Synthesis of Nitrogen, Oxygen, Sulfur and Selenium Containing Five-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 Family Members

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

November 2018

Vanaparthi Satheesh

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

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CERTIFICATE

This is to certify that Mr. Vanaparthi Satheesh has been working under my supervision since July 2013. I am forwarding his thesis entitled "*Synthesis of Nitrogen, Oxygen, Sulfur and Selenium Containing Five-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 — Prof. Tharmalingam Punniyamurthy

November 2018 — Supervisor

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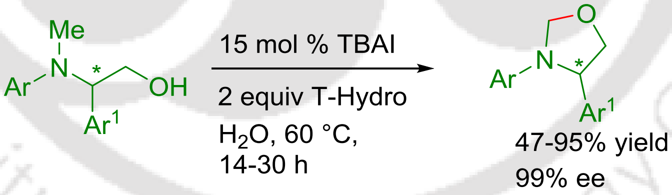
Vanaparthi Satheesh

Abstract

The thesis has six chapters. The first chapter describes the synthesis of oxazolidines *via* an intramolecular C(sp^3)-H alkoxylation of *N*-methyl amino alcohol. In the second chapter, the synthesis of substituted imidazolidines is presented *via* an intramolecular C(sp^3)-H alkylamination of *N*-methyl 1,2-diamines. The third chapter focuses on domino ring opening and oxidative cyclization of styrene oxides with *N*-methylanilines. In the fourth chapter, Al(salen)Cl-catalyzed cycloaddition of optically active aziridines with isoselenocyanates is discussed. The fifth chapter deals with $BF_2OTf{\cdot}Et_2O$-catalyzed cycloaddition of thiirane with isothiocyanates, isoselenocyanates and carbodiimides. The sixth chapter is focused on the Pd-catalyzed *ortho*-alkylation of amides with epoxides.

Chapter I. TBAI-Catalyzed Oxidative Cyclization of 1,2-Amino Alcohols: Synthesis of Oxazolidines

Oxazolidines are an important class of heterocyclic compounds possessing wide variety of medicinal and biological properties. This chapter describes tetrabutylammonium iodide (TBAI)-catalyzed intramolecular C(sp^3)-H functionalization of *N*-methyl 1,2-amino alcohols for the synthesis of oxazolidines (Scheme 1). This protocol is general to access 1,3-oxazolidines in good to high yields.

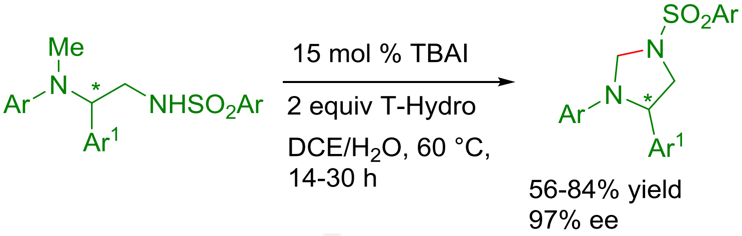


J. Org. Chem. **2016**, *81*, 9792.

Scheme 1. TBAI-Catalyzed Annulation of *N*-Methyl Amino Alcohols

Chapter II. TBAI-Catalyzed Oxidative Cyclization of 1,2-Diamines: Synthesis of Imidazolidines

Development of synthetic routes for the construction of imidazolidine structural motifs have been a topic of immense interest in recent years due to their presence in a number of natural products and biologically active compounds. In addition, they are used as the catalysts and ligands. This chapter presents the TBAI-catalyzed intramolecular C(sp^3)-H functionalization of *N*-methyl 1,2-diamines for the construction of substituted imidazolidines (Scheme 2).

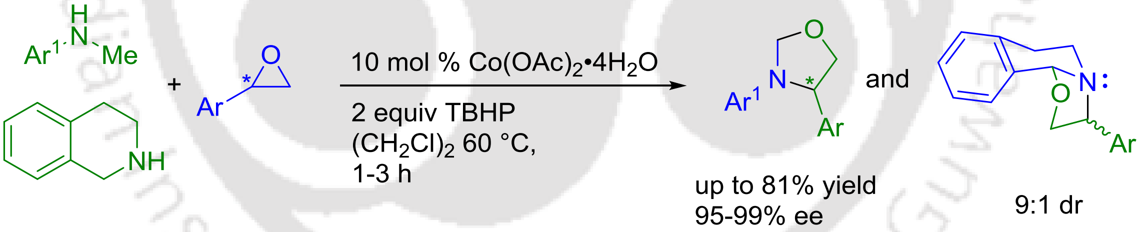


J. Org. Chem. **2016**, *81*, 9792.

Scheme 2. TABI-Catalyzed Annulation of *N*-Methyl 1,2-Diamines

Chapter III. Cobalt-Catalyzed Domino Ring Opening/C-H Functionalization of Styrene Oxides with *N*-Methylanilines

Transition metal-catalyzed domino reactions have attracted considerable attention in synthetic chemistry due to the advantages of atom economy and greater diversity. The chapter covers the Co-catalyzed domino synthesis of substituted 1,3-oxazolidines from *N*-alkylanilines and styrene oxides in presence of ^{t}BuOOH (Scheme 3). This reaction involves the ring opening followed by *C-O* bond formation *via* C(sp^3)-H functionalization.

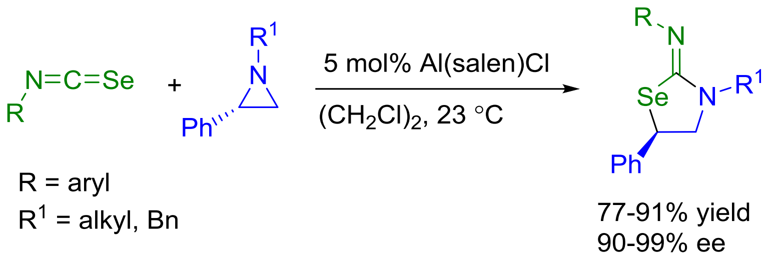


Chem. Commun. **2018**, *54*, 11813.

Scheme 3. Co-Catalyzed Domino Synthesis of Substituted Oxazolidines

Chapter IV. Aluminium-Catalyzed [3+2]-Cycloaddition of Chiral Aziridines with Isoselenocyanates

The construction of C-Se bonds has received considerable attention due to their presence in molecules that are of biological, pharmaceutical and material interest. This chapter covers the stereospecific Al-catalyzed [3+2]-cycloaddition of chiral aziridines with isoselenocyanates with excellent optical purities (Scheme 4).

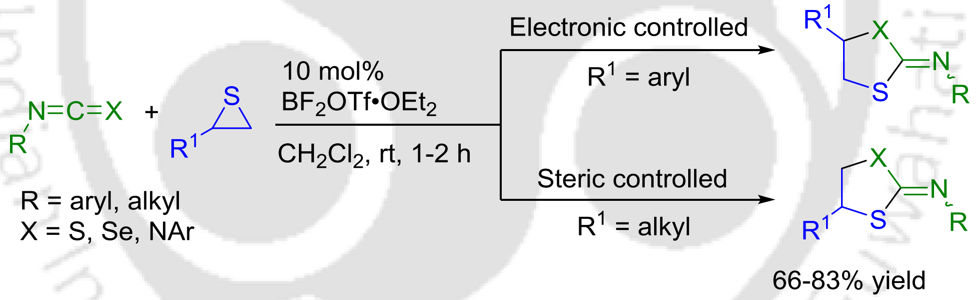


Adv. Synth. Catal. **2018**, DOI: 10.1002/adsc.201801116

Scheme 4. Al-Catalyzed [3+2]-Cycloaddition of Aziridines with Isoselenocyanates

Chapter V. $BF_2OTf•OEt_2$-Catalyzed Ring Expansion of Thiiranes with Heterocumulenes

Cycloaddition of heterocumulenes with three-membered heterocycles provide a promising approach for the synthesis of five-membered heterocycles. This chapter reports a $BF_2OTf•OEt_2$-catalyzed cycloaddition of thiirane with isothiocyanates, isoselenocyanates and carbodiimides (Scheme 5). This protocol is general to access 2-imino-1,3-dithiolanes, 2-imino-1,3-thiaselenolanes and 2-imIno-1,3-thiazolidines in good to high yields.

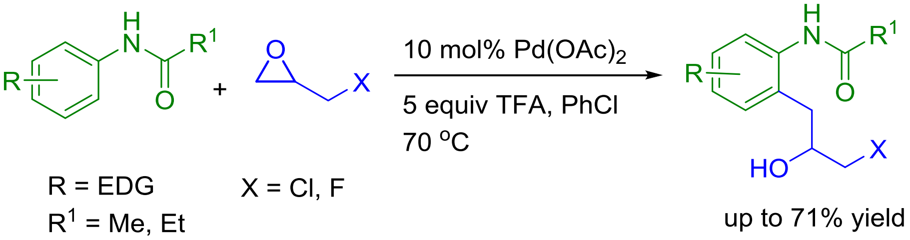


Asian J. Org. Chem. **2018**, *7*, 1583.

Scheme 5. Lewis Acid-Catalyzed [3+2]-Cycloaddition of Thiiranes with Heterocumulenes

Chapter VI. Palladium-Catalyzed *ortho*-Selective Alkylation of Amides with Epihalohydrins

Heteroatom directed site-selective C-H activation has attracted considerable attention in recent years. This chapter describes the *ortho*-selective alkylation of arenes with epihalohydrins employing $Pd(OAc)_2$ with excellent regioselectivity (Scheme 6).



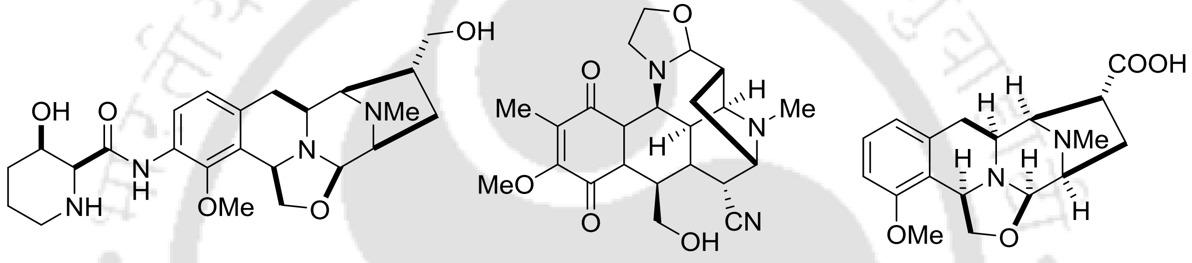
Scheme 6. Pd-Catalyzed *ortho*-C(*sp*^{2})-H Alkylation of Amides

Contents

Chapter I

TBAI-Catalyzed Oxidative Cyclization of 1,2-Amino Alcohols: Synthesis of Oxazolidines

Oxazolidines are widely encountered in natural products which show interesting biological activities. For examples, tetrazomine, quinocarcin and cyanocycline A,[1] which display the biological activities like antimicrobial,[2] anticancer,[3] antitubercular[4] and anti-inflammatory.[5] Besides they have been exploited as catalysts,[6] ligands,[7] auxiliaries[8] and intermediates[9] in synthetic organic chemistry.



Tetrazomine **Cyanocycline A** **Quinocarcin**

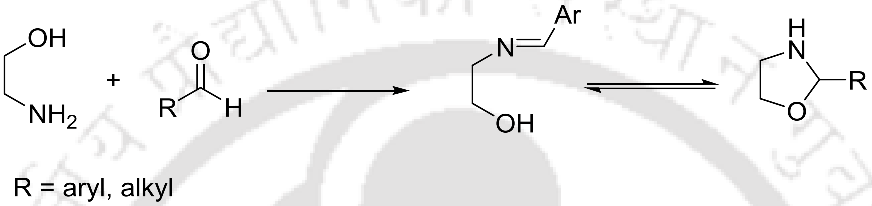
Figure 1. Examples of Oxazolidine Moiety Containing Natural Products

Recently, the construction of nitrogen heterocycles *via* tertiary amine C-H functionalization has explosive growth since most of the nitrogen heterocyles have found applications in the field of pharmaceutical and biological sciences.[10] In general, C(sp^3)-H bond activation *via* oxidative iminium ion generation followed by nucleophilic attack is well studied as cross-dehydrogenative coupling (CDC).[11] Nowadays this concept has paid more attention because of the significant advantages like atom economy and free from the requirement of the pre-functionalization of the substrates. Metal and metal-free intermolecular C-C and C-heteroatom bond formation through CDC process have been well documented.[12,13] Despite these studies, the intramolecular approach of this concept is still in high demand to produce the nitrogen containing heterocycles.

1.1 Strategies for the Synthesis of Oxazolidines

1.1.1 Classical Method

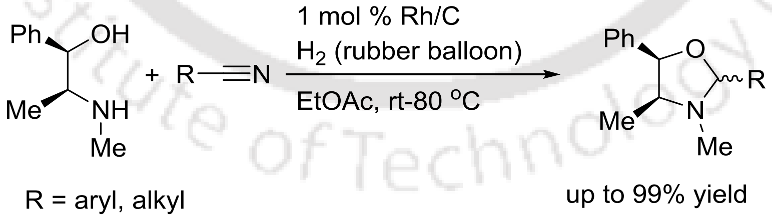
Generally, the traditional method for the construction of substituted oxazolidines starts from the condensation of 1,2-amino alcohol with aldehyde (Scheme 1).[14] However, *in situ* removal of water and the substrate scope are limited to this method.



Scheme 1. Classical Method for the Synthesis of Oxazolidines

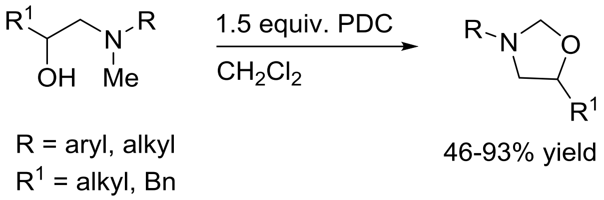
1.1.2 Modern Methods

To overcome the above drawback, metal and metal-free synthesis have been developed. Rh/C-catalysed synthesis of 1,3-oxazolidines using 1,2-amino alcohols and nitriles has been documented. The catalytic quantities of Rh/C in atmospheric pressure of hydrogen delivers the 1,3-oxazolidines in good yields (Scheme 2).[15] This reaction proceeds through the semi-hydrogenation of the nitrile followed by condensation with amino alcohol.



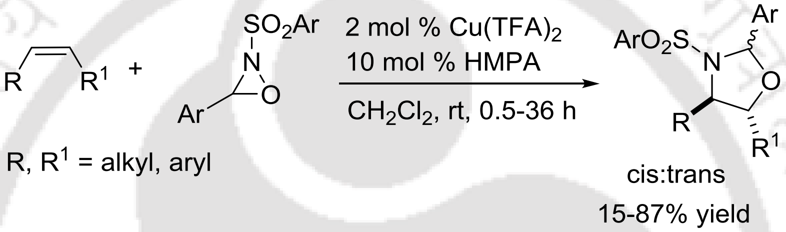
Scheme 2. Rh-Catalyzed Synthesis of 1,3-Oxazolidines from Amino Alcohols and Nitriles

Janda and co-workers discovered pyridinium dichromate (PDC) mediated synthesis of 5-substituted 1,3-oxazolidines from *N*-aryl-*N*-methyl amino alcohols (Scheme 3).[16]



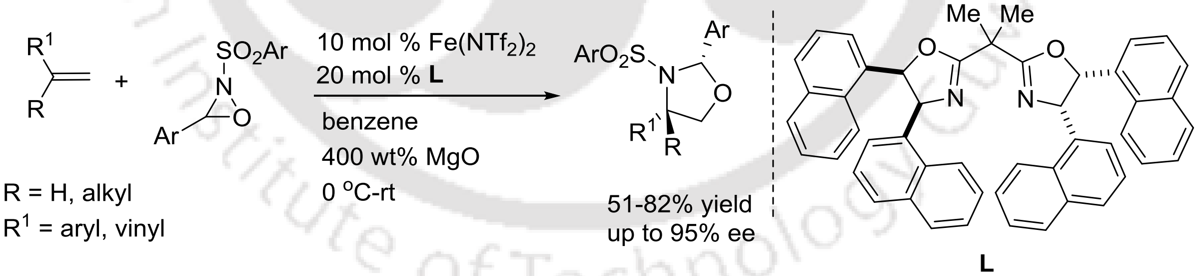
Scheme 3. PDC-Mediated Synthesis of 1,3-Oxazolidines

Yoon and co-workers discovered Cu-catalyzed coupling of oxaziridines with styrenes or electron-rich olefins to yield oxazolidines in regioselective manner (Scheme 4).[17] This transformation utilizes 2 mol% of $Cu(TFA)_2$ as catalyst to produce the oxazolidines in good to excellent yields.



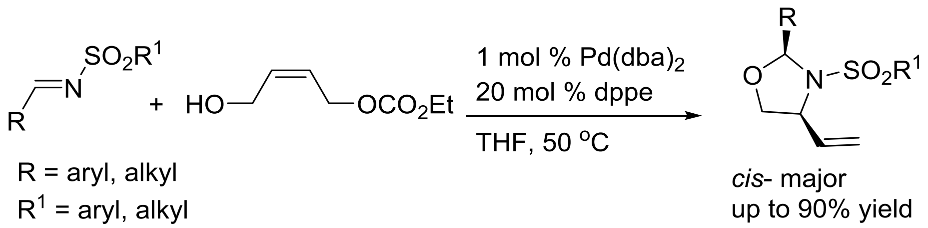
Scheme 4. Cu-Catalyzed Cycloaddition of Oxaziridines with Styrenes

The same research group developed the enantioselective synthesis of oxazolidines from alkenes with oxaziridines using 10 mol% $Fe(NTf_2)_2$ as a catalyst with 20 mol% oxazoline **L** (Scheme 5).[18]



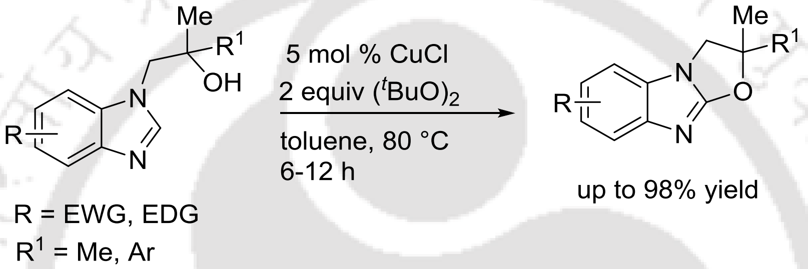
Scheme 5. Fe-Catalyzed Asymmetric Synthesis of 4-Substituted 1,3-Oxazolidines

A Pd-catalyzed diastereoselective cyclization of imines with protected 2-butene-1,4-diols has been reported by Zhu and co-workers (Scheme 6).[19] The transformation requires 1 mol% of $Pd(dba)_2$ and 20 mol% of dppe to yield the desired product with up to 90% yield.



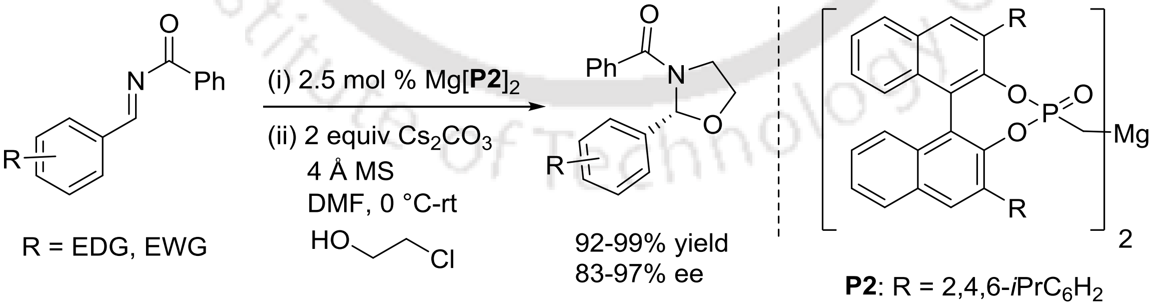
Scheme 6. Pd-Catalyzed Diastereoselective Synthesis of Oxazolidines

Kanai group established an intramolecular alkoxylation of azoles using 5 mol% CuCl as a catalyst and di-*tert*-butyl peroxide (DTBP) as an oxidant at 80 °C (Scheme 7).[20] The reaction produced oxazoimidiazoles in high yield.



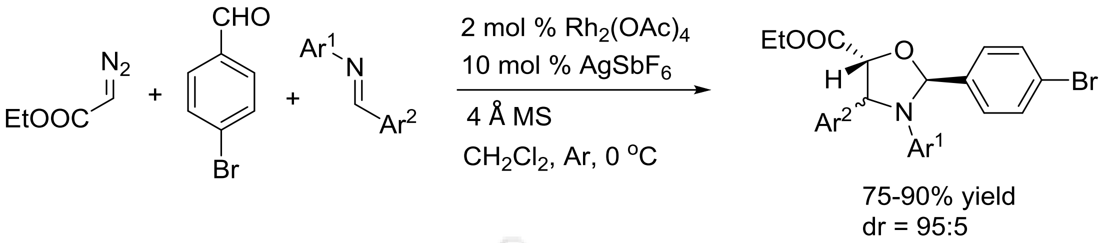
Scheme 7. Cu-Catalyzed Intramolecular C(sp^2)-H Alkoxylation of Azoles

Antilla and co-workers reported the synthesis of enantioenriched 2-aryl-1,3-oxazolidines (Scheme 8).[21] This protocol utilizes 9-anthryl derived chiral BINOL magnesium phosphate as the catalyst to the enantioselective addition of alcohol to imines followed by 5-*exo*-tet cyclization of hemiaminal intermediates. The protocol delivers the oxazolidine with excellent enantioselectivity.



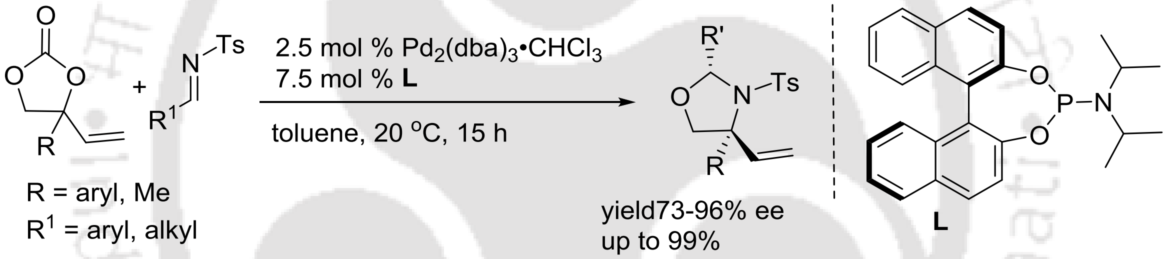
Scheme 8. Mg-Catalyzed Synthesis of Oxazolidines

Hu and co-workers reported a Rh(II)-catalyzed diastereoselective 1,3-dipolar cycloaddition of carbonyl ylides with aldimines (Scheme 9).[22] In this reaction, 2 mol% of $Rh_2(OAc)_4$ as the catalyst and 10 mol% of $AgSbF_6$ as a co-catalyst were used to afford *cis*-1,3-oxazolidines with high stereoselectivity.



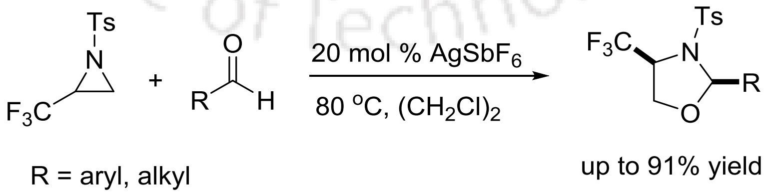
Scheme 9. 1,3-Dipolar Cycloaddition of Aldimines with Carbonyl Ylides

Zhang group demonstrated the diastereoselective synthesis of 4-vinyloxazolidines through decarboxylative cycloaddition of vinyl ethylene carbonates with imines (Scheme 10).[23] Palladium complex *in situ* generated from $Pd_2(dba)_3$•$CHCl_3$ and phosphoramidite **L** is involved as the catalyst under mild conditions to complete the transformation.



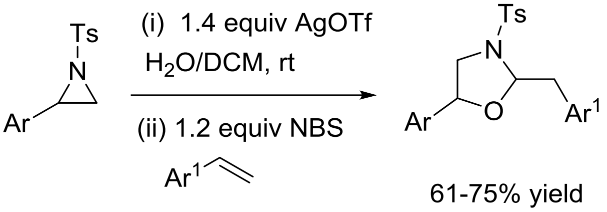
Scheme 10. Pd-Catalyzed Decarboxylative Cycloaddition of 2-Vinylethylene Carbonates and Imines

Hanamoto group reported [3+2]-cycloaddition of 2-trifluoromethyl-*N*-tosylaziridine with various aldehydes in the presence of $AgSbF_6$ at 80 °C (Scheme 11).[24] The protocol produced 4-trifluoromethyl-1,3-oxazolidine with excellent stereoselectivity.



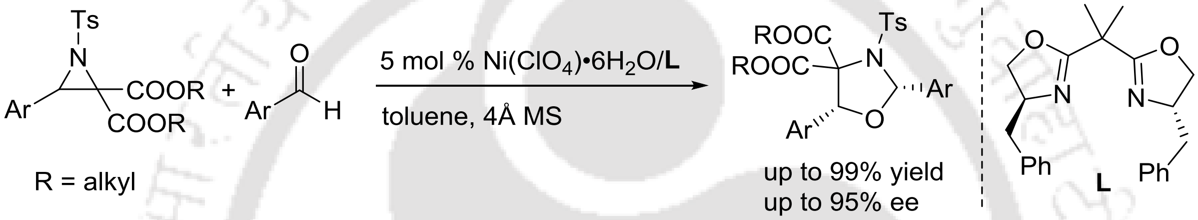
Scheme 11. Ag-Promoted Cycloaddition of 2-Trifluoromethyl Aziridine with Aldehydes

Synthesis of 1,3-oxazolidine is reported from aziridines *via in situ* generation of amino alcohol followed by difunctionalization of styrenes (Scheme 12).[25] The tandem ring-opening/closing reaction of aziridine delivers the oxazolidines. In this protocol, AgOTf is used as the catalyst and H_2O is used for the hydroxylation.



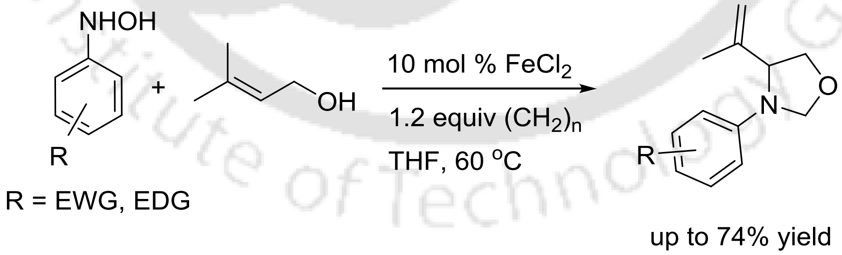
Scheme 12. Ag-Catalyzed Synthesis of Oxazolidines from Aziridines

Ni-bisoxazoline-catalyzed [3+2]-cycloaddition of *N*-tosylaziridines with aldehydes has been accomplished in good yields and high optical purities (Scheme 13).[26]



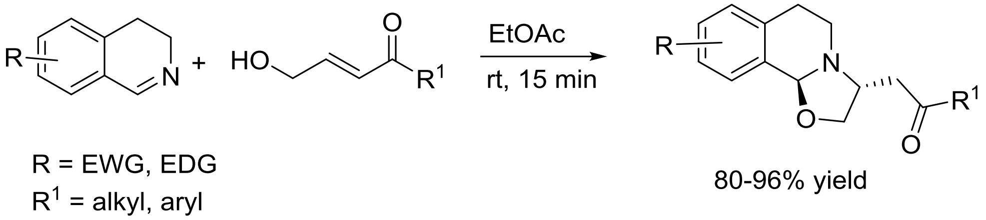
Scheme 13. Ni-Catalyzed Cycloaddition of Aziridines and Aldehydes

Fe-catalyzed synthesis of substituted *N*-aryl oxazolidines is reported *via* the coupling of aryl hydroxylamines with allyl alcohols in the presence of formaldehyde (Scheme 14).[27] This catalytic method is most effective for *para*-substituted aryl hydroxylamines and 3-methyl allyl alcohols. Additionally, acid catalyzed demethylenation of oxazolidines was allowed to access *N*-aryl amino alcohols in good yields.



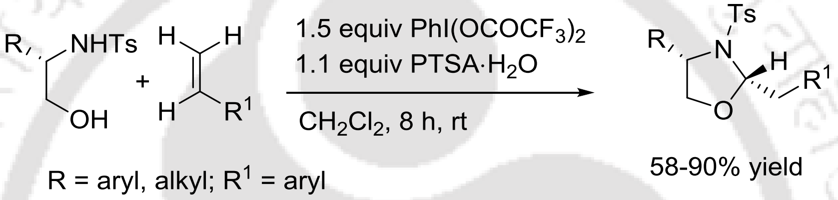
Scheme 14. Fe-Catalyzed Synthesis of *N*-Aryl Oxazolidines

Yang group developed a greener tandem addition of 3,4-dihydroisoquinolines to γ-hydroxy-α,β-unsaturated ketones to deliver oxazolo[2,3-a]tetrahydroisoquinolines (Scheme 15).[28] This domino addition proceeds *via* the catalyst free green medium to afford the target molecules in good to excellent yields.



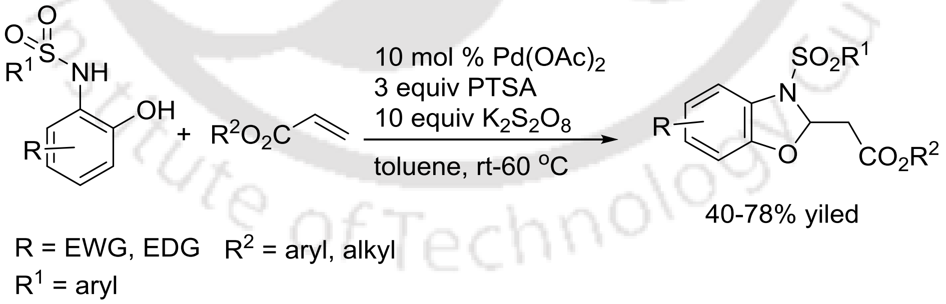
Scheme 15. Cycloaddition of Dihydroisoquinolines with *γ*-Hydroxy-*α, β*-Unsaturated Ketone

Hypervalent iodine mediated geminal aminooxygenation of styrenes is reported to yield oxazolidines (Scheme 16).[29] This transformation requires 1.5 equiv. of $PhI(OCOCF_3)_2$ and 1.1 equiv. of $PTSA{\bullet}H_2O$ as an activator to produce the oxazolidines in high yields.



Scheme 16. Synthesis of 1,3-Oxazolidines *via* Geminal Aminooxygenation of Vinylarenes

Pd-catalyzed synthesis of benzoxazolidine is reported from sulfamidophenol and terminal alkene (Scheme 17).[30] This reaction involves the initial formation of Pd-catalyzed enesulfonamide, which undergoes nucleopalladation by the intramolecular annulation and subsequent protodepalladation using TsOH to afford the benzoxazolidine.

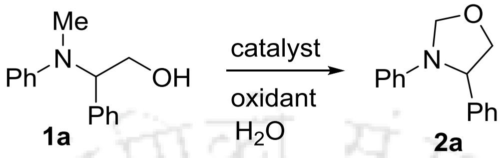


Scheme 17. Pd-Catalyzed Oxamidation of Alkenes

1.2 Present Study

In this chapter we present a metal-free protocol for the synthesis of substituted oxazolidines from *N*-methyl amino alcohol *via* C-H functionalization/C-O bond formation using TBAI as a catalyst and T-Hydro as an oxidant. Table 1 covers the optimization of the conditions using amino alcohol **1a** as a model substrate in the presence of iodides and oxidants on water. Gratifyingly, the reaction occurred to produce oxazolidine **2a** in 55% when **1a** was stirred with 15 mol % of TBAI and 2 equiv of T-Hydro at room temperature under air (entry 1).

Table 1. Optimization of the Reaction Conditions



Entry	Catalyst (15 mol %)	Oxidant (2 equiv)	Temp (°C)	Yield (%)^{a,b}
1	TBAI	T-Hydro	rt	55
2	TBAI	30% H_2O_2	rt	5
3	TBAI	DTBP	rt	0
4	TBAI	T-Hydro	40	80
5	TBAI	T-Hydro	60	95(100)^{c,d}
6	NaI	T-Hydro	60	0
7	KI	T-Hydro	60	0
8	I_2	T-Hydro	60	30
9	TBAI	T-Hydro	60	61^{e},65^{f}
10	-	T-Hydro	60	0

[a] Amino alcohol **1a** (0.5 mmol), catalyst (15 mol %), oxidant (1 mmol), H_2O (1 mL), 24 h.

[b] Isolated yield.

[c] Determined by 400 MHz ^{1}H NMR.

[d] Under N_2 atmosphere.

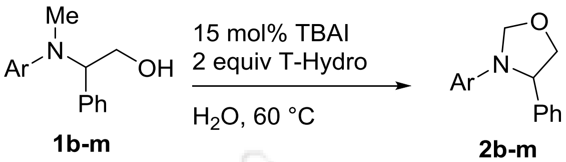
[e] TBAI (10 mol %) used.

[f] T-Hydro (0.75 mmol) used.

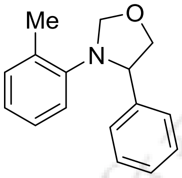
The use of 30% H_2O_2 and di-*tert*-butyl peroxide (DTBP) in place of T-Hydro led to inferior results (entries 2-3). However, increasing the reaction temperature (60 °C) furnished the target product in 100% conversion and selectivity (entries 4-5). Similar results were observed using N_2 atmosphere (entry 5). In a set of iodides screened, TBAI, NaI, KI and I_2, the former furnished the best results (entries 6-8). Decreasing the amount of TBAI (10 mol %) or T-

Hydro (1.5 equiv) led to the formation of **2a** in < 65% yield (entry 9). A control experiment confirmed that the target heterocycle was not formed in the absence of TBAI (entry 10).

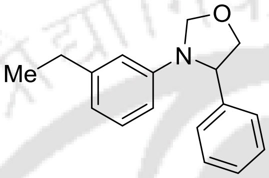
Table 2. Reaction of *N*-Aryl Substituted Substrates[a,b]



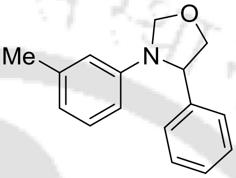
1b-m **2b-m**



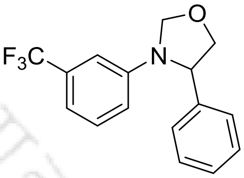
2b, 30 h, 0 %



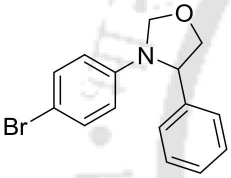
2c, 20 h, 86%



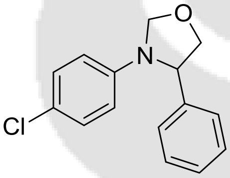
2d, 24 h, 84%



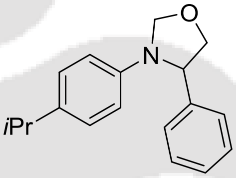
2e, 30 h, 55%



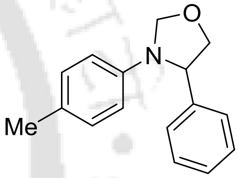
2f, 24 h, 77%



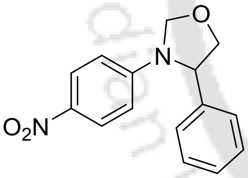
2g, 24 h, 81%



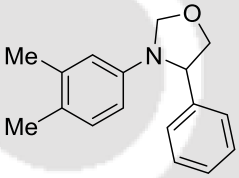
2h, 17 h, 88%



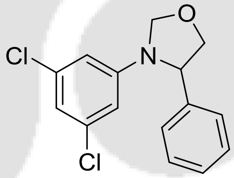
2i, 24 h, 84%



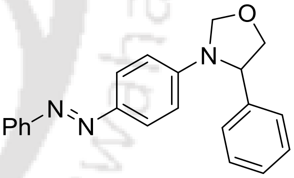
2j, 30 h, 0%



2k, 20 h, 85%



2l, 26 h, 70%

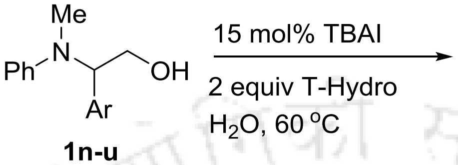


2m, 30 h, 47%

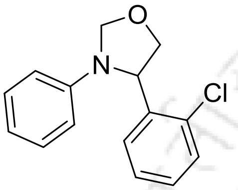
[a] Reaction conditions: Substrate **1b-m** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), H_2O (1 mL), 60 °C.
[b] Isolated yield.

Having the optimal condition, the reaction of amino alcohols **1b-m** having substitution in *N*-aryl ring was investigated (Table 2). The substrate **1b** bearing substitution at 2-position with methyl group showed no product **2b** formation, which may be due to the steric hindrance of the methyl functionality. However, the reaction of **1c-e** containing substitution at 3-position with ethyl, methyl and trifluoromethyl groups gave **2c-e** in 55-86% yields. Similarly, the substrates **1f-i** having substitution at 4-position with bromo, chloro, isopropyl and methyl groups produced the oxazolidines **2f-i** in 77-88% yields. In contrast, **1j** with strong electron withdrawing nitro group failed to produce **2j**, which may be due to the delocalization of nitrogen lone pair in *N*-aryl ring towards the nitro group and not available for the single electron transfer (SET) reduction of iodine to I$^-$ (Scheme 16, step ii).

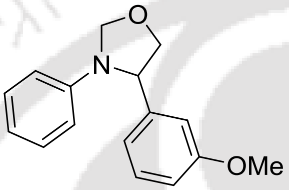
Table 3. Reaction of 2-Aryl Substituted Substrates^{a,b}



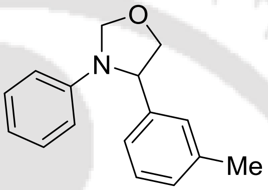
1n-u **2n-u**



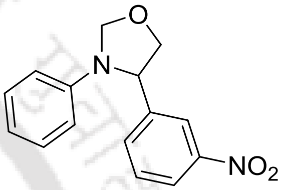
2n, 28 h, 75%



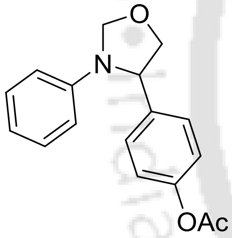
2o, 18 h, 87%



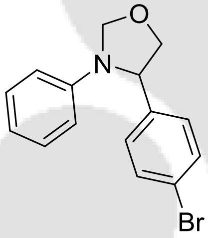
2p, 24 h, 81%



2q, 30 h, 65%

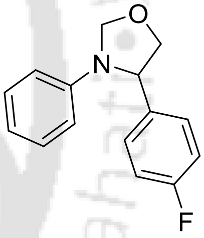


2r, 18 h, 85%



2s, 24 h, 79%

2t, 24 h, 78%



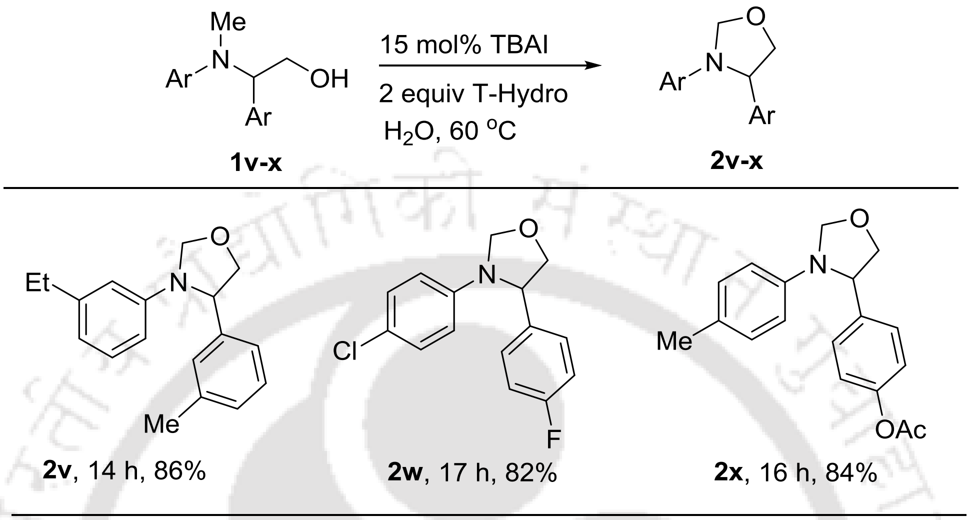
2u, 24 h, 84%

[a] Reaction conditions: Substrate **1n-u** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), H_2O (1 mL), 60 °C.

[b] Isolated yield.

However, the reaction of **1k** and **1l** bearing 3,4-dimethyl and 3,5-dichloro functionalities furnished **2k** and **2l** in 85 and 70% yields, respectively, whereas **1m** containing 4-azobenzene substituent afforded **2m** in good yield. Next, the reaction of the substrates bearing substitution at 2-aryl ring was explored (Table 2). The substrate **1n** bearing 2-chloro substituent underwent reaction to provide **2n** in 75% yield. The reaction of **1o-q** having substitution at 3-position with methoxy, methyl and nitro functionalities furnished the target oxazolidines **2o-q** in 65-87% yields, whereas **1r-u** containing substitution at 4-position with acetoxy, bromo, chloro and fluoro groups afforded the substituted oxazolidines **2r-u** in 78-85% yields.

Table 4. Reaction of *N*- and 2-Aryl Substituted Substrates[a,b]



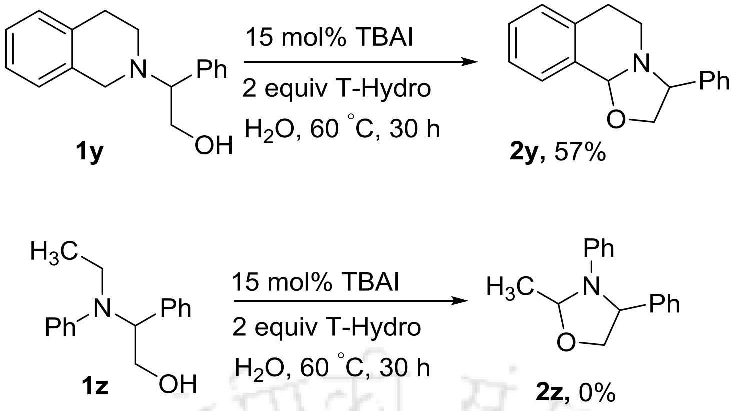
1v-x **2v-x**

2v, 14 h, 86% **2w**, 17 h, 82% **2x**, 16 h, 84%

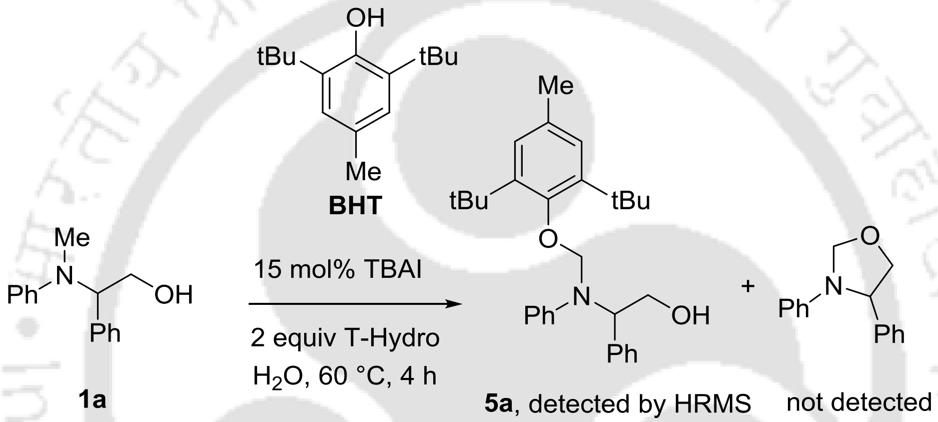
[a]Reaction conditions: Substrate **1v-x** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), H_2O (1 mL), 60 °C.

[b]Isolated yield**.**

The reaction of the substrates bearing substitution in both aryl rings was further examined (Table 3). Substrate **1v** having substitution at 3-position with methyl and ethyl groups underwent reaction to give **2v** in 86% yield. The reaction of **1w-x** having substitution at 4-position with chloro, fluoro, methyl and acetoxy functionalities afforded **2w** and **2x** in 82% and 84% yields, respectively. The reaction condition is also compatible for the cyclization of tetrahydroisoquinoline derivative **1y**, affording the tricyclic oxazolidine **2y** in good yield (Scheme 4). Under these conditions, *N*-ethyl substrate **1z** showed no cyclization and the formation of **2z** was not observed. In case of optically active substrates, the reaction proceeded with high optical purities (Scheme 20). The substrates **1a'** and **1c'** underwent reaction to produce **2a**' and 2**c**' in 99% and 98% ee, respectively. These results suggest that the reaction provides a potential route to construct the oxazolidines with high optical purities.

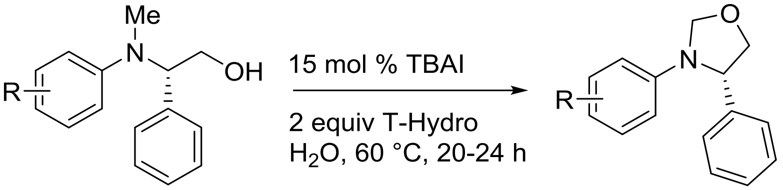


Scheme 18. Reaction of Tetrahydroisoquinoline and *N*-Ethyl Substrates



Scheme 19. Radical Scavenger Experiments

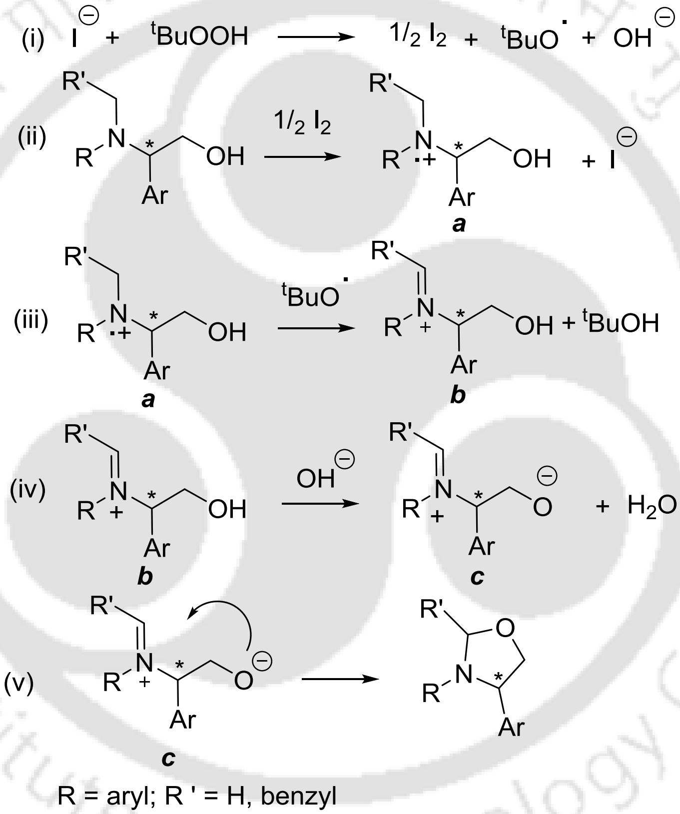
To get insight into the catalytic pathway, the reaction of **1a** was performed with BHT (Scheme 19). HRMS analysis of the reaction mixtures revealed the formation of BHT adduct **5a** as a sole product, which suggests that the reaction involves a radical intermediate. Thus, the oxidation of TBAI by T-Hydro may give iodine, *tert*-butoxyl radical and hydroxyl ion (Scheme 21, step i). Single electron transfer (SET) reduction of iodine may regenerate the catalyst with the formation of the radical cation ***a*** (Scheme 21, step ii). Homolysis of methyl C-H bond is induced by *tert*-butoxyl radical may give the imine ***b***, which may convert into the target heterocycle **2** *via* the intermediate ***c*** (Scheme 21, steps iv and v). The tertiary benzylic C-H bond is intact, which may be due to its steric hindrance towards the *tert*-butoxyl radical compared to that of the methyl C-H bond. In these reactions, TBAI and TBHP are dissolved in water, while the substrate **1** is floated on the surface of the water, and the mixture is stirred. After completion, the product **2** is separated out as liquid on the surface of water, which can be easily isolated. The reaction may take place in the interface of oil-water droplets.



1a', 1c'

2a', R = H, 95% (99% ee)
2c', R = 3-Et, 86% (98% ee)

Scheme 20. Reaction of Optically Active Substrates



Scheme 21. Proposed Reaction Pathway

In summary, we described an oxidative cyclization of *N*-methyl 1,2-amino alcohol for the construction of the substituted oxazolidines employing TBAI catalyst in the presence of T-Hydro at moderate temperature. The use of water as the solvent, metal-free, regioselectivity and substrate scope are the salient features. Optically active substrates can be converted to enantiospecifically pure 1,3-oxoazolidines.

1.3 Experimental Section

1.3.1 General Information. Anilines, styrenes, styrene oxide, 1,2,3,4-tetrahydroisoquinoline, *m*-CPBA (77%), T-Hydro, DTBP (98%), I_2, 30% aq. H_2O_2, BHT (>99%), TBAI (99%), NaI (99%), KI (99%) and $Cu(OTf)_2$ (98%) were purchased from commercial source and used as received. All reactions were performed in pure water (>5 MΩ cm @ 25 °C, total organic content < 30 ppb). The reactions were monitored by analytical TLC on silica gel G/GF 254 plates. The column chromatography was performed with 60-120 mesh silica gel. NMR (^{1}H and ^{13}C) spectra were recorded on 600 and 400 MHz spectrometers using $CDCl_3$ as a solvent and TMS as an internal standard. The data are accounted as follows: chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and dd = doublet of doublets. Melting points were determined with melting point apparatus and are uncorrected. Optical rotations were determined using polarimeter with a 50 mm path length cell at 589 nm at 23 °C. FT-IR spectra recorded on an IR spectrometer. HRMS were analyzed with Q-TOF instrument. HPLC analysis was carried out with Daicel Chiralcel OD and OJ columns.

1.3.2 Procedure for the Synthesis of *N*-Methylanilines. In an oven dried two-necked 50 mL round bottom flask, NaOMe was prepared by adding sodium metal (10 mmol) portion wise in dry MeOH (20 mL) at 0 ºC. Aniline (2 mmol) and paraformaldehyde (5 mmol) were added to a freshly prepared NaOMe at room temperature (26 °C), and the reaction mixture was allowed to stir for 2 h at 90 ^{o}C to generate an imine intermediate. The resultant mixture was reacted with $NaBH_4$ (3 mmol) at 0 ºC, and then refluxed for the additional 2 h. The reaction mixture was then cooled to room temperature, and the solvent was evaporated on a rotary evaporator to give a residue that was diluted with CH_2Cl_2 (15 mL) then washed with water (5 mL). The organic layer dried over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane as an eluent.

1.3.3 Procedure for the Preparation of *N*-Methyl Amino Alcohols 1a-x. The reaction mixture of epoxide (1 mmol), *N*-methylaniline (1 mmol) and $Cu(OTf)_2$ (5 mol%) in $(CH_2Cl)_2$ was allowed to stir at room temperature. Upon completion, the crude product was purified by column chromatography on 60-120 mesh silica gel using ethyl acetate in hexane to afford the pure products.

1.3.4 Procedure for the Synthesis of Oxazolidines 2a-y. To a mixture of the substituted 1,2-amino alcohols **1a-y** (0.5 mmol), TBAI (15 mol %) and water (1 mL) was added T-Hydro (1.0 mmol) at room temperature under air. The substrate **1a-y** was floated on the surface of the water as oil and the resultant mixture was stirred at 60 °C. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature, treated with saturated $Na_2S_2O_3$ (500 μL) and ethyl acetate (5 mL). The organic layer was separated, dried (Na_2SO_4) and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

3,4-Diphenyloxazolidine 2a′. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.61; pale yellow liquid; yield 95% (107 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.30-7.28 (m, 1H), 7.19 (t, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H) 5.33 (d, *J* = 1.8 Hz, 1H), 5.04 (d, *J* = 1.8 Hz, 1H), 4.71 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.41 (t, *J* = 7.8 Hz, 1H), 3.99 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 141.6, 129.4, 129.0, 127.7, 126.4, 117.9, 112.9, 83.0, 75.9, 61.9; FT-IR (neat) 3061, 3028, 2928, 2864, 1600, 1508, 1495, 1346, 1166, 1090, 749, 692 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{15}NO$ 226.1226, found 226.1225; $[\alpha]_D^{20}$ = +159.0 (c= 0.2, $CHCl_3$); HPLC analysis: 99% ee [Daicel Chiralcel OD column, hexane/*i*PrOH = 90:10, flow rate: 1 mL/min, λ = 254 nm, t_R = 4.94 min (minor), 8.36 min (major)].

3-(3-Ethylphenyl)-4-phenyloxazolidine 2c′. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.62; pale yellow liquid; yield 86% (109 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.29-7.27 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.33-6.30 (m, 2H), 5.33 (d, *J* = 2 Hz, 1H), 5.03 (d, *J* = 2 Hz, 1H), 4.70 (dd, *J* = 6.8, 4.4 Hz, 1H), 3.39 (t, *J* = 7.6 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.4 Hz, 1H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 145.3, 141.8, 129.3, 129.0, 127.7, 126.4, 117.6, 112.5, 110.5, 83.0, 75.9, 61.9, 29.3, 15.7; FT-IR (neat) 3030, 2963, 2929, 2869, 1603, 1493, 1453, 1356, 1166, 1090, 759, 697 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$

calcd for $C_{17}H_{19}NO$ 254.1539, found 254.1539; $[\alpha]_D^{20}$ = +28.0 (c= 0.2, $CHCl_3$); HPLC analysis: 98% ee [Daicel Chiralcel OJ column, hexane/*i*PrOH = 85:15, flow rate: 1 mL /min, λ = 254 nm, t_R = 6.31 min (minor), 13.53 min (major)].

4-Phenyl-3-(*m*-tolyl)oxazolidine 2d. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.62; pale yellow liquid; yield 84% (100 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 4H), 7.29-7.27 (m, 1H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.32 (s, 1H), 6.30 (d, *J* = 8.4 Hz, 1H), 5.32 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 1.8 Hz, 1H), 4.70 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.38 (t, *J* = 8.4 Hz, 1H), 3.98 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 141.8, 139.2, 129.3, 129.0, 127.7, 126.4, 118.8, 113.6, 110.2, 83.0, 75.9, 61.8, 22.0; FT-IR (neat) 3063, 3032, 2921, 2863, 1605, 1493, 1453, 1356, 1170, 1089, 945, 840 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{17}NO$ 240.1383, found 240.1383.

4-Phenyl-3-(3-(trifluoromethyl)phenyl)oxazolidine 2e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless liquid; yield 55% (81 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.31-7.28 (m, 1H), 7.23 (t, *J* = 8.4 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 6.59 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.33 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 1H), 4.72 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.00 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.1, 140.7, 131.8 (q, $J_{C\text{-}F}$ = 31.5 Hz), 129.8, 128.1, 126.3, 124.7 (q, $J_{C\text{-}F}$ = 93.0 Hz), 115.9, 114.3 (q, $J_{C\text{-}F}$ = 4.5 Hz), 109.1 (q, $J_{C\text{-}F}$ = 3.0 Hz), 82.7, 76.0, 61.8; FT-IR (neat) 3061, 3031, 2923, 2868, 1615, 1508, 1493, 1459, 1372, 1166, 1121, 782, 697 cm^{-1}; HRMS (APCI) m/z $[M+H]^+$ calcd for $C_{16}H_{14}F_3NO$ 294.1100, found 294.1097.

3-(4-Bromophenyl)-4-phenyloxazolidine 2f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.59; pale yellow liquid; yield 77% (117 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.34 (d, *J* = 8.4 Hz, 2H), 5.27 (d, *J* = 2.4 Hz, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 140.9, 132.1, 129.1, 128.0, 126.3, 144.5, 109.9, 82.8, 76.0, 61.9; FT-IR (neat) 3061, 3028, 2923, 2853, 1595, 1505, 1489, 1360, 1165, 1089, 944, 807, 757 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{15}H_{14}BrNO$ 304.0332, found 304.0328.

3-(4-Chlorophenyl)-4-phenyloxazolidine 2g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.59; pale yellow liquid; yield 81% (105 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.38 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.41 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.96 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 141.0, 129.3, 129.1, 128.0, 126.3, 122.8, 114.0, 82.9, 76.0, 62.0; FT-IR (neat) 3063, 3028, 2924, 2854, 1601, 1504, 1493, 1358, 1166, 1095, 810 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{15}H_{14}ClNO$ 260.0837, found 260.0836.

3-(4-Isopropylphenyl)-4-phenyloxazolidine 2h. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.63; pale yellow liquid; yield 88% (117 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.28 (d, *J* = 6.6, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 6.44 (d, *J* = 7.8 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 1.8 Hz, 1H), 4.66 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.37 (t, *J* = 7.2 Hz, 1H), 3.95 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.81-2.76 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 142.0, 138.4, 129.0, 127.7, 127.3, 126.5, 113.0, 83.3, 75.9, 62.3, 33.3, 24.4; FT-IR (neat) 3064, 3028, 2959, 2926, 2867, 1618, 1520, 1346, 1157, 1090, 816, 757, 704 cm^{-1}; HRMS (APCI) m/z [M+H]$^+$ calcd for $C_{18}H_{21}NO$ 268.1696, found 268.1697.

4-Phenyl-3-(*p*-tolyl)oxazolidine 2i. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.62; colorless liquid; yield 84% (100 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.29-7.26 (m, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.8 Hz, 1H), 4.40 (t, *J* = 8.4 Hz, 1H), 3.96 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 141.7, 129.9, 129.0, 127.7, 127.1, 126.4, 113.1, 83.3, 75.9, 62.1, 20.5; FT-IR (neat) 3063, 3027, 2918, 2861, 1621, 1522, 1452, 1340, 1170, 1090, 804 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{16}H_{17}NO$ 240.1383, found 240.1385.

3-(3,4-Dimethylphenyl)-4-phenyloxazolidine 2k. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.63; brown liquid; yield 85% (108 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ

7.36-7.32 (m, 4H), 7.27-7.25 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.31 (d, *J* = 1.8 Hz, 1H), 6.24 (dd, *J* = 7.8, 2.4 Hz, 1H), 5.30 (d, *J* = 1.8 Hz, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 4.65 (dd, *J* = 6.6, 4.8 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.94 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.7, 141.9, 137.6, 130.5, 129.0, 127.6, 126.4, 126.0, 114.6, 110.6, 83.4, 75.9, 62.0, 20.4, 18.9; FT-IR (neat) 3060, 3025, 2921, 2859, 1617, 1513, 1452, 1354, 1274, 1089, 800, 717, 700 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{19}NO$ 254.1539, found 254.1539.

3-(3,5-Dichlorophenyl)-4-phenyloxazolidine 2l. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.59; pale yellow liquid; yield 70% (103 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.2 Hz, 2H), 7.32-7.28 (m, 3H), 6.70 (t, *J* = 1.8 Hz, 1H), 6.31 (d, *J* = 1.2 Hz, 2H), 5.24 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6 Hz, 4.2 Hz, 1H), 4.39 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.98 (dd, *J* = 8.4, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 140.3, 135.7, 129.3, 128.2, 126.2, 117.6, 111.1, 82.4, 75.9, 61.6; FT-IR (neat) 3084, 3029, 2923, 2853, 1592, 1557, 1463, 1344, 1167, 1093, 820, 708 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{13}C_{l2}NO$ 294.0447, found 294.0448.

(*E*)-4-Phenyl-3-(4-(phenyldiazenyl)phenyl)oxazolidine 2m. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.56; orange liquid; yield 47% (77 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 9.0 Hz, 4H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.39-7.29 (m, 6H), 6.54 (d, *J* = 9.0 Hz, 2H), 5.38 (d, *J* = 2.4 Hz, 1H), 5.14 (d, *J* = 2.4 Hz, 1H), 4.84 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.45 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.04 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.3, 147.0, 145.0, 140.8, 129.9, 129.2, 129.1, 128.1, 126.4, 125.2, 122.5, 112.7, 82.4, 76.0, 61.7; FT-IR (neat) 3061, 3025, 2959, 2922, 2851, 1602, 1515, 1497, 1389, 1373, 1140, 1088, 821, 766 cm^{-1}; HRMS (APCI) m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_3O$ 330.1601, found 330.1601.

4-(2-Chlorophenyl)-3-phenyloxazolidine 2n. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.58; pale yellow liquid; yield 75% (97 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 6.0 Hz, 1H), 7.25-7.20 (m, 4H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 2H), 5.35 (s, 1H), 5.11 (d, *J* = 4.2 Hz, 1H), 5.01 (s, 1H), 4.47 (t, *J* = 7.8 Hz, 1H), 4.06 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 138.6, 132.4, 129.8, 129.6, 128.9, 127.9, 127.4, 118.1, 112.9, 82.6, 74.5, 59.2; FT-IR (neat) 3064, 3036, 2924, 2857, 1600, 1508, 1497, 1348, 1171, 1092, 744, 691 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{14}ClNO$ 260.0837, found 260.0836.

4-(3-Methoxyphenyl)-3-phenyloxazolidine 2o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.41$; colorless liquid; yield 87% (111 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.96 (d, *J* =7.8 Hz, 1H), 6.91 (s, 1H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 145.3, 143.5, 130.1, 129.4, 118.7, 117.9, 113.0, 112.9, 112.1, 83.0, 75.8, 61.9, 55.4; FT-IR (neat) 3040, 2997, 2935, 2866, 2835, 1600, 1508, 1495, 1346, 1284, 1146, 1091, 749, 692 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{17}NO_2$ 256.1332, found 256.1337.

3-Phenyl-4-(*m*-tolyl)oxazolidine 2p. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.62$; pale yellow liquid; yield 81% (97 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.2 Hz, 1H), 7.20-7.15 (m, 4H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 2H), 5.33 (d, *J* = 2.4 Hz, 1H), 5.02 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.39 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 141.7, 138.7, 129.4, 128.9, 128.5, 127.0, 123.5, 117.8, 112.9, 83.0, 76.0, 62.0, 21.7; FT-IR (neat) 3051, 3025, 2922, 2853, 1600, 1506, 1384, 1343, 1277, 1087, 1033, 788 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{17}NO$ 240.1383, found 240.1386.

4-(3-Nitrophenyl)-3-phenyloxazolidine 2q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.53$; yellow liquid; yield 65% (88 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (t, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.21 (dd, *J* = 9.0, 7.2 Hz, 2H), 6.79 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 2H), 5.38 (d, *J* = 2.4 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 4.79 (dd, *J* = 6.6, 3.6 Hz, 1H), 4.42 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.00 (dd, *J* = 8.4, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.9, 144.6, 144.4, 132.6, 130.1, 129.7, 123.0, 121.5, 118.6, 113.0, 83.1, 75.5, 61.4; FT-IR (neat) 3031, 2964, 2928, 2867, 1603, 1494, 1454, 1355, 1172, 1091, 948, 848, 782 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{14}N_2O_3$ 271.1077, found: 271.1077.

4-(3-Phenyloxazolidin-4-yl)phenyl acetate 2r. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; pale yellow liquid; yield 85% (120 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 9.0 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.69 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.37 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 150.2, 145.1, 139.2, 129.5, 127.4, 122.1, 118.1, 113.0, 83.0, 75.8, 61.4, 21.4; FT-IR (neat) 3065, 3033, 2956, 2854, 1764, 1600, 1507, 1368, 1215, 1196, 1089, 749, 692 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NO_3$ 284.1281, found 284.1287.

4-(4-Bromophenyl)-3-phenyloxazolidine 2s. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.58; pale yellow liquid; yield 79% (120 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 2H), 5.31 (s, 1H), 5.00 (s, 1H), 4.65 (t, *J* = 6.0 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 3.95 (dd, *J* = 8.4 Hz, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 140.8, 132.1, 129.5, 128.1, 121.5, 118.1, 112.9, 82.9, 75.7, 61.3; FT-IR (neat) 3041, 2986, 2866, 2828, 1599, 1507, 1487, 1345, 1170, 1010, 823, 749, 692 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{14}BrNO$ 304.0332, found 304.0331.

4-(4-Chlorophenyl)-3-phenyloxazolidine 2t. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.58; pale yellow liquid; yield 78% (101 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33-7.29 (m, 4H), 7.18 (t, *J* = 7.8 Hz, 2H), 6.76 (t, *J* = 7.2, Hz 1H), 6.46 (d, *J* = 8.4 Hz, 2H), 5.31 (s, 1H), 5.00 (s, 1H), 4.66 (t, *J* = 5.4 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 3.94 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 140.3, 133.5, 129.5, 129.2, 127.8, 118.1, 112.9, 82.9, 75.7, 61.3; FT-IR (neat) 3063, 3040, 2924, 2854, 1600, 1508, 1495, 1346, 1167, 1090, 828, 747, 691 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{14}ClNO$ 260.0837, found 260.0840.

4-(4-Fluorophenyl)-3-phenyloxazolidine 2u. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.57; pale yellow liquid; yield 84% (102 mg); ^{1}H NMR (600 MHz, $CDCl_3$) 7.33 (t, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 5.33 (s, 1H), 5.01 (s, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.38 (t, *J* = 7.8 Hz, 1H), 3.96 (dd, *J* = 7.2, 3.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, $J_{C\text{-}F}$ = 244.5 Hz), 145.0, 137.4, 129.5, 128.0 (d, $J_{C\text{-}F}$ = 7.5 Hz), 118.0, 115.9 (d, $J_{C\text{-}F}$ = 21.0 Hz), 112.9, 82.9, 75.9, 61.2; FT-IR (neat) 3064, 3040, 2929, 2865, 1600, 1508, 1497, 1351, 1222, 1154, 1090, 836, 749, 692 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{14}FNO$ 244.1132, found 244.1132.

