0.43
Formula weight, Fw	51.83
Crystal system	orthorhombic
Space group	P 21 21 21
Hall group	P 2ac 2ab
Unit cell dimensions	a = 5.5812(3)Å b = 16.1683(11)Å c = 19.0660(14)Å $\alpha = 90^o$, $\beta = 90^o$ $\gamma = 90^o$
Volume, V/Å^3	1720.5(2)
Z	28
Dx, g cm-3	1.401
Mu (mm-1)	0.241
F000	752.0
h, k, l max	7, 22, 26
Temperature, T/K	100 K
Theta(max)	30.061
Nref	5032
Parameters refined	235
R (reflections)	0.0366(4394)
wR2 (reflections)	0.0945(5032)
GOF (F^2)	1.043
CCDC No.	**2047120**

Crystal Structure of compound (2*R*,3*S*,4*S*)-2-(3,4-dichlorophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile, 4j:



4j



Moiety Formula	C_{22} H_{15} Cl_2 N O_2
Sum Formula	C3.67 H2.50 Cl0.33 N0.17 O0.33
Formula weight, Fw	66.04

Crystal system	orthorhombic
Space group	P 21 21 21
Hall group	P 2ac 2ab
Unit cell dimensions	a = 6.2728(4)Å b = 12.0399(8)Å c = 24.8487(18)Å $\alpha = 90^o$, $\beta = 90^o$ $\gamma = 90^o$
Volume, V/Å^3	1876.7(2)
Z	24
Dx, g cm-3	1.402
Mu (mm-1)	0.363
F000	816.0
h, k, l max	8, 16, 34
Temperature, T/K	100 K
Theta(max)	30.042
Nref	5475
Parameters refined	245
R (reflections)	0.0385(4086)
wR2 (reflections)	0.0858(5475)
GOF (F^2)	0.939
CCDC No.	**2047123**

5.7. References:

1. (a) Asai, F.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1991**, *30*, 3091. (b) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc. Perkin Trans.* 1 **1986**, 701. (c) Ee, G. C. L.; Mah, S. H.; Teh, S. S.; Rahmani, M.; Go, R.; Taufiq-Yap, Y. H. *Molecules* **2011**, *16*, 9721. (d) Zhang, X.-F.; Xie, L.; Liu, Y.; Xiang, J.-F.; Li, L.; Tang, Y.-L. *J. Mol. Struct.* **2008**, *888*, 145. (e) Nishimura, S.; Taki, M.; Takaishi, S.; Iijima, Y.; Akiyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 505. (f) Tada, M.; Okuno, K.; Chiba, K.; Ohnishi, E.; Yoshii, T. *Phytochemistry* **1994**, *35*, 539. (g) Appendino, G.; Nano, G. M.; Viterbo, D.; Munno, G. D.; Cisero, M.; Palmisano, G.; Aragno, M. *Helv. Chim. Acta.* **1991**, *74*, 495. (h) Batra, J. K.; Kang, G. J.; Jurd, L.; Hamel, E. *Biochem. Pharmacol.* **1988**, *37*, 2595. (i) Zhang, K.; Ding, W.; Sun, J.; Zhang, B.; Lu, F.; Lai, R.; Zou, Y.; Yedid, G. *Biochimie* **2014**, *107*, 203. (j) Yang, J.; Liu, G. Y.; Dai, F.; Cao, X. Y.; Kang, Y.; Hu, L. M.; Tang, J. J.; Li, X. Z.; Jin, X. L.; Zhou, B. *Bioorg. Med. Chem. Lett.* **2011**,

21, 6420. (k) Cabaret, D.; Adediran, S. A.; Gonzalez, M. J. G.; Pratt, R. F.; Wakselman, M. *J. Org. Chem*. **1999**, *64*, 713.

2. (a) Ballerini, E.; Minuti, L.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **2009**, *74*, 4311. (b) Song, F.; Lu, S.; Gunnet, J.; Xu, J. Z.; Wines, P.; Proost, J.; Liang, Y.; Baumann, C.; Lenhard, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *J. Med. Chem*. **2007**, *50*, 2807.
3. For selected recent examples, see: (a) Enders, D.; Wang, C.; Yang, X.; Raabe, G. *Adv. Synth. Catal*. **2010**, *352*, 2869. (b) Dong, S.; Liu, X.; Zhang, Y.; Lin, L.; Feng, X. *Org. Lett*. **2011**, *13*, 5060. (c) Jacobsen, C. B.; Albrecht, L.; Udmark, J.; Jørgensen, K. A. *Org. Lett*. **2012**, *14*, 5526. (d) Engl, O. D.; Fritz, S. P.; Käslin, A.; Wennemers, H. *Org. Lett*. **2014**, *16*, 5454. (e) Hejmanowska, J.; Albrect, A.; Pięta, J.; Albrecht, Ł. *Adv. Synth. Catal.* **2015**, *357*, 3843. (f) Zhang, S. -Y.; Lv, M.; Yin, S.-J.; Li, N. –K.; Zhang, J.-Q.; Wang, X.-W. *Adv. Synth. Catal.* **2016**, *358*, 143. (g) Nakamura, S.; Toda, A.; Sano, M.; Hatanaka, T.; Funahashi, Y. *Adv. Synth. Catal*. **2016**, *358*, 1029. (h) Jin, H.; Cho, S. M.; Hwang, G.-S.; Ryu, D. H. *Adv. Synth. Catal.* **2017**, *359*, 163. (i) Chen, Y.-h.; Sun, X.-L.; Guan, H.-S.; Liu, Y.-K. *J. Org. Chem*. **2017**, *82*, 4774. (j) Li, G.-T.; Li, Z.-K.; Gu, Q.; You, S.-L. *Org. Lett.* **2017**, *19*, 1318. (k) Zhang, X.-Z.; Gan, K.-J.; Liu, X.-X.; Deng, Y.-H.; Wang, F.-X.; Yu, K.-Y.; Zhang, J.; Fan, C.-A. *Org. Lett*. **2017**, *19*, 3207. (l) Zhang, Z.-P.; Chen, L.; Li, X.; Cheng, J.-P. *J. Org. Chem*. **2018**, *83*, 2714. (m) Mondal, B.; Pan, S. C. *Adv. Synth. Catal.* **2018**, *360*, 4348. For a review on the asymmetric construction of 3,4-dihydrocoumarins, see: (o) Leitis, Z. *Chem. Heterocycl. Compd*. **2016**, *52*, 527-529.
4. (a) Alden-Danforth, E.; Scerba, M. T.; Lectka, T. *Org. Lett*. **2008**, *10*, 4951. (b) Lv, H.; You, L.; Ye, S. *Adv. Synth. Catal*. **2009**, *351*, 2822. (c) Lee, A.; Scheidt, K. A. *Chem. Commun*. **2015**, *51*, 3407. (d) Caruana, L.; Mondatori, M.; Corti, V.; Morales, S.; Mazzanti, A.; Fochi, M.; Bernardi, L. *Chem. Eur. J*. **2015**, *21*, 6037. (e) Yu, X.-Y.; Chen, J.-R.; Wei, Q.; Cheng, H.-G.; Liu, Z.-C.; Xiao, W.-J. *Chem. Eur. J.* **2016**, *22*, 6774. (f) Zhang, Y.-C.; Zhu, Q.-N.; Yang, X.; Zhou, L.-J.; Shi, F. *J. Org. Chem.* **2016**, *81*, 1681. (g) Wu, B.; Yu, Z.; Gao, X.; Lan, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed*. **2017**, *56*, 4006. (h) Zhou, J.; Wang, M.-L.; Gao, X.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun.* **2017**, *53*, 3531. (i) Jin, J.-H.; Li, X.-Y.; Luo, X.; Fossey, J. F.; Deng, W.-P. *J. Org. Chem.* **2017**, *82*, 5424. (j) Zhu, Y.; Zhang, W.-Z.; Zhang, L.; Luo, S. *Chem.*

Eur. J. **2017**, *23*, 1253. (k) Zhang, T.; Ma, C.; Zhou, J.-Y.; Mei, G.-J.; Shi, F. *Adv. Synth. Catal*. **2018**, *360*, 1128. (l) Spanka, M.; Schneider, C. *Org. Lett*. **2018**, *20*, 4769. (m) Cui, L.; Lv, D.; Wang, Y.; Fan, Z.; Li, Z.; Zhou, Z. *J. Org. Chem*. **2018**, *83*, 4221. (n) Lv, D.; Zhao, M.; Wang, Y.; Zhou, Z. *Org. Biomol. Chem*. **2019**, *17*, 9636.

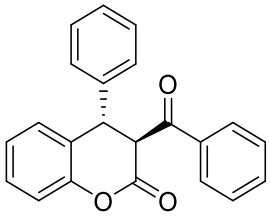
5. (a) Duan, C.; Ye, L.; Xu, W.; Li, X.; Chen, F.; Zhao, Z.; Li, X. *Chin. Chem. Lett*. **2018**, *29*, 1273. (b) Mondal, B.; Balha, M.; Pan, S. C. *Org. Biomol. Chem*. **2019**, *17*, 7849. (c) Echemendía, R.; da Silva, G. P.; Kawamura, M. Y.; de la Torre, A. F.; Corrêa, A. G.; Ferreira, M. A. B.; Rivera, D. G.; Paixão, M. W. *Chem. Commun.* **2019**, *55*, 286. (d) Xu, K.; Liu, H.; Hou, Y.; Shen, J.; Liu, D.; Zhang, W. *Chem. Commun.* **2019**, *55*, 13295. (e) Liu, H.; Sun, Z.; Xu, K.; Zheng, Y.; Liu, D.; Zhang, W. *Org. Lett*. **2020**, *22*, 4680. (f) Göricke, F.; Haseloff, S.; Laue, M.; Schneider, M.; Brumme, T.; Schneider, C. *J. Org. Chem*. **2020**, *85*, 11699.
6. For selected recent examples, see: (a) Zhao, J.-J.; Sun, S.-B.; He, S.-H.; Wu, Q.; Shi, F. *Angew. Chem. Int. Ed*. **2015**, *54*, 5460. (b) Alamsetti, S. K.; Spanka, M.; Schneider, C. *Angew. Chem. Int. Ed*. **2016**, *55*, 2392. (c) Chen, P.; Wang, K.; Guo, W.; Liu, X.; Liu, Y.; Li, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 3689. (d) Wang, Z.; Sun, J. *Org. Lett*. **2017**, *19*, 2334. (e) Wang, Z.; Wang, T.; Yao, W.; Lu, Y. *Org. Lett.* **2017**, *19*, 4126. (f) Tu, M.-S.; Liu, S.-J.; Zhong, C.; Zhang, S.; Zhang, H.; Zheng, Y.-L.; Shi, F. *J. Org. Chem.* **2020**, *85*, 5403.
7. CCDC 2047120 contains the crystallographic data for **3u**.
8. CCDC 2047123 contains the crystallographic data for **4j**.
9. APEX 2, SAINT, SADABS Bruker AXS Inc., Madison, WI, USA, **2012**.
10. G. M. Sheldrick, *SHELXL-2013*, University of Göttingen: Göttingen, Germany, **2013**.
11. (a) Meier, B.; Dumez, J.-N.; Stevanato, G.; Hill-Cousins, J. T.; Roy, S. S.; Håkansson, P.; Mamone, S.; Brown, R. C. D.; Pileio, G.; Levitt, M. H. *J. Am. Chem. Soc.* **2013**, *135*, 18746. (b) Chen, M.-W.; Cao, L.-L.; Ye, Z.-S.; Jiang, G.-F.; Zhou, Y.-G. *Chem. Commun*. **2013**, *49*, 1660.
12. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672. (b) Berkessel, A.; Mukherjee, S.; Muller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudorfl, J.-M.; Lex, J. *Org. Biomol. Chem*. **2006**, *4*, 4319. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967. (d) Tripathi, C. B.; Kayal, S.; Mukherjee, S. *Org. Lett*. **2012**, *14*, 3296.

13. McCooey, S. H.; Connon, S. J. *Angew. Chem.* **2005**, *117*, 6525.

14. (a) Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450. (b) Manoni, F.; Connon, S. J. *Angew. Chem. Int. Ed*. **2014**, *53*, 2628. (c) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416.

