Stereospecific Opening and Cyclization of the Strained Ring Systems for the Synthesis of Six-Membered Heterocycles

A Thesis Submitted

in Partial Fulfilment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated To

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

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

Guwahati
January 2022

Bijay Ketan Das

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Bijay Ketan Das has been working under my supervision since July 2016. I am forwarding his thesis entitled "*Stereospecific Opening and Cyclization of the Strained Ring Systems for the Synthesis of Six-Membered Heterocycles*" being submitted for the Ph.D. degree of this institute. I certify that he has fulfilled all the requirements according to the rules of this institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati
January 2022

Prof. Tharmalingam Punniyamurthy
Supervisor

ACKNOWLEDGEMENT

Firstly, I want to thank my mentor and supervisor, **Prof. Tharmalingam Punniyamurthy** for introducing me to the fascinating world of synthetic chemistry and gave me the privilege and liberty to carry out this research work. I am highly indebted to him for his keen interest, valuable guidance, strong motivation, constant support and encouragement. Thank you, Sir! for always challenging and helping me to achieve this goal. I will be forever grateful of the opportunities you have given me and the doors you have opened.

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To my wonderful friends at IIT Guwahati: It gives me an immense pleasure to express my affable gesture to my Ph.D. batch mates (July, 2016), research scholars in the chemistry department and B.Sc., M.Sc. friends for their support and joyful moments shared with them.

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Finally, I profoundly render my deep regards to my beloved parents (Mr. Chitta Ranjan Das & Mrs. Swarnamoyee Samanta Das), brother (Chandan Tilak Das) and sister (Madhabi Lata Maity) for their endless patience, countless sacrifices, sincere encouragement and inspiration. Thank you for believing in my vision and providing me the wings of freedom and opportunity to chase my dreams. It was surely very tedious without your blessings and moral support. I owe a lot to your love, care, affection and blessings.

Last but not the least my words are insufficient to thank the almighty God and I surrender myself to Him, for showering His blessings upon me for making me able to sew up this thesis work.

God bless you all!

Bijay Ketan Das

List of Abbreviations

Å	angstrom (10^{-8} cm)
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CCDC	Cambridge crystallographic data centre
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CH_2Cl_2	Dichloromethane
$(CH_2Cl)_2$	1,2-dichloroethane
D-A	Donor-Acceptor
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
ee	enantiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FT-IR	fourier transform infrared spectroscopy
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	Hertz
IREDs	imine reductases
KBr	potassium bromide
K_2CO_3	potassium carbonate
m/z	mass to charge ratio
mCPBA	meta-chloro peroxybenzoic acid
mp	melting point

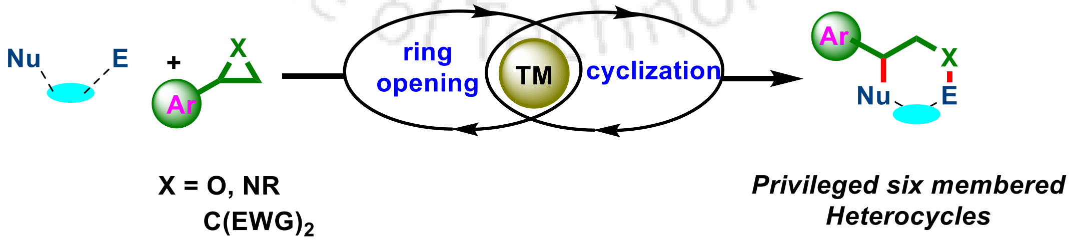
Me	methyl
MeOH	methanol
MHz	megahertz
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
Pr	propyl
Ts	*p*-toluenesulfonyl
R_f	retardation factor
rt	room temperature
SnAP	stannyl amine protocol
SLAP	Silicon amine protocol
SET	single-electron transfer
THF	tetrahydrofuran
TLC	thin layer chromatography
μL	Microliter

Abstract

The thesis is divided into four chapters. The first chapter describes the general introduction to the opening and cyclization of the strained ring systems for the synthesis of six-membered heterocycles. The second chapter focuses on the synthesis of piperazines and tetrahydropyrazines through stereospecific ring-opening and cycloisomerization of aziridines with *N*-propargylamines. Third chapter covers stereospecific synthesis of substituted 1,4-oxazine via Zn/Ag Relay catalyzed ring opening/hydroalkoxylation of oxiranes with *N*-propargylamines. Chapter four deals with the stereospecific assembly of tetrahydroquinolines *via* tandem ring-opening/oxidative cyclization of donor-acceptor cyclopropanes with *N*-alkyl anilines.

Chapter I Opening/Cyclization of the Strained Ring Systems for the Synthesis of Six-Membered Heterocycles

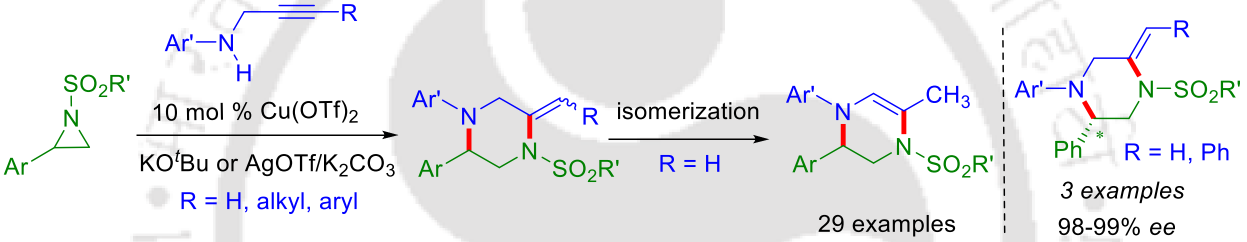
In organic chemistry, heterocyclic compounds are essential structural scaffolds. Six-membered heterocycles are abundant in nature as well as in synthetic products, which find several uses in drug development and material research. Recently, carbon-carbon and carbon-heteroatom bonds formation by ring expansion of three-membered strained ring systems such as aziridine, oxiranes, and D-A cyclopropane have provided a great synthetic space for easy access to structurally complex scaffolds. Due to their ring strain and electrophilic character, these three-membered rings have been employed as an attractive target for the selective synthesis of six-membered heterocycles through ring-scission. In this chapter, the synthetic methodologies based on ring-opening and cyclization of strained ring systems for synthesizing highly functionalized six-membered heterocycles, which are already available in the literature, have been provided.



Scheme 1. Roadmap to Six-Membered Heterocycle Synthesis

Chapter II Reaction of Reactive Aziridines with *N*-Propargylamines: Stereospecific Synthesis of Piperazines and Tetrahydropyrazines

Piperazines and their synthetic equivalents remain important substructures in pharmaceutical drug discovery. Because of the significance of this motif, many approaches to its construction have been established. Recently, Lewis acid-catalyzed tandem ring-opening/cyclization using aziridines has emerged as a potential synthetic technique for building *N*-containing heterocycle frameworks. Herein, we present a $Cu(OTf)_2$-catalyzed stereospecific nucleophilic ring-opening of *N*-sulfonylaziridines with propargyl amines followed by hydroamination with base or AgOTf/base to get piperazines. Piperazines with an exocyclic methylene double bond easily isomerize to teratrahydropyrazines.

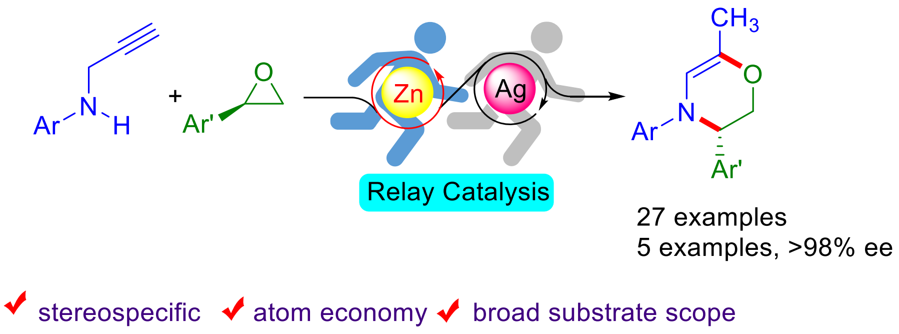


Org. Lett. **2018**, *20*, 4444.

Scheme 2. Cu-Catalyzed Ring-Opening/Hydroamination

Chapter III Reaction of Oxiranes with *N*-Propargylamines: Stereospecific Synthesis of 1,4-Oxazines

1,4-Oxazines and their saturated counterpart morpholines are privileged heterocyclic motifs that are present in numerous of pharmaceutical, agrochemical and biological molecules. Despite significant synthetic progress in this field, the development of an ideal strategy for the preparation of 1,4-oxazines in a stereospecific manner from simple components is thus desirable. In this regard, the Lewis acid-enabled ring expansion reactions of oxiranes have emerged as a fascinating chemical transformation for gaining access to complex molecular assemblies. The work described herein established a one-pot relay approach that enables Zn-catalyzed stereospecific ring-opening of oxiranes using propargylamines, followed by hydroalkoxylation with the help of AgOAc/base to yield a library of substituted 1,4-oxazines. Optically active oxiranes are coupled with excellent enantiomeric purity.

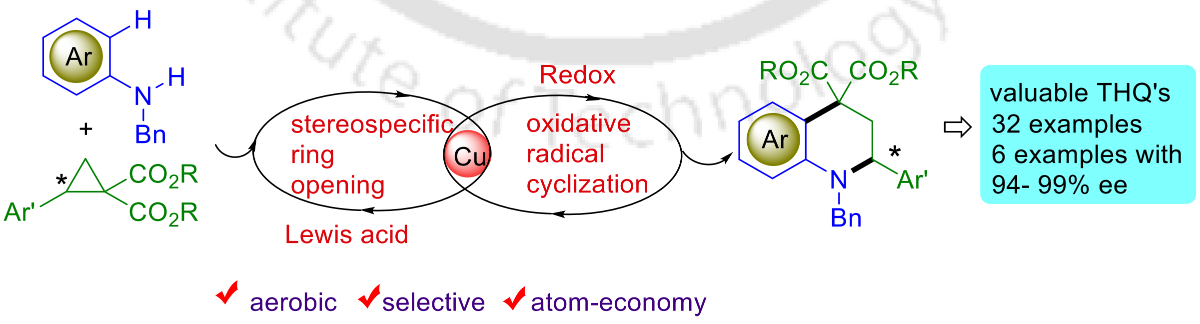


Manuscript submitted.

Scheme 3. Zn/Ag Relay-Catalyzed Ring-Opening/Hydroalkoxylation

Chapter IV Reaction of D-A Cyclopropanes with *N*-Alkyl Anilines: Stereospecific Assembly of Tetrahydroquinolines

1,2,3,4-Tetrahydroquinolines with C2 functionality replicate the structural features of a privileged family of six-membered aza-heterocycles with a broad bioactive spectrum and chiral auxiliaries. With the rising concern about atom economy and efficiency, developing an optimum technique for creating these heterocycle scaffolds from simple components is desirable. In this context, using donor-acceptor D-A cyclopropanes as the 1,3-zwitterion equivalent in (3+3)-cycloaddition has emerged as a valuable technique in synthesizing six-membered heterocycles. Here, we presented an aerobic copper-catalyzed tandem reaction of *N*-alkyl anilines with donor-acceptor cyclopropanes for the construction of tetrahydroquinolines *via* a sequential stereospecific ring opening and oxidative cyclization. The catalyst plays a dual role as a Lewis acid as well as redox catalyst.



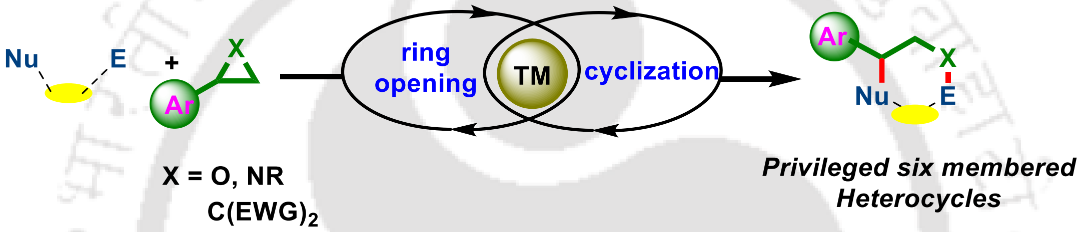
Chem. Commun. **2019**, *55*, 8083.

Scheme 4. Cu-Catalyzed Tandem Ring-Opening/Oxidative Cyclization

Contents

Chapter I

Opening/Cyclization of the Strained Ring Systems for the Synthesis of Six-membered Heterocycles



Opening/Cyclization of the Strained Ring Systems for the Synthesis of Six-Membered Heterocycles

In synthetic organic chemistry, heterocyclic compounds are essential structural scaffolds. Many heterocyclic compounds are well known, and their number is constantly increasing due to their practical application in pharmaceutical and material sciences.[1] Six-membered heterocycles are abundant in nature and synthetic products. They have a wide range of applications in drug discovery, vitamins and medicinally active compounds such as antibiotic, anticancer, anti-inflammatory, antidepressant, antifungal and antibacterial properties (Figure 1).[2] Because of the growing importance and use of heterocycles in organic chemistry, effective techniques for synthesizing them using readily available starting materials with step and atom economy and excellent stereoselectivity remain highly desirable.

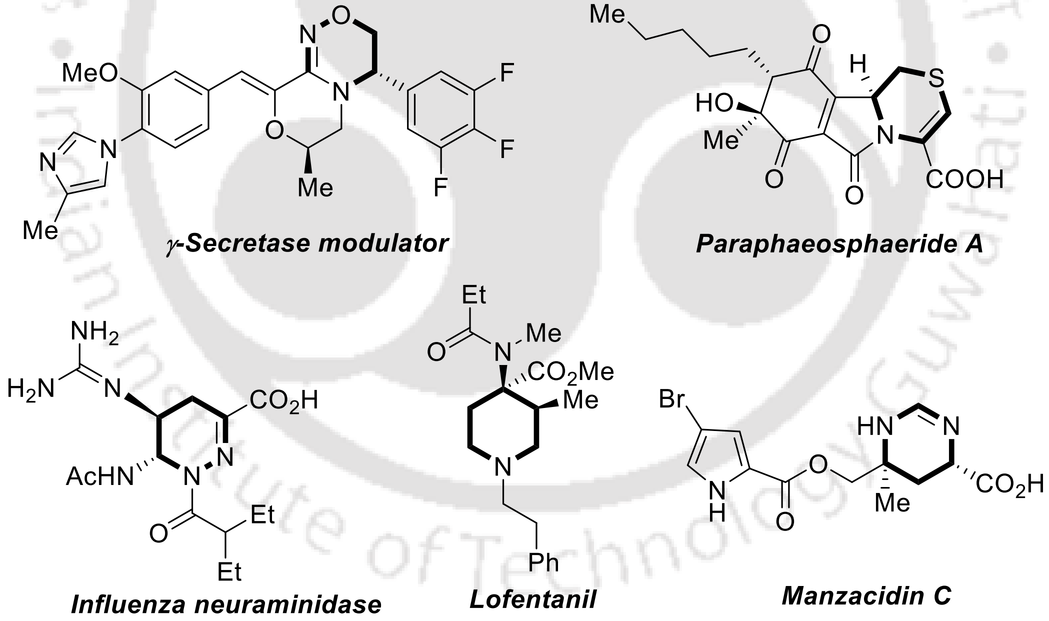
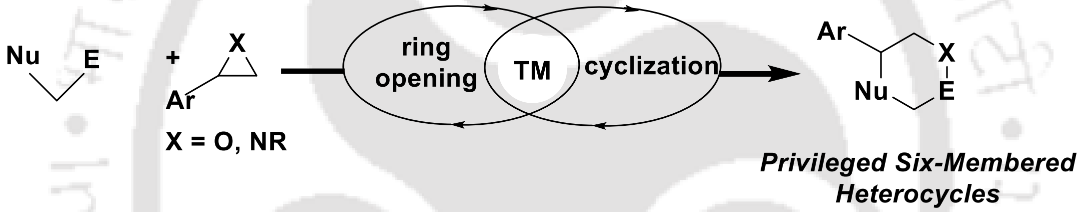


Figure 1. Selected Examples of Six-Membered Bio-active Drug

Recently, the formation of carbon-carbon and carbon-heteroatom bonds via ring expansion of three-membered strained ring systems such as aziridines, oxiranes and D-A cyclopropane have opened up a large synthetic space for quick access to structurally complex frameworks.[3] Because of their ring strain and electrophilic nature, these three-membered rings have been used as an attractive target for the selective synthesis of six-membered heterocycles *via* ring-scission. In this section, we present the methodologies based on the opening/cyclization of strained ring systems for the synthesis of highly functionalized six-membered heterocycles. This synthetic strategy has been used to the preparation of enormous oxygen, nitrogen and sulfur containing six-membered heterocycles.

1.1 Roadmap to Six-Membered Heterocycle Synthesis

This high strain energy associated with three-membered rings is a crucial driving factor behind the synthesis of value-added ring-opening fabrication products. Using Lewis acid or transition-metal catalyst, the three-membered ring is opened and coupled with a suitable nucleophile to generate a six-membered heterocycle (Scheme 1). In recent years, several new strained ring expansions for six-membered heterocycles such as pyrimidines, oxazines, quinolones *etc.*, have been discovered.

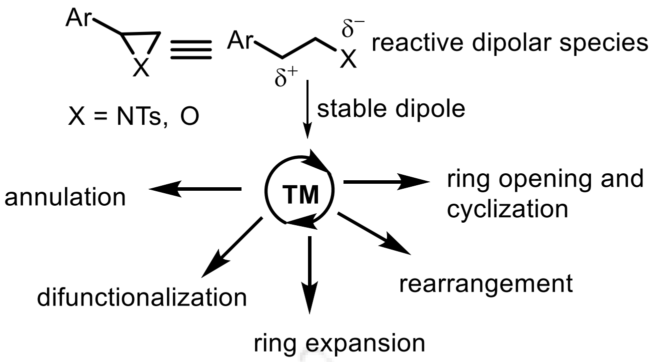


Scheme 1. Ring-Opening/Cyclization Strategy

1.2 Six-Membered Heterocycle Synthesis

1.2.1 Using Three-Membered Heterocycles

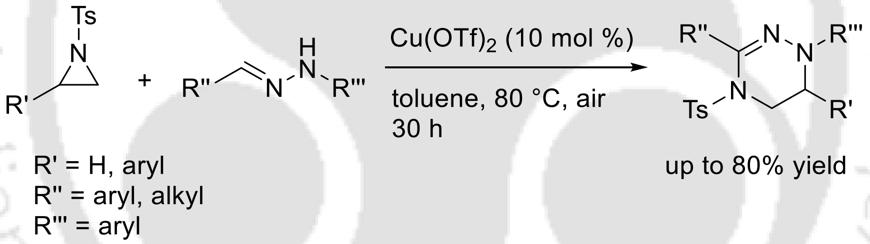
The aziridine and oxirane moieties are among the most valuable three-membered strained ring systems in organic chemistry. It has, however, primarily focused on ring-opening by nucleophiles and cycloaddition of masked zwitterionic 1,3-dipoles generated by carbon-heteroatom bond cleavage (Scheme 2). Significant attention has been devoted in recent years to study the contribution of aziridines and oxirane in the formation of a wide range of functionalized nitrogen and oxygen-containing six-membered heterocycles.



Scheme 2. Reactivities of Aziridine/Oxirane Towards Dipolarophiles.

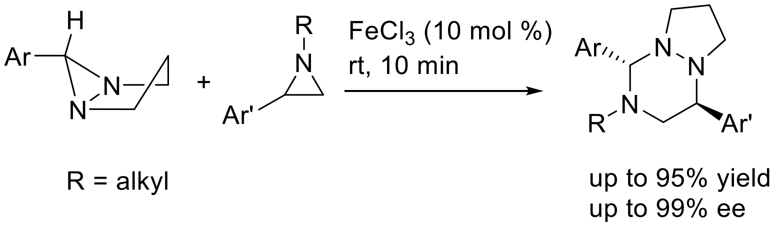
1.2.1.1 Synthesis of Triazines

Wang group described a Cu-catalyzed tandem reaction of *N*-tosylaziridines with hydrazones under aerobic conditions to give the functionalized tetrahydrotriazines (Scheme 3).[4] The process involves a nucleophilic ring-opening and intramolecular oxidative amidation. The use of inexpensive Cu catalyst and air as the ideal oxidant is a significant practical advantage.



Scheme 3. Cu-Catalyzed Tandem Reaction

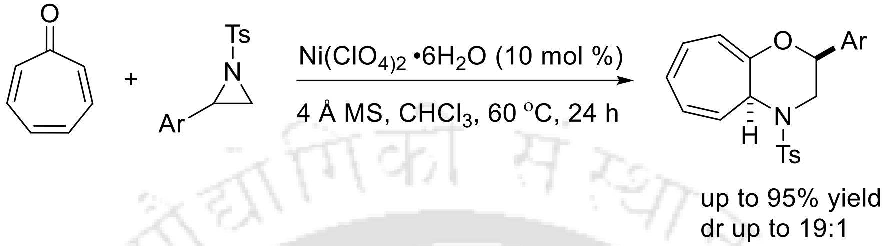
Our group reported a Fe-catalyzed stereospecific (3+3)-annulation of aziridines with diaziridines to furnish [1,2,4]-triazines in high yield at room temperature (Scheme 4).[5] The use of an inexpensive iron salt catalyst, substrate scope and enantiomeric purity are the important practical features.



Scheme 4. Fe-Catalyzed (3+3)-Cycloaddition

1.2.1.2 Synthesis of 1,4-Oxazines

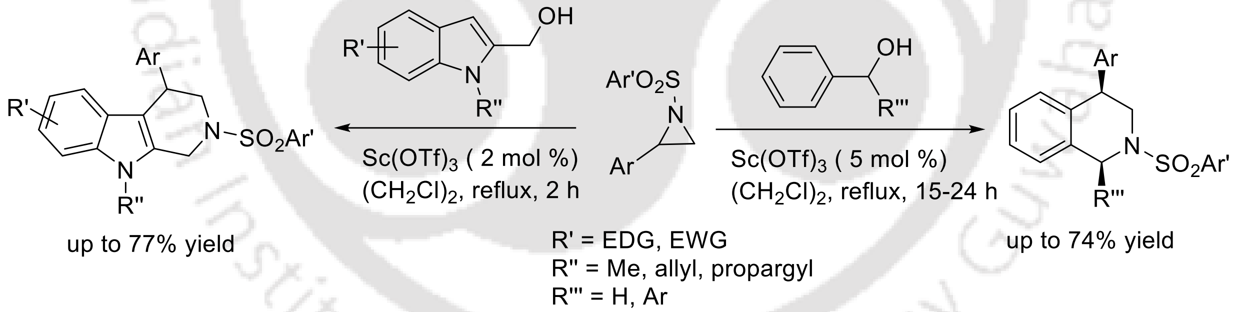
Guo and co-workers developed a nickel-catalyzed (8+3)-cycloaddition of tropones with 2-aryl-*N*-tosylaziridines to give oxazine derivatives with good diastereoselectivities (Scheme 5).[6] A wide range of aziridines reacted under mild reaction conditions in moderate to excellent yields.



Scheme 5. Ni-Catalyzed (8+3)-Cycloaddition

1.2.1.3 Synthesis of Tetrahydro-β-Carbolines and Tetrahydroisoquinolines

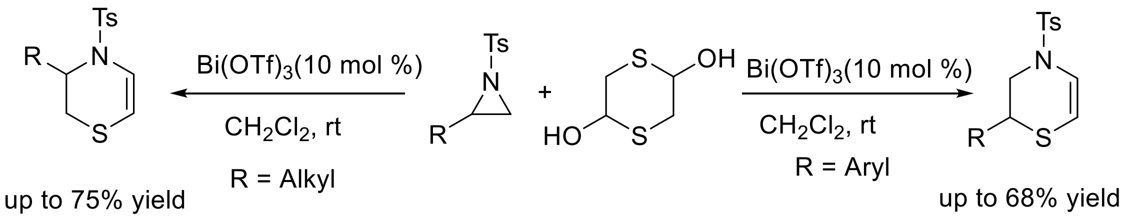
Wang and co-workers developed a Lewis acid-catalyzed (3+3)-annulation of benzylic alcohols and aziridines to synthesize tetrahydro-β-carbolines and tetrahydroisoquinolines (Scheme 6).[7] This method features the use of readily available starting material, broad substrate scope and mild reaction conditions.



Scheme 6. Sc-Catalyzed (3+3)-Annulation

1.2.1.4 Synthesis of Thiazines

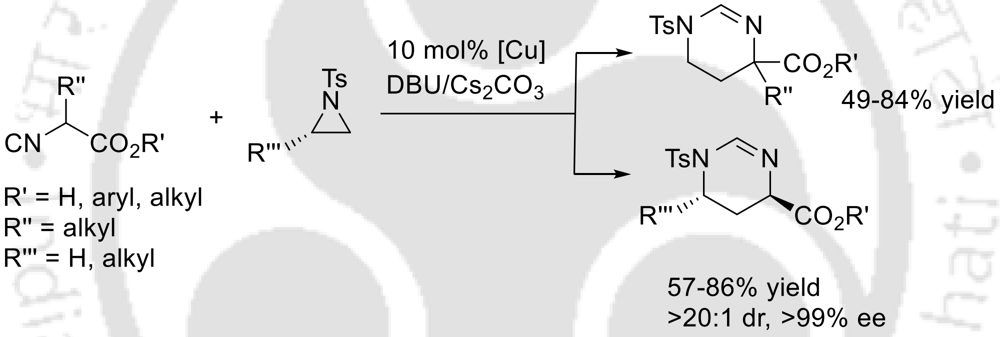
Our group demonstrated a Bi-catalysed domino C-N/C-S bonds formation of *N*-sulfonyl-aziridines with 1,4-dithiane-2,5-diol to provide 3,4-dihydro-1,4-thiazines at room temperature (Scheme 7).[8] The use of Bi(OTf)$_3$ as a catalyst, atom economy and regioselectivity are the important practical features.



Scheme 7. Bi-catalysed domino C-N/C-S bonds formation

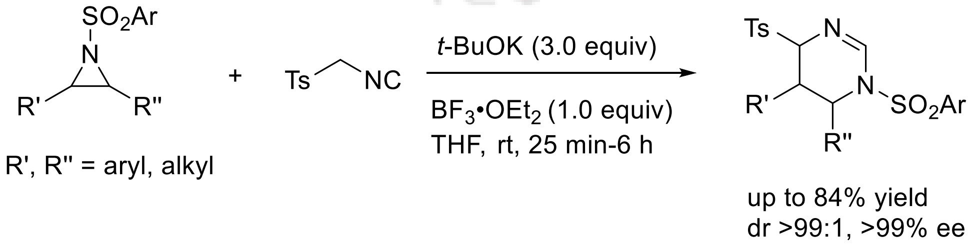
1.2.1.5 Synthesis of Pyrimidines

Zhao and co-workers developed a stereoselective (3+3)-cycloaddition of isocyanoacetates with aziridines to provide substituted tetrahydropyrimidines (Scheme 8).[9] Enantiopure aziridines react to deliver disubstituted tetrahydropyrimidines bearing a 1,3-diamino unit in good yields as a single stereoisomer.



Scheme 8. Cu-catalysed (3+3)-Cycloaddition

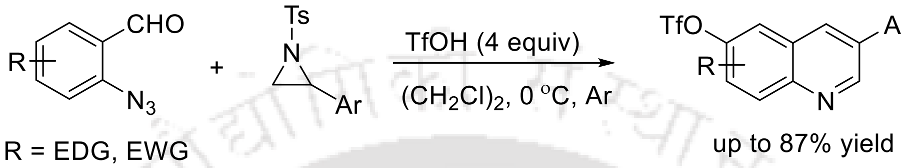
Ghorai group established the synthesis of tetrahydropyrimidines by cyclizing activated aziridines with α-acidic isocyanides (Scheme 9).[10] The transformation proceeds via Lewis acid-mediated S_N2-type ring-opening of activated aziridines with α-carbanion of the isocyanides followed by 6-*endo-dig* cyclization to furnish the product in excellent diastereoselectivity.



Scheme 9. Domino Ring-Opening Cyclization

1.2.1.6 Synthesis of Quinoline

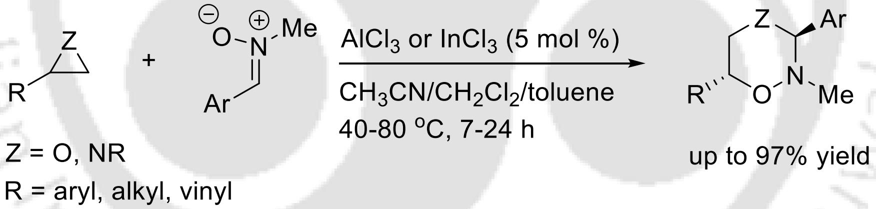
Wan and co-workers developed the synthesis of quinoline derivatives by ring-opening and cyclization of 2-aryl-1-tosylaziridines with 2-azidobenzaldehydes in the presence of TfOH (Scheme 10).[11] Aziridine has been utilized as a two-carbon surrogate to afford quinoline in moderate to good yields.



Scheme 10. Ring-Opening and Cyclization of Aziridines with Aryl Azides

1.2.1.7 Synthesis of Dioxazines and Oxadiazines

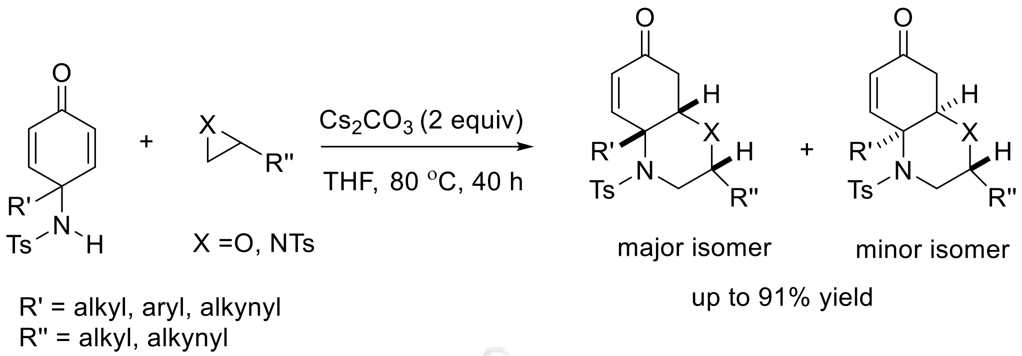
Selander and co-workers established selective annulation of nitrones with oxiranes and aziridines to synthesize dioxazine and oxadiazine derivatives using Al or In catalysts (Scheme 11).[12] This protocol demonstrates a broad substrate scope and provides access to new structural motifs in high yields and excellent selectivity.



Scheme 11. (3+3)-Annulation with Nitrones

1.2.1.8 Synthesis of Morpholines and Piperazines

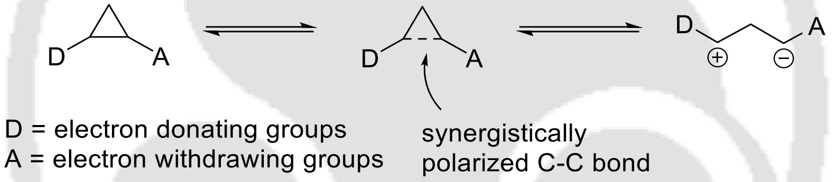
Chegondi and co-workers developed a highly diastereoselective desymmetrization approach to synthesize fused bicyclic morpholines and piperazines (Scheme 12).[13] The reaction proceeded via regioselective ring-opening of epoxides and aziridines with *p*-quinamines followed by Michael addition. The stereoselectivity of the annulation involves a chairlike six-membered transition state with minimized 1,3-diaxial interactions.



Scheme 12. (3+3)-annulation of *p*-Quinamine with *N*-Tosylaziridine

1.2.2 Using Three-Membered Carbocycles

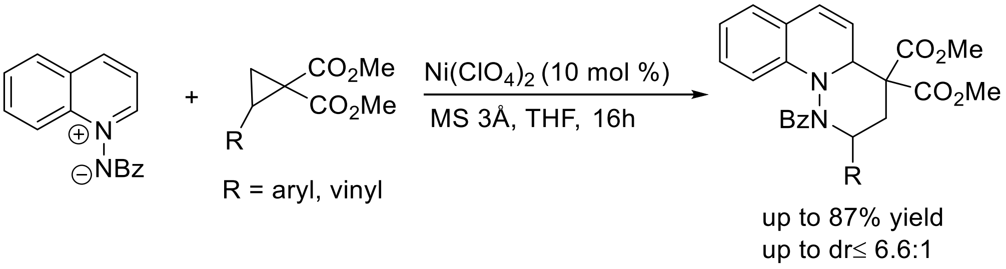
A literature review is presented on the utilization of simple cyclopropane precursors in synthesizing six-membered heterocycles such as oxazines, piperidines, isoquinoline, and other heterocycles. Lewis acid promotion/catalysis and thermal methods for ring cleavage of cyclopropanes are described.



Scheme 13. Reactivity of Donor-Acceptor Cyclopropanes

1.2.2.1 Synthesis of Dihydroquinoline

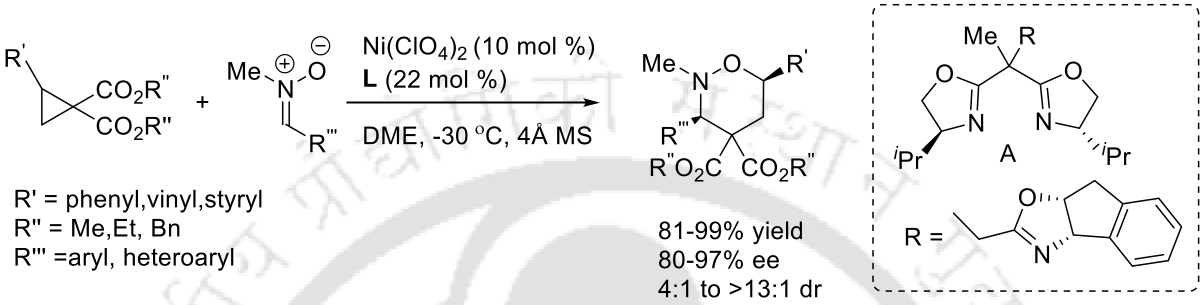
Charette and co-workers reported the synthesis of tricyclic dihydroquinoline derivatives via cycloaddition of aromatic azomethine imines with D-A cyclopropane using $Ni(ClO_4)_2$ as a catalyst (Scheme 14).[14] A stepwise mechanism was proposed which consists of a nucleophilic opening of the cyclopropane followed by a diastereoselective ring closure reaction.



Scheme 14. (3+3)-Cycloaddition with Azomethine Imines

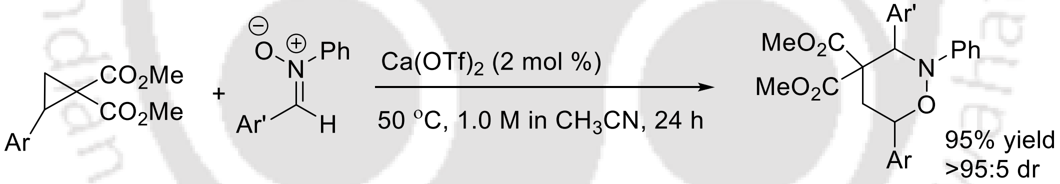
1.2.2.2 Synthesis of 1,2 Oxazines

Tang group developed a diastereoselective cycloaddition of D-A cyclopropanes with nitrones using oxazoline–Ni^{II} complex in the presence of molecular sieves (Scheme 15).[15] Combination of asymmetric cycloaddition and the kinetic resolution/cycloaddition provided straightforward access to both enantiomers of tetrahydro-1,2-oxazines.



Scheme 15. (3+3)-Annulation with Nitrones

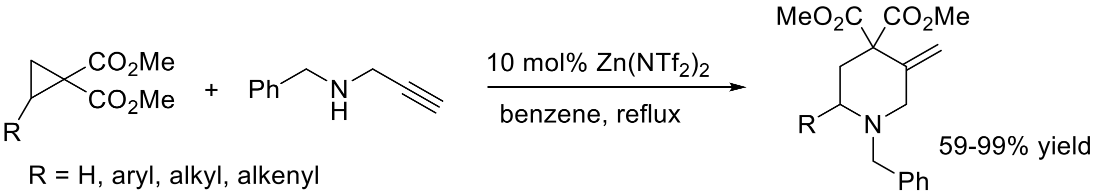
Nolin and co-workers reported a Ca(OTf)$_2$-catalyzed diastereoselective 1,3-dipolar cycloaddition of nitrones with D-A cyclopropanes (Scheme 16).[16] The reaction proceeds with good to excellent yields and diastereoselectivity.



Scheme 16. (3+3)-Annulation with Nitrones

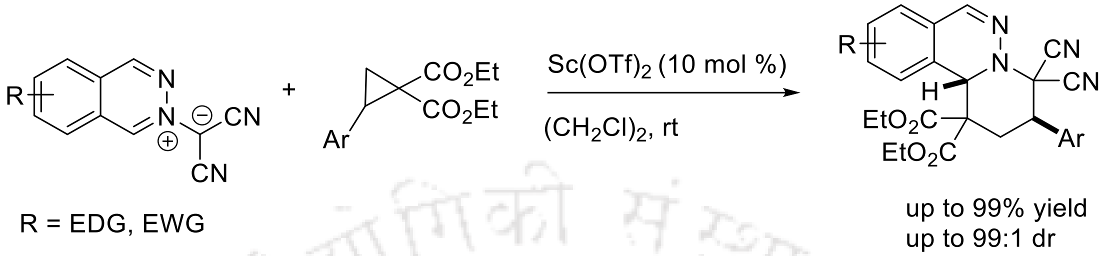
1.2.2.3 Synthesis of Piperidines

Kerr and co-workers developed a Zn-catalyzed reaction of cyclopropane with benzyl-protected propargyl amines to furnish substituted piperidines in excellent yields (Scheme 17).[17] The reaction proceeds *via* a tandem cyclopropane ring-opening/Conia-ene cyclization.



Scheme 17. Zn-Catalyzed Tandem Cyclization

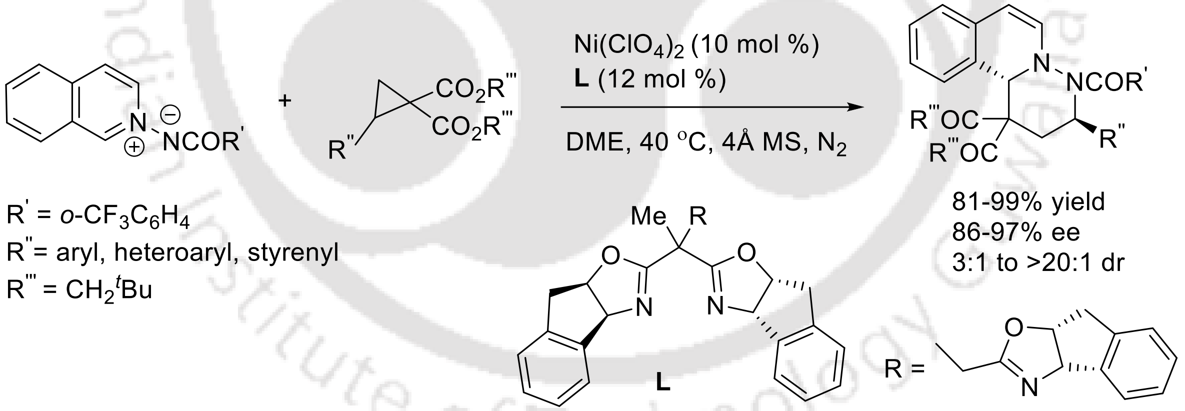
Guo and co-workers developed a $Sc(OTf)_3$ catalyzed (3+3)-cycloaddition of phthalazinium dicyanomethanides with D-A cyclopropanes to provide 3,4-dihydro-1*H*-pyrido[2,1-a]phthalazines in high yield and diastereoselectivities (Scheme 18).[18]



Scheme 18. (3+3)-Cycloaddition

1.2.2.4 Synthesis of Isoquinoline

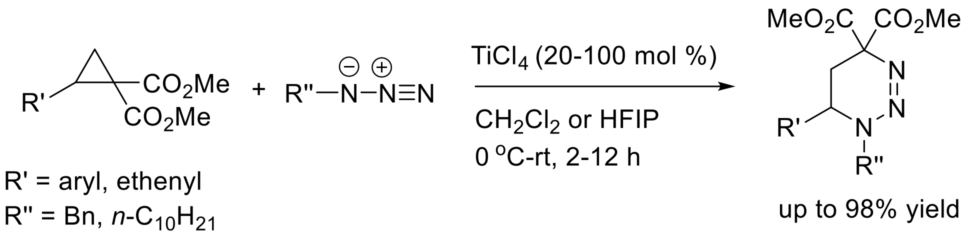
Tang and co-workers developed a (3+3)-cycloaddition of D-A cyclopropane with aromatic azomethine imines using In-TOX **L**/Ni^{II} to provide a tricyclic dihydroisoquinoline derivatives (Scheme 19).[19] Experimental results and density functional theory (DFT) study indicate that the π–π interaction between the indane group of the ligated sidearm and the phenyl group of the cyclopropane plays a vital role in the control of enantioselectivity.



Scheme 19. (3+3)-Cycloaddition with Aromatic Azomethine Imines

1.2.2.5 Synthesis of Triazinines

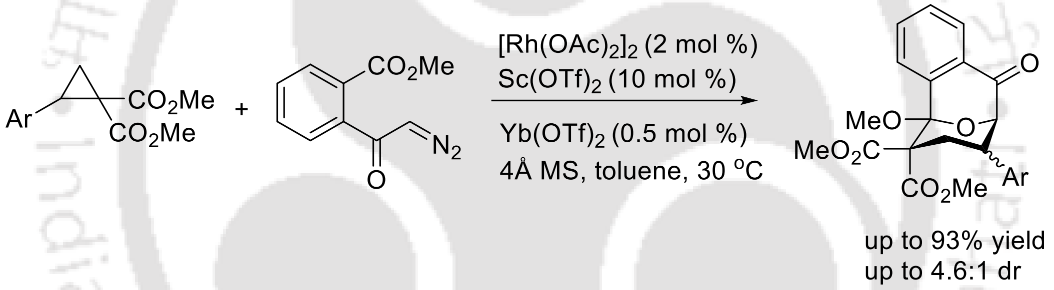
Xu and co-workers discovered a $TiCl_4$ promoted (3+3)-cycloaddition of D-A cyclopropane with azides to afford triazinines in good yields (Scheme 20).[20] Stoichiometric and substoichiometric versions were investigated through judicious choice of solvent.



Scheme 20. (3+3)-Cycloaddition with Azides

1.2.2.6 Synthesis of Pyran

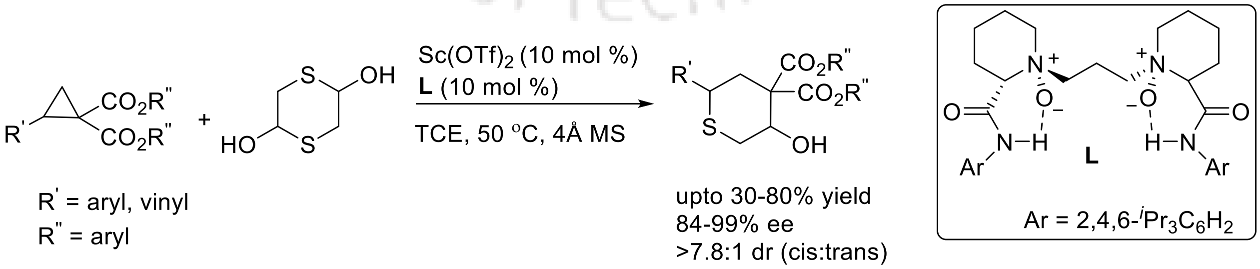
Werz and co-workers reported the first (3+3)-annulation process of D-A cyclopropanes with carbonyl ylides using synergistic dirhodium(II) and Lewis acid catalysis (Scheme 21).[21] The $Rh_2(OAc)_4$-catalyzed decomposition of diazo carbonyl compounds generated carbonyl ylides *in situ*, which reacted with cyclopropanes to afford multiply substituted pyran scaffolds in high yield and diastereoselectivity.



Scheme 21. (3+3)-Annulation with Carbonyl Ylides

1.2.2.7 Synthesis of Thiopyranols

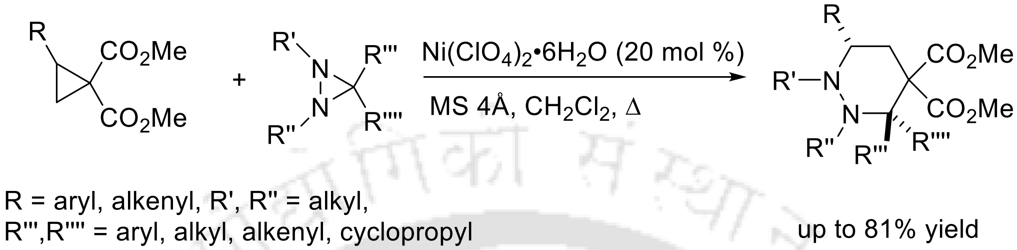
Feng and co-workers developed an enantioselective (3 + 3)-annulation of D-A cyclopropanes with mercaptoacetaldehyde in the presence of a *N,N'*-dioxide-Sc(III) complex (Scheme 22).[22] The chiral tetrahydrothiopyranols were obtained with excellent enantioselectivities.



Scheme 22. (3+3)-Annulation with Mercaptoacetaldehyde

1.2.2.8 Synthesis of Pyridazines

Trushkov and co-workers reported (3+3)-annulation of D-A cyclopropanes with diaziridines to afford perhydropyridazine derivatives in high yields and diastereoselectivity under mild Lewis acid catalysis (Scheme 23).[23]

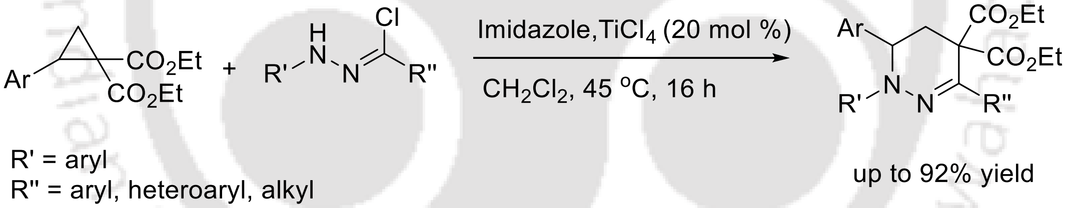


R = aryl, alkenyl, R', R'' = alkyl,
R''',R'''' = aryl, alkyl, alkenyl, cyclopropyl

up to 81% yield

Scheme 23. (3+3)-Annulation with Diaziridines

Werz and co-workers developed an efficient (3+3)-cycloaddition of D-A cyclopropanes with nitrile imines using a catalytic amount of $TiCl_4$ to access various structurally diverse pyridazine derivatives (Scheme 24).[24] The nitrile imines were generated *in situ* from hydrazonyl chlorides by treatment with imidazole.

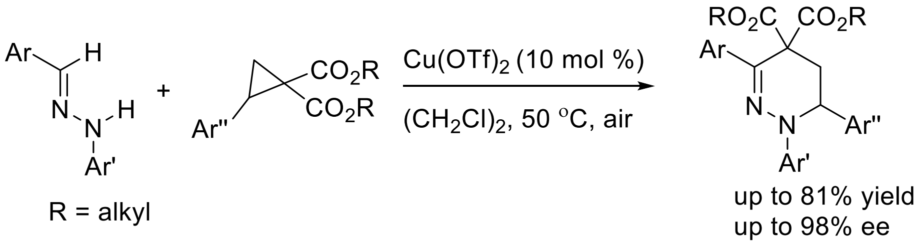


R' = aryl
R'' = aryl, heteroaryl, alkyl

up to 92% yield

Scheme 24. (3+3)-Cycloaddition with Nitrile Imines

Our group reported an aerobic copper-catalyzed tandem reaction of the readily accessible hydrazones with D-A cyclopropanes for the construction of tetrahydropyridazine structural frameworks *via* a sequential nucleophilic ring opening (S_N2) and aerobic oxidative C-C bond formation (Scheme 25).[25]



R = alkyl

up to 81% yield
up to 98% ee

Scheme 25. (3+3)-Annulation with hydrazones

1.3 Objectives of the Thesis

Several methods are available for the construction of six-membered heterocycles by forming C-N, C-O, or C-C bond or the sequential formation of C-X (X = O, N) bond followed by C-C bond. Most of the procedures display a large tolerance toward functional groups and generally proceed to excellent yields. The above-mentioned study identifies the following areas for further research.

- The studies on the production of six-membered heterocycles employing strained ring systems are restricted to (3+3), (4+2)-cycloaddition, and tandem strategies. There is a wide range of domino ring-opening and cyclization approaches that may be used with the proper nucleophile.
- For a number of previously investigated transformations, enantioselective modifications have not been found. As a result, these scaffolds must be prepared in enantiospecific manner.
- Expensive Rh, Ir or Ru complexes may restrict the scalability and sustainability of these procedures. As a result, from a practical standpoint, the development of low-cost or metal-free catalytic systems for these processes remains important.
- The studies regarding the assembly of functionalized piperazine and morpholine have been explored using conventional methods. Development of an alternative approach via domino ring opening of aziridine and oxirane with propargyl amine can be achieved.
- Dual Cu catalysis can be used for the synthesis of tetrahydroquinoline framework using DA cyclopropane and *N*-benzyl aniline
- Because of low toxicity and ease of handling, the copper-catalyzed domino reaction toward cyclic compounds has been gaining attention recently.

1.4 References

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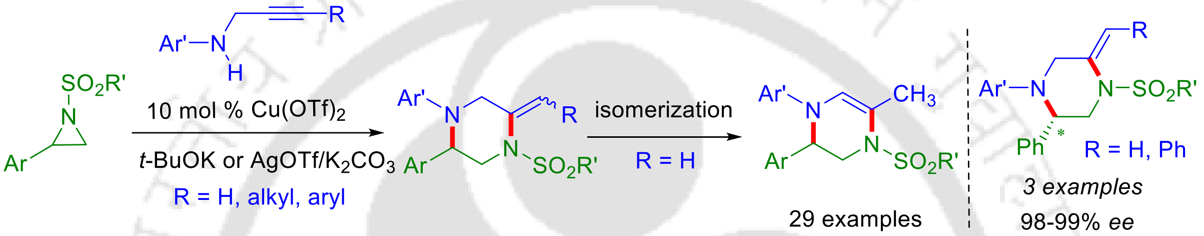
Chapter II

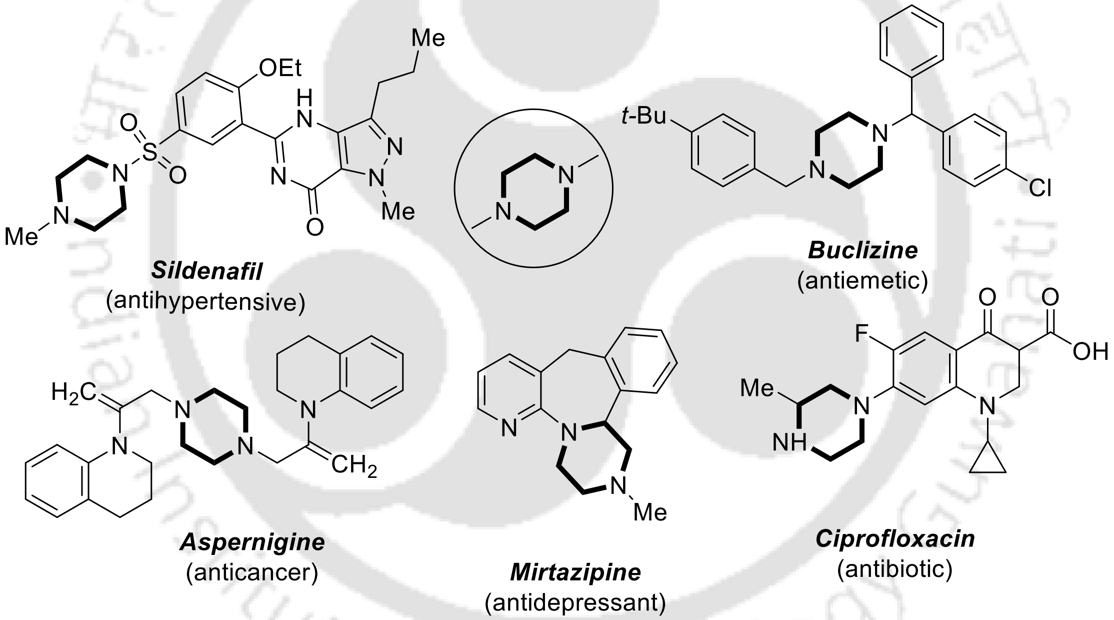
Reaction of Reactive Aziridines with N-Propargylamines: Stereospecific Synthesis of Piperazines and Tetrahydropyrazines



Org. Lett. ***2018***, *20*, *4444.*

Reaction of Reactive Aziridines with *N*-Propargylamines: Stereospecific Synthesis of Piperazines and Tetrahydropyrazines

C-N bond formation[1] is one of the most fundamental reactions due to the prevalence of nitrogen-containing heterocycles as core subunits in a broad spectrum of therapeutic and bioactive natural products.[2] Among these, piperazines and their synthetic equivalents continue to be essential substructures for pharmaceutical drug development (Figure 1).[3] As a result, many approaches for their fabrication have been created.[4,5] With the emergence of the concepts of atom economy[6] and efficiency,[7] it is thus desirable to establish a practical and universal strategy for preparing these heterocyclic scaffolds.