3-(3-Ethylphenyl)-4-(*m*-tolyl)oxazolidine 2v. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.63; colorless liquid; yield 86% (115 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.2 Hz, 1H), 7.19-7.16 (m, 2H), 7.11-7.09 (m, 2H), 6.62 (d, *J* = 7.2 Hz, 1H), 6.35-6.32 (m, 2H), 5.33 (s, 1H), 5.02 (s, 1H), 4.66 (t, *J* = 5.4 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 3.98 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.57 (q, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.19 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 145.5, 141.9, 138.6, 129.3, 128.8, 128.5, 127.0, 123.5, 117.5, 112.5, 110.5, 83.0, 75.9, 62.0, 29.3, 21.7, 15.7; FT-IR (neat) 3030, 2963, 2928, 2868, 1604, 1494, 1454, 1355, 1172, 1092, 948, 783, 695 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{21}NO$ 268.1696, found 268.1709.

3-(4-Chlorophenyl)-4-(4-fluorophenyl)oxazolidine 2w. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.57; colorless liquid; yield 82% (114 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.03 (t, *J* = 8.4 Hz 2H), 6.36 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 1.8 Hz, 1H), 4.63 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.39 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.93 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) 163.3 (d, $J_{C\text{-}F}$ = 244.5 Hz), 143.5, 136.8, 129.3, 127.9 (d, $J_{C\text{-}F}$ = 7.5 Hz), 123.0, 116.1 (d, $J_{C\text{-}F}$ = 22.5 Hz), 114.0, 82.9, 75.9, 61.3; FT-IR (neat) 3045, 2987, 2926, 2867, 1604, 1509, 1493, 1357, 1168, 1095, 809, 767 cm^{-1}; HRMS (APCI) m/z $[M+H]^+$ calcd for $C_{15}H_{13}ClFNO$ 278.0742, found 278.0738.

4-(3-(*p*-Tolyl)oxazolidin-4-yl)phenyl acetate 2x. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.51; colorless liquid; yield 84% (125 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 8.4 Hz, 2H), 5.30 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 1.8 Hz, 1H), 4.65 (dd, *J* = 7.2, 5.4 Hz, 1H), 4.37 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.95 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.29 (s, 3H), 2.23 (s, 3H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 150.1, 143.1, 139.3, 130.0, 127.4, 122.1, 113.1, 83.3, 75.8, 61.6, 21.4, 20.5; FT-IR (neat) 3032, 3007, 2983, 2921, 2862, 1764, 1619, 1523, 1505, 1368, 1215, 1197, 1162, 1089, 803 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}NO_3$ 298.1438, found 298.1437.

3-Phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline 2y. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.48; colorless liquid; yield 57% (72 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.42-7.40 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.30-7.26 (m, 3H), 7.19-7.17 (m, 1H), 5.45 (s, 1H), 4.47 (t, *J* = 8.0 Hz, 1H), 4.32 (t, *J* = 10.2 Hz, 1H), 3.89 (dd, 8, 6.4, 1H), 3.08-2.98 (m, 3H), 2.85-2.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 135.7, 132.9, 128.8, 128.7, 128.3, 128.2, 127.4, 126.8, 126.6, 90.3, 71.4, 68.8, 46.9, 29.4; FT-IR (neat) 3062, 3027, 2924, 2852, 1604, 1494, 1395, 1384, 1126, 1029, 937, 746, 700; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NO$ 252.1383, found 252.1384.

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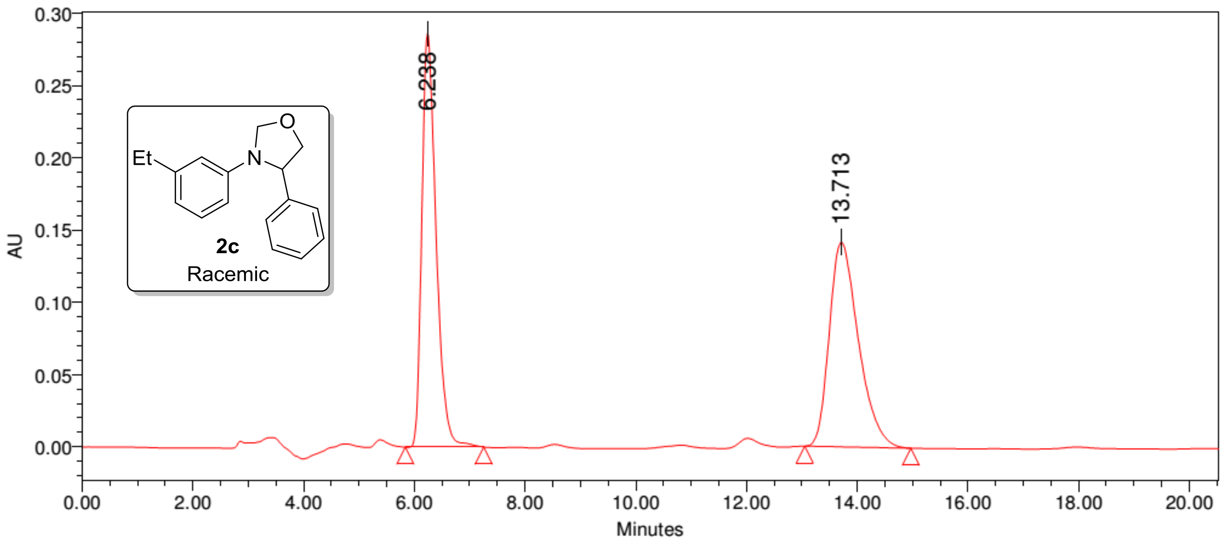
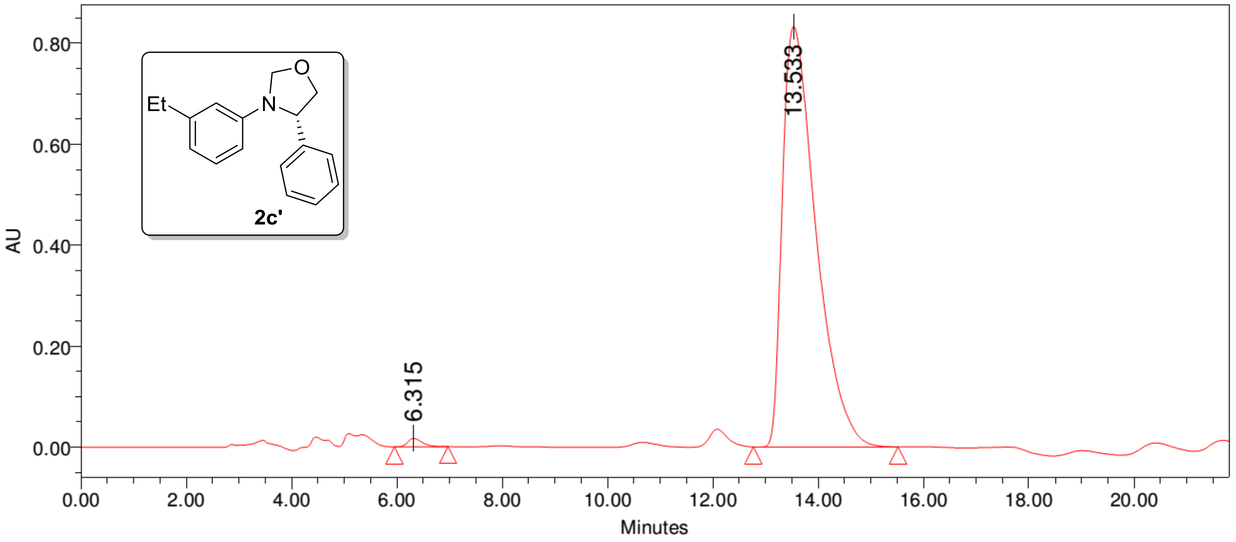
1.5 Selected HPLC Chromatograms



Peak Results

	RT	Height (µV)	% Area
1	6.238	286467	49.67
2	13.713	141642	50.33



Peak Results

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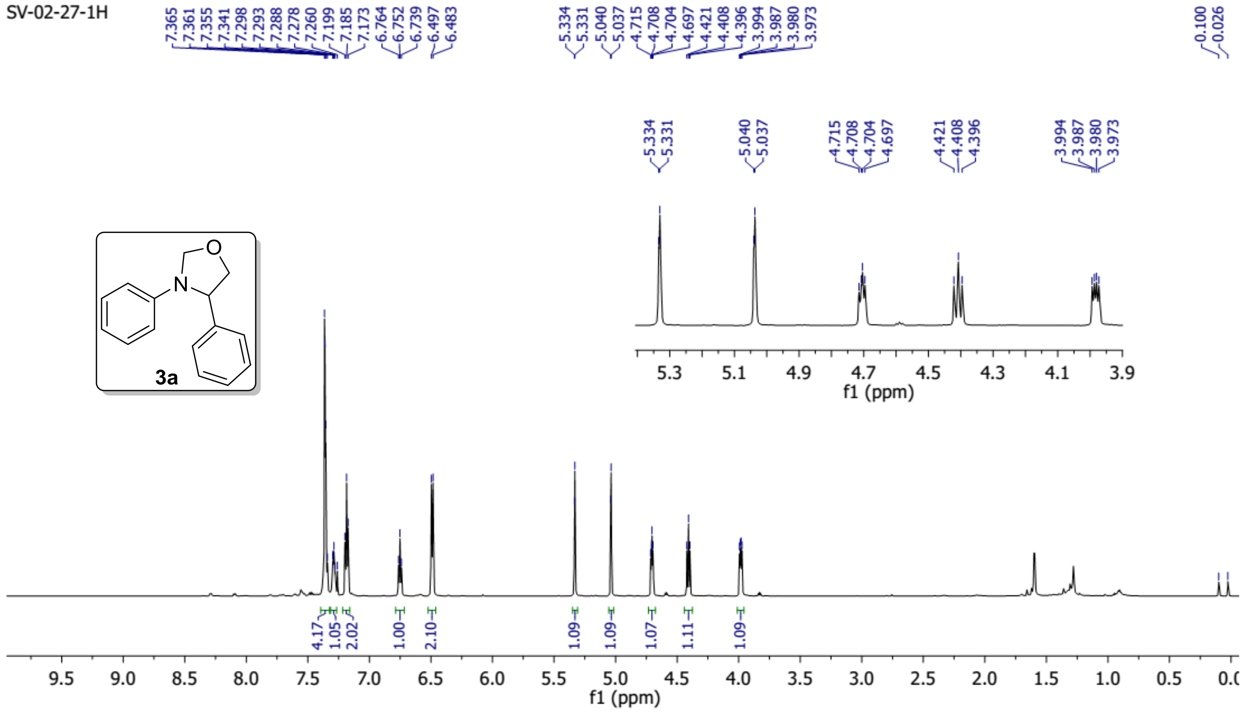
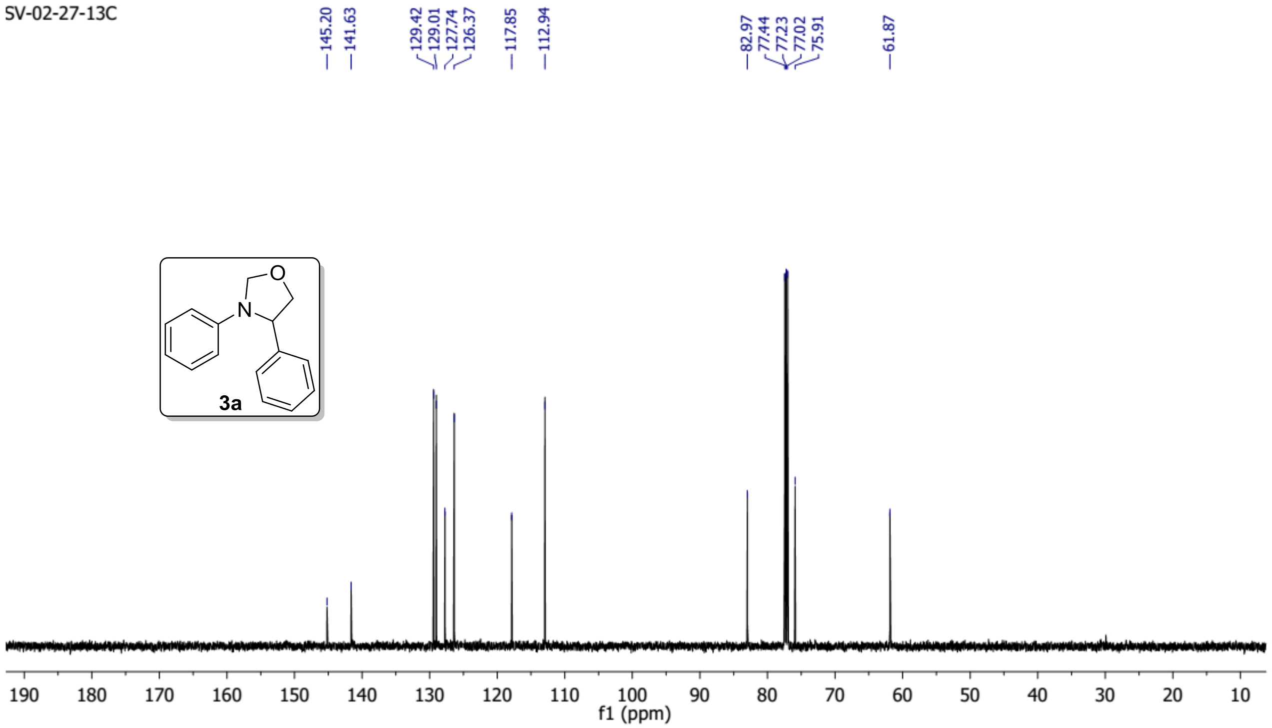
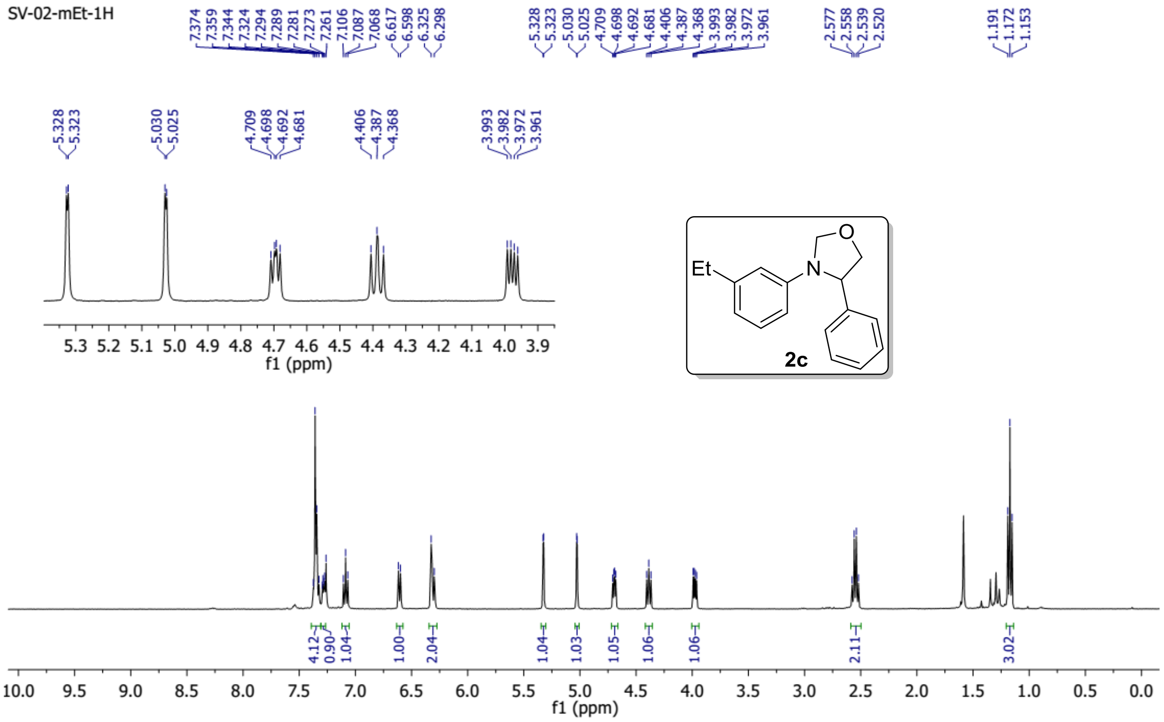
2	13.533	832869	99.16

1.6 Selected NMR Spectra




SV-02-27-13C
145.20
141.63
129.42
129.01
127.74
126.37
117.85
112.94
82.97
77.44
77.23
77.02
75.91
61.87
O
N
3a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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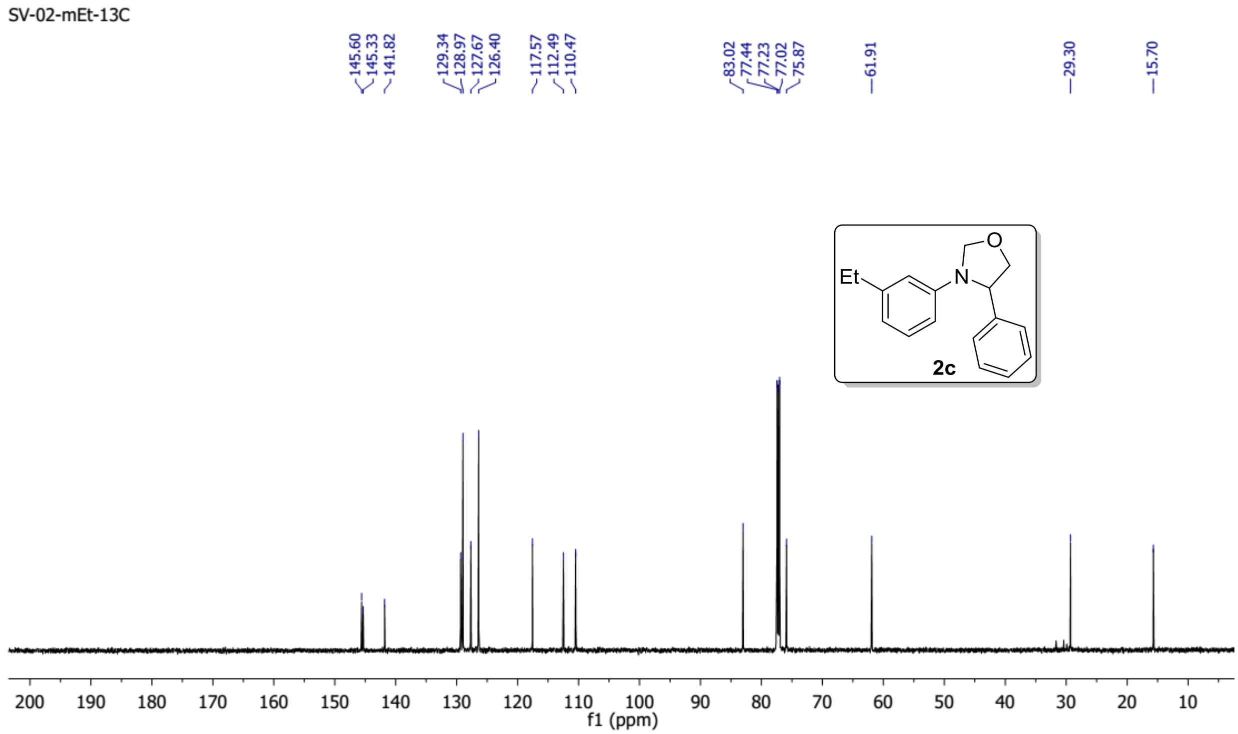
7.374
7.359
7.344
7.324
7.294
7.289
7.281
7.273
7.261
7.106
7.087
7.068
6.617
6.598
6.325
6.298
5.328
5.323
5.030
5.025
4.709
4.698
4.692
4.681
4.406
4.387
4.368
3.993
3.982
3.972
3.961
2.577
2.558
2.539
2.520
1.191
1.172
1.153
5.328
5.323
5.030
5.025
4.709
4.698
4.692
4.681
4.406
4.387
4.368
3.993
3.982
3.972
3.961
5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9
f1 (ppm)
Et
N
O
2c
4.12
0.90
1.04
1.00
2.04
1.04
1.03
1.05
1.06
1.06
2.11
3.02
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)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145.33
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129.34
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127.67
126.40
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112.49
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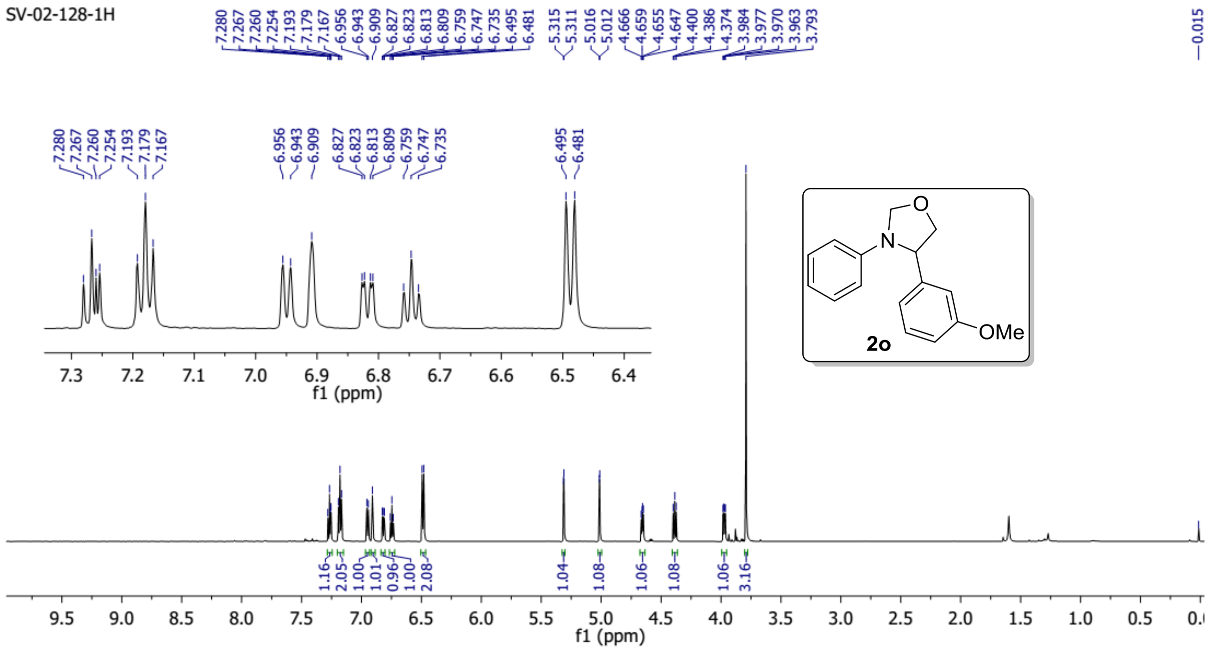
83.02
77.44
77.23
77.02
75.87
61.91
29.30
15.70
Et
N
O
2c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)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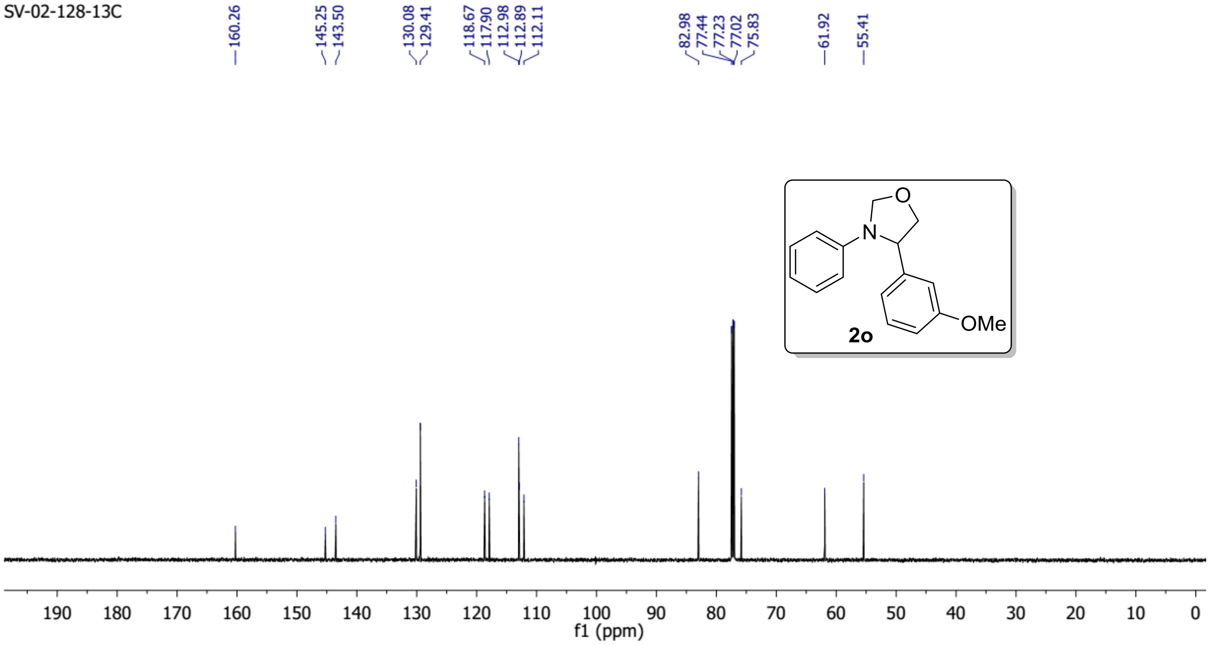
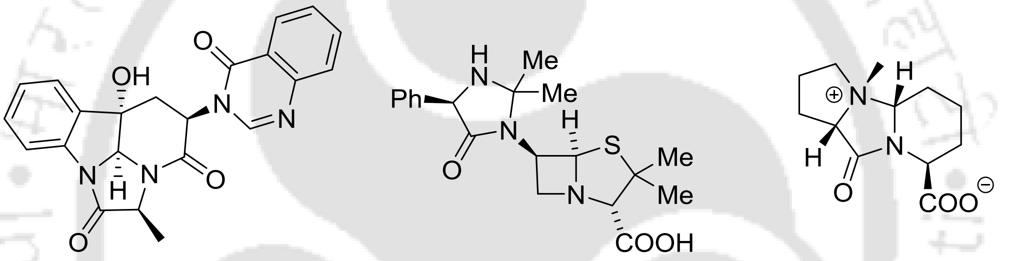
7.267
7.260
7.254
7.193
7.179
7.167
6.956
6.943
6.909
6.827
6.823
6.813
6.809
6.759
6.747
6.735
6.495
6.481
5.315
5.311
5.016
5.012
4.666
4.659
4.655
4.647
4.400
4.386
4.374
3.984
3.977
3.970
3.963
3.793
-0.015
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
f1 (ppm)
N
O
OMe
2o
1.16
2.05
1.00
1.01
0.96
1.00
2.08
1.04
1.08
1.06
1.08
1.06
3.16
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)


SV-02-128-13C
160.26
145.25
143.50
130.08
129.41
118.67
117.90
112.98
112.89
112.11
82.98
77.44
77.23
77.02
75.83
61.92
55.41
O
N
OMe
2o
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Chapter II

TBAI-Catalyzed Oxidative Cyclization of 1,2-Diamines: Synthesis of Imidazolidines

Imidazolidines are important structural scaffolds found in many biological compounds possessing a wide range of properties such as anti-inflammatory, antimicrobials, antiparasitic, α-adrenergic receptor agonist, antiarrhythmic, anticonvulsants and anti-trypanosoma cruzi agents.[1] They are also found in many natural products including (-)-aplaminal, chaetominine and (-)-dysibetaine PP (Figure 1).[2] Imidazolidine moieties have been also used as organo-catalysts and ligands.[3] Considerable efforts have thus been made on the development of synthetic routes for the construction of imidazolidines.



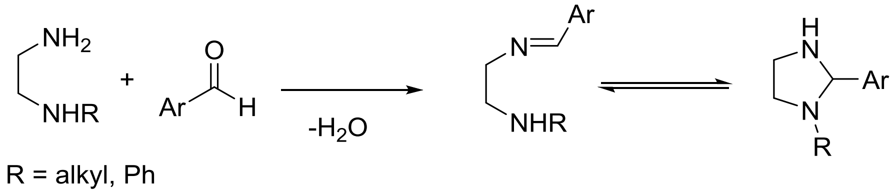
Chaetominine **Hetacillin** **(-)-Dysibetaine PP**

Figure 1. Examples of Natural Products Contaning Imidazolidine Motifs

2.1 Strategies for the Synthesis of Imidazolidines

2.1.1 Classical Method

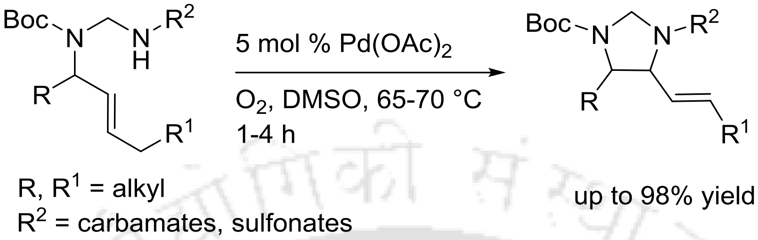
The most common method involves the condensation of 1,2-diamine with aldehyde to furnish the imidazolidines (Scheme 1).[4] However, these protocols are often suffer due to the limited substrate scope and harsh reaction conditions.



Scheme 1. Classical Method for the Synthesis of Imidazolidines

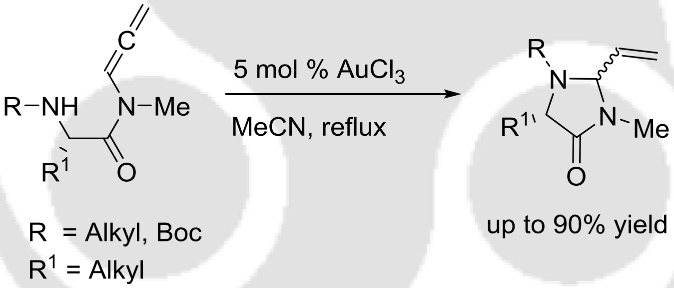
2.1.2 Modern Methods

Hiemstra and co-workers have reported a Pd-catalyzed oxidative cyclization of aminals to give imidazolidines in good yields (Scheme 2).[5]

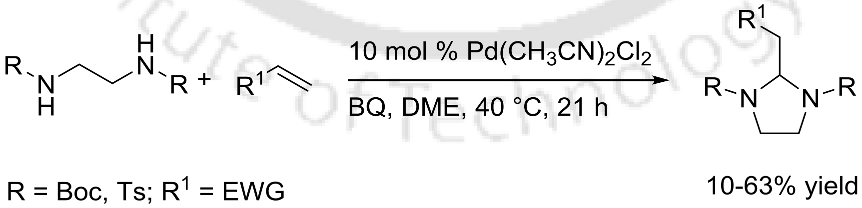


Scheme 2. Pd-Catalyzed Synthesis of Imidazolidines

Au-catalyzed synthesis of 2-vinylimidazolidines has been demonstrated by Manzo and co-workers (Scheme 3).[6] The α-amino allenamides undergo intramolecular cyclization by amino group attack on the inside double bond of the 1,2-diene. This transformation produces *cis*-imidazolidines as the major product.



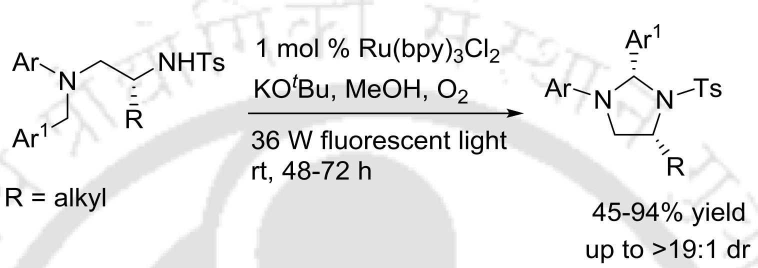
Scheme 3. Au-Catalyzed Intramolecular Hydroamination of α-Amino Allenamides



Scheme 4. Pd-Catalyzed Aza-Wacker Reaction for the Synthesis of Imidazolidines

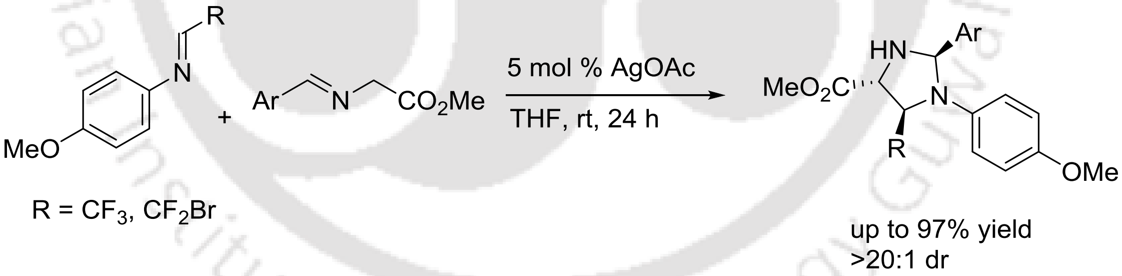
Pd-catalyzed aza-Wacker reaction of *N*-tosyl and *N*-Boc protected 1,2-diamines with electron deficient alkenes has been reported using $(CH_3CN)_2PdCl_2$ as the catalyst and benzoquinone as an oxidant (Scheme 4).[7] The reaction is sequential to produce imidazolidines *via* enamine formation followed by cyclization.

Xiao and co-workers described a Ru-catalyzed visible light-induced intramolecular cyclization of *N*-alkyl-1,2-diamines to produce the imidazolidines (Scheme 5).[8] This reaction is carried out using the combination of 1 mol % $Ru(bpy)_3Cl_2$ and KO^tBu in MeOH under visible light. This intramolecular cyclization exhibits a 19:1 diastereoselectivity.



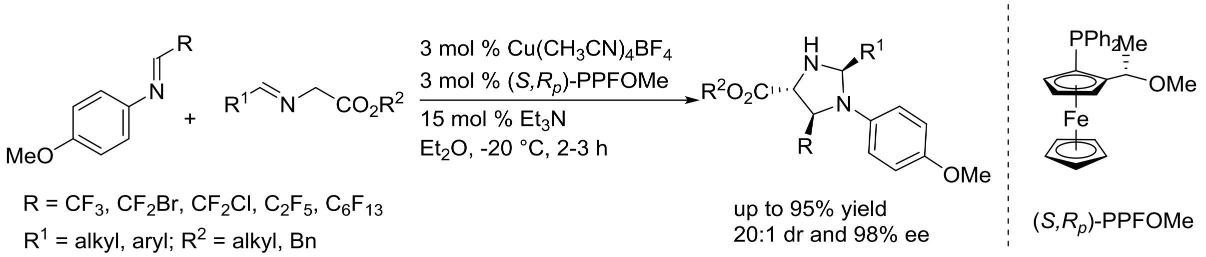
Scheme 5. Ru-Catalyzed Intramolecular Oxidative Cyclization of 1,2-Diamines

Wu and co-workers described a Ag-catalyzed 1,3-dipolar cycloaddition to diastereoselective synthesis of imidazolidines employing imines and azomethine ylides (Scheme 6).[9] This reaction has been carried out using 5 mol % AgOAc to produce the imidazolidines in good yields.



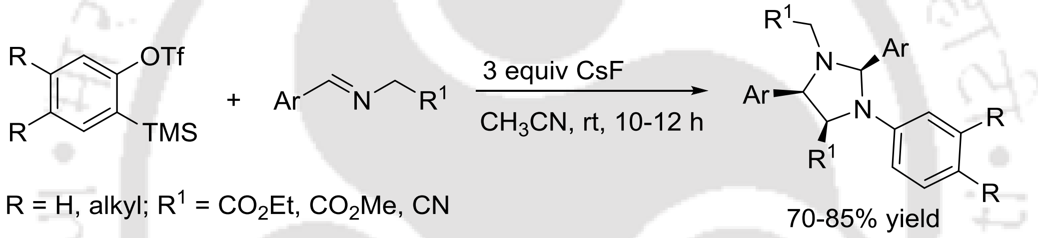
Scheme 6. Ag-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with Imines

Cu/(*S*,*Rp*)-PPFOMe catalyzed asymmetric synthesis of fluorinated imidazolidines is reported *via* the 1,3-dipolar cycloaddition of azomethine ylides with various fluorinated imines (Scheme 7).[10] The optimal catalytic system exhibits extremely high reactivity and excellent enantioselectivity.



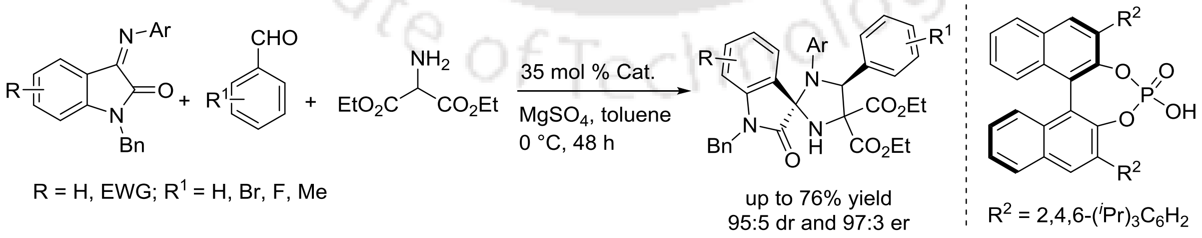
Scheme 7. Cu-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Imines

A domino synthesis of imidazolidines has been reported by Hwu and co-workers from 2-(trimethylsilyl)aryl triflates and Schiff bases employing an equivalent amount of CsF in CH_3CN (Scheme 8).[11] The *in situ* generated azomethine ylides from aryne and Schiff base is cyclized with another Schiff base to produce the imidazolidines in good yields.



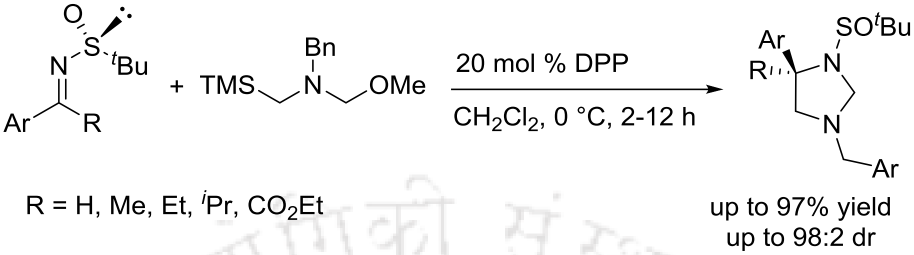
Scheme 8. CsF-Mediated Aryne-Induced Domino Synthesis of Imidazolidines

Shi group reported a chiral phosphoric acid catalyzed three component procedure for the construction of spiro[imidazolidine-2,3'-oxindole] (Scheme 9).[12] In this reaction, isatin-derived imines, aldehydes and an amino-ester involve the formation of azomethine ylides and 1,3-dipolar cycloaddition to yield the spiro-derivated imidazolidines in good yields.



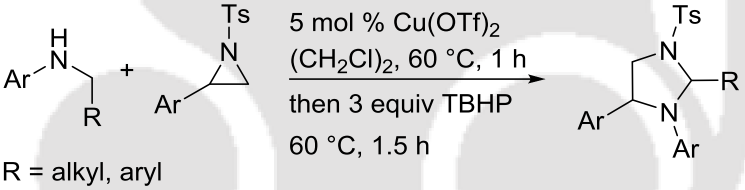
Scheme 9. Chiral Phosphoric Acid Catalyzed Three-Component Synthesis of Imidazolidines

Asymmetric cycloaddition of *N*-sulfinylimines with non-stabilized azomethine ylide has been reported for the synthesis of 2-arylbenzothiazoles using diphenyl phosphate (DPP) at 0 °C (Scheme 10).[13] The imidazolidines can be deprotected into the diamine in acidic medium.

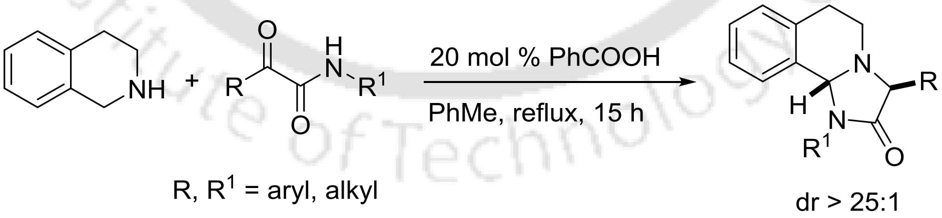


Scheme 10. Asymmetric Cycloaddition of Nonstabilized Azomethine Ylides and *N*-Sulfinylimines

Cu-catalyzed coupling of *N*-sulfonyl aziridines with *N*-alkylanilines is reported *via* the domino ring opening followed and *sp*^{3} C-H functionalization (Scheme 11).[14] This reaction involves the combination of 10 mol% Cu(OTf)$_2$ and 2 equiv. of TBHP to produce the imidazolidine in good yields.



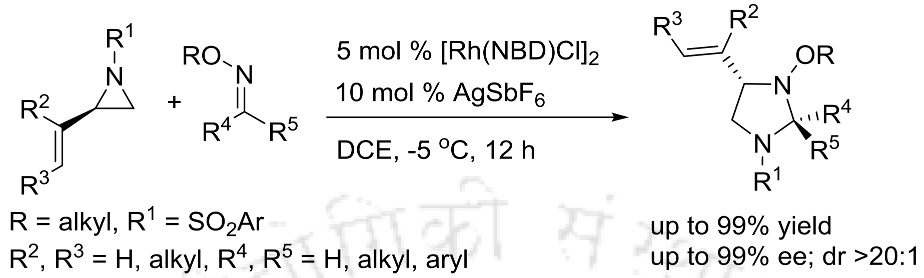
Scheme 11. Cu-Catalyzed Domino Ring Opening and Oxidative Cyclization of Activated Aziridines with *N*-Alkylanilines



Scheme 12. Synthesis of Functionalized Imidazolidines *via* Amine Redox-Annulation

Seidel group demonstrated a redox-annulation of *α*-ketoamides and cyclic secondary amines, such as 1,2,3,4-tetrahydroisoquinoline, pyrrolidine, piperidine and morpholine, to provide the polycyclic functionalized imidazolidines (Scheme 12).[15] Catalytic amount of benzoic acid accelerates this transformation.

Rh-catalyzed intermolecular [3+2]-cycloaddition of chiral vinyl aziridines and oxime ethers has been successfully developed (Scheme 13).[16] This reaction delivers enantioenriched imidazolidines with up to 99% ee by a chirality-transfer strategy.



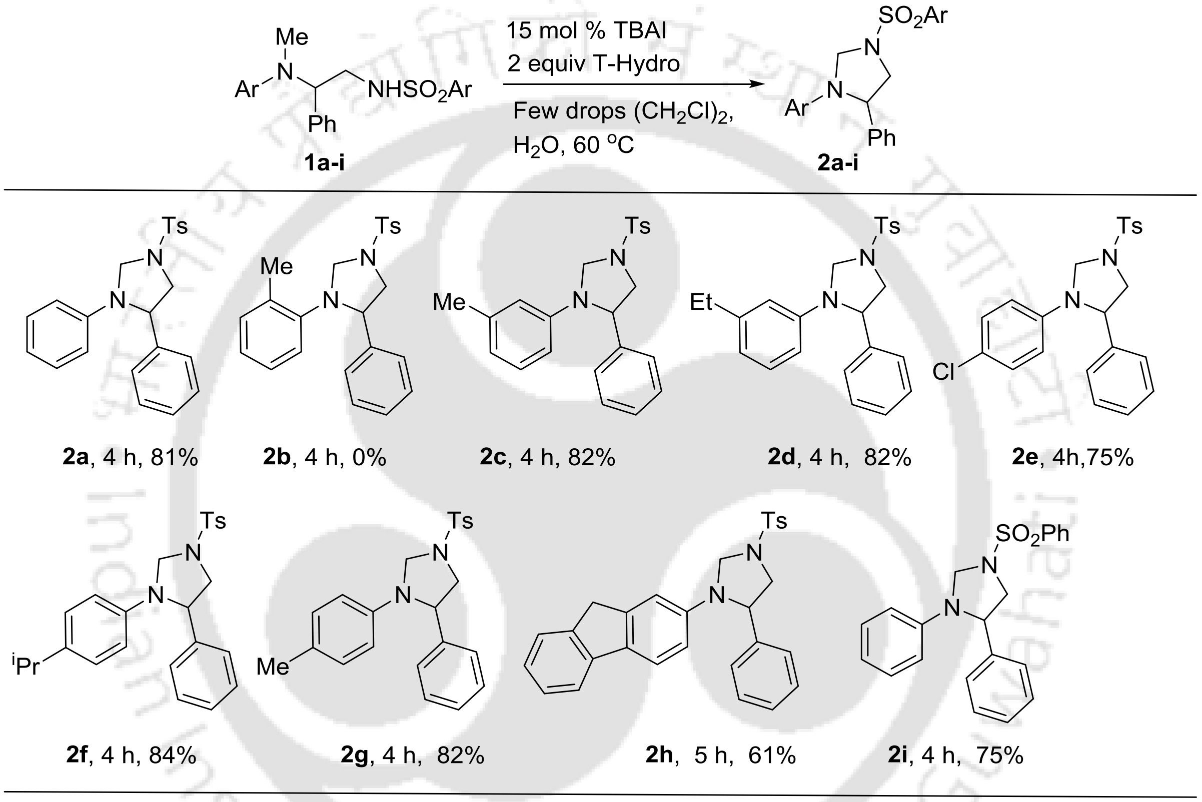
Scheme 13. Rh-Catalyzed [3+2]-Cycloaddition of Oxime Ethers with Vinyl Aziridines

2.2 Present Study

The reaction condition presented in chapter 1 was extended to the oxidative cyclization of *N*-methyl 1,2-dimines to produce substituted imidazolidines. The reaction took place efficiently to produce the imidazolidines in high yields (Table 1). The best results observed in the presence of a few drops (200 µl) of 1,2-dichloroethane (DCE), which assists the solid substrate to be gummy and float on the surface of water. The substrate **1a** underwent reaction to give imidazolidine **2a** in 81% yield. Next, the reaction of the substrates bearing substitution in *N*-aryl ring was performed. As above, the reaction of **1b** containing 2-methyl group showed no cyclization to furnish **2b**. However, the substrates **1c-d** having substitution at 3-position with methyl and ethyl functionalities afforded imidazolidines **2c-d** in 82% yield. Similarly, the substrates **1e-g** bearing substitution at 4-position with chloro, isopropyl and methyl groups underwent cyclization to afford the imidazolidines **2e-g** in 75-84% yields, whereas **1h** with *N*-fluorene furnished **2h** in 61% yield. In addition, the substrate **1i** having *N*-phenylsulfonyl substituent underwent reaction to furnish the imidazolidine **2i** in 75% yield.

Next, the reaction of the substrates with substitution in 2-aryl ring was pursued (Table 2). The substrates **1j-k** bearing substitution at 2-position with chloro and methyl groups produced imidazolidines **2j** and **2k** in 76 and 73% yields, respectively. The reaction of **1l-m** having substitution at 3-position with bromo and chloro functionalities furnished imidazolidines **2l-m** in 78-80% yields. Similarly, the substrates **1n-s** containing substitution at 4-position with acetoxy, chloro, bromo, fluoro, methyl and chlormethyl groups underwent reaction to afford the imidazolidines **2n-s** in 73-81% yields. In addition, **1t** with 2,4-dimethyl group cross-coupled to give **2t** in 72% yield, whereas **1u** having naphthyl functionality furnished imidazolidine **2u** in 71% yield.

Table 1. Reaction of *N*-Aryl Substituted Substrates [a,b]



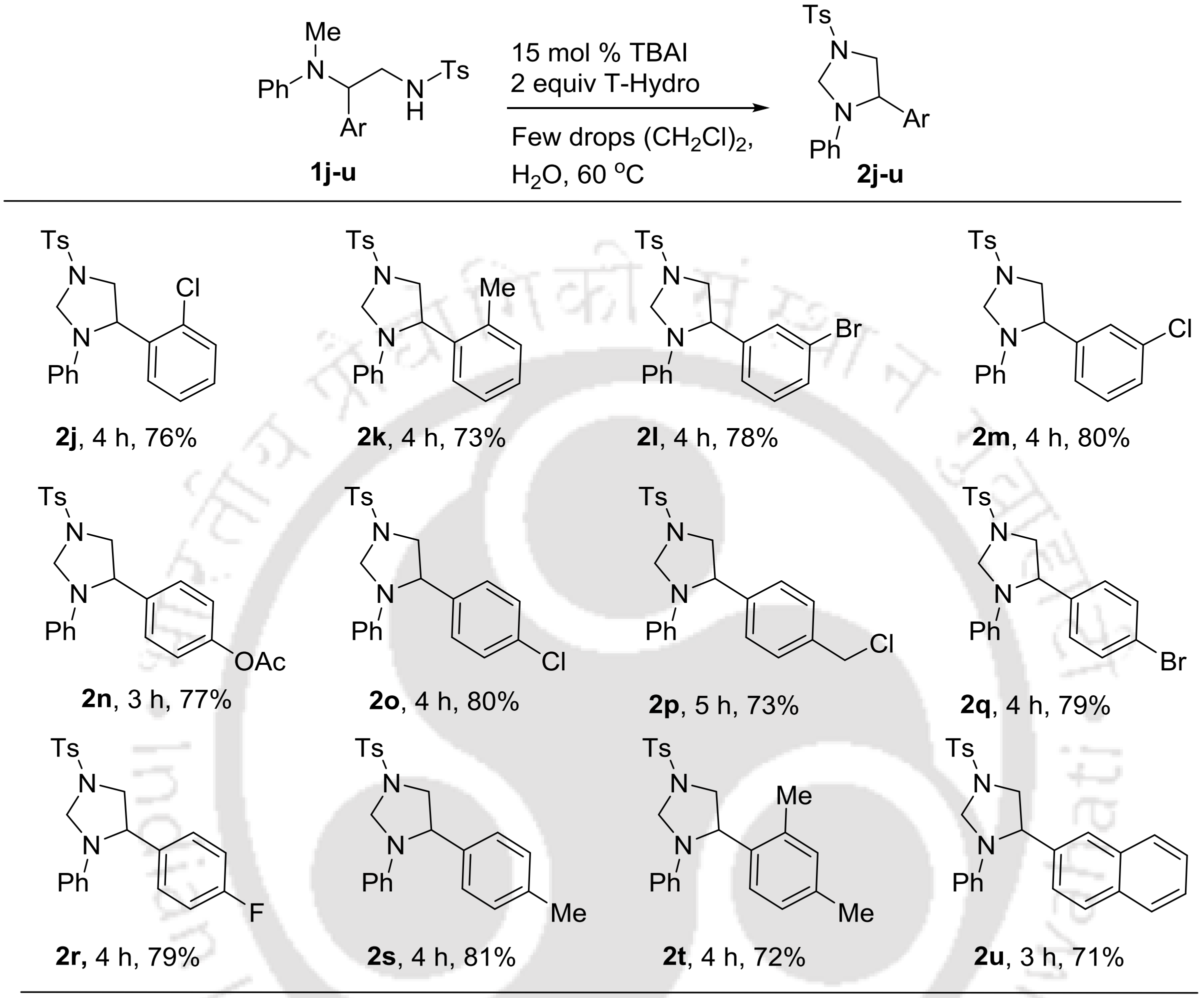
2a, 4 h, 81%
2b, 4 h, 0%
2c, 4 h, 82%
2d, 4 h, 82%
2e, 4h,75%
2f, 4 h, 84%
2g, 4 h, 82%
2h, 5 h, 61%
2i, 4 h, 75%

[a] Reaction conditions: substrate **1a-i** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), $(CH_2Cl)_2$ (few drops), H_2O (1 mL), 60 °C.

[b] Isolated yield.

Finally, the reaction of tetrahydroisoquinoline derivatives was investigated (Table 3). The substrate **1v** underwent reaction to provide imidazolidine **2v** in 63% yield. Similarly, the reaction of **1w** and **1x** bearing 2-chloro and 3-methyl groups afforded imidazolidines **2w** and **2x** in 56 and 67% yields, respectively, whereas **1y-z** bearing at 4-position with bromo and fluoro groups produced imidazolidines **2y-z** in 57-59% yields. In addition, the substrate **1aa** with 2,4-dimethyl group underwent reaction to furnish **2aa** in 62% yield, while **1ab** with *N*-phenylsulfonyl group instead of *N*-tosyl functionality cyclized to afford **2ab** in 60% yield.

Table 2. Reaction of 2-Aryl Substituted Substrates[a,b]



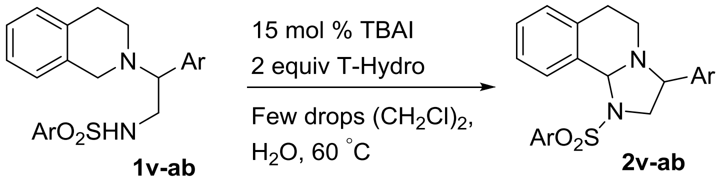
2j, 4 h, 76%
2k, 4 h, 73%
2l, 4 h, 78%
2m, 4 h, 80%
2n, 3 h, 77%
2o, 4 h, 80%
2p, 5 h, 73%
2q, 4 h, 79%
2r, 4 h, 79%
2s, 4 h, 81%
2t, 4 h, 72%
2u, 3 h, 71%

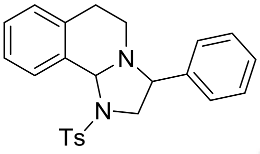
[a] Reaction condition: substrate **1j-u** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), $(CH_2Cl)_2$ (few drops), water (1 mL), 60 °C.

[b] Isolated yield.

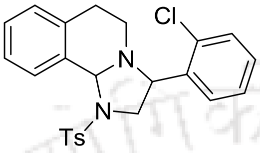
In case of optically active substrates, the reaction proceeded with high optical purities (Scheme 14). The reaction of **1a'** and **1g'** was performed as the representative examples. The reaction occured to produce **2a'** and **2g'** in 99% and 98% ee, respectively. These results suggest that the reaction provides a potential route to construct the imidazolidines in high optical purities.

Table 3. Reaction of Tetrahydroisoquinoline Derivatives[a,b]

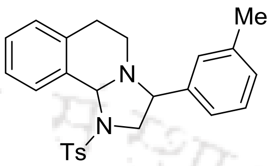




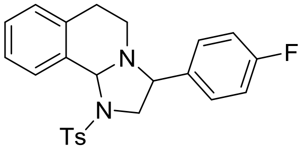
2v, 5 h, 63%



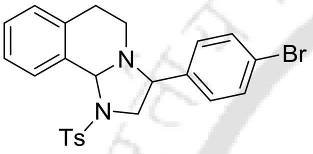
2w, 6 h, 56%



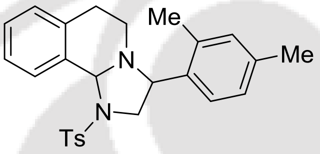
2x, 5 h, 67%



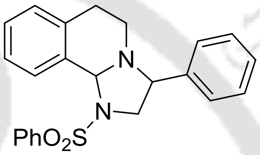
2y, 6 h, 59%



2z, 5 h, 57%



2aa, 5 h, 62%

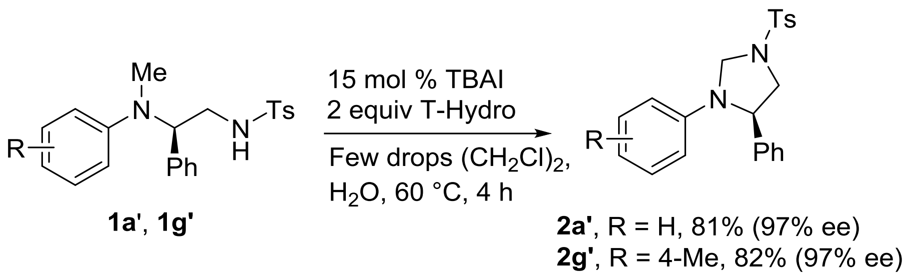


2ab, 5 h, 60%

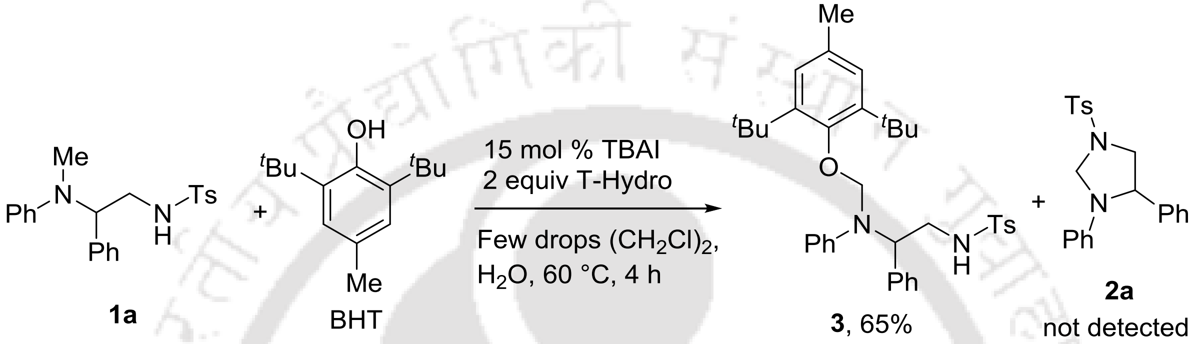
[a] Reaction conditions: substrate **1v-ab** (0.5 mmol), TBAI (15 mol %), T-Hydro (1 mmol), $(CH_2Cl)_2$ (few drops), water (1 mL), 60 °C.

[b] Isolated yield.

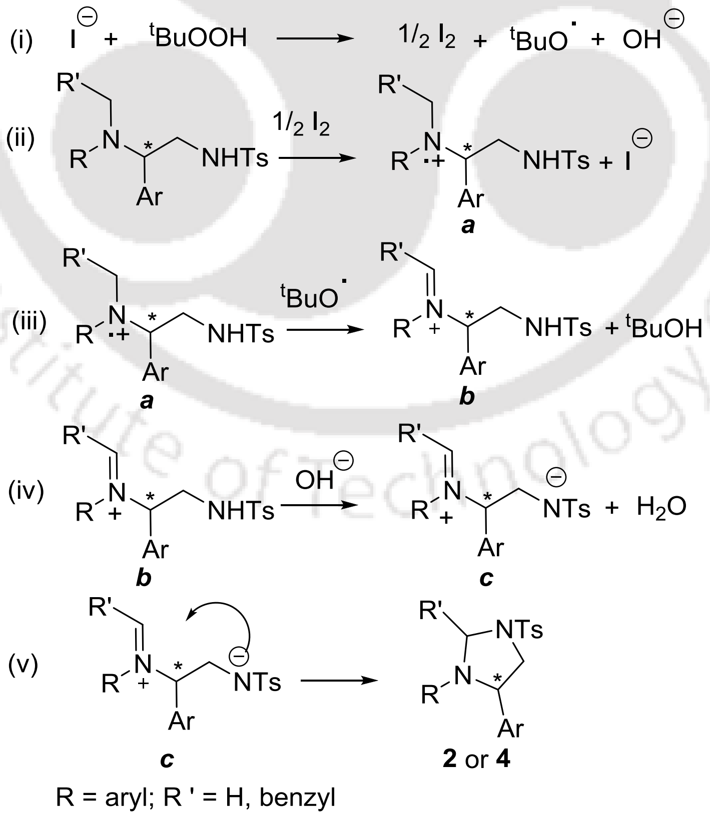
To get insight into the catalytic pathway, the reaction of **1a** was performed with BHT (Scheme 15) and BHT adduct **3** was formed as the sole product in 65% yield, which suggests that the reaction involves a radical intermediate. Thus, the oxidation of TBAI by T-Hydro may give iodine, *tert*-butoxyl radical and hydroxyl ion (Scheme 16, step i). Single electron transfer (SET) reduction of iodine may regenerate the catalyst with the formation of the radical cation **a** (Scheme 16, step ii). Homolysis of methyl C-H bond is induced by *tert*-butoxyl radical may give the iminium **b**, which may convert into the target heterocycles **2** *via* the intermediate **c** (Scheme 16, steps iv and v). The tertiary benzylic C-H bond is intact, which may be due to its steric hindrance towards the *tert*-butoxyl radical compared to that of the methyl C-H bond. In these reactions, TBAI and TBHP are dissolved in water, while the substrates **1** are floated on the surface of the water, and the mixture is stirred. After completion, the products **2** are separated out as colorless solid or liquid on the surface of



Scheme 14. Reaction of Optically Active Substrates



Scheme 15. Radical Scavenger Experiments



Scheme 16. Plausible Reaction Mechanism

water, which can be easily isolated. The reaction may take place in the interface of oil-water droplets.

In conclusion, we described the oxidative cross-coupling of *N*-alkyl C-H bond with alkyl N-H bond for the construction of the functionalized imidazolidines using TBAI in the presence of T-Hydro at moderate temperature. This process is selective and provides the imidazolidines in high yields. Chiral 1,2-*N*-methyl diamines can be cyclized in high optical purity.

2.3 Experimental Section

2.3.1 General Information. (*S*)-(+)-2-Phenylglycinol, DMAP (99%), chloramine-T and benzyltriethylammonium chloride were purchased from commercial source and used as received. Melting points were determined with a Büchi B-540 apparatus and values are uncorrected. Other general information was followed as presented in chapter 1.

2.3.2 Procedure for the Preparation of Aziridines. A solution of chloramine-T (1.1 mmol) and iodine (0.10 mmol) was added to a stirred solution of alkene (1.0 mmol) and benzyltriethylammonium chloride (0.05 mmol) in CH_2Cl_2/H_2O (2:1, 15 mL) at room temperature under N_2 and the stirring was continued for 24 h. The reaction mixture was treated with a saturated $Na_2S_2O_3$ (2 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave a residue that was purified on a silica gel (60-120 mesh) column chromatography using hexane and ethyl acetate as an eluent.

2.3.3 Procedure for the Preparation of Chiral Aziridine. To a stirred solution of (*S*)-(+)-2-phenylglycinol (1.0 mmol), TsCl (2.5 mmol) and DMAP (0.05 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (3.0 mmol) in dry CH_2Cl_2 (5 mL). The mixture was allowed to reach to room temperature and the stirring was continued for 24 h. The mixture was then treated with a saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave a residue that was purified on a silica gel (60-120 mesh) column chromatography using hexane and ethyl acetate as an eluent.

2.3.4 Procedure for the Preparation of 1,2-Diamines. A mixture of aziridine (1.0 equiv) and *N*-methylaniline (2.0 equiv.) was stirred at 100 °C. After completion, the residue was purified on silica gel column chromatography using ethyl acetate in hexane.

2.3.5 Procedure for the Synthesis of Imidazolidines 2a-ab. To substituted 1,2-diamines **1a-ab** (0.5 mmol) and 1,2-dichloroethane (three drops, ~200 µl), water (1 mL), TBAI (15 mol %) and T-hydro (1.0 mmol) were added. The substrate **1a-ab** with 1,2-dichloroethane was floated on the surface of the water, and the resultant mixture was stirred at 60 °C. The progress of the reaction was monitored by TLC using hexane and ethyl acetate as an eluent. After completion, the reaction mixture was cooled to room temperature, and treated with saturated $Na_2S_2O_3$ (500 µL) and ethyl acetate (5 mL). The organic layer was separated, dried over Na_2SO_4 and evaporated to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent.

3,4-Diphenyl-1-tosylimidazolidine 2a′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.55$; colorless solid; yield 81% (153 mg); mp 126-127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.26-7.22 (m, 5H), 7.13-7.10 (m, 4H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 6.0 Hz, 1H), 4.53 (t, *J* = 5.4 Hz, 1H), 3.92 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.46 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 144.5, 140.6, 132.9, 130.1, 129.3, 129.1, 128.0, 127.9, 126.1, 118.4, 113.2, 66.2, 61.7, 55.7, 21.8; FT-IR (KBr) 3059, 3025, 2953, 2923, 2850, 1599, 1506, 1384, 1348, 1163, 1090, 1029, 814, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{22}N_2O_2S$ 379.1475, found 379.1473; $[\alpha]_D^{20}$ = -26.0 (c= 0.2, $CHCl_3$); HPLC analysis: 97% ee [Daicel Chiralcel OD column, hexane/*i*PrOH = 85:15, flow rate: 1 mL/min, λ = 215 nm, t_R = 9.49 min (major), 17.30 min (minor)].

4-Phenyl-3-(*m*-tolyl)-1-tosylimidazolidine 2c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.56$; colorless solid; yield 82% (161 mg); mp 133-134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.25-7.22 (m, 4H), 7.11 (d, *J* = 6.0 Hz, 2H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.22 (s, 1H), 6.16 (d, *J* = 7.8 Hz, 2H), 5.06 (d, *J* = 5.4 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.54 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.89 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.45 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.40 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 144.4, 140.7, 139.1, 133.0, 130.0, 129.1, 129.0, 128.0, 127.8, 126.1, 119.4, 113.9, 110.5, 66.3, 61.6, 55.7, 21.9, 21.8; FT-IR (KBr) 3064, 3025, 2961, 2921, 2850, 1604, 1493, 1384, 1350, 1163, 1091, 1030, 813, 764 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{24}N_2O_2S$ 393.1631, found 393.1630.

3-(3-Ethylphenyl)-4-phenyl-1-tosylimidazolidine 2d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; pale yellow liquid; yield 82% (166 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.25-7.21 (m, 5H), 7.11 (d, *J* = 6.0 Hz, 2H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.23 (s, 1H), 6.18 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 5.4 Hz, 1H), 4.54 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.91 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.46 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.52 (q, *J* = 7.8 Hz, 2H), 2.40 (s, 3H), 1.12 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 145.1, 144.4, 140.8, 133.0, 130.0, 129.2, 129.0, 128.0, 127.8, 126.1, 118.2, 112.9, 110.8, 66.3, 61.8, 55.7, 29.3, 21.8, 15.7; FT-IR (neat) 3059, 3025, 2925, 2848, 1599, 1504, 1354, 1163, 1091, 816, 746 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{24}H_{26}N_2O_2S$ 407.1788, found 407.1791.

3-(4-Chlorophenyl)-4-phenyl-1-tosylimidazolidine 2e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; pale yellow liquid; yield 75% (155 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (m, 5H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.27 (d, *J* = 9.0 Hz, 2H), 4.98 (d, *J* = 6.0 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.45 (t, *J* = 6.6 Hz, 1H), 3.97 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.43 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 140.0, 133.1, 130.1, 129.2, 129.1, 128.1, 128.0, 126.0, 123.4, 114.3, 66.3, 61.8, 55.8, 21.8; FT-IR (neat) 3067, 3025, 2925, 2889, 2820, 1601, 1507, 1346, 1162, 1024, 785, 748 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{22}H_{21}ClN_2O_2S$ 413.1085, found 413.1079.