5.8. Characterization Data of Products:

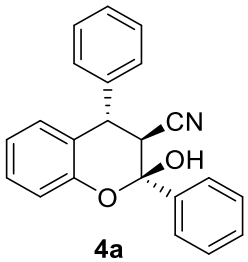
(3S,4S)-3-benzoyl-4-phenylchroman-2-one (3a)



3a

Compound **3a** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; White solid (25.6 mg, 78% yield); **M.P.** = 134-135 ^{o}C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.90 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 3H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 3H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.02 (d, *J* = 7.2 Hz, 1H), 4.82 (d, *J* = 7.2 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.6, 165.4, 151.2, 139.5, 135.6, 134.2, 129.5, 129.3, 129.1, 129.0, 128.9, 128.1, 128.1, 125.3, 124.2, 117.2, 55.0, 44.5; **HRMS (+ESI):** Calc for $C_{22}H_{20}NO_3$ $[M+NH_4]^+$ 346.1438; found: 346.1446; The ee value 98% (t_{major} = 15.0 min, t_{minor} = 18.6 min) was determined by HPLC analysis using Lux® 5 μm Cellulose-4 with *n*-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(2R,3S,4S)-2-hydroxy-2,4-diphenylchromane-3-carbonitrile (4a)

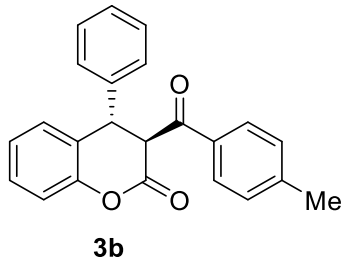


4a

Compound **4a** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; Colorless Sticky type (5.9 mg, 18% yield); **Diastereomeric ratio:** 5.6:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.81 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.55 – 7.43 (m, 3.4H), 7.43 – 7.27 (m, 5.3H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1.1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 5.7 Hz, 0.1H), 4.68 (d, *J* = 12.3 Hz, 1H), 3.45 (d, *J* = 5.7 Hz, 0.1H), 3.41 (d, *J* = 2.2 Hz, 1H), 3.17 (dd, *J* = 12.3, 2.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 151.5, 140.3, 140.1, 130.1, 129.8, 129.5, 129.3, 129.0, 128.8, 128.3, 126.4, 123.5, 122.5, 117.8, 117.6, 96.4, 46.6, 43.9; **HRMS (+ESI):** Calc for $C_{22}H_{17}NNaO_2$ $[M+Na]^+$ 350.1151; found:

350.1165; The ee value of major diastereomer 94% (t_{major} = 13.1 min, t_{minor} = 18.9 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

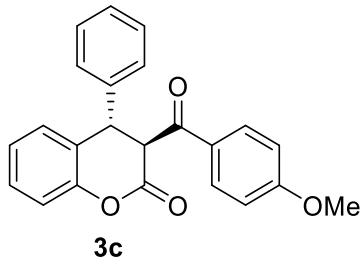
(3S,4S)-3-(4-methylbenzoyl)-4-phenylchroman-2-one (3b)



3b

Compound **3b** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; White solid (27.7 mg, 81% yield); **M.P.** = 181-182 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.80 (d, *J* = 8.2 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 3H), 7.26 (d, *J* = 8.4 Hz, 3H), 7.19 (t, *J* = 7.0 Hz, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 4.97 (d, *J* = 6.9 Hz, 1H), 4.79 (d, *J* = 6.9 Hz, 1H), 2.41 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.0, 165.5, 151.2, 145.3, 139.6, 133.1, 129.8, 129.5, 129.3, 129.1, 129.0, 128.1, 128.0, 125.2, 124.2, 117.1, 55.0, 44.6, 21.9; **HRMS (+ESI):** Calc for $C_{23}H_{19}O_3$ $[M+H]^+$ 343.1329; found: 343.1344; The ee value 98% (t_{major} = 20.4 min, t_{minor} = 14.5 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

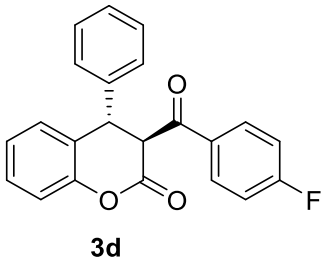
(3S,4S)-3-(4-methoxybenzoyl)-4-phenylchroman-2-one (3c)



3c

Compound **3c** was purified by silica gel column chromatography using 7 to 10% EtOAc in hexane; White solid (28 mg, 78% yield); **M.P.** = 111-113 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ**: 7.91 (d, *J* = 8.9 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 3H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 3H), 4.97 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 191.7, 165.5, 164.4, 151.2, 139.8, 131.4, 129.5, 129.2, 129.0, 128.5, 128.0, 128.0, 125.2, 124.2, 117.1, 114.3, 55.8, 54.8, 44.6; **HRMS (+ESI):** Calc for $C_{23}H_{19}O_4$ $[M+H]^+$ 359.1278; found: 359.1290; The ee value 96% (t_{major} = 26.9 min, t_{minor} = 17.6 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 200 nm, 25 °C.

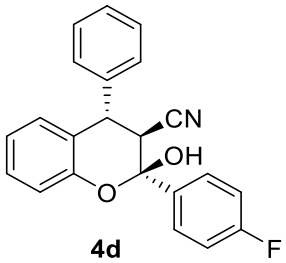
(3S,4S)-3-(4-fluorobenzoyl)-4-phenylchroman-2-one (3d)



3d

Compound **3d** was purified by silica gel column chromatography using 3% EtOAc in hexane; Colorless sticky type (26.3 mg, 76% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.92 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 3H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.91 (d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 7.8 Hz, 1H), 4.81 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 192.0, 167.7, 165.2, 165.1, 151.1, 139.3, 132.3, 132.3, 131.7, 131.7, 129.5, 129.3, 128.9, 128.2, 128.2, 125.3, 124.4, 117.1, 116.4, 116.2, 54.8, 44.3; **HRMS (+ESI):** Calc for $C_{22}H_{19}FNO_3$ $[M+NH_4]^+$ 364.1343; found: 364.1353; The ee value 95% (t_{major} = 22.2 min, t_{minor} = 13.4 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

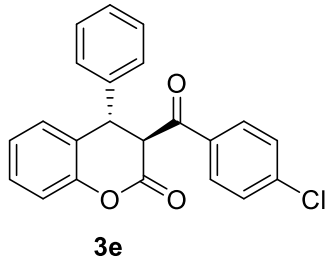
(2R,3S,4S)-2-(4-fluorophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile (4d)



4d

Compound **4d** was purified by silica gel column chromatography using 3% EtOAc in hexane; Colorless sticky type (3.5 mg, 10% yield); **Diastereomeric ratio:** 3.2:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.87 – 7.76 (m, 2.5H), 7.46 – 7.28 (m, 6.7H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.21 – 7.12 (m, 2.6H), 7.10 (d, *J* = 8.2 Hz, 0.6H), 7.02 – 6.97 (m, 1.5H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 5.6 Hz, 0.3H), 4.66 (d, *J* = 12.3 Hz, 1H), 3.42 (d, *J* = 5.8 Hz, 1.6H), 3.13 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 151.3, 140.0, 138.4, 136.4, 136.3, 130.3, 129.8, 129.5, 129.4, 129.3, 129.1, 128.9, 128.7, 128.6, 128.5, 128.5, 128.4, 123.4, 122.6, 122.4, 121.7, 118.1, 117.8, 117.6, 116.0, 115.96, 115.8, 96.1, 96.0, 46.7, 45.1, 43.9, 41.5; **HRMS (+ESI):** Calc for $C_{22}H_{17}FNO_2$ $[M+H]^+$ 346.1238; found: 346.1236; The ee value of the major diastereomer 91% (t_{major} = 13.3 min, t_{minor} = 37.3 min) was determined by HPLC analysis using Lux® 5 μm Amylose-2 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^oC.

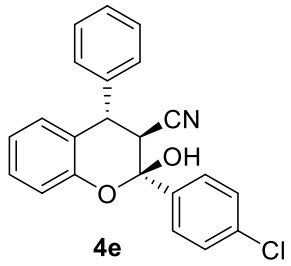
(3S,4S)-3-(4-chlorobenzoyl)-4-phenylchroman-2-one (3e)



3e

Compound **3e** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; Colorless solid (15.6 mg, 43% yield); **M.P.** = 113-114 ^{o}C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 7.81 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.35 – 7.28 (m, 4H), 7.18 (dd, *J* = 7.0, 4.8 Hz, 3H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.93 (d, *J* = 8.0 Hz, 1H), 4.81 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$) δ:** 192.4, 165.2, 151.1, 140.8, 139.2, 134.2, 130.3, 129.5, 129.4, 129.3, 129.0, 128.2, 128.2, 125.4, 124.4, 117.1, 54.8, 44.3; **HRMS (+ESI):** Calc for $C_{22}H_{15}ClNaO_3$ $[M+Na]^+$ 385.0602; found: 385.0621; The ee value 92% (t_{major} = 26.0 min, t_{minor} = 14.9 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(2R,3S,4S)-2-(4-chlorophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile (4e)

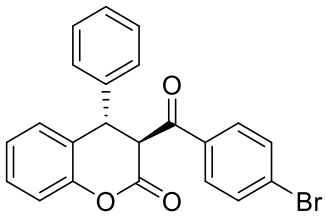


4e

Compound **4e** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; Colorless sticky type (9.4 mg, 26% yield); **Diastereomeric ratio:** 4.8:1; **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 7.79 – 7.72 (m, 2.3H), 7.64 – 7.49 (m, 0.6H), 7.49 – 7.43 (m, 2.9H), 7.42 – 7.33 (m, 3.8H), 7.33 – 7.27 (m, 2.5H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 0.3H), 7.03 – 6.97 (m, 1.5H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 5.5 Hz, 0.3H), 4.66 (d, *J* = 12.3 Hz, 1H), 3.41 (d, *J* = 5.5 Hz, 1.5H), 3.12 (d, *J* = 12.4 Hz, 1H); **^{13}C NMR (100 MHz, CDCl$_3$) δ:** 151.7, 151.2, 139.9, 139.0, 138.9, 138.3, 136.3, 130.2, 129.8, 129.7, 129.5, 129.4, 129.3, 129.1, 129.1, 129.1, 128.9, 128.5, 128.4, 128.0, 127.9, 123.4, 122.6, 122.5, 118.1, 117.8, 117.5, 96.1, 96.0, 46.5, 44.9, 43.8, 41.4; **HRMS (+ESI):** Calc for $C_{22}H_{17}ClNO_2$ $[M+H]^+$ 362.0942; found: 362.0967; The ee value of the major diastereomer 99% (t_{major} = 18.1 min, t_{minor} = 42.8 min) was determined by HPLC analysis using Lux® 5 μm Amylose-2 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(3S,4S)-3-(4-bromobenzoyl)-4-phenylchroman-2-one (3f)

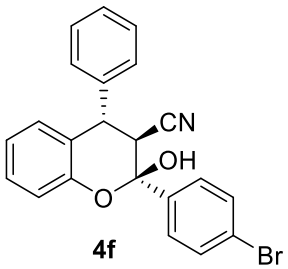
Compound **3f** was purified by silica gel column chromatography using 2% EtOAc in hexane; Colorless solid (16.7 mg, 41% yield); **M.P.** = 135-136 ^{o}C; **Diastereomeric ratio:**



3f

>20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.73 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 3H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.18 (t, *J* = 6.9 Hz, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 4.92 (d, *J* = 8.1 Hz, 1H), 4.80 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 192.7, 165.2, 151.0, 139.1, 134.6, 132.4, 130.3, 129.6, 129.5, 129.3, 128.9, 128.2, 128.2, 125.4, 124.4, 117.1, 54.8, 44.2; **HRMS (+ESI):** Calc for $C_{22}H_{16}BrO_3$ $[M+H]^+$ 407.0277; found: 407.0287; The ee value 97% (t_{major} = 27.9 min, t_{minor} = 15.7 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

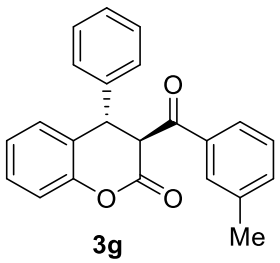
(2R,3S,4S)-2-(4-bromophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile (4f)



4f

Compound **4f** was purified by silica gel column chromatography using 2% EtOAc in hexane; Colorless sticky type (13 mg, 32% yield); **Diastereomeric ratio:** 4.5:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.68 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.65 (d, *J* = 12.3 Hz, 1H), 3.42 (s, 1H), 3.12 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 151.2, 139.9, 139.3, 132.1, 129.8, 129.5, 129.3, 128.9, 128.4, 128.3, 124.6, 123.3, 122.6, 117.8, 117.4, 96.1, 46.4, 43.8; **HRMS (+ESI):** Calc for $C_{22}H_{20}BrN_2O_2$ $[M+NH_4]^+$ 423.0703; found: 423.0707; The ee value of the major diastereomer 98% (t_{major} = 17.8 min, t_{minor} = 46.8 min) was determined by HPLC analysis using Lux® 5 μm Amylose-2 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 ^{o}C.