Sildenafil
(antihypertensive)

Buclizine
(antiemetic)

Aspernigine
(anticancer)

Mirtazipine
(antidepressant)

Ciprofloxacin
(antibiotic)

Figure 1. Selected Examples of Piperazine Containing Drugs

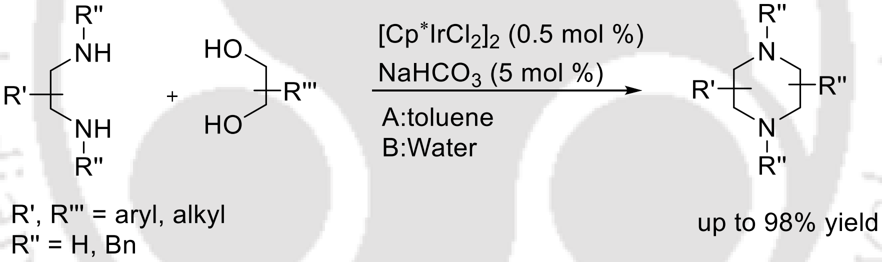
Lewis acid-catalyzed tandem ring-opening/cyclization involving aziridines has emerged as a potential synthetic technique for building *N*-containing heterocycle frameworks.[8] Aziridines can create 1,3-dipolar or zwitterion components in cascade reactions due to their intrinsic ring strain, allowing for various follow-up reactions.[9] Taking advantage of such capability, Lewis acid-catalyzed ring-opening and subsequent reactions of aziridine are thoroughly investigated. Herein, we described a $Cu(OTf)_2$-catalyzed stereospecific nucleophilic ring-opening of *N*-sulfonylaziridines with propargylamines, followed by hydroamination with base or AgOTf/base to generate piperazines. Piperazines with an exocyclic methylene double bond easily isomerize to teratrahydropyrazines. This recently discovered reaction illustrates the use of propargylamines as an amphoteric molecule, providing a unified and operationally easy way to construct piperazines and tetrahydropyrazines with a wide range of functional groups.

2.1 Strategies for the Synthesis of Piperazines and Tetrahydropyrazines

2.1.1 Synthesis of Piperazine

2.1.1.1 Cyclo-Condensation

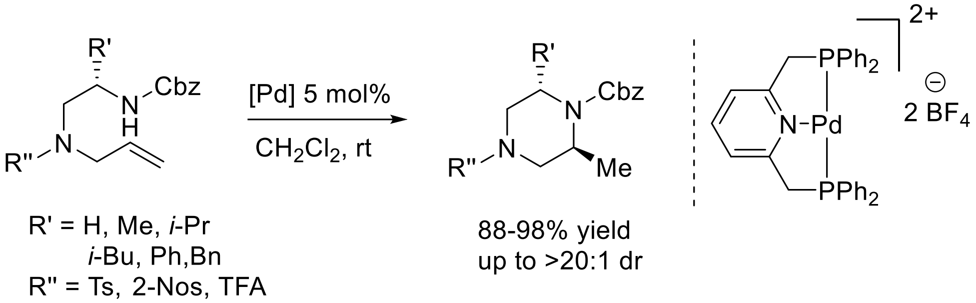
Madsen and co-workers developed an Ir-catalyzed synthesis of piperazines by cyclocondensation of 1,2-diols and 1,2-diamines (Scheme 1).[10] This constitutes a green and atom-economical transformation that can be performed in aqueous media and only produces water as a by-product.



Scheme 1. Ir-Catalysed Cyclo-Condensation

2.1.1.2 Hydroamination

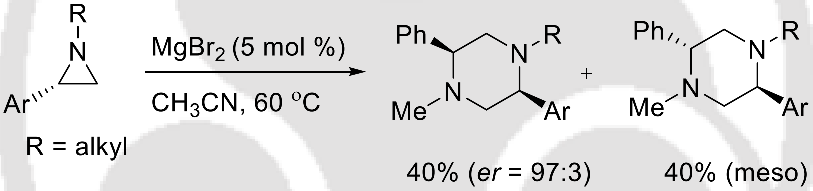
Michael and co-workers reported a highly diastereoselective intramolecular hydroamination for the modular synthesis of 2,6-disubstituted piperazines (Scheme 2).[11] The stereochemistry of the piperazines was determined to be trans by X-ray crystallography, which also showed the preferred conformation of the 2,6-disubstituted piperazine to be a twist-boat due to the $A_{1,3}$ strain.



Scheme 2. Intramolecular Hydroamination of Aminoalkene

2.1.1.3 Dimerization of Aziridines

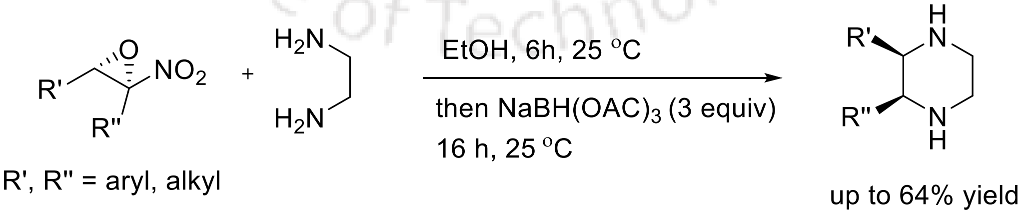
Luisi and co-workers described a Lewis acid catalyzed dimerization of aziridines to obtain 2,5-disubstituted piperazines (Scheme 3).[12] Non-activated *N*-alkyl aziridines underwent ring-opening with another aziridine followed by ring-closure in the presence of $MgBr_2$ to give the piperazines in good to excellent yield.



Scheme 3. Mg-Catalyzed Dimerization of Aziridines

2.1.1.4 (4+2)-Cycloaddition

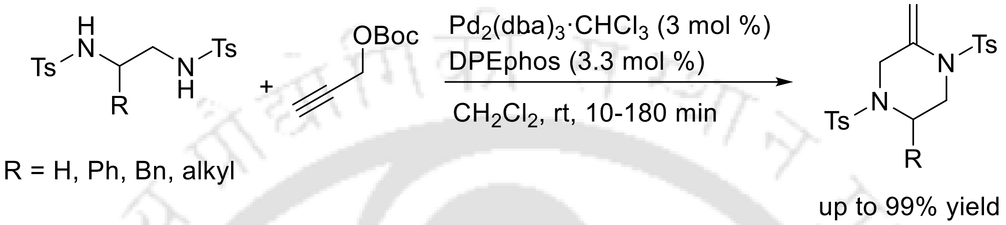
González and co-workers reported synthesis of piperazine via treatment of nitroepoxide with 1,2-diamine followed by hydride reduction of the resulting tetrahydropyrazine intermediates (Scheme 4).[13]



Scheme 4. (4+2)-Cycloaddition of Nitroepoxides with Diamines

2.1.1.5 Decarboxylative Cyclization

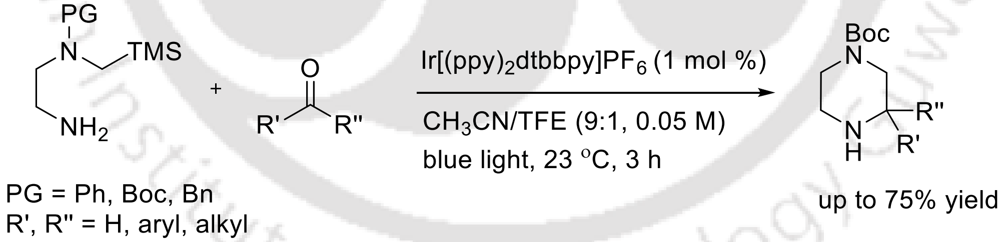
Rawal and co-workers reported the synthesis of substituted piperazines via a palladium-catalyzed decarboxylative cyclization reaction of propargyl carbonates with bisnitrogen nucleophiles (Scheme 5).[14] This process involves coupling two carbons of a propargyl unit with various diamine to provide the product in good to excellent yields with high regio- and stereoselectivity.



Scheme 5. Pd-Catalyzed Decarboxylative Cyclization

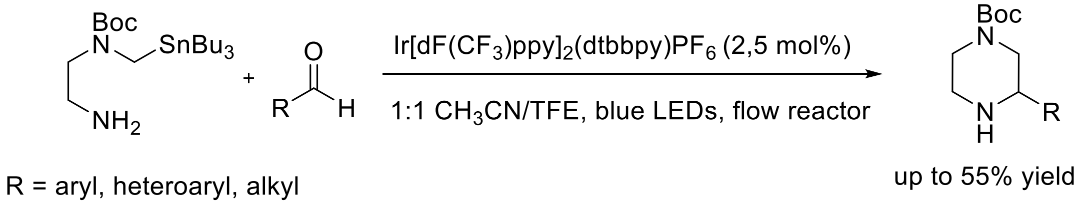
2.1.1.6 Photocatalytic synthesis

Bode and co-workers described the photoredox catalysis approach to develop silicon-based SLAP reagents for the one-step conversion of aldehydes and ketones into piperazines (Scheme 6).[15] The mild and attractive reaction conditions, excellent tolerance of unprotected functional groups and the ready availability of tailored SLAP reagents differentiate this chemistry.



Schem 6. Photocatalytic Synthesis from Silicon Reagents

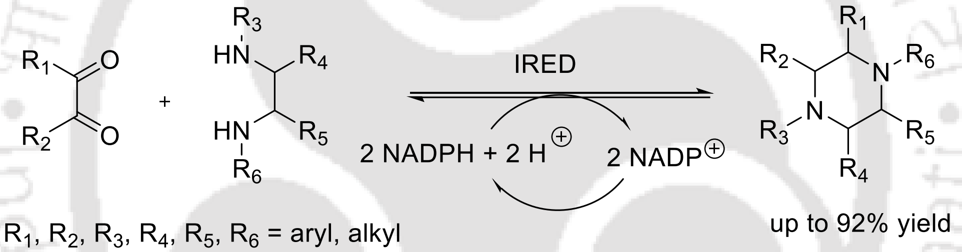
The same group used photoredox catalysis for the synthesis of piperazine from commercially available SnAP reagents and aldehydes (Scheme 7).[16] This continuous flow method offers a simplified reaction work-up that shows excellent functional group tolerance with no product inhibition.



Scheme 7. Continuous Flow Conditions with SnAP Reagents

2.1.1.7 Biocatalytic synthesis

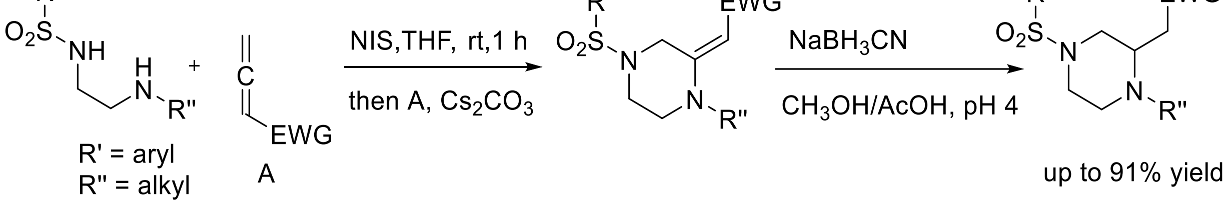
Nestl and co-workers demonstrated the direct synthesis of piperazines from 1,2-dicarbonyl and 1,2-diamine substrates utilizing Myxococcus stipitatus R-selective imine reductase as a biocatalyst (Scheme 8).[17] Under moderate reaction conditions, several N- and C-substituted piperazines with high activity and excellent enantioselectivity were produced.



Scheme 8. Biocatalytic Synthesis from 1,2-dicarbonyl and 1,2-diamine

2.1.1.8 Diamination

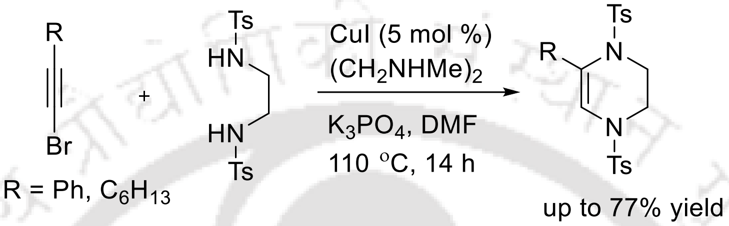
Dai and co-workers described an amphoteric diamination strategy that involves combining readily available 1,4-diamine derivatives with electron-deficient allenes via a (4 + 2)-cyclization to produce piperazines (Scheme 9).[18] According to mechanistic investigations, the formation of mono-iodinated or chlorinated diamine intermediates is crucial for the desired transformation.



Scheme 9. Intermolecular Diamination

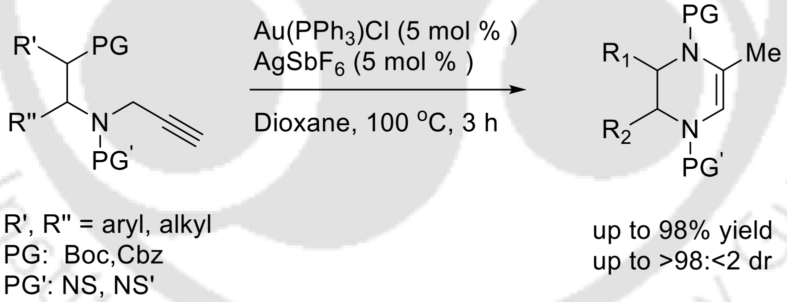
2.1.2 Synthesis of Tetrahydropyrazines

Urabe and co-workers described the synthesis of tetrahydropyrazine using a copper-catalyzed double amination of haloacetylenes (Scheme 10).[19] The proposed reaction path demonstrated that following the initial alkynylation of sulfonamide with haloacetylene, the second amination of the acetylenic bond occurred in a 6-*endo*-dig fashion under copper catalysis, yielding the product.



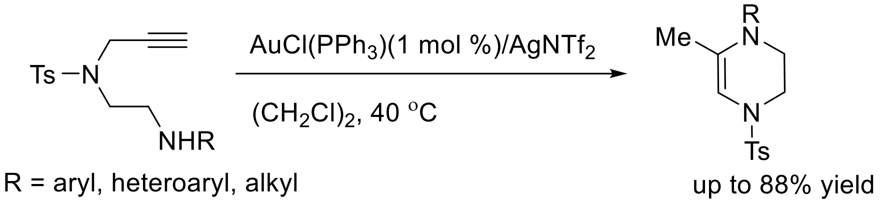
Scheme 10. Cu-Catalyzed Double Amination

Nelson and co-workers developed a gold-catalyzed cyclization to yield tetrahydropyrazines (Scheme 11).[20] Manipulation of the tetrahydropyrazines, by reduction or using multicomponent reactions, produced libraries of substitutionally diverse piperazines with lead-like molecular properties.



Scheme 11. Au-Catalyzed Cyclization

Huang group reported a simple method for synthesizing piperazine derivatives using gold (I)-catalyzed 6-*exo*-cyclization (Scheme 12).[21] Based on deuterium labelling studies, a plausible mechanism for cascade cyclization and isomerization to generate tetrahydropyrazine has been demonstrated.



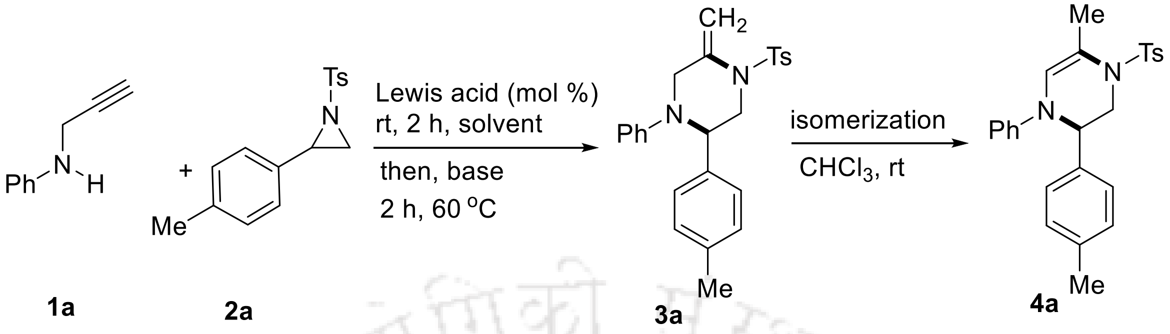
Scheme 12. Au-Catalyzed 6-*exo*-Cyclization

2.2 Present Study

This chapter presented a Cu-catalyzed stereospecific nucleophilic ring-opening of *N*-sulfonylaziridines with *N*-propargylamines followed by hydroamination to produce piperazines. Exocyclic methylene double bonds in piperazines easily isomerize to teratrahydropyrazines. We started our optimization studies with propargylamine **1a** and *N*-tosylaziridine **2a** as the standard substrates using a series of Lewis acids, bases and solvents (Table 1). To our delight, piperazine **3a** was produced in 34% yield when the reaction was carried out with 10 mol % AgOTf and 1.2 equiv *t*-BuOK in 1,2-dichloroethane. The yield increased to 73% using Cu(OTf)$_2$ as a catalyst, whereas AgOAc, AgSbF$_6$, Sc(OTf)$_3$, Bi(OTf)$_3$ and Zn(OTf)$_2$ produced inferior results (entries 2-8). In a set of bases surveyed, *t*-BuOK was superior to *t*-BuOLi, DBU and DABCO (entries 9-11). Among the solvents screened, dichloromethane, THF, toluene, DMSO and 1,2-dichloroethane, the latter gave the best results (entries 12-15). Control experiments confirmed that the target product was not formed without Cu(OTf)$_2$ and base (entries 16-17). Recrystallization of **3a** in CH$_3$CN gave crystals, whose structure was determined by X-ray analysis. Compound **3a** was stable in aprotic solvents such as ethyl acetate and CH$_3$CN, however, in CHCl$_3$, the methylene double bond isomerized to afford tetrahydropyrazine **4a** as a sole product that may be attributed to the acidic nature of CHCl$_3$.[22]

With the optimal reaction conditions, we studied the scope of the procedure using a series of aziridines **2b-o** and propargylamine **1a** as a standard substrate (Table 2). The reaction of 2-phenylaziridine **2b** provided **4b** in 67% yield. The reaction was performed on 1 mmol scale and the piperazine **4b** was produced in 63% yield. Aziridines **2c** and **2d** with a methyl group in the aryl ring furnished **4c** and **4d** in 69 and 71% yields, respectively. Aziridines having 4-chloro **2e**, 4-bromo **2f**, 4-acetoxy **2g** and 4-Ph **2h** groups in the aryl ring, successfully afforded the heterocycles **4e-h** in 48-65% yields. Gratifyingly, a 4-chloromethyl functionality **2i** in the aryl ring

Table 1. Optimization of the Reaction Conditions[a]



entry	Lewis acid (10 mol %)	base	solvent	yield (**3a**, %)[b]
1	AgOTf	*t*-BuOK	$(CH_2Cl)_2$	34
2	AgOAc	*t*-BuOK	$(CH_2Cl)_2$	trace
3	$AgSbF_6$	*t*-BuOK	$(CH_2Cl)_2$	-[c]
4	**$Cu(OTf)_2$**	***t*-BuOK**	**$(CH_2Cl)_2$**	**73**
5	$Cu(OAc)_2$	*t*-BuOK	$(CH_2Cl)_2$	0
6	$Sc(OTf)_3$	*t*-BuOK	$(CH_2Cl)_2$	0
7	$Bi(OTf)_3$	*t*-BuOK	$(CH_2Cl)_2$	0
8	$Zn(OTf)_2$	*t*-BuOK	$(CH_2Cl)_2$	45
9	$Cu(OTf)_2$	*t*-BuOLi	$(CH_2Cl)_2$	27
10	$Cu(OTf)_2$	DBU	$(CH_2Cl)_2$	23
11	$Cu(OTf)_2$	DABCO	$(CH_2Cl)_2$	n.d.
12	$Cu(OTf)_2$	*t*-BuOK	CH_2Cl_2	66
13	$Cu(OTf)_2$	*t*-BuOK	THF	trace
14	$Cu(OTf)_2$	*t*-BuOK	toluene	trace
15	$Cu(OTf)_2$	*t*-BuOK	DMSO	n.d.
16	$Cu(OTf)_2$	-	$(CH_2Cl)_2$	n.d.
17	-	*t*-BuOK	$(CH_2Cl)_2$	n.d.

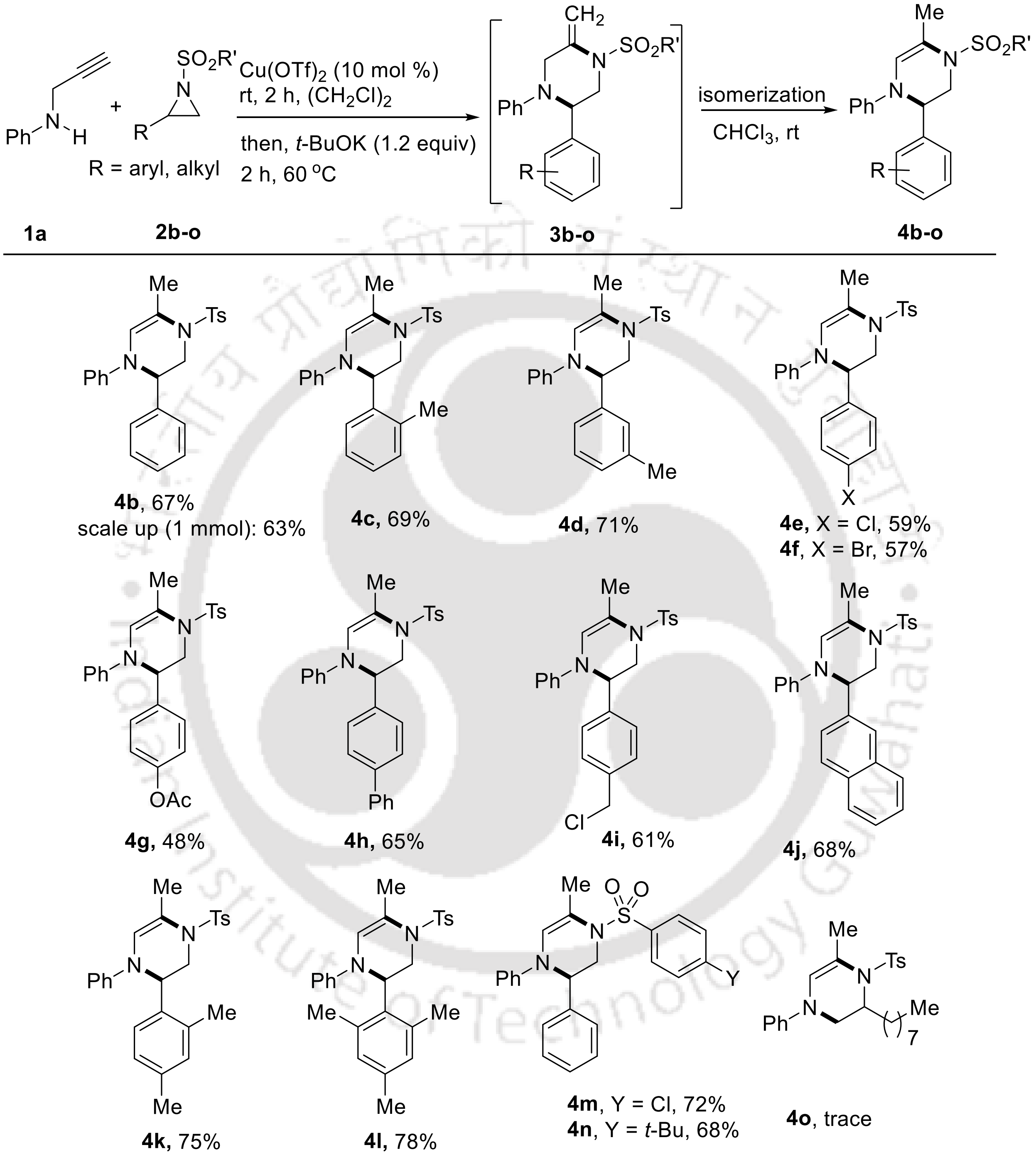
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), Lewis acid (10 mol %), solvent (2 mL), 2 h, rt; then, base (0.24 mmol), 2 h, 60 °C. [b] Isolated yield. [c] Complex mixture. n.d. = not detected

was also tolerated under standard conditions to give **4i** in 61% yield. Moreover, bulky substitutions were found to be amenable. Hence, 2-naphthyl **2j**, 2,4-dimethylphenyl **2k** and 2,4,6-trimethylphenyl **2l** substituted aziridines underwent reaction to furnish the tetrahyropyrazines congeners **4j-l** in 68-78% yields. In addition, *N*-sulfonylaziridine precursors **2m** and **2n** were proven successful substrates giving **4m** and **4n** in 72 and 68% yields, respectively. Under these conditions, 2-alkylaziridine **2o** underwent nucleophilic ring opening with propargylamine however, the cyclization was not effective.

Next, the reaction of diverse propargylamines **1b-n** were tested with aziridine **2b** as a standard substrate (Table 3). The substrates bearing 2-chloro **1b** and 2-bromo **1c** groups in the aryl ring successfully conveyed **4p** and **4q** in 69 and 71% yields, respectively. Recrystallization of **4q** in hexane and ethyl acetate (9:1) gave crystals, whose structure was determined using X-ray analysis. In addition, the substrates containing 3-chloro **1d**, 3-ester **1e**, 3-methyl **1f** and 3-nitro **1g** substituents converted to tetrahydropyrazines **4r-u** in 51-73% yields. Similarly, the reaction of the substrates bearing 4-bromo **1h**, 4-chloro **1i**, 4-fluoro **1j**, 4-iodo **1k**, 4-methoxy **1l** and 4-trifluoromethoxy **1m** functional groups occurred to afford **4v-aa** in 55-73% yields. Further, the substrates **1n** and **1o** bearing benzyl and cyclohexyl groups participated in the reaction to furnish **4ab** and **4ac** in 51 and 41% yields respectively. Whereas, Boc-protected propargylamine **1p** failed to provide the target product.

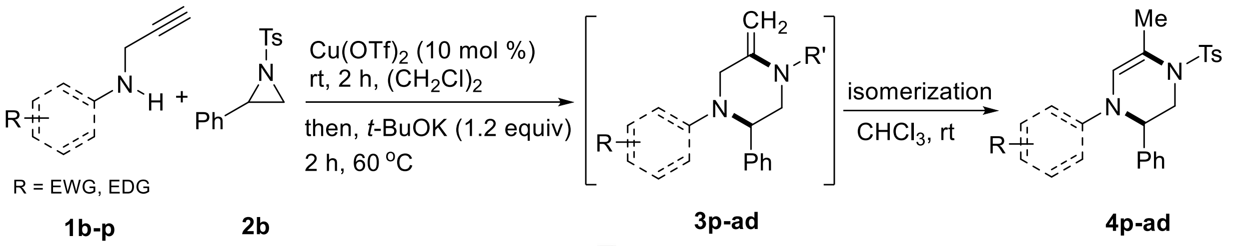
The utility of the protocol was extended to the coupling of propargylamines **1q-t** bearing internal alkynes (Table 4). The nucleophilic ring opening of aziridines readily occurred, however, the base mediated cyclization was unsuccessful. Thus, we studied the cyclization process via activating the triple bond using Lewis acid, which efficiently took place employing 10 mol % AgOTf and 1 equiv of K_2CO_3 at 80 °C in CH_3CN. For example, propargylamine **1q** having Ph substituent underwent reaction to give **3ae** in 67% yield as a 1:9 mixture of *E:Z* isomers. Similar results were observed with the substrates bearing 4-methxoyphenyl **1r** and 2-thiophene **1s** substituents, affording piperazines **3af** and **3ag** in 61 and 59% yields, respectively, whereas **1t** having a methyl substituent underwent reaction to furnish **3ah** in 51% yield as a 2:1 mixture of *E*:*Z* isomers. Recrystallization of **3ae** in CH_3CN gave single crystals, whose structure was determined by X-ray analysis. The crystal structure shows a π -π interaction between the Ph and Ts rings, which might be attributed to the double bond to exist predominately in *Z*-configuration.

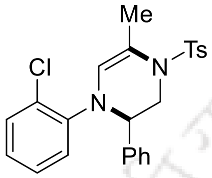
Table 2. Substrate Scope with Respect to *N*-Sulfonylaziridines[a]



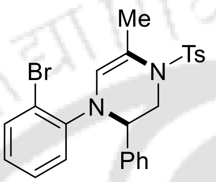
[a]Reaction conditions: **1a** (0.2 mmol), **2b-o** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), (CH$_2$Cl)$_2$ (2 mL), rt, 2 h; then, *t*-BuOK (0.24 mmol), 60 °C, 2 h. Double bond isomerization: CHCl$_3$, rt, 12 h.

Table 3. Substrate Scope with Respect to Terminal Alkynes[a]

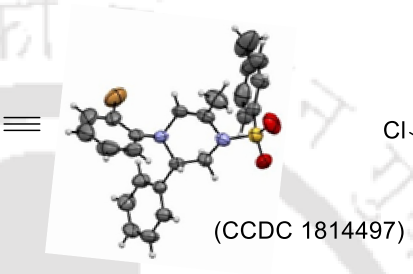


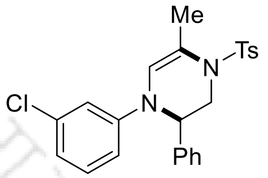


4p, 69%

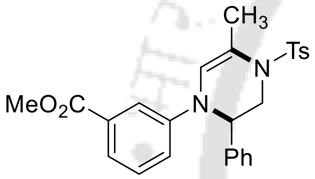


4q, 71%

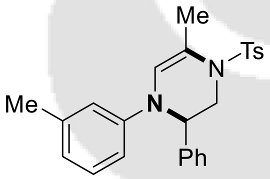




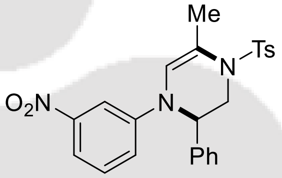
4r, 72%



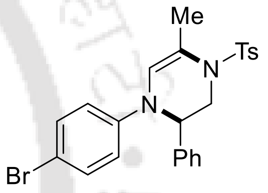
4s, 65%



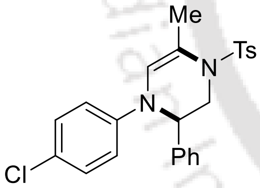
4t, 51%



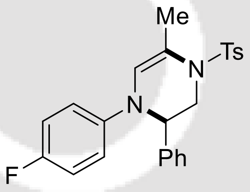
4u, 73%



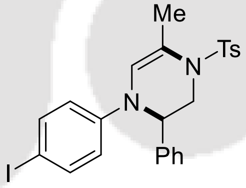
4v, 71%



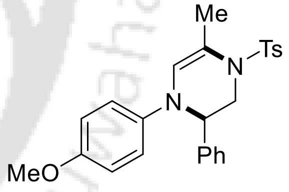
4w, 73%



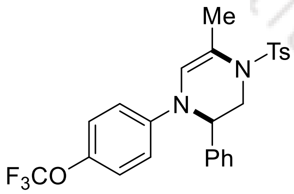
4x, 68%



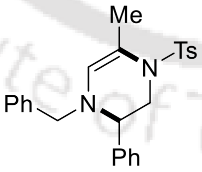
4y, 67%



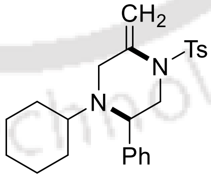
4z, 55%



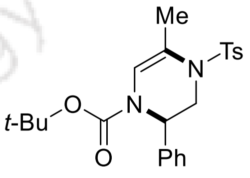
4aa, 71%



4ab, 51%



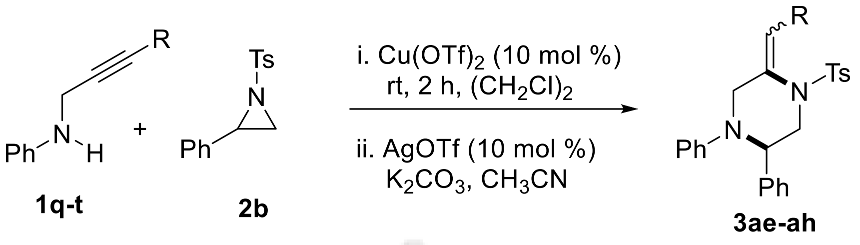
4ac, 41%

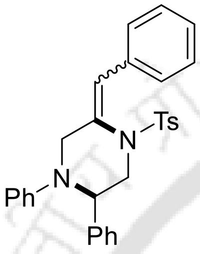


4ad, nr

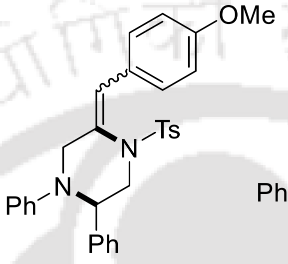
[a]Reaction conditions: **1b-p** (0.2 mmol), **2b** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), $(CH_2Cl)_2$ (2 mL), rt, 2 h; then, *t*-BuOK (0.24 mmol), 60 ºC, 2 h. Double bond isomerization: $CHCl_3$, 12 h. nr = no reaction.

Table 4. Substrate Scope with Respect to Internal Alkynes[a]

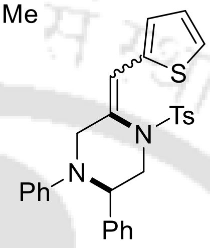




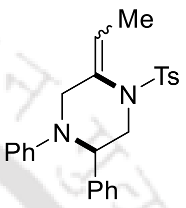
3ae, 67%
E:Z = 1:9



3af, 61%
E:Z = 1:9



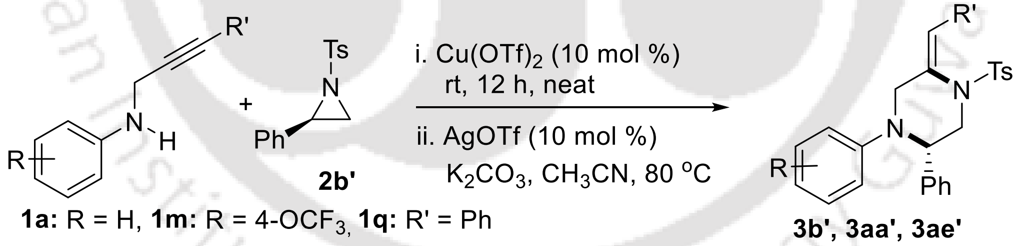
3ag, 59%
E:Z = 1:19

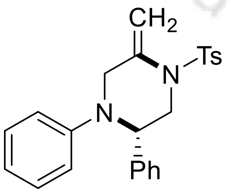


3ah, 51%
E:Z = 2:1

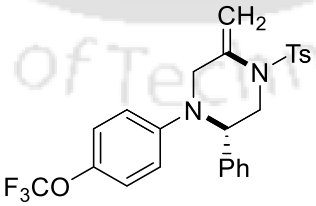
[a]Reaction conditions: **1q-t** (0.2 mmol), **2b** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), (CH$_2$Cl)$_2$ (2 mL), rt, 2 h; then, AgOTf (10 mol %), K$_2$CO$_3$ (0.2 mmol), CH$_3$CN, 80 °C, 8-10 h.

Table 5. Reaction with Chiral Aziridine 2b'[a]

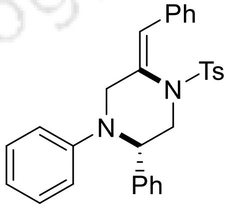




3b', 63%, 98% *ee*



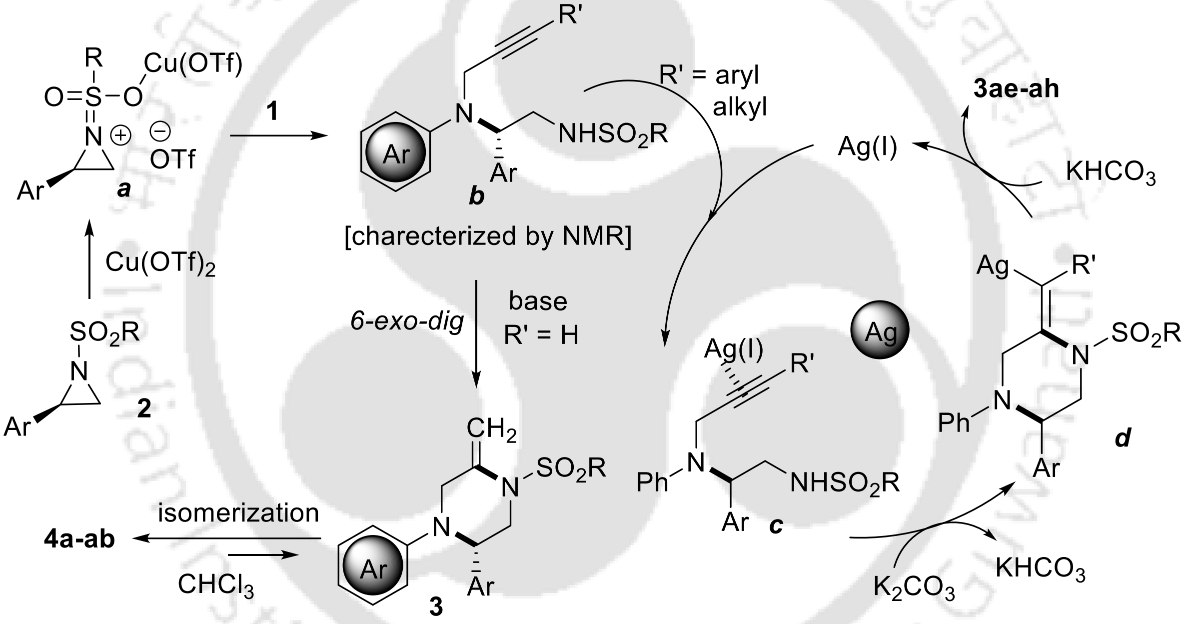
3aa', 66%, >99% *ee*



3ae', 62%, >99% *ee*

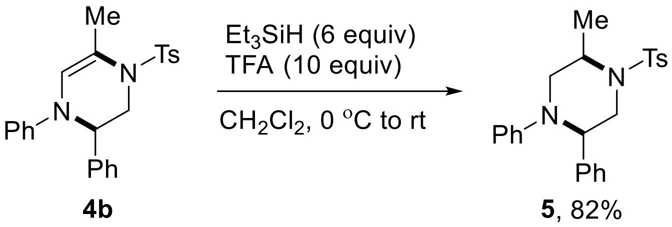
[a]Reaction conditions: **1a**, **1m**, **1q** (0.2 mmol), (*R*)-**2b'** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), rt, 2 h; then, AgOTf (10 mol %), K$_2$CO$_3$ (0.2 mmol), CH$_3$CN, 80 °C, 6 h.

To gain insight into the mechanism, the reaction of optically active (*R*)-2-phenylaziridine **2b'** was investigated with amines **1a**, **1m** and **1q** as the representative substrates (Table 5). The coupling occurred efficiently to give piperazines **3b'**, **3aa'** and **3ae'** in 98, 99 and 99% *ee*s, respectively. These results suggest that the procedure can be applied for the construction of piperazines with high enantiomeric purities. Thus, chelation of $Cu(OTf)_2$ with aziridine can generate Cu(II) intermediate ***a*** that can lead to a stereospecific S_N2 nucleophilic ring opening of aziridine **2** with propargylamine **1** to yield ***b***.[23] Base mediated 6-*exo-dig* cyclization of ***b*** can give the piperazines. Alternatively, AgOTf can activate the triple bond[12f] to provide ***c*** that can lead to base assisted hydroamination to furnish piperazines (Scheme 13).



Scheme 13. Proposed Reaction Pathway

Finally, the hydrogenation of tetrahydropyrazine **4b** was studied as the representative example (Scheme 14). The reaction can be accomplished using Et_3SiH in the presence of CF_3COOH in dichloromethane to produce piperazine **5** in 82% yield, which is important in biological and medicinal sciences.



Scheme 14. Synthesis of Piperazine

In conclusion, a stereo- and regiospecific copper-catalyzed S_N2 nucleophilic ring opening of aziridines with propargylamines and subsequent *6-exo-dig* cyclization has been demonstrated to produce piperazines with functional group diversities. Optically active aziridine can be coupled with high enantiomeric purity.

2.3 Experimental Section

2.3.1 General Information. Copper(II) triflate (98%) and potassium *tert*-butoxide (98%) were purchased from Aldrich and chloramine-T hydrate (95%) was purchased from Merck, and used as received. Aziridines and propargylamines were prepared according to the reported procedure.[24-25] Column chromatography was performed with Rankem silica gel (60-120 mesh). DRX-400 Varian spectrometer and Bruker Avance III 600 spectrometer were used for recording NMR (^1H and ^{13}C) spectra using $CDCl_3$ as solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (J) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublets, and br s = broad singlet. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotation was determined by using Perkin Elmer-343 Polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD column using *iso*-propanol and hexane as eluent. FT-IR spectra were collected on Thermo Fisher Scientific IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Single crystal X-ray data were determined using Bruker SMART APEX-II CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation ($\lambda = 0.71073$ Å) at 298(2) K. The crystal structure was solved by direct method using SHELXL-97 (Göttingen, Germany) and refined with full-matrix least squares on F^2 using SHELXL-97.

2.3.2 Procedure for the Preparation of *N*-Propargylamines.[24] An oven-dried round-bottomed flask, equipped with a magnetic stirring bar was charged with anilines (20 mmol), potassium carbonate (10 mmol, 1.38 g) and *N*,*N*-dimethylformamide (DMF, 25 mL). The mixture was stirred for 5 min at room temperature, and then a solution of propargyl bromide (80% solution in toluene, 5 mmol, 594 mg) in *N*,*N*-dimethylformamide (DMF, 5 mL) was added to the flask dropwise. The resulting mixture was then stirred at room temperature for 15 h. The resultant mixture was diluted with ethyl acetate (20 mL) and washed with brine. The aqueous phase was extracted twice with ethyl acetate (2 ×10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexane-ethyl acetate as an eluent to afford *N*-propargylamines.

2.3.3 General Procedure for Preparation of *N*-Tosyl Aziridines.[25] To a stirred solution of alkenes (1.0 mmol) and benzyltriethylammonium chloride (0.05 mmol, 11.4 mg) in CH_2Cl_2/H_2O (2:1, 15 mL) were added chloramine-T (1.1 mmol, 250.8 mg) and iodine (0.1 mmol, 25.4 mg) at room temperature under N_2. The stirring was continued for 24 h, then treated with a saturated $Na_2S_2O_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying (Na_2SO_4) and evaporation of the solvent on a rotary evaporator gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

2.3.4 Procedure for the Preparation of Chiral Aziridine. To a stirred solution of (*R*)-(−)-2-Phenylglycinol (1.0 mmol, 137 mg), TsCl (2.2 mmol, 420 mg) and DMAP (0.05 mmol, 6 mg) in dry CH_2Cl_2 (20 mL) at 0 °C was added a solution of Et_3N (3.0 mmol) in dry CH_2Cl_2 (5 mL). The resultant mixture was allowed to warm at room temperature and the stirring was continued for 24 h. The mixture was then treated with a saturated NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate (9:1) as an eluent.

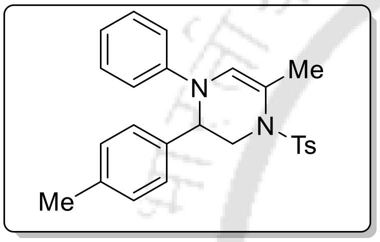
2.3.5 General Procedure for the Synthesis of Tetrahydropyrazine. A mixture of *N*-propargylamine (0.2 mmol), *N*-sulfonyl arylaziridine (0.24 mmol), $Cu(OTf)_2$ (0.02 mmol, 7.23 mg) and $(CH_2Cl)_2$ (2 mL) were stirred at room temperature (25 ^{o}C) for 2 h using $CaCl_2$ guard tube. Then, potassium *tert*-butoxide (0.24 mmol, 26.88 mg) was added to the same pot and the resulting mixture was then stirred at 60 °C for 2 h. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The mixture was washed with water (5 mL) and extracted with dichloromethane (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent, which were dissolved in $CHCl_3$ and left overnight to undergo double bond isomerization to give tetrahydropyrazines as the sole product.

2.3.6 General Procedure for the Coupling of Aziridines with Internal Alkynes. A mixture of aziridine **2b** (0.6 mmol, 164 mg), propargyl amines (0.5 mmol), $Cu(OTf)_2$ (0.05 mmol, 18 mg) were stirred in $(CH_2Cl)_2$ at room temperature for 2 h. The crude residue was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent. The ring opening product was then stirred with AgOTf (10 mol %, 5.14 mg) and K_2CO_3 (0.2 mmol, 27.6 mg) in CH_3CN (2 mL) at 80 ^{o}C for 8 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The reaction was allowed to cool at room temperature and extracted with ethyl acetate (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent

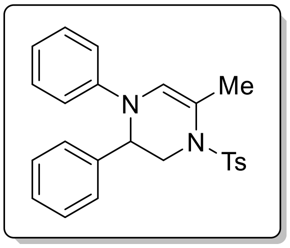
2.3.7 Scale up Synthesis of Tetrahydropyrazine. A mixture of *N*-propargylamine **1a** (1 mmol, 131 mg), 2-phenylaziridine **2b** (1.2 mmol, 327.6 mg), $Cu(OTf)_2$ (0.1 mmol, 36 mg) and $(CH_2Cl)_2$ (10 mL) were stirred at room temperature (25 ^{o}C) for 2 h using $CaCl_2$ guard tube. Then, potassium *tert*-butoxide (1.2 mmol, 134.4 mg) was added to the same pot and the resulting mixture was then stirred at 60 °C for 2 h. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (30 mL). The mixture was washed with water (10 mL) and extracted with dichloromethane (2 x 15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent, which were dissolved in $CHCl_3$ and left overnight to undergo double bond isomerization to give tetrahydropyrazine **4b**.

2.3.8 General Procedure for the Stereospecific Coupling of Aziridines with Propargyl Amine.

A mixture of aziridine **2b'** (0.24 mmol, 65 mg), propargyl amines (0.2 mmol), Cu(OTf)$_2$ (0.02 mmol, 7.3 mg) were stirred at room temperature for 12 h. The crude residue was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent. The ring opening product was then stirred with AgOTf (10 mol %) and K_2CO_3 (0.2 mmol, 27 mg) in CH_3CN (2 mL) at 80 °C for 2 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as an eluent. The reaction was allowed to cool at room temperature and extracted with ethyl acetate (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent.

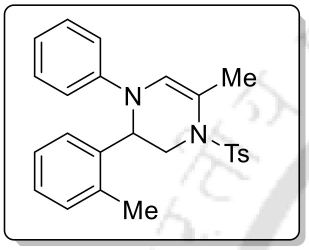


5-Methyl-1-phenyl-2-(*p*-tolyl)-4-tosyl-1,2,3,4-tetrahydropyrazine 4a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.66; colorless solid; mp 132-132 °C; yield 72% (60 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.14-7.09 (m, 4H), 7.04-6.98 (m, 4H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 2H), 6.22 (s, 1H), 4.55 (t, *J* = 4.8 Hz, 1H), 4.16 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.76 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 144.8, 143.2, 137.7, 137.3, 135.6, 129.64, 129.63, 129.2, 127.2, 126.6, 120.5, 117.1, 116.2, 112.40, 57.6, 51.6, 21.7, 21.3, 19.6; FT-IR (KBr) 2923, 2854, 1639, 1598, 1502, 1452, 1344, 1163, 1093, 1036, 811, 748, 690, 669 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1799.

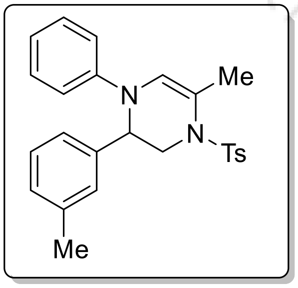


5-Methyl-1,2-diphenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.65; colorless solid; mp 119-120 °C;

yield 67% (54 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.26-7.22 (m, 3H), 7.14-7.10 (m, 6H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 2H), 6.23 (s, 1H), 4.58 (t, *J* = 4.8 Hz, 1H), 4.19 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.77 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.34 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8, 143.3, 138.7, 137.7, 129.7, 129.2, 128.9, 127.7, 127.2, 126.7, 120.6, 117.1, 116.3, 112.6, 57.9, 51.5, 21.6, 19.5; FT-IR (KBr) 3061, 3032, 2925, 1668, 1597, 1499, 1452, 1347, 1251, 1161, 1101, 1047, 975, 749 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{24}H_{24}N_2O_2S$: 405.1631, found: 405.1648.

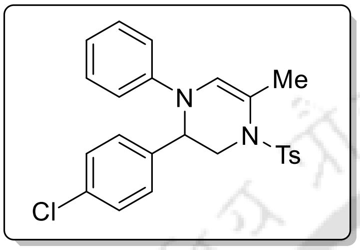


5-Methyl-1-phenyl-2-(*o*-tolyl)-4-tosyl-1,2,3,4-tetrahydropyrazine 4c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.67; colorless solid; mp 137-138 ^{o}C; yield 69% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.14-7.10 (m, 4H), 7.10-7.06 (m, 2H), 6.99-6.96 (m, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.55-6.53 (m, 2H), 6.35 (s, 1H), 4.66 (t, *J* = 4.8 Hz, 1H), 3.90-3.84 (m, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 143.4, 137.7, 136.5, 134.3, 130.9, 129.6, 129.1, 127.6, 127.2, 126.8, 126.7, 120.6, 119.2, 116.3, 112.9, 55.2, 50.3, 21.6, 19.5, 19.4; FT-IR (KBr) 2924, 1668, 1597, 1499, 1459, 1346, 1250, 1161, 1091, 1049, 975, 813, 750 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1794.

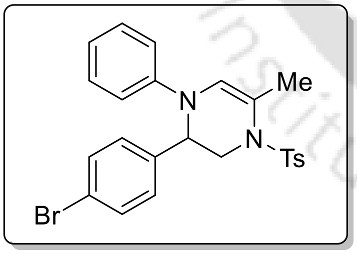


5-Methyl-1-phenyl-2-(*m*-tolyl)-4-tosyl-1,2,3,4-tetrahydropyrazine 4d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.66; colorless solid; mp 128-129 ^{o}C; yield 71% (59 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.14-7.10 (m, 5H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J*

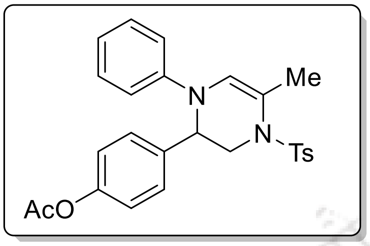
= 7.8 Hz, 2H), 6.23 (s, 1H), 4.55 (t, *J* = 4.8 Hz, 1H), 4.17 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.78 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 143.2, 138.7, 138.5, 137.6, 129.6, 129.2, 128.8, 128.5, 127.3, 127.2, 123.7, 120.5, 117.1, 116.2, 112.7, 58.0, 51.7, 21.7, 21.6, 19.6; FT-IR (KBr) 2923, 2855, 1669, 1597, 1499, 1347, 1094, 693 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1798.



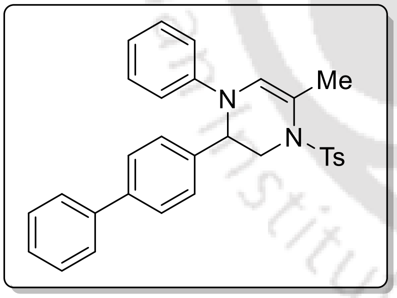
2-(4-Chlorophenyl)-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; thick liquid; yield 59% (52 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.16-7.13 (m, 6H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.82 (t, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.23 (s, 1H), 4.68 (t, *J* = 3.6 Hz, 1H), 4.30 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.71 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.38 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 143.3, 137.8, 137.3, 133.6, 129.7, 129.4, 129.0, 128.1, 126.9, 120.8, 116.0, 115.9, 112.4, 57.6, 51.1, 21.7, 19.7; FT-IR (neat) 2924, 2854, 1666, 1597, 1499, 1380, 1347, 1252, 1161, 1093, 1050, 1014, 976, 874, 814 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClN_2O_2S$: 439.1242, found: 439.1235.



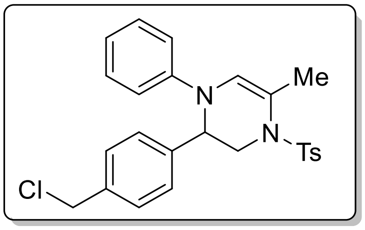
2-(4-Bromophenyl)-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; thick liquid; yield 57% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), 7.31-7.27 (m, 2H), 7.16-7.12 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 4.66 (t, *J* = 4.0 Hz, 1H), 4.30 (dd, *J* = 13.6, 4.4 Hz, 1H), 3.70 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.39 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 143.3, 137.9, 137.8, 132.0, 129.7, 129.4, 128.4, 126.9, 121.8, 120.8, 115.9, 115.8, 112.4, 57.7, 50.9, 21.7, 19.8; FT-IR (neat) 2923, 2853, 1637, 1463, 1379, 1261, 1111, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}BrN_2O_2S$: 483.0736, found: 483.0734.



