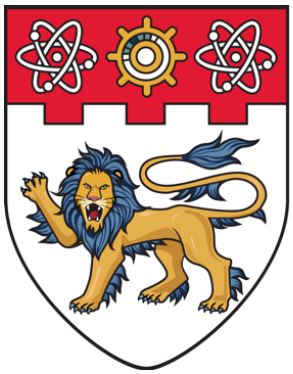


NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

CARBENE-CATALYZED ENANTIOSELECTIVE ACCESS TO BIOACTIVE DIHYDROPYRIDAZINONES AND ATROPOSELECTIVE ACCESS TO BINAPHTHYL LIGANDS

MONDAL BIVAS

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2022

CARBENE-CATALYZED ENANTIOSELECTIVE ACCESS TO BIOACTIVE DIHYDROPYRIDAZINONES AND ATROPOSELECTIVE ACCESS TO BINAPHTHYL LIGANDS

MONDAL BIVAS

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

A thesis submitted to the Nanyang Technological University in partial fulfilment of the requirement for the degree of Doctor of Philosophy

2022

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

04th August, 2021

. . . . . .
Date

. . . . . .
Mondal Bivas

Supervisor Declaration Statement

I have reviewed the content and presentation style of this thesis and declare it of sufficient grammatical clarity to be examined. To the best of my knowledge, the thesis is free of plagiarism and the research and writing are those of the candidate's except as acknowledged in the Author Attribution Statement. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

Aug 4, 2021

Date

Prof. Yonggui Robin Chi

Authorship Attribution Statement

This thesis contains material from 1 paper published in the following peer-reviewed journal in which I am listed as an author.

Chapter 2 is published as B. Mondal, R. Maiti, X. Yang, J. Xu, W. Tian, J.-L. Yan, X. Li, Y. R. Chi Carbene-catalyzed enantioselective annulation of dinucleophilic hydrazones and bromoenals for access to aryl-dihydropyridazinones and related drugs. *Chemical Science* **12**, 8778-8783 (2021). DOI: 10.1039/d1sc01891d.

The contributions of the co-authors are as follows:

- B. Mondal conducted most of the experiments and wrote the initial manuscript draft.
- R. Maiti, X. Yang, J. Xu, and J.-L. Yan performed part of the experiments.
- W. Tian and X. Li contributed to product design regarding potential bioactivities.
- Y. R. Chi conceptualized and directed the project and finalized the manuscript draft.
- All authors contributed to discussions

04th August, 2021

. . . . . .
Date

. . . . . .
Mondal Bivas

Abstract

Development of new methodology for quick access to important molecular motifs is a growing field of research in synthetic organic chemistry. In this aspect, N-heterocyclic carbene (**NHC**) has witnessed a significant achievement, specifically in asymmetric synthesis, in last two decades. Special attention has been given to efficient asymmetric access to bioactive molecules and other valuable scaffolds with potential applications. In this thesis, we have introduced two interesting **NHC**-catalyzed methodology development for access to biologically active dihydropyridazinone scaffolds and bicyclic vinyl esters, a precursor to binaphthyl-based ligands.

In chapter 1, different activation modes enabled by **NHC** have been discussed briefly. This includes three main domains of **NHC**-catalysis, (a) chemistry of umpoled acyl-anion, (b) catalysis involving homoenolate intermediate, and (c) acyl-azolium chemistry.

In chapter 2, we have discussed a new (3+3)-cycloaddition reaction between rarely explored umpoled 1,3-dinucleophiles from arylidene hydrazones and α,β-unsaturated acylazolium to access biologically important 6-aryl dihydropyridazinone scaffolds in excellent outcome (up to 89% yield and 98.5:1.5 e.r.). Further, we have discussed the conversion of the products from our catalytic cycle to clinically approved drugs (Levosimendan, Pimobendan) and bioactive molecules (DNMDP, Meribendan).

In chapter 3, we have demonstrated an unprecedented carbene-catalyzed dynamic kinetic resolution (DKR) on bicyclic ketone/enol to access atropo-enriched enolic ester in excellent yield (up to 95%) and moderate optical purity (up to 91.5:8.5 e.r.). Worthy to note this is the first example of **NHC**-catalyzed DKR process to access axially chiral compounds. We also have discussed that many ligands have the similar scaffolds with the product from our catalytic cycle. In the end, we have shown the importance of our methodology by formal synthesis of a ligand from our catalytic product with high efficiency.

Acknowledgements

First of all, I am eternally grateful to Nanyang Technological University for awarding me Nanyang Research Fellowship. Without the financial support from the University, I could not be able to pursue this Ph.D journey.

I would also like to take this opportunity to express my sincere gratitude and respect to my supervisor, Professor Yonggui Robin Chi for his continuous support, guidance, and patience. The freedom which he provided me throughout my Ph.D studies helped me to grow both academically and personally.

My gratitude also extends to my Thesis Advisory Committee (TAC) members, Prof. Shuzhou Li and Prof. Zhao Yanli, for their advice, support, and guidance.

I am truly thankful to all current and previous lab members for their assistance and advice throughout my Ph.D. especially, Dr. Liu Yingguo , Dr. Pankaj Kumar Majhi, Dr. Rakesh Maiti, Dr. Yang Xing, Dr. Jia-Lei Yan, Dr. Hao Lin, Dr. Ren Shichao, Dr. Chen Xingkuan , Dr. Zhou Leijin, Dr. Yongtao Xei, Dr. Wang Fangxin, Dr. Zhou Shitian, Dr. Liu Bin, and Song Runjiang.

Moreover, I really appreciate the CBC instrument lab staff for their continuous assistance with laboratory instruments, Ms. Goh Ee Ling for NMR machine, Dr. Li Yongxin for X-ray analysis and Ms. Zhu Wenwei for mass spectroscopy analysis. I am also thankful to Ms. Ai Hua, Ms. Lim Yen Lin and Ms. Tan Si Min and other staff for their help with teaching labs instruments usage such as IR spectrometer and Polarimeter. I would also like to convey my gratitude to Ms. Lee Yean Chin and Ms. Koh Su Ping for their help in administrative work.

Next, I am grateful to all my friends from the SPMS for their help and encouragement during the journey. I thank to Roshayed, Deblin, Jit, and Mrinmoy just to name a few.

Last but not least, I would like to thank my family, particularly my mom and brother for their love and encouragement throughout my PhD study.

Table of Contents

Publications

1. **B. Mondal**, R. Maiti, X. Yang, J. Xu, W. Tian, J.-L. Yan, X. Li, Y. R. Chi, Carbene-catalyzed enantioselective annulation of dinucleophilic hydrazones and bromoenals for access to aryl-dihydropyridazinones and related drugs, *Chemical Science* **2021**, *12*, 8778.

2. R. Maiti, J. Xu, J.-L. Yan, **B. Mondal**, X. Yang, H. Chai, L. Hao, Z. Jin, Y. R. Chi, Carbene-catalyzed selective addition of isothioureas to enals for access to sulphurcontaining 5,6-dihyropyrimidin-4-ones, *Org. Chem. Front*., **2021**, *8*, 743.

3. X. Yang, Y. Xie, J. Xu, S. Ren, **B. Mondal**, L. Zhou, W. Tian, X. Zhang, L. Hao, Z. Jin, Y. R. Chi, Carbene-Catalyzed Activation of Remote Nitrogen Atoms of (Benz)imidazole-Derived Aldimines for EnantioselectiveSynthesis of Heterocycles, *Angew.Chem. Int. Ed.* **2021**, *60*, 7906.

4. R. Maiti, J.-L. Yan, X. Yang, **B. Mondal**, J. Xu, H. Chai, Z. Jin, Y. R. Chi, Carbene-catalyzed asymmetric hydrophosphination (ahp) of α-bromoenals to prepare diarylalkyl and trialkyl phosphines. *Angew. Chem. Int. Ed.* **2021**, *133*, 26820.

5. J.-L. Yan, R. Maiti, S.-C. Ren, T. Li, W. Tian, J. Xu, **B. Mondal**, Y. R. Chi, Carbene-catalyzed atroposelective synthesis of axially chiral styrenes bearing acyclic alkenes. *Nat. Comm.*, DOI: 10.1038/s41467-021-27771-x.

Abbreviations

Ac	Acetyl
Ar	aryl
Boc	*tert*–butyloxycarbonyl
Bn	benzyl
Bu	butyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DKR	dynamic kinetic resolution
dr	diastereomeric ratio
e.r.	enantiomeric ratio
Equiv	equivalent
ESI	electrospray ionization
HRMS	High resolution mass spectrometry
HPLC	High-performance liquid chromatography
^{i}Pr	isopropyl
Mes	mesityl
NHC	*N*-heterocyclic carbene
TBS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography

α	alpha
β	beta
γ	gamma
δ	delta
π	pi
σ	sigma
Ω	Omega

Chapter 1

Introduction

1.1 Brief introduction of N-heterocyclic carbene (NHC) and different classes of NHC catalysts

N-Heterocyclic carbene (**NHC**) is a special class of carbene, where the carbenoid carbon is directly attached with the electron-rich nitrogen atom, and hence electron donation from nitrogen makes **NHC** electron rich-molecule. As a consequence, **NHC**s have found tremendous application in organic catalysis and as a ligand with metal centers. Although, **NHC** as an organic catalyst was discovered as early as 1940,[1] the rapid development of this field has been made in last two decades.[2] At the beginning, Wanzlick and co-workers have contributed significantly to develop this field by studying **NHC** and its dimer.[3-4] After that different kinds of **NHC** precursors, such as thiazolium salt, imidazolium salt, and triazolium salt have developed. Finally, in 1991, a breakthrough was made by Ardeungo in this field by isolating stable crystalline carbene. Two bulky and electron-rich adamentyl nucleus attached with the two nitrogen atoms of the Ardeungo's imidazolium carbene made it possible to isolate in a crystalized form via inhibiting dimerization and increasing its' stability (Figure 1.1). This ground-breaking discovery made the foundation for future research in this field.[5]

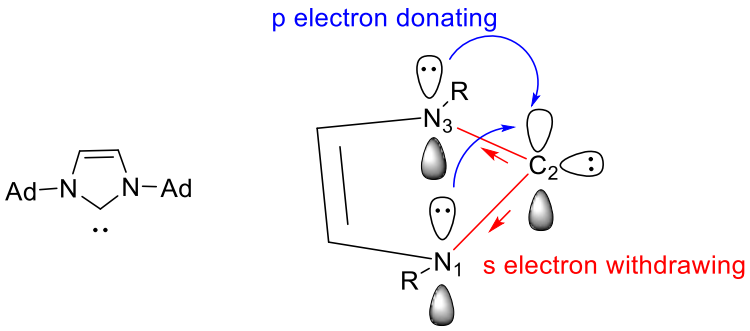
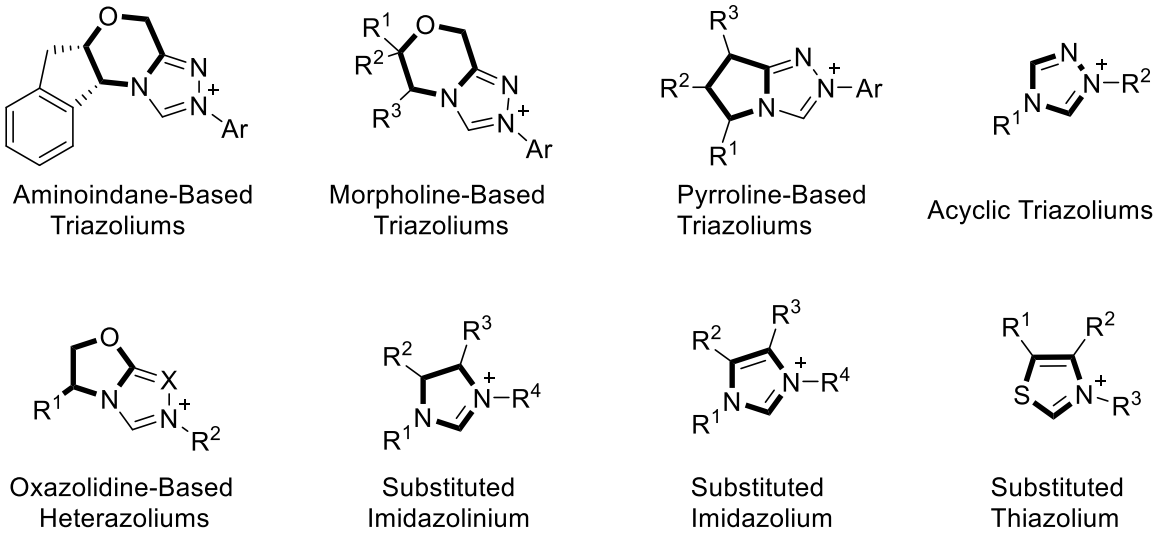


Figure 1.1 Electronic structure of the first stable **NHC** in its ground state

For different asymmetric reactions, several **NHC** catalysts have been developed. Thiazolium salts were commonly employed as an **NHC** catalyst precursor in the early stages of **NHC** catalysis. In later stage, a number of triazolium and imidazolium based **NHC**s with

various chiral moiety or substituents were developed. **NHC** precursors have been classified into eight types based on their chemical structures, such as (1) aminoindanol-based triazoliums, (2) morpholine-based triazoliums, (3) pyroline-based triazoliums. (4) acyclic triazoliums, (5) oxazolidine-based heterazoliums, (6) imidazoline-based heterazoliums, (7) imidazole-based heterazoliums, (8) thiazole-based heterazoliums (Scheme 1.1).[2]



Scheme 1.1 NHC precursors containing various backbones

1.2 Different modes of reactions enabled by NHC Catalysis

To date, **NHC** catalyst has been explored to activate different kinds of carbonyl compounds, such as aldehyde, ester, acid, and its' derivatives.[2,6-10] **NHC** catalyst has witnessed tremendous success in activating carbonyl compounds in different positions, such as, α, β, γ, or even more remote positions. In this chapter, we will focus mainly on three important

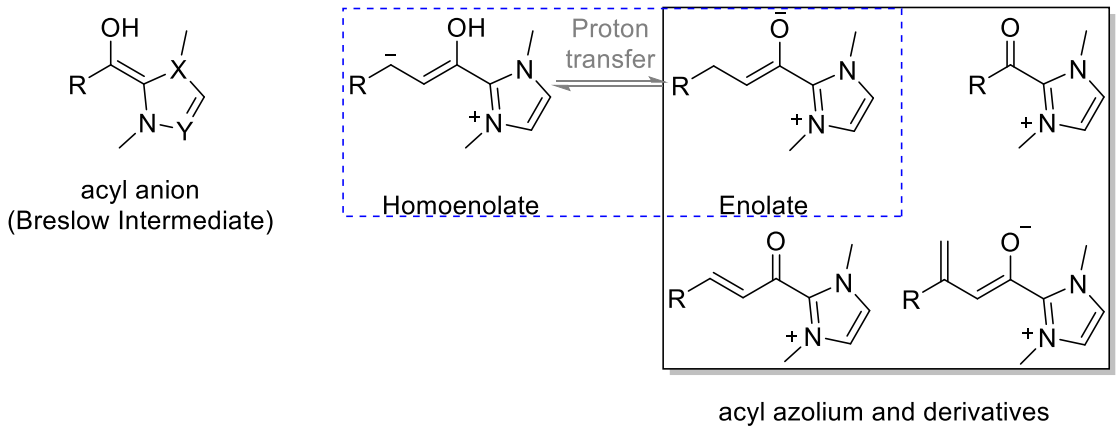


Figure 1.2 Different types of **NHC**-catalyzed activation mode

reactivity modes of **NHC**. They are a) umpolung acyl anion catalysis, b) homoenolate intermediate catalysis, and c) catalysis involving acyl azolium ion (Figure 1.2).

1.3 NHC-catalysis involving umpolung acyl anion intermediate

Benzoin reaction is the earliest reaction developed in this field. The electrophilic character of aldehydic carbon changed to nucleophilic character under **NHC**-catalyzed condition, which can be viewed as acyl anion equivalent, was proposed by Breslow, and this kind of phenomenon of polarity reversion is called "umpolung".[10-11] This **NHC**-catalyzed umpolung chemistry had been explored widely, particularly in benzoin and Stetter reactions.

1.3.1 NHC-catalyzed benzoin reactions

Although **NHC** was discovered as an organic catalyst as early as 1940, the development of different kinds of activation modes of **NHC** was started after the discovery of benzoin condensation by the group of Ukai in 1943, utilizing thiazolium salt-derived carbene as catalyst in place of cyanide ion. Few years later, after a detailed mechanistic investigation, in 1958 Breslow, proposed the mechanism of this benzoin condensation reaction. According to the pro-

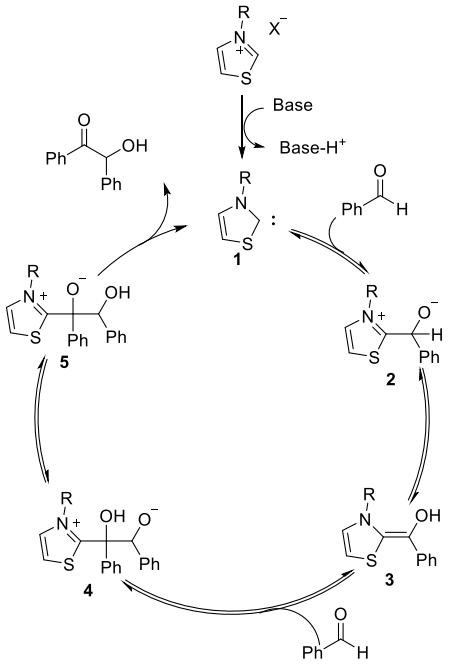
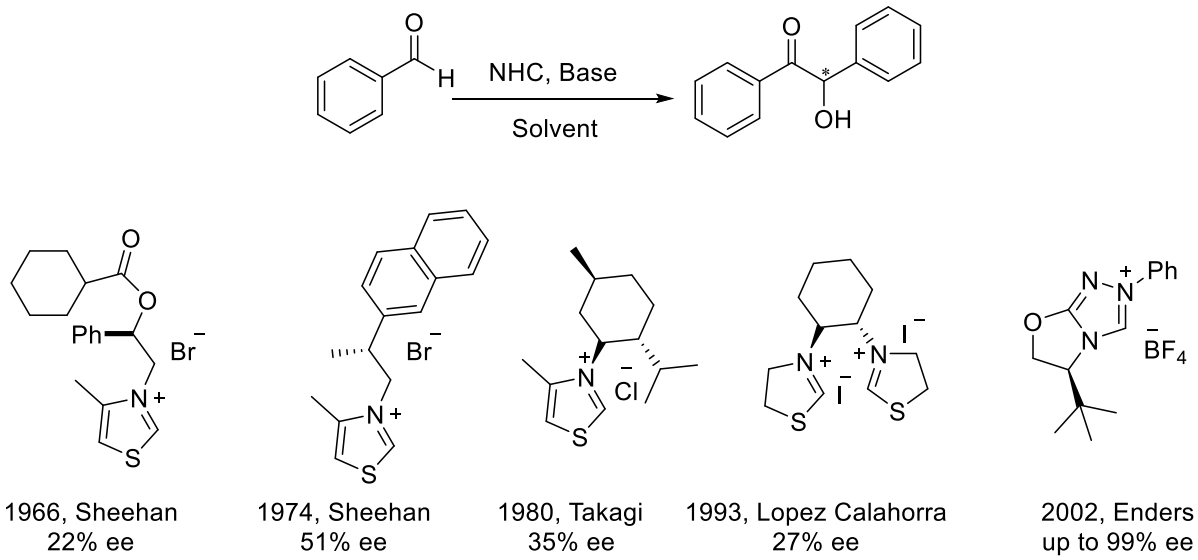


Figure 1.3 Mechanism of the benzoin reaction catalyzed by **NHC**

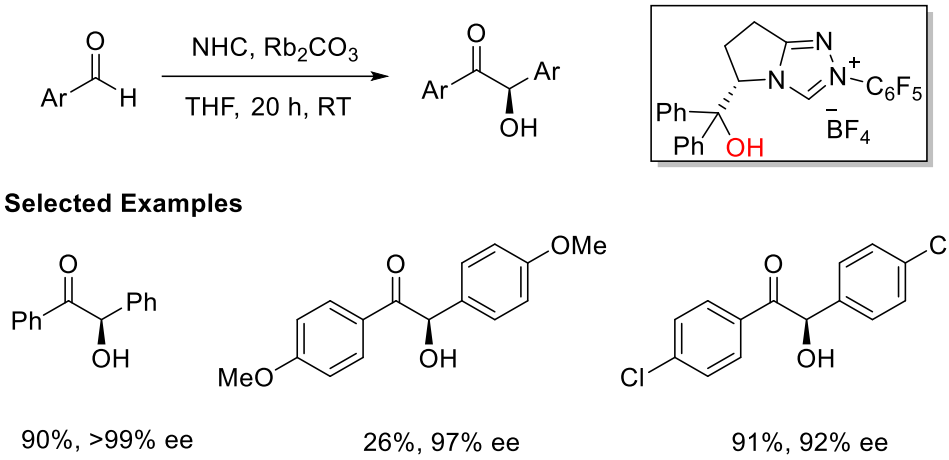
posed mechanism[12] (Figure 1.3), carbene **1** (generated from the precatalyst) attacks benzaldehyde to form the zwitterionic intermediate **2**. Intermediate **2** upon proton exchange generates the key Breslow intermediate **3**. Intermediate **3** is like an enamine, which attacks another molecule of benzaldehyde and forms the intermediate **4**. Intermediate **4** upon proton exchange goes to intermediate **5**. Then the intermediate **5** dissociates and forms the benzoin product and regenerates the catalyst, which again undergoes another cycle. Following the discovery of the catalytic mechanism, chiral carbenes were used to develop an asymmetric version of the benzoin reaction. The group of Sheehan tried to achieve asymmetric version of the Benzoin reaction catalyzed by chiral thiazolium **NHC** catalyst.[13] But they got only a moderate ee (~22%) value in their reaction system. After that, many groups tried to develop very efficient carbene catalyzed asymmetric benzoin reactions (Scheme 1.2). It was until 2002, when Enders reported highly enantioselective (up to 99% ee) version of this reaction using morpholine-based chiral triazolium **NHC**-precatalyst.[14]



Scheme 1.2 NHC-catalyzed asymmetric benzoin reaction

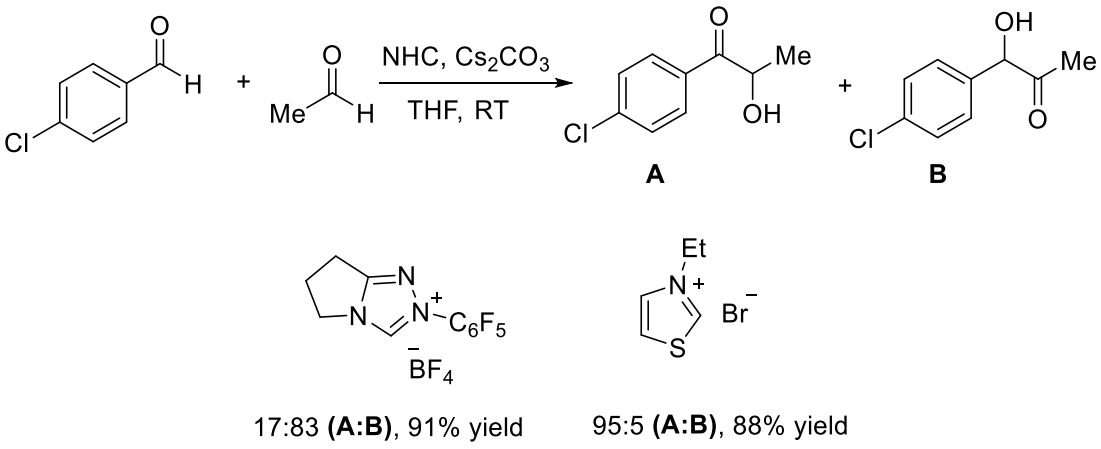
Connon and Zeitler come up with a highly efficient catalytic system to give the benzoin product up to 90% yield and >99% ee (Scheme 1.3).[15] They have used a chiral triazolium **NHC**

precatalyst containing H-bond donor hydroxyl (OH) group. The role of this hydroxyl group in the reaction is quite remarkable, and this catalytic system is the best till now.



Scheme 1.3 Benzoin condensation utilizing H-bond donor **NHC**

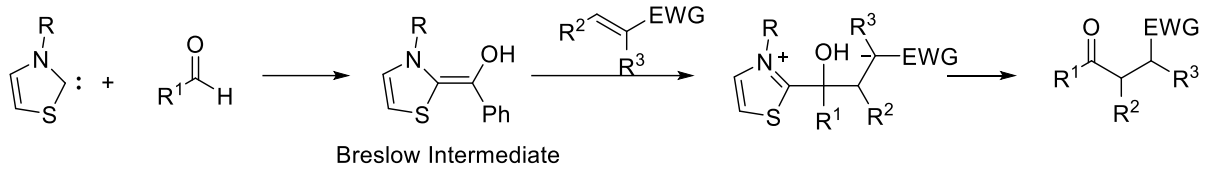
Apart from the homo benzoin coupling, cross benzoin coupling has also been studied to form C-C bond between two different aldehydes. For example, Yang reported cross benzoin reaction between aromatic aldehyde and aliphatic aldehyde in presence of thiazolium and triazolium precatalysts (Scheme 1.4). They made an interesting observation in that reaction.[16-17] They found that when thiazolium precatalyst was used, aromatic aldehyde was going to form the Breslow intermediate preferentially, while triazolium precatalyst was going to form Breslow intermediate with aliphatic aldehyde and gave the corresponding cross benzoin products, respectively.



Scheme 1.4 Yang's cross-benzoin condensation

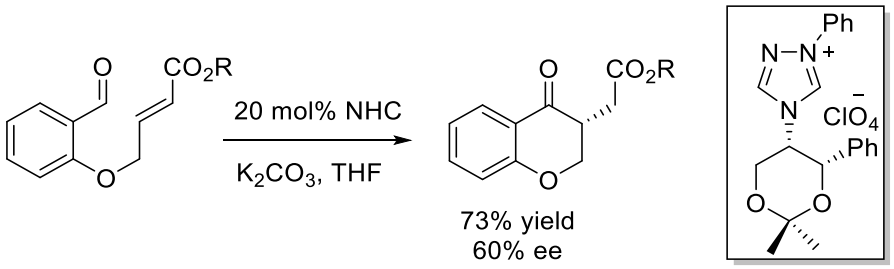
1.3.2 NHC-catalyzed Stetter reactions

Apart from an aldehyde, an electron-deficient Michael acceptor could also be attacked by an **NHC**-derived Breslow intermediate. This kind of reaction was first developed by Stetter and co-workers[18] and is known as "Stetter Reaction" (Scheme 1.5).

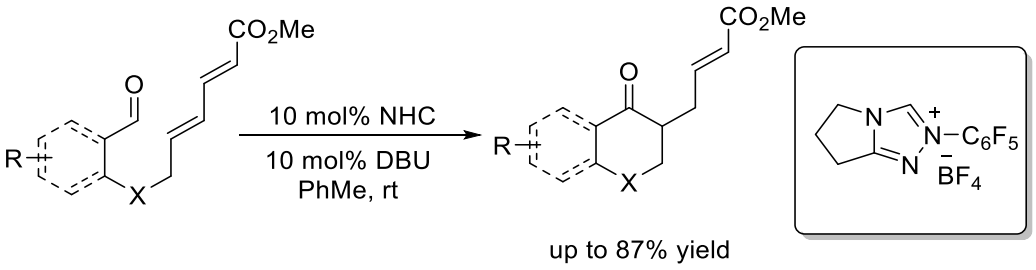


Scheme 1.5 Basic pathway of Stetter reaction

Enders first reported an example of intramolecular asymmetric Stetter reaction in 1996 by utilizing acyclic chiral triazolium salt as **NHC** precatalyst with good yield (73%) and enantioselectivity (60%) (Scheme 1.6). Since then, both intramolecular and intermolecular Stetter reactions have been extensively studied in literature. Built on Ender's work, Law and McErLean have extended the work to 1,6-Michael acceptor (Scheme 1.7).[19]



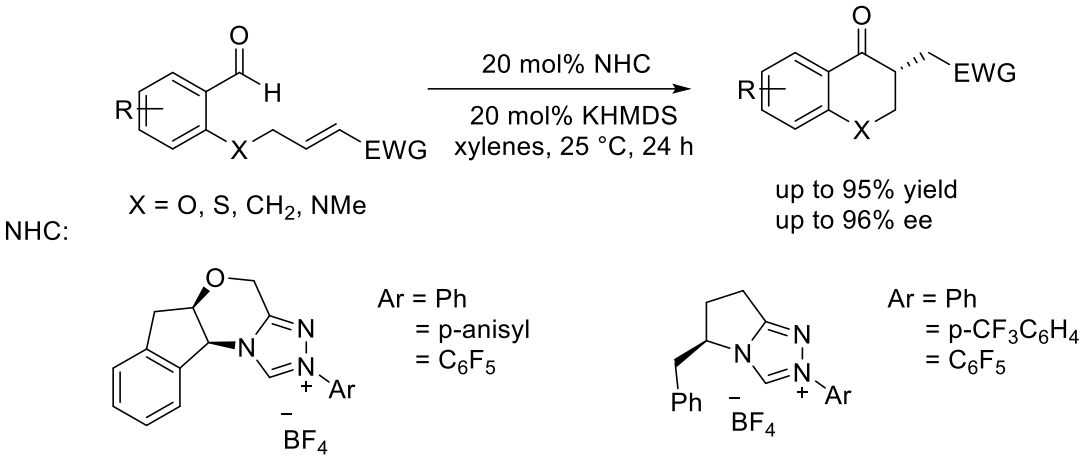
Scheme 1.6 Ender's Intramolecular Stetter Reaction



Scheme 1.7 McErlean's extended Stetter reaction

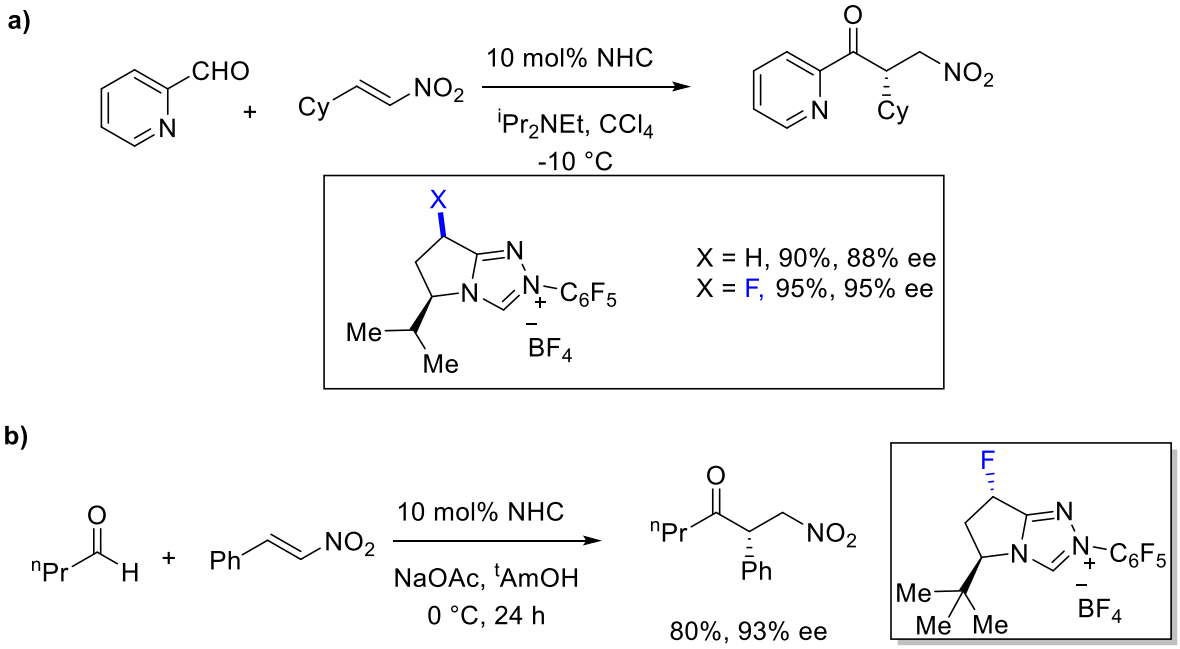
Rovis also had reported extensive studies of this intramolecular Stetter reaction using both amonidanol-based chiral triazolium and pyrrolidine-based chiral triazolium **NHC**

precursor and their catalytic system provided the desired products in high yield and enantioselectivity (Scheme 1.8).[20-22]



Scheme 1.8 Rovis's asymmetric intramolecular Stetter reaction

Apart from the intramolecular Stetter reaction, Rovis and co-workers had also reported intermolecular Stetter reaction in latter stage. For example, they had reported Stetter reaction between aryl aldehyde and nitroalkene utilizing a new kind of fluorinated triazolium catalyst (Scheme 1.9a).[23] They had found that this fluorinated triazolium precatalyst was superior to other non-fluorinated precatalysts. In another report in 2012 Rovis *et al*. has exemplified similar

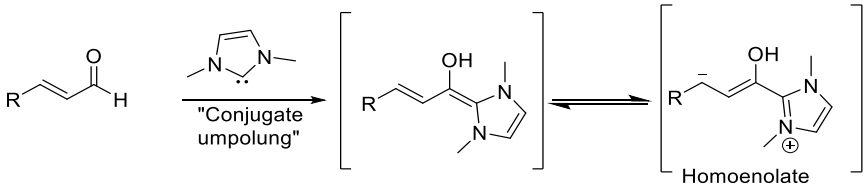


Scheme 1.9 Rovis's asymmetric intermolecular Stetter Reaction

Stetter reaction between aliphatic aldehyde and nitrostyrene (Scheme 1.9b).[24] Again, in this piece of work, fluorinated **NHC** precursor was proved to be superior.

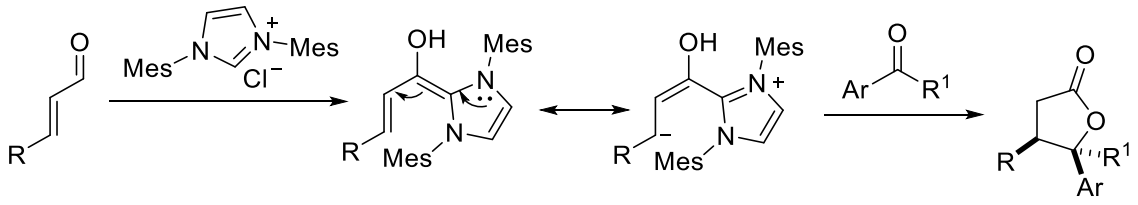
1.4 NHC-catalyzed homoenolate formation

Other than the aldehydes, *α,β*-unsaturated aldehydes could also be activated by **NHC** and *β*-carbanion could be generated. Addition of the carbene to carbonyl functionality of *α,β*-unsaturated aldehydes generated the extended Breslow intermediate. Due to the conjugation, the negative charge of the acyl anion could now be conjugated to the *β*-carbon of the system and showed nucleophilic character (Scheme 1.10).



Scheme 1.10 Generation of homoenolate

Bode and Glorius had first reported the **NHC**-derived homoenolate intermediate in 2004 independently.[25-27] Bode reported the synthesis of γ-butyrolactone (41% - 87% yield and up to 5:1 diastereoselectivity) by (3+2) annulation between **NHC** derived homoenolates and a-

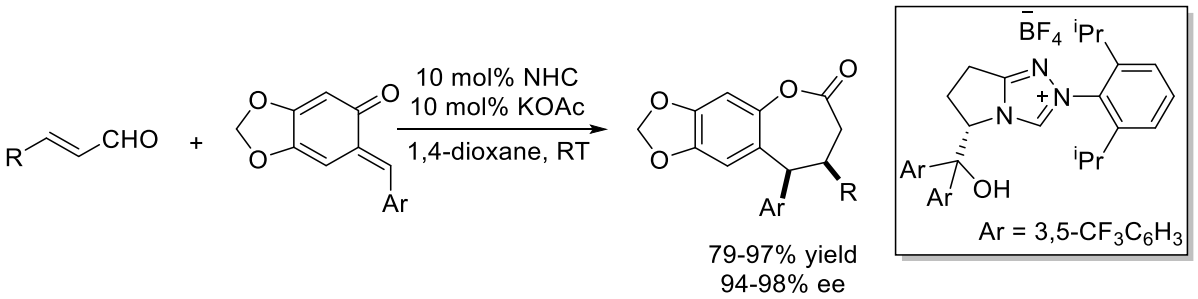


a) Bode's Condition	b) Glorius's Condition
R^1 = H	R^1 = H or CF_3
8 mol% NHC	5 mol% NHC
7 mol% DBU,	10 mol% ^{t}BuOK
THF/ ^{t}BuOH(10:1)	THF
RT, 15 h	RT, 16 h
41-87% yield, d.r. 3:1-5:1	32-70% yield, d.r. 2:1-4:1

Scheme 1.11 (a) Bode's [3+2] annulation of enal with aldehydes; (b) Glorius' annulation of enal with aldehydes or activated ketones.

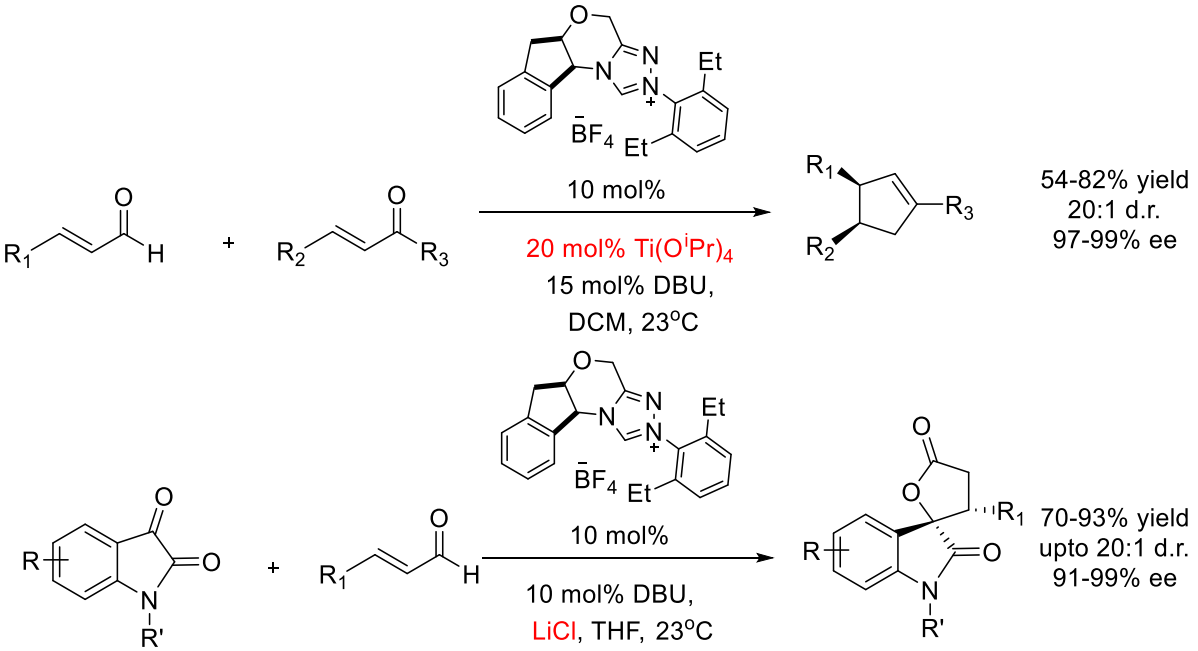
ryl aldehydes (Scheme 1.11a). At the same time, Glorius had reported a similar reaction with activated trifluoromethyl ketone or aldehyde electrophile. Glorius also got the γ-butyrolactones in 32% - 70% yield and up to 4:1 diastereoselectivity (Scheme 1.11b). After these two reports, various kinds of electrophiles such as imines, ketones, istains, enones etc. was explored to react with the homoenolate intermediate. The desired products were obtained in high yields and enantioselectivities.[25-26, 28-34]

The Ye group reported a (4+3) annulation reaction between enal and *o*-quinone in 2013.[32] Both aliphatic and aromatic enals worked well in their reaction conditions to give the desired seven-membered lactone in high yield and excellent enantioselectivity (Scheme 1.12).



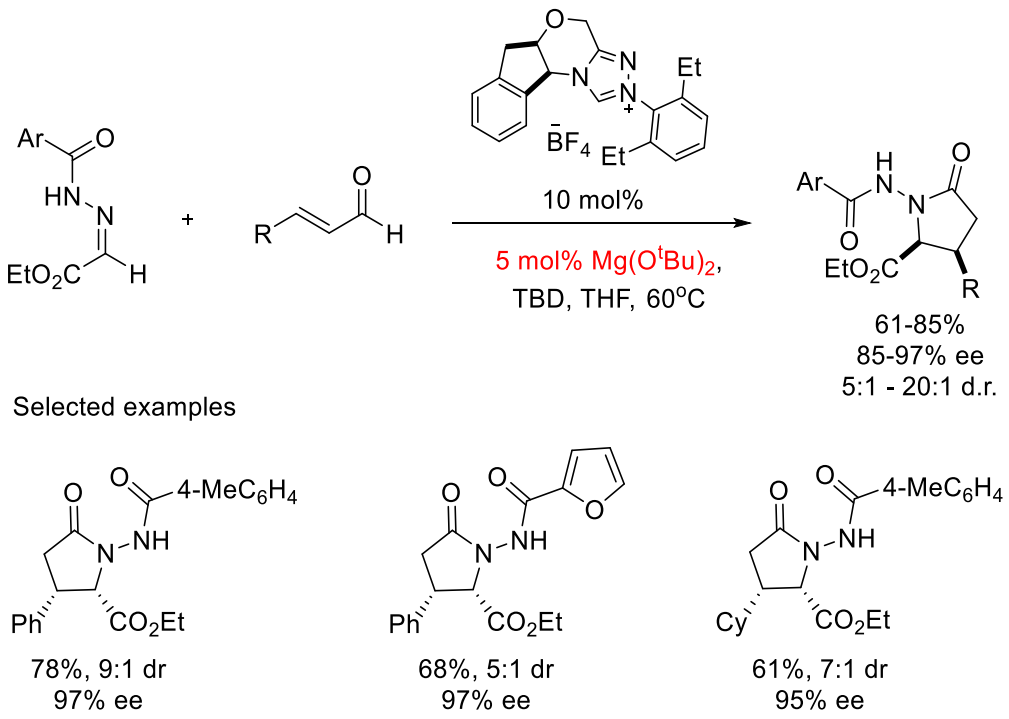
Scheme 1.12 Ye's [4+3] annulation via homoenolate.

NHC/Lewis acid co-operative catalysis was also explored in various reactions



Scheme 1.13 Lewis acid & **NHC**-carbene cooperative catalysis

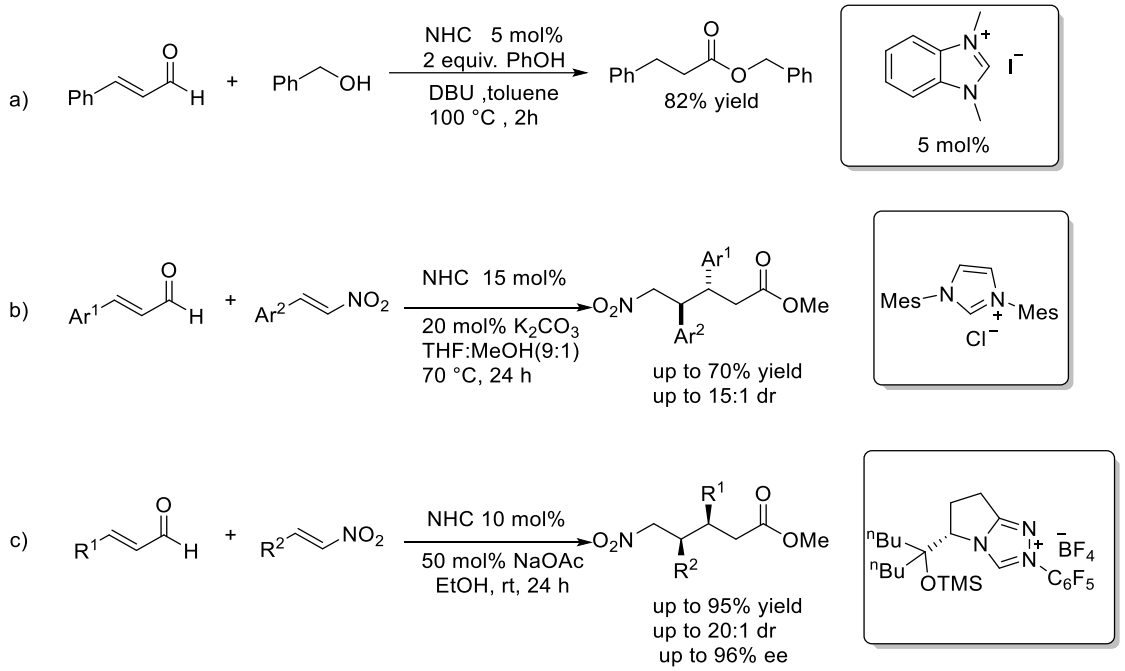
involving homoenolate intermediates. Different kinds of Lewis acids such as Lithium chloride (LiCl), Titanium (IV) isopropoxide ($Ti(O^iPr)_4$) were used as a secondary catalyst with the **NHC** to improve the efficiency of the catalytic system (Scheme 1.13). For example, the group of Scheidt reported Mg^{2+}/**NHC** cooperative catalysis for (3+2) cycloaddition between hydrazones and **NHC**-derived homoenolate (Scheme 1.14).[34] According to their mechanism, the Lewis acid (Mg^{2+}) increased the electrophilicity of hydrazone by the Lewis acid-base interaction with the N-atom of the hydrazone and hence facilitated the homoenolate addition. They used chiral aminoindanol-based triazolium **NHC** to get the annulated product in high yield and excellent enantioselectivity.



Scheme 1.14 Scheidt's enantioselective [3+2] annulations promoted by $Mg(O^tBu)_2$

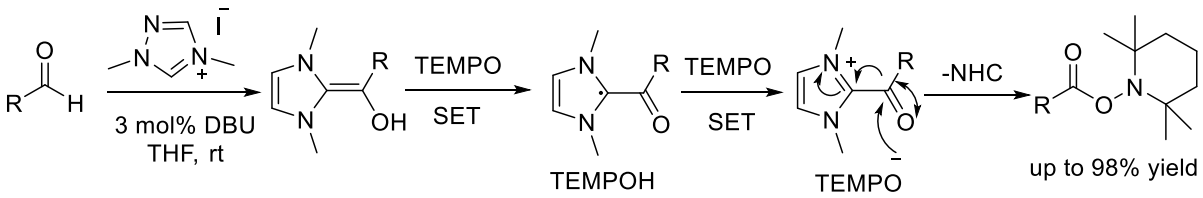
Other than the annulation reactions, non-annulative processes have also been explored in **NHC**-catalyzed reactions of extended Breslow intermediates. For example, Schedit has reported the protonation of homoenolate both in α- and β-position, and the resulting acyl azolium intermediate was trapped by benzyl alcohol to give the corresponding ester (Scheme

1.15a).[35] In 2009, Nair group has demonstrated a diastereoselective 1,4-addition reaction between homoenolate and nitroalkene to produce δ-nitro ester (Scheme 1.15b).[36] Following the seminal work by Nair, Rovis group has demonstrated an asymmetric version of that reaction using chiral triazolium salt precatalyst in excellent yield and stereoselectivity (Scheme 1.15c).[37]



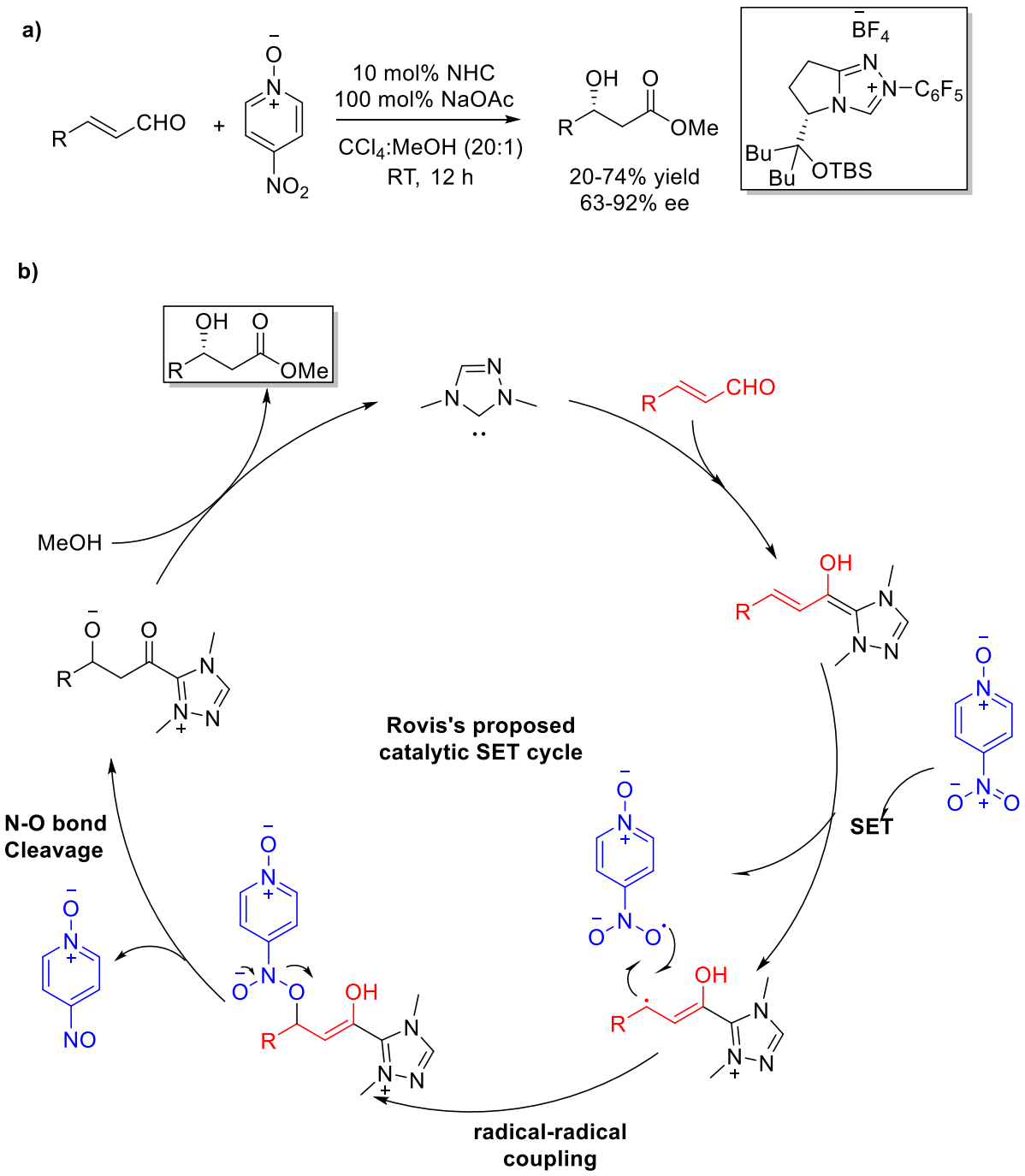
Scheme 1.15 Selected examples for non-annulative reaction via homoenolate

Apart from the different annulative and non-anulative reactions via homoenolate pathways involving electron pair reactivity, this intermediate is competent to be involved in single-electron transfer pathways. Inspired by the nature, Studer and co-workers first reported this kind of reaction (Scheme 1.16).[38] In their reaction, they used TEMPO as an oxidant. According to their proposed mechanism, the Breslow intermediate was oxidized by transferring single electron twice to TEMPO and generating the ester product from TEMPO.



Scheme 1.16 Carbene catalyzed SET oxidation with TEMPO.

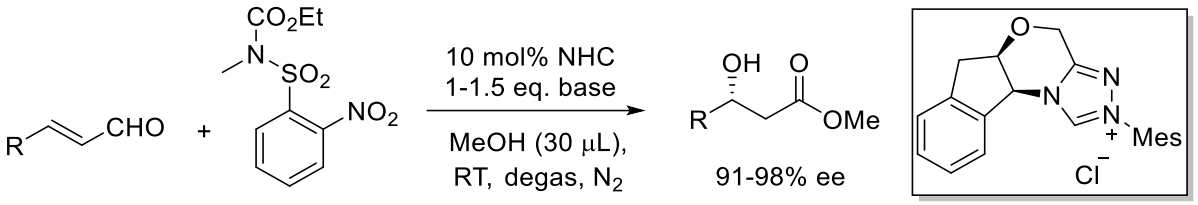
In 2014, both Rovis and Chi group independently reported the SET reaction from (Scheme 1.17 and Scheme 1.18) extended Breslow intermediate in presence of electron-deficient nitro



Scheme 1.17 a) Rovis' β-hydroxylation of enal via radical process, b) proposed catalytic cycle

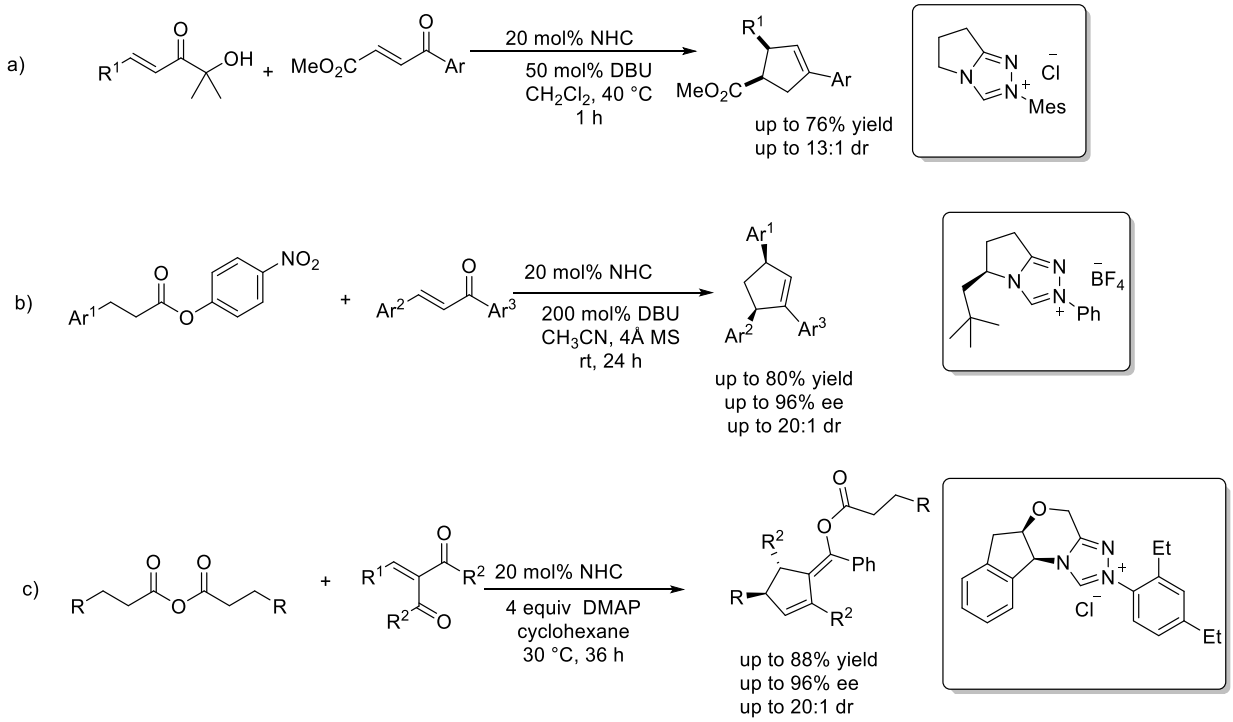
compounds as single electron acceptors.[39-42] According to their proposed mechanism, electron-deficient nitro compounds acted as a single electron acceptor from the **NHC** derived

homoenolate intermediate. After scavenging single electron, the resulted **NHC**-bound radical coupled with the nitro radical at β-position and subsequent N-O bond cleavage gave the β-hydroxy ester product in excellent enantioselectivity. Further advancement of similar radical activation mode studied by Rovis, Chi, Ye, and Sun in other instances.[43-45]



Scheme 1.18 Chi's β-hydroxylation of enal

Instead of enals, other substrates were also used to make homoenolate. Bode and coworkers discovered that α-hydroxy enones were good substitutes for enal in the generation of homoenolates



Scheme 1.19 Selected examples for alternative excess of homoenolate

in N-heterocyclic carbene catalysis (Scheme 1.19a). However, the usage of bulky chiral **NHC** was limited due to rising steric demands at the carbonyl center. In 2013, our group

demonstrated the activation of saturated esters to generate nucleophilic center at β-carbon. (Scheme 1.19b). To produce homoenolate equivalent, saturated esters with a good leaving group, such as 4-nitrophenol, were employed. When enone was employed as an electrophile, chiral cyclopentene derivatives were produced. Electrophiles such as trifluoromethyl ketones and hydrazones also performed well in the process.[46] This approach, however, was confined to β-aryl substituted esters. Our lab addressed this challenge by activating anhydride substrate by **NHC** to produce homoenolate analogous intermediate.[47] In this instance, both β-aryl and β-alkyl-substituted anhydrides were used to react with enone substrate. High yields and enantiomeric ratios were found for cyclopentene derivatives. (Scheme 1.19c).

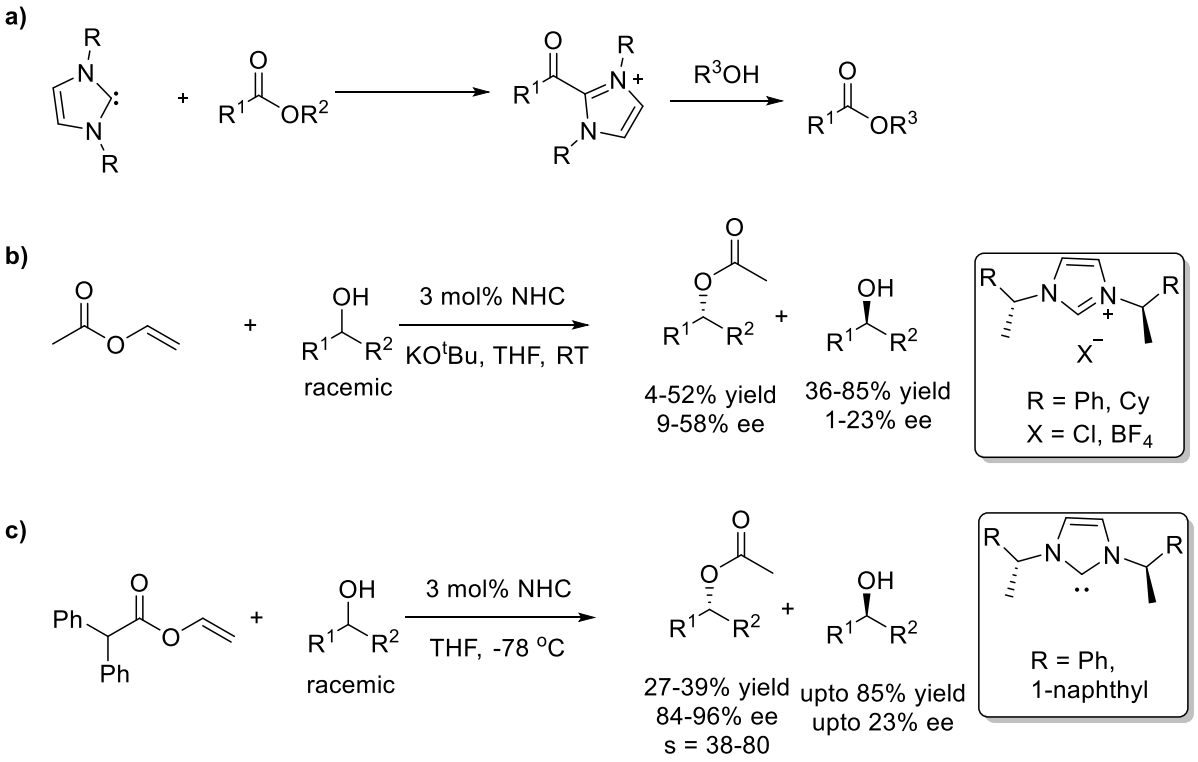
1.5 Catalysis involving acylazolium intermediates

Apart from the reactions involving umpolung chemistry, non-umpolung processes catalyzed by **NHC** had also been developed remarkably. In this context, reactions involving acyl azolium and azolium enolate achieved remarkable progress in last two decades. We will review this sector of reactions in four groups depending on the reactive site: (a) transesterification reactions; (b) chemistry of azolium enolates (activation of α-carbon); (c) chemistry of α,β-unsaturated acyl azolium (activation of β-carbon); and (d) vinyl azolium enolate chemistry (activation of γ-carbon)

1.5.1 Transesterification reactions

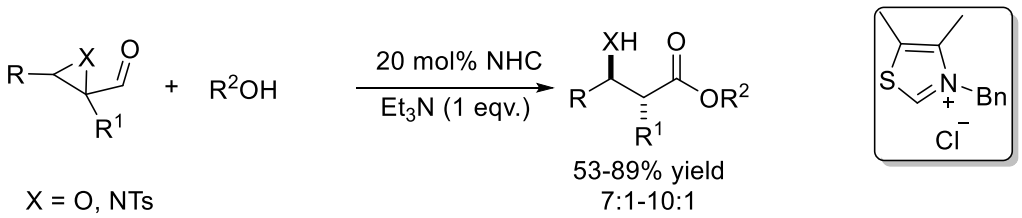
In 2002, transesterification reaction was first reported by Hedrick and Nolan (Scheme 1.20a).[48-49] After that, different research groups explored this type of reaction.[50-51] Majority of these works involve saturated acyl azolium as intermediate. The group of Suzuki and Maruoka in 2004, reported kinetic resolution of secondary alcohol via this transesterification reaction using chiral **NHC** catalyst. Suzuki[52-53] did this reaction by using vinyl acetate as a precursor of acylazolium in presence of chiral imidazolium salt precatalyst and got the ester product in 9-

58% ee value (Scheme 1.20b). An improved strategy by Maruoka[54] using more bulkier vinyl ester (vinyl diphenyl acetate) resulted in better resolution of the alcohol (Scheme 1.20c).



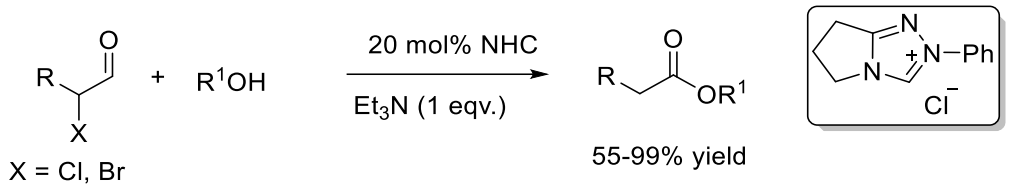
Scheme 1.20 Transesterification reactions by **NHC**

Aldehyde was also found to give the similar transesterification reaction after the internal oxidation of the Breslow intermediate. In this context, Bode group in 2004 had reported **NHC**-catalyzed diastereoselective synthesis β-hydroxy or amino ester (Scheme 1.21).[55] They used epoxy or aziridinyl aldehyde as substrate, which after forming the Breslow intermediate oxidized to the acyl azolium by internal redox reaction and made the route for transesterification reaction.



Scheme 1.21 Bode's internal-redox reaction to form the ester

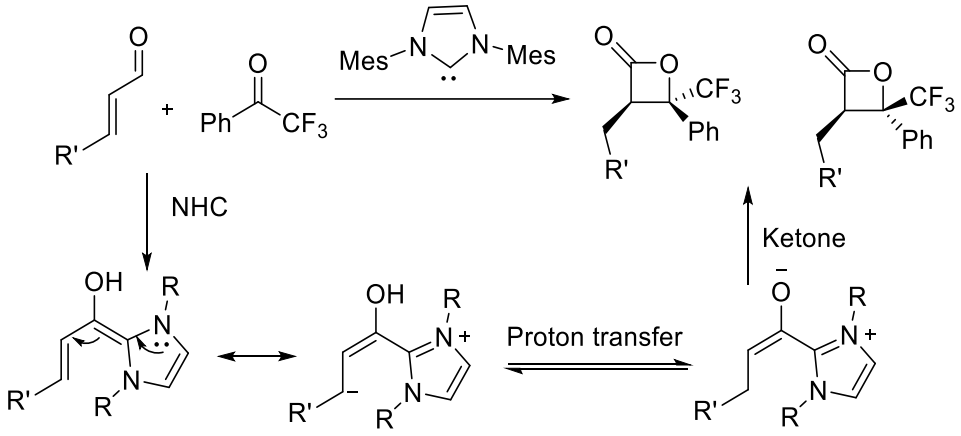
Similar transesterification reaction utilizing self-oxidizable Breslow intermediate was also reported by the Rovis group later (Scheme 1.22).[56] They had used α-oxidizable aldehydes such as α-chloro or α-bromo aldehyde. The acyl azolium intermediate formed via the elimination of the leaving group (chloride or bromide) from α-position.



Scheme 1.22 Rovis' **NHC**-catalyzed internal-redox reaction

1.5.2 Chemistry of azolium enolates (activation of α-carbon)

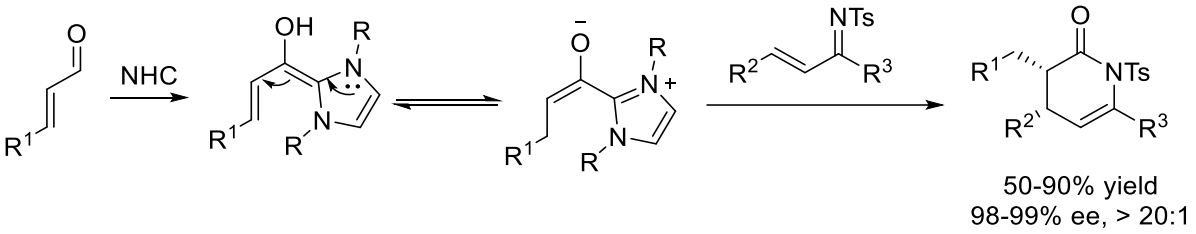
In the beginning of exploring homoenolate reactivity, Glorius group made an interesting observation. They found that the generation of β-lactone as a side product.[27] To find out explanation behind side product formation, they came up with the fact that there was another reactivity mode, named "enolate activation", was working via the protonation at the β-position of the homoenolate, rendering the nucleophilic α-carbon (Scheme 1.23).



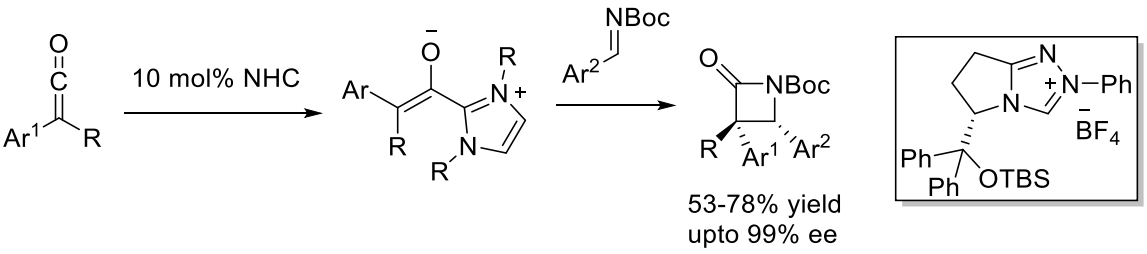
Scheme 1.23 β-Protonation of homoenolate and enolate reactivity mode

At that time, Bode group disclosed a (4+2) cycloaddition reaction exploiting enolate activation (Scheme 1.24).[57] They used α,β-unsaturated aldehyde to make the enolate intermediate via protonation of homoenolate at β-position. Then, the enolate intermediate coupled with imine derived from α,β-unsaturated aldehyde to form 6-membered lactam

derivative in high yield and excellent stereoselectivity. After that many examples had been reported applying this chemistry.[58] Due to the importance of this intermediate in forming complex and valuable molecular architecture, many research groups also tried to generate this intermediate in other ways. Ye[59] and Smith[60] independently in 2008 reported the generation of this intermediate from ketene as a starting material. Ye reported a (2+2) cycloaddition strategy to generate β-lactam using this azolium enolate and imine derived from aldehyde (Scheme 1.25). Ye also had reported a (2+4) cycloaddition strategy to trap this azolium enolate by a enone to generate 6-membered lactone in excellent yield and enantioselectivity.[61]

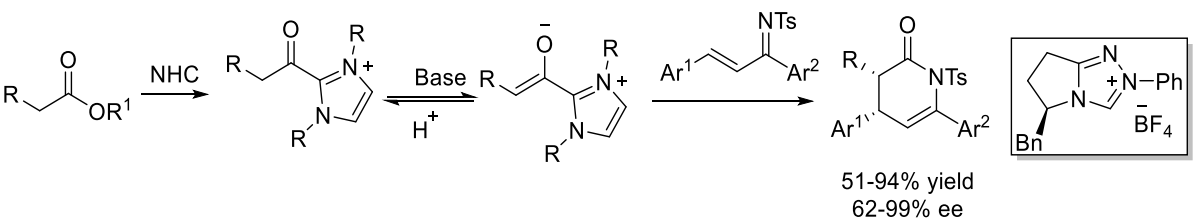


Scheme 1.24 Bode's [4+2] cycloaddition using enolate reactivity mode



Scheme 1.25 [2+2] annulation of ketene derived azolium enolate by Ye

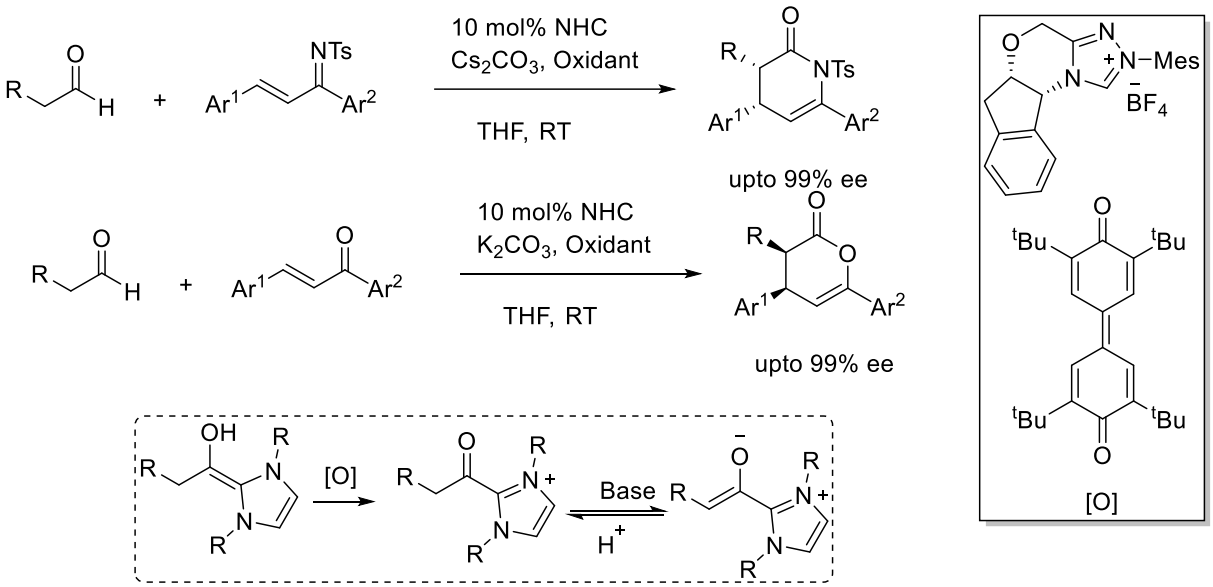
Chi group demonstrated the formation of azolium enolate in a very interesting way, called "backward pathway" (Scheme 1.26).[62] They made acylazolium from carboxylic esters. Now, as the acyl azolium intermediate is more electron-deficient, it will increase the acidity of the hydrogen attached with α-C. Hence, this system could enolize very easily and azolium



Scheme 1.26 [4+2] cycloadditions of activated esters with chalcone imines

enolate intermediate formed. They have trapped this intermediate by chalcone-derived imines in (2+4) cycloaddition reaction to form six-membered lactone in moderate to excellent yield and enantioselectivity.

