

Organocatalytic Asymmetric Synthesis of Imidazolidines, Pyrrolidines, Oxazolidines and Dihydroquinolones

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

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January 2019





***Dedicated
to
My Parents and Sisters***





INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

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

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

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled “***Organocatalytic Asymmetric Synthesis of Imidazolidines, Pyrrolidines, Oxazolidines and Dihydroquinolones***” which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Soumendranath Mukhopadhyay (Roll No: 136122009) 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

January, 2019

Dr. Subhas Chandra Pan

Supervisor



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Sincerely,
Soumendranath Mukhopadhyay



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Abbreviation

APCI	Atmospheric pressure chemical ionization	DMSO	Dimethylsulfoxide
Å	Angstrom	dr	Diastereomeric ratio
Ar	Aryl group	EtOAc	Ethyl acetate
Bn	Benzyl	ee	Enantiomeric excess
br	Broad	equiv.	Equivalent
Bu	Butyl	ESI	Electrospray ionization
CCDC	Cambridge crystallographic data centre	Et	Ethyl
COSY	Correlation spectroscopy	EWG	Electron withdrawing group
CH ₂ Cl ₂	Dichloromethane	FT-IR	Fourier transform infrared spectroscopy
CHCl ₃	Chloroform	g	Grams
CPME	Cyclopentyl methyl ether	h	Hours
Cy	Cyclohexyl	HPLC	High performance liquid chromatography
°C	Degree celsius	HRMS	High resolution mass spectrometry
d	Doublet or day	Hz	Hertz
dd	Doublet of doublet	<i>i</i>	Iso
ddd	Doublet of doublet of doublet	<i>J</i>	Coupling constant
δ	Chemical shift or delta	KBr	Potassium Bromide
DCE	1,2-Dichloroethane	m	Multiplet
DCM	Dichloromethane	<i>m</i>	<i>meta</i>
DMF	N,N-Dimethylformamide	<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid

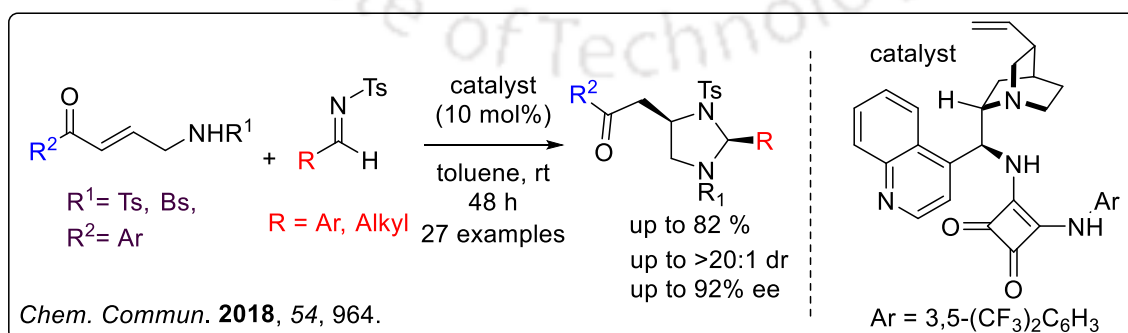
Me	Methyl	THF	Tetrahydrofuran
mg	Miligram	<i>t</i>	<i>tert</i>
mL	Mililitre	TMS	Tetramethylsilane
mmol	Milimole	Tol	Tolyl
Mp	Melting point	Ts	Tosyl
MS	Molecular seive	uv	Ultra violet
MTBE	Methy tertiary butyl ether	XRD	X-ray diffraction
<i>n</i>	Normal		
NMR	Nuclear magnetic resonance		
NOESY	Nuclear overhauser enhancement spectroscopy		
NBS	<i>N</i> -Bromo succinamide		
<i>o</i>	<i>ortho</i>		
ORTEP	Oak ridge thermal ellipsoid plot program		
<i>p</i>	<i>Para</i>		
Ph	Phenyl		
Pr	propyl		
ppm	Parts per million		
<i>p</i> -TSA	<i>p</i> -Toluenesulfonic acid		
q	Quartet		
rt	Room temperature		
s	Singlet		

Abstract

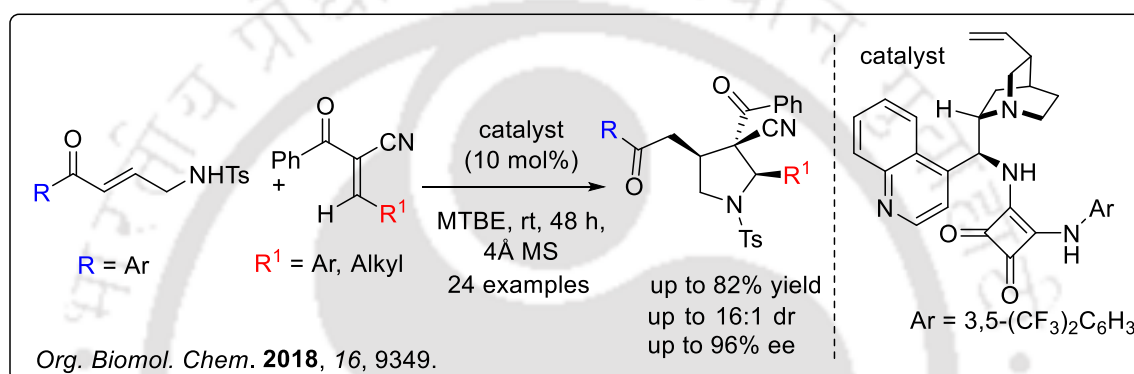
The present thesis, entitled as “**Organocatalytic Asymmetric Synthesis of Imidazolidines, Pyrrolidines, Oxazolidines and Dihydroquinolones**” have been divided into six chapters based on the results achieved from the experimental works performed during the entire course of the PhD research programme.

Chapter 1 narrates a brief introduction and the literature review about asymmetric organocatalysis. The reactive nature of different H-bonding catalysts including bifunctional thiourea and squaramide catalysts has been discussed, since these catalysts were mainly used in the works demonstrated in the thesis. Also a detailed discussion about the organocatalytic cascade reactions, hetero Michael cascade reaction using thiourea and squaramide catalysts have been done here. Finally a preliminary idea about the organocatalytic asymmetric Michael and Mannich reactions leading to the construction of quaternary stereogenic centres has been elaborated here.

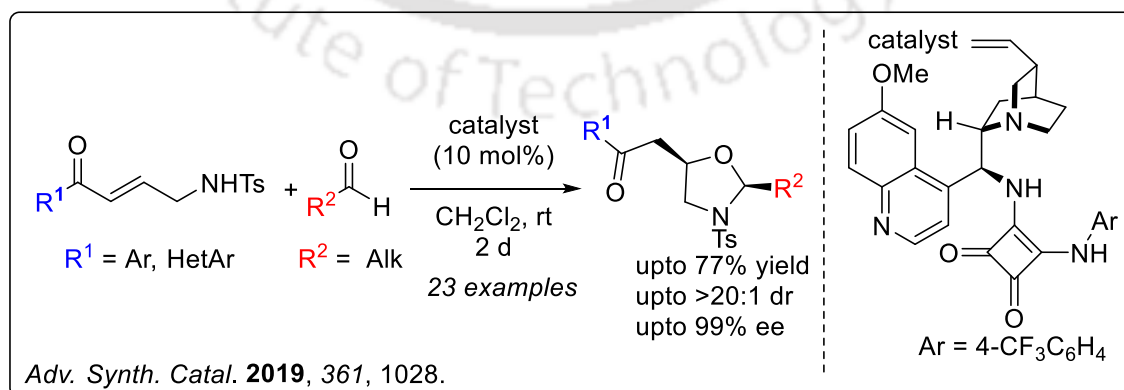
Chapter 2 demonstrates first highly diastereo- and enantioselective synthesis of 2,4-disubstituted imidazolidinines *via* a domino addition-*aza*-Michael reaction. Bidentate aminomethyl enones and *N*-tosyl imines have been used as substrates in this cyclization reaction. Bifunctional squaramide catalysts were successfully employed to achieve excellent enantio- and diastereoselectivities for the substituted imidazolidines. Synthetic utility of the methodology has been explored by performing few reaction including Baeyer-Villiger oxidation. The mild reaction conditions and operational simplicity are the key features for this methodology to be applied in the synthesis of natural product bearing chiral imidazolidine motifs.



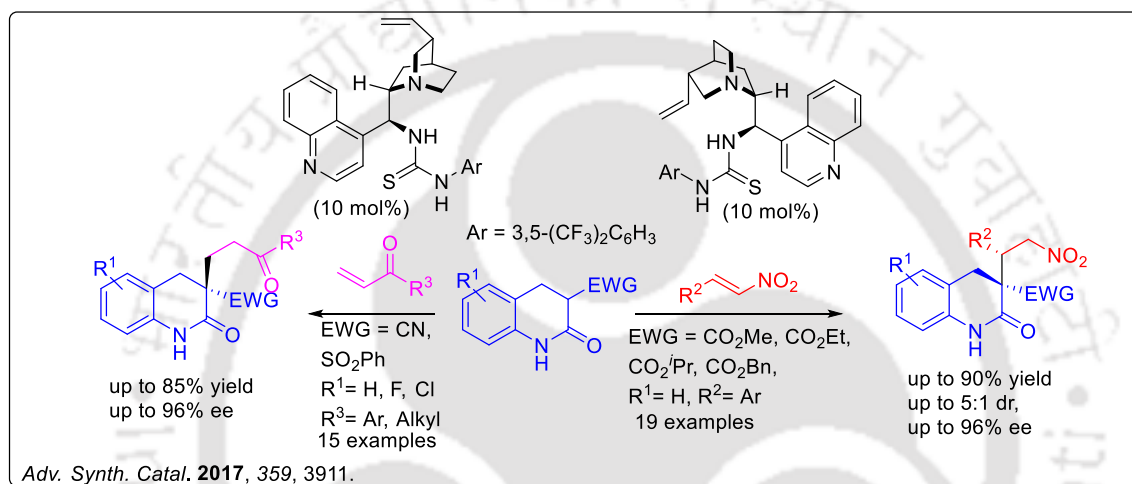
Chapter 3 describes bifunctional squaramide mediated organocatalytic asymmetric cascade reaction for the construction of highly substituted pyrrolidines having stereogenic quaternary centre at 3-position. Bidentate *N*-tosyl aminomethyl enone and *trans*- α -cyano- α,β -unsaturated ketone were utilized as the reaction partners in this reaction. Pyrrolidine derivatives having cyano and keto functionalities were isolated with high diastereo- and good to high enantioselectivities. Synthetic utility of our reaction have been explored by performing the Baeyer-Villiger oxidation. This methodology is a mild and simple protocol for the synthesis of biologically important pyrrolidine molecules.



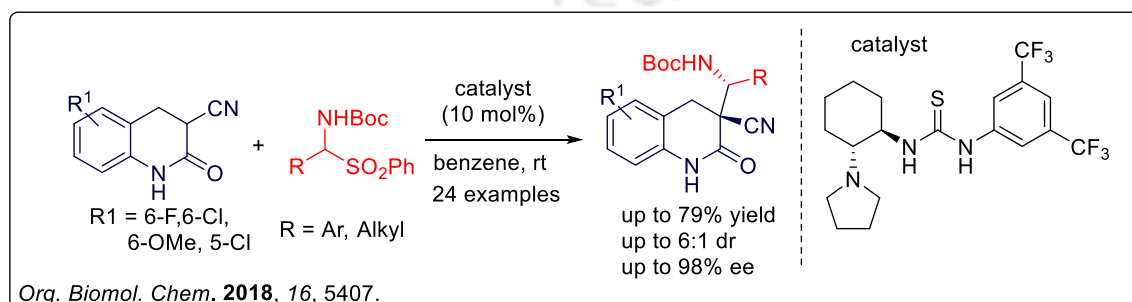
Chapter 4 reveals an unprecedented organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines proceeds through hemiaminal formation followed by intramolecular *oxa*-Michael reaction between alkyl aldehydes and *N*-tosyl aminomethyl enones. Bifunctional squaramide catalyst derived from quinine amine furnished the oxazolidine derivatives with excellent enantio- and diastereoselectivities. The significance of this reaction have been shown by performing few reactions including the synthesis of linear 1,2-aminoalcohol.



Chapter 5 illustrates first organocatalytic asymmetric Michael reaction for the synthesis of biologically important 3,3-disubstituted-3,4-dihydro-2-quinolones. Cinchona alkaloid derived bifunctional amino-thiourea catalysts were found to be the best catalysts and the products were isolated in high enantio- and good diastereoselectivities. By substrate tuning, both vinyl ketones and nitroolefins were employed in the reaction. Also, the usefulness of our methodology was shown *via* important synthetic operations of the products. Dihydroquinolones having stereogenic quaternary centres are significant intermediates in many natural products and pharmaceutical agents.



Chapter 6 delineates the first organocatalytic asymmetric Mannich reaction for the synthesis of optically active 3,3-disubstituted-3,4-dihydro-2-quinolones. This method is potent for the synthesis of biologically important 3,3-disubstituted-dihydro-2-quinolones. *N*-Boc imine precursor amidosulfones were used for this purpose. Cyclohexyldiamine derived bifunctional amino-thiourea catalyst was quite efficient to provide the products in high enantio- and good diastereoselectivities. Few synthetic transformations have been performed to strengthen the synthetic potential of our methodology.



Each of these chapters contain introduction, previous reported works, present result and discussion, experimental section, references, along with characterization data of products including few selective spectral data. Overall, this thesis discussed some new and efficient strategies for the enantioselective synthesis of different heterocyclic compounds using amino methyl enones and substituted dihydroquilonones.







Chapter 1 ***General Introduction***



1.1. Asymmetric synthesis:

Asymmetric synthesis or enantioselective synthesis established as highly demanding in the field organic synthesis over the few decades. Enantiomerically pure compounds such as different enantiomers or diastereomers of a molecule exhibit different biological activities. For example (*S*)-dopa is effective for restoring nerve function and used as drug for the treatment of Parkinson disease while the other enantiomer (*R*)-dopa is quite toxic in nature (Figure 1). Due to such unique properties of the isomers, synthesis of optically pure compounds is highly desirable, particularly in pharmaceutical industries. The widely-known methods for the synthesis of different chiral compounds are resolution techniques, using chiral pool reagents strategies, chiral auxiliary approaches and generation of asymmetry by means of chiral catalysts. Among all these methods, catalytic asymmetric reactions are the efficient strategies in the field of asymmetric synthesis since it does not require the addition of chiral reagents and also atom economical as it avoids the addition-elimination of chiral auxiliaries. The leading methods to achieve catalytic asymmetric syntheses are bio-catalysis, transition metal catalysis and organocatalysis.¹

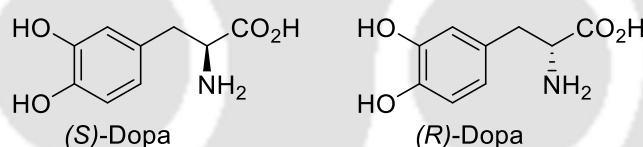
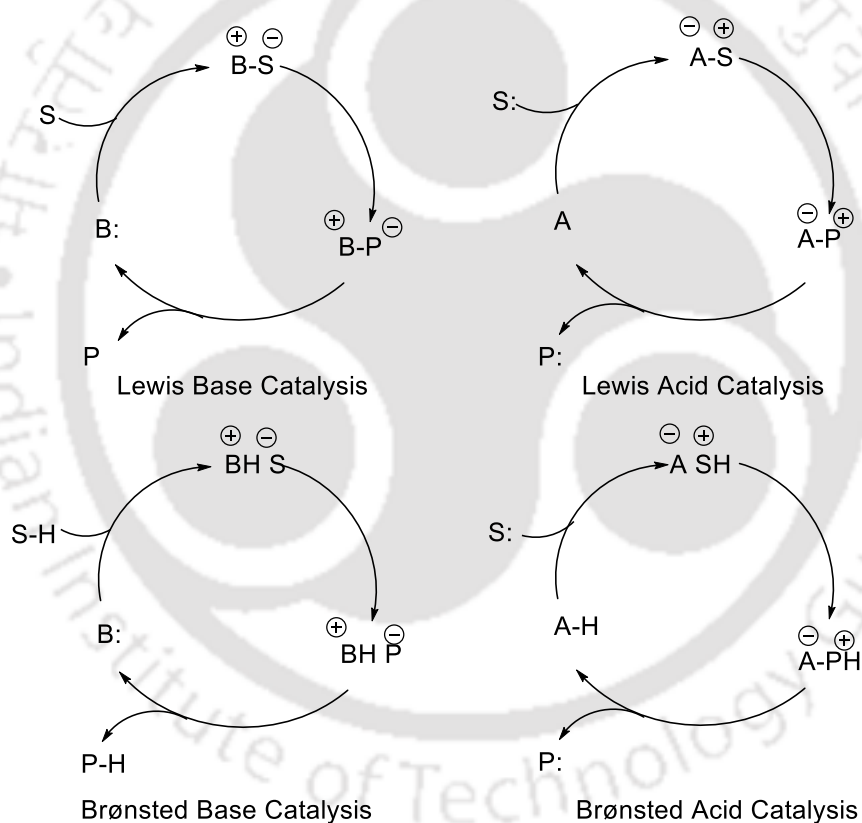


Figure 1: Structural description of (*S*)-Dopa and (*R*)-Dopa

1.2. Asymmetric organocatalysis:

In past few years enzyme and metal based catalysts have been applied for the synthesis of different enantiomerically enriched compounds.¹ Though enzyme based catalysts are highly efficient and enantioselective but these catalysts have some drawbacks such as low specificity, instability at higher temperature and pH dependent. These are applicable for limited number of reactions.² On the contrary, transition metal based catalysts are used effectively to perform a number of asymmetric transformations for examples, asymmetric hydroxylation and epoxidation. However, metal based catalyst may leave toxic of traces in the product.² Recently, purely small organic molecules have emerged as highly selective and efficient catalysts in addition to metal based catalysts and

biocatalysts in many catalytic reactions. As a result, organocatalysts got tremendous importance for the synthesis of different enantiomerically enriched compounds. The term asymmetric organocatalysis describes the advancement of reaction rate through the addition of substoichiometric amount of chiral organic compounds consisting of carbon, hydrogen, nitrogen and other non-metals.³ In the case of organocatalysis the use of organic molecules as chiral catalysts complement the conventional organometallic and biological approaches for asymmetric catalysis. In 1912, Bredig group first reported organocatalytic enantioselective reaction of aldehydes with HCN using cinchona alkaloid catalyst.⁴ In general, organocatalysis can be classified as: (i) Lewis base, (ii) Lewis acid, (iii) Brønsted acid and (iv) Brønsted base catalysis (Scheme 1.1).^{1b}



Scheme 1.1: Classification of organocatalysts

For a Lewis base catalyzed reaction, at first the catalyst undergoes nucleophilic addition to the substrate (S) to form an intermediate and the resulting intermediate reacts further to provide the product (P) leaving the catalyst for further turnover.^{1b} On the other hand Lewis acid catalyst accelerates the reaction through the coordination to the nucleophilic substrates ($S:$) resulting in the formation of intermediates. Then the resulting

intermediate will be converted to the desired product with the regeneration of catalyst.^{1b} For Brønsted base catalysis, catalytic cycle initiates through deprotonation of the substrate (S) followed by chemical transformation of the activated complex to furnish the product (P) and the catalyst becomes free for another catalytic cycle.^{1c} Brønsted acid catalyst forms an intermediate through the protonation of the substrates (S) and the corresponding ion pair reacts further to deliver the product (P).^{1d}

1.3. Hydrogen-bonding catalysis:

Catalysis through H-bonding plays a pivotal role in the field of non-covalent organocatalysis. In recent times H-bonding catalysis emerged as a powerful and efficient approach in asymmetric catalysis. H-bonding catalysts use to play major role in molecular recognition and also participate in the activation of substrates in large number of enantioselective transformation reactions. Generally, small organic molecules having H-bond donor ability are fruitful for the activation of electrophiles by lowering the LUMO of the substrates.⁵ This type of catalysis is generally classified as acid catalysis. Phosphoric acid, urea, thiourea, and squaramide catalysts are well known H-bonding catalysts. In 1960, Curran group first introduced urea catalyzed allylation of cyclic α -sulfinyl radicals with allyltributylstannane.⁶ Later, Sigman and Jacobsen reported chiral thiourea mediated enantioselective Strecker reaction of *N*-allyl aldimines.⁷ Schreiner and coworkers first showed the effects on the activity of thiourea catalyst by simply changing *N*-aryl substituent to *N*-trifluoromethyl phenyl substituent.⁸ Very recently, squaramide catalysts have been used as an effective alternate to previously known urea and thiourea catalysts. After the first report by Rawal's group, squaramide catalysis has established as a new branch of H-bonding catalysis.⁹

1.4. Bifunctional thiourea and squaramide catalysts:

Bifunctional thiourea and squaramide catalysts are the combination of Brønsted acid and base in the same molecular framework. These type of catalysts can play dual role to activate both nucleophiles and electrophiles synergistically.¹⁰ In recent years the use of these bifunctional catalysts became one of the leading approaches to achieve various enantioselective transformations.¹¹ In 2003, Takemoto group successfully explored the idea of hydrogen bonding catalysis through conjugate addition of malonates to

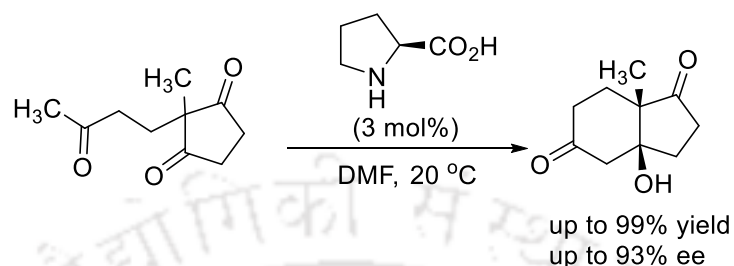
nitroolefins in the presence of cyclohexyl derived bifunctional thiourea catalyst.¹² Connon and co-workers also disclosed the concept of hydrogen bonding catalysis by performing similar type of reactions in the presence of cinchona alkaloid derived bifunctional thiourea catalyst.¹³ Deng *et al.* efficiently applied bifunctional thiourea catalyst to perform enantioselective Mannich reaction.¹⁴ Earlier Rawal group introduced a new class of bifunctional catalyst by replacing thiourea moiety by bis-amides of squaric acid.⁹ Since then squaramide catalysts became the useful replacement for thiourea catalyst. Chiral thiourea and squaramide catalysts are effectively used in a number of asymmetric reactions such as aldol reactions, conjugate additions, Mannich reactions and domino or tandem reactions.¹⁵

1.5. Organocatalytic cascade or domino reaction:

Over the last few years enantioselective cascade or domino reaction became one of the most powerful and widely used technique for the synthesis of different optically active compounds having multiple stereogenic centres with varied structural frameworks.¹⁶ According to Tietze, domino or cascade reaction can be classified as the type of reactions that involve two or more bond forming reactions under the same reaction conditions without further addition of catalysts and reagents in the next step.¹⁷ It is worth mentioning that organocatalytic domino or cascade reaction strategies are the leading methods for the construction of carbocycles as well as heterocycles having different functionalities in a single or stepwise manner.¹⁸ Organocatalytic asymmetric hetero-Michael cascade reactions such as *aza*-Michael,¹⁹ *oxa*-Michael²⁰ and *sulfa*-Michael²¹ reactions are considered to be potent methods for the synthesis of highly substituted chiral heterocyclic compounds. Due to such unique properties of organocatalytic asymmetric cascade or domino reactions, it got immense importance in pharmaceutical industries for the synthesis of drugs.²² Many research groups are involved for the development of new and efficient strategies for domino reactions which are atom economical to avoid the use of time consuming protection deprotection steps as well as the isolation of intermediates.²³

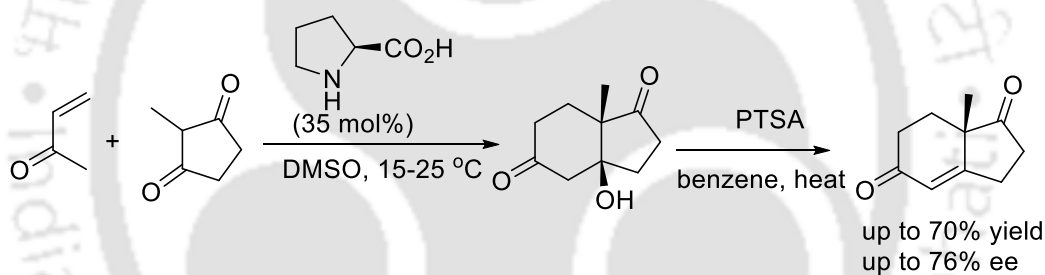
Earlier in 1970 Hajos, Parrish at Hoffmann-La Roche and Eder, Sauer and Wiechert at Schering simultaneously reported proline-catalyzed intramolecular enantioselective aldol

reaction of 2,2-disubstituted cyclic 1,3-diketones for the synthesis of bicyclic diketones. These two reports can be regarded as the pioneering works in the field of organocatalytic asymmetric domino reactions (Scheme 1.2).^{24, 25}



Scheme 1.2: Proline catalyzed intramolecular aldol reaction

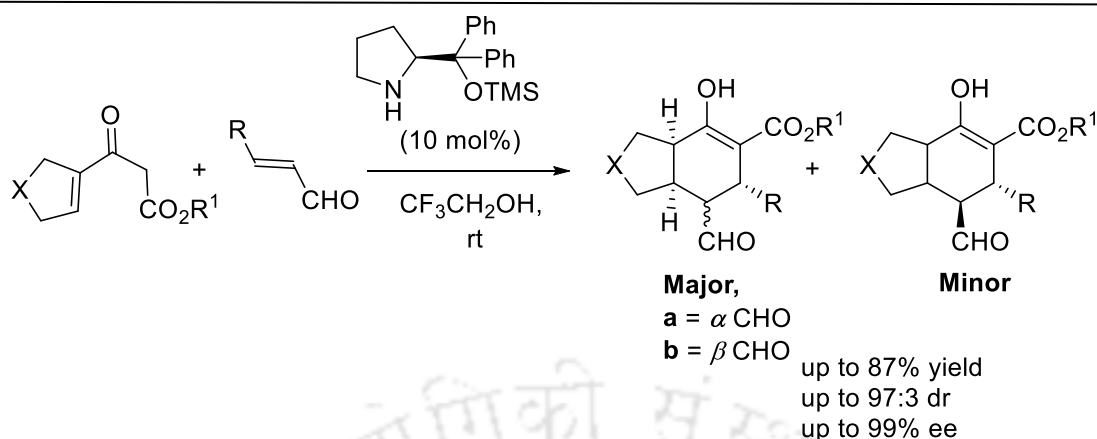
Later in 2000, Barbas group developed chiral secondary amine catalyzed enantioselective annulation for the synthesis of Weiland-Meischer ketone (Scheme 1.3).²⁶



Scheme 1.3: Secondary amine catalyzed enantioselective annulation

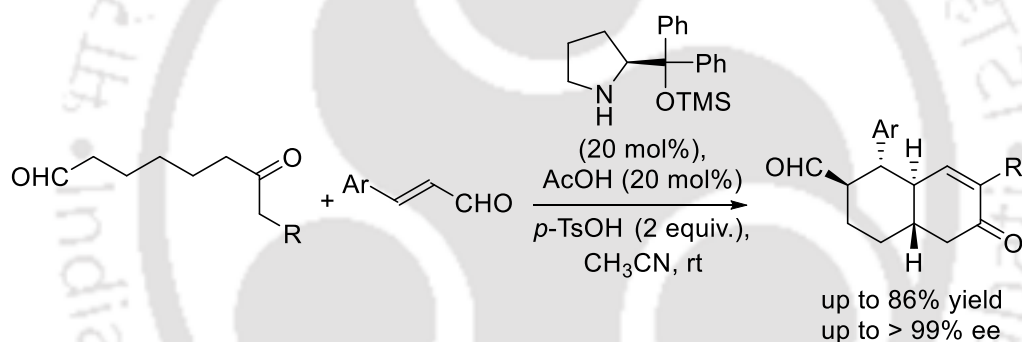
1.5.1. Domino reactions operate *via* iminium-enamine activation mode:

Berner group reported a Michael-Michael cascade reaction approach for the enantioselective synthesis of highly substituted fused carbocycles *via* iminium-enamine mode of activation between conjugated esters and α,β -unsaturated aldehydes. Chiral secondary amines were found to be effective to achieve high enantioselectivities (Scheme 1.4).²⁷



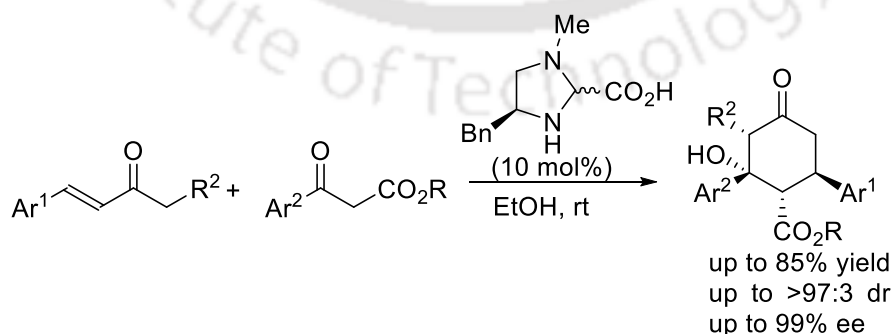
Scheme 1.4: Secondary amine catalyzed Michael-Michael cascade reaction

A chiral secondary amine catalyzed highly enantioselective synthesis of functionalized octahydro-6-oxo-1-phenylnaphthalene-2-carbaldehydes *via* domino Michael-Michael technique has been developed by Liao and coworkers (Scheme 1.5).²⁸



Scheme 1.5: Secondary amine catalyzed domino Michael-Michael reaction

Jørgensen group developed enantio- and diastereoselective synthesis of substituted cyclohexanones through an organocatalytic asymmetric cascade reaction between β -keto esters and α,β -unsaturated ketones (Scheme 1.6).²⁹

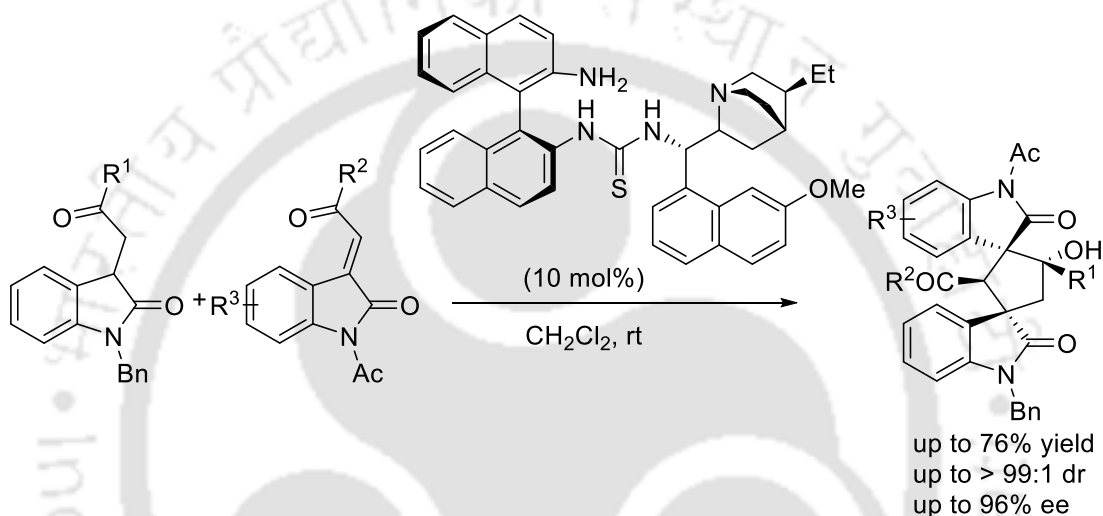


Scheme 1.6: Enantioselective synthesis of cyclohexanone

1.5.2. Domino reactions using bifunctional thiourea and squaramide catalysts:

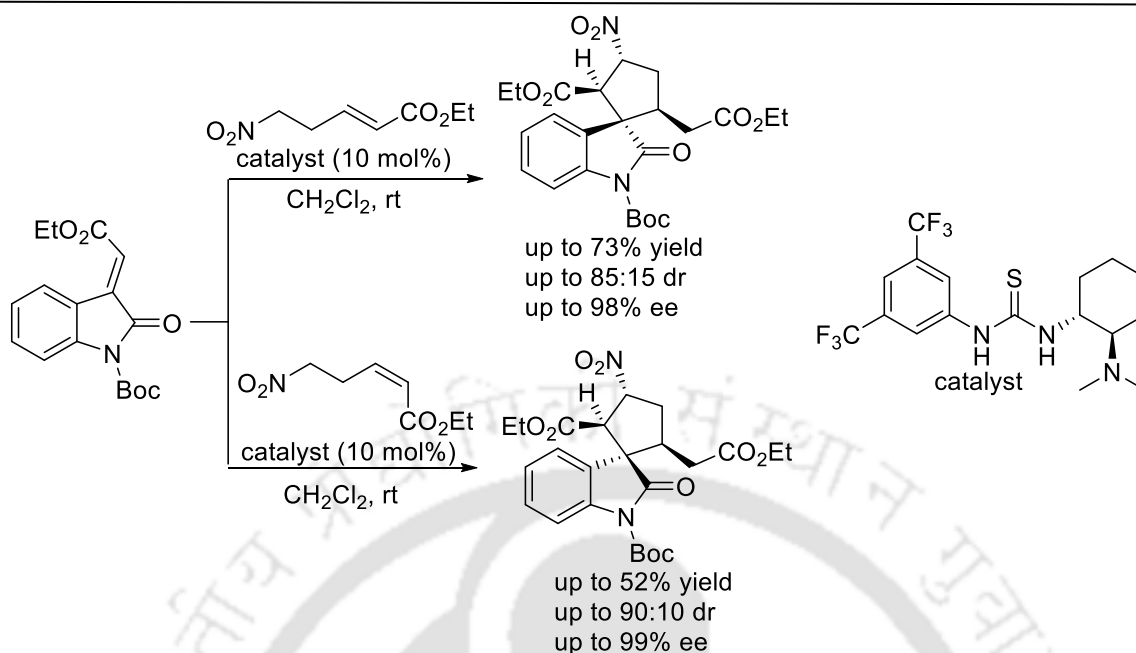
In the past few years, bifunctional thiourea and squaramide catalysts were enormously applied to perform different enantio- and diastereoselective domino or cascade reactions for efficient syntheses of various highly functionalized carbocycles and heterocyclic compounds.

In 2011 Barbas *et al.* demonstrated thiourea catalyzed domino Michael-aldol reaction for the synthesis of bispirooxindoles with good stereoselectivities (Scheme 1.7).³⁰



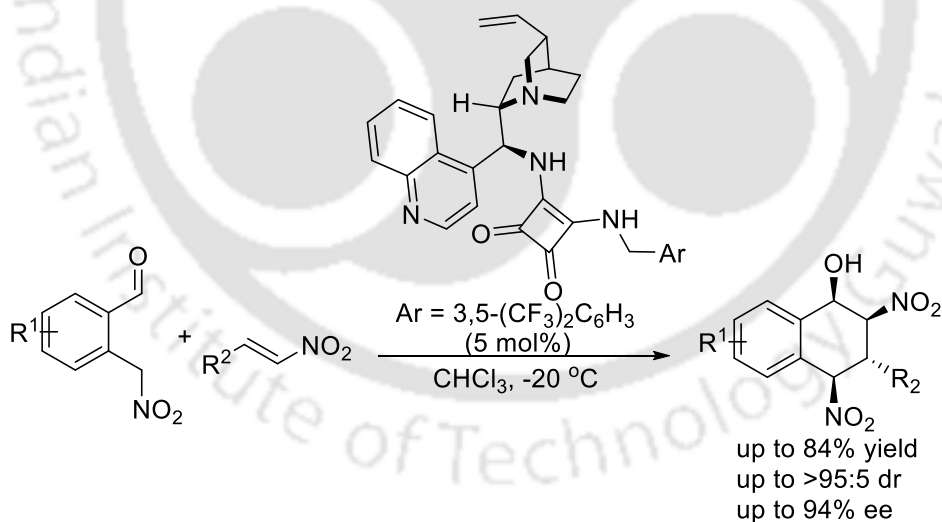
Scheme 1.7: Thiourea mediated domino Michael-aldol reaction

A highly enantioselective cascade reaction for the synthesis of five membered spirocarbocyclic oxindoles has been reported by Quintavalla group. Takemoto catalyst was found to be the best catalyst to achieve high enantiomeric excess (Scheme 1.8).³¹



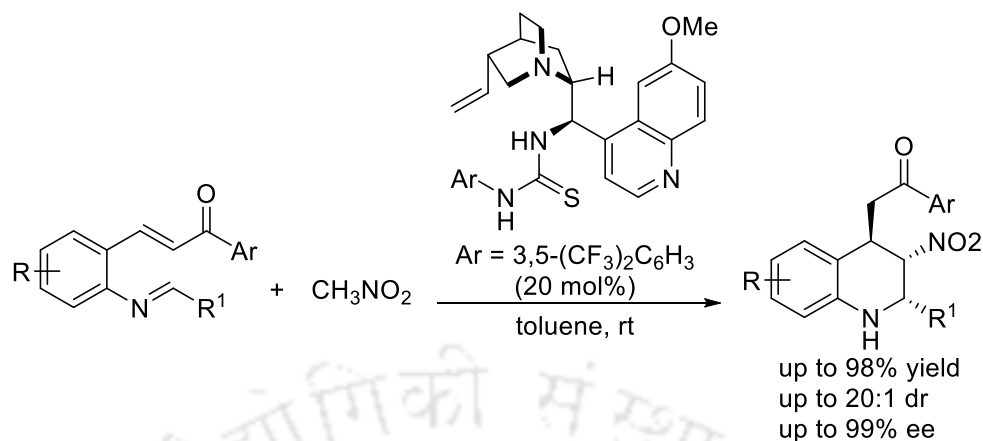
Scheme 1.8: Enantioselective synthesis spirocarbocyclic oxindoles

Enders group introduced squaramide catalyzed asymmetric synthesis of tetrahydronaphthalenes *via* domino Michael/Henry reaction with good diastereo and enantioselectivities (scheme 1.9).³²



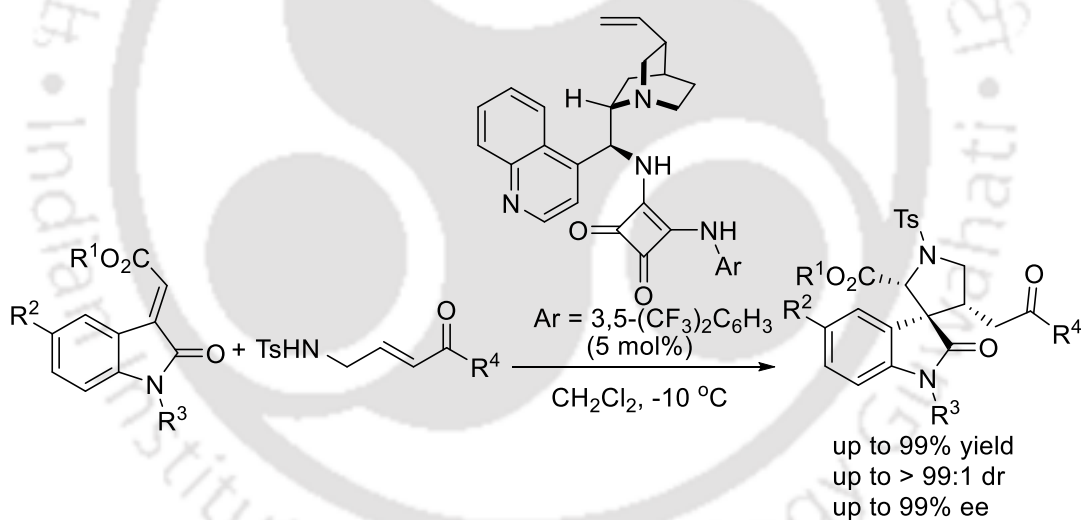
Scheme 1.9: Enantioselective synthesis tetrahydronaphthalenes

Xu group reported a convenient route for the synthesis of highly substituted tetrahydroquinolones *via* quinidine derived thiourea catalyzed domino Michael/*aza*-Henry reaction strategy (Scheme 1.10).³³



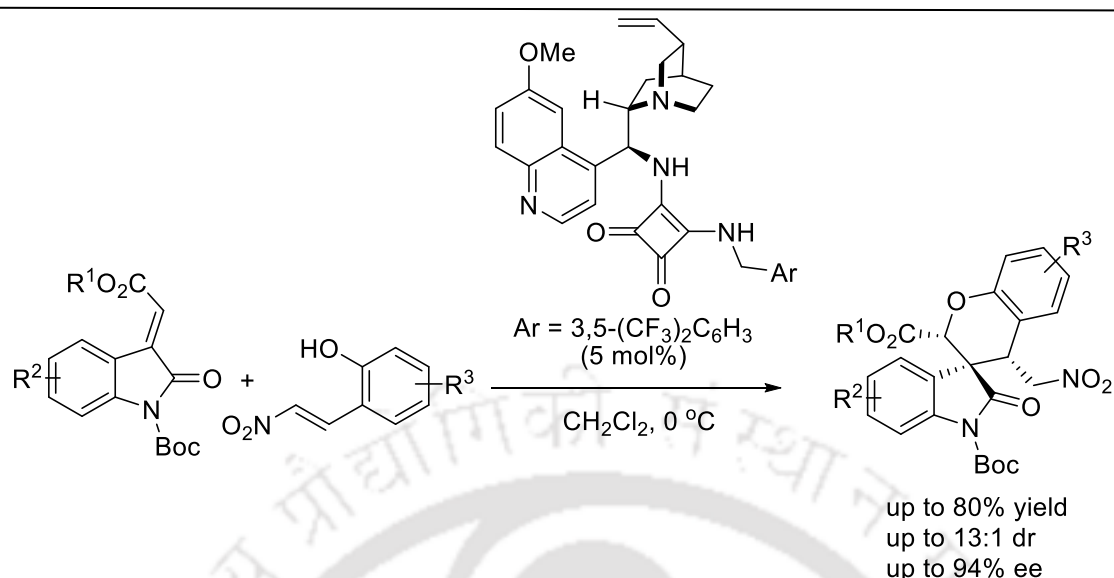
Scheme 1.10: Synthesis of tetrahydroquinolones

An efficient approach for the enantioselective synthesis of spiro [pyrrolidine-3,3'-oxindole] has been explored by Du and coworkers. Reaction proceeds through squaramide catalyzed *aza*-Michael/Michael cascade reaction to provide the expected products in good stereoselectivities (Scheme 1.11).³⁴



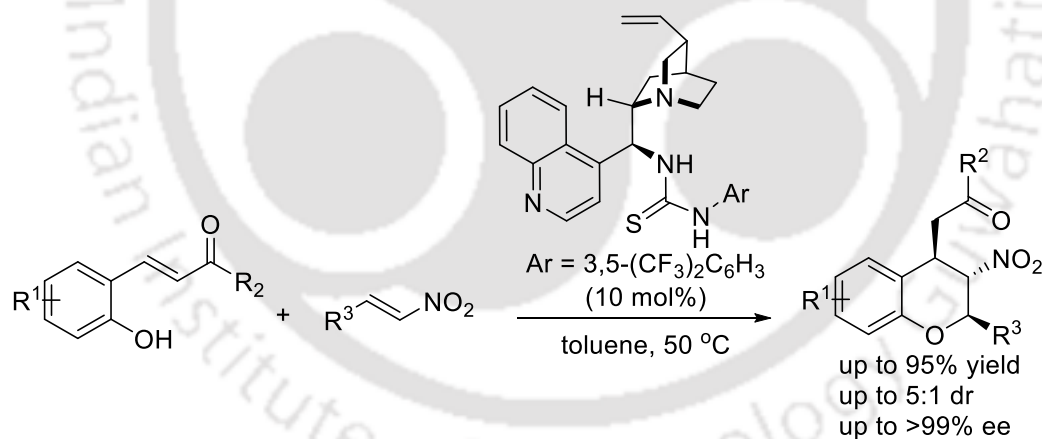
Scheme 1.11: Squaramide catalyzed *aza*-Michael/Michael cascade reaction

Mao *et al.* successfully applied domino oxa/aza-Michael Michael reaction technique for the construction of substituted spiro [chroman-3,3'-oxindole] derivatives. Quinine derived bifunctional squaramide catalyst was used to obtain the products with good diastereo- and enantioselectivities (Scheme 1.12).³⁵



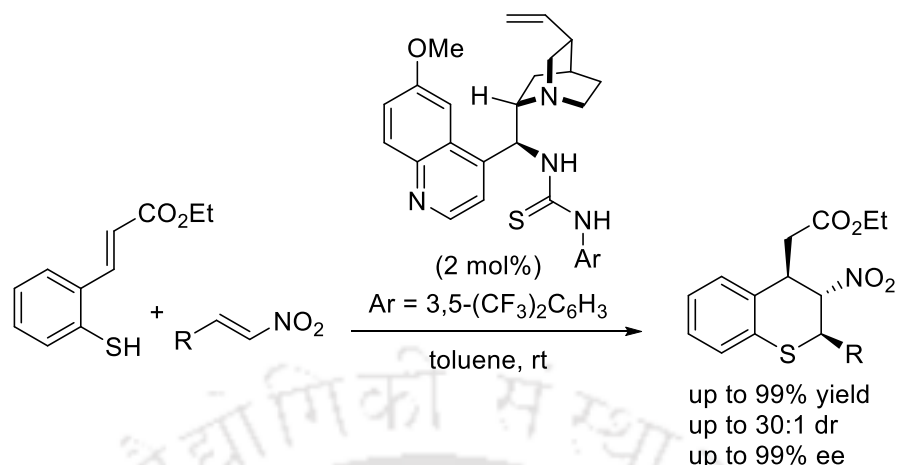
Scheme 1.12: Squaramide catalyzed domino *oxa/aza*-Michael Michael reaction

Recently, a highly enantioselective *oxa*-Michael-Michael cascade reaction protocol for the construction of substituted chromans has been explored by Singh and coworkers. Substituted chromans were obtained with high enantiomeric excess in the presence of a cinchona alkaloid derived bifunctional thiourea catalyst (Scheme 1.13).³⁶



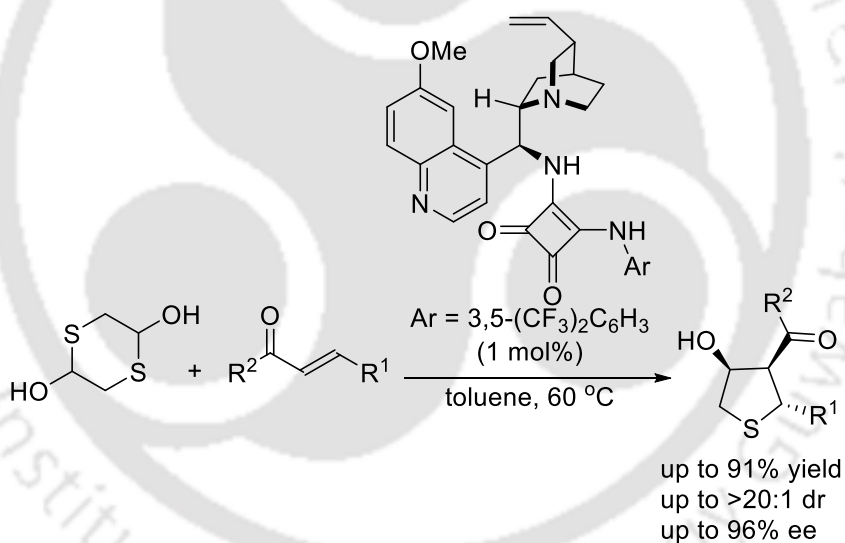
Scheme 1.13: Enantioselective synthesis of chromans

Wang group reported chiral bifunctional thiourea mediated *sulfa* Michael-Michael cascade reaction for the synthesis of highly functionalized thiochromans with excellent enantio- and diastereoselectivities (Scheme 1.14).³⁷



Scheme 1.14: Thiourea mediated synthesis of thiochromans

A chiral bifunctional squaramide catalyst induced enantioselective *sulfa*-Michael cascade reaction between 1,4-dithiane-2,5-diol and chalcones for the construction of tetrahydrothiophenes has been introduced by Xu and coworkers (Scheme 1.15).³⁸



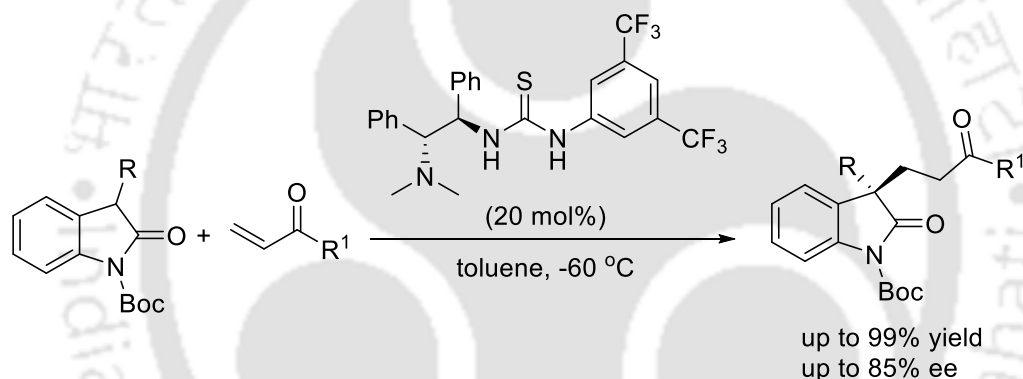
Scheme 1.15: Squaramide catalyzed *sulfa*-Michael cascade reaction

1.6. Organocatalytic asymmetric Michael reaction leading to construction of stereogenic quaternary centres:

Michael addition is widely recognized as one of the most general and versatile methods for the construction of C-C bonds in organic synthesis. It is mainly the conjugate addition of a carbanion or a nucleophile to α,β -unsaturated compounds. Organocatalytic asymmetric Michael reactions play a pivotal role for the synthesis of bioactive and naturally occurring compounds.³⁹ The first pioneering report on organocatalytic

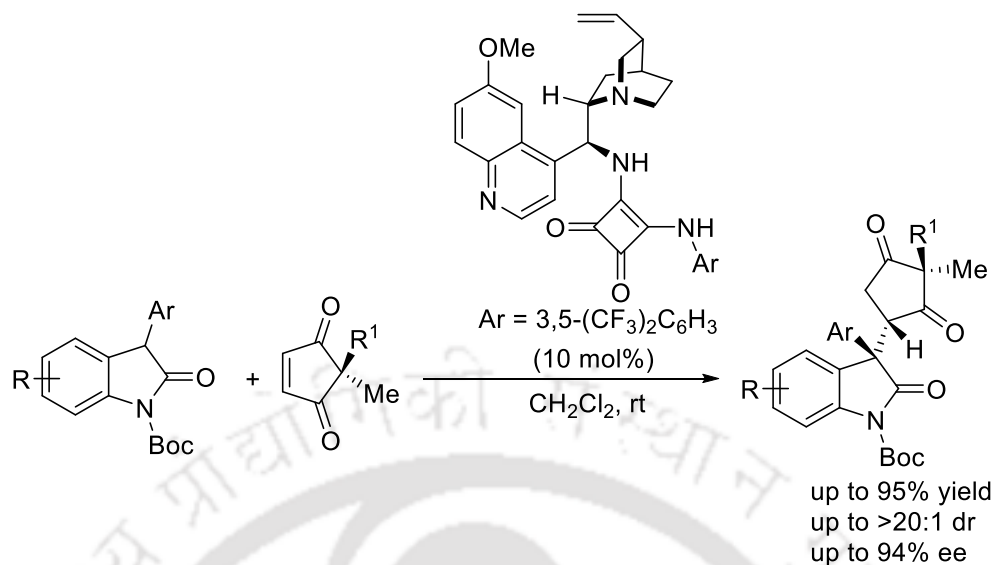
asymmetric Michael reaction was introduced by Wynberg group.^{39a} Later Connon and Takemoto group individually reported thiourea catalyzed enantioselective conjugate addition of malonates to nitroolefins.^{12, 13} Organocatalytic asymmetric Michael reactions of trisubstituted carbonyl compounds to vinyl ketones and nitroolefins are powerful approaches for the construction of valuable structural motifs having a quaternary centre.⁴⁰ A diverse range of carbonyl compounds such as oxindoles, 1,3-dicarbonyls, malonates have been engaged to the Michael addition reaction with vinyl ketones and nitroolefins.

Cheng and coworkers reported bifunctional thiourea catalyzed Michael addition of *N*-Boc oxindoles with vinyl ketones for the construction of quaternary stereogenic centre (Scheme 15).⁴¹



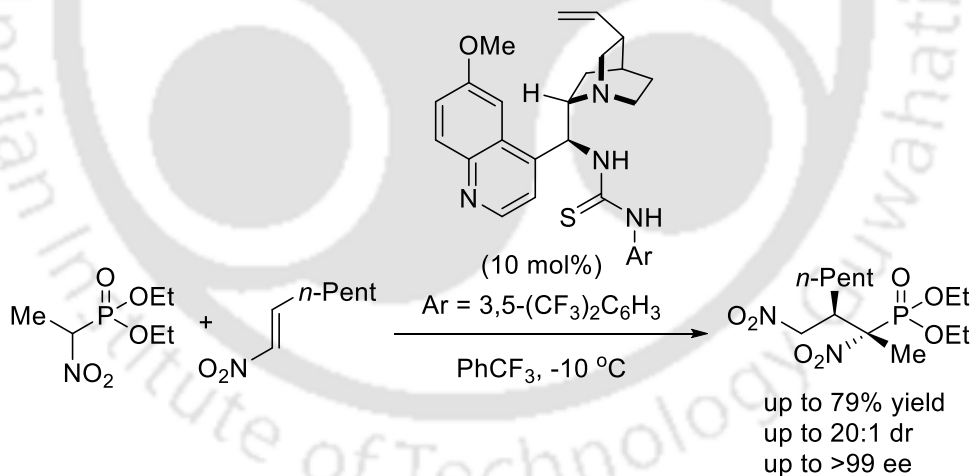
Scheme 1.16: Thiourea catalyzed Michael addition of *N*-Boc oxindoles

Very recently Enders group has explored bifunctional squaramide catalyzed Michael addition for the desymmetrization of prochiral cyclopent-4-ene-1,3-diones with good stereoselectivities. Substituted *N*-Boc oxindoles and prochiral cyclopent-4-ene-1,3-diones were employed as the substrates and corresponding products were obtained with two stereogenic quaternary centres (Scheme 1.17).⁴²



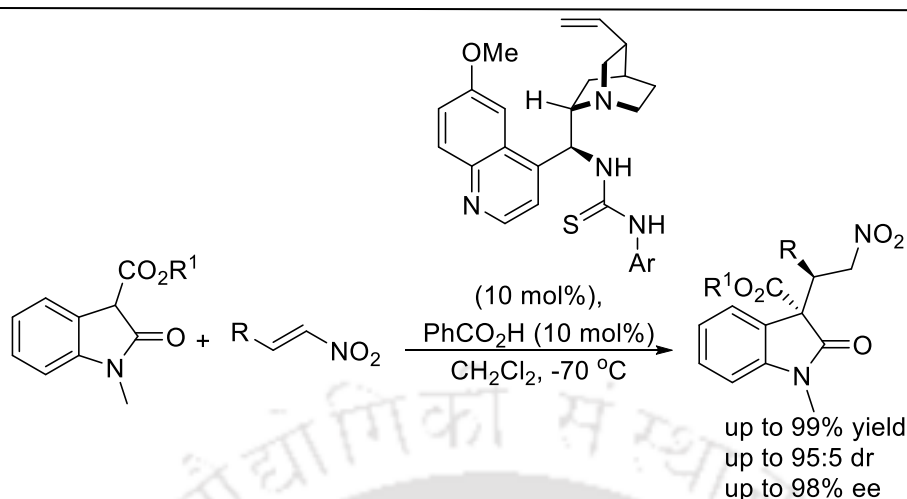
Scheme 1.17: Squaramide catalyzed desymmetrization reaction

A highly enantio and diastereoselective Michael addition of nitrophosphonate to nitroolefins has been demonstrated by Mukherjee and coworkers. Quinine derived bifunctional thiourea catalyst furnished the product bearing adjacent quaternary and tertiary centres (Scheme 1.18).⁴³



Scheme 1.18: Thiourea catalyzed Michael reaction of nitrophosphonate

Chen *et al.* reported an enantioselective Michael addition of 3-substituted 2-oxindoles to nitroolefins. A combination of bifunctional thiourea and benzoic acid catalyst was used to achieve good stereoselectivities (Scheme 1.19).⁴⁴

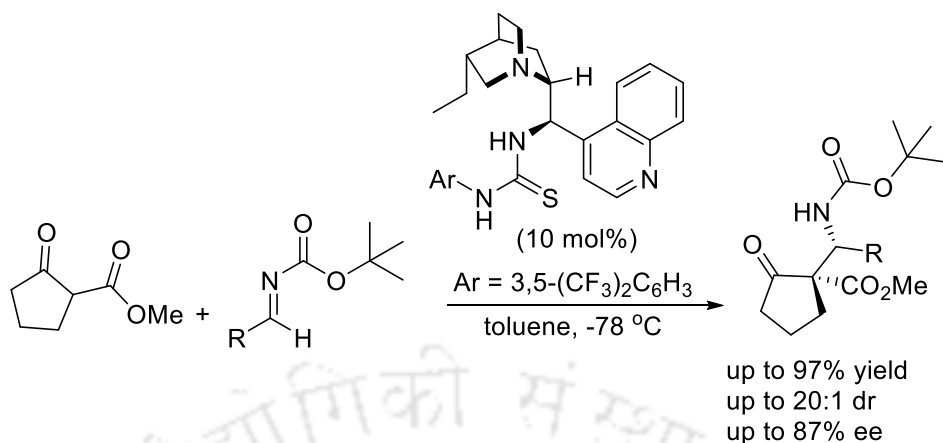


Scheme 1.19: Enantioselective Michael addition of oxindoles

1.7. Organocatalytic asymmetric Mannich reaction leading to construction of stereogenic quaternary centres:

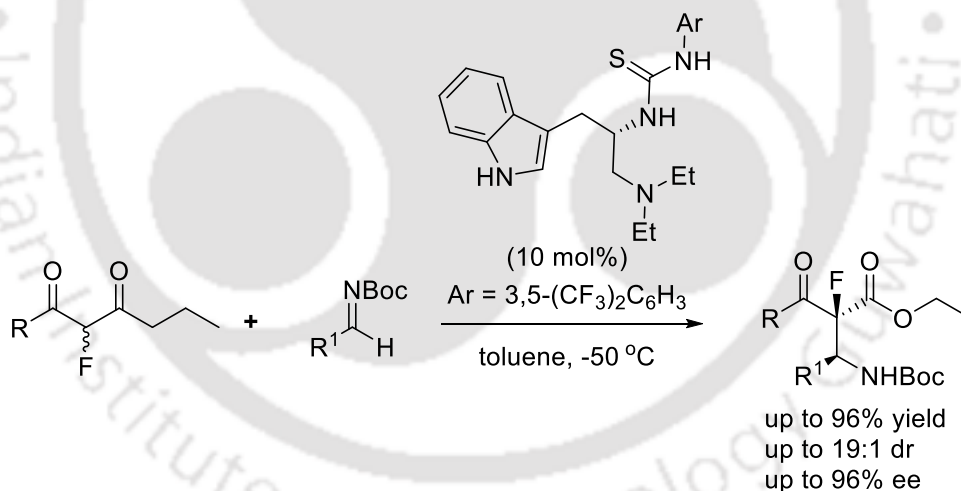
Asymmetric Mannich reaction is one of the well-known C-C bond forming methods that can be performed in enantio- and diastereoselective fashion. Nowadays, organocatalytic asymmetric Mannich reaction⁴⁵ is a potent method for the synthesis of chiral β -aminocarbonyl compounds. Since the first report on organocatalytic asymmetric Mannich reaction by Barbas group,^{45a} tremendous efforts have been made by many research groups for the development of enantioselective Mannich reactions. Deng and coworkers delineated bifunctional thiourea mediated asymmetric Mannich reaction of malonates and *N*-Boc imines.¹⁴ A vast range of activated carbonyl compounds such as β -ketoesters, 1,3-dicarbonyls, oxindoles and malonate esters have been engaged in the reaction providing valuable building blocks.⁴⁶

One of the earliest report on thiourea mediated enantioselective Mannich reaction was introduced by Dixon and coworkers. Cinchona alkaloid derived bifunctional thiourea catalyst was successfully employed for the direct Mannich reaction between cyclic β -keto esters and *N*-Boc imines (Scheme 1.20).⁴⁷



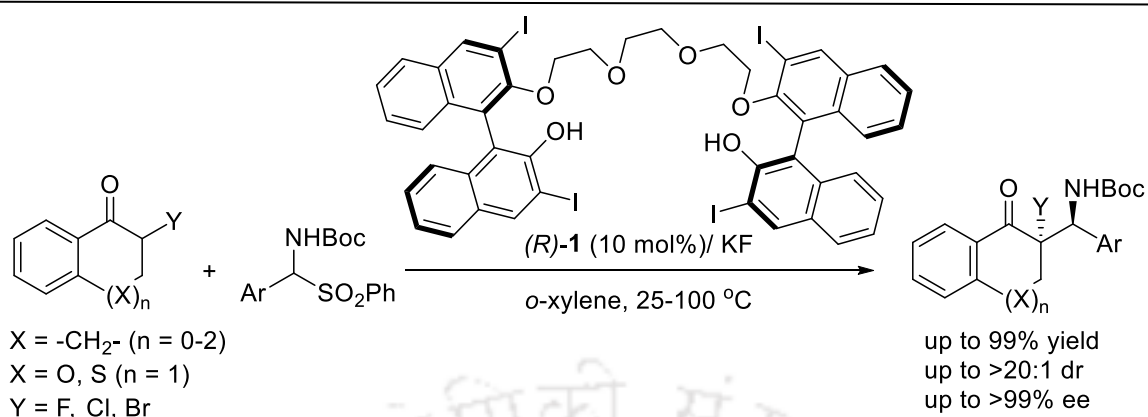
Scheme 1.20: Thiourea mediated enantioselective Mannich reaction

Yixin Lu group unfolded thiourea catalyzed asymmetric Mannich reaction of α -fluoro- β -keto ester for the construction of amino carbonyl compounds having fluorinated quaternary carbon stereocentre. A novel tryptophan derived bifunctional thiourea catalyst was engaged in the reaction to achieve good enantio- and diastereoselectivities (Scheme 1.21).⁴⁸



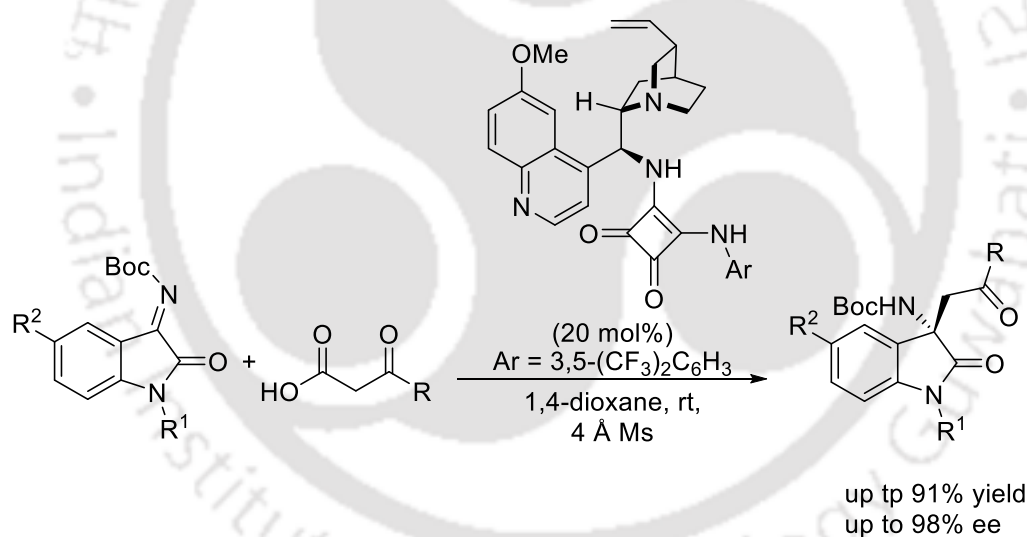
Scheme 1.21: Enantioselective Mannich reaction of α -fluoro- β -keto ester

A direct enantio and diastereoselective Mannich reaction for the synthesis of chiral β -fluoroamines with adjacent quaternary carbon stereocentre *via* cooperative cation-anion binding catalysis has been explored by Song group (Scheme 1.22).⁴⁹



Scheme 1.22: Enantioselective Mannich reaction for the construction of quaternary centre

Very recently Kaur *et al.* reported a chiral squaramide catalyzed decarboxylative Mannich reaction between β -keto acid and isatin derived *N*-Boc imines for the generation of stereogenic quaternary centre (Scheme 21).⁵⁰



Scheme 1.23: Enantioselective decarboxylative Mannich reaction

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Reaction. Bifunctional squaramide catalysts were found to be efficient for this reaction. A few transformations of the products have been demonstrated.

$R^1 = \text{Ts, Bs,}$
 $R^2 = \text{Ar}$

$R = \text{Ar, Alkyl}$

catalyst (10 mol%)
toluene, rt
48 h
27 examples

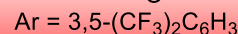
up to 82 % yield
up to >20:1 dr
up to 92% ee

Ar = 3,5-(CF₃)₂C₆H₃

$\text{R}^1 = \text{Ts, Bs,}$
 $\text{R}^2 = \text{Ar}$
 $\text{R} = \text{Ar, Alkyl}$

catalyst (10 mol%)
 toluene, rt
 48 h
 27 examples

up to 82 % yield
 up to >20:1 dr
 up to 92% ee





2.1. Introduction:

Chiral imidazolidine motifs are widely used in organic and bioorganic chemistry. Molecules having chiral imidazolidine scaffolds are prevalent intermediates and frequently found in many natural products and in a range of biologically active compounds.¹ Besides, it has well-known application as synthetic reagents such as chiral catalysts and ligands.² Imidazolidine moieties could introduce unique benefits to drug discovery and thus have valuable applications in medicinal chemistry. Optically active imidazolidines are important intermediates with broad applications in organic synthesis. Fumiquinazoline A and B **I** are natural alkaloids, compounds **II** and **III** possess antipyretic and anticonvulsant and aldose reductase inhibitory activities respectively³ (Figure 1). Apart from these, chiral imidazolidines are well known organocatalysts and ligands to achieve various enantioselective transformations² (Figure 1).

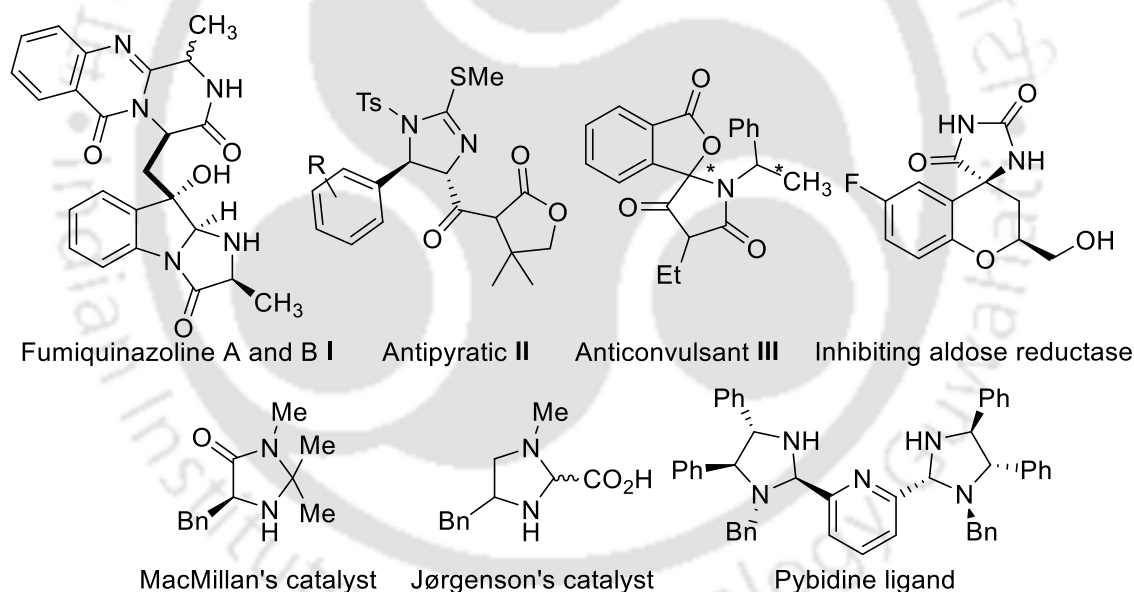


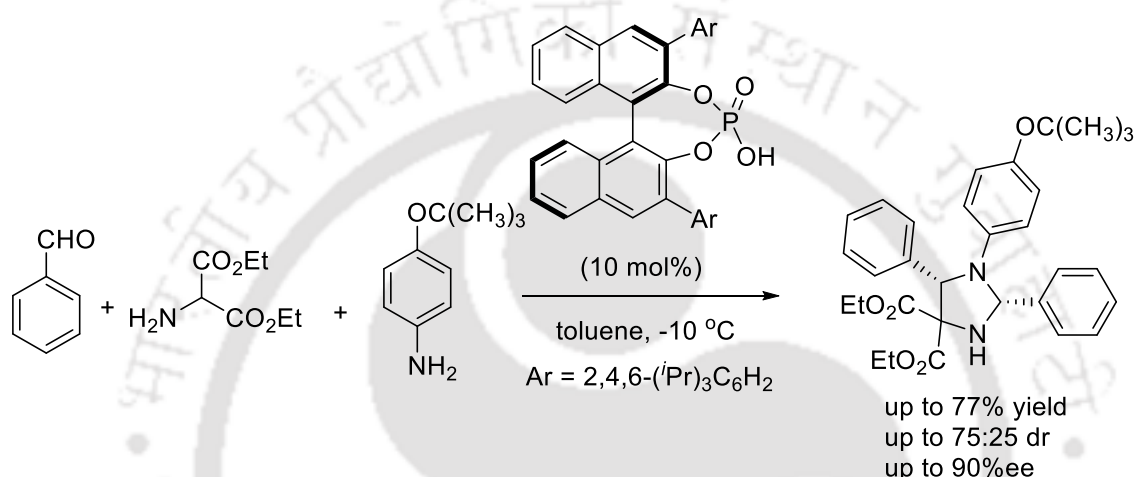
Figure 1: Biologically active compounds, organocatalysts and ligands containing chiral imidazolidines scaffolds

Due to these impressive activities and significant applications, a number of scientists are engaged in the synthesis of imidazolidines. Thus it is highly desirable to prepare chiral imidazolidines in efficient ways. Representative strategies for the synthesis of imidazolidines are 1,3-dipolar cycloaddition⁴ of azomethine ylides and imines. Initially, the enantioselective synthesis relied on the use of optically active starting materials such

as chiral imines or chiral azomethine ylides.⁵ Though few catalytic asymmetric approaches have been documented,⁶⁻¹⁰ organocatalytic versions are still less.

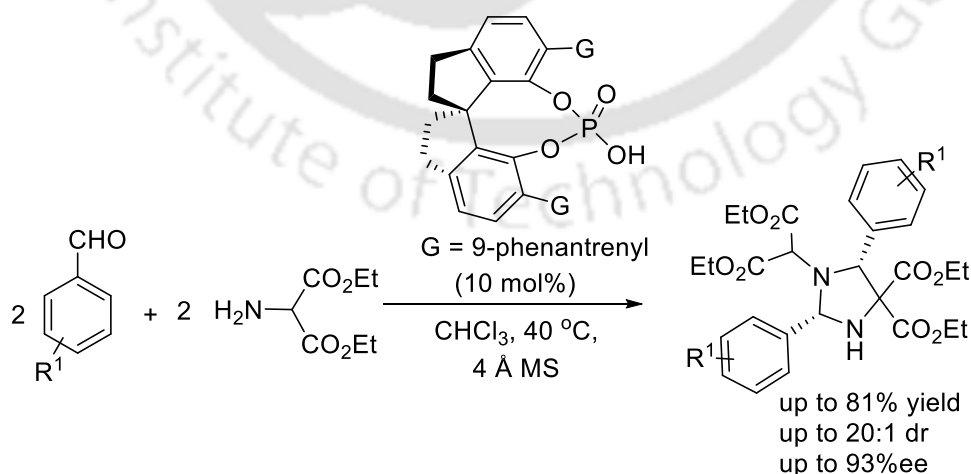
2.2. Reported strategies for the synthesis of chiral imidazolidines:

Gong *et al.* first developed chiral phosphoric acid catalyzed three component reaction for the synthesis of tetra-substituted imidazolidines. This is a simple methodology for the preparation of substituted chiral imidazolidine moieties *via* Brønsted acid catalyst activation (Scheme 2.1).⁶



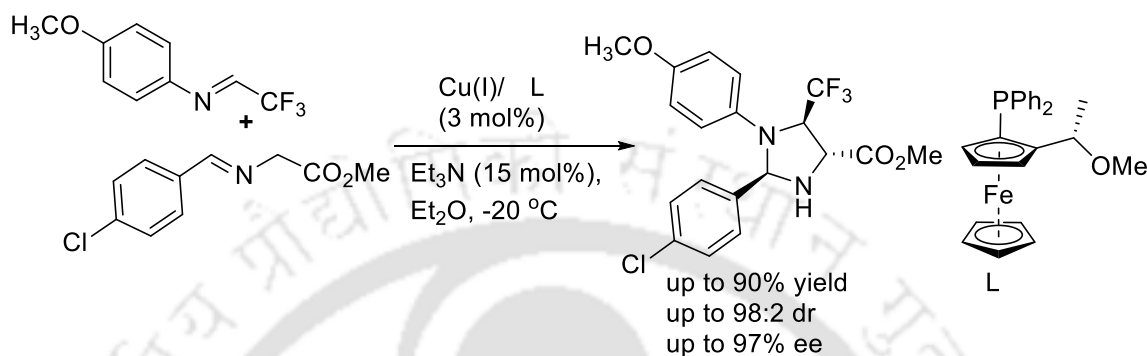
Scheme 2.1: Phosphoric acid catalyzed enantioselective three component reaction

Tu and coworkers reported catalytic asymmetric homo-1,3-dipolar cycloaddition of azomethine ylides to obtain tetrasubstituted imidazolidines. SPINOL-derived chiral phosphoric acid catalyst provided the best result with good enantio- and excellent diastereoselectivities (Scheme 2.2).⁷



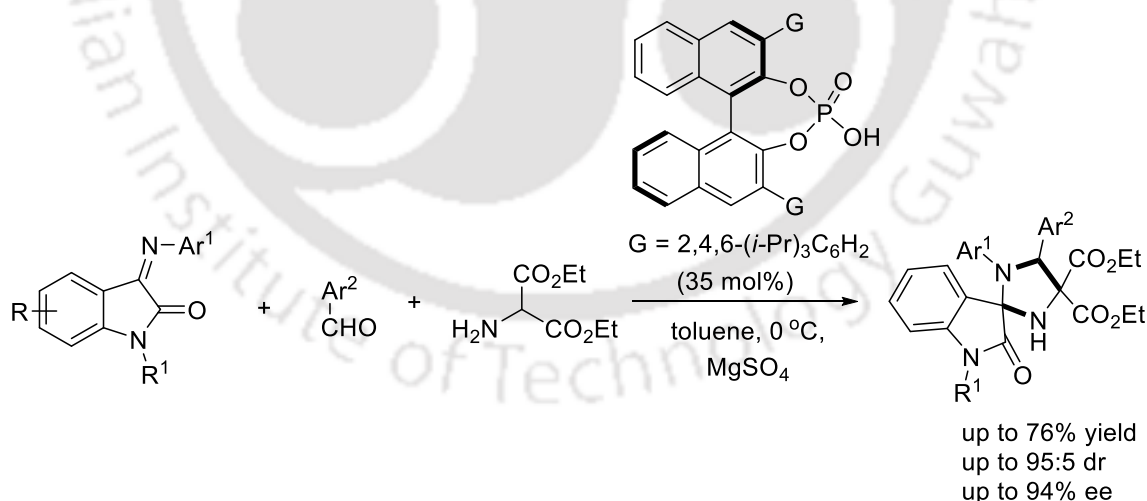
Scheme 2.2: Phosphoric acid catalyzed cycloaddition for the synthesis of substituted imidazolidines

Cu(I)-catalyzed enantioselective exo-selective 1,3-dipolar cycloaddition protocol between azomethine ylides and imines has been explored by Wang group. Cu(I)/(S,R_p)-PPFOMe catalyst afforded *trans*-2,4-imidazolidines with good selectivities (Scheme 2.3).⁸



Scheme 2.3: Cu (I)-catalyzed 1,3-dipolar cycloaddition for the preparation of chiral imidazolidines

Very recently, Shi group has developed a catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides with isatin derived imines for the construction of spiro[imidazolidine-2,3-oxindole]-motifs in a chemoselective fashion (Scheme 2.4).⁹



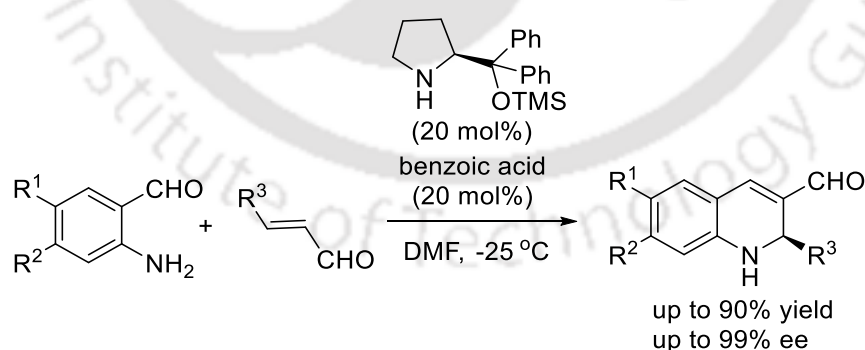
Scheme 2.4: Catalytic enantioselective cycloaddition for the synthesis of spiro[imidazolidine-2,3-oxindole]motifs

2.3. Previous reports on domino *aza*-Michael reaction for the construction of heterocyclic compounds:

Organocatalytic domino reactions are efficient methods for the synthesis of different carbocycles, heterocycles, fused compounds and spiro compounds in a concerted way. Organocatalytic enantioselective domino reaction is an elegant protocol for the construction of different optically active complex molecules in a single operation. These chiral molecules have potential biological activities and are prevalent moieties in many natural products.

Organocatalytic asymmetric domino *aza*-Michael cyclization reaction¹¹ is one of the well-known methodologies for the synthesis of different chiral *N*-containing heterocyclic compounds, such as, isoxazolines, 1,2-oxazines, pyrrolidines, amino indanols in a simple way. Due to such importance of domino *aza*-Michael reaction, recently many groups are engaged for the development of different organocatalytic domino *aza*-Michael reactions.

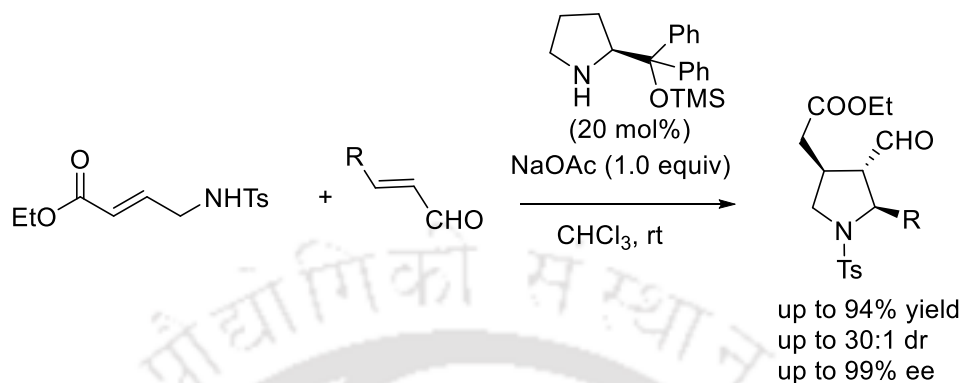
For example, Cordova *et al.* reported an organocatalytic asymmetric synthesis of 1,2-dihydroquinolines using 2-amino benzaldehydes and cinnamaldehydes as the reaction partners. Diphenyl prolinol TMS ether catalyst was found to be the best catalyst for this reaction and delivered the corresponding products with good yields and high enantioselectivities. (Scheme 2.5)¹²



Scheme 2.5: Organocatalytic asymmetric synthesis of 1,2-dihydroquinolines

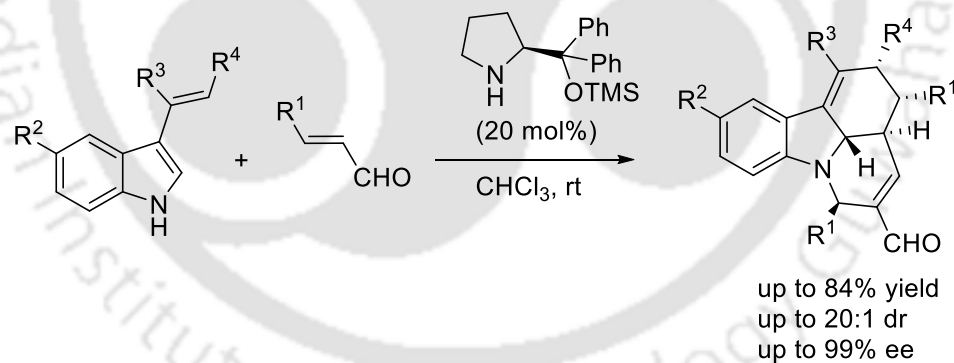
In 2008, Wang and coworkers reported diphenylprolinol TMS ether catalyzed highly enantioselective synthesis of substituted pyrrolidines *via* domino *aza*-Michael addition

strategy. The reaction outcome was very good and the products were isolated with high enantio and diastereoselectivities (Scheme 2.6).¹³



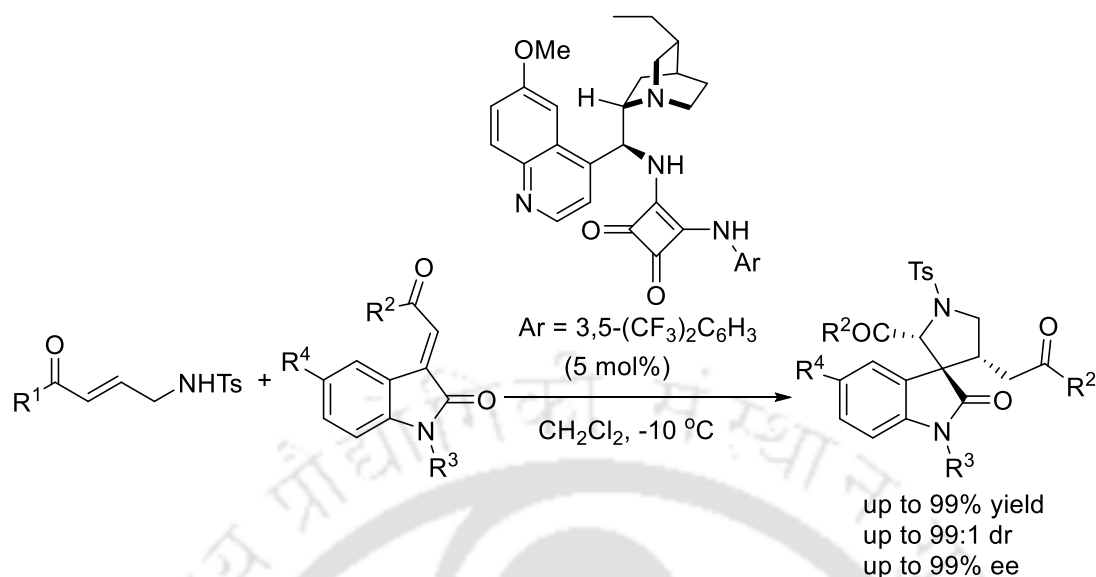
Scheme 2.6: Secondary amine catalyzed domino *aza*-Michael addition for the synthesis of substituted pyrrolidines

Enders group demonstrated an enantioselective cascade reaction including Diels-Alder/*aza*-Michael/Aldol condensation for the synthesis of tetracyclic pyridocarbazole derivatives. Excellent enantio- and diastereoselectivities were obtained using diphenyl prolinol TMS ether as the catalyst (Scheme 2.7).¹⁴



Scheme 2.7: Enantioselective cascade reaction for the synthesis of tetracyclic pyridocarbazole derivatives

Very recently Du *et al.* reported *epi*-hydroquinine squaramide catalyzed highly enantio and diastereoselective synthesis of spiro[pyrrolidine-3,3'-oxindole]s. The reaction proceeds through domino *aza*-Michael/Michael addition reaction (Scheme 2.8).¹⁵

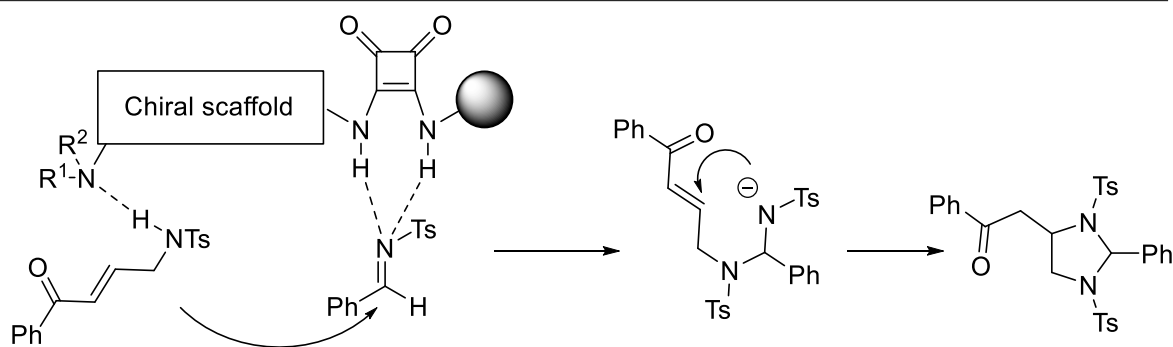


Scheme 2.8: Squaramide catalyzed domino addition for the synthesis of spiro[pyrrolidine-3,3'-oxindole]s

2.4. Concept:

Chiral imidazolidines have wide spread application in bioorganic chemistry and also used as chiral catalyst and ligands. Thus it is highly advisable to prepare different chiral imidazolidine derivatives in a simple way. There are only few reports for the synthesis of chiral imidazolidines, however catalytic asymmetric synthesis of 2,4-disubstituted imidazolidines have never been reported. Realizing the significance of chiral imidazolidines, here in we wish to report bifunctional thiourea and squaramide catalyzed efficient protocol for the synthesis of 2,4-disubstituted imidazolidines. We used *N*-tosyl amino methyl enone and tosyl imines as the substrates. Imines bond could be activated by thiourea or squaramide moiety. Tertiary amine functionality of catalyst will deprotonate the amino methyl enones and the corresponding addition followed by *aza*-Michael reaction will afford the imidazolidine products (Scheme 2.9).





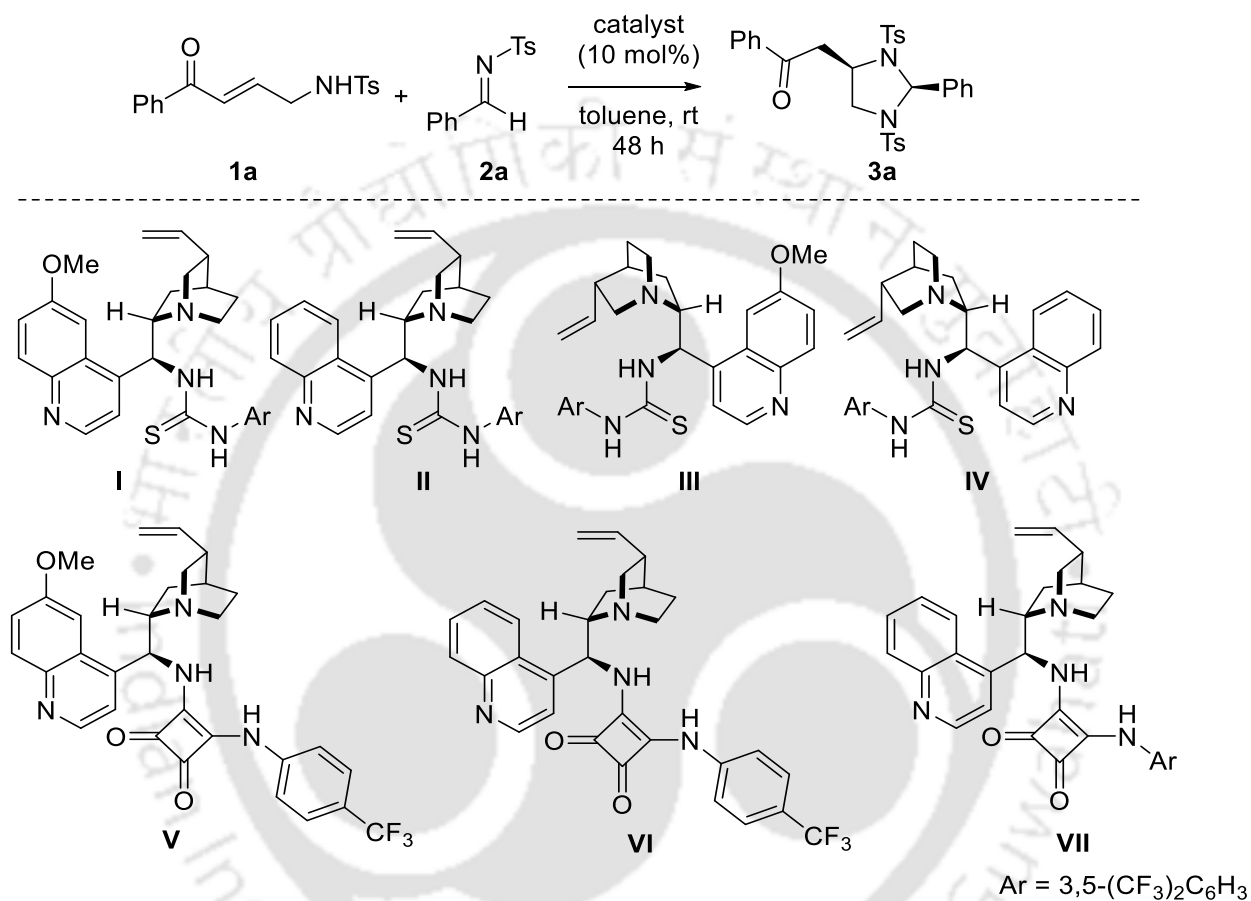
Scheme 2.9: Proposed route for the synthesis of chiral imidazolidines

2.5. Result and discussion:

Initially, the optimization of the reaction was started by performing a reaction between *N*-tosyl aminomethyl enone **1a**¹⁶ and (*E*)-*N*-benzylidene-4-methyl benzenesulfonamide **2a** in presence of quinine derived bifunctional thiourea catalyst **I** in toluene solvent at room temperature (Table 1). Pleasingly, the domino addition to the imine followed by aza-Michael reaction proceeded smoothly to deliver the expected imidazolidine product. After 48 hours the desired *cis*-2,4-disubstituted imidazolidine product **3a** was isolated in 70% yield with 10:1 diastereomeric ratio and 43% ee (entry 1). To improve the enantioselectivity of desired product other bifunctional thiourea catalysts were employed in the reaction. Cinchonidine derived thiourea catalyst **II** provided the product **3a** with slight improvement in enantioselectivity and with similar diastereomeric ratio (entry 2). Inferior results were obtained in case of quinidine and cinchonine derived thiourea catalysts **III** and **IV** in both cases enantioselectivities decreased though diastereoselectivities remained same (entries 3-4). To enhance the enantio- and diastereoselectivity for the product, different bifunctional squaramide catalysts were engaged in the reaction (entries 5-7). Delightfully, in the case of quinine derived squaramide catalyst **V**, both the diastereomeric ratio and enantiomeric excess got improved. The product **3a** was isolated in 75% yield with 16:1 diastereomeric ratio and 70% ee (entry **V**). Enantioselectivity got enhanced to 77% in the presence of cinchonidine derived squaramide catalyst **VI** (entry 6). Finally the enantioselectivity

increased to 90% with cinchonidine derived catalyst **VII** having bis-trifluoromethylphenyl moiety (entry 7).

Table 1. Catalyst screening



entry ^a	catalyst	yield (%) ^b	dr ^c	ee (%) ^d
1	I	70	10:1	43
2	II	72	10:1	51
3	III	70	10:1	28
4	IV	68	10:1	40
5	V	75	16:1	70
6	VI	79	16:1	77

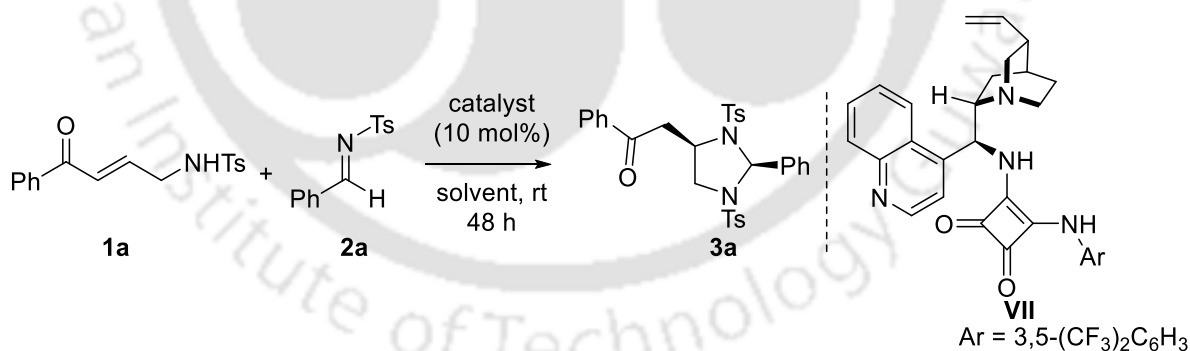
7	VII	82	16:1	90
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^aReaction conditions: 0.05mmol of **1a** and 0.075 mmol **2a** in 0.2 mL solvent using 10 mol% catalyst at rt for 48 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC using stationary phase chiral column.

2.5.1. Solvent screening:

In order to improve the enantio- and diastereoselectivity of the product further, the reaction was performed with catalyst **VII** in different solvents. Enantiomeric excess decreased to 84% in MTBE solvent but diastereomeric ratio remain unchanged (Table 2, entry 2). Then the effect of other ethereal solvents was investigated (entries 3-5). Enantioselectivity did not improve in diisopropyl ether solvent (entry 3). In diethyl ether solvent the product was obtained in 16:1 dr with 85% ee (entry 4). Enantiomeric excess further got enhanced to 89% in diphenyl ether solvent (entry 5). Slightly lesser enantioselectivity was obtained in dichloromethane solvent (entry 6). Trifluorotoluene solvent delivered the product with decrease in enantiomeric excess. Thus toluene was the best solvent (82% yield, 16:1 diastereomeric ratio and 90% ee).

Table 2. Solvent screening



entry ^a	solvent	yield (%) ^b	dr ^c	ee (%) ^d
1	toluene	82	16:1	90
2	MTBE	79	16:1	84
3	diisopropyl ether	76	16:1	84
4	diethyl ether	75	16:1	85

5	diphenyl ether	80	16:1	89
6	CH ₂ Cl ₂	78	16:1	88
7	PhCF ₃	79	16:1	86

^aReaction conditions: 0.05mmol of **1a** and 0.075 mmol **2a** in 0.2 mL solvent using 10 mol% catalyst at rt for 48 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC using stationary phase chiral column.

2.5.2. Substrate scope:

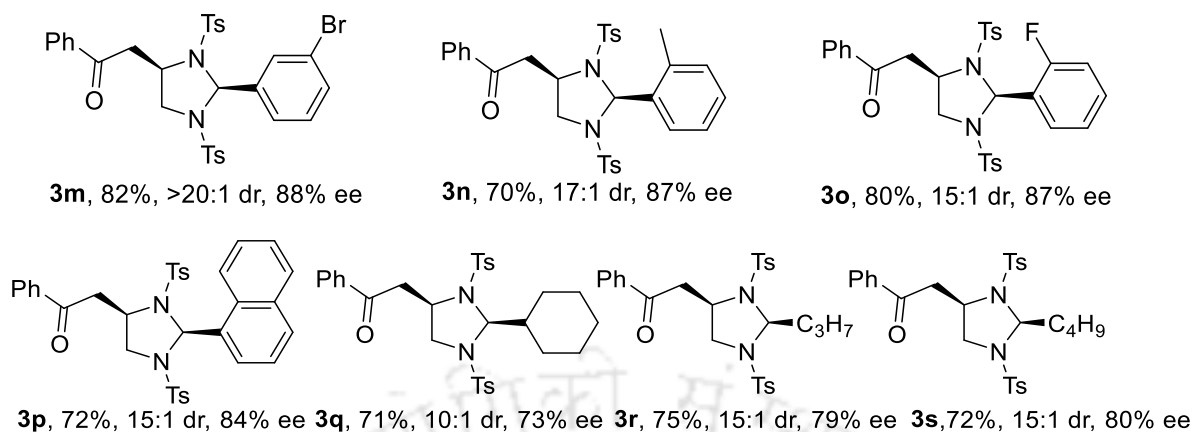
After identifying the best optimized reaction conditions, the scope and generality of the reaction was studied. Initially different tosyl imines **2** were prepared and engaged in the reaction (Table 3). Delightfully, high enantioselectivities were achieved in most of the cases excellent enantio and diastereoselectivities were maintained. A variety of electron donating, electron withdrawing and electron neutral substitutions at the *ortho*-, *meta*- and *para*- positions of the aryl groups were well tolerated. Initially different 4-alkyl substituted *N*-tosyl imines were investigated in the reaction and the outcome was very promising. Imine **2b** having *para*-methyl substituent provided the desired product **3b** in 79% yield with 18:1 diastereomeric ratio and 92% enantiomeric excess. 4-*i*pr Substituted imine **2c** afforded product **3c** with good yield and with high enantio and diastereomeric excess. The expected product was isolated with similar enantioselectivity from 4-*tert*-butyl substituted imine **2d**. Smooth conversion was achieved with 4-halosubstituted imines and pleasingly, the products were isolated with excellent diastereo- and enantioselectivities. To our delight, imine **2e** bearing 4-F substituent provided product **3e** as a single diastereomer and with 90% enantiomeric excess. For 4-Cl and 4-Br substituted imines the desired products **3f** and **3g** were obtained in high enantiomeric excess and only single diastereomer was detected. Interestingly imines **2h** and **2i** having electron withdrawing substituents responded well and delivered products **3h** and **3i** with good diastereomeric ratios and high enantiomeric excesses. Then different *meta* substituted imines were tested in the reaction and here also good results were maintained. 3-Methyl substituted imine **2j** provided product **3j** with 76% yield, 15:1 diastereomeric ratio and 89% enantiomeric excess. Surprisingly, *meta* halo substituted imines delivered products **3k**, **3l** and **3m** as single diastereomer and enantioselectivity values were 90%,

90% and 88% respectively. The reaction outcome remain unaltered for *ortho* substituted imines **2n** and **2o** respectively and the products **3n** and **3o** were isolated with good enantioselectivities.

Product **3p** derived from 1-naphthaldehyde derived imine **2p** was isolated with acceptable enantioselectivity. Interestingly, imines containing different aliphatic groups such as cyclohexyl, *n*-propyl and *n*-butyl participated well in the reaction. However, the enantioselectivities of the products **3q-3s** slightly decreased.

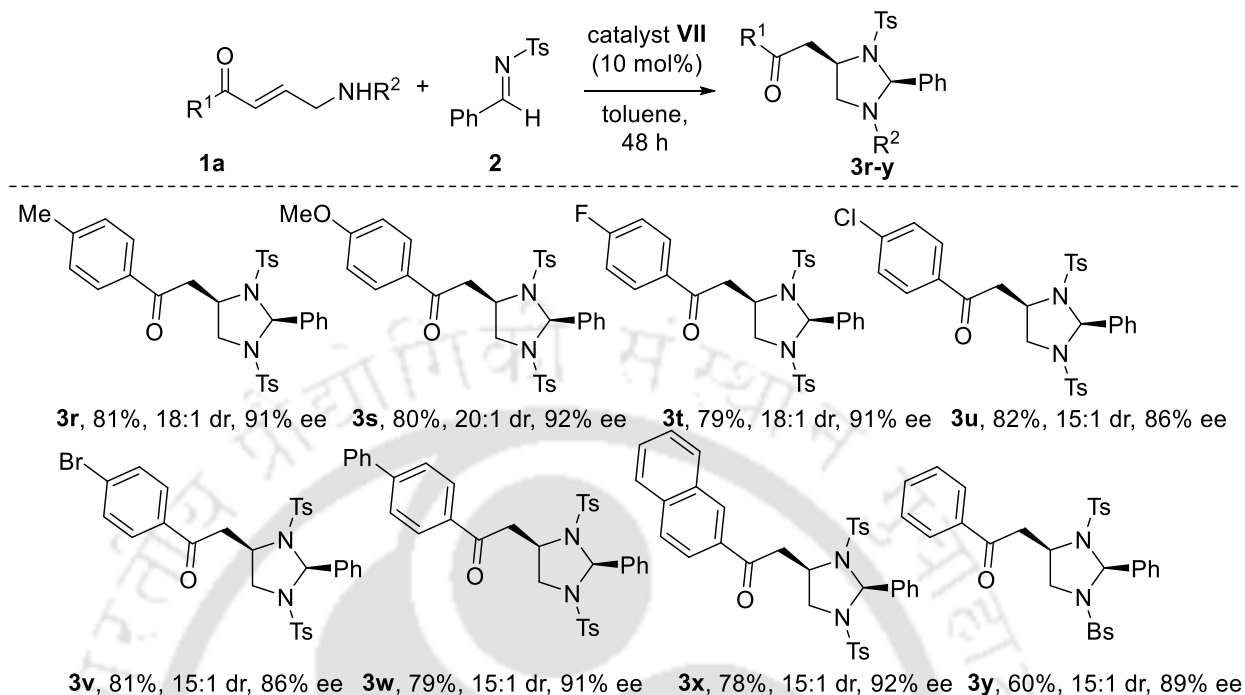
Table 3. Scope of *N*-tosyl imines^{a,b,c,d}

3a, 82%, 16:1 dr, 90% ee	3b, 79%, 18:1 dr, 92% ee	3c, 75%, 15:1 dr, 90% ee
3d, 72%, 15:1 dr, 91% ee	3e, 80%, >20:1 dr, 90% ee	3f, 80%, >20:1 dr, 90% ee
3g, 78%, >20:1 dr, 85% ee	3h, 77%, 10:1 dr, 90% ee	3i, 80%, 15:1 dr, 89% ee
3j, 76%, 15:1 dr, 89% ee	3k, 80%, >20:1 dr, 90% ee	3l, 80%, >20:1 dr, 90% ee



^aReaction conditions: 0.1 mmol of **1a** and 0.15 mmol **2** in 0.4 mL solvent using 10 mol% catalyst at rt for 48 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC using stationary phase chiral column.

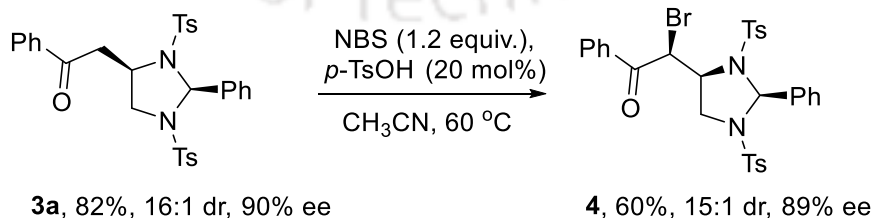
The scope of the reaction was further extended by varying amino methyl enone motif. Different amino methyl enones were prepared and examined under the optimized reaction conditions (Table 4). For examples, enone having *para*-tolyl group delivered product **3r** in 81% yield, 18:1 diastereomeric ratio and 91% enantiomeric excess. The desired product **3s** was isolated in 92% ee and excellent diastereomeric ratio 20:1 from enone containing 4-anisyl group. Then different 4-halo substituted amino methyl enones were introduced in the reaction. To our delight, 4-fluoro substituted enone provided product **3t** with excellent enantio and diastereoselectivity. Slight diminution in enantioselectivity was observed for 4-chloro substituted product **3u**. For 4-bromo substituted enone the enantioselectivity of the product **3v** was similar to that of the 4-chloro substituted product **3u**. Pleasingly, enone having biphenyl motif participated well in the reaction and furnished product **3w** in 79% yield, 15:1 diastereomeric and 91% enantiomeric excess. Promising result was also obtained for 2-naphthyl substituted enone. Then the scope was further elaborated by changing the tosyl group of the amino methyl enone to brosyl group and the reaction outcome was very satisfactory. The desired product **3y** was obtained with 15:1 diastereomeric ratio and 89% enantiomeric excess.

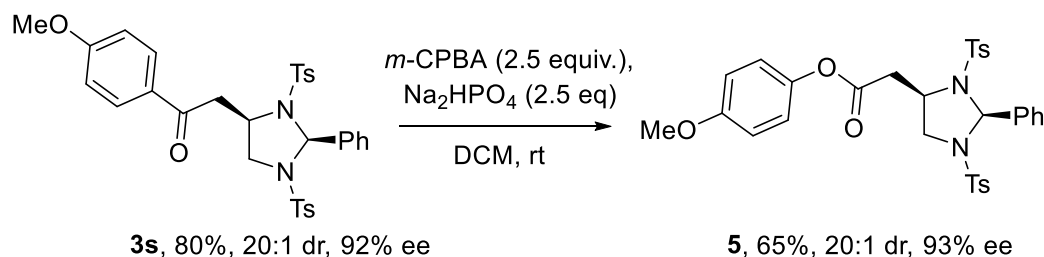
Table 4. Scope of amino methyl enones^{a,b,c,d}


^aReaction condition: 0.1 mmol of **1a** and 0.15 mmol **2** in 0.4 mL solvent using 10 mol% catalyst at rt for 48 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC using stationary phase chiral column.

2.5.3. Synthetic transformation of **3a** and **3s**:

To demonstrate the synthetic usefulness of our methodology, few reactions were performed with the chiral products. First the treatment of **3a** with *N*-bromosuccinamide in acetonitrile solvent at 60 °C provided monobrominated product **4** in 60% yield, 15:1 dr and 88% enantiomeric excess. The relative structure was confirmed from 1D NOE. Then Baeyer-Villiger oxidation on **3s** was carried out with *m*-CPBA and the desired ester **5** was isolated with retention of both enantio and diastereoselectivity (Scheme 2.10).

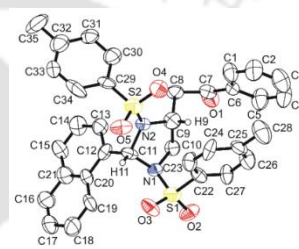
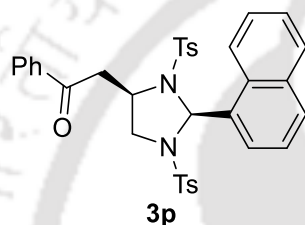




Scheme 2.10: Synthetic transformations

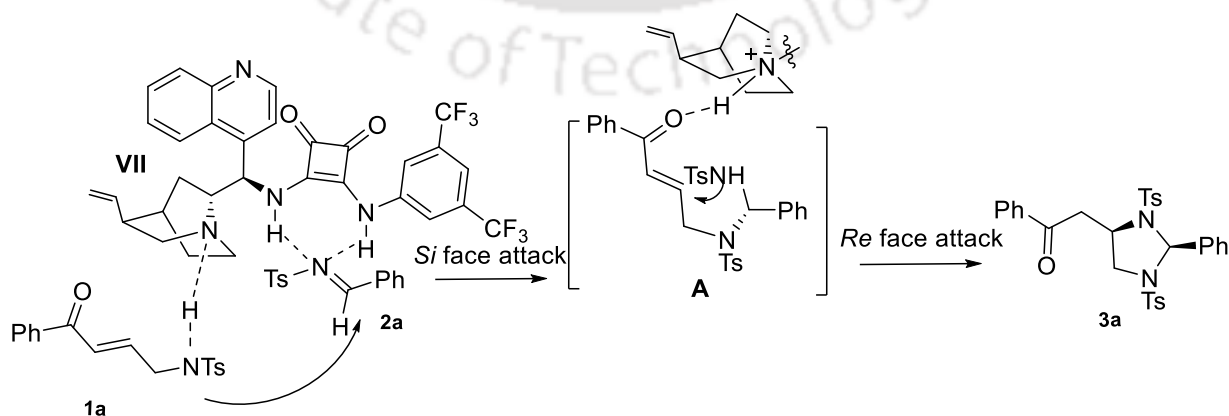
2.5.4. Absolute configuration 3p:

The absolute structure of product **3p** was determined to be (2*S*,4*R*) by X-ray crystallography¹⁷ and the configuration of other products are expected to be same by analogy.