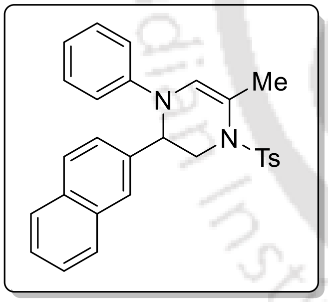
Methyl 4-(5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazin-2-yl)benzoate 4g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.36; thick liquid; yield 48% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.17-7.11 (m, 6H), 6.98-6.95 (m, 2H), 6.81 (t, *J* = 7.2 Hz, 1H) 6.67 (d, *J* = 7.8 Hz, 2H), 6.20 (s, 1H), 4.61 (t, *J* = 4.2 Hz, 1H), 4.20 (dd, *J* = 13.2, 4.8 Hz, 1H), 3.75 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 150.2, 144.7, 143.4, 137.6, 136.1, 129.7, 129.3, 127.7, 127.2, 122.0, 120.8, 116.7, 116.3, 112.7, 57.5, 51.3, 21.6, 21.4, 19.6; FT-IR (neat) 2926, 1761, 1597, 1503, 1347, 1202, 1162, 1094, 1048, 1017, 912, 874, 814 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{26}N_2O_4S$: 463.1686, found: 463.1691.



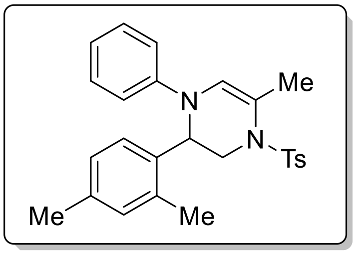
2-([1,1'-Biphenyl]-4-yl)-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.37; thick liquid; yield 65% (62 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.45-7.42 (m, 4H), 7.38-7.33 (m, 3H), 7.18-7.13 (m, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 7.8, 2H), 6.25 (s, 1H), 4.68 (t, *J* = 4.2 Hz, 1H), 4.30 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.80 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.21 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8, 143.2, 140.6, 140.4, 137.78, 137.70, 129.6, 129.3, 129.0, 127.5, 127.16, 127.14, 120.6, 116.5, 116.0, 112.5, 57.7, 51.4, 21.5, 19.8; FT-IR (neat) 2924, 1663, 1597, 1498, 1346, 1252, 1161, 1096, 875, 811, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_2O_2S$: 481.1944, found: 481.1954.



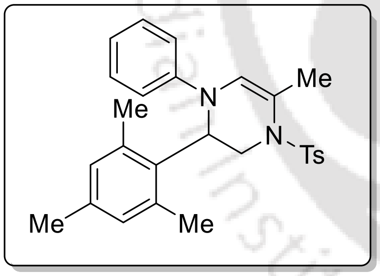
2-(4-(Chloromethyl)phenyl)-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; thick liquid; yield 61% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.29-7.26 (m, 2H), 7.17-7.11 (m, 6H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.22 (s, 1H), 4.67-4.65 (m, 1H), 4.56 (s, 2H), 4.25 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.75-3.71 (m, 1H), 2.35 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8, 143.3, 139.1, 137.8, 136.9, 129.7, 129.3, 129.2, 127.2, 127.1, 120.7, 116.6, 116.1, 112.7, 57.8, 51.2, 46.1, 21.6, 19.4; FT-IR (neat) 2925, 1668, 1597, 1499, 1382, 1346, 1251, 1161, 976, 874, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}ClN_2O_2S$: 453.1398, found: 453.1402.



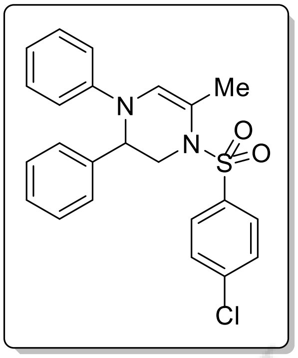
5-Methyl-2-(naphthalen-2-yl)-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.37; thick liquid; yield 68% (62 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.47-7.41 (m, 3H), 7.31-7.29 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.13-7.10 (m, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.72-6.68 (m, 4H), 6.32 (s, 1H), 4.85 (t, *J* = 4.2 Hz, 1H), 4.48 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.81 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.16 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 142.9, 137.5, 136.0, 133.6, 133.1, 129.35, 129.30, 129.0, 128.2, 127.8, 126.9, 126.2, 126.1, 125.8, 124.5, 120.6, 116.1, 115.8, 112.4, 58.4, 51.2, 21.5, 20.0; FT-IR (neat) 2924, 2854, 1664, 1597, 1499, 1458, 1255, 1160, 1094, 1049, 975, 814, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_2O_2S$: 455.1788, found: 455.1786.



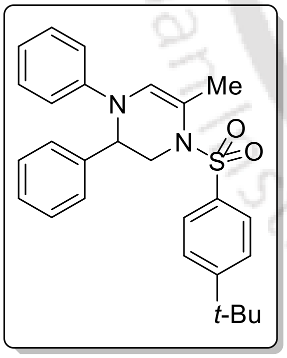
2-(2,4-Dimethylphenyl)-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.67$; colorless solid; mp 150-151 °C; yield 75% (64 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.13-7.06 (m, 4H), 6.94 (s, 1H), 6.83-6.72 (m, 3H), 6.54 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 4.61 (t, *J* = 5.2 Hz, 1H), 3.90-3.81 (m, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 143.3, 137.6, 137.1, 134.1, 133.4, 131.7, 129.6, 129.1, 127.5, 127.2, 126.6, 120.5, 119.3, 116.3, 112.7, 54.9, 50.4, 21.6, 21.2, 19.6, 19.3; FT-IR (KBr) 2924, 2854, 1665, 1597, 1499, 1456, 1347, 1162, 1091, 875, 814, 737 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{28}N_2O_2S$: 433.1944, found: 433.1946.



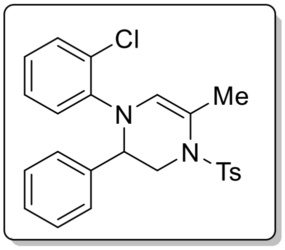
2-Mesityl-5-methyl-1-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; colorless solid; mp 156-157 °C; yield 78% (69 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.99-6.97 (m, 2H), 6.77 (s, 1H), 6.73-6.70 (m, 1H), 6.61 (s, 1H), 6.36-6.33 (m, 3H), 4.43 (dd, *J* = 10.8, 6.0 Hz, 1H), 4.08 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.39-3.35 (m, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 143.6, 136.9, 136.4, 135.2, 131.7, 130.6, 129.6, 129.3, 128.4, 127.3, 123.3, 120.3, 116.2, 114.6, 54.2, 49.0, 21.4, 20.8, 20.6, 20.2 19.6; FT-IR (KBr) 2924, 2855, 1668, 1597, 1498, 1454, 1347, 1315, 1163, 1089, 961 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{27}H_{30}N_2O_2S$: 447.2101, found: 447.2107.



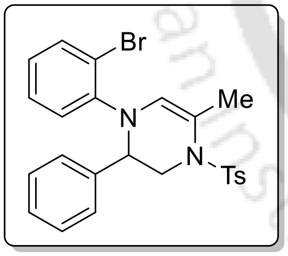
4-((4-Chlorophenyl)sulfonyl)-5-methyl-1,2-diphenyl-1,2,3,4-tetrahydropyrazine 4m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; thick liquid; yield 72% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.26-7.23 (m, 5H), 7.16-7.11 (m, 4H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.71-6.69 (m, 2H), 6.27 (s, 1H), 4.75 (t, *J* = 3.6 Hz, 1H), 4.37 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.74 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 139.3, 138.8, 138.6, 129.4, 129.3, 129.0, 128.5, 127.8, 126.6, 120.7, 116.4, 115.8, 111.8, 58.2, 51.2, 19.7; FT-IR (neat) 3029, 2926, 1668, 1597, 1500, 1252, 1164, 1092, 976, 757 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{23}H_{21}ClN_2O_2S$: 425.1085, found: 425.1082.



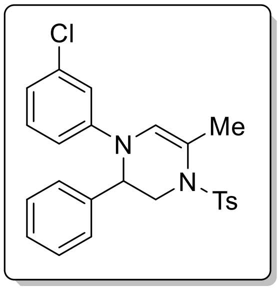
4-((4-(*tert*-Butyl)phenyl)sulfonyl)-5-methyl-1,2-diphenyl-1,2,3,4-tetrahydropyrazine 4n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.67; thick liquid; yield 68% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.38-7.37 (m, 2H), 7.25-7.21 (m, 3H), 7.12-7.08 (m, 4H), 6.79 (t, *J* = 7.2, 1H), 6.64 (d, *J* = 7.8, 2H), 6.25 (s, 1H), 4.45-4.43 (m, 1H), 4.10 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.80 (dd, *J* = 13.8, 3.6 Hz, 1H), 2.10 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.2, 144.8, 138.7, 137.3, 129.2, 128.9, 127.8, 127.1, 126.7, 126.1, 120.8, 117.9, 116.6, 112.4, 57.5, 51.7, 35.2, 31.2, 19.7; FT-IR (neat) 2962, 2927, 2869, 1667, 1597, 1499, 1455, 1385, 1252, 1165, 1100, 1048, 971, 871, 754 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}N_2O_2S$: 447.2101, found: 447.2114.



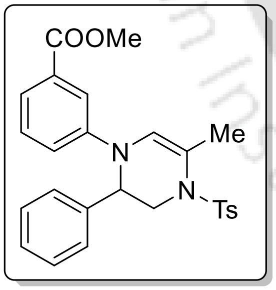
1-(2-Chlorophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.65$; colorless solid; mp 134-135 °C; yield 69% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.17-7.11 (m, 4H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.92-6.84 (m, 2H), 6.46 (d, *J* = 7.6 Hz, 1H), 5.92 (s, 1H), 4.10-3.98 (m, 2H), 3.42-3.36 (m, 1H), 2.49 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8, 142.2, 137.4, 135.9, 130.7, 130.3, 129.9, 128.6, 128.04, 128.03, 127.4, 127.1, 126.7, 126.0, 124.3, 109.4, 56.1, 52.5, 21.7, 20.0; FT-IR (KBr) 2924, 2853, 1657, 1594, 1477, 1343, 1257, 1161, 1085, 969, 704 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClN_2O_2S$: 439.1242, found: 439.1249.



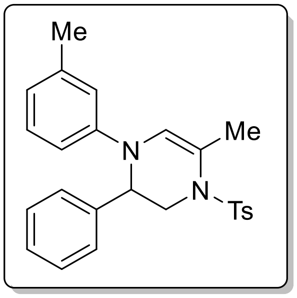
1-(2-Bromophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.54$; light brown solid; mp 136-137 °C; yield 71% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 2H), 7.43-7.36 (m, 3H), 7.17-7.09 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.79 (t, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.90 (s, 1H), 4.11-4.07 (m, 1H), 4.00-3.97 (m, 1H), 3.43-3.37 (m, 1H), 2.49 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8, 143.6, 137.4, 135.9, 133.9, 129.9, 128.6, 128.07, 128.06, 127.7, 127.5, 126.9, 126.5, 124.6, 120.7, 109.5, 56.2, 52.5, 21.7, 20.0; FT-IR (KBr) 2925, 2854, 1658, 1594, 1472, 1342, 1254, 1161, 1084, 1026, 970, 896, 730 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}BrN_2O_2S$: 483.0736, found: 483.0741.



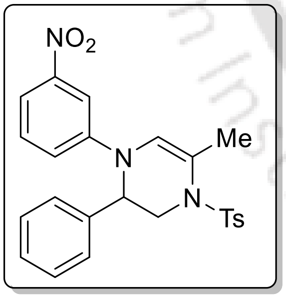
1-(3-Chlorophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.56$; colorless solid; mp 119-120 °C; yield 72% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.29-7.26 (m, 3H), 7.14-7.12 (m, 4H), 7.00 (t, *J* = 8.4 Hz, 1H), 6.76-6.74 (m, 1H), 6.64 (t, *J* = 1.8 Hz, 1H), 6.50-6.48 (m, 1H), 6.17 (s, 1H), 4.58 (t, *J* = 4.8 Hz, 1H), 4.18 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.79 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.34 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 143.5, 138.2, 137.6, 135.0, 130.1, 129.7, 129.1, 128.0, 127.2, 126.6, 120.4, 116.3, 116.0, 114.5, 114.0, 58.2, 51.7, 21.6, 19.4; FT-IR (KBr) 2923, 2854, 1644, 1595, 1562, 1491, 1453, 1385, 1340, 1231, 1157, 1119, 1093, 1025, 881, 763 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClN_2O_2S$: 439.1242, found: 439.1248.



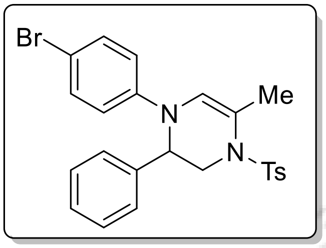
Methyl 3-(5-methyl-2-phenyl-4-tosyl-3,4-dihydropyrazin-1(2*H*)-yl)benzoate 4s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.45$; thick liquid; yield 65% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45-7.41 (m, 4H), 7.27-7.25 (m, 3H), 7.15-7.12 (m, 5H), 6.76-6.74 (m, 1H), 6.28 (s, 1H), 4.61 (t, *J* = 4.8 Hz, 1H), 4.16 (dd, *J* = 13.8, 5.4 Hz, 1H), 3.87 (s, 3H), 3.82 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.33 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 144.7, 143.4, 138.2, 137.6, 131.0, 129.7, 129.2, 129.1, 127.9, 127.2, 126.7, 121.4, 120.3, 116.9, 116.7, 113.9, 52.4, 51.7, 21.6, 19.5; FT-IR (neat) 2950, 1720, 1600, 1492, 1451, 1348, 1252, 1161, 1104, 753 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{26}N_2O_4S$: 463.1686, found: 463.1672.



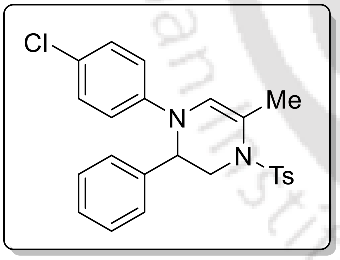
5-Methyl-2-phenyl-1-(*m*-tolyl)-4-tosyl-1,2,3,4-tetrahydropyrazine 4t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.67; thick liquid; yield 51% (43 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41-7.40 (m, 2H), 7.27-7.26 (m, 1H), 7.25-7.23 (m, 2H), 7.15-7.13 (m, 4H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.8, 1H), 6.52-6.51 (m, 1H), 6.44 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.20 (s, 1H), 4.59 (t, *J* = 4.2 Hz, 1H), 4.20 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.75 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 143.2, 139.0, 138.8, 137.8, 129.7, 129.0, 128.9, 127.7, 127.3, 126.8, 121.6, 117.15, 117.14, 113.7, 112.4, 57.9, 51.4, 21.8, 21.6, 19.5; FT-IR (neat) 2923, 2854, 1637, 1603, 1493, 1452, 1348, 1252, 1161, 1101, 1053, 976, 914, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1799.



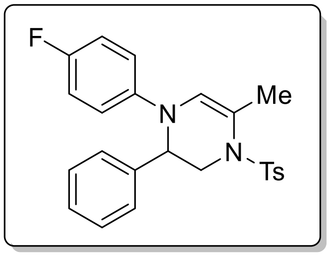
5-Methyl-1-(3-nitrophenyl)-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 149-150 °C; yield 73% (65 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61-7.59 (m, 1H), 7.50 (t, *J* = 2.4 Hz, 1H), 7.45-7.43 (m, 2H), 7.30-7.26 (m, 3H), 7.22 (t, *J* = 8.4 Hz, 1H), 7.15-7.12 (m, 4H), 6.91-6.89 (m, 1H), 6.27-6.26 (m, 1H), 4.66 (t, *J* = 4.2 Hz, 1H), 4.19 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.86 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.32 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 145.2, 143.7, 137.6, 129.9, 129.8, 129.3, 128.3, 127.2, 126.5, 121.0, 116.2, 115.6, 114.7, 110.0, 58.5, 51.9, 21.6, 19.4; FT-IR (KBr) 2923, 2854, 1619, 1526, 1488, 1345, 1250, 1160, 1098, 1049, 810, 735 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3O_4S$: 450.1482, found: 450.1485.



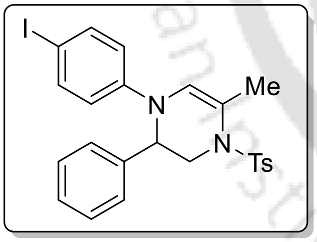
1-(4-Bromophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.70$; thick liquid; yield 71% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.28-7.26 (m, 3H), 7.20-7.10 (m, 6H), 6.52 (d, *J* = 8.4 Hz, 2H), 6.17 (s, 1H), 4.52 (t, *J* = 4.8 Hz, 1H), 4.14 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.81 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.34 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 143.4, 138.2, 137.5, 132.0, 129.7, 129.1, 127.9, 127.2, 126.6, 117.7, 116.9, 113.9, 112.9, 58.0, 51.7, 21.6, 19.5; FT-IR (neat) 2924, 1667, 1589, 1492, 1452, 1349, 1271, 1247, 1161, 1100, 976, 870, 811 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}BrN_2O_2S$: 483.0736, found: 483.0738.



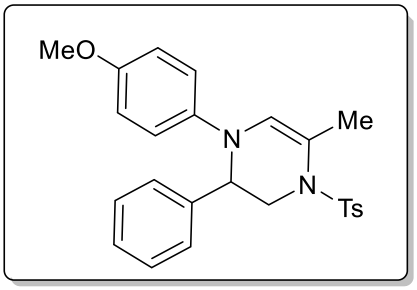
1-(4-Chlorophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.55$; thick liquid; yield 73% (64 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.26-7.25 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.11-7.09 (m, 2H), 7.05-7.04 (m, 2H), 6.56-6.54 (m, 2H), 6.17 (s, 1H), 4.50 (t, *J* = 4.8, 1H), 4.11 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.82 (dd, *J* = 13.2, 4.2 Hz, 1H), 2.34 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.4, 143.3, 138.3, 137.5, 129.7, 129.1, 127.9, 127.3, 126.7, 125.6, 117.4, 117.2, 113.7, 58.1, 51.8, 21.6, 19.5; FT-IR (neat) 2923, 2852, 1666, 1596, 1495, 1381, 1349, 1272, 1247, 1161, 1101, 1048, 976, 870, 813, 704 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}ClN_2O_2S$: 439.1242, found: 439.1243.



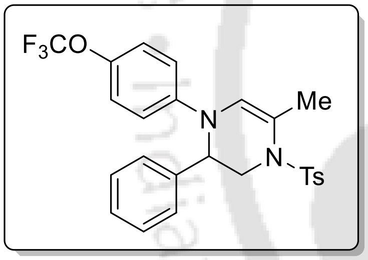
1-(4-Fluorophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; thick liquid; yield 68% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 7.8, 1.8 Hz, 2H), 6.80-6.77 (m, 2H), 6.56-6.54 (m, 2H), 6.12 (s, 1H), 4.34-4.32 (m, 1H), 3.99-3.95 (m, 1H), 3.84 (dd, *J* = 13.2, 3.6 Hz, 1H), 2.37 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5 (J_{C-F} = 239.1 Hz), 143.4, 141.5 (J_{C-F} = 2.4 Hz), 138.4, 137.2, 129.7, 129.0, 127.9, 127.4, 126.8, 119.1, 118.9 (J_{C-F} = 7.65 Hz), 115.7 (J_{C-F} = 22.5 Hz), 112.3, 58.0, 51.8, 21.7, 19.6; FT-IR (neat) 2925, 1666, 1599, 1509, 1452, 1382, 1348, 1228, 1162, 1100, 1047, 976, 873, 816, 735 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}FN_2O_2S$: 423.1537, found: 423.1546.



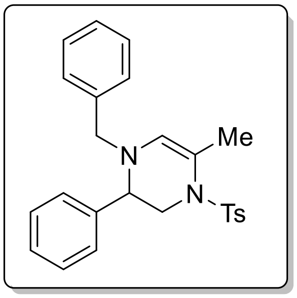
1-(4-Iodophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.57; brown solid; mp 152-153 °C; yield 67% (71 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 4H), 7.26 (br s, 3H), 7.13-7.10 (m, 4H), 6.42 (d, *J* = 8.4 Hz, 2H), 6.17 (s, 1H), 4.55 (t, *J* = 4.8 Hz, 1H), 4.17 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.81 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.34 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 143.4, 138.2, 137.9 137.6, 129.7, 129.1, 127.9, 127.2, 126.6, 118.0, 116.4, 114.2, 82.5, 58.0, 51.7, 21.6, 19.5; FT-IR (KBr) 2924, 2854, 1583, 1490, 1349, 1160, 1101, 810, 704 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}IN_2O_2S$: 531.0598, found: 531.0607.

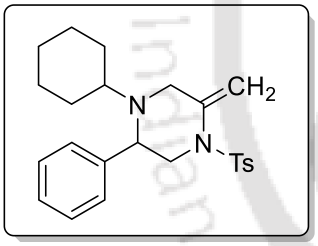


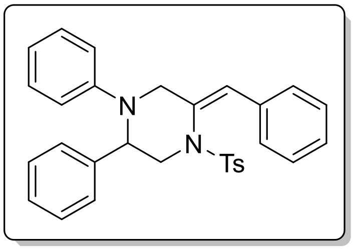
1-(4-Methoxyphenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.66$; thick liquid; yield 55% (47 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.24-7.20 (m, 5H), 7.09-7.06 (m, 2H), 6.65-6.62 (m, 2H), 6.55-6.52 (m, 2H), 6.10 (s, 1H), 4.22-4.20 (m, 1H), 3.89-3.82 (m, 2H), 3.67 (s, 3H), 2.39 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.7, 143.4, 139.2, 138.7, 137.0, 129.7, 128.8, 127.8, 127.5, 127.0, 120.8, 119.9, 114.3, 110.9, 57.8, 55.6, 51.9, 21.7, 19.7; FT-IR (neat) 2926, 1662, 1511, 1453, 1382, 1347, 1244, 1162, 1101, 1036, 976, 873, 816, 703 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_3S$: 435.1737 found: 435.1740.



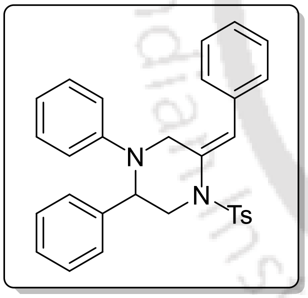
5-Methyl-2-phenyl-4-tosyl-1-(4-(trifluoromethoxy)phenyl)-1,2,3,4-tetrahydropyrazine 4aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.33$; thick liquid; yield 71% (70 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.29-7.25 (m, 3H), 7.14-7.12 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.18 (s, 1H), 4.54 (t, *J* = 4.2 Hz, 1H), 4.16 (dd, *J* = 13.2, 5.4 Hz, 1H), 3.80 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.33 (s, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.49, 143.47, 142.6, 138.3, 137.5, 129.7, 129.1, 128.0, 127.2, 126.6, 123.2 ($J_{C\text{-}F}$ = 254.7 Hz), 122.1, 116.8, 116.7, 114.0, 58.3, 51.7, 21.6, 19.4; FT-IR (neat) 3063, 3031, 2927, 1669, 1609, 1453, 1510, 1351, 1257, 1162, 1103, 706 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{23}F_3N_2O_3S$: 489.1454, found: 489.1427.


1-Benzyl-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine 4ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; thick liquid; yield 51% (43 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.34-7.29 (m, 4H), 7.23-7.21 (m, 1H), 7.19-7.16 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.80 (d, *J* = 7.2 Hz, 2H), 5.75 (s, 1H), 3.92 (dd, *J* = 14.4, 3.6 Hz, 1H), 3.75 (d, *J* = 14.4 Hz, 1H), 3.37 (d, *J* = 14.4 Hz, 1H), 3.13 (dd, *J* = 14.4, 10.2 Hz, 1H), 2.78 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.41 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.4, 137.8, 136.3, 134.7, 129.6, 129.0, 128.5, 128.39, 128.37, 127.7, 127.6, 127.2, 126.2, 109.5, 55.2, 54.4, 52.4, 21.9, 20.6; FT-IR (neat) 2924, 2853, 2345, 1650, 1384, 1345, 1165, 1112, 1027, 908, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1790.

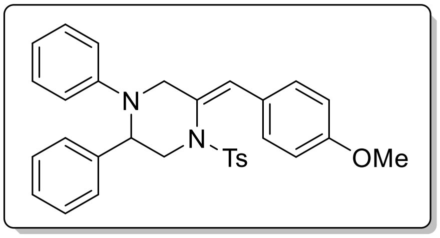

1-Cyclohexyl-5-methylene-2-phenyl-4-tosylpiperazine 4ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.62$; thick liquid; yield 41% (33 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.34-7.27 (m, 7H), 5.05 (s, 1H), 4.76 (s, 1H), 4.03 (dd, *J* = 12.6, 3.6 Hz, 1H), 3.74 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.30 (d, *J* = 13.2 Hz, 1H), 3.12 (dd, *J* = 12.6, 10.8 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.42 (s, 3H), 2.30-2.25 (m, 1H), 1.56-1.45 (m, 3H), 1.31-1.24 (m, 2H), 1.04-0.77 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 140.6, 140.1, 136.9, 129.8, 128.8, 128.0, 127.9, 127.6, 103.8, 62.6, 58.5, 53.2, 50.1, 31.5, 26.3, 25.7, 24.6, 21.7; FT-IR (neat) 3454, 2927, 2854, 1639, 1451, 1346, 1163, 1092, 701cm-1; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{30}N_2O_2S$: 411.2101 found: 411.2117.



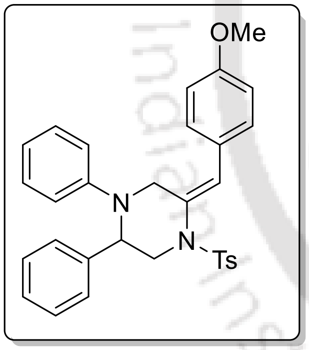
(*Z*)-2-Benzylidene-4,5-diphenyl-1-tosylpiperazine 3ae. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.55$; colorless solid; mp 157-158 °C; yield 67% (64 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.30-7.25 (m, 4H), 7.23-7.20 (m, 2H), 7.17-7.10 (m, 8H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 2H), 6.45 (s, 1H), 4.49-4.47 (m, 1H), 4.03 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.85 (d, *J* = 12.6 Hz, 1H), 3.69-3.64 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.9, 144.0, 139.6, 136.1, 135.3, 131.7, 129.6, 129.15, 129.11, 128.7, 128.1, 128.0, 127.9, 127.65, 127.63, 127.4, 121.3, 119.3, 60.3, 57.1, 53.8, 21.7; FT-IR (KBr) 2923, 1635, 1597, 1492, 1450, 1359, 1163, 1089, 951, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_2O_2S$: 481.1944, found: 481.1946; **3ac'**: yield 62% (60 mg), $[\alpha]_D^{25}$ = -25.20 (c= 0.1, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL OD, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 12.93 min (major), 9.93 min (minor)].



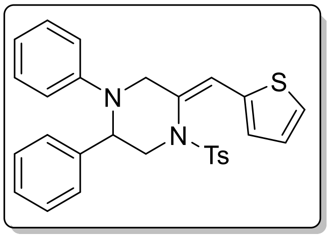
(*E*)-2-Benzylidene-4,5-diphenyl-1-tosylpiperazine. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.35 (m, 4H), 7.30-7.26 (m, 6H), 7.21-7.19 (m, 2H), 7.04-7.02 (m, 2H), 6.74 (d, *J* = 7.8 Hz, 2H), 6.67 (t, *J* = 7.2 Hz, 1H) , 6.39 (d, *J* = 8.4 Hz, 2H), 5.35-5.34 (m, 1H), 5.24-5.21 (m, 1H), 4.90 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.43-4.39 (m, 1H), 4.14-4.10 (m, 1H), 3.80 (dd, *J* = 15.0, 11.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.5, 143.8, 143.1, 139.0, 138.6, 136.2, 129.2, 129.1, 129.0, 128.4, 128.0, 127.8, 127.5, 127.1, 126.3, 119.9, 117.6, 113.5, 61.0, 57.5, 45.9, 21.8.



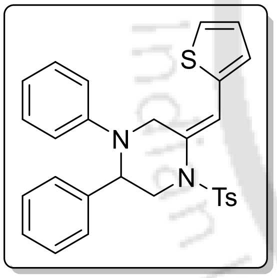
(*Z*)-2-(4-Methoxybenzylidene)-4,5-diphenyl-1-tosylpiperazine 3af. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; yellow solid; mp 170-171 °C; yield 61% (62 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.28-7.24 (m, 4H), 7.21-7.17 (m, 4H), 7.15-7.08 (m, 3H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 4H), 6.39 (s, 1H), 4.43-4.41 (m, 1H), 4.04 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.81 (d, *J* = 12.0 Hz, 1H), 3.78 (s, 3H), 3.67-3.61 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 150.0, 144.0, 139.6, 136.4, 130.6, 129.9, 129.6, 129.0, 128.7, 128.1, 127.8, 127.7, 127.5, 127.4, 121.3, 119.4, 113.5, 60.2, 57.3, 55.3, 53.9, 21.7; FT-IR (KBr) 3059, 3030, 2837, 1453, 2837, 1605,1503, 1453, 1356, 1249, 1162, 1089, 1031, 679, 551 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{31}H_{30}N_2O_3S$: 511.2050, found: 511.2028.



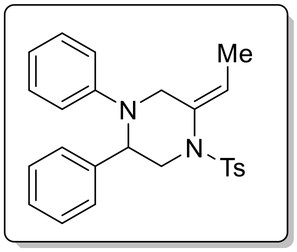
(*E*)-2-(4-Methoxybenzylidene)-4,5-diphenyl-1-tosylpiperazine. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), 7.30-7.26 (m, 5H), 7.19-7.17 (m, 2H), 7.05-7.01 (m, 2H), 6.81-6.79 (m, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 6.67 (t, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 2H), 5.26-5.23 (m, 2H), 4.89 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.42-4.38 (m, 1H), 4.11-4.06 (m, 1H), 3.81 (s, 3H), 3.79 (dd, *J* = 15.0, 11.4 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.8, 149.5, 143.3, 143.0, 138.6, 136.1, 131.3, 129.4, 129.16, 129.13, 129.0, 127.5, 127.1, 126.3, 118.2, 117.5, 113.5, 113.2, 61.0, 57.4, 55.4, 45.9, 21.8.



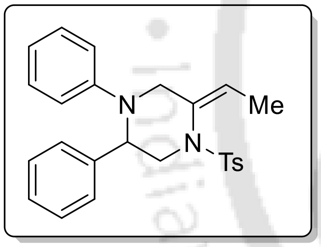
(*Z*)-1,2-Diphenyl-5-(thiophen-2-ylmethylene)-4-tosylpiperazine 3ag. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.54$; thick liquid; yield 59% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.27-7.26 (m, 1H), 7.15-7.13 (m, 4H), 7.12-7.06 (m, 4H), 6.93-6.91 (m, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.76 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 2H), 4.15 (dd, *J* = 9.6, 4.2 Hz, 1H), 4.08 (dd, *J* = 13.8, 3.6 Hz, 1H), 3.72 (d, *J* = 12 Hz, 1H), 3.59-3.56 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1, 144.5, 139.3, 137.4, 137.0, 130.0, 129.8, 129.4, 129.0, 128.6, 128.5, 127.66, 127.60, 127.4, 125.9, 123.8, 122.2, 120.8, 59.2, 57.1, 54.0, 21.8; FT-IR (neat) 3061, 3028, 2923, 2853, 1597, 1493, 1453, 1355, 1162, 1088, 736 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_2O_2S_2$: 487.1508, found: 487.1489.



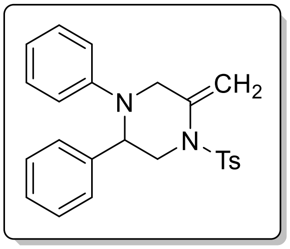
(*E*)-1,2-Diphenyl-5-(thiophen-2-ylmethylene)-4-tosylpiperazine. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.30-7.26 (m, 3H), 7.25 (m, 2H), 7.21-7.20 (m, 1H), 7.129-7.121 (m, 1H), 7.06-7.03 (m, 2H), 6.94-6.92 (m, 1H), 6.78 (d, *J* = 7.8 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 2H), 5.49-5.49 (m, 1H), 5.28-5.25 (m, 1H), 4.84 (dd, *J* = 15.6, 5.0 Hz, 1H), 4.39-4.36 (m, 1H), 4.11-4.06 (m, 1H), 3.77 (dd, *J* = 15.6, 11.4 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.5, 143.2, 141.4, 138.5, 137.1, 135.9, 129.2, 129.1, 129.0, 127.5, 127.3, 127.2, 126.8, 126.3, 125.6, 119.7, 117.8, 113.8, 60.9, 57.2, 46.1, 21.8.



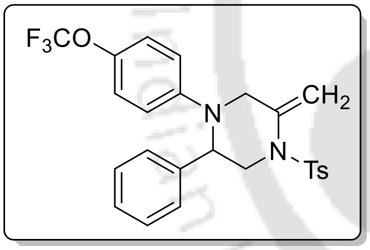
(*E*)-2-Ethylidene-4,5-diphenyl-1-tosylpiperazine 3ah. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.72$; colorless solid; mp 158-159 °C; yield 51% (43 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.37-7.34 (m, 2H), 7.29-7.25 (m, 3H), 7.04-7.01 (m, 2H) 6.84 (d, *J* = 8.4 Hz, 2H), 6.66 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 2H), 5.09-5.04 (m, 2H) 4.74 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.28-4.24 (m, 1H), 3.95-3.91 (m, 1H), 3.67-3.62 (m, 1H), 2.21 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4, 143.3, 139.0, 138.6, 137.1, 129.5, 129.1, 127.5, 126.8, 126.3, 117.3, 114.2, 113.0, 61.9, 56.8, 44.5, 23.4, 21.7; FT-IR (KBr) 3060, 2966, 2924, 1656, 1597, 1504, 1447, 1397, 1341, 1243, 1159, 1093, 746 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788, found: 419.1791.



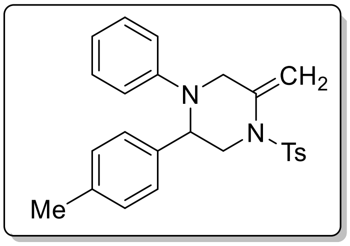
(*Z*)-2-Ethylidene-4,5-diphenyl-1-tosylpiperazine. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.22-7.13 (m, 5H), 7.09-7.06 (m, 2H), 6.78 (t, *J* = 7.2, 1H), 6.61 (d, *J* = 7.8 Hz, 2H), 5.73-5.70 (m, 1H), 4.25-4.23 (m, 1H), 3.90 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.65 (d, *J* = 12.6 Hz, 1H), 3.55-3.51 (m, 1H), 3.35-3.33 (m, 1H), 2.44 (s, 3H), 1.72 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.9, 144.2, 139.6, 136.7, 131.8, 130.0, 129.0, 128.6, 128.0, 127.5, 127.3, 126.9, 121.1, 119.1, 59.6, 56.1, 53.7, 21.8, 14.4.



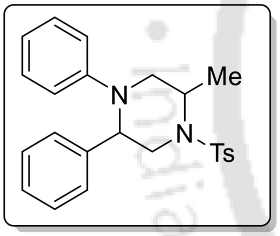
2-Methylene-4,5-diphenyl-1-tosylpiperazine 3b'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; colorless solid; mp 123-124 °C; yield 63% (51 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.36-7.28 (m, 5H), 7.08-6.99 (m, 4H), 6.69 (t, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 2H), 5.19 (s, 1H), 4.68 (s, 1H), 4.62-4.60 (m, 1H), 4.38 (dd, *J* = 14.4, 5.4 Hz, 1H), 4.05-3.99 (m, 2H), 3.76 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.9, 144.1, 140.3, 139.3, 135.4, 129.6, 129.19, 129.16, 127.9, 127.3, 126.3, 118.2, 113.4, 99.0, 61.8, 50.5, 49.2, 21.7; HRMS (ESI) m/z [M+H]+ calcd for $C_{24}H_{24}N_2O_2S$: Exact Mass: 405.1631, found: 405.1613; $[\alpha]_D^{25}$ = +20.80 (c= 0.1, $CHCl_3$); HPLC: 98% *ee* [CHIRALCEL OD, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 22.45 min (major), 9.18 min (minor)].



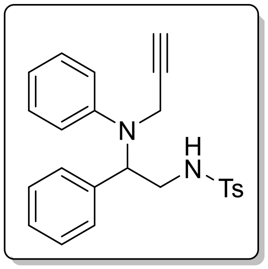
2-Methylene-5-phenyl-1-tosyl-4-(4-(trifluoromethoxy)phenyl) piperazine 3aa'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.33; sticky liquid; yield 66% (65 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.36-7.27 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 6.38-6.37 (m, 2H), 5.24 (s, 1H), 4.68 (s, 1H), 4.55-4.53 (m, 1H), 4.43 (dd, *J* = 14.4, 5.4 Hz, 1H), 4.02 (s, 2H), 3.69 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.7, 144.3, 141.0, 139.7, 139.0, 135.4, 129.5, 129.3, 128.1, 127.3, 126.1, 122.1, 113.7, 99.1, 62.1, 50.2, 49.1, 21.5; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{24}N_2O_2S$: Exact Mass: 489.1454, found: 489.1427; $[\alpha]_D^{25}$ =+ 41.60 (c= 0.3, $CHCl_3$); HPLC: >99% ee [CHIRALCEL OD, hexane/*i*PrOH = 92:8, flow rate: 1 mL /min, λ = 254 nm, t_R = 12.04 min (major), 10.93 min (minor)].



2-Methylene-4-phenyl-5-(*p*-tolyl)-1-tosylpiperazine 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.57$; colorless solid; mp 135-136 °C; yield 73% (62 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.19-7.11 (m, 4H), 7.07-7.00 (m, 4H), 6.70-6.66 (m, 4H), 6.45-6.42 (m, 2H), 5.19 (s, 1H), 4.66 (s, 1H), 4.59-4.56 (m, 1H), 4.37 (dd, *J* = 14.0, 5.2 Hz, 1H), 4.05-3.97 (m, 2H), 3.73-3.68 (m, 1H), 2.34 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.0, 144.0, 139.4, 137.6, 137.3, 135.4, 129.8, 129.5, 129.1, 127.3, 126.2, 118.1, 113.3, 98.9, 61.5, 50.6, 49.2, 21.7, 21.3; FT-IR (KBr) 2924, 2854, 1638, 1597, 1502, 1461, 1344, 1163, 1115, 912 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_2S$: 419.1788 found: 419.1794.



2-Methyl-4,5-diphenyl-1-tosylpiperazine 5. Triethylsilane (6.0 mmol, 68 mg) was added to a solution of tetrahydropyrazine **4b** (1.0 mmol, 40 mg) and trifluoroacetic acid (10 mmol, 80 µL) in CH_2Cl_2 (2 mL) at 0 °C and slowly allowed to warm to room temperature and the progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. The reaction mixture was quenched with saturated K_2CO_3 and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with brine, drying (Na_2SO_4), and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.65$; sticky liquid; yield 82% (66 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.4, 2H), 7.25-7.17 (m, 5H), 7.0-7.01 (m, 4H), 6.73 (t, *J* = 7.2, 1H), 6.55 (d, *J* = 7.8 Hz, 2H), 4.25-4.22 (m, 1H), 4.10-4.07 (m, 1H), 3.99-3.95 (m, 1H), 3.47 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.19-3.10 (m, 2H), 2.30 (s, 3H).1.34 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.9, 143.4, 140.1, 137.2, 129.8, 128.92, 128.90, 127.7, 127.0, 126.7, 120.4, 118.3, 61.4, 54.4, 50.0, 46.6, 21.7, 17.0; FT-IR (KBr) 3060, 2961, 2924, 1597, 1503, 1451, 1385, 1340, 1162, 1093, 727 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}N_2O_2S$: 407.1788, found: 407.1772.



4-Methyl-N-(2-phenyl-2-(phenyl(prop-2-yn-1-yl)amino)ethyl)benzenesulfonamide 4b'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.16$; thick liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.32-7.20 (m, 7H), 7.12 (d, *J* = 7.2, 2H), 6.88-6.83 (m, 3H), 5.00-4.96 (m, 2H), 3.82-3.73 (m, 3H), 3.48-3.43 (m, 1H), 2.41 (s, 3H), 2.23 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.3, 143.6, 137.3, 137.1, 129.9, 129.4, 129.1, 128.2, 127.3, 127.2, 119.7, 115.4, 81.1, 72.9, 61.2, 44.4, 36.8, 21.7; FT-IR (neat) 3292, 3061, 3030, 2925, 1597, 1502, 1450, 1386, 1329, 1159, 1093 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_2O_2S$: 405.1631 found: 405.1657.

Crystal Data and Structure Refinement for 4q and 3ae at 293(2)

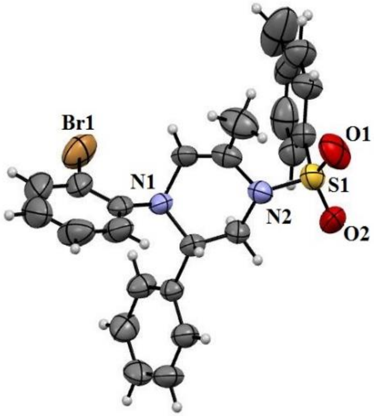


Figure 2. ORTEP diagram of 1-(2-bromophenyl)-5-methyl-2-phenyl-4-tosyl-1,2,3,4-tetrahydropyrazine **4q** with 50% ellipsoid (CCDC 1814497).

Identification code	**4q**
Empirical formula	$C_{24}H_{23}BrN_2O_2S$
Formula weight	483.41
Crystal habit, colour	block , colorless
Crystal size, mm^3	0.4 x 0.3 x 0.2
Temperature, T/K	296 (2)
Wavelength, λ/Å	0.71073
Crystal system	Triclinic
Space group	'P -1'
Unit cell dimensions	a = 10.2794(8) Å
	b = 10.4862(9) Å
	c = 12.3688(13) Å
	α =112.647(9)
	β = 99.529(8)
	γ = 103.959(7)
Volume, V/Å^3	1143.33(18)
Z	2
Calculated density, Mg·m^{-3}	1.404
Absorption coefficient, μ/mm^{-1}	1.911
F(000)	496
θ range for data collection	2.90 to 25°
Limiting indices	$-12 \leq h \leq 12, -12 \leq k \leq 11, -14 \leq l \leq 14$
Reflection collected / unique	4037/ 2616 [R(int) = 0.0233]
Completeness to θ	99.90 % (θ = 25°)
Absorption correction	Multi-scan
Max. and min. transmission	1.000 and 0.71639
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4037/8/ 273
Goodness–of–fit on F^2	1.099

Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0571, *wR*2 = 0.1368
R indices (all data)	*R*1 = 0.0919, *wR*2 = 0.1586

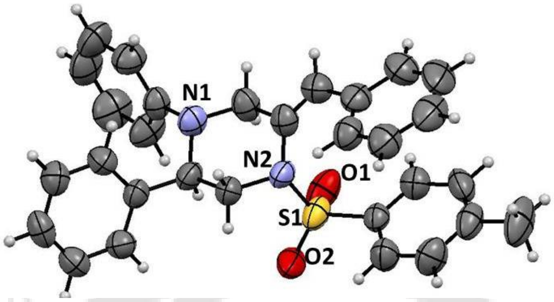


Figure 3. ORTEP diagram of (*Z*)-2-benzylidene-4,5-diphenyl-1-tosylpiperazine **3ae** with 50% ellipsoid (CCDC 1844200).

Identification code	**3ae**
Empirical formula	$C_{30} H_{28} N_2 O_2 S$
Formula weight	480.60
Crystal habit, colour	Block, Colorless
Crystal size, mm^3	0.4 x 0.35 x 0.21
Temperature, *T*/K	296(2) K
Wavelength, *λ*/Å	0.71073
Crystal system	'Triclinic'
Space group	'P -1'
Unit cell dimensions	a = 10.0844(7) Å b = 10.8754(7) Å c = 12.8570(9) Å α = 109.829(4) β = 105.174(4) γ = 94.782(4)
Volume, *V*/Å^3	1256.98(15)

Z	2
Calculated density, Mg·m^{-3}	1.270
Absorption coefficient, μ/mm^{-1}	0.159
F(000)	508.0
θ range for data collection	1.77 to 25°
Limiting indices	$-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-14 \leq l \leq 15$
Reflection collected / unique	4363/2688
Completeness to θ	98.20% ($\theta = 25°$)
Absorption correction	Multi-scan
Max. and min. transmission	0.983 and 0.957
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	4363/0/ 317
Goodness–of–fit on F^2	1.050
Final *R* indices [*I*>2sigma(*I*)]	R1 = 0.0603, wR2 = 0.1671
R indices (all data)	R1 = 0.1017, wR2 = 0.1919

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16. Jindakun, C.; Hsieh, S.-Y.; Bode, J. W. *Org. Lett.* **2018**, *20*, 2071.
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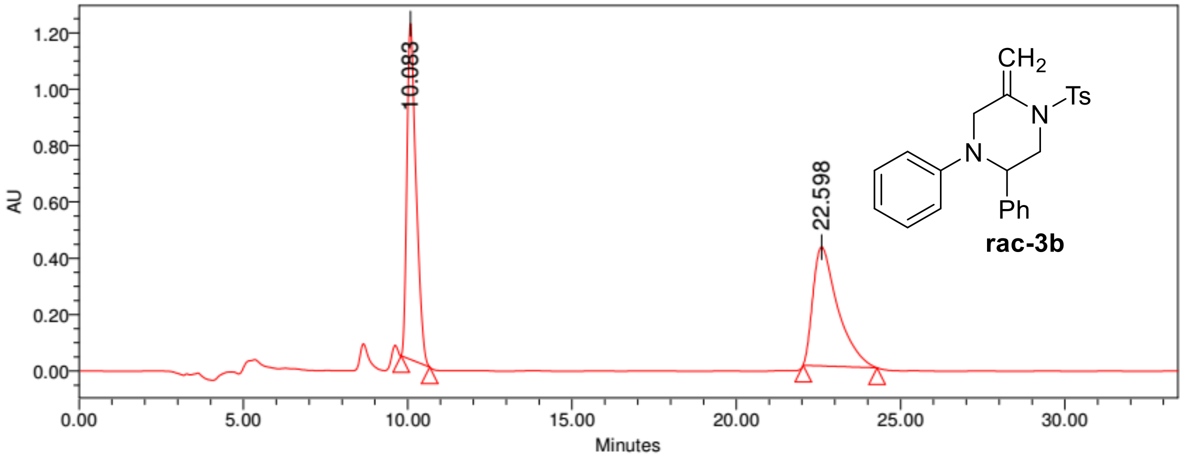
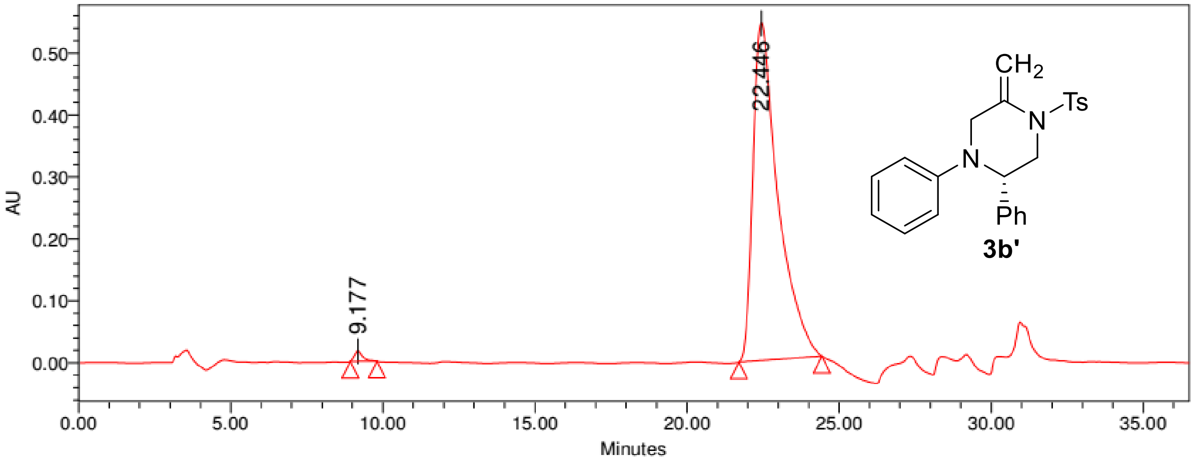
2.5 Selected HPLC Chromatograms



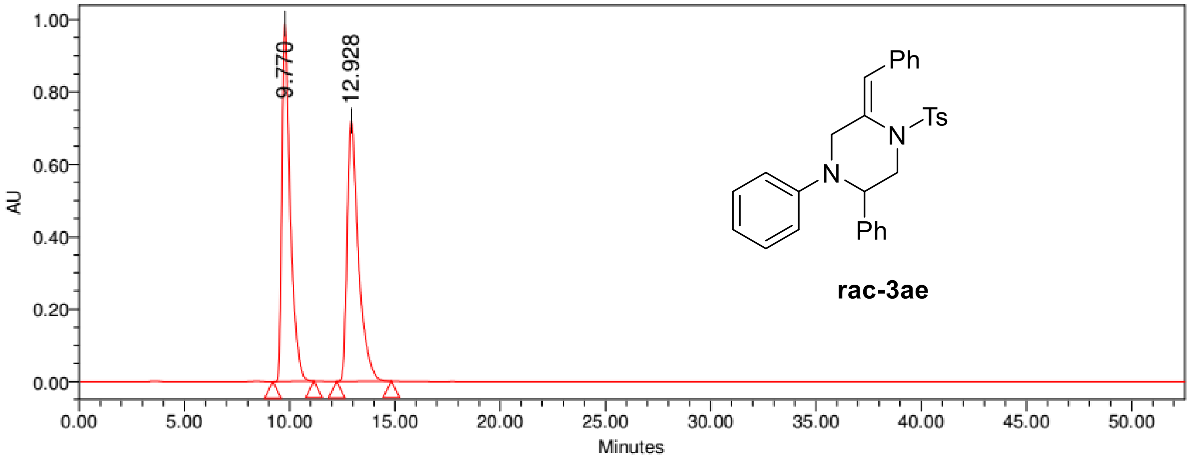
Peak Results

	RT	Height (µV)	% Area
1	10.083	1192202	50.84
2	22.598	422094	49.16



Peak Results

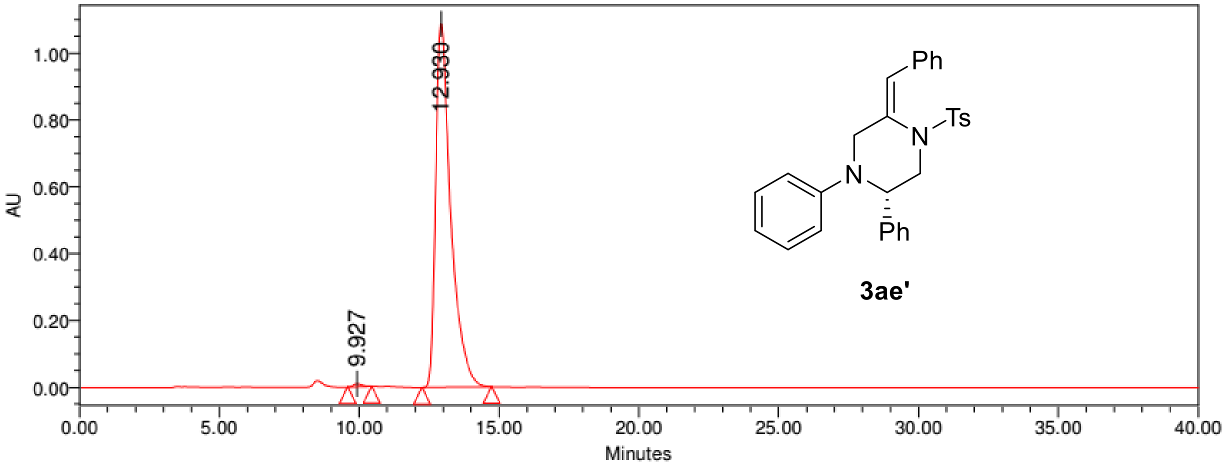
	RT	Height (µV)	% Area
1	9.177	16641	1.01
2	22.446	544462	98.99



rac-3ae

Peak Results

	RT	Height (µV)	% Area
1	9.770	989167	50.16
2	12.928	720421	49.84

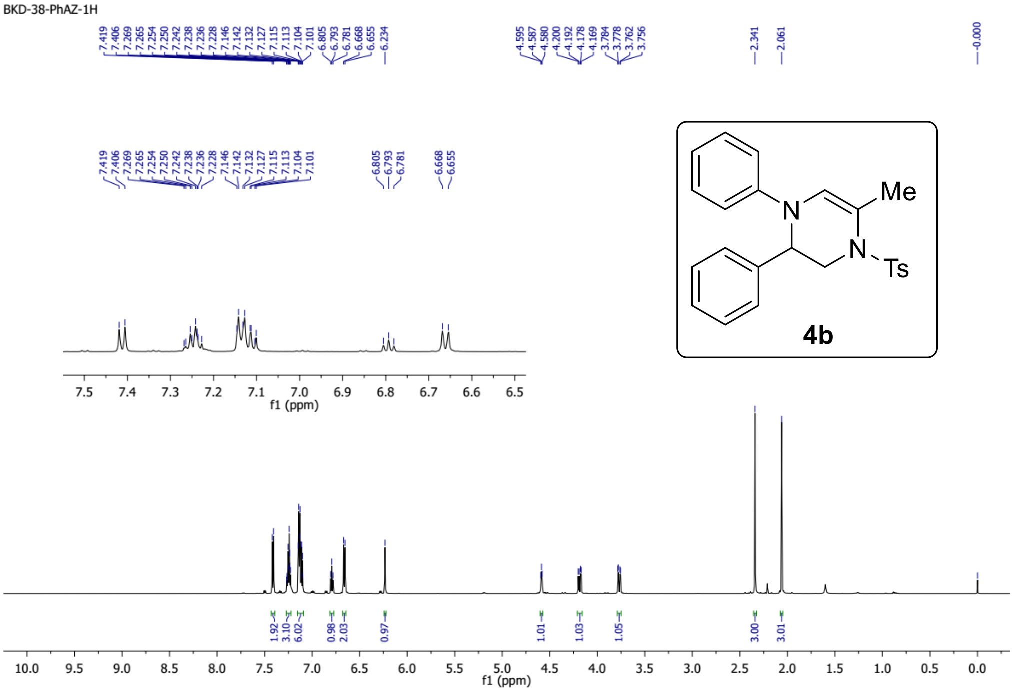


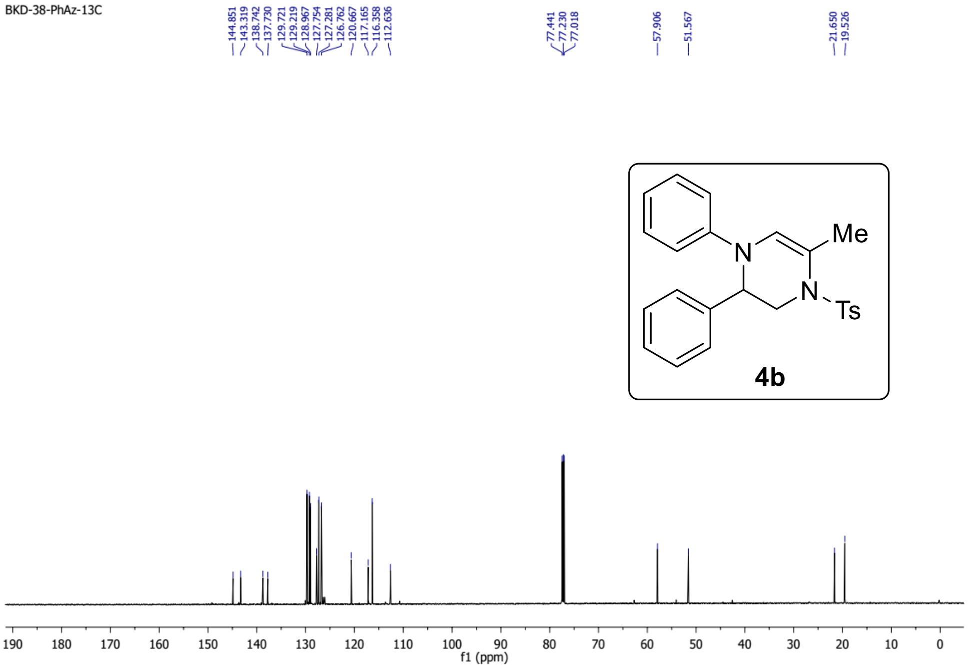
3ae'