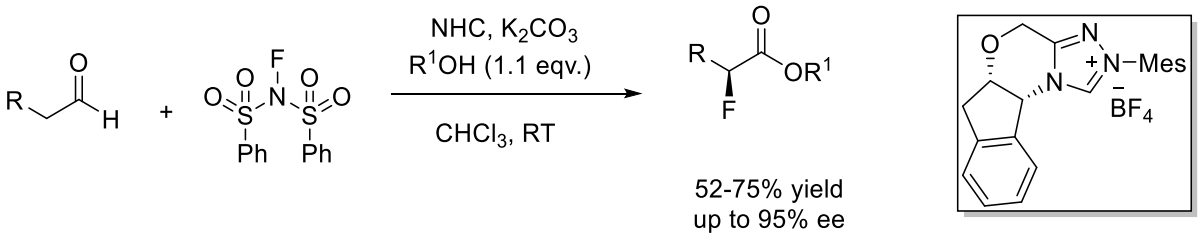
Generation of acyl azolium from saturated aldehyde was also reported in oxidative condition. Both the Rovis[63] group and Chi[64] group in 2013, independently reported (4+2) hetero Diels-Alder reaction, between azolium enolate generated from saturated aliphatic aldehyde and α,β-unsaturated imines or enones (Scheme 1.27). The reaction went through the formation of acyl azolium under external oxidant and was followed by enolization to form azolium enolate and condensation with the electrophilic partner.



Scheme 1.27 Generation of azolium enolate from alkyl aldehydes

Other than these annulation reactions, an interesting asymmetric α-fluorination reaction using azolium enolate intermediate was reported by the group of Sun[65] and Wang[66] independently in 2014 (Scheme 1.28). NFSI was used as an oxidant in their reaction system to oxidize the Breslow intermediate. After the deprotonation of the α-H from acyl azolium, azolium enolate formed, which attacked electrophilic NFSI to form α-fluoro ester in moderate

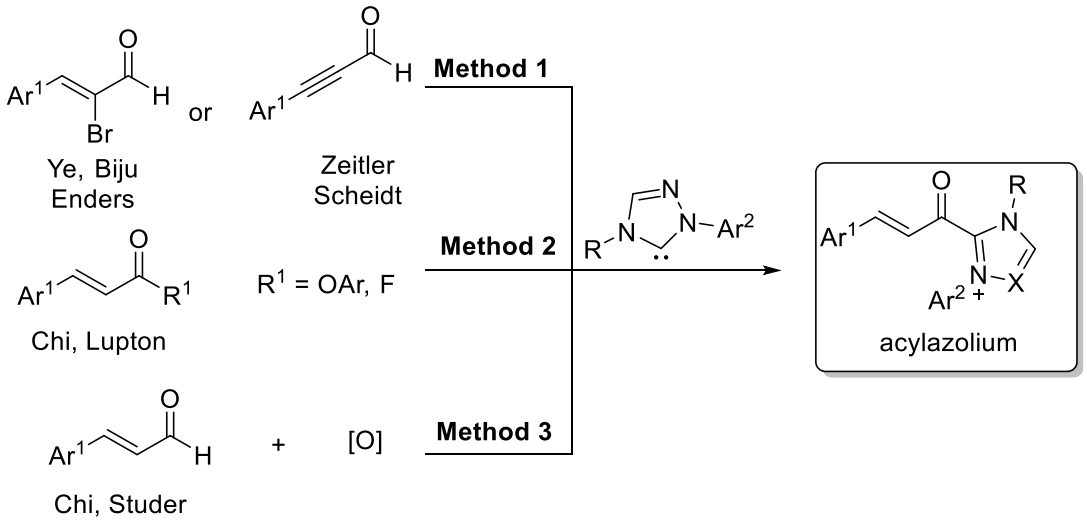
to excellent yield and enantioselectivity. Thus, in their reaction system, dual role of NFSI (oxidant and fluorinating agent) was demonstrated.



Scheme 1.28 Enolate generation for α-fluorination of aldehydes using NFSI

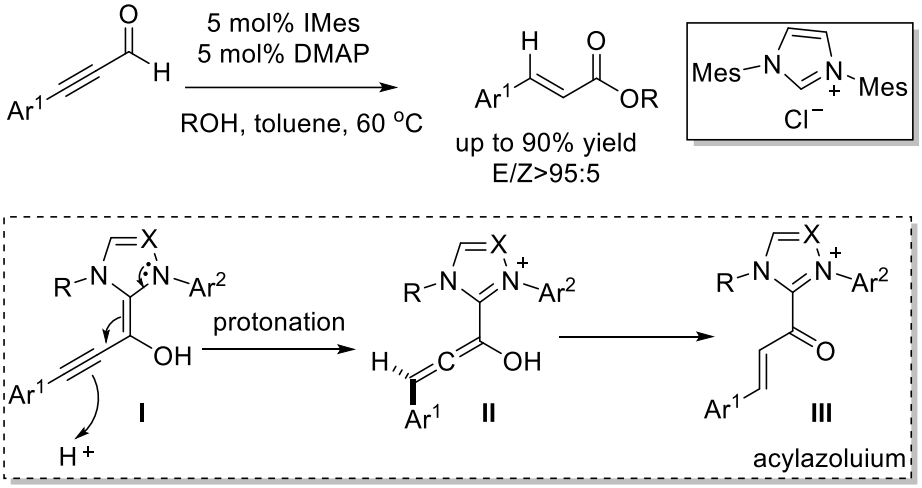
1.5.3 Chemistry of α,β-unsaturated acyl azolium (activation of β-carbon)

Apart from activation of β-carbon via homoenolate, there is another strategy to activate this position via the formation of α,β-unsaturated acyl azolium intermediate, an example of another non-umpoled intermediate. It is also worthy to mention that this activation mode is the most explored so far in **NHC** catalysis. This catalytic strategy improves the electrophilicity of the α,β-unsaturated carbonyls by lowering down the LUMO energy. There are several methods available to generate this intermediate (Scheme 1.29).[2] Activation of aldehydes containing internal redox functionality (like α-bromo enal, ynal) is one of the best ways to get this intermediate. Other typical approaches involve coupling of **NHC** with unsaturated acyl fluoride, activated ester, in-situ generated mixed anhydrides. Oxidation of unsaturated Breslow intermediate by external oxidant also can generate this intermediate.



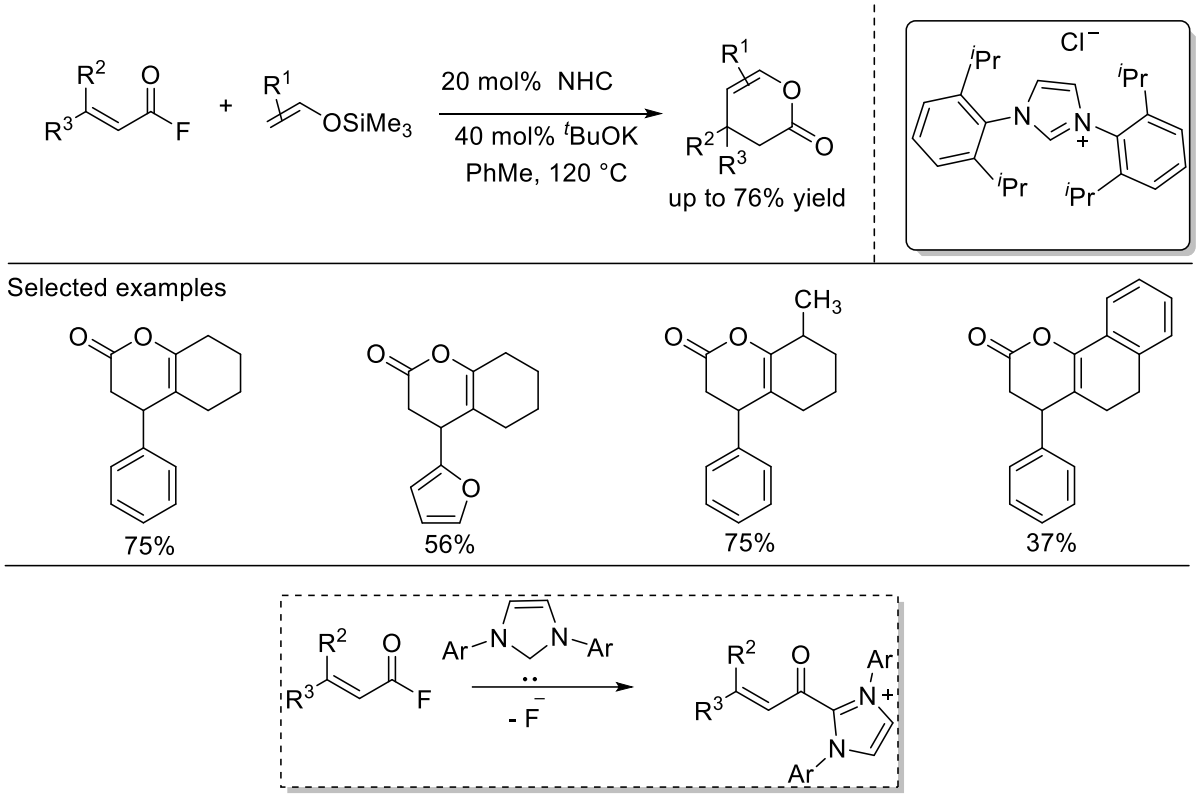
Scheme 1.29 Different precursors of unsaturated acyl azolium

Zeitler *et al*. in 2006 reported the formation of α,β-unsaturated acyl azolium from ynals (Scheme 1.30).[67] The reaction proceeded through the internal proton transfer from the Breslow intermediate **I** to generate intermediate **II**, followed by tautomerization to form the unsaturated acyl azolium **III**. Finally, intermediate **III** upon being trapped by alcohol gave the unsaturated ester in good yield and diastereoselectivity.



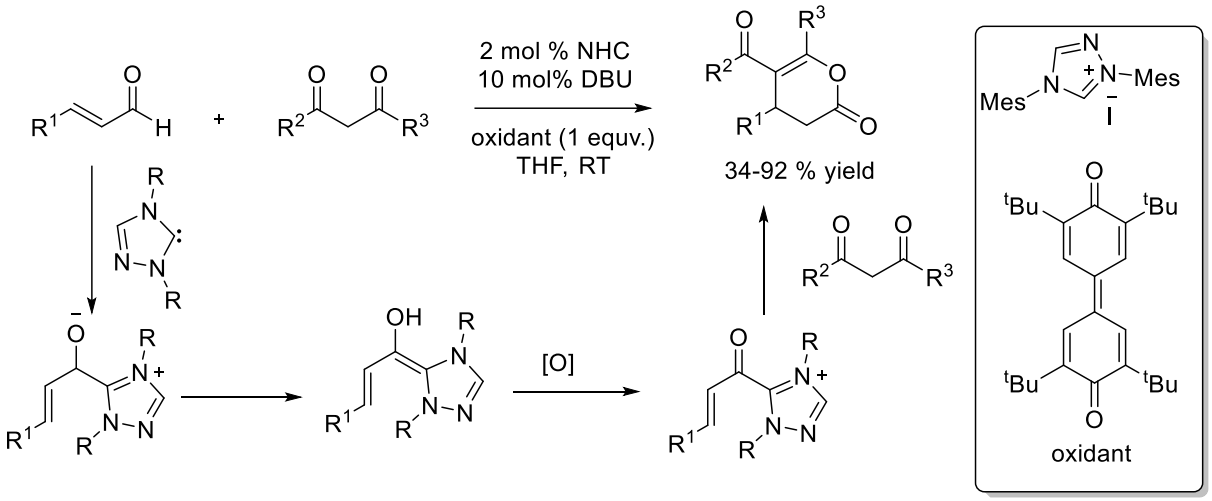
Scheme 1.30 Esterification of ynals

Lupton and co-workers reported a (4+2)-cycloaddition reaction between enol ether and unsaturated acyl azolium, generated from unsaturated acyl fluoride (Scheme 1.31).[68-69] The reaction proceeded by the generation of α,β-unsaturated acyl azolium by replacing the fluoride by carbene to form the key unsaturated acyl azolium intermediate. Then, Michael addition by enol ether followed by tautomerization and cyclization resulted in formation of six-membered lactone products in 37-76% yield.



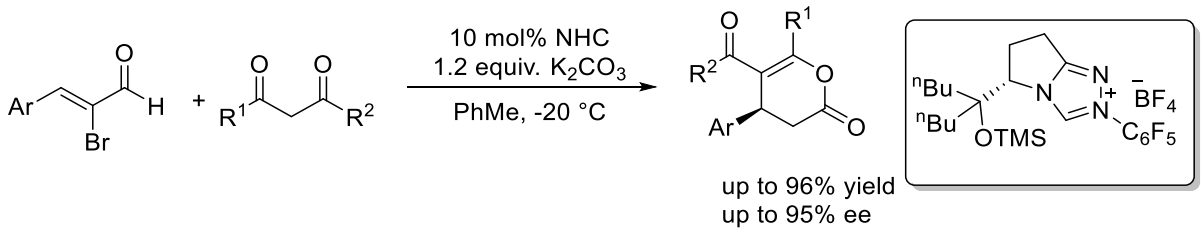
Scheme 1.31 Formation of α, β-unsaturated acyl azolium from acyl fluoride

In 2010, Studer *et al*. first disclosed the oxidation of unsaturated Breslow intermediate by an external oxidant (Scheme 1.32).[70-71] They reported a mild and bulky quinone as a proficient oxidant to generate unsaturated acylazolium, which undergo (3+3) cycloaddition with 1,3-dicarbonyl to generate six-membered lactones readily.



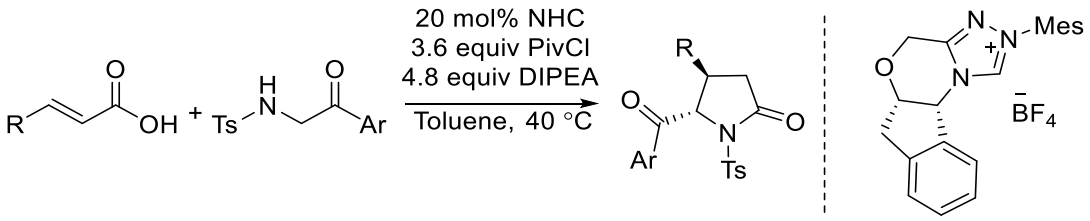
Scheme 1.32 Generation of unsaturated acyl azolium with external oxidant

Ye *et al*. revealed related (3+3) cycloaddition reaction.[72] Stable α-bromoenal was used by them to generate the key unsaturetd acylazolium intermediate, and followed by a Michael addition and cyclization with 1,3-dicarbonyl compound gave similar 3,4-dihydropyranones. Later, they developed an asymmetric version of this reaction employing chiral triazolium salt as **NHC** precursor to get the product in excellent yield enantioselectivity (Scheme 1.33).



Scheme 1.33 Generation of acylazolium intermediate from bromoenal

Ye and colleagues expanded the source of unsaturated acyl azolium further by employing readily available carboxylic acid as a precursor (Scheme 1.34). The acid was activated in-situ by pivaloyl chloride to form the mixed anhydride, which was further activated by **NHC** catalyst to construct the key intermediate. Latter this strategy was applied to make different annulated products.[72]

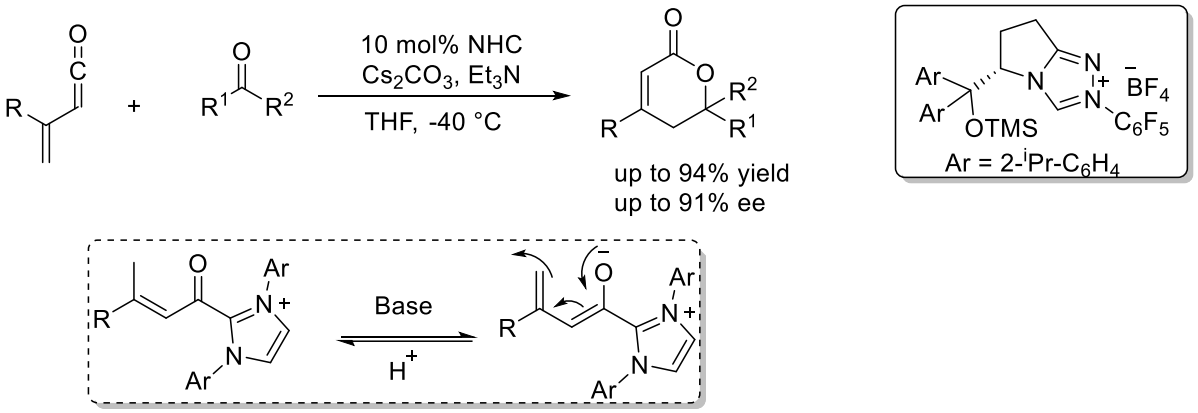


Scheme 1.34 Ye's protocol using carboxylic acid as the starting material

1.5.4 Vinyl azolium enolate chemistry (activation of γ-carbon)

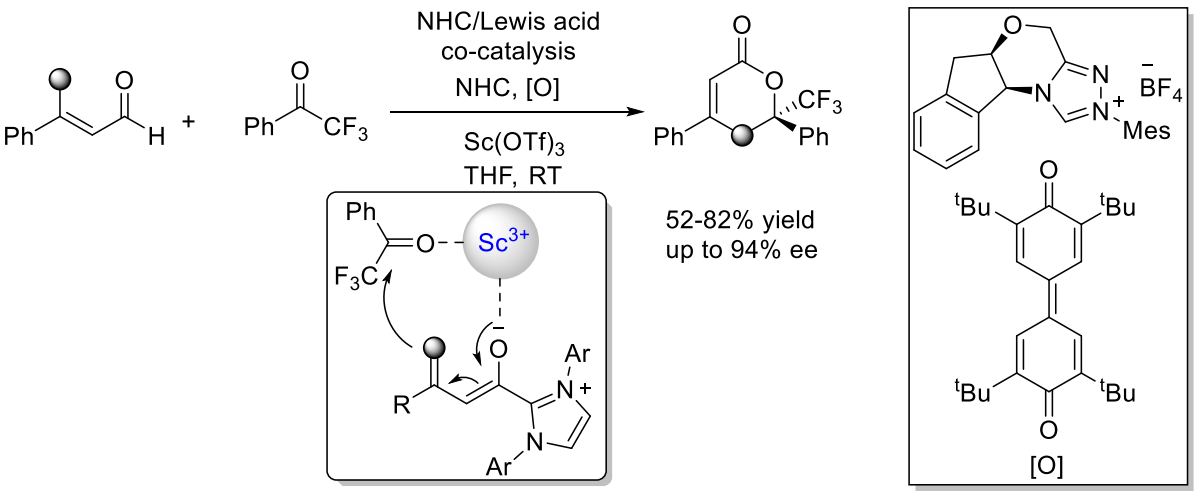
α,β-Unsaturated acyl azolium intermediate having a β-methyl group exerts electron-withdrawing property even at remote β-substitution and increase the acidity of the hydrogen of β-methyl group, hence facile the generation of vinyl azolium enolate intermediate under **NHC** catalysis condition. In 2011, Ye *et al.* first reported this kind of intermediate. They generated

this intermediate by the activation of in-situ generated α,β-unsaturated ketene by **NHC** (Scheme 1.35).[73-74] The reaction proceeded by the elimination of HCl to generate the ketene intermediate, followed by the attack of **NHC** to form the key vinyl azolium enolate intermediate. Subsequently, the **NHC**-bound intermediate underwent a formal (4+2)-cycloaddition with trifluoromethyl ketone. Enantioselectivity in their system was challenging due to less chance to control the enantioselectivity at distal γ-position.



Scheme 1.35 (4+2)-Annulations of ketenes with activated ketones

In 2013, Chi lab reported an interesting **NHC**/Lewis acid co-operative strategy to improve the stereocontrol of this kind of reaction (Scheme 1.36).[75] They have used oxidative strategy to generate the vinyl azolium enolate rather than HCl elimination from acyl chloride.



Scheme 1.36 Cooperative catalysis for enantioselective [4+2] reaction

The key intermediate was formed by the oxidation of the Breslow intermediate from β-methyl enal and was followed by the elimination of proton. Then (4+2) cycloaddition with trifluoromethyl ketone resulted in γ-lactone products in good yield and excellent enantioselectivity.

1.6 Research design and summary of works

NHC has witnessed tremendous success as an organic catalyst in last two decades, specifically in the field of asymmetric synthesis. Various novel reactive modes as discussed earlier have emerged to develop new methodologies, which found their application to accessing architecturally close, potentially valuable compounds. While constructing new methodologies for straightforward design of novel molecules with proven applications still in demand. Recently, our laboratory has developed few noteworthy methodologies in this direction, such as asymmetric access to phthalidyl prodrugs[76-77], biologically important carboxylic acid derivatives ((*R*)-ibuprofen ester, (*R*)-ketoprofen ester)[78-79], and P-stereogenic potential ligand precursors[80]. Therefore, we aim further to design new **NHC**-catalyzed methodologies to enrich the library of molecules with proven applications.

In chapter 2 of this thesis, we have discussed a (3+3)-cycloaddition reaction between a rarely explored umpoled 1,3-dinucleophiles from arylidene hydrazones and α,β-unsaturated acylazolium. *N*-monosubstituted hydrazone from aldehydes containing electron-withdrawing group (such as -COR, $-CF_3$) has the potential to act as 1,3-dinucleophile. But aryl aldehyde derived such hydrazones as 1,3-dinucleophile has barely been explored before. We have discussed our observations in exploring hydrazones from aryl aldehyde as 1,3-dinucleophile in **NHC**-catalyzed (3+3) cycloaddition reaction. Further, we have discussed the conversion of the product from our catalytic cycle to marketed drugs (Levosimendan, Pimobendan) and bioactive molecules (DNMDP, Meribendan).

In chapter 3, we have demonstrated an interesting dynamic kinetic resolution on bicyclic ketone/enol to access atropo-enriched bicyclic enolic ester. We also have discussed that, many ligands have the similar scaffolds with the product from our catalytic cycle. At the end, we demonstrate the importance of our methodology by formal synthesis of a ligand from our product with high efficiency.

1.7 References

1. Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn* **1943,** *63*, 296
2. Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T., *Chem. Rev.* **2015,** *115*, 9307.
3. Wanzlick, H.-W.; Schönherr, H.-J., *Angew. Chem. Int. Ed.* **1968,** *7*, 141
4. Schönherr, H. J.; Wanzlick, H. W. *Justus. Liebigs. Ann. der. Chem.* **1970,** *731*, 176.
5. Arduengo, A. J.; Harlow, R. L.; Kline, M., *J. Am. Chem. Soc.* **1991,** *113*, 361.
6. Fang, X.; Chen, X.; Lv, H.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2011,** *50*, 11782.
7. Fang, X.; Chen, X.; Chi, Y. R., *Org. Lett.* **2011,** *13*, 4708.
8. Hao, L.; Chuen, C.; Ganguly, R.; Chi, Y., *Synlett* **2013,** *24*, 1197.
9. Xu, J.; Jin, Z.; Chi, Y. R., *Org. Lett.* **2013,** *15*, 5028.
10. Bugaut, X.; Glorius, F., *Chem. Soc. Rev.* **2012,** *41*, 3511.
11. Seebach, D., *Angew. Chem. Int. Ed.* **1979,** *18*, 239.
12. Breslow, R., *J. Am. Chem. Soc.* **1958,** *80*, 3719.
13. Sheehan, J. C.; Hunneman, D. H., *J. Am. Chem. Soc.* **1966,** *88*, 3666.
14. Enders, D.; Kallfass, U., *Angew. Chem. Int. Ed.* **2002,** *41*, 1743.
15. Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J., *J. Org. Chem.* **2009,** *74*, 9214.
16. Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W., *Org. Lett.* **2011,** *13*, 880.
17. Jin, M. Y.; Kim, S. M.; Mao, H.; Ryu, D. H.; Song, C. E.; Yang, J. W., *Org. Biomol. Chem.* **2014,** *12*, 1547.
18. Stetter, H.; Schreckenberg, M., *Angew. Chem. Int. Ed.* **1973,** *12*, 81.
19. Law, K. R.; McErlean, C. S. P., *Chem. Eur. J.* **2013,** *19*, 15852.
20. Kerr, M. S.; Read de Alaniz, J.; Rovis, T, *J. Am. Chem. Soc.* **2002,** *124*, 10298.
21. de Alaniz, J. R.; Rovis, T., *Synlett* **2009,** *2009*, 1189.
22. de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T., *J. Org. Chem.* **2008,** *73*, 2033.

23. DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T., *J. Am. Chem. Soc.* **2009,** *131*, 10872.

24. DiRocco, D. A.; Noey, E. L.; Houk, K. N.; Rovis, T., *Angew. Chem. Int. Ed.* **2012,** *51*, 2391.

25. Burstein, C.; Glorius, F., *Angew. Chem. Int. Ed.* **2004,** *43*, 6205.

26. Sohn, S. S.; Rosen, E. L.; Bode, J. W., *J. Am. Chem. Soc.* **2004,** *126*, 14370.

27. Burstein, C.; Tschan, S.; Xie, X.; Glorius, F., *Synthesis* **2006,** 2418.

28. Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F., *J. Am. Chem. Soc.* **2016,** *138*, 7840.

29. Mukherjee, S.; Mondal, S.; Patra, A.; Gonnade, R. G.; Biju, A. T., *Chem. Comm.* **2015,** *51*, 9559.

30. Guo, C.; Fleige, M.; Janssen-Müller, D.; Daniliuc, C. G.; Glorius, F., *Nat. Chem.* **2015,** *7* , 842.

31. Chen, X.; Fang, X.; Chi, Y. R., *Chem. Sc.* **2013,** *4*, 2613.

32. Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S., *Angew. Chem. Int. Ed.* **2013,** *52*, 8607.

33. Zhao, X.; DiRocco, D. A.; Rovis, T., *J. Am. Chem. Soc.* **2011,** *133*, 12466.

34. Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A., *Nat. Chem.* **2010,** *2*, 766.

35. Chan, A.; Scheidt, K. A., *Org. Lett.* **2005,** *7*, 905.

36. Nair, V.; Sinu, C. R.; Babu, B. P.; Varghese, V.; Jose, A.; Suresh, E., *Org. Lett.* **2009,** *11*, 5570.

37. White, N. A.; DiRocco, D. A.; Rovis, T., *J. Am. Chem. Soc.* **2013,** *135*, 8504.

38. Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A., *Angew. Chem. Int. Ed.* **2008,** *47*, 8727.

39. Du, Y.; Wang, Y.; Li, X.; Shao, Y.; Li, G.; Webster, R. D.; Chi, Y. R., *Org. Lett.* **2014,** *16*, 5678.

40. Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R., *J. Am. Chem. Soc.* **2015,** *137*, 2416.

41. White, N. A.; Rovis, T., *J. Am. Chem. Soc.* **2015,** *137*, 10112.

42. White, N. A.; Rovis, T., *J. Am. Chem. Soc.* **2014,** *136*, 14674.

43. Chen, X.-Y.; Chen, K.-Q.; Sun, D.-Q.; Ye, S., *Chem. Sc.* **2017,** *8*, 1936.

44. Yang, W.; Hu, W.; Dong, X.; Li, X.; Sun, J., N, *Ang. Chem. Int. Ed.* **2016,** *55*, 15783.

45. Li, B.-S.; Wang, Y.; Proctor, R. S. J.; Zhang, Y.; Webster, R. D.; Yang, S.; Song, B.; Chi, Y. R., *Nat. Comm.* **2016,** *7*, 12933.

46. Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R., *Nat. Chem.* **2013,** *5*, 835.

47. Jin, Z.; Chen, S.; Wang, Y.; Zheng, P.; Yang, S.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2014,** *53*, 13506.

48. Grasa, G. A.; Kissling, R. M.; Nolan, S. P., *Org. Lett.* **2002,** *4*, 3583.

49. Connor, E. F.; Nyce, G. W.; Myers, M.; Möck, A.; Hedrick, J. L., *J. Am. Chem.Soc.* **2002,** *124*, 914.

50. Grasa, G. A.; Güveli, T.; Singh, R.; Nolan, S. P., *J. Org. Chem.* **2003,** *68*, 2812.

51. Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L., *Org. Lett.* **2002,** *4*, 3587.

52. Suzuki, Y.; Muramatsu, K.; Yamauchi, K.; Morie, Y.; Sato, M., *Tetrahedron* **2006,** *62*, 302.

53. Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M., *Chem. Comm.* **2004,** 2770.

54. Kano, T.; Sasaki, K.; Maruoka, K., *Org. Lett.* **2005,** *7*, 1347.

55. Chow, K. Y.-K.; Bode, J. W., *J. Am. Chem. Soc.* **2004,** *126*, 8126.

56. Reynolds, N. T.; Read de Alaniz, J.; Rovis, T., *J. Am. Chem. Soc.* **2004,** *126*, 9518.

57. He, M.; Struble, J. R.; Bode, J. W, *J. Am. Chem. Soc.* **2006,** *128*, 8418.

58. He, M.; Uc, G. J.; Bode, J. W., *J. Am. Chem. Soc.* **2006,** *128*, 15088.

59. Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S., *Org. Lett*. **2008,** *10*, 277.

60. Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D., *Org. Biomol. Chem.* **2008,** *6* , 1108-1113.

61. Zhang, Y.-R.; Lv, H.; Zhou, D.; Ye, S., *Chem. Eur. J.* **2008,** *14*, 8473.

62. Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R., *Org. Lett*. **2012,** *14* , 2154.

63. Zhao, X.; Ruhl, K. E.; Rovis, T., *Angew. Chem. Int. Ed.* **2012,** *51*, 12330.

64. Mo, J.; Yang, R.; Chen, X.; Tiwari, B.; Chi, Y. R., *Org. Lett*. **2013,** *15*, 50.

65. Dong, X.; Yang, W.; Hu, W.; Sun, J., *Angew. Chem. Int. Ed.* **2015,** *54*, 660.

66. Li, F.; Wu, Z.; Wang, J., *Angew. Chem. Int. Ed.* **2015,** *54*, 656.

67. Zeitler, K., *Org. Lett*. **2006,** *8*, 637.

68. Ryan, S. J.; Candish, L.; Lupton, D. W., *J. Am. Chem. Soc.* **2009,** *131*, 14176.

69. Ryan, S. J.; Candish, L.; Lupton, D. W., *J. Am. Chem. Soc.* **2011,** *133*, 4694.

70. De Sarkar, S.; Studer, A., *Angew. Chem. Int. Ed.* **2010,** *49*, 9266.

71. De Sarkar, S.; Grimme, S.; Studer, A., *J. Am. Chem. Soc.* **2010,** *132*, 1190.

72. Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S., *Ang. Chem. Int. Ed.* **2014,** *53*, 11611.

73. Shen, L.-T.; Shao, P.-L.; Ye, S., *Ad. Syn. Catal*. **2011,** *353*, 1943.

74. Wang, X.-N.; Zhang, Y.-Y.; Ye, S., *Ad. Syn. Catal*. **2010,** *352*, 1892.

75. Mo, J.; Chen, X.; Chi, Y. R., *J. Am. Chem. Soc.* **2012,** *134*, 8810.

76. Liu, Y.; Chen, Q.; Mou, C.; Pan, L.; Duan, X.; Chen, X.; Chen, H.; Zhao, Y.; Lu, Y.; Jin, Z.; Chi, Y. R., Nat. Commun. 2019, 10, 1675.

77. Liu, Y.; Majhi, P. K.; Song, R.; Mou, C.; Hao, L.; Chai, H.; Jin, Z.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2020,** *59*, 3859.

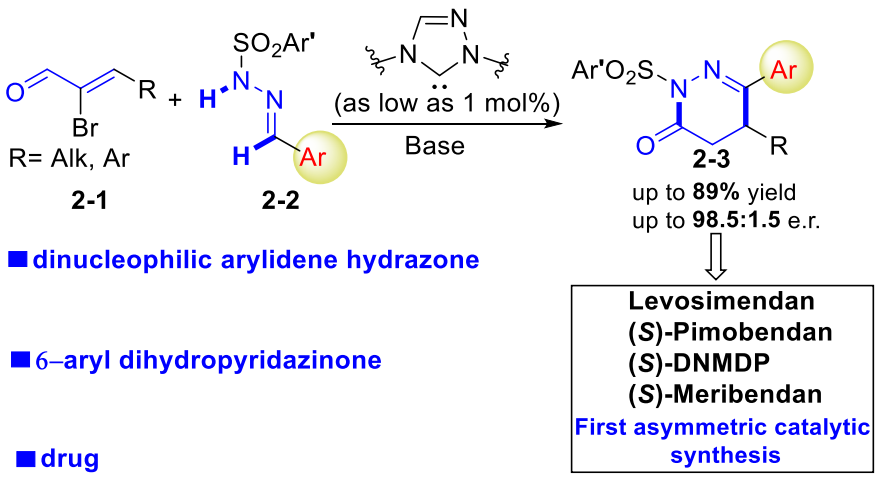
78. Chen, X.; Fong, J. Z.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B. A.; Chi, Y. R., *J. Am. Chem. Soc.* **2016,** *138*, 7212.

79. Liu, B.; Song, R.; Xu, J.; Majhi, P. K.; Yang, X.; Yang, S.; Jin, Z.; Chi, Y. R., *Org. Lett.* **2020,** *22*, 3335.

80. Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B. A.; Chi, Y. R., *J. Am. Chem. Soc.* **2016,** *138*, 7524.

Chapter 2

Carbene-Catalyzed Enantioselective Annulation of Dinucleophilic Hydrazones and Bromoenals for Access to Aryl-Dihydropyridazinones and Related Drugs



2.1 Introduction

4,5-Dihydropyridazinones and their derivatives, especially those bearing aryl substituents at the 6-position, display a broad range of pharmacological activities.[1] Some members of this family have already made their way into the market, such as Levosimendan[2] and Pimobendan[3] are used for the treatment of heart disease of humans and animals respectively (Fig. 2.1a). Other members of this family, such as (-)-KCA 1490 (bonchodilatory and anti-inflammatory activity),[4] Meribendan (potent PDE III inhibitor),[5] and (*R*)-DNMDP (cancer cytotoxic modulator)[6] have shown promising activities in biological studies (Fig. 2.1a). Traditionally, these structural motifs can be accessed by condensation of substituted γ-keto carboxylic acids or its derivatives with hydrazines (Fig. 2.1b), whereas asymmetric access relies on either chiral resolution of the products[4, 5, 7] or the use of optically enriched starting materials[8]. It is worth to note that access to chiral starting materials (1,4-dicarbonyl compounds) used in these syntheses remains challenging in organic chemistry.[9] Another approach to construct these heterocyclic moieties involves formal [4+2] cycloaddition between in situ generated 3-aryl azoalkenes and two carbon synthons (Fig. 2.1b).[10] One asymmetric example of these formal [4+2] reactions was demonstrated using isothiourea as the organic catalysts to control enantioselectivity at the C4-position.[10a] There is no success on catalytic asymmetric access to C5 stereogenic (Fig. 2.1a) of these 4,5-dihydropyridazinones.

We're interested in designing N-heterocyclic carbene-catalyzed reactions for preparation or modification of bioactive molecules for medicinal and agriculture uses.[11] Herein, we disclose a carbene catalyzed asymmetric annulation between *N*-monosubstituted arylidene hydrazones (precursor of 1,3-dinucleophile) and bromoenals[12] (common 1,3-dinucleophilic hydrazones from trifluoroacetaldehyde and glyoxal derivatives[13] have been explored in **NHC**-catalyzed reactions[13c-d] as demonstrated in Fig. 2.1c) to afford highly enantiopure 6-aryl-4,5-dihydropyridazinones (Fig. 2.1d). *N*-monosubstituted hydrazones containing an electron-with-

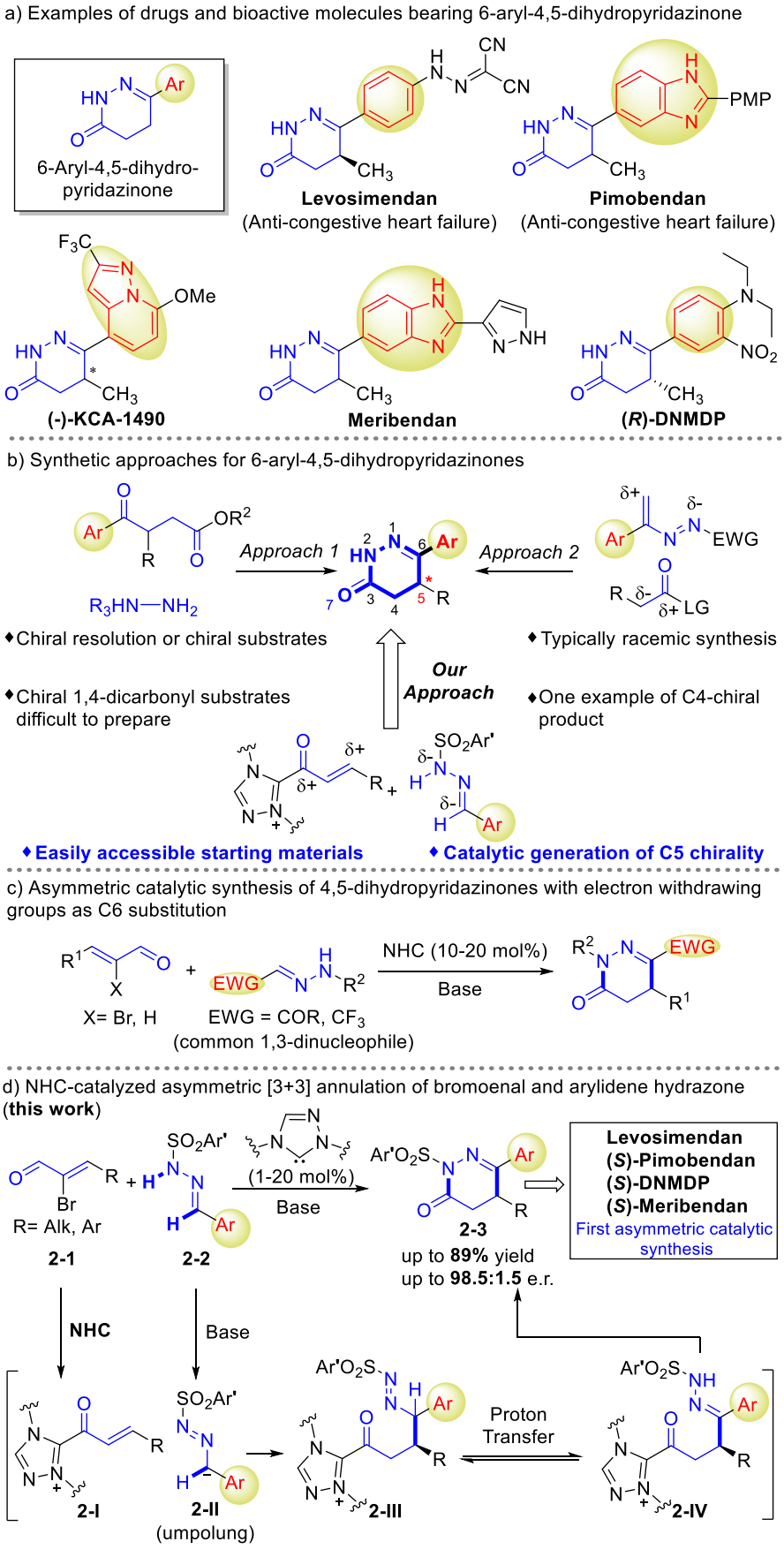


Figure 2.1 Strategies to access 6-aryl-4,5-dihydrpyridazinones.

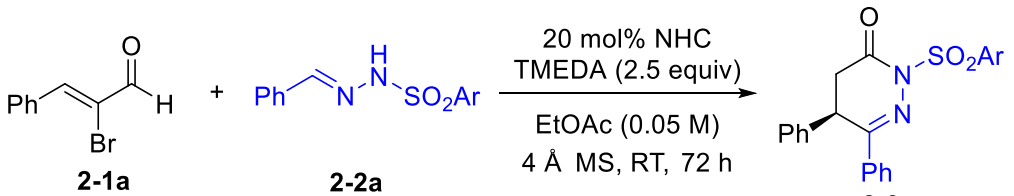
drawing group (e.g., -COR, -CF_3)[13] at azomethine carbon have been used widely as 1,3-dinucleophiles after the pioneering study by Vicario[14] in 2012. On the contrary, *N*-monosubstituted hydrazones from aryl aldehydes rarely showed such character as 1,3-dinucleophiles. This is probably because of the comparatively less stable anionic character at azomethine carbon and an unfordable tendency for proton transfer to regenerate *N*-centered nucleophile (Fig. 2.1d). Therefore, aryl aldehydes-derived *N*-monosubstituted hydrazones were barely used as precursors of effective 1,3-dinucleophiles in asymmetric catalysis.[13g, 15] Key steps in our reaction involve the umpolung of the arylidene hydrazone (**2-2**) to form the intermediate **2-II** and followed by a chemo-selective 1,4-addition to **NHC**-bound α,β-unsaturated acyl azolium **2-I** to form intermediate **2-III**. Intermediate **2-III** upon intramolecular proton transfer leads to intermediate **2-IV** that undergoes cyclization to form 6-aryl-4,5-dihydropyridazinone products with good yields and high enantioselectivities. A broad range of hydrazones from aryl and heteroaryl aldehydes were well tolerated in our reaction conditions. Straight forward transformations of our products lead to clinically approved drugs (Levosimendan and Pimobendan) and several other bioactive molecules without any erosion of the e.r. values (scheme 2.3). It is worth mentioning that, previously reported procedures to access these drugs and bioactive molecules comprised longer steps and used chiral resolutions or chiral starting materials.[4-6, 7c-f, 8e]

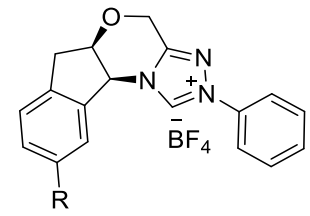
2.2. Results and discussion

We initiated our studies using readily available α-bromo cinnamaldehyde **2-1a** and *p*-nosyl protected hydrazone **2-2a** as the model substrates to search for suitable precatalyst and reaction conditions. Initially, we screened some **NHC** precatalyst in ethylacetate solvent and in presence of tetramethylethylenediamine (TMEDA) base. Results of catalyst optimisation was given in Table 2.1. The aminoindanol-derived precatalyst with an N-phenyl substitution

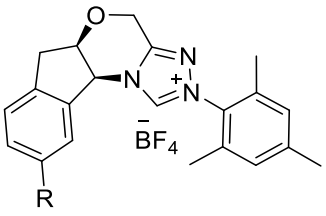
(**2-A**)[16] led to the formation of the desired product **2-3a** in moderate yield and enantioselectivity. Installing a nitro (-NO2) group in the aminoindanol moiety of precatalyst **2-A** (to get precatalyst **2-B**)[17] improved the enantioselectivity, albeit with poor yield. Replacing the N-phenyl substituent of precatalyst **2-A** by electron-rich and bulky N-mesityl substituent (to get precatalyst **2-C**)[18] gave the product in improved yield (74%), although the e.r. value dropped down to 71:29. As expected, switching to more sterically hindered **NHC** precatalyst **2-D**[19] with a bromo atom on aminoindanol motif further boosted the e.r. value, although a diminishing yield was obtained. Ultimately, we found out that the use of nitro (-NO_2) substituted aminoindanol scaffold containing **NHC** precatalyst **2-E**[19] could give the desired

Table 2.1 Screening of **NHC** precatalyst[a, b]

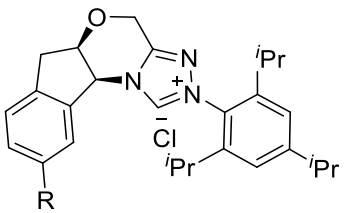




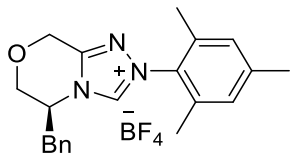
2-A: R = H; 44%, 78.5:21.5 e.r.
2-B: R = NO_2; 21%, 90:10 e.r.



2-C: R = H; 74%, 71:29 e.r.
2-D: R = Br; 64%, 87:13 e.r.
2-E: R = NO_2; 72%, 95:5 e.r.



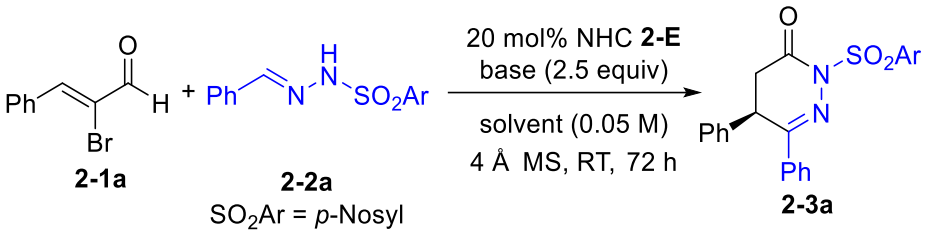
2-F: R = H; 58%, 61:39 e.r.
2-G: R = Br; 56%, 88:12 e.r.
2-H: R = NO_2; 48%, 89.5:10.5 e.r.



2-I; 83%, 80:20 e.r.

[a] Reaction condition: **2-1a** (0.1 mmol.), **2-2a** (0.05 mmol), **NHC** precatalyst (20 mol%), TMEDA (2.5 equiv), EtOAc (0.05 M), MS (100 mg/ml) at RT for 72 h. [b] Yield determined by ^{1}H NMR, based on **2-2a**, by using 1,3,5-trimethoxybenzene as internal standard. The e.r. was determined via chiral-phase HPLC analysis. MS = molecular sieves, TMEDA = tetramethylethylenediamine.

Table 2.2 Solvents, Bases and Amount of Catalyst Loading Screening[a,b]



Entry	Base	Solvent	Yield (%)	e.r.
1	TMEDA	DCM	51	93:7
2	TMEDA	Dioxane	56	92.5:7.5
3	TMEDA	MTBE	32	94:6
4	TMEDA	Et_2O	54	93:7
5	TMEDA	Tol.	74	93:7
6	TMEDA	PhCl	77	93.5:6.5
7	TMEDA	EtOAc	72	95:5
8	K_2CO_3	EtOAc	72	94:6
9	K_3PO_4	EtOAc	67	93.5:6.5
10	Cs_2CO_3	EtOAc	90	93:7
11	DABCO	EtOAc	83	93.5:6.5
12	DIPEA	EtOAc	64	94:6
13	DMAP	EtOAc	-[c]	-[c]
14[d]	TMEDA	EtOAc	72(**71**)	**95:5**
15[e]	TMEDA	EtOAc	57	95:5
16[f]	TMEDA	EtOAc	52	95.5:4.5

[a] Reaction condition: **2-1a** (0.1 mmol.), **2-2a** (0.05 mmol), Base (2.5 equiv), solvent (.05 M), MS (100 mg/ml) at RT for 72 h. [b] Yield determined by ^{1}H NMR, based on **2-2a**, by using 1,3,5-trimethoxybenzene as internal standard. The e.r. was determined via chiral-phase HPLC analysis. [c] No cyclization product was detected. Only direct amide formation was detected. [d] 10 mol% **NHC 2-E** and 0.075 mmol of **2-1a** were used. The yield in the parenthesis is the isolated yield. [e] 5 mol% **NHC 2-E** was used. [f] 1 mol% **NHC 2-E** was used, and the reaction was carried out using 1.0 mmol of **2-1a** and 0.5 mmol of **2-2a**. MS = molecular sieves, TMEDA = tetramethylenediamine.

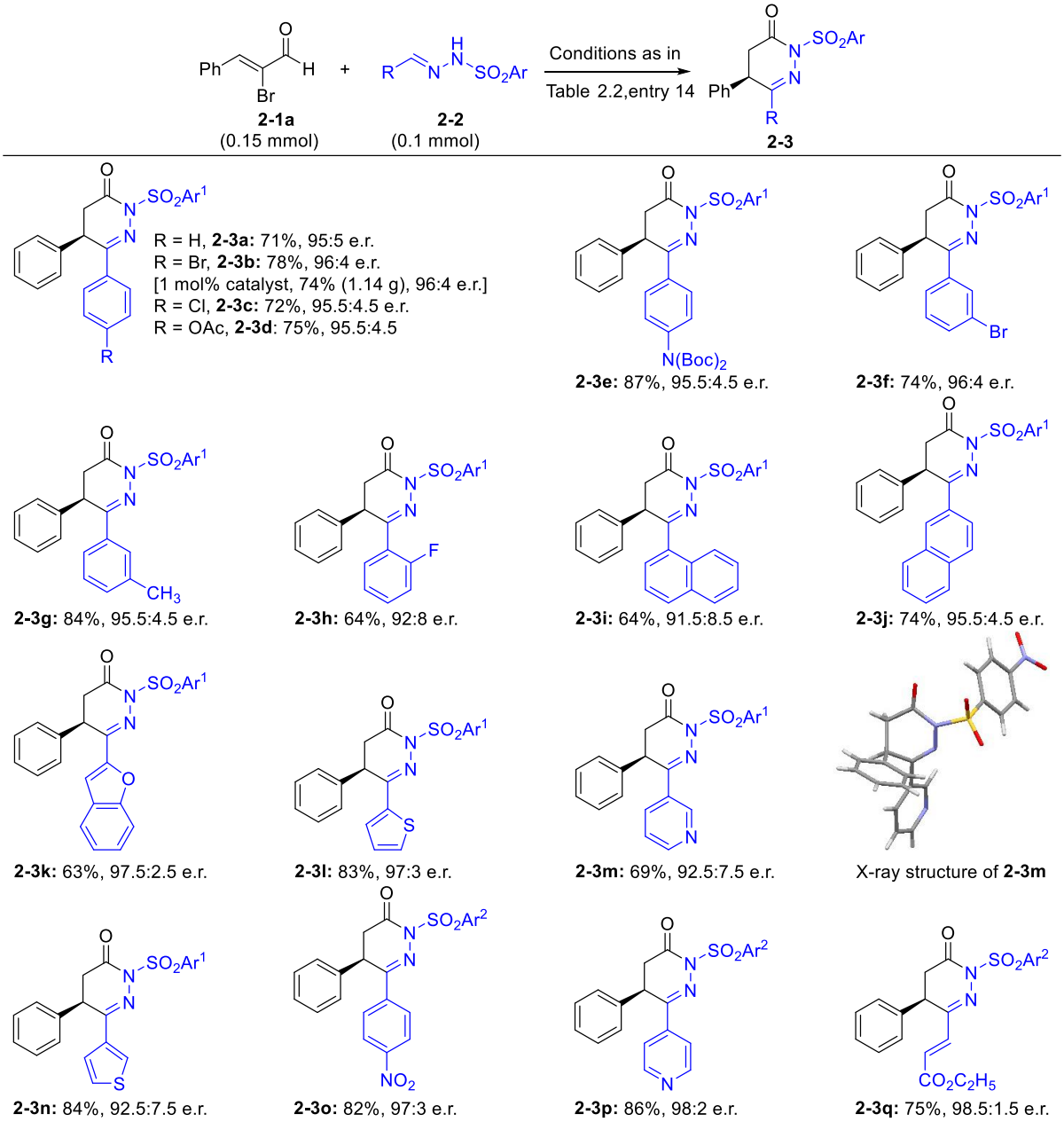
product in 72% yield and 95:5 e.r. In the hope for further improvement, we replaced the mesityl group of **2-C** with the bulky 1,3,5-triisopropyl phenyl group (to get precatalyst **2-F**)[19]. However, poorer enantioselectivity and yield were detected. **NHC** precatalyst **2-G**[19] and **2-H**[19] derieved from **2-F** by installing bromo (-Br) atom and nitro ($-NO_2$) group respectively in the aminoindanol moiety of **2-F** were also show poorer outcome. Switching to morpholine based **NHC** precatalyst **2-I**[20] also did not able to improve the result further. Thus, **NHC** precatalyst **2-E** was chosen to be the optimal catalyst for further optimization of reaction conditions.

Next, we screened some other solvents (in place of EtOAc) using **NHC** precatalyst **2-E** in presence of TMEDA to improve the yield as well as the e.r. of our reaction. From the screening of different polar (DCM, Dioxane) (Table 2.2, entry 1-2) and non-polar solvents (MTBE, Et_2O, Toluene, PhCl) (Table 2.2, entry 3-6) we found that, in case of PhCl the yield improved slightly to 77% but the e.r. value of our reaction droped down to 93.5:6.5 (Table 2.2, entry 6). So, we further screen different bases (in place of TMEDA) considering our initially chosen solvent, EA, as the best solvent. Different kinds of inorganic (K_2CO_3, K_3PO_4, Cs_2CO_3) (Table 2.2, entry 8-10) and organic (DABCO, DIPEA, DMAP) (Table 2.2, entry 11-13) bases were successful to produce the desired product. Although, in some of the bases like K_2CO_3 (Table 2.2, entry 8), Cs_2CO_3 (Table 2.2, entry 10), DABCO (Table 2.2, entry 11) gave better yield than our initially chosen base TMEDA, but the e.r. value is best for the base TMEDA with slightly lower yield. Unfortunately, we found that in case of DMAP (Table 2.2, entry 13), only direct amide formation was detected. After getting EtOAc and TMEDA as optimal solvent and base respectively in presence of **NHC** precatalyst **2-E**, we tried to lower down the catalyst loading. We found that decreasing the catalyst loading of **NHC** precatalyst **2-E** from 20 mol% to 10 mol% did not affect the reaction outcome and the annulated product was isolated in 71% yield (Table 2.2, entry 14). Further decreasing the precatalyst loading to 5 mol% did not affect the e.r. value but resulted into lower yield (Table 2.2, entry 15). Interestingly, our reaction worked

in 1 mol% catalyst loading and gave the desired product in 52% yield and 95.5:4.5 e.r. value (Table 2.2, entry 16). After optimizing solvents, bases and catalyst loading we concluded that entry 14 of Table 2.2 as our optimal condition.

With the optimized reaction conditions in hand (Table 2.2, entry 14), we moved to evaluate the generality of this reaction. The scope of various hydrazones was examined first with α-bromo cinnamaldehyde (**2-1a**) as the model substrate and the results are shown in Scheme 2.1. Different kinds of substituted phenyl rings [such as halogens, -OAc, -$N(Boc)_2$ and methyl group at the *ortho*, *meta*, and *para* positions] at azomethine carbon of hydrazones were all tolerated and gave the desired products in good yields and excellent e.r. values (**2-3a – 2-3h**). Interestingly, gram-scale synthesis of **2-3b** with 1 mol% precatalyst loading could furnish the product in 74% yield and 96:4 e.r. The phenyl ring of **2-2a** could also be replaced by 1-napthyl and 2-napthyl without affecting the yield and e.r. value of the products (**2-3i – 2-3j**) significantly. A diverse set of heteroaryls such as 2-benzothiophenyl, 2-thiophenyl, 3-thiophenyl and 3-pyridyl at azomethine carbon of hydrazones afforded the desired products in excellent yield and e.r. values (**2-3k – 2-3n**). The absolute configuration of **2-3m** was confirmed by X-ray analysis.[21] Most of the time *p*-nosyl (*p*-Ns) protected hydrazones gave our desired products in excellent outcomes, unfortunately, similar hydrazones bearing highly electron-deficient phenyl ring at azomethine position were degraded under our catalytic conditions. Thus, tosyl protected hydrazones (**2-2o – 2-2p**) had used in our reaction, giving the products (**2-3o – 2-3p**) in good yields and excellent enantioselectivities. Surprisingly, vinyl hydrazone **2-2q** was also compatible to provide the corresponding product (**2-3q**) in 75% yield and 98.5:1.5 e.r. value.

Scheme 2.1. Scope of hydrazone substrates.[a]

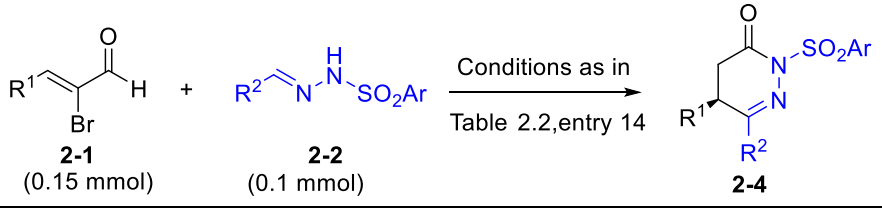


[a] Reaction condition as in Table 2.2, entry 14. Yields (after silica gel chromatography purification) based on **2-2**. Reaction time 72-84 h. The e.r. value was determined via chiral-phase HPLC analysis. SO_2Ar^1= *p*-Nosyl, SO_2Ar^2= Tosyl.

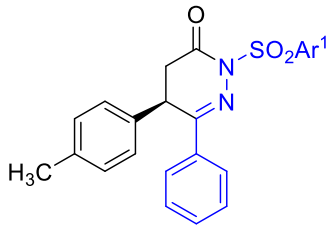
We next examined the scope of bromoenals, results are summarized in Scheme 2.2. Different kinds of electron-donating and withdrawing substitutions at the β-phenyl ring (such as methyl, halogens, methoxyl at the *ortho*, *meta*, and *para* positions) of the bromoenal worked well in our reaction conditions and gave the annulated products in good to excellent yields and

high enantioselectivities (**2-4a – 2-4g**). The β-phenyl ring of the bromoenal could also be replaced by 2-napthyl ring without affecting the result significantly (**2-4h)**. As 5-methyl substitution in 6-aryl-4,5-dihydropyridazinone is crucial from the viewpoint of existing drugs and bioactive molecules[2-6] (Fig. 2.1a), we further examined the reaction of α-bromocrotonaldehyde with some hydrazones. For example, hydrazone containing 2-fluoro phenyl as azomethine substitution was coupled with α-bromocrotonaldehyde to obtain the product **2-4i** in moderate yield and excellent enantioselectivity. With the aim to prepare precursors of clinical drugs and bioactive molecules utilizing our methodology, products **2-4j** and **2-4k** were obtained in moderate to good yields and excellent enantioselectivities by coupling corresponding hydrazones with α-bromocrotonaldehyde. Notably, in case of **2-4j** *o*-nosyl protected hydrazone was used over *p*-nosyl protected hydrazone due to its instability in our reaction conditions and the reagents were added inside the glove box, as we found the hydrazone decomposed in our reaction condition and hence resulted in lower yield, when the reagents were added outside. Higher homologues of α-bromocrotonaldehyde, for example, β-ethyl substituted bromoenal had also been used to couple with hydrazone derieved from 4-nitrobenzaldehyde to give the product **2-4l** in good yield and excellent enantioselectivity. Notably, in case of **2-4l** tosyl protected hydrazone instead of nosyl protected hydrazone was used, to avoid the decomposition of the hydrazone in the reaction condition.

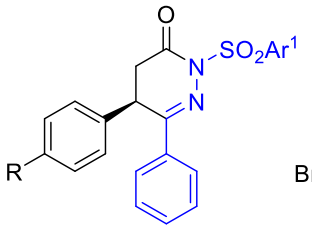
Scheme 2.2. Scope of α-bromoenal substrates.[a]



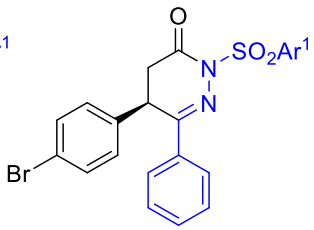
2-1 (0.15 mmol) + **2-2** (0.1 mmol) → **2-4**



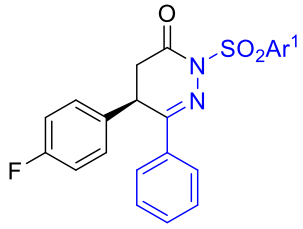
2-4a: 60%, 92:8 e.r.



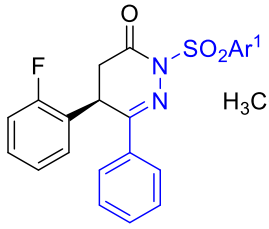
2-4b: 66%, 95:5 e.r.



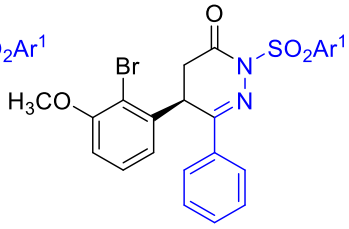
2-4c: 89%, 89:11 e.r.



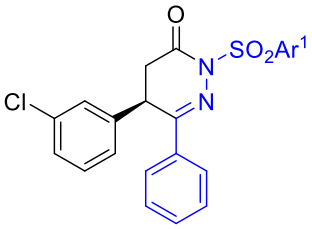
2-4d: 86%, 95.5:4.5 e.r.



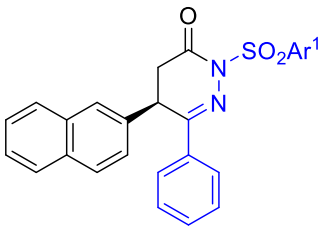
2-4e: 73%, 97:3 e.r.



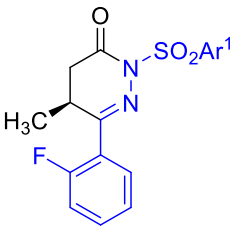
2-4f: 61%, 96:4 e.r.



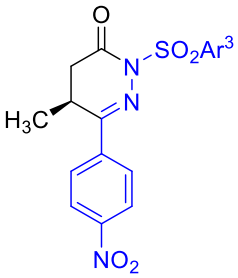
2-4g: 83%, 95:5 e.r.



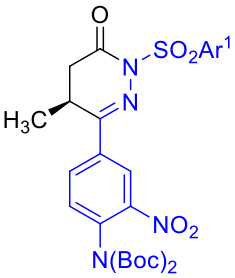
2-4h: 76%, 92:8 e.r.



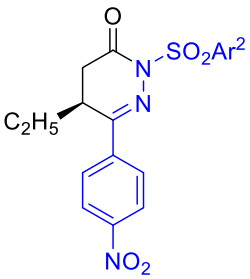
2-4i: 51%, 93:7 e.r.



2-4j: 48%, 96:4 e.r.[b,c]



2-4k: 65%, 96:4 e.r.[b]



2-4l: 60%, 97:3 e.r.[b,d]

[a] Reaction condition as in Table 2.2, entry 14. Yields (after silica gel chromatography purification) based on **2-2**. Reaction time 72-84 h. The e.r. value was determined via chiral-phase HPLC analysis. SO_2Ar^1= *p*-Nosyl, SO_2Ar^2= Tosyl, SO_2Ar^3= *o*-Nosyl. [b] NaOAc and THF were used as the base and solvent, respectively. [c] Reagents were added in the glovebox. The reaction was carried out at 0 °C for 24 h with 20 mol% precatalyst and 0.2 mmol bromoenal. [d]. 0.2 mmol bromoenal was used.

A rationale for the reaction stereoselectivity has illustrated in Figure 2.2 for product **2-3m** based on the absolute configuration of **2-3m**. Si-face of the **NHC**-bound α,β-unsaturated

acyl azolium is blocked by the catalyst and specifically the presence of the nitro (-NO_2) groupon catalyst makes the Si-face less available for the nucleophile. So, it is more favourable to intercept the **NHC**-bound α,β-unsaturated acyl azolium from the Re-face resulting in the formation of the (*R*)-**2-3a** stereoselectively.

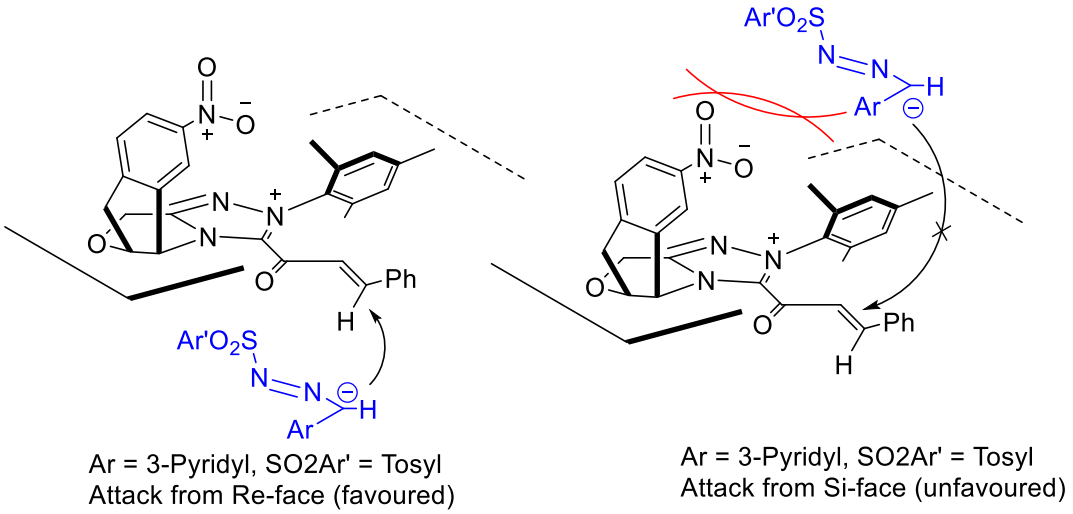
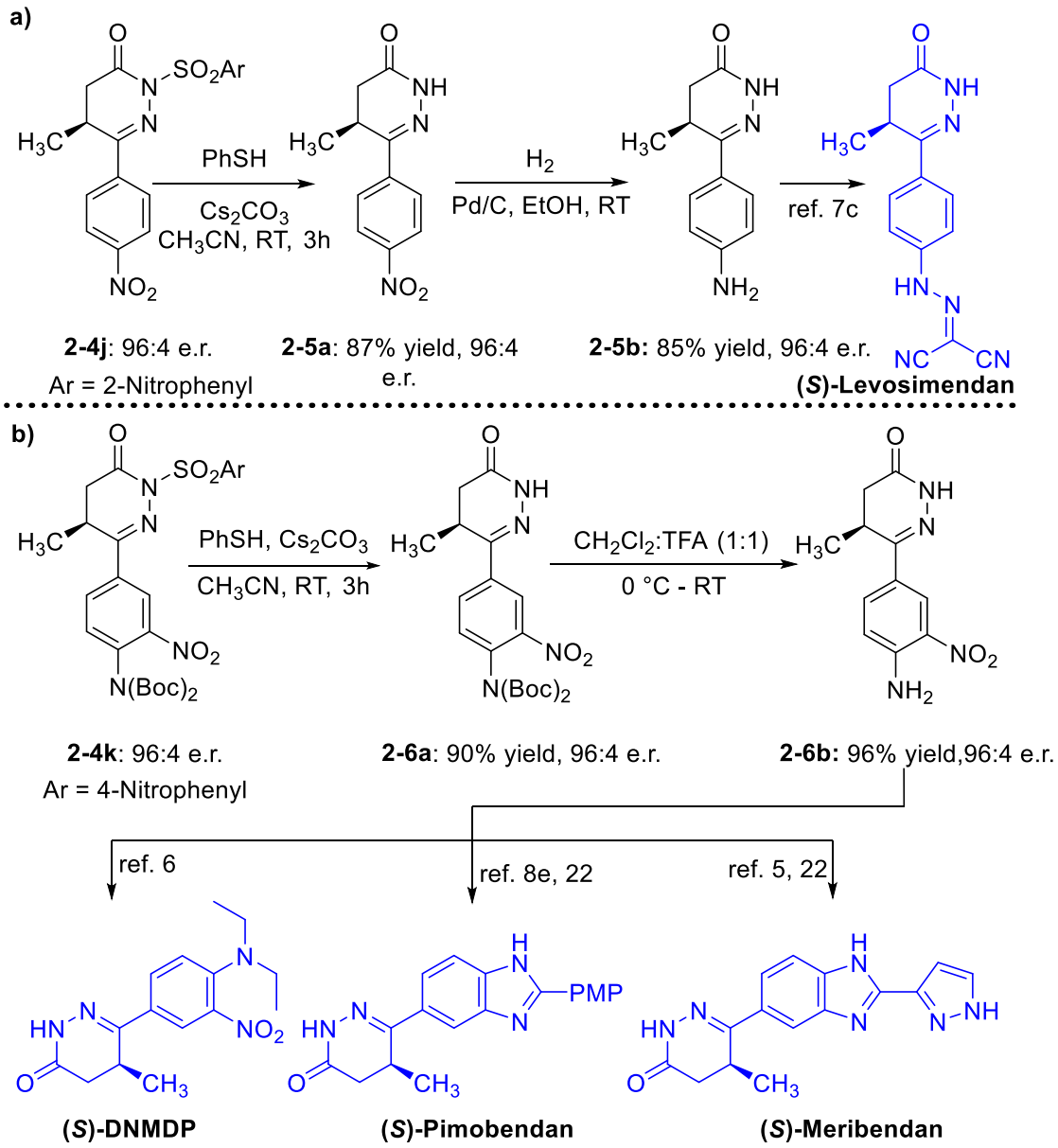


Figure 2.2. Proposed TS model for stereoselectivity.

The chiral 4,5-dihydropyridazinone molecules from our catalytic reaction were readily transformed to marketed drugs and other bioactive molecules (Scheme 2.3). For example, intermediate **2-5b**, the precursor of Levosimendan (clinical drug), had been obtained without any degradation of e.r. value from optically enriched **2-4j** (96:4 e.r.) through thiophenol mediated nosyl deprotection, followed by Pd/C-catalyzed hydrogenation (scheme 2.3a).[7c] Successive deprotection of *p*-nosyl group and two Boc groups of the product **2-4k** (96:4 e.r.) gave the intermediate **2-6b** in high yield without any erosion of the e.r. value (scheme 2.3b). Intermediate **2-6b** is the precursor for cancer cytotoxic modulator DNMDP[6], drug Pimobendan[8e,22] and bioactive Meribendan[5,22] (scheme 2.3b).

Scheme 2.3. Synthesis of marketed-drugs and bioactive molecules



2.3. Conclusions

In summary, we have developed a carbene-catalyzed enantioselective formal [3+3] annulation strategy for the construction of 6-aryl-4,5-dihydropyridazinones. The reaction proceeds via the umpolung of aryl aldehyde-derived hydrazones and followed by a chemoselective 1,4-addition to **NHC**-bound acyl azolium intermediate. A broad scope of functional groups is well tolerated on both of the bromoenal and hydrazone

substrates, with all the corresponding products afforded in good to excellent yields and enantioselectivities. Scalable synthesis with low precatalyst loading (1 mol%) could also give the annulated products in good results. Applications of our reaction products allow enantiomeric access to marketed drugs and bioactive molecules.

2.4 Experimental Section

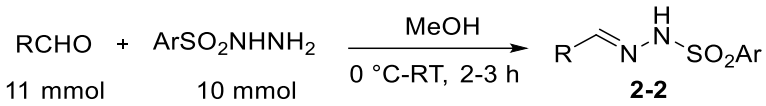
2.4.1 General Informations

Commercially available materials purchased from TCI or Sigma Aldrich were used as received. All reactions were carried out under nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Ethyl acetate was dried by Na_2SO_4 and THF was distilled from sodium-benzophenone. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254nm and 365 nm). ^{1}H, ^{13}C, and ^{19}F NMR were recorded on Bruker BBFO 400 MHz NMR, Bruker AV400 MHz NMR, Bruker AV300 MHz NMR Bruker AV500 MHz NMR spectrometer with tetramethylsilane as the internal standard and were calibrated using residual undeuterated solvent ($CDCl_3$: ^{13}C NMR = 77.16; CD_3OD: ^{13}C NMR = 49.00, ^{1}H NMR = 3.31) and tetramethylsilane (^{1}H NMR = 0.00) as internal references. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J) are reported in Hertz (Hz). High Resolution Mass spectra (HRMS) were recorded by using Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of er was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows:

$[\alpha]_{\pi}^{D}$ (c in g per 100 mL solvent). α-Bromoenals[23] were synthesized according to previous literature procedure.

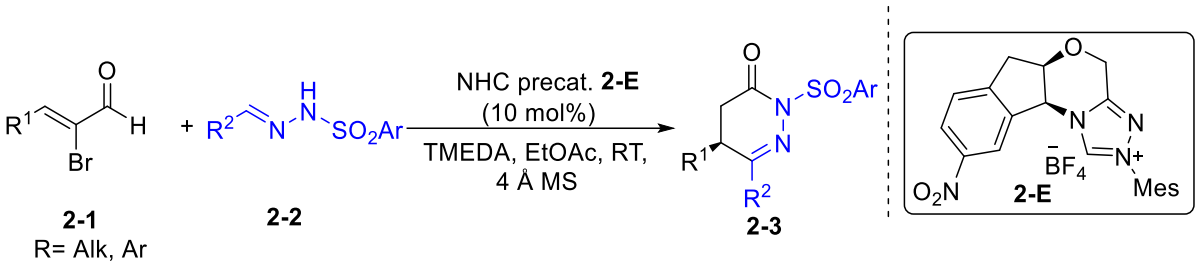
2.4.2 General experimental procedure

2.4.2.1 General procedure to synthesis of hydrazones



Literature procedure[24] was followed with slight modification. A round-bottom flask equipped with a stirring bar and aldehyde (11 mmol, 1.0 equiv) in MeOH (10 mL) was cooled down to 0 °C and sulfonyl hydrazide (10 mmol, 1.0 equiv) was added. Resulting mixture was stirred at room temperature for 2-3 hours. After the completion of the reaction (monitored by TLC analysis), precipitate was filtered and washed by 10 ml cold MeOH to afford pure hydrazone products (**2-2**) in usually >80% yield.

