Studies Towards Stereoselective C-C/C-Heteroatom Bond Formations of Strained Rings

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DOCTOR OF PHILOSOPHY

By

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Dedicated To

My

Grandparents

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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 2023

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CERTIFICATE

This is to certify that Mr. Manmath Mishra has been working under my supervision since September 2017. I am forwarding his thesis entitled "Studies Towards Stereoselective C-C/C-Heteroatom Bond Formations of Strained Rings" 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
December 2021

Prof. Tharmalingam Punniyamurthy
Supervisor

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List of Abbreviations

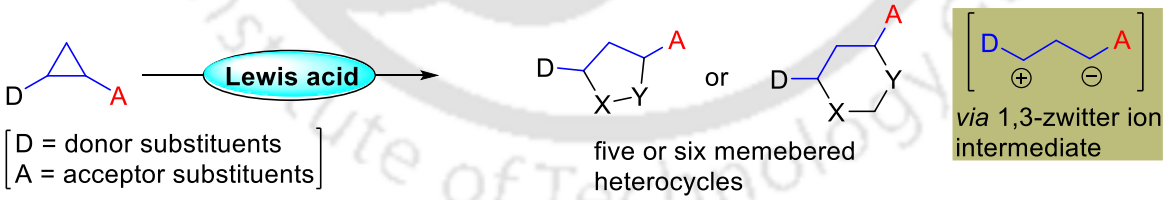
AcOH	acetic acid
Ac	acetyl
acac	acetylacetone
Å	angstrom (10-8 cm)
aq.	aqueous
aq. HCl	aqueous hydrochloric acid
Ar	aryl
Bn	benzyl
B_2Pin_2	bis(pinacolato)diboron
BHT	2,6-di-*tert*-butyl-4-methylphenol
CCDC	Cambridge crystallographic data centre
CH_3CN	acetonitrile
D-A	donor-acceptor
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMSO	dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
ee	enatiomeric excess
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FT-IR	fourier transform infrared spectroscopy
HRMS	high-resolution mass spectrometry
HPLC	high performance liquid chromatography
Hz	hertz
^{i}Pr	iso-propyl
m/z	mass to charge ratio
mCPBA	meta-chloro peroxybenzoic acid
mp	melting point

Abstract

The thesis is categorized into four chapters. The first chapter describes the general introduction to the opening and cyclization of the D-A cyclopropane systems for the synthesis of biologically important heterocycles. The second chapter demonstrates a Stereospecific Cu(II)-Catalyzed Domino Ring Opening/Oxidative Alkylation of D-A Cyclopropanes with Hydrazones. The third chapter describes a Co(II)-catalyzed stereospecific C-N/C-O bond formation of oxiranes with hydrazones. The fourth chapter deals on the regioselective (3+2)-cycloaddition of D-A cyclopropanes with 2,4-dienals followed by C-O bond formation to synthesize biologically important pyrans. The fifth chapter proposes a ligand controlled enantioselective synthesis of tetrahydropyrans using oxiranes and hydrazones as the coupling partners.

Chapter I. General introduction to ring opening and cyclization of D-A cyclopropanes

Nitrogen- and oxygen-containing heterocycles are among the most prevalent moieties found in both pharmaceutical and naturally occouring compounds. Reaserch and development into these coumpounds is of high interest and of ongoing importance in organic synthesis. Recently, C-C and C-heteroatom bonds formation by ring expansion of three-membered strained ring systems, particularly in D-A cyclopropanes have provided a great synthetic space for easy access to structurally complex scaffolds. The inherent ring strain and electrophilic character made them an attractive building blocks for the selective synthesis of five, six and seven-membered heterocycles through ring-scission. In this chapter, the studies behind the background, reactivity and synthetic methodologies of ring-opening and cyclization of D-A cyclopropanes are discussed .

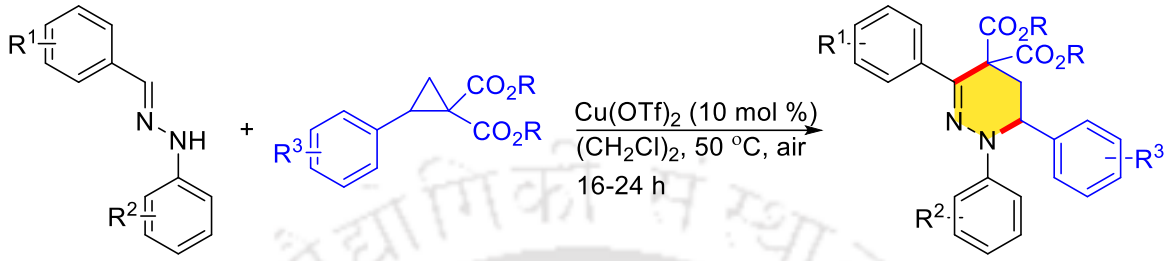


Scheme 1. Lewis acid Catalyzed Ring Opening and Cyclization of D-A Cyclopropanes

Chapter II. Copper(II)-Catalyzed Stereospecific Synthesis of Pyridazines

Tetrahydropyridazines and their synthetic analogues represent an imperious class of aza-heterocycles as they display unique biological properties. In this vein, a simple operational strategy could be sought out using readily available starting materials for their efficient synthesis. Recently, Lewis acid catalyzed cycloaddition reactions of D-A cyclopropanes has emerged as a synthetic route for the robust construction of biologically important carbo- and

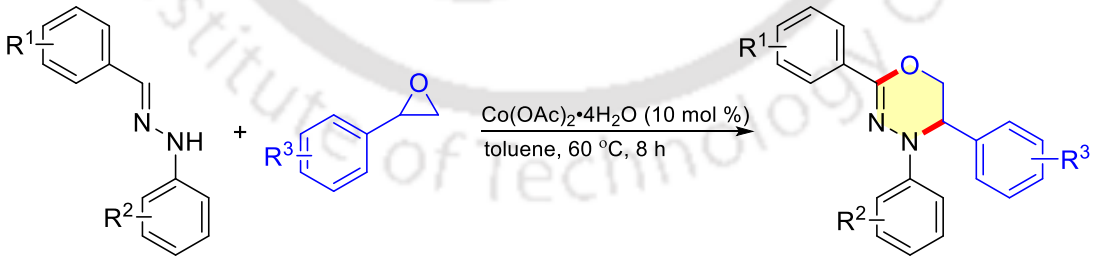
hetero-cycles. This chapter describes the stereospecific ring opening and an oxidative cyclization of D-A cyclopropanes with reactive hydrazones in presence of Cu(OTf)2 catalyst. The method offers an one-pot C-C and C-N bond forming strategy under mild reaction conditions (Scheme 1). Enantiopure D-A cyclopropanes were also efficiently coupled and air as the oxidant is an attractive feature.



Scheme 2. Stereospecific Cu(II)-Catalyzed C-C and C-N bond formation of D-A Cyclopanes with Hydrazones

Chapter III. Cobalt(II)-Catalyzed Stereospecific Synthesis of Oxadiazines

Heterocycles with three-heteroatoms are privileged structural frameworks due to their interesting biological and medicinal properties. Among them, oxadiazines are of great interests as they display diverse applications in medicinal and agricultural sciences. Epoxides are versatile building blocks and the selective cleavage of C-C and C-O bonds provide potential approach to diverse oxygen containing heterocycles. On the other hand, the Co-catalyzed annulation reactions have recently appeared as a sustainable synthetic tool as they are less-expensive and minimally toxic. This chapter demonstrates a Co(II)-catalyzed stereospecific ring opening and C-O bond forming cascade of hydrazones with reactive oxiranes. The reaction is aerobic and biologically important oxadiazines were synthesized with excellent yields and enantiopurities.

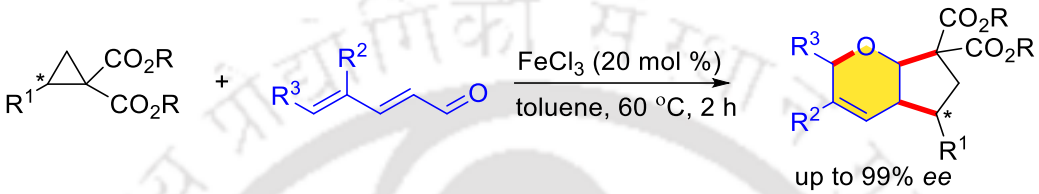


Scheme 3. Stereospecific Co(II)-Catalyzed C-N and C-O Bond Forming Cascade of Hydrazones with Oxiranes

Chapter IV. Iron(III)-Catalyzed Stereoselective Synthesis of Pyrans

Pyran is an important prevalent structural subunit present in a broad spectrum of natural products, such as sugars, coumarins, flavonoids and xanthones and also are used as anti-cancer agents. Therefore, swift construction of pyrans from readily available starting materials under

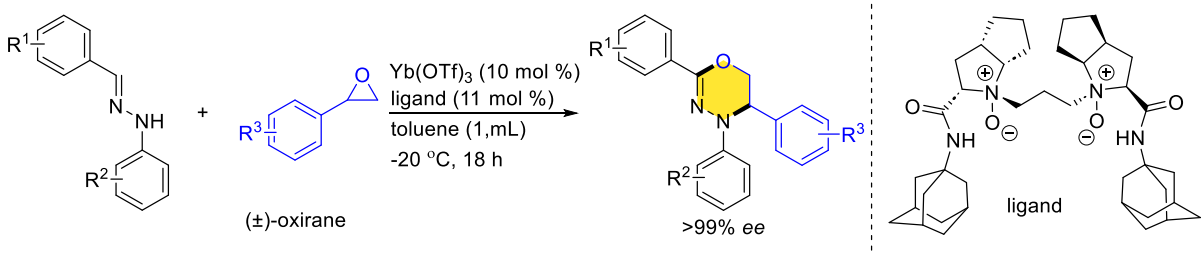
mild and economic conditions would be worthy rewarding task. 2,4-Dienals in presence of Lewis or Brønsted acid can transforms into an oxyallyl cation intermediate, which can further be trapped by suitable carbon or heteroatom- based nucleophiles in an interrupted *iso*-Nazarov process to synthesize valuable organic parallels. This chapter describes the regioselective synthesis of pyrans from readily available D-A cyclopropanes with 2,4-dienals in presence of benign $FeCl_3$-catalyst (Scheme 3). The sequential three C-C and C-O bond forming cascade under a single operation *via* a ketene intermediate is noteworthy achievement. Enantiopure pyran derivatives were also synthesized efficiently.



Scheme 4. Fe(III)-Catalyzed Sequential C-C and C-O Bond Forming Cascade of D-A Cyclopropanes With 2,4-Dienals.

Chapter V. Enantioselective Synthesis of Tetrahydropyridazines

Transition metal doped chiral ligand catalyzed enantioselective strategies plays an important role in modern asymmetric synthesis owing to their high modifiability, ease of handling, as well as their environmentally friendly nature. In this regard, N-and O-containing multidentate chiral ligands can be complexed with transition metals to synthesize stereoselective organic compounds. To worthy mention is here, a series of C2-symmetry chiral bisoxazolines, Py-Boxes, chiral bulky salen complexes, chiral N,N-oxides as well as chiral bimetallic phosphoric acid ligands can be used for this noble aim. This chapter delivers the enantioselective synthesis of oxadiazines from racemic oxiranes with hydrazones using chiral Yb-adamantyl *N,N*-oxide complex (Scheme 4). The strategy is operationally simple and the oxadiazines were produced with excellent enatioselectivities.



Scheme 5. Yb-adamantyl *N,N*-oxide Complex Assisted Enantioselective Synthesis of Oxadiazines.

Contents

Chapter I

Overview

Reaction of Donor-Acceptor Cyclopropanes in Organic Synthesis

1.1 Introduction

In recent past, the use of strained three-membered entities has led to innovative and effective transformations, resulting in the creation of complex cyclic and acyclic organic compounds that would otherwise be challenging to achieve. Cyclopropanes are useful synthetic building blocks for organic chemists due to their high π character, inherent angle strain, and intrinsic torsional strain.[1] In particular, the donor-acceptor (D-A) cyclopropanes have gained prominence, where the C-C bond polarization is facilitated by the vicinal donor and acceptor substituents leading to important organic transformations. In 2003, Reissig delved into the synthetic applications of D-A cyclopropane derivatives as intermediates in natural product synthesis.[2] Notably, the D-A cyclopropanes are stable unless the C-C bonds were activated. Traditionally, electron-withdrawing functionalities such as carbonyl, sulfonyl, and nitro groups, function as acceptors, while moieties with electron-rich aryl groups, heteroatoms, alkyl, or alkenyl groups act as donors. Generally, amongst the two arrangements for donor and

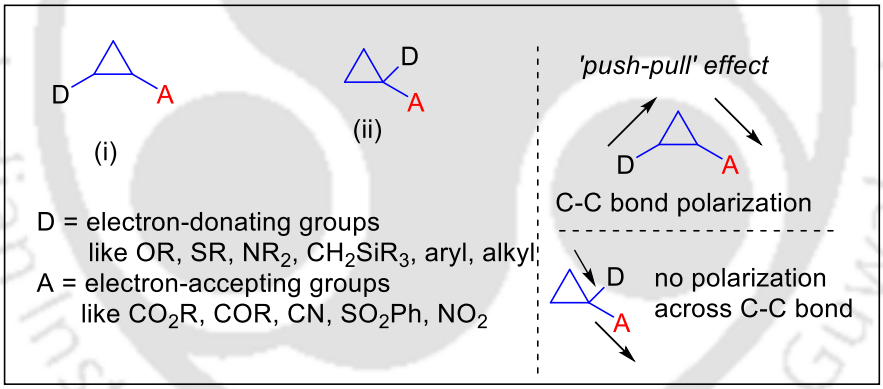


Figure 1. Vicinal *vs*. geminal D-A cyclopropanes

acceptor groups such as vicinal and geminal positioning the donor and acceptor groups positioned vicinally run in a controllable, push-pull fashion, leading to enhanced polarization of the C-C bond between the two adjacent groups (Figure 1).[3] The push-pull effect persuades polarization in the ring and various pathways for ring-opening are feasible *viz.*,

(i) Heterolytic ring opening

(ii) Homolytic cleavage

(iii) Formal cycloaddition

The heterolytic ring opening leads to formation of a zwitterionic intermediate hence could react steadily with an electrophile, nucleophile as well as dipolarophiles. By convention the

nucleophiles attack at the electrophilic carbon of the ring and successive ring opening occurs. On the other hand, the homolytic cleavage forms a diradical species depending upon the substrates nature and consequently undergo a reaction with dipolarophiles to yield biologically active heterocycles. However, the formal cycloaddition follows a stepwise mechanism, where the ring opening and cyclization extensively controlled by the vicinal substituents. Evidently, these reactivities of D-A cyclopropanes are considered to be directed by the generation of a 1,3-dipole (Figure 2). Therefore, this 1,3-dipoles are created in activated D-A cyclopropanes when the energy barrier significantly decreases in thermodynamically driven conditions such as, (i) thermal activation, (ii) activation by Lewis or Brønsted acids/bases, and (iii) catalysis by transition metals. Apart from the 1,3 zwitterionic species, 1,2- and 1,4-zwiterionic species are also observed upon isomerization thus diverse cyclic scaffolds can be formed.

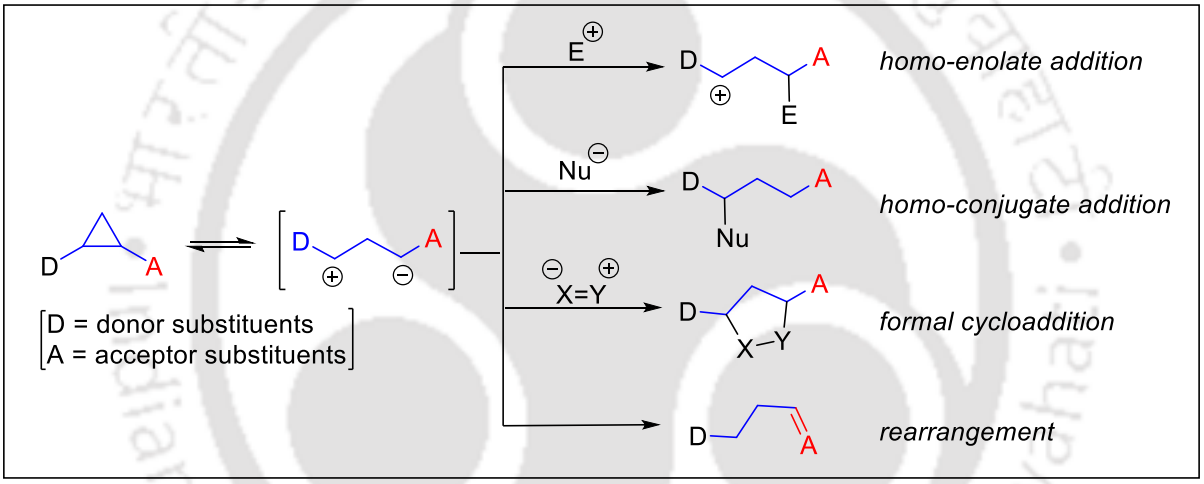


Figure 2. Reactivities of D-A cyclopropanes

1.2 Ring Opening Reactions

The ring-opening reactions of activated D-A cyclopropanes with nucleophiles, electrophiles, or radicals serves as a valuable approach for constructing open-chain structures. Consequently, monofunctionalized products are formed when a stabilized anion formed by the attack of a nucleophile on the ring at donor site trapped by a proton while the neutralized negative charge by an electrophile leading to1,3-bisfunctionalized scaffolds. Such ring-opening reactions are usually conducted under organocatalytic approach as well as Lewis acid catalysis however, the former resulted in a lower yield than the transition metal catalysts. Also, the ring opening of enantiopure D-A cyclopropanes by heteroatomic and carbon nucleophiles gives rises to the idea of whether the enantiomeric excess is retained during the chemical transformation. Primary and secondary amines[4] are useful for the synthesis of amino-functionalized acyclic

organic compounds while primary and secondary alcohols[5] undergo a nucleophilic ring opening to *O,O*-acetals. In case of alkylcyclopropane-1,1-diesters the competing C2 and C3 attack on the ring is observed to face a low chemoselectivity.[6] This lower in chemoselectivity and overall reaction yield depends upon the nucleophilicity as well as the extent of activation in the ring. By using a strong electron-withdrawing group at the acceptor site the activation of a three-membered ring allows the ring opening of D-A cyclopropanes to be performed by weaker *N*-nucleophiles, specifically aniline derivatives.[7] Utilizing Lewis acids for the external activation of electrophilic D-A cyclopropanes frequently facilitates gentle ring opening, enhancing the process efficiency significantly.[8]

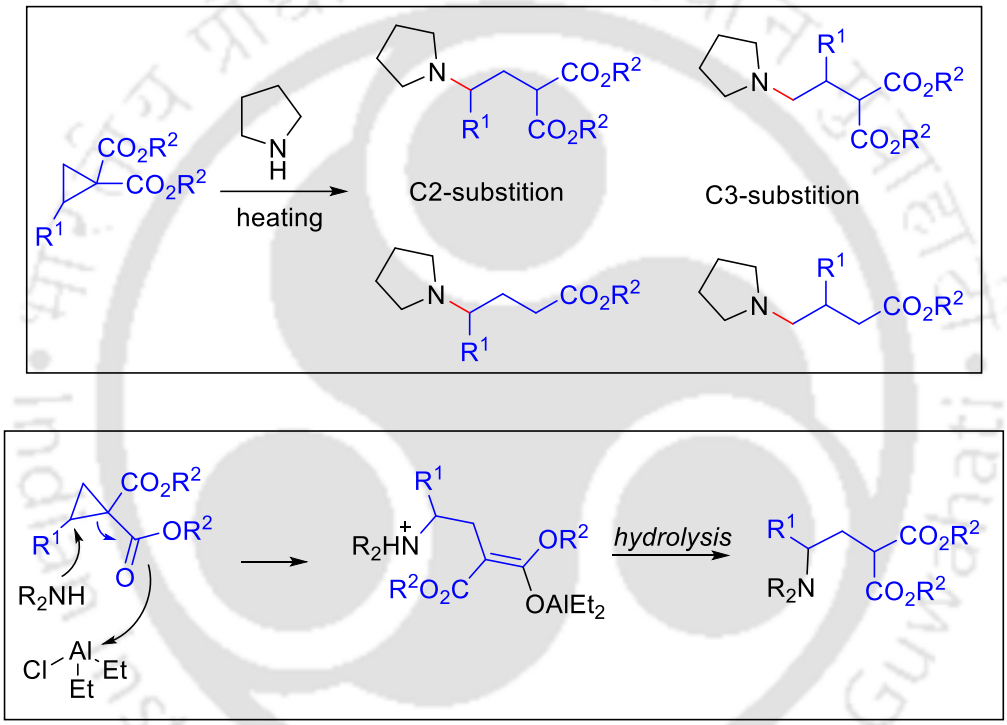


Figure 3. Chemoselectivity in alkyl-substituted D-A cyclopropanes with secondary amine

1.3 Rearrangement Reactions

Rearrangements serve as a swift and efficient approach to access intricate chemical frameworks in a highly atom-economical manner. In case of strained systems rearrangements can readily take place upon ring-opening and further reactions can lead to the formation of new fused hetero- as well as carbocycles. Therefore, these rearrangements are categorized into three main classes:

(i) rearrangements of vinyl cyclopropanes

(ii) acid-promoted rearrangements

(iii) radical rearrangements.

The rearrangements in D-A cyclopropanes may occur by the virtue of C-C bond cleavage upon treatment with acid resulting in a generation of highly electrophilic centre. The adjacent group then migrate to generate more stabilized intermediate. Evidently, the heteroatoms next to the electrophilic site provides the necessary stabilization to promote rearrangement. Typically, the acceptor unit involved in the reaction is either activated by a Lewis or Brønsted acid, or it is generated in situ as a highly reactive intermediate.[9] This reactive intermediate then undergoes a ring enlargement reaction by intramolecularly attacking the α-position adjacent to the donating motif. Vinylcyclopropane rearrangements are independent on their placement of donor and acceptor groups as compared to D-A cyclopropanes. Further, these transformations are believed to occur through either a diradical two-step process or an orbital symmetry-controlled pericyclic pathway.[10]

1.4 Cycloaddition Reaction

For over last few decades, D-A cyclopropanes have been synthetically useful building blocks for the synthesis of substituted five, six and seven-membered carbo- and heterocyclic motifs *via* annulation with alkenes, alkynes, allenes, enol ethers, enamines and myriads of diene functionalities (Table 1). When chiral substrates, chiral Lewis acids were used, diastereo- and enantioselective products are observed. Johnson and co-workers developed a $Sn(OTf)_2$/ $SnCl_4$-catalyzed reactions of aldehydes with aryl- or alkyl-substituted cyclopropanes to construct 2,5-cis-configured tetrahydrofurans with a high diastereoselectivity.[11] Although the cycloaddition of D-A cyclopropanes with aldehydes and ketones were first investigated in the year 1990s, the aryl and alkyl donor groups provide high regio and stereoselective cyclic ethers. Waser and co-workers synthesized amino-substituted tetrahydrofurans in an Fe(III)-catalyzed [3+2]-cycloaddition of aminocyclopropanes with aldehydes.[14] Yang group proposed the construction of 2,5-*trans*-configured products by adding catalytic amounts of $AlCl_3$, where the choice of aldehyde determines the absolute configuration of the final products.[15] Later, 2,5-*trans*-derivatives of tetrahydrofuran was reported by Niggemann and co-workers in a Ca(II)-catalyzed cycloaddition reaction. The D-A cyclopropanes in the above cycloaddition contain a alkyne group as donor substituents. Therefore, carbonyl compounds undergo cycloadditions with D-A cyclopropanes to yield tetrahydrofurans and in other hand, tetrahydropyrroles are synthesized using the nitrogen-containing heteroanalogous carbonyl systems; such as imines and oximes. At the pioneering research, Carreira and co-workers utilized MgI_2 as a catalyst for

these transformations.[30] Soon after, Carson and Kerr developed the $Yb(OTf)_3$ assisted [3+2]-cycloaddition for the similar transformations.[16] It has been observed that the reactivity of electron-poor pyridine derivatives is similar to the reactivity of the commonly used imines with D-A cyclopropanes. A $SnCl_4$-catalyzed reaction of aryl-substituted D-A cyclopropanes with alkenes was described where a consecutive annulation occurred to give indanes.[19] In another report, the formation of indane derivatives was enabled by changing $BF_3{\cdot}OEt_2$ as the Lewis acid.[31] The first ever [4+3]-cycloadditons of D-A cyclopropanes have been documented using 1,3-diphenylisobenzofurans and anthracenes as coupling partners.[32] In a different approach, alkoxy-substituted D-A cyclopropanes were coupled with nitriles to yield pyrrole derivatives.[23] In a difference of reactivity, the reaction of D-A cyclopropanes with isothiocyanates exclusively led to the formation of thiolactams while no pyrrolidine derivatives were found.[24-25]

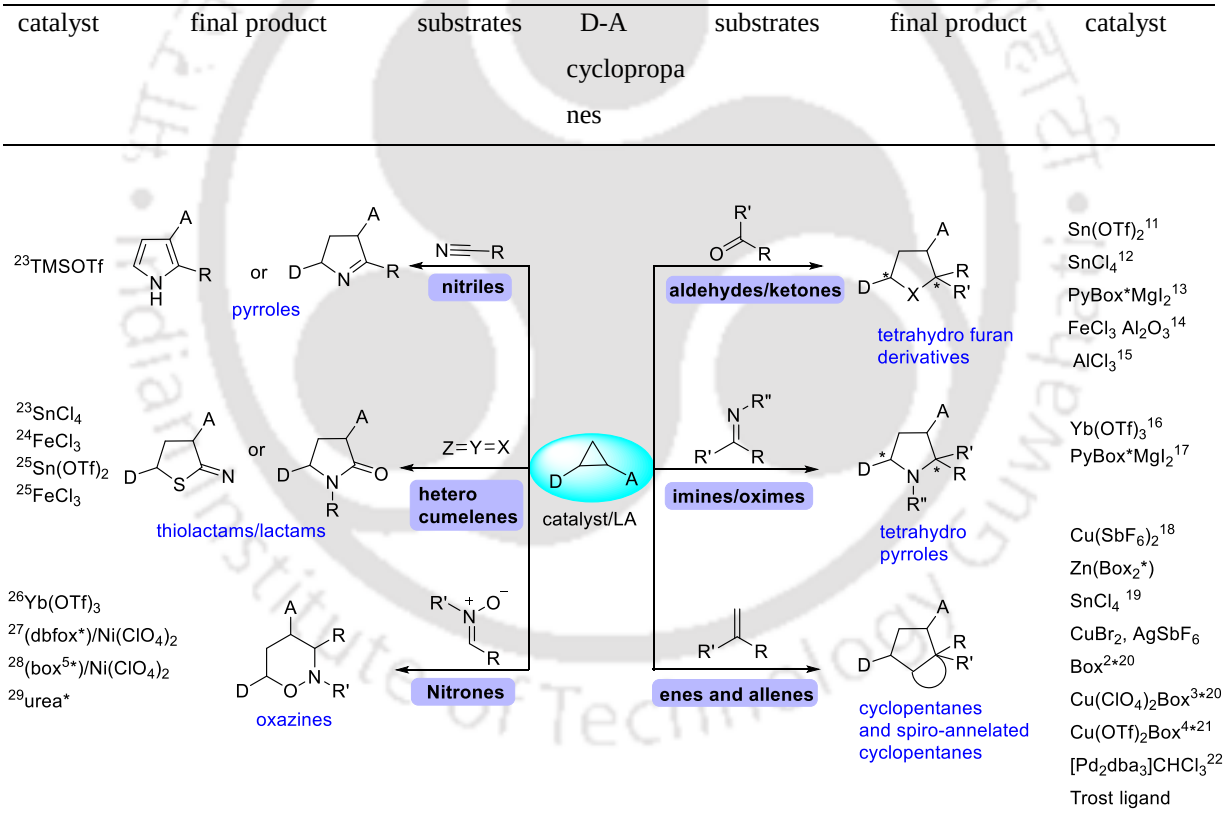


Table 1. Cycloaddition reactions of D-A cyclopropanes with 1,2- and 1,3-dipolarophiles

To get six-membered-ring systems, 1,3-dipoles are employed, which can undergo a formal [3+3]-cycloaddition reactions with D-A cyclopropanes. Nitrones and nitronates were used for this purpose, which allowed for the preparation of oxazine derivatives. The nitrone can also be created in a one-pot in situ reaction from a carbonyl and hydroxylamine. Sibi *et al*. described

the first enantioselective method to synthesize tetrahydro-1,2-oxazines by employing chiral bisoxazoline-Ni(II) catalysts.[27] Following to the above report, Tang and co-workers studied the significant increase in diastereoselectivity by switching to trisoxazoline-Ni(II) catalyst.[28] Mattson and co-workers replaced one of the ester groups by a nitro group and carried out the desired reaction in the presence of a urea catalyst.[29] Bicyclic nitroso acetals can be synthesized in a formal [3+3]-cycloadditions of cyclic nitronates with D-A cyclopropanes using $Yb(OTf)_3$ catalyst. Tetrahydro-1,2-oxazines prepared from D-A cyclopropanes and nitrones have played an important role in the synthesis of highly substituted pyrroles as well as in the total synthesis of the complex natural product (+)-nakadomarin A. Aromatic azomethine imines are another class of substrates which undergo [3+3]-cycloadditions with D-A cyclopropanes to afford tetrahydropyrazines.

1.5 Friedel-Crafts Reactions

Most recently, the D-A cyclopropanes have participated in one of the important class of Friedel-Crafts type alkylation reaction with a series of electron rich arenes and heteroarenes. In the presence of a Lewis acid, *N*,*N*-dimethylanilines, benzofurans, phenols, 2-naphthols and

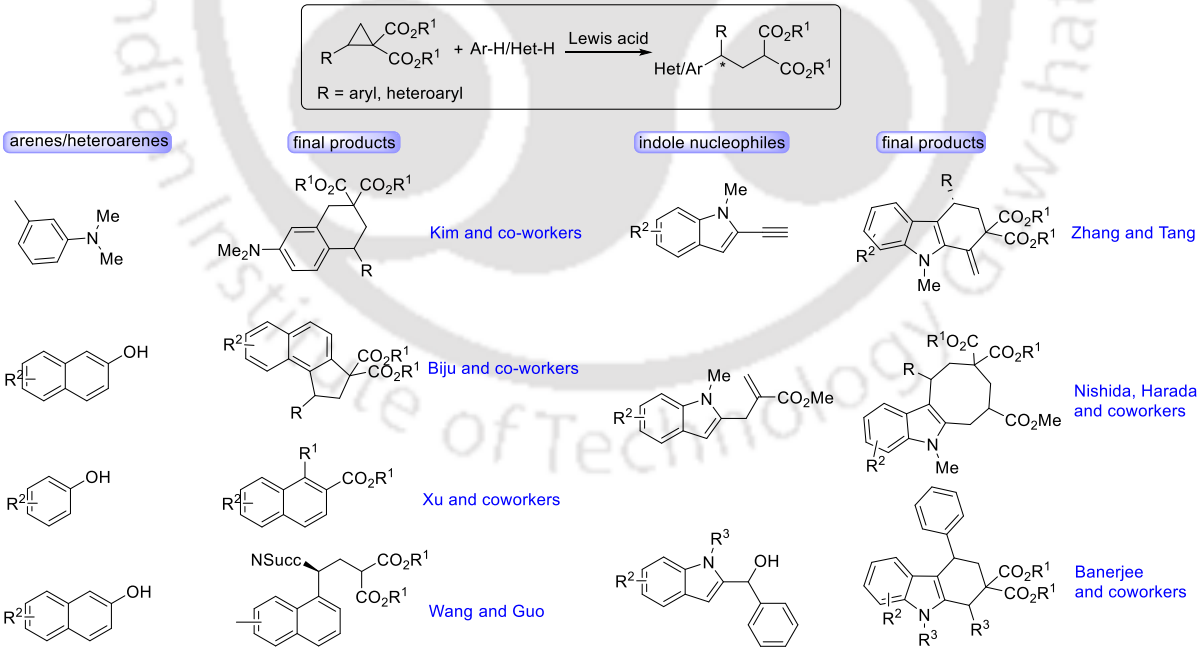


Figure 4. Recent studies in Friedel-Crafts reactions of D-A cyclopropanes with arenes and indole nucleophiles

indoles can undergo a swift ring-opening transformation to produce a wide range of acyclic and cyclic compounds, which has many biological importance and interest. As most of the studies deals with cyclopropane systems containing two geminal acceptor groups, only a few reports where mono-activated cyclopropanes have been developed to date. As a result of which the reactivity of D-A cyclopropanes with electron-rich arenes and indoles are only documented yet.

In summary, the main aim of this thesis is to utilize strained rings for the construction of biologically active heterocyclic scaffolds. In addition, the exploitation of benign transition metal catalysts for the tandem C-C and C-heteroatom bond formations in a single operational process and the stereoselective ring openings are achieved. Chapter 2 covers the stereospecific ring opening of D-A cyclopropanes with bisarylhydrazones followed by an oxidative ring closure. The chapter 3 describes the stereospecific ring opening/oxidative C-O bond formation of oxiranes with bisarylhydrazones, while chapter 4 discusses the cascade C-C and C-O bond formation of D-A cyclopropanes with 2,4-dienals *via* an *in-situ* ketene intermediate. In chapter 5, the enantioselective synthesis of oxadiazines are explained using a chiral *N,N*-oxide and Yb-complex catalytic approach.

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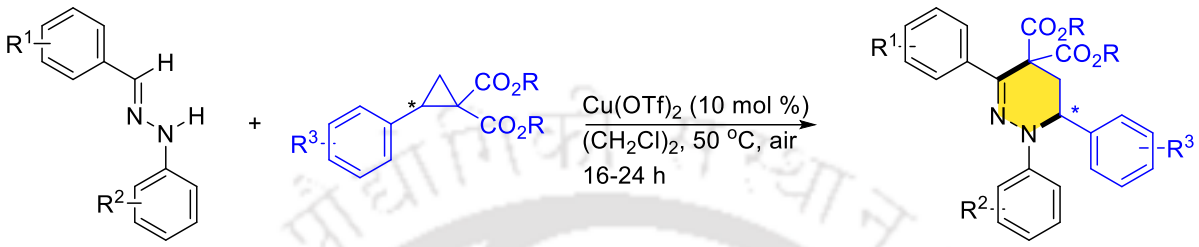
Chapter II

Copper(II)-Catalyzed Stereospecific Synthesis of Pyridazines



✔ *Aerobic* ✔ *Stereospecific* ✔ *High optical purity* ✔ *atom economy*

J. Org. Chem. **2019**, *84*, 10901

Copper(II)-Catalyzed Stereospecific Synthesis of Pyridazines

Tetrahydropyridazines and their synthetic analogues represent an imperious class of aza-heterocycles as they display unique biological properties.[1] Consequently, significant synthetic contribution has thus been made for the construction of these privileged scaffolds (Figure 1).[2] In this vein, a simple operational strategy could be sought out using readily available starting materials.

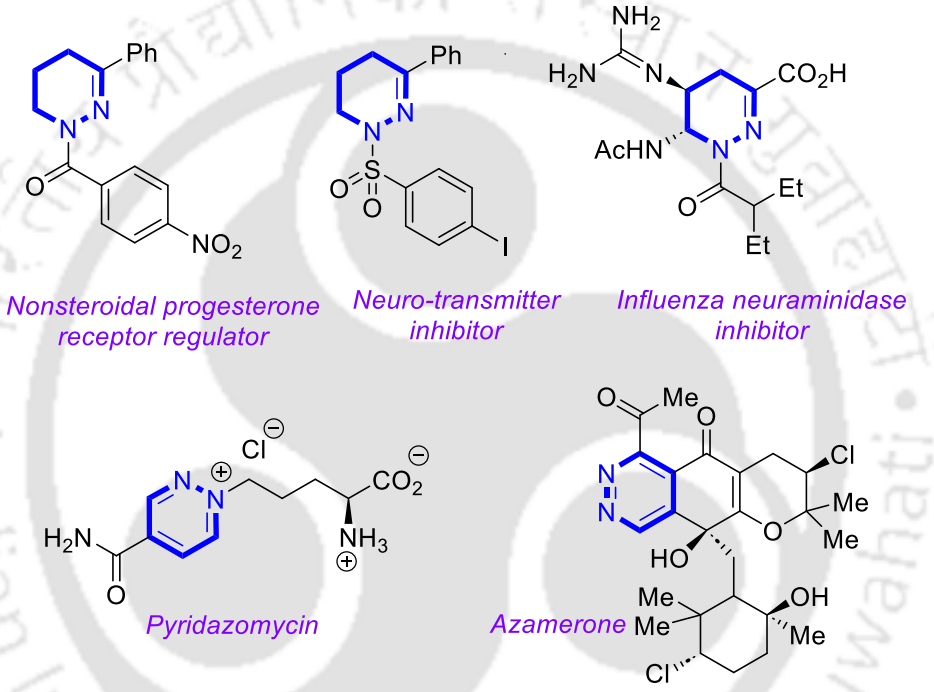


Figure 1. Examples of Biologically Active Pyridazine Derivatives.

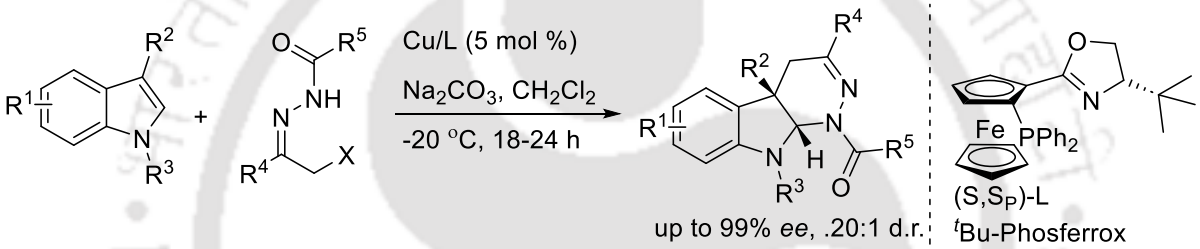
Donor-acceptor (D-A) cyclopropanes are the versatile building blocks in organic synthesis and have been enjoying a marked renaissance in the field of natural product synthesis.[3] Due to the inherent ring strain (27.5 kcal mol^{-1})[4] and vicinal substitution pattern it can efficiently undergo ring-opening,[5] rearrangement[6] and cycloaddition[7] reactions. As a result, biologically important five, six as well as seven membered carbo- and heterocyclic scaffolds can be synthesized from the Lewis acid catalyzed cycloaddition reactions of D-A cyclopropanes with suitable dipolarophiles. In addition, merging stereospecific and C-H functionalization for the construction of tetrahydropyridazine frameworks using optically active D-A cyclopropanes would be valuable.[8] Herein, we have developed stereospecific Cu(II)-catalyzed domino nucleophilic ring (S_N2)

opening and intramolecular oxidative C(sp^2)-H alkylation of D-A cyclopropanes with hydrazones to afford tetrahydropyridazines. From a control experiment it was observed that air acts as a terminal oxidant and helps in the oxidation.[9] Optically active D-A cyclopropanes can be coupled in high optical purities (89-98% ee). The reaction is atom economical and generates water as the by-product.

2.1 Literature

2.1.1 C2,C3-Annulation

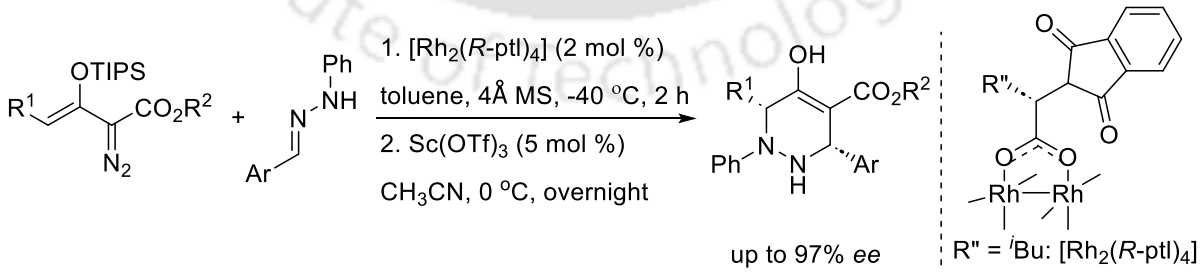
Wang and co-workers reported a Cu(I)-catalyzed asymmetric C2,C3-annulation of indoles with in *situ* formed azoalkenes to afford functionalized pyridazines [2,3]-fused indolines (Scheme 1).[10] The tetrahydropyridazine moiety constructed simultaneously, constitutes the core of numerous pharmaceuticals.



Scheme 1. Cu(I)-Catalyzed Asymmetric Annulation

2.1.2 Vinylogous N-H Insertion

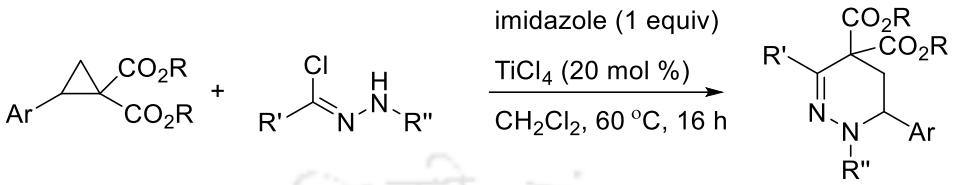
Rh-carbene-directed enantioselective vinylogous N-H insertion and Lewis acid-catalyzed diastereoselective Mannich addition using enoldiazoacetates in combination with hydrazones has been accomplished (Scheme 2).[11] The two-step procedure followed a vinylogous N-H insertion and then Lewis acid catalyzed diastereoselective cyclization.



Scheme 2. Rh-carbene-directed N-H insertion

2.1.3 [3+3]-Cycloaddition

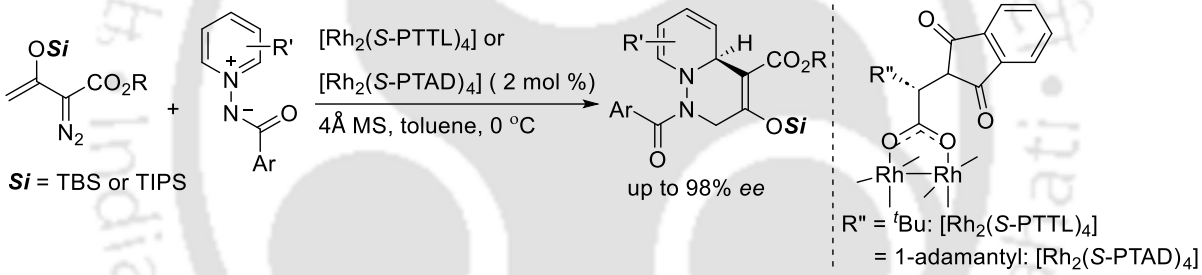
Werz and co-workers demonstrated [3+3]-cycloadditions of *in situ* generated nitrile imines from D-A cyclopropanes with hydrazonyl chlorides to access tetrahydropyridazines (Scheme 3).[12] The imines were generated using stoichiometric amount of base plays the key role in the cycloaddition



Scheme 3. [3+3]-Cycloadditions of in *situ* Nitrile Imines

2.1.4 Dearomative Cyclization

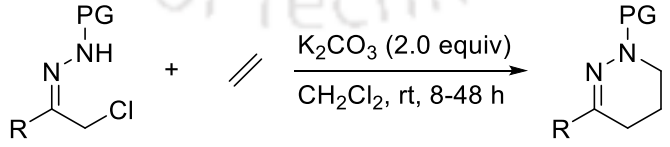
An enantioselective [3+3]-cycloaddition of *N*-iminopyridinium ylides with enol diazoacetates has been achieved in the presence of a chiral dirhodium catalyst (Scheme 4).[13] The highly substituted pyridazines were formed through a dearomative process *via* a metal enolate carbenes.



Scheme 4. Rh-Catalyzed [3+3]-Cycloaddition

2.1.5 [4+2]-Cycloaddition

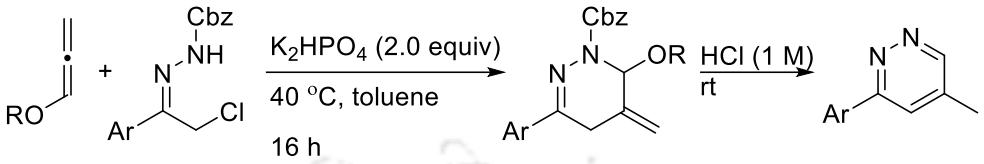
Luo and Lv reported a [4+2]-cycloaddition of *in situ* generated 1,2-diaza-1,3-dienes with olefins to synthesize tetrahydropyridazine scaffolds (Scheme 5).[14] The reaction has been accomplished under basic conditions.



Scheme 5. Base-Mediated [4+2]-Cycloaddition

2.1.6 Cycloaddition of Allenes

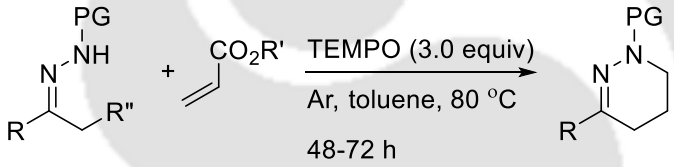
Synthesis of 1,4,5,6-tetrahydropyridazines and pyridazines *via* [4+2]-cycloaddition of alkoxyallenes with 1,2-diaza-1,3-dienes have been achieved under basic conditions (Scheme 6).[15] The pyridazine conversion was brought out by acidification in 1M HCl to further aromatization.



Scheme 6. [4+2]-Cycloaddition of Alkoxyallenes

2.1.7 Aza-Diels-Alder Reaction

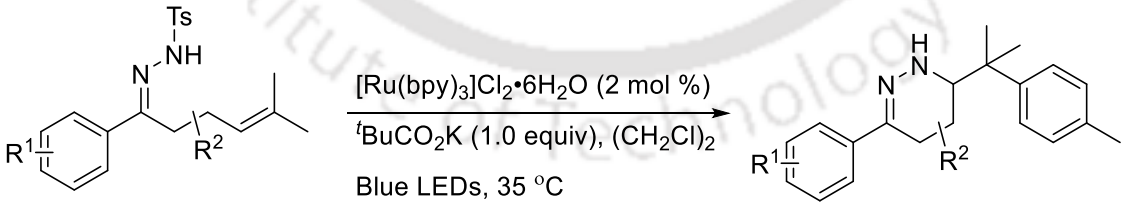
Han group reported a TEMPO-mediated aza-Diels-Alder reaction using ketohydrazones and olefins to synthesize biologically active tetrahydropyridazines (Scheme 7).[16]



Scheme 7. [4+2]-Cycloaddition of Ketohydrazones with Olefins

2.1.8 Aminoarylation

Liu and co-workers described photoredox-neutral alkene aminoarylation for the synthesis of 1,4,5,6-tetrahydropyridazines (Scheme 8).[17] The catalytic reaction is redox-neutral, and enables the construction of diazacycles containing a synthetically challenging all-carbon quaternary centre.

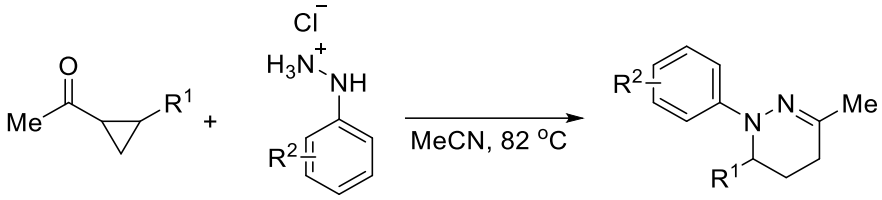


Scheme 8. Ru-Catalyzed Redox-neutral Cyclization

2.1.9 Rearrangement

Tomilov and co-workers presented the rearrangement of cyclopropylketone arylhydrazones generated *in situ* from arylhydrazine hydrochlorides and ketones to form tetrahydropyridazanies

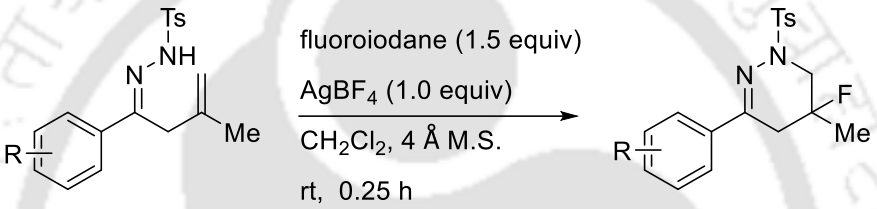
(Scheme 9).[18] The method extended for tryptamines *via* domino Cloke-Stevens/Grandberg rearrangement.



Scheme 9. Catalyst-Free Rearrangement

2.1.10 Fluorocyclization

Browne and Stuart disclosed a mechanochemical synthesis of fluorinated tetrahydropyridazines by fluorocyclization of β,γ-unsaturated hydrazones and oximes with the fluoroiodane reagent.[19]



Scheme 10. Fluorocyclization of β,γ-Unsaturated Hydrazones

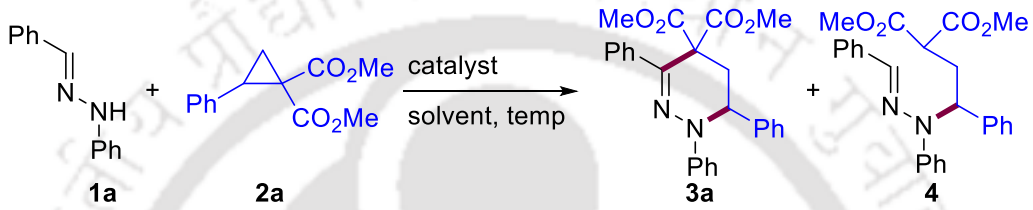
Hence, the above studies summarize an idea to construct tetrahydropyridazine scaffolds engaging cycloaddition as a common tool. However, the conventional complex reaction conditions and tedious routes to prepare the starting materials for such transformations can be avoided by the employment of widely available building blocks as well as a robust Lewis acid catalyzed [3+3] cycloaddition reaction. In this realm, the cycloaddition of D-A cyclopropanes with hydrazones can serve the purpose.

2.2 Present Study

In this study, a method for synthesizing tetrahydropyridazines through copper(II)-catalyzed stereospecific ring opening and C-H alkylation of D-A cyclopropanes with hydrazones is presented. Optimization studies commenced with (*E*)-1-benzylidene-2-phenylhydrazine **1a** and D-A cyclopropane **2a** as the model substrates along with systematic exploration of different Lewis acids and solvents (Table 1). To our delight, tetrahydropyridazine **3a** was produced in 41% yield along with 47% uncyclized **4**, when the reaction was carried out engaging 10 mol % $Cu(OTf)_2$ for 16 h in toluene at room temperature (entry 1). Successive screening of solvents led to enhance the

yield to 63% utilizing $(CH_2Cl)_2$, whereas CH_2Cl_2, THF and PhCl produced inferior results (entries 2-5). In a set of Lewis acids screened, $Cu(OTf)_2$ exhibited superior performance compared to $Sc(OTf)_3$, $Zn(OTf)_2$, $Yb(OTf)_3$ and AgOTf (entries 3 and 6-9). Gladly, increase of the temperature to 50 °C enhanced the yield to 82% with a trace amount of **4** (entry 10). Further increment of temperature (80 °C), however, led to drop the yield to 70%, which might be due to the low stability of the imine C=N bond (entry 11). A control experiment confirmed that **3a** was not formed in the absence of the catalyst (entry 12).