3-(4-Isopropylphenyl)-4-phenyl-1-tosylimidazolidine 2f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; yield 84% (176 mg); mp 140-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.26-7.23 (m, 5H), 7.15 (d, *J* = 6.6 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.37 (d, *J* = 8.4 Hz, 2H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.72 (d, *J* = 6.0 Hz, 1H), 4.53 (t, *J* = 6.6 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 1H), 3.46 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.80-2.76 (m, 1H), 2.41 (s, 3H), 1.19 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.4, 143.2, 140.8, 138.9, 132.9, 130.0, 129.0, 127.8, 127.1, 126.1, 113.3, 66.5, 62.0, 55.7, 33.2, 24.3, 21.7; FT-IR (KBr) 3064, 3028, 2957, 2928, 2867, 1615, 1519, 1454, 1351, 1164, 1095, 814, 700 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{25}H_{28}N_2O_2S$ 421.1944, found 421.1945.

4-Phenyl-3-(*p*-tolyl)-1-tosylimidazolidine 2g′. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; colorless solid; yield 82% (161 mg); mp 141-142 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.24-7.20 (m, 5H), 7.10 (d, *J* = 6.0 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.31 (d, *J* = 8.4 Hz, 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.70 (d, *J* = 6.0 Hz, 1H), 4.51 (t, *J* = 6.6 Hz, 1H), 3.91 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.42 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.40 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 144.4, 142.9, 140.7, 133.0, 130.0, 129.8, 129.0, 128.0, 127.8, 126.1, 113.5, 66.6, 61.9, 55.7, 21.8, 20.5; FT-IR (KBr) 3059, 3028, 2923, 2860, 1619, 1521, 1384, 1350, 1163, 1094, 1030, 804, 760 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{24}N_2O_2S$ 393.1631, found 393.1633; $[\alpha]_D^{20}$ = -8.0 (c= 0.2, CHCl$_3$); HPLC analysis: 97% ee [Daicel Chiralcel OD column, hexane/*i*PrOH = 85:15, flow rate: 1 mL/min, λ = 215 nm, t_R = 8.25 min (major), 10.57 min (minor)].

3-(9*H*-Fluoren-2-yl)-4-phenyl-1-tosylimidazolidine 2h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colorless solid; yield 61% (142 mg); mp 232-233 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.70 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.30-7.22 (m, 6H), 7.19-7.13 (m, 3H), 6.58 (s, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 5.4 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 1H), 4.59 (t, *J* = 6.0 Hz, 1H), 3.95 (t, *J* = 8.4 Hz, 1H), 3.74 (s, 2H), 3.48 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 145.1, 144.5, 144.4, 142.4, 142.0, 140.6, 133.1, 132.8, 130.1, 129.1, 128.0, 127.9, 126.9, 126.1, 125.5, 124.9, 120.6, 118.9, 112.2, 110.0, 66.5, 61.8, 55.8, 37.2, 21.8; FT-IR (KBr) 3062, 3027, 2956, 2923, 2853, 1616, 1492, 1457, 1384, 1349, 1162, 1092, 1027, 812, 764 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{29}H_{26}N_2O_2S$ 467.1788, found 467.1790.

3,4-Diphenyl-1-(phenylsulfonyl)imidazolidine 2i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; yield 75% (137 mg); mp 125-126 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.81 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.24-7.20 (m, 3H), 7.12-7.10 (m, 4H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 2H), 5.05

(d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.51 (t, *J* = 6.6 Hz, 1H), 3.92 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.46 (dd, *J* = 10.2, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 140.5, 136.0, 133.5, 129.4, 129.3, 129.1, 128.0, 127.9, 126.0, 118.5, 113.3, 66.2, 61.7, 55.7; FT-IR (KBr) 3062, 3028, 2928, 2857, 1600, 1506, 1446, 1351, 1166, 1095, 1030, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{20}N_2O_2S$ 365.1318, found 365.1319.

4-(2-Chlorophenyl)-3-phenyl-1-tosylimidazolidine 2j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; yield 76% (157 mg); mp 120-121 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.20-7.16 (m, 3H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.03 (t, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.28 (d, *J* = 8.4 Hz, 2H), 5.09 (d, *J* = 6.0 Hz, 1H), 4.84 (dd, *J* = 7.8, 4.2 Hz, 1H), 4.74 (d, *J* = 6.0 Hz, 1H), 4.00 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.54 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.5, 144.4, 137.6, 132.9, 132.3, 130.1, 129.9, 129.4, 129.0, 128.0, 127.5, 127.4, 118.6, 112.9, 66.0, 59.0, 54.1, 21.7; FT-IR (KBr) 3061, 2956, 2923, 2848, 1600, 1506, 1384, 1352, 1164, 1092, 1032, 814, 750, 664 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}ClN_2O_2S$ 413.1085, found 413.1083.

3-Phenyl-4-(*o*-tolyl)-1-tosylimidazolidine 2k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; yield 73% (143 mg); mp 144-145 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.17-7.11 (m, 4H), 7.00-6.96 (m, 2H), 6.73 (t, *J* = 7.2 Hz, 1H), 6.29 (d, *J* = 8.4 Hz, 2H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.61 (t, *J* = 7.2 Hz, 1H), 4.01 (t, *J* = 9.6 Hz, 1H), 3.39 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 144.5, 137.9, 134.2, 133.0, 130.9, 130.0, 129.2, 127.9, 127.5, 126.8, 125.4, 118.3, 113.0, 66.2, 58.8, 54.3, 21.7, 19.4; FT-IR (KBr) 3061, 3025, 2925, 2856, 1599, 1506, 1384, 1350, 1164, 1094, 1032, 814, 750 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{24}N_2O_2S$ 393.1631, found 393.1631.

4-(3-Bromophenyl)-3-phenyl-1-tosylimidazolidine 2l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.53; colorless solid; yield 78% (178 mg); mp 130-131 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.24-7.23 (m, 3H), 7.15-7.11 (m, 3H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 2H), 5.05 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.49 (t, *J* = 6.0 Hz, 1H), 3.90 (t, *J* = 9.6 Hz, 1H), 3.47 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 144.6, 143.2, 132.9, 131.1, 130.7, 130.1, 129.4, 129.1, 127.9, 124.8, 123.2, 118.8, 113.2, 66.2, 61.2, 55.5, 21.8; FT-IR (KBr) 3070, 3022, 2920, 2817, 1600, 1507, 1385, 1346, 1161, 1088, 1024, 847, 747, 665 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}BrN_2O_2S$ 457.0580, found 457.0584.

4-(3-Chlorophenyl)-3-phenyl-1-tosylimidazolidine 2m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; yield 80% (165 mg); mp 140-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.24-7.17 (m, 4H), 7.16-7.13 (m, 2H), 7.07 (s, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.77 (t, *J* = 7.2 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 2H), 5.07 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.51 (t, *J* = 6.6 Hz, 1H), 3.93 (t, *J* = 10.2 Hz, 1H), 3.48 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 144.6, 142.9, 134.9, 132.9, 130.3, 130.0, 129.3, 128.0, 127.9, 126.1, 124.3, 118.7, 113.2, 66.1, 61.2, 55.4, 21.7; FT-IR (KBr) 3061, 3028, 2925, 2889, 2820, 1601, 1508, 1346, 1162, 1027, 849, 758, 667 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}ClN_2O_2S$ 413.1085, found 413.1084.

4-(3-Phenyl-1-tosylimidazolidin-4-yl)phenyl acetate 2n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; pale yellow liquid; yield 77% (168 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.13-7.11 (m, 4H), 6.97 (d, *J* = 7.2 Hz, 2H), 6.74 (t, *J* = 6.6 Hz, 1H), 6.37 (d, *J* = 7.2 Hz, 2H), 5.02 (d, *J* = 5.4 Hz, 1H), 4.74 (d, *J* = 4.8 Hz, 1H), 4.54 (t, *J* = 4.8 Hz, 1H), 3.91 (t, *J* = 8.4 Hz, 1H), 3.44 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 150.2, 144.9, 144.6, 138.0, 132.9, 130.1, 129.4, 128.0, 127.1, 122.2, 118.6, 113.3, 66.2, 61.2, 55.6, 21.7, 21.3; FT-IR (neat) 3028, 2923, 2854, 1758, 1600, 1504, 1351, 1197, 1163, 1015, 912, 752, 666, 599 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{24}N_2O_4S$ 437.1530, found 437.1532.

4-(4-Chlorophenyl)-3-phenyl-1-tosylimidazolidine 2o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.53; colorless solid; yield 80% (165 mg); mp 170-171 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.23-7.19 (m, 4H), 7.13 (t, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 2H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.53 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.90 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.46 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.7, 144.6, 139.2, 133.6, 133.1, 130.1, 129.4, 129.2, 128.0, 127.5, 118.7, 113.2, 66.1, 61.1, 55.6, 21.8; FT-IR (KBr) 3065, 3035, 2922, 2852, 1599, 1506, 1350, 1163, 1091, 813, 778, 664 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}ClN_2O_2S$ 413.1085, found 413.1085.

4-(4-(Chloromethyl)phenyl)-3-phenyl-1-tosylimidazolidine 2p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; yield 73% (156 mg); mp 173-174 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.27-7.23 (m, 4H), 7.13-7.10 (m, 4H), 6.74 (t, *J* = 6.6 Hz, 1H), 6.36 (d, *J* = 7.2 Hz, 2H), 5.03 (d, *J* = 4.8 Hz, 1H), 4.74 (d, *J* = 5.4 Hz, 1H), 4.54 (s, 3H), 3.91 (t, *J* = 7.8 Hz, 1H), 3.45 (dd, *J* = 10.8, 4.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.8, 144.5, 141.0, 137.1, 133.0, 130.1, 129.4, 128.0, 126.5, 118.6, 113.2, 66.2, 61.4, 55.6, 46.0, 21.8; FT-IR (KBr) 3053, 2965, 2921, 2822, 1600, 1508, 1386, 1347, 1161, 1092, 1028, 816, 744, 667 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{23}ClN_2O_2S$ 427.1242, found 427.1240.

4-(4-Bromophenyl)-3-phenyl-1-tosylimidazolidine 2q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.53; colorless solid; yield 79% (180 mg); mp 179-180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 2H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.52 (t, *J* = 4.8 Hz, 1H), 3.91 (dd, *J* = 10.8, 7.8 Hz, 1H), 3.47 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.6, 142.0, 139.7, 133.1, 132.1, 130.0, 129.4, 127.9, 127.8, 121.6, 118.7, 113.2, 66.1, 61.1, 55.5, 21.8; FT-IR (KBr) 3075, 3019, 2897, 2812, 1600, 1504, 1381, 1343, 1158, 1029, 816, 748, 667 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}BrN_2O_2S$ 457.0580, found 457.0583.

4-(4-Fluorophenyl)-3-phenyl-1-tosylimidazolidine 2r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; yield 79% (156 mg); mp 181-182 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 2H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 2H), 5.05 (d, *J* = 5.4 Hz, 1H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.54 (t, *J* = 6.6 Hz, 1H), 3.89 (t, *J* = 9.6 Hz, 1H), 3.45 (dd, *J* = 10.2, 4.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1 (d, $J_{C\text{-}F}$ = 244.5 Hz), 144.7, 144.6, 136.3, 133.0, 130.0, 129.3, 128.0, 127.7

(d, $J_{C\text{-}F}$ = 9.0 Hz), 118.6, 116.0 (d, $J_{C\text{-}F}$ = 22.5), 113.2, 66.1, 61.0, 55.7, 21.7; FT-IR (KBr) 3058, 2923, 2892, 2821, 1601, 1508, 1384, 1346, 1161, 1028, 829, 750, 666 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{22}H_{21}FN_2O_2S$ 397.1381, found 397.1384.

3-Phenyl-4-(*p*-tolyl)-1-tosylimidazolidine 2s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; yield 81% (159 mg); mp 147-148 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 6.0 Hz, 1H), 4.75 (d, *J* = 6.0 Hz, 1H), 4.49 (t, *J* = 6.0 Hz, 1H), 3.90 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.43 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.40 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 144.4, 137.5, 133.0, 130.0, 129.7, 129.3, 128.0, 126.0, 118.4, 113.2, 66.2, 61.4, 55.9, 21.8, 21.3; FT-IR (KBr) 3060, 3029, 2922, 2855, 1599, 1506, 1350, 1163, 1093, 814, 749, 664 cm^{-1} HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{23}H_{24}N_2O_2S$ 393.1631, found 393.1633.

4-(2,4-Dimethylphenyl)-3-phenyl-1-tosylimidazolidine 2t. Analytical TLC on silica gel, 1:9 ethyl acetate/ hexane R_f = 0.56; colorless solid; yield 72% (146 mg); mp 162-163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.97 (s, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.27 (d, *J* = 8.4 Hz, 2H), 5.02 (d, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 6.0 Hz, 1H), 4.56 (t, *J* = 6.6 Hz, 1H), 3.97 (dd, *J* = 10.2, 7.2 Hz, 1H), 3.34 (dd, *J* = 10.8, 6.0 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 144.5, 137.2, 134.9, 134.1, 133.1, 131.7, 130.0, 129.3, 128.0, 127.5, 125.5, 118.2, 113.0, 66.2, 58.8, 54.5, 21.7, 21.2, 19.4; FT-IR (KBr) 3065, 3041, 2921, 2855, 1600, 1506, 1384, 1350, 1164, 1092, 1032, 814, 748, 664 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{24}H_{26}N_2O_2S$ 407.1788, found 407.1782.

4-(Naphthalen-2-yl)-3-phenyl-1-tosylimidazolidine 2u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless solid; yield 71% (152 mg); mp 166-167 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80-7.79 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.69-7.65 (m, 3H), 7.51 (s, 1H), 7.46-7.45 (m, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 2H), 6.72 (t, *J* = 7.2 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 2H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 1H), 4.71 (t, *J* = 5.4 Hz, 1H), 4.02 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.58 (dd, *J* = 10.8, 5.4

Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 144.5, 138.0, 133.4, 133.4, 133.1, 129.9, 129.3, 129.1, 128.0, 127.9, 127.8, 126.5, 126.2, 125.0, 123.9, 118.5, 113.2, 66.2, 61.8, 55.6, 21.7; FT-IR (KBr) 3058, 3047, 2928, 2810, 1599, 1506, 1343, 1158, 1030, 815, 745, 666 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{24}N_2O_2S$ 429.1631, found 429.1628.

3-Phenyl-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 63% (127 mg); mp 137-138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 7.26-7.20 (m, 4H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 2H), 5.94 (s, 1H), 4.10 (t, *J* = 8.4 Hz, 1H), 3.70 (t, *J* = 8.4 Hz, 1H), 3.18 (t, *J* = 9.6 Hz, 1H), 3.16-3.08 (m, 1H), 2.94-2.88 (m, 1H), 2.75-2.72 (m, 1H), 2.53 (s, 3H), 2.40 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 138.8, 134.9, 134.1, 129.9, 129.2, 128.8, 128.6, 128.3, 127.7, 127.6, 127.2, 76.5, 60.9, 55.7, 41.5, 21.9, 21.4; FT-IR (KBr) 3056, 3028, 2950, 2924, 2861, 1598, 1453, 1344, 1157, 1090, 1005, 817, 759, 665 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{24}N_2O_2S$ 405.1631, found 405.1633.

3-(2-Chlorophenyl)-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; colorless solid; yield 56% (123 mg); mp 145-146 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.35-7.31 (m, 3H), 7.30-7.24 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.01 (s, 1H), 4.59 (t, *J* = 7.8 Hz, 1H), 3.87 (t, *J* = 9.0 Hz, 1H), 3.17-3.13 (m, 2H), 2.99-2.92 (m, 1H), 2.78-2.75 (m, 1H), 2.50 (s, 3H), 2.41 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.9, 137.4, 134.6, 134.5, 134.4, 134.0, 129.9, 129.5, 128.9, 128.7, 128.4, 127.9, 127.8, 127.2, 127.1, 76.4, 56.8, 53.8, 41.9, 21.8, 21.5; FT-IR (KBr) 3061, 3022, 2953, 2923, 2850, 1597, 1453, 1347, 1159, 1090, 999, 814, 752, 664 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{23}ClN_2O_2S$ 439.1242, found 439.1243.

3-(*m*-Tolyl)-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless solid; yield 67% (140 mg); mp 151-152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 1H) 7.25 (d, *J* = 7.2 Hz, 1H), 7.11-7.04 (m, 3H), 6.70 (d, *J* = 7.2 Hz, 1H), 6.60 (s, 1H), 5.94 (s, 1H), 4.06 (t, *J* = 8.4 Hz, 1H), 3.68 (t, *J* = 8.4 Hz, 1H), 3.16 (t, *J* = 9.6 Hz, 1H), 3.12-3.07 (m, 1H), 2.94-2.88 (m, 1H), 2.75-2.72 (m, 1H), 2.53 (s, 3H), 2.39 (d, *J* = 16.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 138.9, 138.5, 134.9, 134.2, 134.1, 129.9, 129.2, 129.1, 128.7, 128.6, 128.5, 128.1, 127.7, 127.2, 125.0, 76.6, 60.8, 55.7, 41.5, 21.9, 21.5, 21.4; FT-IR (KBr) 3056, 3025, 2959, 2923, 2851, 1598, 1492, 1453, 1345, 1159, 1091, 1004, 815, 751, 666 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{26}N_2O_2S$ 419.1788, found 419.1789.

3-(4-Fluorophenyl)-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; yield 59% (124 mg); mp 150-151 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 2H), 6.82-6.80 (m, 2H), 5.93 (s, 1H), 4.08 (t, *J* = 7.2 Hz, 1H), 3.68 (t, *J* = 7.8 Hz, 1H), 3.13-3.08 (m, 2H), 2.92-2.86 (m, 1H), 2.72-2.68 (m, 1H), 2.53 (s, 3H), 2.41 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.5 (d, $J_{C\text{-}F}$ = 244.5 Hz), 144.1, 134.8, 134.6, 134.2, 134.0, 129.9, 129.2 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.6, 128.5, 127.8, 127.3, 115.7 (d, $J_{C\text{-}F}$ = 21.0 Hz), 76.5, 60.2, 55.6, 41.5, 21.9, 21.4; FT-IR (KBr) 3062, 3024, 2928, 2901, 1601, 1509, 1453, 1344, 1224, 1159, 1013, 838, 816, 754, 673 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{23}FN_2O_2S$ 423.1537, found 423.1538.

3-(4-Bromophenyl)-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; colorless solid; yield 57% (137 mg); mp 148-149 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.34-7.31 (m, 3H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.93 (s, 1H), 4.06 (t, *J* = 7.8 Hz, 1H), 3.68 (t, *J* = 9.6 Hz, 1H), 3.12-3.09 (m, 2H), 2.89-2.86 (m, 1H), 2.71-2.68 (m, 1H), 2.53 (s, 3H), 2.41 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.2, 138.1, 134.7, 134.1, 131.9, 129.9, 129.3, 129.2, 128.6, 128.5, 127.9, 127.3, 122.0, 76.5, 60.3, 55.4, 41.6, 21.9, 21.4; FT-IR

(KBr) 3054, 3021, 2923, 2852, 1597, 1486, 1345, 1158, 1010, 818, 749, 667 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{23}BrN_2O_2S$ 483.0736, found: 483.0737.

3-(2,4-Dimethylphenyl)-1-tosyl-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; colorless solid; yield 62% (134 mg); mp 161-162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 2H), 7.39-7.35 (m, 3H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.92 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.96 (s, 1H), 4.35 (t, *J* = 7.8 Hz, 1H), 3.75 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.15-3.06 (m, 2H), 2.87-2.79 (m, 2H), 2.54 (s, 3H), 2.41 (d, *J* = 13.8, 1H), 2.29 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.0, 137.1, 136.3, 135.0, 134.2, 133.8, 131.3, 129.9, 129.2, 128.6, 128.5, 127.7, 127.3, 127.2, 126.5, 76.2, 56.5, 54.5, 41.6, 21.9, 21.8, 21.1, 19.4; FT-IR (KBr) 3062, 3021, 2922, 2853, 1598, 1452, 1347, 1159, 1010, 816, 748, 664 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{28}N_2O_2S$ 433.1944, found 433.1941.

3-Phenyl-1-(phenylsulfonyl)-1,2,3,5,6,10b-hexahydroimidazo[2,1-*a*]isoquinoline 2ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 60% (117 mg); mp 140-141 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97-7.95 (m, 3H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.26-7.20 (m, 4H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 5.96 (s, 1H), 4.11 (t, *J* = 7.8 Hz, 1H), 3.71 (t, *J* = 7.8 Hz, 1H), 3.17 (t, *J* = 9.0 Hz, 1H), 3.12-3.08 (m, 1H), 2.93-2.88 (m, 1H), 2.75-2.71 (m, 1H), 2.40 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 137.0, 134.8, 134.1, 133.3, 129.3, 129.2, 128.8, 128.6, 128.5, 128.3, 127.8, 127.6, 127.3, 76.6, 60.8, 55.7, 41.5, 21.4; FT-IR (KBr) 3061, 3027, 2953, 2923, 1606, 1446, 1349, 1161, 1011, 754, 721, 603 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{22}N_2O_2S$ 391.1475, found 391.1486.

2.4 References

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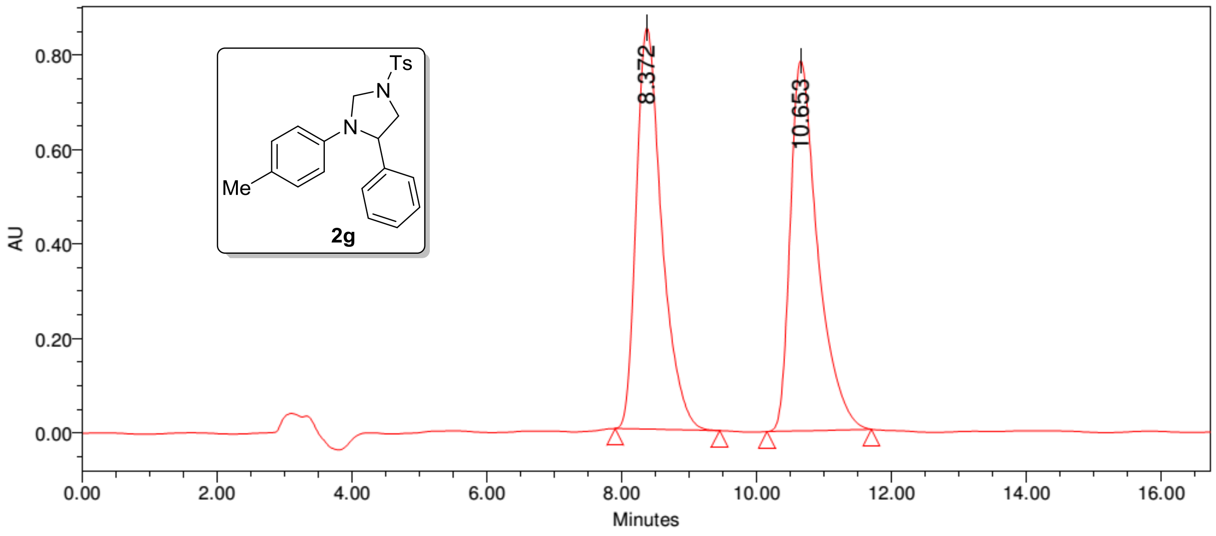
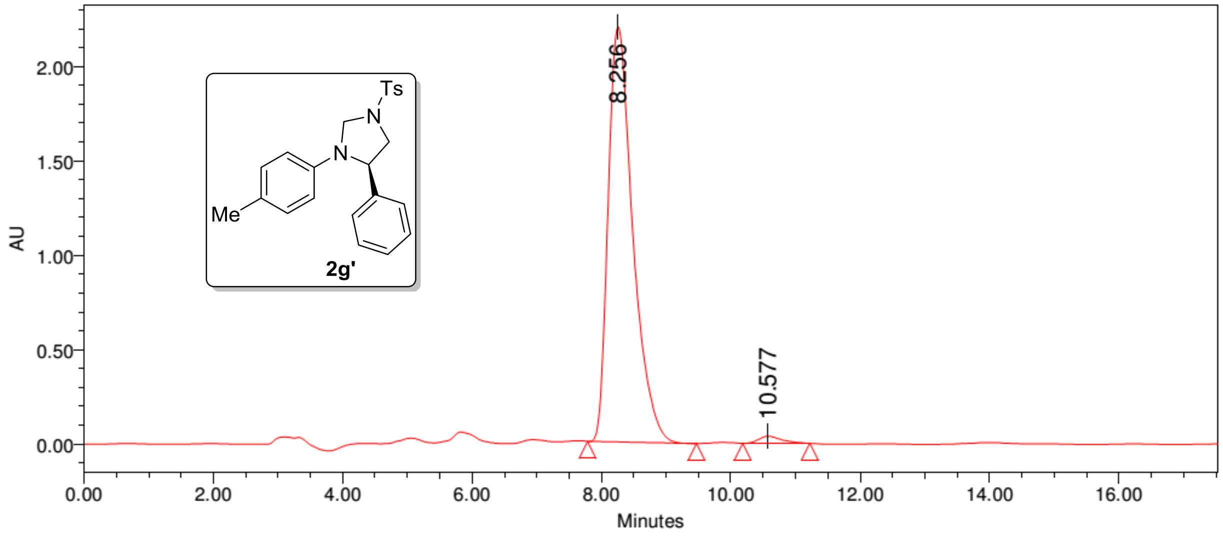
2.5 Selected HPLC Chromatograms



Peak Results

	RT	Height (µV)	% Area
1	8.372	850044	50.08
2	10.653	784687	49.92



Peak Results

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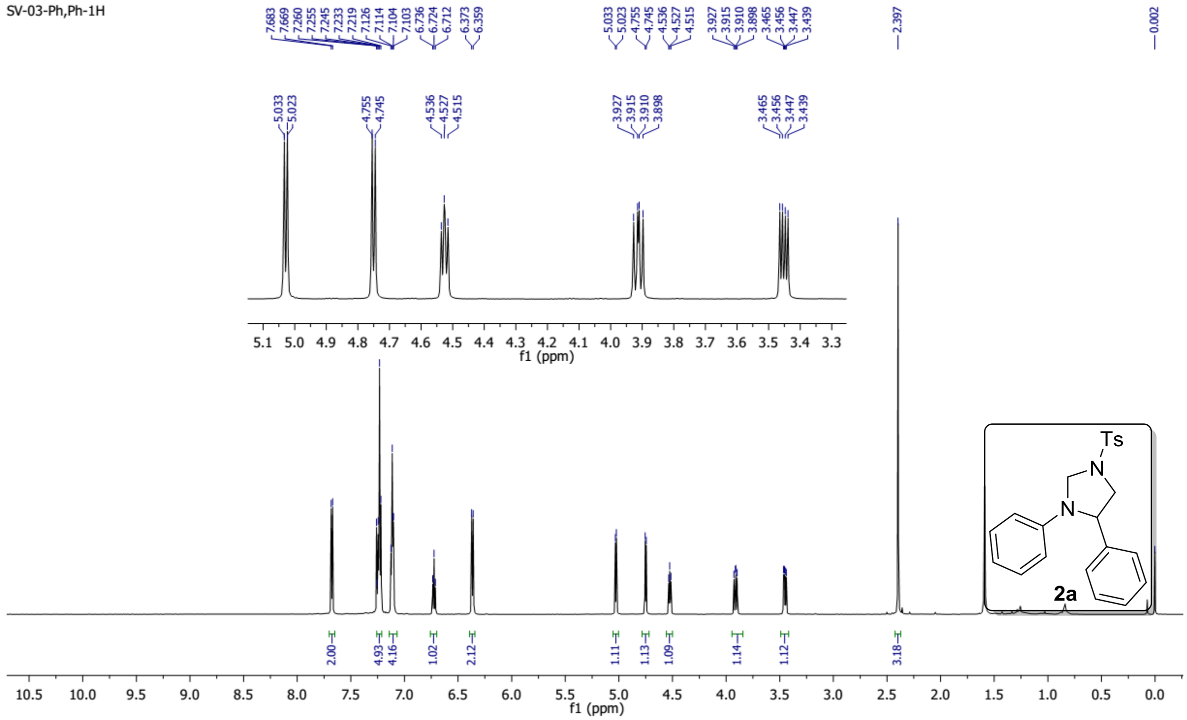
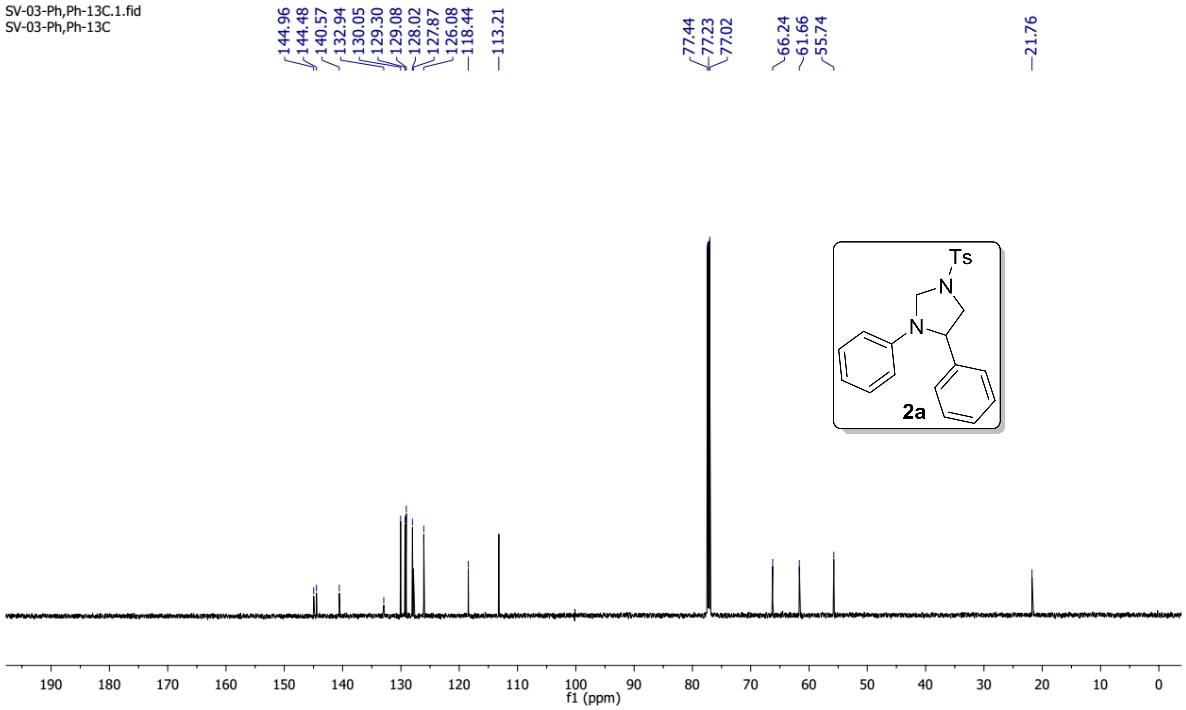
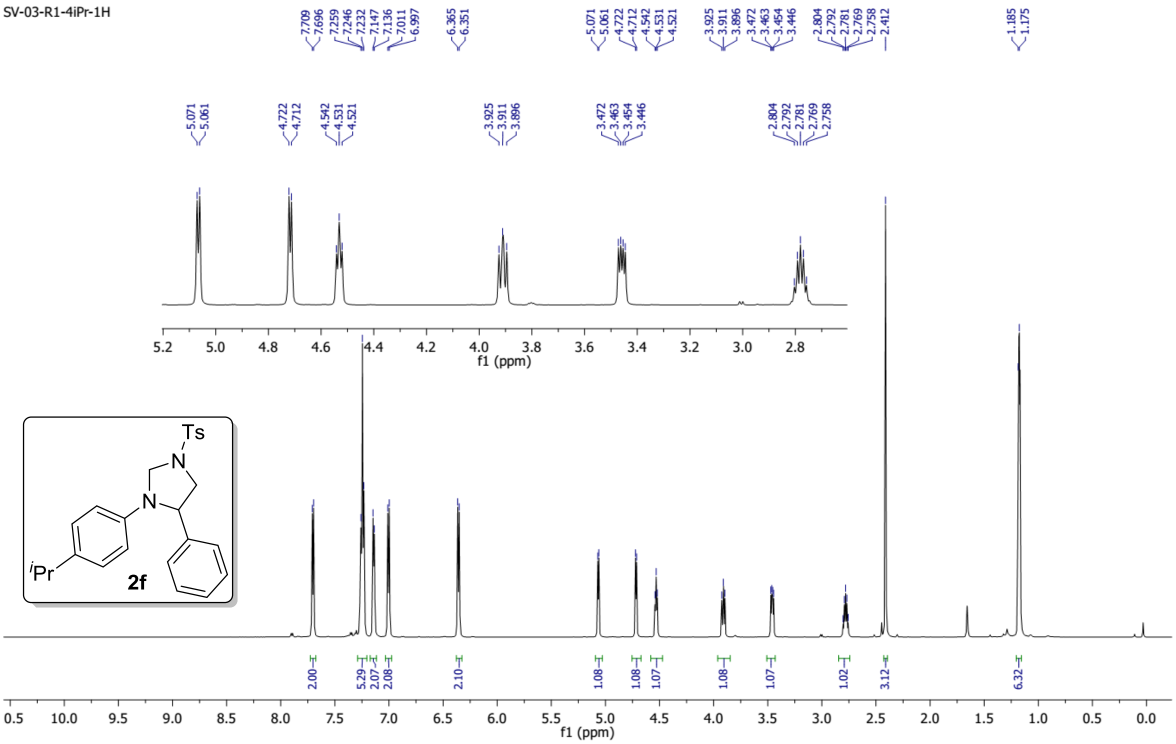
1	8.256	2202403	98.44
2	10.577	37431	1.56

2.6 Selected NMR Spectra



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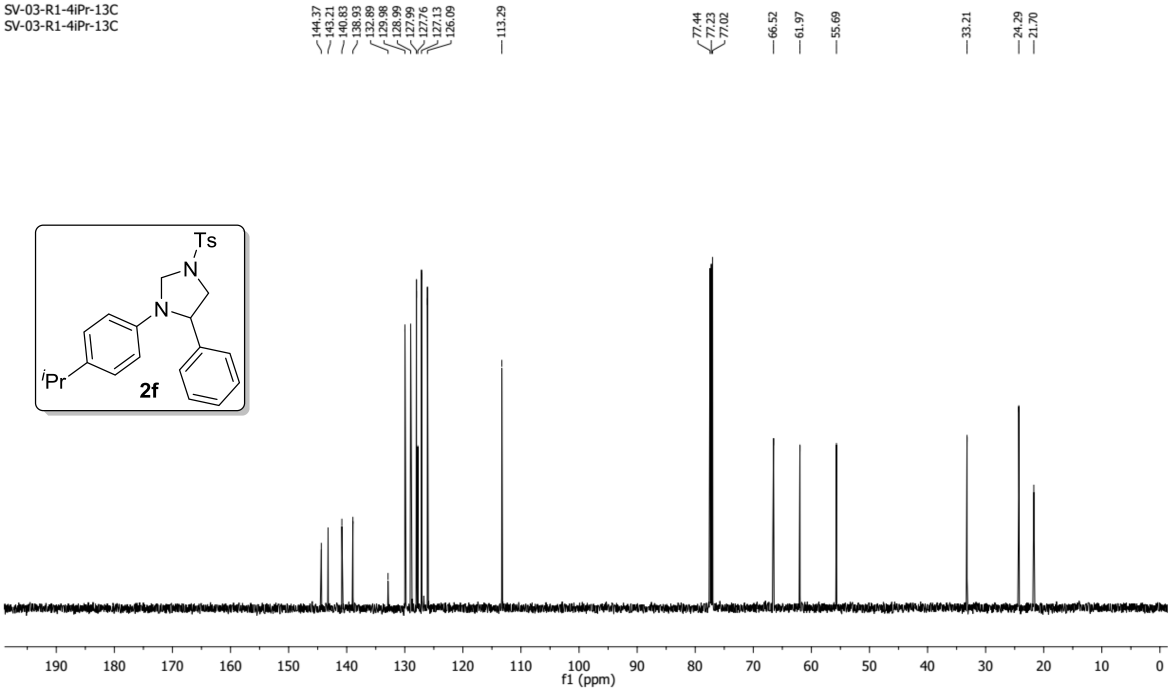
7.696
7.259
7.246
7.232
7.147
7.136
7.011
6.997
6.365
6.351
5.071
5.061
4.722
4.712
4.542
4.531
4.521
3.925
3.911
3.896
3.472
3.463
3.454
3.446
2.804
2.792
2.781
2.769
2.758
2.412
1.185
1.175
2.00
5.29
2.07
2.08
2.10
1.08
1.08
1.07
1.08
1.07
1.02
3.12
6.32
f1 (ppm)
Ts
N
N
^{i}Pr
2f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SV-03-R1-4iPr-13C
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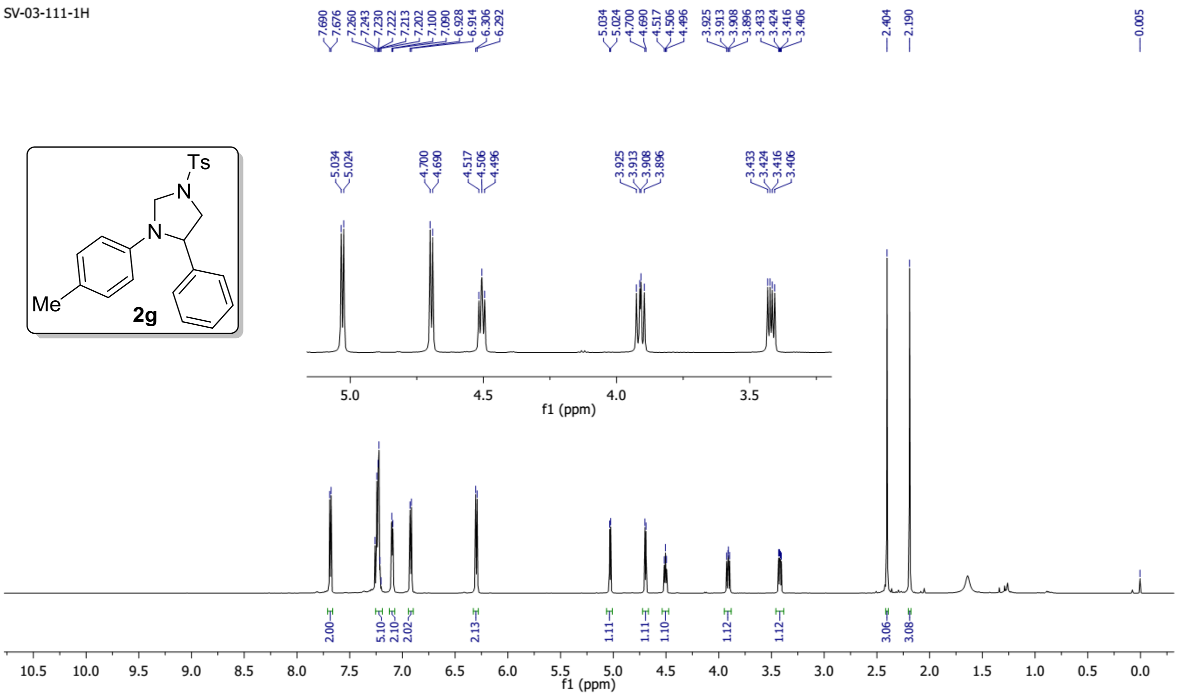
143.21
140.83
138.93
132.89
129.98
128.99
127.99
127.76
127.13
126.09
113.29
77.44
77.23
77.02
66.52
61.97
55.69
33.21
24.29
21.70
f1 (ppm)
Ts
N
N
^{i}Pr
2f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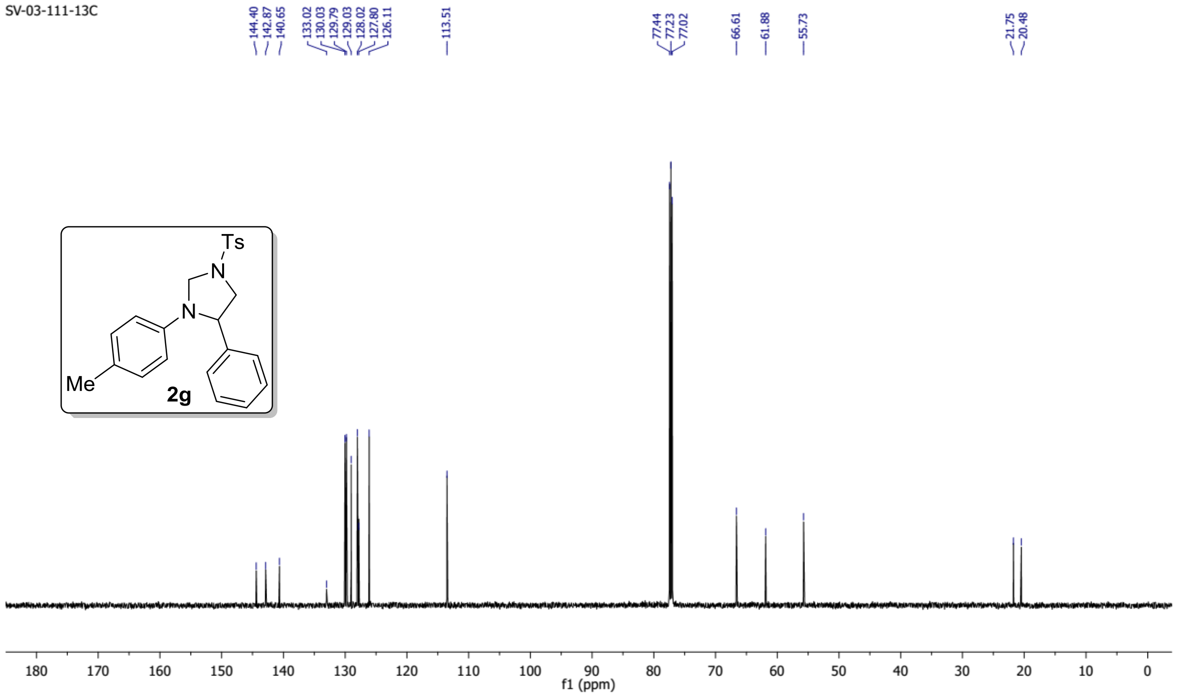
5.034 5.024 4.700 4.690 4.517 4.506 4.496 3.925 3.913 3.908 3.896 3.433 3.424 3.416 3.406
2.404 2.190 0.005
Ts
N
N
Me
2g
2.00 5.10 2.10 2.02 2.13 1.11 1.11 1.10 1.12 1.12 3.06 3.08
f1 (ppm)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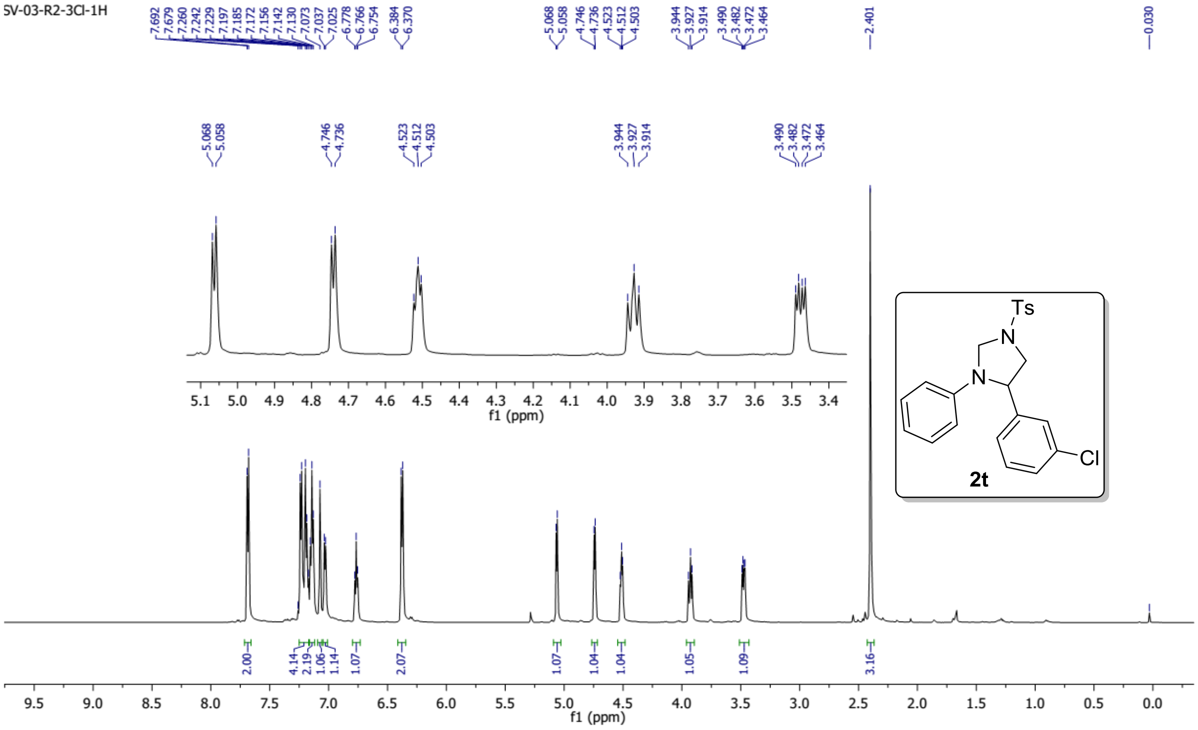
Ts
N
N
Me
2g
f1 (ppm)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7.260
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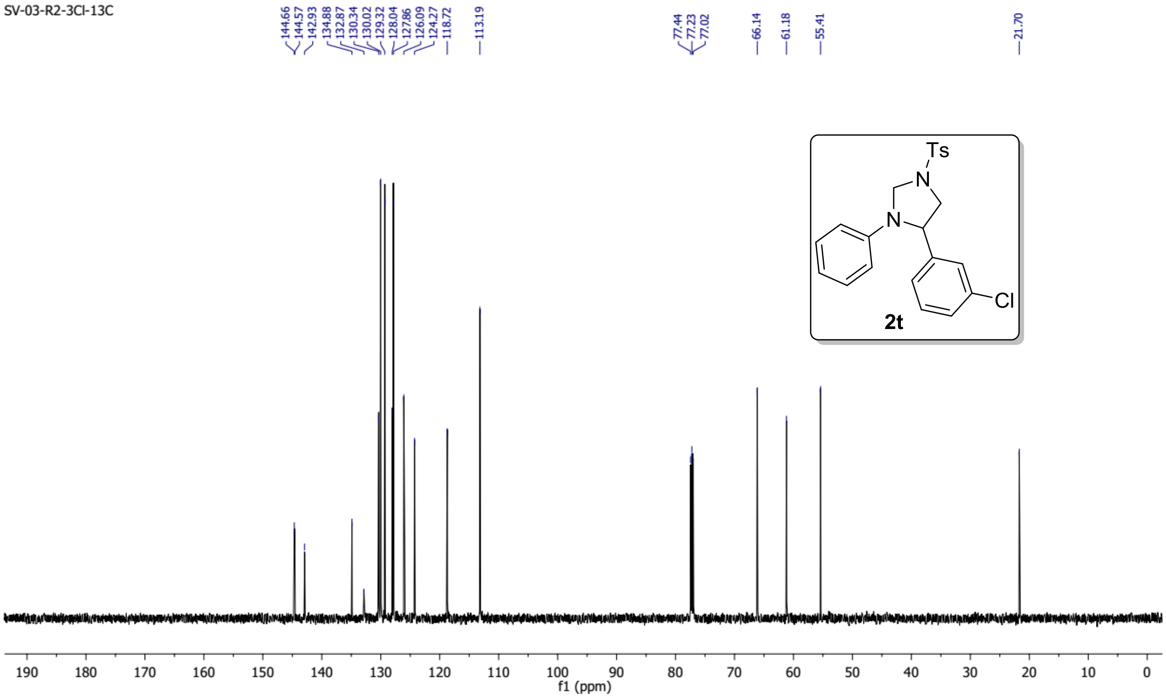
7.025
6.778
6.766
6.754
6.384
6.370
5.068
5.058
4.746
4.736
4.523
4.512
4.503
3.944
3.927
3.914
3.490
3.482
3.472
3.464
2.401
0.030
5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4
f1 (ppm)
Ts
N
N
Cl
2t
2.00
4.14
2.19
1.06
1.14
1.07
2.07
1.07
1.04
1.04
1.05
1.09
3.16
9.5 9.0 8.5 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)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130.02
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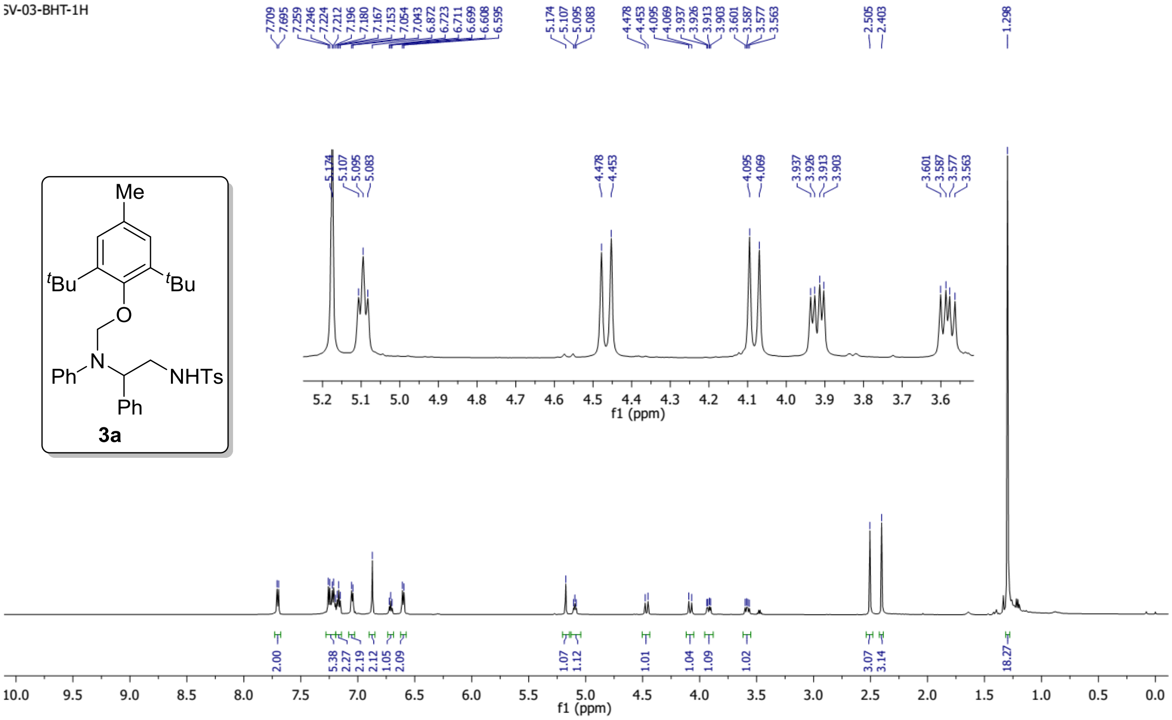
127.86
126.09
124.27
118.72
113.19
77.44
77.23
77.02
66.14
61.18
55.41
21.70
Ts
N
N
Cl
2t
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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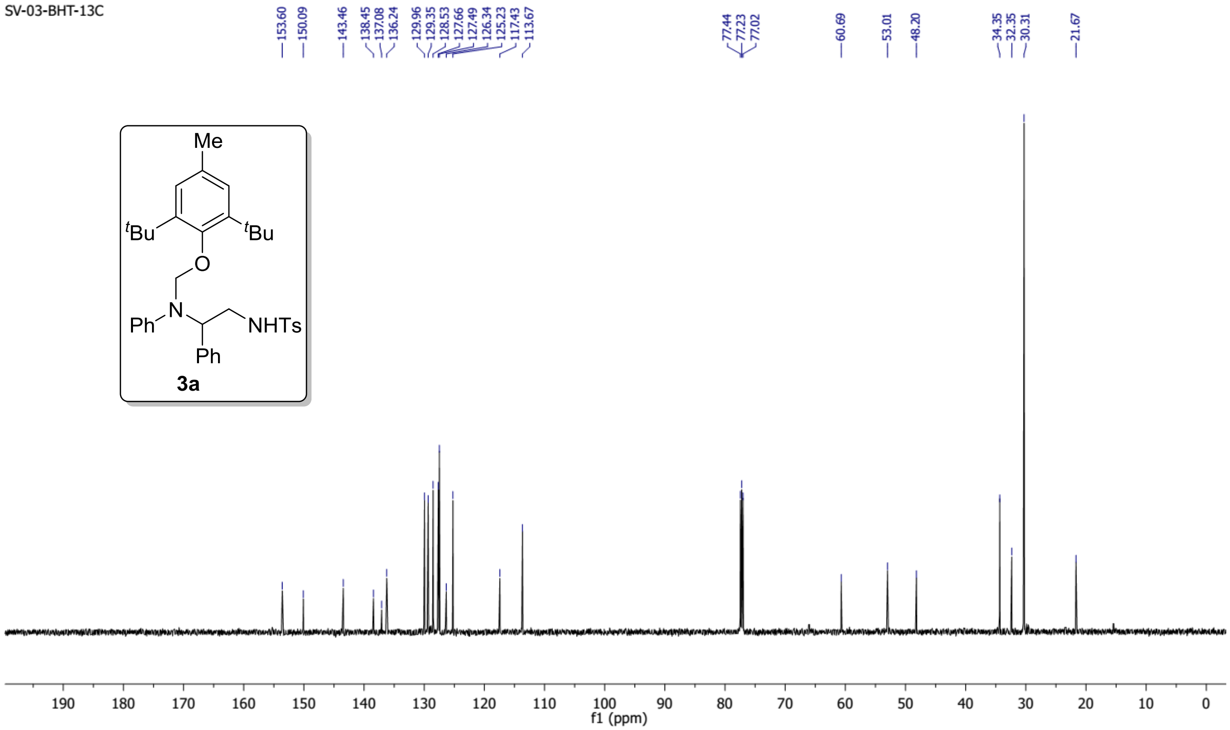
7.043
6.872
6.723
6.711
6.699
6.608
6.595
5.174
5.107
5.095
5.083
4.478
4.453
4.095
4.069
3.937
3.926
3.913
3.903
3.601
3.587
3.577
3.563
2.505
2.403
1.298
Me
ᵗBu
ᵗBu
O
N
Ph
NHTs
Ph
3a
5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6
f1 (ppm)
2.00
5.38
2.27
2.19
2.12
1.05
2.09
1.07
1.12
1.01
1.04
1.09
1.02
3.07
3.14
18.27
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)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150.09
143.46
138.45
137.08
136.24
129.96
129.35
128.53
127.66
127.49
126.34
125.23
117.43
113.67
77.44
77.23
77.02
60.69
53.01
48.20
34.35
32.35
30.31
21.67
Me
ᵗBu
ᵗBu
O
N
Ph
NHTs
Ph
3a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

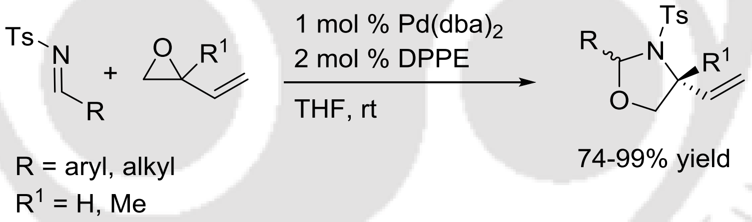
Chapter III

Cobalt-Catalyzed Domino Ring Opening/C-H Functionalization of Styrene Oxides with *N*-Methylanilines

The ring expansion of three-membered heterocycles using transition-metal catalyzed carbon-carbon and carbon-heteroatom bond formation has attracted considerable attention due to their synthetic flexibility and atom economy.[1] Epoxides are widely utilized as intermediates in synthetic organic chemistry because of the electrophilic character as well as their ring strain.[2] 1,3-Oxazolidines are attractive as these structural scaffolds are present in several natural products and biologically active compounds. Considerable efforts are thus made on the construction of diverse functionalized 1,3-oxazolidines.

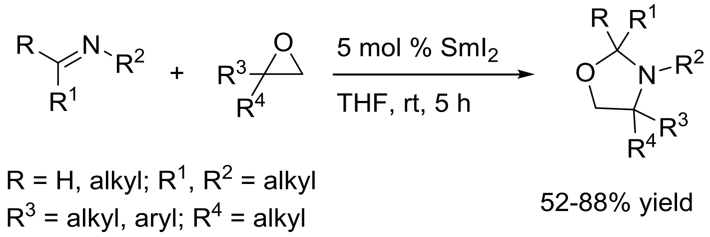
3.1 Strategies for the Synthesis of 1,3-Oxazolidine using Epoxides

Yamamoto group developed a Pd-catalyzed 1,3-oxazolidine synthesis by the ring expansion of 2-vinyl oxiranes with imines (Scheme 1).[3] This regioselective [3+2]-cycloaddition gives 4-vinyl-1,3-oxazolidines at room temperature.



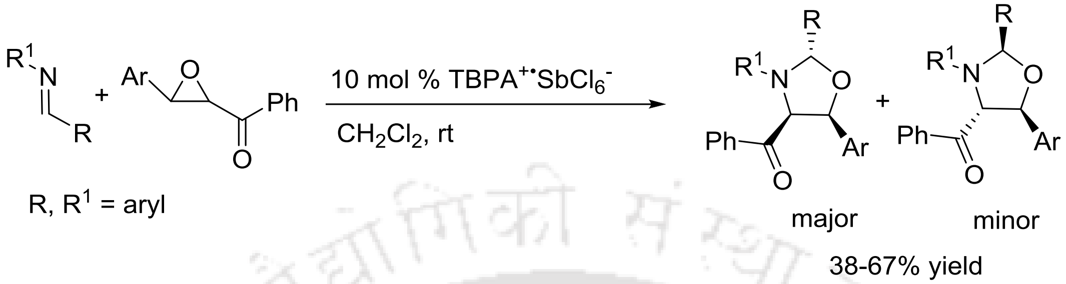
Scheme 1. Pd-Catalyzed Ring Expansion of 2-Vinyl Epoxides with *N*-Tosyl Imines

Ishii and co-workers demonstrated a protocol for the synthesis of variety of 1,3-oxazolidine derivatives with the use of SmI_2 catalyst at room temperature (Scheme 2).[4]



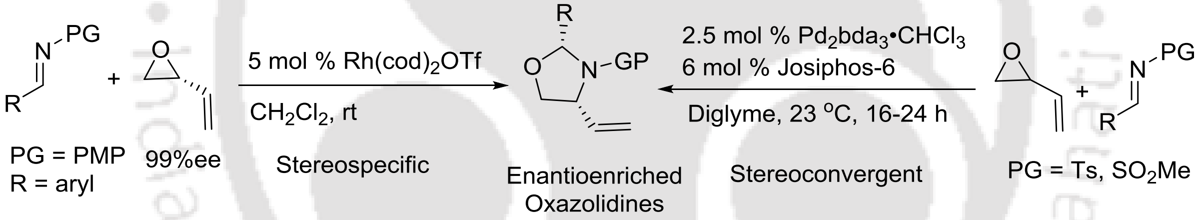
Scheme 2. Sm-Catalyzed Synthesis of Oxazolidines

Liu group reported cation radical induced [3+2]-cycloaddition of chalcone epoxides with imines (Scheme 3).[5] TBPA•SbCl$_6$ is used as the catalyst to provide the oxazolidines with up to 67% yield.



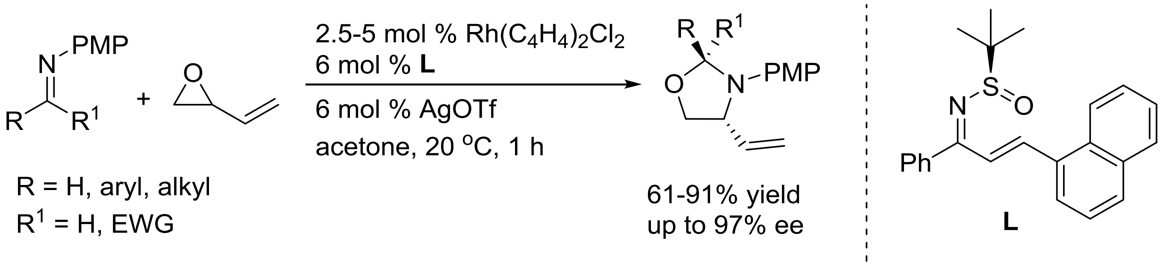
Scheme 3. [3+2]-Cycloaddition Chalcone Epoxides with Imines

Jarvo and co-workers developed the synthesis of enantioenriched 1,3-oxazolidines using the Rh(cod)$_2$OTf-catalyzed stereospecific reaction between optically active 2-vinyl oxiranes and imines (Scheme 4).[6] Whereas, Pd$_2$bda$_3$·CHCl$_3$ is used as the catalyst to deliver the products in stereoconvergent manner.



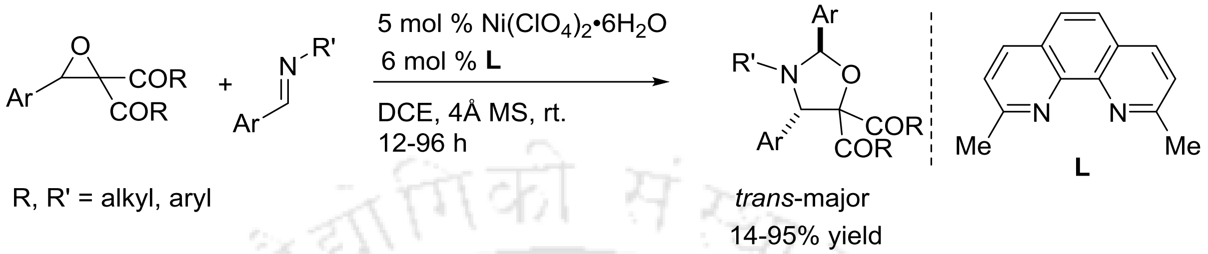
Scheme 4. Rh- and Pd-Catalyzed Synthesis of Enantioenriched 1,3-Oxazolidines

Rh-catalyzed formal cycloaddition between 2-vinyl oxirane and imines has been successfully achieved using chiral sulfur olefin (Scheme 5).[7] Imines derived from isatins, aldehydes and ketones were tolerated to produce the enantioenriched spirooxindole oxazolidines or 1,3-oxazolidines in high yields.



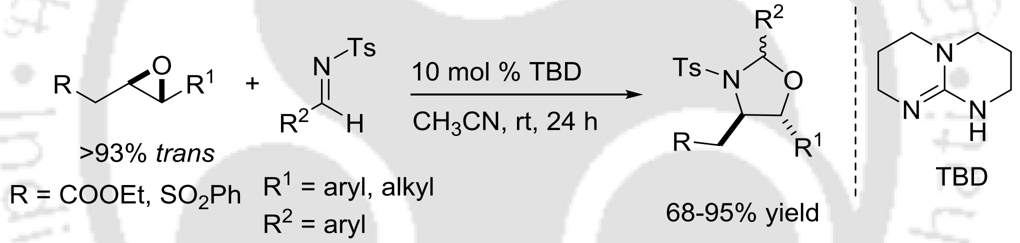
Scheme 5. Rh-Catalyzed Asymmetric Cycloadditions of 2-Vinyloxirane with Imines

Ni-catalyzed formal [3+2]-cycloaddition of imines with carbonyl ylides is reported for the synthesis of 2,4-*trans*-oxazolidines. The protocol produces 2,4-*trans*-oxazolidines as major isomers in high yields (Scheme 6).[8]



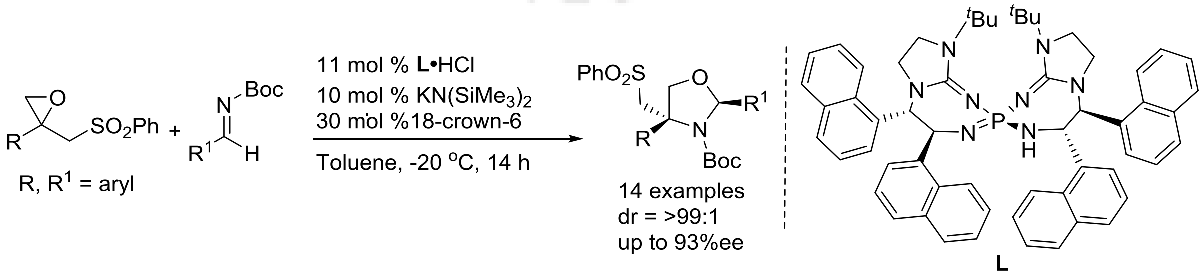
Scheme 6. Ni-Catalyzed Annulation of Donor-Acceptor Oxiranes with Imines

Terada and co-workers studied a Bronsted base catalyzed formal [3+2]-cycloaddition of epoxy esters with imines to afford 2,4,5-trisubstitued 1,3-oxazolidines in high yields (Scheme 7).[9]



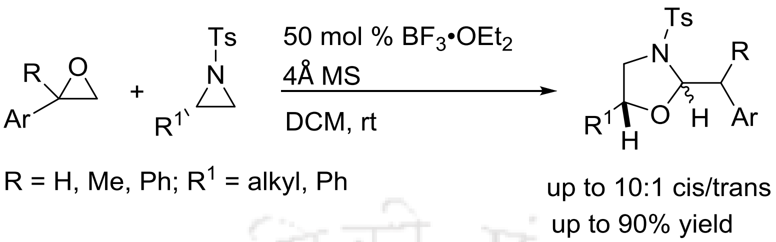
Scheme 7. Bronsted Base Catalyzed Oxiranes and Imines

The same group reported a chiral organosuperbase-catalyzed coupling of *β,γ*-epoxysulfones with imines to produce enantioenriched 1,3-oxazolidines (Scheme 8).[10] This tandem cyclization utilized the bis(guanidino)iminophosphorane as a chiral organosuperbase for the catalysis to access the oxazolidines with high enantiomeric purities.



Scheme 8. Organosuperbase-Catalyzed Synthesis of Enantioselective Oxazolidines

$BF_3{\cdot}OEt_2$ mediated annulation of *N*-tosyl/alkyl aziridines with 2-aryl epoxides is reported to furnish oxazolidines in high yields (Scheme 9)[11].