2.4.2.2 General procedure for the catalytic reactions of bromoenals with hydrazones



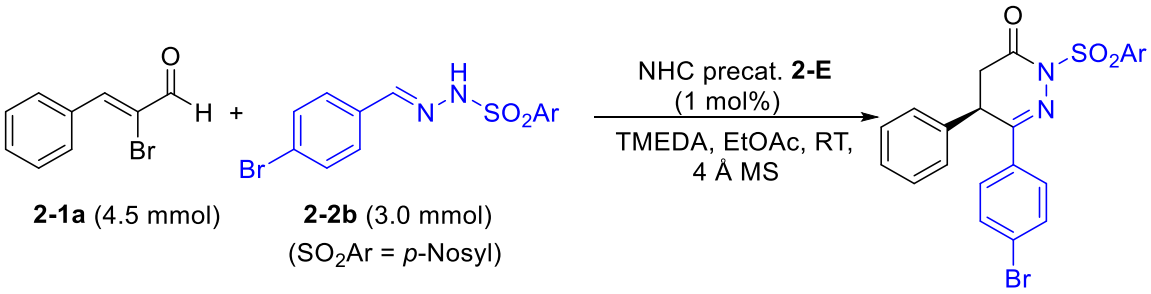
A dry test tube with a stir bar was charged with bromoenal **2-1** (0.15 mmol, 1.5 equiv), hydrazone **2-2** (0.1 mmol, 1.0 equiv), **NHC** precatalyst **2-E** (4.6 mg, 10 mol%), and molecular sieves (100 mg/ml solvent). The tube was evacuated and refilled with nitrogen for three times in a well manner. Then the mixture was dissolved in ethyl acetate (0.05 M). The reaction mixture was cooled down to 0 °C and TMEDA (37.5 µL, 2.5 equiv) was added via a microliter syringe and stirred at room temperature for 72-84h until the hydrazone **2-2** was consumed completely (monitored by TLC). After the reaction was finished, the mixture was concentrated

under vacuum and purified by column chromatography on silica gel (Hexane:EtOAc = 7:3 to 6:4 or Hexane:DCM = 6:4 to 3:7) to afford desired product **2-3**, which was confirmed by ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra, and the enantiomeric ratio was determined by chiral HPLC.

Note: Racemic samples for chiral phase HPLC analysis were prepared using **NHC** below as the **NHC** precatalyst according to the procedure as above.

Achiral NHC

2.4.2.3 Procedure for gram scale synthesis of 2-3b



2-1a (4.5 mmol) **2-2b** (3.0 mmol) (SO_2Ar = *p*-Nosyl)

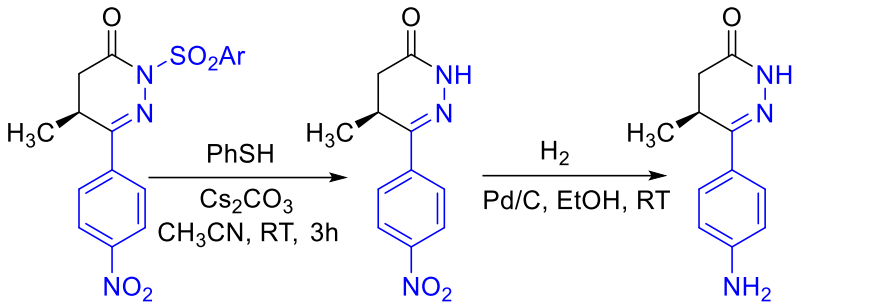
2-3b: 65%, 99.5:0.5 e.r.

A dry 250 ml round bottom flask equipped with a stirring bar was charged with α-bromo cinnamaldehyde (**2-1a**) (949.8 mg, 4.5 mmol, 1.5 equiv), N'-(4-bromobenzylidene)-4-nitrobenzenesulfonohydrazide (**2-2b**) (1.1 g, 3.0 mmol, 1.0 equiv), **NHC** precatalyst **2-E** (14.1 mg, 1 mol%), and molecular sieves (100 mg/ml solvent). The flask was evacuated and refilled with nitrogen for three times in a well manner. Then the mixture was dissolved in EtOAc (0.05 M). The reaction mixture was cooled down to 0 °C and TMEDA was added via a syringe (1.15 ml, 7.5 mmol, 2.5 equiv) and stirred at room temperature for 72-84h untill the hydrazone (**2-2b**) was consumed completely (monitored by TLC). The mixture was concentrated under

vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate = 7:3 to 1:1) to afford desired product **2-3b** in 74% yield (1.14 g) and 96:4 e.r. value.

2.4.3 Transformation of Products

Scheme 2-4. Deprotection and Reduction of 2-4j to Form Levosimendan Precursor 2-5b



2-4j: 96:4 e.r. Ar= 2-Nitrophenyl

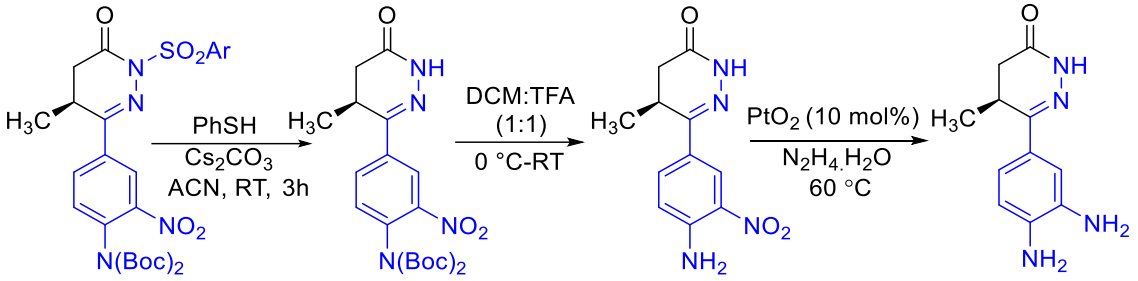
2-5a: 87% yield, 96:4 e.r.

2-5b: 85% yield, 96:4 e.r.

(*S*)-5-methyl-6-(4-nitrophenyl)-4,5-dihydropyridazin-3(2H)-one (**2-5a**): A dry 10 ml round bottom flask equipped with a stirring bar was charged with **2-4j** (83.7 mg, 0.2 mmol, 96:4 e.r.), Cs_2CO_3 (228.1 mg, 0.7 mmol) and 5 ml acetonitrile. Then thiophenol (45 µL, 0.44 mmol) was added dropwise via a syringe. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and purified by silica gel column chromatography (hexane:ethylacetate = 1:1) to afford the product **2-5a** (40.6 mg, 87%, 96:4 e.r).

(*S*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**2-5b**): A 10 ml round bottom flask equipped with a stirring bar was charged with **2-5a** (35 mg, 0.15 mmol, 96:4 e.r.) , 10% Pd on carbon (8.3 mg) and 3 ml ethanol. The resulting suspension was flushed with hydrogen thoroughly and was stirred with a hydrogen balloon for 1h. The crude reaction mixture was filtered through a cellite pad and washed with ethyl acetatate thoroughly. The filtrate was concentrated and purified by silica gel column chromatography (hexane:ethylacetate = 1:1 to 3:7) to give the product **2-5b** (25.9 mg, 85%, 96:4 e.r.).

Scheme 2-5. Transformation of 2-4k to 2-6c



2-4k: 96:4 e.r. Ar= 4-Nitrophenyl **2-6a**: 90% yield, 96:4 e.r. **2-6b:** 96% yield,96:4 e.r. **2-6c:** 70% yield, 96:4 e.r.

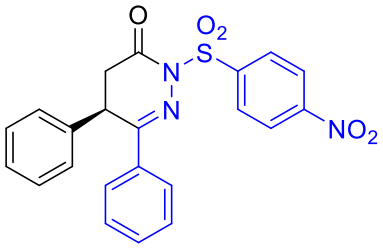
(*S*)-6-(4-Di(tert-butyloxycarbonyl)amino-3-nitrophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**2-6a**): A dry 10 ml round bottom flask equipped with a stirring bar was charged with **2-4k** (134.5 mg, 0.3 mmol, 96:4 e.r.), Cs_2CO_3 (342.1 mg , 1.05 mmol.) and 7.5 ml acetonitrile. Then thiophenol (67.5 µL, 0.66 mmol) was added dropwise via syringe. The mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated and purified by silica gel column chromatography (hexane:ethylacetate = 1:1) to afford the product **2-6a** (121.1 mg, 90%, 96:4 e.r.).

(*S*)-6-(4-amino-3-nitrophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**2-6b**): In a 10 ml round bottom flask equipped with a stirring bar was charged with **2-6a** (89.6 mg, 0.2 mmol) and 1 ml dichloromethane. Then 1 ml trifluoroacetic acid was added dropwise via a syringe at 0 °C and the reaction mixture was stirred at room temperature until the starting material was consumed completely (monitored by TLC). After the reaction was finished the crude reaction mixture was concentrated and the product was purified by silica gel column chromatography (dichloromethane/hexane = 8:2) yielding the product **2-6b** (47.6 mg, 96%, 96:4 e.r.).

(*S*)-6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (**2-6c**): Literature method[22] for racemic substrate was used with slight modification. In a 4 ml vial **2-6b** (24.8 mg, 0.1 mmol), DMF (300 µL) and PtO_2 (10 mol%, 0.01 mmol, 2.3 mg) was added. Then 80 µL hydrazine monohydrate was added slowly and the mixture was stirred at 60 °C. Progress of the reaction was monitored by TLC. After the starting material was consumed, the reaction was filtered, and the filtrate was evaporated. The crude product was purified in silica gel column

chromatography (dichloromethane/methanol = 49:1) yielding the product **2-6c** (15.3 mg, 70%, 96:4 e.r.).

2.4.4 Characterization of products



2-3a

(*R*)-2-((4-nitrophenyl)sulfonyl)-5,6-diphenyl-4,5-dihydropyridazin-3(2H)-one (2-3a)

Yield: 30.9 mg, 71%

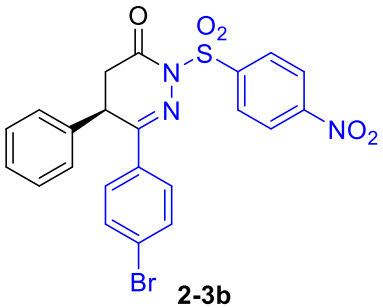
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.46 - 7.43 (m, 1H), 7.42 - 7.39 (m, 2H), 7.24 - 7.21 (m, 3H), 7.03 (d, *J* = 6.5 Hz, 2H), 4.56 (d, *J* = 6.4 Hz, 1H), 3.00 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.91 (d, *J* = 16.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 155.9, 151.0, 143.3, 135.8, 134.0, 131.3, 130.3, 129.7, 129.0, 128.5, 127.0, 126.8, 124.2, 40.2, 37.6 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 436.0967, found: 436.0963

IR ν_{max} (film, cm^{-1}): 1732,1606, 1531, 1131, 1186, 856, 825, 740.

HPLC analysis: 95:5 er, (CHIRALCEL AD-H column, 254 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 34.1 min, t_{minor} = 41.3 min), $[\alpha]_D^{25}$ = -34.8 (c = 1.3, acetone).



2-3b

(*R*)-6-(4-bromophenyl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3b)

Yield: 1.14 g, 74% [40.1 mg, 78% (0.1 mmol scale, 10 mol% catalyst loading)

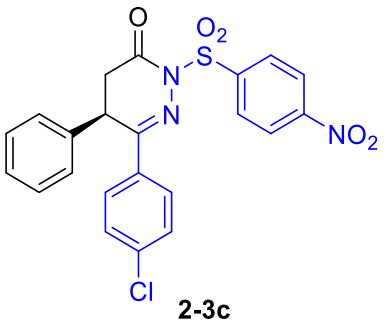
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.29 (d, *J* = 8.9 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.26 - 7.21 (m, 3H), 6.99 (d, *J* = 6.7 Hz, 2H), 4.51 (d, *J* = 5.8 Hz, 1H), 3.02 (dd, *J* = 16.9, 7.2 Hz, 1H), 2.90 (dd, *J* = 16.9, 1.8 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 154.6, 151.0, 143.2, 135.5, 132.9, 132.3, 130.3, 129.8, 128.6, 128.5, 126.7, 126.0, 124.2, 40.2, 37.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 514.0072, found: 514.0070

IR ν_{max} (film, cm^{-1}): 1732, 1607, 1531, 1186, 1008, 736.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, n-hexane/i-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 27.1 min, t_{minor} = 31.2 min), $[\alpha]_D^{25}$ = -23.2 (c = 1.0, acetone)



2-3c

(*R*)-6-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3c)

Yield: 33.8 mg, 72%

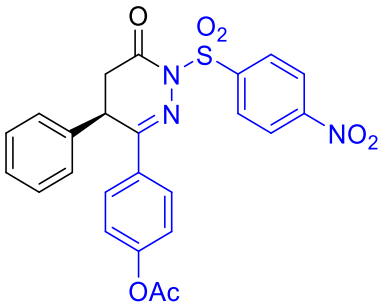
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.99 (d, *J* = 6.8 Hz, 2H), 4.51 (d, *J* = 6.0 Hz, 1H), 3.01 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.90 (dd, *J* = 16.9, 1.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 154.6, 151.0, 143.2, 137.5, 135.5, 132.4, 130.3, 129.8, 129.3, 128.6, 128.3, 126.7, 124.2, 40.2, 37.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 470.0577, found: 470.0576

IR ν_{max} (film, cm^{-1}): 1714, 1606, 1531, 1186, 1089, 856, 837, 744.

HPLC analysis: 95.5:4.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 24.8 min, t_{minor}= 28.0 min), $[\alpha]_D^{25}$ = -31.8 (c = 0.6, acetone)



2-3d

(*R*)-4-(1-((4-nitrophenyl)sulfonyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)phenyl acetate (2-3d)

Yield: 37 mg, 75%

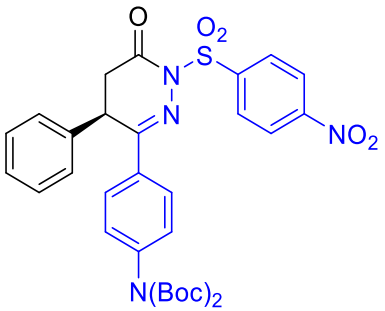
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.24-7.20 (m, *J* = 11.1, 5.2 Hz, 3H), 7.13 (d, *J* = 8.7 Hz, 2H), 7.00 (d, *J* = 6.4 Hz, 2H), 4.53 (d, *J* = 5.6 Hz, 1H), 3.00 (dd, *J* = 16.8, 7.0 Hz, 1H), 2.90 (dd, *J* = 16.8, 1.8 Hz, 1H), 2.31 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 164.4, 154.9, 153.0, 151.1, 143.3, 135.6, 131.6, 130.4, 129.8, 128.6, 128.3, 126.8, 124.2, 122.3, 40.4, 37.6, 21.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 494.1022, found: 494.1022

IR ν_{max} (film, cm^{-1}): 1761, 1718, 1604, 1529, 1188, 1087, 854,742.

HPLC analysis: 95.5:4.5 er, (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 42.3 min, t_{major}= 48.4 min), $[\alpha]_D^{25}$ = -23.3 (c = 1.0, acetone)



2-3e

(*R*)-6-(4-Di(tert-butyloxycarbonyl)aminophenyl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3e)

Yield: 56.6 mg, 87%

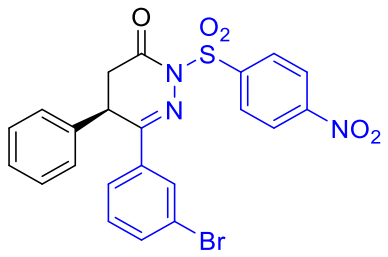
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.29 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.25 – 7.18 (m, 5H), 7.01 – 6.99 (m, 2H), 4.54 (d, *J* = 5.7 Hz, 1H), 3.01 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.89 (dd, *J* = 16.8, 1.6 Hz, 1H), 1.44 (s, 18H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 154.9, 151.7, 151.0, 143.2, 141.9, 135.6, 132.9, 130.3, 129.7, 128.5, 128.4, 127.5, 126.7, 124.2, 83.4, 40.3, 37.5, 28.0 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 651.2125, found: 651.2125

IR ν_{max} (film, cm^{-1}): 1789, 1732, 1714, 1606, 1531, 1263, 1151, 1004, 856, 744.

HPLC analysis: 95.5:4.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 15.9 min, t_{major}= 23.9 min), $[\alpha]_D^{25}$ = -11.5 (c = 3.4, acetone)



2-3f

(*R*)-6-(3-bromophenyl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3f)

Yield: 38 mg, 74%

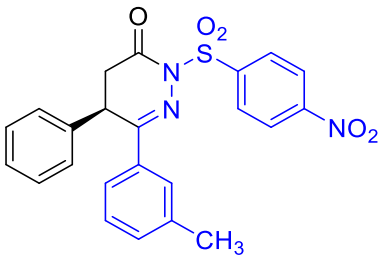
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 – 8.37 (m, 2H), 8.31 – 8.30 (m, 2H), 7.94 (t, *J* = 1.7 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.57 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.28-7.24 (m, 4H), 7.01 – 7.00 (m, 2H), 4.50 (d, *J* = 5.5 Hz, 1H), 3.01 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.91 (dd, *J* = 16.9, 1.9 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 154.3, 151.1, 143.2, 136.0, 135.4, 134.2, 130.5, 130.4, 129.9, 129.9, 128.7, 126.7, 125.6, 124.3, 123.3, 40.3, 37.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 514.0072, found: 514.0068

IR ν_{max} (film, cm^{-1}): 1732, 1606, 1558, 1531, 1186, 1088, 858, 829, 739.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 22.1 min, t_{minor}= 33.5 min), $[\alpha]_D^{25}$ = -38.5 (c = 0.4, acetone)



2-3g

(*R*)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-6-(m-tolyl)-4,5-dihydropyridazin-3(2H)-one (2-3g)

Yield: 37.7 mg, 84%

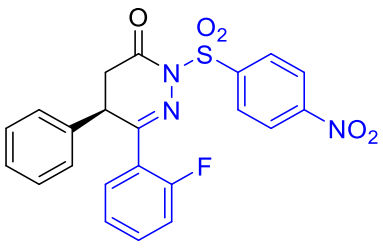
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 7.7, 5.3 Hz, 2H), 8.28 (dd, *J* = 8.8, 2.5 Hz, 2H), 7.63 (s, 1H), 7.55 (d, *J* = 7.1 Hz, 1H), 7.29 – 7.21 (m, 5H), 7.03 – 7.01 (m, 2H), 4.56 (d, *J* = 6.6 Hz, 1H), 2.98 (dd, *J* = 16.9, 6.9 Hz, 1H), 2.90 (d, *J* = 16.9 Hz, 1H), 2.37 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 164.8, 156.2, 151.0, 143.3, 138.8, 135.8, 135.8, 133.9, 132.1, 130.3, 129.6, 128.9, 128.4, 127.5, 126.8, 124.2, 124.2, 40.1, 37.5, 21.6 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 450.1124, found: 450.1121

IR ν_{max} (film, cm^{-1}): 1724, 1643, 1606, 1531, 1188, 1089, 854, 815, 742.

HPLC analysis: 95.5:4.5 er, (CHIRALCEL AD-H column, 220nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 21.6 min, t_{minor}= 36.5 min), $[\alpha]_D^{25}$ = -32.9 (c = 2.3, acetone)



2-3h

(*R*)-6-(2-fluorophenyl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3h)

Yield: 29 mg, 64%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 8.5, 6.1 Hz, 2H), 8.30 (dd, *J* = 8.8, 3.5 Hz, 2H), 7.68 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44-7.40 (m, 1H), 7.25 – 7.15 (m, 4H), 7.06 (ddd, *J* = 11.4, 8.5, 3.1 Hz, 1H), 7.00 (dd, *J* = 6.4, 2.8 Hz, 2H), 4.57 (dd, *J* = 7.0, 2.8 Hz, 1H), 3.06 (dd, *J* = 17.2, 7.1 Hz, 1H), 2.90 (dt, *J* = 17.1, 3.1 Hz, 1H) ppm.

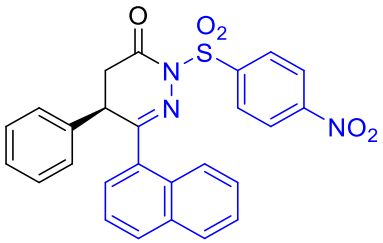
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 160.7 (d, *J* = 252.3 Hz), 155.0, 151.1, 143.1, 135.5, 132.7 (d, *J* = 8.9 Hz), 130.4, 129.5, 128.3, 126.9, 124.9 (d, *J* = 3.4 Hz), 124.2, 122.9 (d, *J* = 11.0 Hz), 116.7 (d, *J* = 22.1 Hz), 42.2 (d, *J* = 6.3 Hz), 37.3.

^{19}F NMR (377 MHz, $CDCl_3$) δ -112.7 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 454.0873, found: 454.0877

IR ν_{max} (film, cm^{-1}): 1732, 1606, 1531, 1489, 1186, 1089, 856, 837, 742.

HPLC analysis: 92:8 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 26.3 min, t_{major}= 27.7 min), $[\alpha]_D^{25}$ = -46.9 (c = 1.7, acetone)



2-3i

(*R*)-6-(naphthalen-1-yl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3i)

Yield: 31.1 mg, 64%

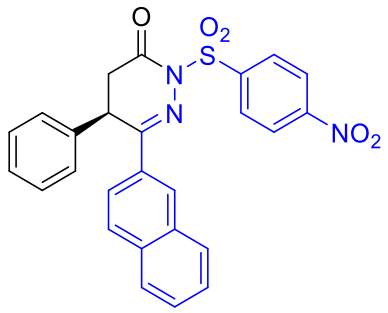
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 – 8.34 (m, 2H), 8.32 – 8.30 (m, 3H), 7.90-7.88 (m, 2H), 7.58 – 7.55 (m, 2H), 7.44 – 7.40 (m, 2H), 7.24 – 7.22 (m, 3H), 7.06-7.04 (m, 2H), 4.50 (dd, *J* = 7.0, 2.6 Hz, 1H), 3.19 (dd, *J* = 17.3, 7.0 Hz, 1H), 3.03 (dd, *J* = 17.3, 2.6 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.0, 158.7, 151.1, 143.1, 135.6, 134.1, 132.3, 131.2, 130.6, 130.5, 129.6, 128.9, 128.4, 127.7, 127.3, 127.1, 126.6, 125.2, 124.9, 124.2, 43.8, 37.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 486.1124, found: 486.1128

IR ν_{max} (film, cm^{-1}): 1732, 1647, 1533, 1184, 854, 740, 723.

HPLC analysis: 91.5:8.5 er, (CHIRALCEL AD-H column, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 32.7 min, t_{minor}= 55.4 min), $[\alpha]_D^{25}$ = -19.9 (c = 0.8, acetone)



2-3j

(*R*)-6-(naphthalen-2-yl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3j)

Yield: 35.9 mg, 74%

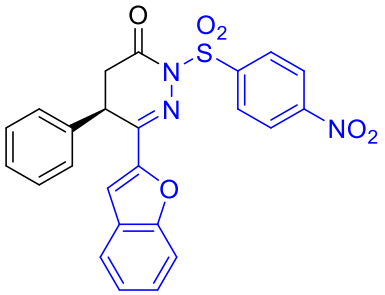
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.34 (m, 2H), 8.33 – 8.30 (m, 2H), 8.12 – 8.08 (m, 2H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.52 (dtd, *J* = 14.8, 6.9, 1.3 Hz, 2H), 7.24 – 7.22 (m, 3H), 7.09-7.06 (m, 2H), 4.75 (dd, *J* = 6.6, 1.8 Hz, 1H), 3.06 (dd, *J* = 16.9, 6.7 Hz, 1H), 2.97 (dd, *J* = 16.9, 2.1 Hz, 1H) ppm

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 155.8, 151.0, 143.3, 135.8, 134.6, 132.9, 131.3, 130.4, 129.7, 129.0, 129.0, 128.5, 128.0, 127.9, 127.7, 127.02, 126.8, 124.2, 123.4, 39.9, 37.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 486.1124, found: 486.1122

IR ν_{max} (film, cm^{-1}): 1732,1633, 1531, 1186, 1087, 854, 817, 740..

HPLC analysis: 95.5:4.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 37.3 min, t_{minor}= 42.9 min), $[\alpha]_D^{25}$ = 36.1 (c = 1.7, acetone)



2-3k

(*R*)-6-(benzofuran-2-yl)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-4,5-dihydropyridazin-3(2H)-one (2-3k)

Yield: 29.9 mg, 63%

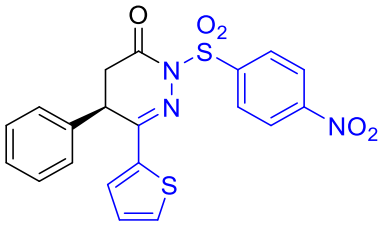
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.28 (t, *J* = 3.6 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.06 – 7.05 (m, 2H), 4.63 (d, *J* = 5.7 Hz, 1H), 3.06 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.96 (dd, *J* = 16.9, 1.8 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 155.8, 151.1, 149.8, 148.3, 143.1, 135.7, 130.5, 129.7, 128.6, 127.8, 127.4, 127.1, 126.7, 124.2, 124.0, 122.3, 112.2, 110.3, 39.6, 36.9 ppm

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 476.0916, found: 476.0914

IR ν_{max} (film, cm^{-1}): 1720, 1593, 1531, 1182, 1155, 1089, 1004, 941, 848, 817, 740.

HPLC analysis: 97.5:2.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 44.1 min, t_{minor}= 47.1 min), $[\alpha]_D^{25}$ = 17.4 (c = 1.2, acetone)



2-3l

(*R*)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-6-(thiophen-2-yl)-4,5-dihydropyridazin-3(2H)-one (2-3l)

Yield: 36.6 mg, 83%

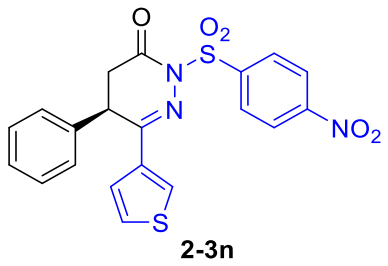
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.29 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 5.1 Hz, 1H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.25 – 7.21 (m, 3H), 7.03-7.00 (m, 3H), 4.50 (d, *J* = 5.3 Hz, 1H), 3.03 (dd, *J* = 16.9, 7.0 Hz, 1H), 2.92 (dd, *J* = 16.9, 2.0 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 152.0, 151.0, 143.1, 138.8, 135.7, 130.9, 130.4, 129.7, 129.7, 128.5, 128.0, 126.8, 124.2, 41.0, 37.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 442.0531, found: 442.0528

IR ν_{max} (film, cm^{-1}): 1732, 1531, 1186, 854, 742, 721.

HPLC analysis: 97:3 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 39.7 min, t_{minor}= 52.3 min), $[\alpha]_D^{25}$ = -39.9 (c = 0.7, acetone)



2-3n

(*R*)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-6-(thiophen-3-yl)-4,5-dihydropyridazin-3(2H)-one (2-3n)

Yield: 37.1 mg, 84%

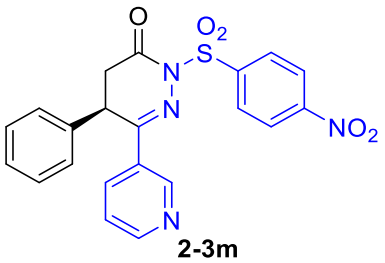
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 5.1 Hz, 1H), 7.60 – 7.59 (m, 1H), 7.36 (dd, *J* = 5.1, 2.9 Hz, 1H), 7.22 - 7.21 (m, 3H), 7.02 – 7.00 (m, 2H), 4.46 (d, *J* = 5.5 Hz, 1H), 3.01 (dd, *J* = 16.9, 7.1 Hz, 1H), 2.89 (dd, *J* = 16.8, 1.9 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.6, 152.3, 151.0, 143.3, 137.0, 135.8, 130.3, 129.7, 128.5, 127.6, 127.2, 126.8, 126.1, 124.2, 41.1, 37.4.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 442.0531, found: 442.0529

IR ν_{max} (film, cm^{-1}): 1722, 1606, 1531, 1186, 1087, 856, 740.

HPLC analysis: 92:8 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 43.3 min, t_{minor}= 54.1 min), $[\alpha]_D^{25}$ = -14.7 (c = 1.5, acetone)



2-3m

(*R*)-2-((4-nitrophenyl)sulfonyl)-5-phenyl-6-(pyridin-3-yl)-4,5-dihydropyridazin-3(2H)-one (2-3m)

Yield: 30.1 mg, 69%

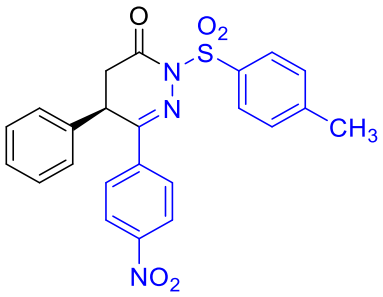
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (d, *J* = 1.6 Hz, 1H), 8.66 (d, *J* = 3.7 Hz, 1H), 8.39 (d, *J* = 8.8 Hz, 2H), 8.32 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.36 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.29 – 7.23 (m, 3H), 7.01 (d, *J* = 6.6 Hz, 2H), 4.54 (d, *J* = 6.1 Hz, 1H), 3.06 (dd, *J* = 16.9, 7.3 Hz, 1H), 2.92 (dd, *J* = 16.9, 1.7 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 153.3, 151.9, 151.1, 148.2, 143.1, 135.3, 134.3, 130.4, 129.9, 128.8, 126.8, 124.3, 123.8, 40.4, 37.5.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 437.0920, found: 437.0921

IR ν_{max} (film, cm^{-1}): 1728, 1537, 1180, 1147, 1087, 983, 854, 853, 738, 704.

HPLC analysis: 92.5:7.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 36.8 min, t_{minor}= 45.6 min), $[\alpha]_D^{25}$ = -32.3 (c = 1.1, acetone)



2-3o

(*R*)-6-(4-nitrophenyl)-5-phenyl-2-tosyl-4,5-dihydropyridazin-3(2H)-one (2-3o)

Yield: 37 mg, 82%

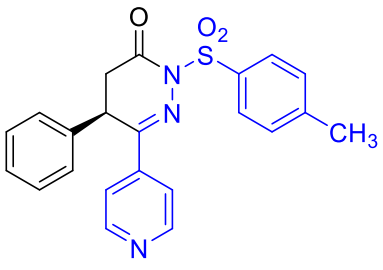
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.9 Hz, 2H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.94 (d, *J* = 7.1 Hz, 2H), 4.51 (d, *J* = 6.4 Hz, 1H), 3.05 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.84 (dd, *J* = 16.6, 1.5 Hz, 1H), 2.46 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.5, 151.5, 148.9, 145.9, 140.2, 135.7, 134.6, 129.9, 129.8, 129.0, 128.6, 127.8, 126.7, 124.0, 40.8, 37.7, 21.9 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 450.1124, found: 450.1122

IR ν_{max} (film, cm^{-1}): 1728, 1597, 1519, 1192, 1176, 856, 821, 744

HPLC analysis: 97:3 er, (CHIRALCEL AD-H column, 254 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 31.2 min, t_{minor}= 46.7 min), $[\alpha]_D^{25}$ = -41.5 (c = 2.3, acetone)



2-3p

(*R*)-5-phenyl-6-(pyridin-4-yl)-2-tosyl-4,5-dihydropyridazin-3(2H)-one (2-3p)

Yield: 34.9 mg, 86%

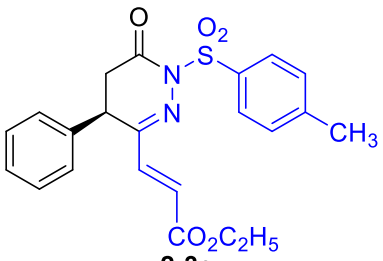
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (brs, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 5.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.93 (d, *J* = 7.0 Hz, 2H), 4.45 (d, *J* = 6.2 Hz, 1H), 3.02 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.83 (dd, *J* = 16.6, 1.7 Hz, 1H), 2.46 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 151.4, 150.5, 145.8, 141.7, 135.8, 134.7, 129.9, 129.8, 129.0, 128.6, 126.8, 120.7, 40.5, 37.7, 21.9 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 406.1225, found: 406.1217

IR ν_{max} (film, cm^{-1}): 1722, 1593, 1190, 1174, 1143, 1089, 827, 704, 675, 551.

HPLC analysis: 98:2 er, (CHIRALCEL OD column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 23.7 min, t_{major}= 55.9 min), $[\alpha]_D^{25}$ = -33.5 (c = 1.7, acetone)



2-3q

Ethyl (R,E)-3-(1-((4-nitrophenyl)sulfonyl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridazin-3-yl)acrylate (2-3q)

Yield: 32 mg, 75%

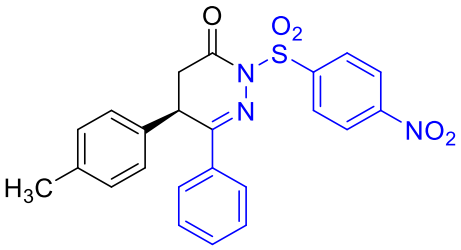
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 16.3 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.21 (dt, *J* = 23.0, 7.2 Hz, 3H), 6.87 (d, *J* = 7.3 Hz, 2H), 6.18 (d, *J* = 16.3 Hz, 1H), 4.25 – 4.16 (m, 3H), 2.92 (dd, *J* = 16.6, 7.5 Hz, 1H), 2.76 (dd, *J* = 16.6, 1.7 Hz, 1H), 2.46 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 163.7, 152.8, 145.8, 139.8, 135.7, 134.5, 129.8, 129.7, 129.0, 128.4, 126.6, 126.3, 61.3, 39.5, 37.3, 21.9, 14.3.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 427.1328, found: 427.1326

IR ν_{max} (film, cm^{-1}): 1728, 1635, 1597, 1190, 1033, 736, 702, 590.

HPLC analysis: 98.5:1.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 13.6 min, t_{minor}= 19.2 min), $[\alpha]_D^{25}$ = 0.6 (c = 2.5, acetone)



2-4a

(*R*)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-5-(p-tolyl)-4,5-dihydropyridazin-3(2H)-one (2-4a)

Yield: 26.9 mg, 60%

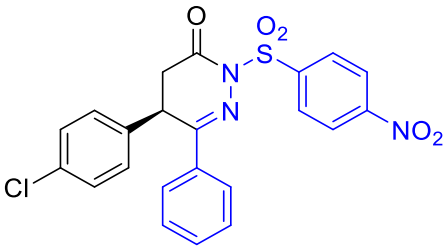
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.79 – 7.77 (m, 2H), 7.43 – 7.39 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 4.52 (d, *J* = 5.9 Hz, 1H), 2.98 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.88 (dd, *J* = 16.8, 1.7 Hz, 1H), 2.27 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 157.8, 156.1, 151.0, 143.3, 138.3, 134.1, 132.7, 131.2, 130.3, 129.0, 127.0, 126.7, 124.2, 39.9, 37.6, 21.1 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 450.1124, found: 450.1122

IR ν_{max} (film, cm^{-1}): 1722, 1606, 1531, 1184, 1141, 1087, 856, 742, 682, 619, 596, 543.

HPLC analysis: 92:8 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 23.8 min, t_{major}= 31.4 min), $[\alpha]_D^{25}$ = -41.4 (c = 1.2, acetone)



2-4b

(*R*)-5-(4-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4b)

Yield: 31 mg, 66%

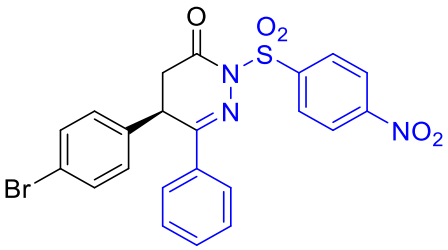
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 2H), 7.48 – 7.39 (m, 3H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 5.4 Hz, 1H), 2.99 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.89 (dd, *J* = 17.1, 1.9 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 155.6, 151.1, 143.1, 134.5, 134.2, 133.7, 131.5, 130.4, 129.9, 129.1, 128.3, 126.9, 124.2, 39.5, 37.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 470.0577, found: 470.0580

IR ν_{max} (film, cm^{-1}): 1732, 1606, 1531, 1186, 1089, 856, 817, 736, 545.

HPLC analysis: 95:5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 27.7 min, t_{major}= 37.1 min), $[\alpha]_D^{25}$ = -24.1 (c = 1.9, acetone)



2-4c

(*R*)-5-(4-bromophenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4c)

Yield: 46.1 mg, 89%

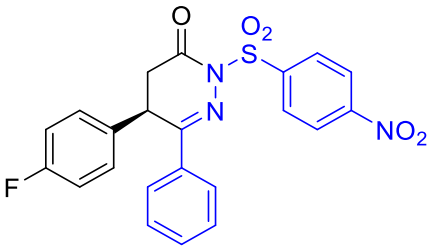
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 – 8.37 (m, 2H), 8.32 – 8.30 (m, 2H), 7.77 – 7.75 (m, 2H), 7.43 – 7.41 (m, 1H), 7.41 (dd, *J* = 15.4, 8.1 Hz, 4H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.52 (d, *J* = 5.5 Hz, 1H), 2.99 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.89 (dd, *J* = 17.1, 1.9 Hz, 1H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 155.5, 151.1, 143.1, 134.7, 133.7, 132.9, 131.5, 130.4, 129.1, 128.6, 126.9, 124.3, 122.6, 39.6, 37.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 514.0072, found: 514.0067

IR ν_{max} (film, cm^{-1}): 1728, 1606, 1531, 1186, 1147, 1010, 856, 742.

HPLC analysis: 89:11 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 36.88 min, t_{minor}= 26.23 min), $[\alpha]_D^{25}$ = -27.1 (c = 2.6, acetone)



2-4d

(*R*)-5-(4-fluorophenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4d)

Yield: 38.9 mg, 86%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.05 (dd, *J* = 8.6, 5.1 Hz, 2H), 6.95 (t, *J* = 8.5 Hz, 2H), 4.55 (d, *J* = 6.1 Hz, 1H), 2.99 (dd, *J* = 17.1, 7.0 Hz, 1H), 2.89 (dd, *J* = 17.1, 1.8 Hz, 1H) ppm.

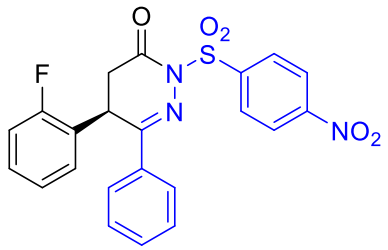
^{13}C NMR (126 MHz, $CDCl_3$) δ 164.5, 162.5 (d, *J* = 248.3 Hz), 155.8, 151.1, 143.1, 133.7, 131.5 (d, *J* = 3.5 Hz), 131.4, 130.4, 129.1, 128.7 (d, *J* = 8.2 Hz), 126.9, 124.2,116.7 (d, *J* = 21.8 Hz), 39.4, 37.6 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.0 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 454.0873, found: 454.0874

IR ν_{max} (film, cm^{-1}): 1728, 1606, 1531, 1186, 856, 840, 817, 744, 684.

HPLC analysis: 95.5:4.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 22.0 min, t_{major}= 24.67 min), $[\alpha]_D^{25}$ = -16.8 (c = 1.9, acetone)



2-4e

(*R*)-5-(2-fluorophenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4e)

Yield: 33.1 mg, 73%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (q, *J* = 9.0 Hz, 4H), 7.76 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.29-7.25 (m, 1H), 7.12 – 7.08 (m, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 4.84 (dd, *J* = 6.6, 2.0 Hz, 1H), 3.00 – 2.91 (m, 2H) ppm.

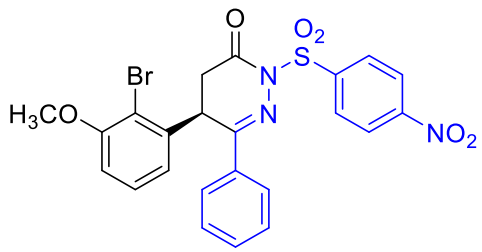
^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 160.3 (d, *J* = 247.0 Hz), 154.6, 151.0, 143.1, 133.4, 131.3, 130.5 (d, *J* = 8.5 Hz), 130.3, 128.9, 127.8 (d, *J* = 2.9 Hz), 126.7, 125.1 (d, *J* = 3.6 Hz), 124.3, 122.7 (d, *J* = 14.1 Hz), 116.5 (d, *J* = 21.6 Hz), 36.0 (d, *J* = 1.1 Hz), 34.1 (d, *J* = 2.8 Hz) ppm.

^{19}F NMR (377 MHz, $CDCl_3$) δ -117.1 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 454.0873, found: 454.0872

IR ν_{max} (film, cm^{-1}): 1732, 1531, 1188, 1095, 856, 812, 740, 684, 555.

HPLC analysis: 97.5:2.5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 23.5 min, t_{major} = 27.3 min), $[\alpha]_D^{25}$ = -42.3 (c = 1.3, acetone)



2-4f

(*R*)-5-(3-methoxyphenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4f)

Yield: 33.1 mg, 61%

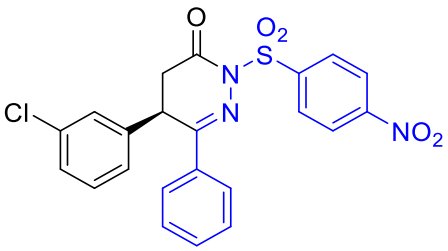
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.1 Hz, 2H), 8.36 (d, *J* = 9.0 Hz, 2H), 7.73 – 7.72 (m, 2H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.3 Hz, 2H), 6.65 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.20 (d, *J* = 2.9 Hz, 1H), 4.90 (dd, *J* = 7.5, 1.5 Hz, 1H), 3.62 (s, 3H), 2.99 (dd, *J* = 16.8, 7.5 Hz, 1H), 2.91 (dd, *J* = 16.8, 1.7 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 159.7, 154.7, 151.1, 143.1, 135.4, 134.9, 133.4, 131.4, 130.3, 129.1, 126.8, 124.4, 114.7, 114.4, 113.4, 55.5, 40.8, 35.7 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 544.0178, found: 544.0174

IR ν_{max} (film, cm^{-1}):1732, 1531, 1188, 1172, 856, 825, 738, 684.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 33.8 min, t_{major}= 38.0 min), $[\alpha]_D^{25}$ = -84.4 (c = 2.0, acetone)



2-4g

(*R*)-5-(3-chlorophenyl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (4g)

Yield: 38.9 mg, 83%

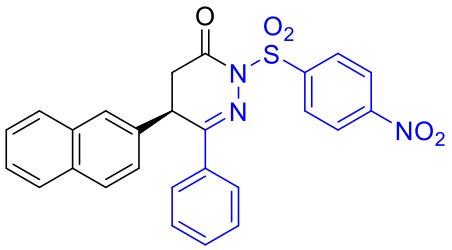
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.30 (d, *J* = 8.9 Hz, 2H), 7.78 – 7.76 (m, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.23 – 7.18 (m, 2H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.92 (s, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 3.04 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.87 (dd, *J* = 16.8, 1.5 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 154.7, 151.1, 143.2, 137.9, 135.5, 133.6, 131.5, 131.1, 130.3, 129.1, 128.8, 126.9, 126.9, 125.1, 124.4, 40.0, 37.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 470.0577, found: 470.0577

IR ν_{max} (film, cm^{-1}): 1728, 1606, 1593, 1573, 1531, 1263, 1087, 856, 773, 744, 623, 543.

HPLC analysis: 95:5 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 21.9 min, t_{minor}= 26.2 min), $[\alpha]_D^{25}$ = -45.4 (c = 2.1, acetone)



2-4h

(*R*)-5-(naphthalen-2-yl)-2-((4-nitrophenyl)sulfonyl)-6-phenyl-4,5-dihydropyridazin-3(2H)-one (2-4h)

Yield: 36.8 mg, 76%

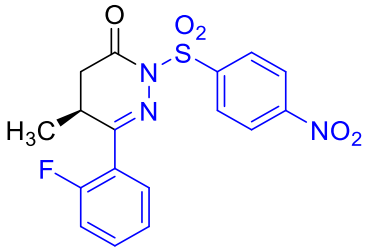
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.20 (m, 4H), 7.85– 7.83 (m, 2H), 7.76 (t, *J* = 7.9 Hz, 2H), 7.54 – 7.52 (m, 1H), 7.49 – 7.39 (m, 5H), 7.36 (s, 1H), 7.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 4.71 (d, *J* = 4.7 Hz, 1H), 3.09 (dd, *J* = 16.7, 6.5 Hz, 1H), 3.02 (dd, *J* = 16.7, 2.2 Hz, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 155.9, 150.9, 143.3, 134.1, 133.3, 133.0, 132.9, 131.3, 130.2, 129.9, 129.1, 127.8, 127.0, 127.0, 126.9, 125.5, 124.5, 124.1, 40.3, 37.2 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 486.1124, found: 486.1121

IR ν_{max} (film, cm^{-1}): 1722, 1184, 1170, 1136, 744, 723.

HPLC analysis: 92:8 er, (CHIRALCEL AD-H column, 254 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 38.7 min, t_{major}= 55.9 min), $[\alpha]_D^{25}$ = -100.4 (c = 1.3, acetone)



2-4i

(*S*)-6-(2-fluorophenyl)-5-methyl-2-((4-nitrophenyl)sulfonyl)-4,5-dihydropyridazin-3(2H)-one (2-4i)

Yield: 19.9 mg, 51%

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 – 8.38 (m, 2H), 8.35 – 8.33 (m, 2H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.27 – 7.24 (m, 1H), 7.17 – 7.13 (m, 1H), 3.37-3.30 (m, 1H), 2.74 (dd, *J* = 17.4, 6.2 Hz, 1H), 2.55 (dd, *J* = 17.4, 3.3 Hz, 1H), 1.23 (d, *J* = 7.3 Hz, 3H) ppm.

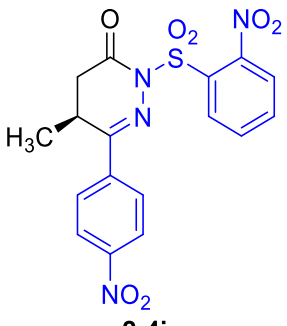
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 160.9 (d, *J* = 251.0 Hz), 158.5 (d, *J* = 2.0 Hz), 151.1, 143.2, 132.8 (d, *J* = 8.7 Hz), 130.5, 130.4 (d, *J* = 2.5 Hz), 125.0 (d, *J* = 3.3 Hz), 124.3, 122.7 (d, *J* = 11.8 Hz), 116.7 (d, *J* = 22.3 Hz), 36.5, 31.3 (d, *J* = 5.8 Hz), 15.6 (d, *J* = 2.5 Hz) ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 392.0716, found: 392.0720

IR ν_{max} (film, cm^{-1}): 1730, 1614, 1531, 1188, 1163, 854, 767, 740.

HPLC analysis: 93:7 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 18.4 min, t_{major}= 20.2 min), $[\alpha]_D^{25}$ = 65.7 (c = 0.5, acetone)



2-4j

(*S*)-5-methyl-6-(4-nitrophenyl)-2-((2-nitrophenyl)sulfonyl)-4,5-dihydropyridazin-3(2H)-one (2-4j)

Yield: 20.1 mg, 48%

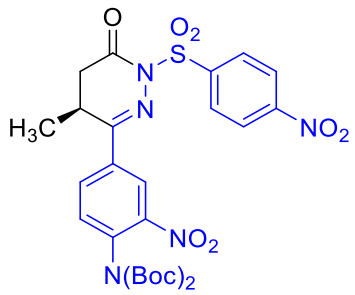
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 - 8.51 (m, 1H), 8.30 (d, *J* = 8.9 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.86-7.80 (m, 3H), 3.52-3.45 (m, 1H), 2.92 (dd, *J* = 16.7, 6.6 Hz, 1H), 2.61 (dd, *J* = 16.7, 1.4 Hz, 1H), 1.31 (d, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 153.6, 149.1, 148.4, 139.6, 135.5, 134.8, 132.2, 131.8, 127.8, 124.8, 124.2, 35.8, 29.1, 16.4.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 419.0661, found: 419.0657

IR ν_{max} (film, cm^{-1}): 1732, 1539, 1519, 1184, 852, 732, 576.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 43.8 min, t_{minor}= 60.3 min), $[\alpha]_D^{25}$ = -5.4 (c = 0.3, acetone)



2-4k

(*S*)-6-(4-Di(tert-butyloxycarbonyl)amino-3-nitrophenyl)-5-methyl-2-((4-nitrophenyl)sulfonyl)-4,5-dihydropyridazin-3(2H)-one (2-4k)

Yield: 41.1 mg, 65%

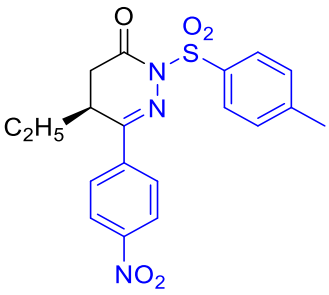
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 – 8.41 (m, 3H), 8.35 (d, *J* = 8.9 Hz, 2H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 3.45 – 3.40 (m, 1H), 2.75 (dd, *J* = 17.3, 6.3 Hz, 1H), 2.65 (d, *J* = 17.2 Hz, 1H), 1.44 (s, 18H), 1.29 (d, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 155.1, 151.2, 150.2, 146.2, 143.0, 135.4, 134.1, 132.3, 131.3, 130.5, 124.4, 123.0, 84.5, 36.1, 28.7, 27.9, 16.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 634.1819, found: 634.1820

IR ν_{max} (film, cm^{-1}): 1797, 1766, 1732, 1714, 1531, 1274, 1188, 1120, 914, 854, 742, 686, 599.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 22.2 min, t_{major}= 32.4 min), $[\alpha]_D^{25}$ = 109.6 (c = 1.2, acetone)



2-4l

(*S*)-5-ethyl-6-(4-nitrophenyl)-2-tosyl-4,5-dihydropyridazin-3(2H)-one (2-4l)

Yield: 24.1 mg, 60%

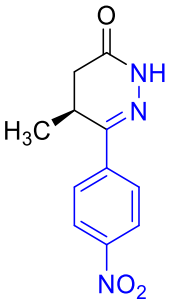
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.27 (m, 2H), 8.03 – 7.99 (m, 4H), 7.35 (d, *J* = 8.1 Hz, 2H), 3.24 - 3.19 (m, 1H), 2.74 (dd, *J* = 17.3, 1.9 Hz, 1H), 2.67 – 2.63 (m, 1H), 2.44 (s, 3H), 1.73 – 1.50 (m, 2H), 0.91 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 154.0, 149.0, 145.8, 140.1, 134.6, 129.8, 129.0, 127.7, 124.1, 35.2, 33.5, 23.4, 21.9, 11.3.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 402.1124, found: 402.1129

IR ν_{max} (film, cm^{-1}):1724, 1597, 1591, 1174, 1087, 854, 721, 547.

HPLC analysis: 97:3 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 23.8 min, t_{major}= 35.5 min), $[\alpha]_D^{25}$ = 116.0 (c =1.3 , acetone)



2-5a

(*S*)-5-methyl-6-(4-nitrophenyl)-4,5-dihydropyridazin-3(2H)-one (2-5a)

Yield: 40.6 mg, 87%

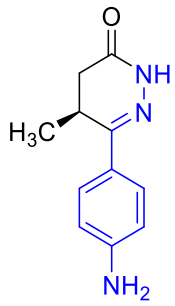
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (brs, 1H), 8.29 – 8.26 (m, 2H), 7.95 – 7.92 (m, 2H), 3.43 – 3.36 (m, 1H), 2.77 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.55 (dd, *J* = 17.0, 0.9 Hz, 1H), 1.29 (d, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 151.6, 148.5, 140.5, 126.8, 124.1, 33.9, 28.2, 16.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 234.0879, found: 234.0869

IR ν_{max} (film, cm^{-1}): 3226, 1681, 1645, 1597, 1514, 1192, 1035, 858, 756, 732.

HPLC analysis: 96:4 er, (CHIRALCEL OJ-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 20.7 min, t_{minor} = 24.3 min), $[\alpha]_D^{25}$ = 476.5 (c = 0.6, acetone)



2-5b

(*S*)-6-(4-aminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (2-5b)

Yield: 25.9 mg, 85%

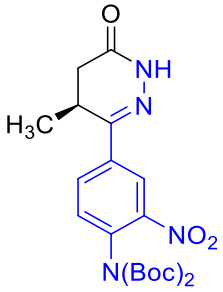
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (brs, 1H), 7.58 (d, *J* = 8.6 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 3.92 (brs, 2H), 3.33-3.27 (m, 1H), 2.68 (dd, *J* = 16.9, 6.8 Hz, 1H), 2.44 (d, *J* = 16.8 Hz, 1H), 1.24 (d, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 154.6, 148.3, 127.5, 124.6, 114.9, 34.0, 28.1, 16.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 204.1137, found: 204.1127

IR ν_{max} (film, cm^{-1}): 3369, 1645, 1608, 1033, 842, 721.

HPLC analysis: 96:4 er, (CHIRALCEL OJ-H column, 254 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 79.9 min, t_{major} = 84.5 min), $[\alpha]_D^{25}$ = 380.5 (c = 0.3, MeOH)



2-6a

(*S*)-6-(4-Di(tert-butyloxycarbonyl)amino-3-nitrophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (2-6a)

Yield: 121.1 mg, 90%

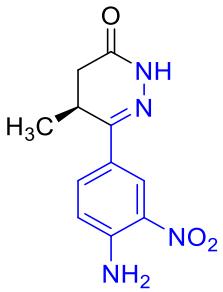
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.99 (bs, 1H), 8.46 (d, *J* = 1.9 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 3.43 - 3.47 (m, 1H), 2.79 (dd, *J* = 17.0, 6.9 Hz, 1H), 2.57 (d, *J* = 17.0 Hz, 1H), 1.44 (s, 18H), 1.31 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.4, 150.8, 150.3, 146.1, 135.6, 134.0, 131.8, 130.5, 122.4, 84.3, 33.8, 28.0, 27.9, 16.3 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 449.2036, found: 449.2035

IR ν_{max} (film, cm^{-1}): 3419, 1797, 1697, 1683, 1593, 1274, 1151, 1120, 738.

HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 254 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 8.5 min, t_{major}= 10.6 min), $[\alpha]_D^{25}$ = 211.1 (c = 0.9, acetone)



2-6b

(*S*)-6-(4-amino-3-nitrophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (2-6b)

Yield: 47.6 mg, 96%

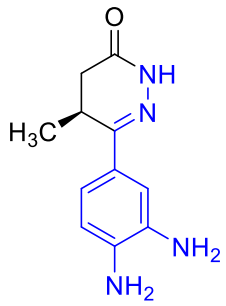
^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, *J* = 2.1 Hz, 1H), 7.93 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 1H), 4.59 (brs, 2H), 3.43 – 3.39 (m, 1H), 2.74 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.37 (dd, *J* = 17.0, 1.4 Hz, 1H), 1.18 (d, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, MeOD) δ 169.4, 154.5, 148.3, 134.0, 131.9, 124.6, 123.9, 120.6, 34.5, 28.6, 16.4 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 249.0988, found: 249.0980

IR ν_{max} (film, cm^{-1}): 3444, 1633, 1265, 1076, 958, 721.

HPLC analysis: 96:4 er, (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{major} = 12.3 min, t_{minor}= 18.9 min), $[\alpha]_D^{25}$ = 122.7 (c = 0.3, MeOH)



2-6c

(*S*)-6-(3,4-diaminophenyl)-5-methyl-4,5-dihydropyridazin-3(2H)-one (6c)

Yield: 15.3 mg, 70%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (brs, 1H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.07 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 3.54 (brs, 4H), 3.33 – 3.26 (m, 1H), 2.68 (dd, *J* = 16.9, 6.8 Hz, 1H), 2.43 (d, *J* = 16.8 Hz, 1H), 1.23 (d, *J* = 7.4 Hz, 3H) ppm.

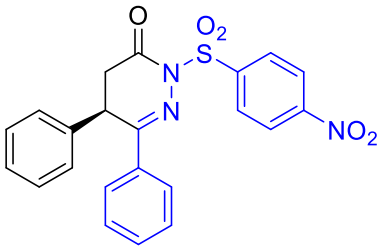
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 154.7, 137.5, 134.5, 126.1, 118.9, 115.7, 114.1, 33.9, 28.0, 16.5 ppm.

HRMS (ESI, m/z): calcd. for $[M+H]^+$: 219.1246, found: 219.1239

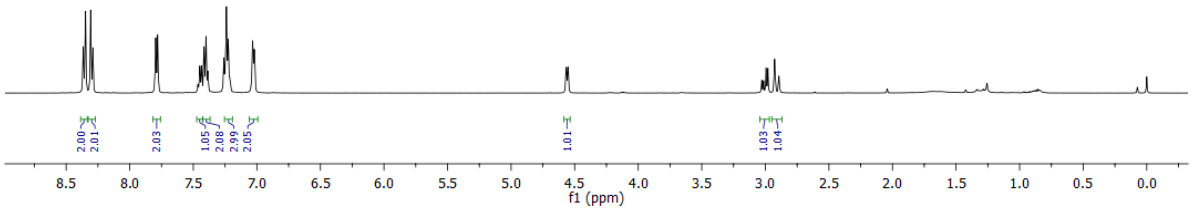
IR ν_{max} (film, cm^{-1}): 3417, 1645, 1078, 1037, 952, 721.

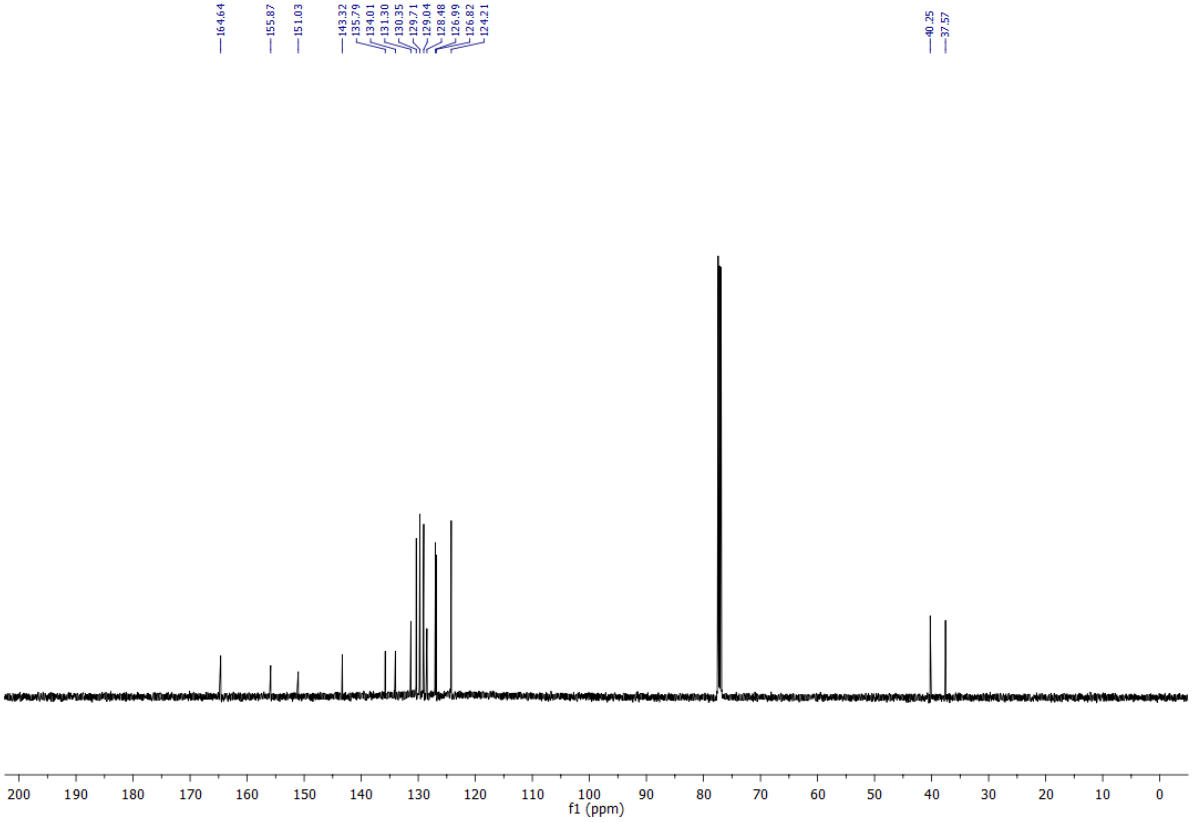
HPLC analysis: 96:4 er, (CHIRALCEL AD-H column, 220 nm, *n*-hexane/*i*-PrOH = 70/30, flow rate = 0.7 mL/min, t_{minor} = 29.8 min, t_{major}=31.4 min), $[\alpha]_D^{25}$ = 60.3 (c = 1.1, MeOH)

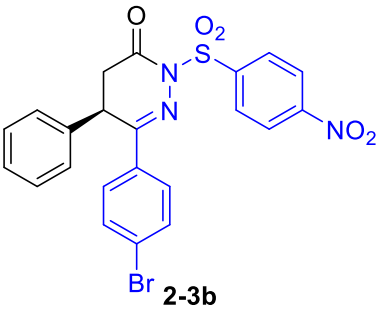
2.4.5. ^{1}H, ^{13}C, and ^{19}F NMR Spectra



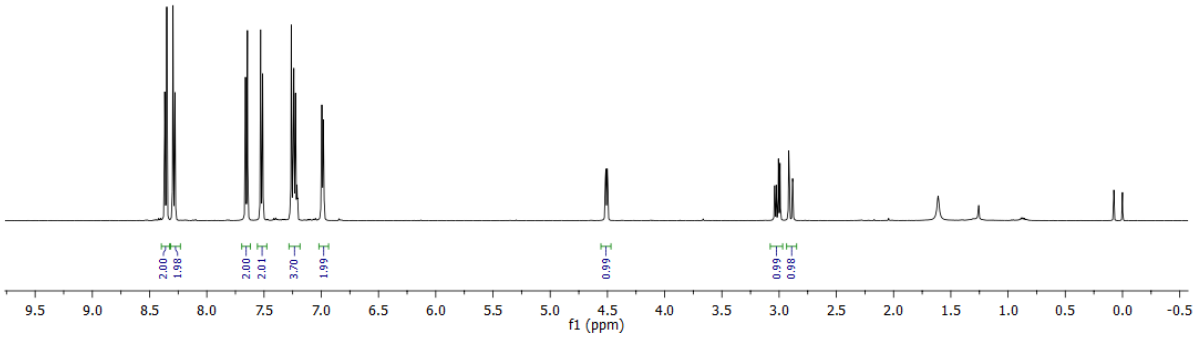
2-3a

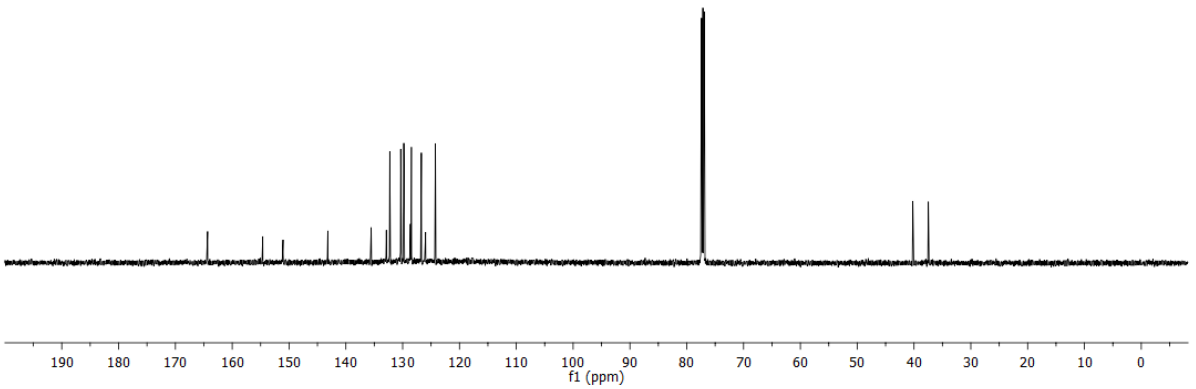


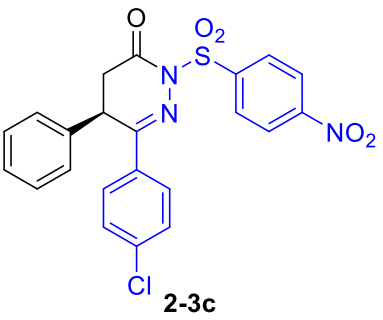




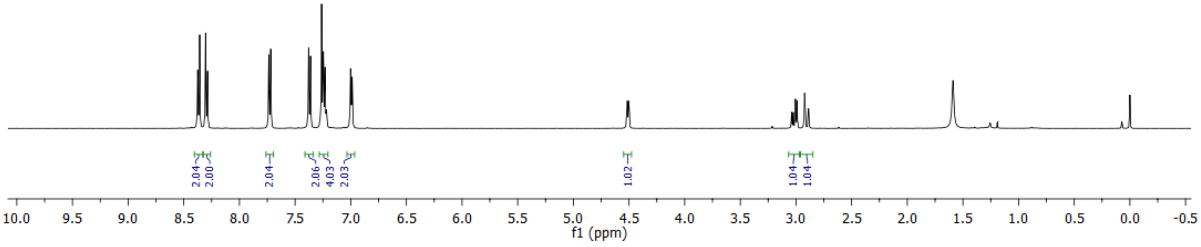
2-3b

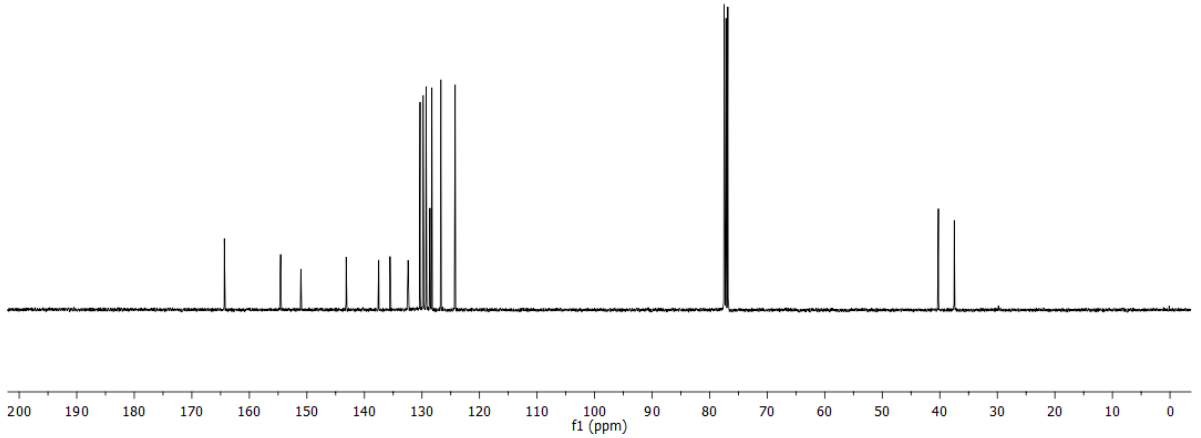


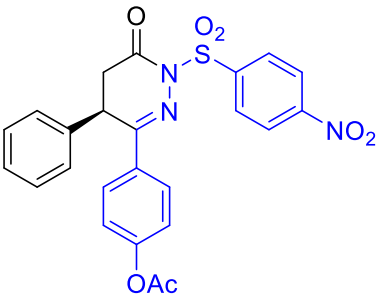




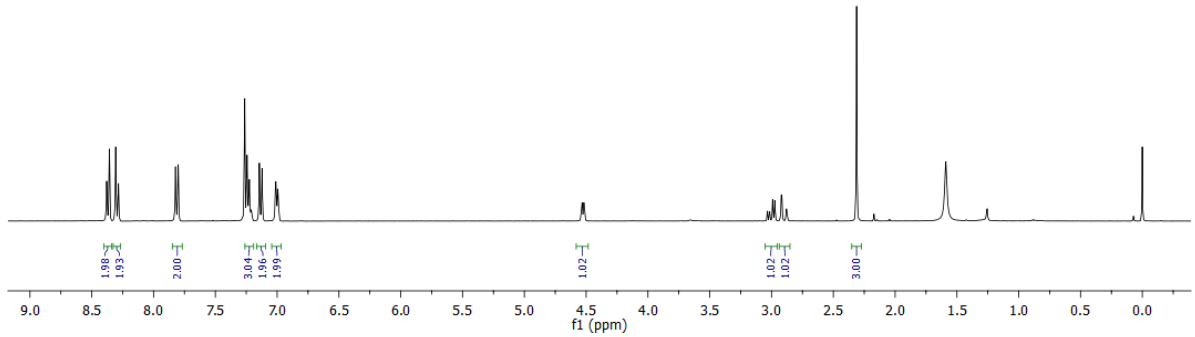
2-3c

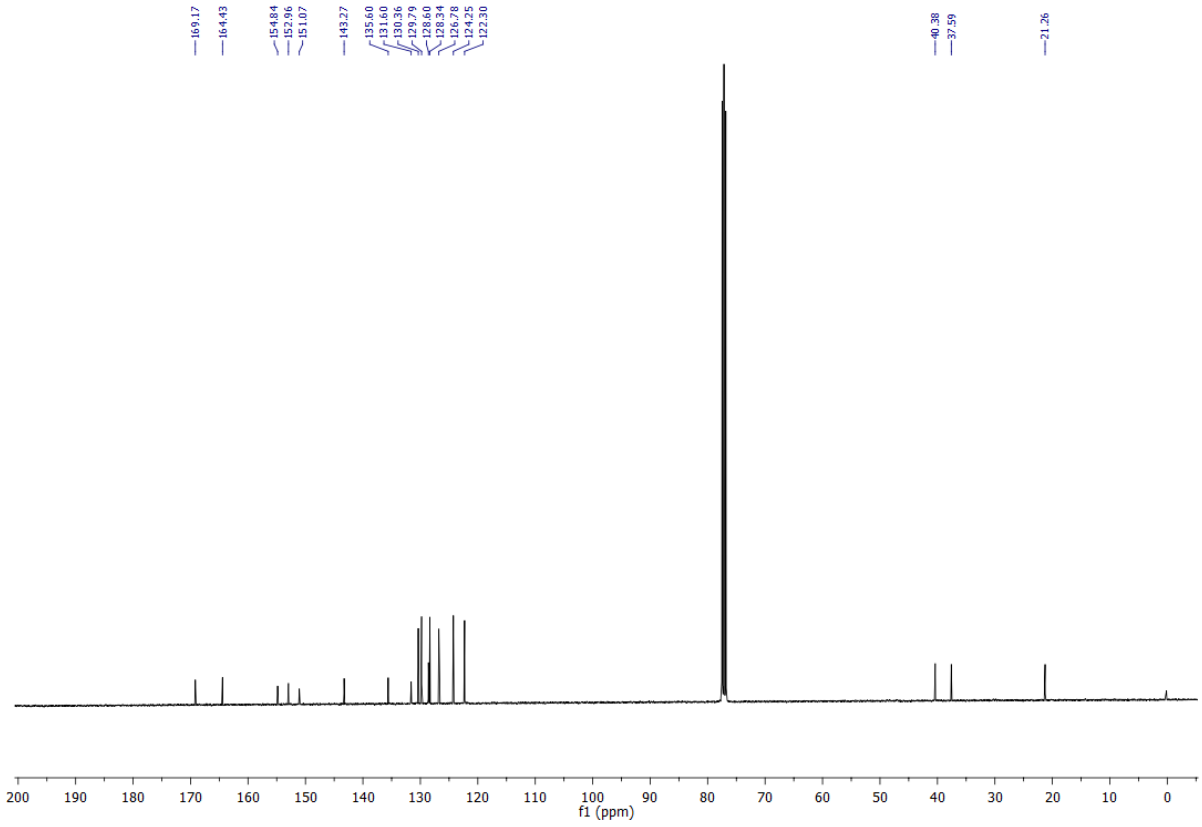


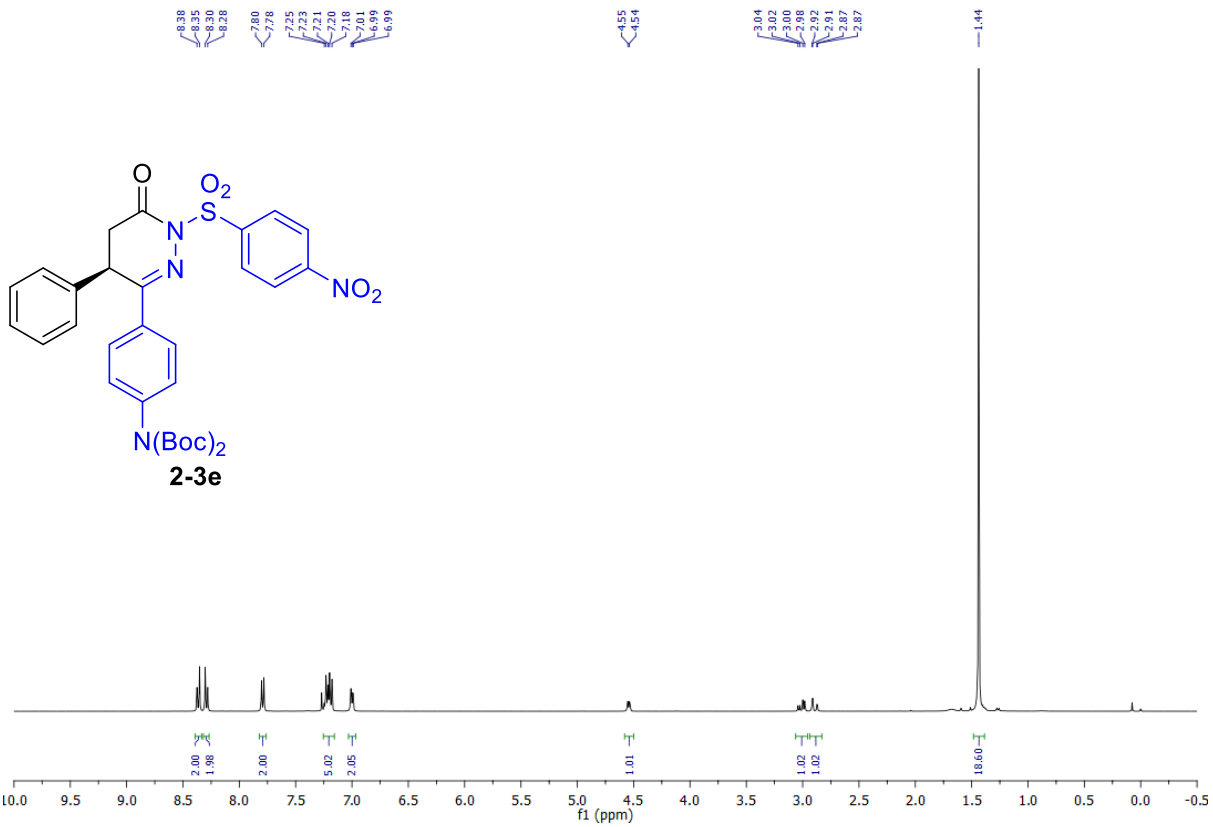



O
O2
S
N
N
NO2
OAc

2-3d

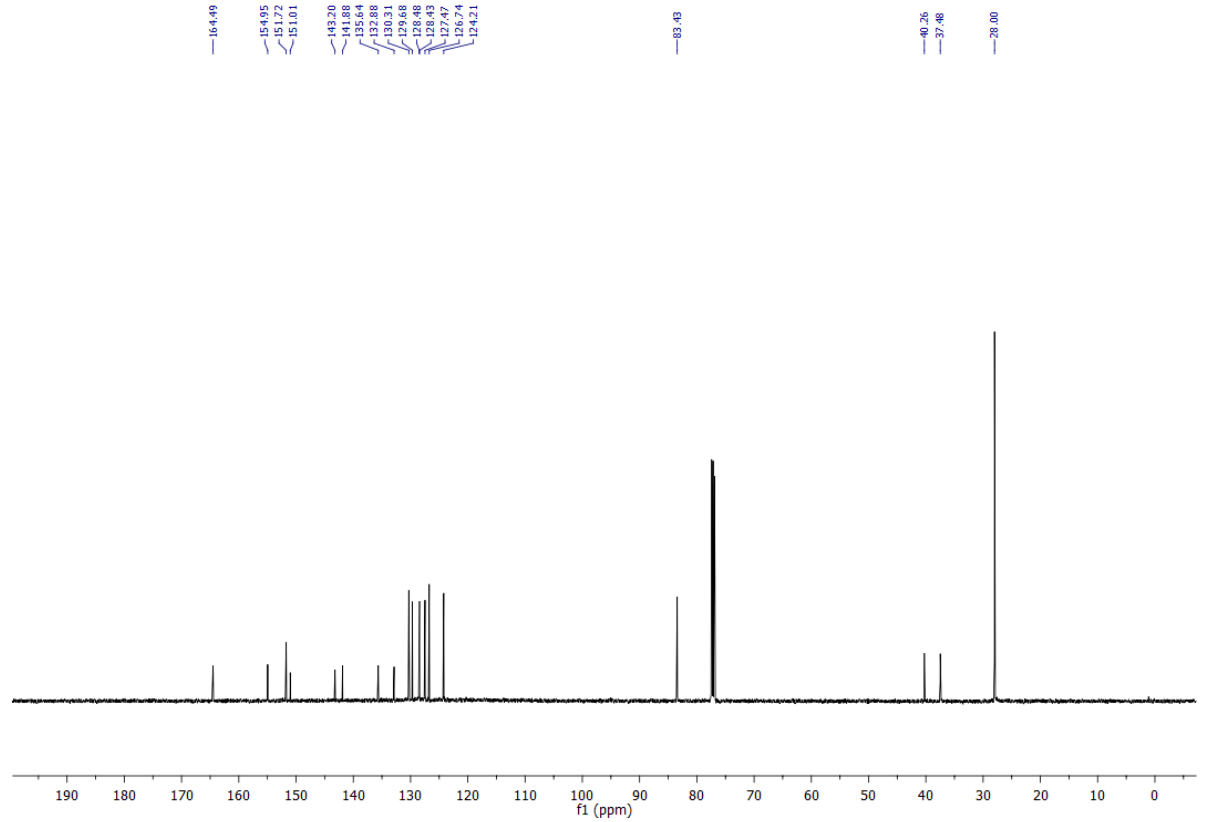

8.38
8.36
8.31
8.28
7.82
7.80
7.24
7.23
7.21
7.20
7.14
7.12
7.01
6.99
4.53
4.52
3.03
3.02
2.99
2.97
2.92
2.88
2.87
2.31
1.98
1.93
2.00
3.04
1.96
1.99
1.02
1.02
1.02
3.00
f1 (ppm)