Table 1. Optimization of the Reaction Conditions[a]



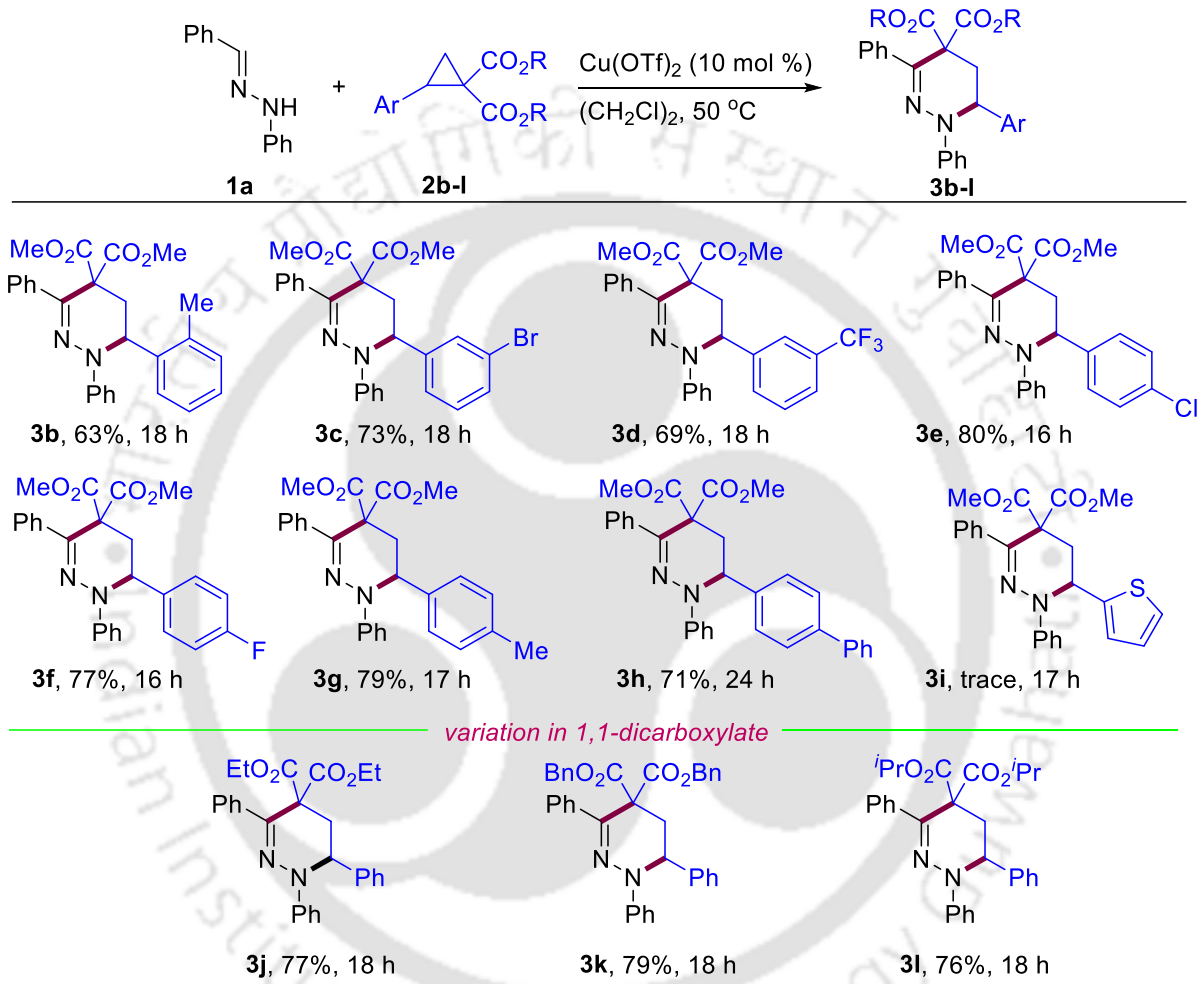
Entry	Catalyst (10 mol %)	Solvent	Yield (%)[b]	
			3a	**4**
1	$Cu(OTf)_2$	toluene	41	47
2	$Cu(OTf)_2$	CH_2Cl_2	30	56
3	$Cu(OTf)_2$	$(CH_2Cl)_2$	63	27
4	$Cu(OTf)_2$	THF	10	17
5	$Cu(OTf)_2$	PhCl	19	24
6	$Sc(OTf)_3$	$(CH_2Cl)_2$	5	81
7	$Zn(OTf)_2$	$(CH_2Cl)_2$	n.d.	trace
8	$Yb(OTf)_3$	$(CH_2Cl)_2$	36	55
9	AgOTf	$(CH_2Cl)_2$	n.d.	23
10[c]	$Cu(OTf)_2$	$(CH_2Cl)_2$	82	trace
11[d]	$Cu(OTf)_2$	$(CH_2Cl)_2$	70	trace
12	-	$(CH_2Cl)_2$	n.d.	n.d.

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (10 mol %), solvent (1.5 mL), rt, 16 h. [b]Isolated yield. [c]Reaction at 50 °C. [d]Reaction at 80 °C. n.d. = not detected.

Following the determination of optimized conditions, the scope of the procedure was further examined using substituted 2-arylcyclopropane-1,1-dicarboxylates **2b-l** with hydrazone **1a** as the

standard substrate (Table 2). Cyclopropane **2b**, with a 2-methyl group on the aryl ring, yielded tetrahydropyridazine 3b in 63% yield. Similarly, meta substituted 3-bromo **2c** and 3-trifluoromethyl **2d** substituted cyclopropanes in the aryl ring provided **3c** and **3d** in 73 and 69% yields, respectively. Cyclopropanes bearing 4-chloro **2e**, 4-fluoro **2f**, 4-methyl **2g**, and 4-phenyl

Table 2. Substrate Scope of D-A Cyclopropanes[a,b]

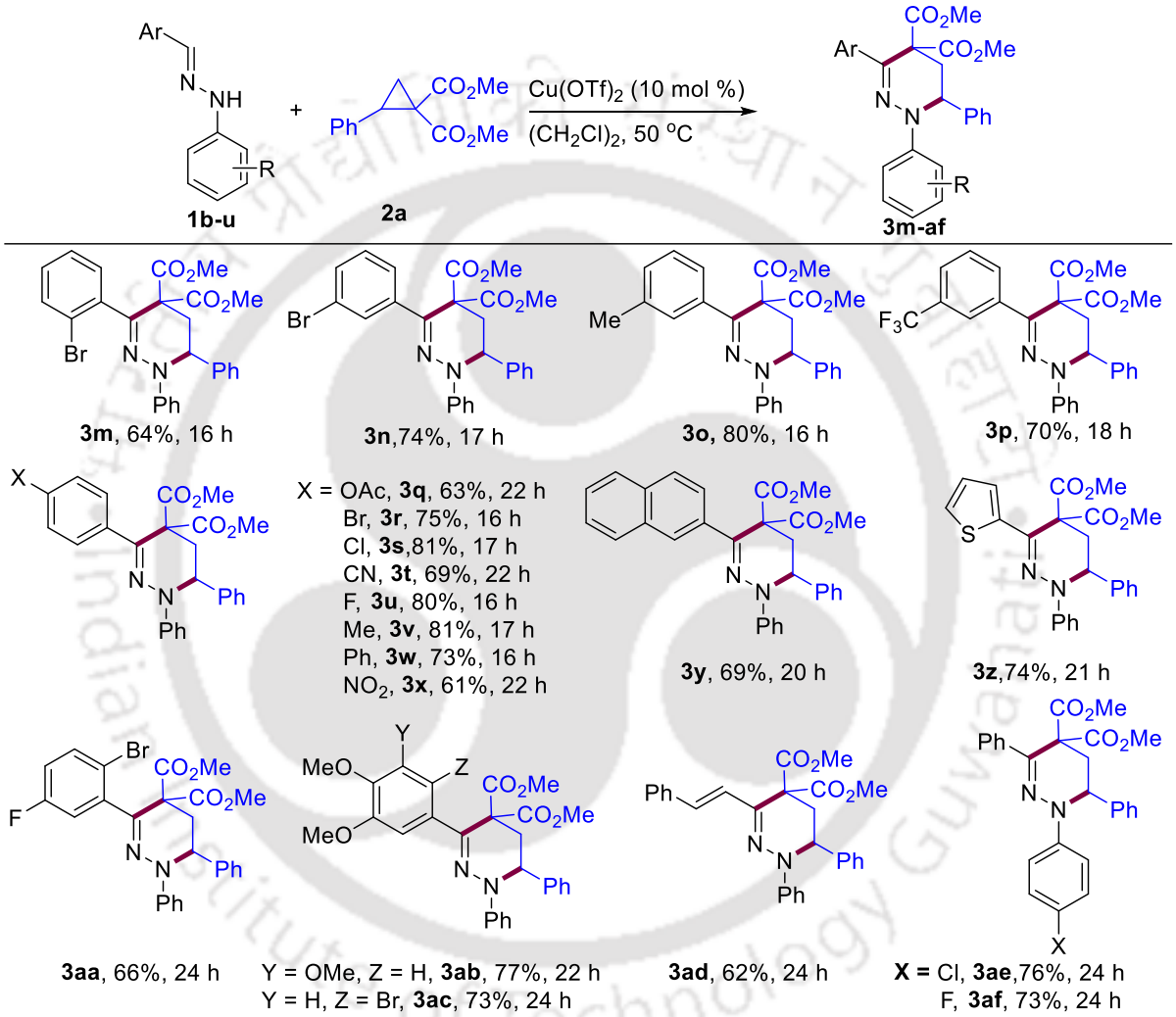


[a]Reaction conditions: **1a** (0.2 mmol), **2b-l** (0.22 mmol), $Cu(OTf)_2$ (10 mol %), $(CH_2Cl)_2$ (1.5 mL), 50 °C. [b]Isolated yield. Bn = benzyl. ^{i}Pr = *iso*-propyl.

2h functionalities on the aryl ring successfully afforded tetrahydropyridazines **3e-h** with 71-80% yields. However, the 2-thienyl-containing cyclopropane **2i** was found to be incompatible, yielding only a trace amount of **3i**. In addition, the study extended to 1,1-diester variants of D-A cyclopropanes **2j-l**, which participated effectively in the reaction, yielding aza-heterocycles **3j-l** with yields of 76-79%. Further, the scope of the procedure was broadened to include a series of hydrazones **1b-u** in combination with D-A cyclopropane **2a**. Various hydrazones featuring both

electron-donating and -withdrawing groups in the aryl rings were explored. The 2-bromo derivative **1b** resulted in tetrahydropyridazine **3m** with a yield of 64%. Additionally, substrates bearing 3-bromo **1c**, 3-methyl **1d**, and 3-trifluoromethyl **1e** groups provided heterocycles **3n-p** with yields ranging from 70% to 80%.

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

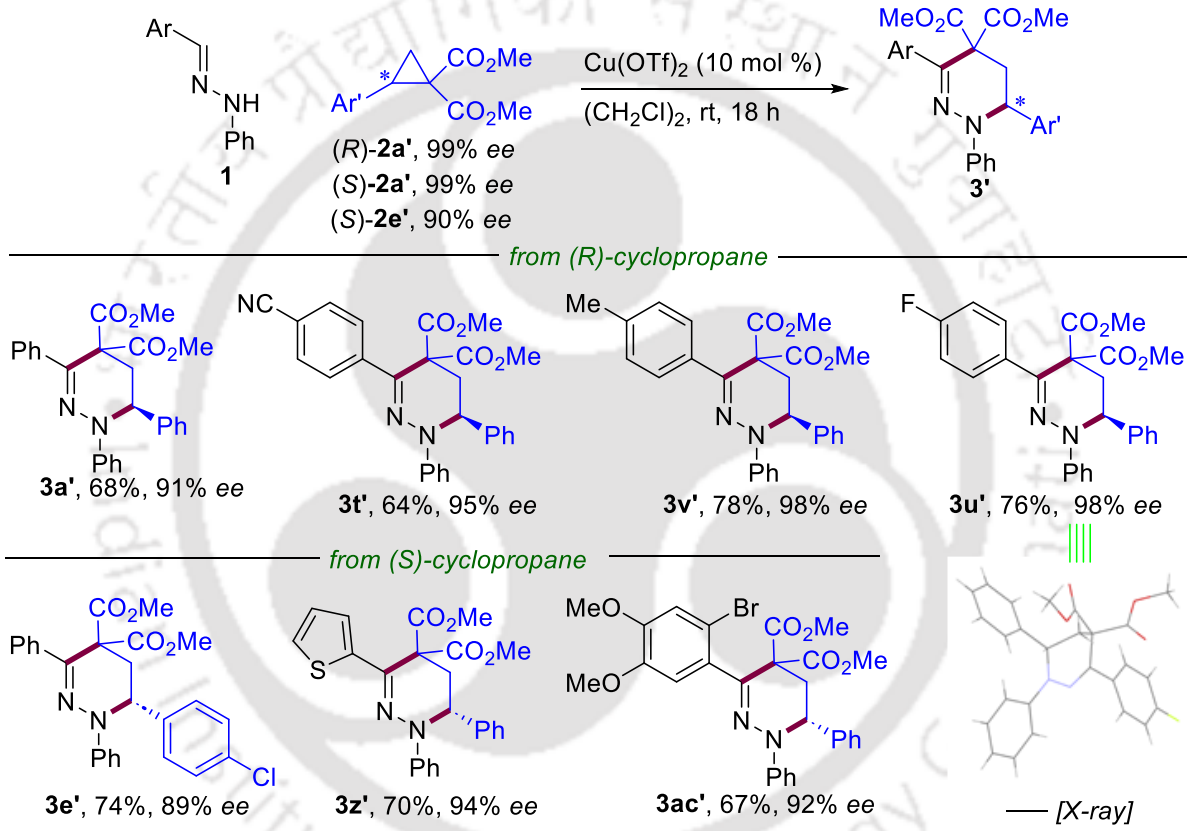


[a]Reaction conditions: **1b-u** (0.2 mmol), **2a** (0.22 mmol), $Cu(OTf)_2$ (10 mol %), $(CH_2Cl)_2$ (1.5 mL), 50 °C. [b]Isolated yield

Similar successful outcomes were observed with hydrazones containing various 4-substituents in the aryl ring. Hydrazones with acetoxy **1f**, bromo **1g**, chloro **1h**, cyano **1i**, fluoro **1j**, methyl **1k**, phenyl **1l**, and nitro **1m** functionalities resulted in the formation of the target products **3q-x** with

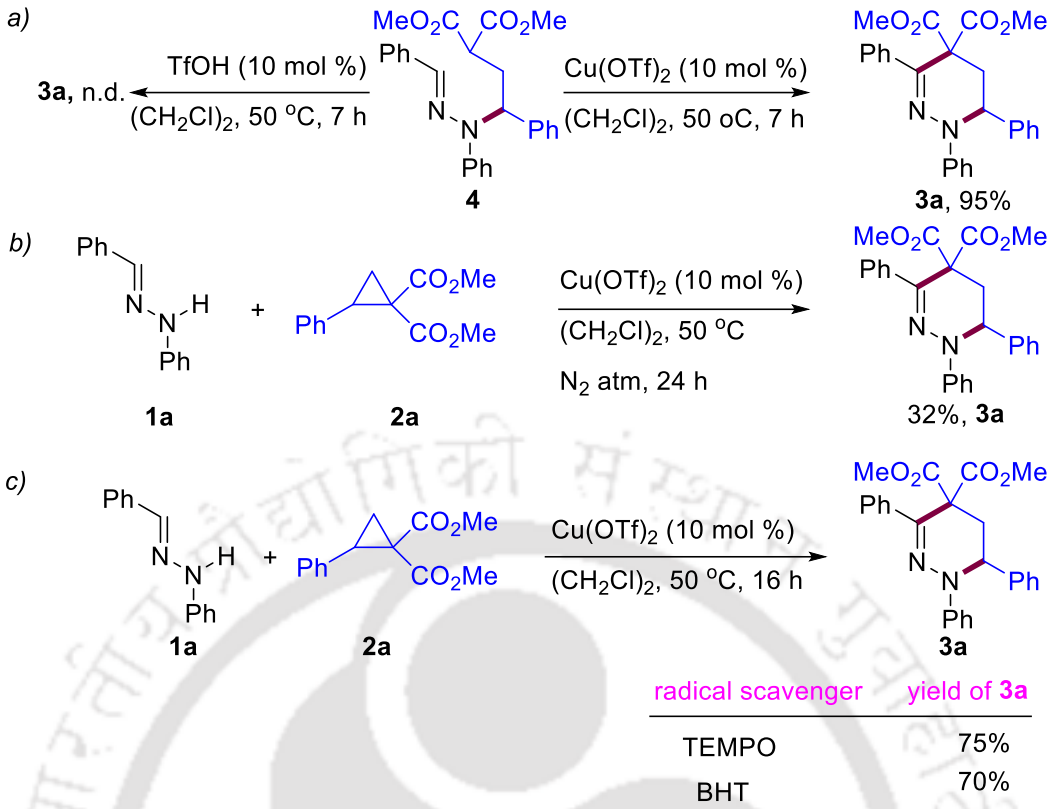
yields ranging from 61% to 81%. Notably, 2-naphthyl (**1n**) and 2-thienyl (**1o**) substrates yielded **3y** and **3z** in 69% and 74%, respectively. Additionally, di- and tri-substituted hydrazones **1p-r** were found to be compatible with the reaction conditions, providing the heterocycles **3aa-ac** in yields ranging from 66% to 77%. Further, vinyl hydrazone **1s** participated in the reaction, yielding **3ad** in 62% yield. Excellent results were also observed with 4-chloro-substituted hydrazone **1t** and 4-fluoro-substituted hydrazone **1u**, yielding products **3ae** and **3af** with yields of 76% and 73%, respectively.

Table 4. Enantiopure Substrates

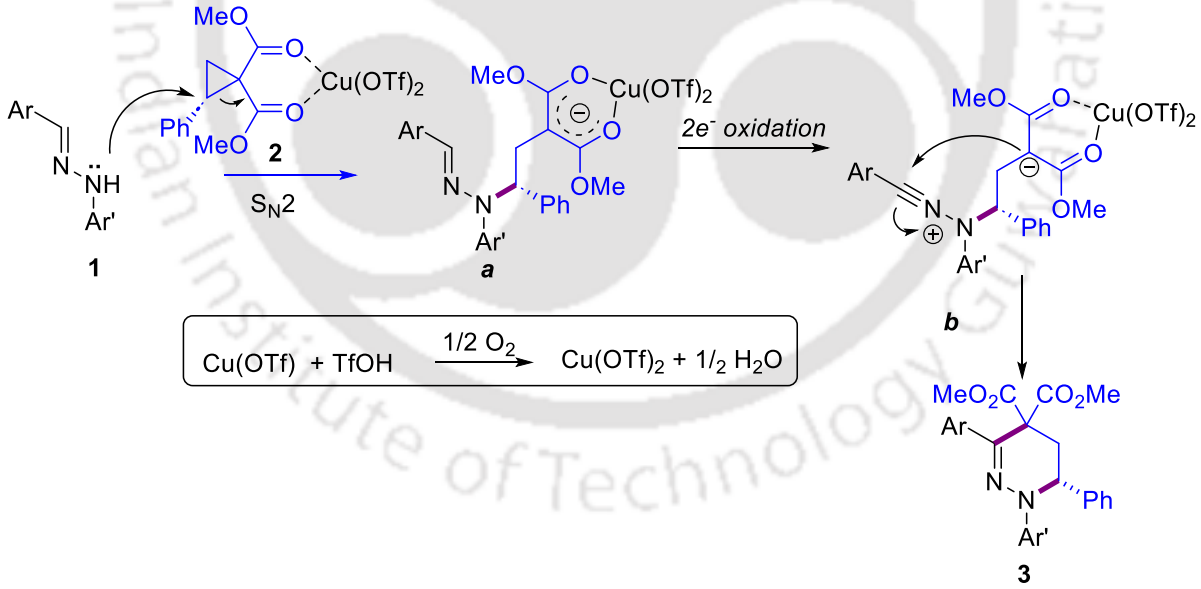


[a]Reaction conditions: **1** (0.2 mmol), **2´** (0.22 mmol), $Cu(OTf)_2$ (10 mol %), $(CH_2Cl)_2$ (1.5 mL), rt, 18 h. [b]Isolated yield.

To assess the stereoselectivity, the coupling of a series of hydrazones was investigated with optically active D-A cyclopropanes (*R*)-**2a′** and (*S*)-**2a′** as representative examples (Table 4). Hydrazone **1a** reacted with (*R*)-**2a′** to yield **3a′** with a high enantiomeric excess (*ee*) of 91%. Similarly, hydrazones containing 4-cyano **1i**, 4-methyl **1k**, and 4-fluoro **1j** groups in the aryl ring produced tetrahydropyridazines **3t′-u′** with excellent ee ranging from 95% to 98%. Likewise, the 4-chlorocyclopropane derivative (*S*)-**2e´** reacted with hydrazone **1a** to afford **3e´** with an *ee* of



Scheme 11. Mechanistic Investigations

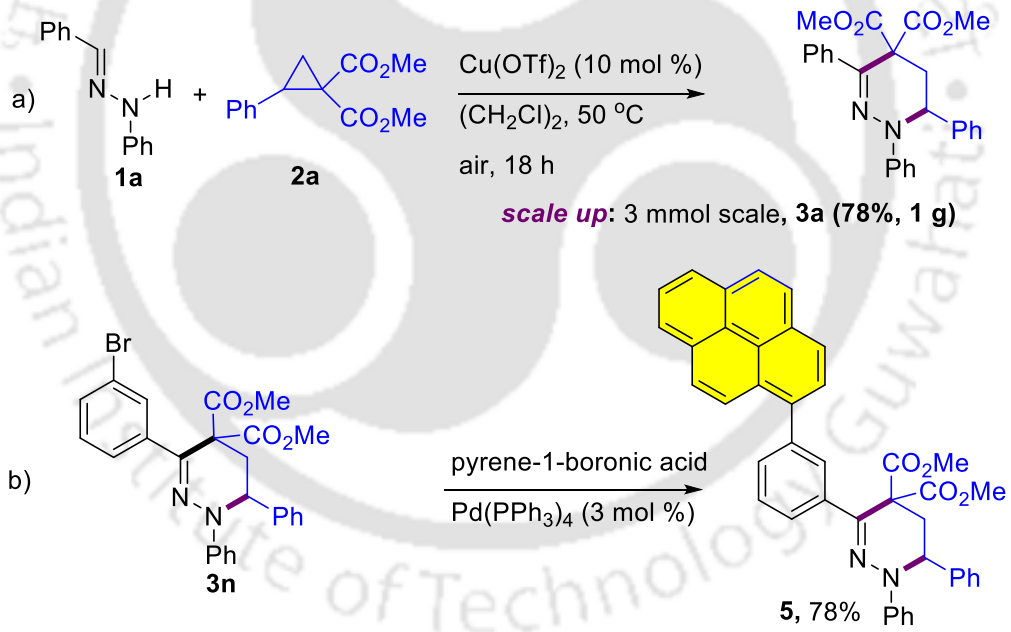


Scheme 12. Plausible Catalytic Cycle

89%. Consistent results were obtained with hydrazones **1o** and **1r** reacted with (*S*)-**2a´**, yielding **3z′** and **3ac´** with impressive *ee* of 94% and 92%, respectively. The absolute configuration of **3u´** was determined using a single-crystal X-ray analysis. These results suggest that the reaction may

proceed through a S_N2 ring opening of D-A cyclopropanes and the construction of functionalized tetrahydropyridazines can be achieved with high optical purities.

To gain insight into the reaction pathway, the reaction of **4** with 10 mol % $Cu(OTf)_2$ in $(CH_2Cl)_2$ yields tetrahydropyridazine **3a** in 95% yield, indicating a likely pathway *via* ring opening of a D-A cyclopropanes (Scheme 11a). The ineffectiveness of TfOH for cyclization suggests a non-Bronsted acid catalysis. In addition, the reduced yield of **3a** from the standard reaction of **1a** and **2a** under N_2 atmosphere implies involvement of an aerobic oxidative pathway (Scheme 11b).[22b] This insight provides valuable understanding into the reaction mechanisms, highlighting the role of $Cu(OTf)_2$ in the ring-opening process and the likely aerobic oxidative pathway in the standard reaction. Further investigations involved radical scavenger experiments with 1 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1 equiv of 2,6-di-tert-butyl-4-methylphenol (BHT), which surprisingly did not inhibit product formation, thus discounting the radical pathway (Scheme 11c).



Scheme 13. Post-Synthetic Utility and Scale-up

This suggests that the $Cu(OTf)_2$-catalyzed S_N2 type nucleophilic ring opening of D-A cyclopropanes **2** with hydrazones **1** likely yields intermediate **4**. Subsequent interaction with $Cu(OTf)_2$ forms Cu(II) species a (Scheme 12), which may then undergo 2e- oxidation[22c] using $Cu(OTf)_2$, possibly generating copper(III) species **b**[22a] capable of cyclizing to product **3**. Aerobic oxidation of Cu(OTf) with TfOH likely regenerates the catalyst, $Cu(OTf)_2$, completing the

catalytic cycle. To demonstrate practical utility, scale-up synthesis on a 3 mmol scale yielded **3a** in 78% yield (Scheme 13a). Furthermore, a bromo-bearing tetrahydropyridazine **3n** was successfully transformed into **5** in 78% yield *via* Suzuki coupling using pyrene-1-boronic acid (Scheme 13b). These findings offer a detailed insight into the reaction mechanism and illustrate its practical applicability through successful scale-up and subsequent transformations.

In conclusion, an aerobic copper-catalyzed domino reaction of the readily accessible hydrazones with D-A cyclopropanes has been achieved for the construction of tetrahydropyridazine structural frameworks via a sequential nucleophilic ring opening (S_N2) and aerobic oxidative C-C bond formation. The method offers a potential route to access optically pure tetrahydropyridazines. The substrate scope, air as the oxidant and functional group competence are the importance practical features.

2.3 Experimental Section

General Information. $Cu(OTf)_2$ (98%), $Sc(OTf)_3$ (99%), $Zn(OTf)_2$ (98%), $Yb(OTf)_3$ (99.99%) and AgOTf (≥98.0%) were purchased from Aldrich and used as received. Hydrazones[20] and cyclopropanes[21] were synthesized according to literature. Merck silica gel G/GF 254 plates were utilized for analytical TLC. Rankem silica gel (60-120 mesh) was employed for column chromatography. DRX-400 Varian and Bruker Avance III 600 and 400 MHz spectrometers were used for recording NMR (^1H and ^{13}C) spectra utilizing $CDCl_3$ as the solvent and TMS (Me_4Si) as an internal standard. Chemical shifts (δ) and spin-spin coupling constant (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet and br s = broad singlet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. Optical rotations were determined by using a PerkinElmer-343 Polarimeter with a 50 mm path length cell at 589 nm at 25 °C. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel AD-H and Chiralpak IC column using 2-propanol and *n*-hexane as an eluent. IR spectra were collected on Perkin Elmer FT-IR spectrometer. Q-Tof ESI-MS instrument (model HAB 273) was used for mass spectra. Single crystal X-ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation and the structure was solved by direct method using SHELXL-16 (Göttingen, Germany).

Preparation of Bisaryl Hydrazones. To a solution of a hydrazine (5.5 mmol, 1.1 equiv) in MeOH (5 mL) was added an aldehyde (5 mmol) slowly. The mixture was stirred at room temperature for 2 h. MeOH was evaporated in vacuo, and the residue was recrystallized from MeOH to afford the *N*-arylhydrazones.

Preparation of D-A Cyclopropanes. A round-bottom flask was charged with the appropriate aldehyde (14.4 mmol), followed by benzene (85 mL), dimethyl malonate (15.8 mmol, 2.0 g), piperidine (1.44 mmol, 123 mg), and acetic acid (2.88 mmol, 173 mg). The flask was equipped with a Dean-Stark trap condenser and the solution was heated to reflux. Upon completion (monitered by TLC), evaporation of the solvent gave the reside, which was purified by silica gel column chromatography using hexane and ethyl acetate as eluent.

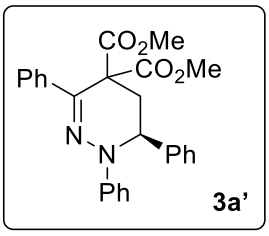
Sodium hydride (2.56 mmol, 60% dispersion in mineral oil, 61 mg) was suspended in DMF (4 mL) under nitrogen. Trimethylsulfoxonium iodide (2.56 mmol, 563 mg) was added, and the solution stirred at ambient temperature for 1 hour. A solution of the appropriate benzylidene malonate (2.13 mmol) in DMF (2 mL) was added, and the reaction mixture allowed to stir at room temperature. Upon completion (as determined by TLC analysis), the solution was poured onto a mixture of ice and 2 M HCl (aq) (10 mL) and extracted with diethyl ether (50 mL). The combined organic layer washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the residue, which was purified by silica gel column chromatography using ethyl acetate and hexane.

Preparation of Chiral Cyclopropanes. To a suspension of NaH (7.93 mmol, 60% oil dispersion, 190 mg) in THF (150 mL) cooled to 0 °C was added dimethyl malonate (7.93 mmol, 1.05 g), and the resulting slurry stirred for 20 min. Bis-mesylate (3.96 mmol, 1.039 g) in THF (50 mL) was then added dropwise over 30 min. The reaction mixture was allowed to warm to RT and brought to reflux overnight. Reaction mixture was cooled to 0 °C, slowly quenched with water and extracted with EtOAc (20 mL). Collected organic extracts were washed with 1 M NaOH (3.0 mL), brine (10 mL), and water (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification was carried out on silica gel column chromatography using hexane and ethyl acetate as eluent.

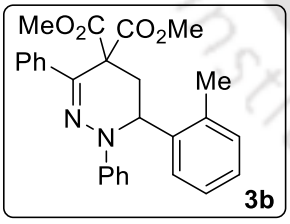
Synthesis of Tetrahydropyridazines. Bisaryl hydrazone **1** (0.2 mmol), cyclopropane **2** (0.22 mmol) and $Cu(OTf)_2$ (0.02 mmol, 7.23 mg) were stirred in $(CH_2Cl)_2$ (1.5 mL) at 50 ^oC using $CaCl_2$ guard tube. Progress of the reaction was monitored using TLC with ethyl acetate and *n*-hexane as an eluent. After completion, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (10 mL), and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using hexane and ethyl acetate as an eluent to give tetrahydropyridazines **3**.

Enantiospecific Tetrahydropyridazine Synthesis. Bisaryl hydrazone **1** (0.2 mmol), optically active cyclopropanes (0.22 mmol) and $Cu(OTf)_2$ (0.02 mmol, 7.23 mg) were stirred at room temperature for 18 h. The work-up procedure was carried out as above described general procedure for the synthesis of tetrahydropyridazines. The *ee* was determined using chiral HPLC analysis.

2.4 Characterization Data

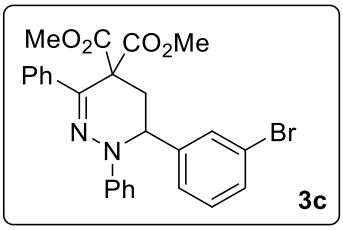


Dimethyl 1,3,6-triphenyl-5,6-dihydro pyridazine-4,4 (1*H*)-dicarboxylate 3a'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; colorless solid; mp 160-161 °C; yield 68% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33-7.31 (m, 5H), 7.29-7.25 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 5.34-5.33 (m, 1H), 3.54 (s, 3H), 3.27 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.13 (s, 3H), 2.93 (dd, *J* = 13.2, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 145.9, 138.2, 138.2, 133.7, 129.1, 128.8, 128.1, 127.8, 127.7, 127.2, 126.9, 120.9, 114.5, 53.9, 53.4, 53.2, 52.5, 33.9; IR (KBr) 2948, 2928, 1753, 1743, 1726, 1594, 1556, 1489, 1449, 1434, 1367, 1348, 1241, 1217, 1172, 1068 cm^{-1}; $[\alpha]_D^{25}$ = +17.95 (c= 0.08, $CHCl_3$); HPLC analysis: 91% ee [Daicel CHIRALCEL AD-H column, hexane/*i*PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 14.44 min (minor), 16.40 min (major)]; HRMS (ESI) m/z [M+H]+ calcd for $C_{26}H_{25}N_2O_4$: 429.1809, found 429.1810.

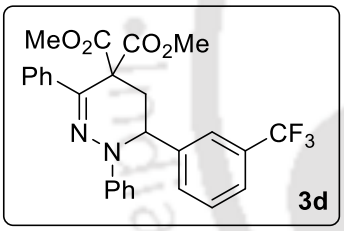


Dimethyl 1,3-diphenyl-6-(o-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-di-carboxylate 3b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 141-142 °C; yield 63% (55.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.22-7.20 (m, 1H), 7.16-7.10 (m, 5H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 8.0 Hz, 1H), 6.82-6.77 (m, 2H), 5.29-5.27 (m, 1H), 3.46 (s, 3H), 3.13 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.06 (s, 3H), 2.71 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 168.6, 145.7, 138.2, 135.7, 134.8, 133.0, 131.1, 129.1, 128.1, 127.8, 127.7, 127.1, 127.0, 126.4, 120.9, 114.4, 53.5, 53.3, 52.6, 51.9, 31.4, 19.2; IR (KBr) 2949, 2853, 1742, 1597, 1562, 1491, 1459,

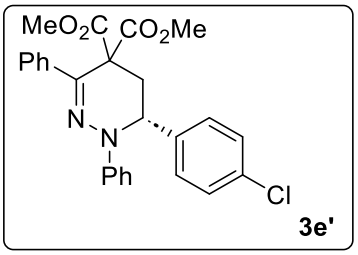
1444, 1462, 1329, 1268, 1249, 1181, 1172, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1965.



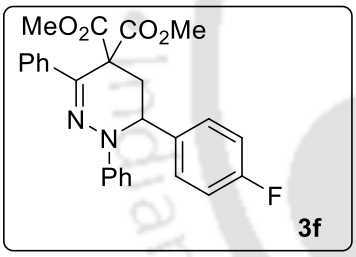
Dimethyl 6-(3-bromophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow solid; mp 159-162 °C; yield 73% (73.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 2H), 7.37-7.33 (m, 4H), 7.30-7.27 (m, 1H) 7.26-7.23 (m, 4H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.93-6.90 (m, 1H), 5.25-5.24 (m, 1H), 3.50 (s, 3H), 3.22 (s, 3H), 3.18 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.87 (dd, *J* =13.8, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 168.5, 145.6, 140.9, 137.9, 133.9, 131.0, 130.5, 129.7, 129.2, 128.2, 128.0, 127.1, 125.6, 122.8, 121.2, 114.4, 53.4, 53.2, 52.7, 33.6; IR (KBr) 3057, 2947, 1752, 1745, 1595, 1496, 1425, 1366, 1216, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0913.



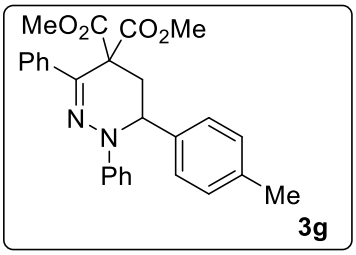
Dimethyl 1,3-diphenyl-6-(3-(trifluoromethyl) phenyl)-5,6-dihydro pyridazine-4,4(1*H*)-dicarboxylate 3d. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.25; colorless solid; mp 80-82 °C; yield 69% (68.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.54-7.52 (m, 2H), 7.42-7.35 (m, 3H), 7.32-7.24 (m, 6H), 6.95-6.92 (m, 1H), 5.37-5.35 (m, 1H), 3.53 (s, 3H), 3.24 (dd, *J* = 13.6, 2.8Hz, 1H), 3.12 (s, 3H), 2.95 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 168.5, 145.6, 139.6, 137.9, 134.1, 131.3 (q, J_{C-F} = 31.9 Hz), 130.5, 129.4, 129.2, 128.2, 128.0, 127.2, 126.7 (q, J_{C-F} = 270.4 Hz), 124.7 (q, J_{C-F} = 3.3 Hz), 123.7 (q, J_{C-F} = 3.7 Hz), 121.3, 114.4, 53.5, 53.4, 53.2, 52.6, 33.5; IR (KBr) 2953, 2924, 2852, 1734, 1597, 1559, 1496, 1444, 1434, 1367, 1328, 1265, 1243, 1166, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}F_3N_2O_4$: 497.1683, found 497.1688.



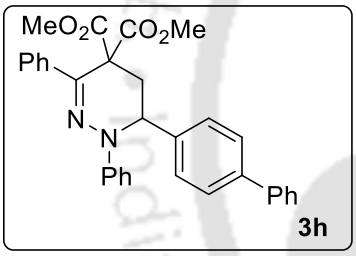
Dimethyl 6-(4-chlorophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3e'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.43; brown solid; mp 190-192 °C; yield 74% (68.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 6.8 Hz, 2H), 7.33-7.25 (m, 7H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.95-6.91 (m, 1H), 5.29-5.27 (m, 1H), 3.53 (s, 3H), 3.22-3.18 (m, 4H), 2.91 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.4, 145.6, 138.8, 136.6, 134.5, 133.2, 129.1, 128.7, 128.3, 128.2, 127.7, 126.7, 121.1, 114.4, 53.7, 53.4, 53.1, 52.5, 33.6; IR (KBr) 2950, 1746, 1760, 1596, 1577, 1494, 1457, 1443, 1365, 1266, 1241, 1216, 1067 cm^{-1}; $[\alpha]_D^{25}$ = +10.39 (c= 0.08, $CHCl_3$); HPLC analysis: 89% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 18.01 min (major), 23.57 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found 463.1440.



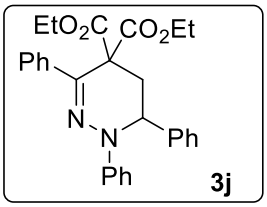
Dimethyl 6-(4-fluorophenyl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.42; brown solid; mp 168-169 °C; yield 77% (68.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.28 (d, 7.2 Hz, 1H), 7.23-7.22 (m, 4H),7.13-7.09 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.91-6.87 (m, 1H), 5.26-5.24 (m, 1H), 3.49 (s, 3H), 3.18-3.15 (m, 4H), 2.86 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.6, 163.4 (J_{C-F} = 244.9 Hz), 145.7, 138.0, 133.94, 133.90, 129.1, 128.7 (J_{C-F} = 8.1 Hz), 128.1, 127.9, 127.2, 121.1, 115.8 (J_{C-F} = 21.5 Hz), 114.4, 53.36, 53.30, 53.2, 52.5, 33.9; IR (KBr) 2949, 1741, 1596, 1560, 1456, 1489, 1345, 1260, 1218, 1155, 1091, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1731.



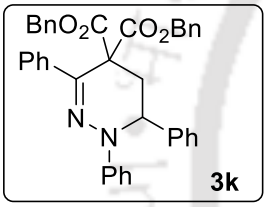
Dimethyl 1,3-diphenyl-6-(*p*-tolyl)-5,6-dihydropyridazine-4,4-(1*H*)-dicarboxylate 3g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; colorless solid; mp 167-168° C; yield 79% (69.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32-7.29 (m, 3H),7.28-7.25 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.30-5.28 (m, 1H), 3.53 (s, 3H), 3.23 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.14 (s, 3H), 2.89 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.8, 138.2, 137.3, 134.9, 133.4, 129.4, 129.0, 128.1, 127.7, 127.1, 126.8, 120.8, 114.4, 53.5, 53.3, 53.2, 52.5, 33.9, 21.2; IR (KBr) 2949, 1740, 1597, 1556, 1452, 1364, 1260, 1243, 1189, 1173, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1961.



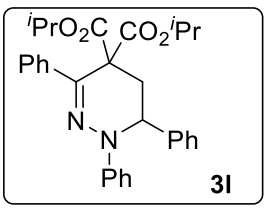
Dimethyl 6-([1,1'-biphenyl]-4-yl)-1,3-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.33; colorless solid; mp 86-87 °C; yield 71% (71.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.58-7.54 (m, 4H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.40-7.25 (m, 10H), 6.94 (t, *J* = 6.8 Hz, 1H), 5.39-5.36 (m, 1H), 3.54 (s, 3H), 3.29 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.13 (s, 3H), 2.95 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.6, 145.9, 140.6, 140.5, 138.2, 137.2, 133.7, 129.1, 129.0, 128.1, 127.8, 127.6, 127.45, 127.42, 127.2, 127.1, 121.0, 114.5, 53.6, 53.4, 53.3, 52.5, 33.8; IR (KBr) 2950, 2924, 2852, 1734, 1598, 1557, 1493, 1443, 1366, 1263, 1242, 1225, 1206, 1112, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{29}N_2O_4$: 505.2122, found 505.2126.



Diethyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.68; brown solid; mp 125-126 °C; yield 77% (70.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.20-7.11 (m, 8H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.79 (t, *J* = 6.8 Hz, 1H), 5.20-5.18 (m, 1H), 3.97-3.89 (m, 1H), 3.87-3.79 (m, 1H), 3.51-3.43 (m, 1H), 3.32-3.24 (m, 1H), 3.11 (dd, *J* = 13.6, 2.8 Hz, 1H), 2.79 (dd, *J* = 13.2, 5.6 Hz, 1H), 0.92 (t, *J* = 6.8 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 168.2, 145.9, 138.5, 138.3, 134.3, 129.0, 128.7, 127.9, 127.79, 127.72, 127.6, 126.9, 120.8, 114.5, 62.4, 61.8, 54.0, 53.7, 33.8, 13.7, 13.6; IR (KBr) 2925, 1749, 1721, 1594, 1561, 1444, 1490, 1364, 1329, 1266, 1226, 1176, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_4$: 457.2122, found 457.2131.

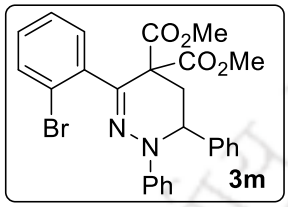


Dibenzyl 1,3,6-triphenyl-5,6-dihydro pyridazine-4,4(1*H*)-dicarboxylate 3k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.65; yellow solid; mp 80-81 °C; yield 79% (91.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 2H), 7.21-7.11 (m, 16H), 7.09-7.07 (m, 2H), 6.98-6.96 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 2H), 6.81-6.77 (m, 1H), 5.18-5.16 (m, 1H), 4.85-4.77 (m, 2H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.14 (d, *J* = 12.4 Hz, 1H), 3.15 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.83 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 168.1, 145.8, 138.4, 138.1, 135.0, 134.6, 133.8, 129.0, 128.8, 128.6, 128.55, 128.53, 128.3, 128.1, 127.8, 127.7, 127.4, 127.0, 120.9, 114.6, 68.2, 67.5, 54.0, 53.9, 53.7, 34.1; IR (KBr) 2923, 2858, 1732, 1638, 1597, 1492, 1454, 1171, 1116, 1064 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{38}H_{33}N_2O_4$: 581.2435, found 581.2447.

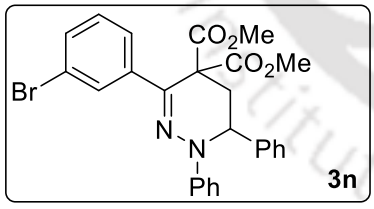


Diisopropyl 1,3,6-triphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3l. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.66; yellow solid; mp 112-113

°C; yield 76% (73.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.38-7.36 (m, 2H), 7.32-7.25 (m, 7H), 7.23-7.20 (m, 3H), 6.89 (t, *J* = 6.8 Hz, 1H), 5.27-5.25 (m, 1H), 4.89 (m, 1H), 4.27 (m, 1H), 3.15 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.92 (dd, *J* = 13.2, 5.6 Hz, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 166.9, 144.9, 138.0, 137.4, 133.9, 127.9, 127.7, 127.0, 126.8, 126.77, 126.72, 125.9, 119.7, 113.7, 69.2, 69.1, 53.3, 53.1, 33.1, 20.48, 20.41, 20.2, 20.0; IR (KBr) 2981, 1734, 1637, 1497, 1455, 1372, 1341, 1266, 1238, 1226, 1204, 1175, 1106, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{33}N_2O_4$: 485.2435, found 485.2447.

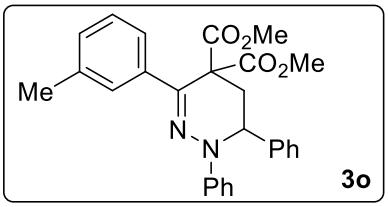


Dimethyl-3-(2-bromophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3m. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; brown solid; mp 108-109 °C; yield 64% (64.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.27-7.21 (m, 3H), 7.20-7.15 (m, 3H), 7.13-7.08 (m, 5H), 6.81-6.77 (m, 1H), 5.22-5.20 (m, 1H), 3.33 (s, 3H), 3.03-3.02 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.6, 146.1, 138.64, 138.61, 133.0, 132.3, 132.0, 129.5, 129.0, 128.7, 127.7, 127.1, 126.8, 124.8, 121.1, 114.8, 54.94, 54.91, 53.1, 52.5, 32.4; IR (KBr) 2951, 2924, 2853, 1735, 1597, 1573, 1496, 1450, 1432, 1367, 1330, 1264, 1238, 1171, 1066 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0915.

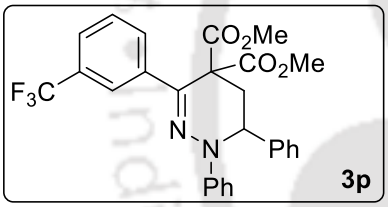


Dimethyl-3-(3-bromophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.39; colorless solid; mp 141-142 °C; yield 74% (74.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.28-7.23 (m, 5H), 7.21 (t, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.96-6.93 (m, 1H), 5.33-5.32 (m, 1H), 3.58 (s, 3H), 3.25 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 168.4, 145.6, 140.1, 137.8, 131.9, 130.6, 130.0, 129.6, 129.2, 128.8, 127.8, 126.8, 125.6, 122.3, 121.3, 114.6, 53.9, 53.5, 53.1, 52.6, 33.7; IR (KBr) 2950, 2924, 1741, 1734, 1595,

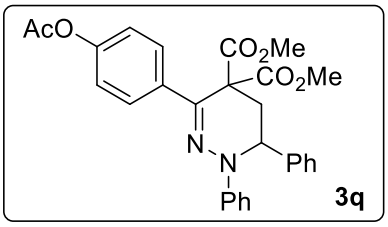
1497, 1328, 1262, 1218, 1060 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.0915.



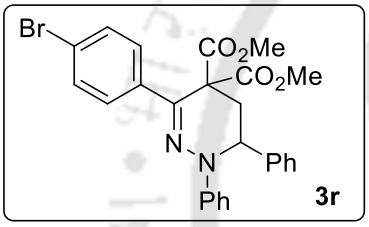
Dimethyl 1,6-diphenyl-3-(*m*-tolyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3o. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 98-99 °C; yield 80% (70.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.22-7.12 (m, 8H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.83-6.79 (m, 1H), 5.22-5.20 (m, 1H), 3.44 (s, 3H), 3.13 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.02 (s, 3H), 2.81 (dd, *J* = 13.6, 5.6 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 168.7, 145.9, 138.2, 138.1, 137.6, 133.8, 129.1, 128.8, 128.6, 128.0, 127.8, 127.7, 126.9, 124.3, 120.8, 114.4, 53.8, 53.35, 53.32, 52.5, 33.9, 21.9; IR (KBr) 2952, 2924, 2853, 1736, 1687, 1596, 1559, 1496, 1433, 1265, 1226, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1973.



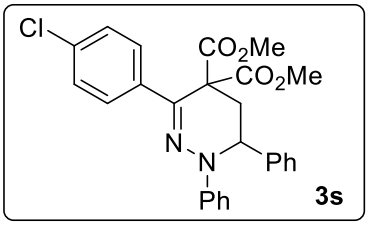
Dimethyl 1,6-diphenyl-3-(3-(trifluoromethyl)phenyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.25; colorless solid; mp 98-99 °C; yield 70% (69.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.33-7.23 (m, 7H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.98-6.91 (m, 1H), 5.36-5.34 (m, 1H), 3.56 (s, 3H), 3.27 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.13 (s, 3H), 2.91 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.4, 145.6, 138.9, 137.9, 132.0, 130.6, 130.4, 130.3, 129.2, 128.8, 128.6, 127.9, 126.8, 124.2 (q, J_{C-F} =3.6 Hz), 123.9 (q, J_{C-F} =3.6 Hz), 121.5, 114.6, 54.0, 53.4, 53.2, 52.6, 33.8; IR (KBr) 2955, 2923, 1761, 1727, 1592, 1565, 1497, 1488, 1369, 1339, 1266, 1219, 1168, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}F_3N_2O_4$: 497.1683, found: 497.1689.



Dimethyl 3-(4-acetoxyphenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane, R_f = 0.29; colorless solid; mp 168-169 °C; yield 63% (61.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.31-7.23 (m, 7H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 9.0 Hz, 2H), 6.93-6.90 (m, 1H), 5.32-5.31 (m, 1H), 3.54 (s, 3H), 3.24 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.90 (dd, *J* = 13.2, 5.4 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 169.5, 168.6, 150.3, 145.7, 138.0, 135.9, 132.7, 129.1, 128.8, 128.2, 127.7, 126.8, 121.1, 121.0, 114.4, 53.7, 53.4, 53.3, 52.6, 33.7, 21.4; IR (KBr) 2924, 2850, 1750, 1686, 1597, 1497, 1435, 1369, 1197 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_6$: 487.1864, found 487.1860.

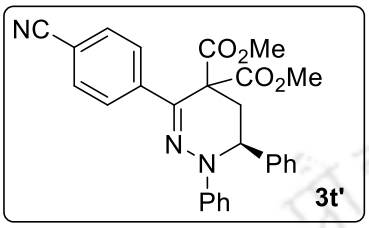


Dimethyl 3-(4-bromophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.39; yellow solid; mp 187-188 °C; yield 75% (75.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.21-7.11 (m, 7H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.85-6.80 (m, 1H), 5.22- 5.20 (m, 1H), 3.45 (s, 3H), 3.13 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.00 (s, 3H), 2.77 (dd, *J* = 13.2, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.3, 145.5, 137.7, 137.0, 132.2, 131.0, 128.9, 128.6, 128.5, 127.6, 126.6, 121.7, 121.0, 114.3, 53.7, 53.2, 53.0, 52.4, 33.5; IR (KBr) 2951, 2924, 2853, 1734, 1636, 1597, 1549, 1497, 1489, 1332, 1266, 1244, 1226, 1173, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}BrN_2O_4$: 507.0914, found 507.1341.

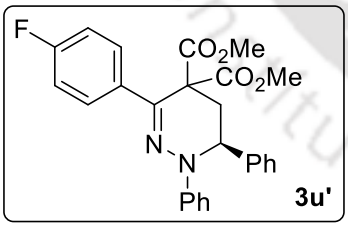


Dimethyl 3-(4-chlorophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.41; brown solid; mp 151-152 °C; yield 81% (74.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4

Hz, 2H), 7.33-7.29 (m, 4H), 7.28-7.23 (m, 5H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.94-6.92 (m, 1H), 5.33-5.31 (m, 1H), 3.56 (s, 3H), 3.25 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 168.5, 145.6, 137.9, 136.7, 133.6, 132.3, 129.1, 128.8, 128.4, 128.2, 127.8, 126.8, 121.2, 114.4, 53.8, 53.4, 53.1, 52.6, 33.7; IR (KBr) 2952, 1755, 1726, 1598, 1549, 1498, 1489, 1451, 1399, 1373, 1337, 1212, 1173, 1068 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found: 463.1429.

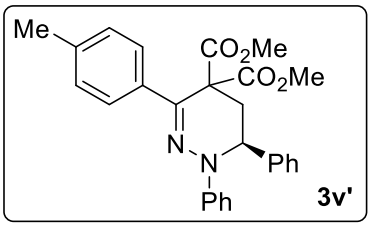


Dimethyl 3-(4-cyanophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3t'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.21; yellow solid; mp 178-179 °C; yield 64% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 9.0 Hz, 2H), 7.32-7.24 (m, 7H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.00-6.95(m, 1H), 5.37-5.36 (m, 1H), 3.58 (s, 3H), 3.29 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.87 (dd, *J* = 13.8, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.2, 145.4, 142.5, 137.5, 131.9, 131.4, 129.2, 128.9, 128.0, 127.2, 126.7, 121.9, 119.3, 114.9, 110.6, 54.1, 53.5, 52.8, 52.7, 33.8; IR (KBr) 2949, 1734, 1597, 1563, 1494, 1450, 1368, 1329, 1260, 1185, 1108, 1034 cm^{-1}; $[\alpha]_D^{25}$ = +24 (c= 0.1, $CHCl_3$); HPLC analysis: 95% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 215 nm, t_R = 38.32 min (minor), 48.39 min (major)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}N_3O_4$: 454.1761, found 454.1770.

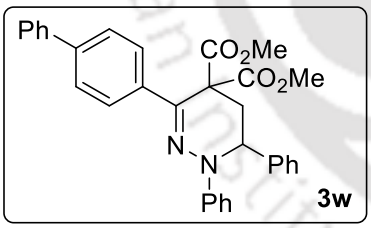


Dimethyl 3-(4-fluorophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3u'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.42; colorless solid; mp 175-176 °C; yield 76% (67.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78-7.75 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.28-7.23 (m, 5H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.05 (t, *J* = 8.4 Hz, 2H), 6.93-6.90 (m, 1H), 5.32-5.31 (m, 1H), 3.53 (s, 3H), 3.24 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.89 (dd, *J* = 13.2, 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 168.6, 163.4 (J_{C-F} = 245.7 Hz), 145.7, 138.0, 134.4 (J_{C-F} = 3.3 Hz), 132.6, 129.1, 129.1 (J_{C-F} = 7.8 Hz), 128.8, 127.8, 126.8, 121.0, 115.1 (J_{C-F} = 21.3 Hz), 114.4, 53.7, 53.4, 53.4, 52.6, 33.6; IR (KBr) 2947, 1750,

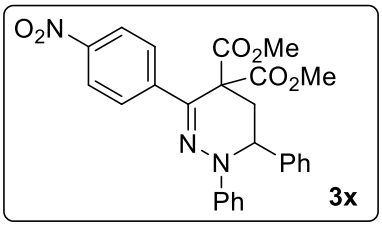
1738, 1600, 1554, 1508, 1496, 1453, 1328, 1240, 1216, 1174, 1160, 1067 cm^{-1}; $[\alpha]_D^{25}$ = +32 (c=0.1, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALPAK IC column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 8.40 min (major), 9.80 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1718.



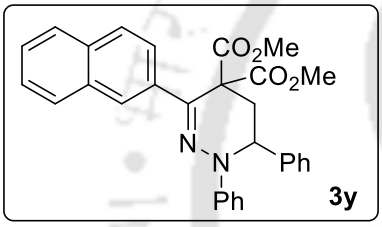
Dimethyl 1,6-diphenyl-3-(p-tolyl)-5,6-dihydropyridazine-4,4-(1*H*)-dicarboxylate 3v'. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yellow solid; mp 141-142 °C; yield 78% (69 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.31-7.28 (m, 4H), 7.25 (t, *J* = 7.2 Hz, 3H), 7.18-7.16 (m, 4H), 6.91 (t, *J* = 7.2 Hz, 1H), 5.31-5.30 (m, 1H), 3.55 (s, 3H), 3.24 (dd, *J* = 13.8, 3.0 Hz, 1H), 3.11 (s, 3H), 2.91 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.9, 138.2, 137.6, 135.4, 133.7, 129.0, 128.8, 128.7, 127.6, 127.0, 126.8, 120.7, 114.3, 53.6, 53.3, 53.2, 52.5, 33.8, 21.3; IR (KBr) 2949, 1759, 1727, 1595, 1575, 1493, 1449, 1430, 1367, 1327, 1272, 1184, 1071 cm^{-1}; $[\alpha]_D^{25}$ = +29.33 (c=0.15, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALPAK IC column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 12.41 min (major), 14.45 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1965, found 443.1964.