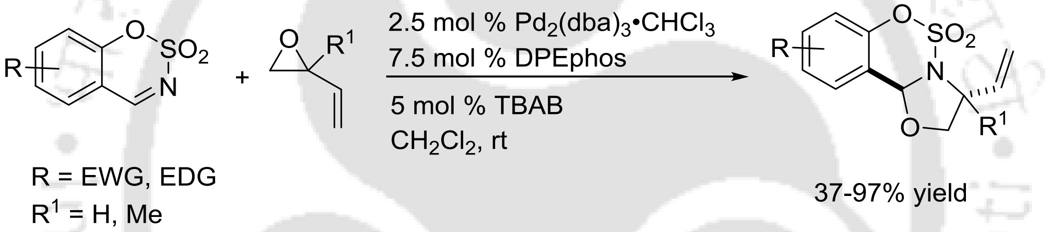


R = H, Me, Ph; R^1 = alkyl, Ph

up to 10:1 cis/trans
up to 90% yield

Scheme 9. [3+2]-Annulation of *N*-Tosyl/alkyl Aziridines with Styrene Oxides

Pd-catalyzed [3+2]-cycloaddition of 2-aryl-2-vinyloxiranes with sulfamate-derived cyclic imines has been documented (Scheme 10).[12] The reaction is regioselective to provide 1,3-oxazepines or 1,3-oxazolidines.



R = EWG, EDG
R^1 = H, Me

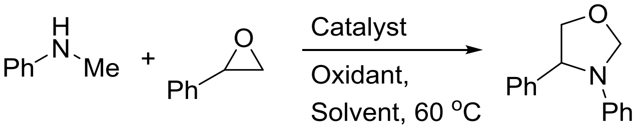
37-97% yield

Scheme 10. Cycloaddition of Cyclic Imines with Vinyloxirane

3.2 Present Study

In this chapter, we report a Co-catalyzed sequential domino synthesis[4] of substituted 1,3-oxazolidines from *N*-alkylaniline and styrene oxides using *tert*-butyl hydroperoxide (TBHP) as an oxidant at moderate temperature. This reaction involves C-O/C-N bond formations *via* S_N2 nucleophilic ring opening followed by C(sp^3)-H functionalization. First, we optimized the reaction employing *N*-methylaniline **1a** with styrene oxide **2a** as the model substrates using a series of Cu(II), Fe(II) and Co(II) salts at varied temperatures (Table 1). Gratifyingly, the coupling occurred to give 1,3-oxazolidine **3a** in 58% yield when the substrates were stirred with 10 mol% of $Cu(OTf)_2$ at 60 ˚C for 1 h in CH_2Cl_2, followed by treatment with

Table 1. Optimization of the Reaction Conditions[a]



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

Entry	Catalyst	Oxidant	Solvent	**3a** (%)[b]
1	$Cu(OTf)_2$	TBHP	CH_2Cl_2	34,[c]42,[d]48,[e] 58
2	$Cu(OAc)_2$	TBHP	CH_2Cl_2	45
3	$Fe(acac)_2$	TBHP	CH_2Cl_2	26
4	$Fe(OAc)_2$	TBHP	CH_2Cl_2	33
5	$Co(acac)_2$	TBHP	CH_2Cl_2	54
6	$Co(OAc)_2{\bullet}4H_2O$	TBHP	CH_2Cl_2	67
7	$CoCl_2$	TBHP	CH_2Cl_2	60
8	$Co(OAc)_2{\bullet}4H_2O$	TBHP	$(CH_2Cl)_2$	73
9	$Co(OAc)_2{\bullet}4H_2O$	TBHP	Toluene	48
10	$Co(OAc)_2{\bullet}4H_2O$	TBHP	CH_3CN	45
11	$Co(OAc)_2{\bullet}4H_2O$	TBHP	THF	32
12	$Co(OAc)_2{\bullet}4H_2O$	DTBP	$(CH_2Cl)_2$	48
13	$Co(OAc)_2{\bullet}4H_2O$	30% H_2O_2	$(CH_2Cl)_2$	20
14	$Co(OAc)_2{\bullet}4H_2O$	O_2	$(CH_2Cl)_2$	14
15	$Co(OAc)_2{\bullet}4H_2O$	-	$(CH_2Cl)_2$	n.d.
16	-	TBHP	$(CH_2Cl)_2$	n.d.

[a] Reaction conditions. **1a** (0.50 mmol), **2a** (0.50 mmol), catalyst (10 mol %), solvent (2 mL), 60° C, 2 h, then oxidant (1 mmol), 60 °C, 1 h.

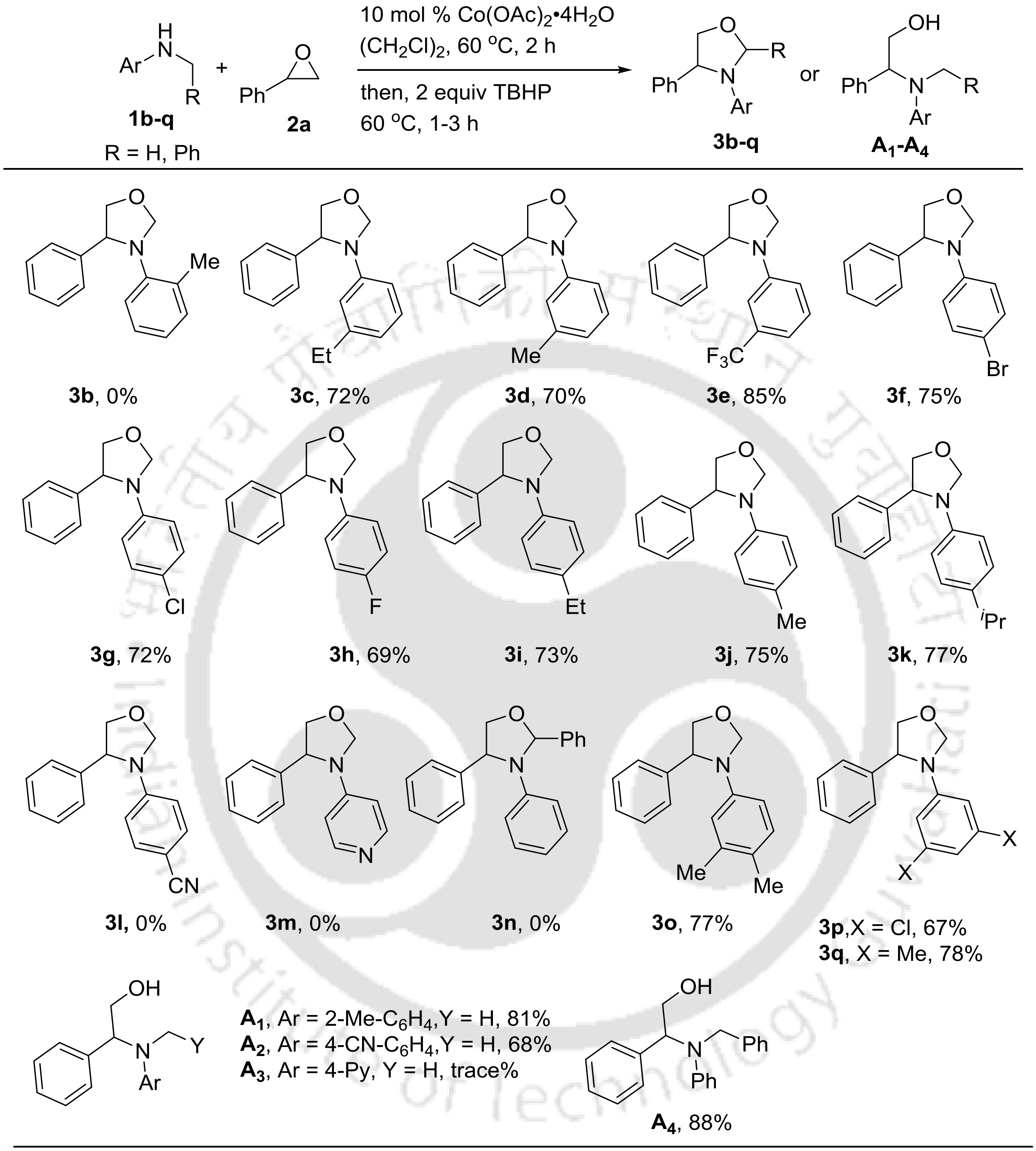
[b] Isolated average yield.

[c] Room temperature.

[d] 50° C.

[e] 1.5 eq. TBHP was used. n.d. = not detected.

Table 2. Reaction of Various *N*-Methylanilines **1** with Styrene Oxide **2a**[a,b]



3b, 0%
3c, 72%
3d, 70%
3e, 85%
3f, 75%
3g, 72%
3h, 69%
3i, 73%
3j, 75%
3k, 77%
3l, 0%
3m, 0%
3n, 0%
3o, 77%
3p,X = Cl, 67%
3q, X = Me, 78%

A_1, Ar = 2-Me-C_6H_4,Y = H, 81%
A_2, Ar = 4-CN-C_6H_4,Y = H, 68%
A_3, Ar = 4-Py, Y = H, trace%
A_4, 88%

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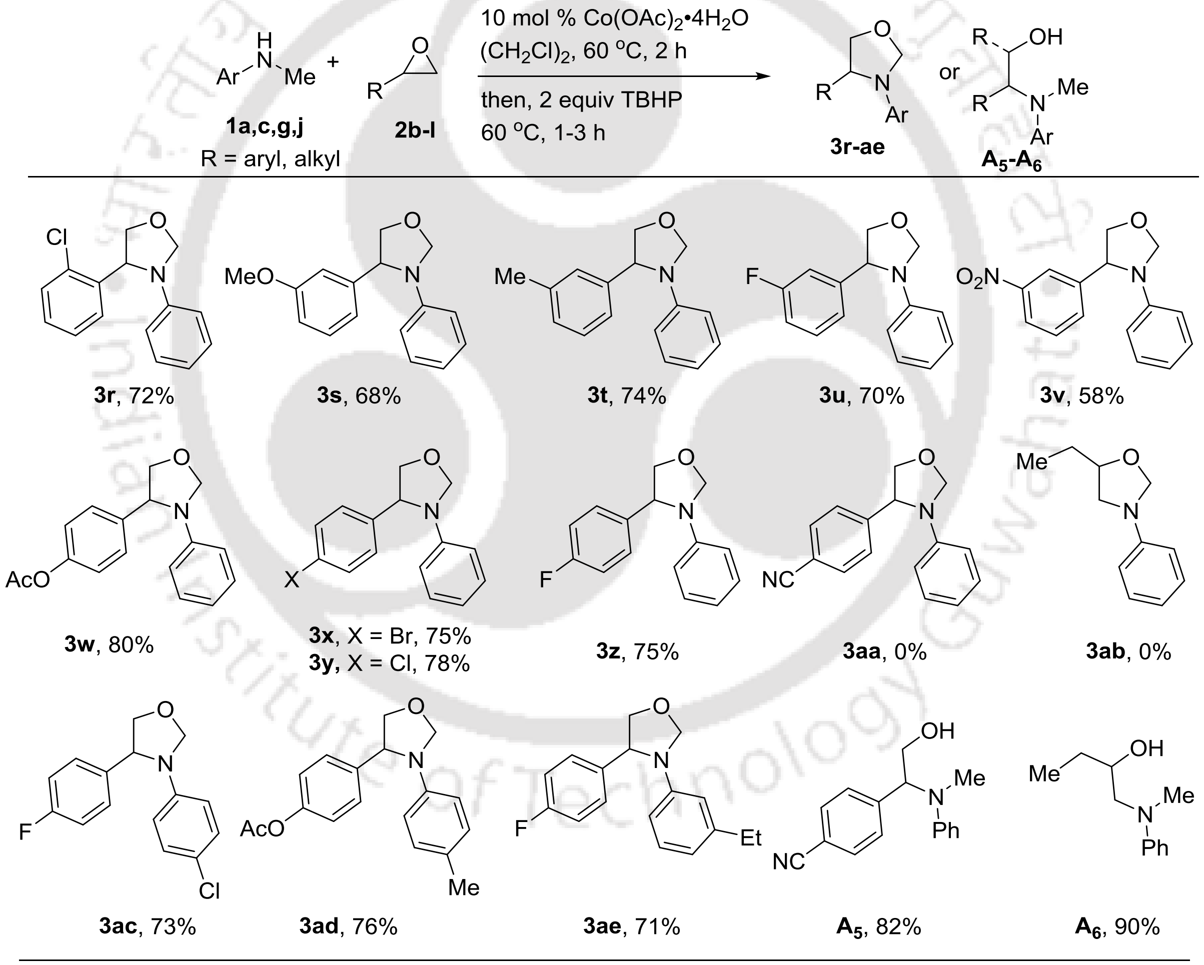
[a] Reaction conditions: *N*-methylaniline **1b-q** (0.50 mmol), epoxide **2a** (0.50 mmol), $Co(OAc)_2·4H_2O$ (10 mol%), $(CH_2Cl)_2$ (2 mL), 60 °C, 2 h, then TBHP (1 mmol), 60 °C, 1-3 h.

[b] Isolated yield.

TBHP and stirring for 2 h (entry 1). Subsequent screening of the catalysts revealed that Co(II) salts are superior to that of Cu(II) and Fe(II) salts (entries 2-7). The best results observed utilizing $Co(OAc)_2{\bullet}4H_2O$ with 67% yield (entry 6). $(CH_2Cl)_2$ was found to the solvent of choice, giving 73% yield, whereas toluene, acetonitrile and THF furnished 32-48% yields (entries 8-11). Screening of the oxidants such as DTBP, 30% H_2O_2 and O_2 led to inferior results (entries 12-14). Control experiments confirmed that the combination of $Co(OAc)_2{\bullet}4H_2O$ and TBHP is essential for this transformation (entries 15-16).

Table 3. Substrate Scope of *N*-Methylanilines **1** and Styrene Oxides **2b-l**[a,b]



1a,c,g,j
R = aryl, alkyl
2b-l
3r-ae
A5-A6

3r, 72% **3s**, 68% **3t**, 74% **3u**, 70% **3v**, 58%

3w, 80% **3x**, X = Br, 75% **3y,** X = Cl, 78% **3z**, 75% **3aa**, 0% **3ab**, 0%

3ac, 73% **3ad**, 76% **3ae**, 71% **A5**, 82% **A6**, 90%

[a] Reaction conditions: *N*-methylaniline **1a,c,g,j** (0.50 mmol), epoxide **2b-l** (0.50 mmol), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), $(CH_2Cl)_2$ (2 mL), 60 °C, 2h, then TBHP (1 mmol), 60 °C, 1-3 h.

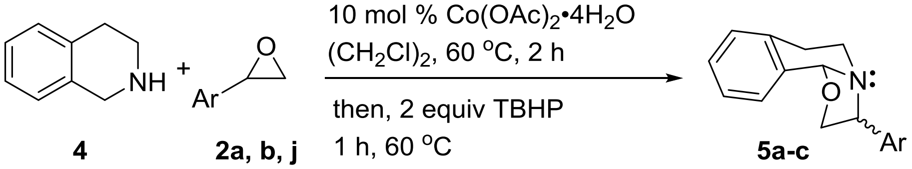
[b] Isolated yield.

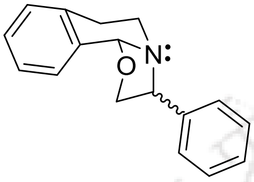
Having optimized the reaction, the scope of the procedure was inspected for a series of *N*-methylanilines **1b-q** with **2a** as a standard substrate (Table 2). *N*-Methylaniline bearing 2-methyl **1b** group underwent reaction to give the ring opening amino alcohol **A_1** in 81% yield and no cyclization was observed that may be due to the steric hindrance of the methyl functionality. However, the reaction of the substrates bearing 3-ethyl **1c**, 3-methyl **1d** and 3-trifluoromethyl **1e** substituents afforded the target heterocycles **3c-e** in 65-72% yields. Similar results observed with the substrates containing 4-bromo **1f**, 4-chloro **1g**, 4-fluoro **1i**, 4-ethyl **1j**, 4-methyl **1k** and 4-isopropyl **1l** substituents, giving **3f-g** and **3i-l** in 72-77% yields, whereas **1h** having 4-cyano group produced the ring opening amino alcohol **A_2** as a sole product in 68% yield, which may be due to the delocalization of nitrogen lone pair with aryl ring. Similarly, the reactions of *N*-methylpyridin-4-amine **1m** and *N*-benzylaniline **1n**, furnished the amino alcohols **A3** and **A4** in a trace amount and 88% yield, respectively, which could be presumably due to the steric hindrance to form the imine cation or the complex formation of Co species with pyridine nitrogen. However, the reaction of the substrates containing 3,4-dimethyl **1o**, 3,5-dichloro **1p** and 3,5-dimethyl **1q** substituents can be performed to afford **3o-q** in 67-78% yields.

Next, we studied the scope of the procedure for the reaction of styrene oxides **2b-l** with *N*-methylaniline **1a** as the standard substrate (Table 3). The reaction of styrene oxides having 2-chloro **2b**, 3-methoxy **2c,** 3-methyl **2d,** 3-fluoro **2e** and 3-nitro **2f** substituents occurred to afford the desired **3r-v** in 58-74% yields. Similarly, the epoxides bearing 4-acetoxy **2g**, 4-bromo **2h**, 4-chloro **2i** and 4-fluoro **2j** groups are well tolerated to furnish the oxazolidines **3w-z** in 75-80% yields, whereas the reaction of **2k** containing 4-cyano group yielded the uncyclized amino alcohol **A_5** in 82% yield. Furthermore, 2-ethylene oxide **2l** underwent the nucleophilic ring opening at the less hindered methylene carbon to give **A_6** in 90% yield, which showed no cyclization. However, the reaction of the epoxides **2g** and **2i** with *N*-methylanilines having 4-chloro **1g**, 4-methyl **1k** and 3-ethyl **1c** groups can be readily accomplished to furnish the oxazolidines **3ac-ae** in 71-76% yields.

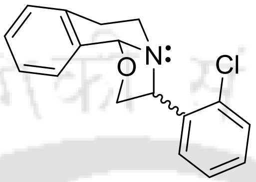
The reaction condition was further extended to the coupling of tetrahydroisoquinoline **4** with styrene oxides (Table 4). Pleasingly, the reactions readily occurred to produce the tricylic heterocyclic scaffolds **5a-c** with good diasteroselectivity in 68-75 % yields.

Table 4. Reaction of Tetrahydroisoquinoline **4** with Styrene Oxides **2a, 2b** and **2j**[a,b,c]

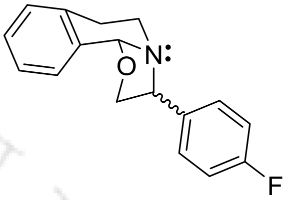




5a, 75%, dr = 9:1



5b, 68%, dr = 9:1



5c, 72%, dr = 9:1

[a] Reaction conditions: *N*-methylaniline **4** (0.50 mmol), epoxide **2a,b,j** (0.50 mmol), $Co(OAc)_2•4H_2O$ (10 mol%), $(CH_2Cl)_2$ (2 mL), 60° C, 2 h, then TBHP (1 mmol), 60 °C, 1 h.

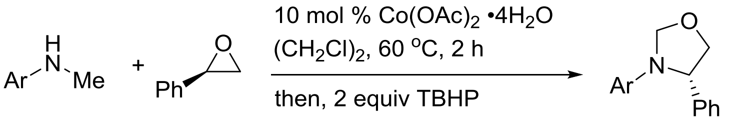
[b] Isolated yield.

[c] dr Calculated from ^1H NMR.

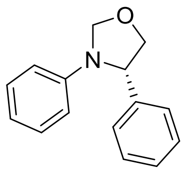
To reveal the stereoselectivity, we studied the reaction of (*R*)-styrene oxide **2a'** with a series of *N*-methylanilines (Table 5). To our delight, the reaction took place stereospecifically to give the 1,3-oxazolidines in high optical purities. For example, *N*-methylaniline having 3-ethyl group **1c** underwent reaction to give **3c'** in 98% ee and 75 % yield. Similar results observed with *N*-methylanilines containing 4-bromo **1f**, 4-chloro **1g**, 4-fluoro **1i**, 4-ethyl **1j**, 4-methyl **1k** and 4-isopropyl **1l** groups, providing **3f'**, **3g'** and **3i'-l'** in 95-98% ee and 70-76% yields. In addition, *N*-methylanilines having 3,4-dimethyl **1o** and 3,5-dimethyl **1q** groups could be coupled to give **3o'** and **3q'** in 97% ee and 73-76% yields. These results suggest that *N*-methylaniline reacts with epoxide presumably *via* a S_N^2 pathway.

To gain insight in the catalytic cycle, we studied the coupling of **1a** and **2a** as the representative example using BHT radical inhibitor (Scheme 11). The reaction produced a trace amount of BHT-adduct **6**, which suggests that a radical intermediate may be involved. When we reacted **A₇** using $Co(OAc)_2•4H_2O$ and TBHP, the oxidative cyclization occurred to give **3a** in 80% yield, which suggests that *N*-methylaniline reacts with epoxide to give an amino alcohol that leads to a cyclization via C(sp^3)-H functionalization (Scheme 12).

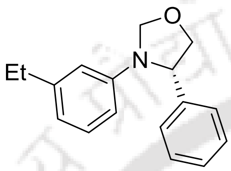
Table 5. Reaction of Different *N*-Methylanilines **1** with (*R*)-Styrene Oxide **2a'**[a,b,c]



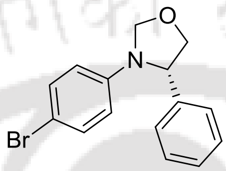
1b-l,o,q **2a'** **3b'-q'**



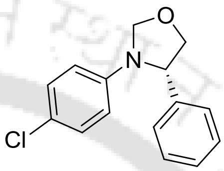
3a, 72%, 98% ee



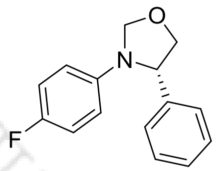
3c', 75%, 98% ee



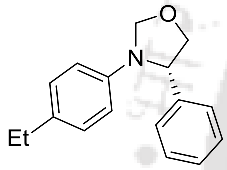
3f', 70%, 95% ee



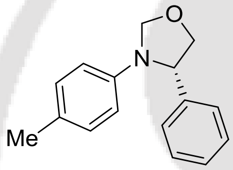
3g', 72%, 97% ee



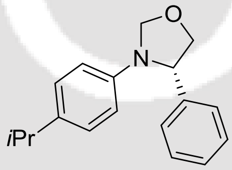
3i', 72%, 95% ee



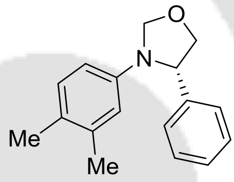
3j', 73%, 98% ee



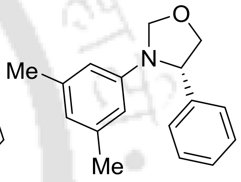
3k', 75%, 99% ee



3l', 76%, 99% ee



3o', 73%, 97% ee



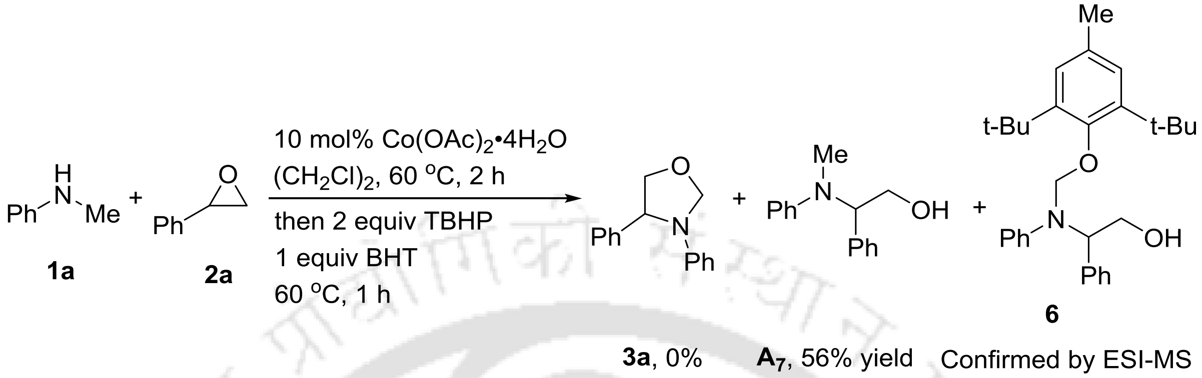
3q', 76%, 97% ee

[a] Reaction conditions: **1b-l,o,q** (0.50 mmol), **2a'** (0.50 mmol), $Co(OAc)_2 \cdot 4H_2O$ (10 mol%), $(CH_2Cl)_2$ (2 mL), 60 °C, 2 h, then TBHP (2 equvi), 60 °C, 1-3 h.

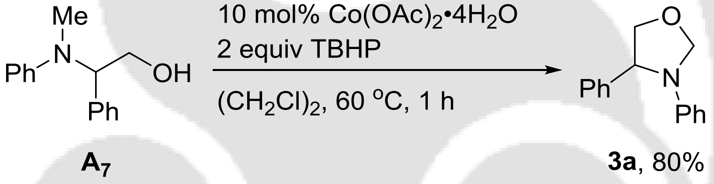
[b] Isolated yield.

[c] Determined by Chiral HPLC.

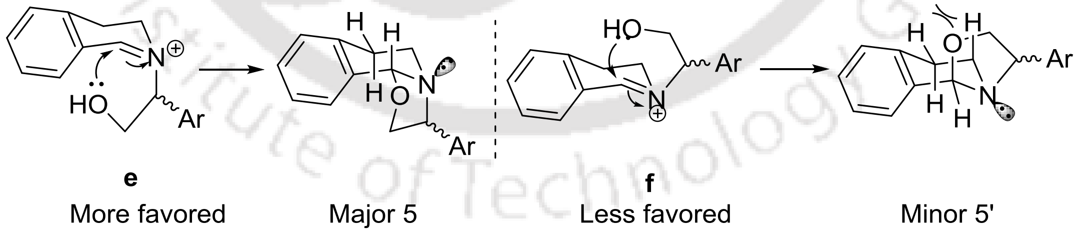
Based on these experimental results and the literature,[13] a proposed catalytic cycle is shown in Scheme 14. The chelation of Co(II) with epoxide oxygen ***a*** may facilitate the nucleophilic ring opening with *N*-methylanilines to give ***b*** *via* S_N2 pathway. The latter can convert into the radical cation ***c*** via a single electron transfer (SET) to Co(III) species, which can be produced from Co(II) with TBHP. Homolytic cleavage of the C-H bond in ***c*** using *t*-butoxy radical/ *t*-butylperoxy radical can give imine ion ***d*** that can lead to intramolecular cyclization to furnish the heterocycle **3**.[14] The Co(II)-Co(III) triggered cleavage of TBHP can give the *t*-butoxy radical. The proposed catalytic cycle also explains the requirement of an excess TBHP. Furthermore, the formation of the major diastereomer **5** can be exemplified through a chair like transition states (TS) ***e*** and ***f*** (Scheme 13). TS ***e*** is favoured because of the evading the undesired interaction, whereas TS ***f*** has 1,3-diaxial interaction.



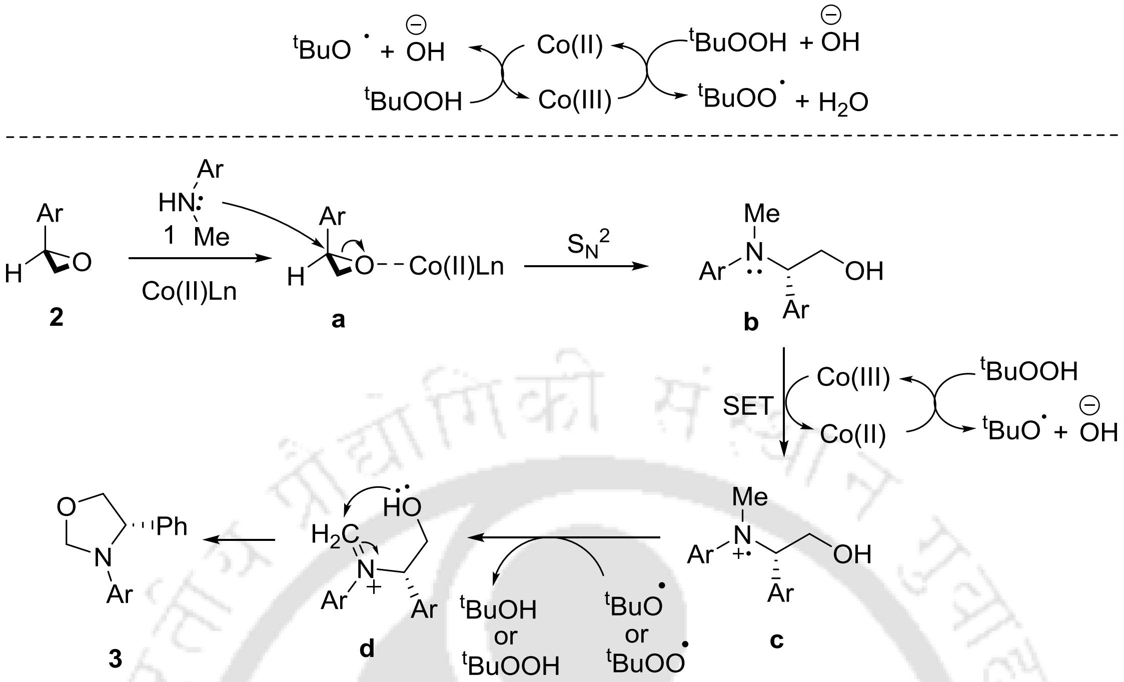
Scheme 11. Radical Trapping Experiment



Scheme 12. Control Experiment



Scheme 13. Stereochemical Model



Scheme 14. Proposed Catalytic Cycle

In conclusion, we presented a Co(II)-catalyzed stereospecific coupling of *N*-methylanilines with styrene oxides to furnish 1,3-oxazolidines *via* a tandem *C-N* and *C-O* bonds formation in the presence of TBHP. Optically active epoxide can be coupled with high enantiomeric purities.

3.3 Experimental Section

3.3.1 General Information. Cu(OAc)$_2$ (98%), Fe(acac)$_2$ (97%), Fe(OAc)$_2$ (95%), Co(acac)$_2$ (97%), Co(OAc)$_2$·4H$_2$O (98%), CoCl$_2$ (98%) and TBHP purchased from commercial source were used as received. The other information was followed as presented in the chapter 1.

3.3.2 Procedure for the *C-N* and *C-O* Bond Formation of Styrene Oxides with *N*-Methylanilines. *N*-Methylaniline (0.5 mmol), epoxide (0.5 mmol) and Co(OAc)$_2$·4H$_2$O (10 mol%) were stirred in (CH$_2$Cl)$_2$ (2 mL) at 60 °C for 2 h. The reaction was cooled to room temperature and treated with TBHP (1 mmol). The mixture was then stirred at 60 °C. The progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the reaction was allowed to cool to room temperature and treated with saturated Na$_2$SO$_3$ (1 mL). After stirring for 1 h, the solution was extracted using CH$_2$Cl$_2$ (3x10 mL). The combined organic solution was washed with brine (1x10 mL) and water (1x10 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 the solvent.

3,4-Diphenyloxazolidine 3a. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.61; pale yellow liquid; 83 mg, yield 73%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37−7.34 (m, 4H), 7.30-7.28 (m, 1H), 7.19 (t, J = 7.2 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H), 6.49 (d, J = 8.4 Hz, 2H), 5.33 (d, J = 2.4 Hz, 1H), 5.04 (d, J = 2.4 Hz, 1H), 4.71 (dd, J = 6.6, 4.2 Hz, 1H), 4.42 (dd, J = 8.4, 6.6 Hz, 1H), 3.99 (dd, J = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 141.6, 129.4, 129.0, 127.7, 126.4, 117.8, 112.9, 82.9, 75.9, 61.8; FT-IR (neat) 3060, 3029, 2929, 2867, 1600, 1504, 1391, 1346, 1211, 1164, 1089, 944, 749, 696 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{15}NO+H]^+$ 226.1226, found 226.1236; **(*S*)-3,4-Diphenyloxazolidine 3a'**. 81 mg, yield 72%; $[\alpha]_D^{23}$ = +156.0 (c= 0.32, $CHCl_3$); HPLC analysis: 98% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 9.70 min (minor), 14.37 min (major)].

3-(3-Ethylphenyl)-4-phenyloxazolidine 3c. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; yellow liquid; 91 mg, yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.37-3.33 (m, 4H), 7.28-7.27 (m, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 6.33-6.30 (m, 2H), 5.32 (d, J = 1.8 Hz, 1H), 5.03 (d, J = 2.4 Hz, 1H), 4.70 (dd, J = 7.2, 4.8 Hz, 1H), 4.39 (t, J = 7.2 Hz, 1H), 3.98 (dd, J = 8.4, 4.2 Hz, 1H), 2.57 (q, J = 7.8 Hz, 2H), 1.17 (t, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.6, 145.3, 141.8, 129.3, 129.0, 127.7, 126.4, 117.6, 112.5, 110.5, 83.0, 75.9, 61.9, 29.3, 15.7; FT-IR (neat) 3063, 3032, 2963, 2928, 2867, 1604, 1493, 1453, 1390, 1355, 1089, 945, 755 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{19}NO+H]^+$ 254.1539, found 254.1549; **(*S*)-3-(3-Ethylphenyl)-4-phenyloxazolidine 3c'**. 95 mg, yield 75%; $[\alpha]_D^{23}$ = +27.0 (c= 0.31, $CHCl_3$); HPLC analysis: 98% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 6.11 min (minor), 10.84 min (major)].

4-Phenyl-3-(*m*-tolyl)oxazolidine 3d. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; pale yellow liquid; 84 mg, yield 70%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.33 (m, 4H), 7.29-7.27 (m, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H), 6.30-6.28 (m, 2H), 5.31 (d, J = 1.8 Hz, 1H), 5.01 (d, J = 1.8 Hz, 1H), 4.69 (dd, J = 6.6, 4.2 Hz, 1H), 4.40 (dd, J =

8.4, 7.2 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 141.8, 139.2, 129.3, 129.0, 127.7, 126.3, 118.8, 113.6, 110.2, 83.0, 75.9, 61.8, 22.0; FT-IR (neat) 3061, 3026, 2920, 2861, 1619, 1521, 1391, 1344, 1088, 944, 803 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{17}NO+H]^+$ 240.1383, found 240.1397.

4-Phenyl-3-(3-(trifluoromethyl)phenyl)oxazolidine 3e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.58; colorless liquid; 96 mg, yield 65%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.30-7.28 (m, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.66 (s, 1H), 6.59 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.33 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 2.4 Hz, 1H), 4.73 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.44 (dd, *J* = 9.0, 7.2 Hz, 1H), 4.01 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.1, 140.7, 132.0 (q, *J* = 31.5 Hz), 129.8, 129.2, 128.1, 126.3, 114.3 (q, *J* = 3.0 Hz), 109.1 (q, *J* = 3.0 Hz), 115.9, 82.7, 76.0, 61.8; FT-IR (neat) 3065, 6032, 2927, 2869, 1614, 1494, 1458, 1371, 1320, 1166, 1122, 1009, 948, 852 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{14}F_3NO+H]^+$ 294.1100, found 294.1124.

3-(4-Bromophenyl)-4-phenyloxazolidine 3f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; pale yellow liquid; 114 mg, yield 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 7.25 (d, *J* = 9.0 Hz, 2H), 6.34 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.98 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.43 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.8, 140.7, 131.9, 128.9, 127.8, 126.1, 114.3, 109.7, 82.6, 75.8, 61.7; FT-IR (neat) 3063, 3028, 2989, 2925, 2857, 1594, 1491, 1390, 1357, 1164, 1088, 944, 807, 753 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}BrNO+H]^+$ 304.0332, found 304.0333; **(*S*)-3-(4-Bromophenyl)-4-phenyloxazolidine 3f'**. 106 mg, yield 70%; $[\alpha]_D^{22}$ = +92.07 (c= 3.2, $CHCl_3$); HPLC analysis: 95% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 10.39 min (minor), 12.27 min (major)].

3-(4-Chlorophenyl)-4-phenyloxazolidine 3g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; pale yellow liquid; 94 mg, yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 7.11 (d, *J* = 9.0 Hz, 2H), 6.38 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.8 Hz, 1H), 4.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 141.0, 129.3, 129.1, 127.9, 126.3, 122.8, 114.0, 82.9, 76.0, 62.0; FT-IR (neat) 3063, 3026, 2925, 2858, 1600, 1493, 1391, 1354, 1092, 944, 809 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}ClNO+H]^+$ 260.0837, found 260.0847; **(*S*)-3-(4-Chlorophenyl)-4-phenyloxazolidine 3g'.** 93 mg, yield, 72%; $[\alpha]_D^{24}$ = +72.6 (c= 0.22, $CHCl_3$); HPLC analysis: 99% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 10.34 min (minor), 13.42 min (major)].

3-(4-Fluorophenyl)-4-phenyloxazolidine 3i. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.59; yellow liquid; 84 mg, yield 69%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.31-7.27 (m, 1H), 6.89 (t, *J* = 9.0, 2H), 6.41-6.39 (m, 2H), 5.29 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.64 (dd, *J* = 6.6, 4.8 Hz, 1H), 4.43 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.96 (dd, *J* = 8.4, 4.2 Hz, 1H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.9 (*J* = 234 Hz), 141.89 (*J* = 1.5 Hz), 141.3, 129.1, 127.9, 126.4, 115.97 (*J* = 22.5 Hz), 113.7 (*J* = 7.5 Hz), 83.4, 76.0, 62.4; FT-IR (neat) 3059, 3029, 2929, 2968, 1673, 1515, 1392, 1350, 1226, 1161, 1090, 945, 815 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}FNO+H]^+$ 244.1132, found 244.1142. **(*S*)-3-(4-Fluorophenyl)-4-phenyloxazolidine 3i′**. 88 mg, yield, 72%; $[\alpha]_D^{23}$ = +40.6 (c= 0.33, $CHCl_3$); HPLC analysis: 95% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 8.45 min (minor), 12.92 min (major)].

3-(4-Ethylphenyl)-4-phenyloxazolidine 3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow liquid; 93 mg, yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.44 (d, *J* = 8.4 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 4.67 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.38 (t, *J* = 7.6 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.55 (q, *J* = 7.2 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 141.8, 133.7, 129.0, 128.8, 127.7, 126.4, 113.1, 83.3, 75.9, 62.2, 28.1, 16.1. FT-IR (neat) 3063, 3031, 2963, 2928, 2862, 1604, 1493, 1453, 1390, 1355, 1261, 1166, 1089, 945 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{19}NO+H]^+$ 254.1539, found 254.1546. **(*S*)-3-(4-Ethylphenyl)-4-phenyloxazolidine 3j'.** 93 mg, yield, 73%; $[\alpha]_D^{23}$ = +26.6 (c= 0.33, $CHCl_3$); HPLC analysis: 98% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 6.87 min (minor), 9.52 min (major)].

4-Phenyl-3-(*p*-tolyl)oxazolidine 3k. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.62$; yellow liquid; 90 mg, yield 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.33 (m, 4H), 7.29-7.27 (m, 1H), 7.00-6.99 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 8.4 Hz, 2H), 5.32 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.67 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.41 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.2, 141.7, 129.9, 129.0, 127.7, 127.1, 126.4, 113.0, 83.3, 75.9, 62.1, 20.5. FT-IR (neat) 3063, 3028, 2923, 2856, 1620, 1521, 1452, 1341, 1164, 1089, 944, 804, 755 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{17}NO+H]^+$ 240.1383, found 240.1392. **(*S*)-4-Phenyl-3-(*p*-tolyl)oxazolidine 3k′**. 90 mg, yield, 75%; $[\alpha]_D^{23}$ = +85.0 (c= 1.3, $CHCl_3$); HPLC analysis: 99% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 8.59 min (minor), 12.02 min (major)].

3-(4-*Iso*propylphenyl)-4-phenyloxazolidine 3l. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.62; pale yellow liquid; 103 mg, yield 77%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.32 (m, 4H), 7.28-7.27 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 5.31 (d, *J* = 1.8 Hz, 1H), 4.99 (d, *J* = 2.4 Hz, 1H), 4.65 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.38 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.96 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.81-2.76 (m, 1H), 1.18 (d, *J* = 2.4 Hz, 3H), 1.17 (d, *J* = 2.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.5, 141.9, 138.3, 129.0, 127.7, 127.3, 126.4, 113.0, 83.3, 75.9, 62.9, 33.3, 24.4; FT-IR (neat) 3028, 2958, 2928, 2867, 2755, 1616, 1519, 1454, 1390, 1345, 1194, 1165, 1090, 946 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{18}H_{21}NO+H]^+$ 268.1696, found 268.1699; **(*S*)-3-(4-*Iso*propylphenyl)-4-phenyloxazolidine 3l'.** 102 mg, yield 76%; $[\alpha]_D^{23}$ = +46.0 (c= 0.2, $CHCl_3$); HPLC analysis: 97% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 4.80 min (minor), 8.10 min (major)].

3-(3,4-Dimethylphenyl)-4-phenyloxazolidine 3o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; yellow liquid; 98 mg, yield 77%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.27-7.25 (m, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.31 (d, *J* = 1.8 Hz, 1H), 6.24 (dd, *J* = 7.8, 2.4 Hz, 1H), 5.30 (d, *J* = 1.8 Hz, 1H), 5.98 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.38 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.95 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.6, 141.9, 137.6, 130.4, 129.0, 127.6, 126.4, 126.0, 114.5, 110.6, 83.3, 75.9, 62.0, 20.4, 18.9; FT-IR (neat) 3063, 3026, 2923, 2854, 1617, 1512, 1453, 1346, 1166, 1088, 949, 800 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{19}NO+H]^+$ 254.1539, found 254.1544; **(*S*)-3-(3,4-Dimethylphenyl)-4-phenyloxazolidine 3o'.** 93 mg, yield 73 %; $[\alpha]_D^{23}$ = +47.0 (c= 0.17, $CHCl_3$); HPLC analysis: 97% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 8.55 min (minor), 10.25 min (major)].

3-(3,5-Dichlorophenyl)-4-phenyloxazolidine 3p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless liquid; 99 mg, yield 67%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2H), 7.32-7.28 (m, 3H), 6.70 (t, *J* = 1.8 Hz, 1H), 6.31 (d, *J* = 1.8 Hz, 2H), 5.24 (d, *J* = 6.6, 3.6 Hz, 1H), 4.97 (d, *J* = 8.4, 6.6 Hz, 1H), 4.67 (dd, *J* = 6.6, 3.6 Hz, 1H), 4.40 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.99 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.3, 140.3, 135.7, 129.3, 128.2, 126.2, 117.6, 111.1, 82.4, 75.9, 61.6; FT-IR (neat) 3084, 3028, 2959, 2923, 2856, 1592, 1556, 1462, 1390, 1126, 1092, 1024, 982, 820, 705 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{13}C_{l2}NO+H]^+$ 294.0447, found 294.0463.

3-(3,5-Dimethylphenyl)-4-phenyloxazolidine 3q. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.62; yellow liquid; 99 mg, yield 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.33 (m, 4H), 7.29-7.27 (m, 1H), 6.42 (s, 1H), 6.12 (s, 2H), 5.30 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.69 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.37 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.97 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.21 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 142.0, 139.1, 129.0, 127.6, 126.4, 120.0, 110.9, 83.1, 75.9, 61.8, 21.8; FT-IR (neat) 3063, 3032, 2953, 2923, 2855, 1602, 1456, 1362, 1216, 1157, 1090, 945, 819, 754 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{19}NO+H]^+$ 254.1539, found 254.1546; **(S)-3-(3,5-Dimethylphenyl)-4-phenyloxazolidine 3q'.** Yield 96 mg, 76%; $[\alpha]_D^{23}$ = +56.2 (c= 0.2, $CHCl_3$); HPLC analysis: 97% ee [Daicel Chiralcel OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL/min, λ = 254 nm, t_R = 5.05 min (minor), 12.80 min (major)].

4-(2-Chlorophenyl)-3-phenyloxazolidine 3r. **An**alytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless liquid; 94 mg, yield 72%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.24-7.19 (m, 4H), 6.77 (t, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 2H), 5.34 (d, *J* = 1.8 Hz, 1H), 5.10 (dd, *J* = 7.2, 3.0 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 4.47 (dd, *J* = 9.0, 7.0 Hz, 1H), 4.05 (dd, *J* = 8.4, 3.0 Hz, 1H); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 144.7, 138.6, 132.4, 129.8, 129.6, 128.9, 127.9, 127.4, 118.1, 112.9, 82.7, 74.5, 59.2; FT-IR (neat) 3063, 2993, 2926, 2864, 1600, 1505, 1391, 1348, 1264, 1170, 1091, 1035, 945, 746 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}ClNO+H]^+$ 260.0837, found 260.0845.

4-(3-Methoxyphenyl)-3-phenyloxazolidine 3s. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless liquid; 87 mg, yield 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28-7.25 (m, 1H), 7.19-7.16 (m, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 6.82 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 5.01 (d, J = 2.4 Hz, 1H), 4.66 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.40 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.3, 145.3, 143.5, 130.1, 129.4, 118.7, 117.9, 113.0, 112.9, 112.1, 83.0, 75.8, 61.9, 55.4; FT-IR (neat) 3040, 2998, 2933, 2866, 2836, 1600, 1494, 1346, 1261, 1148, 1090, 1045, 973, 946, 786, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{17}NO_2+H]^+$ 256.1332, found 256.1341.

3-Phenyl-4-(*m*-tolyl)oxazolidine 3t. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless liquid; 89 mg, yield 74%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.8 Hz, 1H), 7.21-7.16 (m, 4H), 7.12 (d, *J* = 7.2 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 2H), 5.34 (d, *J* = 2.4 Hz, 1H), 5.04 (d, *J* = 2.4 Hz, 1H), 4.68 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.41 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.99 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3, 141.7, 138.7, 129.4, 128.9, 128.6, 126.9, 123.4, 117.8, 112.9, 83.0, 76.0, 61.9, 21.7; FT-IR (neat) 3032, 2961, 2920, 2860, 1601, 1506, 1390, 1345, 1258, 1172, 1090, 946, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{17}NO+H]^+$ 240.1383, found 240.1389.

4-(3-Fluorophenyl)-3-phenyloxazolidine 3u. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.40; brown liquid; 85 mg, yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 9.6 Hz, 1H), 6.98 (t, *J* = 9.2 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.33 (d, *J* = 2.0 Hz, 1H), 5.02 (d, *J* = 2.0 Hz, 1H), 4.71 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.39 (t, *J* = 8.4 Hz, 1H), 4.00 (dd, *J* = 8.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (d, *J* = 245.0 Hz), 145.0, 130.6 (d, *J* = 8.0 Hz), 129.5, 122.0 (d, *J* = 3.0 Hz), 118.2, 114.8 (d, *J* = 22.0 Hz), 113.5 (d, *J*

= 22.0 Hz), 113.0, 82.9, 75.6, 61.5, 61.51; FT-IR (neat) 3436, 3064, 2991, 2929, 2867, 1601, 1503, 1448, 1391, 1347, 1173, 1089, 947, 871, 788, 750 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}FNO+H]^+$ 244.1132, found 244.1146.

4-(3-Nitrophenyl)-3-phenyloxazolidine 3v. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.40; brown liquid; 78 mg, yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 2.0 Hz, 1H), 8.16-8.13 (m, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.8, 7.6 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 2.4 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 4.80 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.44 (dd, *J* = 8.8, 7.2 Hz, 1H), 4.01 (dd, *J* = 8.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 144.6, 144.4, 132.6, 130.1, 129.7, 123.0, 121.5, 118.6, 113.0, 83.1, 75.5, 61.6.; FT-IR (neat) 3032, 2965, 2929, 2867, 1600, 1496, 1454, 1355, 1201, 1172, 1091, 945, 848 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}N_2O_3+H]^+$ 271.1077, found 271.1070.

4-(3-Phenyloxazolidin-4-yl)phenyl acetate 3w. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless liquid; 114 mg, yield 80%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.69 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.38 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.97 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 150.2, 145.1, 139.9, 129.5, 127.4, 122.1, 118.0, 113.0, 83.0, 75.8, 61.4, 21.4; FT-IR (neat) 3063, 3035, 2957, 2924, 2854, 1761, 1600, 1505, 1366, 1196, 1088, 1014, 942, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{17}NO_3+H]^+$ 284.1281, found 284.1286.

4-(4-Bromophenyl)-3-phenyloxazolidine 3x. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; brown liquid; 114 mg, yield 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.65 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.39 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.95 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.88, 140.79, 132.13, 129.50, 128.14, 121.54, 118.13, 112.91, 82.93, 75.67, 61.33; FT-IR (neat) 3043, 2989, 2926, 2864, 1599, 1505, 1403, 1346, 1263, 1165, 1070, 943, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}BrNO+H]^+$ 304.0332, found 304.0330.

4-(4-Chlorophenyl)-3-phenyloxazolidine 3y. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; pale yellow liquid; 101 mg, yield 78%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32-7.28 (m, 4H), 7.20 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 6.46 (d, *J* = 7.8 Hz, 2H), 5.31 (d, *J* = 2.4 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.67 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.39 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.95 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 140.3, 133.5, 129.5, 129.2, 127.8, 118.1, 112.9, 82.9, 75.7, 61.3; FT-IR (neat) 3065, 3045, 2957, 2924, 2854, 1599, 1493, 1346, 1162, 1089, 1013, 643, 746cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}ClNO+H]^+$ 260.0837, found 260.0838.

4-(4-Fluorophenyl)-3-phenyloxazolidine 3z. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; brown liquid; 92 mg, yield 75%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.34 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 9.0 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 2H), 5.35 (d, *J* = 2.4 Hz, 1H), 5.03 (d, *J* = 2.4 Hz, 1H), 4.71 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.41 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.98 (dd, *J* = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, *J* = 224.5 Hz), 145.0, 137.4 (d, *J* = 3.0 Hz), 129.5, 127.9 (d, *J* = 9.0 Hz), 118.0, 116.0 (d, *J* = 21.0 Hz), 112.9, 82.9, 75.9, 61.2; FT-IR (neat) 3040, 2994, 2928, 2865, 1836, 1601, 1507, 1348, 1222, 1155, 1090, 943, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{14}FNO+H]^+$ 244.1132, found 244.1144.

3-(4-Chlorophenyl)-4-(4-fluorophenyl)oxazolidine 3ac. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.58; pale yellow liquid;101 mg, yield 73% ; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.27 (m, 2H), 7.12 (d, *J* = 9.0 Hz, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 9.0 Hz, 2H), 5.28 (d, *J* = 2.4 Hz, 1H), 4.96 (d, *J* = 2.4 Hz, 1H), 4.64 (dd, *J* = 6.6, 4.2 Hz, 1H), 4.40 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.94 (dd, *J* = 9.0, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.3 (d, *J* = 244.5 Hz), 143.5, 136.8 (d, *J* = 3.0 Hz), 129.3, 127.9 (d, *J* = 127.0 Hz), 123.0, 116.1 (d, *J* = 21.0 Hz), 114.0, 82.9, 75.9, 61.3; FT-IR (neat) 3073, 3049, 2992, 2925, 2860, 1601, 1507, 1391, 1356, 1223, 1156, 1093, 945, 810, 765 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{13}ClFNO+H]^+$ 278.0742 found 278.0749.

4-(3-(*p*-Tolyl)oxazolidin-4-yl)phenyl acetate 3ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; yellow liquid; 113 mg, yield 76%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 8.4 Hz, 2H), 5.30 (d, *J* = 2.4 Hz, 1H), 4.97 (d, *J* = 2.4 Hz, 1H), 4.66 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.38 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.96 (dd, J = 8.4, 4.2 Hz, 1H), 2.29 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 150.1, 143.1, 139.3, 130.0, 127.4, 127.3, 122.1, 113.1, 83.3, 75.8, 61.6, 21.4, 20.5; FT-IR (neat) 3006, 2923, 2860, 1763, 1619, 1521, 1366, 1214, 1088, 943,804 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{18}H_{19}NO_3+H]^+$ 298.1438, found 298.1448.

3-(3-Ethylphenyl)-4-(4-fluorophenyl)oxazolidine 3ae. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; brown liquid; 97 mg, yield 71%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 7.2 Hz, 1H), 6.30-6.27 (m, 2H), 5.32 (d, *J* = 1.2 Hz, 1H), 5.00 (d, *J* = 2.4 Hz, 1H), 4.68 (dd, *J* = 7.2, 4.2 Hz, 1H), 4.37 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.95 (dd, *J* = 8.4, 4.2 Hz, 1H), 2.56 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, *J* = 243.0 Hz), 145.7, 145.1, 137.6 (d, *J* = 3.0 Hz), 129.4, 128.0 (d, *J* = Hz), 117.7, 115.9 (d, *J* = 21.0 Hz), 112.5, 110.4, 83.0, 75.8, 61.2, 29.3, 15.7; FT-IR (neat) 3041, 2962, 2926, 2856, 1604, 1507, 1455, 1356, 1223, 1155, 1090, 945, 836, 752cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{18}FNO+H]^+$ 272.1445, found 272.1447.

3-Phenyl-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinoline 5a. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless liquid; 95 mg, yield 75%; 9:1 mixture of diasteroisomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.42-7.41 (m, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.29-7.25 (m, 3H), 7.19-7.17 (m, 1H), 5.45 (s, 1H), 4.47 (t, *J* = 7.8 Hz, 1H), 4.32 (t, *J* = 6.6 Hz, 1H), 3.82 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.08-2.97 (m, 3H), 2.83-2.80 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.9, 135.7, 132.9, 128.8, 128.7, 128.3, 128.3, 127.4, 126.8, 126.6, 90.3, 71.4, 68.8, 46.9, 29.3; FT-IR (neat) 3063, 3030, 2924, 2853, 1711, 1682, 1455, 1373, 1314, 1234, 1030, 941, 746, 699 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{17}NO+H]^+$ 252.1383, found 252.1394.

3-(2-Chlorophenyl)-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinoline 5b. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless liquid; 97 mg, yield 68%; 9:1 mixture of diasteroisomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 1H), 7.42 (m, 2H), 7.30-7.19 (m, 5H), 5.37 (s, 1H), 4.68-4.59 (m, 2H), 3.63 (dd, *J* = 7.6, 5.6 Hz, 1H), 3.14-2.99 (m, 3H), 2.84-2.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 129.8, 128.9, 128.5, 128.5, 128.3, 127.6, 127.2, 126.6, 100.2, 90.3, 70.9, 67.2, 47.2, 29.9; FT-IR (neat) 3066, 2953, 2924, 2853, 1649, 1464, 1440, 1396, 1257, 1127, 1034, 942, 750 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{16}ClNO+H]^+$ 286.0993, found 286.1003.

3-(4-Fluorophenyl)-2,3,6,10b-tetrahydro-5H-oxazolo[2,3-a]isoquinoline 5c. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane $R_f = 0.50$; colorless liquid; 97 mg, yield 72%; 9:1 mixture of diasteroisomers; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43-7.40 (m, 3H), 7.28-7.25 (m, 2H), 7.19-7.17 (m, 1H), 7.05 (t, *J* = 8.4 Hz, 2H), 5.42 (s, 1H), 4.45 (t, *J* = 7.8 Hz, 1H), 4.28 (t, *J* = 7.2 Hz, 1H), 3.77 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.07-2.95 (m, 3H), 2.83-2.80 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.1 (d, *J* = 244.5 Hz), 137.6 (d, *J* = 4.5 Hz), 135.6, 132.9, 128.7, 128.4 (d, *J* = 7.5 Hz), 128.4, 128.3, 126.7, 115.7 (d, *J* = 21 Hz), 90.2, 71.5, 68.1, 46.9, 29.2; FT-IR (neat) 3067, 2957, 2924, 2854, 1637, 1508, 1424, 1223, 1154, 1096, 1033, 834, 746 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{17}H_{16}FNO+H]^+$ 270.1289, found 270.1301.

2-(Methyl(*o*-tolyl)amino)-2-phenylethan-1-ol A_1. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane $R_f = 0.40$; yellow liquid; 97 mg, yield 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 3H), 7.24-7.19 (m, 3H), 7.11-7.01 (m, 2H), 6.89 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.12 (t, *J* = 6.8 Hz, 1H), 4.22 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.82 (dd, *J* = 11.2, 6.4 Hz, 1H), 2.55 (s, 3H), 2.46 (s, 3H), 2.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 137.8, 134.3, 131.4, 128.9, 128.4, 127.9, 126.5, 124.5, 123.7, 68.6, 63.1, 38.0, 18.7; FT-IR (neat) 3434, 3062, 3028, 2949, 2881, 2796, 1637, 1598, 1491, 1452, 1252, 1033, 911,767 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{19}NO+H]^+$ 242.1539, found 242.1530.

4-((2-Hydroxy-1-phenylethyl)(methyl)amino)benzonitrile A_2. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.38$; yellow liquid; 85 mg, yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 9.2 Hz, 2H), 7.37-7.31 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.17 (dd, *J* = 8.8, 5.2 Hz, 1H), 4.23 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.15 (dd, *J* =

11.2, 8.8 Hz, 1H), 2.90 (s, 3H), 2.19 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 137.3, 133.6, 129.0, 128.9, 127.9, 126.9, 120.4, 112.6, 77.4, 63.2, 62.5, 32.5; FT-IR (neat) 3438, 3062, 2955, 2921, 2214, 1605, 1518, 1385, 1347, 1180, 1110, 1063, 817, 755, 702 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{16}N_2O+H]^+$ 253.1335, found 253.1352.

2-(Benzyl(phenyl)amino)-2-phenylethan-1-ol A_4. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.40; yellow liquid; 133 mg, yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 7H), 7.14-7.08 (m, 5H), 6.18 (d, *J* = 8.4 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 5.08 (t, *J* = 6.8 Hz, 1H), 4.45 (d, *J* = 17.1 Hz, 1H), 4.37 (d, *J* = 17.1 Hz, 1H) 4.00 (d, *J* = 6.8 Hz, 2H), 1.90 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 139.8, 138.1, 129.3, 128.9, 127.8, 127.7, 127.1, 126.9, 118.94, 116.1, 65.2, 63.2, 51.0; FT-IR (neat) 3559, 3060, 3029, 2926, 2884, 1597, 1499, 1451, 1348, 1249, 1158, 1033, 990, 949,746 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{21}H_{21}NO+H]^+$ 304.1696, found 304.1696.

4-(2-Hydroxy-1-(methyl(phenyl)amino)ethyl)benzonitrile A_5. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow liquid; 103 mg, yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$) 7.61 (d, *J* = 8.4 Hz, 2H), 7.29-7.25 (m, 4H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.08 (t, *J* = 7.2 Hz, 1H), 4.18-4.10 (m, 2H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 143.7, 132.6, 129.7, 128.2, 119.2, 118.8, 115.0, 111.8, 64.6, 61.8, 32.7; FT-IR (neat) 3440, 3063, 3034, 2957, 2924, 2216, 1604, 1519, 1386, 1346, 1178, 1111, 1063, 818 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{16}H_{16}N_2O+H]^+$ 253.1335, found 253.1350.

1-(Methyl(phenyl)amino)butan-2-ol A_6. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.40; brown liquid; 81 mg, yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.78 (t, *J* = 7.2 Hz, 1H), 3.88-3.82 (m, 1H), 3.31-3.20 (m, 2H), 2.96 (s, 3H), 2.37 (br s, 1H), 1.61-1.47 (m, 2H), 1.05 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 129.3, 117.5, 113.5, 70.7, 60.3, 39.5, 27.6, 10.1; FT-IR (neat) 3410, 3093, 3061, 2964, 2931, 2877, 1600, 1505, 1369, 1242, 1208, 987, 856, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{11}H_{17}NO+H]^+$ 180.1383, found 180.1408.

2-(Methyl(phenyl)amino)-2-phenylethan-1-ol A_7. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.40; yellow liquid; 64 mg, yield 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.84 (t, *J* = 7.2 Hz, 1H), 5.13 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.18-4.10 (m, 2H), 2.74 (s, 3H), 2.22 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 137.7, 129.4, 128.7, 127.7, 127.4, 118.5, 114.9, 64.7, 61.9, 32.3; FT-IR (neat) 3401, 3087, 3060, 3027, 2943, 2816, 1598, 1504, 1450, 1379, 1319, 1065, 1030, 900, 750 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $[C_{15}H_{17}NO+H]^+$ 228.1383, found 228.1398.