2.5.5. Proposed mechanism:

Based on the absolute structure, a plausible transition state has been drawn, which dictates a bifunctional mode of activation by the catalyst. Since the *Re* face of C=N bond of **2a** is blocked by the squaramide moiety, the addition of deprotonated **1a** will take place only from the *Si* face to provide intermediate **A**. Next the intermediate **A** undergoes *aza*-Michael addition from the *Re* face of the enone moiety to provide product **3a** (Scheme 2.11).



Scheme 2.11: Proposed mechanism

2.6. Conclusion:

In conclusion, this report reveals the first catalytic asymmetric synthesis of 2,4-disubstituted imidazolidines. This method depicts an unprecedented amine addition to imines followed by *aza*-Michael reaction. This is an operationally simple and mild procedure for the synthesis of chiral imidazolidines in good to high yields with high diastereo and enantioselectivities. Also few derivatizations of the chiral products including diastereoselective bromination have been carried out. Thus our methodology could be useful for the synthesis of natural products and bioactive compounds having imidazolidine moieties.

2.7. Experimental section:

General information:

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH₂ under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na₂SO₄ and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

¹H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in CDCl₃; chemical shift values (δ, ppm) were reported in the standard fashion with reference to either tetramethylsilane (TMS) (δ(H) 0.00 ppm) or CHCl₃ (δ(H) 7.26 ppm). ¹³C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in CDCl₃; chemical shifts (δ, ppm) were reported relative to CHCl₃ (δ(C) 77.23 ppm, central line of triplet. Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (*J*) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray

ionization (ESI) technique. IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-K α irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F² using SHELXL-2014.

A. General procedure for the synthesis of tosyl imines 2a-2s:

Tosyl imines were prepared following literature procedures.¹⁸

B. General procedure for the synthesis of amino methyl enones 1a-1i:

Amino methyl enones were prepared according to the reported procedure.¹⁵

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

Thiourea catalysts (I-IV) were prepared according to the reported procedure.¹⁹

Squaramide catalyst was prepared according to the reported procedure.²⁰

D. General procedure for the synthesis of chiral imidazolidines:

Under argon atmosphere, compound *N*-tosyl aminomethyl enone **1** (0.05 mmol), tosyl imines **2** (0.075 mmol) and catalyst **VII** (10 mol %) were added in a round bottom flask and toluene 0.2 mL was added to it. Then the reaction mixture stirred at room temperature under argon atmosphere for 48 hours. After the reaction was completed as monitored by TLC. The product was purified by column chromatography using 13-15 % ethyl acetate in hexane as eluent.

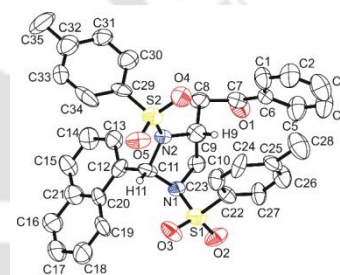
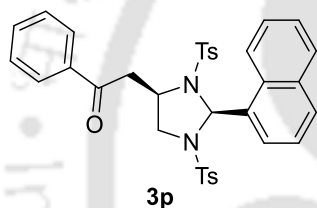
E. General procedure for the synthesis of compound 4:

To a solution of **3a** (0.1 mmol) in 0.4 mL CH₃CN was added *N*-bromosuccinimide (NBS, 0.12 mmol) and *p*-toluenesulfonic acid (*p*-TsOH, 0.02 mmol). The reaction mixture was stirred at 60 °C for 4 hours. Then the reaction mixture was diluted with ether, washed successively with H₂O, saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by column chromatography using 12% ethyl acetate in hexane.

F. General procedure for the synthesis of compound 5:

To a solution of **3s** (0.1 mmol) in CH₂Cl₂ (4 mL), was added disodium hydrogen phosphate (0.25 mmol) and *m*-CPBA (0.25 mmol). The reaction mixture was stirred at room temperature for 6 hours. The mixture was poured into water (2 mL) and saturated sodium hydrogen carbonate (2 mL), the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ twice. The combined organic layers were dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography using 15% ethyl acetate in hexane.

Crystal structure of compound 2-((2*S*,4*R*)-2-(41aphthalene-1-yl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone **3p**



Empirical formula	C ₃₅ H ₃₂ N ₂ O ₅ S ₂
Formula weight	623.74
CCDC Number	1581446
Crystal habit, colour	Needle, White
Crystal size, mm ³	0.16 × 0.10 × 0.08
Temperature, <i>T</i>	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	P 212121
Unit cell dimensions	<i>a</i> = 8.2494(10) Å <i>b</i> = 13.4963(14) Å <i>c</i> = 27.994(4) Å <i>α</i> = 90.00°, <i>β</i> = 90.00° <i>γ</i> = 90.00°
Volume, <i>V</i> (Å ³)	3116.8(7)
<i>Z</i>	4

CHAPTER 2

Calculated density, $\text{Mg}\cdot\text{m}^{-3}$	1.329
Absorption coefficient, μ (mm^{-1})	0.217
$F(000)$	1308.0
θ range for data collection	2.89 to 25.00°
Limiting indices	$-8 \leq h \leq 9, -16 \leq k \leq 15, -33 \leq l \leq 31$
Reflection collected/unique	11414/5461 [$R(\text{int})=0.1085$]
Completeness to θ	99.8% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.613/0.418
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data/restraints/parameters	2816/0/217
Goodness-of-fit on F^2	1.074
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.1019, wR2 = 0.1368$
R indices (all data)	$R1 = 0.2380, wR2 = 0.1818$
Largest diff. peak and hole	0.50 and $-0.31 \text{ e}\cdot\text{\AA}^{-3}$
Flack parameters	0.11

2.8 References:

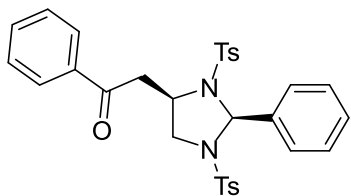
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- (17) CCDC 1581446 contains the crystallographic data for **3p**.

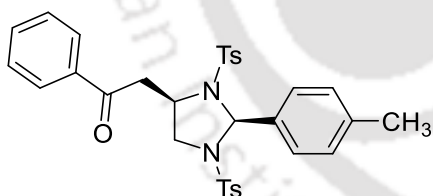
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2.9. Characterization Data of Products:

1-phenyl-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3a):

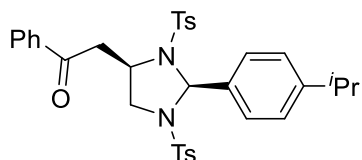
This compound was prepared according to the general procedure D. White sticky solid (44.8 mg, yield: 82%); **Diastereomeric ratio:** 16:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.32 (m, 5H), 7.25 (d, *J* = 8.2 Hz, 2H), 6.60 (s, 1H), 4.29 (dt, *J* = 17.7, 8.9 Hz, 1H), 4.02 – 3.95 (m, 2H), 3.03 – 2.98 (m, 1H), 2.93 (dd, *J* = 12.1, 7.3 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.31 (s, 1H), 2.26 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 197.7, 144.7, 144.3, 139.2, 136.1, 135.5, 133.9, 133.9, 130.2, 130.0, 128.9, 128.7, 128.7, 128.5, 128.2, 127.9, 127.1, 76.1, 56.6, 52.3, 45.0, 21.9, 21.8; **FT-IR (thin film):** 1678, 1601, 1568, 1452, 1352, 1215, 1161, 1088, 766 cm⁻¹; **HRMS (+ESI):** Calc for C₃₁H₃₁N₂O₅S₂ [M+H]⁺ 575.1669; found: 575.1676; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, *τ*_{major} = 13.7 min, *τ*_{minor} = 19.0 min); Enantiomeric excess: 90%.

1-phenyl-2-((2*S*,4*R*)-2-(*p*-tolyl)-1,3-ditosylimidazolidin-4-yl)ethanone (3b)

This compound was prepared according to the general procedure D. White sticky solid (46.5 mg, yield: 85%); **Diastereomeric ratio:** 18:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.85 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.58 (dd, *J* = 12.0, 7.8 Hz, 3H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 6.53 (s, 1H), 4.32 – 4.23 (m, 1H), 4.02 – 3.91 (m, 2H), 3.03 (dd, *J* = 17.9, 10.5 Hz, 1H), 2.94 (dd, *J* = 12.0, 7.2 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H), 2.33 (s, 1H), 2.28 (s, 1H), 2.26 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 197.7, 144.6, 144.3, 138.6, 136.3, 136.1, 135.5, 134.0, 133.9, 130.2, 129.9, 129.4, 128.9, 128.5, 128.2, 127.9, 127.0, 76.1, 56.6, 52.3, 45.0, 21.9, 21.8, 21.3; **FT-IR (thin film):** 1675, 1601, 1566, 1450, 1352, 1216, 1161, 1088, 805 cm⁻¹; **HRMS (+ESI):** Calc for C₃₂H₃₃N₂O₅S₂ [M+H]⁺ 589.1825; found: 589.1826; The enantiomeric ratio was determined by HPLC analysis

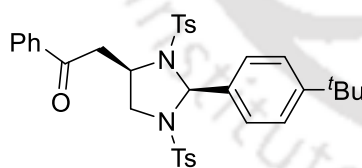
using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 13.9$ min, $\tau_{\text{minor}} = 23.0$ min); Enantiomeric excess: 92%.

2-((2*S*,4*R*)-2-(4-isopropylphenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3c)



This compound was prepared according to the general procedure D. White sticky solid (46.2 mg, yield: 85%); **Diastereomeric ratio:** 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.86 (d, $J = 7.4$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 3H), 7.44 (dd, $J = 18.0, 8.0$ Hz, 4H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.20 (d, $J = 8.1$ Hz, 2H), 6.55 (s, 1H), 4.34 – 4.23 (m, 1H), 4.03 – 3.96 (m, 2H), 3.04 (dd, $J = 17.9, 10.4$ Hz, 1H), 2.93 (ddd, $J = 20.7, 12.9, 7.1$ Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H), 1.25 (d, $J = 7.0$ Hz, 6H); **^{13}C NMR (125 MHz, CDCl_3):** δ 197.7, 149.5, 144.6, 144.2, 136.5, 136.2, 135.6, 134.0, 133.9, 130.2, 129.9, 128.9, 128.5, 128.3, 127.9, 127.1, 126.8, 76.1, 56.6, 52.3, 45.0, 34.0, 24.2, 24.2, 21.9, 21.8; **FT-IR (thin film):** 1683, 1600, 1569, 1457, 1353, 1215, 1161, 789 cm^{-1} ; **HRMS (+APCI):** Calc for $\text{C}_{34}\text{H}_{37}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 617.2138; found: 617.2139; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 10.1$ min, $\tau_{\text{minor}} = 14.8$ min); Enantiomeric excess: 90%.

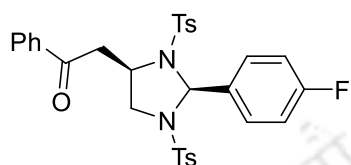
2-((2*S*,4*R*)-2-(4-(*tert*-butyl)phenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3d)



This compound was prepared according to the general procedure D. White sticky solid (45.4 mg, yield: 72%); **Diastereomeric ratio:** 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.87 (d, $J = 7.3$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.60 – 7.54 (m, 3H), 7.44 (dd, $J = 17.0, 8.2$ Hz, 4H), 7.37 – 7.32 (m, 4H), 7.22 (d, $J = 8.1$ Hz, 2H), 6.55 (s, 1H), 4.32 – 4.23 (m, 1H), 4.01 (ddd, $J = 8.9, 7.4, 4.7$ Hz, 2H), 3.05 (dd, $J = 17.9, 10.4$ Hz, 1H), 2.94 (dd, $J = 12.1, 7.4$ Hz, 1H), 2.46 (s, 3H), 2.41 (s, 3H), 2.28 (s, 1H), 2.24 (s, 1H), 1.32 (s, 9H); **^{13}C NMR (125 MHz, CDCl_3):** δ 197.8, 151.7, 144.6, 144.2, 136.2, 136.1, 135.7, 134.0, 133.9, 130.2, 129.9, 128.9, 128.6, 128.3, 127.9, 126.8, 125.6, 76.1, 56.6, 52.3, 45.1, 34.8, 31.5, 21.9, 21.8; **FT-IR (thin film):** 1680, 1600, 1567, 1457, 1352, 1216, 1161, 1089, 789 cm^{-1} ; **HRMS (+ESI):** Calc for

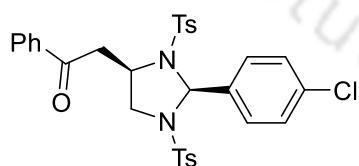
$C_{35}H_{39}N_2O_5S_2$ $[M+H]^+$ 631.2295; found: 631.2295; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 9.2 min, τ_{minor} = 12.11 min); Enantiomeric excess: 91%.

2-((2*S*,4*R*)-2-(4-fluorophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3e)



This compound was prepared according to the general procedure D. White sticky solid (47.4 mg, yield: 80%); **Diastereomeric ratio**: > 20:1; **1H NMR (600 MHz, $CDCl_3$)**: δ 7.85 (d, J = 7.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.3 Hz, 3H), 7.52 (dd, J = 8.5, 5.3 Hz, 2H), 7.46 (t, J = 7.8 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 7.7 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 6.52 (s, 1H), 4.33 – 4.22 (m, 1H), 4.00 – 3.91 (m, 2H), 3.01 (dd, J = 17.9, 10.4 Hz, 1H), 2.95 (dd, J = 12.1, 7.1 Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 197.6, 163.0 (d, J = 246 Hz), 144.9, 144.5, 136.0, 135.2, 135.1, 134.0, 133.7, 130.2, 130.0, 129.0, 129.0, 128.5, 128.2, 127.9, 115.7, 115.5, 75.6, 56.6, 52.3, 44.9, 21.9, 21.8; **FT-IR (thin film)**: 1682, 1601, 1565, 1463, 1377, 1225, 1162, 1088, 792 cm^{-1} ; **HRMS (+ESI)**: Calc for $C_{31}H_{30}FN_2O_5S_2$ $[M+H]^+$ 593.1575; found: 593.1572; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 13.3 min, τ_{minor} = 20.9 min); Enantiomeric excess: 90%.

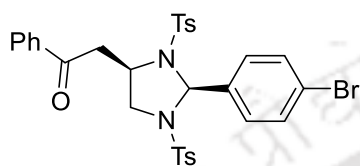
2-((2*S*,4*R*)-2-(4-chlorophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3f)



This compound was prepared according to the general procedure D. White sticky solid (48.7 mg, yield: 80%); **Diastereomeric ratio**: > 20:1; **1H NMR (600 MHz, $CDCl_3$)**: δ 7.85 (d, J = 7.3 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 3H), 7.46 (dd, J = 17.6, 8.1 Hz, 4H), 7.33 (dd, J = 10.9, 8.4 Hz, 4H), 7.25 (d, J = 6.8 Hz, 2H), 6.50 (s, 1H), 4.31 – 4.23 (m, 1H), 3.98 – 3.92 (m, 2H), 3.00 (dd, J = 17.9, 10.4 Hz, 1H), 2.93 (dd, J = 12.1, 7.1 Hz, 1H), 2.46 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)**: δ 197.6, 144.9, 144.6, 137.9, 136.1, 135.3, 134.8, 134.0, 133.7, 130.3, 130.1, 129.0, 128.9, 128.6, 128.5, 128.2, 127.9, 75.6, 56.7, 52.3,

44.9, 21.9, 21.8; **FT-IR (thin film)**: 1680, 1601, 1566, 1461, 1356, 1215, 1160, 791 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{31}\text{H}_{30}\text{ClN}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 609.1279; found: 609.1277; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 13.7$ min, $\tau_{\text{minor}} = 23.9$ min); Enantiomeric excess: 90%.

2-((2*S*,4*S*)-2-(4-bromophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3g)

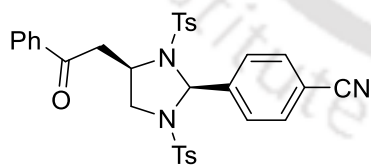


This compound was prepared according to the general procedure D. White sticky solid (5.09 mg, yield: 78%);

Diastereomeric ratio: > 20:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.85 (d, $J = 7.4$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz,

2H), 7.58 (d, $J = 8.3$ Hz, 3H), 7.46 (dd, $J = 16.5, 8.2$ Hz, 4H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 7.0$ Hz, 2H), 6.48 (s, 1H), 4.30 – 4.22 (m, 1H), 3.99 – 3.90 (m, 2H), 3.00 (dd, $J = 17.9, 10.4$ Hz, 1H), 2.93 (dd, $J = 12.0, 7.1$ Hz, 1H), 2.47 (s, 3H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 197.6, 144.9, 144.6, 138.5, 136.1, 135.3, 134.0, 133.7, 131.9, 130.3, 130.1, 129.0, 128.9, 128.5, 128.3, 127.9, 123.0, 75.6, 56.7, 52.4, 44.9, 21.9, 21.8; **FT-IR (thin film)**: 1679, 1598, 1569, 1448, 1346, 1213, 1162, 1092, 792 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{31}\text{H}_{30}\text{BrN}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 653.0774; found: 653.0776; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 14.2$ min, $\tau_{\text{minor}} = 26.0$ min); Enantiomeric excess: 85%.

4-((2*S*,4*R*)-4-(2-oxo-2-phenylethyl)-1,3-ditosylimidazolidin-2-yl)benzonitrile (3h)



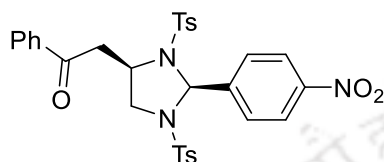
This compound was prepared according to the general procedure D. White sticky solid (46.1 mg, yield: 77%);

Diastereomeric ratio: 10:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.84 (d, $J = 7.4$ Hz, 2H), 7.74 (d, $J = 8.2$ Hz,

2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 3H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.2$ Hz, 2H), 6.54 (s, 1H), 4.29 – 4.23 (m, 1H), 3.98 – 3.93 (m, 2H), 2.95 (ddd, $J = 19.3, 15.0, 8.8$ Hz, 2H), 2.47 (s, 3H), 2.44 (s, 3H); **^{13}C NMR (125 MHz, CDCl_3)**: δ 197.4, 145.2, 144.9, 144.7, 136.0, 134.9, 134.1, 133.4, 132.6, 130.4, 130.2, 129.0, 128.6, 128.2, 128.0, 127.9, 118.7, 112.8, 75.4, 56.8, 52.5, 44.8, 22.0, 21.9; **FT-IR (thin film)**: 2230, 1678, 1599, 1567, 1453, 1351,

1303, 1214, 1160, 1093, 802 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{32}\text{H}_{30}\text{N}_3\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+600.1621$; found: 600.1621; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 $^{\circ}\text{C}$, 254 nm, $\tau_{\text{major}} = 22.7$ min, $\tau_{\text{minor}} = 55.4$ min); Enantiomeric excess: 90%.

2-((2*S*,4*S*)-2-(4-nitrophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3i)

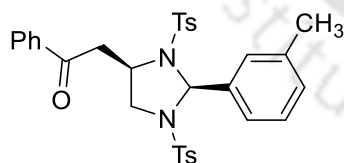


This compound was prepared according to the general procedure D. White sticky solid (49.5 mg, yield: 80%);

Diastereomeric ratio: 15:1; **^1H NMR (600 MHz, CDCl_3)**: δ 8.22 (d, $J = 8.8$ Hz, 2H), 7.85 (d, $J = 7.3$ Hz,

2H), 7.76 (t, $J = 8.3$ Hz, 4H), 7.59 (dd, $J = 10.2, 7.9$ Hz, 3H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 6.56 (s, 1H), 4.29-4.25 (m, 1H), 3.99 – 3.92 (m, 2H), 3.01-2.92 (m, 2H), 2.47 (s, 3H), 2.44 (s, 3H), 2.33 (s, 1H), 2.24 (s, 1H); **^{13}C NMR (125 MHz, CDCl_3)**: δ 197.4, 148.3, 146.5, 145.2, 144.9, 136.0, 134.9, 134.1, 133.3, 130.4, 130.2, 129.0, 128.6, 128.3, 128.2, 128.0, 124.0, 75.3, 56.9, 52.5, 44.8, 22.0, 21.9; **FT-IR (thin film)**: 1678, 1601, 1570, 1525, 1450, 1348, 1213, 1162, 1091, 790 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{31}\text{H}_{30}\text{N}_3\text{O}_7\text{S}_2$ $[\text{M}+\text{H}]^+620.1520$; found: 620.1521; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 $^{\circ}\text{C}$, 254 nm, $\tau_{\text{major}} = 23.9$ min, $\tau_{\text{minor}} = 68.11$ min); Enantiomeric excess: 89%.

1-phenyl-2-((2*S*,4*R*)-2-(*m*-tolyl)-1,3-ditosylimidazolidin-4-yl)ethanone (3j)



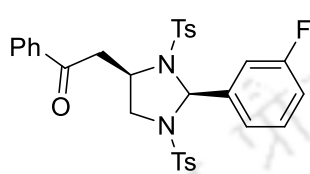
This compound was prepared according to the general procedure D. White sticky solid (44.7 mg, yield: 76%);

Diastereomeric ratio: 15:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.85 (d, $J = 7.5$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.58

(dd, $J = 14.1, 7.8$ Hz, 3H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 7.7$ Hz, 1H), 7.27 – 7.20 (m, 4H), 7.12 (d, $J = 7.5$ Hz, 1H), 6.55 (s, 1H), 4.32 – 4.24 (m, 1H), 3.99 (ddd, $J = 21.1, 14.9, 5.3$ Hz, 2H), 3.01 (dd, $J = 17.9, 10.4$ Hz, 1H), 2.95 (dd, $J = 12.0, 7.3$ Hz, 1H), 2.46 (s, 3H), 2.42 (s, 3H), 2.31 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 197.7, 144.7, 144.3, 139.1, 138.4, 136.1, 135.7, 134.0, 133.9, 130.2, 129.9, 129.5, 128.9, 128.6, 128.5, 128.2, 127.9, 127.7, 124.1, 76.2, 56.7, 52.2, 45.0, 21.9, 21.8,

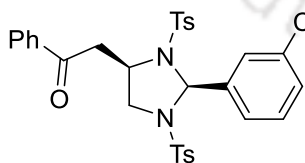
21.7; **FT-IR (thin film)**: 1678, 1602, 1566, 1450, 1350, 1216, 1160, 1089, 785 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 589.1825; found: 589.1827; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 12.2 min, τ_{minor} = 15.9 min); Enantiomeric excess: 89%.

2-((2*S*,4*R*)-2-(3-fluorophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3k)



This compound was prepared according to the general procedure D. White sticky solid (47.4 mg, yield: 80%); **Diastereomeric ratio**: >20:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.78 (d, J = 7.3 Hz, 2H), 7.68 (d, J = 8.2 Hz, 2H), 7.51 (dd, J = 13.7, 7.8 Hz, 3H), 7.38 (t, J = 7.8 Hz, 3H), 7.32 (s, 1H), 7.28 (d, J = 8.1 Hz, 2H), 7.24 – 7.20 (m, 2H), 7.19 (d, J = 8.1 Hz, 2H), 4.24 – 4.15 (m, J = 10.4, 7.3, 3.7 Hz, 1H), 3.97 – 3.86 (m, J = 21.1, 15.0, 5.3 Hz, 2H), 2.93 (dd, J = 17.9, 10.4 Hz, 1H), 2.86 (dd, J = 12.1, 7.3 Hz, 1H), 2.39 (s, 3H), 2.35 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 197.4, 162.8 (d, J = 245 Hz), 144.7, 144.4, 141.9 (d, J = 6 Hz), 135.9, 135.2, 133.8, 133.5, 130.2, 130.1, 130.1, 129.9, 128.8, 128.4, 128.1, 127.7, 122.6, 122.6, 115.7, 115.5, 114.2, 114.0, 75.3, 56.5, 52.2, 44.7, 21.7, 21.6; **FT-IR (thin film)**: 1678, 1601, 1566, 1450, 1353, 1214, 1160, 1089, 789 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{31}\text{H}_{30}\text{FN}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 593.1575; found: 593.1576; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 12.2 min, τ_{minor} = 15.9 min); Enantiomeric excess: 90%.

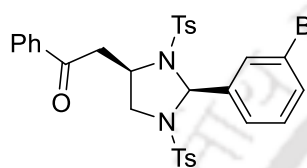
2-((2*S*,4*R*)-2-(3-chlorophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3l)



This compound was prepared according to the general procedure D. White sticky solid (49.9 mg, yield: 80%); **Diastereomeric ratio**: >20:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.88 (d, J = 7.3 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H), 7.63 (t, J = 6.7 Hz, 2H), 7.60 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 7.41 – 7.33 (m, 4H), 7.29 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 9.8 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.58 (s, 1H), 4.33 – 4.26 (m, 1H), 4.07 – 3.97 (m, 2H), 3.03 (dd, J = 18.0, 10.4 Hz, 1H), 2.94 (dd, J = 12.2, 7.3 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 2.36 (s, 1H), 2.29 (s, 1H); **^{13}C NMR (100**

MHz, CDCl₃): δ 197.5, 144.9, 144.6, 141.4, 136.0, 135.2, 134.7, 134.0, 133.6, 130.3, 130.1, 130.0, 128.9, 128.5, 128.2, 127.8, 127.2, 125.5, 75.5, 56.7, 52.3, 44.8, 22.0, 21.8; **FT-IR (thin film)**: 1679, 1600, 1567, 1451, 1353, 1248, 1162, 1088, 788 cm⁻¹; **HRMS (+ESI)**: Calc for C₃₁H₃₀ClN₂O₅S₂ [M+H]⁺ 609.1279; found: 609.1271; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 12.6 min, τ_{minor} = 15.9 min); Enantiomeric excess: 90%.

2-((2*S*,4*R*)-2-(3-bromophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3m)

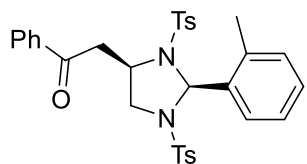


This compound was prepared according to the general procedure D. White sticky solid (53.5 mg, yield: 82%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃)**:

δ 7.88 (d, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (dd, *J* = 11.7, 7.9 Hz, 3H), 7.56 – 7.51 (m, 2H), 7.47 (dd, *J* = 13.8, 6.0 Hz, 3H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.24 (m, 3H), 6.52 (s, 1H), 4.35 – 4.26 (m, 1H), 4.02 (ddd, *J* = 21.1, 15.0, 5.3 Hz, 2H), 3.03 (dd, *J* = 17.9, 10.4 Hz, 1H), 2.96 (dd, *J* = 12.1, 7.2 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 197.5, 145.0, 144.6, 142.0, 136.0, 135.3, 134.0, 133.6, 131.9, 130.3, 130.2, 130.1, 130.0, 129.0, 128.5, 128.2, 127.8, 126.0, 122.8, 75.5, 56.8, 52.3, 44.8, 21.9, 21.8; **FT-IR (thin film)**: 1678, 1600, 1567, 1449, 1352, 1161, 1090, 789 cm⁻¹; **HRMS (+ESI)**: Calc for C₃₁H₃₀BrN₂O₅S₂ [M+H]⁺ 653.0774; found: 653.0775; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 20.9 min, τ_{minor} = 22.2 min); Enantiomeric excess: 88%.

1-phenyl-2-((2*S*,4*R*)-2-(*o*-tolyl)-1,3-ditosylimidazolidin-4-yl)ethanone (3n)



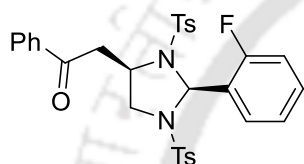
This compound was prepared according to the general procedure D. White sticky solid (41.2 mg, yield: 70%);

Diastereomeric ratio: 17:1; **¹H NMR (600 MHz, CDCl₃)**: δ

7.98 – 7.93 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.15 (dd, *J* = 12.9, 7.7 Hz, 3H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.59 (s, 1H), 4.29 – 4.23 (m, 1H), 4.20 (dd, *J* = 17.6, 3.1 Hz, 1H), 4.07 (dd,

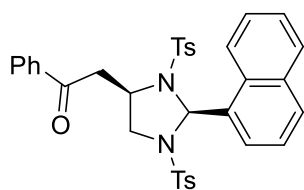
$J = 12.0, 7.1$ Hz, 1H), 3.26 (dd, $J = 17.6, 10.3$ Hz, 1H), 3.13 (dd, $J = 12.0, 7.8$ Hz, 1H), 2.64 (s, 3H), 2.45 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 197.6, 144.6, 144.1, 137.1, 137.0, 136.2, 135.1, 134.0, 133.9, 131.3, 130.1, 129.8, 129.0, 128.9, 128.3, 128.2, 127.7, 127.6, 126.1, 74.1, 56.2, 52.4, 44.3, 21.9, 21.7, 19.8; FT-IR (thin film): 1678, 1601, 1566, 1450, 1349, 1216, 1159, 1088, 792 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 589.1825; found: 589.1828; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 16.0$ min, $\tau_{\text{minor}} = 19.2$ min); Enantiomeric excess: 87%.

2-((2*S*,4*R*)-2-(2-fluorophenyl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3o)



This compound was prepared according to the general procedure D. White sticky solid (47.3 mg, yield: 80%); Diastereomeric ratio: 15:1; ^1H NMR (600 MHz, CDCl_3): δ 7.96 (d, $J = 7.1$ Hz, 2H), 7.70 (d, $J = 8.3$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 7.52 – 7.46 (m, 4H), 7.29 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.0$ Hz, 3H), 7.03 – 6.97 (m, 1H), 6.23 (s, 1H), 4.31 – 4.23 (m, 1H), 4.08 (dd, $J = 17.9, 3.0$ Hz, 1H), 3.76 (dd, $J = 11.1, 7.3$ Hz, 1H), 3.41 (dd, $J = 17.9, 10.4$ Hz, 1H), 3.23 (dd, $J = 11.3, 6.4$ Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 197.8, 160.7 (d, $J = 249$ Hz), 144.7, 144.2, 136.2, 134.0, 133.9, 133.2, 131.0, 130.9, 130.2, 129.7, 129.0, 128.3, 128.0, 126.6 (d, $J = 3$ Hz), 124.3 (d, $J = 4.5$ Hz), 116.2, 116.0, 72.7, 56.3, 52.7, 44.5, 21.9, 21.8; FT-IR (thin film): 1678, 1602, 1566, 1456, 1358, 1162, 1089, 789 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{31}\text{H}_{30}\text{FN}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 593.1575; found: 593.1580; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 20.3$ min, $\tau_{\text{minor}} = 26.3$ min); Enantiomeric excess: 87%.

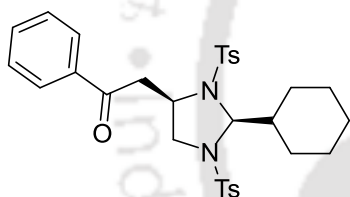
2-((2*S*,4*R*)-2-(5*a*phthalene-1-yl)-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3p)



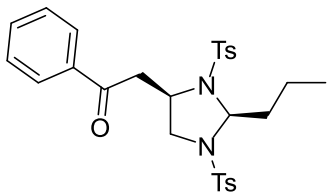
This compound was prepared according to the general procedure D. White sticky solid (44.9 mg, yield: 72%); Diastereomeric ratio: 15:1; ^1H NMR (600 MHz, CDCl_3): δ 8.80 (d, $J = 8.6$ Hz, 1H), 7.98 (d, $J = 7.4$ Hz, 1H), 7.87 (dt, $J =$

16.7, 8.3 Hz, 2H), 7.66 (t, $J = 7.3$ Hz, 1H), 7.62 (t, $J = 6.9$ Hz, 1H), 7.56 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.7$ Hz, 1H), 7.43 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.13 (d, $J = 8.2$ Hz, 1H), 4.46 (dd, $J = 17.5, 3.0$ Hz, 1H), 4.44 – 4.37 (m, 1H), 4.02 (dd, $J = 13.0, 6.7$ Hz, 1H), 3.31 (dd, $J = 17.5, 10.2$ Hz, 1H), 2.82 (dd, $J = 13.1, 8.7$ Hz, 1H), 2.46 (s, 1H), 2.32 (s, 1H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 197.7, 144.7, 144.5, 136.3, 135.3, 134.3, 134.1, 134.0, 133.7, 131.2, 130.1, 130.0, 129.8, 129.0, 128.9, 128.8, 128.4, 128.2, 126.8, 126.2, 126.0, 124.9, 124.3, 74.4, 56.8, 52.3, 44.2, 21.9, 21.7; **FT-IR (thin film)**: 1686, 1601, 1566, 1449, 1348, 1272, 1158, 1088, 813 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{35}\text{H}_{36}\text{N}_3\text{O}_5\text{S}_2$ $[\text{M}+\text{NH}_4]^+$ 642.2091; found: 642.2095; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 15.4$ min, $\tau_{\text{major}} = 21.4$ min); Enantiomeric excess: 84%.

2-((2*S*,4*R*)-2-cyclohexyl-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3q)



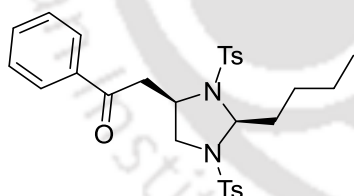
This compound was prepared according to the general procedure D. White sticky solid (41.2 mg, yield: 70%); **Diastereomeric ratio**: 10:1; **^1H NMR (600 MHz, CDCl_3)**: δ 7.94 (d, $J = 7.3$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.57 (d, $J = 8.3$ Hz, 3H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.2$ Hz, 2H), 5.42 (d, $J = 6.5$ Hz, 1H), 4.15 – 4.09 (m, 2H), 4.04 – 3.92 (m, $J = 10.6, 3.1$ Hz, 1H), 3.05 (dd, $J = 17.9, 10.2$ Hz, 1H), 2.85 (dd, $J = 13.0, 8.9$ Hz, 1H), 2.46 (s, 3H), 2.39 (s, 3H), 1.97 (d, $J = 9.2$ Hz, 1H), 1.84 (d, $J = 8.9$ Hz, 1H), 1.75 (d, $J = 8.7$ Hz, 3H), 1.70 – 1.57 (m, 4H), 1.15 (d, $J = 14.2$ Hz, 2H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 197.9, 144.6, 144.1, 136.2, 136.2, 133.9, 133.6, 130.1, 129.9, 129.0, 128.9, 128.3, 127.9, 79.5, 77.6, 56.2, 52.9, 45.4, 44.8, 29.9, 28.4, 26.3, 26.1, 21.9, 21.8; **FT-IR (thin film)**: 2854, 1680, 1601, 1566, 1451, 1350, 1217, 1160, 1088, 886 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{31}\text{H}_{37}\text{N}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 581.2138; found: 581.2133; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 11.5$ min, $\tau_{\text{minor}} = 13.6$ min); Enantiomeric excess: 73%.

1-phenyl-2-((2*S*,4*R*)-2-propyl-1,3-ditosylimidazolidin-4-yl)ethanone (3r)

This compound was prepared according to the general procedure D. White sticky solid (40.5 mg, yield: 75%);

Diastereomeric ratio: 15:1; **¹H NMR (600 MHz, CDCl₃):**

δ 7.92 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.34 (t, J = 6.2 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.97 (dd, J = 17.9, 3.1 Hz, 1H), 3.74 (dd, J = 11.8, 7.4 Hz, 1H), 3.16 (dd, J = 17.9, 10.3 Hz, 1H), 3.01 (dd, J = 11.9, 7.3 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.90 – 1.79 (m, 2H), 1.52 (dd, J = 14.3, 7.1 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H). **¹³C NMR (150 MHz, CDCl₃):** δ 197.8, 144.4, 144.2, 136.2, 135.2, 134.0, 133.8, 130.1, 129.9, 129.0, 128.3, 128.3, 127.9, 75.5, 55.8, 51.8, 45.5, 39.7, 21.9, 21.8, 18.4, 13.9; **FT-IR (thin film):** 2960, 2927, 2873, 1680, 1600, 1589, 1451, 1349, 1216, 1162, 1091, 816 cm⁻¹; **HRMS (+ESI):** Calc for C₂₈H₃₃N₂O₅S₂ [M+H]⁺ 541.1825; found: 541.1829; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.7 min, τ_{minor} = 18.7 min); Enantiomeric excess: 79%.

2-((2*S*,4*R*)-2-butyl-1,3-ditosylimidazolidin-4-yl)-1-phenylethanone (3s)

This compound was prepared according to the general procedure D. White sticky solid (39.9 mg, yield: 72%);

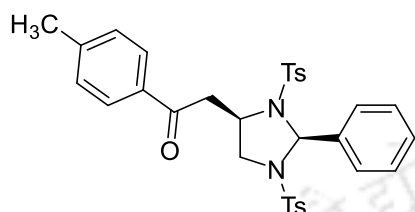
Diastereomeric ratio: 15:1; **¹H NMR (600 MHz,**

CDCl₃): δ 7.93 (d, J = 7.2 Hz, 2H), 7.67 (d, J = 8.3 Hz,

2H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 5.33 (t, J = 6.2 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.98 (dd, J = 17.9, 3.1 Hz, 1H), 3.76 (dd, J = 11.8, 7.4 Hz, 1H), 3.16 (dd, J = 17.9, 10.3 Hz, 1H), 3.02 (dd, J = 11.9, 7.3 Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H), 1.91 – 1.79 (m, 2H), 1.49 – 1.42 (m, 2H), 1.41 – 1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 197.8, 144.4, 144.2, 136.2, 135.2, 134.0, 133.8, 130.1, 129.9, 129.0, 128.3, 128.3, 127.9, 75.7, 55.8, 51.8, 45.5, 37.3, 27.1, 22.5, 21.9, 21.8, 14.2; **FT-IR (thin film):** 2956, 2927, 2865, 1680, 1601, 1567, 1451, 1350, 1216, 1161, 1091, 785 cm⁻¹; **HRMS (+ESI):** Calc for C₂₉H₃₅N₂O₅S₂ [M+H]⁺ 555.1982; found: 555.1973; The enantiomeric

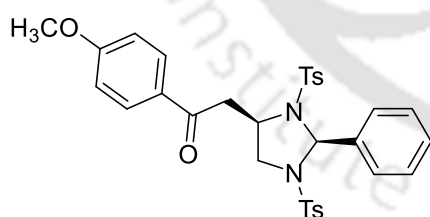
ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.1$ min, $\tau_{\text{minor}} = 18.1$ min); Enantiomeric excess: 80%.

2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)-1-(*p*-tolyl)ethanone (3t)



This compound was prepared according to the general procedure D. White sticky solid (47.6 mg, yield: 81%); **Diastereomeric ratio:** 18:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.75 (dd, $J = 14.1, 8.2$ Hz, 2H), 7.59 (d, $J = 8.3$ Hz, 1H), 7.53 (d, $J = 7.3$ Hz, 1H), 7.37 – 7.32 (m, 2H), 7.24 (dd, $J = 7.9, 4.7$ Hz, 2H), 6.59 (s, 1H), 4.31 – 4.23 (m, 1H), 4.01 – 3.91 (m, $J = 21.0, 15.0, 5.3$ Hz, 1H), 3.03 – 2.89 (m, $J = 19.3, 15.0, 8.9$ Hz, 1H), 2.46 (s, 1H), 2.42 (s, 1H), 2.40 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 197.3, 144.9, 144.7, 144.3, 139.3, 135.5, 134.0, 133.7, 130.2, 130.0, 129.6, 128.7, 128.7, 128.5, 128.4, 127.9, 127.1, 76.1, 56.7, 52.3, 44.9, 21.9, 21.8; **FT-IR (thin film):** 1675, 1601, 1565, 1353, 1161, 811 cm⁻¹; **HRMS (+ESI):** Calc for C₃₂H₃₃N₂O₅S₂ [M+H]⁺ 589.1825; found: 589.1826; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 14.6$ min, $\tau_{\text{minor}} = 21.7$ min); Enantiomeric excess: 91%.

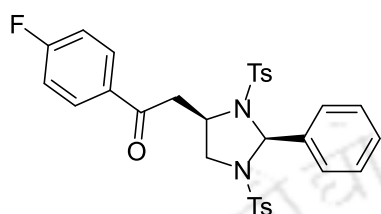
1-(4-methoxyphenyl)-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3u)



This compound was prepared according to the general procedure D. White sticky solid (48.3 mg, yield: 80%); **Diastereomeric ratio:** 20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.82 (d, $J = 8.9$ Hz, 2H), 7.76 (d, $J = 8.2$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.53 (d, $J = 7.3$ Hz, 2H), 7.37 – 7.31 (m, 4H), 7.24 (d, $J = 8.1$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 6.58 (s, 1H), 4.32 – 4.23 (m, 1H), 3.97 (dd, $J = 12.0, 7.4$ Hz, 1H), 3.91 (dd, $J = 17.6, 3.2$ Hz, 1H), 3.86 (s, 3H), 3.00 – 2.91 (m, 2H), 2.46 (s, 3H), 2.41 (s, 2H); **¹³C NMR (125 MHz, CDCl₃):** δ 196.2, 164.2, 144.7, 144.3, 139.3, 135.6, 134.0, 130.6, 130.2, 130.0, 129.3, 128.7, 128.7, 127.9, 127.1, 114.1, 76.1, 56.8, 55.7, 52.3, 44.6, 21.9, 21.8; **FT-IR (thin film):** 1668, 1601, 1566, 1458, 1350, 1306, 1161, 1092, 826 cm⁻¹; **HRMS**

(+ESI): Calc for $C_{32}H_{36}N_3O_6S_2$ $[M+NH_4]^+$ 622.2040; found: 622.2040; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 17.6 min, τ_{minor} = 27.7 min); Enantiomeric excess: 92%.

1-(4-fluorophenyl)-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3v)

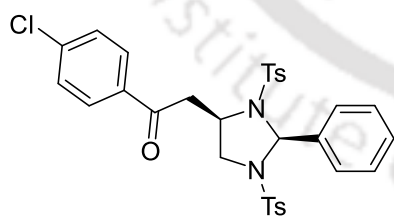


This compound was prepared according to the general procedure D. White sticky solid (46.8 mg, yield: 79%);

Diastereomeric ratio: 18:1; **1H NMR (600 MHz, $CDCl_3$):** δ 7.87 (dd, J = 8.8, 5.4 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 7.2 Hz, 2H), 7.37 – 7.33 (m, 4H), 7.25 (d, J = 8.2 Hz, 2H), 7.11 (t, J = 8.5 Hz, 2H), 6.59 (s, 1H), 4.33 – 4.23 (m, 1H), 4.04 – 3.91 (m, J = 21.2, 15.0, 5.3 Hz, 2H), 3.03 – 2.89 (m, J = 19.3, 15.0, 8.8 Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 196.1, 166.3 (d, J = 253.75 Hz) 144.8, 144.4, 139.2, 135.5, 133.9, 133.1 (d, J = 2.5 Hz), 131.0, 130.9, 130.2, 130.0, 128.8, 128.7, 128.6, 127.9, 127.1, 116.2, 116.0, 76.1, 56.6, 52.3, 44.9, 21.9, 21.8; **FT-IR (thin film):** 1680, 1600, 1568, 1459, 1370, 1159, 790 cm^{-1} ;

HRMS (+ESI): Calc for $C_{31}H_{33}FN_3O_5S_2$ $[M+NH_4]^+$ 610.1840; found: 610.1846; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 14.2 min, τ_{minor} = 20.2 min); Enantiomeric excess: 91%.

1-(4-chlorophenyl)-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3w)

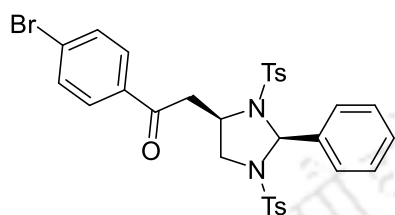


This compound was prepared according to the general procedure D. White sticky solid (49.8 mg, yield: 82%);

Diastereomeric ratio: 15:1; **1H NMR (600 MHz, $CDCl_3$):** δ 7.77 (t, J = 8.9 Hz, 4H), 7.60 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.35 (dd, J = 7.7, 3.8 Hz, 5H), 7.25 (d, J = 8.1 Hz, 2H), 6.59 (s, 1H), 4.31-4.23 (m, J = 7.2, 5.6 Hz, 1H), 4.02-3.90 (m, J = 21.2, 15.0, 5.3 Hz, 2H), 3.01-2.98 (m, J = 19.4, 15.0, 8.7 Hz, 2H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.5, 144.8, 144.4, 140.4, 139.2, 135.5, 134.4, 133.8, 130.2, 130.0, 129.7, 129.3, 128.8, 128.7, 128.6, 127.9, 127.1, 76.1, 56.6, 52.2, 44.9, 21.9, 21.8; **FT-IR (thin film):** 1680, 1601, 1566, 1353, 1249, 1159 cm^{-1} ; **HRMS**

(+ESI): Calc for $C_{31}H_{30}ClN_2O_5S_2$ $[M+H]^+$ 609.1279; found: 609.1277; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 24.7 min, τ_{minor} = 38.2 min); Enantiomeric excess: 86%.

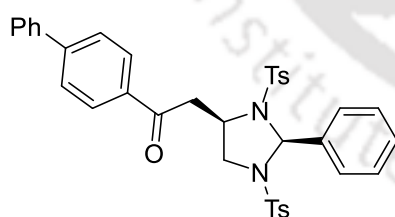
1-(4-bromophenyl)-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3x)



This compound was prepared according to the general procedure D. White sticky solid (52.9 mg, yield: 81%);

Diastereomeric ratio: 15:1; **1H NMR (400 MHz, $CDCl_3$):** δ 7.76 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.5 Hz, 2H), 7.59 (t, J = 8.4 Hz, 4H), 7.53 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.1 Hz, 5H), 7.25 (d, J = 9.1 Hz, 2H), 6.59 (s, 1H), 4.33 – 4.21 (m, 1H), 3.95 (ddd, J = 21.2, 14.9, 5.3 Hz, 2H), 3.03 – 2.88 (m, 2H), 2.46 (s, 3H), 2.42 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 196.7, 144.8, 144.4, 139.2, 135.5, 134.8, 133.8, 132.3, 130.2, 130.0, 129.7, 129.1, 128.8, 128.7, 128.5, 127.9, 127.1, 76.1, 56.6, 52.2, 44.9, 21.9, 21.8; **FT-IR (thin film):** 1680, 1602, 1566, 1461, 1352, 1212, 1162, 1089, 790, 590 cm^{-1} ; **HRMS (+ESI):** Calc for $C_{31}H_{33}BrN_3O_5S_2$ $[M+NH_4]^+$ 670.1040; found: 670.1020; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 25.6 min, τ_{minor} = 41.1 min); Enantiomeric excess: 86%.

1-([1,1'-biphenyl]-4-yl)-2-((2*S*,4*R*)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3y)

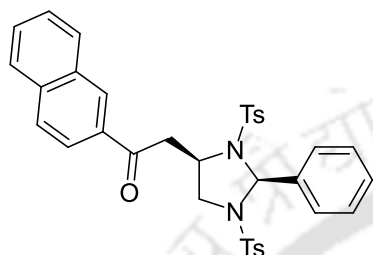


This compound was prepared according to the general procedure D. White sticky solid (51.3 mg, yield: 79%);

Diastereomeric ratio: 15:1; **1H NMR (500 MHz, $CDCl_3$):** δ 7.93 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.65 – 7.61 (m, 4H), 7.57 (d, J = 7.1 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.43 (d, J = 7.3 Hz, 1H), 7.39 – 7.35 (m, 4H), 7.27 (d, J = 8.3 Hz, 2H), 6.63 (s, 1H), 4.38 – 4.29 (m, 1H), 4.07 – 3.98 (m, 2H), 3.02 (ddd, J = 19.3, 15.0, 8.8 Hz, 2H), 2.48 (s, 3H), 2.44 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.3, 146.6, 144.7, 144.4, 139.8, 139.3, 135.6, 134.8, 134.0, 130.2, 130.0, 129.2, 128.9, 128.8, 128.7, 128.6, 128.6, 127.9, 127.5, 127.5, 127.1, 76.1, 56.7, 52.3, 45.0, 21.9, 21.8; **FT-IR (thin film):** 1676, 1602, 1566, 1492, 1451, 1404, 1351, 1217, 1161, 1090, 791, 670 cm^{-1} ; **HRMS (+ESI):**

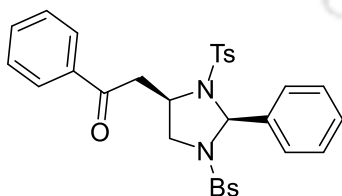
Calc for $C_{37}H_{35}N_2O_5S_2$ $[M+H]^+$ 651.1982; found: 651.1987; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 21.4$ min, $\tau_{\text{minor}} = 52.7$ min); Enantiomeric excess: 91%.

1-(59aphthalene-2-yl)-2-((2S,4R)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (3z)



This compound was prepared according to the general procedure D. White sticky solid (48.6 mg, yield: 78%); **Diastereomeric ratio:** 15:1; **1H NMR (500 MHz, $CDCl_3$):** δ 8.37 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.88 (dd, $J = 12.6, 5.1$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.63 – 7.59 (m, 1H), 7.59 – 7.54 (m, 1H), 7.36 (dd, $J = 10.0, 7.8$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 6.63 (s, 1H), 4.39 – 4.29 (m, 1H), 4.14 (dd, $J = 17.7, 3.3$ Hz, 1H), 4.05 (dd, $J = 12.1, 7.4$ Hz, 1H), 3.13 (dd, $J = 17.7, 10.4$ Hz, 1H), 2.99 (dd, $J = 12.1, 7.3$ Hz, 1H), 2.46 (s, 1H), 2.41 (s, 1H); **^{13}C NMR (125 MHz, $CDCl_3$):** δ 197.7, 144.8, 144.4, 139.3, 136.0, 135.6, 133.9, 133.4, 132.6, 130.4, 130.2, 130.0, 129.9, 129.1, 128.9, 128.7, 128.8, 128.6, 128.0, 127.9, 127.2, 127.1, 123.5, 76.1, 56.9, 52.3, 45.1, 21.9, 21.8; **FT-IR (thin film):** 1677, 1602, 1566, 1472, 1353, 1161, 1088 790 cm^{-1} ; **HRMS (+ESI):** Calc for $C_{33}H_{35}N_2O_5S_2$ $[M+H]^+$ 625.1825; found: 625.1829; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 16.0$ min, $\tau_{\text{minor}} = 26.8$ min); Enantiomeric excess: 92%.

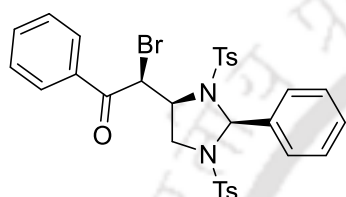
2-((2S,4R)-1,3-bis((4-bromophenyl)sulfonyl)-2-phenylimidazolidin-4-yl)-1-phenylethanone(3z')



This compound was prepared according to the general procedure D. White sticky solid (38.3 mg, yield: 60%); **Diastereomeric ratio:** 15:1; **1H NMR (600 MHz, $CDCl_3$)** δ 7.84 (d, $J = 7.2$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.59 – 7.56 (m, 2H), 7.54 (d, $J = 8.8$ Hz, 1H), 7.49 (d, $J = 6.5$ Hz, 2H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.35 (dd, $J = 7.8, 3.0$ Hz, 4H), 6.54 (s, 1H), 4.32 – 4.27 (m, 1H), 4.01 (dd, $J = 11.9, 7.5$ Hz, 1H), 3.95 (dd, $J = 18.0, 3.2$ Hz, 1H), 3.01 (ddd, $J = 15.0, 13.8, 8.8$ Hz,

2H), 2.48 (s, 2H); ^{13}C NMR (150 MHz, CDCl_3): δ 197.7, 145.0, 138.9, 137.5, 136.0, 134.0, 133.8, 132.7, 130.3, 129.3, 129.0, 128.9, 128.8, 128.6, 128.5, 128.3, 127.0, 76.3, 56.6, 52.4, 45.0, 21.9; FT-IR (thin film): 1678, 1601, 1566, 1389, 1353, 1304, 1160, 1095, 798 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{30}\text{H}_{28}\text{BrN}_2\text{O}_5\text{S}_2$ $[\text{M}+\text{H}]^+$ 639.0618; found: 639.0616; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 16.4 min, τ_{minor} = 24.0 min); Enantiomeric excess: 89%.

(S)-2-bromo-1-phenyl-2-((2S,4S)-2-phenyl-1,3-ditosylimidazolidin-4-yl)ethanone (4)

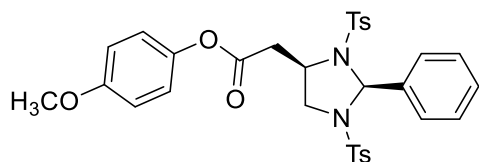


This compound was prepared according to the general procedure E. White sticky solid (38.1 mg, yield: 60%);

Diastereomeric ratio: 15:1; ^1H NMR (600 MHz, CDCl_3):

δ 7.79 (d, J = 7.5 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.61 – 7.57 (m, 3H), 7.45 (t, J = 7.8 Hz, 2H), 7.34 (d, J = 8.0 Hz, 3H), 7.30 (dd, J = 8.0, 2.4 Hz, 4H), 6.70 (s, 1H), 5.89 (d, J = 4.2 Hz, 1H), 4.17 (td, J = 7.2, 4.2 Hz, 1H), 4.08 (dd, J = 12.4, 7.1 Hz, 1H), 3.58 (dd, J = 12.5, 7.2 Hz, 1H), 2.45 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 192.6, 145.2, 144.6, 138.6, 135.4, 134.4, 133.9, 133.3, 130.2, 130.1, 129.1, 129.1, 128.9, 128.6, 128.5, 128.1, 127.5, 75.7, 60.4, 50.2, 48.6, 21.9, 21.8; FT-IR (thin film): 1683, 1599, 1569, 1493, 1452, 1404, 1349, 1210, 1161, 1089, 788 592 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{31}\text{H}_{33}\text{BrN}_3\text{O}_5\text{S}_2$ $[\text{M}+\text{NH}_4]^+$ 670.1040; found: 670.1041; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 16.4 min, τ_{minor} = 24.6 min); Enantiomeric excess: 88%.

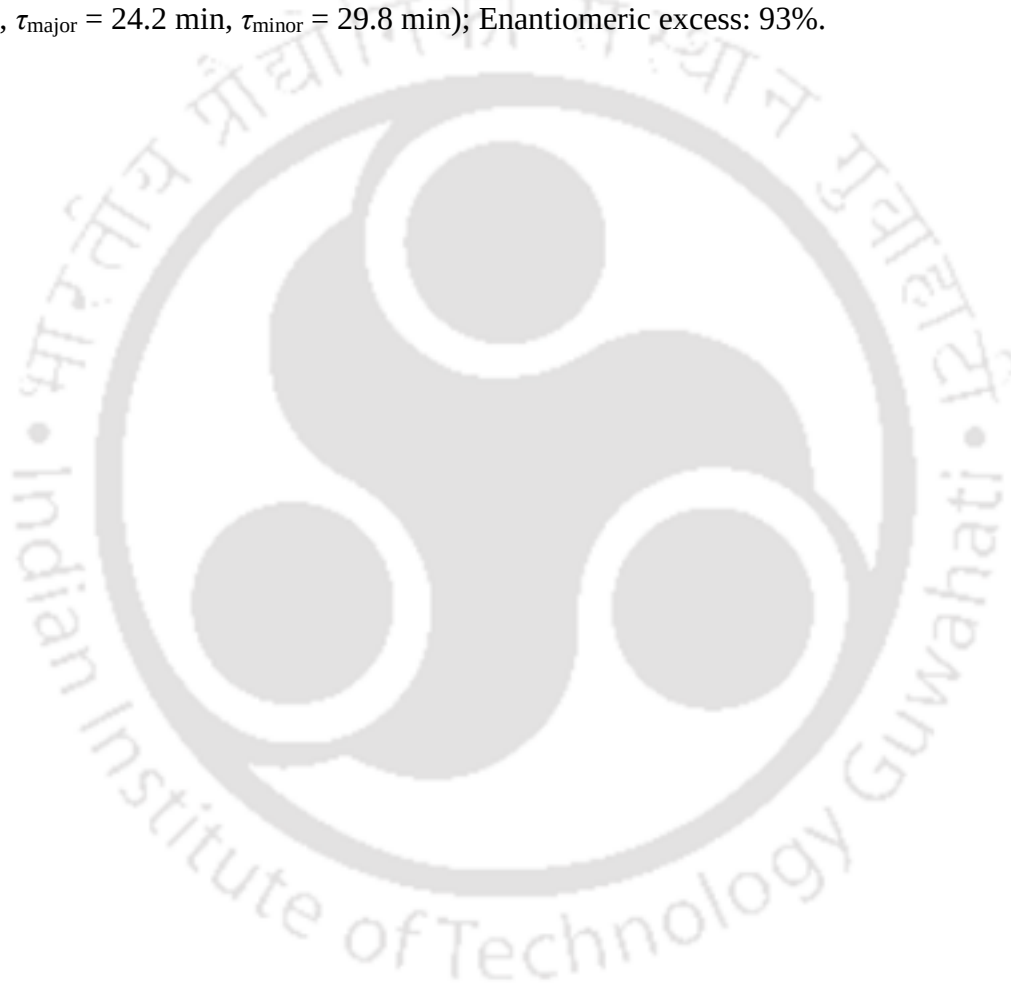
4-methoxyphenyl 2-((2S,4R)-2-phenyl-1,3-ditosylimidazolidin-4-yl)acetate (5)



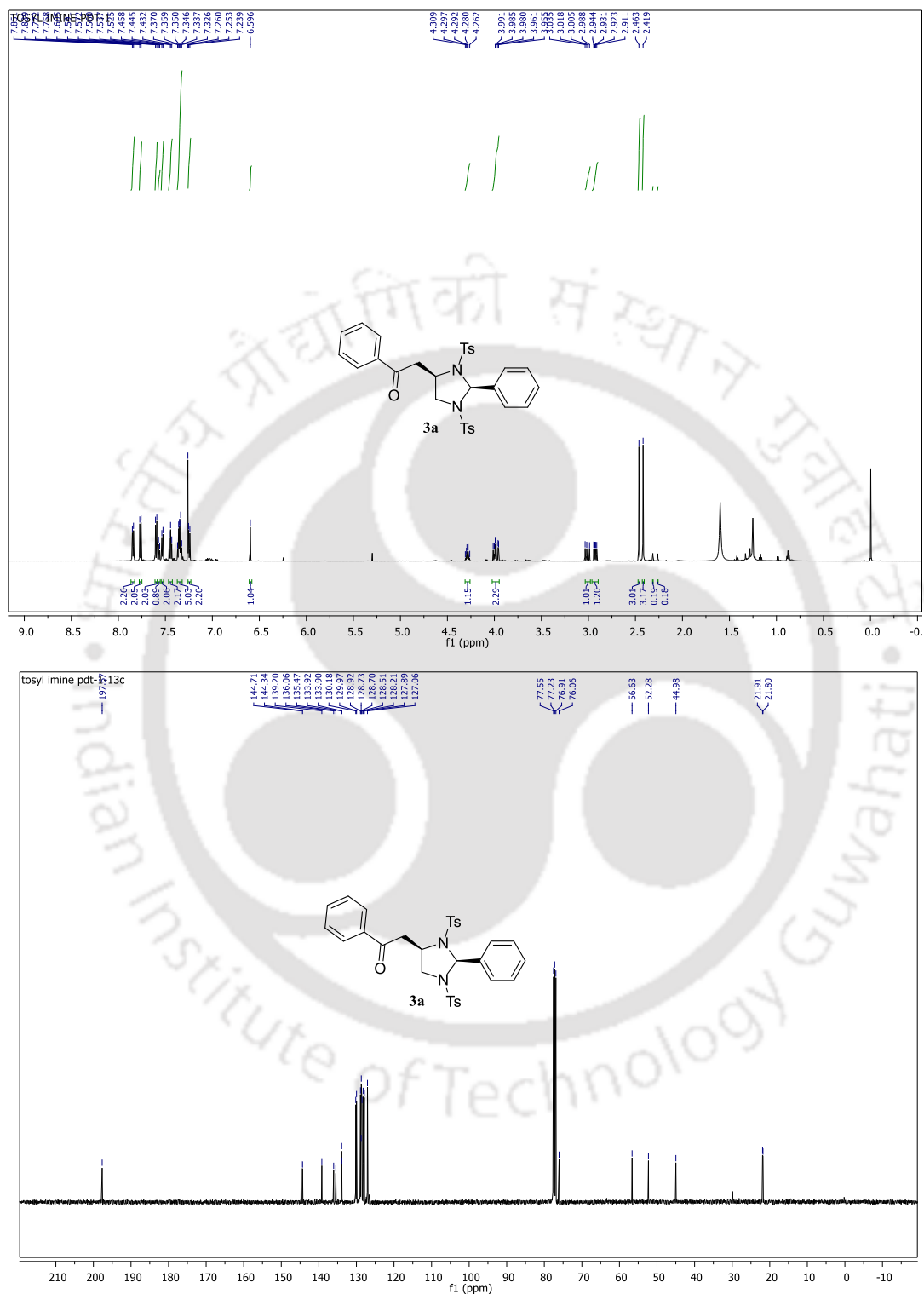
This compound was prepared according to the general procedure F. White sticky solid (40.3 mg, yield: 65%); **Diastereomeric ratio:** 20:1; ^1H

NMR (600 MHz, CDCl_3): δ 7.77 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 6.8 Hz, 2H), 7.34 (dd, J = 7.5, 4.9 Hz, 5H), 7.25 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 6.57 (s, 1H), 4.24 – 4.16 (m, 1H), 3.89 (dd, J = 12.2, 7.3 Hz, 1H), 3.79 (s, 3H), 3.40 (dd, J = 17.2, 4.1

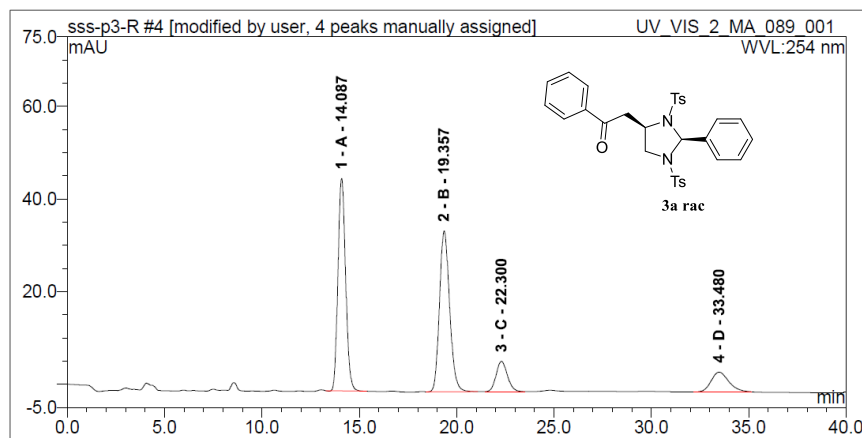
Hz, 1H), 3.05 (dd, $J = 12.2, 7.5$ Hz, 1H), 2.67 (dd, $J = 17.2, 9.8$ Hz, 1H), 2.45 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3): δ 169.7, 157.7, 144.8, 144.5, 143.9, 138.9, 135.3, 134.1, 130.2, 130.1, 128.8, 128.7, 128.5, 128.0, 127.1, 122.3, 114.7, 76.5, 56.2, 55.8, 51.9, 40.0, 21.9, 21.8; FT-IR (thin film): 1752, 1601, 1570, 1504, 1455, 1351, 1249, 1163, 1094, 818 cm^{-1} ; HRMS (+APCI): Calc for $\text{C}_{32}\text{H}_{33}\text{N}_2\text{O}_7\text{S}_2$ $[\text{M}+\text{H}]^+$ 621.1724; found: 621.1724; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (87:13 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 24.2$ min, $\tau_{\text{minor}} = 29.8$ min); Enantiomeric excess: 93%.



2.10. Selected NMR spectra and HPLC chromatogram:

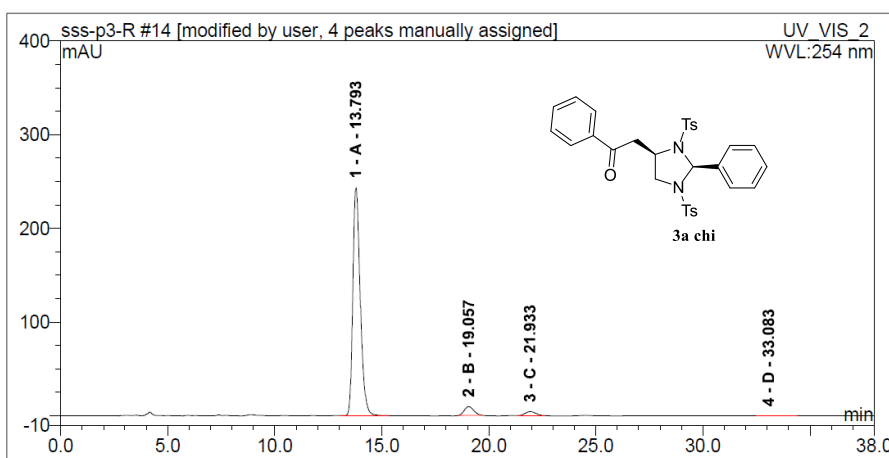


SSS-P3-R

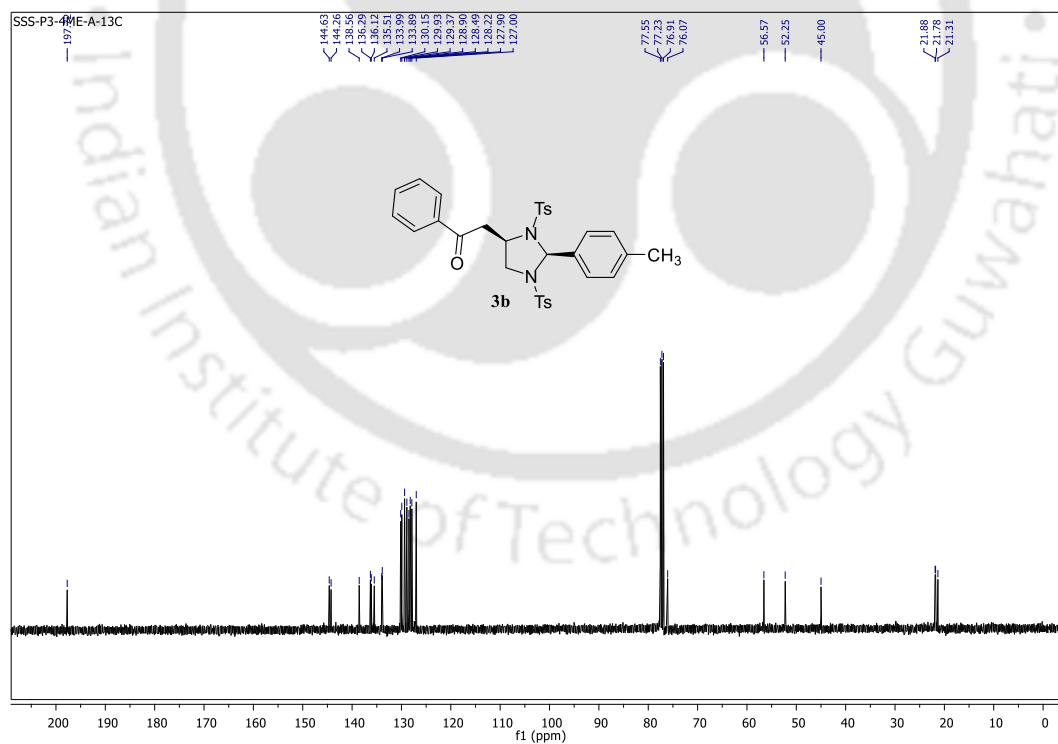
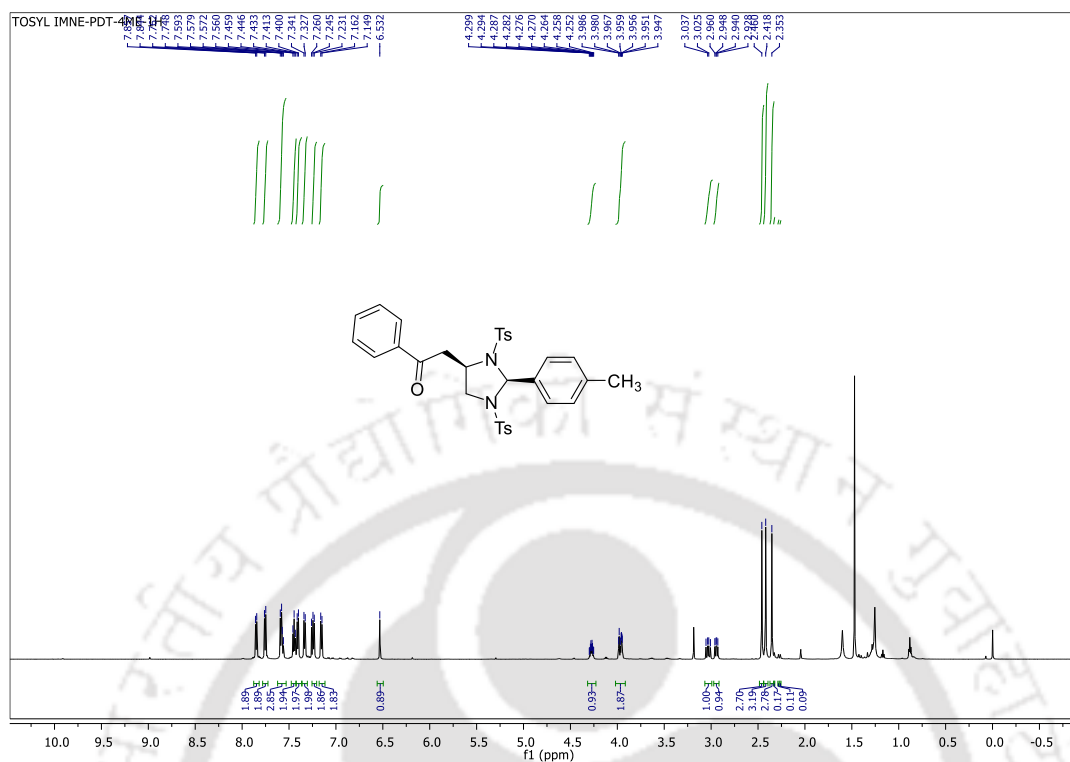


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		14.09	20.89646	41.17071749	45.86199	n.a.
2 B		19.36	21.00237	41.37938791	34.75123	n.a.
3 C		22.30	4.370546	8.610956681	6.537	n.a.
4 D		33.48	4.486	8.838937923	4.273	n.a.

SSS-P3-C

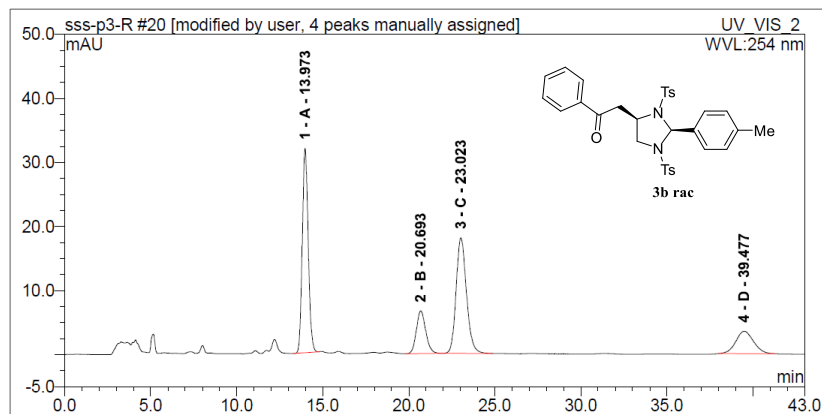


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		13.79	97.35032	92.7899128	243.0535	n.a.
2 B		19.06	4.889236	4.660198289	9.51786	n.a.
3 C		21.93	2.463203	2.347813715	4.28139	n.a.
4 D		33.08	0.212	0.2020751991	0.190	n.a.



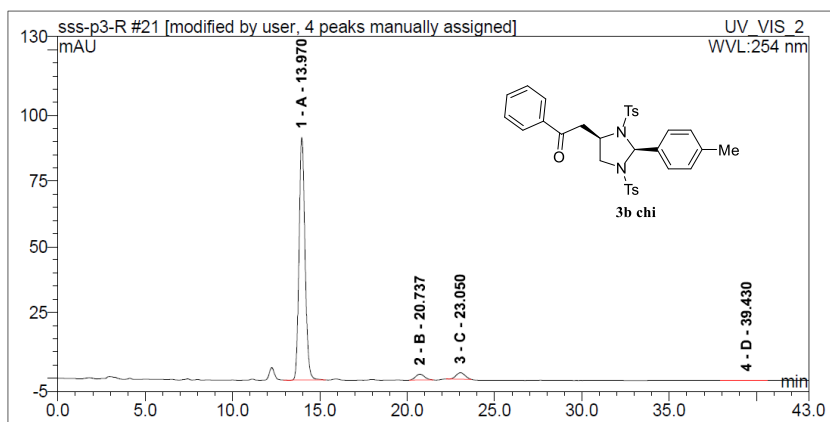
Organocatalytic Asymmetric Synthesis of 2,4-Disubstituted Imidazolidines

SSS-P3-4ME-R

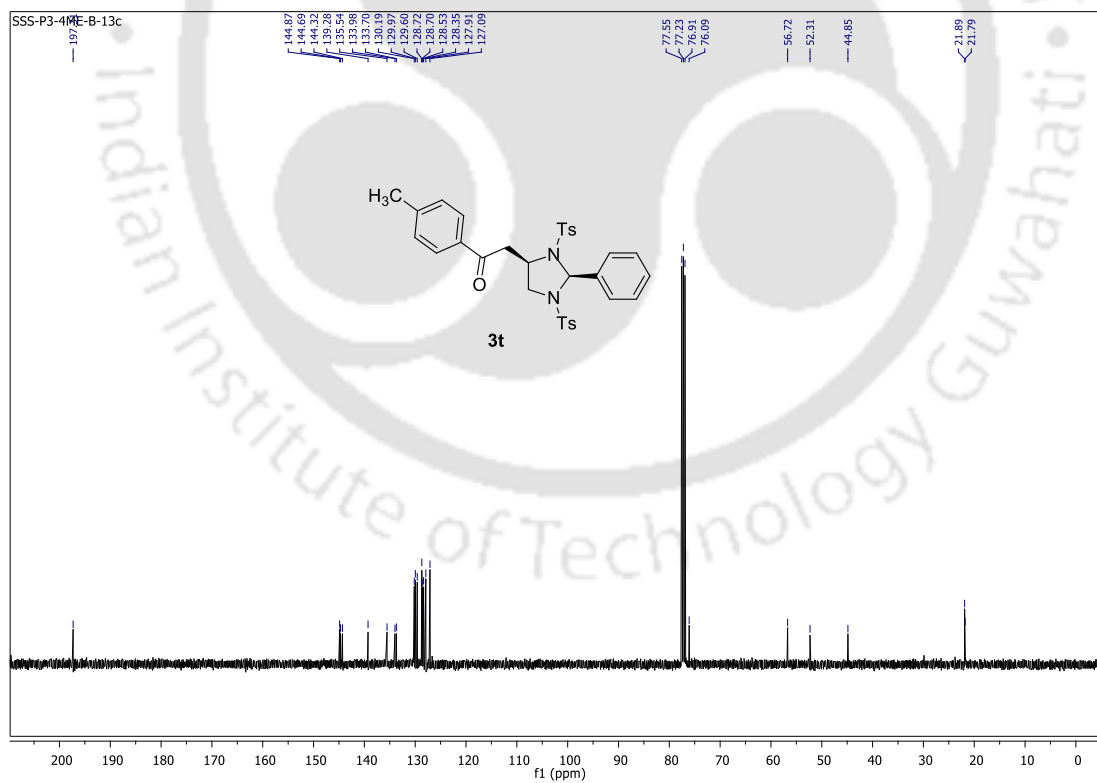
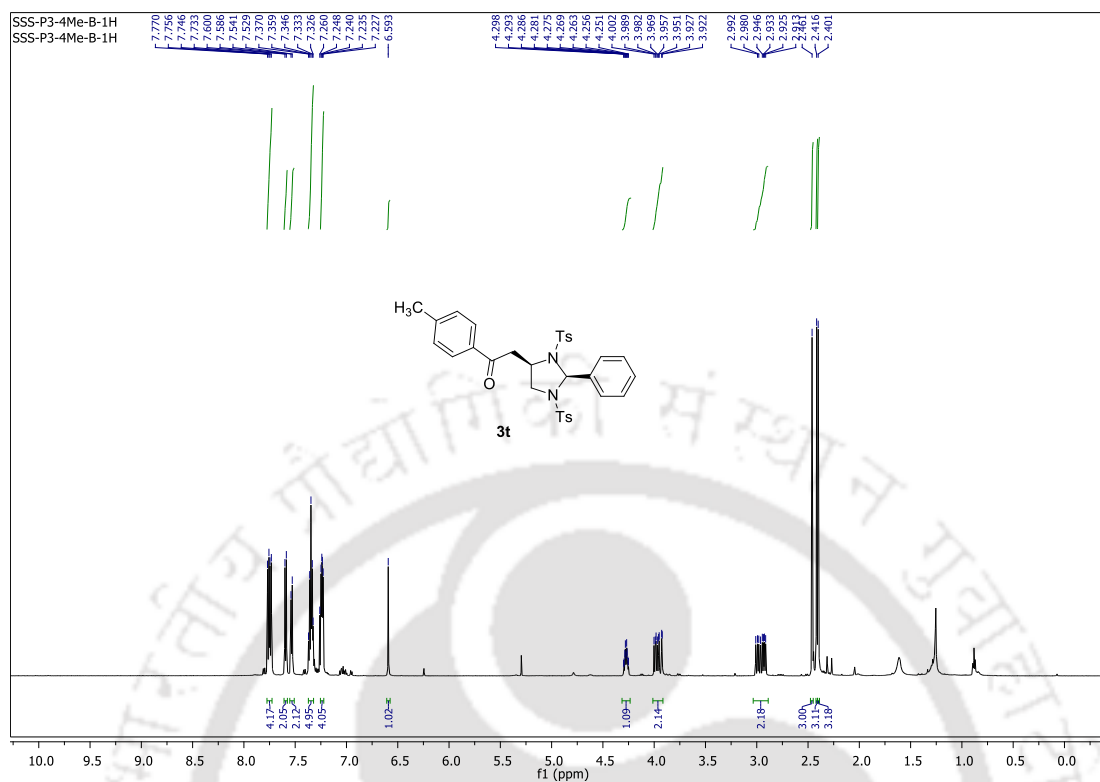


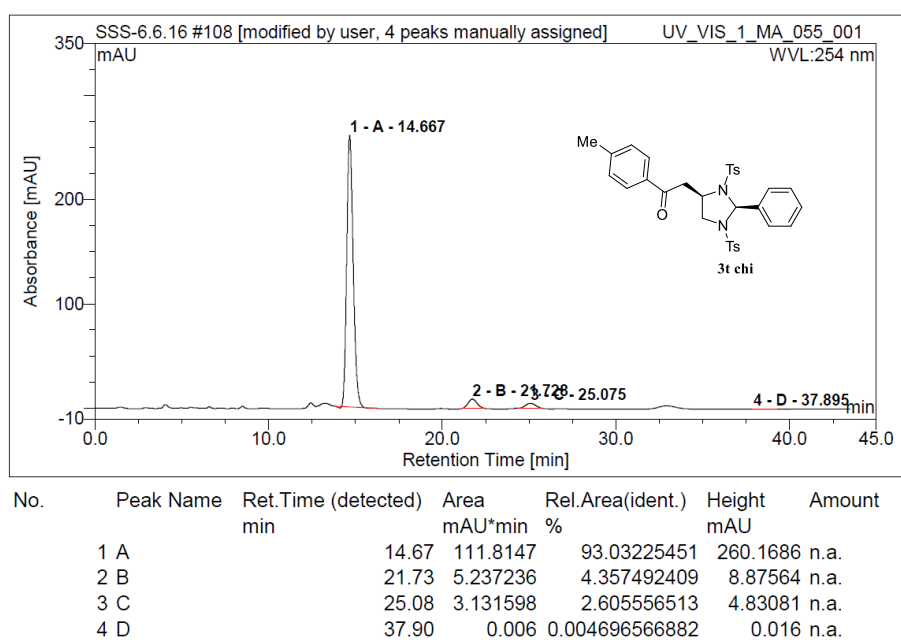
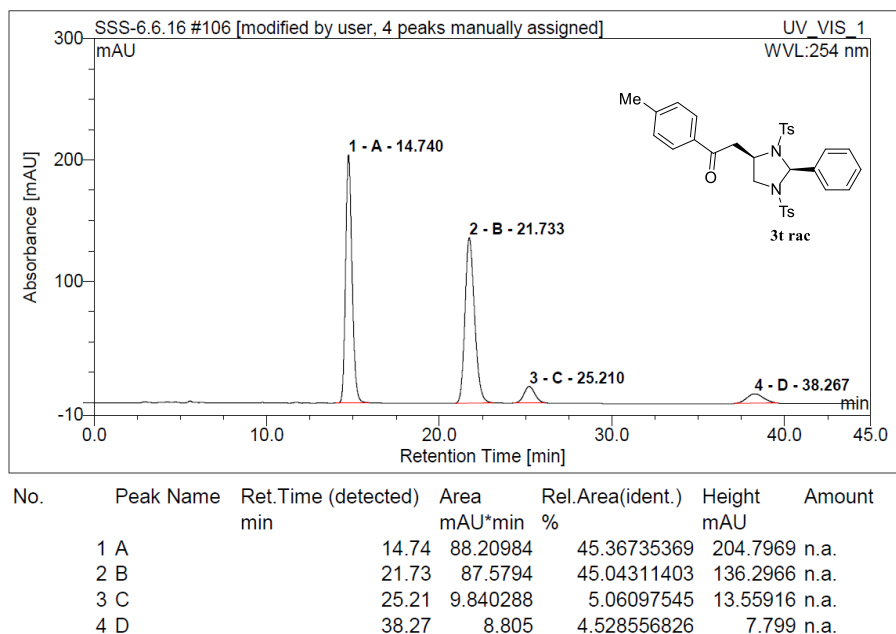
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		13.97	12.65595	37.58155158	31.90634	n.a.
2 B		20.69	4.217285	12.52312798	6.65758	n.a.
3 C		23.02	12.60138	37.41951527	18.05942	n.a.
4 D		39.48	4.201	12.47580517	3.505	n.a.

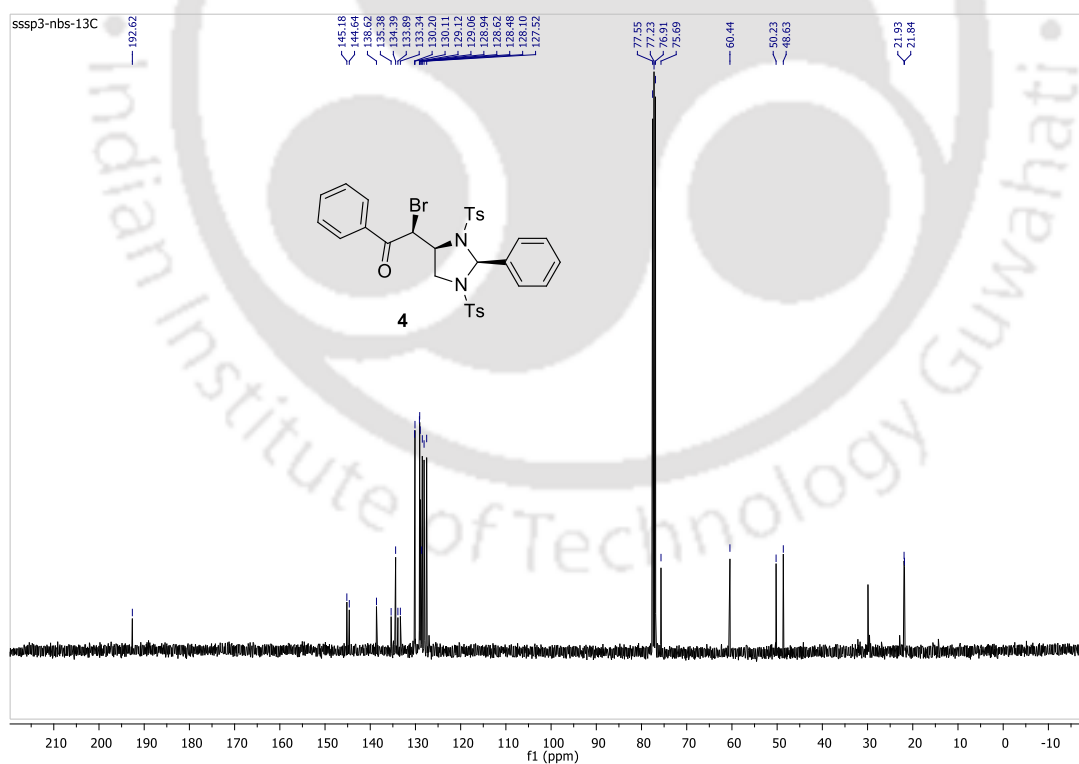
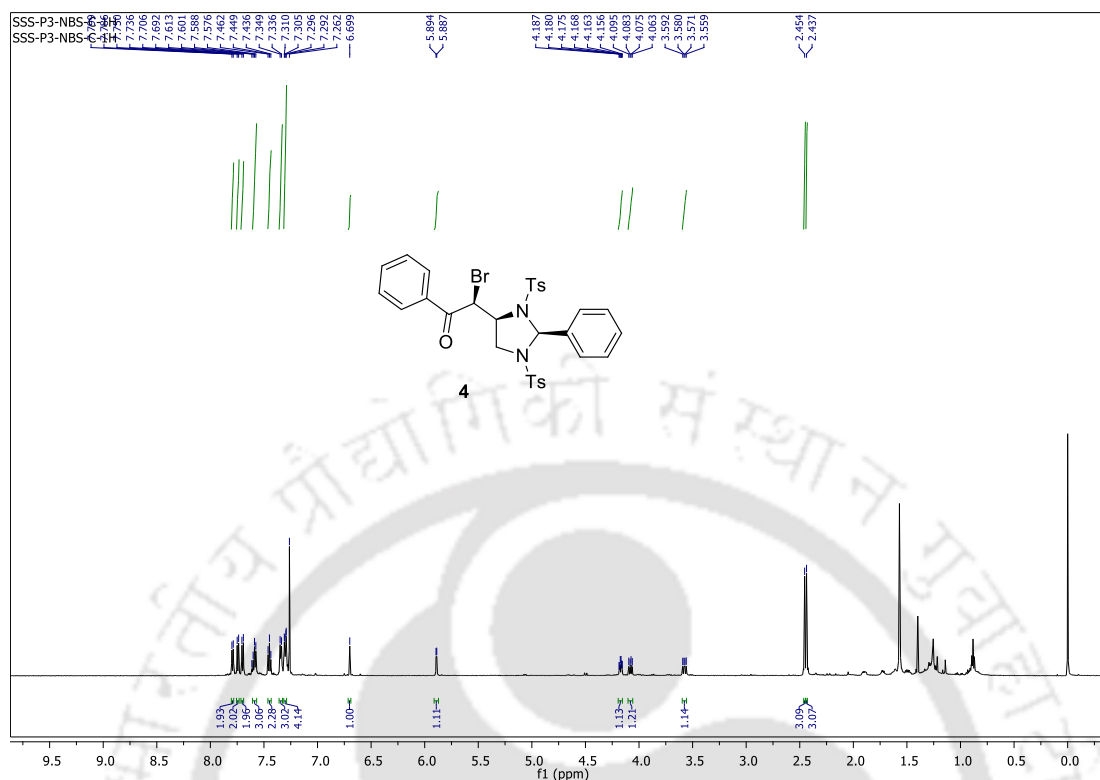
SSS-P3-4ME-C



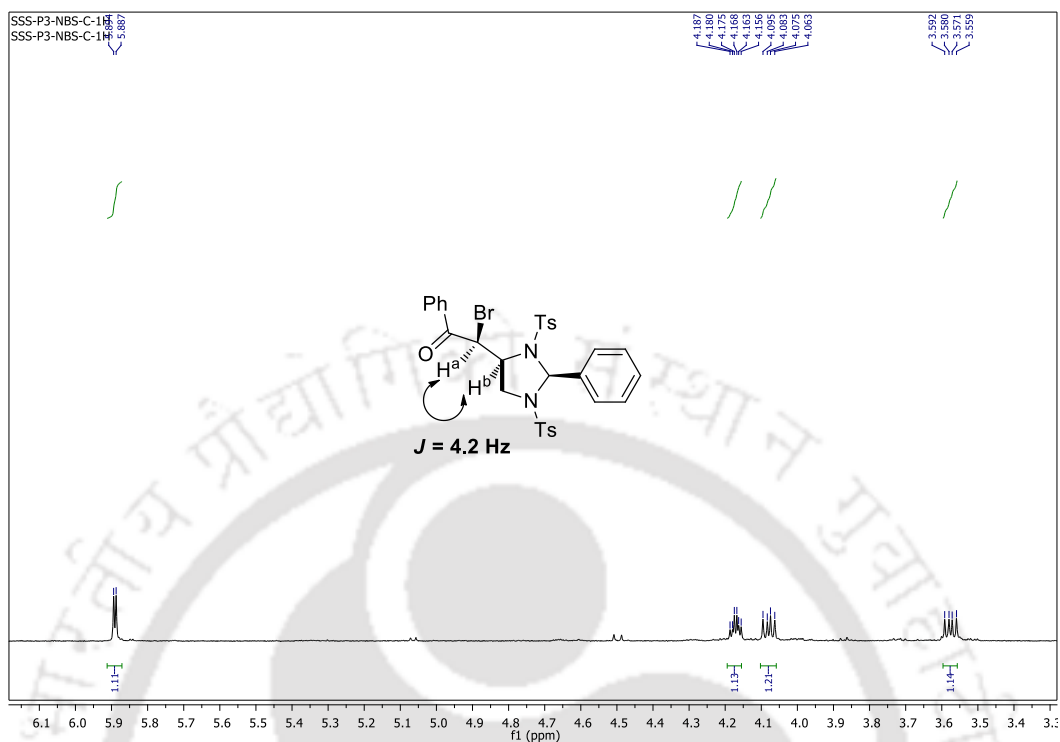
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		13.97	36.53821	92.76407318	92.31777	n.a.
2 B		20.74	1.334463	3.387966453	2.24736	n.a.
3 C		23.05	1.425202	3.618335473	2.42352	n.a.
4 D		39.43	0.090	0.2296248909	0.084	n.a.



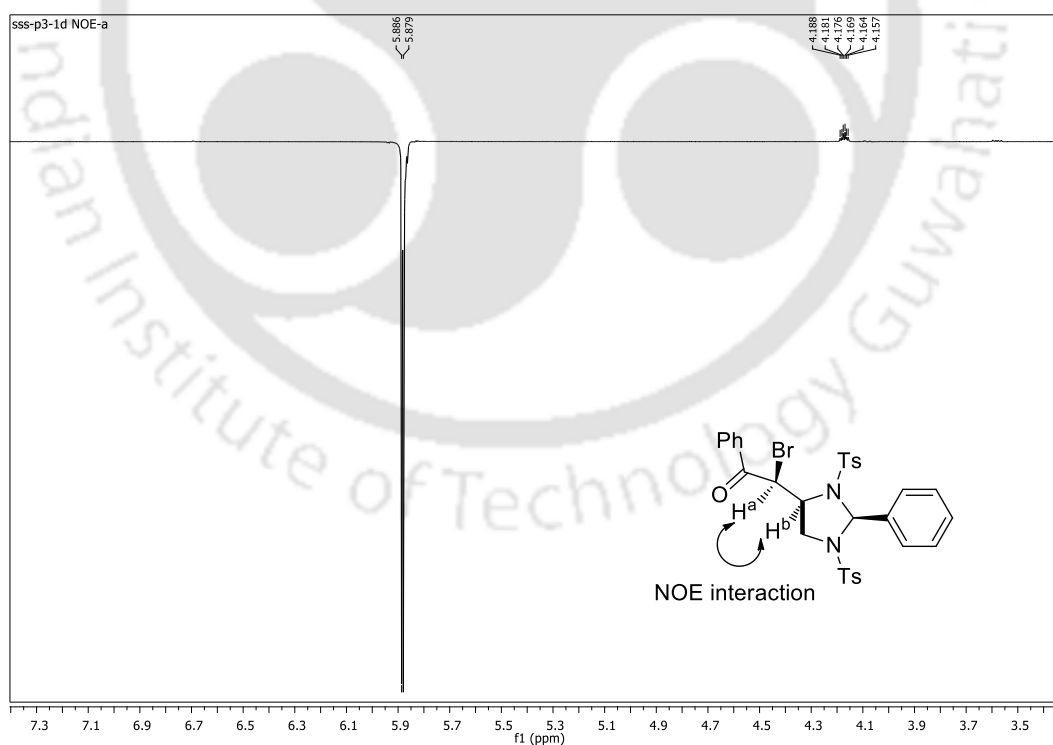


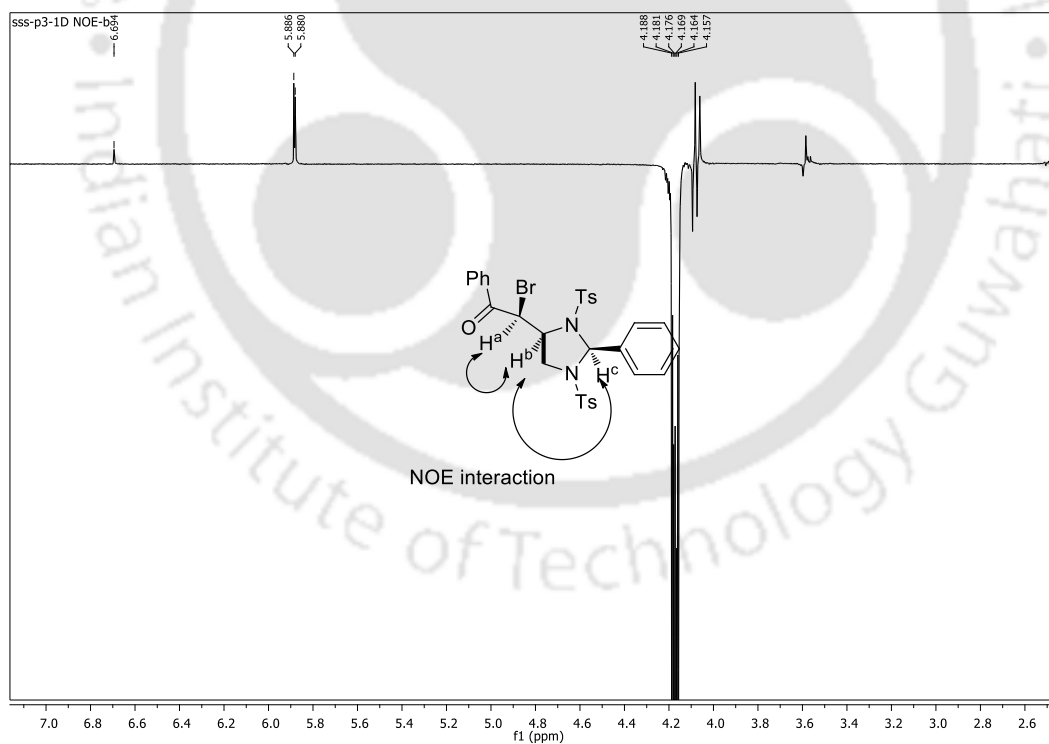
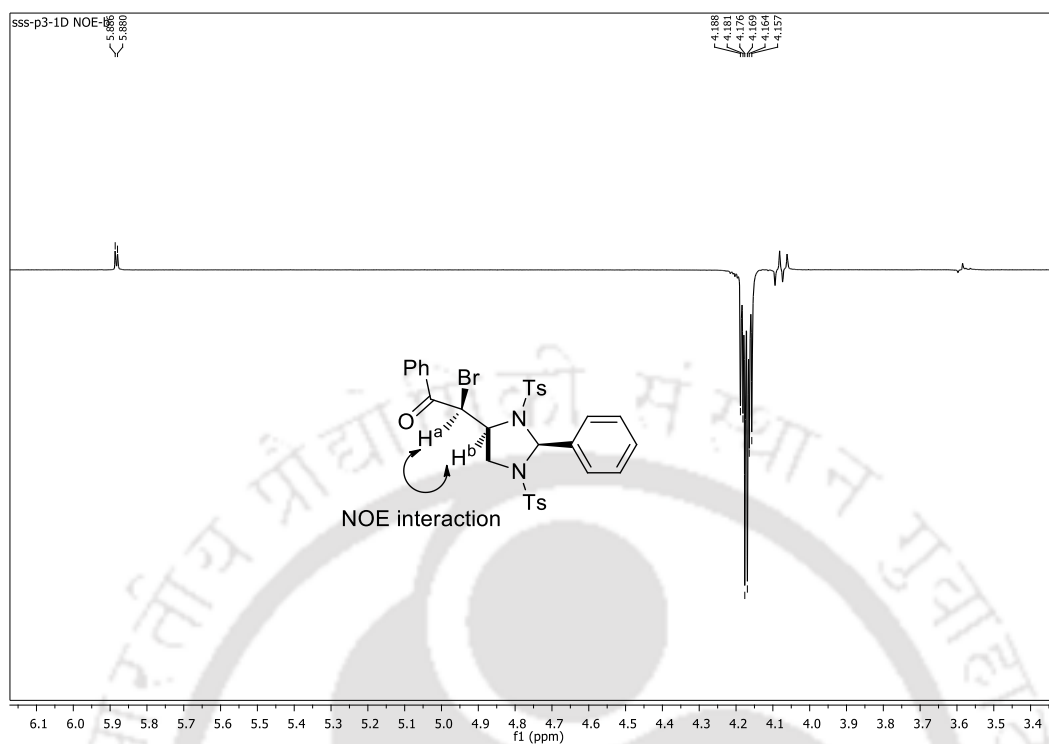


Comparison J value of the adjacent proton for compound 4:



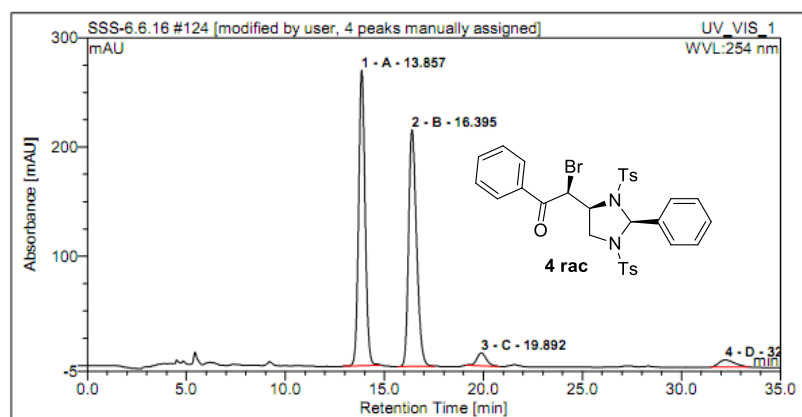
Compound 4 1D NOE of different protons:





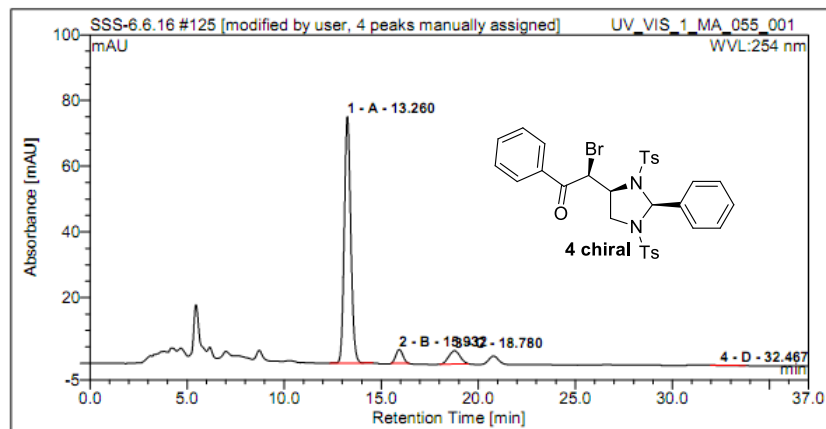
Organocatalytic Asymmetric Synthesis of 2,4-Disubstituted Imidazolidines

SSS-P3-NBS-R

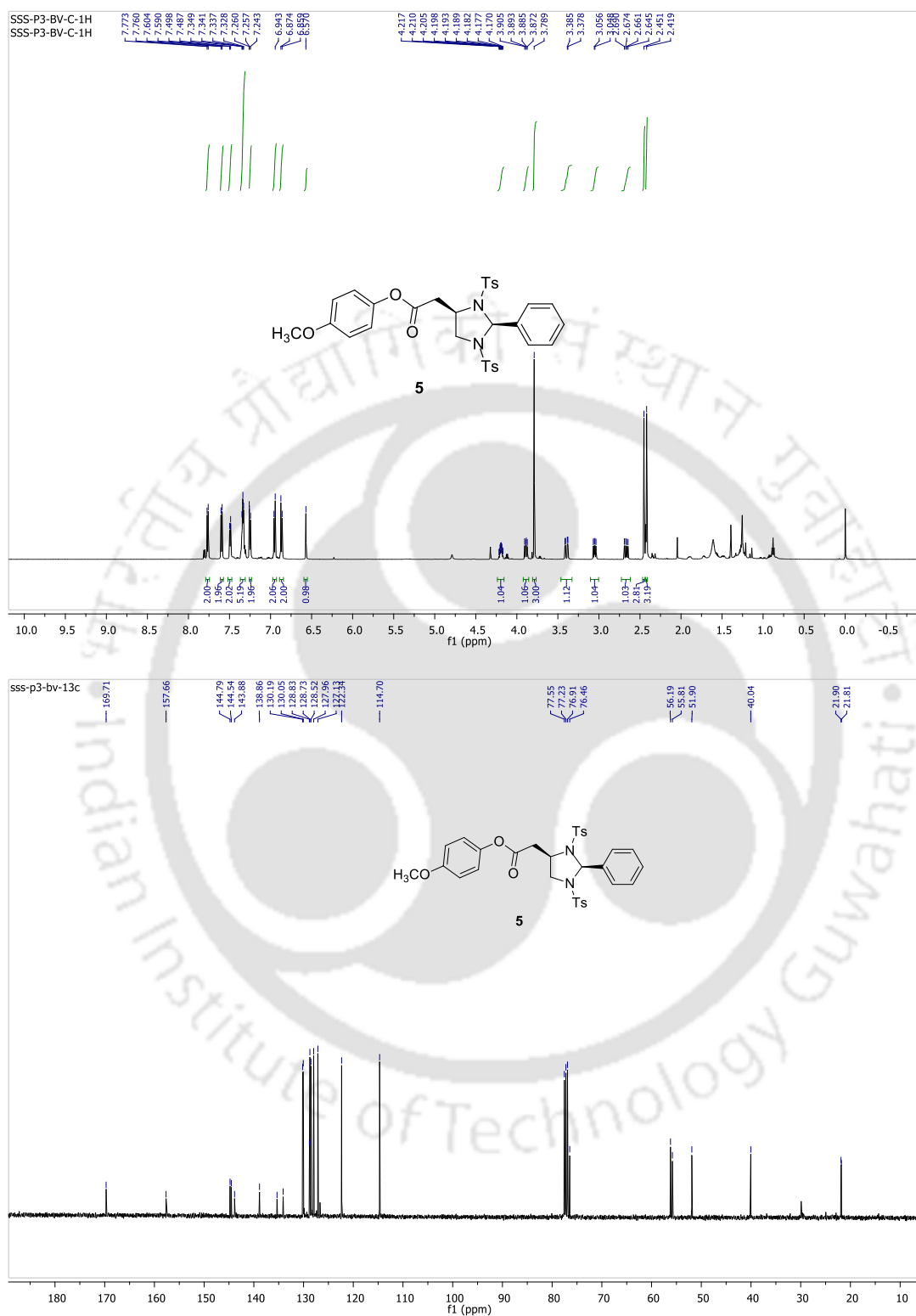


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.86	102.2676	47.44828049	270.6064	n.a.
2	B	16.40	100.8053	46.76982225	216.7069	n.a.
3	C	19.89	6.49195	3.012018459	11.6778	n.a.
4	D	32.22	5.970	2.769878803	6.444	n.a.

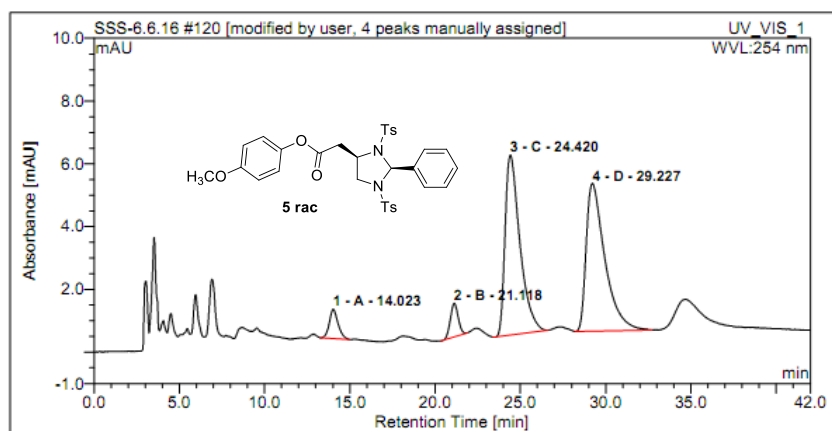
SSS-P3-NBS-C



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.26	29.20714	86.49684898	75.16062	n.a.
2	B	15.93	1.79941	5.328945192	4.23263	n.a.
3	C	18.78	2.713036	8.034647878	4.03434	n.a.
4	D	32.47	0.047	0.1395579529	0.045	n.a.

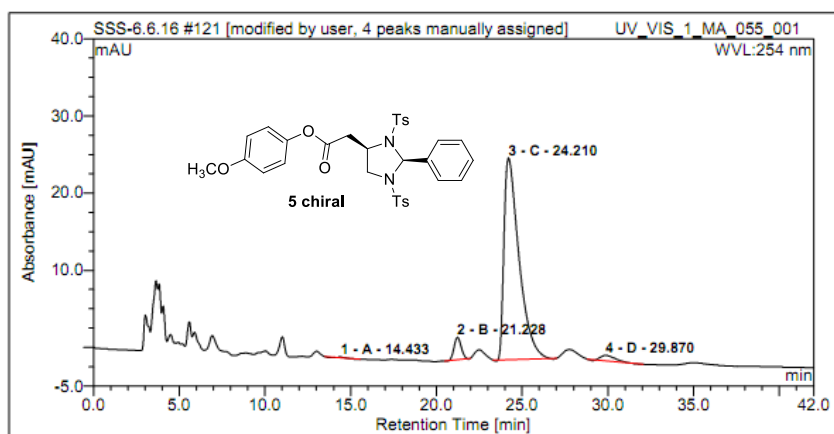


SSS-P3-BV-R



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		14.02	0.555169	4.323580805	0.93296	n.a.
2 B		21.12	0.567634	4.420650888	1.0685	n.a.
3 C		24.42	5.761318	44.86833296	5.72664	n.a.
4 D		29.23	5.956	46.38743535	4.701	n.a.

SSS-P3-BV-c



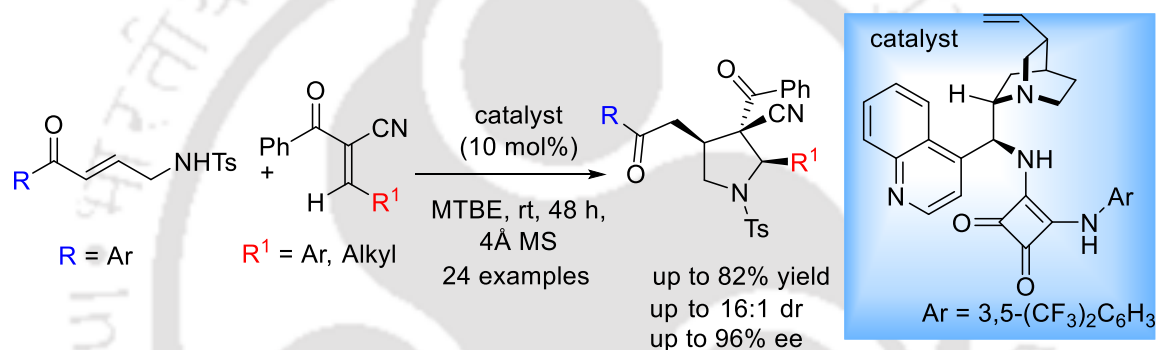
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		14.43	0.011724	0.04107684971	0.10592	n.a.
2 B		21.23	1.366432	4.78746524	2.89477	n.a.
3 C		24.21	26.50578	92.86629921	26.13889	n.a.
4 D		29.87	0.658	2.305158703	0.692	n.a.