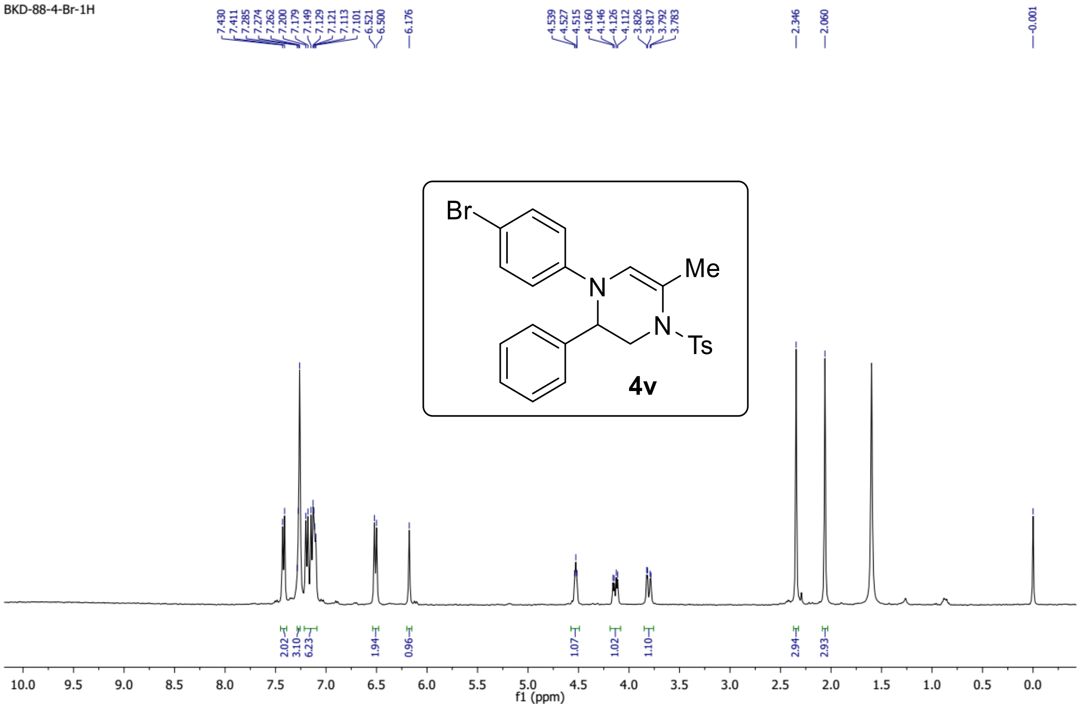
Peak Results

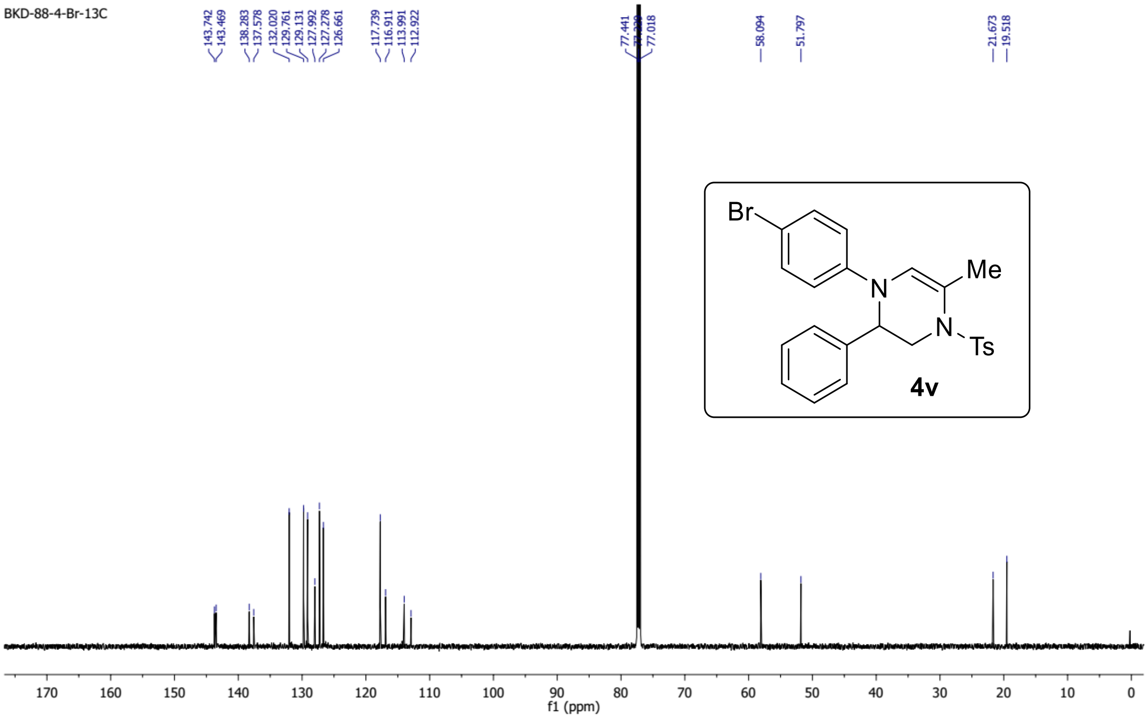
	RT	Height (µV)	% Area
1	9.927	8629	0.45
2	12.930	1087813	99.55

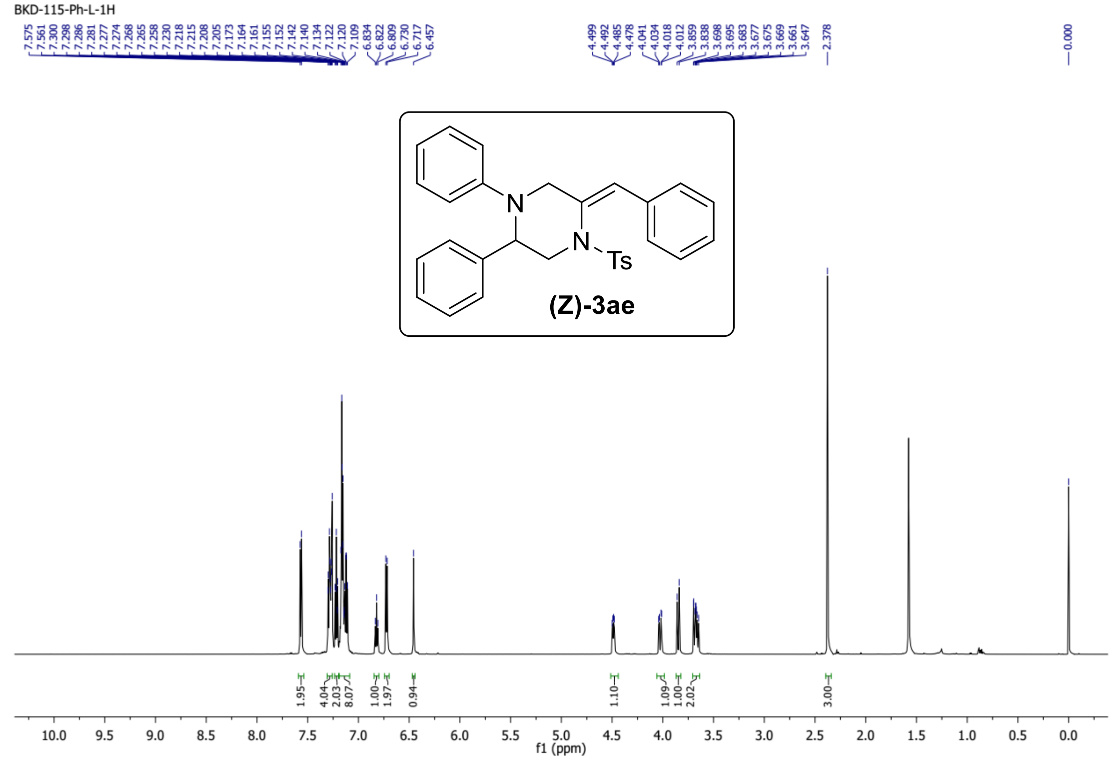
2.6 Selected NMR (^{1}H and ^{13}C) Spectra

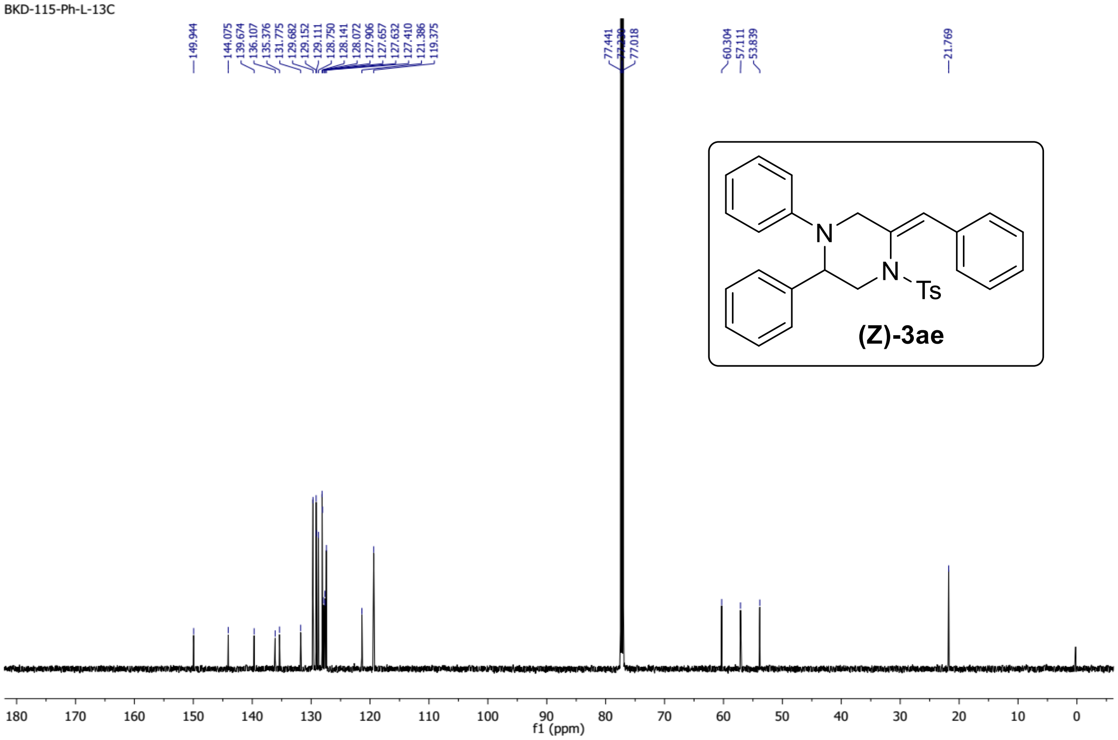





BKD-88-4-Br-1H
7.430
7.411
7.285
7.274
7.262
7.200
7.179
7.149
7.129
7.121
7.113
7.101
6.521
6.500
6.176
4.539
4.527
4.515
4.160
4.146
4.126
4.112
3.826
3.817
3.792
3.783
2.346
2.060
-0.001
Br
N
Me
N
Ts
4v
2.02
3.10
6.23
1.94
0.96
1.07
1.02
1.10
2.94
2.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

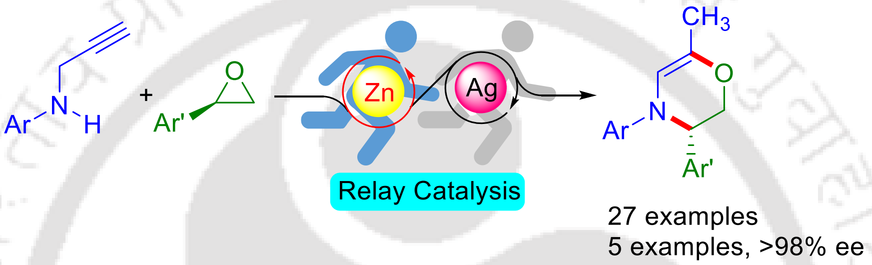

BKD-88-4-Br-13C
143.742
143.469
138.283
137.578
132.020
129.761
129.131
127.992
127.278
126.661
117.739
116.911
113.991
112.922
77.441
77.018
58.094
51.797
21.673
19.518
Br
N
Me
N
Ts
4v
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


BKD-115-Ph-L-1H
7.575
7.561
7.300
7.298
7.286
7.281
7.277
7.274
7.268
7.265
7.258
7.230
7.218
7.215
7.208
7.205
7.173
7.164
7.161
7.155
7.152
7.142
7.140
7.134
7.122
7.120
7.109
6.834
6.822
6.809
6.730
6.717
6.457
4.499
4.492
4.485
4.478
4.041
4.034
4.018
4.012
3.859
3.838
3.698
3.695
3.683
3.677
3.675
3.669
3.661
3.647
2.378
0.000
N
N
Ts
(Z)-3ae
1.95
4.04
2.03
8.07
1.00
1.97
0.94
1.10
1.09
1.00
2.02
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


BKD-115-Ph-L-13C
149.944
144.075
139.674
136.107
135.376
131.775
129.682
129.152
129.111
128.750
128.141
128.072
127.906
127.657
127.632
127.410
121.386
119.375
77.441
77.230
77.018
60.304
57.111
53.839
21.769
N
N
Ts
(Z)-3ae
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Chapter III

Reaction of Oxiranes with N-Propargylamines: Stereospecific Synthesis of 1,4-Oxazines



✓ stereospecific ✓ atom economy ✓ broad substrate scope

Manuscript submitted.

Reaction of Oxiranes with *N*-Propargylamines: Stereospecific Synthesis of 1,4-Oxazines

The transition-metal-catalyzed synthesis of C-O bond[1] has been considered a key focus in chemical space because of the prevalence of oxygen-containing heterocycles in a variety of naturally occurring alkaloids and medicines with extensive therapeutic uses.[2] Among them, 1,4-oxazines and their saturated congener morpholines (tetrahydro-1,4-oxazines) are found near value-added and powerful pharmacophore units such as finafloxacin, reboxetin, emorfazone, aprepitant, and linezolid, which have antibacterial, antidepressant, analgesic, and antiemetic properties (Figure 1).[3] As a result, significant synthetic progress has been made in constructing these structural frameworks. Despite advances in this area, stereospecific synthesis of these structural scaffolds remains difficult from an atom- and step-economical standpoint.[4] In keeping with this broad aim, designing and developing an effective method for their synthesis from simple feedstocks with stereoselectivity control is desirable.

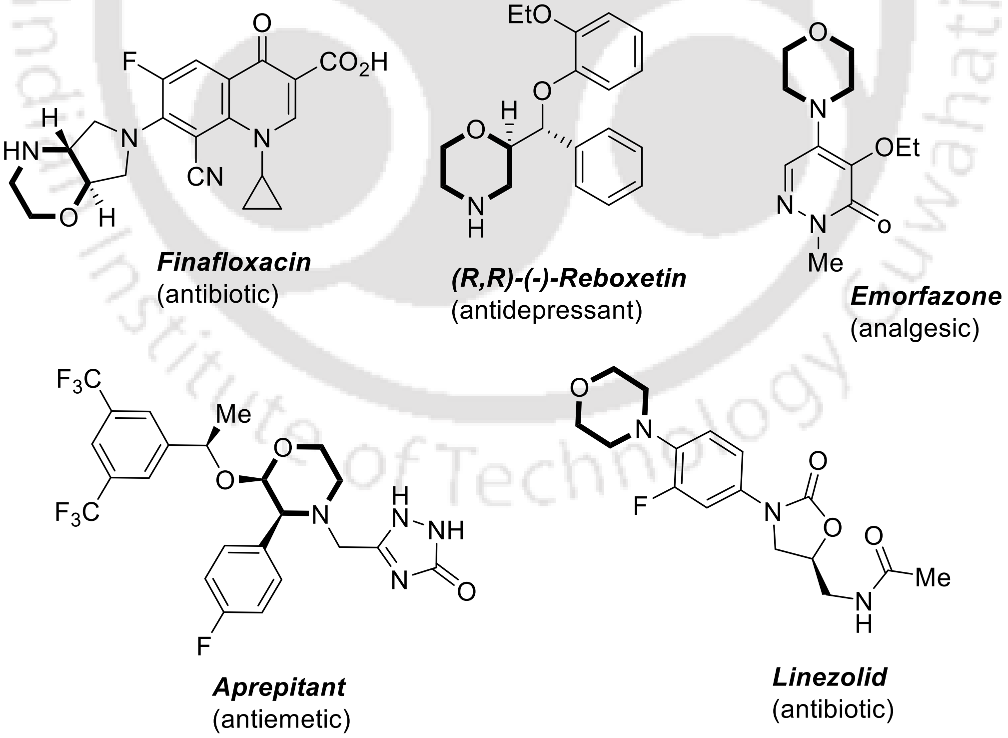

Finafloxacin (antibiotic)
(R,R)-(-)-Reboxetin (antidepressant)
Emorfazone (analgesic)
Aprepitant (antiemetic)
Linezolid (antibiotic)

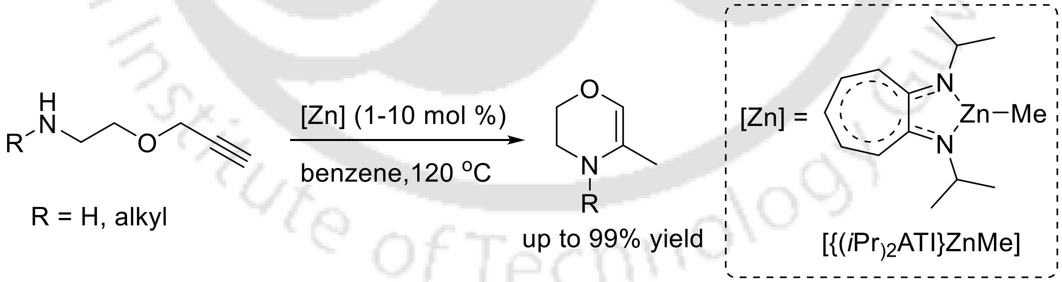
Figure 1. Selected Examples of Drugs Containing Morpholine Core

Oxiranes are one of the smallest heterocyclic units and are employed as potential building blocks for the robust creation of a wide variety of oxygen-containing heterocycles.[5] The stapled architecture, along with the inherent ring strain embedded within their three-membered cyclic framework, renders them amenable to stereo- and regioselective inter and intramolecular ring-opening reactions with a variety of carbon and heteroatomic nucleophiles. In this regard, the Lewis acid-enabled ring expansion reactions of oxiranes have emerged as a fascinating chemical transformation for gaining access to complex molecular assemblies.[6] The work described herein established a one-pot relay approach that enables Zn-catalyzed stereospecific ring-opening of oxiranes using propargylamines, followed by hydroalkoxylation with the help of AgOAc/base to yield a library of substituted 1,4-oxazines. Additionally, optically active oxiranes are coupled with excellent enantiomeric purity. This approach provided an operationally straightforward way for synthesizing stereochemically enriched oxazine derivatives by overcoming the shortcomings associated with the traditional methods.

3.1 Strategies for the Synthesis of 1,4-Oxazine

3.1.1 Hydroamination

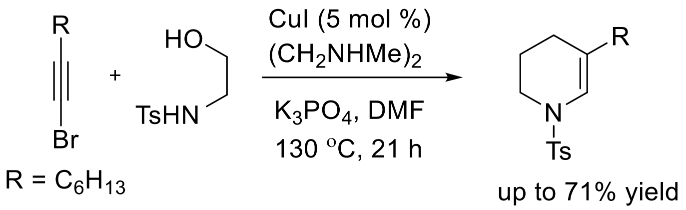
Blechert group demonstrated a Zn-catalyzed intramolecular hydroamination of alkynes to produce 1,4-oxazines (Scheme 1).[7] A wide range of polar functional groups, including ethers, thioethers, and amides were exploited by the reaction conditions.



Scheme 1. Zn-Catalyzed Hydroamination

3.1.2 (4+2)-Cycloaddition

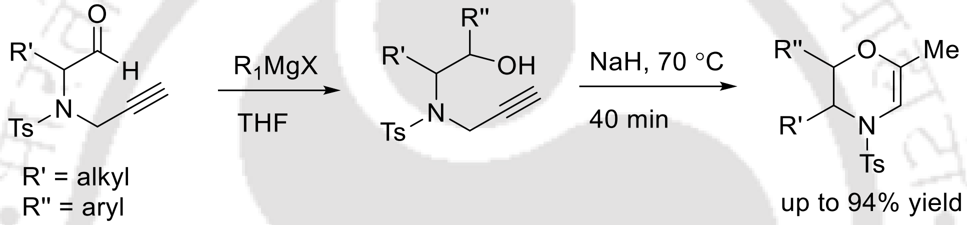
Urabe and co-workers reported a simple method for producing 1,4-oxazines by copper-catalyzed (4+2)-cycloaddition of 1-halo-1-alkynes and hydroxyl *N*-tosylethanolamines (Scheme 2).[8]



Scheme 2. Cu-Catalyzed (4+2)-Cycloaddition

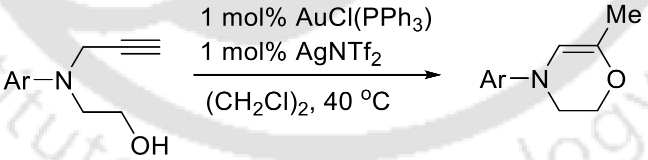
3.1.3 Hydroalkoxylation

Wang and co-workers developed a method to synthesize 1,4-oxazine without solvent and metal (Scheme 3).[9] Regioselective cyclization occurred to afford the *exo-dig* product exclusively. The Grignard reaction is a key synthetic step to produce high diastereomeric compounds *via* Cram's rule and was well supported by DFT calculations.



Scheme 3. Base Mediated *exo-dig* Cyclization

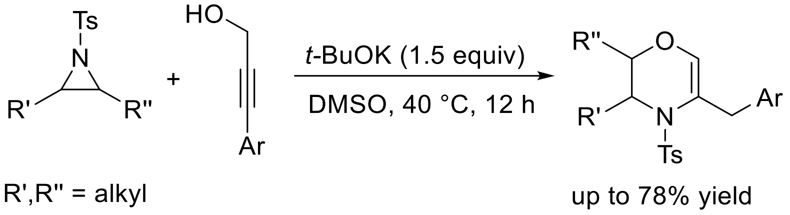
Huang group established a synthetic route to oxazine derivatives through gold(I)-catalyzed 6-*exo-dig*-cyclization (Scheme 4).[10] The reaction involves the cascade cyclization and isomerization to produce the six-membered ring.



Scheme 4. Au-Catalyzed 6-*exo-dig* Cyclization

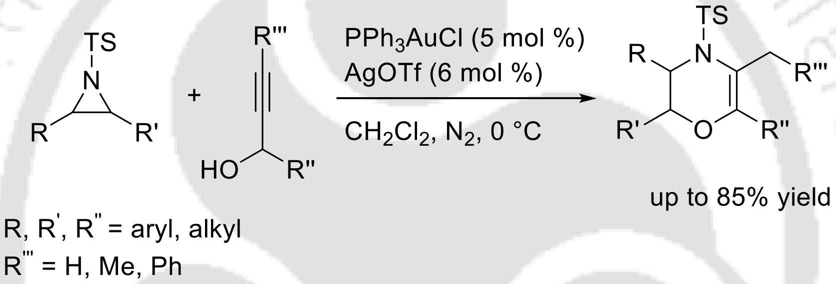
3.1.4 Ring Opening/Cyclization with Aziridine

Zhou and co-workers developed an efficient route to dihydroxazine derivatives via tandem ring-opening/closing reactions of *N*-Ts aziridines with aryl proparglic alcohols using *t*-BuOK as an effective promoting reagent (Scheme 5).[11] This strategy offers a concise platform for the construction of six-membered ring systems under mild conditions with high atom economy.



Scheme 5. Base Mediated Cyclization

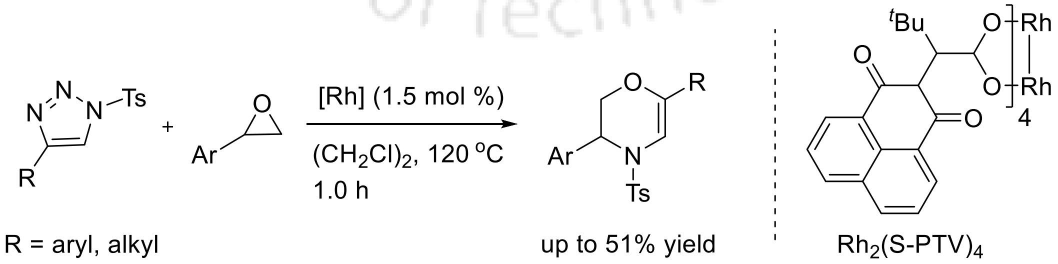
Xu and co-workers developed a synthetic method for constructing oxazine derivatives from readily available aziridines and propargyl alcohols (Scheme 6).[12] A tandem nucleophilic ring-opening of aziridine/6-*exo-dig* cyclization/double bond isomerization sequence was achieved using gold(I) catalysis, which served as a π acid and also a σ acid to realize the dual activation of both reactants in this reaction.



Scheme 6. Au-Catalyzed Tandem Cyclization

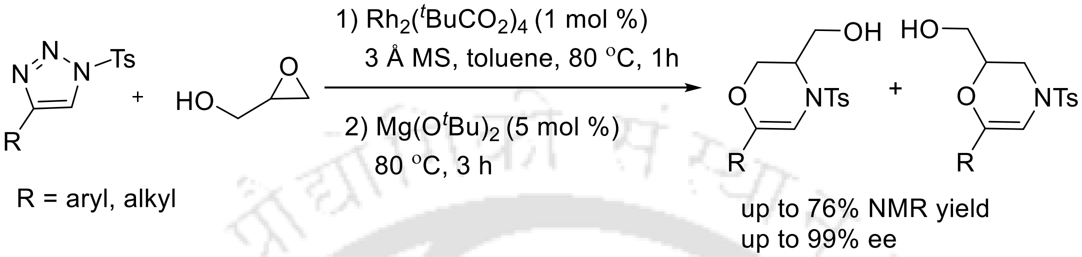
3.1.5 Denitrogenetive Annulation with Triazole

Chen and co-workers described an efficient protocol for preparing a library of substituted 1,4-oxazine derivatives via Rh-catalyzed reaction of epoxides and triazoles (Scheme 7).[13] The reaction involves the generation of α-imino Rh(II) carbene species through denitrogenative transannulation of triazoles and ring-opening of epoxides.



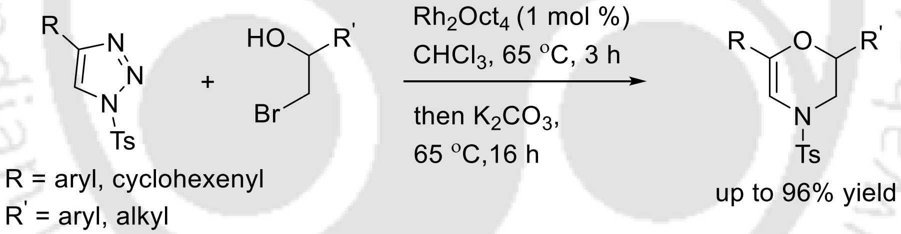
Scheme 7. Rh-Catalyzed Transannulation

Lee group developed a Rh(II)/Mg(O^{t}Bu)$_2$-catalyzed tandem reaction for the synthesis of 1,4-oxazine derivatives from *N*-sulfonyl-1,2,3-triazoles and glycidols through sequential O−H insertion of Rh(II) carbene and subsequent Lewis acid-catalyzed regioselective epoxide ring-opening (Scheme 8).[14]



Scheme 8. Rh(II)-Catalyzed Transannulations of Triazoles to Oxazine

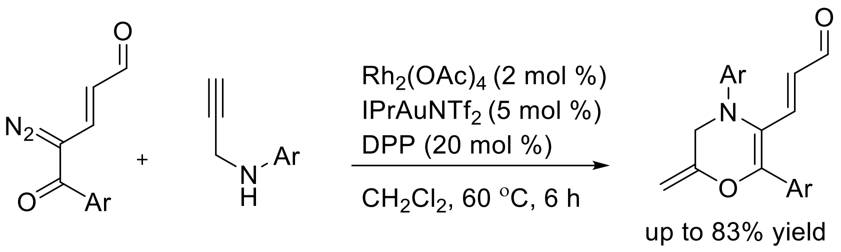
Stewart and co-workers reported a Rh(II)-catalyzed reaction between 1-tosyl-1,2,3-triazoles and halohydrins to provide 2,6- substituted 1,4-oxazines (Scheme 9).[15] The reaction mechanism was proposed to undergo a rhodium carbenoid 1,3- insertion into O−H followed by an annulation.



Scheme 9. Rh-Catalyzed Tandem Annulation

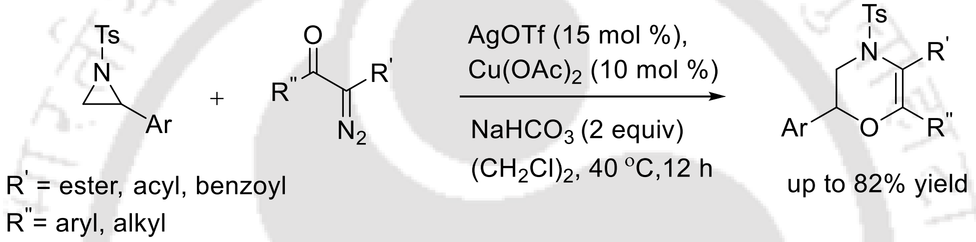
3.1.6 Annulation with Dizo Ketones

Katukojvala and co-workers reported a Rh(II)/Brønsted acid and Au(I)-catalyzed direct (3+3)-annulation of enaldiazo ketones with *N*-propargyl anilines, resulting enal-functionalized 1,4-oxazines (Scheme 10).[16]



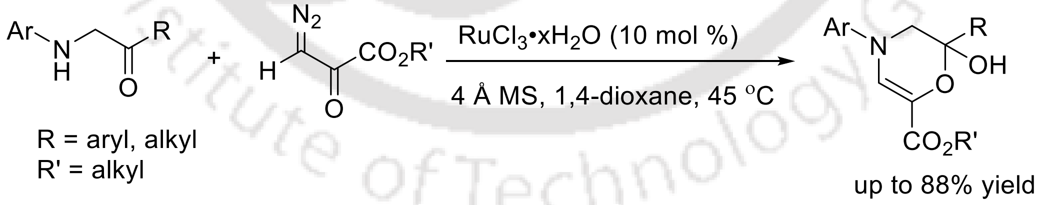
Scheme 10. Rh(II)/Brønsted Acid and Au(I)-Catalyzed (3+3)-Annulation

Wan group showed as (3+3)-cycloaddition of diazocarbonyl compounds with *N*-tosylaziridines through synergetic catalysis of AgOTf and $Cu(OAc)_2$ to provide substituted 2H-1,4-oxazine derivatives (Scheme 11).[17]



Scheme 11. [Ag]/[Cu] Synergetic Catalysis

Xing group developed an efficient strategy for constructing 1,4-oxazines starting from simple α-amino ketones and diazo pyruvates (Scheme 12).[18] This transformation is efficiently catalyzed by $RuCl_3$ through a tandem N–H insertion/cyclization sequence via an enol formation.

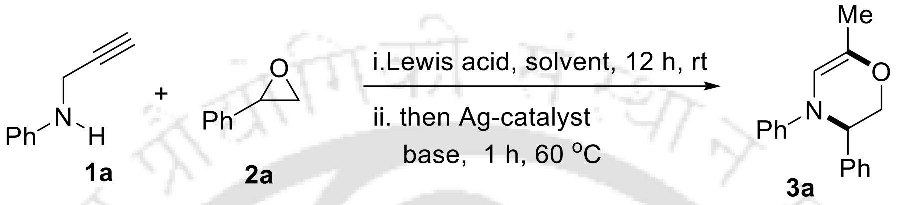


Scheme 12. Tandem N–H Insertion/Cyclization

3.2 Present Study

We here present a one-pot relay process to synthesize 1,4-oxazines *via* sequential Zn-catalyzed ring opening of oxirane with *N*-propargylamines followed by Ag-catalyzed hydroalkoxylation through 6-*exo-dig* mode. Our optimization studies were initiated with *N*-phenyl propargylamine **1a** and 2- phenyloxirane **2a** as the test substrates using a series of Lewis acids, Ag-catalysts, bases and solvents (Table 1). Delightfully, oxazine **3a** was formed in 34% yield using 10 mol % $Cu(OTf)_2$ in combination with 10 mol % AgOAc and 1.2 equiv of K_2CO_3 in CH_3CN, while control experiments without involving Ag-catalyst and base failed to produce the desired product (entries1-3). Interestingly, the employment of $Zn(OTf)_2$ as catalyst led to improve the overall yield to 82%, whereas other Zn-salts such as $Zn(NTf_2)_2$ and $ZnCl_2$ showed inferior results (entries 4-6).

Table 1. Optimization of the Reaction Conditions[a]

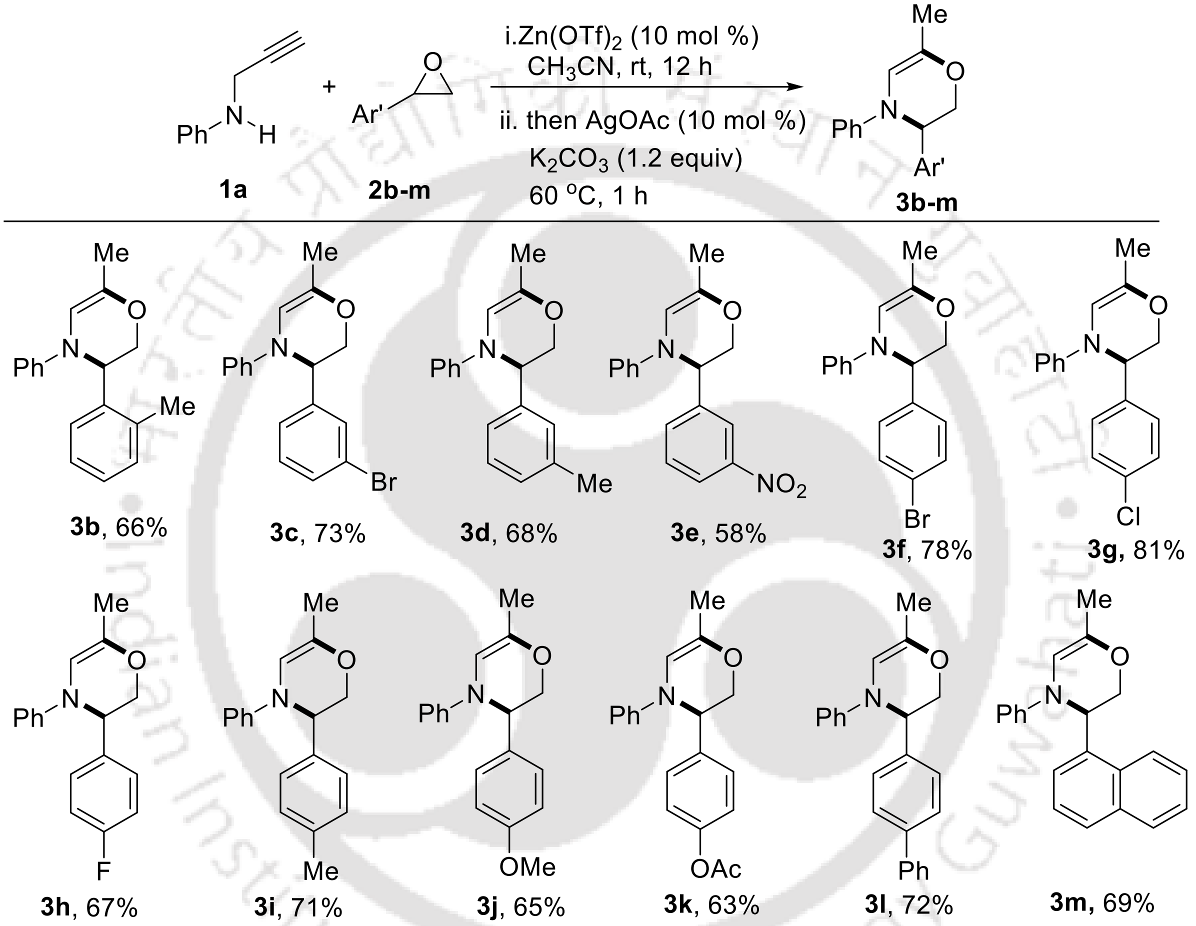


Entry	Lewis acid	Ag-catalyst	Base	Solvent	Yield (%)[b]
1	$Cu(OTf)_2$	-	-	CH_3CN	n.d.
2	$Cu(OTf)_2$	AgOAc	-	CH_3CN	trace
3	$Cu(OTf)_2$	AgOAc	K_2CO_3	CH_3CN	34
4	**$Zn(OTf)_2$**	**AgOAc**	**K_2CO_3**	**CH_3CN**	**82**
5	$Zn(NTf_2)_2$	AgOAc	K_2CO_3	CH_3CN	72
6	$ZnCl_2$	AgOAc	K_2CO_3	CH_3CN	n.d.
7	$Zn(OTf)_2$	AgOTf	K_2CO_3	CH_3CN	73
8	$Zn(OTf)_2$	AgTFA	K_2CO_3	CH_3CN	68
9	$Zn(OTf)_2$	$AgNO_3$	K_2CO_3	CH_3CN	43
10	$Zn(OTf)_2$	AgOAc	K_2CO_3	toluene	78
11	$Zn(OTf)_2$	AgOAc	K_2CO_3	THF	21
12	$Zn(OTf)_2$	AgOAC	K_2CO_3	MeOH	n.d.
13	$Zn(OTf)_2$	AgOAC	K_2CO_3	$(CH_2Cl)_2$	trace
14	$Zn(OTf)_2$	AgOAC	Na_2CO_3	CH_3CN	53
15	$Zn(OTf)_2$	AgOAC	$NaHCO_3$	CH_3CN	74
16	$Zn(OTf)_2$	AgOAC	DBU	CH_3CN	63

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), Lewis acid (10 mol %), solvent (2 mL), 12 h, rt; then, [Ag]-source (10 mol %), base (0.24 mmol), 1 h, 60 °C. [b]Isolated yield. n.d. = not detected.

In a set of Ag-catalysts studied, AgOAc, AgOTf, AgTFA and $AgNO_3$, the former gave the best result (entries 7-9). Among the solvents screened, CH_3CN was found to be the solvent of choice, while toluene, THF, MeOH and $(CH_2Cl)_2$ gave <78% yield (entries 10-13). In case of the base, K_2CO_3 was found to be superior to Na_2CO_3, $NaHCO_3$ and DBU (entries 14-16).

Table 2. Substrate Scope of Oxirane[a,b]



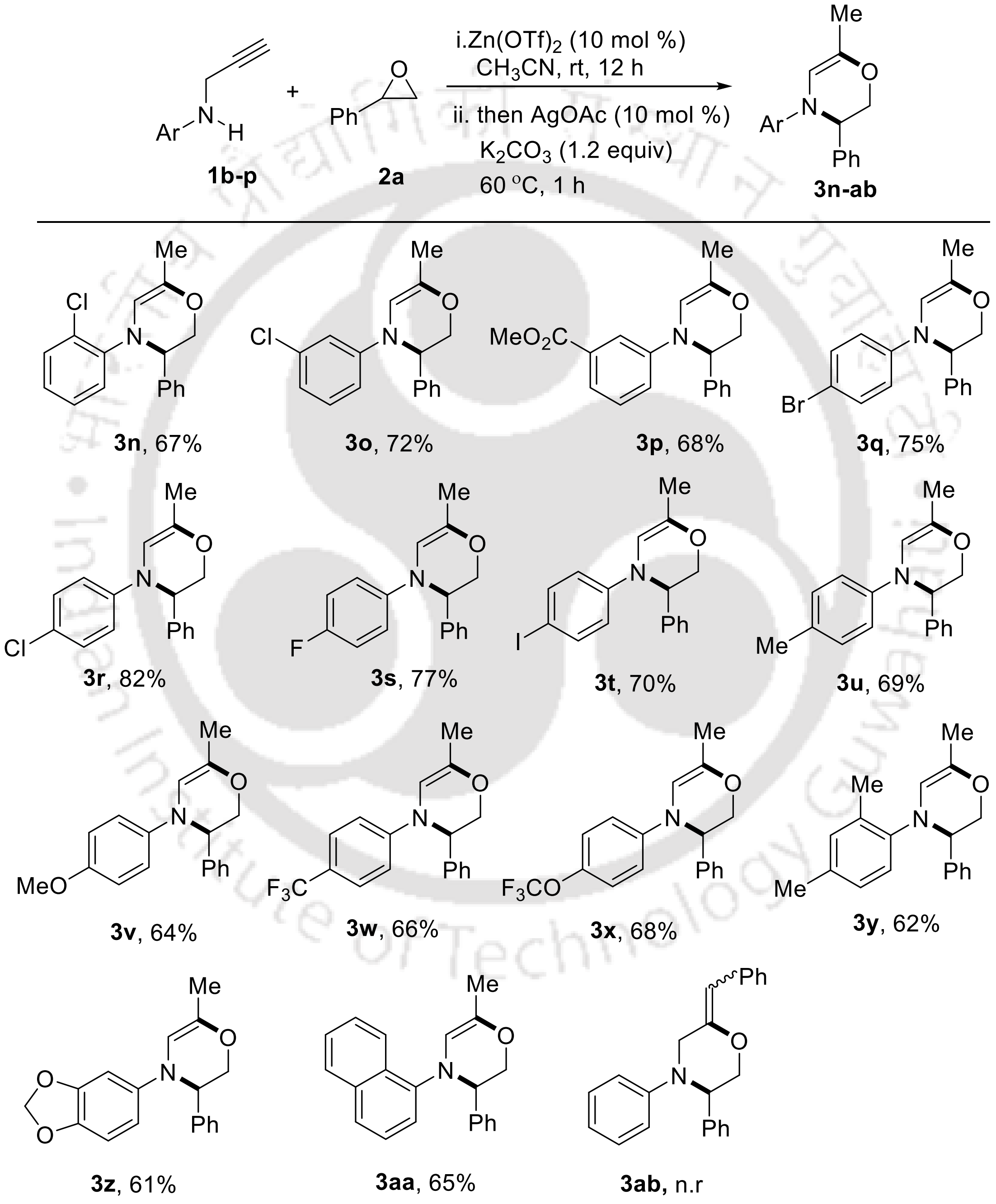
3b, 66% **3c**, 73% **3d**, 68% **3e**, 58% **3f**, 78% **3g**, 81%

3h, 67% **3i**, 71% **3j**, 65% **3k**, 63% **3l**, 72% **3m**, 69%

[a]Reaction conditions: **1a** (0.2 mmol), **2b-m** (0.24 mmol), $Zn(OTf)_2$ (10 mol %), CH_3CN (2 mL), rt, 12 h; then, AgOAc (10 mol %), K_2CO_3 (0.24 mmol), 60 °C, 1 h. [b]Isolated yield.

Having optimized the reaction conditions, the scope of the protocol was investigated using a series of oxiranes **2b-m** with *N*-phenyl propargylamine **1a** as a standard substrate (Table 2). Oxirane with 2-methyl **2b** group in the aryl ring afforded **3b** in 66% yield. Similarly, the reaction of oxiranes having 3-bromo **2c**, 3-methyl **2d** and 3-nitro **2e** groups proceeded smoothly to furnish **3c-e** in 68-73% yields. Moreover, oxiranes bearing substituents at the 4-position comprising both electron-rich and electron-deficient functionalities such as bromo **2f**, chloro **2g**, fluro **2h**, methyl **2i**, methoxy **2j**, acetoxy **2k** and phenyl **2l** groups participated efficiently, producing the desired heterocycles **3f-l** in 63-81% yields. Furthermore, bulky polycyclic aromatic substituted oxirane, for example 2-(naphthalen-1-yl)oxirane **2m** underwent the reaction to deliver **3m** in 69% yield.

Table 3. Substrate Scope of Amines.[a,b]



1b-p **2a** **3n-ab**

3n, 67% **3o**, 72% **3p**, 68% **3q**, 75%

3r, 82% **3s**, 77% **3t**, 70% **3u**, 69%

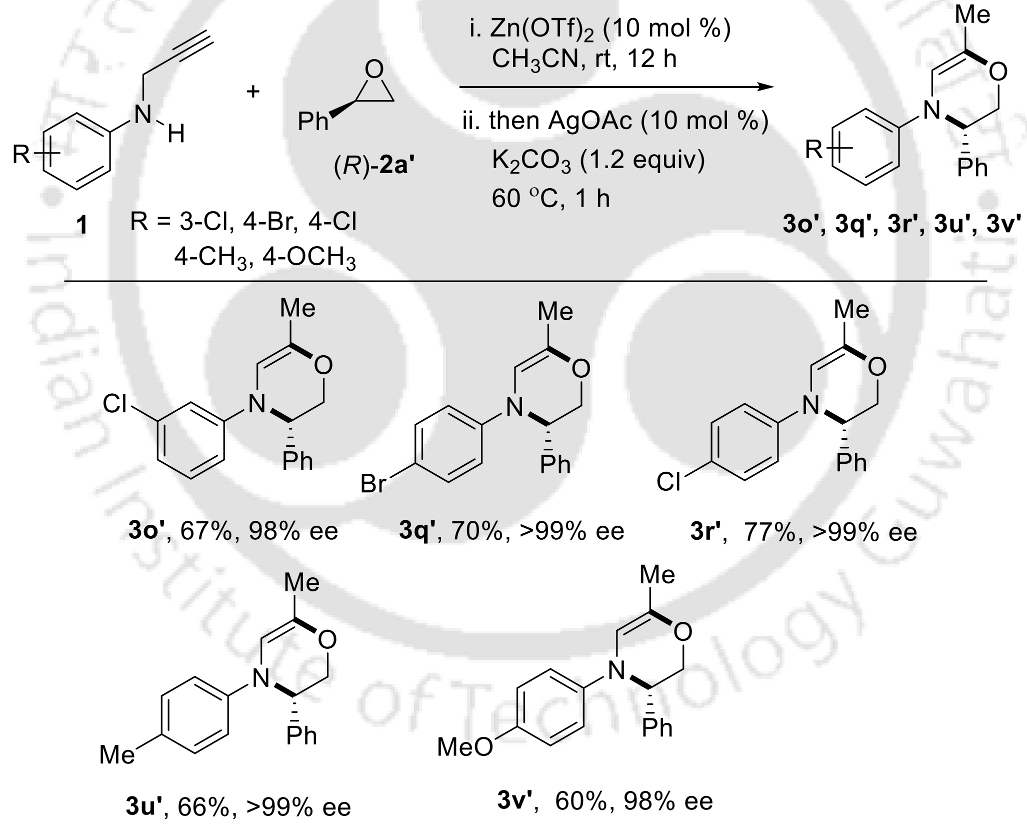
3v, 64% **3w**, 66% **3x**, 68% **3y**, 62%

3z, 61% **3aa**, 65% **3ab,** n.r

[a]Reaction conditions: **1b-p** (0.2 mmol), **2a** (0.24 mmol), Zn(OTf)$_2$ (10 mol %), CH$_3$CN (2 mL), rt, 12 h; then, AgOAc (10 mol %), K$_2$CO$_3$ (0.24 mmol), 60 °C, 1 h. [b]Isolated yield. n.r. = no reaction

Next, the scope of the reaction was extended using diverse *N*-aryl propargylamines **1b-p** with 2-phenyloxirane **2a** as a standard substrate (Table 3). The amines bearing 2-chloro **1b**, 3-chloro **1c** and 3-methoxycarbonyl **1d** groups in the aryl ring successfully participated to furnish **3n-p** in 67-72% yields. In addition, the substrates with 4-bromo **1e**, 4-chloro **1f**, 4-fluoro **1g**, 4-iodo **1h**, 4-methyl **1i**, 4-methoxy **1j**, 4-trifluoromethyl **1k** and 4-trifluoromethoxy **1l** functionalities reacted smoothly to afford **3q-x** in 64-82% yields. Gratifyingly, 2,4-dimethyl **1m**, 1,3 benzodioxol **1n** and 1-naphthyl **1o** substituents were also found amenable under the standard condition, delivering the corresponding 1,4 oxazines **3y-aa** in 61-65% yields. It is worth mentioning that internal alkyne **1p** was reluctant to produce the desired target.