3.4 References

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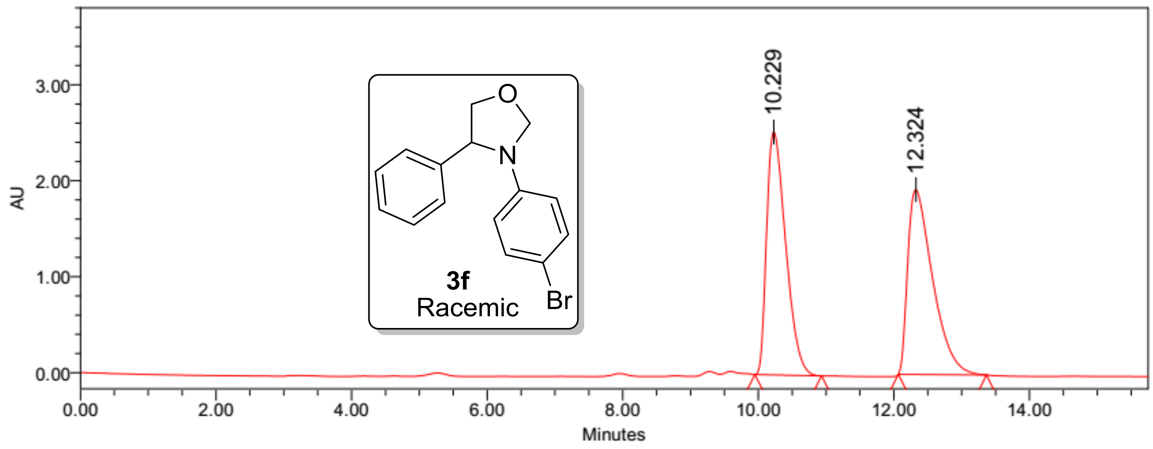
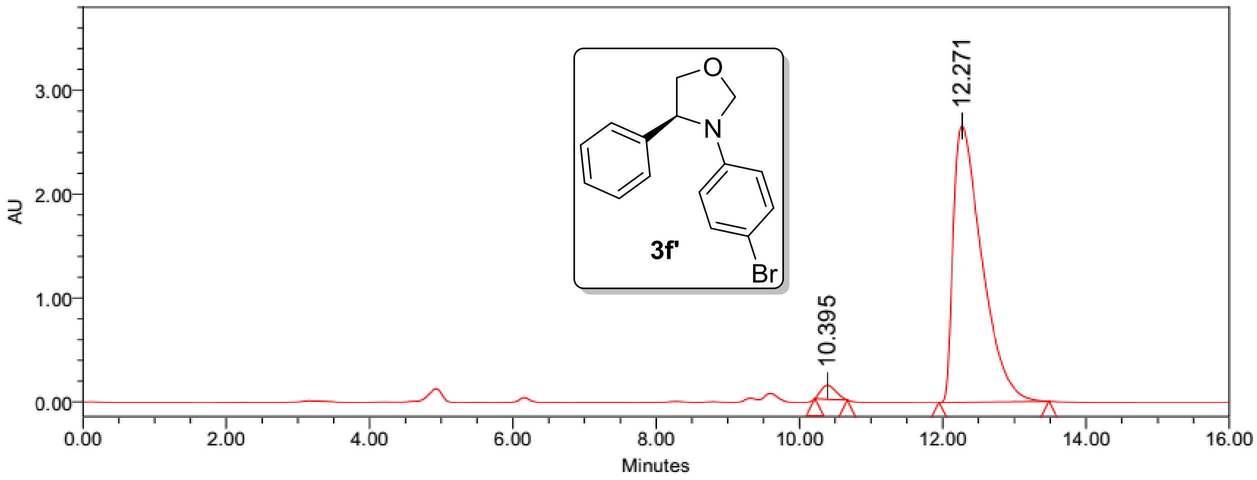
3.5 Selected HPLC Chromatograms



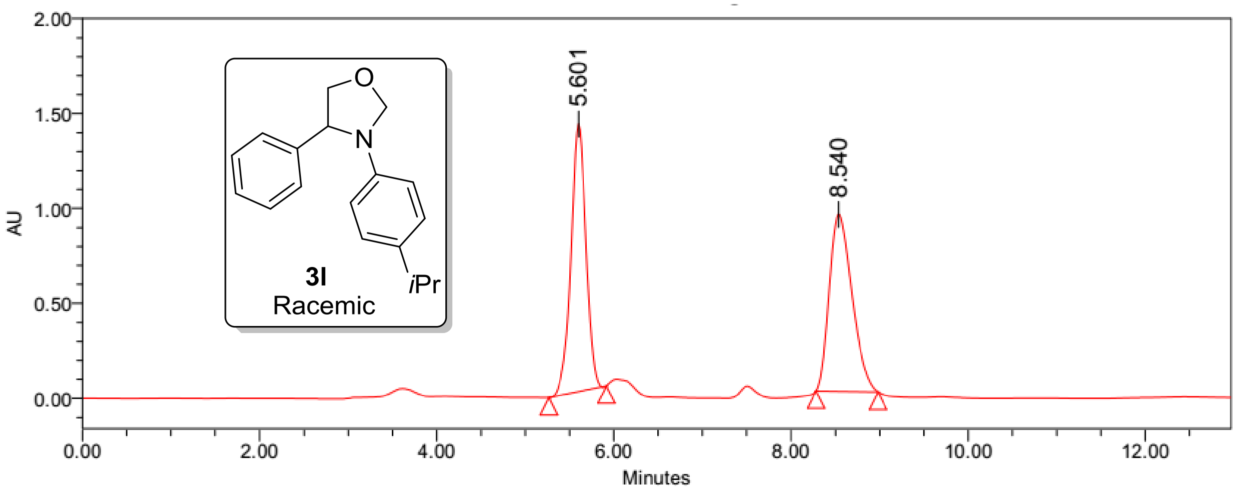
Peak Results

	RT	Height (μV)	% Area
1	10.229	2533391	50.12
2	12.324	1928176	49.88



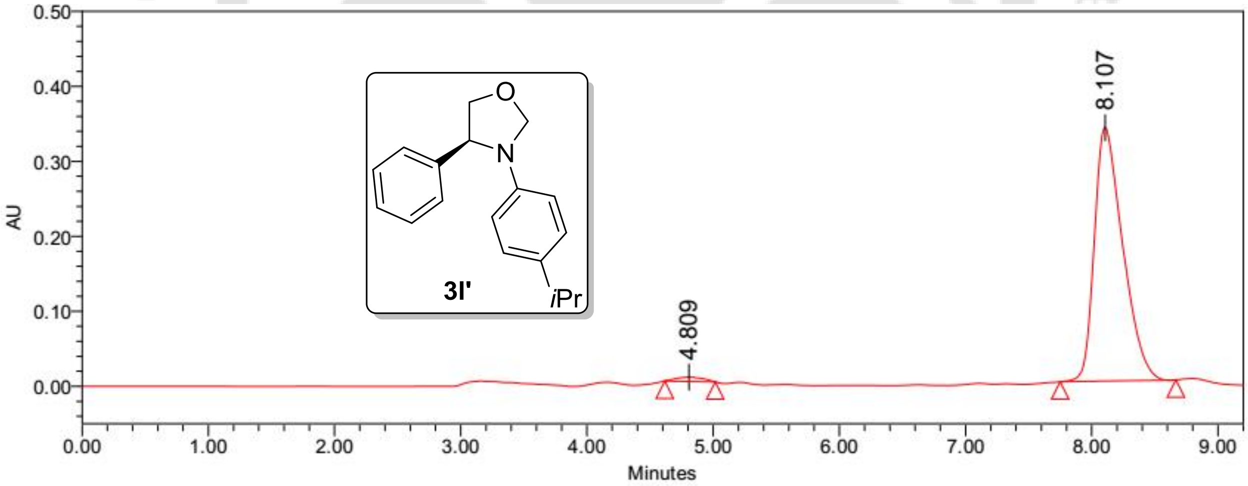
Peak Results

	RT	Height (μV)	% Area
1	10.395	132157	2.53
2	12.271	2663180	97.47



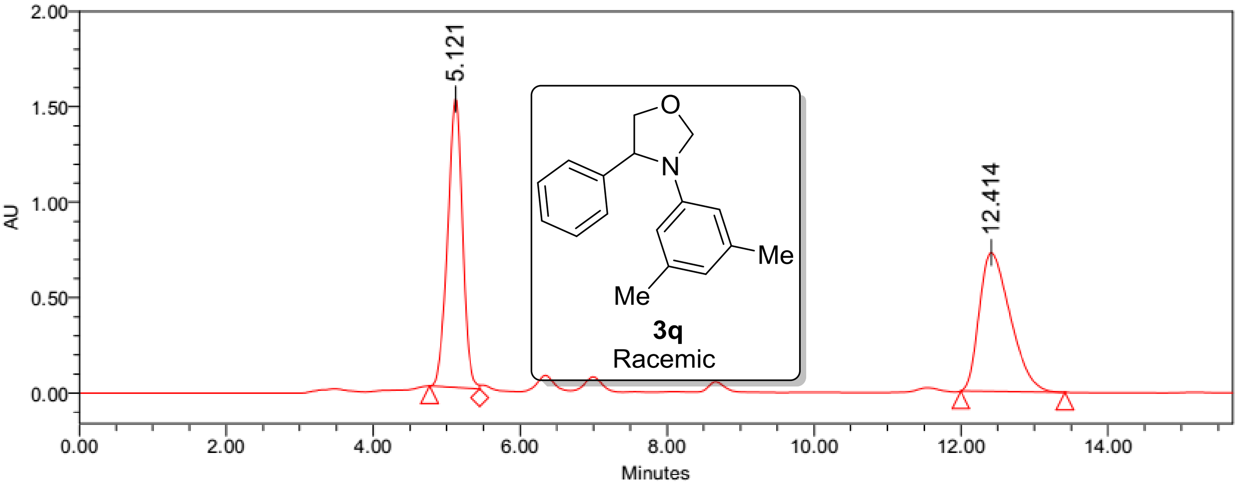
Peak Results

	RT	Height (μV)	% Area
1	5.601	1409422	49.90
2	8.540	935027	50.10



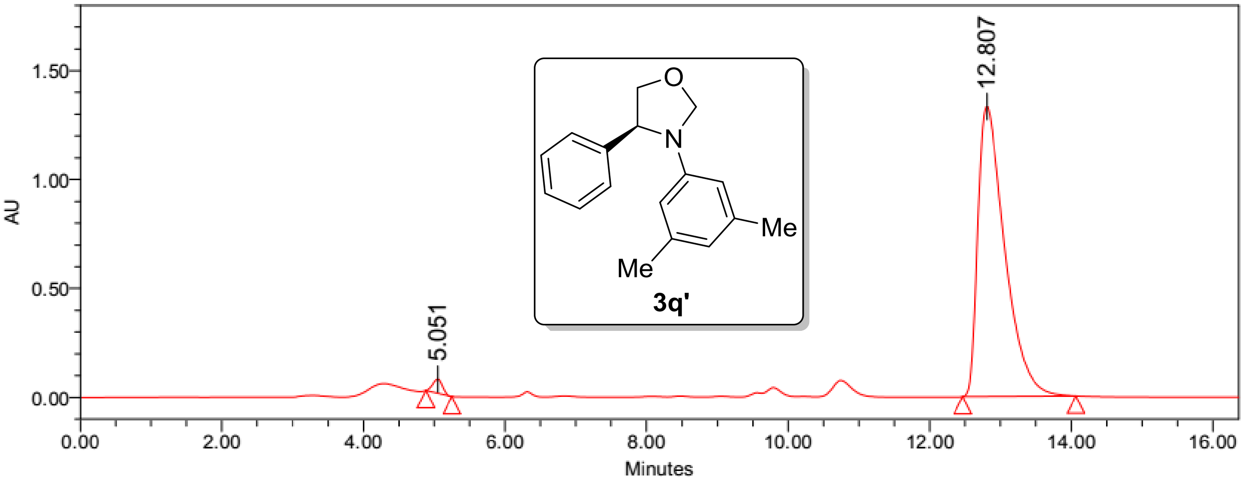
Peak Results

	RT	Height (μV)	% Area
1	4.809	5741	1.61
2	8.107	339400	98.39



Peak Results

	RT	Height (µV)	% Area
1	5.121	1515064	49.71
2	12.414	728142	50.29



Peak Results

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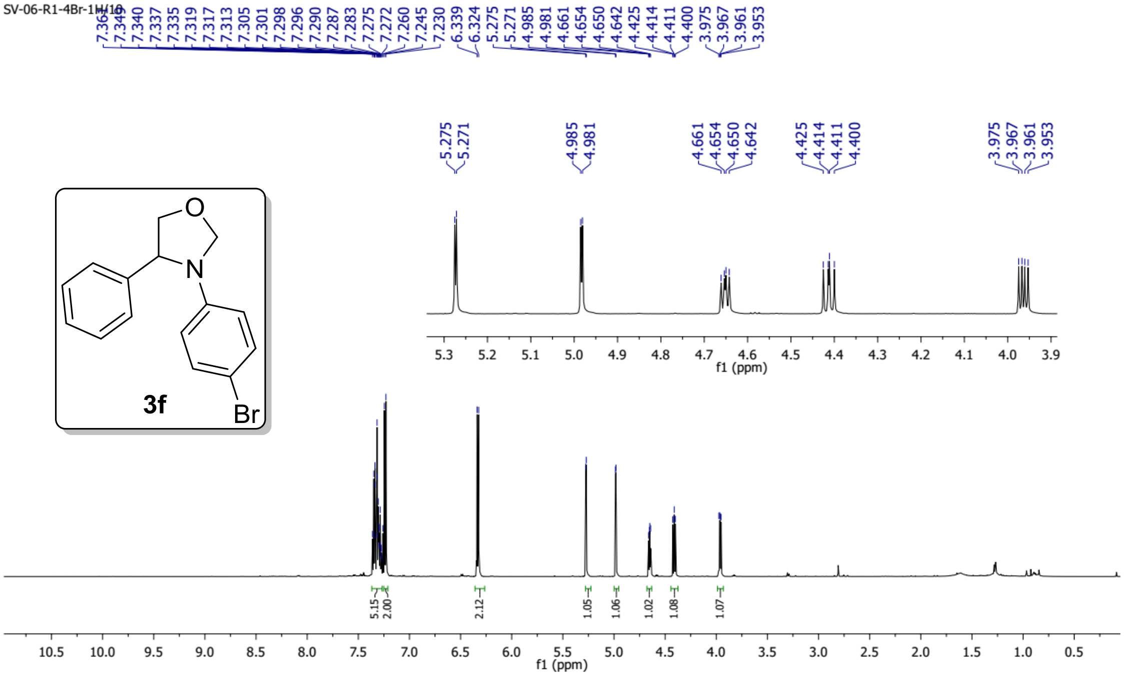
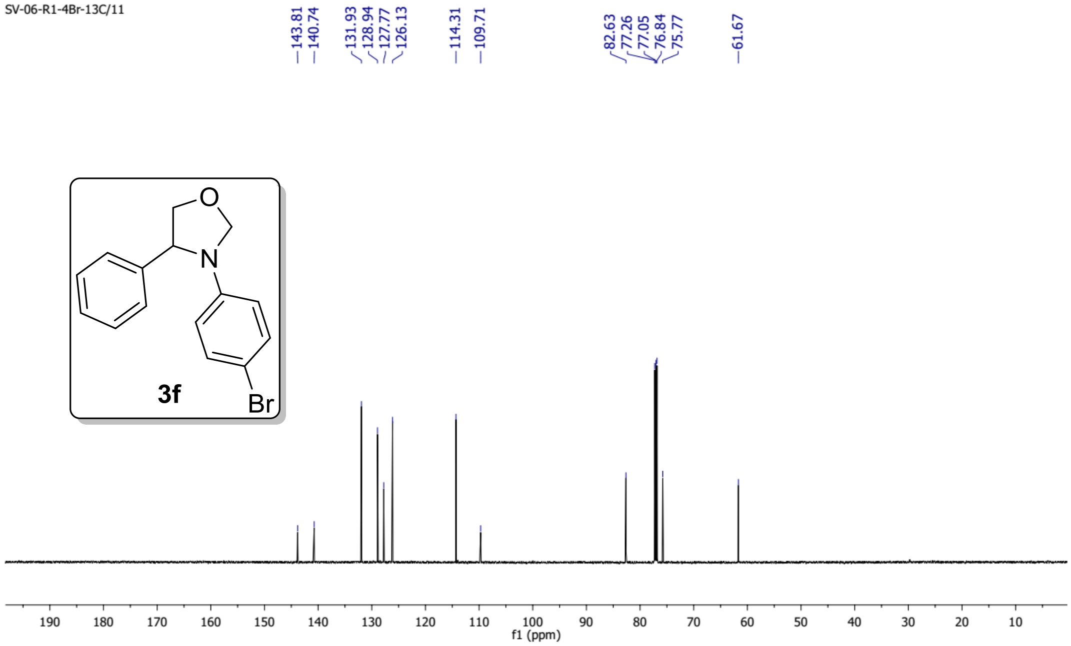
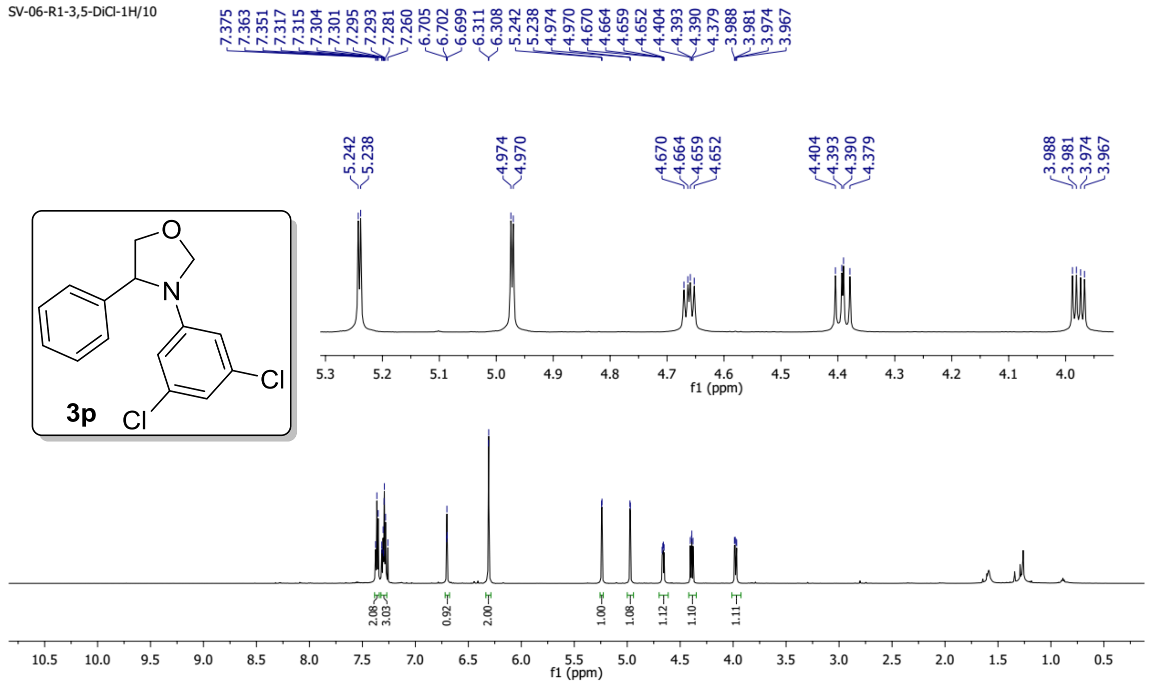
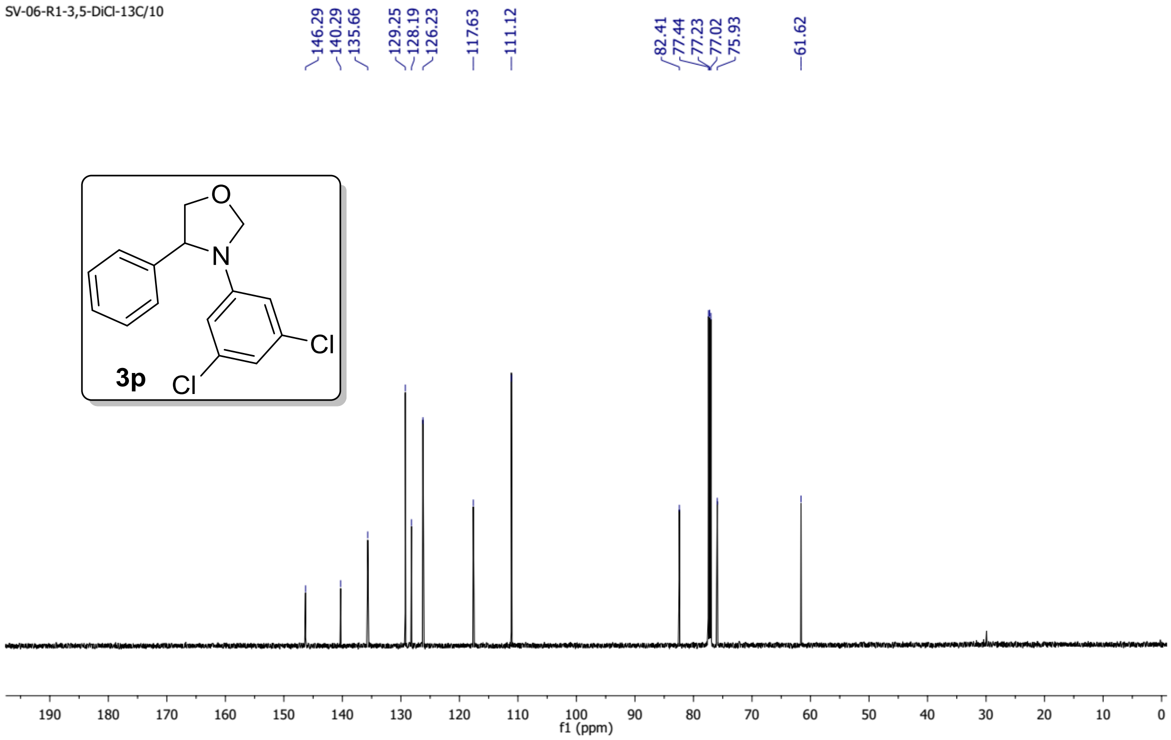
1	5.051	64189	1.67
2	12.807	1333216	98.33

3.6 Selected NMR Spectra






SV-06-R1-3,5-DiCl-1H/10
7.375
7.363
7.351
7.317
7.315
7.304
7.301
7.295
7.293
7.281
7.260
6.705
6.702
6.699
6.311
6.308
5.242
5.238
4.974
4.970
4.670
4.664
4.659
4.652
4.404
4.393
4.390
4.379
3.988
3.981
3.974
3.967
3p
O
N
Cl
Cl
2.08
3.03
0.92
2.00
1.00
1.08
1.12
1.10
1.11
f1 (ppm)


SV-06-R1-3,5-DiCl-13C/10
146.29
140.29
135.66
129.25
128.19
126.23
117.63
111.12
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77.44
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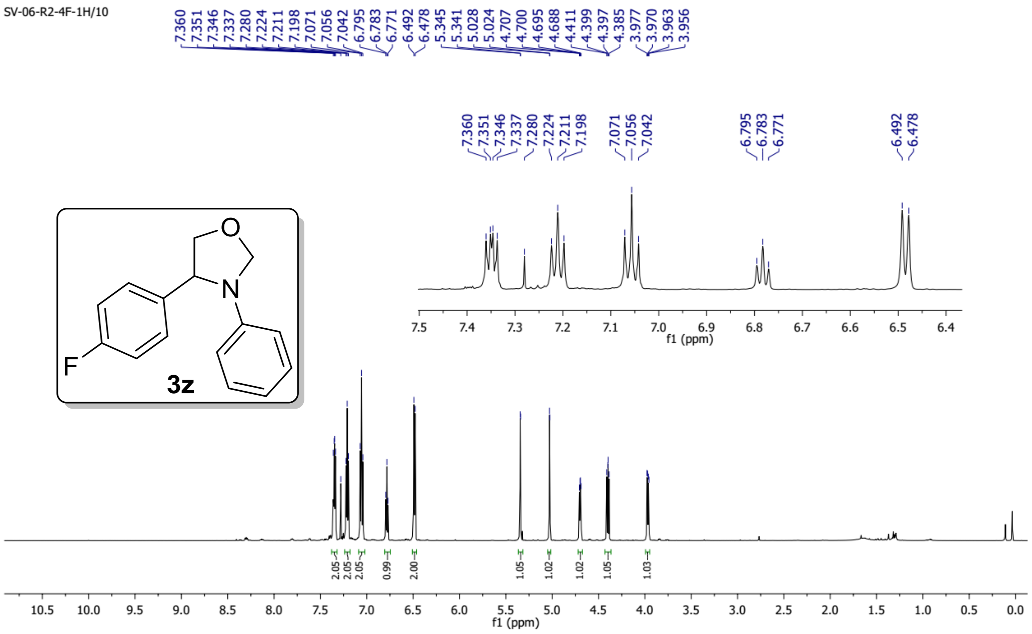
75.93
61.62
3p
O
N
Cl
Cl
f1 (ppm)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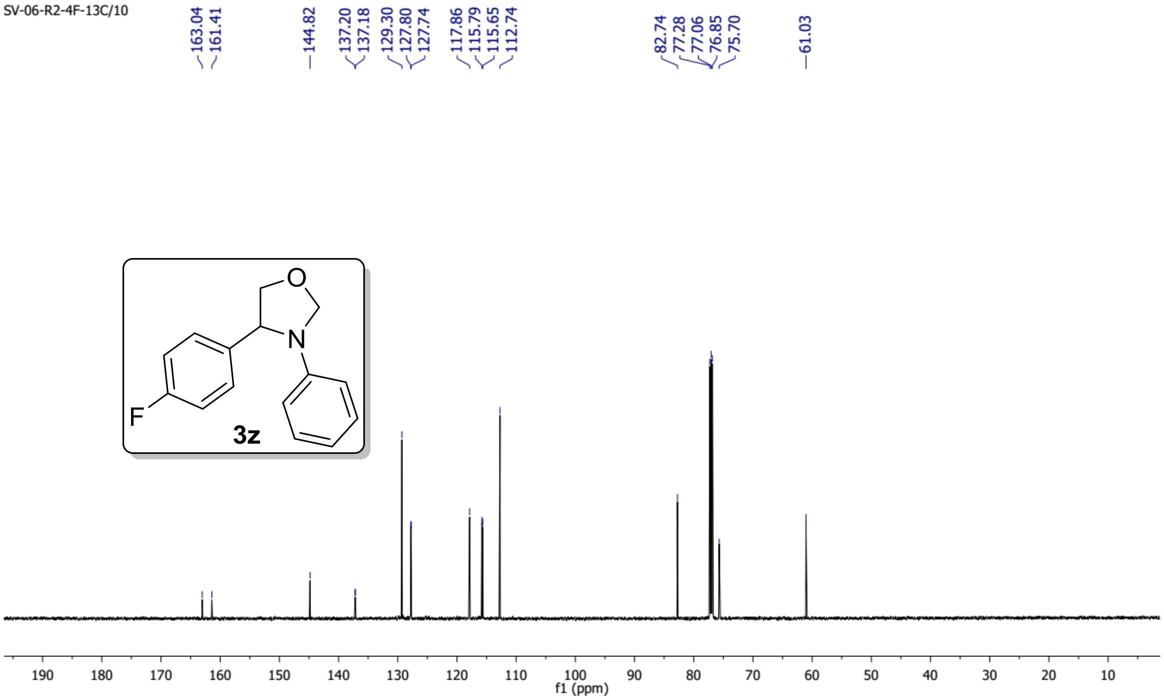
7.360
7.351
7.346
7.337
7.280
7.224
7.211
7.198
7.071
7.056
7.042
6.795
6.783
6.771
6.492
6.478
5.345
5.341
5.028
5.024
4.707
4.700
4.695
4.688
4.411
4.399
4.397
4.385
3.977
3.970
3.963
3.956
O
N
F
3z
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
6.5
6.4
f1 (ppm)
2.05
2.05
2.05
0.99
2.00
1.05
1.02
1.02
1.05
1.03
10.5
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)


SV-06-R2-4F-13C/10
163.04
161.41
144.82
137.20
137.18
129.30
127.80
127.74
117.86
115.79
115.65
112.74
82.74
77.28
77.06
76.85
75.70
61.03
O
N
F
3z
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Chapter IV

Aluminium-Catalyzed [3+2]-Cycloaddition of Chiral Aziridines with Isoselenocyanates

The chemistry of organoselenium compounds has attracted considerable attention because of their interesting biological and medicinal properties.[1] Among them, selenazolidines are found in many biologically active compounds exhibiting anticancer and anti-mutagenic properties.[2] They can protect oxidant-induced DNA damage and also act as an inducible nitric oxide synthase (iNOS) inhibiter.[3] Therefore, synthesis of selenium heterocycles is an attractive goal of pharmaceutical research. Some of the biologically active selenazolidine motifs are illustrated in Figure 1.

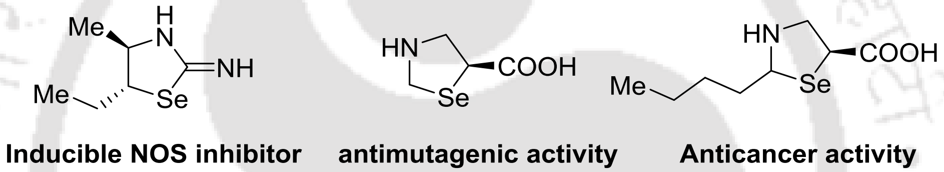
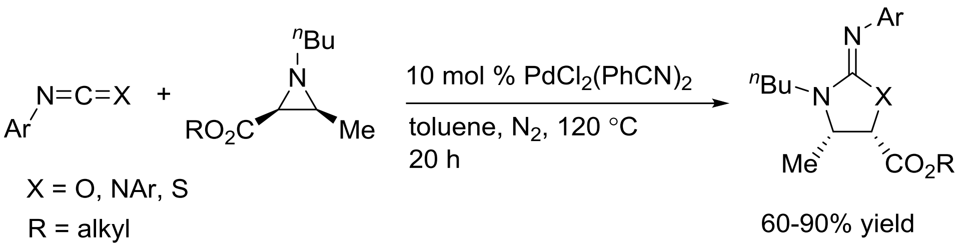


Figure 1. Some Biologically Active Selenazolidines

Aziridines are versatile building blocks for the development of nitrogen heterocycles.[4] The transformations of aziridines with isocyanates, iosthiocyanates and carbodiimide are well documented,[5] and few studies are focused on enantioselective version of these reactions. Despite these studies of the ring expansion of aziridine with isoselenocyanates are limited.

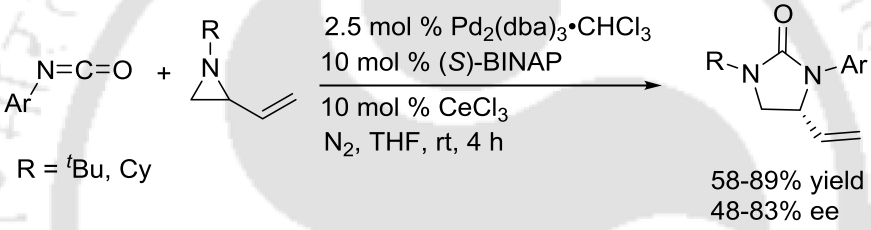
4.1 Aziridine Ring Expansion to Enantioenriched Azolidines

Alper group reported a Pd-catalyzed cycloaddition of aziridines with heterocumulenes to produce enantioenriched 2-iminoazolidines (Scheme 1).[6] The reaction is reported employing $PdCl_2(PhCN)_2$ as the catalyst to produce regio- and stereospecific azolidines with retention of the stereochemistry.



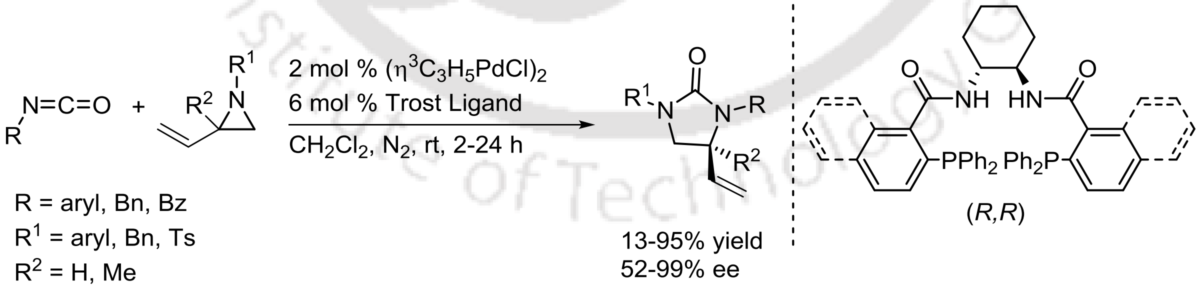
Scheme 1. Stereospecific Pd-Catalyzed Ring Expansion of Chiral Unactivated Aziridines with Heterocumulenes

The same group demonstrated the enantioselective cycloaddition of *N*-alkyl-2-vinylaziridines with *N*-aryl isocyanates using the combination of $Pd_2(dba)_3CHCl_3$ and $CeCl_3$ as the catalysts and (*S*)-BINAP in THF at room temperature (Scheme 2).[7] The corresponding imidazolidin-2-ones have been obtained in high yields and enantiomeric excess.



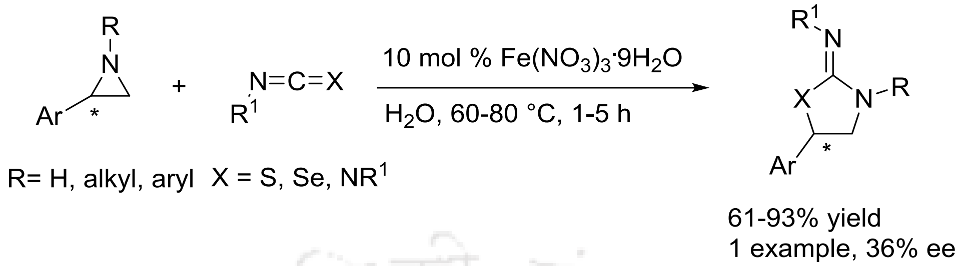
Scheme 2. [3+2]-Cycloaddition of Vinylaziridines with Isocyanates

Trost and co-workers described the asymmetric [3+2]-cycloaddition of 2-vinyl aziridines with isocyanates using 2 mol% (η^3-$C_3H_5PdCl)_2$ as the catalyst with the Trost ligand (Scheme 3).[8] The protocol produces the imidazolidin-2-ones with enantioselectivity up to 99%.



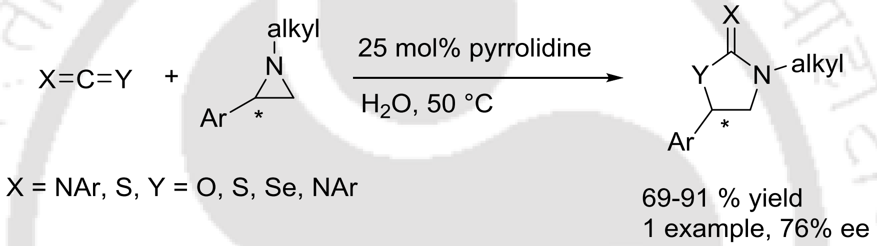
Scheme 3. Enantioselective Cycloaddition of 2-Vinylaziridines with Isocyanates Employing Trost Ligand

Our group presented a Fe-catalyzed [3+2]-cycloaddition of aziridines with isocyanates, isothiocyanates, isoselenocyanates, carbodiimides and carbon disulfide. The reaction takes place in aqueous suspension at moderate temperature (Scheme 4).[9] In case of optically active aziridines, selenazolidines is formed with up to 36% ee.



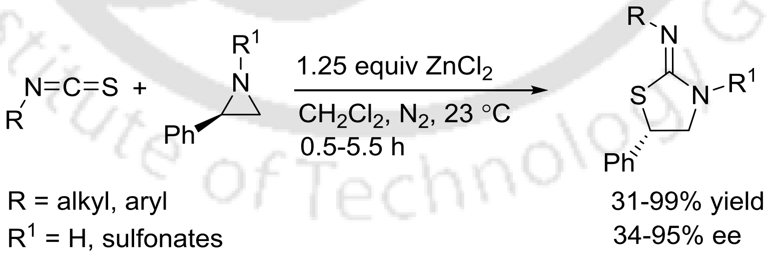
Scheme 4. Fe-Catalyzed Cycloaddition of Aziridines with Isoselenocyanates

Our group also demonstrated pyrroldine-mediated [3+2]-cycloaddition of aziridines with heterocumulenes (Scheme 5).[10] This methodology provides thiazolidines with up to 76% ee.



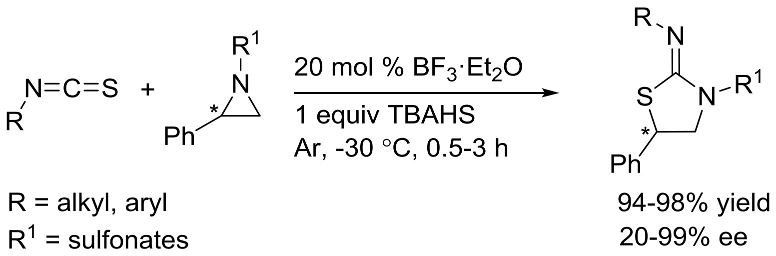
Scheme 5. Pyrrolidine-Catalyzed Cycloaddition of Aziridines with Heterocumulenes

A stereospecific Zn-mediated [3+2]-cycloaddition of *N*-alkyl/aryl isothiocyanates with chiral *N*-H- and *N*-sulfonylaziridines is reported (Scheme 6).[11] This $ZnCl_2$-mediated transformation provides enantioselectivity up to 99%.



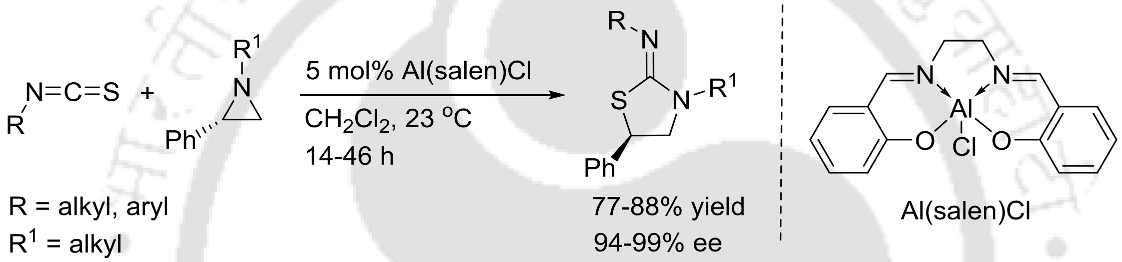
Scheme 6. Zn-Mediated Stereospecific Reaction of Chiral Aziridines with Isothiocyanates

Ghorai group reported the stereospecific synthesis of 2-iminothiazolidines employing $BF_3 \cdot Et_2O$ as a catalyst and tetrabutylammonium hydrogen sulfate (TBAHS) as an additive from isothiocyanates and *N*-sulfonylaziridines (Scheme 7).[12] The *trans*-2,3-disubstituted *N*-tosylaziridines provides 2-iminothiazolidines with 99% dr.



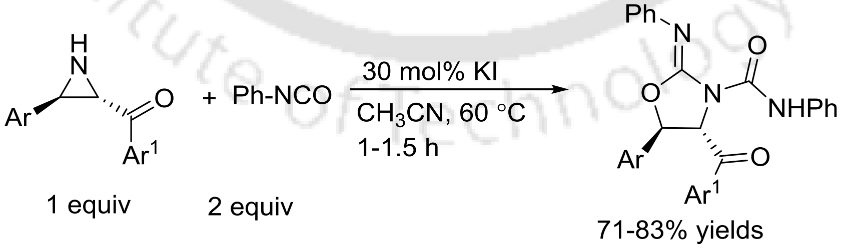
Scheme 7. $BF_3{\cdot}Et_2O$-Catalyzed Stereospecific Synthesis of 2-Iminothiazolidines

Our group presented the synthesis of 2-iminothiazolidines *via* the stereospecific [3+2]-cycloaddition of unactivated aziridines with isothiocyanates using Al(salen)Cl (Scheme 8).[13] This protocol is successful to yield 2-iminothiazolidines with 94-99% ee.



Scheme 8. Al-Catalyzed [3+2]-Cycloaddition of Chiral aziridines and Isothiocyanates

The KI-catalyzed stereo- and regioselective ring expansion of keto-aziridines with 2 equiv. of phenylisocyanate is reported (Scheme 9).[14] The reaction consumes 2 equiv. of phenylisocyanate to produce 1-phenylcarbamoyl aziridine followed by ring expansion with other phenylisocyanate to produce *trans*-2-iminooxazolidines.



Scheme 9. KI-Catalyzed Ring Expansion of *trans*-NH-Ketoaziridines with Isocyanates

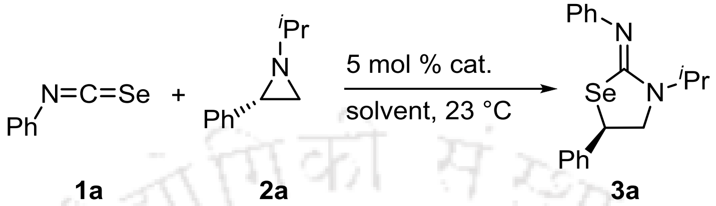
4.2 Present Study

In this chapter, we report an enantioselective [3+2]-cycloaddition of unactivated chiral aziridines with isoselenocyanates to produce substituted iminoselenozolidines using Al(salen)Cl catalyst. The reaction is simple, regio-, stereospecific and effective at room temperature with high enantiomeric purities. First, we optimized the reaction condition utilizing isoselenocyanate **1a** and (*S*)-2-phenylaziridine **2a** as the model substrates employing salen based Fe(III) **C1**, Co(II) **C2**, Cu(II) **C3**, Ti(IV) **C4** and Al(III) **C5** Lewis acids as the catalysts (Table 1). To our delight, the cyclization occurred to give (*R*)-2-iminoselenazolidine **3a** in 93% ee and 89% yield when the substrates were stirred with 5 mol% **C5** at room temperature for 23 h in CH_2Cl_2, whereas the reaction using **C3** gave 27% ee and 88% yield (entries 1-2). In contrast, **C1-2** and **C-4** showed no catalytic activities and the formation of **3a** was not observed. Subsequent studies of the Al-catalysts revealed that **C6** with electron donating 4-OMe group afforded superior results (95% ee) compared to **C7** having electron withdrawing 4-nitro group (90% ee) (entries 3-4). The enantiomeric purity was further enhanced to 97% using $(CH_2Cl)_2$, while CH_3CN, THF, $CHCl_3$ and toluene yielded 87-96% ee (entries 6-9). Control experiment confirmed that the target heterocycle was not formed in the absence of the catalyst (entry 10).

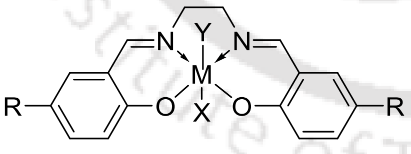
Next, the substrate scope was studied using a series of isoselenocyanates **1b-i** with aziridine **2a** (Table 2). Substrate **1b** bearing 2-methoxy group in the aryl ring underwent reaction to produce **3b** in 96% ee and 80% yield. The reaction of **1c-g** having the substitution at the 4-position of the aryl ring with chloro, ethyl, iodo, methyl and methoxy groups furnished **3c-g** in 90-98% ee and 83-91% yields. Similar result observed with **1h** having 3,4-dimethyl group, giving **3h** in 97% ee and 89% yield, whereas naphthyl isoselenocyanate **1i** underwent reaction to furnish **3i** in 99% ee and 86% yield.

The utility of the protocol was further extended to the coupling of a series of isoselenocyanates with 1-alkyl-(*S*)-2-phenylaziridines **2b-j** (Table 3). The reaction of isoselenocyanate **1f** having 4-methyl group underwent reaction with aziridines bearing 1-cyclohexyl **2c**, 1-ethyl **2d**, 1-isobutyl **2e**, 1-benzyl **2f**, 1-(4-bromobenzyl) **2g**, 1- (4-fluorobenzyl) **2h** and 1-(4-methoxybenzyl) **2i** and 1-methylnaphthyl **2j** groups produced the heterocyclic scaffolds **3k-r** in 98-99% ee and 79-90% yields, while **2b** having *N*-Boc failed react to give **3j**, which may be due to the electron withdrawing nature of Boc group.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Yield (%)[b]	ee (ee)[c]
1	**C3**	CH_2Cl_2	88	27
2	**C5**	CH_2Cl_2	89	93
3	**C6**	CH_2Cl_2	85	95
4	**C7**	CH_2Cl_2	95	90
5	**C5**	$(CH_2Cl)_2$	90	97
6	**C5**	CH_3CN	89	96
7	**C5**	THF	60	87
8	**C5**	$CHCl_3$	86	96
9	**C5**	Toluene	86	96
10	-	$(CH_2Cl)_2$	n.d.	-



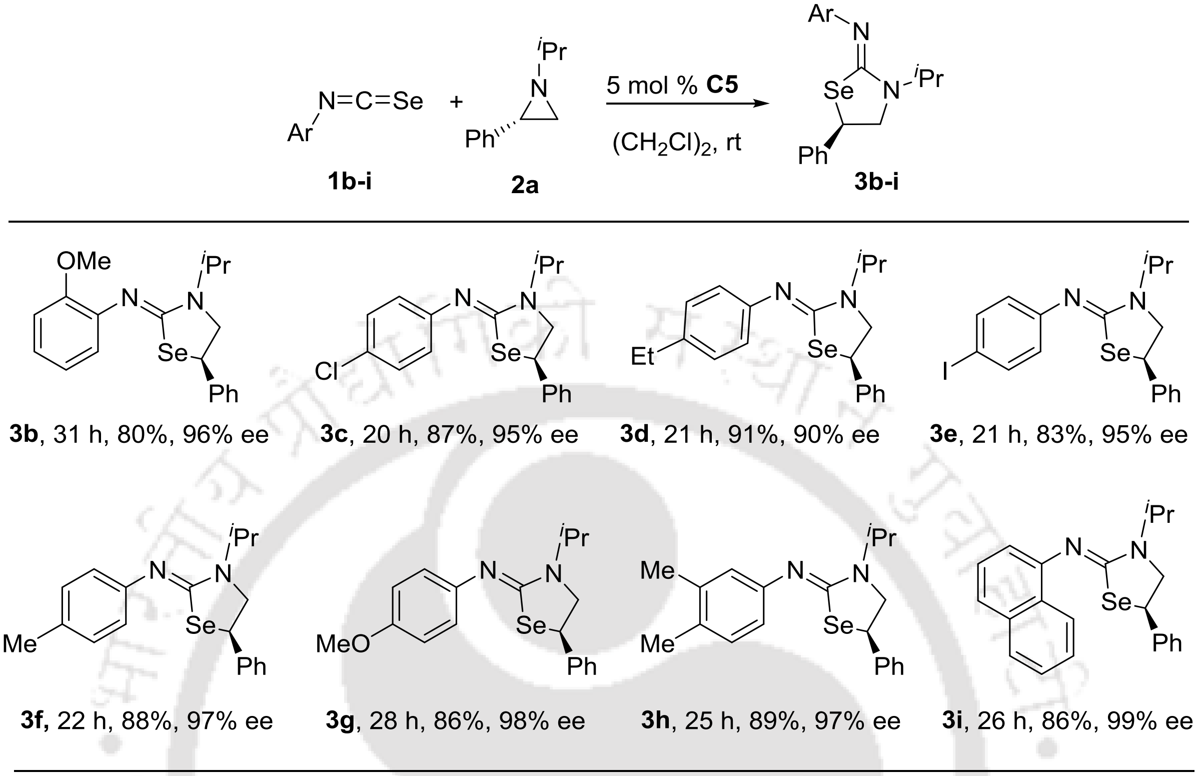
C1 M = Fe, R = H, X = Cl, Y = 0
C2 M = Co, R = H, X and Y = 0
C3 M = Cu, R = H, X and Y = 0
C4 M = Ti, R = H, X and Y = Cl
C5 M = Al, X = Cl, R = H, Y = 0
C6 M = Al, X = Cl, R = OMe, Y = 0
C7 M = Al, X = Cl, R = NO_2, Y = 0

[a] Reaction conditions: Isoselenocyanate **1a** (0.25 mmol), aziridine **2a** (0.25 mmol), catalyst (5 mol %), solvent (1.0 mL), 23 °C, 23 h.

[b] Isolated yield. n.d. = not detected.

[c] Determined by chiral HPLC using Daicel OJ-H column with hexane : ^{i}PrOH (9:1).

Table 2. Reaction of Substituted Isoselenocyanates with *N*-Isopropyl Aziridine **2a**[a,b,c]



3b, 31 h, 80%, 96% ee

3c, 20 h, 87%, 95% ee

3d, 21 h, 91%, 90% ee

3e, 21 h, 83%, 95% ee

3f, 22 h, 88%, 97% ee

3g, 28 h, 86%, 98% ee

3h, 25 h, 89%, 97% ee

3i, 26 h, 86%, 99% ee

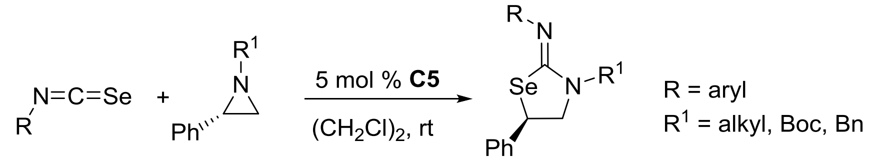
[a] Reaction conditions: Isoselenocyanates **1b−i** (0.25 mmol), aziridine **2a** (0.25 mmol), **C2** (5 mol %), $(CH_2Cl)_2$ (1.0 mL), 23 °C, air.

[b] Isolated yield.

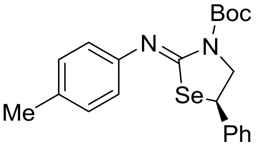
[c] Determined by chiral HPLC analysis.

However, naphthyl isoselenocyanate **1d** with aziridine having 1-cyclohexyl **2c** and 1-benzyl **2f** groups underwent reaction to provide **3s** and **3t** in 97% ee (81%) and 98% ee (78%), respectively. Similar results observed with isoselenocyanate **1g** bearing 4-methoxy group with aziridine **2e**, affording **3u** in 99% ee and 77% yield. Further, the coupling of isoselenocyanate **1e** with aziridines **2f** and **2g** having 1-benzyl group can be accomplished to furnish the scaffolds **3v** and **3w** in 92% ee (80%) and 94% ee (78%) respectively. The absolute configuration of the heterocycle **3** has been assigned based on the single crystal X-ray analysis of **3b** (Figure 2).

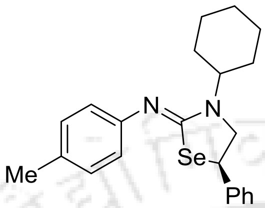
Table 3. Reaction of Substituted Isoselenocyanates with Substituted Aziridines[a,b,c]



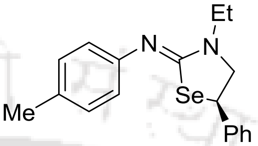
1 **2b-j** **3j-w**



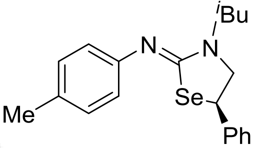
3j, 24 h, 0%



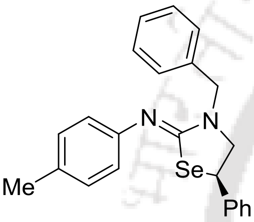
3k, 27 h, 79%, 99% ee



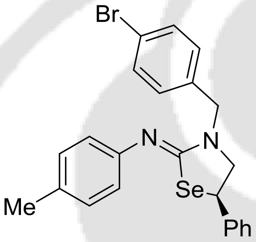
3l, 24 h, 90%, 99% ee



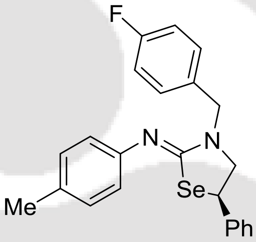
3m, 24 h, 89%, 96% ee



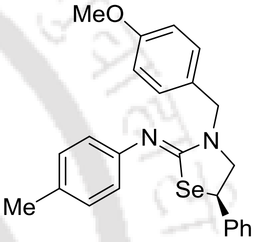
3n, 28 h, 83%, 98% ee



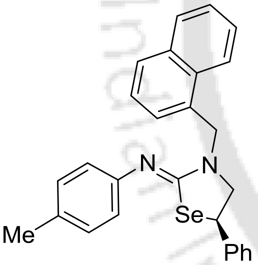
3o, 30 h, 85%, 99% ee



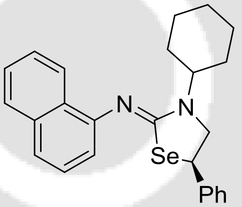
3p, 31 h, 86%, 99% ee



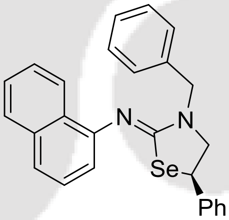
3q, 28 h, 83%, 98% ee



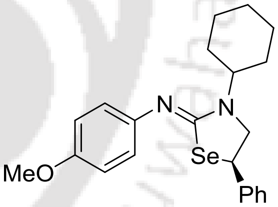
3r, 61 h, 90%, 98% ee



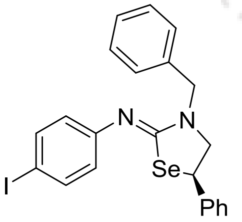
3s, 32 h, 81%, 97% ee



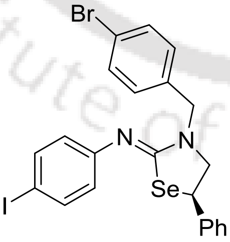
3t, 27 h, 78%, 98% ee



3u, 36 h, 77%, 99% ee



3v, 32 h, 80%, 92% ee



3w, 30 h, 78%, 94% ee

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[a] Reaction conditions: Isoselenocyanates **1** (0.25 mmol), aziridine **2b-j** (0.25 mmol), **C2** (5 mol %), $(CH_2Cl)_2$ (1.0 mL), 23 °C, air.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

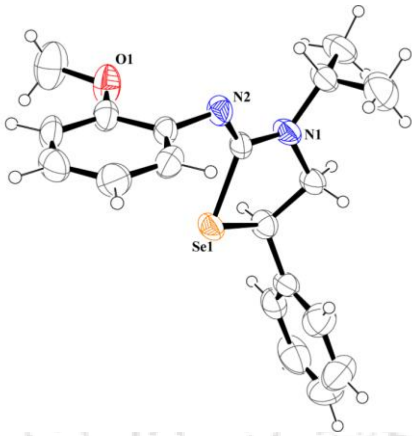
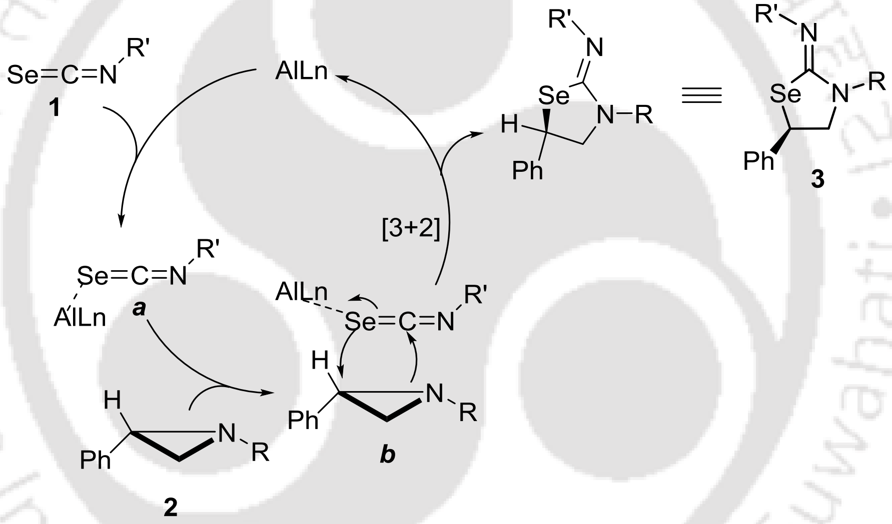


Figure 2. ORTEP Diagram of **3b** with 30% Ellipsoid (CCDC 1584169).



Scheme 9. Proposed Catalytic Cycle

To gain insight into the mechanism, the experimental and DFT studies[15] suggest that chelation of isoselenocyanate **1** with Al-salen may lead to the formation of Al-complex ***a***, which can couple with aziridine through a concerted S_N2 pathway ***b*** to produce the target products **3** (Scheme 9).

In summary, the Al-catalyzed stereospecific tandem C-N/C-Se bond formation of isoselenocyanates with (*S*)-2-phenylaziridines has been developed at room temperature. The high optical purity, mild reaction conditions and using simple Al-catalysis are the advantages of this protocol.

4.3 Experimental Section

4.3.1 General Information. Aziridines,[16] isoselenocyanates[9,17] and catalysts[18] were prepared according to the reported procedure. HPLC analysis was carried out using Daicel Chiralcel OD, OD-H and OJ-H columns. Single crystal X-ray analysis was done using CCD diffractometer equipped with 1.75 kW sealed-tube Mo-K*α* irradiation (λ= 0.71073 Å) at 298(2) K, and the structure was solved by direct methods using SHELXS-97 (Göttingen, Germany) and refined with full-matrix least-squares on F^2 using SHELXL-97. The other information was followed as presented in chapter 1.

4.3.2 Procedure for the Preparation of Chiral Aziridines.[16b] Aldehyde (2 mmol) was added to a solution of (S)-(+)-2-Phenylglycinol (1 mmol) in ethanol (5 mL) and allowed to stir for 2 h at room temperature, and then $NaBH_4$ (3 mmol) was added at 0 °C and allowed the reaction to stirr for 4 h. After completion, the solvent was removed on a rotary evaporator. The residue was extracted using water and CH_2Cl_2 (3×10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator. The residue was further reacted with TsCl (1.2 mmol) and DMAP (10 mg) in dry CH_2Cl_2 (20 mL) at 0 °C were added a solution of Et_3N (1.5 mmol) in dry CH_2Cl_2 (5 mL). Then, the mixture was allowed to room temperature and the stirring was continued for 24 h. The mixture was then treated with a saturated NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4) and evaporated on a rotary evaporator to give a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as eluent.

4.3.3 Procedure for the Cycloaddition of Isoselenocyanates with Chiral Aziridines. Isoselenocyanate (0.25 mmol), aziridine (0.25 mmol) and Al-catalyst (5 mol %) were stirred in $(CH_2Cl)_2$ (1 mL) at room temperature. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then evaporated on a rotary evaporator and the residue was purified on a silica gel column chromatography using a mixture of hexane and ethyl acetate.

(*R*,*Z*)-3-Isopropyl-N,5-diphenyl-1,3-selenazolidin-2-imine 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; yellow liquid; yield 90% (78 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.28-7.25 (m, 3H), 7.04 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 2H), 4.82-4.75 (m, 2H), 3.92 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.71 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.31(d, *J* = 6.6 Hz, 3H) 1.30 (d, *J* = 6.6 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 153.6, 140.3, 129.0, 128.9, 127.9, 127.8, 123.3, 121.8, 54.0, 47.4, 42.2, 20.2, 19.5; FT-IR (neat) 3056, 3027, 2971, 2928, 2869, 1630, 1589, 1489, 1453, 1402, 1363, 1243, 1205, 1184, 1161, 1125, 1069, 1023 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{20}N_2Se$ 345.0864, found 345.0876; $[\alpha]_D^{26}$ = +21 (c= 0.22, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 11.23 min (major), 21.06 min (minor)].

(*R*,*Z*)-3-Isopropyl-*N*-(2-methoxyphenyl)-5-phenyl-1,3-selenazolidin-2-imine 3b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; colorless solid; yield 80% (75 mg); mp 109-110 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 6.0 Hz, 1H), 6.86-6.84 (m, 2H), 4.84-4.77 (m, 2H), 3.91 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.81 (s, 3H), 3.69 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 151.9, 143.1, 140.5, 128.8, 127.9, 127.8, 124.3, 122.4, 120.9, 111.8, 56.1, 54.4, 47.5, 42.2, 20.2, 19.5; FT-IR (KBr) 3025, 2970, 2923, 2869, 1623, 1586, 1493, 1464, 1401, 1363, 1234, 1204, 1184, 1110, 1047, 1026 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{22}N_2OSe$ 375.0970, found 375.0974; $[\alpha]_D^{24}$ = +40 (c= 0.86, $CHCl_3$); HPLC analysis: 96% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 95:5, flow rate: 1 mL /min, λ = 215 nm, t_R = 9.39 min (minor), 10.08 min (major)].

(*R*,*Z*)-*N*-(4-Chlorophenyl)-3-isopropyl-5-phenyl-1,3-selenazolidin-2-imine 3c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.49; yellow liquid; yield 87% (83 mg); yield 87%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.26-7.23 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.89-6.87 (m, 2H), 4.80 (t, *J* = 7.8 Hz, 1H), 4.75-4.70 (m, 1H), 3.88 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.69 (dd, *J* = 10.8, 7.8 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 6H), 1.26 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.2, 152.1, 140.1, 129.0, 128.9, 128.4, 128.1, 127.8, 123.2, 54.1, 47.5, 42.5, 20.2, 19.5; FT-IR (neat) 3059, 3025, 2973, 2928, 2870, 1615, 1584, 1485, 1404, 1364, 1274, 1244, 1205, 1185, 1162, 1088, 1067, 1009 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}ClN_2Se$ 379.0475, found 379.0485; $[\alpha]_D^{24}$ = +75 (c= 0.44, $CHCl_3$); HPLC analysis: 95% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 9.23 min (major), 11.48 min (minor)].

(*R*,*Z*)-*N*-(4-Ethylphenyl)-3-isopropyl-5-phenyl-1,3-selenazolidin-2-imine 3d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; yellow liquid; yield 91% (85 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.26-7.24 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.79-4.72 (m, 2H), 3.89 (dd, *J* = 10.2, 6.6 Hz, 2H), 3.69 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.61 (dd, *J* = 15.6, 7.8 Hz, 2H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); 1.22 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 151.4, 140.5, 139.2, 128.9, 128.4, 128.0, 127.9, 121.6, 54.1, 47.5, 42.3, 28.5, 20.3, 19.6, 15.8; FT-IR (neat) 3025, 2958, 2924, 2853, 1625, 1598, 1504, 1459, 1380, 1185, 1121, 1070, 836 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{24}N_2Se$ 373.1177, found 373.1192; $[\alpha]_D^{22}$ = +45 (c= 0.54, $CHCl_3$). HPLC analysis: 90% ee [Daicel CHIRALCEL OJ-H column, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 8.18 min (major), 15.79 min (minor)].

(*R*,*Z*)-*N*-(4-Iodophenyl)-3-isopropyl-5-phenyl-1,3-selenazolidin-2-imine 3e. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; colorless liquid; yield 83% (97 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 6.0 Hz, 1H), 6.75 (m, 2H), 4.83 (t, *J* = 7.2 Hz, 1H), 4.77-4.73 (m, 1H), 3.91 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.71 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 153.2, 140.1, 138.0, 129.0, 128.1, 127.8, 124.2, 86.9, 54.2, 47.5, 42.5, 20.3, 19.6; FT-IR (neat) 3052, 3025, 2968, 2924, 2850, 1614, 1572, 1479, 1403, 1362, 1273, 1243, 1205, 1184, 1067, 1001 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}IN_2Se$ 470.9831, found 470.9831; $[\alpha]_D^{24}$ = +61 (c = 0.31, $CHCl_3$); HPLC analysis: 94% ee [Daicel CHIRALCEL OJ-H column, hexane/ ^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 10.90 min (major), 12.30 min (minor)].

(*R*,*Z*)-3-Isopropyl-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; yellow liquid; yield: 88% (79 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.26-7.24 (m, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.86 (dd, *J* = 10.2, 1.8 Hz, 2H), 4.79-4.73 (m, 2H), 3.89 (dd, *J* =

10.8, 6.6 Hz, 1H), 3.68 (dd, *J* = 7.8, 9.0 Hz, 1H), 2.29 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 151.3, 140.5, 132.7, 129.7, 128.9, 128.0, 127.9, 121.6, 54.1, 47.5, 42.3, 21.1, 20.3, 19.5; FT-IR (neat) 3024, 2971, 2923, 2868, 1624, 1601, 1505, 1453, 1400, 1363, 1205, 1184, 1068, 924 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{22}N_2Se$ 359.1021, found 359.1023; $[\alpha]_D^{27}$ = +74 (c= 0.1, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 12.01 min (major), 25.68 min (minor)].

(*R*,*Z*)-3-Isopropyl-*N*-(4-methoxyphenyl)-5-phenyl-1,3-selenazolidin-2-imine 3g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 86% (81 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 4.72-4.64 (m, 2H), 3.82 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.69 (s, 3H), 3.61 (dd, *J* = 10.2, 7.8 Hz, 1H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 156.0, 147.2, 140.4, 128.9, 128.0, 127.8, 122.6, 114.2, 55.6, 54.1, 47.4, 42.3, 20.3, 19.5; FT-IR (neat) 3031, 2970, 2928, 2867, 2831, 1618, 1504, 1463, 1400, 1363, 1295, 1239, 1204, 1184, 1068, 1035, 977 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{22}N_2OSe$ 375.0970, found 375.0972; $[\alpha]_D^{28}$ = +88 (c= 0.1, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 80:20, flow rate: 1 mL /min, λ = 215 nm, t_R = 13.13 min (major), 51.05 min (minor)].

(*R*,*Z*)-*N*-(3,4-Dimethylphenyl)-3-isopropyl-5-phenyl-1,3-selenazolidin-2-imine 3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless liquid, yield 89% (83 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.07-7.05 (m, 1H), 6.83-6.82 (m, 1H), 6.77-6.76 (m, 1H), 4.83-4.80 (m, 2H), 3.92 (dd, *J* = 10.8 Hz, 6.6 Hz, 1H), 3.71 (t, *J* = 9.0 Hz, 1H), 2.26-2.25 (m, 6H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.32 (d, *J* = 4.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 151.4, 140.3, 131.2, 130.1, 128.8, 127.8, 127.7, 123.0, 118.6, 53.9, 47.3, 42.1, 20.2, 20.0, 19.4, 19.3; FT-IR (neat) 3025, 2970, 2922, 2866, 1626, 1597, 1497, 1453, 1396, 1363, 1285, 1243, 1203, 1184, 1068, 1001 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{24}N_2Se$ 373.1177, found 373.1179; $[\alpha]_D^{24}$ = +60 (c= 0.1, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane ^{i}PrOH = 85:15, flow rate: 1 mL /min, λ = 215 nm, t_R = 9.34 min (major), 16.48 min (minor)].

(*R*,*Z*)-3-Isopropyl-*N*-(naphthalen-1-yl)-5-phenyl-1,3-selenazolidin-2-imine 3i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; pale yellow liquid, yield 86% (85 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19-8.18 (m, 1H), 7.79-7.78 (m, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.45-7.44 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.36-7.33 (m, 1H), 7.29 (t, *J* = 7.2Hz, 2H), 7.25-7.22 (m, 1H), 7.00 (d, *J* = 6.6 Hz, 1H), 4.99-4.95 (m, 1H), 4.77 (t, *J* = 7.2 Hz, 1H), 3.94 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.74 (dd, *J* = 10.2, 7.8 Hz, 1H) 1.39 (d, *J* = 7.2 Hz, 3H), 1.37 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.7, 150.3, 140.4, 134.4, 128.9, 128.8, 128.0, 127.9, 127.8, 126.2, 126.1, 125.3, 124.1, 123.4, 115.3, 54.3, 47.7, 42.2, 20.5, 19.8 ; FT-IR (neat) 3053, 2971, 2928, 2867, 1614, 1570, 1503, 1453, 1389, 1363, 1245, 1207, 1184, 1081, 1066, 1040, 1014 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{22}N_2Se$ 395.1021, found 395.1036; $[\alpha]_D^{24}$ = +34 (c= 0.35, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 12.37 min (major), 20.65 min (minor)].

(*R*,*Z*)-3-Cyclohexyl-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless liquid; yield 79% (79 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.27-7.24 (m, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 4.76 (t, *J* = 7.2 Hz, 1H), 4.37-4.33 (m, 1H), 3.93 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.73 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.29 (s, 3H), 2.02-1.96 (m, 2H), 1.82-1.80 (m, 2H), 1.69-1.67 (m, 1H), 1.47 (m, 4H), 1.10-1.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.8, 151.4, 140.6, 132.7, 129.7, 128.9, 127.9, 127.8, 121.7, 55.6, 55.4, 42.3, 30.9, 30.3, 26.1, 26.0, 25.9, 21.1; FT-IR (neat) 3061, 3022, 2928, 2854, 1623, 1600, 1506, 1451, 1399, 1262, 1241, 1206, 1181, 1007 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{26}N_2Se$ 399.1334, found 399.1338; $[\alpha]_D^{27}$ = +118 (c= 0.1, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 5.83 min (major), 11.67 min (minor)].

(*R*,*Z*)-3-Ethyl-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; colorless liquid; yield 90% (78 mg); ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.34-7.24 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.85 (t, *J* = 6.8 Hz, 1H), 3.93 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.78 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.73-3.61 (m, 2H), 2.30 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 151.2, 140.5, 132.8, 129.7, 129.0, 128.0, 127.9, 121.6, 59.2, 42.4, 42.3, 21.1, 12.4; FT-IR (neat) 3025, 2970, 2924, 2857, 1627, 1601, 1504, 1454, 1288, 1244, 1209, 1189, 1076, 883, 821 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{24}N_2Se$ 345.0864, found 345.0882. $[\alpha]_D^{23}$ = +48 (c= 0.11, $CHCl_3$). HPLC analysis: 99% ee [Daicel CHIRALCEL OJ-H column, hexane/*i*PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 14.32 min (major), 17.90 min (minor)].

(*R*,*Z*)-3-Isobutyl-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.56; yellow liquid; yield 89% (83 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.27-7.24 (m, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 2H), 4.85 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.91 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.76 (dd, *J* = 10.2, 7.8 Hz, 1H), 3.51 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.35 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.29 (s, 3H), 2.11-2.04 (m, 1H), 0.98 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 151.4, 140.1, 132.7, 129.7, 128.9, 128.0, 127.9, 121.6, 60.5, 54.9, 42.6, 27.6, 21.1, 20.5, 20.4; FT-IR (neat) 3025, 2957, 2924, 2867, 2853, 1629, 1600, 1506, 1463, 1404, 1382, 1286, 1243, 1209, 1186, 1106 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{24}N_2Se$ 373.1177, found 373.1193; $[\alpha]_D^{27}$ = +62 (c= 0.1, $CHCl_3$); HPLC analysis: 96% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 7.47 min (major), 10.55 min (minor)].

(*R*,*Z*)-3-Benzyl-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; colorless liquid; yield 83% (85 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.8 Hz, 2H), 7.29-7.27 (m, 4H), 7.23-7.14 (m, 4H), 7.03 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 4.83 (d, *J* = 15 Hz, 1H), 4.76 (t, *J* = 7.8 Hz, 1H), 4.66 (d, *J* = 15.0 Hz, 1H), 3.71 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.57 (dd, *J* = 10.2, 8.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 151.0, 139.9, 137.4, 133.0, 129.8, 128.9, 128.8, 128.6, 128.0, 127.9, 127.7, 121.5, 58.9, 51.1, 42.5, 21.1; FT-IR (neat) 3022, 2958, 2922, 2856, 1627, 1600, 1506, 1453, 1355, 1282, 1243, 1211, 1180, 1077, 1028 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{22}N_2Se$ 407.1021, found 407.1023; $[\alpha]_D^{24}$ = +20 (c= 0.7,

$CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 80:20, flow rate: 1 mL /min, λ = 215 nm, t_R = 23.32 min (minor), 49.96 min (major)].