Chapter 3

Organocatalytic Asymmetric Synthesis of Highly Substituted Pyrrolidines Bearing Stereogenic Quaternary Centre at 3- Position

Abstract: An organocatalytic asymmetric cascade reaction has been developed for the synthesis of highly substituted pyrrolidines having stereogenic quaternary centre at 3-position. *N*-tosyl aminomethyl enone and *trans*- α -cyano- α,β -unsaturated ketone were utilized as the reaction partners in this method. Cinchonidine derived bifunctional amino-squaramide catalyst was the best to provide the products in high enantio- and diastereoselectivities.





3.1. Introduction:

Highly functionalized optically active pyrrolidines are versatile structural motifs which are prevalent in many biologically active natural products and are present in range of pharmaceutical agents (Figure 1).¹ Optically active highly substituted pyrrolidine moieties are the core structures of many natural products and drugs.² Compounds containing chiral pyrrolidine motifs have impressive biological activities such as neuroexcitatory amino acid antagonist, antidiabetic, antimicrobial activities and used as local anesthetic drugs.² Moreover, optically active pyrrolidines have numerous applications in asymmetric synthesis.

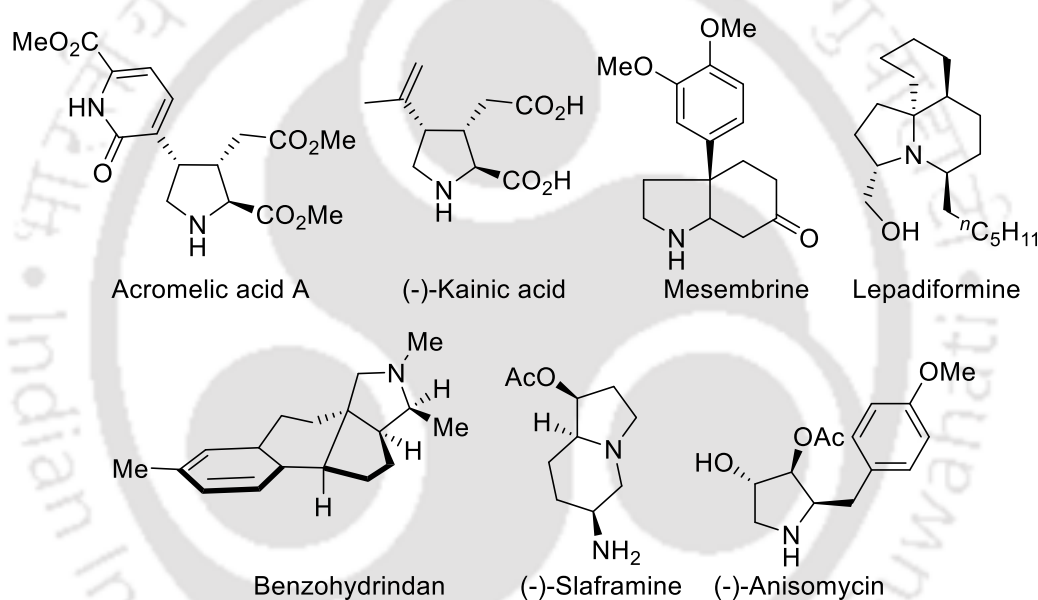
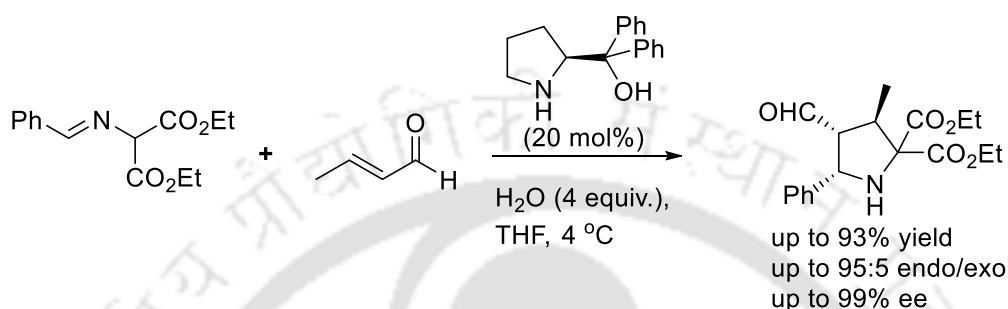


Figure 1: Representative naturally occurring alkaloids having pyrrolidine skeleton

They are widely used as ligands in metal mediated reactions³ and as organocatalysts for a variety of enantioselective transformations.⁴ Thus pyrrolidine motif has drawn significant attention from synthetic organic chemists, and a variety of enantioselective methods have been developed. In recent years both transition metal catalyzed and organocatalytic approaches have been documented.^{5,6} Despite so many methods, pyrrolidines having a stereogenic quaternary centre⁷ have been less reported though such skeleton is present in mesembrine, lepadiformine and benzohydrindan etc.⁸

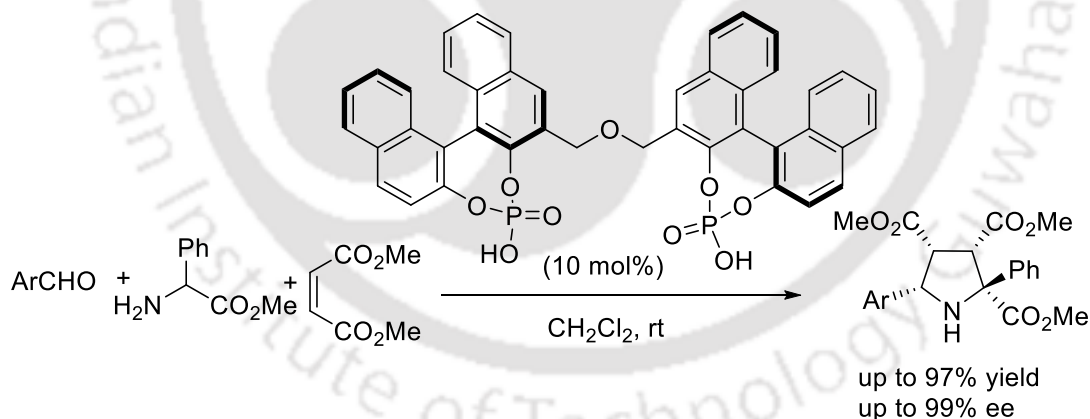
3.2. Reported strategies for the synthesis of chiral pyrrolidines:

Jose L. Vicario and coworkers reported α,α -diphenylprolinol catalyzed organocatalytic enantioselective [3+2] cycloaddition reaction between α,β -unsaturated aldehydes with azomethine ylides for the synthesis of enantiomerically enriched pyrrolidines with good yields and high enantiomeric excesses (Scheme 3.1).⁹



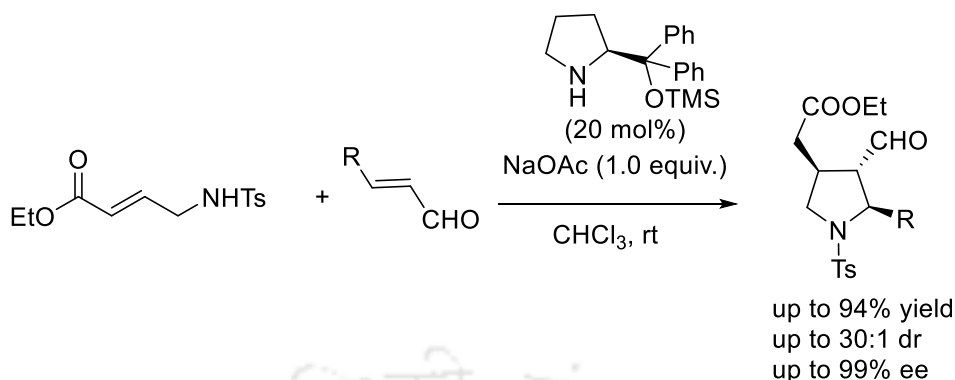
Scheme 3.1: Enantioselective [3+2] cycloaddition reaction for the synthesis of pyrrolidines

In 2011, Gong *et al.* explored a [3+2] cycloaddition reaction between maleic ester and *in situ* generated azo-methine ylides from aldehydes and α -arylglycine methyl esters to generate highly substituted pyrrolidines having a stereogenic quaternary centre at 2-position (Scheme 3.2).¹⁰



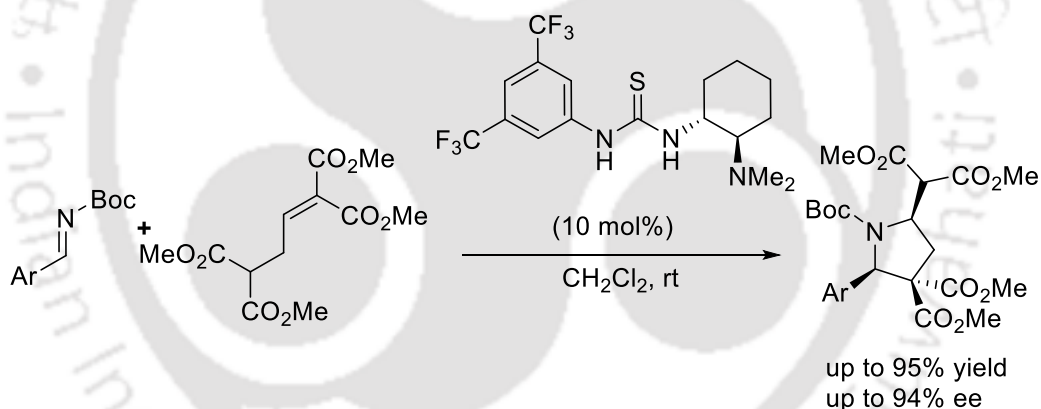
Scheme 3.2: Phosphoric acid mediated cycloaddition for the construction of chiral pyrrolidines

A highly enantio and diastereoselective domino *aza*-Michael addition approach for the synthesis of highly substituted pyrrolidines had been developed by Wang group (Scheme 3.3).¹¹



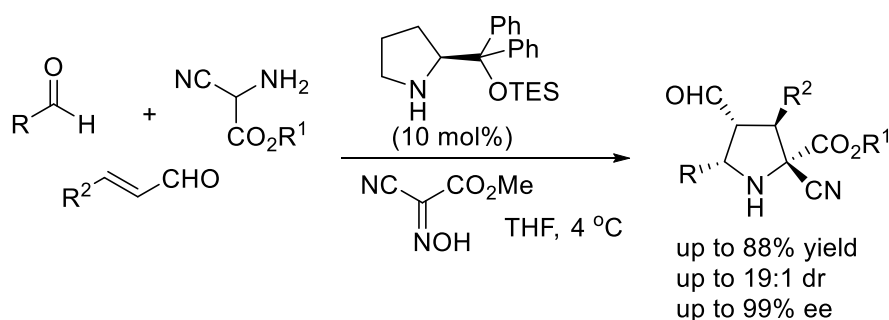
Scheme 3.3: Secondary amine catalyzed enantioselective domino addition for the synthesis of pyrrolidines

Dieter Enders *et al.* revealed bifunctional thiourea catalyzed domino Mannich/*aza*-Michael reaction of γ -malonate substituted α,β -unsaturated esters and N-protected aldimines for the synthesis of polysubstituted pyrrolidines with excellent enantioselectivities (Scheme 3.4).¹²



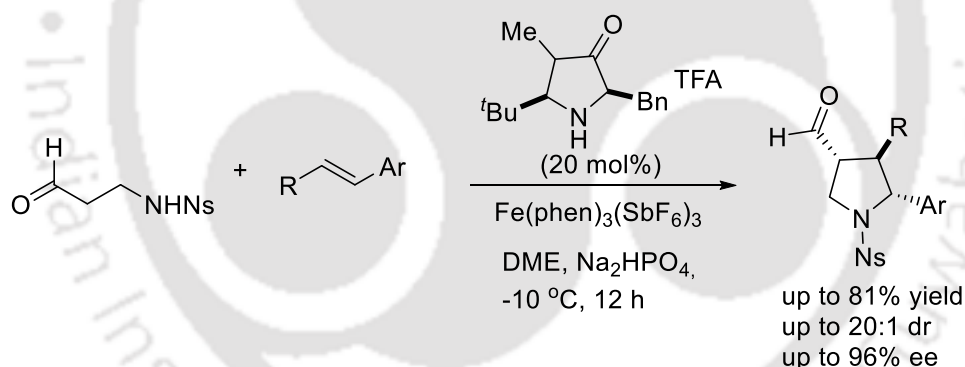
Scheme 3.4: Thiourea catalyzed domino Mannich/*aza*-Michael reaction for the synthesis of pyrrolidines

Cordova group disclosed [3+2] cycloaddition reaction between aldehydes, protected α -cyanoglycine esters and enals for the synthesis of polysubstituted pyrrolidines. A combination of chiral secondary amine catalyst and hydrogen bond donating catalyst were found to be effective to achieve high diastereo and enantioselectivities (Scheme 3.5).¹³



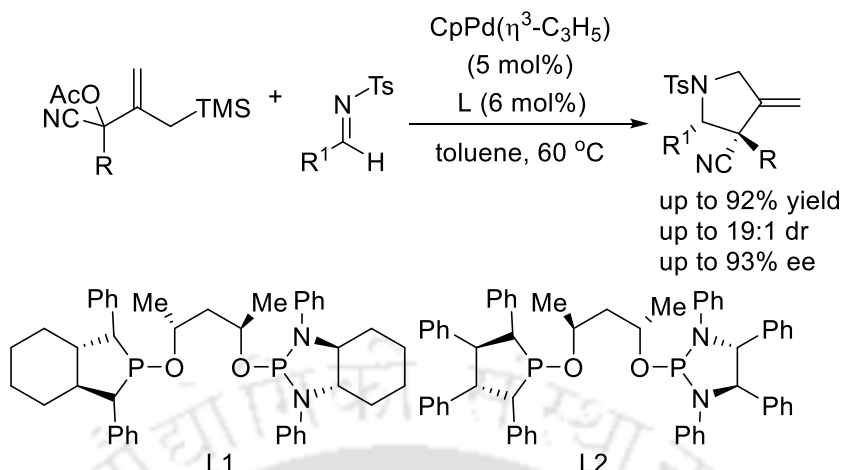
Scheme 3.5: [3+2] cycloaddition for synthesis of polysubstituted pyrrolidines

An enantioselective organo-SOMO cycloaddition strategy for the synthesis of chiral substituted pyrrolidines derivatives has been proposed by MacMillan group. A new method of SOMO-activated enantioselective [3+2] couplings of aldehydes and conjugated olefins has been explored to furnish the desired pyrrolidine moieties which were isolated with moderate to good diastereomeric ratio and good enantioselectivities (Scheme 3.6).¹⁴



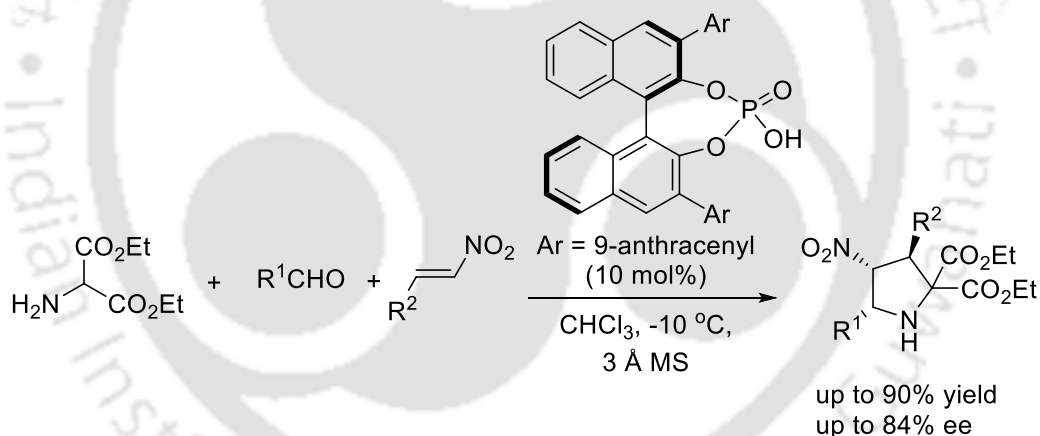
Scheme 3.6: Enantioselective organo-SOMO cycloaddition

Herbage and coworkers have described Pd-catalyzed asymmetric [3+2] cycloaddition of trimethylenemethanes for the synthesis of substituted pyrrolidines bearing all carbon quaternary centres (Scheme 3.7).¹⁵



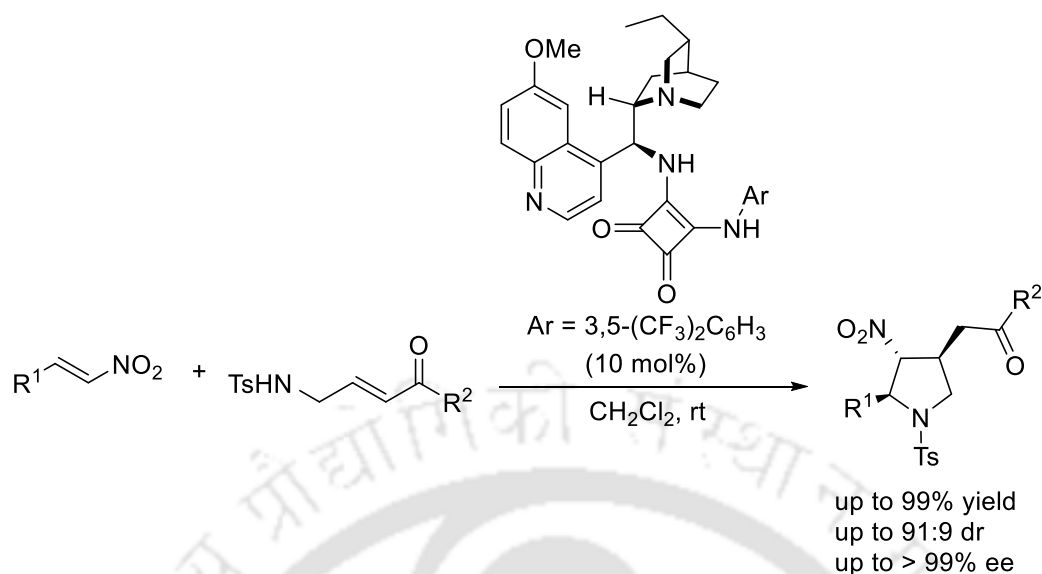
Scheme 3.7: Pd-catalyzed asymmetric synthesis of substituted pyrrolidines

He and coworkers manifested a phosphoric acid catalyzed one-pot three component 1,3-dipolar cycloaddition reaction of an aldehyde, α -aminomalonate, and nitroolefin for the enantioselective synthesis of structurally diverse pyrrolidine derivatives (Scheme 3.8).¹⁶



Scheme 3.8: Phosphoric acid catalyzed synthesis of pyrrolidine derivatives

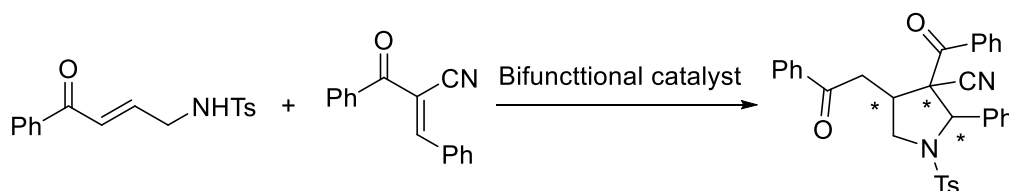
A chiral bifunctional squaramide catalyzed synthesis of chiral polysubstituted pyrrolidines *via* domino *aza*-Michael/Michael addition between tosyl amino methyl enones and nitroolefins has been reported by Du *et al.* epi-Hydroquinine derived bifunctional squaramide catalyst afforded the desired products in good diastereo and enantioselectivities (Scheme 8).¹⁷

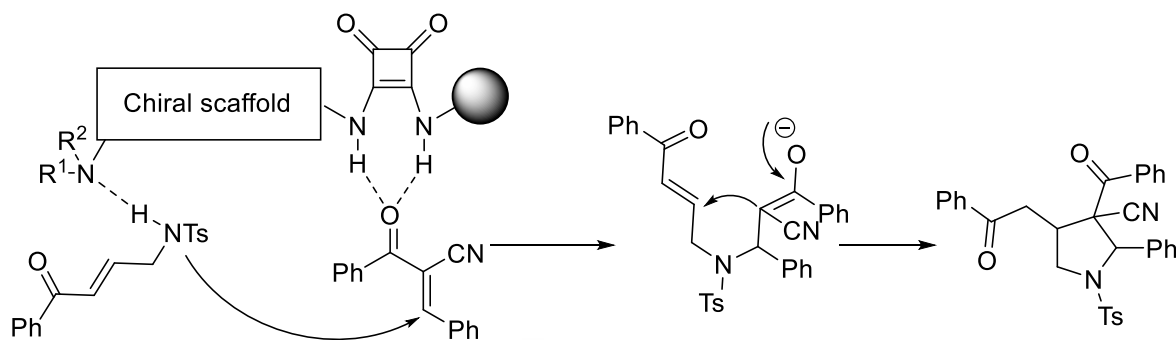


Scheme 3.9: Squaramide catalyzed synthesis of chiral pyrrolidines

3.3. Concept:

Chiral polysubstituted pyrrolidines are important structural intermediates present in many natural products and frequently observed in a plethora of pharmaceutical agents. Besides, pyrrolidine cores are widely used both as organocatalysts and as ligand in many enantioselective transformations. However, simple pyrrolidines having stereogenic centre at 3-position was hardly reported.¹⁸ Realizing the potential of pyrrolidines in bioactive compounds, we embarked in a convenient synthesis of highly substituted pyrrolidines having stereogenic centre at 3-position. We used tosyl amino methyl enone and *trans*- α -cyano- α,β -unsaturated ketone as the substrate. The carbonyl functionality of *trans*- α -cyano- α,β -unsaturated ketone would be activated by the thiourea or the squaramide motifs. Tertiary amine part of catalyst would abstract the proton from the amino methyl enones and the corresponding cascade reaction would take place to deliver the desired product (Scheme 3.10).





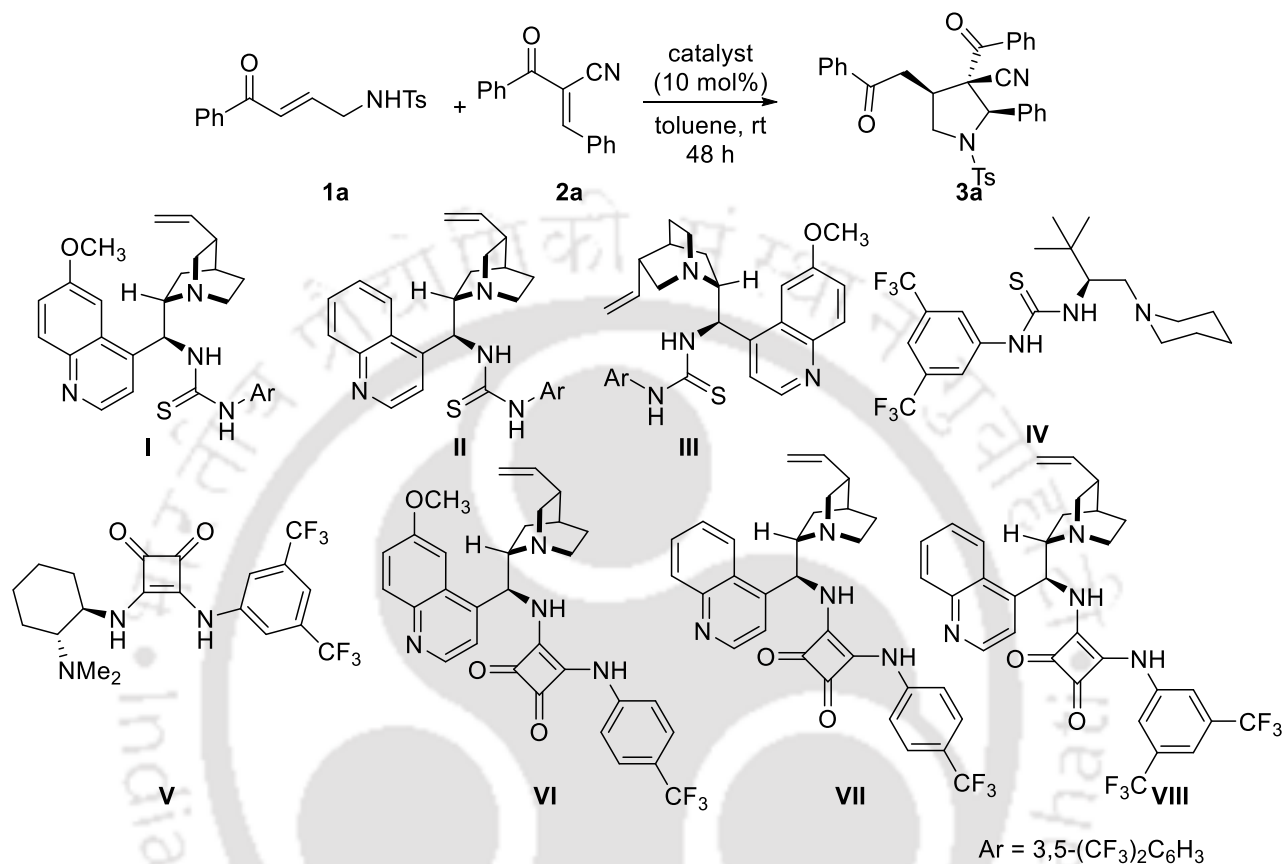
Scheme 3.10: Plausible route for the synthesis of pyrrolidines

3.4. Result and discussion:

We started an experiment by performing a model cascade reaction between *N*-tosyl aminomethyl enone **1a**¹⁹ and *trans*- α -cyano- α,β -unsaturated ketone **2a** in the presence of quinine derived bifunctional thiourea catalyst **I** in toluene solvent at room temperature (Table 1). To our delight, after stirring for 2 days, the expected pyrrolidine product **3a** was obtained in 60% yield and 10:1 diastereomeric ratio in moderate enantiomeric excess (entry 1). Similar enantioselectivity was detected with cinchonidine derived catalyst **II** (entry 2). Enantioselectivity slight decreased with quinidine derived thiourea catalyst **III** (entry 3). Interestingly the enantioselectivity got slightly enhanced to 45% ee with *tert*-leucine derived bifunctional thiourea catalyst **IV** (entry 4) though diastereomeric ratio remained same. To improve the enantio and diastereoselectivity for the product, we turned our attention to employ different squaramide catalysts in the reaction. For example, with cyclohexyl derived squaramide catalyst **V**, the diastereomeric ratio for the product got improved to 15:1 but enantioselectivity did not improve (entry 5). Then different cinchona alkaloid derived squaramide catalysts were employed in the reaction (entries 6-8). Gratifyingly, these catalysts were found to be effective for our reaction and a higher diastereo- as well as enantioselectivities were attained. Quinine derived squaramide catalyst **VI** bearing 4-trifluoromethyl moiety provided the product in 72% yield, 15:1 diastereomeric ratio and 50% enantiomeric excess (entry 6). The enantioselectivity was slightly improved to 55% with cinchonidine derived squaramide catalyst **VII** (entry 7). Finally the best catalyst was found to be **VIII**

having bis trifluoromethyl substituted aryl group and the product **3a** was obtained in 78% yield with 15:1 dr and 60% ee (entry 8).

Table 1. Catalyst screening



entry ^a	catalyst	yield(%) ^b	dr ^c	ee(%) ^d
1	I	60	10:1	30
2	II	62	10:1	31
3	III	65	10:1	25
4	IV	68	10:1	45
5	V	70	15:1	45
6	VI	72	15:1	50
7	VII	75	15:1	55
8	VIII	78	15:1	60

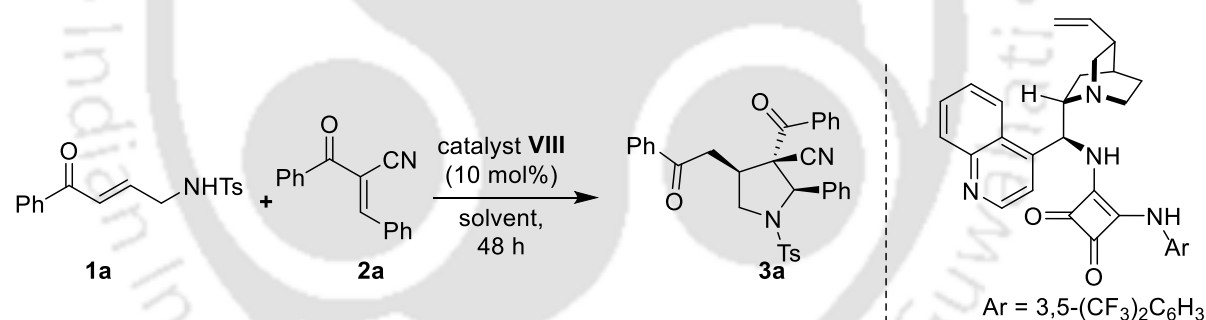
^aReaction condition: 0.05 mmol of **1a** with 0.075 mmol of **2a** in 0.2 mL solvent using 10 mol% catalyst at room temperature for 2 days. ^bIsolated combined yield after silica gel column chromatography.

^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC. ^eWith 4Å MS.

3.4.1. Solvent screening:

To enhance the enantioselectivity, the reaction was carried out with catalyst **VIII** in different solvents (Table 2). In trifluorotoluene solvent the desired product was isolated with similar enantio and diastereoselectivity (entry 2). Mixed results were obtained in halogenated solvents (entries 3-5). For example, enantioselectivity got decreased in dichloromethane solvent (entry 3). In 1,2-dichloroethane solvent the product was isolated with 15:1 diastereomeric ratio and 50% enantiomeric excess (entry 4). Interestingly, with chloroform solvent the enantioselectivity got improved to 63% with similar diastereomeric ratio (entry 5). Then we became interested to screen different ether solvents. Diethyl ether solvent provided **3a** in 79% yield with 68% ee (entry 6). Gratifyingly, the enantioselectivity for the product **3a** got promoted to 89% in MTBE solvent (entry 7). Finally, the best result was obtained in MTBE solvent using 4Å molecular sieves and **3a** was isolated in 80% yield with 15:1 dr and 91% ee (entry 8).

Table 2. Solvent screening



entry ^a	solvent	yield (%) ^b	dr ^c	ee(%) ^d
1	toluene	78	15:1	60
2	TFT	78	15:1	61
3	CH ₂ Cl ₂	75	15:1	43
4	DCE	71	15:1	50
5	CHCl ₃	76	15:1	63
6	Et ₂ O	79	15:1	68
7	MTBE	80	15:1	89

8 ^e	MTBE	80	15:1	91
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^aReaction condition: 0.05 mmol of **1a** with 0.075 mmol of **2a** in 0.2 mL solvent using 10 mol% catalyst at room temperature for 2 days. ^bIsolated combined yield after silica gel column chromatography.

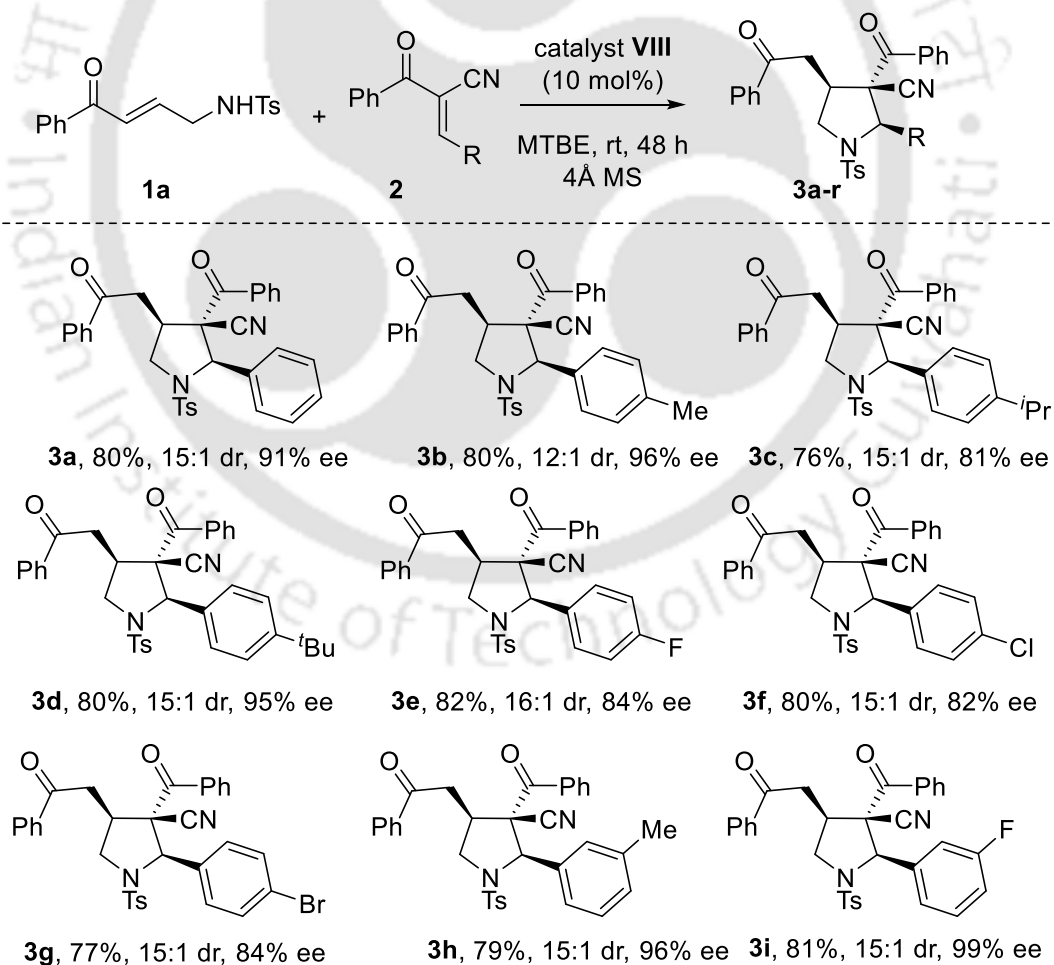
^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC. ^eWith 4Å MS.

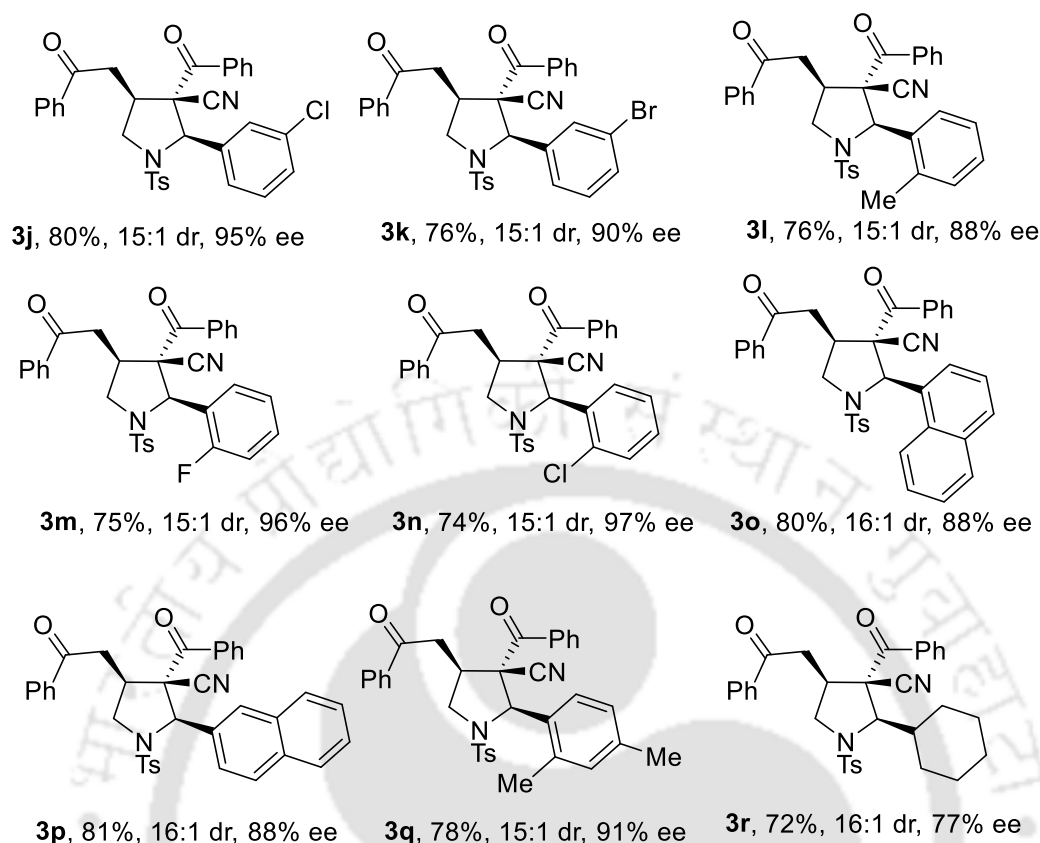
3.4.2. Substrate scope:

Having established the optimal conditions for the corresponding cascade reaction, the scope and generality of the reaction has been explored. Initially the olefin substitution of *trans*- α -cyano-enone **2** was varied and examined under the reaction conditions with **1a** (Table 3). In general, the diastereoselectivity remained very high (10:1 to 15:1 dr) for different aryl substituted α -cyano-enones. Delightfully, different substitutions on the aryl groups were tolerated to afford the desired pyrrolidine derivatives with good to excellent enantiomeric excesses. Initially different 4-alkylsubstituted aryl group containing enones were engaged in the reaction. Enone having *para*-tolyl moiety delivered product **3b** with 80% yield, 12:1 diastereomeric ratio and 96% enantiomeric excess. Then enones having 4-*t*Bu group and 4-*i*Pr group reacted smoothly to provide the expected products **3c** and **3d** respectively. In case of 4-*i*Pr substituted enone the product **3c** was obtained with slight diminution in enantioselectivity. But 4-*t*Bu substituted enone provided the product **3d** with excellent enantioselectivity. Similarly, different 4-halo substituted enones reacted smoothly to provide products **3e-3g** in acceptable yields with good enantioselectivities. 4-Fluoro substituted enone took part readily and delivered the product **3e** in 82% yield with 16:1 diastereomeric ratio and 84% enantiomeric excess. In case of 4-Cl and 4-Br substituted enones, the desired products **3f** and **3g** were obtained in good enantioselectivities and as single diastereomer. In case of 4-Cl and 4-Br substituted enones the desired products **3f** and **3g** were obtained with excellent diastereomeric ratios and good enantiomeric excesses. In the next part of the substrate scope study different *meta*-substituted enones were investigated. Pleasingly, excellent enantio and diastereoselectivities were obtained for products **3h-3k**. For example, enone bearing *meta*-tolyl substituent provided the product **3h** in 76% yield, 15:1 diastereomeric ratio and 96% enantiomeric excess. Notably, product **3i** having *meta*-fluoro phenyl group was isolated in 81% yield with 15:1 dr and 99% ee. Enone having *meta*-chloro motif reacted smoothly to deliver product **3j** with high enantio and diastereomeric ratio. Promising

result was obtained for *meta*-bromo substituted enone. Then *ortho*-substituted enones **2l-2n** were screened and gratifyingly very satisfactory results were achieved. Though excellent enantioselectivities were detected for products **3m-3n** having 2-halo substitutions, slight lower enantioselectivity was detected for **3l** having *ortho*-tolyl group. Naphthyl substituted enones **2o-2p** also participated well in the reaction to provide the products with good results. Interestingly, the scope of the reaction was further explored by employing an enone with disubstituted aryl moiety; 2,4-dimethyl phenyl substituted enone gave the product **3q** with high enantio and diastereoselectivity. Then we became interested to employ an aliphatic enone in our reaction. Delightfully the reaction progressed well with cyclohexyl substituted enone **2r** to afford acceptable yields of the product **3r** albeit moderate enantiomeric excess was obtained.

Table 3. Scope of α -cyano-enone in pyrrolidine formation ^{a,b,c,d}



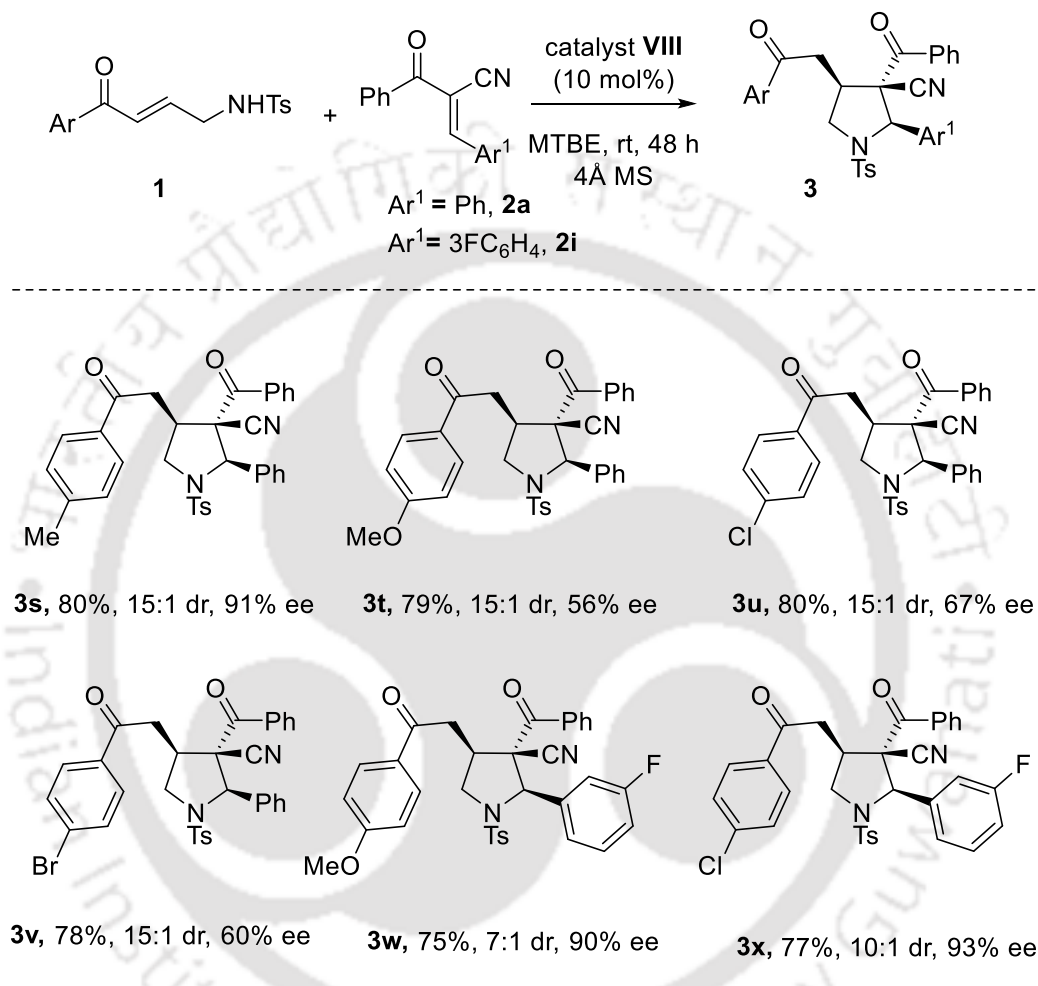


^aReaction conditions: 0.1 mmol of **1a** with 0.15 mmol of **2a** in 0.4 mL MTBE using 10 mol% **VIII** and 100 mg 4Å MS. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC.

In the next, we prepared a range of aryl substituted *N*-tosyl aminomethyl enones **1** and employed in the reaction with *trans*- α -cyano-enones **2a** and **2i** (Table 4). It turned out that the reaction outcome varied significantly except diastereomeric ratios and only *para*-substitutions on the aryl group resulted in acceptable enantioselectivities. For example *para*-tolyl substituted *N*-tosyl aminomethyl enone **1b** reacted smoothly with **2a** to deliver the corresponding product **3s** in 80% yield with 15:1 dr and 91% ee. A decrease in enantioselectivity was observed with 4-anisyl substituted *N*-tosyl aminomethyl enone **1c**. Also, moderate enantiomeric excesses were obtained for products **3u-3v** having 4-halo substituted aryl groups. Interestingly, the enantioselectivities got enhanced when **2i** was used as the reaction partner. For example, aminomethyl enone **1c** reacted with **2i** to deliver product **3x** in 75% yield with 7:1 dr and 90% ee. The outcome was also excellent

with 4-chloro substituted enone **1d** where the product **3y** was obtained in 93% ee with 10:1 dr.

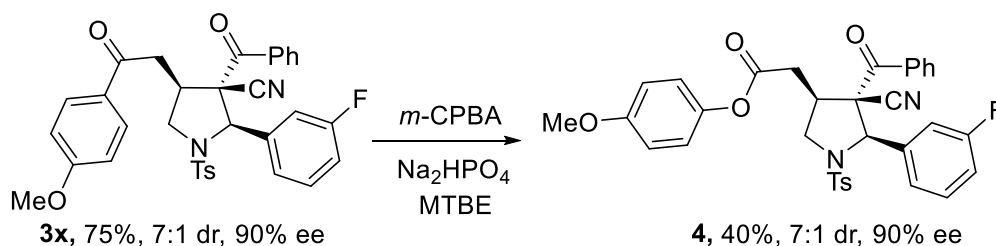
Table 4. Employment of different *N*-tosyl aminomethyl enone in the reaction^{a,b,c,d}



^aReaction conditions: 0.1 mmol of **1a** with 0.15 mmol of **2a** in 0.4 mL MTBE using 10 mol% **VIII** and 100 mg 4 Å MS. ^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC.

3.4.3. Synthetic transformation of **3x**:

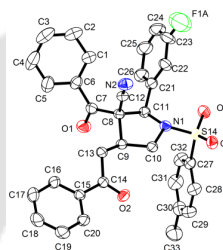
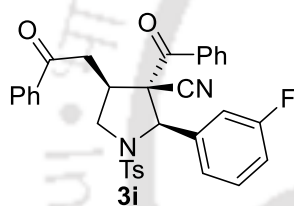
The usefulness of our method was further shown by performing a synthetic transformation of the chiral product. Baeyer-Villiger oxidation of **3x** was carried out with *m*-CPBA to furnish the desired ester **4** in perfect preservation of diastereo and enantioselectivity (Scheme 3.11).



Scheme 3.11: Synthetic transformation of **3x**

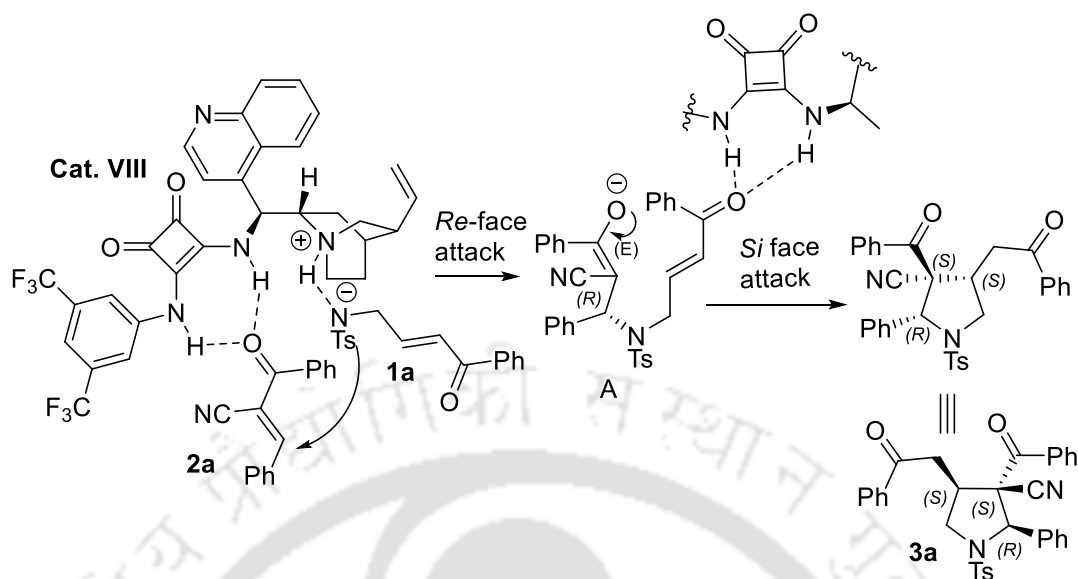
3.4.4. Absolute configuration of **3i**:

The absolute configuration of **3i** was derived from X-ray crystallography and found to be (2*R*,3*S*,4*S*).²⁰ Thus configuration of other products are supposed to be same by analogy.



3.4.5. Proposed mechanism:

Based on the absolute configuration, a plausible mechanism has been drawn in Scheme 3.12. It is expected that the bifunctional squaramide catalyst **VIII** activates both reactants **1a** and **2a** simultaneously. The carbonyl functionality of **2a** would be activated by squaramide motif of **VIII** from *Si* face. Thus the *aza*-Michael reaction proceeds through *Re* face of to provide intermediate **A**. Finally an intramolecular Michael reaction on the *Si* face of enone generates pyrrolidine **3a** (Scheme 3.12).



Scheme 3.12: Proposed mechanistic cycle

3.5. Conclusion:

In summary this report reveals an organocatalytic asymmetric synthesis of 2,3,3,4-tetrasubstituted pyrrolidines *via* double Michael strategy. The pyrrolidine products bearing cyano and keto groups were obtained in moderate to good yields with high diastereo- and good to high enantioselectivities. A Baeyer Villiger oxidation was also carried out to show the synthetic utility of our reaction. The reactants utilized in this method are easily available. The methodology is also attractive because of its mild reaction conditions and broad scope; and thus could be applied in the synthesis of biologically important pyrrolidines.

3.6. Experimental section:

General information:

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH₂ under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na₂SO₄ and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. Silica gel (60-120 mesh size) was used for column chromatography.

¹H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in CDCl₃; chemical shift values (δ, ppm) were reported in the standard fashion with reference to either tetramethylsilane (TMS) (δ(H) 0.00 ppm) or CHCl₃ (δ(H) 7.26 ppm). ¹³C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in CDCl₃; chemical shifts (δ, ppm) were reported relative to CHCl₃ (δ(C) 77.23 ppm, central line of triplet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (*J*) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) technique. IR spectra were recorded on Perkin Elmer instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F² using SHELXL-2014.

A. General procedure for the synthesis of amino methyl enones 1a-1g:

Amino methyl enones were prepared according to the reported procedure.²¹

B. General procedure for the synthesis of α -cyano-enones 2a-2r:

α -Cyano-enones were prepared following literature procedures.²²

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

Thiourea and squaramide catalysts were prepared according to the reported procedure.²³

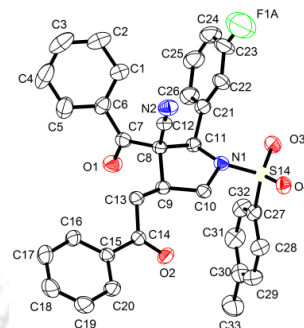
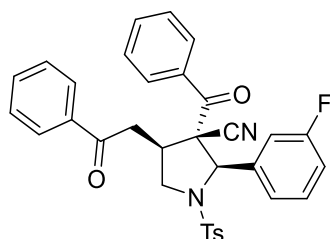
D. General procedure for the synthesis of chiral pyrrolidines 3:

Under argon atmosphere, *N*-tosyl aminomethyl enone **1** (0.05 mmol), *trans*- α -cyano- α,β -unsaturated ketone **2** (0.075 mmol) and catalyst **VIII** (10 mol %) were added in a round bottom flask. Then methyl tertiary butyl ether (MTBE) 0.2 mL was mixed with the reaction mixture. Next 4 Å MS (for 0.1 mmol of **1a**, 100 mg MS) was added to the reaction mixture. Then the reaction mixture was stirred at room temperature for 2 days under argon atmosphere. After completion of the reaction as monitored by TLC, the crude product was purified by column chromatography using 15-18 % ethyl acetate in hexane as eluent.

E. General procedure for the synthesis of compound 4:

To a solution of **3x** (0.1 mmol) in MTBE (4 mL), was added disodium hydrogen phosphate (0.3 mmol) and *m*-CPBA (0.3 mmol). The reaction mixture was stirred at room temperature for 48 hours. Then the solvent was evaporated and the crude product was purified by column chromatography using 15% ethyl acetate in hexane as the eluent.

Crystal structure of compound (2*R*,3*S*,4*S*)-3-benzoyl-2-(3-fluorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile 3i



Empirical formula	C ₃₃ H ₂₇ FN ₂ O ₄ S
Formula weight	566.66
CCDC Number	1862234
Crystal habit, colour	Needle, White
Crystal size, mm ³	0.25 × 0.18 × 0.18
Temperature, <i>T</i>	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	<i>a</i> = 9.7629(4) Å <i>b</i> = 11.7118(6) Å <i>c</i> = 13.5050(7) Å <i>α</i> = 90.002(4)°, <i>β</i> = 91.798(4)° <i>γ</i> = 112.093(4)°
Volume, <i>V</i> (Å ³)	1429.97(13)
<i>Z</i>	2
Calculated density, Mg·m ⁻³	1.3159
Absorption coefficient, μ (mm ⁻¹)	0.161
<i>F</i> (000)	592.5
θ range for data collection	6.04 to 50.00°
Limiting indices	-13 ≤ <i>h</i> ≤ 11, -15 ≤ <i>k</i> ≤ 14, -16 ≤ <i>l</i> ≤ 18
Reflection collected/unique	11400/5030 [<i>R</i> (int)=0.0239]
Completeness to θ	99.8% (θ = 25.00°)

CHAPTER 3

Max. and min. transmission	0.817/1.000
Refinement method	‘SHELXL–97 (Sheldrick, 1997)’
Data/restraints/parameters	5030/0/379
Goodness–of–fit on F^2	1.068
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0594$, $wR2 = 0.1533$
R indices (all data)	$R1 = 0.0793$, $wR2 = 0.1689$
Largest diff. peak and hole	0.53 and $-0.58 \text{ e} \cdot \text{\AA}^{-3}$



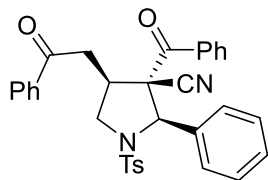
3.7. References:

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3.9. Characterization Data of Products:

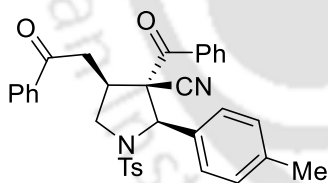
(2R,3S,4S)-3-benzoyl-4-(2-oxo-2-phenylethyl)-2-phenyl-1-tosylpyrrolidine-3-carbonitrile (3a)

This compound was prepared according to the general procedure

D. White sticky solid (43.8.4 mg, yield: 80%); **Diastereomeric**

ratio: 15:1; **¹H NMR (400 MHz, CDCl₃):** δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.42 –

7.33 (m, 3H), 7.32 – 7.23 (m, 9H), 7.16 (t, *J* = 7.9 Hz, 2H), 4.88 (s, 1H), 4.32 (dd, *J* = 11.8, 7.3 Hz, 1H), 3.60 – 3.46 (m, 1H), 3.28 – 3.17 (m, 1H), 3.18 – 3.08 (m, 1H), 3.01 (dd, *J* = 17.3, 4.4 Hz, 1H), 2.38 (s, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 196.1, 191.6, 144.6, 136.0, 135.8, 135.3, 134.1, 134.0, 133.6, 130.2, 129.6, 129.5, 129.0, 128.8, 128.5, 128.23, 128.2, 128.1, 117.2, 72.0, 65.0, 53.2, 42.8, 38.2, 21.9; **FT-IR (thin film):** 1682, 1601, 1567, 1448, 1356, 1162, 848 cm⁻¹; **HRMS (+ESI):** Calc for C₃₃H₂₉N₂O₄S [M+H]⁺ 549.1843; found 549.1837; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.9 min, τ_{major} = 24.9 min); Enantiomeric excess: 91%.

(2R,3S,4S)-3-benzoyl-4-(2-oxo-2-phenylethyl)-2-(*p*-tolyl)-1-tosylpyrrolidine-3-carbonitrile (3b)

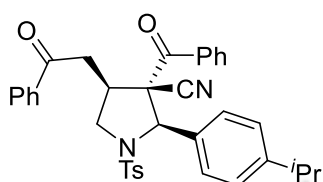
This compound was prepared according to the general procedure D. White sticky solid (43.8 mg, yield: 78%);

Diastereomeric ratio: 12:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.84 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz,

2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.41 – 7.35 (m, 4H), 7.31 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 4.93 (s, 1H), 4.39 (dd, *J* = 11.8, 7.3 Hz, 1H), 3.69 – 3.53 (m, 1H), 3.28 (ddd, *J* = 10.3, 9.4, 4.1 Hz, 1H), 3.23 (dd, *J* = 17.3, 9.2 Hz, 1H), 3.11 (dd, *J* = 17.3, 4.2 Hz, 1H), 2.48 (s, 3H), 2.37 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.2, 191.7, 144.6, 139.5, 135.9, 135.3, 134.0, 133.9, 133.4, 132.7, 130.2, 129.6, 129.5, 129.0, 128.4, 128.2, 128.1, 128.0, 117.3, 71.9, 65.0, 53.2, 42.7, 38.2, 21.9, 21.5; **FT-IR (thin film):** 1683, 1599, 1569, 1449, 1353, 1231, 1165, 1090, 789 cm⁻¹; **HRMS (+ESI):** Calc for C₃₄H₃₁N₂O₄S [M+H]⁺ 563.1999; found 563.1984; The enantiomeric ratio was determined by HPLC analysis using Daicel

Chiralpak IA column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 21.2$ min, $\tau_{\text{minor}} = 24.6$ min); Enantiomeric excess: 95%.

(2R,3S,4S)-3-benzoyl-2-(4-isopropylphenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3c)

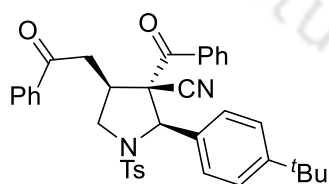


This compound was prepared according to the general procedure D. White sticky solid (44.8 mg, yield: 76%);

Diastereomeric ratio: 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.86 (d, $J = 8.1$ Hz, 2H), 7.66 (d, $J = 7.9$ Hz, 2H), 7.57 (t, $J =$

7.1 Hz, 1H), 7.49 – 7.40 (m, 3H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.28 (t, $J = 10.8$ Hz, 4H), 7.21 (t, $J = 7.7$ Hz, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 4.85 (s, 1H), 4.44 (dd, $J = 11.7, 7.7$ Hz, 1H), 3.61 (t, $J = 11.3$ Hz, 1H), 3.35 (dt, $J = 15.7, 11.5$ Hz, 1H), 3.22 (dd, $J = 17.6, 9.3$ Hz, 1H), 3.10 (dd, $J = 17.6, 4.4$ Hz, 1H), 2.92 (dt, $J = 13.7, 6.9$ Hz, 1H), 2.46 (s, 3H), 1.26 (d, $J = 7.1$ Hz, 6H); **^{13}C NMR (150 MHz, CDCl_3):** δ 196.2, 191.5, 150.5, 144.5, 136.0, 135.2, 134.0, 133.9, 133.6, 132.6, 130.1, 129.7, 129.0, 128.3, 128.3, 128.2, 128.1, 126.8, 117.4, 72.0, 65.0, 53.0, 42.3, 38.3, 34.1, 24.2, 24.1, 21.9; **FT-IR (thin film):** 1680, 1600, 1568, 1450, 1333, 1232, 1158, 1090, 892 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{36}\text{H}_{38}\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$ 608.2578; found 608.2584; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 7.1$ min, $\tau_{\text{major}} = 18.4$ min); Enantiomeric excess: 81%.

(2R,3S,4S)-3-benzoyl-2-(4-(tert-butyl)phenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3d)



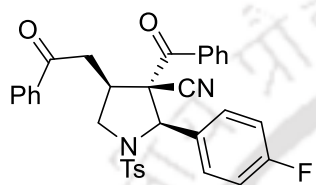
This compound was prepared according to the general procedure D. White sticky solid (48.4 mg, yield: 80%);

Diastereomeric ratio: 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.86 (d, $J = 7.4$ Hz, 2H), 7.65 (d, $J = 8.2$ Hz, 2H), 7.57 (t,

$J = 7.4$ Hz, 1H), 7.45 (dt, $J = 15.5, 7.6$ Hz, 3H), 7.36 – 7.30 (m, 4H), 7.30 – 7.26 (m, 4H), 7.20 (t, $J = 7.9$ Hz, 2H), 4.83 (s, 1H), 4.45 (dd, $J = 11.7, 7.7$ Hz, 1H), 3.61 (t, $J = 11.3$ Hz, 1H), 3.44 – 3.32 (m, 1H), 3.22 (dd, $J = 17.6, 9.4$ Hz, 1H), 3.11 (dd, $J = 17.6, 4.5$ Hz, 1H), 2.46 (s, 3H), 1.33 (s, 9H); **^{13}C NMR (150 MHz, CDCl_3):** δ 196.2, 191.4, 152.7, 144.4, 136.0, 135.2, 134.0, 133.9, 133.6, 132.2, 130.1, 129.7, 129.0, 128.3, 128.2, 128.1,

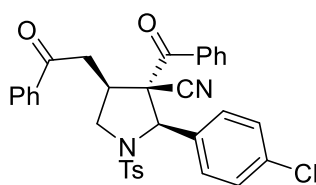
128.1, 125.7, 117.4, 71.9, 64.9, 53.0, 42.2, 38.3, 34.9, 31.5, 21.9; **FT-IR (thin film):** 1680, 1601, 1567, 1416, 1331, 1239, 1159, 1087, 788 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{37}\text{H}_{38}\text{N}_2\text{OS}$ $[\text{M}+\text{H}]^+$ 605.2469; found 605.2460; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 14.9$ min, $\tau_{\text{major}} = 37.7$ min); Enantiomeric excess: 95%.

(2R,3S,4S)-3-benzoyl-2-(4-fluorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3e)



This compound was prepared according to the general procedure D. White sticky solid (46.4 mg, yield: 82%); **Diastereomeric ratio:** 16:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.84 (d, $J = 7.6$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.47 – 7.42 (m, 4H), 7.38 (t, $J = 7.0$ Hz, 4H), 7.30 (t, $J = 7.9$ Hz, 2H), 7.04 (t, $J = 8.5$ Hz, 2H), 4.97 (s, 1H), 4.40 (dd, $J = 11.8, 7.2$ Hz, 1H), 3.65 – 3.55 (m, 1H), 3.31 – 3.26 (m, 1H), 3.26 – 3.20 (m, 1H), 3.12 (dd, $J = 17.0, 4.0$ Hz, 1H), 2.48 (s, 3H); **^{13}C NMR (150 MHz, CDCl_3):** δ 196.0, 191.3, 164.2, 162.6, 144.8, 135.9, 135.3, 134.3, 134.0, 133.3, 131.7, 131.6, 130.2, 130.1, 130.0, 129.5, 129.0, 128.6, 128.2, 128.1, 117.2, 115.9, 115.8, 71.3, 64.9, 53.1, 42.8, 38.2, 21.9; **FT-IR (thin film):** 1684, 1601, 1569, 1511, 1450, 1354, 1229, 1162, 1088, 825 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{33}\text{H}_{28}\text{FN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 567.1748; found 567.1736; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 11.3$ min, $\tau_{\text{major}} = 42.9$ min); Enantiomeric excess: 83%.

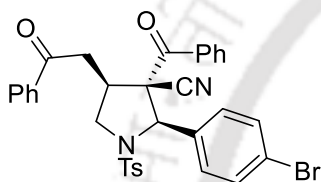
(2R,3S,4S)-3-benzoyl-2-(4-chlorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3f)



This compound was prepared according to the general procedure D. White sticky solid (46.6 mg, yield: 80%); **Diastereomeric ratio:** 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.81 (d, $J = 8.6$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.46 – 7.31 (m, 11H), 7.28 (t, $J = 3.8$ Hz, 2H), 4.96 (s, 1H), 4.42 (dd, $J = 11.8, 7.5$ Hz, 1H), 3.62 (t, $J = 11.3$ Hz, 1H), 3.32 (ddd, $J = 15.6, 10.0, 4.7$ Hz, 1H), 3.20

(dd, $J = 17.7, 9.1$ Hz, 1H), 3.09 (dd, $J = 17.7, 4.6$ Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 195.0, 191.4, 144.7, 140.5, 135.6, 135.2, 134.2, 134.1, 133.5, 130.2, 129.7, 129.6, 129.6, 129.3, 128.8, 128.5, 128.3, 128.1, 117.2, 72.0, 64.9, 53.1, 42.7, 38.2, 21.9; FT-IR (thin film): 1684, 1596, 1570, 1490, 1453, 1356, 1162, 1088, 799 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{33}\text{H}_{28}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 583.1453; found 583.1444; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{minor}} = 12.5$ min, $\tau_{\text{major}} = 36.5$ min); Enantiomeric excess: 82%.

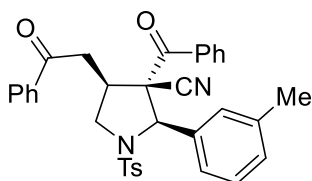
(2R,3S,4S)-3-benzoyl-2-(4-bromophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3g)



This compound was prepared according to the general procedure D. White sticky solid (48.3 mg, yield: 77%);

Diastereomeric ratio: 15:1; ^1H NMR (400 MHz, CDCl_3): δ 7.72 (d, $J = 7.3$ Hz, 2H), 7.58 (d, $J = 8.2$ Hz, 2H), 7.46 (t, $J = 7.4$ Hz, 1H), 7.40 (d, $J = 7.4$ Hz, 1H), 7.33 (dd, $J = 18.1, 8.1$ Hz, 6H), 7.27 (d, $J = 8.1$ Hz, 2H), 7.20 (t, $J = 7.9$ Hz, 2H), 7.16 (d, $J = 7.0$ Hz, 2H), 4.88 (s, 1H), 4.28 (dd, $J = 11.8, 6.9$ Hz, 1H), 3.56 – 3.42 (m, 1H), 3.21 – 2.95 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.0, 191.2, 144.9, 135.9, 135.3, 135.0, 134.3, 134.0, 133.4, 131.9, 130.3, 129.8, 129.5, 129.0, 128.6, 128.2, 128.1, 123.7, 117.1, 71.2, 64.7, 53.2, 43.0, 38.1, 21.9; FT-IR (thin film): 1682, 1599, 1566, 1489, 1448, 1355, 1163, 1072, 789 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{33}\text{H}_{28}\text{BrN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 627.0948; found 627.0944; The enantiomeric ratio was determined by HPLC analysis using Phenomenex column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{minor}} = 15.3$ min, $\tau_{\text{major}} = 46.6$ min); Enantiomeric excess: 84%.

(2R,3S,4S)-3-benzoyl-4-(2-oxo-2-phenylethyl)-2-(*m*-tolyl)-1-tosylpyrrolidine-3-carbonitrile (3h)

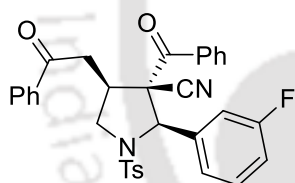


This compound was prepared according to the general procedure D. White sticky solid (44.4 mg, yield: 79%);

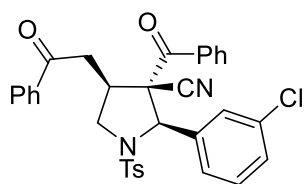
Diastereomeric ratio: 15:1; ^1H NMR (600 MHz, CDCl_3): δ 7.85 (d, $J = 7.3$ Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J =$

7.4 Hz, 1H), 7.49 (t, $J = 7.4$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 2H), 7.38 (dd, $J = 16.5, 7.7$ Hz, 4H), 7.28 – 7.22 (m, 3H), 7.18 (d, $J = 7.1$ Hz, 2H), 7.12 (s, 1H), 4.95 (s, 1H), 4.44 (dd, $J = 11.8, 7.4$ Hz, 1H), 3.60 (t, $J = 11.3$ Hz, 1H), 3.30 (ddd, $J = 11.1, 9.6, 6.9$ Hz, 1H), 3.22 (dd, $J = 17.6, 9.3$ Hz, 1H), 3.11 (dd, $J = 17.5, 4.5$ Hz, 1H), 2.47 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 196.2, 191.7, 144.5, 138.4, 136.0, 135.6, 135.3, 134.1, 134.0, 133.7, 130.4, 130.1, 129.6, 129.0, 128.8, 128.7, 128.4, 128.2, 128.1, 125.3, 117.2, 72.0, 65.0, 53.1, 42.8, 38.2, 21.9, 21.6; FT-IR (thin film): 1683, 1601, 1568, 1450, 1355, 1239, 1161, 1087, 743 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{34}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 563.1999; found 563.1980; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (Initially polarity was 92:8 *n*-Hexane/2-PrOH and at 35.798 min polarity was increased to 75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 21.3$ min, $\tau_{\text{major}} = 48.4$ min); Enantiomeric excess: 96%

(2R,3S,4S)-3-benzoyl-2-(3-fluorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3i)

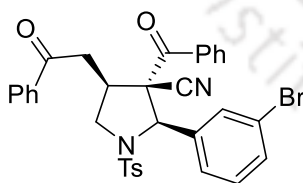


This compound was prepared according to the general procedure D. White sticky solid (45.9 mg, yield: 81%); **Diastereomeric ratio:** 15:1; ^1H NMR (600 MHz, CDCl_3): δ 7.84 (d, $J = 7.3$ Hz, 2H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.54 – 7.50 (m, 1H), 7.48 – 7.42 (m, 4H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.31 (t, $J = 7.9$ Hz, 3H), 7.18 – 7.11 (m, 2H), 7.08 (t, $J = 8.4$ Hz, 1H), 5.04 (s, 1H), 4.40 (dd, $J = 11.9, 6.9$ Hz, 1H), 3.62 – 3.55 (m, 1H), 3.25 (dd, $J = 6.1, 3.4$ Hz, 1H), 3.23 (t, $J = 7.0$ Hz, 1H), 3.13 (t, $J = 10.7$ Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3): δ 196.0, 191.3, 163.6, 162.0, 144.9, 138.5 (d, $J = 5$ Hz), 135.9, 135.3, 134.3, 134.1, 133.3, 130.3, 129.5, 129.0, 128.6, 128.2 (d, $J = 5$ Hz), 123.8 (d, $J = 2$ Hz), 117.0, 116.7, 116.5, 115.4, 115.2, 71.2, 64.8, 53.2, 43.1, 38.1, 21.9; FT-IR (thin film): 1682, 1600, 1568, 1489, 1450, 1355, 1162, 1087, 845 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{33}\text{H}_{28}\text{FN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 567.1748; found 567.1735; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (Initially the polarity was 93:7 *n*-Hexane/2-PrOH and at 32.984 min the polarity was increased to 70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 26.7$ min, $\tau_{\text{major}} = 45.8$ min); Enantiomeric excess: 98%.

(2R,3S,4S)-3-benzoyl-2-(3-chlorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3j)

This compound was prepared according to the general procedure D. White sticky solid (46.6 mg, yield: 80%);

Diastereomeric ratio: 15:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.84 (d, *J* = 7.3 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.31 (dd, *J* = 15.9, 7.5 Hz, 5H), 5.03 (s, 1H), 4.42 (dd, *J* = 11.8, 7.1 Hz, 1H), 3.65 – 3.54 (m, 1H), 3.31 – 3.25 (m, 1H), 3.23 (t, *J* = 11.3 Hz, 1H), 3.14 (dd, *J* = 16.7, 3.7 Hz, 1H), 2.48 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.0, 191.1, 144.9, 138.0, 135.9, 135.2, 134.7, 134.3, 134.1, 133.4, 130.3, 130.1, 129.7, 129.5, 129.0, 128.6, 128.3, 128.2, 128.1, 126.4, 116.9, 71.1, 64.7, 53.1, 43.1, 38.1, 21.9; **FT-IR (thin film):** 1682, 1596, 1574, 1481, 1445, 1228, 1163, 1052, 787 cm⁻¹; **HRMS (+ESI):** Calc for C₃₃H₂₈ClN₂O₄S [M+H]⁺ 583.1453; found 583.1458; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (Initially the polarity was 93:7 *n*-Hexane/2-PrOH and at 34.039 min the polarity was increased to 70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 27.4 min, τ_{major} = 51.4 min); Enantiomeric excess: 95%.

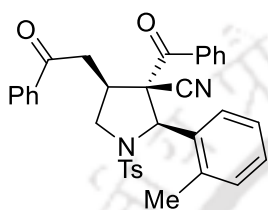
(2R,3S,4S)-3-benzoyl-2-(3-bromophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3k)

This compound was prepared according to the general procedure D. White sticky solid (47.7 mg, yield: 76%);

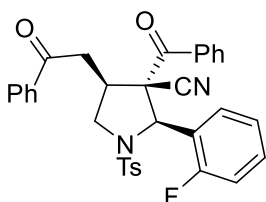
Diastereomeric ratio: 15:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.87 – 7.82 (m, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.51 – 7.48 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.42 – 7.34 (m, 4H), 7.32 (dd, *J* = 8.3, 7.6 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 5.03 (s, 1H), 4.42 (dd, *J* = 11.8, 7.1 Hz, 1H), 3.62 – 3.54 (m, 1H), 3.29 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.22 (d, *J* = 9.0 Hz, 1H), 3.14 (dd, *J* = 17.0, 4.1 Hz, 1H), 2.48 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.0, 191.1, 144.9, 138.2, 135.9, 135.2, 134.4, 134.1, 133.5, 132.6, 131.1, 130.3, 130.2, 129.5, 129.0, 128.7, 128.2, 128.1, 126.9, 122.8, 116.9, 70.9, 64.7, 53.1, 43.1, 38.1, 21.9; **FT-IR (thin film):** 1681, 1600, 1567, 1449, 1349, 1160, 1085, 788 cm⁻¹

¹; **HRMS (+ESI)**: Calc for C₃₃H₂₈BrN₂O₄S [M+H]⁺ 627.0948; found 627.0948; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (Initially the polarity was 93:7 *n*-Hexane/2-PrOH and at 35.047 min the polarity was increased to 70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 29.0 min, τ_{major} = 54.9 min); Enantiomeric excess: 91%.

(2R,3S,4S)-3-benzoyl-4-(2-oxo-2-phenylethyl)-2-(*o*-tolyl)-1-tosylpyrrolidine-3-carbonitrile (3l)



This compound was prepared according to the general procedure D. White sticky solid (42.7 mg, yield: 76%); **Diastereomeric ratio**:15:1; **¹H NMR (600 MHz, CDCl₃)**: δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 3H), 7.28 (t, *J* = 6.9 Hz, 1H), 7.26 – 7.21 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 5.30 (d, *J* = 5.7 Hz, 1H), 4.46 (dd, *J* = 11.6, 7.2 Hz, 1H), 3.59 (t, *J* = 11.1 Hz, 1H), 3.46 (td, *J* = 10.8, 4.1 Hz, 1H), 3.24 (dd, *J* = 17.6, 9.6 Hz, 1H), 3.14 (dd, *J* = 17.5, 4.1 Hz, 1H), 2.46 (s, 3H), 1.94 (s, 3H); **¹³C NMR (150 MHz, CDCl₃)**: δ 196.2, 191.3, 144.5, 136.1, 136.0, 134.7, 134.4, 134.2, 134.0, 130.6, 130.1, 129.5, 129.2, 129.0, 128.9, 128.5, 128.3, 128.0, 126.7, 117.4, 66.7, 64.3, 52.8, 43.0, 38.2, 21.9, 19.6; **FT-IR (thin film)**: 1682, 1599, 1565, 1491, 1448, 1349, 1159, 1081, 786 cm⁻¹; **HRMS (+ESI)**: Calc for C₃₄H₃₁N₂O₄S [M+H]⁺ 563.1999; found 563.1995; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.5 min, τ_{major} = 23.6 min); Enantiomeric excess: 87%.

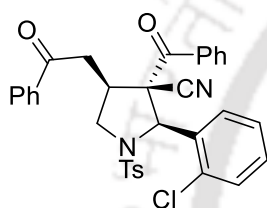


(2S,3S,4S)-3-benzoyl-2-(2-fluorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3m)

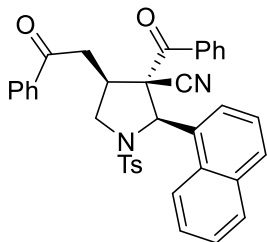
This compound was prepared according to the general procedure D. White sticky solid (42.4 mg, yield: 75%); **Diastereomeric ratio**: 15:1; **¹H NMR (600 MHz, CDCl₃)**: δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.81 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 6.8 Hz, 3H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.44 (dd, *J* = 13.3, 5.7 Hz, 4H), 7.40 – 7.37 (m, 1H), 7.31 (t, *J* = 7.9 Hz, 3H), 6.94 (t, *J* = 9.2 Hz, 1H), 5.40 (s, 1H), 4.38

(dd, $J = 12.1, 6.7$ Hz, 1H), 3.59 (dd, $J = 12.0, 10.3$ Hz, 1H), 3.24 – 3.08 (m, 3H), 2.49 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 196.0, 190.6, 161.0, 159.4, 144.9, 135.9, 134.9, 134.2, 134.0, 131.0, 130.9, 130.3, 129.4, 129.0, 128.6, 128.3, 128.2, 125.0, 124.3, 124.2, 117.1, 63.9, 53.0, 43.5, 38.0, 21.9; **FT-IR (thin film)**: 1686, 1599, 1569, 1489, 1450, 1354, 1224, 1163, 1088, 789 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{33}\text{H}_{28}\text{FN}_2\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$ 584.2014; found 584.2019; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 26.5$ min, $\tau_{\text{major}} = 31.0$ min); Enantiomeric excess: 96%.

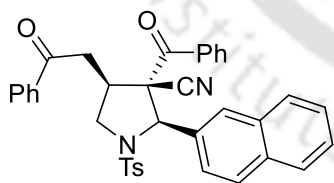
(2*S*,3*S*,4*S*)-3-benzoyl-2-(2-chlorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3n)



This compound was prepared according to the general procedure D. White sticky solid (43.1 mg, yield: 74%); **Diastereomeric ratio**: 15:1; ^1H NMR (600 MHz, CDCl_3): δ 8.05 (d, $J = 9.2$ Hz, 1H), 7.85 (dd, $J = 14.3, 7.7$ Hz, 4H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.54 – 7.50 (m, 2H), 7.50 – 7.46 (m, 3H), 7.45 (t, $J = 8.0$ Hz, 3H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.28 (dd, $J = 10.5, 5.4$ Hz, 3H), 5.53 (s, 1H), 4.34 (dd, $J = 12.1, 6.4$ Hz, 1H), 3.62 (dd, $J = 11.9, 9.6$ Hz, 1H), 3.21 (dd, $J = 18.3, 6.8$ Hz, 2H), 3.13 (t, $J = 10.9$ Hz, 1H), 2.50 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): δ 196.1, 190.3, 144.9, 136.0, 134.8, 134.7, 134.4, 134.0, 133.6, 132.5, 130.7, 130.6, 130.3, 129.5, 129.4, 129.0, 128.52, 128.50, 128.2, 127.7, 117.1, 66.7, 63.6, 53.0, 43.3, 38.1, 22.0; **FT-IR (thin film)**: 1685, 1600, 1568, 1448, 1353, 1222, 1160, 1085 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{33}\text{H}_{28}\text{ClN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 583.1453; found 583.1453; The enantiomeric ratio was determined by HPLC analysis using Daicel Phenomenex Lux C1 column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 17.9$ min, $\tau_{\text{major}} = 39.1$ min); Enantiomeric excess: 96%.

(2R,3S,4S)-3-benzoyl-2-(naphthalen-1-yl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3o)

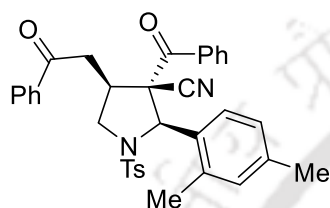
This compound was prepared according to the general procedure D. White sticky solid (47.9 mg, yield: 80%); **Diastereomeric ratio:** 16:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.17 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.85 (dd, J = 19.8, 8.3 Hz, 3H), 7.74 (d, J = 8.2 Hz, 2H), 7.66 (t, J = 7.7 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (dd, J = 13.6, 5.8 Hz, 3H), 7.40 (d, J = 8.0 Hz, 2H), 7.32 (dd, J = 16.0, 8.1 Hz, 2H), 7.24 – 7.19 (m, 1H), 7.18 (d, J = 7.5 Hz, 2H), 7.04 (t, J = 7.9 Hz, 2H), 5.99 (s, 1H), 4.47 (dd, J = 11.9, 7.1 Hz, 1H), 3.70 (dd, J = 11.8, 10.4 Hz, 1H), 3.45 – 3.37 (m, 1H), 3.29 (dd, J = 17.7, 9.7 Hz, 1H), 3.14 (dd, J = 17.7, 4.0 Hz, 1H), 2.50 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.1, 192.2, 144.7, 136.0, 134.8, 134.0, 133.6, 133.3, 132.1, 131.0, 130.2, 129.9, 129.4, 129.2, 129.0, 128.3, 128.2, 128.1, 127.4, 126.9, 125.8, 125.7, 121.7, 117.3, 66.3, 65.1, 53.2, 44.0, 38.2, 22.0; **FT-IR (thin film):** 1679, 1600, 1569, 1450, 1352, 1237, 1159, 1085, 886 cm⁻¹; **HRMS (+ESI):** Calc for C₃₇H₃₁N₂O₄S [M+H]⁺ 599.1999; found 599.197; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.9 min, τ_{major} = 25.4 min); Enantiomeric excess: 87%.

(2R,3S,4S)-3-benzoyl-2-(naphthalen-2-yl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3p)

This compound was prepared according to the general procedure D. White sticky solid (48.4 mg, yield: 81%); **Diastereomeric ratio:** 16:1; **¹H NMR (600 MHz, CDCl₃)** δ 7.86 (d, J = 8.5 Hz, 4H), 7.70 (d, J = 8.2 Hz, 4H), 7.58 (dd, J = 13.6, 6.4 Hz, 3H), 7.51 – 7.48 (m, 2H), 7.46 – 7.42 (m, 3H), 7.42 – 7.38 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.15 (t, J = 7.9 Hz, 2H), 5.20 (s, 1H), 4.49 (dd, J = 11.8, 7.4 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.41 – 3.32 (m, 1H), 3.30 – 3.25 (m, 1H), 3.15 (dd, J = 17.7, 4.6 Hz, 1H), 2.44 (s, 3H); **¹³C NMR (150 MHz, CDCl₃)** δ 196.2, 191.7, 144.6, 136.0, 135.3, 134.1, 134.0, 133.9, 133.7, 133.2, 133.0, 130.2, 129.5, 129.0, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 126.9, 126.6, 117.3, 72.0, 65.0, 53.2, 43.0, 38.2, 21.9; **FT-IR (thin**

film): 1682, 1599, 1569, 1448, 1350, 1231, 1163, 1087, 788 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{37}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 599.1999; found 599.199; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.7 min, τ_{major} = 32.9 min); Enantiomeric excess: 88%.

(2R,3S,4S)-3-benzoyl-2-(2,4-dimethylphenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3q)

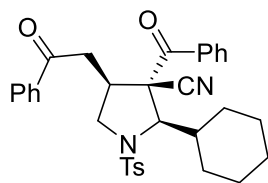


This compound was prepared according to the general procedure D. White sticky solid (44.9 mg, yield: 78%);

Diastereomeric ratio: 15:1; **^1H NMR (600 MHz, CDCl_3):**

δ 7.88 (d, J = 7.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.51 (d, J = 7.4 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.26 (dd, J = 9.1, 6.7 Hz, 2H), 7.15 (d, J = 7.7 Hz, 1H), 6.84 (s, 1H), 5.25 (s, 1H), 4.43 (dd, J = 11.7, 7.2 Hz, 1H), 3.58 (t, J = 11.2 Hz, 1H), 3.43 (dd, J = 20.6, 10.7 Hz, 1H), 3.23 (dd, J = 17.6, 9.6 Hz, 1H), 3.12 (dd, J = 17.5, 4.1 Hz, 1H), 2.47 (s, 3H), 2.34 (s, 3H), 1.89 (s, 3H); **^{13}C NMR (150 MHz, CDCl_3):** δ 196.3, 191.5, 144.4, 138.9, 136.0, 135.8, 134.8, 134.4, 134.1, 133.9, 131.3, 130.0, 129.5, 129.0, 128.5, 128.3, 128.1, 127.6, 117.5, 66.7, 64.5, 52.8, 43.0, 38.2, 21.9, 21.4, 19.5; **FT-IR (thin film)**: 1684, 1600, 1568, 1455, 1357, 1160, 1081, 789 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{35}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 577.2156; found 577.2134; The enantiomeric ratio was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.4 min, τ_{major} = 49.5 min); Enantiomeric excess: 91%.

(2R,3S,4S)-3-benzoyl-2-cyclohexyl-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3r)



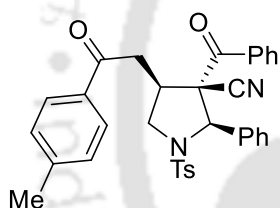
This compound was prepared according to the general procedure D. White sticky solid (39.9 mg, yield: 72%);

Diastereomeric ratio: 16:1; **^1H NMR (600 MHz, CDCl_3):** δ

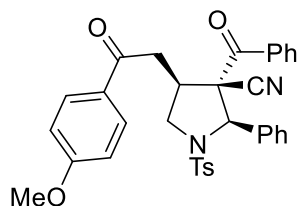
7.87 (d, J = 7.4 Hz, 2H), 7.83 (d, J = 7.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H),

7.44 (t, $J = 7.8$ Hz, 2H), 7.32 (d, $J = 8.1$ Hz, 2H), 4.36 (d, $J = 6.5$ Hz, 1H), 4.19 (dd, $J = 13.1, 6.7$ Hz, 1H), 3.26 (dd, $J = 17.6, 4.8$ Hz, 1H), 3.19 – 3.08 (m, 2H), 2.92 – 2.79 (m, 1H), 2.44 (s, 3H), 2.12 – 2.03 (m, 1H), 2.01 (d, $J = 12.3$ Hz, 1H), 1.85 (d, $J = 12.6$ Hz, 1H), 1.74 (d, $J = 10.9$ Hz, 1H), 1.68 (d, $J = 12.7$ Hz, 1H), 1.43 – 1.27 (m, 5H), 1.19 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 196.3, 192.0, 144.4, 136.0, 135.2, 135.0, 133.9, 133.8, 130.1, 129.2, 129.0, 128.9, 128.3, 128.2, 117.8, 71.3, 62.5, 54.0, 43.12, 43.11, 38.6, 31.6, 29.8, 26.5, 26.4, 26.1, 21.9; FT-IR (thin film): 1685, 1599, 1571, 1450, 1350, 1228, 1158, 1086, 780 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{33}\text{H}_{35}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 555.2312; found 555.2322; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 7.1$ min, $\tau_{\text{major}} = 18.4$ min); Enantiomeric excess: 78%.

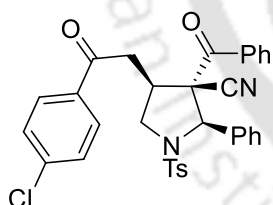
(2R,3S,4S)-3-benzoyl-4-(2-oxo-2-(*p*-tolyl)ethyl)-2-phenyl-1-tosylpyrrolidine-3-carbonitrile (3s)



This compound was prepared according to the general procedure D. White sticky solid (45.0 mg, yield: 80%); Diastereomeric ratio: 15:1; ^1H NMR (400 MHz, CDCl_3) δ 7.72 (dd, $J = 16.1, 8.2$ Hz, 4H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.43 – 7.34 (m, 9H), 7.26 (dd, $J = 8.8, 7.1$ Hz, 4H), 4.99 (s, 1H), 4.40 (dd, $J = 11.8, 7.4$ Hz, 1H), 3.67 – 3.56 (m, 1H), 3.30 (dt, $J = 22.4, 7.6$ Hz, 1H), 3.20 (dd, $J = 17.3, 9.0$ Hz, 1H), 3.08 (dd, $J = 17.3, 4.5$ Hz, 1H), 2.47 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 195.8, 191.7, 145.0, 144.6, 135.8, 135.4, 134.1, 133.5, 133.4, 130.2, 129.7, 129.6, 129.5, 128.8, 128.5, 128.4, 128.2, 128.1, 117.3, 72.1, 65.0, 53.3, 42.9, 38.1, 21.9; FT-IR (thin film): 1683, 1602, 1566, 1494, 1451, 1352, 1166, 1089, 761 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{34}\text{H}_{31}\text{N}_2\text{O}_4\text{S}$ $[\text{M}+\text{NH}_4]^+$ 580.2265; found 580.2276; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 12.0$ min, $\tau_{\text{major}} = 16.8$ min); Enantiomeric excess: 91%.

(2R,3S,4S)-3-benzoyl-4-(2-(4-methoxyphenyl)-2-oxoethyl)-2-phenyl-1-tosylpyrrolidine-3-carbonitrile (3t)

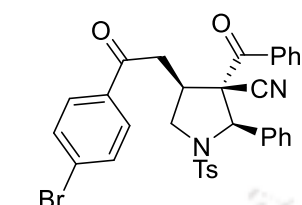
This compound was prepared according to the general procedure D. White sticky solid (45.7 mg, yield: 79%); **Diastereomeric ratio:** 15:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.84 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.2 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.44 – 7.35 (m, 9H), 7.30 – 7.26 (m, 2H), 6.91 (d, J = 8.9 Hz, 2H), 5.00 (s, 1H), 4.41 (dd, J = 11.8, 7.5 Hz, 1H), 3.87 (s, 3H), 3.63 (t, J = 11.3 Hz, 1H), 3.34 – 3.26 (m, 1H), 3.20 (dd, J = 17.4, 9.2 Hz, 1H), 3.08 (dd, J = 17.4, 4.7 Hz, 1H), 2.49 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 194.6, 191.6, 164.1, 144.6, 135.8, 135.4, 134.0, 133.4, 130.6, 130.2, 129.9, 129.6, 129.5, 129.0, 128.8, 128.4, 128.2, 128.1, 126.6, 117.3, 114.1, 72.0, 65.0, 55.7, 53.3, 43.0, 37.8, 21.9; **FT-IR (thin film):** 1676, 1601, 1568, 1511, 1457, 1355, 1260, 1164, 1089, 736 cm⁻¹; **HRMS (+ESI):** Calc for C₃₄H₃₁N₂O₅S [M+NH₄]⁺ 579.1948; found 579.1955; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.8 min, τ_{major} = 13.9 min); Enantiomeric excess: 57%.

(2R,3S,4S)-3-benzoyl-4-(2-(4-chlorophenyl)-2-oxoethyl)-2-phenyl-1-tosylpyrrolidine-3-carbonitrile (3u)

This compound was prepared according to the general procedure D. White sticky solid (46.6 mg, yield: 80%); **Diastereomeric ratio:** 15:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.81 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.46 – 7.34 (m, 11H), 7.31 – 7.26 (m, 2H), 4.96 (s, 1H), 4.42 (dd, J = 11.8, 7.5 Hz, 1H), 3.62 (t, J = 11.3 Hz, 1H), 3.32 (ddd, J = 16.3, 10.5, 4.7 Hz, 1H), 3.20 (dd, J = 17.7, 9.1 Hz, 1H), 3.10 (dd, J = 17.7, 4.7 Hz, 1H), 2.50 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 195.0, 191.4, 144.7, 140.5, 135.6, 135.2, 134.2, 134.1, 133.4, 130.2, 129.7, 129.6, 129.6, 129.3, 128.8, 128.5, 128.2, 128.1, 117.2, 72.0, 64.8, 53.1, 42.7, 38.2, 21.9; **FT-IR (thin film):** 1685, 1597, 1567, 1491, 1448, 1355, 1235, 1163, 1090, 842 cm⁻¹; **HRMS (+ESI):** Calc for C₃₃H₂₈ClN₂O₄S [M+H]⁺ 583.1453; found 583.1456; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column

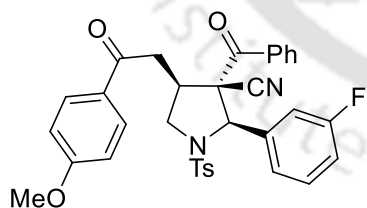
(80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 15.5 min, τ_{major} = 16.9 min); Enantiomeric excess: 67%.

(2*R*,3*S*,4*S*)-3-benzoyl-4-(2-(4-bromophenyl)-2-oxoethyl)-2-phenyl-1-tosylpyrrolidine-3-carbonitrile (3v)



This compound was prepared according to the general procedure D. White sticky solid (48.9 mg, yield: 78%); **Diastereomeric ratio:** 15:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.71 (dt, J = 16.3, 7.1 Hz, 4H), 7.60 (d, J = 8.5 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.45 – 7.32 (m, 9H), 7.29 – 7.26 (m, 2H), 4.96 (s, 1H), 4.42 (dd, J = 11.8, 7.5 Hz, 1H), 3.62 (t, J = 11.3 Hz, 1H), 3.36 – 3.28 (m, 1H), 3.19 (dd, J = 17.7, 9.1 Hz, 1H), 3.09 (dd, J = 17.7, 4.7 Hz, 1H), 2.50 (s, 3H); **^{13}C NMR (150 MHz, CDCl_3):** δ 195.2, 191.4, 144.7, 135.6, 135.2, 134.6, 134.2, 133.5, 132.3, 130.2, 129.7, 129.6, 129.6, 129.4, 129.3, 128.8, 128.7, 128.5, 128.2, 128.1, 117.2, 72.0, 64.8, 53.1, 42.7, 38.2, 21.9; **FT-IR (thin film):** 1685, 1598, 1566, 1492, 1448, 1355, 1163, 1069, 789 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{33}\text{H}_{28}\text{BrN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 627.0948; found 627.0949; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 17.4 min, τ_{major} = 18.4 min); Enantiomeric excess: 60%.

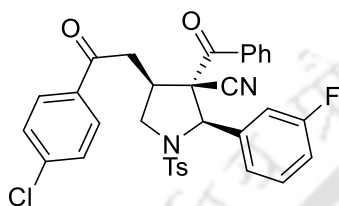
(2*R*,3*S*,4*S*)-3-benzoyl-2-(3-fluorophenyl)-4-(2-(4-methoxyphenyl)-2-oxoethyl)-1-tosylpyrrolidine-3-carbonitrile (3w)



This compound was prepared according to the general procedure D. White sticky solid (44.7 mg, yield: 75%); **Diastereomeric ratio:** 7:1; **^1H NMR (400 MHz, CDCl_3):** δ 7.81 (d, J = 8.9 Hz, 2H), 7.71 (d, J = 8.2 Hz, 2H), 7.53 – 7.46 (m, 3H), 7.38 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 7.9 Hz, 3H), 7.10 (dt, J = 17.6, 8.0 Hz, 3H), 6.89 (d, J = 8.9 Hz, 2H), 5.07 (s, 1H), 4.37 (dd, J = 11.8, 7.1 Hz, 1H), 3.85 (s, 3H), 3.59 (dd, J = 11.6, 10.7 Hz, 1H), 3.25 (ddd, J = 12.9, 7.3, 3.8 Hz, 1H), 3.21 – 3.03 (m, 2H), 2.48 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 194.4, 191.3, 164.2, 144.8, 138.7 (d, J = 7 Hz), 135.4, 134.2, 130.6, 130.2, 129.6, 129.5, 129.2, 128.6, 128.2, 123.8 (d, J = 3 Hz), 117.0, 116.6, 116.4, 115.4, 115.2, 114.1, 71.2, 64.9, 55.7, 53.3, 43.4, 37.7, 21.9;

FT-IR (thin film): 1674, 1601, 1490, 1452, 1356, 1260, 1165, 751 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{34}\text{H}_{30}\text{FN}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$ 597.1845; found 597.1852; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 19.6 min, τ_{major} = 21.1 min); Enantiomeric excess: 90%.

(2*R*,3*S*,4*S*)-3-benzoyl-4-(2-(4-chlorophenyl)-2-oxoethyl)-2-(3-fluorophenyl)-1-tosylpyrrolidine-3-carbonitrile (3x)

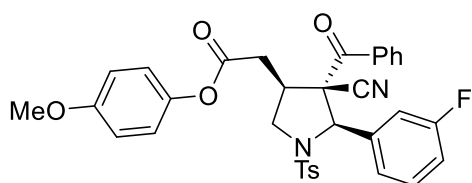


This compound was prepared according to the general procedure D. White sticky solid (46.3 mg, yield: 77%);

Diastereomeric ratio: 10:1; **^1H NMR (400 MHz, CDCl_3):**

δ 7.78 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 7.4 Hz, 1H), 7.47 (d, J = 7.4 Hz, 2H), 7.39 (dd, J = 13.4, 8.4 Hz, 4H), 7.30 (t, J = 7.9 Hz, 3H), 7.15 – 7.06 (m, 3H), 5.04 (s, 1H), 4.38 (dd, J = 11.8, 7.3 Hz, 1H), 3.64 – 3.51 (m, 1H), 3.27 (ddd, J = 10.4, 7.7, 4.9 Hz, 1H), 3.22 – 3.06 (m, 2H), 2.48 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 194.9, 191.1, 164.1, 161.6, 144.9, 140.6, 138.5 (d, J = 7 Hz), 135.3, 134.3 (d, J = 7 Hz), 133.6, 130.2, 129.6, 129.5, 129.3, 128.6, 128.2, 123.9 (d, J = 3 Hz), 117.0, 116.7, 116.5, 115.5, 115.3, 71.2, 64.7, 53.1, 43.0, 38.1, 21.9; **FT-IR (thin film):** 1686, 1597, 1567, 1489, 1450, 1401, 1356, 1163, 1090, 805 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{33}\text{H}_{27}\text{ClFN}_2\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 601.1359; found 601.1361; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 15.2 min, τ_{major} = 16.7 min); Enantiomeric excess: 93%.

4-methoxyphenyl 2-((3*S*,4*S*,5*R*)-4-benzoyl-4-cyano-5-(3-fluorophenyl)-1-tosylpyrrolidin-3-yl)acetate (4)



This compound was prepared according to the general procedure D.

White sticky solid (24.5 mg, yield: 40%);

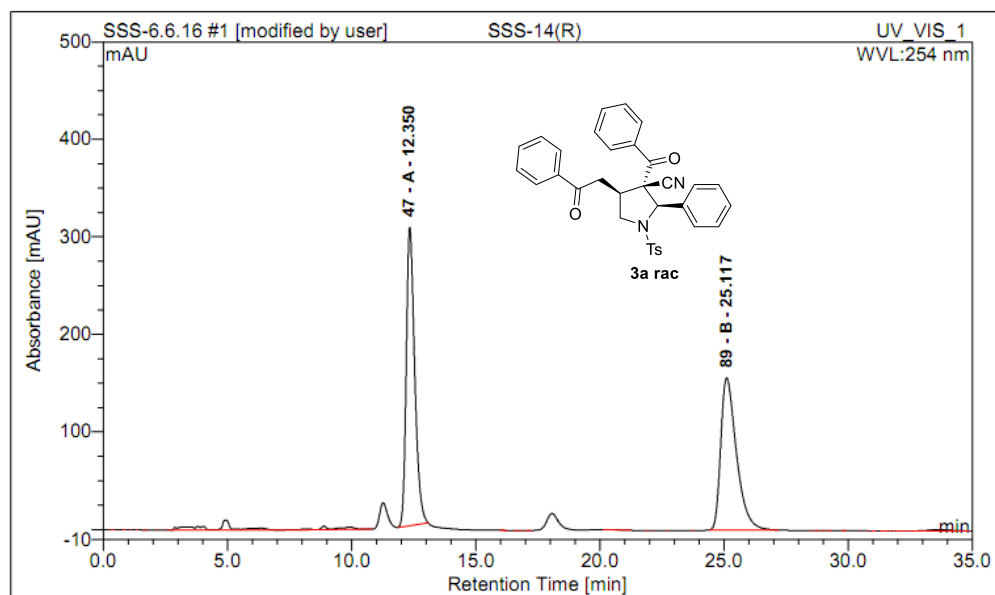
Diastereomeric ratio: 7:1; **^1H NMR (400**

MHz, CDCl_3) δ 7.65 (d, J = 8.3 Hz, 2H), 7.53 (t, J = 8.1 Hz, 2H), 7.46 (d, J = 7.4 Hz, 2H), 7.36 – 7.27 (m, 5H), 7.14 – 7.07 (m, 2H), 6.90 (td, J = 9.3, 5.2 Hz, 4H), 5.04 (s,

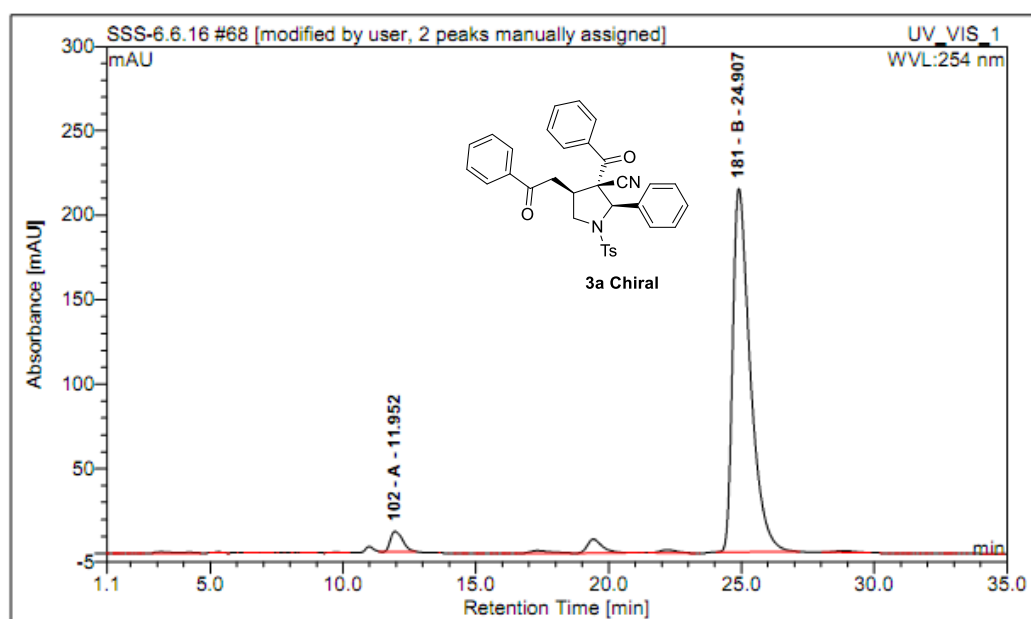
1H), 4.36 (dd, $J = 11.8, 7.4$ Hz, 1H), 3.80 (s, 3H), 3.68 (t, $J = 11.4$ Hz, 1H), 3.27 – 3.11 (m, 1H), 2.76 (qd, $J = 16.9, 7.3$ Hz, 2H), 2.46 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3)**: δ 191.0, 169.1, 157.8, 144.9, 143.8, 138.3 (d, $J = 8$ Hz), 135.1, 134.5, 133.6, 130.5, 130.4, 130.3, 129.6, 128.7, 128.1, 123.9 (d, $J = 3$ Hz), 122.2, 116.6 (d, $J = 2$ Hz), 115.5, 115.3, 114.8, 71.4, 64.5, 55.8, 52.9, 43.5, 36.9, 21.9; **FT-IR (thin film)**: 1754, 1601, 1566, 1507, 1359, 1248, 1159, 876 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{34}\text{H}_{30}\text{FN}_2\text{O}_6\text{S}$ $[\text{M}+\text{H}]^+$ 613.1803; found 613.1804; The enantiomeric ratio was determined by HPLC analysis using Phenomenex lux C1 column (88:12 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 77.7\text{min}$, $\tau_{\text{major}} = 83.8$ min); Enantiomeric excess: 90%.



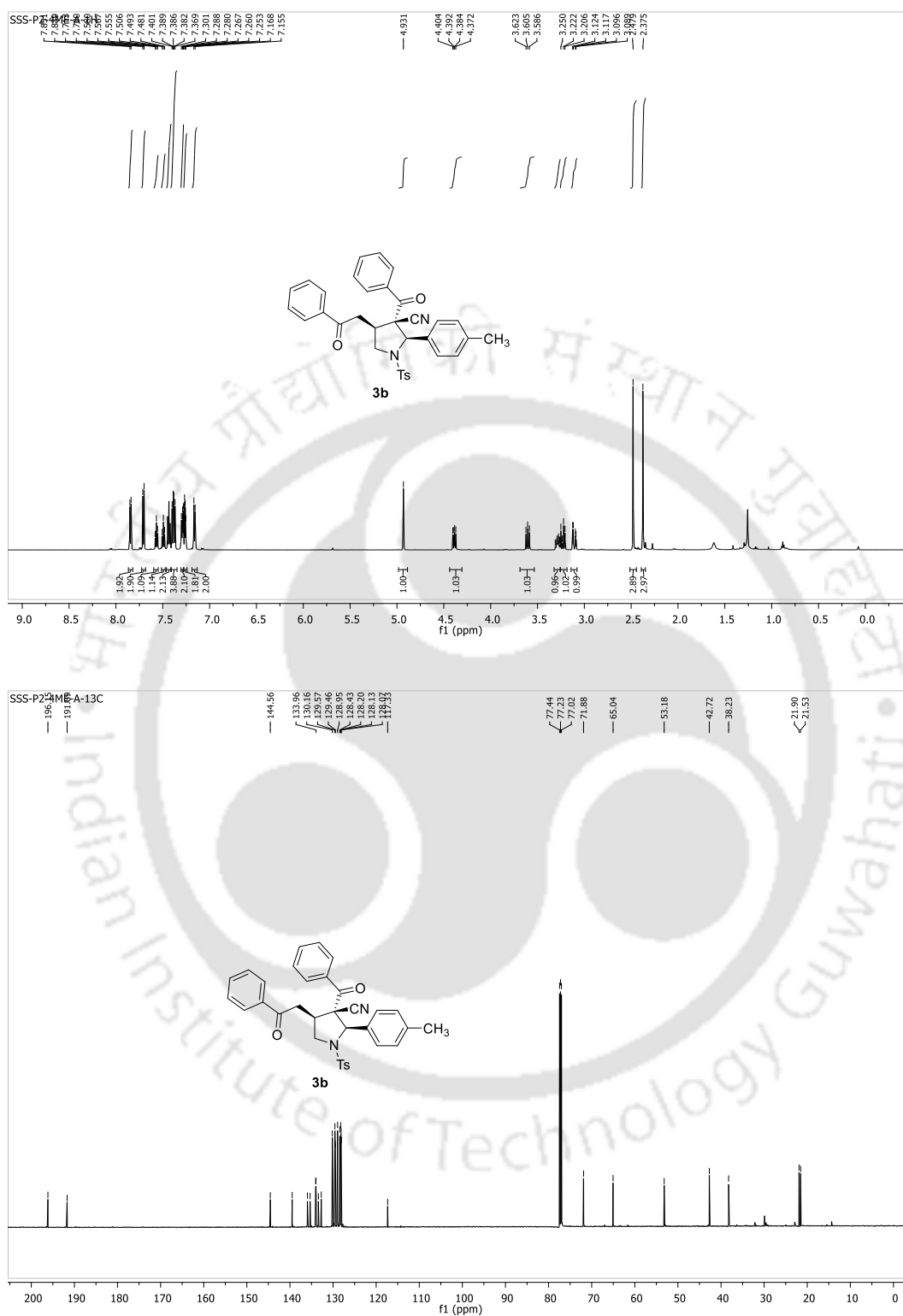


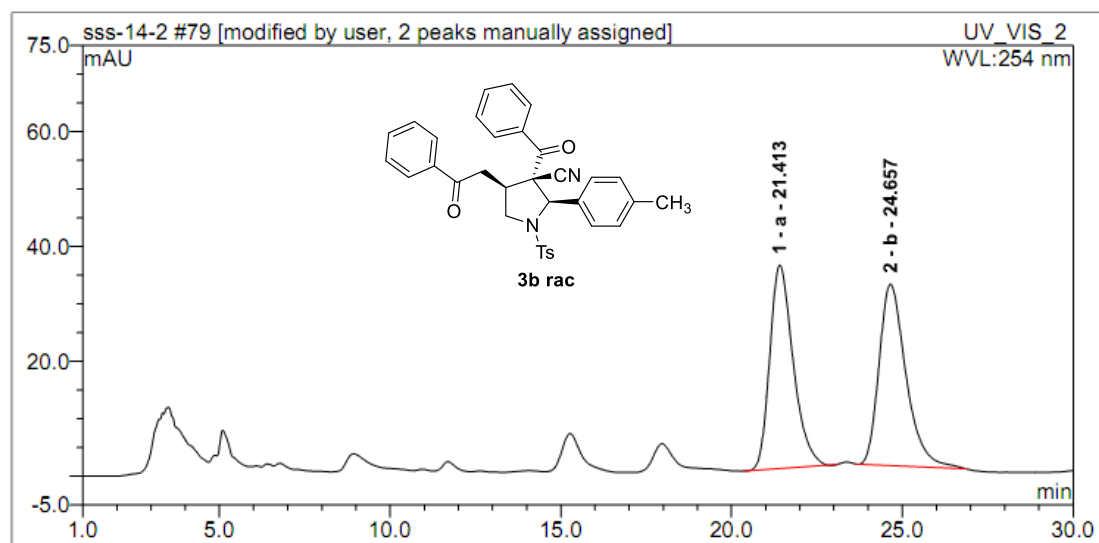


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
47 A		12.35	119.9935	51.18584357	305.9554	n.a.
89 B		25.12	114.434	48.81415643	156.038	n.a.