(3S,4S)-3-(3-methylbenzoyl)-4-phenylchroman-2-one (3g)

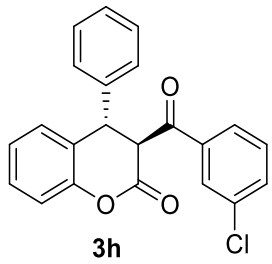


3g

Compound **3g** was purified by silica gel column chromatography using 2% EtOAc in hexane; Colorless sticky type (27 mg, 79% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.68 (d, *J* = 6.4 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.30 (s, 1H), 7.26 (t, *J* =

7.2 Hz, 1H), 7.22 – 7.17 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.98 (d, *J* = 7.3 Hz, 1H), 4.80 (d, *J* = 7.3 Hz, 1H), 2.39 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 193.7, 165.5, 151.2, 139.6, 139.1, 135.7, 135.0, 129.5, 129.5, 129.3, 129.0, 129.0, 128.1, 128.1, 126.1, 125.2, 124.2, 117.2, 55.1, 44.5, 21.6; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_3$ $[M+NH_4]^+$ 360.1594; found: 360.1605; The ee value 97% (t_{major} = 11.0 min, t_{minor} = 9.8 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

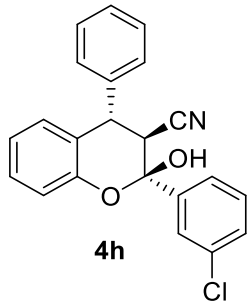
(3S,4S)-3-(3-chlorobenzoyl)-4-phenylchroman-2-one (3h)



3h

Compound **3h** was purified by silica gel column chromatography using 1 to 2% EtOAc in hexane; Colorless sticky type (7.6 mg, 21% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.82 (t, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.53 (m, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.31 (s, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 6.9 Hz, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 4.92 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 192.5, 165.1, 151.0, 139.0, 137.5, 135.5, 134.1, 130.4, 129.6, 129.3, 129.1, 128.9, 128.3, 126.9, 125.4, 124.4, 117.2, 54.8, 44.2; **HRMS (+ESI):** Calc for $C_{22}H_{19}ClNO_3$ $[M+NH_4]^+$ 380.1048; found: 380.1049; The ee value 97% (t_{major} = 13.5 min, t_{minor} = 10.4 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

(2R,3S,4S)-2-(3-chlorophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile (4h)

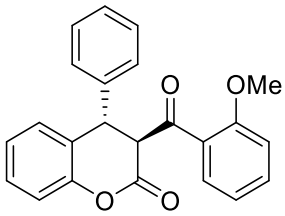


4h

Compound **4h** was purified by silica gel column chromatography using 1 to 2% EtOAc in hexane; Colorless sticky type (15.6 mg, 43% yield); **Diastereomeric ratio:** 3.2:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.83 – 7.80 (m, 0.3H), 7.80 – 7.77 (m, 1H), 7.72 (ddd, *J* = 5.7, 2.7, 1.8 Hz, 1.3H), 7.47 – 7.39 (m, 4H), 7.38 (d, *J* = 7.3 Hz, 2H), 7.36 – 7.27 (m, 3.9H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 0.3H), 7.03 – 6.97 (m, 1.6H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 5.7 Hz, 0.3H), 4.66 (d, *J* = 12.3 Hz, 1H), 3.50 (s, 1.3H), 3.43 (d, *J* = 5.7 Hz, 0.3H), 3.14 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 151.7,

151.1, 142.4, 142.3, 139.9, 138.3, 135.0, 134.9, 130.3, 130.3, 130.2, 129.8, 129.5, 129.4, 129.3, 129.1, 128.9, 128.5, 128.4, 126.8, 126.7, 124.8, 124.7, 123.3, 122.7, 122.5, 121.7, 118.1, 117.8, 117.3, 116.5, 95.9, 95.7, 46.4, 44.7, 43.8, 41.4; **HRMS (+ESI):** Calc for $C_{22}H_{17}ClNO_2$ $[M+H]^+$ 362.0942; found: 362.0943; The ee value of the major diastereomer 93% (t_{major} = 19.8 min, t_{minor} = 29.8 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (96:4) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

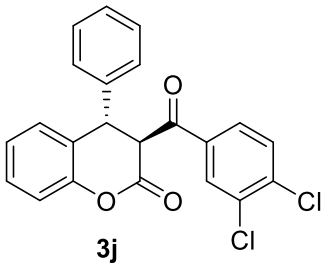
(3S,4S)-3-(2-methoxybenzoyl)-4-phenylchroman-2-one (3i)



3i

Compound **3i** was purified by silica gel column chromatography using 7% EtOAc in hexane; Colorless oil type (5.4 mg, 15% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.50 (d, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 3H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 7.07 – 6.94 (m, 4H), 6.86 (d, *J* = 7.7 Hz, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 4.67 (d, *J* = 6.3 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 194.9, 165.9, 158.5, 151.6, 139.9, 135.0, 131.7, 129.2, 129.0, 128.4, 128.1, 127.8, 125.8, 125.0, 124.1, 121.5, 117.3, 111.9, 59.9, 56.0, 44.5; **HRMS (+ESI):** Calc for $C_{23}H_{19}O_4$ $[M+H]^+$ 359.1278; found: 359.1280; The ee value 96% (t_{major} = 18.9 min, t_{minor} = 24.5 min) was determined by HPLC analysis using Lux® 5 μm Cellulose-4 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(3S,4S)-3-(3,4-dichlorobenzoyl)-4-phenylchroman-2-one (3j)

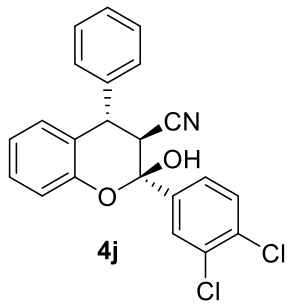


3j

Compound **3j** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; Colorless sticky type (8.7 mg, 22% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.93 (d, *J* = 2.1 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.36 – 7.27 (m, 4H), 7.21 – 7.16 (m, 3H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 8.9 Hz, 1H), 4.83 (d, *J* = 9.2 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 191.6, 165.0, 151.0, 138.9, 138.9, 135.7, 133.9, 131.2, 130.8, 129.6, 129.4, 128.9, 128.3, 127.8, 126.7, 125.4, 124.5, 117.1, 54.6, 44.1; **HRMS (+ESI):** Calc for $C_{22}H_{18}Cl_2NO_3$ $[M+NH_4]^+$ 414.0658; found: 414.0665; The ee value 99% (t_{major} = 24.3 min,

t_{minor} = 11.7 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

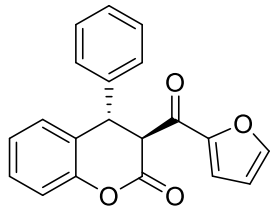
(2R,3S,4S)-2-(3,4-dichlorophenyl)-2-hydroxy-4-phenylchromane-3-carbonitrile (4j)



4j

Compound **4j** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; White semisolid (18.6 mg, 47% yield); **Diastereomeric ratio:** 4.1:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.90 (d, *J* = 2.1 Hz, 0.2H), 7.88 (d, *J* = 2.1 Hz, 1H), 7.66 (dd, *J* = 8.4, 2.2 Hz, 1.2H), 7.55 (dd, *J* = 8.4, 4.4 Hz, 1.3H), 7.45 – 7.27 (m, 6.6H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 0.3H), 7.02 – 6.91 (m, 2.5H), 6.81 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 5.7 Hz, 0.2H), 4.64 (d, *J* = 12.3 Hz, 1H), 3.58 (s, 1.2H), 3.40 (d, *J* = 5.7 Hz, 0.2H), 3.12 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 151.5, 151.0, 140.6, 140.4, 139.7, 138.1, 134.5, 134.4, 133.3, 133.2, 130.9, 130.2, 129.8, 129.5, 129.4, 129.4, 129.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.6, 128.4, 126.1, 126.0, 123.2, 122.8, 122.6, 121.6, 118.1, 117.7, 117.2, 116.5, 95.6, 95.5, 46.3, 44.7, 43.7, 41.3; **HRMS (+ESI):** Calc for $C_{22}H_{19}Cl_2N_2O_2$ $[M+NH_4]^+$ 413.0818; found: 413.0812; The ee value of the major diastereomer 90% (t_{major} = 20.8 min, t_{minor} = 33.8 min) was determined by HPLC analysis using Lux® 5 µm Amylose-2 with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(3S,4S)-3-(furan-2-carbonyl)-4-phenylchroman-2-one (3k)

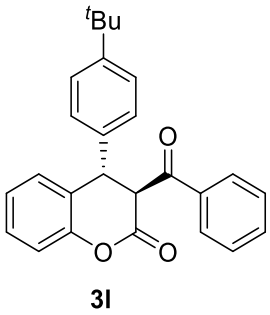


3k

Compound **3k** was purified by silica gel column chromatography using 7% EtOAc in hexane. White solid (13.1 mg, 41% yield). M.P. = 195-196 °C. **Diastereomeric ratio:** >20:1. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 7.59 (s, 1H), 7.30 (t, *J* = 7.3 Hz, 3H), 7.25 – 7.21 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 4.85 (d, *J* = 9.0 Hz, 1H), 4.81 (d, *J* = 8.9 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 181.9, 165.1, 152.0, 151.3, 147.4, 139.0, 129.4, 129.3, 128.9, 128.4, 128.1, 125.2, 124.6, 119.2, 117.1, 113.3, 55.1, 43.8. **HRMS (+ESI):** Calc for $C_{20}H_{14}NaO_4$ $[M+Na]^+$ 341.0784; Found: 341.0786. The ee value 78% (t_{major} = 17.9 min, t_{minor} = 13.0 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/

i-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 274 nm, 25 ^{o}C.

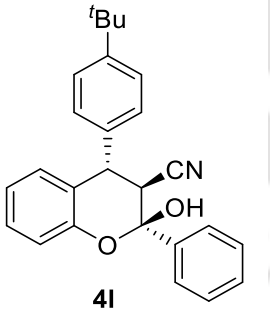
(3S,4S)-3-benzoyl-4-(4-(tert-butyl)phenyl)chroman-2-one (3l)



3l

Compound **3l** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; Pale yellow sticky type (28.5 mg, 74% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 7.90 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.35 – 7.29 (m, 3H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.08 (t, *J* = 7 Hz, 1H), 6.96 (d, *J* = 7.3 Hz, 1H), 5.00 (d, *J* = 6.1 Hz, 1H), 4.73 (d, *J* = 6.1 Hz, 1H), 1.28 (s, 9H); **^{13}C NMR (100 MHz, CDCl$_3$) δ:** 193.6, 165.4, 151.2, 151.0, 136.6, 135.5, 134.1, 129.2, 129.1, 129.1, 129.0, 127.5, 126.4, 125.2, 124.0, 117.2, 55.5, 44.3, 34.7, 31.4; **HRMS (+ESI):** Calc for $C_{26}H_{28}NO_3$ $[M+NH_4]^+$ 402.2064; found: 402.2069; The ee value 90% (t_{major} = 9.9 min, t_{minor} = 8.2 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^{o}C.