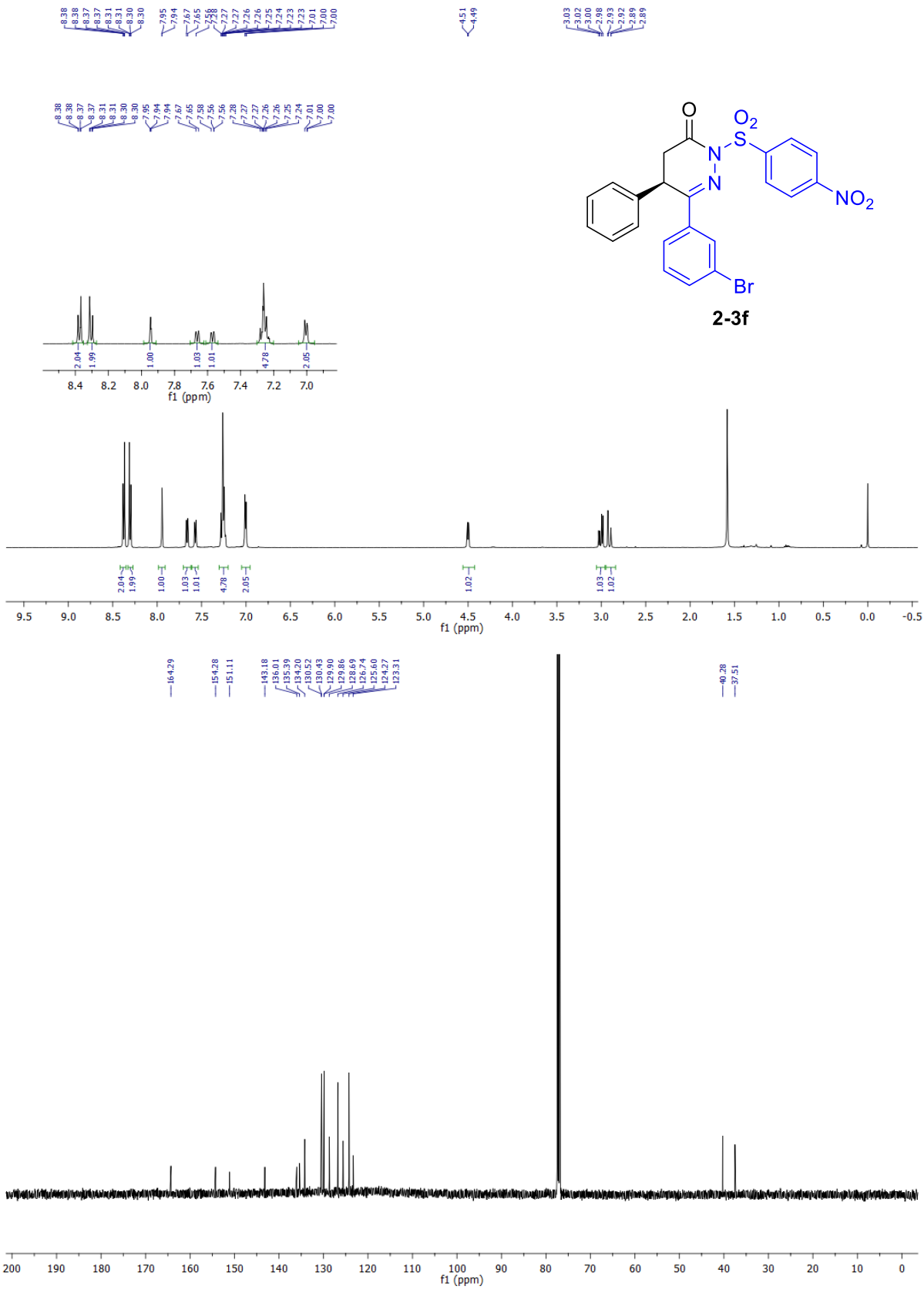

169.17
164.43
154.84
152.96
151.07
143.27
135.60
131.60
130.36
129.79
128.60
128.34
126.78
124.25
122.30
40.38
37.59
21.26
f1 (ppm)


O
O2
S
N
N
NO2
N(Boc)2

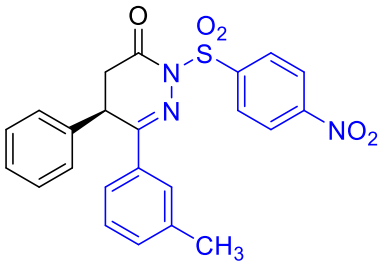
2-3e

8.38
8.35
8.30
8.28
7.80
7.78
7.25
7.23
7.21
7.20
7.18
7.01
6.99
6.99
4.55
4.54
3.04
3.02
3.00
2.98
2.92
2.91
2.87
2.87
1.44
2.00
1.98
2.00
5.02
2.05
1.01
1.02
1.02
18.60
f1 (ppm)

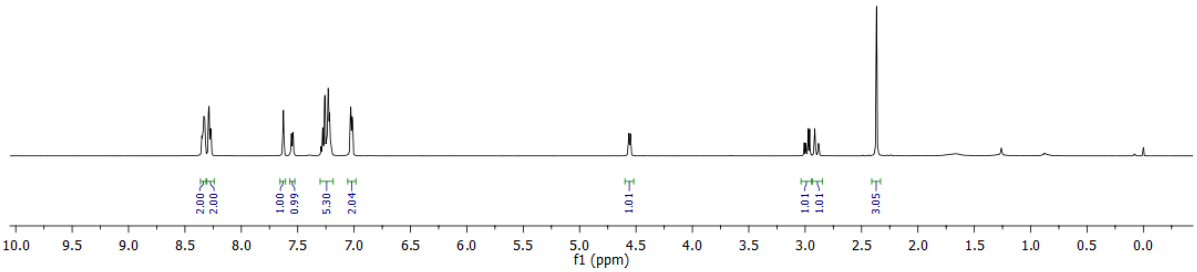

164.49
154.95
151.72
151.01
143.20
141.88
135.64
132.88
130.31
129.68
128.48
128.43
127.47
126.74
124.21
83.43
40.26
37.48
28.00
f1 (ppm)

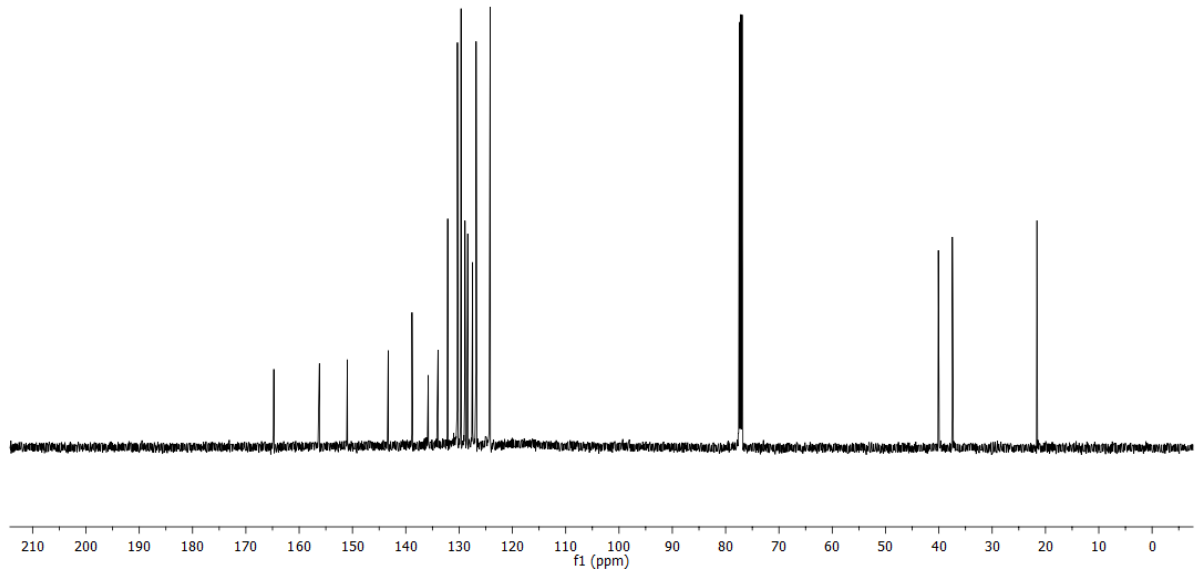


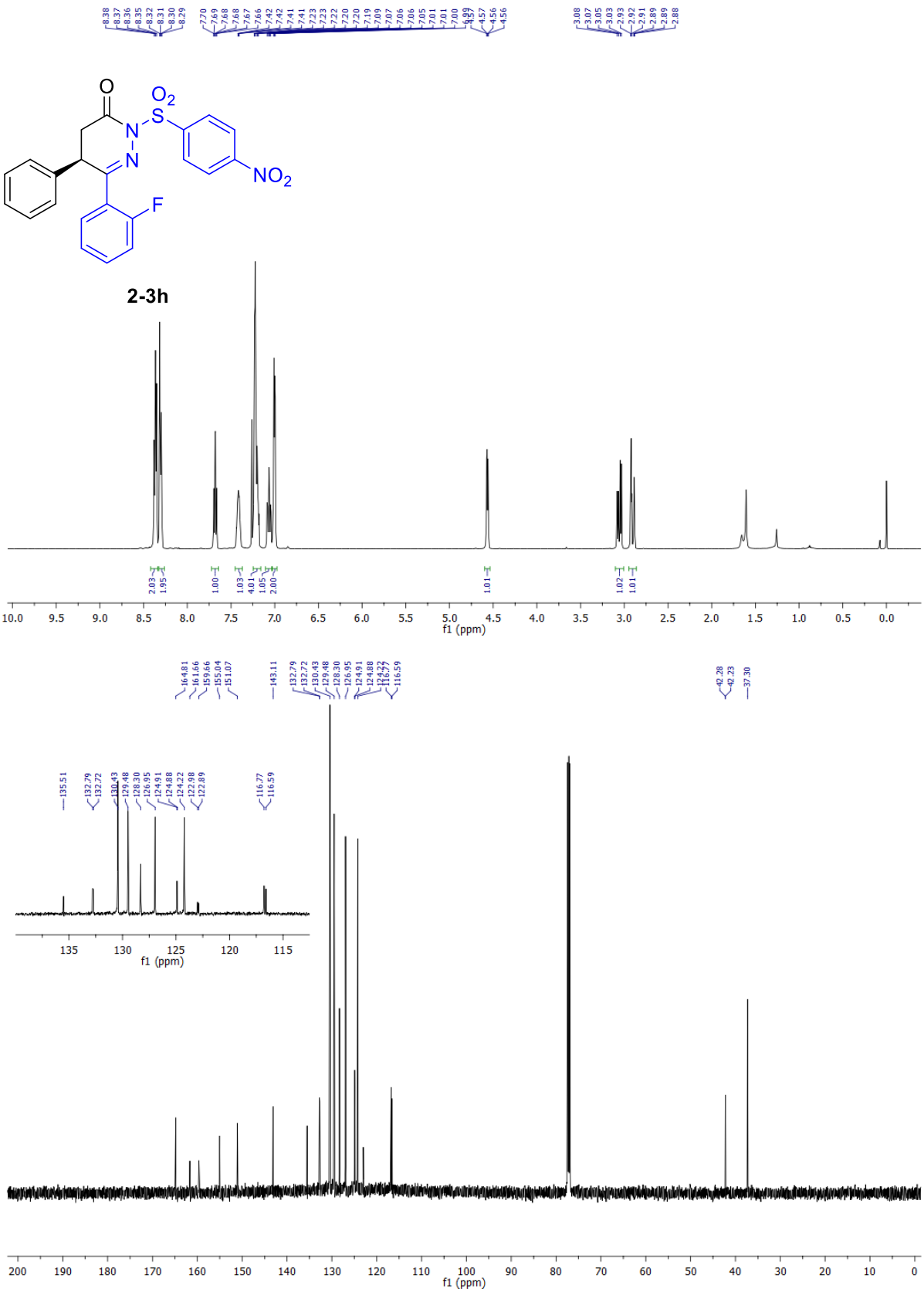
2-3f

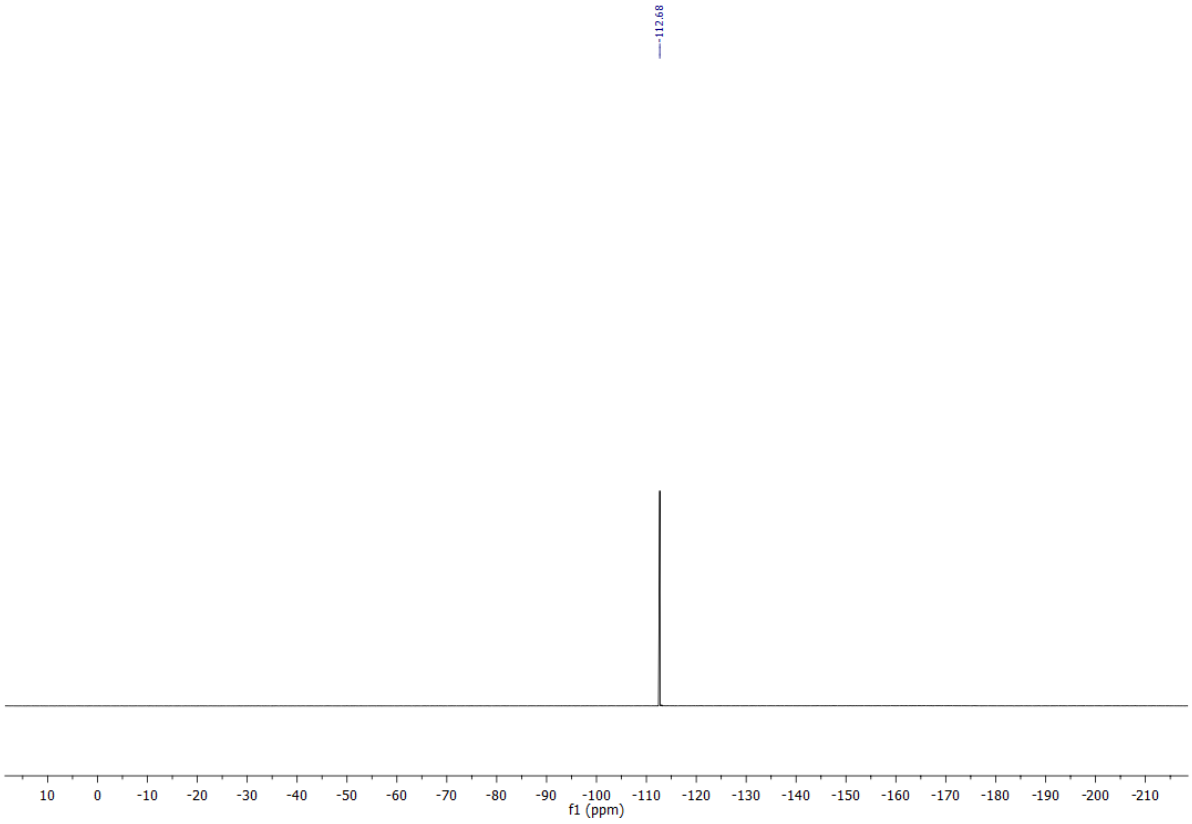


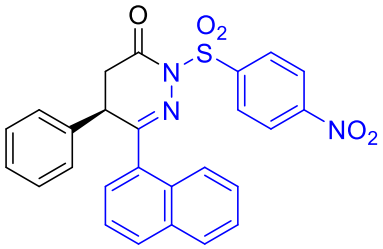
2-3g



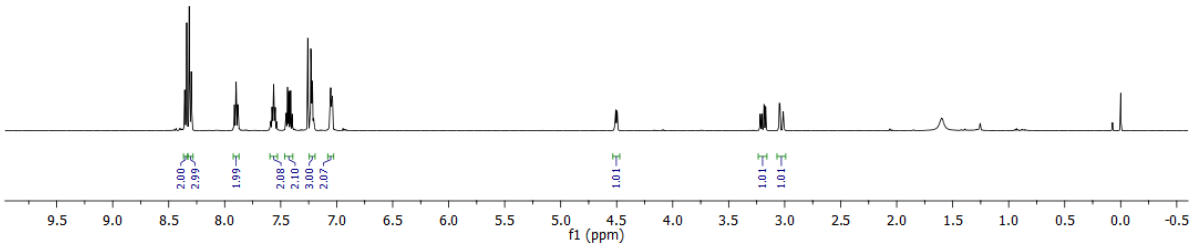


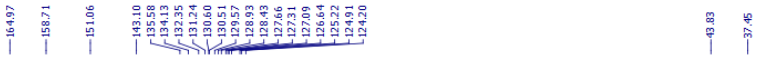

2-3h
f1 (ppm)
f1 (ppm)

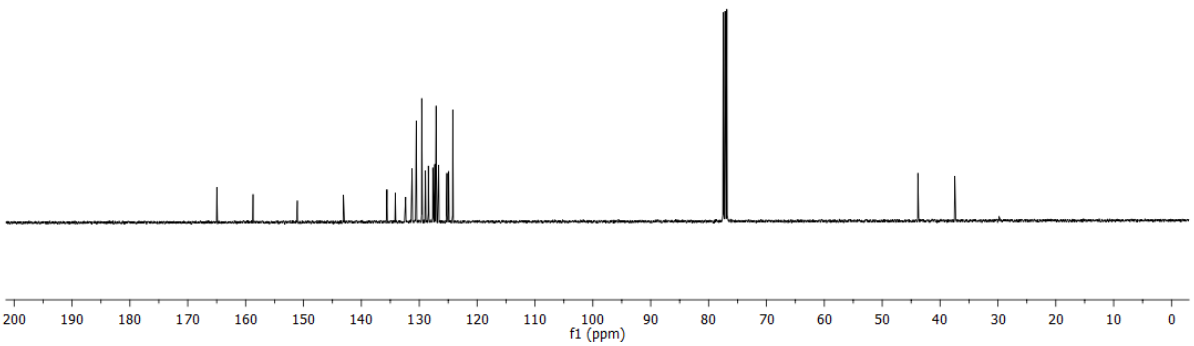

-112.68
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

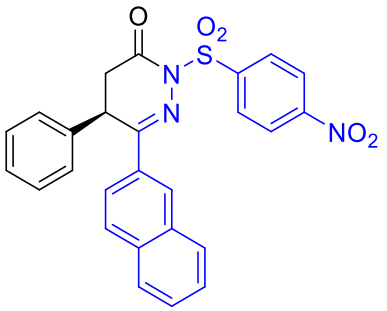


2-3i

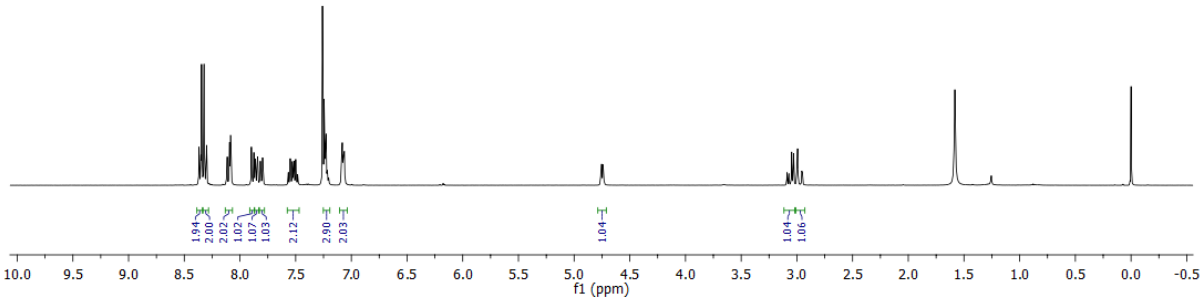


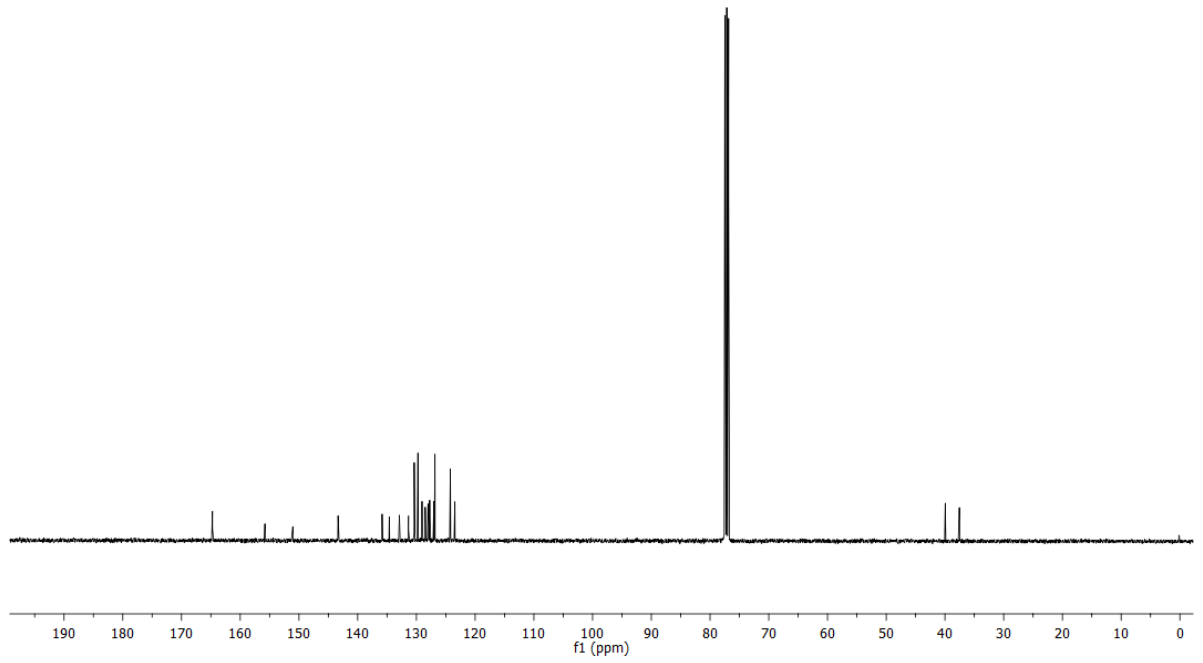


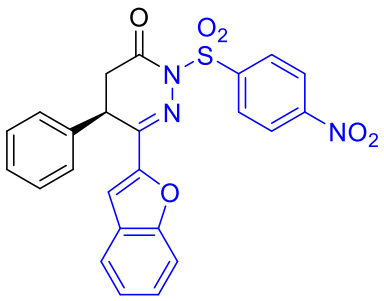




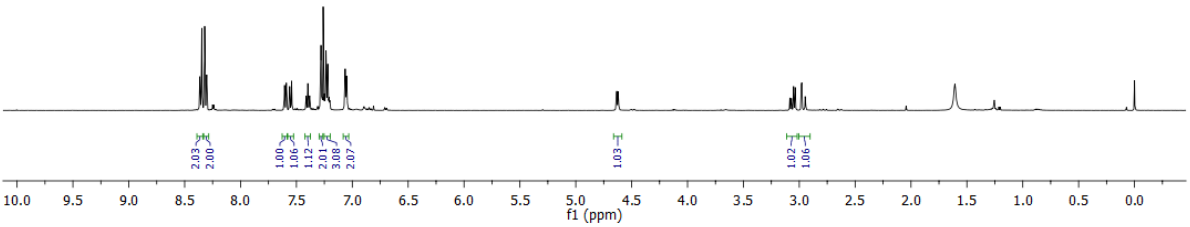
2-3j

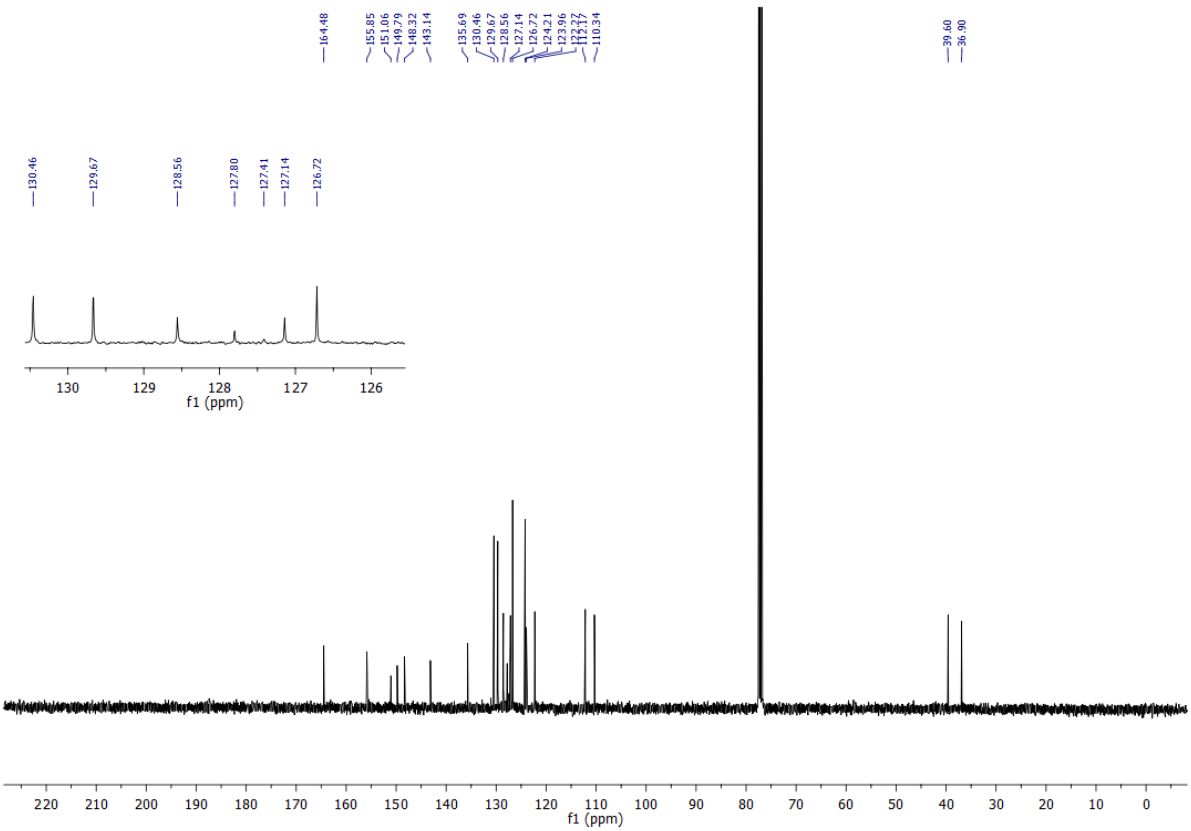


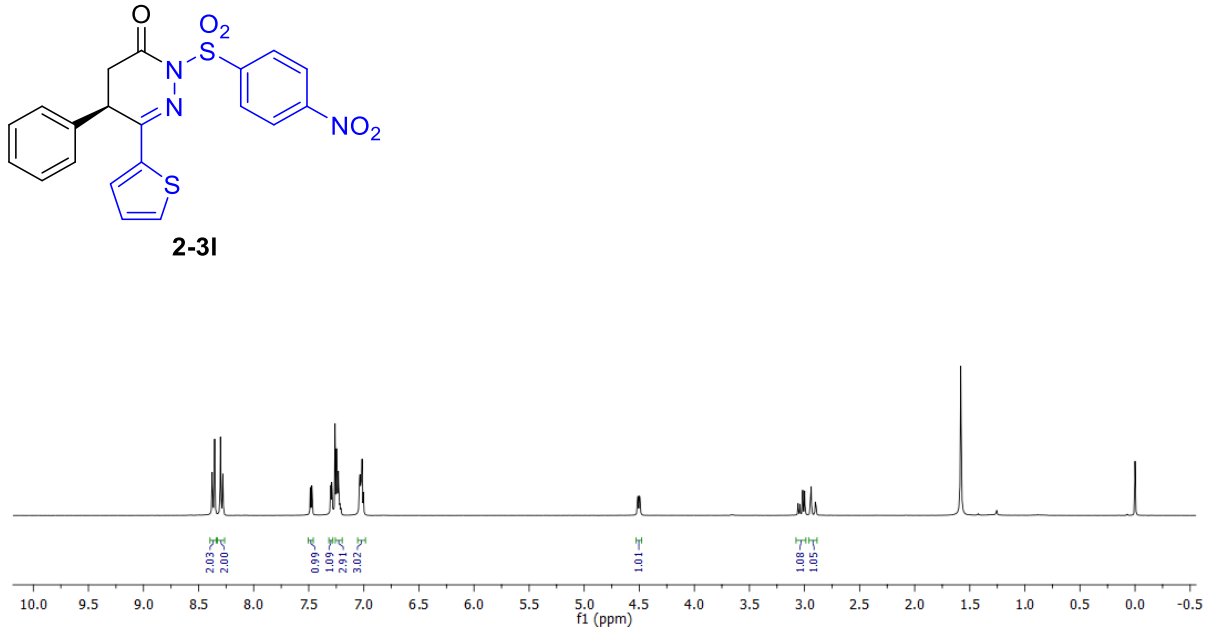




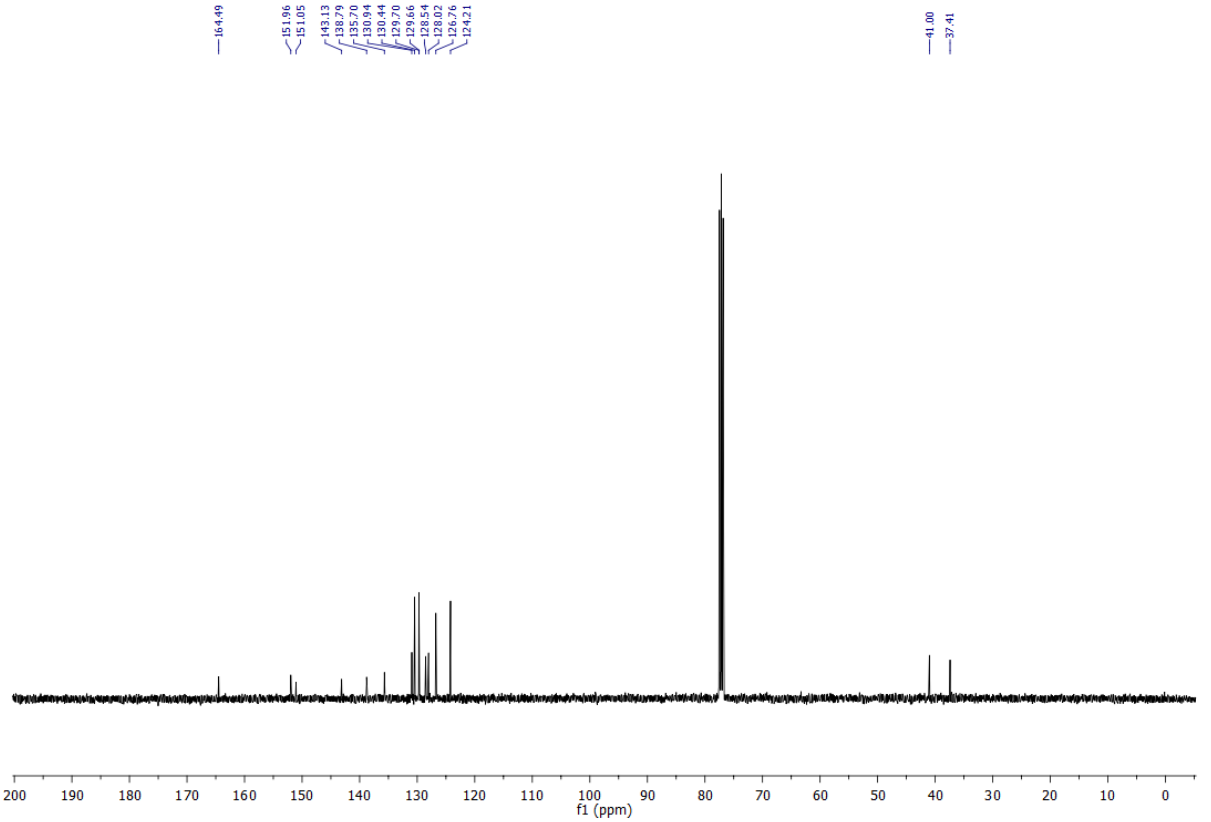
2-3k



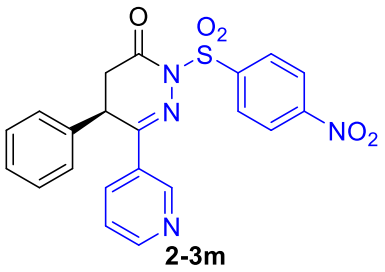



8.38
8.35
8.30
8.28
7.49
7.47
7.30
7.29
7.25
7.23
7.22
7.22
7.21
7.03
7.03
7.02
7.00
4.51
4.50
3.06
3.04
3.02
3.00
2.94
2.94
2.90
2.90
O
O2
S
N
N
NO2
S
2.03
2.00
0.99
1.09
2.91
3.02
1.01
1.08
1.05
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

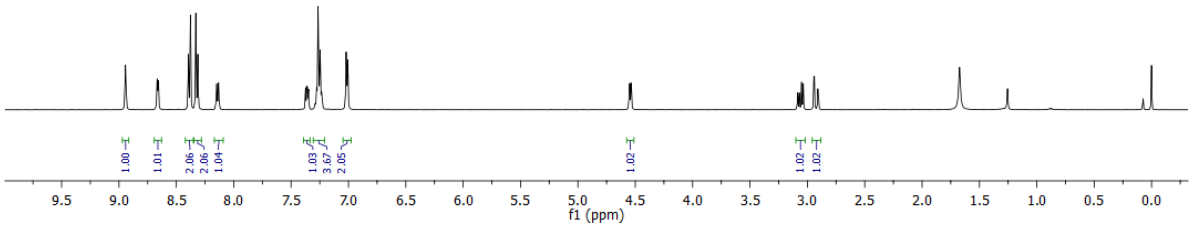
2-3l

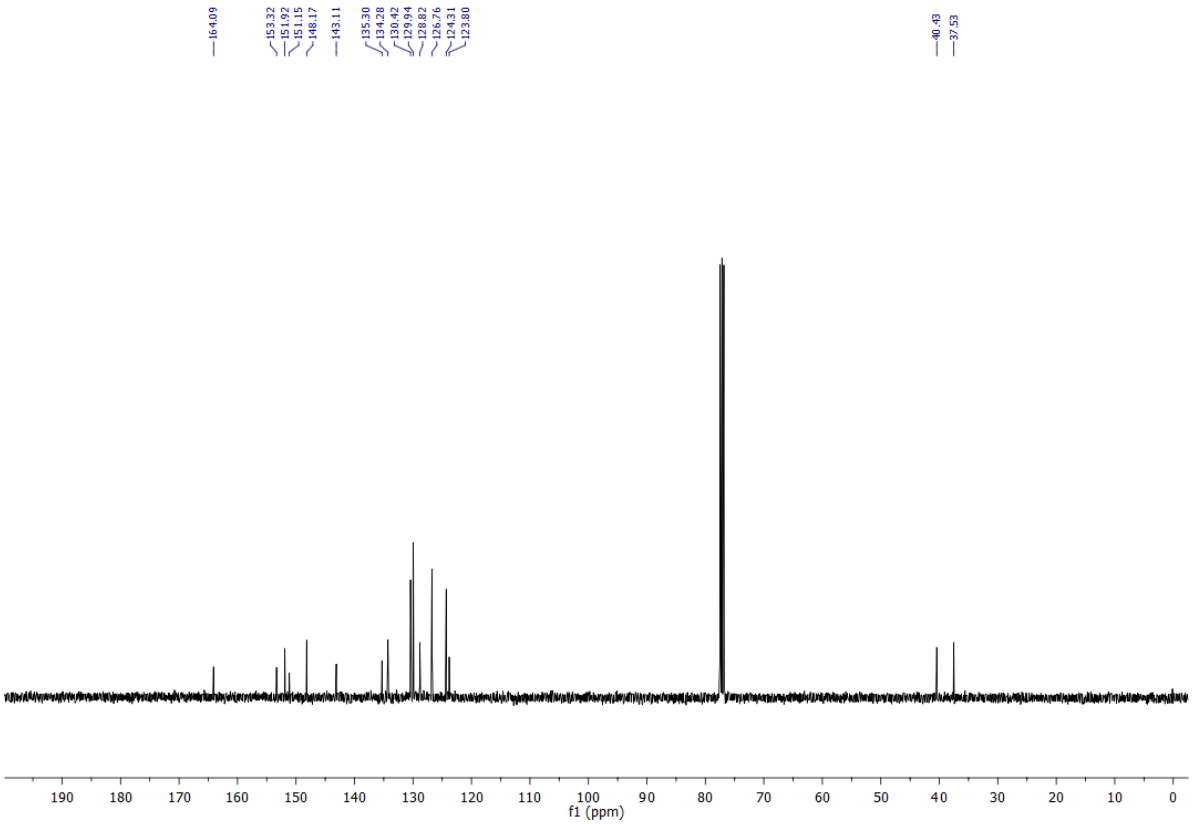

164.49
151.96
151.05
143.13
138.79
135.70
130.94
130.44
129.70
129.66
128.54
128.02
126.76
124.21
41.00
37.41
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

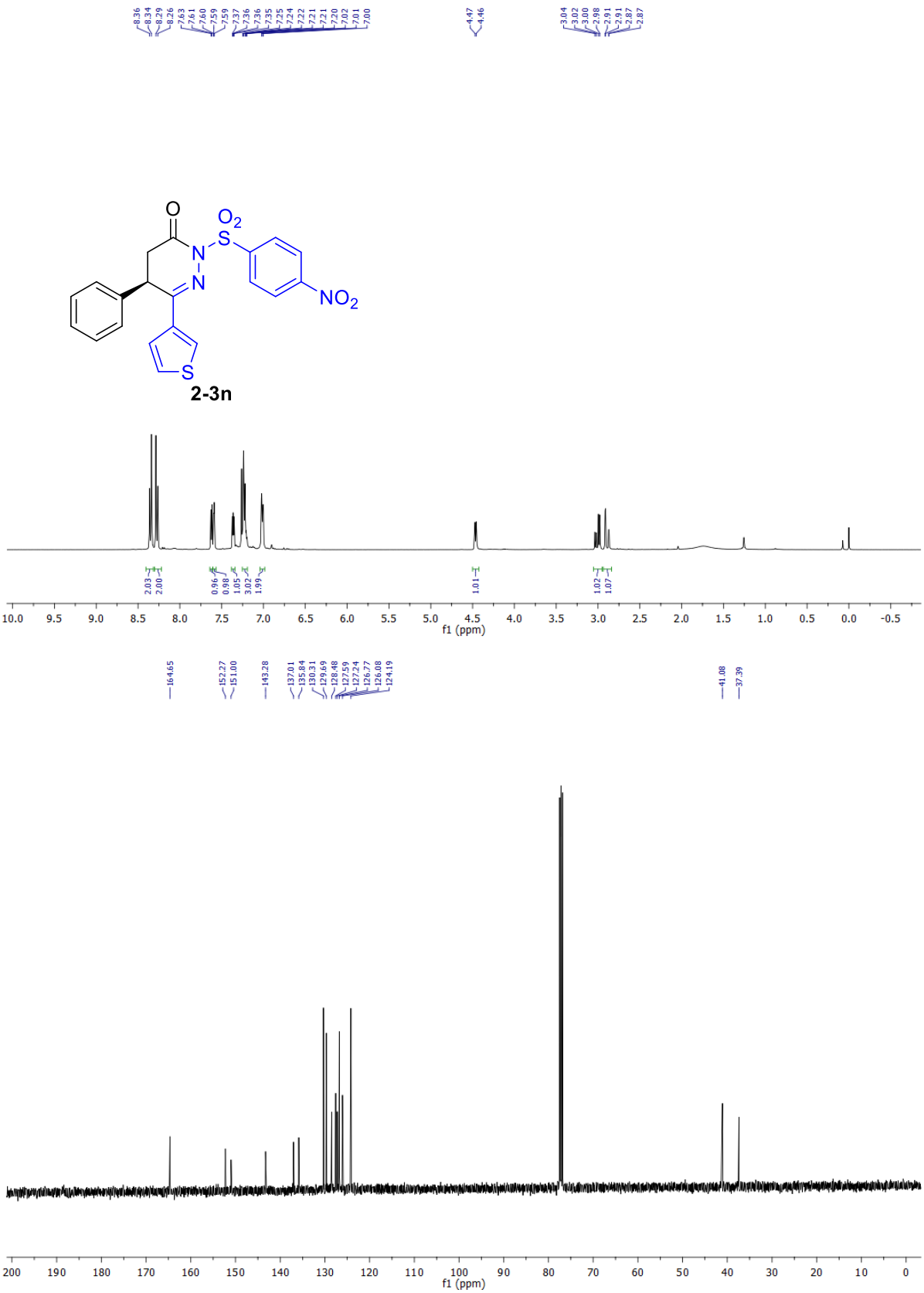

8.94
8.94
8.67
8.66
8.39
8.38
8.33
8.31
8.15
8.13
7.37
7.36
7.36
7.35
7.29
7.28
7.27
7.25
7.23
7.02
7.01
4.55
4.54
3.08
3.07
3.05
3.04
2.94
2.94
2.91
2.91

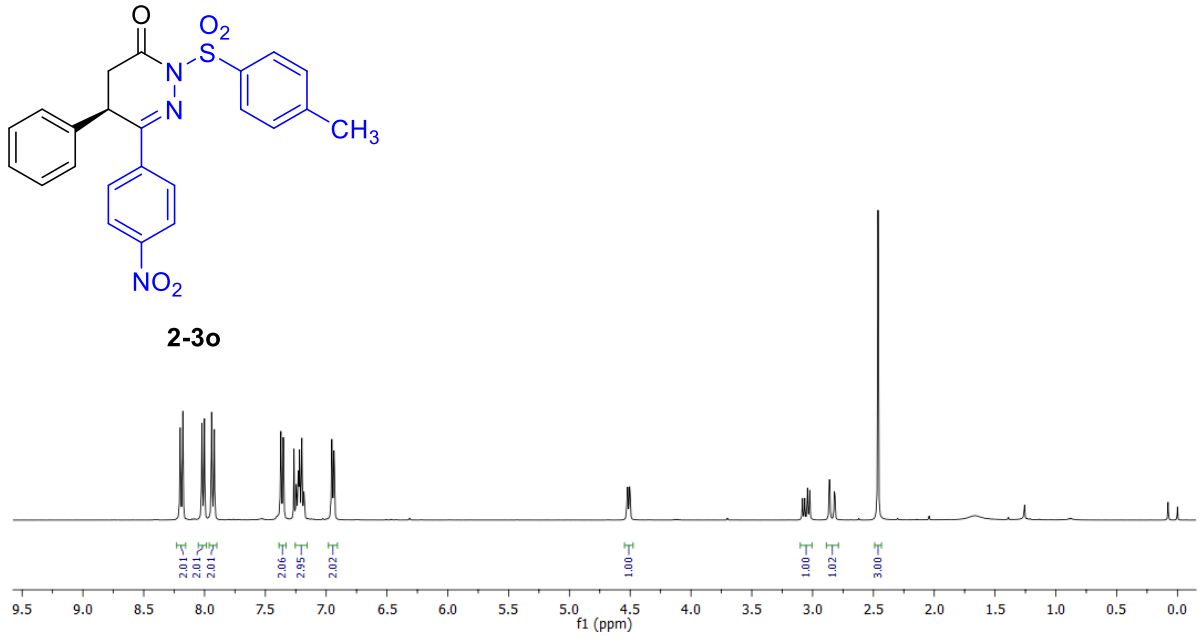

O
O2
S
N
N
NO2
N

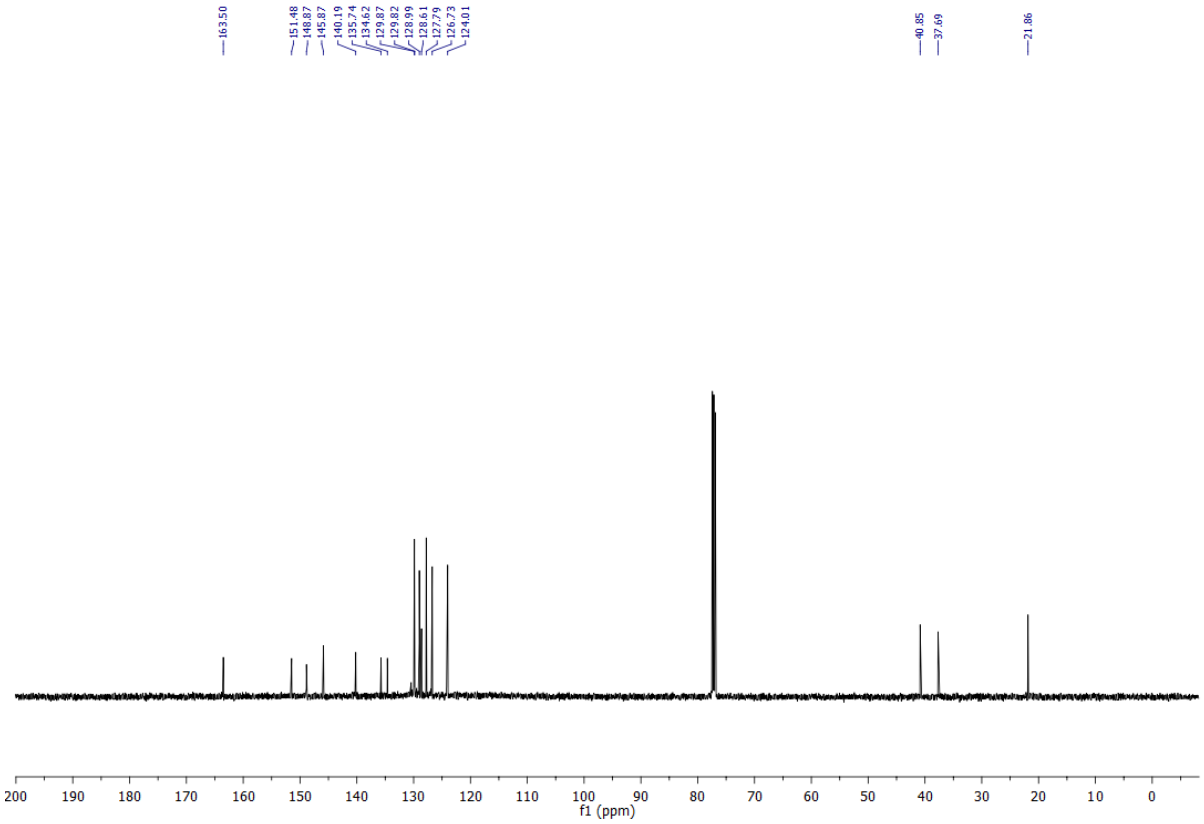
2-3m

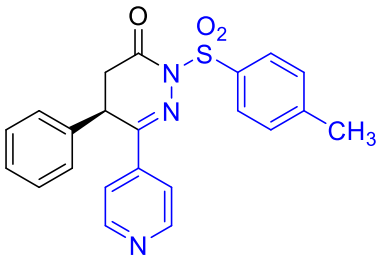

1.00
1.01
2.06
2.06
1.04
1.03
3.67
2.05
1.02
1.02
1.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


164.09
153.32
151.92
151.15
148.17
143.11
135.30
134.28
130.42
129.94
128.82
126.76
124.31
123.80
40.43
37.53
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


8.36
8.34
8.29
8.26
7.63
7.61
7.60
7.59
7.59
7.37
7.36
7.36
7.35
7.25
7.24
7.22
7.21
7.21
7.20
7.02
7.01
7.00
4.47
4.46
3.04
3.02
3.00
2.98
2.91
2.91
2.87
2.87
O
O2
S
N
N
NO2
S
2-3n
2.03
2.00
0.96
0.98
1.05
3.02
1.99
1.01
1.02
1.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)
164.65
152.27
151.00
143.28
137.01
135.84
130.31
129.69
128.48
127.59
127.24
126.77
126.08
124.19
41.08
37.39
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

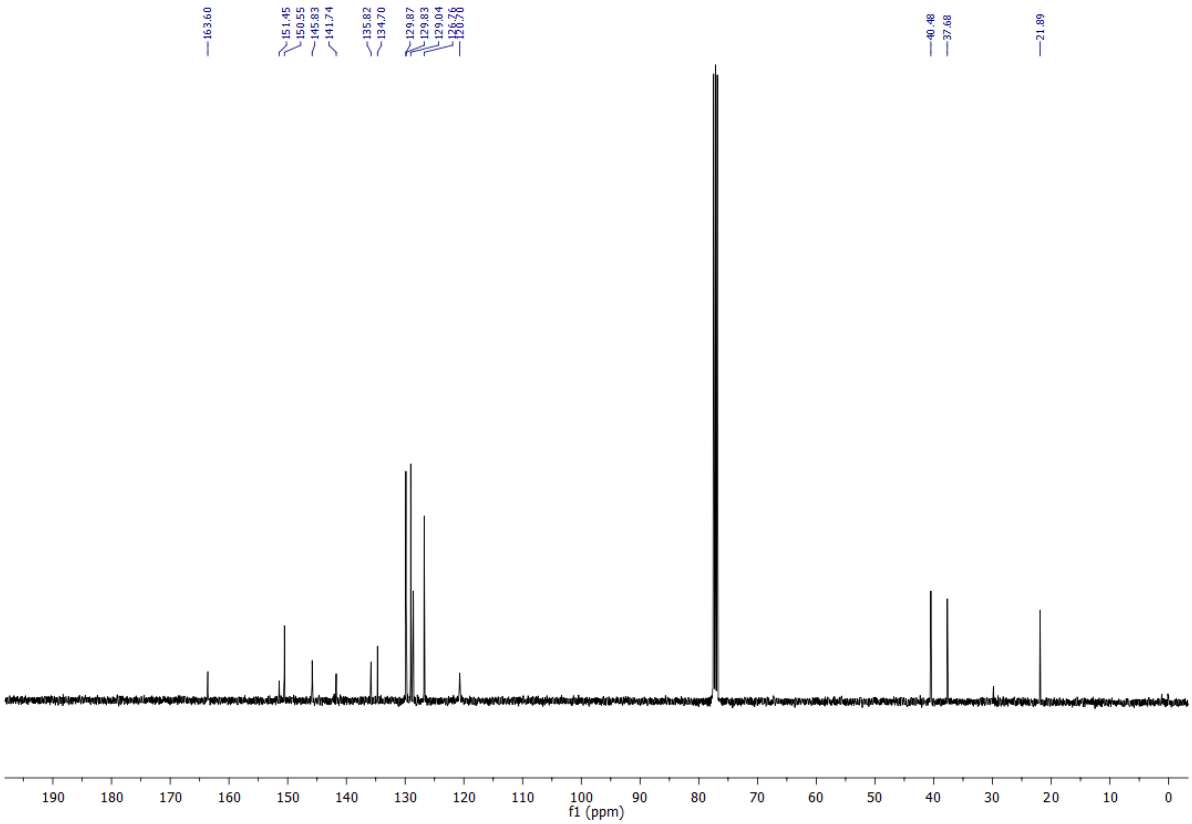

8.20
8.18
8.02
8.00
7.94
7.92
7.37
7.35
7.25
7.23
7.22
7.20
7.18
6.95
6.94
4.52
4.51
3.08
3.06
3.04
3.02
2.86
2.86
2.82
2.82
2.46
O
O2
S
N
N
CH3
NO2
2-3o
2.01
2.01
2.01
2.06
2.95
2.02
1.00
1.00
1.02
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


163.50
151.48
148.87
145.87
140.19
135.74
134.62
129.87
129.82
128.99
128.61
127.79
126.73
124.01
40.85
37.69
21.86
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

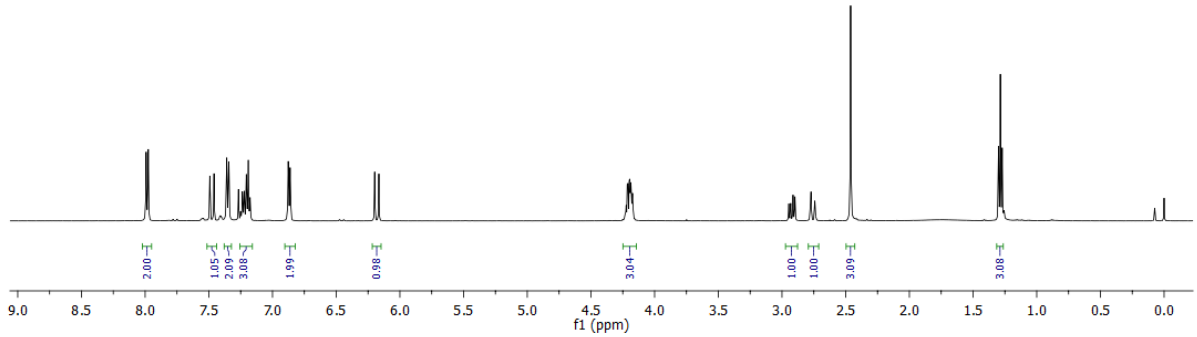

O
O2
S
N
N
CH3
N

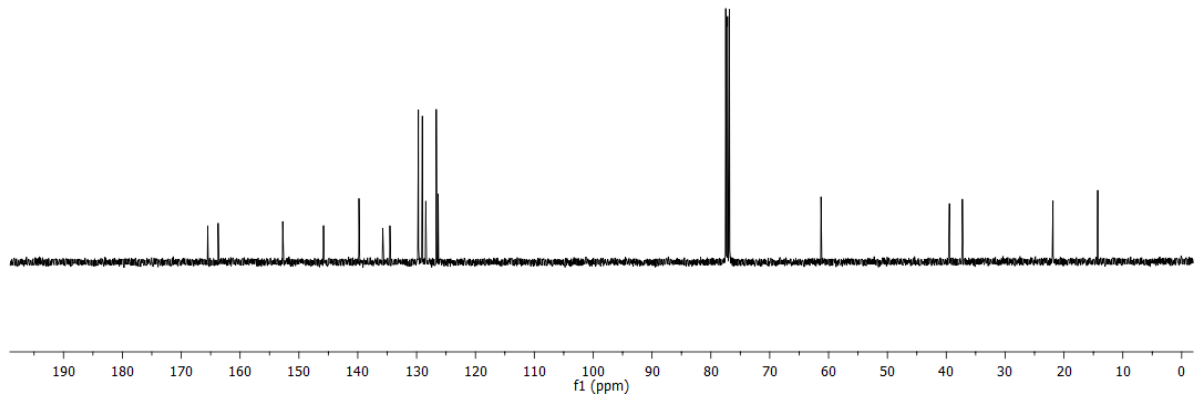
2-3p

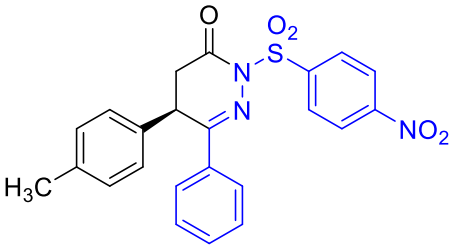
8.65
8.03
8.01
7.62
7.61
7.37
7.35
7.26
7.25
7.24
7.23
7.22
7.20
7.18
7.18
6.94
6.92
4.45
4.44
3.05
3.04
3.01
2.99
2.86
2.85
2.81
2.81
2.46
1.97
2.00
1.98
2.07
2.96
2.02
1.03
1.04
1.04
3.06
f1 (ppm)


163.60
151.45
150.55
145.83
141.74
135.82
134.70
129.87
129.83
129.04
128.78
120.70
40.48
37.68
21.89
f1 (ppm)

2-3q

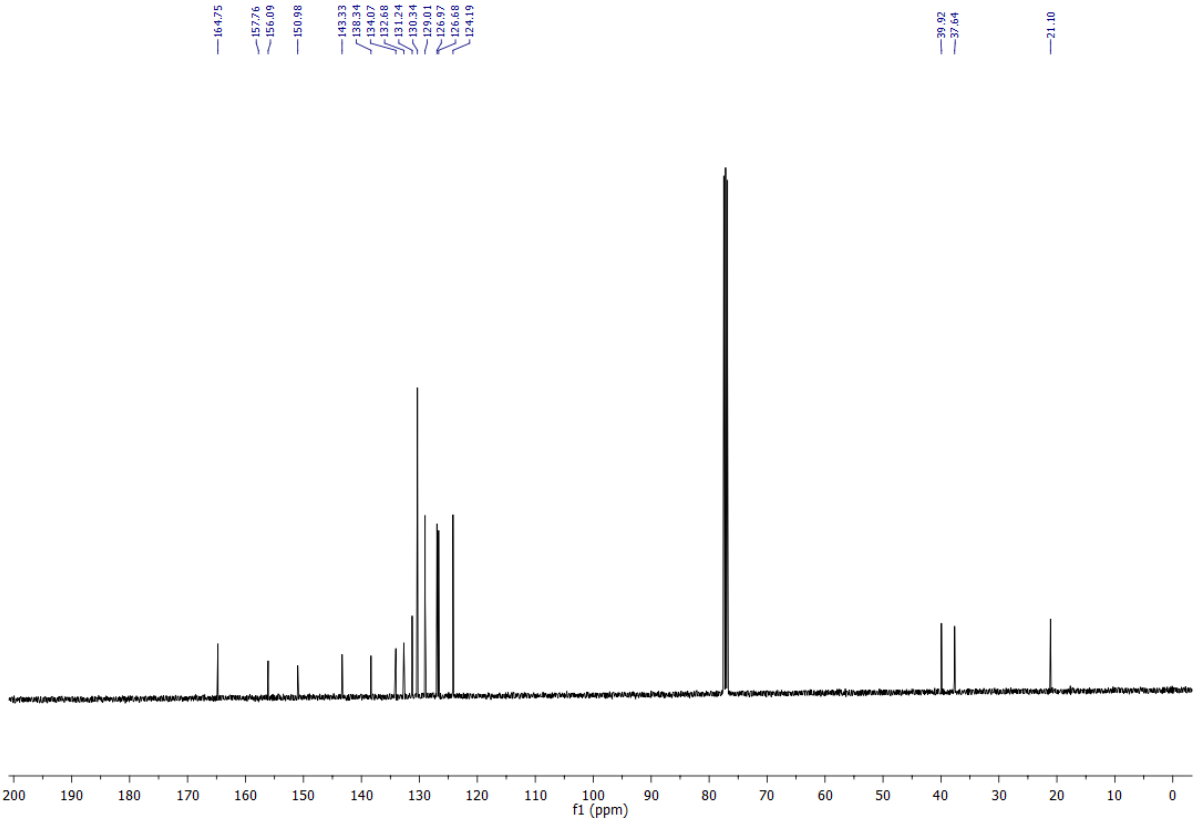


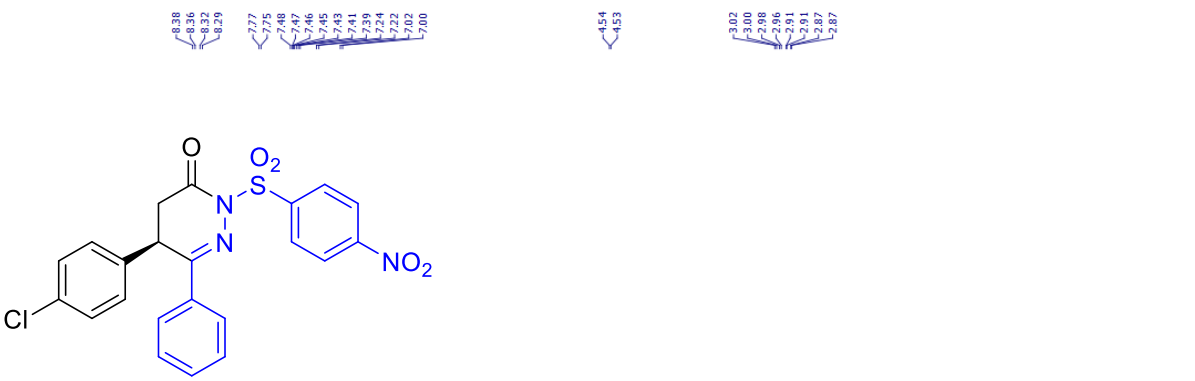



O
O_2
S
N
N
NO_2
H_3C

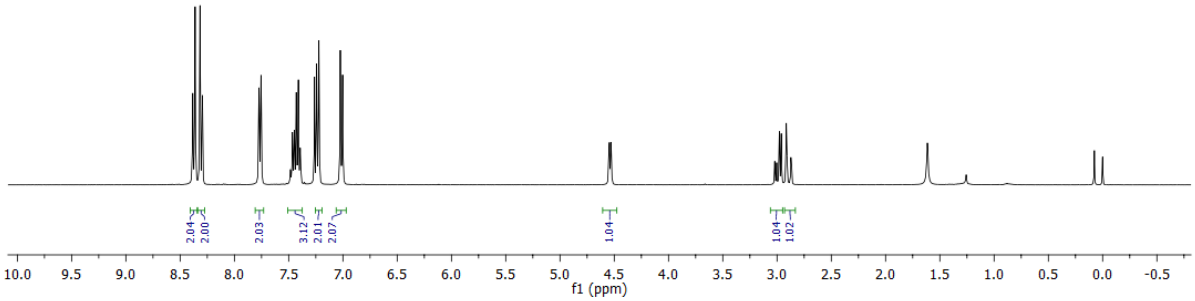
2-4a

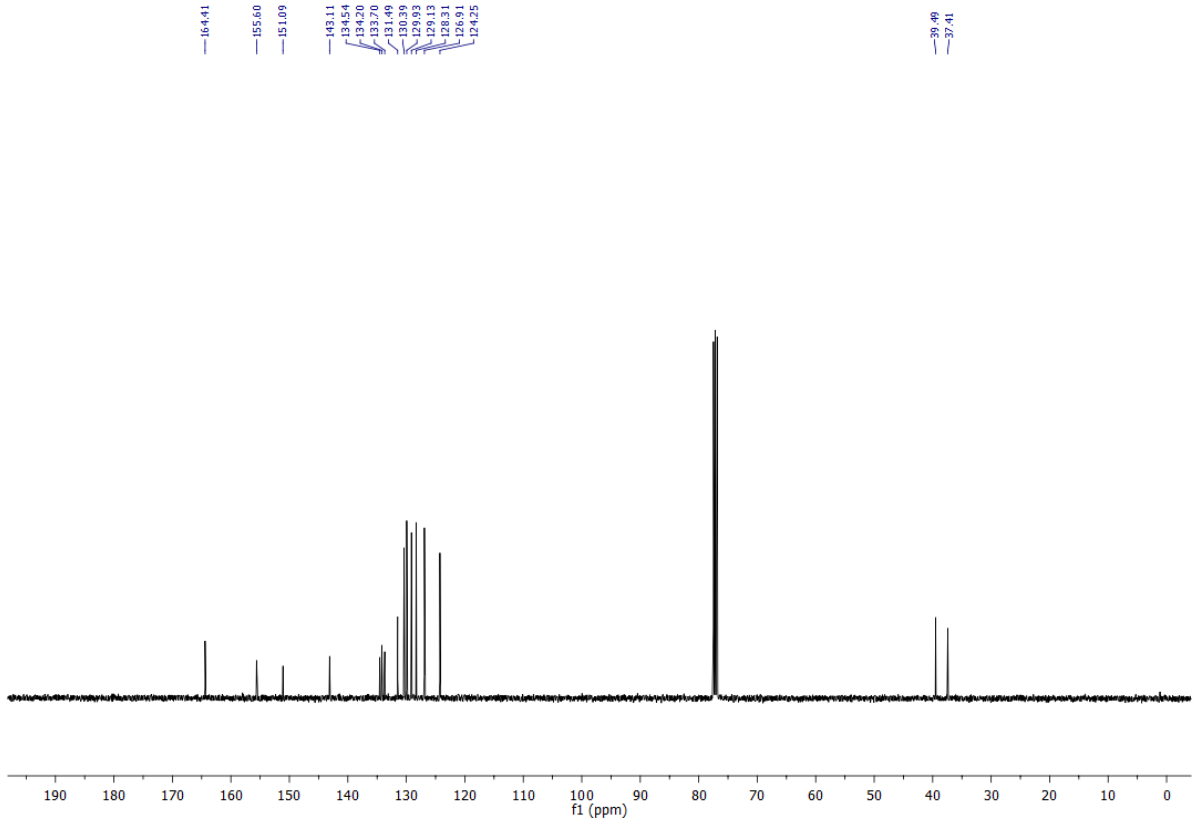
8.37
8.35
8.31
8.29
7.79
7.78
7.77
7.43
7.41
7.03
7.01
6.91
6.89
4.52
4.51
3.01
3.00
2.97
2.95
2.90
2.90
2.86
2.86
2.27
2.00
1.92
1.98
3.00
1.98
2.00
0.97
1.00
1.01
3.01
f1 (ppm)

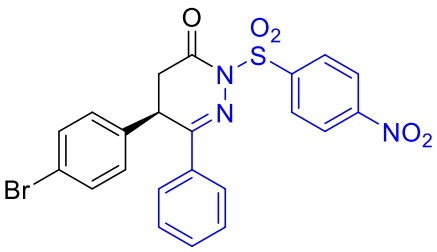

164.75
157.76
156.09
150.98
143.33
138.34
134.07
132.68
131.24
130.34
129.01
126.97
126.68
124.19
39.92
37.64
21.10
f1 (ppm)


8.38
8.36
8.32
8.29
7.77
7.75
7.48
7.47
7.46
7.45
7.43
7.41
7.39
7.24
7.22
7.02
7.00
4.54
4.53
3.02
3.00
2.98
2.96
2.91
2.91
2.87
2.87
O
O2
S
N
N
NO2
Cl