Table 4. Enantiospecific Synthesis.[a,b]



3o', 67%, 98% ee

3q', 70%, >99% ee

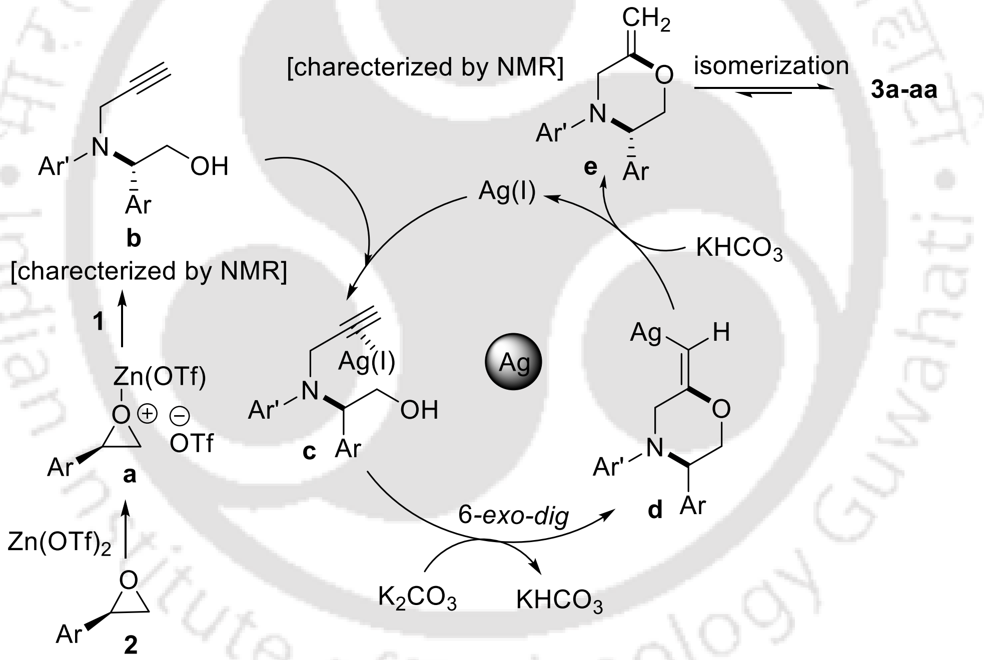
3r', 77%, >99% ee

3u', 66%, >99% ee

3v', 60%, 98% ee

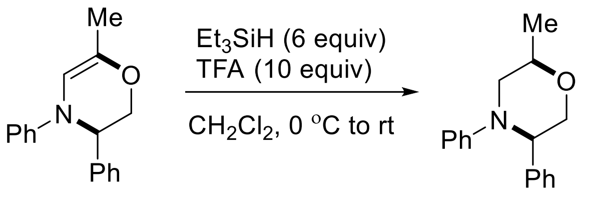
[a]Reaction conditions: **1c, 1e, 1f, 1i** and **1j** (0.1 mmol), **2a'** (0.12 mmol), Zn(OTf)$_2$ (10 mol %), CH$_3$CN (1 mL), rt, 12 h; then, AgOAc (10 mol %), K$_2$CO$_3$ (0.24 mmol), 60 °C, 1 h. [b]Isolated yield

To get insight into the mechanism, the reaction of a set of substituted amines were examined employing optically active 2-phenyloxirane (*R*)-**2a′** (Table 4). Propargylamine bearing 3-chloro group **1c** underwent the reaction efficiently to afford **3o'** in 98% ee. Similarly, the reaction of 4-bromo **1e**, 4-chloro **1f**, 4-methyl **1i** and 4-methoxy **1j** substituted amines delivered highly enantioenriched oxazines **3q'**, **3r'**, **3u'** and **3v'** in >98% ee. These results suggest that the protocol is enantiospecific and can be exploited to furnish oxazines with high optical purities. Thus chelation of the oxirane with $Zn(OTf)_2$ can lead to the formation of intermediate **a** which then underwent regiospecific S_N2-type nucleophilic ring opening with propargylamine to yield **b** (Scheme 13).[19] Concurrently, the Ag(I)-promoted activation of the triple bond can lead to generate intermediate **c**. Finally, the base mediated hydroalkoxylation *via* 6-*exo*-*dig* cyclization furnishes morpholine **e** which then isomerizes to 1,4 oxazine.



Scheme 13. Possible Reaction Mechanism

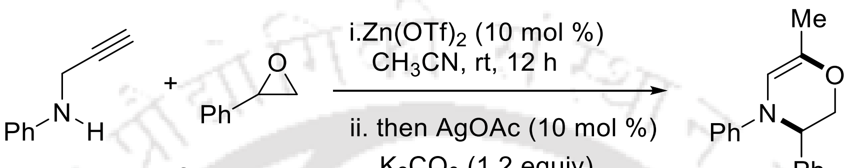
To illustrate the synthetic utility, the hydrogenation of 1,4 oxazine **3a** was performed as a representative example (Scheme 6). The reaction using triethylsilane in the presence of trifluoroacetic acid furnished morpholine **4** as a mixture of isomers in 87% yield, which is an important building block in bioactive pharmaceuticals. In addition, the scale-up of the reaction was examined employing **1a** (3 mmol) and **2a** (3.6 mmol) under the standard optimal condition (Scheme 7). **3a** was formed in 63% yield, which suggests the scalability of the protocol.



3a

4, 87%, dr = 2.6:1

Scheme 6. Synthetic utility



1a (3 mmol) **2a** (3.6 mmol)

3a, 63%

Scheme 7. Scale-up Synthesis

In conclusion, we have described a one-pot concise method to produce functionalized 1,4-oxazines *via* Zn/Ag-catalyzed sequential ring opening/hydroalkoxylation of oxiranes with *N*-propargylamines. The regioselectivity, functional group diversities and the implementation of optically pure oxiranes towards the synthesis of highly enantioenriched 1,4-oxazines are the important practical features.

3.3 Experimental Section

3.3.1 General Information. Anilines, styrenes, styrene oxides, mCPBA, $Cu(OTf)_2$, $Zn(OTf)_2$, $Zn(NTf_2)_2$, AgOTf, AgOAc, $AgNO_3$, AgTFA were purchased from Sigma Aldrich and used as received. (*R*)-styrene oxide was purchased from TCI chemicals. *N*-propargylamine and Oxirane[20] were prepared according to the reported procedure. Solvents were purchased from Merck, distilled by the standard protocol and stored over molecular sieves under nitrogen atmosphere prior to use. Column chromatography was performed with Rankem silica gel (60-120 mesh). Bruker Avance III 400, Bruker Avance III 500 and Bruker Avance III 600 spectrometers were used for recording NMR spectra using $CDCl_3$ as a solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (*J*) are reported in ppm and Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublet and br s = broad singlet. Optical rotation was determined by using Rudolph autopol I automatic polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OJ-H and AD column using iso-propanol and hexane as eluent. FT-IR spectra were collected on Thermo Fisher Scientific IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra.

3.3.2 General Procedure for the Preparation of *N*-Propargylamines

Propargylamines were prepared according to the procedure reported in chapter 2

3.3.3 General Procedure for Preparation of Styrene oxide[20]. $NaHCO_3$ was added to a stirring solution of styrene (2 mmol) in dichloromethane (5 mL) at 0 ºC. The flask was then fitted with an addition funnel containing mCPBA (2.2 mmol) dissolved in dichloromethane (3 mL). The mCPBA solution was added dropwise through the addition funnel over 0.5 h. The reaction was then stirred at 0 ºC for an additional 0.5 h and then allowed to warm to room temperature and stirred overnight. After completion, the reaction mixture was then diluted with dichloromethane (2 × 10 mL), washed with saturated solution of sodium carbonate (2 × 10 mL) and sodium thiosulfate (2 × 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using ethyl acetate and hexane as an eluent to give styrene oxide.

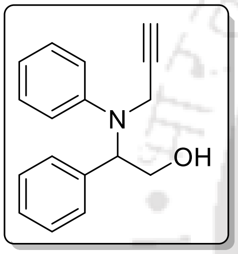
3.3.4 General Procedure for the Synthesis of 1,4-Oxazine. A mixture of *N*-propargylamine (0.2 mmol), oxirane (0.24 mmol), $Zn(OTf)_2$ (0.02 mmol, 7.23 mg) and CH_3CN (2 mL) were stirred at room temperature for 12 h under air. Then, AgOAc (0.02 mmol, 3.32 mg) and K_2CO_3 (0.2 mmol) were added to the same pot and the resulting mixture was then stirred at 60 ºC for 1 h. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate(10 mL). The mixture was washed with water (5 mL) and extracted with ethyl acetate(2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent to give 1,4 oxazine as the sole product.

3.3.5 Large Scale Synthesis of 1,4-Oxazine

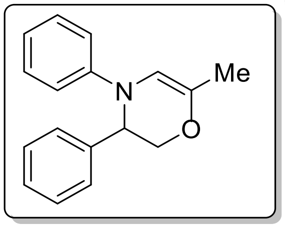
A mixture of *N*-propargylamine **1a** (3 mmol, 393 mg), oxirane **2a** (3.6 mmol, 432 mg), $Zn(OTf)_2$ (0.3 mmol, 108 mg) and CH_3CN (3 mL) were stirred at room temperature for 12 h under air. Then, AgOAc (0.3 mmol, 50 mg) and K_2CO_3 (3.6 mmol) were added to the same pot and the resulting mixture was then stirred at 60 °C for 1 h. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The mixture was washed with water (10 mL) and extracted with ethyl acetate (2 x 15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent, to give 1,4 oxazine **3a**.

3.3.6 General Procedure for the Stereospecific Coupling of Oxirane with Propargyl Amine

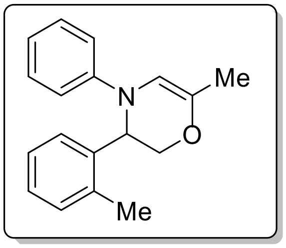
N-Propargyl aniline **1** (0.2 mmol), chiral oxirane (*R*)-**2a′** (0.24 mmol) and $Zn(OTf)_2$ (0.02 mmol, 3.32 mg) were subjected to the above described general procedure for the oxazine synthesis. The enantiomeric excess was determined using chiral HPLC.



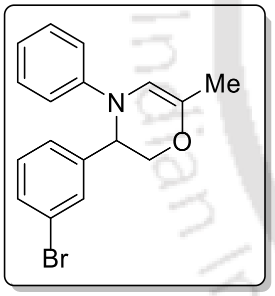
2-Phenyl-2-(phenyl(prop-2-yn-1-yl)amino)ethan-1-ol 3. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.20$; thick liquid; ^1H NMR (600 MHz, $CDCl_3$) δ 7.37-7.35 (m, 2H), δ 7.32-7.28 (m, 3H), 7.26-7.25 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 7.8 Hz, 1H), 5.16-5.14 (m, 1H), 4.27-4.20 (m, 2H), 4.06-3.98 (m, 2H), 2.34 (t, *J* = 2.4 Hz, 1H), 2.30 (br s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.9, 137.9, 129.4, 129.0, 127.9, 127.4, 119.2, 115.0, 81.5, 72.5, 63.7, 63.1, 36.4.; FT-IR (neat) 2924, 1733, 1597, 1503, 1452, 1373, 1264, 1045, 748, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO$: 252.1383 found: 252.1362.



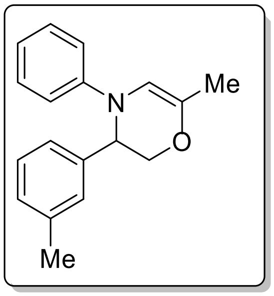
6-Methyl-3,4-diphenyl-3,4-dihydro-2H-1,4-oxazine 3a. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane $R_f = 0.98$; thick liquid; yield 82% (41 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.28-7.24 (m, 4H), 7.20-7.19 (m, 1H), 7.14-7.11 (m, 2H), 6.73-6.69 (m, 3H), 5.94 (s, 1H), 4.76-4.75 (m, 1H), 4.34 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.09 (dd, *J* = 10.2, 2.4 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 139.6, 135.4, 129.5, 128.8, 127.4, 126.5, 118.9, 113.8, 104.4, 69.1, 57.4, 17.9; FT-IR (neat) 2919, 2878, 1740, 1679, 1591, 1491, 1365, 1205, 1089, 808, 747, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{18}NO$: 252.1383, found: 252.1371.



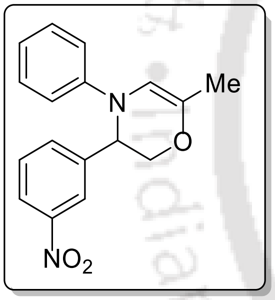
6-Methyl-4-phenyl-3-(*o*-tolyl)-3,4-dihydro-2H-1,4-oxazine 3b. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane R_f = 0.95; thick liquid; yield 66% (35 mg); ^{1}H NMR (400 MHz, $CDCl_3$)) δ 7.20-7.17 (m, 1H), 7.15-7.07 (m, 4H), 7.05-7.01 (m, 1H), 6.70-6.66 (m, 1H), 6.64-6.61 (m, 2H), 6.07 (s, 1H), 4.89 (s, 1H), 4.18 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.07 (dd, *J* = 10.4, 2.8 Hz, 1H), 2.38 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 137.5, 134.8, 133.7, 131.0, 129.4, 127.5, 126.8, 126.6, 118.9, 113.7, 105.6, 67.6, 54.9, 19.4, 17.9; FT-IR (neat) 3025, 1739, 1678, 1599, 1400, 1228, 1037, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO$: 266.1539, found: 266.1555.



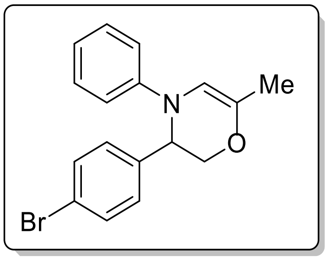
3-(3-Bromophenyl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3c. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 73% (48 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.38 (m, 1H), 7.33-7.30 (m, 1H), 7.18-7.10 (m, 4H), 6.74-6.68 (m, 3H), 5.91 (s, 1H), 4.71 (s, 1H), 4.30 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.04 (dd, *J* = 10.4, 2.4 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 142.1, 135.7, 130.6, 130.4, 129.6, 129.5, 125.2, 123.0, 119.3, 113.9, 104.2, 68.7, 57.2, 17.9; FT-IR (neat) 2979, 2877, 1596, 1499, 1390, 1362, 1204, 1091, 750, 691 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}BrNO$: 330.0488, found: 330.0499.



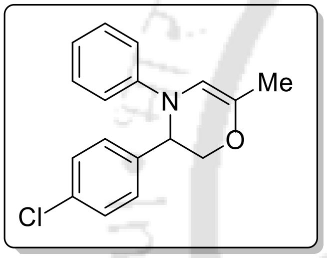
6-Methyl-4-phenyl-3-(*m-tolyl*)-3,4-dihydro-2H-1,4-oxazine 3d. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane R_f = 0.95; thick liquid; yield 68% (36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (m, 3H), 7.04-6.98 (m, 3H), 6.73-6.67 (m, 3H), 5.93 (s, 1H), 4.70 (s, 1H), 4.32 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.06 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.25 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 139.6, 138.4, 135.4, 129.4, 128.7, 128.2, 127.1, 123.6, 118.8, 113.8, 104.4, 69.1, 57.4, 21.7, 17.9; FT-IR (neat) 3025, 2921, 2875, 1742, 1676, 1599, 1499, 1364, 1230, 1091, 752, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO$: 266.1539, found: 266.1557.



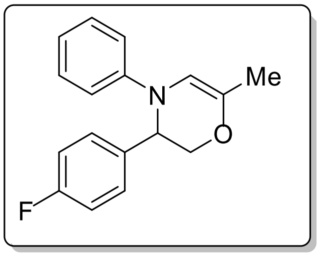
6-methyl-3-(3-nitrophenyl)-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.76; brown liquid; yield 61% (36 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15-8.14 (m, 1H), 8.08-8.06 (m, 1H), 7.60-7.58 (m, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.17-7.13 (m, 2H), 6.78 – 6.74 (m, 1H), 6.73-6.72 (m, 2H), 5.96 (s, 1H), 4.87 (s, 1H), 4.37 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.11 (dd, *J* = 11.0, 2.5 Hz, 1H), 1.78 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.9, 145.4, 142.1, 136.1, 132.9, 129.9, 129.7, 122.7, 121.9, 119.7, 114.1, 104.2, 68.4, 57.4, 17.8; FT-IR (neat) 2925, 1738, 1666, 1598, 1527, 1499, 1347, 1201, 1088, 809, 752, 691 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}N_2O_3$: 297.1234, found: 297.1228.



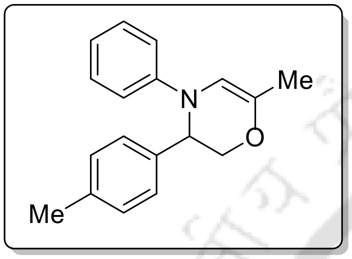
3-(4-Bromophenyl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3f. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 78% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H), 7.16-7.12 (m, 4H), 6.74-6.69 (m, 3H), 5.92 (s, 1H), 4.72 (s, 1H), 4.30 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.06 (dd, *J* = 10.8, 2.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.7, 135.6, 132.0, 129.5, 128.4, 121.3, 119.2, 113.9, 104.3, 68.8, 57.1, 17.9; FT-IR (neat) 2923, 2855, 1741, 1674, 1597, 1495, 1364, 1230, 1102, 1010, 751, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}BrNO$: 330.0488, found: 330.0497.



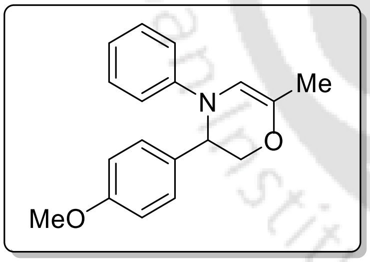
3-(4-chlorophenyl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3g. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane R_f = 0.91; thick liquid; yield 81% (46 mg);); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.22 (m, 2H), 7.20-7.11 (m, 4H), 6.74-6.69 (m, 3H), 5.92 (s, 1H), 4.73 (s, 1H), 4.30 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.07 (dd, *J* = 10.4, 2.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 138.2, 135.6, 133.2, 129.5, 129.1, 128.0, 119.2 113.9, 104.3, 68.9, 57.1, 17.9; FT-IR (neat) 2922, 2875, 1741, 1678, 1598, 1498, 1390, 1364, 1205, 1091, 750, 693 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for : $C_{17}H_{17}ClNO$: 286.0993, found: 286.1002.



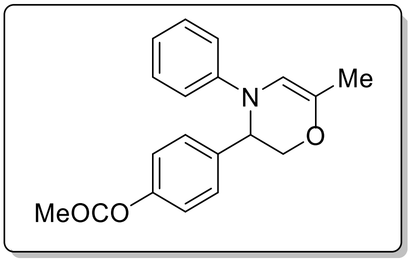
3-(4-Fluorophenyl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3h. Analytical TLC on silica gel, 4:96 ethyl acetate/hexane R_f = 0.88; thick liquid; yield 67% (36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.19 (m, 2H), 7.16-7.11 (m, 2H), 6.97-6.92 (m, 2H), 6.73-6.70 (m, 3H), 5.92 (s, 1H), 4.74 (s, 1H), 4.29 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.06 (dd, *J* = 10.8, 2.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (J_{C-F} = 243.8 Hz), 145.5, 135.5, 135.4 (J_{C-F} = 3.0 Hz), 129.5, 128.2 (J_{C-F} = 8.0 Hz), 119.1, 115.8 (J_{C-F} = 21.3 Hz), 113.9, 104.3, 69.0, 56.9, 17.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.6; FT-IR (neat) 2927, 2879, 1741, 1675, 1599, 1504, 1398, 1227, 1091, 752, 696 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}FNO$: 270.1289, found: 270.1310.



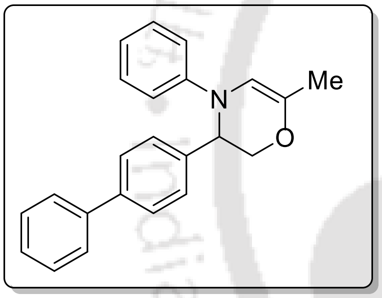
6-Methyl-4-phenyl-3-(*p*-tolyl)-3,4-dihydro-2H-1,4-oxazine 3i. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane R_f = 0.98; thick liquid; yield; 71% (37 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21-7.18 (m, 4H), 7.15-7.13 (m, 2H), 6.80-6.75 (m, 3H), 6.00 (s, 1H), 4.80 (s, 1H), 4.38 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.13 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.32 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 137.0, 136.5, 135.3, 129.6, 129.4, 126.4, 118.8, 113.8, 104.4, 69.2, 57.2, 21.3, 17.9; FT-IR (neat) 2922, 2870, 1740, 1679, 1596, 1502, 1365, 1230, 1037, 747, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO$: 266.1539, found: 266.1558.



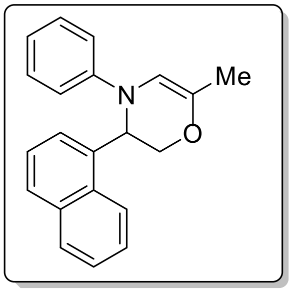
3-(4-methoxyphenyl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3j. Analytical TLC on silica gel, 6:94 ethyl acetate/hexane R_f = 0.86; thick liquid; yield; 65% (36 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.16 (m, 1H), 7.14-7.10 (m, 2H), 6.85-6.82 (m, 1H), 6.79-6.78 (m, 1H), 6.73-6.67 (m, 4H), 5.93 (s, 1H), 4.71 (s, 1H), 4.32 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.06 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.69 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0, 145.5, 141.4, 135.3, 129.9, 129.4, 118.9, 118.8, 113.8, 112.6, 112.4, 104.4, 69.1, 57.4, 55.3, 17.9; FT-IR (neat) 2935, 2841, 1739, 1669, 1508, 1453, 1367, 1229, 1031, 835, 735, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{20}NO_2$: 282.1489, found: 282.1492.



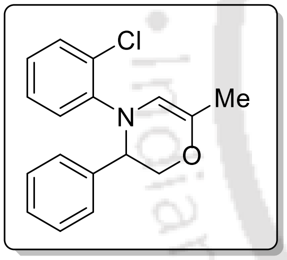
4-(6-Methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazin-3-yl)phenyl acetate 3k. Analytical TLC on silica gel, 15:85 ethyl acetate/hexane $R_f = 0.65$; thick liquid; yield 63% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.23 (m, 2H), 7.15-7.10 (m, 2H), 7.00-6.96 (m, 2H), 6.72-6.69 (m, 3H), 5.90 (s, 1H), 4.74 (s, 1H), 4.32 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.05 (dd, *J* = 10.4, 2.4 Hz, 1H), 2.20 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 150.0, 145.6, 137.2, 135.6, 129.5, 127.7, 121.9, 119.1, 113.9, 104.2, 68.9, 57.1, 21.3, 17.9; FT-IR (neat) 2923, 2853, 1748, 1673, 1597, 1500, 1368, 1195, 1014, 751, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_3$: 310.1438, found: 310.1446.



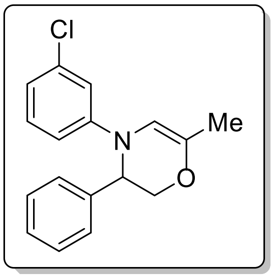
3-([1,1'-Biphenyl]-4-yl)-6-methyl-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3l. Analytical TLC on silica gel, 8:92 ethyl acetate/hexane $R_f = 0.84$; thick liquid; yield 72% (47 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.47 (m, 4H), 7.35-7.30 (m, 4H), 7.26-7.23 (m, 1H), 7.16-7.12 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.72-6.69 (m, 1H), 5.96 (s, 1H), 4.80 (s, 1H), 4.37 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.10 (dd, *J* = 10.5, 2.5 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.7, 141.1, 140.4, 138.7, 135.5, 129.5, 128.9, 127.7, 127.4, 127.3, 127.0, 119.0, 113.9, 104.5, 69.1, 57.4, 17.9; FT-IR (neat) 2919, 2875, 1687, 1596, 1500, 1392, 1205, 1089, 747, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{22}NO$: 328.1696, found: 328.1688.



6-Methyl-3-(naphthalen-1-yl)-4-phenyl-3,4-dihydro-2H-1,4-oxazine 3m. Analytical TLC on silica gel, 9:91 ethyl acetate/hexane $R_f = 0.81$; thick liquid; yield 69% (41 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.59-7.55 (m, 1H), 7.53-7.50 (m, 1H), 7.46-7.45 (m, 1H), 7.38-7.35 (m, 1H), 7.15-7.12 (m, 2H), 6.75-6.72 (m, 3H), 6.22 (s, 1H), 5.59 (s, 1H), 4.52-4.49 (m, 1H), 4.27-4.25 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 134.5, 133.7, 130.0, 129.7, 129.4, 128.2, 126.5, 125.8, 125.6, 124.8, 122.0, 118.9, 113.7, 105.2, 68.1, 54.6, 17.9; FT-IR (neat) 2916, 2878, 1671, 1596, 1500, 1202, 1026, 747, 692 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{20}NO$: 302.1539, found: 302.1553.

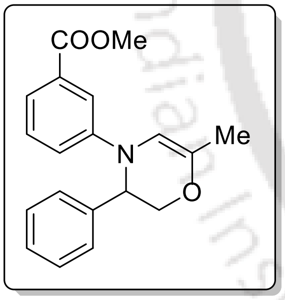


4-(2-Chlorophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3n. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane $R_f = 0.97$; thick liquid; yield 67% (38 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.29 (m, 2H), 7.24-7.20 (m, 3H), 7.16-7.12 (m, 1H), 7.07-7.01 (m, 2H), 6.86-6.83 (m, 1H), 5.43 (s, 1H), 4.66-4.65 (m, 1H), 4.20 (dd, *J* = 10.5, 4.0 Hz, 1H), 4.02 (dd, *J* = 11.0, 3.0 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 139.2, 137.2, 130.9, 128.44, 128.41, 127.3, 127.24, 127.20, 125.1, 124.1, 108.3, 68.5, 59.9, 17.7; FT-IR (neat) 2952, 2919, 1740, 1684, 1585, 1475, 1381, 1312, 1205, 1056, 755, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ClNO$: 286.0993, found: 286.0998.

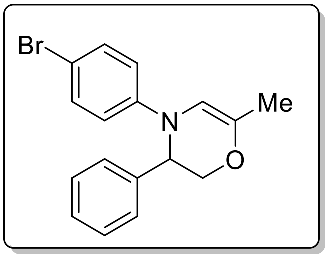


4-(3-Chlorophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3o. Analytical TLC on silica gel, 9:97 ethyl acetate/hexane $R_f = 0.97$; thick liquid; yield 72% (41 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.22-7.17 (m, 3H), 7.01 (t, *J* = 8.0 Hz, 1H), 6.71-6.70 (m, 1H), 6.67-6.64 (m, 1H), 6.57-6.54 (m, 1H), 5.88 (s, 1H), 4.72 (s, 1H), 4.34 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.08 (dd, *J* = 10.4, 2.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 138.9, 136.4, 135.3, 130.4, 129.0, 127.6, 126.4, 118.7, 113.6, 111.8, 103.8, 69.1, 57.3, 17.9; FT-IR (KBr) 2955, 2925, 1737, 1684, 1585, 1478, 1453, 1384, 1205, 1086, 755, 695 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for : $C_{17}H_{17}ClNO$: 286.0993, found: 286.0996.

3o': yield 67% (19 mg), $[\alpha]_D^{25}$ = +33.00 (c= 0.1, $CHCl_3$); HPLC: 98% *ee* [CHIRALCEL OJ-H, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 20.06 min (major), 8.60 min (minor)].



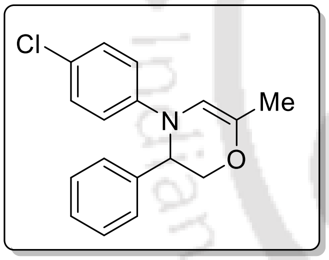
Methyl 3-(6-methyl-3-phenyl-2,3-dihydro-4H-1,4-oxazin-4-yl)benzoate 3p. Analytical TLC on silica gel, 9:91 ethyl acetate/hexane $R_f = 0.88$; thick liquid; yield 68% (42 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.447-7.440 (m, 1H), 7.36-7.34 (m, 1H), 7.28-7.23 (m, 4H), 7.21-7.18 (m, 1H), 7.16-7.14 (m, 1H), 6.85-6.83 (m, 1H), 5.98 (s, 1H), 4.78 (s, 1H), 4.34 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.09 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.80 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 145.5, 139.1, 136.2, 131.3, 129.5, 128.9, 127.6, 126.5, 119.8, 117.9, 114.5, 104.0, 69.1, 57.3, 52.3, 17.9; FT-IR (neat) 2950, 1718, 1678, 1600, 1489, 1445, 1231, 1108, 1039, 735, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_3$: 310.1438, found: 310.1445.



4-(4-Bromophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine

3q. Analytical TLC on silica gel, 6:94 ethyl acetate/hexane $R_f = 0.93$; thick liquid; yield 75% (49 mg); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.28-7.24 (m, 5H), 6.66-6.63 (m, 2H), 5.93 (s, 1H), 4.76 (s, 1H), 4.39 (dd, J = 10.5, 2.0 Hz, 1H), 4.15 (dd, J = 10.5, 2.5 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 139.1, 136.1, 132.2, 129.0, 127.6, 126.5, 115.4, 110.9, 104.1, 69.1, 57.4, 17.9; FT-IR (neat) 2919, 2875, 1740, 1679, 1588, 1489, 1367, 1205, 1075, 808, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}BrNO$: 330.0488, found: 330. 0499.

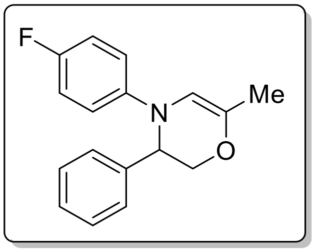
3q': yield 70% (23 mg), $[\alpha]_D^{25}$ = +29.00 (c= 0.1, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL OJ-H, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 22.07 min (major), 10.98 min (minor)].



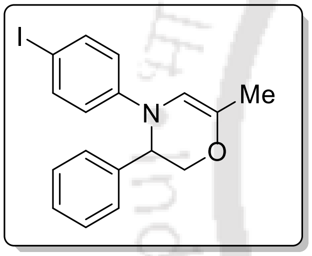
4-(4-Chlorophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine

3r. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane $R_f = 0.97$; thick liquid; yield 82% (47 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.22-7.19 (m, 3H), 7.08-7.04 (m, 2H), 6.65-6.62 (m, 2H), 5.88 (s, 1H), 4.70 (s, 1H), 4.33 (dd, J = 10.8, 2.0 Hz, 1H), 4.09 (dd, J = 10.8, 2.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.1, 139.1, 135.9, 129.3, 128.9, 127.6, 126.5, 123.7, 114.9, 104.2, 69.1, 57.4, 17.9; FT-IR (neat) 2925, 2870, 1742, 1687, 1585, 1475, 1381, 1202, 1084, 753, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}ClNO$: 286.0993, found: 286.0999.

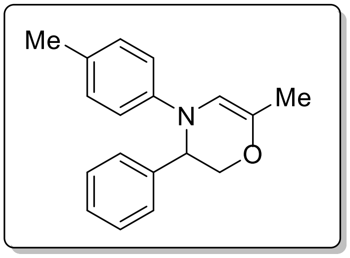
3r': yield 77% (22 mg), $[\alpha]_D^{25}$ = +12.00 (c= 0.1, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL OJ-H, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 22.47 min (major), 10.00 min (minor)].



4-(4-fluorophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3s. Analytical TLC on silica gel, 91:9 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 77% (42 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 5H), 6.84-6.79 (m, 2H), 6.68 – 6.63 (m, 2H), 5.84 (s, 1H), 4.67 (s, 1H), 4.31 (dd, J = 10.8, 2.4 Hz, 1H), 4.06 (dd, J = 10.8, 2.8 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 ($J_{C\text{-}F}$ = 236.3 Hz), 142.6, 139.6, 135.5, 128.9, 127.5, 126.5, 116.0 ($J_{C\text{-}F}$ = 22.2 Hz), 115.5 ($J_{C\text{-}F}$ = 7.5 Hz), 105.0, 69.0, 58.2, 17.8; ^{19}F NMR (377 MHz, $CDCl_3$) δ -126.0; FT-IR (neat) 2925, 2857, 1741, 1674, 1509, 1223, 1111, 822, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}FNO$: 270.1289, found: 270.1268.



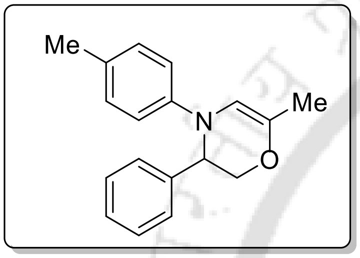
4-(4-Iodophenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3t. Analytical TLC on silica gel, 4:96 ethyl acetate/hexane R_f = 0.97; thick liquid; yield 70% (53 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.24 (m, 3H), 6.56-6.54 (m, 2H), 5.93 (s, 1H), 4.76 (s, 1H), 4.40 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.15 (dd, *J* = 11.0, 3.0 Hz, 1H),1.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 139.0, 138.1, 136.3, 129.0, 127.6, 126.5, 115.9, 103.9, 80.2, 69.2, 57.2, 17.9; FT-IR (neat) 2916, 2875, 1728, 1676, 1580, 1489, 1365, 1205, 1089, 805, 733, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{17}INO$: 378.0349, found: 378.0363.



6-Methyl-3-phenyl-4-(p-tolyl)-3,4-dihydro-2H-1,4-oxazine 3u. Analytical TLC on silica gel, 4:96 ethyl acetate/hexane R_f = 0.96; thick solid; yield 69% (37 mg);

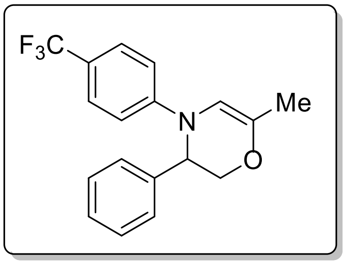
^{1}H NMR (600 MHz, CDCl$_3$) δ 7.27-7.23 (m, 4H), 7.20-7.17 (m, 1H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 5.90 (s, 1H), 4.72 (s, 1H), 4.32 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.06 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.16 (s, 3H); 1.76 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 143.7, 139.8, 135.0, 130.0, 128.8, 128.3, 127.4, 126.6, 114.1, 104.8, 69.0, 57.7, 20.5, 17.9; FT-IR (neat) 2922, 2866, 1742, 1677, 1513, 1453, 1366, 1227, 1043, 758, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{18}H_{20}NO$: 266.1539, found: 266.1552.

3u': yield 65% (17 mg), $[\alpha]_D^{25}$ = +19.00 (c= 0.1, CHCl$_3$); HPLC: >99% *ee* [CHIRALCEL AD, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 5.58 min (major), 4.68 min (minor)].

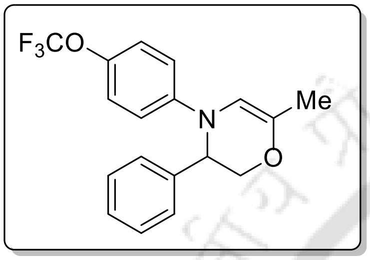


4-(4-Methoxyphenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3v. Analytical TLC on silica gel, 6:94 ethyl acetate/hexane R_f = 0.82; thick liquid; yield 64% (36 mg); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.27-7.23 (m, 4H), 7.19-7.17 (m, 1H), 6.71-6.67 (m, 4H), 5.81 (s, 1H), 4.64 (s, 1H), 4.28 (dd, *J* = 10.5, 2.0 Hz, 1H), 4.04 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.65 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.3, 140.8, 140.1, 134.9, 128.8, 127.4, 126.7, 116.2, 114.9, 105.7, 68.9, 58.6, 55.9, 17.8; FT-IR (neat) 2935, 1739, 1670, 1509, 1366, 1225, 1030, 836, 732, 699 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{18}H_{20}NO_2$: 282.1489, found: 282.1459.

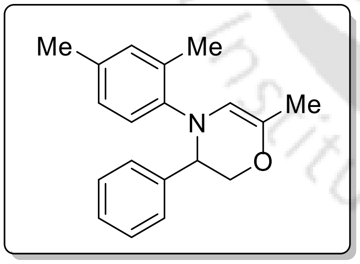
3v': yield 60% (17 mg), $[\alpha]_D^{25}$ = +77.00 (c= 0.1, CHCl$_3$); HPLC: 98% *ee* [CHIRALCEL OJH, hexane/*i*PrOH = 95:05, flow rate: 1 mL /min, λ = 254 nm, t_R = 27.62 min (major), 14.00 min (minor)].



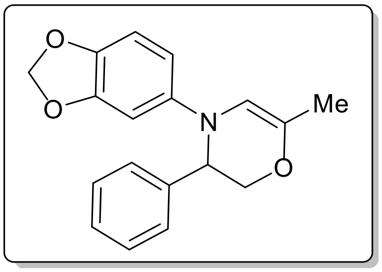
6-Methyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-1,4-oxazine 3w. Analytical TLC on silica gel, 9:91 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 66% (42 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.35 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (m, 2H), 7.22-7.20 (m, 3H), 6.73 (d, *J* = 8.4 Hz, 2H), 5.98 (s, 1H), 4.78 (s, 1H), 4.37 (dd, *J* = 10.8, 1.8 Hz, 1H), 4.13 (dd, *J* = 10.8, 3.0 Hz, 1H), 1.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.2, 138.5, 137.0, 129.0, 127.8, 126.8 (q, *J* = 3.75 Hz), 126.4, 125.8(q , *J* = 268.6 Hz), 120.2 (q, *J* = 32.1 Hz), 112.6, 103.4, 69.3, 56.9, 17.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ -61.2; FT-IR (neat) 2922, 2878, 1740, 1682, 1613, 1522, 1395, 1321, 1106, 1064, 819, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO$: 320.1257, found: 320.1264.



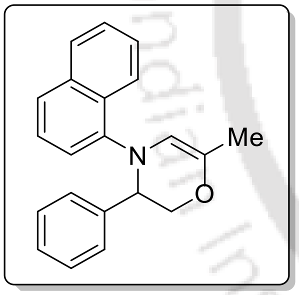
6-Methyl-3-phenyl-4-(4-(trifluoromethoxy)phenyl)-3,4-dihydro-2H-1,4-oxazine 3x. Analytical TLC on silica gel, 4:96 ethyl acetate/hexane R_f = 0.95; thick liquid; yield 68% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.24-7.21 (m, 3H), 6.99-6.96 (m, 2H), 6.69-6.65 (m, 2H), 5.89 (s, 1H), 4.71 (s, 1H), 4.34 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.09 (dd, *J* = 10.4, 2.8 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.3, 141.5, 139.1, 136.1, 129.0, 127.7, 126.4, 122.5, 114.2, 104.2, 69.1, 57.6, 17.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ -58.4; FT-IR (neat) 2925, 2857, 1743, 1680, 1511, 1259, 1224, 1163, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{17}F_3NO_2$: 336.1206, found: 336.1180.



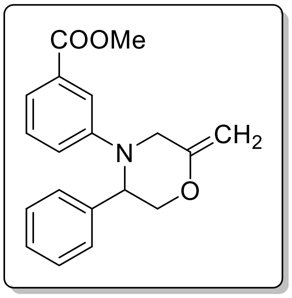
4-(2,4-dimethylphenyl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3y. Analytical TLC on silica gel, 3:97 ethyl acetate/hexane R_f = 0.97; thick liquid; yield 62% (35 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.27 (m, 2H), 7.23-7.21 (m, 2H), 7.15-7.13 (m, 1H), 6.89-6.86 (m, 2H), 6.83-6.81 (m, 1H), 5.33 (s, 1H), 4.34-4.33 (m, 1H), 4.12 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.97 (dd, *J* = 10.2, 2.4 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.9, 140.0, 136.0, 133.1, 132.4, 132.3, 128.4, 127.18, 127.10, 126.9, 123.7, 109.7, 68.3, 60.8, 20.8, 19.1, 17.7; FT-IR (neat) 2919, 2861, 1740, 1673, 1500, 1453, 1221, 1039, 758, 698 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{19}H_{22}NO$: 280.1696, found: 280.1699.



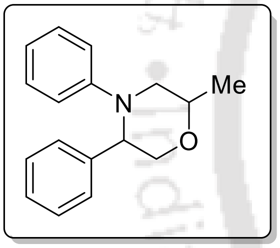
4-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3z. Analytical TLC on silica gel, 4:96 ethyl acetate/hexane $R_f = 0.96$; thick liquid; yield 61% (36 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.22 (m, 4H), 7.20-7.17 (m, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.347-6.343 (m, 1H), 6.16 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.78-5.76 (m, 3H), 4.62 (s, 1H), 4.28 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.03 (dd, *J* = 10.2, 2.4 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.5, 142.2, 140.9, 139.8, 135.1, 128.8, 127.4, 126.6, 108.6, 107.1, 105.5, 101.0, 97.6, 68.9, 58.8, 17.8; FT-IR (neat) 2920, 1738, 1674, 1628, 1485, 1366, 1200, 1086, 1034, 930, 734, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{18}H_{18}NO_3$: 296.1281 found: 296.1262.



6-methyl-4-(naphthalen-1-yl)-3-phenyl-3,4-dihydro-2H-1,4-oxazine 3aa. Analytical TLC on silica gel, 7:93 ethyl acetate/hexane $R_f = 0.93$; thick liquid; yield 65% (39 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01(d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.40-7.36 (m, 2H), 7.35-7.32 (m, 1H), 7.29-7.23 (m, 4H), 7.21-7.17 (m, 1H), 7.08-7.06 (m, 1H), 5.54 (m, 1H), 4.63-4.62 (m, 1H), 4.19 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.03 (dd, *J* = 10.4, 2.4 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 139.6, 137.6, 135.1, 128.9, 128.7, 128.6, 127.3, 127.1, 126.0, 125.7, 125.6, 124.0, 123.8, 119.5, 109.3, 68.2, 61.3, 17.8; FT-IR (neat) 3057, 2923, 2871, 1738, 1676, 1578, 1454, 1396, 1226, 1105, 775, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{21}H_{20}NO$: 302.1539, found: 302.1546.



Methyl 3-(2-methylene-5-phenylmorpholino)benzoate 3p'. Analytical TLC on silica gel, 8:92 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 71% (44 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.41-7.36 (m, 4H), 7.32-7.29 (m, 1H), 7.22-7.20 (m, 1H), 6.80-6.78 (m, 1H), 4.73 (t, *J* = 4.8, 1H), 4.48 (dd, *J* = 12.0, 4.2 Hz, 1H), 4.37-4.28 (m, 3H), 4.20 - 4.16 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 155.7, 148.5, 139.9, 130.9, 129.2, 128.9, 127.9, 126.7, 119.2, 118.1, 114.0, 87.1, 69.5, 61.3, 52.2, 46.0; FT-IR (neat) 2950, 1717, 1678, 1599, 1489, 1445, 1231, 1108, 1037, 735, 698 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{19}H_{20}NO_3$: Exact Mass: 310.1438, found: 310.1447.



2-Methyl-4,5-diphenylmorpholine 4. Triethylsilane (6.0 mmol, 68 mg) was added to a solution of 1,4 oxazine **3a** (1.0 mmol, 40 mg) and trifluoroacetic acid (10 mmol, 80 µL) in CH_2Cl_2 (2 mL) at 0 °C and slowly allowed to warm to room temperature and the progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. The reaction mixture was quenched with saturated K_2CO_3 and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layer was washed with brine, drying (Na_2SO_4), and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent.

Data for major diastereomer **4a:** Analytical TLC on silica gel, 2:98 ethyl acetate/hexane R_f = 0.92; thick liquid; yield 63% (32 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.21 (m, 2H), 7.13-7.10 (m, 2H), 7.06-7.02 (m, 3H), 6.87-6.86 (m, 2H), 6.80-6.77 (m, 1H), 4.08 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.92-3.89 (m, 1H), 3.87 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.48-3.45 (m, 1H), 3.39 (dd, *J* = 12.0, 2.4 Hz, 1H), 2.62-2.59 (m, 1H), 1.16 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.6, 139.4, 128.8, 128.5, 128.0, 127.3, 123.2, 122.8, 74.1, 72.9, 62.6, 62.4, 19.0; FT-IR (neat) 2960, 1742, 1675, 1597, 1494, 1450, 1259, 1223, 1095, 1023, 801, 752, 695 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{17}H_{20}NO$: Exact Mass: 254.1539, found: 254.1532.

Data for minor diastereomer **4b.** Analytical TLC on silica gel, 2:98 ethyl acetate/hexane $R_f = 0.92$; thick liquid; yield 24% (12 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.21 (m, 2H), 7.18-7.10 (m, 5H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 4.68 (s, 1H), 4.30 (dd, *J* = 12.0, 1.8 Hz, 1H), 4.08 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.80-3.77 (m, 1H), 3.34 (dd, *J* = 12.6, 3.0 Hz, 1H), 3.02-2.98 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6, 139.5, 129.4, 128.4, 128.2, 127.0, 118.7, 115.2, 72.0, 70.8, 57.1, 49.6, 19.2; FT-IR (neat) 2922, 1596, 1498, 1451, 1379, 1237, 1108, 1081, 1030, 992, 750, 695 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{17}H_{20}NO$: Exact Mass: 254.1539, found: 254.1525.

3.4 References

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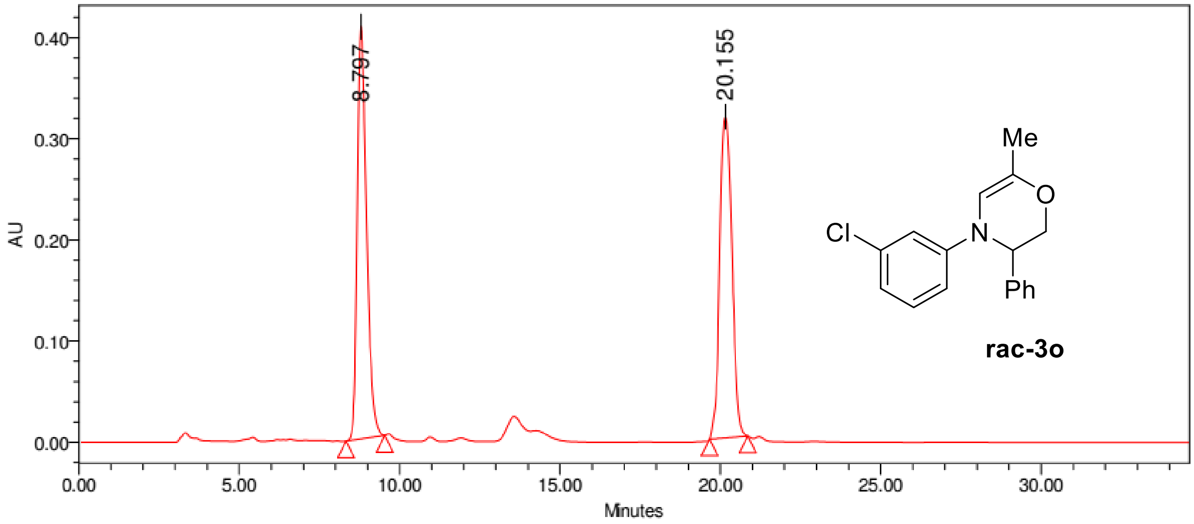
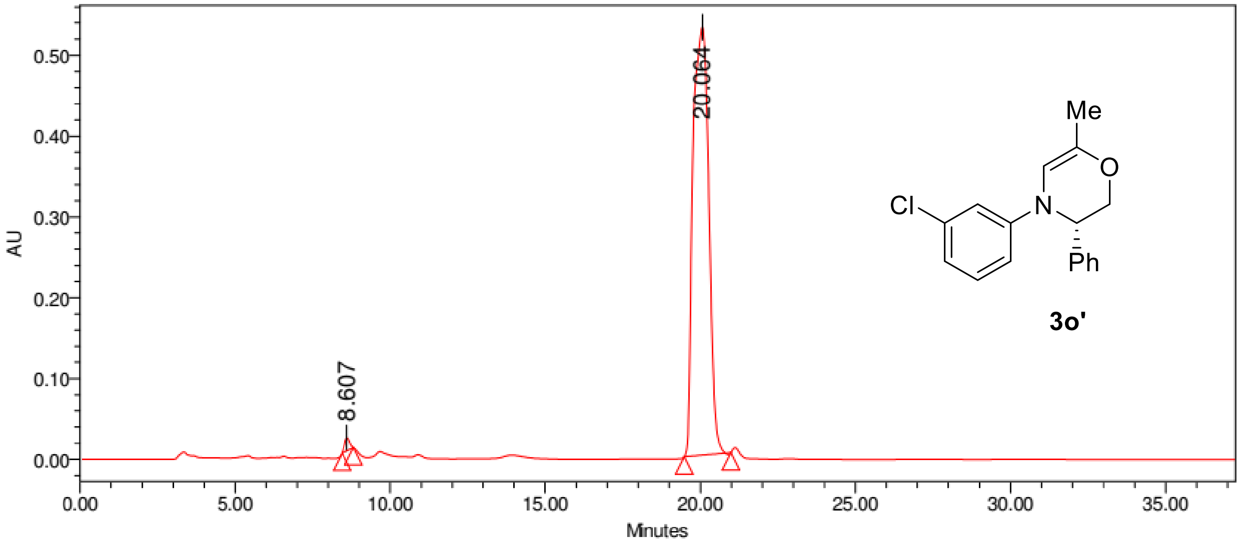
3.5 Selected HPLC Chromatogram



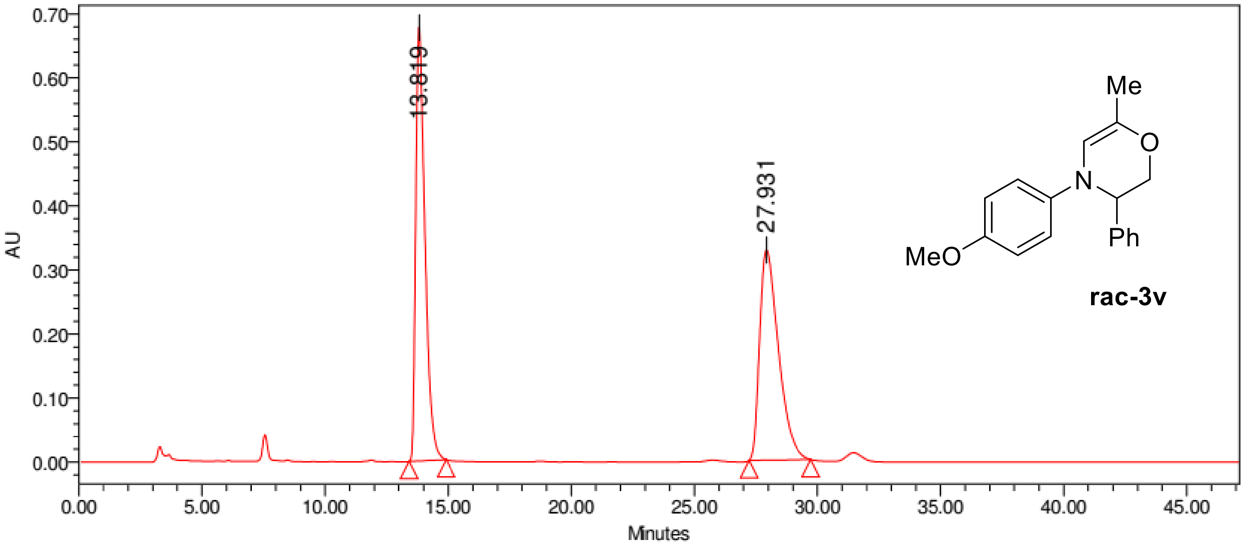
Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	8.333	9.533	8.797	407873	49.46
2	19.667	20.850	20.155	317537	50.54



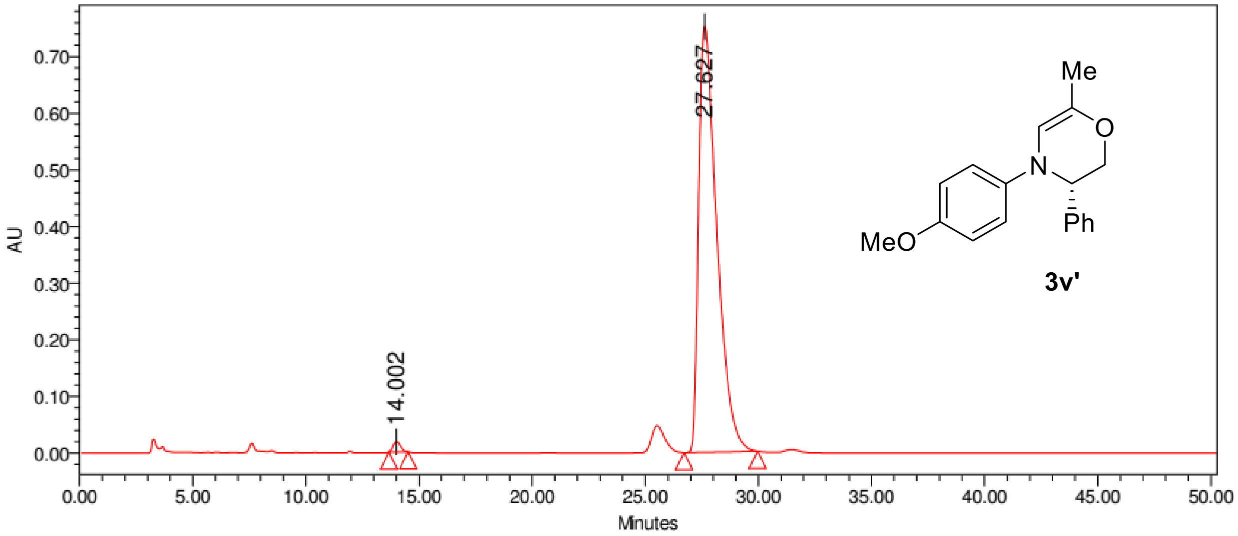
Peak Results

	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	I38	8.450	8.817	8.607	15915	0.96
2		19.483	20.983	20.064	529827	99.04