(2R,3S,4S)-4-(4-(tert-butyl)phenyl)-2-hydroxy-2-phenylchromane-3-carbonitrile (4l)

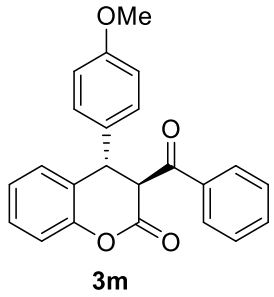


4l

Compound **4l** was purified by silica gel column chromatography using 2 to 3% EtOAc in hexane; Yellow sticky type (5.8 mg, 15% yield); **Diastereomeric ratio:** 3.3:1; **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 7.83 (d, *J* = 1.8 Hz, 0.3H), 7.80 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.53 – 7.41 (m, 4H), 7.39 (d, *J* = 4.1 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.27 (m, 0.6H), 7.25 (dd, *J* = 1.5, 0.8 Hz, 0.3H), 7.21 (d, *J* = 8.3 Hz, 2.6H), 7.11 (d, *J* = 7.1 Hz, 0.6H), 7.06 – 6.96 (m, 1.6H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.94 (d, *J* = 5.5 Hz, 0.3H), 4.65 (d, *J* = 12.3 Hz, 1H), 3.44 (d, *J* = 5.6 Hz, 0.3H), 3.40 (s, 1.2H), 3.15 (d, *J* = 12.3 Hz, 1H), 1.33 (s, 2.6H), 1.31 (s, 9H); **^{13}C NMR (100 MHz, CDCl$_3$) δ:** 152.0, 151.5, 151.3, 151.1, 140.5, 140.4, 136.9, 135.3, 130.1, 130.0, 129.9, 129.4, 129.1, 128.9, 128.9, 128.7, 126.3, 126.3, 126.1, 125.9, 123.6, 122.4, 122.2, 122.1, 118.1, 117.8, 117.8, 117.0, 96.4, 96.2, 46.7, 45.0, 43.4, 41.0, 34.8, 34.8, 31.5, 29.9; **HRMS (+ESI):** Calc for $C_{26}H_{29}N_2O_2$ $[M+NH_4]^+$ 401.2224; found: 401.2250; The ee value of the major diastereomer 95% (t_{major} = 7.1 min,

t_{minor} = 9.7 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

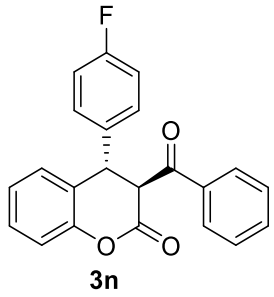
(3S,4S)-3-benzoyl-4-(4-methoxyphenyl)chroman-2-one (3m)



3m

Compound **3m** was purified by silica gel column chromatography using 7% EtOAc in hexane; Yellow solid (19.4 mg, 54% yield); **M.P.** = 166-167 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.88 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.95 (d, *J* = 7.6 Hz, 1H), 4.76 (d, *J* = 7.6 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.7, 165.5, 159.3, 151.1, 135.8, 134.1, 131.3, 129.2, 129.1, 128.9, 128.9, 125.2, 124.6, 117.1, 114.8, 55.5, 55.1, 43.7; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_4$ $[M+NH_4]^+$ 376.1543; found: 376.1545; The ee value 91% (t_{major} = 20.6 min, t_{minor} = 17.2 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

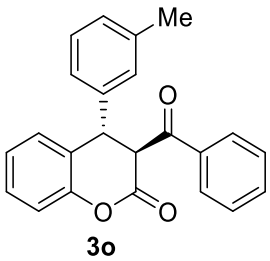
(3S,4S)-3-benzoyl-4-(4-fluorophenyl)chroman-2-one (3n)



3n

Compound **3n** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; White solid (26.3 mg, 76% yield); **M.P.** = 140-141 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.87 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.21 – 7.14 (m, 3H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 8.0 Hz, 1H), 4.82 (d, *J* = 8.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.4, 165.2, 163.2, 161.5, 151.1, 135.8, 135.1, 135.1, 134.3, 129.9, 129.9, 129.4, 129.1, 128.9, 128.8, 125.3, 124.2, 117.2, 116.5, 116.4, 54.9, 43.6; **HRMS (+ESI):** Calc for $C_{22}H_{15}FNaO_3$ $[M+Na]^+$ 369.0897; found: 369.0907; The ee value 93% (t_{major} = 26.3 min, t_{minor} = 18.9 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

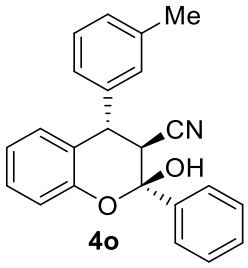
(3S,4S)-3-benzoyl-4-(m-tolyl)chroman-2-one (3o)



3o

Compound **3o** was purified by silica gel column chromatography using 3% EtOAc in hexane; Colorless sticky type (20.9 mg, 61% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.90 (d, *J* = 7.4 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.20 (dd, *J* = 13.4, 7.7 Hz, 2H), 7.08 (dd, *J* = 14.0, 7.3 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.00 (d, *J* = 6.9 Hz, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.6, 165.4, 151.1, 139.5, 139.2, 135.6, 134.2, 129.4, 129.2, 129.1, 129.0, 128.9, 128.9, 128.7, 125.2, 124.9, 124.2, 117.1, 55.1, 44.5, 21.7; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_3$ $[M+NH_4]^+$ 360.1594; found: 360.1600; The ee value 98% (t_{major} = 22.0 min, t_{minor} = 14.7 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

(2R,3S,4S)-2-hydroxy-2-phenyl-4-(m-tolyl)chromane-3-carbonitrile (4o)

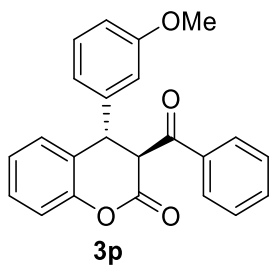


4o

Compound **4o** was purified by silica gel column chromatography using 3% EtOAc in hexane; Yellow sticky type (11.3 mg, 33% yield); **Diastereomeric ratio:** 3.8:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.85 – 7.78 (m, 2.5H), 7.52 – 7.44 (m, 3.8H), 7.32 – 7.26 (m, 1.2H), 7.24 (d, *J* = 2.8 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 0.8H), 7.16 (d, *J* = 7.4 Hz, 0.3H), 7.13 (dd, *J* = 12.1, 8.0 Hz, 2H), 7.09 (s, 1.3H), 7.00 (d, *J* = 8.3 Hz, 1.3H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 5.5 Hz, 0.3H), 4.63 (d, *J* = 12.3 Hz, 1H), 3.45 (d, *J* = 2.0 Hz, 1H), 3.44 (s, 0.2H), 3.43 (d, *J* = 2.7 Hz, 0.3H), 3.19 (dd, *J* = 12.3, 2.0 Hz, 1H), 2.37 (s, 0.7H), 2.34 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 152.0, 151.4, 140.4, 140.3, 140.0, 138.9, 138.6, 138.4, 131.0, 130.1, 130.0, 129.8, 129.4, 129.1, 129.1, 128.9, 128.9, 128.9, 128.7, 127.9, 127.2, 126.7, 126.4, 126.3, 123.6, 122.4, 122.2, 121.9, 118.1, 117.7, 117.7, 116.8, 96.4, 96.2, 46.4, 45.0, 43.8, 41.4, 22.9, 21.7; **HRMS (+ESI):** Calc for $C_{23}H_{23}N_2O_2$ $[M+NH_4]^+$ 359.1754; found: 359.1755; The ee value of the major diastereomer 98% (t_{major} = 10.1 min, t_{minor} = 12.7 min) was determined by HPLC analysis using Daicel Chiralpak ID

with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

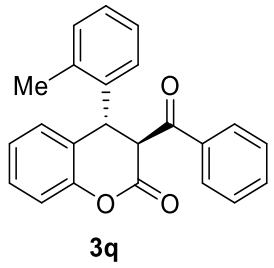
(3S,4S)-3-benzoyl-4-(3-methoxyphenyl)chroman-2-one (3p)



3p

Compound **3p** was purified by silica gel column chromatography using 6 to 8% EtOAc in hexane; Pale yellow semisolid (25.1 mg, 70% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.90 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 2.8 Hz, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 6.72 (s, 1H), 4.99 (d, *J* = 7.1 Hz, 1H), 4.76 (d, *J* = 7.1 Hz, 1H), 3.74 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.5, 165.3, 160.3, 151.1, 141.1, 135.6, 134.2, 130.6, 129.3, 129.1, 129.0, 128.96, 125.3, 124.0, 120.2, 117.2, 114.2, 113.1, 55.5, 55.0, 44.5; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_4$ $[M+NH_4]^+$ 376.1543; found: 376.1551; The ee value 84% (t_{major} = 23.9 min, t_{minor} = 15.7 min) was determined by HPLC analysis using Lux® 5 μm Cellulose-4 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

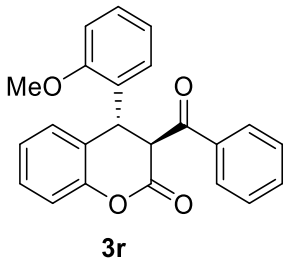
(3S,4S)-3-benzoyl-4-(o-tolyl)chroman-2-one (3q)



3q

Compound **3q** was purified by silica gel column chromatography using 3% EtOAc in hexane; Colorless sticky type (23.6 mg, 69% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.86 (d, *J* = 7.3 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.96 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.9, 166.0, 151.1, 137.2, 137.0, 136.6, 134.0, 131.3, 129.0, 128.95, 128.8, 128.5, 127.9, 127.1, 126.9, 125.7, 125.3, 116.9, 53.0, 39.1, 20.0; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_3$ $[M+NH_4]^+$ 360.1594; found: 360.1604; The ee value 97% (t_{major} = 18.0 min, t_{minor} = 14.6 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

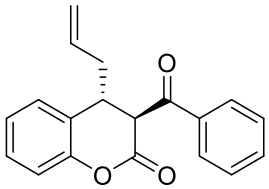
(3S,4S)-3-benzoyl-4-(2-methoxyphenyl)chroman-2-one (3r)



3r

Compound **3r** was purified by silica gel column chromatography using 6% EtOAc in hexane; Yellow sticky type (28 mg, 78% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 8.07 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.12 (d, *J* = 3.4 Hz, 1H), 4.93 (d, *J* = 3.4 Hz, 1H), 3.93 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 194.2, 165.6, 156.6, 152.0, 134.9, 134.2, 129.4, 129.3, 129.3, 129.1, 128.9, 128.9, 127.6, 125.1, 122.3, 121.4, 117.1, 111.1, 55.3, 54.8, 40.8; **HRMS (+ESI):** Calc for $C_{23}H_{19}O_4$ $[M+H]^+$ 359.1278; found: 359.1291; The ee value 92% (t_{major} = 17.7 min, t_{minor} = 12.8 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

(3S,4R)-4-allyl-3-benzoylchroman-2-one (3s)

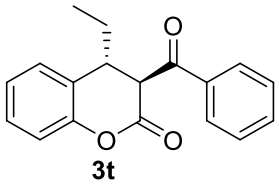


3s

Compound **3s** was purified by silica gel column chromatography using 4 to 5% EtOAc in hexane; Colorless sticky type (12.3 mg, 42% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.86 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 1H), 7.11 – 7.06 (m, 2H), 5.89 – 5.79 (m, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 5.19 (d, *J* = 17.0 Hz, 1H), 4.85 (d, *J* = 2.5 Hz, 1H), 3.39 (ddd, *J* = 8.4, 5.6, 2.5 Hz, 1H), 2.55 – 2.39 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.9, 165.5, 151.0, 134.5, 134.3, 133.4, 129.2, 129.2, 129.0, 128.3, 125.0, 123.1, 120.5, 117.3, 53.3, 40.0, 39.8; **HRMS (+ESI):** Calc for $C_{19}H_{20}NO_3$ $[M+NH_4]^+$ 310.1438; found: 310.1439; The ee value 86% (t_{major} = 13.4 min, t_{minor} = 12.6 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (94:6) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

(3S,4R)-3-benzoyl-4-ethylchroman-2-one (3t)