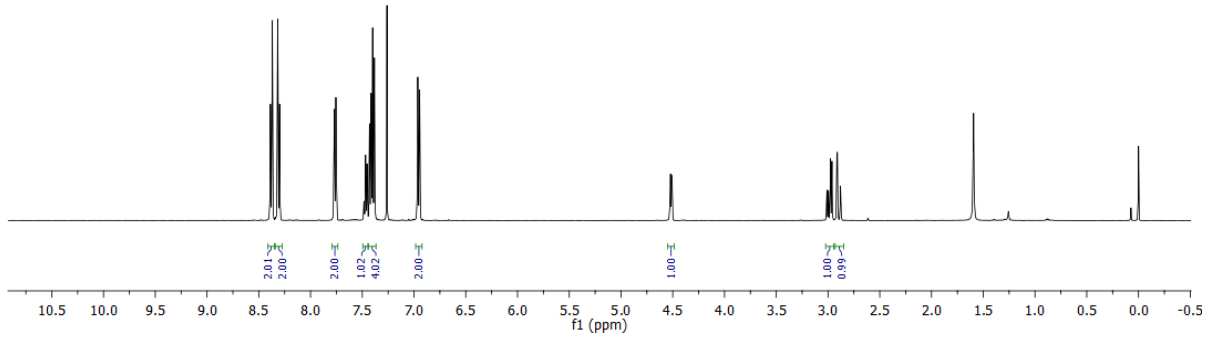
2-4b

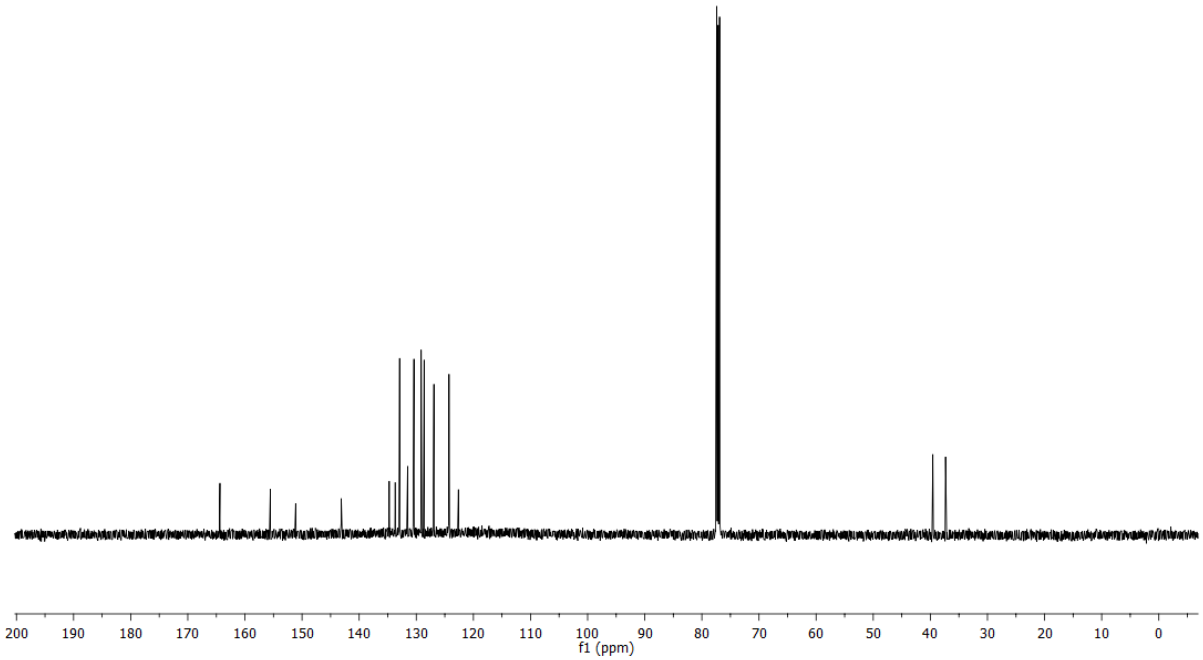

2.04
2.00
2.03
3.12
2.01
2.07
1.04
1.04
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

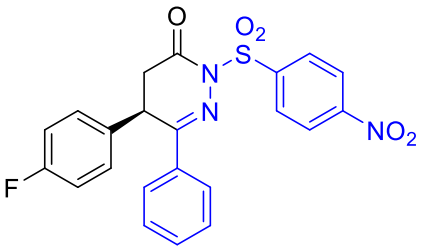

164.41
155.60
151.09
143.11
134.54
134.20
133.70
131.49
130.39
129.93
129.13
128.31
126.91
124.25
39.49
37.41
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



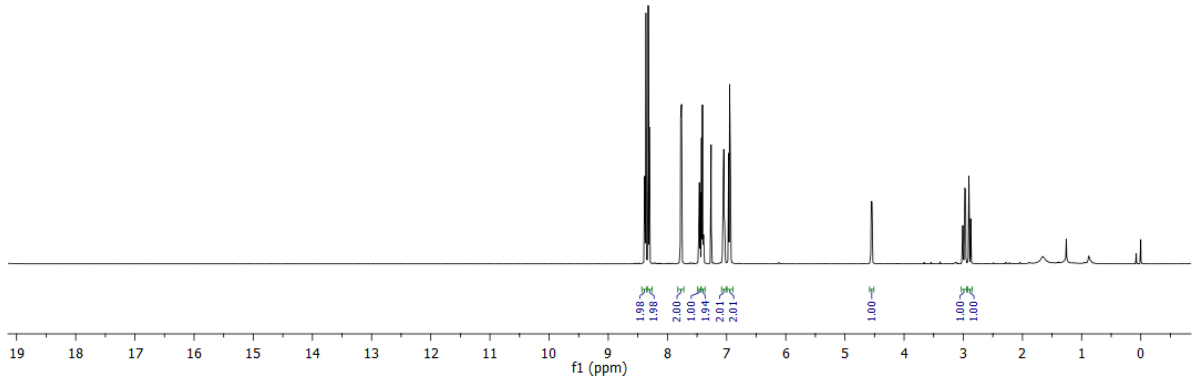
2-4c

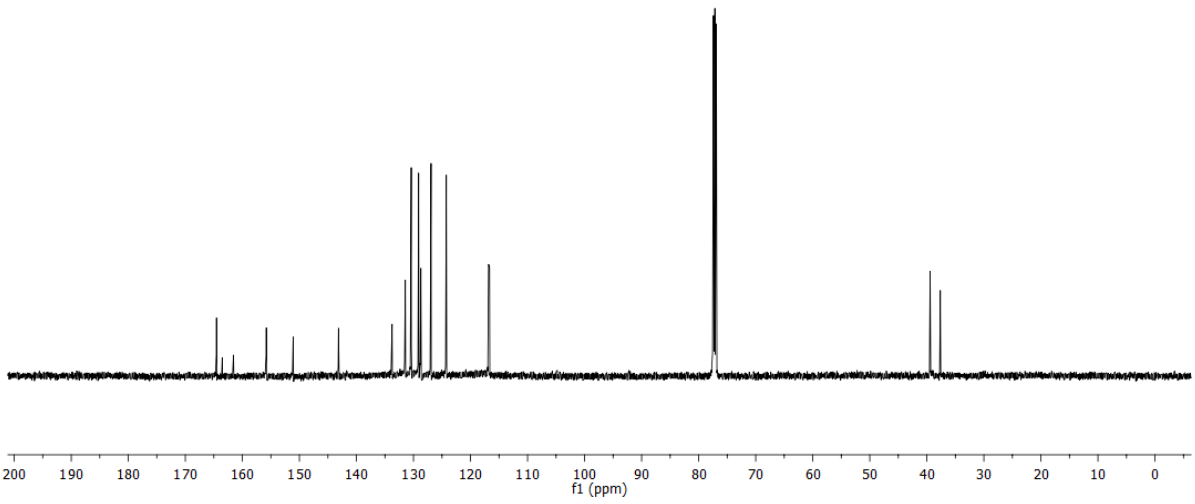


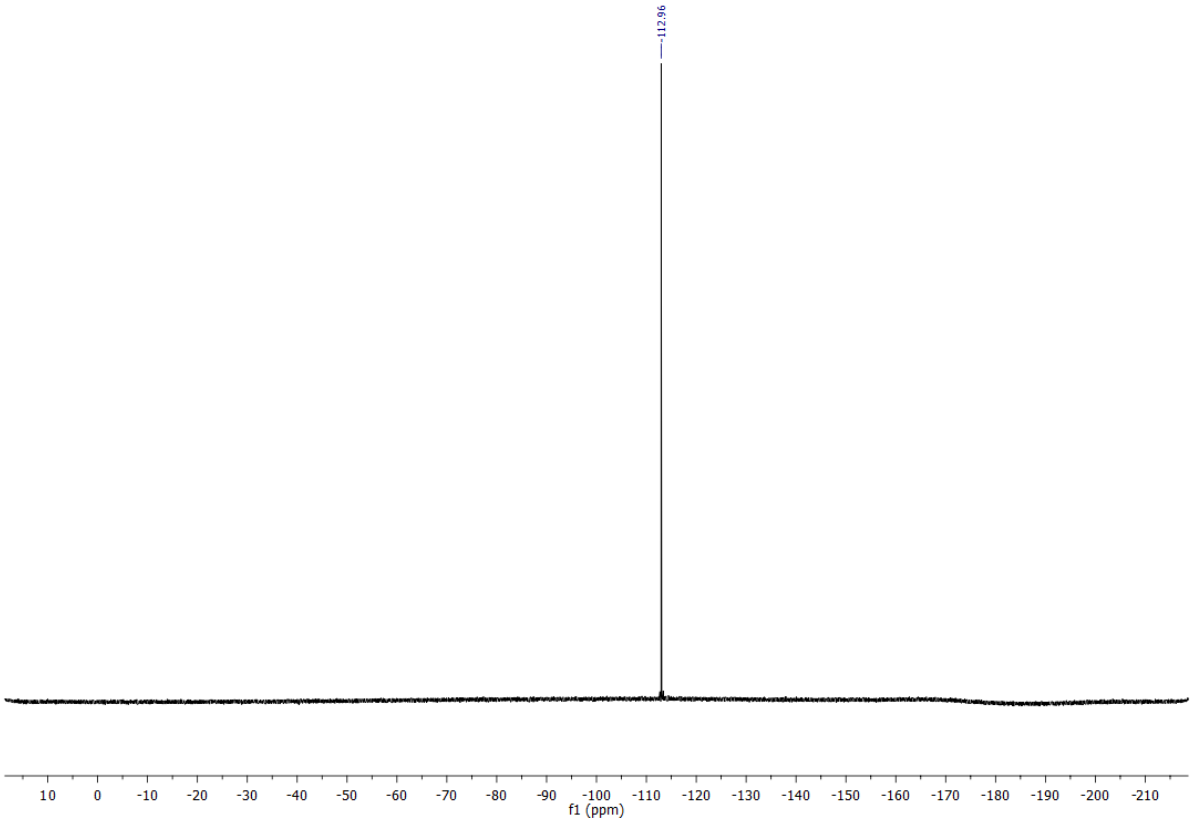


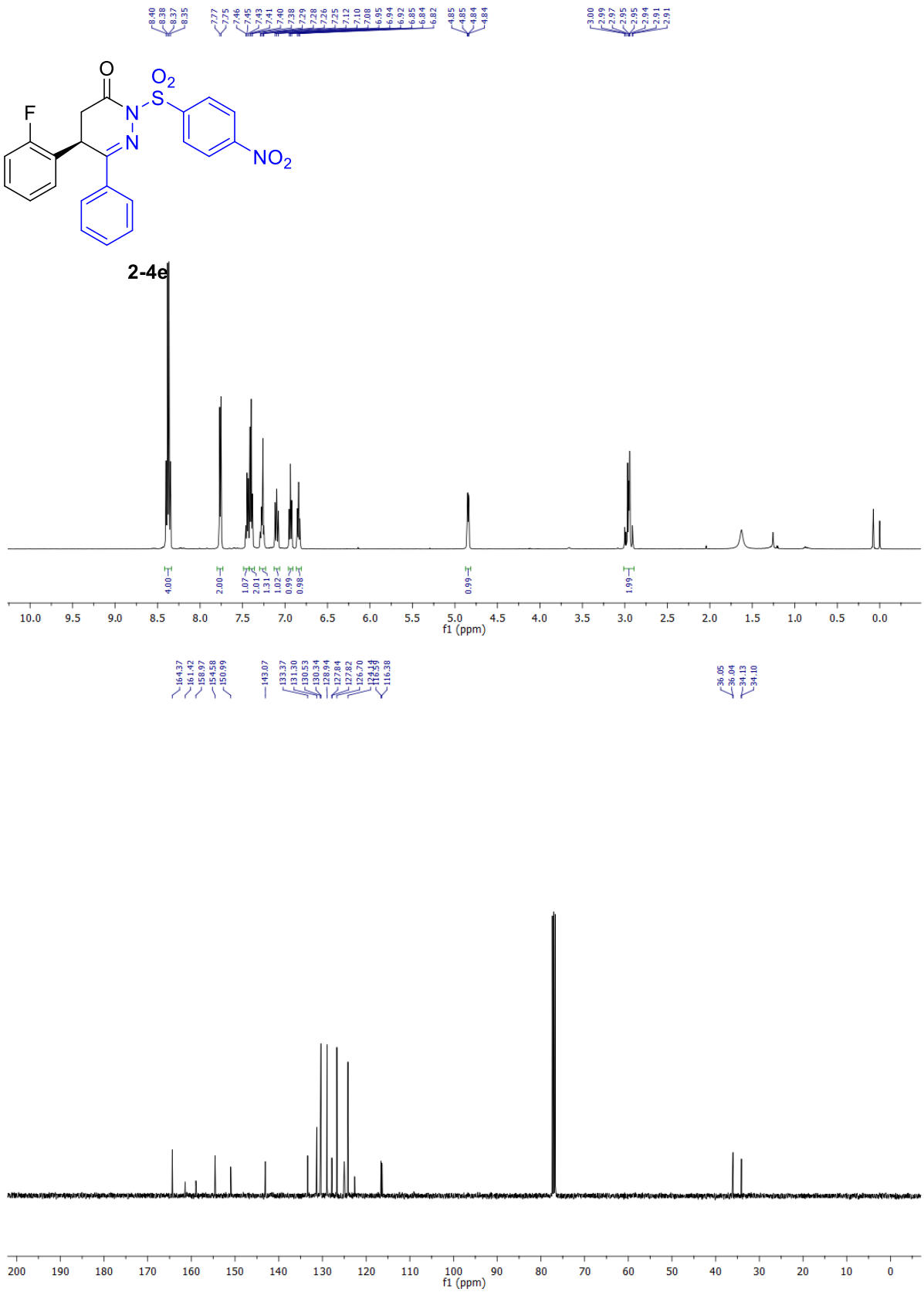


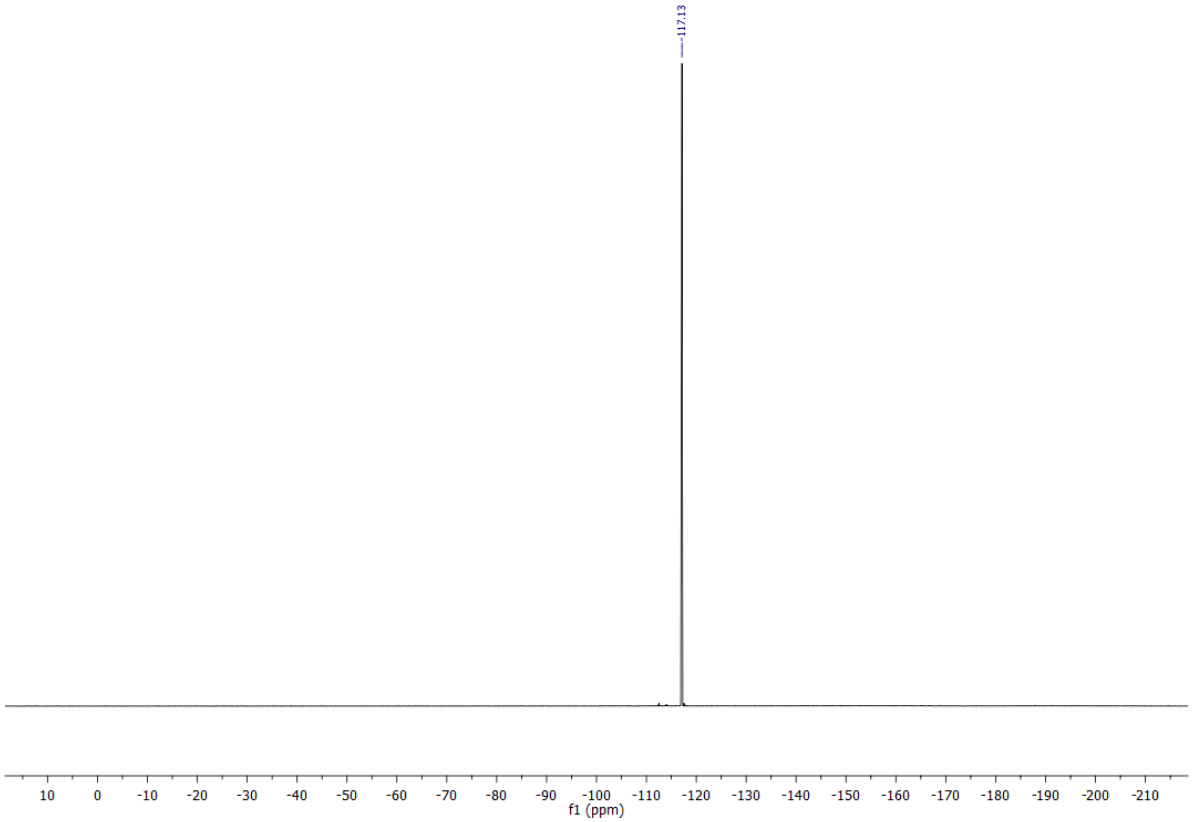
2-4d

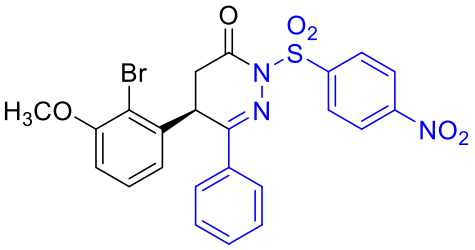




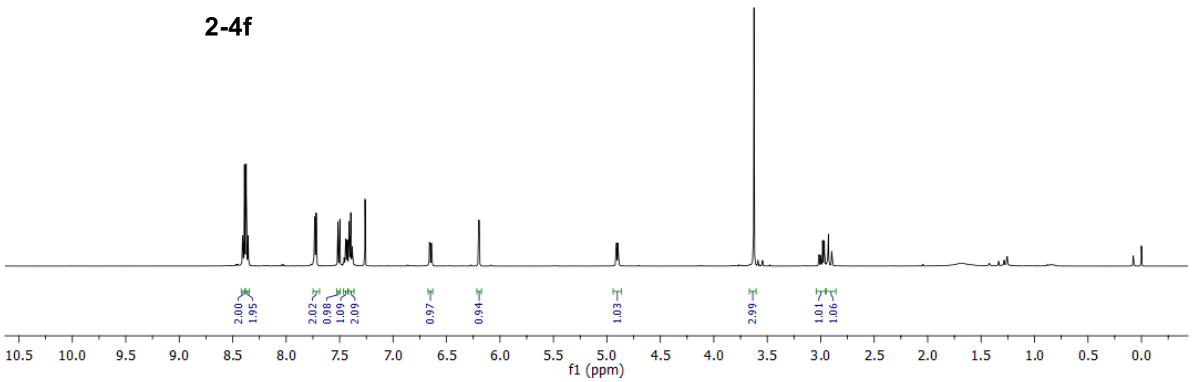

-112.96
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

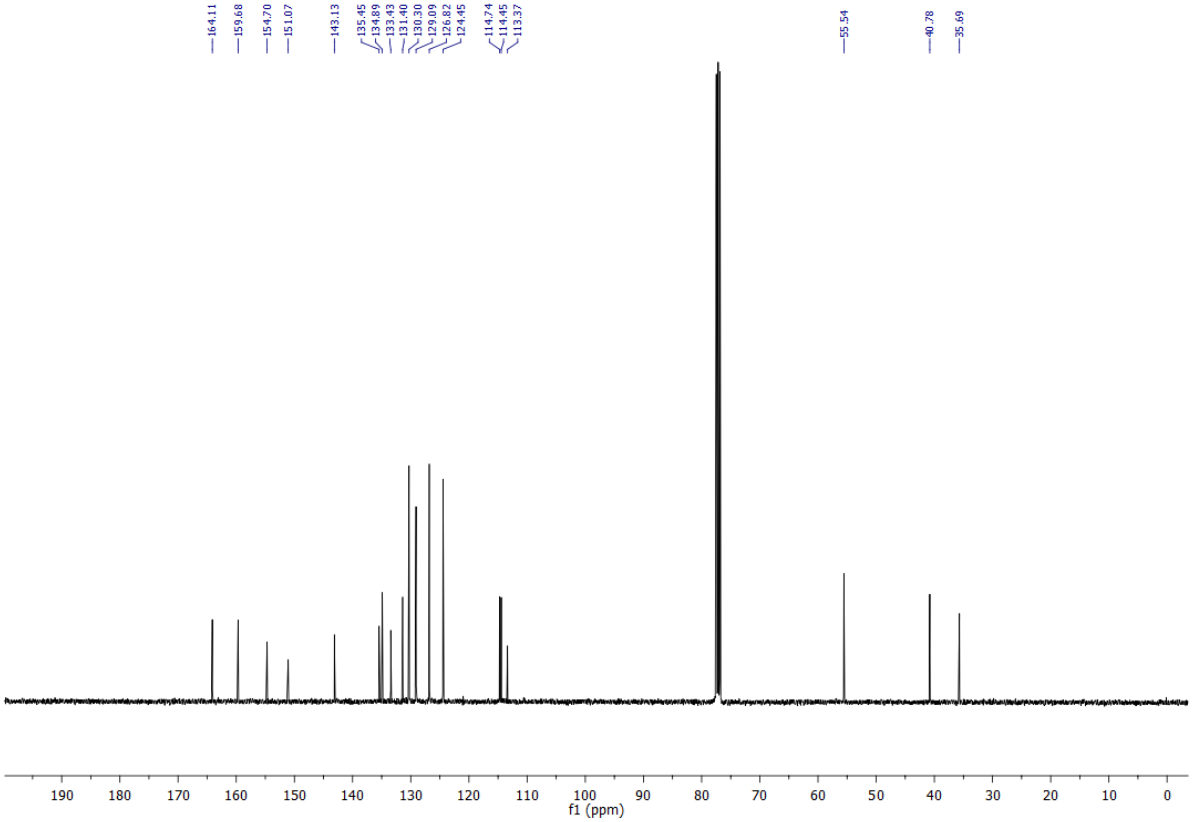

2-4e
f1 (ppm)
f1 (ppm)

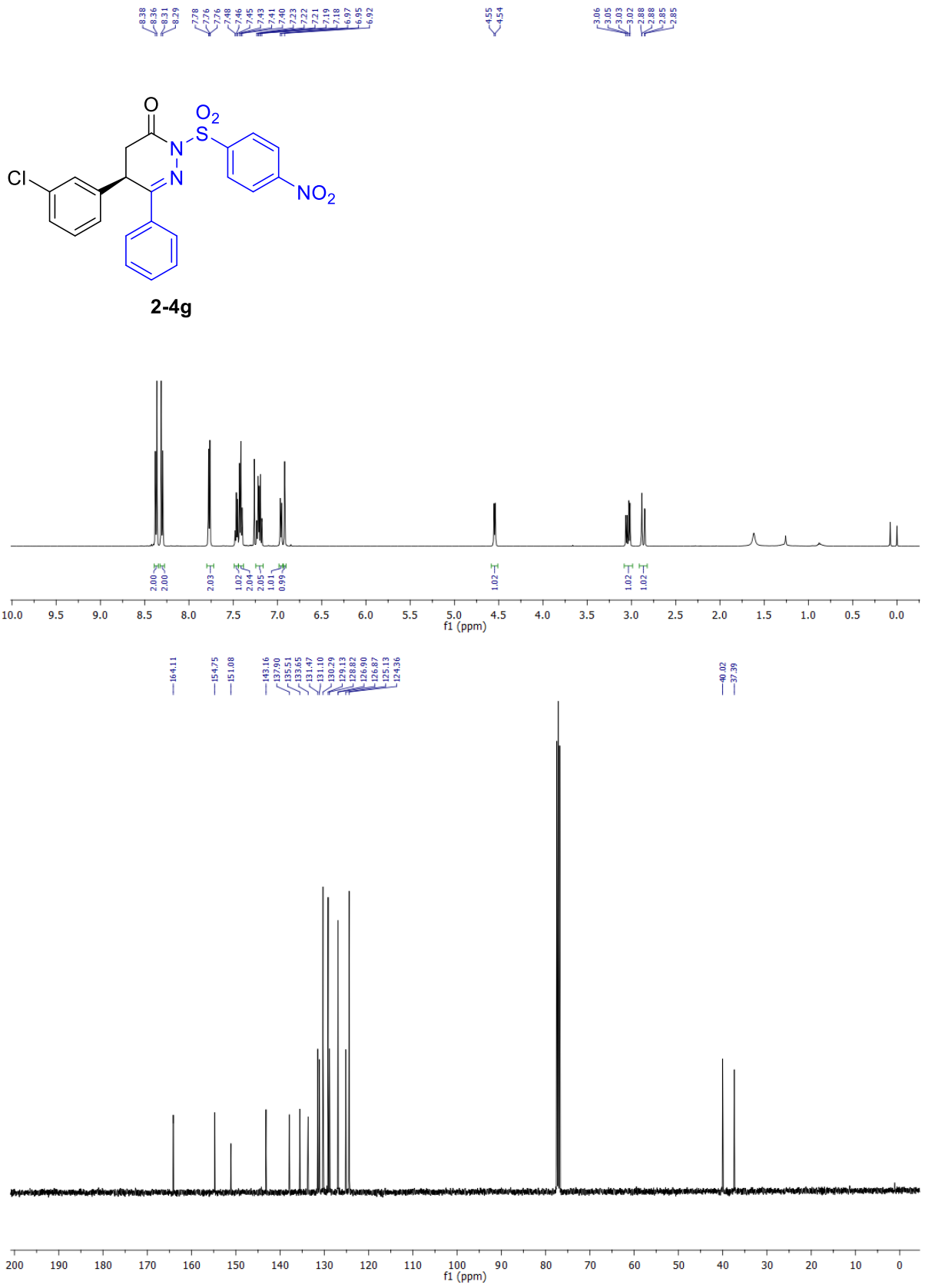

-117.13
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)



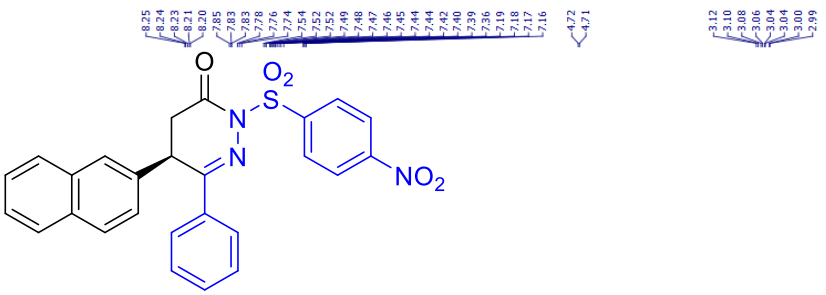
2-4f



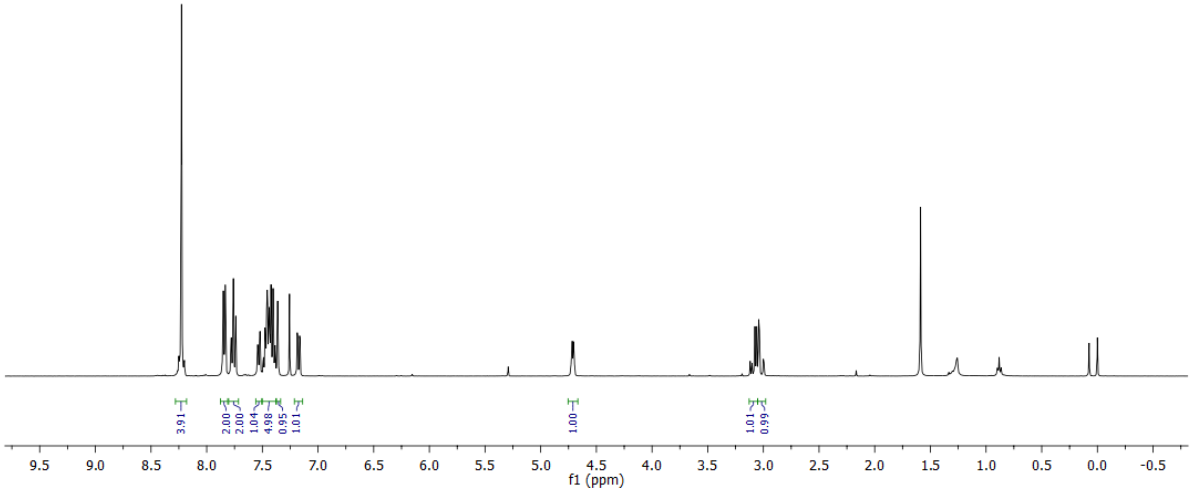


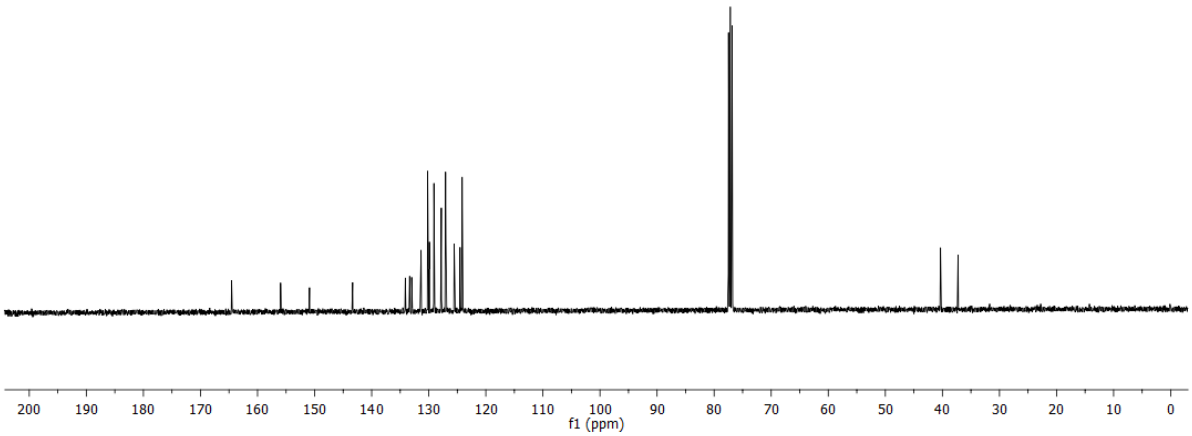

8.38
8.36
8.31
8.29
7.78
7.76
7.76
7.76
7.48
7.46
7.45
7.43
7.41
7.40
7.23
7.22
7.21
7.19
7.18
6.97
6.95
6.92
4.55
4.54
3.06
3.05
3.03
3.02
2.88
2.88
2.85
2.85
O
O2
S
N
N
Cl
NO2
2.00
2.00
2.03
1.02
2.04
2.05
1.01
0.99
1.02
1.02
1.02
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
164.11
154.75
151.08
143.16
137.90
135.51
133.65
131.47
131.10
130.29
129.13
128.82
126.90
126.87
125.13
124.36
40.02
37.39
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

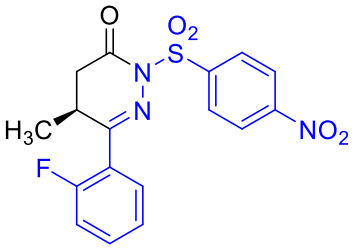
2-4g



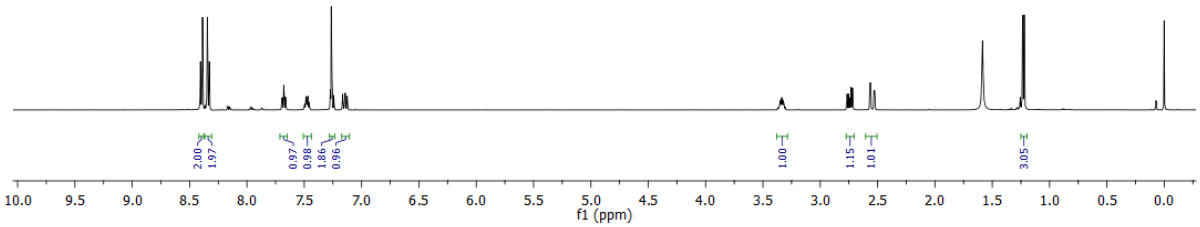
2-4h

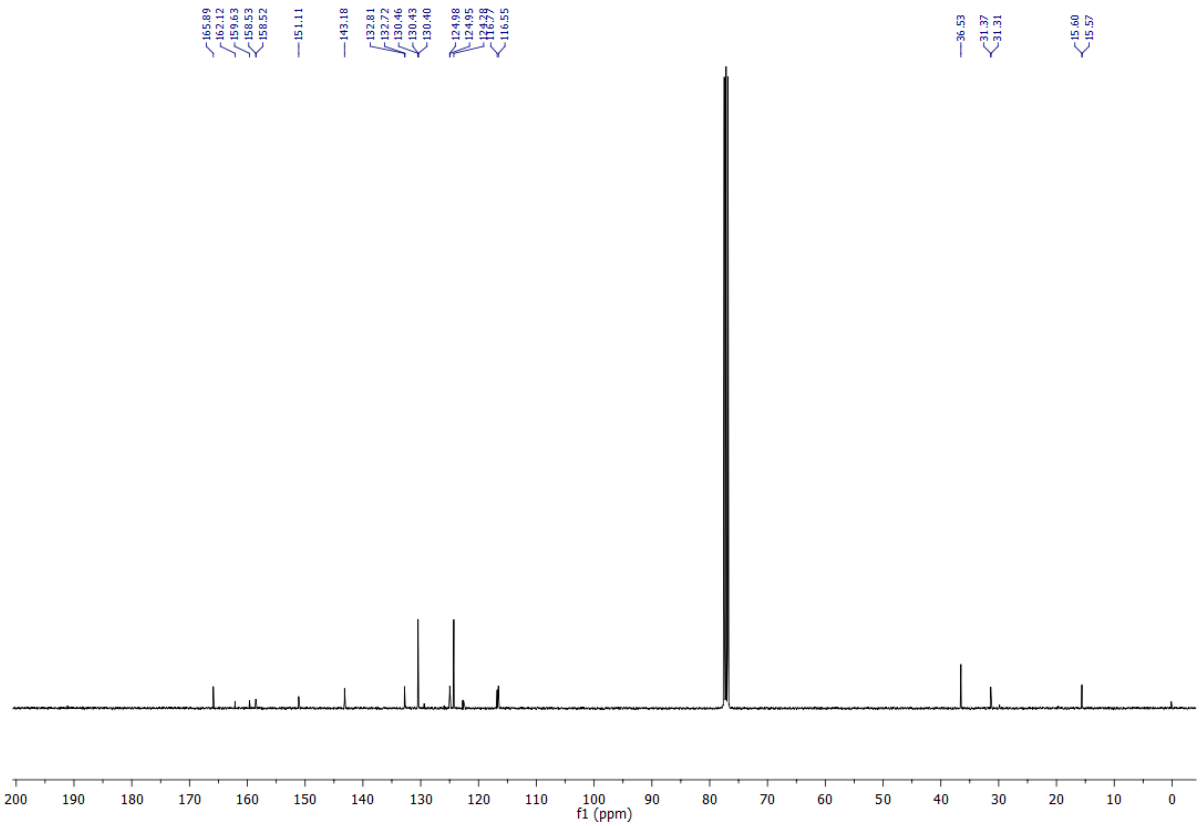


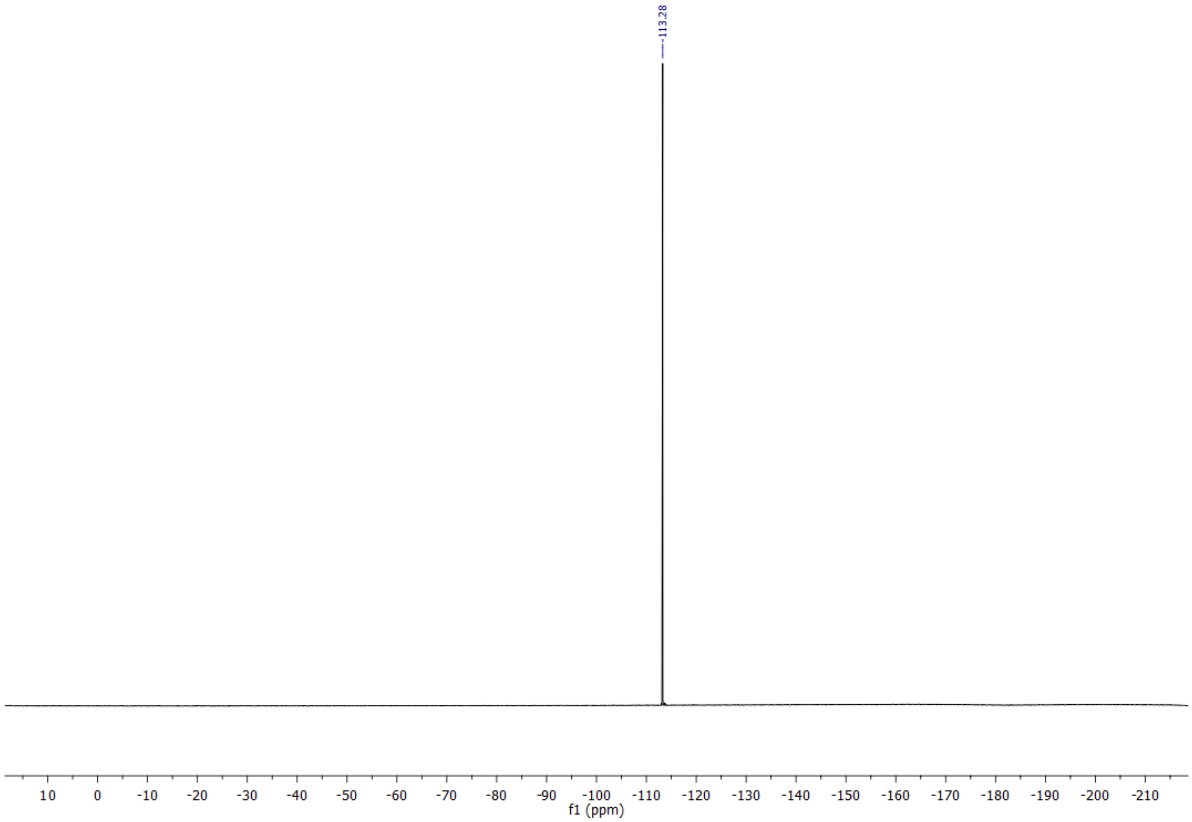


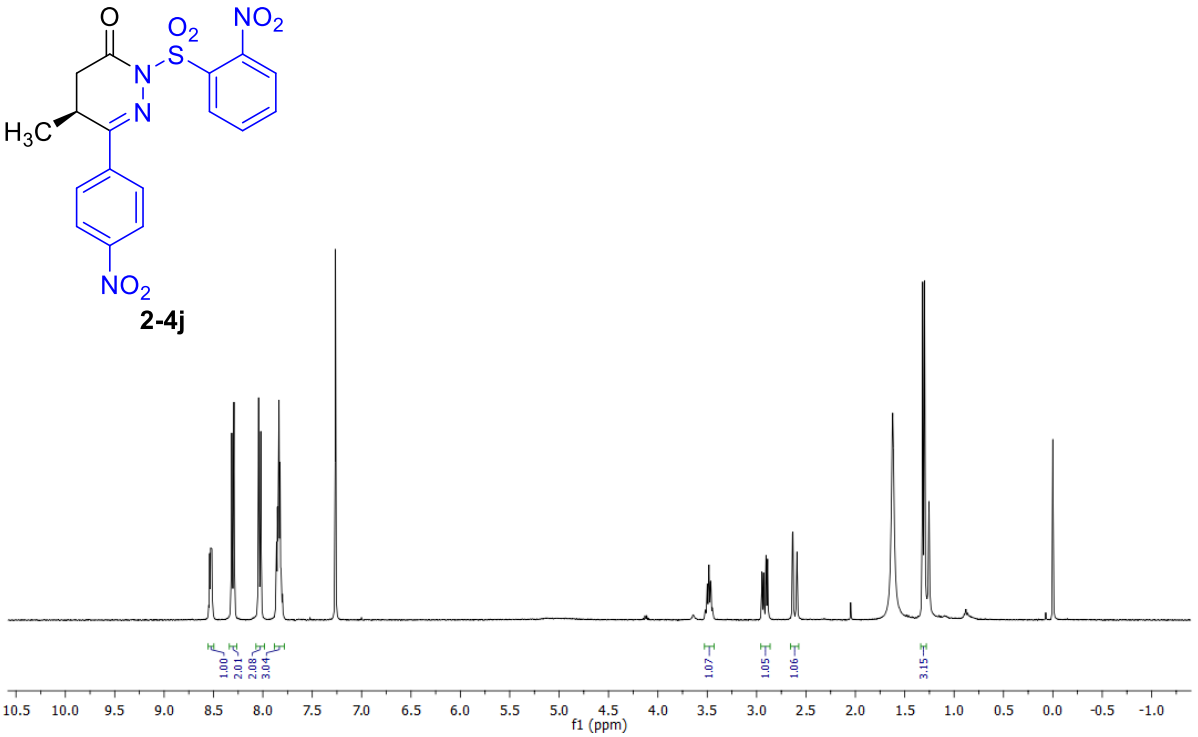


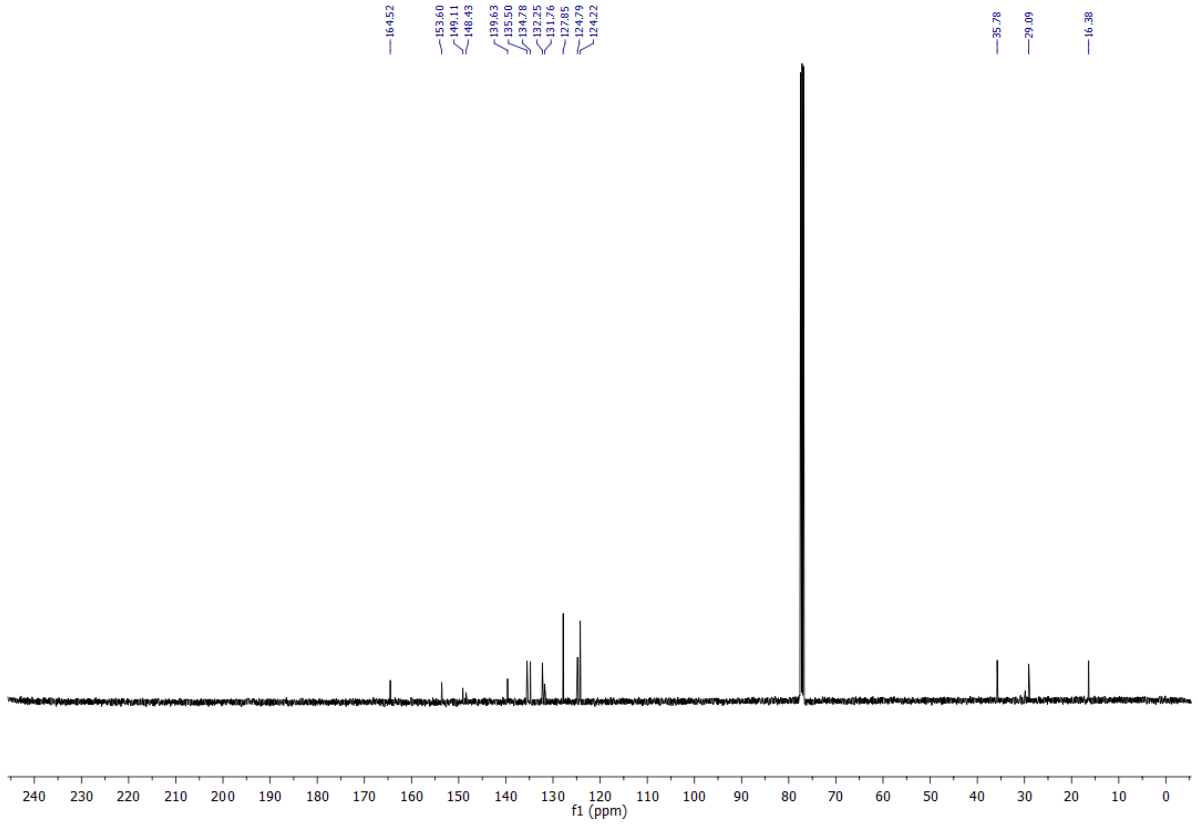
2-4i

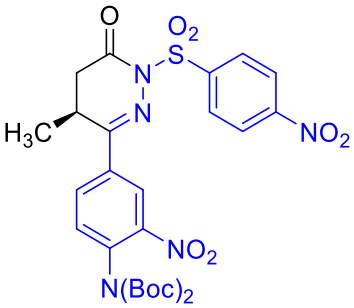





-113.28
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

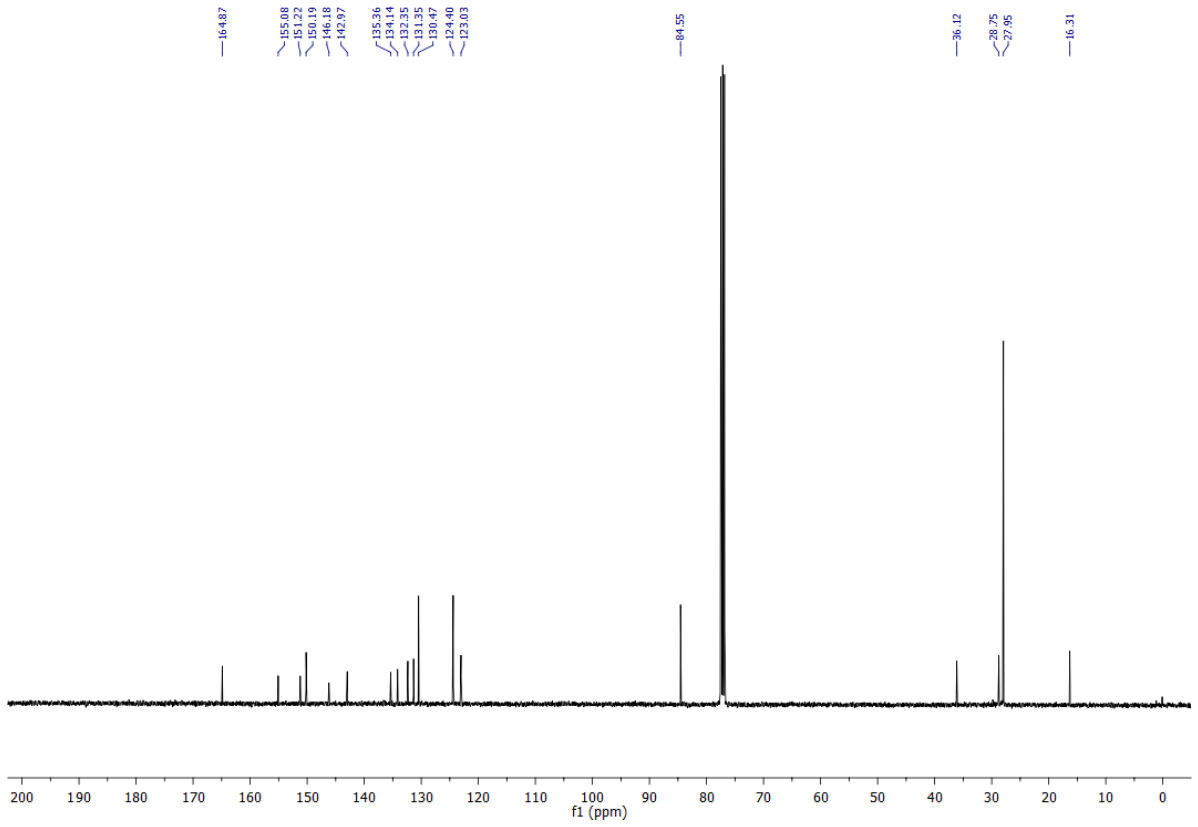

O
O2
NO2
S
N
N
H3C
NO2
2-4j
f1 (ppm)

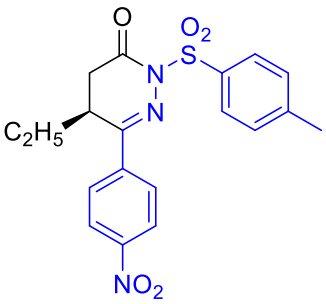

f1 (ppm)


O
O2
N
S
N
H3C
NO2
NO2
N(Boc)2

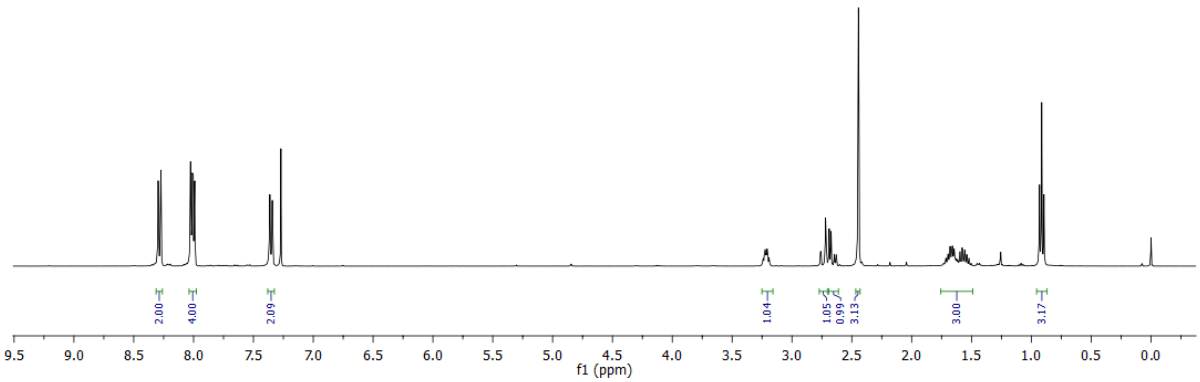
2-4k

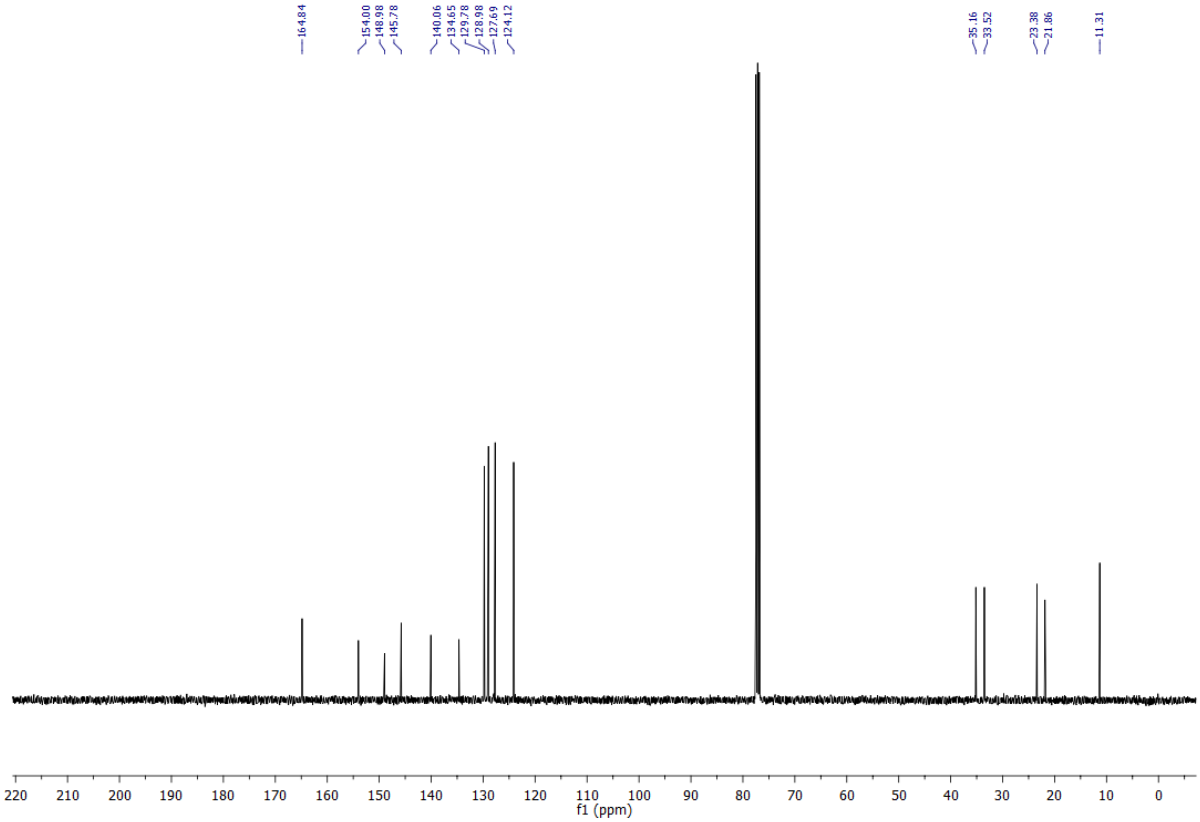
8.43
8.42
8.41
8.36
8.34
8.18
8.18
8.17
8.16
7.46
7.45
3.45
3.44
3.42
3.41
3.40
2.77
2.76
2.74
2.73
2.66
2.63
1.44
1.30
1.29
3.01
2.00
0.95
0.94
0.98
0.98
1.00
18.59
3.10
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

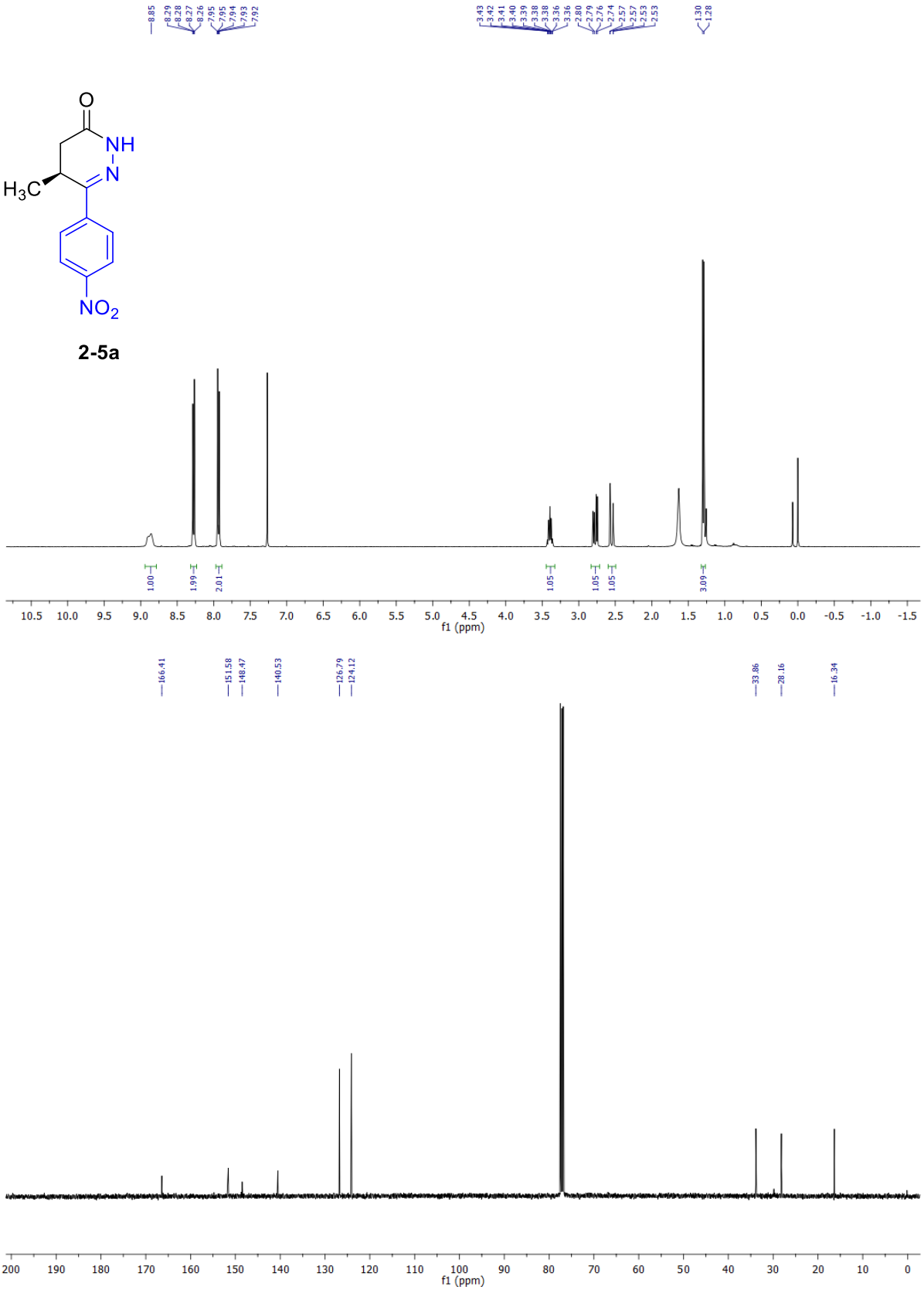

164.87
155.08
151.22
150.19
146.18
142.97
135.36
134.14
132.35
131.35
130.47
124.40
123.03
84.55
36.12
28.75
27.95
16.31
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

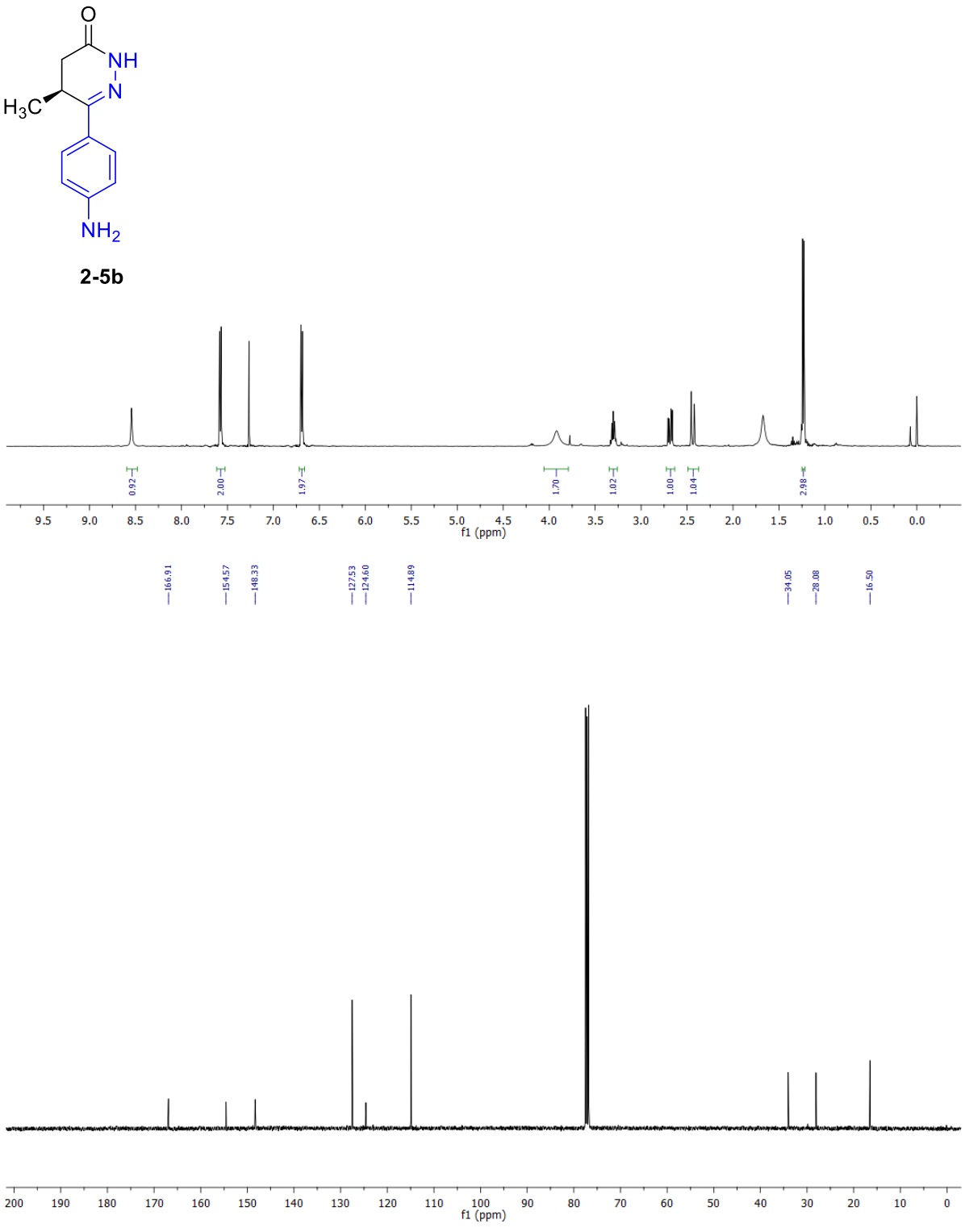


2-4l

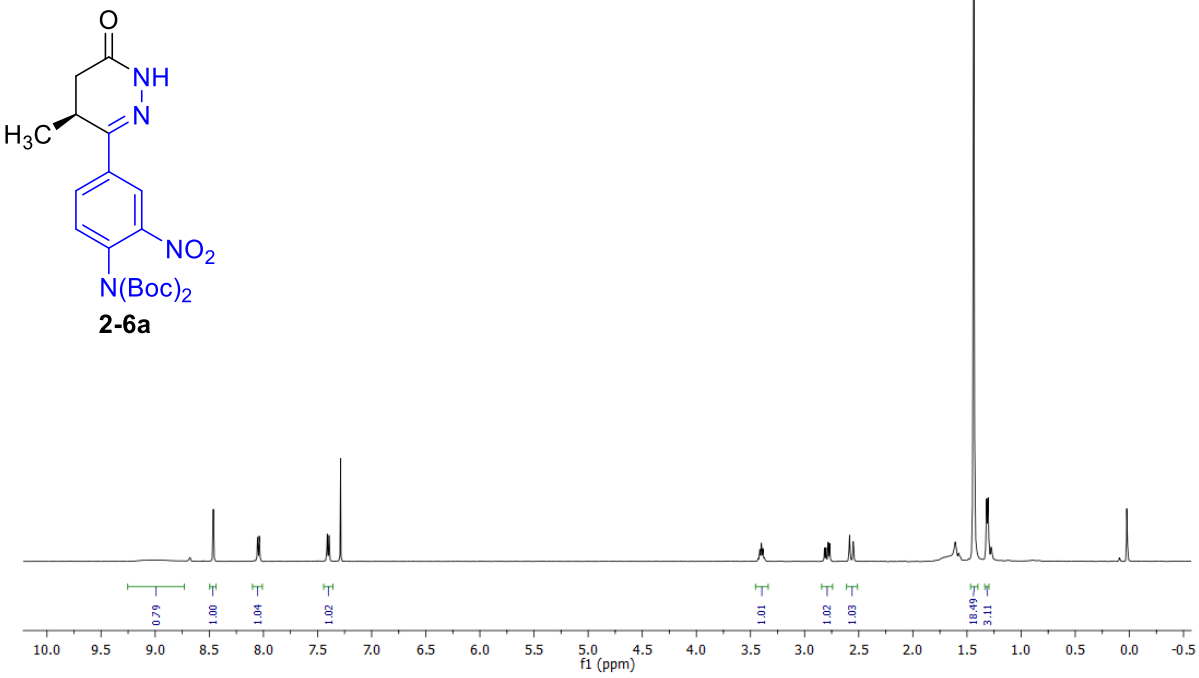





8.85
8.29
8.28
8.27
8.26
7.95
7.95
7.94
7.93
7.92
3.43
3.42
3.41
3.40
3.39
3.38
3.38
3.36
3.36
2.80
2.79
2.76
2.74
2.57
2.57
2.53
2.53
1.30
1.28
O
NH
N
H3C
NO2
2-5a
1.00
1.99
2.01
1.05
1.05
1.05
3.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)
166.41
151.58
148.47
140.53
126.79
124.12
33.86
28.16
16.34
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

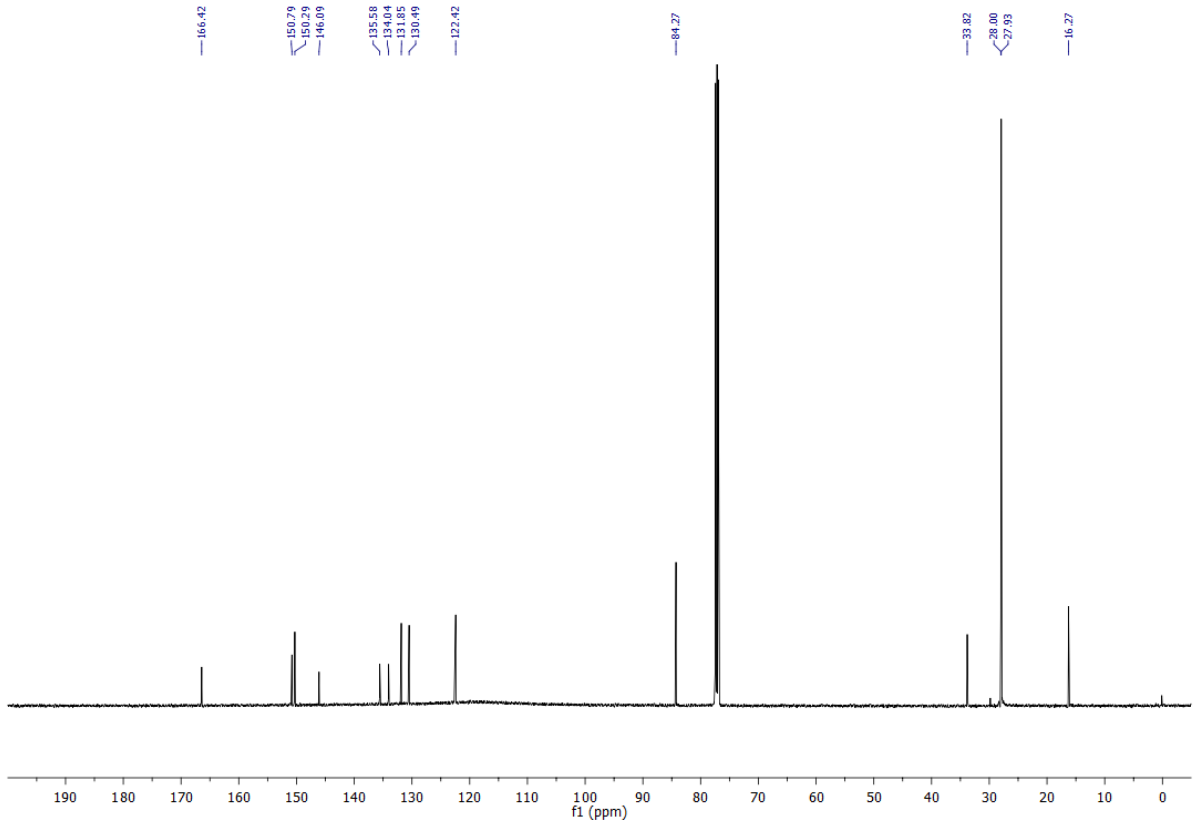

8.54
7.59
7.57
6.70
6.68
3.92
3.33
3.32
3.30
3.29
3.27
2.71
2.69
2.67
2.66
2.45
2.42
1.24
1.23
O
NH
N
H3C
NH2
0.92
2.00
1.97
1.70
1.02
1.00
1.04
2.98
f1 (ppm)
166.91
154.57
148.33
127.53
124.60
114.89
34.05
28.08
16.50
f1 (ppm)

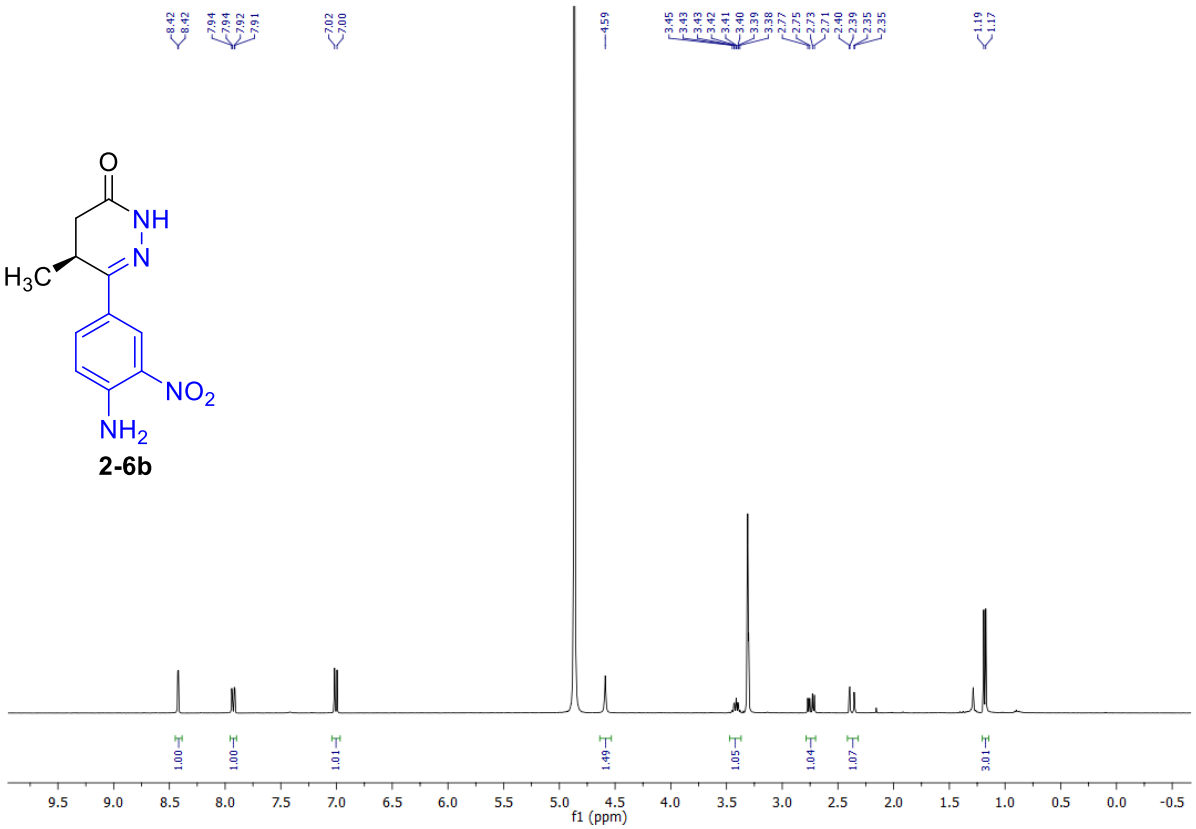
2-5b


O
NH
N
H3C
NO2
N(Boc)2

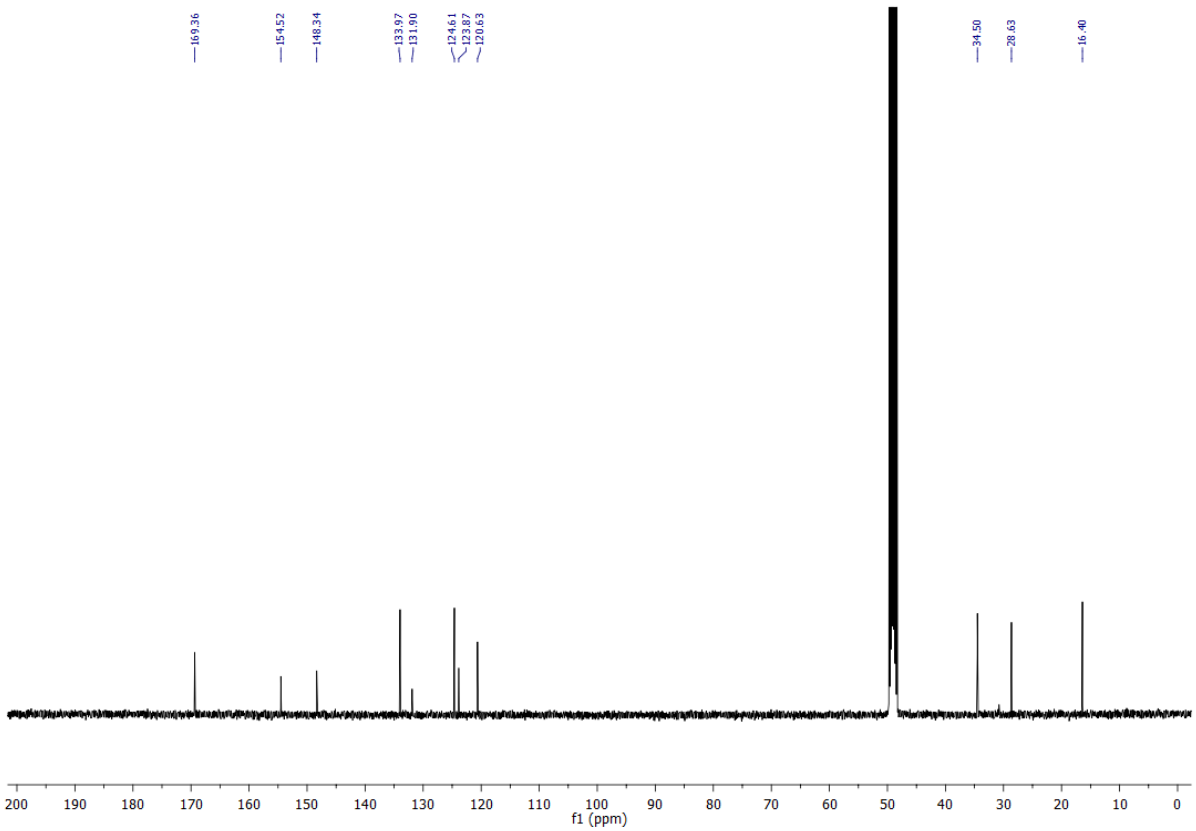
2-6a

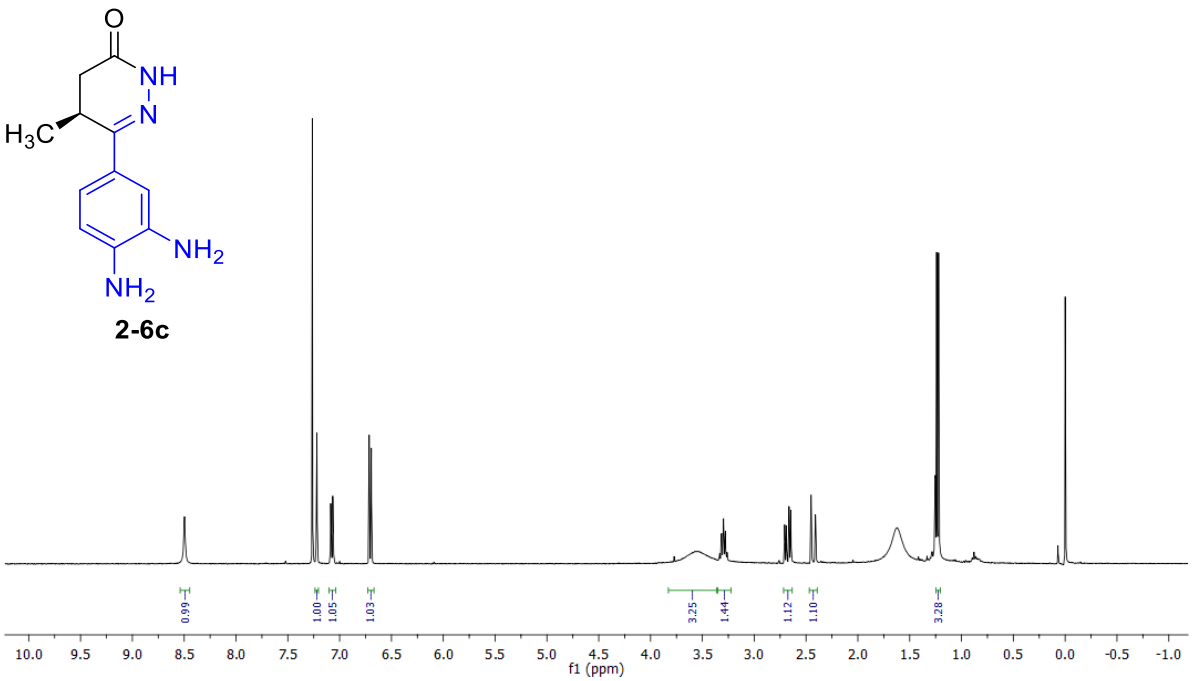
8.99
8.46
8.46
8.05
8.05
8.04
8.03
7.41
7.39
3.43
3.41
3.40
3.39
3.37
2.82
2.80
2.78
2.77
2.58
2.55
1.44
1.32
1.30
0.79
1.00
1.04
1.02
1.01
1.02
1.03
18.49
3.11
f1 (ppm)


166.42
150.79
150.29
146.09
135.58
134.04
131.85
130.49
122.42
84.27
33.82
28.00
27.93
16.27
f1 (ppm)

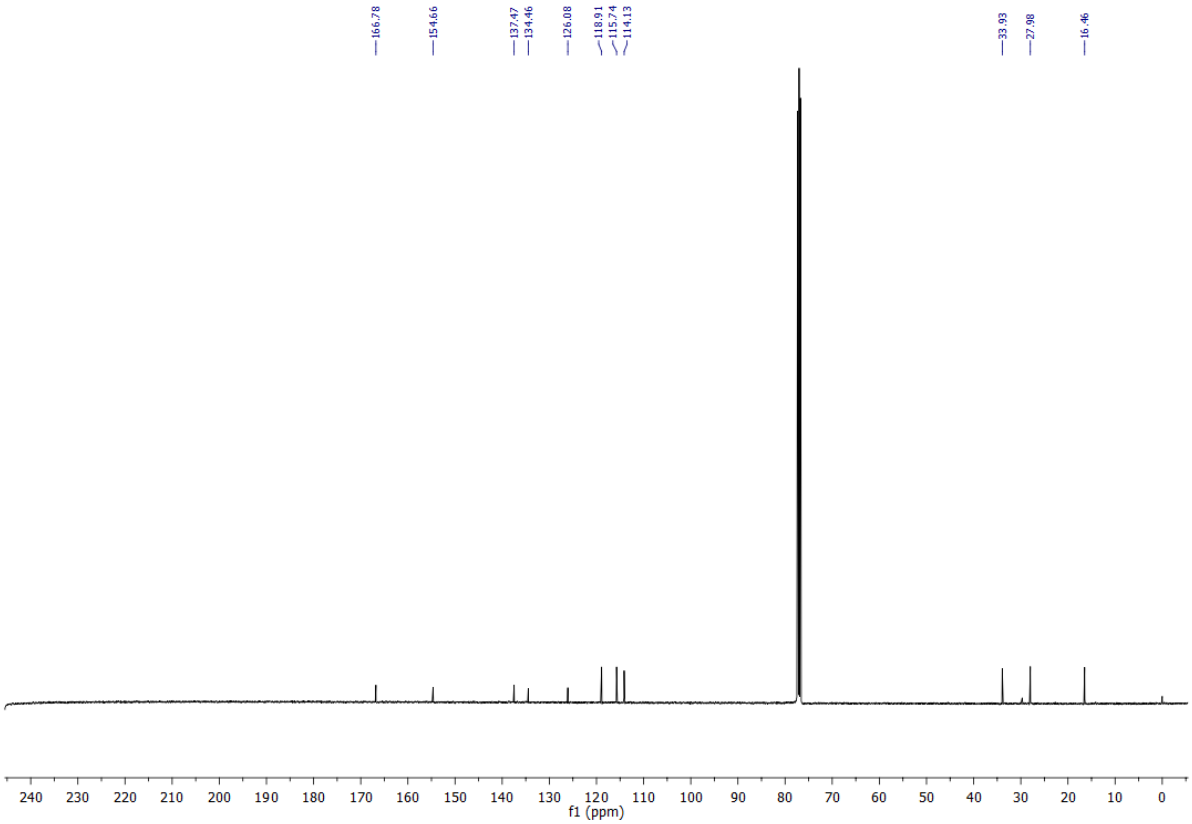

8.42
8.42
7.94
7.94
7.92
7.91
7.02
7.00
4.59
3.45
3.43
3.43
3.42
3.41
3.40
3.39
3.38
2.77
2.75
2.73
2.71
2.40
2.39
2.35
2.35
1.19
1.17
O
NH
N
H3C
NO2
NH2
1.00
1.00
1.01
1.49
1.05
1.04
1.07
3.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

2-6b


169.36
154.52
148.34
133.97
131.90
124.61
123.87
120.63
34.50
28.63
16.40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.50
7.22
7.22
7.09
7.08
7.07
7.06
6.71
6.69
3.54
3.33
3.31
3.30
3.28
3.26
2.71
2.69
2.66
2.65
2.45
2.41
1.24
1.22
O
NH
N
H3C
NH2
NH2
0.99
1.00
1.05
1.03
3.25
1.44
1.12
1.10
3.28
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

2-6c


166.78
154.66
137.47
134.46
126.08
118.91
115.74
114.13
33.93
27.98
16.46
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

2.5 Notes and references

1. For selected reviews, see: a) R. Bansal, S. Thota, *Med. Chem. Res.* **2013**, *22*, 2539; b) S. Dubey, P. A. Bhosle, *Med. Chem. Res.* **2015,** *24*, 3579; For selected examples, see: c) R. Bansal, D. Kumar, R. Carron, C. de la Calle, *Eur. J. Med. Chem.* **2009**, *44*, 4441; d) M. Thyes, H. D. Lehmann, J. Gries, H. Koenig, R. Kretzschmar, J. Kunze, R. Lebkuecher, D. Lenke, *J. Med. Chem.* **1983**, *26*, 800; e) S. Demirayak, A. C. Karaburun, I. Kayagil, K. Erol, B. Sirmagul, *Arch. Pharm. Res.* **2004**, *27*, 13; f) S. Ovais, K. Javed, S. Yaseen, R. Bashir, P. Rathore, R. Yaseen, A. D. Hameed, M. Samim, *Eur. J. Med. Chem.* **2013**, *67*, 352; g) J. Singh, V. Saini, A. Kumar, R. Bansal, *Bioorg. Chem.* **2017**, *71*, 201; h) D. Sharma, R. Bansal, *Med. Chem. Res.* **2016**, ***25***, 1574.
2. For selected examples, see: a) Z. Papp, I. Édes, S. Fruhwald, S. G. De Hert, M. Salmenperä, H. Leppikangas, A. Mebazaa, G. Landoni, E. Grossini, P. Caimmi, A. Morelli, F. Guarracino, R. H. G. Schwinger, S. Meyer, L. Algotsson, B. G. Wikström, K. Jörgensen, G. Filippatos, J. T. Parissis, M. J. G. González, A. Parkhomenko, M. B. Yilmaz, M. Kivikko, P. Pollesello, F. Follath, *Int. J. Cardiol.* **2012**, *159*, 82; b) M. S. Nieminen, S. Fruhwald, L. M. A. Heunks, P. K. Suominen, A. C. Gordon, M. Kivikko, P. Pollesello, *Heart Lung Vessel* **2013**, *5*, 227; c) A. Mebazaa, M. S. Nieminen, M. Packer, A. Cohen-Solal, F. X. Kleber, S. J. Pocock, R. Thakkar, R. J. Padley, P. Põder, M. Kivikko, f. t. SURVIVE Investigators, *JAMA* **2007**, *297*, 1883.
3. For selected examples, see: a) J. Brett, C. Wylie, J. Brown, *Clin. Toxicol.* **2020**, *58*, 146; b) M. Baron Toaldo, M. Pollesel, A. Diana, *J. Vet. Cardiol.* **2020**, *28*, 37.
4. K. Ochiai, N. Ando, K. Iwase, T. Kishi, K. Fukuchi, A. Ohinata, H. Zushi, T. Yasue, D. R. Adams, Y. Kohno, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5451.

