Direct C(sp^3)-H Functionalization of Aliphatic Amines

A Dissertation

Submitted in partial fulfilment of the

Requirements for the Degree of

Doctor of Philosophy

by

Sujit Mahato

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781039

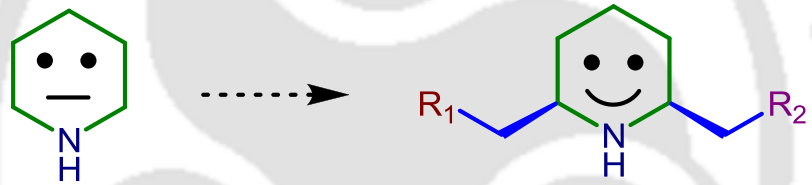
INDIA

August 2016

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Sujit Mahato

Direct C(sp^3)-H Functionalization of Aliphatic Amines



Department of Chemistry

Indian Institute of Technology Guwahati

August 2016

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Statement

The work contained in this thesis entitled "**Direct C(sp^3)-H Functionalization of Aliphatic Amines**" is the outcome of the research work carried out by me under the supervision of Dr. C. K. Jana, Department of Chemistry, Indian Institute of Technology Guwahati, India.

In the present thesis the general practice of the scientific observations are reported and whenever needed, the work on the findings of other investigators are described and thus due acknowledgements have been made.

11th August, 2016

Sujit Mahato
(Roll No: 11612227)
Department of Chemistry,
IIT Guwahati
Guwahati, Assam, India-781039

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "*Direct C(sp^3)-H Functionalization of Aliphatic Amines"* which is being submitted to the Indian Institute of Technology Guwahati for the award of Doctor of Philosophy in Chemistry by Mr. Sujit Mahato (Roll No: 11612227) was carried out by him under my supervision at this institute. The work presented in his thesis is original and that has not been submitted elsewhere for a degree.

Guwahati

August, 2016

Dr. Chandan K. Jana

Supervisor

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Dedicated to my family members

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

~Acknowledgements~

I would like to appreciate all the peoples around me who have assisted and guided me throughout my academic journey. Without their contributions this thesis would not have been a reality.

First of all, I would like to express my sincere gratitude to my supervisor Dr. C. K. Jana for his constant guidance and support throughout my research work. I am indebted to him for inspiring me towards scientific research.

I would like to acknowledge my doctoral committee members Prof. Gopal Das, Dr. Subhas Chandra Pan and Dr. A. S. Achalkumar for their valuable suggestions and encouragements which helped a lot to improve my thesis.

I am thankful to Prof. Latha Rangan, Dept. of Bioscience and Bioengineering, IIT Guwahati for giving me the opportunity to work in her lab. My special thanks to Anuma Singh for her endless support for biological tests and preparing the manuscript during the collaboration. Also thanks to Ishani, Reshmi and Sanjana for their assistance to improve the writing.

I take the opportunity to thank IIT Guwahati for the fellowship. I am thankful to IIT Guwahati, Department of Chemistry and Central Instruments Facilities for providing research facilities and instrumental facilities. I will always remain thankful to scientific staff of CIF and department of chemistry.

I thank my labmates Surajit and Soumita for their contribution in my research work. Also thankful to other lab members Dr. Mrityunjaya Asthana, Ashraful, Subhrakanti, Sumana, Santanu, Anisha for their help and co-operation. I specially thank Dr. Faizi, Dr. Chandani Das, Dr. Barun Dutta, Dr. Samir Gharai, Utpal, Sourav, Debasish, Saugata, Harikrishna, Supriyoda, Sujoyda, Somnathda for their motivation, encouragements and constant support. Their company and moral supports in all my successes and failures always inspired me lot. I would like to thank all my PhD batch mates who helped during my work and for making a friendly environment.

Finally, my concluding gratitude is reserved for my family members whose constant faith in me has been a blessing and a motivation. Their encouragement was always appreciated, and their pride is deeply touching. I am always grateful to the almighty god who is the creator of everything.

Sincerely

Sujit Mahato

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

List of Publications and Presentations

Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun*. **2014**, *50*, 332.	"Diastereoselective α-C-H Functionalization of Aliphatic *N*-heterocycles: An Efficient Route to Ring Fused Oxazines."
Haldar, S.; **Mahato, S**.; Jana, C. K. *Asian J. Org. Chem.* **2014**, *3*, 44.	"Metal and Oxidant Free Direct C(sp^3)-H Arylation of Pyrrolidine"
Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv.* **2014**, *4*, 46214.	"Divergent Reaction: Metal & Oxidant Free Direct C-H Aryloxylation and Hydride Free Formal Reductive *N*- benzylation of *N*-heterocycles."
Mandal, S.; **Mahato, S**.; Jana, C. K. *Org. Lett.* **2015**, *17*, 3762.	"Direct β-C(sp^3)-H Functionalization of Aliphatic Amines to α, β-Unsaturated Imines, Aldehydes and Chromenes.
Mahato, S.; Singh, A.; Rangan, L.; Jana, C. K. *Eur. J. Phar. Sci.* **2016**, *88*, 202.	"Synthesis, *In silico* studies and *In vitro* evaluation for antioxidant and antibacterial properties of diarylmethylamines: A novel class of structurally simple and highly potent pharmacophore"
Mahato, S.; Jana, C. K. *Chem. Rec.* **2016**, *16*, 1477.	"Classical Reaction Driven Stereo-and Regio-selective C(sp^3)-H Functionalization of Aliphatic Amines"
Mahato, S.; Jana, C. K. *Org. Biomol. Chem.* **2017** doi: 10.1039/c6ob02257j	"Iterative C(sp^3)-H Functionalization for the Syntheses of Difunctionalized Secondary Aliphatic Amines"

Presentations

2014	Poster	***Frontiers in Chemical Sciences, FICS-2014***	IIT Guwahati, India. 04-06th December.
2015	Oral Talk	***ChemConvene 2015***	Department of Chemistry, IIT Guwahati, India. 08th April.
2016	Poster	***18th CRSI National Symposium in Chemistry***	Panjab University, Chandigarh and INST Mohali, India 05-07th February.
2016	Poster	***FABACTCS2016***	IIT Guwahati, 03-04th Nov.

Members of Doctoral Committee

Dr. Chandan K. Jana (Supervisor)

Prof. Gopal Das (Chairman)

Dr. Subhas Chandra Pan (Member)

Dr. A. S. Achalkumar (Member)

Content

Abbreviations

Ac	Acetyl
APCI	Atmospheric pressure chemical ionization
aq.	Aqueous
BHT	Butylated hydroxytoluene
Boc	*tert*-butoxycarbonyl
^{t}Bu	*tertiary*-butyl
Cat.	Catalytic/catalyst
$CDCl_3$	Chloroform-*d*
CAN	Ceric ammonium nitrate
cFDA	Carboxyfluorescein diacetate
CH_3CN	Acetonitrile
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless enhancement by polarization transfer
δ	Chemical shift
DNBA	3,5-Dinitrobenzoic acid
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
d. r.	Diastereomeric ratio
Et_3N	Triethylamine
EtOAc	Ethyl acetate
ESI	Electrospray ionization
EtOH	Ethanol
FESEM	Field emission scanning electron microscopy
g	Gram
h	Hour(s)
Hg	Mercury
HRMS	High resolution mass spectrometry
Hz	Hertz
FTIR	Fourier transform infrared spectroscopy
LRMS	Low resolution mass spectrometry
MeOH	Methanol
µg	Microgram
µL	Microlitre
mL	Millilitre
mmol	Millimole
mM	Millimolar
MS	Molecular sieves
NMR	Nuclear magnetic resonance
NOESY	Nuclear overhauser enhancement spectroscopy
Ph	Phenyl
PI	Propidium iodide
^{i}Pr	isopropyl
*p*TSA	*p*-Toluenesulfonic acid
rt	Room temperature
THF	Tetrahydrofuran
THIQ	1,2,3,4-Tetrahydroisoquinoline
TMS	Tetramethylsilane

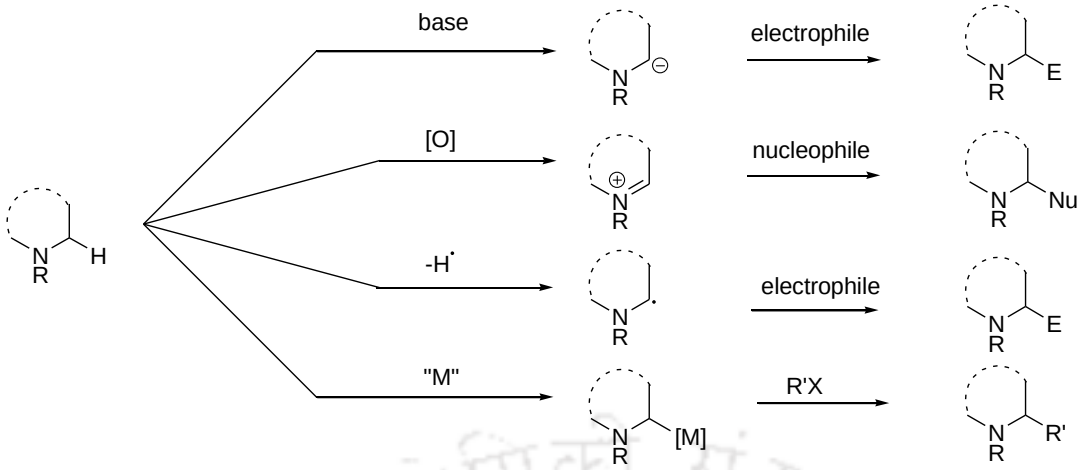
भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Abstract

The contents of this thesis entitled "***Direct C(sp^3)-H Functionalization of Aliphatic Amines"*** have been divided into eight chapters based on the results of experimental works performed during the complete course of the research period. In recent years, direct activation of C-H bonds to form C-C or C-X bond is one of the important topic of synthetic organic chemistry. The first chapter of the thesis presents a review on different aspects of C-H functionalization of aliphatic amines. Other chapters (2-5) mainly emphasize on the C-O and C-C bond formations via direct C(sp^3)-H functionalization. Chapter 2 and 3 illustrates diastereoselective α-C(sp^3)-H functionalization of aliphatic amines. Chapter 2 describes a general route to access ring fused oxazines via silver mediated C-H oxygenation reaction. Chapter 3 describes the synthesis of di-functionalized aliphatic *N*-heterocycles via relayed C-H functionalization. Chapter 4 demonstrates microwave assisted metal and oxidant free direct C-H aryloxylation of *N*-heterocycles. Chapter 5 illustrates synthesis of α,β-unsaturated aldehydes, chromenes, chromene-2-ol derivatives through direct β-C(sp^3)-H functionalization of aliphatic amines. Chapter 6 discusses about the synthesis, *in silico* studies and *in vitro* evaluation for antioxidant and antibacterial properties of diarylmethylamines. Finally, Chapter 7 and Chapter 8 contain the experimental details and copies of ^{1}H and ^{13}C NMR data respectively.

Chapter 1: C(sp^3)-H Functionalization of Aliphatic Amines

This chapter describes the brief history of C-H functionalization of aliphatic amines, challenges for direct C-H functionalization, various strategies adopted to address those challenges, and advantages of C-H functionalization over traditional approach in organic synthesis. Various strategies which were employed for the C-H functionalization of aliphatic amines have been shown in **Scheme 1**. In the first class of amine C–H functionalization, a strong base was used for the formation of carbanion next to the nitrogen. The carbanion subsequently reacted with a series of various electrophiles to produce functionalized amine. In oxidative approach, amine was converted to an iminium ion which is then reacted with a suitable nuclophile. The iminium ion can be generated by various means: a) direct oxidation using standard oxidizing agents b) electrochemical oxidation c) photochemical oxidation d) metal mediated dehydrogenation or e) intra or inter molecular hydride transfer.



Scheme 1: Approaches towards amine functionalization

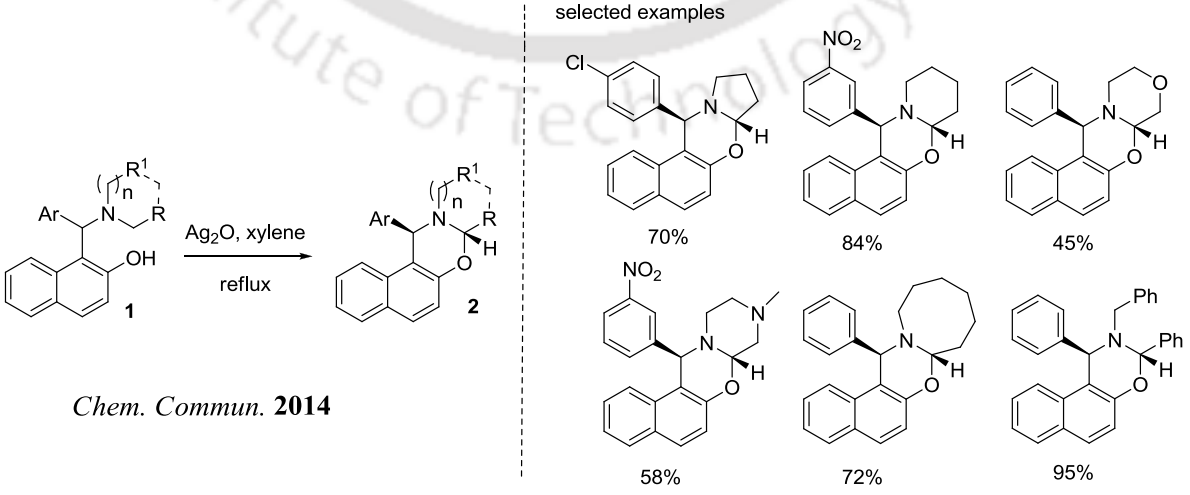
In radical approach, abstraction of a hydrogen atom occurred, leaving a α-amino radical species. The radical intermediate was then reacted with suitable radical donor or acceptor. The transition-metal-catalyzed approach functionalizes the C–H bond with the help of a suitable metal.

Different ways of amine functionalization have its own potential for the conversion of amine to its functionalized derivative. In concern to the ecological viability, which requires the consideration of atom efficiency as well as less involvement of toxic materials like metallic reagent and oxidants, methods developed have significant limitations. As for example, the deprotonation methods do not involve ambient conditions. Moreover, the commercial unavailability and long synthetic route to achieve (-) sparteine makes it a difficult to access other enantiomer of functionalized product via these reactions. The α–aminocarbanions generated in presence of chiral amine are configurationally unstable at temperatures above -50 °C and unactivated electrophiles are very hard to react at such temperatures. Furthermore, stereoselective α-lithiation of piperidine and piperazine derivatives were remain unsuccessful. Reactions involving carbon–hydrogen (C–H) bond oxidation required use of super-stoichiometric amount of oxidants which significantly limits the scope of the reaction. Undoubtly photo-induced method was a break-through in the field of amine functionalization. But the uses of sophisticated valuable transition metal catalyst reduce its practical utility. Anodic oxidation method was successful only for pyrrolidine derivatives, but remain ineffective for six, seven and eight membered cyclic amines, such as piperidine, piperizine and morpholine. Redox-neutral ways are attracting method for the construction of a desired functionalized product. Sometimes addition of Lewis/Bronsted acid

or base enhances the reaction rate but require higher temperature to reach the goal. Importantly, pyrrolidine or tetrahydroisoquinoline was employed as only substrate to show the efficiency of this method and other secondary amines (piperidine, acyclic amine) provided poor/no yield. Therefore, development of methodology for direct functionalization of aliphatic amine that can be applied for broad class of substrates under ecological viable condition would be an important contribution to the field.

Chapter 2: Diastereoselective *α*-C-H Oxygenation of Aliphatic Amines: A General Route to Ring Fused Oxazines

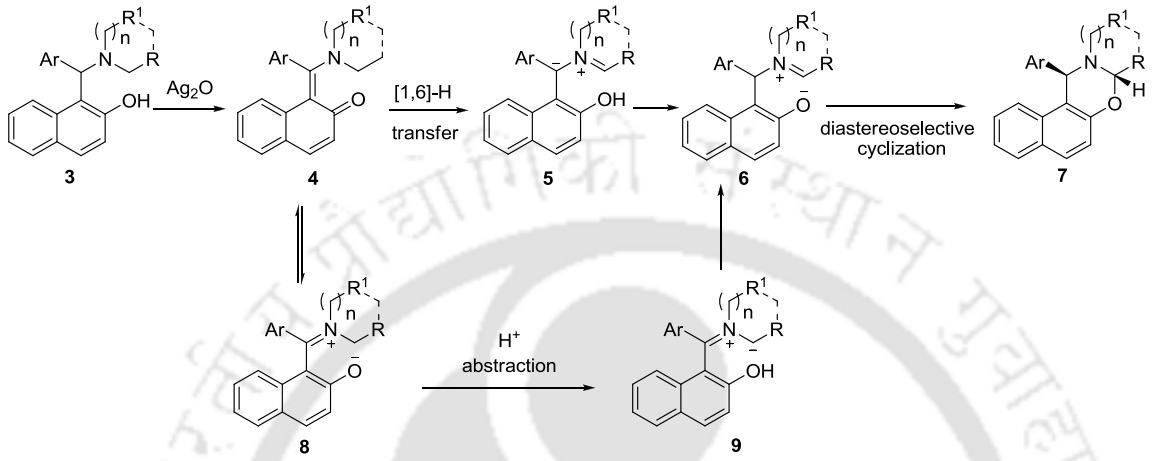
The aim of the thesis is to address the challenge of direct C-H functionalizaton of unreactive cyclic and acyclic aliphatic amine. This chapter focuses on the silver oxide mediated diastreoselective intramolecular oxidative *α*-oxygenation of *N*-heterocycles. In this context, a novel method for direct C-H functionalization of saturated *N*-heterocycles leading to the easy access to synthetically as well as biologically important and structurally diverse ring-fused oxazines was developed. After a series of experiment, the best result was obtained from a reaction of Betti base with silver oxide in xylene at 140 ^{o}C (**Scheme 2**). Diversely substituted aromatic aldehyde based substrates were screened for the C‑H functionalization of pyrrolidine. It was observed that the substrates which derived from electron rich aromatic aldehydes, provided relatively lower yields in comparison to the substrates that are derived from either electro-neutral or electron deficient aldehydes. The method is operationally simple, scalable, highly diastereoselective, and equally efficient to functionalize broad class of both cyclic and acyclic amines including the ones that are difficult to functionalize by other methods. This route provides an efficient synthesis of dihydro-1,3- oxazines.



Chem. Commun. **2014**

Scheme 2: Silver oxide mediated C-H oxygenation

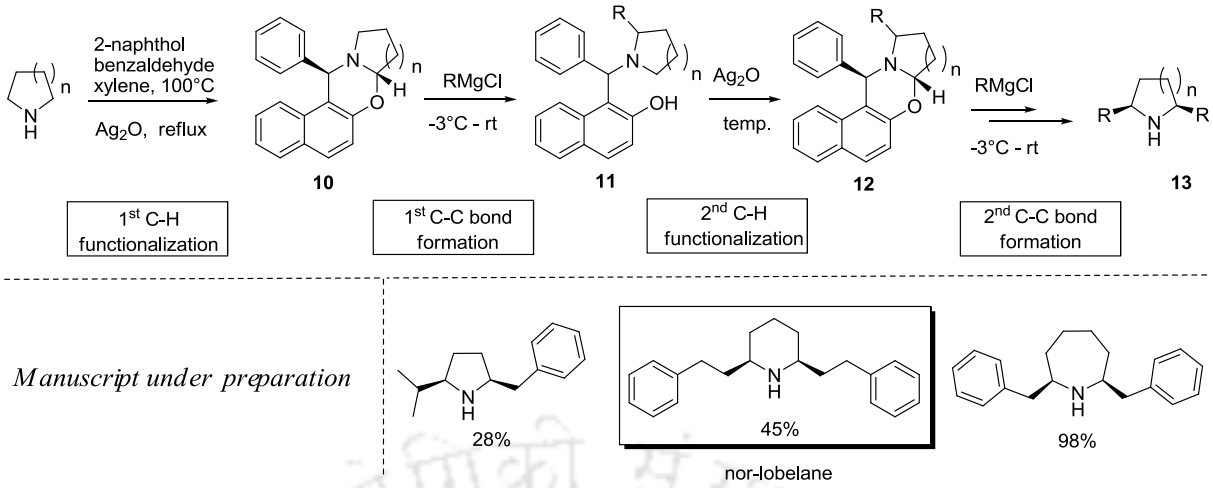
Based on the experimental findings and literature reports a plausible mechanism has been proposed for this transformation (**Scheme 3**). Silver oxide mediated the oxidation of amino alcohol **3** to corresponding quinone methide **4**. Zwitter ion **6** was formed from **4** either via [1, 6]-hydrogen shift or via mesomerization. Diastereoselective intermolecular cyclization of **6** provided desired oxazine **7 (Scheme 3)**.



Scheme 3: Mechanistic proposal for oxazine synthesis.

Chapter 3: Iterative C(sp^3)-H Functionalization for the Syntheses of Di-functionalized Secondary Aliphatic Amines

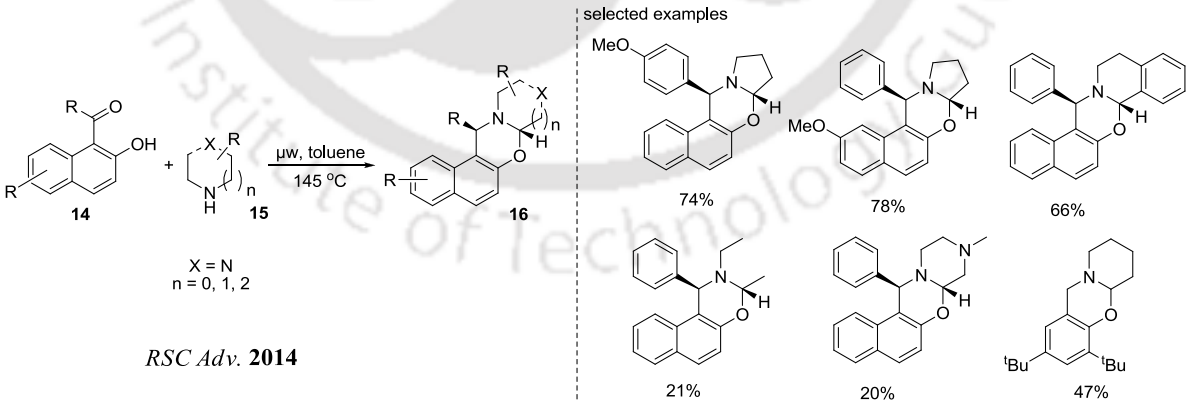
Disubstituted pyrrolidines, piperidines occur ubiquitously in many natural products, biologically active compounds, and in functional materials. Particularly lobelane, six membered di-functionalized *N*-heterocycle, is an important compound having [3H]DTBZ binding affinity at the vesicular monoamine transporter-2 (VMAT2). Either multistep synthetic route or pre-functionalized *N*-heterocycles have been applied to access those di-functionalized amines which reduces the practical utility of the method. An efficient, practical method for the synthesis of structurally diverse di-substituted *N*-heterocycles through successive *α*-functionalization of *N*-heterocycles have been developed. The two substituents at the *α*-position of the *N*-heterocycles could be varied easily by the choice of appropriate Grignard reagents. The synthetic potential of this sequential strategy was specifically demonstrated by the efficient synthesis of the *nor*-lobelane, a piperidine based alkaloid (**Scheme 4)**. The method also allows the synthesis of different di-substituted *N*-heterocycles.



Scheme 4: Di-functionalized amines through iterative synthesis

Chapter 4: Metal and Oxidant Free Direct C-H Aryloxylation of *N*-Heterocycles

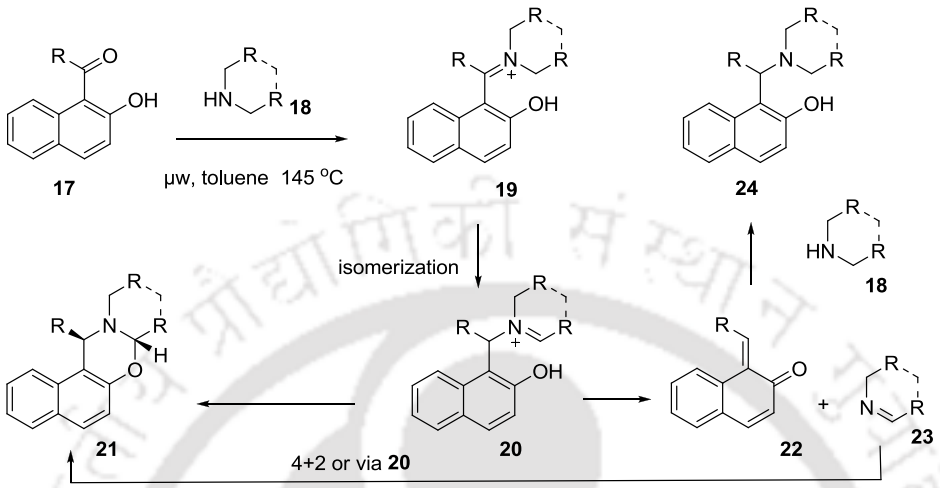
Ring fused oxazines are very important molecules because of their interesting bio-activities and for their use in synthesis of functionalized *N*-heterocycles. Metal and oxidant mediated direct C-H functionalization were mainly employed for their preparation. In this chapter, a metal, oxidant and other additive free novel method for direct C-H aryloxylation of aliphatic *N*-heterocycles has been presented. Structurally diverse ring-fused oxazines were produced via heating a mixture of suitable carbonyl compound and amine under microwave irradiation (**Scheme 5**). Mechanistic studies suggested that the reaction proceeded through quinone methide intermediate.



Scheme 5: α-Oxygenation of *N*-heterocycles

It is proposed that first carbonyl compound **17** reacted with secondary amine **18** to produce iminium ion **19**. Iminium ion **19** then isomerized to **20**. The iminium ion **20** could either intra-molecularly cyclised to oxazine **21** or could be dissociated to generate quinone methide **22.**

Subsequently quinone methide **22** could also react with cyclic imine **23** via [4+2] cycloaddition to give the corresponding oxazine **21**. In the presence of excess amine **18**, the quinone methide could produce the *N*-benzylated product **24** (**Scheme 6**). *N*-Benzylated heterocycle **24** was isolated on use of excess **18**.

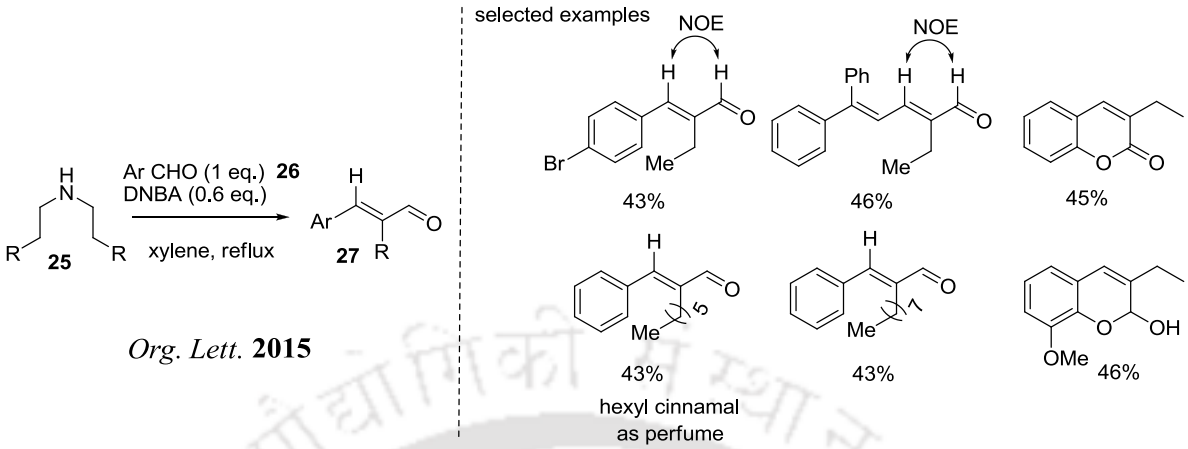


Scheme 6: Proposed mechanistic pathway

Chapter 5: Direct *β*-C(sp^3)-H Functionalization of Aliphatic Amines to Conjugated Aldehydes, Chromenes, Chromene 2-ol

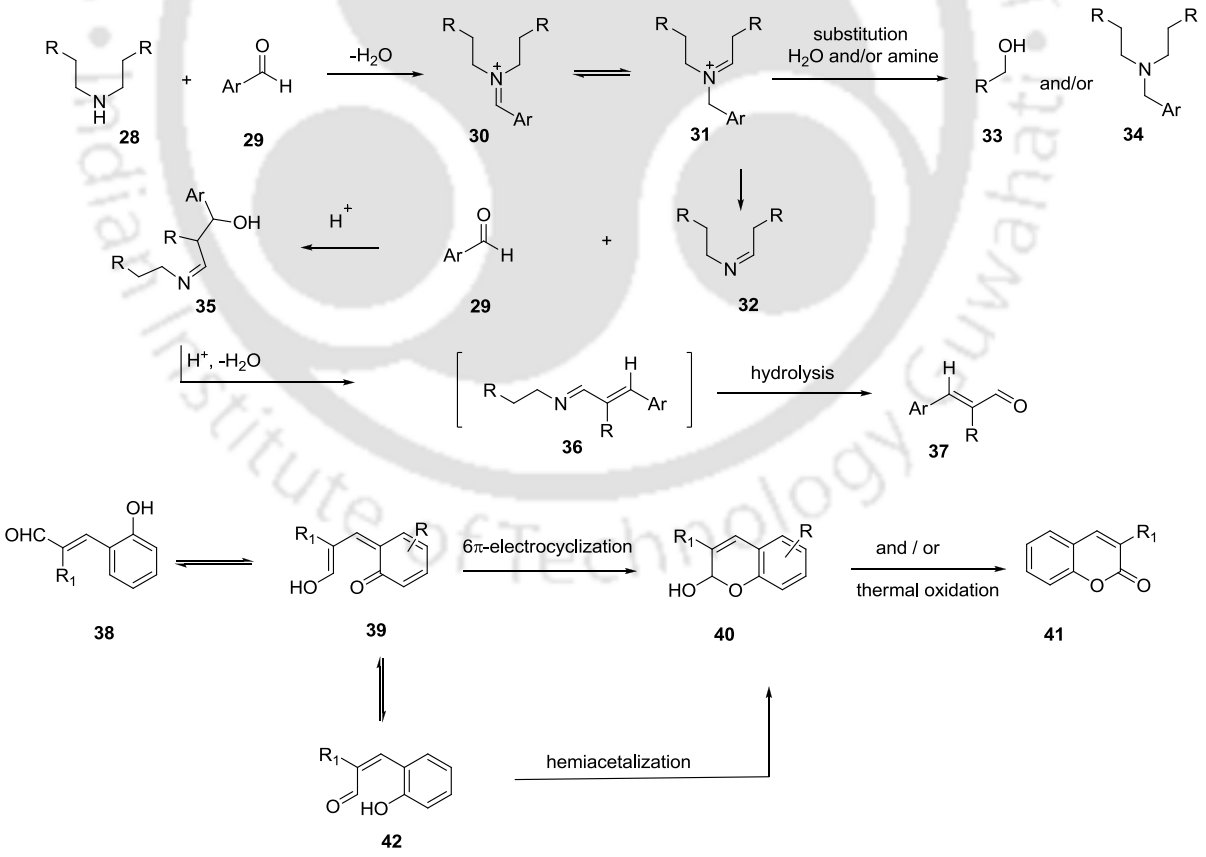
Various synthetic methodologies were developed for the preparation of *α*-C-H functionalization of amines. On the other hand, although indirect pathways are known for the preparation of *β*-functionalized amine, reports on direct functionalization of more challenging *β*-C(sp^3)-H bonds are only very few. The existing methods uses either metal- and/or oxidant-based reagent/catalyst to achieve direct *β*-C(sp^3)-H functionalization of amines. A metal-free method for direct *β*-C(sp^3)-H functionalization of aliphatic amines have been developed. The method is based on a reaction that yields enamine directly from corresponding aliphatic amine **25**, which otherwise requires the aid of metallic reagent and/or external oxidant. The reaction is operationally simple, general and highly efficient in functionalizing both cyclic and acyclic amines. Acyclic amines provided 2-alkyl cinnamaldehyde **27** and benzopyran derivatives with excellent *E/Z*-selectivity. Preparation of unsaturated aldehydes, primarily via cross-aldol reaction, remained inefficient due to the associated undesired self-condensation and polymerization reaction. These complications can be potentially avoided during their syntheses via this operationally simple method utilizing amine as the formal aldol-donor. Different dialkylamines were reacted with various aldehydes providing structurally diverse 2-alkylated cinnamaldehyde derivatives (**Scheme 7**). Many of them can be considered as

potential aroma substances for use in fragrance industry. Particularly, hexyl cinnamal is a natural aroma found in essential oil of *Chamomile* and used in perfume.



Scheme 7: Direct β-C(sp^3)-H functionalization of aliphatic amines

A mechanistic proposal for the metal- and oxidant-free direct β-C-H functionalization of secondary amine is presented in **Scheme 8**.



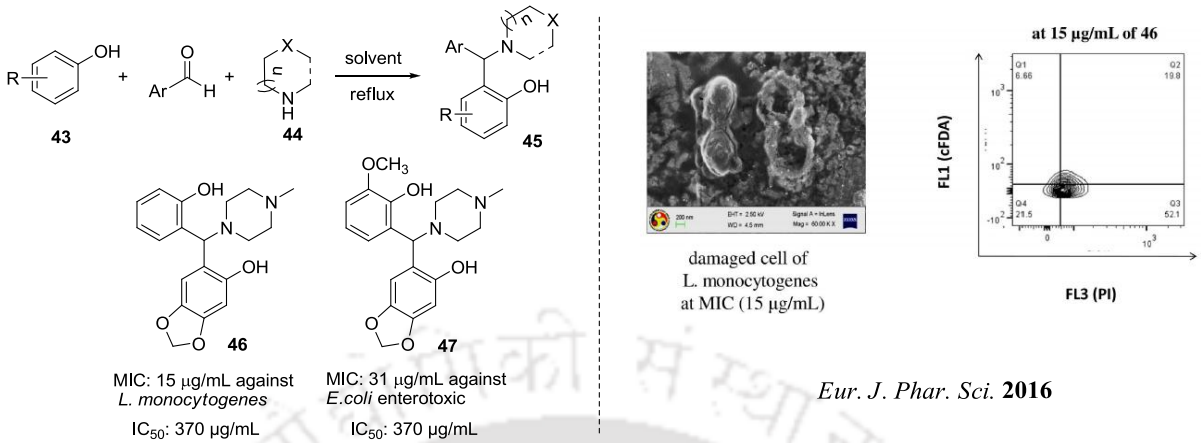
Scheme 8: Plausible mechanism for β-functionalization of aliphatic acyclic amines

Aldehyde **29** condensed with secondary aliphatic amine **28** providing iminium ion **30**, which then rearranged to isomeric iminium ion **31**. Nucleophilic substitution reaction occurred at the benzylic or allylic position of **31** to release imine **32** and benzyl alcohol **33** or benzyl amine **34**. Subsequent reaction of enamine, formed from imine **32,** with aldehyde **29** provided *α, β*-unsaturated imine **36** via intermediate alcohol **35**. The unstable imine **36** underwent hydrolysis providing conjugated aldehyde **37**. Similar to enal **37**, compound **38** was formed for salicylaldehyde based substrates on reaction with acyclic amines. The hydroxy group of salicylaldehyde promoted intramolecular cyclization providing chromene-2-ol **40** that underwent subsequent oxidation to coumarin derivatives **41**. Ring closing occurred either via thermal 6π-electrocyclization of *o*-quinone methide **39** or through intramolecular hemiacetalization of **42** (**Scheme 8**).

Chapter 6: Synthesis, *In silico* Studies and *In vitro* Evaluation for Antioxidant and Antibacterial Properties of Diarylmethylamines

In recent years the treatment of some bacterial infections has become more complicated because of the increase in bacterial resistance against conventional antibacterial agents. Also, many of the known potential antibacterial agents are structurally complex and thus these are difficult to obtain with adequate quantity. Hence, identification of new class of safe, highly effective and easily accessible chemotherapeutic agents becomes inevitable. In this context, diarylmethylamines belong to a promising class of molecules because of their important pharmacological profile, structural simplicity and easy accessibility. This chapter describes *in silico* studies and *in vitro* evaluation for antioxidant and antibacterial properties of diarylmethylamines. In quest of the potent and novel class of antimicrobial compounds, a set of structurally diverse diarylmethylamines/Betti bases were designed and synthesized. Suitable aldehydes were condensed with different secondary amines in the presence of electron rich phenolic compounds to obtain the desired diarylmethylamines (**Scheme 9**). The antimicrobial behaviour of novel diarylmeyhylamines against *Listeria monocytogenes* and *Escherichia coli* enterotoxic were investigated in collaboration with Prof. L. Rangan. It was found that the Betti bases showed significant antibacterial activity compared to the corresponding oxazines. The antibacterial action of synthesized compounds was evaluated by microbroth dilution assay. The anti-bacterial activity was further supported by flow cytometry and FESEM imaging. DPPH-assay was employed to evaluate their antioxidant behaviour. The physico-chemical parameters of synthesized compounds were determined by *in*

silico studies. The present study revealed that diarylmethylamine derived from sesamol to be more potent than one derived from 2- naphthol and phenol based compounds.



Scheme 9: Synthesis and evaluation of novel antibacterial compounds

Compound **46** containing sesamol and *N*- methyl piperazine was found to be the most potent (MIC: 15 µg/mL) against Gram-positive (*L. monocytogenes*) bacteria. It showed antibacterial effect through the damage of bacterial cell membrane which was confirmed by FC and FESEM analyses. Other compounds showed moderate or no activity against Gram-negative bacteria. Compounds **46** and **47** also showed strong free radical scavenging activity (370 µg/mL) similar to BHT (184 µg/mL) in DPPH assay.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

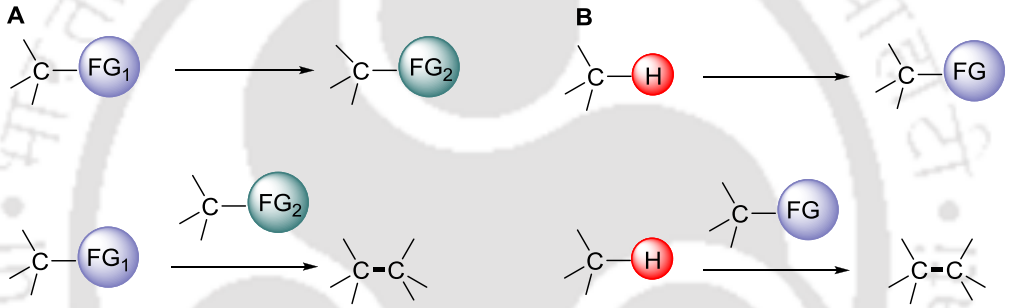
Chapter 1

C(sp^3)-H Functionalization of Aliphatic Amines

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

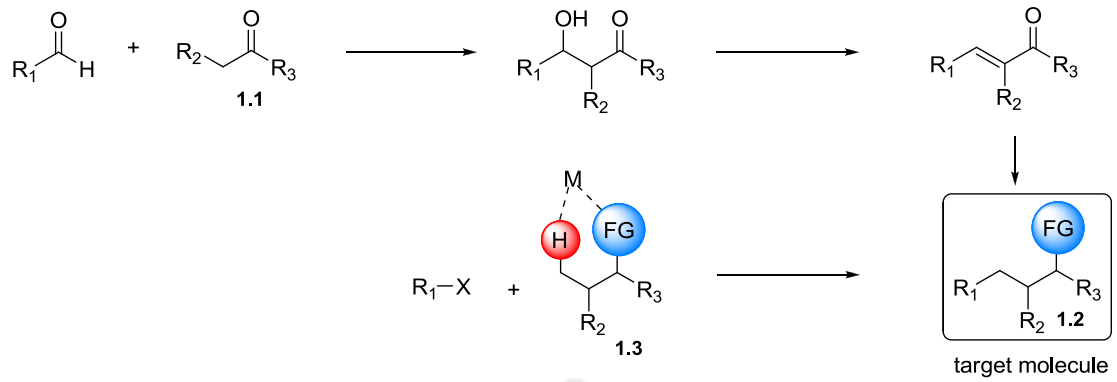
1.1 Introduction

Nature produces a large number of molecules having C–H bonds, starting from simple hydrocarbon methane to complex molecules such as proteins and enzymes. Nature has its own way to functionalize C-H bonds as it routinely uses C–H oxidation, generally mediated by oxygen-activating heme- and non-heme iron enzymes, to directly install oxidized functionality onto the pre-formed framework of complex molecules. In contrast, the synthetic approaches suffer a lot of difficulty as traditional organic methods rely heavily on reactions, which require extensive functional group manipulation including protection-deprotection sequences, to add oxidized functionality in a molecule (**Scheme 1**, **A**). Due to the lack of empty orbitals of low energy or filled orbitals of high energy that could readily participate in a chemical reaction, the C-H bond remains inert towards a synthetic reaction.



Scheme 1: (**A**) Traditional approach to organic synthesis by means of functional group (FG) transformation. (**B**) Synthesis by means of C–H bond functionalization.

Two fundamental challenges are associated with the direct functionalization of C-H bonds. 1) Reactivity-'activating' a inert C-H bond so that it permits the barrier of chemical attack; 2) Selectivity-targeting a specific C-H bond among the other available C-H bonds in the molecule.[1] The approaches for the direct functionalization of C-H bonds to C-C, C-O or C-N bonds not only streamlines the existing synthesis but also contributes for changing the way chemists think about chemical reactivity to plan chemical syntheses. Therefore, precise one step transformation of ubiquitous C-H bonds to C-C or C-X (X = N or O) without disrupting other functionality is hugely demanded for syntheses. Modern synthetic organic chemistry utilizes direct transformation of C-H bond as it is advantageous in the context of atom and step economy (**Scheme 1**, **B**).[2] For example, the straightforward synthesis of target molecule **1.2** from starting material **1.3** overcomes the barrier of multiple transformations that are used in classical synthesis of same target **1.2** starting from compound **1.1** (**Scheme 2**).



Scheme 2: Multistep reaction vs direct C-H Functionalization

The vast area of chemistry deals with many natural and unnatural compounds with biological relevence.[3] Functionalized amine unit builds the framework of a large number of these molecules. Therefore, functionalized amines have a unique importance in drug discovery. Selected examples of some natural products containing pyrrolidine and piperidine are given below (**Figure 1)**. [4]

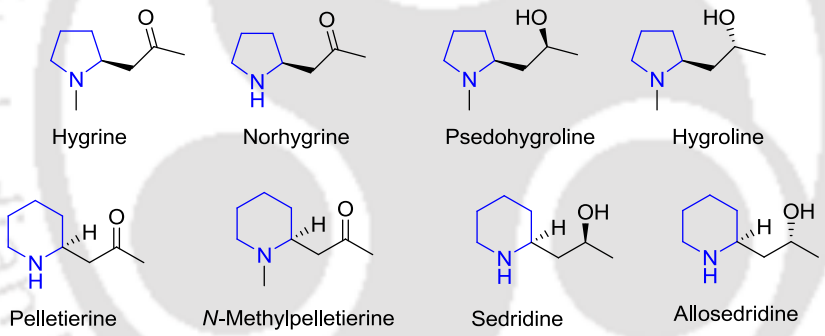


Figure 1: 2-Substituted pyrrolidine and piperidine based natural products

Many drugs have been designed to mimic or to interfere with the action of natural amine neurotransmitters. For example phenylephrine, an acyclic amine, is a selective α_1-adrenergic receptor agonist of the phenethylamine class used primarily as a decongestant, as an agent to dilate the pupil, and to increase blood pressure.[5] Amoxapine is a well-known secondary amine tricyclic antidepressant, which is a member of dibenzoxazepine family.[6] Moxifloxacin containing functionalized pyrrolidine and piperidine unit is a fluoroquinolone antibacterial agent and marketed worldwide as the hydrochloride salt for oral treatment and also used in an ophthalmic solution (eye drops) for the treatment of conjunctivitis.[7] A few other examples are depicted below (**Figure 2)**.[8,9]

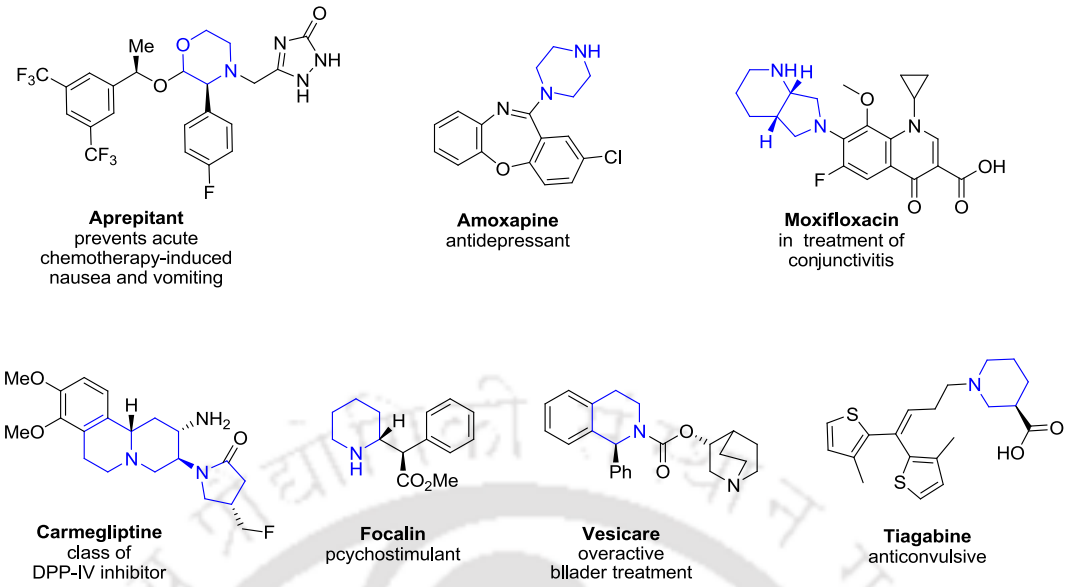
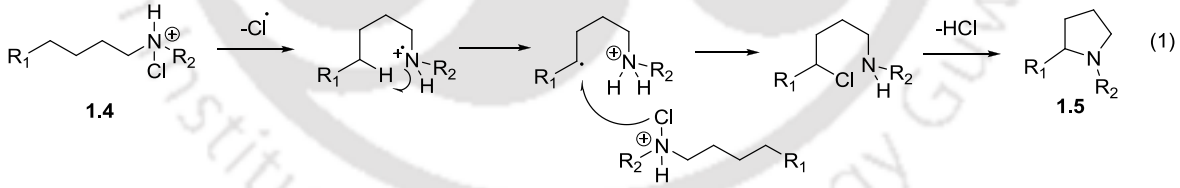


Figure 2: Top retailing drug molecules containing 6-membered heterocycles in market

1.2 Approaches to amine C–H functionalization

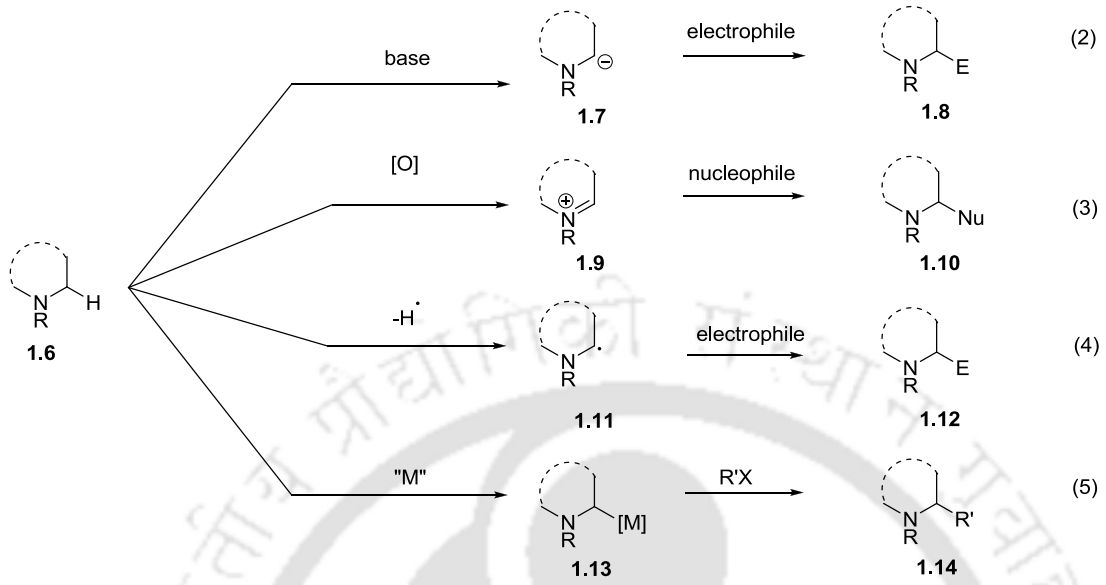
Early approaches for the selective functionalization of C-H bond relied on radical chemistry. Hofmann-Löffler-Freytag reaction is an example where thermal or photochemical decomposition of *N*-halogenated amine **1.4** occurs in the presence of a strong acid to form a highly reactive intermediate that provides the cyclic amine **1.5** (**Scheme 3**, eq. 1).[10]



Scheme 3: Intramolecular C–H functionalization

Functionalized amines are available as a major class of medicinal drugs in market. Thus it is necessary to develop methods for amine functionalization.[11] In spite of the difficulty in functionalizing α-C(sp^3)-H bond in aliphatic amines, a number of different approaches have been developed.[12] In the first class of amine C–H functionalization, a strong base was used for the formation of carbanion next to the nitrogen. The carbanion **1.7** subsequently reacted with a series of various electrophiles to produce functionalized amine **1.8** (**Scheme 4**, eq. 2).

The next class is an oxidative approach (**Scheme 4**, eq. 3). In this method, amine **1.6** was converted to an iminium ion **1.9**, which is then reacted with a suitable nucleophile.



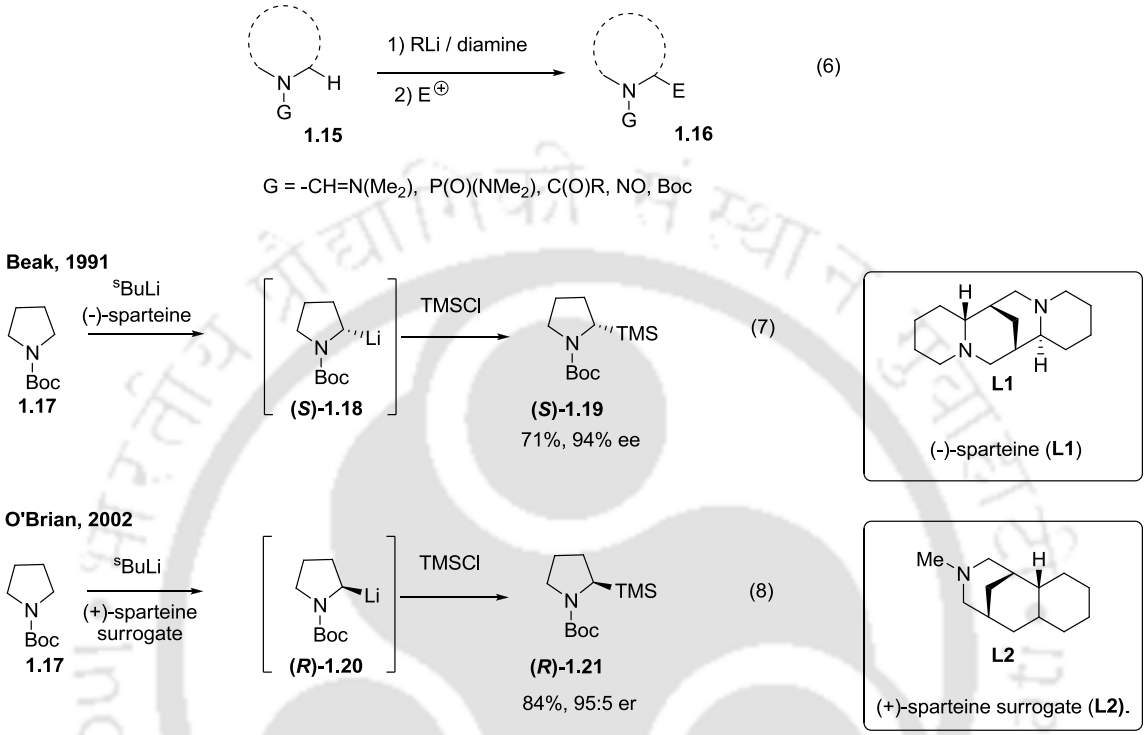
Scheme 4: Major approaches to α-C–H functionalization of aliphatic amines

The iminium ion can be generated by various means: either via a) direct oxidation using standard oxidizing agents; b) electrochemical oxidation; c) photochemical oxidation; d) metal mediated dehydrogenation or e) intra or inter molecular hydride transfer. In radical approach, abstraction of a hydrogen atom occurred, leaving a *α*-amino radical species of the type **1.11**. The radical intermediate was then reacted with suitable radical donor or acceptor (**Scheme 4**, eq. 4). The transition metal catalyzed approach functionalizes the C–H bond with the help of a suitable metal (**Scheme 4**, eq. 5). There are a number of different subtypes of these four pathways, but most amine C–H functionalizations proceed through one of these approaches.

1.3 Amine C–H functionalization through deprotonation

The oldest reported method for the direct functionalization of nitrogen-containing aliphatic heterocycles involved *α*-lithiation with alkyllithium/diamine complexes followed by electrophilic substitution.[13] Many dipole-stabilizing groups, like formadine, phosphoramide, amide, nitroso, oxazoline, and *tert*-butyl carbamate functionalities were effective for *α*-lithiation of tertiary-amines.[12a] Among these, the *tert*-butyl carbamate (Boc) protecting group was widely used due to easy availability, practicality and ease of installation/removal. A general strategy and selected examples are described below

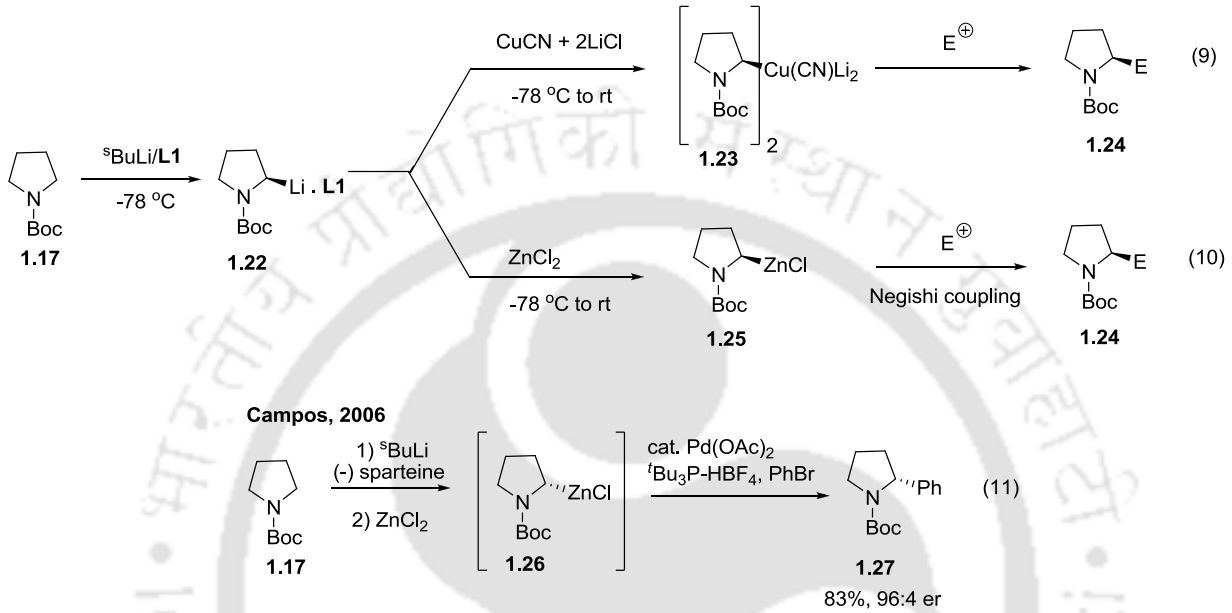
(**Scheme 5**, eq. 6). Different other examples in the field of C-H functionalization were reviewed in different occasion.[14,15] The pioneering work for *α*-functionalization of *N*-Boc pyrrolidine was developed by Beak and co-workers in 1991. They reported that in presence of chiral diamine (-)-sparteine and ^{s}BuLi deprotonation of *N*-Boc pyrrolidine **1.17** occurred at *α* position to nitrogen functionality. The resulting chiral organolithium complex **1.18**



Scheme 5: Amine C–H functionalization through deprotonation

was subsequently trapped by suitable electrophiles at low temperatures to give enantio-enriched product **1.19** with good yield and high enantioselectivity (**Scheme 5**, eq. 7).[16] However, the commercial unavailability and long synthetic route to obtain (+)-sparteine, made it difficult to access the other enantiomer of the functionalized product from these reactions.[17] In 2002, O'Brian and co-workers reported an analogue of (+)-sparteine which allowed for the synthesis of other enantiomer **(*R*)-1.21** with comparable *enantiomeric excess* (**Scheme 5**, eq. 8).[17] For stereoselective reactions with less reactive electrophiles, transmetallation of organolithium compound to other metals was necessary. Many organocuprate or organozinc reagents, for example, are configurationally stable up to room temperature (**Scheme 6**, eq. 9 and eq. 10).[12] Accordingly, Campos and co-workers prepared organozinc **1.26** via transmetalation of organolithium **(*S*)-1.18** with $ZnCl_2$. A Negishi cross-coupling with resulting organozinc species provided functionalized pyrrolidine **1.27**

(**Scheme 6**, eq. 11).[18] Although the deprotonative approach was quite useful for the functionalization of amines, stereoselective reactions at -78 °C were limited to very reactive electrophiles such as aldehydes, TMSCl, Me_2SO_4, epoxides and other activated electrophiles. The α-aminocarbanions generated with chiral amine ligands are configurationally unstable at temperatures above -50 °C and unactivated electrophiles hardly react at such temperatures.