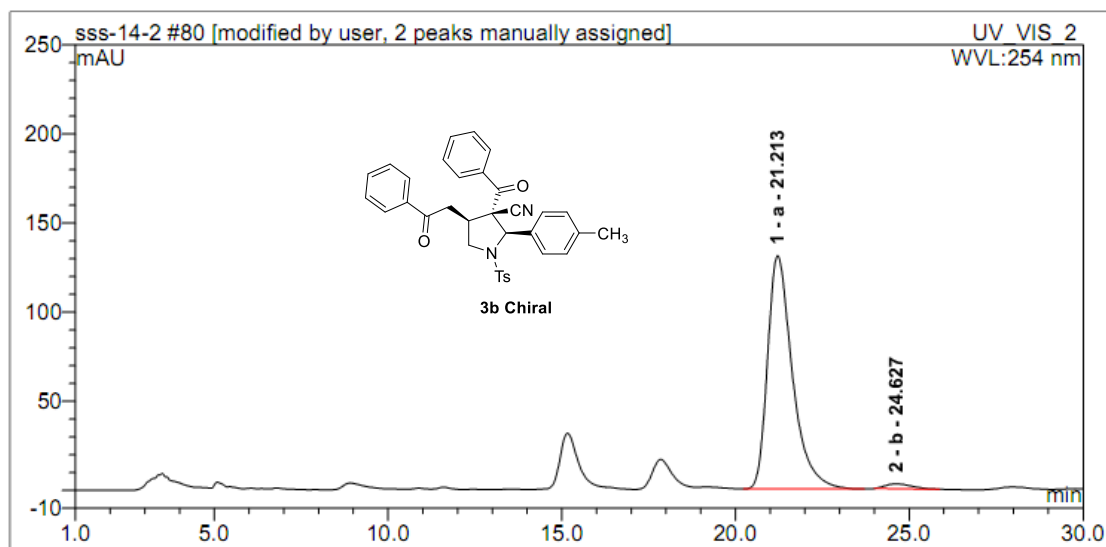


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
102 A		11.95	6.223216	3.647795857	11.84795	n.a.
181 B		24.91	164.379	96.35211932	215.153	n.a.

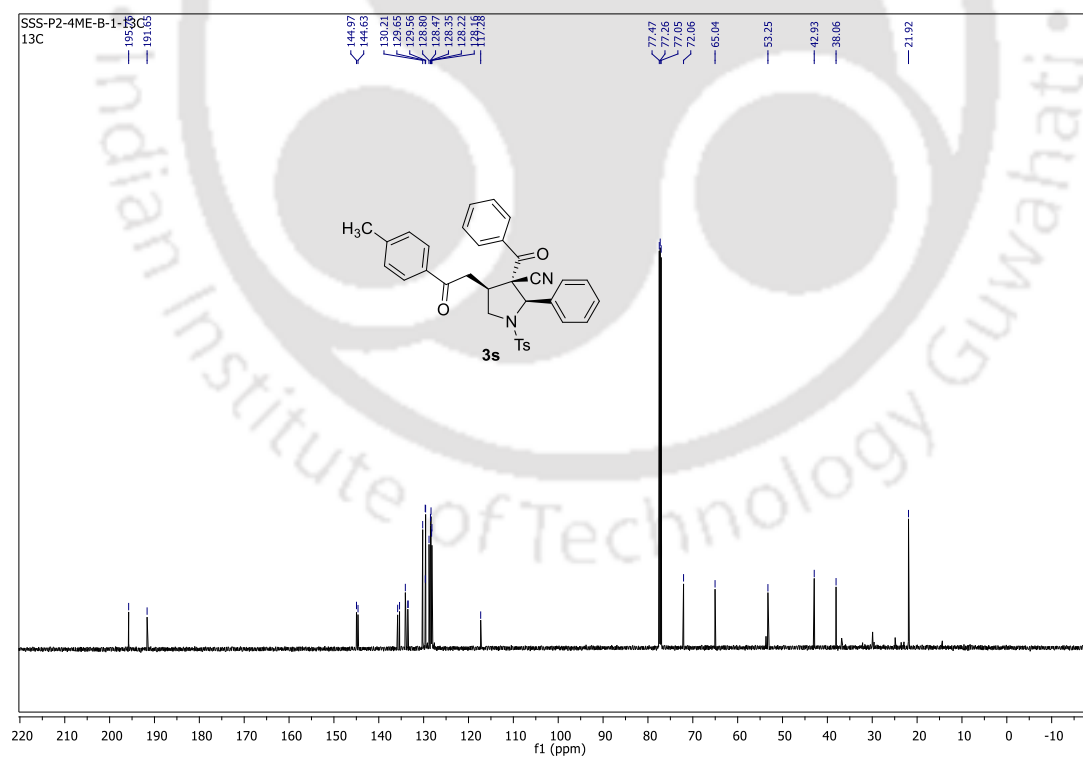
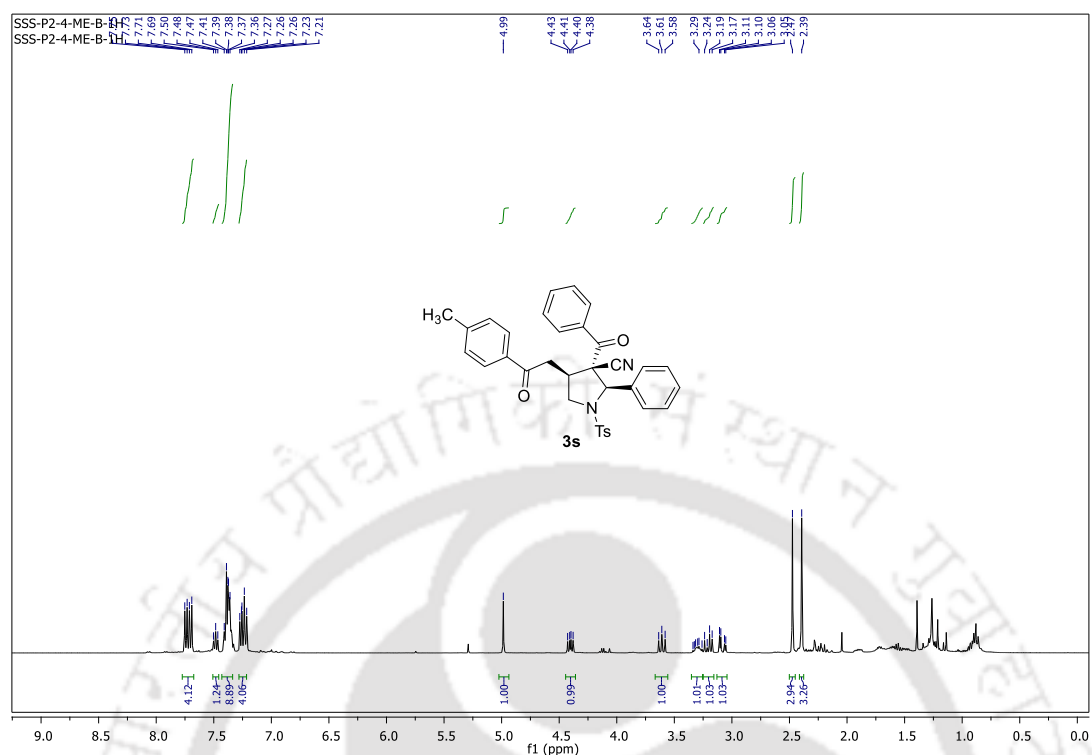


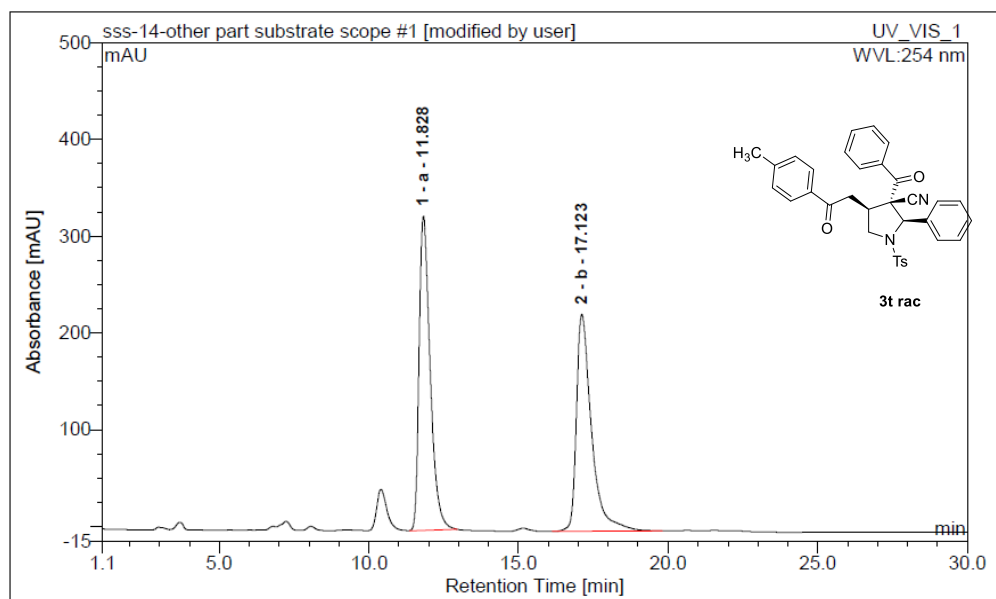


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		21.41	28.15373	49.33569561	35.40188	n.a.
2 b		24.66	28.912	50.66430439	31.609	n.a.

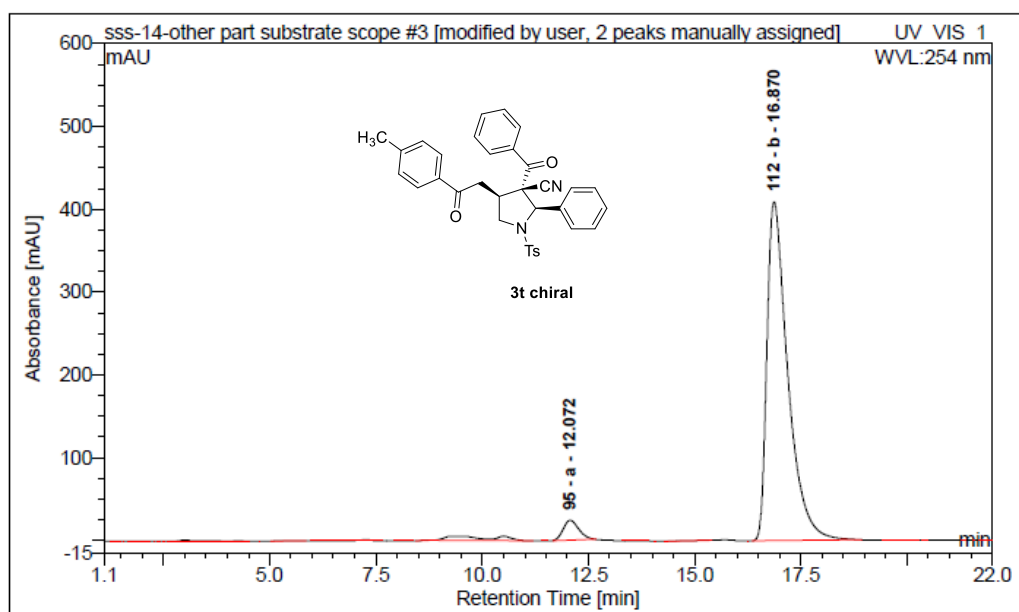


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		21.21	108.6271	97.79521062	130.9079	n.a.
2 b		24.63	2.449	2.204789378	2.780	n.a.

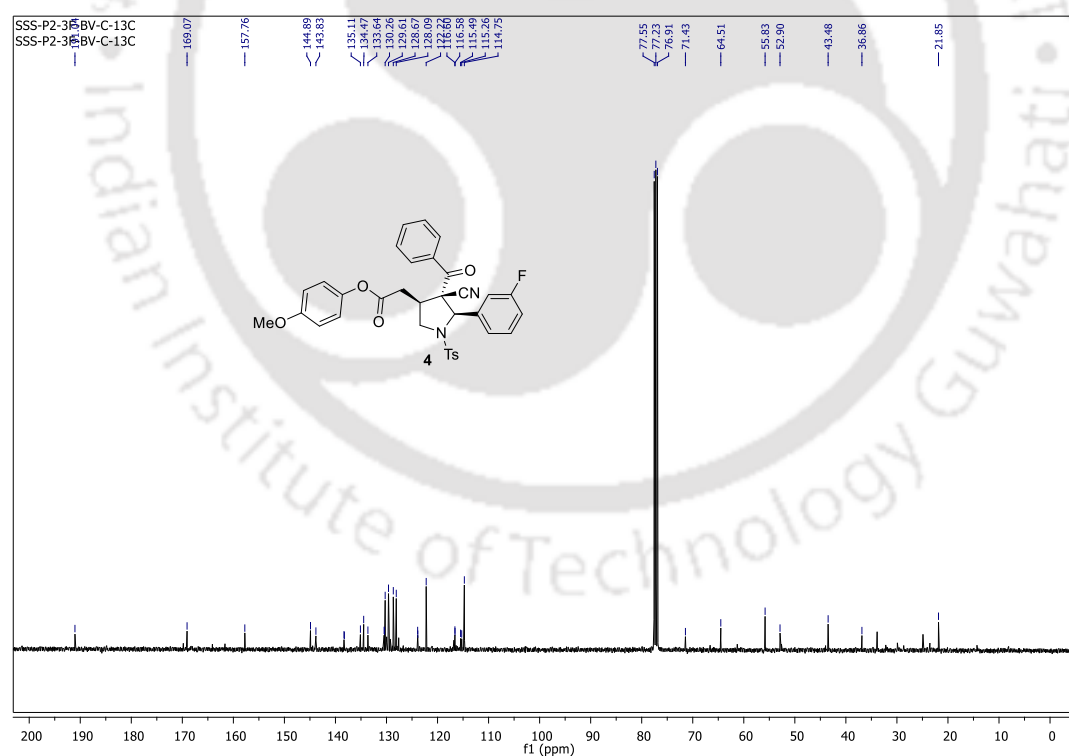
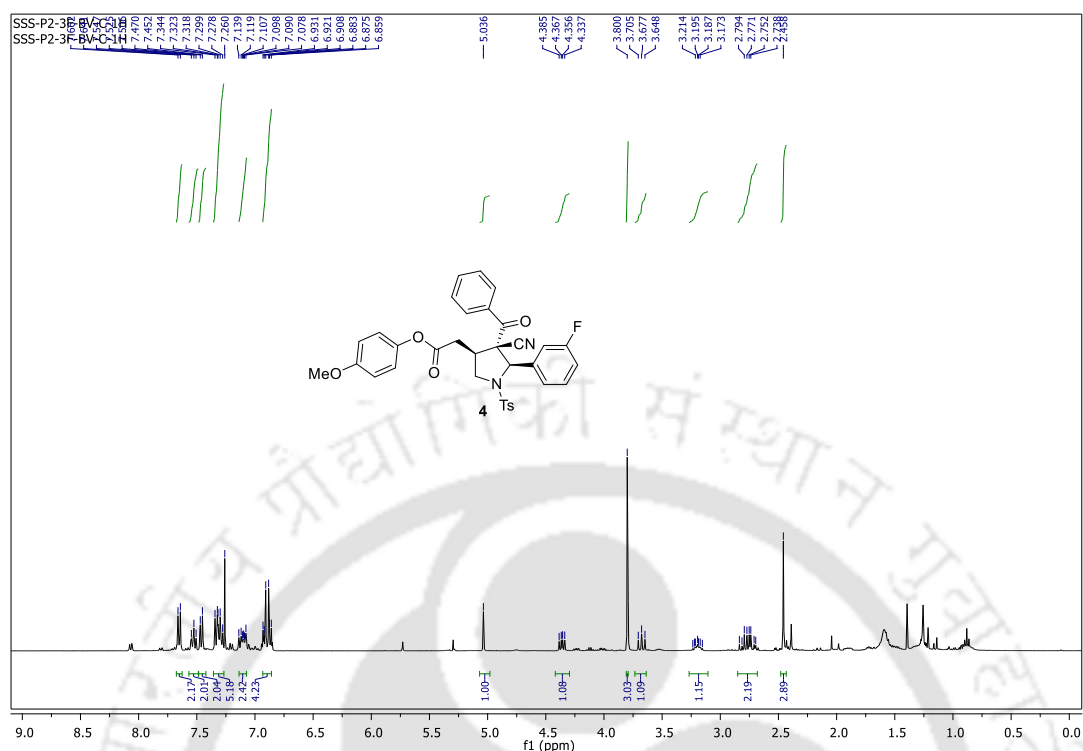


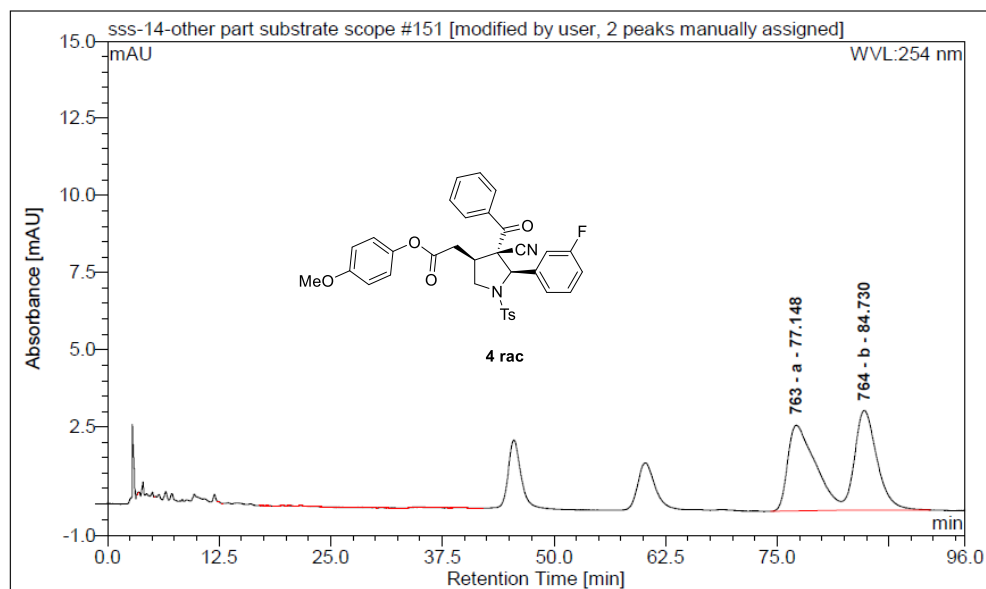


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	11.83	138.9023	51.44223966	324.4802	n.a.
2	b	17.12	131.114	48.55776034	224.110	n.a.

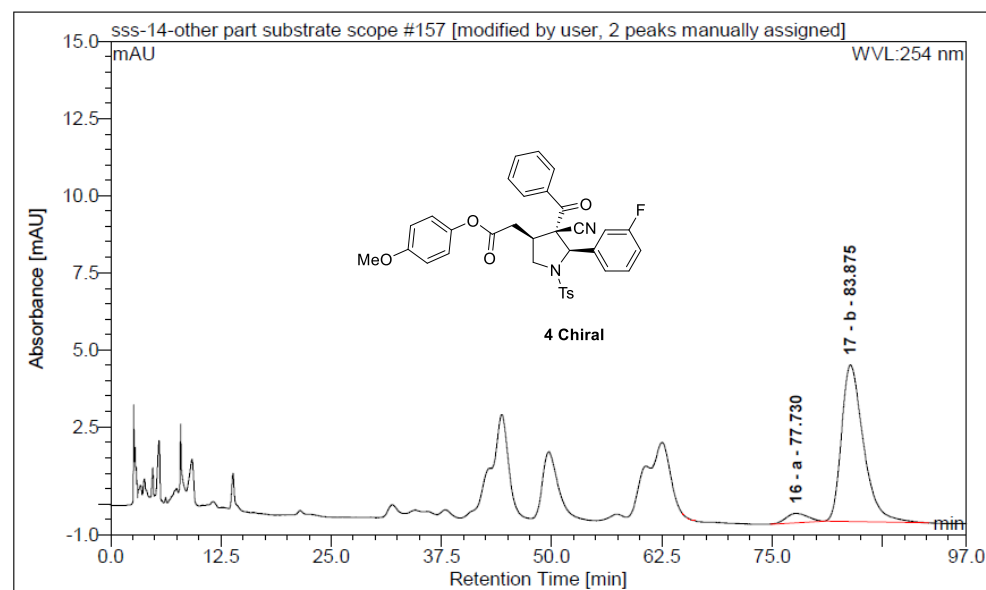


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
95	a	12.07	10.15986	4.181661049	24.03188	n.a.
112	b	16.87	232.802	95.81833895	409.541	n.a.





No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
763	a	77.15	9.888247	51.20815972	2.77624	n.a.
764	b	84.73	9.422	48.79184028	3.231	n.a.



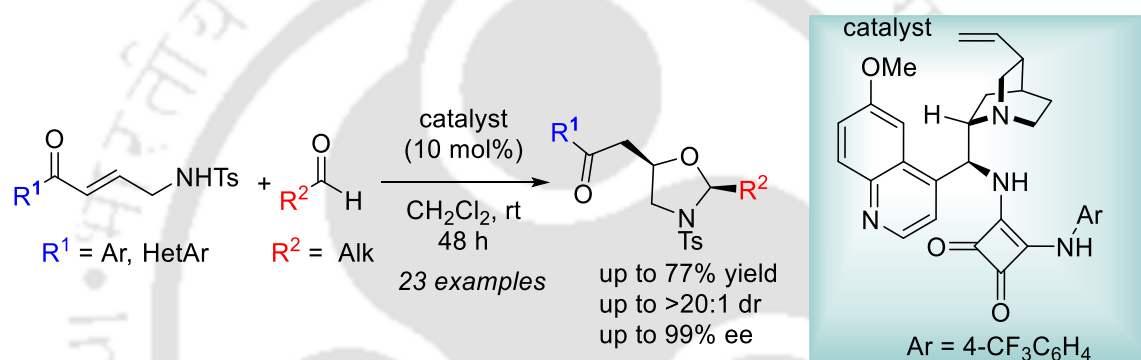
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
16	a	77.73	0.844845	5.444061447	0.30631	n.a.
17	b	83.88	14.674	94.55593855	5.079	n.a.



Chapter 4

Organocatalytic Asymmetric Synthesis of 2,5-Disubstituted Oxazolidines

Abstract: An unprecedented organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines has been developed *via* hemiaminal formation followed by intramolecular oxa-Michael reaction between alkyl aldehydes and *N*-tosyl aminomethyl enones. Quinine derived bifunctional squaramide catalyst was found to be efficient for this reaction. With 10 mol% of the catalyst, excellent results were obtained for a variety of alkyl aldehydes and *N*-tosyl aminomethyl enones under mild reaction conditions.





4.1. Introduction:

Chiral oxazolidines are versatile intermediate in organic synthesis. Compounds having chiral oxazolidine moieties are prevalent in many biologically active natural products and drugs.¹ Substituted oxazolidines are important structural motifs for polycyclic tetrahydroisoquinoline alkaloids such as quinocarcin and terazomine both of which possess antitumor activity (Figure 1). Besides, chiral oxazolidines are utilized as chiral auxiliaries and chiral ligands in a range of asymmetric transformations.² Also they can be converted to valuable 1,2-amino alcohols which are present in a variety of natural products and pharmaceutically active compounds. Optically active oxazolidines are useful intermediates for the construction of β -amino carbonyl compounds. Thus the interest for the synthesis of enantiopure oxazolidines had grown tremendously over the last few years. However, the enantioselective synthesis of oxazolidines mainly focused on chiral pool synthesis employing chiral amino alcohols or chiral epoxides.³ Most of these methods deal with the use of chiral reagents or require stoichiometric amount of the catalyst. Nevertheless, the catalytic asymmetric synthesis of oxazolidines has been rarely developed.⁴

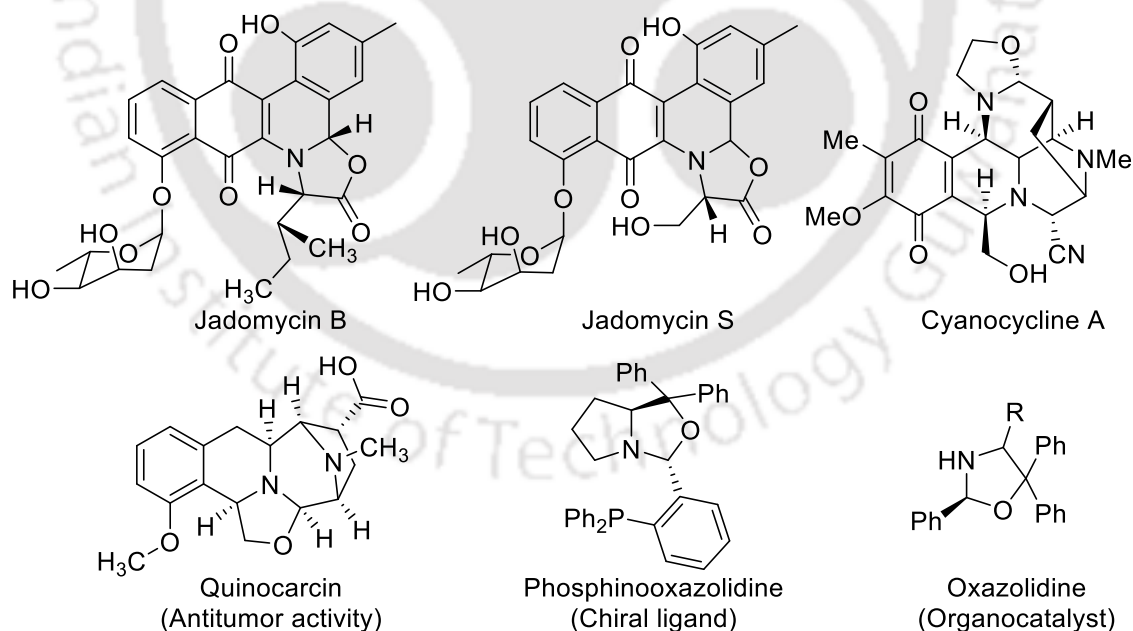
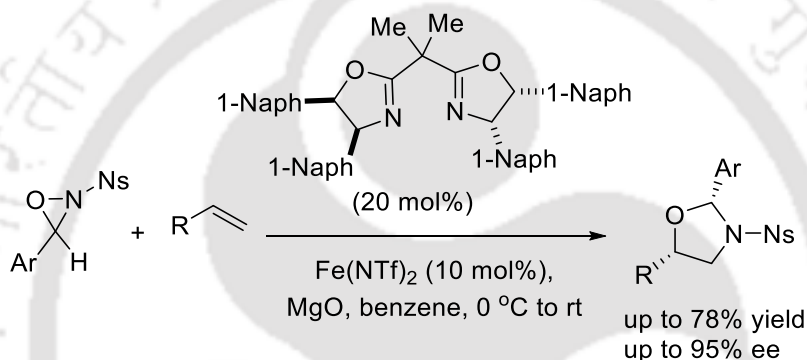


Figure 1: Biologically active compounds, organocatalyst and ligand containing chiral oxazolidine motifs

Also, the reported asymmetric methods mainly concerned about the synthesis of 2,4-disubstituted oxazolidines and 2,5-disubstituted oxazolidines have been overlooked.³ Besides, the activation of aldehydes by H-bonding catalyst for the synthesis of 2,5-disubstituted oxazolidines has never been applied.

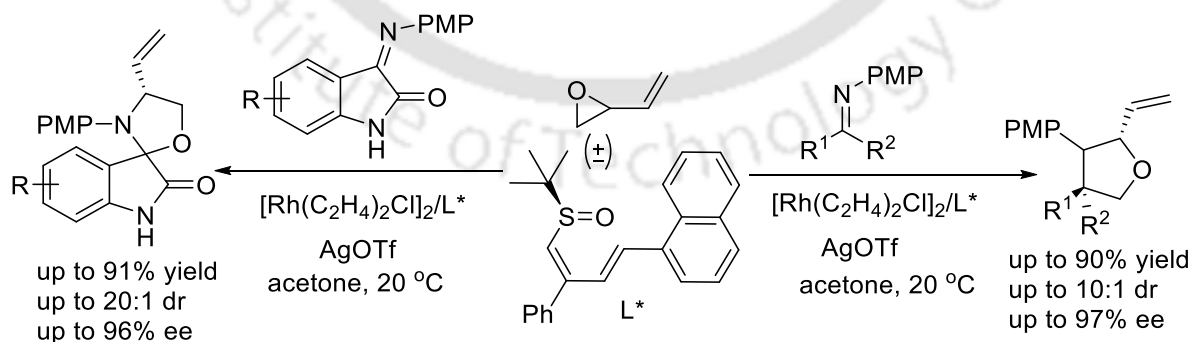
4.2. Reported strategies for the synthesis of chiral oxazolidines:

In 2012 Yoon *et al.* explored a novel iron (II) bis(oxazoline) complex catalyzed regioselective and enantioselective oxyamination of styrene with *N*-sulfonyl aziridines for the synthesis of 2,5-disubstituted oxazolidines. This method delivered the substituted oxazolidines products in good yields and with high enantiomeric excesses (Scheme 4.1).⁵



Scheme 4.1: Fe (II) catalyzed oxyamination for the synthesis of oxazolidines

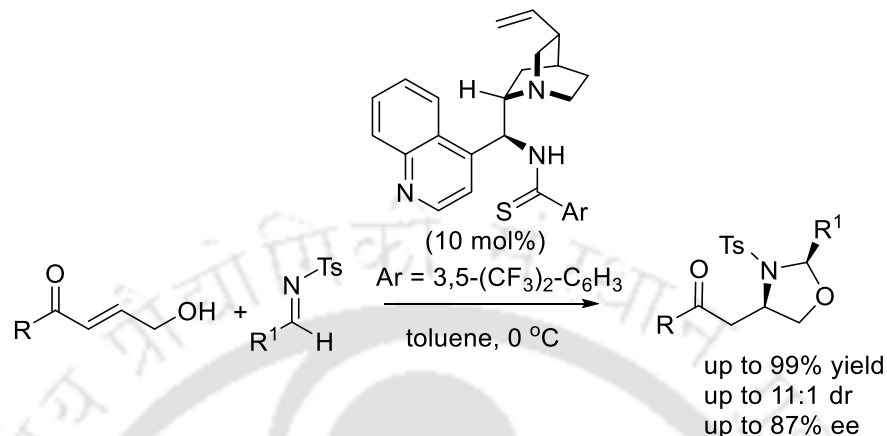
A rhodium catalyzed enantioselective formal [3+2] cycloaddition between racemic butadiene sulfur monoxide and imines to furnish spirooxindoles and 1,3-oxazolidines *via* dynamic kinetic resolution or kinetic resolution has been demonstrated by Du and coworkers (Scheme 4.2).⁶



Scheme 4.2: Rh catalyzed formal [3+2] cycloaddition for the synthesis of oxazolidines

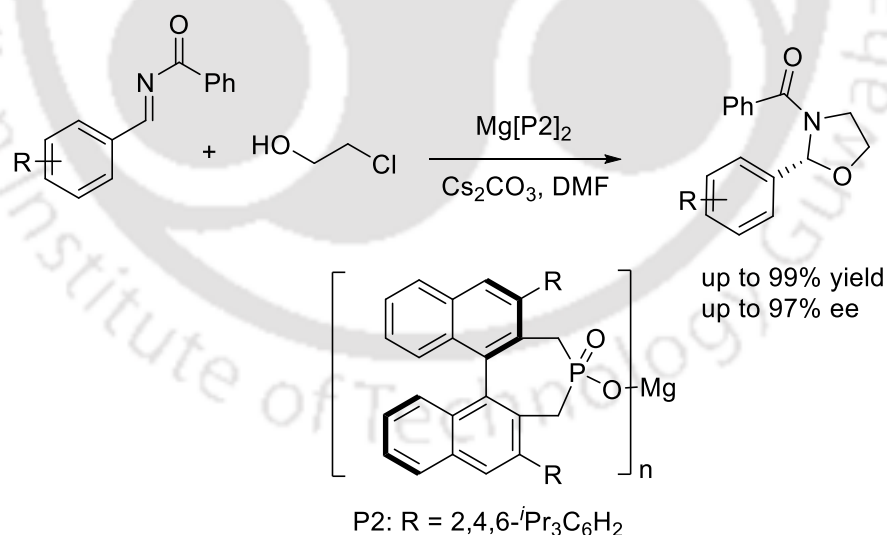
Matsubara group developed organocatalytic asymmetric synthesis of 2,4-disubstituted oxazolidines *via* intramolecular *aza*-Michael reaction strategy. Cinchona alkaloid derived

bifunctional thiourea catalysts were found to be efficient and delivered the oxazolidines products with good diastereomeric ratios and moderate enantiomeric excesses. (Scheme 4.3).⁷



Scheme 4.3: Thiourea catalyzed *aza*-Michael reaction for the synthesis of 2,4-disubstituted oxazolidines

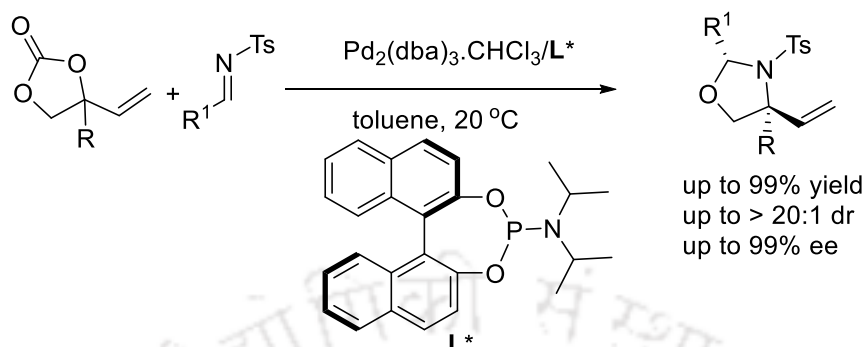
A highly efficient 9-anthryl derived chiral BINOL magnesium phosphate catalyzed asymmetric one pot synthesis of oxazolidines has been reported by Antilla group with excellent enantioselectivities (Scheme 4.4).⁸



Scheme 4.4: Enantioselective synthesis of 1,3-oxazolidines

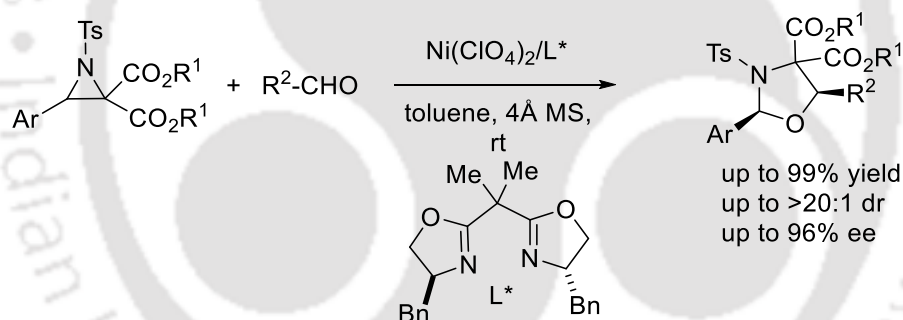
Zhang group disclosed a highly enantio and diastereoselective synthesis of 2,4-disubstituted oxazolidines using a Pd-catalyzed decarboxylative cycloaddition of vinyl ethylene carbamates with *N*-tosyl imines. A combination of [Pd₂(dba)₃].CHCl₃ and

phosphoramidite ligand **L*** delivered the desired oxazolidines in good yields with high enantio- and diastereoselectivities (Scheme 4.5).⁹



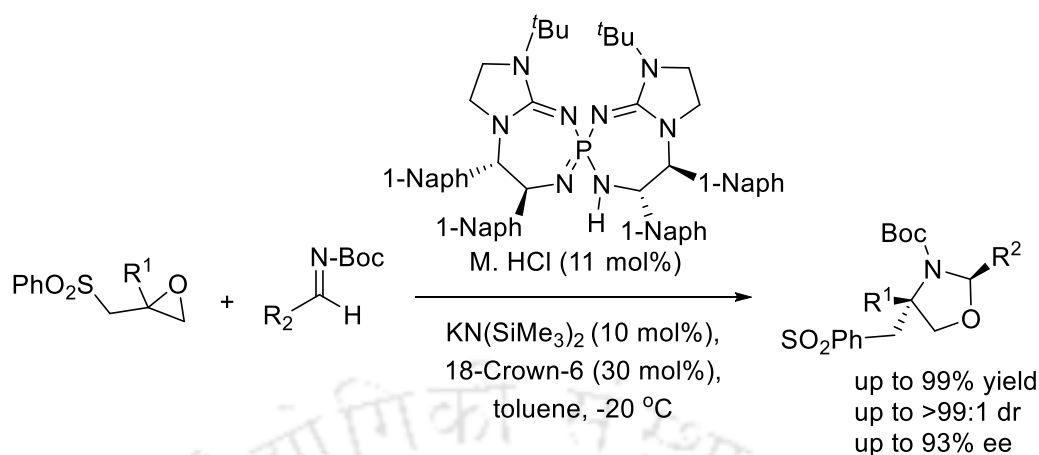
Scheme 4.5: Pd-catalyzed decarboxylative cycloaddition for the synthesis of 2,4-disubstituted oxazolidines

An enantioselective [3+2] cycloaddition between *N*-tosylaziridines and aldehydes catalyzed by Ni (II)-bisoxazolidine complex for the synthesis of chiral 1,3-oxazolidine derivatives has been proposed by Zhang and coworkers (Scheme 4.6).¹⁰



Scheme 4.6: Ni (II) catalyzed [3+2] cycloaddition for the synthesis of chiral 1,3-oxazolidines

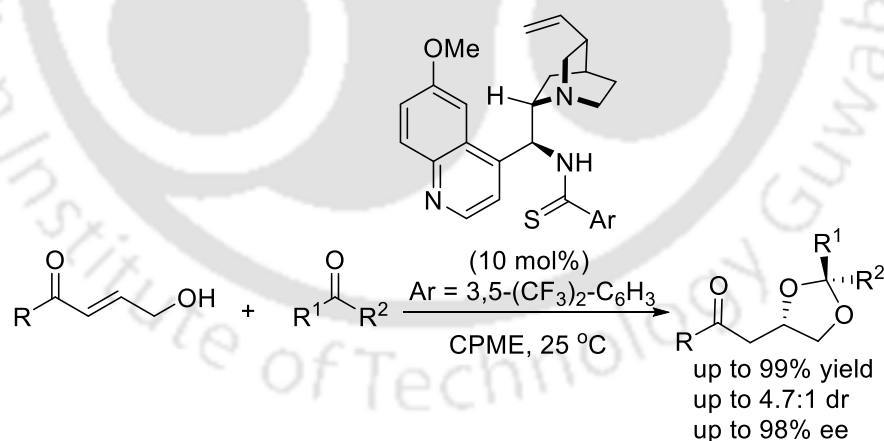
Terrada and coworkers manifested a novel enantioselective formal [3+2] cycloaddition of racemic epoxides and imines leading to the construction of enantioenriched 1,3-oxazolidines. High diastereo- and enantioselectivities were obtained by employing bis(guanidino) imino phosphorane as a chiral organosuperbase catalyst (Scheme 4.7).¹¹



Scheme 4.7: Chiral organosuperbase catalyzed [3+2] cycloaddition

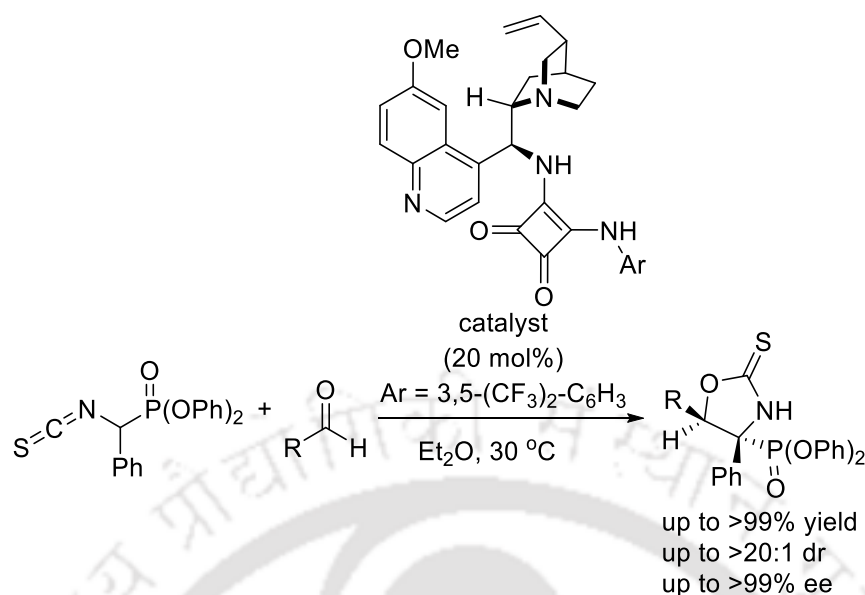
4.3. Selective tandem or cascade reactions of aldehydes for the construction of heterocyclic compounds:

A novel organocatalytic asymmetric cascade reaction for the synthesis of chiral 1,3-dioxalones as demonstrated by Matsubara group proceeds through a formal [3+2] cycloaddition addition strategy. Quinine derived bifunctional catalyst found to be efficient for the activation of aldehydes through H-bonding and furnished the products with high enantiomeric ratios and moderate diastereomeric ratios (Scheme 4.8).¹²



Scheme 4.8: Thiourea catalyzed [3+2] cycloaddition for the synthesis of chiral 1,3-dioxalones

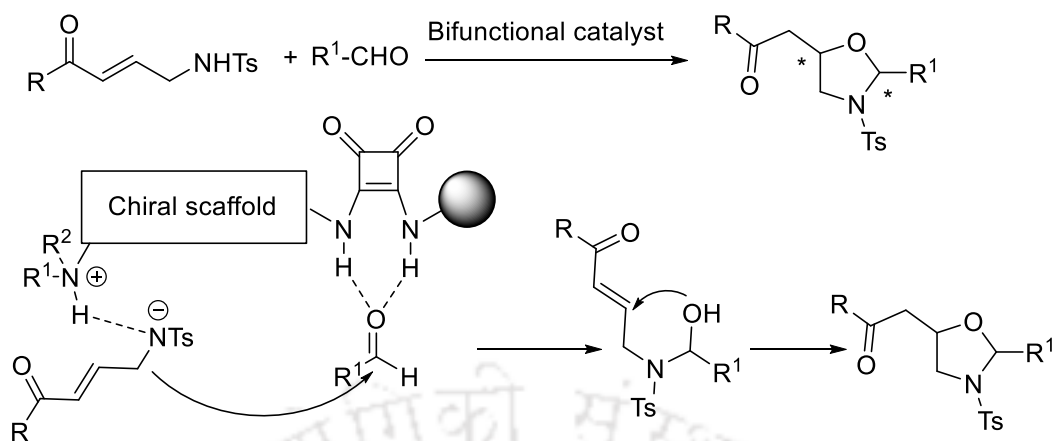
Wang *et al.* reported enantioselective synthesis of optically active 4,5-disubstituted-2-thioxooxazolidin-4-yl phosphonate via a cascade reaction of α -isothiocyanato phosphonate and aldehyde. Quinine derived bifunctional squaramide catalyst activated both phosphonate and aldehyde reactants to provide the expected products in good yields and with high enantio- and diastereoselectivities (Scheme 4.9).¹³



Scheme 4.9: Thiourea catalyzed synthesis of optically active phosphonates

4.4. Concept:

Chiral oxazolidine is an important structural unit frequently found in many biologically active compounds and pharmaceutical agents. Besides, chiral oxazolidines have huge applications as chiral auxiliaries and chiral ligands in many enantioselective transformations. Chiral oxazolidines can be easily converted to 1,2-amino alcohols which are common in many natural products. Thus it is important to synthesize enantioenriched oxazolidines in a simple and efficient way. Most of the reported methods for the synthesis of chiral oxazolidines focused on the use of chiral amino alcohols and chiral epoxides. Catalytic asymmetric synthesis of oxazolidines are less common. However, the reported protocols focused mainly on the synthesis of 2,4-disubstituted oxazolidines. Notably, synthesis of 2,5-disubstituted oxazolidines have been overlooked. Realizing the potential of chiral oxazolidines in bioactive compounds, we envisioned to develop the first organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines *via* a cascade reaction strategy. We used *N*-tosyl amino methyl enones and aldehydes as the substrates. The carbonyl functionality of aldehyde will be activated by the thiourea or the squaramide motifs. Tertiary amine part of catalyst will abstract the proton from the amino methyl enones and the corresponding cascade reaction will take place to deliver the desired product (Scheme 4:10).



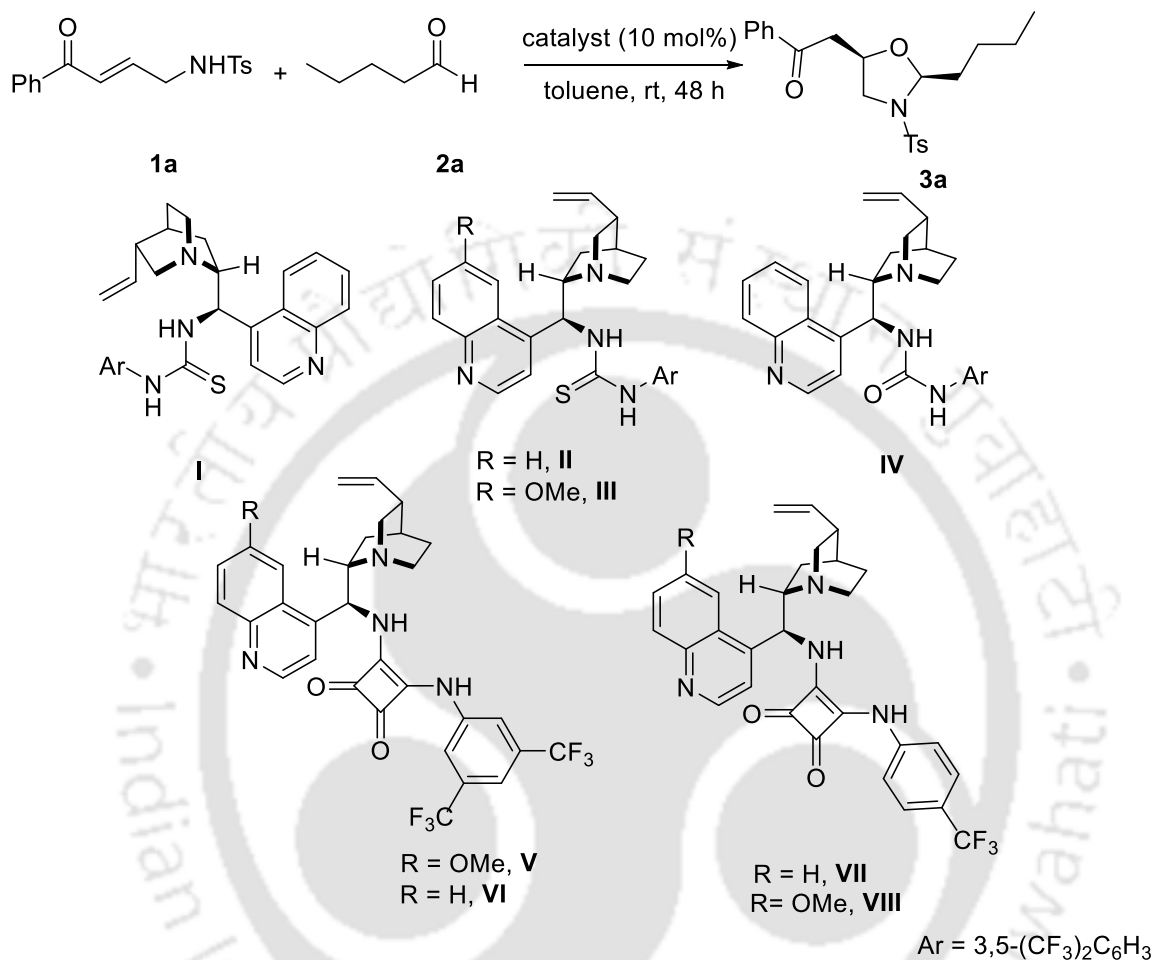
Scheme 4.10: Proposed route for the synthesis of 2,5-disubstituted oxazolidines

4.5. Result and discussion:

The optimization study was initiated by performing a model reaction between *N*-tosyl aminomethyl enone **1a**¹⁴ and *n*-pentanal **2a** in presence of cinchonine derived bifunctional thiourea catalyst **I** in toluene solvent at room temperature (Table 1). Pleasingly, after stirring for 2 days, the desired 2,5-disubstituted oxazolidine product **3a** was isolated in 70% yield with >20:1 dr and in 84% ee (entry 1). The enantioselectivity got improved to 92% ee with cinchonidine derived thiourea catalyst **II** (entry 2). Similar enantioselectivity was observed with quinine derived thiourea catalyst **III** (entry 3). Employment of cinchonidine derived urea catalyst could not improve the enantioselectivity of the product and 89% enantiomeric excess was observed (entry 4). To elevate the enantioselectivity of the product further, we turned our attention to screen different cinchona alkaloid derived squaramide catalysts in our reaction (Table 1, entries 5-8). Quinine derived squaramide catalyst **V** having bis-trifluoromethyl substituted aryl group furnished the desired product with 73% yield, however the enantioselectivity was similar (entry 5). Interestingly, the enantioselectivity increased to 92% with cinchonidine derived squaramide catalyst **VI** (Table 1, entry 6). To improve the enantioselectivity for the product further, we turned our attention to screen different squaramide catalysts bearing *para*-trifluoromethyl group. Cinchonidine derived squaramide catalyst **VII** having *para*-trifluoromethyl group provided the expected product in 70% yield with >20:1 dr and in 91% enantiomeric excess (entry 7). Finally the best result was achieved with quinine derived squaramide catalyst

VIII having *para*-trifluoromethyl group and the oxazolidine product was obtained in 74% yield with >20:1 dr and in 94% enantiomeric excess (entry 8).

Table 1. Catalyst screening



entry ^a	catalyst	yield(%) ^b	dr ^c	ee(%) ^d
1	I	70	>20:1	84
2	II	71	>20:1	92
3	III	72	>20:1	92
4	IV	69	>20:1	89
5	V	73	>20:1	89
6	VI	72	>20:1	92

7	VII	70	>20:1	91
8	VIII	74	>20:1	94

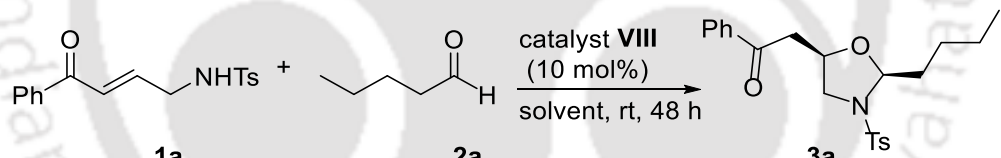
^aReaction conditions: 0.075 mmol of **1a** and 0.15 mmol of **2a** in 0.5 mL toluene using 10 mol% catalyst.

^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC.

4.5.1. Solvent screening:

To further improve the enantioselectivity, the reaction was performed with catalyst **VIII** in different solvents (Table 2). In trifluorotoluene solvent enantioselectivity of the desired product **3a** was similar to toluene solvent (entry 2). Similar enantioselectivity was obtained in diethyl ether solvent (entry 3). To further augment the enantioselectivity of the expected product halogenated solvents were engaged in the reaction (entries 4-5). Chloroform solvent afforded the substituted oxazolidine product with similar enantiomeric excess (entry 4). Finally dichloromethane emerged as the best solvent and afforded the product **3a** in 95% ee with >20:1 dr (entry 5).

Table 2. Solvent screening



entry ^a	solvent	yield(%) ^b	dr ^c	ee(%) ^d
1	toluene	74	>20:1	94
2	TFT	72	>20:1	94
3	Et ₂ O	71	>20:1	94
4	CHCl ₃	75	>20:1	94
5	CH ₂ Cl ₂	76	>20:1	95

^aReaction conditions: 0.075 mmol of **1a** and 0.15 mmol of **2a** in 0.5 mL solvent using 10 mol% catalyst.

^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC.

4.5.2. Substrate scope:

After identifying the best optimized conditions, we turned our attention to explore the scope and generality of the methodology for oxazolidine synthesis. At the beginning, different alkylaldehydes were investigated under the optimized reaction conditions with **1a** (Table 3). It turned out that a range of aliphatic linear and branched aldehydes could participate smoothly in the reaction and the outcome was very satisfactory.

Table 3. Scope of oxazolidines with different aldehydes ^{a,b,c,d}

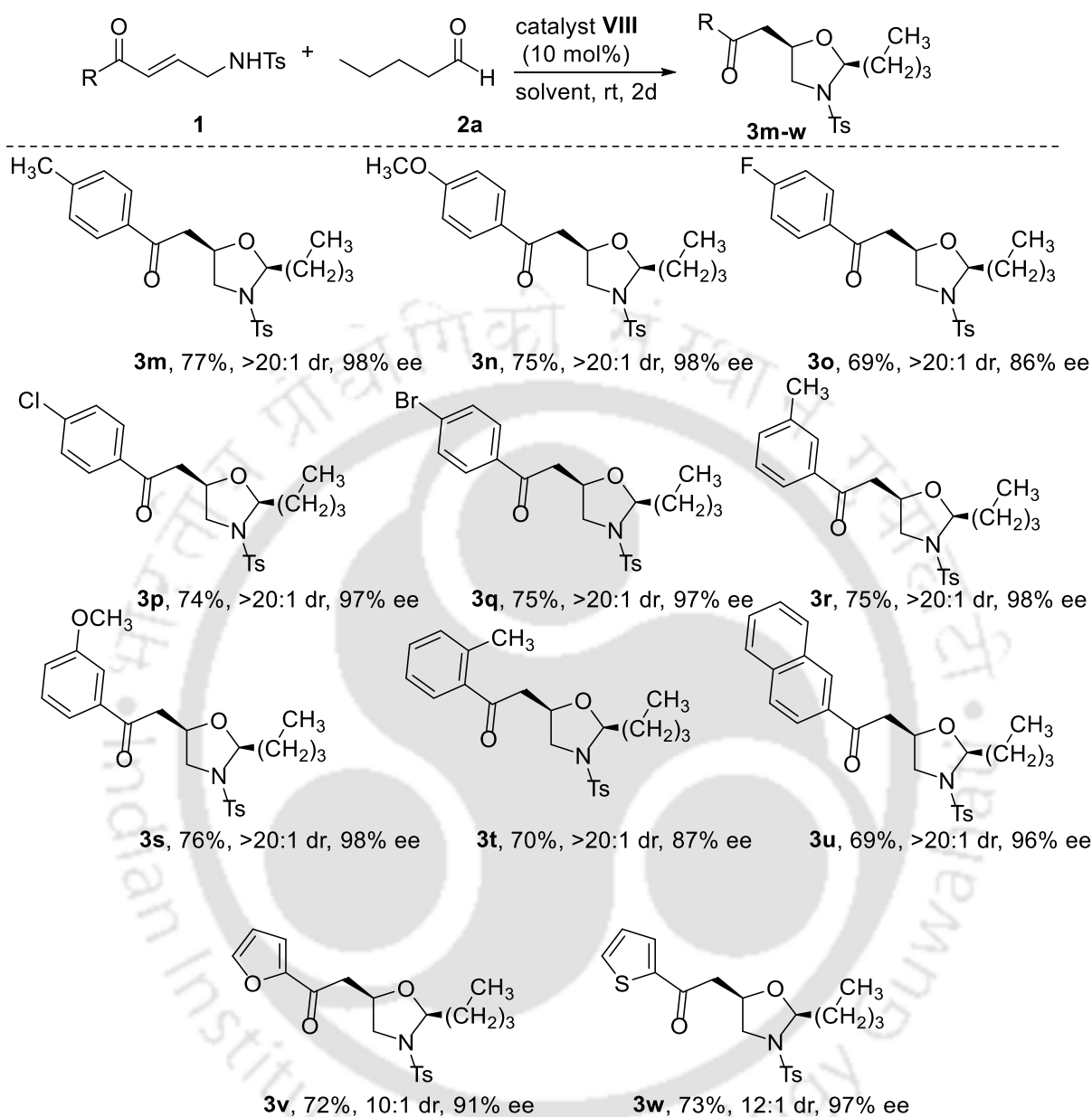
 3a , 76%, >20:1 dr, 95% ee	 3b , 75%, >20:1 dr, 94% ee	 3c , 74%, >20:1 dr, 99% ee
 3d , 73%, >20:1 dr, 94% ee	 3e , 75%, >20:1 dr, 90% ee	 3f , 68%, >20:1 dr, 92% ee
 3g , 73%, >20:1 dr, 94% ee	 3h , 71%, >20:1 dr, 94% ee	 3i , 70%, >20:1 dr, 99% ee
 3j , 76%, >20:1 dr, 92% ee	 3k , 72%, >20:1 dr, 98% ee	 3l , 75%, >20:1 dr, 96% ee

^aReactions were carried out with 0.075 mmol of **1a** and 0.15 mmol of **2a** in 0.5 mL CH₂Cl₂ at rt for 48 h.

^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC

Gratifyingly, in all of the cases, only a single diastereomer was detected. Such as, propanal reacted smoothly to afford the product **3b** as a single diastereomer in 75% yield and 94% enantiomeric excess. The desired oxazolidine **3c** was isolated with good yield and high enantiomeric excess from butyraldehyde **2c**. Then higher order linear aldehydes were engaged in the reaction and it is quite remarkable that the reaction outcome was excellent for linear aldehydes **2d-2l**. For example hexanal reacted smoothly to furnish the product **3d** in 73% yield with 94% ee and as a single diastereomer. Heptanal delivered the expected product **3e** with 90% enantiomeric excess. High enantioselectivity was achieved for product **3f** obtained from octanal. The reaction outcome was excellent for nonanal and the expected product **3g** was isolated with 94% enantiomeric excess. Pleasingly, decanal afforded the desired product **3h** with good yield and high enantioselectivity. Very satisfactory result was also achieved with dodecanal (**2i**) and the product **3i** was isolated in 99% ee. Excellent enantioselectivity was obtained for the product **3j** derived from hydrocinnamaldehyde. Moreover, smooth conversion was also detected with branched aldehyde like isovaleraldehyde and product **3k** was isolated in 72% yield with >20:1 dr and 98% enantiomeric excess. Cyclohexanecarbaldehyde also took part smoothly in the reaction and furnished the product **3l** with 96% enantiomeric excess.

To further extend the scope of the reaction, different *N*-tosyl aminomethyl enones **1** were screened (Table 4). Initially different *N*-tosyl amino methyl enones having substitutions on the aryl group were prepared and engaged in the reaction. Gratifyingly, a range of substitutions at the *ortho*-, *meta*- and *para*- positions of the aryl group were tolerated well and satisfactory results were obtained. Almost, every cases the products were isolated as a single diastereomer with high enantio and diastereoselectivities (Table 4). Initially, different *para*-substituted aryl groups containing aminomethyl enones were screened and delightfully excellent enantioselectivities were observed (Table 4). For example, enone having *p*-tolyl group **1b** reacted well to deliver product **3m** in 75% yield with 98% ee. The desired product **3n** was isolated with high enantio and diastereoselectivity from enone bearing *para*-anisyl moiety. Then different 4-halo substituted enones were investigated in the reaction and the reaction outcome was very promising. Enone bearing 4-fluoro substituent furnished the product **3o** with slight diminution in enantioselectivity. Interestingly, 4-chloro substituted enone delivered the expected product **3p** in 74% yield with 97% enantiomeric excess as a single diastereomer.

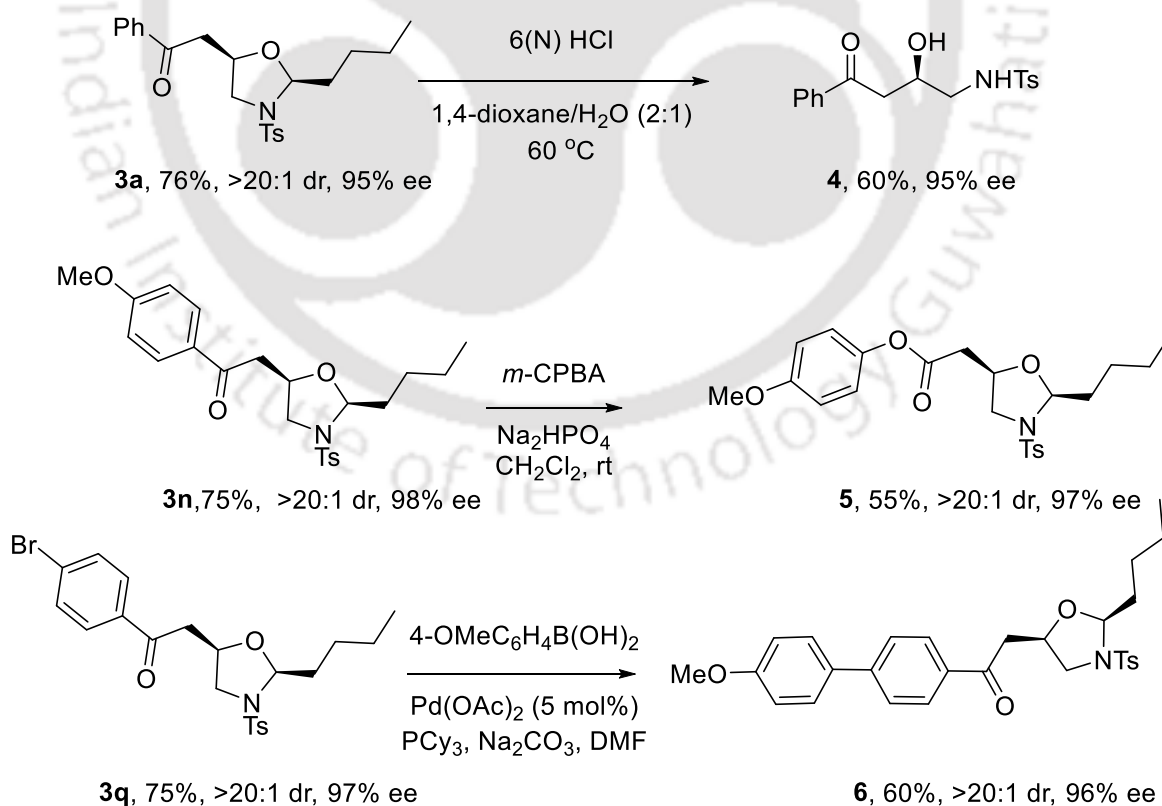
Table 4. Scope of oxazolidines with different *N*-tosyl aminomethyl enones^{a,b,c,d}^aReactions were carried out with 0.075 mmol of **1** and 0.15 mmol of **2a** in 0.5 mL CH₂Cl₂ at rt for 48 h.^bIsolated yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by HPLC.

High enantiomeric excess of 97% was observed for the product **3q** having 4-Br substitution. Then we turned our attention to screen different *meta*-substituted enones and delightfully high enantioselectivities were observed. Enone containing *m*-tolyl group provided the product **3r** in 76% yield and 98% enantiomeric excess. *meta*-Anisyl substituted enone reacted well to produce the desired product with high enantiomeric excess. *ortho*-Substituted enone also responded well and from *ortho*-tolyl substituted

enone the product was isolated with good yield and enantiomeric excess. Enone **1j** having 2-naphthyl group also participated in the reaction to afford product **3u** in 69% yield and 96% ee. Moreover, heteroaromatic groups can also be incorporated in the enone moiety and smooth conversions were detected. The products **3v** and **3w** having 2-furyl and 2-thienyl motifs were isolated in high enantioselectivities.

4.5.3. Synthetic transformations of chiral products:

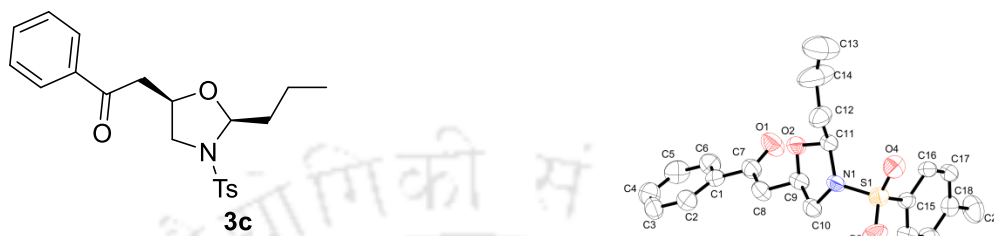
The synthetic utility of our method was displayed by performing few reactions on **3a**, **3n** and **3q**. Initially, an acid mediated hydrolysis of oxazolidine **3a** was carried out with 6(N) hydrochloric acid. The linear 1,2-amino alcohol **4** was isolated in 60% yield with preservation of enantiopurity. Then Baeyer-Villiger oxidation of **3n** resulted in the formation of ester **5** in 55% yield and here also the enantioselectivity was almost similar. Finally, a Suzuki coupling reaction was performed between **3q** and 4-methoxyphenylboronic acid. Gratifyingly, the desired product **6** was formed in 60% yield with retention of enantiopurity (Scheme 4.11).



Scheme 4.11: Synthetic transformations of chiral products

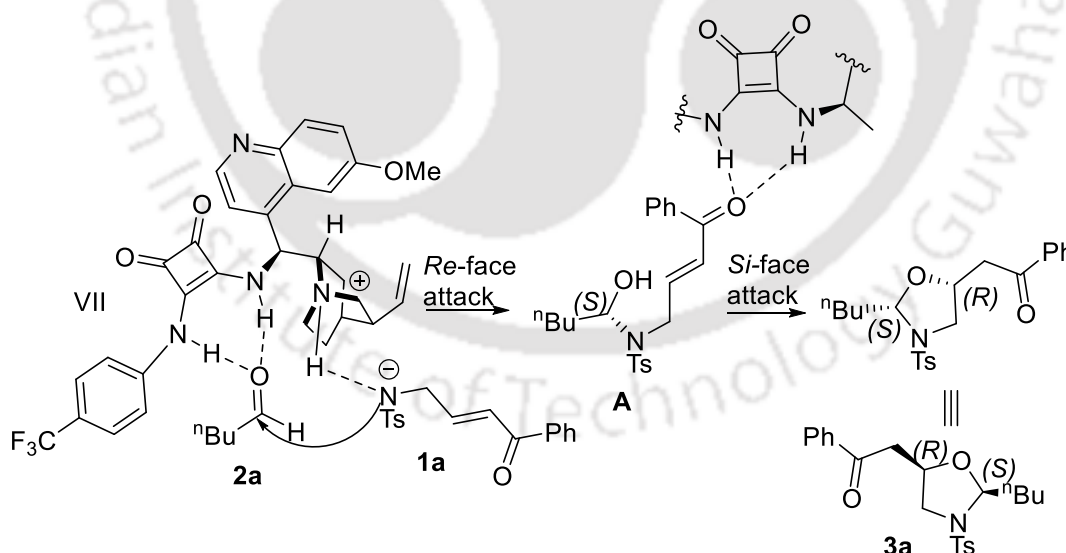
4.5.4. Absolute configuration 3c:

The absolute configuration of the product **3c** was solved to be (2*S*, 5*R*) by X-ray crystallography.¹⁹ The absolute structure of other products are believed to be same by analogy



4.5.5. Proposed mechanism:

Based on the absolute configuration, a probable mechanism has been shown in Scheme 4.12. It is assumed that aldehyde **2a** is activated by the squaramide moiety of the catalyst **VIII** whereas the tertiary amino motif of **VIII** deprotonates **1a**. Since the *Si* face of **2a** is blocked by catalyst **VIII**, addition of *N*-tosylamino group on the aldehyde **2a** takes place from *Re* face to provide hemiaminal **A**. Hemiaminal **A** then undergoes an intramolecular oxa-Michael reaction on the *Si* face of the enone to generate product **3a** (Scheme 4.12).



Scheme 4.12: Proposed mechanistic cycle

4.6. Conclusion:

In summary, this report delineates the first organocatalytic asymmetric synthesis of 2,5-disubstituted oxazolidines *via* hemiaminal formation/Michael reaction between simple alkyl aldehydes and *N*-tosyl aminomethyl enones. The oxazolidine products were isolated in good yields and with excellent diastereo- and enantioselectivities. Also, few synthetic transformations have been demonstrated including a synthesis of linear 1,2-aminoalcohol. Realizing the significance of high pharmaceutical importance and other utilities of oxazolidines, the newly synthesized products will be fruitful for the development of new drugs and ligands/catalysts.

4.7. Experimental section:

General information:

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

^1H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in CDCl_3 ; chemical shift values (δ , ppm) were reported in the standard fashion with reference to either tetramethylsilane (TMS) ($\delta(\text{H})$ 0.00 ppm) or CHCl_3 ($\delta(\text{H})$ 7.26 ppm).

^{13}C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in CDCl_3 ; chemical shifts (δ , ppm) were reported relative to CHCl_3 ($\delta(\text{C})$ 77.23 ppm, central line of triplet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (J) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization

(ESI) technique. IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-K α irradiation (λ = 0.71073 Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F² using SHELXL-2014.

A. General procedure for the synthesis of amino methyl enones 1a-1l:

Amino methyl enones were prepared according to the reported procedure.²⁰

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

Thiourea and squaramide catalysts were prepared according to the reported procedure.²¹

D. General procedure for the synthesis of chiral oxazolidines:

Under argon atmosphere, *N*-tosyl aminomethyl enone **1a** (0.075 mmol), aldehyde **2a** (0.15 mmol) and catalyst **VIII** (10 mol %) were placed in a round bottom flask and toluene (0.5 mL) was added to it. Then the reaction mixture was stirred at room temperature under argon atmosphere. After completion of the reaction as monitored by TLC, the product was purified by column chromatography using 8-12 % ethyl acetate in hexane as eluent.

E. General procedure for the synthesis of compound 4:

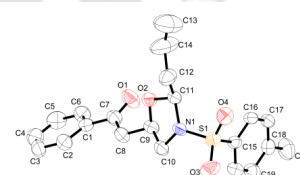
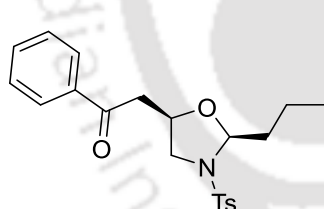
To a solution of **3a** (0.1 mmol) in 1,4-dioxane/H₂O (2:1, 0.4 mL), 6 (N) HCl (40 μ L) was added and the reaction mixture was heated to 60 °C for 4 h. Then the reaction mixture was cooled to room temperature. Next the reaction mixture was neutralized with sodium bicarbonate solution and the aqueous layer was extracted with ethyl acetate thrice. Then the combined organic layers were dried over Na₂SO₄ and evaporated. Finally the crude product was evaporated and purified by silica gel column chromatography using 35% ethyl acetate in hexane.

F. General procedure for the synthesis of compound 5:

To a solution of **3n** (0.1 mmol) in DCM (4 mL) disodium hydrogenphosphate (0.25 mmol) and *m*-CPBA (0.25 mmol) were added. Then the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (2 mL) and the aqueous layer was extracted with DCM twice. Then the combined organic layers were evaporated and the crude product was purified by column chromatography using 15% ethyl acetate in hexane.

G. General procedure for the synthesis of compound 6:

To a round bottom flask 10 mL **3q** (0.1 mmol), Pd(OAc)₂ (5 mol%), PCy₃ (5 mol%), 4-methoxy phenyl boronic acid and Na₂CO₃ (0.2 mmol) were added under nitrogen atmosphere. Then 0.5 mL DMF was added to the reaction mixture which was stirred at room temperature for overnight. Next H₂O was added to the mixture that was extracted with ethyl acetate. Then the combined organic layers were again washed with H₂O twice and the organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was finally purified by column chromatography (15% ethyl acetate in hexane).

Crystal data and structure refinement for chiral compound (CCDC No. 1862326)

Empirical formula	C ₂₁ H ₂₅ NO ₄ S
Formula weight	387.49
CCDC Number	1862326
Crystal habit, colour	Needle, White
Crystal size, mm ³	0.30 × 0.25 × 0.20
Temperature, <i>T</i>	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	P21
Unit cell dimensions	<i>a</i> = 8.3006(8) Å <i>b</i> = 5.9266(4) Å <i>c</i> = 20.9303(16) Å <i>α</i> = 90.00°, <i>β</i> = 95.643(10)° <i>γ</i> = 90.00°

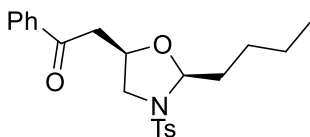
Volume, V (Å ³)	1024.66(14)
Z	2
Calculated density, Mg·m ⁻³	1.256
Absorption coefficient, μ (mm ⁻¹)	0.183
$F(000)$	412.0
θ range for data collection	2.93 to 25°
Limiting indices	$-5 \leq h \leq 9, -7 \leq k \leq 6, -24 \leq l \leq 24$
Reflection collected/unique	8912/ 4015 [$R(\text{int})=0.0329$]
Completeness to θ	99.78% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.947/0.964
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data/restraints/parameters	2995/1/247
Goodness-of-fit on F^2	1.045
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0605, wR_2 = 0.1274$
R indices (all data)	$R_1 = 0.0943, wR_2 = 0.14900$
Largest diff. peak and hole	0.17 and $-0.23 \text{ e} \cdot \text{\AA}^{-3}$

4.8. References:

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- (3) For a review see: (a) Ref. 2b. For selected recent examples, see: (b) Sriramurthy, V.; Barcan, G. A.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12928. (c) Kondoh, A.; Odaira, K.; Terada, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 11240.
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- (5) Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2012**, *134*, 12370.
- (6) Liu, Z.; Feng, X.; Du, H. *Org. Lett.* **2012**, *14*, 3154.
- (7) Fukata, Y.; Asano, K.; Matsubara, S. *Chem. Lett.* **2013**, *42*, 355.
- (8) Nimmagadda, S. K.; Zhang, Z.; Antilla, J. C. *Org. Lett.* **2014**, *16*, 4098.
- (9) Yang, L.; Khan, A.; Zhang, R.; Jin, L. Y.; Zhang, Y. J. *Org. Lett.* **2015**, *17*, 6230.
- (10) Wu, X.; Zhou, W.; Wu, H.-H.; Zhang, J. *Chem. Commun.* **2017**, *53*, 5661.
- (11) Kondoh, A.; Akahira, S.; Oishi, M.; Terada, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 6299.
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- (13) Cao, Y.-M.; Shen, F.-F.; Zhang, F.-T.; Zhang, J.-L.; Wang, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 1862.
- (14) For asymmetric reactions with **1a**, see: (a) Li, J.-H.; Wen, H.; Liu, L.; Du, D.-M. *Eur. J. Org. Chem.* **2016**, 2492. (b) Mukhopadhyay, S.; Pan, S. C. *Chem. Commun.* **2018**,

- 54, 964. (c) Zhao, B.-L.; Du, D.-M. *Asian J. Org. Chem.* **2015**, *4*, 1120. (d) Zhang, Z.-F.; Zhang, C.-L.; Gao, Z.-H.; Ye, S. *Chem. - Eur. J.* **2018**, *24*, 8302
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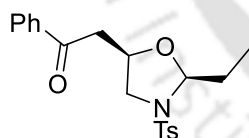
4.9. Characterization Data of Products:

2-((2S,5R)-2-butyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3a)

This compound was prepared according to the general procedure D. Colourless liquid (22.8 mg, yield: 76%);

Diastereomeric ratio: >20:1; **¹H NMR (400 MHz,**

CDCl₃): δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.61 – 7.54 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.05 (dd, *J* = 6.1, 4.0 Hz, 1H), 4.04 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.65 (ddt, *J* = 9.7, 7.8, 5.3 Hz, 1H), 3.45 (dd, *J* = 17.4, 5.1 Hz, 1H), 2.99 (ddd, *J* = 25.2, 14.7, 8.7 Hz, 2H), 2.44 (s, 3H), 1.89 – 1.79 (m, 1H), 1.78 – 1.68 (m, 1H), 1.43 – 1.33 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 196.9, 144.4, 136.4, 134.8, 133.8, 130.3, 128.9, 128.3, 128.0, 91.6, 73.3, 52.5, 42.5, 36.3, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1683, 1598, 1566, 1456, 1352, 1092 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₈NO₄S [M+H]⁺ 402.1734; found 402.1738; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (95:5 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 13.6 min, τ_{minor} = 15.1 min); Enantiomeric excess: 95%.

2-((2S,5R)-2-ethyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3b)

This compound was prepared according to the general procedure D.

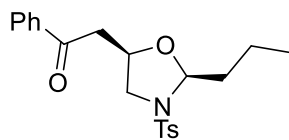
Colourless liquid (21 mg, yield: 75%); **Diastereomeric ratio:**

>20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.79

(d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.03 (dd, *J* = 5.4, 4.1 Hz, 1H), 4.04 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.66 (ddd, *J* = 13.2, 10.3, 5.4 Hz, 1H), 3.45 (dd, *J* = 17.4, 5.2 Hz, 1H), 3.02 (dd, *J* = 12.0, 9.7 Hz, 1H), 2.96 (dd, *J* = 17.4, 7.7 Hz, 1H), 2.44 (s, 3H), 1.89 – 1.83 (m, 1H), 1.81 – 1.76 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.9, 144.4, 136.4, 134.7, 133.9, 130.3, 128.9, 128.2, 128.0, 92.2, 73.3, 52.6, 42.4, 29.4, 21.8, 8.2; **FT-IR (thin film):** 1681, 1602, 1568, 1457, 1350, 1216, 1161, 1088, 789 cm⁻¹; **HRMS (+ESI):** Calc for C₂₀H₂₄NO₄S [M+H]⁺ 374.1421; found 374.1433; The enantiomeric ratio was determined by HPLC

analysis using Daicel Chiralpak IB column (98:2 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 28.4$ min, $\tau_{\text{minor}} = 31.5$ min); Enantiomeric excess: 94%.

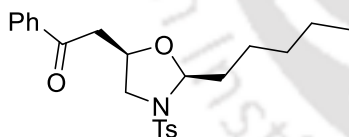
1-phenyl-2-((2*S*,5*R*)-2-propyl-3-tosyloxazolidin-5-yl)ethan-1-one (3c)



This compound was prepared according to the general procedure D. Colourless liquid (21.5 mg, yield: 74%); **Diastereomeric**

ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.88 (d, $J = 8.4$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.59 (s, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.06 (dd, $J = 6.0$, 4.1 Hz, 1H), 4.04 (dd, $J = 12.1$, 5.6 Hz, 1H), 3.65 (ddd, $J = 14.8$, 9.1, 5.4 Hz, 1H), 3.44 (dd, $J = 17.4$, 5.1 Hz, 1H), 2.99 (ddd, $J = 25.2$, 14.8, 8.7 Hz, 2H), 2.44 (s, 3H), 1.86 – 1.77 (m, 1H), 1.74 – 1.68 (m, 1H), 1.46 (ddd, $J = 32.5$, 18.1, 11.6 Hz, 2H), 0.95 (t, $J = 7.4$ Hz, 3H); **¹³C NMR (151 MHz, CDCl₃):** δ 196.9, 144.4, 136.4, 134.7, 133.9, 130.3, 128.9, 128.2, 128.0, 91.4, 73.3, 52.4, 42.5, 38.6, 21.8, 17.5, 14.1; **FT-IR (thin film):** 1683, 1601, 1566, 1352, 1245, 1163, 1090 cm⁻¹; **HRMS (+ESI):** Calc for C₂₁H₂₆NO₄S [M+H]⁺ 388.1577; found 388.1788; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (98:2 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 24.9$ min, $\tau_{\text{minor}} = 28.6$ min); Enantiomeric excess: 99%.

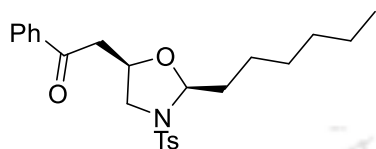
2-((2*S*,5*R*)-2-pentyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3d)



This compound was prepared according to the general procedure D. Colourless liquid (22.7 mg, yield: 73%); **Diastereomeric ratio:** >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.88 (d, $J = 7.5$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 6.0$, 4.0 Hz, 1H), 4.04 (dd, $J = 12.0$, 5.6 Hz, 1H), 3.70 – 3.59 (m, 1H), 3.45 (dd, $J = 17.4$, 5.1 Hz, 1H), 3.03 (dd, $J = 12.0$, 9.7 Hz, 1H), 2.96 (dd, $J = 17.4$, 7.8 Hz, 1H), 2.44 (s, 3H), 1.88 – 1.78 (m, 1H), 1.75 – 1.70 (m, 1H), 1.45 – 1.37 (m, 2H), 1.31 (dd, $J = 6.9$, 3.4 Hz, 4H), 0.89 (t, $J = 6.4$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.4, 36.5, 31.8, 23.7, 22.8, 21.8, 14.3; **FT-IR (thin film):** 1681, 1601, 1565, 1352, 1214, 1163, 1090, 803 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₄S [M+H]⁺ 416.1890; found 416.1906; The enantiomeric ratio was determined by HPLC analysis

using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 16.7$ min, $\tau_{\text{minor}} = 18.7$ min); Enantiomeric excess: 90%.

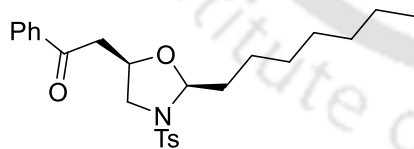
(2*R*,3*S*,4*S*)-3-benzoyl-2-(4-fluorophenyl)-4-(2-oxo-2-phenylethyl)-1-tosylpyrrolidine-3-carbonitrile (3e):



This compound was prepared according to the general procedure D. Colourless liquid (24.1 mg, yield: 75%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.88 (d, $J = 7.3$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 6.0, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.69 – 3.59 (m, 1H), 3.45 (dd, $J = 17.4, 5.1$ Hz, 1H), 2.99 (ddd, $J = 25.2, 14.7, 8.7$ Hz, 2H), 2.44 (s, 3H), 1.82 (ddd, $J = 14.2, 9.5, 4.4$ Hz, 1H), 1.76 – 1.70 (m, 1H), 1.41 (ddd, $J = 17.5, 13.8, 7.2$ Hz, 2H), 1.30 (dd, $J = 15.4, 8.2$ Hz, 6H), 0.88 (t, $J = 6.9$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.4, 36.5, 32.0, 29.2, 24.0, 22.8, 21.8, 14.3; **FT-IR (thin film):** 1683, 1601, 1566, 1452, 1352, 1214, 1162, 1091, 788 cm⁻¹; **HRMS (+ESI):** Calc for C₂₄H₃₂NO₄S [M+H]⁺ 430.2047; found 430.2075; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 16.2$ min, $\tau_{\text{minor}} = 18.2$ min); Enantiomeric excess: 92%.

2-((2*S*,5*R*)-2-heptyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3f)

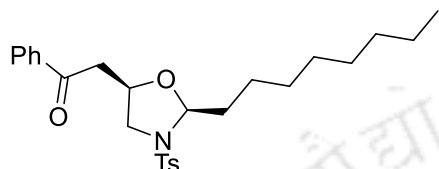


This compound was prepared according to the general procedure D. Colourless liquid (22.6 mg, yield: 68%);

Diastereomeric ratio: >20:1; **¹H NMR (400 MHz,):** δ 7.88 (d, $J = 7.2$ Hz, 2H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 5.05 (dd, $J = 6.1, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.65 (ddt, $J = 10.6, 7.7, 5.3$ Hz, 1H), 3.45 (dd, $J = 17.4, 5.1$ Hz, 1H), 2.99 (ddd, $J = 25.2, 14.7, 8.7$ Hz, 2H), 2.44 (s, 3H), 1.83 (ddd, $J = 20.0, 11.8, 7.8$ Hz, 1H), 1.73 (ddd, $J = 14.1, 9.6, 5.1$ Hz, 1H), 1.46 – 1.38 (m, 2H), 1.34 – 1.26 (m, 8H), 0.88 (t, $J = 6.9$ Hz, 3H); **¹³C NMR (100 MHz,):** δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.5, 36.6, 32.0, 29.6, 29.5, 24.1, 22.9, 21.8, 14.3; **FT-IR (thin**

film): 1683, 1602, 1566, 1466, 1353, 1215, 1161, 1090, 790 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{25}\text{H}_{34}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 444.2203; found 444.2205; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (95:5 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 12.2$ min, $\tau_{\text{minor}} = 13.7$ min); Enantiomeric excess: 94%.

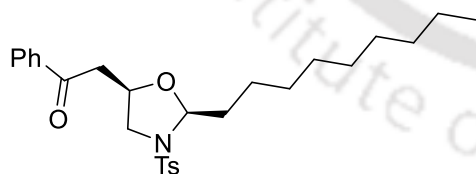
2-((2*S*,5*R*)-2-octyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3g)



This compound was prepared according to the general procedure D. Colourless liquid (25 mg, yield: 73%);

Diastereomeric ratio: >20:1; **^1H NMR (600 MHz, CDCl_3)** δ 7.88 (d, $J = 7.3$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 6.1, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.71 – 3.59 (m, 1H), 3.45 (dd, $J = 17.4, 5.1$ Hz, 1H), 2.99 (ddd, $J = 25.2, 14.7, 8.7$ Hz, 2H), 2.43 (s, 3H), 1.82 (ddd, $J = 14.2, 9.9, 4.7$ Hz, 1H), 1.72 (dt, $J = 19.7, 5.7$ Hz, 1H), 1.41 (ddd, $J = 17.5, 13.5, 7.0$ Hz, 2H), 1.32 – 1.24 (m, 10H), 0.88 (t, $J = 7.0$ Hz, 3H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.5, 36.5, 32.1, 29.8, 29.6, 29.5, 24.1, 22.9, 21.8, 14.4; **FT-IR (thin film)**: 1683, 1602, 1566, 1465, 1354, 1215, 1160, 1090, 784 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{26}\text{H}_{36}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 458.2360; found 458.2467; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.4$ min, $\tau_{\text{minor}} = 17.4$ min); Enantiomeric excess: 94%.

2-((2*S*,5*R*)-2-nonyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3h)

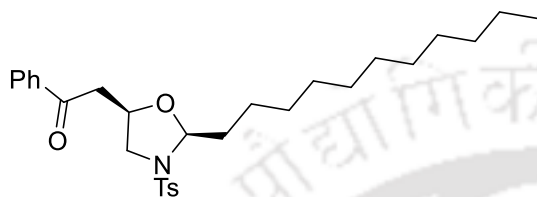


This compound was prepared according to the general procedure D. Colourless liquid (25.1 mg, yield: 71%); **Diastereomeric ratio**: >20:1; **^1H**

NMR (600 MHz, CDCl_3): δ 7.88 (d, $J = 7.3$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 6.0, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.69 – 3.58 (m, 1H), 3.45 (dd, $J = 17.4, 5.1$ Hz, 1H), 2.99 (ddd, $J = 25.2, 14.7, 8.7$ Hz, 2H), 2.44 (s, 3H), 1.82 (ddd, $J = 14.2, 10.0, 5.4$ Hz, 1H), 1.76 – 1.68 (m, 1H), 1.41 (ddd, $J = 17.5, 13.2, 7.0$ Hz, 2H), 1.33 – 1.24 (m, 12H), 0.88 (t, $J = 7.0$ Hz, 3H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.5, 36.5,

32.1, 29.8, 29.7, 29.6, 29.5, 24.1, 22.9, 21.8, 14.4; **FT-IR (thin film):** 1682, 1601, 1567, 1459, 1352, 1214, 1161, 1090, 886 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{27}\text{H}_{38}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 472.2516; found 472.2513; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.0$ min, $\tau_{\text{minor}} = 16.9$ min); Enantiomeric excess: 94%.

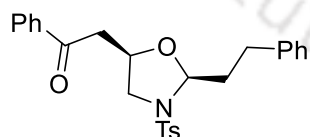
1-phenyl-2-((2*S*,5*R*)-3-tosyl-2-undecyloxazolidin-5-yl)ethan-1-one (3i):



This compound was prepared according to the general procedure D. Colourless liquid (26.2 mg, yield: 70%); **Diastereomeric ratio:** >20:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.88

(d, $J = 7.3$ Hz, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 5.05 (dd, $J = 6.1, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.68 – 3.61 (m, 1H), 3.45 (dd, $J = 17.4, 5.1$ Hz, 1H), 3.03 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.96 (dd, $J = 17.4, 7.8$ Hz, 1H), 2.44 (s, 3H), 1.82 (ddd, $J = 14.2, 9.5, 5.1$ Hz, 1H), 1.76 – 1.69 (m, 1H), 1.44 – 1.38 (m, 2H), 1.33 – 1.25 (m, 18H), 0.88 (t, $J = 7.0$ Hz, 3H); **^{13}C NMR (150 MHz, CDCl_3):** δ 196.9, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 91.6, 73.3, 52.4, 42.5, 36.6, 32.1, 29.9, 29.88, 29.85, 29.81, 29.6, 29.6, 24.1, 22.9, 21.8, 14.4; **FT-IR (thin film):** 1684, 1601, 1565, 1354, 1214, 1163, 1091 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{29}\text{H}_{42}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 500.2829; found 500.2838; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 14.5$ min, $\tau_{\text{minor}} = 17.0$ min); Enantiomeric excess: 99%.

2-((2*S*,5*R*)-2-phenethyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3j):

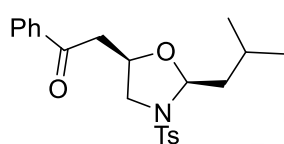


This compound was prepared according to the general procedure D. White sticky solid (25.6 mg, yield: 76%);

Diastereomeric ratio: >20:1; **^1H NMR (600 MHz, CDCl_3):** δ 7.92 – 7.85 (m, 2H), 7.73 (d, $J = 8.2$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz, 1H), 7.46 (t, $J = 7.8$ Hz, 2H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 3H), 7.21 (dd, $J = 13.7, 6.7$ Hz, 3H), 5.05 (dd, $J = 5.9, 3.8$ Hz, 1H), 4.05 (dd, $J = 12.0, 5.6$ Hz, 1H), 3.70 (dt, $J = 13.3, 5.5$ Hz, 1H), 3.45 (dd, $J = 17.4, 5.2$ Hz, 1H), 3.08 (dd, $J = 12.0, 9.6$ Hz, 1H), 2.97 (dd, $J = 17.5, 7.7$ Hz, 1H), 2.83 – 2.79 (m, 1H), 2.76 – 2.70 (m, 1H), 2.44 (s, 3H), 2.23 – 2.17 (m, 1H), 2.10 – 2.04 (m, 1H); **^{13}C NMR**

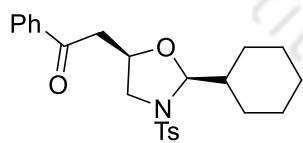
(150 MHz, CDCl₃): δ 196.9, 144.5, 141.5, 136.4, 134.4, 133.9, 130.3, 128.9, 128.7, 128.6, 128.2, 128.0, 126.1, 90.8, 73.4, 52.6, 42.3, 37.8, 30.2, 21.8; **FT-IR (thin film)**: 1682, 1601, 1566, 1451, 1351, 1215, 1162, 1090 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₆H₂₈NO₄S [M+H]⁺ 450.1734; found 450.1738; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 11.9 min, τ_{minor} = 16.9 min); Enantiomeric excess: 92%.

2-((2*S*,5*R*)-2-isobutyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3k):



This compound was prepared according to the general procedure D. Colourless liquid (21.68 mg, yield: 72%); **Diastereomeric ratio**: >20:1; **¹H NMR (600 MHz, CDCl₃)** δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 5.09 (dd, *J* = 7.4, 4.4 Hz, 1H), 4.05 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.64 (tt, *J* = 10.3, 5.4 Hz, 1H), 3.45 (dd, *J* = 17.4, 5.0 Hz, 1H), 3.05 (dd, *J* = 12.1, 9.6 Hz, 1H), 2.95 (dd, *J* = 17.4, 7.9 Hz, 1H), 2.44 (s, 3H), 1.82 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.78 – 1.72 (m, 1H), 0.96 (dd, *J* = 6.6, 2.7 Hz, 6H); **¹³C NMR (150 MHz, CDCl₃)**: δ 197.0, 144.4, 136.4, 134.7, 133.8, 130.3, 128.9, 128.2, 128.0, 90.6, 73.3, 52.2, 45.6, 42.7, 24.6, 23.4, 22.6, 21.8; **FT-IR (thin film)**: 1683, 1598, 1565, 1449, 1384, 1351, 1163, 1091, 792 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₂H₂₈NO₄S [M+H]⁺ 402.1734; found 402.1733; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 16.8 min, τ_{minor} = 18.7 min); Enantiomeric excess: 98%.

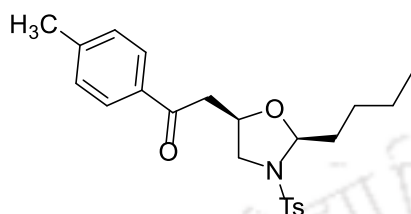
2-((2*S*,5*R*)-2-cyclohexyl-3-tosyloxazolidin-5-yl)-1-phenylethan-1-one (3l):



This compound was prepared according to the general procedure D. Colourless liquid (24.0 mg, yield: 75%); **Diastereomeric ratio**: >20:1; **¹H NMR (600 MHz, CDCl₃)**: δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.93 (d, *J* = 4.7 Hz, 1H), 4.10 (dd, *J* = 12.5, 5.5 Hz, 1H), 3.51 (dt, *J* = 10.2, 3.8 Hz, 1H), 3.42 (dd, *J* = 17.3, 5.0 Hz, 1H), 2.98 – 2.87 (m, 2H), 2.43 (s, 3H), 1.78 (t, *J* = 15.5 Hz, 4H), 1.68 – 1.58 (m, 4H), 1.11 (dd, *J* = 26.0, 13.5 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃)**: δ 197.0, 144.4, 136.4, 135.0, 133.8, 130.3, 128.9, 128.3, 128.0, 94.8, 73.1, 52.8, 43.6, 42.4, 28.7, 26.6, 26.5, 26.2, 26.0, 21.8; **FT-IR (thin film)**: 1683, 1598, 1449, 1351, 1162, 1092, 997, 792 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₄H₃₀NO₄S [M+H]⁺ 428.1890;

found 428.1893; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 17.1 min, τ_{minor} = 19.0 min); Enantiomeric excess: 96%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(*p*-tolyl)ethan-1-one (3*m*)

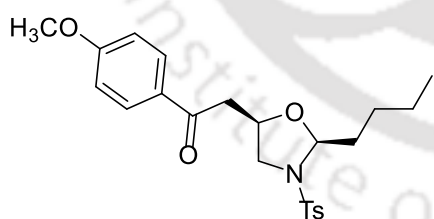


This compound was prepared according to the general procedure D. Colourless liquid (23.9 mg, yield: 77%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.78 (dd, *J* = 8.1, 5.2 Hz, 4H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.05 (dd, *J* = 6.0,

4.0 Hz, 1H), 4.04 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.63 (ddd, *J* = 13.4, 10.3, 5.4 Hz, 1H), 3.42 (dd, *J* = 17.3, 5.1 Hz, 1H), 3.02 (dd, *J* = 12.0, 9.7 Hz, 1H), 2.93 (dd, *J* = 17.3, 7.8 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 1.86 – 1.80 (m, 1H), 1.77 – 1.70 (m, 1H), 1.38 (ddd, *J* = 21.2, 11.2, 4.9 Hz, 4H), 0.91 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.5, 144.8, 144.4, 134.7, 134.0, 130.3, 129.6, 128.4, 128.0, 91.5, 73.4, 52.5, 42.3, 36.3, 26.2, 22.7, 21.9, 21.8, 14.3; **FT-IR (thin film):** 1679, 1604, 1568, 1461, 1350, 1161, 1092, 789 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₄S [M+H]⁺ 416.1890; found 416.1892; The enantiomeric ratio was determined by HPLC analysis using Daicel phenomenex Lux C1 column (92:8 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.2 min, τ_{major} = 20.7 min); Enantiomeric excess: 98%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(4-methoxyphenyl)ethan-1-one (3*n*)



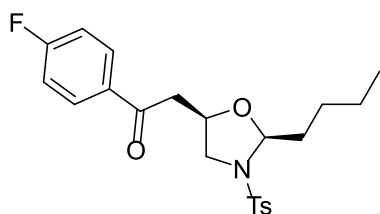
This compound was prepared according to the general procedure D. Colourless liquid (24.2 mg, yield: 75%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.85 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H),

5.04 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.03 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.86 (s, 3H), 3.63 (dq, *J* = 10.3, 5.4 Hz, 1H), 3.39 (dd, *J* = 17.2, 5.1 Hz, 1H), 3.02 (dd, *J* = 12.0, 9.7 Hz, 1H), 2.90 (dd, *J* = 17.2, 7.8 Hz, 1H), 2.43 (s, 3H), 1.88 – 1.78 (m, 1H), 1.76 – 1.69 (m, 1H), 1.44 – 1.33 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 195.4, 164.0, 144.4, 134.7, 130.6, 130.2, 129.5, 128.0, 114.0, 91.5, 73.4, 55.7, 52.5, 42.1, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1675, 1602, 1566, 1465, 1351, 1262, 1162, 1090, 775 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₅S [M+H]⁺ 432.1839; found 432.1849; The

enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (88:12 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 18.8$ min, $\tau_{\text{major}} = 40.8$ min); Enantiomeric excess: 98%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(4-fluorophenyl)ethan-1-one (3o)

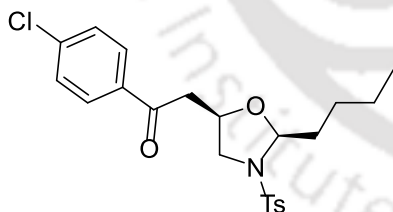


This compound was prepared according to the general procedure D. Brown sticky solid (21.7 mg, yield: 69%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.91 (dd, $J = 8.8, 5.4$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.12 (t, $J = 8.6$ Hz, 2H),

5.05 (dd, $J = 6.0, 4.0$ Hz, 1H), 4.03 (dd, $J = 12.0, 5.5$ Hz, 1H), 3.68 – 3.57 (m, 1H), 3.40 (dd, $J = 17.3, 5.2$ Hz, 1H), 3.03 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.93 (dd, $J = 17.3, 7.6$ Hz, 1H), 2.44 (s, 3H), 1.83 (ddd, $J = 13.8, 9.1, 4.3$ Hz, 1H), 1.74 – 1.69 (m, 1H), 1.42 – 1.33 (m, 4H), 0.90 (t, $J = 7.2$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 195.3, 167.1, 165.4, 144.4, 134.7, 131.0, 130.9, 130.3, 128.0, 116.2, 116.0, 91.6, 73.2, 52.4, 42.3, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1680, 1601, 1567, 1468, 1352, 1235, 1160, 894 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₇FNO₄S [M+H]⁺ 420.1639; found 420.1641; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IC column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 27.0$ min, $\tau_{\text{major}} = 30.3$ min); Enantiomeric excess: 86%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(4-chlorophenyl)ethan-1-one (3p)

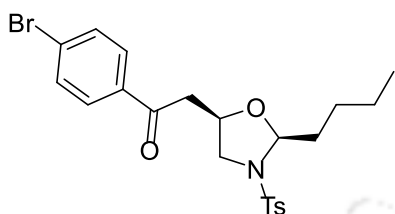


This compound was prepared according to the general procedure D. Colourless liquid (24.1 mg, yield: 74%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.82 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H), 5.05 (dd, $J = 5.9, 4.1$ Hz, 1H), 4.03 – 4.00 (m, 1H), 3.63 (dd, $J = 9.4, 7.6$ Hz, 1H), 3.39 (dd, $J = 17.4, 5.2$ Hz, 1H), 3.02 (dd, $J = 11.9, 9.8$ Hz, 1H), 2.93 (dd, $J = 17.4, 7.5$ Hz, 1H), 2.44 (s, 3H), 1.85 – 1.80 (m, 1H), 1.75 – 1.69 (m, 1H), 1.41 – 1.33 (m, 4H), 0.90 (t, $J = 7.1$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 195.7, 144.5, 140.4, 134.72, 134.70, 130.3, 129.7, 129.3, 128.0, 91.6, 73.1, 52.4, 42.4, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1684, 1590, 1463, 1350, 1162, 1092, 990, 794 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₇ClNO₄S [M+H]⁺ 436.1344; found 436.1341; The enantiomeric ratio was determined by HPLC analysis using Phenomenex

Lux C1 column (92:8 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 17.6$ min, $\tau_{\text{major}} = 29.5$ min); Enantiomeric excess: 97%.

1-(4-bromophenyl)-2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)ethan-1-one (3q)

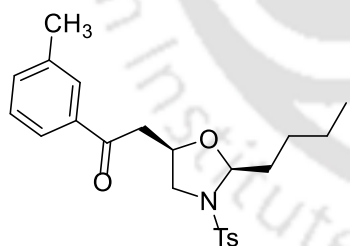


This compound was prepared according to the general procedure D. Colourless liquid (27.0 mg, yield:

75%); **Diastereomeric ratio:** >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.77 (d, $J = 8.2$ Hz, 2H), 7.74 (d, $J = 8.5$ Hz, 2H), 7.61 – 7.56 (m, 2H), 7.36 (d, $J = 8.1$ Hz,

2H), 5.04 (dd, $J = 6.0, 4.1$ Hz, 1H), 4.02 (dd, $J = 12.0, 5.5$ Hz, 1H), 3.69 – 3.58 (m, 1H), 3.38 (dd, $J = 17.4, 5.3$ Hz, 1H), 3.02 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.92 (dd, $J = 17.4, 7.5$ Hz, 1H), 2.43 (s, 3H), 1.82 (ddd, $J = 14.3, 9.6, 4.5$ Hz, 1H), 1.75 – 1.68 (m, 1H), 1.36 (ddd, $J = 19.8, 12.1, 5.7$ Hz, 4H), 0.90 (t, $J = 7.1$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 195.9, 144.5, 135.1, 134.7, 132.2, 130.3, 129.7, 129.1, 128.0, 91.6, 73.1, 52.3, 42.3, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1684, 1584, 1462, 1350, 1243, 1161, 1092, 789 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₇BrNO₄S [M+H]⁺ 480.0839; found 480.0837; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (92:8 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 19.5$ min, $\tau_{\text{major}} = 50.8$ min); Enantiomeric excess: 97%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(*m*-tolyl)ethan-1-one (3r)



This compound was prepared according to the general procedure D. Colourless liquid (23.3 mg, yield: 75%);

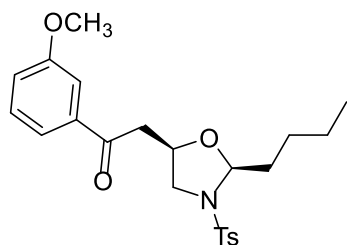
Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):**

δ 7.79 (d, $J = 8.2$ Hz, 2H), 7.70 – 7.65 (m, 2H), 7.35 (tt, $J = 15.3, 7.6$ Hz, 4H), 5.05 (dd, $J = 6.0, 4.0$ Hz, 1H), 4.04 (dd, $J = 12.0, 5.5$ Hz, 1H), 3.67 – 3.58 (m, 1H), 3.43 (dd, $J = 17.4, 5.1$ Hz, 1H), 3.02 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.95 (dd, $J = 17.4, 7.8$ Hz, 1H), 2.44 (s, 3H), 2.39 (s, 3H), 1.83 (ddd, $J = 14.4, 9.8, 4.6$ Hz, 1H), 1.76 – 1.70 (m, 1H), 1.42 – 1.33 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H);

¹³C NMR (150 MHz, CDCl₃): δ 197.1, 144.4, 138.8, 136.4, 134.7, 134.6, 130.3, 128.8, 128.7, 128.0, 125.5, 91.5, 73.3, 52.5, 42.5, 36.3, 26.2, 22.7, 21.8, 21.6, 14.3; **FT-IR (thin film):** 1679, 1602, 1567, 1464, 1351, 1245, 1161, 1090, 781 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₄S [M+H]⁺ 416.1890; found 416.1895; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (98:2 *n*-Hexane/2-PrOH,

1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 18.1$ min, $\tau_{\text{minor}} = 20.0$ min); Enantiomeric excess: 98%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(3-methoxyphenyl)ethan-1-one (3s)



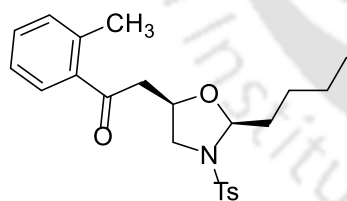
This compound was prepared according to the general procedure D. Colourless liquid (24.5 mg, yield: 76%);

Diastereomeric ratio: >20:1; **¹H NMR (600 MHz, CDCl₃):**

δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.45 (d, $J = 7.7$ Hz, 1H), 7.40 (d, $J = 2.0$ Hz, 1H), 7.35 (t, $J = 8.4$ Hz, 3H), 7.13 – 7.09 (m, 1H),

5.05 (dd, $J = 6.0, 4.1$ Hz, 1H), 4.04 (dd, $J = 12.1, 5.5$ Hz, 1H), 3.83 (s, 3H), 3.63 (qd, $J = 10.2, 5.4$ Hz, 1H), 3.43 (dd, $J = 17.4, 5.1$ Hz, 1H), 3.02 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.95 (dd, $J = 17.5, 7.8$ Hz, 1H), 2.43 (s, 3H), 1.87 – 1.79 (m, 1H), 1.78 – 1.69 (m, 1H), 1.42 – 1.33 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.7, 160.0, 144.4, 137.72, 134.71, 130.3, 129.9, 128.0, 120.9, 120.3, 112.3, 91.5, 73.3, 55.7, 52.4, 42.6, 36.3, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1679, 1599, 1569, 1462, 1349, 1256, 1161, 1090, 852 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₅S [M+H]⁺ 432.1839; found 432.1840; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (88:12 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.7$ min, $\tau_{\text{minor}} = 17.2$ min); Enantiomeric excess: 98%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(*o*-tolyl)ethan-1-one (3t)



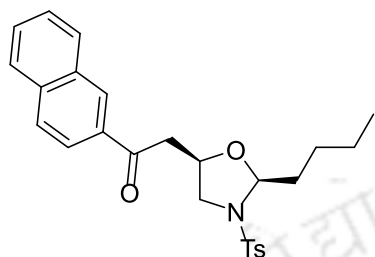
This compound was prepared according to the general procedure D. Colourless liquid (21.8 mg, yield: 70%);

Diastereomeric ratio: >20:1; **¹H NMR (400 MHz, CDCl₃):** δ

7.77 (d, $J = 8.2$ Hz, 2H), 7.59 (d, $J = 7.2$ Hz, 1H), 7.37 (dd, $J = 16.6, 7.9$ Hz, 3H), 7.24 (t, $J = 6.9$ Hz, 2H), 5.04 (dd, $J = 6.1, 4.0$ Hz, 1H), 3.99 (dd, $J = 11.9, 5.6$ Hz, 1H), 3.66 (ddd, $J = 12.8, 9.6, 5.7$ Hz, 1H), 3.35 (dd, $J = 17.1, 5.7$ Hz, 1H), 3.04 (dd, $J = 11.9, 9.6$ Hz, 1H), 2.90 (dd, $J = 17.1, 7.2$ Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H), 1.88 – 1.77 (m, 1H), 1.76 – 1.68 (m, 1H), 1.36 (ddd, $J = 16.4, 11.8, 6.5$ Hz, 4H), 0.90 (t, $J = 7.0$ Hz, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 200.4, 144.4, 138.8, 137.0, 134.9, 132.4, 132.1, 130.2, 129.0, 128.0, 126.0, 91.6, 73.5, 52.4, 45.1, 36.2, 26.2, 22.7, 21.8, 21.7, 14.2; **FT-IR (thin film):** 1680, 1602, 1568, 1461, 1351, 1161, 1091, 882 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₄S [M+H]⁺ 416.1890; found 416.1889; The enantiomeric ratio was

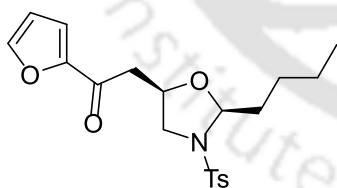
determined by HPLC analysis using Daicel Chiralpak IB column (97:3 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.3$ min, $\tau_{\text{minor}} = 18.2$ min); Enantiomeric excess: 87%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(naphthalen-2-yl)ethan-1-one (3u)



This compound was prepared according to the general procedure D. Colourless liquid (23.3 mg, yield: 69%); **Diastereomeric ratio:** >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.40 (s, 1H), 7.94 (d, *J* = 6.5 Hz, 2H), 7.90 – 7.84 (m, 2H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.62 (t, *J* = 7.9 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.07 (dd, *J* = 6.0, 4.0 Hz, 1H), 4.08 (dd, *J* = 12.1, 5.5 Hz, 1H), 3.69 (ddd, *J* = 13.1, 10.4, 5.4 Hz, 1H), 3.59 (dd, *J* = 17.1, 5.2 Hz, 1H), 3.13 – 3.03 (m, 2H), 2.42 (s, 3H), 1.85 (ddd, *J* = 14.3, 9.6, 4.6 Hz, 1H), 1.78 – 1.73 (m, 1H), 1.47 – 1.36 (m, 4H), 0.91 (d, *J* = 7.2 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃)** δ 196.8, 144.4, 136.0, 134.7, 133.8, 132.6, 130.3, 130.2, 129.8, 129.0, 128.8, 128.0, 128.0, 127.2, 123.6, 91.6, 73.4, 52.5, 42.5, 36.3, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1676, 1566, 1602, 1467, 1352, 1161, 788 cm⁻¹; **HRMS (+ESI):** Calc for C₂₆H₃₀NO₄S [M+H]⁺ 452.1890; found 452.1894; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 23.9$ min, $\tau_{\text{major}} = 32.3$ min); Enantiomeric excess: 96%.