Peak Results

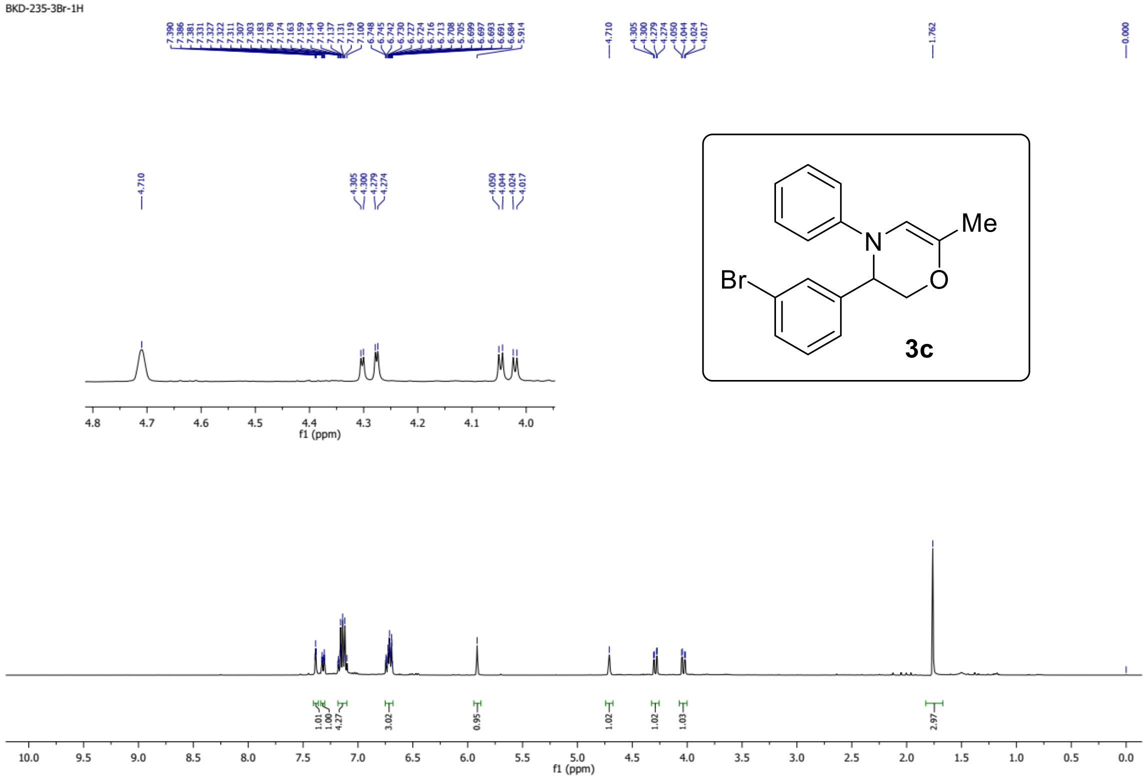
	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	13.417	14.917	13.819	677455	50.16
2	27.233	29.733	27.931	328378	49.84

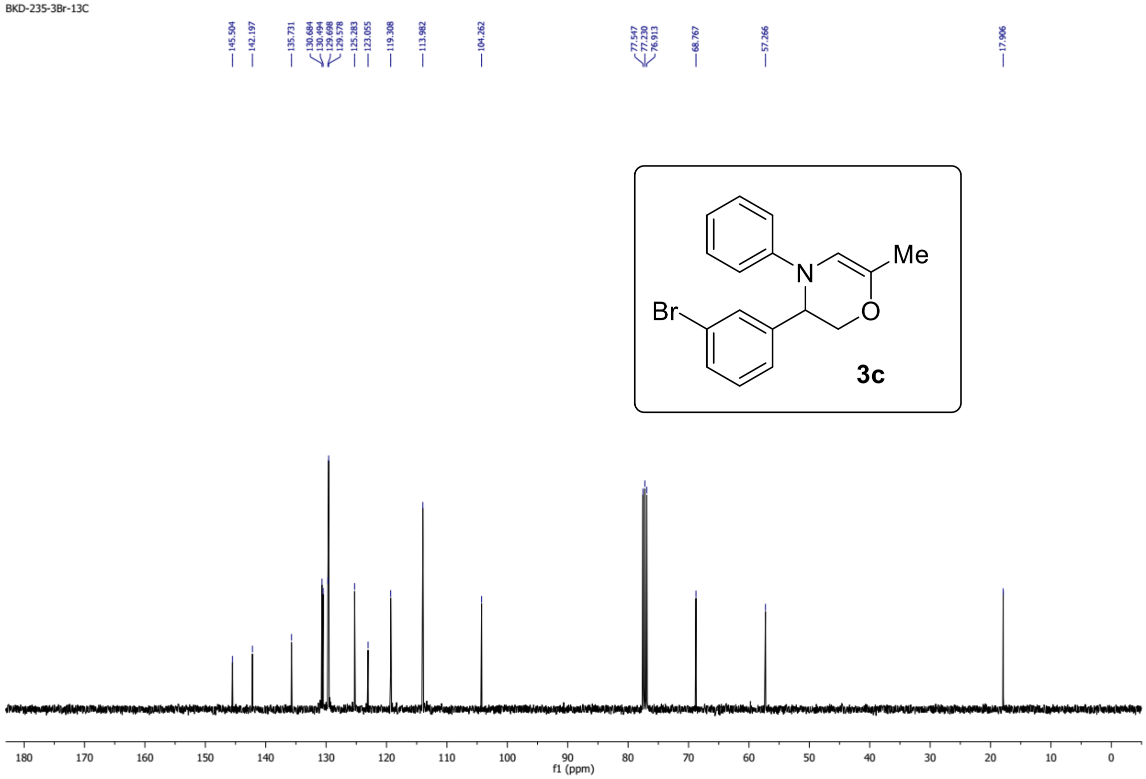


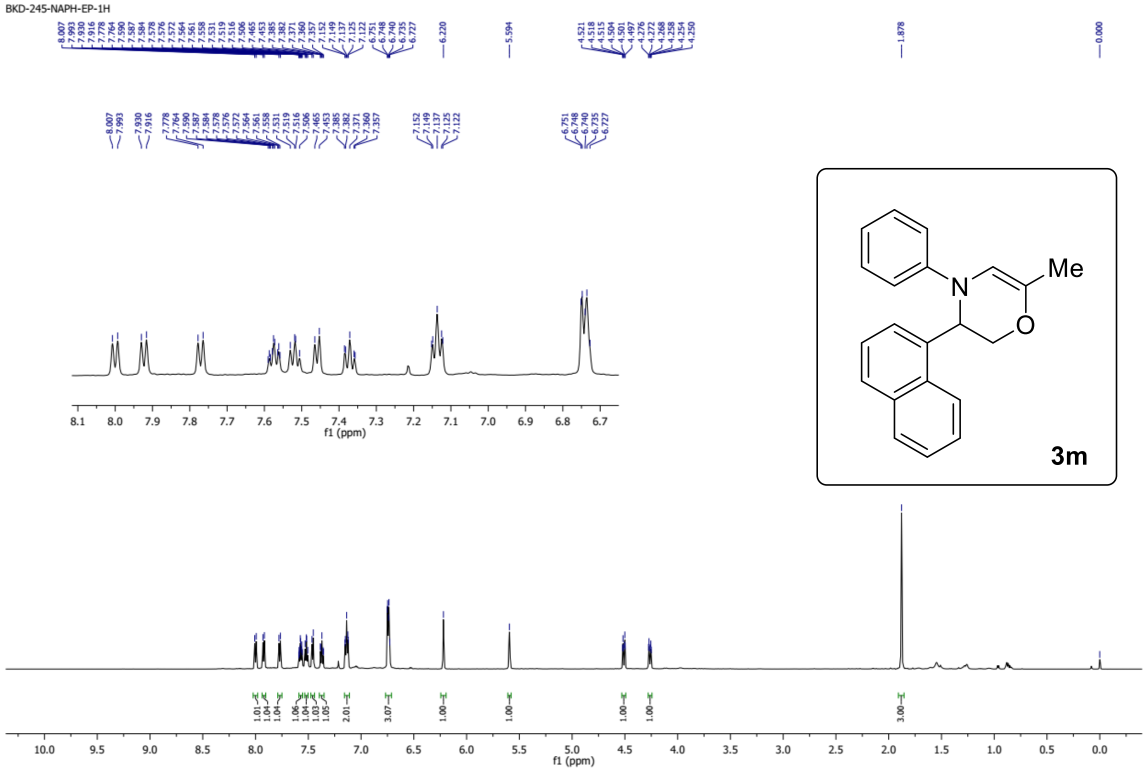
Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	13.667	14.517	14.002	18013	0.98
2	26.717	29.967	27.627	751870	99.02

3.6 Selected NMR (^{1}H and ^{13}C) Spectra



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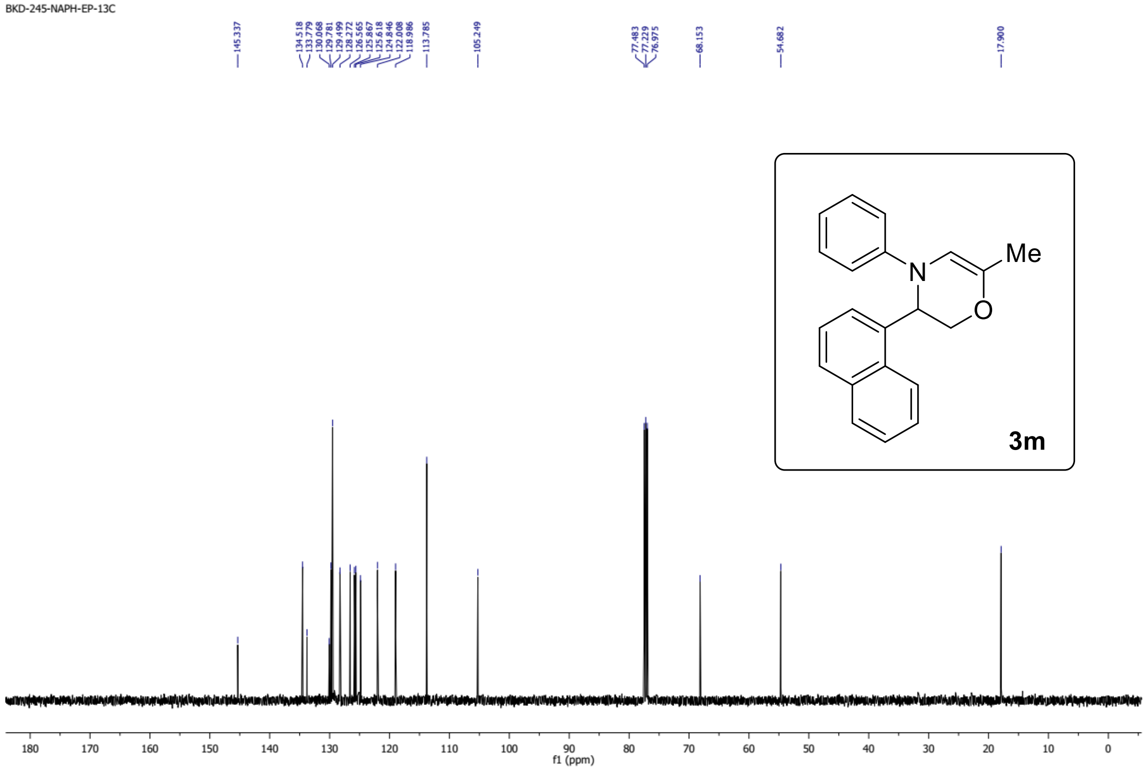
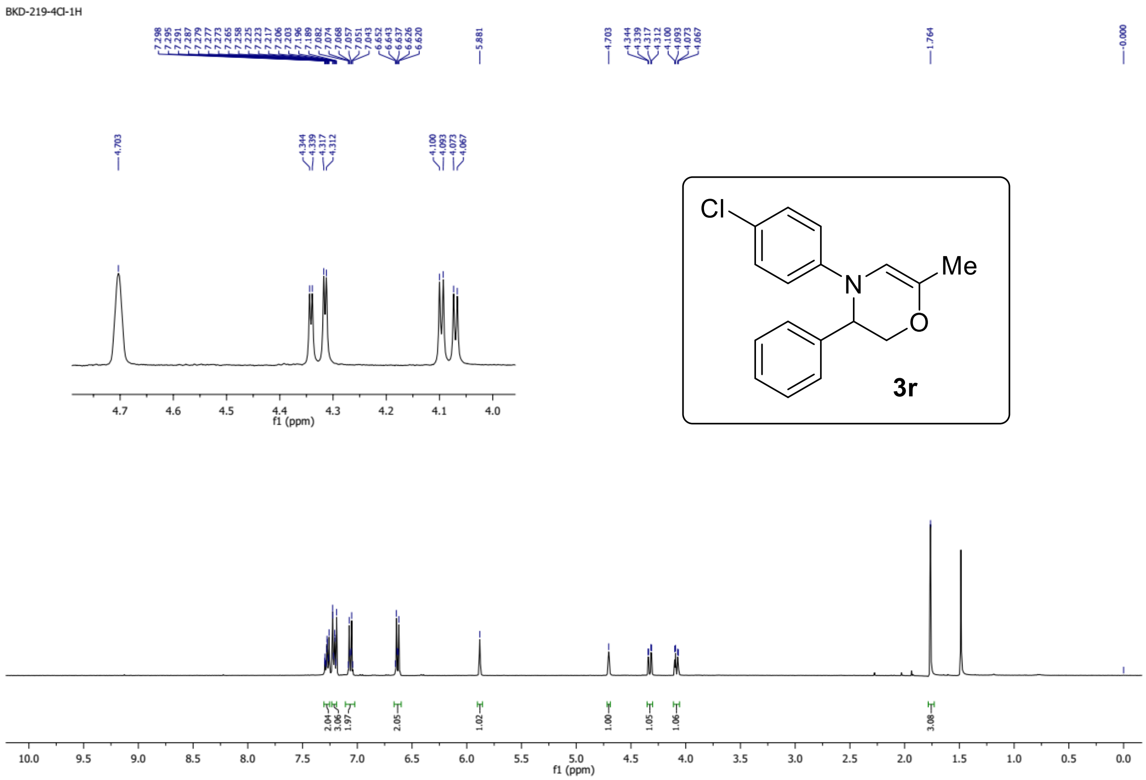
6.220
5.594
1.878
0.000
f1 (ppm)
Me
N
O
3m


BKD-245-NAPH-EP-13C
145.337
134.518
133.779
130.068
129.781
129.499
128.272
126.565
125.867
125.618
124.846
122.008
118.986
113.785
105.249
77.483
77.229
76.975
68.153
54.682
17.900
f1 (ppm)
Me
N
O
3m


BKD-219-4Cl-1H
7.298
7.295
7.291
7.287
7.279
7.277
7.273
7.265
7.258
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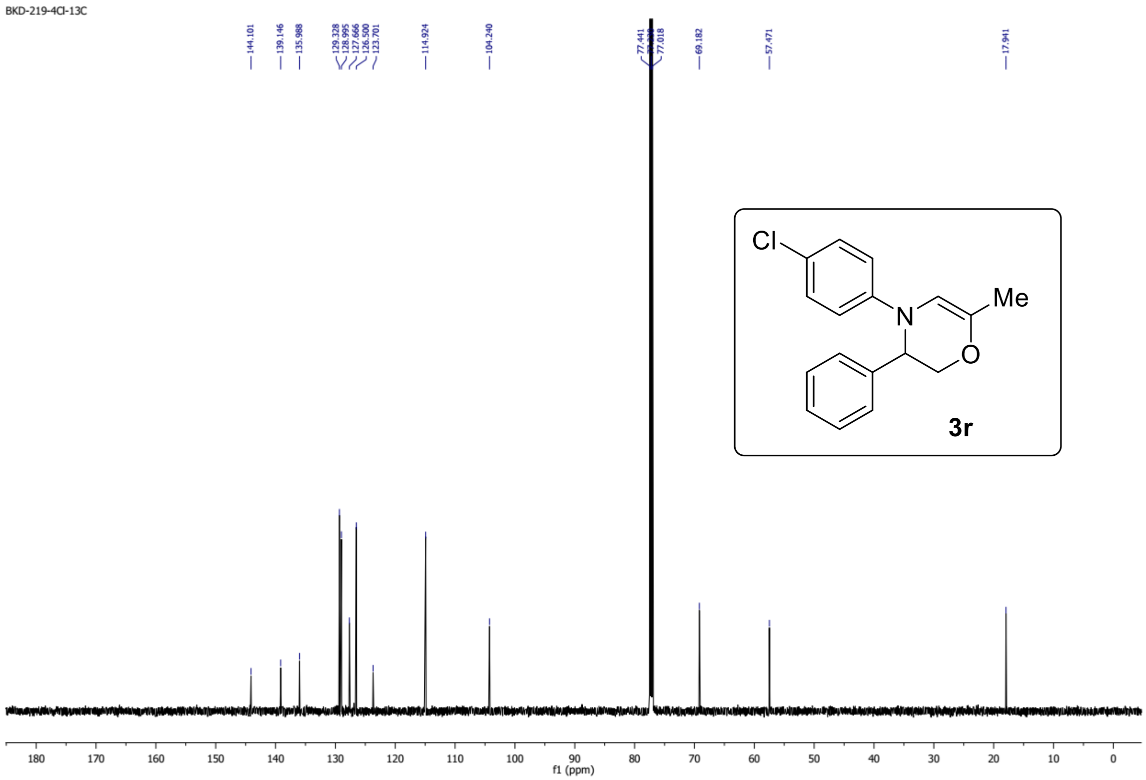
7.223
7.217
7.206
7.203
7.196
7.189
7.082
7.074
7.068
7.057
7.051
7.043
6.652
6.643
6.637
6.626
6.620
5.881
4.703
4.344
4.339
4.317
4.312
4.100
4.093
4.073
4.067
1.764
0.000
Cl
N
Me
O
3r
2.04
3.06
1.97
2.05
1.02
1.00
1.05
1.06
3.08
f1 (ppm)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129.328
128.995
127.666
126.500
123.701
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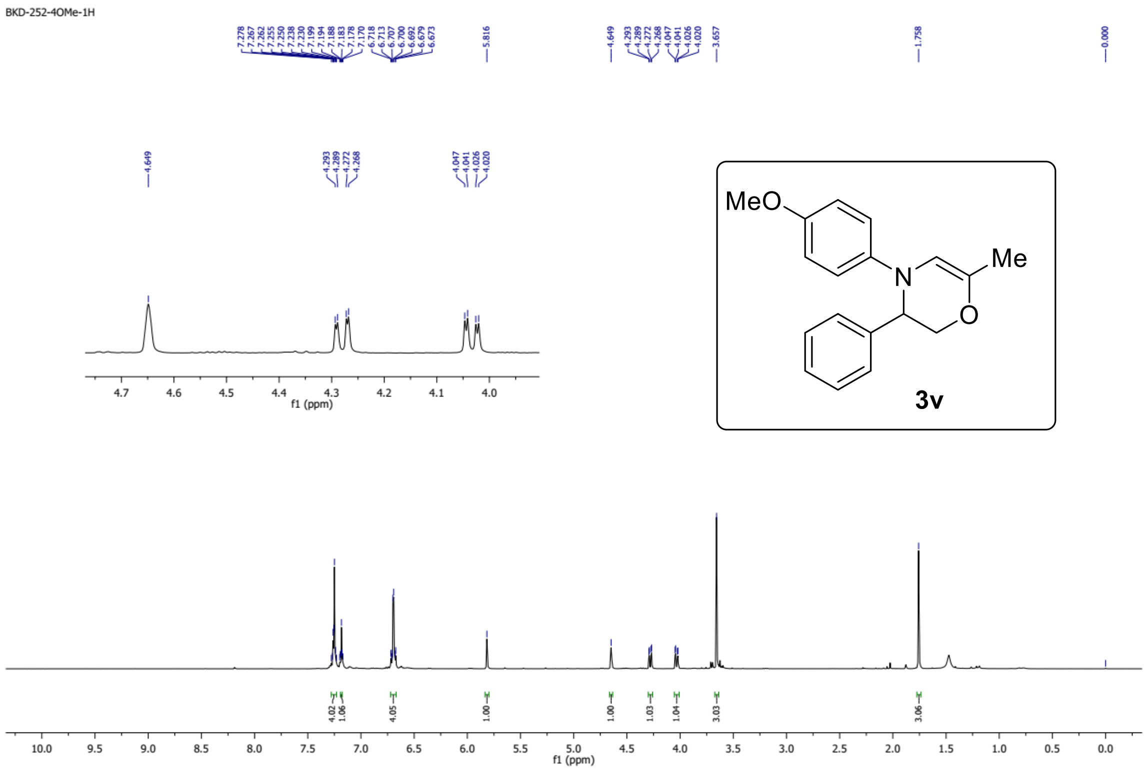
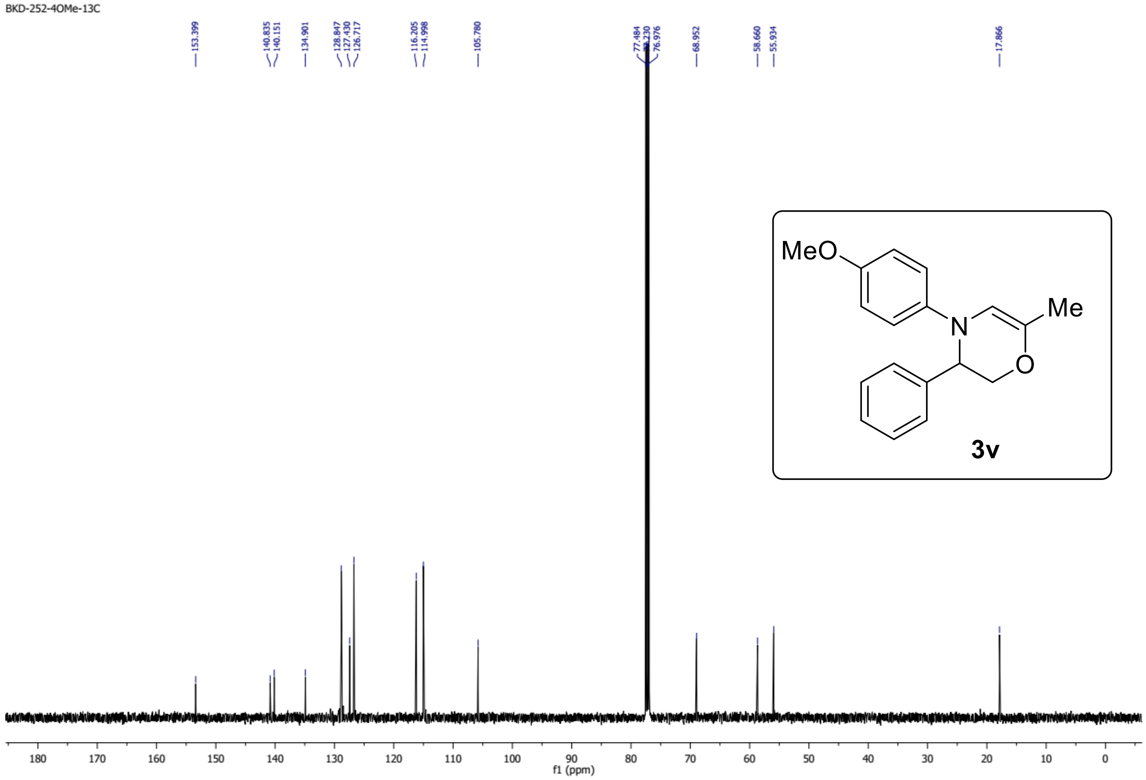
77.441
77.018
69.182
57.471
17.941
Cl
N
Me
O
3r
f1 (ppm)


BKD-252-4OMe-1H
7.278
7.267
7.262
7.255
7.250
7.238
7.230
7.199
7.194
7.188
7.183
7.178
7.170
6.718
6.713
6.707
6.700
6.692
6.679
6.673
5.816
4.649
4.293
4.289
4.272
4.268
4.047
4.041
4.026
4.020
3.657
1.758
0.000
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
f1 (ppm)
MeO
N
Me
O
4.02
1.06
4.05
1.00
1.00
1.03
1.04
3.03
3.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

3v


BKD-252-4OMe-13C
153.399
140.835
140.151
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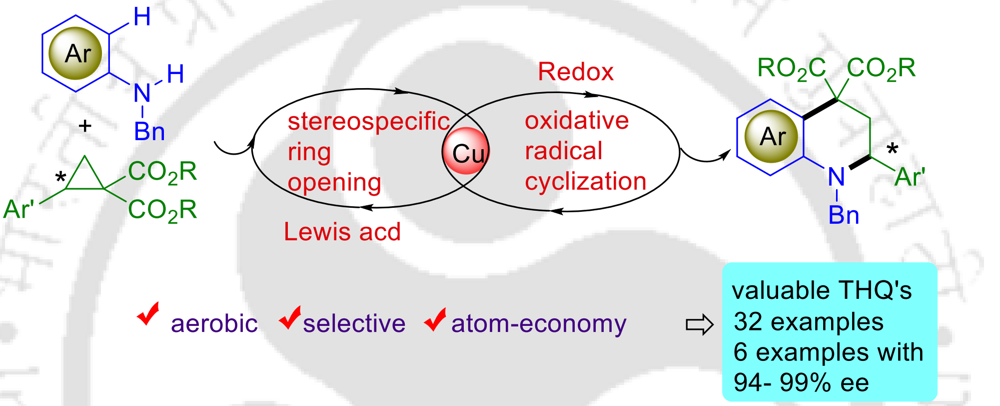
128.847
127.430
126.717
116.205
114.998
105.780
77.484
77.230
76.976
68.952
58.660
55.934
17.866
MeO
N
Me
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3v

Chapter IV

Reaction of D-A Cyclopropanes with N-Alkyl Anilines: Stereospecific Assembly of Tetrahydroquinolines



Chem. Commun. **2019**, *55*, 8083.

Reaction of D-A Cyclopropanes with *N*-Alkyl Anilines: Stereospecific Assembly of Tetrahydroquinolines

Nitrogen-containing saturated heterocyclic scaffolds are common in natural products and bioactive compounds.[1] Among these, 1,2,3,4-tetrahydroquinolines with C2 functionality replicate the structural characteristics of a privileged class of six-membered aza-heterocycless that display broad bioactive spectrum (Figure 1).[2] Significant synthetic progress has therefore achieved in the creation of these structural frameworks and their chiral equivalents. With the rising concern about atom economy and efficiency,[3] developing an ideal approach for constructing these heterocycle scaffolds from simple components is therefore desirable.

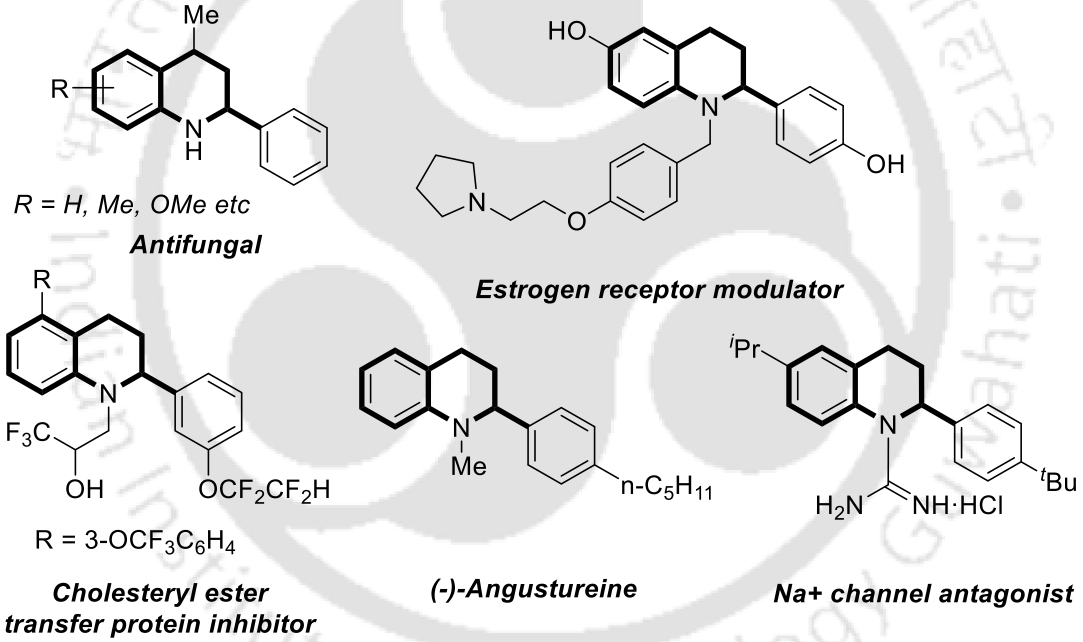


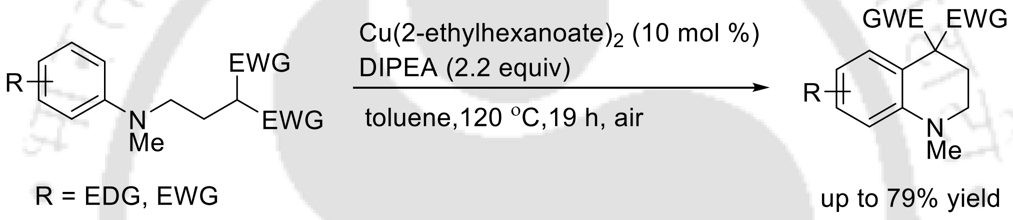
Figure 1. Selected Examples of Bi-oactive Tetrahydroquinolines.

In this context, using donor-acceptor (D-A) cyclopropanes as the 1,3-zwitterion equivalent,[4] (3+3)-cycloaddition[5] has emerged as a useful method in synthesizing six-membered heterocycles. Taking advantage of the ring strain (27.5 kcal mol^{-1}) and vicinal substitution[6] of D-A groups, the ring-opening,[7] rearrangement[8] and cycloaddition[9] reactions are studied. However, in (3+3)-annulation, the scope and kinds of expended dipoles are limited or formed *in-situ* by the stoichiometric addition of base. Recently, transition-metal-catalyzed C-H functionalization [10] has shown unprecedented development to achieve molecular complexity. Herein, we presented a stereospecific Cu-catalyzed[11] ring-opening and oxidative cyclization method for producing bio-relevant 2-aryl tetrahydroquinolines from D-A cyclopropanes and *N*-alkyl anilines.[12] This process uses Cu as a dual catalyst and combines the oxidative cyclization idea with traditional ring-opening to understand the target scaffolds.

4.1 Strategies for the Synthesis of Tetrahydroquinolines

4.1.1 Oxidative C-C Coupling

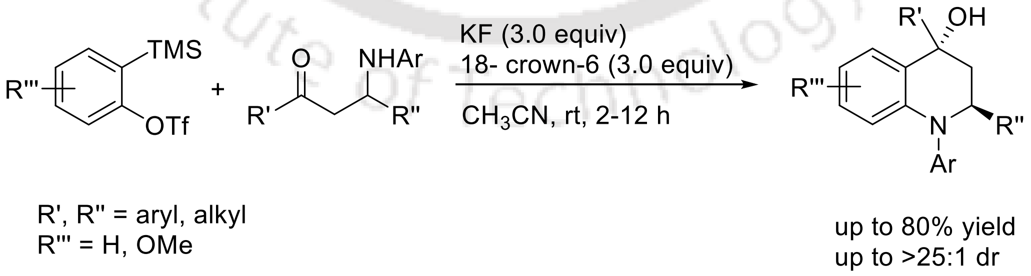
Taylor group described the synthesis of tetrahydroquinolines from linear precursors through direct C-H and Ar-H coupling (Scheme 1).[13] Cu(2-ethylhexanoate)$_2$ has been found as effective catalyst for this reaction, which uses atmospheric oxygen as the re-oxidant.



Scheme 1. Cu-Catalyzed Direct C-H and Ar-H Coupling

4.1.2 Insertion-Cyclization

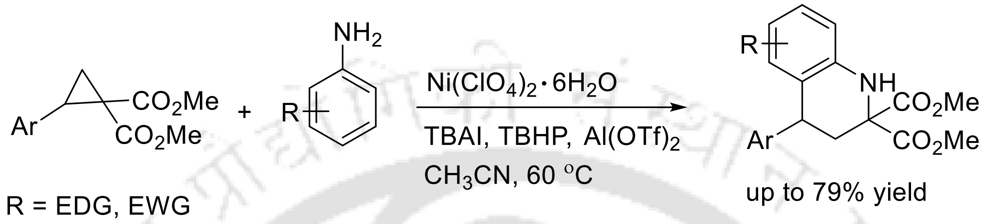
Dai and co-workers developed an insertion-cyclization reaction of arynes with β-amino ketones to obtain *N*-aryl tetrahydroquinolines in high diastereoselectivity (Scheme 2).[14] A quaternary carbon center is produced in this technique, and the reaction can be scaled up.



Scheme 2. Cascade Insertion-Cyclization with Arynes

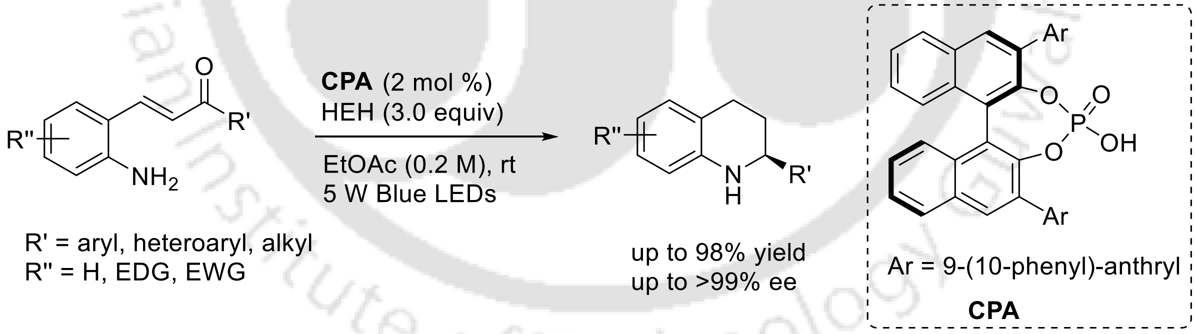
4.1.3 Relay Catalysis

Luo and co-workers have developed a catalytic (3+1)-annulation reaction between cyclopropane and aromatic amine based on the relay catalysis strategy (Scheme 3).[15] Lewis acid-catalyzed nucleophilic ring-opening of cyclopropane with aromatic amine and (hypo)iodite-catalyzed C−N bond formation are combined for the synthesis of tetrahydroquinolines.



Scheme 3. Ni/(hypo)iodite-Catalyzed Relay

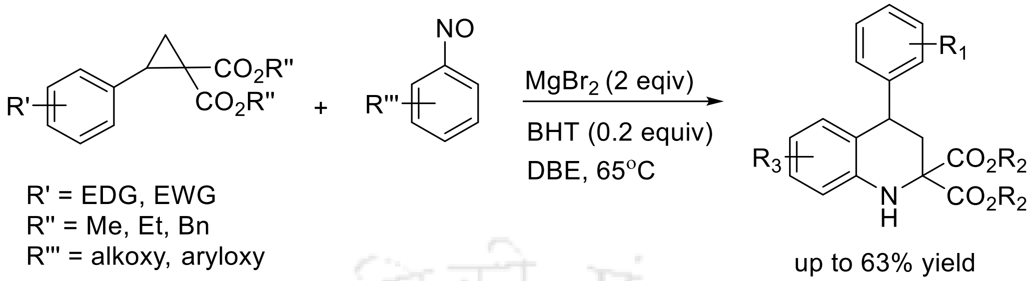
Yang and co-workers reported an efficient method by merging Brønsted acid catalysis with visible-light induction for the synthesis of tetrahydroquinolines (Scheme 4).[16] This approach directly converts 2-aminoenones to tetrahydroquinolines with good enantioselectivities through a relay visible-light-induced cyclization/chiral phosphoric acid-catalyzed transfer hydrogenation reaction.



Scheme 4. Visible-Light Induction/Brønsted Acid Catalysis in Relay

4.1.4 Dual Catalysis

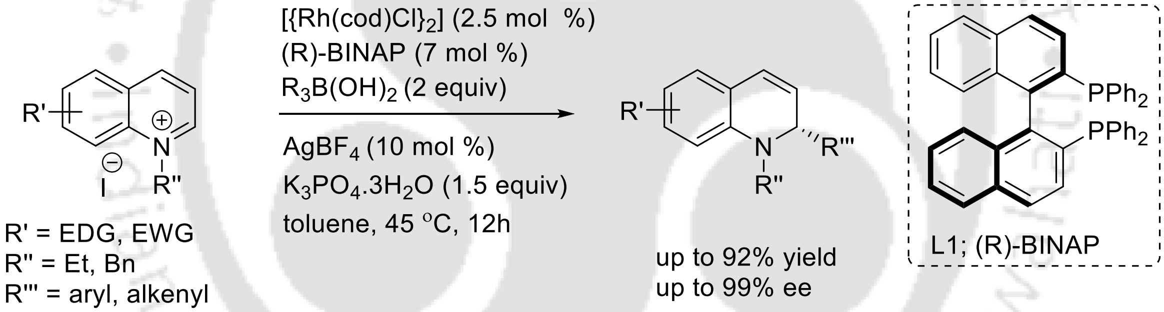
Studer and co-workers described a stereospecific (3+3)-annulation of DA cyclopropanes and nitrosoarenes in the presence of a stoichiometric quantity of $MgBr_2$ to get useful C-8 brominated tetrahydroquinolines (Scheme 5).[17] Lewis acid has a dual role in this sequence: it first functions as a “classical” Lewis acid for DA cyclopropane activation and then as a reagent (bromide anion donor) in the arene bromination process.



Scheme 5. (3 + 3)-Annulation with Cyclopropane

4.1.5 Dearomative Arylation

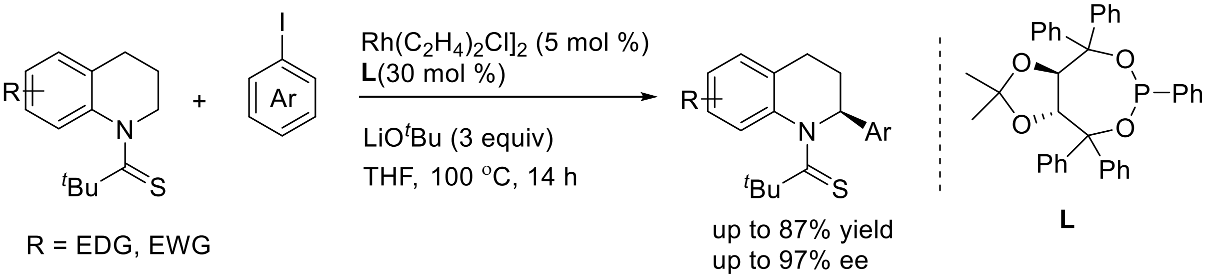
Wang group developed an enantioselective Rh-catalyzed nucleophilic addition for dearomative arylation of quinolinium salts employing organic boronic acids as nucleophiles (Scheme 6).[18] This protocol's synthetic usefulness is proven by the formal asymmetric synthesis of bioactive tetrahydroquinoline.



Scheme 6. Rh-catalyzed Dearomative Arylation

4.1.6 Transition Metal-Catalyzed C-H Arylation

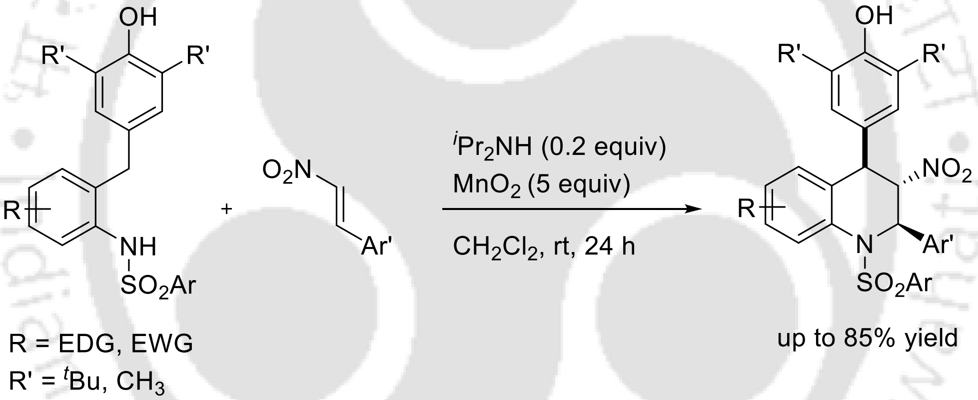
Glorius group reported a ligand enabled chiral Rh-catalyzed C-H arylation of tetrahydroquinolines to access 2-aryl derivatives (Scheme 7).[19] This redox-neutral methodology provides a new synthetic route to a *N*-arylated heterocycles with high chemoselectivity and enantioselectivity.



Scheme 7. Rh-catalyzed C-H Arylation

4.1.7 (4 + 2)-Annulation

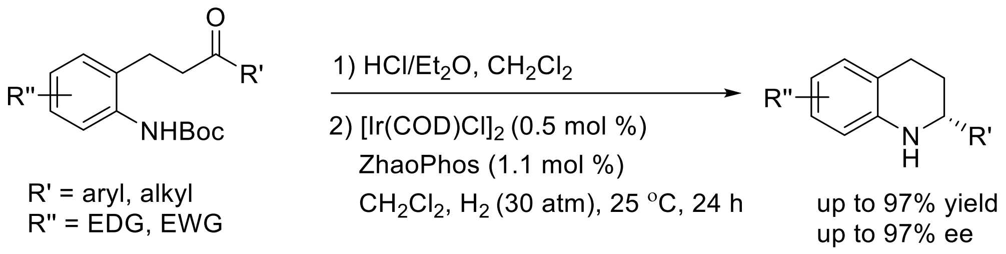
Hu and co-workers developed a formal (4+2)-annulation reaction between *in-situ* generated *p*-quinone methides and nitroalkenes using an aza-Michael/1,6-conjugate addition reaction sequence (Scheme 8).[20] Under mild conditions, this unique cascade reaction occurs in excellent yield, allowing easy access of 4-aryl-substituted tetrahydroquinolines.



Scheme 8. Aza-Michael/1,6-Conjugate Addition

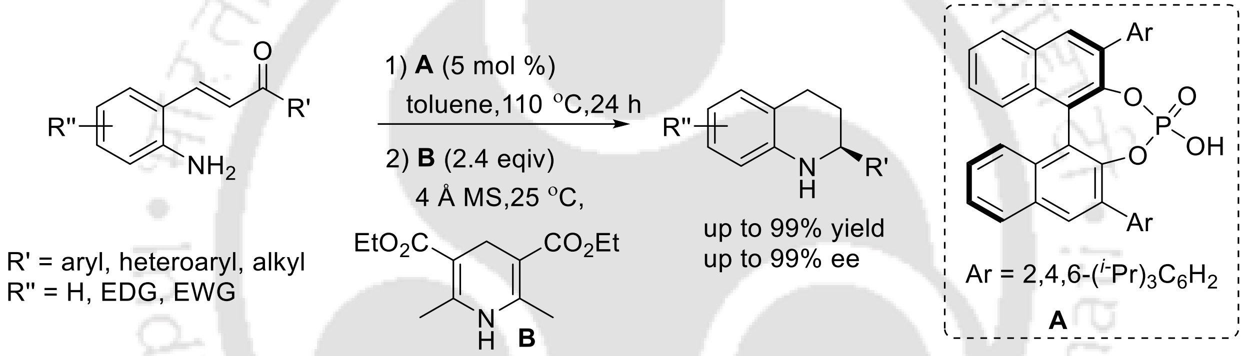
4.1.8 Asymmetric Reductive Amination

Zhang group established an asymmetric synthesis of chiral tetrahydroquinolines utilizing an Ir/ZhaoPhos catalytic system through a one-pot *N*-Boc deprotection/intramolecular asymmetric reductive amination sequence (Scheme 9).[21] The strong Brønsted acid HCl plays a crucial role in this transformation providing chloride ions to interact with the thiourea moiety in ZhaoPhos, therefore offering good enantiocontrol.



Scheme 9. *N*-Boc deprotection/Intramolecular Asymmetric Reduction

Cheon and co-workers established the asymmetric synthesis of chiral tetrahydroquinolines from 2-aminochalcones utilizing chiral phosphoric acids as the catalyst (Scheme 10).[22] The utility of this approach has been successfully demonstrated in the highly efficient synthesis of estrogen receptor modulator.

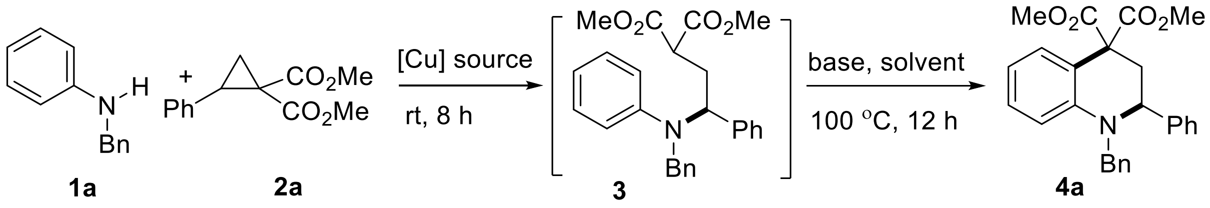


Scheme 10. Cyclization/Asymmetric Reduction

4.2 Present Study

In this chapter, we wish to disclose a stereospecific Cu-catalyzed ring opening and oxidative cyclization to produce 2-aryl tetrahydroquinolines utilizing cyclopropanes and *N*-alkyl anilines. We initiated the optimization studies with *N*-benzylaniline **1a** and cyclopropane **2a** as the model substrates using a series of copper(II) sources, bases and solvents (Table 1). To our delight, the neat substrates underwent reaction to produce **3** in 100% conversion and selectivity using 10 mol % Cu(OTf)$_2$ as a Lewis acid at room temperature under air and when the mixture was treated with DMF *in situ* and stirred at 100 °C proceeded an oxidative cyclization to furnish tetrahydroquinoline **4a** in 30% yield (entry 1). Subsequent screening of bases led to produce **4a** as a sole product utilizing K$_2$CO$_3$, whereas the reaction using t-BuOK, Cs$_2$CO$_3$, Na$_2$CO$_3$ and DBU afforded <73% yield (entries 2-6). Copper salts such as Cu(OAc)$_2$, CuCl$_2$ and CuBr$_2$ were not effective, which

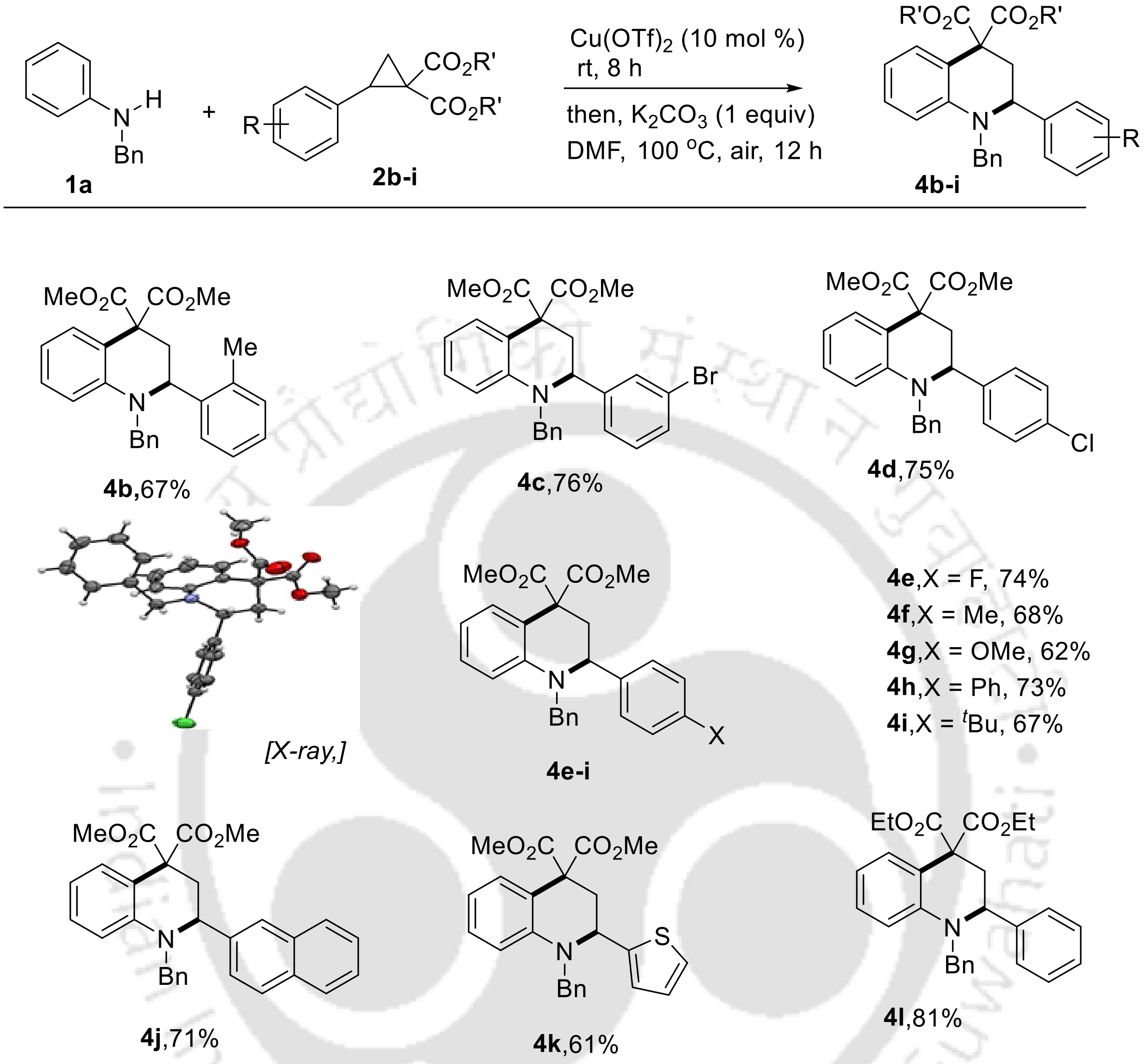
Table 1. Optimization of the Reaction Conditions[a]



Entry	[Cu] Source	Base	Solvent	**3**[b]	**4a**[b]
1	Cu(OTf)$_2$	-	DMF	60	30
2	**Cu(OTf)$_2$**	**K$_2$CO$_3$**	**DMF**	**n.d.**	**82**
3	Cu(OTf)$_2$	^{t}BuOK	DMF	14	70
4	Cu(OTf)$_2$	Cs$_2$CO$_3$	DMF	75	12
5	Cu(OTf)$_2$	Na$_2$CO$_3$	DMF	16	67
6	Cu(OTf)$_2$	DBU	DMF	trace	73
7	Cu(OAc)$_2$	K$_2$CO$_3$	DMF	n.d.	trace
8	CuCl$_2$	K$_2$CO$_3$	DMF	n.d.	n.d.
9	CuBr$_2$	K$_2$CO$_3$	DMF	n.d.	n.d.
10	Cu(OTf)$_2$	K$_2$CO$_3$	DMSO	20	63
11	Cu(OTf)$_2$	K$_2$CO$_3$	toluene	70	21
12	Cu(OTf)$_2$	K$_2$CO$_3$	CH$_3$CN	80	09
13	Cu(OTf)$_2$	K$_2$CO$_3$	THF	70	23
14	Cu(OTf)$_2$	K$_2$CO$_3$	(CH$_2$Cl)$_2$	86	n.d
15[c]	Cu(OTf)$_2$	K$_2$CO$_3$	DMF	73	14
16	-	K$_2$CO$_3$	DMF	n.d.	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), [Cu] source (10 mol %), 8 h, rt; then, base (0.2 mmol), solvent (2 mL), 12 h, air, 100 °C. [b]Isolated yield. [c]At 80 °C. n.d. = not detected

Table 2. Substrate Scope of cyclopropanes[a,b]

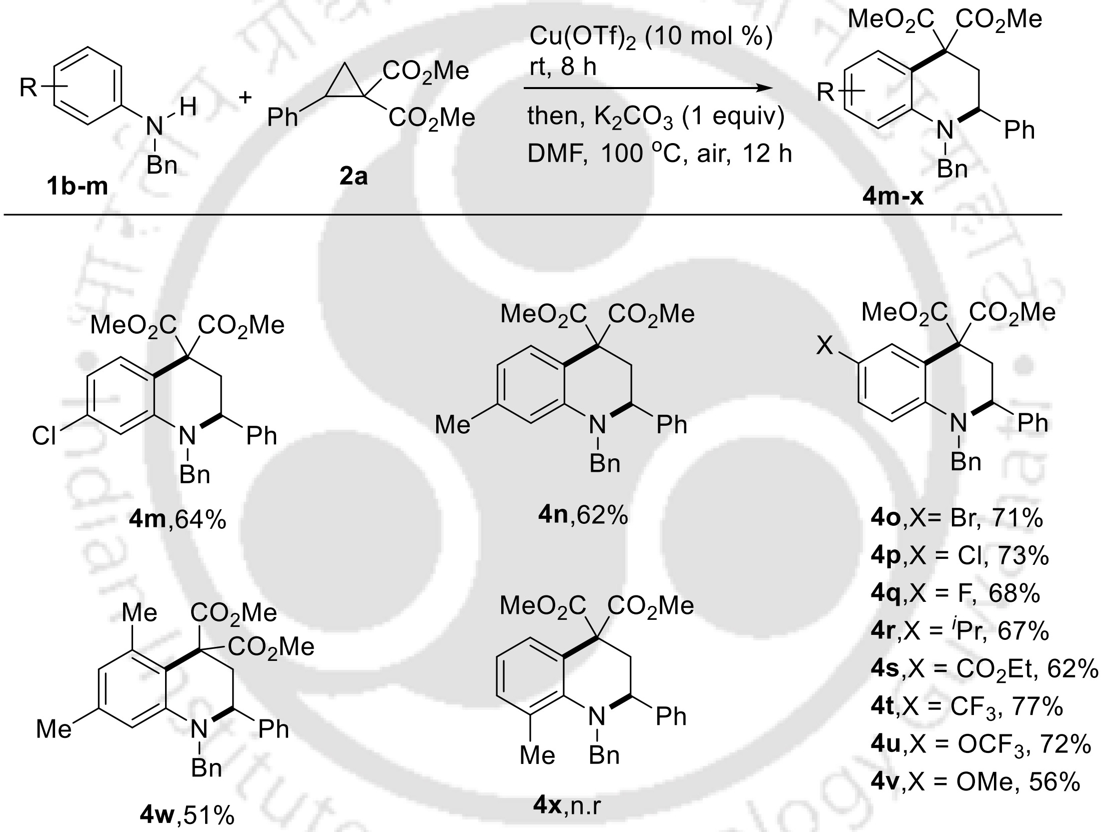


[a]Reaction conditions: **1a** (0.2 mmol), **2b-l** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), 8 h; then K_2CO_3 (0.2 mmol), 100 °C, DMF (2 mL), air, 12 h. [b]Isolated yield.

suggest that the Lewis acidity of the catalyst is crucial (entries 7-9). DMF was found to be the solvent of choice, while $(CH_2Cl)_2$, DMSO, toluene, CH_3CN and THF gave inferior results (entries 10-14). Decreasing the temperature (80 °C) led to slow the cyclization (entry 15). Control experiment confirmed that without $Cu(OTf)_2$ no reaction was observed and the substrates **1a** and **2a** were recovered intact (entry 16).