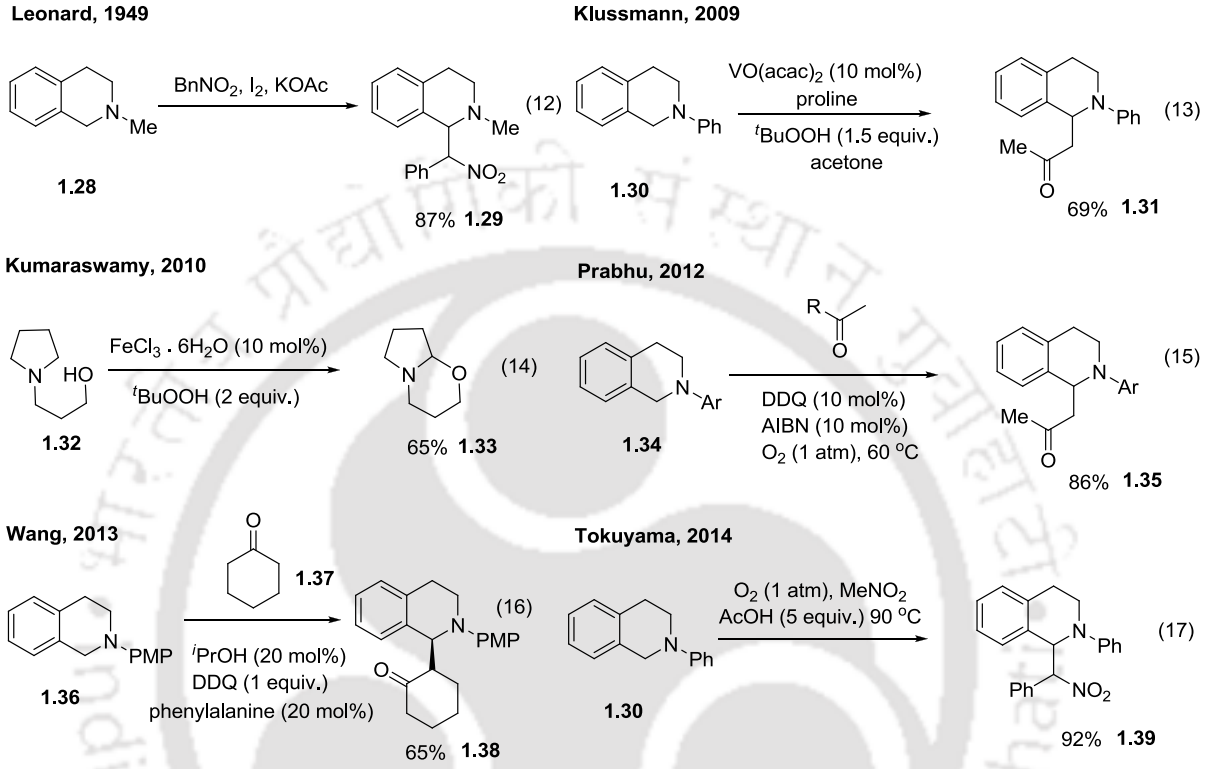


Scheme 6: Transmetallation strategy

1.4 Oxidative approaches to C–H functionalization

The use of external oxidants like iodine, molecular oxygen and peroxides are quite common to generate an iminium ion.[19] Stoichiometric amount of molecular iodine, was used in the Henry-type reaction as demonstrated by Leonard and co-workers (**Scheme 7**, eq. 12).[20] Many catalytic approaches using transition metal catalyst have been developed for this type of reaction, usually using either oxygen or peroxides as the terminal oxidant. Klussmann and co-workers published a tandem $VO(acac)_2$/proline catalyzed oxidative C-H functionalization of tetrahydroisoqunoline derivative **1.30**. However, the isolated products were racemic due to facile racemisation of β-amino-ketones (**Scheme 7**, eq. 13).[21] The use of less expensive $FeCl_3 . 6H_2O$ was successesfully shown by Kumaraswamy and co-workers to catalyze the oxidation of even challenging substrates **1.32** for producing cyclic *N*,*O*-acetal **1.33** (**Scheme 7**, eq. 14).[22] Prabhu and co-workers reported synthesis of α-functionalized product **1.35** from *N*-phenyl tetrahydroisoquinoline **1.34** when reacted with different nucleophile in the presence of DDQ and molecular oxygen. (**Scheme 7**, eq. 15).[23]

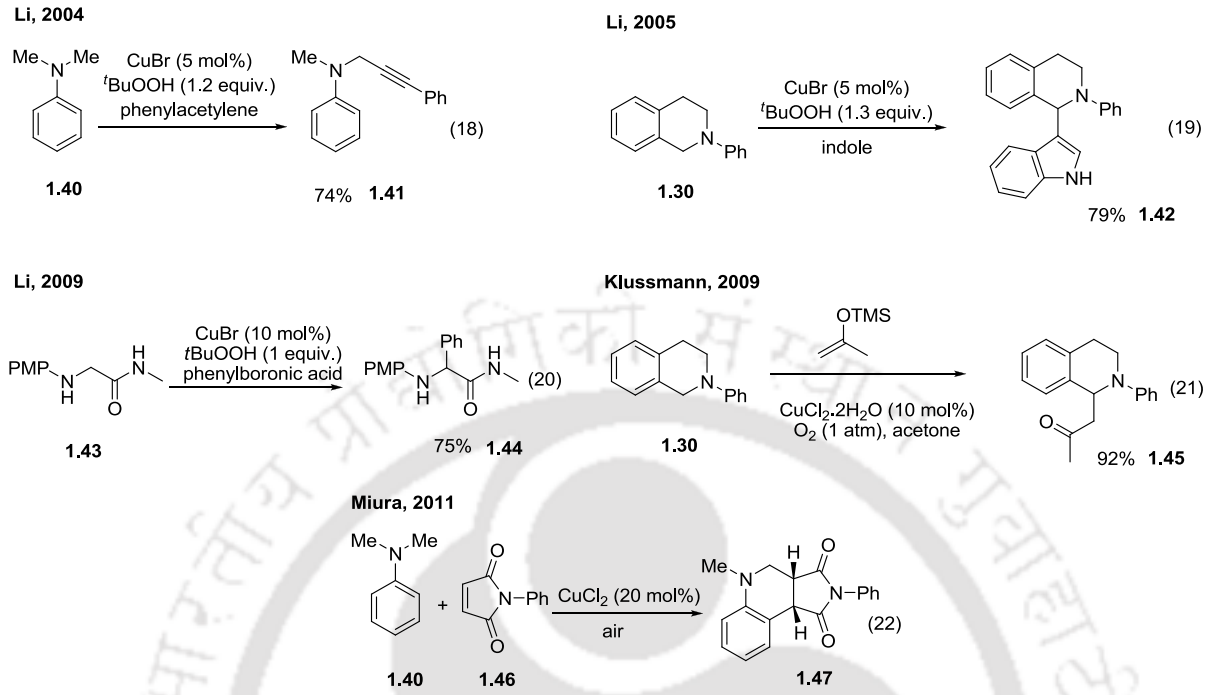
Wang and co-workers have shown enantioselective oxidative Mannich-reaction of **1.36**, using phenylalanine as asymmetric organocatalyst and DDQ as stoichiometric oxidant, to provide the desired product **1.38** (**Scheme 7**, eq. 16).[24] In 2014, Tokuyama and co-workers used acetic acid as an additive and molecular oxygen as oxidant to functionalize **1.30** to its α-substituted derivative **1.39** via an aza-Henry type reaction (**Scheme 7**, eq. 17).[25]



Scheme 7: Oxidative approaches to C–H functionalization

Extensive use of copper has been reported in literature in transition-metal catalyzed methodologies for the oxidative α-functionalization of cyclic tertiary amines with a variety of classical chemical oxidants (^{t}BuOOH, O_2). Oxidation with copper salt was demonstrated by Li and co-workers in 2004. They have shown that C-C bond can be constructed via oxidative coupling of C(sp^3)-H bond of amine **1.40** with C(sp)-H of alkynes (**Scheme 8**, eq. 18).[26] In addition, Li and coworkers extended the reaction using malonates and malononitrile,[27] nitroalkanes,[28] indoles as the coupling partner with amine (**Scheme 8**, eq. 19).[29] In 2009, the same group expanded the reaction for the functionalization of secondary amines **1.43** using phenylboronic acids (**Scheme 8**, eq. 20).[30] Klussmann and co-workers reported a copper-catalyzed Mannich-reaction, using silyl enol ethers as the nucleophile, to convert **1.30** to **1.45** (**Scheme 8**, eq. 21).[31] In 2011, Miura and co-workers published a

copper mediated cycloaddition reaction of *N*,*N*-dimethyl aniline **1.40** with di-keto amine **1.46** yielding polycyclic product **1.47** (**Scheme 8**, eq. 22).[32]

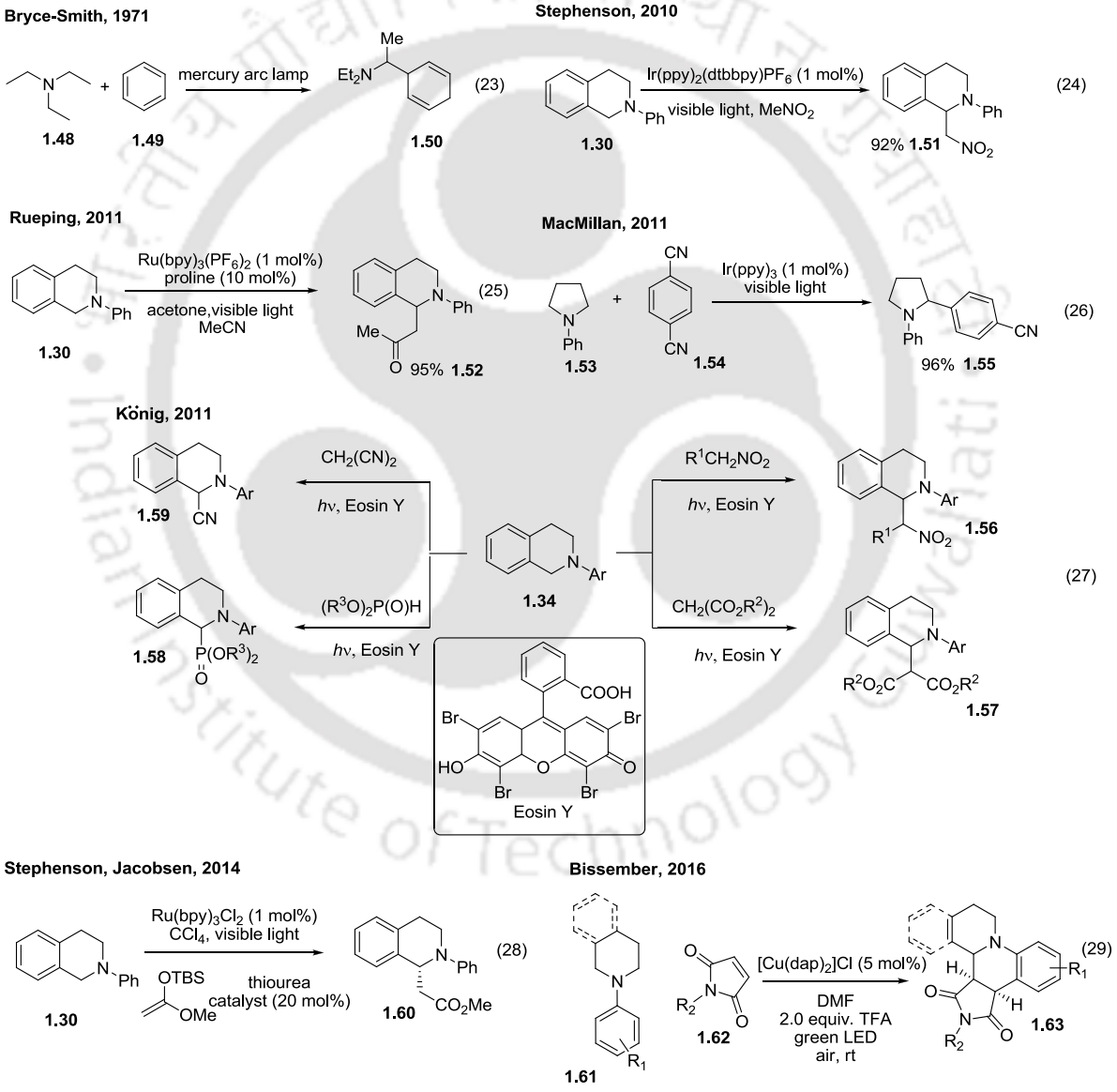


Scheme 8: Cu-catalyzed functionalization of amines

1.5 Photochemical methods for amine functionalization

In synthetic organic chemistry, visible light provides a powerful tool for conversation of cyclic tertiary amines to its α-functionalized products. This method involves combination of UV-visible light and photo-catalyst for the generation of iminium intermediates. After 2010, the photochemical method for functionalization of amines has been extensively developed. Early reports by Bryce-Smith of photochemical transformation involved addition of benzene to triethylamine upon irradiation with mercury arc lamp (**Scheme 9**, eq. 23).[33] In 2010, iridium based photo-catalyst was used by Stephenson and co-workers for the oxidation of *N*-phenyl tetrahydroisoquinoline **1.30** in an aza-Henry type reaction using visible light (**Scheme 9**, eq. 24).[34] Later Rueping group have also demonstrated photo-catalyzed alkylation of *N*-phenyltetrahydoisoquinoline **1.30** using ruthenium based photocatalyst. (**Scheme 9**, eq. 25).[35] A similar photocatalytic method was developed by MacMillan and co-workers for α-C-H arylation reaction of aliphatic amine **1.53** (**Scheme 9**, eq. 26).[36] König and co-workes described oxidative α-coupling reactions of *N*-aryl tetrahydroisoquinolines **1.34** with different pronucleophiles such as nitromethane, dialkyl malonates, dialkyl phophonates and malononitrile in the presence of using the organic dye

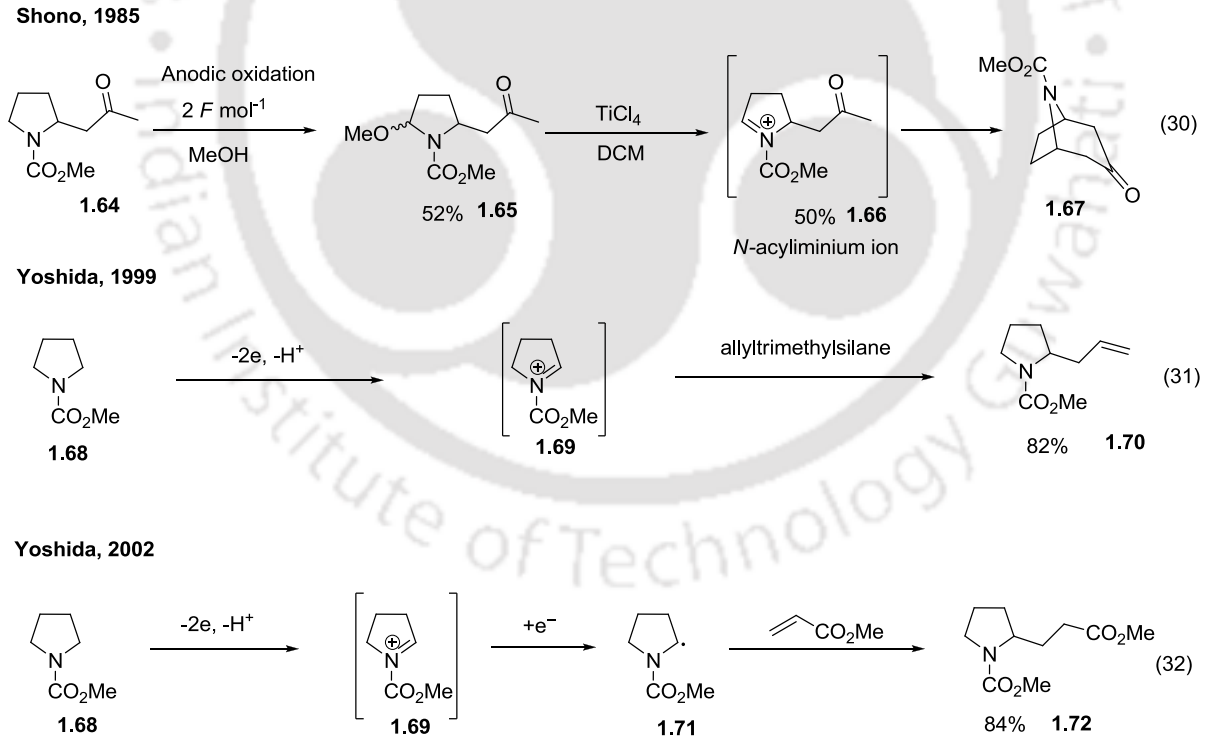
Eosin Y as a photocatalyst (**Scheme 9**, eq. 27).[37] In 2014, the groups of Stephenson and Jacobsen reported enantioselective oxidative C–H functionalization of tetrahydroisoquinoline derivatives **1.30** using a combination of photo-redox and asymmetric anion-binding catalysis (**Scheme 9**, eq. 28).[38] Photocatalyzed oxidation of tertiary amine generated a iminium ion equivalent under mild conditions which was subsequently trapped in a stereo-selective nucleophilic addition reactions assisted by a chiral H-bond donor catalyst. Recently, in 2016, Bissember and co-workers described Brønsted acid mediated copper(I)-catalyzed *α*-C−H bond functionalization of *N*-aryltetrahydroisoquinoline **1.61** in the presence of green LED (**Scheme 9**, eq. 29).[39]



Scheme 9: Photo-induced amine functionalization

1.6 Electrochemical methods for amine functionalization

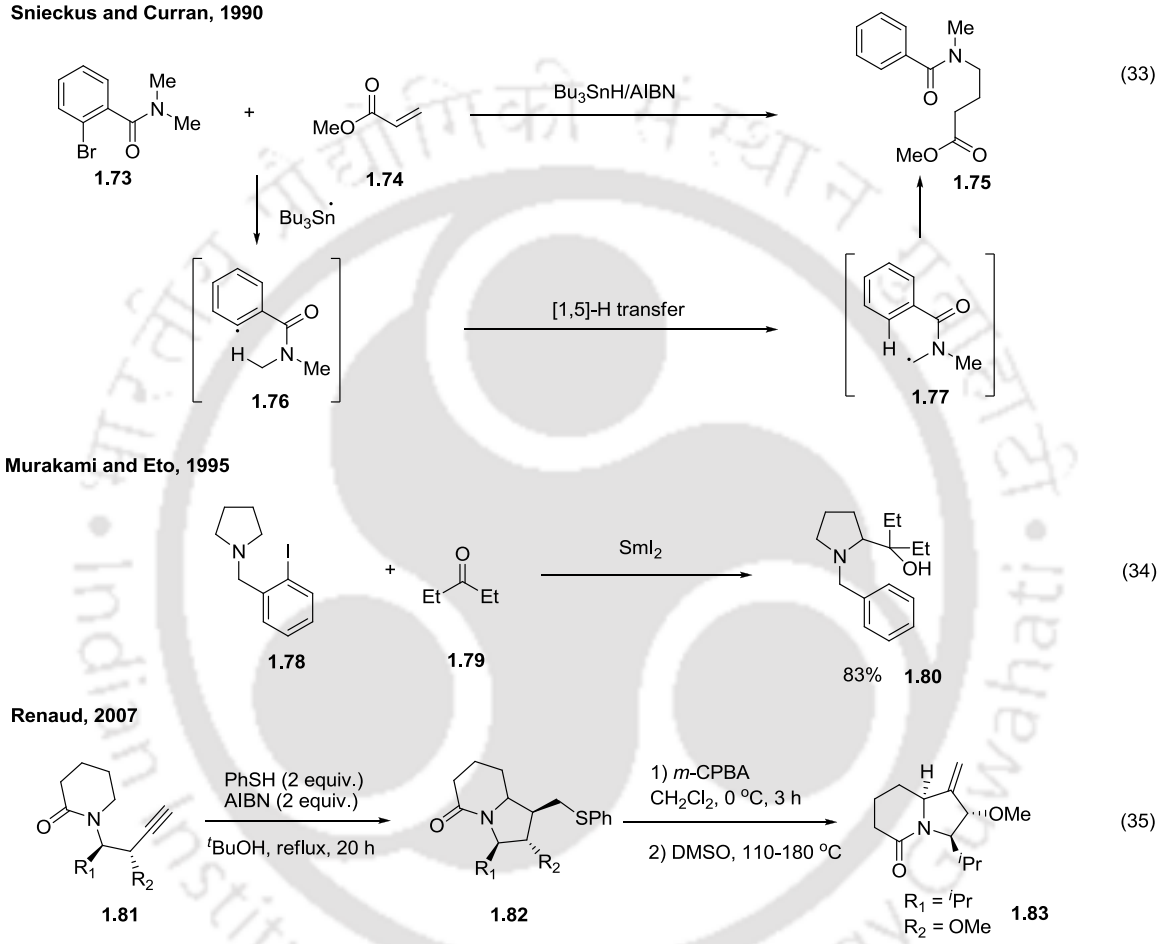
Among the various oxidative methods for α-C-H functionalization of tertiary amines via an iminium ion intermediate, anodic oxidation has the potential advantage as compared to oxidant-based reaction that produce unwanted waste from chemical oxidants. One early example of anodic oxidation of *N*-heterocycles to deliver the corresponding α-aminal **1.65** was described by Shono and co-workers in 1985.[40] This method involved oxidation of cyclic amine **1.64** to corresponding *N*-acyliminium ion and its subsequent reaction with nucleophilic solvent. Further treatment of **1.65** with Lewis acid generated an *N*-acyliminium ion which upon consequent reaction gave bicyclic product **1.67** (**Scheme 10**, eq. 30). In 1999, Yoshida and co-workers developed a "cation-pool" method involving generation and accumulation of cationic intermediates **1.69** through electrolysis and followed by nucleophilic addition under oxidant free conditions (**Scheme 10**, eq. 31).[41] In 2002, the same group extended the cation-pool method to generate radical species **1.71** which subsequently gave the amine functionalized product **1.72** (**Scheme 10**, eq. 32).[42]



Scheme 10: Electrochemical amine C–H functionalization

1.7 Amine functionalization through radical formation

The highly reactive radical species are also useful towards the amine C-H functionalization. The well-known tin hydride based radical reactions have been reported by several groups as the efficient method to access complex structures such as polycyclic compounds.



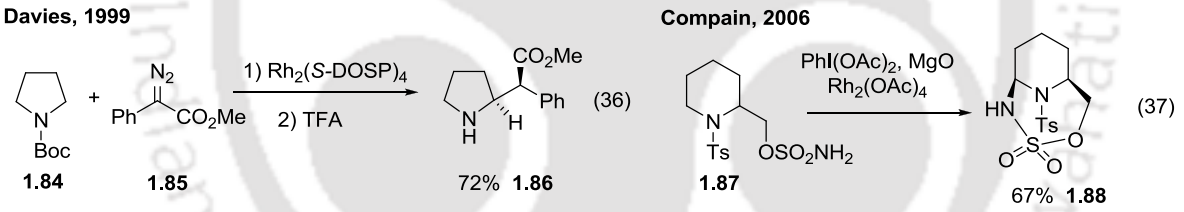
Scheme 11: Amine functionalizations via radical formation

In 1990, Snieckus, Curran and co-workers disclosed areaction of *ortho*-halobenzamides **1.73** with Bu_3SnH/AIBN producing an α-aminoalkyl radical **1.77** via [1,5]-H transfer. The radical was subsequently coupled with electrophiles such as methyl or ethyl acrylate **1.74** to furnish the product **1.75** (**Scheme 11**, eq. 33).[43] Nitrogen heterocycles were also functionalized directly using samarium diiodide (**Scheme 11**, eq. 34).[44] To reduce the toxic metals involved in these radical reactions, chemists were encouraged to investigate for more environmentally benign reactions. Such kind of reaction appeared in 2007 by Renaud and co-workers. They reported a tin-free radical-cascade reaction of **1.81** with thiophenol in

refluxing ^{t}BuOH to produce **1.82**. The reaction involved [1,5]-hydrogen-transfer/cyclization process using thiophenol as a versatile reagent to generate alkenyl radicals. Thioether group of **1.82** was easily eliminated delivering indolizidone derivatives **1.83** (**Scheme 11**, eq. 35).[45]

1.8 Transition metal catalyzed approaches to C–H functionalization

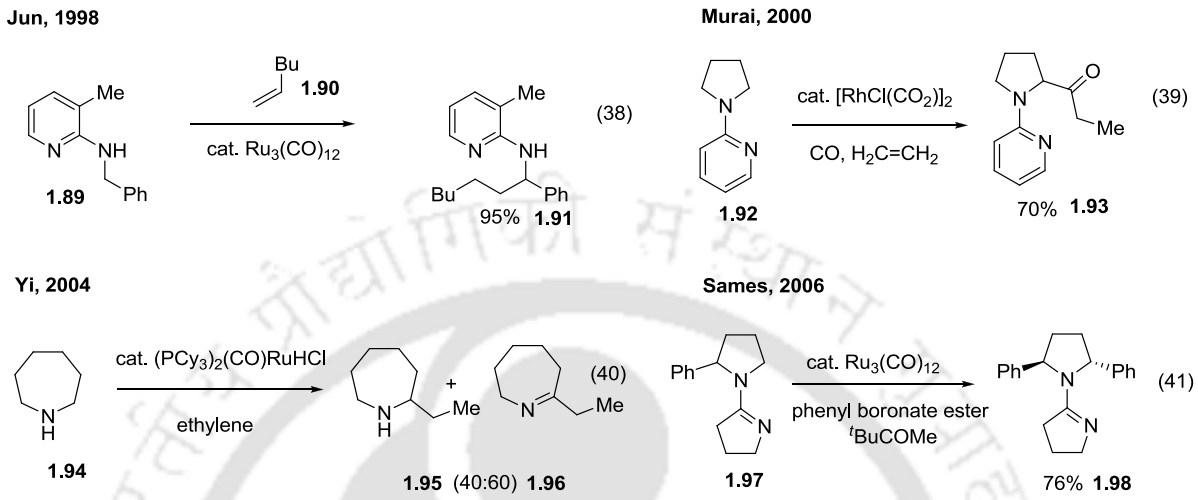
Transition metals play a significant role in synthetic organic chemistry. The valuable metals give a suitable platform for organic transformation. Transition-metal catalyzed functionalization of amine C–H bonds proceeds through both outer-sphere and inner-sphere mechanisms.[12] The outer-sphere pathway generally involves the use of a dirhodium catalyst to facilitate the insertion of a carbenoid or nitrenoid species into a C–H bond.[46] In 1999, Davies and co-workers introduced a chiral dirhodium catalyst for the formation of α-functionalized pyrrolidine derivative **1.86** from *N*-acylated pyrrolidine **1.84** (**Scheme 12**, eq. 36).[47] The insertion of a nitrene to an amine α-C–H bond was reported by Compain and co-workers in 2006, where amine **1.87** underwent an intramolecular annulation to form aminal **1.88** (**Scheme 12**, eq. 37).[48]



Scheme 12: Carbenoid and nitrenoid insertions

Amine functionalizations through inner-sphere mechanism proceed via the oxidative addition of the C–H bond to the metal complex. The organometalic intermediates thus produced were reacted in different way to obtain functionalized amines. In 1998, Jun and co-workers reported the use of $Ru_3(CO)_{12}$ as a catalyst for the conversion of benzyl amine **1.89** to α-substituted amine **1.91** (**Scheme 13**, eq. 38).[49] It was proposed that the pyridinyl nitrogen of **1.89** acts as a directing group for metalation reaction. Murai and co-workers have contributed extensively to the general area of transition metal-catalyzed C–H activation. In 2000, they showed carbonyl insertion to pyrrolidine C-H bond in **1.92** using carbon monoxide, ethylene and a rhodium catalyst (**Scheme 13**, eq. 39).[50] The scope of the reaction was limited with respect to olefin coupling partner. Good yields were obtained solely with ethylene. In 2004, Yi and co-workers demonstrated alkylation of cyclic

secondary amines **1.94** ethylene in the presence of a ruthenium complex (**Scheme 13**, eq. 40).[51] Only few secondary amines yielded **1.95** and others gave imine **1.96**. In 2006, the *α*-arylation of pyrrolidines using $Ru_3(CO)_{12}$ and aryl boronate ester was achieved by the Sames group (**Scheme 13**, eq. 41).[52]

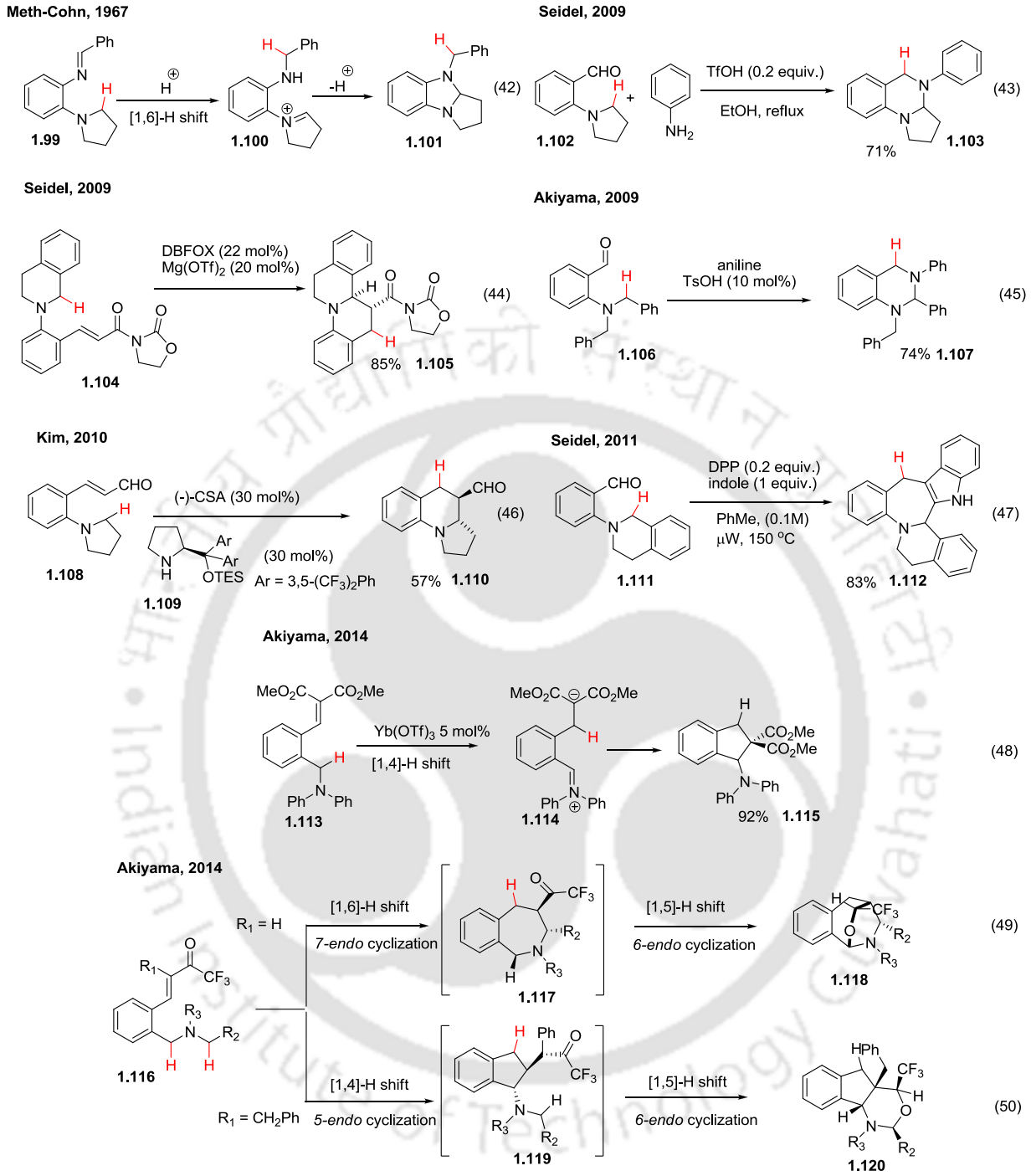


Scheme 13: Transition metal catalyzed amine functionalization

1.9 Redox-neutral C-H functionalization

1.9.1 Through intramolecular hydride shift

Intramolecular [1,5]- or [1,6]-hydride shift from tertiary amine (*tert*-amino effect[53]) followed by ring closure reaction also offers a mechanistically distinct way for the amine functionalization. Sometimes the use of a Brønsted or Lewis acid catalyst facilitate the [1,5]- or [1,6]-hydride transfer step.[12b] One such reaction reported by Meth-Cohn and co-workers in 1967 (**Scheme 14**, eq. 42).[54] The reaction involved [1,6]-hydride transfer from an aryl pyrrolidine to imine in **1.99** leading to iminium **1.100** which after ring closing yielded aminal **1.101**. In 2009, the Seidel group reported Brønsted acid catalyzed reaction of **1.102** to cyclic aminal **1.103** via [1,5]-H-transfer. (**Scheme 14**, eq. 43).[55] In the same year they also published an asymmetric C-H functionalization based on the *tert*-amino effect using Mg(II)-DBFOX complex as a Lewis acid catalyst (**Scheme 14**, eq. 44).[56] In 2009, Akiyama group published a Brønsted acid promoted cyclization reaction of tertiary amino-benzaldehydes **1.106** with primary amines to yield cyclised product **1.107** (**Scheme 14**, eq. 45).[57] In 2010, Kim and co-workers successfully developed asymmetric organo-catalytic reaction of amine **1.108** in presence of camphorsulphonic acid to furnish the enantio-enriched product **1.110** (**Scheme 14**, eq. 46).[58]



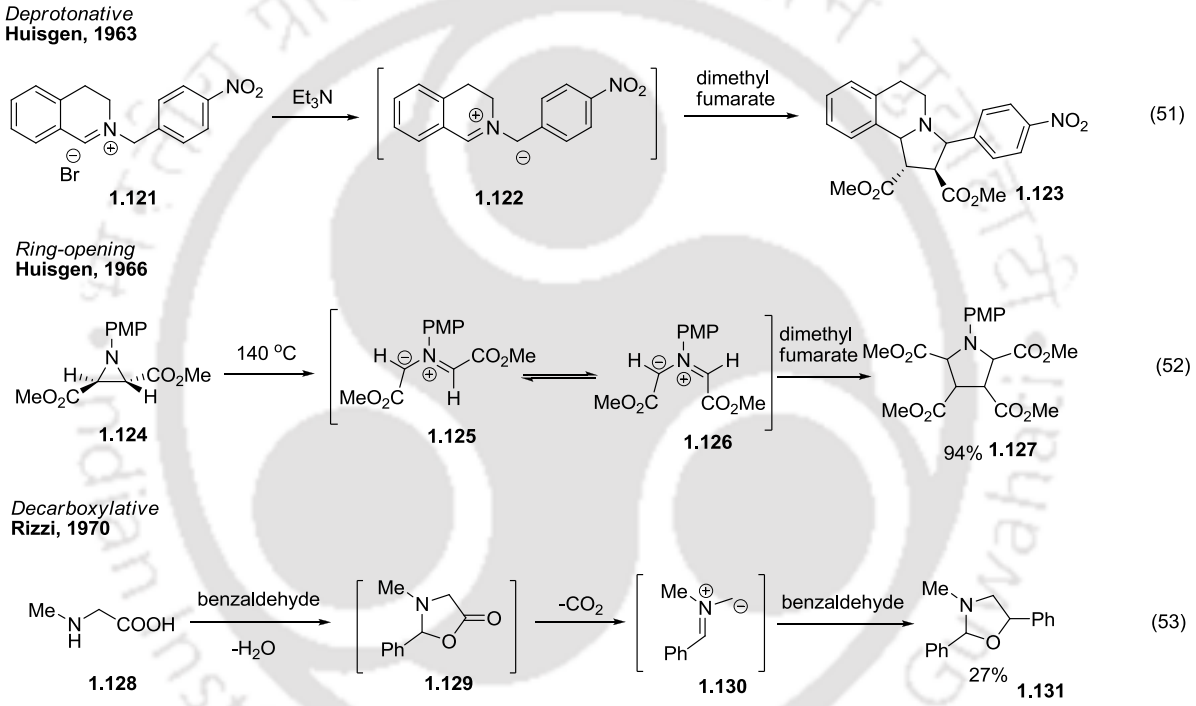
Scheme 14: Amine functionalization involving *tert*-amino effect

An acid-catalyzed redox-neutral annulation of **1.111** through [1,5]-hydride shift/ring-closure sequence leading to the formation of azepinoindole **1.112** was reported by Seidel and co-workers in 2011 (**Scheme 14**, eq. 47).[59] Akiyama group achieved $Yb(OTf)_3$-catalyzed [1,4]-hydride shift/cyclization of **1.113**, producing aminoindane **1.115** (**Scheme 14**, eq. 48).[60] The same group also reported $C(sp^3)$−H bond functionalization of amine **1.116** (**Scheme 14**, eq.

49). Bicyclo[3.2.2]nonane skeleton **1.118** was formed via a [1,6]- and [1,5]-hydride shift sequence and sequential [1,4]- and [1,5]-hydride shift led to construction of a linear tricyclic skeleton **1.120** (**Scheme 14**, eq. 50).[61]

1.9.2 Via azomethine ylide intermediates

Azomethine ylides are versatile precursor for many organic transformations. Once generated, it can undergo [3+2] cycloaddition. The ylide can also be protonated to result iminium ion which can undergo reaction with a nucleophile.[62] Azomethine ylides are commonly prepared via either deprotonative pathway, through the ring-opening of a neutral species or decarboxylative pathway.

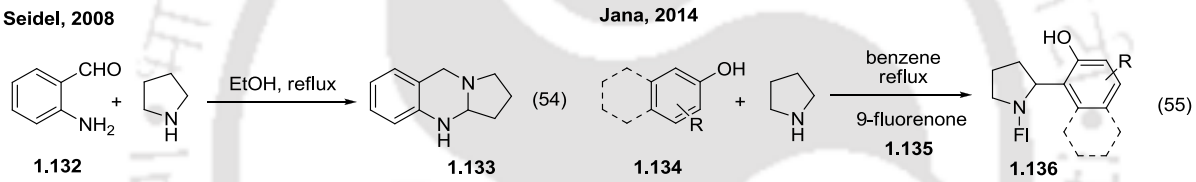


Scheme 15: Azomethine ylide in amine functionalization

A deprotonative way was illustrated by Huisgen and co-workers involving deprotonation of an iminium ion **1.121**.[63] (**Scheme 15**, eq. 51). The resulting ylide **1.122** was then reacted with dimethyl fumarate to furnish the product **1.123**. The same group also applied ring-opening pathway to generate ylide **1.125**, which was further reacted with dimethyl fumarate to provide functionalized amine **1.127** (**Scheme 15**, eq. 52).[64] Rizzi and co-workers described formation of ylide **1.130** through decarboxylative pathway. First, amino acid **1.128** condensed with an aldehyde or ketone to form an oxazolidone intermediate **1.129** which was decarboxylated under heating condition forming the desired azomethine ylide **1.130**. The ylide **1.130** was reacted further with benzaldehyde to provide the product **1.131**

(**Scheme 15**, eq. 53).[65] As natural *α*-amino acids are easily available, this pathway can be a useful method for azomethine ylide generation. Recently, there have been a number of new reports on redox-neutral annulations which proceed through azomethine ylide intermediates.[66]

Thermal condendsation reaction also serves as an attracting method for construction of highly functionalized molecular structures through the intramolecular *α*-functionalization of tertiary amines. Azomethine ylide was formed via thermal condensation-deprotonation sequence. The regio-isomeric ylide was protonated to provide iminium ion which subsequently reacted with nucleophile intra or intermolecularly producing *α*-functionalized amine. For example, Seidel and co-workers have applied thermal reaction of *o*-aminobenzaldehydes **1.132** with amines to yield ring-fused aminals **1.133** (**Scheme 16**, eq. 54).[67] Direct intermolecular *α*-C–H arylation of pyrrolidine has been reported by Jana group under metal and oxidant free condition (**Scheme 16**, eq. 55).[68]



Scheme 16: Thermal condensation reactions for amine functionalization.

Different ways of amine functionalization have its own potentiality for the conversion of amine to its functionalized derivative. In concern to the ecological viability, which requires the consideration of atom efficiency as well as less involvement of toxic materials, methods developed have some limitations. As for example, the deprotonation methods do not involve ambient conditions. Moreover, the commercial unavailability and long synthetic route to achieve (-)-sparteine makes it difficult to access other enantiomer of functionalized product via these reactions. The *α*-aminocarbanions generated with chiral amine ligands are configurationally unstable at temperatures above -50 °C and unactivated electrophiles are very hard to react at such temperatures. Furthermore, stereoselective *α*-lithiation of piperidine and piperazine derivatives were remain unsuccessful. Reactions involving carbon–hydrogen (C–H) bond oxidation require use of super-stoichiometric amount of oxidants which significantly limits the scope of the reaction. Undoubtly photo-induced methods are a break-through in the field of amine functionalization. But uses of sophisticated valuable transition metal catalyst reduces its practical utility. Anodic oxidation

method was successful only for pyrrolidine derivatives, but remain ineffective for six, seven, eight membered amines, such as piperidine, piperizine and morpholine. Redox-neutral ways are attracting method for the construction of a desired functionalized product. Sometimes addition of Lewis/Bronsted acid or base enhances the reaction rate but require higher temperature to reach the goal. Importantly, pyrrolidine or tetrahydroisoquinoline were employed as only substrates to show the efficiency of this method and other secondary amines (piperidine, acyclic amine) provided poor/no yield. Therefore, development of methodology for direct functionalization of aliphatic amines that can be applied for broad class of aliphatic amines under ecologically viable condition would be an important contribution to field.

References

[1] Bergman, R. G. *Nature* **2007**, *446*, 391.
[2] Trost, B. M. *Science,* **1991**, *254*, 1471.
[3] Cragg, G. M.; Newman, D. J. *Biochim. Biophys. Acta*. **2013**, *1830*, 3670.
[4] a) Felpin, F.-X.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10127; (b) Lourenco, A. M.; Máximo, P.; Ferreira, L. M.; Pereira, M. M. A. *Studies in Natural Products Chemistry: Bioactive Natural Products (Part H)*; A. Rahman, Ed.; Elsevier: Amsterdam, **2002**; Vol. 27, pp 233. c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773; d) Yang, X.; Shi, Q.; Lai, C.-Y.; Chen, C.-Y.; Ohkoshi, E.; Yang, S.-C.; Wang, C.-Y.; Bastow, K. F.; Wu, T.-S.; Pan, S.-L.; Teng, C.-M.; Yang, P.-C.; Lee, K.-H. *J. Med. Chem.* **2012**, *55*, 6751; e) Morriello, G. J.; Wendt, H. R.; Bansal, A.; Salvo, J. D.; Feighner, S.; He, J.; Hurley, A. L.; Hreniuk, D. L.; Salituro, G. M.; Reddy, M. V.; Galloway, S. M.; McGettigan, K. K.; Laws, G.; McKnight, C.; Doss, G. A.; Tsou, N. N.; Black, R. M.; Morris, J.; Ball, R. G.; Sanfiz, A. T.; Streckfuss, E.; Struthers, M.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1865; f) Wagner, F. F.; Comins, D. L. *Tetrahedron* **2007**, *63*, 8065; g) Dieter, R. K.; Chen, N.; Watson, R. T. *Tetrahedron* **2005**, *61*, 3221; h) Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinholt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818; i) Ohnmachta, C. J.; Patel, R.; Lutz, R. E. *J. Med. Chem.* **1971**, *14*, 926.
[5] Horak, F.; Zieglmayer, P.; Zieglmayer, R.; Lemell, P.; Yao, R.; Staudinger, H.; Danzig, M. *Ann. Allergy Asthma Immunol.* **2009**, *102*, 116.
[6] Kinney, J. L; Evans, R. L. *Clin. Pharm.* **1982**, *1*, 417.
[7] http://www.medicinenet.com/moxifloxacin-oral/article.htm (accessed on 10.01.2016)
[8] http://cbc.arizona.edu/njardarson/group/sites/default/files/Top 200 Brand-name Drugs by Total US Prescriptions in 2010sm_0.pdf.(accessed on 10.01.2016)
[9] Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265.
[10] Hofmann, A. W. *Berichte* **1885**, *18*, 109.

[11] Vitaku, E.; Ilardi, E. A.; Njardarson, J. T.; Top 200 Pharmaceutical Products by US Retail Sales in 2012.http://cbc.arizona.edu/njardarson/group/top-pharmaceuticalsposter.
[12] a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069; b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092.
[13] Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197.
[14] Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471.
[15] a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552; b) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed.* **1997**, *36*, 2282.
[16] Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708.
[17] Dearden, M. J.; Firkin, C. R.; Hermet, J. P. R.; O'Brian, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870.
[18] Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C. *J. Am. Chem. Soc.* **2006**, *128*, 3538.
[19] Jones, K. M.; Klussmann, M. *Synlett* **2012**, *23*, 159.
[20] Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3408.
[21] Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169.
[22] Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem.* **2010**, *75*, 3916.
[23] Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. Eur. J.* **2012**, *18*, 5160.
[24] Zhang, G.; Ma, Y.; Wang, S.; Kong, W.; Wang, R. *Chem. Sci.* **2013**, *4*, 2645.
[25] Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*, 4194.
[26] Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.
[27] Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, *2005*, 3173.
[28] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672.
[29] Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.
[30] Zhao, L.; Basle, O.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4106.
[31] Sureshkumar, D.; Sud, A.; Klussmann, M. *Synlett* **2009**, *10*, 1558.
[32] Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 6447.
[33] Bryce-Smith, D.; Clarke, M. T.; Gilbert, A.; Klunklin, G.; Manning, C. *J. Chem. Soc. D* **1971**, 916.
[34] Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.
[35] Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360.
[36] McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.
[37] Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852.
[38] Bergonzini, G.; Schindler, C. S.; Wallentin, C. J.; Jacobsen, E. N.; Stephenson, C. R. J. *Chem. Sci.* **2014**, *5*, 112.
[39] Nicholls, T. P.; Constable,G. E.; Robertson, J. C.; Gardiner, M. G.; Bissember, A. C. *ACS Catal.* **2016**, *6*, 451.
[40] Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243.
[41] Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546.
[42] Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30.

[43] Snieckus, V.; Cuevas, J. C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.
[44] Murakami, M.; Hayashi, M.; Ito, Y. *Appl. Organometallic. Chem*. **1995**, *9*, 385.
[45] Beaufils, F.; Dénès, F.; Renaud, P. *Org. Lett.* **2007**, *9*, 4375.
[46] Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
[47] Davies, H. M. L.; Hansen, T.; Hopper, D. W.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509.
[48] Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493.
[49] Jun, C. H.; Hwang, D. C.; Na, S. J. *Chem. Commun.* **1998**, 1405.
[50] Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.
[51] Yi, C. S.; Yun, S. Y. *Organometallics* **2004**, *23*, 5392.
[52] Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.
[53]Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem*. Vol. 14 (Eds.: A. R. Katritzky, A. J. Boulton), Academic Press, Amsterdam, **1972**, pp. 21.
[54] Meth-Cohn, O.; Naqui, M. A. *Chem. Commun.* **1967**, 1157.
[55] Zheng, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419.
[56] Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226.
[57] Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524.
[58] Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847.
[59] Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100.
[60] Mori, K.; Kurihara, K.; Akiyama, T. *Chem. Commun.* **2014**, *50*, 3729.
[61] Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744.
[62] a) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, **2002**; Vol. 59; b) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105; c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765; d) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484; e) Nyerges, M.; Toth, J.; Groundwater, P. W. *Synlett* **2008**, 1269.
[63] Huisgen, R.; Grashey, R.; Steingruber, E. *Tetrahedron Lett.* **1963**, *4*, 1441.
[64] Huisgen, R.; Scheer, W.; Szeimies, G.; Huber, H. *Tetrahedron Lett.* **1966**, *7*, 397.
[65] Rizzi, G. P. *J. Org. Chem.* **1970**, *35*, 2069.
[66] a) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784; b) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434.
[67] Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416.
[68] Haldar, S.; Mahato, S.; Jana, C. K. *Asian J. Org. Chem.* **2014**, *3*, 44.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Chapter 2

Diastereoselective *α*-C-H Oxygenation of Aliphatic Amines: A General Route to Oxazines

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

2.1 Introduction

Functionalized aliphatic *N*-heterocycles and *α*-substituted acyclic secondary amines are widespread key structural motif of many bioactive natural products and different medicinal drugs.[1] Moreover, diversely *α*-substituted cyclic or acyclic secondary amines are of particular interest in organic synthesis due to their ability to act as the chiral scaffolds in various asymmetric transformations.[2] Some *α*–functionalized chiral secondary amines which are frequently used in various asymmetric organic transformation are shown in **figure 1**.

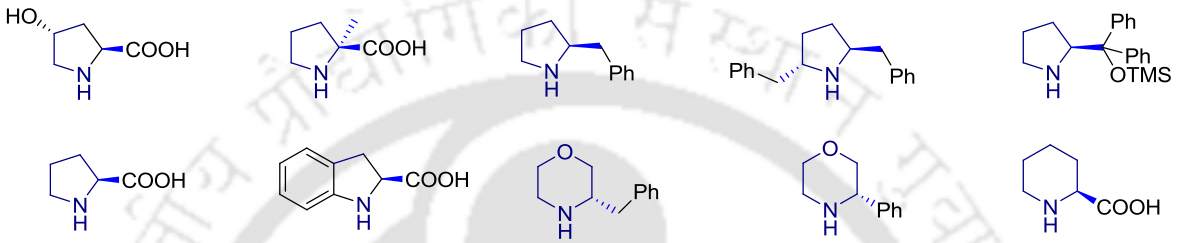


Figure 1: Frequently used chiral *α*-functionalized *N*-heterocycles

The oxazine moiety are also effective functionality in the field of medicinal chemistry. The oxazines exhibit a wide range of pharmacological activities including antibacterial,[3] fungicidal,[4] antitumor,[5] and antituberculosis (**Figure 2**).[6]

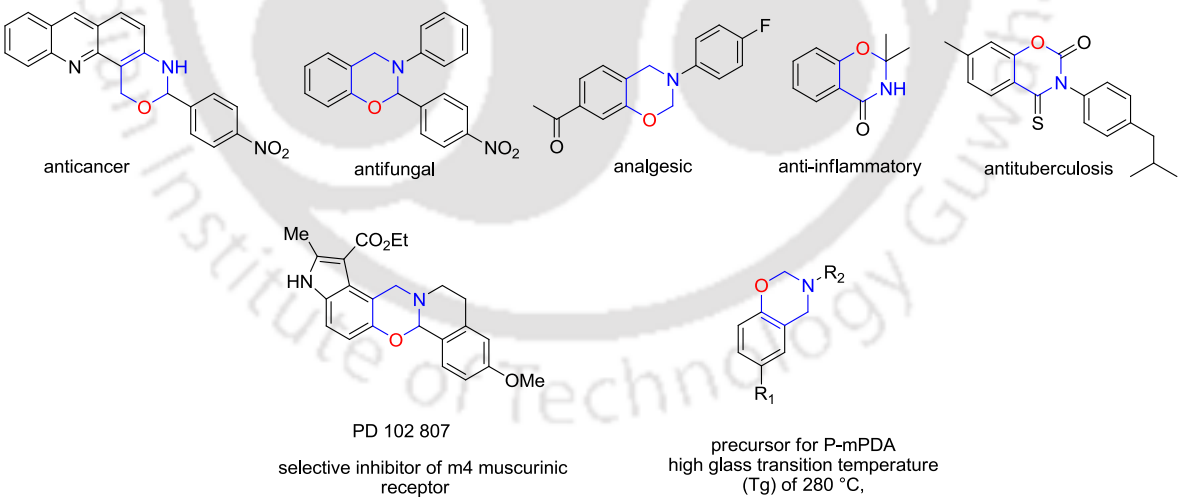
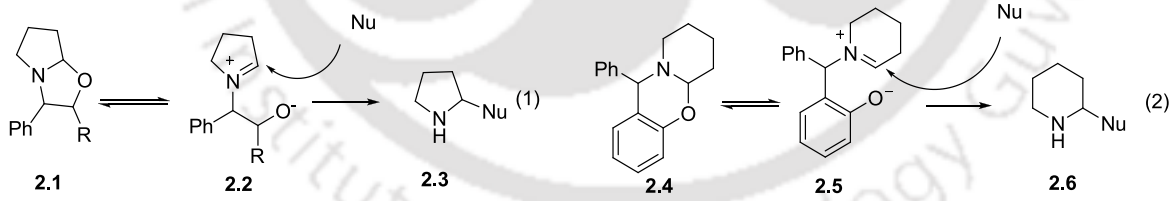


Figure 2: Oxazines in the field of pharmaceutical and material chemistry

A large number of natural products and synthetic intermediates consist of *N,O*-acetal moiety.[7] Study revealed that benzoxazine acts as nonsteroidal progesterone receptor agonists, as antibacterial agents and as reverse transcriptase inhibitor for human immuno-deficiency virus (HIV).[8] For example, benzo[*e*][1,3]oxazine such as PD 102 807 (**Figure 2)** has been

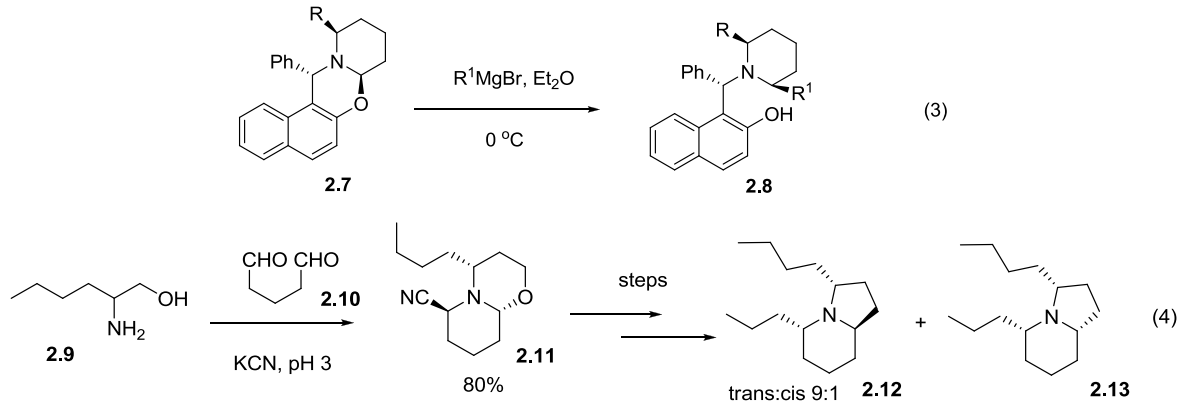
identified as a potent and selective inhibitors of the m4 muscarinic receptor.[9] The oxazine based compounds also play a significant role in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease.[10] Polybenzoxazines, obtained from the thermally activated ring-opening polymerization of 1,3-benzoxazine monomers, are a novel class of thermosetting phenolic resins possessing unusual set of competitive material properties.[11]

Large number of synthetic strategies have been reported in literature for direct α-C-H functionalization of aliphatic amines. Nucleophilic addition to the iminium ion is one of the widely used method for the formation of C-C bond. The iminium ions are usually formed from a secondary amine and a carbonyl compound. Oxazolidine/oxazine also considered as a masked equivalent of an iminium ion. This property of oxazolidine/oxazine has been successfully utilized for the synthesis of a variety of naturally occurring and synthetic pyrrolidine and piperidine derivative.[12] For example, oxazole **2.1** and oxazine **2.4** were utilised for the formation of α–functionalized piperidine. Cleavage of C-O bond produces iminium ion **2.2** and **2.5** which can be subsequently trapped by any nucleophile. Availability of wide range of nucleophile makes this strategy very versatile for functionalization of amines. Again the debenzylation is also easily achievable to get the corresponding α-functionalized secondary amine **2.3** and **2.6** (**Scheme 1**, eq. 1 and eq. 2).[13] The additional advantage of the use of oxazole **2.1** and oxazine **2.4** comes from the presence of chiral center which induces the chirality during the formation of new stereogenic center.



Scheme 1: Use of oxazole and oxazine as masked iminium ion

Ring-fused oxazoles and oxazines can be used as intermediates in the synthesis of *N*-substituted aminoalcohols, bioactive natural products and chiral catalysts.[14] For example, Hu and co-workers reported synthesis of functionalized product **2.8** by reacting oxazine **2.7** with Grignard reagent (R^1MgBr) in diethyl ether at 0 ^oC (**Scheme 2**, eq. 3).[14c] Grierson reported an efficient method for the preparation of indolizidine alkaloids **2.12** and **2.13** by utilizing oxazine **2.11** (**Scheme 2**, eq. 4).[15]



Scheme 2: Synthetic use of oxazines

The following templates are often used for the construction of piperidine alkaloids (**Figure 3**).[16]

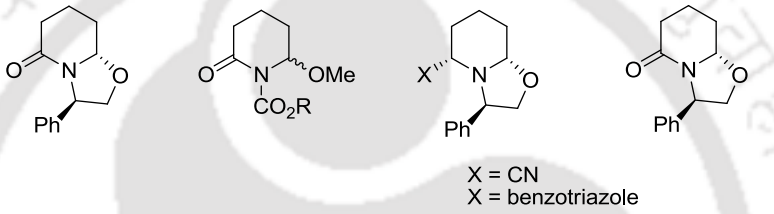
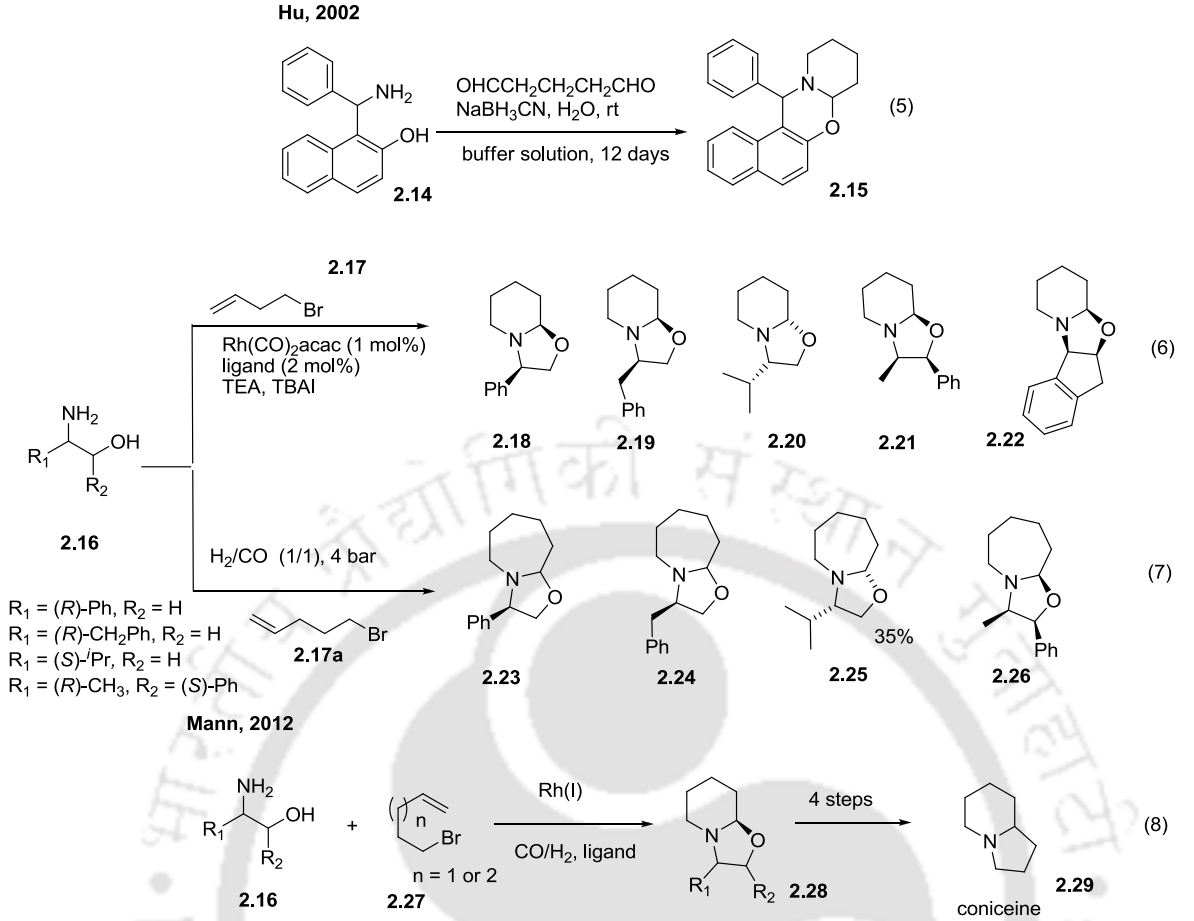


Figure 3: Oxazines for the construction of functionalized piperidines

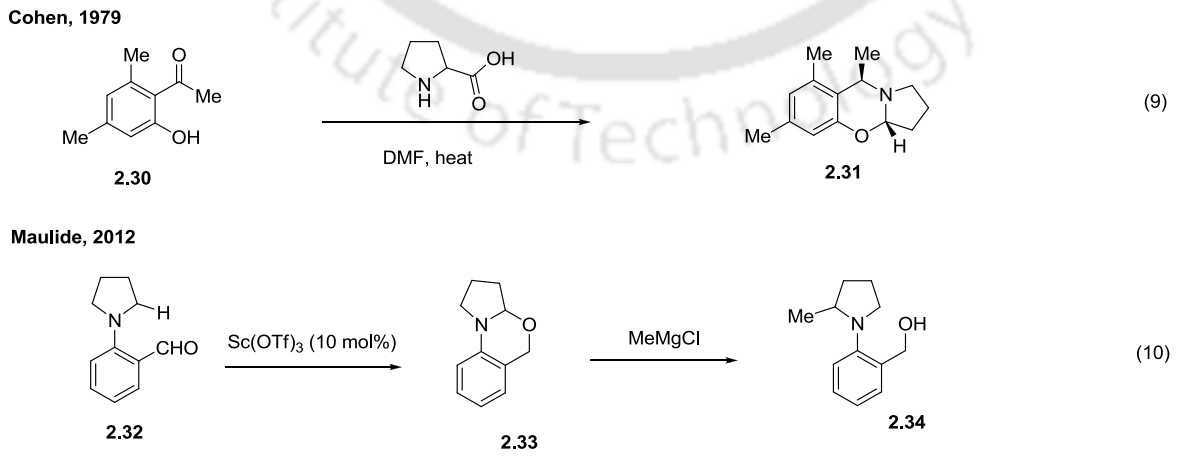
2.2 Known methods for oxazine syntheses

Ring-fused oxazoles and oxazines are versatile precursor for the synthesis of *α*-functionalized cyclic amines and this protocol was applied efficiently for the syntheses of various natural products. Therefore, several methods have been reported so far for the synthesis oxazines.[17] Mainly *N*-cycloalkylation strategy was employed for the synthesis of ring-fused oxazine. In this strategy, the amino-hydroxy compounds can be *N*-cycloalkylated using dihalide or dialdehyde in the presence of variety of bases and reducing agent, respectively.[18] This strategy was utilized for the synthesis of various six and seven membered *N*-heterocycles.[16] In 2002, Hu and co-workers utilised the cycloalkylaton strategy to prepare oxazine **2.15** from amino naphthol **2.14** by treating with pentane -1,5-dial in the presence of $NaBH_3CN$ in an aqueous buffer solution (Na_2HPO_4-KH_2PO_4) over 12 days (**Scheme 3**, eq. 5). The reaction time can be shortened considerably by increasing the ratio of EtOH in the reaction solvent.[19] A number of bicyclic oxazolidine **2.18-2.26** were obtained from chiral *N*-alkenylamino alcohols **2.16** via transient cyclic iminium intermediates that underwent an intramolecular cyclization **(Scheme 3**, eq. 6 and 7). The oxazolidine **2.28** was successfully utilised to yield (+/-) coniceine **2.29 (Scheme 3**, eq. 8).[16]



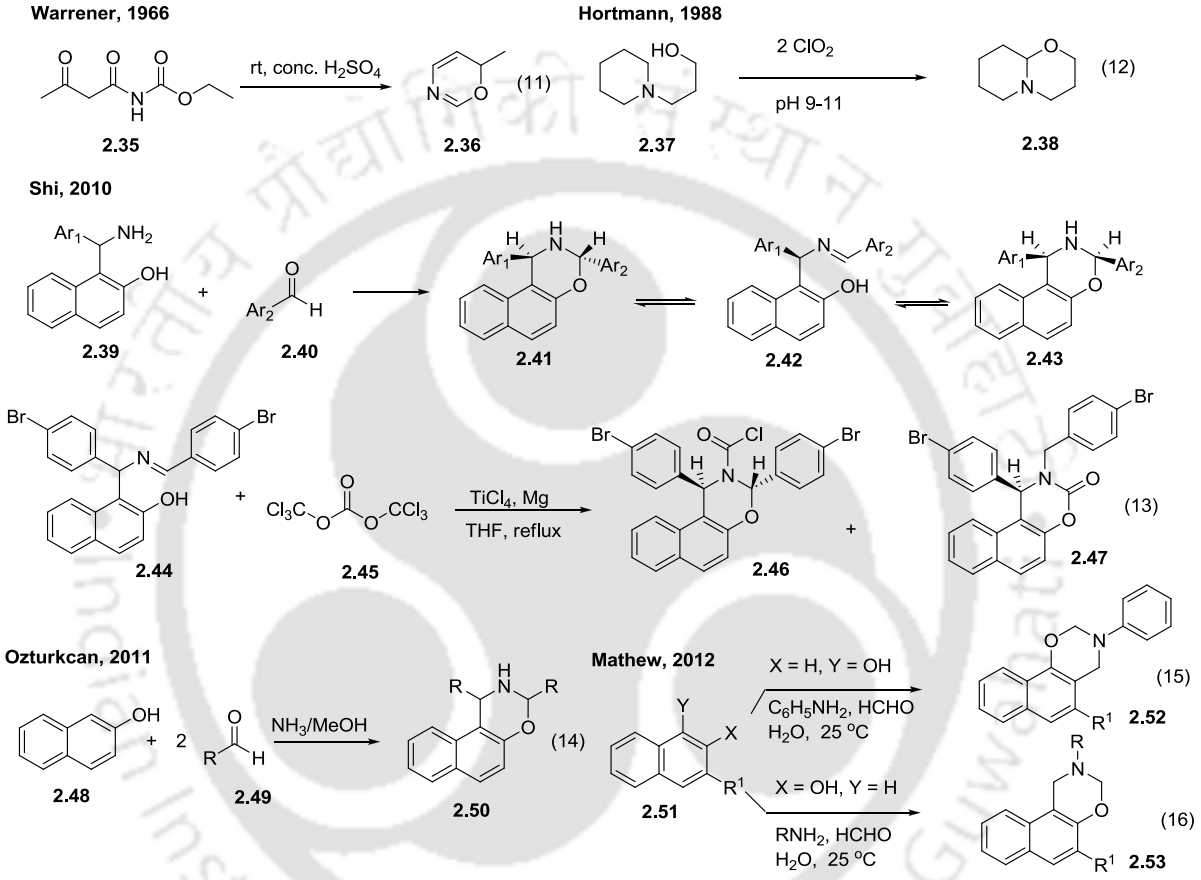
Scheme 3: Ring-fused oxazine through cycloalkylation

Direct functionalization of *N*-heterocycles is advantageous in contrast to the multistep *N*-cycloalkylation strategy. Along this line, in 1979, Cohen and co-workers discovered that 2-hydroxy-6-methylacetophenones **2.30** could condense decarboxylatively with proline to form benzoxazine **2.31** via an azomethine intermediate (**Scheme 4**, eq. 9).[20]



Scheme 4: Ring fused oxazine via direct functionalization

The direct *α*-functionalization of pyrrolidine to acetal **2.33** has been described by Maulide and co-workers **(Scheme 4**, eq. 10).[21] These intermediate *N*,*O*-acetals were then exposed to Grignard reagents to produce *α*-alkylated and *α*-arylated amines **2.34**. Several other methods were used for the synthesis of oxazine. In 1966 Warrener and co-workers synthesized 6-methyl-1,3-oxazine **2.36** from *N*-Acetyacetyl urethane **2.35** reacting with concentrated sulphuric acid in room temperature for 24 h (**Scheme 5**, eq. 11).[22]



Scheme 5: Other methods for oxazine formation

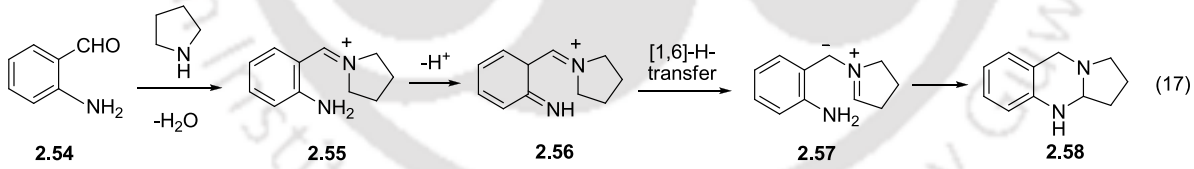
In 1988, Hortmann and co-workers described an unique method for the synthesis of tetrahydro [1,3]-oxazine **2.38** from tertiary amino alcohols **2.37** in the presence of ClO_2 in basic media (**Scheme 5**, eq. 12).[23] This methodology was successful only for five and six membered cyclic amines. In 2010, Shi and co-workers selectively synthesized a series of new naphtho[1,2-*e*][1,3]oxazine derivative **2.46** via a chemo-selective reaction of 1,3-diaryl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine **2.41** (**Scheme 5**, eq. 13).[24] In 2011, a Mannich-type aminoalkylation reaction of 2-naphthol with various aldehydes was applied by Ozturkcan and co-workers for the synthesis of 1,3-disubstituted-2,3-dihydro-1*H*–naphthoxazine **2.50** (**Scheme 5**, eq. 14).[25] In 2012, Mathew and co-workers reported synthetic strategy for the

construction of a series of 3,4-dihydro-2*H*-benzo[e][1,3]oxazines **2.52** and **2.53** by using condensation of 2-naphthol, primary amine and aldehyde (**Scheme 5**, eq. 15 and 16). They also showed that the synthesized compounds are active against microorganism.[26]

The majority of the ring fused oxazines known in the literature were synthesized from the cycloalkylation of 1,3-aminoalcohols with dialdehydes/dihalide that limits the versatility and thus applicability of the method. Moreover, reported methods are well applicable to certain type of substrate and remain ineffective to others. The difficulty to remove *N*-substituent, which is essential for functionalization has been added as an additional problem for the method to be considered for its practical application.