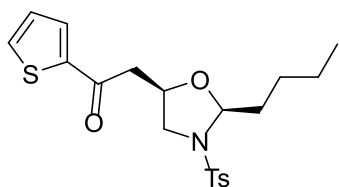
2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(furan-2-yl)ethan-1-one (3v)



This compound was prepared according to the general procedure D. Colourless liquid (21.1 mg, yield: 71%); **Diastereomeric ratio:** >20:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 3.6 Hz, 1H), 6.53 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.04 (dd, *J* = 6.1, 4.0 Hz, 1H), 3.95 (dd, *J* = 12.0, 5.5 Hz, 1H), 3.59 (dt, *J* = 12.9, 5.6 Hz, 1H), 3.25 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.83 (dd, *J* = 16.8, 7.3 Hz, 1H), 2.43 (s, 3H), 1.81 (ddd, *J* = 14.1, 9.5, 4.3 Hz, 1H), 1.76 – 1.70 (m, 1H), 1.38 (ddd, *J* = 21.8, 10.7, 6.2 Hz, 4H), 0.90 (t, *J* = 7.1 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 185.7, 152.4, 147.0, 144.4, 134.7, 130.3, 127.9, 118.0, 112.7, 91.6, 72.8, 52.2, 42.0, 36.2, 26.1, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1673, 1601, 1567, 1467, 1394, 1349, 1247, 1162, 1090, 788 cm⁻¹; **HRMS (+ESI):** Calc for C₂₀H₂₆NO₅S [M+H]⁺ 392.1526; found 392.1528;

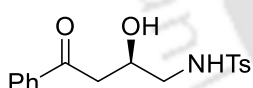
The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 13.2$ min, $\tau_{\text{major}} = 29.5$ min); Enantiomeric excess: 91%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(thiophen-2-yl)ethan-1-one (3w)

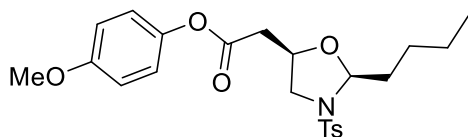


Colourless liquid (22.3 mg, yield: 73%); **Diastereomeric ratio:** >20:1; **^1H NMR (400 MHz, CDCl_3):** δ 7.75 (d, $J = 8.1$ Hz, 2H), 7.65 (d, $J = 4.0$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 7.13 – 7.07 (m, 1H), 5.04 (dd, $J = 5.9, 4.1$ Hz, 1H), 3.97 (dd, $J = 12.0, 5.5$ Hz, 1H), 3.61 (dt, $J = 13.0, 5.5$ Hz, 1H), 3.33 (dd, $J = 16.7, 5.4$ Hz, 1H), 3.05 (dd, $J = 12.0, 9.7$ Hz, 1H), 2.89 (dd, $J = 16.7, 7.5$ Hz, 1H), 2.42 (s, 3H), 1.85 – 1.78 (m, 1H), 1.72 (dd, $J = 9.2, 5.6$ Hz, 1H), 1.40 – 1.32 (m, 4H), 0.89 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 189.6, 144.4, 143.8, 134.7, 134.6, 132.8, 130.3, 128.5, 128.0, 91.6, 73.1, 52.3, 42.9, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1655, 1602, 1567, 1464, 1416, 1351, 1239, 1161, 1091, 802 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{20}\text{H}_{26}\text{NO}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 408.1298; found 408.1296; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 14.8$ min, $\tau_{\text{major}} = 20.1$ min); Enantiomeric excess: 97%.

(*R*)-*N*-(2-hydroxy-4-oxo-4-phenylbutyl)-4-methylbenzenesulfonamide (4)

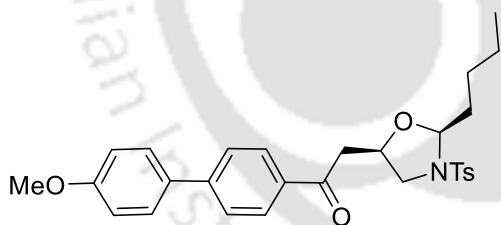


This compound was prepared according to the general procedure E. White solid (20.0 mg, yield: 60%); **^1H NMR (400 MHz, CDCl_3):** δ 7.92 (d, $J = 7.2$ Hz, 2H), 7.76 (d, $J = 8.3$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.05 (t, $J = 6.2$ Hz, 1H), 4.39 – 4.26 (m, 1H), 3.59 (s, 1H), 3.24 – 3.11 (m, 3H), 3.04 (dt, $J = 12.6, 6.2$ Hz, 1H), 2.43 (s, 3H); **^{13}C NMR (100 MHz, CDCl_3):** δ 200.4, 143.8, 137.0, 136.5, 134.1, 130.0, 129.0, 128.4, 127.3, 66.7, 48.0, 42.2, 21.7; **FT-IR (thin film):** 1675, 1598, 1566, 1447, 1319, 1256, 1156, 1090 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{17}\text{H}_{20}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$ 334.1108; found 334.1094; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 11.7$ min, $\tau_{\text{major}} = 15.3$ min); Enantiomeric excess: 95%.

4-methoxyphenyl 2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)acetate (5)

This compound was prepared according to the general procedure F. Colourless liquid (24.5 mg, yield: 55%); **Diastereomeric ratio**: >20:1; **¹H**

NMR (600 MHz, CDCl₃): δ 7.74 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 9.1 Hz, 2H), 5.10 (dd, J = 6.0, 4.2 Hz, 1H), 3.91 (dd, J = 11.9, 5.6 Hz, 1H), 3.79 (s, 3H), 3.58 (dq, J = 9.6, 6.1 Hz, 1H), 3.13 (dd, J = 11.9, 9.6 Hz, 1H), 2.85 (dd, J = 16.4, 6.1 Hz, 1H), 2.64 (dd, J = 16.4, 7.2 Hz, 1H), 2.42 (s, 3H), 1.84 (ddd, J = 19.6, 9.8, 4.5 Hz, 1H), 1.80 – 1.69 (m, 1H), 1.45 – 1.33 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 169.1, 157.6, 144.5, 143.8, 134.7, 130.3, 127.9, 122.3, 114.7, 92.0, 72.9, 55.8, 51.9, 38.2, 36.2, 26.2, 22.7, 21.8, 14.3; **FT-IR (thin film):** 1754, 1602, 1566, 1508, 1352, 1248, 1193, 1158, 792 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₃₀NO₆S [M+H]⁺ 448.1788; found 448.1789; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (88:12 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 21.5 min, τ_{major} = 39.7 min); Enantiomeric excess: 97%.

2-((2*S*,5*R*)-2-butyl-3-tosyloxazolidin-5-yl)-1-(4'-methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (6)

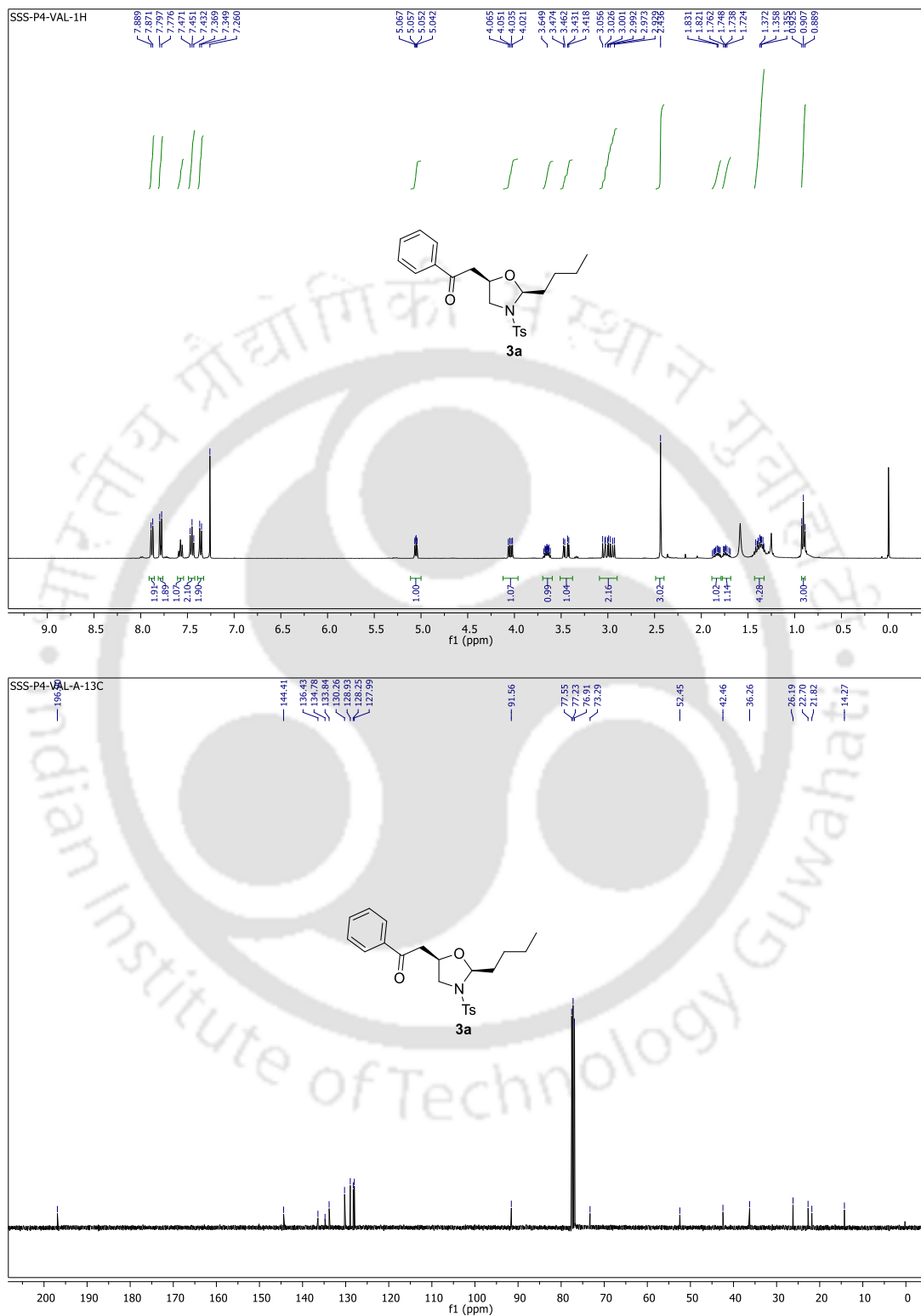
This compound was prepared according to the general procedure G. Brown sticky solid (30.4 mg, yield: 60%); **Diastereomeric ratio**: >20:1;

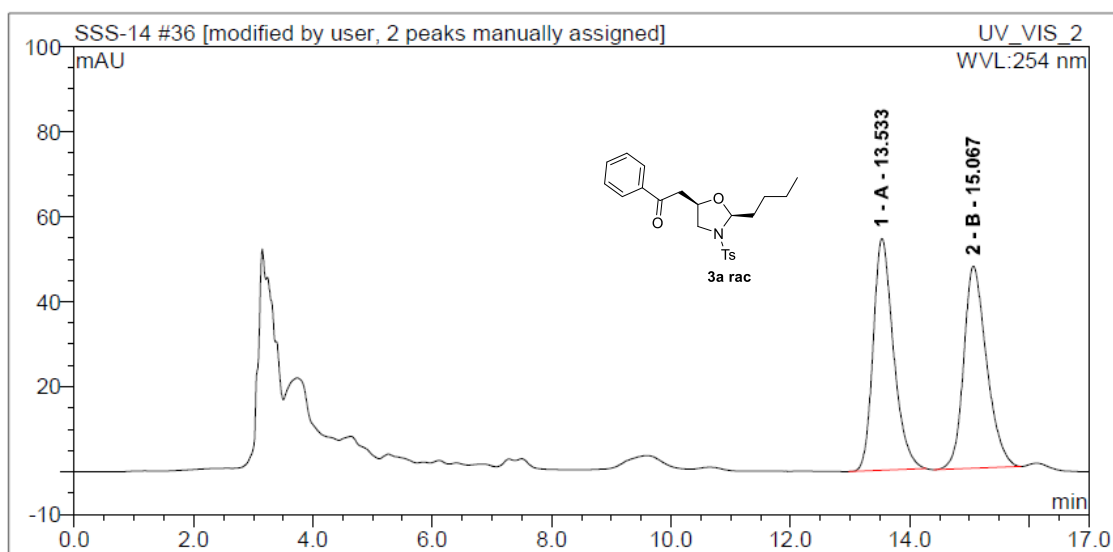
¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.39 – 7.34 (m, 2H), 7.00 (d, J = 8.9 Hz, 2H), 5.06 (dd, J = 6.0, 4.0 Hz, 1H), 4.06 (dd, J = 12.0, 5.6 Hz, 1H), 3.86 (s, 3H), 3.67 (ddt, J = 10.6, 7.8, 5.4 Hz, 1H), 3.47 (dd, J = 17.3, 5.1 Hz, 1H), 3.01 (ddd, J = 25.1, 14.7, 8.7 Hz, 2H), 2.44 (s, 3H), 1.90 – 1.80 (m, 1H), 1.78 – 1.71 (m, 1H), 1.44 – 1.34 (m, 4H), 0.91 (t, J = 7.1 Hz, 3H); **¹³C NMR (101 MHz, CDCl₃):** δ 196.4, 160.2, 146.1, 144.4, 134.7, 134.5, 132.2, 132.1, 130.3, 128.9, 128.6, 128.0, 126.9, 114.6, 91.5, 73.4, 55.6, 52.5, 52.5, 42.4, 36.3, 26.2, 22.7, 21.83, 21.82, 21.81, 14.3; **FT-IR (thin film):** 1673, 1602, 1566, 1464, 1350, 1250, 1161, 1090, 770 cm⁻¹; **HRMS (+ESI):** Calc for C₂₉H₃₄NO₅S [M+H]⁺ 508.2152; found 508.2151; The enantiomeric ratio was determined by HPLC analysis using Daicel

Chiralpak IB column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 25.9 min, τ_{major} = 50.8 min); Enantiomeric excess: 96%.

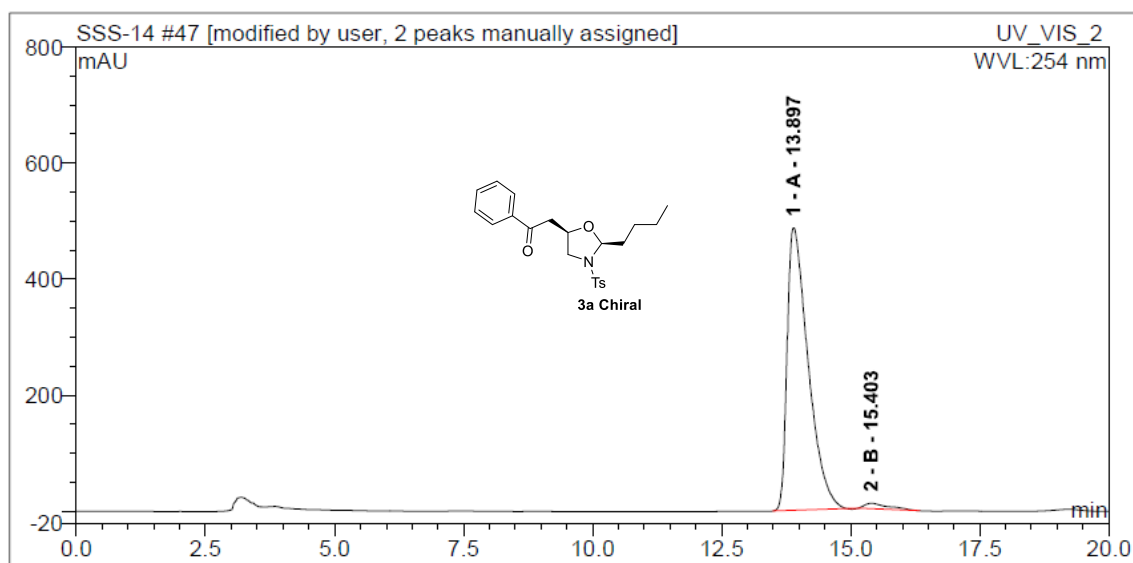


4.10. Selected NMR spectra and HPLC chromatogram:

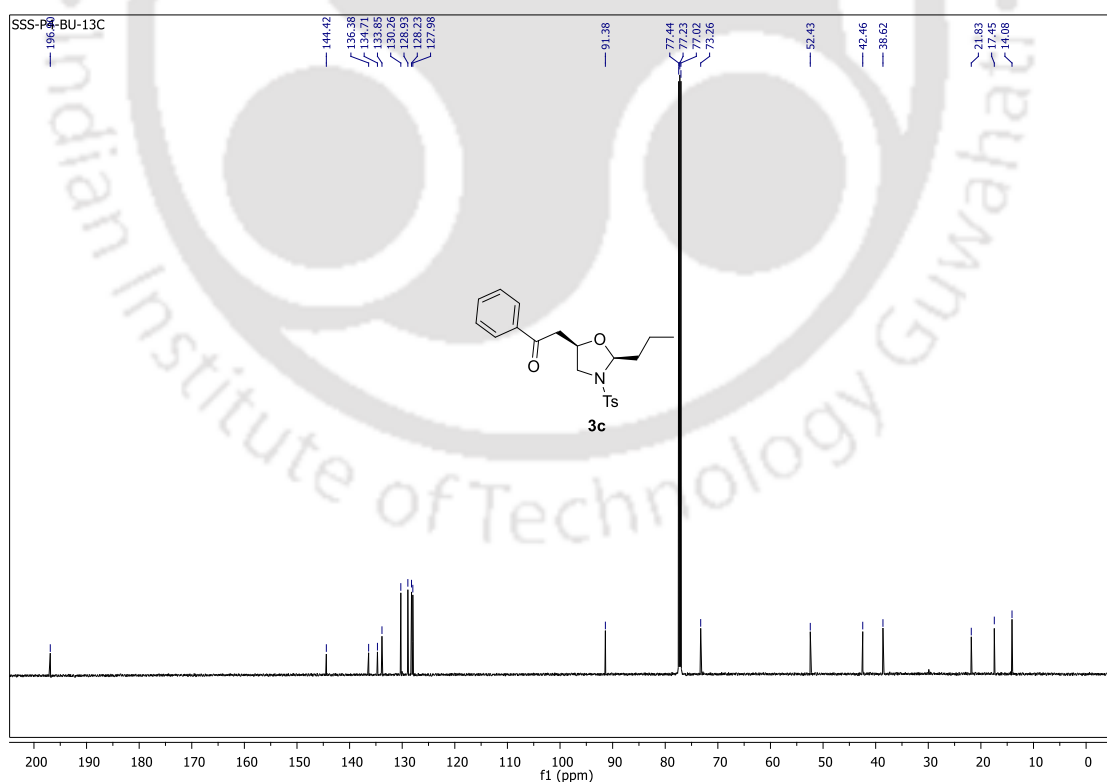
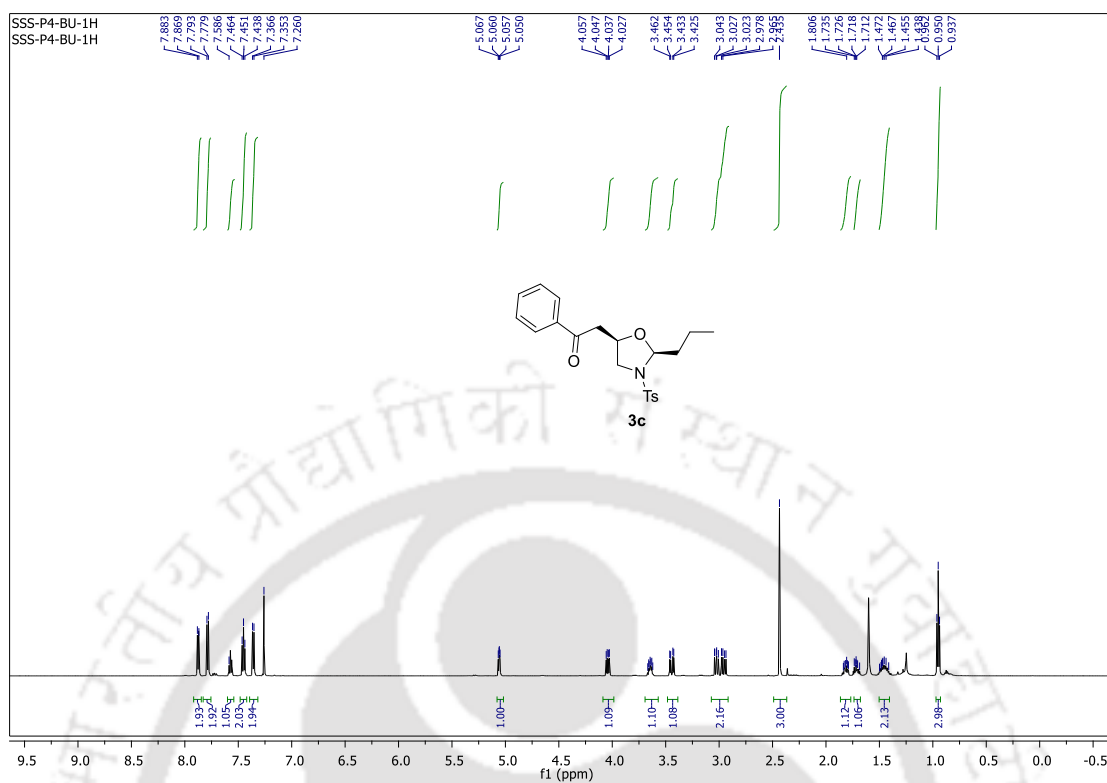


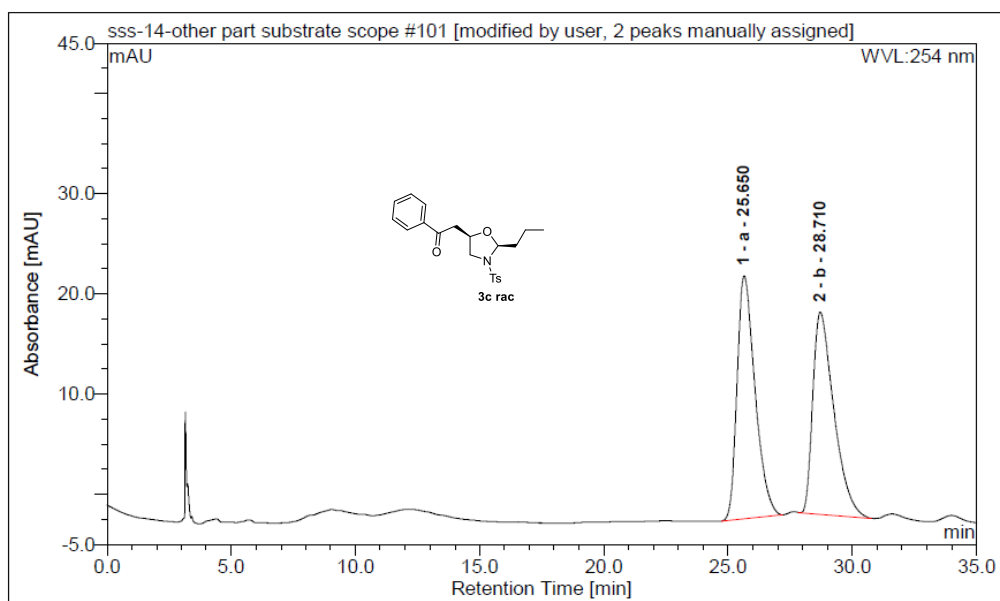


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
	1 A	13.53	21.57534	50.43998729	54.4783	n.a.
	2 B	15.07	21.199	49.56001271	47.471	n.a.

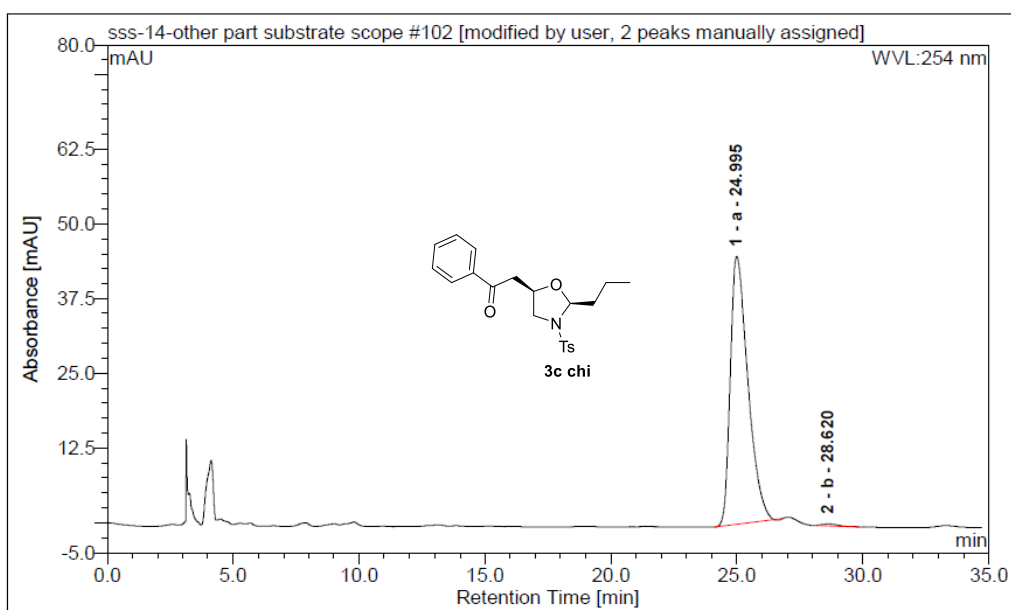


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
	1 A	13.90	228.7675	97.83593125	486.402	n.a.
	2 B	15.40	5.060	2.164068751	9.278	n.a.

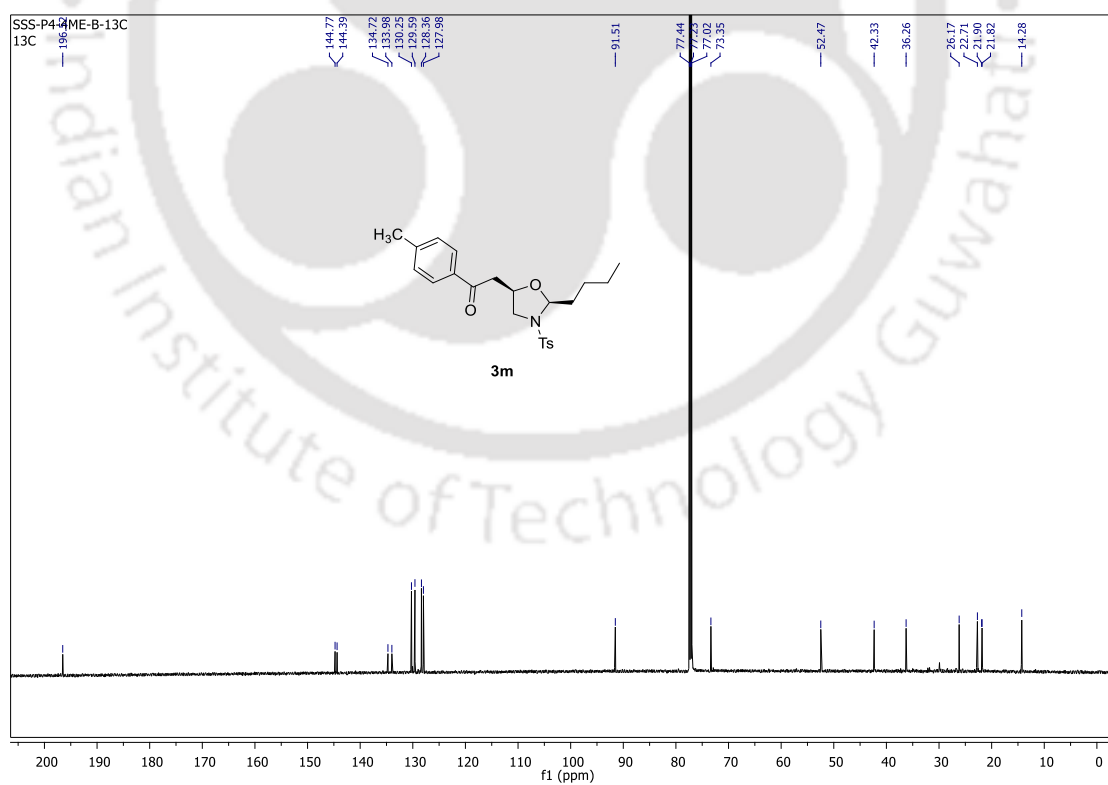
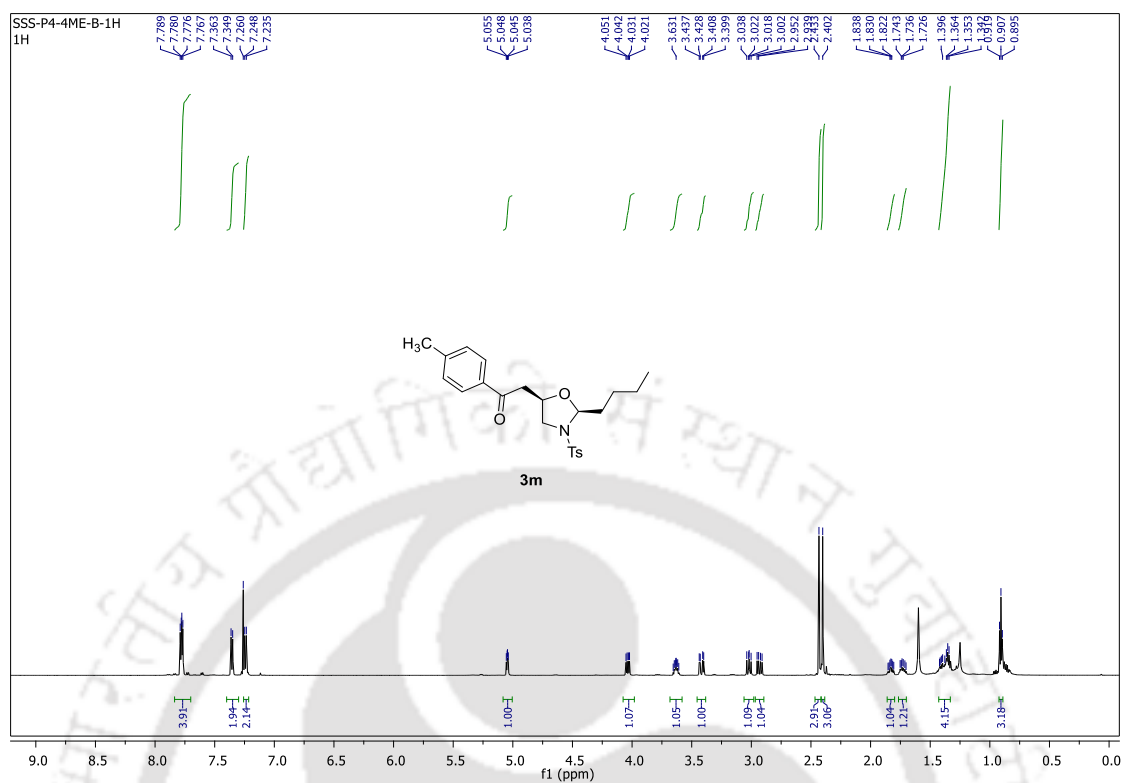


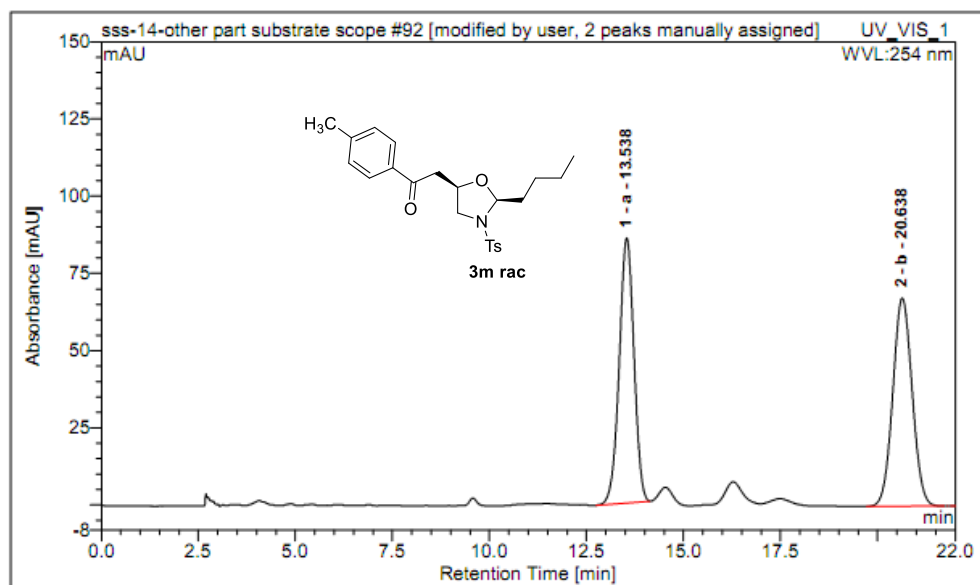


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	25.65	20.3065	50.62849924	24.2287	n.a.
2	b	28.71	19.802	49.37150076	20.185	n.a.

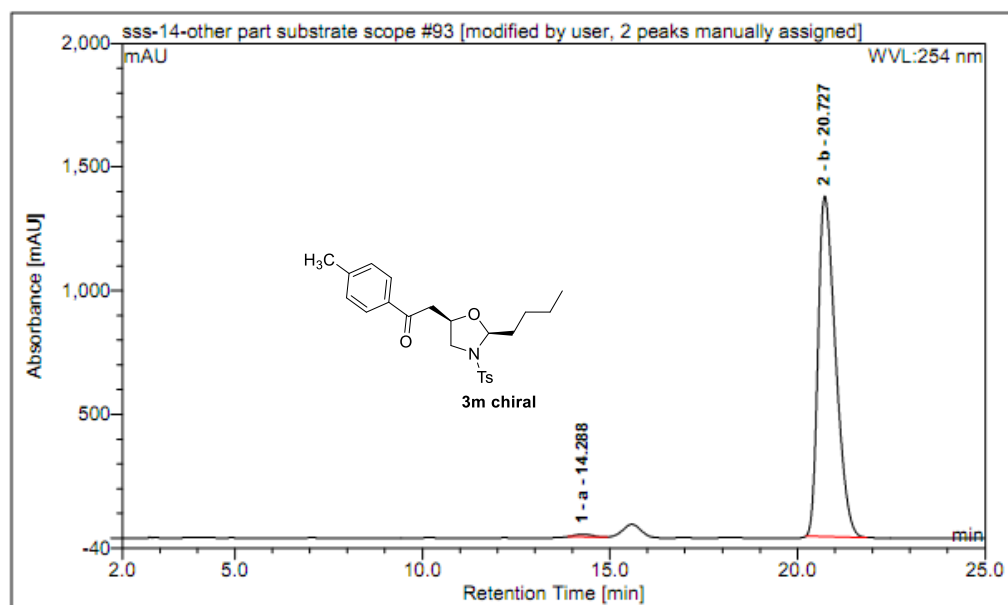


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	25.00	36.33599	99.51804205	44.86319	n.a.
2	b	28.62	0.176	0.4819579517	0.273	n.a.

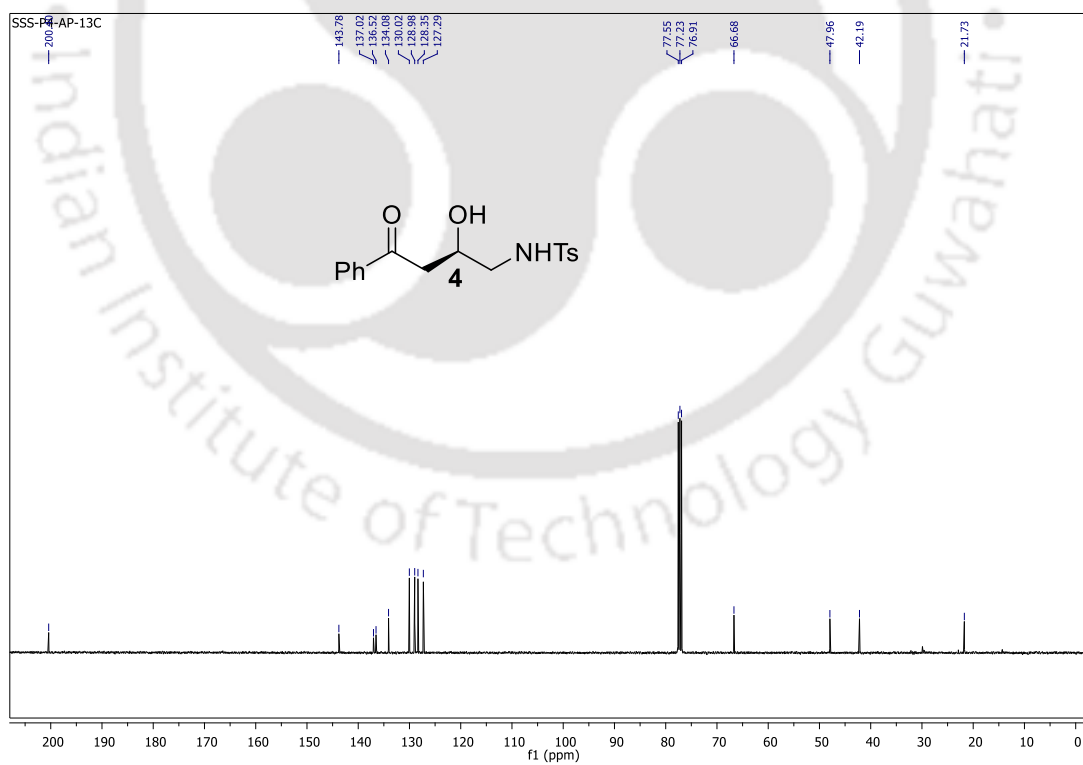
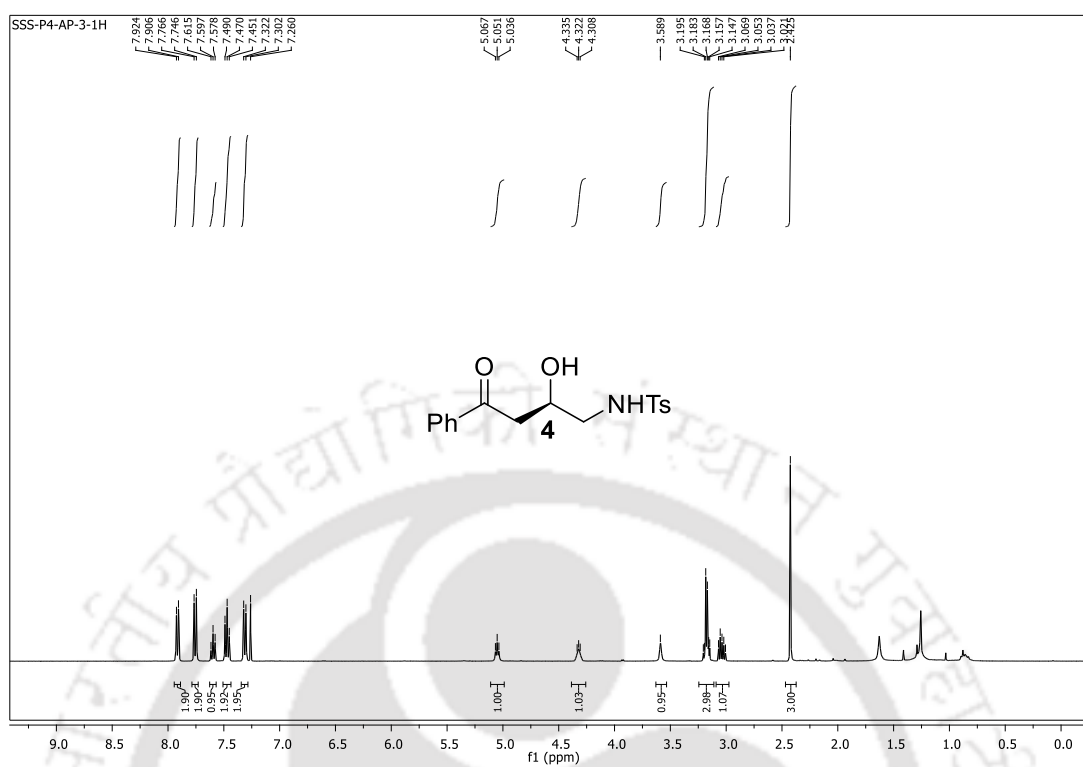


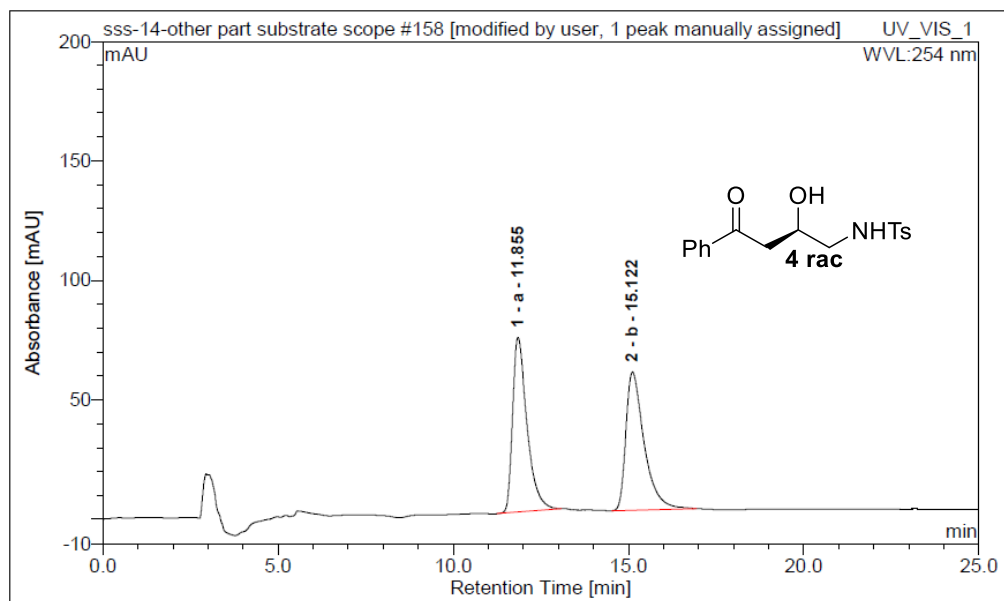


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		13.54	37.66768	49.19221768	85.76562	n.a.
2 b		20.64	38.905	50.80778232	67.371	n.a.

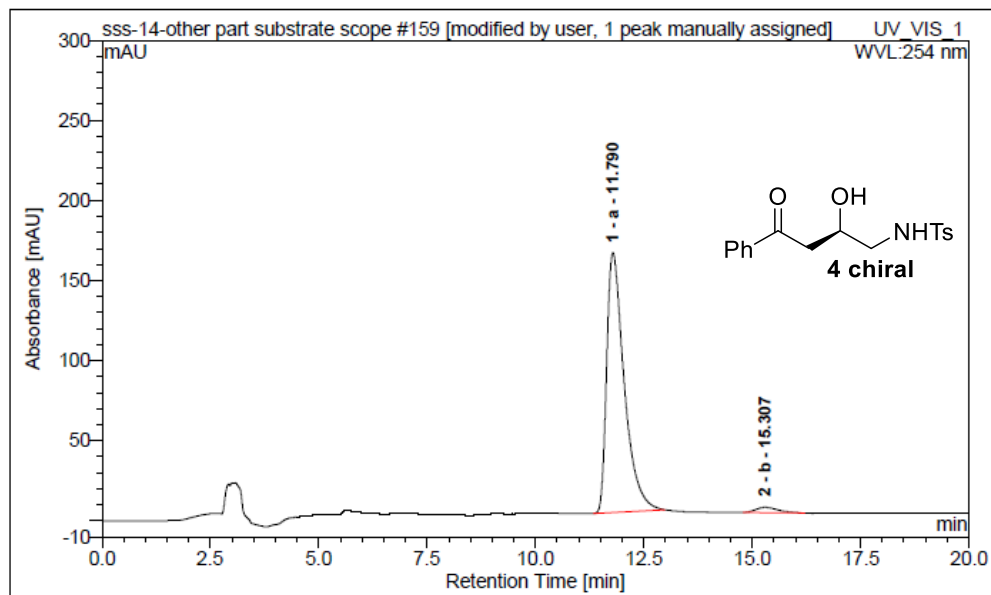


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		14.29	5.090323	0.680623555	10.59893	n.a.
2 b		20.73	742.801	99.31937644	1376.720	n.a.

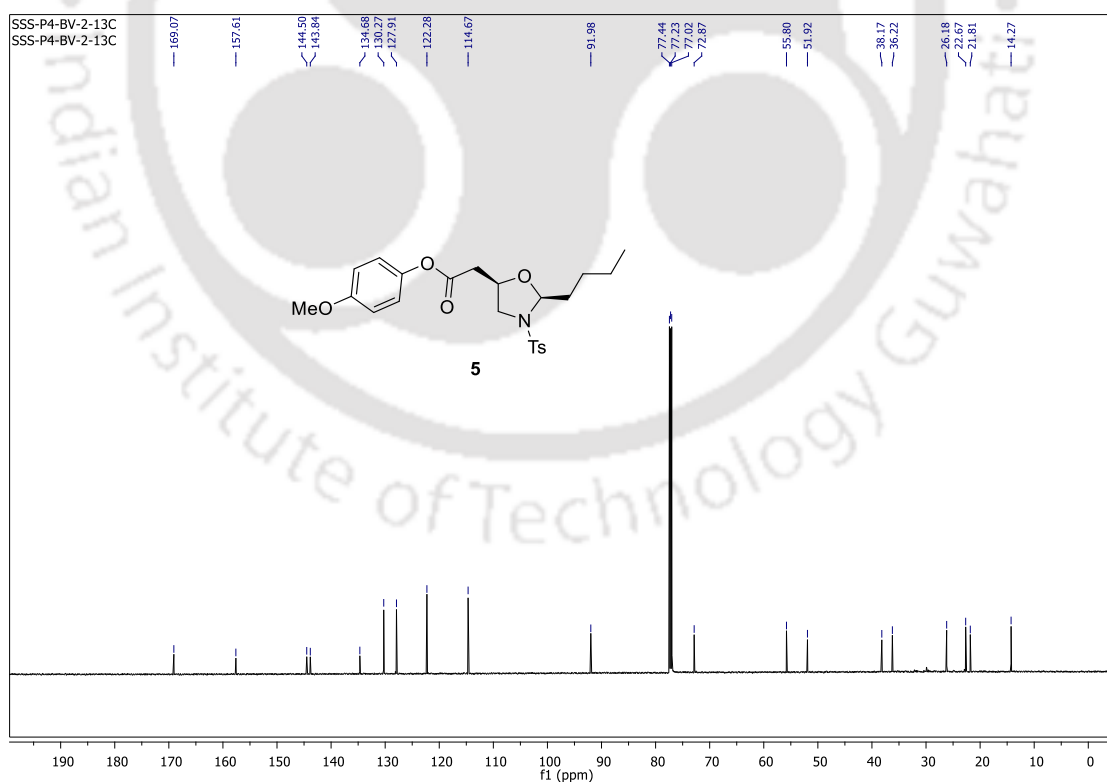
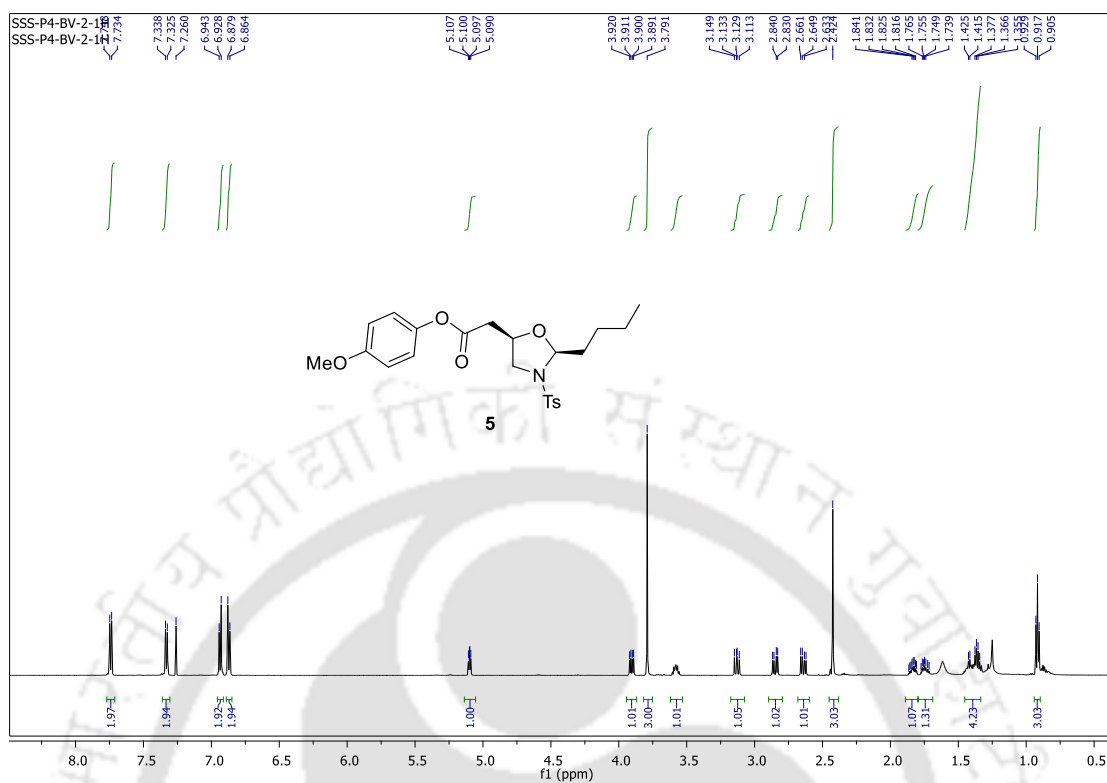


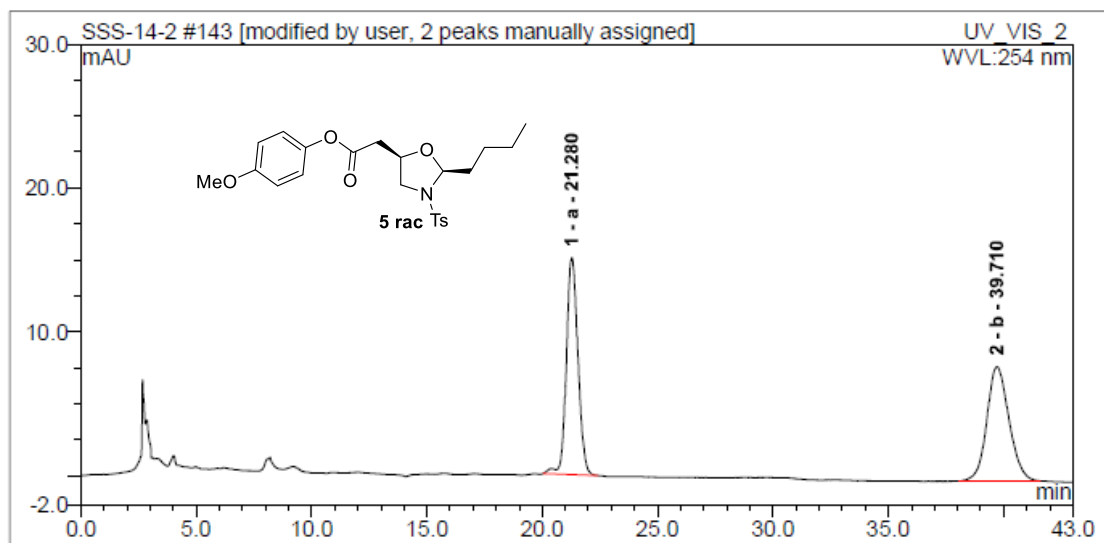


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		11.86	34.79505	49.92306873	73.04622	n.a.
2 b		15.12	34.902	50.07693127	57.783	n.a.

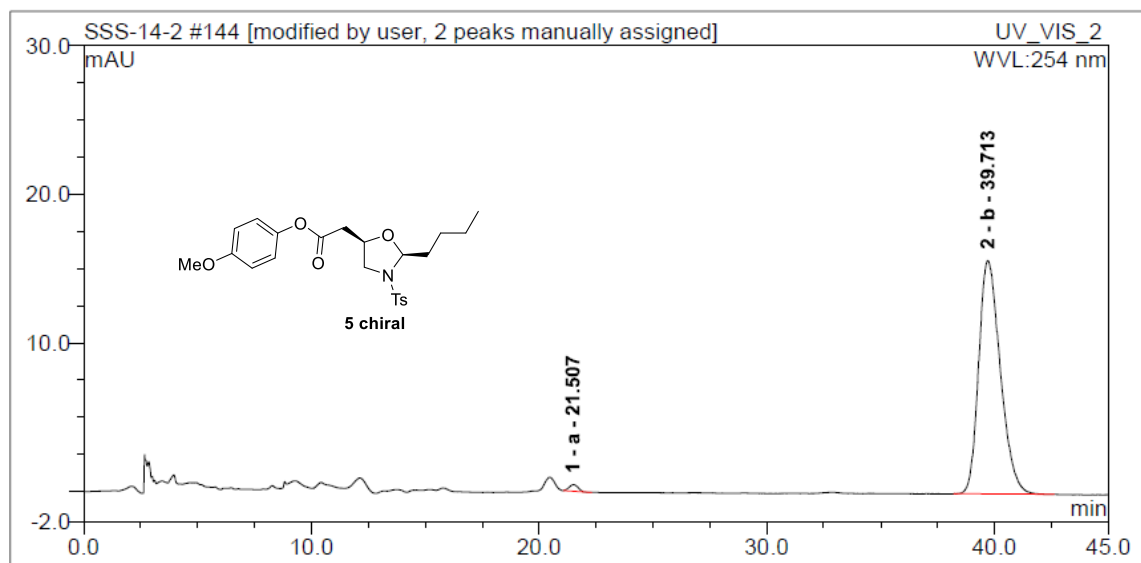


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		11.79	76.00177	97.45818683	162.2847	n.a.
2 b		15.31	1.982	2.541813167	3.281	n.a.

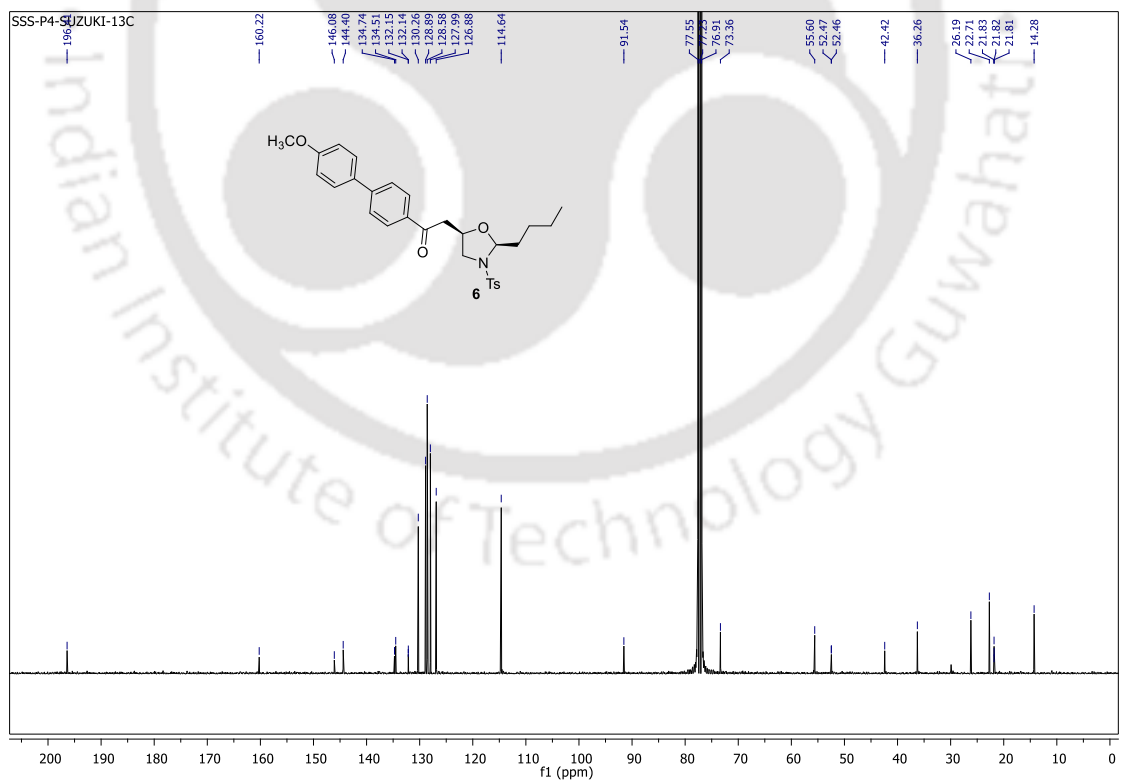
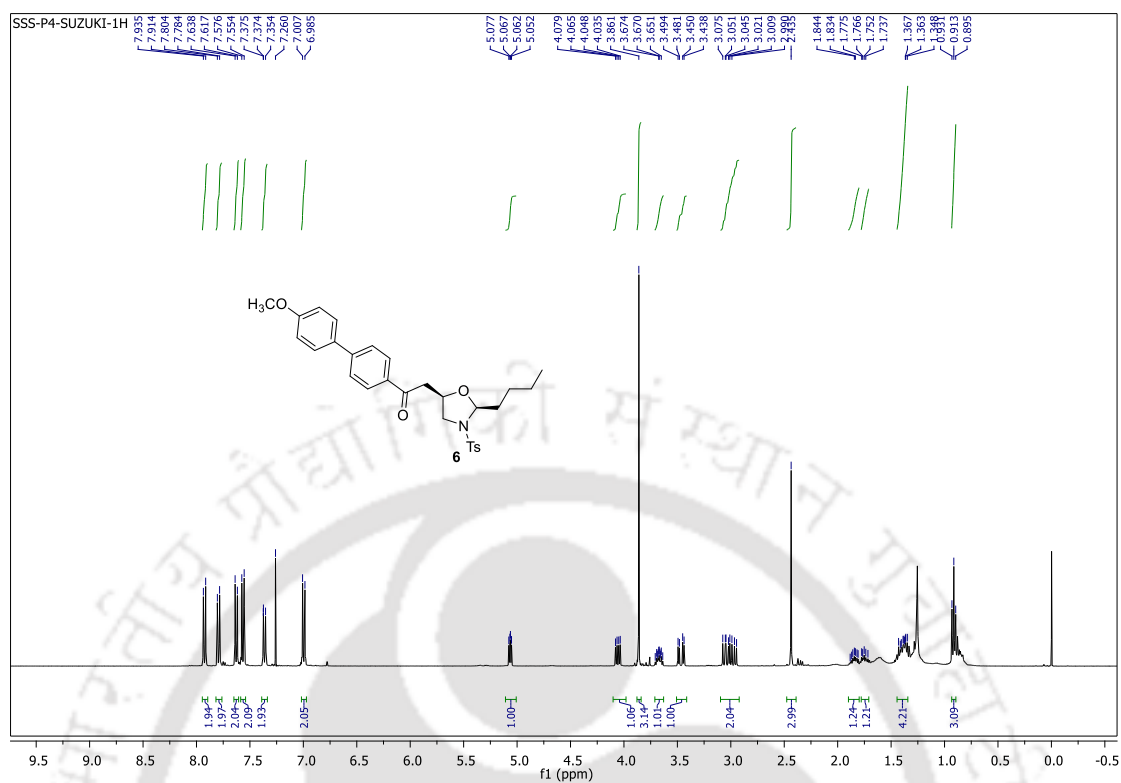


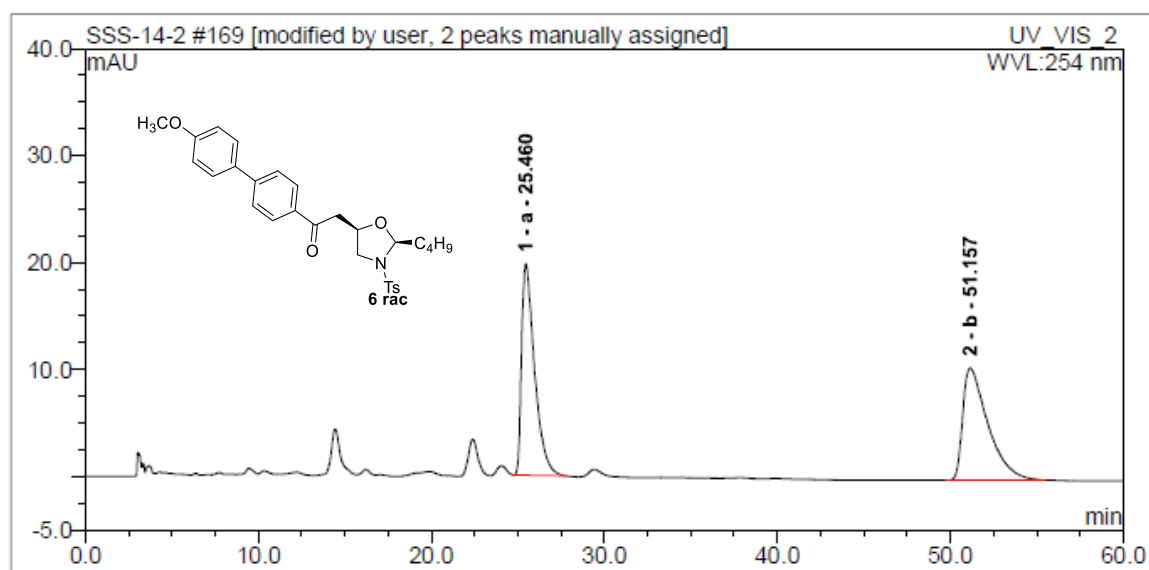


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		21.28	8.826181	49.9476407	15.08241	n.a.
2 b		39.71	8.845	50.0523593	7.953	n.a.

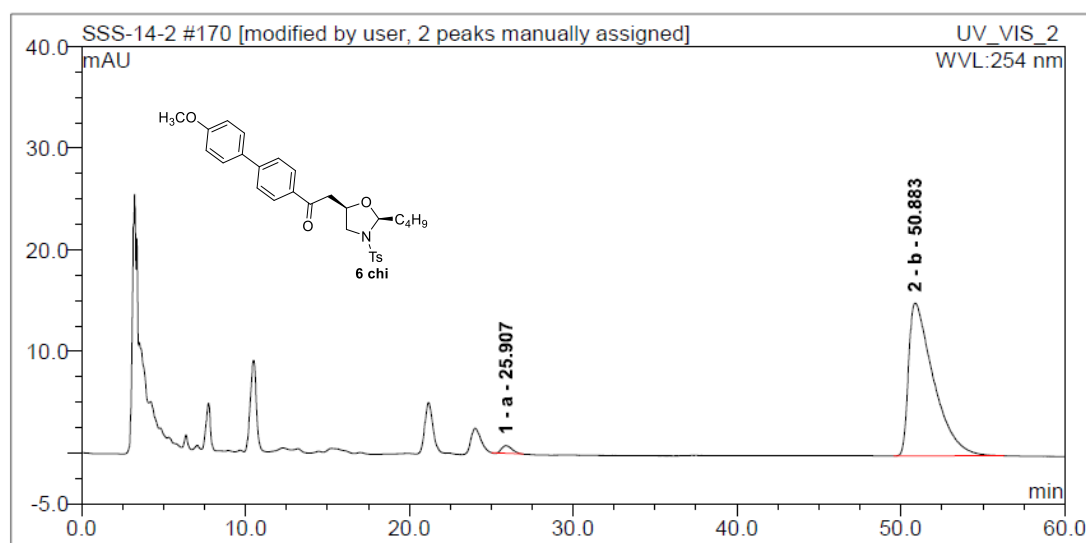


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		21.51	0.198594	1.136346472	0.44307	n.a.
2 b		39.71	17.278	98.86365353	15.696	n.a.





No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		25.46	17.24599	49.36518791	19.77099	n.a.
2 b		51.16	17.690	50.63481209	10.490	n.a.



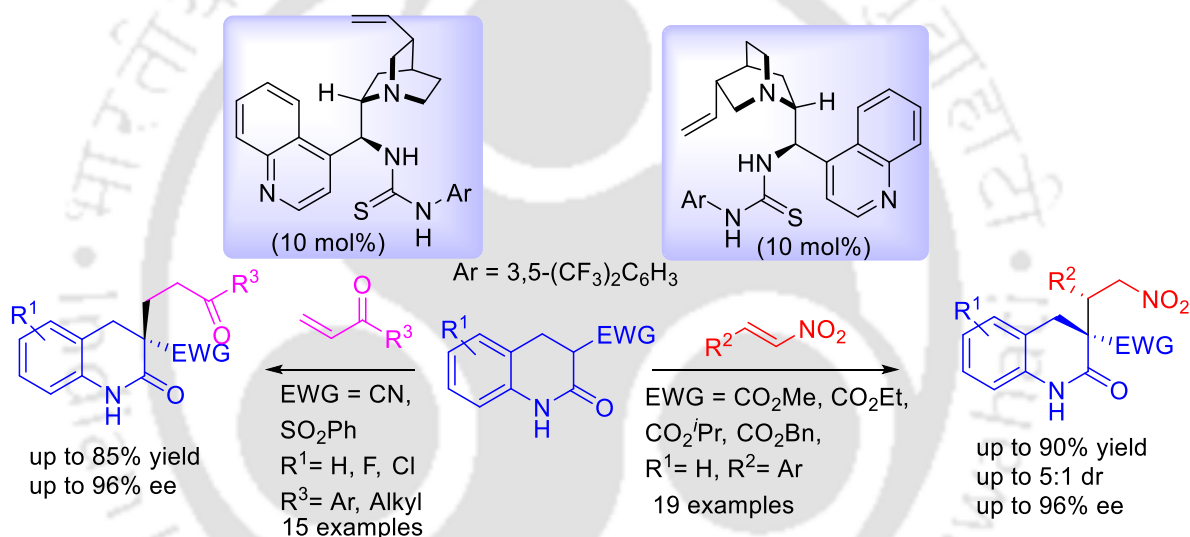
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 a		25.91	0.559005	2.059351919	0.77201	n.a.
2 b		50.88	26.586	97.94064808	15.068	n.a.



Chapter 5

Organocatalytic Asymmetric Synthesis of 3,3-Disubstituted 3,4-Dihydro-2-Quinolones via Michael Addition Strategy

Abstract: The first organocatalytic asymmetric reaction employing 3,4-dihydro-2-quinolone has been developed leading to the synthesis of biologically important 3,3-disubstituted-dihydro-2-quinolones. Cinchona alkaloid derived bifunctional amino-thiourea catalysts were found to be the best catalysts. The products were obtained in high enantio- and good diastereoselectivities. Also few synthetic transformations have been demonstrated to augment synthetic utility of the methodology.





5.1. Introduction:

Substituted 3,4-dihydroquinolin-2(1*H*)-ones, are important structural motifs which are extensively found in plethora of natural products and widespread application as pharmaceutical agents (Figure 1).¹ Functionalized 3,4-dihydroquinolin-2(1*H*)-one is a heterocyclic motif that is present in many natural alkaloids, biologically active commercial drugs and have attracted significant attention in view of their 5-HT_{2c} receptor antagonism, NMDA antagonism, cardiovascular, anti-inflammatory as well as HIV-1 reverse transcriptase inhibitor activities.¹ Thus it is highly desirable to synthesize differently substituted 3,4-dihydroquinolin-2(1*H*)-ones in an efficient and straightforward way. Also, it is equally important to develop enantiopure synthesis of these compounds as many of them are chiral (Figure 1). Asymmetric synthesis of these compounds are important as many of them have chiral centres and in general two enantiomers perform in totally different ways. Though a number of syntheses of 3,4-dihydroquinolin-2(1*H*)-one derivatives have been reported,² asymmetric synthesis is less and focused mainly on transition metal catalysis,³ photochemical,⁴ organocatalysis⁵ and other⁶.

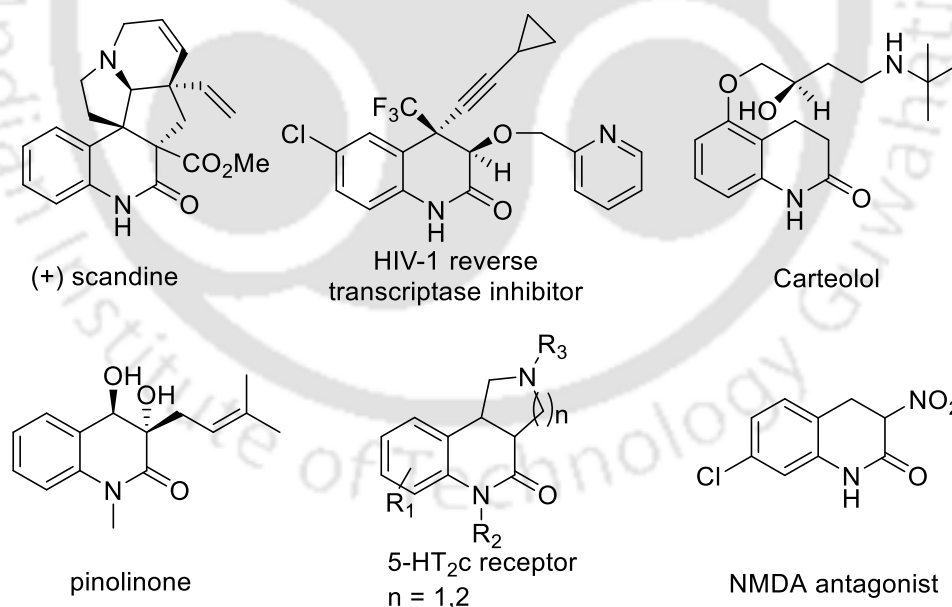


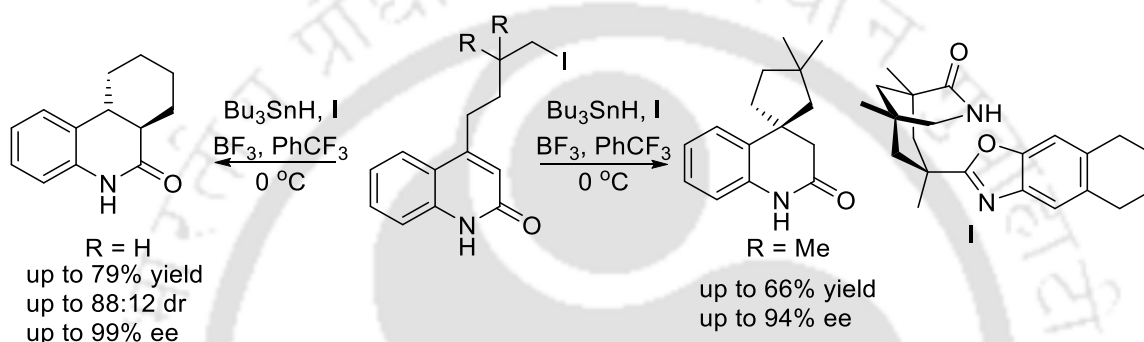
Figure 1: Biologically active compounds containing 3,4-dihydro-2-quinolones

These discoveries documented mainly the synthesis of 3,4-disubstituted dihydroquinolin-2(1*H*)-ones. However the synthesis of chiral 3-substituted and 3,3-disubstituted

dihydroquinolin-2(1H)-ones is over looked though such skeleton is present in pinolinone,^{1f,7} and scandine^{1a,8} (Figure 1).

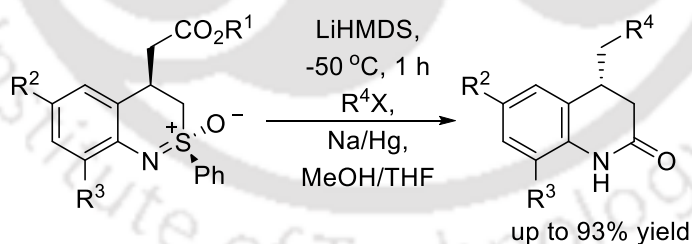
5.2. Reported strategies for the synthesis of chiral dihydroquinolones:

Dressel *et al.* reported an enantioselective radical cyclization of 4-(4'-iodobutyl) quinolones for the synthesis of chiral substituted quinolones. Depending on the different 3'-substitutions (R = H, Me) on the iodobutyl chain, the corresponding 3,4-disubstituted and 4,4-disubstituted dihydroquinolones were formed via *endo* and *exo* mode of cyclizations (Scheme 5.1).⁹



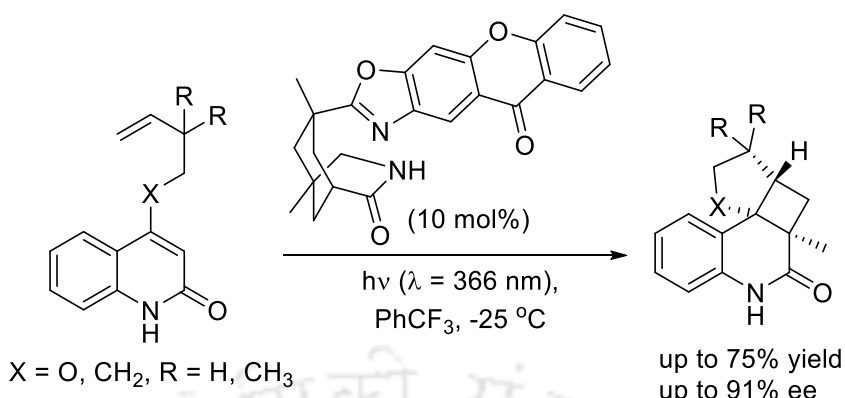
Scheme 5.1: Radical cyclization for the synthesis of dihydroquinolones

Harmata and coworkers developed an efficient protocol for the synthesis of enantiomerically pure 3,4-dihydroquinolin-2(1H)-ones through reductive desulfurization of chiral benzothiazenes (Scheme 5.2).¹⁰



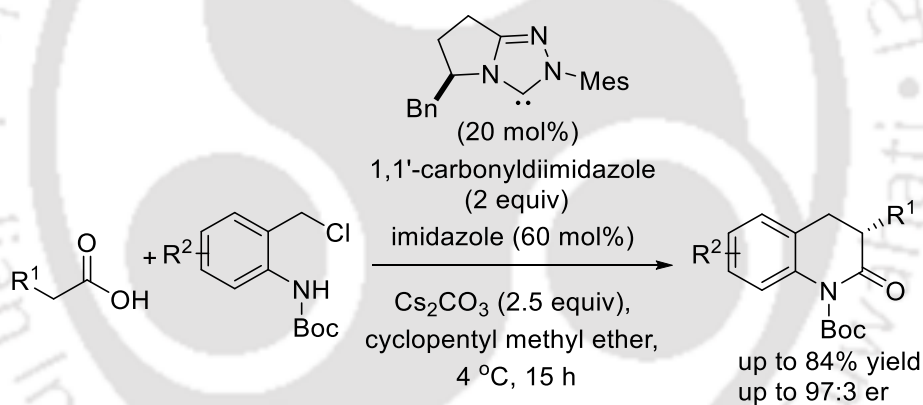
Scheme 5.2: Synthesis of 3,4-dihydroquinolin-2(1H)-ones through reductive desulfurization

Bach group explored [2+2] enantioselective intramolecular photocycloaddition of 4-substituted quinolones for the synthesis of chiral fused 3,4-disubstituted dihydroquinolones. Chiral sensitizer with hydrogen bonding motif was used as the catalyst in this reaction (Scheme 5.3).¹¹



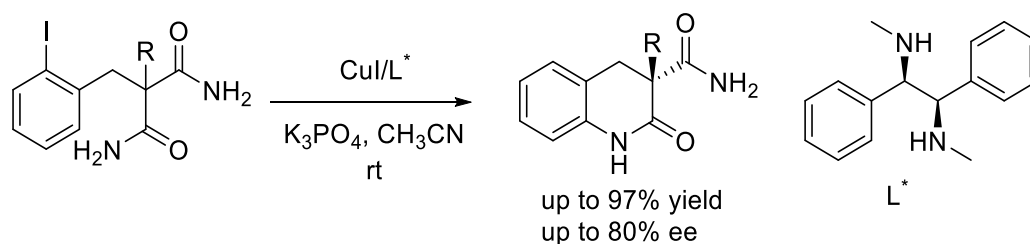
Scheme 5.3: Enantioselective photocycloaddition for the synthesis of 3,4-disubstituted dihydroquinolones

A convenient, NHC catalyzed enantioselective formal [4+2] cycloaddition for the synthesis of dihydroquinolones was developed by Scheidt group. The reaction proceeds through the dual activation of Lewis base (NHC) and *in situ* generated active nucleophiles and electrophiles (Scheme 5.4).¹²



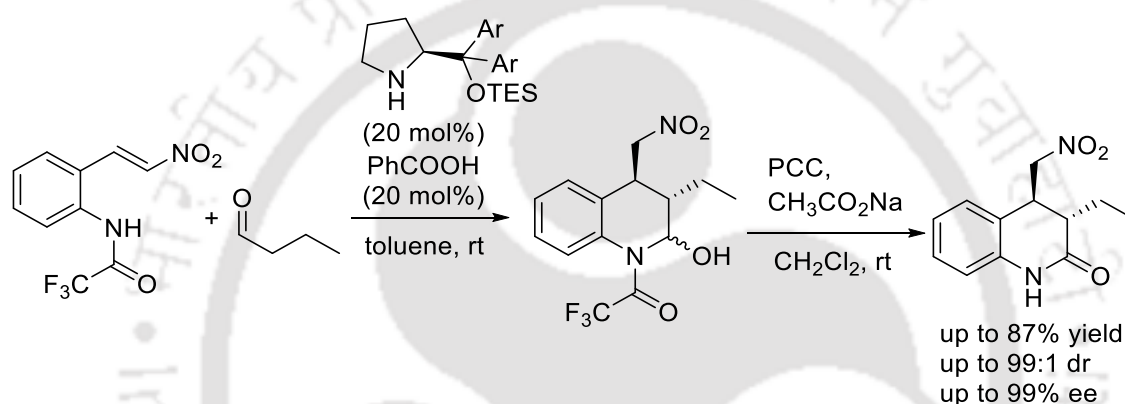
Scheme 5.4: NHC catalyzed enantioselective [4+2] cycloaddition for the synthesis of dihydroquinolones

A Cu(I) catalyzed asymmetric desymmetrization technique for the synthesis of 3,3-disubstituted 3,4-dihydro-2-quinolones was demonstrated by Cai and coworkers. The expected dihydroquinolones were isolated with moderate enantiomeric excess (Scheme 5.5).¹³



Scheme 5.5: Cu (I) catalyzed desymmetrization for the construction of dihydroquinolones

Xu and coworkers demonstrated chiral secondary amine catalyzed Michael-Hemiaminalization/oxidation approach for the synthesis of highly functionalized 3,4-disubstituted dihydro-2(1H)-quinolones (Scheme 5.6).¹⁴

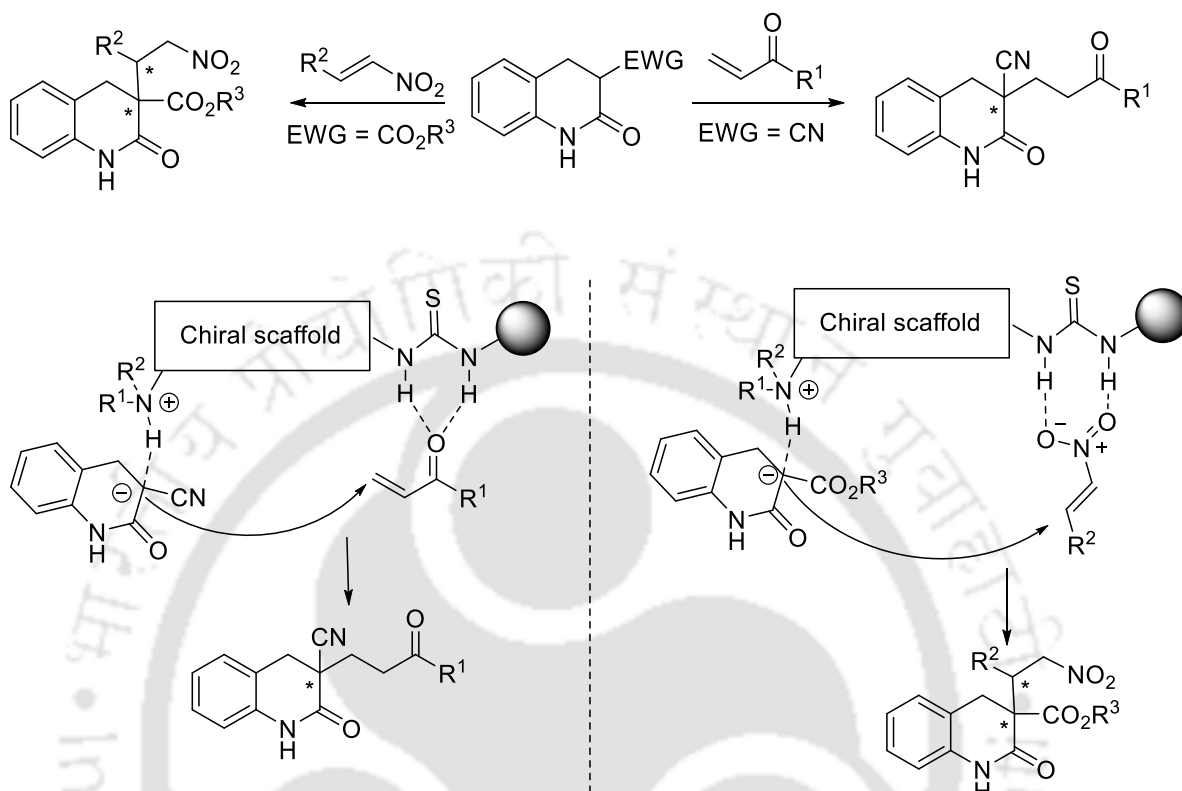


Scheme 5.6: Secondary amine catalyzed synthesis of highly functionalized dihydroquinolones

5.3. Concept:

Functionalized 3,4-dihydroquinolin-2(1H)-one is a heterocyclic motif that is prevalent in many natural alkaloids and pharmaceutical agents. Thus the synthesis of differently substituted 3,4-dihydroquinolin-2(1H)-ones is highly desirable. Despite of significant importance, asymmetric synthesis of 3,4-dihydroquinolin-2(1H)-one derivatives have been overlooked. Herein, we wish to report a direct Michael addition approach for the synthesis of chiral 3,4-dihydro 2-quinolones. However, 3,4-dihydro 2-quinolones were never applied for the Michael addition reaction due its less reactivity. By introducing electron-withdrawing group such as cyano or ester functionality at the 3-position, the reactivity of C-3 atom could be enhanced. We used dihydro-3-cyano-2-quinolone and dihydro-3-carboalkoxy-2-quinolones as the nucleophilic substrates. Vinyl ketones and nitroolefins were used as the electrophiles. Tertiary amine functionality of the catalyst will deprotonate from C-3 atom of the dihydroquinolones and the thiourea moiety will activate

vinyl ketone and nitroolefin through H-bonding to provide the expected addition products (Scheme 5.7).



Scheme 5.7: Proposed route for the synthesis of 3,3-disubstituted 3,4-dihydroquinolin-2(1H)-ones

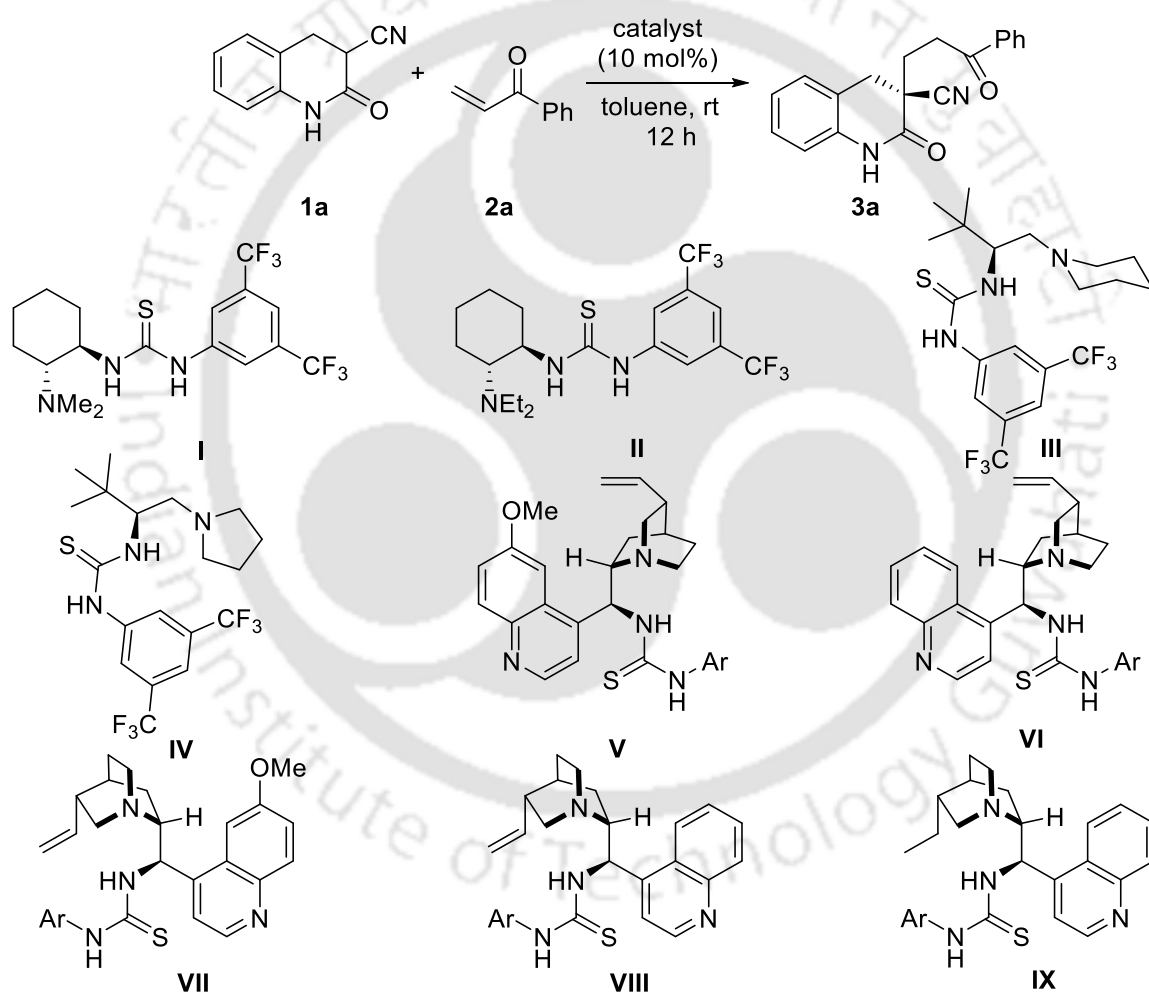
5.4. Result and discussion:

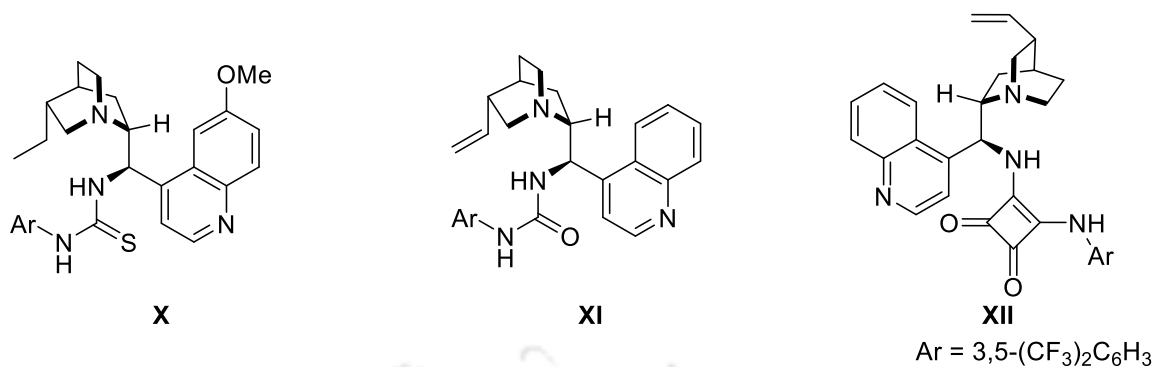
5.4.1. Michael reaction of dihydro-3-cyano-2-quinolone with vinyl ketones:

At the beginning, dihydro-3-cyano-2-quinolone was prepared and engaged to Michael reaction with 1-phenylprop-2-en-1-one in the presence of Takemoto catalyst **I** in toluene solvent (Table 1). Pleasingly, the desired product **3a** was obtained in 80% yield with 84% ee (entry 1). Then the reaction was performed with catalyst **II** bearing $-\text{NEt}_2$ moiety. Unfortunately enantioselectivity of the product drops to 70% (entry 2). Interestingly, the enantioselectivity slightly increased in the presence of *L*-tert-leucine derived thiourea catalysts **III**, **IV** having piperidiny and pyrrolidine moieties respectively (entries 3-4). Then different cinchona alkaloid derived thiourea, urea and squaramide catalysts were employed in the reaction (entries 5-12). Quinine derived thiourea catalyst **V** delivered the product **3a** in 80% yield with 89% ee (entry 5). Excellent enantioselectivity (92% ee) was

achieved with cinchonidine derived thiourea catalyst **VI** (entry 6). Quinidine and cinchonine derived thiourea catalysts **VII** and **VIII** furnished the product **3a** with 88% and 87% enantioselectivities respectively (entries 7-8). Next catalysts **IX** and **X** derived from hydrocinchonine and quinine respectively were screened however product **3a** was obtained with lesser enantioselectivities (9-10). Similar level of enantioselectivity was observed in the case of cinchonine derived urea catalyst **XI** (entry 11). Surprisingly, the enantiomeric excess decreased significantly with squaramide catalyst **XII** (entry 12).

Table 1. Catalyst screening





entry ^a	catalyst	yield (%) ^b	ee (%) ^c
1	I	80	84
2	II	68	70
3	III	75	87
4	IV	72	86
5	V	80	89
6	VI	85	92
7	VII	82	88
8	VIII	77	87
9	IX	75	82
10	X	72	80
11	XI	75	80
12	XII	80	78

^aReaction conditions: 0.1 mmol of **1a** and 0.2 mmol of **2a** in 0.5 mL toluene using 10 mol% catalyst at rt for 12 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by chiral HPLC.

5.4.1.1. Solvent screening:

To increase the enantioselectivity of the product further, the reaction was screened with catalyst **VI** in different solvents. The product was isolated with slight less enantiomeric excess in *o*-xylene solvent (Table 2, entry 2). Enantioselectivity of the product further decreased to 80% in *m*-xylene solvent (entry 3). Trifluorotoluene solvent provided the

product with 75% yield and 83% enantiomeric excess (entry 4). Enantioselectivity of the product got increased to 88% in dichloromethane solvent (entry 5). Then MTBE solvent was screened, however, enantioselectivity of the product dropped to 63% (entry 6). Thus the best result was obtained in toluene solvent with 85% yield and 92% enantiomeric excess (entry 1).

Table 2. Solvent screening

entry ^a	solvent	yield(%) ^b	ee (%) ^c
1	toluene	85	92
2	<i>o</i> -xylene	80	86
3	<i>m</i> -xylene	77	80
4	PhCF ₃	75	83
5	DCM	79	88
6	MTBE	70	63

^aReaction conditions: 0.1 mmol of **1a** and 0.2 mmol of **2a** in 0.5 mL solvent using 10 mol% catalyst at rt for 12 h. ^bIsolated yield after silica gel column chromatography. ^cDetermined by chiral HPLC.

5.4.1.2. Substrate scope:

Having optimal condition in hand, the scope and generality of the reaction have been explored. Initially different vinyl ketones were prepared and examined in the reaction (Table 3). Pleasingly, as can be seen, excellent results were obtained with different *para*- and *meta*- substituted phenyl group containing enones. Enone **2b** having *p*-tolyl group delivered product **3b** with 80% yield and 96% ee. Similarly, product **3c** having 4-anisole

moiety was isolated in a high enantioselectivity of 92%. Next different 4-halo substituted aryl enones **2d**, **2e** and **2f** were employed in the reaction. Pleasingly, smooth conversions were observed in every cases and the expected products were obtained with excellent enantioselectivities. Delightfully enone **2g** bearing biphenyl moiety reacted smoothly and furnished the product with 79% yield and 93% enantiomeric excess. Aryl enone having electron withdrawing nitro group at *para*- position delivered the corresponding product **3h** with lesser enantioselectivity. Different *meta*- substituted enones **2i-2j** also participated well in the reaction and the products were isolated with high enantioselectivities. The reaction outcome was excellent for disubstituted aryl enone **2k** and high enantioselectivity was achieved. Heteroaromatic enone **2l** was also tested in the reaction and a decrease in enantioselectivity was observed for product **3l**.

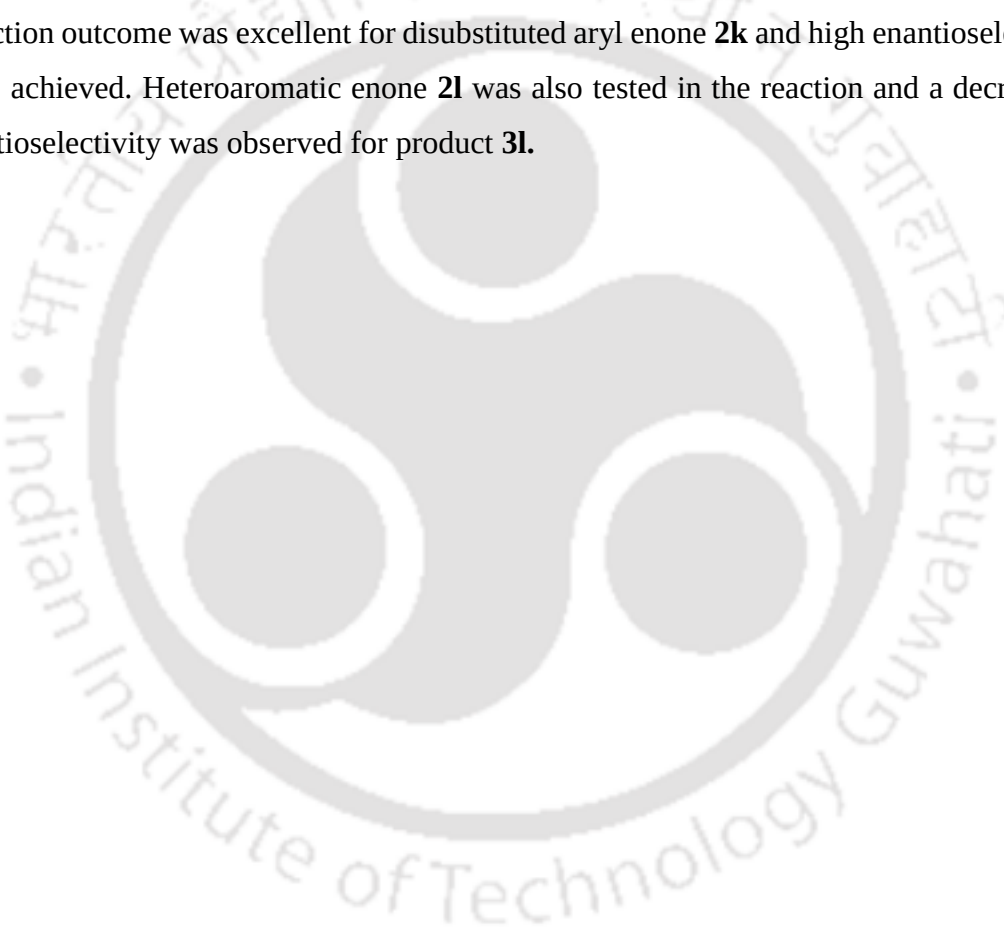
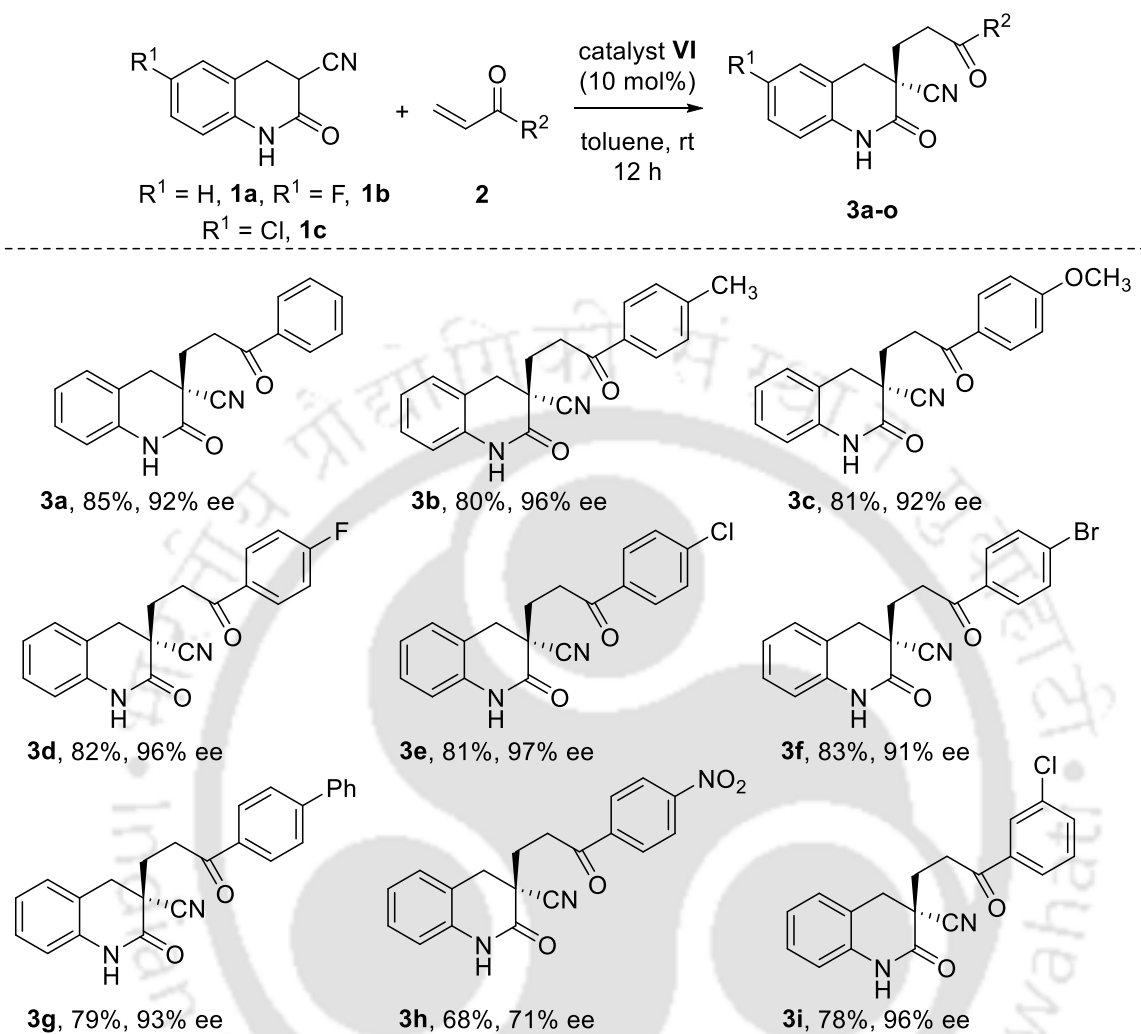
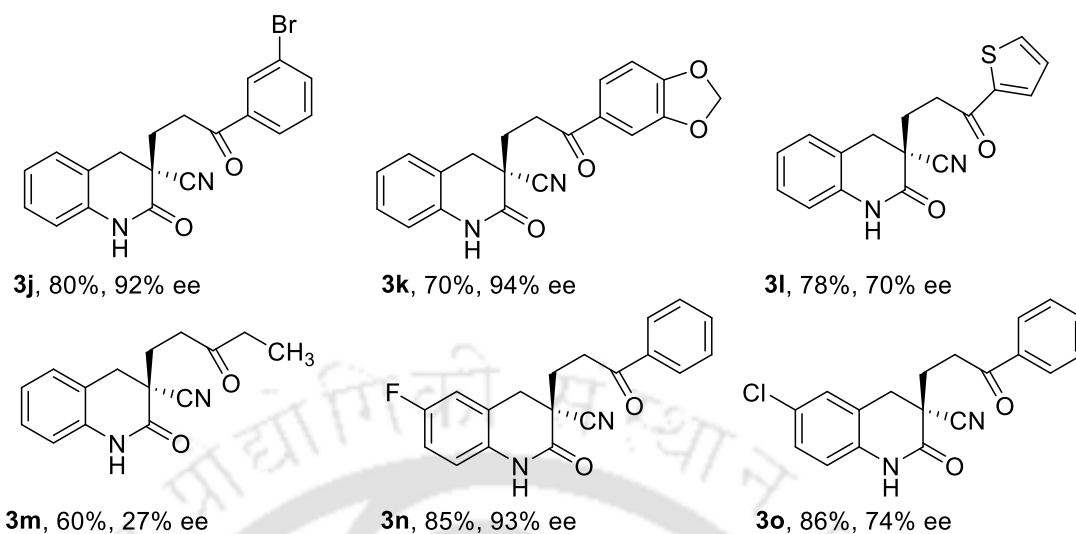


Table 3. Substratescope^{a,b,c,d}





^aUnless otherwise mentioned, reactions were carried out with 0.15 mmol of **1** with 0.3 mmol of **2** in 0.75 mL toluene using 10 mol% **VI** at rt for 12 h. ^bIsolated yield after silica gel column chromatography.

^cDetermined by chiral HPLC

Aliphatic enone **2m** also participated in the reaction however lower enantioselectivity was observed.

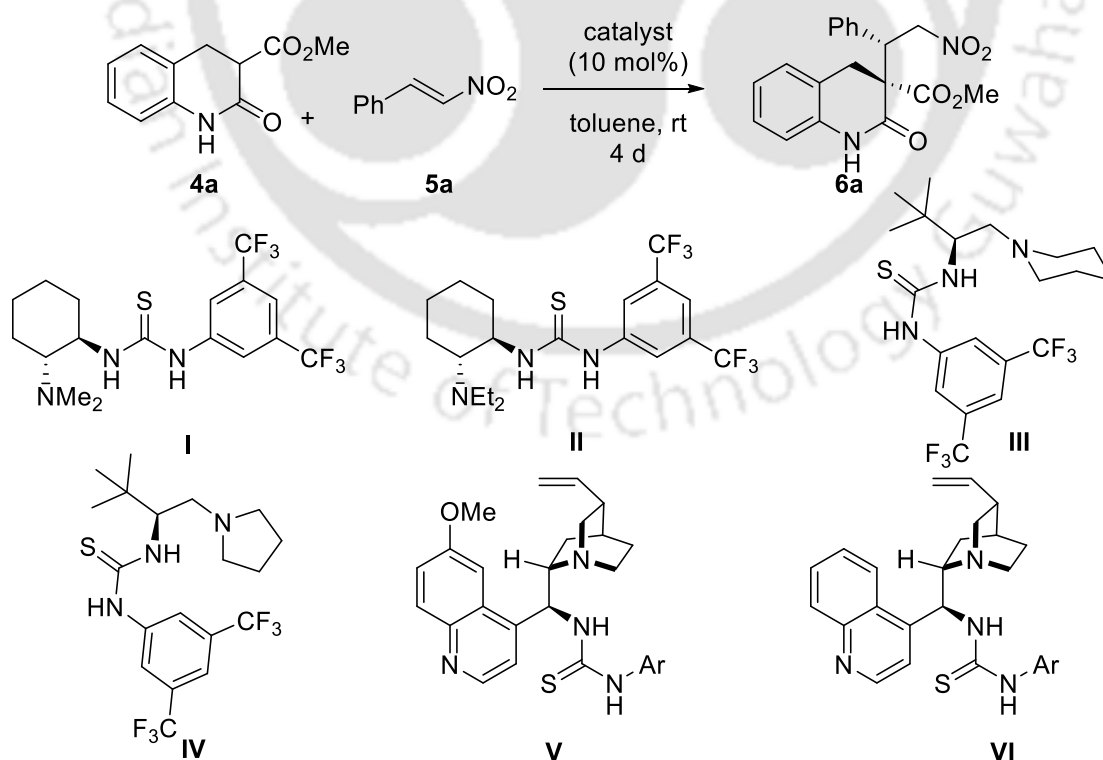
In the next phase we became interested to employ other dihydroquinolones in our reaction and mixed results were obtained. Delightfully, after performing a reaction between 6-fluoro dihydroquinolone **1b** and vinyl ketone **2a**, the desired product **3n** was isolated in 85% yield with 93% ee. However, enantioselectivity dropped to 74% ee for product **3o** when 6-chloroderivative **1c** was employed.

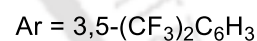
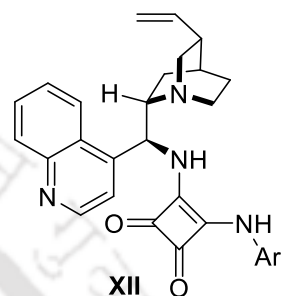
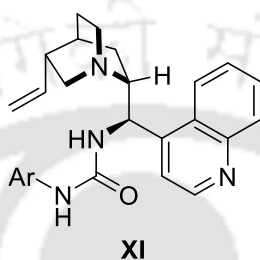
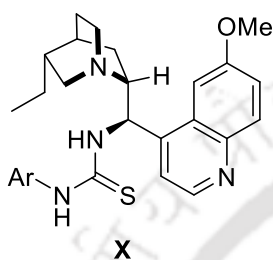
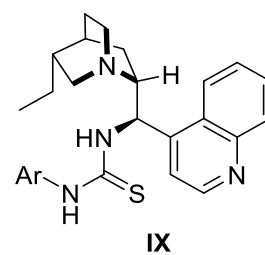
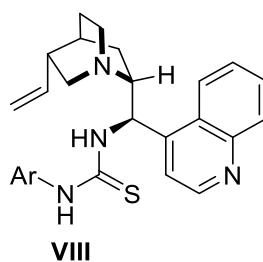
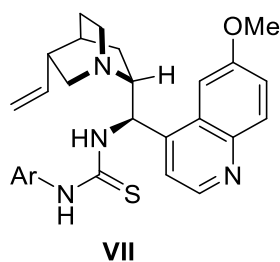
5.4.2. Michael reaction of dihydro-3-carbomethoxy-2-quinole with nitroolefins:

We initially prepared dihydro-3-carbomethoxy-2-quinolone **4a** and employed in the Michael reaction with nitroolefin **5a** in the presence of various thiourea, urea and squaramide catalysts in toluene solvent (Table 4). Gratifyingly, the desired product **6a** was isolated with 82% combined yield, 2:1 diastereomeric ratio and 78% ee for the major diastereomer in the presence of Takemoto catalyst **I** (entry 1). However, the enantioselectivity dropped to 60% with cyclohexyl derived thiourea catalyst **II** having –NEt₂ moiety (entry 2). Pleasingly, the enantioselectivity of the product got enhanced with

L-tert-leucine derived thiourea catalysts **III** and **IV** (entries 3-4). Then different cinchona alkaloid derived thiourea catalysts were engaged in the reaction (entries 5-10). Quinine derived thiourea catalyst **V** provided the product with 85% yield, 2:1 dr and 80% ee for the major diastereomer (entry 5). Enantioselectivity improved to 90% in the case of cinchonidine derived thiourea catalyst **VI** (entry 6). Catalyst **VII** having quinidine motif delivered the product with little increase in enantioselectivity (entry 7). The enantioselectivity got enhanced to 93% with cinchonine derived thiourea catalyst **VIII** though similar diastereoselectivity was observed (entry 8). Hydrocinchonine derived thiourea catalyst **IX** delivered **6a** with a similar ee but the yield was very less (entry 9). Both hydroquinidine thiourea and cinchonine urea catalysts **X** and **XI** provided the product with diminution in enantioselectivity (entries 10-11). Finally, with cinchonidine squaramide catalyst, enantioselectivity of the product significantly dropped to 76% (entry 12). Thus the best catalyst turned out to be cinchonine derived thiourea catalyst **VIII** which provided the product **6a** in 90% combined yield with 93% ee of the major diastereomer in 2:1 diastereomeric ratio.