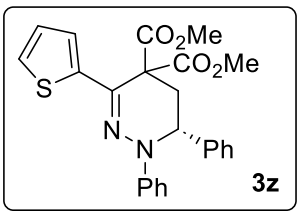
Dimethyl 3-([1,1'-biphenyl]-4-yl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.33; yellow solid; mp 87-88 °C; yield 73% (73.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.63-7.57 (m, 4H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.36-7.32 (m, 1H), 7.30-7.20 (m, 7H), 7.17 (d, *J* = 7.2 Hz, 2H), 6.90 (t, *J* = 6.8 Hz, 1H), 5.33-5.30 (m, 1H), 3.55 (s, 3H), 3.25 (dd, *J* = 13.6, 2.8 Hz, 1H), 3.11 (s, 3H), 2.90 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.6, 145.9, 140.9, 140.3, 138.1, 137.2, 133.3, 129.1, 128.9, 128.8, 127.7, 127.4, 127.1, 126.9, 126.7, 121.0, 114.5, 53.8, 53.4, 53.2, 52.5, 34.0; IR (KBr) 2949, 1758, 1597, 1562, 1541, 1495, 1432, 1450, 1328, 1216, 1172, 1065 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{29}N_2O_4$: 505.2122, found 505.2134.



Dimethyl 3-(4-nitrophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.16; yellow solid; mp 182-183 °C; yield 61% (57.7 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.6 Hz, 2H), 7.95 (d, *J* = 9.6 Hz, 2H), 7.33-7.30 (m, 5H), 7.28-7.25 (m, 2H) 7.15 (d, *J* = 6.6 Hz, 2H), 7.01-6.98 (m, 1H), 5.389-5.384 (m, 1H), 3.59 (s, 3H), 3.33 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 168.2, 146.7, 145.3, 144.3, 137.4, 131.1, 129.3, 128.9, 128.0, 127.2, 126.7, 123.5, 122.1, 115.0, 54.2, 53.7, 52.83, 52.81, 33.8; IR (KBr) 2956, 2924, 2852, 1733, 1596, 1543, 1512, 1491, 1451, 1435, 1378, 1366, 1263, 1213, 1105, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}N_3O_6$: 474.1660, found 474.1659.

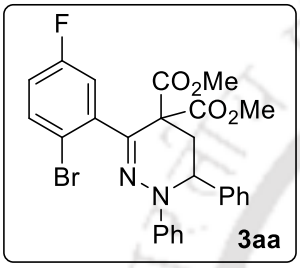


Dimethyl 3-(naphthalen-2-yl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicar-boxylate 3y. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.31; brown solid; mp 182-183 °C; yield 69% (65.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 3.0 Hz, 1H), 7.96 (s, 1H), 7.75-7.71 (m, 3H), 7.38-7.33 (m, 2H), 7.24-7.14 (m, 7H), 7.12-7.08 (m, 2H), 6.83 (t, *J* = 7.2 Hz, 1H), 5.26-5.23 (m, 1H), 3.39 (s, 3H), 3.19 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.03 (s, 3H), 2.84 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.7, 145.9, 138.2, 135.7, 133.6, 133.3, 133.0, 129.1, 128.8, 128.7, 127.7, 127.6, 127.6, 126.9, 126.1, 126.1, 126.0, 125.4, 121.1, 114.6, 53.9, 53.4, 53.3, 52.5, 34.0; IR (KBr) 2948, 1754, 1726, 1595, 1557, 1495, 1450, 1431, 1365, 1248, 1223, 1174, 1105, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{30}H_{27}N_2O_4$: 479.1965, found 479.1971.

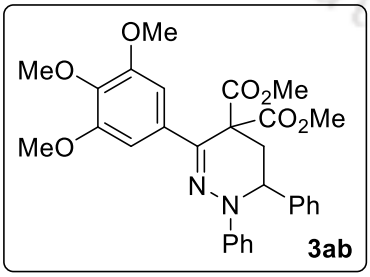


Dimethyl 1,6-diphenyl-3-(thiophen-2-yl)-5,6-dihydropyridazine-4,4-(1*H*)-dicarboxylate 3z'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.32; brown

solid; mp 185-186 °C; yield 70% (60.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.13 (m, 7H), 7.11 (d, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 7.2 Hz, 2H), 6.90-6.89 (m, 1H), 6.85-6.79 (m, 2H), 5.23-5.20 (m, 1H), 3.55 (s, 3H), 3.17 (dd, *J* = 13.2, 2.4 Hz, 1H), 3.03 (s, 3H), 2.80 (dd, *J* = 13.6, 5.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 167.9, 145.4, 143.9, 137.5, 129.8, 129.1, 128.8, 127.3, 126.7, 125.1, 124.4, 121.1, 114.4, 53.58, 53.56, 53.0, 52.6, 33.5; IR (KBr) 2949, 2840, 1747, 1733, 1595, 1558, 1497, 1450, 1433, 1322, 1242, 1225, 1177, 1067 cm^{-1}; $[\alpha]_D^{25}$ = +17.91 (c= 0.07, $CHCl_3$); HPLC analysis: 94% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 19.79 min (minor), 21.03 min (major)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_2O_4S$: 435.1373, found 435.1380.

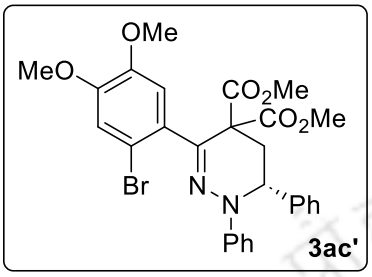


Dimethyl 3-(2-bromo-5-fluorophenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow solid; mp 149-150 °C; yield 66% (69.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 10.0, 3.2 Hz, 1H), 7.51-7.47 (m, 1H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.19-7.08 (m, 7H), 6.86-6.78 (m, 2H), 5.22-5.20 (m, 1H), 3.35 (s, 3H), 3.07-2.98 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.4, 162.6 (J_{C-F} =245.5 Hz), 145.9, 140.3 (J_{C-F} =8.6 Hz), 138.2, 134.0 (J_{C-F} =8.1 Hz), 130.9 (J_{C-F} =2.2 Hz), 129.0, 128.7, 127.8, 127.0, 121.4, 119.6 (J_{C-F} =23.6 Hz), 119.0 (J_{C-F} =3.4 Hz), 116.8 (J_{C-F} =22.2 Hz), 114.8, 54.8, 54.6, 53.2, 52.6, 32.2; IR (KBr) 3068, 2947, 1749, 1738, 1576, 1492, 1325, 1260, 1062 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{23}BrFN_2O_4$: 525.0820, found 525.0821.

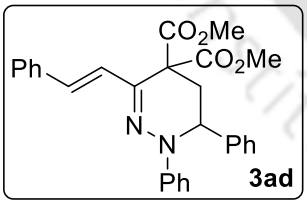


Dimethyl 1,6-diphenyl-3-(3,4,5-trimethoxyphenyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.11; yellow solid; mp 101-102 °C; yield 77% (79.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 3H), 7.26-7.22 (m, 4H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.08 (s, 2H), 6.93-6.89 (m, 1H), 5.33-

5.31 (m, 1H), 3.89 (s, 6H), 3.88 (s, 3H), 3.57 (s, 3H), 3.15 (dd, *J* = 13.2, 2.8 Hz, 1H), 3.12 (s, 3H), 2.89 (dd, *J* = 13.6, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.4, 152.6, 145.5, 137.9, 133.6, 133.0, 128.9, 128.6, 127.6, 126.7, 120.8, 114.1, 104.5, 60.9, 56.0, 53.6, 53.4, 53.2, 52.3, 33.6; IR (KBr) 2951, 2929, 1732, 1687, 1588, 1495, 1451, 1432, 1369, 1261, 1202, 1172, 1063 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{29}H_{31}N_2O_7$: 519.2126, found 519.2132.

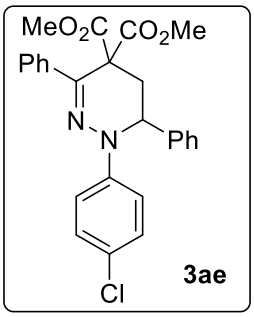


Dimethyl 3-(2-bromo-4,5-dimethoxyphenyl)-1,6-diphenyl-5,6-dihydropyridazine-4,4(1H)-dicarboxylate 3ac'. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.08; brown solid; mp 159-160 °C; yield 67% (75.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.24-7.15 (m, 7H), 7.08 (s, 1H), 6.88-6.85 (m, 1H), 5.27-5.25 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.42 (s, 3H), 3.13-3.06 (m, 2H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.8, 149.2, 147.7, 146.2, 138.6, 131.7, 130.8, 129.0, 128.7, 127.7, 127.1, 121.1, 115.6, 114.9, 114.8, 114.6, 56.3, 56.1, 55.0, 54.8, 53.1, 52.4, 32.1; IR (KBr) 2952, 2850, 1735, 1598, 1497, 1439, 1387, 1328, 1263, 1208, 1172,1065 cm^{-1}; $[\alpha]_D^{25}$ = -42.50 (c= 0.08, $CHCl_3$); HPLC analysis: 92% ee [Daicel CHIRALCEL AD-H column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL /min, λ = 254 nm, t_R = 27.17 min (major), 45.49 min (minor)]; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}BrN_2O_6$: 567.1125, found 567.1122.

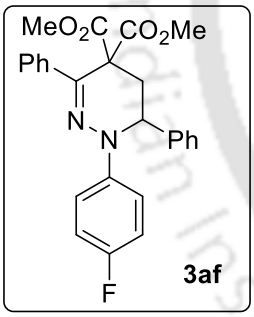


Dimethyl (*E*)-1,6-diphenyl-3-styryl-5,6-dihydro pyridazine-4,4(1*H*)-dicarboxylate 3ad. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.13; yellow solid; mp 96-97 °C; yield 62% (56.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.26-7.21 (m, 2H), 7.19-7.11 (m, 8H), 7.04-6.99 (m, 3H), 6.85-6.81 (m, 1H), 6.78 (d, *J* = 16.4 Hz, 1H), 5.23-5.21 (m, 1H), 3.68 (s, 3H), 3.10 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.06 (s, 3H), 2.82 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 168.3, 145.7, 137.7, 137.6, 133.1, 129.2, 129.1, 128.8, 128.7, 127.77, 127.74, 126.86, 126.82, 126.4, 121.2, 114.7, 53.8, 53.6, 52.7, 52.6, 33.2; IR

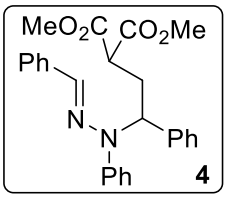
(KBr) 2954, 2923, 2852, 1734,1596, 1542, 1496, 1450, 1434, 1371, 1264, 1224, 1197, 1102, 1067 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_4$: 455.1965, found 455.1966.



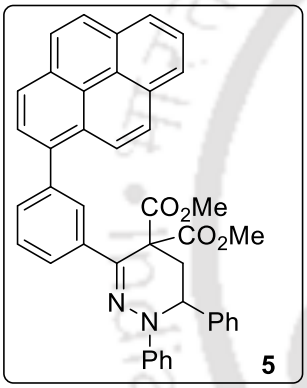
Dimethyl 1-(4-chlorophenyl)-3,6-diphenyl-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 3ae. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yello solid; mp 139-140 °C; yield 76% (70.2 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 3H), 7.26-7.24 (m, 1H), 7.20-7.19 (m, 4H), 7.15 (d, *J* = 7.2 Hz, 2H), 5.27-5.25 (m, 1H), 3.53 (s, 3H), 3.23 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.11 (s, 3H), 2.92 (dd, *J* = 13.8, 6.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 168.5, 144.4, 137.9, 137.7, 134.5, 129.0, 128.9, 128.2, 128.0, 127.9, 127.2, 126.8, 125.8, 115.6, 53.8, 53.38, 53.35, 52.6, 33.9; IR (KBr) 2951, 2924, 1757, 1727, 1557, 1489, 1370, 1329, 1223, 1212, 1069 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}ClN_2O_4$: 463.1419, found 463.1419.



Dimethyl 1-(4-fluorophenyl)-3,6-diphenyl-5,6-dihydropyridazine-4,4-(1*H*)-dicarboxylate 3af. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; yellow solid; mp 97-98 °C; yield 73% (65.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.38-7.25 (m, 6H), 7.22-7.15 (m, 4H), 6.94 (t, *J* = 8.4 Hz, 2H), 5.25-5.23 (m, 1H), 3.54 (s, 3H), 3.21 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.13 (s, 3H), 2.92 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 168.4, 158.8 (J_{C-F} = 237.9 Hz), 142.1 (J_{C-F} = 2.2 Hz), 137.9, 137.8, 133.6, 130.4, 128.6, 127.9, 127.6 (J_{C-F} = 3.1 Hz), 126.9, 126.6, 115.57 (J_{C-F} = 28.9 Hz), 115.50, 54.0, 53.2, 53.1, 52.4, 33.8; IR (KBr) 2952, 2852, 1735, 1689, 1599, 1505, 1444, 1369, 1330, 1266, 1226, 1176, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{24}FN_2O_4$: 447.1715, found 447.1717.



Dimethyl (*E*)-2-(2-(2-benzylidene-1-phenylhydrazineyl)-2-phenyl-ethyl) malonate 4. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; yellow liquid; yield 81% (69.6 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 2H), 7.37-7.31 (m, 6H), 7.30-7.21 (m, 6H), 6.95 (d, *J* = 7.2 Hz, 2H), 4.58 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.89-3.87 (m, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 3.29-3.24 (m, 1H), 2.63-2.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 145.1, 141.1, 136.9, 134.8, 129.7, 128.6, 128.5, 127.8, 127.75, 127.72, 127.1, 126.7, 126.0, 67.9, 52.7, 52.7, 49.6, 33.8; IR (neat) 2924, 2853, 1758, 1728, 1597, 1563, 1494, 1452, 1435, 1364, 1338, 1263, 1228, 1189, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_2O_4$: 431.1965, found 431.1966.



Dimethyl-1,6-diphenyl-3-(3-(pyren-1-yl)phenyl)-5,6-dihydropyridazine-4,4(1*H*)-dicarboxylate 5. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; colorless solid; mp 208-209 °C; yield 78% (48.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28-8.19 (m, 4H), 8.15-8.10 (m, 2H), 8.08-8.02 (m, 4H), 7.91 (d, *J* = 6.8 Hz, 1H), 7.58-7.53 (m, 2H), 7.33-7.26 (m, 6H), 7.24-7.20 (m, 3H), 6.89 (t, *J* = 7.2 Hz, 1H), 5.35-5.33 (m, 1H), 3.57 (s, 3H), 3.27 (dd, *J* = 13.6, 3.2 Hz, 1H), 3.11 (s, 3H), 2.96 (dd, *J* = 13.6, 5.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.8, 168.6, 145.8, 140.9, 138.3, 138.1, 138.0, 133.4, 131.6, 131.2, 130.7, 130.1, 129.5, 129.1, 128.8, 128.7, 128.2, 127.8, 127.64, 127.62, 127.60, 126.9, 126.2, 126.1, 125.6, 125.2, 125.17, 125.13, 125.0, 124.8, 121.0, 114.5, 53.9, 53.4, 52.6, 33.9, 32.1; FT-IR(neat) 2924, 2853, 1758, 1728, 1597, 1563, 1494, 1452, 1364, 1338, 1263, 1228, 1189, 1070 cm^{-1}; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{42}H_{33}N_2O_4$: 629.2435, found 629.2966.

Crystal Structure and Data of 3u'

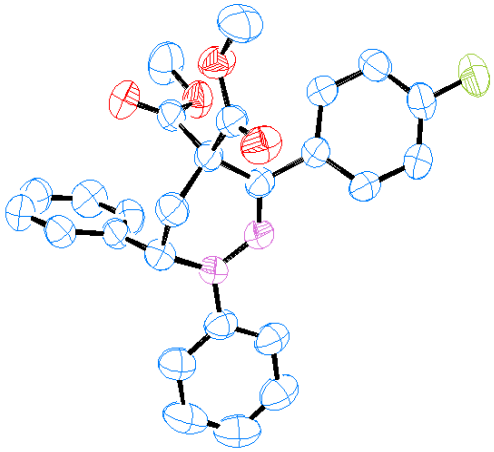


Figure 2. ORTEP diagram of **3u'** with 50% ellipsoid. (CCDC 1895630). H-Atoms are omitted for clarity.

Identification code	**3u´**
CCDC Number	1895630
Empirical formula	$C_{26}H_{23}FN_2O_4$
Formula weight	446.46
Crystal habit, color	Needle / colorless
Crystal size, mm^3	0.29 x 0.24 x 0.18
Temperature, *T*/K	293 (2)
Wavelength, λ/Å	0.71073
Crystal system	orthorhombic
Space group	'P 21 21 21'
Unit cell dimensions	a = 10.2417(18)Å
	b = 10.911(2)Å
	c = 20.105(3)Å
	$\alpha = \beta = \gamma$ = 90.00°
Volume, *V*/$Å^3$	2246.7(7)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.320
Absorption coefficient, μ/mm^{-1}	0.095

$F(000)$	936
θ range for data collection	2.03 to 25.991°
Limiting indices	$-12 \leq h \leq 12$, $-13 \leq k \leq 13$, $-24 \leq l \leq 24$
Reflection collected / unique	4435/2505 [R(int)= 0.1715]
Completeness to θ	100 % (θ = 25.991°)
Absorption correction	none
Max. and min. transmission	0.983/0.973
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	4435/0/ 302
Goodness–of–fit on F^2	0.999
Final R indices [I>2sigma(I)]	$R1$ = 0.0608, $wR2$ = 0.1415
R indices (all data)	$R1$ = 0.1253, $wR2$ = 0.1802

2.5 References

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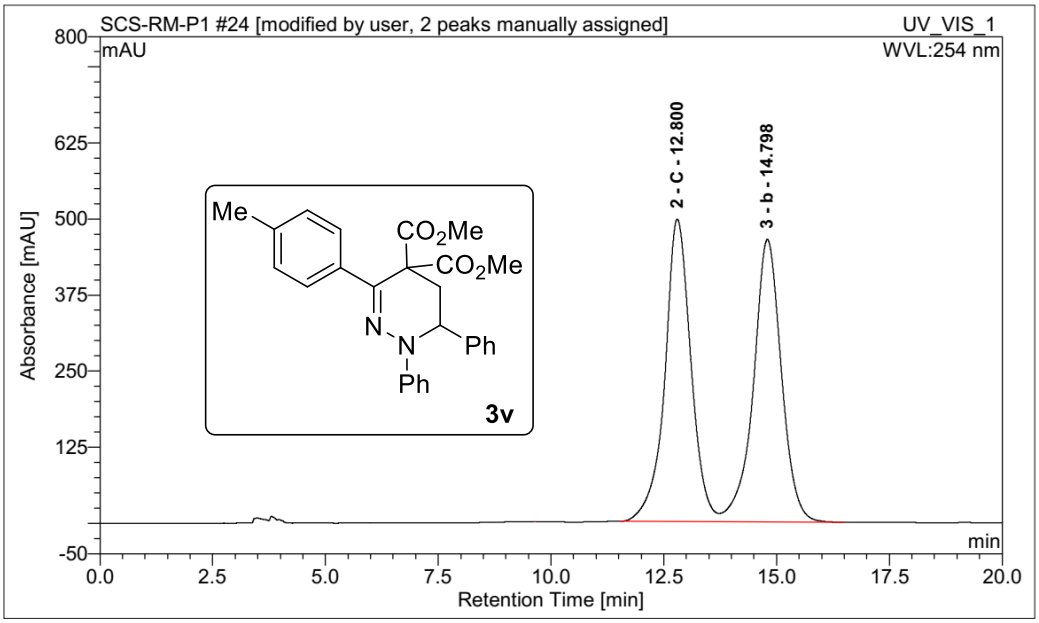
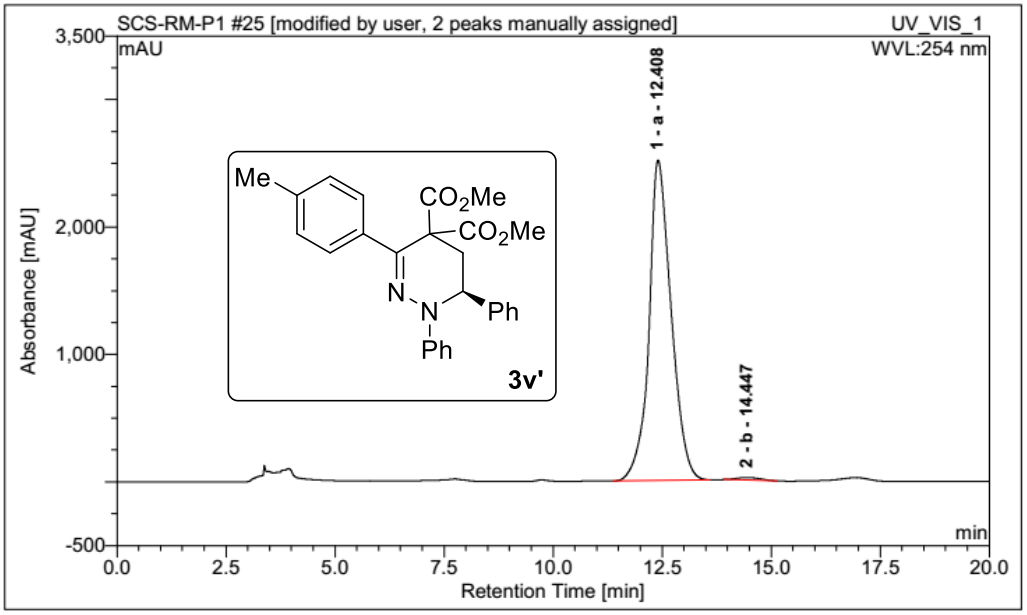
2.6 HPLC chromatograms

MM-4Me-Rac



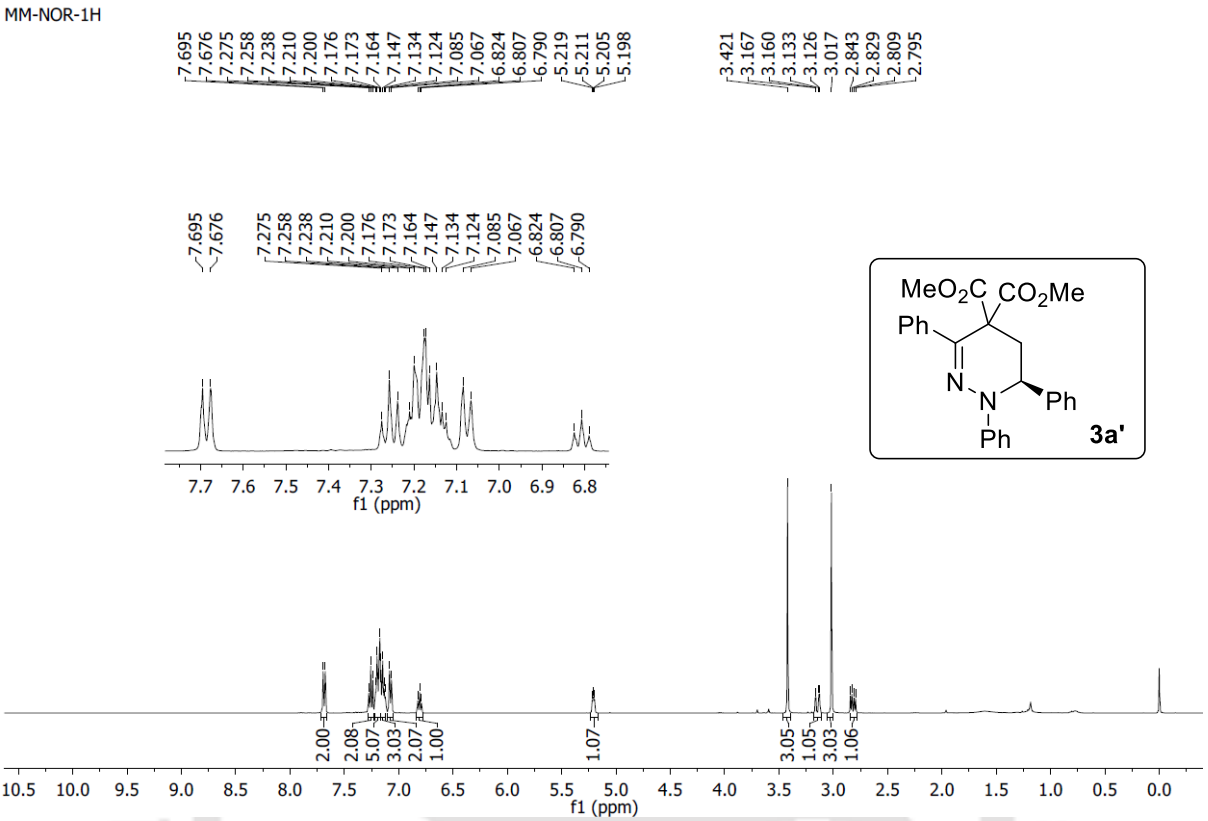
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
2	C	12.80	333.5791	49.84424434	497.2429	n.a.
3	b	14.80	335.664	50.15575566	464.511	n.a.

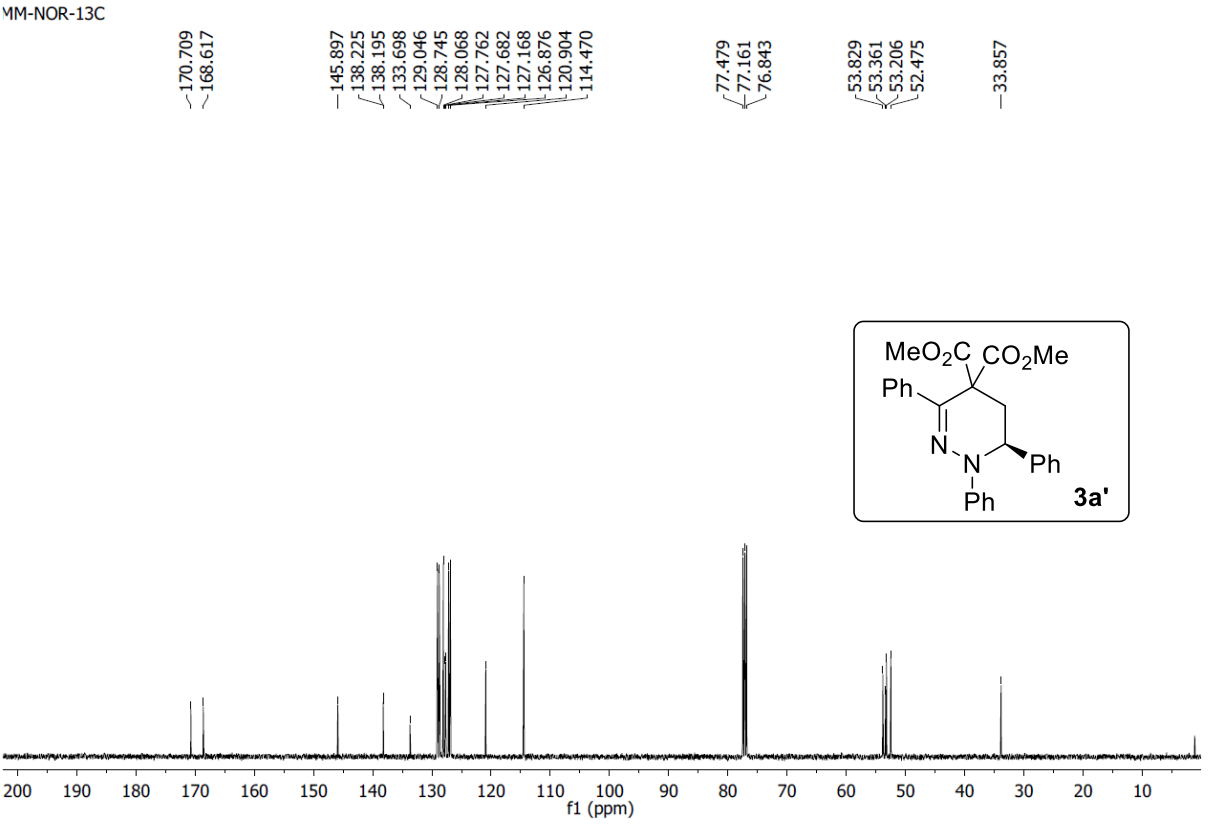
MM-4ME-HYD-CHI

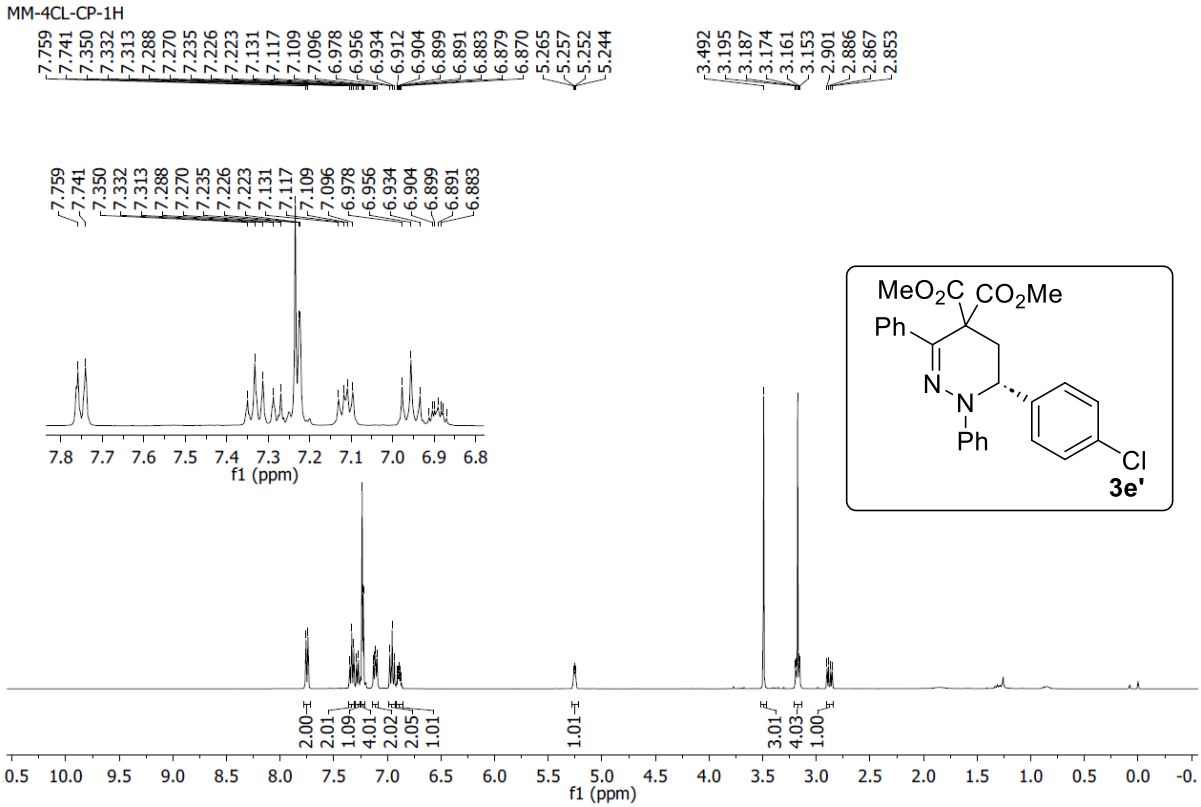


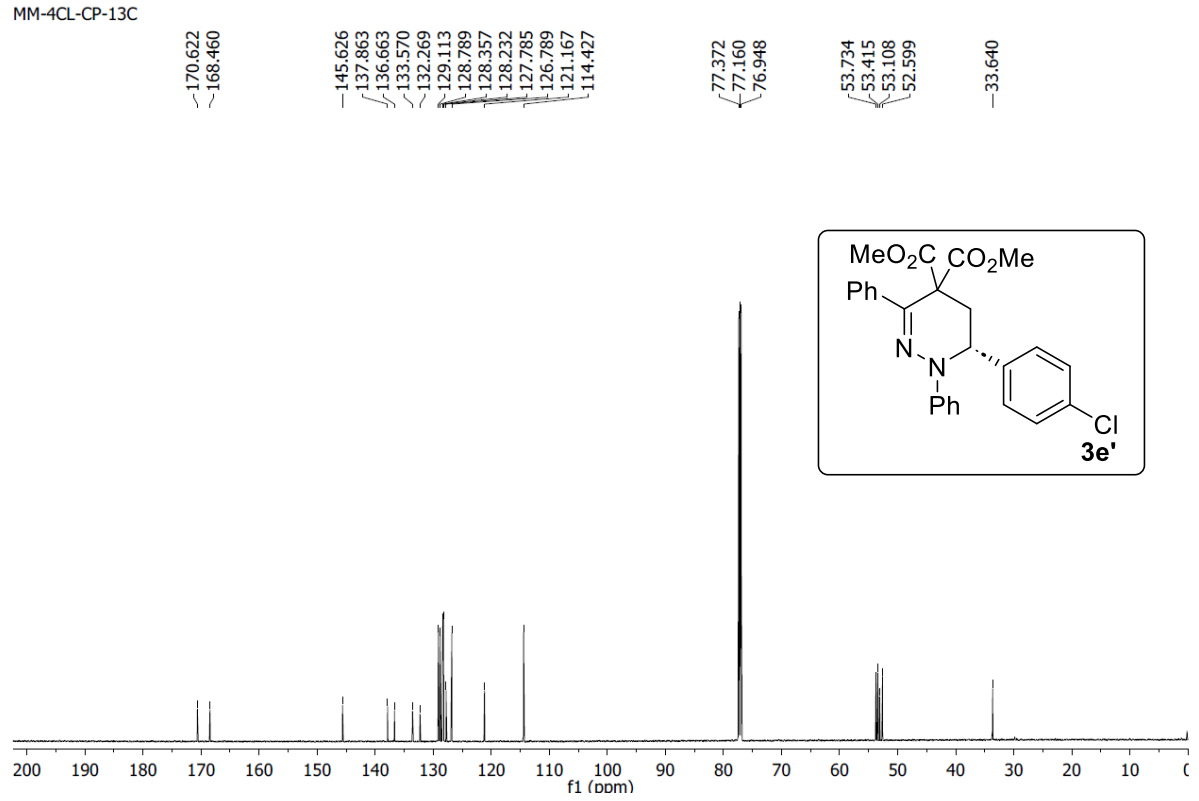
No.	Peak Name	Ret.Time (detected) min	Area mAU*min	Rel.Area(ident.) %	Height mAU	Amount
1	a	12.41	1483.083	99.15069274	2515.169	n.a.
2	b	14.45	12.704	0.8493072578	20.441	n.a.

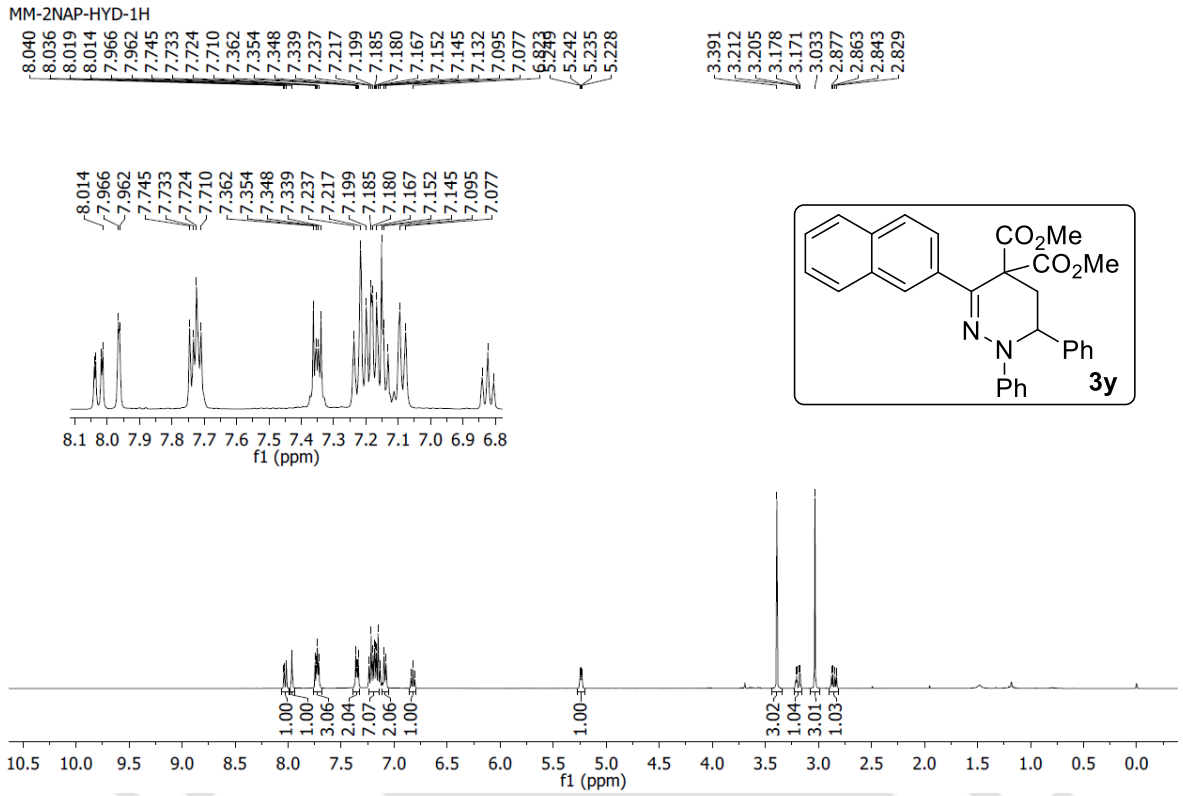
2.7 Selected NMR Spectra

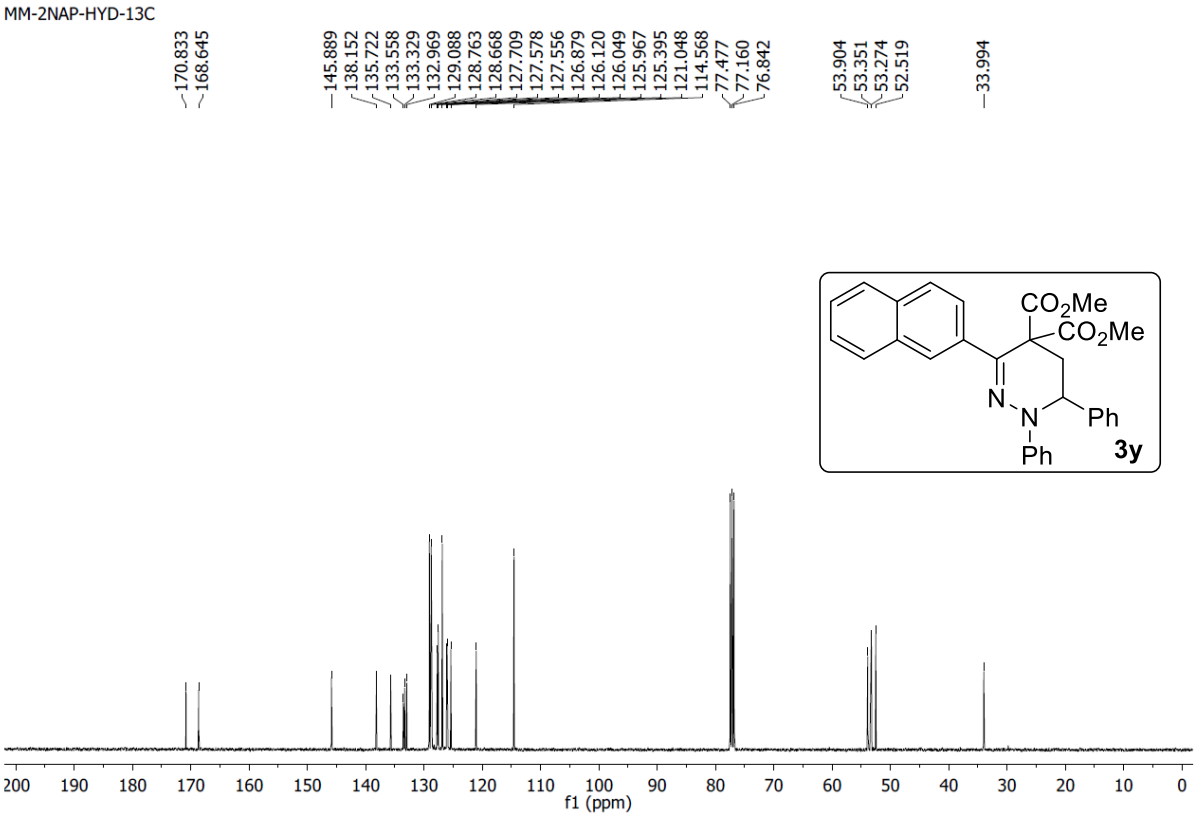






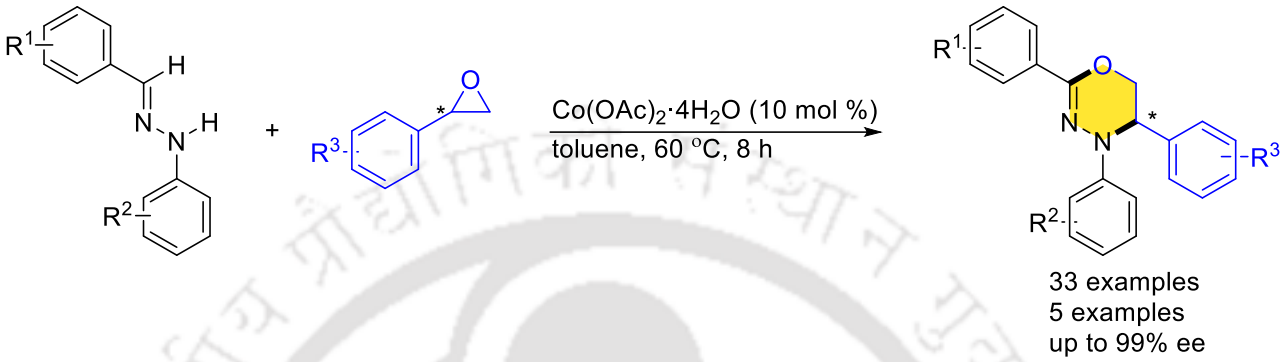






Chapter-III

Cobalt(II)-Catalyzed Stereospecific Synthesis of Oxadiazines

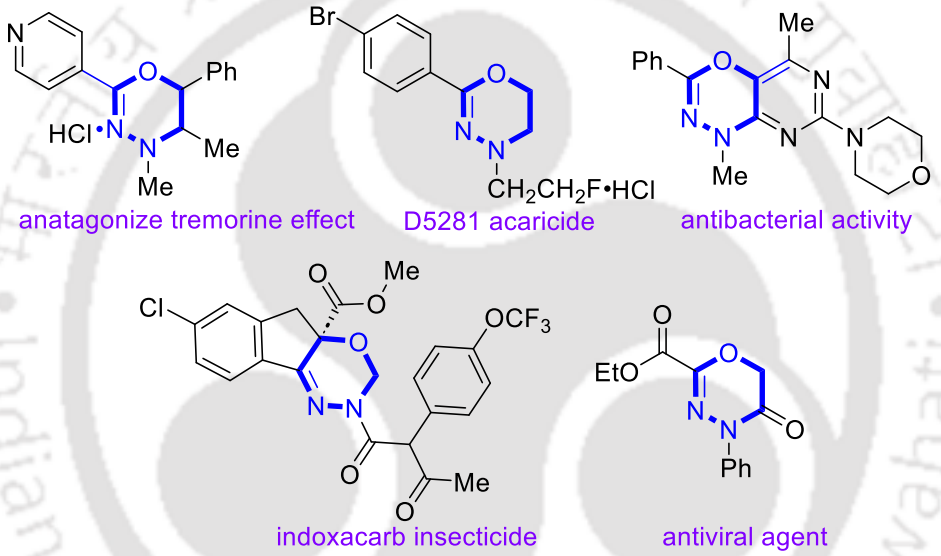


✔ *Aerobic* ✔ *Stereospecific* ✔ *Dual catalysis* ✔ *Tandem C-O and C-N Bond Formation*

Chem. Commun., **2022**, *58*, 7090

Cobalt(II)-Catalyzed Stereospecific Synthesis of Oxadiazines

Heterocyclic compounds with three-heteroatoms are privileged structural frameworks due to their interesting biological and medicinal properties.[1] Among them, oxadiazines are of great interests as they display diverse applications in medicinal and agricultural sciences (Figure 1).[2] Development of effective synthetic methods to expeditiously generate these heterocyclic scaffolds from simple substrates would thus be useful. Epoxides are versatile building blocks and their inherent ring strain can be explored for the selective cleavage of C-C and C-O bonds.[3,4] Few studies are focused on the [3+n]-cycloaddition of epoxides with [1,n] dipoles,[5]



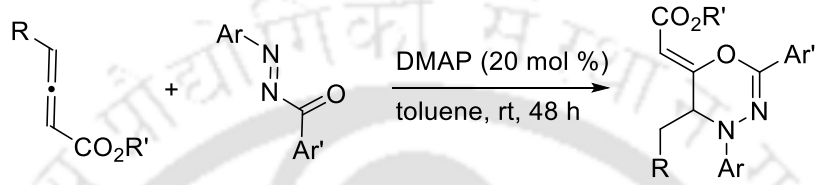
which are attractive as they can provide potential approach for the tandem carbon-carbon and carbon-heteroatom bonds formation that can lead to diverse oxygen containing heterocycles. The annulation through C=C and C=N bonds has been generally observed with reductive cyclization.[6] Further, the C-H functionalization using the transition-metal-catalysis affords a powerful synthetic tool for the construction of regioselective carbon-heteroatom bonds.[7,8] Rh, Ru and Pd-based catalytic systems have been considerably explored, whereas efforts are made on the use of the abundant first-row transition-metals.[9] Cobalt is ecologically benign and readily available whose catalysis for the selective cascade C-N and C-O bond formation would be valuable.[10] In addition, the use of air as the oxidant is attractive as the E-factor can be reduced.[11,12] Herein, we report an aerobic cobalt(II)-catalyzed stereospecific ring expansion of styrene oxides with hydrazones to produce oxadiazines merging the stereospecific ring opening

and oxidative C-H functionalization using air as the oxidant. The reaction takes place by radical pathway and generates H_2O_2 as by-product

3.1 Literature

3.1.1 [4+2]-Cycloaddition

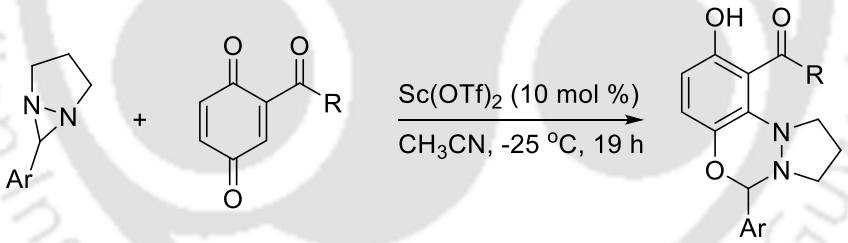
Wang and Meng described an efficient DMAP-catalyzed [2+4]-cycloaddition of allenoates and *N*-acyldiazenes (Scheme 1).[13] The reaction involved embedding three heteroatoms into a six-membered ring and generated 1,3,4-oxadiazine derivatives in moderate to good yields.



Scheme 1. [4+2]-Cycloaddition of Allenoates and *N*-Acyldiazenes

3.1.2 [3+3]-Cycloaddition

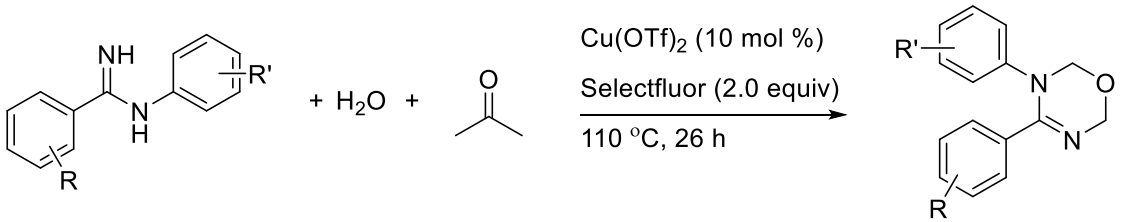
Luo and Wang combinely reported a formal [3+3]-cycloaddition of diaziridines with quinones to synthesize 1,3,4-oxadiazines (Scheme 2).[14] The synergistic activation of diaziridines in presence of $Sc(OTf)_3$ enables the reaction with dipolar quinones.



Scheme 2. Synergistic cycloaddition of diaziridines with quinones

3.1.3 Cycloaddition of Amidines

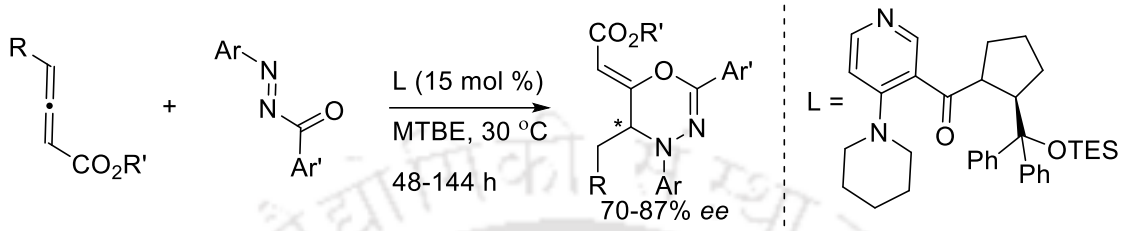
Ma group disclosed an efficient synthesis of 1,3,5-oxadiazines from amidines in wet DMSO (Scheme 3).[15] DMSO acts as a dual carbon synthon and water offered the oxygen atom to construct the oxadiazine ring.



Scheme 3. Cycloaddition of Amidines With DMSO

3.1.4 Cycloaddition of Allenoates

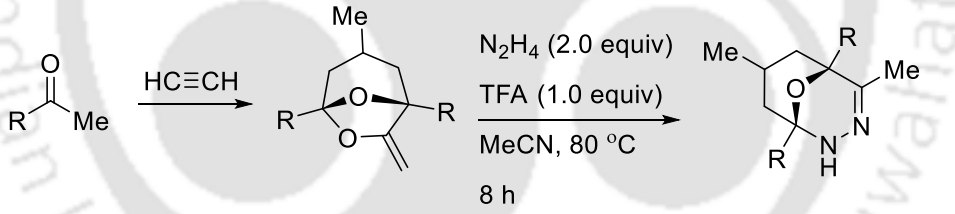
An organocatalytic [4+2]-cycloaddition of allenoates with N-acyldiazines for the synthesis of optically active 1.3.4-oxadiazines was presented by Li and co-workers (Scheme 4).[16] The enantioselective reaction was carried out through L-proline-derived DMAP analogue.



Scheme 4. Asymmetric Synthesis of Oxadiazines

3.1.5 Intramolecular Organization

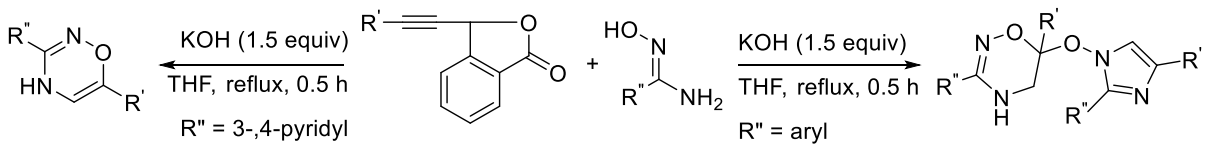
Trofimov and co-workers reported an acid-catalyzed diastereoselective reaction of hydrazine with 6,8-dioxabicyclo[3.2.1]octanes, the products of the superbase-promoted self-organization of acetylene with ketones (Scheme 5).[17] Pharmaceutically related bridgehead dihydro-1,3,4-oxadiazines are synthesized in up to 94% yield



Scheme 5. Diastereoselective Synthesis of Oxadiazines

3.1.6 Migratory Cyclization

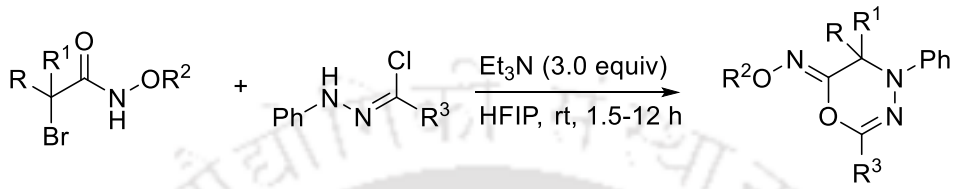
Wen and Li developed a 1,2-migration and cyclization of a variety of alkynylbenziodoxolones (EBXs) and amidoximes under basic conditions for the construction of divergent oxadiazines (Scheme 6).[18] The selectivity was controlled by varying the substituents of the amidoximes under metal-free conditions.



Scheme 6. 1,2-Migration/Cyclization

3.1.7 Dipolar [3+3]-Cycloaddition

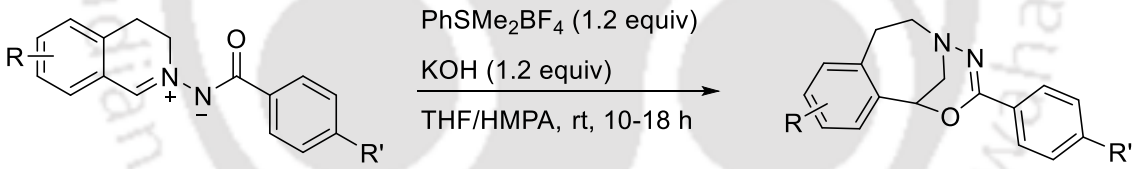
Zhao and co-workers reported a 1,3-dipolar [3+3]-cycloaddition of α-halohydroxamate-based azaoxyallylcations with hydrazonoyl chloride-derived nitrile imines for the synthesis of oxadiazines (Scheme 7).[19] The cycloaddition was prompted by stoichiometric amount of base for the efficient production of desired cycloadduct.