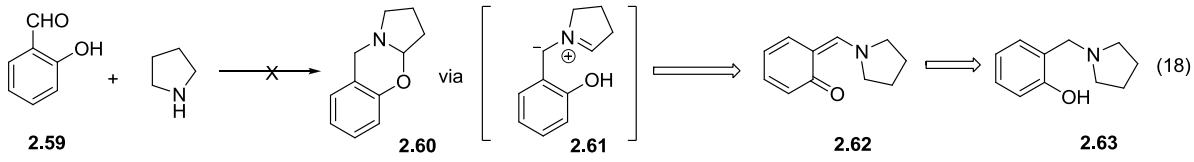
2.3 Aim of this work

The aim of this work is to address the challenges of direct C-H functionalizaton of unreactive cyclic and acyclic amines. The plan was to develop a very general route to access a broad class of oxazines derived from very easily available and versatile starting material and expand the scope of their use in the synthesis of the functionalized saturated amines. During literature studies, it was found that ring-fused aminal **2.58** was obtained from the corresponding amino-aldehyde derivative **2.54** when reacted with various secondary amine.[26] It was proposed that quinoidal intermediate **2.56** formed from iminium intermediate **2.55** undergo a [1,6]-hydrogen transfer to form dipolar intermediate **2.57**, which ultimately provided final product **2.58** (**Scheme 6**, eq. 17).[27]



Scheme 6: Formation of ring fused aminal

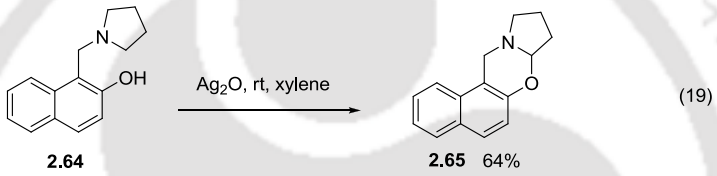
Similarly, it was anticipated that the reaction of salicylaldehyde **2.59** and pyrrolidine could provide corresponding benzoxazine **2.60**. Unfortunately, all the attempts were unsuccessful.



Scheme 7: Assumption for oxazine formation

2.4 Results

Then alternative ways were searched to form desired oxazine **2.60**. It was realized that the target oxazine **2.60** can be obtained from the corresponding zwiterionic intermediate **2.61**. In this regard, it was envisioned that the [1,6]-hydrogen (alpha to nitrogen) shift in the *o*-quinone methide **2.62** will yield to the desired intermediate **2.61** (**Scheme 7**, eq. 18). Related hydrogen transfer reaction is known in the literature.[28] The desired *o*-quinone methide can be prepared from the starting phenol **2.63** which can be easily obtained from the Mannich type reaction. Therefore, 2-hydroxybenzylamine was reacted with silver oxide under various conditions. However, the desired oxazine **2.60** was not formed. Interestingly, the Betti base **2.64** on reaction with silver oxide in xylene at room temperature provided desired oxazine **2.65** with 64% isolated yield (**Scheme 8**, eq. 19).

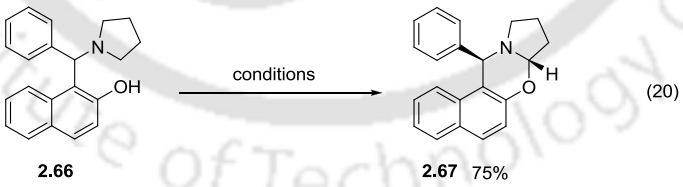


Scheme 8: Synthesis of naphthoxazine

2.5 Optimization of reaction condition

Encouraged by the first result, Betti base **2.66** then reacted with Ag_2O under the same condition producing 15% of the desired oxazine **2.67** (eq. 20).

Table 1. Variation of reagents and reaction conditions to obtained the best yields of desired product[a]



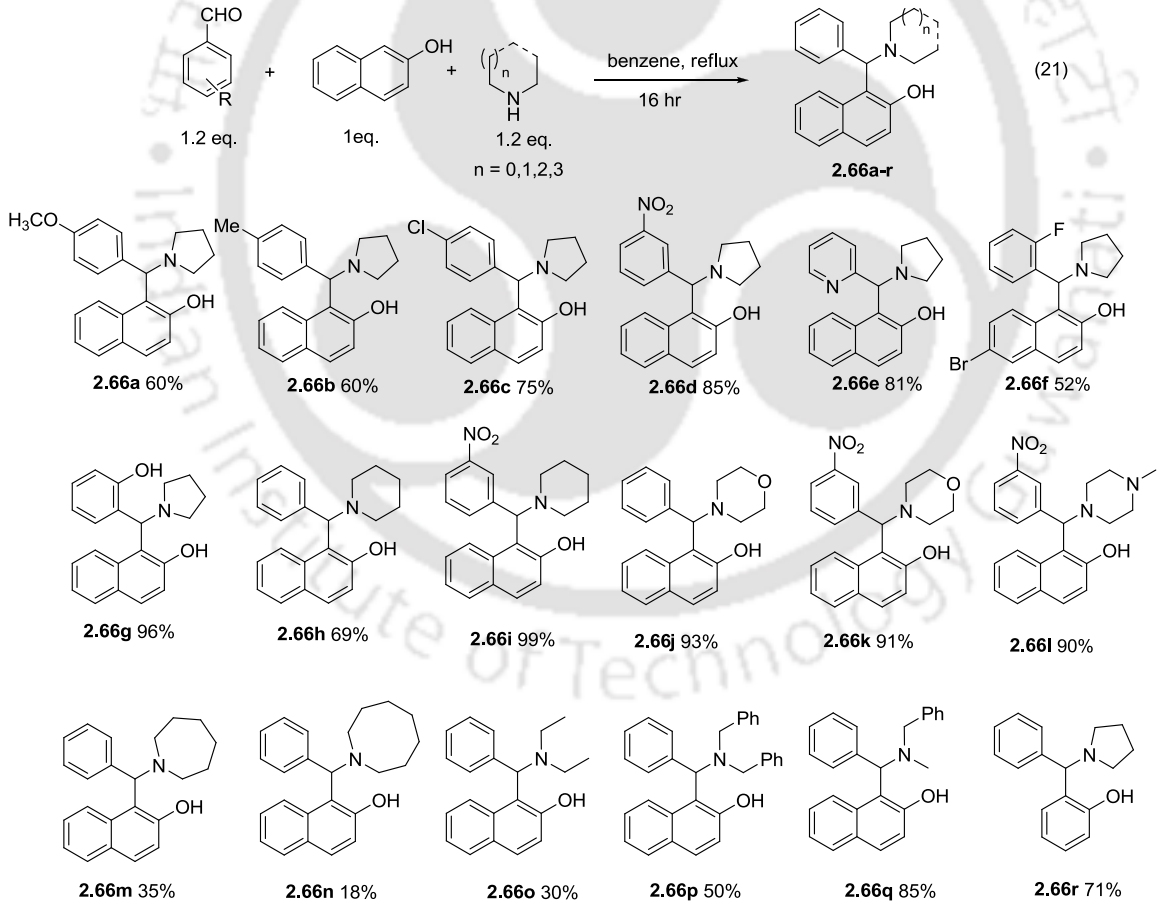
Entry	Oxidant	Solvent	Temperature	Time	Yield %
1	Ag_2O	Toluene	RT	24 h	15
2	Ag_2O	Toluene	120 °C	18 h	40
3	$FeCl_3$	Toluene	120 °C	18 h	trace
4	CAN	Acetonitrile	80 °C	18 h	trace
5	DDQ	Toluene	120 °C	18 h	-
6	I_2	Toluene	rt or reflux	18 h	-
7	Ag_2O	*m*-xylene	Reflux	18 h	75
8[b]	$AgNO_3$	*m*-xylene	Reflux	18 h	25

[a] Reactions were carried out in distilled solvents with 1.0 mmol of **2.66**, 1.2 eq. of oxidant. [b] 2 eq. of $AgNO_3$ was used.

The yield of the oxazine increased to 40% when the reaction was carried out under reflux condition in toluene. Ferric chloride, iodine and DDQ in toluene were applied as the oxidant separately. But trace amount of product was detected for $FeCl_3$ and iodine. On the other hand, DDQ resulted a complex mixture. Cerric ammonium nitrate in acetonitrile was also used producing trace amount of product. Pleasingly, very good yield (75%) of desired oxazine was achieved with silver oxide as the catalyst in refluxing *m*-xylene. However, silver nitrate under the same condition exhibited significantly lower activity to provide 15% of the product (**Table 1**).

2.6 Substrate Scope

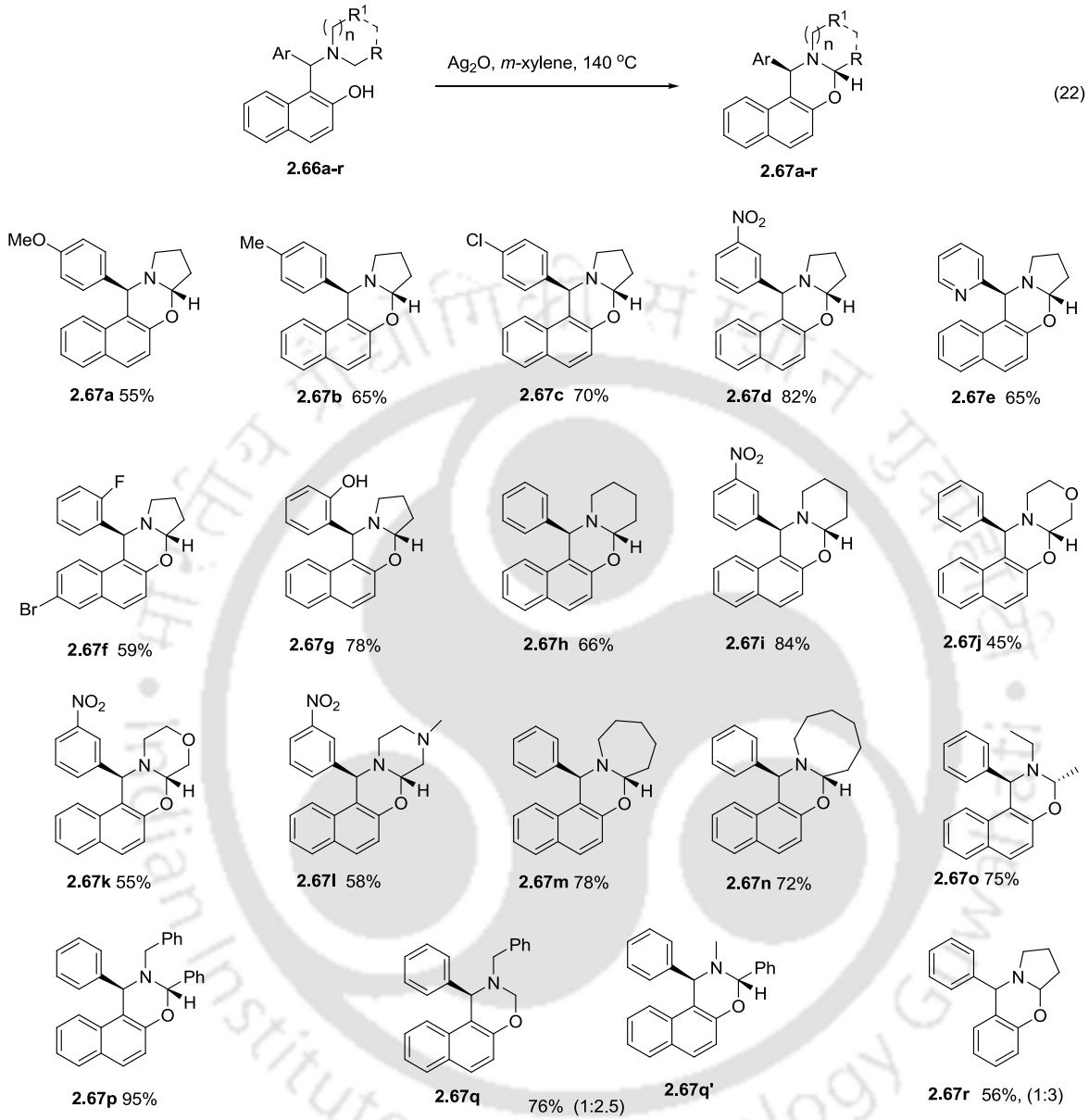
To investigate the scope of the reaction, variety of diarylmethylamines were readily prepared by the condensation of 2-naphthol, aromatic aldehydes and amines in benzene under reflux condition (**Scheme 8**, eq. 21).



Scheme 8: Preparation of Betti bases

Electron deficient aryl aldehyde gave higher yield compared to electro-neutral or electron rich aryl aldehydes. Lower yields were also obtained for seven, eight membered amine and acyclic secondary amine. Betti bases derived from various amines were reacted with silver oxide under optimized condition to obtain the corresponding oxazines (**Scheme 9**, eq. 22**)**. It was found that the substrates **2.66a-b** derived from electron rich aromatic aldehydes provided relatively lower yield in comparison to the substrates **2.66c-d** that are derived from either electro-neutral or electron deficient aldehyde (**Scheme 9**, eq. 22). In this series, Betti base **2.66d** resulted from pyrrolidine and *m*-nitro benzaldehyde gave corresponding naphthoxazine **2.67d** with highest yield (82%). Substituted 2-naphthol derivative **2.66f** also satisfactorily gave corresponding oxazine **2.67f** with good yield (59%). Among two hydroxy groups present at *ortho*-position of two different aromatic ring in the starting material **2.66g**, hydroxy group of naphthalene was reacted exclusively to give the oxazine **2.67g**. Six member saturated heterocyclic amines are less reactive towards the direct α-functionalization.[21] Accordingly, naphthoxazine **2.67h** was obtained via functionalization of piperidine derivative with little lower yield (66%). The yield of morpholine based oxazine **2.67j** was further reduced. The oxazine **2.67j** was isolated in 45% yield along with the 26% of unreacted starting material **2.66j**. The increased yields of corresponding oxazines **2.67i** (89%) and **2.67k** (55%) were obtained by employing the corresponding substrates derived from the electron deficient 3-nitro benzaldehyde. In the same way, functionalization of *N*-methyl piperizine proceeded with similar efficiency to provide 58% of the desired product **2.67l**. Alpha C-H aryloxylation of higher membered aliphatic *N*-heterocycles also occurred smoothly. Hexamethyleneamine and heptamethylene amine based substrates **2.66m** and **2.66n** provided desired oxazines **2.67m** and **2.67n**, respectively with very good yields. Importantly, for all the cases the desired naphtho-1,3-oxazines were isolated as single diastereoisomer and for most of the compounds the stereo- configuration was assigned based on their respective X-ray crystal structures. Substrates **2.66o-q** derived from the acyclic saturated secondary amines were also investigated to test the generality of the method. In all cases, very good to excellent yields of the corresponding oxazines **2.67o-r** were obtained (**Scheme 9**, eq. 22). The reaction temperature of 30 ^{o}C was sufficient for diethylamine derivative **2.66o** to provide the desired product **2.67o** with 75% yield. On the other hand, dibenzyl amine derivative **2.66p** reacted under the reflux condition to give 95% of the desired product **2.67p**. Oxazines **2.67o** and **2.67p** were also isolated as the single diastereoisomer. However, in presence of methylbenzyl amine group in **2.66q**, two regio-isomeric oxazines **2.67q** and **2.67q'** (1:2.5) were formed.

For the oxazine **2.67r**, the diastereoselectivity was decreased drastically when exchanging the naphthyl moiety with a phenyl group.

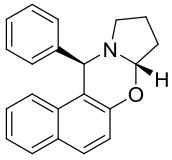
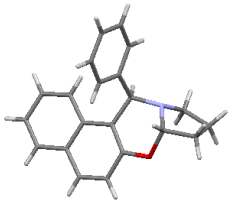
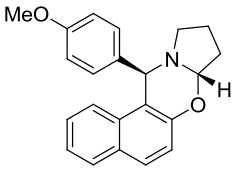
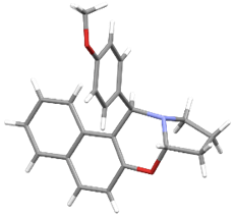
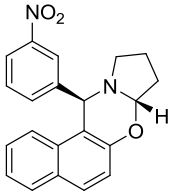
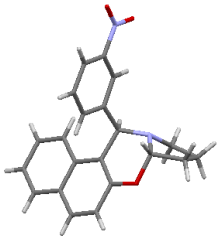
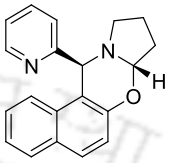
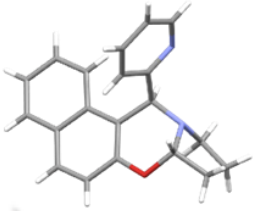
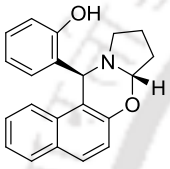
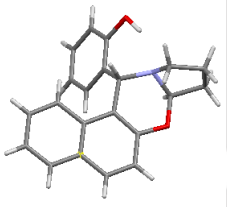
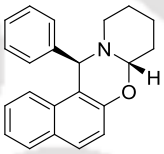
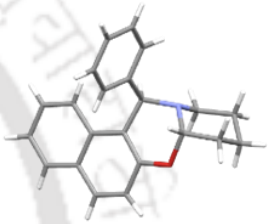
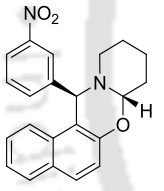
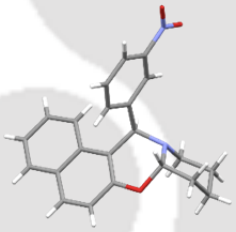
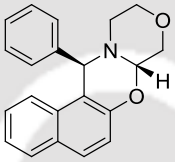
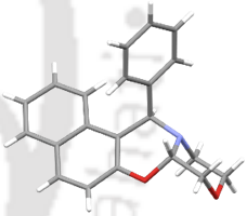
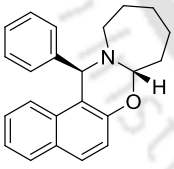
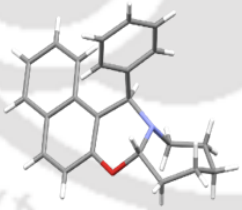
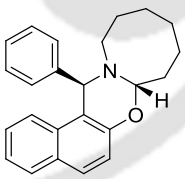
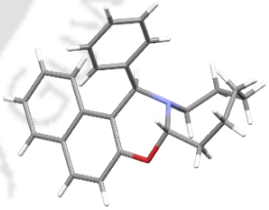
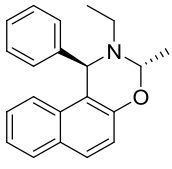
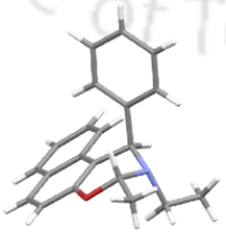
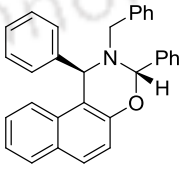
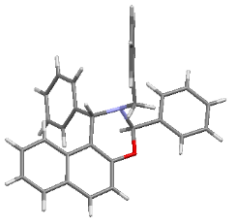


Scheme 9: Functionalization of various secondary amines

2.7 Crystal structures of oxazines

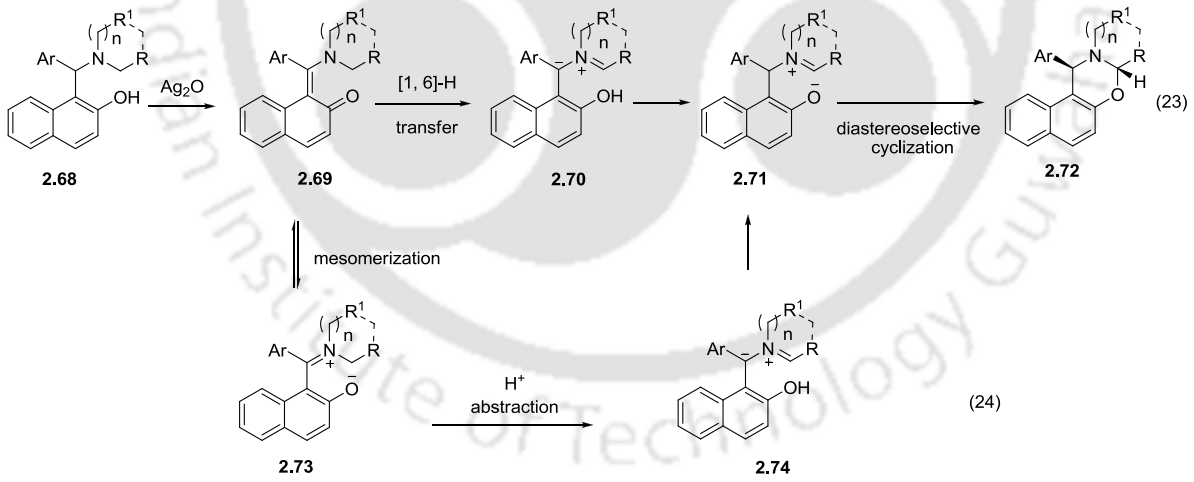
The relative configuration of the oxazine was confirmed by X-ray crystallographic analysis. The structures of compounds have been shown below (**Table 2**).

Table 2: Selected oxazines and their X-ray crystal structures

Compound	Crystal structure	Compound	Crystal structure
 **2.67**		 **2.67a**	
 **2.67d**		 **2.67e**	
 **2.67g**		 **2.67h**	
 **2.67i**		 **2.67j**	
 **2.67m**		 **2.67n**	
 **2.67o**		 **2.67p**	

Based on the experimental outcome and the literature precedence a probable mechanistic explanation for this unprecedented transformation has been suggested. Ag_2O is well studied and extensively used reagent to generate *o*-quinone methide.[29] Therefore, Betti base **2.68** on

treatment with Ag_2O furnished *o*-quinone methide **2.69**. Quinonic oxygen is good H-acceptor[30] and alpha-hydrogen of tertiary amines is known to intramolecularly migrate to suitably positioned acceptor (*tert*-amino effect).[31] Therefore [1,6]-hydrogen shift lead to produce zwitterionic intermediate **2.70**.[32] Protonation of **2.70** and subsequent diastereoselective cyclization of the resulting iminium ion **2.71** gave rise to *trans* (relative to C-Ar and C-O-) oxazine **2.72** (**Scheme 10**, eq. 23). Alternatively, **2.71** can also be formed via mesomerization of quinone methide **2.69** followed by a proton transfer (**Scheme 10**, eq. 24). In a related study, Fülöp and co-workers showed that *trans*-oxazines are thermodynamically more stable as compared to *cis*-isomer.[33] Cyclization occurred in a way to selectively position the aryl group at the convex face of the molecule and thus to minimize the steric repulsion with R- and the naphthyl moiety. This was further supported from the observation of lower selectivity in case of oxazine **2.67** when naphthyl was replaced by a phenyl group. The electron-withdrawing group on Ar- and electron donating nature of R- will stabilize the zwiterionic intermediate **2.70**. Thus better yields for the substrates (**2.67d** & **2.67p**) with nitro group on Ar- and Ph- as R- are supportive for **2.70**. Expected lower yield for morpholine derivative is due to the reduced stability of zwiterionic intermediate **2.70** because of the negative inductive effect of ring oxygen atom (**Scheme 10**, eq. 23).

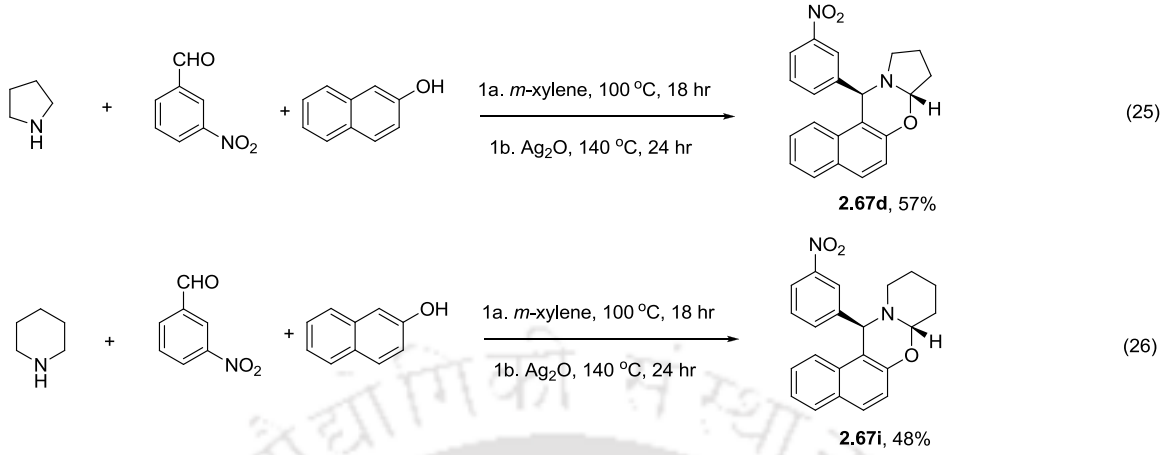


Scheme 10: Proposed mechanism

2.8 One pot synthesis of oxazine

To explore the possibility of coupling C-H functionalization process with three components Betti reaction, a mixture of aldehyde, *β*-naphthol and amine to be functionalized was allowed to react at 80 ^oC in xylene prior to the addition of Ag_2O into the same reaction mixture. Expected five member naphthoxazine **2.67d** gave higher yield (57%) as compare to six

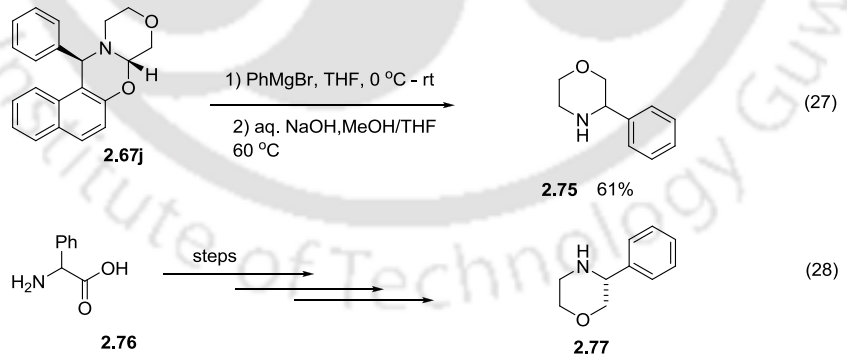
membered oxazine **2.67i** (48%) (**Scheme 11**, eq. 25 and 26).



Scheme 11: One pot syntheses of oxazines

2.9 Synthetic application

Substituted morpholine derivative is an important structural unit of biologically active molecules. Moreover, it is used as chiral reagent for asymmetric synthesis.[34,35] Considering oxazine as masked iminium ion,[36] oxazine **2.67j** was reacted with phenyl magnesium bromide. The hydroxy naphthyl group was subsequently removed by aq. NaOH-MeOH in THF to give α-functionalized amine **2.75** with 61% yield (**Scheme 12**, eq. 27). However, reported method for the synthesis of α-phenyl morpholine involved multistep synthetic strategy starting from phenyl alanine (**Scheme 12**, eq. 28).[37]



Scheme 12: Synthesis of α-phenyl morpholine.

At the same time, similar work was published by Maycock and co-workers for the synthesis of dihydro-1,3-oxazines through Cu^{+2}-mediated C-O bond formation.[38] Recently, Hajra group developed a method for redox-neutral [3+2]-cycloadditions using pyrrolidine and benzaldehyde to form the oxazole.[39]

2.10 Summary

In summary, an unprecedented, operationally simple, versatile and diastereoselective protocol has been developed to access synthetically as well as biologically important oxazines via α-C-H aryloxylation of aliphatic amines. The methodology is very general and thus worked well for wide range of saturated aliphatic amine based substrates, some of them were otherwise difficult to functionalize. Additionally, its synthetic potential is exemplified by a straightforward and elegant synthesis of 3-phenylmorpholine. Therefore, it was believed that the synthetic methodology presented has the promising ability to be utilized widely as the general and practical approach to functionalize aliphatic amines.

References

[1] a) Felpin, F.-X.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10127; b) Lourenco, A. M.; Máximo, P.; Ferreira, L. M.; Pereira, M. M. A. *Studies in Natural Products Chemistry: Bioactive Natural Products (Part H)*; A. Rahman, Ed.; Elsevier: Amsterdam, 40, **2002**; Vol. 27, pp 233; c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773; For selected reports see d) Yang, X.; Shi, Q.; Lai, C.-Y.; Chen, C.-Y.; Ohkoshi, E.; Yang, S.-C.; Wang, C.-Y.; Bastow, K. F.; Wu, T.-S.; Pan, S.-L.; Teng, C.-M.; Yang, P.-C.; Lee, K.-H. *J. Med. Chem.* **2012**, *55*, 6751; e) Morriello, G. J.; Wendt, H. R.; Bansal, A.; Salvo, J. D.; Feighner, S.; He, J.; Hurley, A. L.; Hreniuk, D. L.; Salituro, G. M.; Reddy, M. V.; Galloway, S. M.; McGettigan, K. K.; Laws, G.; McKnight, C.; Doss, G. A.; Tsou, N. N.; Black, R. M.; Morris, J.; Ball, R. G.; Sanfiz, A. T.; Streckfuss, E.; Struthers, M.; Edmondson, S. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1865.

[2] a) Hu, P.; Hu, J.; Jiao, J.; Tong, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 5319; b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[3] Waisser, K.; Gregor, K.; Kubicova, L.; Klimesova, V.; Kunes, J.; Machacek, M.; Kaustova, J. *Eur. J. Med. Chem.* **2000**, *35*, 733.

[4] Arthington- Skaggs, B. A.; Motley, M.; Warnock, D.W.; Morrison, C. J. *J. Clin. Microbiol.* **2000**, *38*, 2254.

[5] Benameur, L.; Bouaziz, Z.; Nebois, P.; Bartoli, M. H.; Boitard, M.; Fillion, H. *Chem. Pharm. Bull.* **1996**, *44*, 605.

[6] Petrlìková, E.; Waisser, K.; Divišová, H.; Husáková, P.; Vrabcová, P.; Kuneš, J.; Kolář, K.; Stolařìková, J. *Bioorg. Med. Chem.* **2010**, *18*, 8178.

[7] Tang, Z.; Zhu, Z.; Xia, Z.; Liu, H.; Chen, J.; Xiao, W.; Ou, X. *Molecules* **2012**, *17*, 8174.

[8] a) Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Zhang, Z. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 1313; b) Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. *Eur. J. Med. Chem***. 2010**, *45*, 1502; c) Cocuzza, A. J.; Chidester, D. R.; Cordova, B. C.; Jeffrey, S.; Parsons, R. L.; Bacheler, L. T.; Erickson-Viitanen, S.; Trainor, G. L.; Ko, S. S. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1177.

[9] Augelli-Szafran, C. E.; Jaen, J. C.; Moreland, D. W.; Nelson, C. B.; Penvose-Yi, J. R.; Schwarz, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1991.
[10] Wang, L.; Ankati, H.; Akubathini, S. K.; Balderamos, M.; Storey, C. A.; Patel, A. V.; Price, V.; Kretzschmar, D.; Biehl, E. R.; D'Mello, S. R. *J. Neurosci. Res.* **2010**, *88*, 1970.
[11] Shitong, R.; Xin, Y.; Xiaojuan, Z.; Ying, Z.; Wei, H. *J. Appl. Polym. Sci.* **2015**, *132*, 41920.
[12] Li, Z.; Bohle, S.; Li, C.-J. *Proc. Natl. Acda. Sci. U.S.A.* **2006**, *103*, 8928.
[13] Cheng, G.; Wang, X.; Zhu, R.; Chao, C.; Xu, J.; Hu, Y. *J. Org. Chem.* **2011**, *76*, 2694.
[14] a) Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron* **2001**, *57*, 6089; b) Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1667; c) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem*. **2005**, *70*, 1897.
[15] Zeller, E.; Grierson, D. S. *Heterocycles* **1988**, *27*, 1575.
[16] Zill, N.; Schoenfelder, A.; Girard, N.; Taddei, M.; Mann, A. *J. Org. Chem*. **2012**, *77*, 2246.
[17] a) Katritzky, A. R.; Xu, Y.-J.; Jain, R. *J. Org. Chem.* **2002**, *67*, 8234; b) Burke, W. J.; Stephens, C. W. *J. Am. Chem. Soc.* **1952**, *74*, 1518; c) Mathew, B. P.; Nath, M. *J. Heterocycl. Chem.* **2009**, *46*, 1003; d) Tang, Z.; Zhu, Z.; Xia, Z.; Liu, H.; Chen, J.; Xia, W.; Ou, X.; *Molecules* **2012**, *17*, 8174; e) Chen, C.-K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829; f) Kienzle, F. *Tetrahedron Lett.* **1983**, *24*, 2213; g) Okimoto, M.; Ohashi, K.; Yamamori, H.; Nishikawa, S.; Hoshi, M.; Yoshida, T. *Synthesis* **2012**, *44*, 1315; h) Mathis, C. L.; Gist, B. M.; Frederickson, C. K.; Midkiff, K. M.; Marvin, C. C. *Tetrahedron Lett.* **2013**, *54*, 2101; i) Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. *RSC Adv.* **2012**, *2*, 4065; i) Pandey, G.; Kumaraswamy, G.; Reddy, P. Y. *Tetrahedron* **1992**, *48*, 8295.
[18] Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Synlett* **2008**, *15*, 2373.
[19] Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem. Soc. Parkin Trans*. *1*, **2002**, 2900.
[20] Cohen, N.; Blount, J. F.; Lopresti, R. J.; Trullinger, D. P. *J. Org. Chem.* **1979**, *44*, 4005.
[21] Jurberg, I. D.; Peng, B.; Wostefeld, E.; Wasserloos, M.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 1950.
[22] Warrener, R. N.; Cain, E. N. *Tetrahedron Lett.* **1966**, *28*, 3231.
[23] Chen, C. K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829.
[24] Shi, D.; Rong, S.; Dou, G.; Wang, M. *J. Comb. Chem*. **2010**, *12*, 25.
[25] Ozturkcan, S. A.; Turhan, K.; Turgut, Z. *J. Chem. Soc. Pak*. **2011**, *33*, 941.
[26] Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P.K.; Nath. M. *Eur. J. Med. Chem*. **2010**, *45*, 1502.
[27] Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc*. **2008**, *130*, 416.
[28] a) Mori, K.; Sueoka, S.; Akiyama, T. *J. Am. Chem. Soc*. **2011**, *133*, 2424; b) Reinhoudt, D. N.; Visser, G. W.; Verboom, W.; Benders, P. H.; Pennings, M. L. M. *J. Am. Chem. Soc.* **1983**, *105*, 4775.
[29] Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.
[30] a) Thommen, C.; Jana, C. K.; Neuburger, M.; Gademann, K. *Org. Lett.* **2013**, *15*, 1390; b) Batista, V. S.; Crabtree, R. H.; Konezny, S. J.; Luca, O. R.; Praetorius, J. M. *New J. Chem*. **2012**, *36*, 1141; c) Iqbal, J.; Tangellamudi, N. D.; Dulla, B.; Balasubramanian, S. *Org. Lett.* **2012**, *14*, 552; d) Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1978**, *56*, 733.

[31] Mátyus, P.; Éliás, O.; Tapolcsnyi, P.; Polonka-Bálint, A.; Halász-Dajka, B. *Synthesis* **2006**, 2625.

[32] Verma, V.; Singh, K.; Kumar, D.; Klapötke, T. M.; Stierstorfer, J.; Narasimhan, B.; Qazi, A. K.; Hamid, A.; Jaglan, S. *Eur. J. Med. Chem*. **2012**, *56*, 195.

[33] Szatmári, I.; Heydenreich, M.; Koch, A.; Fülöp, F.; Kleinpeter, E. *Tetrahedron* **2013**, *69*, 7455.

[34] a) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641; b) Wilkinson, M. C. *Tetrahedron Lett*. **2005**, *46*, 4773.

[35] Lanman, B. A.; Myers, A. G. *Org. Lett*. **2004**, *6*, 1045.

[36] Vasylyev, M.; Alper, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1287.

[37] Charrier, J.-D.; Young, S. C.; Davis, C. J.; Studley, J. *PCT Int. Appl.* (**2013**), WO 2013049719 A1.

[38] Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 9791.

[39] Rahman, M.; Bagdi, A. K.; Mishra, S.; Hajra, A. *Chem. Commun*. **2014**, *50*, 2951.

Chapter 3

Iterative C(sp^3)-H Functionalization for the Syntheses of Difunctionalized Secondary Aliphatic Amines

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

3.1 Introduction

Disubstituted pyrrolidines and piperidines occur ubiquitously in many natural products, biologically active compounds, and in functional materials.[1] The pyrrolidine ring represents one of the most ubiquitous heterocyclic motifs found in naturally occurring compounds. In 1970's first pyrrolidinic alkaloids were found in the *Solenopsis ants* venom.[2] 2,5-dialkylated pyrrolidines extracted from venemous ants and frogs[3] have shown insecticidal[4,5] hemolytic and anticholinergic activities.[6] Polyhydroxypyrrolidines often found in Campanulaceae and Fabaceae families, which are structurally related to monosaccharides and named as "azasugars", have shown very potent activity as enzymes inhibitors.[7] It is worthy of note that besides the use of these compounds as chemotherapeutic agents, the 2,5-disubstituted chiral pyrrolidines possessing a C_2-symmetry may be used as very powerful catalysts in asymmetric reactions.

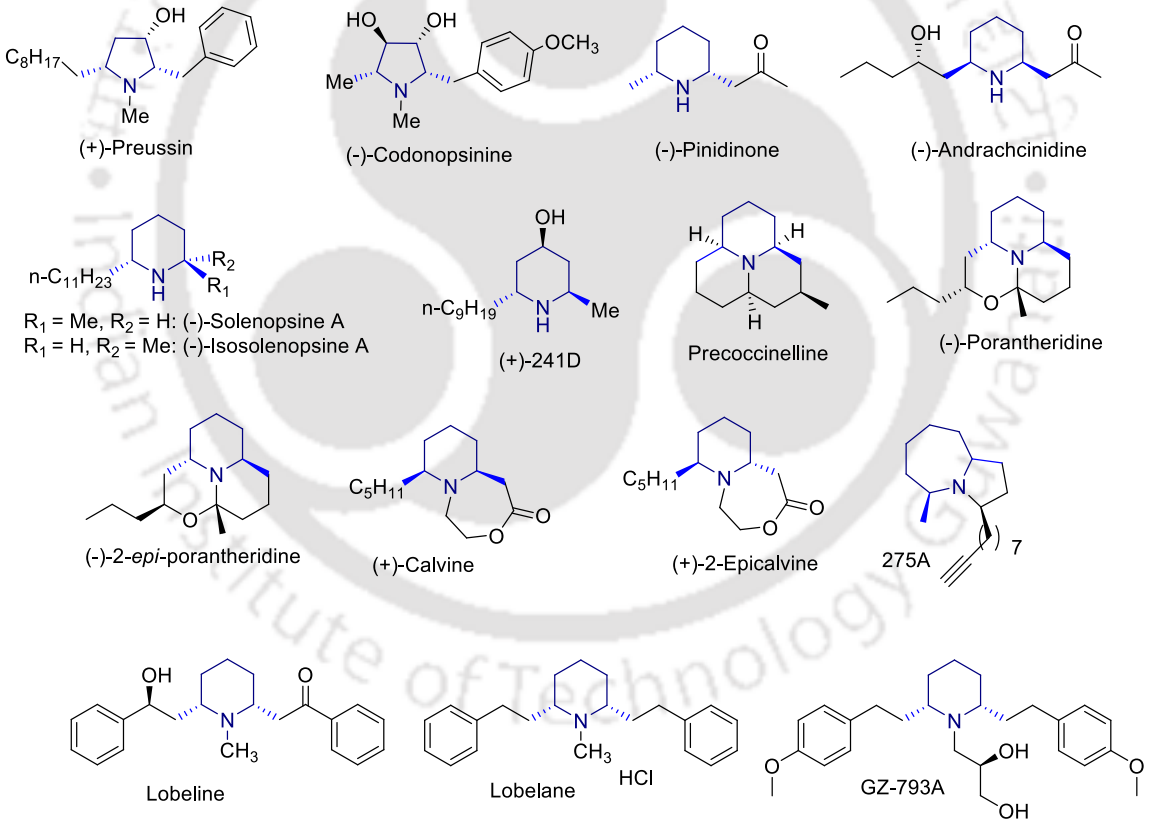


Figure 1: Examples of bioactive di-functionalized alkaloids

Difunctionalized piperidine unit is also present in a major class of natural products. Among them lobelane and its analogues, which are 2,6-difunctionalized piperidine are important in the field of neuroscience (**Fig. 1**).[8] Lobeline, a lipophilic alkaloidal constituent of Indian tobacco *(Lobelia inflata),* has been reported to have many nicotine-like effects.

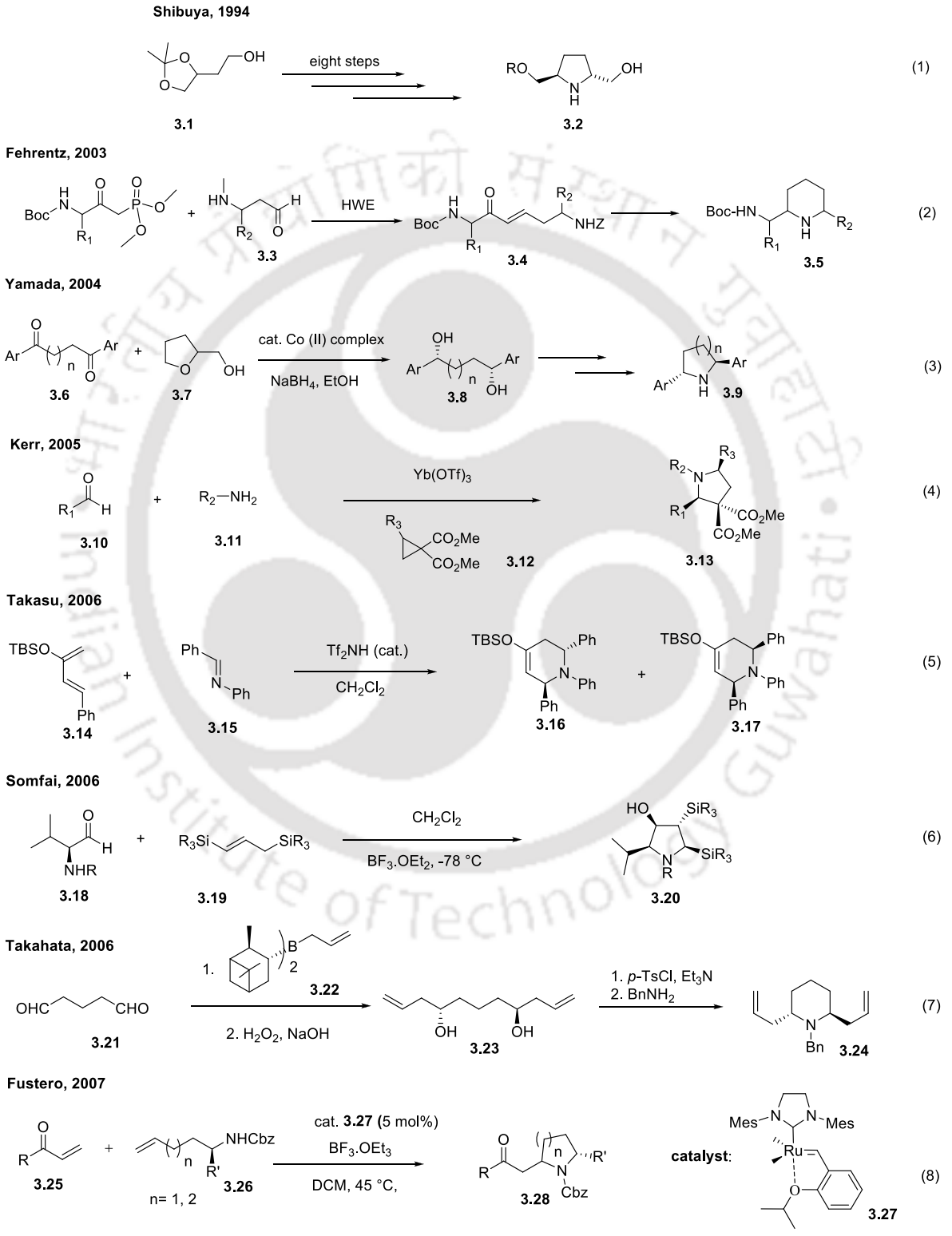
The reports from Crooks and co-workers group revealed that lobelane, exhibited low affinity for nicotinic receptors and enhanced affinity and selectivity for VMAT2 compared to its parent compound Lobeline.[9,10]

Several reports appeared in the literature on the stereo-selective syntheses of 2,5-disubstituted pyrrolidines due to their interesting biological profile. Moreover, due to low natural abundance very few studies on their biological activity and mechanism of action have been performed. However, synthesis of 2,6-disubstituted piperidine,[11] 2,7-disubstituted azetidine[12] derivatives are very rare. Direct functionalization of these heterocyclic ring is usually difficult due to their inherent low reactivity. Therefore, general method for the direct difunctionalization that works for a wide range of aliphatic amines would be advantageous.

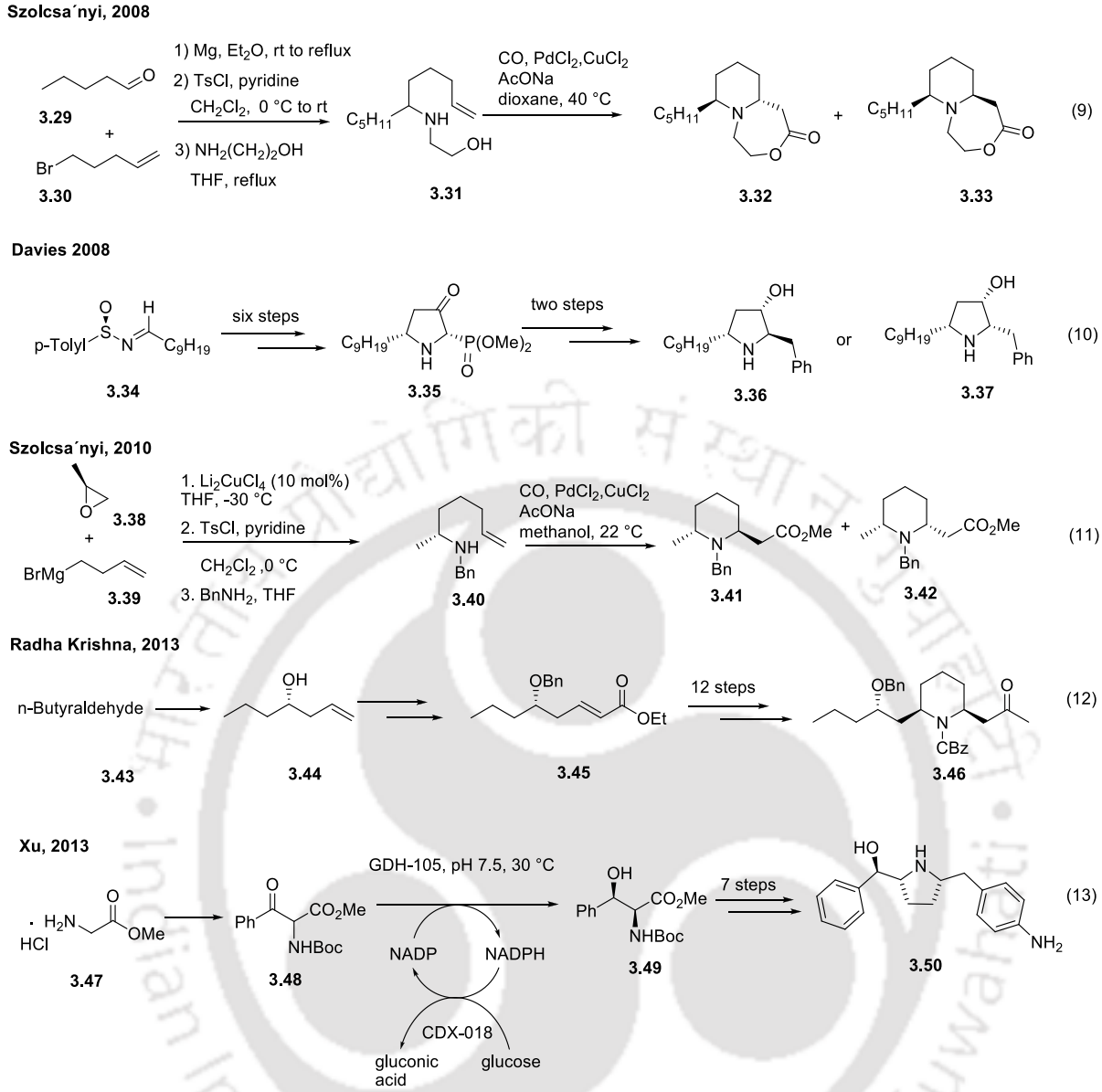
3.2 Multistep syntheses of di-functionalization of *N*-heterocycles

Several synthetic strategies were developed for the synthesis of di-functionalized *N*-heterocycles due to their interesting bioactivities. Mainly multistep synthetic sequence was utilized for the formation of *N*-heterocycles having desired functionality. In 1994, Shibuya and co-workers developed a method for the synthesis of *trans*-5-substituted 2-hydroxymethylpyrrolidine derivative.[13] The acetonide **3.1** obtained from (*S*)-malic acid, was converted to difunctionalized pyrrolidine **3.2** via eight linear synthetic steps (**Scheme 1a**, eq. 1)**.** In 2003, synthesis of 2,6-disubstituted piperidines bearing α-amino acid side-chain was developed by Fehrentz and co-workers .[14] Synthesis involved a Horner-Wadsworth-Emmons condensation and *N*-cycloalkylation as the key steps (**Scheme 1a**, eq. 2). In 2004, Yamada and co-workers reported a sodium borohydride reduction of various diketones to obtain the corresponding optically pure diols, which were efficiently transformed into the optically pure C_2-symmetrical 2,5-difunctionalized pyrrolidine derivative[15] (**Scheme 1a**, eq. 3). In 2005, Kerr and co-workers, reacted aldimines, generated *in situ* from aldehydes **3.10** and primary amines **3.11**, with various 1,1-cyclopropanediesters **3.12** in the presence of catalytic $Yb(OTf)_3$ to furnish polysubstituted pyrrolidine **3.13** (**Scheme 1a**, eq. 4).[16] In 2006, Takasu and co-workers developed an imino Diels–Alder reaction of 2-siloxydienes **3.14** with aldimines **3.15** catalyzed by triflic imide leading to form substituted piperidin-4-ones **3.16** and **3.17** (**Scheme 1a**, eq. 5).[17] Lewis acid promoted [3 + 2]-annulation of amino aldehydes **3.18** and silanes **3.19** provided a route for the construction of densely functionalized pyrrolidines **3.20** (**Scheme 1a**, eq. 6).[18] 2,6-diallylpiperidine derivative **3.24** was prepared by Takahata and co-workers by the double assymmetric allylboronation of glutraldehyde followed by an aminocyclization (**Scheme 1a**, eq. 7).[19] In 2007, Fustero

reported a cross metathesis intramolecular aza-Michael tandem reaction catalyzed by a Hoveyda-Grubbs second generation catalyst **3.27** in presence of BF_3-OEt_2 allowing rapid access to protected 2,5-substituted pyrrolidine and 2-substituted piperidine **3.28** (**Scheme 1a**, eq. 8).[20]



Scheme 1a: Syntheses of di-substituted *N*-heterocycles



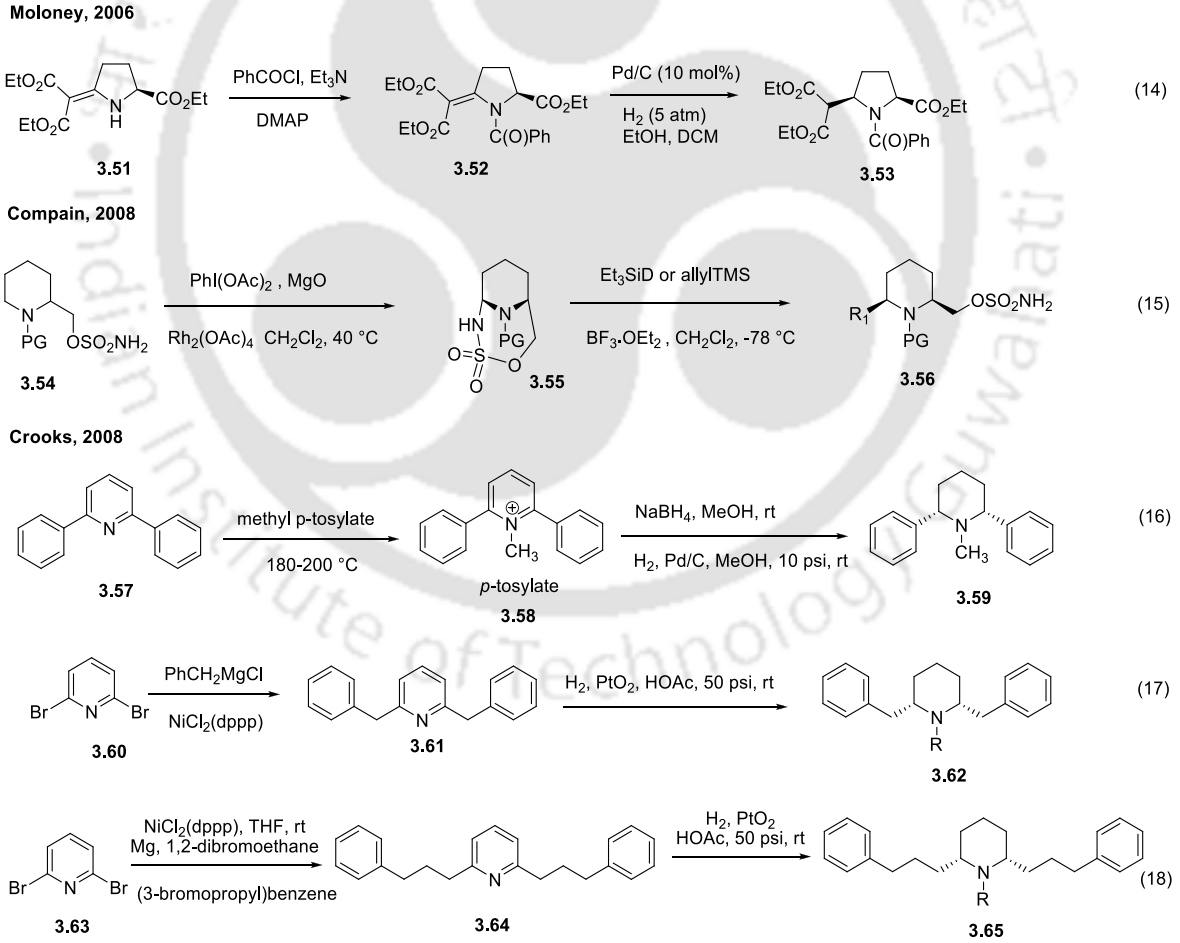
Scheme 1b: Syntheses of di-substituted *N*-heterocycles

In 2008, racemic syntheses of the ladybird beetle alkaloid calvine **3.32** and epicalvine **3.33**, over four steps starting from hexanal **3.29** and pentenyl bromide **3.30**, was demonstrated by Szolcsányi and co-workers (**Scheme 1b**, eq. 9).[21] The intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol was used as a key step in the synthesis. In 2008, Davies and his group reported a method for the preparation of difunctionalized pyrrolidine unit **3.37** starting from (+)-3-oxo pyrrolidine 2-phosphonate **3.35** which was prepared in six steps from sulfinimine **3.34** (**Scheme 1b**, eq. 10).[22] This methodology was employed in the asymmetric synthesis of the potent antifungal agent (+)-preussin and its *trans* analogue. In 2010, the synthesis of naturally occurring piperidine alkaloid (-)-pinidinone **3.41** was achieved by Szolcsányi and his research group using $PdCl_2/CuCl_2$-catalysed intramolecular

methoxyaminocarbonylation of *N*-benzyl protected alkenyl amine **3.40** (**Scheme 1b**, eq. 11).[23] Total synthesis of the 2,6-disubstituted piperidine alkaloid (-)-andrachcinidine **3.46** was reported by Radha Krishna and co-workers using Keck's asymmetric allylation, Sharpless epoxidation, nucleophilic substitution, and intramolecular aza- Michael addition as the key steps (**Scheme 1b**, eq. 12).[24] Enantioselective synthesis of *cis*-2,5-disubstituted pyrrolidine **3.50** has been reported by Xu and co-workers employing enzymatic DKR during reduction of racemic substrate (**Scheme 1b**, eq. 13).[25]

3.3 Syntheses using pre-functionalized *N*-Heterocycles

In 2006, Moloney and co-workers reported synthesis of 2,5-disubstituted pyrrolidine derivative **3.53** by reduction of enamines **3.52** derived from **3.51** (**Scheme 2**, eq. 14).[26] Compain and co-workers synthesized di-substituted piperidine **3.56** from 2-sulfamoyloxymethyl piperidine derivative **3.54** (**Scheme 2**, eq. 15).[27]



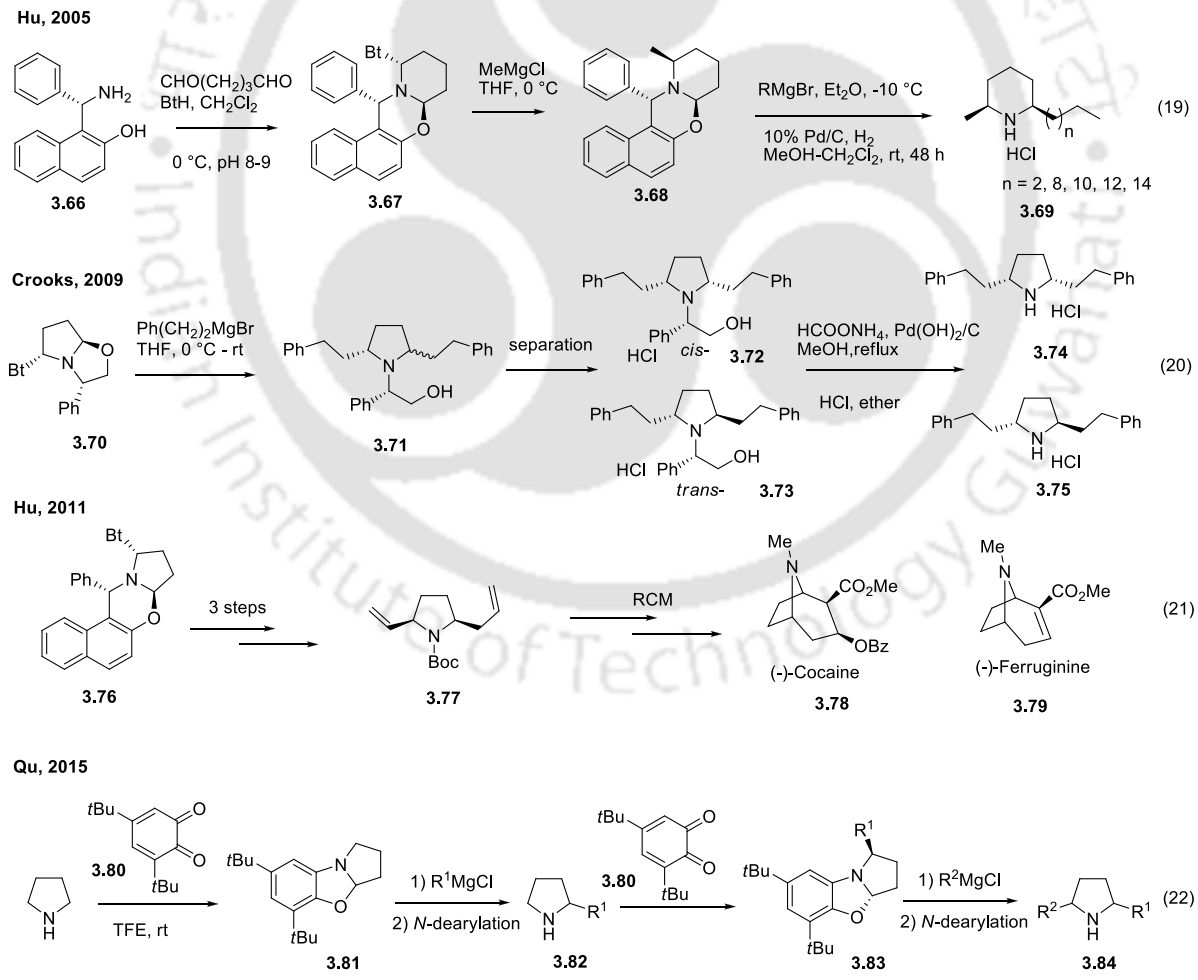
Scheme 2: Indirect syntheses of di-substituted *N*-heterocycles

Indirect way for the preparation of disubstituted piperidine from corresponding pyridine

derivative was published by Crooks and co-workers.[28] *N*-methylation of 2,6-biphenylpyridine **3.57** and reduction of the resulting quaternary ammonium salt **3.58** with $NaBH_4$ followed by catalytic hydrogenation over Pd-C yielded bifunctionalized **3.59** (**Scheme 2**, eq. 16). 2,6-disubstituted pyridine **3.61** and **3.64** were utilised for the synthesis of **3.62** and **3.65** respectively, by catalytic hydrogenation over Adams catalyst (PtO_2) at high pressure of hydrogen (**Scheme 2**, eq. 17 and eq. 18).