Table 4. Catalyst screening





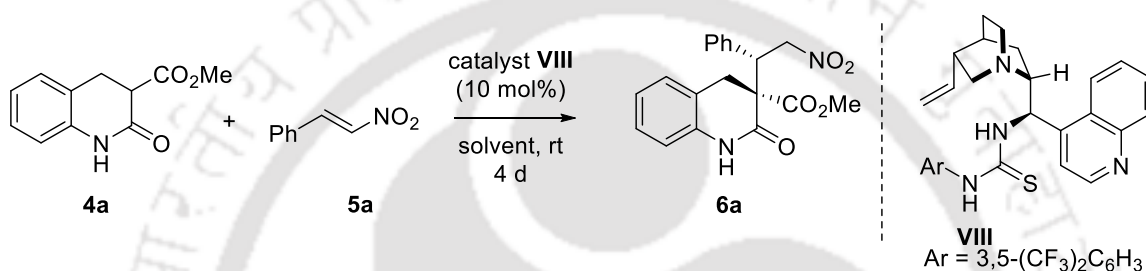
entry ^a	catalyst	yield(%) ^b	dr ^c	ee(%) ^d
1	I	82	2:1	78
2	II	82	2:1	60
3	III	55	2:1	88
4	IV	50	2:1	85
5	V	85	2:1	82
6	VI	87	2:1	90
7	VII	85	2:1	91
8	VIII	90	2:1	93
9	IX	45	2:1	93
10	X	75	2:1	81
11	XI	80	2:1	80
12	XII	75	2:1	76

^aReaction conditions: 0.1 mmol of **5a** and 0.2 mmol **4a** in 0.3 mL toluene using 10 mol% catalyst at RT for 4 days. ^bCombined yield of isolated product. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC and of the major diastereomer.

5.4.2.1. Solvent screening:

To improve the diastereoselectivity and enantioselectivity of the product the reaction was performed in different solvents in the presence of cinchonine derived thiourea catalyst. In MTBE solvent product, the major diastereomer **6a** was isolated with 75% yield, 2:1 dr and 91 % enantiomeric excess. The enantioselectivity slightly decreased in trifluorotoluene solvent. Inferior result was obtained in dichloromethane solvent with 80% enantiomeric excess.

Table 5. Solvent screening^{a,b,c,d,e,f}



entry ^a	solvent	yield(%) ^b	dr ^c	ee(%) ^d
1	toluene	90	2:1	93
2	MTBE	75	2:1	91
3	TFT	80	2:1	89
4	DCM	85	2:1	80

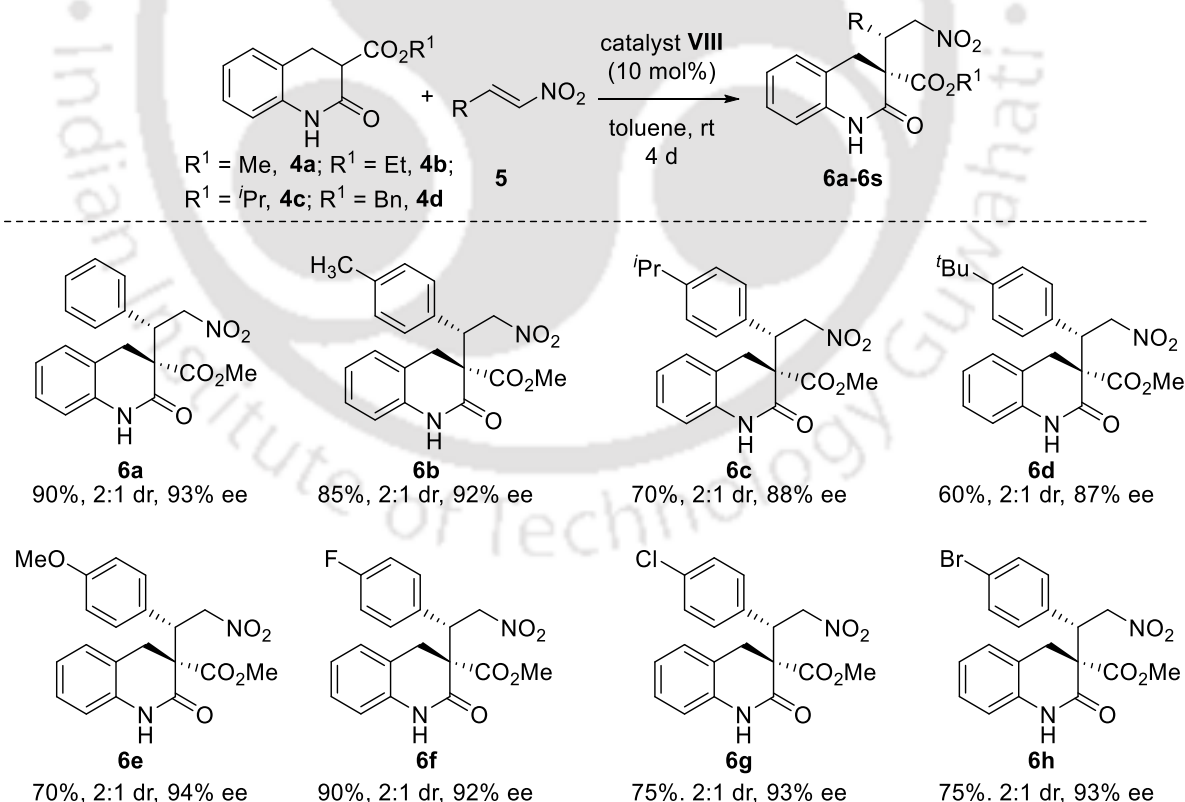
^aReaction conditions: 0.1 mmol of **5a** and 0.2 mmol **4a** in 0.3 mL solvent using 10 mol% catalyst at rt for 4 days. ^bCombined yield of isolated product. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC and of the major diastereomer.

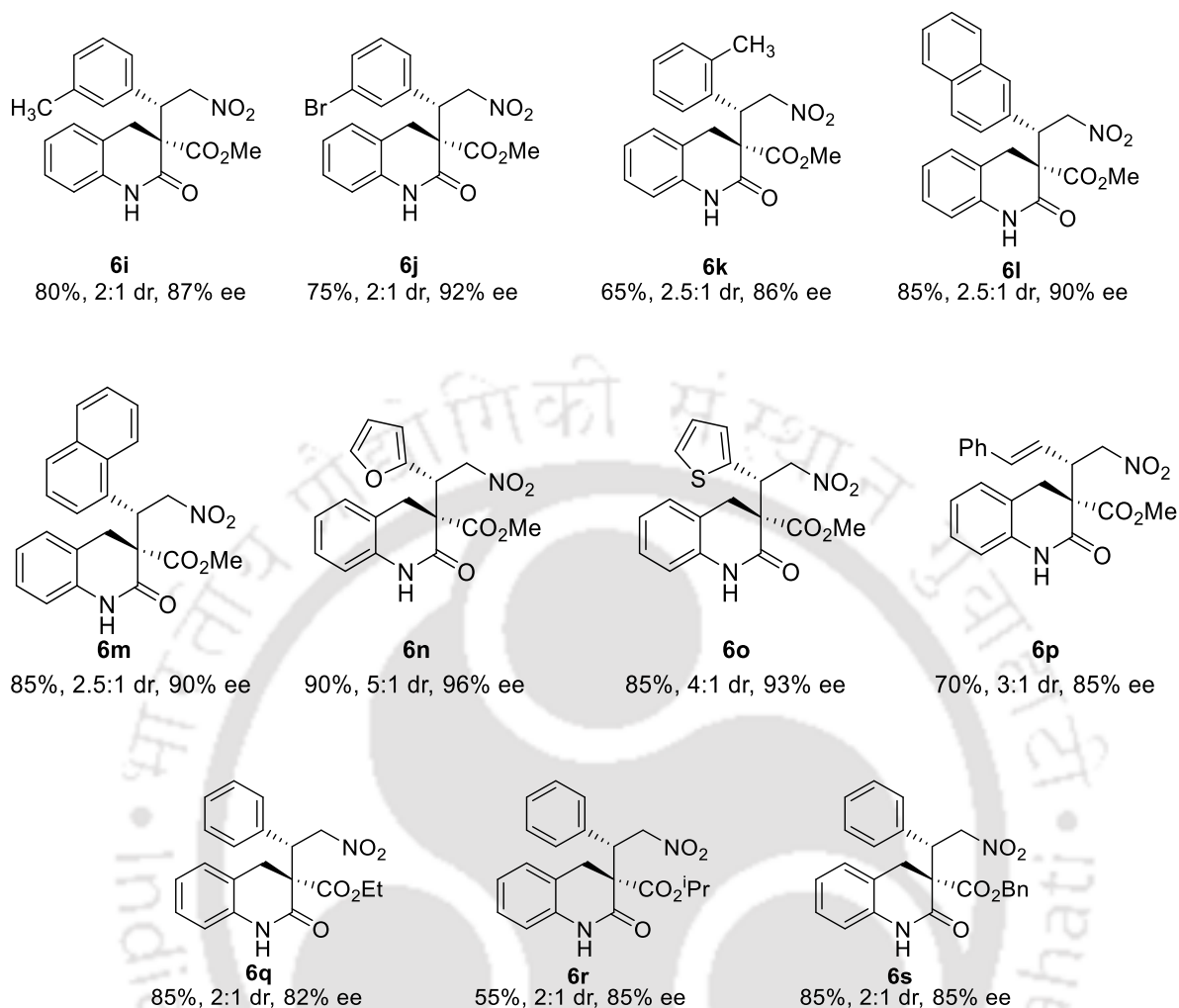
5.4.2.2. Substrate scope:

After identifying the best condition, we started to explore the scope of the Michael reaction and the outcome is summarized in Table 6. A variety of nitroolefins having different groups at the *para*-, *meta*- and *ortho*- position of the phenyl ring reacted smoothly in the reaction irrespective of their electronic nature. 4-Methyl substituted nitroolefin **5b** delivered the major product **6b** with 92% ee. Lesser enantioselectivities were obtained for 4-isopropyl and 4-*tert*butyl substituted nitroolefins. *Para*-anisyl substituted nitroolefin participated well in the reaction and high enantioselectivity was achieved. In the next phase

different 4-halo substituted nitroolefins were engaged in the reaction and excellent results were obtained. For *para*- fluoro substituted nitroolefin the product **6f** was obtained with 2:1 diastereomeric ratio and 92% ee. 4-Chloro and 4-bromo substituted nitroolefins furnished the products **6g**, **6h** with similar enantio and diastereoselectivities. Moreover, different *meta*-substituted nitroolefins reacted smoothly. *m*-tolyl substituted nitroolefin delivered the product **6i** with good enantiomeric excess. Excellent enantioselectivity for product **6j** was obtained after reaction with 3-bromo substituted nitroolefin. The reaction outcome was also satisfactory for *ortho*- substituted nitroolefin **5k**. Naphthyl substituted nitroolefins were also screened. Though 2-naphthyl substituted nitroolefin delivered product **6l** with 90% ee, a decrease in enantioselectivity to 83% was observed for 1-naphthyl substituted product **6m**. Interestingly heteroaromatic group substituted nitroolefins **5n** and **5o** were found to be best substrates in this reaction.

Table 6. Substratescope



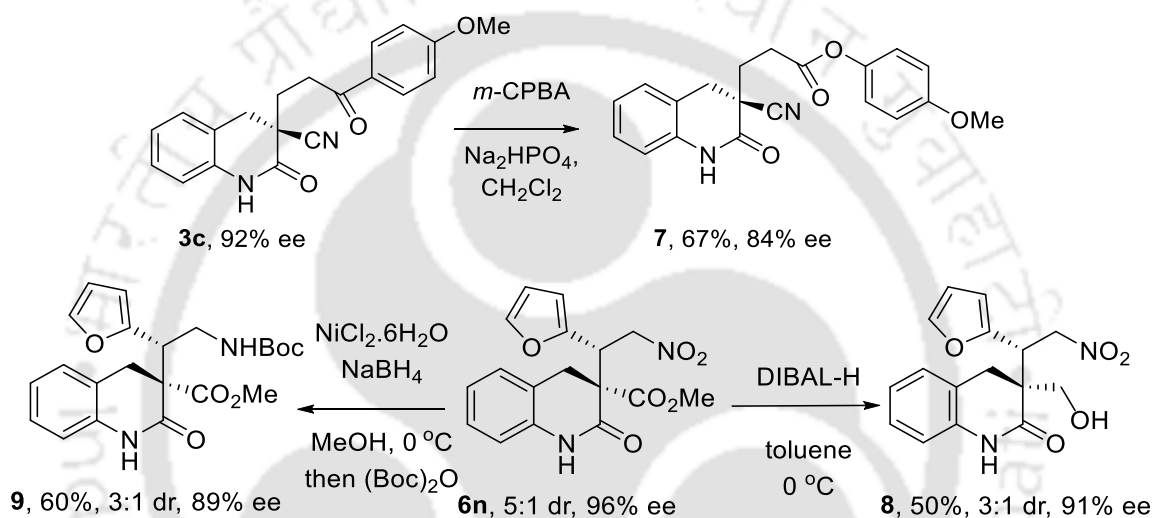


^aReaction conditions: Unless otherwise mentioned, 0.2 mmol of **4a** and 0.4 mmol of **5** in 0.6 mL toluene using 10 mol% **VIII** at rt. ^bCombined yield of the isolated product. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC and of the major diastereomer.

The products **6n** and **6o** were isolated not only with better enantiomeric excesses (96% ee and 93% ee respectively) but also with good diastereomeric ratios. Cinnamyl substituted nitroolefin also provided product **6p** with good enantiomeric excess. In the next phase the scope was further extended by engaging other dihydroquinolones in the reaction. Dihydroquinolones **4b**, **4c** and **4d** having different ester functionalities provided the products with similar diastereoselectivities and in acceptable enantioselectivities.

5.5.3. Synthetic transformations of **3c** and **6n**:

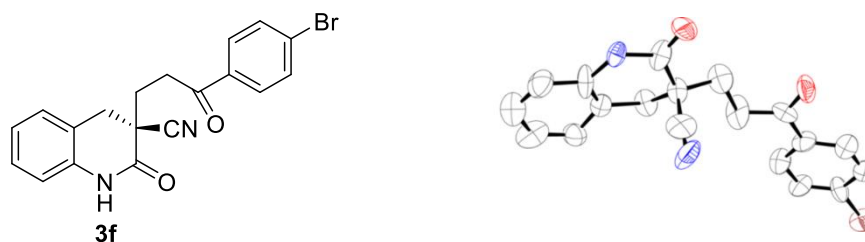
To explore the synthetic utility of our methodology, few reactions were performed using chiral products **3c** and **6n** (Scheme 8). Initially Baeyer villager reaction was carried out on **3c** and thus ester **7** was isolated with slight diminution in enantioselectivity. Next a selective reduction of the ester with DIBAL-H provided the expected alcohol **8** in moderate yield with slight decrease in enantiopurity. Similarly treatment of **6n** with $\text{NiCl}_2\text{-NaBH}_4$ reduction followed by Boc-anhydride treatment produced *N*-Boc derivative **9** with almost similar enantioselectivity (Scheme 5.8).



Scheme 5.8: Synthetic transformation of chiral products **3c** and **6n**.

5.5.4. Absolute configuration of **3f** and **6o**:

The absolute structure of **3f** was solved by X-ray crystallography and was found to be (*R*).¹⁵ Thus other products derived from vinyl ketone reactions are expected to have same absolute structure by analogy.

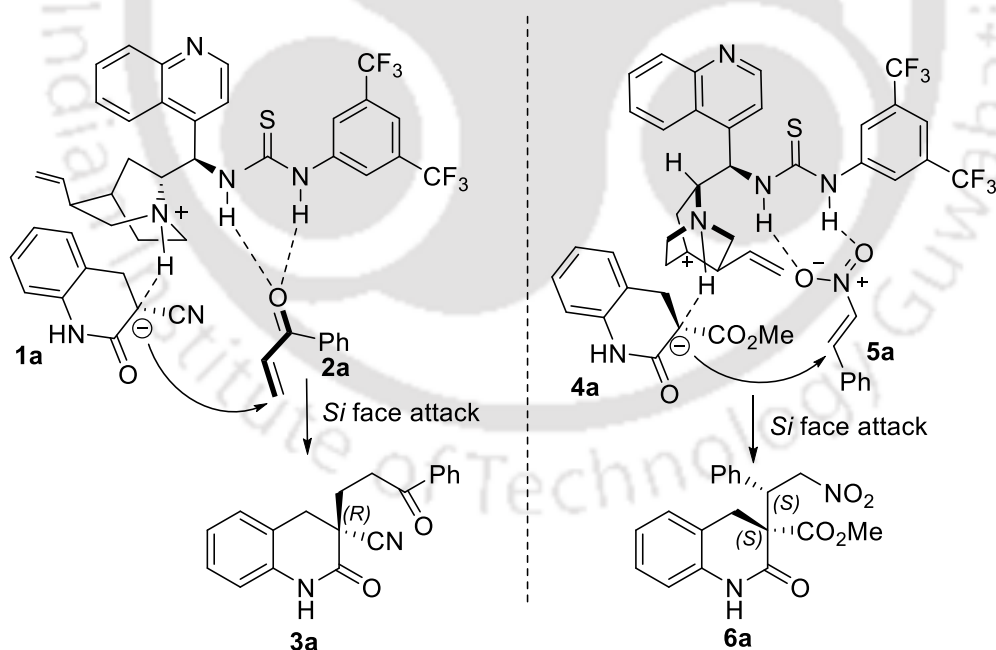


Similarly, the relative and absolute structure of **6o** was elucidated to be (*S,S*) by X-ray crystallography¹⁶ and other compounds are assumed to be of same configuration.



5.5.5. Proposed mechanism:

Based on the absolute structures of **3f** and **6o**, two plausible transition states have been drawn which dictates a bifunctional mode of activation by the catalyst. It depicts that the tertiary amine functionality of catalyst **VI** activates dihydroquinolone **1a** from the *Re* face and thus *Si* face is exposed for the addition, and consequently (*R*)-**3a** was formed. On the other hand dihydroquinolone **4a** will be activated by the catalyst **VIII** from the *Re* face and the corresponding addition will take place from the *Si* face of the dihydroquinolone to deliver the product with (*S,S*) configuration (Scheme 5.9).



Scheme 5.9: Plausible mechanism for the synthesis of 3,3-disubstituted 3,4-dihydro-2-quinolones

5.6. Conclusion:

In conclusion we have developed a novel organocatalytic Michael reaction for the asymmetric synthesis of 3,3-disubstituted 3,4-dihydro-2-quinolones. By substrate tuning, both vinyl ketones and nitroolefins were employed and the products were obtained in moderate to good yields with high enantioselectivities. Also, the usefulness of our methodology was shown *via* important synthetic operations of the products. The dihydroquinolone products having one or two stereogenic centres are significant in pharmaceuticals and could be applied in the synthesis of biologically important quinolones.

5.7. Experimental section:

General information:

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

^1H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in CDCl_3 ; chemical shift values (δ , ppm) were reported in the standard fashion with reference to either tetramethylsilane (TMS) ($\delta(\text{H})$ 0.00 ppm) or CHCl_3 ($\delta(\text{H})$ 7.26 ppm).

^{13}C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in CDCl_3 ; chemical shifts (δ , ppm) were reported relative to CHCl_3 ($\delta(\text{C})$ 77.23 ppm, central line of triplet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (J) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization

(ESI) technique. IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-K α irradiation ($\lambda = 0.71073$ Å) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F² using SHELXL-2014.

A. General procedure for the synthesis of dihydroquilones 1a-1c and 4a-4d:

Dihydroquilones **1a-1c** and **4a-4d** were prepared according to literature procedure.¹⁷

A. General procedure for the synthesis of enones 2a-2o:

Enones were prepared following literature procedures.¹⁸

B. General procedure for the synthesis of nitroolefins 1a-1i:

Nitroolefins were prepared according to the reported procedure.¹⁹

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

Thiourea catalysts (**I-XI**) were prepared according to the reported procedures.²⁰ Squaramide catalyst **XII** was prepared according to the reported procedure.²¹

D. General procedure for the synthesis of compound 3:

Under argon atmosphere, compound **1** namely dihydro-3-cyano-2-quinolone (0.15 mmol), enone **2** (0.3 mmol) and catalyst **VI** (10 mol%) were placed in a round bottom flask. Toluene 0.75 mL was added to it. Then the reaction mixture stirred at room temperature under argon atmosphere. After the reaction was completed as monitored by TLC, the product was purified by column chromatography using 25-30% ethyl acetate in hexane as eluent.

E. General procedure for the synthesis of compound 6:

In an oven dried round bottomed flask, dihydro-3-carbomethoxy-2-quinolone **4** (0.2 mmol), nitroolefin **5** (0.4 mmol) and catalyst **VIII** (10 mol %) were added under argon atmosphere. Toluene (0.6 mL) was added to the reaction mixture via a syringe and it was stirred at room temperature under argon. After the reaction was completed as monitored by TLC, the reaction mixture was directly subjected to column chromatography on silica gel using 20% EtOAc/Hexane as an eluent to obtain the desired product **6**.

F. General procedure for the synthesis of compound 7:

To a solution of **3c** (0.1 mmol) in CH₂Cl₂ (4 mL) were added disodium hydrogen phosphate (0.25 mmol) and *m*-CPBA (0.25 mmol). The reaction mixture was stirred at room temperature for 6h. After that the mixture was poured into water (2 mL) and saturated sodium hydrogen carbonate (2 mL) solution. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ twice. The combined organic layer was dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography using 25% ethyl acetate in hexane.

G. General procedure for the synthesis of compound 8:

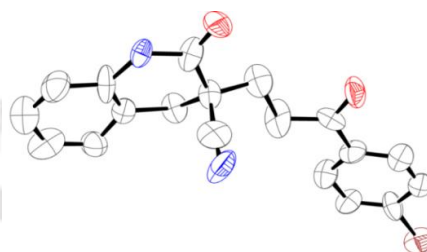
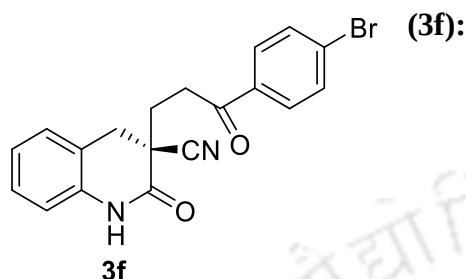
To a stirred solution of **3n** in toluene (0.2 mL), a solution of DIBAL-H (1 M in toluene, 5 equiv.) was added drop wise at 0 °C. After the completion of the reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over Na₂SO₄, concentrated under vacuum and the crude product was purified by column chromatography using 40% ethyl acetate in hexane.

H. General procedure for the synthesis of compound 9:

The compound **3n** (0.1 mmol) was dissolved in 0.1 mL MeOH and NiCl₂·6H₂O (2 equiv.) was added under argon atmosphere at room temperature. After 10 min, the mixture was cooled to 0 °C and NaBH₄ (6 equiv.) was added in portion resulting the formation of a black solution. The reaction mixture was stirred for 5 min at 0 °C before the addition of (Boc)₂O (3 equiv.). The mixture was allowed to stir at 0 °C overnight. The reaction was quenched with saturated NH₄Cl solution and diluted with CH₂Cl₂ twice. The combined

organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography using 30% ethyl acetate in hexane.

Crystal data and structure refinement for chiral compound (CCDC No. 1523234)

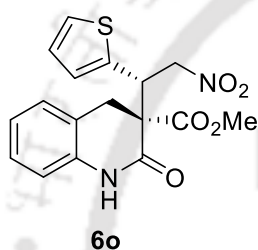


Empirical formula	$\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_2\text{Br}$
Formula weight	383.24
CCDC Number	1523234
Crystal habit, colour	Needle, White
Crystal size, mm^3	$0.40 \times 0.30 \times 0.20$
Temperature, T	296(2)
Wavelength, λ (Å)	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	$a = 5.7907(8)$ Å $b = 16.082(4)$ Å $c = 18.129(4)$ Å $\alpha = 90.00^\circ$, $\beta = 90.00^\circ$ $\gamma = 90.00^\circ$
Volume, V (Å ³)	1688.3(6)
Z	4
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.508
Absorption coefficient, μ (mm^{-1})	2.448
$F(000)$	776
θ range for data collection	3.39 to 25.00°
Limiting indices	$-4 \leq h \leq 6$, $-11 \leq k \leq 19$, $-12 \leq l \leq 21$
Reflection collected/unique	4125/ 2816 [$R(\text{int}) = 0.1111$]
Completeness to θ	99.7% ($\theta = 25.00^\circ$)

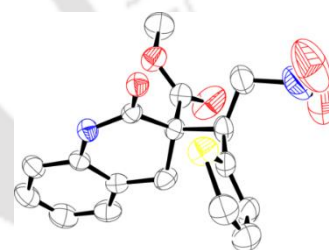
CHAPTER 5

Max. and min. transmission	0.613/0.418
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data/restraints/parameters	2816/0/217
Goodness-of-fit on F^2	0.944
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0930$, $wR_2 = 0.1299$
R indices (all data)	$R_1 = 0.2501$, $wR_2 = 0.2113$
Largest diff. peak and hole	0.716 and $-0.648 \text{ e} \cdot \text{\AA}^{-3}$

Crystal data and structure refinement for chiral compound (CCDC No. 1522057)



(6o):



Empirical formula	$\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_5\text{S}$
Formula weight	359.37
CCDC Number	1522057
Crystal habit, colour	Block, Brown
Crystal size, mm^3	$0.29 \times 0.24 \times 0.18$
Temperature, T	296(2)
Wavelength, $\lambda(\text{\AA})$	0.71073
Crystal system	monoclinic
Space group	' $P 2_1/c$ '
Unit cell dimensions	$a = 9.3891(5) \text{\AA}$ $b = 7.7761(4) \text{\AA}$ $c = 23.6648(15) \text{\AA}$ $\alpha = 90.00^\circ$, $\beta = 91.381(5)^\circ$ $\gamma = 90.00^\circ$
Volume, $V(\text{\AA}^3)$	1727.29(17)
Z	4
Calculated density, $\text{Mg} \cdot \text{m}^{-3}$	1.382

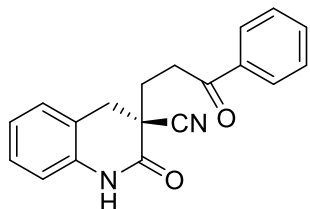
Absorption coefficient, μ (mm ⁻¹)	0.217
$F(000)$	748.0
θ range for data collection	3.14° to 25.00°
Limiting indices	$-10 \leq h \leq 11, -8 \leq k \leq 9,$ $-28 \leq l \leq 15$
Reflection collected/unique	6799/3043 [$R(\text{int}) = 0.0219$]
Completeness to θ	99.8% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.962/0.939
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data/restraints/parameters	3043/0/227
Goodness-of-fit on F^2	1.074
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0770, wR2 = 0.1956$
R indices (all data)	$R1 = 0.0970, wR2 = 0.2099$
Largest diff. peak and hole	0.796 and $-0.273 \text{ e} \cdot \text{\AA}^{-3}$

5.8. References:

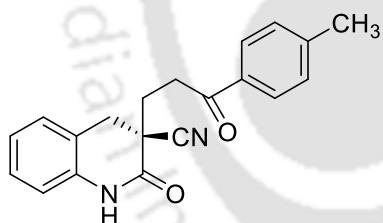
- (1) For selected examples, see: (a) Tominaga, M.; Tone, H.; Nakagawa, K.; Takada, K.; Hoshino, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1981**, *29*, 2166. (b) Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 798. (c) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893. (d) Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1344. (e) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Vitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943. (f) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701. (g) Chen, M.; Shao, C.-L.; Meng, H.; She, Z.-G.; Wang, C.-Y. *J. Nat. Prod.* **2014**, *77*, 2720.
- (2) For selected references, see: (a) Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264. (b) Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785. (c) Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 7503. (d) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881. (e) Turner, K. L.; Baker, T. M.; Islam, S.; Procter, D. J.; Stefaniak, M. *Org. Lett.* **2006**, *8*, 329. (f) Felpin, F.-X.; Coste, J.; Zakri, C.; Fouquet, E. *Chem. Eur. J.* **2009**, *15*, 7238. (g) Zhou, W.; Zhang, L.; Jiao, N. *Tetrahedron* **2009**, *65*, 1982. (h) de Araujo, A. D.; Christensen, C.; Buchardt, J.; Kent, S. B. H.; Alewood, P. F. *Chem. Eur. J.* **2011**, *17*, 13983. (i) Zhang, L.; Sonaglia, L.; Stacey, J.; Lautens, M. *Org. Lett.* **2013**, *15*, 2128. (j) Mai, W.-P.; Wang, J.-T.; Yang, L.-R.; Yuan, J.-W.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *Org. Lett.* **2014**, *16*, 204. (k) Li, B.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1125.
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- (14) Xia, A. -B.; Zhang, X.-L.; Wang, T.; Du, X.-H.; Xu, D.-Q.; Xu, Z.-Y. *New J. Chem.* **2015**, *39*, 5088.
- (15) CCDC 1523234 contains the crystallographic data for **3f**.
- (16) CCDC 1522057 contains the crystallographic data for **60**.
- (17) (a) Bugarin, A.; Jones, K. D.; Connell, B. T. *Chem. Commun.* **2010**, *46*, 1715. (b) Shi, Z.; Tong, Q.; Leong, W. W. Y.; Zhong, G. *Chem. Eur. J.* **2012**, *18*, 9802.
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- (21) Yang, W.; Du, D. M. *Org. Lett.* **2010**, *12*, 5450.

5.9. Characterization Data of Products:

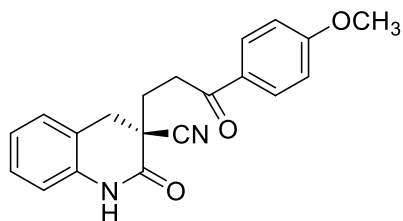
(R)-1,2,3,4-tetrahydro-2-oxo-3-(3-oxo-3-phenylpropyl)quinoline-3-carbonitrile(3a):

This compound was prepared according to the general procedure D. White solid (38.7 mg, yield: 85%); **m.p.** 230 - 231 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.41 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 9.9 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 15.7 Hz, 1H), 3.42 – 3.29 (m, 2H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.24 – 2.11 (m, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 197.9, 165.5, 136.5, 135.4, 133.7, 128.9, 128.3, 124.7, 119.3, 118.8, 115.9, 44.2, 36.5, 34.5, 29.9, 28.4; **FT-IR (thin film):** 1695, 1674, 1597, 1490, 1447, 1435, 1366, 1219, 1291, 1214 cm⁻¹; **HRMS (+ESI):** Calc for C₁₉H₁₇N₂O₂ [M+H]⁺ 305.1285; found: 305.1286; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.3 min, τ_{minor} = 21.2 min); Enantiomeric excess: 91%.

(R)-1,2,3,4-tetrahydro-2-oxo-3-(3-oxo-3-*p*-tolylpropyl)quinoline-3-carbonitrile(3b)

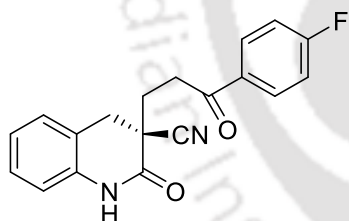
This compound was prepared according to the general procedure D. White solid (38.1 mg, yield: 80%); **m.p.** 211 - 212 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.20 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.19 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.55 (d, *J* = 15.8 Hz, 1H), 3.34 (dt, *J* = 9.4, 5.5 Hz, 2H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.40 (s, 3H), 2.22 – 2.16 (m, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 197.5, 165.8, 144.5, 135.4, 134.0, 129.6, 129.0, 128.9, 128.4, 124.6, 119.3, 118.9, 116.0, 44.3, 36.4, 34.3, 28.4, 21.9; **FT-IR (thin film):** 1691, 1668, 1607, 1596, 1491, 1438, 1363, 1293 cm⁻¹; **HRMS (+ESI):** Calc for C₂₀H₁₉N₂O₂ [M+H]⁺ 319.1441; found 319.1447; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.8 min, τ_{minor} = 23.6 min); Enantiomeric excess: 96%.

(R)-1,2,3,4-tetrahydro-3-(3-(4-methoxyphenyl)-3-oxopropyl)-2-oxoquinoline-3-carbonitrile (3c)



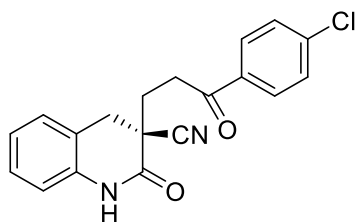
This compound was prepared according to the general procedure D. White solid (40.5 mg, yield: 81%); **m.p.** 193 - 194 °C; **¹H NMR (600 MHz, CDCl₃)**: δ 9.03 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.55 (d, *J* = 15.8 Hz, 1H), 3.33 – 3.28 (m, 2H), 3.17 (d, *J* = 15.8 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.19 – 2.14 (m, 1H); **¹³C NMR (150 MHz, CDCl₃)**: δ 196.4, 166.0, 163.9, 135.5, 130.6, 129.6, 129.0, 128.8, 124.6, 119.3, 119.0, 116.1, 114.0, 55.7, 44.3, 36.4, 34.1, 28.5; **FT-IR (thin film)**: 1693, 1668, 1600, 1574, 1492, 1423, 1315, 1303, 1259, 1175 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₀H₁₉N₂O₃ [M+H]⁺ 353.1390; found 353.1390; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 23.0 min, τ_{minor} = 43.1 min); Enantiomeric excess: 92%.

(R)-3-(3-(4-fluorophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3d)



This compound was prepared according to the general procedure D. White solid (39.6 mg, yield: 82%); **m.p.** 229 - 230 °C; **¹H NMR (600 MHz, CDCl₃)**: δ 8.56 (s, 1H), 8.03 – 7.90 (m, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.1 Hz, 3H), 6.83 (d, *J* = 7.7 Hz, 1H), 3.56 (d, *J* = 15.7 Hz, 1H), 3.38-3.32 (m, *J* = 22.7, 9.7, 5.7 Hz, 2H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.20 – 2.15 (m, 1H); **¹³C NMR (150 MHz, CDCl₃)**: δ 196.3, 165.6, 135.3, 132.9, 130.9 (d, *J* = 9.0 Hz), 129.0 (d, *J* = 18.0 Hz), 124.7, 119.2, 118.8, 116.1, 116.0, 44.2, 36.5, 34.5, 28.4; **FT-IR (thin film)**: 1693, 1672, 1597, 1510, 1491, 1437, 1409, 1362, 1291, 1236, 1213, 1158 cm⁻¹; **HRMS (+ESI)**: Calc for C₁₉H₁₆FN₂O₂ [M+H]⁺ 323.1190; found: 323.1191; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 16.5 min, τ_{minor} = 23.6 min); Enantiomeric excess: 96%.

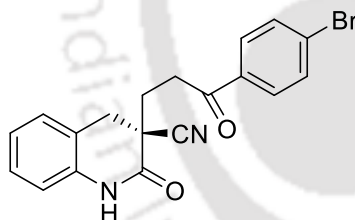
(R)-3-(3-(4-chlorophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3e)



This compound was prepared according to the general procedure D. White solid (41.1mg, yield: 81%); **m.p.** 212 - 213 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.82 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.24 (s, 1H), 7.23 – 7.20 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.8

Hz, 1H), 3.56 (d, *J* = 15.7 Hz, 1H), 3.42 – 3.36 (m, 1H), 3.33-3.27 (m, *J* = 18.0, 9.8, 5.2 Hz, 1H), 3.17 (d, *J* = 15.7 Hz, 1H), 2.45-2.40 (m, *J* = 14.9, 9.7, 5.6 Hz, 1H), 2.19-2.14 (m, *J* = 14.7, 9.8, 5.2 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.7, 165.7, 140.2, 135.3, 134.8, 129.7, 129.2, 129.1, 128.9, 124.7, 119.2, 118.8, 116.0, 44.2, 36.5, 34.5, 28.3; **FT-IR (thin film):** 1696, 1678, 1588, 1488, 1435, 1370, 1293, 1217, 1095 cm⁻¹; **HRMS (+ESI):** Calc for C₁₉H₁₆ClN₂O₂ [M+H]⁺ 339.0895; found: 339.0896; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.6 min, τ_{major} = 16.0 min); Enantiomeric excess: 97%.

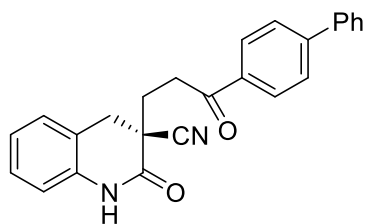
(R)-3-(3-(4-bromophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3f)



This compound was prepared according to the general procedure D. White solid (47.5 mg, yield: 83%); **m.p.** 230 - 231 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.32 (s, 1H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.23 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.81

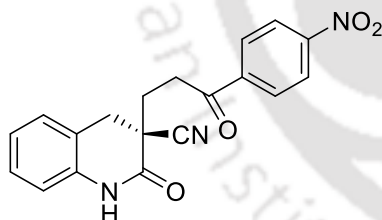
(d, *J* = 7.7 Hz, 1H), 3.56 (d, *J* = 15.7 Hz, 1H), 3.40 – 3.35 (m, 1H), 3.31 (dd, *J* = 14.2, 9.0 Hz, 1H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.19 – 2.14 (m, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.9, 165.4, 135.3, 135.2, 132.2, 129.8, 129.1, 129.0, 128.9, 124.7, 119.3, 118.7, 115.9, 44.2, 36.6, 34.6, 28.4; **FT-IR (thin film):** 1694, 1672, 1585, 1485, 1435, 1364, 1292, 1211, 1072 cm⁻¹; **HRMS (+ESI):** Calc for C₁₉H₁₆BrN₂O₂ [M+H]⁺ 383.0390; found: 383.0386; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 19.2 min, τ_{minor} = 42.6 min); Enantiomeric excess: 91%.

(R)-3-(3-([1,1'-biphenyl]-4-yl)-3-oxopropyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carbonitrile (3g)



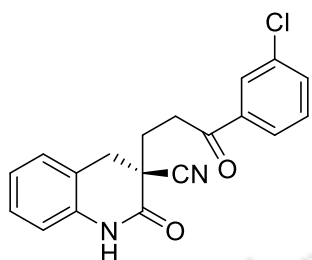
This compound was prepared according to the general procedure D. White solid (45.0 mg, yield: 79%); **m.p.** 218 - 219 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.97 (s, 1H), 8.01 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.23 (dd, *J* = 15.1, 7.5 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 3.57 (d, *J* = 15.8 Hz, 1H), 3.46-3.43 (m, *J* = 15.6, 9.7, 5.6 Hz, 1H), 3.40 – 3.35 (m, 1H), 3.19 (d, *J* = 15.8 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.23 – 2.18 (m, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 197.5, 165.9, 146.3, 139.9, 135.4, 135.2, 129.2, 129.0, 128.9, 128.5, 127.5, 124.6, 119.2, 118.9, 116.1, 44.3, 36.5, 34.5, 28.4; **FT-IR (thin film):** 1696, 1674, 1595, 1491, 1437, 1399, 1367, 1292 cm⁻¹; **HRMS (+ESI):** Calc for C₂₅H₂₁N₂O₂ [M+H]⁺ 381.1598; found 381.1598; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 23.3 min, τ_{minor} = 31.9 min); Enantiomeric excess: 93%.

(R)-3-(3-(4-nitrophenyl)-3-oxopropyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carbonitrile (3h)



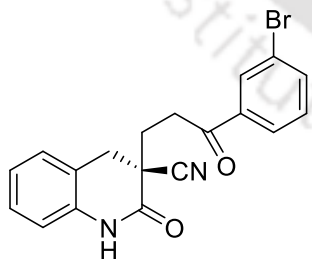
This compound was prepared according to the general procedure D. White sticky solid (31.4 mg, yield: 60%); **¹H NMR (600 MHz, CDCl₃):** δ 8.29 (d, *J* = 8.7 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.57 (d, *J* = 15.8 Hz, 1H), 3.49 (ddd, *J* = 18.3, 9.6, 5.6 Hz, 1H), 3.37 (ddd, *J* = 18.3, 9.5, 5.2 Hz, 1H), 3.19 (d, *J* = 15.8 Hz, 1H), 2.46 (ddd, *J* = 14.8, 9.5, 5.6 Hz, 1H), 2.25 – 2.15 (m, 1H); **¹³C NMR (150 MHz, CDCl₃)** δ 196.5, 165.1, 150.8, 140.9, 135.3, 129.4, 129.2, 129.0, 124.8, 124.2, 119.3, 118.6, 115.8, 44.0, 36.7, 35.3, 28.3; **FT-IR (thin film):** 1696, 1563, 1525, 1347, 1319, 1277, 1206, 1132, 854, 792 cm⁻¹; **HRMS (+ESI):** Calc for C₂₅H₂₀N₃O₅ [M+H]⁺ 460.1461; found: 460.1461; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (60:40 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 17.5 min, τ_{minor} = 22.2 min); Enantiomeric excess: 71%.

(R)-3-(3-(3-chlorophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3h)



This compound was prepared according to the general procedure D. White solid (39.5 mg, yield: 78%); **m.p.** 180 - 181 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.04 (s, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.1 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 3.56 (d, *J* = 15.5 Hz, 1H), 3.41 – 3.29 (m, 2H), 3.18 (d, *J* = 15.6 Hz, 1H), 2.46-2.41 (m, *J* = 15.0, 9.7, 5.7 Hz, 1H), 2.21-2.16 (m, *J* = 14.8, 9.8, 5.4 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.6, 165.6, 138.1, 135.5, 135.4, 133.6, 130.3, 129.1, 128.9, 128.3, 126.4, 124.7, 119.3, 118.7, 116.0, 44.2, 36.6, 34.7, 28.4; **FT-IR (thin film):** 1700, 1684, 1595, 1573, 1499, 1484, 1426, 1411, 1291, 1207 cm⁻¹; **HRMS (+ESI):** Calc for C₁₉H₁₆ClN₂O₂ [M+H]⁺ 339.0895; found 339.0891; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 12.7 min, τ_{major} = 13.5 min); Enantiomeric excess: 96%.

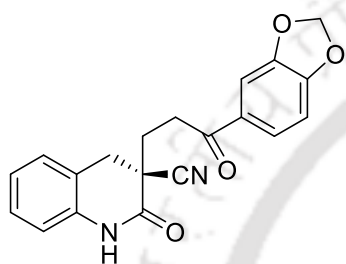
(R)-3-(3-(3-bromophenyl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3i)



This compound was prepared according to the general procedure D. White solid (45.8 mg, yield: 80%); **m.p.** 178 - 179 °C; **¹H NMR (600 MHz, CDCl₃):** δ 8.84 (s, 1H), 8.05 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 5.8 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.56 (d, *J* = 15.7 Hz, 1H), 3.43-3.37 (m, *J* = 17.7, 9.7, 5.6 Hz, 1H), 3.33-3.27 (m, *J* = 18.1, 9.6, 5.2 Hz, 1H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.47-2.42 (m, *J* = 14.9, 9.6, 5.6 Hz, 1H), 2.20-2.15 (m, *J* = 14.7, 9.7, 5.2 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 196.5, 165.8, 138.2, 136.5, 135.3, 131.2, 130.5, 129.1, 128.9,

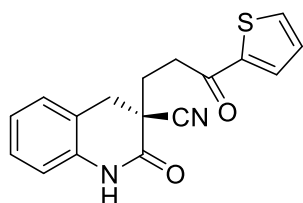
126.8, 124.7, 123.3, 119.2, 118.8, 116.0, 44.2, 36.5, 34.7, 28.3; **FT-IR (thin film)**: 1700, 1684, 1596, 1484, 1420, 1369, 1295, 1212 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{19}\text{H}_{16}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 383.0390; found: 383.0393; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 16.2$ min, $\tau_{\text{minor}} = 23.8$ min); Enantiomeric excess: 92%.

(R)-3-(3-(benzo[d][1,3]dioxol-5-yl)-3-oxopropyl)-1,2,3,4-tetrahydro-2-oxoquinoline-3-carbonitrile (3k)



This compound was prepared according to the general procedure D. White solid (36.6 mg, yield: 70%); **m.p.** 235 - 236 °C; **^1H NMR (600 MHz, CDCl_3)**: δ 7.89 (s, 1H), 7.58 (d, $J = 7.8$ Hz, 1H), 7.41 (s, 1H), 7.26 (s, 1H), 7.22 (d, $J = 7.0$ Hz, 1H), 7.09 (t, $J = 7.0$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.80 (d, $J = 7.7$ Hz, 1H), 6.04 (s, 2H), 3.55 (d, $J = 15.8$ Hz, 1H), 3.30 – 3.27 (m, 2H), 3.17 (d, $J = 15.7$ Hz, 1H), 2.43 – 2.37 (m, 1H), 2.19 – 2.14 (m, 1H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 195.9, 165.2, 152.3, 148.5, 135.3, 131.3, 129.1, 124.7, 124.7, 119.4, 118.8, 115.8, 108.2, 108.0, 102.1, 44.2, 36.5, 34.3, 28.6; **FT-IR (thin film)**: 1700, 1668, 1602, 1490, 1443, 1296, 1117 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 349.1183; found: 349.1188; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (75:25 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 17.2$ min, $\tau_{\text{major}} = 17.2$ min); Enantiomeric excess: 94%.

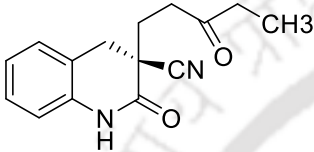
(R)-1,2,3,4-tetrahydro-2-oxo-3-(3-oxo-3-(thiophen-2-yl)propyl)quinoline-3-carbonitrile (3k)



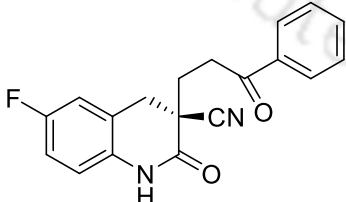
This compound was prepared according to the general procedure D. White solid (36.2 mg, yield: 78%); **m.p.** 160 - 161 °C; **^1H NMR (600 MHz, CDCl_3)**: δ 8.63 (s, 1H), 7.77 (d, $J = 3.1$ Hz, 1H), 7.62 (d, $J = 4.6$ Hz, 1H), 7.24 (d, $J = 7.7$ Hz, 1H), 7.21 (d, $J = 7.3$ Hz, 1H), 7.14 – 7.10 (m, 1H), 7.08 (t, $J = 7.4$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 3.54 (d, $J = 15.8$ Hz, 1H), 3.34 – 3.29 (m, 2H), 3.17 (d, $J = 15.8$ Hz, 1H), 2.46 – 2.41 (m,

1H), 2.21 – 2.16 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 190.7, 165.8, 143.6, 135.4, 134.3, 132.6, 129.0, 128.9, 128.4, 124.6, 119.2, 118.8, 116.1, 44.2, 36.4, 35.0, 28.4; **FT-IR (thin film)**: 1700, 1658, 1597, 1519, 11492, 1248, 1376, 1241, 1057, 760 cm⁻¹; **HRMS (+ESI)**: Calc for C₁₇H₁₅FN₂O₂S [M+H]⁺ 311.0849; found: 311.0850; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 19.4 min, τ_{minor} = 24.7 min); Enantiomeric excess: 70%.

(R)-2-oxo-3-(3-oxobutyl)-1,2,3,4-tetrahydroquinoline-3-carbonitrile (3m)

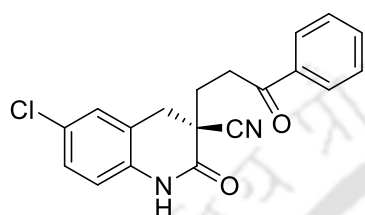
 This compound was prepared according to the general procedure D. White solid (23.04 mg, yield: 60%); **m.p.** 179–180 °C; ¹H NMR (400 MHz, (CD₃)₂SO): δ 10.75 (s, 1H), 7.23 (t, *J* = 8.4 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.7 Hz, 1H), 3.43 (d, *J* = 15.9 Hz, 1H), 3.18 (d, *J* = 15.8 Hz, 1H), 2.65 (ddd, *J* = 16.0, 9.8, 5.8 Hz, 2H), 2.44 (q, *J* = 7.2 Hz, 2H), 2.10 – 1.96 (m, 1H), 1.90 – 1.79 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (100 MHz, (CD₃)₂SO): δ 210.3, 165.7, 137.5, 129.6, 129.3, 124.8, 120.9, 120.6, 116.5, 44.1, 38.0, 36.2, 35.2, 27.9, 8.7; **FT-IR (thin film)**: 1711, 1597, 1563, 1489, 1377, 1279, 1177, 1132, 792 cm⁻¹; **HRMS (+ESI)**: Calc for C₁₅H₁₇N₂O₂ [M+H]⁺ 257.1285; found: 257.1277; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2PrOH, 1.0 mL/min, 25 °C, 254 nm, (τ_{major} = 11.3 min, τ_{minor} = 12.8 min); Enantiomeric excess: 27%.

(R)-6-fluoro-2-oxo-3-(3-oxo-3-phenylpropyl)-1,2,3,4-tetrahydroquinoline-3-carbonitrile (3n)

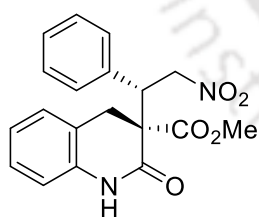
 This compound was prepared according to the general procedure D. White solid (41.1 mg, yield: 85%); **m.p.** 223 – 224 °C; ¹H NMR (600 MHz, CDCl₃): δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 6.98 (t, *J* = 7.8 Hz, 2H), 6.80 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.53 (d, *J* = 15.8 Hz, 1H), 3.40 – 3.34 (m, 2H), 3.16 (d, *J* = 16.1 Hz, 1H), 2.41 – 2.41 (m, 1H), 2.22 – 2.17 (m, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 197.8, 165.4, 158.6, 136.4, 133.8, 131.6, 128.9, 128.3, 117.3, 117.3, 116.1, 115.9, 115.8, 43.9, 36.4, 34.5, 28.3; **FT-IR (thin film)**: 1691, 1670, 1597, 1506,

1447, 1366, 1294, 1213, 1116 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{19}\text{H}_{16}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 323.1190 found 323.1185; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.6 min, τ_{minor} = 21.1 min); Enantiomeric excess: 93%.

(R)-6-chloro-1,2,3,4-tetrahydro-2-oxo-3-(3-oxo-3-phenylpropyl)quinoline-3-carbonitrile (3o)



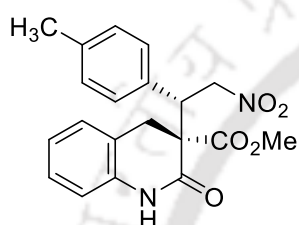
This compound was prepared according to the general procedure D. White solid (43.6 mg, yield: 86%); **m.p.** 210 - 211 °C; **^1H NMR (600 MHz, CDCl_3):** δ 8.26 (s, 1H), 7.95 (d, J = 7.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 6.77 (d, J = 9.1 Hz, 1H), 3.52 (d, J = 15.8 Hz, 1H), 3.40-3.34 (m, J = 18.0, 9.5, 5.6 Hz, 2H), 3.15 (d, J = 15.9 Hz, 1H), 2.47-2.42 (m, J = 14.9, 9.5, 5.7 Hz, 1H), 2.21-2.16 (m, J = 14.8, 9.7, 5.5 Hz, 1H); **^{13}C NMR (150 MHz, CDCl_3):** δ 197.7, 165.7, 136.4, 134.1, 133.8, 129.7, 129.1, 128.9, 129.0, 128.2, 120.9, 118.5, 117.3, 44.0, 36.2, 34.4, 28.3; **FT-IR (thin film):** 1692, 1669, 1597, 1491, 1447, 1435, 1427, 1356, 1292, 1215, 1084, 789 cm^{-1} ; **HRMS (+ESI):** $\text{C}_{19}\text{H}_{16}\text{ClN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 339.0895; found: 339.0895; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 15.8 min, τ_{minor} = 22.2 min); Enantiomeric excess: 74%.



Methyl 3-((S)-2-nitro-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6a)

This compound was prepared according to the general procedure E. White sticky solid (63.7 mg, yield: 90%); **Diastereomeric ratio:** 2:1; **^1H NMR (600 MHz, CDCl_3):** δ 8.54 (s, 1H), 8.33 (s, 0.4H), 7.45 – 7.44 (m, 1H), 7.31 – 7.29 (m, 4H), 7.27 – 7.24 (m, 1H), 7.22 (dd, J = 6.6, 3.0 Hz, 2H), 7.15 (t, J = 7.7 Hz, 0.6H), 7.07 (dd, J = 14.0, 7.4 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 7.5 Hz, 0.5H), 6.86 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.8 Hz, 0.5H), 5.62 (dd, J = 13.9, 10.5 Hz, 0.5H), 5.31 (dd, J = 14.1, 10.5 Hz, 1H), 5.21 (dd, J = 14.1, 3.4 Hz, 1H), 4.86 (dd, J = 14.0, 2.9 Hz, 0.5H), 4.24 (dd, J = 10.5, 2.9 Hz, 0.5H), 3.93 (dd, J = 10.5, 3.3 Hz, 1H), 3.72 (s, 3H), 3.62 (s, 1H), 3.38 (d, J = 16.1 Hz, 1H), 3.15 (d, J = 15.7 Hz, 0.5H), 2.82 (d, J = 15.7

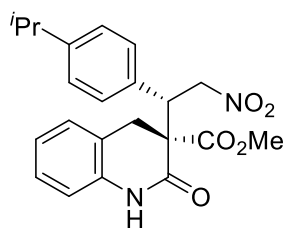
Hz, 0.5H), 2.71 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 170.9, 169.8, 168.6, 168.5, 135.7, 135.7, 135.6, 135.3, 130.0, 129.8, 129.2, 129.0, 128.9, 128.8, 128.5, 128.3, 128.3, 124.4, 124.0, 121.5, 121.1, 115.6, 115.1, 78.4, 78.1, 57.7, 56.5, 53.6, 53.2, 48.9, 45.7, 35.1, 33.7; **FT-IR (thin film)**: 1737, 1679, 1598, 1554, 1491, 1434, 1375, 1296, 1240, 1124, 1082, 757 cm^{-1} ; **HRMS (+APCI)**: Calc for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 355.1288; found: 355.1288; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 15.9$ min, $\tau_{\text{minor}} = 27.1$ min); Enantiomeric excess: 93%.



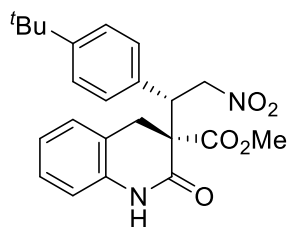
Methyl 3-((S)-2-nitro-1-(p-tolyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6b)

This compound was prepared according to the general procedure E. White sticky solid (62.5 mg, yield: 85%); **Diastereomeric**

ratio: 2:1; ^1H NMR (600 MHz, CDCl_3): δ 8.89 (s, 1H), 8.68 (s, 0.5H), 7.32 (d, $J = 8.1$ Hz, 1H), 7.26 (t, $J = 7.6$ Hz, 1H), 7.14 (t, $J = 7.7$ Hz, 1H), 7.10 (s, 5H), 7.06 (t, $J = 11.0$ Hz, 2H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.95 (t, $J = 7.5$ Hz, 0.6H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.74 (d, $J = 7.9$ Hz, 0.5H), 5.60 (dd, $J = 13.8, 10.5$ Hz, 0.5H), 5.28 (dd, $J = 14.0, 10.5$ Hz, 1H), 5.21 (dd, $J = 14.0, 3.5$ Hz, 1H), 4.85 (dd, $J = 13.8, 2.9$ Hz, 0.5H), 4.21 (dd, $J = 14.3, 3.7$ Hz, 0.5H), 3.91 (dd, $J = 10.4, 3.5$ Hz, 1H), 3.72 (s, 3H), 3.62 (s, 1.4H), 3.36 (d, $J = 16.1$ Hz, 1H), 3.15 (d, $J = 15.7$ Hz, 0.5H), 2.83 (d, $J = 15.6$ Hz, 0.5H), 2.72 (d, $J = 16.1$ Hz, 1H), 2.32 (s, 3H), 2.28 (s, 1.4H); ^{13}C NMR (150 MHz, CDCl_3): δ 171.0, 169.8, 168.9, 168.8, 138.7, 138.5, 135.8, 135.7, 132.4, 132.1, 129.9, 129.8, 129.6, 129.0, 128.5, 128.3, 128.2, 124.3, 123.9, 121.5, 121.2, 115.6, 115.2, 78.4, 78.2, 57.7, 56.4, 53.6, 53.1, 48.5, 45.3, 35.0, 33.7, 22.9, 21.3; **FT-IR (thin film)**: 1743, 1721, 1678, 1596, 1554, 1492, 1434, 1294, 1240, 1120, 1079, 757 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 369.1445; found: 369.1442; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 16.7$ min, $\tau_{\text{major}} = 25.2$ min); Enantiomeric excess: 92%.

Methyl 3-((S)-1-(4-isopropylphenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6c)

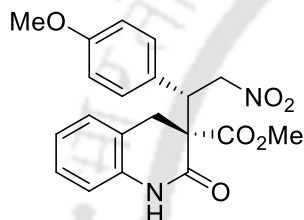
This compound was prepared according to the general procedure E. White sticky solid (55.4 mg, yield: 70%); **Diastereomeric ratio**: 2:1; **¹H NMR (600 MHz, CDCl₃)**: δ 8.32 (s, 1H), 8.16 (s, 0.4H), 7.35 (d, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.13 (dd, *J* = 16.5, 7.6 Hz, 5H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 0.5H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 0.4H), 5.60 (t, *J* = 12.2 Hz, 0.4H), 5.30 – 5.26 (m, 1H), 5.19 (d, *J* = 14.0 Hz, 1H), 4.85 (d, *J* = 13.9 Hz, 1H), 4.19 (d, *J* = 10.1 Hz, 0.4H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 1H), 3.38 (d, *J* = 16.1 Hz, 1H), 3.14 (d, *J* = 15.6 Hz, 0.4H), 2.86 (dt, *J* = 23.9, 11.3 Hz, 2H), 2.74 (d, *J* = 16.0 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 6H), 1.19 (d, *J* = 6.5 Hz, 3H); **¹³C NMR (150 MHz, CDCl₃)**: δ 171.1, 169.8, 168.6, 149.4, 149.3, 135.7, 132.7, 132.3, 129.8, 129.7, 129.1, 128.5, 128.3, 128.2, 127.2, 126.9, 124.3, 123.9, 121.6, 121.3, 115.5, 115.1, 78.5, 78.1, 57.7, 56.5, 53.6, 53.2, 48.6, 45.2, 33.9, 33.6, 24.1, 24.0, 22.9, 22.9; **FT-IR (thin film)**: 1740, 1679, 1597, 1554, 1490, 1433, 1294, 1239, 1122, 1077, 755 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₂H₂₅N₂O₅ [M+H]⁺ 397.1758; found: 397.1758; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, (τ_{minor} = 14.3 min, τ_{major} = 23.8 min); Enantiomeric excess: 88%.

Methyl 3-((S)-1-(4-(tert-butyl)phenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6d)

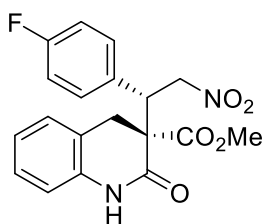
This compound was prepared according to the general procedure E. White sticky solid (49.3 mg, yield: 60%); **Diastereomeric ratio**: 2:1; **¹H NMR (600 MHz, CDCl₃)**: δ 8.08 (s, 1H), 7.95 (s, 0.4H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.24 (s, 1H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.05 (dd, *J* = 19.6, 7.1 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 0.4H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 0.4H), 5.63 – 5.59 (m, 0.4H), 5.30 – 5.26 (m, 1H), 5.18 (d, *J* = 14.0 Hz, 1H), 4.84 (d, *J* = 14.1 Hz, 0.4H), 4.18 (d, *J* = 9.8 Hz, 0.4H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.72 (s, 3H), 3.63 (s, 1H), 3.38 (d, *J* = 16.0

Hz, 1H), 3.14 (d, $J = 15.6$ Hz, 0.4H), 2.83 (d, $J = 15.7$ Hz, 0.4H), 2.74 (d, $J = 16.1$ Hz, 1H), 1.29 (s, 9H), 1.26 (s, 5H); ^{13}C NMR (150 MHz, CDCl_3): δ 171.1, 169.8, 168.5, 168.4, 168.1, 151.7, 151.6, 135.7, 132.3, 131.9, 129.5, 129.4, 129.1, 128.8, 128.7, 128.4, 128.3, 128.2, 126.1, 125.8, 124.3, 123.9, 121.6, 121.3, 115.4, 115.0, 78.5, 78.1, 57.7, 56.5, 53.6, 53.2, 48.5, 45.0, 35.4, 34.7, 33.6, 31.8, 31.5, 31.4; FT-IR (thin film): 1741, 1679, 1597, 1555, 1489, 1434, 1377, 1240, 1077, 1216, 756 cm^{-1} ; HRMS (+ESI): Calc for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 411.1914; found: 411.1914; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IC column (80:20 n -Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{minor}} = 13.7$ min, $\tau_{\text{major}} = 23.9$ min); Enantiomeric excess: 87%.

Methyl 3-((S)-1-(4-methoxyphenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6e)

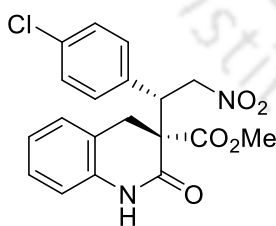


This compound was prepared according to the general procedure E. White sticky solid (53.7 mg, yield: 70%); **Diastereomeric ratio:** 2:1; ^1H NMR (600 MHz, CDCl_3): δ 8.26 (s, 1H), 8.09 (s, 0.5H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.28 – 7.24 (m, 1H), 7.13 (d, $J = 8.8$ Hz, 2H), 7.07 (dd, $J = 17.5, 7.8$ Hz, 1H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 0.6H), 6.83 (dd, $J = 13.4, 8.1$ Hz, 4H), 6.71 (d, $J = 7.8$ Hz, 0.5H), 5.62 – 5.58 (m, 0.5H), 5.30 – 5.25 (m, 1H), 5.16 (dd, $J = 13.9, 3.4$ Hz, 1H), 4.80 (dd, $J = 13.7, 3.0$ Hz, 0.5H), 4.16 (dd, $J = 13.2, 2.6$ Hz, 0.5H), 3.87 (dd, $J = 10.6, 3.3$ Hz, 1H), 3.79 (s, 3H), 3.76 (s, 1H), 3.72 (s, 3H), 3.63 (s, 1H), 3.38 (d, $J = 16.1$ Hz, 1H), 3.13 (d, $J = 15.7$ Hz, 0.5H), 2.84 (d, $J = 15.6$ Hz, 0.5H), 2.72 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 171.0, 169.8, 168.5, 168.5, 159.9, 159.8, 135.7, 135.6, 131.1, 130.9, 129.0, 128.5, 128.3, 128.2, 127.3, 127.0, 124.4, 123.9, 121.6, 121.2, 115.5, 115.1, 114.5, 114.3, 78.5, 78.3, 57.8, 56.6, 55.4, 53.6, 53.2, 48.3, 45.0, 35.2, 33.7; FT-IR (thin film): 1741, 1722, 1680, 1596, 1554, 1514, 1495, 1376, 1180, 1094, 800 cm^{-1} ; HRMS (+APCI): Calc for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 385.1400; found: 385.1400; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 n -Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{major}} = 21.3$ min, $\tau_{\text{minor}} = 34.9$ min); Enantiomeric excess: 94%.



Methyl 3-((S)-1-(4-fluorophenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6f)

This compound was prepared according to the general procedure E. White sticky solid (66.9 mg, yield: 90%); **Diastereomeric ratio:** 2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.88 (s, 1H), 8.62 (s, 0.5H), 7.44 (dd, *J* = 8.3, 5.3 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.25 – 7.22 (m, 2H), 7.16 (t, *J* = 7.6 Hz, 0.7H), 7.07 (dd, *J* = 13.0, 6.0 Hz, 2H), 6.99 (t, *J* = 8.7 Hz, 4H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 0.6H), 5.59 (dd, *J* = 14.0, 10.6 Hz, 0.6H), 5.28 (dd, *J* = 14.0, 10.6 Hz, 1H), 5.18 (dd, *J* = 14.1, 3.2 Hz, 1H), 4.83 (dd, *J* = 13.9, 2.4 Hz, 0.5H), 4.22 (dd, *J* = 10.6, 2.8 Hz, 0.5H), 3.92 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.70 (s, 3H), 3.63 (s, 2H), 3.39 (d, *J* = 16.0 Hz, 1H), 3.15 (d, *J* = 15.6 Hz, 0.5H), 2.80 (d, *J* = 15.5 Hz, 0.5H), 2.71 (d, *J* = 16.1 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 170.8, 169.8, 168.7, 168.6, 163.7 (d, *J* = 18.0 Hz), 162.1 (d, *J* = 19.5 Hz), 135.7, 135.6, 131.8, (d, *J* = 7.5 Hz), 131.6, 131.5, 131.2, 131.0, 128.9, 128.6, 128.4, 128.3, 124.5, 124.1, 121.3, 120.8, 116.2, 116.1, 115.9, 115.8, 115.7, 115.2, 78.3, 78.1, 57.7, 56.5, 53.7, 53.3, 48.1, 45.1, 35.1, 33.8; **FT-IR (thin film):** 1740, 1675, 1597, 1554, 1511, 1492, 1435, 1378, 1285, 1163, 754 cm⁻¹; **HRMS (+APCI):** Calc for C₁₉H₁₈FN₂O₅ [M+H]⁺ 373.1194; found: 373.1194; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 17.8 min, τ_{minor} = 26.0 min); Enantiomeric excess: 92%.

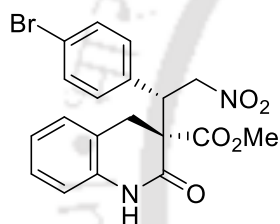


Methyl 3-((S)-1-(4-chlorophenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6g)

This compound was prepared according to the general procedure E. White sticky solid (58.2 mg, yield: 75%); **Diastereomeric ratio:** 2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.56 (s, 1H), 8.30 (s, 0.5H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 3H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 0.5H), 7.07 (t, *J* = 7.6 Hz, 1.5H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 0.6H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 0.5H), 5.60 (dd, *J* = 14.0, 10.6 Hz, 0.5H), 5.30 – 5.26 (m, 1H), 5.16 (dd, *J* = 14.2, 2.7 Hz, 1H), 4.81 (d, *J* = 14.0 Hz, 0.5H), 4.20 (d, *J* = 10.5 Hz, 0.5H), 3.89 (d, *J* = 8.0 Hz, 1H), 3.71 (s, 3H), 3.63 (s, 1H), 3.39 (d, *J* = 16.1 Hz, 1H), 3.14 (d, *J* = 15.6 Hz, 0.5H), 2.79 (d, *J* = 15.5 Hz, 0.5H),

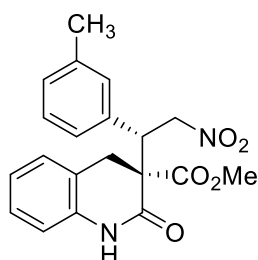
2.69 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 170.8, 169.7, 168.4, 168.3, 135.6, 135.5, 135.0, 134.8, 134.0, 133.8, 131.4, 131.2, 129.4, 129.1, 128.9, 128.7, 128.4, 128.3, 124.5, 124.1, 121.2, 120.8, 115.6, 115.2, 78.1, 77.9, 57.6, 56.4, 53.7, 53.3, 48.3, 45.2, 35.2, 33.8; **FT-IR (thin film)**: 1739, 1676, 1597, 1554, 1492, 1434, 1376, 1294, 1238, 1094, 756 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{19}\text{H}_{18}\text{ClN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 389.0899; found: 389.0893; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 17.9$ min, $\tau_{\text{minor}} = 26.1$ min); Enantiomeric excess: 93%.

Methyl 3-((S)-1-(4-bromophenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6h)



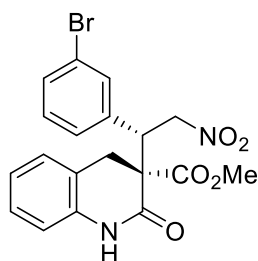
This compound was prepared according to the general procedure E. White sticky solid (64.9 mg, yield: 75%); **Diastereomeric ratio**: 2:1; ^1H NMR (600 MHz, CDCl_3): δ 8.64 (s, 1H), 8.39 (s, 0.5H), 7.44 (d, $J = 8.5$ Hz, 3H), 7.34 (d, $J = 8.5$ Hz, 1H), 7.28 (d, $J = 7.8$ Hz, 0.7H), 7.16 (t, $J = 7.7$ Hz, 1H), 7.14 (t, $J = 7.9$ Hz, 2H), 7.07 (t, $J = 7.1$ Hz, 2H), 7.01 (d, $J = 7.4$ Hz, 1H), 6.97 (t, $J = 7.5$ Hz, 0.5H), 6.87 (d, $J = 7.8$ Hz, 1H), 6.73 (d, $J = 7.9$ Hz, 0.5H), 5.59 (dd, $J = 14.0, 10.7$ Hz, 0.5H), 5.27 (dd, $J = 14.2, 10.5$ Hz, 1H), 5.17 (dd, $J = 14.2, 3.3$ Hz, 1H), 4.82 (dd, $J = 14.1, 2.9$ Hz, 0.5H), 4.19 (dd, $J = 10.6, 2.9$ Hz, 0.5H), 3.89 (dd, $J = 10.5, 3.4$ Hz, 1H), 3.70 (s, 3H), 3.63 (s, 1H), 3.39 (d, $J = 16.1$ Hz, 1H), 3.14 (d, $J = 15.6$ Hz, 0.5H), 2.79 (d, $J = 15.5$ Hz, 0.5H), 2.70 (d, $J = 16.1$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ 170.8, 169.7, 168.5, 168.4, 135.7, 135.6, 134.6, 134.3, 132.4, 132.1, 131.7, 131.5, 128.9, 128.7, 128.4, 128.3, 124.5, 124.1, 123.0, 121.2, 120.8, 115.7, 115.2, 78.1, 77.8, 57.6, 56.4, 53.7, 53.3, 48.3, 45.2, 35.2, 33.8; **FT-IR (thin film)**: 1739, 1720, 1679, 1596, 1552, 1490, 1434, 1375, 1293, 1237, 1206, 1117, 1075, 757 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{19}\text{H}_{18}\text{BrN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 433.0394; found: 433.0398; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 20.9$ min, $\tau_{\text{minor}} = 30.3$ min); Enantiomeric excess: 93%.

Methyl 3-((S)-2-nitro-1-(*m*-tolyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6i)



This compound was prepared according to the general procedure E. White sticky solid (59 mg, yield: 80%); **Diastereomeric ratio:** 2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.93 (s, 1H), 8.68 (s, 0.5H), 7.31 – 7.27 (m, 2H), 7.22 (t, *J* = 6.7 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 0.6H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.09 – 7.05 (m, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 6.2 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 0.4H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 0.5H), 5.63 (dd, *J* = 13.9, 10.5 Hz, 0.5H), 5.33 (dd, *J* = 14.1, 10.4 Hz, 1H), 5.25 (dd, *J* = 14.0, 3.2 Hz, 1H), 4.91 (dd, *J* = 13.9, 2.7 Hz, 0.5H), 4.25 (dd, *J* = 10.3, 2.3 Hz, 0.5H), 3.94 (dd, *J* = 10.4, 3.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 1H), 3.41 (d, *J* = 16.1 Hz, 1H), 3.19 (d, *J* = 15.7 Hz, 0.5H), 2.87 (d, *J* = 15.6 Hz, 0.5H), 2.74 (d, *J* = 16.1 Hz, 1H), 2.34 (s, 5H); **¹³C NMR (150 MHz, CDCl₃):** δ 171.0, 169.8, 168.9, 168.8, 138.8, 138.5, 135.8, 135.7, 135.5, 135.1, 130.8, 130.5, 129.6, 129.5, 129.1, 129.0, 128.8, 128.5, 128.3, 128.2, 126.8, 124.27, 123.9, 121.5, 121.2, 115.6, 115.2, 78.4, 78.1, 57.6, 56.4, 53.6, 53.2, 48.8, 45.6, 35.1, 33.7, 22.8, 21.6; **FT-IR (thin film):** 1740, 1672, 1596, 1554, 1491, 1434, 1376, 1259, 1210, 1128, 752 cm⁻¹; **HRMS (+APCI):** Calc for C₂₀H₂₁N₂O₅ [M+H]⁺ 369.1445; found: 369.1445; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.0 min, τ_{major} = 22.9 min). Enantiomeric excess: 87%.

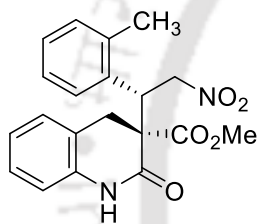
Methyl 3-((S)-1-(3-bromophenyl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6j)



This compound was prepared according to the general procedure E. White sticky solid (64.8 mg, yield: 75%); **Diastereomeric ratio:** 2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.69 (s, 1H), 8.44 (s, 0.4H), 7.61 (s, 0.4H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.42 – 7.41 (m, 1H), 7.39 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 13.9, 6.2 Hz, 2H), 7.09 (dd, *J* = 9.3, 5.2 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 0.5H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 0.5H), 5.59 – 5.55 (m, 0.4H), 5.29 (dd, *J* = 14.4, 10.4 Hz, 1H), 5.18 (dd, *J* = 14.4, 3.2 Hz, 1H), 4.83 (dd, *J* = 14.9, 2.0 Hz, 0.5H), 4.19 (dt, *J* =

10.4, 3.0 Hz, 1H), 3.87 (dd, $J = 10.4, 3.2$ Hz, 1H), 3.72 (s, 3H), 3.64 (s, 1H), 3.40 (d, $J = 16.1$ Hz, 1H), 3.16 (d, $J = 15.6$ Hz, 0.5H), 2.80 (d, $J = 15.5$ Hz, 0.5H), 2.70 (d, $J = 16.1$ Hz, 1H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 170.7, 169.7, 168.4, 168.3, 137.9, 137.6, 135.7, 135.6, 133.1, 132.8, 132.1, 131.9, 130.7, 130.4, 129.0, 128.7, 128.6, 128.4, 128.3, 124.5, 124.1, 123.3, 122.9, 121.1, 120.7, 115.7, 115.2, 78.0, 77.7, 57.6, 56.5, 53.8, 53.3, 48.4, 45.3, 35.1, 33.8; **FT-IR (thin film)**: 1739, 1677, 1597, 1554, 1490, 1433, 1377, 1294, 1077, 756 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{19}\text{H}_{18}\text{BrN}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 433.0394; found: 433.0397; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 17.7$ min, $\tau_{\text{minor}} = 38.1$ min); Enantiomeric excess: 92%.

Methyl3-((S)-2-nitro-1-(*o*-tolyl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6k)

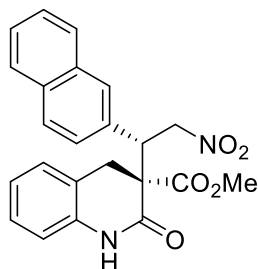


This compound was prepared according to the general procedure E.

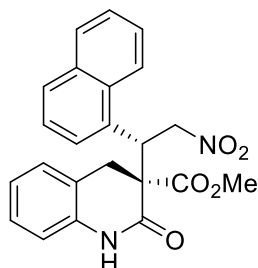
White sticky solid (47.8 mg, yield: 65%); **Diastereomeric ratio**:

2.5:1; **^1H NMR (600 MHz, CDCl_3)**: δ 8.28 (s, 1H), 8.13 (s, 04H), 7.63 (d, $J = 8.5$ Hz, 0.4H), 7.45 (d, $J = 7.5$ Hz, 1H), 7.20 (dd, $J =$

13.5, 7.5 Hz, 3H), 7.16 (dd, $J = 12.2, 7.0$ Hz, 2H), 7.12 (d, $J = 7.3$ Hz, 1H), 7.06 (d, $J = 7.7$ Hz, 0.5H), 6.97 (t, $J = 7.5$ Hz, 1H), 6.95 (d, $J = 7.5$ Hz, 0.4H), 6.91 (d, $J = 7.5$ Hz, 1H), 6.82 (d, $J = 7.9$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 0.4H), 5.61 (dd, $J = 14.0, 10.5$ Hz, 0.4H), 5.42 (dd, $J = 13.4, 3.2$ Hz, 1H), 5.05 (dd, $J = 13.4, 10.8$ Hz, 1H), 4.92 – 4.89 (m, 0.4H), 4.72 (dd, $J = 10.4, 2.5$ Hz, 0.4H), 4.44 (dd, $J = 10.7, 3.1$ Hz, 1H), 3.66 (s, 3H), 3.63 (s, 1H), 3.21 (dd, $J = 15.8, 7.4$ Hz, 1H), 2.81 (d, $J = 15.5$ Hz, 0.4H), 2.76 (d, $J = 16.0$ Hz, 1H), 2.05 (s, 0.6H), 2.04 (s, 3H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 171.3, 170.1, 169.1, 168.8, 138.5, 138.4, 135.7, 135.7, 134.7, 134.6, 131.3, 131.3, 128.8, 128.5, 128.3, 128.3, 127.8, 127.3, 127.3, 126.9, 124.3, 123.9, 121.5, 121.2, 115.4, 115.0, 79.3, 79.1, 58.5, 56.1, 53.7, 53.2, 42.7, 41.3, 34.1, 34.0, 20.5, 19.8; **FT-IR (thin film)**: 1741, 1680, 1597, 1554, 1462, 1377, 1292, 1293, 1205, 1131, 755 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 369.1445; found: 369.1443; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IE column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 13.6$ min, $\tau_{\text{major}} = 15.4$ min); Enantiomeric excess: 86%.

Methyl 3-((S)-1-(naphthalen-2-yl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6l)

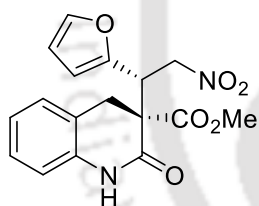
This compound was prepared according to the general procedure E. White sticky solid (68.7 mg, yield: 85%); **Diastereomeric ratio:** 2.5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.66 (s, 1H), 8.41 (s, 0.4H), 7.92 (s, .4H), 7.84 – 7.78 (m, 4H), 7.65 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 0.4H), 7.50 – 7.48 (m, 2H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.40 (d, *J* = 9.5 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.12 (t, *J* = 7.6 Hz, 0.4H), 7.07 (dd, *J* = 13.4, 6.2 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 6.91 (dd, *J* = 17.2, 7.7 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 0.4H), 5.79–5.74 (m, 0.4H), 5.45 (dd, *J* = 14.2, 10.5 Hz, 1H), 5.30 (dd, *J* = 14.2, 3.2 Hz, 1H), 4.94 (dd, *J* = 14.0, 2.6 Hz, 0.5H), 4.41 (dt, *J* = 10.4, 3.0 Hz, 0.4H), 4.12 (dd, *J* = 9.0, 4.9 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 1H), 3.39 (d, *J* = 16.1 Hz, 1H), 3.21 (d, *J* = 15.7 Hz, 0.4H), 2.83 (d, *J* = 15.7 Hz, 0.5H), 2.72 (d, *J* = 16.1 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 171.0, 171.0, 169.9, 168.7, 135.8, 135.6, 133.4, 133.4, 133.3, 133.3, 133.0, 132.7, 129.8, 129.5, 129.1, 129.0, 128.7, 128.6, 128.3, 128.3, 127.8, 126.9, 126.8, 126.7, 126.7, 126.6, 124.4, 123.9, 121.4, 121.1, 115.6, 115.1, 78.5, 78.1, 60.6, 57.8, 56.5, 53.3, 49.1, 45.8, 35.4, 33.8, 32.1, 31.8, 29.9, 29.8, 29.6; **FT-IR (thin film):** 1718, 1672, 1595, 1556, 1492, 1435, 1373, 1283, 1195, 1130, 1035, 789 cm⁻¹; **HRMS (+APCI):** Calc for C₂₃H₂₁N₂O₅ [M+H]⁺ 405.1445; found: 405.1443; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 18.4 min, τ_{major} = 27.3 min). Enantiomeric excess: 90%.

Methyl-3-((S)-1-(naphthalen-1-yl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6m)

This compound was prepared according to the general procedure E. White sticky solid (68.6 mg, yield: 85%); **Diastereomeric ratio:** 1.5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.89 (s, 1H), 8.64 (s, 1H), 8.37 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 6.7 Hz, 0.5H), 7.49 (s, 1H), 7.49 – 7.46 (m, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 11.3, 3.9 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H),

6.93 – 6.80 (m, 4H), 6.72 (d, $J = 7.8$ Hz, 1H), 6.63 (d, $J = 7.5$ Hz, 1H), 5.73 (dd, $J = 14.1$, 10.3 Hz, 1H), 5.64 (dd, $J = 12.8$, 2.3 Hz, 1H), 5.50 (dd, $J = 10.3$, 2.9 Hz, 1H), 5.32 – 5.16 (m, 2H), 5.12 (dd, $J = 14.1$, 3.0 Hz, 1H), 3.69 (s, 2H), 3.57 (s, 3H), 3.25 (d, $J = 15.7$ Hz, 1H), 3.06 (d, $J = 16.1$ Hz, 1H), 2.71 (dd, $J = 26.6$, 15.9 Hz, 2H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 171.1, 169.9, 169.3, 168.9, 135.6, 135.6, 134.1, 134.1, 133.4, 133.1, 132.4, 132.3, 129.4, 129.3, 129.1, 129.0, 128.4, 128.2, 128.2, 127.1, 126.8, 126.1, 126.0, 125.7, 125.7, 125.4, 124.1, 123.8, 123.2, 123.0, 121.6, 121.1, 115.5, 115.1, 79.3, 78.9, 58.4, 56.1, 53.6, 53.2, 40.6, 39.2, 34.5, 33.9; **FT-IR (thin film)**: 1740, 1675, 1595, 1555, 1492, 1428, 1374, 1244, 1204, 1116, 755 cm^{-1} ; **HRMS (+APCI)**: Calc for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 405.1445; found: 405.1444; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IE column (85:15 *n*-Hexane/EtOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 15.6$ min, $\tau_{\text{major}} = 18.4$ min); Enantiomeric excess: 83%.

Methyl 3-((*S*)-1-(furan-2-yl)-2-nitroethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6n)



This compound was prepared according to the general procedure E.

White sticky solid (61.9 mg, yield: 90%); **Diastereomeric ratio:**

5:1; **^1H NMR (600 MHz, CDCl_3)**: δ 8.44 (s, 1H), 8.35 (s, 0.2H),

7.36 (d, $J = 1.2$ Hz, 1H), 7.33 (d, $J = 1.3$ Hz, 0.2H), 7.24 (t, $J = 7.6$

Hz, 1H), 7.16 (t, $J = 7.7$ Hz, 0.3H), 7.11 (d, $J = 7.3$ Hz, 1H), 7.05 (t, $J = 7.7$ Hz, 1H), 6.98

(t, $J = 7.6$ Hz, 0.3H), 6.82 (d, $J = 7.8$ Hz, 1H), 6.74 (d, $J = 7.8$ Hz, 0.2H), 6.36 (d, $J = 3.2$

Hz, 0.2H), 6.33 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.29 (d, $J = 3.3$ Hz, 1H), 5.37 (dd, $J = 13.8$, 10.5

Hz, 0.2H), 5.13 (qd, $J = 14.2$, 6.8 Hz, 2H), 4.77 (dd, $J = 13.8$, 3.0 Hz, 0.2H), 4.54 (dd, $J =$

10.5, 2.9 Hz, 0.2H), 4.30 (dd, $J = 9.6$, 4.0 Hz, 1H), 3.73 (s, 3H), 3.62 (s, 1H), 3.38 (d, $J =$

16.0 Hz, 1H), 3.34 (d, $J = 15.8$ Hz, 0.2H), 2.93 (d, $J = 15.8$ Hz, 0.2H), 2.82 (d, $J = 16.0$

Hz, 1H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 170.0, 169.4, 168.3, 168.1, 149.4, 149.3, 143.2,

143.0, 135.7, 135.5, 128.8, 128.4, 128.3, 128.2, 124.3, 124.0, 121.3, 121.2, 115.7, 115.5,

110.9, 110.8, 110.3, 76.4, 75.8, 57.0, 55.9, 53.6, 53.3, 41.9, 39.4, 33.9, 33.2, 29.9; **FT-IR**

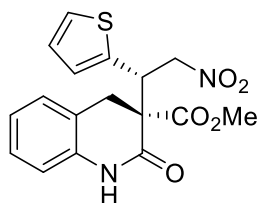
(thin film): 1742, 1676, 1599, 1559, 1493, 1432, 1377, 1200, 1074, 753 cm^{-1} ; **HRMS**

(+APCI): Calc for $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ 345.1081; found: 345.1086; The enantiomeric

ratio of major diastereomer was determined by HPLC analysis using Merck OD column

(85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 20.4$ min, $\tau_{\text{minor}} = 28.6$ min); Enantiomeric excess: 96%.

Methyl 3-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6o)



This compound was prepared according to the general procedure E.

White sticky solid (61.2 mg, yield: 85%); **Diastereomeric ratio:**

4:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.82 (s, 1H), 8.74 (s, 0.2H),

7.29 – 7.26 (m, 2H), 7.24 – 7.22 (m, 0.3H), 7.18 (t, $J = 7.6$ Hz,

0.3H), 7.12 – 7.09 (m, 1H), 7.06 (dd, $J = 11.4, 6.5$ Hz, 2H), 6.98 (t, $J = 7.4$ Hz, 0.3H), 6.93

– 6.89 (m, 2H), 6.81 (d, $J = 3.4$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 0.3H), 5.59 – 5.53 (m, 0.3H),

5.30 – 5.26 (m, 1H), 5.11 (dd, $J = 14.2, 3.1$ Hz, 1H), 4.79 (dd, $J = 13.9, 2.6$ Hz, 0.3H),

4.55 (dd, $J = 9.9, 2.8$ Hz, 0.3H), 4.23 (dd, $J = 10.0, 3.1$ Hz, 1H), 3.78 (s, 3H), 3.64 (s,

0.6H), 3.51 (d, $J = 16.1$ Hz, 1H), 3.17 (d, $J = 15.7$ Hz, 0.3H), 2.98 (d, $J = 15.6$ Hz, 0.3H),

2.82 (d, $J = 16.1$ Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 170.6, 169.8, 168.5, 168.3,

137.4, 137.2, 135.7, 135.6, 129.8, 129.7, 129.2, 128.6, 128.4, 128.3, 127.1, 127.1, 127.0,

126.9, 124.5, 124.1, 121.4, 120.7, 115.7, 115.3, 79.7, 79.1, 58.0, 57.0, 53.7, 53.3, 44.7,

41.1, 35.3, 33.5; **FT-IR (thin film):** 1742, 1674, 1598, 1560, 1492, 1434, 1383, 1248,

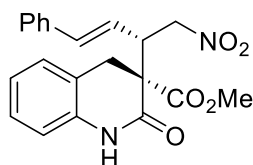
1076, 792 cm⁻¹; **HRMS (+APCI):** Calc for C₁₇H₁₇ClN₂O₅S [M+H]⁺ 361.0853; found:

361.0854; The enantiomeric ratio of major diastereomer was determined by HPLC

analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm,

$\tau_{\text{major}} = 19.0$ min, $\tau_{\text{minor}} = 33.4$ min); Enantiomeric excess: 93%.

Methyl 3-((*S,E*)-1-nitro-4-phenylbut-3-en-2-yl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6p)



This compound was prepared according to the general procedure E.

White sticky solid (53.2 mg, yield: 70%); **Diastereomeric ratio:**

3:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.97 (s, 1H), 7.89 (s, 0.5H),

7.37 – 7.29 (m, 5H), 7.28 (s, 0.5H), 7.27 (s, 1H), 7.18 (t, $J = 7.6$ Hz,

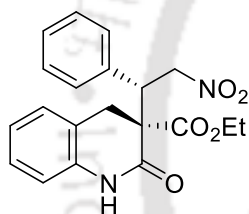
0.5H), 7.14 (dd, $J = 13.7, 7.4$ Hz, 1H), 7.07 (t, $J = 7.4$ Hz, 1H), 6.99 (t, $J = 7.4$ Hz, 0.5H),

6.83 (d, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.8$ Hz, 0.4H), 6.64 (d, $J = 15.8$ Hz, 0.5H), 6.34 (d, J

= 15.8 Hz, 1H), 6.27 (dd, $J = 15.8, 9.5$ Hz, 1H), 6.19 (dd, $J = 15.8, 10.0$ Hz, 0.5H), 5.26

(dd, $J = 13.0, 10.1$ Hz, 0.5H), 4.92 (qd, $J = 13.2, 6.6$ Hz, 2H), 4.55 (dd, $J = 13.1, 2.8$ Hz, 0.5H), 3.73 (s, 3H), 3.64 (s, 1H), 3.54 (d, $J = 15.9$ Hz, 1H), 3.39 (td, $J = 9.4, 3.7$ Hz, 1H), 3.25 (dd, $J = 45.0, 15.8$ Hz, 1H), 3.09 (d, $J = 15.9$ Hz, 1H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 170.7, 170.4, 170.0, 169.1, 168.3, 167.9, 138.1, 137.2, 136.1, 136.0, 135.9, 135.8, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 126.9, 124.4, 124.1, 123.4, 123.1, 121.7, 120.8, 115.5, 115.2, 78.1, 56.4, 55.9, 53.5, 53.3, 44.7, 35.5, 34.1; **FT-IR (thin film)**: 1737, 1680, 1598, 1555, 1493, 1433, 1379, 1295, 1241, 1196, 1080, 792 cm^{-1} ; **HRMS (+APCI)**: Calc for $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 381.1445; found: 381.1446; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IB column (95:5 n -Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{major}} = 31.9$ min, $\tau_{\text{minor}} = 55.4$ min); Enantiomeric excess: 85%.

Ethyl 3-((*S*)-2-nitro-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6q)

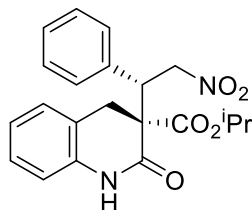


This compound was prepared according to the general procedure E.

White sticky solid (62.6 mg, yield: 85%); **Diastereomeric ratio**: 2:1

^1H NMR (600 MHz, CDCl_3): δ 8.89 (s, 1H), 8.66 (s, 0.3H), 7.47 (d, $J = 6.9$ Hz, 0.7H), 7.30 (dd, $J = 3.7, 2.7$ Hz, 4H), 7.25 (dd, $J = 9.8, 5.3$ Hz, 2H), 7.15 (t, $J = 7.5$ Hz, 0.4H), 7.07 – 7.05 (m, 0.4H), 7.05 – 7.02 (m, 1H), 7.00 (d, $J = 7.4$ Hz, 1H), 6.94 (td, $J = 7.5, 0.6$ Hz, 0.4H), 6.88 (d, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.9$ Hz, 0.3H), 5.70-5.65 (m, 1H), 5.232-5.24 (m, 2H), 4.87-4.84 (m, 0.4H), 4.24-4.22 (m, 0.3H), 4.18 – 4.12 (m, 3H), 4.04-4.01 (m, 0.3H), 3.97 (dd, $J = 10.0, 3.9$ Hz, 1H), 3.32 (d, $J = 16.0$ Hz, 1H), 3.11 (d, $J = 15.5$ Hz, 0.3H), 2.80 (d, $J = 15.5$ Hz, 0.4H), 2.74 (d, $J = 16.0$ Hz, 1H), 1.15 (t, $J = 7.1$ Hz, 3H), 0.99 (t, $J = 7.1$ Hz, 1H); **^{13}C NMR (150 MHz, CDCl_3)**: δ 170.5, 169.3, 169.2, 169.0, 135.9, 135.9, 135.7, 135.4, 130.0, 129.9, 129.2, 128.9, 128.8, 128.7, 128.5, 128.2, 124.2, 123.8, 121.6, 121.3, 115.6, 115.1, 78.5, 78.2, 62.8, 62.4, 57.7, 56.2, 48.8, 45.8, 35.5, 33.9, 14.02, 13.9; **FT-IR (thin film)**: 1732, 1681, 1598, 1554, 1497, 1452, 1377, 1278, 1132, 1029, 764 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 369.1445; found: 369.1442; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 n -Hexane/2-PrOH, 1.0 mL/min, 25 $^\circ\text{C}$, 254 nm, $\tau_{\text{major}} = 11.1$ min, $\tau_{\text{minor}} = 14.2$ min); Enantiomeric excess: 82%.

Isopropyl 3-((S)-2-nitro-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate(6r)



This compound was prepared according to the general procedure E.

White sticky solid (39.7 mg, yield: 52%); **Diastereomeric ratio:**

2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.51 (s, 1H), 8.26 (s, 0.5H),

7.48 (d, *J* = 7.3 Hz, 1H), 7.31-7.27 (m, 6H), 7.23 (t, *J* = 7.2 Hz, 1H),

7.14 (t, *J* = 7.7 Hz, 0.5H), 7.07 (d, *J* = 7.4 Hz, 0.4H), 7.05 – 6.97 (m, 2H), 6.94 (t, *J* = 7.3

Hz, 0.4H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 0.4H), 5.73-5.68 (m, 0.4H), 5.26

(d, *J* = 7.7 Hz, 2H), 4.99 (dt, *J* = 12.6, 6.3 Hz, 1H), 4.91 (dd, *J* = 12.4, 6.2 Hz, 0.4H), 4.19

(d, *J* = 10.4 Hz, 0.4H), 4.02 – 3.94 (m, 1H), 3.25 (d, *J* = 15.9 Hz, 1H), 3.06 (d, *J* = 15.5

Hz, 0.4H), 2.74 (d, *J* = 16.0 Hz, 1H), 1.10 (dt, *J* = 9.3, 4.6 Hz, 6H), 1.08 – 1.06 (m, 1H),

0.92 (dd, *J* = 6.2, 2.8 Hz, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 170.0, 169.2, 169.1, 168.7,

136.0, 135.9, 135.7, 135.5, 130.1, 129.9, 129.2, 128.9, 128.8, 128.6, 128.4, 128.2, 124.2,

123.7, 121.5, 115.5, 115.0, 78.6, 78.2, 70.7, 70.4, 57.8, 56.0, 48.8, 46.0, 34.2, 21.6, 21.6,

21.5, 2; **FT-IR (thin film):** 1727, 1684, 1558, 1492, 1378, 1281, 1244, 1181, 1131, 1104,

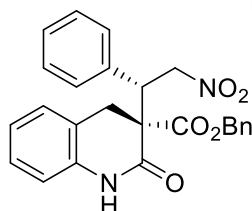
758 cm⁻¹; **HRMS (+ESI):** Calc for C₂₁H₂₃N₂O₅ [M+H]⁺ 383.1601; found: 383.1604; The

enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel

Chiralpak IB column (80:20 *n*-Hexane/EtOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 8.3 min,

τ_{minor} = 14.3 min); Enantiomeric excess: 85%.

Benzyl 3-((S)-2-nitro-1-phenylethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (6s)



This compound was prepared according to the general procedure E.

White sticky solid (73.1 mg, yield: 85%); **Diastereomeric ratio:**

2:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.15 (s, 1H), 7.95 (s, 1H), 7.44

(d, *J* = 6.7 Hz, 2H), 7.32 – 7.26 (m, 6H), 7.23 (dd, *J* = 14.9, 6.6 Hz,

5H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.04 – 6.95 (m, 4H), 6.92 (t, *J* = 7.5

Hz, 1H), 6.82 – 6.77 (m, 1H), 6.69 – 6.61 (m, 1H), 5.64 (dd, *J* = 14.0, 10.7 Hz, 1H), 5.20

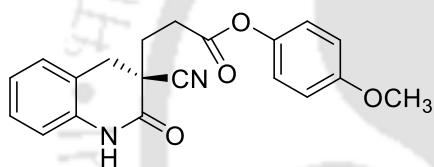
(d, *J* = 8.5 Hz, 1H), 5.13 (d, *J* = 10.6 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.01 (d, *J* = 12.1

Hz, 1H), 4.71 (dd, *J* = 14.0, 2.4 Hz, 1H), 4.21 (d, *J* = 10.4 Hz, 1H), 4.01 – 3.94 (m, 1H),

3.30 (d, *J* = 16.0 Hz, 1H), 3.10 (d, *J* = 15.6 Hz, 1H), 2.80 (d, *J* = 15.6 Hz, 1H), 2.72 (d, *J*

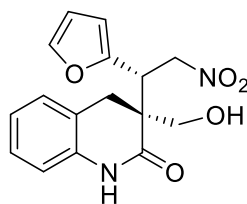
= 16.0 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃)**: δ 170.5, 169.1, 168.7, 168.6, 135.8, 135.7, 135.5, 135.2, 134.9, 134.7, 130.0, 129.9, 129.2, 129.0, 128.9, 128.8, 128.8, 128.7, 128.7, 128.5, 128.5, 128.4, 128.3, 128.3, 124.3, 123.9, 121.4, 121.2, 115.6, 115.1, 78.3, 78.1, 68.4, 68.1, 57.7, 56.2, 48.9, 45.9, 35.4, 33.9; **FT-IR (thin film)**: 1734, 1684, 1596, 1556, 1492, 1454, 1376, 1280, 1183, 1130, 1031, 912, 754 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₅H₂₃N₂O₅ [M+H]⁺ 431.1601; found: 431.1600; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Merck OD column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 16.6 min, τ_{minor} = 21.6 min);); Enantiomeric excess: 85%.

(R)-4-methoxyphenyl 3-(3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl) propanoate (7)



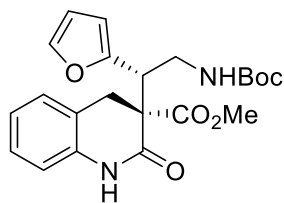
This compound was prepared according to the general procedure F. White sticky solid (23.4mg, yield: 67%); **¹H NMR (600 MHz, CDCl₃)**: δ 8.99 (s, 1H), 7.29 – 7.26 (m, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 7.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 3H), 3.53 (d, *J* = 15.8 Hz, 1H), 3.16 (d, *J* = 15.9 Hz, 1H), 2.93 (t, *J* = 7.9 Hz, 2H), 2.42 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.21 – 2.11 (m, 1H); **¹³C NMR (150 MHz, CDCl₃)**: δ 171.0, 165.5, 157.5, 144.1, 135.4, 129.1, 128.8, 124.7, 122.4, 119.1, 118.5, 116.2, 114.6, 55.8, 44.0, 36.1, 30.3, 28.9; **FT-IR (thin film)**: 1751, 1700, 1597, 1506, 1375, 1298, 1248, 1194, 1166, 1148, 1031, 759 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₀H₂₂N₃O₄ [M+NH₄]⁺ 323.1190; found: 323.1191; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (80:20 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 19.7 min, τ_{minor} = 35.9 min); Enantiomeric excess: 84%.

3-((S)-1-((furan-2-yl)-2-nitroethyl)-3-(hydroxymethyl)-3,4-dihydroquinolin-2(1H)-one
(8)



This compound was prepared according to the general procedure G. Brown gum (16 mg, yield: 50%); **Diastereomeric ratio:** 3:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.87 (s, 0.3H), 8.76 (s, 1H), 7.40 (s, 1H), 7.35 (s, 0.3H), 7.27 (dd, *J* = 9.3, 5.1 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 0.4H), 7.14-7.09 (m, 2H), 7.02 (t, *J* = 7.4 Hz, 0.3H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 0.2H), 6.33 (dd, *J* = 6.0, 2.9 Hz, 1H), 6.30 (d, *J* = 1.6 Hz, 0.2H), 6.15 (d, *J* = 3.1 Hz, 1H), 5.24 (dd, *J* = 13.8, 11.2 Hz, 1H), 4.84 (dd, *J* = 13.9, 3.4 Hz, 1H), 4.74 (dd, *J* = 13.0, 3.4 Hz, 0.2H), 4.50 (dd, *J* = 11.3, 3.3 Hz, 0.2H), 3.87 (dd, *J* = 20.1, 7.9 Hz, 2H), 3.74 (d, *J* = 12.1 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 0.3H), 3.55 (d, *J* = 11.6 Hz, 0.4H), 2.95 (d, *J* = 16.3 Hz, 1H), 2.90 (d, *J* = 4.8 Hz, 0.4H), 2.44 (d, *J* = 16.2 Hz, 1H); **¹³C NMR (150 MHz, CDCl₃):** δ 174.1, 172.8, 149.5, 148.4, 143.3, 143.0, 135.5, 129.3, 128.7, 128.4, 128.2, 124.7, 124.4, 121.5, 121.4, 115.7, 115.3, 110.9, 110.8, 110.6, 75.5, 75.3, 65.2, 64.9, 49.0, 47.9, 39.8, 38.6, 32.1, 31.0; **FT-IR (thin film):** 1671, 1596, 1554, 1493, 1464, 1376, 1257, 1068, 1015, 754 cm⁻¹; **HRMS (+ESI):** Calc for C₁₆H₁₇N₂O₅ [M+H]⁺ 317.1132; found: 317.1130; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 8.9 min, τ_{minor} = 10.2 min); Enantiomeric excess: 91%.

Methyl 3-((S)-2-((tert-butoxycarbonyl)amino)-1-(furan-2-yl)ethyl)-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (9)

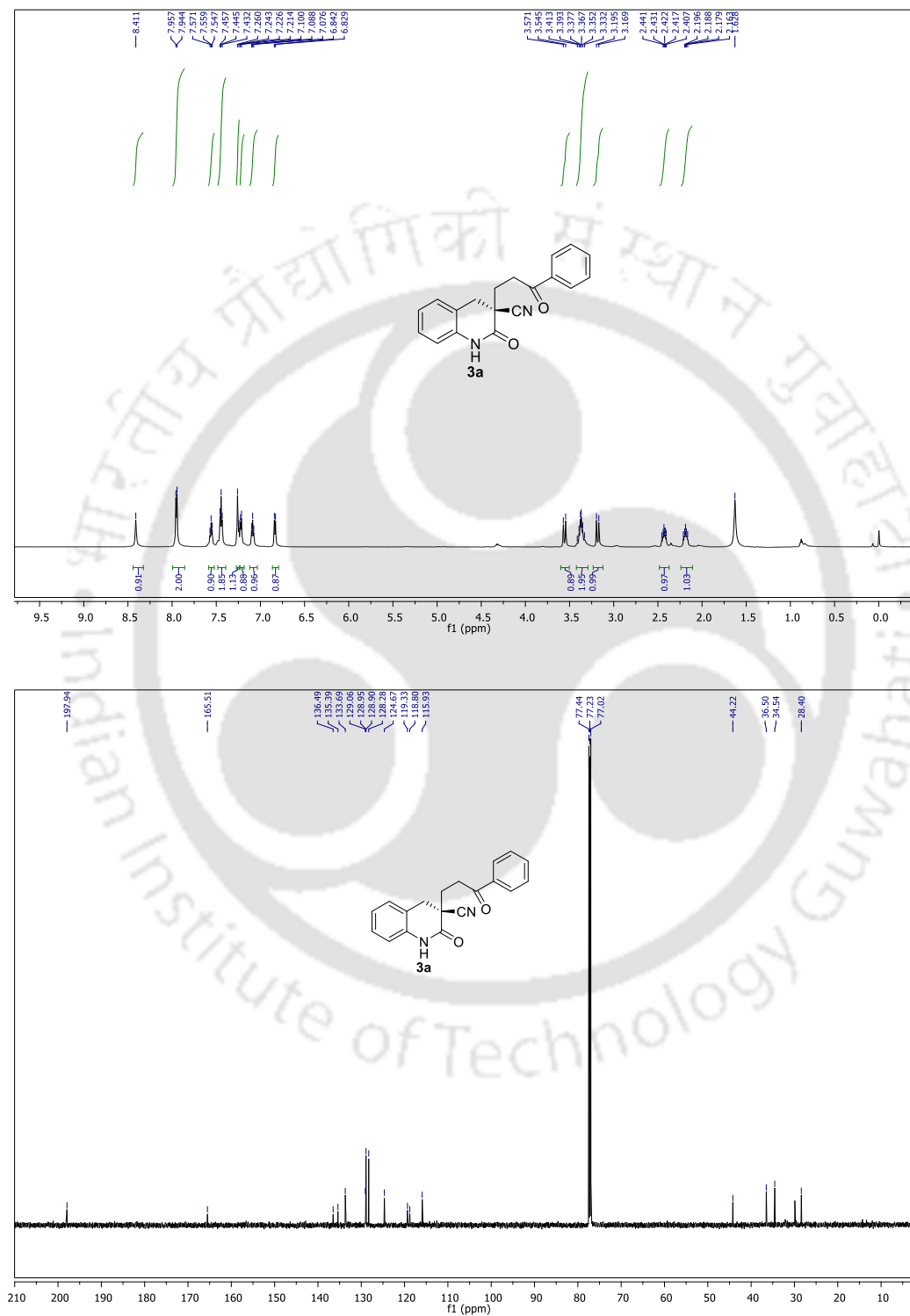


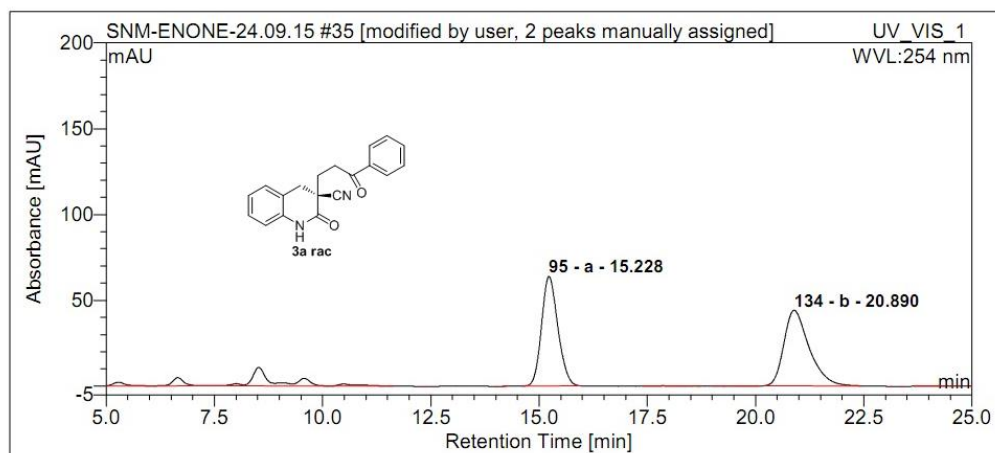
This compound was prepared according to the general procedure H. White gum (25 mg, yield: 60%); **Diastereomeric ratio:** 3:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.28 (s, 0.3H), 8.22 (s, 1H), 7.35 (s, 0.3H), 7.32 (s, 1H), 7.15 (t, *J* = 6.3 Hz, 3H), 6.98 (dd, *J* = 15.4, 7.8 Hz, 2H), 6.73 – 6.70 (m, 2H), 6.31 – 6.29 (m, 3H), 4.74 (s, 0.2H), 4.61 (s, 1H), 4.05 – 4.02 (m, 0.3H), 3.97 – 3.95 (m, 1H), 3.70 (d, *J* = 9.0 Hz, 1H), 3.67 (s, 3H), 3.63 (dd, *J* = 9.3, 5.0 Hz, 2H), 3.52 (s, 1H), 3.38 (s, 1H), 3.02 (d, *J* = 15.7 Hz, 0.3H), 2.91 (d, *J* = 15.9 Hz, 1H), 1.38 (s, 9H), 1.37 (s, 3H); **¹³C NMR (150 MHz, CDCl₃):** δ 169.8, 168.0, 155.7,

152.2, 152.0, 142.7, 142.2, 135.6, 128.6, 127.8, 123.9, 123.8, 122.5, 115.1, 115.1, 110.8, 110.4, 79.6, 56.4, 53.2, 42.3, 40.3, 32.1, 31.8, 28.6; **FT-IR (thin film)**: 1737, 1686, 1598, 1499, 1366, 1245, 1169, 1011, 753 cm^{-1} ; **HRMS (+ESI)**: Calc for $\text{C}_{22}\text{H}_{27}\text{N}_2\text{O}_6$ $[\text{M}+\text{H}]^+$ 415.1864; found: 415.1866; The enantiomeric ratio of major diastereomer was determined by HPLC analysis using Daicel Chiralpak IC column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 15.9$ min, $\tau_{\text{minor}} = 30.3$ min); Enantiomeric excess: 89%.