(*R*,*Z*)-3-(4-Bromobenzyl)-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.51; pale yellow liquid; yield 85% (103 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.29-7.23 (m, 5H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H), 4.85-4.81 (m, 2H), 4.70 (d, *J* = 15.0 Hz, 1H), 3.77 (dd, *J* = 10.2 , 6.6 Hz, 1H), 3.63 (dd, *J* = 10.8 , 8.4 Hz, 1H), 2.32 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 150.7, 139.7, 136.5, 133.1, 131.9, 130.3, 129.1, 129.0, 128.9, 128.1, 127.9, 121.6, 121.4, 59.0, 50.5, 42.6, 21.1; FT-IR (neat) 3028, 2956, 2923, 2850, 1627, 1599, 1504, 1486, 1463, 1349, 1158, 1102, 1011 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{21}BrN_2Se$ 485.0126, found 485.0131; $[\alpha]_D^{27}$ = +18 (c= 0.1, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 21.23 min (major), 36.91 min (minor)].

(*R*,*Z*)-3-(4-Fluorobenzyl)-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colorless liquid; yield 86% (92 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 4H), 7.29-7.22 (m, 3H), 7.10 (d, *J* = 7.8 Hz, 2H), 7.03 (t, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.84-4.82 (m, 2H), 4.73 (d, *J* = 14.4 Hz, 1H), 3.78 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.63 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (d, $^1J_{C\text{-}F}$ = 244.5 Hz), 157.2, 150.7, 139.8, 133.2, 133.1, 130.3 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 129.8, 129.0, 128.1, 127.9, 121.5, 115.7 (d, $^2J_{C\text{-}F}$ = 21.0 Hz), 59.0, 50.4, 42.5, 21.3; FT-IR (neat) 2973, 2923, 2850, 2823, 1629, 1599, 1507, 1451, 1353, 1221, 1155, 1094, 1015, 820, 752 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{21}FN_2Se$ 425.0927, found 425.0933; $[\alpha]_D^{24}$ = +42 (c= 0.1, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD-H column, hexane/^{i}PrOH = 98:02, flow rate: 1 mL /min, λ = 215 nm, t_R = 13.85 min (major), 15.19 min (minor)].

(*R*,*Z*)-3-(4-Methoxybenzyl)-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; colorless liquid; yield 83% (91 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 10.8, 7.2 Hz, 4H), 7.28-7.25 (m, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.90 (dd, *J* = 10.2, 8.4 Hz, 4H), 4.82-4.79 (m, 2H), 4.68 (d, *J* = 15.0 Hz, 1H), 3.81 (s, 3H), 3.76-3.74 (m, 1H), 3.62 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 159.2, 157.0, 151.0, 140.0, 132.9, 130.0, 129.8, 129.5, 128.9, 128.0, 127.9, 121.5, 114.1, 58.9, 55.5, 50.6, 42.5, 21.1; FT-IR (neat) 3025, 2956, 2923, 2850, 1627, 1601, 1511, 1454, 1355, 1302, 1247, 1173, 1107, 1033 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{24}H_{24}N_2OSe$ 437.1127, found 437.1135; [α]$_D^{24}$ = +15 (c= 0.2, CHCl$_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 30.65 min (minor), 34.73 min (major)].

(*R*,*Z*)-3-(Naphthalen-1-ylmethyl)-5-phenyl-*N*-(*p*-tolyl)-1,3-selenazolidin-2-imine 3r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.56; colorless liquid; yield 90% (103 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.62-7.59 (m, 1H), 7.56-7.54 (m, 1H), 7.46-7.40 (m, 2H), 7.19-7.17 (m, 2H), 7.14-7.10 (m, 5H), 6.99 (d, *J* = 7.8 Hz, 2H), 5.39 (d, *J* = 14.4 Hz, 1H), 5.10 (d, *J* = 15.0 Hz, 1H), 4.69 (t, *J* = 7.8 Hz, 1H), 3.71 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.59 (dd, *J* = 10.8, 7.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.8, 151.0, 140.0, 134.1, 133.4, 133.1, 132.2, 129.8, 128.9, 128.8, 128.77, 127.9, 127.74, 127.72, 126.7, 126.3, 125.3, 124.9, 121.6, 58.5, 49.8, 42.2, 21.2; FT-IR (neat) 3058, 2955, 2923, 2853, 1628, 1606, 1506, 1456, 1384, 1204, 1120, 1019, 820 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{27}H_{24}N_2Se$ 457.1177, found 457.1187; [α]$_D^{22}$ = +28 (c= 0.8, CHCl$_3$). HPLC analysis: 98% ee [Daicel CHIRALCEL OJ-H column, hexane/*i*PrOH = 80:20, flow rate: 1 mL /min, λ = 215 nm, t_R = 25.43 min (major), 38.29 min (minor)].

(*R*,*Z*)-3-Cyclohexyl-*N*-(naphthalen-1-yl)-5-phenyl-1,3-selenazolidin-2-imine 3s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.60; colorless liquid; yield 81% (88 mg); ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.21-8.19 (m, 1H), 7.84-7.82 (m, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.50-7.49 (m, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.29-7.26 (m, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 4.81 (t, *J* = 7.2 Hz, 1H), 4.63-4.60 (m, 1H), 4.04 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.83 (dd, 10.8, 7.8 Hz, 1H), 2.16-2.13 (m, 2H), 1.94-1.90 (m, 2H), 1.77-1.74 (m, 1H), 1.61-1.52 (m, 4H), 1.20-1.14 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.8, 150.4, 140.6, 134.4, 128.9, 128.0, 127.9, 127.8, 126.2, 125.3, 124.2, 123.4, 115.5, 56.0, 55.5, 42.3, 31.0, 30.5, 26.2, 26.1, 26.0; FT-IR (neat) 3058, 2925, 2847, 1615, 1570, 1505, 1451, 1386, 1243, 1208, 1178, 1071, 1041, 1012 cm^{-1}; HRMS (ESI) m/z

$[M+H]^+$ calcd for $C_{25}H_{26}N_2Se$ 435.1334, found 435.1336; $[\alpha]_D^{26}$ = +35 (c= 0.2, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 95:05, flow rate: 1 mL /min, λ = 215 nm, t_R = 8.24 min (major), 16.50 min (minor)].

(*R*,*Z*)-3-Benzyl-*N*-(naphthalen-1-yl)-5-phenyl-1,3-selenazolidin-2-imine 3t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; colorless liquid; yield 78% (87 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 7.8, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.48-7.33 (m, 9H), 7.28-7.23 (m, 4H), 7.05 (d, *J* = 7.2 Hz, 1H), 5.10 (d, *J* = 14.4 Hz, 1H), 4.88-4.85 (m, 2H), 3.89 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.76 (dd, *J* = 10.8, 8.4 Hz, 1H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.0, 150.2, 139.8, 137.5, 134.5, 129.0, 128.9, 128.8, 128.6, 128.1, 127.94, 127.90, 127.8, 126.3, 126.2, 125.3, 124.2, 123.6, 115.1, 59.2, 51.3, 42.5; FT-IR (neat) 3003, 2958, 2922, 2856, 1625, 1571, 1505, 1454, 1384, 1260, 1210, 1180, 1101, 1074, 1019 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{22}N_2Se$ 443.1021, found 443.1021; $[\alpha]_D^{25}$ = +40 (c= 0.29, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 19.87 min (major), 39.87 min (minor)].

(*R*,*Z*)-3-Cyclohexyl-*N*-(4-methoxyphenyl)-5-phenyl-1,3-selenazolidin-2-imine 3u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless liquid; yield 77% (80 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 8.2 Hz, 2H), 7.26-7.24 (m, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 4.76 (t, *J* = 7.2 Hz, 1H), 4.36-4.32 (m, 1H), 3.93 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 10.2, 7.8 Hz, 1H), 2.02-2.96 (m, 2H), 1.82-1.80 (m, 2H), 1.69-1.67 (m, 1H), 1.47-1.40 (m, 4H), 1.11-1.07 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 156.1, 147.5, 140.7, 129.0, 128.0, 127.9, 122.8, 114.3, 55.7, 55.6, 55.4, 42.4, 30.9, 30.3, 26.2, 26.1, 26.0; FT-IR (neat) 3000, 2957, 2923, 2850, 1620, 1504, 1462, 1451, 1402, 1383, 1237, 1205, 1180, 1098, 1035 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{26}N_2OSe$ 415.1283, found 415.1296; $[\alpha]_D^{24}$ = +27.69 (c= 0.26, $CHCl_3$); HPLC analysis: 97% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 90:10, flow rate: 1 mL /min, λ = 215 nm, t_R = 8.76 min (major), 26.06 min (minor)].

(*R*,*Z*)-3-Benzyl-*N*-(4-iodophenyl)-5-phenyl-1,3-selenazolidin-2-imine 3v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; colorless liquid; yield 80% (104 mg); ^{1}H

NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.4 Hz, 2H), 7.36-7.33 (m, 5H), 7.31-7.24 (m, 5H), 6.77 (d, *J* = 9.0 Hz, 2H), 4.88-4.85 (m, 2H), 4.72 (d, *J* = 14.4 Hz, 1H), 3.81 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.67 (dd, *J* = 10.8, 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) 157.3, 153.0, 139.6, 138.1, 137.2, 129.0, 128.9, 128.6, 128.2, 127.9, 127.8, 124.1, 87.1, 59.0, 51.1, 42.8; FT-IR (neat) 3025, 2961, 2920, 2850, 1624, 1573, 1479, 1453, 1385, 1354, 1277, 1202, 1179, 1159, 1002, 827 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{19}IN_2Se$ 518.9831, found 518.9841; $[\alpha]_D^{24}$ = +34 (c= 0.33, $CHCl_3$); HPLC analysis: 92% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 75:25, flow rate: 1 mL /min, λ = 215 nm, t_R = 20.15 min (minor), 30.11 min (major)].

(*R*,*Z*)-3-(4-Bromobenzyl)-*N*-(4-iodophenyl)-5-phenyl-1,3-selenazolidin-2-imine 3w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.55; colorless liquid; yield 85% (127 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.64-7.58 (m, 5H), 7.10 (d, *J* = 8.4 Hz, 2H), 5.21 (dd, *J* = 7.8, 6.6 Hz, 1H), 5.15 (d, *J* = 15.0 Hz, 1H), 5.02 (d, *J* = 14.4 Hz, 1H), 4.13 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.99 (dd, *J* = 10.8, 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.3, 152.8, 139.4, 138.2, 136.2, 132.0, 130.3, 129.1, 128.3, 127.9, 124.0, 121.7, 87.2, 59.1, 50.5, 42.8; FT-IR (neat) 3025, 2959, 2920, 2848, 1667, 1620, 1574, 1484, 1402, 1282, 1244, 1208, 1165, 1069, 1012, 1002, 831 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{18}BrIN_2Se$ 596.8936, found 596.8940; $[\alpha]_D^{24}$ = +28 (c= 0.5, $CHCl_3$); HPLC analysis: 94% ee [Daicel CHIRALCEL OJ-H column, hexane/^{i}PrOH = 70:30, flow rate: 1 mL /min, λ = 215 nm, t_R = 21.41 min (major), 41.37 min (minor)].

4.4 References

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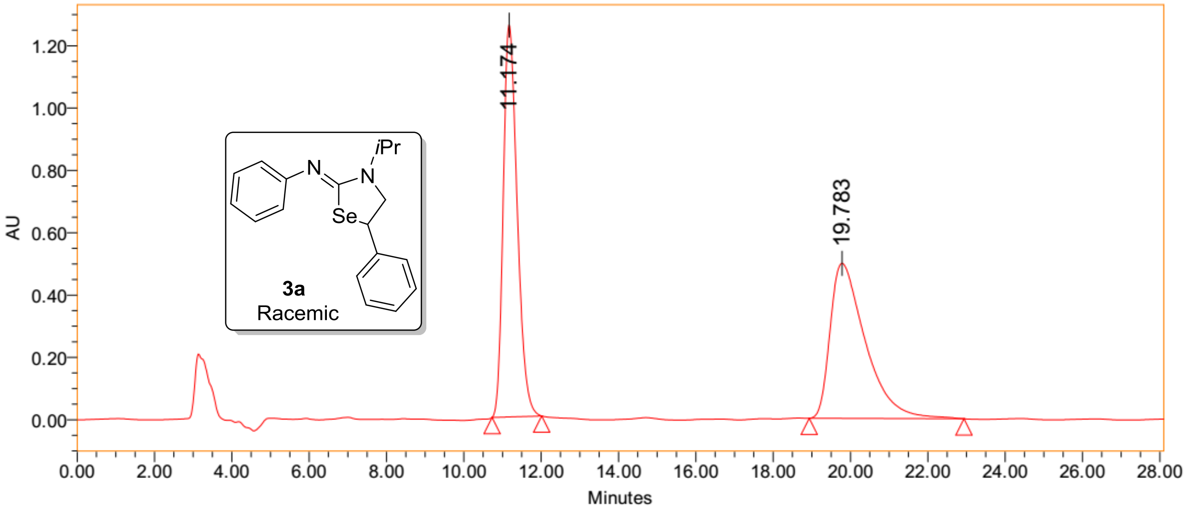
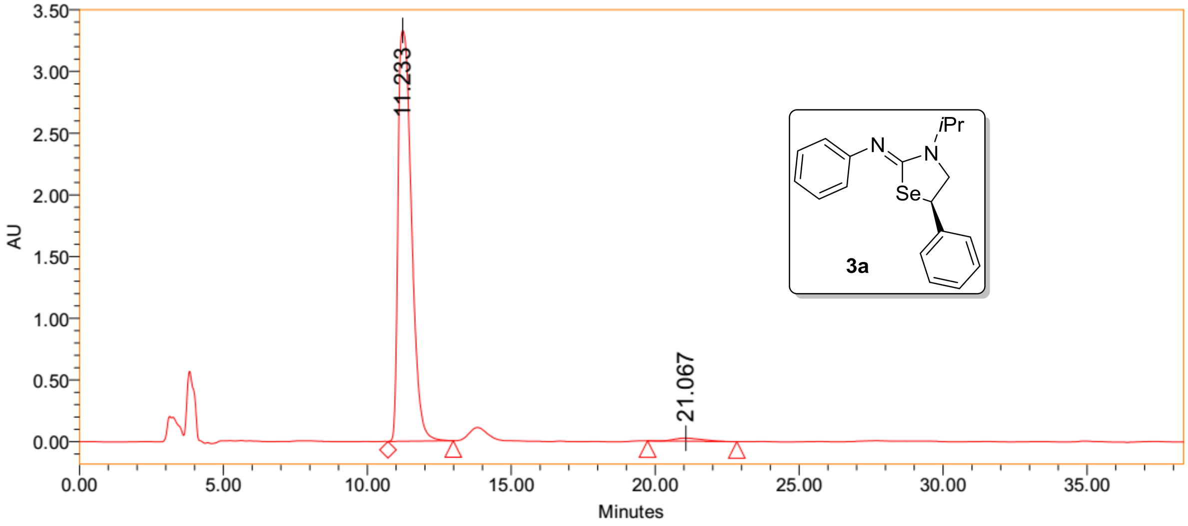
4.5 Selected HPLC Chromatograms



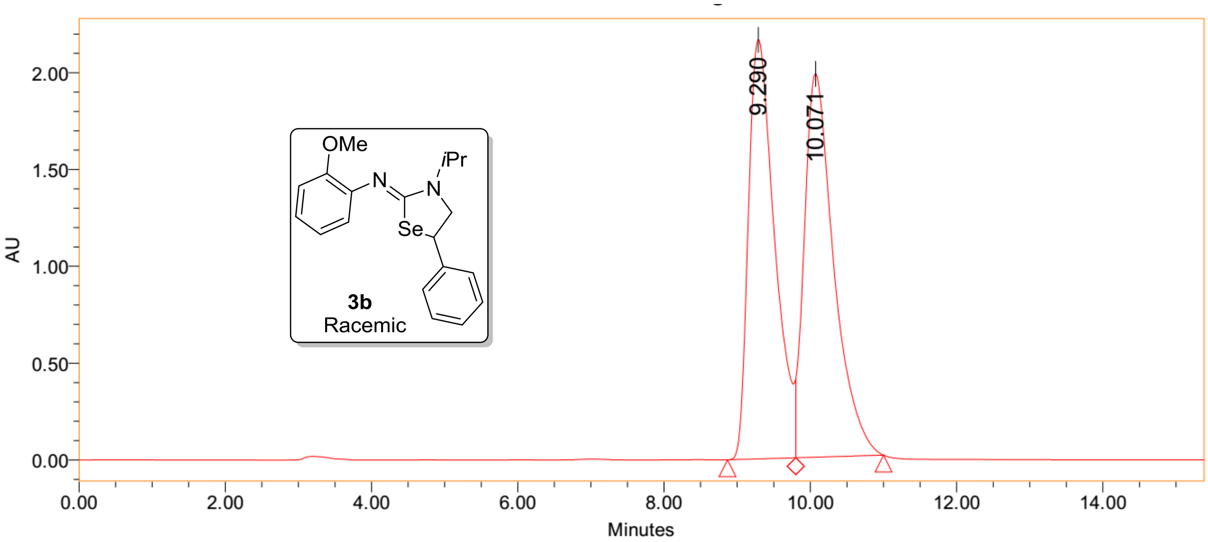
Peak Results

	RT	Height (μV)	% Area
1	11.174	1258782	50.08
2	19.783	497598	49.92



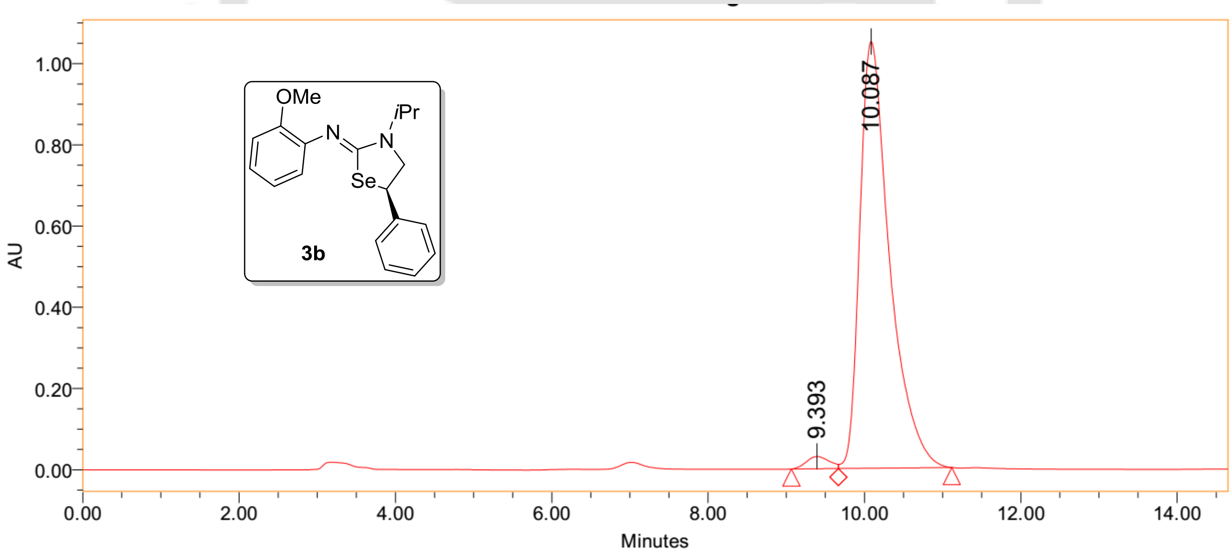
Peak Results

	RT	Height (μV)	% Area
1	11.233	3329237	98.42
2	21.067	24814	1.58



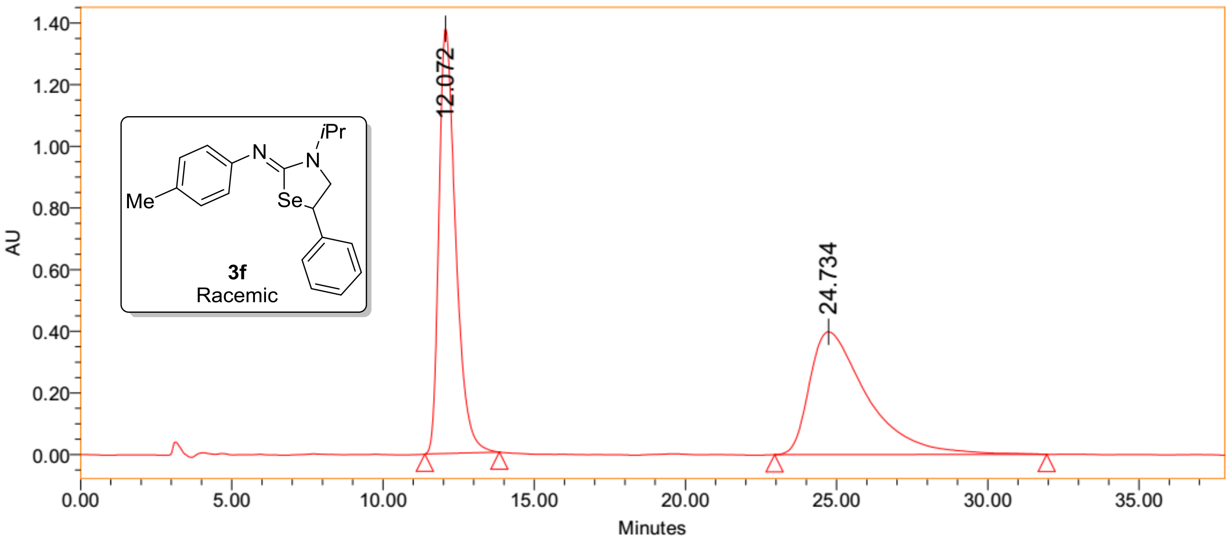
Peak Results

	RT	Height (μV)	% Area
1	9.290	2168068	49.30
2	10.071	1982160	50.70



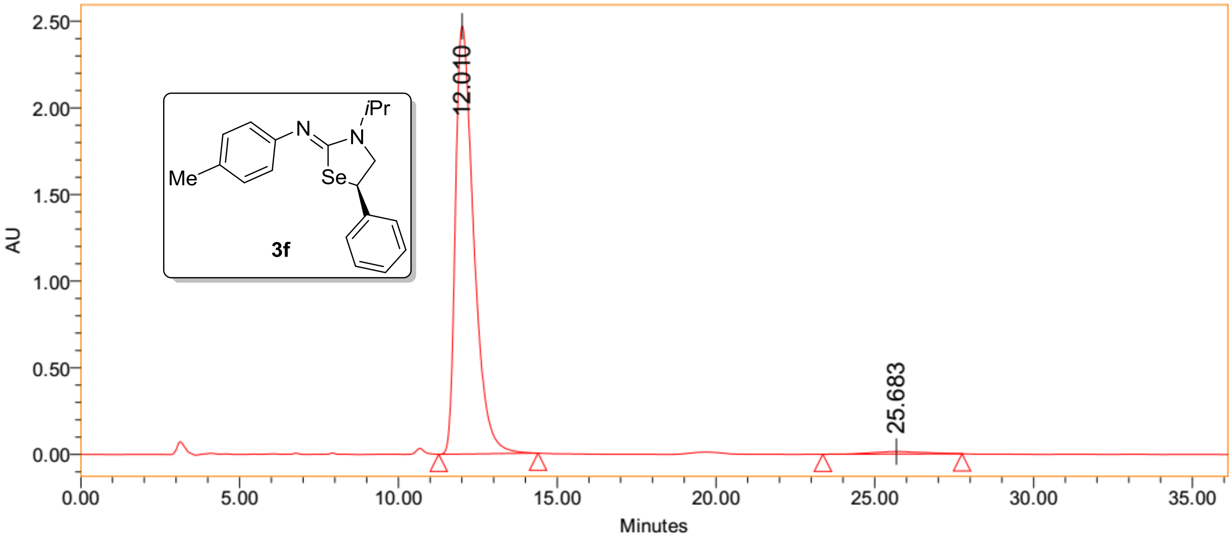
Peak Results

	RT	Height (μV)	% Area
1	9.393	30200	2.16
2	10.087	1051576	97.84



Peak Results

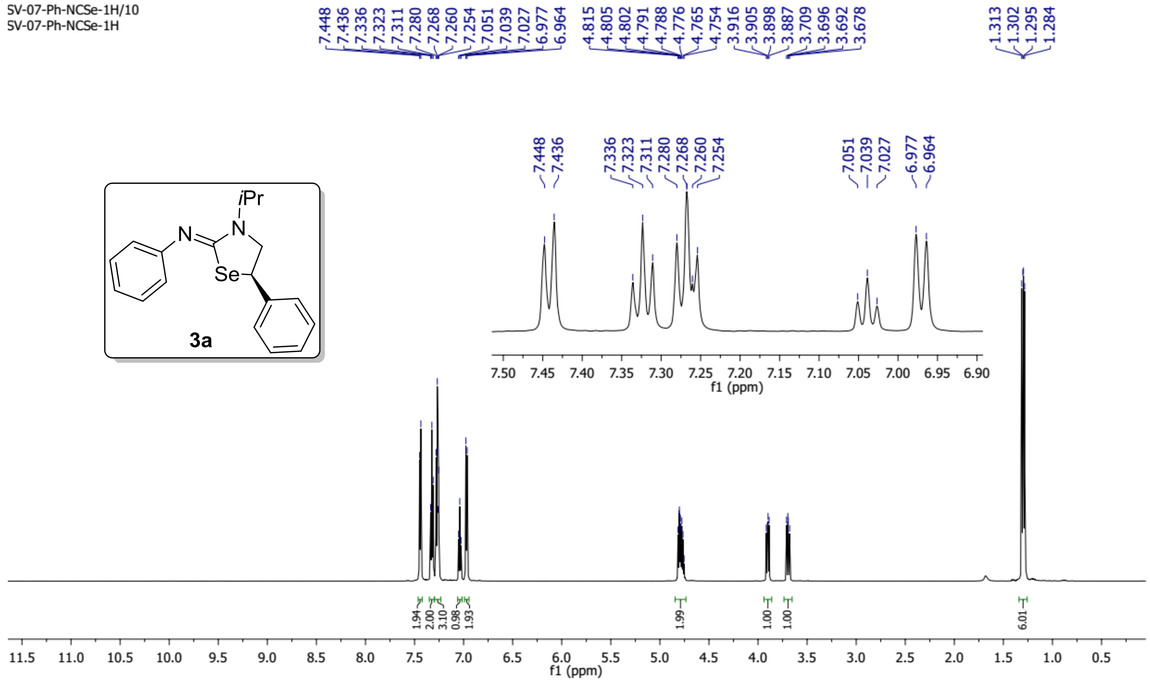
	RT	Height (μV)	% Area
1	12.072	1378021	50.07
2	24.734	398205	49.93

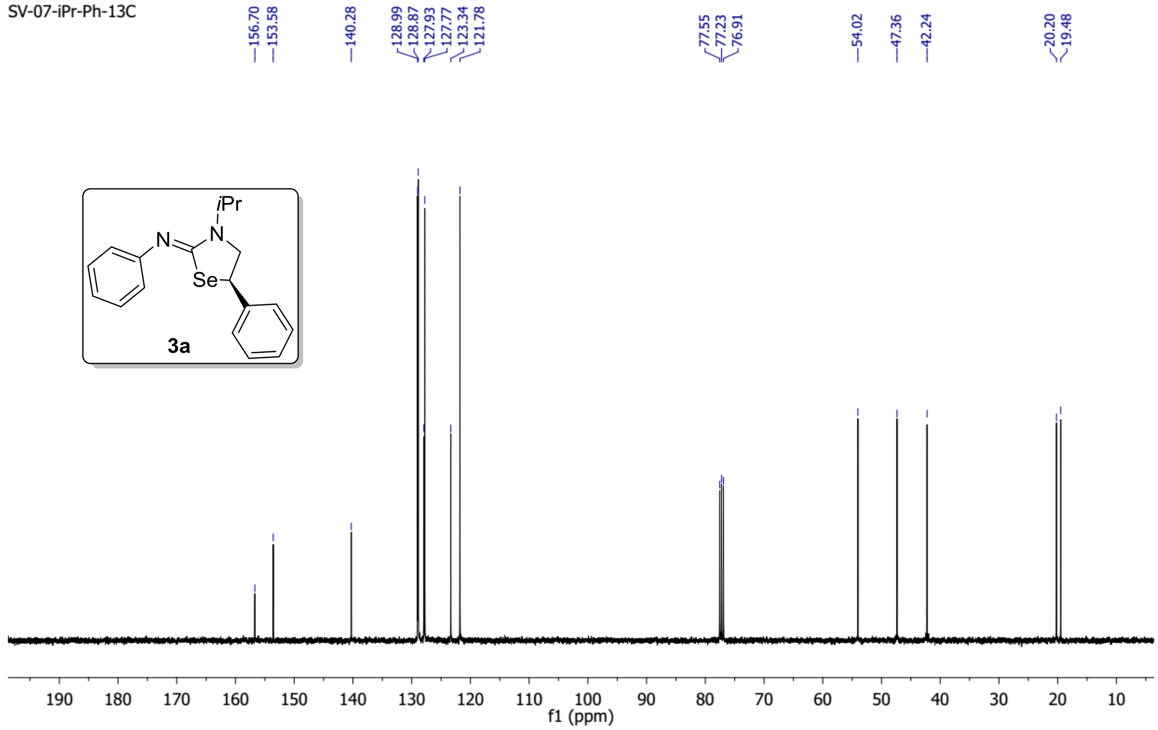


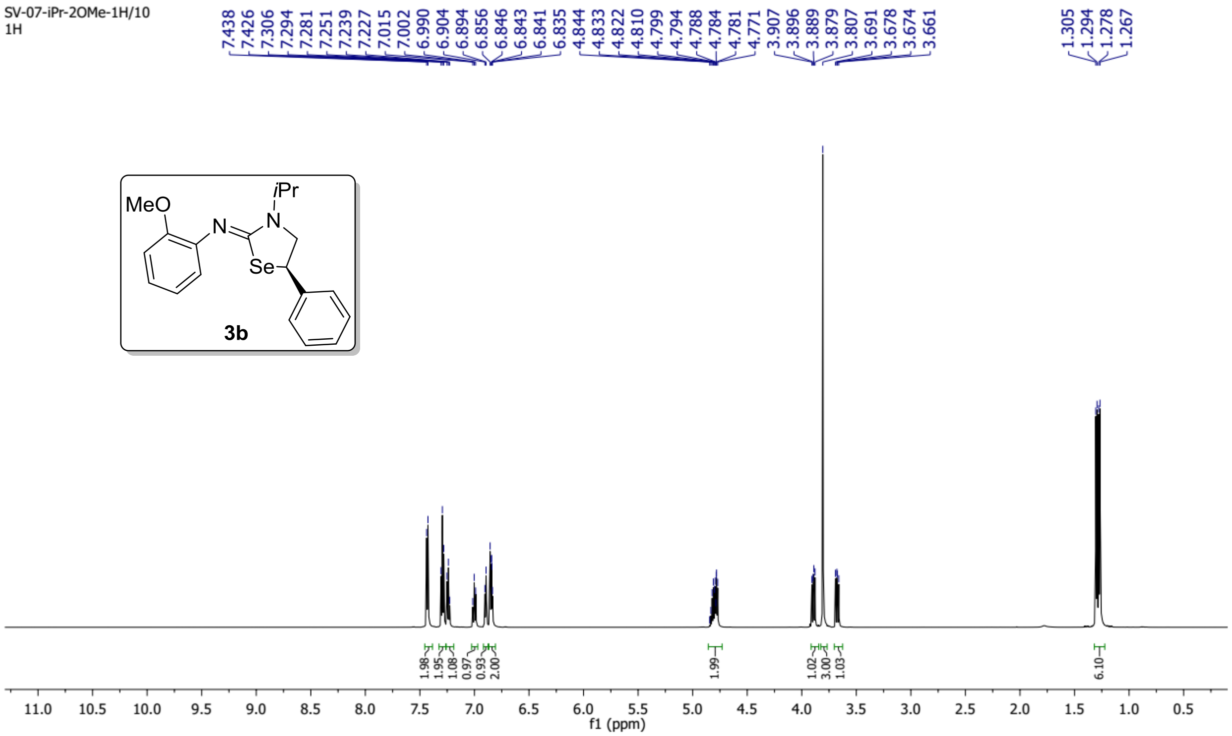
Peak Results

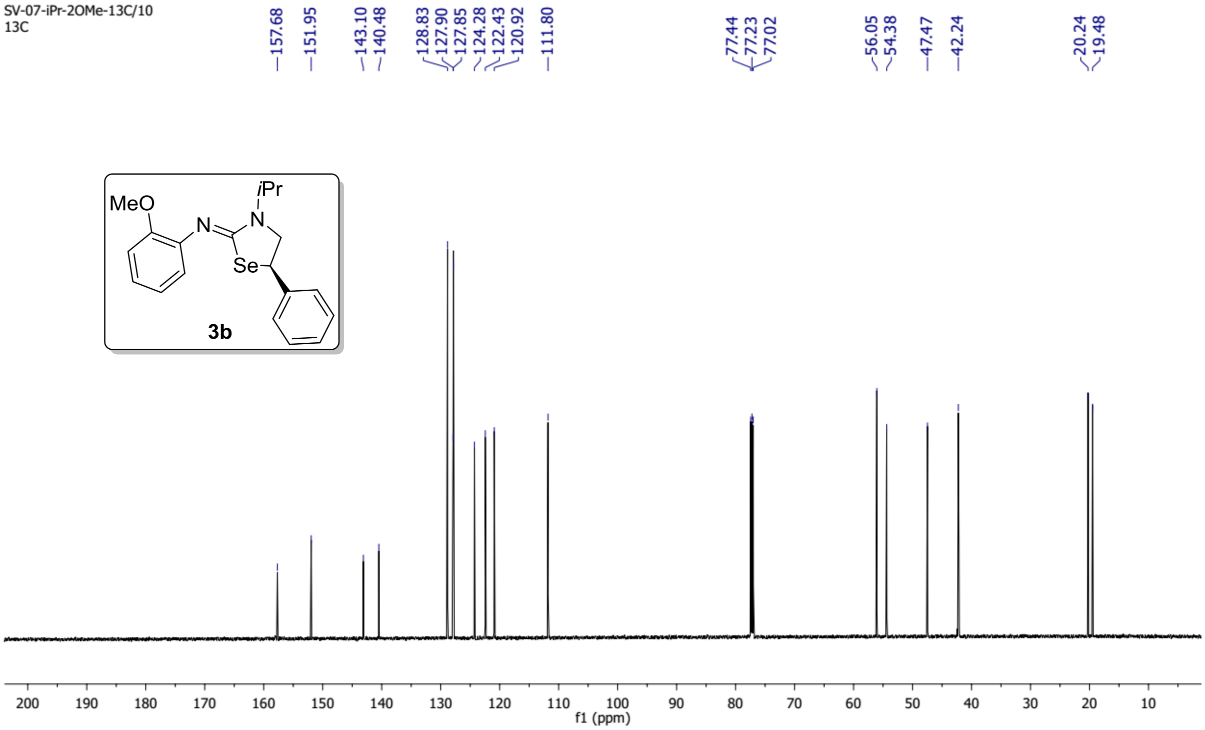
	RT	Height (μV)	% Area
1	12.010	2469430	98.45
2	25.683	13606	1.55

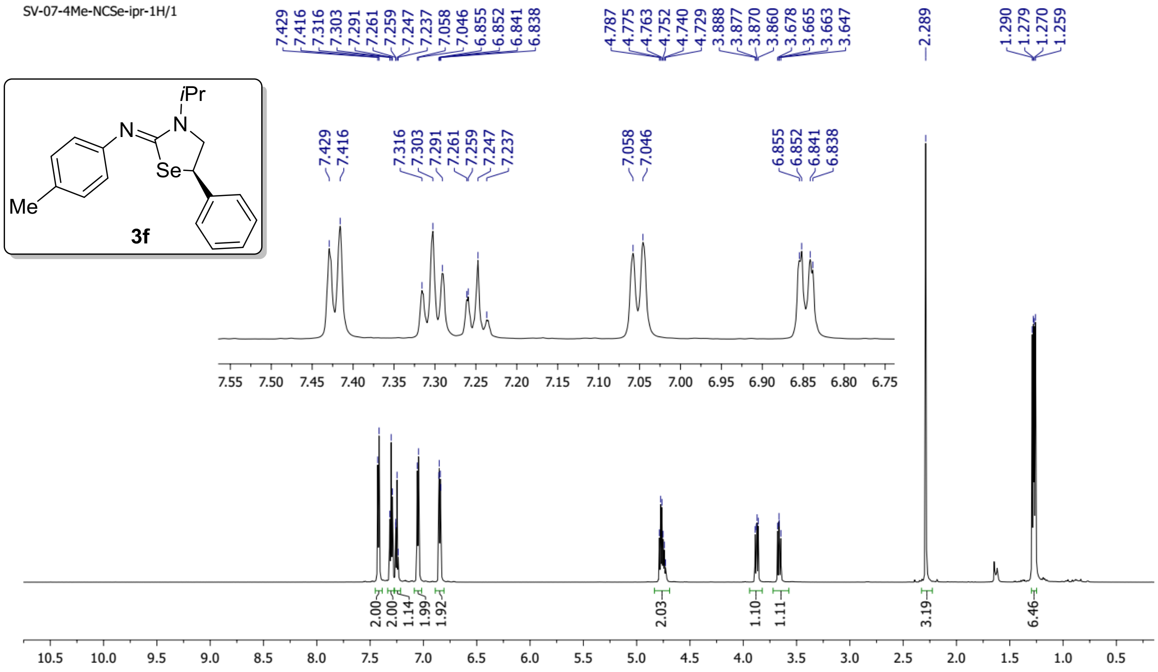
4.6 Selected NMR Spectra

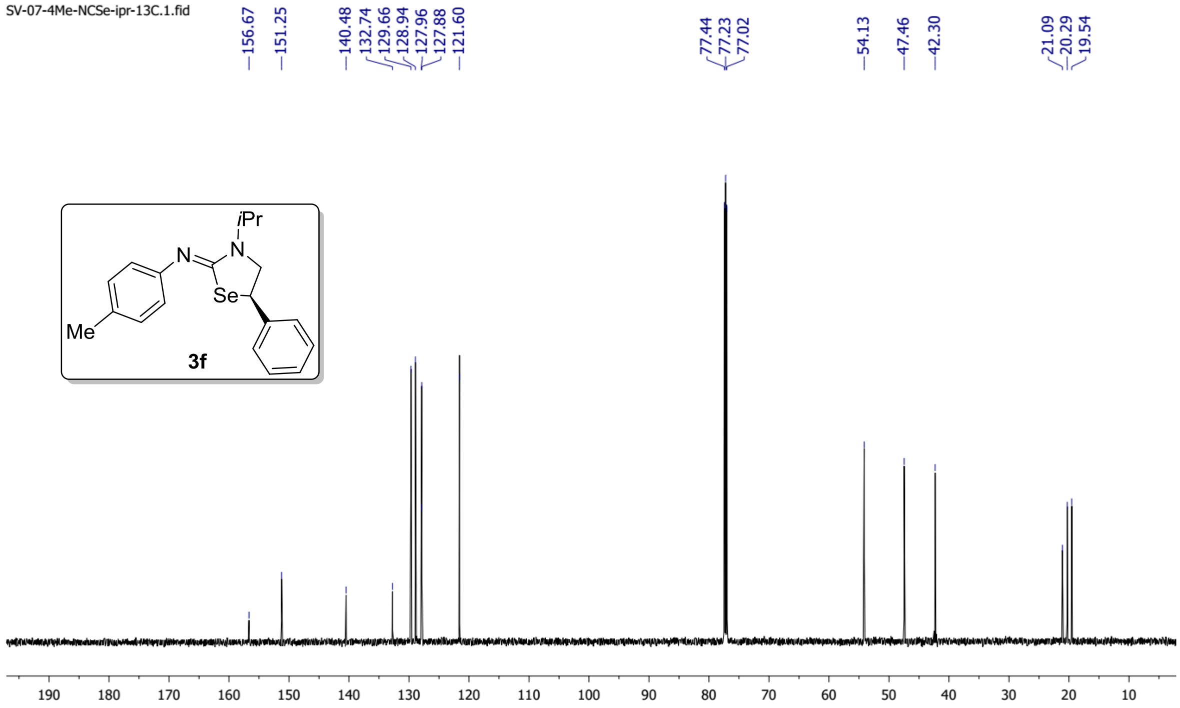





SV-07-iPr-2OMe-1H/10
1H
7.438
7.426
7.306
7.294
7.281
7.251
7.239
7.227
7.015
7.002
6.990
6.904
6.894
6.856
6.846
6.843
6.841
6.835
4.844
4.833
4.822
4.810
4.799
4.794
4.788
4.784
4.781
4.771
3.907
3.896
3.889
3.879
3.807
3.691
3.678
3.674
3.661
1.305
1.294
1.278
1.267
MeO
N
N
*i*Pr
Se
3b
1.98
1.95
1.08
0.97
0.93
2.00
1.99
1.02
3.00
1.03
6.10
11.0
10.5
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
f1 (ppm)


SV-07-iPr-2OMe-13C/10
13C
157.68
151.95
143.10
140.48
128.83
127.90
127.85
124.28
122.43
120.92
111.80
77.44
77.23
77.02
56.05
54.38
47.47
42.24
20.24
19.48
MeO
N
N
*i*Pr
Se
3b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


SV-07-4Me-NCSe-ipr-1H/1
7.429 7.416 7.316 7.303 7.291 7.261 7.259 7.247 7.237 7.058 7.046 6.855 6.852 6.841 6.838
4.787 4.775 4.763 4.752 4.740 4.729 3.888 3.877 3.870 3.860 3.678 3.665 3.663 3.647
2.289
1.290 1.279 1.270 1.259
iPr
N
N
Se
Me
3f
2.00 2.00 1.14 1.99 1.92 2.03 1.10 1.11 3.19 6.46
7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80 6.75
10.5 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


SV-07-4Me-NCSe-ipr-13C.1.fid
156.67
151.25
140.48 132.74 129.66 128.94 127.96 127.88 121.60
77.44 77.23 77.02
54.13
47.46
42.30
21.09 20.29 19.54
iPr
N
N
Se
Me
3f
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

Chapter V

$BF_2OTf{\bullet}OEt_2$-Catalyzed Ring Expansion of Thiiranes with Heterocumulenes

The ring expansion chemistry has a notable impact in organic synthesis.[1] Five-membered *N*, *S* or *Se*-heterocycles have considerable importance in terms of biological and medicinal activities. Especially, iminodithiolane and iminothiazolidines are found in many biologically active compounds that exhibit anti-inflammatory, antidepressant and anti-Alzheimer activities.[2] Apart from that, these also act as the insecticides and pesticides.[3] In addition, iminodithiolane is used as ligand in metal complex[4] and iminothiazolidine is also used as organo-catalyst.[5] Figure 1 illustrates some biologically important 2-iminodithiolanes and 2-iminothiazolidines.

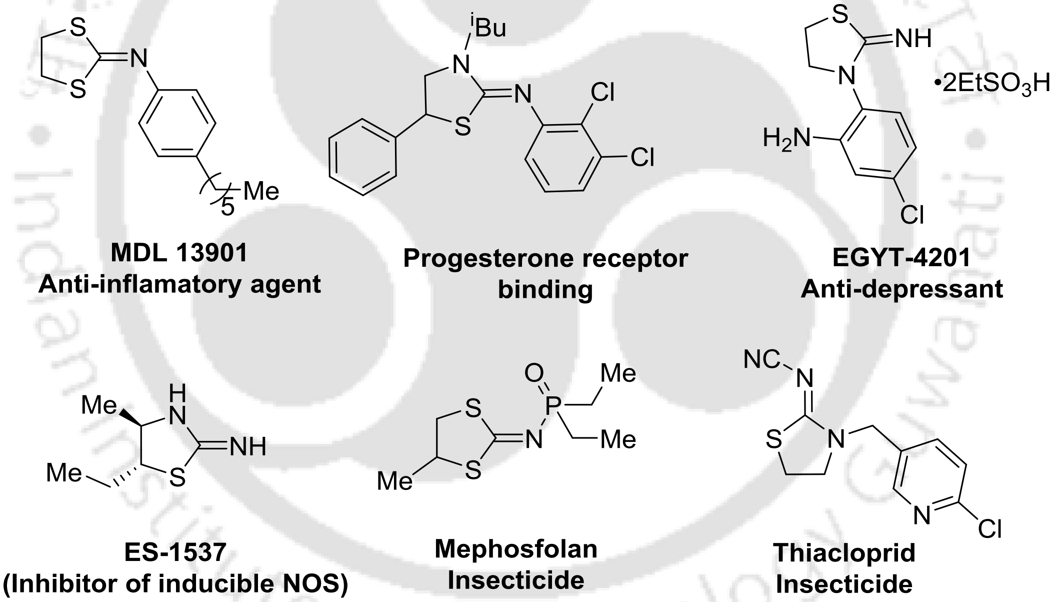
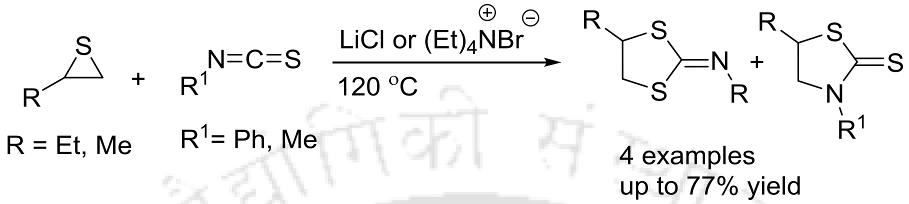


Figure 1. Examples of Some Biologically Active Iminothiazolidines and Iminodithiolanes

[3+2]-Cycloaddition of three-membered heterocycles such as aziridine, oxirane and thiirane with heterocumulenes provide a powerful synthetic strategy for the construction of five-membered heterocycles. Among these, aziridine and oxirane are well-documented,[6] whereas thiirane is less investigated because the nature of desulfurization and subsequent metal sulfide formation.[7-11]

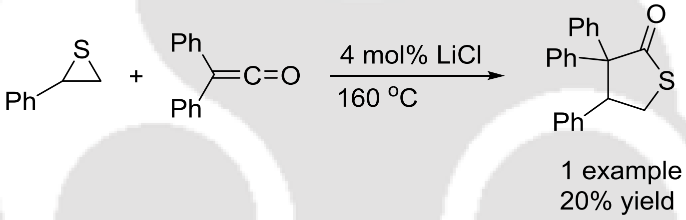
5.1 Cycloaddition of Thiiranes with Heterocumulenes

The [3+2]-cycloaddition of thiirane with isothiocyanates has been developed using LiCl or Et_4NBr at 120 °C to produce 1,3-dithiolan-2-imine and thiazolidine-2-thione (Scheme 1).[8] The protocol suffers with harsh reaction condition and lack of selectivity.



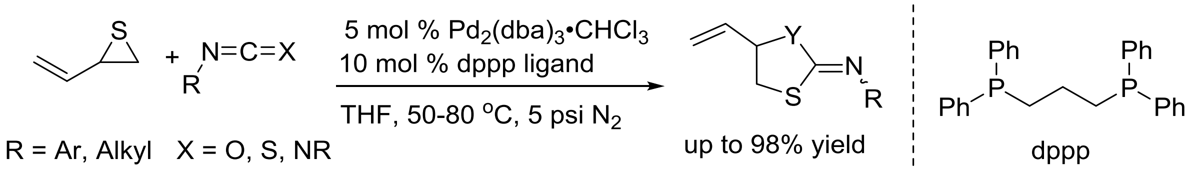
Scheme 1. [3+2]-Cycloaddition of 2-Alkylthiiranes with Isothiocyanates

LiCl-catalyzed ring expansion of 2-phenylthiirane with diphenyl ketene is demonstrated at 60 °C to afford thiolactone (Scheme 2).[9] The protocol suffers from decomposition of thiirane and lack of substrate scope.



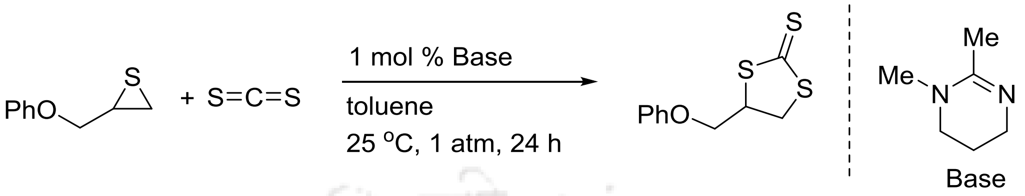
Scheme 2. LiCl-Catalyzed Cycloaddition of 2-Phenylthiirane and Ketene

Alper group reported the Pd-catalyzed coupling of 2-vinylthiirane with heterocumulenes to produce sulfur-containing five-membered heterocycles (Scheme 3).[10] In this reaction, $Pd_2(dba)_3{\cdot}CHCl_3$ is used as the catalyst and bidendate phosphine (dppp) is used as the ligand to afford 1,3-thiazolidines *via* [3+2]-cycloaddition of 2-vinylthiirane with carbodiimide, isocyanates and ketenimines.



Scheme 3. Pd-Catalyzed Ring Expansion of 2-Vinylthiirane with Heterocumulenes

The ring expansion of thiirane with carbondisulfide is reported to afford the cyclic trithiocarbonates under mild conditions (Scheme 4).[11] In this protocol, 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine is used as the catalyst.



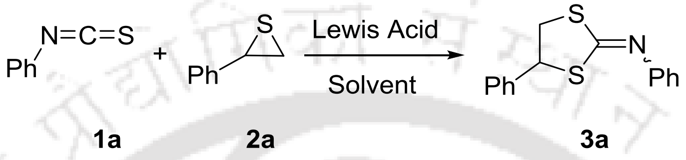
Scheme 4. Ring Expansion of Thiirane with Carbondisulfide

5.2 Present Study

In this chapter, we present a catalytic method for the ring expansion of aryl and alkyl thiiranes with substituted isothiocyanates, isoselenocyanates and carbodiimides to give 2-iminodithiolanes, 2-iminothiaselenolanes and 2-iminothiazolidines, respectively. The advantages of protocol are the regioselectivity and broad substrate scope. First, optimization of the reaction was performed using phenyl isothiocyanate **1a** and 2-phenylthiirane **2a** as the model substrates in the presence of a series of Lewis acids (Table 1). To our delight, the reaction occurred to give **3a** as a 2:3 mixtures of *E* and *Z*-isomers in 58% yield when the substrates were reacted using 10 mol% TMSOTf in $(CH_2Cl)_2$ at room temperature (entry 1). The yield increased to 68% using $BF_2OTf \bullet OEt_2$, whereas TMSCl and $BF_3 \cdot OEt_2$ afforded 43 and 58% yields, respectively (entries 2-4). In contrast, metal triflates, $Cu(OTf)_2$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$ and AgOTf, showed no cycloaddition presumably due to the complex formation as well as desulphurization (entries 5-9). The utilization of CH_2Cl_2 as a solvent led to improve the yield to 77%, whereas the reaction using $CHCl_3$, toluene and CH_3CN produced moderate yields (entries 10-13). A control experiment confirmed that **3a** was not formed in the absence of the catalyst (entry 14).

Next, the scope of the procedure was explored for the reaction of a series of *N*-aryl/alkyl isothiocyanates **1** employing thiirane **2a** as a standard substrate (Table 2). Isothiocyanates bearing substitution at the 4-position of the aryl ring, with bromo **1b**, ethyl **1c**, isopropyl **1d**, iodo **1e**, methoxy **1f**, methyl **1g** and thiomethyl **1i** groups underwent reaction to give thiazolidines **3b-g** and **3i** in 70-83% yields, whereas **1h** bearing a 4-nitro group was unable to provide the expected product, which may be due to the delocalization of the nitrogen lone pair in the aryl ring. However, the reaction of **1j-n** containing 2-methyl, and 2,4-, 2,6-, 3,4- and 3,5-dimethyl groups can be coupled to furnish **3j-n** in 70-77% yields. Furthermore, isothiocyanates bearing *N*-2-naphthyl **1o** and *N*-butyl **1p** substituents underwent reaction to provide **3o** and **3p** in 69 and 75% yields, respectively.

Table 1. Optimization of Reaction Conditions[a]



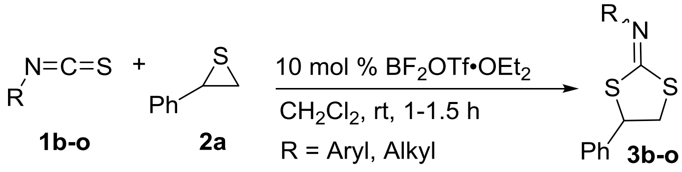
Entry	Catalyst	Solvent	Yield (%)[b]
1	TMSOTf	$(CH_2Cl)_2$	51
2	TMSCl	$(CH_2Cl)_2$	43
3	BF_3•OEt_2	$(CH_2Cl)_2$	58
4	BF_2OTf•OEt_2	$(CH_2Cl)_2$	68
5	$Cu(OTf)_2$	$(CH_2Cl)_2$	n.d.
6	$Sc(OTf)_3$	$(CH_2Cl)_2$	n.d.
7	$Bi(OTf)_3$	$(CH_2Cl)_2$	n.d.
8	$Yb(OTf)_3$	$(CH_2Cl)_2$	n.d.
9	AgOTf	$(CH_2Cl)_2$	n.d.
10	BF_2OTf•OEt_2	CH_2Cl_2	77
11	BF_2OTf•OEt_2	$CHCl_3$	54
12	BF_2OTf•OEt_2	Toluene	26
13	BF_2OTf•OEt_2	CH_3CN	38
14	-	CH_2Cl_2	n.d.

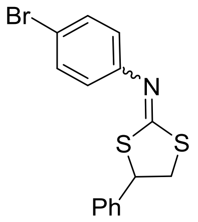
[a] Reaction conditions: phenyl isothiocyanate **1a** (0.5 mmol), 2-phenylthiirane **2a** (1.5 mmol), catalyst (10 mol %), solvent (1 mL), rt, 1 h.

[b] Isolated yield.

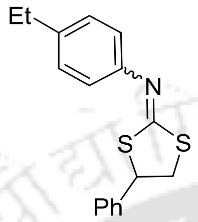
n.d = Not detected.

Table 2. Reaction of Substituted *N*-Aryl/Alkyl isothiocyanates with 2-Phenylthiirane[a,b,c]

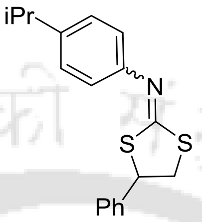




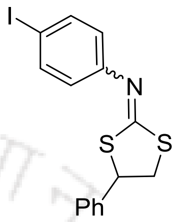
3b, 1 h, 72%
Z/*E* = 1/1.5



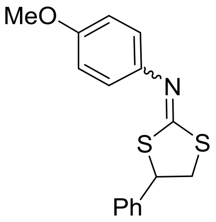
3c, 1 h, 80%
Z/*E* = 1/1.4



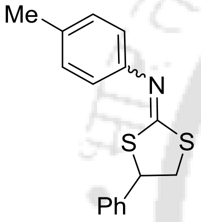
3d, 1 h, 81%
Z/*E* = 1/1.4



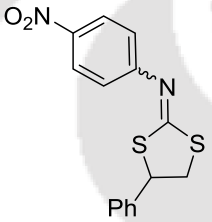
3e, 1 h, 70%
Z/*E* = 1/1.5



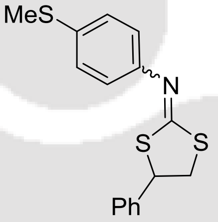
3f, 1 h, 83%
Z/*E* = 1/1.3



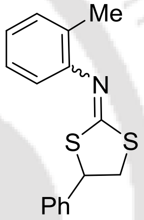
3g, 1 h, 78%
Z/*E* = 1/1.3



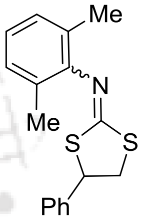
3h, 1.5 h, 0%



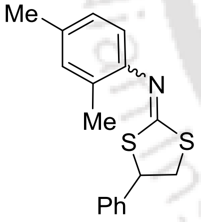
3i, 1 h, 80%
Z/*E* = 1/1.1



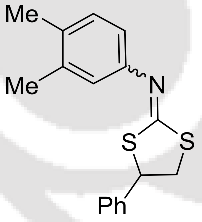
3j, 1.5 h, 74%
Z/*E* = 1/1.3



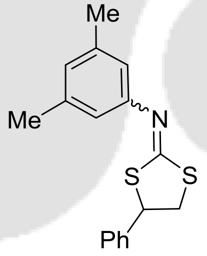
3k, 1.5 h, 70%
Z/*E* = 1/1.4



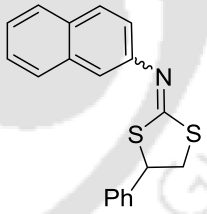
3l, 1 h, 77%
Z/*E* = 1/1.4



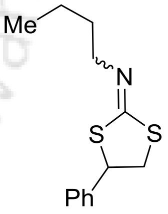
3m, 1 h, 75%
Z/*E* = 1/1.3



3n, 1 h, 75%
Z/*E* = 1/1.2



3o, 1 h, 69%
Z/*E* = 1/1.2



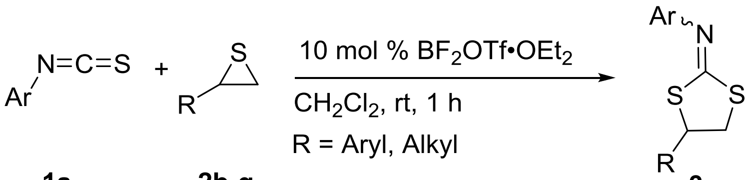
3p, 1.5 h, 75%
Z/*E* = 1/1.1

[a] Reaction conditions: Aryl/alkyl isothiocyanate **1b-o** (0.5 mmol), 2-phenylthiirane **2a** (1.5 mmol), BF$_2$OTf•OEt$_2$ (10 mol %), CH$_2$Cl$_2$ (1 mL), rt.

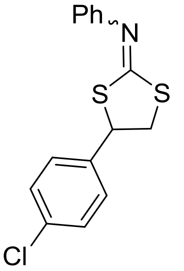
[b] Isolated yield.

[c] *Z*/*E* ratio calculated from ^{1}H NMR spectrum.

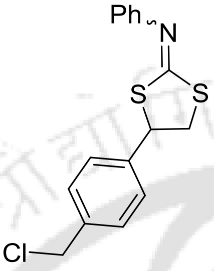
Table 3. Reaction of *N*-Aryl Isothiocyanates with 2-Aryl/Alkylthiiranes[a,b,c]



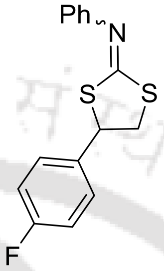
1a **2b-g** **3q-u**



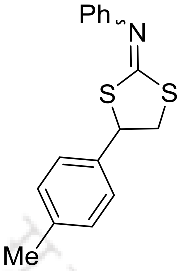
3q, 1 h, 74%
Z/*E* = 1/1.4



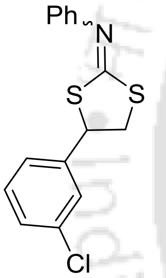
3r, 1.5 h, 65%
Z/*E* = 1/1.2



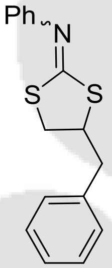
3s, 1 h, 71%
Z/*E* = 1/1.4



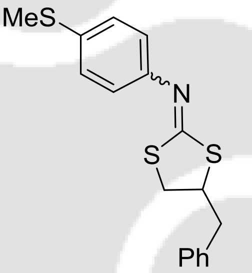
3t, 1 h, 75%
Z/*E* = 1/1.1



3u, 1 h, 75%
Z/*E* = 1/1.4



3v, 1 h, 76 %
Z/*E* = 1.1/1



3w, 1 h, 78 %
Z/*E* = 1.1/1

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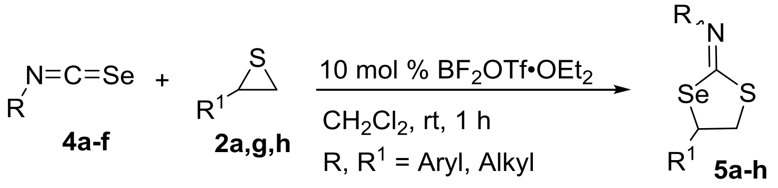
[a] Reaction conditions: isothiocyanate **1a** (0.5 mmol), 2-aryl/alkylthiirane **2b-g** (1.5 mmol), $BF_2OTf•OEt_2$ (10 mol %), CH_2Cl_2 (1 mL), rt.

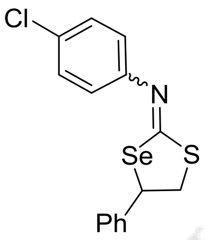
[b] Isolated yield.

[c] *Z*/*E* ratio calculated from ^{1}H NMR spectrum.

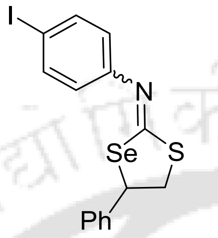
The reaction scope was extended to the coupling of a series of 2-aryl/alkylthiiranes with phenyl isothiocyanate **1a** as a standard substrate (Table 3). Thiirane bearing substitution at the 4-position of the aryl ring with chloro **2b**, chloromethyl **2c**, fluoro **2d** and methyl **2e** functionalities produced **3q-t** in 65-75% yields. The reaction of 3-chloro substituted thiirine **2f** furnished **3u** in 75% yield. In addition, the reaction of 2-benzylthiirane **2g** with isothiocynates **1a** and **1i** afforded **3v** and **3w** in 76 and 78% yields, respectively.

Table 4. Reaction of *N*-Aryl/Alkyl Isoselenocyanates with 2-Aryl/Alkylthiiranes[a,b,c]

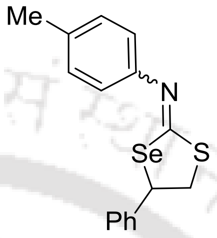




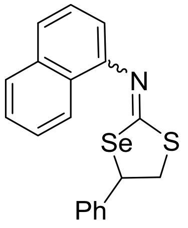
5a, 1 h, 75%
Z/*E* = 4/1



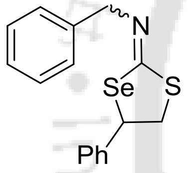
5b,1 h, 68%
Z/*E* = 3/1



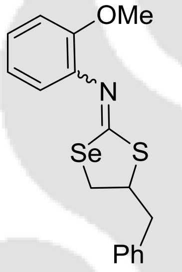
5c, 1 h, 72%
Z/*E* = 5/1



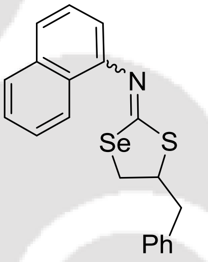
5d, 1 h, 65%
Z/*E* = 4/1



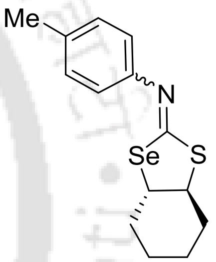
5e, 1.5 h, 76%
Z/*E* = 3/1



5f, 1 h, 72 %
Z/*E* = 3.4/1



5g, 1 h, 75 %
Z/*E* = 10/1



5h, 1 h, 78 %
Z/*E* = 4/1

[a] Reaction conditions: Isoselenocyanates **4a-f** (0.5 mmol), thiirane **2a,g,h** (1.5 mmol), $BF_2OTf\cdot OEt_2$ (10 mol %), CH_2Cl_2 (1 mL), rt.

[b] Isolated yield.

[c] *Z*/*E* ratio calculated from ^1H NMR spectrum.

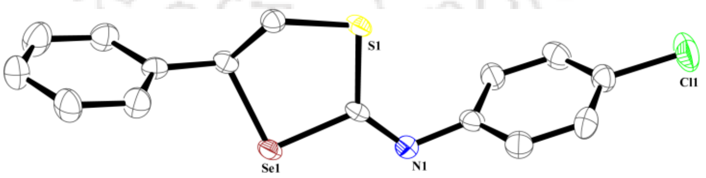


Figure 2. ORTEP Diagram of **5a** with 30% Ellipsoid. H-Atoms are omitted for the clarity (CCDC no. 1826976).

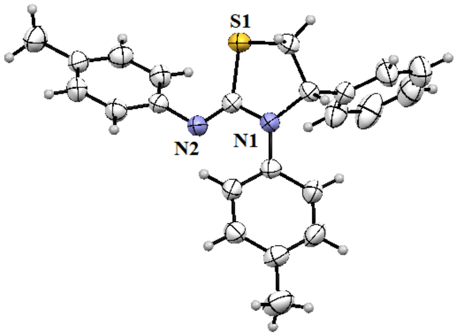
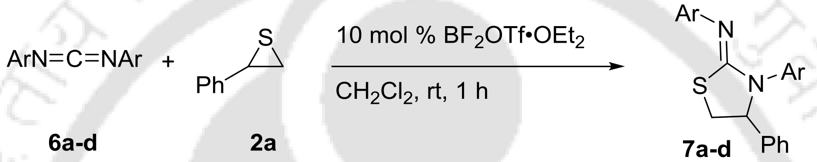
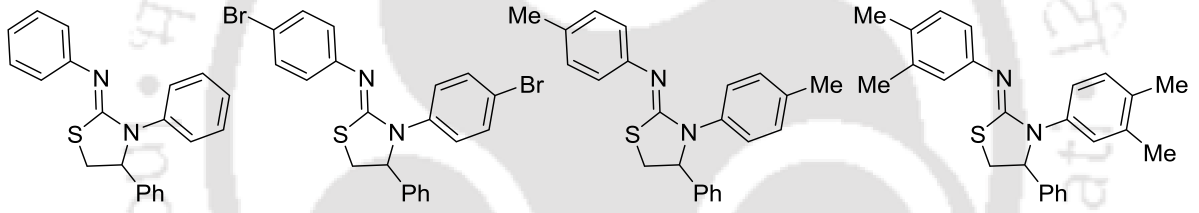


Figure 3. ORTEP Diagram of **7c** with 30% Ellipsoid. (CCDC no. 1846053).

Table 5. Reaction of Carbodiimides with 2-Phenylthiirane[a,b]





7a, 67%. **7b**, 66%. **7c,** 70% **7d**, 69%

[a]Reaction conditions: carbodiimide **6a-d** (0.5 mmol), 2-phenylthiirane **2a** (1.5 mmol), BF$_2$OTf•OEt$_2$ (10 mol %), CH$_2$Cl$_2$ (1.0 mL), rt.

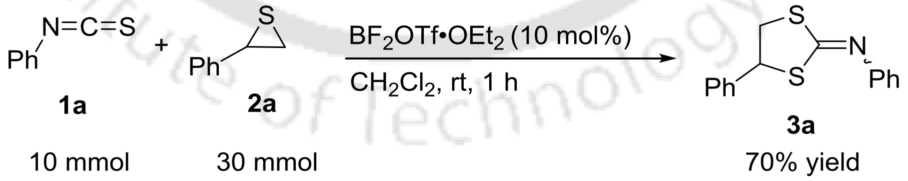
[b]Isolated yield.