3.4 Difunctionalization through oxazine and oxazole

The ring fused oxazines and oxazoles moiety are excellent precursor for the preparation of di-functionalized *N*-heterocycles. In 2005, using this strategy, dialkylation of piperidine was achieved by Hu and co-workers. The synthesis of alkaloidal natural product (2*S*,6*R*)-dihydropinidine (as hydrochloride) **3.69** was achieved in four steps starting from (*S*)-Betti base **3.66** (**Scheme 3**, eq. 19).[29]

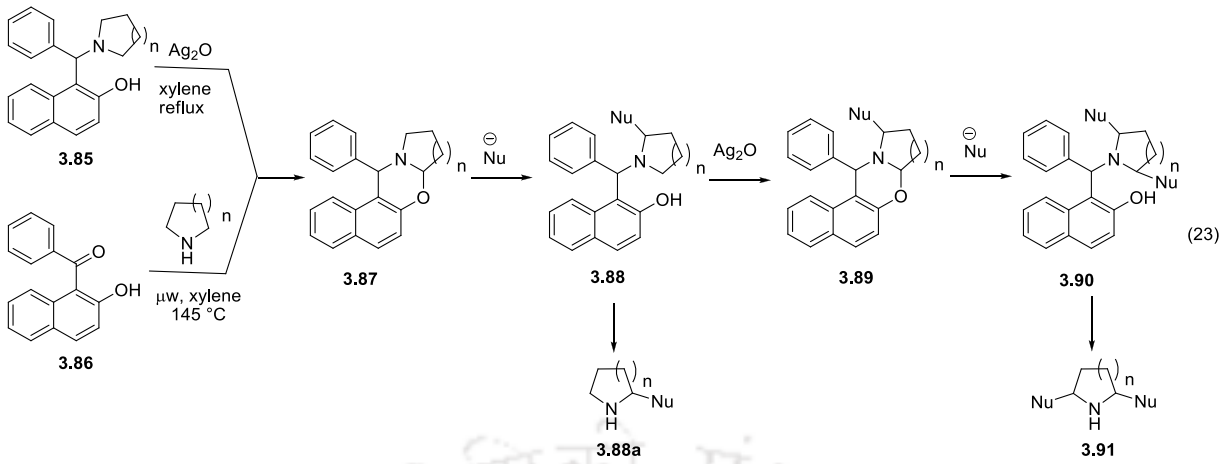


Scheme 3: Syntheses of di-substituted *N*-heterocycles using oxazines and oxazoles

A very similar strategy has been reported by Crook and co-workers for the difunctionalization of pyrrolidine starting from L-phenylglycinol and succinaldehyde to afford the key synthon **3.70** Addition of a 6-fold excess of phenethylmagnesium chloride to synthon **3.70** at room temperature led to the formation of 2:1 mixture of the *cis*- and *trans*-configured diastereomers of **3.72** and **3.73**. The diastereomers, **3.72** and **3.73**, were hydrogenolyzed separately by catalytic-transfer hydrogenation in the presence of ammonium formate in refluxing methanol to get the difunctionalized pyrrolidine **3.74** and **3.75** as hydrochloride salt (**Scheme 3**, eq. 20).[30] In 2011, Hu co-workers also reported a method for the difunctionalization of pyrrolidine which was further utilized to construct the alkaloid Cocaine **3.78** and Ferruginine **3.79** (**Scheme 3**, eq. 21).[31] By using *o*-benzoquinone **3.80** as an internal oxidant, the regio- and diastereoselective direct functionalization of the pyrrolidine was reported by Qu and co-workers to obtain disubstituted pyrrolidines **3.84** (**Scheme 3**, eq. 22).[32] This method was only limited for functionalization of pyrrolidine and by this method *α*-phenylation was not achieved. Moreover, two difficult *N*-dearylation steps were involved to obtain difunctionalized pyrrolidine. To that end, direct C-H oxygenation strategies which were developed recently[33,34] were planned to apply for the synthesis of difunctionalized *N*-heterocycles.

3.5 Design of strategy

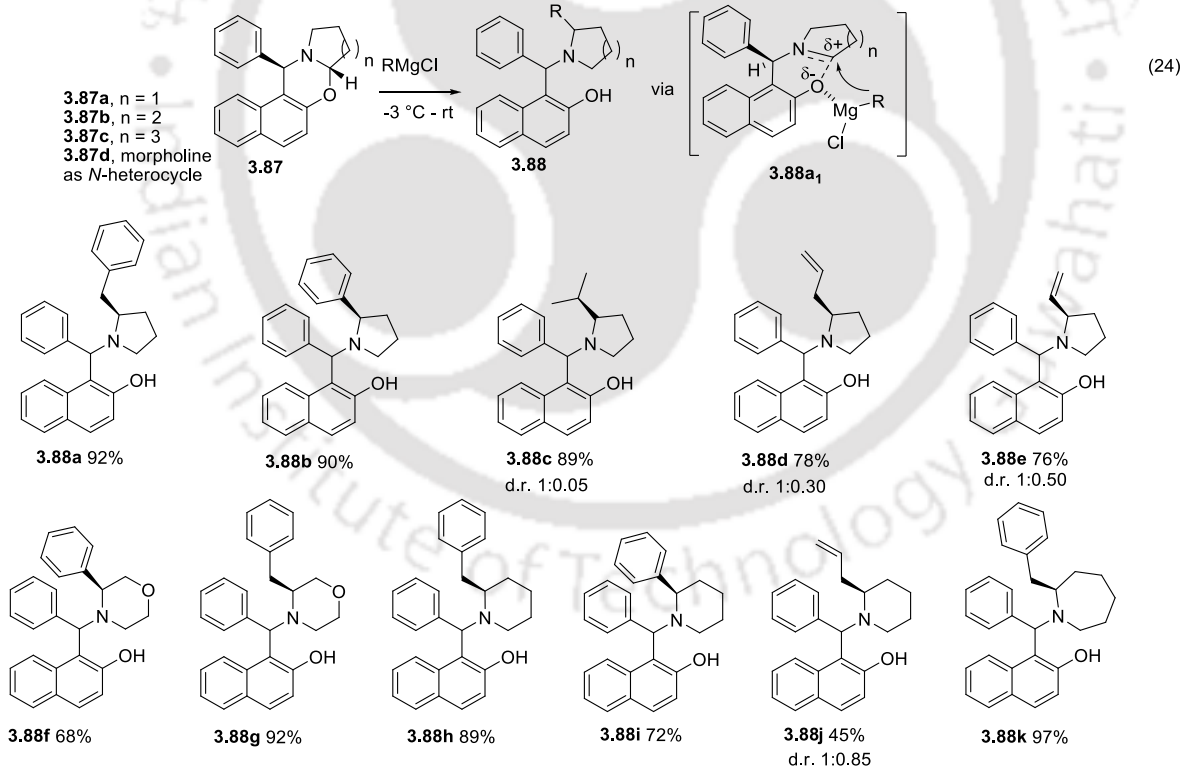
It was anticipated that, oxazines **3.87**, which were easily prepared either via Ag-mediated reaction or via redox neutral process, can be reacted with nucleophile to obtain the first C-C bond formation. The resulting naphthol derivatives **3.88** would be well suited for the next C-H oxygenation leading to the corresponding ring fused oxazines **3.89**. The oxazines can be reacted further with the nucleophile for the second C-C bond formation. Thus iterative C-H oxygenation and C-C bond formation would allow easy access to the structurally diverse *N*-heterocycles with one or more than one *α*-substitutents. Moreover, diversely substituted *N*-heterocycle containing Betti Bases **3.88** and **3.90** and ring fused oxazines **3.89**, which are difficult to access directly from the corresponding substituted amine, can be obtained in the synthetic sequence. The method would be more viable in the context of step economy and atom economy as it avoids repetitive removal of *N*-substituents and its installation which is required for di-functionalization of *N*-heterocycles (**Scheme 4**, eq. 23).[32] Oxazines were prepared following the method described in Chapter 2 and 4. Then the oxazine **3.87a** was treated with different Grignard reagents (RMgBr, R = benzyl-, Ph-, $PhCH_2CH_2$-, isopropyl-, allyl-, vinyl-) to get different mono-functionalized *N*-heterocycles (**3.88a-e**).



(23)

Scheme 4: Synthetic strategy for the iterative difunctionalization of *N*-heterocycles

Betti Bases containing mono-functionalized pyrrolidine were isolated with good to very good yields (**Scheme 5**, eq. 24). Similarly, oxazines derived from piperidine **3.87b**, azepane **3.87c** and morpholine **3.87d** were reacted with suitable Grignard reagents to obtain the desired diarylmethylamine derivatives **3.88f-k** with very good to excellent yields (**Scheme 5**, eq. 24).



(24)

Scheme 5: First C-C bond formation

It was possible to introduce aryl, allyl, branched alkyl and vinyl moieties at the *α*-position of *N*-heterocycles. Seven membered oxazine reacted smoothly with benzylmagnesium chloride

to produce functionalized amine **3.88k** with maximum isolated yield (97%) (**Scheme 5**, eq. 24). Diarylmethylamines **3.88c-e** and **3.88j** bearing mono-functionalized *N*-heterocycles were isolated as the mixture of diastereomers. However, **3.88a-b**, **3.88f-i** and **3.88k** were isolated as the single diastereomer. The relative *syn*- stereochemistry of **3.88b** and **3.88f** were confirmed from the single crystal X-ray diffraction analysis (**Fig 2**). Stereo configurations of others were assigned in analogy. Grignard reagents probably approached through the opposite side of aryl moiety (as shown in **3.88a$_1$**), avoiding steric interaction to provide the observed diastereoselectivity (**Scheme 5**, eq. 24). Relatively bulky Grignard reagents (e.g. PhMgBr, $PhCH_2MgCl$) provided better diastereoselectivity as compared to vinyl or allylmagnesium bromide.

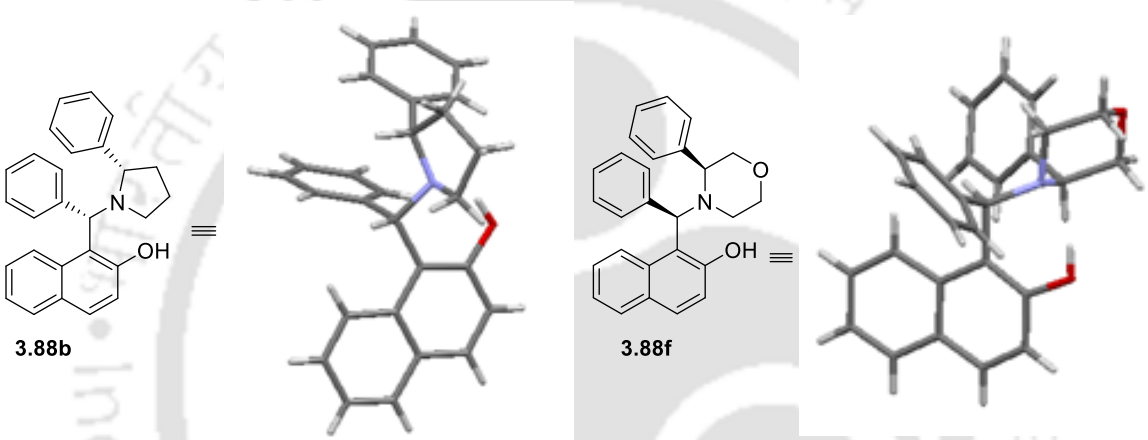
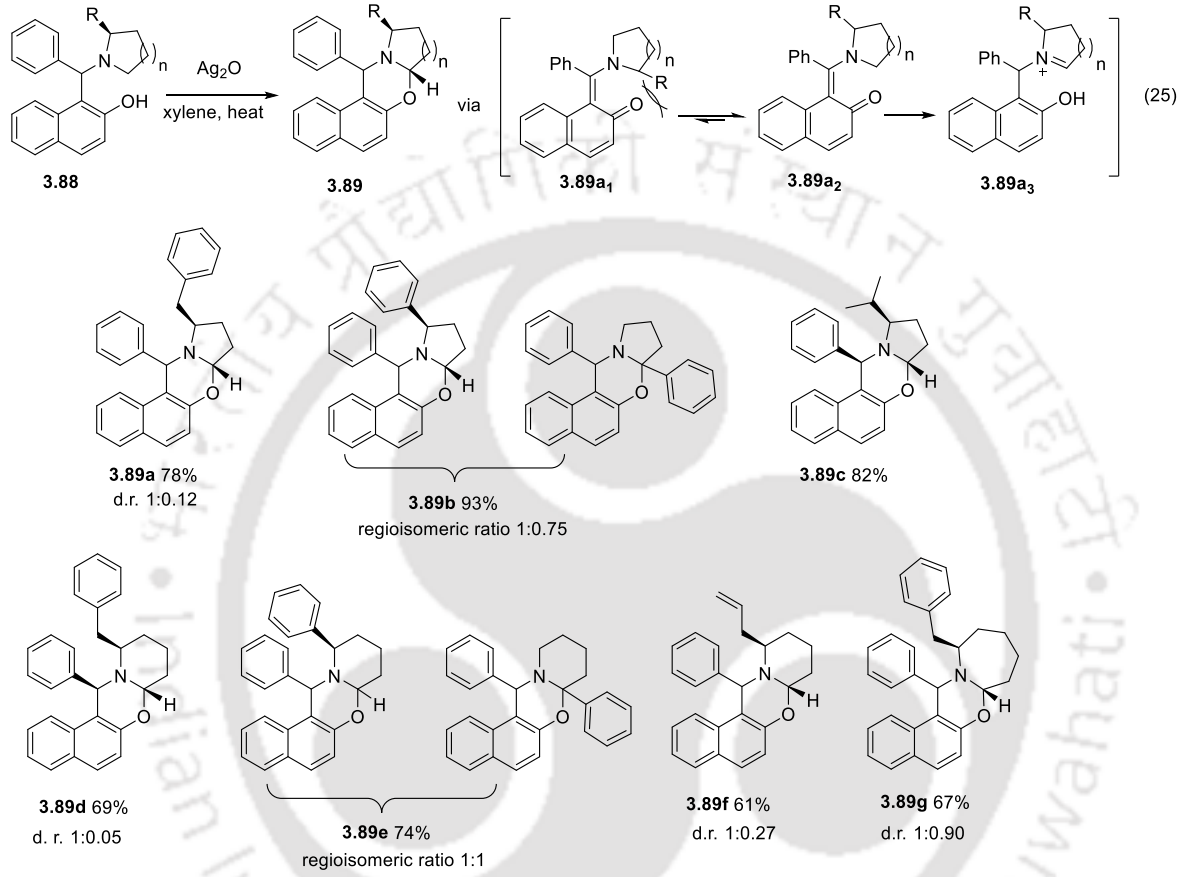


Figure 2: Crystal structure of Betti Bases **3.88b** and **3.88f**

3.6 Second C-H functionalization

The second C-H oxygenation of Betti base **3.88** was investigated next. The reaction of **3.88a** with Ag_2O at 60 ^oC in xylene provided expected product **3.89a** with 78% isolated yield (**Scheme 6**, eq. 25). Room temperature was sufficient to provide desired oxazine **3.89b** from **3.88b** with excellent yield. Oxazines were isolated as mixture of diastereomer. Very good stereoselectivity was observed for the formation of **3.89a** and **3.89c-d**. The relative stereochemistry of major isomer of **3.89c** and **3.89d** were confirmed from X-ray crystallography (**Fig. 3**). The stereochemistry of others was assigned in analogy. The reduction in yields of the corresponding cyclised products **3.89d-f** were observed for piperidine based substrate. Azepane derivative **3.89g** was also isolated with little less yield as compared to the pyrrolidine derivative. In the event of second C-O bond formation, regioisomeric oxazines were formed from aminonaphthol having α-phenyl *N*-heterocycles **3.89b** and **3.89e**. Due to the presence of steric repulsion in **3.89a$_1$**, conformer **3.89a$_2$**

preferentially underwent [1,6]-H transfer to form less substituted iminium ion **3.89a$_3$** (**Scheme 6**, eq. 25). Subsequent diastereoselective cyclization of **3.89a$_3$** occurred, leading to *trans*-substituted *N,O*-acetal **3.89**. However, mixtures of regio-isomers were obtained for **3.89b** and **3.89e** probably due to isomerization of **3.89a$_3$** (if R = Ph) to more stable carbocation adjacent to the phenyl group.



Scheme 6: Second C-H oxygenation of aminonaphthols

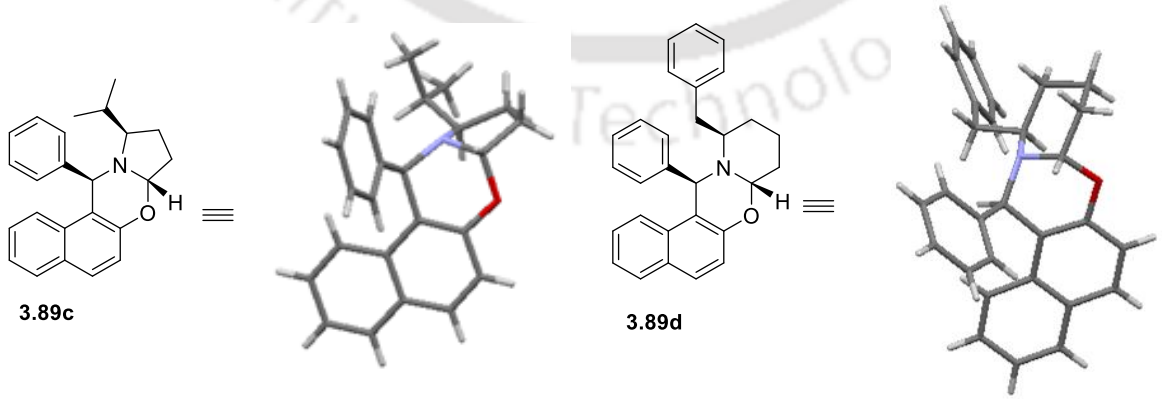
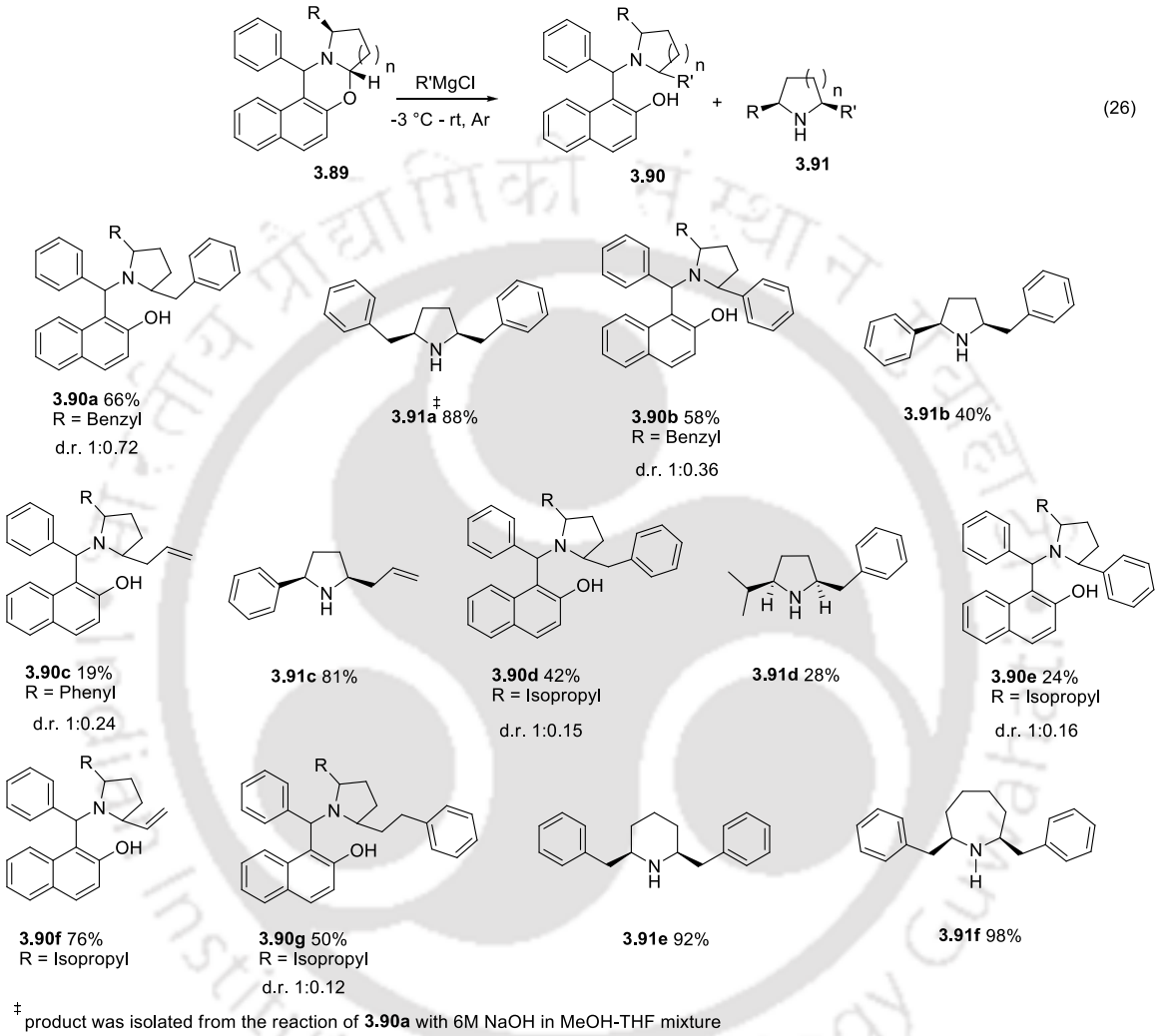


Figure 3: Crystal structure of oxazines **3.89c** and **3.89d**

3.7 Second C-C bond formation

Studies on second C-C bond formation was carried out by employing mono-functionalized oxazine **3.89** reacting with various Grignard reagents (RMgX, R = vinyl-, Ph-, benzyl-, $PhCH_2CH_2$-). Nucleophilic addition of Grignard reagents to *N*,*O*-acetal **3.89** yielded a set of 2,5-difunctionalized products **3.90a-g** in good yields (**Scheme 7**, eq. 26).

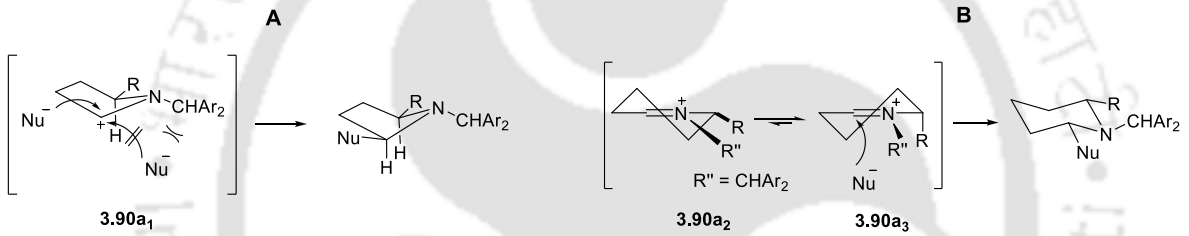


Scheme 7: Isolation of difunctionalized *N*-heterocycles

N-debenzylation was achieved during the column chromatography to isolate the corresponding 2,5-disubstituted pyrrolidines with moderate to good yield along with the *N*-substituted products. Although, *N*-substituted products were isolated as an inseparable mixture of diastereomers, 2,5 disubstituted secondary amines were isolated as single *syn*-isomer after removal of *N*-substituents. For analytical purpose the cleavage of **3.90a** was performed to isolated **3.91a**. However, compounds **3.91b-d** were isolated during the alumina column chromatographic separation of the corresponding diarylmethylamines

3.90b-d. In a similar way, piperidine and azepane based *N*,*O*- acetals were also reacted with the Grignard reagents. Interestingly, the only corresponding difunctionalized piperidine **3.91e** and azepane derivative **3.91f** were isolated with excellent yield and *syn*-selectivity. The relative stereochemistry of **3.91a**, **3.91c** and **3.91e** were confirmed by comparing the NMR-data of reported compound.[28,35,36] Relative geometry of other difunctionalized secondary amines were assigned in analogy (**Scheme 7**, eq. 26).

In the second C-C bond formation step, the addition of nucleophile favoured to approach from the less hindered site of **3.90a$_1$** where –$CHAr_2$ group prefers to remain in the opposite side of R- to avoid steric interaction (**Scheme 8**, **A**).[37] The observed diastereoselectivity in the second nucleophilic addition to piperidine based substrate can be rationalized through an axial approach of the nucleophile to the half-chair-like conformation of **3.90a$_3$**, that might be favoured as compared to its ring flipped isomer **3.90a$_2$** having substantial amount of $A^{1,2}$ strain (**Scheme 8**, **B**).[38]

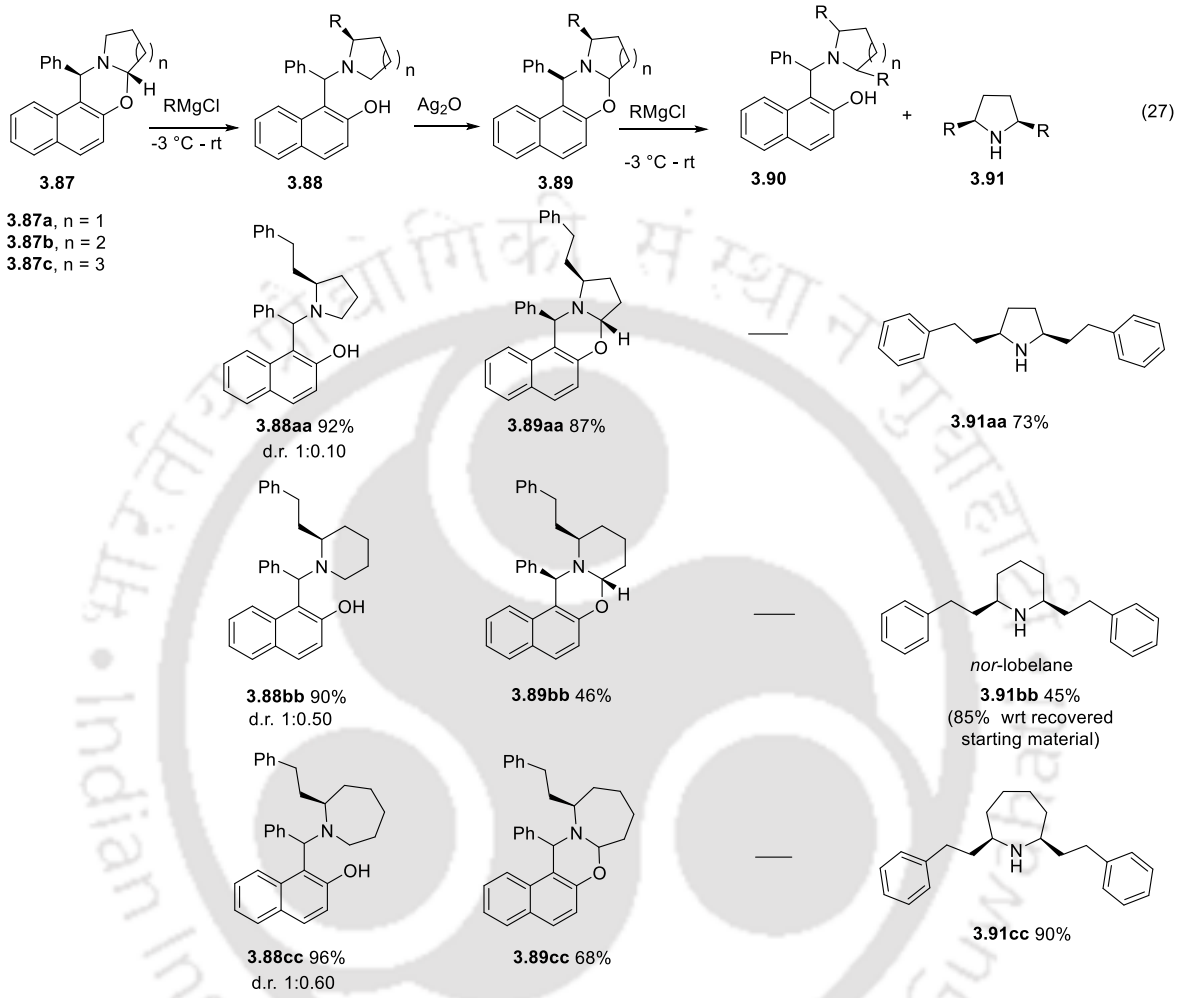


Scheme 8: Plausible approach of nucleophile for *syn*-selectivity

3.8 Preparation of *nor*-lobelane and its analogues

This novel iterative difunctionalization strategy was applied for the total synthesis of *nor*-lobelane. *nor*-Lobelane, an analogue of lobelane, is a neuroactive alkaloid isolated from *Lobelia inflata*. The successive C-H oxygenation and addition of $PhCH_2CH_2MgBr$ to the *N*,*O*- acetal **3.87a-c**, followed by removal of *N*-substituent would lead to the *nor*-lobelane and and its derivatives **3.91aa-cc**. Accordingly, oxazine **3.87b** (n = 2) was reacted with phenethylmagnesium chloride followed by Ag_2O-mediated second C-H oxygenation of naphthol derivative **3.88b** provided 46% of cyclised product **3.89bb**. Further, the crude oxazine treated with phenethylmagnesium chloride to obtained the *nor*-lobelane **3.91bb (**45%) along with unreacted staring material **3.89bb** (48%). The spectroscopic data of **3.91bb** was in agreement with the reported values.[39] Similarly, this method was also successful for the synthesis of five and seven membered analogues (**3.91aa** and **3.91cc**) of *nor*-lobalane derivatives with very good yields (**Scheme 9**, eq. 27).

The complex ^{1}H NMR and ^{13}C NMR spectra were found for **3.88a-k**, **3.88aa-cc** and **3.90a-g** probably due to restricted rotation of the substituted *N*-heterocycle moiety and or restricted inversion of the nitrogen center.[29,40] The diastereoselectivity of the compounds were determined by ^{1}H NMR.



Scheme 9: Syntheses of *nor*-lobalane derivative and its analogues

3.9 Summary

In summary, an efficient and practical method for the synthesis of structurally diverse *syn*-2,5 disubstituted *N*-heterocycles was developed. The two substituents at the *α*-position of the *N*-heterocycles could be varied easily by the choice of appropriate Grignard reagents. The synthetic potential of this sequential strategy was specifically demonstrated by the efficient synthesis of the neuroactive natural product *nor*-lobelane and its derivatives.

References

[1] a) Fodor, G. B.; Colasanti, B. in *Alkaloids: Chemical and Biological Perspectives*, ed. W. W. Pelletier, John Wiley and Sons, New York, **1985**, vol. 3, pp. 57; b) Schneider, M. J. in *Alkaloids: Chemical and Biological Perspectives*, ed. W. W. Pelletier, Elsevier, New York, **1996**, vol. 10, pp. 247; c) Daly, J. W.; Garraffo, H. M.; Spande, T. F. in *Alkaloids: Chemical and Biological Perspectives*, ed. W. W. Pelletier, Elsevier, New York, **1999**,Vol. 13, pp. 92; d) Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation, Reactivity and Synthetic Applications of Piperidine and its Derivatives*, Elsevier: Amsterdam, **1991**; *e*) Struntz, G. M.; Findlay, J. A. in *The Alkaloids, vol. 26*, ed. A. Brossi, Academic, New York, **1985**, pp. 89.

[2] Pichon, M.; Figadère, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927.

[3] Creighton, W. S. *Bull. Mus. Comp. Zool.* **1950**, *1*, 104

[4] Bacos, D.; Basselier, J. J.; Celerler, J. P.; Lange, C.; Marx, E.; Lhommet, G.; Escoubas, P.; Lemaire, M.; Clement, J. L. *Tetrahedron Lett.* **1988**, *29*, 3061.

[5] Clement, J. L.; Lemaire, M.; Lange, C.; Lhommet, G.; Celerier, J. P.; Basselier, J. J.; Cassier, P. *Fr. Appl.* 84/6980.

[6] Ronzani, N.; Lajat, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1131.

[7] Massiot, G.; Delaude, C. "*The Alkaloids*", Brossi, A. Ed. Academic Press, New-York, **1986**, *27*, 269.

[8] a) Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharma*. **2002**, 63, 89; b) Vartak, A. P.; Nickell, J. R.; Chagkutip, J.; Dwoskin, L. P.; Crooks, P. A. *J. Med. Chem.* **2009**, *52*, 7878.

[9] Miller, D. K.; Crooks, P. A.; Zheng, G.; Grinevich, V. P.; Norrholm, S. D.; Dwoskin , L. P. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 1035,

[10] Beckmann, S. J.; Siripurapu, K. B.; Nickell, J. R.; Horton, D. B.; Denehy, E. D.; Vartak, A.; Crooks, P. A.; Dwoskin, L. P.; Bardo, M. T. *J. Pharmacol. Exp. Ther.* **2010**, *335*, 841.

[11] a) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Takahashi, H. *Heterocycles* **1997**, *46*, 385; b) Pache, S.; Botuha, C.; Franz, R.; Kündig, E. P. *Helv. Chim. Acta* **2000**, *83*, 2436.

[12] Powell, B. F.; Reichenthal, J.; Overberger, C. G.; Anselme, J. P. *J. Heterocycl. Chem.* **1980**, *17*, 219.

[13] Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Chem. Commun*. **1994**, 455.

[14] Boeglin, D.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Eur. J. Org. Chem.* **2003**, 3139.

[15] Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1434.

[16] Carson, C. A.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 8242.

[17] Takasu, K.; Shindoh, N.; Tokuyama, H.; Iharay, M. *Tetrahedron* **2006**, *62*, 11900.

[18] Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc*. **2006**, *128*, 12646.

[19] Takahata, H.; Saito, Y.; Ichinose, M. *Org. Biomol. Chem.* **2006**, *4*, 1587.

[20] Fustero, S.; Jimenez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700.

[21] Szolcsányi, P.; Gracza, T.; Špánik, I. *Tetrahedron Lett.* **2008**, *49*, 1357.

[22] Davis, F. A.; Zhang, J.; Qiu, H.; Wu, Y. *Org. Lett*. **2008**, *10*, 1433.

[23] Csatayova, K.; Španik, I.; Ďurišova, V.; Szolcsanyi, P. *Tetrahedron Lett.* **2010**, *51*, 6611.

[24] Radha Krishna, P.; Reddy, B. K. *Tetrahedron: Asymmetry* **2013**, *24*, 758.

[25] Xu, F.; Chung, J. Y. L.; Moore, J. C.; Liu, Z.; Yoshikawa, N.; Hoerrner, R. S.; Lee, J.; Royzen, M.; Cleator, E.; Gibson, A. G.; Dunn, R.; Maloney, K. M.; Alam, M.; Goodyear, A.; Lynch, J.; Yasuda, N.; Devine, P. N. *Org. Lett*. **2013**, *15*, 1342.
[26] Hussaini, S. R.; Moloney, M. G. *Org. Biomol. Chem.*, **2006**, *4*, 2600.
[27] Toumieux, S.; Compain, P. Martin, O. R. *J. Org. Chem.* **2008**, *73*, 2155.
[28] Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6509.
[29] Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897.
[30] Vartak, A. P.; Nickell, J. R.; Chagkutip, J.; Dwoskin, L. P.; Crooks, P. A. *J. Med. Chem*. **2009**, *52*, 7878.
[31] Cheng, G.; Wang, X.; Zhu, R.; Shao, C.; Xu, J.; Hu, Y. *J. Org. Chem*. **2011**, *76*, 2694.
[32] Cheng, Y.-F.; Rong, H.-J.; Yi, C.-B.; Yao, J.-J.; Qu, J. *Org. Lett*. **2015**, *17*, 4758.
[33] Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun.* **2014**, *50*, 332.
[34] Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv.* **2014**, *4*, 46214.
[35] Fraser, R. R.; Passannanti, S. *Synthesis* **1976**, *8*, 540.
[36] Bubnov, Y. N.; Klimkina, E. V.; Lavrinovich, L. I.; Zykov, A. Y.; Ignatenko, A. V. *Russ. Chem. Bull*. **1999**, *48*, 1696.
[37] Shono, T.; Fujita, T.; Matsumura, Y. *Chem. Lett*. **1991**, 81.
[38] Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.
[39] Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Norrholm, S. D.; Crooks, P. A. *J. Med. Chem.* **2005**, *48*, 5551.
[40] Huang, P.-J. J.; Youssef, D.; Cameron, T. S.; Jha, A. *Arkivoc* **2008**, 165.

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

Chapter 4

Metal and Oxidant Free Direct C-H Aryloxylation of *N*-Heterocycles

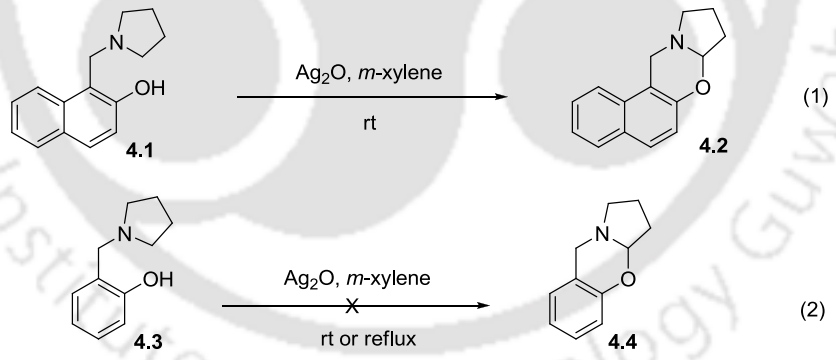
भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

4.1 Introduction

Literature studies presented in Chapter 2 showed that the direct α-functionalization of C(sp^3)-H bond of *N*-heterocycles has been achieved either using transition metal catalysts with/without co-oxidants or employing only oxidant. Iminium ion formed in turn reacted with various nucleophiles providing functionalized amines.[1] Among the different strategies developed to accomplish the direct oxygenation of amine α-C−H bonds, mostly oxidant[2] and metal mediated reactions were employed with amines or protected amines (carbamates, amidines, *N*-aryl amines etc.) to obtain oxazine. Oxazines are important compounds both in chemistry and biology as described in chapter 2 and 3. Thus, the development of a method which works well under metal and oxidant free condition is desirable.

4.2 Plan for metal and oxidant free C-H oxygenation

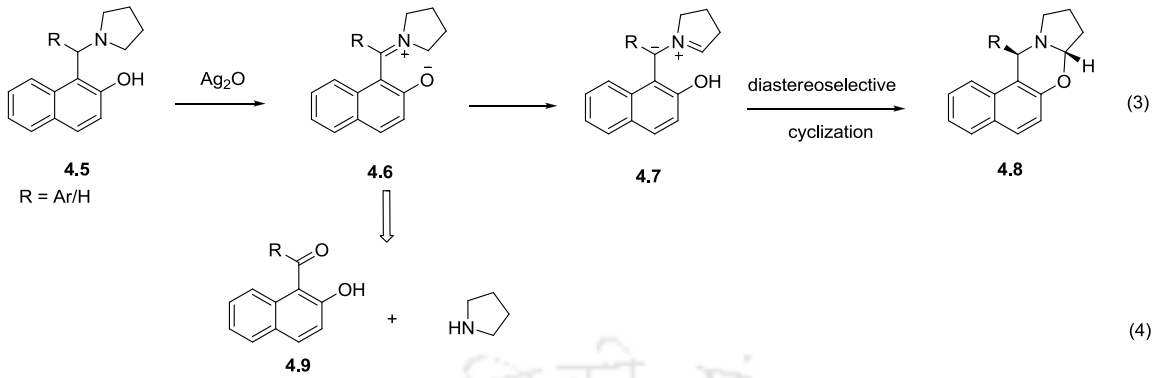
During the studies on silver promoted oxidative cyclization of Betti bases (Chapter 2), it was observed that the 2-hydroxynaphthalenylmethyl pyrrolidine **4.1** provided the desired oxazine **4.2** (**Scheme 1**, eq. 1). On the other hand, corresponding 2-hydroxyphenylmethyl pyrrolidine **4.3** did not produce expected oxazine **4.4** under the same reaction conditions (**Scheme 1**, eq. 2).



Scheme 1: Formation of oxazine **4.2**

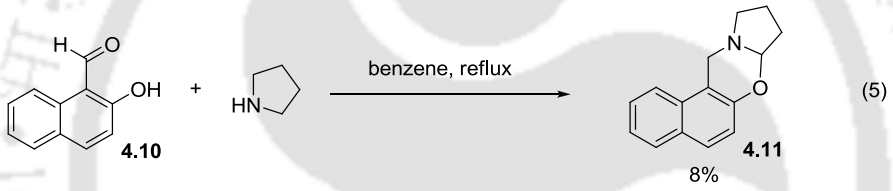
It was anticipated that, in contrast to salicylaldehyde based substrate **4.3**, substituents at 5 and 6 position in naphthyl based substrate probably helps to promote the cyclization process. It was believed that in the silver assisted reaction, iminium ion **4.6** has mediated the cyclization reaction through zwitter ion **4.7** producing desired oxazine **4.8** (**Scheme 2**, eq. 3). It was thought that the intermediate **4.6** can also be formed from the reaction of simple carbonyl **4.9** and secondary amine under metal and oxidant free reaction conditions (**Scheme 2**, eq. 4). Thus, in this way, it would be possible to obtain desired oxazine **4.8** avoiding use

of metallic reagent and hazardous oxidants.



Scheme 2: Hypothesis for metal and oxidant free C-H oxygenation

To test the hypothesis, 2-hydroxy naphthaldehyde was reacted with pyrrolidine under reflux in benzene. Satisfactorily, the formation of desired compound **4.11** was observed with 8% yield (**Scheme 3**, eq. 5).



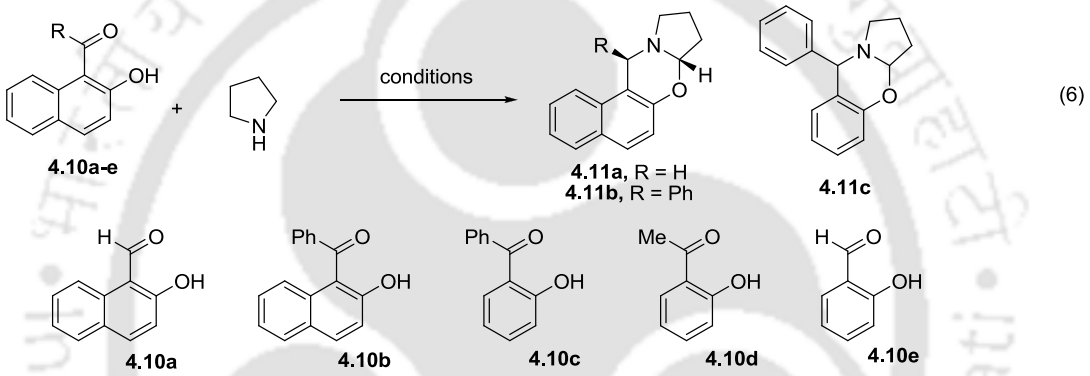
Scheme 3: Reaction of 2-hydroxy naphthaldehyde with pyrrolidine

4.3 Optimization of reaction condition

Different reaction conditions were screened to increase the yield of the reaction (**Table 1**). The same reaction was performed under microwave irradiation using 1 equivalent of 2-hydroxy naphthaldehyde **4.10** and 2 equivalent of pyrrolidine at 100 ^{o}C for 10 minutes to obtain desired oxazine with 38% isolated yield. Increasing in reaction time to 20 min enhanced the yield of desired product **4.11** slightly to 42% (entry 3). Molecular sieves and $MgSO_4$ were added to sequester the water released during the condensation reaction but the yield of the product did not improve. Polar protic solvent ethanol and high reaction temperature (170 ^{o}C) in xylene were also not able to increase the yield. Increasing relative stoichiometry of starting ketone **4.10** (2.5 equivalent) with respect to amine increased the isolated yield substantially to 72% of a reaction carried out in toluene at 130 ^{o}C under microwave irradiation. The presence of basic and acidic additives such as KOAc and PTSA, respectively, lowered the formation of desired compound under the same reaction conditions. The use of triethylamine did not affect the yield of the product. The best result for the C-H oxygenation of pyrrolidine was obtained from a reaction of 1.2 equivalent of phenyl 2-

hydroxynaphthyl ketone **4.10b** with 1 equivalent of pyrrolidine in toluene at 130 °C. Like in silver mediated reaction, the desired oxazine **4.11b** was isolated as single diastereoisomer with 86% yield (entry 14). Increasing the reaction temperature to 145 °C, the yield was further increased to 96%. The identical reaction under reflux condition provided lower yield (49%). On the other hand, 2-hydroxybenzophenone **4.10c** provided only 43% of the C-H functionalized product **4.11c**. However, the product was isolated as a mixture (1:3) of diastreoisomers. 2-Hydroxyacetophenone **4.10d** and salicylaldehyde **4.10e** failed to provide corresponding functionalized product under the same reaction conditions.

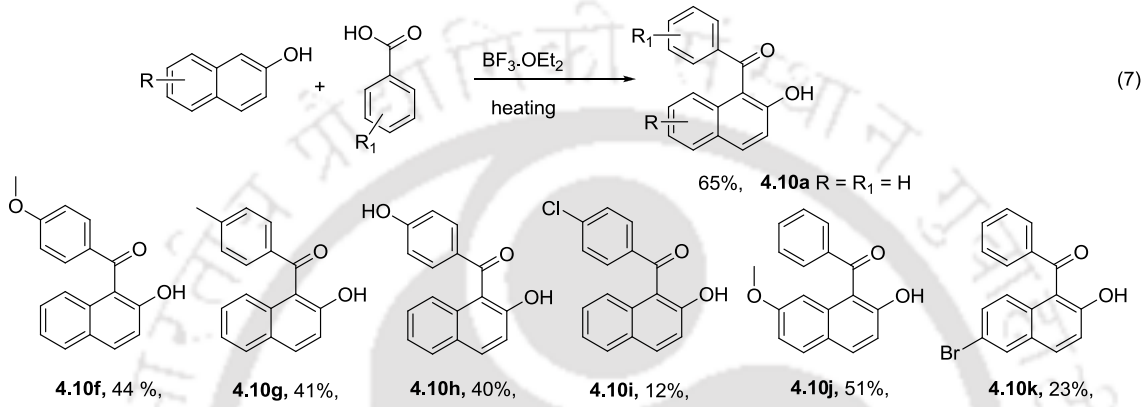
Table 1: Screening of reaction conditions and carbonyl compounds for direct C-H oxygenation



Entry	Carbonyl compound (eq.)	Solvent	Temperature	Time	Additives	Isolated yield (%)
1	**4.10a** (0.5)	Benzene	Reflux	12 h	--	8
2	**4.10a** (0.5)	Benzene	µw, 100 °C	10 min	--	38
3	**4.10a** (0.5)	Benzene	µw, 100 °C	20 min	--	42
4	**4.10a** (0.5)	Benzene	µw, 100 °C	20 min	4Å MS	25
5	**4.10a** (0.5)	Benzene	µw, 100 °C	20 min	$MgSO_4$	15
6	**4.10a** (0.3)	Ethanol	µw, 100 °C	20 min	--	15
7	**4.10a** (0.5)	Xylene	µw, 170 °C	20 min	4Å MS	40
8	**4.10a** (2.5)	Benzene	µw, 100 °C	20 min	--	65
9	**4.10a** (2.5)	Toluene	µw, 130 °C	20 min	--	72
10	**4.10a** (2.5)	Toluene	µw, 130 °C	40 min	--	72
11	**4.10a** (2.5)	Toluene	µw, 130 °C	20 min	KOAc	39
12	**4.10a** (2.5)	Toluene	µw, 130 °C	20 min	PTSA	15
13	**4.10a** (2.5)	Toluene	µw, 130 °C	20 min	Et_3N	70
14	**4.10b** (1.2)	Toluene	µw, 130 °C	20 min	--	86
15	**4.10b** (1.2)	Toluene	µw, 145 °C	20 min	--	96 (**4.11b**)
16	**4.10b** (1.2)	Toluene	reflux	24 h	--	49
17	**4.10c** (1.2)	Toluene	µw, 145 °C	20 min	--	43 (**4.11c**)
18	**4.10d** (1.0)	Toluene	µw, 145 °C	20 min	--	--
19	**4.10e** (1.0)	Xylene	µw, 130 °C	20 min	--	--

4.4 Preparation of hydroxy ketone derivatives

To examine the scope of the reaction, various α-hydroxy ketone were prepared according to literature procedure (**Scheme 4**).[3] Friedel Crafts benzoylation of β-naphthol with benzoic acid in presence of BF_3-Et_2O under heating condition gave corresponding naphthophenone with good yield (**4.10a**). 4-Methoxy, 4-methyl, 4-hydroxy benzoic acids gave moderate yields (**4.10f-h**). 7-Methoxy β-naphthol also provided desired hydroxy ketone derivatives. However, low yield was observed for **4.10i** and **4.10k** (**Scheme 4**, eq. 7).

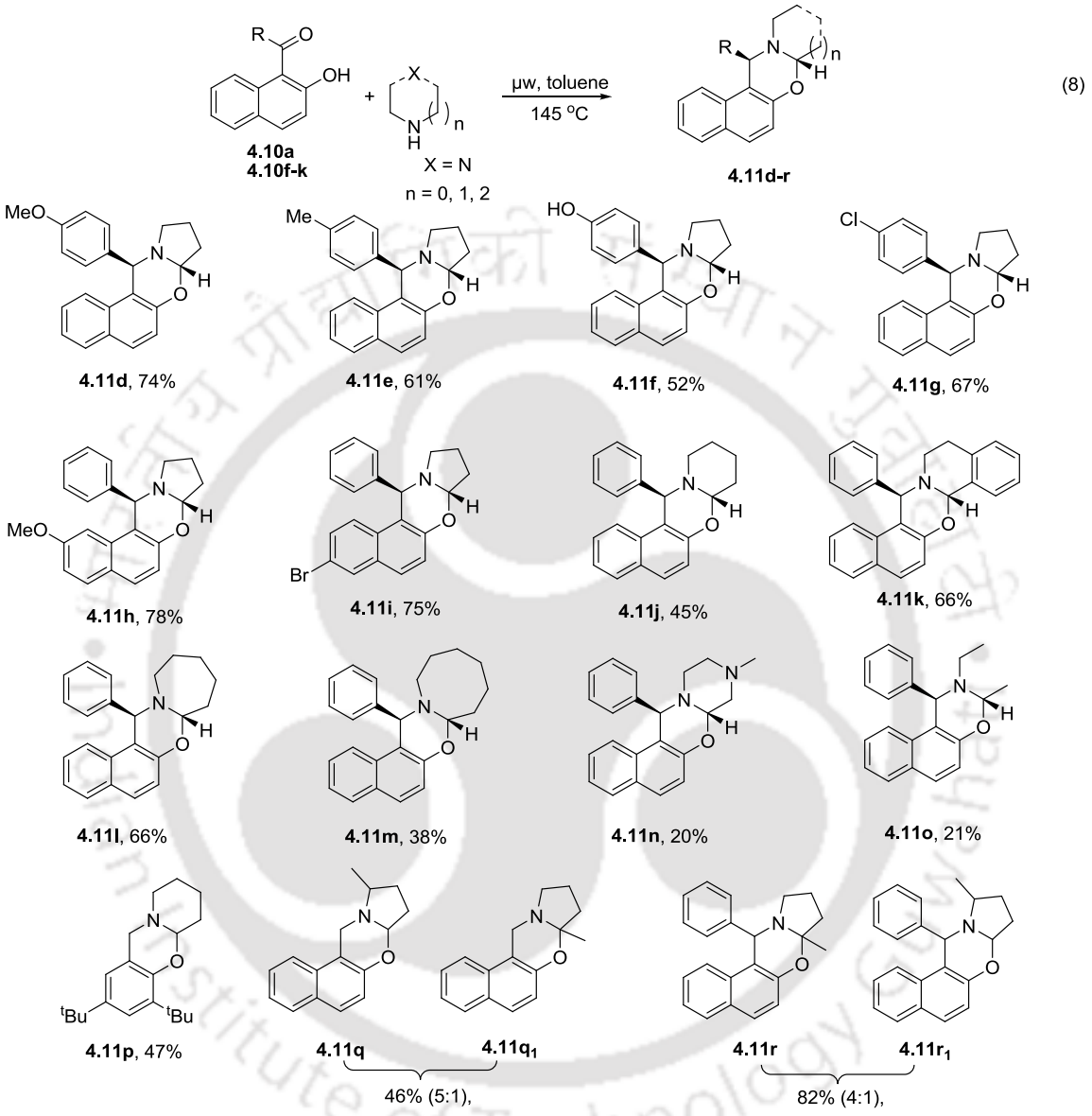


(7)

Scheme 4: Preparation of various hydroxy ketones

Various 2-hydroxy naphthyl 1-aryl ketone **4.10a**, **4.10f-k** were reacted under optimized condition for the direct α-C-H oxygenation of pyrrolidine. Substituted aryl and napthyl moiety in hydroxyl ketone **4.10j-k** served as good substrates for C-H functionalization of pyrrolidine (**4.11d-e**, **4.11g-i**). Oxazines were isolated as a single diastereomer with very good yields. For the case of oxazine **4.11f** little less yield (52%) was observed probably because the less solubility of starting ketone **4.10h** in toluene. Other cyclic amines like piperidine, tetrahydroisoquinoline, azepane and eight membered cyclic secondary amines were also oxygenated, producing corresponding oxazines (**4.11j**-**m**) under this metal and oxidant free reaction conditions (**Scheme 5**, eq. 8). Comparatively lower yields for oxazines **4.11n** and **4.11o** were observed through functionalization of *N*-methyl piperizine and diethyl amine respectively. 3,5-Ditertiary butyl salicylaldehyde was also successfully reacted with piperidine to give the cyclized product **4.11p** (**Scheme 5**, eq. 8). 2-substituted pyrrolidine was also utilized for the C-H aryloxylation. In this regard, 2-methyl pyrrolidine and 2-hydroxy naphthaldehyde were reacted under the same condition. The expected mixture of oxazines **4.11q** and **4.11q$_1$** were isolated as 46% yield with 5:1 regio-selectivity. The same substituted amine gave the mixture of cyclized products **4.11r** and **4.11r$_1$** (4:1) with very good yield (82%) when reacted with ketone **4.10a**. The mixtures of regio-isomers were formed for both

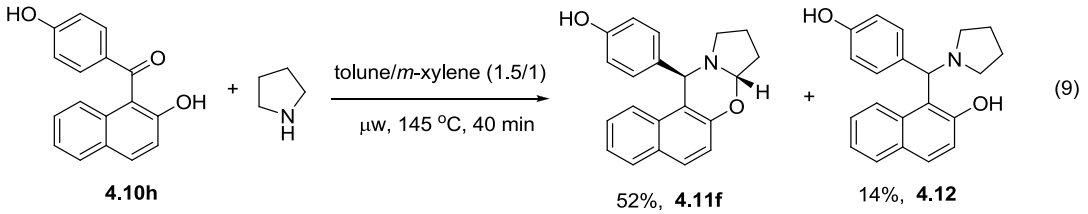
the cases with reverse regio-selectivity (**Scheme 5**). The existence of possible steric hindrance arising from the presence of a substituent at the benzylic position in **4.11r** was probably the reason for the reverse in regio-selectivity.



Scheme 5: Metal and oxidant free direct C-H aryloxylation of *N*-heterocycles

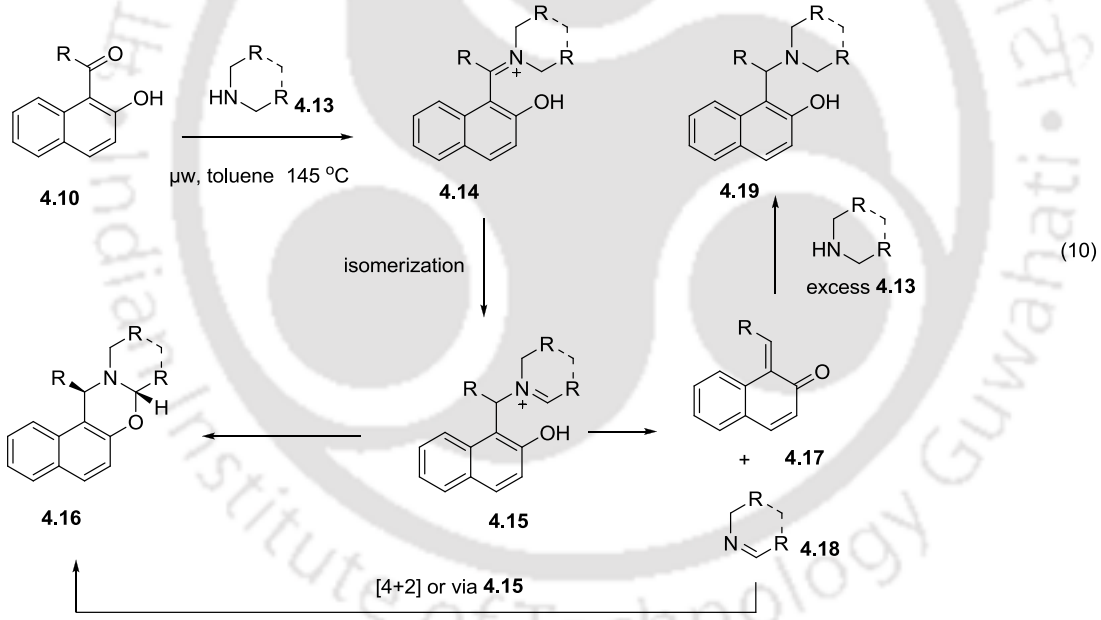
4.5 Mechanistic proposal for oxazine formation

During the course of the optimization, we have isolated cyclic oxazine **4.11f** (52%) along with undesired non-cyclic *N*-benzylated product **4.12** with 14% yield (**Scheme 6**, eq. 9).



Scheme 6: Formation of oxazine and *N*-benzylated pyrrolidine

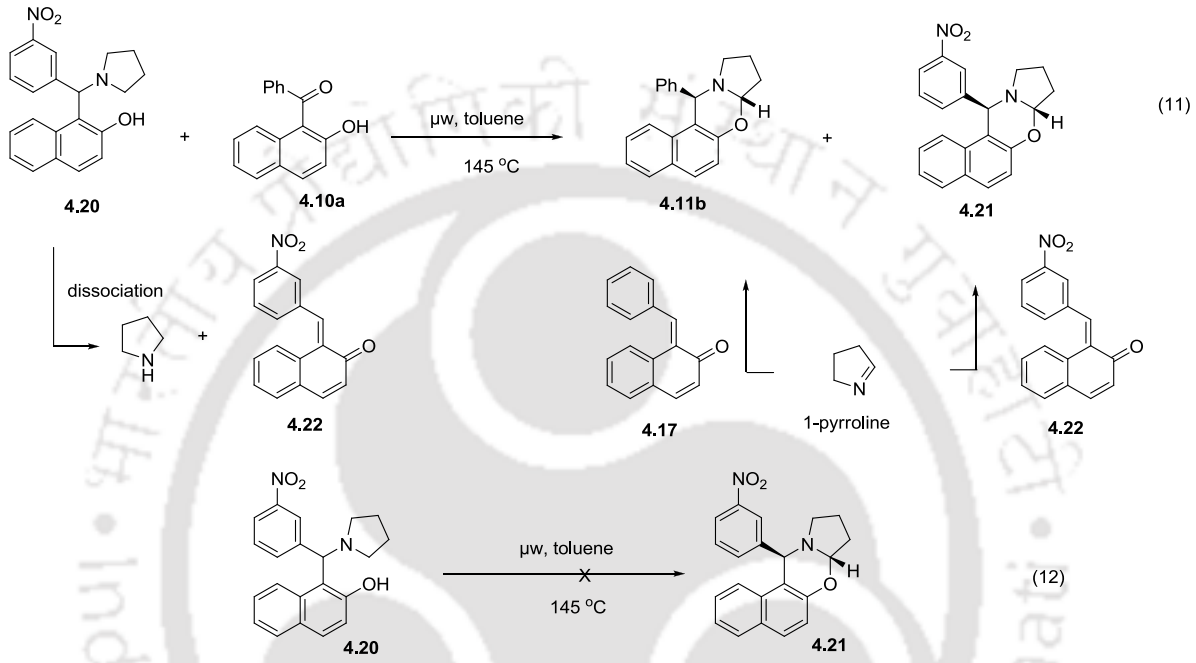
It was proposed that first carbonyl compound **4.10** was reacted with secondary amine **4.13** to produce iminium ion **4.14**. Iminium ion **4.14** then isomerized to **4.15**. The iminium ion **4.15** could either intra-molecularly cyclized to oxazine **4.16** or could be dissociated to generate quinone methide **4.17.** Subsequently quinone methide **4.17** could also react with cyclic imine **4.18** either by [4+2]-cycloaddition or via **4.15** to give the corresponding oxazine **4.16**. In the presence of excess amine **4.13** the quinone methide could produce the *N*-benzylated product **4.19** (**Scheme 7**, eq. 10)



Scheme 7. Mechanistic proposal

To better understand the reaction pathway, a reaction of hydroxy ketone **4.10a** with diarylmethylamine **4.20** was performed in toluene at 145 °C under microwave irradiation for 20 min (**Scheme 8**, eq. 11). Two oxazines **4.11b** and **4.21** were isolated. However, on heating diarylmethylamine **4.20** under the same reaction condition did not yield the cyclic compound **4.21** (**Scheme 8**, eq. 12). This results of forming cross products suggested dissociation of **4.20** which occurred under the thermal condition producing pyrrolidine and quinone methide **4.22**. Then pyrrolidine reacted with ketone **4.10a** to form corresponding iminium ion related to **4.15**

which subsequently dissociated to give quinone methide **4.17** and 1-pyrroline as described in **Scheme 8**. 1-pyrroline then partitioned during its subsequent reactions with quinone methides **4.17** and **4.22** to give corresponding oxazines **4.11a** and **4.21** respectively. The observation supported the mechanistic pathway involving *o*-quinone methide intermediate. During the preparation of the manuscript, a similar reaction of *N*-heterocycles was reported by Seidel and co-workers.[4]



Scheme 8: Control experiments

4.6 Summary

Either multisteps protocols via *N*-cycloalkylation or metal and oxidant mediated methods were commonly used to prepare the ring fused oxazines. A novel microwave assisted metal and oxidant free alpha oxygenation of secondary aliphatic amines has been developed.[5] This methodology was elegant and applicable to various secondary amines. Mechanistic studies suggested that the reaction proceeded via quinone methide intermediate.