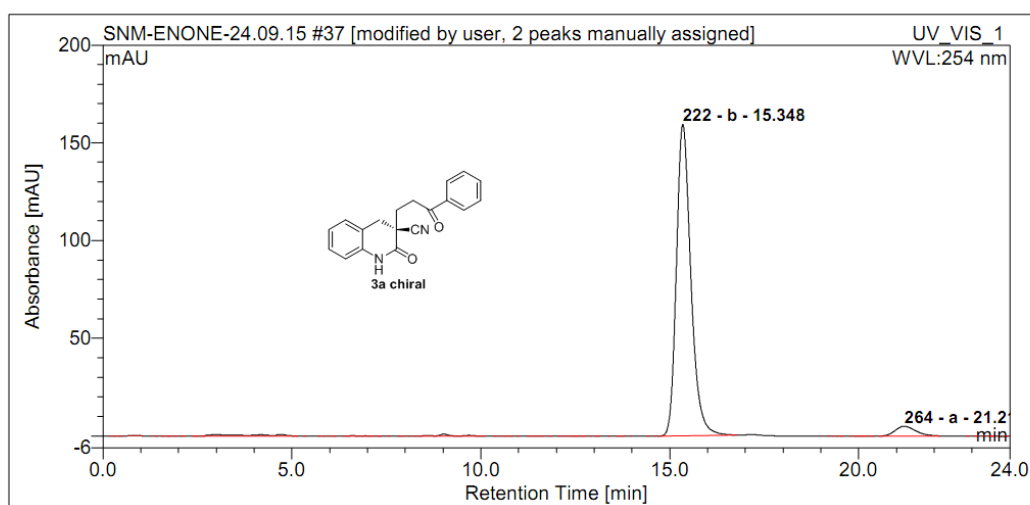


5.10. Selected NMR spectra and HPLC chromatogram:

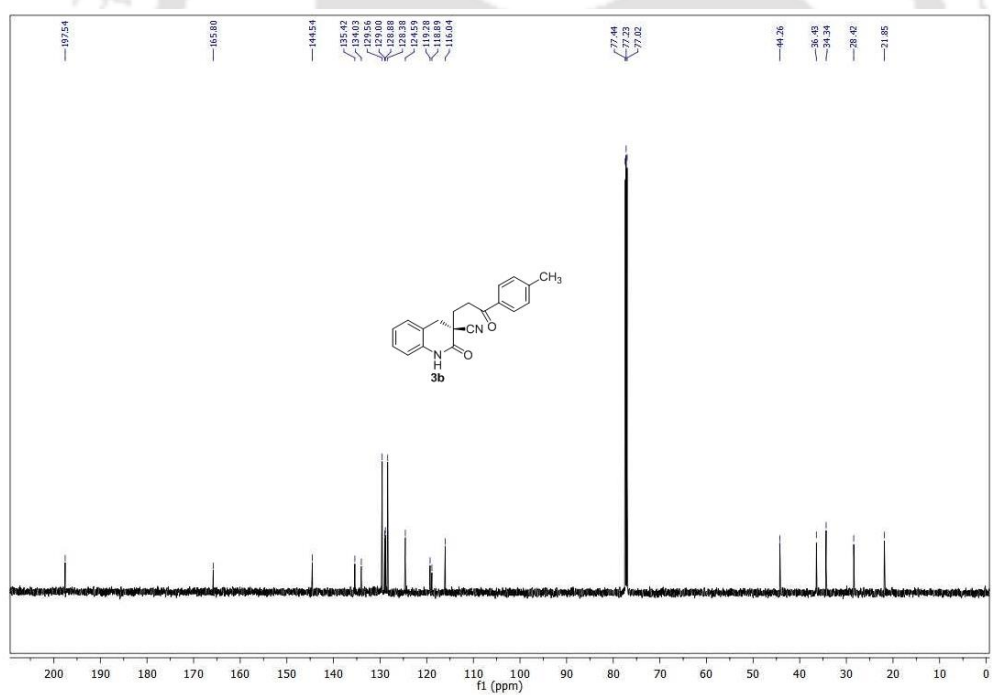
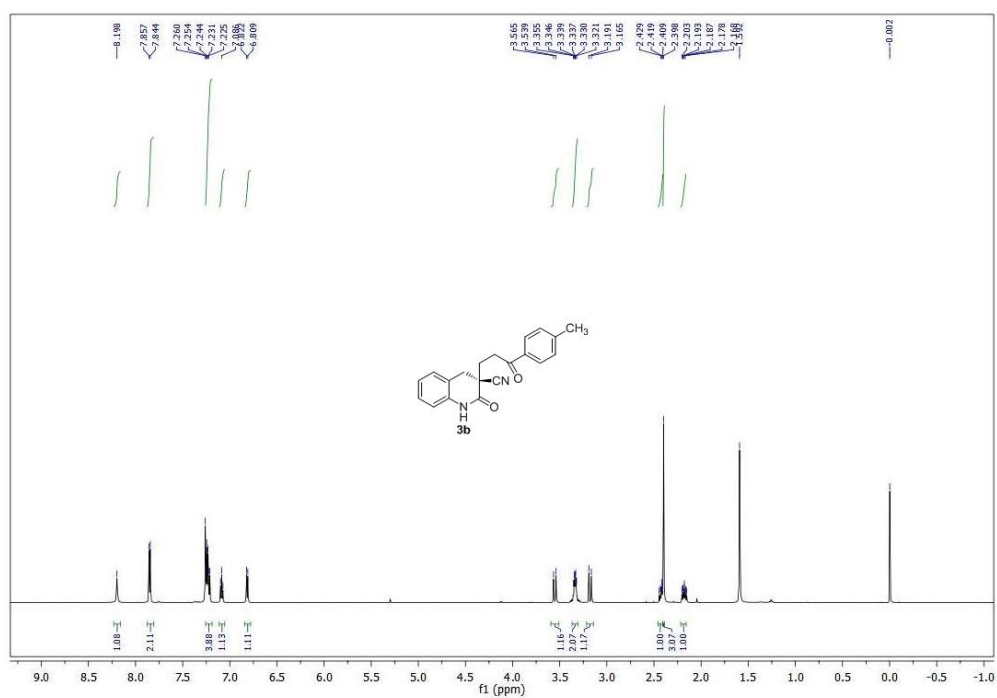


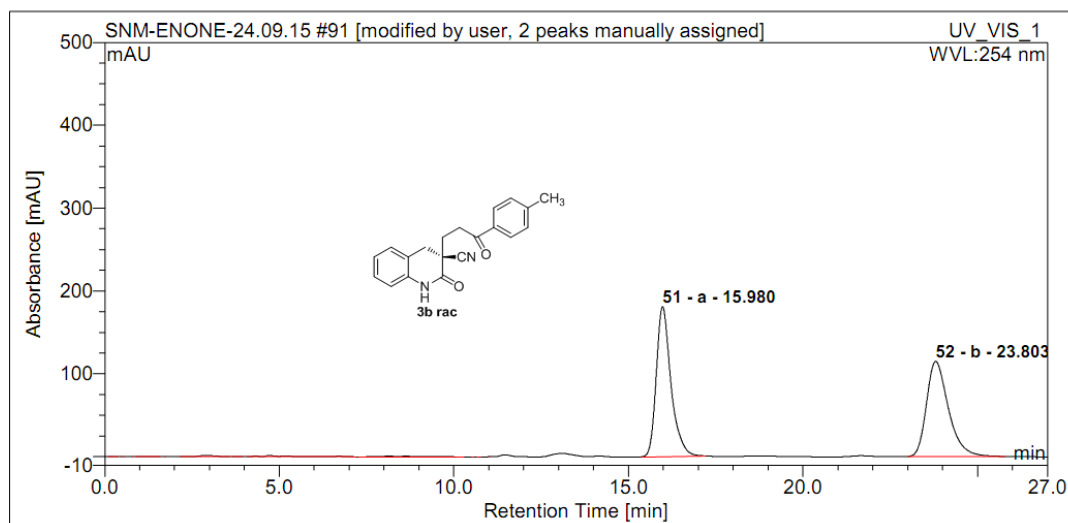


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
95 a		15.23	28.84316	49.1235649	63.98525	n.a.
134 b		20.89	29.872	50.8763622	44.092	n.a.

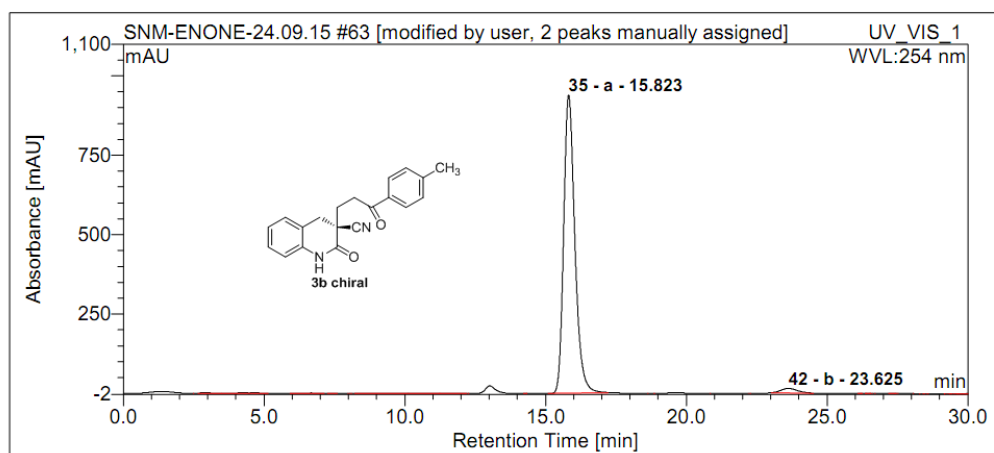


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
222 b		15.35	70.73641	95.68027135	159.3447	n.a.
264 a		21.21	3.194	4.319728646	5.030	n.a.

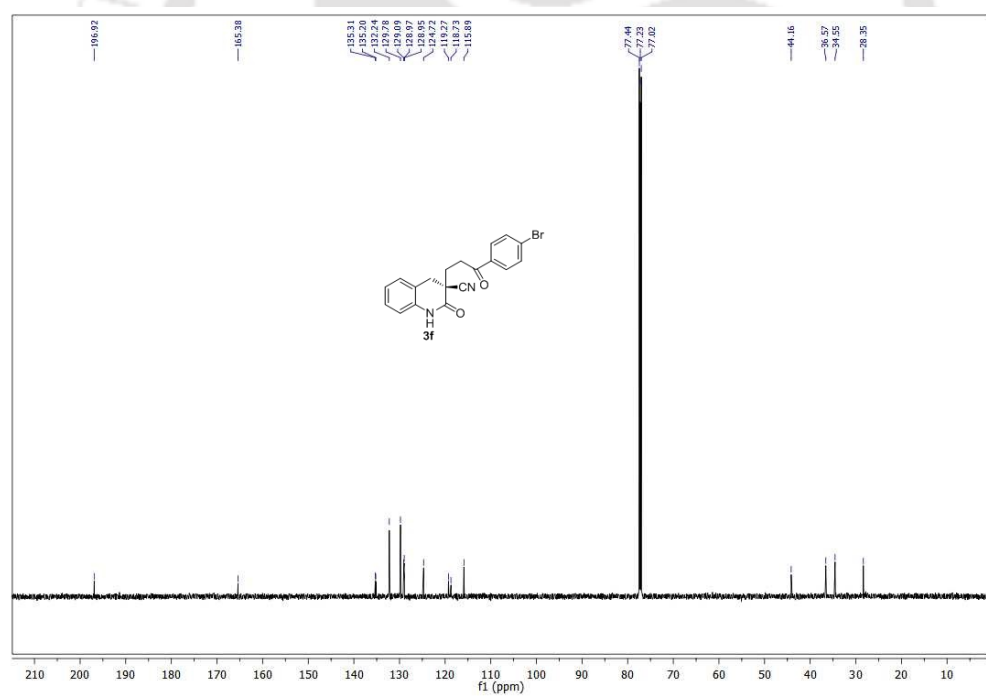
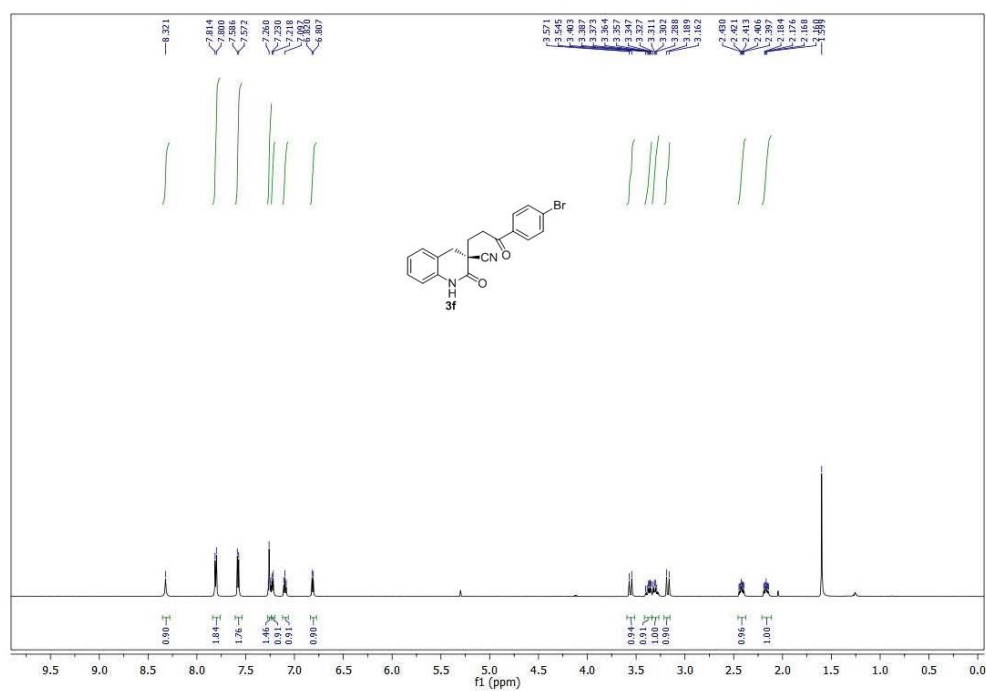




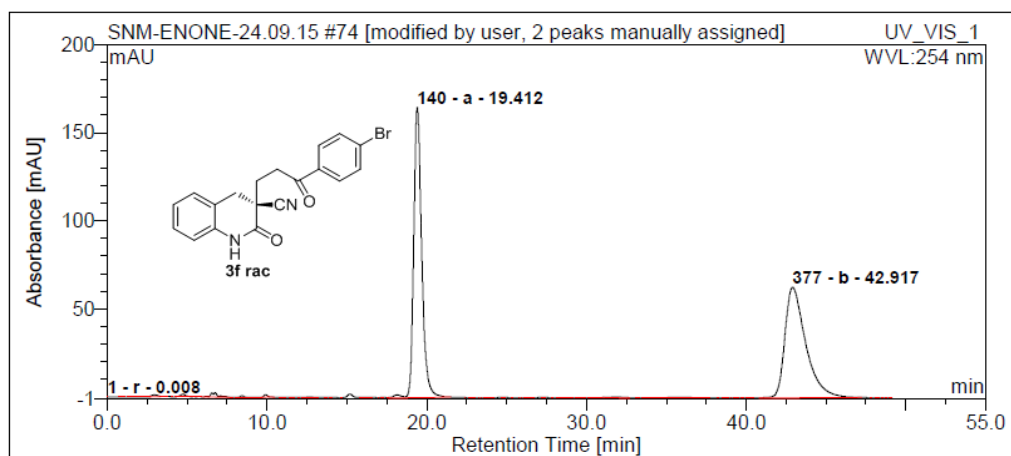
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
51 a		15.98	88.05679	51.22624469	180.8974	n.a.
52 b		23.80	83.841	48.77375531	114.929	n.a.



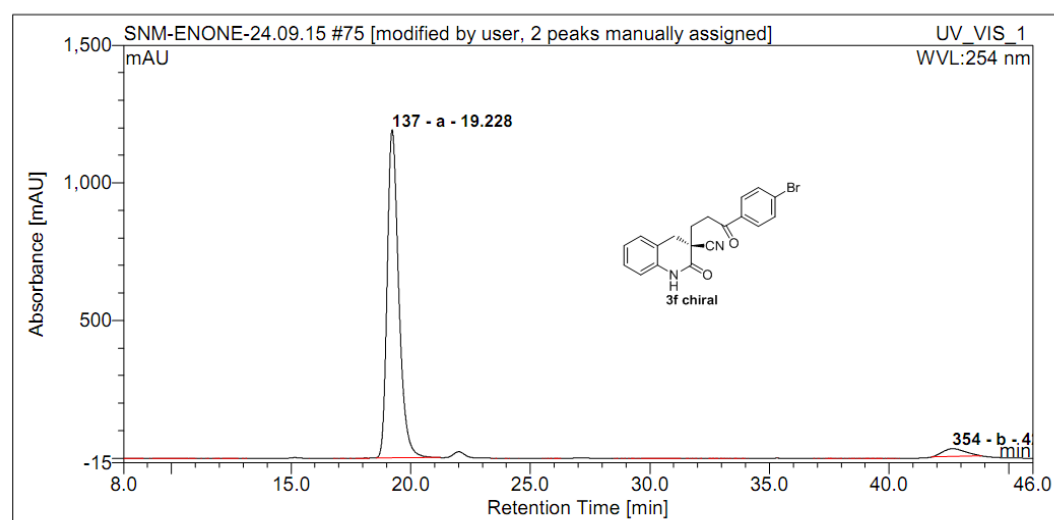
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
35 a		15.82	431.5728	97.79259606	939.2296	n.a.
42 b		23.63	9.742	2.207403938	14.503	n.a.



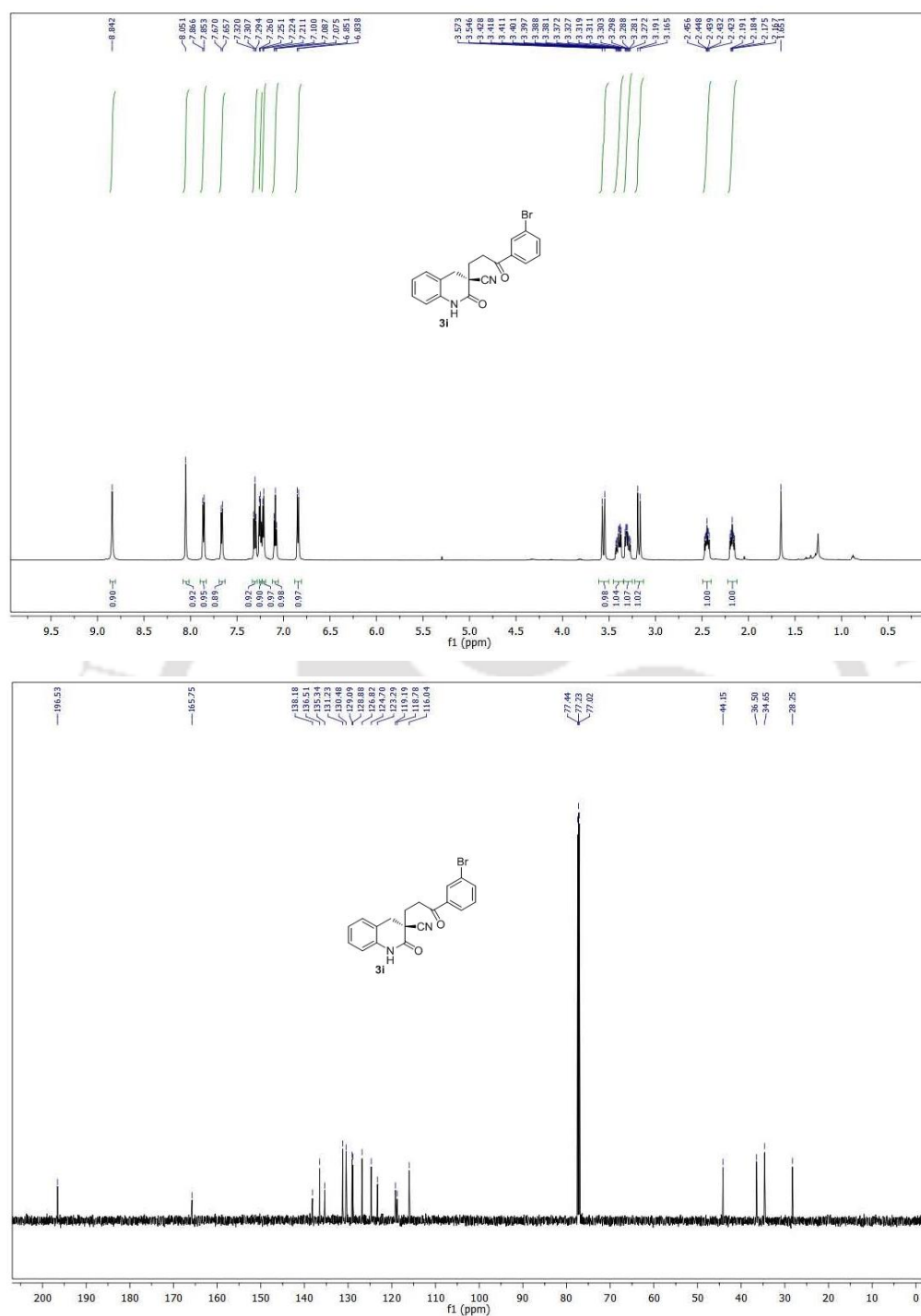
CHAPTER 5

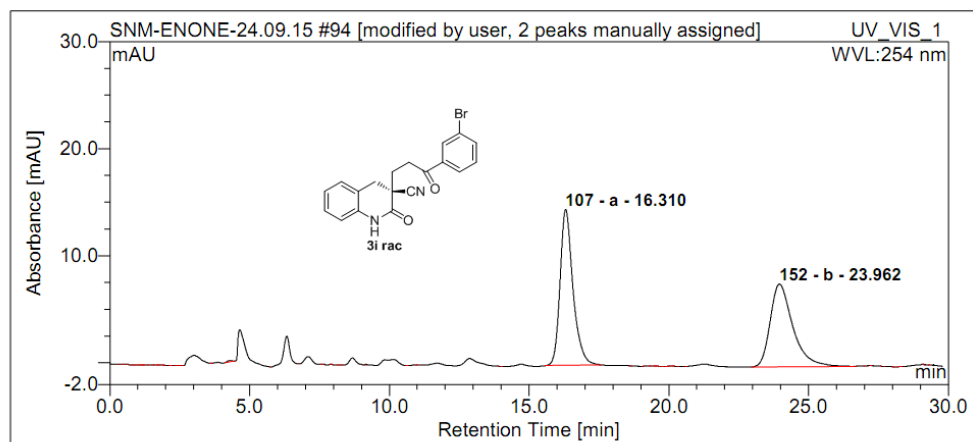


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
140 a		19.41	95.14022	50.17188071	164.4989	n.a.
377 b		42.92	94.488	49.82810927	62.699	n.a.

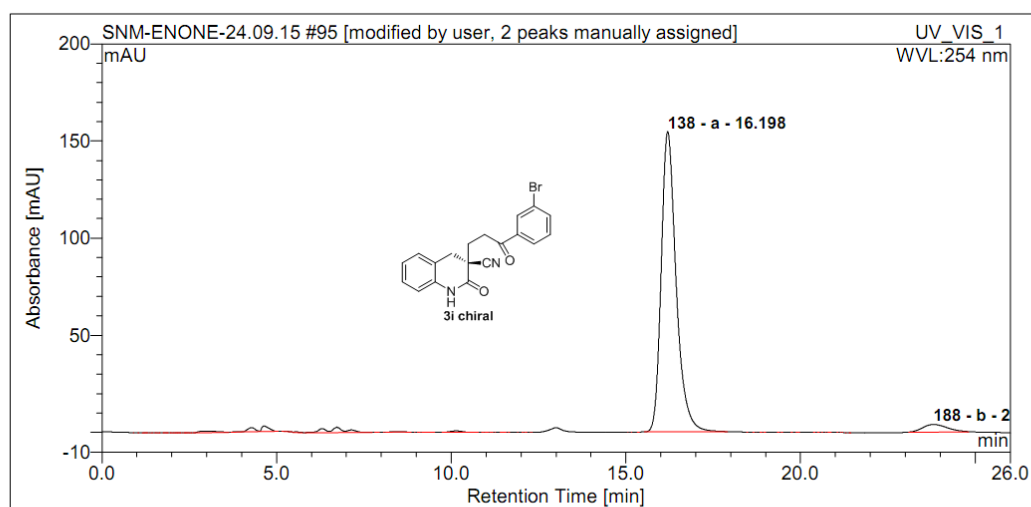


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
137 a		19.23	667.2516	95.51865557	1191.441	n.a.
354 b		42.66	31.305	4.481344432	27.901	n.a.

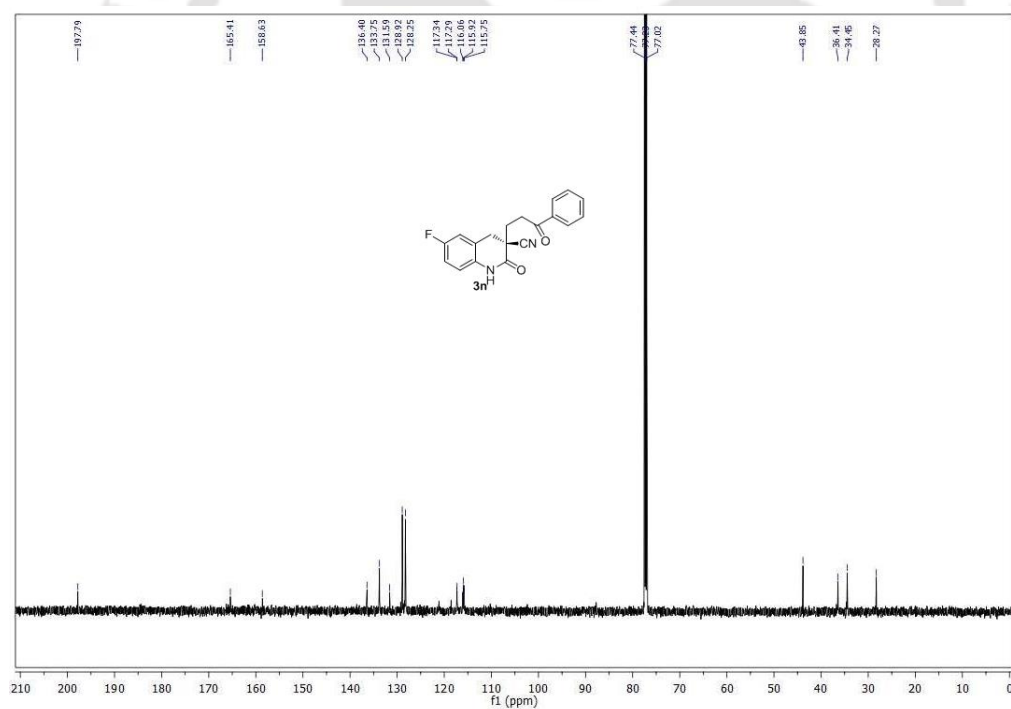
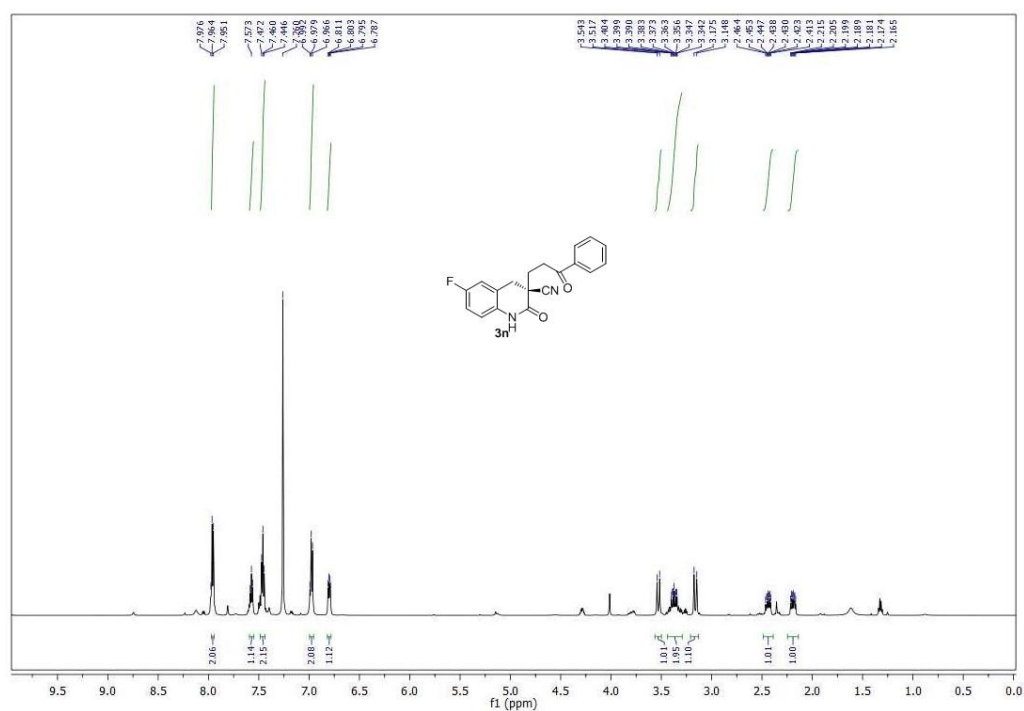


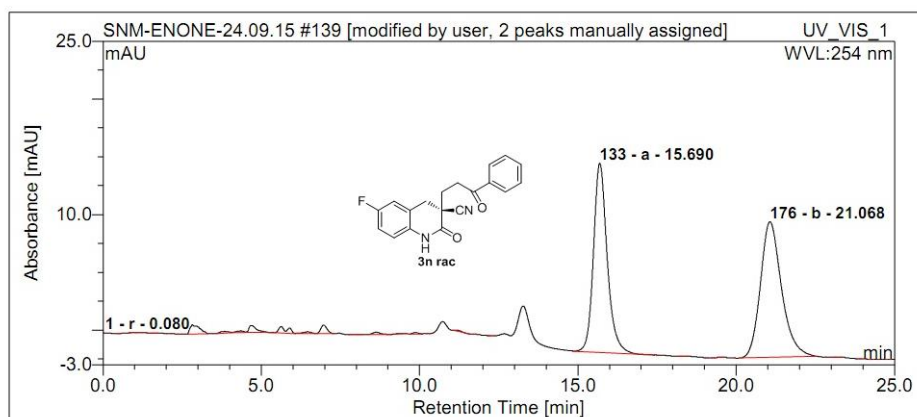


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
107 a		16.31	7.799707	51.918058	14.57746	n.a.
152 b		23.96	7.223	48.081942	7.718	n.a.

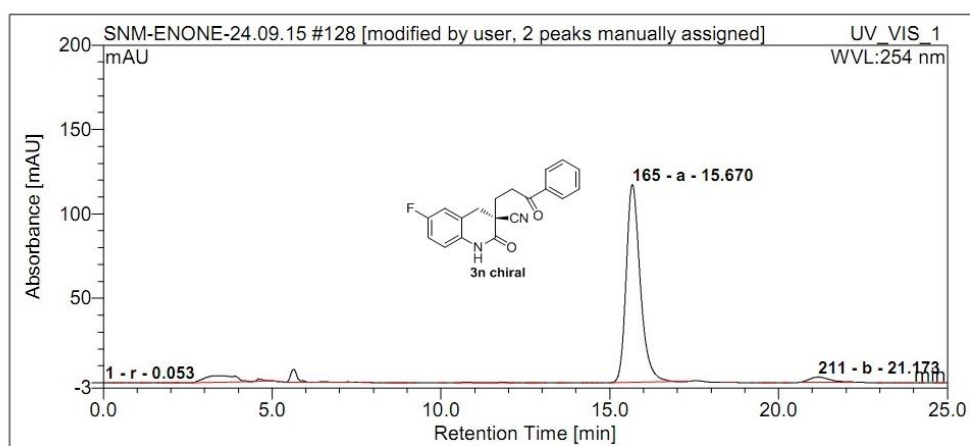


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
138 a		16.20	76.47517	96.05912317	154.4941	n.a.
188 b		23.80	3.137	3.940876829	3.868	n.a.

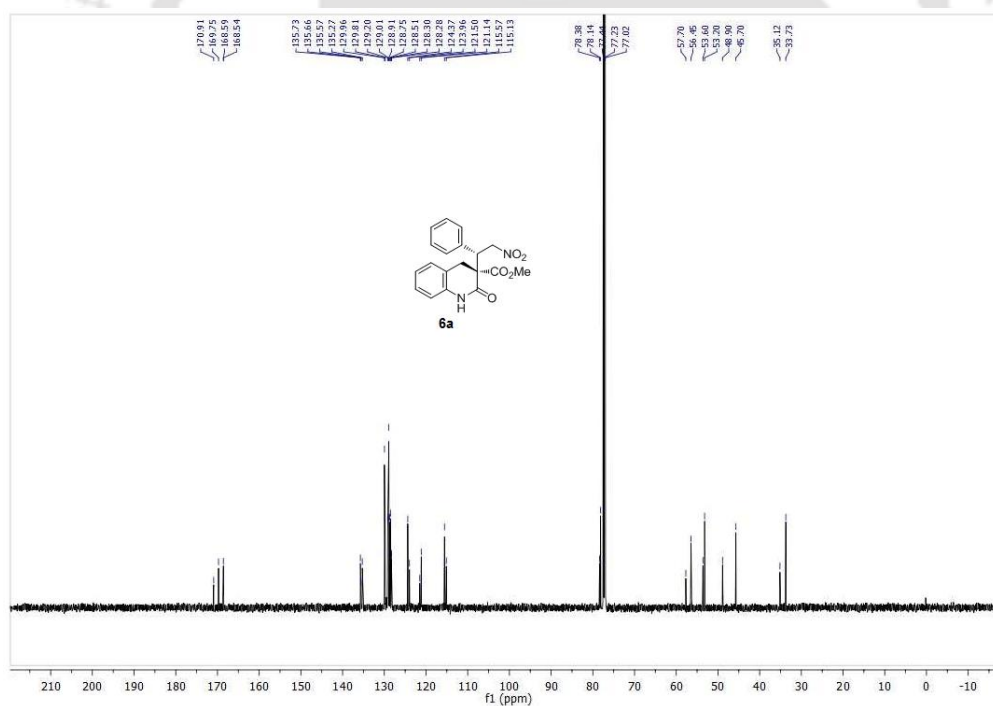
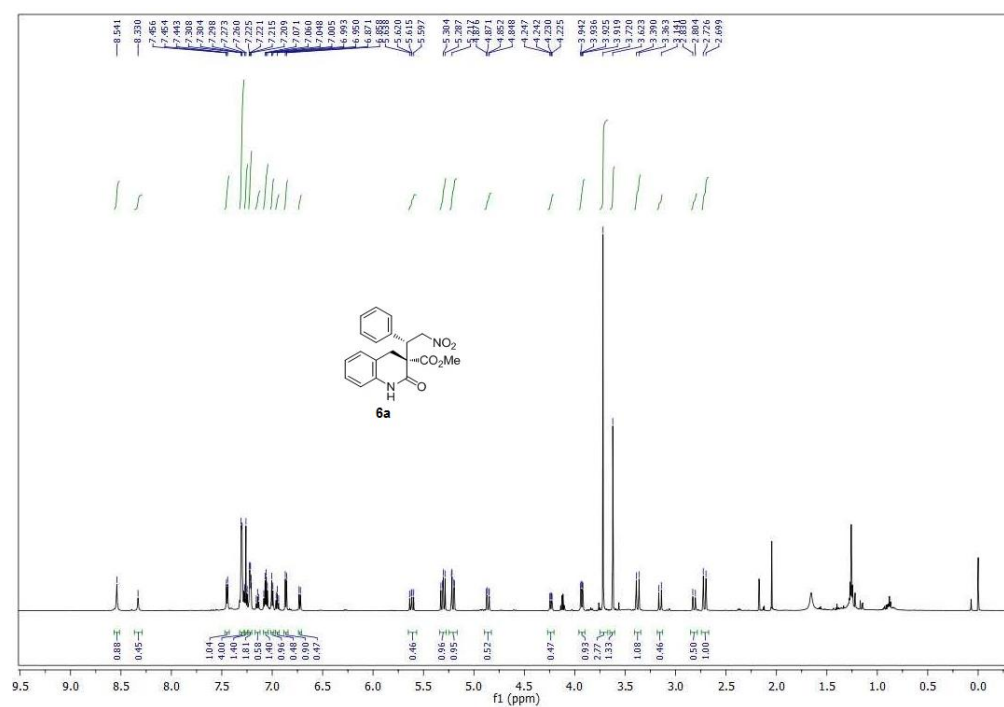


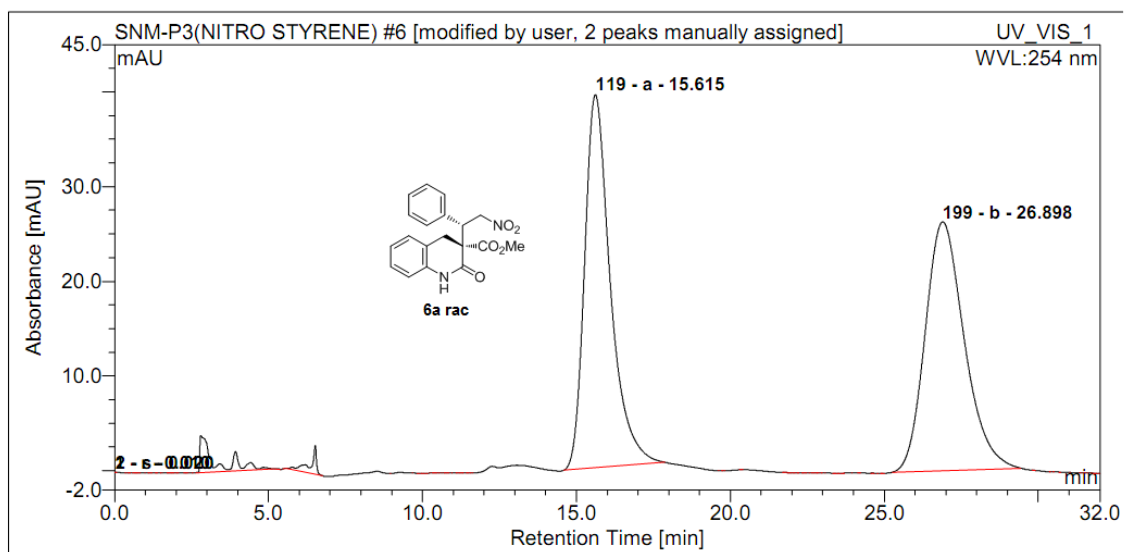


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
133 a		15.69	8.218014	47.5595302	16.38073	n.a.
176 b		21.07	9.061	52.44017562	11.751	n.a.

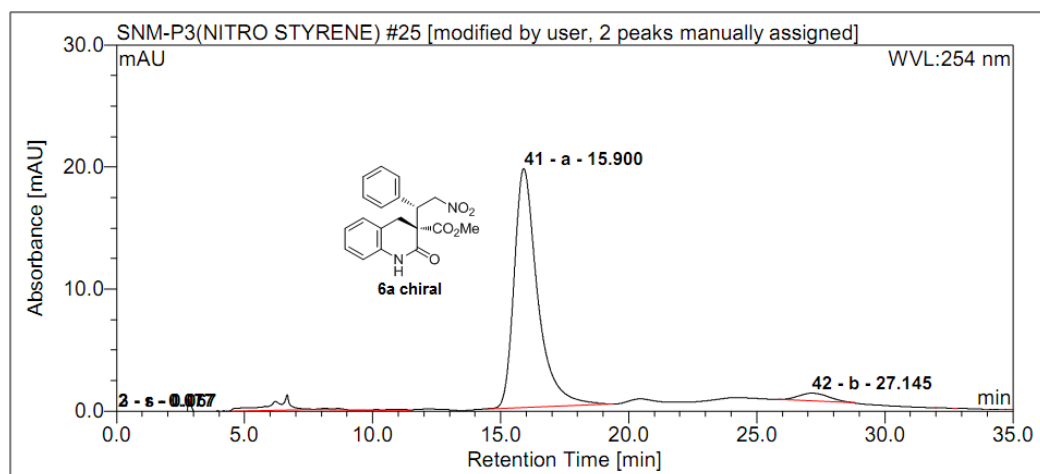


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
165 a		15.67	56.43731	96.45382192	117.2187	n.a.
211 b		21.17	2.075	3.546140698	3.021	n.a.

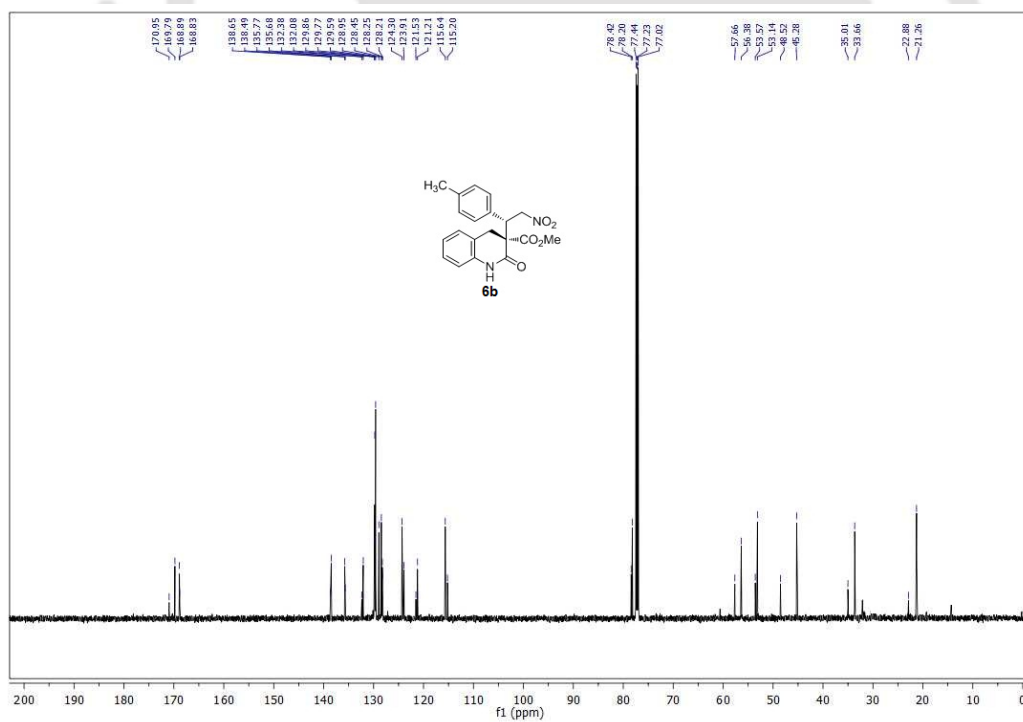
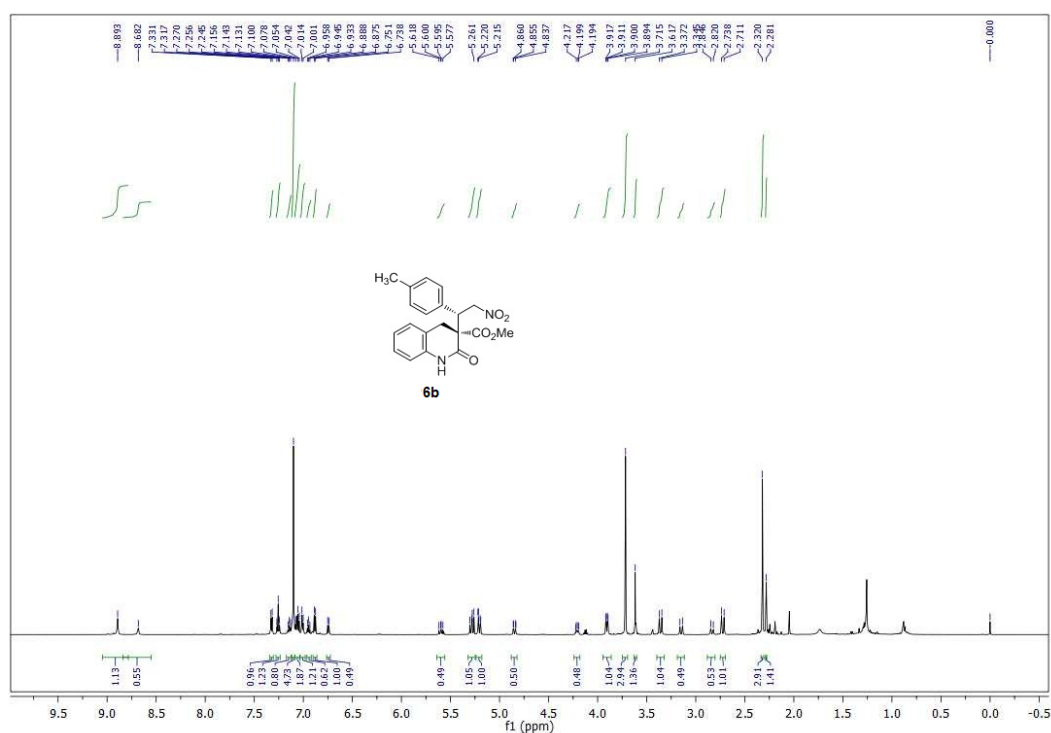


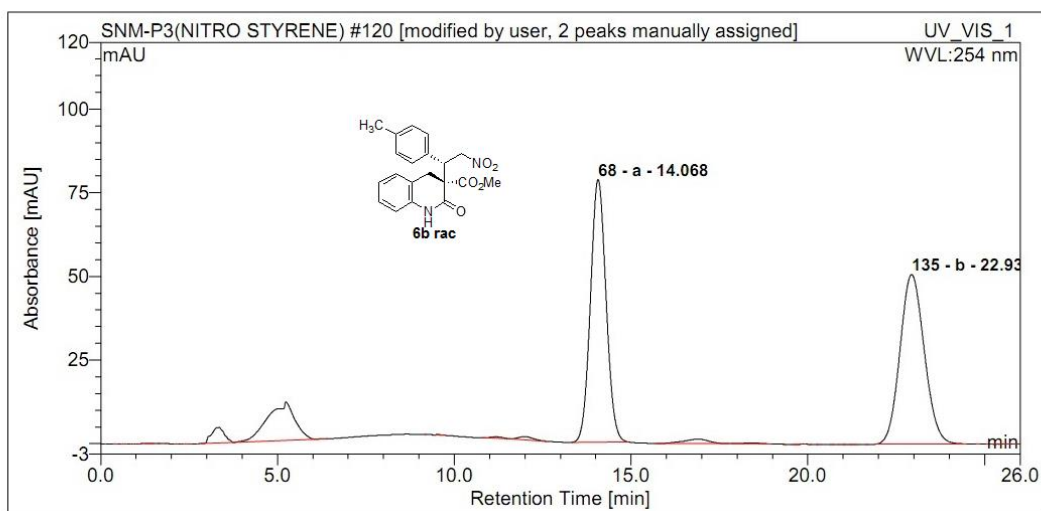


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
119 a		15.62	38.11071	49.68992212	39.39482	n.a.
199 b		26.90	38.586	50.31003356	26.257	n.a.

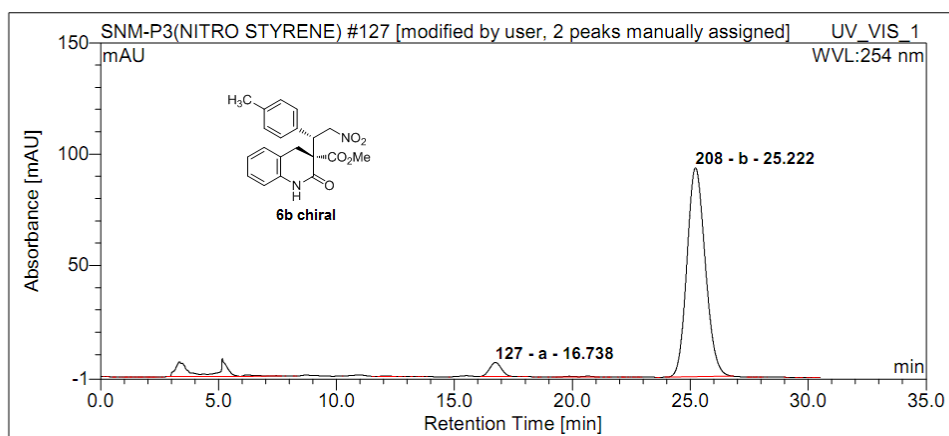


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
3 r		0.08	0.000295	0.001357746628	0.00257	n.a.
41 a		15.90	20.80114	95.8218112	19.58312	n.a.
42 b		27.15	0.907	4.176827441	0.644	n.a.

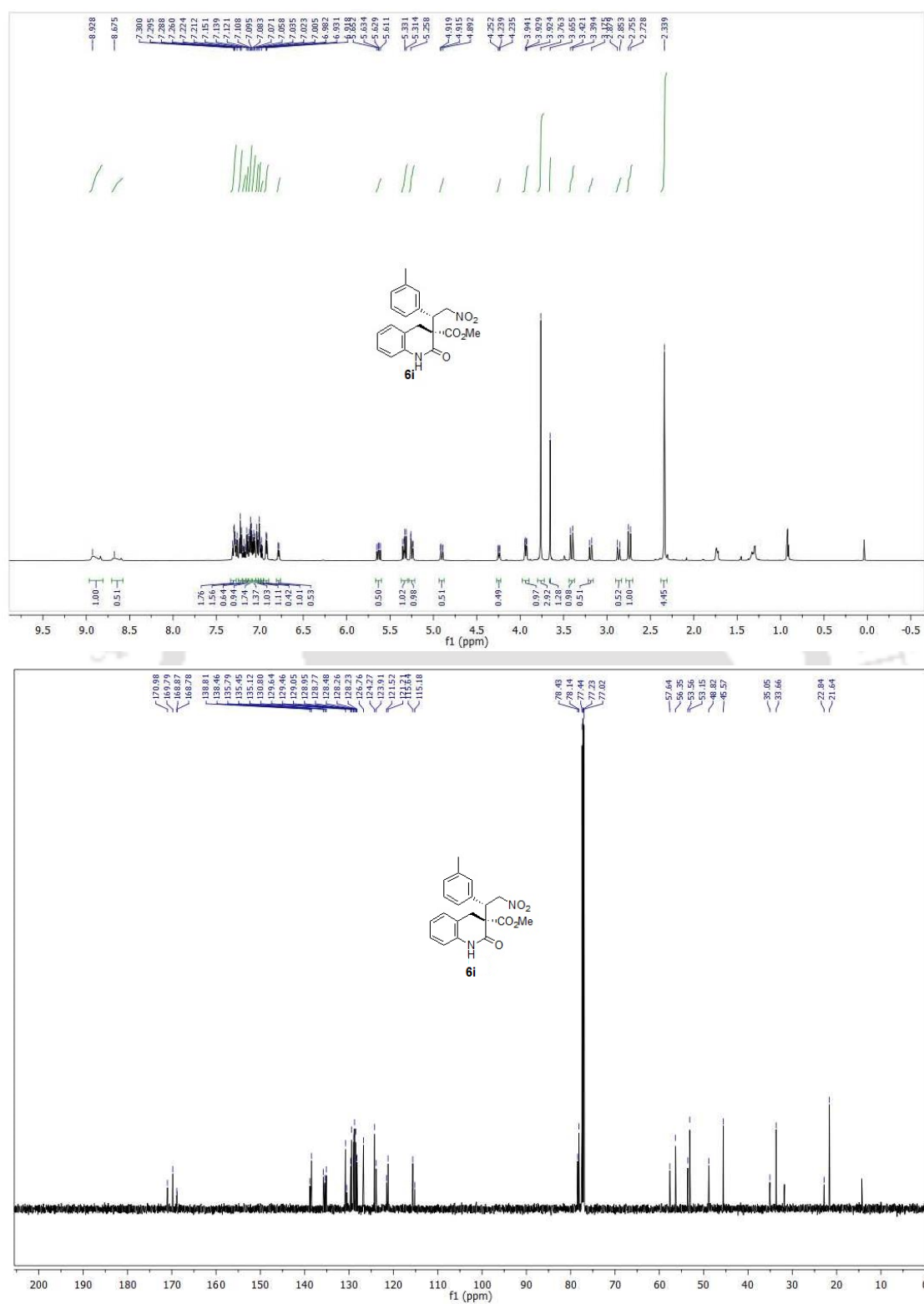




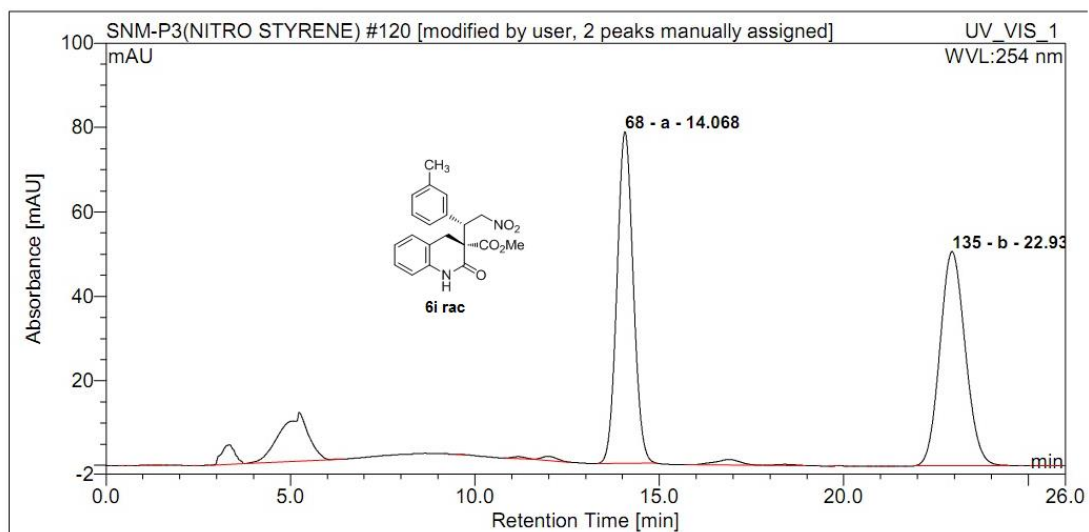
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
68 a		14.07	40.12315	49.83664595	78.50752	n.a.
135 b		22.94	40.386	50.16335405	50.717	n.a.



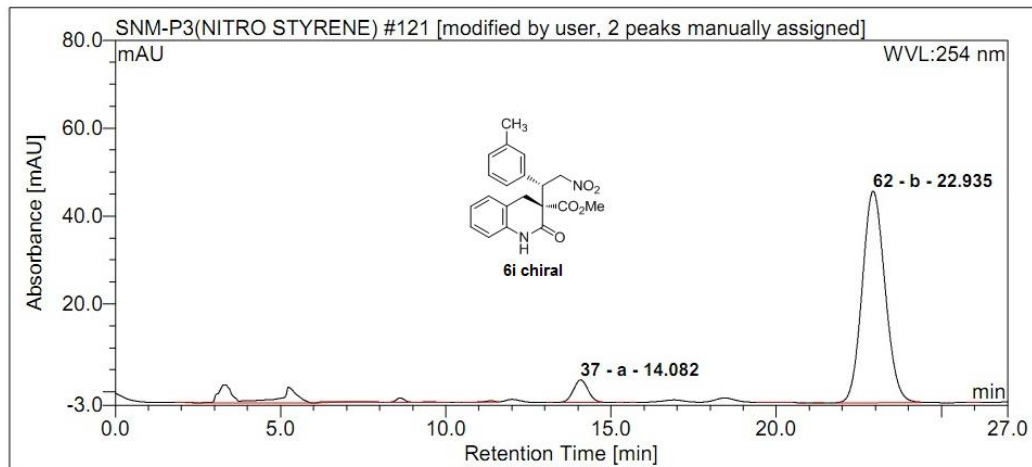
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
127 a		16.74	3.639951	4.125477232	6.25455	n.a.
208 b		25.22	84.591	95.87452277	94.008	n.a.



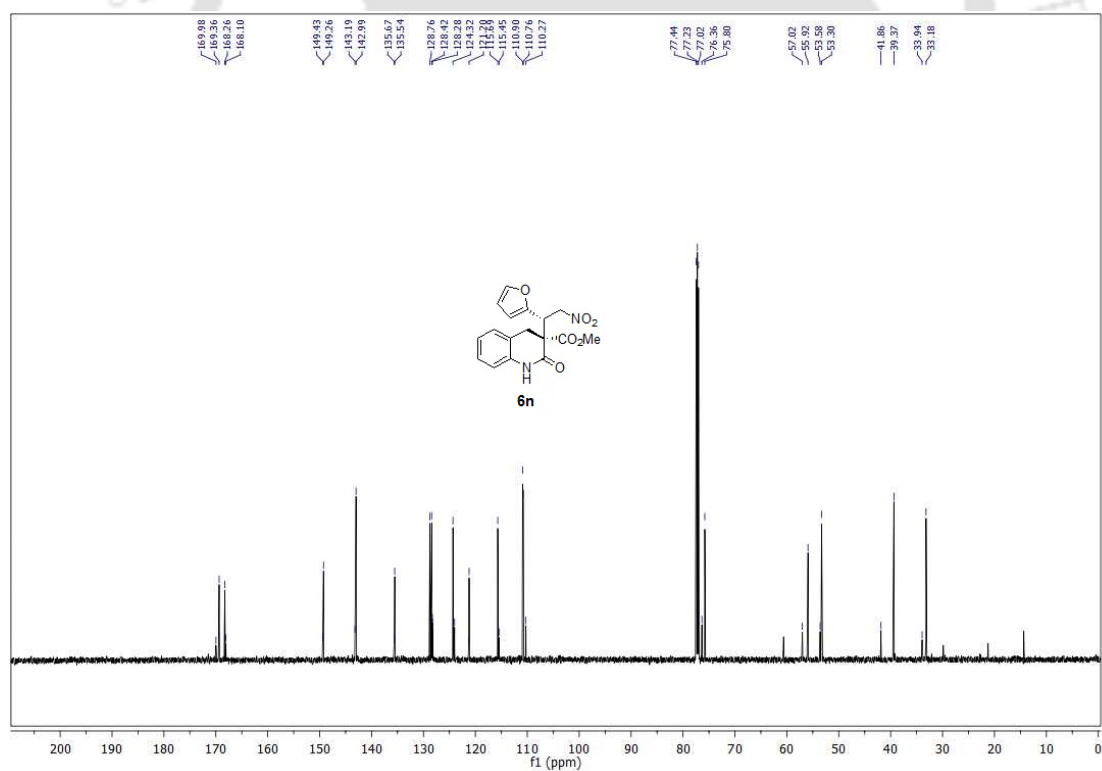
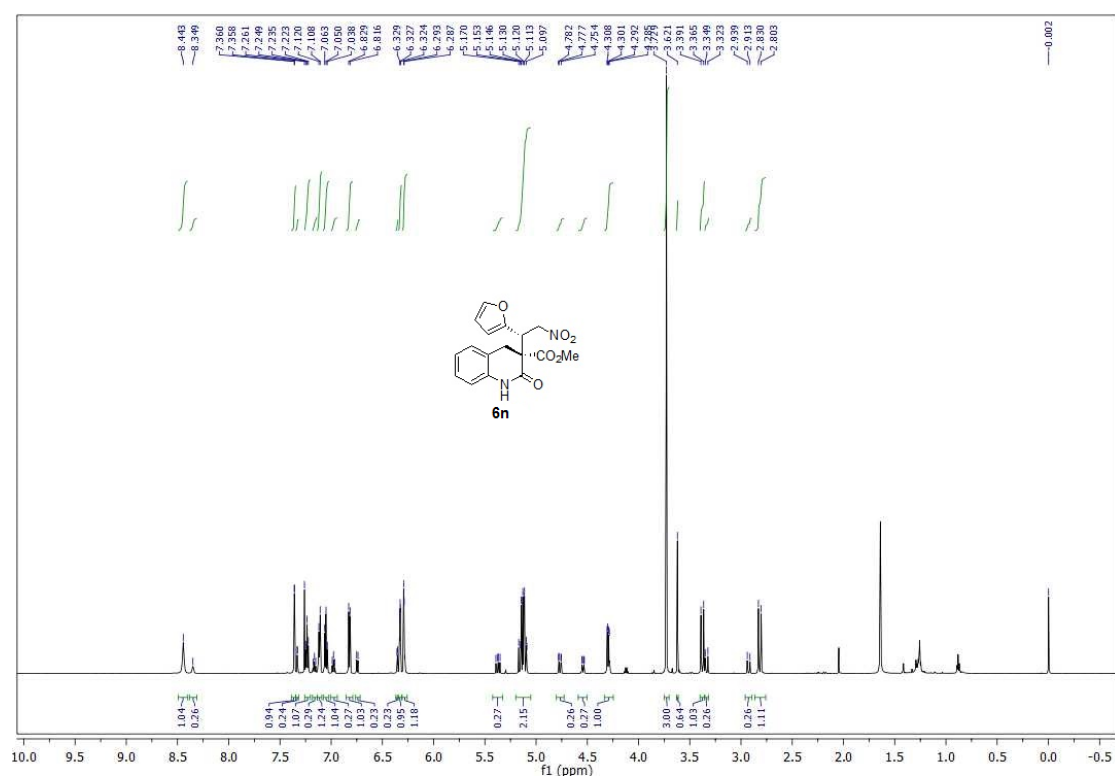
CHAPTER 5



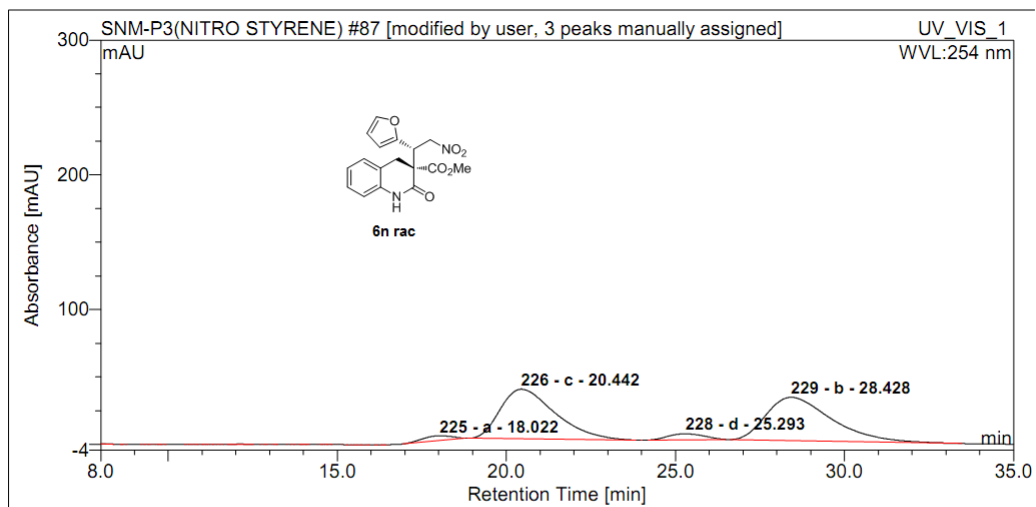
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
68 a		14.07	40.12315	49.83664595	78.50752	n.a.
135 b		22.94	40.386	50.16335405	50.717	n.a.



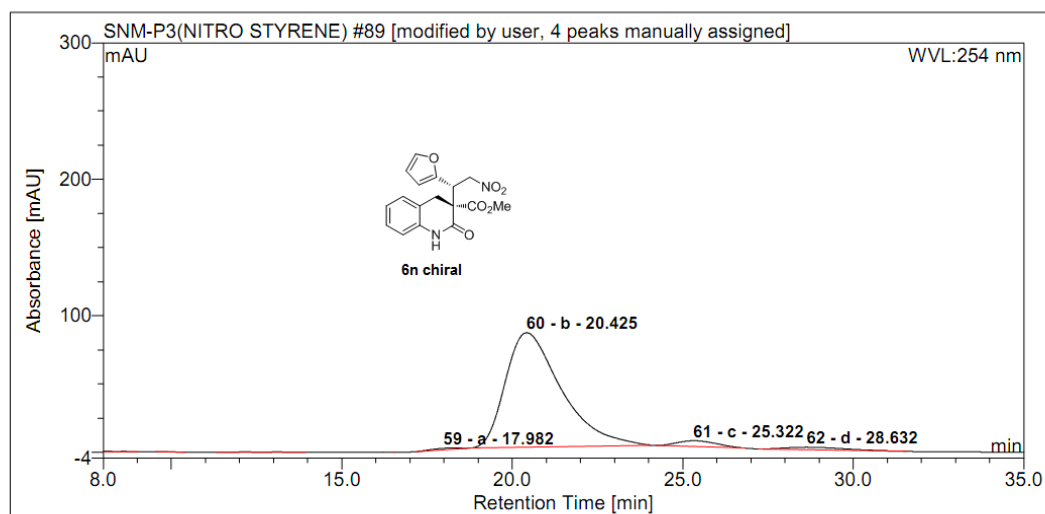
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
37 a		14.08	2.594833	6.319012031	5.10444	n.a.
62 b		22.94	38.469	93.68098797	48.117	n.a.



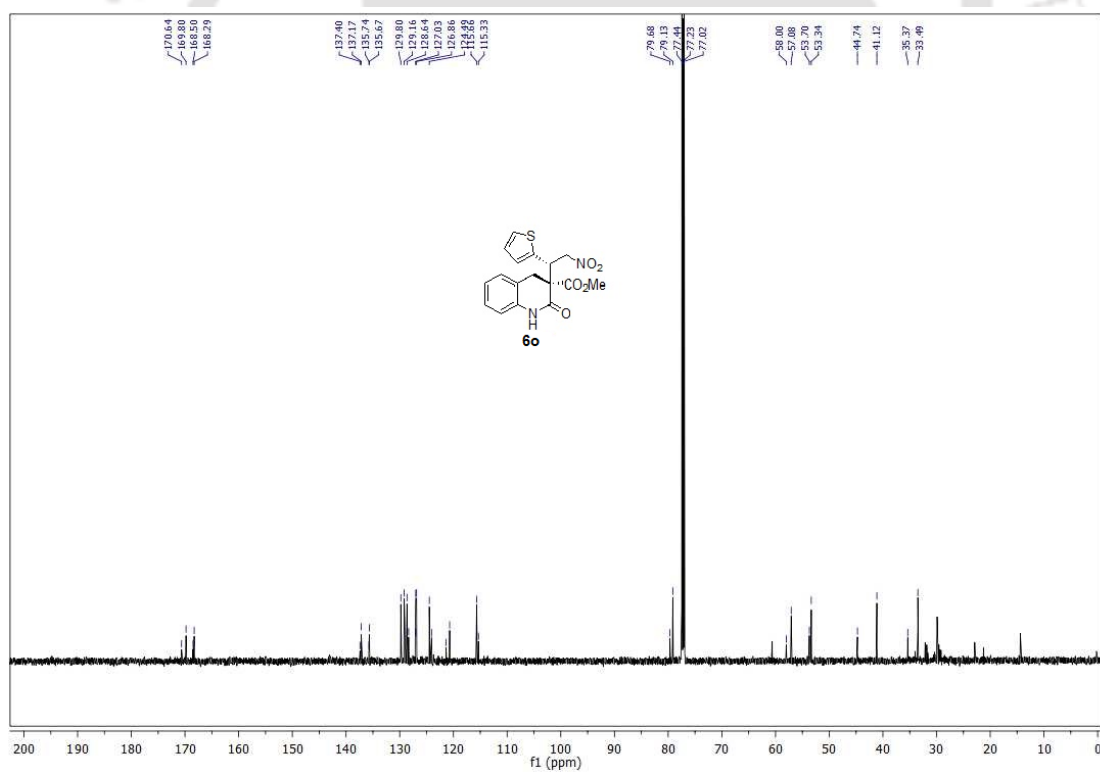
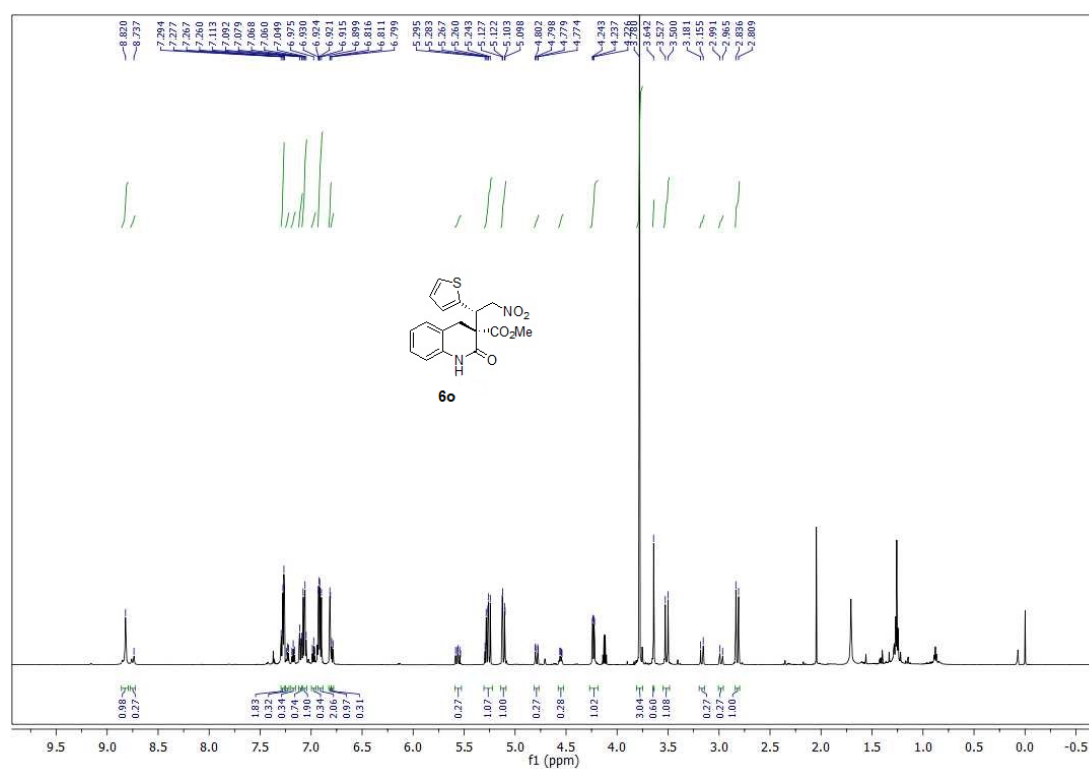
CHAPTER 5

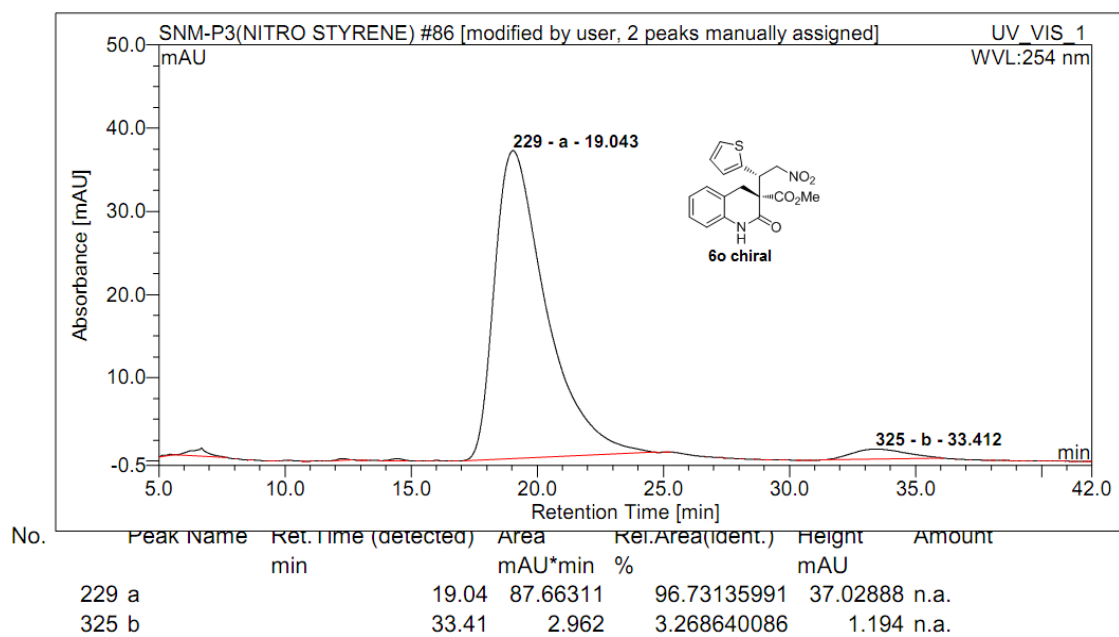
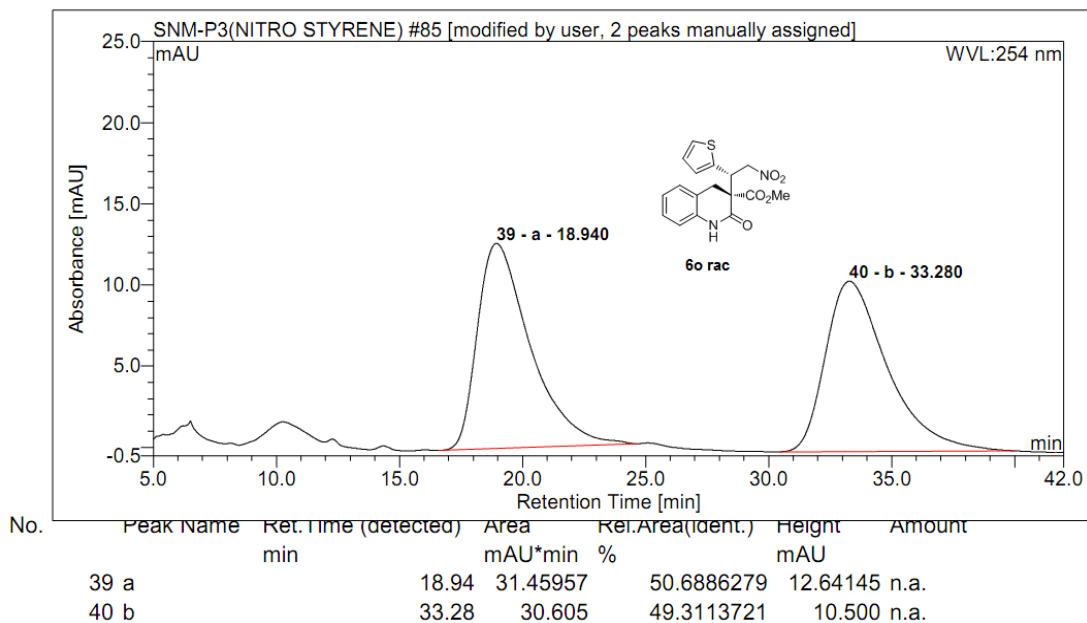


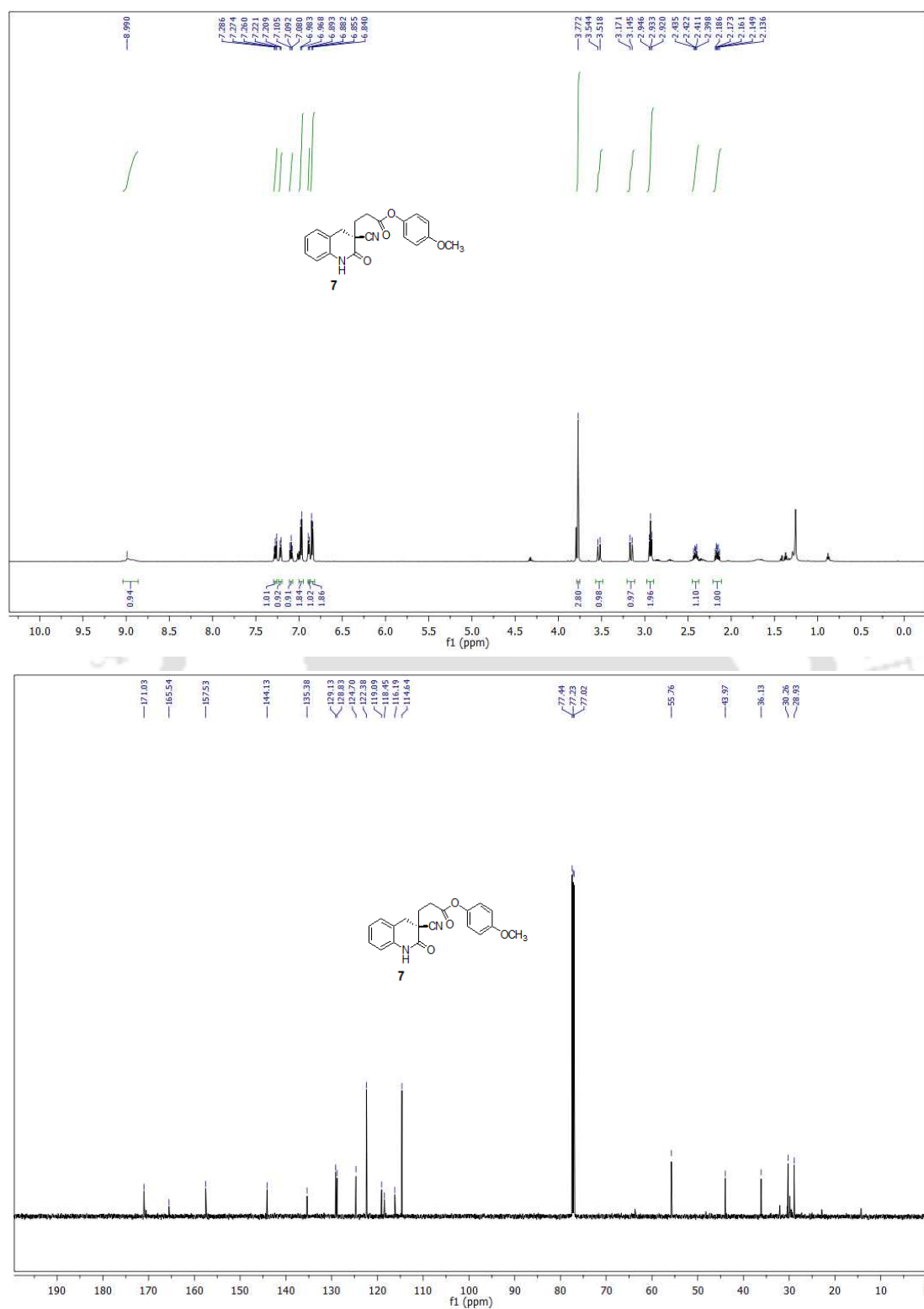
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
225 a		18.02	3.619415	2.403434871	3.46983	n.a.
226 c		20.44	69.66422	46.25980283	36.87482	n.a.
228 d		25.29	5.378038	3.571229824	4.38946	n.a.
229 b		28.43	71.932	47.76553247	32.064	n.a.

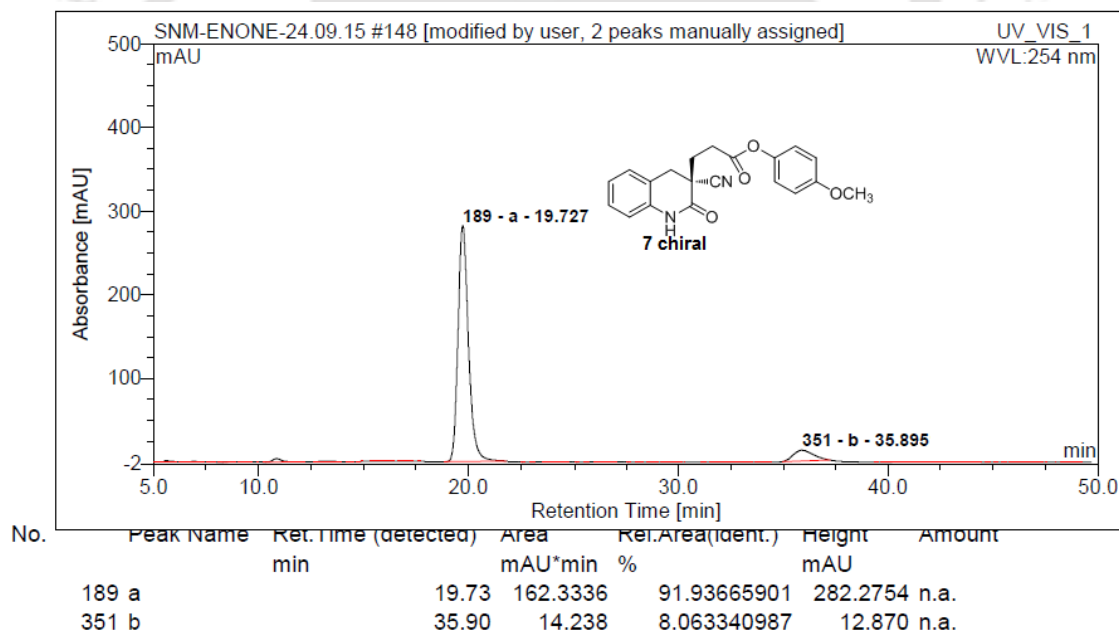
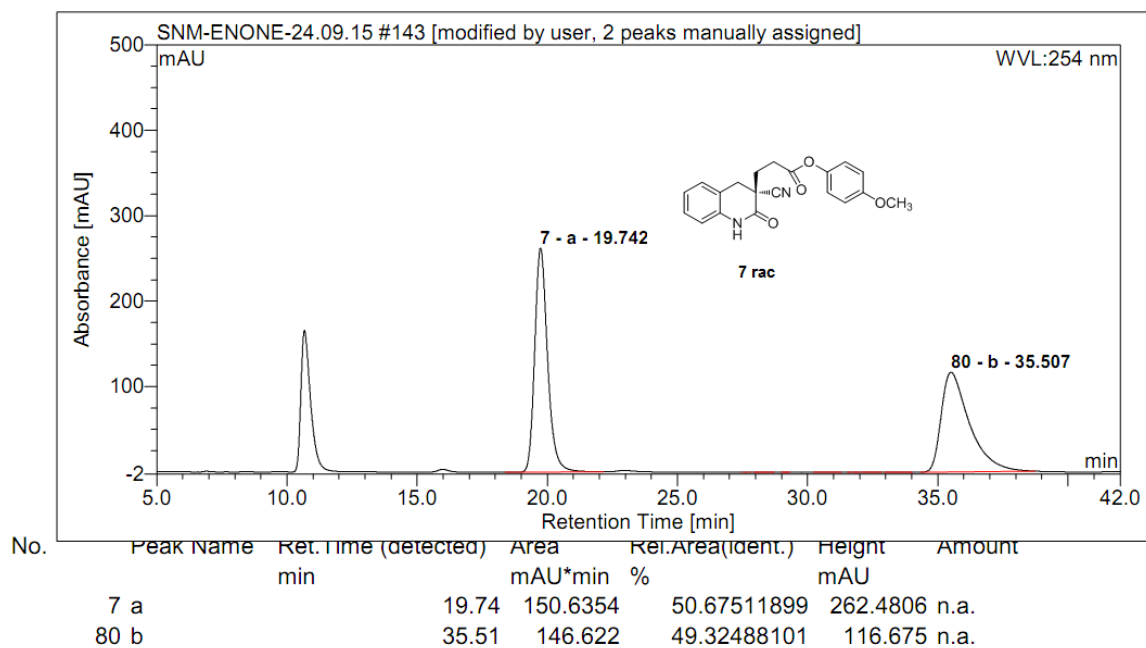


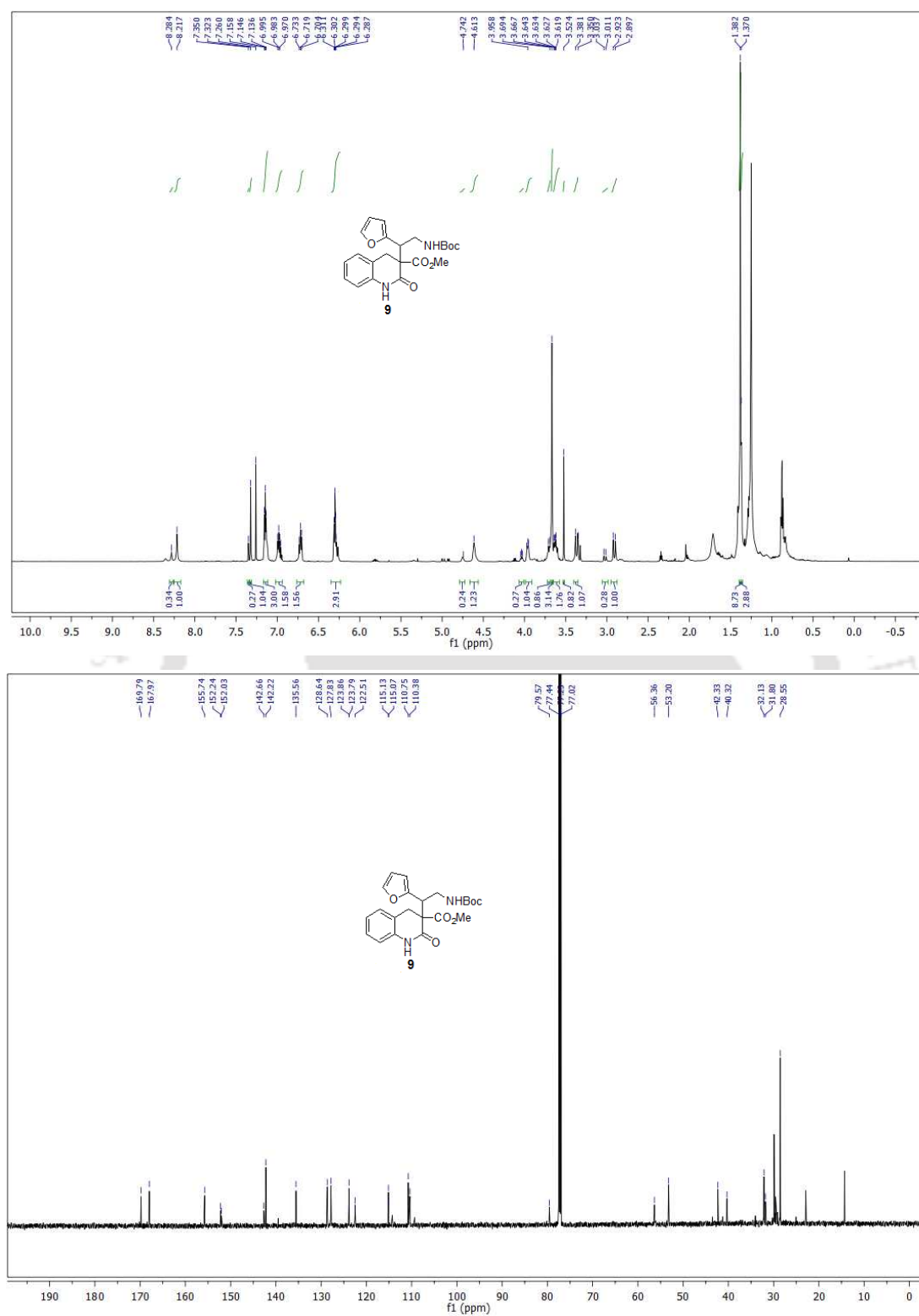
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
59 a		17.98	0.854643	0.506443049	1.04942	n.a.
60 b		20.43	158.4468	93.89217823	83.6942	n.a.
61 c		25.32	5.764719	3.416048259	4.30902	n.a.
62 d		28.63	3.688	2.185330467	1.855	n.a.

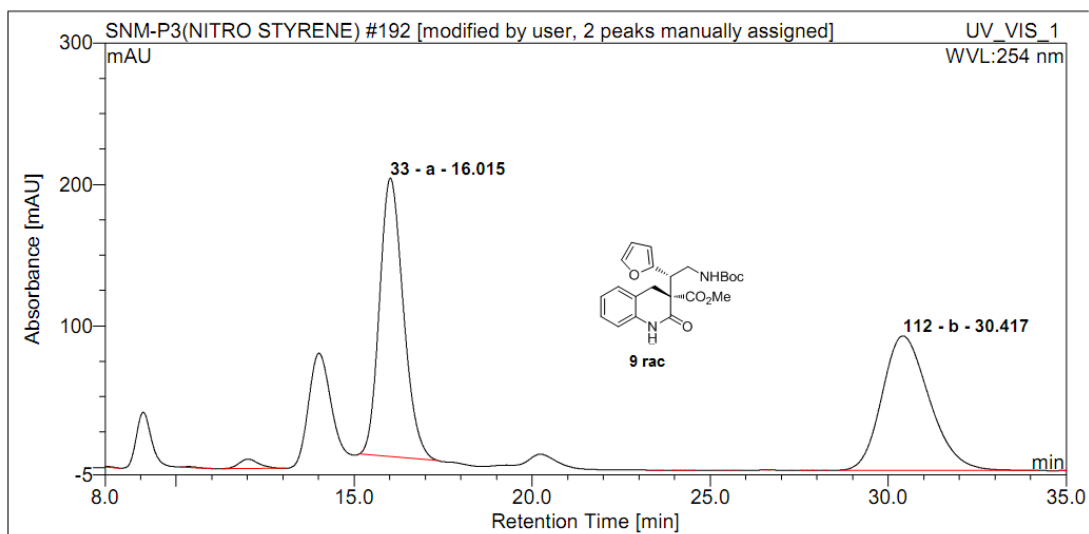




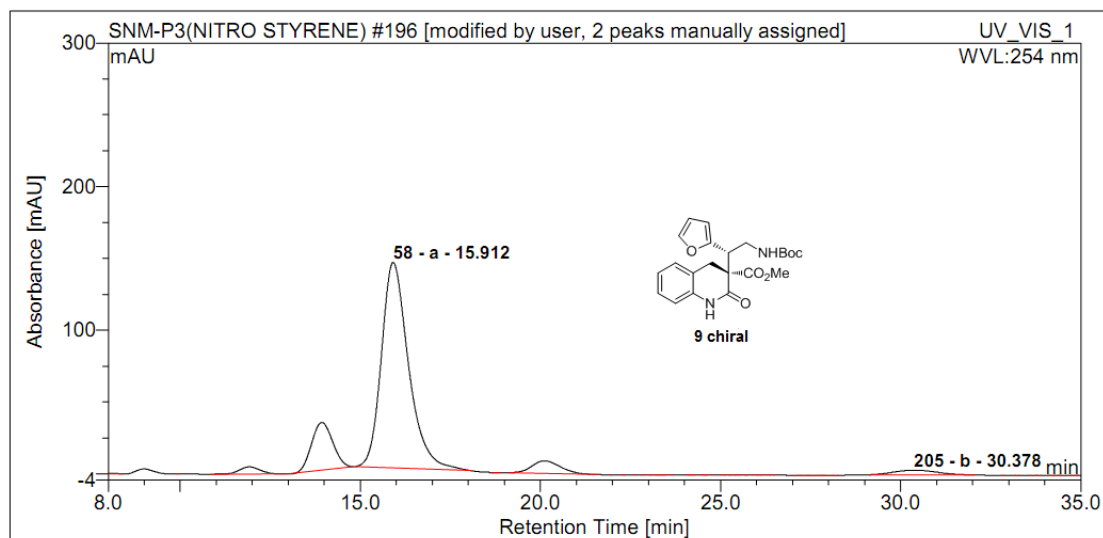








No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
33 a		16.02	152.9238	51.15874528	196.8879	n.a.
112 b		30.42	145.996	48.84125472	95.023	n.a.

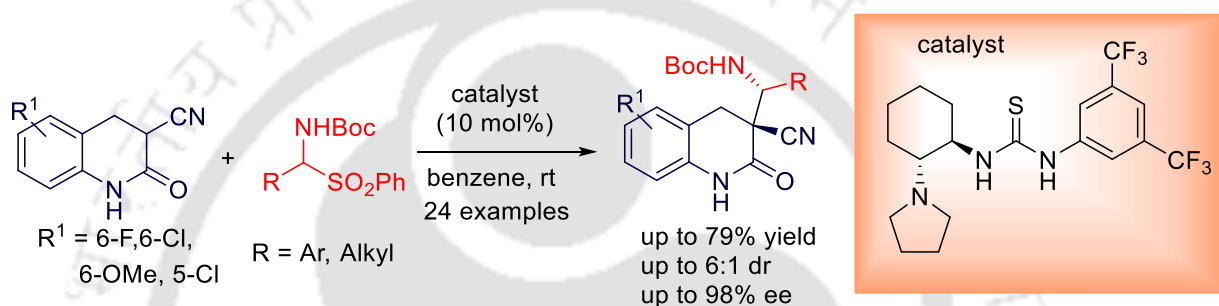


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
58 a		15.91	125.2083	96.54699205	143.0433	n.a.
205 b		30.38	4.478	3.453007948	3.196	n.a.

Chapter 6

Organocatalytic Asymmetric Mannich Reaction for the Synthesis of 3,3-Disubstituted-3,4-Dihydro-2-Quinolones

Abstract: The first organocatalytic asymmetric Mannich reaction employing 3,4-dihydro-2-quinolone has been developed for the synthesis of biologically important 3,3-disubstituted-dihydro-2-quinolones. *N*-Boc imine precursor amidosulfones were used for this purpose. Cyclohexyldiamine derived bifunctional amino-thiourea catalysts were employed to provide the products in high enantio and good diastereoselectivities.





6.1. Introduction:

Functionalized 3,4-dihydroquinolin-2(1*H*)-ones are prevalent in many natural alkaloids and commercial drugs (Figure 1).¹ Substituted 3,4-dihydroquinolin-2(1*H*)-ones are important core structures in many natural products and have displayed impressive biological activities such as 5-HT_{2c} receptor antagonists, NMDA antagonists, cardiovascular, anti-inflammatory as well as HIV-1 reverse transcriptase inhibitor.¹ Besides, dihydroquinolones are also used as the necessary building unit for the synthesis of drugs.¹ Thus the construction of enantiomerically pure substituted 3,4-dihydroquinolin-2(1*H*)-ones in an efficient and straightforward approach is highly desirable. Despite significant importance, there are few reports on asymmetric synthesis of dihydroquinolones and rely on transition metal catalysis,² photochemical,³ organocatalysis⁴ and other.⁵ These discoveries documented mainly for the synthesis of chiral 4-substituted and 3,4-disubstituted dihydroquinolin-2(1*H*)-ones. However, the synthesis of chiral 3-substituted and 3,3-disubstituted dihydroquinolin-2(1*H*)-one is considerably less,⁶ though such skeleton is present in Penigenolone A⁷ and (+)-Meloscine.⁷

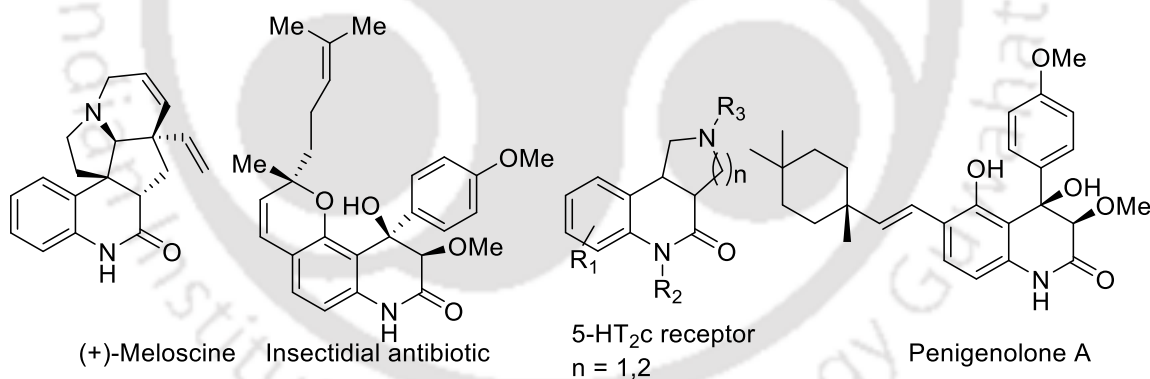
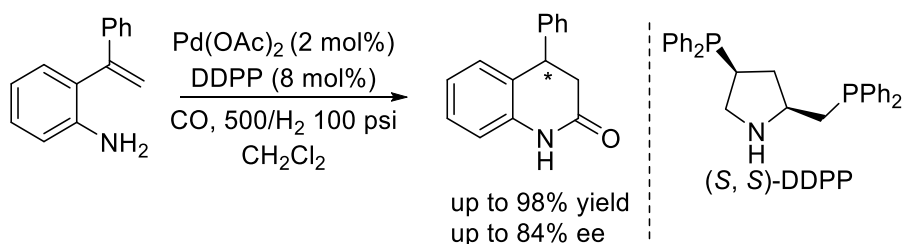


Figure 1: Biologically active compounds containing 3,4-dihydro-2-quinolones

6.2. Selective approaches for the synthesis of chiral dihydroquinolones

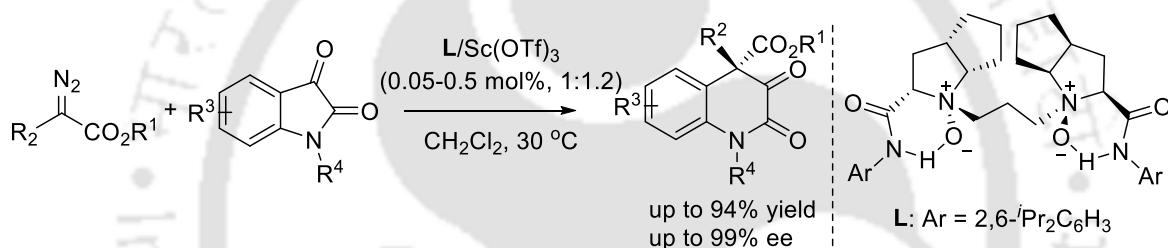
In 2004, Alper group reported an efficient protocol for the synthesis of 4-substituted dihydroquinolones *via* enantioselective cyclocarbonylation of 2-vinylanilines. A combination of Pd(OAc)₂ and (2*S*, 4*S*)-(-)-4-diphenylphosphino-2-

(diphenylphosphinomethyl) pyrrolidine was used as the catalyst to provide the products with moderate enantioselectivities (Scheme 6.1).⁸



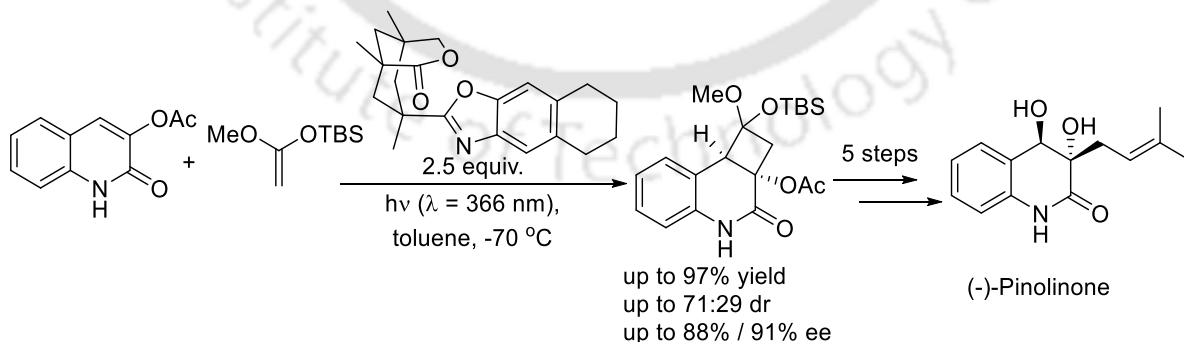
Scheme 6.1: Enantioselective cyclocarbonylation for the synthesis of dihydroquinolones

A metal catalyzed enantioselective ring expansion reaction of isatin and α -alkyl- α -diazoesters for the construction of highly functionalized 2-quinolones bearing quaternary centre at 4-position was described by Feng and coworkers. Substituted dihydroquinolones were obtained with high yields and enantioselectivities (Scheme 6.2).⁹



Scheme 6.2: Metal catalyzed ring expansion for the synthesis of 2-quinolones

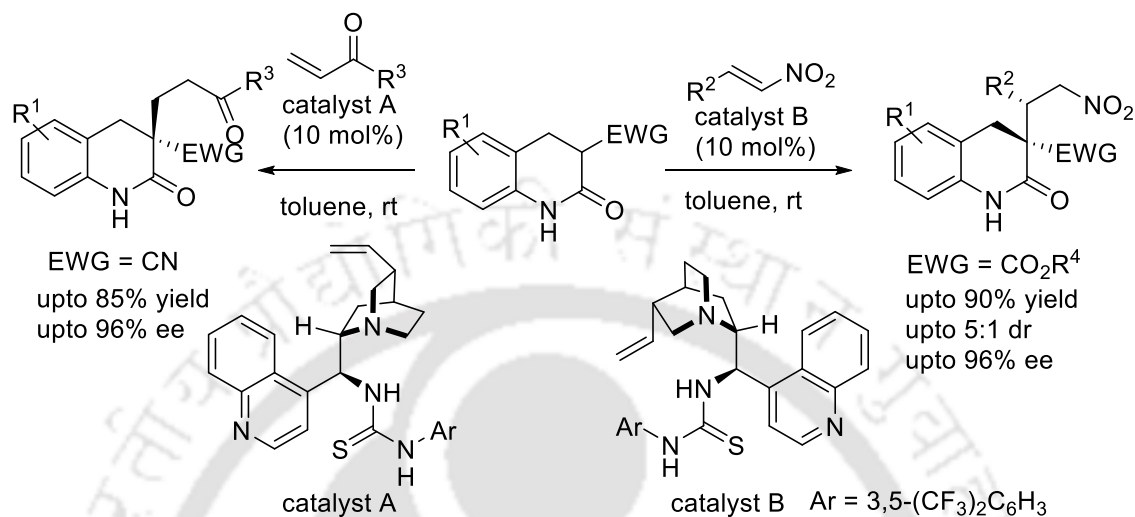
Mayr *et al.* developed an asymmetric, intermolecular [2+2] photocycloaddition of 3-acetoxyquinolone for the synthesis of natural product (-)-Pinolinone. Substituted 3,4-dihydro-2-quinolones were isolated as intermediates in good yields and enantiomeric excesses and also a total synthesis of Pinolinone was developed (Scheme 6.3).¹⁰



Scheme 6.3: Asymmetric [2+2] photocycloaddition for the synthesis of Pinolinone

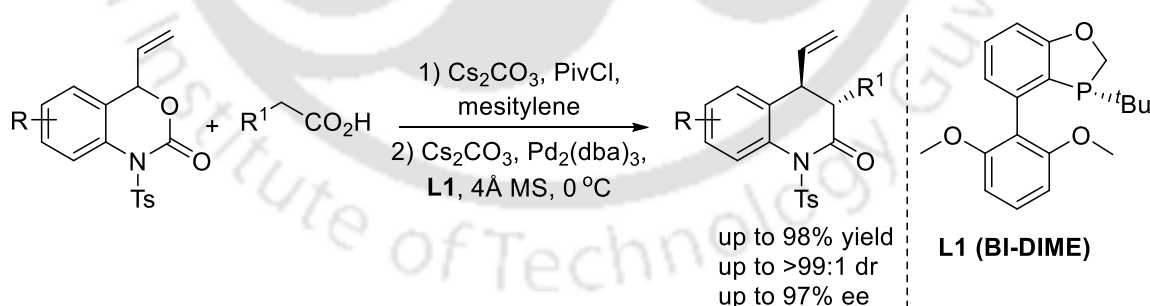
Very recently, our group has reported a direct Michael addition approach for the highly enantioselective synthesis of 3,3-disubstituted dihydroquinolones. Dihydroquinolones

were used as the active nucleophiles, vinyl ketones and nitroolefins were employed as the electrophiles. Corresponding Michael addition provided the 3,3-disubstituted dihydroquinolones with high enantiomeric excesses (Scheme 6.4).¹¹



Scheme 6.4: Thiourea catalyzed synthesis of 3,3-disubstituted dihydroquinolones

A convenient approach for the enantioselective synthesis of 3,4-dihydro-2-quinolones was disclosed by Deng group. Reaction operates through Pd-catalyzed decarboxylative [4+2]-cycloaddition of 4-vinyl benzoxazinanones with carboxylic acids. Substituted dihydroquinolones were obtained with excellent enantiomeric excesses using chiral phosphorous ligand (Scheme 6.5).⁷

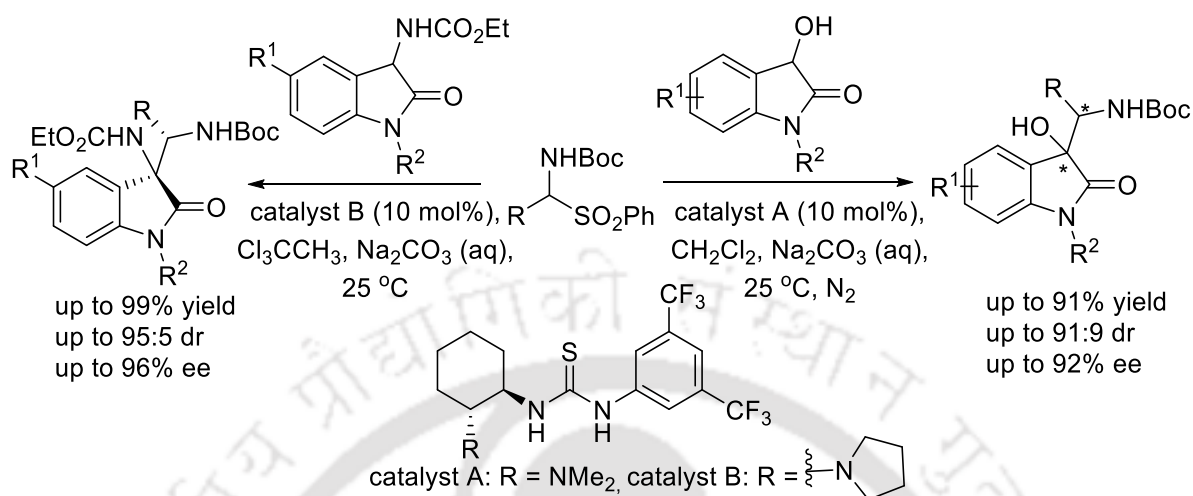


Scheme 6.5: Enantioselective decarboxylative [4+2]-cycloaddition of 3,4-dihydro-2-quinolones

6.3. Previous reports on Mannich reaction with *in situ* generated *N*-Boc imines from amidosulfones

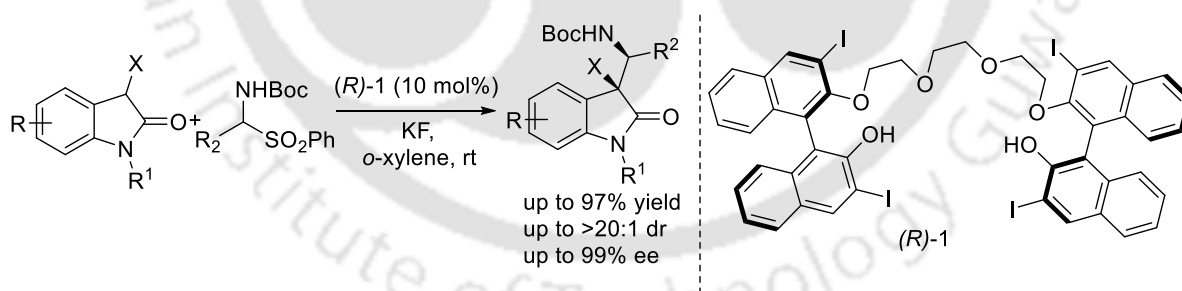
Chen group reported organocatalytic asymmetric Mannich reactions of 3-aminoxindoles and 3-hydroxyoxindoles with *in situ* generated *N*-Boc imines from amidosulfones.