Scheme 7. [3+3]-Cycloaddition of Nitrile Imines with Azaoxyallylcations

3.1.8 Ring Expansion Reaction

Soeta and Ukaji reported a ring expansion reaction of *C,N*-cyclic-*N′*-acyl azomethine imines with sulfonium ylide generated *in situ* from the sulfonium salt for swift delivery of oxadiazines (Scheme 8).[20] A wide range of C,N-cyclic N′-acyl azomethine imines were applicable to this reaction.



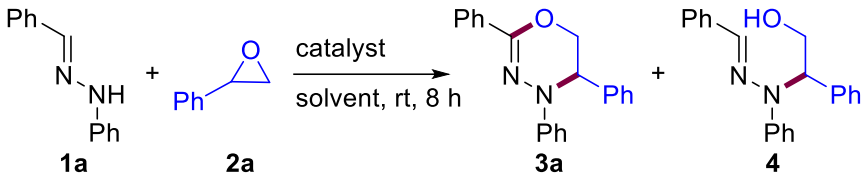
Scheme 8. Ring Expansion of Azomethine Imines

The literatures discussed above focuses on the synthesis of biologically important oxadiazine moieties through cycloaddition reaction as well as intramolecular rearrangement. However, the reaction conditions were either harsh or effective when excess amount of catalysts were used. Therefore, oxiranes can be engaged as a building block for the swift construction of oxadiazines as it contains an O-heteroatom and owing to its high reactivity in presence of a Lewis acid catalyst.

3.2 Present Study

This chapter describes a Co(II)-catalyzed tandem C-C and C-O bond formation of oxiranes with hydrazones, leading to the synthesis of biologically relevant oxadiazine scaffolds. Initial

Table 1. Optimization of the Reaction Conditions[a]



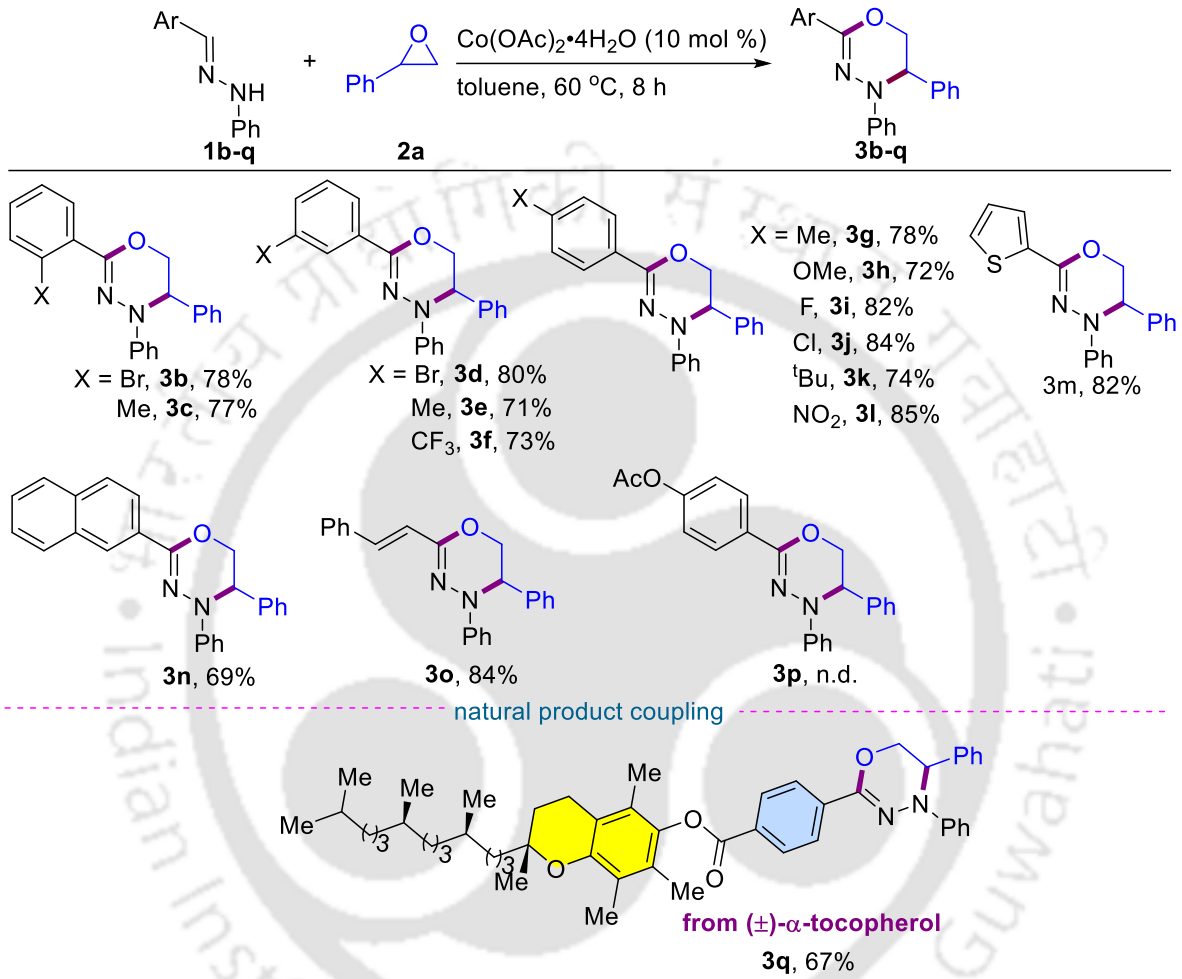
Entry	Catalyst	Solvent	Yield (%)[b]	
			3a	**4**
1	$Bi(OTf)_3$	$(CH_2Cl)_2$	trace	75
2	$Sc(OTf)_3$	$(CH_2Cl)_2$	trace	72
3	$Yb(OTf)_3$	$(CH_2Cl)_2$	trace	68
4	$Cu(OTf)_2$	$(CH_2Cl)_2$	21	69
5	$CoCl_2$	$(CH_2Cl)_2$	40	28
6	$FeCl_3$	$(CH_2Cl)_2$	14	20
7	$Ni(ClO_4)_2•6H_2O$	$(CH_2Cl)_2$	15	25
8	$Co(OAc)_2•4H_2O$	$(CH_2Cl)_2$	54	12
9	$Co(OAc)_2•4H_2O$	CH_2Cl_2	52	25
10	$Co(OAc)_2•4H_2O$	toluene	70	9
11	$Co(OAc)_2•4H_2O$	PhCl	58	27
12	$Co(OAc)_2•4H_2O$	THF	47	25
13[c]	$Co(OAc)_2•4H_2O$	toluene	82	trace
14[d]	$Co(OAc)_2•4H_2O$	toluene	69	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.22 mmol), catalyst (10 mol %), solvent (1.5 mL), rt, 8 h. [b]Isolated yield. [c]Reaction temperature 60 °C. [d]Reaction temperature 80 °C.

optimization studies were conducted using (E)-1-benzylidene-2-phenylhydrazine **1a** and 2-phenyloxirane **2a** as model substrates, exploring various catalysts at different temperatures (Table 1). Promisingly, the reaction proceeded to yield oxadiazine **3a** in 82% yield, with a trace amount of **4**, when the substrates were stirred with 10 mol % $Co(OAc)_2·4H_2O$ in toluene for 8 hours at 60 °C under air (entry 13). Among the catalysts tested, including $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $CoCl_2$, $FeCl_3$, $Ni(ClO_4)_2·6H_2O$, and $Co(OAc)_2·4H_2O$, $Co(OAc)_2·4H_2O$ provided the most favourable result (entries 2-8). Toluene emerged as the solvent of choice,

surpassing CH_2Cl_2, PhCl, and THF, which produced lower yields (entries 9-12). The optimal temperature was found to be 60 °C; increasing the temperature to 80 °C reduced the yield to 69% (entry 14).

Table 2. Substrate Scopes of Hydrazones[a,b]

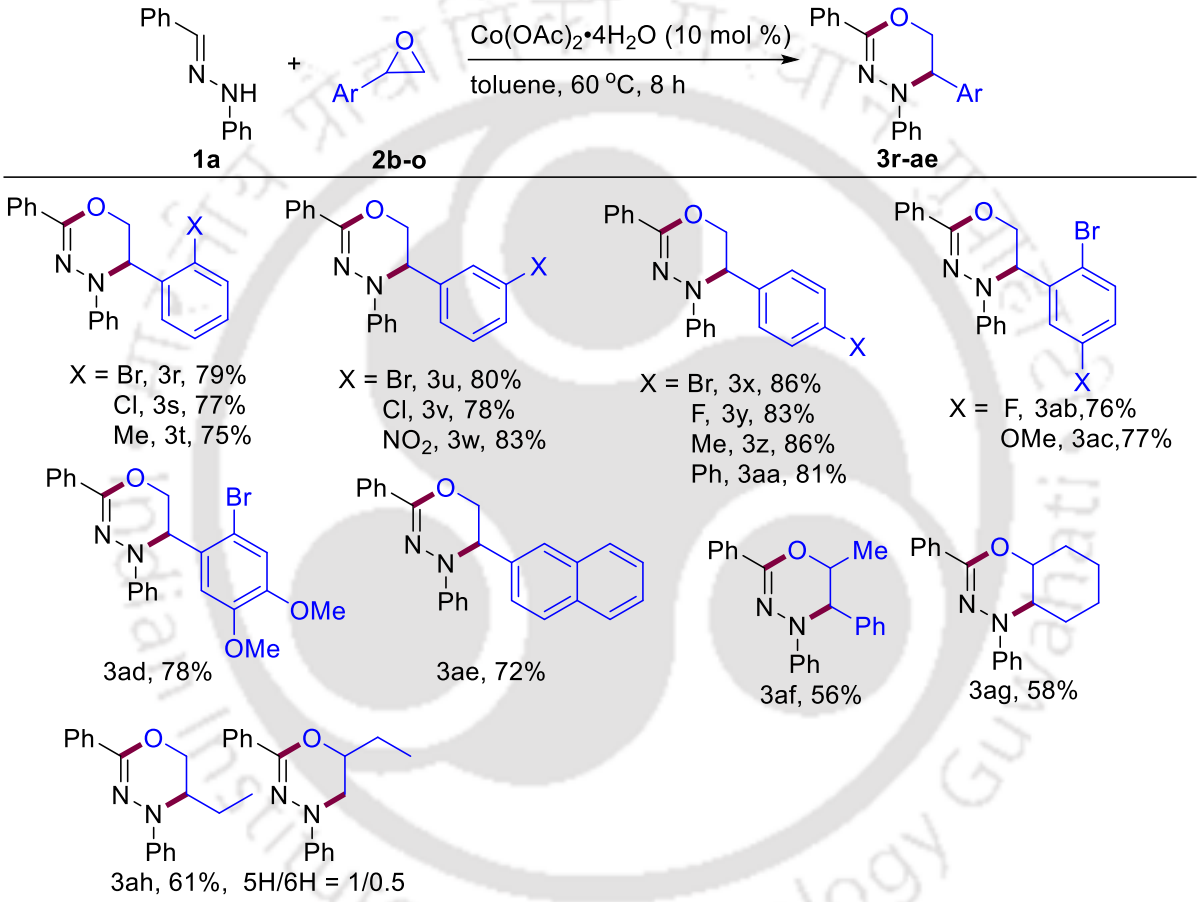


[a]Reaction conditions: **1b-q** (0.2 mmol), **2a** (0.22 mmol), $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), toluene (1.5 mL), 60 °C, 8 h. [b]Isolated yield.

With the optimized reaction conditions established, we explored the substrate scope using substituted hydrazones **1b-q**, with oxirane **2a** as the model substrate (Table 2). Hydrazones carrying substituents at the 2-position of the aryl ring, such as bromo **1b** and methyl **1c** groups, underwent the reaction to yield **3b** and **3c** in 78% and 77% yields, respectively. Transitioning to hydrazones bearing substituents at the 3-position, including bromo **1d**, methyl **1e**, and trifluoromethyl **1f** groups, afforded the heterocycles **3d-f** in 71-80% yields. Hydrazones with both electron-rich and -deficient groups at the 4-position of the aryl ring, such as methyl **1g**,

methoxy **1h**, fluoro **1i**, chloro **1j**, tert-butyl **1k**, and nitro **1l** functionalities, reacted to produce the oxadiazines **3g-l** in 72-85% yields. Moreover, 2-thienyl **1m** and 2-naphthyl **1n** substrates provided **3m** and **3n** in 82% and 69% yields, respectively. Styryl-substituted hydrazone **1o** reacted to yield **3o** in 84% yield, whereas **1p**, bearing the 4-acetoxy group, proved to be an unsuccessful substrate. However, hydrazone **1q** having (±)-α-tocopherol substituent participated to give **3q** in 67% yield.

Table 3. Substrate Scopes of Oxiranes[a,b]



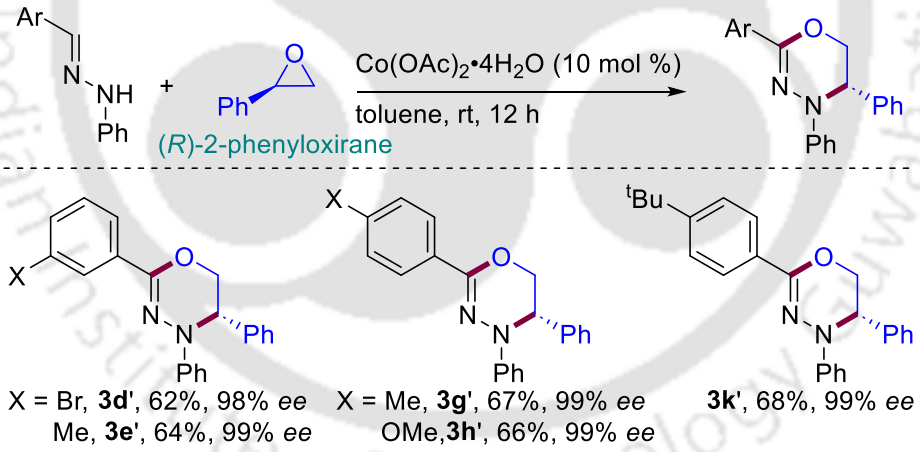
[a]Reaction conditions: **1a** (0.2 mmol), **2b-o** (0.22 mmol), $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), toluene (1.5 mL), 60 °C, 8 h. [b]Isolated yield.

The reaction conditions were extended to include the coupling of various styrene oxides **2b-o** with hydrazone **1a** as the standard substrate (Table 3). Styrene oxides bearing substitutions at the 2-position of the aryl ring, such as bromo **2b**, chloro **2c**, and methyl **2d** groups, underwent the reaction to yield the heterocycles **3r-t** in yields ranging from 75% to 79%. Similar results were observed for styrene oxides with substitutions at the 3-position of the aryl ring, including bromo **2e**, chloro **2f**, and nitro **2g** groups, providing **3u-w** in yields of 78% to 83%.

Additionally, reactions of styrene oxides with substitutions at the 4-position, such as bromo **2h**, fluoro **2i**, methyl **2j**, and phenyl **2k** groups, produced **3x-aa** in yields ranging from 81% to 86%. Furthermore, 2-bromo-5-fluoro **2l**, 2-bromo-5-methoxy **2m**, and 2-bromo-4,5-dimethoxy **2n** substituted styrene oxides reacted smoothly, yielding **3af** in yields of 76% to 78%. Notably, a 2-naphthyl **2o** substrate efficiently produced oxadiazine **3ae** in a yield of 72%. In addition, 2-methyl-3-phenyloxirane **2p** and cyclohexene oxide **2q** underwent cyclization to produce **3af** and **3ag** in 56% and 58% yields. Whereas epoxybutane **2p** gave two inseparable regioisomers in 61% yield.

To elucidate the stereoselectivity, we investigated the reaction of optically active (*R*)-styrene oxide **2a′** with various hydrazones (Table 4). Hydrazones bearing 3-bromo **1d** and 3-methyl **1e** groups yielded **3d′** and **3e′** in 98% and 99% ee, respectively. Likewise, hydrazones featuring 4-methyl **1g**, 4-methoxy **1h**, and 4-*tert*-butyl **1k** groups in the aryl ring produced oxadiazines **3g′**, **3h′** and **3k′** in >99% *ee*. These outcomes suggest an enantiospecific epoxide opening *via* an anti-periplanar pathway, leading to oxidative cyclization.

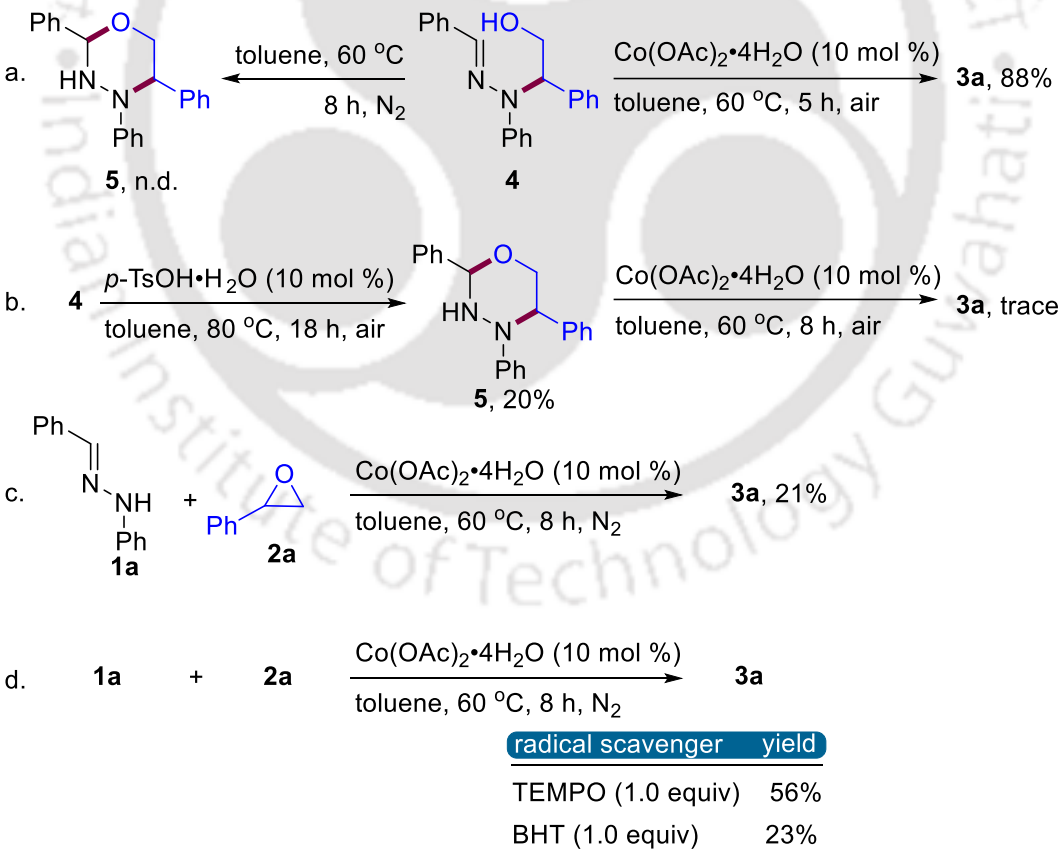
Table 4. Enantiospecific Substrates[a,b]



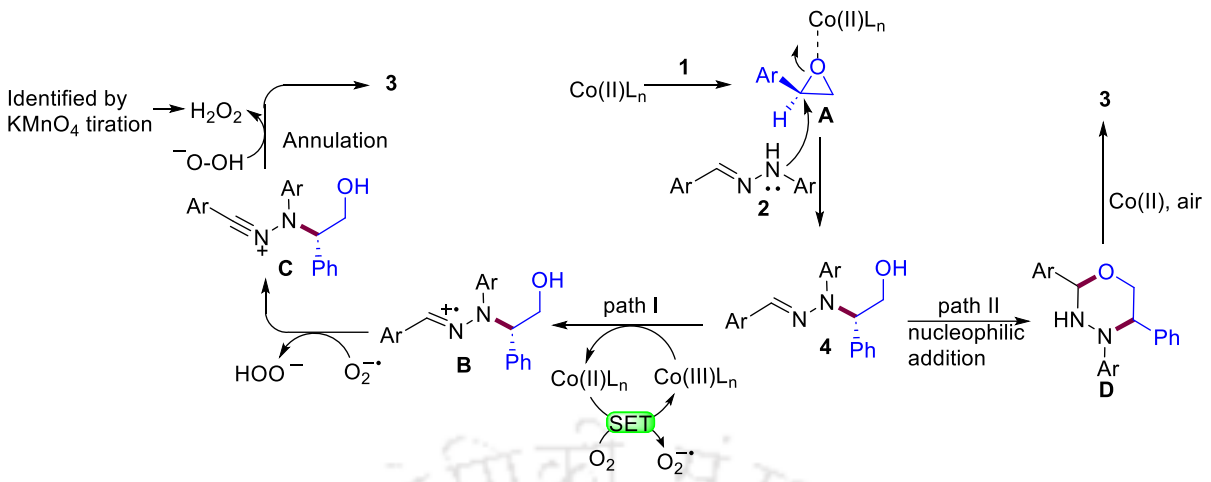
[a]Reaction conditions, **3d-k** (0.2 mmol), **2a′** (0.22 mmol), $Co(OAc)_2 \cdot 4H_2O$ (10 mol %), toluene (1 mL), 12 h, rt. [b]Isolated yield.

To delve into the reaction pathway, we examined the reaction of **4** using $Co(OAc)_2 \cdot 4H_2O$ under air, observing the formation of **3a** in 88% yield (Scheme 9a). This result suggests the potential involvement of intermediate **4** in the reaction. Furthermore, we monitored the reaction of **4** using 600 MHz ^1H NMR in the absence of $Co(OAc)_2 \cdot 4H_2O$ under a N_2 atmosphere.[11] Neither the formation of **5** nor the product **3a** was observed. Subsequently, we conducted the

cyclization of **4** with 1.1 equiv of p-TsOH·H_2O, yielding **5** in a 20% yield as a 1:4 mixture of diastereomers (Scheme 9b). However, the latter underwent oxidation under standard conditions, resulting in trace amounts of **3a**, indicating its minor pathway involvement (Scheme 3, path II). Additionally, the reaction of **1a** with **2a** yielded a reduced yield of 21% under a N_2 atmosphere, suggesting that air facilitates the oxidative C-O bond formation (Scheme 9c). Further, the use of radical scavengers, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT), led to a decrease in yield, indicating a radical pathway (Scheme 9d). Thus, the chelation of Co(II)Ln with **2** can potentially yield intermediate **A**, which stereospecifically reacts with hydrazone **1** to yield 4 (Scheme 10). Thus, aerobic oxidation of Co(II)Ln can give Co(III)Ln that can oxidize **4** to cation radical **B** by single electron transfer (SET) (path I, major).[11f] Homolytic cleavage of the imine C-H bond can give the iminium ion **C** and peroxide anion, which can cyclize to yield target **3** with H_2O_2. Furthermore, Co-catalyzed nucleophilic addition can give **5** that can lead to product **3** *via* an aerobic oxidation using Co-catalysis (path II, minor).

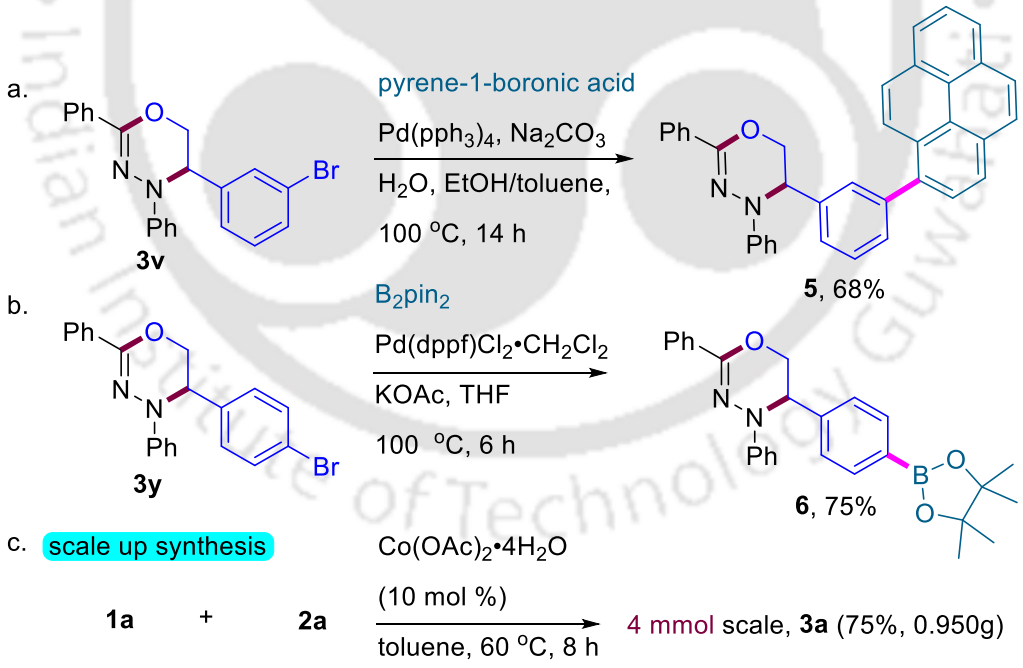


Scheme 9. Mechanistic Investigations



Scheme 10. Plausible Catalytic Cycle

To reveal the post-synthetic utilities, the C-C cross-coupling of oxadiazine **3v** with 1-pyreneboronic acid was investigated using Pd-catalysis to deliver **6** in 68% yield (Scheme 11a). Furthermore, C-B coupling of **3y** with bis(pinacolato)diboron was achieved in 75% yield (Scheme 11b). In addition, the scale-up synthesis was investigated using **1a** and **2a** as the representative substrates (Scheme 11c). The reaction occurred to produce **3a** in 75% yield.



Scheme 11. Post-Synthetic Utility and Scale-up

In conclusion, a Co(II)-catalyzed stereospecific cascade C-N and C-O bonds formations of styrene oxides with hydrazones has been achieved to produce oxadiazines under air. The use

of cobalt as the bifunctional catalyst and use of air as the oxidant are the important practical features.

3.3 Experimental Section

General Information. $Co(OAc)_2•4H_2O$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $CoCl_2$, $FeCl_3$, $Ni(ClO_4)•6H_2O$ and (*R*)-styrene oxide purchased from Aldrich and used as received. Styrene oxides and hydrazones were prepared according to literature.[21,22] Merck silica gel G/GF 254 plates were used for the analytical TLC and rankem silica gel (60-120 mesh) was used for the column chromatography. NMR (^1H and ^{13}C) spectra were recorded in Bruker Avance III 400, 500 and 600 spectrometers using $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (*J*) are reported in ppm and in Hz, respectively and other data are reported as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = multiplet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier Transform Infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (model HAB 273) was used for mass spectra. Optical rotations were determined using a Rudolph Autopol I Automatic Polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD column using *iso*-propanol and hexane as eluent. Single-crystal X-ray data was collected using Brucker SMART APEX-II CCD area detector using Mo-Kα irradiation and the structure was solved by using *SHELXL-16* (Gottingen, Germany).

General Procedure for the Synthesis of Oxadiazines. Hydrazone **1** (0.2 mmol), styrene oxide **2** (0.22 mmol) and $Co(OAc)_2•4H_2O$ (0.02 mmol, 5.0 mg) were stirred in toluene (1 mL) at 60 °C for the appropriate time. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using n-hexane as the eluent to give **3**.

Gram-Scale Synthesis of 3a. Hydrazone **1a** (4 mmol, 784 mg), styrene oxide **2a** (4.4 mmol, 528 mg) and $Co(OAc)_2•4H_2O$ (10 mol %, 100 mg) were stirred in toluene (10 mL) at 60 °C. After completion (determined by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL) and washed with water (5 mL). Drying (Na_2SO_4) and

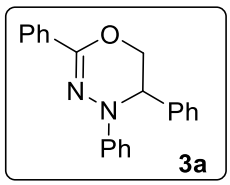
evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using n-hexane as the eluent to give **3a** in 75% yield.

Synthesis of 6. The heterocycle **3v** (0.2 mmol, 78 mg), 1-pyreneboronic acid (0.2 mmol, 50 mg), $Pd(PPh_3)_4$ (0.002, 2.3 mg), Na_2CO_3 (0.2 mmol, 22 mg) and H_2O (50 μL) in toluene : EtOH (1:1, 2 mL) were heated to reflux at 110 ^oC for 14 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 mL) and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane /EtOAc (19:1) as an eluent to give **6** in 68% yield (64 mg).

Synthesis of 7. The heterocycle **3y** (0.2 mmol, 79 mg), B_2pin_2 (0.2 mmol, 50 mg), KOAc (0.4 mmol, 40 mg) and $Pd(dppf)Cl_2•CH_2Cl_2$ (0.01 mmol, 8 mg) were stirred in THF (3 mL) at 100 ^oC for 6 h under N_2 atmosphere. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (30 mL). The organic layer was separated and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane/EtOAc (19:1) as an eluent to give 6 in 75% yield (66 mg).

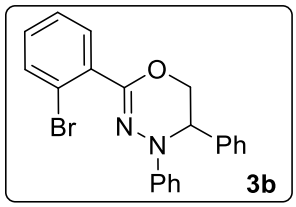
Enantiospecific Oxadiazine Synthesis. Hydrazone **1g** (0.2 mmol, 42 mg), (*R*)-styrene oxide **2a**' (0.22 mmol, 24 mg) and catalyst (0.02 mmol) were stirred for 12 h at room temperature. The workup and purification were carried out as above-described general procedure for oxadiazines. The *ee* was determined using chiral HPLC analysis.

3.4 Characterization Data

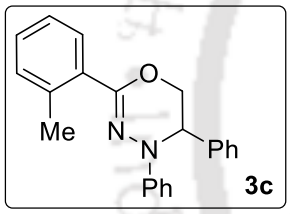


2,4,5-Triphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3a. Red solid; mp 172-174 ^oC; yield 82% (52 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.42-7.38 (m, 3H), 7.36-7.33 (m, 2H), 7.30-7.29 (m, 4H), 7.27-7.25 (m, 3H), 6.87 (t, *J* = 7.2 Hz, 1H), 5.25 (s, 1H), 4.63-4.62 (m, 1H), 4.60-4.58 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.80, 143.33, 138.53, 132.46, 129.15, 129.11, 129.09, 128.28, 127.84, 126.50, 125.31, 119.58,

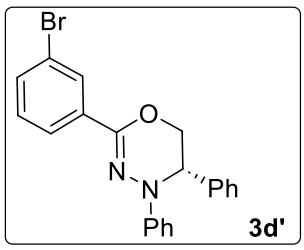
112.99, 67.72, 55.76; FT-IR (neat) 2931, 1596, 1494, 1271, 1168, 1109, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{19}N_2O^+$: 315.1492, found: 315.1495.



2-(2-Bromophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3b. colorless solid; mp 135-137 °C; yield 78% (61 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 2H), 7.39-7.34 (m, 5H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.28-7.23 (m, 5H), 6.86 (t, *J* = 6.6 Hz, 1H), 5.27 (s, 1H), 4.66-4.64 (m, 1H), 4.61-4.59 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.63, 143.37, 138.41, 134.01, 133.62, 130.80, 130.34, 129.14, 129.10, 127.88, 127.20, 126.52, 121.55, 119.78, 113.04, 67.75, 55.65; FT-IR (neat) 2926, 1595, 1495, 1379, 1260, 1069, 747 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0595.

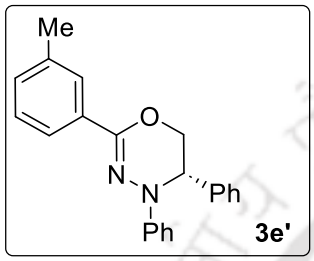


4,5-Diphenyl-2-(*o*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3c. Colorless solid; mp 97-99 °C; yield 77% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.6 Hz, 1H), 7.39-7.33 (m, 4H), 7.32-7.26 (m, 6H), 7.22-7.20 (m, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 5.26 (s, 1H), 4.626-4.621 (m, 2H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.85, 144.61, 138.52, 136.94, 131.69, 131.46, 129.16, 129.07, 128.86, 128.16, 127.81, 126.53, 125.71, 119.44, 112.79, 67.67, 55.42, 22.76; FT-IR (neat) 2931, 1596, 1493, 1376, 1265, 1165, 1053, 738 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1649.

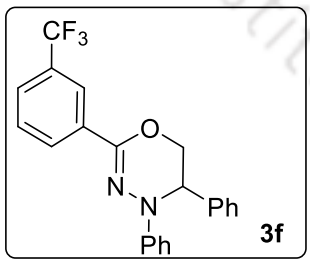


(*S*)-**2-(3-Bromophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3d′.** Red solid; mp 156-158 °C; yield 62% (49 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.36-7.33 (m, 2H), 7.30-7.26

(m, 6H), 7.24-7.22 (m, 2H), 6.88 (t, *J* = 6.8 Hz, 1H), 5.26 (s, 1H), 4.64-4.61 (m, 1H), 4.59-4.55 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.54, 141.94, 138.21, 134.41, 131.84, 129.80, 129.20, 129.17, 128.22, 127.95, 126.40, 123.78, 122.51, 119.95, 113.10, 67.77, 55.76; $[\alpha]_D^{25}$ = +18.00 (c = 0.05, $CHCl_3$); HPLC analysis: 98% *ee* [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.86 min (major), 09.70 min (minor)]; FT-IR (neat) 2919, 2851, 1594, 1497, 1381, 1261, 1169, 1114, 998, 886, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0595.

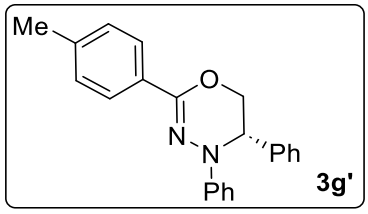


(*S*)-4,5-Diphenyl-2-(*m*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3e′. Red solid; mp 160-162 °C; yield 64% (42 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76-7.74 (m, 2H), 7.34-7.32 (m, 2H), 7.30-7.27 (m, 5H), 7.25 (t, *J* = 8.4 Hz, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.24 (s, 1H), 4.62-4.60 (m ,1H), 4.59-4.57 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.81, 143.46, 138.54, 137.91, 132.36, 129.90, 129.14, 129.09, 128.21, 127.82, 126.49, 125.87, 122.51, 119.53, 112.96, 67.70, 55.75, 21.63; $[\alpha]_D^{25}$ = +32.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% *ee* [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.30 min (major), 08.45 min (minor)]; FT-IR (neat) 2923, 1595, 1493, 1369, 1275, 1108, 1031, 791 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1646.

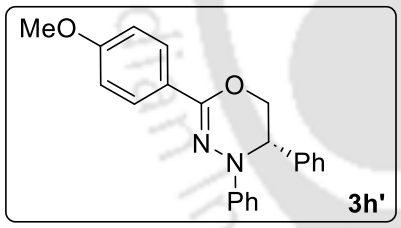


4,5-Diphenyl-2-(3-(trifluoro-methyl)-phenyl)-5,6-dihydro-4H 1,3,4-oxadiazine 3f. Colorless solid; mp 155-157 °C; yield 73% (56 mg); 1H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.26-7.24 (m, 2H), 7.21-7.18 (m, 5H), 7.15-7.13 (m, 2H), 6.79 (t, *J* = 6.5 Hz, 1H), 5.17 (s, 1H), 4.57-4.54 (m, 1H), 4.51-4.49 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.52, 142.05, 138.16, 133.21, 131.12 (J_{C-F} = 31.95 Hz), 129.24, 129.21, 128.76, 128.34, 128.00, 127.07 (J_{C-}

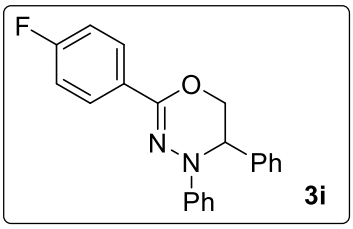
$_F$ = 270.75 Hz), 126.39, 125.49 (J_{C-F} = 3.45 Hz), 122.10 (J_{C-F} = 3.6 Hz), 120.06, 113.14, 67.82, 55.80; FT-IR (neat) 2923, 1597, 1497, 1370, 1324, 1260, 1124, 1072, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{18}F_3N_2O$+: 383.1366, found: 383.1354.



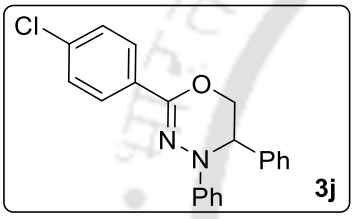
(*S*)-**4,5-Diphenyl-2-(*p*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3g'**. Colorless solid; mp 156-158 °C; yield 67% (44 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.8 Hz, 2H), 7.35-7.31 (m, 2H), 7.29-7.27 (m, 4H), 7.25-7.20 (m, 5H), 6.87-6.83 (m, 1H), 5.23 (s, 1H), 4.62-4.56 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.85, 143.57, 139.14, 138.61, 129.71, 129.12, 129.08, 128.99, 127.79, 126.52, 125.28, 119.41, 112.92, 67.72, 55.73, 21.52;: $[\alpha]_D^{25}$ = +30.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% *ee* [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.37 min (major), 11.24 min (minor)]; FT-IR (neat) 2931, 1600, 1496, 1388, 1252, 1170, 1109, 1030, 836 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1645.



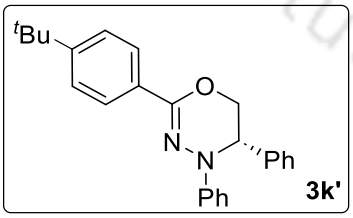
(***S***)-**2-(4-Methoxyphenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3h'**. Yellow solid; mp 214-216 °C; yield 66% (45 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.24-7.21 (m, 2H), 7.19-7.14 (m, 5H), 7.12-7.11 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.74 (t, *J* = 6.5 Hz, 1H), 5.12 (s, 1H), 4.50-4.46 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.53, 145.90, 143.49, 138.62, 129.11, 129.06, 127.77, 126.84, 126.53, 125.15, 119.28, 113.68, 112.84, 67.77, 55.68, 55.47; $[\alpha]_D^{25}$ = +26.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% *ee* [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 07.75 min (major), 13.49 min (minor)]; FT-IR (neat) 2932, 1599, 1495, 1387, 1252, 1169, 1109, 1029, 836 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O_2^+$: 345.1598, found: 345.1598.



2-(4-Fluorophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3i. Yellow solid; mp 192-194 °C; yield 82% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.36-7.33 (m, 2H), 7.30-7.25 (m, 5H), 7.23-7.20 (m, 2H), 7.10-7.05 (m, 2H), 6.88-6.84 (m, 1H), 5.24 (s, 1H), 4.64-4.61 (m, 1H), 4.60-4.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.75, 162.28, 145.75, 142.72, 138.39, 129.17, 129.14, 128.63, 128.60, 127.89, 127.27, 127.19, 126.47, 119.65, 115.37, 115.16, 112.99, 67.84, 55.68; FT-IR (neat) 2936, 1598, 1496, 1272, 1164, 1108, 747 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}FN_2O^+$: 333.1398, found: 333.1398.

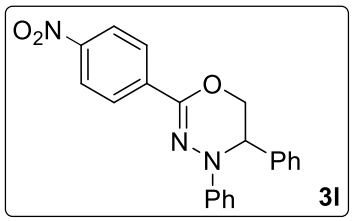


2-(4-Chlorophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3j. Red solid; mp 158-160 °C; yield 84% (58 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.36-7.33 (m, 4H), 7.30-7.26 (m, 6H), 7.23-7.21 (m, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 5.25 (s, 1H), 4.63-4.61 (m, 1H), 4.59-4.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.65, 142.55, 138.33, 134.93, 130.92, 129.19, 129.16, 128.48, 127.92, 126.58, 126.44, 119.82, 113.06, 67.79, 55.74; FT-IR (neat) 2923, 1597, 1493, 1389, 1272, 1170, 1103, 1010, 834, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}ClN_2O^+$: 349.1102, found: 349.1114.

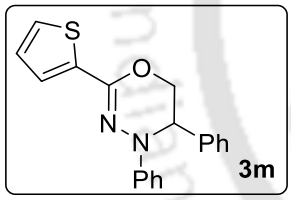


(***S***)**-2-(4-(Tert-Butyl) phenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3k'.** Colorless solid; mp 148-150 °C; yield 68% (50 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.24-7.21 (m, 2H), 7.19-7.17 (m, 4H), 7.15-7.12 (m, 3H), 6.75 (t, *J* = 6.8 Hz, 1H), 5.14 (s, 1H), 4.52-4.49 (m, 1H), 4.48-4.45 (m, 1H) 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.33, 145.86, 143.52, 138.61, 129.74, 129.13, 129.07, 127.78, 126.53, 125.24, 125.11, 119.40, 112.89, 67.68, 55.77, 34.87, 31.40;

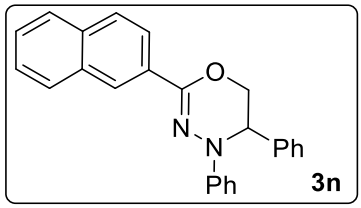
$[\alpha]_D^{25}$ = +66.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% *ee* [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 04.61 min (major), 10.21 min (minor)]; FT-IR (neat) 2960, 1597, 1495, 1337, 1269, 1169, 1057, 841 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{27}N_2O^+$: 371.2118, found: 371.2118.



2-(4-Nitrophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3l. Red solid; mp 165-167 °C; yield 85% (61 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.2 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.28-7.24 (m, 2H), 7.22-7.19 (m, 3H), 7.17-7.14 (m, 4H), 6.83 (t, *J* = 7.2 Hz, 1H), 5.21-5.20 (m, 1H), 4.58-4.55 (m, 1H), 4.50-4.47(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.74, 145.23, 141.47, 138.26, 137.93, 129.29, 129.27, 128.13, 126.29, 125.64, 123.69, 120.66, 113.42, 67.75, 55.98; FT-IR (neat) 2943, 1584, 1497, 1333, 1270, 1170, 850, 741 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}N_3O_3^+$: 360.1343, found: 360.1341.

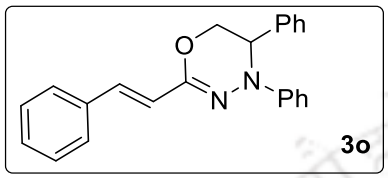


4,5-Diphenyl-2-(thiophen-2-yl)-5,6-dihydro-4H-1,3,4-oxadiazine 3m. Black solid; mp 158-160 °C; yield 82% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.38 (m, 1H), 7.37-7.34 (m, 2H), 7.30-7.26 (m, 6H), 7.21-7.20 (m, 2H), 7.04 (t, *J* = 4.2 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 4.59 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.46, 141.18, 138.27, 136.25, 129.14, 127.89, 127.35, 126.48, 126.47, 125.33, 119.67, 112.95, 67.96, 55.86; FT-IR (neat) 2928, 1596, 1495, 1447, 1374, 1267, 1168, 1033, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{17}N_2OS^+$: 321.1056, found: 321.1062.

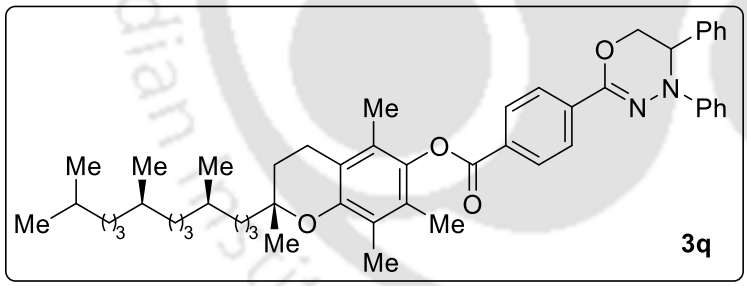


2-(Naphthalen-2-yl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3n. Colorless solid; mp 248-250 °C; yield 69% (51 mg); ^{1}H NMR (600 MHz, $CDCl_3$)

δ 8.26 (s, 1H), 8.21-8.19 (m, 1H), 7.87-7.85 (m, 3H), 7.50-7.49 (m, 2H), 7.36-7.33 (m, 2H), 7.32-7.29 (m, 7H), 6.90-6.87 (m, 1H), 5.30 (s, 1H), 4.70-4.68(m, 1H), 4.67-4.64 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.76, 143.43, 138.54, 133.75, 133.19, 129.74, 129.20, 129.15, 128.61, 127.89, 127.88, 127.82, 126.55, 126.49, 126.41, 124.53, 123.11, 119.72, 113.06, 67.82, 55.87; FT-IR (neat) 2955, 1597, 1497, 1368, 1274, 1171, 1098, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{21}N_2O^+$: 365.1648, found: 365.1645.

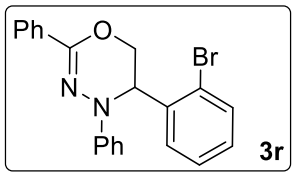


(*E*)-4,5-diphenyl-2-styryl-5,6-dihydro-4H-1,3,4-oxadiazine 3o. White solid; mp 107-109 °C; yield 84% (57 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.2 Hz, 1H),7.37-7.34 (m, 4H), 7.31-7.25 (m, 6H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 16.2 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 16.2 Hz, 1H), 5.21 (s, 1H), 4.56-4.55 (m, 1H), 4.53-4.51 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.40, 145.05, 138.49, 136.48, 131.29, 129.18, 129.15, 128.82, 128.20, 127.91, 126.89, 126.43, 120.50, 119.91, 113.07, 67.34, 55.99.; FT-IR (neat) 2926, 1595, 1495, 1370, 1165, 1030, 749 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{23}H_{21}N_2O^+$: 341.1648, found: 341.1648.

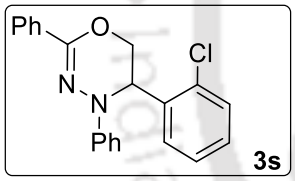


(*R*)-2,5,7,8-tetramethyl-2 ((4R,8R)-4,8,12-trimethyl tridecyl)chroman-6-yl 4-(4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl) benzoate 3q. Yellow solid; mp 181-183 °C; yield 67% (103 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.27-7.24 (m, 2H), 7.21-7.19 (m, 4H), 7.18-7.16 (m, 3H), 6.80 (t, *J* = 6.6 Hz, 1H), 5.19 (s, 1H), 4.57-4.55 (m, 1H), 4.52-4.50 (m, 1H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.05 (s, 3H), 1.98 (s, 3H), 1.94 (s, 3H), 177-1.74 (m, 1H), 1.709-1.702 (m, 1H), 1.49 (s, 4H), 1.46-1.43 (m, 2H), 1.32-1.31 (m, 3H), 1.19-1.18 (m, 8H), 1.07-1.06 (m, 3H), 1.00 (s, 4H), 0.80-0.77 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.10, 149.61, 145.52, 142.45, 140.77, 138.27, 137.04, 130.19, 129.56, 129.24, 129.21, 128.00, 127.06, 126.41, 125.28, 125.20, 123.28, 120.19, 117.64, 113.26, 75.23, 67.74, 55.93,

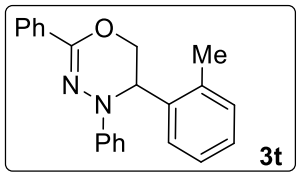
39.52, 37.71, 37.69, 37.60, 37.54, 37.44, 32.94, 32.93, 32.87, 28.13, 24.97, 24.95, 24.60, 24.36, 23.83, 22.87, 22.78, 21.19, 20.78, 19.90, 19.83, 19.81, 19.79, 19.75, 13.20, 12.35, 12.00. FT-IR (neat) 2923, 1731, 1581, 1454, 1374, 1271, 1167, 1052 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{51}H_{67}N_2O_4^+$: 771.5095, found: 771.5110.



5-(2-Bromophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3r. Colorless solid; mp 185-187 ^oC; yield 79% (62 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.54-7.51 (m, 1H), 7.33-7.25 (m, 3H), 7.19-7.15 (m, 2H), 7.08-7.06 (m, 2H), 7.05-7.00 (m, 3H), 6.76 (t, *J* = 7.2 Hz, 1H), 5.48-5.47 (m, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.43 (dd, *J* = 10.4Hz, 2.8Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.25, 143.22, 136.87, 133.37, 132.28, 129.61, 129.24, 129.22, 128.74, 128.34, 128.23, 125.33, 121.93, 119.77, 112.71, 65.37, 55.57; FT-IR (neat) 2929, 1597, 1495, 1331, 1174, 1111, 1025 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for :$C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0598.

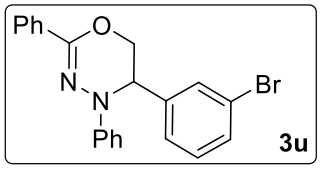


5-(2-Chlorophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3s. Colorless solid; mp 173-175 ^oC; yield 77% (54 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0Hz, 2.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.32-7.25 (m, 3H), 7.19-7.15 (m, 2H), 7.14-7.07 (m, 3H), 7.04-6.98 (m, 2H), 6.76 (t, *J* = 7.2 Hz, 1H), 5.53-5.52 (m, 1H), 4.66-4.63 (m, 1H), 4.46-4.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.27, 143.14, 135.35, 132.31, 132.01, 130.09, 129.30, 129.24, 129.21, 128.62, 128.34, 127.61, 125.33, 119.76, 112.68, 65.33, 53.35; FT-IR (neat) 2925, 1597, 1495, 1387, 1332, 1271, 1174, 1110, 1035 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}ClN_2O^+$: 349.1102, found: 349.1102.

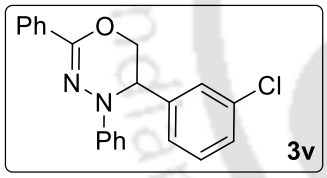


2,4-Diphenyl-5-(*o*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3t. Colorless solid; mp 174-176 ^oC; yield 75% (50 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.43-7.38 (m, 3H), 7.28-7.25 (m, 3H), 7.21-7.18 (m, 1H), 7.17-7.16 (m, 2H), 7.09-

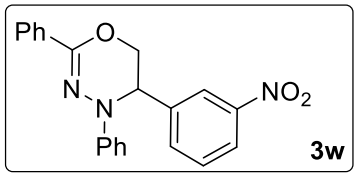
7.05 (m, 2H), 6.85 (t, *J* = 7.8 Hz, 1H), 5.38 (s, 1H), 4.544-4.541 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.62, 142.89, 136.28, 133.83, 132.44, 131.12, 129.14, 129.06, 128.30, 127.90, 126.87, 126.78, 125.28, 119.58, 112.90, 65.60, 53.32, 19.25. ; FT-IR (neat) 2921, 1597, 1493, 1382, 1336, 1273, 1192, 1105, 747 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1647



5-(3-Bromophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3u. Yellow solid; mp 150-152 ºC; yield 80% (63 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.47 (s, 1H), 7.43-7.39 (m, 4H), 7.31-7.28 (m, 3H), 7.23 (d, *J* = 7.8 Hz, 2H),7.19 (d, *J* = 4.8 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 5.22 (s, 1H), 4.61-4.59 (m, 1H), 4.57-4.55 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.56, 143.42, 141.01, 132.23, 131.13, 130.74, 129.51, 129.24, 128.33, 125.34, 125.27, 123.19, 119.88, 112.97, 67.37, 55.44; FT-IR (neat) 2934, 1600, 1499, 1454, 1367, 1230, 1168, 1075, 744 cm^{-1} ; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0594.

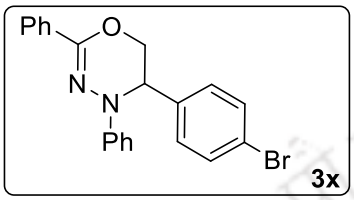


5-(3-Chlorophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3v. Red solid; mp 191-193 ºC; yield 78% (54 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.33-7.28 (m, 3H), 7.20-7.16 (m, 5H), 7.14-7.11 (m, 2H), 7.05-7.04 (m, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 5.11 (s, 1H), 4.51-4.48 (m, 1H), 4.47-4.43 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.54, 143.39, 140.74, 135.00, 132.22, 130.46, 129.24, 128.32, 128.20, 126.64, 125.33, 124.78, 119.85, 112.94, 67.37, 55.48. FT-IR (neat) 2928, 1597, 1493, 1387, 1271, 1112, 1003, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}ClN_2O^+$: 349.1102, found: 349.1101.