References

[1] a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069; b) Murahashi, S.-I.; Imada, Y. in *Transition Metals for Organic Synthesis*, Vol. 2, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 497; c) Shu, X. Z.; Xia, X. F.; Yang, Y. F.; Ji, K. G.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2009**, *74*, 7464.

[2] Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 74.
[3] Kumar, A.; Ahmed, P.; Maurya, R. A.; Singh, A. B.; Srivastava, A. K. *Eur. J. Med. Chem.* **2009**, *44*, 109.
[4] Richers, M. T.; Breugst, M.; Platonova, A. Yu.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, *136*, 6123.
[5] Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv.* **2014**, *4*, 46214.

Chapter 5

Syntheses of Conjugated Aldehydes, Chromenes, Chromene 2-ol Through Direct β-C(sp^3)-H Functionalization of Aliphatic Amines

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

5.1 Introduction

The *β*-functionalized aliphatic amines are very important in synthetic organic chemistry as well as in medicinal chemistry. Various natural and synthetic biologically active molecules are built on *β*-functionalized *N*-heterocycles.[1] Lanopylin B1 and their derivatives are examples of natural products having *α,β*-unsaturated pyrroline unit which acts as human lanosterol synthase inhibitor (**Fig. 1**).[2] Moreover, *α,β*-unsaturated imines are of particular interest because they can participate in different reactions producing various functionalized amines. Small molecules containing *α,β*-unsaturated carbonyl groups show versatile biological activities such as antitumor, anti-inflammatory and antimalarial properties.[3] Extensive use of *α,β*-unsaturated aldehydes are found in fragnance and cosmetic industry. Specially, 2-alkyl substituted cinnamaldehyde derivatives find direct application in perfume and cosmetic industry. Citral, an *α,β* unsaturated aldehyde wgich is present in the oils of several plants, is used as flavouring agent (**Fig. 1**). Jasminaldehyde, another example of *α,β* unsaturated aldehyde, is a traditional perfumery product (**Fig. 1**).[4]

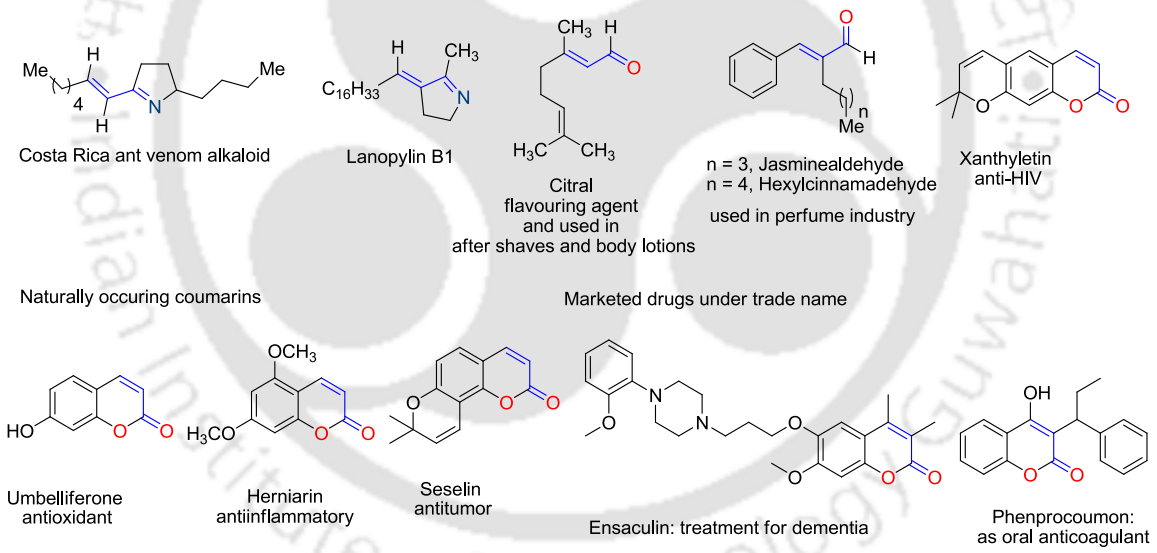


Figure 1: Some important imines, unsaturated aldehydes and chromene derivatives.

In addition, they are key intermediates of various biologically important compounds such as flavanones derivatives.[5] Syntheses of these compounds, primarily via cross-aldol reaction, faces several problems due to the undesired reactions such as polyaldolisation, oligomerisation of the product.[6]

Benzo-4-pyrones and benzopyran-2-ol, which are also known as chromones (coumarin) and chromene-2-ol respectively, are important medicinal pharmacophore that appears in many natural compounds.[7] It is well known that certain natural and synthetic chromene

derivatives exhibit several biological activities such as antitumor, antivascular[8], antimicrobial[9], antioxidant,[10] antifungal,[11] anticoagulant, estrogenic,[12] antiviral,[13] anticancer[14], anti-HIV[15], herbicidal, analgesic and anticonvulsant activities.[16] Lipophilic nature of the benzopyran derivative helps to cross the cell membrane easily causing its antimicrobial activity. Umbelliferone (7-hydroxycoumarin), a naturally occurring coumarin derivative isolated from *Ferula communis*, was found to exhibit significant anticancer effects via the induction of apoptosis, cell cycle arrest and DNA fragmentation in HepG2 cancer cells (**Fig. 1**).[17] Chilin and co-workers have identified the coumarin moiety as an attractive casein kinase 2 (CK2) inhibitor.[18]

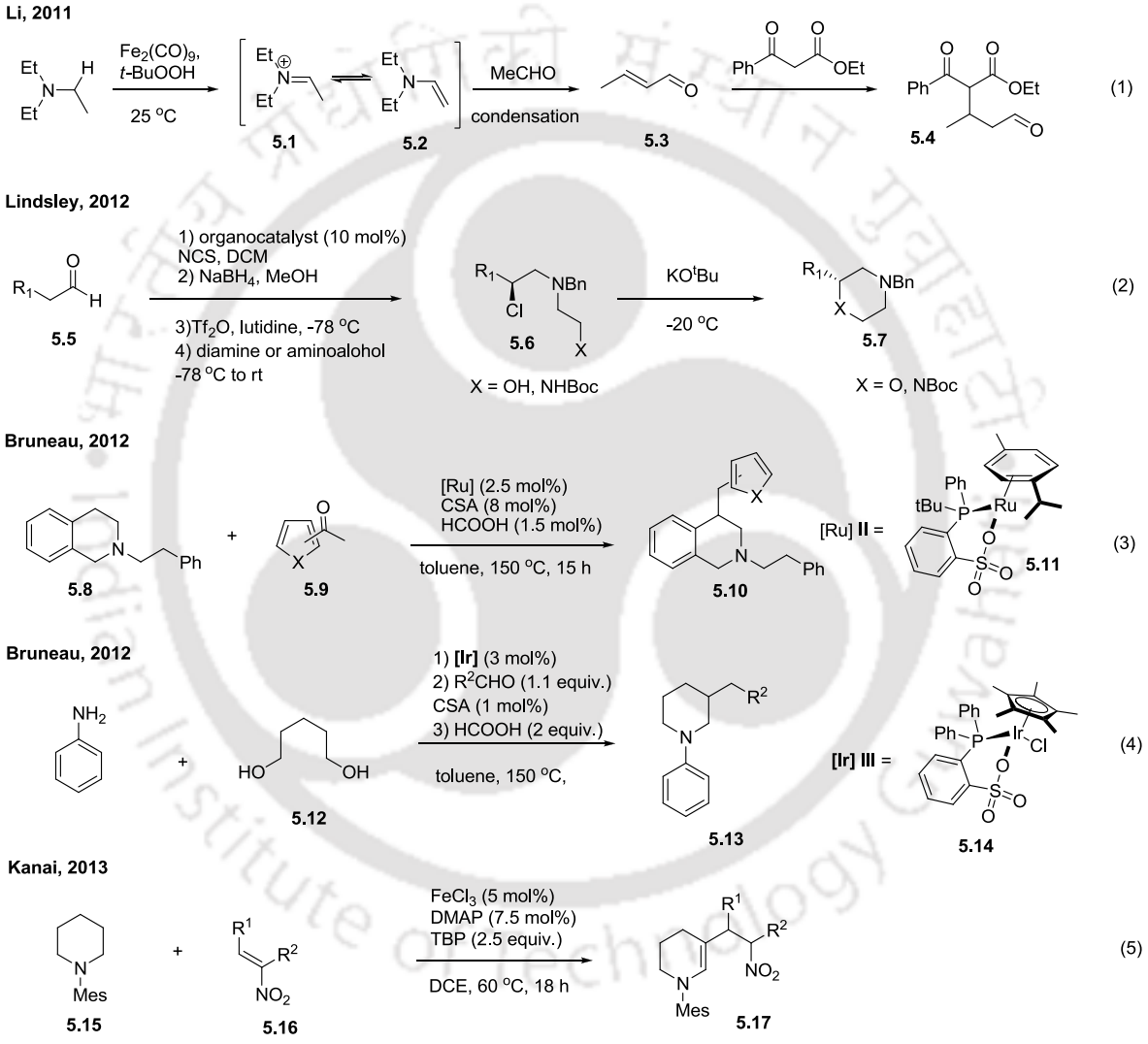
In addition to their medicinal activities, chromene derivatives also play an important role in the production of highly effective fluorescent dyes for synthetic fibers, daylight fluorescent pigments and exhibits skin-photosensitizing activity.[19,20,21] Therefore, there is a need to develop new synthetic route for accessing these molecules with diverse functionality.

5.2 Selected examples of *β*-functionalization of amines

Presence of the amine group provides convenient way for the installation of various functional groups at its *α*-position. Therefore, in the literature, a large number of methodologies for *α*-C-H functionalization of saturated amine has been reported.[22,23] However, the *β*-C(sp^3)-H bond remains inert and thus less facile towards direct functionalization. On the other hand, although several indirect pathways were known for the preparation of *β*-functionalized amine,[24] reports on direct functionalization of more challenging *β*-C(sp^3)-H bonds are only very few.[25] In 2011, Li and co-workers reported the formation of *α,β*-unsaturated aldehydes **5.3** by oxidation of triethylamine with TBHP in presence of iron-catalyst. Subsequently enal **5.3** were utilized for further C-C coupling reactions with 1,3-dicarbonyl compounds to achieve dicarbonyl derivative **5.4** (**Scheme 1**, eq. 1).[26] In 2012, Lindsley and co-workers reported enantioselective synthesis of *β*-functionalized morpholines and piperazines from a common intermediate **5.6**.[24b] Enantioselective chlorination of aldehyde **5.5** followed by amination occurred producing **5.6** which after base-induced cyclization yielded desired *β*-functionalized *N*-heterocycle **5.7** (**Scheme 1**, eq. 2). In 2012, Bruneau and co-workers developed ruthenium-catalyzed direct method for *β*-alkylation of the tetrahydroisoquinoline **5.8** using various heteroaromatic aldehydes **5.9** to produce 4-substituted tetrahydroisoquinoline derivatives **5.11** (**Scheme 1**, eq. 3).[27] In the same year, they reacted aniline, diol **5.12**, and aldehyde to produce *β*-functionalized *N*-arylpiperidines **5.13** in the presence of iridium(III) complex **5.14** via double *N*-alkylation strategy (**Scheme**

1, eq. 4).[28] In 2013, Kanai and co-workers developed an iron-catalyzed direct dehydrogenative *β*-functionalization of cyclic and acyclic amine **5.15** under mild conditions using nitroalkene **5.16** as a coupling partner to produce **5.17** (**Scheme 1**, eq. 5).[29]

It was evident that most of the known methods for direct *β*-C(sp^3)-H functionalization required the use of oxidants, metallic reagent and/or sensitive reaction conditions. The development of a simple method, which excludes the use of hazardous metal and oxidants and can offer more environmentally benign process, was highly desirable.

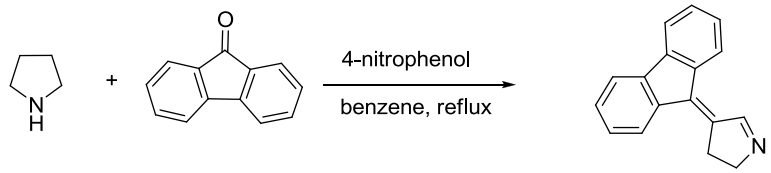


Scheme 1: Syntheses of *β*-functionalized aliphatic amines

5.3 Reaction of aliphatic acyclic amines with aldehydes

During the development of direct *α*-C-H arylation of amine, pyrrolidine was reacted in the presence of 9-fluorenone and *p*-nitrophenol in refluxing benzene. However, it was observed that, instead of desired C-H arylated product, compound **5.18** was formed with 26% yield (eq. 6). It was realized that the reaction would provide the opportunity to achieve direct *β*-C-H

functionalization of aliphatic amines under simple reaction conditions without using metal- or oxidant-based reagents or catalyst.[30] Furthermore, the method will have potential to provide privileged structures in single step without using pre-oxidized or pre-functionalized substrates.



(6)

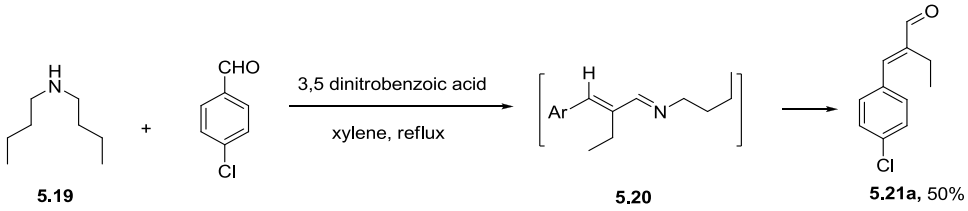
5.18, 26%

Therefore, investigation of the reaction was performed further for acyclic saturated secondary amines as the potential substrates for *β*-C-H functionalization. A reaction of *N*,*N*-dibutylamine **5.19** with *p*-chloro benzaldehyde was performed under the reaction conditions optimized for *N*-heterocycles. However, the homologated unsaturated aldehyde **5.21** was isolated with 50% yield instead of desired unsaturated imine **5.20** (eq. 7). Unsaturated aldehydes were widely used in organic synthesis for the preparation of bioactive natural and unnatural compounds.[31] Specially, 2-alkyl substituted cinnamaldehyde derivatives find direct application in perfume and cosmetic industry.[32] Syntheses of these compounds, primarily via cross-aldol reaction, remained inefficient due to the associated undesired self-condensation and polymerization reaction.[33] For example, cross-aldol reactions with acetaldehyde enolates yielded self-condensation products with aliphatic aldehyde partners.[34] This difficulty can be circumvented with *C*-silated imines[35] but the preparation and purification of these *C*-silated imines are difficult. Wittig,[36] Horner-Emmons,[37] and Peterson type reagents[38] are generally not compatible with base sensitive functional groups and sometimes require additional synthetic steps to generate enals. Methodologies utilizing transmetalation strategy often meets with incompatibility with other functional groups. These complications could be potentially avoided during their syntheses via this operationally simple method utilizing amine as the formal aldol-donor.

As the best yield was observed for *β*-functionalization of aliphatic amines in xylene at reflux temperature, the same solvent was utilized for the transformation.[30] Various reactions were performed changing the conditions like temperature and equivalent of dibutylamine. Amount of additive (3,5-dinitro benzoic acid) also varied for the improvement of yield of desired compound. When 2.5 equivalent of dibutylamine and 1 equivalent of aldehyde was reacted in presence of 0.6 equivalent of additive, 50% of product **5.21a** was isolated as the highest yield. When no additive was added, only 24% of desired product was isolated. Using

of 4 eq. of dibutylamine gave slightly lower yield of target product (43 %) (**Table 1**).

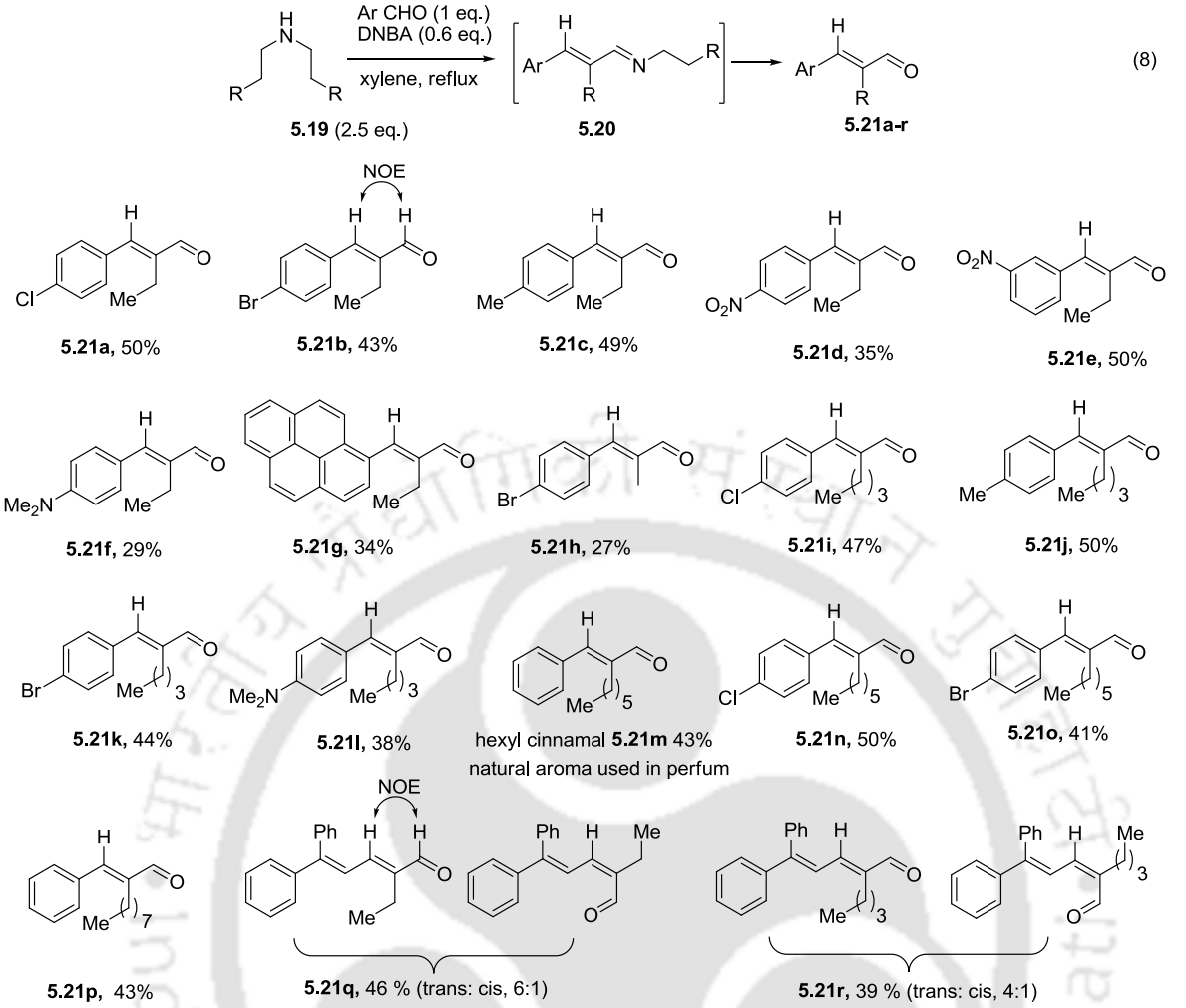
Table 1: Reaction optimization for homologation of aldehydes



5.19 **5.20** **5.21a,** 50% (7)

Entry	Dibutyl amine (equiv.)	Additives (equiv.)	Solvent,Temp	Time (h)	Yield (%)
1	2.5	3,5-$(NO_2)_2PhCO_2H$(0.6)	xylene, 140 °C	26	50
2	1	3,5-$(NO_2)_2PhCO_2H$(0.6)	xylene, 140 °C	26	39
3	2.5	…..	xylene, 140 °C	26	24
4	2.5	3,5-$(NO_2)_2PhCO_2H$ (1)	xylene, 140 °C	26	48
5	2.5	3,5-$(NO_2)_2PhCO_2H$(0.6)	xylene, 140 °C	26	24
6	4.0	3,5-$(NO_2)_2PhCO_2H$(0.6)	xylene, 140 °C	26	43

After having the initial result, it was realized that the reaction will provide the opportunity to achieve direct homologation of aromatic aldehyde from aliphatic amines under simple reaction conditions without using metal-catalyst or oxidant-based reagents. Furthermore, the method will have potential to provide privileged structures in a single step without using pre-oxidized or pre-functionalized substrates. Therefore, the reaction was investigated further for a wide range of substrates. Different dialkylamines were reacted with various aldehydes providing structurally diverse 2-alkylated cinnamaldehyde derivatives **5.21a-r** (**Scheme 2**, eq. 8). Many of them can be considered as potential aroma substances for use in fragrance industry. Particularly, hexyl cinnamal (**5.21m**) is a natural aroma found in essential oil of chamomile and used in perfume. Aldehydes with or without electron donating or electron withdrawing substituent in the aryl moiety were equally efficient in providing corresponding conjugated aldehyde. Electron donating group present in aromatic ring (**5.21a-c**) gave good yield. Aromatic aldehyde containing nitro- and *N*,*N*-dimethyl amine in *para*- position gave lower yield (**5.21d**, **5.21f**). Relatively lower yield of the product **5.21g** (34%) was obtained using anthranaldehyde. Dihexylamine, dioctyl amine and dodecyl amine were utilized and gave good yields when reacted with different aromatic aldehydes (**5.21i-o**). Hexyl cinnamal (**5.21m**) which is used as a natural aroma in perfume industry was successfully prepared by the reaction of benzaldehyde and dioctylamine.



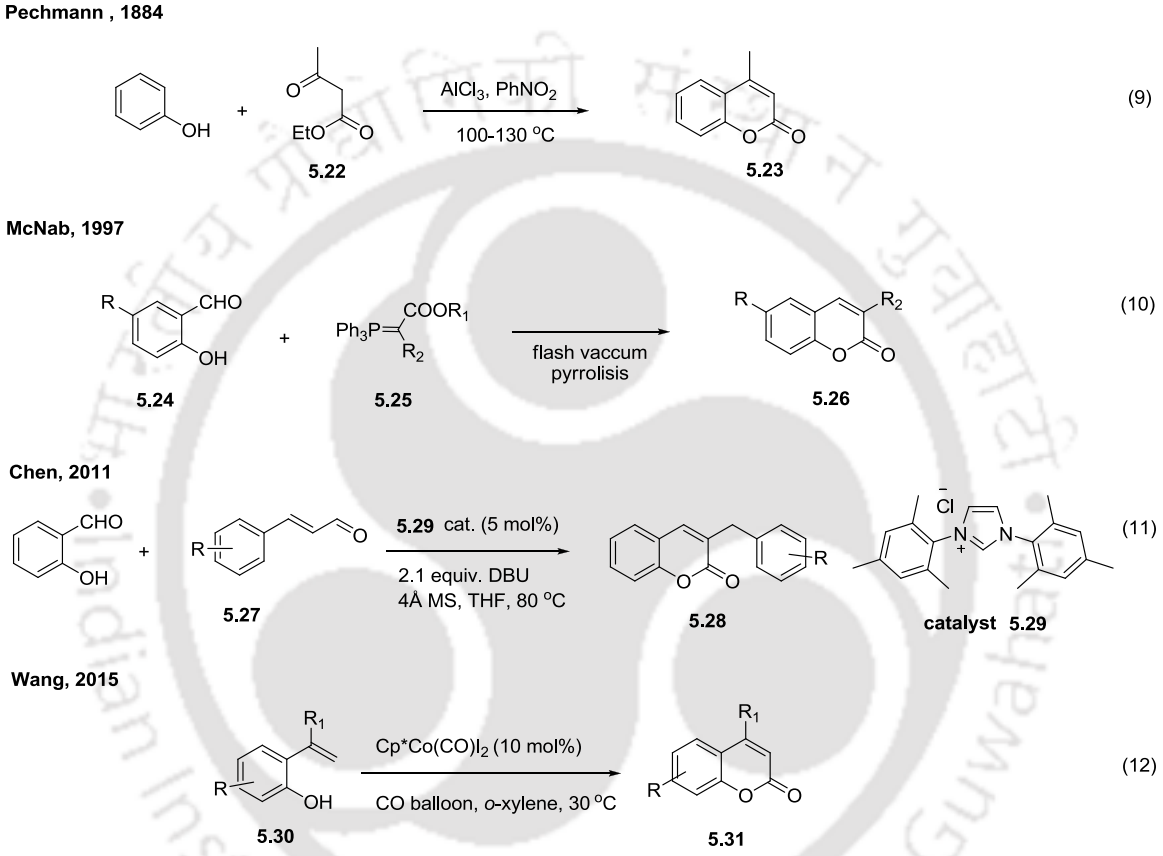
Scheme 2: Preparation of unsaturated aldehydes

Similarly, 2-phenyl cinnamaldehyde derivative was also employed successfully to obtain conjugated aldehydes (**5.21q-r**) with good yields. Conjugated aldehydes were found to have thermodynamically more stable *E*-geometry in the double bond. Geometry of 5.21b and 5.21q were assigned from the NOE studies (see in **Chapter 7**, Experimental Section). However, mixtures of *E*- and *Z*-isomers were found for aldehyde **5.21g** and dienals **5.21q-r**.

5.4 Scope of *β*-functionalization of acyclic amines with salicylaldehydes

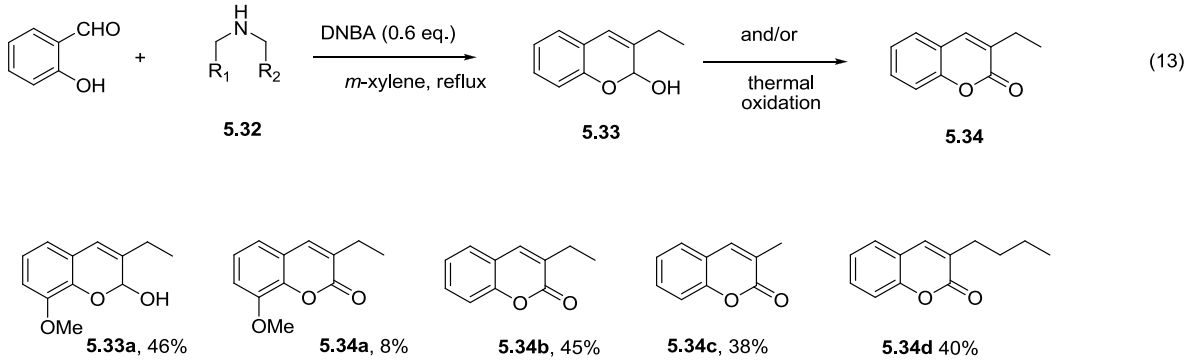
Various reports for the preparation of coumarin and their derivatives have appeared in literature.[39] Coumarin derivatve **5.23** can be afforded by means of Pechmann condensation,[39a] starting from a phenol and a carboxylic acid or ester **5.22** in the presence of $AlCl_3$ (**Scheme 3**, eq. 9**)**. McNab and co-workers described a Wittig type reaction of the aldehyde **5.24** with the phosphoranes **5.25** by flash vaccum pyrrolysis to give coumarin derivative **5.26** (**Scheme**

3, eq. 10**).** [40] In 2011, a number of 3-benzyl-chromen-2-ones derivative **5.28** were synthesized by Chen and co-workers by *N*-heterocyclic carbene- catalyzed (**5.29**) selective condensation reactions between cinnamaldehydes **5.27** and salicylaldehyde (**Scheme 3**, eq. 11).[41] In 2015, Wang and co-workers developed Cp*Co(III)-catalyzed annulations of 2-alkenylphenols **5.30** with CO for the synthesis of coumarin derivatives **5.31** (**Scheme 3**, eq. 12).[42] The drawback of the above methodologies include either use of metal reagent/catalyst or requirement of very high temperature to obtain the desired product.



Scheme 3: Various strategies for preparation of coumarin derivatives

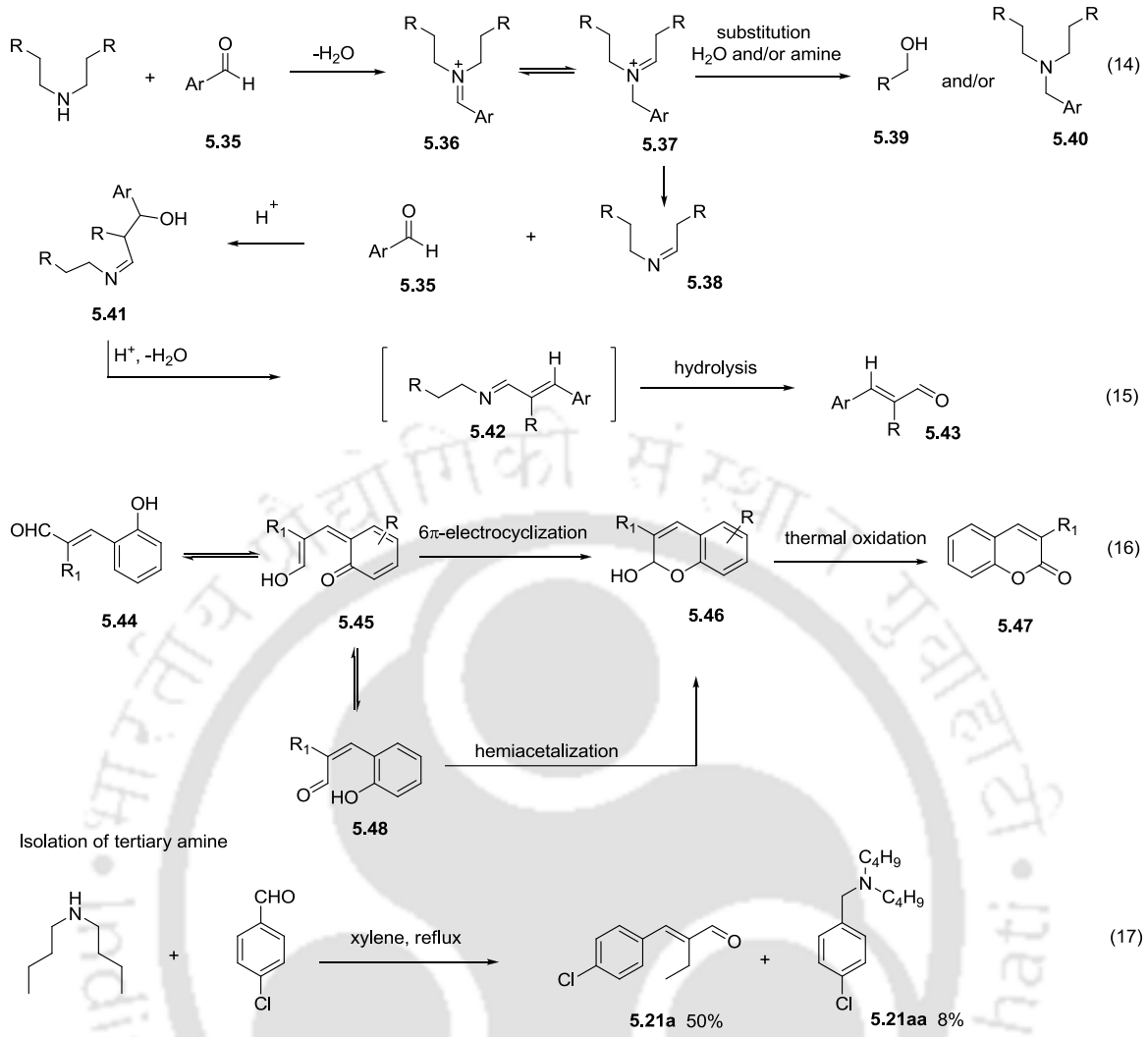
The optimized conditions were employed to evaluate the scope of the C-C homologation with salicylaldehydes and related *o*-hydroxy aldehydes. Gratifyingly, coumarin derivatives were isolated from the reaction of salicylaldehyde and dibutylamine in refluxing xylene (**Scheme 4**, eq. 13). Further, different aromatic aldehydes such as *o*-vanillin, 2,4-dichloro-6-hydroxybenzaldehyde were also reacted with dialkylamine to afford structurally diverse benzopyran derivatives (**5.33a** and **5.34a-d**). 2-Alkyl coumarins were obtained from the reaction of salicylaldehyde while *o*-vanillin gave chromene-2-ol as the major product. Interestingly, coumarin and/or chromene-2- ol derivatives (**5.33a** and **5.34a-d**) with *Z*- double bond were obtained on reaction with 2-hydroxyaldehydes.



Scheme 4: Preparation of coumarin derivatives

5.5 Proposed mechanism of direct *β*-functionalization

A mechanistic proposal for the metal- and oxidant-free direct *β*-C-H functionalization of secondary amine has been presented in **Scheme 5** (eq. 14 and eq. 15) Aldehyde **5.35** condensed with secondary aliphatic amine providing iminium ion **5.36**, which then rearranged to isomeric iminium ion **5.37**. Nucleophilic substitution reaction occurred at the benzylic or allylic position of **5.37** to release imine **5.38** and benzyl alcohol **5.39** or benzyl amine **5.40**. Subsequent reaction of enamine, formed from imine **5.38**, with aldehyde **5.35** provided *α,β*-unsaturated imine **5.42** via intermediate alcohol **5.41**. The unstable imine **5.42** underwent hydrolysis providing conjugated aldehyde **5.43**. Similar to **5.43**, compound **5.44** formed for salicylaldehyde based substrates on reaction with acyclic amines. The hydroxy group of salicylaldehyde promoted intramolecular cyclization providing chromene-2-ol **5.46** that underwent subsequent oxidation to coumarin derivatives **5.47**. Ring closing occurred either via thermal 6π-electrocyclization of *o*-quinone methide **5.45** or through intramolecular hemiacetalization of **5.48** (**Scheme 5**, eq. 16).[43] Attempts were made to isolate benzyl amine **5.40** as the support for the mechanistic proposal. Tertiary Amine **5.21aa** corresponding to **5.40** was isolated along with the conjugated aldehyde **5.21a** from a reaction of dibutylamine and 4-chloro-benzaldehyde under standard condition (**Scheme 5**, eq. 17). It is evident from the proposed mechanism, a maximum yield of 50% is expected for functionalized product **5.43**. Moreover, acyclic amines were functionalized providing unsaturated aldehydes (via successive hydrolysis of imine **5.42**) which are reactive and volatile in nature. Probably, due to these reasons, relatively lower isolated yields were obtained for unsaturated aldehydes **5.43**.



Scheme 5: Plausible reaction mechanism

5.6 Summary

A novel method for the direct *β*-C(sp^3)-H functionalization of aliphatic amines has been developed. Aliphatic amines reacted with aldehyde under simple reaction conditions producing a series of 2-alkyl cinnamaldehyde and chromene-2-ol/-one derivatives including natural aromas. Aliphatic amines were used in this method as a surrogate of aldehyde. Therefore, this will be promising methodology for the preparation of enals as it avoids self-condensation or polymerization of aldehydes in cross-aldol reaction. Enamines were formed *in situ* directly from corresponding aliphatic amines without the aid of metal based reagents and external oxidant.

References

[1] Felpin, F.-X.; Lebreton, J. *Tetrahedron* **2004**, *60*, 10127.
[2] Sakano, Y.; Shibuya, M.; Matsumoto, A.; Takahashi, Y.; Tomoda, H.; Ōmura, S.; Ebizuka, Y. *J. Antibiot.* **2003**, *56*, 817.
[3] a) Tatsuzki, J.; Bastow, K. F.; Nakagawa-Goto, K.; Nakamura, S.; Itokawa, H.; Lee, K.-H. *J. Nat. Prod.* **2006**, *69*, 1445; b) Harvey, A. J.; Baell, J. B.; Toovey, N.; Homerick, D.; Wulff, H. *J. Med. Chem.* **2006**, *49*, 1433; c) Liu, M.; Wilairat, P.; Go, M.-L. *J. Med. Chem.* **2001**, *44*, 4443; d) Zwaagstra, M. E.; Timmerman, H.; Tamura, M.; Tohma, T.; Wada, Y.; Onogi, K.; Zhang, M.-Q. *J. Med. Chem.* **1997**, *40*, 1075.
[4] Climent, M. J.; Corma, A.; Fornés, V.; Guil-Lopez, R.; Iborra, S. *Adv. Synth. Catal*. **2002**, *344*, 1090.
[5] Lévai, A.; Simon, A.; Jenei, A.; Kálmán, G.; Jekő, J.; Tóth, G. *Arkivoc* **2009**, 161.
[6] Vermoortele, F.; Ameloot, R.; Vimont, A.; Serre, C.; De Vos, D. *Chem. Commun.*, **2011**, *47*, 1521.
[7] Egan, D.; O'Kennedy, E.; Moran, E.; Cox, D.; Prosser, E.; Thornes, R. D. *Drug. Metab. Rev.* **1990**, *22*, 503.
[8] Henriette, G.; Lorraine, L.; Bettina, H.; Clemence, D.; Kelly, D.; Irenej, K. *Mol. Cancer. Ther*. **2004**, *3*, 1375.
[9] Chetan, B. S.; Nimesh, M. S.; Manish, P. P., Ranjan, G. P. *J. Serb. Chem. Soc*. **2012**, *77*, 1.
[10] Milan, M.; Mirjana, M.; Desanka, B.; Sanja. M.; Neda, N.; Vladimir, M. *Int. J. Mol. Sci*. **2011**, *12*, 2822.
[11] Suresh, T.; Arunima, V.; Atin, K.; Sandeep, G.; Prarthana, V. R.; Ganesh, R. K. *Acta. Pol. Pharm*. **2010**, *67*, 423.
[12] Nareshkumar, J.; Jiayi X.; Ramesh, M. K.; Fuyong, D.; Guo J.- Z.; Emmanuel P. *J. Med. Chem.* **2009**, *52*, 7544.
[13] Mori, J.; Iwashima, M.; Takeuchi, M.; Saito, H. *Chem. Pharm. Bull.* **2006**, *54*, 391.
[14] Aliaa, M. K.; Manal, M. K.; Eman k, A. E.; Heba, A. H. E. *Int. J. Pharm. Res. Develop.* **2012**, *4*, 310.
[15] Denish, C. K.; Hetal, K. P.; Nilesh, K. G. *Asian J. Biochem. Pharm. Res.* **2012**, *2*, 126.
[16] Bhat, M. A.; Siddiqui, N.; Khan, S. A. *Acta Pol. Pharm.* **2008**, *65*, 235.
[17] Yu, S.; Hu, D.; Zhang, J. *Mol. Med. Rep.* **2015**, *12*, 3869.
[18] Chilin, A.; Battistutta, R.; Bortolato, A.; Cozza, G.; Zanatta, S.; Poletto, G.; Mazzorana, M.; Zagotto, G.; Uriarte, E.; Guiotto, A.; Pinna, L. A.; Meggio, F.; Moro, S. *J. Med. Chem*. **2008**, *51*, 752.
[19] Zhang, Y. Y.; Meng, X. M.; Wang, X. L.; Xu, L. X. *Dyes and Pigment* **2003**, *56*, 189.
[20] Christie, R. M.; Chih-Hung, L. *Dyes and Pigments* **1999**, *42*, 85.
[21] Signore, G.; Nifosı`, R.; Albertazzi, L.; Storti, B.; Bizzarri, R. *J. Am. Chem. Soc.* **2010**, *132*, 1276.
[22] a) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317; b) Haibach, M. C.; Seidel, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 5010; c) Peng, B.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 13274; d) Shi, L.; Xia, W.; *Chem. Soc. Rev.* **2012**, *41*, 7687; f) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.;

Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2012**, *18*, 10092; e) Jones, K. M.; Klussmann, M. *Synlett* **2012**, 159; f) Doye, S. *Angew. Chem. Int. Ed.* **2001**, *40*, 3351.

[23] a) Xie, Z.; Liu, L.; Chen, W.; Zheng, H.; Xu, Q.; Yuan, H.; Lou, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3904; b) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744; c) Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv.*, **2014**, *4*, 46214; d) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.*, **2014**, *136*, 6123; e) Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun.* **2014**, *50*, 332; f) Chen, W.; Wilde, R. G.; Seidel, D. *Org. Lett.* **2014**, *16*, 730.

[24] a) Blanco-Lomas, M.; Campos, P. J.; Sampedro, D. *Eur. J. Org. Chem*. **2012**, *2012*, 6328; b) O'Reilly, M. C.; Lindsley, C. W. *Org. Lett.* **2012**, *14*, 2910.

[25] a) Shi, Z.; Yu, P.; Loh, T.-P.; Zhong, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7825; b) Barber, D. M.; Sanganee, H. J.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 5290; c) Kim, M.; Park, Y.; Jeong, B.-S.; Park, H.; Jew, S. *Org. Lett.* **2010**, *12*, 2826.

[26] Liu, W.; Liu, J.; Ogawa, D.; Nishihara, Y.; Guo, X.; Li, Z. *Org. Lett.* **2011**, *13*, 6272.

[27] Boudiar, T.; Sahli, Z.; Sundararaju, B.; Achard, M.; Kabouche, Z.; Doucet, H.; Bruneau, C. *J. Org. Chem.* **2012**, *77*, 3674

[28] Yuan, K.; Jiang, F.; Sahli, Z.; Achard, M.; Roisnel, T.; Bruneau, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 8876.

[29] Takasu, N.; Oisaki, K.; Kanai, M. *Org. Lett.* **2013**, *15*, 1918.

[30] Mandal, S.; Mahato, S.; Jana, C. K. *Org. Lett.* **2015**, *17*, 3762.

[31] a) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem. Int. Ed*. **2008**, *47*, 6634; b) Gotoh, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 2859; c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905.

[32] Surburg, H.; Panten, J. *Common Fragrance and Flavor Materials: Preparation, Properties and Uses*, Wiley-VCH, Weinheim, **2006**, ISBN: 978-3-527-31315-0.

[33] Vermoortele, F.; Ameloot, R.; Vimont, A.; Serre, C.; De Vos, D. *Chem. Commun.* **2011**, *47*, 1521.

[34] Mahata, P. K.; Barun, O.; Ila, H.; Junjappa, H. *Synlett* **2000**, 1345.

[35] a) Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* **1990**, *31*, 349; b) Bellassoued, M.; Majidi, A. *J. Org. Chem.* **1993**, *58*, 2517.

[36] a) Zhou, G.; Hu, Q.-Y.; Corey, E. J. *Org. Lett.* **2003**, *5*, 3979; b) Hudson, R. D. A.; Manning, A. R.; Gallagher, J. F.; Garcia, M. H.; Lopes, N.; Asselberghs, I.; Boxel, R. V.; Persoons, A.; Lough, A. J. *J. Organomet. Chem.* **2002**, *655*, 70.

[37] a) Michel, P.; Rassat, A.; Daly, J. W.; Spande, T. F. *J. Org. Chem.* **2000**, *65*, 8908; b) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393; c) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann.-Recl.* **1997**, *7*, 1283; d) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405; e) Ando, K. *Tetrahedron Lett.* **1995**, *36*, 4105.

[38] a) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *1*, 7; b) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229.

[39] a) Pechmann, V. H.; Duisberg, C. *Chem. Ber.* **1884**, *17*, 929; b) Horning, E. C. *Organic Synthesis*; Wiley: New York, **1955**; *Vol. III*, p 281; c) Bose, D. S.; Rudradas, A. P.; Hari Babu,

M. *Tetrahedron Lett.* **2002**, *43*, 9195; d) De, S. K.; Gibbs, R. A. *Synlett* **2005**, 1231; e) Potdur, M. K.; Mohile, S. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2001**, *42*, 9285; f) Kandekar, A. C.; Khadikar, B. M. *Synlett* **2002**, 152; g) Gu, Y.; Zhang, J.; Duan, Z.; Deng, Y. *Adv. Synth. Catal.* **2005**, *347*, 512; h) Gunnewegh, E. A.; Hoefnegal, A. J.; Van Bekkum, H. *J. Mol. Catal. A: Chem.* **1995**, *100*, 87; i) Frere, S.; Thiery, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2791.

[40] Cartwright, G. A.; McNab, H. *J. Chem. Res.* (*S*), **1997**, 296.

[41] Jiang, Y.; Chen, W.; Lu, W. *RSC Adv.*, **2012**, *2*, 1540.

[42] Liu, X.-G.; Zhang, S.-S.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Wang, H. *Org. Lett.* **2015**, *17*, 5404.

[43] Majumdar, N.; Korthals, K. A.; Wulff, W. D. *J. Am. Chem. Soc.* **2012**, *134*, 1357.

Chapter 6

Synthesis, *In silico* Studies and *In vitro* Evaluation for Antioxidant and Antibacterial Properties of Diarylmethylamines

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

6.1 Introduction

The discovery of penicillin as antimicrobial in 1920s dramatically reduces the morbidity and mortality of human and animals from infectious diseases. Since the 60's a very limited number of antibacterial agents has been introduced as to the market (**Figure 1**).[1]

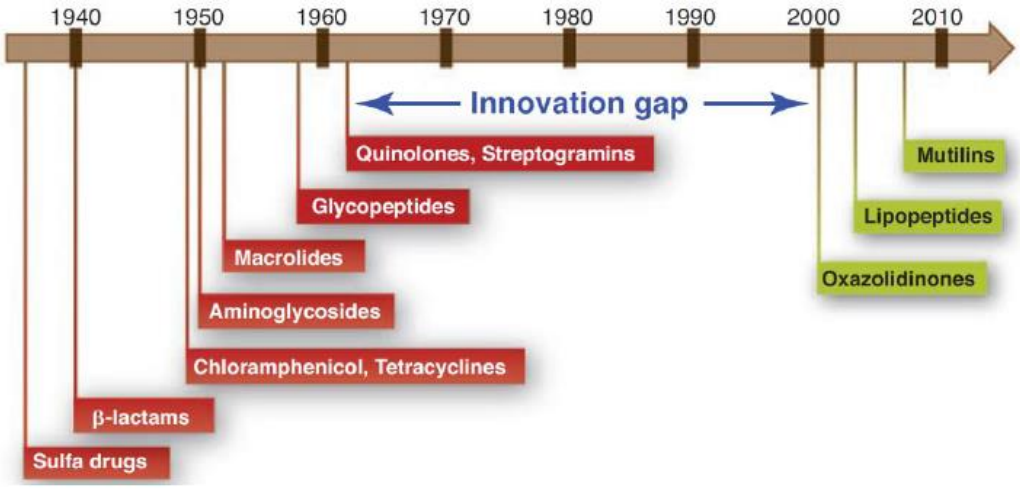


Figure 1: Timeline of the discovery of the most important antibiotic classes, illustrating the innovation gap (**Fischbach & Walsh, 2009**).

In recent years, the treatment of some bacterial infections has become more complicated because of the increase in bacterial resistance against conventional antibacterial agents. Some bacterial strains have developed resistance from antibiotic action, either by mutagenesis or by acquiring new genes from other bacteria. Resistance mechanisms involved efflux pump that expel antibiotics out of the cells and enzymes that modify or degrade the antibiotic molecule.[2] Today, emergence of multidrug-resistant bacterial pathogens leads the researchers and clinicians to a challenging task to identify new potential anti-bacterial agents. Therefore, efforts are ongoing for the development of new class of antibacterial agents.[3,4,5,6] Many of the known potential antibacterial agents are structurally complex and thus these are difficult to obtain with adequate quantity.[7,8] Hence, identification of new class of safe, highly effective and easily accessible chemotherapeutic agents becomes inevitable. In this context, diarylmethylamines belong to a promising class of molecules because of their important pharmacological profile,[9,10] structural simplicity and easy accessibility.[11] Moreover, many of the molecules containing diarylmethylamine scaffold are currently used as pharmaceutical drugs. The examples include Levocetirizine, Zyrtec, Solifenacin, Meclozine (**Figure 2**). Diarylmethylamine or amino-napthols showed similar activity as clinically used selective estrogen receptor modulators (SERMs).[12,13,14,15]

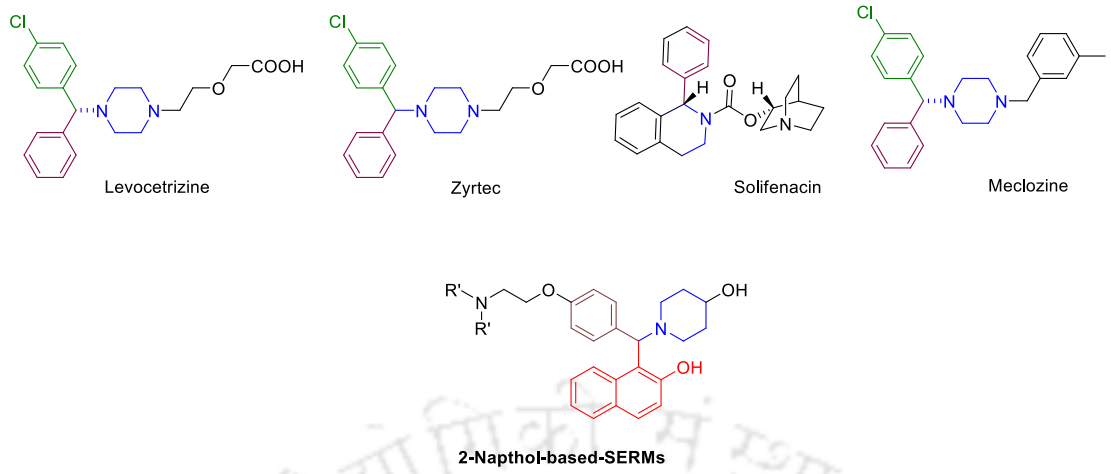


Figure 2: Important diarylmethylamines as pharmaceutical drugs

The *α*-oxygenated derivatives of aminonaphthol/Betti base, (i.e. oxazines) are also very important class of heterocycles, attracting synthetic interest due to its bioactivities and antagonism against pathogens.[16] Variety of substituted 1,3-oxazine derivatives possess important bioactivity like antimicrobial,[17] anticancer,[18] fungicidal,[19] analgesic,[20] anti-inflammatory [21] and antibacterial [22] etc. Compounds having sesamol moiety including Betti bases are of particular interest because of their potent antibacterial, antifungal and antioxidant property along with nitric oxide radical scavenging activity.[23] Mathew and co-workers reported the biological activity of a series of 3,4-dihydro-2*H*-benzo[*e*]-, 2,3-dihydro-1*H*-naphtho[1,2-*e*]- and 3,4-dihydro-2*H*-naphtho[2,1-*e*][1,3]oxazine derivatives which were assessed against gram-negative and gram-positive bacteria.[24] It was observed that some of the screened compounds have shown significant *in vitro* antimicrobial effect. A series of oxazines were synthesized through *α*-C-H functionalization of diarylmethylamines/Betti bases (**Chapter 2** and **4**). To check the potency of the synthesized compounds, oxazine **6.2c** and **6.2d** were tested for the antibacterial activity against *Staphylococcus aureus* and *Listeria monocytogenes* as gram-positive bacteria and *Escherichia coli* enterotoxic, ETEC (MTCC 723) and *Salmonella paratyphi* as gram-negative bacteria (**Figure 3**). Preliminary results showed moderate activity which was similar to the reported data.[25] Next, the antimicrobial behaviour of diarylmeyhylamines **6.1a** and **6.1b** were investigated against the same bacteria. It was found that the class of Betti bases **6.1a** and **6.1b** showed better antibacterial activity as compared to the class of oxazines **6.2c** and **6.2d** (**Table 1**). In quest of the potent and novel class of antimicrobial compounds, it was planned to design and synthesize a set of structurally diverse diarylmethylamines/Betti bases.

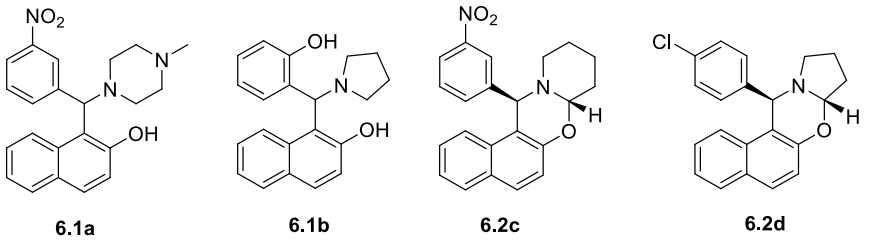


Figure 3: Diarylmethylamines vs. oxazines

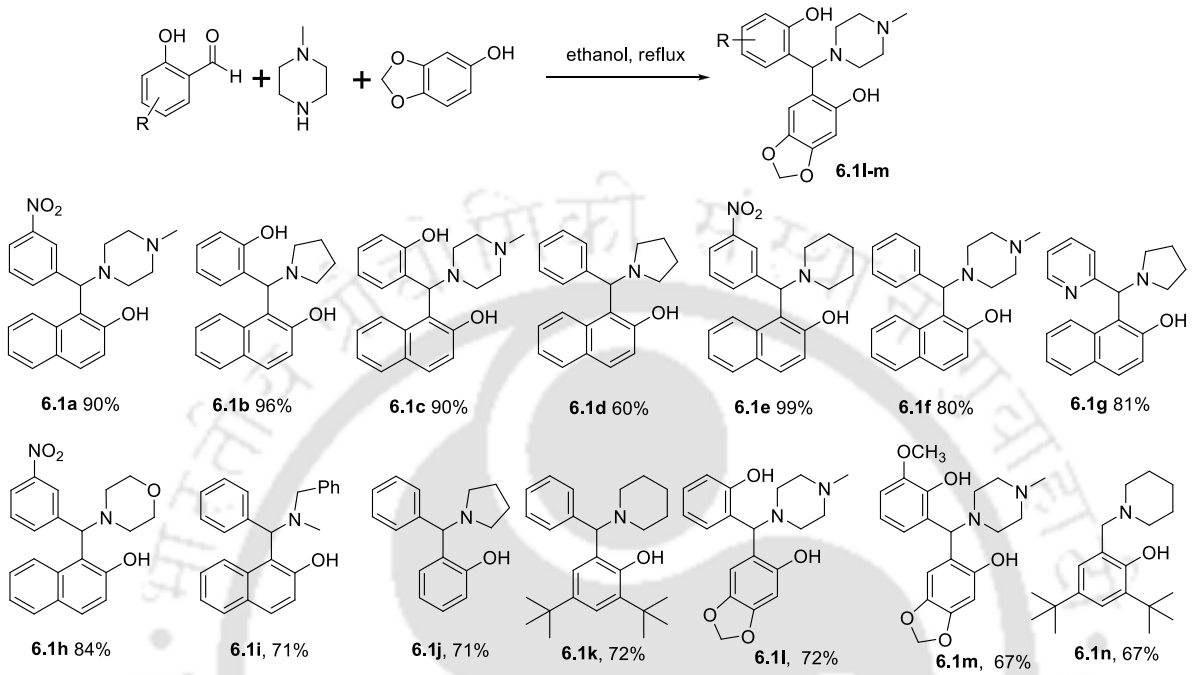
Table 1: The minimum inhibitory concentration (MIC) (µg/mL) of compound **6.1a-b**, **6.2c-d** against selected gram-positive and gram-negative bacteria.

Compounds	*S. aureus*	*L. monocytogenes*	*E. coli* enterotoxic	*S. paratyphi*
6.2c	250	500	250	500
6.2d	125	1000	250	500
6.1a	125	62.5	250	62.5
6.1b	250	62.5	250	250

6.2 Design and synthesis of novel diarylmethylamines

Various diarylmethylamines **6.1a-n** were synthesized via three component condensation reaction. Suitable aldehydes were condensed with different secondary amines in the presence of electron rich phenolic compounds to obtain the desired tertiary amines (**Scheme 1**).[13] 2-Naphthol was employed as the nucleophile for the synthesis of diarylmethylamines **6.1a-h**, having either *N*-heterocycle or *N,O*- and *N,N*-diheterocycle, with very good to excellent yields (up to 96%). Similarly, diarylmethylamine **6.1i** containing acyclic amine was synthesized from 2-naphthol, benzaldehyde and *N*-benzylmethylamine. On the other hand, phenol and 2,4-di-tert-butyl phenol provided diarylmethylamines **6.1j** and **6.1k** respectively. Sesamol is a naturally occurring compound and present in many bioactive molecules.[14,15] Therefore, superior bioactivity was anticipated for the diarylmethylamine containing sesamol moiety. Accordingly, to incorporate sesamol moiety, sesamol was selected as the nucleophile in place of 2-naphthol. The reaction of sesamol and *N*-methyl piperazine with salicylaldehyde and vanillin in refluxing ethanol provided the desire diarylmethylamines **6.1l** and **6.1m**, respectively, with very good isolated yields. An

interesting antioxidant property was also anticipated for compounds **6.1l** and **6.1m** due to the presence of electron rich aromatic units. Arylmethylamine **6.1n** was synthesized from 3,5-di-tert-butylsalicyldehyde via a hydride free formal reductive benzylation of piperidine under microwave heating.[16]



Scheme 1: Synthesis of different diarylmethylamines

Further, the antibacterial action of synthesized compounds was evaluated by microbroth dilution assay and flow cytometry which was confirmed by FESEM imaging. DPPH-assay was employed to evaluate their antioxidant behaviour. The physico-chemical parameters of synthesized compounds were determined by *in silico* studies.

6.3 Biological evaluation

6.3.1 Antibacterial studies

In vitro studies to evaluate antimicrobial properties for all the synthetic compounds have been carried out in collaboration with Prof. L. Rangan (Dept. of Bioscience and Bioengineering, Indian Institute of Technology Guwahati). The present study revealed that the antibacterial activity of compound varies with different functional group(s) present in the compound. Two pathogenic strains of bacteria were used in this study. Most of the

compounds were showing MIC values between 0.015 and 1 mg/mL. The activity data are presented in **Table 2**.

Table 2. The minimum inhibitory concentration (MIC) (µg/mL) of compounds **6.1a-n** against selected gram-positive and gram-negative bacteria.

Compounds*	Gram (+) ve *L. monocytogenes* (LM)	Gram (-) ve *E. coli* enterotoxic (ETEC)
6.1a	62.5	250
6.1b	62.5	250
6.1c	31.2	-
6.1d	250	-
6.1e	500	250
6.1f	31.2	31.2
6.1g	250	125
6.1h	-	250
6.1i	250	1000
6.1j	250	250
6.1k	-	250
6.1l	15.6	31.2
6.1m	62.5	31.2
6.1n	-	250

*Positive control – Kanamycin (5 µg/mL)

Compound **6.1a** with 3-nitrophenyl and *N*-methyl piperazine units was effective against gram-positive bacteria with MIC at 62.5 µg/mL and found less susceptible against gram-negative bacteria. Compound **6.1b** having 2-hydroxy phenyl and pyrrolidine moiety was found to have similar activity. On the other hand, compound **6.1c** with *N*-methyl piperazine showed pronounced activity against gram-positive bacteria, *L. monocytogenes* (LM) with MIC of 31.2 µg/mL. However, it was ineffective against *E. coli* enterotoxic. Reduced activity of compound **6.1d** as compared to **6.1b** was observed by replacing 2-OH-phenyl with phenyl group. Similar reduction in antibacterial activity was found for

compound **6.1e**, when *N*-methyl piperazine in **6.1a** was replaced by pyrrolidine. An enhanced activity was found for **6.1f** having *N*-methyl piperazine unit compared to **6.1d** having pyrrolidine moiety. Interestingly, compound **6.1f** was found to be very effective against both gram-positive and gram-negative bacteria with MIC value of 31.2 µg/mL. A moderate activity was found for compounds **6.1g**, **6.1h**, and **6.1i** containing aromatic heterocycles, morpholine, and acylic amine respectively. Similar activities were found for phenol based compounds **6.1j**, **6.1k** and **6.1n**. These observations indicated that electron rich aromatics (like 2-OH phenyl, 2-napthol) and *N*-methyl piperazine moiety are important for obtaining antibacterial activity. Therefore, in a hope to get more potent candidate, diarylmethylamine **6.1l** and **6.1m** were synthesized incorporating naturally occurring electron rich phenol derivative, sesamol, instead of 2-napthol. Pleasingly, compound **6.1l** was found to be the most effective with MIC value of 15.6 and 31.2 µg/mL against gram-positive bacteria and gram-negative bacteria, respectively. Its methoxy analogue **6.1m** also showed similar activity for both gram-positive and gram-negative bacteria. The potency of compound **6.1l** might be contributed by *o*-quinone methide that is generated by the decomposition of the compound in culture media.[26]

Resazurin based micro broth dilution assay was also employed to study the antibacterial activity of **6.1l**. The colour change appeared at its MIC (15.6 µg/mL) due to the formation of pink coloured resorufin (**Figure 4**).

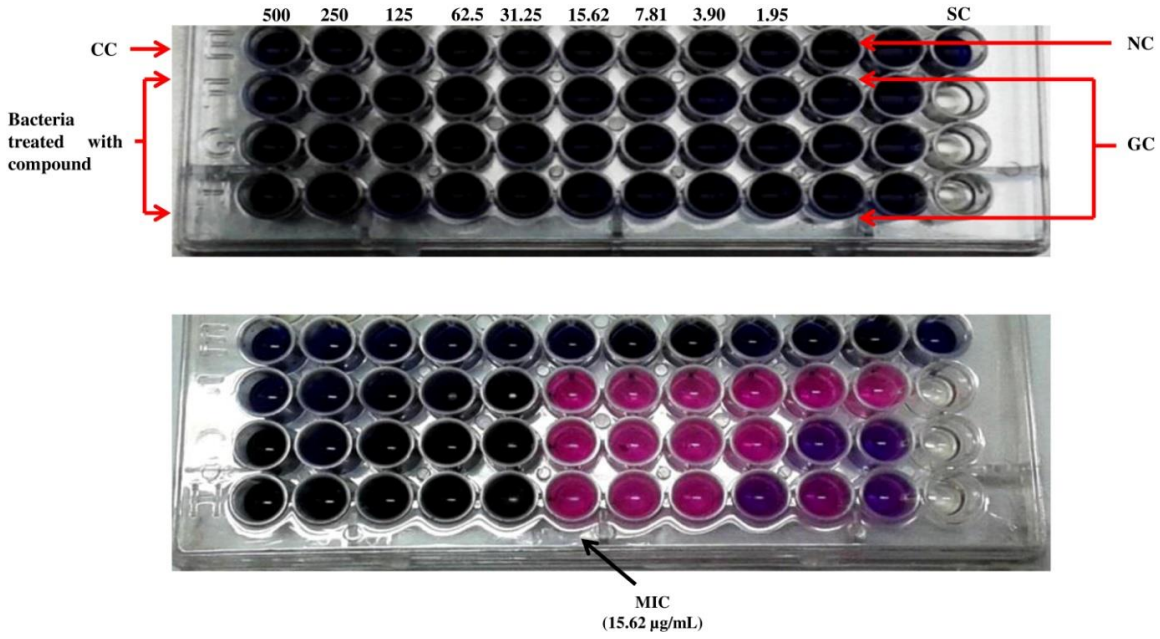


Figure 4: Colorimetric microbroth dilution assay of compound **6.1l** (µg/mL) against *L. monocytogenes.*CC, compound control; GC, growth control; NE, negative control; SC, sterility control.