With the optimized condition in hand, the scope of the procedure was investigated with cyclopropanes **2b-l** bearing substituted aryl rings using **1a** as a standard substrate (Table 2). The substrate bearing 2-methyl **2b** substituent underwent reaction to produce **4b** in 67% yield. The reaction of **2c** having 3-bromo congener afforded **4c** in 76% yield. Similar results were observed with the substrates containing substitution at the 4-position with chloro **2d**, fluoro **2e**, methyl **2f**, methoxy **2g**, phenyl **2h** and *tert*-butyl **2i** groups, delivering the aza-heterocycles **4d-i** in 62-75% yields. Intriguingly, 2-naphthyl **2j** and 2-thienyl **2k** containing substrates converted into the target products **4j** and **4k** in 71 and 61% yields, respectively, whereas a 1,1-diester variant cyclopropane **2l** was proven compatible, delivering **4l** in 81% yield.

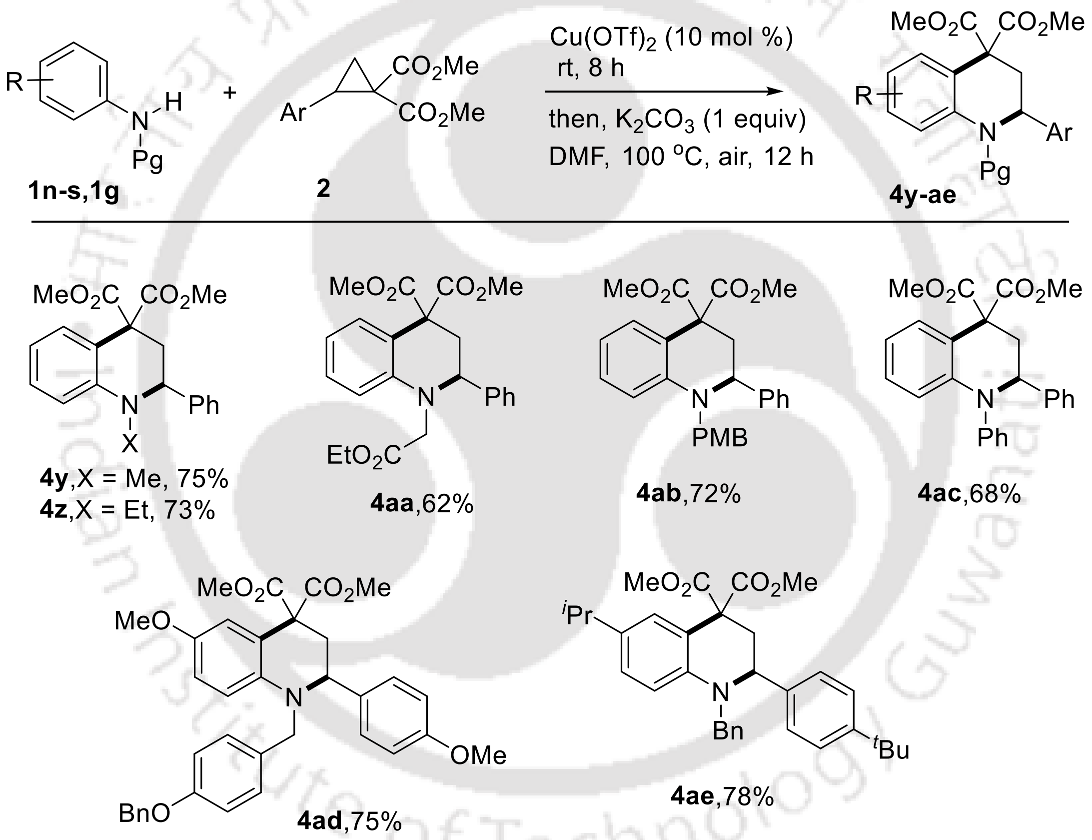
Table 3. Substrate Scope of *N*-Benzylanilines.[a,b]



[a]Reaction conditions: **1b-m** (0.2 mmol), **2a** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), 8 h; then 100 °C, K_2CO_3 (0.2 mmol), DMF (2 mL), air, 12 h. [b]Isolated yield. n.r. = no reaction

Next, the scope of the method was expanded for the synthesis of tetrahydroquinolines using a series of *N*-benzylanilines **1b-m** with cyclopropane **2a** as the standard substrate (Table 3). *N*-Benzylanilines bearing both the electron-donating and withdrawing groups in the aryl ring successfully participated. The reaction of the substrates containing 3-chloro **1b** and 3-methyl **1c** substituents gave **4m** and **4n** in 64 and 62% yields, respectively. The substrates bearing the substitution at the 4-position with bromo **1d**, chloro **1e**, fluoro **1f** and isopropyl **1g** functionalities underwent reaction to provide **4o-r** in 67-73% yields, while the substrates with carboxylate **1h**, trifluoromethyl **1i** and trifluoromethoxy **1j** groups conveyed **4s-u** in 62-77% yields. In addition, the reaction of **1k** having 4-methoxy group furnished **4v** in 56% yield, whereas a 3,5-dimethyl substituted **1l** delivered **4w** in 51% yield. However, 2-methyl bearing **1m** showed no reaction, which may be attributed to the bulkiness of the methyl group.

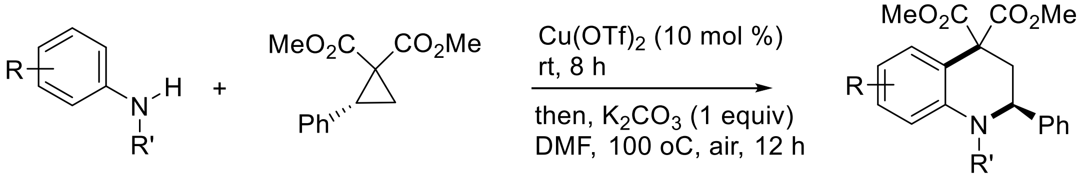
Table 4. Effect of Protecting Groups.[a,b]



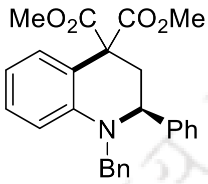
[a]Reaction conditions: **1b-m** (0.2 mmol), **2a** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), 8 h; then 100 °C, K$_2$CO$_3$ (0.2 mmol), DMF (2 mL), air, 12 h. [b]Isolated yield. n.r. = no reaction.

The tandem strategy was then tried with some synthetically useful protecting groups (Table 4). *N*-Protecting groups, such as methyl **1n**, ethyl **1o**, ethyl acetate **1p**, *p*-methoxybenzyl **1q** (PMB), phenyl **1r**, *p*-benzyloxybenzyl **1s** and benzyl **1g** attached anilines were proven successful coupling partners, giving **4y-ae** in 62-78% yields.

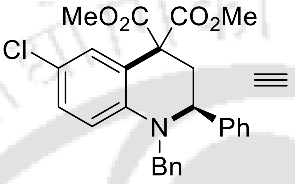
Table 4. Enantiospecific Synthesis.[a,b]



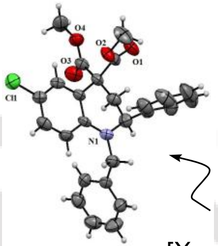
1a (*R*)-**2a'**, >99% ee 4'



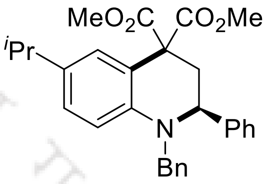
4a',81%, >99% ee



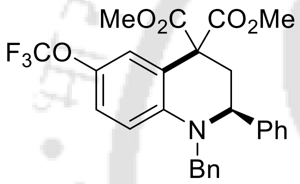
4p',72%, >99% ee



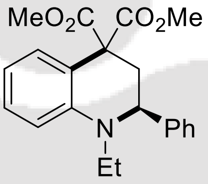
[X-ray]



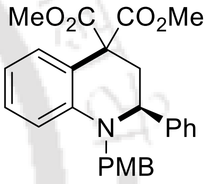
4r',66%, >99% ee



4u',69%, 97% ee



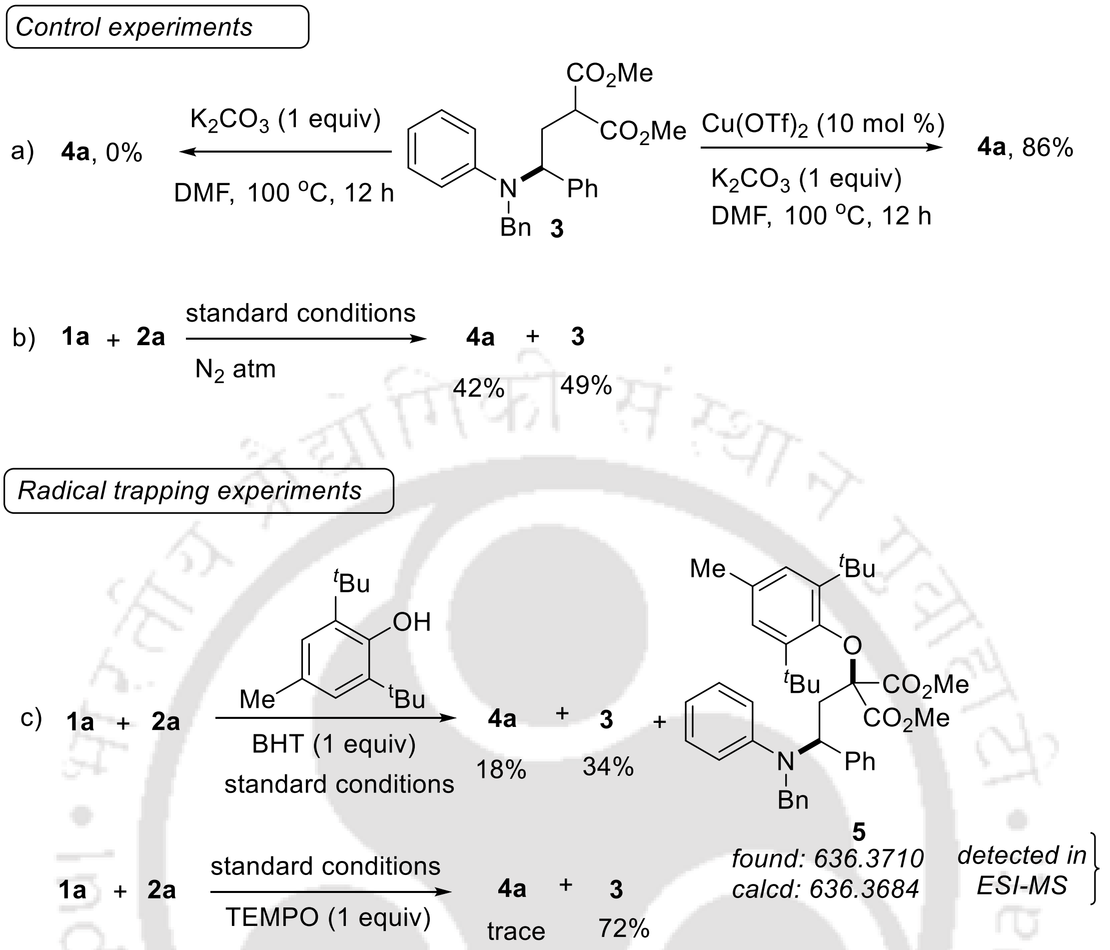
4z',72%, 97% ee



4ab',71%, 94% ee

[a]Reaction conditions: **1a** (0.2 mmol), (*R*)-**2a′** (0.24 mmol), Cu(OTf)$_2$ (10 mol %), 8 h; then K$_2$CO$_3$ (0.2 mmol), 100 °C, DMF (2 mL), air, 12 h. [b]Isolated yield.

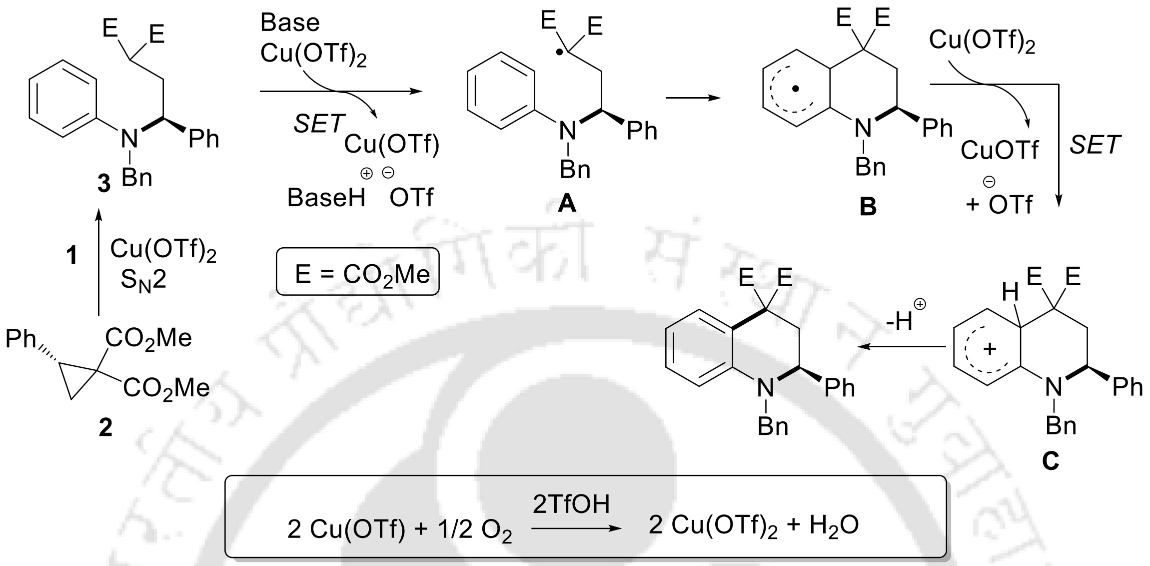
To disclose the stereochemical outcome, the coupling of a series of *N*-benzylanilines was examined with optically active cyclopropane (*R*)-**2a′** as a representative example (Table 4). Interestingly, the reaction occurred stereospecifically to yield the target heterocyclic scaffolds. For example, aniline derivative **1a** reacted to furnish **4a′** in >99% ee, while the substrates having 4-chloro, 4-isopropyl and 4-trifluromethoxy substituents underwent reaction to produce **4p′**, **4r′** and **4u′** in 97-99% *ee*. Similar results were perceived with anilines bearing *N*-ethyl **1o** and *N*-PMB **1q** substituents, providing **4z′** and **4ab′** in 97 and 94% *ee*, respectively. The absolute configuration of **4p′** was determined using the single-crystal X-ray analysis. These results suggest that the reaction proceeds via the stereospecific ring opening and the synthesis of tetrahydroquinolines can be achieved with high enantiomeric purities.



Scheme 11. Preliminary Mechanistic Investigations.

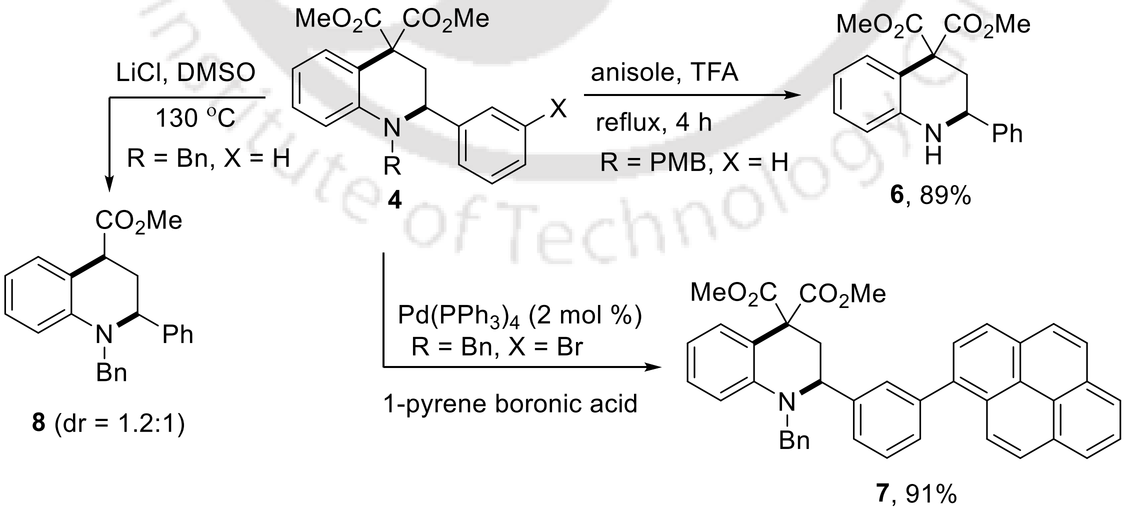
To get insight in the reaction pathway, the reaction of **3** was conducted using 10 mol % Cu(OTf)$_2$ and the heterocycle **4a** was obtained in 86% yield, whereas the cyclization failed in the absence of Cu(OTf)$_2$, which suggest that Cu(OTf)$_2$ catalyses the ring opening as well as the oxidative cyclization (Scheme 11a). In addition, the reaction under N$_2$ gave a mixture of **4a** and **3**, which suggests that air is involved in the Cu-catalyzed oxidative cyclization (Scheme 11b). Further, the radical scavenger experiments using BHT and TEMPO significantly attenuated the formation of **4a** bolstered the involvement of the radical intermediate (Scheme 11c).[23] The ESI-MS analysis revealed the formation of BHT adduct **5**. These results suggest that the Cu(OTf)$_2$-catalyzed stereospecific ring opening of **2** with *N*-alkyl anilines **1** can deliver **3** with an inverted configuration that can react with Cu(OTf)$_2$ to produce the malonyl radical **A** with Cu(OTf) and TfOH by a single electron transfer (SET). Cyclization of **A** can lead to the formation of the aryl radical **B** that can convert to **C** via the SET. Deprotonation of **C** can give the target products **4** and TfOH (Scheme

12).[14] Aerobic oxidation of Cu(OTf) with TfOH can regenerate Cu(OTf)₂ to complete the catalytic cycle. Thus, Cu(OTf)₂ plays a dual role as Lewis acid as well as the redox catalyst in this synthesis.



Scheme 12. Proposed Reaction Pathway.

The synthetic utility was reflected by the removal of PMB protecting group from **4ab** to furnish **6** in 89% yield. A bromo containing THQ **4c** was modified to **7** in 91% yield via Suzuki-cross-coupling utilizing pyrene-1-boronic acid (Scheme 13). In addition, the Krapcho decarboxylation of **4a** produced **8** in 77% yield as a 6:5 mixture of diastereomers.



Scheme 13. Post-Synthetic Utilities.

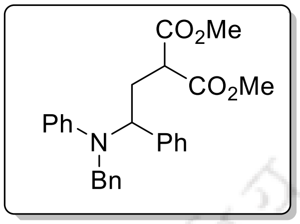
In conclusion, copper-catalyzed tandem reaction of *N*-alkyl anilines with cyclopropanes is established for the construction of tetrahydroquinolines via the Lewis acid catalyzed stereospecific ring opening and the oxidative cyclization. The method offers a practical prospective strategy for the synthesis of tetrahydroquinolines with high enantiomeric purities. Stereoselectivity and aerobic conditions are the significant practical features.

4.3 Experimental Section

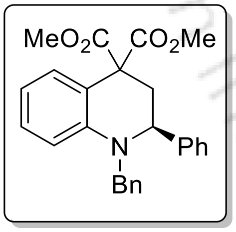
4.3.1 General Information. $Cu(OTf)_2$ (98%), $Cu(OAc)_2$ (98%), $CuCl_2$ (97%) and $CuBr_2$ (99.9%) were purchased from Aldrich and used as received. Cyclopropanes[24,25] and *N*-alkyl anilines[26] were prepared according to the reported procedure. Column chromatography was performed with Rankem silica gel (60-120 mesh). Bruker Avance III 400 and Bruker Avance III 600 spectrometers were used for recording NMR spectra using $CDCl_3$ as a solvent and Me_4Si as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (J) are reported in ppm and Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, dd = doublet of doublet and br s = broad singlet. Melting points were determined with a Büchi B-540 apparatus and are uncorrected. Optical rotation was determined using Perkin Elmer-343 Polarimeter. HPLC analysis was carried out with Waters-2489 instrument using Daicel Chiralcel AD-H column using iso-propanol and hexane as eluent. FT-IR spectra were collected on Thermo Fisher Scientific IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for recording mass spectra. Single crystal X-ray data were collected using Bruker SMART APEX-II CCD diffractometer, which is equipped with 1.75 kW sealed-tube Mo-Kα irradiation (λ = 0.71073 Å) at 298(2) K. The crystal structure was solved by the direct method using SHELXL-97 (Göttingen, Germany) and refined with full-matrix least squares on F2 using SHELXL-97.

4.3.2 General Procedure for the Synthesis of Tetrahydroquinolines. *N*-Alkyl aniline **1** (0.2 mmol), cyclopropane **2** (0.24 mmol) and $Cu(OTf)_2$ (0.02 mmol, 7.2 mg) were stirred at room temperature for 6 h. Then, K_2CO_3 (0.2 mmol, 22 mg) and DMF (2 mL) were added and the resulting mixture was stirred at 100 °C for 12 h under air. The progress of the reaction was monitored using TLC with ethyl acetate and hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The resultant mixture was washed with ice cold brine (5 mL) and cold water (5 mL). The aqueous solution was extracted with ethyl acetate (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent to give analytically pure tetrahydroquinoline scaffolds.

4.3.3 Procedure for the Enantiospecific Synthesis of Tetrahydroquinolines. *N*-Alkyl aniline **1** (0.2 mmol), chiral cyclopropane **(*R*)-2a′** (0.24 mmol) and Cu(OTf)$_2$ (0.02 mmol, 7.2 mg) were subjected to the above described general procedure for the tetrahydroquinoline synthesis. The enantiomeric excess was determined using chiral HPLC.

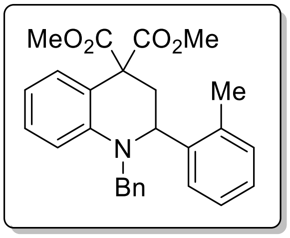


Dimethyl 2-(2-(benzyl(phenyl)amino)-2-phenylethyl) malonate 3. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.42; thick liquid; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.42-7.34 (m, 5H), 7.32-7.23 (m, 7H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 5.26 (t, *J* = 7.8, 1H), 4.43 (d, *J* = 16.8 Hz, 1H), 4.35 (d, *J* = 16.8 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.76-3.74 (m, 1H), 2.77-2.69 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 169.9, 169.8, 149.4, 139.5, 139.2, 129.2, 128.7, 128.5, 127.9, 127.7, 127.0, 126.6, 118.7, 116.2, 52.8, 52.8, 50.0, 49.1, 31.1; FT-IR (neat) 3061, 3029, 2953, 2847,1731, 1628, 1598, 1501, 1452, 1436, 1265, 1223, 1155, 1064, 751, 697 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{28}NO_4$: 418.2013 found: 418.2011.

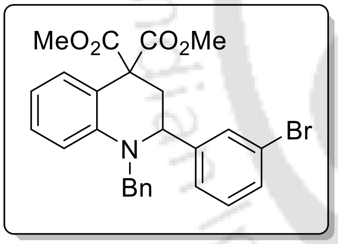


(*S*)-Dimethyl 1-benzyl-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4a′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.43; sticky liquid; yield 81% (67 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.22-7.03 (m, 10H), 7.01 (d, *J* = 7.8 Hz, 2H), 6.66-6.64 (m, 2H), 4.58 (d, *J* = 16.8 Hz, 1H), 4.47-4.45 (m, 1H), 3.98 (d, *J* = 16.8 Hz, 1H), 3.68 (s, 3H), 3.45 (s, 3H), 2.90-2.87 (m, 1H), 2.64-2.60 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.7, 171.3, 145.0, 141.9, 138.1, 129.5, 129.0, 128.7, 128.5, 127.6, 127.4, 127.09, 127.01, 119.8, 117.0, 113.5, 59.1, 57.1, 53.2, 52.8, 52.7, 38.3; FT-IR (neat) 3062, 3028, 2952, 1733, 1602, 1495, 1451, 1240, 1099 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{26}NO_4$: 416.1856, found: 416.1860; $[\alpha]_D^{25}$ =

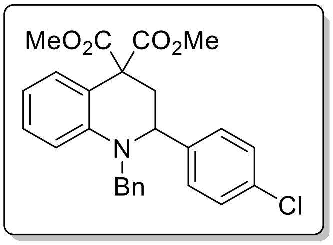
+42.00 (c= 0.1, $CHCl_3$); HPLC: >99% ee [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 24.34 min (major), 11.83 min (minor)].



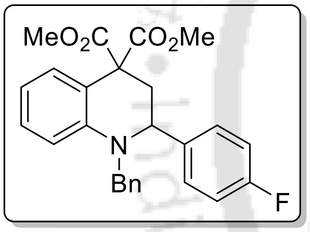
Dimethyl 1-benzyl-2-(*o*-tolyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; sticky liquid; yield 67% (56 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17-7.09 (m, 5H), 7.07-7.02 (m, 4H), 6.96 (d, *J* = 7.8 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 1H), 6.66 (t, *J* = 7.8, 1H), 4.62-4.58 (m, 2H), 3.92 (d, *J* = 16.2 Hz, 1H), 3.67 (s, 3H), 3.47 (s, 3H), 2.80 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.51 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 171.4, 145.6, 139.7, 137.9, 135.9, 130.83, 130.81, 129.5, 129.1, 128.6, 127.4, 127.3, 127.1, 126.4, 119.8, 116.9, 113.6, 57.2, 53.2, 52.9, 52.8, 36.5, 18.8; FT-IR (neat) 3027, 2951, 1734, 1602, 1495, 1453, 1240, 1135, 1101, 1025, 748, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_4$: 430.2013, found: 430.2014.



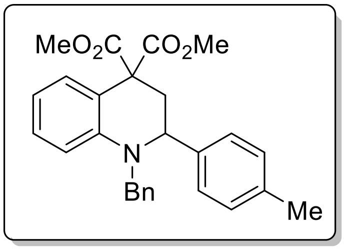
Dimethyl 1-benzyl-2-(3-bromophenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; sticky liquid; yield 76% (75 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.19-7.02 (m, 7H), 7.00-6.97 (m, 2H), 6.72-6.65 (m, 2H), 4.61 (d, *J* = 16.4 Hz, 1H), 4.42-4.38 (m, 1H), 3.96 (d, *J* = 16.4 Hz, 1H), 3.67 (s, 3H), 3.53 (s, 3H), 2.85 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.55 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.2, 144.9, 144.7, 137.8, 130.9, 130.5, 130.3, 129.6, 129.1, 128.6, 127.25, 127.22, 126.1, 122.8, 120.0, 117.5, 113.8, 58.7, 57.1, 53.2, 52.9, 38.3; FT-IR (neat) 3028, 2951, 2924, 2853, 1733, 1601, 1572, 1496, 1450, 1434, 1342, 1240, 1067, 1026, 749, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}BrNO_4$: 494.0961, found: 494.0962.



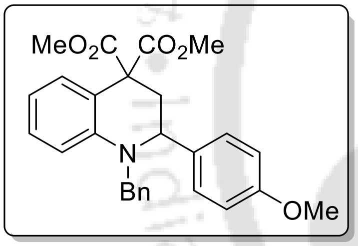
Dimethyl 1-benzyl-2-(4-chlorophenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.46; colorless crystal; mp 122-123 ^{o}C; yield 75% (67 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27-7.05 (m, 11H), 6.76-6.73 (m, 2H), 4.65 (d, *J* = 16.4 Hz, 1H), 4.50-4.47(m, 1H), 4.01 (d, *J* = 16.4 Hz, 1H), 3.75 (s, 3H), 3.57 (s, 3H), 2.93 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.62 (dd, *J* = 13.6, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.5, 171.3, 145.0, 140.6, 137.8, 133.4, 129.6, 129.1, 128.93, 128.91, 128.6, 127.23, 127.20, 120.0, 117.4, 113.7, 58.5, 57.1, 53.2, 52.95, 52.90, 38.4; FT-IR (KBr) 3028, 2951, 1733, 1601, 1575, 1495, 1493, 1450, 1343, 1240, 1089, 1014, 937, 835, 751, 699 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{25}ClNO_4$: 450.1467, found: 450.1468.



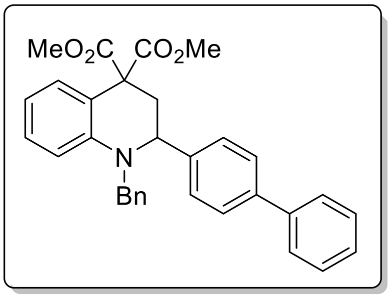
Dimethyl 1-benzyl-2-(4-fluorophenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.36; sticky liquid; yield 74% (64 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18-7.04 (m, 7H), 7.00-6.97 (m, 2H), 6.90-6.86 (m, 2H), 6.68-6.64 (m, 2H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.44-4.40 (m, 1H), 3.95 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.51 (s, 3H), 2.86 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.56 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.6, 171.3, 163.1 ($J_{C\text{-}F}$ = 244.2 Hz), 145.0, 138.0, 137.7 ($J_{C\text{-}F}$ = 3.1 Hz), 129.6, 129.15, 129.13 ($J_{C\text{-}F}$ = 7.8 Hz), 128.6, 127.18, 127.14, 119.9, 117.3, 115.6 ($J_{C\text{-}F}$ = 21.3 Hz), 113.7, 58.5, 57.2, 53.2, 52.9, 52.8, 38.5; ^{19}F NMR (377 MHz, CDCl$_3$) δ -114.91; FT-IR (neat) 3030, 2952, 2922, 2852, 1733, 1644, 1602, 1502, 1451, 1345, 1235, 1161, 1100, 1059, 841, 749, 699 cm-1;HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{26}H_{25}FNO_4$: 434.1762, found: 434.1763.



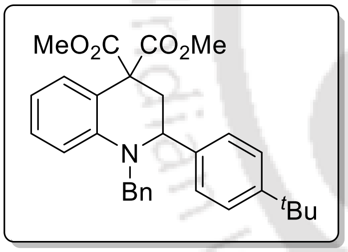
Dimethyl 1-benzyl-2-(*p*-tolyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.47$; sticky liquid; yield 68% (58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-6.98 (m, 11H), 6.66-6.62 (m, 2H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.43-4.39 (m, 1H), 3.98 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.49 (s, 3H), 2.87-2.83 (m, 1H), 2.61-2.55 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.4, 145.2, 139.0, 138.2, 137.3, 129.49, 129.42, 129.0, 128.5, 127.4, 127.1, 126.9, 120.0, 117.0, 113.6, 59.0, 57.3, 53.1, 52.8, 52.6, 38.6, 21.2; FT-IR (neat) 3025, 2952, 2923, 2853, 1733, 1602, 1496, 1451, 1346, 1240, 1126, 1103, 1026, 824, 753, 699, 667 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_4$: 430.2013, found: 430.2014.



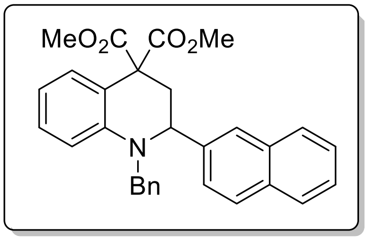
Dimethyl 1-benzyl-2-(4-methoxyphenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.50$; brown sticky liquid; yield 62% (60 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-6.99 (m, 9H), 6.75-6.73 (m, 2H), 6.67-6.63 (m, 2H), 4.56 (d, *J* = 16.8 Hz, 1H), 4.41-4.37 (m, 1H), 3.98 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.52 (s, 3H), 2.85 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.58 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.5, 159.1, 145.3, 138.3, 133.9, 129.5, 129.1, 128.6, 128.5, 127.1, 126.9, 119.9, 117.0, 114.1, 113.6, 58.6, 57.3, 55.5, 53.2, 52.9, 52.6, 38.6; FT-IR (neat) 3027, 2952, 2849, 1733, 1603, 1509, 1451, 1302, 1245, 1173, 1030, 836, 751,699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_5$: 446.1962, found: 481. 446.1985.



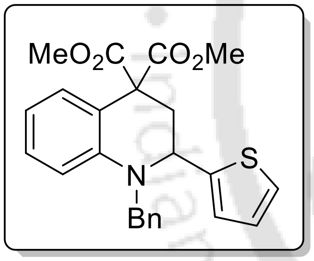
Dimethyl 2-([1,1'-biphenyl]-4-yl)-1-benzyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.41$; sticky liquid; yield 73% (71 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.51 (m, 4H), 7.45-7.41 (m, 2H), 7.36-7.32 (m, 1H), 7.28-7.10 (m, 9H), 6.78-6.72 (m, 2H), 4.71 (d, *J* = 16.8 Hz, 1H), 4.61-4.57 (m, 1H), 4.13 (d, *J* = 16.8 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 3H), 3.01 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.74 (dd, *J* = 13.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.4, 145.1, 141.1, 140.9, 140.6, 138.1, 129.5, 129.1, 129.0, 128.6, 127.9, 127.5, 127.4, 127.2, 127.2, 127.0, 119.9, 117.1, 113.6, 59.0, 57.2, 53.2, 52.8, 38.4; FT-IR (neat) 3027, 2951, 2852, 1733, 1601, 1495, 1450, 1347, 1103, 1026, 843, 698, 667 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{30}NO_4$: 492.2169, found: 492.2170.



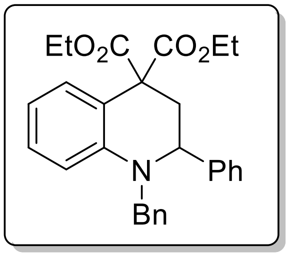
Dimethyl 1-benzyl-2-(4-(*tert*-butyl) phenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 3i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.56$; sticky liquid; yield 67% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.01 (m, 11H), 6.65-6.62 (m, 2H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.48-4.44 (m, 1H), 4.02 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.89 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.64 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.3, 150.4, 145.0, 138.7, 138.3, 129.4, 129.1, 128.5, 127.1, 127.0, 126.9, 125.5, 119.5, 116.9, 113.3, 58.9, 57.1, 53.1, 52.7, 38.1, 34.6, 31.5; FT-IR (neat) 3028, 2954, 2868, 1733, 1602, 1496, 1451, 1435, 1345, 1240, 1026, 839, 750, 697 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{34}NO_4$: 472.2482, found: 472.2491.



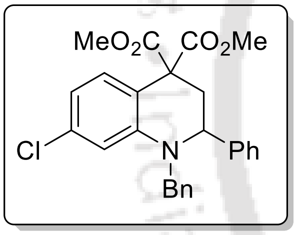
Dimethyl 1-benzyl-2-(naphthalen-2-yl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.37; semi solid; yield 71% (66 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.74-7.66 (m, 3H), 7.54 (s, 1H), 7.40-7.37 (m, 2H), 7.28-7.26 (m, 1H), 7.18-7.05 (m, 5H), 7.01-6.98 (m, 2H), 6.73-6.66 (m, 2H), 4.65-4.59 (m, 2H), 4.03 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.38 (s, 3H), 2.93 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.70 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$ δ 171.7, 171.4, 145.2, 139.5, 138.1, 133.4, 133.1, 129.6, 129.0, 128.7, 128.6, 128.0, 127.8, 127.2, 127.0, 126.6, 126.4, 126.1, 125.1, 120.1, 117.2, 113.7, 59.3, 57.4, 53.2, 52.8, 52.7, 38.4; FT-IR (neat) 3026, 2951, 2923, 2852, 1733, 1601, 1496, 1450, 1436, 1351, 1239, 1129, 1100, 1058, 1026, 751, 698 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for C$_{30}$H$_{28}$NO$_4$: 466.2013, found: 466.2015.



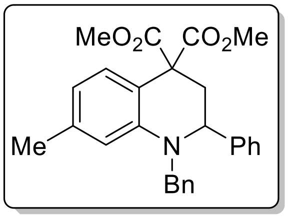
Dimethyl 1-benzyl-2-(thiophen-2-yl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.36; brown sticky liquid; yield 61% (51 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20-7.03 (m, 8H), 6.82-6.80 (m, 1H), 6.77-6.76 (m, 1H), 6.70-6.64 (m, 2H), 4.73 (dd, *J* = 8.8, 4.8 Hz, 1H), 4.60 (d, *J* = 16.4 Hz, 1H), 4.08 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 2.97 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.69 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.5, 171.4, 146.1, 144.7, 138.2, 129.5, 129.1, 128.6, 127.2, 127.1, 126.5, 126.0, 125.1, 120.3, 117.7, 114.4, 57.3, 55.0, 53.2, 53.0, 52.9, 39.4; FT-IR (neat) 3028, 2952, 2922, 2851, 1733, 1602, 1494, 1435, 1355, 1242, 1199, 1023, 851, 750, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for C$_{24}$H$_{24}$NO$_4$S: 422.1421, found: 422.1423.



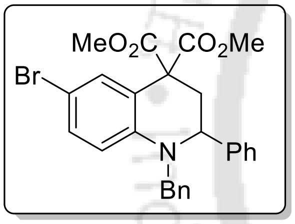
Diethyl 1-benzyl-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.41$; sticky liquid; yield 81% (71 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22-7.10 (m, 9H), 7.07-7.04 (m, 1H), 7.02-7.00 (m, 2H), 6.67-6.64 (m, 2H), 4.57 (d, *J* = 16.8 Hz, 1H), 4.49-4.46 (m, 1H), 4.25-4.20 (m, 1H), 4.13-4.07 (m, 1H), 4.02-3.96 (m, 2H), 3.88-3.82 (m, 1H), 2.87-2.84 (m,1H), 2.61-2.56 (m, 1H), 1.19-1.17 (m, 3H), 1.12-1.09 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 171.0, 145.2, 142.2, 138.2, 129.3, 129.2, 128.7, 128.5, 127.7, 127.5, 127.1, 126.9, 119.9, 117.0, 113.5, 62.0, 61.9, 59.4, 57.1, 52.8, 38.3, 14.2, 14.1; FT-IR (neat) 3029, 2981, 1730, 1602, 1495, 1451, 1299, 1237, 1094, 1059, 1029, 862, 747, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{30}NO_4$: 444.2169, found: 444.2177.



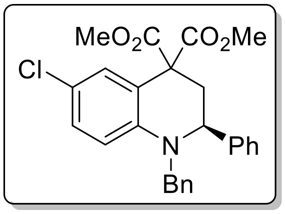
Dimethyl 1-benzyl-7-chloro-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate. 4m Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.47$; sticky liquid; yield 64% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.23-7.13 (m, 6H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.00-6.95 (m, 3H), 6.65-6.60 (m, 2H), 4.55 (d, *J* = 16.8 Hz, 1H), 4.48-4.45 (m, 1H), 3.98 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.88-2.85 (m, 1H), 2.63-2.59 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.9, 146.1, 141.2, 137.2, 135.3, 130.2, 128.8, 128.7, 127.8, 127.38, 127.32, 127.0, 118.0, 116.9, 113.0, 58.9, 56.5, 53.3, 52.9, 52.6, 37.7; FT-IR (neat) 3028, 2951, 1734, 1597, 1562, 1494, 1451, 1432, 1357, 1240, 1105, 1055, 1027, 849, 754, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}ClNO_4$: 450.1467, found: 450.1469.



Dimethyl 1-benzyl-7-methyl-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.51$; sticky liquid; yield 62% (53 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.08 (m, 8H), 7.02-6.99 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.52-6.47 (m, 2H), 4.62 (d, *J* = 16.4 Hz, 1H), 4.42 (dd, *J* = 8.4, 4.8 Hz, 1H), 3.97 (d, *J* = 16.8 Hz, 1H), 3.67 (s, 3H), 3.43 (s, 3H), 2.86 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.61 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.5, 145.1, 142.0, 139.4, 138.3, 129.0, 128.69, 128.60, 127.6, 127.5, 127.2, 127.0, 118.1, 116.9, 114.0, 59.0, 56.9, 53.2, 52.8, 52.7, 38.3, 21.9; FT-IR (neat) 3026, 2949, 2924, 2852, 1734, 1609, 1505, 1449, 1238, 1135, 1026, 940, 754, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_4$: 430.2013, found: 430.2014.

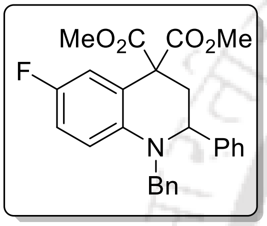


Dimethyl 1-benzyl-6-bromo-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.47$; semi solid; yield 71% (70 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.07 (m, 10H), 7.99-6.97 (m, 2H), 6.53-6.50 (m, 1H), 4.52-4.45 (m, 2H), 3.99 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.47 (s, 3H), 2.90-2.85 (m, 1H), 2.62-2.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.8, 144.1, 141.5, 137.5, 132.2, 131.7, 128.8, 128.7, 127.8, 127.4, 127.2, 127.0, 121.6, 115.1, 108.9, 59.3, 56.9, 53.4, 53.1, 52.8, 38.1; FT-IR (neat) 3029, 2952, 2922, 2852, 1734, 1594, 1493, 1452, 1347, 1239, 1132, 1025, 802, 754, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}BrNO_4$: 494.0961, found: 494.0962.

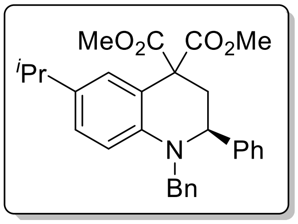


(*S*)-Dimethyl 1-benzyl-6-chloro-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4p′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.44$;

crystalline solid; mp 165-166 °C; yield 72% (65 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23-7.07 (m, 8H), 7.03-6.97 (m, 4H), 6.57 (d, *J* = 8.8 Hz, 1H), 4.52-4.45 (m, 2H), 3.99 (d, *J* = 16.8 Hz, 1H), 3.69 (s, 3H), 3.46 (s, 3H), 2.88 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.60 (dd, *J* = 13.6, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.1, 170.8, 143.7, 141.5, 137.6, 129.4, 128.9, 128.8, 128.7, 127.8, 127.4, 127.2, 127.0, 121.8, 121.2, 114.6, 59.2, 56.9, 53.3, 53.0, 52.9, 38.2; FT-IR (KBr) 3028, 2951, 1734, 1599, 1494, 1452, 1346, 1239, 1134, 1061, 1025, 803, 753, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}ClNO_4$: 450.1467, found: 450.1465; $[\alpha]_D^{25}$ = +32.00 (c= 0.1, CHCl$_3$); HPLC: >99% *ee* [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 16.10 min (major), 8.68 min (minor)].

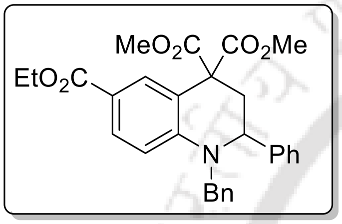


Dimethyl 1-benzyl-6-fluoro-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; sticky liquid; yield 68% (58 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23-7.07 (m, 8H), 7.00-6.98 (m, 2H), 6.84-6.76 (m, 2H), 6.56 (dd, *J* = 9.2, 4.8 Hz, 1H), 4.49-4.41 (m, 2H), 3.97 (d, *J* = 16.8 Hz, 1H), 3.69 (s, 3H), 3.49 (s, 3H), 2.89 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.58 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.1, 170.8, 155.8 ($J_{C\text{-}F}$ = 234.3 Hz), 141.8, 141.6, 137.9, 128.7,128.6 127.7, 127.4, 127.1, 121.0 ($J_{C\text{-}F}$ = 7.2 Hz), 116.2, 116.0, 115.8 ($J_{C\text{-}F}$ = 23.55 Hz), 114.4 ($J_{C\text{-}F}$ = 7.9 Hz), 59.3, 57.1, 53.3, 53.2, 53.0, 38.5; ^{19}F NMR (377 MHz, CDCl$_3$) δ −127.87; FT-IR (neat) 3028, 2953, 1733, 1602, 1499, 1453, 1434, 1243, 1166, 1024, 803, 755, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{25}FNO_4$: 434.1762, found: 434.1764.

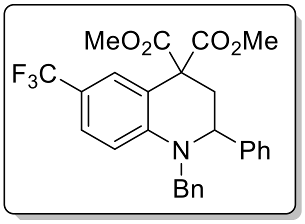


(*S*)-Dimethyl 1-benzyl-6-isopropyl-2-phenyl-2,3-dihydroquino-line-4,4(1*H*)-dicarboxylate 4r′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; brown oil; yield 66% (60 mg); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20-7.09 (m, 8H), 7.02-7.00 (m, 2H), 6.95-6.92 (m, 1H), 6.90-6.89 (m, 1H), 6.60 (d, *J* = 8.4 Hz,1H), 4.54 (d, *J* = 16.4 Hz, 1H), 4.41

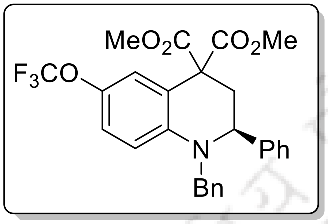
(dd, *J* = 9.2, 4.8 Hz, 1H), 3.96 (d, *J* = 16.4 Hz, 1H), 3.68 (s, 3H), 3.46 (s, 3H), 2.86 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.78-2.68 (m, 1H), 2.60 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.14 (d, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.5, 143.3, 142.2, 138.5, 137.2, 128.6, 128.5, 127.6, 127.5, 127.35, 127.30, 127.1, 126.9, 119.4, 113.4, 59.2, 57.3, 53.1, 53.0, 52.7, 38.5, 33.1, 24.2; FT-IR (neat) 3028, 2958, 2871, 1733, 1615, 1505, 1452, 1351, 1239, 1089, 1061, 1026, 949, 814, 752, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{32}NO_4$: 458.2326, found: 458.2331; $[\alpha]_D^{25}$ = +32.00 (c= 0.1, $CHCl_3$); HPLC: >99% *ee* [CHIRALCEL AD-H, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 11.31 min (major), 10.03 min (minor)].



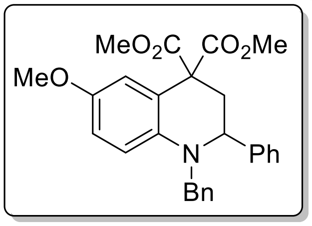
6-Ethyl 4,4-dimethyl 1-benzyl-2-phenyl-2,3-dihydroquino-line-4,4,6(1*H*)-tricarboxylate 4s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.35; sticky liquid; yield 62% (58 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.74 (m, 2H), 7.25-7.14 (m, 6H), 7.10-7.07 (m, 2H), 7.00-6.97 (m, 2H), 6.66 (d, *J* = 8.8 Hz, 1H), 4.67 (d, *J* = 16.8 Hz, 1H), 4.56 (dd, *J* = 8.0, 5.2 Hz, 1H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.07 (d, *J* = 17.2 Hz, 1H), 3.70 (s, 3H), 3.43 (s, 3H), 2.92-2.88 (m, 1H), 2.67 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.8, 166.7, 148.5, 141.0, 137.1, 131.3, 131.2, 128.9, 128.8, 127.9, 127.39, 127.37, 126.9, 118.8, 118.7, 112.4, 60.4, 59.4, 56.7, 53.3, 53.0, 52.6, 37.6, 14.6; FT-IR (neat) 3027, 2981, 2953, 2852, 1734, 1705, 1608, 1512, 1451, 1308, 1241, 1171, 1061, 1026, 929, 756, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{30}NO_6$: 488.2068, found: 488.2069.



Dimethyl 1-benzyl-2-phenyl-6-(trifluoromethyl)-2,3-dihydroquinoline-4,4(*1H*)-dicarboxylate 4t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.37; colorless solid; mp 116-117 °C; yield 77% (74 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.24-7.14 (m, 6H), 7.08 (d, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 1H), 4.62-4.56 (m, 2H), 4.07 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.40 (s, 3H), 2.92 (dd, *J* = 13.8, 5.4 Hz, 1H), 2.68 (dd, *J* = 13.8, 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 170.6, 147.4, 140.9, 137.1, 128.89, 128.87, 128.0, 127.4, 127.3, 126.8, 126.7 (q, *J* = 3.5 Hz), 126.6 (q, *J* = 3.8 Hz), 125.8 (q, *J* = 268.9 Hz), 118.8, 118.6 (q, *J* = 32.2 Hz), 112.7, 59.3, 56.5, 53.4, 53.0, 52.8, 37.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -61.02; FT-IR (KBr) 3030, 2953, 1735, 1619, 1519, 1494, 1453, 1435, 1334, 1273, 1156, 1123 1087, 754, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}F_3NO_4$: 484.1730, found: 484.1734.

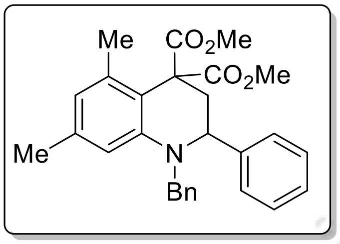


(*S*)-Dimethyl 1-benzyl-2-phenyl-6-(trifluoromethoxy)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4u′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.36; semi solid; yield 69% (68 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.08 (m, 8H), 7.02-6.97 (m, 3H), 6.94-6.90 (m, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.54-4.48 (m, 2H), 4.03 (d, *J* = 16.8 Hz, 1H), 3.69 (s, 3H), 3.44 (s, 3H), 2.89 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.63 (dd, *J* = 13.6, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.7, 144.0, 141.4, 139.9, 137.6, 128.8, 128.7, 127.9, 127.4, 127.2, 126.9, 122.7, 122.4, 122.1 (q, *J* = 254.1 Hz), 120.1, 113.8, 59.4, 56.9, 53.3, 53.1, 53.0, 37.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ -58.38; FT-IR (neat) 3029, 2956, 2924, 2853, 1737, 1604, 1502, 1454, 1435, 1377, 1261, 1162, 1025, 804, 762, 700 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{25}F_3NO_5$: 500.1679, found: 500.1680; $[\alpha]_D^{25}$ = +46.00 (c= 0.1, $CHCl_3$); HPLC: >97% *ee* [CHIRALCEL AD-H, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 9.51 min (major), 5.92 min (minor)].

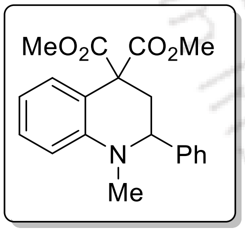


Dimethyl 1-benzyl-6-methoxy-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; sticky liquid; yield 56% (50 mg); ^{1}H NMR (600 MHz, CDCl3) δ 7.22-7.10 (m, 8H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.69-6.66 (m, 2H), 6.60 (d, *J* = 9.0 Hz, 1H), 4.48 (d, *J* = 16.2 Hz, 1H), 4.39-4.37 (m, 1H), 3.92 (d, *J* = 16.2 Hz, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.52 (s, 3H), 2.89-2.86 (m, 1H), 2.57-2.53

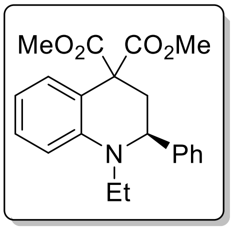
(m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.3, 151.3, 142.3, 139.5, 138.4, 128.7, 128.5, 127.6, 127.5, 127.2, 126.9, 121.5, 115.0, 114.8, 114.7, 59.2, 57.5, 55.8, 53.26, 53.24, 53.0, 39.0; FT-IR (neat) 2953, 2924, 2852, 1734, 1501, 1453, 1242, 1053, 803, 755, 701 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for $C_{27}H_{28}NO_5$: 446.1962, found: 446.1972.