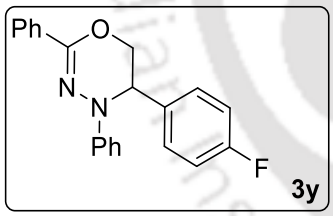


5-(3-Nitrophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3w. Red solid; mp 145-147 ºC; yield 83% (60 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25

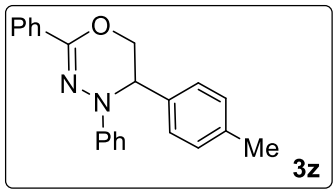
(s,1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.97-7.96 (m, 2H), 7.58-7.57(m, 1H), 7.48 (t, *J* = 8.4 Hz, 1H), 7.43-7.42 (m, 3H), 7.33-7.31 (m, 2H), 7.25-7.24 (m, 2H), 6.92 (t, *J* = 7.2 Hz, 1H), 5.38 (s, 1H), 4.67-4.65 (m, 1H), 4.64-4.62 (m, 1H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.85, 145.29, 143.64, 140.77, 132.81, 131.93, 130.24, 129.45, 129.34, 128.37, 125.34, 123.03, 121.65, 120.17, 112.91, 67.17, 55.27. FT-IR (neat) 2924, 1596, 1494, 1348, 1107, 1059, 737 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}N_3O_3^+$: 360.1343, found: 360.1345



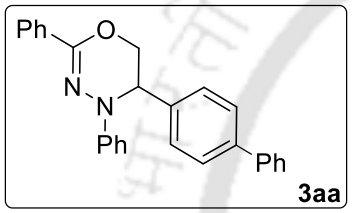
5-(4-Bromophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3x. Yellow solid; mp 172-174 ºC; yield 86% (67 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.4Hz, 1.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.42-7.38 (m, 3H) 7.28 (t, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 5.21 (s, 1H), 4.587-4.583 (m, 2H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.58, 143.43, 137.57, 132.28, 132.22, 129.25, 129.23, 128.33, 125.31, 121.83, 119.86, 112.98, 67.49, 55.31. FT-IR (neat) 2923, 1597, 1492, 1387, 1168, 1071, 1010, 748 cm^{-1}, HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0596.



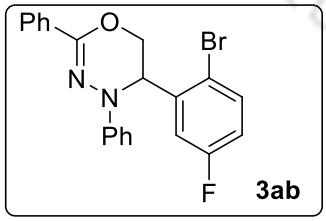
5-(4-Fluorophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3y. Colorless solid; mp 150-152 ºC; yield 83% (55 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.33-7.28 (m, 3H), 7.20-7.15 (m, 4H), 7.14-7.11 (m, 2H), 6.92 (t, *J* = 8.4 Hz, 2H), 6.79-6.76 (m, 1H), 5.14 (s, 1H), 4.48 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.16, 161.53, 145.61, 143.35, 134.20, 134.18, 132.28, 129.20, 128.31, 128.22, 128.17, 125.29, 119.75, 116.13, 115.99, 112.96, 67.69, 55.13; FT-IR (neat) 2929, 1597, 1498, 1385, 1228, 1108, 1056, 749 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}FN_2O^+$: 333.1398, found: 333.1397.



2,4-diphenyl-5-(*p*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3z. Colorless solid; mp 124-126 °C; yield 86% (56 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.2 Hz, 2H), 7.40-7.35 (m, 3H), 7.26-7.23 (m, 4H), 7.16 (dd, *J* = 22.2 Hz, 7.8 Hz, 4H), 6.85 (t, *J* = 6.6 Hz, 1H), 5.21 (s, 1H), 4.60-4.55 (m, 2H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.86, 143.30, 137.54, 135.50, 132.51, 129.80, 129.14, 129.04, 128.26, 126.41, 125.32, 119.52, 113.01, 67.85, 55.55, 21.22; FT-IR (neat) 2925, 1596, 1493, 1387, 1369, 1308, 1271, 1200, 1167, 1109, 1033, 766 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1648.

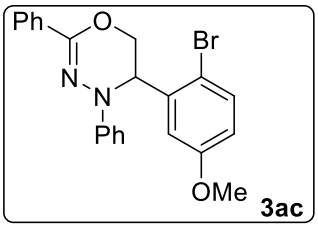


5-([1,1'-Biphenyl]-4-yl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxa-diazine 3aa. Colorless solid; mp 151-153 °C; yield 81% (63mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.45-7.40 (m, 5H), 7.37-7.33 (m, 3H), 7.31-7.29 (m, 4H), 6.91-6.87 (m, 1H), 5.30 (s, 1H), 4.68-4.65 (m, 1H), 4.63-4.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.80, 143.36, 140.80, 140.73, 137.52, 132.44, 129.20, 129.13, 128.88, 128.30, 127.88, 127.46, 127.19, 126.96, 125.33, 119.64, 113.01, 67.71, 55.55. FT-IR (neat) 2924, 1597, 1493, 1385, 1109, 840, 759 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{23}N_2O^+$: 391.1805, found: 391.1812.

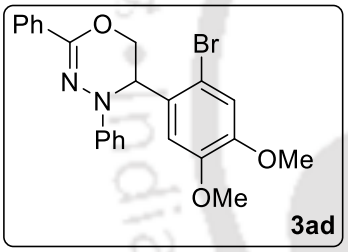


5-(2-Bromo-5-fluorophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4 oxadiazine 3ab. yellow solid; mp 185-187 °C; yield 76% (62 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.62-7.60 (m, 1H), 7.43-7.42 (m, 3H), 7.31-7.28 (m, 3H), 7.18-7.17 (m, 2H), 6.91-6.87 (m, 3H), 5.54 (s, 1H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.54 (d, *J* = 10.2 Hz, 1H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.27, 161.62, 145.06, 143.33, 139.35, 139.30, 134.65, 134.60, 132.06, 129.40, 129.32, 128.39, 125.39, 120.05, 117.05, 116.90, 116.29, 116.12, 115.82,

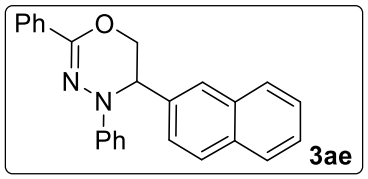
115.80, 112.70, 65.07, 55.69; FT-IR (neat) 1596, 1491, 1386, 1326, 1247, 1184 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{21}H_{17}BrFN_2O^+$: 411.0503, found: 411.0521.



5-(2-Bromo-5-methoxyphenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3ac. Colorless solid; mp 178-180 ^oC; yield 77% (65 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.96-7.95 (m, 2H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.42-7.38 (m, 3H), 7.30-7.27 (m, 2H), 7.19-7.18 (m, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.72-6.70 (m, 2H), 5.53 (s, 1H), 4.75-4.73 (m, 1H), 4.54-4.52 (m, 1H), 3.58 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.48, 145.34, 143.34, 137.92, 133.94, 132.30, 129.23, 128.34, 125.37, 119.79, 115.08, 114.61, 112.79, 112.01, 65.40, 55.66, 55.40; FT-IR (neat) 1591, 1466, 1291, 1229, 1112 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{22}H_{20}BrN_2O_2^+$: 423.0703, found: 423.0706.

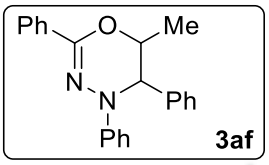


5-(2-Bromo-4,5-dimethoxyphenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3ad. Brown liquid; yield 78% (71 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.43-7.39 (m, 3H), 7.31-7.28 (m, 2H), 7.22-7.20 (m, 2H), 7.09 (s, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.66 (s, 1H), 5.50 (s, 1H), 4.72 (d, *J* = 10.8Hz, 1H), 4.56-4.53 (m, 1H), 3.87 (s, 3H), 3.55 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.24, 148.91, 145.48, 143.61, 132.25, 129.27, 129.21, 129.08, 128.36, 125.28, 119.86, 115.88, 112.95, 111.68, 111.04, 65.95, 56.31, 55.94, 55.33; FT-IR (neat) 1596, 1491, 1271, 1172, 1109 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{23}H_{22}BrN_2O_3^+$: 453.0808, found: 453.0826.

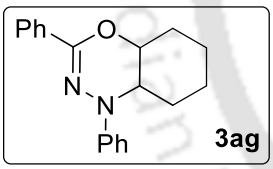


5-(Naphthalen-2-yl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3ae. White solid; mp 156-158 ^oC; yield 72% (53 mg); ^1H NMR (400 MHz, $CDCl_3$) δ

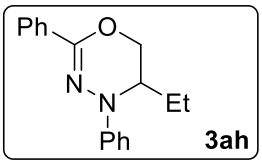
7.87-7.85 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 1H),7.73-7.70 (m, 1H), 7.67-7.65 (m, 1H), 7.61 (s, 1H), 7.36-7.33 (m, 3H), 7.31-7.27 (m, 3H), 7.20-7.14 (m, 4H), 6.78-6.74 (m, 1H), 5.30 (s, 1H), 4.63-4.60 (m, 1H), 4.54-4.51 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.86, 143.41, 135.89, 133.50, 133.02, 132.45, 129.18, 129.16, 129.10, 128.29, 128.15, 127.78, 126.43, 126.18, 125.61, 125.32, 124.20, 119.67, 113.11, 67.55, 56.13; FT-IR (neat) 2923, 1597, 1495, 1269, 1359, 1184, 1112, 815, 746 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{21}N_2O^+$: 365.1648, found: 365.1648.



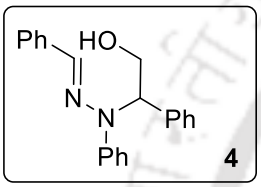
6-Methyl-2,4,5-triphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3af. Brown liquid; yield 56% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-8.01 (m, 2H), 7.44-7.42 (m, 2H), 7.41-7.39 (m, 1H), 7.32-7.29 (m, 2H), 7.28-7.27 (m, 3H), 7.26-7.23 (m, 4H), 6.82 (t, *J* = 7.2 Hz, 1H), 5.01 (d, *J* = 2.4 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.75, 143.38, 136.85, 132.50, 129.09, 129.03, 128.70, 128.34, 128.32, 127.90, 125.38, 119.35, 112.86, 70.36, 60.40, 17.94; FT-IR (neat) 2927, 1490, 1446, 1350, 1261, 1171 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1657.



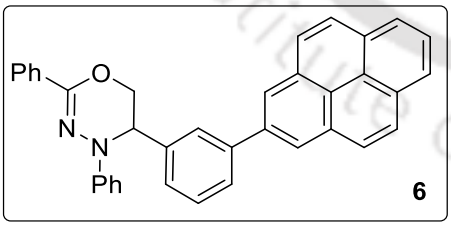
1,3-Diphenyl-4a,5,6,7,8,8a-hexahydro-1H-benzo[e][1,3,4]oxadiazine 3ag. Brown loquid; yield 58% (34 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89-7.87 (m, 2H), 7.38-7.35 (m, 5H),7.29-7.28 (m, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 4.31-4.28 (m, 1H), 2.85-2.81(m, 1H), 2.29-2.26(m, 1H), 1.96-1.94(m, 1H), 1.90 (d, *J* = 13.2 Hz), 1.80-1.78 (m, 1H), 1.55-1.53 (m, 1H), 1.51-1.48 (m, 1H), 1.36-1.34 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.08, 145.51, 132.93, 129.09, 128.67, 128.09, 125.63, 125.25, 125.02, 77.88, 60.91, 30.84, 29.35, 24.48, 24.07; FT-IR (neat) 2934, 1626, 1485, 1326, 1236, 1090 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{21}N_2O^+$: 293.1648, found: 293.1641.



5-ethyl-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3ah. Red liquid; yield 61% (32 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95-7.93 (m, 3H), 7.41-7.36 (m, 4H), 7.35-7.32 (m, 3H), 7.31-7.29 (m, 1H), 7.27-7.26 (m, 3H), 6.91 (t, *J* = 6.6 Hz, 0.56H), 6.87 (t, *J* = 7.2 Hz, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.38-4.36 (m, 0.54H), 4.34-4.32 (m, 1H), 4.06-4.04(m, 1H), 3.95 (dd, *J* = 8.4 Hz, 11.4 Hz, 0.59H), 3.30 (dd, *J* = 7.2 Hz, 11.4Hz, 0.62Hz), 1.92-1.87 (m, 0.77H), 1.82-1.77 (m, 2H), 1.18(t, *J* = 7.2 Hz, 1.5H), 1.08 (t, *J* = 7.8 Hz, 3H); FT-IR (neat) 2924, 1493, 1386, 1273, 1171, 1064 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{17}H_{19}N_2O^+$: 267.1492, found: 267.1490.

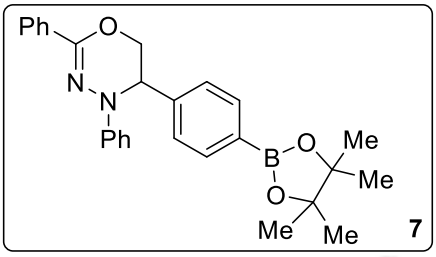


(*E*)-2-(2-Benzylidene-1-phenylhydrazineyl)-2-phenylethan-1-ol 4. Brown liquid; yield 77% (49 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 2H), 7.37-7.35 (m, 6H), 7.326-7.320 (m, 1H), 7.30-7.27 (m, 4H), 7.26-7.24 (m, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 4.80 (dd, *J* = 9.0 Hz, 3.6 Hz, 1H), 4.60-4.57 (m, 1H), 4.01 (dd, *J* = 11.4 Hz, 3.6 Hz, 1H), 3.56 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.59, 139.31, 136.17, 135.83, 129.82, 128.77, 128.52, 128.13, 128.06, 127.82, 127.80, 127.24, 125.98, 72.12, 66.09; FT-IR (neat) 2928, 1561, 1489, 1447, 1365, 1143, 1029, 754 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{21}N_2O^+$: 317.1648, found: 317.1623.

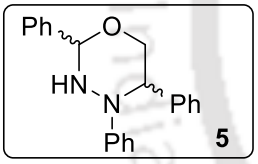


2,4-Diphenyl-5-(3-(pyren-2-yl) phenyl)-5,6-dihydro-4H-1,3,4-oxadiazine 6. White solid; mp 182-184 °C; yield 68% (64 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 2H), 8.09-8.06 (m, 3H), 8.01 (t, *J* = 7.2 Hz, 2H), 7.97-7.96 (m, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.57 (s, 3H), 7.42 (s, 4H), 7.30-7.28 (m, 5H), 6.89 (s, 1H), 5.41 (s, 1H), 4.77-4.76 (m, 1H), 4.70-4.68 (m, 1H); ^{13}C (150 MHz, $CDCl_3$) δ 145.76, 143.46, 141.83, 138.35, 137.17, 132.50, 131.56, 131.04, 130.80, 130.07, 129.49, 129.21, 129.15, 128.96, 128.53, 128.32, 127.70, 127.68, 127.60, 127.49, 126.08, 125.49, 125.37, 125.18, 125.06,

125.04, 124.97, 124.95, 124.69, 119.68, 113.14, 68.02, 55.76; FT-IR (neat) 2924, 1586, 1476, 1369, 1237, 1187, 1054, cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{37}H_{27}N_2O_2^+$: 515.2118, found: 515.2122.



2,4-Diphenyl-5-(4-(4,4,5,5-tetra methyl-1,3,2 dioxa borolan-2-yl) phenyl)-5,6-dihydro-4H-1,3,4-oxadiazine 7. yellow solid; mp 185-187 °C; yield 75% (66 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.30-7.26 (m, 3H), 7.20 (s, 1H), 7.19-7.17 (m, 2H), 7.15-7.11 (m, 3H), 6.75 (t, *J* = 6.5 Hz, 1H), 5.14 (S, 1H), 4.52-4.50 (m, 1H), 4.49-4.47 (m, 1H), 1.22 (s, 12H); ^{13}C (150 MHz, $CDCl_3$) δ 145.83, 143.44, 141.64, 135.58, 132.41, 129.14, 129.08, 128.25, 125.90, 125.31, 119.66, 113.11, 56.01, 24.97, 24.94; FT-IR (neat); 1614, 1401, 1359, 1319, 1224, 1142 cm^{-1}; HRMS (ESI) m/z [M+H]+ calcd for : $C_{27}H_{30}BN_2O_3^+$: 441.2344, found: 441.2335.



2,4,5-Triphenyl-1,3,4-oxadiazinane 5. red solid. Mp 155-157 °C; yield 20% (10 mg) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 0.27H), 7.41-7.40 (m, 2H), 7.37-7.36 (m, 2H), 7.34-7.32 (m, 4H), 7.30-7.27 (m, 7H), 7.19-7.18 (m, 0.88 H), 7.15-7.12 (m, 1.76H), 7.03-7.00 (m, 1.62H), 6.87 (t, *J* = 7.2 Hz, 0.21H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.41 (s, 0.24H), 6.28 (s, 1H), 5.457-5.453(m, 0.25H), 5.39 (q, *J* = 4.8 Hz, 1H), 4.62-4.59(m, 0.25H), 4.36 (dd, *J* = 2.4 Hz, 11.4 Hz, 0.25H), 4.08 (dd, *J* = 4.8 Hz, 12.0 Hz, 1H) 3.87 (dd, *J* = 8.4 Hz, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.68, 138.89, 137.13, 134.34, 131.44, 129.37, 129.25, 129.21, 129.17, 129.13, 129.07, 128.89, 128.49, 128.45, 128.36, 127.99, 127.05, 126.40, 126.21, 122.03, 120.84, 119.63, 114.63, 111.79, 77.36, 74.84, 74.73, 72.97, 66.79, 65.92, 58.65; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{21}H_{21}N_2O^+$: 317.1648, found: 317.1643.

Crystal Data and Structure Refinement

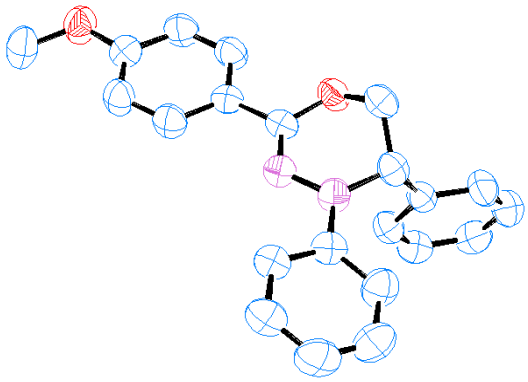


Figure 2. ORTEP diagram of **3h** with 50% ellipsoid (CCDC 2069088). H-Atoms are omitted for clarity.

Identification code	**3h**
CCDC No.	2069088
Empirical formula	C_{22} H_{20} N_2 O_2
Formula weight	344.15
Crystal habit, colour	Needle/colourless
Temperature,T/K	296K
Wavelength, λ/Å	0.71073
Crystal System	monoclinic
Space group	'P 21/c'
Unit cell dimensions	a = 14.2857(15)Å
	b = 5.8924(5)Å
	c = 21.571(2)Å
	α = 90, β = 91.328(4), γ = 90
Volume, V/Å	1815.3(3)
Z	4
Calculated density, $g{\cdot}cm^{-3}$	1.260
Absorption coefficient, μ/mm^{-1}	0.081
F(000)	728.0
θ range for data collection	2.34 to 25.10 °C
Limiting indices	$-17 \leq h \leq 17, -7 \leq k \leq 7, -25 \leq l \leq 25$
Reflection collected/unique	3187/2373

Completeness to θ	99% (θ = 25.047)
Absorption correction	none
Refinement method	'SHELXL-2014/7 (Sheldrick, 2014)'
Data / restraints / parameters	3187/0/236
Goodness-of-fit on F^2	0.900
Final *R* indices[I>2sigma(I)]	R1 = 0.0427, wR2 = 0.1277
R indices (all data)	R1 = 0.0618, wR2 = 0.1466

3.5 References

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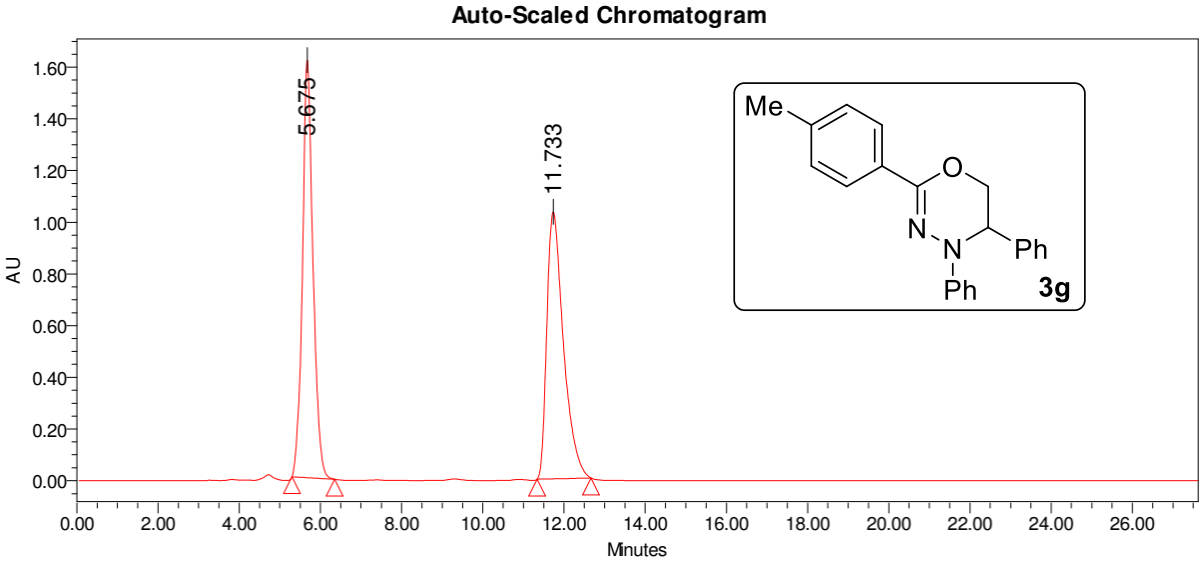
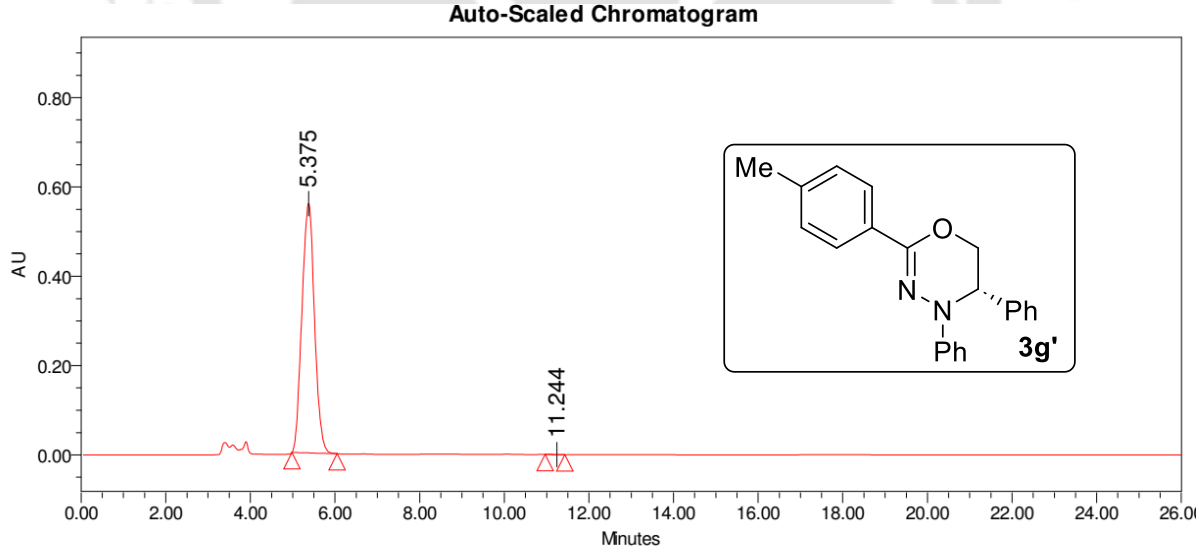
3.6 HPLC Chromatograms



Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	5.300	6.350	5.675	1620615	49.93
2	11.333	12.667	11.733	1032900	50.07

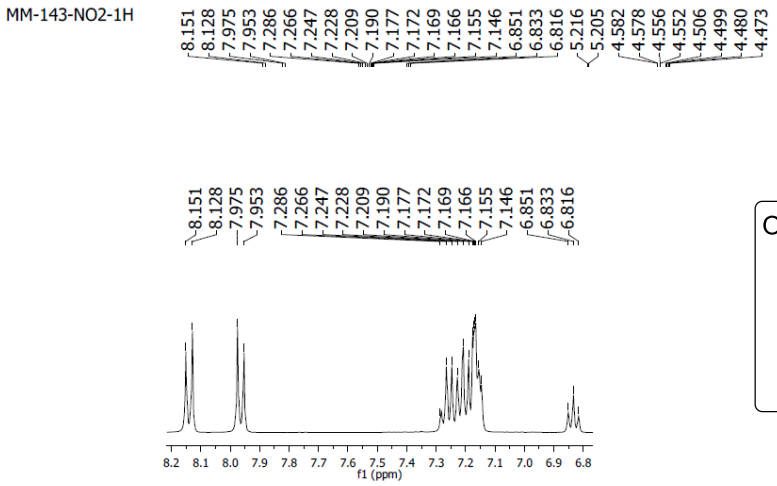


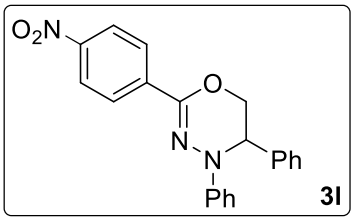
Peak Results

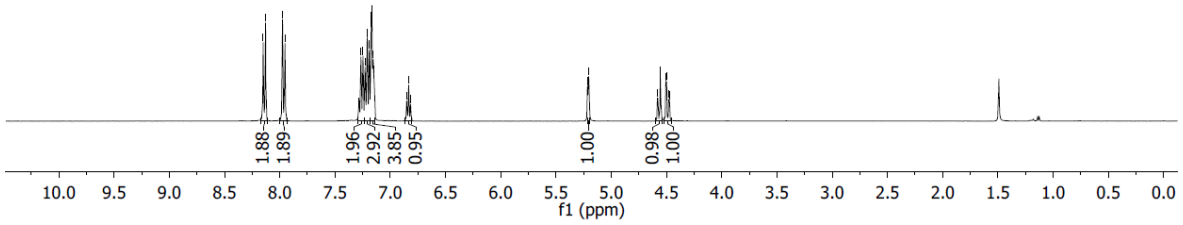
	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		4.983	6.050	5.375	559699	99.99
2	I37	10.967	11.433	11.244	-63	0.01

3.7 Selected NMR Spectra

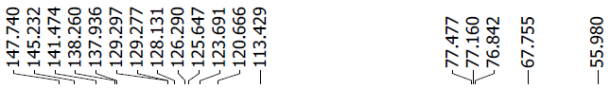
MM-143-NO2-1H

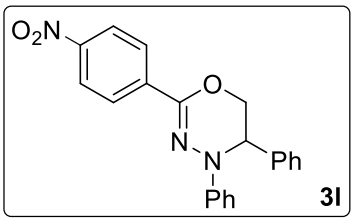


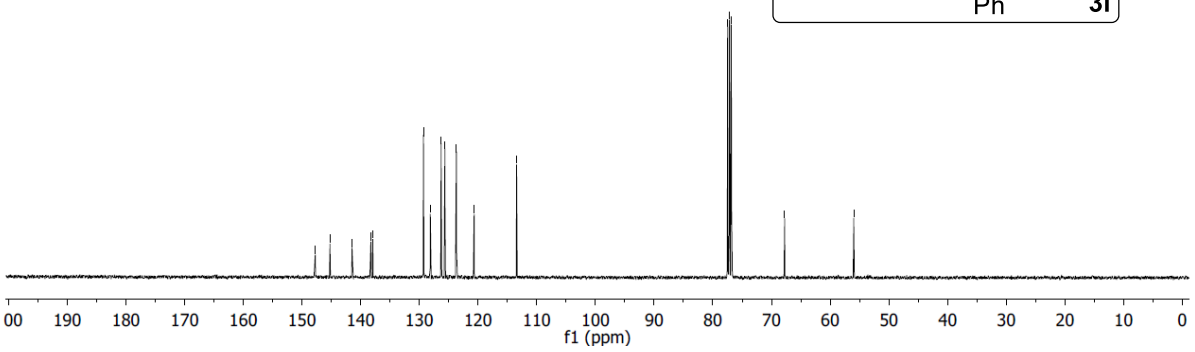


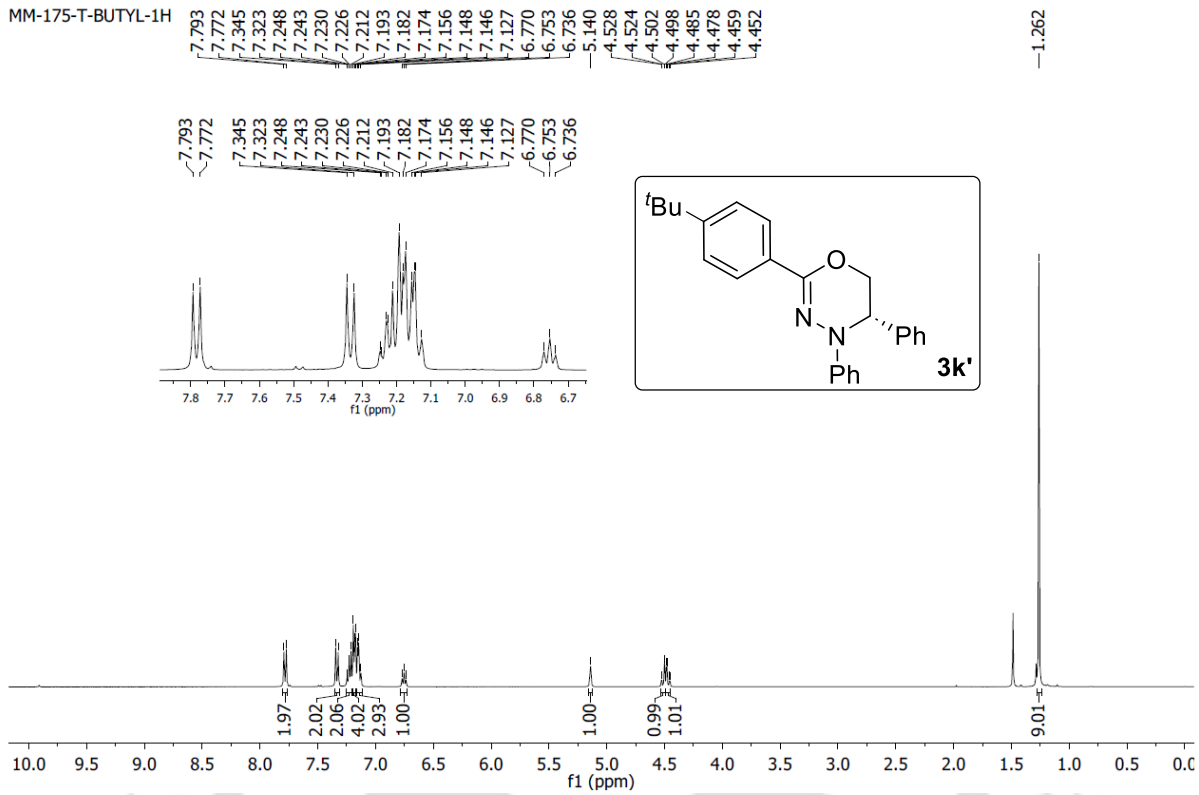


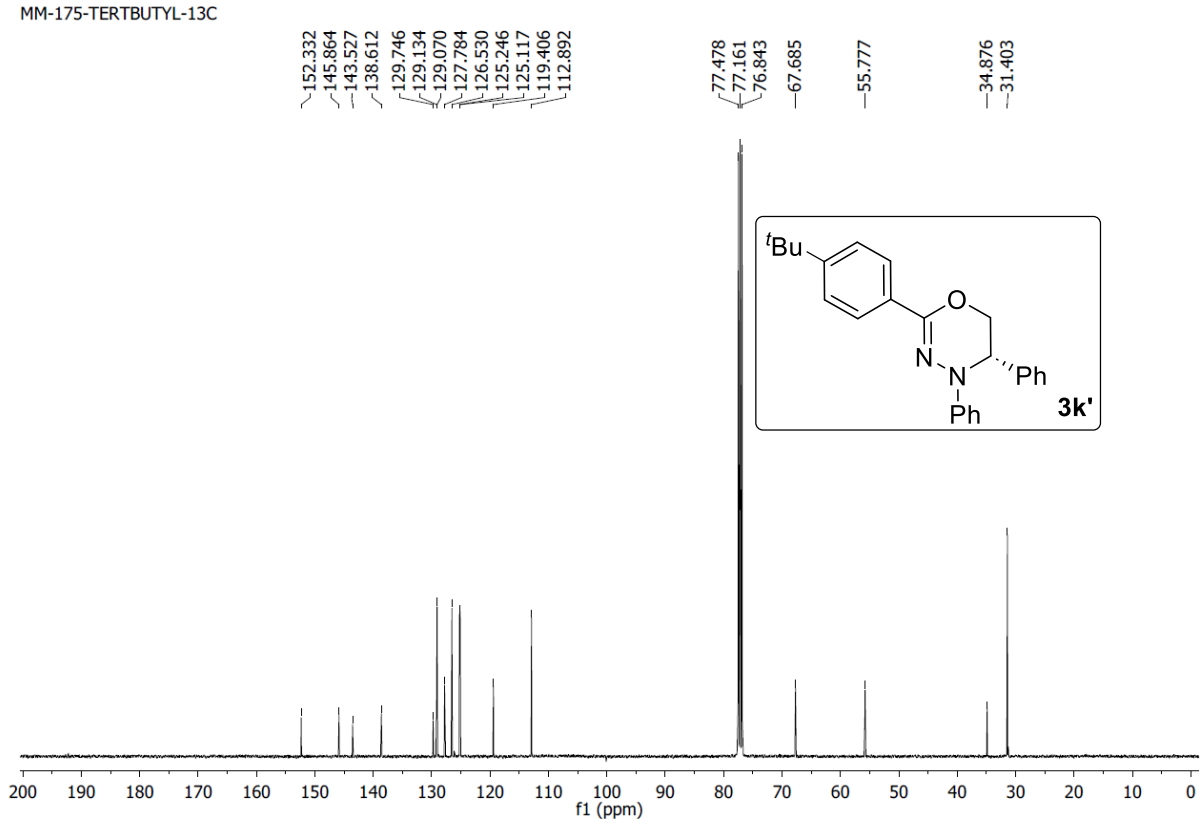
MM-143-NO2-13C

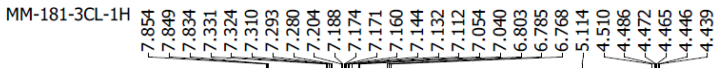


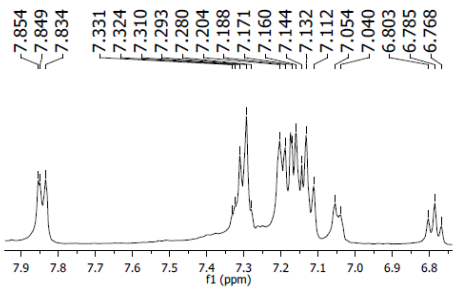


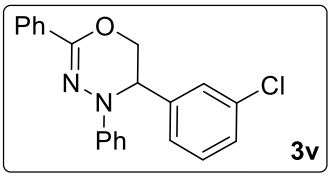


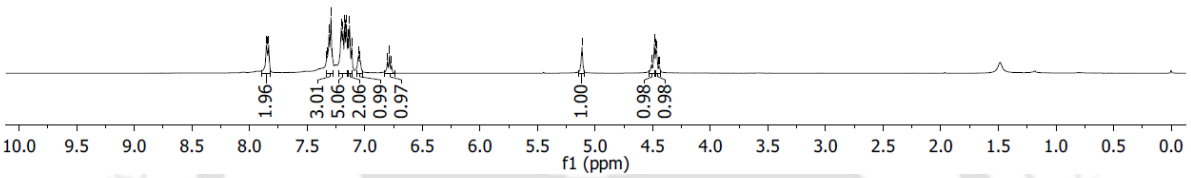


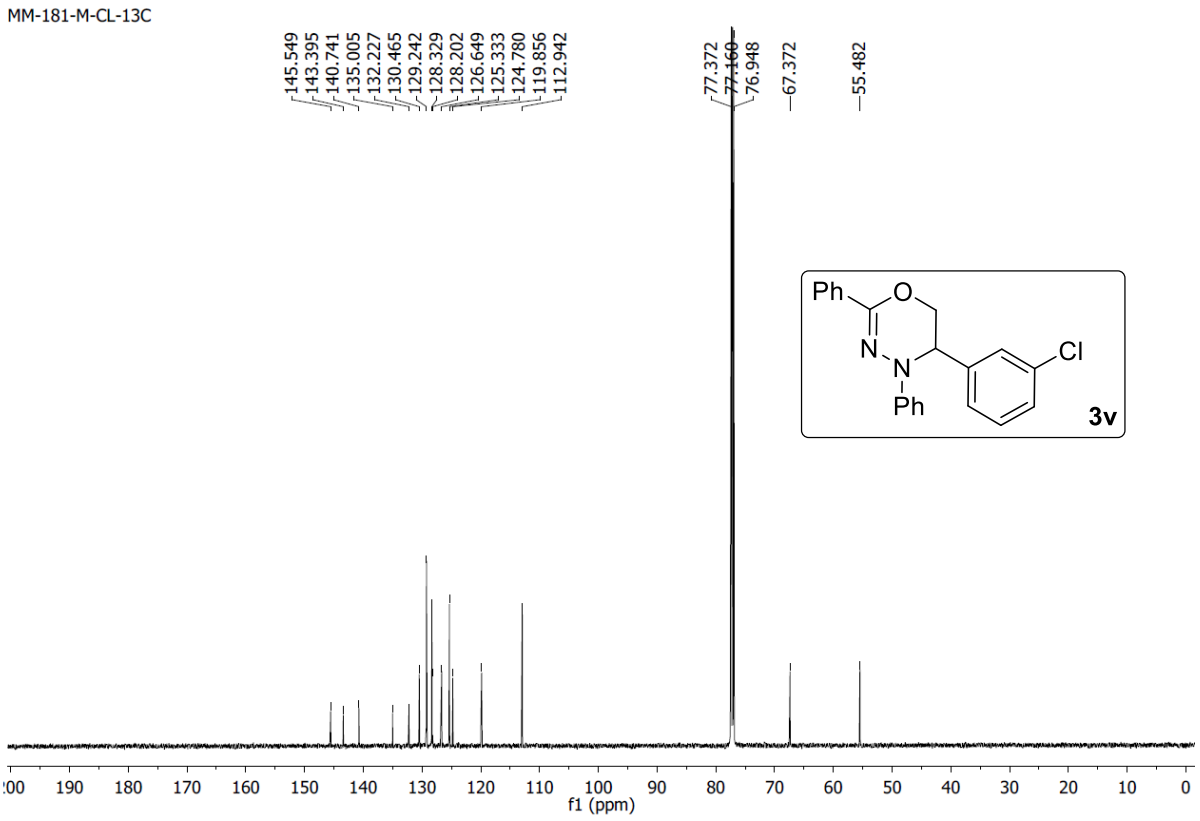






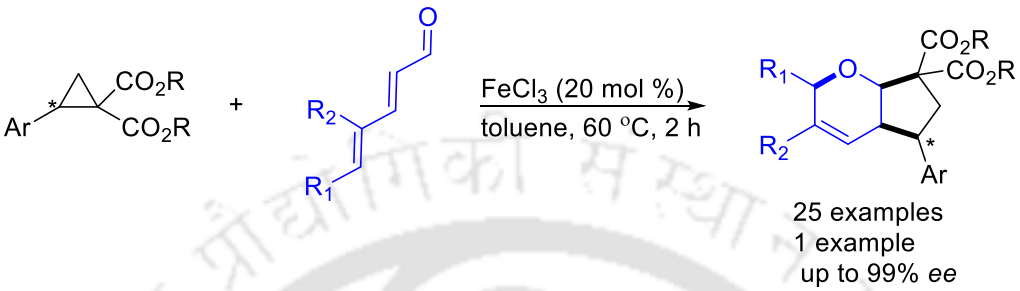






Chapter-IV

Iron(III)-Catalyzed Stereoselective Synthesis of Pyrans



✔ *high enatiopurity* ✔ *regeoselective* ✔ *benign iron catalyst*

Chemm. Commun., **2024**, *60*, 2788.

Iron(III)-Catalyzed Stereoselective Synthesis of Pyrans

Pyran is an important prevalent structural subunit and present in a broad spectrum of natural products, such as sugars, coumarins, flavonoids, xanthones etc.[1] The pyran containing natural products are often used as anti-cancer agents, so they have grabbed more attention in their commercial synthesis (Figure 1). Therefore, rapid construction of pyrans from readily available starting materials would be worthy rewarding task.[2] Hence, the multiple bond formation strategy in a single chemical operation would be attractive for the strategy. Aldehydes, especially unsaturated aldehydes are the celebrated precursors in organic synthesis. Notably, α,β,γ,δ-di-unsaturated aldehydes could allow the construction of C-C or C-hetero bonds leaving behind the unsaturated C=C bond for further modification.[3] Precisely, 2,4-dienals in presence of Lewis or Brønsted acid can transform into an oxyallyl cation intermediate, therefore can be useful to synthesize valuable organic parallels by suitable carbon or heteroatom-based nucleophiles in an interrupted iso-Nazarov process.[4] However, the cycloaddition at C2-C3 backbone is quite challenging due to the competing 1,2- as well 1,4-additions in 2,4-dienals.[5] In this context, D-A cyclopropanes can be casted as valuable coupling partners to achieve skeletal diversity as well as efficient functionality.[6] The easy availability as well as their masked 1,3-zwitterionic blueprint have positioned them into a special rank in wide range of organic reactions.[7] Towards this goal, a sustainable and eco-friendly catalytic approach would be praise worthy in organic synthesis. In this context, iron catalyzed reactions are gaining prominence in synthetic chemistry due to their associated economic and environmental benefits.[8] Herein, we presented an efficient Fe-catalyzed domino [3+2]-cycloaddition of D-A cyclopropanes with 2,4-dienals *via* ketene intermediate followed by a C-O bond forming cascade to synthesize biologically important pyran derivatives. The reaction is regio- and stereospecific. The biologically active mutated substrates were cyclized efficiently.

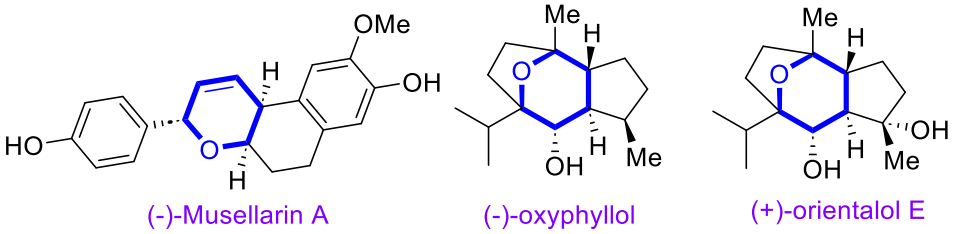
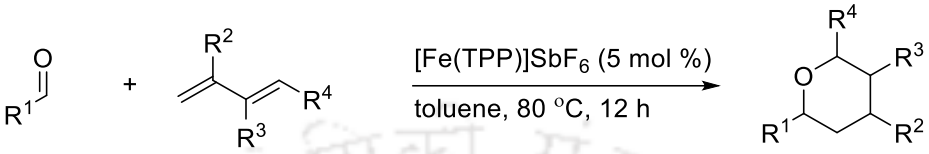


Figure 1. Examples of biologically active pyrans

4.1 Literature Survey

4.1.1 [4+2]-Cycloaddition

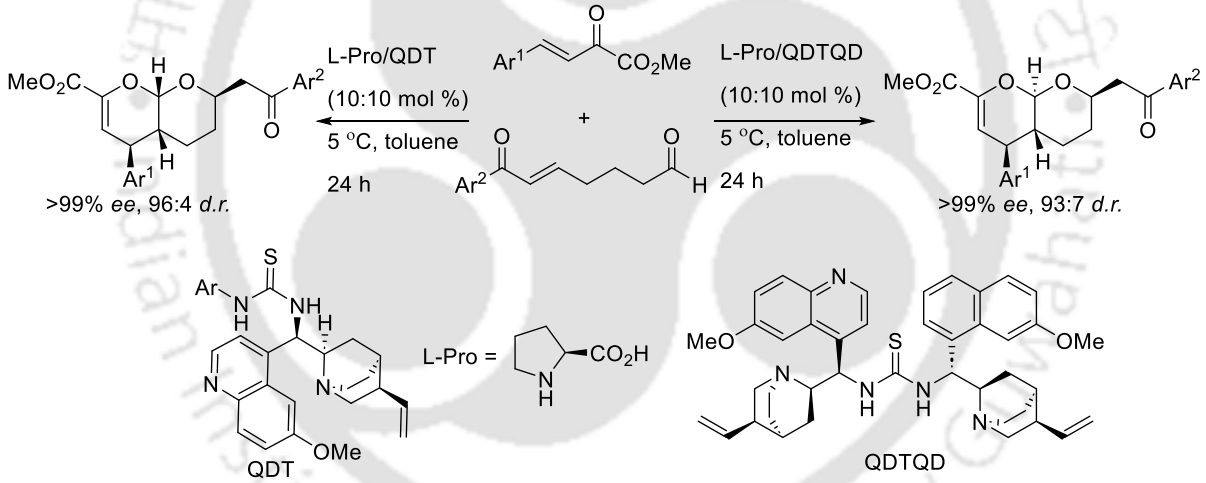
A cationic iron-porphyrin catalyzed [4+2]-cycloaddition of unactivated dienes with aldehydes was disclosed by Kurahashi and Matsubara (Scheme 1).[9] The reaction affords a chemoselective transformation to pyrans *via* hetero Diels-Alder reaction.



Scheme 1. Iron-porphyrin Catalyzed Hetero-Diels-Alder Reaction

4.1.2 Aza-Diels-Alder Reaction

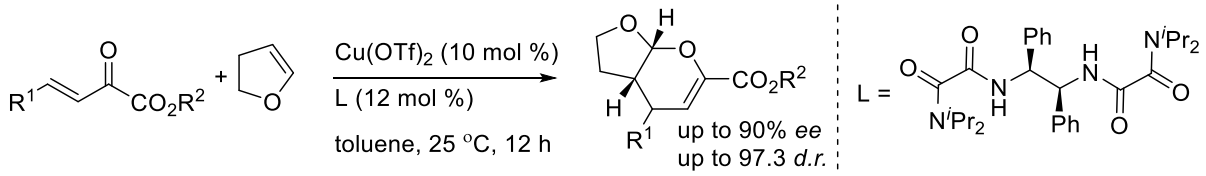
Zhao and co-workers described a modularly designed organocatalysis for the enantio- and diastereoselective synthesis of *cis*- and *trans* pyrans (Scheme 2).[10] The diastereodivergent catalysis was effectively produced the respective isomers *via* aza-Diels-Alder reaction.



Scheme 2. Diastereodivergent Catalysis for *cis*- and *trans*-Pyrans

4.1.3 Oxo-Diels-Alder Reaction

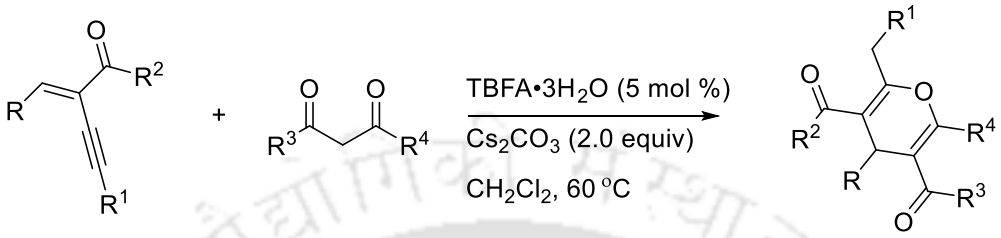
Wang, Xia and Wang combinedly demonstrated an oxo-Diels-Alder reaction of β,γ-unsaturated α-ketoesters with 2,3-dihydrofuran to synthesize enantiopure pyrans (Scheme 3).[11] The chiral bis-oxalamides brought out high enantio- and diasteroselectivity via carbonyl co-ordination.



Scheme 3. Enantio- and Diasteroselective Synthesis of Pyrans

3.1.4 Phase-Transfer Catalysis

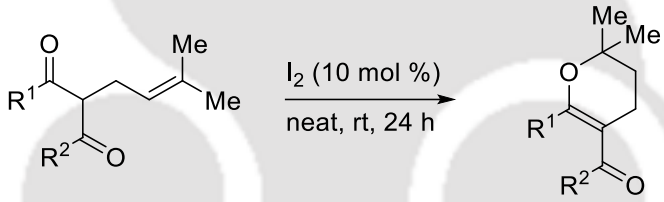
4*H*-Pyran derivatives were prepared in moderate to good yields under the mild reaction conditions by nucleophilic addition to electron-deficient 1,3-conjugated enynes with phase-transfer catalysis by Wang and Liang (Scheme 4).[12]



Scheme 4. Metal-free annulation reaction of enynes with malonates

3.1.5 Intramolecular Cyclization

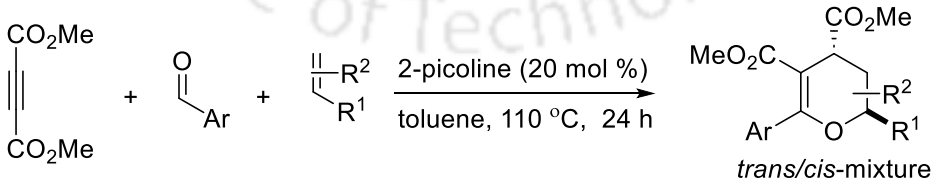
Legault and Nguyen reported a practical synthesis of substituted pyrans and furans using molecular iodine (Scheme 5).[13] The method described was performed under solvent-free conditions at an ambient temperature.



Scheme 5. Molecular Iodine Catalyzed Annulation

3.1.6 [2+2+2]-Cycloaddition

Saito group reported a 2-picoline catalyzed [2+2+2]-cycloaddition of acetylene dicarboxylate, aldehydes and alkenes to synthesize pyrans in high regioselectivity (Scheme 6).[14] The protocol is metal-free and the pyrans were produced in moderate to good yields.

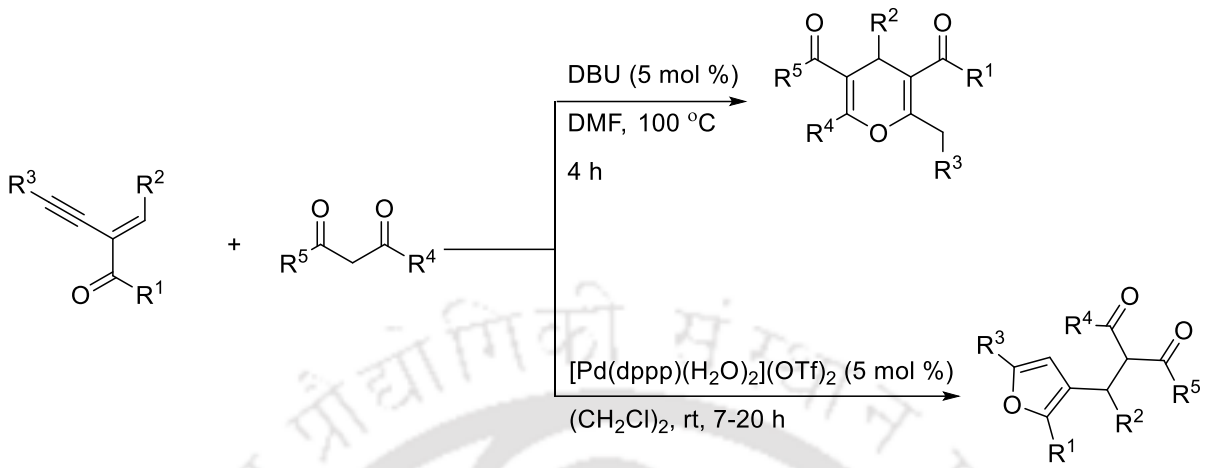


Scheme 6. Regioselective synthesis of pyrans

3.1.7 Regiodivergent Tandem Michael Addition/Cyclization

A catalyst-controlled regiodivergent tandem Michael addition/cyclization of 2-(1-alkynyl)-2-alken-1-ones with 1,3-dicarbonyl compounds was developed by Zhang and co-workers

(Scheme 7).[15] DBU-catalyzed cycloaddition gave pyrans while cationic Pd(II) yielded the furans regioselectively.



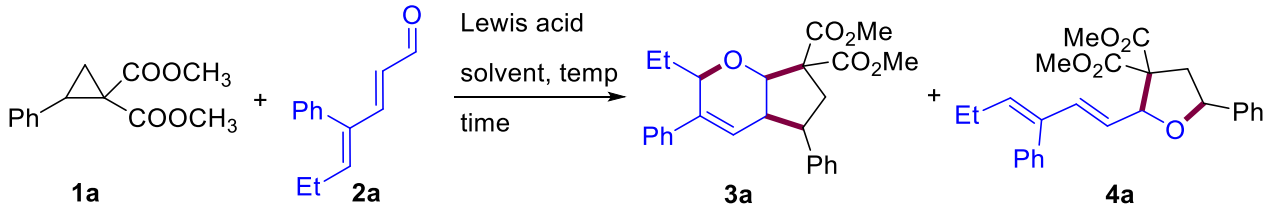
Scheme 7. Catalyst Controlled Regioselective Synthesis of Pyrans and Furans

Pyrans are the important class of biologically active compounds exhibiting interesting medicinal properties as anticancer agents. The above studies elaborate their synthesis emphasizing on cycloaddition strategy and Diels-Alder reactions. Towards this goal, D-A cyclopropanes could be helpful as it can provide a 1,3-synthon and taking 2,4-dienals as the coupling partner for this robust transformation.