In general, it was observed from current study that compounds except **6.1f, 6.1l** and **6.1m** were less effective against gram-negative bacteria. This is possibly owing to the fact that gram-negative bacteria have lipopolysaccharides (LPS) as outer membrane which renders bacteria to be more resistant to molecules having hydrophilic groups.[27] However, presence of hydrophobic substituent like 2,4-di-*tert*-butyl-phenol and piperidine in compound **6.1k** and **6.1n** did not exhibit activity against gram-positive bacteria. Damage to the bacterial tissues through some pro-oxidant effects involving the phenolic hydroxyl group has also been attributed.[28,29]

6.3.2 Flow cytometry analysis

Multiparametric FC was carried out to better assess the antibacterial potential of the most promising compound **6.1l** against LM. Unstained, cFDA-stained, PI-stained, cFDA and PI double stained cells served as controls which enabled to set the FCM detectors. Bacterial cells were exposed to compound **6.1l** at 7.8, 15.6 (MIC) and 31.2 µg/mL and then simultaneously stained with cFDA and PI. The quadrants of the contour plots were set to ease the illustration of different subpopulations of bacteria and unstained cells appeared in the lower left quadrant. The vehicle control (DMSO) and untreated bacterial cells showed minimum relative fluorescence intensity of PI. But, the positive control (heat killed) showed significant increase ($p < 0.01$, Tukey's post hoc test) in relative fluorescence intensity of PI (98.4%) in tested bacteria with respect to vehicle control. This confirmed that the major cell populations existed as membrane compromised or dead. The dual-parameter contour plots indicate the existence of three main subpopulations of compound-treated LM and showed dynamic changes of the membrane integrity with the increase in concentration of compound (**Figure 5**). These subpopulations were identified as live, dead and membrane compromised bacteria based on their differential staining characteristics with PI and cFDA.

The cFDA-stained subpopulation ($cFDA^+$ PI^-) decreased with increasing concentrations of compound **6.1l** and accounted for 81.2, 6.66 and 0.31% of the total population after exposure to compound at 7.8, 15.6 and 31.2 µg/mL, respectively. Whereas, the fraction that stained only with PI ($cFDA^-$ PI^+) increased from 1.99, 52.1 and 87.5% after exposure to compound at 7.8, 15.6 and 31.2 µg/mL respectively, and was scored as the dead population.

The partial hydrophilic nature of compound **6.1l** allows it to penetrate microbial cells and induce alterations in structure and function of the bacterium. This possibly resulted in the loss of microbial viability.[27] The percent double-stained LM cells ($cFDA^+$ PI^+) showed a subtle fluctuation during the course of the compound stress exposure. This fraction constituted 2.24, 19.8 and 2.22% of the total population after treatment with compound at 7.8, 15.6 and 31.2 µg/mL and was recognized as "viable but non culturable state" (VBNC). Cells entering the VBNC state often exhibit dwarfing, and a number of major metabolic changes occur, including reductions in nutrient transport, respiration rates, changes in membrane fatty acid composition and macromolecular synthesis.[30] *L. monocytogenes* is known for its diverse physiological states including viable, dead and membrane compromised population in a heterogeneous sample.[31,32] In the present study, similar behaviour was confirmed with the help of multicolour flow analysis.

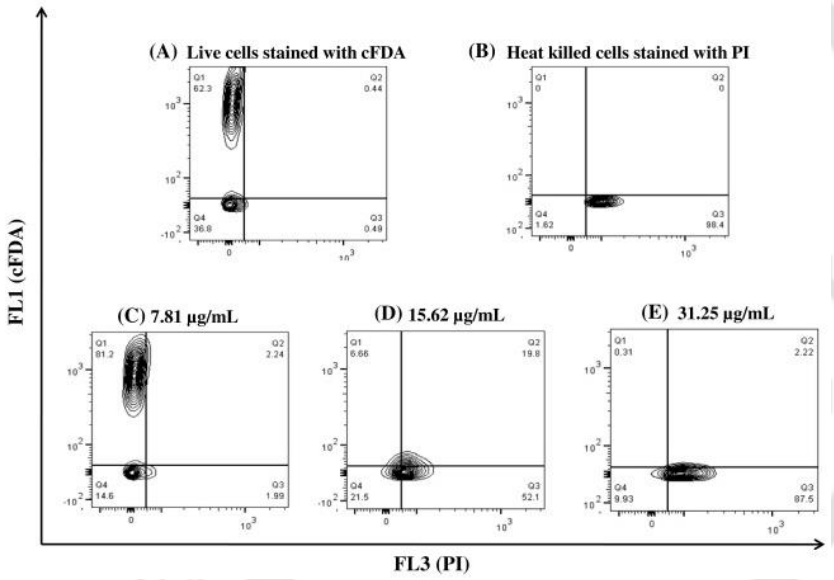


Figure 5. Dual parameter contour plot for viability assessment of *L. monocytogenes* against compound **6.1l** by flow cytometry. Proper control cells stained with cFDA and PI (A) and (B) and bacteria treated with (C) 7.81 µg/mL; (D) 15.62 µg/mL and (E) 31.25 µg/mL. Three main subpopulations, corresponding to viable cFDA-stained cells (upper left quadrant), injured cells double stained with PI and cFDA (upper right quadrant), and dead PI-stained cells (lower right quadrant), can be readily differentiated.

Interestingly, it was observed that PI relative fluorescence intensity was maximum when the cells were subjected to heat treatment indicating significant damage and depolarization of the bacterial cell membrane. Stressed population of cells could maintain cell metabolic

activity, as determined by the fluorescent dyes. The efficacy of compound **6.1l** as potential antibacterial agent has been confirmed using flow analysis.

6.3.3 FESEM analysis

The most susceptible gram-positive bacterium (*L. monocytogenes*) was examined by FESEM to observe morphological changes caused by treatment with compound **6.1l** (**Figure 6**). FESEM images of untreated LM showed intact, smooth cell surface with defined cell features (**Fig. 6A**). Heat killed and kanamycin treated cells showed complete membrane disruption (**Fig. 6B** and **6C**). Shrinking, membrane disintegration and prominent damage of the cell wall was observed in bacterial cells treated with the compound (**Fig. 6D-F**). These findings indicate that compound caused lysis of the bacterium by degrading cell wall and affecting cytoplasmic membrane. Similar phenomenon has also been found in related studies on gram-positive bacteria.[33]

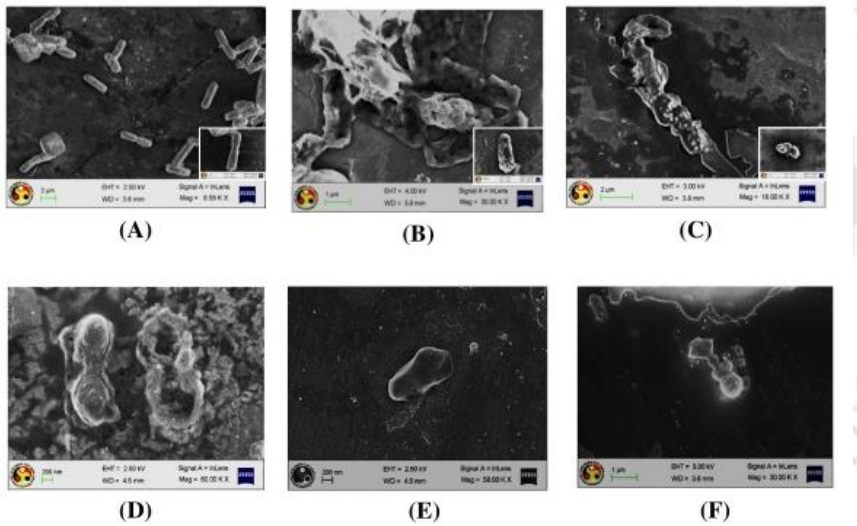


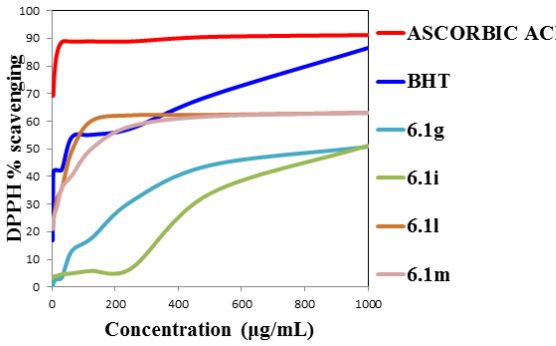
Figure 6: Field emission scanning electron micrograph of *L. monocytogenes* (LM) (A) untreated bacteria, (B) positive control as heat killed cells, (C) cells treated with antibiotic kanamycin, and (D-F) bacterial cells after treatment with compound **6.1l** at its MIC showing damage in cell membrane, dwarfism and blebbing.

6.4 Antioxidant activity

Antioxidant property of the synthesized compounds has been tested next. A wide variety of methods have been developed for the estimation of antioxidant potential.[34] Among them, DPPH assay is extensively used due to its stability, and its simple reaction system.[33] The method is based on the reduction of DPPH to the non-radical form DPPH-H by a hydrogen-

donating antioxidant.[33] Various concentrations of compounds (1 mg/mL-1.95 µg/mL) showed radical scavenging activities in a dose dependent manner (**Figure 7**). The IC_{50} was determined for the compounds and also for the positive control, BHT and ascorbic acid. As anticipated, we found that both the compounds **6.1l** (IC_{50} = 370 µg/mL) and **6.1m** (IC_{50} = 428 µg/mL) containing sesamol moiety showed DPPH radical scavenging activity which are comparable to that of BHT (IC_{50} = 184 µg/mL). Compound **6.1g** (IC_{50} = 817 µg/mL) and **6.1i** (IC_{50} = 958 µg/mL) showed lower activity than BHT. Other compounds remain ineffective towards radical scavenging activity. The high radical scavenging capacity of sesamol moiety

in compounds **6.1l** and **6.1m** is probably due to the presence of free hydroxyl group in its structure.[29]



Compounds	IC_{50} (µg/mL)
6.1g	817
6.1i	958
6.1l	370
6.1m	428
BHT	184
Ascorbic Acid	112

Figure 7. DPPH scavenging activity of selected compounds. BHT used as positive control at varying concentration ranging 1 mg/mL-1.95 µg/mL.

6.5 Summary

In summary, various diarylmethylamines/Betti bases have been synthesized using simple and efficient synthetic protocol. These compounds were evaluated for their antibacterial activity against gram-positive and gram-negative bacteria. The present study revealed that diarylmethylamine derived from sesamol to be more potent than one derived from 2-naphthol and phenol based compounds. Compound **6.1l** containing sesamol and *N*- methyl piperazine was found to be the most potent against gram-positive (*L. monocytogenes*) bacteria. It showed antibacterial effect through the damage of bacterial cell membrane which was confirmed by FC and FESEM analyses. Other compounds showed moderate or no activity against gram-negative bacteria. Compounds **6.1l** and **6.1m** also showed strong free radical scavenging activity similar to BHT in DPPH assay. Interesting antibacterial activity and promising drug likeness properties, obtained from *in silico* studies (see experimental section), signified the compound **6.1l** to be considered as a potential

antibacterial agent. Further studies on this novel class of antibacterial agents are ongoing to find more potent candidate.

References

[1] Fischbach, M. A.; Walsh, C. T. *Science* **2009**, *325*, 1089.
[2] Wright, G. D. *BMC Biol.* **2010**, *8*, 123.
[3] Chopde, H. N.; Meshram, J. S.; Pandhurnekar, C. P.; Pagadala, R.; Jonnalagadda, S. B. *J. Heterocycl. Chem.* **2016**, *53*, 824.
[4] Jogi, P. S.; Meshram, J. S.; Sheikh, J. *Lett. Drug. Des. Disco.* **2013**, *10*, 283.
[5] Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. *Eur. J. Med. Chem.* **2010,** *45*, 1502.
[6] Krizsan, A; Volke, D.; Weinert, S.; Sträter, N.; Knappe, D.; Hoffmann, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 12236.
[7] Erb, W.; Zhu, J. *Nat. Prod. Rep*. **2013**, *30*, 161.
[8] Bedeschi, A.; Fonte, P.; Fronza, G.; Fuganti, C.; Serra, S. *Nat. Prod. Commun.* **2014**, *9*, 237.
[9] Gerlach, M.; Maul, C. US 20040147570, **2004**.
[10] Gyémánt, N.; Engi, H.; Schelz, Z.; Szatmári, I.; Tóth, D.; Fülöp, F.; Molnár, J.; de Witte, P. A. M. *Br. J. Cancer* **2010**, *103*, 178.
[11] Betti, M. *Gazz. Chim. Ital.* **1900**, *30*, 301.
[12] Labrie, F.; Labrie, C.; Bélanger, A.; Simard, J.; Gauthier, S.; Luu-The, V.; Mérand, Y.; Giguere, V.; Candas, B.; Luo, S.; Martel, C.; Singh, S. M.; Fournier, M.; Coquet, A.; Richard, V.; Charbonneau, R.; Charpenet, G.; Tremblay, A.; Tremblay, G.; Cusan, L.; Veilleux, R. *J. Steroid Biochem. Mol. Biol*. **1999**, *69*, 51.
[13] Jordan, V. C.; Gradishar, W. J. *Mol. Asp. Med.* **1997**, *18*, 167.
[14] Yadav, Y.; MacLean, E. D.; Bhattacharyya, A.; Parmar, V. S.; Balzarini, J.; Barden, C. J.; Too, C. K. L.; Jha, A. *Eur. J. Med. Chem*. **2011**, *46*, 3858.
[15] Jha, A.; Yadav, Y.; Naidu, A. B.; Rao, V. K.; Kumar, A.; Parmar, V. S.; MacDonald, W. J. Too, C. K. L.; Balzarini, J.; Barden, C. J.; Cameron, T. S. *Eur. J. Med. Chem*. **2015**, *92*, 103.
[16] Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. *Eur. J. Med. Chem.* **2010**, *45*,1502.
[17] Sawant, R.; Bhangale, L.; Wadekar, J.; Gaikwad, P. *Farmacia* **2012**, *60*, 32.
[18] Ouberai, M.; Asche, C.; Carrez, D.; Croisy, A.; Dumy, P.; Demeunynck, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4641.
[19] Tang, Z.; Zhu, Z.; Xia, Z.; Liu, H.; Chen, J.; Xiao, W.; Ou, X. *Molecules* **2012,** *17*, 8174.
[20] Gökhan, N.; Erdoğan, H.; Durlu, N. T.; Demirdamar, R. *II Farmaco* **1999**, *54*, 112.
[21] Khalaj, A.; Abdollahi, M.; Kebriaeezadeh, A.; Adibpour, N.; Pandi, Z.; Rasoulamini, S. *Indian J. Pharmacol.* **2002,** *34*, 184.
[22] Beach, M.; Frechette, R. WO Patent 19728167 A1 **1997**.

[23] Singh, H.; Sindhu, J.; Khurana, J. M.; Sharma, C.; Aneja, K. R. *RSC Adv.* **2014**, *4*, 5915.
[24] Mathew, B. P.; Kumar, A.; Sharma, S.; Shukla, P. K.; Nath, M. *Eur. J. Med. Chem.* **2010**, *45*, 1502.
[25] Abou-Elmagd, W. S. I.; Hashem, A. I. *Med. Chem. Res.* **2013**, *22*, 2005.
[26] Evans, G. B.; Furneaux, R. H.; Gravestock, M. B.; Lynch, G. P.; Scott, G. K. *Bioorg. Med. Chem.* **1999**, *7*, 1953.
[27] Nazzaro, F.; Fratianni, F.; Martino, L. D.; Coppola, R.; Feo, V. D. *Pharmaceuticals* **2013**, *6*, 1451.
[28] Hatano, T.; Kusuda, M.; Tsugawa, M.; Taniguchi, S.; Shiota, S.; Tsuchiya. T.; Matsumoto, T. Chapter II: Effects of natural polyphenols on methicillin-resistant *Staphylococcus aureus* in relation to their chemical and physical properties. ISBN: 978-1-60456-232-3 *Phytochemistry Research Progress* **2008**, 31.

[29] Kumar, C. M.; Singh, S. A. *J. Food Sci. Technol*. **2015**, *52*, 2934.
[30] Porter, J.; Edwards, C.; Pickup, R. W. *J. Appl. Bacteriol.* **1995**, *79*, 399.
[31] Besnard, V.; Federighi, M.; Cappelier, J. M. *Food Microbiol.* **2000**, *17*, 697.
[32] Oliver, J. D. *J. Microbiol.* **2005**, *43,* 93.
[33] Ghosh, S.; Ozek, T.; Tabanca, N.; Ali, A.; Rehman, J.; Khan, I. A.; Rangan, L. *Ind Crops. Prod.* **2014**, *53,* 111.
[34] Prior, L.; Wu, X.; Schaich, K. *J. Agric. Food Chem.* **2005**, *3*, 4290.

Chapter 7

Experimental Section

भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

7.1 Experimental Section:

General: All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in oven-dried glassware under an argon atmosphere. THF and Diethylether (Et_2O) were freshly distilled from Sodium under argon. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus(V)oxide (P_2O_5). Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. Commercial grade xylene, benzene and toluene were distilled before use. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich Acros, Merck and Spectrochem.

^{1}H ^{13}C NMR spectroscopy: *Varian Mercury plus 400 MHz* (at 298 K). Chemical shifts, δ (in ppm), are reported relative to TMS (δ (^{1}H) 0.0 ppm, δ (^{13}C) 0.0 ppm) which was used as the inner reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^{1}H) 7.26 ppm, δ (^{13}C) 77.0 ppm; CD_3OD, (^{1}H) 3.31 ppm, δ (^{13}C) 49.0 ppm) were used for calibration.

Column chromatography: Merck or Spectrochem silica gel 60-120 or neutral alumina (Merck or Fischer Scientific) under gravity.

FT-IR: spectra were recorded on Perkin Elmer Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR Grade).

MS (ESI or APCI-HRMS): Mass spectra were recorded on an Agilent Accurate-Mass Q-TOF LC/MS 6520, and peaks are given in *m/z* (% of basis peak).

X-RD: X–ray crystallographic data were collected using a Bruker SMART APEX–II CCD diffractometer, equipped with a fine focus 1.75 kW sealed tube Mo−Kα radiation (l = 0.71073 Å) at 296(2) K, with increasing w (width of 0.3° per frame) at a scan speed of 3 s/frame. Structures were solved by direct methods using SHELXS–97 and refined with full-matrix least squares on F^2 using SHELXL–97. Using Olex2[1], structure was solved with the Superflip[2] structure solution program using Charge Flipping and refined with the

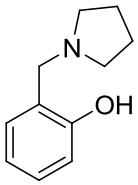
[1] Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K. Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339.
[2] Palatinus, L.; Chapuis, G. *J. Appl. Cryst.* **2007**, *40*, 786.

olex2.refine[3] refinement package using Gauss–Newton minimization. All then non–hydrogen atoms were refined anisotropically.

7.2 Diastereoselective α-C-H Oxygenation of Aliphatic Amines: A General Route to Oxazines

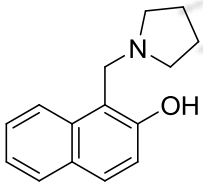
Experimental procedure:

2-((pyrrolidin-1-yl)methyl)phenol (2.63): Pyrrolidine (0.34 mL, 4.09 mmol) was added to



a solution of salisaldehyde (0.43 mL, 4.09 mmol) in 2 mL of ethanol and the reaction mixture was stirred at room temperature for 2.5 h. Then $NaBH_4$ (0.15 g, 4.09 mmol) was added and the reaction mixture was stirred for another 16 h at that temperature. The reaction was then quenched with aqueous 1M HCl (100 μL) solution and the organic solvents were removed under vacuum. Then the mixture was diluted with brine and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried (Na_2SO_4), concetrated in vaccua and the crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 6) to afford **2.63**[4] as brown oil (0.32 g, 45 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.66 (br. s, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 3.79 (s, 2H), 2.60 (s, 4H), 1.82 – 1.81 (m, 4H).

1-((pyrrolidin-1-yl)methyl)naphthalen-2-ol (2.64): Paraformaldehyde (0.16 g, 4.99 mmol)



was heated at 70 °C in benzene (4 mL) for 1 h with stirring. Then mixture was cooled to room temperature and pyrrolidine (0.41 mL, 4.99 mmol), 2-naphthol (0.60 g, 4.16 mmol) were added to the mixture. Then the mixture was refluxed for 18 h. After that the reaction mixture was cooled and the product crystalized as a brown solid on long standing (4 days) at room temperature. Then the solid was washed with a mixture of hexane and ethyl acetate (15:1, 3 X 15 mL) to get amino alcohol **2.64**[5] as light brown solid (0.82 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.6 Hz, 1H), 7.76 – 7.74 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.29 – 7.27

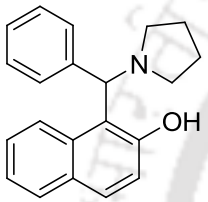
[3] olex2.refine (Bourhis, L. J.; Dolomanov, O.V.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. in preparation, 2011).
[4] Assimomytis, N.; Sariyannis, Y.; Stavropoulos, G.; Tsoungas, P. G.; Varvounis, G. *Synlett* **2009**, 2777.
[5] Huang, J. P.; Stanley, T. C.; Jha, A. *Tetrahedron Lett.* **2009**, *50*, 51.

(m, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 4.29 (s, 2H), 2.74 (br. s, 4H), 1.93 – 1.88 (m, 4H) (-OH proton was not detected).

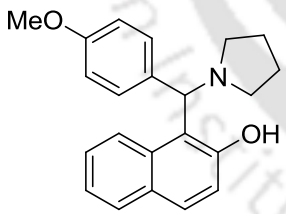
General procedure for the syntheses of Betti base (GP 1):

2-Naphthol or phenol was added to a solution of secondary amine and aldehyde in benzene and the mixture was refluxed for 16 h. After the disappearance of the starting material indicated from TLC, the solvent was removed under reduced pressure and the crude product was subjected to silica gel chromatography or crystalization to afford the amino naphthol/phenol derivatives.

1-(phenyl(pirrolidine-1-yl)methyl)naphthalen-2-ol (2.66): According to GP 1: 2-Naphthol (1.00 g, 6.94 mmol), benzaldehyde (0.85 mL, 8.33 mmol), pyrrolidine (0.85 mL, 10.41 mmol) in benzene 10 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66**[6] as light yellow solid (1.26 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 8.6 Hz, 1H), 7.70 – 7.68 (m, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.62 – 7.59 (m, 2H), 7.39 – 7.35 (m, 1H), 7.28 – 7.17 (m, 4H), 7.15 (d, *J* = 9.2 Hz, 1H), 5.13 (s, 1H), 3.29 (br. s, 1H), 2.65 (br. s, 1H), 2.25 (br. s, 1H), 1.85 (br. s, 5H) (-OH proton was not detected).



1-((4-methoxyphenyl)(pyrrolidine-1-yl)methyl)naphthalen-2-ol (2.66a): According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), *p*-methoxy benzaldehyde (0.20 mL, 1.66 mmol), pyrrolidine (0.17 mL, 2.08 mmol) in benzene 2 mL for 20 h and SiO_2-column chromatography (hexane :ethyl acetate, 20:1) **2.66a**[7] as light orange solid (0.28 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.22 – 7.19 (m, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 1H), 3.71 (s, 3H), 3.21 (br. s, 1H), 2.66 (br. s, 1H), 2.21 (br. s, 2H), 1.84 (s, 4H) (-OH proton was not detected).



[6] Lu, J.; Xu, X.; Wang, S.; Wang, C.; Hu, Y.; Hu, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, *24*, 2900.
[7] Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2011,** *52,* 4957.

1-((pyrrolidine-1-yl)(*p*-tolyl)methyl)naphthalen-2-ol (**2.66b):** According to GP 1: 2-Naphthol (0.40 g, 2.77 mmol), 4-methyl benzaldehyde (0.39 mL, 3.32 mmol), pyrrolidine (0.27 mL, 3.32 mmol) in benzene 4 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66b**[7] as brownish solid (0.53 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.92 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8 Hz, 2H), 7.35 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.20 (dt, *J* = 6.8 Hz, *J* = 1.2 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H) 5.09 (s, 1H), 3.26 – 1.84 (m, 8H), 2.25 (s, 3H).

1-((4-chlorophenyl)(pyrrolidine-1-yl)methyl)naphthalen-2-ol (**2.66c):** According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), *p*-chloro benzaldehyde (0.23 g, 1.66 mmol), pyrrolidine (0.17 mL, 2.08 mmol) in benzene 2 mL for 20 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) **2.66c**[7] as colorless solid (0.44 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.74 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.14 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 1H), 3.26 – 1.84 (m, 8H).

1-((3-nitrophenyl)(pyrrolidin-1-yl)methyl)napthalen-2-ol (**2.66d):** According to GP 1: 2-Naphthol (0.40 g, 2.8 mmol), *m*-nitro benzaldehyde (0.50 g , 3.32 mmol), pyrrolidine (0.27 mL, 3.32 mmol) in benzene 4 mL for 20 h and crystallization to afford **2.66d** as yellow solid (0.40 g, 42%). FTIR (KBr): $\tilde{\nu}$ = 3449, 3086, 2969, 2816, 1621, 1599, 1533, 1468, 1455, 1415, 147, 1313, 1237, 1104, 954, 908, 867, 830, 822, 814, 752, 737, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.49 (s, 1H), 8.46 (s, 1H), 8.08 – 8.06 (m, 1H), 8.00 – 7.98 (m, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.71 (t, *J* = 8.7 Hz, 2H), 7.45 –7.40 (m, 2H), 7.28 – 7.24 (m, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 5.25 (s, 1H), 3.40 – 1.64 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 148.3, 143.5, 134.6, 131.6, 130.2, 130.0, 129.2, 128.7, 126.9, 123.4, 123.0, 122.8, 120.6, 120.1, 115.6, 69.9, 53.6 (br.), 23.5. HRMS (ESI) exact mass calculated for $C_{21}H_{21}N_2O_3^+$ ([M + H]$^+$): 349.1547; Found: 349.1551

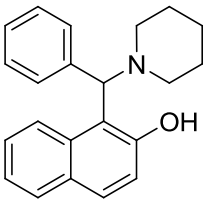
1-((pyridine-2-yl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol (2.66e): According to GP 1: 2-Naphthol (1.00 g, 6.94 mmol), 2-pyridine carboxaldehyde (0.79 mL , 8.33 mmol), pyrrolidine (0.85 mL, 10.41 mmol) in benzene 6 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 15:1) to afford **2.66e** as white solid (1.72 g, 81 %). FTIR (KBr): $\tilde{\nu}$ = 3430, 2971, 2834, 2816, 1622, 1600, 1586, 1519, 1469, 1433, 1353, 1311, 1272, 1146, 1121, 953, 826, 778, 752 719, 629 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 13.73 (s, 1H), 8.48 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.59 (m, 3H), 7.43 (td, *J* = 7.8, 1.6 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.21 – 7.16 (m, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 7.00 – 6.97 (m, 1H), 5.41 (s, 1H), 2.86 – 2.72 (m, 2H), 2.47 – 2.34 (m, 2H), 1.84 – 1.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.8, 155.7, 148.5, 137.1, 132.2, 129.7, 128.6, 128.9, 126.3, 122.8, 122.7, 122.5, 121.8, 119.9, 115.6, 72.6, 53.1, 23.4. HRMS (ESI) exact mass calculated for $C_{20}H_{21}N_2O^+$ ($[M + H]^+$): 305.1648; Found: 305.1659.

6-bromo-1-((2-fluorophenyl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol (2.66f): According to GP 1: 6-Bromo-2-naphthol (0.40 g, 1.79 mmol), 2-fluoro benzaldehyde (0.23 mL, 2.15 mmol), pyrrolidine (0.18 mL, 2.15 mmol) in benzene 4 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66f** as yellowish solid (0.37 g, 52 %). ^1H NMR (400 MHz, $CDCl_3$) δ = 14.00 (s, 1H), 7.83 (s, 1H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.63 – 7.56 (m, 2H), 7.44 – 7.41 (m, 1H), 7.18 – 7.14 (m, 2H), 7.08 – 7.05 (m, 1H), 7.03 – 6.98 (m, 1H), 5.61 (s, 1H), 3.28 – 3.22 (m, 1H), 2.71 (t, *J* = 7.0 Hz, 1H), 2.36 – 2.28 (m, 2H), 1.92 – 1.76 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 161.1, 158.7, 156.7, 130.7, 130.7, 130.1, 129.9, 129.9, 129.8, 128.9, 127.9, 127.8, 125.4, 122.9, 122.9, 121.2, 116.3, 115.6, 115.4, 60.9, 54.9, 51.2, 23.7, 23.4. HRMS (ESI) exact mass calculated for $C_{21}H_{20}BrFNO^+$ ($[M + H]^+$): 400.0707; Found: 400.0712.

1-((2-hydroxyphenyl)(pyrrolidin-1-yl)methyl)naphthalen-2-ol (2.66g): According to GP 1: 2-Naphthol (0.28 g, 1.96 mmol), salicylaldehyde (0.25 mL, 2.35 mmol), pyrrolidine (0.24 mL, 2.94 mmol) in benzene 4 mL in reflux condition for 16 h slow evaporation under ambient condition and washing (hexane, 15 mL) the resulting solid to afford **2.66g** (0.59 g, 96%) as white solid. FTIR (KBr): $\tilde{\nu}$ = 3461, 3056, 2950, 1838, 1615, 1584, 1559, 1057, 1451, 1365, 1275, 1237, 1142, 957, 824, 753, 693, 667, 630, 559, 549, 544, 453 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ = 7.80 (d, *J* = 8.7 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H),

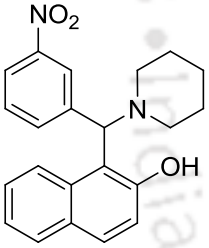
7.04 (t, *J* = 7.4 Hz, 1H), 6.94 – 6.89 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.56 (t, *J* = 7.5 Hz, 1H), 5.80 (s, 1H), 3.21 – 2.86 (m, 2H), 2.61 – 2.31 (m, 2H), 1.82 – 1.68 (m, 4H).^{13}C NMR (101 MHz, DMSO-d_6) δ = 156.4, 154.6, 132.4, 129.4, 129.3, 129.2, 129.0, 128.3, 127.8, 126.9, 122.8, 121.7, 120.3, 120.2, 117.7, 116.0, 61.3, 51.6 (br. 2C) 23.5 (2C). HRMS (ESI) exact mass calculated for $C_{21}H_{22}NO_2^+$ ([M + H]$^+$): 320.1645; Found: 320.1641.

1-(phenyl(piperidine-1-yl)methyl)naphthalen-2-ol (**2.66h):** According to GP 1: 2-



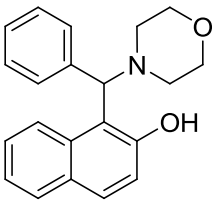
Naphthol (0.20 g, 1.40 mmol), benzaldehyde (0.14 mL, 1.40 mmol), piperidine (0.14 mL, 1.40 mmol) in benzene 2 mL for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66h**[6] as white solid (0.31 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.67 (m, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.37 – 7.33 (m, 1H), 7.27 – 7.17 (m, 4H), 7.14 (d, *J* = 8.9 Hz, 1H), 5.08 (s, 1H), 3.32 – 1.58 (m, 10H) (-OH proton was not detected).

1-((3-nitrophenyl)(piperidine-1-yl)methyl)naphthalen-2-ol (**2.66i):** According to GP 1:



2-Naphthol (0.30 g, 2.08 mmol), *m*-nitro benzaldehyde (0.38 g, 2.50 mmol), piperidine (0.25 mL, 2.50 mmol) in benzene 3 mL for 16 h and crystallization to afford **2.66i** as yellow solid (0.75 g, 99%). FTIR (KBr): $\tilde{\nu}$ = 3422, 3091, 2954, 2850, 2807, 1620, 1597, 1533, 1474, 1449, 1343, 1271, 1237, 1155, 1084, 1069, 830, 816, 749, 734, 690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.60 (s, 1H), 8.40 (s, 1H), 8.07 – 8.04 (m, 1H), 7.98 – 7.89 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.46 – 7.38 (m, 2H), 7.28 – 7.22 (m, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 5.19 (s, 1H), 3.52 – 1.11 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.6, 148.4, 142.1, 135.0, 132.1, 130.1, 129.1, 128.7, 126.9, 123.9, 123.1, 123.0, 122.8, 120.5, 120.2, 115.2, 71.2, 54.6, 52.6, 26.0, 24.0 (restricted inversion of amine leading to 1 carbon more in count). HRMS (ESI) exact mass calculated for $C_{22}H_{23}N_2O_3^+$ ([M + H]$^+$): 363.1703; Found: 363.1685.

1-((morpholino(phenyl)methyl)naphthalen-2-ol (2.66j): According to GP 1: 2-Naphthol

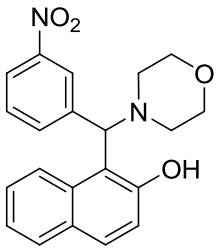


(0.20 g, 1.39 mmol), benzaldehyde (0.17 mL, 1.66 mmol), morpholine (0.14 mL, 1.66 mmol) in benzene 2 mL for 14 h and crystallization to afford **2.66j**[8] as colorless crystal (0.41 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =

[8] Ganesan, S. S.; Rajendran, N.; Sundarakumar, S. I.; Ganesan, A.; Pemiah, B. *Synthesis* **2013**, *45*, 1564.

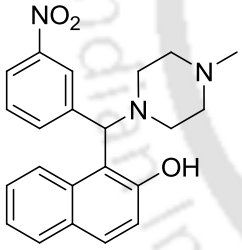
13.12 (s, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.56 – 7.55 (m, 2H), 7.39 – 7.34 (m, 1H), 7.27 – 7.24 (m, 2H), 7.22 – 7.17 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 1H), 3.79 – 3.65 (m, 4H), 3.08 (br. s, 1H), 2.41 – 2.25 (m, 3H).

1-(morpholino(3-nitrophynyl)methyl)naphthalen-2-ol (**2.66k):** According to GP 1: 2-



Naphthol (0.50 g, 3.47 mmol), *m*-nitro benzaldehyde (0.63 mg, 4.16 mmol), morpholine (0.36 mL, 4.16 mmol) in benzene 6 mL for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 6) to afford **2.66k** as yellow foam (1.08 g, 85%). FTIR (KBr): $\tilde{\nu}$ = 3425, 3070, 2959, 2850, 1621, 1599, 1530, 1466, 1449, 1349, 1272, 1234, 1118, 947, 873, 829, 815, 747, 734, 688 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 12.85 (s, 1H), 8.46 (s, 1H), 8.02 – 8.00 (m, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.341 – 7.35 (m, 2H), 7.23 –7.19 (m, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 1H), 3.87 – 2.39 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.8, 148.5, 141.0, 135.0, 132.0, 130.5, 130.2, 129.2, 128.9, 127.1, 124.0, 123.3, 123.0, 120.5, 120.0, 114.1, 71.0, 66.7, 52.0 (br.). HRMS (ESI) exact mass calculated for $C_{21}H_{21}N_2O_4$ ($[M + H]^+$): 365.1496; Found: 365.1485.

1-((4-methylpiperazin-1-yl)(3-nitrophenyl)methyl)naphthalen-2-ol (**2.66l):** According to



GP 1: 2-Naphthol (1.00 g, 6.94 mmol), *m*-nitro benzaldehyde (1.25 g, 8.32 mmol), *N*-methyl piperizine (0.92 mL, 8.32 mmol) in benzene 8 mL for 16 h and SiO_2-column chromatography (DCM : MeOH 50 : 1) to afford **2.66l** as yellow solid (2.58 g, 98%). FTIR (KBr): $\tilde{\nu}$ = 3453, 2939, 2850, 2809, 1623, 1600, 1529, 1465, 1413, 1347, 1291, 1235, 1155, 1137, 1102, 1087, 949, 812, 735, 690, 666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 13.03 (s, 1H), 8.44 (s, 1H), 8.08 – 8.00 (m, 1H), 7.98 – 7.90 (m, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.66 (m, 2H), 7.42 – 7.37 (m, 2H), 7.25 – 7.21 (m, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 1H), 3.32 – 2.32 (m, 8H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.1, 148.4, 141.6, 135.0, 132.0, 130.3, 130.1, 129.1, 128.8, 127.0, 123.9, 123.2, 122.9, 120.5, 120.0, 114.6, 70.6, 54.9, 53.4, 51.4, 45.7 (restricted inversion of amine leading to 1 carbon more in count). HRMS (ESI) exact mass calculated for $C_{22}H_{24}N_3O_3^+$ ($[M + H]^+$): 378.1812; Found: 378.1813.

1-((azepan-1-yl)(phenyl)methyl)naphthalen-2-ol (**2.66m):** According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), benzaldehyde (0.17 mL, 1.66 mmol), hexamethyleneimine (0.19 mL, 1.66 mmol) in benzene 2 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66m**[6] as colorless solid (0.16 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.6 Hz, 1H), 7.58 – 7.51 (m, 4H), 7.28 – 7.25 (m, 1H), 7.15 – 7.10 (m, 3H), 7.07 – 7.03 (m, 2H), 5.19 (s, 1H), 2.67 – 2.42 (m, 4H), 1.72 – 1.40 (m, 8H) (-OH proton was not detected).

1-((azocan-1-yl)(phenyl)methyl)naphthalen-2-ol (**2.66n):** According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), benzaldehyde (0.17 mL, 1.66 mmol), heptamethyleneimine (0.21 mL, 1.66 mmol) in benzene 2 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66n** as yellow oil (85 mg, 18%). FTIR (KBr): $\tilde{\nu}$ = 3453, 2923, 2851, 1621, 1600, 1519, 1453, 1415, 1267, 1237, 1157, 1111, 958, 815, 743, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.09, (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.64 – 7.61 (m, 4H), 7.36 (t, *J* = 8.4 Hz, 1H), 7.22 – 7.19 (m, 2H), 7.17 – 7.13 (m, 3H), 5.26 (s, 1H), 2.73 (br. s, 4H), 1.65 – 1.59 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.3, 140.9, 132.2, 129.5, 129.1, 129.0, 128.8, 128.7, 127.9, 126.5, 122.4, 121.0, 120.1, 117.3, 69.8, 53.0, 27.0, 26.8, 25.4. HRMS (ESI) exact mass calculated for $C_{24}H_{28}NO^+$ ($[M + H]^+$): 346.2165; Found: 346.2162.

1-((diethylamino)(phenyl)methyl)naphthalen-2-ol (2.66o): According to GP 1: 2-Naphthol (0.35 g, 2.43 mmol), benzaldehyde (0.29 mL, 2.91 mmol), diethyl amine (0.30 mL, 2.91 mmol) in benzene 3 mL for 32 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66o**[8] as yellowish solid (0.49 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.31 (s, 1H), 7.87 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.68 – 7.62 (m, 2H), 7.38 – 7.34 (m, 1H), 7.28 – 7.20 (m, 2H), 7.20 – 7.15 (m, 2H), 7.13 (d, *J* = 8.9 Hz, 1H), 5.44 (s, 1H), 2.78 – 2.70 (m, 4H), 1.04 (br. s, 6H).

1-((dibenzylamino)(phenyl)methyl)naphthalen-2-ol (2.66p): According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), benzaldehyde (0.17 mL, 1.66 mmol), dibenzylamine (0.32 mL, 1.66 mmol) in benzene 2 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66p** as yellow solid (0.25 g, 50%). FTIR (KBr): $\tilde{\nu}$ = 3444, 3060, 3027, 2924, 2851, 1621, 1600, 1584, 1519, 1494, 1467, 452, 1414, 1363, 1266, 1235, 1103, 1082, 1060, 1028, 945, 839, 817, 745, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 13.94 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.53 (s, 2H), 7.40 (t, *J* = 8.4 Hz, 1H), 7.28 – 7.22 (m, 7H), 7.14 – 7.09 (m, 9H), 5.53 (s, 1H), 3.77 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.8, 139.9, 132.0, 130.0, 129.4, 129.2, 129.1, 128.9, 128.6, 128.1, 127.6, 126.7, 122.7, 121.2, 120.0, 116.1, 67.2, 53.6. (overlap at aromatic region leading less number of carbon in count) HRMS (ESI) exact mass calculated for $C_{31}H_{28}NO^+$ ($[M + H]^+$): 430.2165; Found: 430.2171.

1-((*N*-benzyl-*N*-methylamino)(phenyl)methyl)naphthalen-2-ol (2.66q): According to GP 1: 2-Naphthol (0.20 g, 1.39 mmol), benzaldehyde (0.17 mL, 1.66 mmol), *N*-methyl benzyl amine (0.32 mL, 1.66 mmol) in benzene 2 mL for 18 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.66q**[9] as white solid (0.34 g, 71%). ^1H NMR (400 MHz, $CDCl_3$) δ = 14.31 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.71 – 7.66 (m, 5H), 7.41 – 7.37 (m, 1H), 7.33 – 7.16 (m, 9H), 5.22 (s, 1H), 3.55 (br. s, 2H), 1.04 (br. s, 3H).

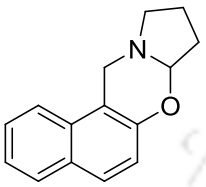
2-(phenyl(pyrrolidin-1-yl)methyl)phenol (2.66r): According to GP 1: Phenol (0.50 g, 5.31 mmol), benzaldehyde (0.65 mL , 6.37 mmol), pyrrolidine (0.52 mL, 6.37 mmol) in benzene 5 mL for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **2.66s**[10] as yellow oil (0.95 g, 71 %). ^1H NMR (400 MHz, $CDCl_3$) δ = 12.33 (s, 1H), 7.46 – 7.44 (m, 2H), 7.26 – 7.22 m, 2H), 7.20 – 7.18 (m, 1H), 7.09 – 7.05 (m, 1H), 6.95 – 6.93 (m, 1H), 6.85 – 6.83 (m, 1H), 6.68 (td, *J* = 7.4, 1.1 Hz, 1H), 4.36 (s, 1H), 2.61 br. s, 2H), 2.46 – 2.45 (m, 2H), 1.80 – 1.77 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.7, 142.2, 128.8, 128.4, 128.3, 127.9, 127.8, 126.8, 119.2, 116.9, 75.8, 53.3, 23.6.

[9] Dong, Y.; Sun, J.; Wang, X.; Xu, X.; Cao, L.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 1667.
[10] Candeias, N. R.; Veiros, L. F.; Afonso, C. A. M.; Gois, P. M. P. *Eur. J. Org. Chem.* **2009**, *12*, 1859.

General procedure for the syntheses of oxazines (GP 2):

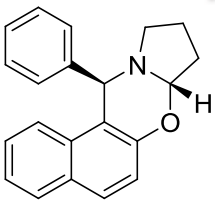
To a solution of Betti base in xylene was added silver oxide and the reaction mixture was refluxed for 24 h. Then the reaction mixture was cooled to room temperature, filtered through a pad of celite and celite cake was washed with ethylacetate. The combined solvents were removed under vacuum and the crude product was subjected to silica gel column chromatography to afford the analytically pure oxazine.

7a,8,9,10-Tetrahydro-11*H*-7-oxa-10a-aza-cyclopenta[*b*]phenanthrene (2.65): According



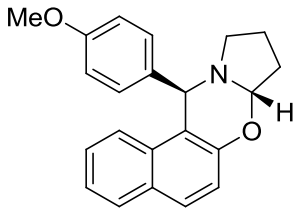
to GP 2: Betti base **2.64** (0.25 g, 1.1 mmol), Ag_2O (0.30 g, 1.32 mmol) stirred at room temperature for 24 hours in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **2.65** as yellow solid (0.16 g, 64 %). FTIR (KBr): $\tilde{\nu}$ = 2979, 2959, 2926, 2838, 1622, 1598, 1513, 1469, 1434, 1397, 1229, 1131, 884, 821, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, *J* = 8.0 Hz, 1H), 7.69 – 7.65 (m, 2H), 7.54 – 7.50 (m, 1H), 7.42 – 7.38 (m, 1H), 7.08 (d, *J* = 8.9 Hz, 1H), 5.25 – 5.08 (m, 1H), 4.64 (d, *J* = 17.1 Hz, 1H), 4.30 (d, *J* = 17.0 Hz, 1H), 3.17 (td, *J* = 8.4, 3.2 Hz, 1H), 3.01 (q, *J* = 8.4 Hz, 1H), 2.28 – 2.19 (m, 2H), 2.16 – 2.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.5, 131.7, 129.0, 128.7, 128.0, 126.5, 123.4, 121.2, 119.0, 110.5, 90.2, 50.0, 44.0, 32.1, 21.3. HRMS (ESI) exact mass calculated for $C_{15}H_{16}NO^+$ ($[M + H]^+$): 226.1226; Found: 226.1221.

***rac*-(7a*S*,11*R*)-11-Phenyl-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza-cyclopenta**



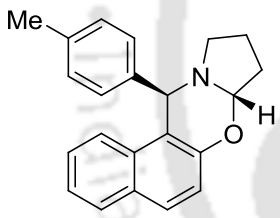
[*b*]phenanthrene (2.67): According to GP 2: Betti base **2.66** (0.10 g, 0.33 mmol), Ag_2O (91 mg, 0.39 mmol) refluxed for 18 h in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67**[6] as brown solid (75 mg, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.7 – 7.74 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.40 – 7.37 (m, 1H), 7.30 – 7.22 (m, 6H), 7.07 (d, *J* = 8.9 Hz, 1H), 5.45 (s, 1H), 5.09 (d, *J* = 3.3 Hz, 1H), 3.36 – 3.31 (m, 1H), 2.92 (q, *J* = 8.3 Hz, 1H), 2.11 – 1.95 (m, 5H).

***rac*-(7a*S*,11*R*)-11-(4-Methoxy-phenyl)-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza-**



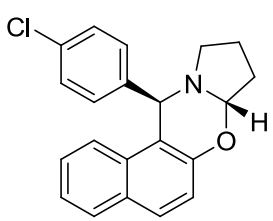
cyclopenta [*b*]phenanthrene (2.67a): According to GP 2: Betti base **2.66a** (0.28 g, 0.84 mmol), Ag_2O (0.23 g, 1.01 mmol) refluxed for 18 h in *p*-xylene 3 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67a** as light yellow solid (0.15 g, 55%). FTIR (KBr): $\tilde{\nu}$ = 2956, 2923, 2831, 1653, 1623, 1597, 1511, 1464, 1260,1244, 1234, 1178, 1029, 814, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.73 (m, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.41 – 7.38 (m, 1H), 7.31–7.22 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.40 (s, 1H), 5.09 (d, *J* = 3.4 Hz, 1H), 3.75 (s, 3H), 3.33 – 3.28 (m, 1H), 2.89 (q, *J* = 8.4 Hz, 1H), 2.10 – 1.97 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.8, 151.8, 135.8, 132.6, 132.3, 129.9, 129.0, 128.6, 126.6, 123.1, 122.8, 118.9, 113.8, 110.7, 86.5, 55.8, 55.3, 50.4, 32.1, 21.1. HRMS (ESI) exact mass calculated for $C_{22}H_{22}NO_2$ ($[M + H]^+$): 332.1645; Found: 332.1660

***rac*-(7a*S*,11*R*)-11-p-Tolyl-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza-cyclopenta**



[*b*]phenanthrene (2.67b): According to GP 2: Betti base **2.66b** (0.20 g, 0.64 mmol), Ag_2O (0.18 g, 0.76 mmol) refluxed for 18 h in *p*-xylene 3 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67b** as light yellow solid (0.13 g, 65%). FTIR (KBr): $\tilde{\nu}$ = 2959, 2923, 2836, 1620, 1597, 1510, 1467, 1233, 990, 816, 756 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.69 (m, 2H), 7.27 – 7.25 (m, 2H), 7.14 – 7.12 (m, 2H) 7.07 – 7.05 (m, 4H), 5.41 (s, 1H), 5.09 (d, *J* = 3.2 Hz, 1H), 3.33 – 3.29 (m, 1H), 2.92 – 2.86 (m, 1H), 2.29 (s, 3H), 2.09 – 1.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.8, 140.6, 136.8, 132.6, 129.2, 129.1, 129.0, 128.7, 128.6, 126.5, 123.0, 122.8, 118.9, 110.6, 86.4, 56.1, 50.4, 32.1, 21.2, 21.1. HRMS (ESI) exact mass calculated for $C_{22}H_{22}NO^+$ ($[M + H]^+$): 316.1696; Found: 316.1680.

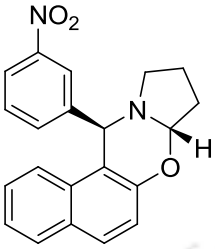
***rac*-(7a*S*,11*R*)-11-(4-Chloro-phenyl)-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza**



cyclopenta [*b*]phenanthrene (2.67c): According to GP 2: Betti base **2.66c** (0.10 g, 0.24 mmol), Ag_2O (82 mg, 0.35 mmol) refluxed for 18 h in *p*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67c** as light yellow solid (70 mg, 70%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2924, 2845, 1654, 1618, 1601, 1261, 1092, 1023, 804 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78 – 7.75

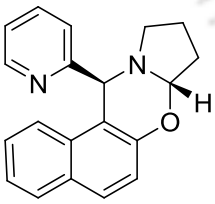
(m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.9 Hz, 1H), 5.41 (s, 1H), 5.02 (d, *J* = 3.2 Hz, 1H), 3.36 – 3.30 (m, 1H), 2.90 (q, *J* = 8.3 Hz, 1H), 2.17 – 1.96 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.9, 142.0, 133.1, 132.5, 130.3, 129.3, 129.0, 128.8, 128.6, 126.8, 123.2, 122.6, 119.0, 109.9, 86.4, 55.7, 50.5, 32.2, 21.1. HRMS (ESI) exact mass calculated for $C_{21}H_{19}ClNO^+$ ($[M + H]^+$): 336.1150; Found: 336.1150.

***rac*-(7a*S*,11*R*)-11-(3-Nitro-phenyl)-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza-cyclopenta**



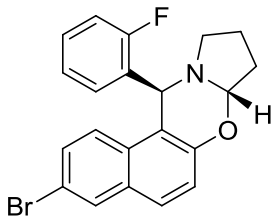
[*b*]phenanthrene (2.67d): According to GP 2: Betti base **2.66d** (0.20 g, 0.57 mmol), Ag_2O (0.16 g, 0.69 mmol) refluxed for 18 h in *p*-xylene 3 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67d** as brown solid (0.16 g, 82%). FTIR (KBr): $\tilde{\nu}$ = 2694, 2839, 1621, 1596, 1529, 119, 1526, 1464, 1346, 1231, 1069, 890, 816, 808, 678 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.33 – 7.26 (m, 3H), 7.13 – 7.05 (m, 1H), 5.51 (s, 1H), 4.97 (s, 1H), 3.44 – 3.32 (m, 1H), 3.00 – 2.88 (m, 1H), 2.18 – 1.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.1, 148.7, 145.7, 134.8, 132.3, 129.8, 129.3, 129.1, 128.9, 127.0, 124.0, 123.4, 122.5, 122.2, 119.2, 108.9, 86.3, 55.6, 50.6, 32.2, 21.1. HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2O_3^+$ ($[M + H]^+$): 347.1390; Found: 347.1395.

***rac*-(7a*S*,11*S*)-11-Pyridin-2-yl-7a,8,9,10-tetrahydro-11*H*-7-oxa-10a-aza-cyclopenta**

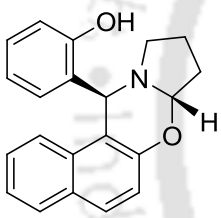


[*b*]phenanthrene (2.67e): According to GP 2: Betti base **2.66e** (0.21 g, 0.66 mmol), Ag_2O (0.18 g, 0.79 mmol) refluxed for 18 h in *m*-xylene 3 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **2.67e** as brown solid (0.13 g, 65%). FTIR (KBr): $\tilde{\nu}$ = 2994, 2961, 2918, 2828, 1622, 1598, 1585, 1464, 1434, 1397, 1269, 1240, 1211, 1134, 991, 898, 835, 820, 767, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 – 8.70 (m, 1H), 7.75 – 7.71 (m, 2H), 7.50 (td, *J* = 7.7, 1.6 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.24 (m, 2H), 7.17 – 7.14 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.59 (s, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 3.48 – 3.43 (m, 1H), 2.96 (q, *J* = 8.5 Hz, 1H), 2.27 – 1.98 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1, 151.9, 150.2, 136.8, 132.4, 129.3, 129.1, 128.7, 126.7, 123.2, 122.8, 122.5, 122.4, 118.9, 109.6, 86.4, 58.9, 50.9, 32.1, 20.8. HRMS (ESI) exact mass calculated for $C_{20}H_{19}N_2O^+$ ($[M + H]^+$): 303.1492; Found: 303.1494.

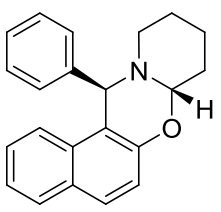
(7a*S*,12*S*)-3-bromo-12-(2-fluorophenyl)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-b][1,3]oxazine (2.67f): According to GP 2: Betti base **2.66f** (40 mg, 0.11 mmol), Ag_2O (30 mg, 0.13 mmol) stirred at 80 °C for 18 h in *m*-xylene 1 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **2.67f** as brown solid (25 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (s, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 1H), 7.24 – 7.14 (m, 3H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 5.74 (s, 1H), 5.12 (s, 1H), 3.75 – 3.69 (m, 1H), 3.43 – 3.37 (s, 1H), 2.95 – 2.89 (m, 1H), 2.18 – 1.95 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.8 (d, *J* = 248.4 Hz), 152.8, 130.7, 130.6, 130.5, 130.4, 130.0, 129.9, 129.4 (d, *J* = 9.1 Hz), 128.4, 124.3, 124.0 (d, *J* = 4.0 Hz), 120.2, 116.9, 115.9 (d, *J* = 21.2 Hz), 109.7, 86.6, 50.5, 49.8 (d, *J* = 4.0 Hz), 32.1, 21.1. HRMS (ESI) exact mass calculated for $C_{21}H_{18}BrFNO^+$ ([M + H]$^+$): 398.0550; Found: 398.0557.



2-((7a*S*,12*R*)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-12-yl)phenol (**2.67g**): According to GP 2: Betti base **2.66g** (30 mg, 0.09 mmol), Ag_2O (26 mg, 0.11 mmol) stirred at room temperature for 48 h in *m*-xylene and ethanol (1:1) 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **2.67g** as brown solid (23 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.95 (s, 1H), 7.79 (dd, *J* = 15.1, 8.4 Hz, 2H), 7.49 – 7.47 (m, 1H), 7.41 – 7.33 (m, 2H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.60 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 7.7 Hz, 1H), 5.74 (s, 1H), 5.19 (s, 1H), 3.37 – 3.32 (m, 1H), 2.87 – 2.80 (m, 1H), 2.16 – 2.08 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.9, 150.9, 133.1, 130.0, 129.8, 129.4, 128.9, 128.8, 127.2, 125.8, 123.7, 122.6, 119.9, 118.9, 117.2, 108.3, 86.1, 54.0, 48.3, 32.0, 21.2. HRMS (ESI) exact mass calculated for $C_{21}H_{19}NO_2^+$([M + H]$^+$): 318.1489; Found: 318. 1484.

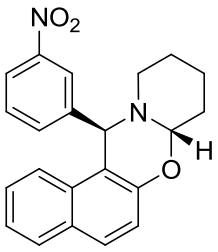


***rac*-(7a*S*,12*R*)-12-Phenyl-8,9,10,11-tetrahydro-7a*H*12*H*-7-oxa-11a-aza-benzo[*a*]anthracene (2.67h):** According to GP 2: Betti base **2.66h** (0.10 g, 0.31 mmol), Ag_2O (87 mg, 0.38 mmol) refluxed for 18 h in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford **2.67h**[6] as colorless solid (0.13 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.75 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.29 – 7.20 (m, 7H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.15 (s, 1H), 4.89 (m, 1H), 2.91 – 2.80



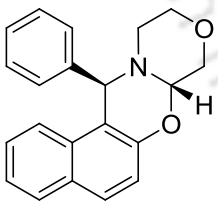
(m, 2H), 1.99 – 1.91 (m, 1H), 1.81 – 1.70 (m, 3H), 1.62 – 1.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4, 143.1, 132.4, 129.5, 129.0, 128.6, 128.2, 127.2, 126.5, 123.1, 122.9, 118.8, 111.3, 81.5, 62.9, 48.5, 29.6, 25.5, 18.4 (overlap at aromatic region leading to 1 carbon less in count).

***rac*-(7a*S*,12*R*)-12-(3-Nitro-phenyl)-8,9,10,11-tetrahydro-7a*H*12*H*-7-oxa-11a-aza-benzo**



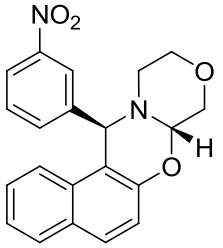
[*a*]anthracene (2.67i): According to GP 2: Betti base **2.66i** (0.30 g, 0.82 mmol), Ag_2O (0.23 g, 0.99 mmol) refluxed for 18 h in *m*-xylene 4 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford **2.67i** as yellow solid (0.23 g, 84%). FTIR (KBr): $\tilde{\nu}$ = 2959, 2925, 1619, 1596, 1521, 1529, 1465, 1434, 1403, 1346, 1235, 1205, 11193, 1117, 1102, 1070, 999, 971, 931, 816, 808, 719, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (s, 1H), 8.11 – 8.06 (m, 1H), 7.82 – 7.79 (m, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.72 – 7.40 (m, 1H), 7.39 – 7.35 (m, 1H), 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 5.20 (s, 1H), 4.76 (t, *J* = 2.4 Hz, 1H), 2.95 – 2.81 (m, 2H), 2.02 – 1.92 (m, 1H), 1.85 – 1.69 (m, 3H), 1.65 – 1.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.5, 148.6, 145.2, 135.5, 132.5, 129.7, 129.1, 129.0, 128.9, 126.9, 124.4, 123.4, 122.4, 122.2, 118.9, 109.7, 81.4, 62.1, 48.5, 29.5, 25.4, 18.2. HRMS (ESI) exact mass calculated for $C_{22}H_{21}N_2O_3^+$ ([M + H]$^+$): 361.1547; Found: 361.1549.

***rac*-(7a*S*,12*R*)-12-Phenyl-7a,8,10,11-tetrahydro-12*H*-7,9-dioxa-11a-aza-**



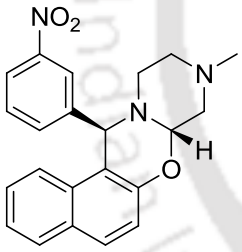
benzo[*a*]anthracene (2.67j): According to GP 2: Betti base **2.66j** (0.25 g, 0.79 mmol), Ag_2O (0.22 g, 0.95 mmol) refluxed for 18 h in *m*-xylene 4 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67j** as white solid (0.11 g, 45%) along with recovered starting material (66 mg, 26%). FTIR (KBr): $\tilde{\nu}$ = 3070, 2918, 2863, 1621, 1597, 1465, 1232, 1134, 1126, 1024, 972, 878, 861, 748, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.71 (m, 2H), 7.40 – 7.18 (m, 9H), 5.19 (s, 1H), 4.69 (s, 1H), 4.04 (d, *J* = 12.1 Hz, 1H), 3.95 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.85 (td, *J* = 11.3, 2.5 Hz, 1H), 3.60 (dd, *J* = 12.1, 1.3 Hz, 1H), 3.17 (td, *J* = 11.4, 3.5 Hz, 1H), 2.74 (d, *J* = 11.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 151.9, 142.1, 132.3, 129.9, 129.8, 129.7, 128.8, 128.8, 127.6, 126.8, 123.5, 122.8, 119.0, 110.5, 79.8, 68.0, 66.0, 62.1, 46.6. HRMS (ESI) exact mass calculated for $C_{21}H_{20}NO_2^+$ ([M + H]$^+$): 318.1489; Found: 318.1492.

***rac*-(7a*S*,12*R*)-12-(3-Nitro-phenyl)-7a,8,10,11-tetrahydro-12*H*-7,9-dioxa-11a-aza-benzo**



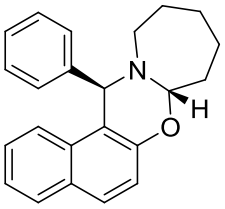
[*a*]anthracene (2.67k): According to GP 2: Betti base **2.66k** (0.20 g, 0.55 mmol), Ag_2O (0.15 g, 0.66 mmol) refluxed for 24 h in *m*-xylene 2 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 10) to afford **2.67k** as yellow solid (0.11 g, 55%). FTIR (KBr): $\tilde{\nu}$ = 2975, 2904, 2850, 1624, 1599, 1530, 1519, 1470, 1438, 1348, 1324, 1276, 1259, 1238, 1216, 1166, 1133, 1094, 1057, 977, 943, 879, 858, 814, 750, 738, 715, 686, 671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.82 – 7.793 (m, 2H), 7.42 – 7.37 (m, 2H), 7.33 – 7.21 (m, 4H), 5.25 (s, 1H), 4.57 (s, 1H), 4.06 (d, *J* = 12.8 Hz, 1H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.88 (t, *J* = 11.6 Hz, 1H), 3.61 (d, *J* = 12.4 Hz, 1H), 3.21 (dt, *J* = 3.2, *J* = 11.2 Hz, 1H), 2.80 (d, *J* =11.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 152.0, 148.7, 144.3, 135.5, 132.2, 130.1, 129.3, 129.1, 127.1, 124.4, 123.7, 122.8, 122.1, 119.1, 109,1, 79.4, 68.5, 66.7, 61.6, 47.6. (overlap at 129 leading to 1 carbon less in count). HRMS (ESI) exact mass calculated for $C_{21}H_{19}N_2O_4^+$ ([M + H]$^+$): 363.1339; Found: 363.1339.