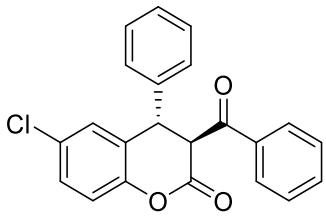
Compound **3t** was purified by silica gel column chromatography using 5% EtOAc in hexane; Colorless sticky type (9.5 mg, 34% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR**



3t

(600 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 4.79 (d, *J* = 2.1 Hz, 1H), 3.24 – 3.20 (m, 1H), 1.86 – 1.71 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.8, 165.9, 151.0, 134.5, 134.3, 129.2, 129.0, 128.9, 128.7, 124.8, 123.3, 117.3, 54.7, 41.9, 28.9, 11.4; **HRMS (+ESI):** Calc for $C_{18}H_{20}NO_3$ $[M+NH_4]^+$ 298.1438; found: 298.1439; The ee value 70% (t_{major} = 16.0 min, t_{minor} = 14.1 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (95:5) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

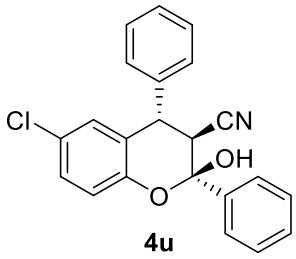
(3S,4S)-3-benzoyl-6-chloro-4-phenylchroman-2-one (3u)



3u

Compound **3u** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; White solid (22.5 mg, 62% yield); **M.P.** = 168-169 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.89 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 4.97 (d, *J* = 6.8 Hz, 1H), 4.75 (d, *J* = 6.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.1, 164.7, 149.7, 138.8, 135.4, 134.4, 130.4, 129.7, 129.4, 129.2, 129.0, 128.8, 128.5, 127.9, 125.9, 118.6, 54.8, 44.5; **HRMS (+ESI):** Calc for $C_{22}H_{19}ClNO_3$ $[M+NH_4]^+$ 380.1048; found: 380.1050; The ee value 97% (t_{major} = 26.4 min, t_{minor} = 22.9 min) was determined by HPLC analysis using CHIRAL ART amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(2R,3S,4S)-6-chloro-2-hydroxy-2,4-diphenylchromane-3-carbonitrile (4u)

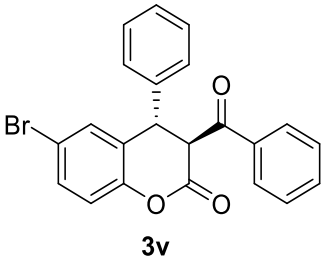


4u

Compound **4u** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; Yellow sticky type (5.8 mg, 16% yield); **Diastereomeric ratio:** 2.5:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.79 (ddd, *J* = 7.3, 5.5, 1.8 Hz, 2.4H), 7.52 – 7.35 (m, 8.4H), 7.31 – 7.27 (m, 2H), 7.24 (dd, *J* = 2.5, 0.9 Hz, 0.4H), 7.19 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.16

– 7.00 (m, 1.4H), 7.00 – 6.97 (m, 0.5H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.73 (dd, *J* = 7.6, 1.6 Hz, 0.3H), 4.92 (d, *J* = 5.6 Hz, 0.4H), 4.63 (d, *J* = 12.3 Hz, 1H), 3.48 (s, 1.4H), 3.43 (d, *J* = 5.6 Hz, 0.4H), 3.15 (d, *J* = 12.3 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 150.7, 150.1, 140.0, 139.9, 139.3, 137.7, 130.3, 130.2, 130.1, 129.5, 129.4, 129.3, 129.3, 129.1, 129.0, 129.0, 128.9, 128.8, 128.7, 128.6, 127.5, 126.3, 126.2, 125.2, 119.6, 119.3, 117.3, 116.5, 96.6, 96.4, 46.36, 44.7, 43.9, 41.5; **HRMS (+ESI):** Calc for $C_{22}H_{16}ClNNaO_2$ $[M+Na]^+$ 384.0762; found: 384.0743; The ee value of the major diastereomer 94% (t_{major} = 8.8 min, t_{minor} = 12.1 min) was determined by HPLC analysis using Daicel Chiralpak ID with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

(3S,4S)-3-benzoyl-6-bromo-4-phenylchroman-2-one (3v)

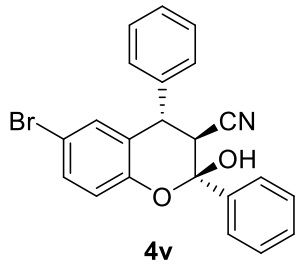


3v

Compound **3v** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; Colorless solid (16.3 mg, 40% yield); **M.P.** = 185-186 °C; **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.89 (d, *J* = 7.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.44 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 1H), 7.06 (s, 1H), 4.97 (d, *J* = 6.6 Hz, 1H), 4.74 (d, *J* = 6.6 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.1, 164.6, 150.3, 138.8, 135.3, 134.4, 132.4, 131.7, 129.7, 129.2, 129.0, 128.5, 127.9, 126.2, 119.0, 117.9, 54.8, 44.4; **HRMS (+ESI):** Calc for $C_{22}H_{19}BrNO_3$ $[M+NH_4]^+$ 424.0543; found: 424.0542; The ee value 99% (t_{major} = 26.4 min, t_{minor} = 24.2 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(2R,3S,4S)-6-bromo-2-hydroxy-2,4-diphenylchromane-3-carbonitrile (4v)

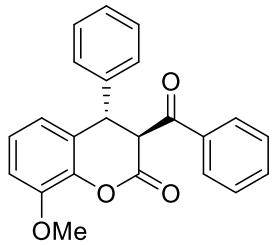
Compound **4v** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; Colorless sticky type (8.9 mg, 22% yield); **Diastereomeric ratio:** 3.8:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.80 (d, *J* = 1.7 Hz, 0.5H), 7.78 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 3.8H), 7.45 – 7.37 (m, 3.8H), 7.36 (d, *J* = 7.2 Hz, 0.8H), 7.33 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 2H), 7.12 (s, 0.3H), 7.02 – 6.98 (m, 0.4H), 6.93 (s, 1H), 6.89



4v

(d, *J* = 8.7 Hz, 1H), 4.93 (d, *J* = 5.7 Hz, 0.3H), 4.64 (d, *J* = 12.3 Hz, 1H), 3.54 (s, 1.2H), 3.42 (d, *J* = 5.7 Hz, 0.3H), 3.14 (dd, *J* = 12.3, 1.9 Hz, 1H); **^{13}C NMR (150 MHz, CDCl$_3$) δ:** 151.2, 150.7, 139.9, 139.8, 139.5, 139.2, 132.2, 132.0, 131.9, 131.8, 130.3, 130.2, 130.1, 129.5, 129.4, 129.3, 129.0, 128.95, 128.7, 128.6, 126.3, 126.2, 125.7, 124.2, 120.1, 119.7, 117.3, 116.5, 114.8, 114.7, 96.6, 96.4, 46.4, 44.7, 43.8, 41.4; **HRMS (+ESI):** Calc for $C_{22}H_{16}BrNNaO_2$ $[M+Na]^+$ 428.0257; found: 428.0275; The ee value of the major diastereomer 87% (t_{major} = 14.7 min, t_{minor} = 11.9 min) was determined by HPLC analysis using Lux® 5 μm Amylose-2 with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 1.0 mL/min, 220 nm, 25 °C.

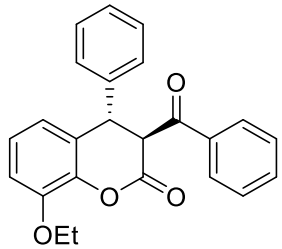
(3S,4S)-3-benzoyl-8-methoxy-4-phenylchroman-2-one (3w)



3w

Compound **3w** was purified by silica gel column chromatography using 6 to 7% EtOAc in hexane; Colorless sticky type (18.6 mg, 52% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, CDCl$_3$) δ:** 7.89 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.02 (t, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.79 (d, *J* = 7.0 Hz, 1H), 3.94 (s, 3H); **^{13}C NMR (150 MHz, CDCl$_3$) δ:** 193.3, 164.7, 147.8, 140.5, 139.5, 135.7, 134.2, 129.5, 129.1, 129.0, 128.1, 128.07, 125.3, 125.1, 120.3, 111.8, 56.4, 55.0, 44.6; **HRMS (+ESI):** Calc for $C_{23}H_{22}NO_4$ $[M+NH_4]^+$ 376.1543; found: 376.1558; The ee value 94% (t_{major} = 25.4 min, t_{minor} = 39.6 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (85:15) as the eluent, flow: 1.0 mL/min, 254 nm, 25 °C.

(3S,4S)-3-benzoyl-8-ethoxy-4-phenylchroman-2-one (3x)

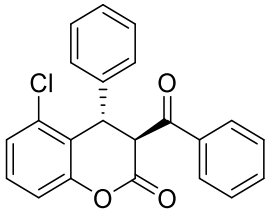


3x

Compound **3x** was purified by silica gel column chromatography using 6 to 7% EtOAc in hexane; Colorless sticky type (15.3 mg, 41% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, CDCl$_3$) δ:** 7.90 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J*

= 7.6 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 4.98 (d, *J* = 7.1 Hz, 1H), 4.79 (d, *J* = 7.1 Hz, 1H), 4.20 – 4.11 (m, 2H), 1.50 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.4, 164.9, 147.2, 140.7, 139.5, 135.7, 134.1, 129.4, 129.1, 129.0, 128.1, 128.05, 125.4, 125.0, 120.2, 113.2, 65.1, 55.0, 44.6, 15.0; **HRMS (+ESI):** Calc for $C_{24}H_{24}NO_4$ $[M+NH_4]^+$ 390.1700; found: 390.1702; The ee value 98% (t_{major} = 10.9 min, t_{minor} = 25.2 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (80:20) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

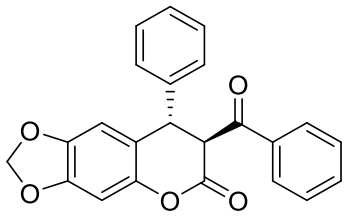
(3S,4S)-3-benzoyl-5-chloro-4-phenylchroman-2-one (3y)



3y

Compound **3y** was purified by silica gel column chromatography using 3 to 4% EtOAc in hexane; Colorless sticky type (11.2 mg, 31% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 8.01 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.20 – 7.14 (m, 4H), 4.98 (d, *J* = 1.1 Hz, 1H), 4.94 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 192.5, 163.9, 152.4, 138.9, 134.7, 134.1, 134.1, 129.9, 129.7, 129.4, 129.3, 128.4, 127.3, 126.3, 121.5, 116.0, 57.3, 43.3; ; **HRMS (+ESI):** Calc for $C_{22}H_{19}ClNO_3$ $[M+NH_4]^+$ 380.1048; found: 380.1056; The ee value 58% (t_{major} = 12.5 min, t_{minor} = 13.8 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (92:8) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

(7S,8S)-7-benzoyl-8-phenyl-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3z)

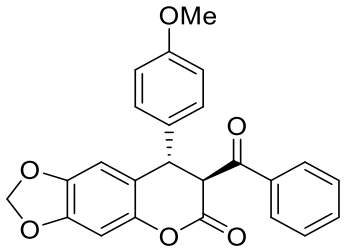


3z

Compound **3z** was purified by silica gel column chromatography using 8 to 10% EtOAc in hexane; Yellow sticky type (28.3 mg, 76% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.89 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.28 – 7.24 (t, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 6.71 (s, 1H), 6.33 (s, 1H), 5.95 (s, 2H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.65 (d, *J* = 6.5 Hz, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 193.6, 165.3, 148.0, 145.8, 145.0, 139.7, 135.5, 134.2, 129.6, 129.2, 129.0, 128.2, 127.9, 116.0, 107.8, 102.0, 99.2, 55.3, 44.56; **HRMS**

(+ESI): Calc for $C_{23}H_{20}NO_5$ $[M+NH_4]^+$ 390.1336; found: 390.1347; The ee value 99% (t_{major} = 13.2 min, t_{minor} = 12.2 min) was determined by HPLC analysis using Daicel Chiralpak IA with *n*-hexane/*i*-PrOH (70:30) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

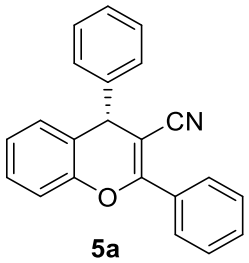
(7S,8S)-7-benzoyl-8-(4-methoxyphenyl)-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromen-6-one (3z')



3z'

Compound **3z'** was purified by silica gel column chromatography using10% EtOAc in hexane; Pale yellow semisolid (27.4 mg, 68% yield); **Diastereomeric ratio:** >20:1; **^{1}H NMR (600 MHz, $CDCl_3$) δ:** 7.88 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.69 (s, 1H), 6.31 (s, 1H), 5.94 (d, *J* = 2.2 Hz, 2H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$) δ:** 193.7, 165.5, 159.3, 147.9, 145.6, 144.9, 135.6, 134.2, 131.5, 129.1, 129.0, 128.9, 126.3, 116.5, 114.8, 107.8, 102.0, 99.2, 55.5, 55.3, 43.7; **HRMS (+ESI):** Calc for $C_{24}H_{22}NO_6$ $[M+NH_4]^+$ 420.1442; found: 420.1467; The ee value 96% (t_{major} = 24.7 min, t_{minor} = 21.8 min) was determined by HPLC analysis using CHIRAL ART Amylose-C with *n*-hexane/*i*-PrOH (75:25) as the eluent, flow: 1.0 mL/min, 254 nm, 25 ^oC.