3.2 Present Study

We commenced the study with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** and (2*E*,4*Z*)-4-phenylhepta-2,4-dienal **2a** as the model substrates (Table 1). The reactions were carried out using Lewis acids, $Cu(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $Zn(OTf)_2$ and $CoCl_2$ in $(CH_2Cl)_2$ at room temperature for 4 h afforded the 1,2-cycloadduct **4a** exclusively. However, $FeCl_3$ gave the targeted cycloadduct **3a** in 31% yield along with **4a** in 27% yield. Among the solvents screened, toluene was found to be the best, while $(CH_2Cl)_2$, THF, CH_3CN, and HFIP proved to be less effective for the protocol. To mention, the use of stoichiometric amount of $FeCl_3$ only appreciably increases the regioselective transformation of cycloadduct **3a**. To our delight, the selectivity of the target **3a** increased upon the treatment of 20 mol % $FeCl_3$ in toluene at room temperature for 4 h. Increasing the reaction temperature to 60 °C for 2 h, the yield of **3a** improved to 78%. Further increment to 80 °C resulted in a lower yield. In addition, Brønsted acids were futile to bring out the transformation. In a control experiment it was observed that none of the cycloadducts were formed in the absence of the catalyst.

Table 1. Optimization of the Reaction Conditions[a]



Entries	Lewis acid (10 mol %)	Solvents	Additive	Yield[b]	
				3a	**4a**
1	$Cu(OTf)_2$	$(CH_2Cl)_2$		n.d.	58
2	$Yb(OTf)_3$	$(CH_2Cl)_2$		n.d.	65
3	$Sc(OTf)_3$	$(CH_2Cl)_2$		n.d.	62
4	$Zn(OTf)_2$	$(CH_2Cl)_2$		n.d.	trace
5	$CoCl_2$	$(CH_2Cl)_2$		n.d.	trace
6	$FeCl_3$	$(CH_2Cl)_2$		31	27
7	$FeCl_3$	CH_3CN		28	25
8	$FeCl_3$	THF		trace	12
9	$FeCl_3$	HFIP		n.d.	21
10	$FeCl_3$	toluene		35	27
11[c]	$FeCl_3$	toluene		47	38
12[d]	$FeCl_3$	toluene		51	40
13[e]	$FeCl_3$	toluene		45	52
14[f]	$FeCl_3$	toluene		78	10
15[g]	$FeCl_3$	toluene		72	12
16	TfOH	toluene		n.d.	n.d.
17	$TsOH·H_2O$	toluene		n.d.	n.d.
18	$FeCl_3$	toluene	$Sc(OTf)_3$	38	47
19	$FeCl_3$	toluene	$Yb(OTf)_3$	39	47
20	$FeCl_3$	toluene	$TsOH·H_2O$	32	51
21		toluene		n.d.	n.d.

[a]Reaction conditions; **1a** (0.1 mmol), **2a** (0.12 mmol), bIsolated yield; Lewis acid (10 mol %), additive (10 mol %), solvent (1.5 mL), under air, 4 h, room temperature. [b]Isolated yield. [c]$FeCl_3$

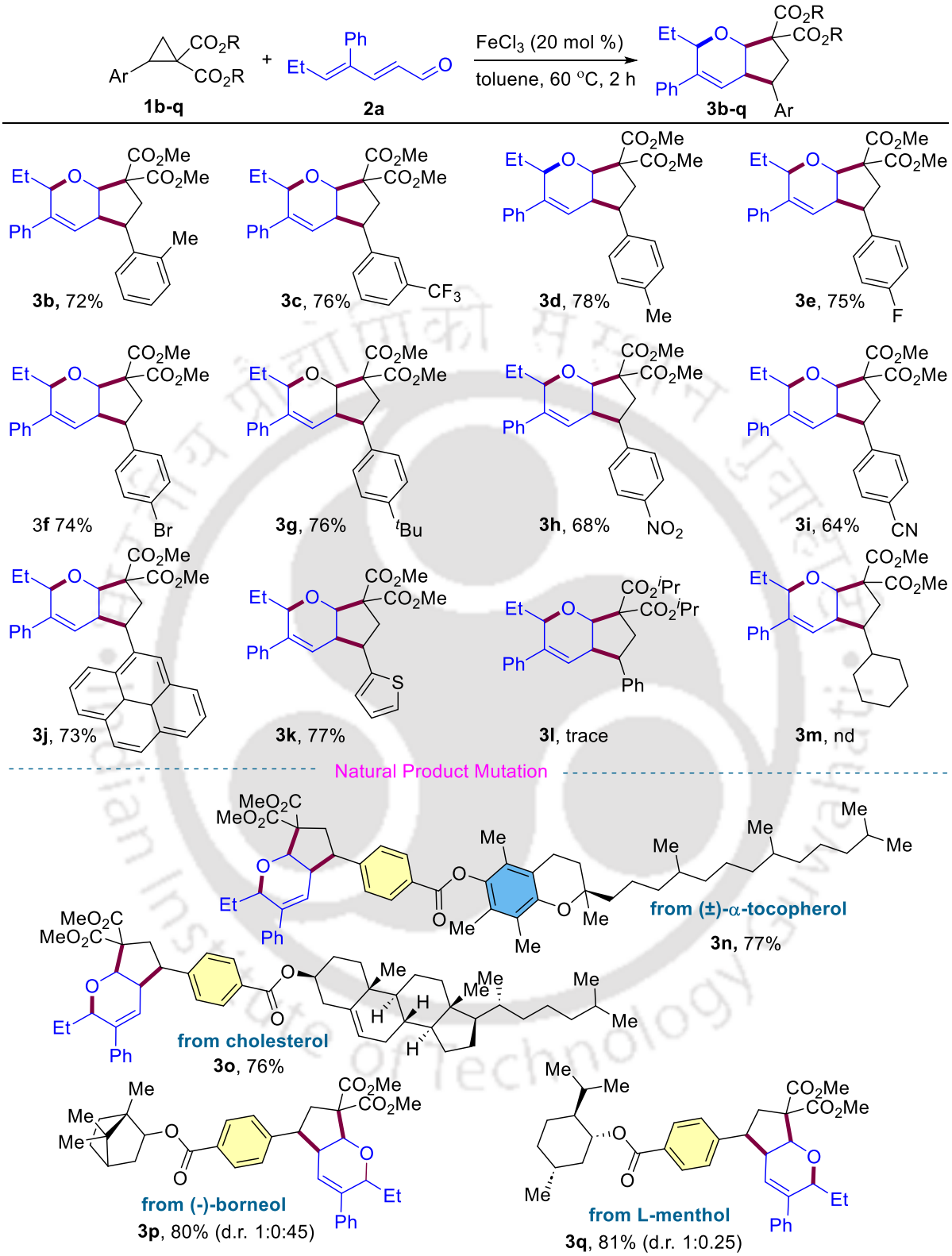
(20 mol %). [d]$FeCl_3$ (30 mol %). [e]$FeCl_3$ (0.5 equiv). [f]$FeCl_3$ (20 mol %), and 60 °C, 2 h. [g]$FeCl_3$ (20 mol %) and 80 °C, 2 h.

We next investigated the scope of the regioselective reaction by engaging the substituted D-A cyclopropanes (**1b-q**) with (2*E*,4*Z*)-4-phenylhepta-2,4-dienal **(2a)** as the model substrate (Table 2). The 2-tolyl D-A cyclopropane **1b** underwent the cycloaddition readily furnishing **3b** in 72% yield. Electron-withdrawing 3-CF_3 substituent **1c** well tolerated and delivered **3c** in 76% yield. The 4-substituted D-A cyclopropanes i.e. 4-methyl **1d**, 4-fluoro **1e**, 4-bromo **1f**, 4-*tert*-butyl **1g**, 4-nitro **1h** and 4-cyano **1i** were efficiently converted into the cycloadducts **3d-i** in 64-78% yields. In addition, 2-pyrene **1j** and heterocyclic thienyl **1k** conveyed the target products **3j** and **3k** in 73% and 77% yields, respectively. Under this condition, a diester variant of the D-A cyclopropane **1l** gave the cycloadduct **3l** in trace amount whereas cyclohexyl **1m** was an unsuccessful substrate. Gratifyingly, the natural product derived D-A cyclopropanes such as (±)-α-tocopherol **1n** and cholesterol **1o** successfully followed the strategy and produced the privileged **3n** and **3o** in 77% and 76% yields respectively. Similarly, terpenoid derived D-A cyclopropane **1p** and **1q** were able to give desired **3p** (*dr* 1:0.45) and **3q** (*dr* 1:0.25) in 80% and 81% yield respectively.

We next evaluated the diversification of 2,4-dienals **2b-i** with dimethyl 2-phenylcyclopropane-1,1-dicarboxylate **1a** as the standard substrate (Scheme 3). Presence of aliphatic substituents at the C-5 position of 2,4-dienals such as methyl **2b**, *iso*-propyl **2c** and *iso*-butyl **2d** afforded the desired **3r**, **3s** and **3t** in 61-76% yields. In contrast, aliphatic *trans*,*trans*-2,4-hexadienal **2e** and *trans*,*trans*-2,4-nonadienal **2f** were amenable to the reaction affording **3u** and **3v** in 83% and 86% yields, respectively. Intriguingly, a 2-naphthyl substituent **2g** installed at C-5 position of the 2,4-dienal served to the sequence delivering **3w** in 78% yield. However, the thiophene derived dienal **2h** gave **3x** in trace amount, while biphenyl dienal **2i** was unable to afford the desired cycloadduct.

To shed light on the reaction mechanism, we carried out several control experiments. First, to check the stereospecificity, the reaction of (*R*)-cyclopropane **1a′** was investigated with (2*E*,4*Z*)-4-phenylhepta-2,4-dienal **2a** (Scheme 8). The coupling occurred efficiently to produce **3a′** in high enantiopurity i.e. >99% ee. This result indicated a stereoselective S_N2 ring opening of the D-A cyclopropane. Further, a reaction of **1a** and **2a** independently in presence of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavengers were demonstrated (Scheme 9a). However, the reaction remained unaffected, thus

Table 2. Substrate Scope of D-A Cyclopropanes[a,b]

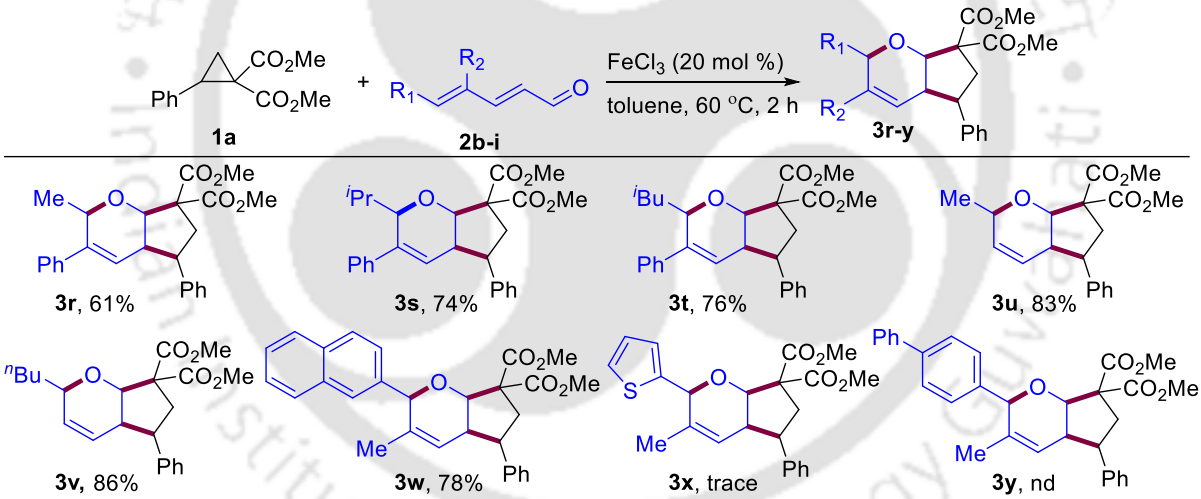


[a]Reaction conditions; **1b-q** (0.1 mmol), **2a** (0.12 mmol), $FeCl_3$ (20 mol %), toluene (1.5 mL), 60 °C, 2 h. [b]Isolated yield. n.d. = not detected.

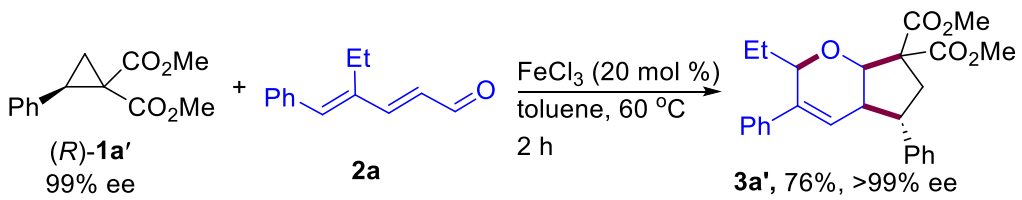
ruled out an involvement of a radical pathway. In addition, a lactam **6** was detected by *ESI-MS* upon treating the imine **5** to the standard reaction condition in presence of **1a** and **2a** (Scheme 9b). This result signposted the formation of ketene intermediate **7** which might undergo a formal [2+2] cycloaddition reaction with the imine. Thus, $FeCl_3$-catalyzed 1,5-H shift[18a-c] of 2,4-dienal **2a** may deliver the ketene **7**, which can couple with D-A cyclopropane **1a** *via* S_N2 ring opening to form the cycloadduct **8**[7d] (Scheme 10). In another 1,5-H shift, the allylic intermediate **9** may undergo a nucleophilic attack on C-5 centre[18d] to give the product **3a.**

To further demonstrate the usability of this strategy, a scale-up reaction was investigated using 3 mmol of **1a** with **2a** as the representative substrates to produce the cycloadduct **3a** in 62% yield (Scheme 11a). In addition, a Krapcho decarboxylation of **3a** was carried out in presence of LiCl in DMSO. The resulting monoester **10** was found to be in 67% yield (*dr* 1:0.25) (Scheme 11b).

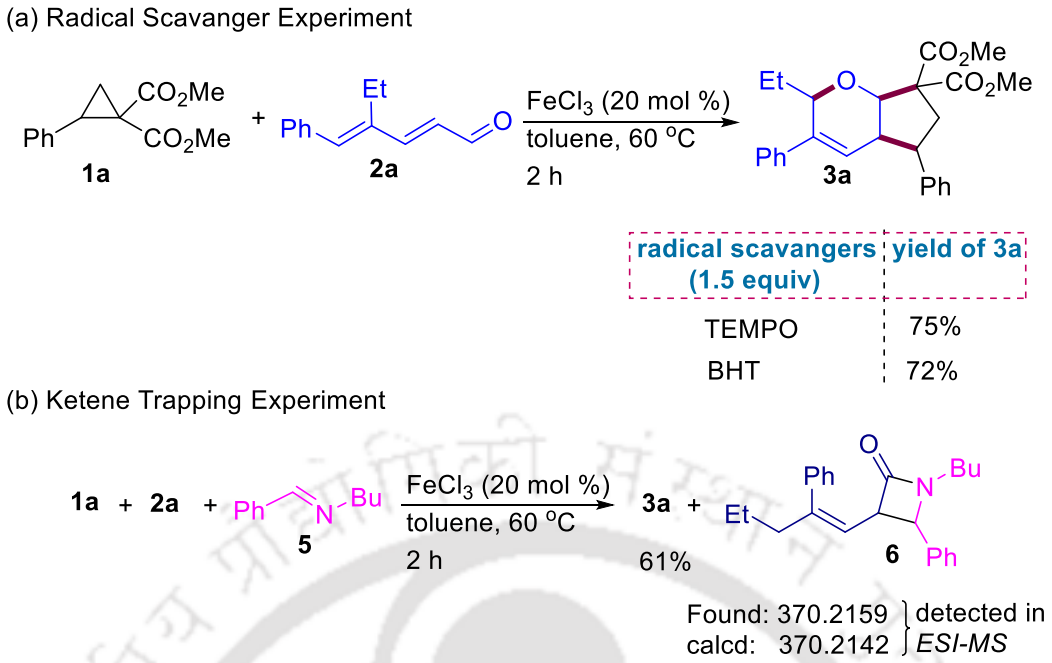
Table 3. Substrate Scope of 2,4-Dienals[a,b]



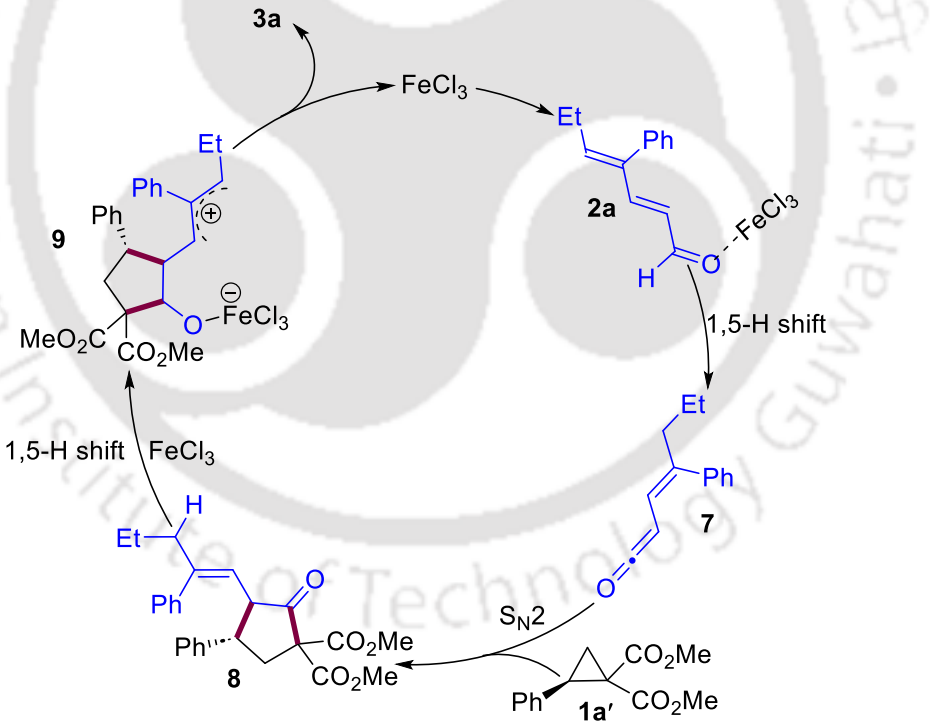
[a]Reaction conditions; **1a** (0.1 mmol), **2b-i** (0.12 mmol), $FeCl_3$ (20 mol %), toluene (1.5 mL), 60 °C, 2 h. [b]Isolated yield. n.d. = not detected.



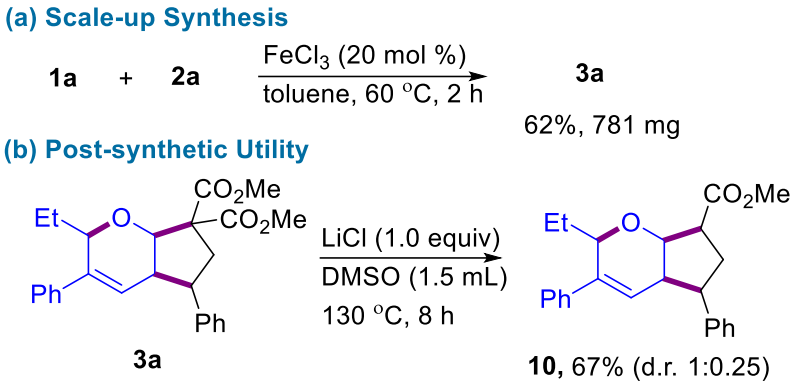
Scheme 8. Stereospecificity Experiment



Scheme 9. Preliminary Mechanistic Investigations



Scheme 10. Plausible Catalytic Cycle



Scheme 11. Scale-up and Post-Synthetic Utility

In conclusion, a Fe-catalyzed regioselective C-C/C-O bond forming cascade of D-A cyclopropanes with 2,4-dienals has been efficiently delivered. It described a sequential stereospecific cycloaddition followed by a nucleophilic O-attack to construct biologically active hexahydro pyrans. The simple operational method, functional group tolerance and using inexpensive Fe-catalyst are the important practical features.

3.3 Experimental Section

General Information. $FeCl_3$ (98%), $Yb(OTf)_3$ (99.99%), $Cu(OTf)_2$ (98%), $Sc(OTf)_3$ (99%), $Zn(OTf)_2$ (98%), $CoCl_2$ (97%), TfOH (≥99%), $TsOH{\cdot}H_2O$ (≥98%), *trans*,*trans*-2,4-hexadienal (95%) and *trans*,*trans*-2,4-nonadienal (>85.0%) of SRL, Aldrich and TCI were used as received. D-A cyclopropanes and 2,4-dienals were prepared according to literature.[16,17] Merck silica gel G/GF 254 plates were used for the analytical TLC and rankem silica gel (100-200 mesh) was used for the column chromatography. NMR (^1H and ^{13}C) spectra were recorded in Bruker Avance III 400, 500 and 600 spectrometers using $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (*J*) are reported in ppm and in Hz, respectively and other data are reported as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, bt = broad triplet and m = multiplet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier Transform Infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (model HAB 273) was used for mass spectra. Optical rotation was determined using a Rudolph Autopol I Automatic Polarimeter. HPLC analysis was carried out using Waters-2489 with YMC Chiral ART Cellulose-SC column using *iso*-propanol and hexane as eluent. Single-crystal X-ray data was collected using Brucker

SMART APEX-II CCD area detector using Mo-Kα irradiation and the structure was solved by using *SHELXL-18* (Gottingen, Germany).

Preparation of D-A Cyclopropanes. To a stirred solution of aldehyde (5 mmol) in benzene (10 mL), dimethyl malonate (5 mmol, 660 mg), piperidine (0.5 mmol, 50 μL) and acetic acid (0.5 mmol, 28 μL) were added and the solution was heated to reflux in an oil bath. After completion, evaporation of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate and hexane as an eluent. Sodium hydride (4 mmol, 60% dispersion in mineral oil, 96 mg) was suspended in dimethylformamide (DMF) (10 mL) under nitrogen. Trimethylsulfoxonium iodide (3.85 mmol, 847 mg) was added, and the solution was stirred for 1 h at room temperature. A solution of the appropriate benzylidene malonate (3.5 mmol) in DMF (1 mL) was added, and the reaction mixture was stirred overnight at room temperature. After completion (monitored by TLC), the solution was poured onto a mixture of ice and 2N HCl (5 mL) and extracted with ethyl acetate (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatograph using ethyl acetate and hexane as an eluent to give cyclopropanes.

Preparation of Chiral Cyclopropane 1a′. To a stirred solution of (*R*)-1-phenylethane-1,2-diol (2.2 mmol, 304 mg) in CH_2Cl_2 (5 mL) at 0 °C was added NEt_3 (6.5 mmol, 1 mL). After 10 min, a solution of MsCl (5.4 mmol, 618 mg) in CH_2Cl_2 (1 mL) was added for 1 h dropwise. The resultant mixture was warmed to room temperature and the stirring was continued for an additional 4 h. The reaction mixture was poured to 1N HCl (5 mL) and extracted using CH_2Cl_2 (30 mL). The combined organic layer was washed with 1N HCl (5 mL), saturated $NaHCO_3$ (5 mL) and water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was used in the next step. To a suspension of sodium hydride (0.9 mmol, 60% dispersion in mineral oil, 22 mg) in THF (5 mL) was added a solution of dimethyl malonate (0.6 mmol, 79 mg) in THF (0.5 mL) for 20 min at 0 °C. The resultant mixture was treated with a solution of the above-prepared bismesylate (0.3 mmol, 88 mg) in THF (0.5 mL) dropwise (0 °C). The reaction mixture was stirred under reflux for 24 h in an oil bath, poured into water (2 mL) and extracted with ethyl acetate (15 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatograph using ethyl acetate and hexane as an eluent to afford the chiral cyclopropanes **1a′**.

Preparation of 2,4-Dienal. To a freshly prepared solution of Ph_3PCHCO_2Et (3 mmol, 1 g) in THF (20 mL) at 0 °C, sodium hydride (4.5 mmol, 60% dispersion in mineral oil, 110 mg) was

added slowly followed by the enals (2.5 mmol). After the reaction completed (monitored by TLC), the mixture was quenched with H_2O (15 mL). THF was evaporated under reduced pressure and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic solution was washed with brine (10 mL), dried (Na_2SO_4) and concentrated and used for next step without further purification.

The crude product was diluted with 20 mL toluene at -78 °C under an argon atmosphere, and DIBAL-H (5.0 mL) was added dropwise. After the reaction completed (monitored by TLC), the mixture was quenched with aqueous NH_4Cl (5.0 mL). The solid was removed by filtration through celite. The filtrate was extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4), concentrated and used for next step without further purification.

The crude product was diluted with DMSO (5 mL), and IBX (4.5 mol, 1.2 g) was added. After the reaction completed (monitored by TLC), the solid was removed by filtration through celite. The filtrate was extracted with CH_2Cl_2 (30 mL). The combined organic layer was washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography using ethyl acetate and hexane to give **2a-h**.

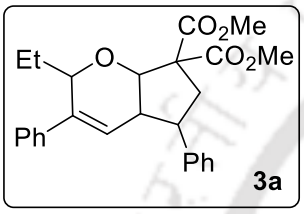
Preparation of dihydro-2*H*-pyran 3. D-A cyclopropanes **1a-q** (0.1 mmol), 2,4-dienals **2a-h** (0.11 mmol) and $FeCl_3$ (20 mol %, 3 mg) were stirred in toluene (1.5 mL) at 60 °C for 2 h using $CaCl_2$ drying tube in an oil bath. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL) and washed with water (2 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using ethyl acetate and hexane as the eluent to give the desired cycloadduct **3a-y**.

Enantiospecific Synthesis of dihydro-2H-pyran 3a'. (*R*)-Cyclopropane **1a'** (0.1 mmol, 23 mg), 2,4-dienal **2a** (0.11 mmol, 19 mg) and $FeCl_3$ (0.02 mmol, 3.0 mg) were stirred at 60 ^oC for 2 h in an oil bath. The purification was carried out as above-described general procedure. The *ee* was determined using chiral HPLC analysis.

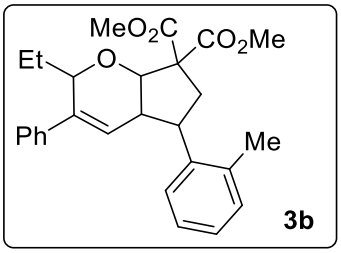
Gram-Scale Synthesis of 3a. Cyclopropane **1a** (3 mmol, 700 mg), 2,4-dienal **2a** (3.3 mmol, 613 mg) and $FeCl_3$ (20 mol %, 97 mg) were stirred in toluene (10 mL) at 60 °C for 2 h. The purification was carried out as above-described general procedure and the cycloadduct **3a** was obtained in 62% yield (781 mg).

Synthesis of 10. Compound **3a** (0.07 mmol, 30 mg), DMSO (2 mL), water (0.5 mL) and LiCl (0.21 mmol, 8.0 mg) were placed in a 10 mL round bottomed flask equipped with a magnetic stirrer and fitted with a condenser. The mixture was heated at 130 °C in an oil bath for 8 h. After completion (monitored by TLC), the reaction mixture was cooled to room temperature, poured into ice cold water and washed with brine (5 mL). The organic layer was collected over ethyl acetate (10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as an eluent to give **10** in 68% yields (17 mg)**.**

3.4 Characterization Data

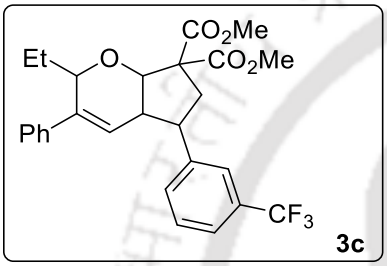


Dimethyl 2-ethyl-3,5-diphenyl-4a,5,6,7a-*tetra*-hydro-cyclopenta-[b]pyran-7,7(2H)-dicarboxylate 3a. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.45; Yellow sticky liquid; yield 78% (34 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.36 (m, 2H), 7.35-7.34 (m, 4H), 7.32-7.30 (m, 1H), 7.29-7.27 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 15.6 Hz, 1H), 5.79 (t, *J* = 7.2 Hz, 1H), 5.37-5.35 (m, 2H), 5.12 (dd, *J* = 6.6 Hz, 15.6 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 3.14 (dd, *J* = 7.2 Hz , 13.2 Hz, 1H), 2.26 (dd, *J* = 8.4 Hz, 13.2 Hz, 1H), 1.97-1.92 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.2, 142.3, 139.7, 138.1, 137.2, 136.8, 129.5, 128.5, 128.2, 127.6, 126.9, 125.5, 125.2, 83.3, 79.9, 65.1, 52.8, 52.6, 42.7, 22.6, 14.2; FT-IR (neat) 2955, 1732, 1608, 1515, 1435, 1259, 1167, 1074 cm^{-1}; **3a′**: $[\alpha]_D^{25}$ = +20 (*c* = 0.02, $CHCl_3$); HPLC analysis: 99% ee [YMC Chiral ART Cellulose-SC column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R = 7.82 min (major), 10.97 min (minor)]; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{29}O_5^+$: 421.2010, found: 421.2002.

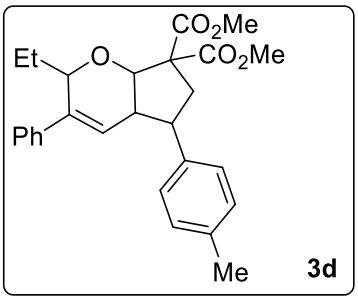


Dimethyl 2-ethyl-3-phenyl-5-(o-tolyl)-4a,5,6,7a-tetra-hydro-cyclopenta[b]pyran-7,7(2H)-dicarboxylate 3b. Analytical TLC on silica gel, 2:98 ethyl

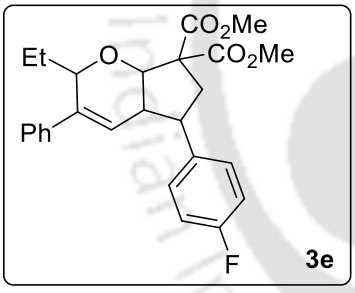
acetate/hexane; R_f = 0.50; Yellow sticky liquid; yield 72% (33 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.31-7.29 (m, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.13-7.11 (m, 3H), 6.69 (d, *J* = 15.6 Hz, 1H), 5.78 (t, *J* = 7.2 Hz, 1H), 5.52 (t, *J* = 7.8 Hz, 1H), 5.40 (d, *J* = 6.6 Hz, 1H), 5.13 (dd, *J* = 7.2 Hz, 15.6 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 3.18 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.31 (s, 3H), 2.08 (dd, *J* = 8.4 Hz, 13.2 Hz, 1H), 1.97-1.92 (m, 2H), 0.94 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.0, 169.3, 140.6, 139.8, 138.1, 137.1, 136.8, 134.2, ,130.4, 129.5, 128.2, 127.2, 126.9, 126.2, 125.3, 124.2, 83.2, 77.5, 65.0, 52.8, 52.6, 41.5, 22.6, 19.3, 14.2; FT-IR (neat) 2955, 1733, 1601, 1492, 1435, 1373, 1246, 1169, 1072 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{27}H_{30}NaO_5^+$: 457.1985, found: 457.1980.



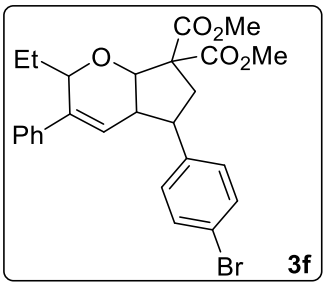
Dimethyl 2-ethyl-3-phenyl-5-(3-(trifluoromethyl)phenyl)-4a,5,6,7a-tetrahydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3c. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.42; Yellow sticky liquid; yield 76% (25 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.53 (t, *J* = 6.6 Hz, 2H), 7.48-7.45 (m, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 15.0 Hz, 1H), 5.80 (t, *J* = 7.8 Hz, 1H), 5.41 (t, *J* = 7.2 Hz, 1H), 5.38 (d, *J* = 7.2 Hz, 1H), 5.10 (dd, *J* = 6.6 Hz, 15.0 Hz, 1H), 3.68 (s, 3H), 3.62 (s, 3H), 3.17 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.23 (dd, *J* = 7.8 Hz, 13.2 Hz, 1H), 1.97-1.92 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.0, 143.4, 139.7, 138.0, 137.4,, 137.1, 131.2, 129.5, 129.0, 128.9, 128.2, 127.0, 126.9, 124.9, 124.4, 122.3, 83.5, 79.2, 65.0, 52.9, 52.7, 42.5, 22.6, 14.2; FT-IR (neat) 2956, 1732, 1601, 1493, 1328, 1258, 1164, 1072 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1649.



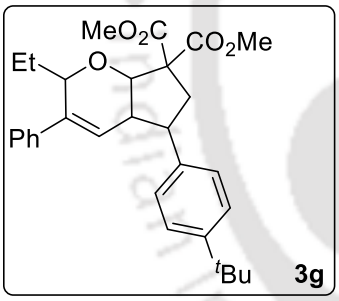
Dimethyl 2-ethyl-3-phenyl-5-(p-tolyl)-4a,5,6,7a-tetra-hydro-cyclo-penta[b]pyran-7,7(2H)-dicarboxylate 3d. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.52; Yellow sticky liquid; yield 78% (34 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 2H), 7.28-7.20 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.13-7.11 (m, 2H), 7.09 (d, *J* = 6.8 Hz, 2H), 6.63 (d, *J* = 15.2 Hz, 1H), 5.74 (t, *J* = 7.6 Hz, 1H), 5.32-5.37 (m, 2H), 5.08 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H), 3.66 (s, 3H), 3.57 (s, 3H), 3.08 (dd, *J* = 6.8 Hz 13.2 Hz, 1H) 2.31 (s, 3H), 2.21 (dd, *J* = 8.4 Hz, 13.2 Hz, 1H) 1.95-1.87 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 169.3, 139.8, 139.2, 138.1, 137.2, 137.1, 136.7, 129.5, 129.2, 128.2, 126.9, 125.5, 125.3, 83.2, 79.8, 65.1, 52.8, 52.5, 42.7, 22.6, 21.2, 14.2; FT-IR (neat) 2960, 1732, 1683, 1518, 1488, 1249, 1203, 1071cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{31}O_5^+$: 435.2166, found: 435.2164.



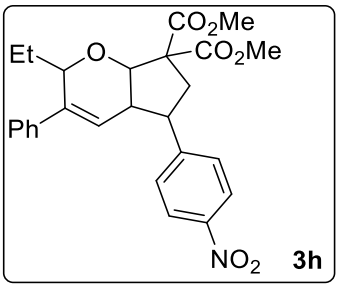
Dimethyl 2-ethyl-5-(4-fluorophenyl)-3-phenyl-4a,5,6,7a-tetra-hydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3e. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.40; Yellow sticky liquid; yield 75% (34 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.33 (m, 2H), 7.30-7.27 (m, 3H), 7.09-7.07 (m, 2H), 7.03-6.98 (m, 2H), 6.63 (d, *J* = 15.6 Hz, 1H), 5.76 (t, *J* = 7.6 Hz, 1H), 5.33-5.28 (m, 2H), 5.06 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 3.66 (s, 3H), 3.58 (s, 3H), 3.08 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.18 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H) 1.95-1.87 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.2, 163.5, 161.0, 139.7, 138.0, 137.96, 137.93, 137.3, 137.0, 129.5, 128.2, 127.3, 127.2, 127.0, 125.0, 115.5, 115.3, 83.4, 79.4, 65.1, 52.9, 52.6, 42.7, 22.6, 14.2; FT-IR (neat) 2958, 1736, 1603, 1511, 1436, 1226, 1158, 1078 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{26}H_{27}FNaO_5^+$: 461.1735, found: 461.1735.



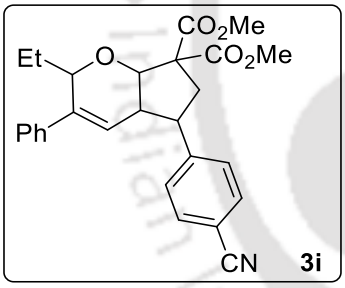
Dimethyl 5-(4-bromophenyl)-2-ethyl-3-phenyl-4a,5,6,7a-tetrahydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3f. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.40; Yellow sticky liquid; yield 74% (36 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 15.6 Hz, 1H), 5.78 (t, *J* = 7.2 Hz, 1H), 5.33 (d, *J* = 7.2 Hz, 1H), 5.30 (t, *J* = 7.2 Hz, 1H), 5.08 (dd, *J* = 6.6 Hz, 15.0 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.11 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.18 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 1.96-1.91 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.1, 141.4, 139.7, 138.0, 137.4, 137.0, 131.6, 129.5, 128.2, 127.2, 127.0, 125.0, 121.3, 83.4, 79.2, 65.0, 52.9, 52.6, 42.5, 22.6, 14.2; FT-IR (neat) 2925, 1732, 1489, 1434, 1265, 1220, 1174, 1070 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{28}BrO_5^+$: 499.1115, found: 499.1113.



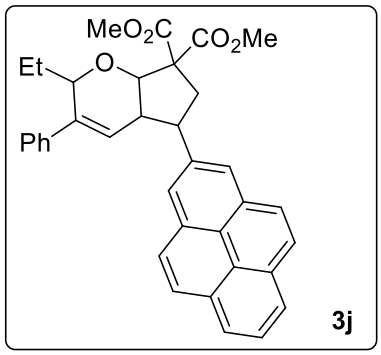
Dimethyl 5-(4-(tert-butyl)phenyl)-2-ethyl-3-phenyl-4a,5,6,7a-tetrahydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3g. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.52; Yellow sticky liquid; yield 76% (36 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.35 (m, 4H), 7.30-7.26 (m, 4H), 7.11 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 15.6 Hz, 1H), 5.76 (t, *J* = 7.2 Hz, 1H), 5.34-5.31 (m, 2H), 5.10 (dd, *J* = 6.6 Hz, 15.6 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.10 (dd, *J* = 6.6 Hz, 13.2 Hz, 1H), 2.26 (dd, *J* = 8.4 Hz, 13.2 Hz, 1H), 1.96-1.91 (m, 2H), 1.32 (s, 9H), 0.93 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 169.4, 150.6, 139.8, 139.1, 138.1, 137.1, 136.7, 129.5, 128.2, 126.9, 125.47, 125.43, 125.3, 83.2, 79.8, 65.1, 52.8, 52.6, 42.6, 34.6, 31.4, 22.6, 14.3; FT-IR (neat) 2957, 1734, 1681, 1513, 1490, 1434, 1254, 1198, 1068 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{30}H_{37}O_5^+$: 477.2636, found: 477.2654.



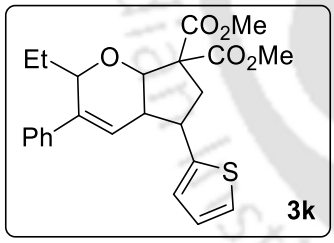
Dimethyl 2-ethyl-5-(4-nitrophenyl)-3-phenyl-4a,5,6,7a-tetra-hydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3h. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.35; Red sticky liquid; yield 68% (31 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.38-7.34 (m, 3H), 7.10-7.07 (m, 2H), 6.65 (d, *J* = 15.6 Hz, 1H), 5.78 (t, *J* = 7.6 Hz, 1H), 5.41 (t, *J* = 7.6 Hz, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 5.06 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 3.65 (s, 3H), 3.59 (s, 3H), 3.17 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.16 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H), 1.96-1.89 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 168.9, 149.9, 147.4, 139.6, 137.9, 137.7, 137.4, 129.5, 128.3, 127.0, 126.2, 124.6, 123.9, 83.8, 78.9, 64.9, 53.0, 52.8, 42.4, 22.7, 14.2; FT-IR (neat) 2956, 1734, 1684, 1601, 1520, 1435, 1380, 1258, 1178, 1075 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{28}NO_7^+$: 466.1860, found: 466.1872.



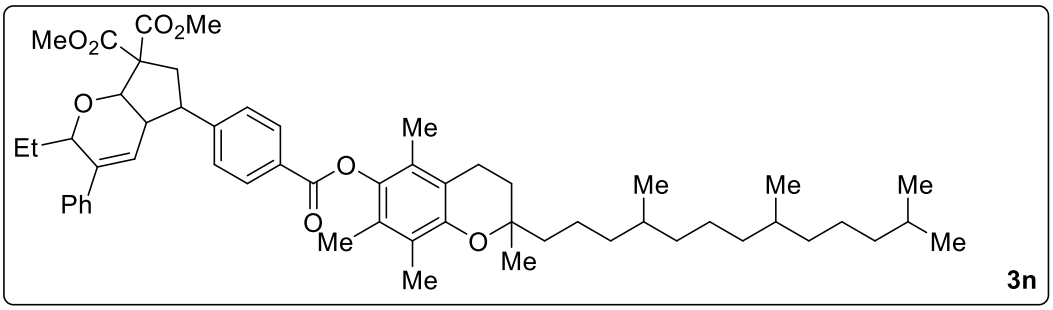
Dimethyl 5-(4-cyanophenyl)-2-ethyl-3-phenyl-4a,5,6,7a-tetra-hydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3i. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.45; Red sticky liquid; yield 64% (28 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.30-7.29 (m, 1H), 7.09-7.07 (m, 2H), 6.64 (d, *J* = 15.6 Hz, 1H), 5.76 (t, *J* = 7.6 Hz, 1H), 5.36 (t, *J* = 7.6 Hz, 1H), 5.32 (d, *J* = 6.8 Hz, 1H), 5.06 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 3.64 (s, 3H), 3.59 (s, 3H), 3.15 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.15 (dd, *J* = 8.0 Hz, 13.2 Hz, 1H), 1.96-1.88 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 168.9, 147.9, 139.6, 137.9, 137.6, 137.3, 132.4, 129.5, 128.2, 127.0, 126.1, 124.6, 118.9, 111.4, 83.7, 79.0, 64.9, 53.0, 52.7, 42.4, 22.6, 14.2; FT-IR (neat) 2954, 2282, 1732, 1607, 1504, 1436, 1334, 1277, 1224, 1154 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{28}NO_5^+$: 446.1962, found: 446.1957.



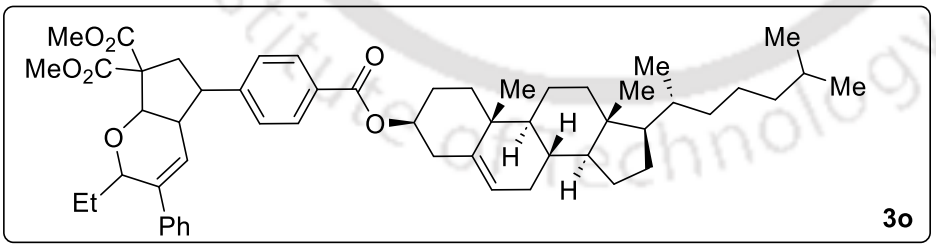
Dimethyl 2-ethyl-3-phenyl-5-(pyren-2-yl)-4a,5,6,7a-tetra-hydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3j. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.35; Colorless solid; mp 160-161 °C; yield 73% (41 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 9.0 Hz, 1H), 8.24-8.19 (m, 4H), 8.08-8.03 (m, 4H), 7.20-7.17 (m, 3H), 7.06-7.05 (m, 2H), 5.794 (dd, *J* = 1.2 Hz, 6.0 Hz, 1H), 4.97 (d, *J* = 3.0 Hz, 1H), 4.84-4.83 (m, 1H), 4.65-4.60 (m, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.58 (dd, *J* = 7.8 Hz, 13.8 Hz, 1H), 3.16-3.12 (m, 1H), 2.24-2.20 (m, 1H), 1.77-1.73 (m, 1H), 1.56-1.51 (m, 1H), 0.97 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 169.4, 141.6, 140.3, 135.4, 131.6, 131.1, 130.1, 129.8, 128.3, 127.6, 127.5, 127.2, 127.0, 126.3, 126.1, 125.4, 125.2, 125.1, 125.08, 125.00, 124.2, 123.5, 122.9, 80.3, 63.9, 52.9, 52.7, 47.4, 46.0, 42.1, 26.8, 9.1; FT-IR (neat) 2951, 1731, 1602, 1492, 1244, 1171, 1068 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{36}H_{32}NaO_5^+$: 567.2142, found: 567.2132.



Dimethyl 2-ethyl-3-phenyl-5-(thiophen-2-yl)-4a,5,6,7a-tetra-hydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3k. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.50; Colorless solid; mp 138-139 °C ; yield 77% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21-7.15 (m, 4H), 6.98-6.96 (m, 1H), 6.88-6.87 (m, 1H), 6.84-6.82 (m, 2H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.67 (d, *J* = 15.0 Hz, 1H), 5.27 (dd, *J* = 2.0 Hz, 9.0 Hz, 1H), 4.58 (d, *J* = 4.0 Hz, 1H), 4.42-4.40 (m, 1H), 3.87-3.82 (m, 1H), 3.796-3.793 (m, 6H), 3.25-3.19 (m, 1H), 3.10-3.04 (m, 1H), 2.66 (dd, *J* = 7.6 Hz, 13.6 Hz, 1H), 1.56-1.51 (m, 2H), 0.82 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 168.8, 145.6, 141.5, 140.9, 128.1, 126.7, 126.5, 126.5, 125.5, 124.0, 123.7, 80.0, 75.1, 65.0, 52.9, 52.6, 41.6, 40.9, 39.9, 26.7, 9.8; FT-IR (neat) 2953, 1732, 1599, 1493, 1434, 1266, 1238, 1195, 1116, 1062 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}O_5S^+$: 427.1586, found: 427.1584.

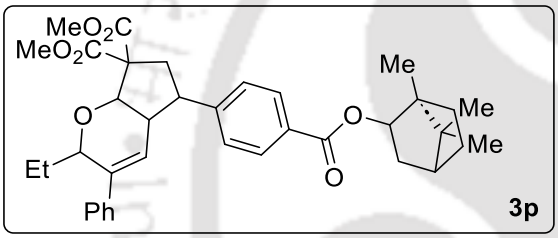


Dimethyl 2-ethyl-3-phenyl-5-(4-(((2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6-yl)-oxy) carbonyl) phenyl)-4a,5,6,7a-tetrahydro cyclopenta[b]pyran-7,7(2H)-dicarboxylate 3n. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.60; Yellow sticky liquid; yield 77% (67 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 15.0 Hz, 1H), 5.78 (t, *J* = 7.2 Hz, 1H), 5.42 (t, *J* = 7.2 Hz, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 5.09 (dd, *J* = 6.6 Hz, 15.0 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.18 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.61 (t, *J* = 6.0 Hz, 1H), 2.22 (dd, *J* = 7.8 Hz, 13.2 Hz, 1H), 2.11 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.95-1.90 (m, 2H), 1.84-1.81 (m, 1H), 1.78-1.75 (m, 1H), 1.54-1.50 (m, 2H), 1.39-1.37 (m, 4H), 1.28-1.24 (m, 10H), 1.15-1.11 (m, 3H), 1.10-1.06 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.87-0.84 (m, 14H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.1, 165.0, 149.6, 148.2, 140.7, 139.7, 138.0, 137.5, 137.1, 130.5, 129.5, 128.8, 128.2, 127.0, 125.5, 125.2, 124.9, 123.2, 83.6, 79.4, 75.2, 65.0, 52.9, 52.7, 42.5, 39.5, 37.6, 37.5, 37.4, 32.93, 32.92, 28.1, 24.9, 24.5, 22.8, 22.7, 22.6, 21.1, 20.7, 19.89, 19.83, 14.2, 13.1, 12.3, 11.9; FT-IR (neat) 2926, 1733, 1612, 1576, 1457, 1435, 1333, 1270, 1174, 1089 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{56}H_{77}O_8^+$: 877.5613, found: 877.5625.



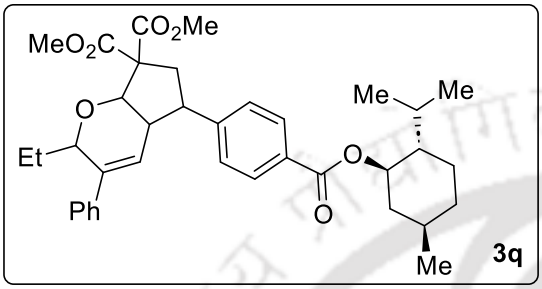
Dimethyl 5-(4-((((3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)-oxy)-carbonyl)phenyl)-2-ethyl-3-phenyl-4a,5,6,7a-tetrahydro-cyclopenta[b]pyran-7,7(2H)-dicarboxylate 3o. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.58; Yellow sticky liquid; yield 76% (65 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz,

2H) 7.37-7.33 (m, 4H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.0 Hz, 1H), 6.64 (d, *J* = 15.5 Hz, 1H), 5.77 (t, *J* = 7.5 Hz, 1H), 5.417-5.410 (m, 1H), 5.37 (t, *J* = 7.5 Hz, 1H), 5.34 (d, *J* = 6.5 Hz, 1H), 5.07 (dd, *J* = 7.0 Hz, 15.5 Hz, 1H), 4.87-4.81 (m,1H), 3.76 (d, *J* = 8.5 Hz, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.13 (dd, *J* = 7.0 Hz, 13.0 Hz, 1H), 2.46 (d, *J* = 8.0 Hz, 1H), 2.18 (dd, *J* = 8.0 Hz, 13.5 Hz, 1H), 2.03-1.97 (m, 4H), 1.92 (t, *J* = 7.5 Hz, 2H), 1.85-1.81 (m, 1H) 1.74-1.71 (m, 1H), 1.53-1.45 (m, 5H), 1.35-1.33 (m, 3H), 1.27-1.23 (m, 3H), 1.13-1.09 (m, 3H), 1.06 (s, 4H), 1.03-0.97 (m, 4H), 0.93-0.90 (m, 6H), 0.87 (dd, *J* = 2.0 Hz, 6.5 Hz, 6H), 0.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.1, 165.9, 147.4, 139.8, 139.7, 138.0, 137.4, 137.1, 130.1, 129.9, 129.5, 128.2, 127.0, 125.2, 125.0, 122.9, 83.6, 79.4, 74.7, 65.0, 56.8, 56.2, 52.9, 52.7, 50.2, 42.4, 39.8, 39.6, 38.3, 37.1, 36.8, 36.3, 35.9, 32.08, 32.03, 28.3, 28.1, 28.0, 24.4, 23.9, 22.9, 22.7, 22.6, 21.2, 19.5, 18.8, 14.2, 12.0; FT-IR (neat) 2949, 1735, 1717, 1613, 1436, 1374, 1272, 1177, 1111, 1017 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{54}H_{72}NaO_7^+$: 855.5170, found: 855.5162.

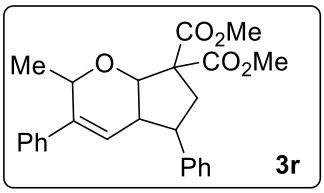


Dimethyl 2-ethyl-3-phenyl-5-(4-((((1S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)carbonyl)phenyl)-4a,5,6,7a-tetra-hydro-cyclo-penta[b]pyran-7,7(2H)-dicarboxylate 3p. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.40; Yellow sticky liquid; yield 80% (48 mg); 1:0.45 mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 2.8H, major + minor), 7.40-7.33 (m, 5.7H, major + minor), 7.31-7.29 (m, 1.8H, major + minor), 7.24 (s, 0.7H, minor), 7.10-7.08 (m, 1.9H, major + minor), 6.65 (d, *J* = 15.6 Hz, 1H, major), 5.91 (t, *J* = 7.6 Hz, 0.4H, minor), 5.77 (t, *J* = 7.6 Hz, 1H, major), 5.72 (s, 0.4H, minor), 5.37 (t, *J* = 7.6 Hz, 1.4H, major + minor), 5.33 (d, *J* = 6.8 Hz, 1H, major), 5.08 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H, major), 4.94-4.88 (m, 1.6H, major + minor), 3.64 (s, 3H, major), 3.59 (s, 3H, major), 3.53 (s, 1.2H, minor), 3.345-3.340 (s, 1.2H, minor), 3.14 (dd, *J* = 7.2 Hz, 13.2 Hz, 1.4H, major + minor), 2.34 (dd, *J* = 6.0 Hz, 12.8 Hz, 1H, major), 2.21-2.17 (m, 1.3H, major + minor), 2.158-2.155 (m, 1.7H, major + minor), 2.13-2.10 (m, 1.7H, major + minor), 2.01-1.94 (m, 1.7H, major + minor), 1.92-1.88(m, 2.6H, major + minor), 1.74 (d, *J* = 11.6 Hz, 3.3H, major + minor), 1.10 (d, *J* = 12.4 Hz, 2.6H, major + minor), 0.94 (s, 3H, major + minor), 0.93 (d, *J* = 4.8 Hz, 6H, major + minor), 0.90 (s, 3.3H, major + minor), 0.79 (d, *J* = 7.2 Hz, 4.2H, major + minor); ^{13}C NMR (150 MHz, $CDCl_3$)

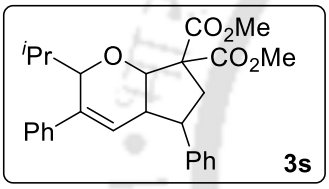
δ 169.98, 169.96, 169.12, 168.6, 166.07, 166.03, 147.9, 147.4, 139.7, 138.0, 137.4, 137.1, 136.6, 133.3, 129.93, 129.90, 129.8, 129.5, 128.2, 127.8, 127.1, 127.0, 125.3, 125.29, 125.26, 124.99, 86.57, 83.62, 83.61, 79.44, 79.15, 74.9, 65.03, 65.01, 52.99, 52.95, 52.69, 52.47, 47.42, 42.58, 42.55, 42.30, 41.15, 41.12, 34.48, 34.43, 32.0, 31.6, 29.84, 29.81, 26.7, 26.6, 23.86, 23.84, 22.8, 22.6, 22.18, 22.12, 20.89, 20.88, 16.74, 16.72, 16.6, 14.4, 14.27, 14.26; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{37}H_{45}O_7^+$: 601.3160, found: 601.3153.