5. R. Jonas, M. Klockow, I. Lues, H. Prücher, H. J. Schliep, H. Wurziger, *Eur. J. Med. Chem.* **1993**, *28*, 129.
6. L. de Waal, T. A. Lewis, M. G. Rees, A. Tsherniak, X. Wu, P. S. Choi, L. Gechijian, C. Hartigan, P. W. Faloon, M. J. Hickey, N. Tolliday, S. A. Carr, P. A. Clemons, B. Munoz, B. K. Wagner, A. F. Shamji, A. N. Koehler, M. Schenone, A. B. Burgin, S. L. Schreiber, H. Greulich, M. Meyerson, *Nat. Chem. Biol*. **2016**, *12*, 102.
7. For selected examples, see: a) R. L. Hudkins, A. L. Zulli, R. Dandu, M. Tao, K. A. Josef, L. D. Aimone, R. C. Haltiwanger, Z. Huang, J. A. Lyons, J. R. Mathiasen, R. Raddatz, J. A. Gruner, *Bioorg. Med. Chem. Lett*. **2012**, *22*, 1504; b) S. Jakkaraj, V. G. Young, Jr., G. I. Georg, *Tetrahedron* **2018**, *74*, 2769; c) H. Singhania, EP3424908A1, **2019**; d) M. Harjula, I. Larma, S. Antila, L. Lehtonen, WO 99/16443, **1999**; e) W. Yan, X. Qi, S. Zhao, N. Liu, CN 104418810 A, **2015**; f) L. Cheng, J. Cai, Q. Fu, Y. Ke, *J. Sep. Sci*. **2019**, *42*, 2482.
8. For selected examples, see: a) Y. Nomoto, H. Takai, T. Ohno, K. Nagashima, K. Yao, K. Yamada, K. Kubo, M. Ichimura, A. Mihara, H. Kase *J. Med. Chem.* **1996**, *39*, 297; b) T. Seki, A. Kanada, T. Nakao, M. Shiraiwa, H. Asano, K. Miyazawa, T. Ishimori, N. Minami, K. Shibata, K. Yasuda, *Chem. Pharm. Bull*. **1998**, *46*, 84; c) A. Kojima, Y. Kohno, *Tetrahedron* **2013**, *69*, 1658; d) B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman, L. Deng *Angew. Chem. Int. Ed.* **2011**, *50*, 10565; e) S. Li, CN 107344933 A, **2017**; f) F. F. Owings, M. Fox, C. J. Kowalski, N. H. Baine, *J. Org. Chem.* **1991**, *56*, 1963.
9. For selected examples, see: a) Y. Kuang, K. Wang, X. Shi, X. Huang, E. Meggers, J. Wu, *Angew. Chem. Int. Ed.* **2019**, *58*, 16859; b) M. Z. Liang, S. J. Meek, *Angew. Chem. Int. Ed.* **2019**, *58*, 14234; c) D. Kaldre, I. Klose, N. Maulide, *Science*, **2018**, *361*, 664; d) S. Huang, L. Kötzner, C. K. De, B. List, *J. Am. Chem. Soc.* **2015**, *137*, 3446.

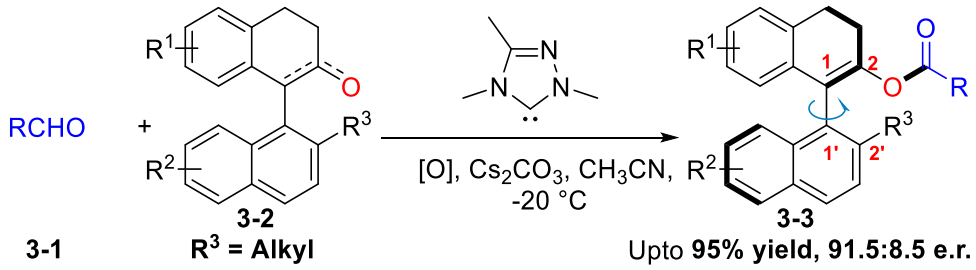
10. a) X. Li, K. Gai, Z. Yuan, J. Wu, A. Lin, H. Yao, *Adv. Synth. Catal*. **2015**, *357*, 3479; b) W. C. Yuan, B. X. Quan, J. Q. Zhao, Y. You, Z. H. Wang, M. Q. Zhou, *J. Org. Chem.* **2020**, *85*, 11812; c) Yin, W. Fang, L. Wang, Z. Gao, F. Li, Z. Wang, Z. *Org. Lett*. **2019**, *21*, 7361; d) L. Duan, X. Wang, Y. Gu, Y. Hou, P. Gong, *Org. Chem. Front.*, **2020**, *7*, 2307.
11. a) B. Liu, R. Song, J. Xu, P. K. Majhi, X. Yang, S. Yang, Z. Jin, Y. R. Chi, *Org. Lett*. **2020**, *22*, 3335; b) J. Sun, F. He, Z. Wang, D. Pan, P. Zheng, C. Mou, Z. Jin, Y. R. Chi, *Chem. Comm.* **2018**, *54*, 6040; c) Y. Liu, Q. Chen, C. Mou, L. Pan, X. Duan, X. Chen, H. Chen, Y. Zhao, Y. Lu, Z. Jin, Y. R. Chi, *Nat. Comm.* **2019**, *10*, 1675; d) Y. Liu, P. K. Majhi, R. Song, C. Mou, L. Hao, H. Chai, Z. Jin, Y. R. Chi, *Angew. Chem. Int. Ed*. **2020**, *59*, 3859.
12. For reviews, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev*. **2007**, *107*, 5606; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev*. **2015**, *115*, 9307; c) X. Chen, H. Wang, Z. Jin, Y. R. Chi, *Chin. J. Chem.* **2020**, *38*, 1167; For selected examples, see: d) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem. Int. Ed.* **2008**, *47*, 8727; e) S. De Sarkar, A. Studer, *Angew. Chem. Int. Ed.* **2010**, *49*, 9266; f) S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190; g) A. Levens, A. Ametovski, D. W. Lupton, *Angew. Chem. Int. Ed.* **2016**, *55*,16136, h) X. Y. Chen, Z. H. Gao, S. Ye, *Acc. Chem. Res.* **2020**, *53*, 690, i) A. Ghosh, A. T. Biju, *Angew. Chem., Int. Ed.* **2020**. DOI: 10.1002/anie.202012581, j) H. Ohmiya, *ACS Catal*. **2020**, *10*, 6862, k) S. Mondal, S. R. Yetra, S. Mukherjee, A. T. Biju, *Acc. Chem. Res*. **2019**, *52*, 425, l) T. K. Das, A. T. K. Biju, *Chem. Commun.*, **2020**, *56*, 8537, m) X. Wu, B. Liu, Y. Zhang, M. Jeret, H. Wang, P. Zheng, S. Yang, B. A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.*, **2016**, *55*, 12280, n) X. Wu, L. Zhou, R. Maiti, C. Mou, L. Pan, Y. R. Chi, *Angew. Chem. Int. Ed.*, **2019**, *58*, 477.

13. a) A. Das, C. M. R. Volla, I. Atodiresei, W. Bettray, M. Rueping, *Angew. Chem. Int. Ed.* **2013**, *52*, 8008; b) C. M. R. Volla, A. Das, I. Atodiresei, M. Rueping, *Chem. Comm.* **2014**, *50*, 7889; c) J.-H. Mao, Z.-T. Wang, Z.-Y. Wang, Y. Cheng, *J. Org. Chem.* **2015**, *80*, 6350; d) C.-L. Zhang, D.-L. Wang, K.-Q. Chen, S. Ye, *Org. Biomol. Chem.* **2015**, *13*, 11255; e) X. Xu, P. Y. Zavalij, W. Hu, M. P. Doyle, *J. Org. Chem.* **2013**, *78*, 1583; f) J.-N. Zhu, W.-K. Wang, J. Zheng, H.-P. Lin, Y.-X. Deng, S.-Y. Zhao, *J. Org. Chem.* **2019**, *84*, 11032; g) W, Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu, J. Ye, *Org. Lett.* **2013**, *15*, 4524.
14. M. Fernández, U. Uria, J. L. Vicario, E. Reyes, L. Carrillo, *J. Am. Chem. Soc.* **2012**, *134*, 11872.
15. a) A. C. Mantovani, T. A. C. Goulart, D. F. Back, G. Zeni, *Chem. Eur. J.* **2014**, *20*, 12663; b) I. R. Siddiqui, Rahila, P. Rai, H. Sagir, M. A. Waseem, *RSC Adv.* **2015**, *5*, 52355.
16. C. D. Campbell, C. Concellón, A. D. Smith, *Tetrahedron: Asymmetry* **2011**, *22*, 797.
17. S. Kuwano, S. Harada, B. Kang, R. Oriez, Y. Yamaoka, K. Takasu, K. Yamada, *J. Am. Chem. Soc.* **2013**, *135*, 11485.
18. M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.
19. C. Zhao, F. Li, J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1820.
20. I. Piel, M. Steinmetz, K. Hirano, R. Fröhlich, S. Grimme, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 4983.
21. CCDC 2062761 (**3n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
22. Q. Tong, J. Chen, X. Cui, Z. Gong, B. Zhang, CN 107522663 A, **2017**.
23. M. Lang, J. Wang, *Eur. J. Org. Chem.*, **2018**, 2958.

24. Z. Cao, S. Yan, C. Zhao, X. Sun, L. Tian, X. Meng, *Tetrahedron*, **2019**, *75*, 130534.

Chapter 3

Carbene-Catalyzed Dynamic Kinetic Resolution Strategy for Atroposelective Synthesis of Bicyclic Enolic Ester and Biaryl Ligands



3.1 Introduction

Motivated by the desire to improve the economic balance of chemical transformations, there has been a growing interest to convert racemates into single stereoisomer without the occurrence of undesired stereoisomer. In this regard, dynamic kinetic resolution (DKR), which facilitates stereo-divergent conversion of both enantiomers of a racemic mixture into a single isomer of the product by establishing an equilibrium among the enantiomers of the racemic starting material, has emerged as a valuable protocol in organic synthesis.[1] Therefore, 100% yield of single stereoisomeric product is possible via DKR (Figure 3.1).[2] Thus, DKR strategy shows solution to the constraint present in traditional kinetic resolution (KR), where theoretically 50% of the racemate can be converted to enantiopure product.[3]

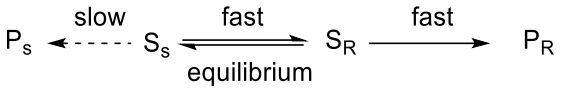
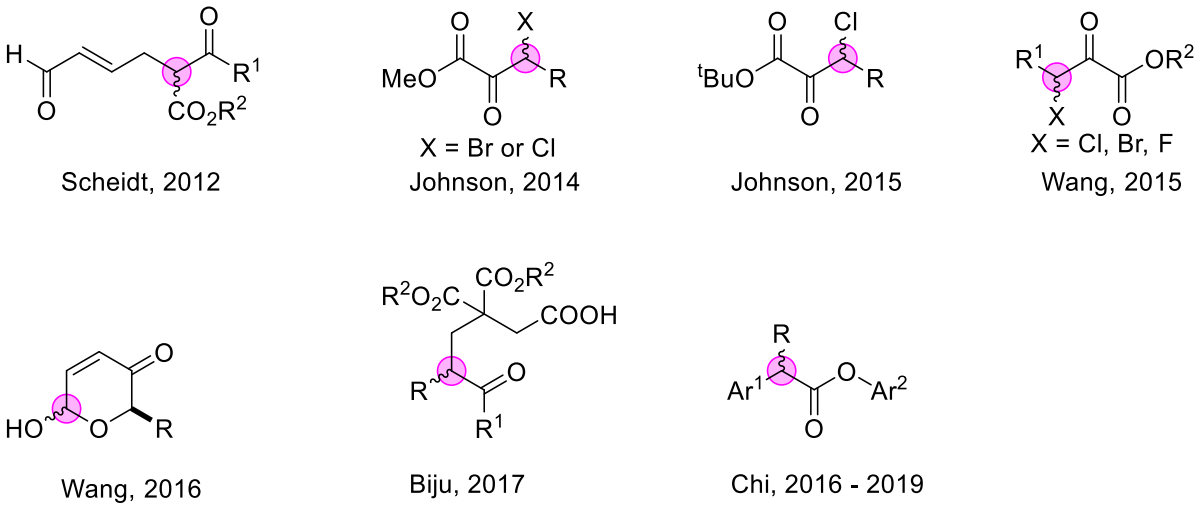


Figure 3.1 Pictorial representation of dynamic kinetic resolution

In recent years N-heterocyclic carbene (**NHC**) also has found its' application in reactions involving DKR.[4] In 2012, Scheidt has first reported the **NHC**-catalyzed dynamic kinetic resolution of racemic β-keto ester.[5] After the seminal report by Scheidt, different **NHC**-catalyzed DKR reactions have been reported by Wang[6-7], Chi[8-9], Biju[10], and others[4, 11-12] (Scheme 3.1). It is worthy to note that, the DKR reactions involving **NHC** reported so far are on the unsymmetrically substituted carbon center.

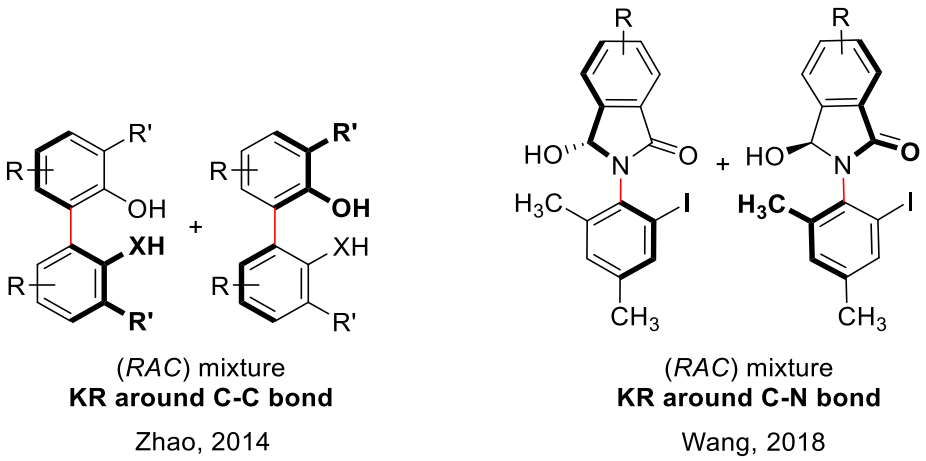
Asymmetric synthesis of centrally chiral molecular architecture by **NHC** organic catalysis has found tremendous progress over the last two decades. Apart from the central chirality, axially chiral motifs have found in many natural products[13] and bio-active molecules[13]. These axially chiral motifs are also used as ligands in metal catalysis[14-15]. On this context, **NHC** has also emerged as an efficient catalyst for asymmetric synthesis of axially chiral molecules.[16] If we look back at the development in this direction, we can see several ex-



Scheme 3.1 Examples of **NHC**-catalyzed DKR reactions on unsymmetrically substituted carbon center

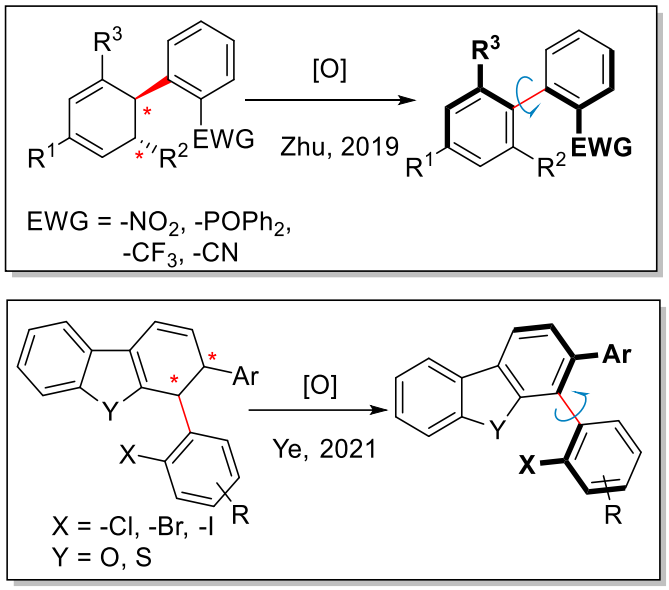
amples of **NHC**-catalyzed atropoisomeric synthesis of axially chiral molecules.

In 2014, Zhao has first reported **NHC**-catalyzed kinetic resolution strategy to make atropo-enriched 1,1′-biaryl-2,2′-diols and amino alcohols (chiral C-C bond) via selective acylation enabled by **NHC** mediated stereogenic acylazolium intermediate (Scheme 3.2).[17] Other than the generation of atropo-enriched C-C bond via KR, atropo-enriched C-N bond generation by this strategy was demonstrated by Wang in 2018 (Scheme 3.2).[18]



Scheme 3.2 Atroposelective KR at C-C and C-N axis

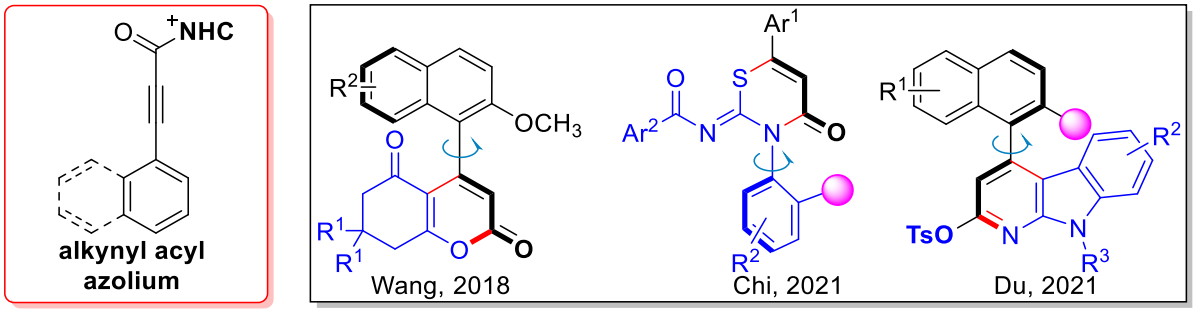
NHC-catalyzed synthesis of central chirality is robust, indeed it is an important approach to transfer the chiral information from chiral center to a chiral axis. Notable progress in this direction was achieved by the group of Zhu[24] and Ye[25] (Scheme 3.4). Notably, reported examples used an oxidative strategy to aromatize properly substituted chiral center containing bicyclic motif, obtained via **NHC**-catalyzed asymmetric reaction, to make axially chiral biaryl system.



Scheme 3.4 Transfer of central chirality to axial chirality in **NHC** catalysis

Strategy to direct formation of atropo-enriched axially chiral system by **NHC**-catalyzed cycloaddition reaction has also emerged. **NHC**-derived chiral alkynyl acyl azolium intermediate has undergo cycloaddition reaction with dinucleophiles to give the axially chiral systems. Important works developed by the group of Wang[26], Chi[27], and Du[28] have been demonstrated in scheme 3.5.

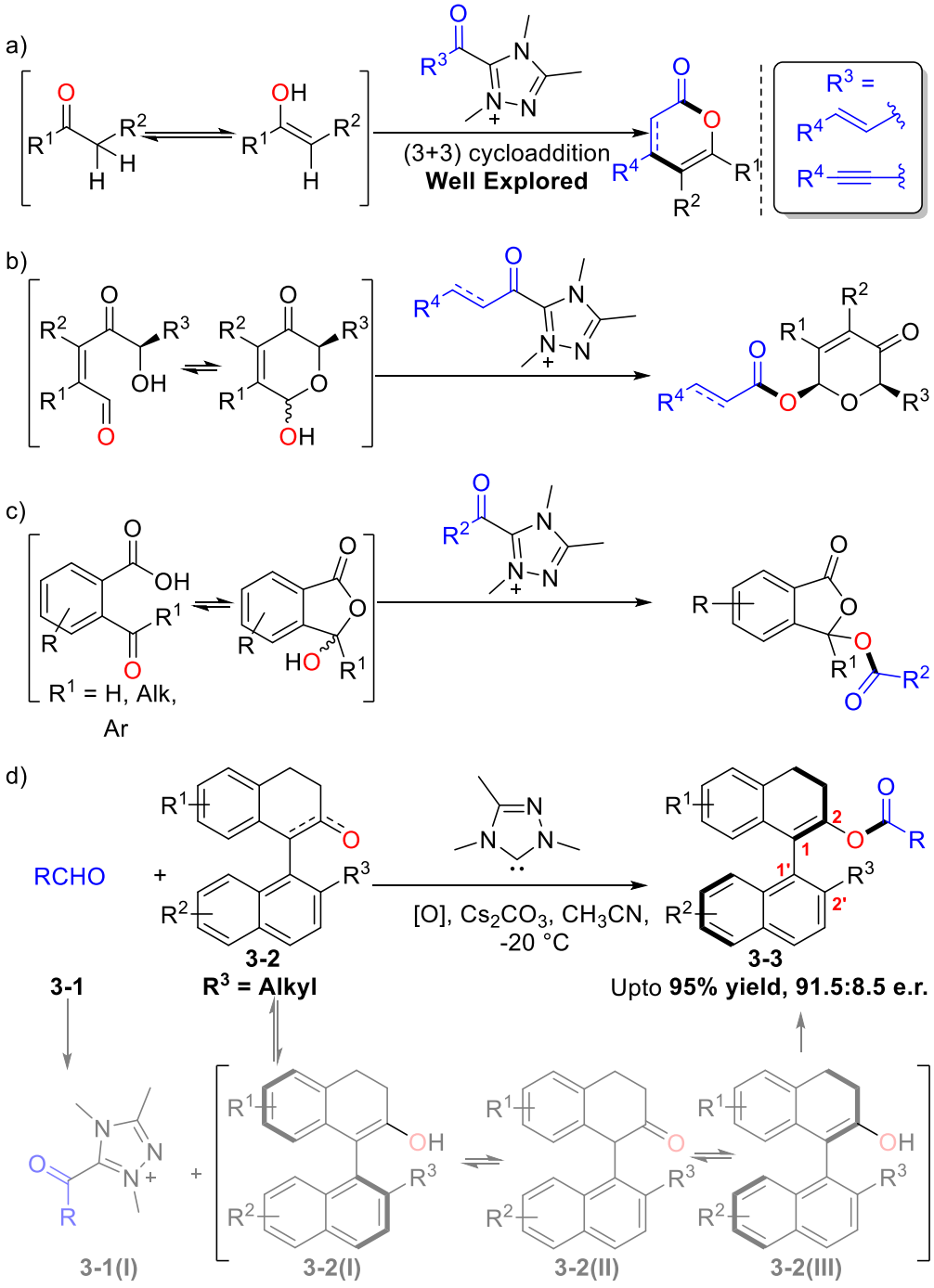
NHC has made remarkable progress in the field of asymmetric transformation. But, DKR and atropo-selective bond formation in this field are still in their infancy. Although, **NHC**-catalyzed DKR reactions have been explored in synthesis of central chirality, atroposelective



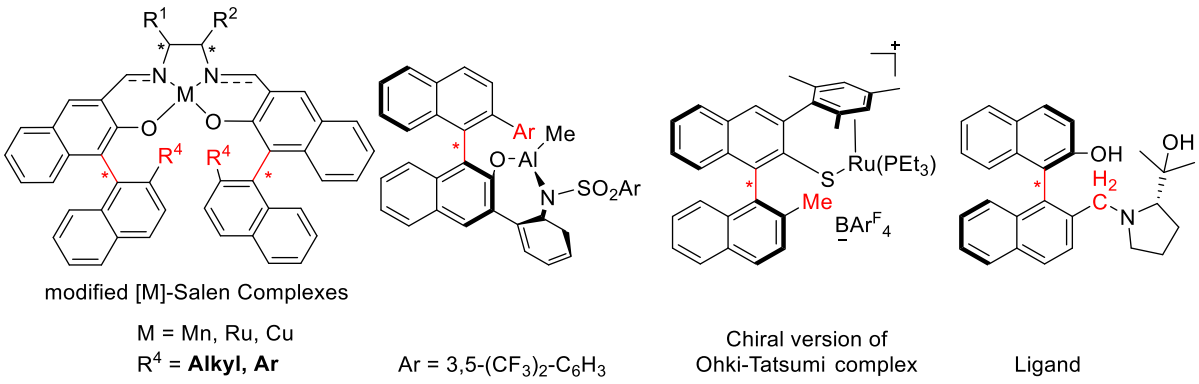
Scheme 3.5 Atroposelective bond formation using alkynyl acyl azolium intermediate

bond formation via this strategy has yet to be achieved. Acyl azolium intermediate, derived from carbene, has been intercepted by different kinds of carbon-centered or heteroatomic nucleophiles. Among these, interception of acylazolium by alcohols for esterification is one of the classical reactions in the arena of carbene organic catalysis. Carbonyl compounds, containing two α-enolizable protons have the potential to act as both α-carbon nucleophile and O-centered nucleophile simultaneously, have been widely used in different types of **NHC**-catalyzed reactions in the last two decades to easily get complex molecular architectures.[26, 29] Most of the reported reactions of such dinucleophilic carbonyls are with vinyl acylazolium[30] or alkynyl acylazolium intermediate[26], where the O-centered nucleophilicities are assisted by the Michael addition from α-carbon (Scheme 3.6a). In 2016, Wang group has reported nucleophilic intermolecular functionalization of aldehydic O-atom via intramolecular hemiacetal formation (Scheme 3.6b).[7] Chi group, in 2019 has reported similar reaction to access bioactive phthalidyl ester derivatives (Scheme 3.6c).[31] To the best of our knowledge direct utilization of the ketone/enol as a O-centered nucleophile[32] in intermolecular reaction is still unknown in **NHC** catalysis. Inspired from these research gaps in **NHC** catalysis, we designed the first **NHC**-catalyzed DKR strategy for direct intermolecular functionalization of nucleophilic O-atom from ketone to access atropo-enriched bicyclic enolic ester scaffolds in high yields and moderate e.r. values (Scheme 3.6d).[33] Our reaction proceeds via the formation of acyl azolium (**3-1(I)**) under oxidative condition, followed by atropo-selective acyl-enol bond

formation with **3-2(III)** (Our starting material **3-2** exists in equilibrium mixture of **3-2(I), 3-2(II), 3-2(III)** via keto-enol tautomerization[33]). Worthy to note that bicyclic enolic ester obtained from our catalytic cycle is a precursor of various 2′-alkyl substituted binaphthyl-based ligands reported in literature (Scheme 3.7).[34-41] We also have demonstrated, simple and efficient conversion of our catalytic product can lead to the important binaphthyl-based ligand.



Scheme 3.6 a) Michael addition assisted O-center nucleophilicity of carbonyl. b) Wang's intermolecular O-center nucleophilicity of carbonyls via hemiacetal/ hemiketal formation. c) Chi's intermolecular O-center nucleophilicity of carbonyls via hemiacetal/ hemiketal to access phthalidyl ester. d) DKR strategy for atroposelective intermolecular O-functionalization of bicyclic ketone/enol (**This Work**).



Scheme 3.7 2′-Alkyl/aryl substituted binaphthyl ligands and their complexes

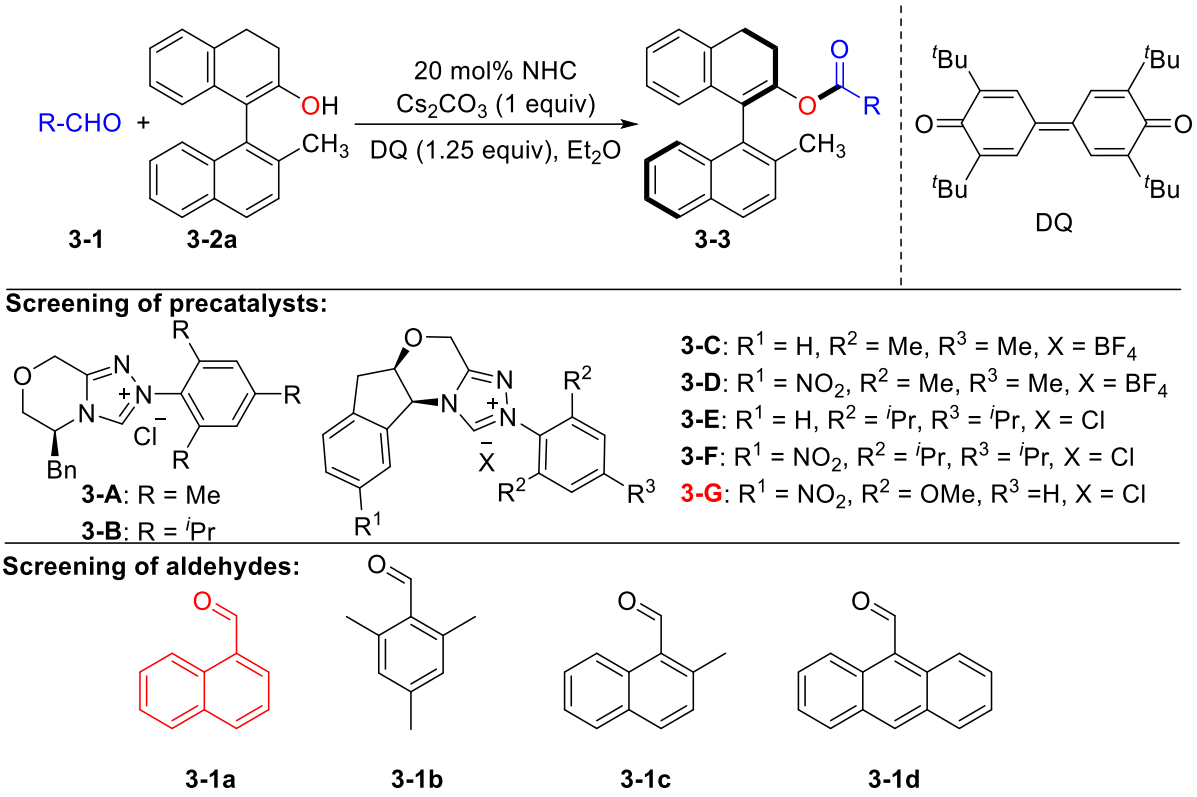
3.2 Result and discussion

3.2.1 Reaction condition optimization

We started our study by using readily available 1-naphthaldehyde (**3-1a**) and bicyclic enol (**3-2a**) as our model substrates to find out optimal precatalyst and reaction conditions. In the first part of Table 3.1 (entry 1-7), we summarized our findings of screening catalysts, and in the second part (entry 8-10), we noted down our observations of changing to different aldehydes. When we carried out our reaction using morpholine-based triazolium **NHC**-precatalyst (**3-A**), we found that the desired product formed in 84% yield, but unfortunately, this catalyst was unable to induce any chirality in our reaction system (Table 3.1, entry 1). Changing the N-mesityl substitution of the precatalyst **3-A** by bulkier and electron-rich N-1,3,5-triisopropyl phenyl motif (to get precatalyst **3-B**) gave our product in 65:35 e.r. value with 68% yield (Table 3.1, entry 2). It seemed morpholine based precatalyst was inefficient to control the chirality, so we switched to examine the efficacy of chiral aminoindanol-derived

NHC precatalysts. Initially, we found that aminoindanol derived precatalyst **3-C** was also unable to induce chirality in our reaction system (Table 3.1, entry 3). But we observed that putting a nitro (-NO_2) substituent in the aminoindanol motif of precatalyst **3-C** (to get precatalyst **3-D**) gave our desired product in 57.5:42.5 e.r. and 82% yield (Table 3.1, entry 4). After realizing that there was sufficient room to modify aminoindanol motif, we started to screen different kinds of precatalysts containing this motif. Changing the N-mesityl substitution of **3-C** by N-1,3,

Table 3.1 Screening of **NHC** precatalysts and aldehydes[a]



Entry	NHC	Aldehyde	Product	Yield (%)[b]	e.r.[c]
1	**3-A**	**3-1a**	**3-3aa**	84	50:50
2	**3-B**	**3-1a**	**3-3aa**	68	65:35
3	**3-C**	**3-1a**	**3-3aa**	86	50:50
4	**3-D**	**3-1a**	**3-3aa**	82	57.5:42.5

5	**3-E**	**3-1a**	**3-3a**	80	56:44
6	**3-F**	**3-1a**	**3-3aa**	71	73:27
7	*ent*-**3-G**	**3-1a**	**3-3aa**	74	78:22
8	*ent*-**3-G**	**3-1b**	**3-3ba**	62	61.5:38.5
9	*ent*-**3-G**	**3-1c**	**3-3ca**	66	55:45
10[d]	*ent*-**3-G**	**3-1d**	**3-3da**	-	-

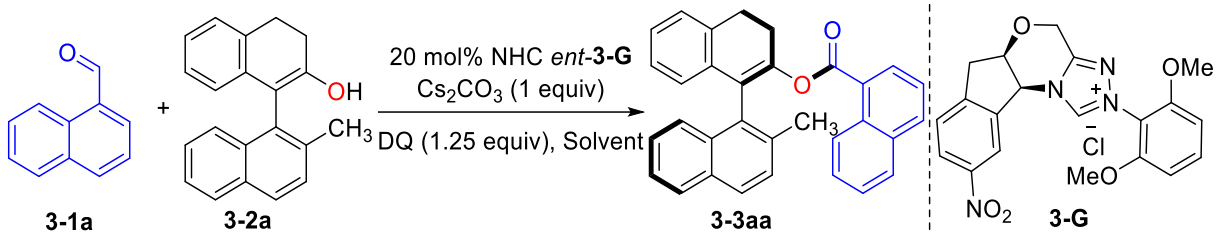
[a]Reaction condition: **3-1** (0.05 mmol.), **3-2a** (1.25 equiv), **NHC** precatalyst (20 mol%), Cs_2CO_3 (1 equiv), DQ (1.25 equiv), Et_2O (.025 M), at RT for 3 h. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard with respect to **3-1**. [c]The e.r. was determined via chiral-phase HPLC analysis. [d]No product was detected.

5-triisopropyl phenyl motif (to get precatalyst **3-E**) also gave the desired product in very poor e.r. value (56:44) but with 80% yield (Table 3.1, entry 5). Then, to our surprise, we observed that by putting a nitro (-NO_2) group at aminoindanol nucleus of **3-E** (to get precatalyst **3-F**) gave our desired product with significant improvement of the enantioselectivity to 73:27 e.r. value but the yield dropped down slightly to 71% (Table 3.1, entry 6). To further improve the e.r. value, we changed the N-1,3,5-triisopropyl phenyl motif of *ent*-**3-F** by N-1,3-dimethoxy phenyl motif (to get precatalyst *ent*-**3-G**), which further enhanced the enantioselectivity to 78:22 e.r. value with 74% yield (Table 3.1, entry **7**). After getting a moderate e.r. value, we screened some other aldehydes (Table 3.1, entries 8-10), but our initially chosen aldehyde gave the best e.r. value among all.

Next, we started to screen different solvents, considering **3-1a** and **3-2a** as our model substrates, by replacing Et_2O to further improve the e.r. value and yield, while keeping the other parameters same (i.e., **NHC** *ent*-**3-G** and Cs_2CO_3 base). First, we screened various polar aprotic solvents (THF, DMSO, EtOAc) (Table 3.2, entry 2-4) in our reaction system. We found that both in THF (Table 3.2, entry 2) and DMSO (Table 3.2, entry 3), the e.r. value decreased slightly to 77:23 (from 78:22 in Et_2O) but the yield of the reactions lowered down drastically

to 47.5% and 34% respectively (from 74% in Et_2O). However, EtOAc (Table 3.2, entry 4) as a solvent improved the e.r. value slightly to 79:21, with 52% yield. But using chlorinated solvent DCM diminished the e.r. value to 76:24 with a slight improvement of the yield to 61% (Table 3.2, entry 5). Then, we found that employing acetonitrile as solvent improved the e.r. value to 80:20 with 56% yield (Table 3.2, entry 6).

Table 3.2 Screening of solvents[a]



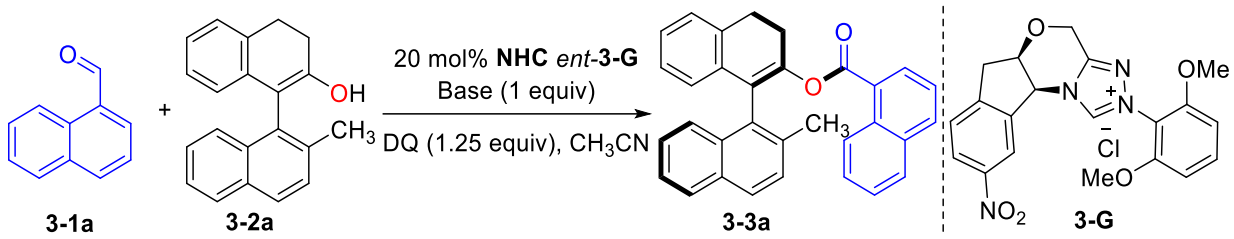
Entry	Solvent	Yield (%)[b]	e.r.[c]
1	Ether	74	78:22
2	THF	47.5	77:23
3	DMSO	34	77:23
4	EtOAc	52	79:21
5	DCM	61	76:24
6	Acetonitrile	56	80:20

[a]Reaction condition: **3-1a** (0.05 mmol), **3-2a** (1.25 equiv), **NHC** *ent*-**3-G** precatalyst (20 mol%), Cs_2CO_3 (1 equiv), DQ (1.25 equiv), Solvent (.025 M), at RT for 3 h. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard with respect to **3-1a**. [c]The e.r. was determined via chiral-phase HPLC analysis.

Therefore, we chose acetonitrile as our optimal solvent and proceeded further to find out the optimal base. The key results of base screening were noted below in Table 3.3. Different kinds of inorganic (K_3PO_4, NaOAc) and organic bases (DMAP, Et_3N, DABCO) were tested in our reaction system (Table 3.3, entry 2-6), but unfortunately none of them were proved to be superior with respect to our initially chosen Cs_2CO_3 base. Then, to further improve the yield,

we repeat our reaction by adding molecular sieves with Cs_2CO_3 base, and we found that the yield improved to 84% and the e.r. value also improved a bit to 82:18 (Table 3.3, entry 7). To eliminate the effect of trace water, we added the reagents of the same reaction inside a glove box, and we found the yield improved further to 91% with 83:17 e.r. value (Table 3.3, entry 8). Lowering down the catalyst loading to 5 mol% did not affect enantioselecvtivity of our reaction, but the yield dropped down a little bit to 90% (Table 3.3, entry 9). To improve the e.r. value further, we carried out our reaction at -20 °C, and the product was isolated in 87.5:12.5 e.r. value with 86% yield (Table 3.3, entry 10).

Table 3.3 Screening of bases[a]



Entry	Base	Yield (%)[b]	e.r.[c]
1	Cs_2CO_3	56	80:20
2	K_3PO_4	56	79:21
3	NaOAc	42	80:20
4	DMAP	43	74.5:25.5
5	Et_3N	12	73:27
6	DABCO	54	79.5:20.5
7[d]	Cs_2CO_3	84	82:18
8[d, e]	Cs_2CO_3	91	83:17
9[d, e, f]	Cs_2CO_3	90	83:17
10[d, e, f, g]	Cs_2CO_3	88 (86)[h]	87.5:12.5

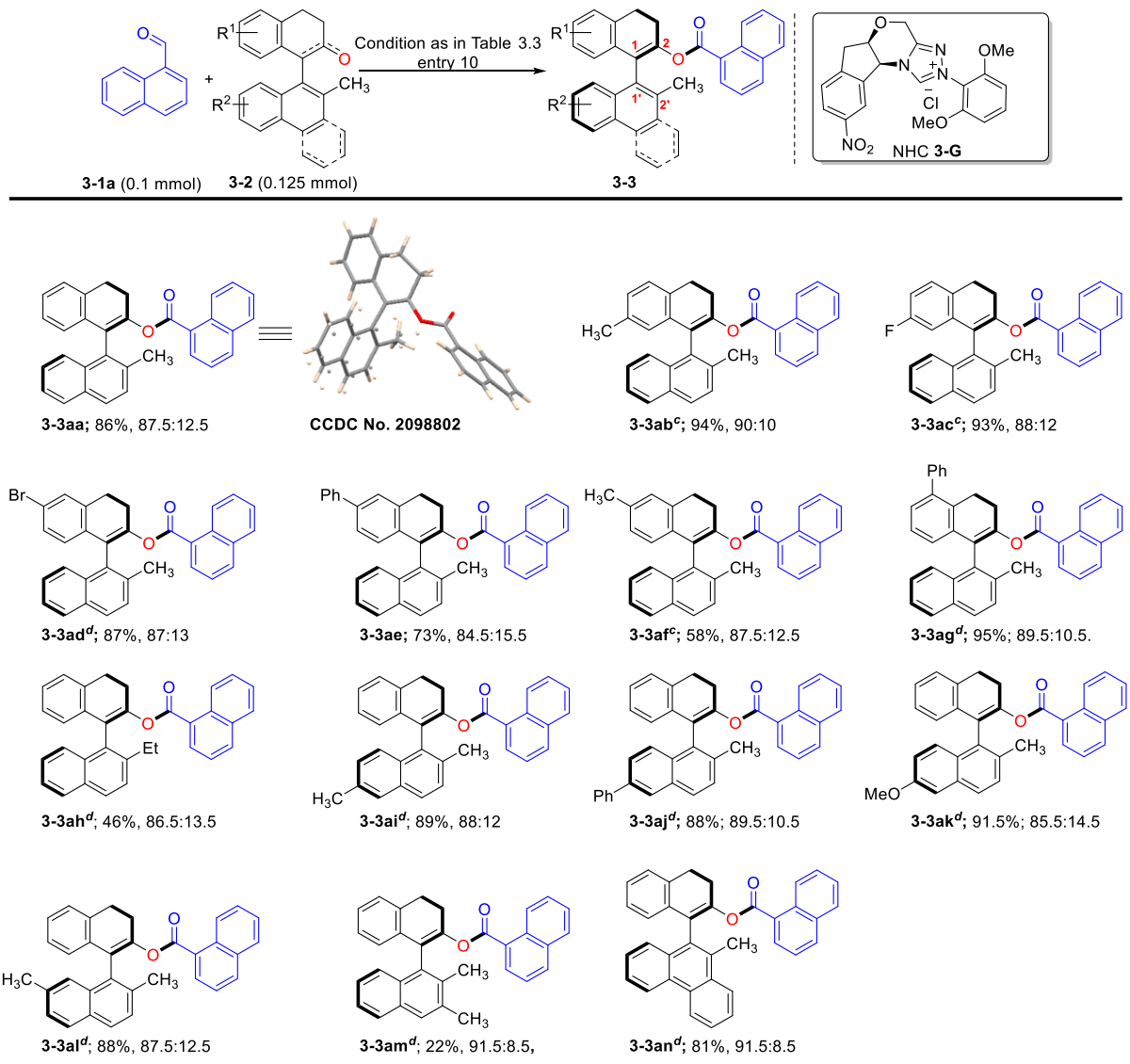
[a]Reaction condition: **3-1a** (0.05 mmol), **3-2a** (1.25 equiv), **NHC** *ent*-**3-G** precatalyst (20 mol%), Base (1 equiv), DQ (1.25 equiv), CH_3CN (.025 M), at RT for 12 h. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard with respect to **3-1a**. [c]The e.r. was determined via chiral-phase HPLC analysis. [d]4 A° MS (100 mg/ml) was used. [e]Reagents were added inside glove box. [f]5 mol% **NHC** *ent*-**3-G** precatalyst was used. [g]Reaction was carried out at -20 ºC for 72 h. [h]Isolated yield in parenthesis.

3.2.2 Substrate scope

After achieving conditions for the proficient synthesis of our product (Table 3.3, entry 10), we moved to evaluate the generality of this reaction with differently substituted bicyclic ketone/enol (**3-2**). The scope was noted down in Table 3.4. Absolute configuration of the products from our catalytic cycle was concluded by determining the absolute configuration of **3-3aa** (**CCDC no 2098802**) by X-ray crystallographic analysis. First, we examined the effect of changing electronic and steric parameters of the ring containing ketone/enol functionality of the bicyclic ketone. Substitution at sterically demanding 7-position, irrespective of electron-rich (-CH_3) or deficient (-F) groups, did not affect the outcome of the reaction significantly (**3-3ab – 3-3ac**). Various substitutions (such as -Br, -Ph, -CH_3) at 6- or 5-positions also gave the enolic ester product in good to excellent yield and moderate enantioselectivity (**3-3ad – 3-3ag**). Then, we moved to examine the tolerence of variyng stereo-electronic factors on the naphthyl ring part of the substrate in reaction outcome. First, we examined the effect of more bulkier group at 2′-position by using ethyl in place of methyl. The desired product was obtained in 46% yield and 86.5:13.5 e.r. value (**3-3ah**). It seems that bulky group at sterically demanding 2′-position made the substrate less reactive towards the catalytic reaction, although there was insignificant effect on the stereoselectivity. Substitution by various groups (such as -CH_3, -Ph, -OMe) at 6′- or sterically encumbered 7′-positions also gave the corresponding axially chiral enolic esters in excellent yield and moderate enantioselectivity (**3-3ai – 3-3al**).Unfortunately, 3′-methyl-substituted ketone as substrate resulted in poor yield (22%), but gave good

enantioselectivity (91.5:8.5 e.r.) (**3-3am**). Probably, the low yield for **3-3am** arised from the fact that the substrate was sluggish to go in enol form to react. We were also delighted to see that changing the 2-methyl naphthalene unit to 9-methylphenanthrene motif also worked smoothly in our reaction conditions and gave desired product in 81% yield and 91.5:8.5 e.r. value (**3-3an**).

Table 3.4 Substrate Scope[a, b]

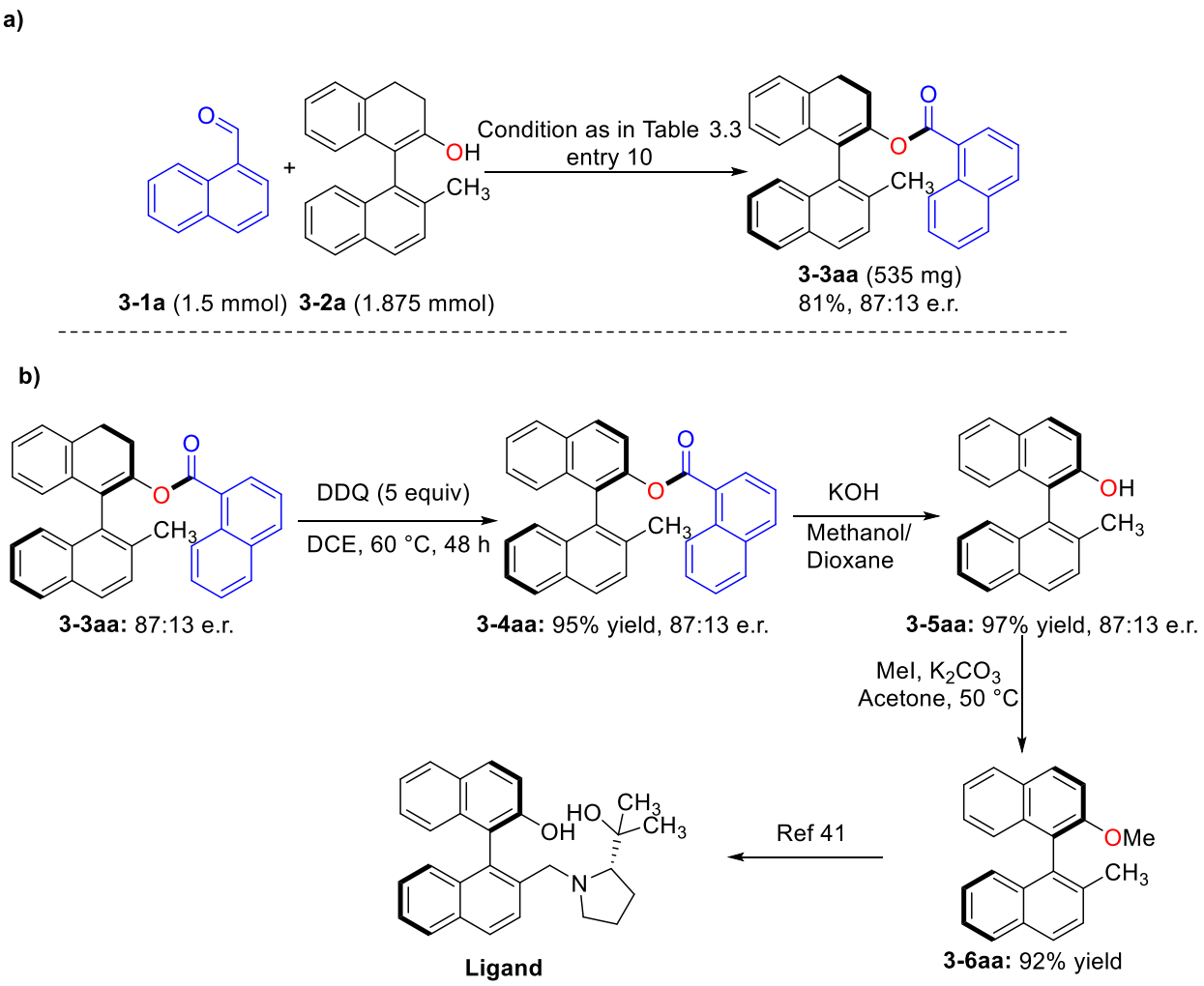


[a]Standard reaction condition: **3-1a** (0.1 mmol), **3-2** (1.25 equiv), **NHC** *ent*-**3-G** precatalyst (5 mol%), Cs_2CO_3 (1 equiv), DQ (1.25 equiv), CH_3CN (.025 M), 4 A° MS (100 mg/ml), -20 °C for 3 days. [b]Isolated yield based on **3-**

1a. The e.r. was determined via chiral-phase HPLC analysis. [c]The reaction was carried out for 4 days. [d]The reaction was carried out for 7 days.

3.2.3 Scale-up reaction and synthetic transformations

For practicality purpose, we carried out a large-scale reaction in 1.5 mmol scale for **3-3aa**, and the product was isolated in 81% yield (535 mg) and 87:13 e.r. value (Scheme 3.7a). We also demonstrated that simple and efficient transformation of our product **3-3aa** leads to important biaryl ligands with proven application (Scheme 3.7b). Upon oxidation of enolic ester **3-3aa** by DDQ resulted in formation of axially chiral biaryl ester **3-4aa** in 95% yield in 87:13 e.r. value. Intermediate **3-6aa,** precursor of bidentate ligands[41] was obtained from **3-4aa** by the hydrolysis of the ester and protection of the phenolic OH group by a methyl group.



Scheme 3.7 a) Scale-up synthesis. b) Formal synthesis of biaryl ligand

3.3 Conclusion

In summary, first example of **NHC**-catalyzed DKR strategy for asymmetric access to axially chiral compound, bicyclic enolic ester was reported. Additionally, this is the first example, where a nucleophilic O-atom from a ketone had been utilized to directly couple with an acyl azolium intermediate in intermolecular reaction catalyzed by **NHC**. The product, bicyclic enolic ester is a valuable precursor for different ligands already reported in literature. We demonstrated the importance of our methodology by doing formal synthesis of a ligand with proven application. Our catalytic reaction has the tolerance over a broad substrate scope. Currently, we are trying to further improve the enantioselectivity and extend the substrate scope of our reaction. Mechanistic study of this reaction is also undergoing in our laboratory.

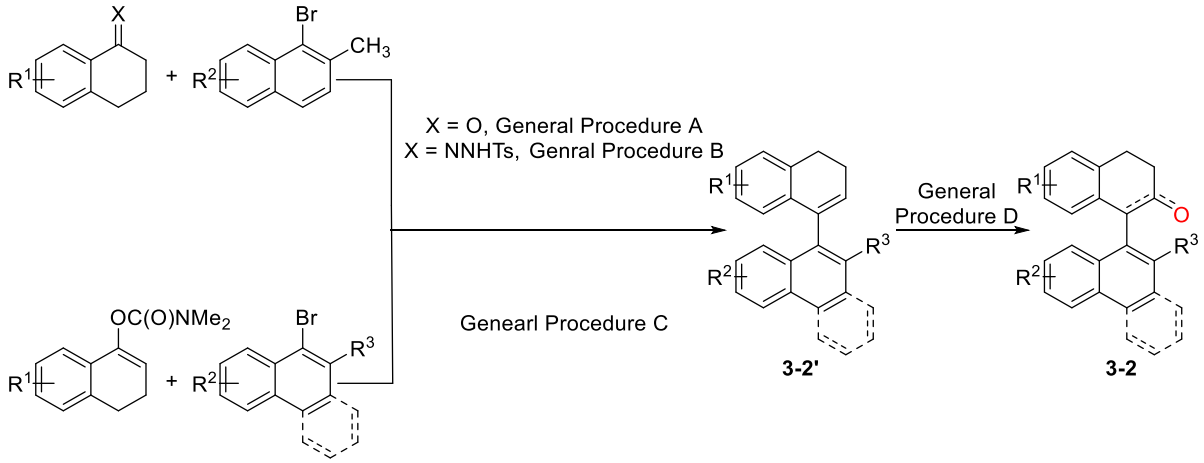
3.4 Experimental section

3.4.1 General information

Please refer to Chapter 2, Section 2.4.1

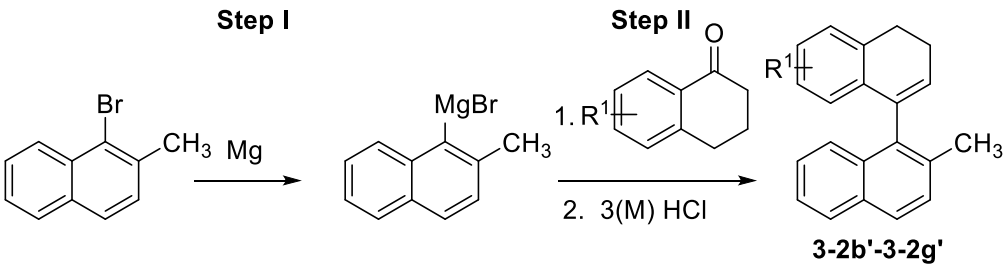
3.4.2 Experimental procedure for synthesis of bicyclic ketone/enol

Enol **3-2a** was made by following the literature procedure.[33] Ketones/enols **3-2b** – **3-2n** were synthesized using the modified literature procedure[33, 42-43] via the sequence depicted bellow, which involve general procedure A, B, C and D.



General Procedure A

Intermediate **3-2b′–3-2g′** was synthesized in two steps following modified literature procedure[33] via general procedure A.



Step I: Preparation of Grignard

1-Bromo-2-methylnaphthalene (1.6 ml, 10 mmol, 1 equiv) and Magnesium turnings (360 mg, 15 mmol, 1.5 equiv) were added to an oven-dried Schlenk tube. The tube was evacuated and refilled with N_2 for three to five times. Then, 20 ml freshly distilled anhydrous THF was added,

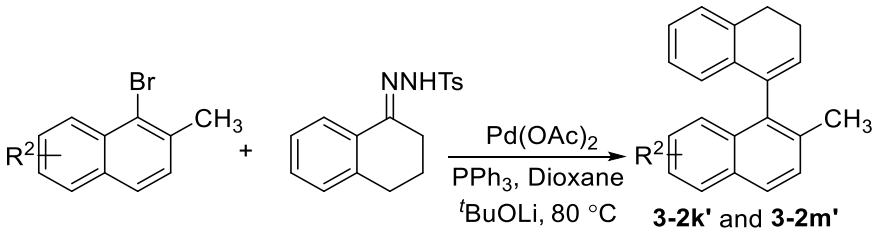
and the resulting suspension was stirred and heated to 60 °C. Then, 1,2-dibromoethane (86 µL, 1 mmol, 0.1 equiv) was added to initiate the reaction and the reaction mixture was continued to stir at reflux for 2 hours.

Step II: Addition of Grignard reagent and elimination reaction

In an oven dried Schlenk tube properly substituted 1-tetralone (1.5 equiv) and anhydrous $CeCl_3$ (2 equiv) was added. Then, the Schlenk tube was evacuated and refilled with N_2 for three to five times, followed by freshly distilled anhydrous THF (10ml/mmol Grignard) was added, and the resulting suspension was stirred vigorously in RT for 2 hours before adding freshly prepared Grignard reagent (1 equiv). After the addition of the Grignard reagent, the resulting suspension stirred in RT for overnight. Then, 3(M) aqueous HCl (10 ml/mmol Grignard) was added to the reaction mixture and the stirring was continued further for another half an hour. After that, the resulting mixture was concentrated by evaporating the THF by rotary evaporation and the aqueous layer was extracted three times by DCM. The combined organic layer was dried by anhydrous Na_2SO_4 and concentrated and purified by silica gel flash column chromatography eluting with hexane to DCM/hexane (1:9) to afford pure **3-2b′–3-2g′**.

General Procedure B

Intermediate **3-2k′** and **3-2m′** was synthesized in one step via a modified literature procedure[42], as depicted bellow.



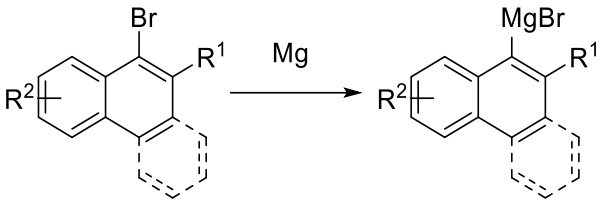
In an oven dried pressure tube was added derivative of 1-bromo-2-methylnaphthalenene (5 mmol, 1.0 equiv), tosyl hydrazone of 1-tetralone (2.35 g, 7.5 mmol, 1.5 equiv), $Pd(OAc)_2$ (112 mg, 0.5 mmol, 10 mol%), PPh_3 (262.1 mg, 1 mmol, 20 mol%), and ^{t}BuOLi (1 g, 12.5 mmol, 2.5 equiv) inside a glove box. Then, the mixture was dissolved by adding 35 ml of anhydrous

dioxane inside glove box. Then the tube was sealed, and the reaction mixture was stirred at 80 °C outside the glove box for 12 hours. After the reaction finished, the reaction was cooled down to RT and the reaction mixture was filtered through a short pad of celite. The filtrate was concentrated and purified by silica gel column chromatography by eluting the product with hexane to DCM/hexane (1:9) to give the pure **3-2k′** and **3-2m′**.

General Procedure C

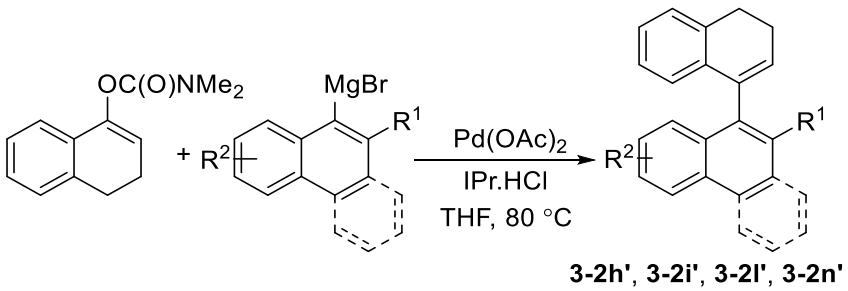
Intermediate **3-2h′**, **3-2i′**, **3-2l′**, and **3-2n′** was synthesized via a modified literature procedure[43], as depicted bellow in two steps.

Step I: Preparation of Grignard



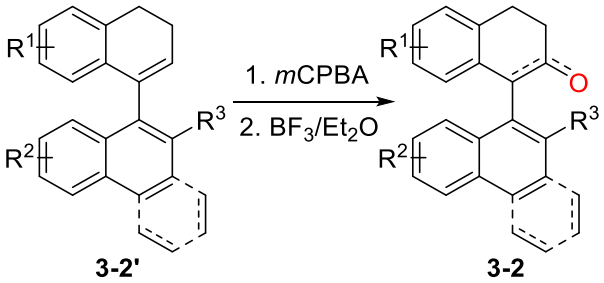
Derivative of 1-bromo-2-alkylnaphthalene (10 mmol, 1 equiv) and Magnesium turnings (360 mg, 1.5 equiv) were added to an oven-dried Schlenk tube. The tube was evacuated and refilled with N_2 for three to five times. Then, 20 ml freshly distilled anhydrous THF was added, and the resulting suspension was stirred and heated to 60 °C. Then, 1,2-dibromoethane (86 µL, 0.1 equiv) was added to initiate the reaction and the reaction mixture was continued to stir at reflux for 2 hours.

Step II: Pd-catalyzed addition of Grignard reagent to enol carbamate



In an oven dried round bottom flux was added dimethyl carbamate of 1-tetralone (1.1 g, 5 mmol, 1 equiv), $Pd(OAc)_2$ (45 mg, 0.2 mmol, 4 mol%), IPr.HCl (136 mg, 0.4 mmol, 8 mol%) and the flux was evacuated and refilled with N_2 for three to five times. Then, freshly distilled 10 ml anhydrous THF was added, followed by freshly prepared Grignard reagent was added (20 ml, 0.5(M), 10 mmol, 2 equiv) and the reaction mixture was stirred at 50 °C overnight. After the reaction was finished the mixture was passed through a short pad of celite and the filtrate was concentrated and purified via silica gel flash column chromatography eluting with hexane to DCM/hexane (1:9) to get the pure **3-2h′**, **3-2i′**, **3-2l′**, and **3-2n′**.

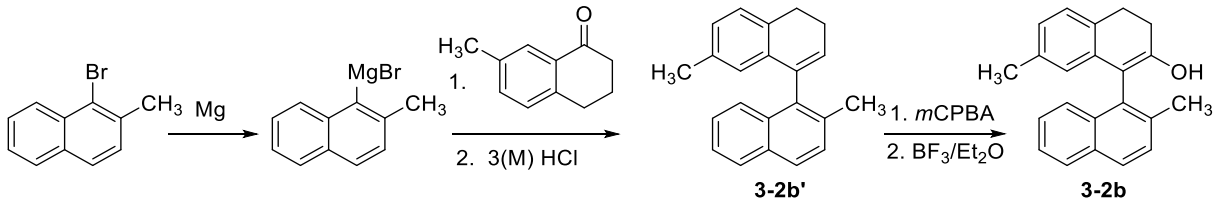
General Procedure D



Alkene **3-2′** was converted to the ketone/enol following the general procedure D.[33] In a round bottom flux was added the alkene **3-2′** (1 equiv) and dissolved in DCM (10 ml/mmol alkene). Then the solution was cooled down to 0 °C and $NaHCO_3$ (2.5 eq.) and *m*CPBA (75% w/w, 2 eq.) was added sequentially. The reaction mixture was stirred 1 h at 0 °C and was quenched by adding saturated aqueous $Na_2S_2O_3$ solution. After that the layers were separated and the organic layer was washed two times by saturated aqueous $Na_2S_2O_3$ solution and followed by brine solution. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to obtain the crude epoxide. The crude epoxide was dissolved in 1:1 Et_2O/DCM (20 ml/mmol alkene) and BF_3-Et_2O (1.6 equiv of alkene) was added and stirred at RT for five minutes. Then, saturated aqueous $NaHCO_3$ was added to quench the reaction and the organic layer was separated. The organic layer was also washed two times with saturated aqueous $NaHCO_3$ followed by brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated,

and the crude product was passed through silica gel column chromatography and/or recrystallization give the ketone/enol **3-2**.