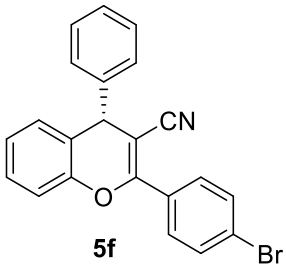
(S)-2,4-diphenyl-4H-chromene-3-carbonitrile (5a)



5a

Compound **5a** was purified by silica gel (60-120 mesh) column chromatography using 2% EtOAc in hexane; White solid (14.5 mg, 67% yield); **M.P.** = 104-105 ^oC; **^{1}H NMR (400 MHz, $CDCl_3$) δ:** 7.89 (dd, *J* = 7.7, 1.6 Hz, 2H), 7.49 (d, *J* = 7.5 Hz, 3H), 7.39 – 7.33 (m, 2H), 7.32 – 7.24 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 4.91 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 160.3, 149.5, 143.8, 132.0, 131.4, 129.6, 129.3, 128.8, 128.8, 128.4, 128.3, 127.9, 125.7, 121.8, 119.1, 117.1, 88.6, 43.4; **HRMS (+ESI):** Calc for $C_{22}H_{16}NO$ $[M+H]^+$ 310.1226; found: 310.1228; The ee value 91% (t_{major} = 7.1 min, t_{minor} = 5.7 min) was determined by HPLC analysis using Daicel Chiralpak AD-H with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 0.75 mL/min, 220 nm, 25 ^oC.

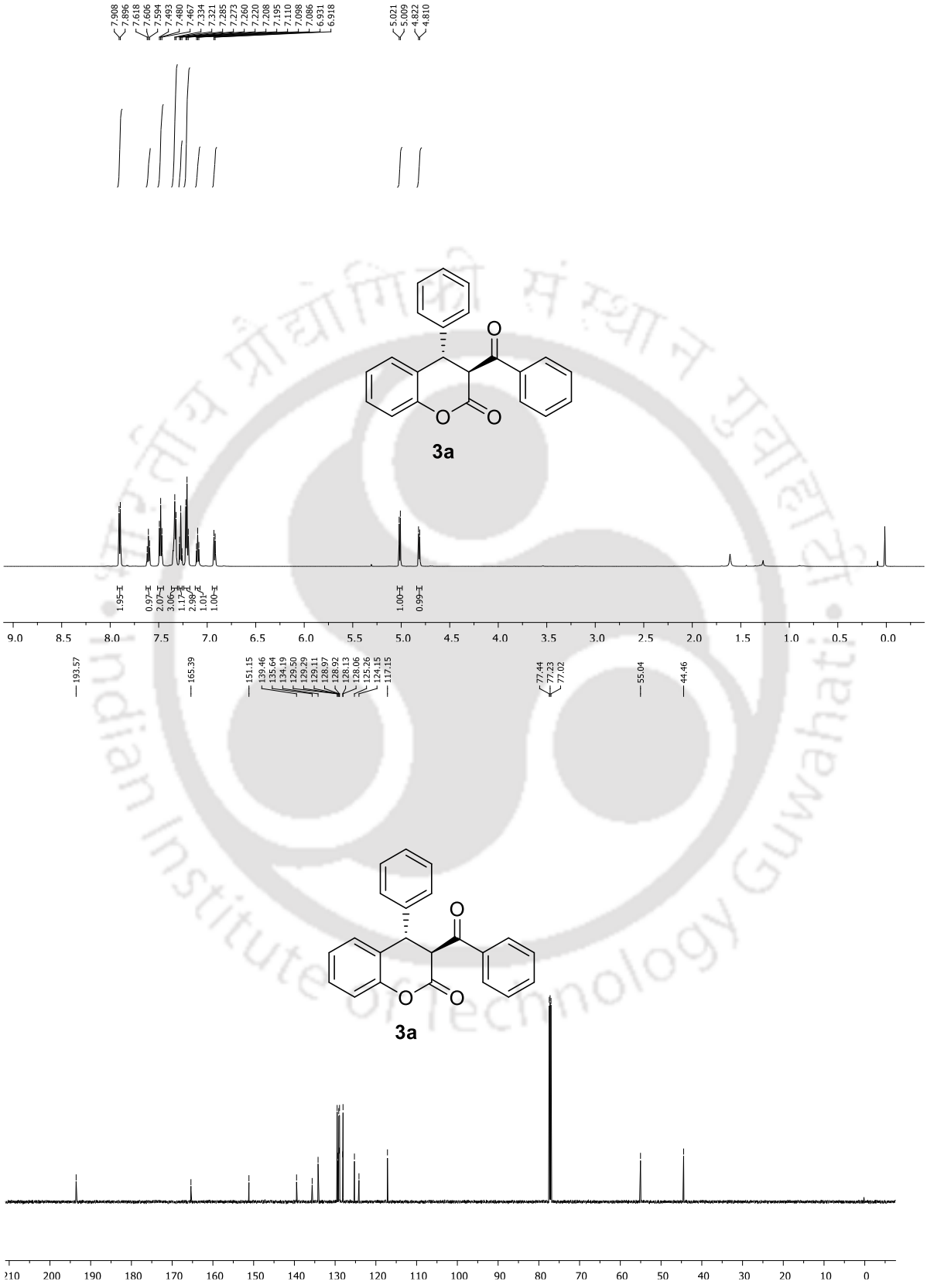
(S)-2-(4-bromophenyl)-4-phenyl-4H-chromene-3-carbonitrile (5f)



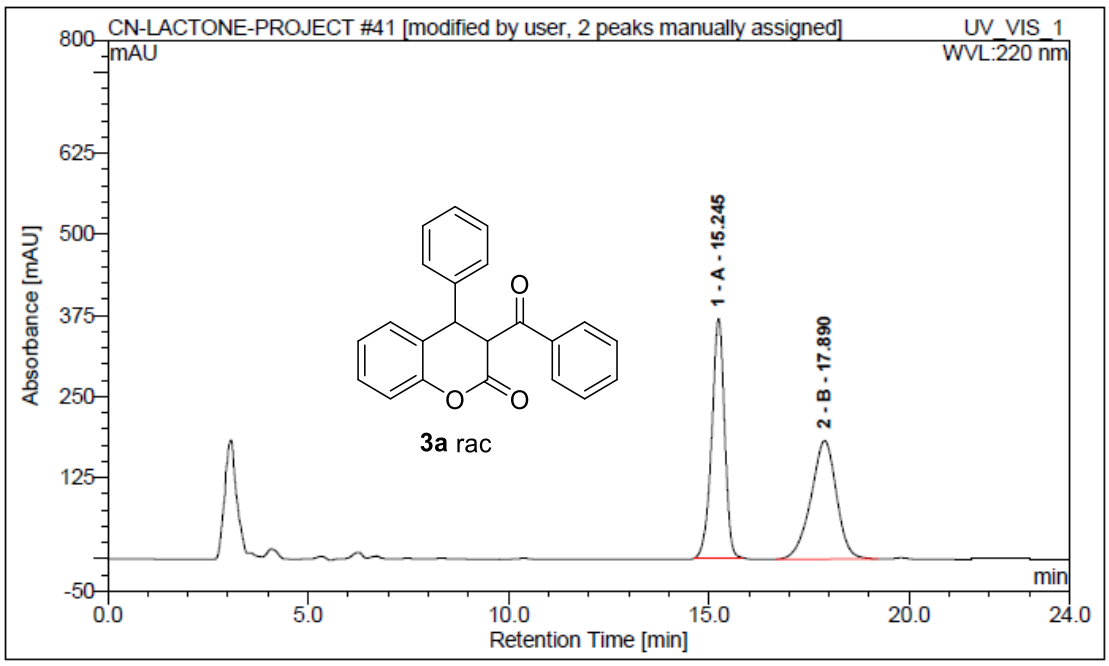
5f

Compound **5f** was purified by silica gel (60-120 mesh) column chromatography using 2% EtOAc in hexane; White solid (16.5 mg, 61% yield); **M.P.** = 142-143 ^{o}C; **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 7.76 (d, *J* = 8.6 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.16 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 4.89 (s, 1H); **^{13}C NMR (100 MHz, $CDCl_3$) δ:** 159.2, 149.4, 143.5, 132.1, 130.8, 129.8, 129.7, 129.3, 128.9, 128.4, 128.0, 125.9, 125.9, 121.6, 118.8, 117.0, 89.0, 43.3; **HRMS (+ESI):** Calc for $C_{22}H_{15}BrNO$ $[M+H]^+$ 388.0332; found: 388.0331; The ee value 88% (t_{major} = 9.1 min, t_{minor} = 7.3 min) was determined by HPLC analysis using Daicel Chiralpak AD-H with *n*-hexane/*i*-PrOH (90:10) as the eluent, flow: 0.75 mL/min, 220 nm, 25 ^{o}C.