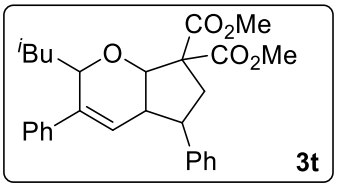
Dimethyl 2-ethyl-5-(4-((((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)phenyl)-3-phenyl-4a,5,6,7a-tetra-hydro-cyclo-penta-[b]-pyran-7,7(2H)-dicarboxylate 3q. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.38; Yellow sticky liquid; yield 81% (51 mg); 1:0.25 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 2H, major), 7.95 (d, *J* = 8.4 Hz, 0.5H, minor), 7.47-7.46 (m, 0.5H, minor), 7.38-7.33 (m, 4.5H, major + minor), 7.29-7.27 (m, 1.2H, major + minor), 7.24 (s, 0.4H, minor), 7.09 (d, *J* = 6.8 Hz, 2H, major), 6.97-6.93 (m, 0.2H, minor), 6.65 (d, *J* = 15.2 Hz, 1H, major), 5.77 (t, *J* = 7.6 Hz, 1H, major), 5.57-5.50 (m, 0.2H, minor), 5.37 (t, *J* = 7.6 Hz, 1H, major), 5.33 (d, *J* = 6.8 Hz, 1H, major), 5.08 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H, major), 4.94-4.88 (m, 1.5H, major + minor), 3.80 (s, 0.74H, minor), 3.64 (s, 3H, major), 3.59 (s, 3H, major), 3.40 (s, 0.68H, minor), 2.21-2.15 (m, 1.36H, major + minor), 2.12-2.09 (m, 1.62H, major + minor), 1.96-1.88 (m, 3.56H, major + minor), 1.74 (d, *J* = 11.6 Hz, 3.32H, major + minor), 1.14-1.07 (m, 4H, major + minor), 0.94-0.90 (m, 13H, major + minor), 0.79 (d, *J* = 6.8 Hz, 5H, major + minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.97, 169.95, 169.1, 169.0, 166.7, 166.3, 147.5, 139.7, 138.0, 137.5, 137.1, 130.2, 130.1, 129.8, 129.7, 129.5, 128.6, 128.2, 127.8, 127.6, 127.1, 127.0, 125.3, 125.2, 124.9, 124.7, 83.6, 80.9, 80.6, 79.4, 79.1, 64.9, 60.1, 53.04, 53.02, 52.9, 52.7, 49.3, 49.2, 48.04, 48.02, 45.2, 45.1, 42.5, 39.1, 38.7, 37.0, 35.2, 32.0, 29.84, 29.80, 29.5, 28.4, 28.2, 27.5, 26.0, 22.8, 22.6, 20.3, 19.8, 19.0, 18.8, 14.4, 14.2, 13.7, 13.4; FT-IR (neat) 2954, 1735, 1712, 1612, 1494, 1435, 1271, 1212, 1176, 1109, 1076 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{37}H_{46}NaO_7^+$: 625.3136, found: 625.3154.



Dimethyl 2-methyl-3,5-diphenyl-4a,5,6,7a-tetra-hydro-cyclo-penta[b]pyran-7,7(2H)-dicarboxylate 3r. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.55; Yellow sticky liquid; yield 61% (25 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 3H), 7.31-7.27 (m, 3H) 7.08 (d, *J* = 6.8 Hz, 2H), 6.66 (d, *J* = 14.8 Hz, 1H), 5.86 (q, *J* = 6.4 Hz, 1H), 5.12 (t, *J* = 7.2 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 4.81 (dd, *J* = 6.4 Hz, 10.4 Hz, 1H), 3.79 (s, 3H), 3.56 (s, 3H), 2.75-2.69 (m, 1H), 2.66-2.61 (m, 1H), 1.57-1.55 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.3, 142.3, 141.2, 137.9, 137.1, 129.6, 129.4, 128.5, 128.2, 127.6, 127.0, 125.5, 124.9, 83.4, 79.9, 65.1, 52.8, 52.6, 42.7, 15.1; FT-IR (neat) 2952, 1732, 1684, 1514, 1434, 1252, 1068 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{25}H_{26}NaO_5^+$: 429.1672, found: 429.1671.

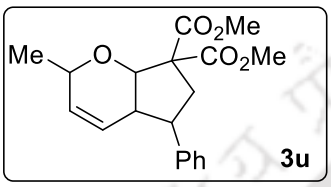


Dimethyl 2-isopropyl-3,5-diphenyl-4a,5,6,7a-tetra-hydro-cyclo-penta[b]pyran-7,7(2H)-dicarboxylate 3s. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.50; Yellow sticky liquid; yield 74% (32 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.296-7.292 (m, 1H), 7.27-7.22 (m, 2H), 7.09 (d, *J* = 6.8 Hz, 2H), 6.62 (d, *J* = 15.6 Hz, 1H), 5.57 (d, *J* = 10.0 Hz, 1H), 5.34-5.31 (m, 1H), 5.04 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 3.10 (dd, *J* = 13.2 Hz, 6.8 Hz, 1H), 2.25-2.16 (m, 2H), 0.90 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.3, 142.4, 142.3, 138.3, 138.0, 137.4, 129.4, 128.5, 128.2, 127.6, 126.9, 125.5, 125.4, 83.3, 79.9, 65.1, 52.8, 52.5, 42.7, 28.3, 23.0; FT-IR (neat) 2956, 1733, 1601, 1494, 1435, 1361, 1255, 1167, 1068 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{31}O_5^+$: 435.2166, found: 435.2185.

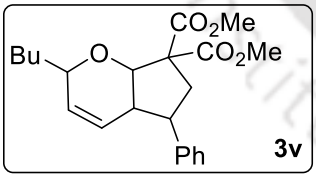


Dimethyl 2-isobutyl-3,5-diphenyl-4a,5,6,7a-tetra-hydro-cyclo-penta[b]pyran-7,7(2H)-dicarboxylate 3t. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.42; Yellow sticky liquid; yield 76% (47 mg); ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.35-7.34 (m, 2H), 7.32-7.31 (m, 4H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.66 (d, *J* = 15.5 Hz, 1H), 5.78 (t, *J* = 7.5 Hz, 1H), 5.34-5.31 (m, 2H), 5.06 (dd, *J* = 7.0 Hz, 15.5 Hz, 1H), 3.65 (s, 3H), 3.58 (s, 3H), 3.10 (dd, *J* = 7.0 Hz, 13.0 Hz, 1H), 2.22 (dd, *J* = 8.0 Hz, 13.5 Hz, 1H), 1.81 (t, *J* = 7.0 Hz, 2H), 1.63-1.58 (m, 2H), 0.82 (dd, *J* = 1.0 Hz, 7.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.3, 142.3, 140.8, 137.3, 134.3, 129.6, 128.5, 128.1, 127.6, 126.9, 125.5, 125.1, 83.3, 79.9, 77.3, 65.1, 64.4, 52.8, 52.6, 42.7, 38.2, 28.8, 22.5, 14.2; FT-IR (neat) 2953, 1733, 1642, 1494, 1365, 1251, 1176, 1067 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{28}H_{32}NaO_5^+$: 471.2142, found: 471.2155.

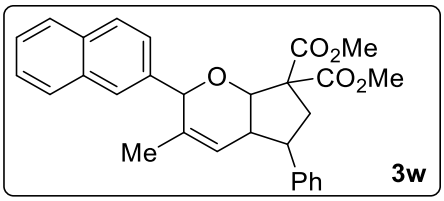


Dimethyl 2-methyl-5-phenyl-4a,5,6,7a-tetra-hydro-cyclo-penta-[b]pyran-7,7(2H)-dicarboxylate 3u. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.40; Yellow sticky liquid; yield 83% (30 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 4H), 7.27-7.25 (m, 1H), 6.39 (dd, *J* = 10.8 Hz, 15.2 Hz, 1H), 6.08-6.01 (m, 1H), 5.78-5.70 (m, 1H), 5.58 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H), 5.43-5.38 (m, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.16 (dd, *J* = 13.2 Hz, 6.8 Hz, 1H) 2.31-2.26 (m, 1H), 1.77-1.74 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.2, 169.3, 142.3, 133.4, 131.1, 130.7, 128.6, 127.6, 125.5, 125.2, 83.0, ,79.8, 65.2, 52.9, 52.7, 42.6, 18.3; FT-IR (neat) 2953, 1732, 1660, 1495, 1254, 1210, 1174, 1066 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{19}H_{22}NaO_5^+$: 353.1359, found: 353.1358.

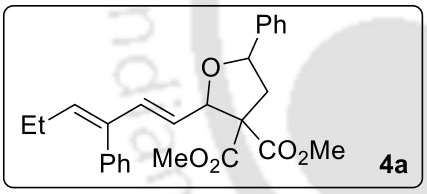


Dimethyl 2-butyl-5-phenyl-4a,5,6,7a-tetra-hydro-cyclo-penta-[b]-pyran-7,7(2H)-dicarboxylate 3v. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.50; Yellow sticky liquid; yield 86% (34 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.32 (m, 3H), 7.25 (s, 2H), 6.39 (dd, *J* = 10.4 Hz, 15.2 Hz, 1H), 6.03 (dd, *J* = 10.4 Hz, 15.2 Hz, 1H), 5.76-5.69 (m, 1H), 5.59 (dd, *J* = 6.8 Hz, 13.2 Hz, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 5.29-5.28 (m, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.17 (dd, *J* = 7.2 Hz, 13.2 Hz, 1H), 2.31-2.26 (m, 1H), 2.09-2.04 (m, 2H), 1.36-1.28 (m, 4H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 169.3, 142.4, 136.7, 133.6, 129.3, 128.6, 127.6, 125.5, 125.3, 83.0, 79.8, 65.3, 52.9, 52.7, 42.6,

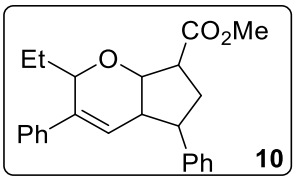
32.4, 31.4, 22.3, 14.0; FT-IR (neat) 2954, 1733, 1658, 1495, 1434, 1253, 1176, 1065 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{22}H_{28}NaO_5^+$: 395.1829, found: 395.1840.



Dimethyl 3-methyl-2-(naphthalen-2-yl)-5-phenyl-4a,5,6,7a-tetrahydrocyclopenta[b]pyran-7,7(2H)-dicarboxylate 3w. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.42; colorless liquid; yield 78% (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.78 (m, 3H), 7.73 (s, 1H), 7.48-7.43 (m, 2H), 7.42 (dd, *J* = 1.6 Hz, 8.4 Hz, 1H), 7.38-7.33 (m, 4H), 7.29-7.25 (m 1H), 6.71-6.67 (m, 2H), 5.58 (dd, *J* = 6.8 Hz, 15.6 Hz, 1H), 5.48 (t, *J* = 7.2 Hz, 1H), 5.45 (d, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.22 (dd, *J* = 6.8 Hz, 13.2 Hz , 1H), 2.34 (dd, *J* = 8.4 Hz, 13.2 Hz , 1H), 2.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1 169.4, 142.3, 137.9, 135.27, 135.22, 133.3, 132.6, 132.3, 128.6, 128.1, 128.0, 127.7, 127.6, 126.2, 126.0, 125.5, 124.2, 83.3, 80.0, 65.4, 52.9, 52.7, 42.7, 14.1; FT-IR (neat) 2954, 1733, 1658, 1495, 1434, 1253, 1176, 1065 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{29}H_{28}NaO_5^+$: 479.1829, found: 479.1830.



Dimethyl 5-phenyl-2-((1*E*,3*Z*)-3-phenyl hexa-1,3-dien-1-yl) dihydro furan-3,3(2H)-dicarboxylate 4a. Analytical TLC on silica gel, 5:95 ethyl acetate/hexane; R_f = 0.45; Yellow sticky liquid; yield 65% (27 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.38-7.35 (m, 4H), 7.32-7.28 (m, 2H), 7.11-7.10 (m, 2H), 6.69 (d, *J* = 15.0 Hz, 1H), 5.79 (t, *J* = 7.2 Hz, 1H), 5.18-5.17 (m, 1H), 5.14-5.10 (m, 1H), 4.84 (dd, *J* = 6.0 Hz, 10.2 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 2.78-2.74 (m, 1H), 2.69-2.65 (m, 1H), 1.96-1.92 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 169.4, 140.0, 139.7, 138.0, 137.8, 137.0, 129.4, 128.5, 128.2, 126.9, 126.6, 125.0, 83.4, 79.9, 65.0, 53.0, 52.6, 42.2, 22.6, 14.2; FT-IR (neat) 2970, 1736, 1599, 1494, 1435, 1365, 1264, 1228, 1217, 1091 cm^{-1}; HRMS (ESI) m/z $[M+Na]^+$ calcd for $C_{26}H_{28}O_5Na^+$: 443.1829, found: 443.1827.



Methyl 2-ethyl-3,5-diphenyl-2,4a,5,6,7,7a-hexahydro-cyclopenta-[b]-pyran-7-carboxylate 10. Analytical TLC on silica gel, 2:98 ethyl acetate/hexane; R_f = 0.45; colorless liquid; yield 67% (25 mg); 1:0.25 mixture of diastereomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.34 (m, 6H, major + minor), 7.32-7.30 (m, 2.5H, major + minor), 7.29-7.26 (m, 1.5H, major + minor), 7.14-7.12 (m, 2H, major), 7.09-7.07 (m, 0.5H, minor), 6.56-6.50 (m, 1.5H, major + minor), 5.73 (t, *J* = 7.6 Hz, 1.25H, major + minor), 5.34 (t, *J* = 7.2 Hz, 0.27H, minor), 5.23 (dd, *J* = 6.8 Hz, 15.2 Hz, 1H, major), 5.08 (t, *J* = 7.6 Hz, 0.28H, minor), 5.02 (dd, *J* = 6.0 Hz, 10.0 Hz, 1H, major), 4.93-4.90 (m, 0.28H, minor), 4.85 (t, *J* = 7.2 Hz, 0.28H, minor), 3.68 (s, 3H, major), 3.55 (s, 0.7H, minor), 3.28-3.23 (m, 0.26H, minor), 2.96-2.90 (m, 1H, major), 2.62-2.55 (m, 1.2H, major + minor), 2.25-2.17 (m, 1.26H, major + minor), 1.96-1.89 (m, 1.5H, major + minor), 0.92 (t, *J* = 7.2 Hz, 3.74H, major + minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 142.0, 139.7, 138.1, 136.6, 136.4, 129.6, 128.7, 128.5, 128.2, 127.7, 126.9, 125.9, 125.5, 82.6, 80.6, 52.1, 51.4, 39.7, 31.7, 29.8, 22.6, 14.3; FT-IR (neat) 2926, 1736, 1601, 1494, 1436, 1369, 1261, 1168, 1048 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{24}H_{27}O_3^+$: 363.1955, found: 363.1952.

Crystal data and Structure Refinement

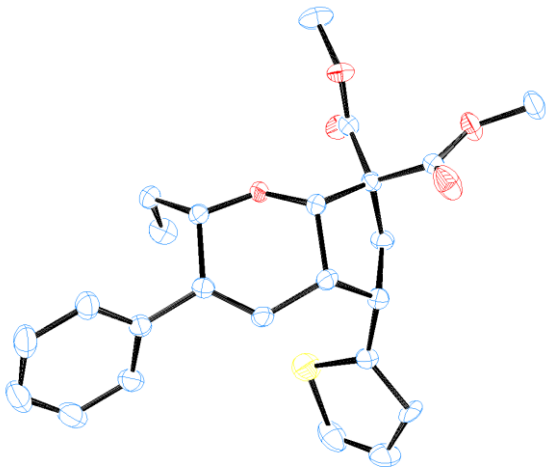


Figure S1. ORTEP diagram of **3k** (CCDC 2298985) with 50% ellipsoid. H-atoms are omitted for clarity.

Identification code	**3k**
CCDC No.	**2298985**
Empirical formula	$C_{24}H_{26}O_5S$
Formula weight	426.15
Crystal habit, colour	Needle/colourless
Temperature,T/K	297 K
Wavelength, λ/Å	0.71073
Crystal System	monoclinic
Space group	'P 21/n'
Unit cell dimensions	a = 10.416(4)Å
	b = 19.090(8)Å
	c = 11.659(5)Å
	α = 90, β = 113.372(13), γ = 90
Volume, V/Å	2128.1(15)
Z	4
Calculated density, $g{\cdot}cm^{-3}$	1.331
Absorption coefficient, μ/mm^{-1}	0.185
F(000)	904.0
θ range for data collection	2.22 to 27.10 °C
Limiting indices	$-13 \leq h \leq 13$, $-24 \leq k \leq 24$, $-14 \leq l \leq 14$
Reflection collected/unique	4194/4663
Completeness to θ	99% (θ = 27.10)
Absorption correction	none
Refinement method	'SHELXL-2018/3 (Sheldrick, 2015)'
Data / restraints / parameters	4663/0/274
Goodness-of-fit on F^2	1.043
Final *R* indices[I>2sigma(I)]	R1 = 0.0633, wR2 = 0.1866
R indices (all data)	R1 = 0.0689, wR2 = 0.1949

3.5 References

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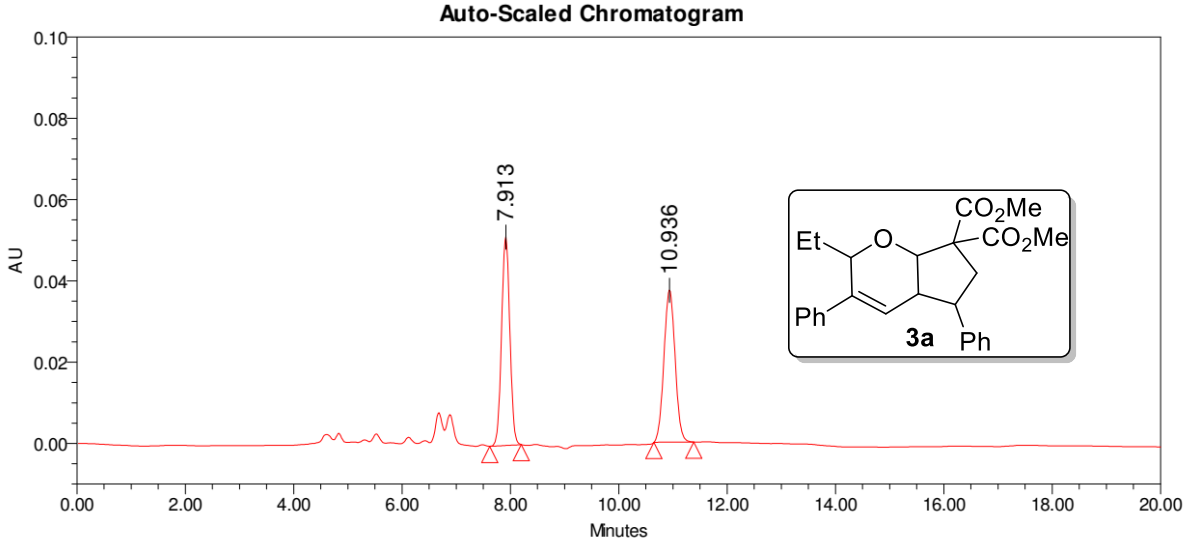
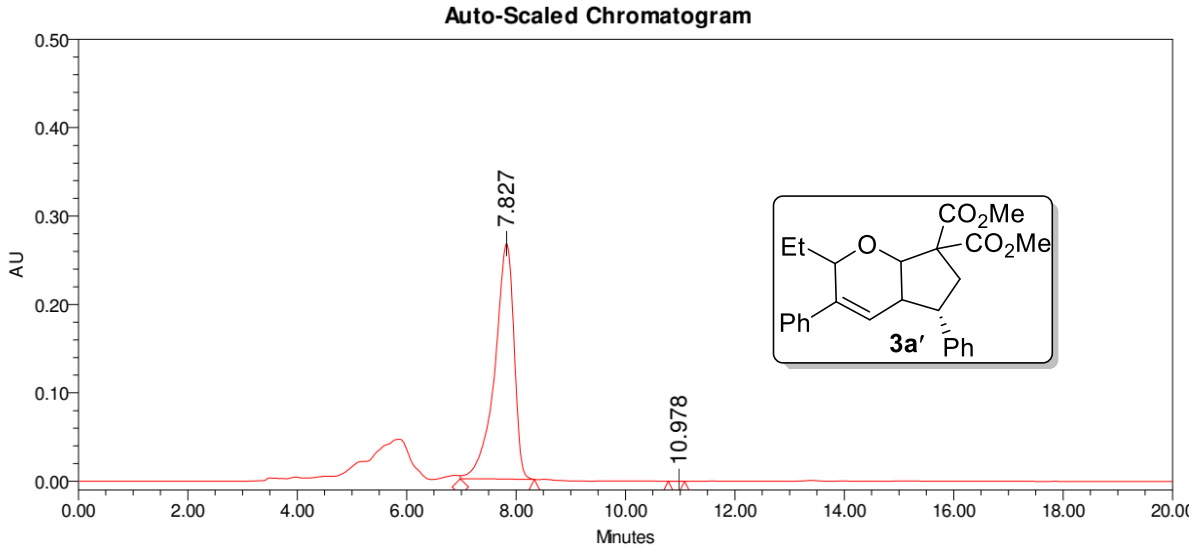
3.6 HPLC Chromatogram



Peak Results

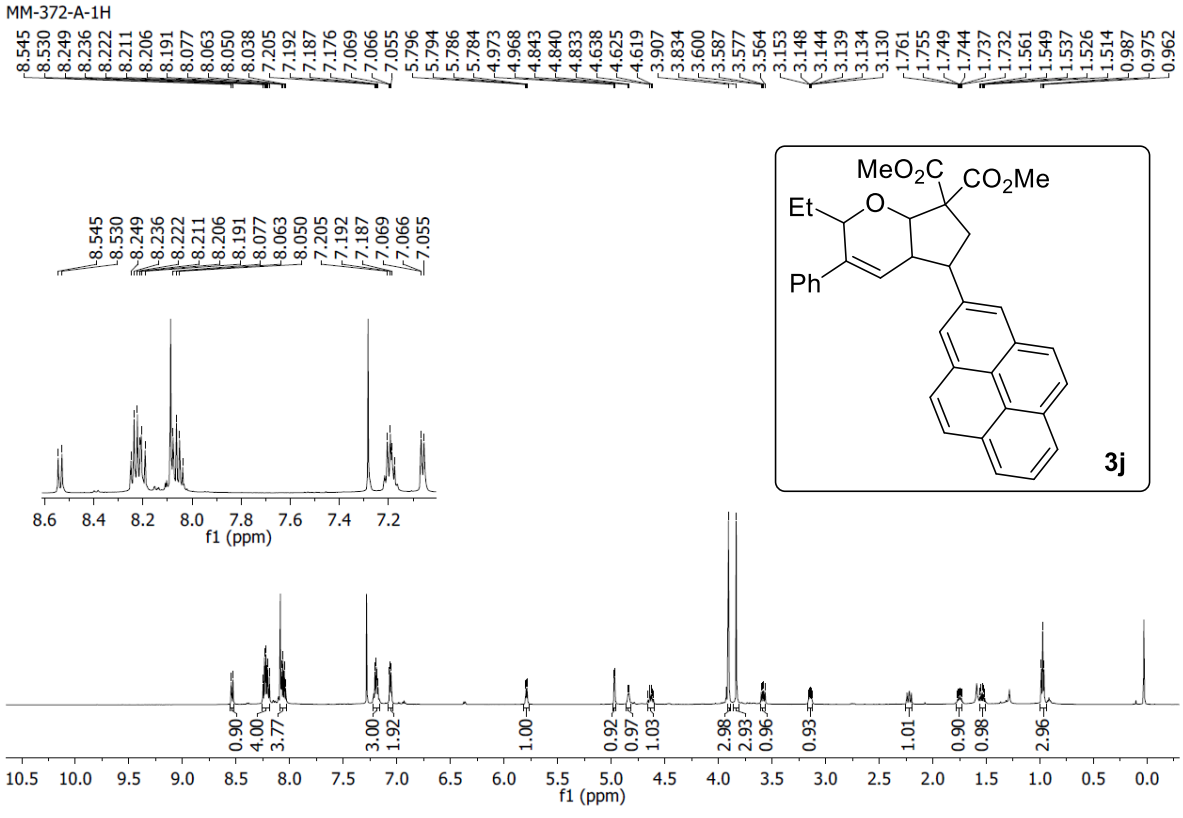
	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	7.617	8.200	7.913	51434	50.39
2	10.650	11.383	10.936	37461	49.61

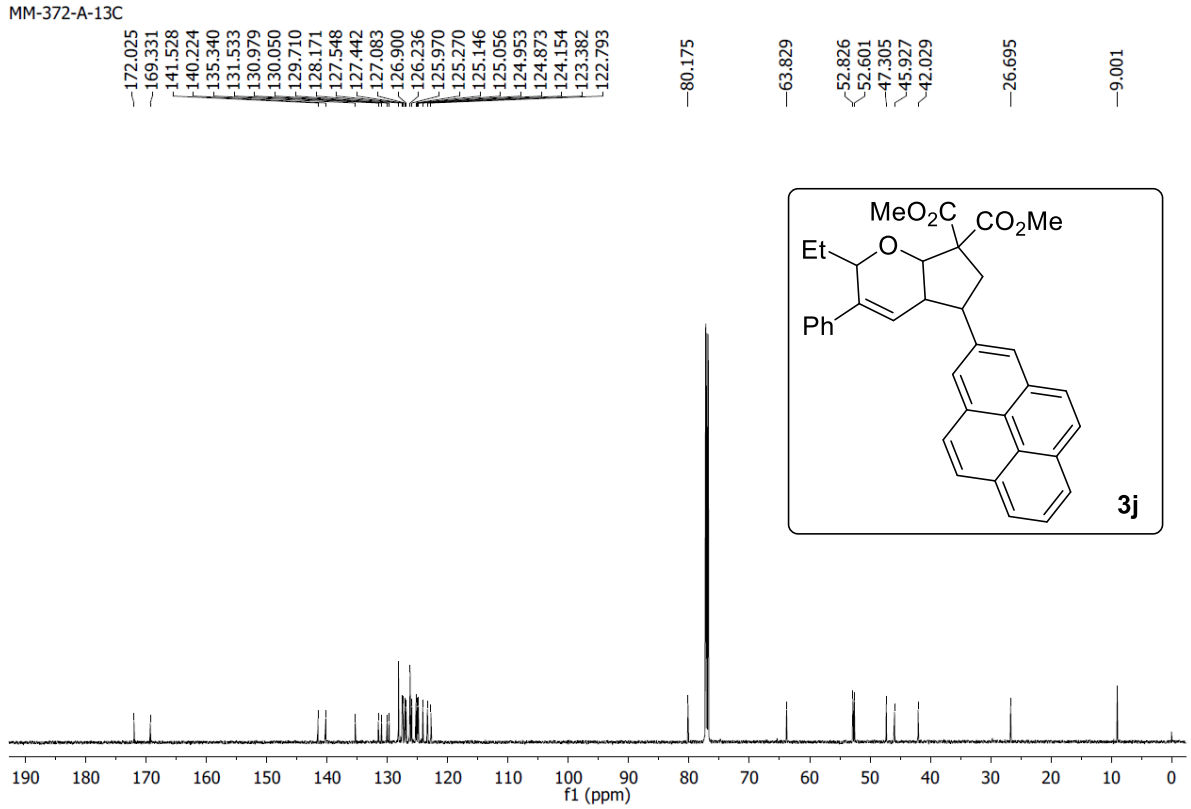


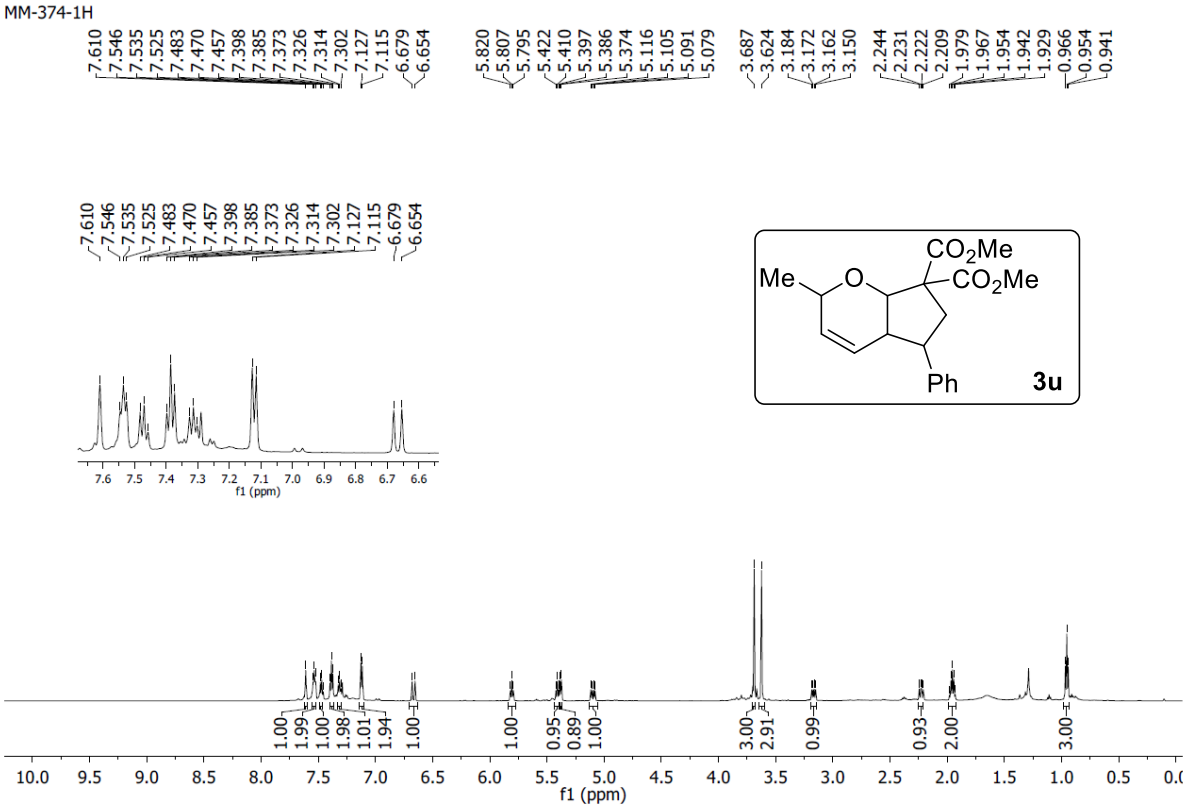
Peak Results

	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		6.983	8.333	7.827	266744	100.00
2	I37	10.783	11.083	10.978	8	0.00

1.7 Selected NMR Spectra







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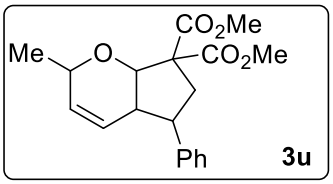
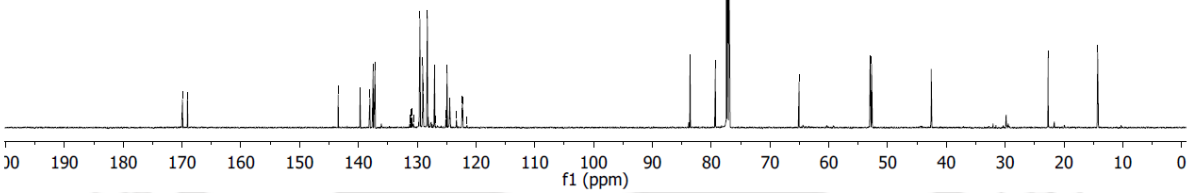
169.919 169.068 143.435 139.708 138.039 137.496 137.182 131.279 131.066 130.852 130.639 129.535 129.062 128.959 128.268 127.043 126.932 125.128 124.914 124.489 124.466 124.441 124.416 123.323 122.350 122.326 122.301 122.276 121.518 83.590 79.293 77.371 77.160 76.948 65.053 52.969 52.727 42.542 22.691 14.268

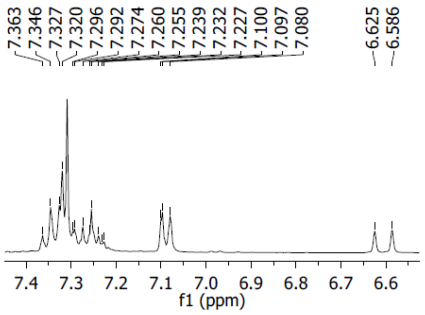


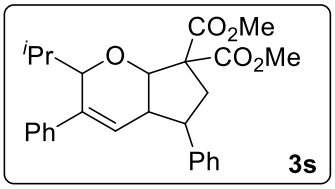
3u



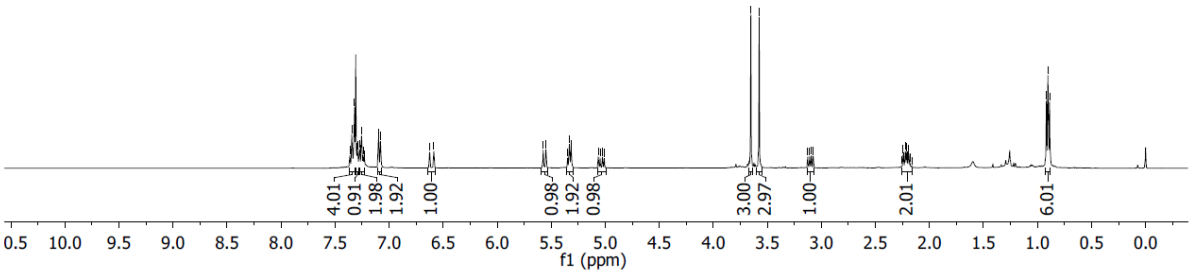
MM-401-A-1H

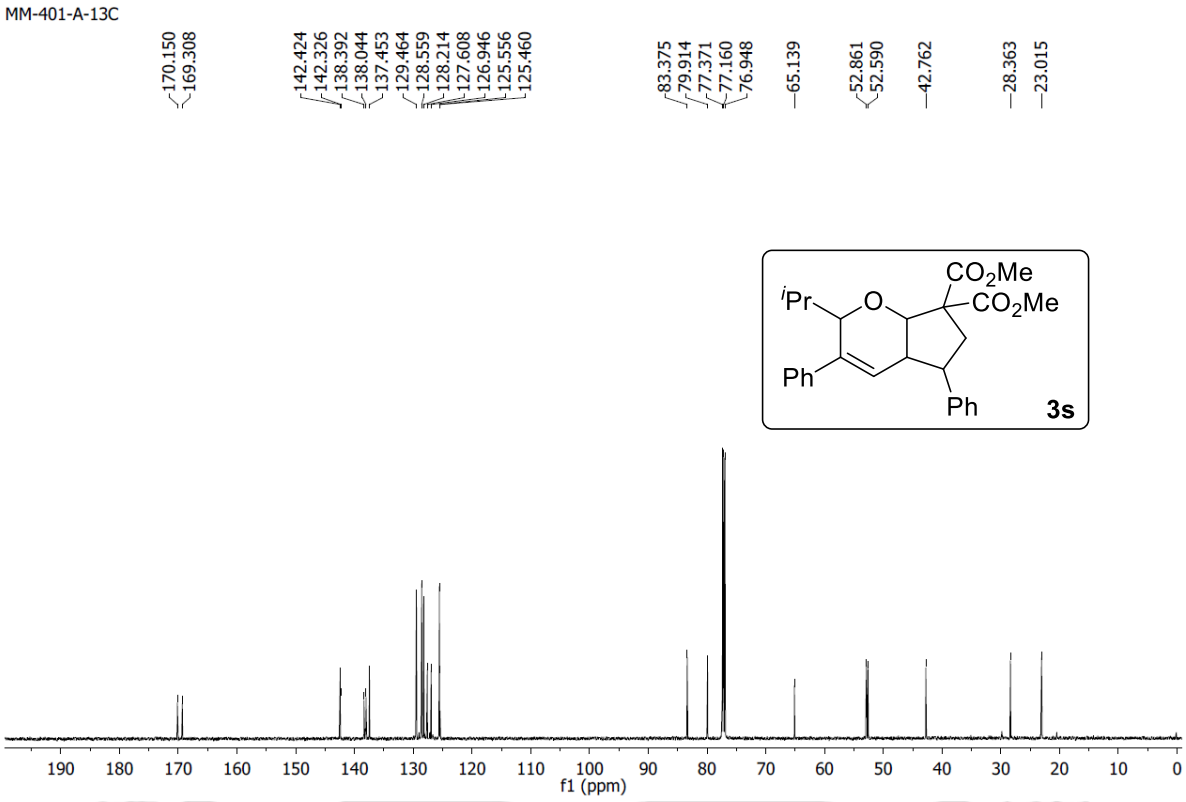
7.363 7.346 7.327 7.320 7.296 7.292 7.274 7.260 7.255 7.239 7.232 7.227 7.100 7.097 7.080 6.625 6.586 5.574 5.549 5.348 5.331 5.316 5.311 5.064 5.047 5.026 5.009 3.653 3.575 3.126 3.109 3.093 3.076 2.254 2.243 2.238 2.223 2.211 2.205 2.196 2.190 2.179 2.163 0.917 0.903 0.888





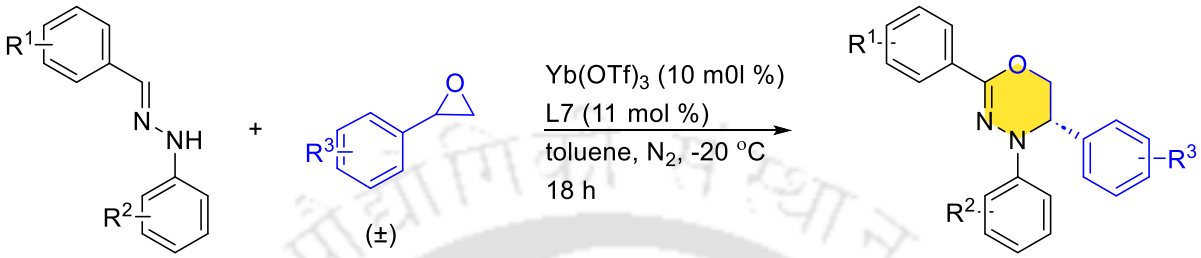
3s





Chapter V

Enantioselective Synthesis of Tetrahydropyridazines



✔ *enantioselective* ✔ *C-N/C-O cascade* ✔ *versatile chiral Yb(III)-N,N'-oxide catalyst*

Chapter V

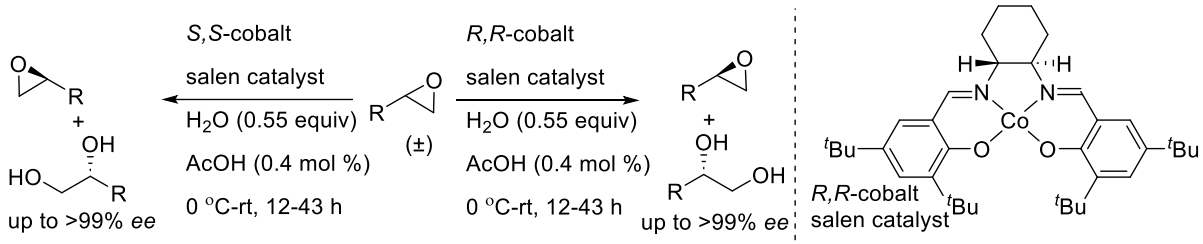
Enantioselective Synthesis of Tetrahydropyridazines

Significant progress has been made in the realm of asymmetric catalysis during the past several decades.[1] Nevertheless, the stereo control of a reaction with multiple steps, where the chirality of the intermediates might be transferred or reconstructed into the final products, remains a fundamental challenge in asymmetric synthesis. Transition metal doped chiral ligand catalyzed enantioselective strategies plays an important role in modern asymmetric synthesis owing to their high modifiability, ease of handling, as well as their environmentally friendly nature.[2] In the evolution of chiral Lewis acid catalysis, the combination of chiral ligands with metal catalysts has emerged as a powerful strategy to achieve enhanced acidity and flexibility of the catalytic systems.[3] However, an important but still missing transformation in this arsenal is direct functionalization of achiral unsaturated three-membered carbo- and heterocycles with the nitrogenous nucleophiles.[4,5] In this regard, N-and O-containing multidentate chiral ligands can be complexed with transition metals to synthesize stereoselective organic compounds.[6] To worthy mention is here, a series of C_2-symmetry chiral bisoxazolines, Py-Boxes, chiral bulky salen complexes, chiral *N*,*N*-oxides as well as chiral bimetallic phosphoric acid ligands can be used for this noble aim.[7] Having this chiral metal-ligand complex in mind, we intended a stereoselective ring opening as well as oxidative cyclization of the versatile three-membered rings with suitable reacting partners. In this chapter, we established a stereoselective synthesis of oxadiazines using racemic styrene oxides and bisaryl hydrazones as the coupling partners. The Yb-L_7 complex, that has been synthesized in our laboratory successfully delivered the desired oxadiazines with high enantiopurity. The scope and selectivity of the reaction have been explored with series of styrene oxides with hydrazones.

5.1 Literature

5.1.1 Hydrolytic Kinetic Resolution

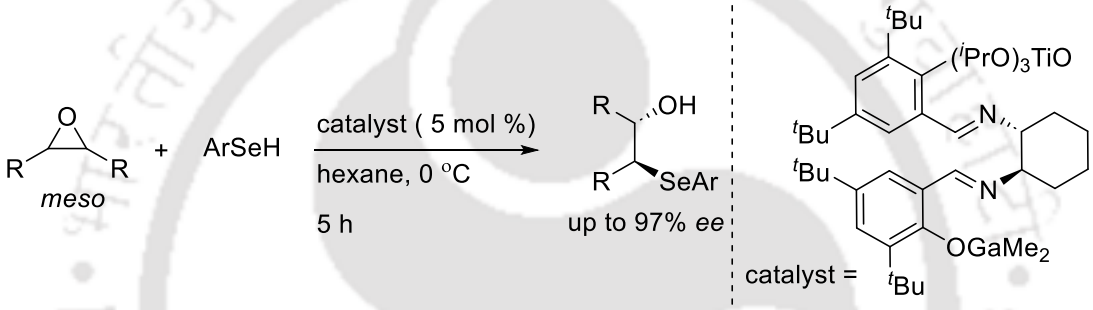
Jacobsen group reported a highly selective hydrolytic kinetic resolution of epoxides using chiral cobalt-salen complex for the synthesis of chiral diols along with epoxides (Scheme 1).[8] The practical standpoints are the use of H_2O as a reactant and low loadings of a recyclable, commercially available catalyst.



Scheme 1. Chiral Diols from Epoxides *via* Kinetic Resolution Process.

5.1.2 Asymmetric Desymmetrization

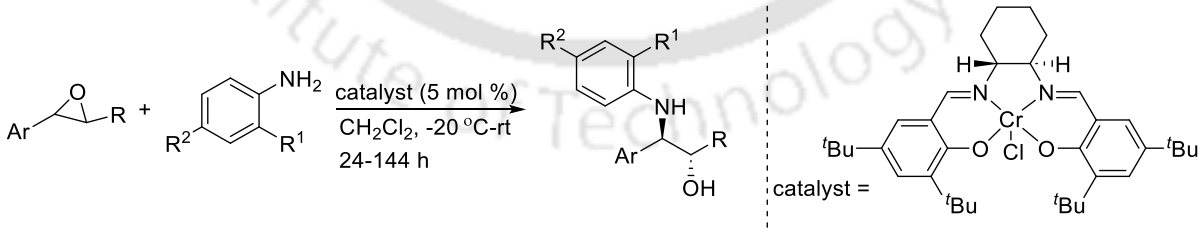
Pan and co-workers developed an enantioselective ring opening of meso epoxides with arylselenols to give optically active β-arylselenoalcohol in <97% ee (Scheme 2).[9] The chiral Ti-Ga-salen heterometallic catalyst was found to be effective for this method.



Scheme 2. Enantioselective Ring Opening of Meso Epoxides

5.1.3 Asymmetric Aminohydroxylation

Sambri and co-workers disclosed the synthesis of enantioenriched *anti*-β-amino alcohols from epoxides and aryl amines using chiral chromium-salen catalyst (Scheme 3).[10] The aminolysis occurred well with complete regio- and diasteroselectivity.

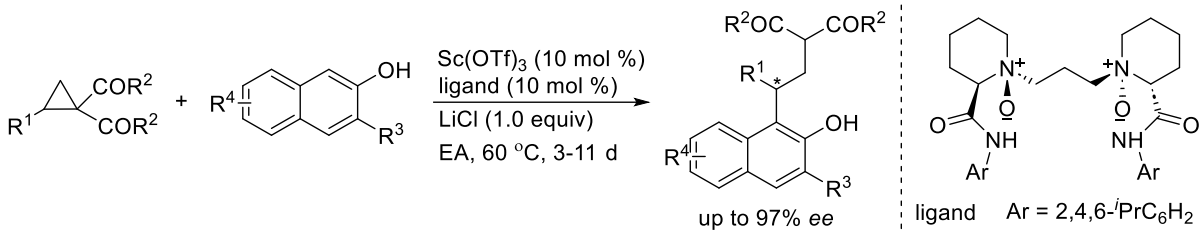


Scheme 3. Synthesis of Enantioenriched *anti*-β-Amino Alcohols

5.1.4 Asymmetric β-Alkylation

Feng group demonstrated asymmetric ring-opening of cyclopropyl ketones with β-naphthols catalyzed by a chiral *N,N′*-dioxide-scandium complex (Scheme 4).[11] They have shown a series

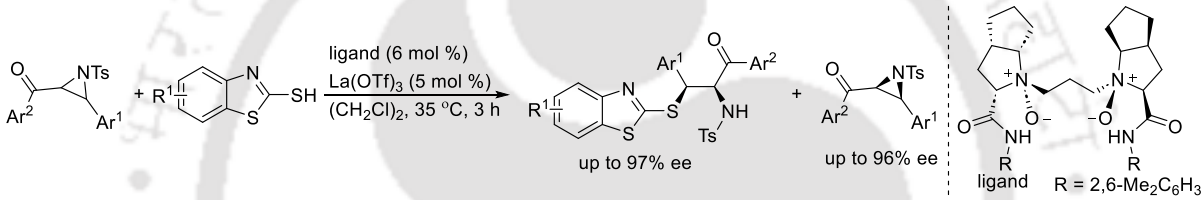
of aromatic or vinyl substituted cyclopropyl ketones reacted with 2-naphthols, providing access to chiral β-naphthol derivatives in good enantioselectivities (up to 97% ee)



Scheme 4. Asymmetric Ring-Opening of Cyclopropyl Ketones with β-Naphthols

5.1.5 Asymmetric β-Thiolation

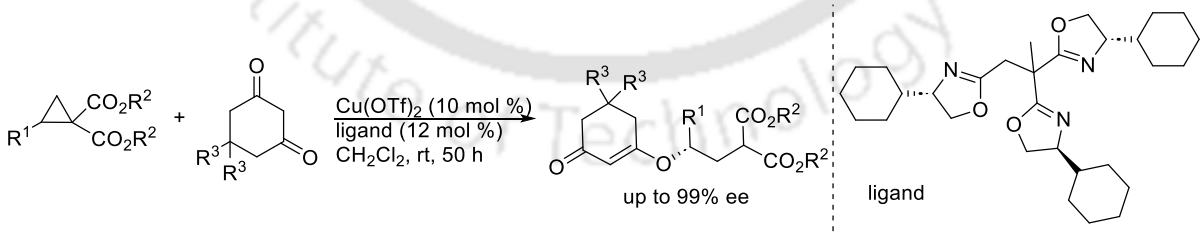
Lin and Feng described the kinetic resolution of aziridines *via* catalytic asymmetric ring-opening with mercaptobenzothiazoles (Scheme 5).[12] A variety of enantioenriched β-amino thioethers and aziridines were reported in good enantioselectivity.



Scheme 5. Asymmetric β-Thiolation via Kinetic Resolution of Aziridines

5.1.6 Asymmetric Alkoxylation

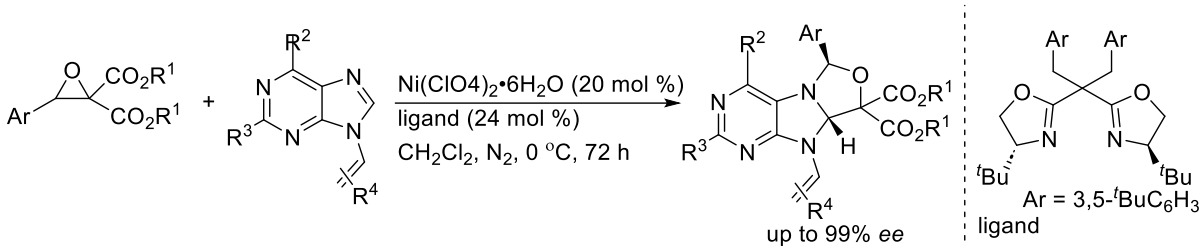
Zhang group reported an asymmetric ring-opening of D-A cyclopropanes with 1,3-cyclodiones for the synthesis of enantioenriched γ-hydroxybutyric acids in presence of Cu(II)/trisoxazoline catalysis.[13]



Scheme 6. Asymmetric Ring-Opening Reactions of D-A Cyclopropanes

5.1.7 Asymmetric Dearomative [3+2]-Cycloaddition

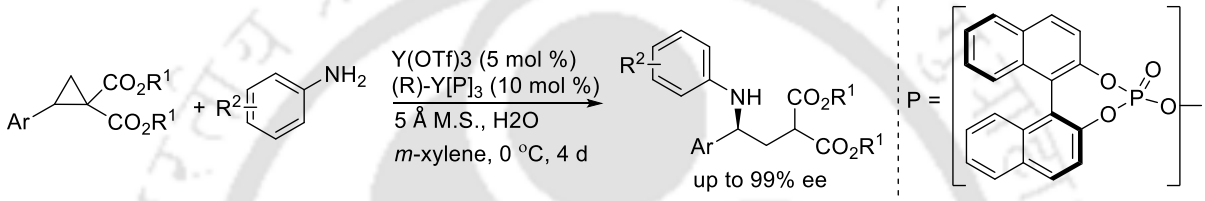
Wang and Guo reported a Ni(II)/bisoxazoline-catalyzed dearomative [3+2]-cycloaddition of substituted purines with D-A oxiranes (Scheme 7).[14] The high chemoselective C-C bond cleavage of the oxiranes accessed the chiral purino-oxazole compounds with ≤ 99% *ee*



Scheme 7. Chemoselective C-C Bond Cleavage of the Oxiranes

5.1.7 Asymmetric Ring-Opening Reaction

Wang and Cundari developed an asymmetric ring-opening of D-A cyclopropane with primary aryl amine using heterobimetallic catalysis (Scheme 8). The chiral amino acids were obtained with high enantioselectivities.[15]



Scheme 8. Asymmetric Amination of Aryl Amines With D-A Cyclopropanes

5.2 Present Study

Herein we described the enantioselective ring opening and cyclization of racemic oxiranes with hydrazones in presence of $Yb(OTf)_3$ and chiral adamntyl *N,N'*-oxide catalyst. Our optimization studies began using (*E*)-1-benzylidene-2-phenylhydrazine **1a** and 2-phenyloxirane **2a** as the model substrates employing a series of Lewis acid catalysts and chiral ligands at various temperatures (Table 2). First, the cyclization in the combination of chiral salen ligand L1 (11 mol %) with $Co(OAc)_2•4H_2O$ (10 mol %) in toluene at room temperature gave only 10% ee with 52% of yields (entry 1). Altering the salen ligand and reaction conditions led to enhance the enantioselectivity to 99% with 17% of yield (entries 2-7). In addition, the chiral bimetallic complex of L3 (11 mol %) with $Cu(OTf)_2$ (10 mol %), $Y(OTf)_3$ (10 mol %) and $Sc(OTf)_3$ (10 mol %) remained ineffective in terms of the yields while the enantioselectivity was excellent (entries 8-10). However, the combinations of chiral py-Box ligands L4 (11 mol %) and L5 (11 mol %) with $Cu(OTf)_2$ (10 mol %) did not bring any significant changes in terms of selectivity as well as yields (entries 11-12). Furthermore, when the combination of chiral *N,N'*-oxide like L6 and L7 (11 mol %) with $Cu(OTf)_2$ and $Yb(OTf)_3$ (10 mol %) led to increase in the yields of

3a to 31% with 99% ee (entries13-16). Thus, $Yb(OTf)_3$ (10 mol %) and chiral N,N′-oxide L7 (11 mol %) at -20 °C with an reaction time of 18 h is our optimization condition.