***rac*-(7a*S*,12*R*)-9-Methyl-12-(3-nitro-phenyl)-8,9,10,11-tetrahydro-7a*H*12*H*-7-oxa-**



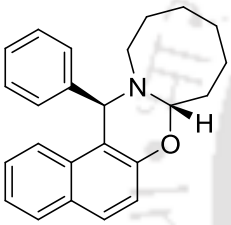
9,11a-diaza-benzo [*a*]anthracene (2.67l): According to GP 2: Betti base **2.66l** (66 mg, 0.17 mmol), Ag_2O (55 mg, 0.19 mmol) heated under 100 ^oC for 24 h in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (DCM : MeOH 100 : 1) to afford **2.67l** as yellow solid (38 mg, 58%). FTIR (KBr): $\tilde{\nu}$ = 2929, 1623, 1529, 1237, 1212, 1159, 1078, 814 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.25 (s, 1H), 8.13 – 8.08 (m, 1H), 7.82 – 7.78 (m, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.33 – 7.29 (m, 2H), 7.26 – 7.20 (m, 2H), 5.28 (s, 1H), 4.70 (m, 1H), 3.25 – 3.19 (m, 1H), 3.14 – 3.12 (m, 1H), 2.95 – 2.89 (m, 2H), 2.48 – 2.42 (m, 1H), 2.36 (s, 3H), 2.20 (dd, *J* = 12.0, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.3, 148.6, 144.8, 135.4, 132.1, 129.7, 129.2, 129.1, 128.9, 126.9, 124.3, 123.5, 122.6, 122.2, 119.4, 109.3, 79.9, 61.2, 57.5, 54.6, 47.9, 46.1. HRMS (ESI) exact mass calculated for $C_{22}H_{22}N_3O_3^+$ ([M + H]$^+$): 376.1656; Found: 376.1672.

***rac*-(7a*S*,13*R*)-13-Phenyl-7a,8,9,10,11,12-hexahydro-13*H*-7-oxa-12a-aza-cyclohepta**



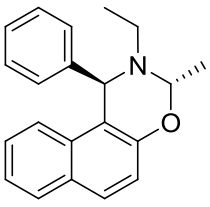
[*b*]phenanthrene (2.67m): According to GP 2: Betti base **2.66m** (0.50 g, 1.51 mmol), Ag_2O (0.42 g, 1.81 mmol) refluxed for 24 h in *m*-xylene 3 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67m**[6] as colorless solid (0.39 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 – 7.62 (m, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.25 – 7.05 (m, 8H), 7.00 (d, *J* = 8.9 Hz, 1H), 5.18 (s, 1H), 4.76 (t, *J* = 7.1 Hz, 1H), 3.20 – 3.04 (m, 1H), 2.62 – 2.49 (m, 1H), 2.12 – 2.05 (m, 1H), 1.81 – 1.50 (m, 5H), 1.42 – 1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.9, 143.1, 132.5, 129.2, 128.9, 128.4, 127.9, 127.0, 126.4, 122.8, 122.6, 118.9, 112.6, 85.2, 64.6, 49.7, 33.9, 30.5, 30.2, 21.8 (overlap at aromatic region leading to 1 carbon less in count). HRMS (ESI) exact mass calculated for $C_{23}H_{24}NO^+$ ($[M + H]^+$): 330.1852; Found: 330.1853.

***rac*-Oxazene 2.67l:** According to GP 2: Betti base **2.66n** (74 mg, 0.21 mmol), Ag_2O (69 mg,



0.26 mmol) refluxed for 24 h in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67n** as light yellow solid (53 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 2963, 2923, 1621, 1596, 1468, 1446, 1404, 1261, 1095, 1920, 1020, 800 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.65 (m, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.26 – 7.12 (m, 8H), 7.01 (d, *J* = 8.9 Hz, 1H), 5.20 (s, 1H), 4.62 – 4.58 (m, 1H), 3.20 – 3.13 (m, 1H), 2.54 – 2.43 (m, 1H), 1.97 – 1.72 (m, 5H), 1.55 – 1.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.7, 143.1, 133.0, 129.6, 129.0, 128.6, 128.2, 127.2, 126.6, 123.1, 122.9, 119.2, 112.6, 86.0, 63.7, 47.0, 30.2, 29.9, 26.4, 25.5, 23.9 (overlap at aromatic region leading to 1 carbon less in count). HRMS (ESI) exact mass calculated for $C_{24}H_{26}NO^+$ ($[M + H]^+$): 344.2009; Found: 344.2009.

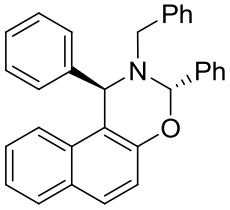
***rac*-(1*R*,3*S*)-2-Ethyl-3-methyl-1-phenyl-2,3-dihydro-1H-naphtho[1,2-*e*][1,3]oxazine**



(2.67o): According to GP 2: Betti base **2.66o** (0.15 g, 0.49 mmol), Ag_2O (0.14 g, 0.59 mmol) stirred in room temperature in *m*-xylene 2 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67o** as brown solid (0.11 g, 73%). FTIR (KBr): $\tilde{\nu}$ = 2964, 2925, 2848, 1651, 1623, 1599, 1513, 1499, 1466, 1449, 1411, 1261, 1236, 1171, 1093, 1051, 1030, 849, 808, 755, 735, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.74 (m, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.38 – 7.27 (m, 8H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.40 (s, 1H), 4.95 (q, *J* = 6.0 Hz, 1H), 3.15 – 3.06 (m, 1H), 2.52 – 2.43 (m, 1H),

1.43 (d, *J* = 6.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 143.4, 133.1, 129.6, 129.1, 128.7, 128.2, 127.2, 126.6, 123.7, 122.9, 118.8, 111.8, 82.6, 59.2, 39.3, 18.8, 15.1 (overlap at aromatic region leading to 1 carbon less in count). HRMS (ESI) exact mass calculated for $C_{21}H_{22}NO^+$ ($[M + H]^+$): 304.1696; Found: 304.1693.

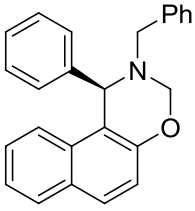
***rac*-(1*R*,3*S*)-2-Benzyl-1,3-diphenyl-2,3-dihydro-1H-naphtho[1,2-*e*][1,3]oxazine (2.67p):**



According to GP 2: Betti base **2.66p** (1.10 g, 2.56 mmol), Ag_2O (0.71 mg, 3.07 mmol) refluxed 20 h in *m*-xylene 10 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **2.67p**[11] as light yellow solid (1.04 g, 95%). FTIR (KBr): $\tilde{\nu}$ = 3022, 2917, 2898, 2881, 2837, 1623, 1597, 1515, 1493, 1466, 1448, 1433, 1396, 1337, 1037, 1233, 1124, 1102, 1066, 1027, 990, 974, 941, 923, 814, 750, 736, 695, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 – 7.81 (m, 1H), 7.70 – 7.68 (m, 1H), 7.43 – 7.20 (m, 19H), 5.99 (s, 1H), 5.39 (s, 1H), 3.90 (d, *J* = 13.9 Hz, 1H), 3.38 (d, *J* = 13.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.8, 143.2, 139.5, 138.2, 133.4, 129.5, 129.4, 129.3, 128.7, 128.5, 128.4, 128.3, 128.1, 127.4, 126.8, 126.6, 123.6, 123.2, 119.0, 112.2, 85.7, 58.1, 49.8 (overlap at aromatic region leading to 2 carbon less in count). HRMS (ESI) exact mass calculated for $C_{31}H_{26}NO^+$ ($[M + H]^+$): 428.2009; Found: 428.2010.

2-Benzyl-1-phenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (2.67q) and *rac*-(1*R*,3*S*)-2-Methyl-1,3-diphenyl-2,3-dihydro-1*H*-naphtho[1,2-*e*][1,3]oxazine (2.67q'): According to GP 2: Betti base **2.66q** (0.26 g, 0.73 mmol), Ag_2O (0.20 g, 0.87 mmol) refluxed 16 h in *m*-xylene 3 mL. SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford diasteriomeric mixtures of **2.67q** & **2.67q'** as colorless solid (0.19 g, 76%). The isomeric ratio (**2.67q** : **2.67q'**, 1: 2.6) was determined from ^{1}H-NMR of the crude product. Diastereomers were further purified for analytical purpose.

2.67q: FTIR (KBr): $\tilde{\nu}$ = 3025, 2997, 2983, 2918, 2852, 16222, 1599, 1511, 1492, 1468, 1451,

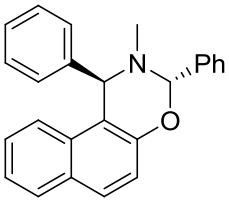


1435, 1402, 1253, 1242, 1226, 1210, 1179, 1141, 1062, 978, 954, 920, 903, 815, 755, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.74 (m, 2H), 7.47– 7.44 (m, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.19 (m, 7H), 7.18 – 7.11 (m, 3H), 5.26 (s, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.71 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.12 (d, *J* = 13.3 Hz, 1H), 3.94 (d, *J* = 13.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ =

[11] Zhang, Y.; Li, Y. H. *Acta Cryst*. **2009**, *E65*, o1796.

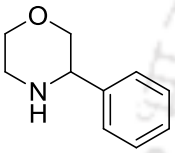
152.1, 143.0, 138.7, 133.0, 129.5, 129.4, 129.3, 129.2, 128.7, 128.6, 128.3, 127.7, 127.4, 126.7, 123.4, 122.8, 118.8, 111.8, 77.9, 57.9, 57.0. HRMS (ESI) exact mass calculated for $C_{25}H_{22}NO^+$ ($[M + H]^+$): 352.1696; Found: 352.1698.

2.67q': FTIR (KBr): $\tilde{\nu}$ = 3060, 3027, 2885, 2798, 1625, 1597, 1512, 1396, 1333, 1232, 1128,



, 989, 942, 923, 810, 751, 705, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.78 (m, 2H), 7.54 – 7.52(m, 2H), 7.45 – 7.20 (m, 12H), 5.77 (s, 1H), 5.40 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ = 152.4, 143.2, 138.1, 133.2, 129.6, 129.3, 128.7, 128.3, 128.2, 128.0, 127.5, 126.7, 126.6, 123.5, 123.1, 119.0, 112.1, 85.4, 63.2, 35.0 (overlap at aromatic region leading to 1 carbon less in count). HRMS (ESI) exact mass calculated for $C_{25}H_{22}NO^+$ ($[M + H]^+$): 352.1696; Found: 352.1694.

3-Phenylmorpholine (2.79): Phenylmagnesiumbromide (1 M in THF, 1.89 mL, 1.89 mmol)



was added dropwise to a powdered oxazine **2.67j** (0.20 g, 0.63 mmol) at 0 °C under argon atmosphere. Then the mixture was stirred at room temperature for 18 h. Then the reaction was quenched by adding saturated aquoues solution of NH_4Cl. The mixture was extracted (3 X 20 mL) with EtOAc. The combined organic layers were dried (Na_2SO_4) and concentrated in vaccuo. The crude product was solidified over long (3 days) standing and solid was washed with ice cold hexane: ethyl acetate 3:1 (5 X 2 mL) to afford the desired amino naphthol (0.21 g, 85%) as white solid. HRMS (ESI) exact mass calculated for $C_{27}H_{26}NO_2^+$ ($[M + H]^+$): 396.1958; Found: 396.1968. Amino naphthol (48 mg, 0.12 mmol) was added to an aqueous solution of NaOH (6 M, 0.12 mL) in THF (0.26 mL) and methanol (0.26 mL). Then the was stirred for 10 h at 80 °C. After the disappearance of the starting material indicated from TLC, the reaction mixture was cooled to room temperature, extracted with diethyl ether (3 X 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuum and the crude product was subjected to neutral alumina column chromatography (DCM : MeOH 500 : 1) to afford **2.79** (12 mg, 61%) as colorless oil. FTIR (KBr): $\tilde{\nu}$ = 3283, 2973, 2850, 1603, 1493, 1455, 1442, 1340, 1316, 1300, 1107, 1075, 908, 880, 885, 756, 700, 647, 525 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40 – 7.28 (m, 5H), 3.94 – 3.81 (m, 3H), 3.66 (td, *J* = 11.3, 2.7 Hz, 1H), 3.40 (dd, *J* = 11.0, 10.2 Hz, 1H), 3.13 (td, *J* = 11.6, 3.3 Hz, 1H), 3.02 – 2.97 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.7, 128.7, 127.9, 127.3, 73.8, 67.4, 60.7, 46.8. HRMS (ESI) exact mass calculated for $C_{10}H_{14}NO^+$ ($[M + H]^+$): 164.1070; Found: 164.1075.

Procedure for one pot synthesis of oxazines 2.67d: 2-naphthol (0.20 g, 1.38 mmol) was added to a solution of pyrrolidine (0.11 mL, 1.38 mmol) and 3-nitrobenzadehyde (0.21 g, 1.38 mmol) in xylene and the mixture was stirred under 100 ^{o}C for 24 h. Then the reaction mixture was cooled to room temperature. Silver oxide (0.48 g, 2.07 mmol) was added, the mixture was heated to reflux and stirred for another 24 h at that temperature. Then the reaction mixture was cooled, filtered through a pad of celite and the celite cake was washed with ethylacetate (3 X 10 mL). The combined solvents were removed under vacuum and the crude product was subjected to SiO_2 column chromatography (EtOAc : Hexane, 1 : 15) to afford the oxazine **2.67d** as yellow solid (0.27 g, 57%). The analytical data is the same as described before.

One pot synthesis of oxazines 2.67i: One pot functionalization of piperidine followed the same procedure as described for **2.67d**. 2-Naphthol (0.20 g, 1.38 mmol), piperidine (0.14 mL, 1.38 mmol), 3-nitrobenzaldehyde (0.21 g, 1.38 mmol), Ag_2O (0.48 g, 2.07 mmol) in 2 mL xylene and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **2.67i** as solid (0.24 g, 48%). The analytical data is the same as described before.

7.2.1 Crystal Data:

Crystal data for 2.67[6]

Table 1: Crystal data and structure refinement for **2.67**

Empirical formula	C_{21} H_{19} N O
Formula weight	301.37
Crystal habit, colour	needle / yellowish
Crystal size, mm^3	0.35 X 0.30 X 0.24 mm
Temperature, *T*	296(2) K
Wavelength, *λ*(Å)	0.71073
Crystal system	monoclinic
Space group	*'P2(1)/c'*
Unit cell dimensions	*a* = 9.7033(6)Å *b* = 6.1115(4)Å *c* = 26.7428(16)Å *α* = 90.00°, *γ* = 90.00°, *β* = 97.569(3)°
Volume, *V*(Å^3)	1572.08(17)
Z	4
Calculated density, Mg·m^{-3}	1.273

Absorption coefficient, μ(mm^{-1})	0.078
F(000)	640
θ range for data collection	1.54° to 28.34°
Limiting indices	$-12 \leq h \leq 12$, $-8 \leq k \leq 7$, $-35 \leq l \leq 35$
Reflection collected / unique	23369 / 2056 [R(int) = 0.1541]
Completeness to θ	99.6% (θ = 28.34°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	2056 / 0 / 208
Goodness–of–fit on F^2	1.067
Final R indices [I>2sigma(I)]	$R1$ = 0.0524, $wR2$ = 0.1054
R indices (all data)	$R1$ = 0.0950, $wR2$ = 0.1129
Largest diff. peak and hole	0.186and – 0.217e·Å^{-3}

Crystal data for 2.67a

Table 2: Crystal data and structure refinement for **2.67a** (CCDC 952462)

Empirical formula	C_{22} H_{21} N O_2
Formula weight	331.40
Crystal habit, colour	columer / colorless
Crystal size, mm^3	0.52 x 0.44 x 0.38 mm
Temperature, T	296(2) K
Wavelength λ(Å)	0.71073
Crystal system	triclinic
Space group	*'p-1'*
Unit cell dimensions	a = 6.5142(6)Å b = 8.4766(7)Å c = 32.727(3)Å α = 89.968(6)°, γ = 72.066(6)°, β = 89.725(6)°
Volume, V(Å^3)	1719.3(3)
Z	4
Calculated density, Mg·m^{-3}	1.280
Absorption coefficient, μ(mm^{-1})	0.082
F(000)	704
θ range for data collection	0.62° to 19.90°
Limiting indices	$-6 \leq h \leq 6$, $-7 \leq k \leq 8$, $-31 \leq l \leq 30$
Reflection collected / unique	14886 / 2306 [R(int) = 0.1751]
Completeness to θ	98.5% (θ = 19.9°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	2306 / 0 / 453
Goodness–of–fit on F^2	1.149
Final R indices [I>2sigma(I)]	$R1$ = 0.0728, $wR2$ = 0.2107
R indices (all data)	$R1$ = 0.0901, $wR2$ = 0.2190
Largest diff. peak and hole	0.243 and –0.262e·Å^{-3}

Crystal data for 2.67d

Table 3: Crystal data and structure refinement for **2.67d**

Empirical formula	C_{21} H_{18} N_2 O_3
Formula weight	346.37
Crystal habit, colour	needle / yellowish
Crystal size, mm^3	0.36X 0.32 X 0.28 mm
Temperature, T	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*'Pca2(1)'*
Unit cell dimensions	a = 8.7131(5) Å b = 15.5575(8) Å c = 12.8693(7) Å α = 90.00°, γ = 90.00°, β = 94.061(2)°
Volume, V(Å^3)	1744.49(16)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.319
Absorption coefficient, μ(mm^{-1})	0.089
F(000)	728
θ range for data collection	2.62° to 30.47°
Limiting indices	$-12 \leq h \leq 10$, $-18 \leq k \leq 22$, $-18 \leq l \leq 18$
Reflection collected / unique	25522 / 3862 [R(int) = 0.0349]
Completeness to θ	97.9% (θ = 30.47°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	3862 / 0 / 235
Goodness–of–fit on F^2	0.686
Final R indices [I>2sigma(I)]	$R1$ = 0.0407, $wR2$ = 0.1124
R indices (all data)	$R1$ = 0.0577, $wR2$ = 0.1297
Largest diff. peak and hole	0.177 and $-0.137 e \cdot Å^{-3}$

Crystal data for 2.67e

Table 4: Crystal data and structure refinement for **2.67e (**CCDC 952463)

Empirical formula	C_{20} H_{18} N_2 O
Formula weight	302.36
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.36 x 0.32 x 0.28 mm
Temperature, T	296(2) K
Wavelength λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P* 21/c'
Unit cell dimensions	a = 10.5276(5)Å b = 8.3530(4)Å c = 18.0400(8)Å

	α = 90.00°, γ = 90.00°, β = 101.988(3)°
Volume, V(Å^3)	1551.79(13)
Z	4
Calculated density, Mg·m^{-3}	1.294
Absorption coefficient, μ(mm^{-1})	0.081
F(000)	640
θ range for data collection	1.98° to 28.23°
Limiting indices	$-13 \leq h \leq 13$, $-8 \leq k \leq 11$, $-16 \leq l \leq 22$
Reflection collected / unique	15036 / 1693 [R(int) = 0.0368]
Completeness to θ	90.0% (θ = 28.23°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	1693 / 0 / 208
Goodness–of–fit on F^2	0.975
Final R indices [I>2sigma(I)]	$R1$ = 0.0529, $wR2$ = 0.1046
R indices (all data)	$R1$ = 0.1305, $wR2$ = 0.1285
Largest diff. peak and hole	0. 133 and –0.174e·Å^{-3}

Crystal data for 2.67g

Table 5: Crystal data and structure refinement for **2.67g**

Empirical formula	C_{21} N O_2 H_{19}
Formula weight	317.14
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.34 X 0.26 X 0.22 mm
Temperature, T	293(2) K
Wavelength, λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*'P b c a'*
Unit cell dimensions	a = 17.556(2) Å b = 6.0965(9) Å c = 30.651(3) Å α = 90.00°, β = 90.00°, γ = 90.00°
Volume, V(Å^3)	3280.6(7)
Z	8
Calculated density, Mg·m^{-3}	1.005
Absorption coefficient, μ(mm^{-1})	0.073
F(000)	1048
θ range for data collection	2.90 to 25.00°
Limiting indices	$-20 \leq h \leq 13$, $-7 \leq k \leq 6$, $-36 \leq l \leq 33$
Reflection collected / unique	7467 / 1151 [R(int) = 0.1069]
Completeness to θ	99.8% (θ = 25.00°)
Refinement method	'SHELXL-97 (Sheldrick, 1997)'
Data / restraints / parameters	1151/0/219
Goodness–of–fit on F^2	0.956
Final R indices [I>2sigma(I)]	$R1$ = 0.0762, $wR2$ = 0.1457
R indices (all data)	$R1$ = 0.1807, $wR2$ = 0.1985
Largest diff. peak and hole	0.178 and –0.273e·Å^{-3}

Crystal data for 2.67h[6]

Table 6: Crystal data and structure refinement for **2.67h**

Empirical formula	C_{22} H_{21} N O
Formula weight	315.40
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.28 X 0.26 X 0.20 mm
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P21/n'*
Unit cell dimensions	*a* = 10.2330(6)Å *b* = 10.1943(6)Å *c* = 16.2308(9)Å α = 90.00°, γ = 90.00°, β = 97.754(5)°
Volume, *V*(Å^3)	1677.69(17)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.249
Absorption coefficient, μ(mm^{-1})	0.076
F(000)	672
θ range for data collection	2.99° to 25.00°
Limiting indices	$-12 \le h \le 12$, $-12 \le k \le 11$, $-19 \le l \le 18$
Reflection collected / unique	5971 / 1961 [*R*(int) = 0.0366]
Completeness to θ	99.8% (θ = 25.00°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	1961 / 0 / 217
Goodness–of–fit on F^2	1.099
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0525, *wR*2 = 0.1267
R indices (all data)	*R*1 = 0.0814, *wR*2 = 0.1503
Largest diff. peak and hole	0.144and −0.186e·Å^{-3}

Crystal data for 2.67i

Table 7: Crystal data and structure refinement for **2.67i** (CCDC 952465)

Empirical formula	C_{22} H_{20} N_2 O_3
Formula weight	360.40
Crystal habit, colour	needle / yellow
Crystal size, mm^3	0.38 x 0.32 x 0.28 mm
Temperature, *T*	296(2) K
Wavelength λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*'Pca2(1)'*
Unit cell dimensions	*a* = 8.8679(18)Å *b* = 15.764(3)Å *c* = 13.088(3)Å

	α = 90.00°, γ = 90.00°, β = 90.00°
Volume, V(Å^3)	1829.7(7)
Z	4
Calculated density, Mg·m^{-3}	1.308
Absorption coefficient, μ(mm^{-1})	0.088
F(000)	760
θ range for data collection	2.58° to 27.59°
Limiting indices	−11 ≤ h ≤ 11, −20 ≤ k ≤ 20, −16≤ l ≤ 16
Reflection collected / unique	19032 / 2632 [R(int) = 0.0680]
Completeness to θ	98.6% (θ = 27.59°)
Refinement method	'SHELXL−97 (Sheldrick, 1997)'
Data / restraints / parameters	2632 / 0 / 244
Goodness−of−fit on F^2	1.011
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.0855
R indices (all data)	R1 = 0.0825, wR2 = 0.1078
Largest diff. peak and hole	0. 282 and −0.280·Å^{-3}

Crystal data for 2.67j

Table 8: Crystal data and structure refinement for **2.67j** (CCDC 952460)

Empirical formula	C_{21} H_{19} N O_2
Formula weight	317.37
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.24 x 0.22 x 0.18 mm
Temperature, T	293(2) K
Wavelength λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P 21/n'*
Unit cell dimensions	a = 16.6693(12)Å b = 6.1313(3)Å c = 17.7664(17)Å α = 90.00°, γ = 90.00°, β = 115.984(11)°
Volume, V(Å^3)	1632.3(2)
Z	4
Calculated density, Mg·m^{-3}	1.291
Absorption coefficient, μ(mm^{-1})	0.083
F(000)	672
θ range for data collection	3.45° to 25.00°
Limiting indices	−18 ≤ h ≤ 19, −6≤ k ≤ 7, −21≤ l ≤ 10
Reflection collected / unique	5126 / 1946 [R(int) = 0.0485]
Completeness to θ	97% (θ = 25.00°)
Refinement method	'SHELXL−97 (Sheldrick, 1997)'
Data / restraints / parameters	1946 / 0 / 217
Goodness−of−fit on F^2	1.091
Final R indices [I>2sigma(I)]	R1 = 0.0550, wR2 = 0.1233
R indices (all data)	R1 = 0.0817, wR2 = 0.1407
Largest diff. peak and hole	0. 216 and −0.211e·Å^{-3}

Crystal data for 2.67m[6]

Table 9: Crystal data and structure refinement for **2.67m**

Empirical formula	C_{23} H_{23} N O
Formula weight	329.42
Crystal habit, colour	needle / yellowish
Crystal size, mm^3	
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P2(1)/n'*
Unit cell dimensions	*a* = 13.6779(8)Å *b* = 15.7357(9)Å *c* = 17.4244(11)Å α = 90.00°, γ = 90.00°, β = 106.959(4)
Volume, *V*($Å^3$)	3587.2(4)
Z	8
Calculated density, $Mg \cdot m^{-3}$	1.220
Absorption coefficient, μ(mm^{-1})	0.074
F(000)	1408
θ range for data collection	1.68° to 21.74°
Limiting indices	$-14 \leq h \leq 14$, $-16 \leq k \leq 16$, $-18 \leq l \leq 18$
Reflection collected / unique	27568 / 2665 [*R*(int) = 0.1065]
Completeness to θ	98.4% (θ = 21.74°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	2665 / 0 / 451
Goodness–of–fit on F^2	1.022
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0598, *wR*2 = 0.1531
R indices (all data)	*R*1 = 0.1037, *wR*2 = 0.1890
Largest diff. peak and hole	0.738and –0. 670e·$Å^{-3}$

Crystal data for 2.67n

Table 10: Crystal data and structure refinement for **2.67n** (CCDC 952458)

Empirical formula	C_{24} H_{25} N O
Formula weight	343.45
Crystal habit, colour	needle / yellowish
Crystal size, mm^3	0.38 x 0.28 x 0.24 mm
Temperature, *T*	293(2) K
Wavelength λ(Å)	0.71073
Crystal system	orthorhombic
Space group	*'Pbca'*
Unit cell dimensions	*a* = 15.2770(6)Å *b* = 12.2434(5)Å *c* = 20.3925(10)Å α = 90.00°, γ = 90.00°, β = 90.00°

Volume, V(Å^3)	3814.3(3)
Z	8
Calculated density, Mg·m^{-3}	1.196
Absorption coefficient, μ(mm^{-1})	0.072
F(000)	1472
θ range for data collection	3.14° to 28.78°
Limiting indices	$-19 \leq h \leq 20$, $-11 \leq k \leq 16$, $-25 \leq l \leq 19$
Reflection collected / unique	10757 / 2091 [R(int) = 0.0506]
Completeness to θ	88.2% (θ = 28.78°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	2091 / 0 / 235
Goodness–of–fit on F^2	0.908
Final R indices [I>2sigma(I)]	R1 = 0.0708, wR2 = 0.2398
R indices (all data)	R1 = 0.1561, wR2 = 0.3194
Largest diff. peak and hole	0. 143 and –0.172e·Å^{-3}

Crystal data for 2.67o

Table 11: Crystal data and structure refinement for **2.67o** (CCDC 952464)

Empirical formula	C_{21} H_{21} N O
Formula weight	303.39
Crystal habit, colour	needle / yellowish
Crystal size, mm^3	0.32 x 0.28 x 0.22 mm
Temperature, T	296(2) K
Wavelength λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P 1 21/c 1'*
Unit cell dimensions	a = 8.4433(3)Å b = 11.6711(4)Å c = 17.1926(6)Å α = 90.00°, γ = 90.00°, β = 94.061(2)°
Volume, V(Å^3)	1689.95(10)
Z	4
Calculated density, Mg·m^{-3}	1.192
Absorption coefficient, μ(mm^{-1})	0.073
F(000)	648
θ range for data collection	2.11° to 25.00°
Limiting indices	$-10 \leq h \leq 10$, $-13 \leq k \leq 13$, $-20 \leq l \leq 20$
Reflection collected / unique	19899 / 1258 [R(int) = 0.1741]
Completeness to θ	99.9% (θ = 25.00°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	1258 / 0 / 210
Goodness–of–fit on F^2	0.89
Final R indices [I>2sigma(I)]	R1 = 0.0479, wR2 = 0.0644
R indices (all data)	R1 = 0.1216, wR2 = 0.0732
Largest diff. peak and hole	0.125 and –0.148e·Å^{-3}

Crystal data for 2.67p[11]

Table 12: Crystal data and structure refinement for **2.67p**

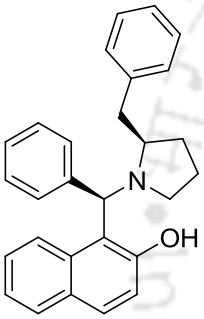
Empirical formula	C_{31} H_{25} N O
Formula weight	427.52
Crystal habit, colour	needle / colorless
Crystal size, mm^3	0.28 X 0.20 X 0.18 mm
Temperature, *T*	296(2) K
Wavelength, λ(Å)	0.71073
Crystal system	monoclinic
Space group	*'P2(1)/n'*
Unit cell dimensions	*a* = 9.06410(10)Å *b* = 23.4826(4)Å *c* = 10.6362(2)Å α = 90.00°, γ = 90.00°, β = 97.5920(10)
Volume, *V*($Å^3$)	2244.06(6)
Z	4
Calculated density, $Mg \cdot m^{-3}$	1.265
Absorption coefficient, μ(mm^{-1})	0.076
F(000)	904
θ range for data collection	1.73° to 38.46°
Limiting indices	$-15 \leq h \leq 14$, $-40 \leq k \leq 41$, $-18 \leq l \leq 17$
Reflection collected / unique	52477 / 6098 [*R*(int) = 0.0447]
Completeness to θ	94.1% (θ = 38.46°)
Refinement method	'SHELXL–97 (Sheldrick, 1997)'
Data / restraints / parameters	6098 / 0 / 298
Goodness–of–fit on F^2	1.043
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0597, *wR*2 = 0.1552
R indices (all data)	*R*1 = 0.1251, *wR*2 = 0.1830
Largest diff. peak and hole	0. 336and −0.189e·$Å^{-3}$

7.3 Iterative C(sp^3)-H Functionalization for the Syntheses of Difunctionalized Secondary Aliphatic Amines

General procedure for First C-C bond formation (GP 3):

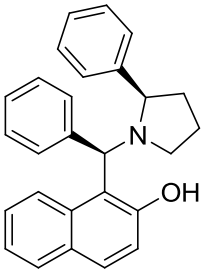
Oxazine (0.3 mmol) was taken in an oven-dried round bottom flask and flashed with argon atmosphere. Suitable Grignard reagent (1M in THF, 0.95 mL) was added dropwise to the oxazine at -3 ^oC. After completion of the reaction (monitored by TLC), the reaction was quenched with saturated NH_4Cl solution (3 mL) and extracted with ethyl acetate (3 X 5 mL). The combined organic layers were dried (over anhydrous Na_2SO_4), concentrated under vacuum and the residue was subjected to neutral alumina column chromatography to get the analytically pure compound.

1-((2-benzylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88a): According to GP 3:



To the oxazine **3.87a** (0.25 g, 0.83 mmol), benzylmagnesium chloride (1 M in THF, 2.5 mL, 2.5 mmol) was added dropwise at -3 ^oC and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford the desired amino naphthol **3.88a** as white solid (0.30 g, 92%). FTIR (KBr): $\tilde{\nu}$ = 3439, 3058, 2962, 2920, 2832, 1619, 1599, 1518, 1466, 1452, 1405, 1270, 1234, 1104, 1089, 951, 816, 758, 743, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 14.13 (s, 1H), 7.84 – 7.82 (m, 1H), 7.71 – 7.67 (m, 4H), 7.37 – 7.26 (m, 4H), 7.24 – 7.09 (m, 5H), 6.62– 6.60 (m, 2H), 5.42 (s, 1H), 3.27 (br. s, 2H), 2.66 – 2.59 (m, 1H), 2.50 – 2.47 (m, 1H), 2.34 – 2.28 (m, 1H), 1.91 – 1.75 (m, 3H), 1.68 – 1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 140.5, 139.4, 132.0, 129.9, 129.8, 129.2, 129.0, 128.9, 128.7, 128.4, 128.4, 126.6, 126.2, 122.5, 121.1, 120.2, 116.9, 71.1, 62.8, 55.9, 43.1, 29.9, 23.7. HRMS (ESI) exact mass calculated for $C_{28}H_{28}NO^+$ ($[M+H]^+$): Cal: 394.2165; Found: 394.2165.

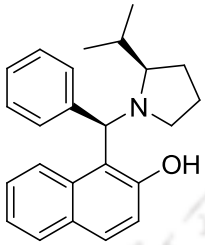
1-(phenyl(2-phenylpyrrolidin-1-yl)methyl)naphthalen-2-ol (3.88b): According to GP 3:



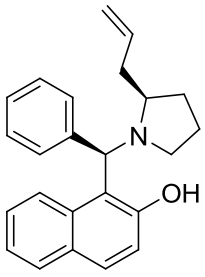
To the oxazine **3.87a** (0.40 g, 1.32 mmol), phenylmagnesium bromide (1 M in THF, 3.9 mL, 3.9 mmol) was added dropwise at 0 ^oC under argon atmosphere for 30 min. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford the desired amino naphthol **3.88b** as white solid (0.45 g, 90%). FTIR (KBr): $\tilde{\nu}$ = 3413, 3059, 3026, 2967, 2869, 1620, 1600, 1583, 1519, 1465, 1450, 1415, 1266, 1234, 1079, 951, 810, 758, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 14.17 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 1H),

7.67 – 7.63 (m, 2H), 7.34 – 7.29 (m, 3H), 7.21 – 7.14 (m, 2H), 7.04 – 7.03 (m, 3H), 6.93 – 6.91 (m, 3H), 6.78 – 6.77 (m, 2H), 5.28 (s, 1H), 3.96 (br. s, 1H), 3.36 (br. s, 1H), 2.72 – 2.66 (m, 1H), 2.39 – 2.32 (m, 1H), 2.13 – 2.03 (m, 1H), 1.99 – 1.86 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6, 140.0, 131.8, 129.6, 129.4, 128.9, 128.6, 128.1 (2C), 128.1, 127.7, 126.9, 126.4, 126.3, 122.4, 121.2, 119.9, 117.0, 70.7, 66.5, 55.2, 35.4, 24.1. HRMS (ESI) exact mass calculated for $C_{27}H_{26}NO^+$ ([M+H]$^+$): Cal: 380.2009; Found: 380.2009.

1-((2-isopropylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88c): According to GP 3: To the oxazine **3.87a** (0.15 g, 0.49 mmol), isopropylmagnesium chloride (2 M in THF, 0.74 mL, 0.74 mmol) was added dropwise at -3 ^{o}C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford an inseparable mixture of diastereomers (1 : 0.05 ratio) of amino naphthol **3.88c** as white solid (0.15 g, 89%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3449, 2970, 2839, 1647, 1622, 1470, 1414, 1268, 1259, 1236, 1100, 1015, 949, 813, 741, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.59 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.68 – 7.65 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.24 – 7.16 (m, 5H), 5.31 (s, 1H), 3.21 – 3.16 (m, 1H), 2.95 – 2.91 (m, 1H), 2.65 – 2.59 (m, 1H), 1.86 – 1.75 (m, 2H), 1.75 – 1.66 (m, 2H), 1.07 – 1.01 (m, 1H), 0.77 (d, *J* = 6.7 Hz, 3H), 0.53 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 140.1, 131.9, 129.7, 129.6, 128.9, 128.5, 128.5, 128.1, 126.4, 122.3, 120.9, 120.0, 117.1, 71.2, 66.3, 55.7, 30.7, 25.4, 24.1, 20.3, 16.1. HRMS (ESI) exact mass calculated for $C_{24}H_{28}NO^+$ ([M+H]$^+$): Cal: 346.2165; Found: 346.2161.

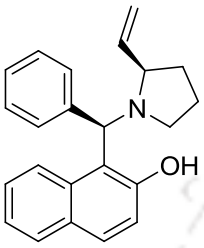


1-((2-allylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88d): Allylmagnesium bromide was prepared by the reaction of allyl bromide (1.66 mmol) and magnesium (1.72 mmol) in dry THF (1.66 mL). After disappearance of the magnesium the freshly prepared allylmagnesium bromide was added (1.5 mL) dropwise to a powdered oxazine **3.87a** (50 mg, 0.17 mmol) at 0 ^{o}C under argon atmosphere. Then the mixture was slowly allowed to reach to room temperature and stirred for 16 h. The crude was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 60) to afford an inseparable mixture of diastereomers (1 : 0.30 ratio) of amino naphthol **3.88d** (44 mg, 78%) as light yellow oil. Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3453, 3062, 2964, 2850, 1639, 1622, 1600, 1584, 1520, 1495, 1454, 1266, 1235, 949, 813, 744, 702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ



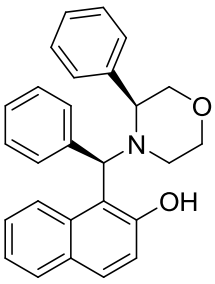
= 14.04 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.63 – 7.61 (m, 2H), 7.36 – 7.32 (m, 1H), 7.18 (m, 5H), 5.57 – 5.46 (m, 1H), 5.36 (s, 1H), 4.96 (d, *J* = 10.1 Hz, 1H), 4.82 (d, *J* = 17.2 Hz, 1H), 3.13 (br. s, 2H), 2.64 – 2.57 (m, 1H), 2.05 – 1.97 (m, 1H), 1.85 – 1.68 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7, 140.2, 135.0, 131.8, 129.6 (2C), 128.9, 128.6 (2C), 128.1, 127.7, 126.4, 122.3, 120.9, 119.9, 117.3, 60.5, 29.9, 29.7, 23.4, 22.7, 21.7. HRMS (ESI) exact mass calculated for $C_{24}H_{26}NO^+$ ($[M+H]^+$): Cal: 344.2009; Found: 344.2001.

1-(phenyl(2-vinylpyrrolidin-1-yl)methyl)naphthalen-2-ol (3.88e): According to GP 3: To



the oxazine **3.87a** (0.10 g, 0.33 mmol), vinylmagnesium bromide (1 M in THF, 0.66 mL, 0.66 mmol) was added dropwise at -3 °C and the mixture was stirred for 6 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 60 with Et_3N 0.1 mL/100 mL) to afford an inseparable mixture of diastereomers (1 : 0.50 ratio) of amino naphthol **3.88e** as yellowish solid (94 mg, 86%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3442, 2919, 2844, 1647, 1622, 1601, 1467, 1453, 1423, 1267, 1236, 813, 744, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.91 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.67 – 7.63 (m, 2H), 7.56 – 7.54 (m, 2H), 7.34 – 7.30 (m, 1H), 7.19 – 7.12 (m, 5H), 5.59 (br. 1H), 5.39 (s, 1H), 4.75 – 4.71 (m, 1H), 4.42 (d, *J* = 16.8 Hz, 1H), 3.54 (br. s, 1H), 2.66 – 2.52 (m, 2H), 2.14 – 1.99 (m, 1H), 1.85 – 1.75 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 141.0, 140.8, 131.9, 129.6, 129.5, 129.0, 128.9, 128.7, 128.6, 128.0, 126.4, 122.4, 121.2, 119.9, 116.7, 68.5, 64.3, 51.6, 31.7, 21.9. HRMS (ESI) exact mass calculated for $C_{23}H_{24}NO^+$ ($[M+H]^+$): Cal: 330.1852; Found: 330.1848.

1-(phenyl(3-phenylmorpholino)methyl)naphthalen-2-ol (3.88f): According to GP 3: To

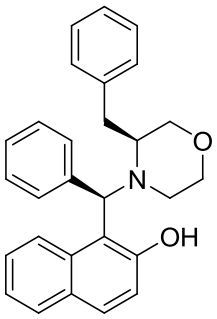


the oxazine **3.87d** (0.12 g, 0.38 mmol), phenylmagnesium bromide (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise at 0 °C and the mixture was stirred for 6 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50 with Et_3N 0.100 mL/ 100 mL) to afford the desired amino naphthol **3.88f**[1] as light yellow solid (0.10 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.50 (s, 1H), 7.74 – 7.71 (m, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.33 – 7.14 (m, 13H), 5.16 (s, 1H), 4.21 – 4.14 (m, 2H), 4.04 – 3.97 (m, 2H), 3.85 – 3.79 (m, 1H), 2.87 – 2.85 (m, 1H), 2.24 –

[1] Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun*. **2014**, *50*, 332.

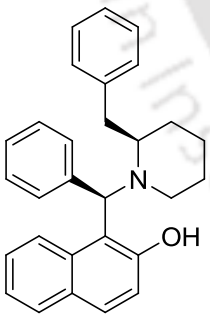
2.22 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.1, 138.7, 132.1, 131.2 (2C), 130.1, 129.9, 129.1, 129.0, 128.8, 128.2 (2C), 128.0, 126.5, 122.8, 121.4, 119.8, 114.9, 71.1, 67.6, 66.8, 59.2, 44.5.

1-((3-benzylmorpholino)(phenyl)methyl)naphthalen-2-ol (3.88g): According to GP 3: To



the oxazine **3.87d** (0.24 g, 0.76 mmol), benzylmagnesium chloride (1 M in THF, 2.3 mL, 2.3 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 40) to afford the desired amino naphthol **3.88g** as white solid (0.28 g, 92%). FTIR (KBr): $\tilde{\nu}$ = 3050, 2956, 2859, 1751, 1621, 1600, 1581, 1497, 1446, 1413, 1266, 1260, 1235, 1117, 1099, 947, 835, 810, 752, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.55 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.83 (br. s, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.37 – 7.34 (m, 3H), 7.30 – 7.21 (m, 2H), 7.14 – 7.12 (m, 3H), 6.65 (br. s, 2H), 5.66 (s, 1H), 3.94 – 3.81 (m, 2H), 3.61 – 3.51 (m, 2H), 3.17 – 3.11 (m, 1H), 3.05 – 2.92 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.1, 138.8, 138.6, 132.5, 129.9, 129.4 (2C), 129.3, 129.0, 128.6 (2C), 128.5, 126.8, 126.4, 122.8, 121.1, 120.2, 116.0, 68.1, 67.9, 67.2, 56.7, 46.4, 26.8. HRMS (ESI) exact mass calculated for $C_{28}H_{28}NO_2^+$ ([M+H]$^+$): Cal: 410.2115; Found: 410.2123.

1-((2-benzylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88h): According to GP 3:

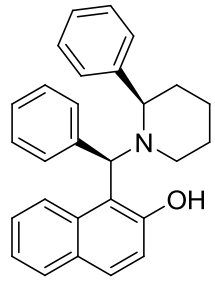


To the oxazine **3.87b** (95 mg, 0.30 mmol), benzylmagnesium chloride (1 M in THF, 0.90 mL, 0.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford the desired amino naphthol **3.88h**[2] as white solid (0.11 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.37 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.43 – 7.40 (m, 1H), 7.36 – 7.27 (m, 4H), 7.24 – 7.21(m, 1H), 7.15 – 7.12 (m, 5H), 6.58 (br. s, 2H), 5.60 (s, 1H), 3.23 – 3.20 (m, 1H), 3.05 – 3.02 (m, 2H), 2.95 – 2.89 (m, 1H), 2.75 (br. s, 1H), 1.83 – 1.70 (m, 3H), 1.59 – 1.46 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8, 139.4, 139.3, 132.3, 129.3, 129.0, 128.9, 128.6, 128.3 (2C), 128.0, 127.9, 126.4, 126.0, 122.3, 120.9, 120.2, 116.9, 68.1, 55.3,

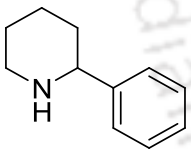
[2] Xu, X.; Lu, J.; Li, R.; Ge, Z.; Dong, Y.; Hu, Y. *Synlett* **2004**, *1*, 122.

45.9, 27.5, 26.8, 25.8, 18.3. HRMS (ESI) exact mass calculated for $C_{29}H_{30}NO^+$ ($[M+H]^+$): Cal: 408.2322; Found: 408.2324.

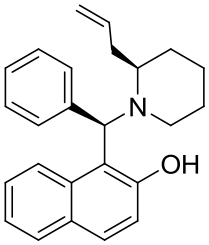
1-(phenyl(2-phenylpiperidin-1-yl)methyl)naphthalen-2-ol (3.88i): Phenylmagnesium bromide was prepared by the reaction of bromobenzene (3.20 mmol) and magnesium (3.30 mmol) in dry THF (3.2 mL). After disappearance of the magnesium, the freshly prepared phenylmagnesium bromide was cooled and added (1.90 mL) dropwise to a powdered oxazine **3.87b** (0.20 g, 0.63 mmol) at 0 °C under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 70) to afford the desired amino naphthol **3.88i**[3] as white solid (0.18 g, 72%) and **3.88i'**[4] (DCM : MeOH, 200 : 1) as reddish oil (25 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.65 (s, 1H), 7.53 – 7.54 (m, 2H), 7.33 (br. s, 3H), 7.18 – 7.11 (m, 3H), 6.95 – 6.84 (m, 8H), 5.60 (s, 1H), 3.71 (br. s, 1H), 2.94 (br. s, 1H), 1.98 – 1.78 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.1, 141.4, 139.1, 131.4, 130.2, 129.2, 128.8, 128.5, 128.2, 128.1, 127.8, 127.3, 126.5, 125.4, 122.5, 121.9, 120.2, 115.7, 70.5, 68.8, 52.3, 35.4, 26.2, 24.5. HRMS (ESI) exact mass calculated for $C_{28}H_{28}NO^+$ ($[M+H]^+$): Cal: 394.2165; Found: 394.2164.



2-Phenylpiperidine (3.88i'): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.29 (m, 4H), 7.26 – 7.22 (m, 1H), 3.60 – 3.57 (m, 1H), 3.21 – 3.18 (m, 1H), 2.84 – 2.76 (m, 1H), 1.90 – 1.88 (m, 1H), 1.81 – 1.78 (m, 1H), 1.67 – 1.65 (m, 1H), 1.57 – 1.49 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 145.2, 128.2, 126.9, 126.5, 62.2, 47.6, 34.7, 25.7, 25.2.



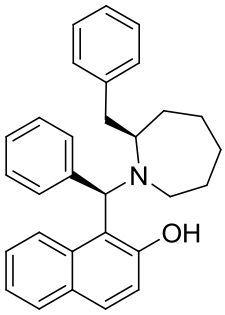
1-((2-allylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88j): According to GP 3: To the oxazine **3.87a** (0.20 g, 0.63 mmol), allylmagnesium bromide (1 M in diethylether, 1.90 mL, 1.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 40) to afford an inseparable mixture of diastereomers (1 : 0.85 ratio) of amino naphthol **3.88j**[3] as white solid (0.10 g, 45%). FTIR (KBr): $\tilde{\nu}$ = 3450, 3058, 2914, 2853,



[3] Xu, X.; Lu, J.; Dong, Y.; Li, R.; Ge, Z.; Hu, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 475.
[4] Hussain, S.; Leipold, F.; Man, H.; Wells, E.; France, S. P.; Mulholland, K. R.; Grogan, G.; Turner, N. J. *ChemCatChem* **2015**, *7*, 579.

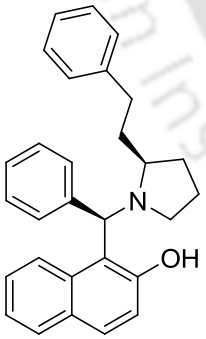
1714, 1622, 1599, 1466, 1263, 1233, 1088, 1028, 957, 812, 745, 700 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{25}H_{28}NO^+$ ([M+H]$^+$): Cal: 358.2165; Found: 358.2158.

1-((2-benzylazepan-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88k): According to GP 3: To



the oxazine **3.87c** (0.10 g, 0.30 mmol), benzylmagnesium chloride (1 M in THF, 0.90 mL, 0.90 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford the desired amino naphthol **3.88k** as white solid (0.12 g, 97%). FTIR (KBr): $\tilde{\nu}$ = 3399, 3058, 2928, 2853, 1618, 1600, 1581, 1576, 1520, 1455, 1420, 1269, 1237, 1153, 1055, 943, 823, 750, 719, 696 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 14.22 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.81 (br. s, 2H), 7.70 – 7.68 (m, 1H), 7.65 – 7.62 (m, 1H), 7.44 – 7.39 (m, 1H), 7.32 – 7.28 (m, 2H), 7.25 – 7.20 (m, 2H), 7.16 – 7.11 (m, 4H), 6.66 (br. s, 2H), 5.69 (s, 1H), 3.42 – 3.38 (m, 1H), 3.15 – 3.12 (m, 1H), 3.04 – 2.93 (m, 2H), 2.71 – 2.65 (m, 1H), 1.95 – 1.80 (m, 2H), 1.66 – 1.36 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7, 140.3, 139.4, 132.2, 131.9, 129.5, 129.5, 128.9, 128.7, 128.4, 127.9, 126.6, 126.1, 126.0, 122.3, 120.6, 119.8, 116.2, 66.4, 59.6, 45.5, 32.3, 28.4, 27.5, 23.6, 22.9. HRMS (ESI) exact mass calculated for $C_{30}H_{32}NO^+$ ([M+H]$^+$): Cal: 422.2478; Found: 422.2475.

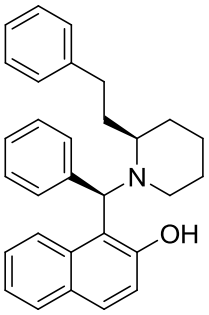
1-((2-phenethylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88aa): According to



GP 3: To the oxazine **3.87a** (0.60 g, 1.99 mmol), phenethylmagnesium chloride (1 M in THF, 4.4 mL, 4.40 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 40) to afford an inseparable mixture of diastereomers (1 : 0.10 ratio) of amino naphthol **3.88aa** as colorless oil (0.72 g, 89%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3061, 3026, 2959, 2857, 1621, 1601, 1520, 1453, 1267, 1237, 950, 814, 744, 700 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.27 (s, 1H), 7.78 – 7.77 (m, 1H), 7.67 – 7.64 (m, 2H), 7.58 – 7.57 (m, 2H), 7.33 – 7.31 (m, 1H), 7.22 – 7.09 (m, 8H), 6.81 – 6.80 (m, 2H), 5.32 (s, 1H), 3.18 (br. s, 1H), 3.03 (s, 1H), 2.59 – 2.55 (m, 1H), 2.39 – 2.35 (m, 1H), 2.21 – 2.18 (m, 1H), 2.07– 2.00 (m, 1H), 1.82 – 1.78 (m, 2H), 1.66 – 1.64 (m, 1H), 1.42 – 1.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 141.6, 140.3, 131.9, 129.7 (2C), 129.0, 128.8 (2C), 128.7, 128.3 (2C),

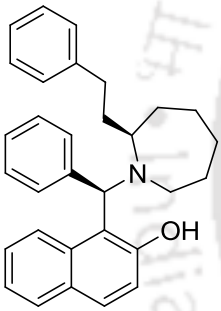
126.5, 125.78, 122.5, 121.1, 120.2, 117.0, 70.6, 60.8, 55.5, 37.5, 32.9, 30.6, 23.6. HRMS (ESI) exact mass calculated for $C_{29}H_{30}NO^+$ ($[M+H]^+$): Cal: 408.2322; Found: 408.2321.

1-((2-phenethylpiperidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.88bb): According to



GP 3: To the oxazine **3.87a** (0.50 g, 1.58 mmol), phenethylmagnesium chlroide (1 M in THF, 4.5 mL, 4.5 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 70) to afford an inseparable mixture of diastereomers (1 : 0.50 ratio) of amino naphthol **3.88bb** as white solid (0.59 g, 90%). FTIR (KBr): $\tilde{\nu}$ = 3478, 3064, 3025, 2936, 2859, 1601, 1583, 1520, 1454, 1416, 1362, 1266, 1238, 1156, 1073, 943, 833, 814, 740, 699 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{30}H_{32}NO^+$ ($[M+H]^+$): Cal: 422.2478; Found: 422.2479.

Amino naphthol (3.88cc): According to GP 3: To the oxazine **3.87a** (0.60 g, 1.58 mmol),



phenethylmagnesium chlroide (1 M in THF, 4.0 mL, 4.0 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastreomers (1 : 0.60 ratio) of amino naphthol **3.88cc** as brown oil (0.75 g, 94%) FTIR (KBr): $\tilde{\nu}$ = 3060, 3026, 2929, 2858, 1621, 1600, 1519, 1495, 1453, 1266, 1236, 1140, 1060, 1029, 946, 815, 744, 699 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{31}H_{34}NO^+$ ($[M+H]^+$): Cal: 436.2636; Found: 436.2638.

General procedure for Second C-O bond formation (GP 4):

Betti Base with mono-functionalized amine (0.18 mmol) was treated with silver oxide (0.22 mmol) in xylene at either room temperature or under heating (60-80 °C) condition to obtain the cyclic oxazine.[1] After completion of the reaction, the reaction mixture passed through small pad of celite and the celite cake was washed with ethyl acetate. The organic layer was concentrated under vaccum and the crude mixture was subjected to neutral alumina column chromatography.

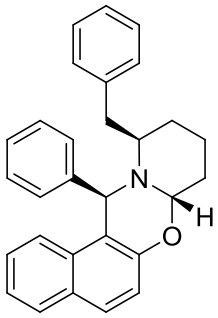
10-benzyl-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (3.89a): According to GP 4: A mixture of Betti base **3.88a** (30 mg, 0.08 mmol), Ag_2O (23 mg, 0.10 mmol) heated at 60 °C for 12 h in *m*-xylene 1 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford an inseparable mixture of diastreomers (1 : 0.12 ratio) of oxazine **3.89a** as a whitish solid (25 mg, 78%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3060, 3026, 2925, 2926, 2852, 1623, 1599, 1515, 1466, 1451, 1234, 1140, 1027, 922, 812, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.69 (m, 2H), 7.25 – 7.16 (m, 13H), 7.06 (d, *J* = 8.9 Hz, 1H), 5.46 (s, 1H), 5.15 – 5.14 (m, 1H), 3.35 – 3.26 (m, 2H), 2.83 – 2.78 (m, 1H), 2.09 – 1.99 (m, 2H), 1.97 – 1.90 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.2, 143.4, 139.2, 132.5, 130.2, 129.3, 128.8, 128.7, 128.5, 128.4, 128.3, 127.2, 126.5, 126.2, 123.0, 122.6, 118.9, 110.4, 87.8, 60.6, 54.4, 42.4, 30.1, 27.8. HRMS (ESI) exact mass calculated for $C_{28}H_{26}NO^+$ ($[M+H]^+$): Cal: 392.2009; Found: 392.2006.

10,12-diphenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (3.89b): According to GP 4: A mixture of Betti base **3.88b** (0.20 g, 0.53 mmol), Ag_2O (0.15 g, 0.63 mmol) stirred at room temperature for 8 h in *m*-xylene 2.5 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of regio-isomer (1 : 0.76 ratio) of oxazine **3.89b** as whitish solid (0.18 g, 93%). FTIR (KBr): $\tilde{\nu}$ = 2961, 2925, 2842, 1620, 1598, 1492, 1463, 1449, 1433, 1241, 1107, 1066, 1027, 921, 813, 754, 694 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{27}H_{24}NO^+$ ($[M+H]^+$): Cal: 378.1852; Found: 378.1864.

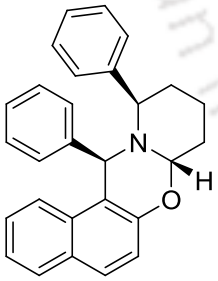
(7a*S*,10*R*,12*R*)-10-isopropyl-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (3.89c): According to GP 4: A mixture of Betti base **3.88c** (92 mg, 0.27 mmol) and Ag_2O (74 mg, 0.32 mmol) heated at 60 °C temperature for 12 h in *m*-xylene 1 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 150) to afford oxazine **3.89c** as a colorless solid (75 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 3058, 2950, 2874, 2817, 1622, 1597, 1509, 1491, 1465, 1386, 1232, 1066, 1012, 892, 814, 751, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.70 (m, 3H), 7.50 – 7.43 (m, 2H), 7.31 – 7.28 (m, 5H), 7.13 (d, *J* = 8.8 Hz, 1H), 5.47 (s, 1H), 5.20 (s, 1H), 3.04 (br. s, 1H), 2.24 (br. s, 1H), 2.09 – 1.98 (m, 2H), 1.89 – 1.84 (m, 1H), 1.75 – 1.73 (m, 1H), 1.09 (d, *J* = 4.0

Hz, 3H), 0.93 (d, J = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.7, 143.8, 132.8, 130.5, 129.1, 129.0, 128.9, 128.5, 127.2, 126.6, 123.0, 122.7, 119.1, 110.7, 88.3, 64.4, 54.3, 30.9, 29.4, 21.6, 20.2, 14.8. HRMS (ESI) exact mass calculated for $C_{24}H_{26}NO^+$ ($[M+H]^+$): Cal: 344.2009; Found: 344.2011.

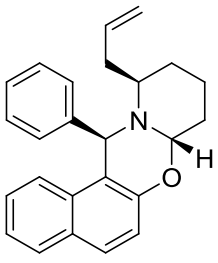
11-benzyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (3.89d): According to GP 4: A mixture of Betti base **3.88h** (25 mg, 0.06 mmol) and Ag_2O (17 mg, 0.07 mmol) refluxed at 140 °C for 18 h in *m*-xylene 1 mL. The crude product was subjected to SiO_2-chromatography (EtOAc : Hexane, 1 : 40) to afford an inseparable mixture of diastreomers (1 : 0.05 ratio) of oxazine **3.89d**[2] as yellowish solid (17 mg, 69%). Following analytical data are given for major isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.74 (m, 2H), 7.29 – 7.22 (m, 8H), 7.13 – 7.08 (m, 4H), 7.03 – 7.01 (m, 2H), 5.91 (s, 1H), 4.98 (s, 1H), 3.46 – 3.41 (m, 1H), 3.10 – 3.05 (m, 1H), 2.72 – 2.66 (m, 1H), 1.97 – 1.92 (m, 1H), 1.81 – 1.74 (m, 1H), 1.61 – 1.52 (m, 3H), 1.45 – 1.35 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.9, 143.6, 139.3, 132.9, 129.5, 129.3, 129.8, 128.9, 128.6, 128.4, 128.3, 127.1, 126.7, 126.2, 123.1, 122.6, 118.7, 110.9, 82.4, 55.8, 54.1, 42.2, 31.9, 29.9, 18.5. HRMS (ESI) exact mass calculated for $C_{29}H_{28}NO^+$ ($[M+H]^+$): Cal: 406.2165; Found: 406.2169.



11,13-diphenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (3.89e): According to GP 4: A mixture of Betti base **3.88i** (34 mg, 0.09 mmol), Ag_2O (23 mg, 0.10 mmol) heated at 60 °C temperature for 12 h in *m*-xylene 1 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford an inseparable mixture of regio-isomer (1 : 1 ratio) of oxazine **3.89e**[2] as light yellow solid (25 mg, 74%). HRMS (ESI) exact mass calculated for $C_{28}H_{26}NO^+$ ($[M+H]^+$): Cal: 392.2009; Found: 392.2009.

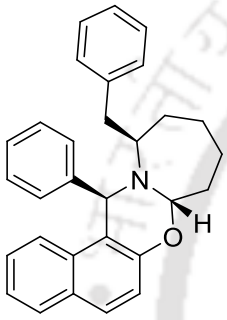


11-allyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (3.89f): According to GP 4: A mixture of Betti base **3.88j** (20 mg, 0.05 mmol) and Ag_2O (15 mg, 0.07 mmol) heated at 80 °C temperature for 12 h in *m*-xylene 0.5 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastereomers (1 : 0.27 ratio) of oxazine **3.89f** as a colorless oil

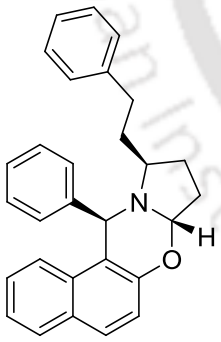


(12 mg, 61%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3061, 2936, 2850, 1650, 1623, 1599, 1466, 1403, 1237, 911, 886, 811, 743, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.72 (m, 2H), 7.40 – 7.37 (m, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 5H), 7.12 (d, *J* = 8.9 Hz, 1H), 5.98 – 5.89 (m, 1H), 5.81 (s, 1H), 5.16 – 5.10 (m, 2H), 4.96 (s, 1H), 2.89 – 2.83 (m, 1H), 2.47 – 2.44 (m, 2H), 1.92 – 1.81 (m, 2H), 1.72 – 1.68 (m, 1H), 1.61 – 1.55 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.7, 143.3, 135.1, 132.7, 129.4, 129.0, 128.7, 128.6, 128.1, 126.9, 126.6, 122.9, 122.3, 118.5, 117.0, 110.8, 82.4, 55.2, 51.9, 38.8, 31.3, 29.7, 18.5. HRMS (ESI) exact mass calculated for $C_{25}H_{26}NO^+$ ($[M+H]^+$): Cal: 356.2009; Found: 356.2006.

Oxazine (3.89g): According to GP 4: A mixture of Betti base **3.88k** (60 mg, 0.14 mmol), Ag_2O (39 mg, 0.17 mmol) heated at 65 ^{o}C temperature for 8 h in *m*-xylene 1 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastereomers with (1 : 0.90 ratio) of oxazine **3.89g** as a colorless oil (40 mg, 67%). FTIR (KBr): $\tilde{\nu}$ = 2959, 2926, 2853, 1723, 1623, 1599, 1514, 1466, 1450, 1260, 1234, 1093, 1078, 806, 746, 700 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{30}H_{30}NO^+$ ($[M+H]^+$): Cal: 420.2322; Found: 420.2310.



10-phenethyl-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (3.89aa): According to GP 4: A mixture of Betti base **3.88aa** (75 mg, 0.18 mmol) and Ag_2O (51 mg, 0.22 mmol) heated at 80 ^{o}C temperature for 16 h in *m*-xylene 1 mL. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastereomers (1 : 0.60 ratio) of oxazine **3.89aa** as colorless oil (65 mg, 87%). FTIR (KBr): $\tilde{\nu}$ = 2953, 2921, 2853, 1627, 1558, 1506, 1466, 1236, 1065, 811, 746, 668 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{29}H_{28}NO^+$ ($[M+H]^+$): Cal: 406.2165; Found: 406.2168.

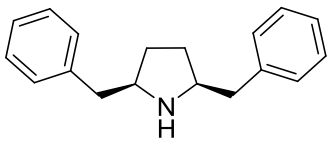


11-phenethyl-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (3.89bb): According to GP 4: A mixture of Betti base **3.88bb** (0.47 g, 1.25 mmol) and Ag_2O (0.35 g, 1.5 mmol) heated at 110 ^oC for 12 h in *m*-xylene 4 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford oxazine **3.89bb** as light green oil (0.22 g, 46%). FTIR (KBr): $\tilde{\nu}$ = 3026, 2925, 2856, 1622, 1601, 1495, 1453, 1262, 1063, 1028, 813, 747, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.78 – 7.76 (m, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.19 (m, 9H), 7.15 – 7.10 (m, 4H), 5.80 (s, 1H), 4.99 (s, 1H), 2.92 – 2.84 (m, 2H), 2.67 – 2.52 (m, 1H), 2.09 – 2.02 (m, 1H), 1.93 (m, 3H), 1.87 – 1.82 (m, 1H), 1.65 – 1.55 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.9, 143.5, 142.7, 133.0, 129.5, 129.2, 128.9, 128.8, 128.6, 128.4, 128.3, 127.2, 126.9, 126.0, 123.1, 122.5, 118.7, 110.9, 82.5, 55.4, 52.7, 36.7, 31.3 (2C), 30.0, 18.8. HRMS (ESI) exact mass calculated for $C_{30}H_{30}NO^+$ ($[M+H]^+$): Cal: 420.2322; Found: 420.2322.