5.9. Selected NMR spectra and HPLC chromatogram:

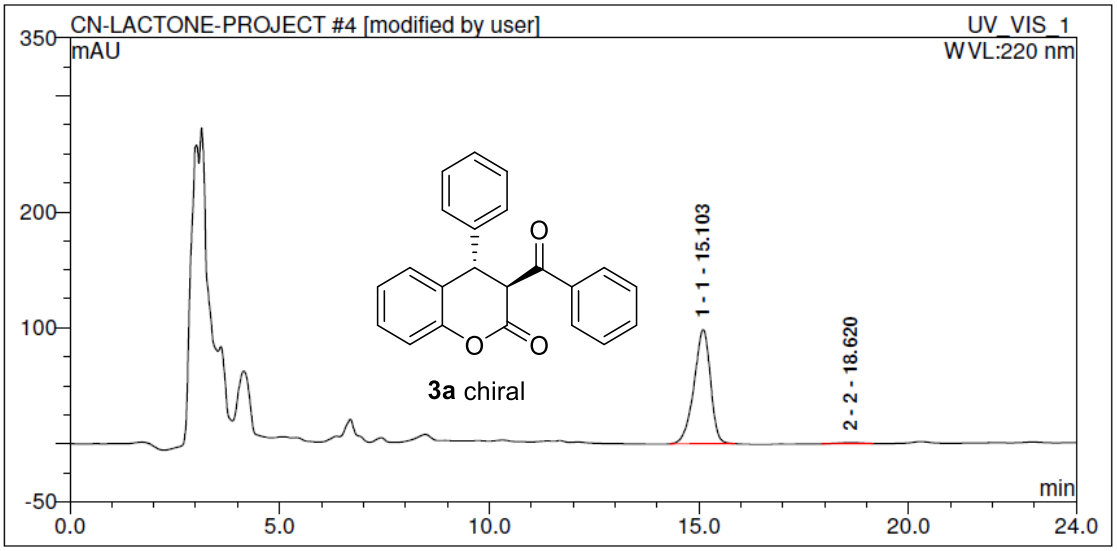


SAL-CN-LAC-LUX-C4-RAC

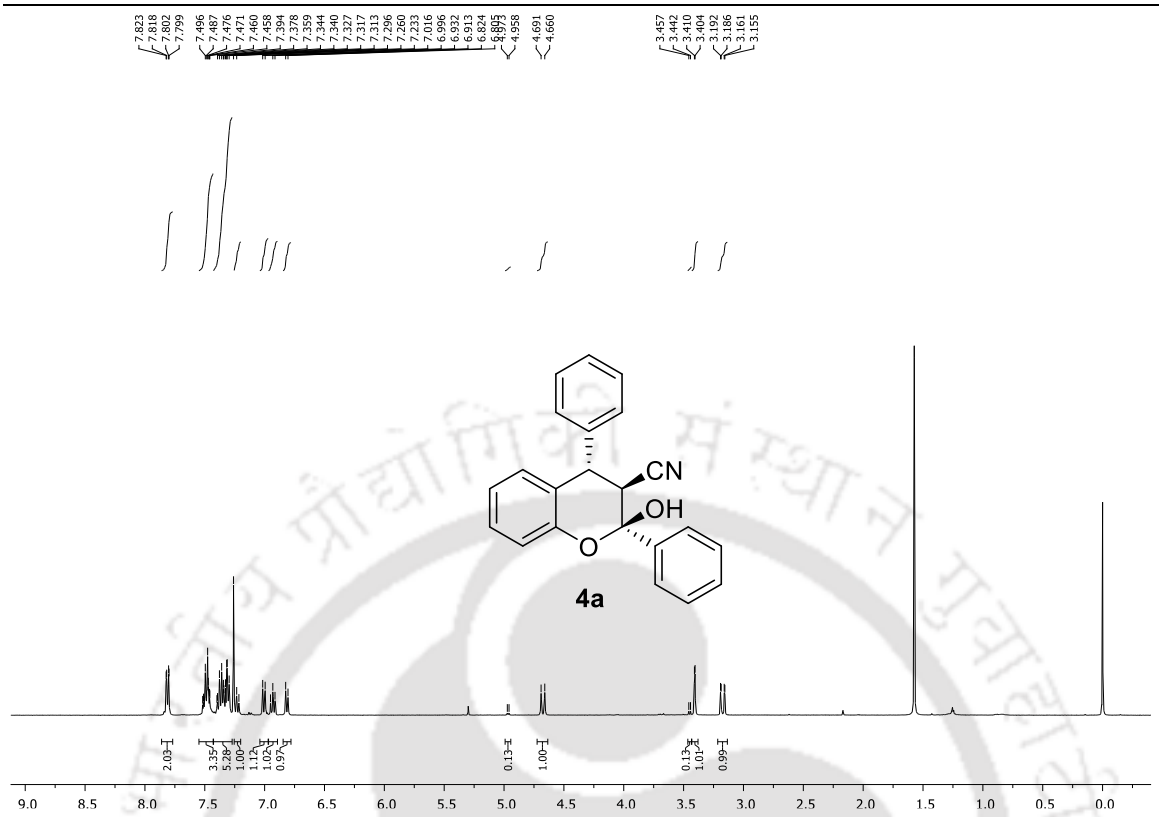


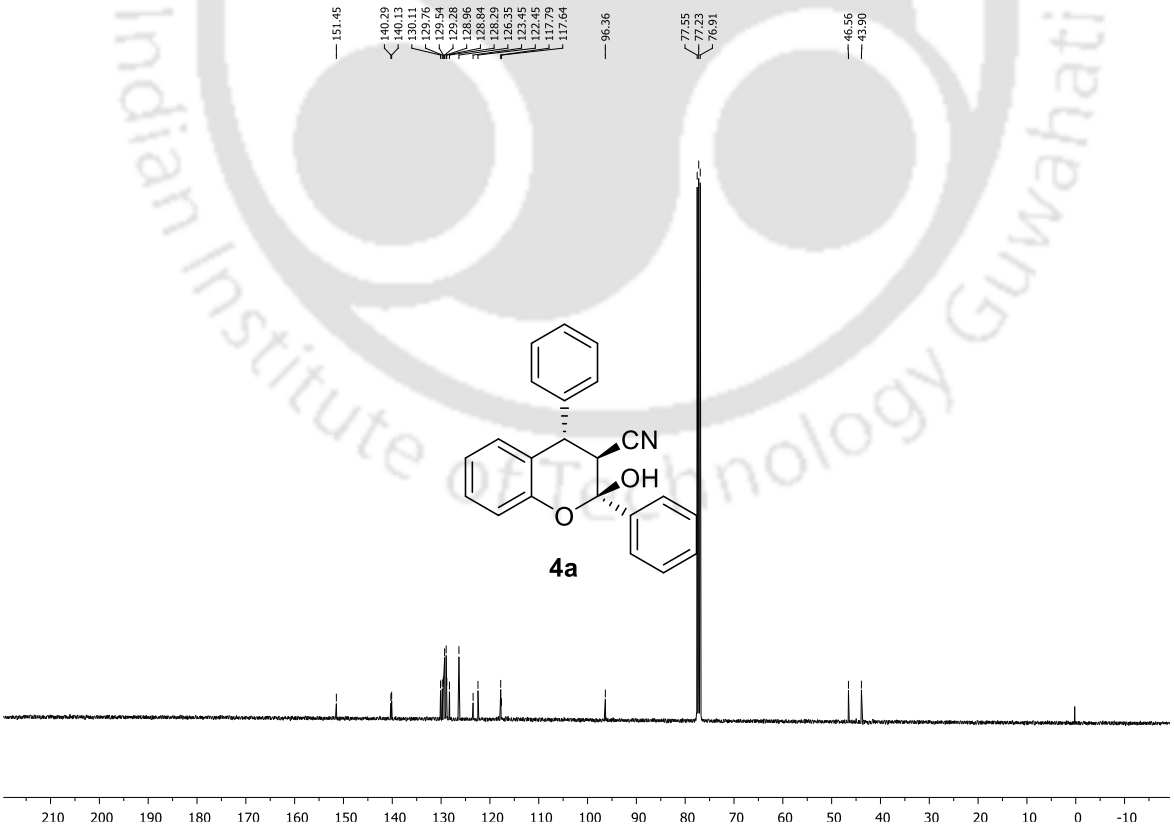
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	15.25	136.4721	50.26780547	368.9556	n.a.
2	B	17.89	135.018	49.73219453	182.886	n.a.

Sal-Ph-CN-CHI-Lux-C4

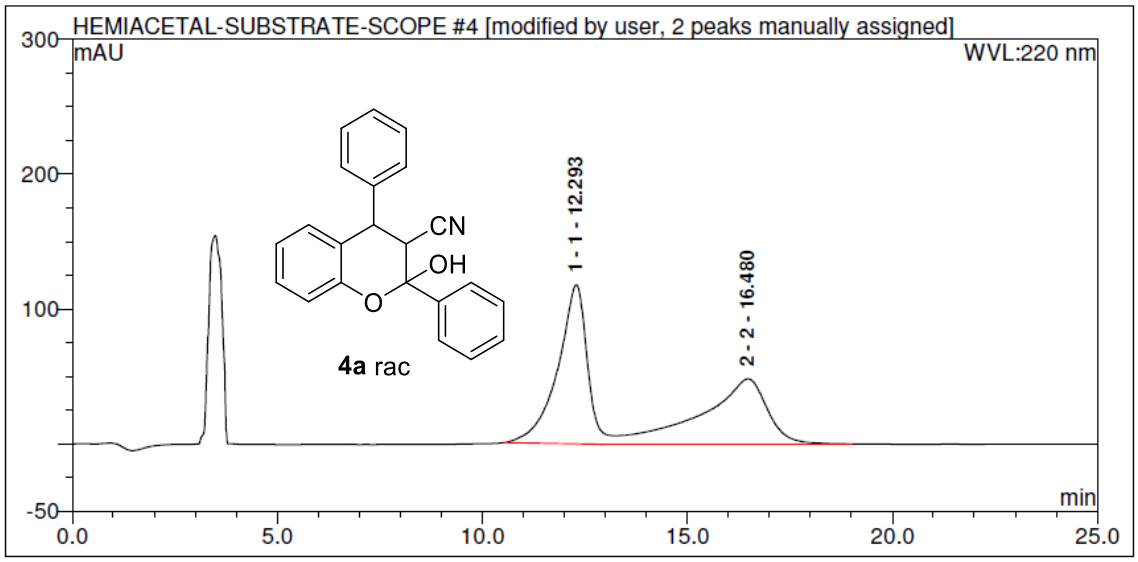


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	15.10	44.67535	98.84935641	98.23277	n.a.
2	2	18.62	0.520	1.150643591	0.823	n.a.