Table 1. Chiral Ligands

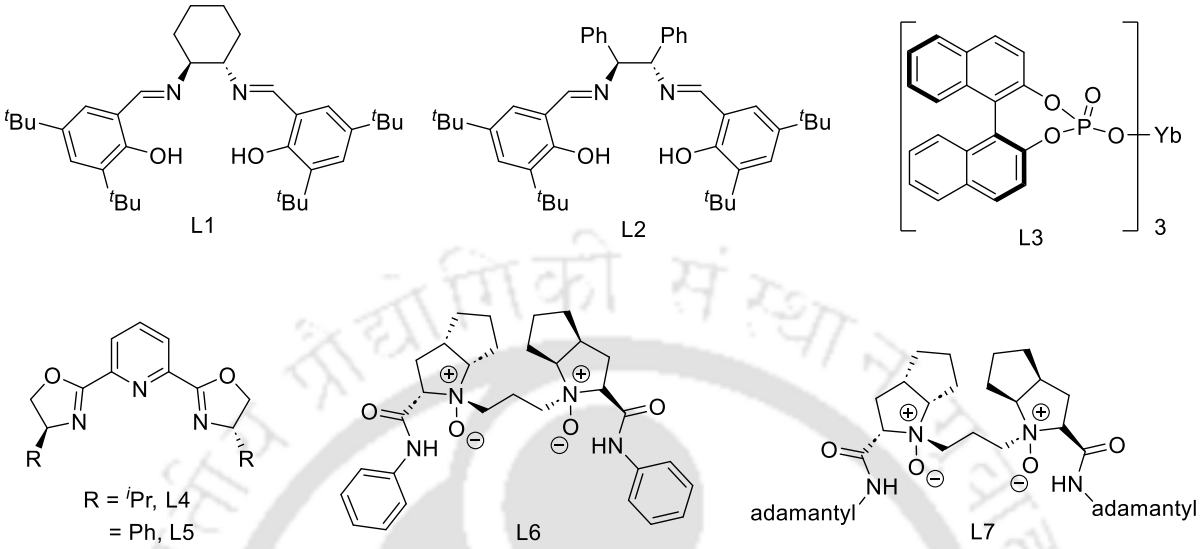
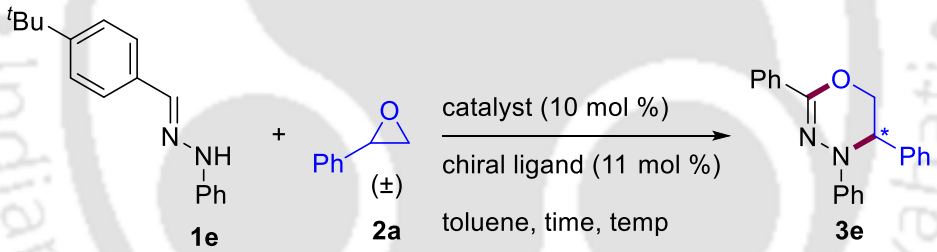


Table 2. Optimization of the Reaction Conditions[a]

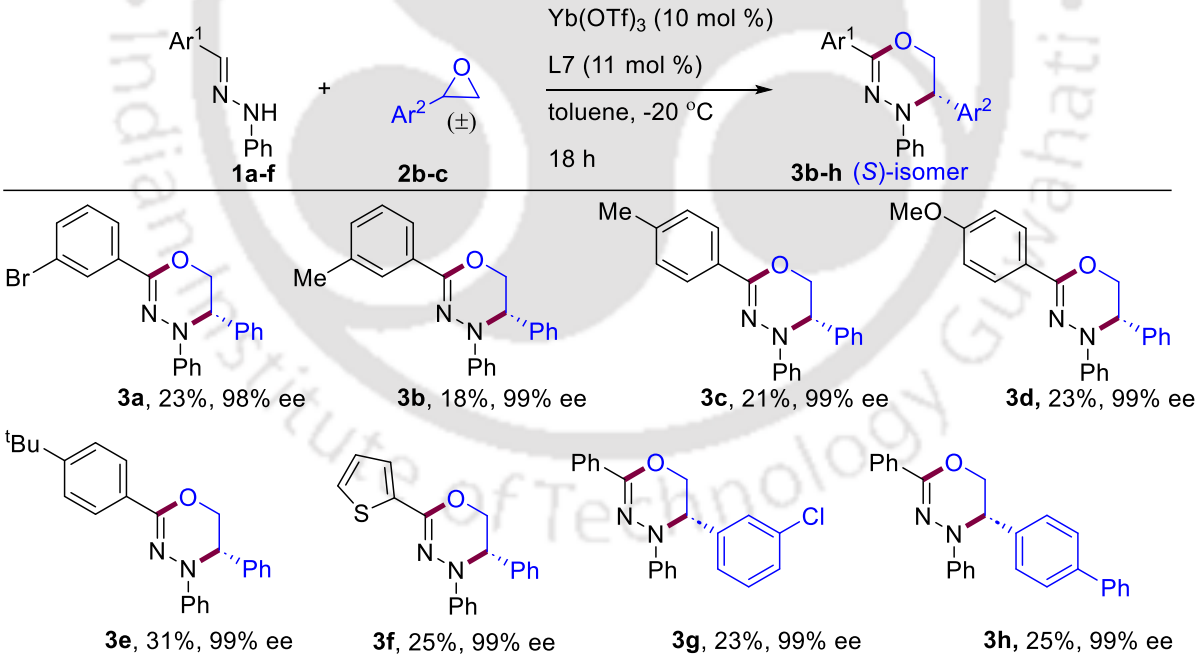


Entry	Ligand	Catalyst	Solvent	Temp	Time	Yield (%)[b]	*ee* (%)[c]
1	L1	$Co(OAc)_2•4H_2O$	toluene	rt	8 h	52	10
2	L1	$Co(OAc)_2•4H_2O$	toluene	0 °C	8 h	35	23
3	L2	$Co(OAc)_2•4H_2O$	toluene	rt	8 h	53	21
4	L2	$Co(OAc)_2•4H_2O$	toluene	0 °C	8 h	32	45
5	L2	$Co(OAc)_2•4H_2O$	toluene	0 °C	6 h	25	80
6	L2	$Co(OAc)_2•4H_2O$	toluene	0 °C	4 h	17	99
7	L2	$Co(OAc)_2•4H_2O$	toluene	0 °C	2 h	11	99

8	L3	$Cu(OTf)_2$	toluene	0 °C	14 h	15	99
9	L3	$Y(OTf)_3$	toluene	0 °C	14 h	14	99
10	L3	$Sc(OTf)_3$	toluene	0 °C	14 h	15	99
11	L4	$Cu(OTf)_2$	toluene	0 °C	14 h	28	23
12	L5	$Cu(OTf)_2$	toluene	0 °C	14 h	31	26
13	L6	$Cu(OTf)_2$	toluene	0 °C	14 h	22	40
14	L7	$Cu(OTf)_2$	toluene	0 °C	14 h	31	60
15	L7	$Yb(OTf)_3$	toluene	-10 °C	18 h	25	80
16	L7	$Yb(OTf)_3$	toluene	-20 °C	18 h	23	99

[a]Reaction conditions: **1e** (0.1 mmol), **2a** (0.12 mmol), catalysts (10 mol %), chiral ligands (11 mol %), toluene (1.0 mL), temp, time. [b]isolated yield. [c]Determined by HPLC analysis.

Table 3. Substrate Scopes of Substituted Hydrazones and Oxiranes[a,b,c]



[a]Reaction conditions: **1b-f** (0.1 mmol), **2b-c** (0.12 mmol), $Yb(OTf)_3$ (10 mol %), L7 (11 mol %), toluene (1.0 mL), -20 °C, 18 h. [b]Isolated yield. [c]Determined by HPLC analysis.

With the optimized reaction conditions, the scope of the procedure was investigated using a series of substituted hydrazones with 2-phenyal oxiranes as standard substrate (Table 3). The

3-substituted hydrazones with bromo **1a** and methyl **1b** groups furnished the cycloadduct **3a** and **3b** in 23 and 18 % yields, respectively, with 99% enantioselectivity. Similarly, the 4-substituted hydrazones i.e., methyl **1c**, methoxy **1d** and tert-butyl **1e** groups afforded the cyclized product **3c-e** in 21-25% of yields with 99% enantioselectivity. The heteterocyclic thienyl **1f** also underwent the cyclization to afford **3f** in 25% yield and 99% enantioselectivity. We also examined the generality of this protocol to some substituted oxiranes **2b-c** using (*E*)-1-benzylidene-2-phenylhydrazine **1a** as representative substrate. The 3-chloro **2b** and 4-phenyl **2c** substituents at the aryl ring of oxirane gave the desired product **3g** and **3h** in 23 and 25% yields respectively with 99% enantioselectivity.

In summary, we have established a enantioselective synthesis of oxadiazines by coupling achiral styrene oxides with bisaryl hydrazones via kinetic resolution The versatile chiral adamantly *N*,*N*-oxide L7 and $Yb(OTf)_3$ combination was found to be crucial for the selectivity. The simple operational condition and low catalytic loading are the practical features.

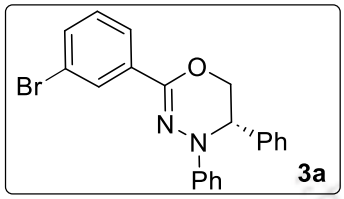
5.3 Experimental Section

General Information. $Co(OAc)_2 \cdot 4H_2O$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$ and 2-phenyl oxirane of Aldrich used as received. Styrene oxides hydrazones and chiral ligands were prepared according to literature.[16-18] Merck silica gel G/GF 254 plates were used for the analytical TLC and rankem silica gel (60-120 mesh) was used for the column chromatography. NMR (^1H and ^{13}C) spectra were recorded in Bruker Avance III 400 and 600 spectrometers using $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) and spin-spin coupling constants (*J*) are reported in ppm and in Hz, respectively, and other data are reported as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = multiplet. Melting points were determined using a Büchi B-540 apparatus and are uncorrected. IR spectra were collected on a PerkinElmer Fourier Transform Infrared (FT-IR) spectrometer. Quadrupole time-of-flight electrospray ionization (ESI) mass spectrometer (model HAB 273) was used for mass spectra. Optical rotations were determined using a Rudolph Autopol I Automatic Polarimeter. HPLC analysis was carried out using Waters-2489 with Daicel Chiralcel OD column using *iso*-propanol and hexane as eluent.

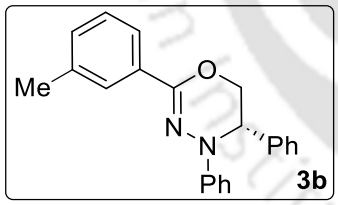
Asymmetric Synthesis of Oxadiazines. In a 10 mL round-bottomed flask $Yb(OTf)_3$ (10 mol %, 6 mg) and chiral ligand L7 (10 mol %, 8 mg) were dissolved in toluene (1.0 mL) in positive flow of N_2 and stirred to -20 ^oC for 30 minutes. To the above mixture, hydrazone **1** (0.1 mmol)

and styrene oxide **2** (0.12 mmol) were added at once and allowed to stir for 18 h. Next, the reaction mixture was brought to room temperature, diluted with ethyl acetate (10 mL) and washed with water (5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a silica gel column chromatography using n-hexane as the eluent to give **3**.

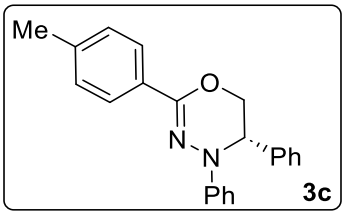
5.4 Characterization Data



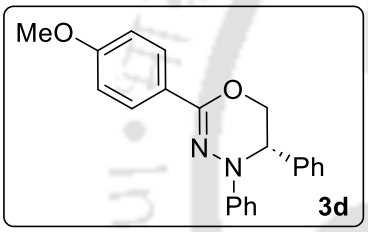
(*S*)-2-(3-Bromophenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3a. Red solid; mp 155-157 ^oC; yield 23% (9 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.32-7.30 (m, 2H), 7.28-7.19 (m, 8H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 4.61-4.52 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.54, 141.94, 138.21, 134.41, 131.84, 129.80, 129.20, 129.17, 128.22, 127.95, 126.40, 123.78, 122.51, 119.95, 113.10, 67.77, 55.76; $[\alpha]_D^{25}$ = +20.00 (c = 0.05, $CHCl_3$); HPLC analysis: 98% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.27 min (major), 09.08 min (minor)]; FT-IR (neat) 2919, 2851, 1594, 1497, 1381, 1261, 1169, 1114, 998, 886, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for : $C_{21}H_{18}BrN_2O^+$: 393.0597, found: 393.0598.



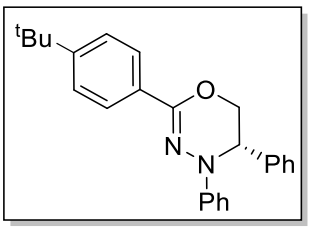
(*S*)-4,5-Diphenyl-2-(*m*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3b. Red solid; mp 162-164 ^oC; yield 18% (7 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 7.76-7.74 (m, 2H), 7.34-7.32 (m, 2H), 7.30-7.27 (m, 5H), 7.25 (t, *J* = 8.4 Hz, 3H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 5.24 (s, 1H), 4.62-4.60 (m ,1H), 4.59-4.57 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.81, 143.46, 138.54, 137.91, 132.36, 129.90, 129.14, 129.09, 128.21, 127.82, 126.49, 125.87, 122.51, 119.53, 112.96, 67.70, 55.75, 21.63; $[\alpha]_D^{25}$ = +33.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.28 min (major), 08.38 min (minor)]; FT-IR (neat) 2923, 1595, 1493, 1369, 1275, 1108, 1031, 791 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1647.



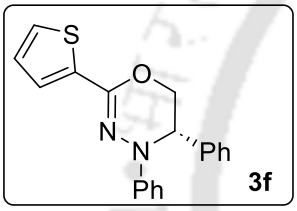
(*S*)-4,5-Diphenyl-2-(*p*-tolyl)-5,6-dihydro-4H-1,3,4-oxadiazine 3c. Colorless solid; mp 156-158 °C; yield 21% (7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 2H), 7.26-7.21 (m, 7H), 7.19-7.17 (m, 2H), 6.82 (t, *J* = 6.8 Hz, 1H), 5.20 (s, 1H), 4.59-4.53 (m, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.85, 143.57, 139.14, 138.61, 129.71, 129.12, 129.08, 128.99, 127.79, 126.52, 125.28, 119.41, 112.92, 67.72, 55.73, 21.52;: $[\alpha]_D^{25}$ = +30.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 05.17 min (major), 11.12 min (minor)]; FT-IR (neat) 2931, 1600, 1496, 1388, 1252, 1170, 1109, 1030, 836 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O^+$: 329.1648, found: 329.1647.



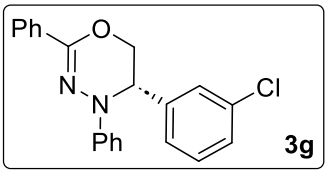
(*S*)-2-(4-Methoxyphenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3d. Yellow solid; mp 214-216 °C; yield 23% (8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.32-7.29 (m, 2H), 7.26-7.23 (m, 4H), 7.22-7.18 (m, 3H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.81 (t, *J* = 6.8 Hz, 1H), 5.20 (s, 1H), 4.59-4.54 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.53, 145.90, 143.49, 138.62, 129.11, 129.06, 127.77, 126.84, 126.53, 125.15, 119.28, 113.68, 112.84, 67.77, 55.68, 55.47; $[\alpha]_D^{25}$ = +27.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 07.64 min (major), 13.38 min (minor)]; FT-IR (neat) 2932, 1599, 1495, 1387, 1252, 1169, 1109, 1029, 836 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{22}H_{21}N_2O_2^+$: 345.1598, found: 345.1596.



(*S*)-2-(4-(*tert*-Butyl)phenyl)-4,5-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3e. Colorless solid; mp 148-150 °C; yield 31% (11 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.32-7.19 (m, 9H), 6.82 (t, *J* = 6.8 Hz, 1H), 5.21 (s, 1H), 4.60-4.53 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.33, 145.86, 143.52, 138.61, 129.74, 129.13, 129.07, 127.78, 126.53, 125.24, 125.11, 119.40, 112.89, 67.68, 55.77, 34.87, 31.40; $[\alpha]_D^{25}$ = +66.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 04.61 min (major), 10.21 min (minor)]; FT-IR (neat) 2960, 1597, 1495, 1337, 1269, 1169, 1057, 841 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{25}H_{27}N_2O^+$: 371.2118, found: 371.2117.

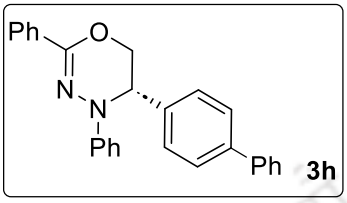


(*S*)-4,5-diphenyl-2-(thiophen-2-yl)-5,6-dihydro-4H-1,3,4-oxadiazine 3f. Black solid; mp 158-160 °C; yield 82% (53 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39-7.38 (m, 1H), 7.37-7.34 (m, 2H), 7.30-7.26 (m, 6H), 7.21-7.20 (m, 2H), 7.04 (t, *J* = 4.2 Hz, 1H), 6.87 (t, *J* = 7.2 Hz, 1H), 5.23 (s, 1H), 4.59 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.46, 141.18, 138.27, 136.25, 129.14, 127.89, 127.35, 126.48, 126.47, 125.33, 119.67, 112.95, 67.96, 55.86; $[\alpha]_D^{25}$ = +54.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 06.78 min (major), 11.27 min (minor)]; FT-IR (neat) 2928, 1596, 1495, 1447, 1374, 1267, 1168, 1033, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{19}H_{17}N_2OS^+$: 321.1056, found: 321.1062.



(*S*)-5-(3-chlorophenyl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3g. Red solid; mp 191-193 °C; yield 23% (8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.83 (m, 2H), 7.33-7.28 (m, 3H), 7.20-7.16 (m, 5H), 7.14-7.11 (m, 2H), 7.05-7.04 (m, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 5.11 (s, 1H), 4.51-4.48 (m, 1H), 4.47-4.43 (m, 1H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 145.54, 143.39, 140.74, 135.00, 132.22, 130.46, 129.24, 128.32, 128.20, 126.64, 125.33, 124.78, 119.85, 112.94, 67.37, 55.48.; $[\alpha]_D^{25}$ = +32.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 06.21 min (major), 13.47 min (minor)]; FT-IR (neat) 2928, 1597, 1493, 1387, 1271, 1112, 1003, 748 cm^{-1}; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{18}ClN_2O^+$: 349.1102, found: 349.1101.



***(S)*-5-([1,1'-biphenyl]-4-yl)-2,4-diphenyl-5,6-dihydro-4H-1,3,4-oxadiazine 3h.** Colorless solid; mp 151-153 °C; yield 25% (10 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 4H), 7.45-7.40 (m, 5H), 7.37-7.33 (m, 3H), 7.31-7.29 (m, 4H), 6.91-6.87 (m, 1H), 5.30 (s, 1H), 4.68-4.65 (m, 1H), 4.63-4.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.80, 143.36, 140.80, 140.73, 137.52, 132.44, 129.20, 129.13, 128.88, 128.30, 127.88, 127.46, 127.19, 126.96, 125.33, 119.64, 113.01, 67.71, 55.55; $[\alpha]_D^{25}$ = +60.00 (c = 0.05, $CHCl_3$); HPLC analysis: 99% ee [Daicel CHIRALCEL OD column, hexane/^{i}PrOH = 97:3, flow rate: 1 mL/min, λ = 254 nm, t_R= 07.18 min (major), 18.92 min (minor)]; FT-IR (neat) 2924, 1597, 1493, 1385, 1109, 840, 759 cm^{-1} HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{27}H_{23}N_2O^+$: 391.1805, found: 391.1812.

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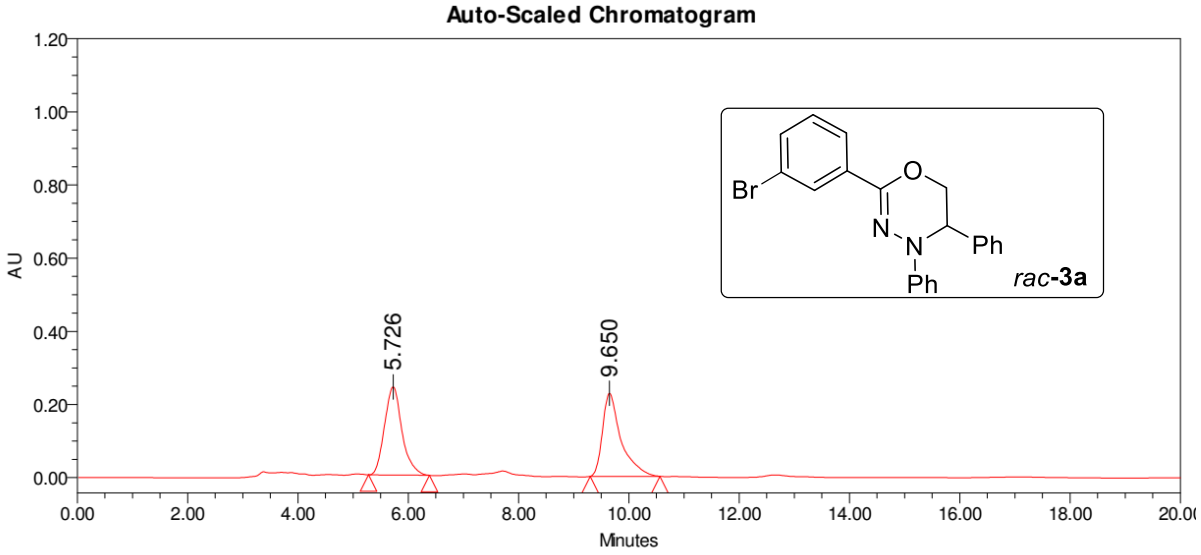
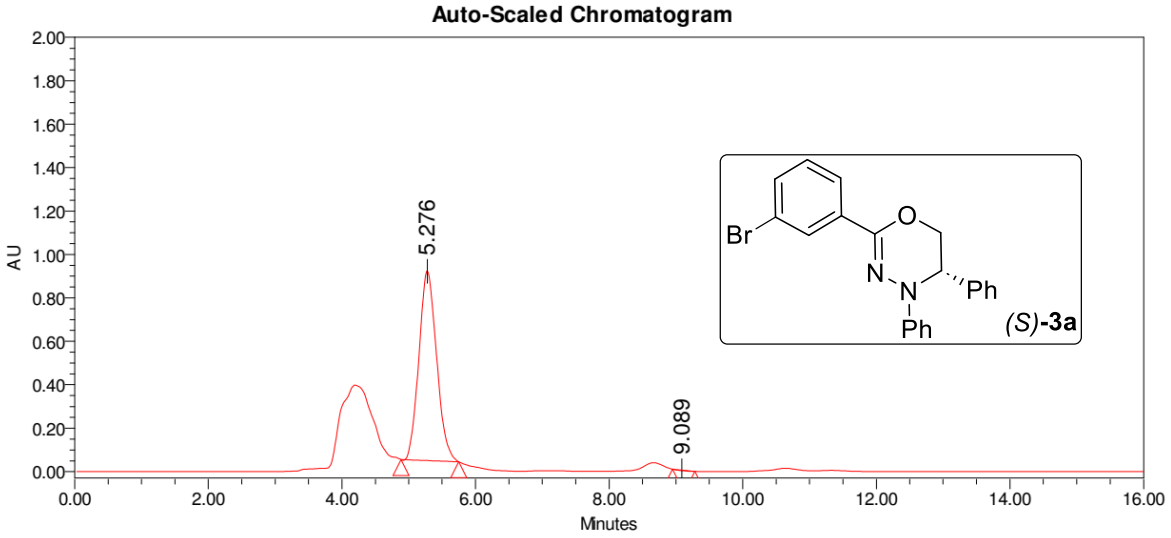
5.6 HPLC Chromatograms



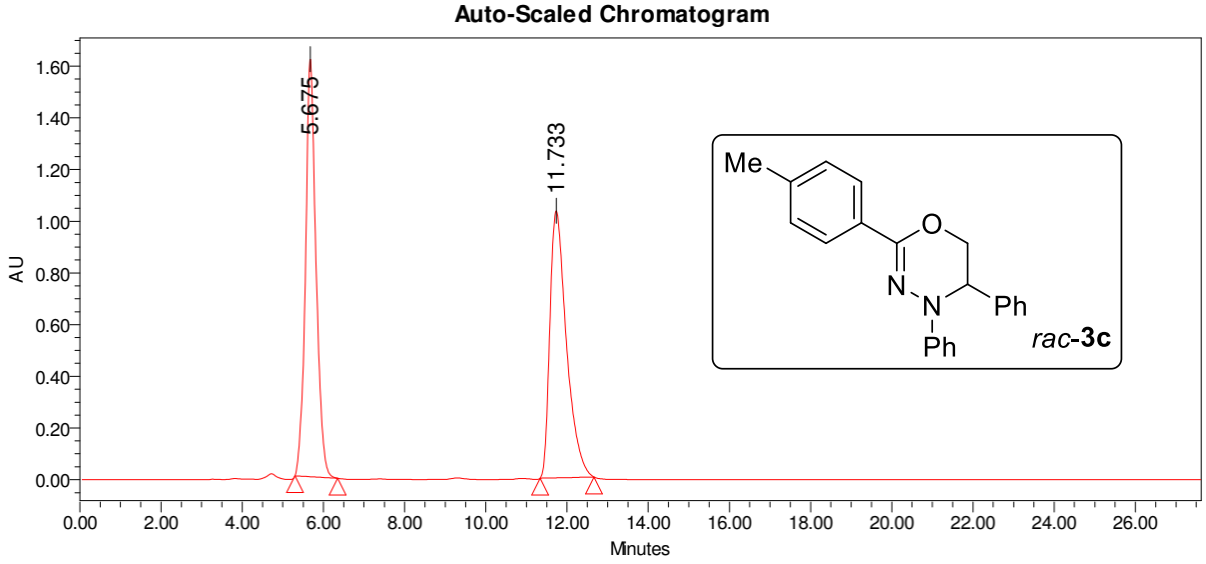
Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	5.283	6.383	5.726	241026	50.13
2	9.300	10.567	9.650	227033	49.87



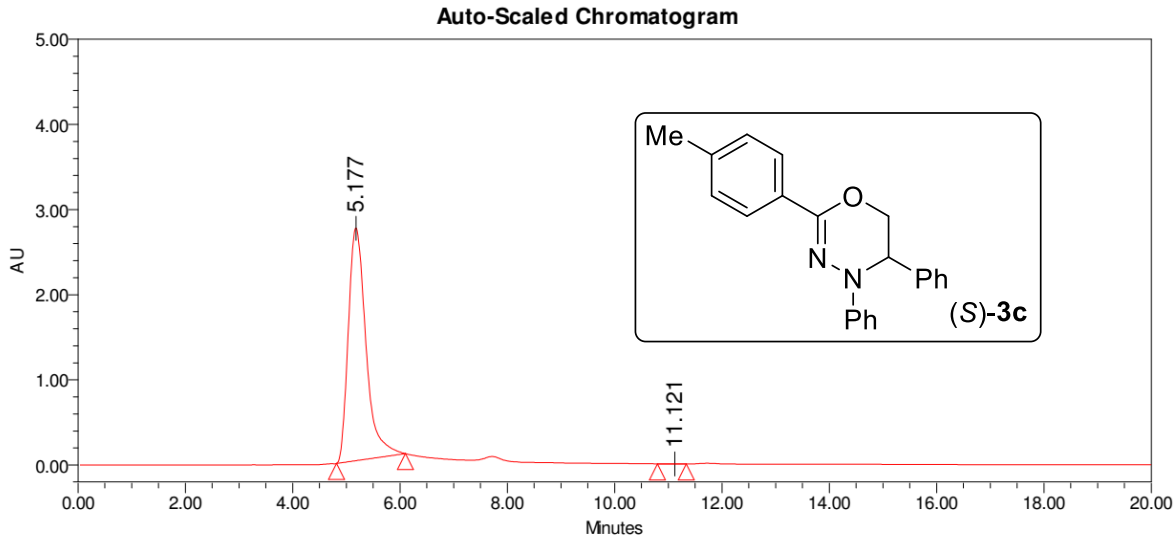
Peak Results

	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		4.883	5.750	5.276	873486	99.79
2	I37	8.950	9.283	9.089	-2608	0.21



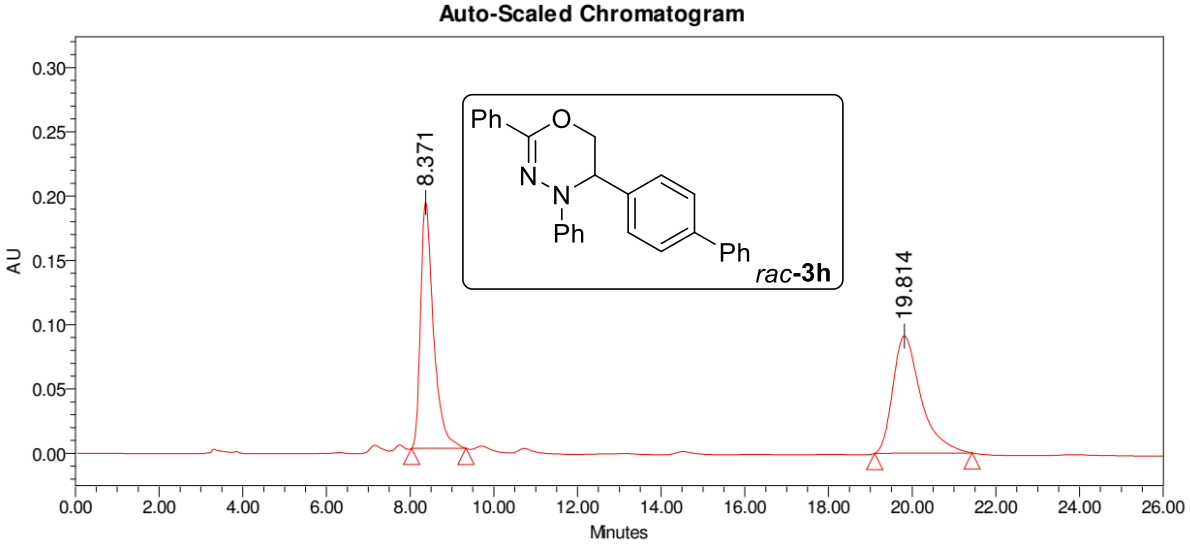
Peak Results

	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	5.300	6.350	5.675	1620615	49.93
2	11.333	12.667	11.733	1032900	50.07



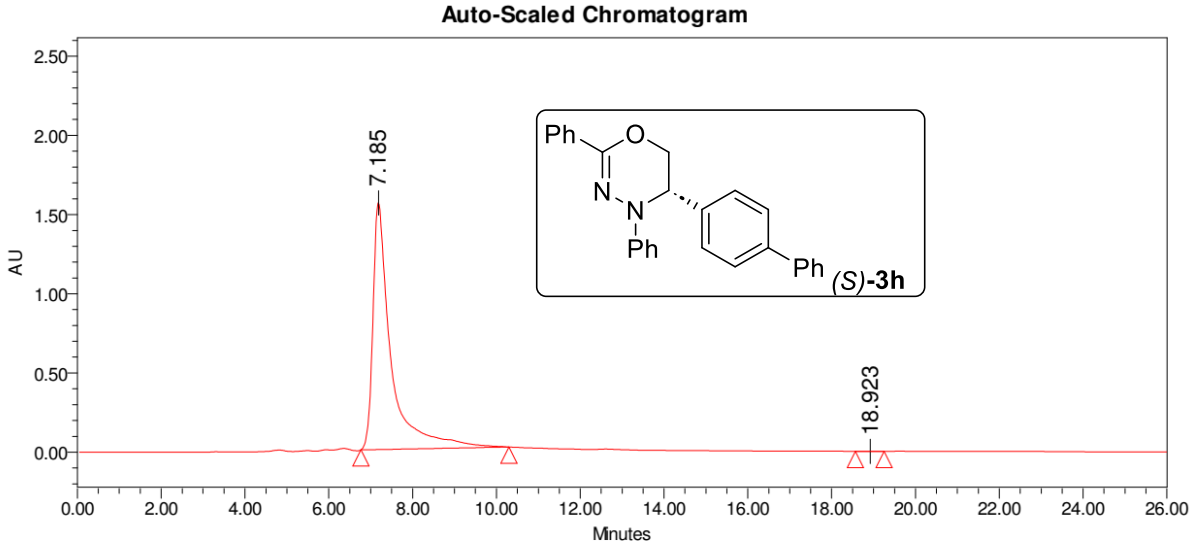
Peak Results

	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		4.817	6.100	5.177	2733194	99.99
2	I37	10.800	11.333	11.121	-157	0.01



Peak Results

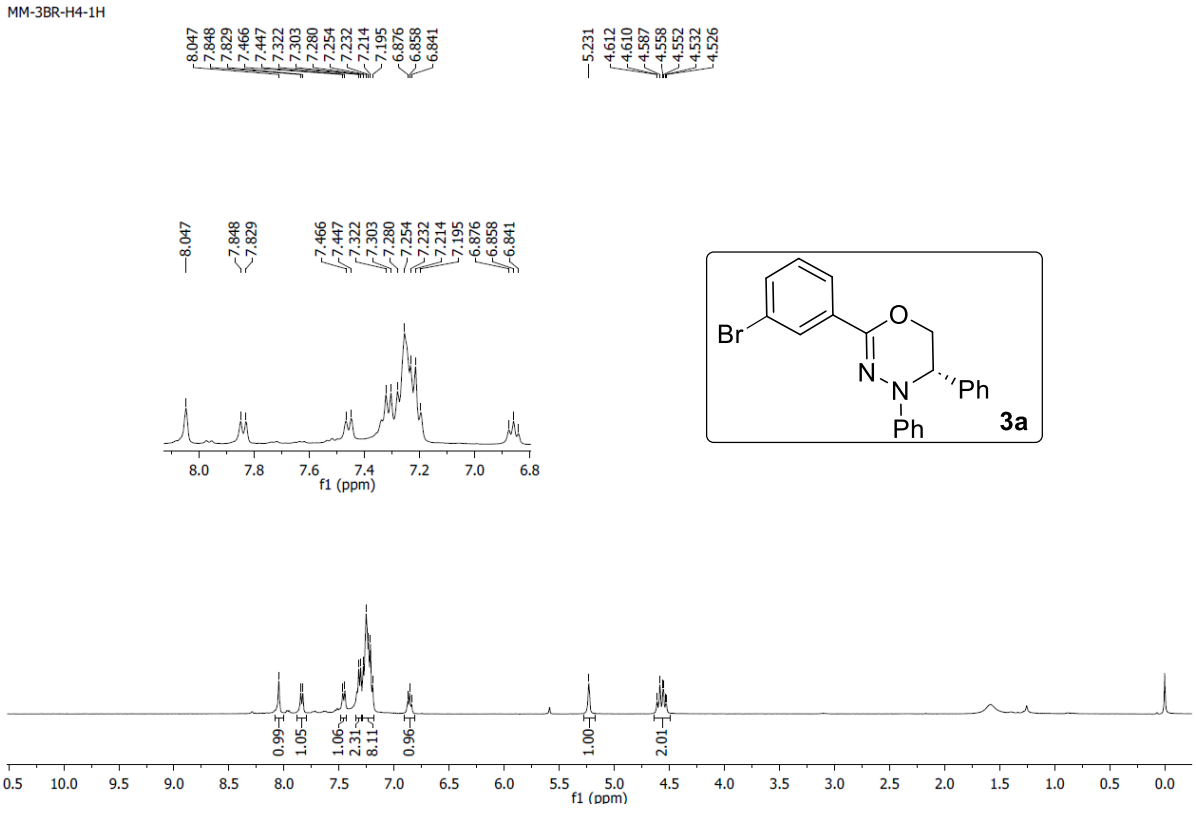
	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1	8.033	9.333	8.371	191351	49.11
2	19.100	21.433	19.814	91102	50.89



Peak Results

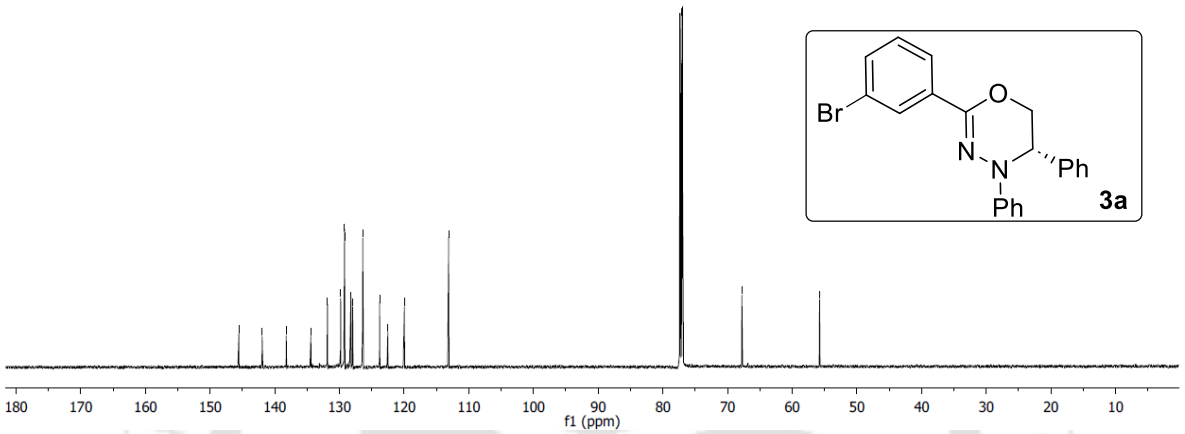
	Peak Codes	Start Time (min)	End Time (min)	RT	Height (µV)	% Area
1		6.767	10.300	7.185	1559120	99.98
2	I37	18.567	19.250	18.923	-299	0.02

5.7 Selected NMR Spectra



MM-3BR-H4-13C

145.547
141.946
138.217
134.416
131.849
129.803
129.208
129.177
128.225
127.954
126.400
123.786
122.514
119.955
113.107
77.371
77.160
76.949
67.777
55.762



MM-4ME-H4-1H

7.819
7.798
7.323
7.305
7.287
7.264
7.256
7.247
7.224
7.215
7.191
7.170
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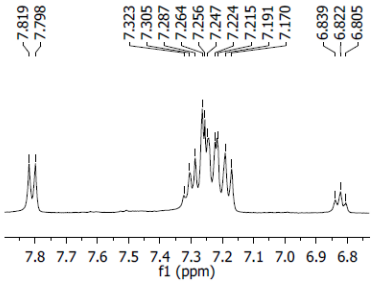
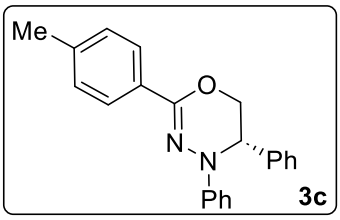
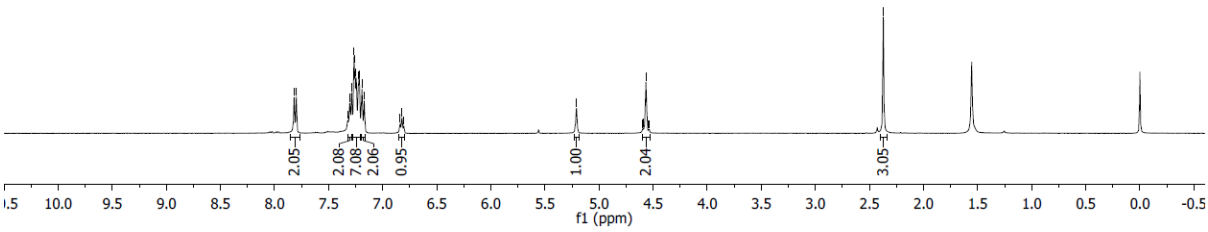
4.566
4.560
4.541
4.534
2.372

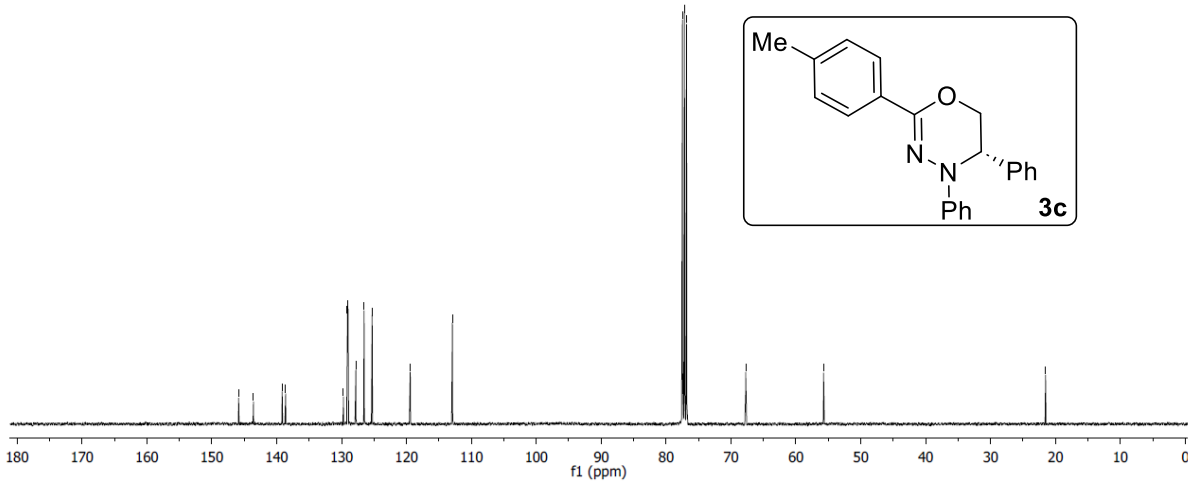






MM-4ME-H4-13C

145.859
143.573
139.144
138.616
129.713
129.128
129.081
128.995
127.793
126.524
125.287
119.415
112.920
77.478
77.161
76.842
67.726
55.736
21.523



MM-4OME-H4-1H

7.864
7.842
7.327
7.309
7.291
7.268
7.256
7.237
7.220
7.204
7.184
6.910
6.888
6.831
6.814
6.797
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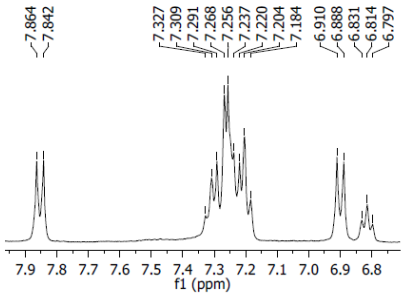
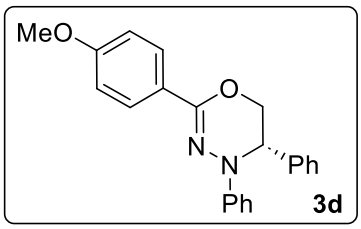
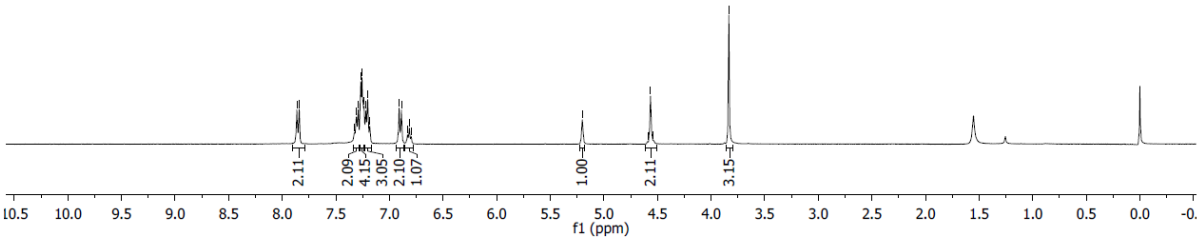
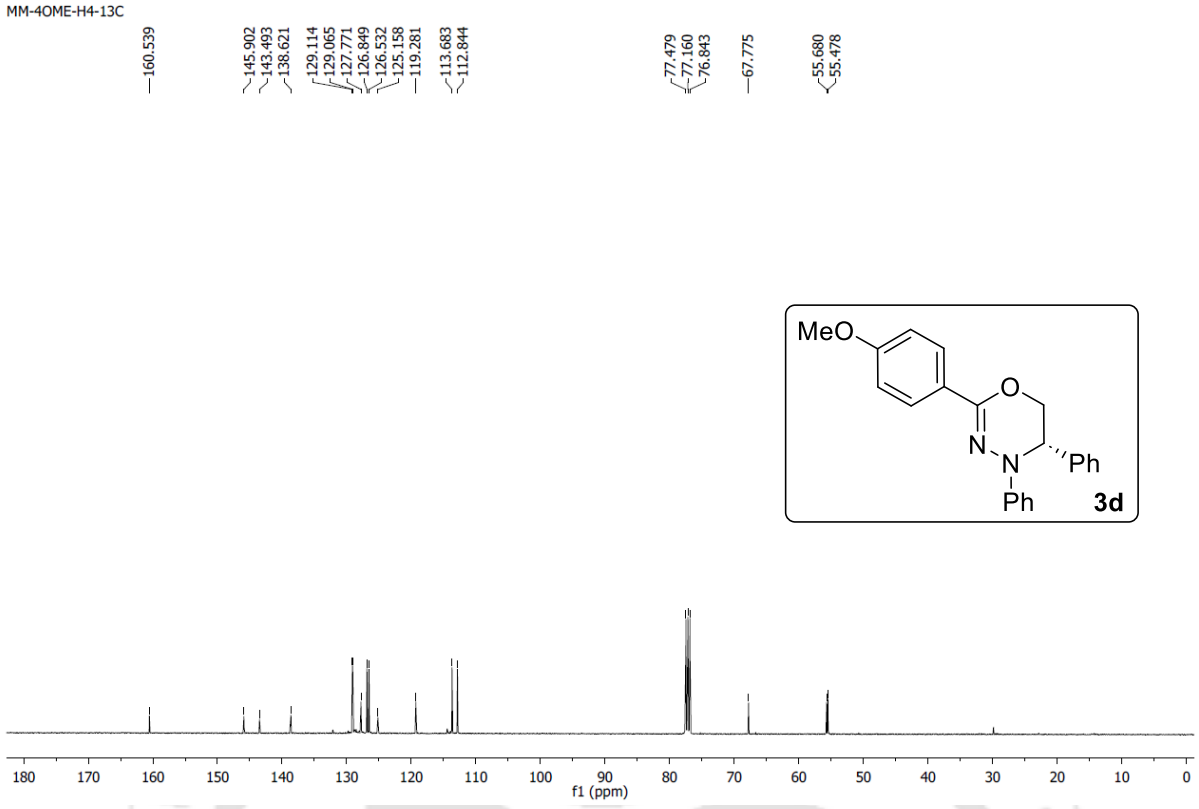
4.590
4.565
4.541
3.834









Conclusions

In chapter 1, the studies emphasizing on the background, reactivity and cyclization of D-A cyclopropanes with transition metal catalysis are discussed. These reports mainly focused in the cyclization of D-A cyclopropanes through a 1,3-zwitteriionic intermediate with the help of Lewis acid catalysts to synthesize biologically relevant heterocyclic scaffolds.

In chapter 2, we have described the stereospecific ring opening and an oxidative cyclization of D-A cyclopropanes with reactive hydrazones in presence of $Cu(OTf)_2$ catalyst. The method offers a one-pot C-C and C-N bond forming strategy under mild reaction conditions. The reaction of broad range of alkyl and aryl hydrazones and D-A cyclopropanes as well as enantiopure D-A cyclopropanes has been accomplished efficiently under this protocol.

In chapter 3, a Co(II)-catalyzed stereospecific ring opening and oxidative C-O bond forming cascade of hydrazones with reactive oxiranes was developed successfully. The reaction is aerobic and biologically important oxadiazines were synthesized with excellent yields and enantiopurities. It is also important to mention that, the Co(II)-catalyst plays crucial role in the stereospecific ring opening of oxiranes with high optical purities.

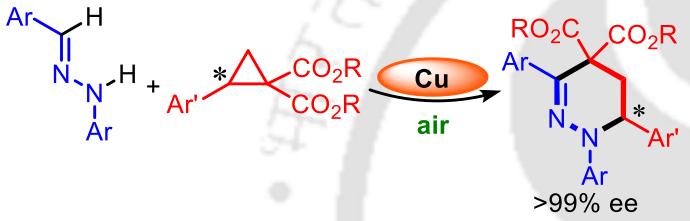
In Chapter 4, we have demonstrated the regioselective synthesis of pyrans from readily available D-A cyclopropanes with 2,4-dienals in presence of benign Fe-catalyst. The sequential three C-C and C-O bond forming cascade under a single operation *via* a ketene intermediate is a noteworthy achievement.

In chapter 5, we have revealed the enantioselective synthesis of oxadiazines from racemic oxiranes with hydrazones using chiral Yb(III)-adamantyl *N,N′*-oxide complex. The strategy is operationally simple and the oxadiazines were produced with excellent enantioselectivities. This protocol also signifies the effect of various chiral ligands in the enantioselective ring opening of oxiranes with *N*-nucleophilic hydrazones.

Thesis Overview

CHAPTER 2

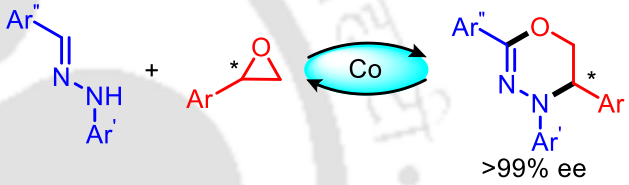
Stereospecific Copper(II)-Catalyzed Domino Ring Opening and Oxidative Alkylation of Donor-Acceptor Cyclopropanes with Hydrazones



♣ aerobic ♣ stereospecific ♣ *C-N/C-C* bond formation

CHAPTER 3

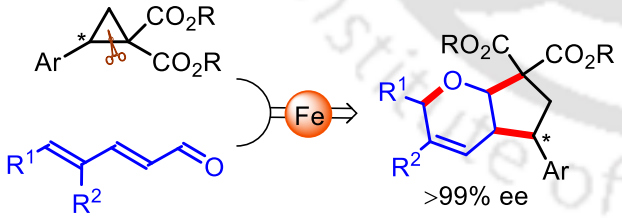
Expedient Cobalt-Catalyzed Stereospecific Cascade C-N and C-O Bonds Formation of Styrene Oxides with Hydrazones



♣ inexpensive ♣ stereospecific ♣ *C-N/C-O* bond formation

CHAPTER 4

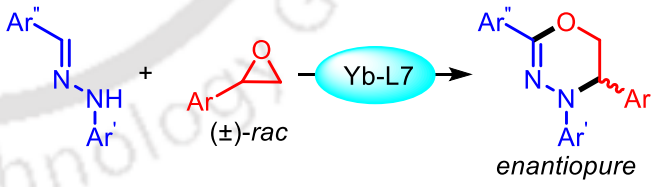
Fe-Catalyzed Regioselective C-C/C-O Bond Formation of D-A Cyclopropanes with 2,4-Dienals



♣ regioselective ♣ enantiopure ♣ *C-C/C-O* bond formation

CHAPTER 5

Yb-*adamantyl N,N*-Oxide assisted Asymmetric Synthesis of Oxadiazines from Oxiranes and Hydrazones



♣ steroselective ♣ ring opening/oxidative etherification
♣ *C-N/C-O* bond formation

List of Publications

1. **Manmath Mishra**, Pinaki Bhusan De, Sourav Pradhan, and Tharmalingam Punniyamurthy, Stereospecific Copper(II)-Catalyzed Tandem Ring Opening/Oxidative Alkylation of Donor–Acceptor Cyclopropanes with Hydrazones: Synthesis of Tetrahydropyridazines, *J. Org. Chem.* **2019**, *84*, 10901.

2. Sourav Pradhan, **Manmath Mishra**, Pinaki Bhusan De, Sonbidya Banerjee, and Tharmalingam Punniyamurthy, Weak Coordination Enabled Switchable C4-Alkenylation and Alkylation of Indoles with Allyl Alcohols, *Org. Lett.*, **2020**, *22*, 1720.

3. Sonbidya Banerjee, **Manmath Mishra**, and Tharmalingam Punniyamurthy, Copper-Catalyzed C7-Selective C-H/N-H Cross-Dehydrogenative Coupling of Indolines with Sulfoximines, *Org. Lett*., **2022**, *24*, 7997.

4. Pallab Karjee, **Manmath Mishra**, Bijoy Debnath and Tharmalingam Punniyamurthy, Expedient $Ni(OTf)_2$/Visible Light Photoredox-Catalyzed Annulation of Donor-Acceptor Cyclopropanes with Cyclic Secondary Amines, *Chem. Commun*., **2022**, *58*, 8670.

5. **Manmath Mishra**, Prabhat Kumar Maharana, Pallab Karjee and Tharmalingam Punniyamurthy, Expedient Cobalt-Catalyzed Stereospecific Cascade C-N and C-O Bond Formation of Styrene Oxides with Hydrazones, *Chem. Commun*., **2022**,*58*, 7090.

6. Kshitiz Verma, **Manmath Mishra**, Prabhat Kumar Maharana, Hemanga Bhattacharyya, Sharajit Saha, and Tharmalingam Punniyamurthy, $Sc(OTf)_3$-Catalyzed Domino C-C/C-N Bond Formation of Aziridines with Quinones *via* Radical Pathway. *Org. Lett.* **2023**, *25*, 7933.

Conferences

Oral Presentation:

1. Manmath Mishra, Pinaki Bhusan De, Sourav Pradhan, and Tharmalingam Punniyamurthy, Stereospecific Copper(II)-Catalyzed Tandem Ring Opening/Oxidative Alkylation of Donor–Acceptor Cyclopropanes with Hydrazones: Synthesis of Tetrahydropyridazines, XV J-NOST, Delhi University, New Delhi, Oct 18-21, 2019

Poster presentation:

2. Manmath Mishra, Pinaki Bhusan De, Sourav Pradhan, and Tharmalingam Punniyamurthy, Stereospecific Copper(II)-Catalyzed Tandem Ring Opening/Oxidative Alkylation of Donor–Acceptor Cyclopropanes with Hydrazones: Synthesis of Tetrahydropyridazines, CRSI NCS-28, IIT Guwahati, March 25-27, 2022
3. **Manmath Mishra**, Prabhat Kumar Maharana, Pallab Karjee and Tharmalingam Punniyamurthy, Expedient cobalt-catalyzed stereospecific cascade C–N and C–O bond formation of styrene oxides with hydrazones, Research Conclave, IIT Guwahati, Guwahati, may 14-16, 2023.