Bifunctional thiourea catalysts delivered the products with good enantio and diastereoselectivities (Scheme 6.6).¹²



Scheme 6.6: Thiourea mediated asymmetric Mannich reaction with amidosulfones

An efficient technique for the synthesis of α -fluoro- β -amino-oxindoles *via* a direct Mannich reaction strategy between 3-fluoro oxindoles and in situ generated *N*-Boc imines was reported by Song and coworkers. Cation-binding catalyst was used to achieve high enantioselectivity of the product (Scheme 6.7).¹³

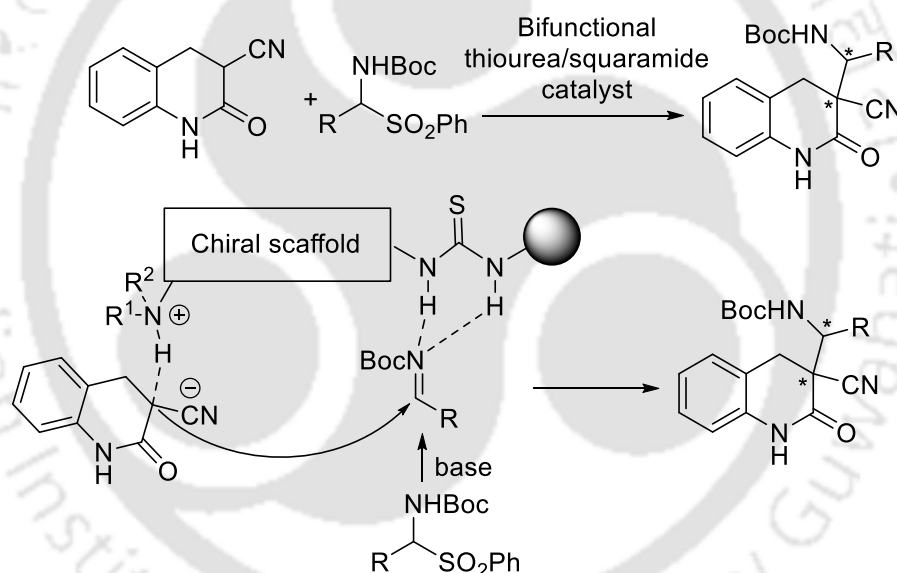


Scheme 6.7: Enantioselective Mannich reaction in presence of cation-binding catalyst

6.4. Concept:

Substituted 3,3-disubstituted 3,4-dihydroquinolin-2(1*H*)-ones are the prevalent intermediates in many natural products and pharmaceutical agents. Due to such impressive biological and medicinal activities of 3,4-dihydroquinolones, it is highly advisable to prepare different optically active 3,4-dihydroquinolin-2(1*H*)-one derivatives in an efficient

and straightforward way. Despite of significant importance, there are few reports related to the enantioselective synthesis of 3,4-dihydroquinolin-2(1H)-ones. Realizing the importance, we decided in a direct Mannich reaction approach for the synthesis of 3,3-disubstituted 3,4-dihydroquinolin-2(1H)-one. We used dihydro-3-cyano-2-quinolones and amidosulfones as the substrates. Thus amidosulfone would generate *N*-Boc imine *in situ* by treatment of a base. Then the reaction was carried out in the presence of different bifunctional thiourea and squaramide catalysts. Tertiary amine functionality of the catalyst will deprotonate 3-substituted dihydroquinolones, and thiourea functionality will activate the *in situ* generated *N*-Boc imines through H-bonding. Finally, the corresponding Mannich reaction would deliver the expected 3,3-disubstituted 3,4-dihydroquinolin-2(1H)-one derivatives (Scheme 6.8).



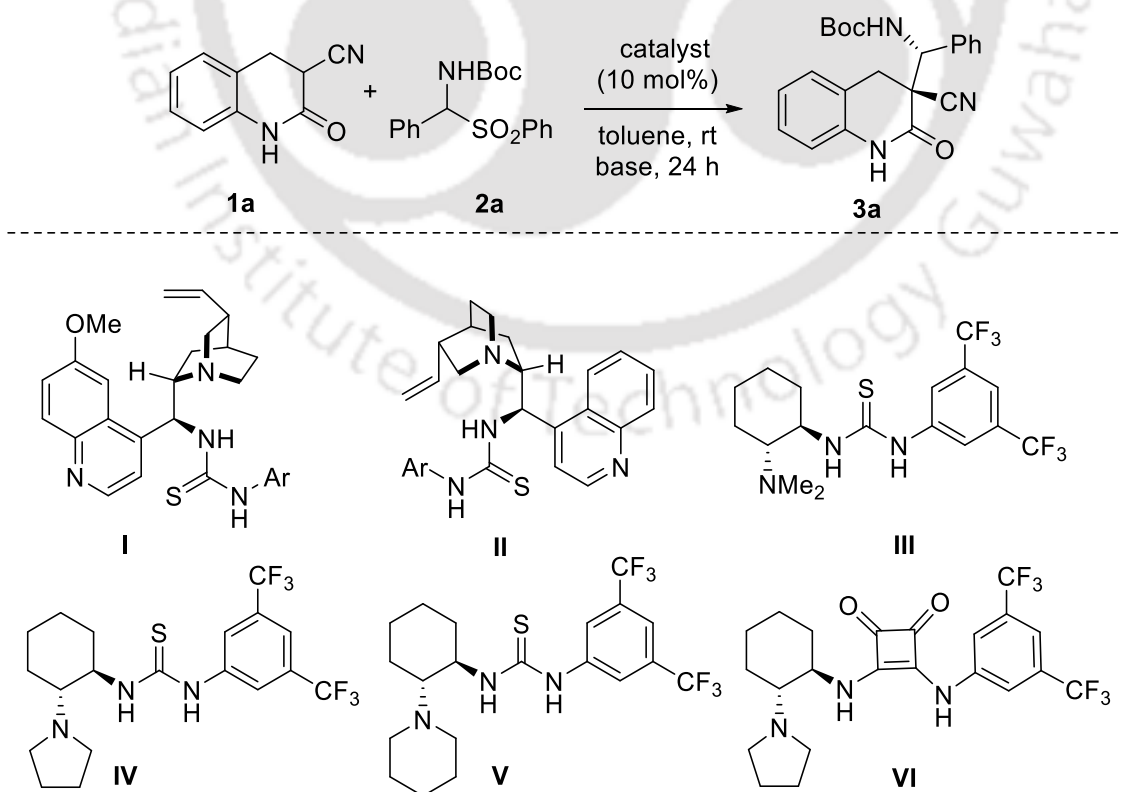
Scheme 6.8: Plausible route for asymmetric Mannich reaction

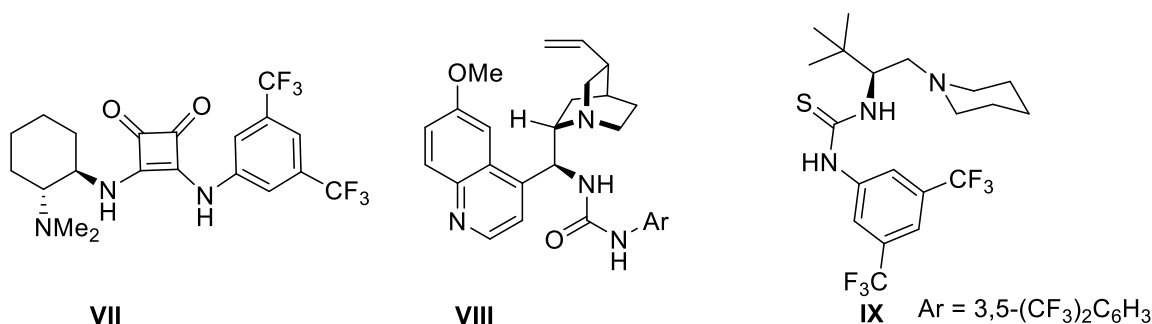
6.5. Result and discussion:

We started our optimization by performing a reaction of dihydro-3-cyano-2-quinolone **1a** with amido sulfone **2a** and sat. Na_2CO_3 solution in toluene solvent at room temperature in the presence of different bifunctional tertiary amino thiourea and squaramide catalysts (Table 1). As can be seen, quinine derived thiourea catalyst **I** provided the desired product **3a** in 60% overall yield and 3:1 diastereomeric ratio with moderate enantiomeric excess for the major diastereomer (entry 1). Diastereoselectivity of the product dropped in the

presence of cinchonine derived thiourea catalyst **II** (entry 2). Then we moved our attention to screen different cyclohexyl derived thiourea and squaramide catalysts (entries 3-7). Pleasingly, both diastereo- and enantioselectivity got enhanced with Takemoto catalyst **III** and the product **3a** was isolated in 70% yield, 3:1 diastereomeric ratio with 56% ee (entry 3). Enantioselectivity and diastereoselectivity of the product **3a** further improved to 79% and 5:1 respectively in the presence of thiourea catalyst **IV** having pyrrolidine moiety (entry 4). Catalyst **V** bearing piperidine motif provided the product with slight less enantio- and diastereoselectivity (entry 5). Then different squaramide catalysts **VI** and **VII** were engaged in the reaction (entries 6-7). Unfortunately, no improvement in the enantio and diastereoselectivity was observed. Changing the thiourea or squaramide moiety with urea motif could not improve the results (entry 8). Quinine derived urea catalyst **VIII** furnished the product with 65% yield, 3:1 dr and 50% ee (entry 8). Finally enantioselectivity got decreased further with *L*-tert-leucine derived thiourea catalyst **IX** (entry 9). Thus cyclohexyl derived thiourea catalyst **IV** having pyrrolidine moiety provided the product **3a** with maximum 72% yield, 5:1 dr and 79% enantiomeric excess for the major diastereomer.

Table 1. Catalyst screening





entry ^a	catalyst	yield (%) ^b	dr ^c	ee (%) ^d
1	I	60	3:1	36
2	II	62	1.5:1	34
3	III	70	4:1	56
4	IV	72	5:1	79
5	V	70	4:1	75
6	VI	68	4:1	77
7	VII	61	3:1	40
8	VIII	65	3:1	50
9	IX	55	3:1	30

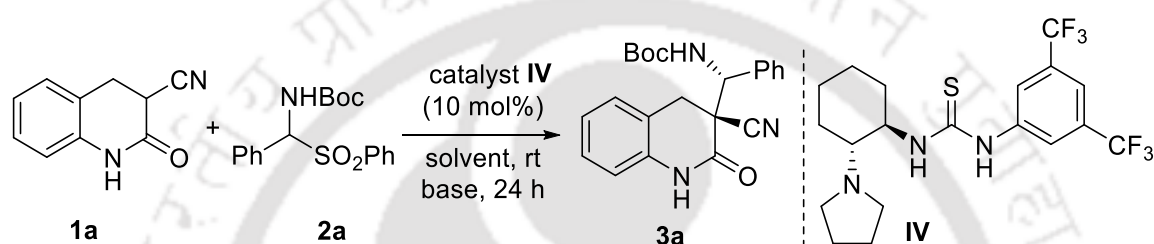
^a Reaction conditions: 0.15 mmol of **1a** with 0.23 mmol of **2a** in 2.5 mL solvent using 10 mol% catalyst and 75 μ L sat. sodium carbonate. ^b Isolated combined yield after silica gel column chromatography. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC and of the major diastereomer.

6.5.1. Solvent screening:

For the improvement of enantio- and diastereoselectivity of the product **3a**, different solvents were screened with catalyst **IV** (Table 2). In trifluorotoluene solvent, diastereoselectivity of the desired product **3a** was similar to toluene solvent but the enantioselectivity got slightly decreased (entry 2). Enantioselectivity of the product further decreased to 65% in dichloromethane solvent (entry 3). In *o*-xylene solvent

enantioselectivity got improved to 75% (entry 4) but in mesitylene solvent enantioselectivity decreased. Gratifyingly, enantioselectivity got enhanced in benzene solvent and the product **3a** was isolated in 75% yield, 5:1 dr and 98% enantiomeric excess (entry 6). Then the reaction was checked by changing the catalyst loading in benzene solvent and the product was isolated with lesser enantioselectivities (entries 7-8). Finally, the reaction was performed in the presence of different base solutions but no improvement in reaction outcome was observed (entries 9-10).

Table 2. Solvent screening



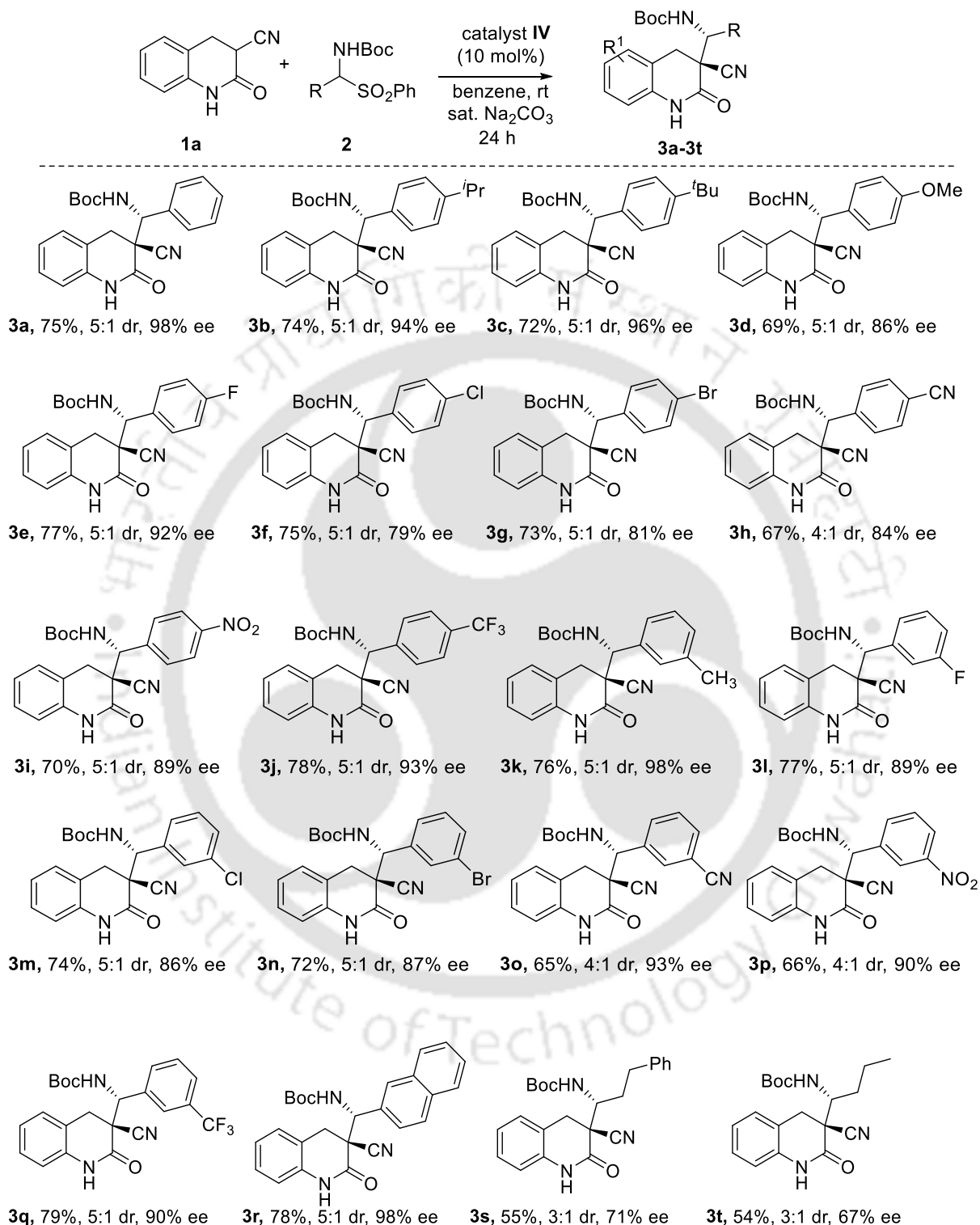
entry ^a	solvent	yield(%) ^b	dr ^c	ee(%) ^d
1	toluene	72	5:1	79
2	TFT	71	5:1	73
3	CH ₂ Cl ₂	70	5:1	65
4	<i>o</i> -xylene	70	5:1	75
5	mesitylene	68	5:1	65
6	benzene	75	5:1	98
7 ^e	benzene	73	5:1	96
8 ^f	benzene	75	5:1	97
9 ^g	benzene	74	5:1	91
10 ^h	benzene	70	5:1	85

^a Reaction conditions: 0.15 mmol of **1a** with 0.23 mmol of **2a** in 2.5 mL solvent using 10 mol% catalyst and 75 μ L sat. sodium carbonate. ^b Isolated combined yield after silica gel column chromatography. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC for the major diastereomer. ^e Reaction carried out 5 mol% catalyst.

^f Reaction carried out with 20 mol% catalyst. ^g Reaction was performed with 75 μ L sat. potassium carbonate solution. ^h Reaction was performed with 75 μ L sat. sodium bicarbonate solution.

6.5.2. Substrate scope:

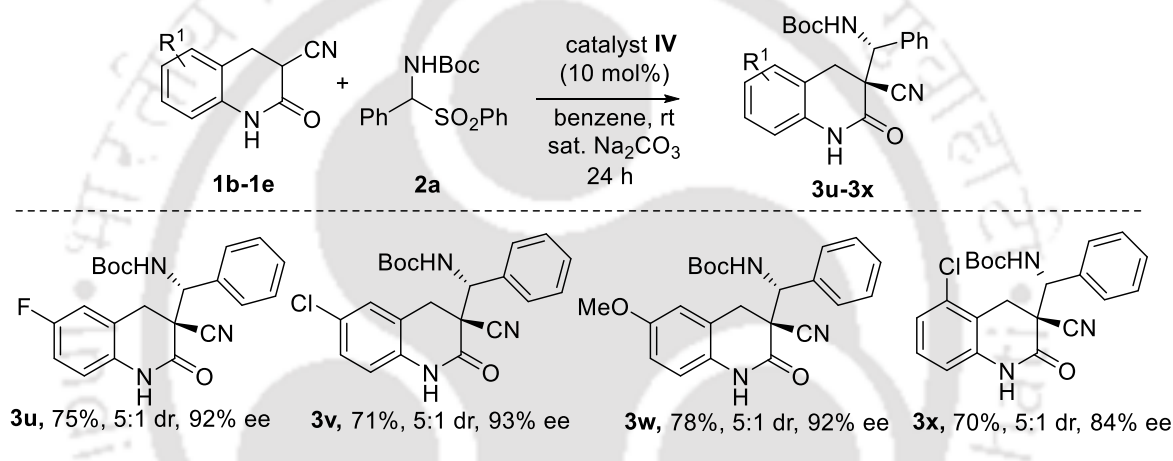
After the optimized condition got established, we turned our attention to explore the scope and generality of the reaction. At the beginning, different amidosulfones were employed in the reaction (Table 3). Pleasingly, different electron poor and electron rich aryl groups were tolerated and good to excellent results were achieved. Sulfones bearing *para*-alkyl groups **2b-2c** reacted smoothly and satisfactory results were obtained. For example, 4-ⁱPr substituted sulfone provided the product **3b** in 74% yield, 5:1 dr and 94% enantiomeric excess. The product **3c** was isolated from 4-^tBu substituted sulfone with excellent enantioselectivity. Similarly, product **3d** having 4-anisole moiety was obtained in 86% enantioselectivity. Then different 4-halo substituted amidosulfones **2e-2g** were employed in the reaction. The reaction outcome was excellent for 4-fluoro substituted sulfone **2e** but other sulfones **2f-2g** delivered the corresponding products with slight lesser enantioselectivities. Interestingly, amidosulfones **2h-2j** having different electron withdrawing groups at *para*-position participated smoothly in the reaction. Sulfones containing cyano and nitro functionalities at the *para*-position delivered products **3h-3i** respectively with good enantioselectivities, though for product **3h** diastereoselectivity dropped to 4:1. Excellent enantioselectivity was achieved for product **3j** having trifluoromethyl group at the 4-position of the phenyl ring. Then different *meta*-substituted amidosulfones **2k-2q** were tested in the reaction. Sulfones containing a range of electron donating, electron withdrawing groups at the *meta*-position of the aryl group responded well in the reaction. In particular excellent 98% ee was obtained for product **3k** having 3-methyl substitution. Different *meta*-halo substituted sulfones **2l-2n** also reacted smoothly and the products were obtained in good enantioselectivities. The reaction outcome remained unaltered for sulfones **2o-2q** containing different electron withdrawing groups at the *meta*-position. Delightfully, excellent enantioselectivity was achieved for 2-naphthyl substituted amido sulphone **2r** and the product was isolated with 98% ee. Then we moved our attention to employ aliphatic amido sulphones in our reaction. Pleasingly, the reaction progressed well to provide the desired products **3s** and **3t** with moderate enantioselectivities.

Table 3. Scope of amido sulfones in the Mannich reaction ^{a,b,c,d}

^aReaction conditions: 0.15 mmol of 1a with 0.23 mmol of 2 in 2.5 mL solvent using 10 mol% catalyst and 75 μ L sat. sodium carbonate. ^bIsolated combined yield after silica gel column chromatography. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC and of the major diastereomer.

In the next part of the investigation, the scope was further explored by engaging differently substituted dihydroquinolones in the reaction and the reaction outcome is summarized in Table 4. For example, 6-F substituted dihydroquinolone **1b** furnished product **3u** in 75% yield, 5:1 dr and 92% enantiomeric excess. Very satisfactory result was obtained for dihydroquinolone **1c** having 6-chloro substituent. Dihydroquinolone **1d** bearing 6-OMe substitution also participated in the reaction to provide high enantioselectivity of the product **3x**. Finally from 5-Cl substituted dihydroquinolone **1e**, product **3x** was isolated with a slight decrease in enantioselectivity possibly due to steric reason.

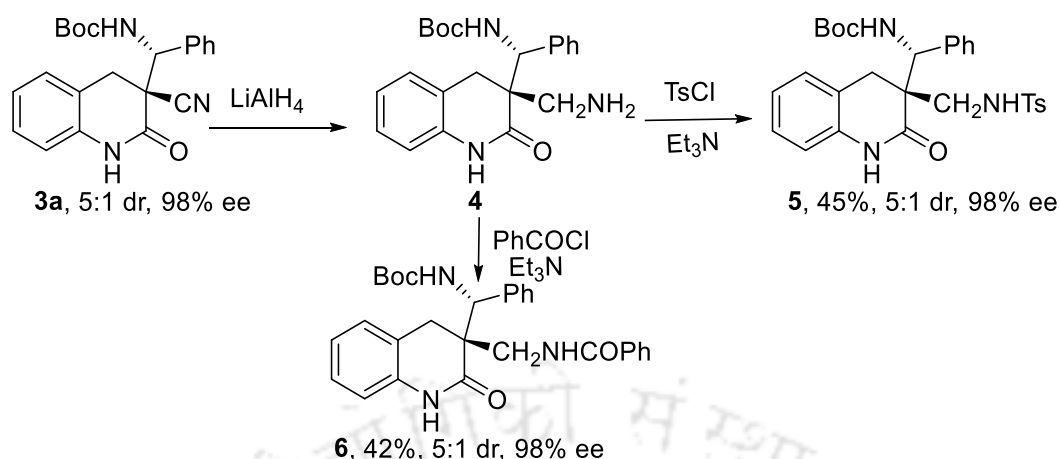
Table 4. Scope of dihydroquinolones in the Mannich reaction^{a,b,c,d}



^a Reaction conditions: 0.15 mmol of **1** with 0.23 mmol of **2a** in 2.5 mL solvent using 10 mol% catalyst and 75 μ L sat. sodium carbonate. ^b Isolated combined yield after silica gel column chromatography. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC and of the major diastereomer.

6.5.3. Synthetic transformations of **3a**:

To explore the synthetic utility of our method, a few reactions were performed. Initially reduction of **3a** with lithium aluminium hydride delivered amine **4**. Next the amine was treated with tosyl chloride and the expected protected amine **5** was obtained with retention of enantio- and diastereoselectivity. Finally benzoyl protection of the amino group provided the product **6** and the enantio- and diastereoselectivity got maintained (Scheme 6.9).



Scheme 6.9: Synthetic transformation of **3a**

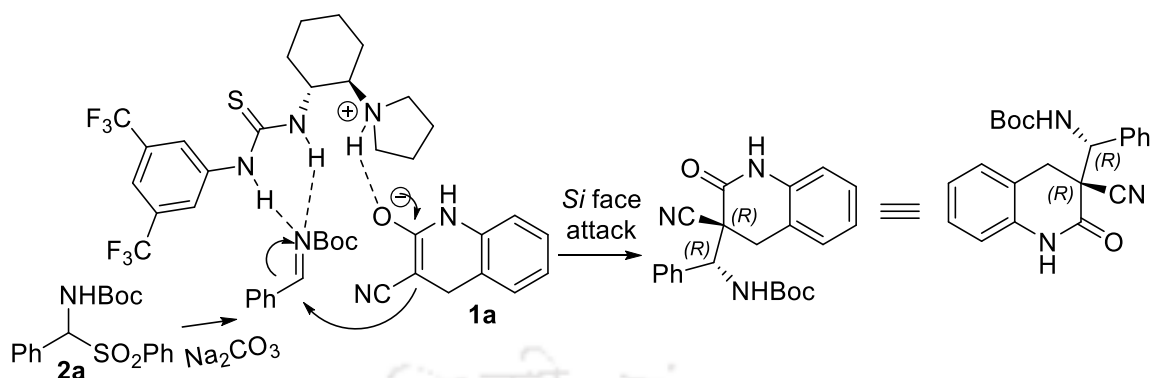
6.5.4. Absolute configuration of **3u**:

The absolute configuration of **3u** was assigned to be (*R,R*) by X-ray crystallography.¹⁴ Thus other products **3** are assumed to have same absolute structure by analogy.



6.5.5. Proposed mechanism:

Based on the absolute configuration, a plausible transition state has been drawn in Scheme 6.10. It is expected that a bifunctional mode of activation by catalyst **IV** operates here. The tertiary amino functionality of **IV** activates dihydroquinolone **1a** from *Si* face and simultaneously the *in situ* generated imine binds with the thiourea functionality of **IV** from *Re* face. Thus the *Re* face addition of enolate (**1a**) takes place on the *Si* face of the imine to provide the desired product **3a** (Scheme 6.10).



Scheme 6.10: Proposed mechanism

6.6. Conclusion:

In conclusion, this report delineates an asymmetric synthesis of 3,3-disubstituted-3,4-dihydro-2-quinolones *via* Mannich reaction approach. Substituted dihydroquinolones bearing carbamate functionalities were obtained in good yields with good to high enantioselectivities. Few synthetic transformations have been performed to augment the synthetic potential of our methodology. The mild reaction conditions, operational simplicity and broad scope are the attractive points for this methodology to be applied in the synthesis of biologically important quinolones.

6.7. Experimental section:

General information:

All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All reactions were carried out in oven dried glassware with magnetic stirring. Dichloromethane was distilled over CaH_2 under argon and stored over 4Å molecular sieves. All other solvents and reagents were purified according to standard procedures. Organic solvents were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Reactions were monitored by TLC on silica gel GF-254 using a combination of hexane and ethyl acetate as eluents. For column chromatography silica gel (60-120 mesh size) was used.

^1H NMR spectra were recorded on a 400 MHz, 500 MHz and 600 MHz spectrometer at 295 K in CDCl_3 ; chemical shift values (δ , ppm) were reported in the standard fashion with

reference to either tetramethylsilane (TMS) ($\delta(\text{H})$ 0.00 ppm) or CHCl_3 ($\delta(\text{H})$ 7.26 ppm). ^{13}C NMR spectra were recorded on a 100 MHz, 125 MHz and 150 MHz spectrometer at 298 K in CDCl_3 ; chemical shifts (δ , ppm) were reported relative to CHCl_3 ($\delta(\text{C})$ 77.23 ppm, central line of triplet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplets), dd (doublet of doublets), dt (doublet of triplets), and br (broad). Coupling constants (J) were recorded in Hertz (Hz).

Enantiomeric excesses were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic compounds. High resolution mass spectra (HRMS) were recorded in Q-TOF using electron spray ionization (ESI) technique. IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet and grinding the sample with KBr (IR Grade). Melting points were measured with a Mel-Tem capillary melting point apparatus.

Single crystal X-ray data were collected using Bruker SMART APEXII CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo- $K\alpha$ irradiation ($\lambda = 0.71073 \text{ \AA}$) at 298(2) K and the structure was solved by direct methods using SHELXS-2014 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-2014.

A. General procedure for the synthesis of dihydroquinolones 1a-1e:

Dihydroquinolones were prepared following literature procedures.¹⁵

B. General procedure for the synthesis of amido sulfones 2a-2x:

Amido sulfones were prepared according to the reported procedure.¹⁶

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

Thiourea and squaramide catalysts (I-IX) were prepared according to the reported procedure.¹⁷

D. General procedure for the synthesis of chiral dihydroquinolones:

Under argon atmosphere, dihydro-3-cyano-2-quinolone **1** (0.15 mmol), amidosulfone **2** (0.23 mmol) and catalyst **V** (10 mol%) were placed in a round bottom flask, benzene (2.5

mL) and 75 μ L saturated Na_2CO_3 solution were added to it. Then the reaction mixture was stirred at room temperature under argon atmosphere. After the reaction was completed as monitored by TLC, the reaction mixture was filtered through a sinter funnel and the filtrate was evaporated. The crude reaction mixture was subjected to column chromatography on silica gel (100-200 mesh) and (230-400 mesh) using 15-20% ethyl acetate in hexane to afford the corresponding products with separation of diastereomers.

E. General procedure for the synthesis of compound 5:

Under argon atmosphere, **3a** (0.15 mmol) in Et_2O (1.5 mL) was added to a suspension solution of LiAlH_4 (0.9 mmol) in 1 mL Et_2O at 0 $^\circ\text{C}$. The mixture was allowed to warm at ambient temperature and was stirred for 4 h. Next water (20 μ L), 15% aqueous NaOH (20 μ L) and water (60 μ L) were sequentially added dropwise at 0 $^\circ\text{C}$. The mixture was allowed to stir at room temperature for 15 min. Then the reaction mixture was filtered through a celite pad and washed with diethyl ether. The filtrate was concentrated *in vacuo* and the corresponding amine was used for the next step without further purification.

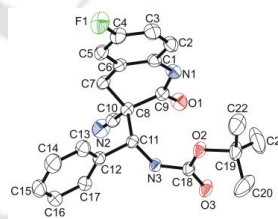
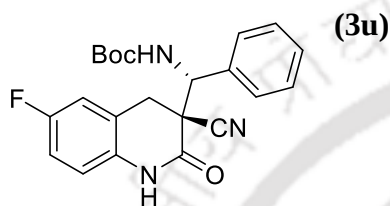
To a round-bottom flask were added sequentially amine (0.1 mmol), CH_2Cl_2 (3 mL), Et_3N (0.1 mmol) and TsCl (0.1 mmol), and the reaction was stirred for 24 h at room temperature. Then the mixture was poured into water (2 mL) and the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer was dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography using 30% ethyl acetate in hexane.

F. General procedure for the synthesis of compound 6:

Under argon atmosphere, **3a** (0.15 mmol) in Et_2O (1.5 mL) was added to a suspension solution of LiAlH_4 (0.9 mmol) in 1 mL Et_2O at 0 $^\circ\text{C}$. The mixture was allowed to warm at ambient temperature and stirred for 4 h. Next water (20 μ L), 15% aqueous NaOH (20 μ L) and water (60 μ L) were sequentially added dropwise at 0 $^\circ\text{C}$. The mixture was allowed to stir at room temperature for 15 min. Then the reaction mixture was filtered through a celite pad and washed with diethyl ether. The filtrate was concentrated *in vacuo* and the corresponding amine was used for the next step without further purification.

To a round-bottom flask were added sequentially amine (0.1 mmol), CH₂Cl₂ (3 mL), Et₃N (0.1 mmol) and PhCOCl (0.1 mmol). The reaction was stirred for 24 h at room temperature. Then the mixture was poured into water (2 mL) and the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ twice. The combined organic layer was dried over Na₂SO₄ and evaporated. The crude product was purified by column chromatography using 30% ethyl acetate in hexane.

Crystal data and structure refinement for chiral compound (CCDC No. 1831432)



Empirical formula	C ₂₂ H ₂₂ FN ₃ O ₃
Formula weight	395.4
CCDC Number	1831432
Crystal habit, colour	Needle, White
Crystal size, mm ³	0.18 × 0.12 × 0.08
Temperature, T	293(2)
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	P2(1)/c
Unit cell dimensions	<i>a</i> = 11.8968(11)Å <i>b</i> = 18.4254(17)Å <i>c</i> = 10.7033(8)Å <i>α</i> = 90.00°, <i>β</i> = 103.556(8)° <i>γ</i> = 90.00°
Volume, <i>V</i> (Å ³)	2280.8(3)
<i>Z</i>	4
Calculated density, Mg·m ⁻³	1.242
Absorption coefficient, <i>μ</i> (mm ⁻¹)	0.091
<i>F</i> (000)	900.0
<i>θ</i> range for data collection	2.95 to 25°

CHAPTER 6

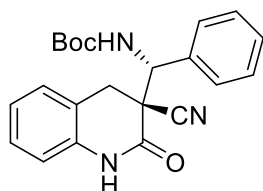
Limiting indices	$-14 \leq h \leq 10, -14 \leq k \leq 21, -11 \leq l \leq 12$
Reflection collected/unique	8912/ 4015 [$R(\text{int})=0.0329$]
Completeness to θ	99.81% ($\theta = 25.00^\circ$)
Max. and min. transmission	0.993/0.987
Refinement method	'SHELXL-97(Sheldrick, 1997)'
Data/restraints/parameters	4015/0/285
Goodness-of-fit on F^2	1.051
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0567, wR_2 = 0.1208$
R indices (all data)	$R_1 = 0.0982, wR_2 = 0.1468$
Largest diff. peak and hole	0.44 and $-0.21 \text{ e} \cdot \text{\AA}^{-3}$

6.8. References:

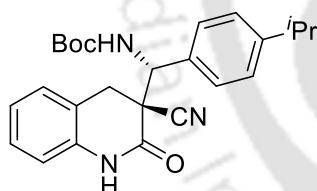
- (1) For selected examples, see: (a) Tominaga, M.; Tone, H.; Nakagawa, K.; Takada, K.; Hoshino, Y.; Watanabe, K. *Chem. Pharm. Bull.* **1981**, *29*, 2166. (b) Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. *Chem. Pharm. Bull.* **1983**, *31*, 798. (c) Hayashi, H.; Miwa, Y.; Miki, I.; Ichikawa, S.; Yoda, N.; Ishii, A.; Kono, M.; Suzuki, F. *J. Med. Chem.* **1992**, *35*, 4893. (d) Ito, C.; Itoigawa, M.; Otsuka, T.; Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2000**, *63*, 1344. (e) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Vitanen, S.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1943. (f) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Omura, S. *Org. Lett.* **2005**, *7*, 5701. (g) Chen, M.; Shao, C.-L.; Meng, H.; She, Z.-G.; Wang, C.-Y. *J. Nat. Prod.* **2014**, *77*, 2720. (h) Flick, A. C.; Ding, H. X.; Leverett, C. A.; Kyne, R. E.; Liu, K. K.-C.; Fink, S. J.; O'Donnell, C. J. *J. Med. Chem.* **2017**, *60*, 6480.
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6.9: Characterization Data of Products:

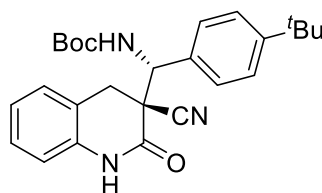
Tert-butyl((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate (3a)

This compound was prepared according to the general procedure D. White sticky solid (42.4 mg, yield: 75%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.43 (s, 1H), 7.45 – 7.35 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 6.3 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 5.64 (d, *J* = 9.0 Hz, 1H), 4.94 (d, *J* = 7.4 Hz, 1H), 3.35 (d, *J* = 16.1 Hz, 1H), 2.72 (d, *J* = 16.1 Hz, 1H), 1.35 (s, 9H); **¹³C NMR(125 MHz, CDCl₃):** δ 164.4, 154.9, 136.0, 135.7, 129.4, 129.3, 129.1, 128.9, 127.7, 124.6, 118.3, 117.5, 116.4, 80.8, 54.8, 51.0, 33.8, 28.3; **FT-IR (thin film):** 1719, 1693, 1599, 1493, 1367, 1243, 1164, 1044 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₄N₃O₃ [M+H]⁺ 378.1812; found 378.1817; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.5 min, τ_{major} = 24.0 min); Enantiomeric excess: 98%.

Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-isopropylphenyl)methyl)carbamate (3b)

This compound was prepared according to the general procedure D. White sticky solid (46.5 mg, yield: 74%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.67 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.63 (d, *J* = 8.8 Hz, 1H), 4.96 (d, *J* = 8.4 Hz, 1H), 3.37 (d, *J* = 16.1 Hz, 1H), 2.95 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.78 (d, *J* = 16.1 Hz, 1H), 1.36 (s, 9H), 1.28 (d, *J* = 6.8 Hz, 6H); **¹³C NMR (100 MHz, CDCl₃):** δ 164.6, 154.9, 150.1, 136.1, 133.0, 129.2, 128.9, 127.7, 127.1, 124.5, 118.4, 116.4, 80.6, 54.6, 51.3, 34.0, 33.8, 28.3, 24.1, 24.0; **FT-IR (thin film):** 1699, 1598, 1495, 1457, 1368, 1252, 1162, 1103, 832 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₃₀N₃O₃ [M+H]⁺ 420.2282; found 420.2280; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 7.1 min, τ_{major} = 18.4 min); Enantiomeric excess: 94%.

Tert-butyl ((R)-(4-(tert-butyl)phenyl)((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)methyl)carbamate (3c)

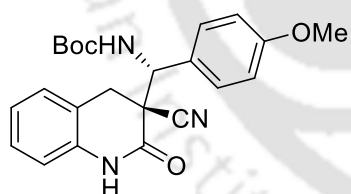


This compound was prepared according to the general procedure D. White sticky solid (46.8 mg, yield: 72%);

Diastereomeric ratio: 5:1; **¹H NMR (600 MHz, CDCl₃)** δ 8.51 (s, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.31 (t, J = 7.7 Hz, 1H),

7.19 (d, J = 8.2 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.97 (d, J = 7.9 Hz, 1H), 5.62 (d, J = 8.7 Hz, 1H), 4.95 (d, J = 8.3 Hz, 1H), 3.35 (d, J = 16.1 Hz, 1H), 2.76 (d, J = 16.2 Hz, 1H), 1.36 (s, 9H), 1.33 (s, 9H); **¹³C NMR (150 MHz, CDCl₃)**: δ 164.4, 155.0, 152.4, 136.1, 132.6, 129.2, 128.9, 127.4, 126.0, 124.5, 118.5, 117.7, 116.3, 80.7, 54.5, 51.3, 34.9, 33.9, 31.5, 28.4; **FT-IR (thin film)**: 1700, 1598, 1495, 1388, 1253, 1161, 1106, 1042 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₆H₃₂N₃O₃ [M+H]⁺ 434.2438; found 434.2435; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 6.7 min, τ_{major} = 12.4 min); Enantiomeric excess: 96%.

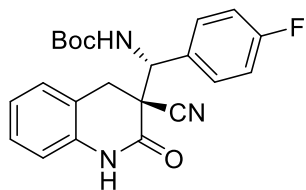
Tert-butyl((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-methoxyphenyl)methyl)carbamate (3d)



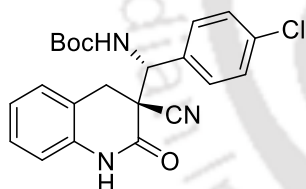
This compound was prepared according to the general procedure D. White sticky solid (42.1 mg, yield: 69%);

Diastereomeric ratio: 5:1; **¹H NMR (600 MHz, CDCl₃)**: δ 7.31 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 7.11 (t, J =

7.4 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.91 (t, J = 7.1 Hz, 3H), 5.55 (d, J = 8.6 Hz, 1H), 4.88 (d, J = 8.3 Hz, 1H), 3.83 (s, 3H), 3.35 (d, J = 16.1 Hz, 1H), 2.73 (d, J = 16.2 Hz, 1H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃)**: δ 164.1, 160.3, 154.9, 135.9, 129.3, 128.9, 128.9, 127.8, 124.6, 118.4, 117.6, 116.1, 114.4, 80.7, 55.6, 54.3, 51.3, 33.8, 28.4; **FT-IR (thin film)**: 1697, 1600, 1511, 1369, 1250, 1168, 1026, 833 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₃H₂₆N₃O₄ [M+H]⁺ 408.1918; found 408.1921; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 11.0 min, τ_{major} = 17.6 min); Enantiomeric excess: 86%.

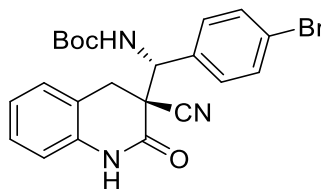
Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-fluorophenyl)methyl)carbamate (3e)

This compound was prepared according to the general procedure D. White sticky solid (45.6 mg, yield: 77%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.43 (s, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 5.67 (d, *J* = 8.1 Hz, 1H), 4.93 (d, *J* = 7.6 Hz, 1H), 3.39 (d, *J* = 16.2 Hz, 1H), 2.73 (d, *J* = 16.2 Hz, 1H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 164.1 (d, *J* = 16.5), 162.4, 154.9, 135.9, 131.8, 129.6 (d, *J* = 9), 129.4, 128.8, 124.8, 118.2, 117.3, 116.4, 116.1 (d, *J* = 21), 80.9, 54.3, 50.9, 33.8, 28.3; **FT-IR (thin film):** 1719, 1695, 1601, 1497, 1368, 1247, 1228, 1156, 1047, 762 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃FN₃O₃ [M+H]⁺ 396.1718; found 396.1722; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 9.3 min, τ_{major} = 14.5 min); Enantiomeric excess: 92%.

Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-chlorophenyl)methyl)carbamate(3f)

This compound was prepared according to the general procedure D. White sticky solid (46.3 mg, yield: 75%); **Diastereomeric ratio:** 5:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.23 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.66 (d, *J* = 8.4 Hz, 1H), 4.89 (d, *J* = 8.4 Hz, 1H), 3.37 (d, *J* = 16.2 Hz, 1H), 2.73 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 163.7, 154.6, 135.6, 135.2, 134.2, 129.2, 129.1, 128.9, 128.7, 124.6, 118.0, 116.9, 116.1, 80.8, 54.2, 50.5, 33.6, 28.2; **FT-IR (thin film):** 1692, 1598, 1494, 1376, 1329, 1160, 1111, 1012, 754 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃ClN₃O₃ [M+H]⁺ 412.1422; found 412.1422; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 9.4 min, τ_{major} = 16.2 min); Enantiomeric excess: 79%.

Tert-butyl ((R)-(4-bromophenyl)((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)methyl)carbamate (3g)

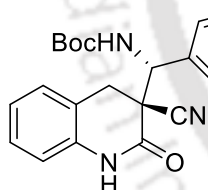


This compound was prepared according to the general procedure D. White sticky solid (49.9 mg, yield: 73%);

Diastereomeric ratio: 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.35 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 1H),

7.14 (dd, *J* = 14.0, 7.9 Hz, 3H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 5.65 (d, *J* = 8.1 Hz, 1H), 4.88 (d, *J* = 7.4 Hz, 1H), 3.37 (d, *J* = 16.2 Hz, 1H), 2.72 (d, *J* = 16.3 Hz, 1H), 1.35 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 164.1, 154.9, 135.8, 134.9, 132.2, 129.5, 129.4, 128.8, 124.8, 123.6, 118.2, 117.1, 116.4, 81.0, 54.4, 50.7, 33.8, 28.3; **FT-IR (thin film):** 1693, 1598, 1565, 1489, 1368, 1247, 1165, 1074, 792 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃BrN₃O₃ [M+H]⁺ 456.0917; found 456.0908; The enantiomeric ratio was determined by HPLC analysis using Daicel ChiralpakIA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.0 min, τ_{major} = 17.0 min); Enantiomeric excess: 81%.

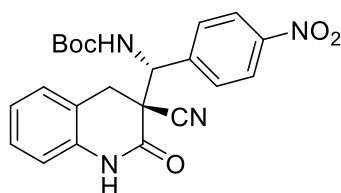
Tert-butyl((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-cyanophenyl)methyl)carbamate (3h)



This compound was prepared according to the general procedure D. White sticky solid (40.4 mg, yield: 67%);

Diastereomeric ratio: 4:1; **¹H NMR (600 MHz, CDCl₃):** δ 7.91 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 2H),

7.36 (t, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 4.94 (d, *J* = 7.4 Hz, 1H), 3.41 (d, *J* = 16.3 Hz, 1H), 2.72 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 163.3, 154.8, 141.1, 135.6, 132.8, 129.7, 128.8, 128.7, 125.1, 118.4, 118.0, 116.7, 116.4, 113.4, 81.4, 54.7, 50.2, 33.8, 28.3; **FT-IR (thin film):** 1697, 1598, 1494, 1370, 1250, 1163, 1019, 836 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₂₂N₄NaO₄ [M+Na]⁺ 425.1584; found 425.1594; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.6 min, τ_{major} = 26.0 min); Enantiomeric excess: 84%.

Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-nitrophenyl)methyl)carbamate (3i)

This compound was prepared according to the general procedure D. White sticky solid (44.3 mg, yield: 70%);

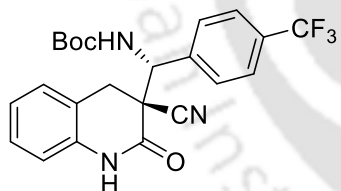
Diastereomeric ratio: 5:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.47 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.7 Hz,

2H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.09 (s, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 5.87 (d, *J* = 4.0 Hz, 1H), 5.01 (d, *J* = 7.9 Hz, 1H), 3.42 (d, *J* = 16.3 Hz, 1H), 2.75 (d, *J* = 16.4 Hz, 1H), 1.35 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 163.6, 154.8, 148.5, 143.1,

135.6, 129.7, 129.0, 128.8, 125.2, 124.2, 118.1, 116.6, 116.5, 81.4, 54.6, 50.1, 33.8, 28.3;

FT-IR (thin film): 1696, 1599, 1525, 1493, 1348, 1248, 1163, 1108, 852, 757 cm⁻¹;

HRMS (+ESI): Calc for C₂₂H₂₃N₄O₅ [M+H]⁺ 423.1663; found 423.1662; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.8 min, τ_{major} = 23.8 min); Enantiomeric excess: 89%.

Tert-butyl((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(4-(trifluoromethyl)phenyl)methyl)carbamate (3j)

This compound was prepared according to the general procedure D. White sticky solid (52.1 mg, yield:

78%); **Diastereomeric ratio:** 5:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.25 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* =

8.1 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 5.75 (d, *J* = 4.5 Hz, 1H), 4.98 (d, *J* = 7.8 Hz, 1H), 3.40 (d, *J* = 16.3 Hz, 1H), 2.73 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 10H); **¹³C NMR (100 MHz, CDCl₃):** δ

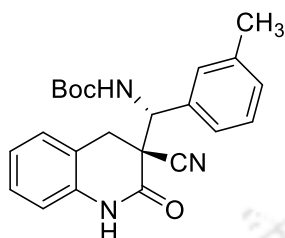
163.8, 154.8, 139.9, 135.7, 131.8, 129.6, 128.9 (q, *J*_{C-F} = 251.2 Hz), 128.8, 128.3, 126.9, 126.0 (q, *J*_{C-F} = 10.5 Hz), 125.0, 118.2, 116.9, 116.4, 81.2, 54.6, 50.5, 33.8, 28.4; **FT-IR**

(thin film): 1692, 1640, 1494, 1425, 1372, 1325, 1248, 1167, 1127, 1069, 845 cm⁻¹;

HRMS (+ESI): Calc for C₂₃H₂₃F₃N₃O₃ [M+H]⁺ 446.1686; found 446.1689; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column

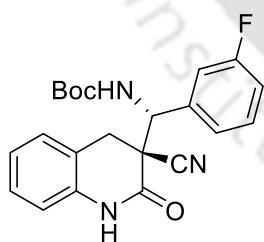
(85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 7.9$ min, $\tau_{\text{major}} = 12.4$ min); Enantiomeric excess: 93%.

Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(*m*-tolyl)methyl)carbamate (3k)



This compound was prepared according to the general procedure D. White sticky solid (44.6 mg, yield: 76%); **Diastereomeric ratio:** 5:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.10 (s, 1H), 7.30 (dd, $J = 15.2, 7.7$ Hz, 2H), 7.20 (d, $J = 7.6$ Hz, 1H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.04 (s, 2H), 7.02 – 6.96 (m, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 5.58 (d, $J = 9.1$ Hz, 1H), 4.90 (d, $J = 8.7$ Hz, 1H), 3.35 (d, $J = 16.1$ Hz, 1H), 2.72 (d, $J = 16.1$ Hz, 1H), 2.36 (s, 3H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 164.4, 154.9, 138.8, 136.0, 135.6, 130.2, 129.3, 129.0, 128.9, 128.4, 124.8, 124.5, 118.4, 117.5, 116.3, 80.7, 54.8, 51.1, 33.9, 28.4, 21.7; **FT-IR (thin film):** 1724, 1690, 1598, 1495, 1372, 1328, 1245, 1161, 1047, 863, 757 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₂₆N₃O₃ [M+H]⁺ 392.1963; found 392.1962; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 10.4$ min, $\tau_{\text{major}} = 18.7$ min); Enantiomeric excess: 98%.

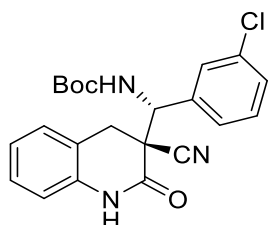
Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(3-fluorophenyl)methyl)carbamate (3l)



White sticky solid (45.6 mg, yield: 77%); **Diastereomeric ratio:** 5:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.18 (s, 1H), 7.36 (dt, $J = 15.1, 7.8$ Hz, 2H), 7.14 (t, $J = 7.6$ Hz, 1H), 7.12 – 7.03 (m, 3H), 6.99 (d, $J = 9.5$ Hz, 1H), 6.94 (d, $J = 7.8$ Hz, 1H), 5.66 (d, $J = 8.5$ Hz, 1H), 4.91 (d, $J = 8.2$ Hz, 1H), 3.38 (d, $J = 16.2$ Hz, 1H), 2.76 (d, $J = 16.3$ Hz, 1H), 1.37 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 164.0 (d, $J = 46.5$), 161.7, 154.9, 135.8, 130.7 (d, $J = 12$), 129.5, 128.9, 124.9, 123.5, 123.5, 118.3, 116.6, 116.3, 115.0 (d, $J = 33$), 81.1, 54.5, 50.7, 33.8, 28.4; **FT-IR (thin film):** 1692, 1595, 1491, 1452, 1369, 1246, 1163, 1015, 757 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃FN₃O₃ [M+H]⁺ 396.1718; found 396.1718; The enantiomeric ratio was determined by HPLC analysis using Daicel

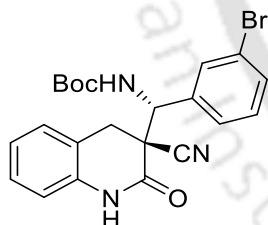
Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{major}} = 11.3$ min, $\tau_{\text{minor}} = 13.7$ min); Enantiomeric excess: 89%.

Tert-butyl ((R)-(3-chlorophenyl))((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)methyl)carbamate (3m)



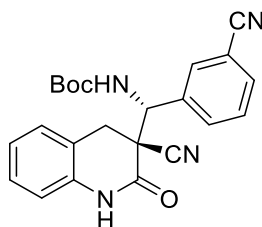
This compound was prepared according to the general procedure D. White sticky solid (45.7 mg, yield: 74%); **Diastereomeric ratio:** 5:1; **^1H NMR (400 MHz, CDCl_3):** δ 8.54 (s, 1H), 7.39 – 7.30 (m, 3H), 7.22 (d, $J = 7.2$ Hz, 2H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 7.4$ Hz, 1H), 6.97 (d, $J = 7.9$ Hz, 1H), 5.70 (d, $J = 7.7$ Hz, 1H), 4.90 (d, $J = 8.2$ Hz, 1H), 3.38 (d, $J = 16.2$ Hz, 1H), 2.75 (d, $J = 16.3$ Hz, 1H), 1.36 (s, 9H); **^{13}C NMR (100 MHz, CDCl_3):** δ 164.1, 154.8, 137.9, 135.8, 134.9, 130.4, 129.6, 129.5, 128.9, 128.2, 125.8, 124.9, 118.2, 117.0, 116.5, 81.1, 54.6, 50.6, 33.9, 28.4; **FT-IR (thin film):** 1694, 1598, 1493, 1433, 1369, 1247, 1165, 1016, 757 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{22}\text{H}_{23}\text{ClN}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 412.1422; found 412.1428; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 8.0$ min, $\tau_{\text{major}} = 15.2$ min); Enantiomeric excess: 87%.

Tert-butyl ((R)-(3-bromophenyl))((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)methyl)carbamate (3n)



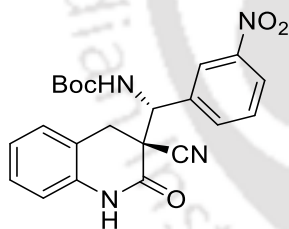
This compound was prepared according to the general procedure D. White sticky solid (49.2 mg, yield: 72%); **Diastereomeric ratio:** 5:1; **^1H NMR (400 MHz, CDCl_3):** δ 8.21 (s, 1H), 7.53 (d, $J = 7.0$ Hz, 1H), 7.33 (d, $J = 11.5$ Hz, 2H), 7.28 (d, $J = 7.3$ Hz, 2H), 7.16 (t, $J = 7.4$ Hz, 1H), 7.06 (d, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 7.8$ Hz, 1H), 5.65 (d, $J = 8.5$ Hz, 1H), 4.88 (d, $J = 8.2$ Hz, 1H), 3.38 (d, $J = 16.2$ Hz, 1H), 2.74 (d, $J = 16.3$ Hz, 1H), 1.37 (s, 9H); **^{13}C NMR (100 MHz, CDCl_3):** δ 163.9, 154.8, 138.1, 135.8, 132.5, 131.2, 130.7, 129.5, 128.9, 126.1, 124.9, 123.0, 118.2, 117.0, 116.4, 81.1, 54.5, 50.7, 33.9, 28.4; **FT-IR (thin film):** 1692, 1643, 1492, 1369, 1246, 1164, 1015, 756 cm^{-1} ; **HRMS (+ESI):** Calc for $\text{C}_{22}\text{H}_{23}\text{BrN}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 456.0917; found 456.0916; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, $\tau_{\text{minor}} = 8.1$ min, $\tau_{\text{major}} = 15.8$ min); Enantiomeric excess: 87%.

Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(3-cyanophenyl)methyl)carbamate (3o)

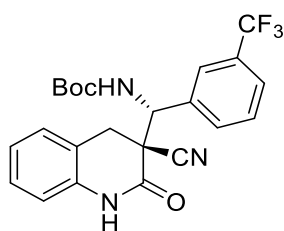


This compound was prepared according to the general procedure D. White sticky solid (39.2 mg, yield: 65%); **Diastereomeric ratio:** 4:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.42 (s, 1H), 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.62 (d, *J* = 6.9 Hz, 1H), 7.59 – 7.47 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.79 (d, *J* = 6.4 Hz, 1H), 4.95 (d, *J* = 7.5 Hz, 1H), 3.42 (d, *J* = 16.3 Hz, 1H), 2.74 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 163.7, 154.8, 137.8, 135.6, 133.0, 132.1, 131.6, 130.0, 129.7, 128.7, 125.3, 118.3, 118.1, 116.7, 116.5, 113.2, 81.4, 54.5, 50.2, 33.9, 28.3; **FT-IR (thin film):** 1739, 1693, 1600, 1490, 1390, 1243, 1160, 1045, 758 cm⁻¹; **HRMS (+ESI):** Calc for C₂₃H₂₂N₄NaO₄ [M+H]⁺ 403.1765; found 403.1781; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 12.4 min, τ_{minor} = 19.0 min); Enantiomeric excess: 93%.

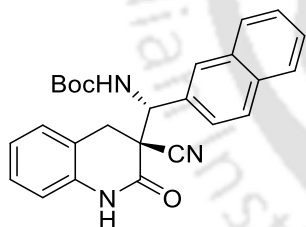
Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(3-nitrophenyl)methyl)carbamate (3p)



This compound was prepared according to the general procedure D. White sticky solid (41.8 mg, yield: 66%); **Diastereomeric ratio:** 4:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.43 (s, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.12 (s, 1H), 7.76 (d, *J* = 6.2 Hz, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.89 (s, 1H), 5.04 (d, *J* = 7.9 Hz, 1H), 3.43 (d, *J* = 16.3 Hz, 1H), 2.79 (d, *J* = 16.2 Hz, 1H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 163.7, 154.9, 148.3, 138.2, 135.5, 133.5, 130.3, 129.7, 128.9, 125.3, 124.3, 123.3, 118.1, 116.6, 81.4, 54.6, 50.2, 33.9, 28.3; **FT-IR (thin film):** 1757, 1715, 1532, 1351, 1250, 1166, 1053, 875 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃N₄O₅ [M+H]⁺ 423.1662; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 13.1 min, τ_{major} = 20.6 min); Enantiomeric excess: 90%.

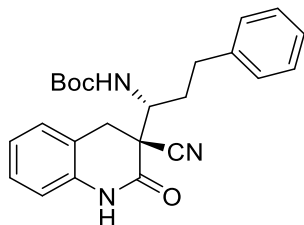
Tert-butyl ((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(3-(trifluoromethyl)phenyl)methyl)carbamate (3q)

This compound was prepared according to the general procedure D. White sticky solid (52.7 mg, yield: 79%); **Diastereomeric ratio**: 5:1; **¹H NMR (400 MHz, CDCl₃)**: δ 8.24 (s, 1H), 7.64 (dd, *J* = 36.2, 6.0 Hz, 3H), 7.38 (dd, *J* = 17.1, 9.5 Hz, 2H), 7.24 – 7.12 (m, 1H), 7.06 (s, 1H), 7.02 – 6.90 (m, 1H), 5.75 (d, *J* = 7.5 Hz, 1H), 5.00 (d, *J* = 2.8 Hz, 1H), 3.41 (d, *J* = 16.2 Hz, 1H), 2.69 (d, *J* = 16.5 Hz, 1H), 1.38 (s, 9H); **¹³C NMR (150 MHz, CDCl₃)**: δ 163.8, 154.9, 136.9, 135.8, 131.3, 131.1, 130.7, 129.8, 129.6, 128.9, 126.2 (q, *J*_{C-F} = 6 Hz), 125.7 (q, *J*_{C-F} = 262.5 Hz), 125.3 (q, *J*_{C-F} = 3 Hz), 118.1, 116.9, 116.4, 81.2, 54.7, 50.7, 33.9, 28.3; **FT-IR (thin film)**: 1701, 1599, 1493, 1458, 1374, 1329, 1167, 1128, 1076, 757 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₃H₂₃F₃N₃O₃ [M+H]⁺ 446.1686; found 446.1687; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 6.4 min, τ_{major} = 10.4 min); Enantiomeric excess: 90%.

Tert-butyl((R)-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(naphthalen-2-yl)methyl)carbamate (3r)

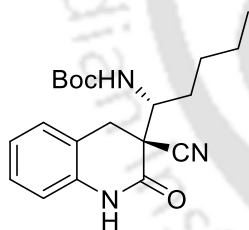
This compound was prepared according to the general procedure D. White sticky solid (49.9 mg, yield: 78%); **Diastereomeric ratio**: 5:1; **¹H NMR (400 MHz, CDCl₃)**: δ 8.22 (s, 1H), 7.88 (dd, *J* = 12.2, 7.0 Hz, 2H), 7.84 – 7.78 (m, 1H), 7.65 (s, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.06 – 6.93 (m, 2H), 5.76 (d, *J* = 8.9 Hz, 1H), 5.11 (d, *J* = 8.8 Hz, 1H), 3.36 (d, *J* = 16.2 Hz, 1H), 2.73 (d, *J* = 16.2 Hz, 1H), 1.37 (s, 9H); **¹³C NMR (100 MHz, CDCl₃)**: δ 164.2, 155.0, 136.0, 133.7, 133.1, 129.4, 129.1, 129.0, 128.4, 128.0, 127.6, 127.0, 126.9, 124.6, 118.5, 117.5, 116.3, 80.9, 55.2, 53.6, 33.9, 28.4; **FT-IR (thin film)**: 1692, 1598, 1493, 1369, 1321, 1246, 1165, 1017, 756 cm⁻¹; **HRMS (+ESI)**: Calc for C₂₆H₂₆N₃O₃ [M+H]⁺ 428.1969; found 428.1970; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.3 min, τ_{major} = 16.8 min); Enantiomeric excess: 98%.

Tert-butyl((R)-1-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)-3-phenylpropyl)carbamate (3s)

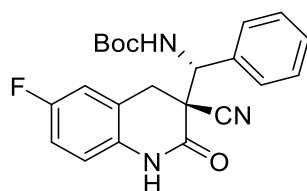


This compound was prepared according to the general procedure D. White sticky solid (33.4 mg, yield: 55%); **Diastereomeric ratio:** 3:1; **¹H NMR (400 MHz, CDCl₃):** δ 7.79 (s, 1H), 7.24 (d, J = 7.5 Hz, 3H), 7.17 (t, J = 7.3 Hz, 1H), 7.11 (dd, J = 13.9, 7.4 Hz, 3H), 7.02 (t, J = 7.5 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.90 (d, J = 10.4 Hz, 1H), 4.11 – 3.99 (m, 1H), 3.35 – 3.21 (m, 2H), 2.78 (dd, J = 21.0, 7.1 Hz, 1H), 2.60 – 2.48 (m, 1H), 2.20 (dd, J = 14.6, 7.3 Hz, 2H), 1.42 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 163.9, 155.8, 140.7, 135.5, 129.0, 128.7, 128.6, 128.5, 126.4, 124.6, 119.7, 117.5, 115.8, 80.5, 52.2, 49.4, 34.5, 33.8, 32.5, 28.5; **FT-IR (thin film):** 1699, 1598, 1541, 1494, 1367, 1249, 1168, 753 cm⁻¹; **HRMS (+ESI):** Calc for C₂₄H₂₈N₃O₃[M+H]⁺ 406.2125; found 406.2127; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak ID column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 22.3 min, τ_{minor} = 30.0 min); Enantiomeric excess: 71%.

Tert-butyl ((R)-1-((R)-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)pentyl)carbamate (3t)

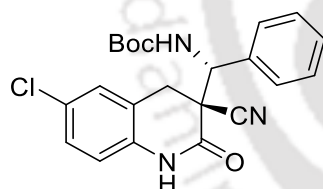


This compound was prepared according to the general procedure D. Brown sticky solid (28.9 mg, yield: 54%); **Diastereomeric ratio:** 3:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.02 (s, 1H), 7.28 – 7.24 (m, 2H), 7.20 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 4.81 (d, J = 10.4 Hz, 1H), 4.07 – 3.94 (m, 1H), 3.33 (q, J = 16.0 Hz, 2H), 1.91 – 1.78 (m, 2H), 1.43 (dd, J = 7.9, 6.3 Hz, 2H), 1.40 (s, 9H), 1.29 (d, J = 4.7 Hz, 2H), 0.87 (d, J = 4.4 Hz, 3H); **¹³C NMR (100 MHz, CDCl₃):** δ 164.2, 156.0, 135.7, 129.1, 128.5, 124.5, 119.8, 117.7, 115.9, 80.3, 52.6, 49.5, 34.6, 31.5, 28.4, 28.3, 22.3, 14.1; **FT-IR (thin film):** 1696, 1597, 1495, 1374, 1248, 1168, 757 cm⁻¹; **HRMS (+ESI):** Calc for C₂₀H₂₈N₃O₃ [M+H]⁺ 358.2125; found 358.2129; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IE column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 20.9 min, τ_{minor} = 24.4 min); Enantiomeric excess: 67%.

Tert-butyl ((R)-((R)-3-cyano-6-fluoro-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate (3u)

This compound was prepared according to the general procedure D. White sticky solid (44.4 mg, yield: 75%);

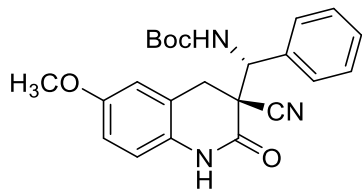
Diastereomeric ratio: 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.35 (s, 1H), 7.51 – 7.33 (m, 3H), 7.29 – 7.26 (m, 2H), 7.04 (t, *J* = 8.4 Hz, 1H), 6.94 (dt, *J* = 8.7, 4.4 Hz, 1H), 6.76 (d, *J* = 7.2 Hz, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 4.94 (d, *J* = 7.3 Hz, 1H), 3.34 (d, *J* = 16.3 Hz, 1H), 2.70 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 163.9 (d, *J* = 9 Hz), 160.2, 158.6, 155.0, 135.5, 132.3, 129.6, 129.2, 127.7, 120.2 (d, *J* = 7.5 Hz), 117.6 (d, *J* = 7.5 Hz), 116.2, 116.0, 115.9, 115.8, 80.9, 54.9, 50.8, 33.8, 28.4; **FT-IR (thin film):** 1715, 1692, 1592, 1492, 1368, 1245, 1167, 1046, 838 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃FN₃O₃ [M+H]⁺ 396.1718; found 396.1724; The enantiomeric ratio was determined by HPLC analysis using Phenomenex Lux C1 column (90:10 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{major} = 10.6 min, τ_{minor} = 13.3 min); Enantiomeric excess: 92%.

Tert-butyl ((R)-((R)-6-chloro-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate (3v)

This compound was prepared according to the general procedure D. White sticky solid (43.7 mg, yield: 71%);

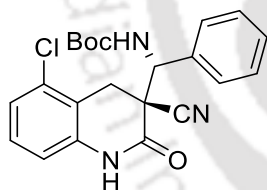
Diastereomeric ratio: 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.08 (s, 1H), 7.42 (dd, *J* = 5.0, 1.7 Hz, 3H), 7.30 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.27 (s, 2H), 7.02 (s, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.94 (d, *J* = 7.9 Hz, 1H), 3.33 (d, *J* = 16.3 Hz, 1H), 2.70 (d, *J* = 16.3 Hz, 1H), 1.36 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 163.8, 155.0, 135.4, 134.7, 129.6, 129.3, 129.3, 128.8, 127.7, 120.1, 117.4, 117.2, 80.9, 55.0, 50.9, 33.7, 28.4; **FT-IR (thin film):** 1715, 1692, 1593, 1492, 1368, 1244, 1167, 1046, 887 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃ClN₃O₃ [M+H]⁺ 412.1422; found 412.1426; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (88:12 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.8 min, τ_{major} = 23.5 min); Enantiomeric excess: 93%.

Tert-butyl ((R)-((R)-3-cyano-6-methoxy-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate (3w)

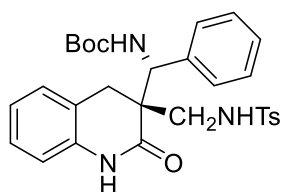


This compound was prepared according to the general procedure D. White sticky solid (47.6 mg, yield: 78%); **Diastereomeric ratio:** 6:1; **¹H NMR (400 MHz, CDCl₃):** δ 8.65 (s, 1H), 7.48 – 7.35 (m, 3H), 7.29 (dd, *J* = 6.6, 2.8 Hz, 2H), 6.93 (dd, *J* = 13.1, 8.7 Hz, 1H), 6.85 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.58 (s, 1H), 5.70 (d, *J* = 8.6 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.32 (d, *J* = 16.2 Hz, 1H), 2.69 (d, *J* = 16.3 Hz, 1H), 1.35 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 164.1, 156.7, 154.9, 135.9, 129.4, 129.0, 127.8, 119.8, 117.5, 117.4, 114.8, 114.0, 80.7, 55.9, 54.9, 50.9, 34.1, 28.4; **FT-IR (thin film):** 1690, 1595, 1506, 1457, 1368, 1246, 1164, 1036, 880, 815 cm⁻¹; **HRMS (+ESI):** Calc for C₂₀H₂₆NO₄S₂ [M+H]⁺ 408.1298; found 408.1296; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IB column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 14.8 min, τ_{major} = 20.1 min); Enantiomeric excess: 97%.

Tert-butyl((R)-((R)-5-chloro-3-cyano-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate (3x)

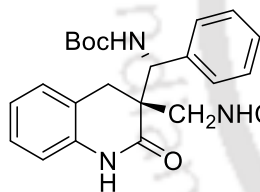


This compound was prepared according to the general procedure E. White sticky solid (43.1 mg, yield: 70%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.26 (d, *J* = 22.6 Hz, 1H), 7.41 (dd, *J* = 5.0, 1.7 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.22 (dd, *J* = 6.6, 2.8 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.91 – 6.85 (m, 1H), 5.59 (d, *J* = 9.2 Hz, 1H), 4.95 (d, *J* = 8.6 Hz, 1H), 3.16 (s, 2H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 164.0, 155.0, 137.4, 135.1, 134.1, 130.0, 129.5, 129.4, 127.7, 125.4, 117.1, 116.9, 114.8, 80.9, 55.2, 51.4, 31.1, 28.4; **FT-IR (thin film):** 1700, 1690, 1586, 1472, 1386, 1312, 1255, 1162, 1101, 785 cm⁻¹; **HRMS (+ESI):** Calc for C₂₂H₂₃ClN₃O₃ [M+H]⁺ 412.1422; found 412.1418; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (85:15 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 7.2 min, τ_{major} = 10.7 min); Enantiomeric excess: 84%.



Tert-butyl((R)-((S)-3-((4-methylphenylsulfonamido)methyl)-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate(5)

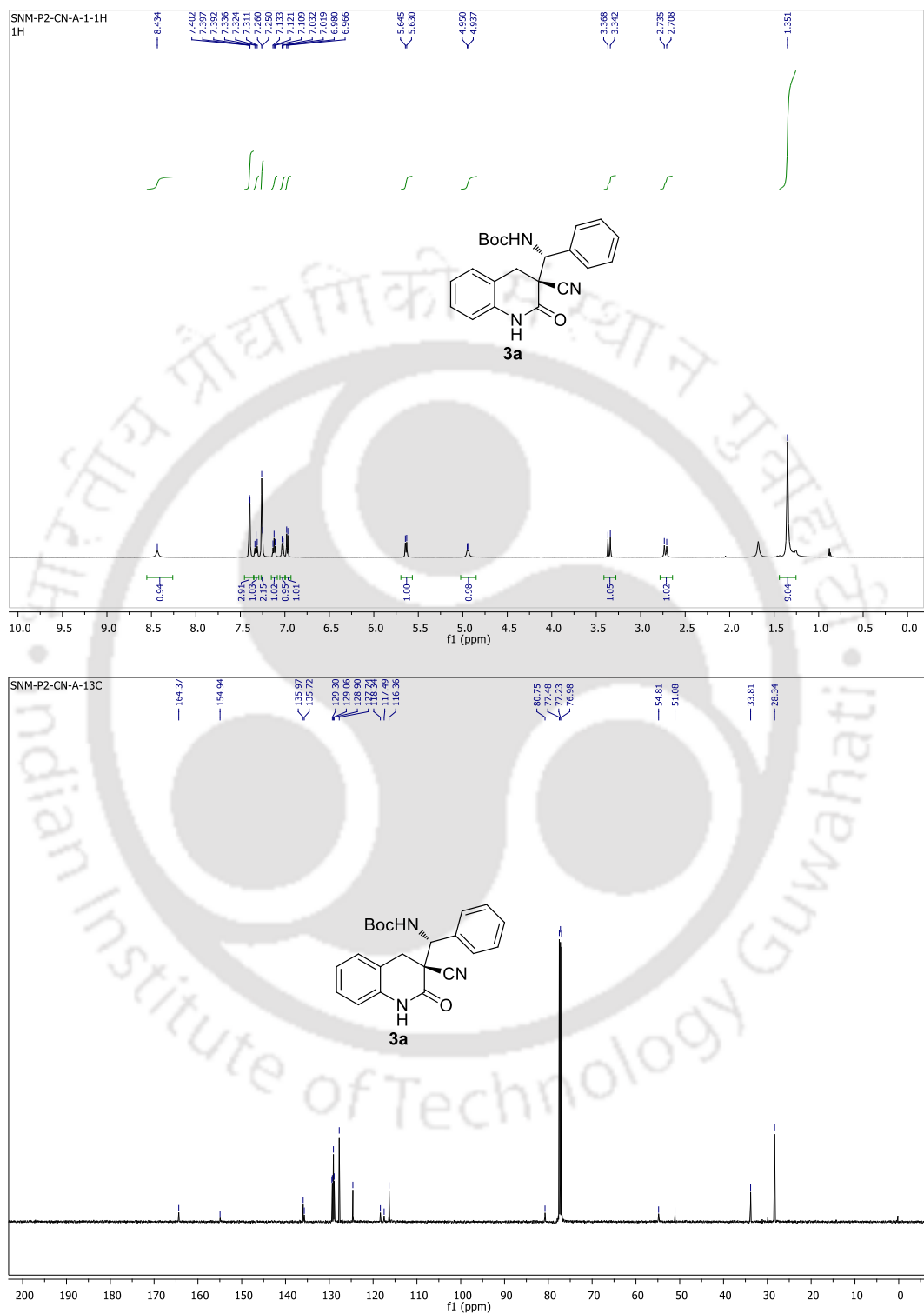
This compound was prepared according to the general procedure E. White sticky solid (36.1 mg, yield: 45%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 9.03 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 15.2, 7.2 Hz, 5H), 7.18 (t, *J* = 6.9 Hz, 2H), 7.07 (t, *J* = 6.7 Hz, 3H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.73 (s, 1H), 4.77 (s, 1H), 3.43 (d, *J* = 17.3 Hz, 2H), 2.67 (dd, *J* = 12.8, 9.2 Hz, 1H), 2.58 (d, *J* = 16.9 Hz, 1H), 2.45 (s, 3H), 1.34 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 172.8, 155.1, 149.2, 143.7, 136.8, 135.7, 130.1, 129.3, 129.0, 128.9, 128.5, 128.3, 128.0, 127.9, 127.2, 124.5, 116.1, 79.9, 60.6, 55.2, 49.0, 44.9, 28.5, 21.8; **FT-IR (thin film):** 1676, 1599, 1494, 1376, 1324, 1160, 1058, 756 cm⁻¹; **HRMS (+ESI):** Calc for C₂₉H₃₃N₂O₅S [M+H]⁺ 536.2214; found 536.2222; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 18.3min, τ_{major} = 28.5 min); Enantiomeric excess: 98%.

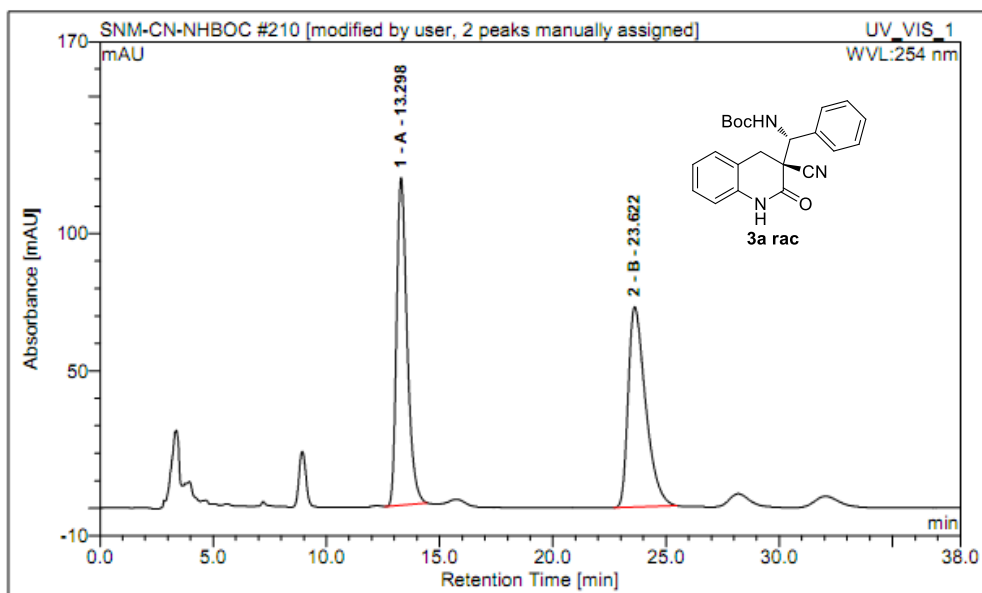


Tert-butyl((R)-((S)-2-oxo-3-(2-oxo-2-phenylethyl)-1,2,3,4-tetrahydroquinolin-3-yl)(phenyl)methyl)carbamate(6)

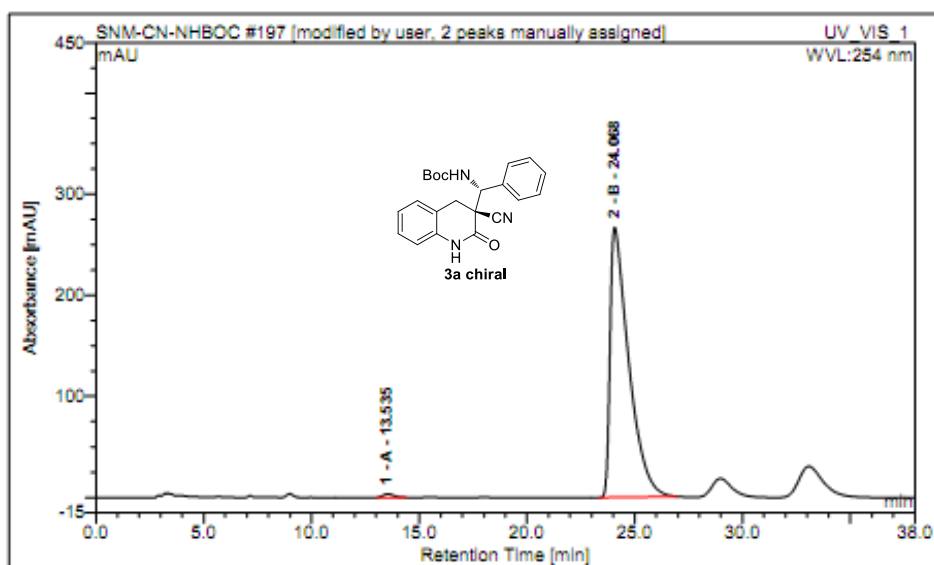
This compound was prepared according to the general procedure F. White sticky solid (30.5 mg, yield: 42%); **Diastereomeric ratio:** 5:1; **¹H NMR (600 MHz, CDCl₃):** δ 8.17 (s, 1H), 8.11 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.20 (dd, *J* = 17.1, 8.7 Hz, 3H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.11 (s, 1H), 3.99 – 3.86 (m, 1H), 3.65 (d, *J* = 6.4 Hz, 1H), 2.95 (d, *J* = 15.6 Hz, 1H), 2.81 (d, *J* = 16.6 Hz, 1H), 1.37 (s, 9H); **¹³C NMR (150 MHz, CDCl₃):** δ 172.6, 167.9, 155.6, 135.9, 134.2, 133.5, 131.8, 130.3, 129.0, 128.7, 128.7, 128.6, 128.3, 128.2, 127.2, 124.2, 115.4, 80.4, 55.3, 50.1, 40.9, 31.8, 28.5; **FT-IR (thin film):** 1705, 1653, 1540, 1489, 1384, 1317, 1171, 1014, 757 cm⁻¹; **HRMS (+ESI):** Calc for C₂₉H₃₂N₃O₄ [M+H]⁺ 486.2387; found 486.2388; The enantiomeric ratio was determined by HPLC analysis using Daicel Chiralpak IA column (70:30 *n*-Hexane/2-PrOH, 1.0 mL/min, 25 °C, 254 nm, τ_{minor} = 10.8 min, τ_{major} = 27.3 min); Enantiomeric excess: 98%.

6.10. Selected NMR spectra and HPLC chromatogram:

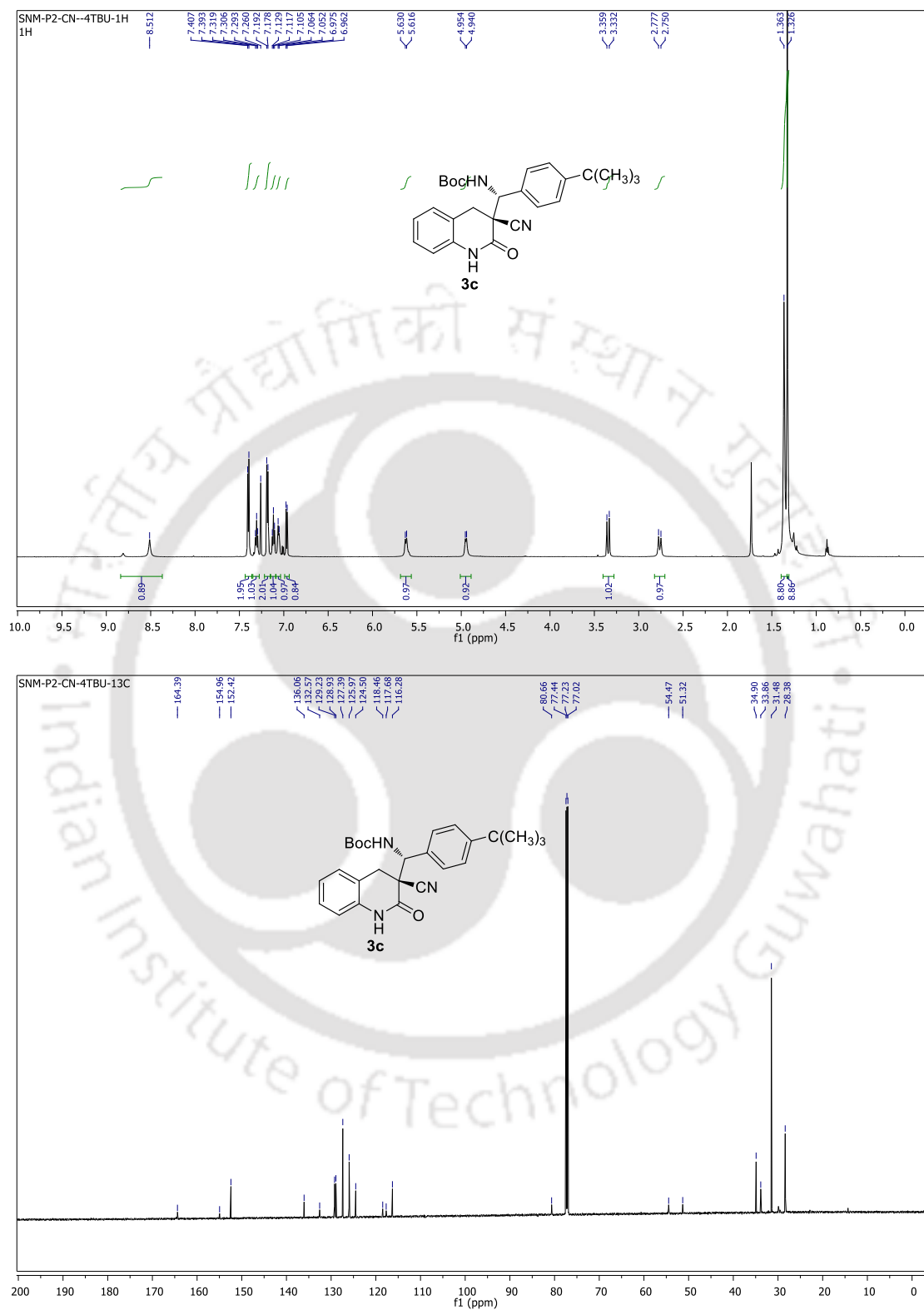


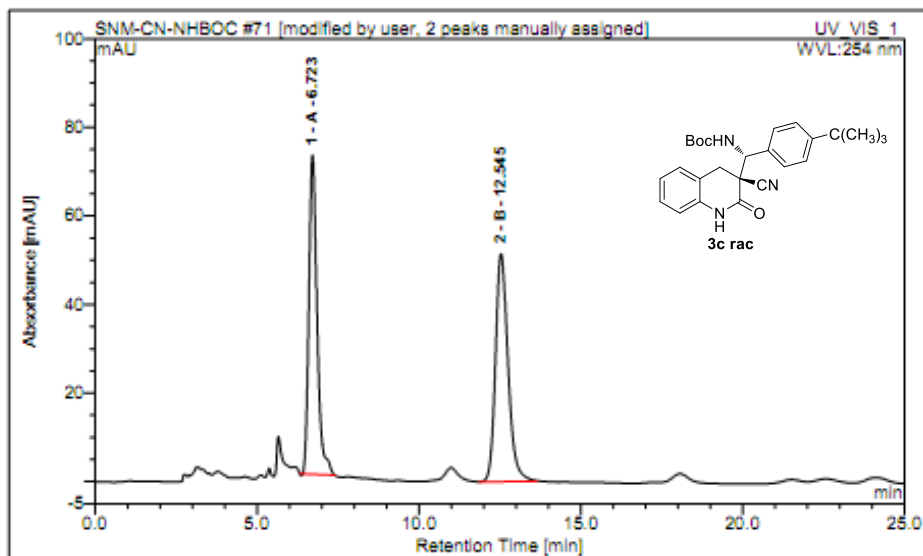


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.30	64.46922	49.67792177	119.3821	n.a.
2	B	23.62	65.305	50.32207823	73.072	n.a.

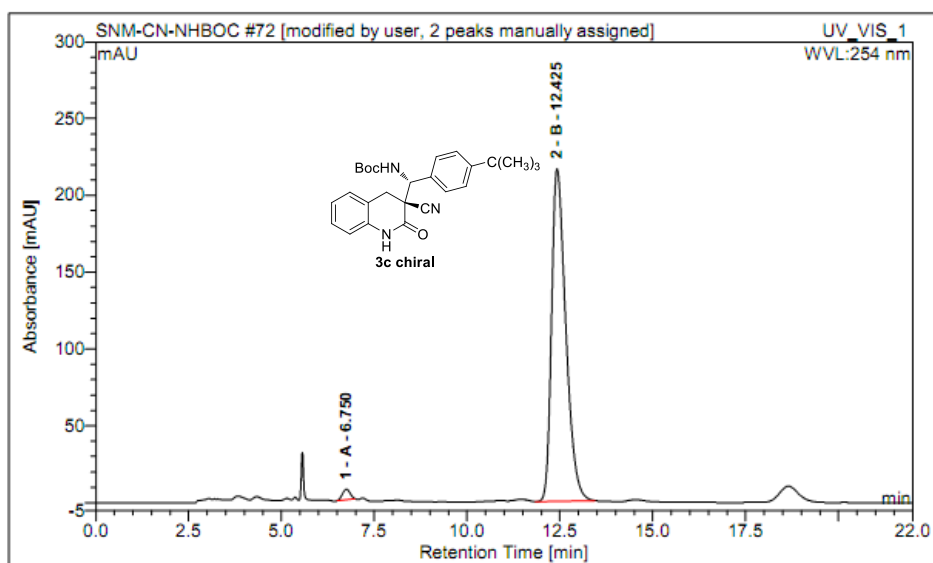


No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	13.54	1.958975	0.7249404456	3.48584	n.a.
2	B	24.07	268.267	99.27505955	267.162	n.a.



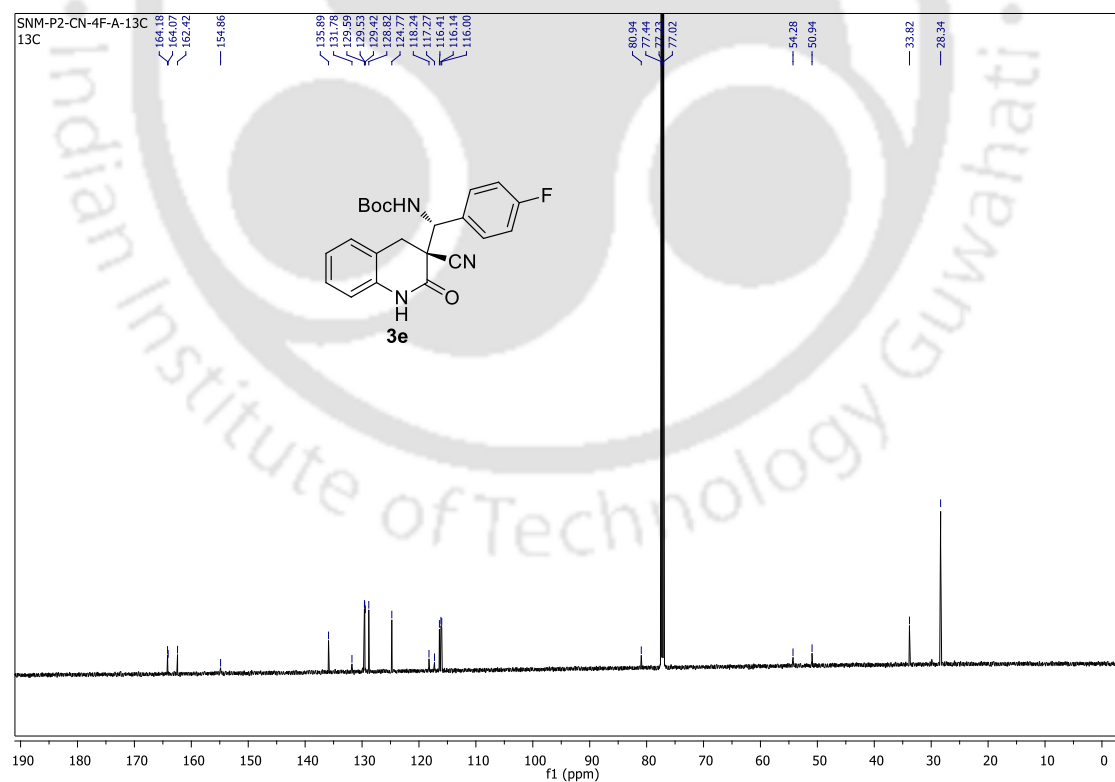
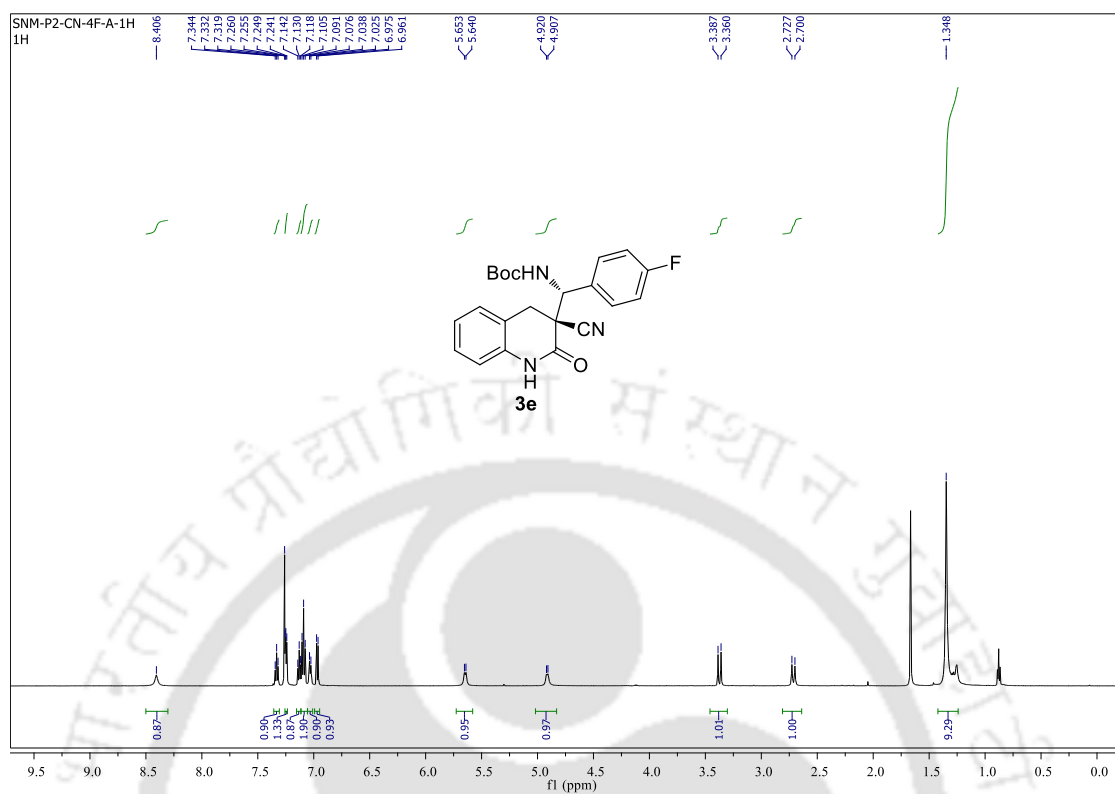


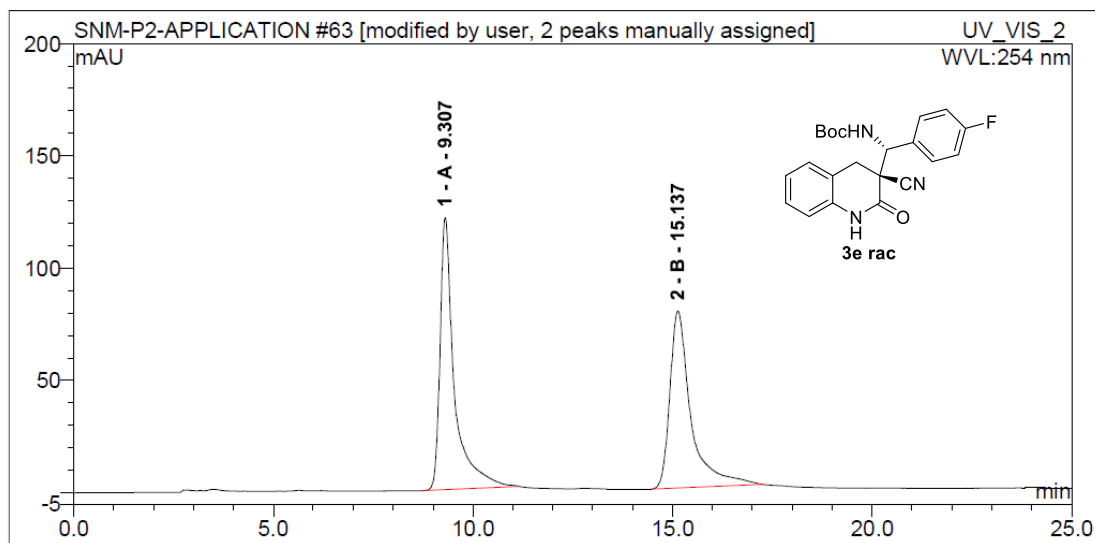
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.72	21.04102	47.87106647	72.11329	n.a.
2	B	12.55	22.913	52.12893353	51.419	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	6.75	1.628575	1.669745436	6.82761	n.a.
2	B	12.43	95.906	98.33025456	216.476	n.a.

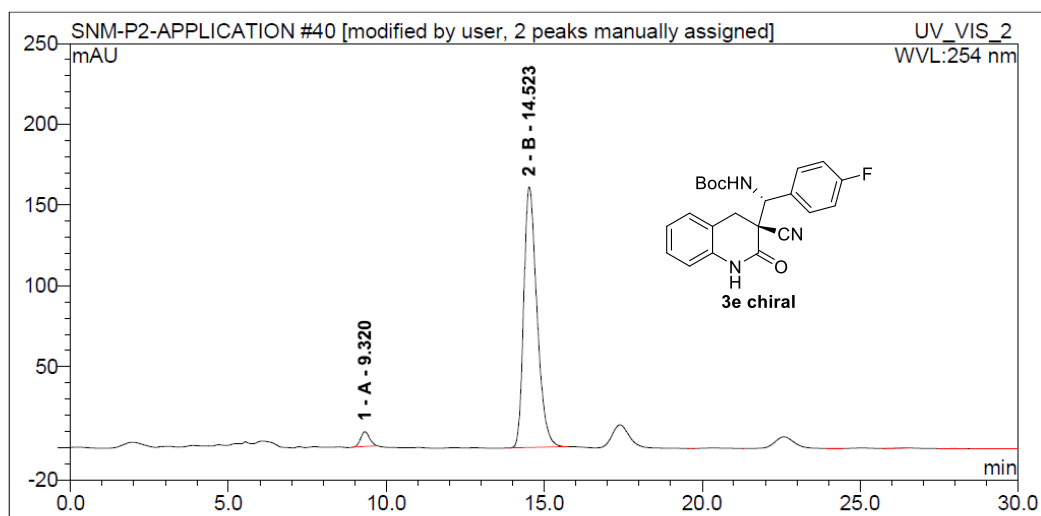
CHAPTER 6





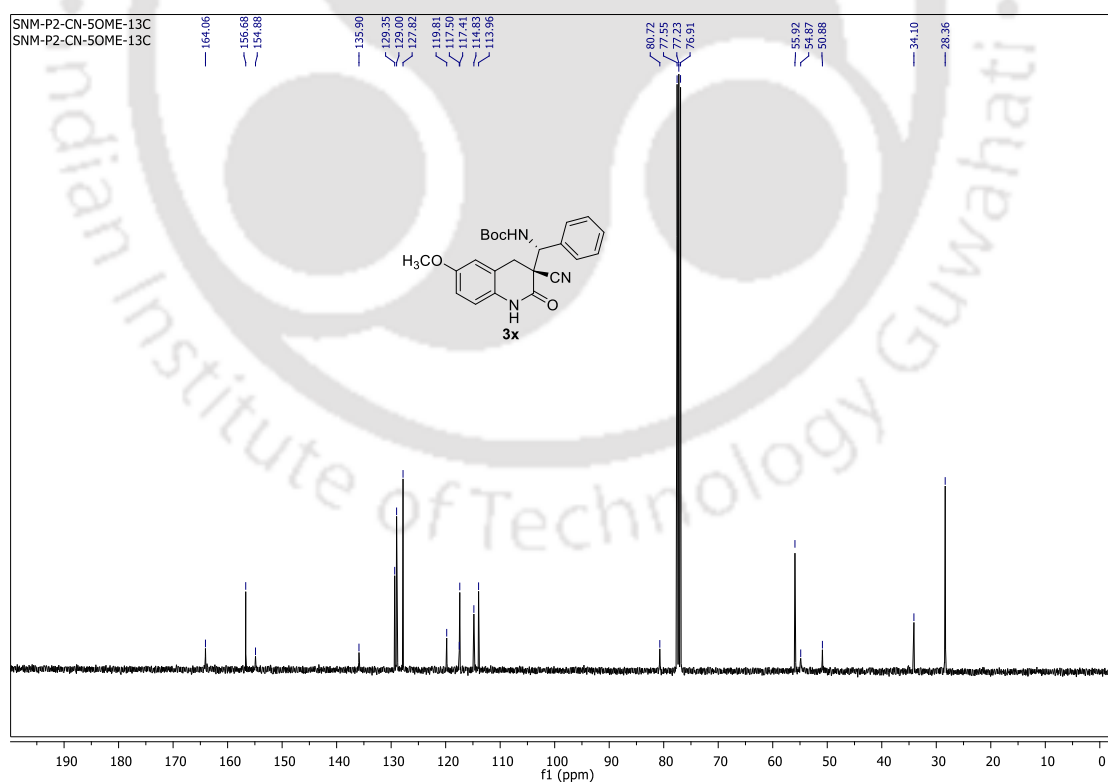
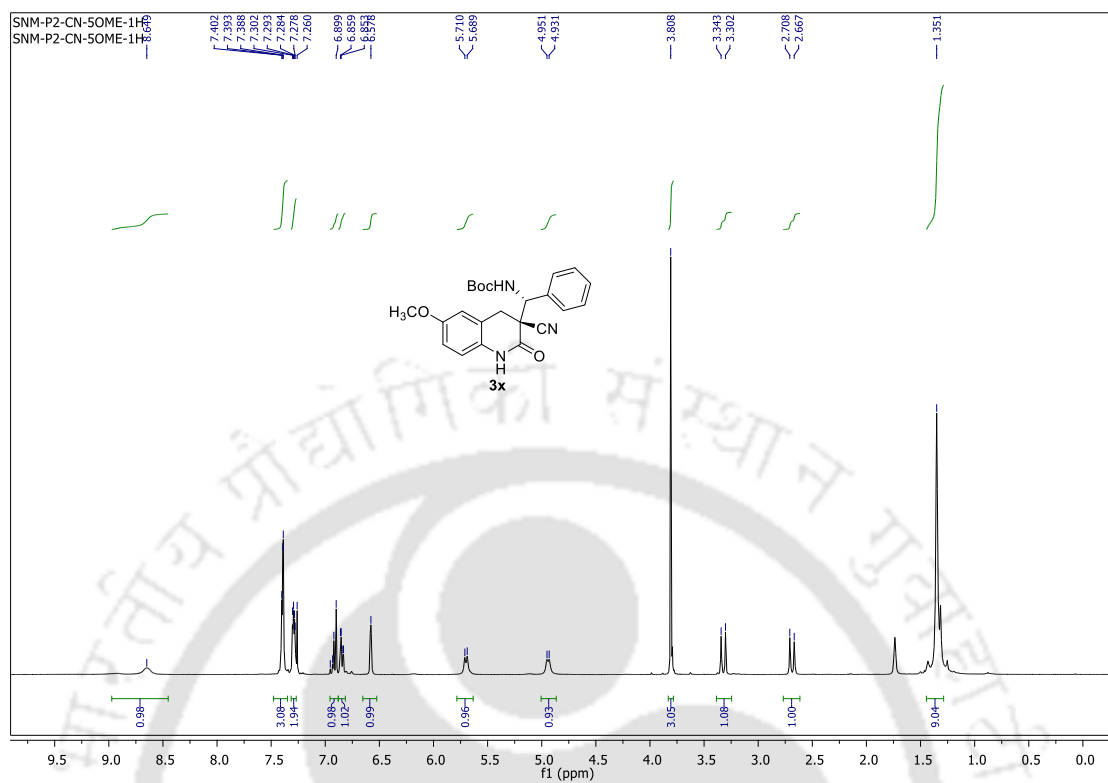
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		9.31	50.16329	50.94421387	120.9652	n.a.
2 B		15.14	48.304	49.05578613	78.630	n.a.

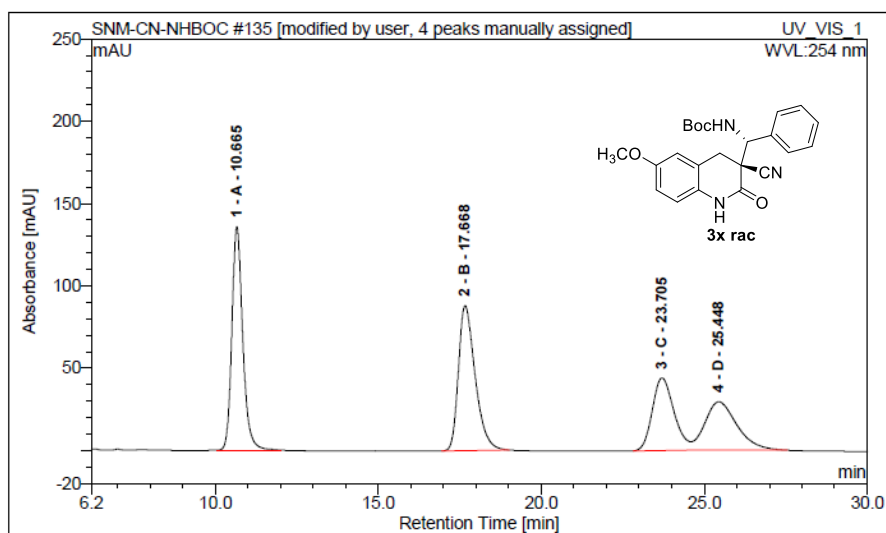
AMS-2-11C



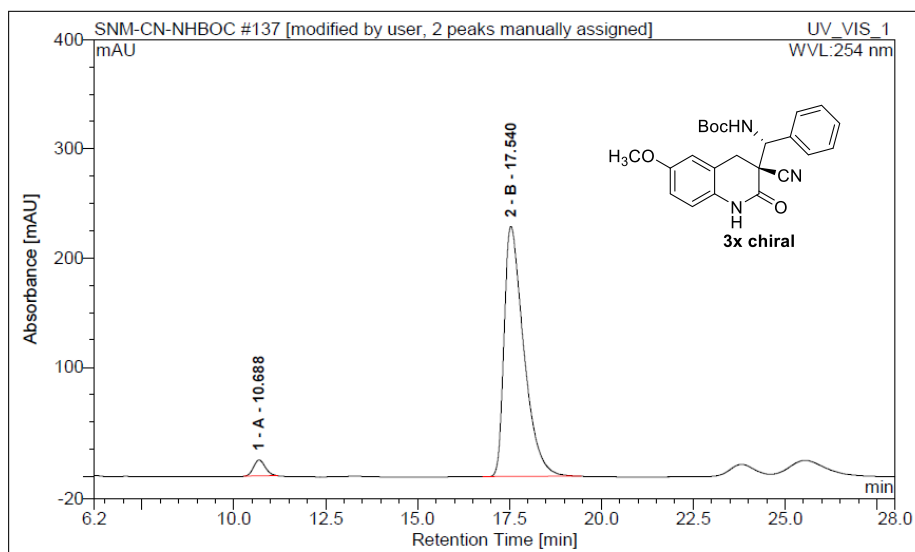
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1 A		9.32	2.974208	3.659658508	9.14231	n.a.
2 B		14.52	78.296	96.34034149	161.373	n.a.

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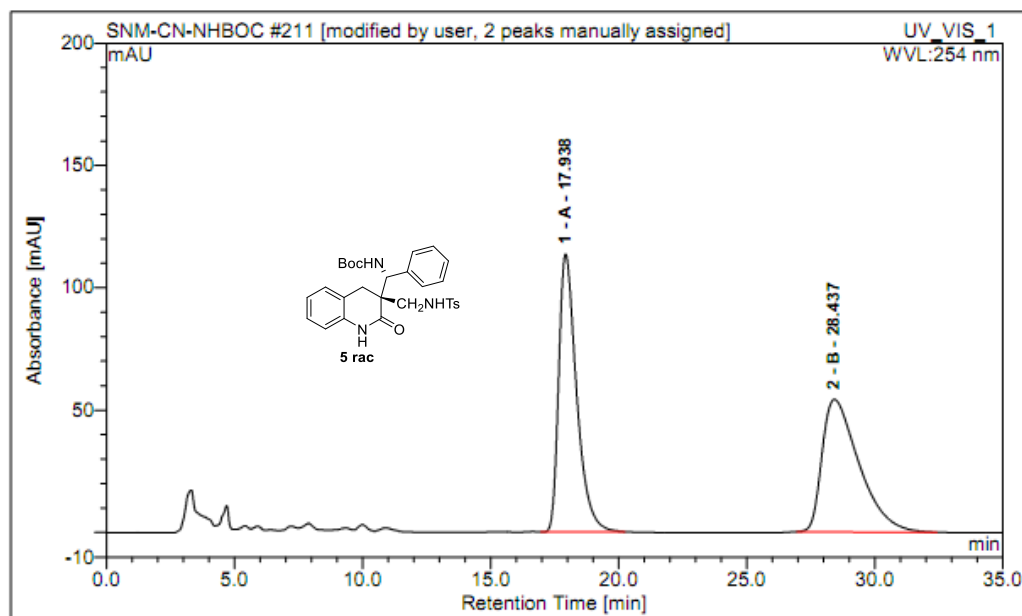




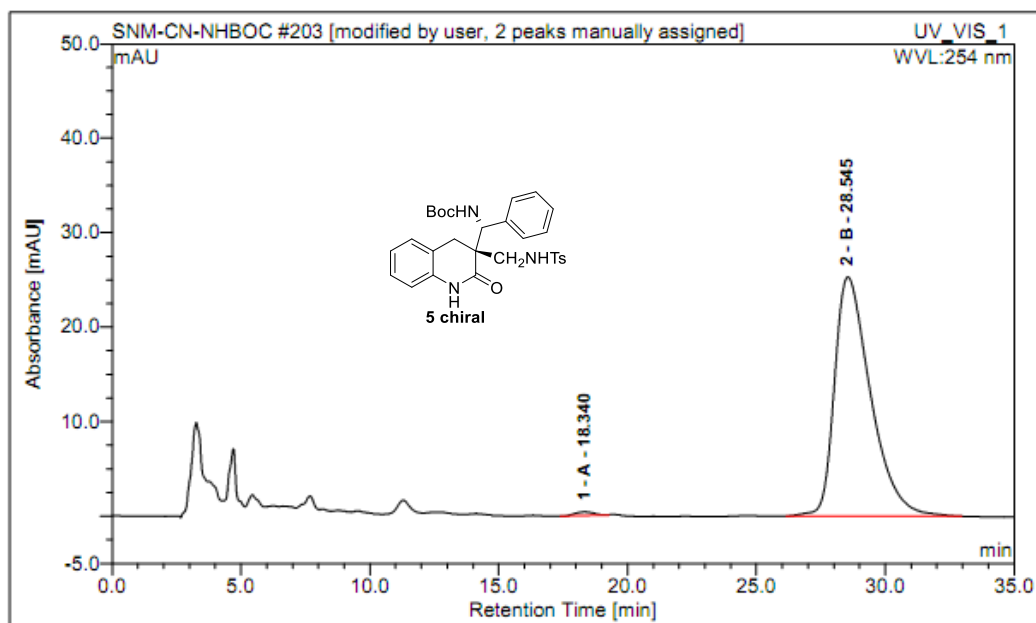
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	10.67	52.48322	30.41939122	135.7668	n.a.
2	B	17.67	52.32263	30.32631509	88.02782	n.a.
3	C	23.71	34.59746	20.05276238	44.1098	n.a.
4	D	25.45	33.129	19.20153131	29.425	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	10.69	5.42617	3.677921219	14.63836	n.a.
2	B	17.54	142.107	96.32207878	228.993	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	17.94	91.62296	50.32049977	113.5988	n.a.
2	B	28.44	90.456	49.67950023	54.086	n.a.



No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	A	18.34	0.305987	0.7407735219	0.38036	n.a.
2	B	28.55	41.000	99.25922648	25.308	n.a.