The utility of the protocol was further studied for the reaction of isoselenocyanates, isocyanates and carbodiimides (Table 4). The reaction of isoselenocyanates bearing substitution at the 4-position of the aryl ring with chloro **4a**, iodo **4b** and methyl **4c** groups was investigated. The reaction took place to produce the heterocycles **5a-c** in 68-75% yields. In addition, 2-naphthyl isoselenocyanate **4d** underwent reaction to give **5d** in 65% yield, whereas the reaction of benzyl isoselenocyanate **4e** delivered **5e** in 76% yield.

Further, alkylthiiranes, benzylthiirane **2g** and cyclohexylthiirane **2h** underwent reaction to produce **5f-h** in 72-78% yields. To reveal the regioselectivity, a proton coupled ^{77}Se NMR was measured for **5c** and **5f** as the representative examples. The doublet at 559.6 ppm ($^{2}J_{\text{Se-H}}$ = 8.2 Hz) in **5c** suggests that the ring opening occurs at the benzylic carbon, whereas the triplet at 445.1 ppm ($^{2}J_{\text{Se-H}}$ = 16.2 Hz) in **5f** reveals that the ring opening takes place at the CH_2 carbon (see SI). Recrystallization of **5a** in a mixture of CH_2Cl_2 and hexane gave single crystal whose structure was determined by X-ray analysis.

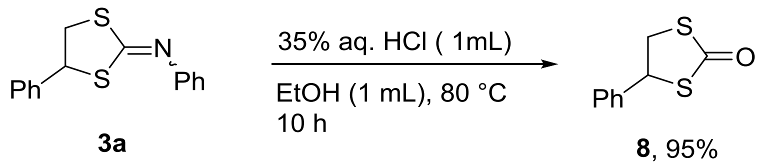
In contrast, under these conditions, isocyanates appeared to not be successful in coupling to thiirane. For examples, the reaction of aryl isocyanates bearing 4-methoxy and 4-nitro substituents in the aryl ring was carried out with 2-phenylthiirane **2a** as a representative substrate. However, no cycloaddition was observed, which may be attributed to the competitive chelation of both *O* and *N* atoms of isocyanates. However, the reaction of carbodiimides bearing *N*-aryl substituents was effective, affording the thiazolidines in high yields (Scheme 5). For examples, carbodiimides bearing *N*-phenyl **6a**, *N*-(4-bromophenyl) **6b**, *N*-(4-methylphenyl) **6c** and *N*-(3,4-dimethylphenyl) **6d** substituents underwent reaction to give the heterocycles **7a-d** in 66-70% yields. It is noteworthy that the products are formed exclusively with *Z*-isomer.[12] This observed *Z*-configuration is further confirmed using the single crystal X-ray analysis of **7c**.

The scale up of the protocol was investigated using **1a** and **2a** as the representative substrates (Scheme 5). The reaction efficiently took place to provide **3a** in 70% yield, which suggests that the reaction can be utilized in gram scale synthesis. In addition, the compound **3a** was hydrolyzed using 35% aq. HCl to afford 1,3-dithiolan-2-one **8** in high yield (Scheme 6).

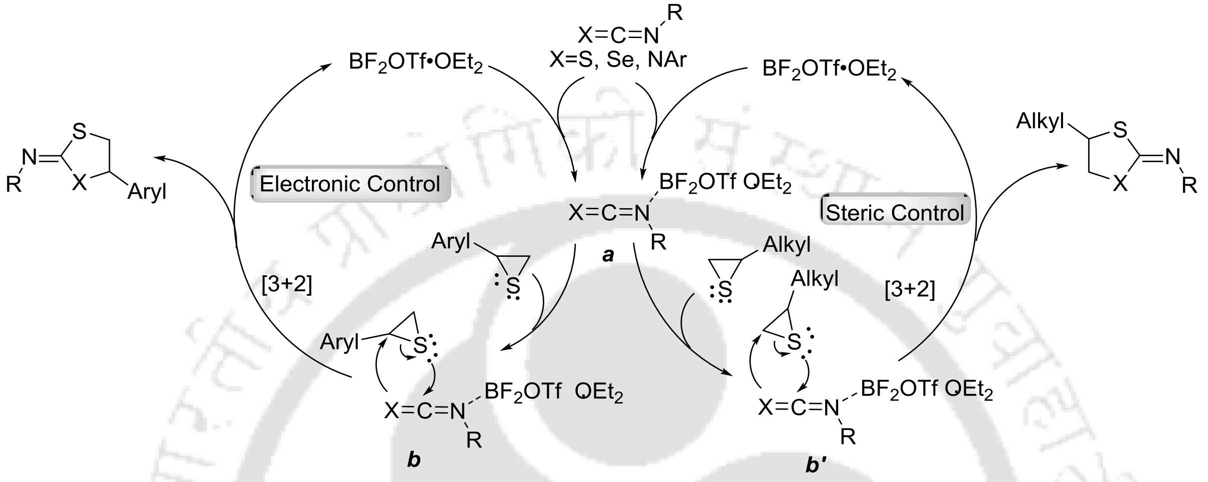


Scheme 5. Gram Scale Synthesis

The proposed catalytic cycle is shown in scheme 7. Coordination of the hard Lewis acid, $BF_2OTf{\bullet}OEt_2$, with the hard base (nitrogen atom) of the heterocumulene can generate the intermediate **A**, which can react with the thiirane sulfur at the electrophilic carbon atom *via* nucleophilic ring opening followed by cyclization to produce the target heterocycles.



Scheme 6. Synthesis of 4-Phenyl-1,3-Dithiolan-2-One



Scheme 7. Proposed Reaction Mechanism

Importantly, the reaction is a switchable regioselective, which depends on the nature of the substrate. In arylthiirane, the ring opening takes place at the electrophilic benzylic carbon due to electronic factor, whereas in alkylthiiranes, the ring opening occurs at the CH_2 carbon likely due to it being the least sterically hindered position.[13] In addition, despite the presence of two reactive sites (C=N and C=S) present in the heterocumulenes, remarkably the cycloaddition occurs chemoselectively to deliver 2-imino heterocycle as a sole product.

In summary, a $BF_2OTf•OEt_2$-catalyzed ring expansion of 2-aryl/alkylthiiranes has been developed with iosthiocyanates, isoselenocyanates and carbodiimides at room temperature. The metal-free conditions, selectivity, scale-up and the substrate scope are the important practical features.

5.3 Experimental Section

5.3.1 General Information: $Sc(OTf)_3$ (99%), $Bi(OTf)_3$, $Yb(OTf)_3$ (99.99%), AgOTf (≥98.0%) and TMSOTf (99%) purchased from commercial sources used as received. Thiiranes, heterocumulens and $BF_2OTf•OEt_2$ were prepared according to literature.[6e,14]

Melting points were determined with a Büchi B-540 apparatus and values are uncorrected. The other information of materials and methods was followed as presented in chapter 1.

5.3.2 Procedure for the [3+2]-Cycloaddition. A mixture of heterocumulene (0.5 mmol), thiirane (1.5 mmol) and $BF_2OTf•OEt_2$ (0.05 mmol) was stirred at room temperature in CH_2Cl_2. Progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and the solution was washed with 5% $NaHCO_3$ (5 mL) and water (3x5 mL). Drying (Na_2SO_4) and evaporation of the solvent yielded a residue, which was purified on a silica gel column chromatography using ethyl acetate and hexane as eluent.

5.3.3 Procedure for the Synthesis of 1,3-Dithiolan-2-One. A mixture of *N*,4-diphenyl-1,3-dithiolan-2-imine (0.3 mmol) and 35% aqueous HCl (1 ml) was refluxed in ethanol (3 ml) for 10 h. Progress of the reaction was monitored by TLC using ethyl acetate and hexane. After completion, the reaction mixture was extracted using ethyl acetate (3 x 10 mL) and washed with 5% aq. $NaHCO_3$ (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.

***N*,4-Diphenyl-1,3-dithiolan-2-imine 3a.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.61$; colorless solid; yield 77% (104 mg); mp 118-119 ^oC; *Z*/*E* = 1.5:1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.44-7.33 (m, 12H), 7.17-7.11 (m, 2H), 7.02-7.01 (m, 4H), 5.15 (m, 2H), 3.73-3.69 (m, 3H), 3.61 (dd, *J* = 12.0, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.9, 152.3, 151.8, 136.6, 136.5, 129.3, 129.2, 129.1, 129.0, 127.9, 127.8, 124.9, 120.4, 58.7, 55.7, 44.4, 41.6 ; FT-IR (KBr) 3060, 3025, 2965, 2921, 2853, 1592, 1484, 1454, 943, 766, 696 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{13}NS_2$ 272.0562, found 272.0556.

***N*-(4-Bromophenyl)-4-phenyl-1,3-dithiolan-2-imine 3b**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 72% (126 mg); mp 158-159 ^oC; *Z*/*E* = 1.4:1; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.6 Hz, 2H), 7.47-7.35 (m, 12H), 6.89 (d, *J* = 7.8 Hz, 4H), 5.15-5.13 (m, 2H), 3.72-3.69 (m, 3H), 3.62 (d, *J* = 11.4Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.9, 151.1, 150.7, 136.4, 136.3, 132.4, 132.3, 129.3, 129.2, 129.1, 129.0, 127.9, 127.8, 122.4, 122.3, 118.0, 58.9, 55.8, 44.5, 41.7; FT-IR (KBr) 3022, 2956, 2915, 2853, 1596, 1453, 1096, 944, 825, 697 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{12}BrNS_2$ 349.9667, found 349.9670.

***N*-(4-Ethylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3c**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 80% (120 mg); mp 116-117 °C; *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.37-7.31 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.95-6.93 (m, 4H), 5.14-5.11 (m, 2H), 3.72-3.68 (m, 3H), 3.60 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.67-2.60 (m, 4H), 1.16-1.21 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 169.1, 150.0, 149.5, 140.9, 140.8, 136.7, 136.6, 129.2, 129.1, 129.0, 128.7, 128.6, 127.9, 127.8, 120.4, 58.6, 55.6, 44.4, 41.5, 28.6, 15.7; FT-IR (KBr) 3025, 2961, 2921, 2872, 2855, 1559, 1501, 1453, 945, 826, 696 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NS_2$ 300.0875, found 300.0876.

***N*-(4-Isopropylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3d**. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.62$; colorless solid; yield 81% (127 mg); mp 102-103 °C; *Z*/*E* = 1.5:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 H, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.38-7.33 (m, 4H), 7.24 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.99-6.98 (m, 4H), 5.14-5.12 (m, 2H), 3.72-3.68 (m, 3H), 3.60 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.95-2.87 (m, 2H), 1.29-1.25 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 169.0, 149.9, 149.4, 145.4, 145.3, 136.7, 136.6, 129.2, 129.1, 128.9, 128.87, 127.84, 127.7, 127.2, 127.1, 120.4, 120.3, 58.5, 55.4, 44.3, 41.4, 33.7, 24.2, 24.1; FT-IR (KBr) 3082, 3052, 3020, 2959, 2921, 2860, 1594, 1500, 1453, 944, 920, 825, 766, 697 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{18}H_{19}NS_2$ 314.1032, found 314.1027.

***N*-(4-Iodophenyl)-4-phenyl-1,3-dithiolan-2-imine 3e.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 70% (139 mg); mp 115-116 °C; *Z*/*E* = 1:1.2; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.43-7.39 (m, 4H), 7.37-7.32 (m, 4H), 6.78-6.76 (m, 4H), 5.17-5.13 (m, 2H), 3.73-3.69 (m, 3H), 3.62 (dd, *J* = 11.4, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.0, 151.8, 151.3, 138.4, 138.3, 136.4, 136.3, 129.3, 127.8, 122.7, 122.7, 88.9, 58.9, 55.9, 44.5, 41.8; FT-IR (KBr)

3060, 3028, 3003, 2957, 2922, 2849, 1595, 1474, 1454, 943, 918, 820, 767, 697 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{12}INS_2$ 397.9529, found 397.9529.

***N*-(4-Methoxyphenyl)-4-phenyl-1,3-dithiolan-2-imine 3f.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; colorless solid; yield 83% (126 mg); mp 106-107 °C; *Z*/*E* = 1:1.3; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.37-7.33 (m, 4H), 6.99-6.98 (m, 4H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.14-5.11 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.71-3.67 (m, 3H), 3.59 (dd, *J* = 12.0, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 168.7, 156.9, 145.5, 145.0, 136.7, 136.6, 129.2, 129.1, 128.94, 128.91, 127.8, 127.77, 121.7, 114.4, 114.3, 58.6, 55.6, 55.4, 44.4, 41.4; FT-IR (KBr) 3028, 3001, 2952, 2909, 2831, 1593, 1500, 1240, 1102, 1036, 944, 829 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NOS_2$ 302.0668, found 302.0672.

4-Phenyl-*N*-(*p*-tolyl)-1,3-dithiolan-2-imine 3g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; colorless solid; yield 78% (111 mg); mp 110-111 °C; *Z*/*E* = 1.3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.44-7.32 (m, 8H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 6.93-6.91 (m, 4H), 5.14-5.12 (m, 2H), 3.72-3.68 (m, 3H), 3.60 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.3, 149.8, 149.3, 136.7, 136.6, 134.5, 134.4, 129.9, 129.8, 129.2, 129.1, 128.9, 127.9, 127.8, 120.4, 58.6, 55.6, 44.4, 41.5, 21.2, 21.1; FT-IR (KBr) 3031, 2966, 2912, 2855, 1597, 1453, 1105, 945, 816, 695 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NS_2$ 286.0719, found 286.0720.

***N*-(4-(Methylthio)phenyl)-4-phenyl-1,3-dithiolan-2-imine 3i.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; colourless solid; yield 80% (127 mg); mp 120-121 °C; *Z*/*E* = 1.1:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.51 (m, 2H), 7.44-7.34 (m, 8H), 7.27-7.25 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.97-6.95 (m, 4H), 5.15-5.12 (m, 2H), 3.72-3.68 (m, 3H), 3.61 (dd, *J* = 11.4,4.8 Hz, 1H), 2.49 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.9, 149.7, 149.2, 136.5, 136.4, 134.33, 134.29, 129.24, 129.18, 129.03, 129.0, 127.9, 127.88, 127.8, 121.21, 121.19, 58.8, 55.6, 44.5, 41.6, 16.63, 16.61; FT-IR (KBr) 3027, 2959, 2918, 2852, 1591, 1482, 1453, 1427, 1210, 1103, 945, 817 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NS_3$ 318.0439, found 318.0435.

4-Phenyl-*N*-(*o*-tolyl)-1,3-dithiolan-2-imine 3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow liquid; yield 74% (106 mg); *Z*/*E* = 1.3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.54 (d, *J* = 7.2 Hz, 2H), 7.44-7.40 (m, 4H), 7.38-7.32 (m, 4H), 7.23-7.15 (m, 4H), 7.08-7.03 (m, 2H), 6.88 (d, *J* = 7.8 Hz, 2H), 5.17-5.12 (m, 2H), 3.74-3.68 (m, 3H), 3.36 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.253 (s, 3H), 2.251 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.3, 151.8, 151.2, 136.8, 136.7, 130.7, 130.6, 129.2, 129.1, 128.9, 127.9, 127.7, 126.7, 124.8, 119.1, 119.0, 58.4, 55.9, 44.3, 41.9, 17.9; FT-IR (KBr) 3060, 3026, 2922, 2850, 1603, 1584, 1484, 1452, 944, 697 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NS_2$ 286.0719, found 286.0726.

***N*-(2,6-Dimethylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3k**: Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; colorless gummy liquid; yield 70% (105 mg); *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.42-7.32 (m, 8H), 7.04-7.01 (m, 4H), 6.97-6.92 (m, 2H), 5.16-5.13 (m, 2H), 3.74-3.64 (m, 4H), 2.19 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 169.5, 151.1, 150.5, 136.8, 129.1, 129.0, 128.9, 128.2, 128.1, 127.7, 127.7, 127.5, 127.3, 124.2, 58.3, 56.1, 44.2, 42.3, 17.9; FT-IR (KBr) 3060, 3028, 2919, 2851, 1603, 1583, 1491, 1452, 1231, 1195, 1089, 938, 767 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NS_2$ 300.0875, found 300.0882.

***N*-(2,4-Dimethylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3l.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 77% (115 mg); mp 57-58 °C; *Z*/*E* = 1.3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.44-7.41 (m, 4H), 7.34-7.33 (m, 4H), 7.06-6.98 (m, 4H), 6.81-6.79 (m, 2H), 5.16-5.11 (m, 2H), 3.73-3.67 (m, 3H), 3.61 (dd, *J* = 11.4, 3.6 Hz, 1H), 2.34 (s, 3H), 2.31 (s, 3H), 2.25 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.0, 149.3, 148.7, 134.2, 131.4, 131.3, 129.1, 129.0, 128.8, 128.7, 127.8, 127.7, 127.1, 118.8, 118.7, 58.2, 55.7, 44.1, 41.8, 21.0, 17.8; FT-IR (KBr) 3063, 3033, 2995, 2960, 2914, 2854, 1590, 1489, 1453, 1205, 946, 932, 815, 693 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NS_2$ 300.0875, found 300.0883.

***N*-(3,4-Dimethylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3m.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 75% (112 mg); mp 76-77 °C; *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.14-7.40 (m, 2H), 7.39-7.36 (m, 2H), 7.34-7.31 (m, 2H), 7.26-7.22 (m, 1H), 7.17 (d, *J* = 6.6 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.80 (s, 2H), 6.77-6.75 (m, 2H), 5.10-5.08 (m, 2H), 3.68-3.64 (m, 3H), 3.56 (dd, *J* = 12.0, 4.9 Hz, 1H), 2.25-2.22 (m, 9H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.0, 150.3, 149.8, 137.6, 137.5, 136.8, 136.7, 133.23, 133.19, 130.4, 130.3, 129.3, 129.2, 129.0, 128.9, 128.5, 128.0, 127.9, 125.6, 121.80, 121.77, 117.7, 58.6, 55.7, 44.4, 41.5, 20.2, 19.6; FT-IR (KBr) 3060, 3026, 2920, 2854, 1588, 1493, 1452, 949, 697 cm^{-1}. HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{17}H_{17}NS_2$ 300.0875, found 300.0874.

***N*-(3,5-Dimethylphenyl)-4-phenyl-1,3-dithiolan-2-imine 3n.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless liquid; yield 75% (112 mg); *Z*/*E* = 1.3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.38-7.33 (m, 4H), 6.81 (s, 1H), 6.78 (s, 1H), 6.65 (s, 4H), 5.14-5.11 (m, 2H), 3.72-3.68 (m, 3H), 3.59 (dd, *J* = 12.0, 4.8 Hz, 1H), 2.34 (s, 6H), 2.31 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 169.0, 152.3, 151.9, 138.9, 138.8, 136.7, 129.2, 129.1, 128.9, 127.8, 127.7, 126.6, 118.0, 58.5, 55.5, 44.3, 41.5, 21.54, 21.52; FT-IR (KBr) 3058, 3029, 3006, 2920, 2959, 1586, 1452, 952, 843, 769, 698 cm^{-1}; HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{17}H_{17}NS_2$ 300.0875, found 300.0869.

***N*-(Naphthalen-2-yl)-4-phenyl-1,3-dithiolan-2-imine 3o.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 69% (112 mg); mp 107-108 °C; *Z*/*E* = 1.2:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.88-7.84 (m, 2H), 77.68-7.63 (m, 2H), 7.58-7.57 (m, 2H), 7.54-7.32 (m, 14H), 7.05 (t, *J* = 6.6 Hz, 2H), 5.24 (dd, *J* = 9.6, 6.0 Hz, 1H), 5.16 (dd, *J* = 10.8, 5.4 Hz, 1H), 3.79 (t, *J* = 11.4 Hz, 1H), 3.73-3.66 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.7, 149.3, 148.7, 136.6, 136.5, 134.4, 134.3, 129.2, 129.1, 129.0, 128.9, 128.03, 128.00, 127.9, 127.7, 126.5, 125.9, 124.9, 123.7, 114.6, 114.5, 58.3, 55.9, 44.2, 41.8; FT-IR (KBr) 3079, 3057, 3023, 2998, 2923, 2850, 1597, 1571, 1452, 1391, 940, 774, 697 cm^{-1}. HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{19}H_{15}NS_2$ 322.0719, found 322.0721.

***N*-Butyl-4-phenyl-1,3-dithiolan-2-imine 3p.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; yellow liquid; yield 75% (94 mg); *Z*/*E* = 1.1:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48-7.45 (m, 4H), 7.39-7.31 (m, 6H), 5.12 (dd, *J* = 10.2, 4.8 Hz, 1H), 5.01 (dd, *J* =

10.2, 5.4 Hz, 1H), 3.72 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.67-3.64 (m, 1H), 3.57-3.53 (m, 1H), 3.50 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.37-3.30 (m, 4H), 1.71-1.65 (m, 4H), 1.43-1.39 (m, 4H), 0.99-0.92 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.0, 167.9, 137.1, 136.8, 129.2, 129.1, 129.0, 128.9, 127.9, 127.8, 59.3, 58.5, 58.4, 55.0, 44.2, 41.4, 32.7, 32.6, 20.79, 20.78, 14.11, 14.09; FT-IR (neat) 3064, 3028, 2957, 2927, 2870, 1658, 1602, 1492, 1453, 1284, 1122, 1073, 900, 767, 737 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{17}NS_2$ 252.0875, found 252.0886.

4-(4-Chlorophenyl)-*N*-phenyl-1,3-dithiolan-2-imine 3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 74% (113 mg); mp 146-147 °C; *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.8 Hz, 2H), 7.38-7.36 (m, 5H), 7.35-7.32 (m, 5H), 7.16-7.11 (m, 2H), 7.00-7.98 (m, 4H), 5.12 (dd, *J* = 10.2, 5.4 Hz, 2H), 3.72-3.55 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 169.4, 152.3, 151.8, 135.3, 135.2, 134.8, 129.4, 129.37, 129.35, 129.32, 129.2, 129.1, 125.03, 125.01, 120.43, 120.38, 57.7, 54.7, 44.4, 41.6; FT-IR (KBr) 3077, 3060, 2962, 2918, 2847, 1590, 1490, 1410, 941, 824, 764, 694 cm^{-1}. HRMS (ESI) m/z [M+H]+ calcd for $C_{15}H_{12}ClNS_2$ 306.0172, found: 306.0173.

4-(4-(Chloromethyl)phenyl)-*N*-phenyl-1,3-dithiolan-2-imine 3r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 65% (104 mg); mp 140-141 °C; *Z*/*E* = 1.2:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.44-7.42 (m, 4H), 7.39-7.32 (m, 6H), 7.16-7.10 (m, 2H), 7.01-6.99 (m, 4H), 5.15 (dd, *J* = 10.2, 5.2 Hz, 2H), 4.59 (m, 4H), 3.72-3.66 (m, 3H), 3.62 (dd, *J* = 12, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.5, 152.3, 151.8, 138.4, 137.0, 136.9, 129.5, 129.4, 129.33, 129.30, 128.3, 128.2, 125.0, 120.5, 58.1, 55.1, 45.8, 45.7, 44.4, 41.6; FT-IR (KBr) 3055, 3028, 2959, 2918, 2853, 1590, 1483, 941, 839, 762, 694 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{14}ClNS_2$ 320.0329, found 320.0320.

4-(4-Fluorophenyl)-*N*-phenyl-1,3-dithiolan-2-imine 3s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 71% (103 mg); mp 137-138 °C; *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.42-7.40 (m, 2H), 7.37-7.32 (m, 4H), 7.16-7.03 (m, 6H), 7.01-7.99 (m, 4H), 5.13 (dd, *J* = 10.2, 5.4 Hz, 2H), 3.70-3.63 (m, 3H), 3.60 (dd, *J* = 11.4, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.1, 169.4, 163.74 (d, J = 247.5 Hz), 163.71 (d, *J* = 247.5 Hz), 152.3, 151.8, 129.6 (d, *J* = 9.0 Hz), 129.6 (d, *J* = 9.0

Hz), 129.50, 129.32, 129.29, 124.98, 124.96, 120.44, 120.39, 116.3 (d, *J* = 22.5 Hz), 116.2 (d, *J* = 22.5 Hz), 57.8, 54.8, 44.5, 41.8; FT-IR (KBr) 3078, 2957, 2922, 2853, 1593, 1509, 1384, 1231, 1094, 1020, 942, 835 cm^{-1}. HRMS (ESI) m/z [M+H]+ calcd for $C_{15}H_{12}FNS_2$ 290.0468, found: 290.0468.

***N*-Phenyl-4-(*p*-tolyl)-1,3-dithiolan-2-imine 3t.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; colorless liquid; yield 75% (108 mg); *Z*/*E* = 1.1:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14-7.40 (m, 2H), 7.38-7.30 (m, 6H), 7.21-7.10 (m, 6H), 7.01-6.99 (m, 4H), 5.14-5.10 (m, 2H), 3.71-3.64 (m, 3H), 3.58 (dd, *J* = 11.4, 4.8 Hz, 1H), 2.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.3, 149.9, 149.3, 136.7, 136.6, 134.5, 134.5, 129.8, 129.2, 129.1, 128.9, 127.9, 127.8, 120.4, 120.4, 58.6, 55.6, 44.4, 41.5, 21.2; FT-IR (neat) 3060, 3028, 2919, 2851, 1603, 1467, 1376, 1231, 1030, 938, 911, 767, 735 cm^{-1}. HRMS (ESI) m/z [M+H]$^+$ calcd for $C_{16}H_{15}NS_2$ 286.0719, found 286.0712.

4-(3-Chlorophenyl)-*N*-phenyl-1,3-dithiolan-2-imine 3u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless solid; yield 75% (114 mg); mp 94-95 ^{o}C; *Z*/*E* = 1.4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.44 (s, 1H), 7.41-7.27 (m, 10H), 7.16-7.11 (m, 2H), 7.00-7.99 (m, 4H), 5.10-5.07 (m, 2H), 3.73-3.60 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.1, 152.3, 151.8, 138.8, 135.1, 135.0, 130.5, 130.4, 129.3, 129.3, 129.2, 129.1, 128.1, 128.0, 126.1, 126.0, 125.0, 125.03, 120.42, 120.37, 57.7, 54.7, 44.3, 41.5; FT-IR (neat) 3056, 3030, 2963, 2923, 2853, 1585, 1475, 1427, 1381, 1208, 1166, 1078, 940, 789, 762 cm^{-1}. HRMS (ESI) m/z [M+H]+ calcd for $C_{15}H_{12}ClNS_2$ 306.0172, found: 306.0172.

4-Benzyl-*N*-phenyl-1,3-dithiolan-2-imine 3v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless liquid; yield 76% (108 mg); *Z*/*E* = 1.1:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.27 (m, 10H), 7.24-7.23 (m, 2H), 7.19-7.17 (m, 2H), 7.14-7.11 (m, 2H), 6.99-6.96 (m, 4H), 4.23-4.18 (m, 1H), 4.14-4.10 (m, 1H), 3.52 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.46 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.34 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.30 (dd, *J* = 11.4, 7.2 Hz, 1H), 3.22 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.16-3.08 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 170.3, 152.3, 152.2, 138.0, 137.9, 129.7, 129.3, 129.1, 129.05, 129.01, 128.5, 127.4, 124.82, 128.80, 120.5, 120.4, 55.7, 52.5, 41.6, 40.5, 40.3, 39.2,; FT-IR (neat) 3029, 2959, 2922, 2852, 1625, 1578, 1490, 1451, 1389, 1261, 1083, 1007, 872, 823 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NS_2$ 286.0719, found 286.0711.

4-Benzyl-*N*-(4-(methylthio)phenyl)-1,3-dithiolan-2-imine 3w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless liquid; yield 78% (130 mg); *Z*/*E* = 1.1:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36-7.29 (m, 4H), 7.80-7.23 (m, 8H), 7.18-7.17 (m, 2H), 6.94-6.91 (m, 4H), 4.23-4.20 (m, 1H), 4.13-4.09 (m, 1H), 3.52 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.45 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.35 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.30 (dd, *J* = 12.0, 7.8 Hz, 1H), 3.20 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.15-3.09 (m, 3H), 2.48 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 170.3, 149.6, 149.5, 138.0, 137.9, 134.2, 134.1, 129.1, 129.0, 128.98, 127.9, 127.88, 127.4, 121.2, 121.17, 55.8, 52.4, 41.7, 40.5, 40.2, 39.1, 16.63, 16.61; FT-IR (neat) 3025, 2956, 2920, 2852, 1575, 1483, 1453, 1435, 1210, 1091, 943, 822 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NS_3$ 332.0596, found 332.0599.

***N*-(4-Chlorophenyl)-4-phenyl-1,3-thiaselenolan-2-imine 5a.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; yield 75% (133 mg); mp 138-139 °C; *Z*/*E* = 4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 6.6 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.38-7.28 (m, 10H), 6.95-6.91 (m, 4H), 5.36 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.31 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.89-3.81 (m, 2H), 3.75 (dd, *J* = 12.6, 4.2 Hz, 1H), 3.64 (dd, *J* = 12.0, 3.6 Hz, 1H);^{13}C NMR (150 MHz, $CDCl_3$) δ 169.2, 152.3, 137.5, 130.5, 129.5, 129.4, 129.3, 129.2, 128.8, 128.1, 127.9, 121.7, 121.2, 55.2, 53.4, 46.3, 43.1; FT-IR (KBr) 3063, 3025, 3003, 2949, 2925, 2854, 1605, 1590, 1478, 1453, 1094, 1008, 888, 694 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{12}ClNSSe$ 353.9617, found 353.9628.

***N*-(4-Iodophenyl)-4-phenyl-1,3-thiaselenolan-2-imine 5b.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; colorless solid; yield 68% (151 mg); mp 141-142 °C; *Z*/*E* = 3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67-7.63 (m, 4H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.37-7.31 (m, 6H), 6.78 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 5.37-5.29 (m, 2H), 3.89-3.81 (m, 2H), 3.64-3.69 (m, 2H);^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 169.3, 153.4, 138.5, 137.5, 129.3, 128.8, 127.9, 122.5, 122.0, 89.3, 55.2, 53.4, 46.3, 43.2; FT-IR (KBr) 3060, 3026, 2955, 2921, 2851, 1587, 1493, 1474, 1451, 1390, 1213, 1098, 1003, 890, 762 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{15}H_{12}INSSe$ 445.8973, found 445.8972.

4-Phenyl-*N*-(*p*-tolyl)-1,3-thiaselenolan-2-imine 5c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 72% (120 mg); mp 88-89 °C; *Z*/*E* = 5:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.36-7.34 (m, 4H), 7.32-7.30 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.90 (d, *J* = 7.8 Hz, 2H), 5.36 (dd, *J* = 10.8, 4.2 Hz, 1H), 5.28 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.87-3.80 (m, 2H), 3.73 (d, *J* = 12.6, 4.8 Hz, 1H), 3.62 (d, *J* = 12.0, 4.8 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.6, 151.5, 137.8, 134.8, 130.0, 129.9, 129.2, 129.1, 128.8, 128.7, 128.6, 128.1, 127.9, 120.2, 119.6, 54.6, 53.1, 46.1, 42.9, 21.2; FT-IR (KBr) 3060, 3025, 2971, 2947, 2912, 1581, 1501, 1452, 965, 889, 698 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NSSe$ 334.0169, found 334.0178.

***N*-(Naphthalen-1-yl)-4-phenyl-1,3-thiaselenolan-2-imine 5d.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; colorless solid; yield 65% (120 mg); mp 107-108 °C; *Z*/*E* = 4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.85-7.84 (m, 2H), 7.66-7.65 (m, 2H), 7.56-7.50 (m, 5H), 7.44-7.40 (m, 6H), 7.34-7.29 (m, 5H), 7.06-7.01 (m, 2H), 5.41-5.40 (m, 1H), 5.27 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.90-3.82 (m, 2H), 3.69-3.67 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.8, 151.0, 137.7, 134.3, 129.2, 128.6, 128.0, 127.9, 126.72, 126.69, 126.0, 125.9, 125.4, 123.8, 113.5, 54.4, 43.2; FT-IR (KBr) 3057, 3023, 2958, 2922, 2853, 1596, 1581, 1570, 1452, 1074, 883, 773, 696 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{15}NSSe$ 370.0163, found 370.0183.

***N*-Benzyl-4-phenyl-1,3-thiaselenolan-2-imine 5e.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.58$; yellow liquid; yield 76% (127 mg); *Z*/*E* = 3:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.50 (m, 4H), 7.39-7.31 (m, 14H), 7.28-7.27 (m, 2H), 5.34 (dd, *J* = 11.4, 4.8 Hz, 1H), 5.28 (dd, *J* = 10.8, 4.2 Hz, 1H), 4.62-4.52 (m, 2H), 4.50-4.43 (m, 2H), 3.90 (dd, *J* = 12.6, 10.8 Hz, 1H), 3.80 (dd, *J* = 12.6, 4.8 Hz, 1H), 3.75 (dd, *J* = 12.6, 10.8 Hz, 1H), 3.54 (dd, *J* = 12.0, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 165.1, 138.9, 138.6, 137.9, 137.6, 129.22, 129.19, 128.72, 128.68, 128.6, 128.12, 128.1, 128.0, 127.3, 127.2, 66.7, 62.5, 55.5, 52.5, 46.2, 42.5; FT-IR (neat) 3062, 3027, 2963, 2922, 2853, 1600, 1492, 1451, 1347, 1261, 1076, 1027, 872, 800, 733 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{15}NSSe$ 334.0163, found 334.0177.

5-Benzyl-*N*-(2-methoxyphenyl)-1,3-thiaselenolan-2-imine 5f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless liquid; yield 72% (131 mg); (*Z*/*E* = 3.4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.23 (m, 8H), 7.19-7.09 (m, 4H), 6.95-6.89 (m, 6H), 4.22-4.20 (m, 1H), 4.16-4.11 (m, 1H), 4.84-4.83 (m, 6H), 3.56-3.55 (m, 2H), 3.42-3.38 (m, 2H), 3.29-3.60 (m, 1H), 3.24-3.21 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.15-3.09 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.6, 150.4, 150.2, 143.2, 138.2, 138.0, 129.13, 129.06, 129.0, 128.97, 128.94, 127.29, 127.27, 126.1, 125.8, 121.0, 120.9, 120.4, 119.8, 111.83, 111.78, 57.6, 56.0, 54.5, 40.9, 40.6, 36.1, 35.1; ^{77}Se NMR (proton coupled) (76 MHz, $CDCl_3$) δ 473.5, 445.2 (t, $^2J_{Se\text{-}H}$ = 16.2 Hz); ^{77}Se NMR (proton decoupled) (76 MHz, $CDCl_3$) δ 473.5 (minor), 445.2 (major); FT-IR (neat) 3025, 2956, 2923, 2852, 1599, 1580, 1489, 1452, 1246, 1111, 1024, 896, 747 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{17}NOSSe$ 364.0269, found 364.0270.

5-Benzyl-*N*-(naphthalen-1-yl)-1,3-thiaselenolan-2-imine 5g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; colorless liquid; yield 75% (144 mg); *Z*/*E* = 10:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02-8.01 (m, 2H), 7.85-7.84 (m, 2H), 7.68-7.64 (m, 2H), 7.51-7.35 (m, 8H), 7.31-7.27 (m, 6H), 7.17-7.16 (m, 1H), 7.00-6.99 (m, 2H), 6.60 (d, *J* = 6.0 Hz, 1H), 4.40-4.37 (m, 1H), 4.20-4.15 (m, 1H), 3.59-3.55 (m, 2H), 3.46-3.37 (m, 2H), 3.28-3.08 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.3, 150.8, 138.2, 134.3, 129.7, 129.1, 129.0, 128.8, 128.3, 128.0, 127.4, 127.3, 126.7, 126.0, 125.9, 125.2, 123.7, 114.3, 113.6, 57.5, 54.4, 40.9, 40.7, 36.0; FT-IR (neat) 3026, 2923, 2853, 1595, 1496, 1452, 1389, 1261, 1080, 1022, 907, 797, 774 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}NSSe$ 384.0320, found 384.0324.

***N*-(*p*-Tolyl)hexahydrobenzo[d][1,3]thiaselenol-2-imine 5h.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; colorless liquid; yield 78% (122 mg); *Z*/*E* = 4:1; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.8 Hz, 4H), 6.85-6.82 (m, 4H), 3.92-3.87 (m, 1H), 3.80-3.75 (m, 1H), 3.71-3.66 (m, 2H), 2.32 (s, 6H), 2.26-2.22 (m, 2H), 2.15-2.10 (m, 2H), 1.96-1.87 (m, 2H), 1.63-1.58 (m, 4H), 1.52-1.44 (m, 4H), 1.31-1.28 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.7, 151.3, 134.6, 134.4, 129.9, 129.8, 120.1, 119.7, 116.4, 60.9, 58.1, 54.9, 54.1, 32.2, 31.1, 29.9, 29.6, 26.4, 26.4, 25.9, 25.8, 22.9, 21.2; FT-IR (neat) 3055, 3029, 2923, 2853, 1595, 1496, 1389, 1261, 1022, 885, 774 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{17}NSSe$ 312.0320, found 312.0308.

(*Z*)-*N*,3,4-Triphenylthiazolidin-2-imine 7a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.52$; brown liquid; yield 67% (111 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.2 Hz, 4H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 8.4 Hz, 3H), 7.26-7.23 (m, 2H), 7.07 (dd, *J* = 15.6, 7.2 Hz, 2H), 7.02 (d, *J* = 7.2 Hz, 2H), 5.40 (dd, *J* = 6.6, 4.8 Hz, 1H), 3.70 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.15 (d, *J* = 10.8, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 152.2, 141.0, 140.2, 129.1, 129.0, 128.9, 128.4, 126.8, 125.0, 124.5, 123.6, 122.0, 67.4, 36.0; FT-IR (neat) 3055, 3026, 2998, 2919, 2845, 1626, 1599, 1511, 1452, 818, 698 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}N_2S$ 331.1263, found 331.1260.

(*Z*)-*N*,3-Bis(4-bromophenyl)-4-phenylthiazolidin-2-imine 7b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.52$; colorless liquid; yield 66% (160 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.0 Hz, 2H), 7.36-7.34 (m, 5H), 7.24-7.22 (m, 4H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.35 (dd, *J* = 6.6, 5.4 Hz, 1H), 3.69 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.17 (dd, *J* = 10.8, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.7, 150.8, 139.7, 139.4, 132.1, 132.0, 129.3, 128.7, 126.8, 126.3, 123.8, 118.4, 116.7, 67.3, 36.0; FT-IR (neat) 3060, 3026, 2920, 2851, 1584, 1494, 1453, 1261, 1207, 1073, 1027, 938, 749 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{16}Br_2N_2S$ 486.9474, found 486.9470.

(*Z*)-4-Phenyl-*N*,3-di-*p*-tolylthiazolidin-2-imine 7c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.52$; yellow solid; yield 70% (126 mg); mp. 129-130°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2H), 7.38-7.31 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.35 (dd, *J* = 7.2, 5.4 Hz, 1H), 3.67 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.14 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.35 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 149.8, 140.3, 138.4, 134.7, 132.7, 129.5, 129.4, 128.9, 129.3, 126.8, 124.7, 121.8, 67.5, 35.8, 21.1, 21.0; FT-IR (neat) 3064, 3025, 2992, 2917, 2856, 1619, 1597, 1505, 1374, 819, 695 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{22}N_2S$ 359.1576, found 359.1572.

(*Z*)-*N*,3-Bis(3,4-dimethylphenyl)-4-phenylthiazolidin-2-imine 7d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.52$; yellow gummy liquid; yield 69% (134 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.05 (t, *J* = 7.8 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 5.33 (dd, *J* = 7.2, 5.4 Hz, 1H), 3.67 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.13 (dd, *J* = 11.4, 5.4 Hz, 1H), 2.26 (s, 3H), 2.24 (s, 3H), 2.16 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.3, 150.2, 140.5, 138.8, 137.0, 133.7, 131.4, 130.0, 129.9, 128.9, 128.3, 126.9, 126.2, 123.3, 122.4, 119.1, 67.6, 35.9, 20.2, 20.1, 19.4; FT-IR (neat) 3060, 3028, 2961, 2921, 2853, 1628, 1597, 1501, 1449, 823, 699 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{26}N_2S$ 387.1889, found 387.1883.

4-Phenyl-1,3-dithiolan-2-one 8. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; brown liquid; yield 95% (56 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.42-7.40 (m, 3H), 5.31 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.85 (dd, *J* = 12.0, 10.2 Hz, 1H), 3.78 (dd, *J* = 11.4, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.9, 136.5, 129.4, 129.3, 127.8, 57.2, 43.1; FT-IR (neat) 3062, 3028, 2959, 2921, 2851, 1734, 1653, 1492, 1452, 1261, 1077, 1024, 934, 868, 767, 734 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_9H_8OS_2$ 197.0089, found 197.0091.

Crystal Data and Structure Refinement for 5a

Identification code	exp_3731
Empirical formula	$C_{15}H_{12}ClNSSe$
Formula weight	352.73
Temperature(K)	566(2)
Radiation	MoKα (λ = 0.71073)
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	5.4761(5)
b/Å	8.5406(7)
c/Å	31.162(2)
α/°	90.00
β/°	91.863(6)
γ/°	90.00
Volume/Å^3	1456.7(2)

Crystal size(mm^3)	0.41 × 0.35 × 0.28
Z	4
Density(Mg /m^{-3})	1.608
Final R[I>2σ(I)]	$R_1 = 0.0450$, $wR_2 = 0.1029$
R(all data)	$R_1 = 0.0633$, $wR_2 = 0.1224$
Reflections collected	4754
Independent reflections	2561[R(int) = 0.0533]
Theta range for data collection	7.08 to 50°
Absorption coefficient(mm^{-1})	2.889
Goodness of fit on F^2	0.925
CCDC No.	1826976

Crystal Data and Structure Refinement for 7c

Identification code	SB05_0m_a
Empirical formula	$C_{23}H_{22}N_2S$
Formula weight	358.48
Temperature(K)	293
Radiation	MoKα (λ = 0.71073)
Crystal system	monoclinic
Space group	P 21/n
a/Å	13.2065(12)
b/Å	6.9746(6)
c/Å	21.0482(19)
α/°	90
β/°	94.919(4)
γ/°	90
V/ Å^3	1931.6(3)
Z	4

Density(Mg /m^{-3})	1.233
Final R[I>2s(I)]	R_1 = 0.0367, wR_2 = 0.0709
R(all data)	R_1 = 0.0444, wR_2 = 0.0738
Collected reflns	9678
Theta range for data collection	3.10 to 21.16
Absorption coefficient(mm^{-1})	0.176
Goodness of fit on F^2	1.225
CCDC No.	1846053

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Adhikari, D.; Lord, R. L.; Baik, M. -H. Nguyen, S. T. *Chem. Commun*. **2014**, *50*, 15187. (h) Adhikari, D. *RSC Adv*. **2015**, *5*, 95379. (i) Bhattacharyya, A.; Kavitha, C. V.; Ghorai, M. K. *J. Org. Chem*. 2016, 81, 6433. (j) Sengoden, M.; Irie, R.; Punniyamurthy, T. *J. Org. Chem*. **2016**, *81*, 11508. (k) Toda,Y.; Gomyou, S.; Tanaka, S.; Komiyama, Y.; Kikuchi, A.;, Suga, H. *Org. Lett*. **2017**, *19*, 5786.

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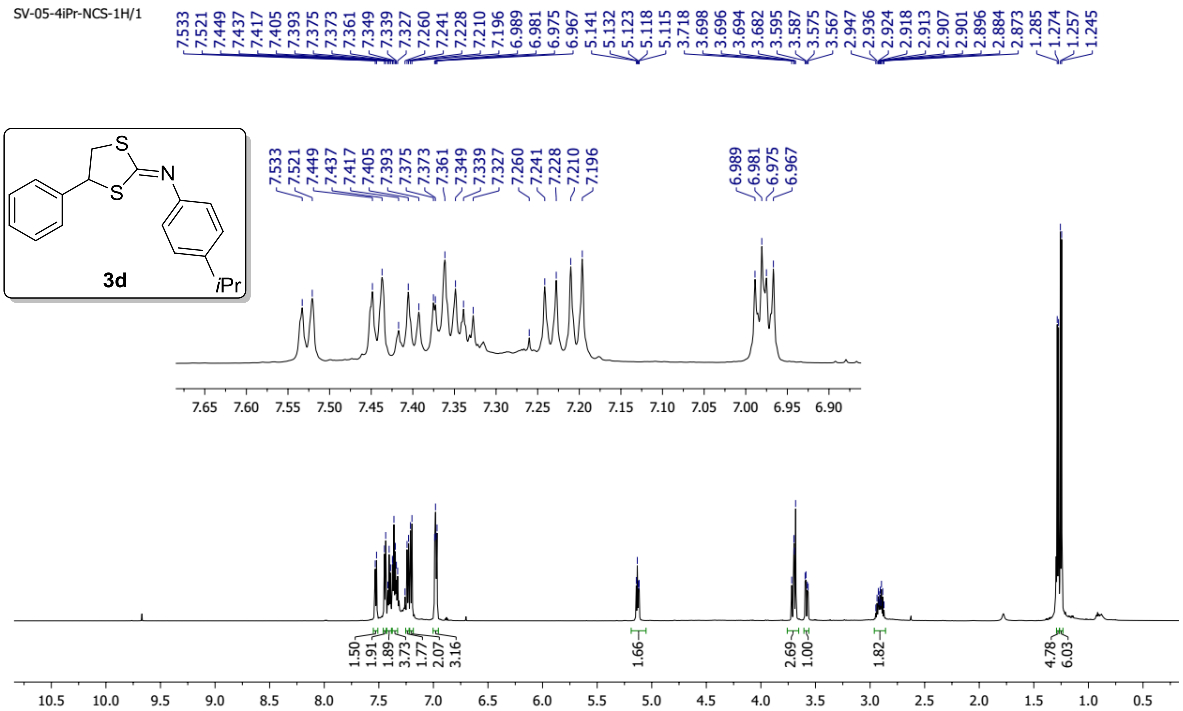
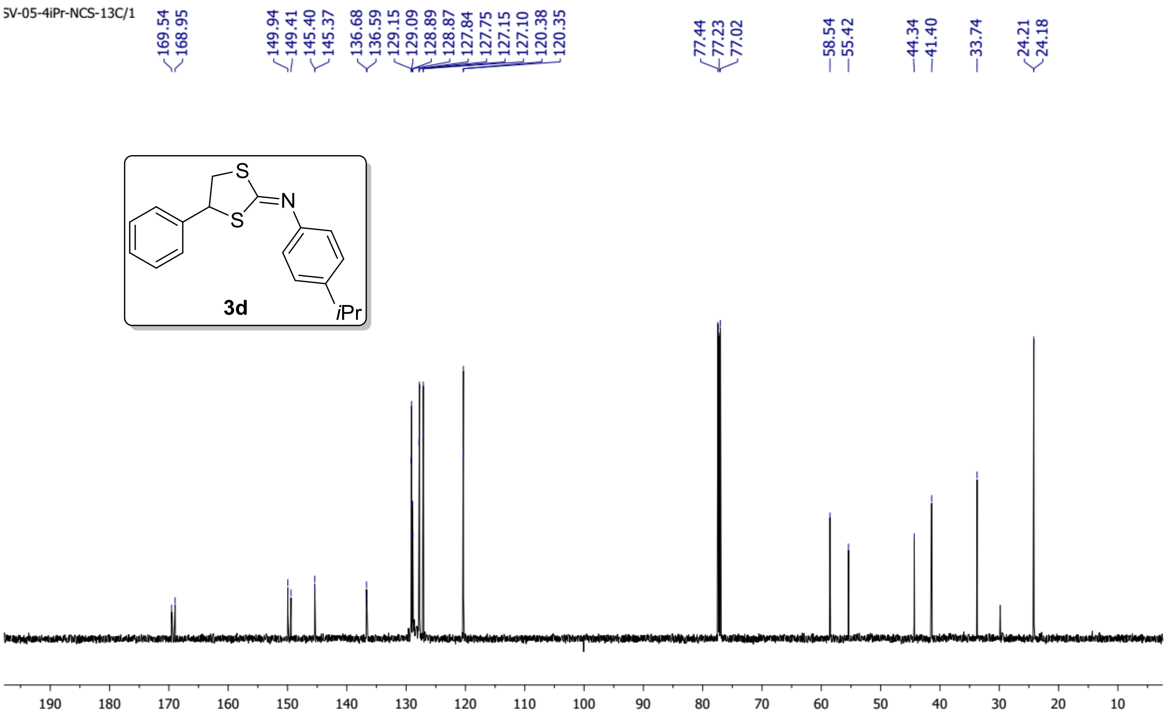
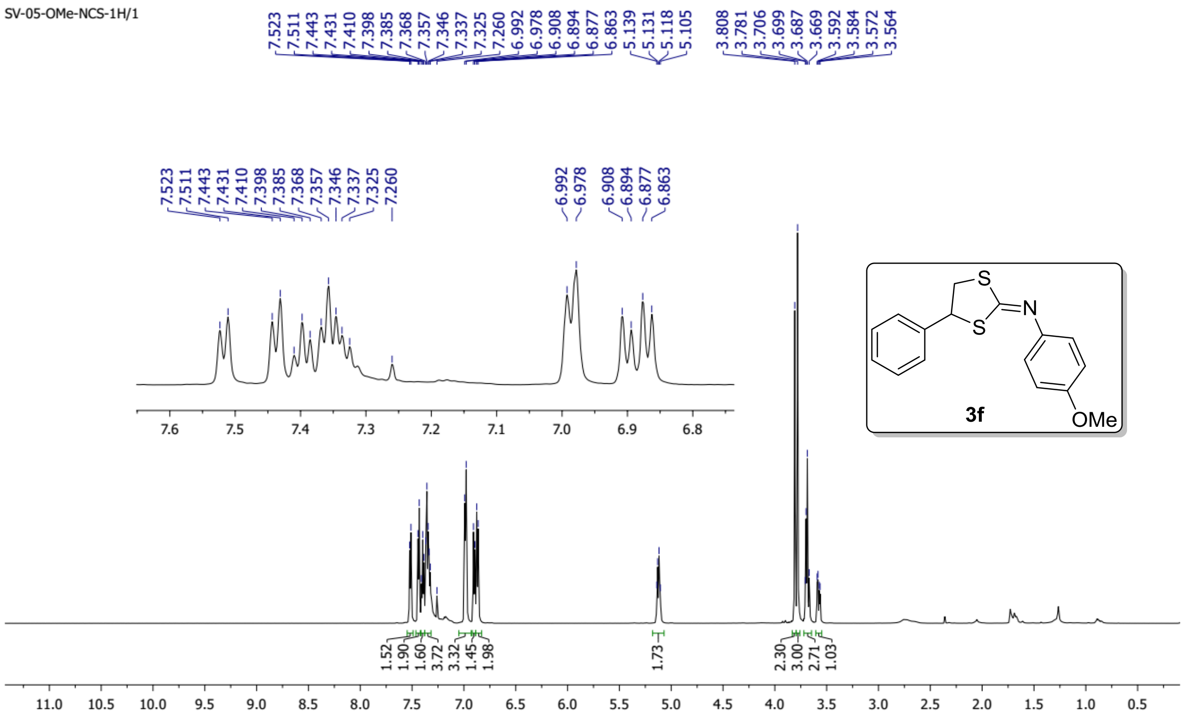
5.5 Selected NMR Spectra



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7.346
7.337
7.325
7.260
6.992
6.978
6.908
6.894
6.877
6.863
5.139
5.131
5.118
5.105
3.808
3.781
3.706
3.699
3.687
3.669
3.592
3.584
3.572
3.564
1.52
1.90
1.60
3.72
3.32
1.45
1.98
1.73
2.30
3.00
2.71
1.03
S
N
S
OMe
3f
11.0 10.5 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
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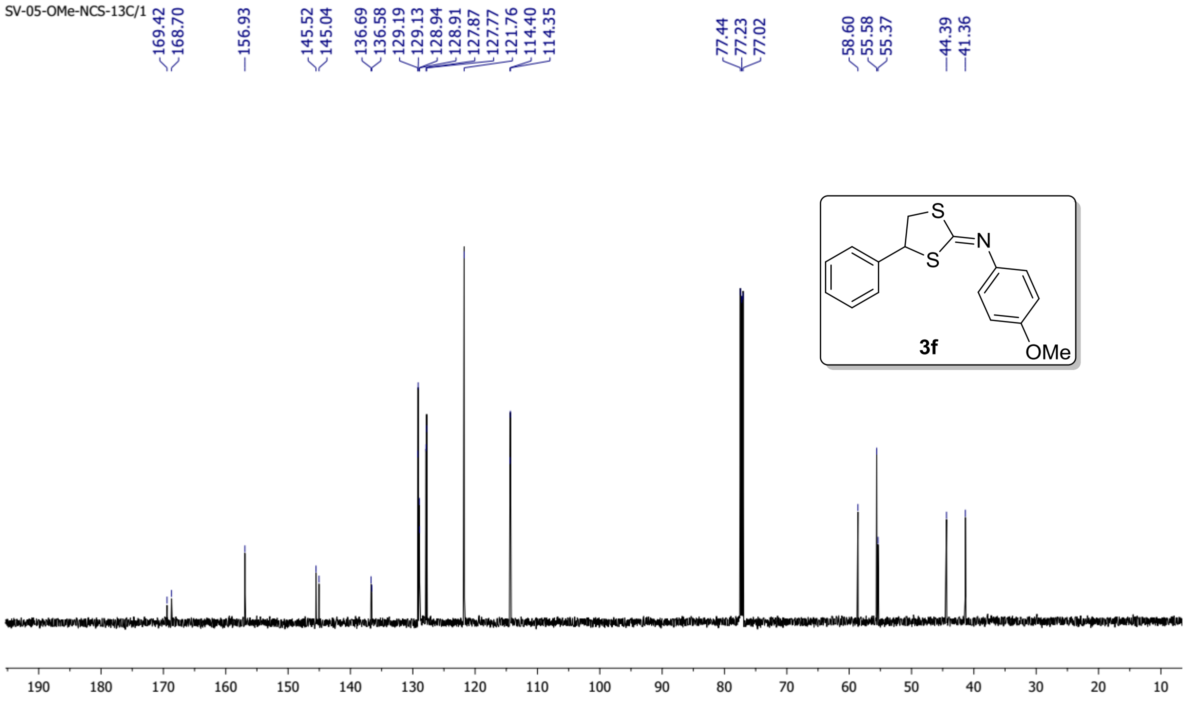
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128.94
128.91
127.87
127.77
121.76
114.40
114.35
77.44
77.23
77.02
58.60
55.58
55.37
44.39
41.36
S
N
S
OMe
3f
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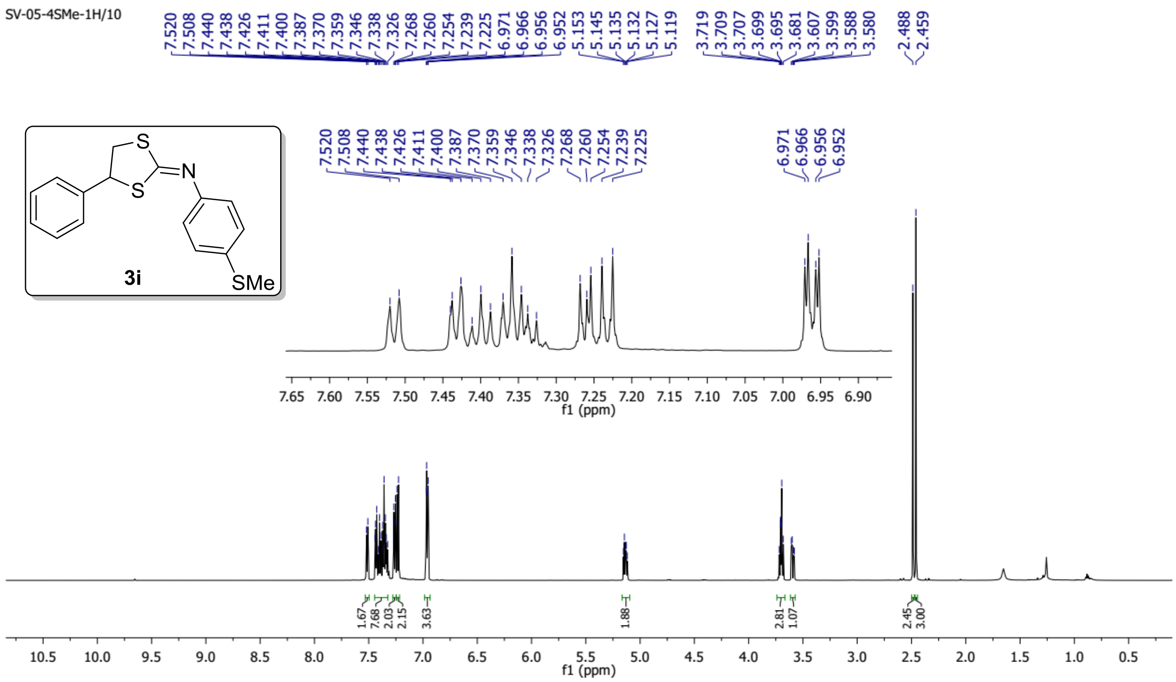
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7.346
7.338
7.326
7.268
7.260
7.254
7.239
7.225
6.971
6.966
6.956
6.952
5.153
5.145
5.135
5.132
5.127
5.119
3.719
3.709
3.707
3.699
3.695
3.681
3.607
3.599
3.588
3.580
2.488
2.459
S
N
S
3i
SMe
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1.07
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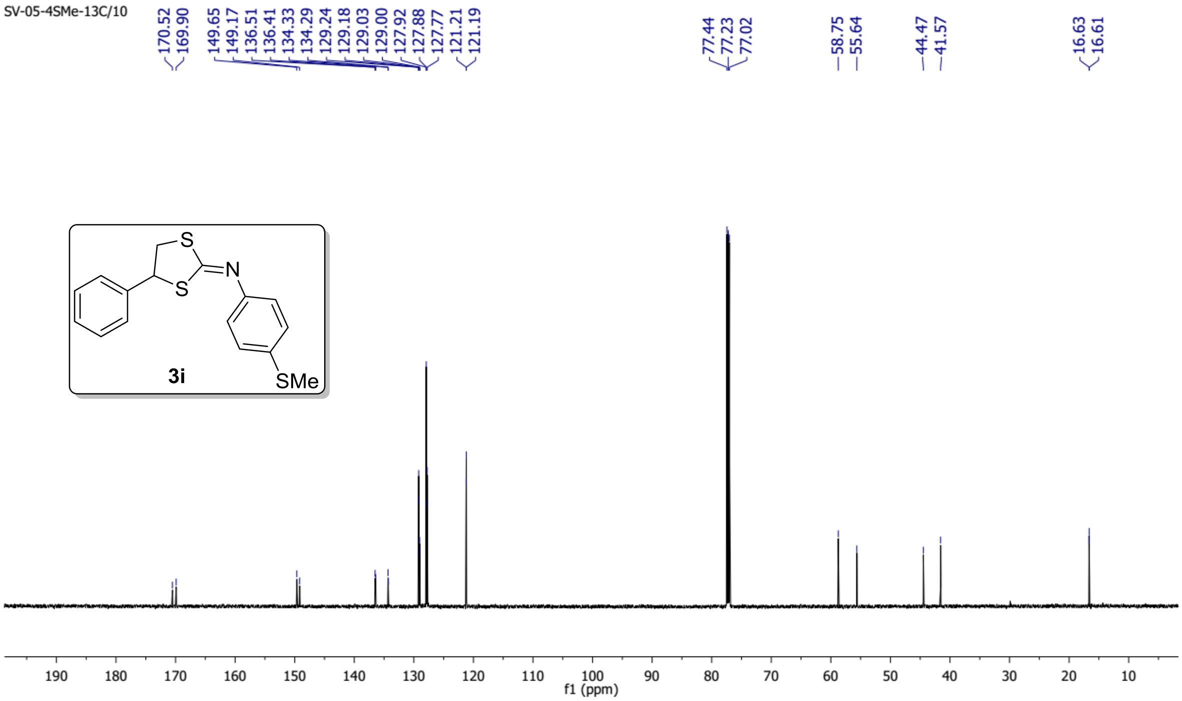
3.00
f1 (ppm)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129.18
129.03
129.00
127.92
127.88
127.77
121.21
121.19
77.44
77.23
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44.47
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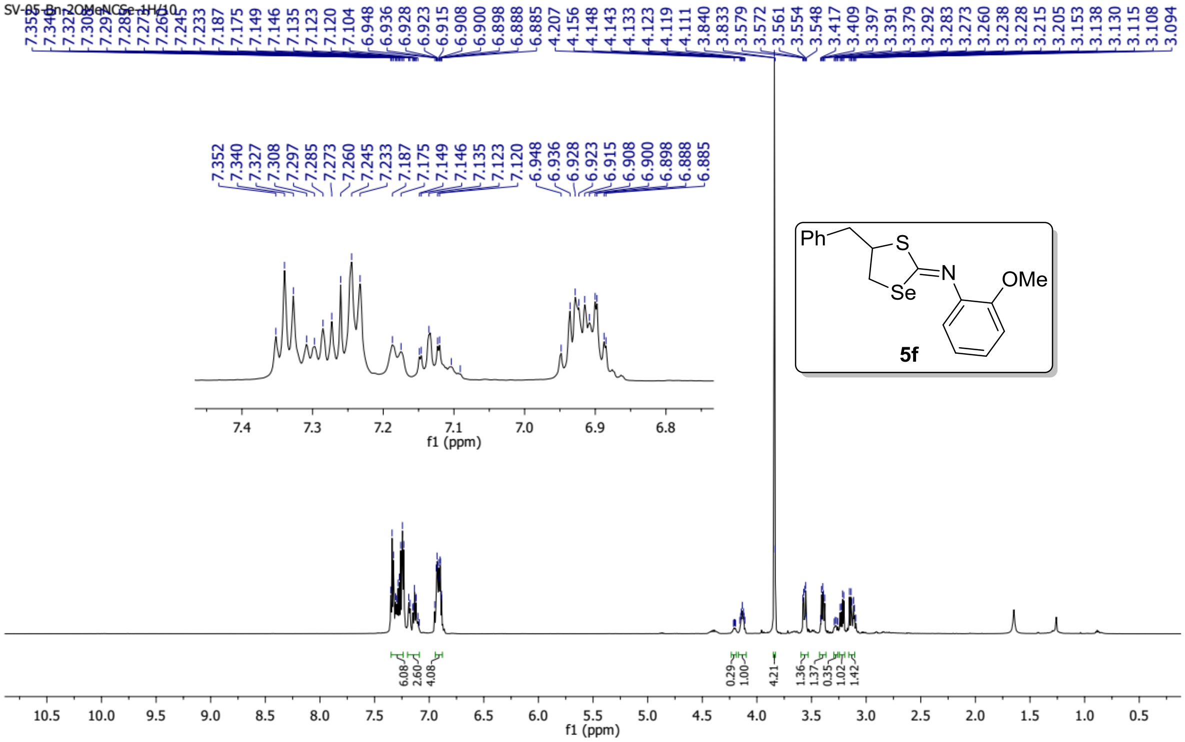
S
N
S
3i
SMe
f1 (ppm)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7.245
7.233
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7.175
7.149
7.146
7.135
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7.120
7.104
6.948
6.936
6.928
6.923
6.915
6.908
6.900
6.898
6.888
6.885
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4.156
4.148
4.143
4.133
4.123
4.119
4.111
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3.833
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3.572
3.561
3.554
3.548
3.417
3.409
3.397
3.391
3.379
3.292
3.283
3.273
3.260
3.238
3.228
3.215
3.205
3.153
3.138
3.130
3.115
3.108
3.094
Ph
S
N
Se
OMe
5f
7.4
7.3
7.2
7.1
7.0
6.9
6.8
f1 (ppm)
6.08
2.60
4.08
0.29
1.00
4.21
1.36
1.37
0.35
1.02
1.42
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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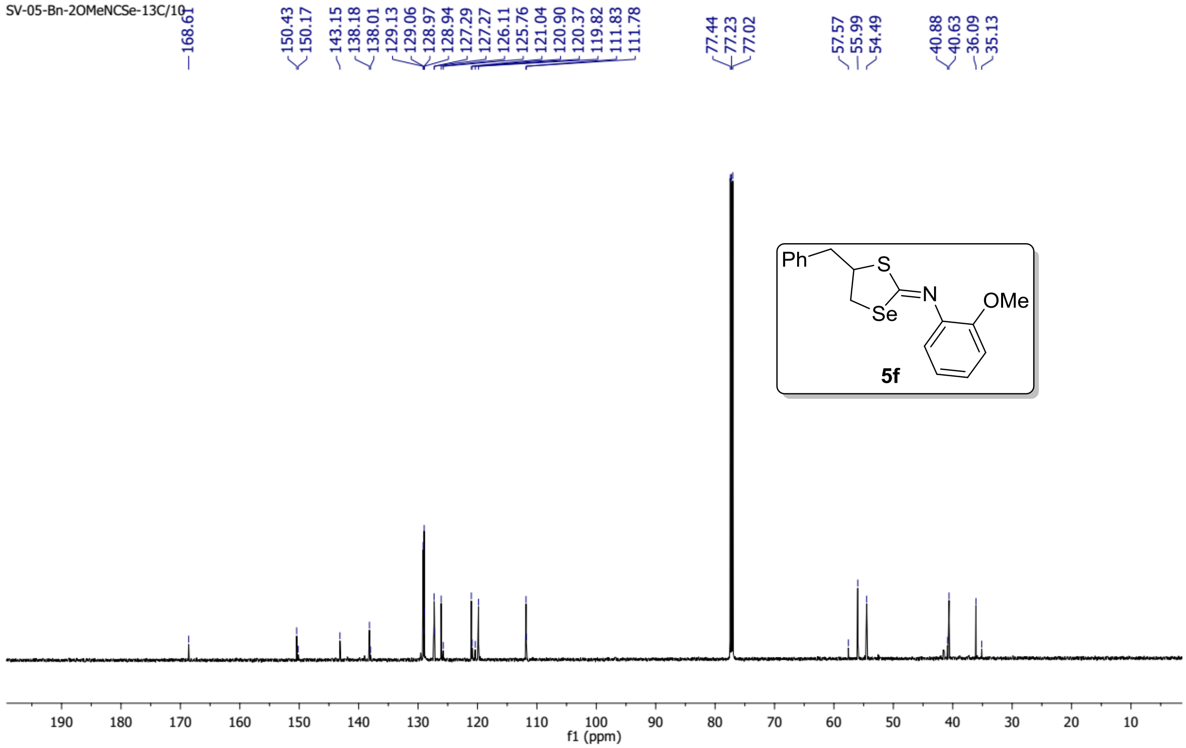
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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128.97
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127.29
127.27
126.11
125.76
121.04
120.90
120.37
119.82
111.83
111.78
77.44
77.23
77.02
57.57
55.99
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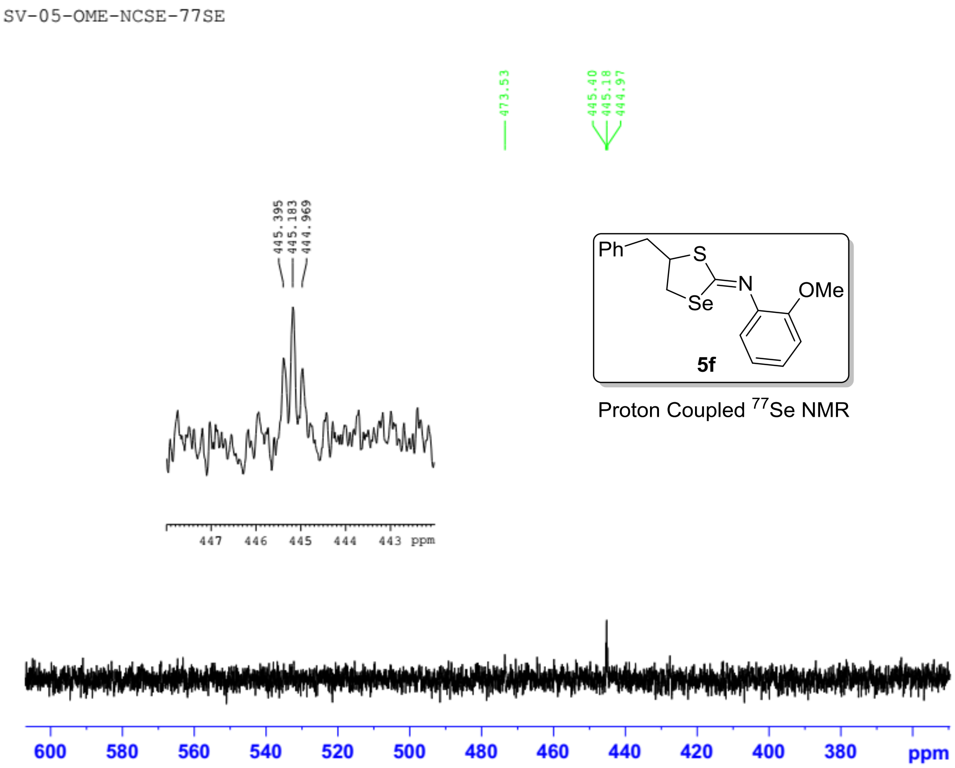
40.88
40.63
36.09
35.13
Ph
S
N
Se
OMe
5f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