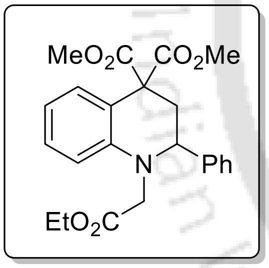
Dimethyl 1-benzyl-5,7-dimethyl-2-phenyl-2,3-dihydroquino-line-4,4(1*H*)-dicarboxylate 4w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.57$; sticky liquid; yield 51% (45 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.10 (m, 9H), 6.95-6.92 (m, 2H), 6.46, (s, 1H), 6.37, (s, 1H), 4.61 (d, *J* = 16.4 Hz, 1H), 4.37 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.92 (d, *J* = 16.4 Hz, 1H), 3.67 (s, 3H), 3.43 (s, 3H), 2.78 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.56 (dd, *J* = 13.2, 9.2 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 172.0, 145.8, 142.4, 138.5, 138.3, 138.1, 128.7, 128.5, 127.6, 127.4, 127.3, 126.9, 122.1, 117.5, 112.9, 56.4, 53.4, 53.1, 52.8, 40.6, 21.7, 20.8; FT-IR (neat) 3027, 2950, 2924, 2856, 1732, 1605, 1572, 1451, 1343, 1234, 1073, 1028, 823, 751, 700 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{28}H_{30}NO_4$: 444.2169, found: 444.2179.



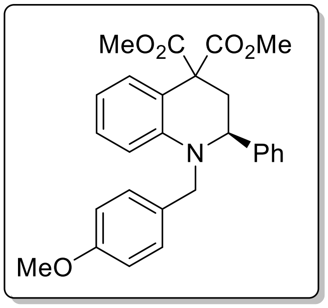
Dimethyl 1-methyl-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; sticky liquid; yield 75% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.24 (m, 2H), 7.20-7.17 (m, 4H), 7.07-7.05 (m, 1H), 6.70-6.65 (m, 2H), 4.29-4.27 (m, 1H), 3.71 (s, 3H), 3.53 (s, 3H), 2.78 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.65 (s, 3H), 2.45-2.41(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 171.72, 146.4, 142.6, 129.6, 129.4, 128.8, 127.6, 127.2, 118.9, 116.7, 112.9, 60.8, 57.2, 53.3, 52.9, 38.9, 37.9; FT-IR (neat) 3026, 2953, 2921, 2852, 1735, 1690, 1604, 1495, 1450, 1351, 1239, 1100, 1061, 751, 701 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{20}H_{22}NO_4$: 340.1543, found: 340.1544.



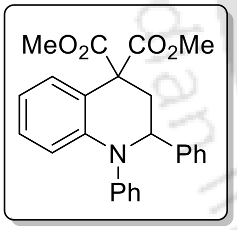
(*S*)-Dimethyl 1-ethyl-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4z′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.61; semi solid; yield 72% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (m, 6H), 7.04-7.02 (m, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 6.65-6.61 (m, 1H), 4.35(dd, *J* = 9.6, 4.4 Hz, 1H), 3.68 (s, 3H), 3.50 (s, 3H), 3.43-3.34 (m, 1H), 2.89-2.80 (m, 1H), 2.76-2.71 (m, 1H), 2.50-2.43 (m, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 145.0, 142.8, 129.47, 129.43, 128.7, 127.6, 127.4, 119.8, 116.6, 113.5, 58.3, 57.3, 53.1, 52.8, 43.2, 38.7, 11.2; FT-IR (neat) 3029, 2952, 1733, 1602, 1573, 1495, 1452, 1344, 1255, 1203, 1096, 1058, 1023 749, 703 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{24}NO_4$: 354.1700, found: 354.1706; $[\alpha]_D^{25}$ = +12.00 (c= 0.1, $CHCl_3$); HPLC: >97% *ee* [CHIRALCEL AD-H, hexane/*i*PrOH = 97:03, flow rate: 1 mL /min, λ = 254 nm, t_R = 10.28 min (major), 8.65 min (minor)].



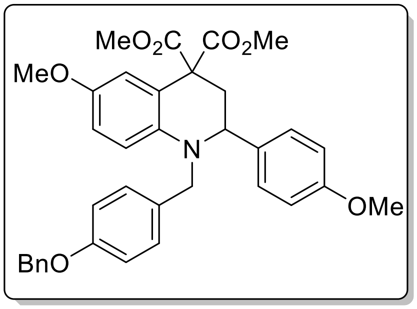
Dimethyl 1-(2-ethoxy-2-oxoethyl)-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; sticky liquid; yield 62% (51 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 7.21-7.17 (m, 2H), 6.79-6.75 (m, 1H), 6.68-6.65 (m, 1H), 4.60 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.09-4.01 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.84 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.55 (dd, *J* = 13.6, 10.8 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.4, 170.7, 145.3, 142.0, 130.3, 129.5, 129.0, 128.1, 127.6, 119.2, 117.8, 112.9, 60.9, 60.0, 57.4, 53.2, 53.0, 51.0, 38.5, 14.2; FT-IR (neat) 2953, 1733, 1603, 1495, 1454, 1435, 1334, 1236, 1193, 1126, 1093, 1026, 749, 703 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{26}NO_6$: 412.1755, found: 412.1756.



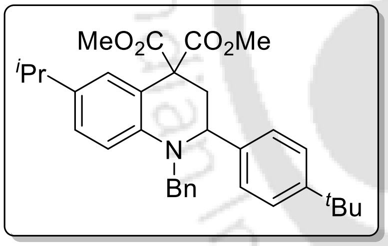
(*S*)-Dimethyl 1-(4-methoxybenzyl)-2-phenyl-2,3-dihydroqui-noline-4,4(1*H*)-dicarboxylate 4ab′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; sticky liquid; yield 71% (63 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.01 (m, 7H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.70-6.62 (m, 4H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.42-4.39 (m, 1H), 3.89 (d, *J* = 16.4 Hz, 1H), 3.67 (s, 3H), 3.66 (s, 3H), 3.46 (s, 3H), 2.88-2.83 (m, 1H), 2.60-2.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 171.3, 158.7, 145.2, 142.1, 129.9, 129.5, 128.9, 128.7, 128.4, 127.6, 127.4, 120.1, 117.0, 113.9, 113.6, 58.8, 57.2, 55.4, 53.1, 52.8, 52.0, 38.5; FT-IR (neat) 3028, 2951, 2838, 1733, 1603, 1509, 1453, 1245, 1175, 1102, 1060, 815, 751, 702 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{28}NO_5$: 446.1962 found: 446.1969; $[\alpha]_D^{25}$ = - 42.00 (c= 0.1, $CHCl_3$); HPLC: >94% *ee* [CHIRALCEL AD-H, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 254 nm, t_R = 34.75 min (major), 16.65 min (minor)].



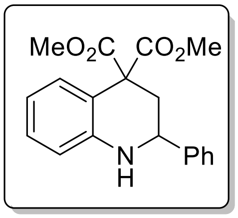
Dimethyl 1,2-diphenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4ac. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; semi solid; yield 68% (54 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.05 (m, 9H), 6.90-6.78 (m, 5H), 4.72-4.68 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.62 (s, 3H), 3.58 (s, 3H), 3.09 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.61 (dd, *J* = 13.6, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.0, 147.6, 144.2, 143.1, 129.2, 129.0, 128.7, 128.4, 127.3, 127.0, 124.5, 123.6, 123.5, 120.13, 120.11, 60.5, 57.4, 53.3, 53.0, 40.6; FT-IR (neat) 3029, 2952, 1733, 1594, 1492, 1449, 1383, 1314, 1249, 1129, 1095, 1056, 1026, 751, 699 cm^{-1}; HRMS (ESI) *m/z* [M+H]+ calcd for $C_{25}H_{24}NO_4$: 402.1700, found: 402.1703.



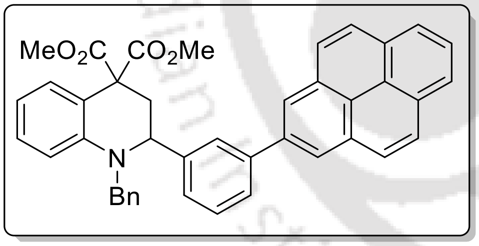
Dimethyl 1-(4-(benzyloxy)benzyl)-6-methoxy-2-(4-methoxyphenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.47; thick liquid; yield 75% (87 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.86-6.68 (m, 7H), 5.02 (s, 2H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.36-4.33 (m, 1H), 3.90 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H), 2.90 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.57 (dd, *J* = 13.6, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.4, 159.0, 157.8, 151.3, 139.8, 137.2, 134.4, 130.7, 128.7, 128.6, 128.5, 128.1, 127.6, 121.8, 115.0, 114.9, 114.84, 114.80, 114.0, 70.1, 58.3, 57.7, 55.8, 55.4, 53.1, 53.0, 52.3, 39.3; FT-IR (neat) 2951, 2836, 1733, 1610, 1584, 1509, 1454, 1245, 1172, 1032, 832, 744, 698 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{35}H_{36}NO_7$: 582.2486, found: 582.2485.



Dimethyl 1-benzyl-2-(4-(tert-butyl)phenyl)-6-isopropyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 4ae. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.68; sticky liquid; yield 78% (80 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.08 (m, 5H), 7.05-7.01 (m, 4H), 6.94-6.88 (m, 2H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.54 (d, *J* = 16.8 Hz, 1H), 4.43-4.40 (m, 1H), 4.01 (d, *J* = 16.8 Hz, 1H), 3.68 (s, 3H), 3.42 (s, 3H), 2.86 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.76-2.69 (m, 1H), 2.62 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.21 (s, 9H), 1.14 (d, *J* = 6.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 171.6, 150.4, 143.3, 138.9, 138.7, 137.0, 128.5, 127.4, 127.28, 127.23, 127.1, 126.8, 125.5, 119.1, 113.3, 59.0, 57.3, 53.1, 53.0, 52.7, 38.3, 34.6, 33.1, 31.5, 24.3, 24.2; FT-IR (neat) 3026, 2958, 2869, 1735, 1615, 1508, 1453, 1434, 1360, 1239, 1142, 1081, 1025, 810, 756, 699 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{33}H_{40}NO_4$: 514.2952, found: 514.2961.

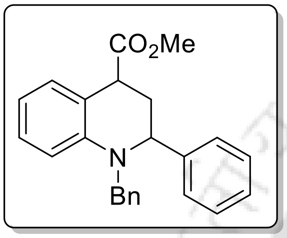


Dimethyl 2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 6.[27] Anisole (2 mL) was added to a stirring solution of **4ab** (0.1 mmol, 50 mg) in TFA (1.5 mL, 1 mmol) and the resultant mixture was heated to reflux for 4 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography to give **6**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.37; yellow solid; mp 124-125 °C; yield 89% (29 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.40-7.29 (m, 4H), 7.15-7.10 (m, 1H), 6.76-6.72 (m, 1H), 6.60-6.58 (m, 1H), 4.47-4.43 (m, 1H), 4.17 (brs, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.81 (dd, *J* = 13.2, 2.8 Hz, 1H), 2.32 (dd, *J* = 13.2, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.7, 144.8, 142.9, 131.1, 129.3, 128.9, 128.2, 126.9, 117.7, 115.7, 115.3, 57.5, 53.7, 53.3, 53.1, 38.6; FT-IR (neat) 3028, 2952, 2848, 1731, 1607, 1490, 1434, 1321, 1253, 1126, 1059, 751, 701 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{20}NO_4$: 326.1387, found: 326.1397.



Dimethyl 1-benzyl-2-(3-(pyren-2-yl)phenyl)-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate 7. Tetrahydroquinoline **4c** (0.1 mmol, 50 mg), $Pd(PPh_3)_4$ (2 mol %, 2.3 mg), pyrene-1-boronic acid (0.2 mmol, 50 mg), Na_2CO_3 (0.2 mmol, 22 mg) and H_2O (50 μL) were refluxed in toluene:EtOH (1:1, 2 mL) for 4 h under N_2 atmosphere. After completion, the reaction mixture was cooled to room temperature and passed through a short pad of celite using CH_2Cl_2 (10 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as an eluent to give **7**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.32; semi solid; yield 91% (56 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13-8.09 (m, 3H), 8.07 (d, *J* = 9.0 Hz, 1H), 8.02 (s, 2H), 7.96-7.93 (m, 2H), 7.76 (s, 1H), 7.45-7.39 (m, 3H), 7.25-7.23 (m, 1H), 7.21-7.18 (m, 2H), 7.16-7.13 (m, 1H), 7.11-7.05 (m, 4H), 6.69-

6.65 (m, 2H), 4.70 (d, *J* = 16.8 Hz, 1H), 4.61-4.58 (m, 1H), 4.18 (d, *J* = 16.8 Hz, 1H), 3.70 (s, 3H), 3.52 (s, 3H), 3.01 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.76 (dd, *J* = 13.2, 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 171.5, 145.2, 142.2, 141.6, 138.2, 137.4, 131.6, 131.1, 130.8, 130.0, 129.7, 129.6, 129.2, 128.7, 128.5, 127.8, 127.7, 127.66, 127.61, 127.19, 127.11, 126.4, 126.2, 125.3, 125.2, 125.1, 125.07, 125.04, 124.8, 119.6, 117.2, 113.6, 59.4, 57.2, 53.3, 53.2, 53.0, 38.4; FT-IR (neat) 2924, 2853, 1732, 1602, 1456, 1451, 1239, 1083, 1029, 848, 750 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{42}H_{34}NO_4$: 616.2482, found: 616.2489.



Methyl 1-benzyl-2-phenyl-1,2,3,4-tetrahydroquinoline-4-carboxylate 8.[28] Tetrahydroquinoline **4a** (41.6 mg, 0.1 mmol), LiCl (12.7 mg, 0.3 mmol) and H_2O (1 drop) were stirred in DMSO (2 mL) at 130 °C for 12 h. The mixture was cooled to room temperature, washed with brine (5 mL) and extracted with ethyl acetate (10 mL). Evaporation of the solvent gave a residue that was purified by silica gel column chromatography using hexane and ethyl acetate as an eluent to furnish **8** in 77% yield as a 6:5 mixture of diastereomers.

Data for major diastereomer**.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; liquid; yield 42% (15 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.09 (m, 10H), 7.06-7.01 (m, 1H), 6.96-6.94 (m, 1H), 6.64-6.59 (m, 2H), 4.69 (d, *J* = 17.2 Hz, 1H), 4.58 (t, *J* = 5.2 Hz, 1H), 4.093 (d, *J* = 17.6 Hz, 1H), 3.75 (t, *J* = 5.6 Hz, 1H), 3.20 (s, 3H), 2.73-2.68 (m, 1H), 2.47-2.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 145.1, 141.8, 138.5, 130.4, 128.7, 128.5, 127.4, 127.0, 126.6, 118.9, 116.4, 112.0, 60.6, 53.0, 51.9, 42.0 32.9; FT-IR (neat) 3028, 2952, 1734, 1602, 1494, 1400, 1451, 1196, 1162, 1124, 1014 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}NO_2$: 358.1802, found: 358.1803.

Data for minor diastereomer**.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; sticky liquid; yield 35% (12 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25-7.10 (m, 10H), 7.03-7.00 (m, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.60-6.54 (m, 2H), 4.66 (t, *J* = 5.4 Hz, 1H), 4.63 (d, *J* = 17.4 Hz, 1H), 4.14 (d, *J* = 17.4 Hz, 1H), 3.67 (s, 3H), 3.62-3.59 (m, 1H), 2.57-2.52 (m, 1H), 2.19-2.16 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.7, 144.9, 143.2, 138.3, 128.9, 128.8, 128.7, 128.1, 127.6, 127.0, 126.9, 126.6, 119.2, 116.4, 111.7, 59.8, 52.9, 52.2, 40.6, 33.4; FT-IR (neat) 3018, 2952, 1733, 1601, 1400, 1451, 1250, 1162, 1123, 1013 cm^{-1}; HRMS (ESI) *m/z* [M+H]$^+$ calcd for $C_{24}H_{24}NO_2$: 358.1802, found: 358.1804.

Crystal Data and Structure Refinement for 4p′ at 293(2)

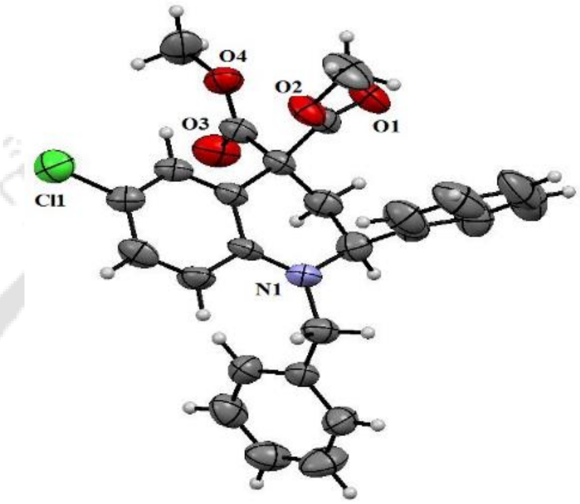


Figure 2. ORTEP diagram of dimethyl (*S*)-1-benzyl-6-chloro-2-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarboxylate **4p′** with 50% ellipsoid (CCDC 1902927).

Identification code	**4p′**
Empirical formula	C_{26} $H_{24}ClNO_4$
Formula weight	449.91
Crystal habit, colour	block /colorless
Crystal size, mm^3	0.4 x 0.3 x 0.2
Temperature, *T*/K	296 K
Wavelength, λ/Å	0.71073
Crystal system	' monoclinic'
Space group	'P 21'
Unit cell dimensions	a =10.5583(10) Å
	b = 9.7573(7) Å
	c = 11.7032(11) Å
	α = 90

	β = 106.984(11)
	γ = 90
Volume, V/Å^3	1153.09(19)
Z	2
Calculated density, Mg·m^{-3}	1.296
Absorption coefficient, μ/mm^{-1}	0.198
F(000)	472
θ range for data collection	2.28 to 28°
Limiting indices	$-14 \leq h \leq 10$, $-12 \leq k \leq 7$, $-8 \leq l \leq 15$
Reflection collected / unique	3728/2194
Completeness to θ	99.90% (θ = 28°)
Absorption correction	Multi-scan
Max. and min. transmission	1.000and 0.768
Refinement method	'SHELXT 2018/2 (Sheldrick, 2018)'
Data / restraints / parameters	3728/1/ 291
Goodness–of–fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0713, wR2 = 0.1584
R indices (all data)	R1 = 0.1065, wR2 = 0.1989

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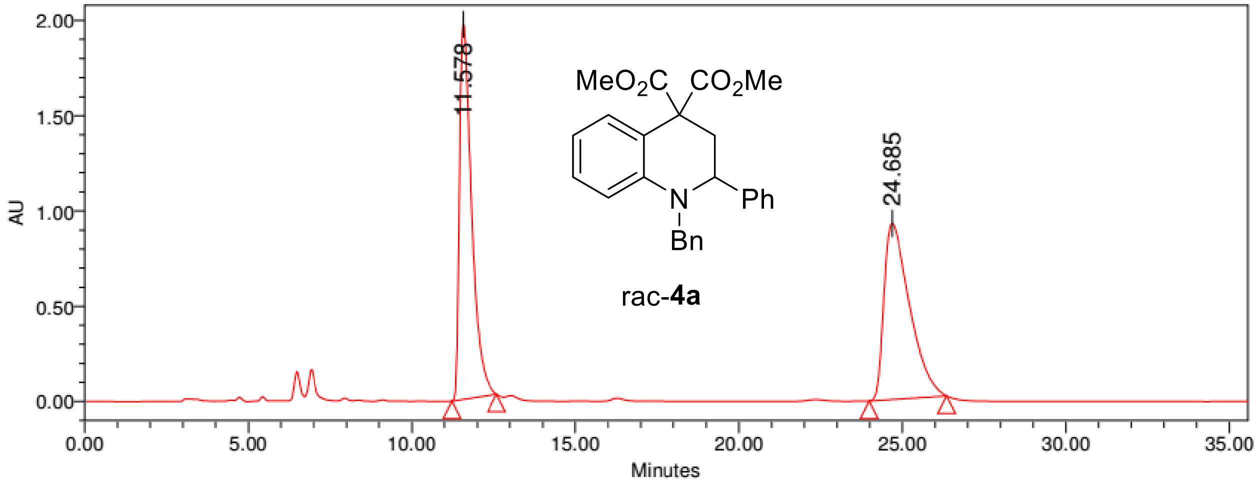
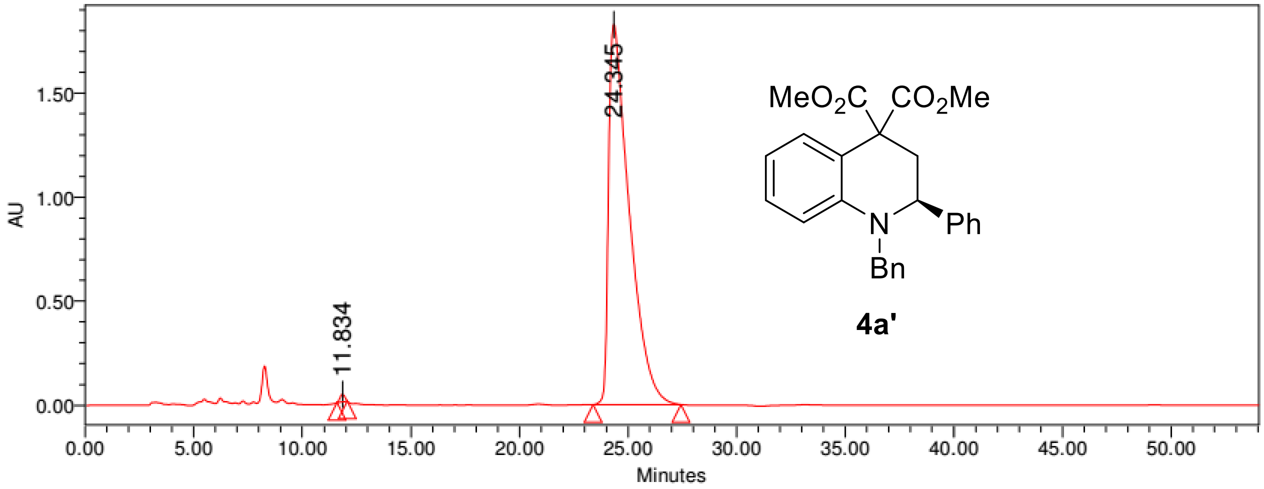
4.5 Selected HPLC Chromatogram



Peak Results

	RT	Height (µV)	% Area
1	11.578	1970222	49.96
2	24.685	924902	50.04



Peak Results

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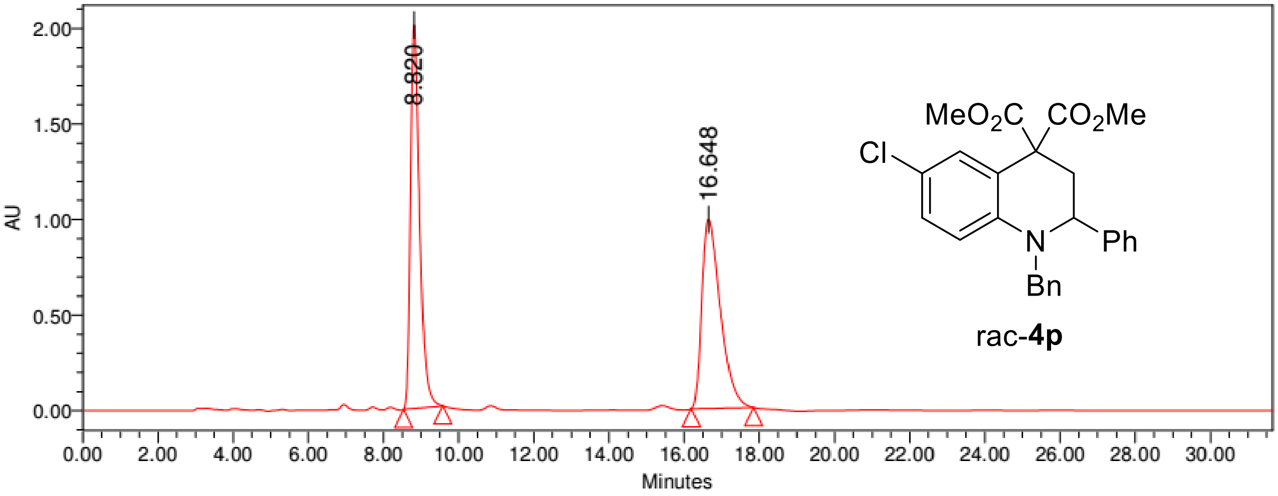
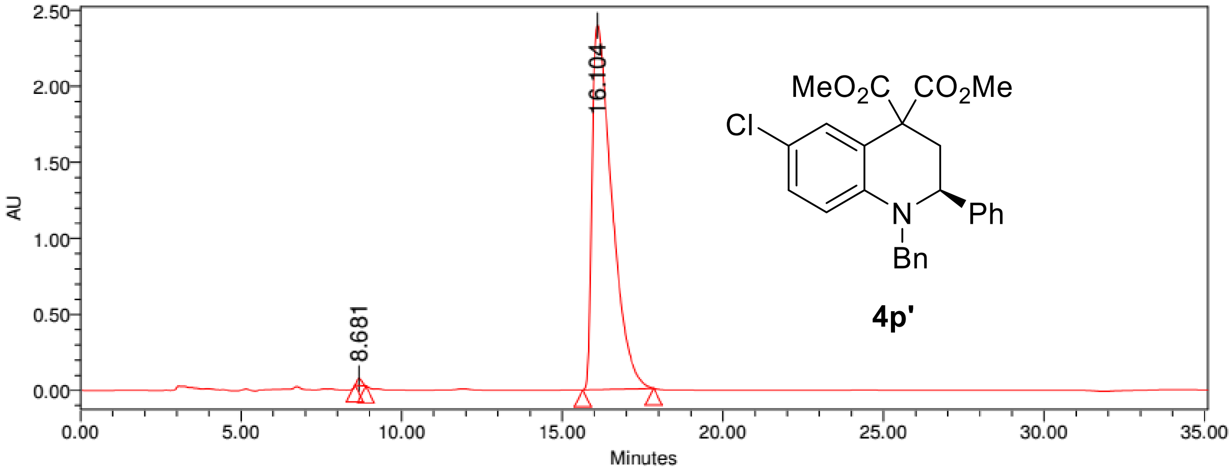


rac-**4p**

Peak Results

	RT	Height (μV)	% Area
1	8.820	2008296	49.82
2	16.648	989772	50.18

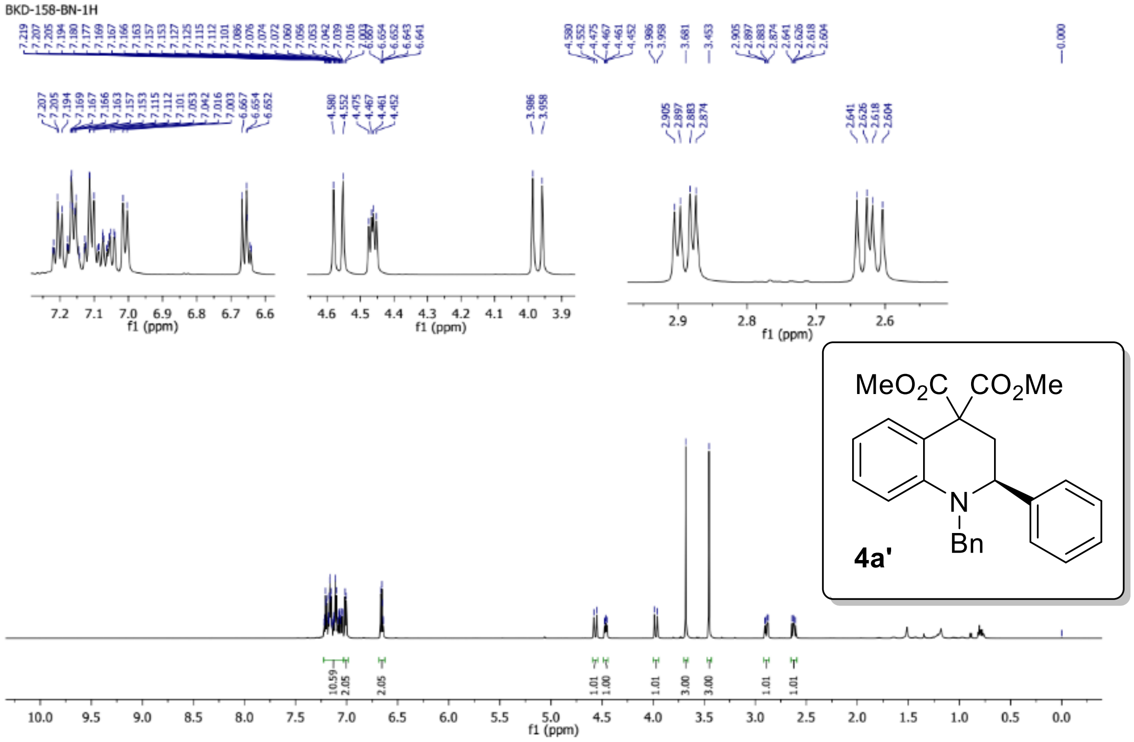


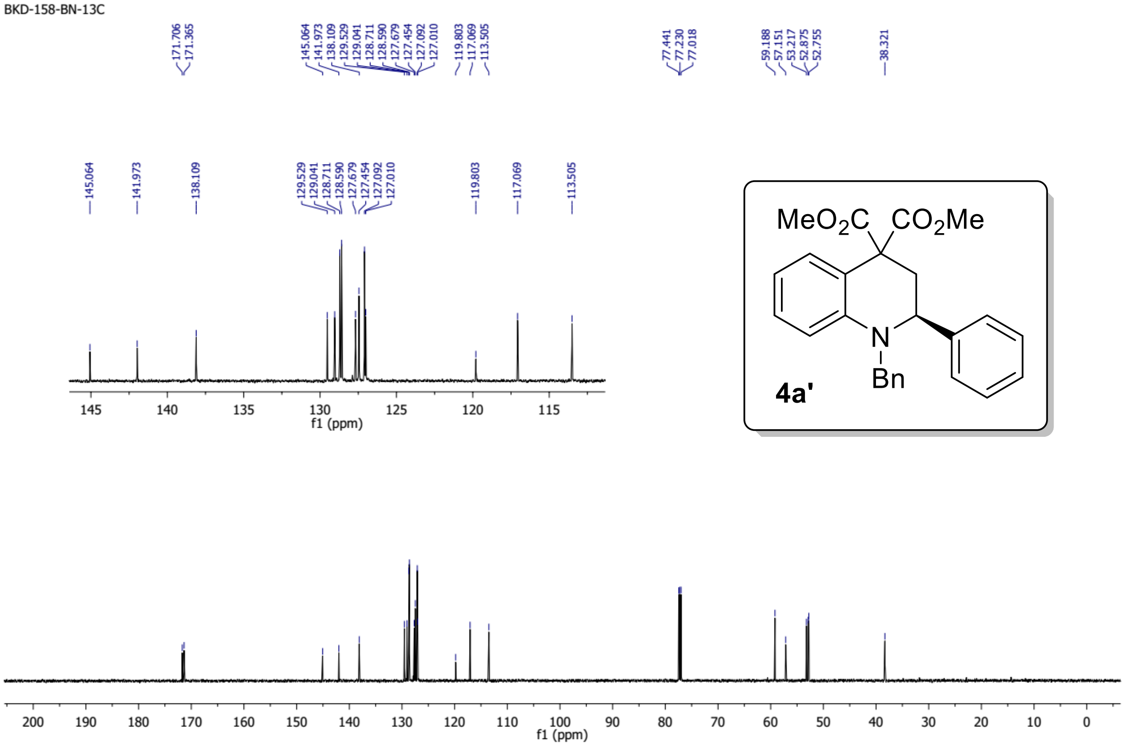
4p'

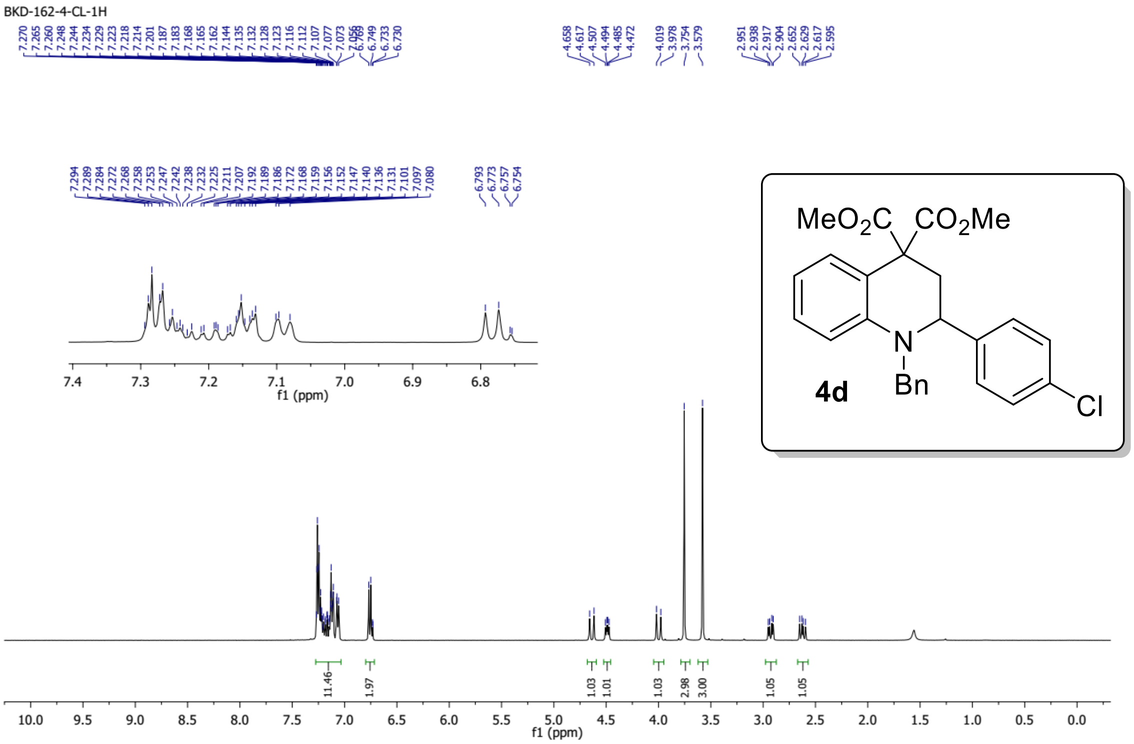
Peak Results

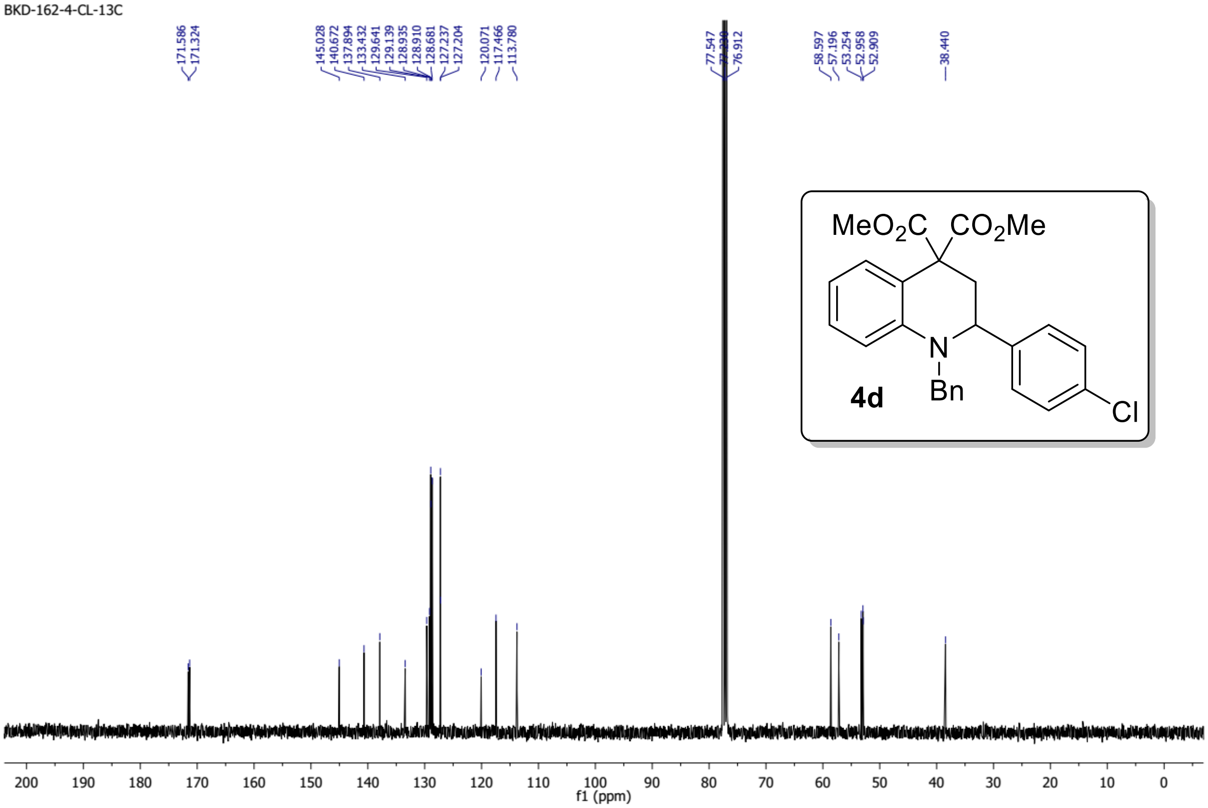
	RT	Height (μV)	% Area
1	8.681	44552	0.47
2	16.104	2396437	99.53

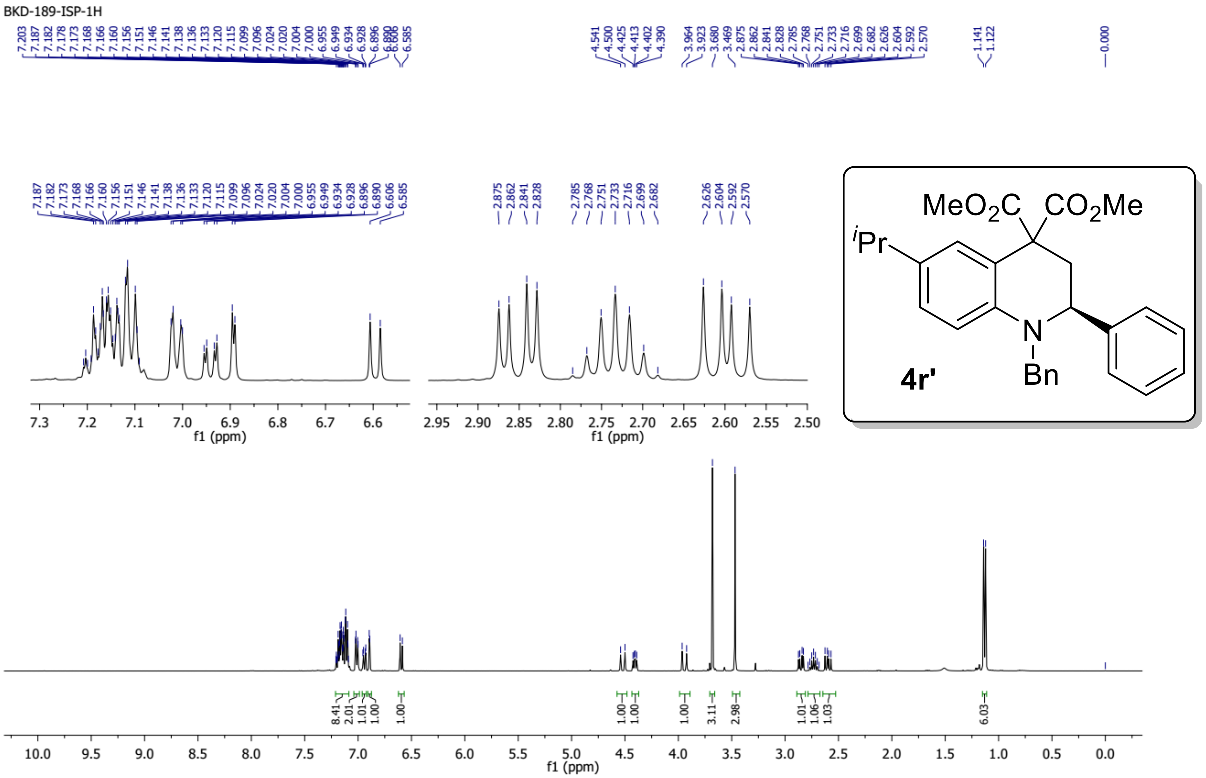
4.6 Selected NMR (^{1}H and ^{13}C) Spectra

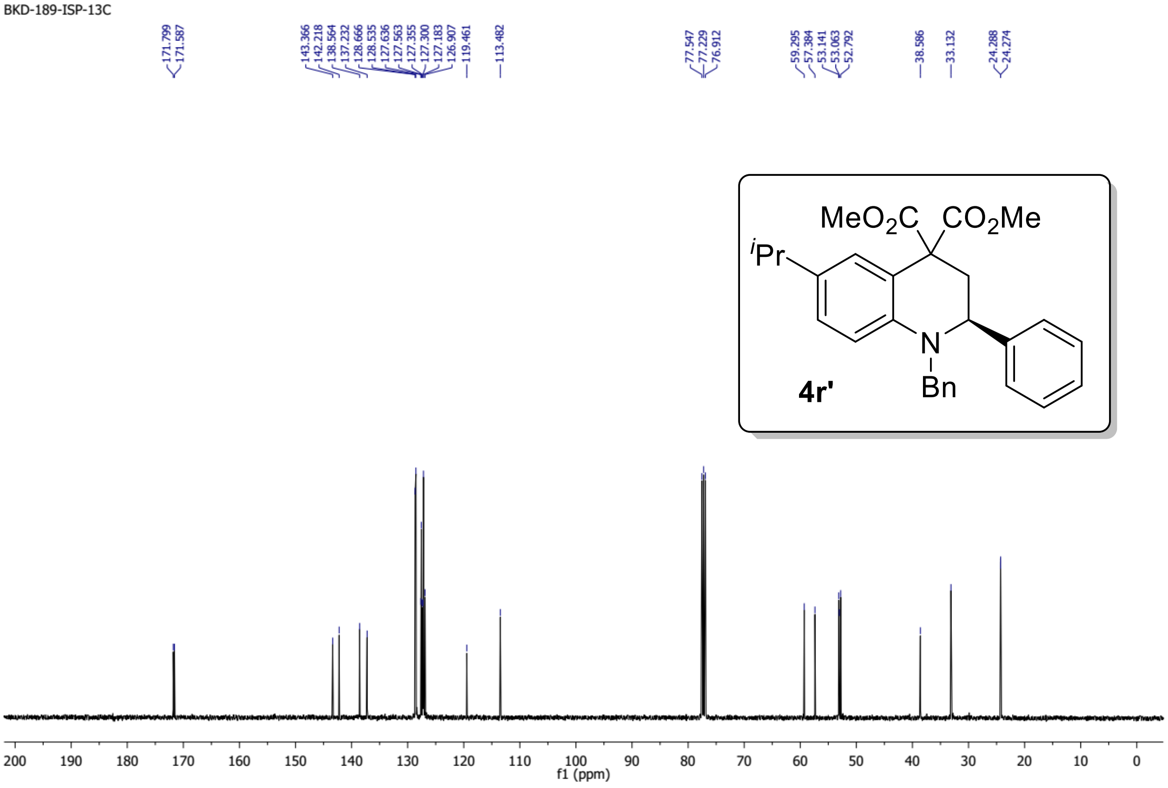




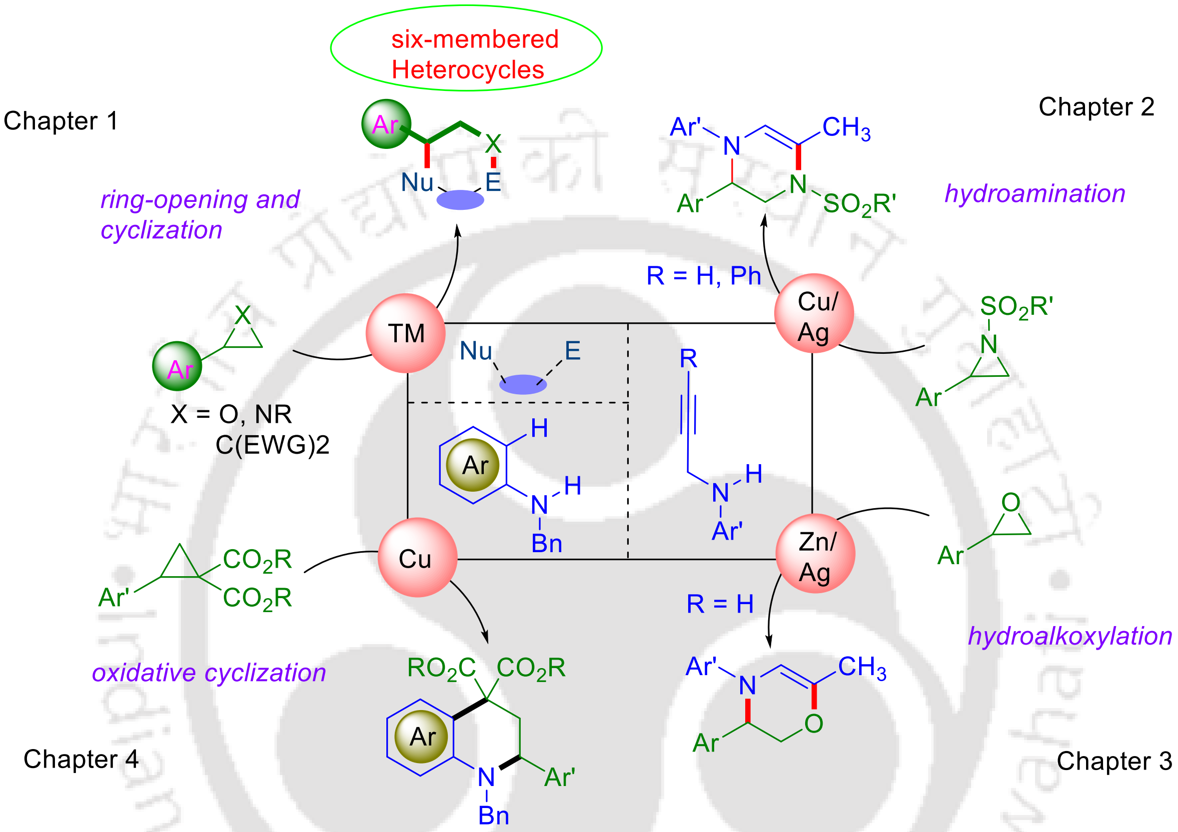

BKD-162-4-CL-1H
7.270
7.265
7.260
7.248
7.244
7.234
7.229
7.223
7.218
7.214
7.201
7.187
7.183
7.168
7.165
7.162
7.144
7.135
7.132
7.128
7.123
7.116
7.112
7.107
7.077
7.073
7.056
6.769
6.749
6.733
6.730
4.658
4.617
4.507
4.494
4.485
4.472
4.019
3.978
3.754
3.579
2.951
2.938
2.917
2.904
2.652
2.629
2.617
2.595
7.294
7.289
7.284
7.272
7.268
7.258
7.253
7.247
7.242
7.238
7.232
7.225
7.211
7.207
7.192
7.189
7.186
7.172
7.168
7.159
7.156
7.152
7.147
7.140
7.136
7.131
7.101
7.097
7.080
6.793
6.773
6.757
6.754
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
MeO$_2$C
CO$_2$Me
N
Bn
Cl
4d
11.46
1.97
1.03
1.01
1.03
2.98
3.00
1.05
1.05
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


BKD-162-4-CL-13C
171.586
171.324
145.028
140.672
137.894
133.432
129.641
129.139
128.935
128.910
128.681
127.237
127.204
120.071
117.466
113.780
77.547
76.912
58.597
57.196
53.254
52.958
52.909
38.440
MeO$_2$C
CO$_2$Me
N
Bn
Cl
4d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


BKD-189-ISP-1H
7.203 7.187 7.182 7.178 7.173 7.168 7.166 7.160 7.156 7.151 7.146 7.141 7.138 7.136 7.133 7.120 7.115 7.099 7.096 7.024 7.020 7.004 7.000 6.955 6.949 6.934 6.928 6.896 6.890 6.606 6.585
4.541 4.500 4.425 4.413 4.402 4.390
3.964 3.923 3.680 3.469 2.875 2.862 2.841 2.828 2.785 2.768 2.751 2.733 2.716 2.699 2.682 2.626 2.604 2.592 2.570
1.141 1.122
0.000
8.41 2.01 1.01 1.00 1.00 1.00 1.00 1.00 3.11 2.98 1.01 1.06 1.03 6.03
f1 (ppm)
MeO2C CO2Me
iPr
N
Bn
4r'


BKD-189-ISP-13C
171.799 171.587
143.366 142.218 138.564 137.232 128.666 128.535 127.636 127.563 127.355 127.300 127.183 126.907 119.461 113.482
77.547 77.229 76.912
59.295 57.384 53.141 53.063 52.792
38.586 33.132 24.288 24.274
f1 (ppm)
MeO2C CO2Me
iPr
N
Bn
4r'

Thesis Overview



Conclusions

Six-membered heterocyclic motifs having O, N and S atoms are privileged structural scaffolds due to their interesting biological and medicinal properties. The development of simple and efficient synthetic methods for their construction are thus important in synthetic chemistry.

Chapter I presented the recent developments on ring expansion of the three-membered strained rings for the synthesis of functionalized six-membered heterocycles. These protocols allow a wide variety of functional groups compatibility under mild reaction conditions. Most of these cyclizations proceed stereo- and regioselectively.

Chapter II covered the stereospecific ring-opening and cycloisomerization of aziridines with propargylamines for the synthesis of functionalized piperazines and tetrahydropyrazines. The reaction proceeds via stereospecific copper-catalyzed S_N2 nucleophilic ring-opening of aziridines with propargylamines and subsequent *6-exo-dig* cyclization. Optically active aziridine can be coupled with high enantiomeric purity.

Chapter III focused on a one-pot relay approach that enables Zn-catalyzed stereospecific ring opening of oxiranes using propargylamines followed by hydroalkoxylation with the aid of AgOAc/base to generate a library of substituted 1,4-oxazines. This reaction provides an effective and regioselective route for the synthesis of oxazines in high yields with excellent optical purity.

Chapter IV described the stereospecific assembly of tetrahydroquinolines via tandem ring-opening/oxidative cyclization of donor-acceptor cyclopropanes with *N*-alkyl anilines. Optically active cyclopropanes reacted with excellent enantiomeric purity. This process uses Cu as a dual catalyst and combines the oxidative cyclization idea with traditional ring-opening to understand the target scaffolds.

List of Publications

1 Stereospecific Ring Opening and Cycloisomerization of Aziridines with Propargylamines: Synthesis of Functionalized Piperazines and Tetrahydropyrazines

Das, B. K.; Pradhan, S.; Punniyamurthy, T. *Org. Lett.* **2018**, *20*, 4444.

2 Stereospecific assembly of tetrahydroquinolines via tandem ring-opening/oxidative cyclization of donor-acceptor cyclopropanes with *N*-alkyl anilines

Das, B. K.; Pradhan, S.; Punniyamurthy, T. *Chem. Commun*. **2019**, *55*, 8083.

3 Recent Advances in Stereoselective Ring Expansion of Spirocyclopropanes: Access to the Spirocyclic Compounds

Sarkar, T.; **Das, B. K.**; Talukdar, K.; Shah, T. A.; Punniyamurthy, T. *ACS Omega*. **2020**, *5*, 26316.

4 Transition-metal-catalyzed stereoselective ring-expansion of vinylaziridines and vinyloxiranes

Sarkar, T.; Talukdar, K.; **Das, B. K**.; Shah, T. A.; Debnath, B.; Punniyamurthy, T. *Org. Biomol. Chem*. **2021**, *19*, 3776.

5 Transition-metal-catalyzed directing group assisted (hetero) aryl C-H functionalization: construction of C-C/C-heteroatom bonds

Sarkar, T.; Shah, T. A.; Maharana, P. K.; Talukdar, K.; **Das, B. K.**; Punniyamurthy, T. *Chem. Rec.* **2021**, DOI: 10.1002/tcr.202100143.

6 Copper-Catalysed sp^3 C-H Bond Functionalization

Karjee, P.; Sarkar, T.; Talukdar, K.; Shah, T. A.; **Das, B. K.**; Punniyamurthy, T. **2021**, *Wiley-VCH*. (manuscript under revision).

7 Zn/Ag Relay Catalyzed Stereospecific Ring Expansion of Oxiranes with *N*-Propargylamines

Das, B. K.; Sarkar, T.; Maharana, P. K.; Punniyamurthy, T. (manuscript submitted).

Conference Attended

Poster Presentations

1. **Bijay Ketan Das**, Sourav Pradhan and Tharmalingam Punniyamurthy, **“**Stereospecific Synthesis of Functionalized Piperazines and Tetrahydropyrazines via Ring Opening and Cycloisomerization of Aziridines with Propargylamines” FICS, Department of Chemistry, IIT Guwahati, July 25th, 2018.
2. **Bijay Ketan Das**, Sourav Pradhan and Tharmalingam Punniyamurthy, “Stereospecific assembly of tetrahydroquinolines via tandem ring-opening/oxidative cyclization of donor-acceptor cyclopropanes with *N*-alkyl anilines” *ICCHD-2020,* Heritage Institute of Technology, Kolkata, January 6th, 2020.