Preparation of 2',7-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2b)



2',7-dimethyl-3,4-dihydro-1,1'-binaphthalene (**3-2b′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 15 ml, 7.5 mmol, 1 eq.), 7-methyl-1-tetralone (1.8 g, 11.25 mmol, 1.5 eq.), $CeCl_3$ (3.7 g, 15 mmol, 2 eq.) in 75 ml THF. The reaction was worked up with 75 ml 3(M) HCl. Product **3-2b′** was isolated in 61% (1.3 g, 4.5 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.75 (m, 3H), 7.40 – 7.30 (m, 3H), 7.11 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.25 (brs, 1H), 5.94 (d, *J* = 1.6 Hz, 1H), 3.02 – 2.95 (m, 2H), 2.59 – 2.47 (m, 2H), 2.31 (s, 3H), 2.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.5, 136.1, 135.2, 133.9, 133.3, 133.0, 132.2, 129.4, 128.8, 127.9, 127.7, 127.5, 127.1, 126.2, 125.9, 125.5, 124.9, 28.0, 23.9, 21.2, 20.4.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}Na^+$: 307.1463 $(M+Na)^+$, found: 307.1454.

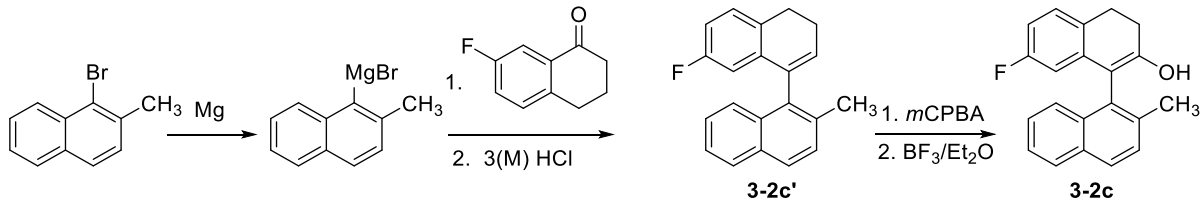
2',7-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2b**) was synthesized following the **general procedure D** by using **3-2b′** (1.2 g, 4.14 mmol), 75% w/w *m*CPBA (1.9 g, 8.28 mmol, 2 eq.), $NaHCO_3$ (869.4 mg, 10.35 mmol, 2.5 eq.), and 80 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent and followed by recrystallization to remove trace impurity in hexane/EA giving the pure **3-2b** (800 mg, 2.66 mmol, 64%).

1H NMR (400 MHz, CDCl3) δ 7.86 (t, *J* = 8.6 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.50 - 7.36 (m, 3H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 1H), 6.03 (s, 1H), 4.58 (brs, 1H), 3.17 – 3.03 (m, 2H), 2.74 – 2.60 (m, 2H), 2.32 (s, 3H), 2.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 137.0, 136.1, 135.9, 133.0, 132.6, 129.2, 129.1, 129.1, 128.4, 128.1, 127.0, 126.7, 125.5, 125.4, 125.1, 123.8, 108.0, 28.3, 26.4, 21.1, 20.0.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1598.

Preparation of 7-fluoro-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2c)



7-fluoro-2'-methyl-3,4-dihydro-1,1'-binaphthalene (**3-2c′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 15 ml, 7.5 mmol, 1 eq.), 7-fluoro-1-tetralone (1.85 g, 11.25 mmol, 1.5 eq.), $CeCl_3$ (3.7 g, 15 mmol, 2 eq.) in 75 ml THF. The reaction was worked up with 75 ml 3(M) HCl. Product **3-2c′** was isolated in 23% (495 mg, 1.7 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.36 - 7.32 (m 1H), 7.15 (dd, *J* = 8.2, 5.8 Hz, 1H), 6.78 (td, *J* = 8.4, 2.7 Hz, 1H), 6.12 (dd, *J* = 10.1, 2.6 Hz, 1H), 6.03 (t, *J* = 4.5 Hz, 1H), 3.03 – 2.90 (m, 2H), 2.58 – 2.51 (m, 2H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 242.5 Hz), 137.2 (d, *J* = 7.3 Hz), 136.2 (d, *J* = 2.1 Hz), 135.5, 134.0, 133.0, 132.3, 131.4 (d, *J* = 3.0 Hz), 130.6, 128.8, 128.7 (d, *J* = 7.8 Hz), 128.0, 127.5, 126.1, 125.8, 125.0, 113.3 (d, *J* = 21.4 Hz), 111.7 (d, *J* = 22.6 Hz), 27.5, 23.8, 20.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.6.

HRMS (ESI, m/z): calculated for $C_{21}H_{18}F^+$: 289.1393 $(M+H)^+$, found: 289.1402.

7-fluoro-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2c**) was synthesized following the **general procedure D** by using **3-2c′** (400 mg, 1.4 mmol), 75% w/w *m*CPBA (644 mg, 2.8 mmol, 2.0 eq.), $NaHCO_3$ (294 mg, 3.5 mmol, 2.5 eq.), and 28 ml 1:1 DCM/Et_2O. By keeping the crude product in -20 °C for 48 hours solid crystals appeared which was further washed with hexane/Et_2O to get the pure **3-2c** in 39% yield (167.2 mg, 0.55 mmol).

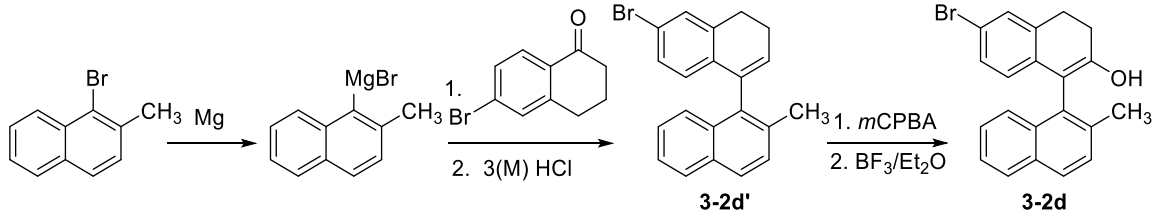
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 13.3, 8.1 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.11 – 7.08 (m, 1H), 6.64 (td, *J* = 8.4, 2.5 Hz, 1H), 5.89 (dd, *J* = 10.4, 2.4 Hz, 1H), 4.69 (brs, 1H), 3.15 – 3.01 (m, 2H), 2.74 – 2.60 (m, 2H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 241.6 Hz), 153.1, 138.4 (d, *J* = 8.0 Hz), 137.1, 133.0, 132.8, 129.1, 128.9, 128.4, 128.1 (d, *J* = 8.2 Hz), 127.6 (d, *J* = 2.9 Hz), 127.0, 125.6, 125.2, 110.6 (d, *J* = 21.5 Hz), 110.1 (d, *J* = 23.2 Hz), 107.8 (d, *J* = 2.2 Hz), 28.0, 26.5, 20.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -116.9.

HRMS (ESI, m/z): calculated for $C_{21}H_{18}FO^+$: 305.1342 $(M+H)^+$, found: 305.1342.

Preparation of 6-bromo-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2d)



6-bromo-2'-methyl-3,4-dihydro-1,1'-binaphthalene (**3-2d′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 8 ml, 4 mmol, 1 eq.), 6-bromo-1-tetralone (1.35 g, 6 mmol, 1.5 eq.), $CeCl_3$ (2 g, 8 mmol, 2 eq.) in 40 ml THF. The reaction was worked up with 40 ml 3(M) HCl. Product **3-2d′** was isolated in 44% (610 mg, 1.75 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.03 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.26 (d, *J* = 8.2 Hz, 1H), 6.00 (t, *J* = 4.5 Hz, 1H), 3.04 – 2.93 (m, 2H), 2.58 - 2.51(m , 2H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 136.0, 135.6, 134.2, 133.9, 133.0, 132.2, 130.6, 129.8, 129.7, 128.8, 128.0, 127.4, 126.4, 126.1, 125.9, 125.0, 120.6, 28.1, 23.5, 20.3.

HRMS (ESI, m/z): calculated for $C_{21}H_{18}Br^+$: 349.0592 $(M+H)^+$, found: 349.0594.

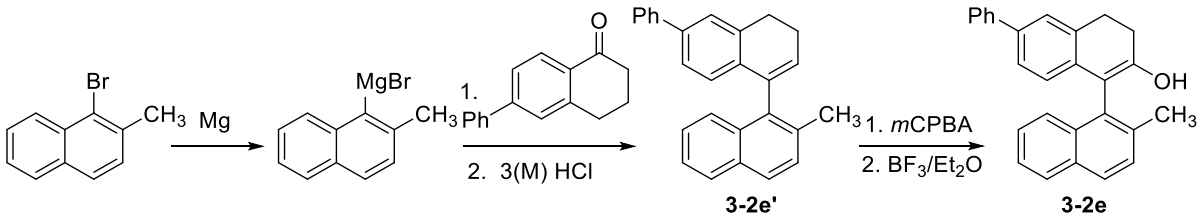
6-bromo-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2d**) was synthesized following the **general procedure D** by using **3-2d′** (593 mg, 1.7 mmol), 75% w/w *m*CPBA (782 mg, 3.4 mmol, 2.0 eq.), $NaHCO_3$ (357 mg, 4.25 mmol, 2.5 eq.), and 34 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 10:90:3 EA/hexane/Et_3N eluent to get the pure **3-2d** in 27% yield (167.2 mg, 0.46 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, *J* = 7.8 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.43 - 7.37 (m, 1H), 7.32 (brs, 1H), 6.99 (d, *J* = 7.0 Hz, 1H), 6.05 (d, *J* = 8.2 Hz, 1H), 3.15- 3.09 (m, 2H), 2.72 - 2.66 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 137.1, 135.2, 134.4, 133.0, 132.8, 130.2, 129.6, 129.2, 128.8, 128.4, 127.0, 125.7, 125.3, 124.7, 117.8, 107.6, 28.5, 26.1, 20.0.

HRMS (ESI, m/z): calculated for $C_{21}H_{18}BrO^+$: 365.0541 $(M+H)^+$, found: 365.0543.

Preparation of 2'-methyl-6-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2e)



2'-methyl-6-phenyl-3,4-dihydro-1,1'-binaphthalene (**3-2e′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 13.8 ml, 6.9 mmol, 1 eq.), 6-phenyl-1-tetralone (2.3 g, 10.3 mmol, 1.5 eq.), $CeCl_3$ (3.4 g, 13.8 mmol, 2 eq.) in 69 ml THF. The reaction was worked up with 69 ml 3(M) HCl. Product **3-2e′** was isolated in 56% (1.36 g, 3.9 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.73 (m, 3H), 7.56 (dd, *J* = 7.0, 5.8 Hz, 2H), 7.47 (s, 1H), 7.43 – 7.36 (m, 4H), 7.36 – 7.26 (m, 2H), 7.15 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 6.00 (t, *J* = 4.5 Hz, 1H), 3.17 – 2.98 (m, 2H), 2.67 – 2.55 (m, 2H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 139.9, 136.5, 136.2, 134.5, 134.0, 133.2, 132.2, 129.4, 128.9, 128.8, 128.0, 127.3, 127.2, 127.1, 126.5, 126.1, 126.0, 125.4, 125.3, 124.9, 28.6, 23.8, 20.4.

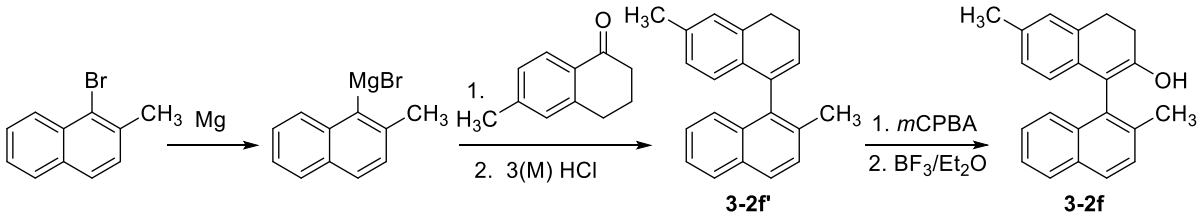
HRMS (ESI, m/z): calculated for $C_{27}H_{23}^+$: 347.1800 $(M+H)^+$, found: 347.1790.

2'-methyl-6-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2e**) was synthesized following the **general procedure D** by using **3-2e′** (935 mg, 2.7 mmol), 75% w/w *m*CPBA (1.25 g, 5.4 mmol, 2.0 eq.), $NaHCO_3$ (567 mg, 6.75 mmol, 2.5 eq.), and 54 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent to get the pure **3-2e** in 57% yield (560 mg, 1.54 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (t, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.46 - 7.43 (m, 2H), 7.41 - 7.37 (m, 3H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 6.27 (d, *J* = 8.0 Hz, 1H), 3.27 – 3.16 (m, 2H), 2.81 – 2.69 (m, 2H), 2.36 (s, 3H).

HRMS (ESI, m/z): calculated for $C_{27}H_{23}O^+$: 363.1749 $(M+H)^+$, found: 363.1758.

Preparation of 2',6-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2f)



2',6-dimethyl-3,4-dihydro-1,1'-binaphthalene (**3-2f′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 5.4 ml, 2.7 mmol, 1 eq.), 6-methyl-1-tetralone (649 mg, 4.05 mmol, 1.5 eq.), $CeCl_3$ (1.3 g, 5.4 mmol,

2 eq.) in 27 ml THF. The reaction was worked up with 27 ml 3(M) HCl. Product **3-2f′** was isolated in 22% (317 mg, 1.2 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.84 (dd, *J* = 8.1, 3.2 Hz, 2H), 7.49 - 7.38 (m, 3H), 7.14 (brs, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 5.99 (t, *J* = 4.5 Hz, 1H), 3.11 - 2.98 (m, 2H), 2.65 - 2.60 (m, 2H), 2.40 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 136.6, 136.5, 136.0, 133.9, 133.2, 132.7, 132.2, 128.8, 128.6, 128.3, 128.2, 127.9, 127.2, 127.1, 126.2, 126.0, 124.9, 28.5, 23.8, 21.3, 20.4.

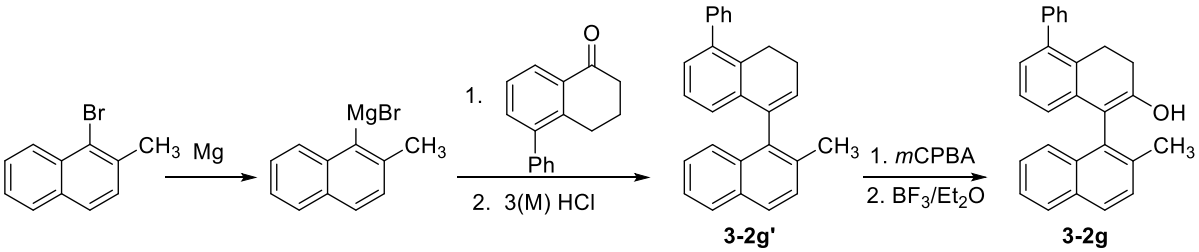
HRMS (ESI, m/z): calculated for $C_{22}H_{20}Na^+$: 307.1463 $(M+Na)^+$, found: 307.1465.

2',6-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2f**) was synthesized following the **general procedure D** by using **3-2f′** (278 mg, .97 mmol), 75% w/w *m*CPBA (449 mg, 1.95 mmol, 2.0 eq.), $NaHCO_3$ (204 mg, 2.4 mmol, 2.5 eq.), and 20 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent to get the pure **3-2e** in 70% yield (206 mg, .68 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.45 - 7.35 (m, 2H), 7.03 (brs, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.10 (d, *J* = 7.8 Hz, 1H), 3.16 - 3.06 (m, 2H), 2.72 - 2.64 (m, 2H), 2.32 (s, 3H), 2.26 (s, 3H).

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1591.

Preparation of 2'-methyl-5-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2g)



2'-methyl-5-phenyl-3,4-dihydro-1,1'-binaphthalene (**3-2g′**) was synthesized following the **general procedure A** by using (2-methylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 14 ml, 7 mmol, 1 eq.), 5-phenyl-1-tetralone (2.3 g, 10.5 mmol, 1.5 eq.), $CeCl_3$ (3.4 g, 14 mmol,

2 eq.) in 70 ml THF. The reaction was worked up with 70 ml 3(M) HCl. Product **3-2g′** was isolated in 57% (1.4 g, 4 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.46 – 7.39 (m, 6H), 7.37 - 7.33 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 6.00 (t, *J* = 4.4 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.47 – 2.41 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.8, 140.7, 137.0, 136.6, 135.7, 134.0, 133.3, 132.2, 129.6, 129.1, 128.8, 128.2, 128.0, 127.3, 127.0, 126.2, 126.1, 126.0, 124.9, 124.2, 25.6, 23.7, 20.5.

HRMS (ESI, m/z): calculated for $C_{27}H_{23}^+$: 347.1800 $(M+H)^+$, found: 347.1793.

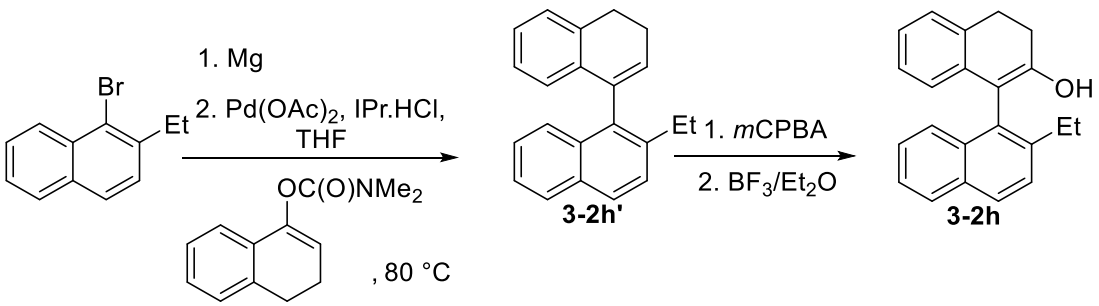
2'-methyl-5-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2g**) was synthesized following the **general procedure D** by using **3-2g′** (1.33 g, 3.8 mmol), 75% w/w *m*CPBA (1.75 g, 7.6 mmol, 2.0 eq.), $NaHCO_3$ (798 mg, 9.5 mmol, 2.5 eq.), and 76 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent to get the pure **3-2e** in 73.6% yield (1 g, 2.8 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (t, *J* = 7.9 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.51 – 7.37 (m, 8H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 1H), 3.12 - 3.06 (m, 2H), 2.62 – 2.56 (m, 2H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 142.0, 140.5, 137.2, 136.6, 133.2, 132.8, 129.6, 129.5, 129.2, 128.7, 128.4, 128.3, 128.2, 127.0, 126.9, 126.8, 126.3, 125.6, 125.6, 122.6, 108.3, 26.33, 26.2, 20.2.

HRMS (ESI, m/z): calculated for $C_{27}H_{23}O^+$: 363.1749 $(M+H)^+$, found: 363.1749.

Preparation of 2'-ethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2h)



2'-ethyl-3,4-dihydro-1,1'-binaphthalene (**3-2h′**) was synthesized following the **general procedure C** by using (2-ethylhylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 20 ml, 10 mmol, 2 eq.). Product **3-2h′** was isolated in 98% (1.4 g, 4.9 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.74 (m, 3H), 7.43 (d, *J* = 8.5 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 7.6 Hz, 1H), 5.98 (t, *J* = 4.5 Hz, 1H), 3.06 – 2.93 (m, 2H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.59 – 2.48 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 136.3, 135.9, 135.8, 135.6, 133.2, 132.2, 129.4, 127.9, 127.6, 127.6, 127.3, 127.1, 126.6, 126.4, 126.0, 125.2, 125.0, 28.4, 27.0, 23.7, 16.1.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}^+$: 285.1643 $(M+H)^+$, found: 285.1638.

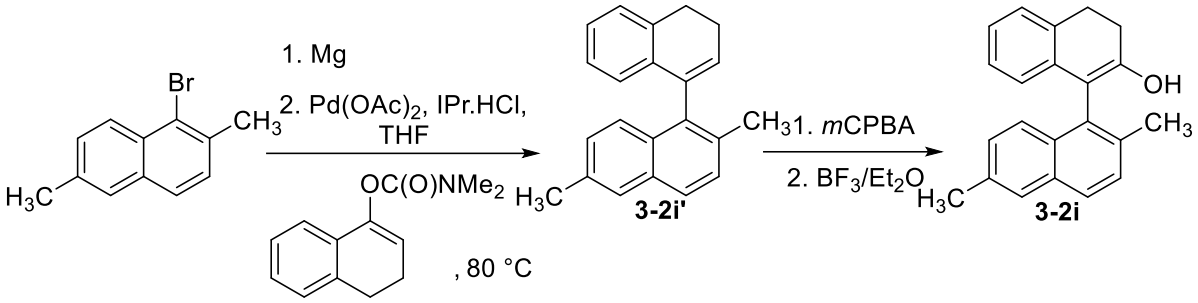
2'-ethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2h**) was synthesized following the **general procedure D** by using **3-2h′** (1.3 g, 4.6 mmol), 75% w/w *m*CPBA (2.1 g, 9.2 mmol, 2 eq.), $NaHCO_3$ (966 mg, 11.5 mmol, 2.5 eq.), and 92 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent and followed by recrystallization to remove trace impurity in hexane/Et_2O giving the pure **3-2h** in 69.5% (961 mg, 3.2 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 - 7.84 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.98 (t, *J* = 7.1 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 6.3 Hz, 1H), 4.60 (brs, 1H), 3.14 (t, *J* = 8.0 Hz, 2H), 2.78 – 2.62 (m, 4H), 1.18 – 1.14 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0, 143.2, 136.7, 133.1, 132.8, 132.1, 129.0, 128.3, 128.3, 127.7, 127.2, 126.9, 126.7, 125.7, 125.6, 124.6, 123.5, 107.9, 28.8, 27.1, 26.3, 15.5.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1602.

Preparation of 2',6'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2i)



2',6'-dimethyl-3,4-dihydro-1,1'-binaphthalene (**3-2i′**) was synthesized following the **general procedure C** by using (2,6-dimethylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 20 ml, 10 mmol, 2 eq.). Product **3-2i′** was isolated in 89% (1.26 g, 4.4 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.59 (brs, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.16 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.10 (td, *J* = 7.4, 1.1 Hz, 1H), 6.92 (t, *J* = 7.1 Hz, 1H), 6.41 (d, *J* = 7.6 Hz, 1H), 5.96 (t, *J* = 4.5 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.59 – 2.52 (m, 2H), 2.46 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.1, 136.0, 135.4, 134.4, 132.9, 132.4, 131.4, 129.2, 128.9, 128.2, 127.6, 127.1, 126.9, 126.7, 126.6, 126.0, 124.9, 28.4, 23.7, 21.6, 20.2.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}Na^+$: 307.1463 $(M+Na)^+$, found: 307.1461.

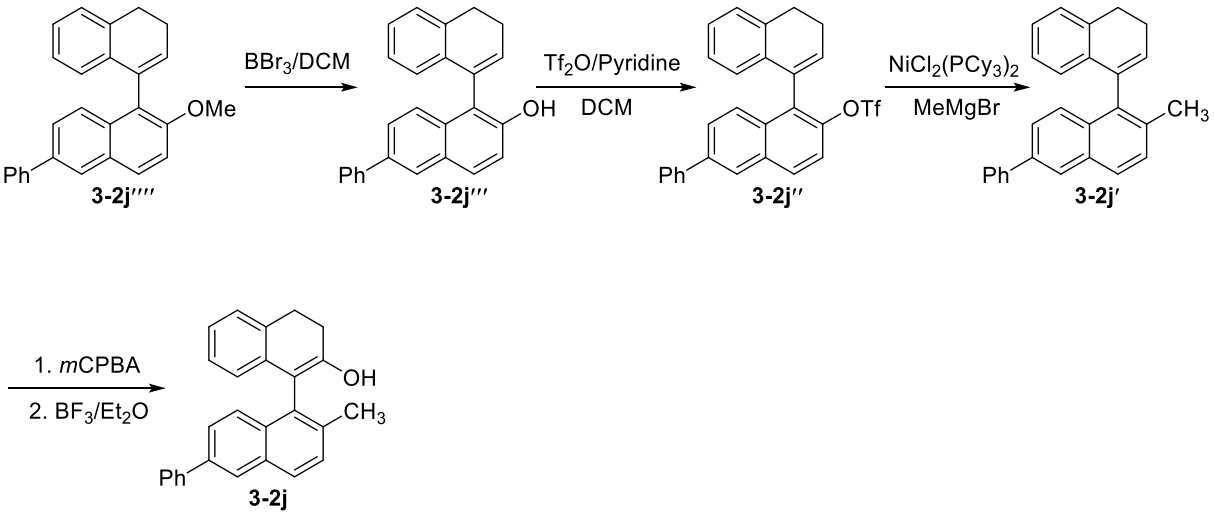
2',6'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2i**) was synthesized following the **general procedure D** by using **3-2i′** (1.26 g, 4.4 mmol), 75% w/w *m*CPBA (2 g, 8.8 mmol, 2 eq.), $NaHCO_3$ (924 mg, 11 mmol, 2.5 eq.), and 88 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent and followed by recrystallization to remove trace impurity in hexane/Et_2O giving the pure **3-2h** in 72% (950 mg, 3.16 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.64 - 7.62 (m 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.22 – 7.18 (m, 2H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.20 (d, *J* = 7.6 Hz, 1H), 4.61 (brs, 1H), 3.18 - 3.07 (m, 2H), 2.77 - 2.64 (m, 2H), 2.48 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 136.2, 136.0, 135.2, 133.0, 132.2, 131.4, 129.2, 129.1, 128.9, 128.0, 127.3, 127.2, 126.8, 125.4, 124.6, 123.3, 108.2, 28.8, 26.3, 21.6, 20.0.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1595.

Preparation of 2'-methyl-6'-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2j)



6-phenyl-3',4'-dihydro-[1,1'-binaphthalen]-2-ol (**3-2j′′′**) was synthesized following the method bellow.

In an oven dried round bottom flux was added 2'-methoxy-6'-phenyl-3,4-dihydro-1,1'-binaphthalene[33] (**3-2j′′′′**) (4.42 g, 12.2 mmol, 1equiv), and the flux was evacuated and refilled with N_2 for 3 times. 120 ml DCM was added to the reaction vessel and the flux was cooled down to -78 °C. Then, BBr_3 (2.4 ml, 25 mmol, 2.05 eq.) was added to the reaction mixture at -78 °C dropwise. After the addition was completed, stirring was continued further 30 minutes at that temperature followed by increase the temperature slowly to RT. After stirring 3 hours at RT, the reaction was quenched by adding saturated aqueous $NaHCO_3$ the organic layer was separated and concentrated. Purification of the crude reaction mixture by silica gel column chromatography, eluting with 1:4 EA/hexane, gave the product **3-2j′′′** in 96% yield (4.1 g, 11.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.4 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.53 (m, 4H), 7.40 - 7.36 (m, 2H), 7.29 - 7.25 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.11 (td, *J* = 7.4, 1.0 Hz, 1H), 6.93 (t, *J* = 7.1 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.21 (t, *J* = 4.4 Hz, 1H), 5.48 (s, 1H), 3.09 – 3.00 (m, 1H), 2.96 – 2.89 (m, 1H), 2.56 - 2.50 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.9, 141.1, 136.1, 136.0, 133.9, 133.0, 132.6, 132.3, 129.8, 129.3, 128.9, 128.0, 127.9, 127.3, 127.1, 127.0, 126.2, 126.1, 125.5, 125.1, 118.7, 117.9, 28.0, 23.7.

HRMS (ESI, m/z): calculated for $C_{26}H_{21}O^+$: 371.1412 $(M+H)^+$, found: 371.1414.

6-phenyl-3',4'-dihydro-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (**3-2j′′**) was synthesized following the method bellow.

In an oven dried round bottom flux, **3-2j′′′** (4 g, 11.5 mmol, 1 eq.) was taken and the flux was evacuated and refilled with N_2 for three times. 70 ml anhydrous DCM was added, and the solution was cooled down to 0 °C. Pyridine (1.87 ml, 23 mmol, 2eq.) was added to the reaction mixture followed by Tf_2O (2.94 ml, 17.25 mmol, 1.5 eq.) was added dropwise at that temperature and stirring was continued 0 °C – RT by monitoring the reaction by TLC. After the reaction was finished 1 (M) aqueous HCl was added, and organic layer was separated and dried over Na_2SO_4 and concentrated and applied to flash column chromatography eluting with DCM/hexane (1:9) gave the intermediate **3-2j′′** in 85% yield (4.7 g, 9.8 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 1.6 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.68 (m, 3H), 7.50 – 7.45 (m, 3H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 3.6 Hz, 1H), 7.14 (td, *J* = 7.4, 0.9 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 6.24 (t, *J* = 4.5 Hz, 1H), 3.13 – 2.97 (m, 2H), 2.65 (td, *J* = 8.1, 4.6 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 140.4, 139.9, 135.9, 134.3, 133.0, 133.0, 132.8, 131.2, 131.2, 130.3, 129.1, 128.0, 127.8, 127.6, 127.5, 127.3, 126.6, 126.0, 125.0, 112.0, 118.6 (q, J = 321.18 Hz), 27.8, 23.7.

^{19}F NMR (377 MHz, $CDCl_3$) δ -74.3.

HRMS (ESI, m/z): calculated for $C_{27}H_{20}F_3O_3S^+$: 481.1085 $(M+H)^+$, found: 481.1080.

2'-methyl-6'-phenyl-3,4-dihydro-1,1'-binaphthalene (**3-2j′**) was synthesized following the method bellow.

In an oven dried Schlenk tube, **3-2j′′** (4.02 g,8.36 mmol, 1 eq.), $NiCl_2(PCy_3)_2$ (435 mg,0.63 mmol, 7.5 mol%) was added and the flux was evacuated and refilled by N_2 for three times. Then anhydrous THF (50 ml) was added to the reaction mixture and the reaction mixture was cooled down to 0 °C. 3 (M) MeMgBr (14 ml, 42 mmol, 5 eq.) was added to the reaction mixture dropwise at the same temperature and the reaction was allowed to slowly warm to RT while the reaction was monitored by TLC. After the reaction was finished, water was added carefully to quench, and the mixture was extracted by EA for three times. The combined organic layer was dried over Na_2SO_4 and concentrated in rotavapor followed by silica gel column chromatography eluting with hexane gave **3-2j′** in 82% yield (2.4 g, 6.9 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 1.4 Hz, 1H), 7.81 (dd, *J* = 11.0, 8.8 Hz, 2H), 7.68 – 7.66 (m, 2H), 7.59 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.34 - 7.30 (m, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 1H), 5.98 (t, *J* = 4.5 Hz, 1H), 3.08 – 2.94 (m, 2H), 2.62 – 2.49 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 137.6, 136.7, 136.2, 136.0, 135.3, 134.1, 132.5, 132.4, 129.4, 129.3, 128.9, 127.7, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7, 125.9, 125.7, 124.9, 28.4, 23.7, 20.4.

HRMS (ESI, m/z): calculated for $C_{27}H_{23}^+$: 347.1800 $(M+H)^+$, found: 347.1797.

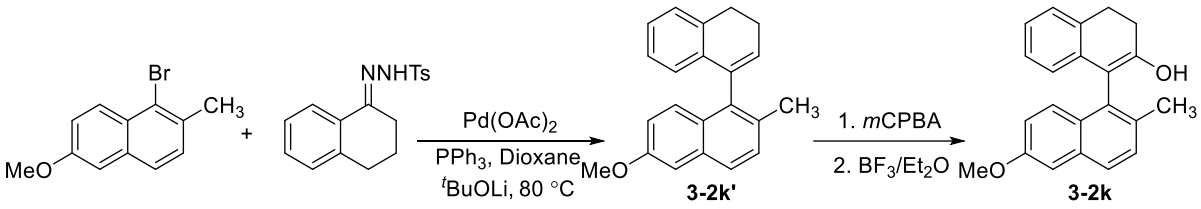
2'-methyl-6'-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2j**) was synthesized following the **general procedure D** by using **3-2j′** (1.94 g, 5.6 mmol), 75% w/w *m*CPBA (2.6 g, 11.2 mmol, 2 eq.), $NaHCO_3$ (1.2 g, 14 mmol, 2.5 eq.), and 112 ml 1:1 DCM/Et_2O. The crude product was directly crystalyzed from hexane/EA to get pure **3-2j** in 69% (1.4 g, 3.9 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (brs, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.70 - 7.65 (m, 3H), 7.50 - 7.36 (m, 3H), 7.36 (t, *J* = 7.1 Hz, 1H), 7.20 (d, *J* = 6.9 Hz, 1H), 7.00 (t, *J* = 7.0 Hz, 1H), 6.90 (t, *J* = 7.1 Hz, 1H), 6.24 (d, *J* = 7.3 Hz, 1H), 4.66 (brs, 1H), 3.22 – 3.09 (m, 2H), 2.79 – 2.66 (m, 2H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 141.1, 138.3, 137.2, 136.1, 133.1, 132.4, 132.2, 129.6, 129.1, 129.0, 129.0, 127.5, 127.3, 127.0, 126.5, 126.2, 126.2, 124.7, 123.2, 108.1, 28.8, 26.4, 20.1.

HRMS (ESI, m/z): calculated for $C_{27}H_{23}O^+$: 363.1749 $(M+H)^+$, found: 363.1743.

Preparation of 6'-methoxy-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2k)



6'-methoxy-2'-methyl-3,4-dihydro-1,1'-binaphthalene (**3-2k′**) was synthesized following the **general procedure B** by using 1-bromo-6-methoxy-2-methylnaphthalene. Product **3-2k′** was isolated in 81% yield (1.22 g, 4.06 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 2H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 1H), 7.11 (d, *J* = 2.6 Hz, 1H), 7.08 (td, *J* = 7.5, 1.1 Hz, 1H), 7.00 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.41 (d, *J* = 7.5 Hz, 1H), 5.95 (t, *J* = 4.5 Hz, 1H), 3.86 (s, 3H), 3.05 – 2.93 (m, 2H), 2.57 – 2.49 (m, 2H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 136.8, 136.3, 136.0, 135.3, 133.3, 131.5, 129.4, 129.2, 128.7, 127.8, 127.6, 127.1, 126.7, 126.1, 124.9, 118.5, 106.0, 55.3, 28.3, 23.7, 20.1.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}ONa^+$: 323.1412 $(M+Na)^+$, found: 323.1405.

6'-methoxy-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2k**) was synthesized following the **general procedure D** by using **3-2k′** (1.2 g, 4 mmol), 75% w/w *m*CPBA (1.84 g, 8 mmol, 2 eq.), $NaHCO_3$ (840 mg, 10 mmol, 2.5 eq.), and 80 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent giving the pure **3-2k** in 21% (270 mg, 0.85 mmol) yield.

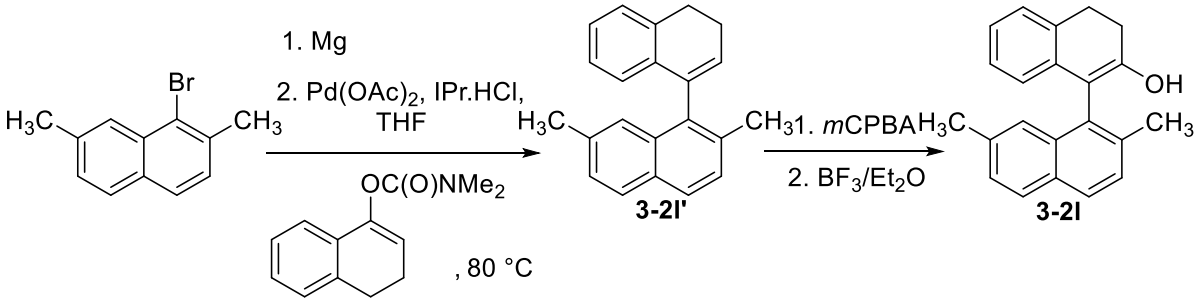
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.21 - 7.14 (m, 2H), 7.08 - 7.03 (t, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 6.88

(t, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 7.4 Hz, 1H), 4.62 (s, 1H), 3.90 (s, 3H), 3.16 - 3.10 (m, 2H), 2.71 - 2.66 (m, 2H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.47, 151.72, 136.16, 134.48, 133.92, 132.17, 129.75, 129.12, 128.57, 127.42, 127.25, 126.75, 124.58, 123.22, 119.30, 108.24, 106.43, 55.44, 28.78, 26.30, 19.77.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O_2^+$: 317.1542 $(M+H)^+$, found: 317.1546.

Preparation of 2',7'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2l)



2',7'-dimethyl-3,4-dihydro-1,1'-binaphthalene (**3-2l′**) was synthesized following the **general procedure C** by using (2,7-dimethylnaphthalen-1-yl) magnesium bromide (0.5 M in THF, 20 ml, 10 mmol, 2 eq.). Product **3-2l′** was isolated in 93% (1.32 g, 4.65 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.54 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.05 (t, *J* = 7.4 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 5.92 (t, *J* = 4.5 Hz, 1H), 3.01 – 2.91 (m, 2H), 2.59 – 2.44 (m, 2H), 2.34 (s, 3H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.0, 135.6, 135.5, 135.3, 133.8, 133.4, 130.5, 129.0, 127.8, 127.8, 127.6, 127.2, 127.0, 127.0, 126.7, 124.9, 124.9, 28.4, 23.7, 22.1, 20.4.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}Na^+$: 307.1463 $(M+Na)^+$, found: 307.1468.

2',7'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (**3-2l**) was synthesized following the **general procedure D** by using **3-2l′** (1.14 g, 4 mmol), 75% w/w *m*CPBA (1.84 g, 8 mmol, 2 eq.), $NaHCO_3$ (840 mg, 10 mmol, 2.5 eq.), and 80 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent and followed by

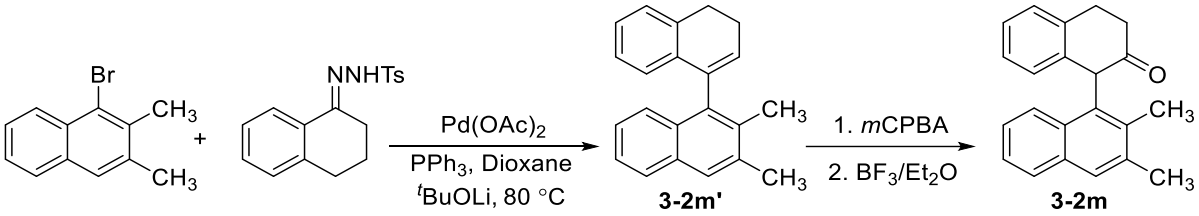
recrystallization to remove trace impurity in hexane/Et_2O giving the pure **3-2l** in 59% (706 mg, 2.35 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (t, *J* = 8.3 Hz, 2H), 7.49 (brs, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.22 (d, *J* = 7.4 Hz, 1H), 4.60 (brs, 1H), 3.15 (t, *J* = 7.9 Hz, 2H), 2.80 – 2.61 (m, 2H), 2.39 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 137.1, 136.6, 136.2, 133.3, 132.3, 131.0, 128.3, 128.3, 128.2, 127.8, 127.2, 126.8, 124.5, 124.3, 123.2, 108.3, 28.8, 26.3, 22.2, 20.1.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1591.

Preparation of 2',3'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-ol (3-2m)



2',3'-dimethyl-3,4-dihydro-1,1'-binaphthalene (**3-2m′**) was synthesized following the **general procedure B** by using 1-bromo-2,3-dimethylnaphthalene. Product **3-2m′** was isolated in 92% (1.3 g, 4.6 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.60 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.08 – 7.04 (m, 1H), 6.88 (t, *J* = 7.7 Hz, 1H), 6.42 (d, *J* = 7.6 Hz, 1H), 5.92 (t, *J* = 4.5 Hz, 1H), 2.98 (td, *J* = 8.3, 3.1 Hz, 2H), 2.52 (ddd, *J* = 16.2, 8.3, 5.0 Hz, 2H), 2.44 (s, 3H), 2.22 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.26, 136.35, 135.96, 135.53, 133.86, 132.31, 131.92, 129.17, 127.61, 127.18, 127.16, 127.08, 126.69, 126.22, 125.07, 125.04, 124.96, 28.38, 23.72, 21.27, 17.30.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}Na^+$: 307.1463 $(M+Na)^+$, found: 307.1464.

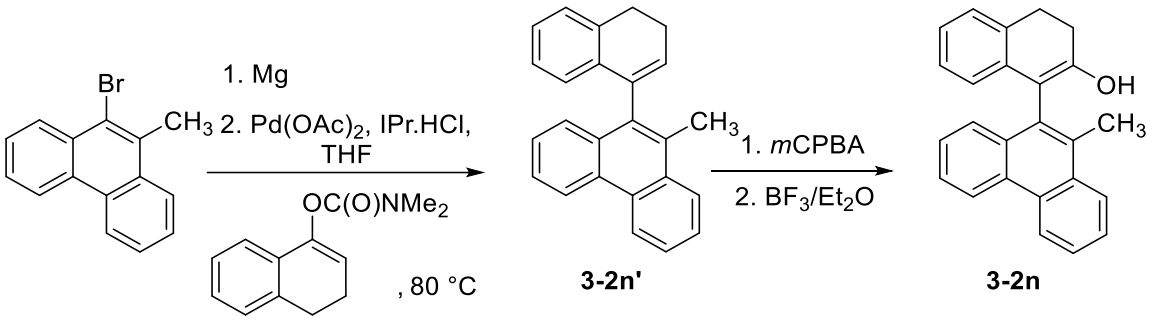
2',3'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2(1H)-one (**3-2m**) was synthesized following the **general procedure D** by using **3-2m′** (1.13 g, 4 mmol), 75% w/w *m*CPBA (1.84 g, 8 mmol, 2 eq.), $NaHCO_3$ (840 mg, 10 mmol, 2.5 eq.), and 80 ml 1:1 DCM/Et_2O. The crude product was directly recrystallized hexane/EA giving the pure **3-2m** in 70% (841 mg, 2.8 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.67 (s, 1H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.15(brs, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 7.5 Hz, 1H), 5.53 (brs, 1H), 3.41 – 3.32 (m, 1H), 3.28 - 3.22 (m, 1H), 2.99 (dt, *J* = 17.1, 4.6 Hz, 1H), 2.80 – 2.75 (m, 1H), 2.48 (s, 3H), 2.09 (brs, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 137.0, 135.9, 135.6, 133.0, 131.5, 128.6, 128.3, 127.7, 127.2, 126.7, 125.3, 124.8, 54.6, 38.2, 28.5, 21.8, 18.0.

HRMS (ESI, m/z): calculated for $C_{22}H_{21}O^+$: 301.1592 $(M+H)^+$, found: 301.1584.

Preparation of 1-(10-methylphenanthren-9-yl)-3,4-dihydronaphthalen-2-ol (3-2n)



9-(3,4-dihydronaphthalen-1-yl)-10-methylphenanthrene (**3-2n′**) was synthesized following the **general procedure C** by using (10-methylphenanthren-9-yl) magnesium bromide (0.5 M in THF, 20 ml, 10 mmol, 2 eq.). Product **3-2n′** was isolated in 76% (1.2 g, 3.8 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.72 (m, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 8.14 – 8.10 (m, 1H), 7.84 – 7.82 (m, 1H), 7.63 – 7.61 (m, 2H), 7.53 – 7.50 (m, 1H), 7.43 – 7.39 (m, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 7.11 (td, *J* = 7.4, 0.9 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 5.99 (t, *J* = 4.5 Hz, 1H), 3.10 – 2.96 (m, 2H), 2.60 – 2.53 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 135.9, 135.4, 135.1, 132.1, 130.6, 130.1, 129.6, 129.5, 127.7, 127.2, 127.2, 126.8, 126.7, 126.2, 125.8, 125.2, 125.2, 123.0, 122.5, 28.3, 23.7, 17.1.

HRMS (ESI, m/z): calculated for $C_{25}H_{21}^{+}$: 321.1643.1643 $(M+H)^{+}$, found: 321.1649.

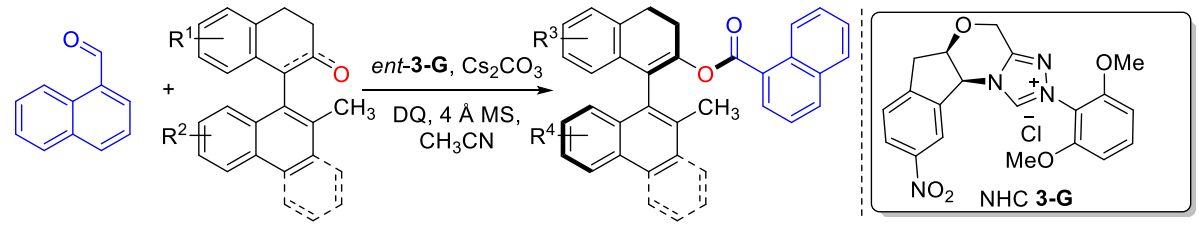
1-(10-methylphenanthren-9-yl)-3,4-dihydronaphthalen-2-ol (**3-2n**) was synthesized following the **general procedure D** by using **3-2n′** (961.3 g, 3 mmol), 75% w/w *m*CPBA (1.38 g, 6 mmol, 2 eq.), $NaHCO_3$ (630 mg, 7.5 mmol, 2.5 eq.), and 60 ml 1:1 DCM/Et_2O. The crude product was isolated by using 5:95:3 EA/hexane/Et_3N to 15:85:3 EA/hexane/Et_3N eluent giving the pure **3-2n** in 70% (704 mg, 2.1 mmol) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 7.8 Hz, 1H), 8.74 (d, *J* = 8.3 Hz, 1H), 8.19 (d, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.1 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.31 (d, *J* = 7.6 Hz, 1H), 3.27 – 3.11 (m, 2H), 2.74 (t, *J* = 8.1 Hz, 2H), 2.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 136.3, 134.3, 132.2, 132.1, 131.3, 130.7, 130.3, 128.2, 127.4, 127.3, 127.0, 126.8, 126.8, 126.5, 125.5, 124.7, 123.6, 123.1, 122.8, 109.0, 28.8, 26.4, 16.7.

HRMS (ESI, m/z): calculated for $C_{25}H_{21}O^{+}$: 337.1592 $(M+H)^{+}$, found: 337.1592.

3.4.3 General procedure for the NHC-catalyzed reaction between 1-naphthaldehyde (3-1a) and bicylic ketone/enol (3-2)

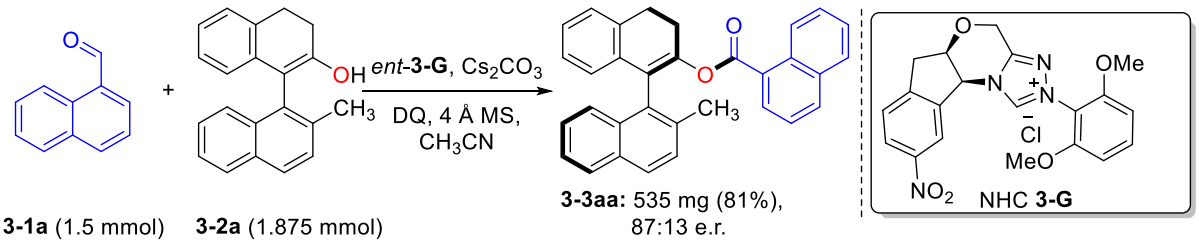


3-1a (0.1 mmol) **3-2** (0.125 mmol) **3-3**

An oven dried test tube with a stir bar was charged with ketone/enol (**3-2**) (0.125 mmol, 1.25 equiv), **NHC** precatalyst *ent*-**3-G** (2.2 mg, 0.005 mmol, 5 mol%), Cs_2CO_3 (32.6 mg, 0.1 mmol, 1 equiv), DQ (50.6 mg, .0125 mmol, 1.25 equiv), 4 Å MS (400 mg), and acetonitrile (4 ml) inside glove box. Then the reaction mixture was taken out from glove box and cooled down to -20 °C and 1-naphthaldehyde (**3-1**) (13.6 µL, 0.1 mmol, 1 equiv) was added via a microliter

syringe and the reaction was continued to stir for 3-7 days. After the reaction finished as indicated by the TLC, the crude reaction mixture was filtered via a short pad of celite and washed thoroughly with DCM. The filtrate was concentrated and purified by silica gel flash column chromatography eluting with 1:9 to 1:4 DCM/hexane.

3.4.4 Procedure for large scale synthesis of 3-3aa



3-1a (1.5 mmol) **3-2a** (1.875 mmol) **3-3aa:** 535 mg (81%), 87:13 e.r.

Large scale synthesis of product **3-3aa** was done following the procedure and stoichiometry as mentioned in section 3.4.3, starting with 203.7 µL (1.5 mmol, 1equiv) 1-naphthaldehyde. The desired product **3-3aa** was isolated in 81% (535 mg, 1.2 mmol) yield and 87:13 e.r. value.

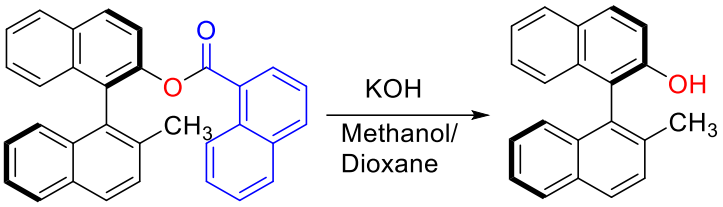
3.4.5 Transformation of product

Synthesis of 3-4aa

3-3aa: 87:13 e.r. **3-4aa:** 95% yield, 87:13 e.r.

A mixture of **3-3aa** (176.2 mg, 0.4 mmol, 87:13 e.r.), DDQ (454 mg, 2 mmol, 5 equiv) in 10 ml DCE was stirred at 60 °C for 48 h and the reaction was monitored by TLC. After all the starting material consumed, the reaction mixture concentrated and transferred to a silica gel column chromatography. Eluting by 1:9 to 3:7 DCM/hexane gives the pure oxidized binaphthyl product **3-4aa** in 95% (166.6 mg, .38 mmol) yield and 87:13 e.r. value.

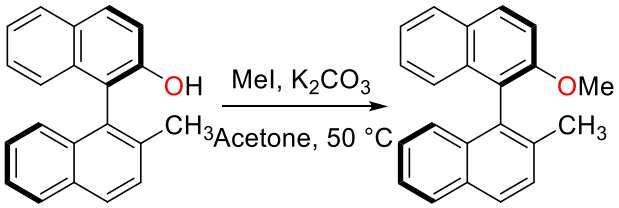
Synthesis of 3-5aa



3-4aa: 87:13 e.r. **3-5aa:** 97% yield, 87:13 e.r.

3-4aa (87.2 mg, 0.2 mmol, 1 equiv) was dissolved in 20 ml 1:1 mixture of methanol/dioxane followed by crushed KOH (33.6 mg, 0.6 mmol, 3 equiv) was added and the resulting suspension was stirred vigorously at RT, while monitoring the progress of the reaction by TLC. After all the starting material consumed, the reaction mixture was quenched by adding 1 (M) HCl and was concentrated to remove the dioxane and methanol. Then, the product was extracted by DCM and followed by column chromatography eluting with hexane/EA (9:1) gave the product **3-5aa** in 97% (55.2 mg, 0.19 mmol) yield and 87:13 e.r. value.

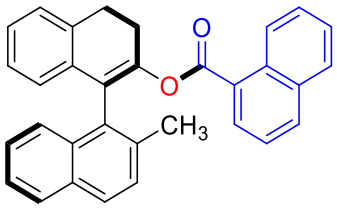
Synthesis of 3-6aa



3-5aa: 87:13 e.r. **3-6aa:** 92% yield

4 ml acetone was added to a 10 ml round bottom flux containing a mixture of **3-5aa** (28.4 mg, 0.1 mmol, 1 equiv) and K_2CO_3 (41.4 mg, 0.3 mmol, 3 equiv). The resulting suspension was stirred vigorously and MeI (15.6 µL, 0.25 mmol, 2.5 equiv) was added dropwise at RT. Resulting mixture was stirred at 50 °C overnight. After the reaction was finished acetone was evaporated and the crude mixture was purified in silica gel column chromatography eluting the product in hexane/EA (1:19) to give the pure **3-6aa** in 92% (27.4 mg, 0.9 mmol) yield.

3.4.6 Characteristization of products



(*R*)-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3aa)

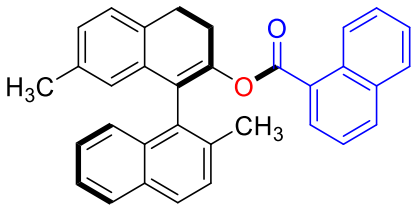
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.91 – 7.88 (m, 1H), 7.84 - 7.80 (m, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.41 – 7.34 (m, 5H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 6.2 Hz, 1H), 7.19 - 7.13 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 3.44 – 3.24 (m, 2H), 3.09 – 2.90 (m, 2H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.4, 134.9, 134.7, 134.2, 133.6, 133.4, 132.8, 132.3, 131.1, 131.0, 130.4, 128.9, 128.4, 128.0, 127.8, 127.6, 127.5, 127.1, 126.9, 126.7, 126.4, 126.2, 125.9, 125.5, 125.3, 125.1, 124.4, 124.3, 29.1, 27.2, 20.2.

HRMS (ESI, m/z): calculated for $C_{32}H_{25}O_2^+$: 441.1855 $(M+H)^+$, found: 441.1862.

$[\alpha]^{21}_D$ = 118.4 (c = 0.6 in $CHCl_3$).

HPLC analysis: 87.5:12.5 e.r. (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 10.3 min, t_{minor}= 9.6 min).



(*R*)-2',7-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ab)

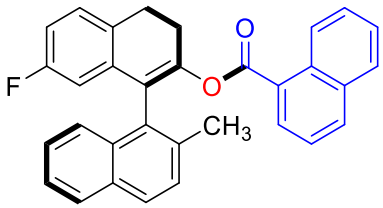
1H NMR (400 MHz, CDCl3) δ 8.04 (d, J = 8.5 Hz, 1H), 7.91 – 7.90 (m, 1H), 7.85 – 7.69 (m, 4H), 7.41 - 7.35 (m, 4H), 7.31 - 7.29 (m, 1H), 7.22 – 7.13 (m, 3H), 6.97 (d, J = 7.4 Hz, 1H), 6.32 (brs, 1H), 3.36 – 3.22 (m, 2H), 3.03 – 2.89 (m, 2H), 2.38 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.4, 136.4, 134.9, 134.6, 133.6, 133.4, 132.8, 132.3, 131.2, 131.0, 130.3, 128.9, 128.4, 128.0, 127.8, 127.7, 127.6, 127.4, 126.7, 126.4, 126.2, 126.0, 125.9, 125.5, 125.1, 124.4, 28.7, 27.3, 21.2, 20.3.

HRMS (ESI, m/z): calculated for $C_{33}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2012.

[α]$^{21}_D$ = 96.1 (c = 0.6 in $CHCl_3$).

HPLC analysis: 90:10 e.r. (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 9.9 min, t_{minor} = 9.0 min).



(*R*)-7-fluoro-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ac)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.87 – 7.81 (m, 3H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.43 – 7.34 (m, 5H), 7.24 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 6.83 (td, *J* = 8.4, 2.6 Hz, 1H), 6.20 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.35 – 3.23 (m, 2H), 3.05 – 2.91 (m, 2H), 2.37 (s, 3H).

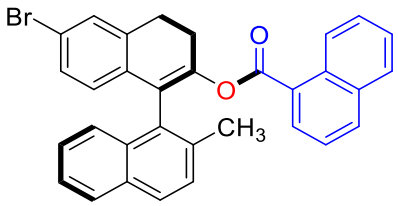
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 162.2 (d, *J* = 242.8 Hz), 149.6, 136.8 (d, *J* = 7.8 Hz), 135.0, 133.6, 133.6, 132.6, 132.3, 131.0, 130.4, 130.4, 129.7 (d, *J* = 3.1 Hz), 128.9, 128.6, 128.6, 128.4, 128.1, 127.7, 126.6, 126.4, 126.2, 125.6, 125.4, 125.2, 124.4, 123.9 (d, *J* = 2.2 Hz), 113.4 (d, *J* = 21.3 Hz), 112.3 (d, *J* = 23.2 Hz), 28.3, 27.3, 21.0.

^{19}F NMR (377 MHz, $CDCl_3$): δ -116.33 - -116.39 (m).

HRMS (ESI, m/z): calculated for $C_{32}H_{24}FO_2^+$: 459.1760 $(M+H)^+$, found: 459.1766.

[α]$^{21}_D$ = 118.4 (c = 0.6 in $CHCl_3$).

HPLC analysis: 88:12 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 10.8 min, t_{minor} = 9.7 min).



(*R*)-6-bromo-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ad)

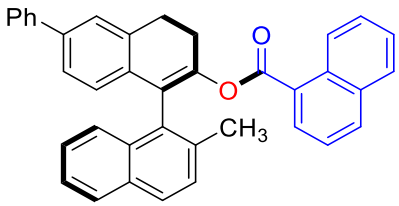
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.85 – 7.81 (m, 3H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.43 -7.34 (m, 6H), 7.24 - 7.20 (m, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.34 (d, *J* = 8.2 Hz, 1H), 3.35 – 3.24 (m, 2H), 3.04 – 2.90 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 148.6, 136.3, 134.9, 133.8, 133.6, 132.6, 132.3, 131.0, 130.5, 130.4, 129.9, 128.9, 128.4, 128.1, 128.0, 127.7, 126.8, 126.6, 126.34, 126.2, 125.6, 125.4, 125.3, 124.4, 123.8, 120.8, 28.8, 26.9, 20.2.

HRMS (ESI, m/z): calculated for $C_{32}H_{24}BrO_2^+$: 519.0960 $(M+H)^+$, found: 519.0962.

$[\alpha]^{21}_D$ = 51.3 (c = 0.6 in $CHCl_3$).

HPLC analysis: 87:13 e.r. (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 11.1 min, t_{minor}= 10.4 min).



(*R*)-2'-methyl-6-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ae)

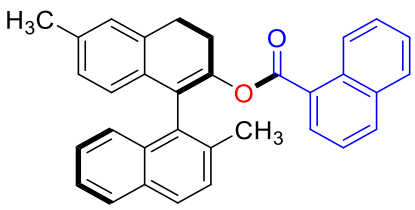
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.94 – 7.92 (m, 1H), 7.85 - 7.77 (m, 3H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 2H), 7.54 (brs, 1H), 7.41 – 7.36 (m, 8H), 7.32 – 7.29 (m, 1H), 7.20 – 7.15 (m, 2H), 6.56 (d, *J* = 7.9 Hz, 1H), 3.46 – 3.35 (m, 2H), 3.09 – 2.97 (m, 2H), 2.41 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 148.4, 141.0, 140.0, 135.0, 134.7, 133.9, 133.6, 133.5, 132.7, 132.3, 131.0, 130.4, 129.0, 128.9, 128.4, 128.0, 127.9, 127.7, 127.5, 127.3, 127.1, 126.6, 126.5, 126.4, 126.2, 125.9, 125.7, 125.6, 125.5, 125.2, 124.4, 124.1, 29.2, 27.2, 20.3.

HRMS (ESI, m/z): calculated for $C_{38}H_{29}O_2^+$: 517.2168 $(M+H)^+$, found: 517.2161.

$[\alpha]^{21}_D$ = 38.2 (c = 0.7 in $CHCl_3$).

HPLC analysis: 84.5:15.5 e.r. (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 14.1 min, t_{minor}= 13.4 min).



(*R*)-2',6-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3af)

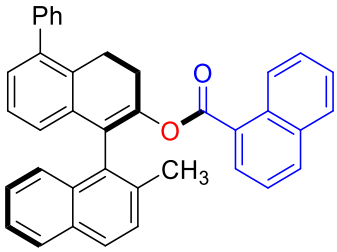
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.7 Hz, 1H), 7.94 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.90 – 7.86 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.39 (m, 5H), 7.28 – 7.17 (m, 3H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 3.42 – 3.28 (m, 2H), 3.09 – 2.95 (m, 2H), 2.43 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 147.5, 137.0, 134.9, 134.2, 133.6, 133.4, 132.8, 132.2, 131.9, 131.2, 131.0, 130.3, 128.8, 128.5, 128.4, 128.0, 127.8, 127.6, 127.4, 126.8, 126.4, 126.2, 125.9, 125.5, 125.3, 125.1, 124.4, 124.2, 29.1, 27.2, 21.3, 20.2.

HRMS (ESI, m/z): calculated for $C_{33}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2007.

$[\alpha]^{21}_D$ = 88.3 (c = 0.7 in $CHCl_3$).

HPLC analysis: 87.5:12.5 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 9.9 min, t_{minor}= 9.5 min).



(*R*)-2'-methyl-5-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ag)

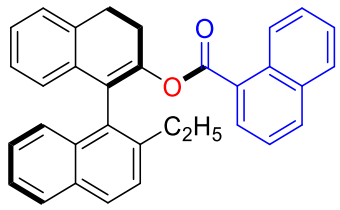
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.7 Hz, 1H), 7.96 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.79 (t, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.45 – 7.36 (m, 10H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.54 (dd, *J* = 7.7, 0.9 Hz, 1H), 3.36 - 3.23 (m, 2H), 2.94 – 2.80 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.5, 141.6, 140.8, 135.2, 135.0, 133.6, 133.5, 132.8, 132.3, 131.5, 131.3, 131.0, 130.4, 129.5, 129.2, 128.9, 128.4, 128.3, 128.0, 127.9, 127.6, 127.1, 126.6, 126.5, 126.5, 126.2, 125.9, 125.5, 125.2, 124.7, 124.5, 124.4, 27.1, 26.5, 20.3.

HRMS (ESI, m/z): calculated for $C_{38}H_{29}O_2^+$: 517.2168 $(M+H)^+$, found: 517.2166.

$[\alpha]^{21}_D$ = 93.5 (c = 0.7 in $CHCl_3$).

HPLC analysis: 89.5:10.5 e.r. (CHIRALCEL ID column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 10.2 min, t_{minor}= 9.6 min).



(*R*)-2'-ethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ah)

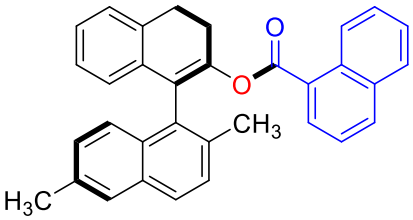
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 1H), 7.90 (dd, *J* = 8.1, 4.8 Hz, 1H), 7.84 – 7.82 (m, 3H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.41 – 7.35 (m, 4H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.22 – 7.13 (m, 3H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 3.41 – 3.27 (m, 2H), 3.09 – 2.94 (m, 2H), 2.79 – 2.67 (m, 2H), 1.16 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.6, 140.7, 135.2, 134.1, 133.6, 133.4, 132.7, 132.3, 131.0, 130.4, 130.3, 128.4, 128.2, 127.9, 127.6, 127.4, 127.1, 127.1, 126.8, 126.7, 126.4, 126.2, 126.1, 125.6, 125.5, 125.2, 124.4, 124.0, 29.1, 27.2, 26.8, 15.2.

HRMS (ESI, m/z): calculated for $C_{33}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2005.

$[\alpha]^{21}_D$ = 105.7 (c = 0.4 in $CHCl_3$).

HPLC analysis: 86.5:13.5 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 10.1 min, t_{minor}= 9.6 min).



(*R*)-2',6'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ai)

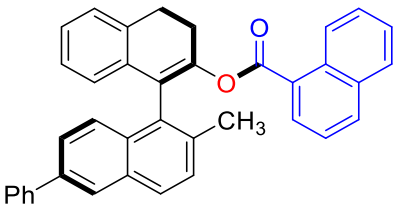
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.79 (dd, *J* = 10.6, 8.9 Hz, 2H), 7.69 (t, *J* = 9.2 Hz, 2H), 7.58 (s, 1H), 7.39 – 7.34 (m, 3H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.22 (m, 2H), 7.19 – 7.12 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 3.37 – 3.28 (m, 2H), 3.06 – 2.90 (m, 2H), 2.45 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.2, 134.7, 134.6, 134.2, 133.9, 133.6, 133.4, 132.5, 131.0, 13.9, 130.3, 128.9, 128.7, 128.4, 127.6, 127.5, 127.2, 127.1, 127.0, 126.9, 126.8, 126.2, 125.7, 125.5, 125.3, 124.4, 29.1, 27.1, 21.6, 20.1.

HRMS (ESI, m/z): calculated for $C_{33}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2019.

$[\alpha]^{21}_D$ = 92.3 (c = 0.9 in $CHCl_3$).

HPLC analysis: 88:12 e.r. (CHIRALCEL IA column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 9.2 min, t_{minor} = 9.7 min).



(*R*)-2'-methyl-6'-phenyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3aj)

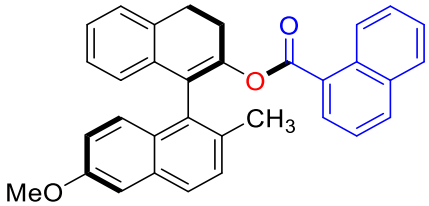
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 1H), 8.03 (brs, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.71 - 7.67 (m, 4H), 7.46 - 7.40 (m, 4H), 7.37 – 7.29 (m, 3H), 7.24 - 7.14 (m, 3H), 6.99 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H), 3.47 – 3.25 (m, 2H), 3.13 – 2.88 (m, 2H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 148.4, 141.2, 137.7, 135.1, 134.7, 134.2, 133.6, 133.5, 132.6, 132.0, 131.0, 131.0, 130.4, 129.3, 128.9, 128.4, 128.1, 127.7, 127.6, 127.4, 127.3, 127.2, 126.9, 126.6, 126.5, 126.2, 126.1, 125.9, 125.5, 125.3, 124.4, 124.3, 29.1, 27.2, 20.2.

HRMS (ESI, m/z): calculated for $C_{38}H_{29}O_2^+$: 517.2168 $(M+H)^+$, found: 517.2164.

$[\alpha]^{21}_D$ = 130.5 (c = 0.7 in $CHCl_3$).

HPLC analysis: 89.5:10.5 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 11.2 min, t_{minor}= 12.1 min).



(*R*)-6'-methoxy-2'-methyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3ak)

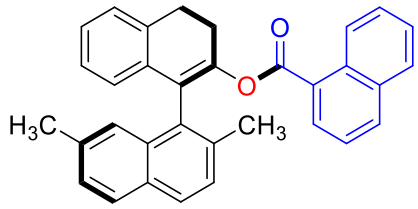
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.41 - 7.35 (m, 3H), 7.27 – 7.24 (m, 2H), 7.21 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 7.07 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.37 – 3.26 (m, 2H), 3.05 – 2.99 (m, 2H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 157.1, 148.3, 134.7, 134.2, 133.6, 133.4, 133.4, 132.5, 131.1, 131.0, 130.4, 129.4, 128.4, 128.2, 127.7, 127.6, 127.5, 127.1, 126.9, 126.7, 126.2, 125.5, 125.3, 124.5, 124.4, 118.9, 106.2, 55.4, 29.0, 27.1, 19.9.

HRMS (ESI, m/z): calculated for $C_{33}H_{26}O_3Na^+$: 493.1780 $(M+Na)^+$, found: 493.1781.

$[\alpha]^{21}_D$ = 109.5 (c = 0.5 in $CHCl_3$).

HPLC analysis: 85.5:14.5 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 12.7 min, t_{minor}= 11.2 min).



(*R*)-2',7'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3al)

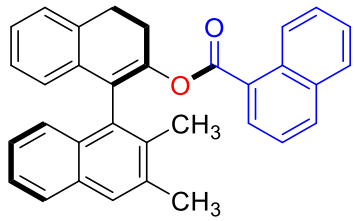
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.74 – 7.70 (m, 3H), 7.65 (brs, 1H), 7.37 – 7.29 (m, 4H), 7.25 – 7.14 (m, 4H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 3.43 – 3.26 (m, 2H), 3.10 - 3.02 (m, 1H), 2.99 – 2.91 (m, 1H), 2.41 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.3, 136.0, 134.9, 134.8, 134.3, 133.6, 133.4, 133.0, 131.0, 130.5, 130.4, 130.3, 128.4, 128.0, 127.9, 127.6, 127.5, 127.5, 127.4, 127.1, 126.9, 126.8, 126.2, 125.5, 125.3, 124.7, 124.4, 124.4, 29.1, 27.2, 22.2, 20.2.

HRMS (ESI, m/z): calculated for $C_{33}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2011.

$[\alpha]^{21}_D$ = 133.7 (c = 0.4 in $CHCl_3$).

HPLC analysis: 87.5:12.5 e.r. (CHIRALCEL IB column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 9.3 min, t_{minor}= 8.9 min).



(*R*)-2',3'-dimethyl-3,4-dihydro-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-3am)

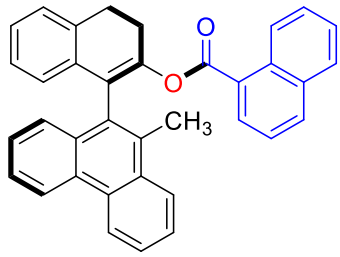
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.74 (dd, *J* = 13.8, 8.0 Hz, 2H), 7.65 (brs, 1H), 7.40 – 7.29 (m, 5H), 7.21 – 7.14 (m, 3H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 3.45 – 3.28 (m, 2H), 3.06 – 2.93 (m, 2H), 2.43 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.3, 135.6, 134.9, 134.9, 134.2, 133.6, 133.4, 132.4, 131.4, 131.1, 131.0, 130.3, 128.4, 127.8, 127.6, 127.5, 127.3, 127.1, 126.9, 126.9, 126.2, 125.9, 125.5, 125.5, 125.2, 124.9, 124.5, 29.1, 27.2, 21.2, 17.2.

HRMS (ESI, m/z): calculated for $C_{32}H_{27}O_2^+$: 455.2011 $(M+H)^+$, found: 455.2017.

$[\alpha]^{21}_D$ = 115.0 (c = 0.3 in $CHCl_3$).

HPLC analysis: 91.5:8.5 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 10.5 min, t_{minor}= 9.6 min).



(*R*)-1-(10-methylphenanthren-9-yl)-3,4-dihydronaphthalen-2-yl 1-naphthoate (3-3an)

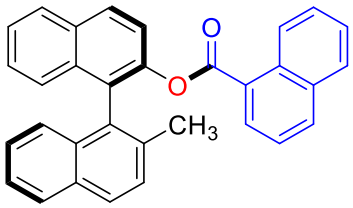
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 18.3, 8.2 Hz, 2H), 8.14 (d, *J* = 7.9 Hz, 1H), 8.01 (dd, *J* = 12.0, 8.6 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.68 – 7.56 (m, 4H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.1 Hz, 1H), 7.32 - 7.27 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.59 (d, *J* = 7.6 Hz, 1H), 3.38 (t, *J* = 8.0 Hz, 2H), 3.03 (t, *J* = 7.9 Hz, 2H), 2.66 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 148.6, 134.8, 134.1, 133.5, 133.4, 132.0, 131.9, 131.3, 130.9, 130.4, 130.1, 129.8, 128.3, 127.5, 127.5, 127.2, 127.1, 126.9, 126.9, 126.7, 126.7, 126.5, 126.2, 126.1, 125.6, 125.4, 125.3, 125.0, 124.4, 123.0, 122.6, 29.1, 27.2, 17.1.

HRMS (ESI, m/z): calculated for $C_{36}H_{27}O_2^+$: 491.2011 $(M+H)^+$, found: 491.2006.

$[\alpha]^{21}_D$ = 76.8 (c = 0.7 in $CHCl_3$).

HPLC analysis: 91.5:8.5 e.r. (CHIRALCEL IC column, 220 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 9.3 min, t_{minor}= 8.9 min).