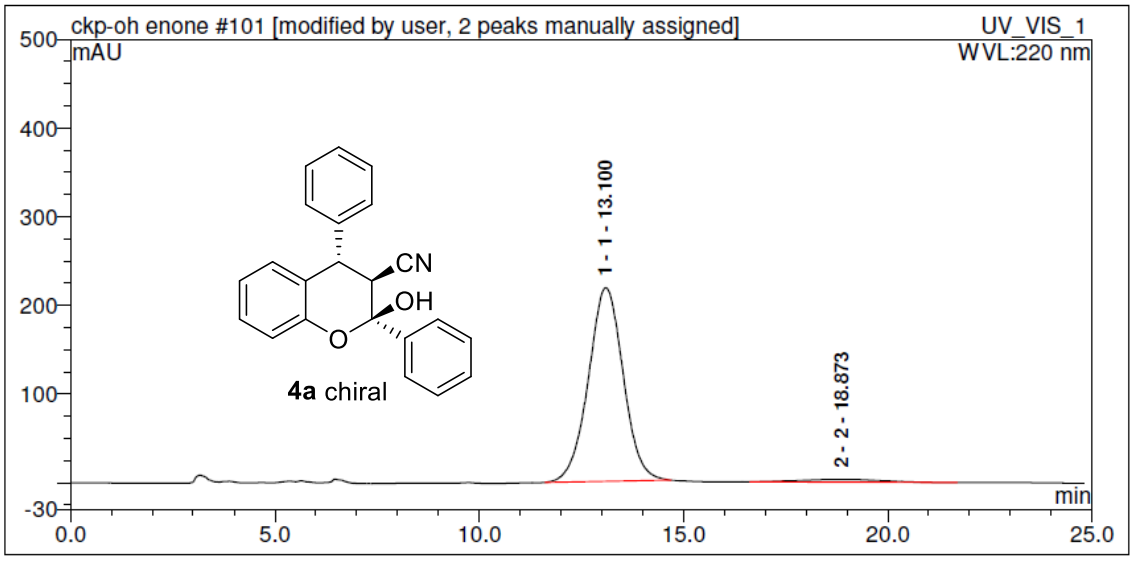




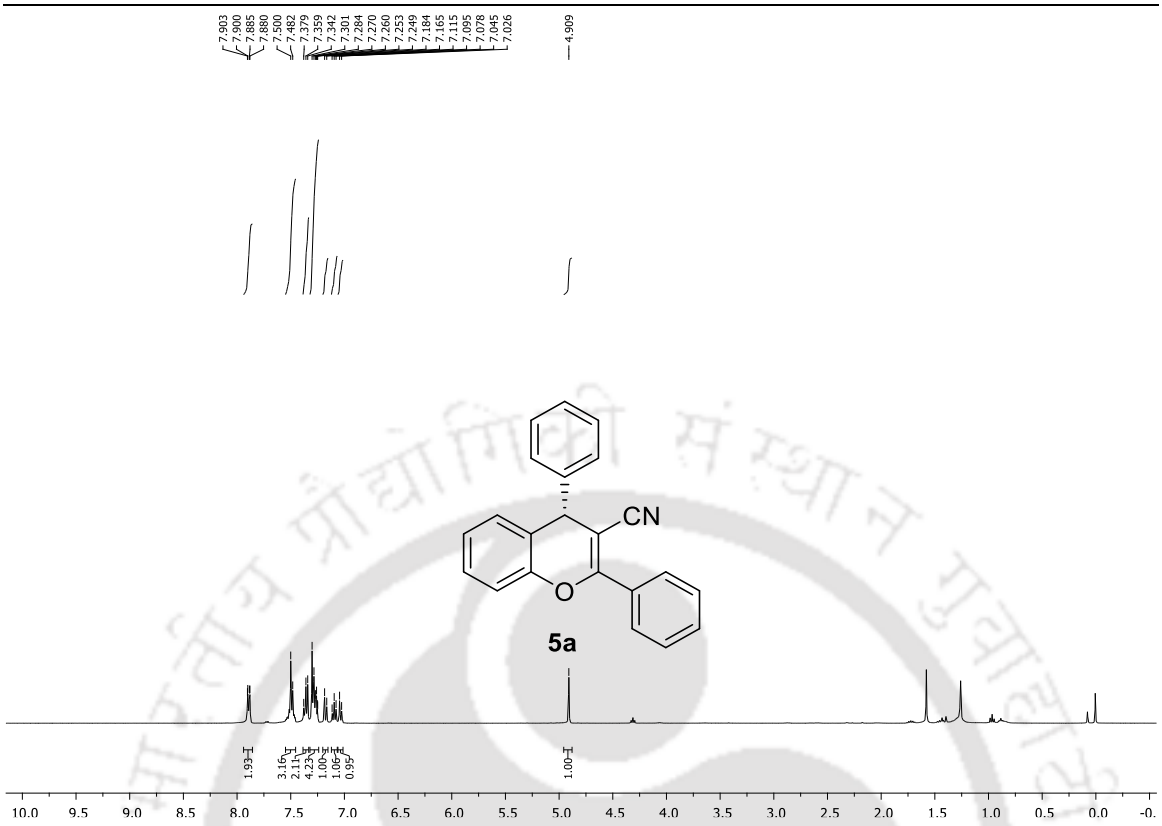
Ph-CN-HEMI-RAC-ID

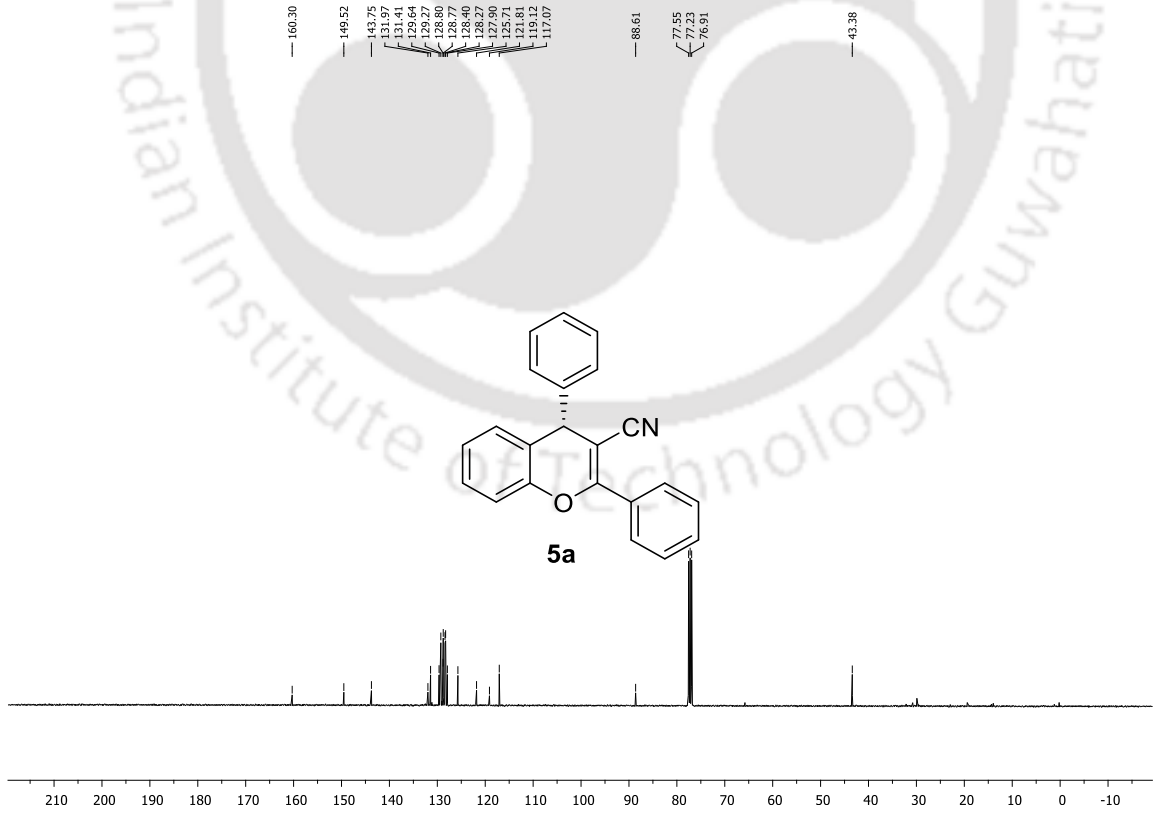


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	12.29	97.24595	51.31021662	117.9519	n.a.
2	2	16.48	92.280	48.68978338	48.304	n.a.

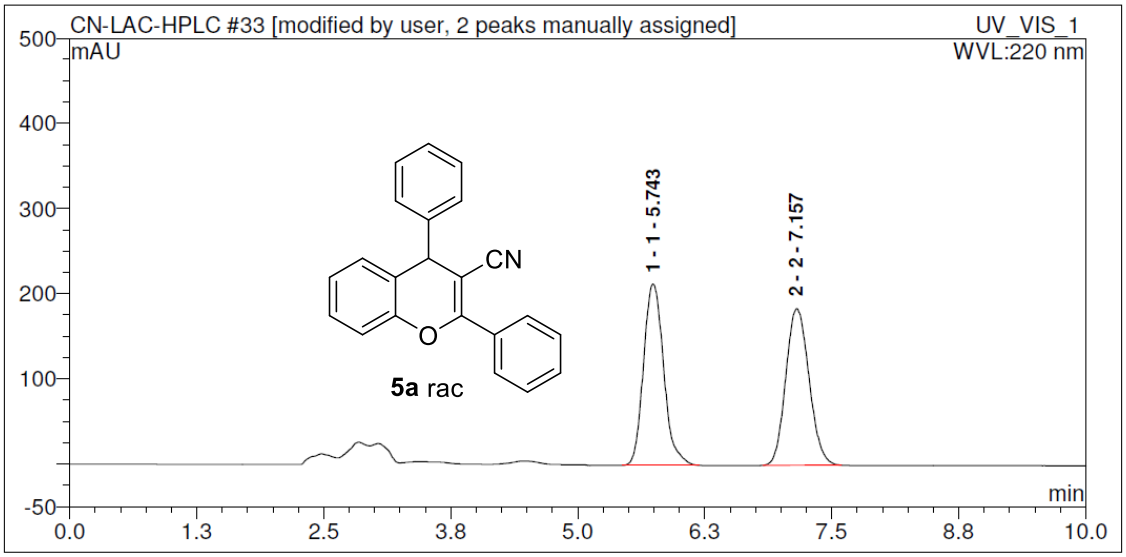


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	13.10	215.8537	96.77278563	218.2557	n.a.
2	2	18.87	7.198	3.227214371	3.161	n.a.



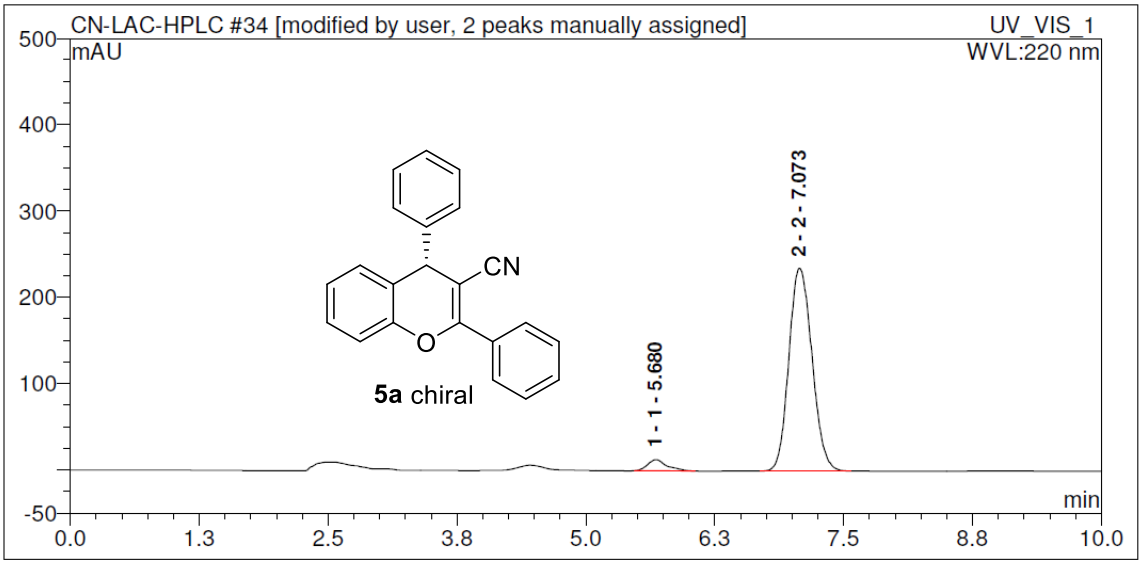


PH-CN-HEMI-PTSA-RAC-AD-H



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.74	48.9811	50.07746577	212.9774	n.a.
2	2	7.16	48.830	49.92253423	183.816	n.a.

PH-CN-HEMI-PTSA-CHI-AD-H



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	1	5.68	2.769882	4.327212904	12.82446	n.a.
2	2	7.07	61.241	95.6727871	234.946	n.a.

List of publications:

1. Maity, R.; **Gharui, C.**; Sil, A. K.; Pan, S. C. Organocatalytic Asymmetric Michael/Hemiketalization/Retro-aldol Reaction of *α*-Nitroketones with Unsaturated Pyrazolones: Synthesis of 3-Acyloxy Pyrazoles. *Org. Lett*. **2017**, *19*, 662.
2. **Gharui, C.**; Singh, S.; Pan, S. C. Chiral Phosphoric Acid Catalyzed Enantioselective Annulation of Acyclic Enecarbamates to *in situ*-Generated *ortho*-Quinone Methides. *Org. Biomol. Chem.* **2017**,*15*, 7272.
3. **Gharui, C.**; Behera, D.; Pan, S. C. Organocatalytic Asymmetric Domino Michael/Acyl Transfer Reaction Between *α*-Nitroketones and *in situ*-Generated *ortho*-Quinone Methides: Route to 2-(1-Arylethyl)phenols. *Adv. Synth. Catal.* **2018**, *360*, 4502.
4. **Gharui, C.**; Pan, S. C. Employment of *α*-Nitroketones in Organic Synthesis. *Org. Biomol. Chem.* **2019**, *17*, 5190.
5. Mukhopadhyay, S.; **Gharui, C.**; Pan, S. C. Applications of Bifunctional Organocatalysts on *ortho*-Quinone Methides. *Asian J. Org. Chem.* **2019**, *8*, 1970.
6. **Gharui, C.**; Prakash, S.; Chopra, D.; Pan, S. C. Organocatalytic Asymmetric Addition of Thioglycolates to *o*-Quinone Methides: A Route to 5-Substituted-5*H*-benzoxathiepine-2(3*H*)-ones. *Org. Biomol. Chem.* **2020**, *18*, 2828.
7. **Gharui, C.**; Parida, C.; Pan, S. C. Organocatalytic Asymmetric Addition of Aromatic *α*-Cyanoketones to *o*-Quinone Methides: Synthesis of 3,4-Dihydrocoumarins and Tetrasubstituted Chromans. *Manuscript accepted*, doi.org/10.1021/acs.joc.1c00435.

Presentations:

- **International Conference on Chemistry for Human Development (ICCHD-2018)**, January 8-10, **2018**, Heritage Institute of Technology, Kolkata, India (Poster presentation).
- **International Conference on Frontiers in Chemical Sciences (FICS-2018)**, December 6-8, **2018**, Indian Institute of Technology Guwahati, India (Poster presentation).
- **XV J-NOST Conference for Research Scholars (XV J-NOST-2019)**, October 18-21, **2019**, Department of Chemistry, University of Delhi, Delhi, India (Oral presentation).