Proton Coupled ^{77}Se NMR

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PROCNO                     1

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PULPROG                   zg
TD                     65536
SOLVENT                CDCl3
NS                        32
DS                         4
SWH                38265.305 Hz
FIDRES              0.583882 Hz
AQ                 0.8563371 sec
RG                     14.46
DW                    13.067 usec
DE                      6.50 usec
TE                     298.0 K
D1                2.00000000 sec
TD0                        1

======== CHANNEL f1 ========
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NUC1                    77Se
P1                     10.00 usec
PLW1             65.00000000 W

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LB                      3.00 Hz
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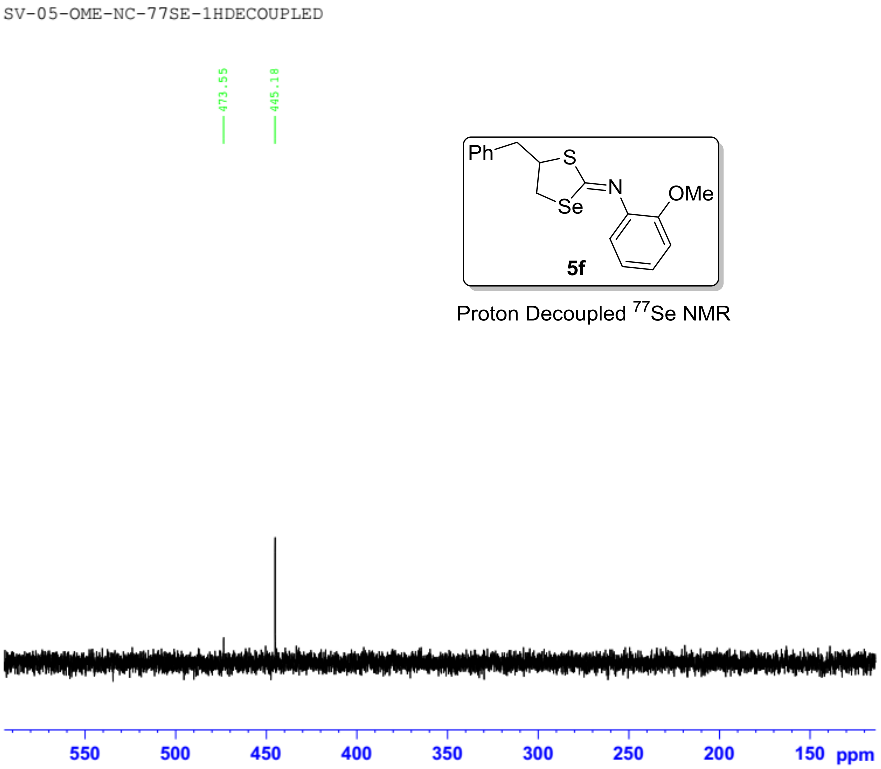

Proton Decoupled ^{77}Se NMR

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PROCNO                    1

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PULPROG              zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      256
DS                        4
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FIDRES             0.693581 Hz
AQ                0.7208960 sec
RG                    11.37
DW                   11.000 usec
DE                     6.50 usec
TE                    298.3 K
D1               2.00000000 sec
D11              0.03000000 sec
TD0                       1

======== CHANNEL f1 ========
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NUC1                   77Se
P1                    10.00 usec
PLW1            65.00000000 W

======== CHANNEL f2 ========
SFO2            400.2316009 MHz
NUC2                     1H
CPDPRG[2            waltz16
PCPD2                 80.00 usec
PLW2            16.00000000 W
PLW12            0.40000001 W
PLW13            0.18108000 W

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LB                     3.00 Hz
GB       0
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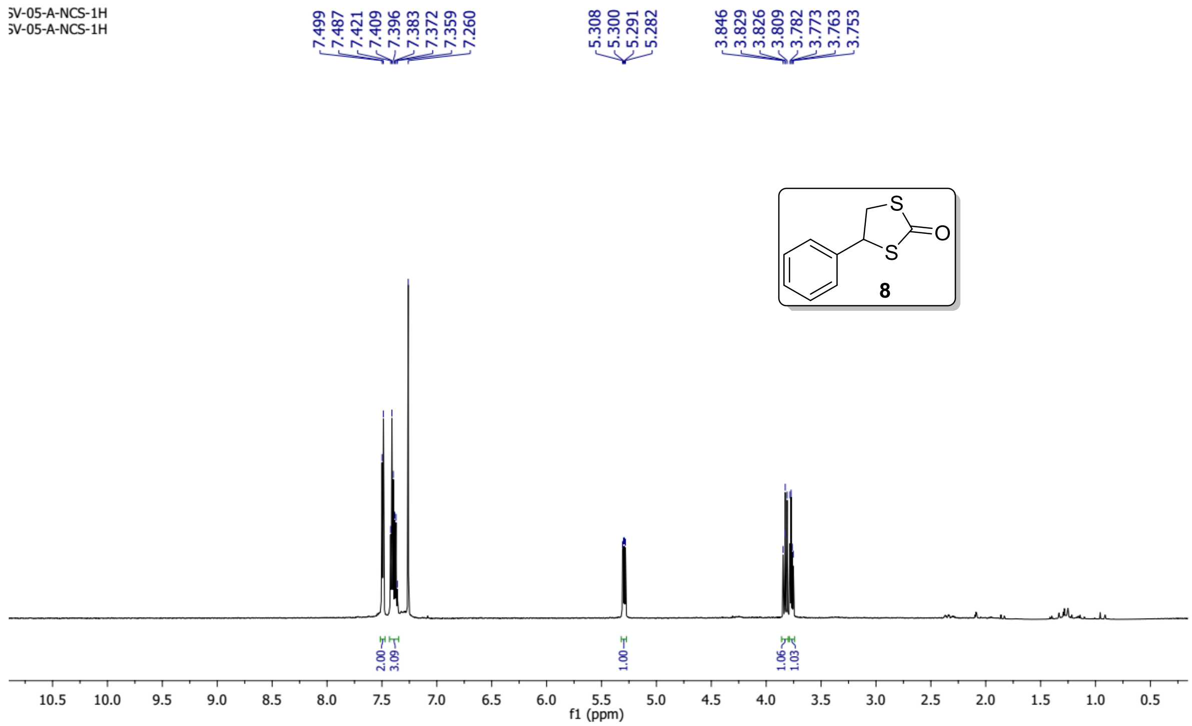
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V-05-A-NCS-1H
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7.260
5.308
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5.291
5.282
3.846
3.829
3.826
3.809
3.782
3.773
3.763
3.753
S
O
S
8
2.00
3.09
1.00
1.06
1.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
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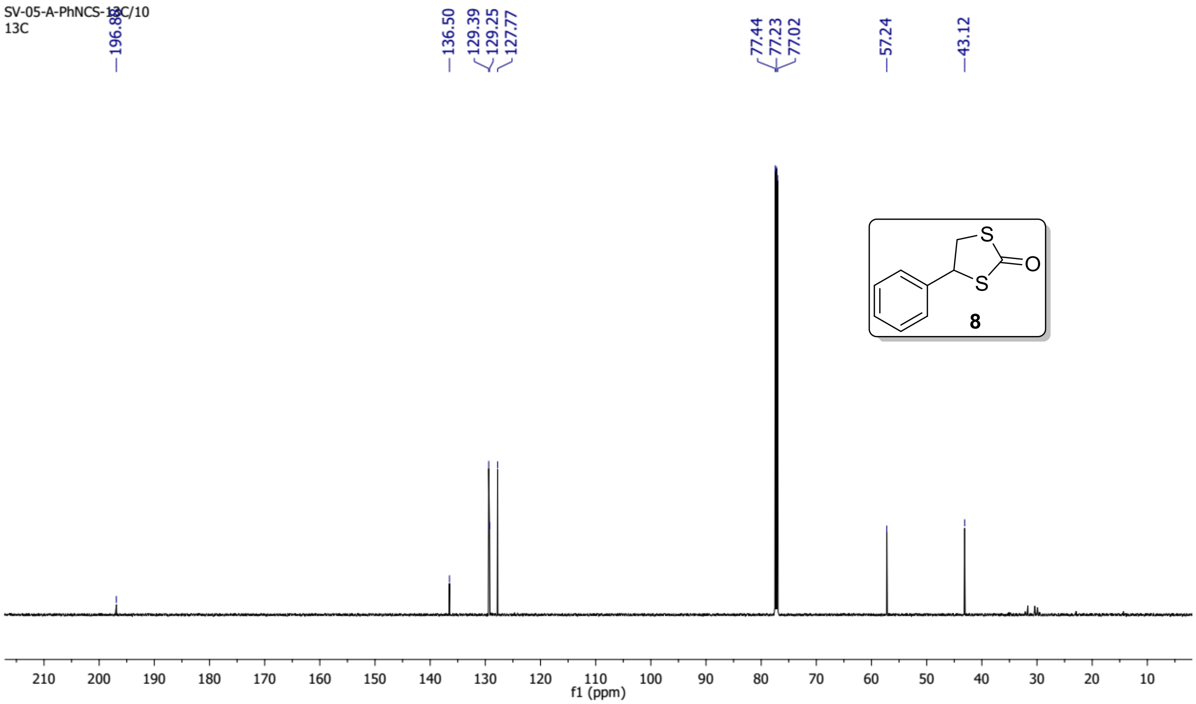
0.5
f1 (ppm)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S
O
S
8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

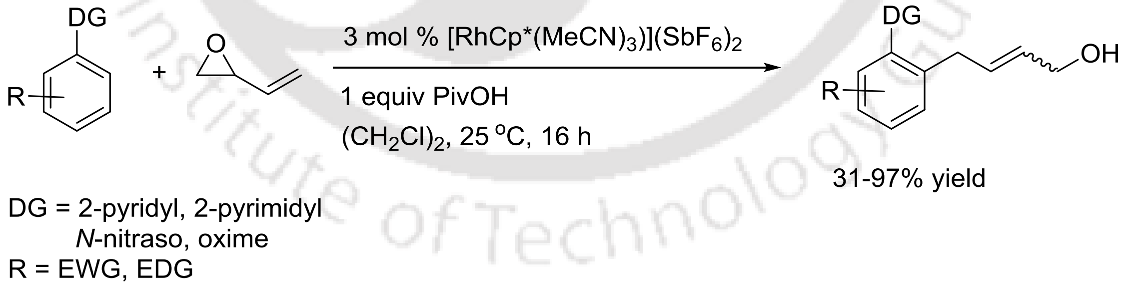
Chapter VI

Palladium-Catalyzed *ortho*-Selective Alkylation of Amides with Epihalohydrines

Amides are essential structural frameworks present in biologically active compounds.[1] In particular, the paracetamol, penicillin and Lysergic acid diethylamide (LSD) are the famous and widely used drugs holding amide moiety. The C-C and C-heteroatom bond formation through the C(sp^2/sp^3)-H bond activation has attracted considerable attention in recent years.[2] Among them, the site-selective C-C/C-hetero bond coupling of arene employing transition-metal-catalysts with coupling partners has occupied unique place,[3] whereas, the site-selective alkylation of arenes has been well studied using different coupling partners.[4] However, limited studies are documented[5-10] for the *ortho*-alkylation of arenes using epoxides due to their low reactivity.

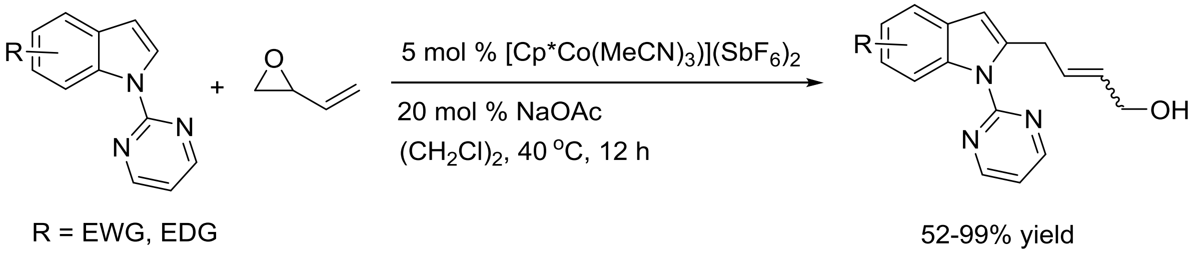
6.1 Strategies for *ortho*-Alkylation of Arenes using Epoxide

Li group developed an efficient Rh-catalyzed *ortho*-alkylation of arenes with 2-vinyloxirane using chelating groups (Scheme 1).[5] The authors used [RhCp*(MeCN)$_3$)](SbF$_6$)$_2$ as the catalyst to furnish the transformation and the allyl alcohol coupling products are obtained as a mixture of stereoisomers.



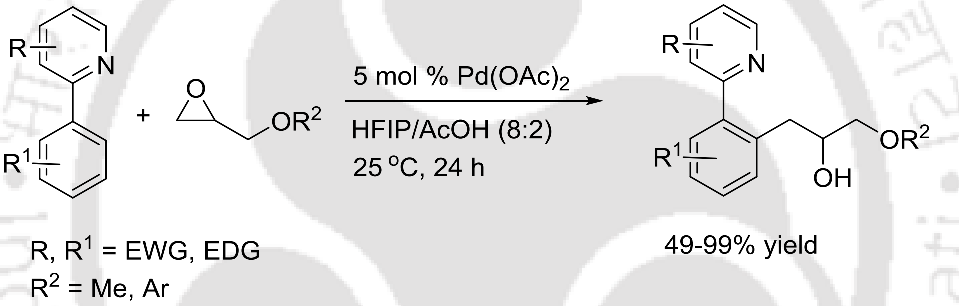
Scheme 1. Rh-Catalyzed *ortho*-Alkylation of Arenes with 2-Vinyloxiranes

The same research group disclosed the Co-catalyzed C-C coupling of *N*-pyrimidinylindoles with 2-vinyloxirane under mild conditions (Scheme 2).[6] This reaction starts with initial *ortho* C-H activation, olefin insertion and *β*-oxygen elimination to furnish alcohols in high yields.



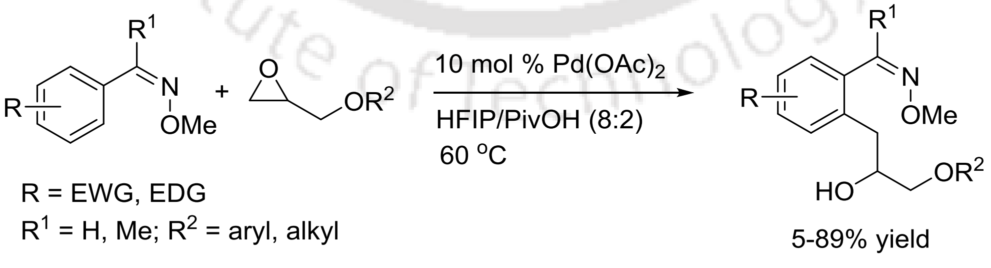
Scheme 2. Co-Catalyzed C-C Coupling of Indoles with 2-Vinyloxirane

Kanai and co-workers developed the Pd-catalyzed *ortho*-selective C-H activation and C-C bond formation of arenes with terminal epoxides (Scheme 3).[7] This transformation is utilized 5 mol% Pd(OAc)$_2$ in a mixture of HFIP/AcOH. This catalytic transformation is scalable and tolerates a broad range of functional groups in good to excellent yields.



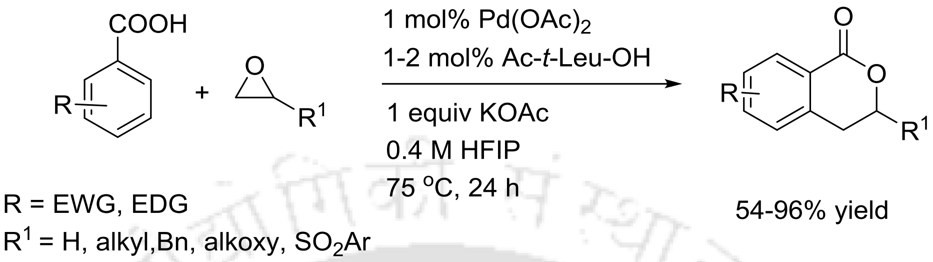
Scheme 3. Pd-Catalyzed Oxirane Opening with 2-Aryl Pyridines

Li group adapted the same reaction conditions to the *ortho*-alkylation of ketoximes (Scheme 4).[8] This protocol is succesful to yield the desired products using 10 mol% Pd(OAc)$_2$ in a mixture of HFIP/PivOH at 60 °C in good yields.



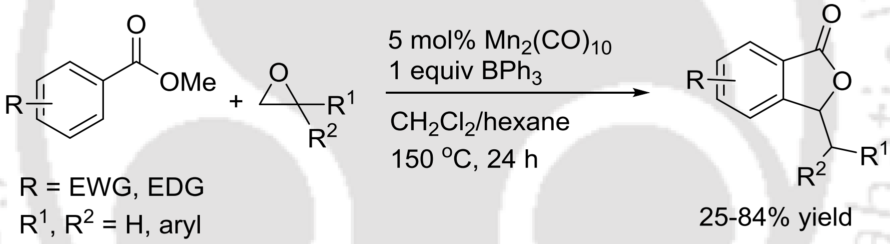
Scheme 4. Pd-Catalyzed *ortho*-Alkylation of Ketoximes *via* the Ring-Opening of Epoxides

Yu and co-workers demonstrated the Pd-catalyzed *ortho*-ring expansion of terminal and internal epoxides with benzoic acids to produce 3,4-dihydroisocoumarins (Schem 5).[9] This method is general for wide variety of substrates using $Pd(OAc)_2$ as the catalyst, Ac-*t*-Leu-OH as the ligand and KOAc as an additive. The formation of potassium countercation is crucial for the metal chelation.



Scheme 5. Pd-Catalyzed *ortho*-Alkylation of Benzoic Acids with Epoxides

$Mn(CO)_{10}$-BPh_3 catalyzed coupling of esters with oxiranes is reported at 150 °C (Scheme 6).[10] Triphenylborane played a crucial role to supportively promote the annulation reaction with up to 84% yield.

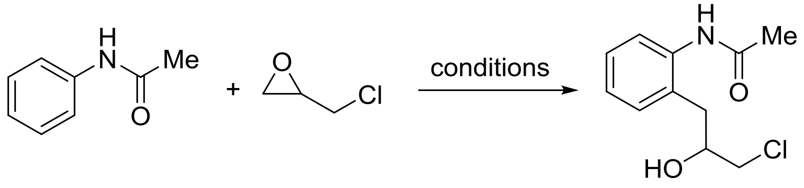


Scheme 6. Synthesis of Isobenzofuranones from Esters and Oxiranes

5.2 Present Study

In this chapter we present the Pd-catalyzed *ortho*-alkylation of benzamides with epoxides. The reaction was optimized using *N*-phenylacetamide **1a** and epichlorohydrin **2a** as model substrates using Pd catalysts at varied temperatures (Table 1). In a set of solvents screened, CH_2Cl_2, THF, CH_3CN, DMSO, toluene, xylene, DMF, DME, ethanol, chlorobenzene and dichlorobenzene, chlorobenzene produced the best results (entry 1-11). Among the Pd salts studied, $Pd(OAc)_2$ exhibited superior results compared to $PdCl_2$ and $Pd(PPh_3)_2Cl_2$ (entries 15-

Table 1. Optimization of the Reaction Conditions[a]



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

Entry	Catalyst (10 mol %)	Additive (5 equiv)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	CF_3COOH	CH_2Cl_2	n.d
2	$Pd(OAc)_2$	CF_3COOH	THF	n.d
3	$Pd(OAc)_2$	CF_3COOH	CH_3CN	trace
4	$Pd(OAc)_2$	CF_3COOH	DMSO	n.d
5	$Pd(OAc)_2$	CF_3COOH	Toluene	40
6	$Pd(OAc)_2$	CF_3COOH	Xylene	10
7	$Pd(OAc)_2$	CF_3COOH	DMF	n.d
8	$Pd(OAc)_2$	CF_3COOH	DME	n.d
9	$Pd(OAc)_2$	CF_3COOH	Ethanol	n.d
10	$Pd(OAc)_2$	CF_3COOH	PhCl	60
11	$Pd(OAc)_2$	CF_3COOH	Dichlorobenzene	40
12	$Pd(OAc)_2$	CF_3COOH	PhCl	28[c]
13	$Pd(OAc)_2$	CF_3COOH	PhCl	29[d], 31[e]
14	$Pd(OAc)_2$	CF_3COOH	PhCl	24[f]
15	$PdCl_2$	CF_3COOH	Toluene	trace
16	$PdCl_2(PPh_3)_2$	CF_3COOH	Toluene	n.d
17	$Pd(OAc)_2$	Triflic acid	PhCl	trace
18	$Pd(OAc)_2$	CH_3COOH	PhCl	trace
19	$Pd(OAc)_2$	Pivalic acid	PhCl	n.d

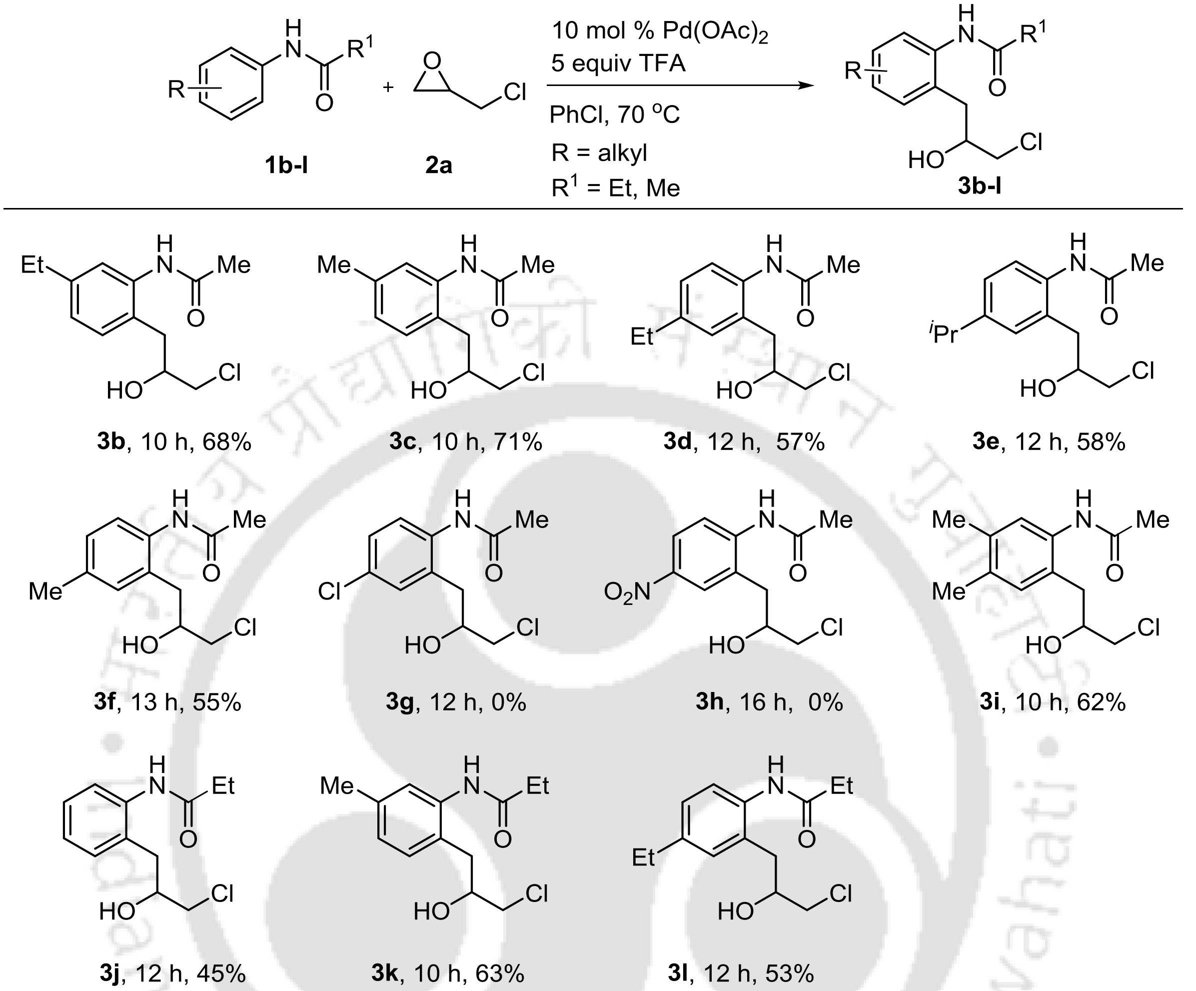
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1 mmol), catalyst (10 mol %), additive (5 equiv) in solvent (1.0 mL) were stirred at 70 ^{0}C for 12 h.

[b] Isolated yield.

[c] Catalyst 5 mol%.

[d] TFA 2.5 equiv. [e] TFA 7.0 equiv. [f] At 40 °C.

Table 2. Reaction of Substituted Amides **1** with Epichlorohydrin **2a**[a,b]



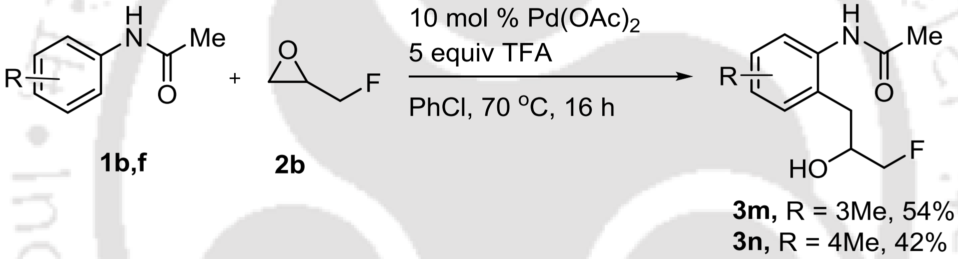
3b, 10 h, 68%
3c, 10 h, 71%
3d, 12 h, 57%
3e, 12 h, 58%
3f, 13 h, 55%
3g, 12 h, 0%
3h, 16 h, 0%
3i, 10 h, 62%
3j, 12 h, 45%
3k, 10 h, 63%
3l, 12 h, 53%

[a] Reaction conditions: **1** (0.5 mmol), **2a** (1 mmol), Pd(OAc)$_2$ (10 mol %), chlorobenzene (1 mL) were stirred at 70 °C.

[b] Isolated yields.

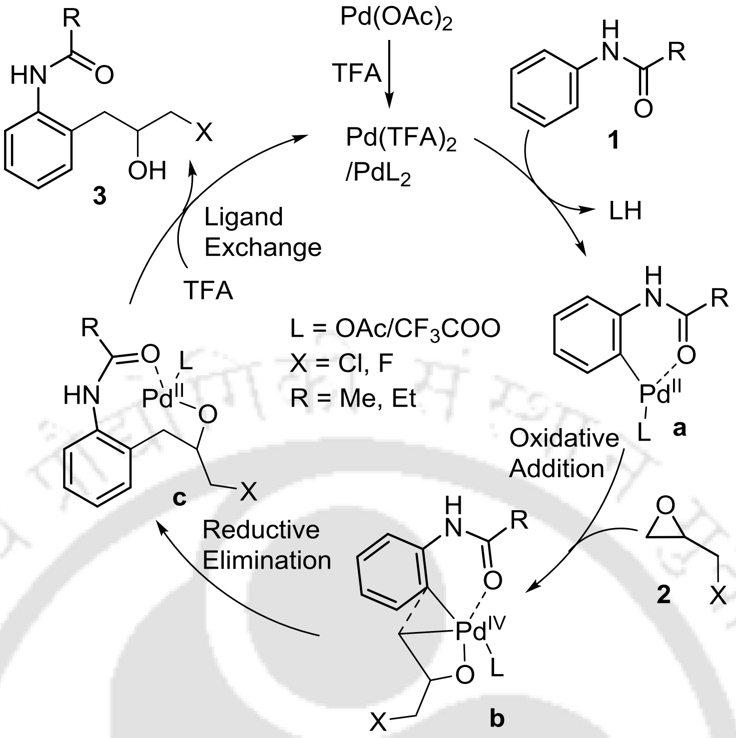
16). In case of additives, CF_3CO_2H gave the best results, whereas CH_3COOH, CF_3SO_3H and pivalic acid (PivOH) were not effective (entry 17-19). Decreasing the quantity of the Pd-source or CF_3CO_2H (TFA) and temperature led to drop the yield to <31% yield (entry 13-14). Control experiments confirmed that there was no reaction occurred in absence of catalyst. We next explored the scope of the protocol for the *ortho*-alkylation of the substituted *N*-arylacetamide (Table 2). The acetanilides having the substitutions 3-ethyl **1b** and 3-methyl **1c** groups on the benzene ring coupled smoothly with epichlorohydrin **2a** to produce **3b** and **3c** in 68 and 71% yields, respectively. Similarly, the substrate bearing substituents at the 4-

position with ethyl **1d**, isopropyl **1e** and methyl **1f** groups coupled with epichlorohydrin **2a** to afford **3d-f** in 55-58% yields. Unlike alkyl substitution, the substrates having 4-Cl and 4-NO_2 **1g-h** groups were unsuccessful to produce the desired **3g-h**, which may be due to the electron deficiency in the aromatic ring. However, the substrate with 3,4-disubstituted methyl group **1i** yielded **3i** in 62%. The protocol was extended to *ortho*-alkylation of propionamides, *N*-phenylpropionamide **1j** having 3-methyl, 4-ethyl and 4-methyl substituents **1j-l** underwent reaction to give the target *ortho*-alkylated products **3j-l** in 48-63% yields. Furthermore, the protocol can be extended to *ortho*-alkylation employing epifluorohydrin to produce fluorinated phenethyl alcohol. In similar fashion, the substrate having methyl substituents on *meta*- **1c** and *para*- **1f** positions afforded the target products **3m** and **3n** in 54% and 42% yields, respectively.



Scheme 7. Reaction of Substituted Acetamides **1b,f** with Epifluorohydrin **2b**

The proposed catalytic cycle is shown in scheme 8. The reaction of acetamides with $Pd(OAc)_2$ may give a six membered cyclopalladated intermediate ***a*** *via* amide chelation assisted C-H bond activation. The intermediate ***a*** may then undergo oxidative addition with epihalohydrin to yield Pd(IV) complex ***b***, which may undergo reductive elimination to form Pd(II) intermediate ***c***, then the intermediate exchanges the ligand to complete the catalytic cycle with regeneration of the Pd(II) species and alkylated products.[11,12] The function of the CF_3COOH may be presumably to tune the electrophilicity of Pd(II) that could improve the C-H activation process.



Scheme 8. Plausible Catalytic Cycle

In summary, we presented the Pd-catalyzed amide assisted *ortho*-alkylation of amide with epihalohydrins as a alkylating source *via* C-H bond activation at moderate temperature. The reaction is regioselective and the alkylated products can be obtained in moderate to good yields.

6.3 Experimental Section

6.3.1 General Information. Epichlorohydrins, $Pd(OAc)_2$ (98%), $PdCl_2$ (>99%), $PdCl_2(PPh_3)_2$ (>99%) TFA, pivolic acid and triflic acid were purchased from commercial source and used as received. Other materials and methods were followed as presented in chapter 1.

6.3.2 Procedure for the Coupling of Amides with Epihalohydrins. A mixture of acetanilide (1.0 equiv), epihalohydrin (2.0 equiv), $Pd(OAc)_2$ (10 mol%) and TFA (5.0 equiv) were stirred in chlorobenzene (1.0 mL) at 70 °C. The reaction mixture was quenched with saturated $NaHCO_3$ (5.0 mL) and the mixture was extracted with ethyl acetate (3 x 25 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.

***N*-(2-(3-Chloro-2-hydroxypropyl)phenyl)acetamide 3a.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09-7.06 (m, 1H), 7.03 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.71-6.67 (m, 1H), 5.11-5.07 (m, 1H), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.14 (br s, 1H), 2.98 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.88 (dd, *J* = 13.6, 9.0 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 145.5, 131.4, 128.7, 119.9, 118.6, 116.0, 72.8, 45.1, 34.1, 21.3; FT-IR (neat) 3376, 2960, 2922, 2858, 1726, 1668, 1630, 1581, 1450, 1369, 1242, 1067, 1020, 965, 820, 722 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{11}H_{14}ClNO_2$ 228.0786, found 228.0791.

***N*-(2-(3-Chloro-2-hydroxypropyl)-5-ethylphenyl)acetamide 3b.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 68%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93 (d, *J* = 7.8 Hz, 1H), 6.55-6.53 (m, 2H), 5.08-5.05 (m, 1H), 4.08 (br s, 1H), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.94 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.84 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.56 (q, *J* = 7.8 Hz, 2H), 2.13 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 145.3, 144.9, 131.3, 118.2, 117.1, 115.4, 72.9, 45.1, 33.7, 28.7, 21.3, 15.6; FT-IR (neat) 3370, 2958, 2920, 2862, 1729, 1670, 1580, 1450, 1369, 1242, 1020, 961, 820, 722 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{18}ClNO_2H$ 256.1099, found 256.1106.

***N*-(2-(3-Chloro-2-hydroxypropyl)-5-methylphenyl)acetamide 3c.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.0 Hz, 1H), 6.52-6.51 (m, 2H), 5.08-5.02 (m, 1H), 4.01 (br s, 1H), 3.69 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.61 (dd, *J* = 11.6, 5.2 Hz, 1H), 2.95 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.84 (dd, *J* = 14.0, 9.2 Hz, 1H), 2.24 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 145.3, 138.5, 131.2, 119.4, 116.9, 116.6, 72.7, 45.0, 33.6, 21.3, 21.3; FT-IR (neat) 3374, 2959, 2923, 2856, 1730, 1630, 1580, 1454, 1371, 1242, 1067, 1028, 960, 818 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{16}ClNO_2H$ 242.0942, found 242.0958.

***N*-(2-(3-Chloro-2-hydroxypropyl)-4-ethylphenyl)acetamide 3d.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; yellow liquid; yield 57%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 7.8, 1.8, 1H), 6.85 (d, *J* = 1.8 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.11-5.07 (m, 1H), 3.96 (br s, 1H), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.97 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.85 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.54 (q, *J* = 7.8 Hz, 2H), 2.13 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 143.2, 134.6, 130.7, 127.9, 120.0, 116.2, 72.9, 45.1, 34.1, 28.1, 21.3, 16.2; FT-IR (neat) 3379, 2960, 2926, 2856, 1731, 1672, 1630, 1583, 1513, 1456, 1371, 1247, 1060, 1028, 967, 825, 804 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{18}ClNO_2H$ 256.1099, found 256.1104.

***N*-(2-(3-Chloro-2-hydroxypropyl)-4-isopropylphenyl)acetamide 3e.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; yellow liquid; yield 58%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.12-5.06 (m, 1H), 3.70 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.62 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.98 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.86-275 (m, 2H), 2.13 (s, 3H), 1.21 (d, *J* = 1.6 Hz, 3H), 1.19 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 142.6, 139.7, 129.3, 126.4, 120.3, 116.4, 72.8, 45.1, 34.1, 33.3, 24.5, 24.4, 21.3; FT-IR (neat) 3378, 3026, 2961, 2920, 2852, 1726, 1668, 1583, 1514, 1440, 1229, 1241, 1065, 1025, 962, 820, 805 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{20}ClNO_2H$ 270.1255, found 270.1280.

***N*-(2-(3-Chloro-2-hydroxypropyl)-4-methylphenyl)acetamide 3f.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow liquid; yield 55%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.83 (s, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.11-5.07 (m, 1H), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.96 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.83 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.22 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 142.9, 131.8, 129.6, 127.9, 120.1, 116.2, 72.9, 45.1, 34.0, 21.3, 20.5; FT-IR (neat) 3410, 2966, 2925, 2870, 2854, 1730, 1671, 1650, 1583, 1514, 1440, 1377, 1220, 1240, 1060, 1026, 828, 725 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{16}ClNO_2H$ 242.0942, found 242.0951.

***N*-(2-(3-Chloro-2-hydroxypropyl)-4,5-dimethylphenyl)acetamide 3i.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown liquid; yield 62%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.52 (s, 1H), 5.09 (m, 1H), 3.69 (dd, *J* =11.4, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.93 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.81 (dd, *J* = 13.8, 9.6 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 142.8, 136.8, 132.4, 126.9, 117.9, 117.7, 73.1, 45.1, 33.6, 21.3, 19.6, 18.8.; FT-IR (neat) 3390, 3026, 2962, 2925, 2875, 2850, 1730, 1642, 1580, 1518, 1450, 1370, 1239, 1066, 1027, 975, 828, 718 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{18}ClNO_2H$ 256.1099, found 256.1110.

_N_-(2-(3-Chloro-2-hydroxypropyl)phenyl)propionamide 3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; yellow liquid; yield 45%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.09-7.06 (m, 1H), 7.02 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.70-6.67 (m, 2H), 5.12-5.07 (m, 1H), 4.15 (br s, 1H), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.4 Hz, 1H), 2.98 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.87 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.44-2.39 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 145.3, 138.5, 131.2, 119.4, 116.9, 116.6, 72.7, 45.0, 33.6, 21.3, 21.3; FT-IR (neat) 3382, 3055, 2962, 2918, 2850, 1734, 1675, 1630, 1580, 1460, 1369, 1240, 1030, 960, 820, 720 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{16}ClNO_2H$ 242.0942, found 242.0950.

_N_-(2-(3-Chloro-2-hydroxypropyl)-5-ethylphenyl)acetamide 3k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.42$; brown liquid; yield 63%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 8.0 Hz, 1H), 6.52-6.51 (m, 2H), 5.08-5.03 (m, 1H), 3.69 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.61 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.94 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.83 (dd, *J* = 14.4, 10.0 Hz, 1H), 2.44 (q, *J* = 7.6 Hz, 2H), 2.23 (s, 3H), 1.19 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 145.4, 138.5, 131.3, 119.5, 117.0, 116.7, 72.7, 45.1, 33.8, 27.9, 21.3, 9.2.; FT-IR (neat) 3404, 2960, 2930, 2870, 2856, 1723, 1661, 1650, 1518, 1465, 1425, 1376, 1220, 1070, 980, 816, 721 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{13}H_{18}ClNO_2H$ 256.1099, found 256.1107.

_N_-(2-(3-Chloro-2-hydroxypropyl)-4-ethylphenyl)propionamide 3l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; brown liquid; yield 53%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.11-5.06 (m, 1H), 4.01 (br s, 1H), 3.70 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.62 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.97 (dd, *J* = 14.4, 5.6 Hz, 1H), 2.84 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.54 (q, *J* = 7.6 Hz, 2H), 2.44-2.38 (m, 2H), 1.19-1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 143.2, 134.5, 130.7, 127.9, 120.0, 116.1, 72.6, 45.2, 34.2, 28.1, 27.9, 16.2, 9.2; FT-IR (neat) 3417, 2966, 2931, 2874, 2856, 1728, 1668, 1516, 1461, 1422, 1377, 1200, 1082, 829, 722 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{14}H_{20}ClNO_2H$ 270.1255, found 270.1282.

***N*-(2-(3-Fluoro-2-hydroxypropyl)-5-methylphenyl)acetamide 3m.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.48$; brown liquid; yield 54%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 8.0 Hz, 1H), 6.52-6.51 (m, 2H), 5.05-4.94 (m, 1H), 4.56-4.48 (m, 1H), 4.44-4.36 (m, 1H), 4.12 (br s, 1H2.90-2.85 (m, 1H), 2.79 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.24 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 145.4, 138.4, 131.4, 119.4, 116.9, 116.6, 83.2 (d, *J* = 173.0 Hz), 72.7 (d, *J* = 18.0 Hz), 31.6 (d, *J* = 6.0 Hz)21.4, 21.3. FT-IR (neat) 3378, 2959, 2925, 2860, 1731, 1634, 1581, 1456, 1245, 1067, 961, 804 cm^{-1}. HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{16}FNO_2H$ 226.1238, found 226.1242.

***N*-(2-(3-Fluoro-2-hydroxypropyl)-4-methylphenyl)acetamide 3n.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.48$; yellow liquid; yield 42%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (dd, *J* = Hz, 1H), 6.81 (s, 1H), 6.60 (d, *J* = Hz, 1H), 5.06-4.98 (m, 1H), 4.54-4.47 (m, 1H), 4.46-4.40 (m, 1H), 2.91-2.87 (m, 1H), 2.78 (dd, *J* = 13.8, 10.2 Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 143.0, 131.9, 129.1, 127.9, 119.9, 116.2, 83.0 (d, *J* = 172.5 Hz), 72.7 (d, *J* = 18.0 Hz), 31.9 (d, *J* = 7.5 Hz), 21.4, 20.5; FT-IR (neat) 3378, 3026, 2961, 2925, 2856, 1731, 1670, 1581, 1513, 1456, 1375, 1240, 1112, 1029, 961, 800 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{12}H_{16}FNO_2H$ 226.1238, found 226.1235.

6.4 References

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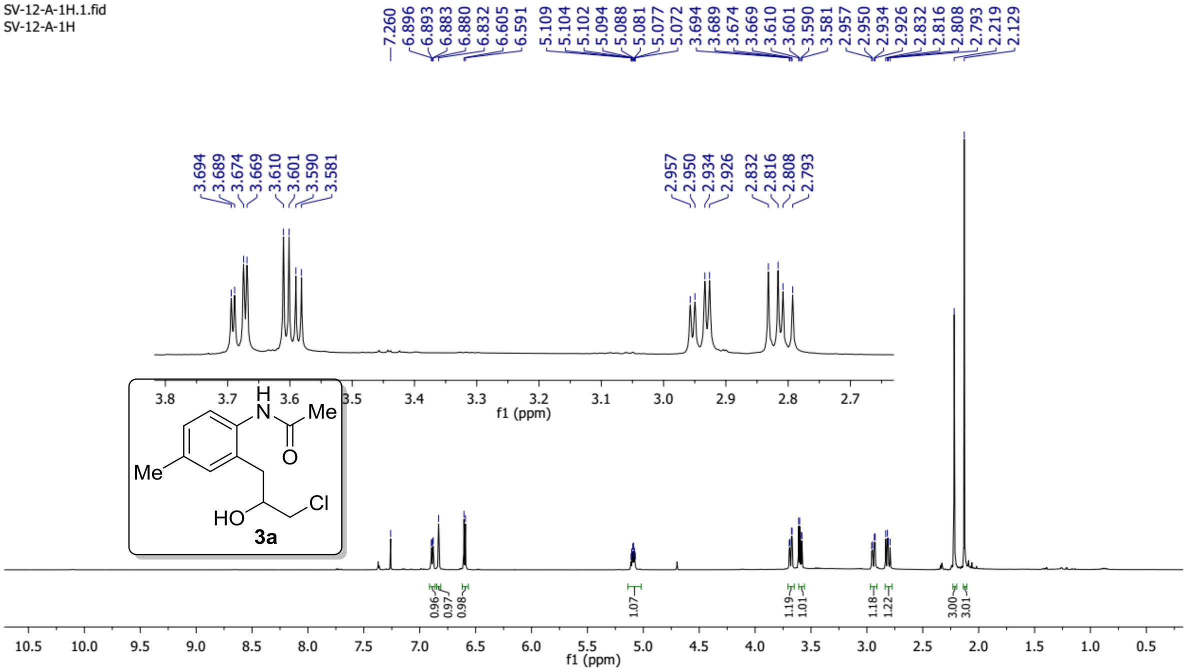
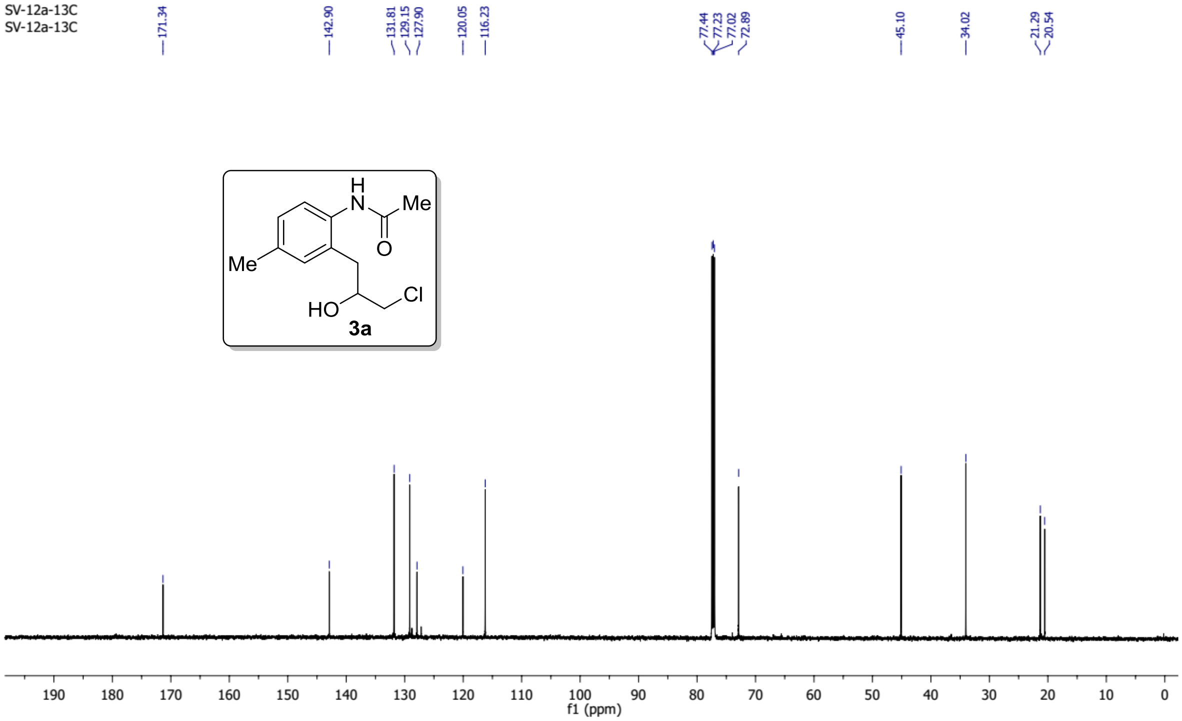
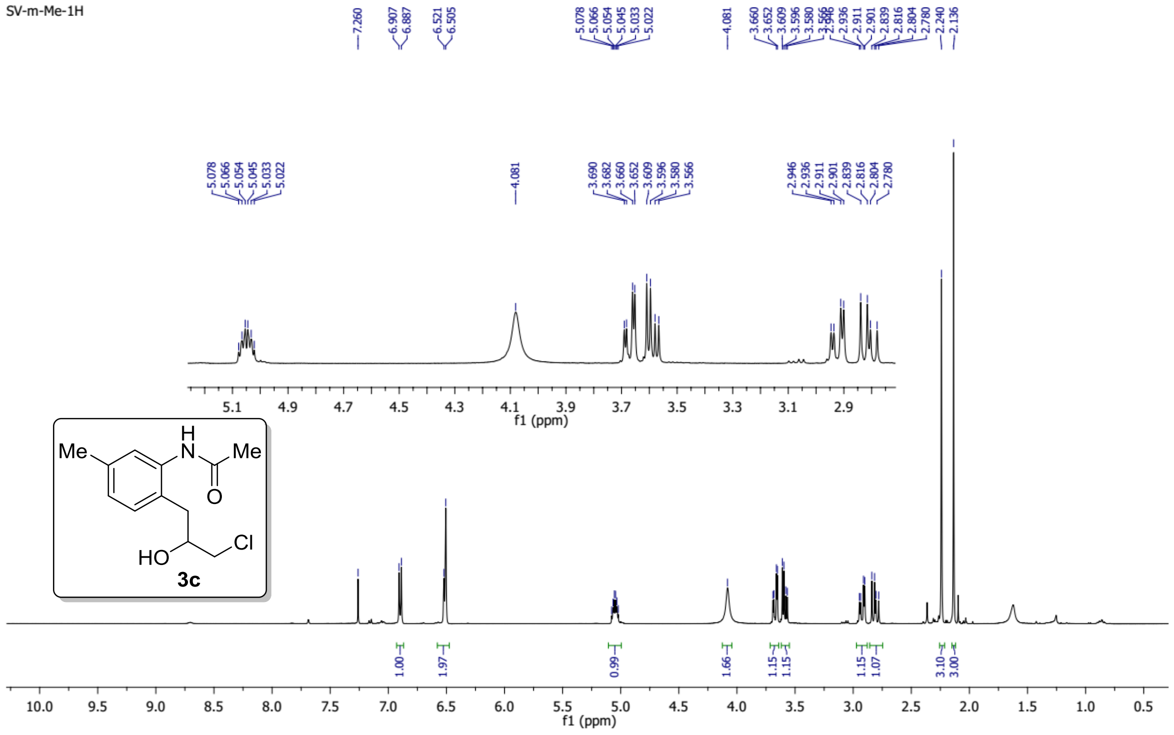
6.5 Selected NMR Spectra



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3.690
3.682
3.660
3.652
3.609
3.596
3.580
3.566
2.946
2.936
2.911
2.901
2.839
2.816
2.804
2.780
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2.136
Me
H
N
Me
O
HO
Cl
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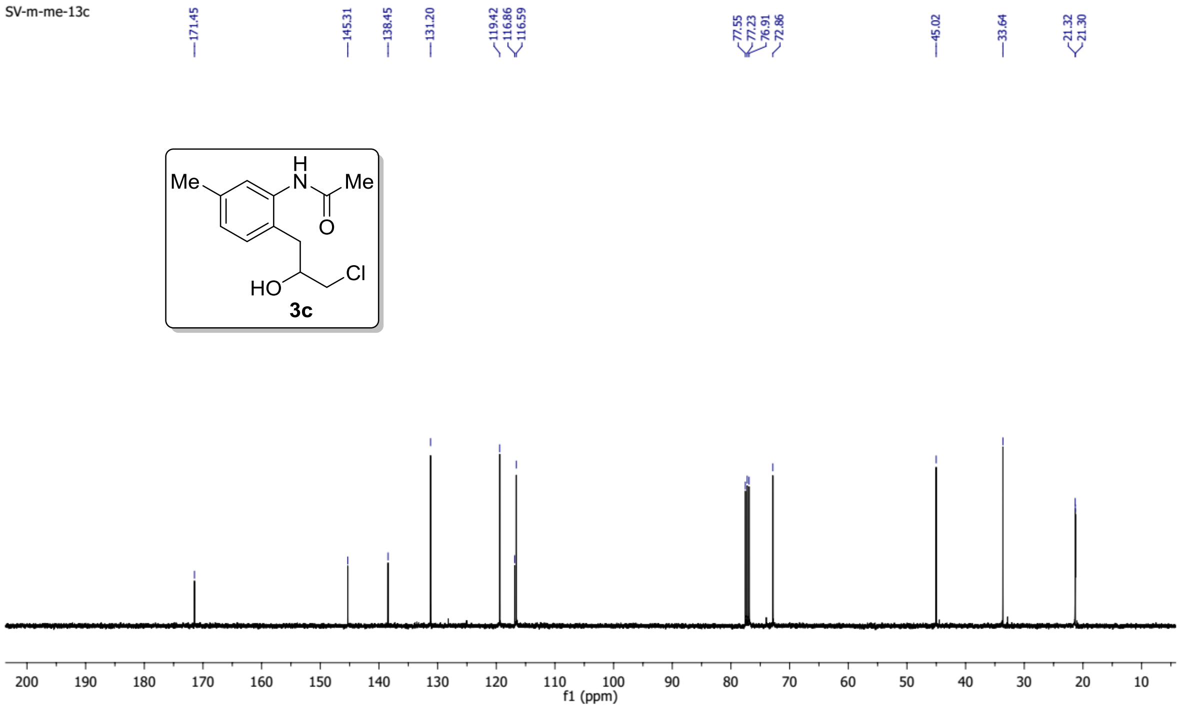
3.00
f1 (ppm)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Me
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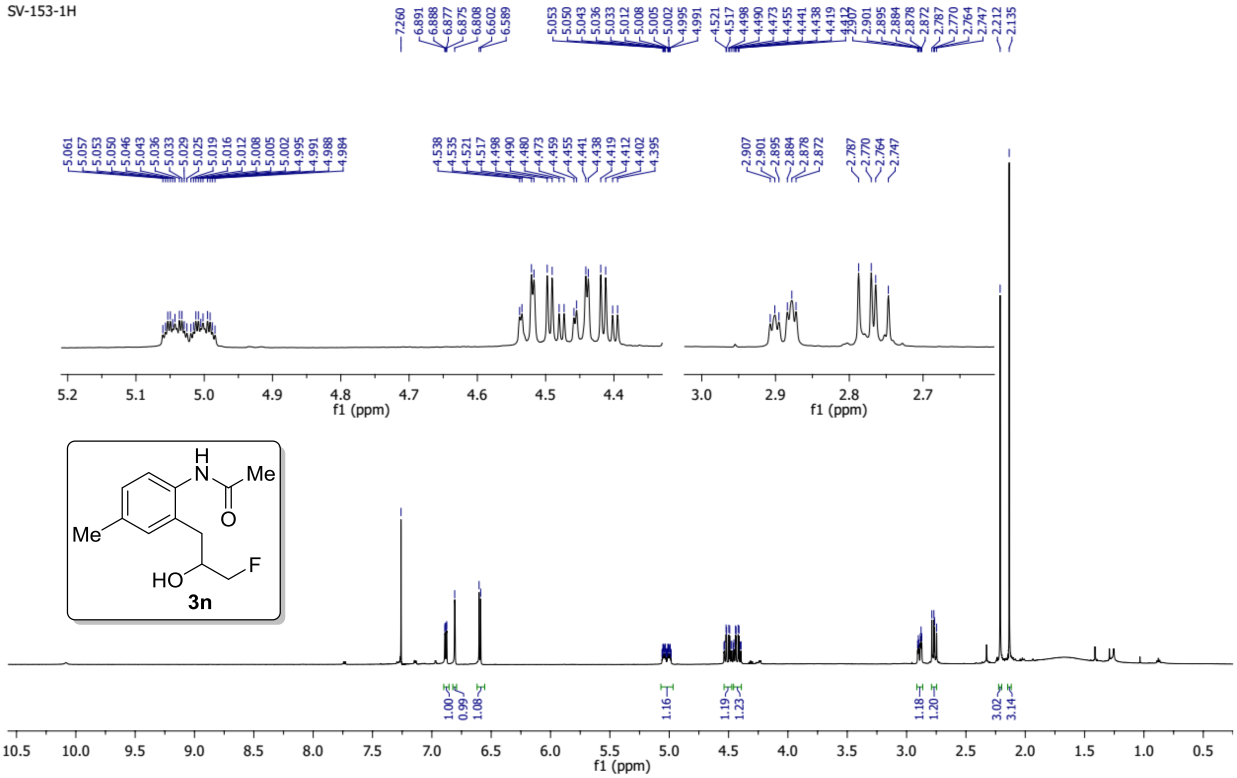
O
HO
Cl
3c
f1 (ppm)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5.033
5.012
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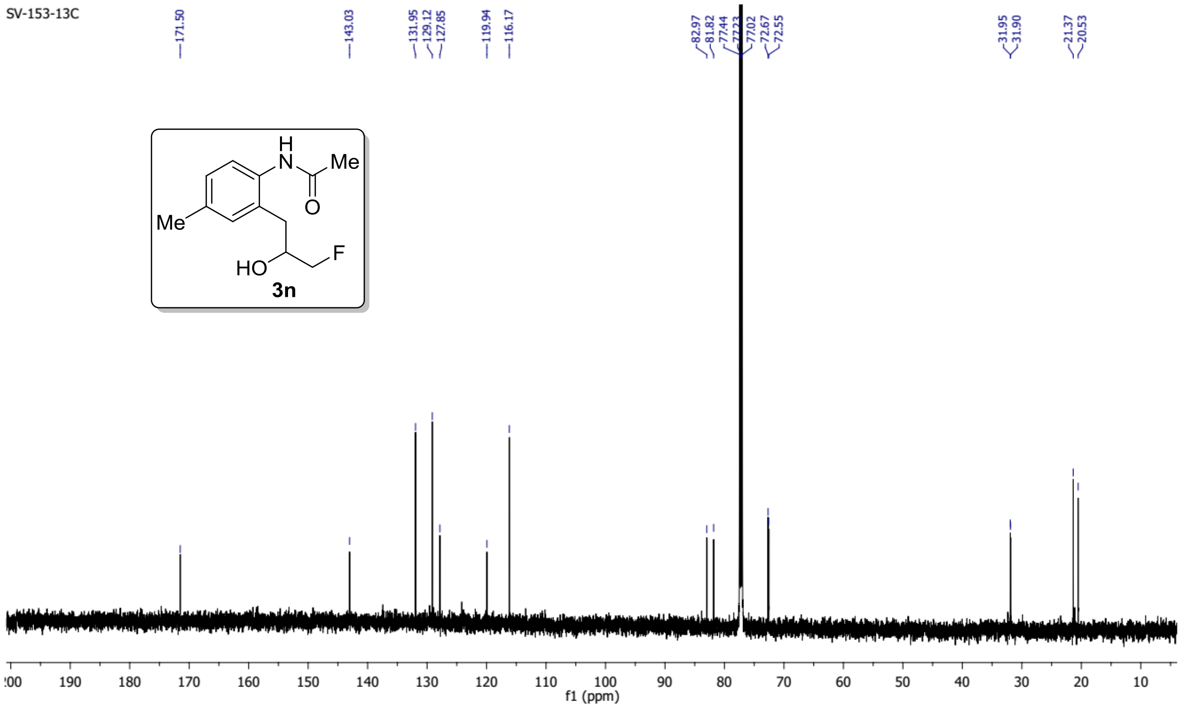
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72.55
31.95
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21.37
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f1 (ppm)
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N
Me
O
Me
F
HO
3n

Conclusion

Five-membered heterocyclic motifs having *O*, *N*, *S* and *Se* atoms are previlaged 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 1 covers a TBAI-catalyzed intramolecular C(sp^3)-H alkoxylation of *N*-methyl amino alcohols for the synthesis of oxazolidines. The reaction is regioselective affording the target heterocycles in good yields. The optically active amino alcohols can be cyclized with high optical purities.

Chapter 2 presents the TBAI-catalyzed intramolecular C(sp^3)-H alkylamination of *N*-methyl 1,2-diamines for the synthesis of imidazolidines. This regioselective protocol affords the target products in high yields. As above, optically active 1,2-diamines can be cyclized with excellent optical purities.

Chapter 3 describes a Co-catalyzed domino synthesis of substituted oxazolidines from *N*-alkyl anilines and epoxides using TBHP as an oxidant. The reaction involves S_N2 type of ring opening of epoxide followed by *C-O* bond formation *via* C(sp^3)–H functionalization to deliver the substituted oxazolidines in high yields and excellent optical purities.

Chapter 4 demonstrates the stereospecific [3+2]-cycloaddition of chiral aziridines with isoselenocyanates using Al-catalyst at room temperature. This transformation provides a regio- and chemoselective route for the synthesis of 2-iminoselenazolidines with excellent optical purity (up to 99%).

Chapter 5 deals with the ring expansion of thiiranes and heterocumulenes using $BF_2OTf{\bullet}OEt$ to produce iminodithialanes, iminselenazolidines and iminothiazolidines with broad substrate scope and functional group diversities.

Chapter 6 illustrates a Pd-catalyzed *ortho*-selective C(sp^2)-H activation arenes and subsequent C-C coupling with epihalohydrines. The reaction provides synthetic tool for the synthesis of *ortho*-acetamide substituted phenethyl alcohols.

List of Publications

1. "On Water" C(*sp*^{3})-H Functionalization/*C-O*/*C-N* Bonds Formations: Synthesis of Functionalized Oxazolidines and Imidazolidines.

   Satheesh, V.; Sengoden, M.; Punniyamurthy, T. *J. Org. Chem*. **2016**, *81*, 9792.
2. Copper(II)-Catalyzed Oxidative Coupling of Anilines, Methyl Arenes, and $TMSN_3$ *via* C(sp^3/sp^2)-H Functionalization and C-N Bond Formation.

   Mahesh, D.; **Satheesh, V**.; Kumar, S. V.; Punniyamurthy, T. *Org. Lett.* **2017**, *19*, 6554.
3. Metal-Free [3+2]-Cycloaddition of Thiiranes with Isothiocyanates, Isoselenocyanates and Carbodiimides: Synthesis of 2-Imino-Dithiolane/Thiaselenolane/Thiazolidines.

   Satheesh, V.; Kumar, S. V.; Vijay, M.; Barik, D. and Punniyamurthy, T. *Asian J. Org. Chem*. **2018**, *7*, 1583.
4. Expedient Stereospecific Co-Catalyzed Tandem *C-N* and *C-O* bond formation of *N*-Methylanilines with Styrene Oxides.

   Satheesh, V.; Kumar, S.V.; Punniyamurthy. T. *Chem. Commun*. **2018**, *54*, 11813.
5. Regiospecific Bi-Catalysed Domino *C-N*/*C-S* Bonds Formation: Synthesis of 1,4-Thiazines/1,4-Thiomorpholines.

   Vijay, M.; **Satheesh, V**.; Kumar, S. V.; and Punniyamurthy, T. *Adv. Synth. Catal*. **2018**, *360*, 3030.
6. Rh-Catalyzed Regioselective C-H Activation and C-C Bond Formation: Synthesis and Photophysical Studies of Indazolo[2,3-a]quinolones.

   Kumar, S. V.; Ellairaja, S.; **Satheesh, V**.; Vasantha, V. S.; Punniyamurthy, T. *Org. Chem. Front*. **2018,** *5*, 2630.
7. Stereospecific Al-Catalysed Tandem C-N/C-Se Bond Formation of Isoselenocyanates with Aziridines: Synthesis and DFT Study.

   Satheesh, V.; Kumar, S.V.; Sengoden, M.; Punniyamurthy. T. *Adv. Synth. Catal*. **2018**, DOI: 10.1002/adsc.201801116.

Conferences Attended

1. A Metal Free Synthesis of Oxazolidines *via* sp3 C-H Functionalization/C-O Bond Formation, **Satheesh, V.;** Sengoden, M.; and Punniyamurthy, T. *International Symposium on Nature Inspired Initiatives in Chemical Trends* (NIICT), organized by IICT Hyderabad, September 19-20th, 2016.
2. "On Water" C(sp^3)-H Functionalization/*C-O* Bond Formation: Synthesis of Functionalized Oxazolidines, **Satheesh, V**.; Sengoden, M.; and Punniyamurthy, T. *XIIth J-NOST Conference for Research Scholars*, Organized by CSIR-CDRI Lucknow, November 24-27th, 2016.
3. Synthesis of Substituted Oxazolidines and Imidazolidines via Intramolecular C(sp^3)-H Functionalization, **Satheesh, V**.; Sengoden, M.; and Punniyamurthy, T. *53rd ACC, Indian Chemical Society*, Organized by Gitam University, Vizag, December 27-29th, 2016.
4. Synthesis of Functionalized Imidazolidines *via* Intramolecular C(sp^3)–H Alkylamination, **Satheesh, V**.; Sengoden, M.; and Punniyamurthy, T. *In-House Symposium*, Organized by Department of Chemistry, IIT Guwahati, July 25th, 2017.
5. An Efficient Aluminum Catalyzed Enantioselective Ring Expansion of Aziridines to 2-Iminoselenazolidines, **Satheesh, V**.; Sengoden, M.; Punniyamurthy, T. *Research Conclave-2018*, Organized by IIT Guwahati, March 08-11th, 2018.