(*R*)-2'-methyl-[1,1'-binaphthalen]-2-yl 1-naphthoate (3-4aa)

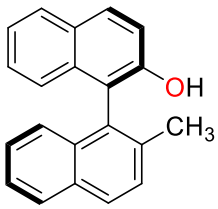
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.88 - 7.82 (m, 3H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.36 - 7.25 (m, 6H), 7.15 (t, *J* = 7.7 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 146.9, 135.7, 133.6, 133.6, 133.5, 133.3, 132.2, 132.1, 131.2, 130.9, 130.4, 129.3, 128.8, 128.4, 128.4, 128.2, 127.9, 127.7, 127.0, 1265, 126.4, 126.2, 126.1, 125.9, 125.5, 125.2, 124.4, 122.4, 20.5.

HRMS (ESI, m/z): calculated for $C_{32}H_{23}O_2^+$: 439.1698 $(M+H)^+$, found: 439.1690.

$[\alpha]^{21}_D$ = 86.9 (c = 1.5 in $CHCl_3$).

HPLC analysis: 87:13 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 18.8 min, t_{minor}= 14.4 min).



(*R*)-2'-methyl-[1,1'-binaphthalen]-2-ol (3-5aa)

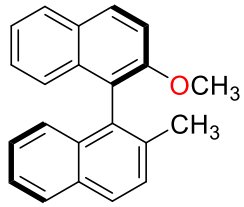
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.92 (m, 4H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.49 (ddd, *J* = 8.1, 6.6, 1.4 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.38 – 7.35 (m, 1H), 7.33 – 7.31 (m, 1H), 7.29 - 7.25 (m, 2H) 7.03 (d, *J* = 8.4 Hz, 1H), 4.87 (s, 1H), 2.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.9, 137.3, 133.4, 133.4, 132.7, 129.9, 129.3, 129.1, 129.1, 128.9, 128.3, 128.2, 127.0, 126.8, 125.7, 125.6, 124.6, 123.5, 117.7, 117.5, 20.2.

HRMS (ESI, m/z): calculated for $C_{21}H_{17}O^+$: 285.1279 $(M+H)^+$, found: 285.1281.

$[\alpha]^{21}_D$ = -57.5 (c = 1.1 in $CHCl_3$).

HPLC analysis: 87:13 e.r. (CHIRALCEL IA column, 254 nm, *n*-hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min, t_{major} = 13.5 min, t_{minor} = 11.8 min).



(*R*)-2-methoxy-2'-methyl-1,1'-binaphthalene (3-6aa)

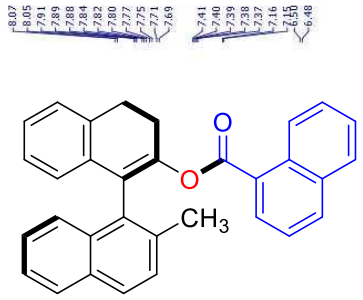
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.0 Hz, 1H), 7.88 - 7.85 (m, 3H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 9.1 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 3.75 (s, 3H), 2.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 135.1, 133.8, 133.4, 132.5, 132.3, 129.5, 129.3, 128.8, 128.1, 128.0, 127.6, 126.7, 126.0, 125.2, 124.8, 123.7, 122.2, 114.0, 56.8, 20.4.

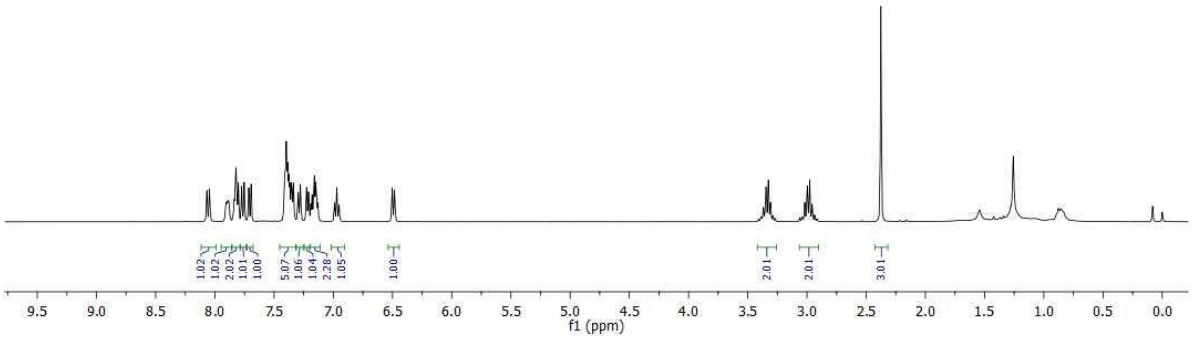
HRMS (ESI, m/z): calculated for $C_{22}H_{19}O^+$: 299.1436 $(M+H)^+$, found: 299.1436.

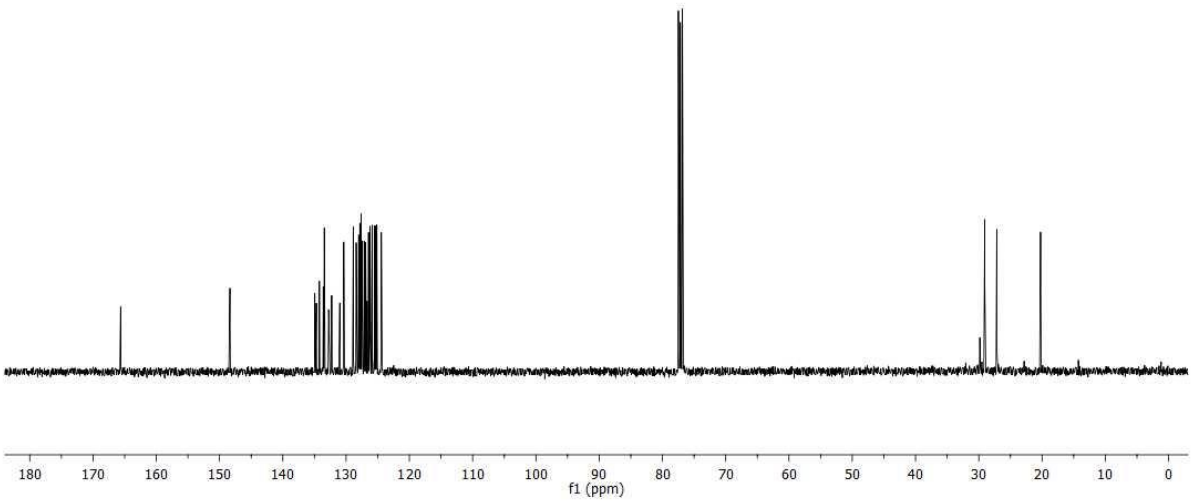
$[\alpha]^{21}_D$ = -11.4 (c = 0.8 in $CHCl_3$).

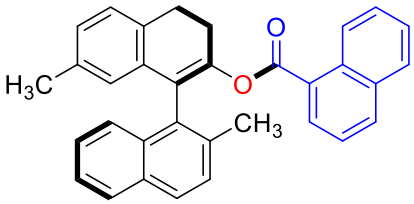
3.4.7. ^{1}H, ^{13}C, and ^{19}F NMR Spectra



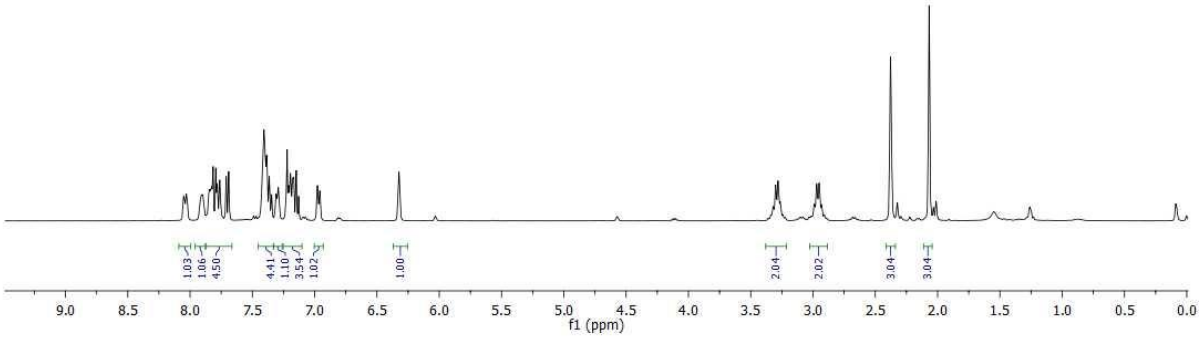
3-3aa

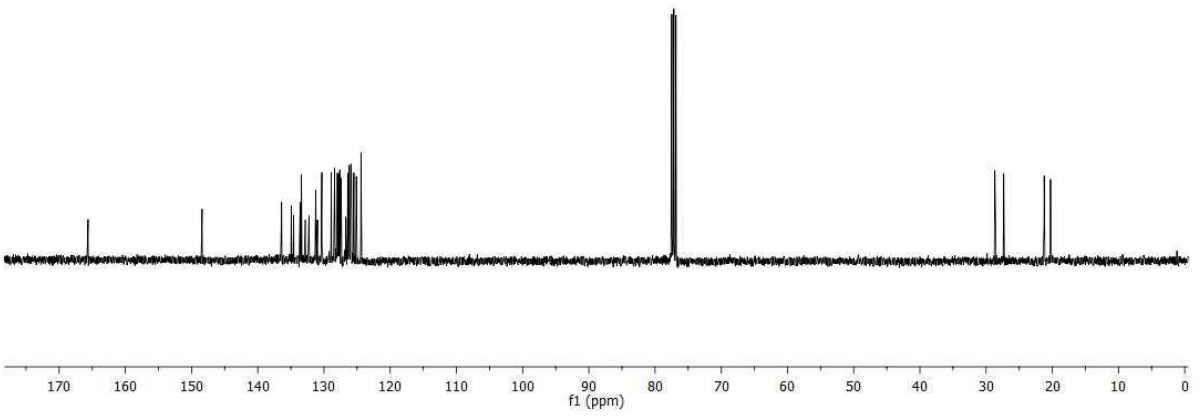


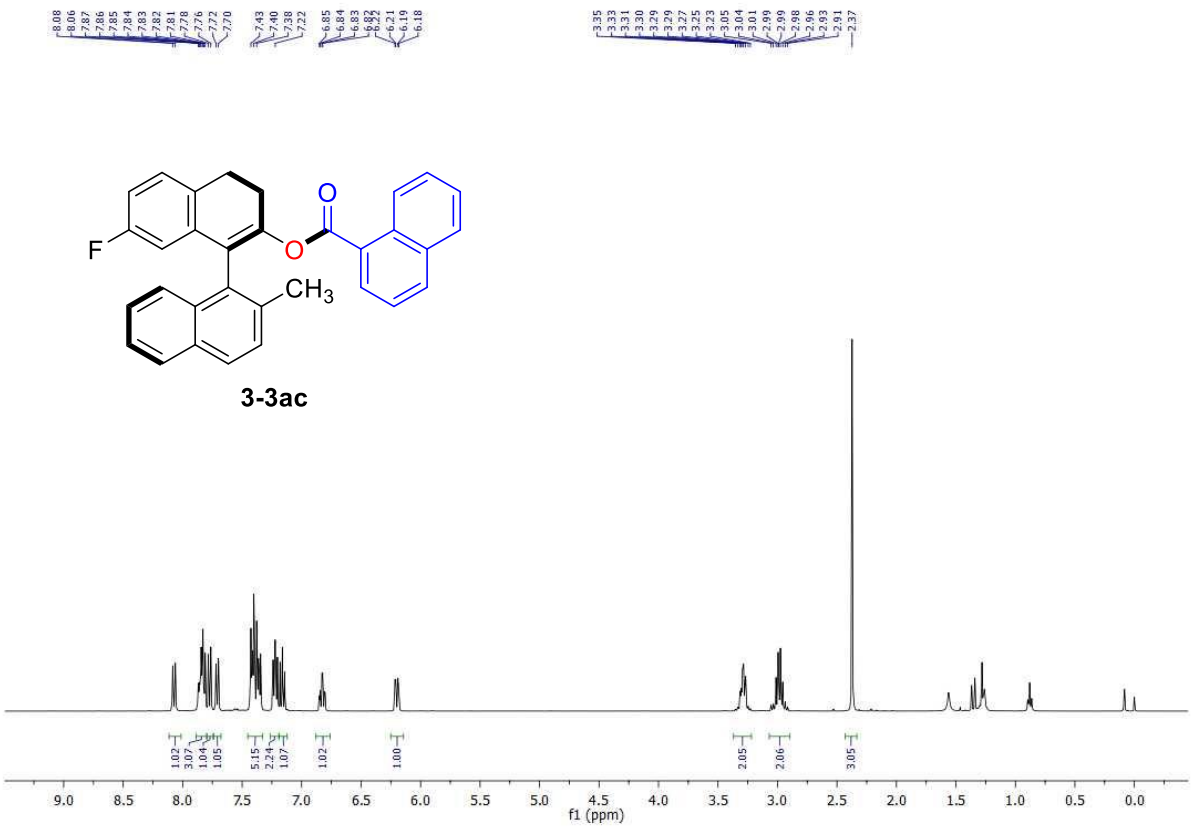




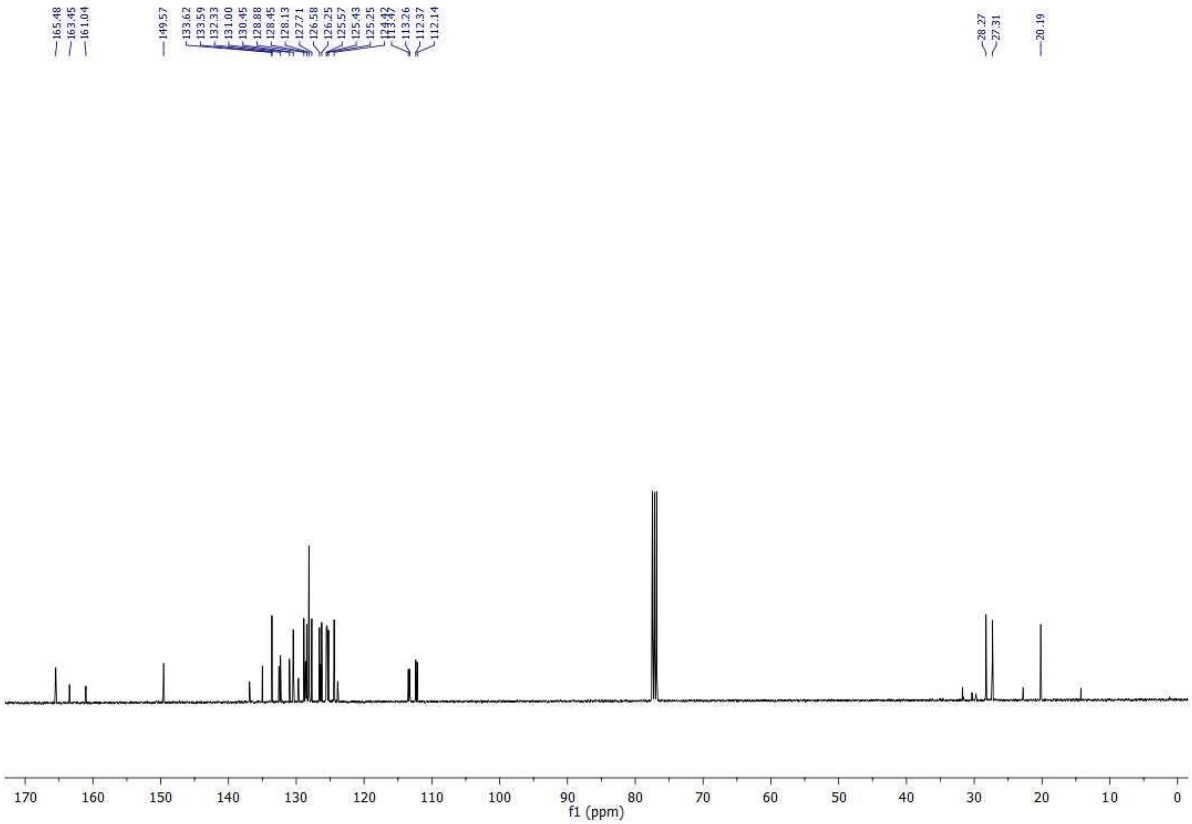
3-3ab

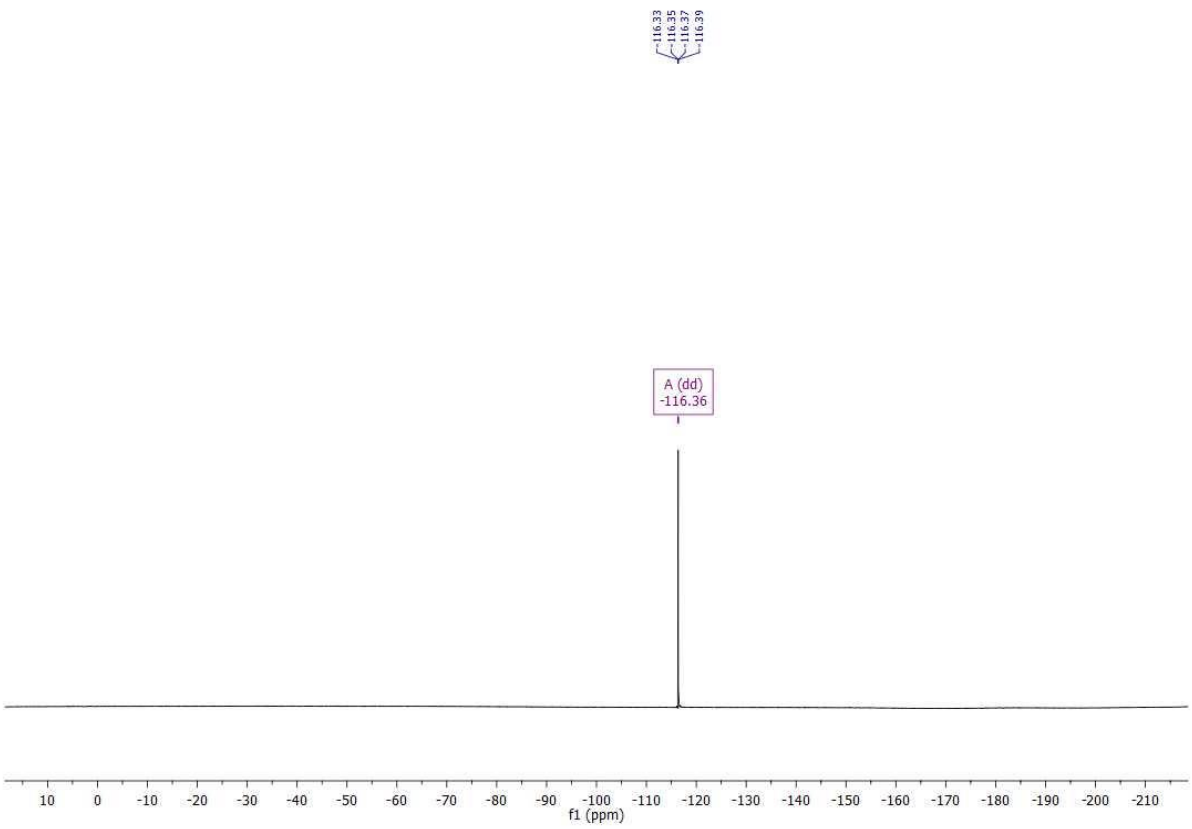


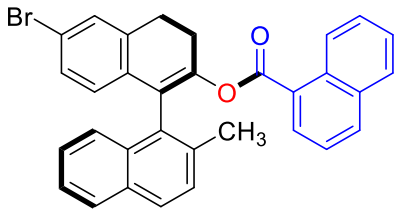




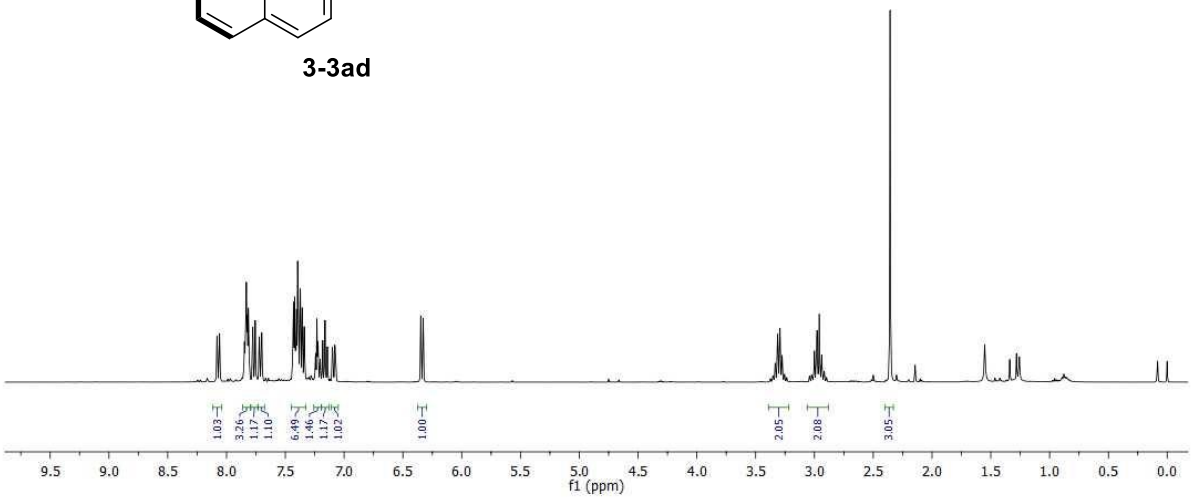
3-3ac

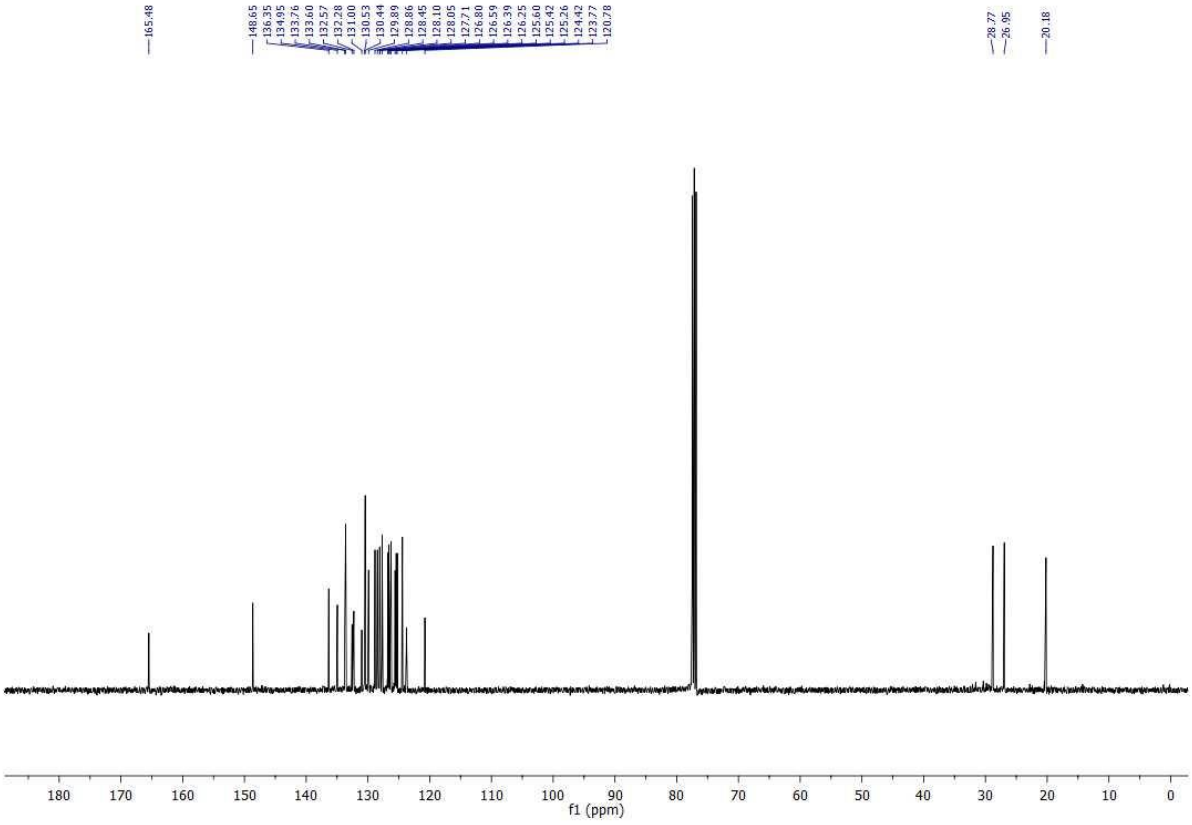


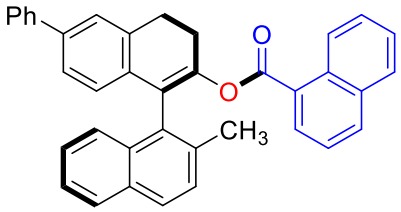

-116.33
-116.35
-116.37
-116.39
A (dd)
-116.36
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)


Br
O
O
CH3

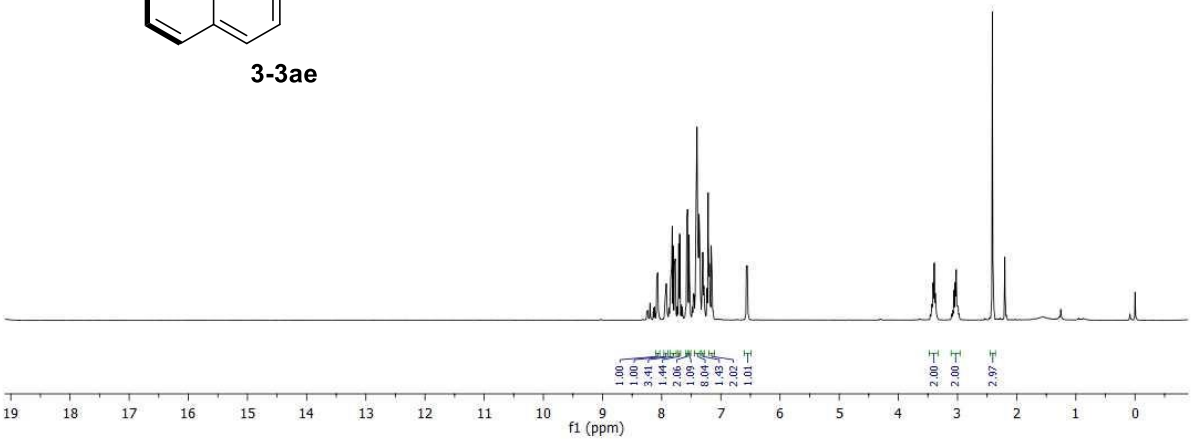
3-3ad

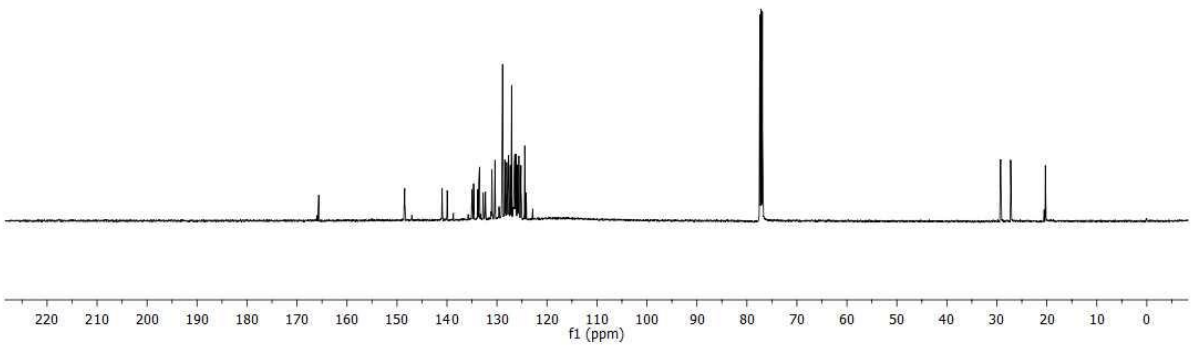

1.03
3.26
1.17
1.10
6.49
1.46
1.17
1.02
1.00
2.05
2.08
3.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

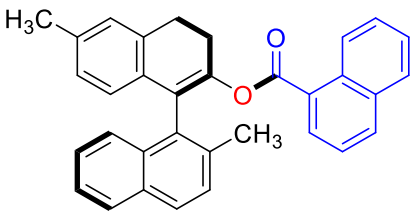

165.48
148.65
136.35
134.95
133.76
133.60
132.57
132.28
131.00
130.53
130.44
129.89
128.86
128.45
128.10
128.05
127.71
126.80
126.59
126.39
126.25
125.60
125.42
125.26
124.42
123.77
120.78
28.77
26.95
20.18
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



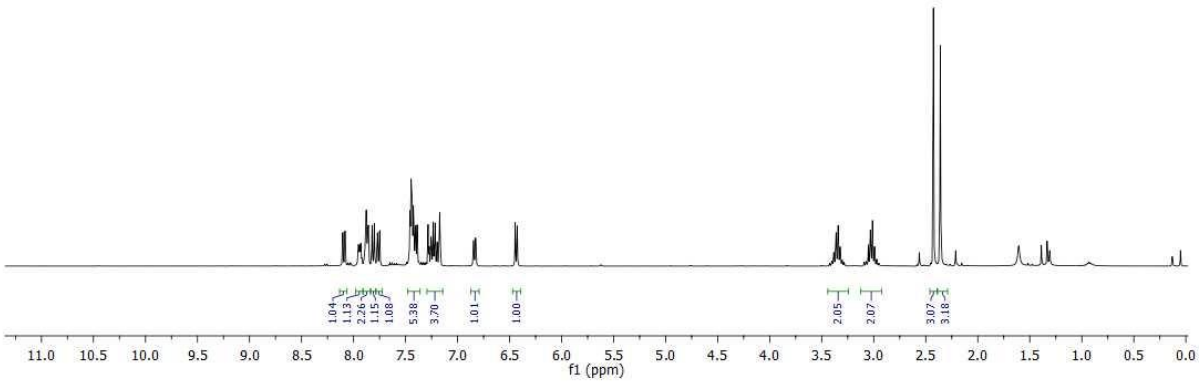
3-3ae

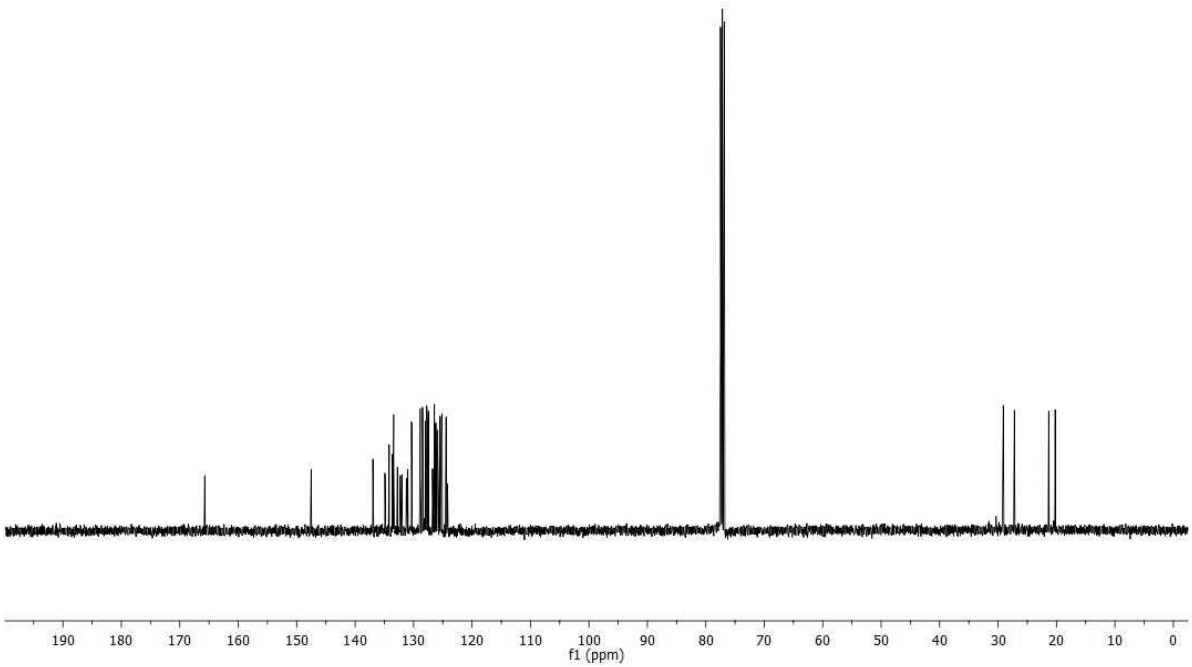


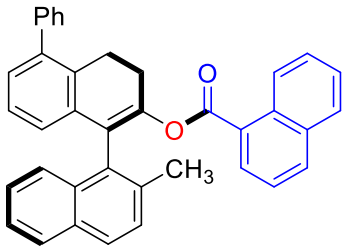




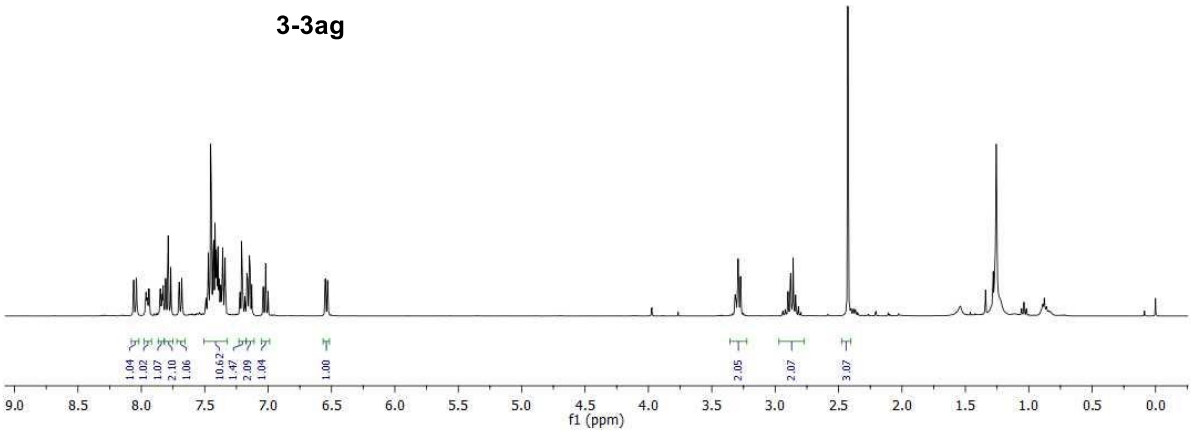
3-3af

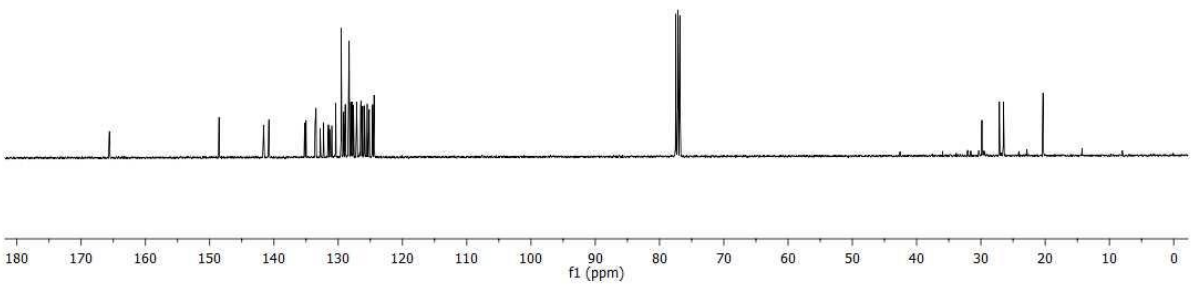


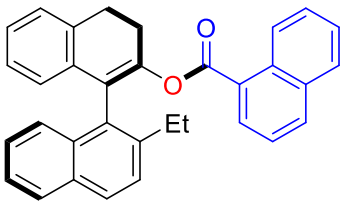



Ph
O
O
CH3

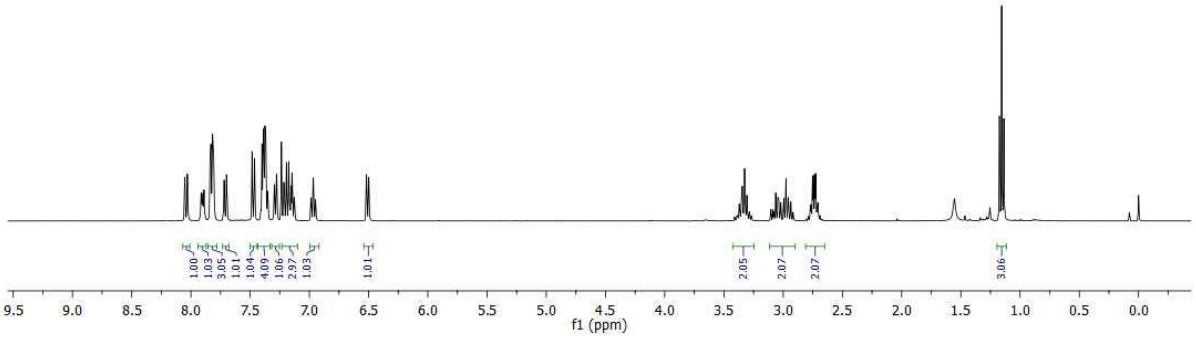
3-3ag

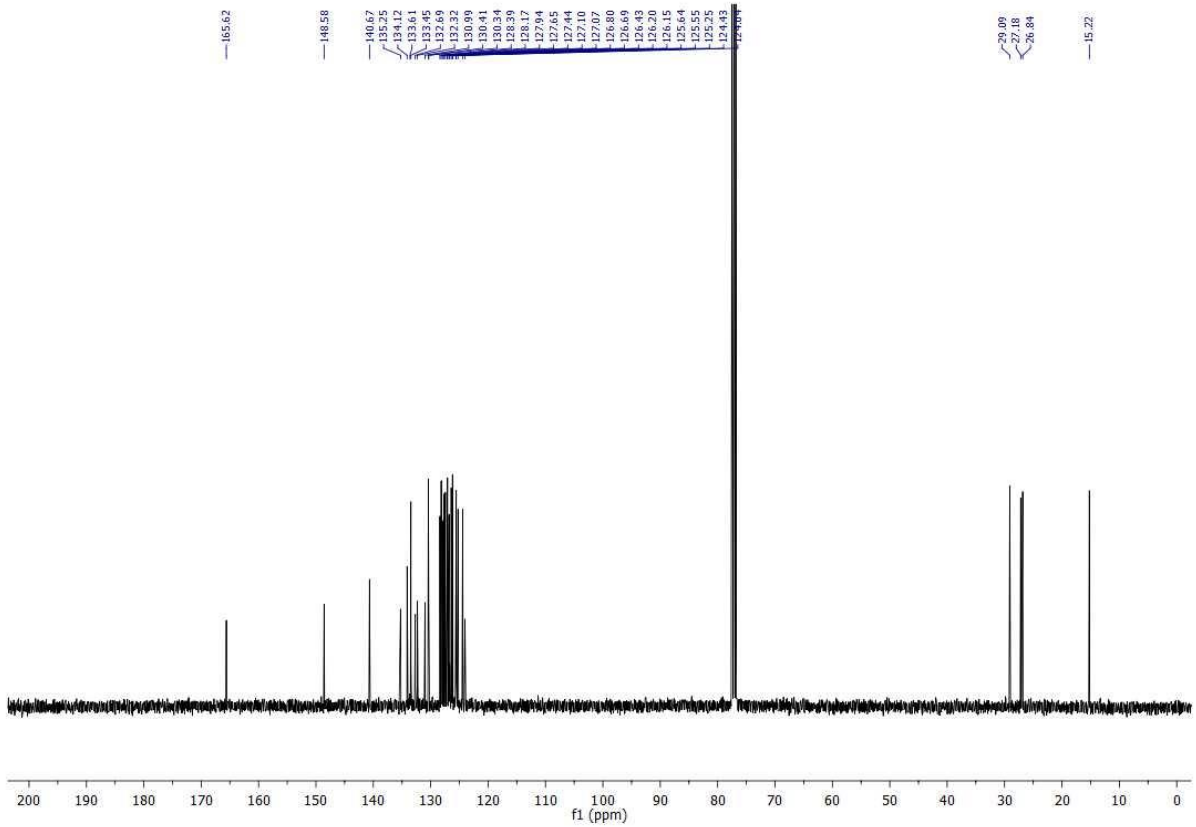

1.04
1.02
1.07
2.10
1.06
10.62
1.47
2.09
1.04
1.00
2.05
2.07
3.07
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

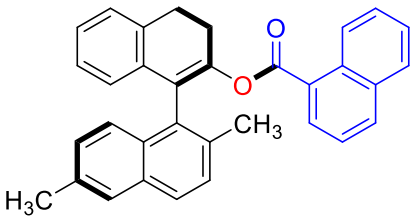

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



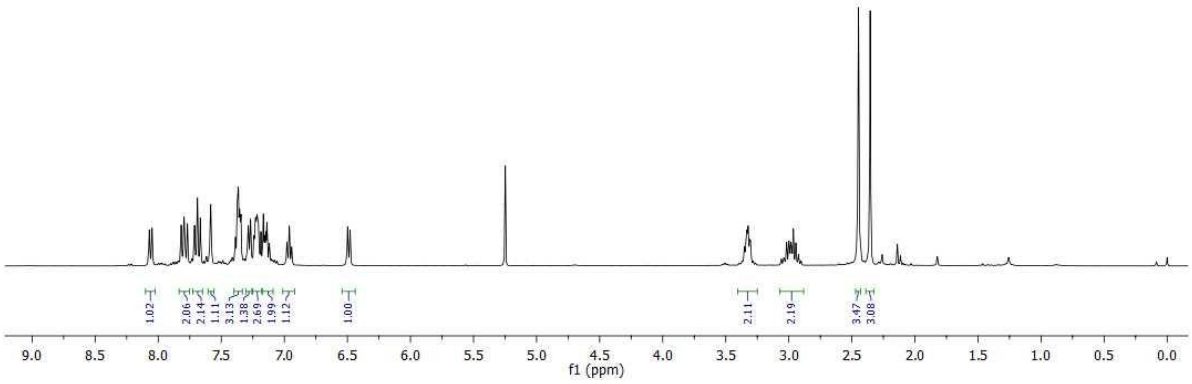
3-3ah

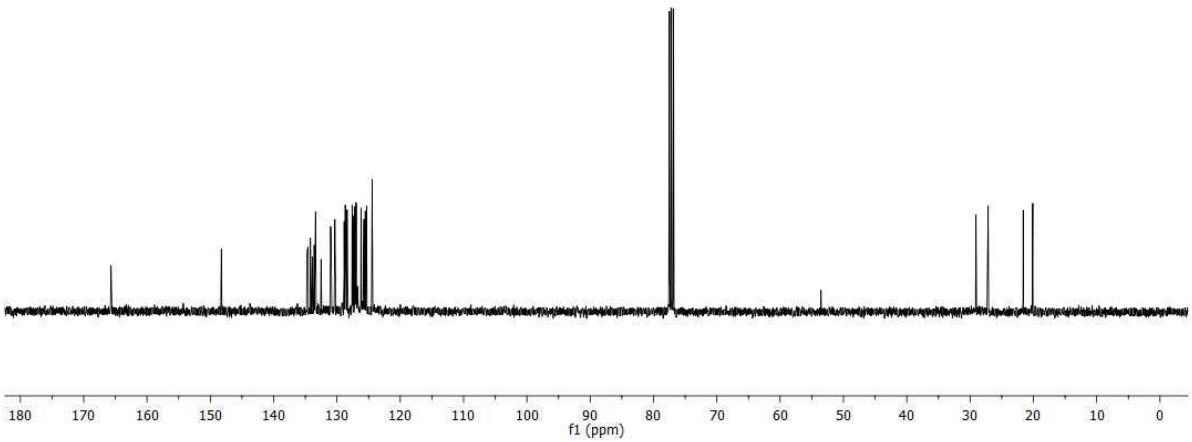


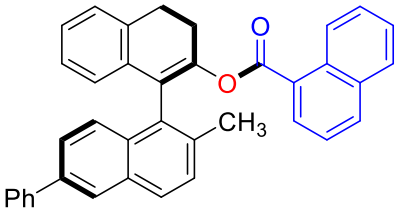



O
O
CH3
H3C

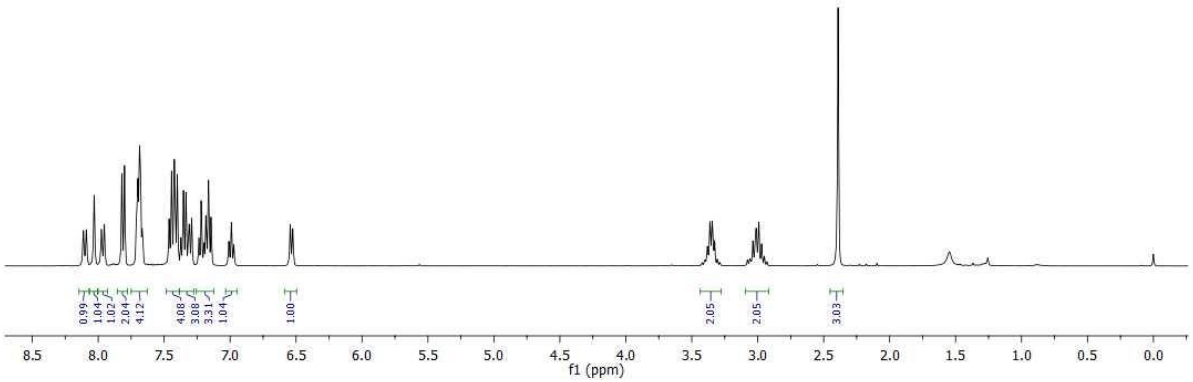
3-3ai

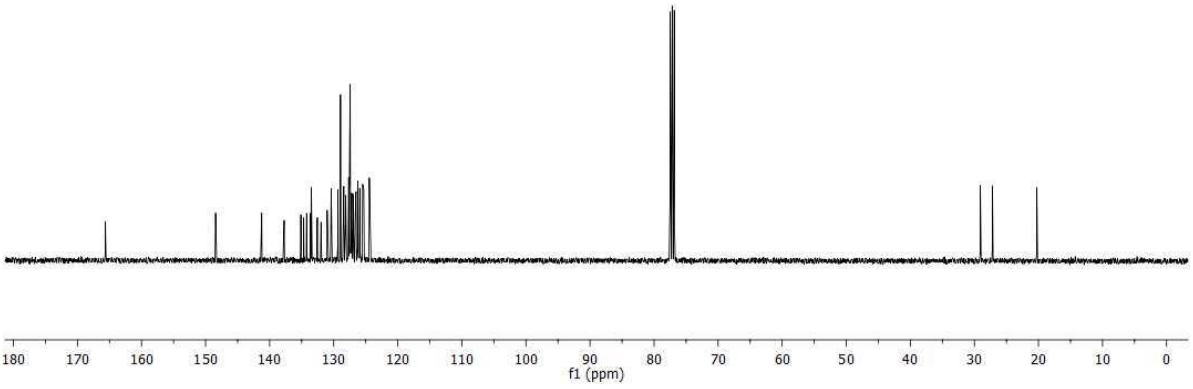

1.02
2.06
2.14
1.11
3.13
1.38
2.69
1.99
1.12
1.00
2.11
2.19
3.47
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

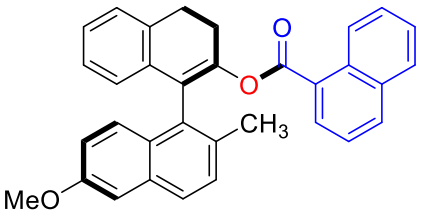

180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



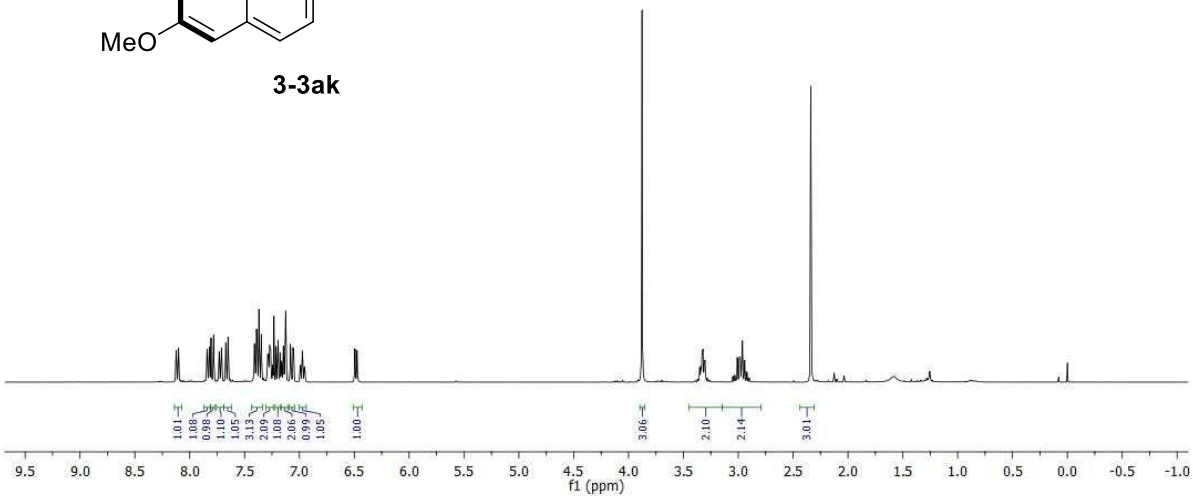
3-3aj

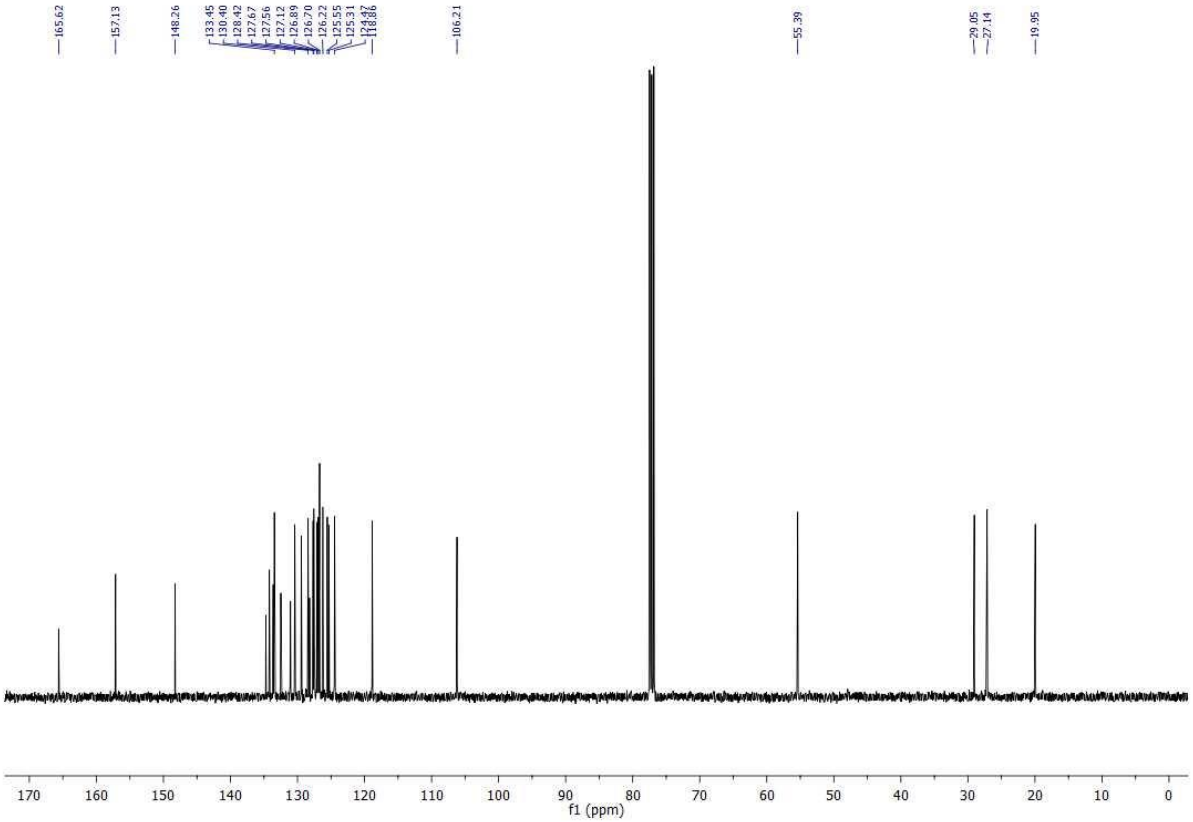


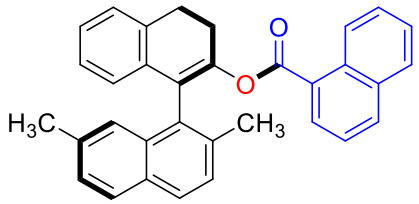




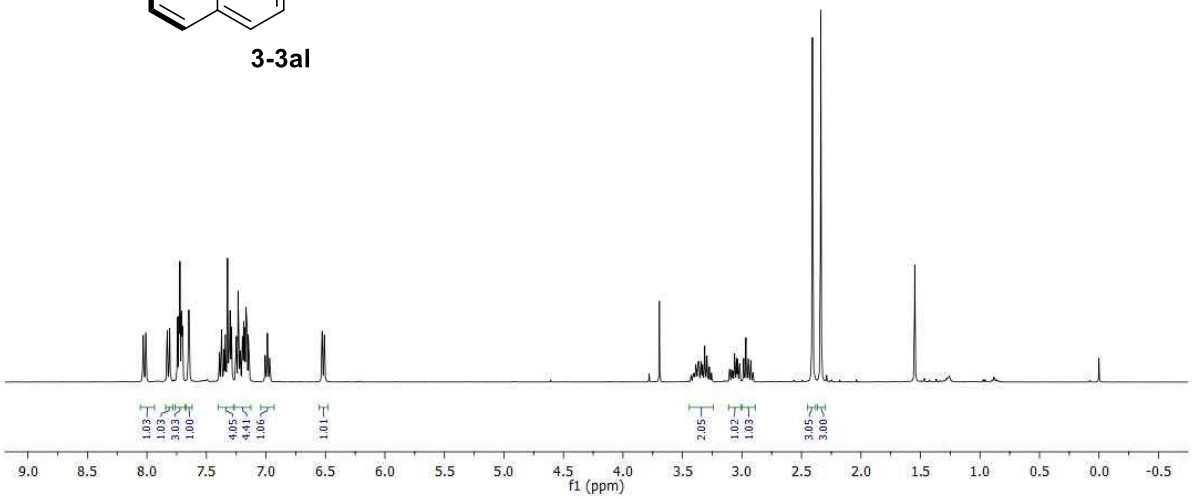
3-3ak

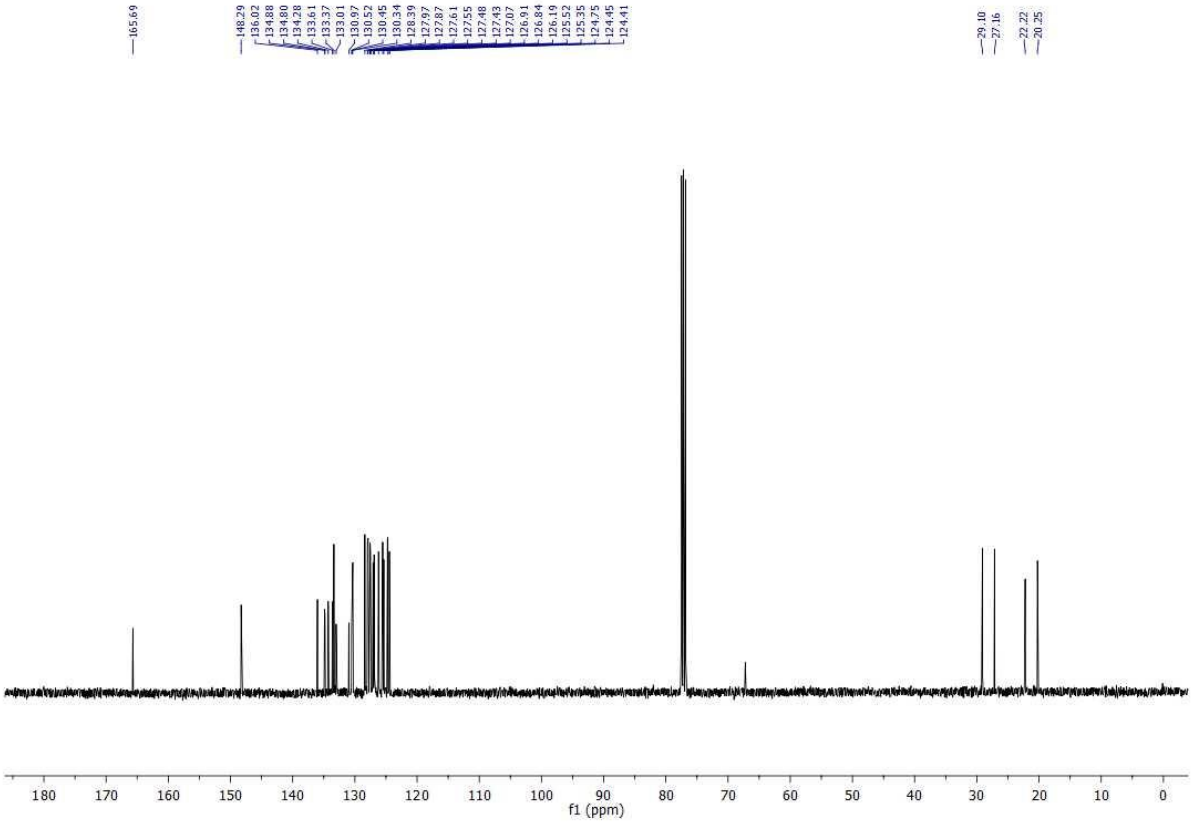


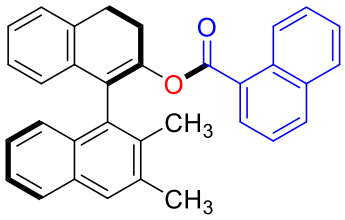




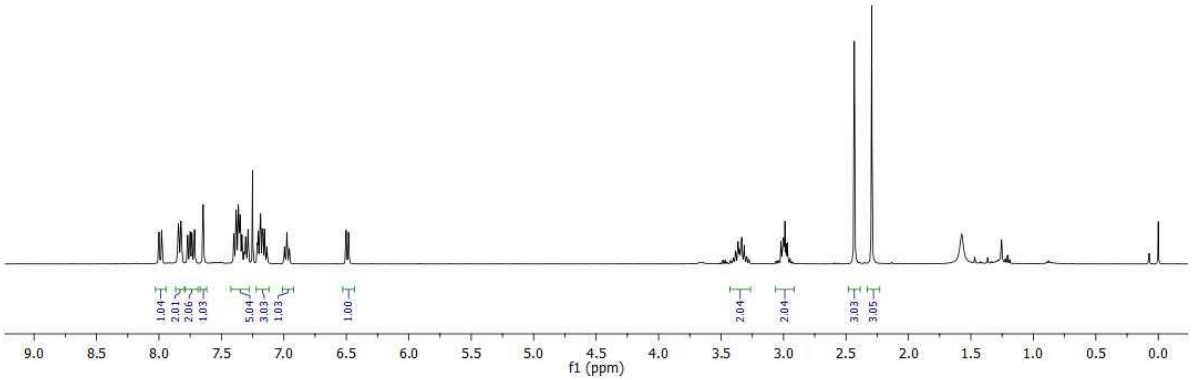
3-3al

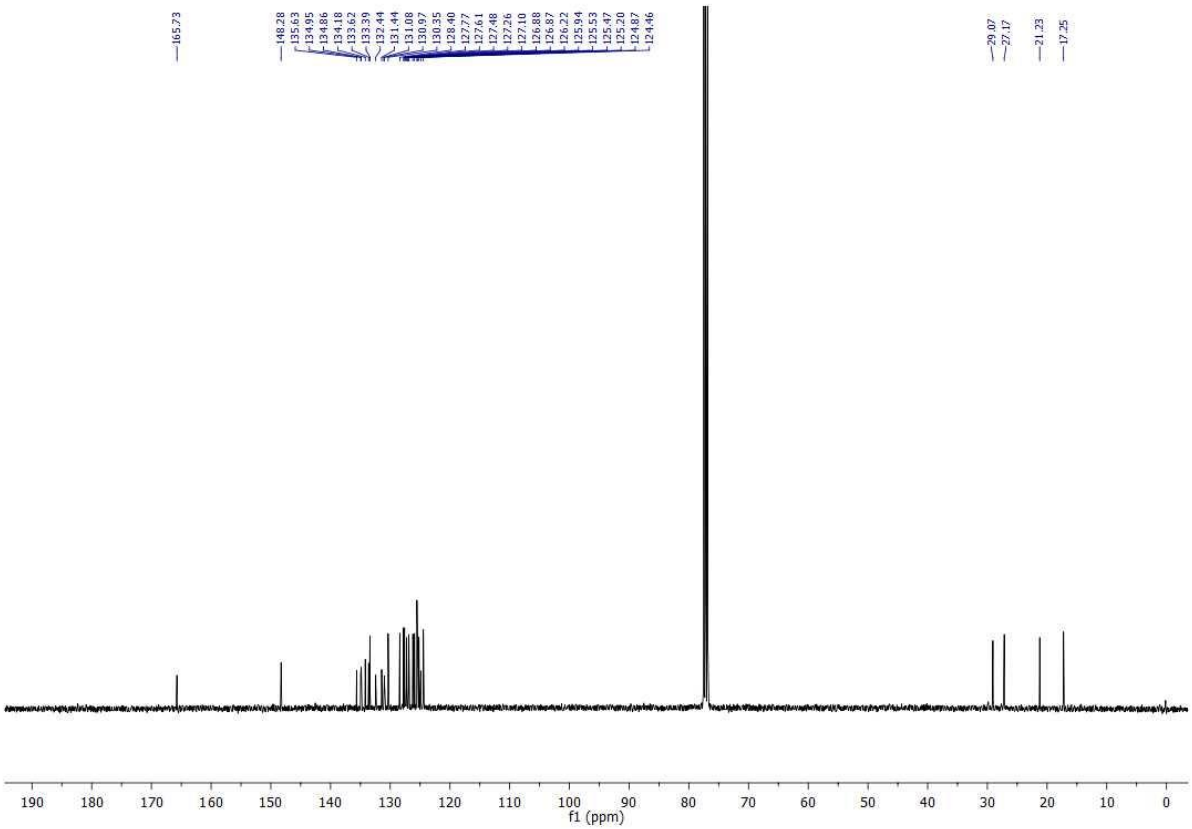


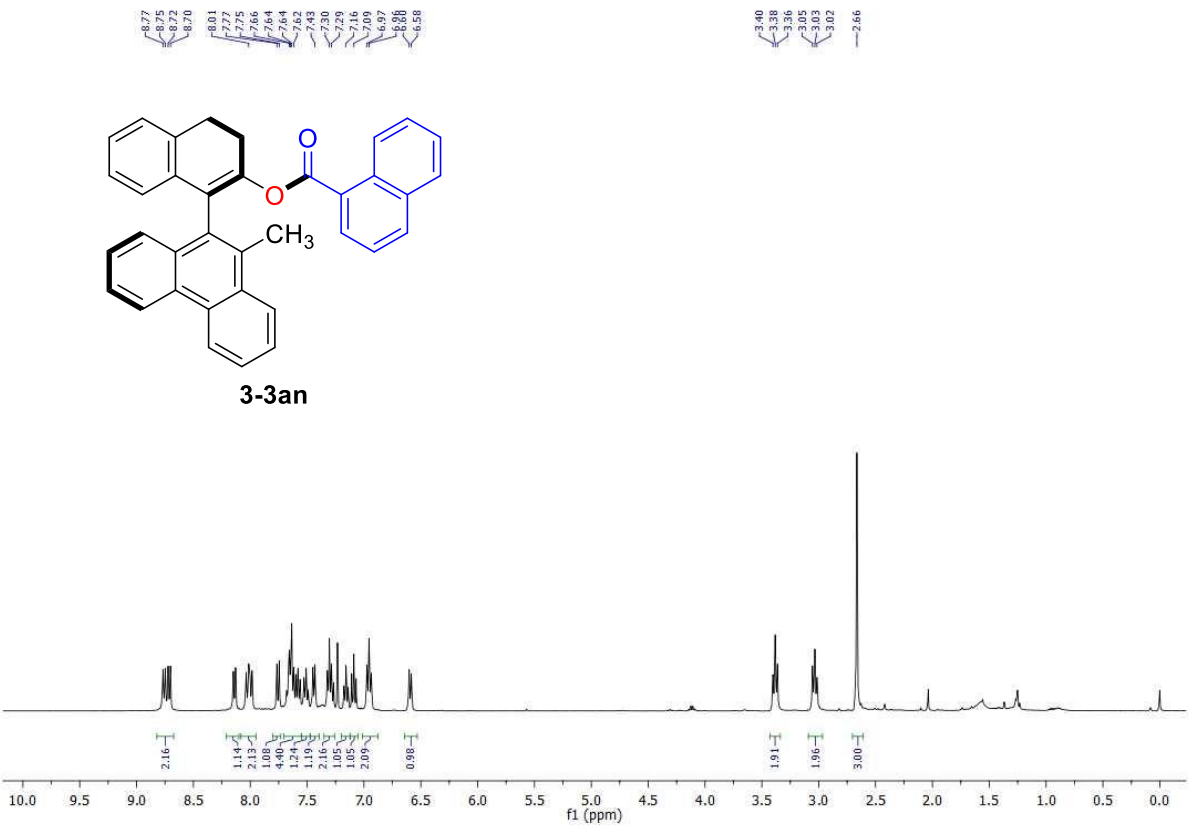




3-3am






8.77
8.75
8.72
8.70
8.01
7.77
7.75
7.66
7.64
7.62
7.43
7.30
7.29
7.16
7.09
6.97
6.88
6.80
6.58
3.40
3.38
3.36
3.05
3.03
3.02
2.66
O
O
CH3
2.16
1.14
2.13
1.08
4.40
1.24
1.19
2.16
1.05
1.05
2.09
0.98
1.91
1.96
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)
165.70
148.63
134.63
134.15
133.54
133.41
132.04
131.89
131.29
130.91
130.39
130.06
129.80
128.33
127.55
127.53
127.22
127.13
126.95
126.90
126.74
126.69
126.51
126.17
126.13
125.60
125.44
125.31
125.04
124.39
123.03
122.62
29.07
27.22
17.13
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3-3an

3.5 References

1. Pellissier, H., *Tetrahedron* **2011,** *67*, 3769.
2. Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E., *Chem. Soc. Rev.* **2001,** *30*, 321.
3. Taylor, J. E.; Bull, S. D.; Williams, J. M., *Chem. Soc. Rev* **2012,** *41*, 2109.
4. Wang, Z.; Pan, D.; Li, T.; Jin, Z., *Chem. Asian J.* **2018,** *13*, 2149.
5. Cohen, D. T.; Eichman, C. C.; Phillips, E. M.; Zarefsky, E. R.; Scheidt, K. A., *Angew. Chem. Int. Ed.* **2012,** *51*, 7309.
6. Wu, Z.; Li, F.; Wang, J., *Angew. Chem. Int. Ed.* **2015,** *54*, 1629.
7. Zhao, C.; Li, F.; Wang, J., *Angew. Chem. Int. Ed.* **2016,** *55*, 1820.
8. Liu, B.; Song, R.; Xu, J.; Majhi, P. K.; Yang, X.; Yang, S.; Jin, Z.; Chi, Y. R., *Org. Lett.* **2020,** *22*, 3335.
9. Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y. R., *Chem. Soc.* **2016,** *138*, 7212.
10. Mondal, S.; Mukherjee, S.; Das, T. K.; Gonnade, R.; Biju, A. T., *ACS Catal*. **2017,** *7*, 3995.
11. Goodman, C. G.; Johnson, J. S., *J. Am. Chem. Soc.* **2014,** *136*, 14698.
12. Goodman, C. G.; Walker, M. M.; Johnson, J. S., *J. Am. Chem. Soc.* **2015,** *137*, 122.
13. Smyth, J. E.; Butler, N. M.; Keller, P. A., *Nat. Prod. Rep.* **2015,** *32*, 1562.
14. Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J., *Chem. Rev.* **2015,** *115*, 11239.
15. Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M., *Chem. Rev.* **2014,** *114*, 9047.
16. Song, R.; Xie, Y.; Jin, Z.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2021**, doi:10.1002/anie.202108630
17. Lu, S.; Poh, S. B.; Zhao, Y., *Angew. Chem. Int. Ed.* **2014,** *53*, 11041.
18. Bie, J.; Lang, M.; Wang, J., *Org. Lett.* **2018,** *20*, 5866.

19. Yang, G.; Guo, D.; Meng, D.; Wang, J., *Nat. Comm.* **2019,** *10*, 3062.

20. Lu, S.; Poh, S. B.; Rong, Z.-Q.; Zhao, Y., *Org. Lett*. **2019,** *21*, 6169.

21. Zhuo, S.; Zhu, T.; Zhou, L.; Mou, C.; Chai, H.; Lu, Y.; Pan, L.; Jin, Z.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2019,** *58*, 1784.

22. Barik, S.; Shee, S.; Das, S.; Gonnade, R. G.; Jindal, G.; Mukherjee, S.; Biju, A. T., *Angew. Chem. Int. Ed.* **2021,** *60*, 12264.

23. Jin, J.; Huang, X.; Xu, J.; Li, T.; Peng, X.; Zhu, X.; Zhang, J.; Jin, Z.; Chi, Y. R., *Org. Lett*. **2021,** *23*, 3991.

24. Xu, K.; Li, W.; Zhu, S.; Zhu, T., *Angew. Chem. Int. Ed.* **2019,** *58*, 17625.

25. Zhang, C.-L.; Gao, Y.-Y.; Wang, H.-Y.; Zhou, B.-A.; Ye, S., *Angew. Chem. Int. Ed.* **2021,** *60*, 13918.

26. Zhao, C.; Guo, D.; Munkerup, K.; Huang, K.-W.; Li, F.; Wang, J., *Nat. Comm.* **2018,** *9*, 611.

27. Li, T.; Mou, C.; Qi, P.; Peng, X.; Jiang, S.; Hao, G.; Xue, W.; Yang, S.; Hao, L.; Chi, Y. R.; Jin, Z., *Angew. Chem. Int. Ed.* **2021,** *60*, 9362.

28. Ma, R.; Wang, X.; Zhang, Q.; Chen, L.; Gao, J.; Feng, J.; Wei, D.; Du, D., *Org. Lett.* **2021,** *23*, 4267.

29. Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T., *Chem. Rev.* **2015,** *115*, 9307.

30. De Sarkar, S.; Studer, A., *Angew. Chem. Int. Ed.* **2010,** *49*, 9266.

31. Liu, Y.; Majhi, P. K.; Song, R.; Mou, C.; Hao, L.; Chai, H.; Jin, Z.; Chi, Y. R., *Angew. Chem. Int. Ed.* **2020,** *59*, 3859.

32. Wang, Y.; Zhang, W. Y.; You, S. L, *J. Am. Chem. Soc*. **2019,** *141*, 2228.

33. Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D., *Nat. Chem.* **2017,** *9*, 558.

34. Sasaki, H.; Irie, R.; Katsuki, T., *Synlett* **1993,** *1993*, 300.

35. Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T., *Tetrahedron* **1994,** *50*, 11827.

36. Kawabata, H.; Omura, K.; Uchida, T.; Katsuki, T., *Chem. Asian J.* **2007,** *2*, 248.

37. Solinas, M.; Meadows, R. E.; Wilson, C.; Blake, A. J.; Woodward, S., *Eur. J. Org. Chem.* **2007,** *2007*, 1613.

38. Ooi, T.; Ohmatsu, K.; Maruoka, K., *J. Am. Chem. Soc.* **2007,** *129*, 2410.

39. Li, F.; Zheng, Z. J.; Shang, J. Y.; Jiang, K. Z.; Lai, G. Q.; Jiang, J. X.; Xu, L. W., *Chem. Asian J.* **2012,** *7*, 2008.

40. Wubbolt, S.; Maji, M. S.; Irran, E.; Oestreich, M., *Chem. Eur. J.* **2017,** *23*, 6213.

41. Yao, C.; Wu, P.; Huang, Y.; Chen, Y.; Li, L.; Li, Y. M., *Org. Biomol. Chem.* **2020,** *18*, 9712.

42. Feng, J.; Li, B.; He, Y.; Gu, Z., *Angew. Chem. Int. Ed.* **2016,** *55*, 2186.

43. Chen, Z.; So, C. M., *Org. Lett.* **2020,** *22*, 3879.