Oxazine (3.89cc): According to GP 4: A mixture of Betti base **3.88cc** (0.26 g, 0.59 mmol) and Ag_2O (0.17 g, 0.72 mmol) heated at 80 ^oC temperature for 12 h in *m*-xylene 0.5 mL. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastreomers (1 : 1 ratio) of oxazine **3.89cc** as a colorless oil (0.175 g, 68%). FTIR (KBr): $\tilde{\nu}$ = 3059, 3025, 2926, 2857, 1622, 1599, 1467, 1450, 1280, 1237, 1045, 813, 745, 699 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{31}H_{32}NO^+$ ($[M+H]^+$): Cal: 434.2478; Found: 434.2464.

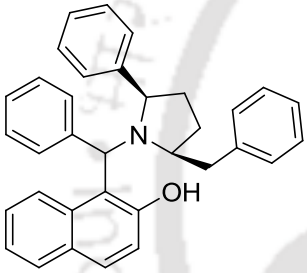
1-((2,5-dibenzylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90a): According to GP 3: To the oxazine **3.89a** (0.15 g, 0.38 mmol), benzylmagnesium chloride (1 M in THF, 1.22 mL, 1.22 mmol) was added dropwise at -3 ^oC and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 50 with Et_3N 100 μL/100 mL) to afford an inseparable mixture of diastreomers (1 : 0.72 ratio) of amino naphthol **3.90a** as whitish solid (0.13 g, 66%). FTIR (KBr): $\tilde{\nu}$ = 3440, 3031, 2924, 2850, 1621, 1600, 1520, 1495, 1467, 1452, 1265, 1235, 1095, 949, 816, 742, 700 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{35}H_{34}NO^+$ ($[M+H]^+$): Cal: 484.2635; Found: 484.2638.

***cis*-2,5-dibenzylpyrrolidine (3.91a)**: Compound **3.90a** (22 mg, 0.05 mmol) was dissolved in



NaOH (6M, 0.2 mL) solution in mixture of THF (0.10 mL) and MeOH (0.10 mL). The reaction mixture was heated at 60 ^{o}C for 4 h. Then the reaction mixture was extracted with ethyl acetate (3 X 5 mL) and the combined organic layers washed with brine and dried over Na_2SO_4. The resulting crude was subjected to neutral alumina column chromatography (DCM) to afford the analytically pure compound **3.91a**[5] as brown oil (10 mg, 88%). FTIR (KBr): $\tilde{\nu}$ = 2923, 2852, 1627, 1602, 1495, 1453, 1269, 1220, 1096, 1029, 747, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.25 (m, 5H), 7.20 – 7.16 (m, 5H), 3.22 – 3.19 (m, 2H), 2.81 – 2.69 (m, 4H), 1.80 – 1.75 (m, 2H), 1.49 – 1.42 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.1, 129.2, 128.6, 126.3, 60.5, 42.9, 30.6. HRMS (ESI) exact mass calculated for $C_{18}H_{22}N^+$ ([M+H]$^+$): Cal: 252.1747; Found: 252.1753.

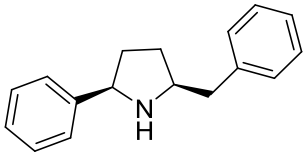
1-((2-benzyl-5-phenylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90b) :



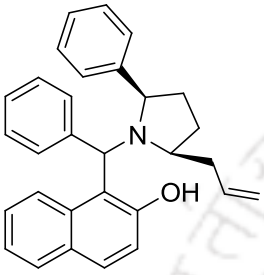
According to GP 3: To the oxazine **3.89b** (40 mg, 0.11 mmol), benzylmagnesium chloride (1 M in THF, 0.42 mL, 0.42 mmol) was added dropwise at -3 ^{o}C and the mixture was stirred for 6 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastereomers (1 : 0.36 ratio) of amino naphthol **3.90b** as white solid (28 mg, 58%) and **3.91b** (by DCM) as brown oil (10 mg, 40%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3060, 2953, 2853, 1653, 1623, 1600, 1492, 1433, 1233, 1027, 883, 812, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.60 (s, 1H), 7.75 – 7.69 (m, 3H), 7.39 (d, *J* = 7.8 Hz, 3H), 7.16 – 7.07 (m, 8H), 6.98 – 6.94 (m, 3H), 6.83 – 6.80 (m, 2H), 6.75 – 6.73 (m, 2H), 5.55 (s, 1H), 4.06 – 4.02 (m, 1H), 3.42 – 3.38 (m, 1H), 2.79 – 2.73 (m, 1H), 2.23 – 2.17 (m, 1H), 2.06 – 2.00 (m, 1H), 1.94 – 1.78 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.0, 143.9, 139.5, 139.4, 131.7, 130.0, 129.8, 129.1, 128.7, 128.3, 128.2, 128.0, 127.7, 127.5, 127.3, 126.5, 126.4, 126.0, 122.5, 120.8, 120.1, 118.3, 72.6, 70.4, 69.3, 41.0, 35.5, 28.1. HRMS (ESI) exact mass calculated for $C_{34}H_{32}NO^+$ ([M+H]$^+$): Cal: 470.2478; Found: 470.2494.

[5] Fraser, R. R.; Passannanti, S. *Synthesis*, **1976**, *8*, 540.

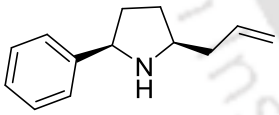
(2S,5R)-2-benzyl-5-phenylpyrrolidine (3.91b): FTIR (KBr): $\tilde{\nu}$ = 2961, 2923, 2852, 1652, 1639, 1495, 1453, 1079, 906, 770, 701 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.25 (m, 5H), 7.15 – 7.13 (m, 3H), 6.77 – 6.75 (m, 2H), 3.15 – 3.09 (m, 1H), 2.99 – 2.96 (m, 1H), 2.10 – 2.03 (m, 2H), 1.84 – 1.71 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 137.8 (2C), 130.5, 128.1, 127.9, 126.6, 126.4, 126.4, 68.9, 48.0, 45.0, 37.5, 24.5. HRMS (ESI) exact mass calculated for $C_{17}H_{20}N^+$ ($[M+H]^+$): Cal: 238.1590; Found: 238.1590.



1-((2-allyl-5-phenylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90c): According to GP 3: To the oxazine **3.89b** (56 mg, 0.15 mmol), allylmagnesium chloride (1 M in THF, 0.44 mL, 0.44 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastreomers (1 : 0.71 ratio) of amino naphthol **3.90c** as reddish oil (12 mg, 19%) and **3.91c**[6] (by DCM) as reddish oil (20 mg, 72%). FTIR (KBr): $\tilde{\nu}$ = 3467, 3067, 2961, 2873, 1621, 1600, 1518, 1467, 1452, 1407, 1266, 1236, 1077, 949, 919, 813, 758, 743, 700 cm^{-1}. HRMS (ESI) exact mass calculated for $C_{30}H_{30}NO^+$ ($[M+H]^+$): Cal: 420.2322; Found: 420.2316.

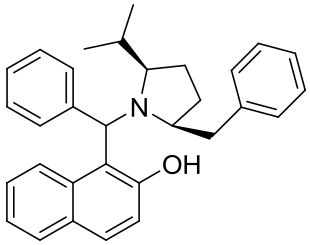


***cis*-2-allyl-5-phenylpyrrolidine (3.91c)**: FTIR (KBr): $\tilde{\nu}$ = 2961, 2924, 2853, 1640, 1623, 1450, 1013, 1027, 912, 756, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.37 (m, 2H), 7.33 – 7.30 (m, 2H), 7.23 (t, *J* = 7.2 Hz, 1H), 5.93 – 5.83 (m, 1H), 5.14 – 5.03 (m, 2H), 4.14 (t, *J* = 8.0 Hz, 1H), 3.30 – 3.23 (m, 1H), 2.34 – 2.30 (m, 2H), 2.20 – 2.11 (m, 1H), 2.01 – 1.92 (m, 1H), 1.76 – 1.66 (m, 1H), 1.60 – 1.51 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 143.2, 131.5, 123.6, 122.1, 121.9, 111.7, 57.8, 53.9, 36.2, 29.1, 26.2. HRMS (ESI) exact mass calculated for $C_{13}H_{18}N^+$ ($[M+H]^+$): Cal:188.1434; Found: 188.1439.



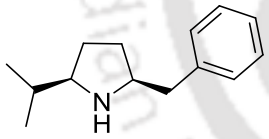
[6] Bubnov, Y. N.; Klimkina, E. V.; Lavrinovich, L. I.; Zykov, A. Y.; Ignatenko, A. V. *Russ. Chem. Bull*. **1999**. *48*, 1696.

1-((2-benzyl-5-isopropylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90d):

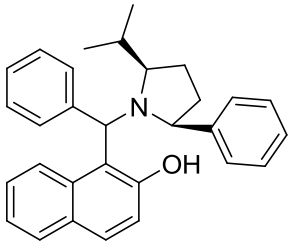


According to GP 3: To the oxazine **3.89c** (0.12 g, 0.35 mmol), benzylmagnesium chloride (1 M in THF, 1.05 mL, 1.05 mmol) was added dropwise at -3 °C and the mixture was stirred for 3 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 60) to afford an inseparable mixture of diastreomers (1 : 0.20 ratio) of amino naphthol **3.90d** as colorless solid (44 mg, 30%) and **3.91d** (by DCM) as reddish oil (20 mg, 28%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3472, 2963, 2925, 2853, 1744, 1622, 1600, 1454, 1265, 1235, 1085, 948, 889, 744, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 13.80 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.24 – 7.18 (m, 7H), 7.07 – 7.05 (m, 3H), 6.58 – 6.56 (m, 2H), 5.81 (s, 1H), 3.61 – 3.57 (m, 1H), 3.19 – 3.16 (m, 1H), 3.00 – 2.96 (m, 1H), 2.04 – 1.96 (m, 1H), 1.86 – 1.76 (m, 1H), 1.66 – 1.56 (m, 3H), 0.73 (d, *J* = 6.5 Hz, 3H), 0.66 – 0.61 (m, 1H), 0.47 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.5, 140.3, 139.7, 131.5, 130.0, 129.3, 129.2, 129.0, 128.9, 128.4, 128.3, 127.0, 126.6, 126.1, 122.7, 120.7, 119.7, 116.9, 65.2, 64.9, 64.5, 33.3, 30.4, 27.4, 23.0, 20.4, 14.7. HRMS (ESI) exact mass calculated for $C_{31}H_{34}NO^+$ ($[M+H]^+$): Cal: 436.2635; Found: 436.2650.

***cis*-2-benzyl-5-isopropylpyrrolidine (3.91d)**: FTIR (KBr): $\tilde{\nu}$ = 3026, 2958, 2871, 1625, 1602, 1495, 1466, 1453, 1384, 1270, 1086, 815, 746, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 3H), 3.26 – 3.20 (m, 1H), 2.86 – 2.81 (m, 1H), 2.74 – 2.69 (m, 1H), 2.66 – 2.60 (m, 1H), 1.84 – 1.75 (m, 2H), 1.57 – 1.48 (m, 1H), 1.46 – 1.37 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 4.0 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 140.4, 129.2, 128.6, 126.2, 65.9, 60.8, 42.8, 34.4, 30.9, 29.2, 20.8, 20.0. HRMS (ESI) exact mass calculated for $C_{14}H_{22}N^+$ ($[M+H]^+$): Cal: 204. 1747; Found: 204.1757.



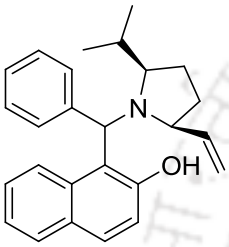
1-((2-isopropyl-5-phenylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90e):



According to GP 3: To the oxazine **3.89c** (60 mg, 0.17 mmol), phenylmagnesium bromide (1 M in THF, 0.52 mL, 0.52 mmol) was added dropwise at 0 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1 : 80 with Et_3N 100 μL/100 mL) to afford an inseparable mixture of diastereomers (1 : 0.16 ratio) of amino naphthol **3.90e** as yellowish solid (52 mg, 76%). Following analytical data are given for major isomer.

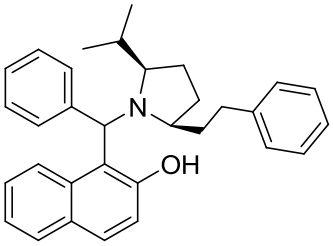
FTIR (KBr): $\tilde{\nu}$ = 3441, 2964, 2923, 2855, 1622, 1453, 1495, 1413, 1385, 1267, 1236, 1077,951, 842, 813, 766, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 14.00 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.48 (br. s, 2H), 7.21 – 7.04 (m, 9H), 6.96 – 6.92 (m, 1H), 6.83 – 6.81 (m, 2H), 5.35 (s, 1H), 4.41 – 4.39 (m, 1H), 3.50 – 3.48 (m, 1H), 2.39 – 2.22 (m, 2H), 1.91 – 1.86 (m, 2H), 0.86 (d, *J* = 6.2 Hz, 3H), 0.80 – 0.76 (m, 1H), 0.50 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6, 141.0, 139.9, 131.8, 130.3, 129.7, 128.7, 128.6, 128.4, 128.3 (2C), 128.2, 127.3, 126.0, 122.2, 120.9, 119.3, 116.6, 69.3, 65.5, 65.0, 31.9, 30.7, 24.6, 20.6, 14.3. HRMS (ESI) exact mass calculated for $C_{30}H_{32}NO^+$ ($[M+H]^+$): Cal: 422.2478; Found: 422.2478.

1-((2-isopropyl-5-vinylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90f):



According to GP 3: To the oxazine **3.89c** (50 mg, 1.58 mmol), vinylmagnesium bromide (1 M in THF, 4.0 mL, 4.0 mmol) was added dropwise at 0 °C and the mixture was stirred for 2.5 h under argon atmosphere. The crude product was subjected to SiO_2-column chromatography (EtOAc : Hexane, 1: 75 with Et_3N 100 μL/100 mL) to afford **3.90f** as light yellow solid (52 mg, 76%). FTIR (KBr): $\tilde{\nu}$ = 3441, 2967, 2930, 1621, 1600, 1452, 1413, 1268, 1236, 1084, 926, 813, 768, 751, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 14.11 (s, 1H), 7.68 – 7.63 (m, 3H), 7.52 (br. s, 2H), 7.25 – 7.23 (d, *J* = 7.0 Hz, 2H), 7.18 – 7.17 (m, 4H), 5.98 – 5.89 (m, 1H), 5.62 (s, 1H), 4.94 – 4.92 (m, 1H), 4.41 (d, *J* = 16.8 Hz, 1H), 3.82 – 3.80 (m, 1H), 3.14 – 3.12 (m, 1H), 2.04 – 1.93 (m, 2H), 1.75 – 1.60 (m, 2H), 0.76 (br. s, 3H), 0.68 – 0.65 (m, 1H), 0.44 – 0.43 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.8, 140.1, 135.1, 131.7, 130.3, 129.6, 128.8, 128.7, 128.2 (2C), 126.2, 122.3, 121.4, 119.9, 119.6, 116.5, 67.3, 65.5, 63.9, 30.7, 30.2, 23.6, 20.5, 14.4. HRMS (ESI) exact mass calculated for $C_{26}H_{30}NO^+$ ($[M+H]^+$): Cal: 372.2322; Found: 372.2322.

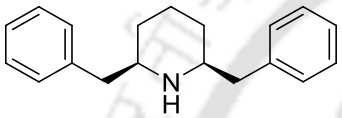
1-((2-isopropyl-5-phenethylpyrrolidin-1-yl)(phenyl)methyl)naphthalen-2-ol (3.90g):



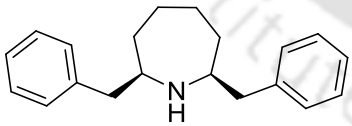
According to GP 3: To the oxazine **3.89c** (0.13 g, 0.37 mmol), phenethylmagnesium chloride (1 M in THF, 1.1 mL, 1.10 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford an inseparable mixture of diastereomers (1 : 0.12 ratio) of amino naphthol **3.90g** as yellowish oil (70 mg, 42%). Following analytical data are given for major isomer. FTIR (KBr): $\tilde{\nu}$ = 3061, 3026, 2926, 2856, 1739, 1622, 1601, 1495, 1466, 1453, 1262, 1235, 1068,

1029, 813, 746, 699 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.02 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.76 – 7.74 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.32 – 7.16 (m, 6H), 7.13 – 7.12 (m, 1H), 7.04 – 7.02 (m, 1H), 7.00 – 6.98 (m, 2H), 6.55 – 6.54 (m, 2H), 5.71 (s, 1H), 3.35 – 3.31 (m, 1H), 3.05 – 3.03 (m, 1H), 2.48 – 2.43 (m, 1H), 2.13 – 2.08 (m, 1H), 2.00 – 1.91 (m, 2H), 1.81 – 1.76 (m, 2H), 1.70 – 1.66 (m, 1H), 1.58 – 1.52 (m, 1H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.66 – 0.62 (m, 1H), 0.46 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 156.7, 141.2, 140.3, 131.5, 130.1, 129.9, 129.1, 128.9, 128.5, 128.4, 128.3, 128.1, 126.9, 125.8, 122.6, 120.7, 119.8, 116.9, 64.4, 64.2, 62.9, 33.3, 30.3, 28.2, 28.1, 23.3, 20.4, 14.7. HRMS (ESI) exact mass calculated for $C_{32}H_{36}NO^+$ ($[M+H]^+$): Cal: 450.2791; Found: 450.2793.

***cis*-2,6-dibenzylpiperidine (3.91e)**: According to GP 3: To the oxazine **3.89d** (25 mg, 0.06 mmol), benzylmagnesium chloride (1 M in THF, 0.4 mL, 0.4 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 30) to afford **3.91e**[7] as brown oil (15 mg, 92%). FTIR (KBr): $\tilde{\nu}$ = 3029, 2925, 2853, 1494, 1453, 1089, 1056, 1030, 747,702 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.20 (m, 4H), 7.16 – 7.15 (m, 2H), 7.12 – 7.10 (m, 4H), 2.70 – 2.66 (m, 2H), 2.63 – 2.53 (m, 4H), 1.80 – 1.77 (m, 1H), 1.66 – 1.63 (m, 2H), 1.22 – 1.13 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.9, 129.1, 128.3, 126.1, 58.4, 43.6, 32.3, 24.6. HRMS (ESI) exact mass calculated for $C_{19}H_{24}N^+$ ($[M+H]^+$): Cal: 266.1903; Found: 266.1893.



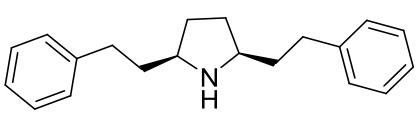
***cis*-2,7-dibenzylazepane (3.91f)**: According to GP 3: To the oxazine **3.89g** (28 mg, 0.07 mmol), benzylmagnesium chloride (1 M in THF, 0.2 mL, 0.2 mmol) was added dropwise at -3 °C and the mixture was stirred for 1 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 30) to afford **3.91f** as light yellow oil (18 mg, 98%). FTIR (KBr): $\tilde{\nu}$ = 3064, 3019, 2915, 2854, 1627, 1602, 1495, 1454, 1261, 1079, 1021, 805,743, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 – 7.09 (m, 6H), 6.96 – 6.94 (m, 4H), 2.77 – 2.72 (m, 2H), 2.68 – 2.64 (m, 2H), 2.43 – 2.38 (m, 2H), 1.78 – 1.64 (m, 6H), 1.48 – 1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 139.3, 128.9, 128.6,



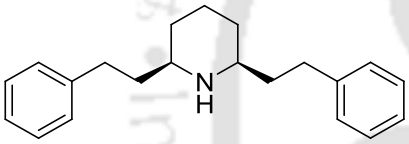
[7] Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Crooks, P. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6509.

126.3, 60.8, 44.1, 37.4, 25.4. HRMS (ESI) exact mass calculated for $C_{20}H_{26}N^+$ ($[M+H]^+$): Cal: 280.2060; Found: 280.2058.

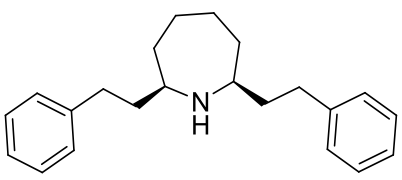
***cis*-2,5-diphenethylpyrrolidine (3.91aa)**: According to GP 3: To the oxazine **3.89aa** (47 mg, 0.12 mmol), phenethylmagnesium chloride (1 M in THF, 0.35 mL, 0.35 mmol) was added dropwise at -3 °C and the mixture was stirred for 12 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (DCM : MeOH, 150 : 1) to afford **3.91aa** as brown oil (23 mg, 73%). FTIR (KBr): $\tilde{\nu}$ = 3450, 3026, 2924, 2853, 1640, 1626, 1602, 1495, 1454, 1236, 1030, 909, 746, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.25 (m, 4H), 7.19 – 7.17 (m, 6H), 3.01 – 2.98 (m, 2H), 2.69 – 2.64 (m, 4H), 2.07 – 1.98 (m, 2H), 1.92 – 1.84 (m, 4H), 1.82 – 1.72 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.3, 128.5 (2C), 126.0, 59.0, 38.3, 33.9, 31.3. HRMS (ESI) exact mass calculated for $C_{20}H_{26}N^+$ ($[M+H]^+$): Cal: 280.2060; Found: 280.2058.



***cis*-2,6-diphenethylpiperidine (3.91bb)**: According to GP 3: To the oxazine **3.89bb** (60 mg, 0.14 mmol), phenethylmagnesium chloride (1 M in THF, 0.72 mL, 0.72 mmol) was added dropwise at -3 °C and the mixture was stirred for 18 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (DCM) to afford **3.91bb**[8] as brown oil (19 mg, 45%). FTIR (KBr): $\tilde{\nu}$ = 3442, 3025, 2924, 2853, 1625, 1602, 1495, 1453, 1030, 747, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.25 (m, 5H), 7.19 – 7.16 (m, 5H), 2.62 (t, *J* = 7.9 Hz, 4H), 2.54 – 2.48 (m, 2H), 1.78 – 1.68 (m, 6H), 1.41 – 1.33 (m, 1H), 1.16 – 1.08 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.3, 128.6, 128.5, 126.0, 56.9, 38.8, 32.6, 32.4, 24.8. HRMS (ESI) exact mass calculated for $C_{21}H_{28}N^+$ ($[M+H]^+$): Cal: 294.2216; Found: 294.2216.



***cis*-2,7-diphenethylazepane (3.91cc)**: According to GP 3: To the oxazine **3.89cc** (25 mg, 0.06 mmol) phenethylmagnesium chloride (1 M in THF, 0.20 mL, 0.20 mmol) was added dropwise at -3 °C and the mixture was stirred for 2 h under argon atmosphere. The crude product was subjected to neutral alumina column chromatography (DCM) to afford **3.91cc** as brown oil (15 mg, 90%). FTIR (KBr): $\tilde{\nu}$ = 3441,



[8] Zheng, G.; Dwoskin, L. P.; Deaciuc, A. G.; Norrholm, S. D.; Crooks, P. A. *J. Med. Chem.* **2005,** *48*, 5551.

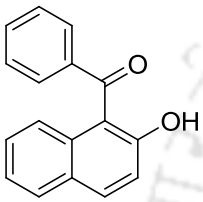
2924, 2853, 1653, 1639, 1495, 1453, 1260, 1078, 1030, 747, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.25 (m, 5H), 7.20 – 7.16 (m, 5H), 2.87 – 2.79 (m, 1H), 2.75 – 2.64 (m, 3H), 2.63 – 2.55 (m, 2H), 1.89 – 1.85 (m, 1H), 1.81 – 1.52 (m, 11H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.5, 128.6 (2C), 126.0, 58.8, 39.9, 37.4, 33.3, 25.5. HRMS (ESI) exact mass calculated for $C_{22}H_{30}N^+$ ($[M+H]^+$): Cal: 308.2373; Found: 308.2364.

7.4 Metal and Oxidant Free Direct C-H Aryloxylation of *N*-Heterocycles

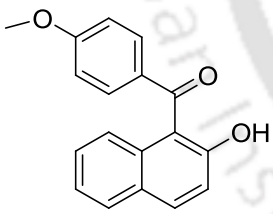
General procedure for preparation of ketones (GP 5):[1]

2-Naphthol (1.44 g, 10 mmol) in 10 mL of $BF_3.OEt_2$ was heated at 60 ^oC to make it soluble. Then benzoic acid (1.1 eq) was added to it and resulting reaction mixture was heated at 100 ^oC for 20 h. Reaction mixture was cooled to room temperature and diluted with water (50 mL). Then the mixture was extracted with EtOAc (3 × 30 mL). Then the combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. The crude product was purified by SiO_2-gel-column chromatography.

(2-Hydroxy-naphthalen-1-yl)-phenyl-methanone (4.10b): According to GP 5: 2-Naphthol (1.44 g, 10.00 mmol), benzoic acid (1.34 g, 11.00 mmol) in 10 mL $BF_3.OEt_2$ for 20 h and SiO_2- column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10b**[2,3] as orange crystal (1.61 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.15 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.450 – 7.47 (m, 1H), 7.35 – 7.31 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.9 Hz, 1H), 7.11 – 7.05 (m, 1H).



(2-Hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methanone (4.10f): According to GP 5: 2-Naphthol (0.57 g, 4.00 mmol), 4-methoxy-benzoic acid (0.66 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 20 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **4.10f**[4] as yellow crystal, (0.49 g, 44 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.59 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.76 – 7.75 (m, 1H), 7.66 – 7.63 (m, 2H), 7.42 – 7.41 (d, *J* = 8.5 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.89 – 6.86 (m, 2H), 3.86 (s, 3H).



[1] Kumar, A.; Ahmad, P.; Maurya, R. A.; Singh, A. B.; Srivastava, A. K. *Eur. J. Med. Chem.* **2009**, *44*, 109.
[2] Park, K. K.; Jeong, J. *Tetrahedron* **2005**, *61*, 545.
[3] Li, W.; Lai, H.; Ge, Z.; Ding, C.; Zhou, Y. *Synth. commun*. **2007**, *37*, 1595.
[4] Negi, A. S.; Dwivedi, I.; Setty, B. S.; Ray, S. *Indian J. Pharm. Sci.* **1994**, *56*, 105.

(2-Hydroxy-naphthalen-1-yl)-p-tolyl-methanone (4.10g): According to GP 5: 2-Naphthol (0.57 g, 4.0 mmol), 4-methyl-benzoic acid (0.59 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 20 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford **4.10g** as yellow crystal, (0.43 gm, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.99 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.37 – 7.34 (m, 1H), 7.28 – 7.22 (m, 2H), 7.19 – 7.15 (m, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.1, 160.9, 143.9, 137.7, 136.0, 132.6, 129.9, 129.4, 128.7, 128.6, 126.8, 126.5, 123.8, 119.3, 114.9, 21.9.

(2-hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methanone (4.10h): According to GP 5: 2-Naphthol (0.58 g, 4.00 mmol), 4-hydroxy benzoic acid (0.61 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10h**[1] as whitish solid (0.42 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.66 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.43 – 7.41(m, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.21 – 7.19 (m, 1H), 6.84 – 6.80 (m, 2H).

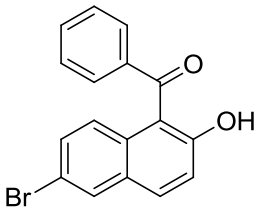
(4-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methanone (4.10i): According to GP 5: 2-Naphthol (0.28 g, 2.0 mmol), 4-chlorobenzoic acid (0.34 g, 2.20 mmol) in 2 mL $BF_3.OEt_2$ for 52 h and SiO_2-column chromatography (EtOAc : Hexane 1 : 30) to afford as **4.10i**[5] brown solid (70 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.09 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.77 – 7.75 (m, 1H), 7.59 – 7.57 (m, 2H), 7.39 – 7.37 (m, 2H), 7.31 – 7.28 (m, 2H), 7.26 – 7.18 (m, 2H).

(2-Hydroxy-7-methoxy-naphthalen-1-yl)-phenyl-methanone (4.10j): According to GP 5: 7-Methoxy-naphthalen-2-ol (0.52 g, 3.00 mmol), benzoic acid (0.40 g, 3.30 mmol) in 3 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10j** as yellow solid (0.43 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.66 (s, 1H), 7.86 – 7.84 (m, 1H), 7.63 – 7.61 (m, 3H), 7.57 – 7.53 (m, 1H), 7.45 – 7.42 (m, 2H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.89 – 6.88 (m, 1H), 6.59 (s, 1H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

[5] Malik, V. P.; Saharia, G. S. *J. Sci & Ind. Res.*, **1956**, *15B*, 633.

δ = 200.9, 163.0, 158.3, 141.0, 136.7, 134.3, 132.39, 130.2, 129.3, 128.8, 123.9, 116.7, 116.1, 113.8, 106.7, 54.6.

(6-Bromo-2-hydroxy-naphthalen-1-yl)-phenyl-methanone (4.10k): According to GP 5:

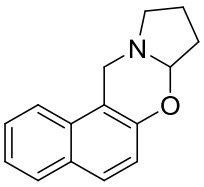


6-Bromo-naphthalen-2-ol (0.44 g, 2.00 mmol), benzoic acid (0.26 g, 2.20 mmol) in 2 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **4.10k** as reddish brown solid (0.15 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.18 (s, 1H), 7.90 – 7.89 (m, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.43 – 7.39 (m, 2H), 7.27 – 7.25 (m, 1H), 7.23 – 7.20 (m, 1H), 7.16 – 7.14 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.1, 161.6, 140.1, 131.1, 130.6, 130.0, 129.6, 128.9, 128.0, 120.6, 119.0, 117.6, 114.6.

General procedure for the preparation of oxazine (GP 6):

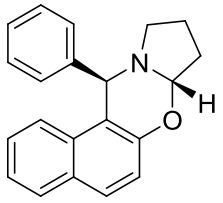
Aldehyde or ketone (0.29 mmol), toluene (1.5 mL) and amine (0.24 mmol) were added successively to an oven dried microwave reaction tube containing a stirring bar. Then the tube was sealed with cap and resulting solution was heated at 145 ºC for 20 min under microwave irradiation (200 watt). Then the reaction mixture was cooled to room temperature. After that the crude mixture was transferred to round bottom flask with DCM. Then the volatiles were removed under vacuum to give gummy liquid. The liquid was subjected to SiO_2-gel column chromatography to afford analytically pure oxazine.

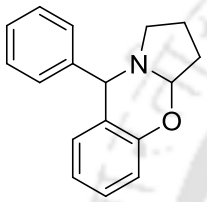
8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11a): According

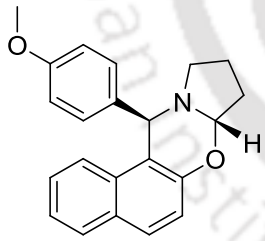


to GP 6: Pyrrolidine (20 µL, 0.24 mmol), 2-hydroxy naphthaldehyde (0.10 g, 0.60 mmol) in 1 mL of toluene 130 ºC under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford **4.11a**[6] brown solid (39 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.64 – 7.63 (m, 2H), 7.49 – 7.46 (m, 1H), 7.36 – 7.34 (m, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 5.14 – 5.13 (m, 1H), 4.62 (d, *J* = 16.9 Hz, 1H), 4.28 (d, *J* = 17.0 Hz, 1H), 3.17 – 3.13 (m, 1H), 2.99 – 2.95 (m, 1H), 2.24 – 2.14 (m, 2H), 2.09 – 1.96 (m, 2H).

[6] Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun*. **2014**, *50*, 332.

***rac*-(7a*S*,12*R*)-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11b):**  According to GP 6: Pyrrolidine (20 µL, 0.24 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (72 mg, 0.29 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11b**[6] as white solid (69 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.67 (m, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.21 – 7.13 (m, 7H), 7.00 (d, *J* = 8.9 Hz, 1H), 5.38 (s, 1H), 5.02 – 4.99 (m, 1H), 3.29 – 3.22 (m, 1H), 2.87 – 2.81 (m, 1H), 2.03 – 1.89 (m, 4H).

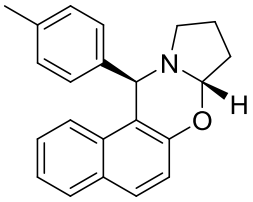
9-phenyl-2,3,3a,9-tetrahydro-1*H*-benzo[e]pyrrolo[2,1-*b*][1,3]oxazine (4.11c):  According to GP 6: 2-Hydroxy benzophenone (48 µL, 0.29 mmol), pyrrolidine (20 µL, 0.24 mmol) in 1 mL of toluene 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford diastereomeric mixture (3:1) of **4.11c**[7] as colorless oil (26 mg, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 – 7.14 (m, 6H), 6.97 – 6.95 (m, 1H), 6.88 – 6.84 (m, 2H), 5.01 – 5.00 (m, 1H), 4.95 (s, 1H), 3.31 – 3.26 (m, 1H), 2.95 – 2.88 (m, 1H), 2.10 – 1.90 (m, 4H).

***rac*-(7a*S*,12*R*)-12-(4-methoxyphenyl)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (4.11d):**  According to GP 6: Pyrrolidine (40 µL, 0.49 mmol), (2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methanone (0.16 g, 0.58 mmol) in 1.5 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane 1 : 40) to afford **4.11d**[6] as whitish solid (0.12 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.73 (m, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.31 – 7.23 (m, 2H), 7.17 – 7.15 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.81 – 6.77 (m, 2H), 5.40 (s, 1H), 5.09 – 5.08 (m, 1H), 3.74 (s, 3H), 3.34 – 3.27 (m, 1H), 2.91 – 2.85 (m, 1H), 2.14 – 1.93 (m, 4H).

***rac*-(7a*S*,12*R*)-12-p-tolyl-8,9,10,12-tetrahydro-7aH-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (4.11e):** According to GP 6: Pyrrolidine (40 µL, 0.49 mmol), 2-hydroxynaphthalen-1-yl)(*p*-tolyl)methanone (0.15 g, 0.58 mmol) in 1.5 mL of toluene at 145

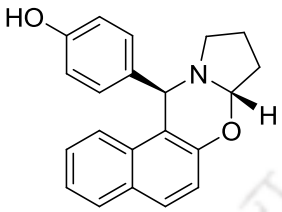
[7] Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 9791.

°C under microwave irradiation for 20 min, SiO_2-column chromatography (EtOAc : Hexane,



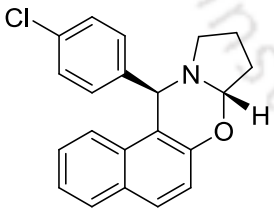
1 : 40) to afford **4.11e**[6,7] as white solid (92 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.17 – 7.11 (m, 2H), 7.04 – 7.02 (m, 2H), 6.98 – 6.94 (m, 3H), 5.30 (s, 1H), 5.00 – 4.98 (m, 1H), 3.19 (t, *J* = 7.6 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.17 (s, 3H), 2.01 – 1.82 (m, 4H).

***rac*-4-((7a*S*,12*R*)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-**



12-yl)phenol (4.11f): According to GP 6: Pyrrolidine (30 µL, 0.36 mmol), 2-hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methanone (0.12 g, 0.44 mmol) in 1.5 mL of toluene and 1mL xylene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **4.11f** as white solid (55 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3441, 2917, 2850, 1625, 1568, 1432, 1421, 1229, 991, 899, 816, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ with added Methanol-d_4) δ = 7.64 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.99 – 6.94 (m, 3H), 6.63 – 6.61 (m, 2H), 5.29 (s, 1H), 5.02 – 5.01 (m, 1H), 3.24 – 3.17 (m, 1H), 2.81 – 2.75 (m, 1H), 2.01 – 1.90 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$ with added Methanol-d_4) δ = 155.7, 150.9, 134.0, 132.0, 129.5, 128.7, 128.4, 128.0, 125.9, 122.6, 122.3, 118.1, 114.7, 110.3, 85.5, 55.6, 49.6, 31.4, 20.3. HRMS exact mass calculated for $C_{21}H_{20}NO_2^+$([M+H]$^+$): 318.1489; Found: 318.1488.

***rac*-(7a*S*,12*R*)-12-(4-chlorophenyl)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-**

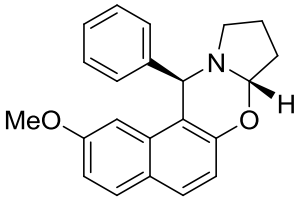


***e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11g):** According to GP 6: Pyrrolidine (16 µL, 0.19 mmol), (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methanone (66 mg, 0.24 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11g**[6,7] as light yellow solid (44 mg, 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.73 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.23 – 7.20 (m, 2H), 7.18 – 7.16 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 5.40 (s, 1H), 5.01 – 4.99 (m, 1H), 3.33 – 3.29 (m, 1H), 2.92 – 2.87 (m, 1H), 2.13 – 2.06 (m, 1H), 2.06 – 1.95 (m, 3H).

***rac*-(7a*S*,12*R*)-2-methoxy-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-**

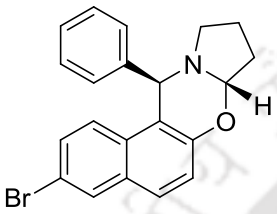
***e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11h):** According to GP 6: Pyrrolidine (30 µL, 0.36 mmol), (2-hydroxy-7-methoxynaphthalen-1-yl)(phenyl)methanone (0.12 g, 0.44 mmol) in 1.5 mL of

toluene at 145 °C under microwave irradiation for 40 min and crystallization and after

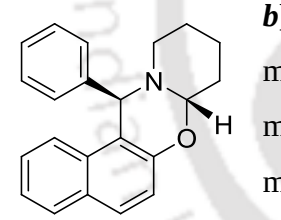


washing (10 X 1 mL of cold EtOAc : Hexane, 1 : 30) to afford **4.11h**[7] as white solid (94 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 – 7.60 (m, 2H), 7.27 – 7.21 (m, 5H), 6.94 – 6.90 (m, 2H), 6.63 (s, 1H), 5.33 (s, 1H), 5.13 – 5.09 (m, 1H), 3.61 (s, 3H), 3.38 – 3.29 (m, 1H), 2.97 – 2.91 (m, 1H), 2.16 – 1.92 (m, 4H).

***rac*-(7a*S*,12*R*)-3-bromo-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11i):** According to GP 6: Pyrrolidine (20 µL, 0.24 mmol), (6-bromo-2-hydroxynaphthalen-1-yl)(phenyl)methanone (95 mg, 0.29 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11i**[7] as brown solid (70 mg, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.89 – 7.87 (m, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.28 – 7.20 (m, 6H), 7.08 (d, *J* = 9.0 Hz, 1H), 5.40 (s, 1H), 5.07 – 5.06 (m, 1H), 3.35 – 3.32 (m, 1H), 2.91 – 2.87 (m, 1H), 2.11 – 1.98 (m, 4H).



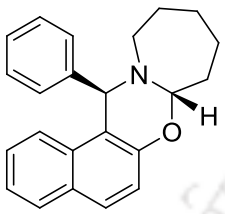
***rac*-(7a*S*,13*R*)-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (4.11j):** According to GP 6: Piperidine (30 µL, 0.30 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (90 mg, 0.36 mmol) in 1 mL of toluene at 145°C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11j**[6,7] as white solid (43 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.28 – 7.23 (m, 7H), 7.14 – 7.12 (m, 1H), 5.17 (s, 1H), 4.90 – 4.88 (m, 1H), 2.87 – 2.83 (m, 2H), 1.98 – 1.95 (m, 1H), 1.81 – 1.72 (m, 3H), 1.60 – 1.97 (m, 2H).



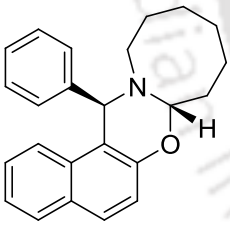
Oxazine (4.11k): According to GP 6: 1,2,3,4-tetrahydroisoquinoline (42 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene 20 min 145 °C under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11k** as white solid (81 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 2921, 2855, 1621, 1597, 1463, 1402, 1257, 1235, 1137, 1091, 1067, 985, 878, 857, 748, 725, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.43 – 7.41 (m, 1H), 7.31 – 7.30 (m, 7H), 7.24 – 7.18 (m, 4H), 7.11 (d, *J* = 9.0 Hz,

1H), 5.65 (s, 1H), 5.43 (s, 1H), 3.40 – 3.24 (m, 2H), 3.11 – 3.08 (m, 1H), 2.89 – 2.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.2, 142.6, 135.2, 133.3, 132.6, 129.5, 129.3, 129.1, 129.0, 128.98, 128.96, 128.8, 128.5, 127.6, 126.8, 126.4, 123.3, 122.9, 119.1, 111.1, 82.4, 62.9, 45.6, 29.6. HRMS (ESI) exact mass calculated for $C_{26}H_{22}NO^+$ ($[M+H]^+$): 364.1696; Found: 364.1684.

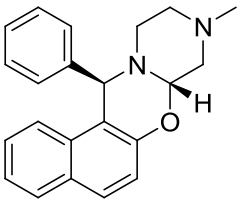
***rac*-(7a*S*,13*R*)-13-Phenyl-7a,8,9,10,11,12-hexahydro-13*H*-7-oxa-12a-aza-cyclohepta [*b*]phenanthrene (4.11l):** According to GP 6: Hexamethyleneimine (30 µL, 0.26 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (79 mg, 0.32 mmol) in 1 mL of toluene 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11l**[6,7] as white solid (57 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.75 – 7.74 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.33 (m, 1H), 7.28 – 7.24 (m, 6H), 7.22 – 7.19 (m, 1H), 7.10 (dd, *J* = 8.9, 2.0 Hz, 1H), 5.29 (s, 1H), 4.87 – 4.85 (m, 1H), 3.26 – 3.22 (m, 1H), 2.69 – 2.67 (m, 1H), 2.22 – 2.17 (m, 1H), 1.89 – 1.82 (m, 2H), 1.78 – 1.71 (m, 2H), 1.67 – 1.64 (m, 1H), 1.50 – 1.44 (m, 1H), 1.43 – 1.35 (m, 1H).



Oxazine (4.11m): According to GP 6: Heptamethyleneimine (40 µL, 0.31 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (94 mg, 0.37 mmol) in 1 mL of toluene first 40 min 100 °C then another 10 min at 145 °C under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 60) to afford **4.11m**[6] as light yellow solid (41 mg, 38%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 – 7.75(m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.33 (m, 1H), 7.29 – 7.21 (m, 7H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.28 (s, 1H), 4.70 – 4.67 (m, 1H), 3.28 – 3.23 (m, 1H), 2.59 – 2.55 (m, 1H), 1.98 – 1.87 (m, 5H), 1.55 – 1.51 (m, 2H), 1.48 – 1.43 (m, 3H).

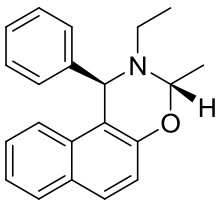


***rac*-(7a*S*,12*R*)-9-Methyl-12-(3-nitro-phenyl)-8,9,10,11-tetrahydro-7a*H*,12*H*-7-oxa-9,11adiaza-benzo [*a*]anthracene(4.11n):** According to GP 6: *N*-methyl piperazine (30µL, 0.27 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.13 g, 0.54 mmol) in 1.5 mL of toluene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 8) to afford **4.11n**[6] as white solid (24 mg, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H),



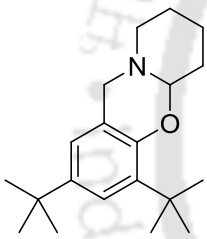
7.35 – 7.33 (m, 1H), 7.28 – 7.25 (m, 3H), 7.24 – 7.21 (m, 5H), 5.23 (s, 1H), 4.83 – 4.81 (m, 1H), 3.21 – 3.17 (m, 1H), 3.11 – 3.09 (m, 1H), 2.89 – 2.88 (m, 2H), 2.45 – 2.39 (m, 1H), 2.34 (s, 3H), 2.21 – 2.17 (m, 1H).

***rac*-(1*R*,3*S*)-2-ethyl-2,3-dihydro-3-methyl-1-phenyl-1*H*-naphtho[1,2-*e*][1,3]oxazine**



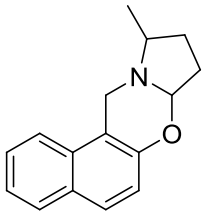
(4.11o): According to GP 6: Diethylamine (35 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene at 145 ^{o}C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane 1 : 80) to afford **4.11o**[6] as brown solid (22 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.71 (m, 2H), 7.33 – 7.07 (m, 9H), 5.40 (s, 1H), 4.94 (m, 1H), 3.09 (m, 1H), 2.46 (m, 1H), 1.46 – 1.42 (m, 3H), 1.27 (m, 3H).

2,4-di-tert-butyl-5a,6,7,8,9,11-hexahydrobenzo[*e*]pyrido[2,1-*b*][1,3]oxazine (4.11p):



According to GP 6: Piperidine (35µL, 0.36 mmol), 3,5-di-*tert*-butyl salicylaldehyde (0.10 g, 0.43 mmol) in 1.5 mL of toluene at 145 ^{o}C under microwave irradiation for 30 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 25) to afford **4.11p** as yellow oil (51 mg, 47%). FTIR (KBr): $\tilde{\nu}$ = 2949, 2865, 1652, 1641, 1479, 1449, 1360, 1226, 1128, 1103, 1069, 879, 870, 758 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.15 (s, 1H), 6.81 (s, 1H), 4.85 – 4.83 (m, 1H), 4.30 (d, *J* = 16.1 Hz, 1H), 3.61 (d, *J* = 16.1 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.54 – 2.51 (m, 1H), 2.01 – 1.98 (m, 1H), 1.87 – 1.83 (m, 1H), 1.78 – 1.70 (m, 3H), 1.61 – 1.57 (m, 1H), 1.40 (s, 9H), 1.29 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.3, 142.0, 136.4, 121.9, 121.7, 118.3, 86.3, 54.7, 48.2, 35.1, 34.4, 31.8, 30.7, 29.9, 25.5, 19.4. HRMS (ESI) exact mass calculated for $C_{20}H_{32}NO^+$ ([M+H]$^+$): 302.2478; Found : 302.2478.

10-methyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11q):



According to GP 6: 2-Hydroxy naphthaldehyde (86 mg, 0.50 mmol), 1-methyl pyrrolidine (20 µL, 0.19 mmol) in 1 mL of toluene at 130 ^{o}C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford inseparable regio-isomeric mixture (~5:1) of **4.11q** as brown solid (22 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2920, 2853, 1635, 1516, 1467, 1434, 1396, 1261, 1228, 1095, 1074, 1016, 860, 811, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.63 (d,

J = 8.8 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.36 – 7.32 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 5.26 – 5.25 (m, 1H), 4.58 (d, *J* = 17.4 Hz, 1H), 4.27 (d, *J* = 17.5 Hz, 1H), 3.15 – 3.10 (m, 1H), 2.29 – 2.03 (m, 4H), 1.23 (d, *J* = 6.0 Hz, 3H). HRMS (ESI) exact mass calculated for $C_{16}H_{18}NO^+$ ($[M+H]^+$): 240.1383; Found: 240.1381.

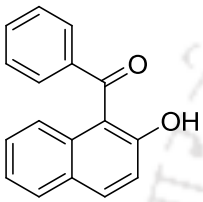
7a-methyl-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine(4.11r): According to GP 6: 2-Methyl pyrrolidine (34 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene at 145 ^oC for 20 min under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford inseparable regio-isomeric mixture (~4:1) of **4.11r** as yellowish oil (85 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 2935, 2850, 1623, 1599, 1514, 1462, 1380, 1241, 1109, 1065, 972, 811, 746, 702, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.78 (m, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.31 – 7.19 (m, 8H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.50 (s, 1H), 3.52 – 3.47 (m, 1H), 3.02 – 2.96 (m, 1H), 2.28 – 2.22 (m, 1H), 2.10 – 2.07 (m, 1H), 1.96 – 1.87 (m, 2H), 1.04 (s, 3H). HRMS (ESI) exact mass calculated for $C_{22}H_{22}NO^+$ ($[M+H]^+$): 316.1696; Found: 316.1685.

7.4 Metal and Oxidant Free Direct C-H Aryloxylation of *N*-Heterocycles

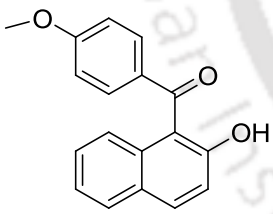
General procedure for preparation of ketones (GP 5):[1]

2-Naphthol (1.44 g, 10 mmol) in 10 mL of $BF_3.OEt_2$ was heated at 60 ^oC to make it soluble. Then benzoic acid (1.1 eq) was added to it and resulting reaction mixture was heated at 100 ^oC for 20 h. Reaction mixture was cooled to room temperature and diluted with water (50 mL). Then the mixture was extracted with EtOAc (3 × 30 mL). Then the combined organic layers were dried (Na_2SO_4) and concentrated in vacuum. The crude product was purified by SiO_2-gel-column chromatography.

(2-Hydroxy-naphthalen-1-yl)-phenyl-methanone (4.10b): According to GP 5: 2-Naphthol (1.44 g, 10.00 mmol), benzoic acid (1.34 g, 11.00 mmol) in 10 mL $BF_3.OEt_2$ for 20 h and SiO_2- column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10b**[2,3] as orange crystal (1.61 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.15 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.450 – 7.47 (m, 1H), 7.35 – 7.31 (m, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.9 Hz, 1H), 7.11 – 7.05 (m, 1H).



(2-Hydroxy-naphthalen-1-yl)-(4-methoxy-phenyl)-methanone (4.10f): According to GP 5: 2-Naphthol (0.57 g, 4.00 mmol), 4-methoxy-benzoic acid (0.66 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 20 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **4.10f**[4] as yellow crystal, (0.49 g, 44 %). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 10.59 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.76 – 7.75 (m, 1H), 7.66 – 7.63 (m, 2H), 7.42 – 7.41 (d, *J* = 8.5 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.21 – 7.18 (m, 1H), 6.89 – 6.86 (m, 2H), 3.86 (s, 3H).



[1] Kumar, A.; Ahmad, P.; Maurya, R. A.; Singh, A. B.; Srivastava, A. K. *Eur. J. Med. Chem.* **2009**, *44*, 109.
[2] Park, K. K.; Jeong, J. *Tetrahedron* **2005**, *61*, 545.
[3] Li, W.; Lai, H.; Ge, Z.; Ding, C.; Zhou, Y. *Synth. commun*. **2007**, *37*, 1595.
[4] Negi, A. S.; Dwivedi, I.; Setty, B. S.; Ray, S. *Indian J. Pharm. Sci.* **1994**, *56*, 105.

(2-Hydroxy-naphthalen-1-yl)-p-tolyl-methanone (4.10g): According to GP 5: 2-Naphthol (0.57 g, 4.0 mmol), 4-methyl-benzoic acid (0.59 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 20 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford **4.10g** as yellow crystal, (0.43 gm, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.99 (s, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.37 – 7.34 (m, 1H), 7.28 – 7.22 (m, 2H), 7.19 – 7.15 (m, 3H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.1, 160.9, 143.9, 137.7, 136.0, 132.6, 129.9, 129.4, 128.7, 128.6, 126.8, 126.5, 123.8, 119.3, 114.9, 21.9.

(2-hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methanone (4.10h): According to GP 5: 2-Naphthol (0.58 g, 4.00 mmol), 4-hydroxy benzoic acid (0.61 g, 4.40 mmol) in 4 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10h**[1] as whitish solid (0.42 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.66 (s, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.59 (m, 2H), 7.43 – 7.41(m, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.23 (m, 1H), 7.21 – 7.19 (m, 1H), 6.84 – 6.80 (m, 2H).

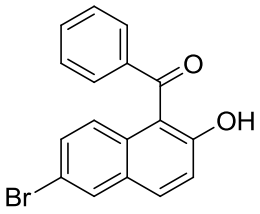
(4-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methanone (4.10i): According to GP 5: 2-Naphthol (0.28 g, 2.0 mmol), 4-chlorobenzoic acid (0.34 g, 2.20 mmol) in 2 mL $BF_3.OEt_2$ for 52 h and SiO_2-column chromatography (EtOAc : Hexane 1 : 30) to afford as **4.10i**[5] brown solid (70 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.09 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.77 – 7.75 (m, 1H), 7.59 – 7.57 (m, 2H), 7.39 – 7.37 (m, 2H), 7.31 – 7.28 (m, 2H), 7.26 – 7.18 (m, 2H).

(2-Hydroxy-7-methoxy-naphthalen-1-yl)-phenyl-methanone (4.10j): According to GP 5: 7-Methoxy-naphthalen-2-ol (0.52 g, 3.00 mmol), benzoic acid (0.40 g, 3.30 mmol) in 3 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford **4.10j** as yellow solid (0.43 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.66 (s, 1H), 7.86 – 7.84 (m, 1H), 7.63 – 7.61 (m, 3H), 7.57 – 7.53 (m, 1H), 7.45 – 7.42 (m, 2H), 7.08 (d, *J* = 8.9 Hz, 1H), 6.89 – 6.88 (m, 1H), 6.59 (s, 1H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)

[5] Malik, V. P.; Saharia, G. S. *J. Sci & Ind. Res.*, **1956**, *15B*, 633.

δ = 200.9, 163.0, 158.3, 141.0, 136.7, 134.3, 132.39, 130.2, 129.3, 128.8, 123.9, 116.7, 116.1, 113.8, 106.7, 54.6.

(6-Bromo-2-hydroxy-naphthalen-1-yl)-phenyl-methanone (4.10k): According to GP 5:

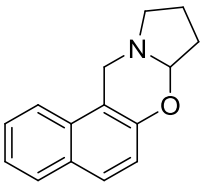


6-Bromo-naphthalen-2-ol (0.44 g, 2.00 mmol), benzoic acid (0.26 g, 2.20 mmol) in 2 mL $BF_3.OEt_2$ for 16 h and SiO_2-column chromatography (EtOAc : Hexane, 1 : 15) to afford **4.10k** as reddish brown solid (0.15 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.18 (s, 1H), 7.90 – 7.89 (m, 1H), 7.83 (d, *J* = 9.0 Hz, 1H), 7.61 – 7.55 (m, 3H), 7.43 – 7.39 (m, 2H), 7.27 – 7.25 (m, 1H), 7.23 – 7.20 (m, 1H), 7.16 – 7.14 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.1, 161.6, 140.1, 131.1, 130.6, 130.0, 129.6, 128.9, 128.0, 120.6, 119.0, 117.6, 114.6.

General procedure for the preparation of oxazine (GP 6):

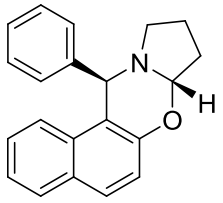
Aldehyde or ketone (0.29 mmol), toluene (1.5 mL) and amine (0.24 mmol) were added successively to an oven dried microwave reaction tube containing a stirring bar. Then the tube was sealed with cap and resulting solution was heated at 145 ºC for 20 min under microwave irradiation (200 watt). Then the reaction mixture was cooled to room temperature. After that the crude mixture was transferred to round bottom flask with DCM. Then the volatiles were removed under vacuum to give gummy liquid. The liquid was subjected to SiO_2-gel column chromatography to afford analytically pure oxazine.

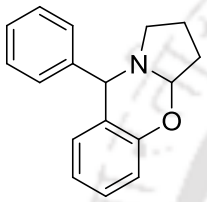
8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11a): According

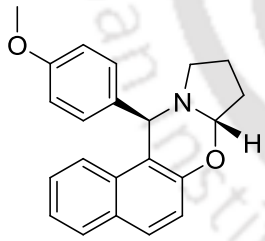


to GP 6: Pyrrolidine (20 µL, 0.24 mmol), 2-hydroxy naphthaldehyde (0.10 g, 0.60 mmol) in 1 mL of toluene 130 ºC under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford **4.11a**[6] brown solid (39 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.64 – 7.63 (m, 2H), 7.49 – 7.46 (m, 1H), 7.36 – 7.34 (m, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 5.14 – 5.13 (m, 1H), 4.62 (d, *J* = 16.9 Hz, 1H), 4.28 (d, *J* = 17.0 Hz, 1H), 3.17 – 3.13 (m, 1H), 2.99 – 2.95 (m, 1H), 2.24 – 2.14 (m, 2H), 2.09 – 1.96 (m, 2H).

[6] Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun*. **2014**, *50*, 332.

***rac*-(7a*S*,12*R*)-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11b):**  According to GP 6: Pyrrolidine (20 µL, 0.24 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (72 mg, 0.29 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11b**[6] as white solid (69 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.67 (m, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.21 – 7.13 (m, 7H), 7.00 (d, *J* = 8.9 Hz, 1H), 5.38 (s, 1H), 5.02 – 4.99 (m, 1H), 3.29 – 3.22 (m, 1H), 2.87 – 2.81 (m, 1H), 2.03 – 1.89 (m, 4H).

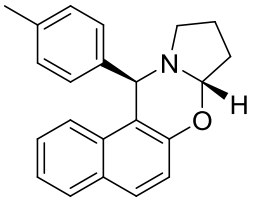
9-phenyl-2,3,3a,9-tetrahydro-1*H*-benzo[e]pyrrolo[2,1-*b*][1,3]oxazine (4.11c):  According to GP 6: 2-Hydroxy benzophenone (48 µL, 0.29 mmol), pyrrolidine (20 µL, 0.24 mmol) in 1 mL of toluene 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford diastereomeric mixture (3:1) of **4.11c**[7] as colorless oil (26 mg, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 – 7.14 (m, 6H), 6.97 – 6.95 (m, 1H), 6.88 – 6.84 (m, 2H), 5.01 – 5.00 (m, 1H), 4.95 (s, 1H), 3.31 – 3.26 (m, 1H), 2.95 – 2.88 (m, 1H), 2.10 – 1.90 (m, 4H).

***rac*-(7a*S*,12*R*)-12-(4-methoxyphenyl)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (4.11d):**  According to GP 6: Pyrrolidine (40 µL, 0.49 mmol), (2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methanone (0.16 g, 0.58 mmol) in 1.5 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane 1 : 40) to afford **4.11d**[6] as whitish solid (0.12 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.73 (m, 1H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.31 – 7.23 (m, 2H), 7.17 – 7.15 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 6.81 – 6.77 (m, 2H), 5.40 (s, 1H), 5.09 – 5.08 (m, 1H), 3.74 (s, 3H), 3.34 – 3.27 (m, 1H), 2.91 – 2.85 (m, 1H), 2.14 – 1.93 (m, 4H).

***rac*-(7a*S*,12*R*)-12-p-tolyl-8,9,10,12-tetrahydro-7aH-naphtho[1,2-e]pyrrolo[2,1-*b*][1,3]oxazine (4.11e):** According to GP 6: Pyrrolidine (40 µL, 0.49 mmol), 2-hydroxynaphthalen-1-yl)(*p*-tolyl)methanone (0.15 g, 0.58 mmol) in 1.5 mL of toluene at 145

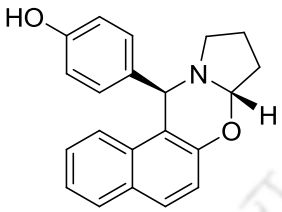
[7] Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock, C. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 9791.

°C under microwave irradiation for 20 min, SiO_2-column chromatography (EtOAc : Hexane,



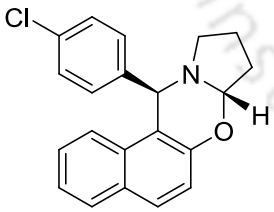
1 : 40) to afford **4.11e**[6,7] as white solid (92 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.17 – 7.11 (m, 2H), 7.04 – 7.02 (m, 2H), 6.98 – 6.94 (m, 3H), 5.30 (s, 1H), 5.00 – 4.98 (m, 1H), 3.19 (t, *J* = 7.6 Hz, 1H), 2.81 – 2.75 (m, 1H), 2.17 (s, 3H), 2.01 – 1.82 (m, 4H).

***rac*-4-((7a*S*,12*R*)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-**



12-yl)phenol (4.11f): According to GP 6: Pyrrolidine (30 µL, 0.36 mmol), 2-hydroxynaphthalen-1-yl)(4-hydroxyphenyl)methanone (0.12 g, 0.44 mmol) in 1.5 mL of toluene and 1mL xylene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 10) to afford **4.11f** as white solid (55 mg, 52%). FTIR (KBr): $\tilde{\nu}$ = 3441, 2917, 2850, 1625, 1568, 1432, 1421, 1229, 991, 899, 816, 668 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$ with added Methanol-d_4) δ = 7.64 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.13 (m, 2H), 6.99 – 6.94 (m, 3H), 6.63 – 6.61 (m, 2H), 5.29 (s, 1H), 5.02 – 5.01 (m, 1H), 3.24 – 3.17 (m, 1H), 2.81 – 2.75 (m, 1H), 2.01 – 1.90 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$ with added Methanol-d_4) δ = 155.7, 150.9, 134.0, 132.0, 129.5, 128.7, 128.4, 128.0, 125.9, 122.6, 122.3, 118.1, 114.7, 110.3, 85.5, 55.6, 49.6, 31.4, 20.3. HRMS exact mass calculated for $C_{21}H_{20}NO_2^+$([M+H]$^+$): 318.1489; Found: 318.1488.

***rac*-(7a*S*,12*R*)-12-(4-chlorophenyl)-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-**

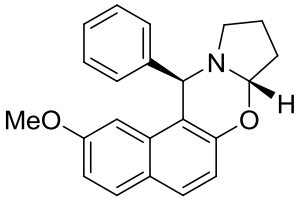


***e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11g):** According to GP 6: Pyrrolidine (16 µL, 0.19 mmol), (4-chlorophenyl)(2-hydroxynaphthalen-1-yl)methanone (66 mg, 0.24 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11g**[6,7] as light yellow solid (44 mg, 67%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.73 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.23 – 7.20 (m, 2H), 7.18 – 7.16 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 1H), 5.40 (s, 1H), 5.01 – 4.99 (m, 1H), 3.33 – 3.29 (m, 1H), 2.92 – 2.87 (m, 1H), 2.13 – 2.06 (m, 1H), 2.06 – 1.95 (m, 3H).

***rac*-(7a*S*,12*R*)-2-methoxy-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-**

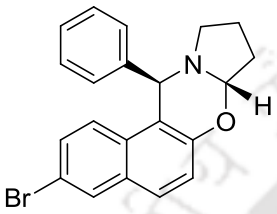
***e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11h):** According to GP 6: Pyrrolidine (30 µL, 0.36 mmol), (2-hydroxy-7-methoxynaphthalen-1-yl)(phenyl)methanone (0.12 g, 0.44 mmol) in 1.5 mL of

toluene at 145 °C under microwave irradiation for 40 min and crystallization and after

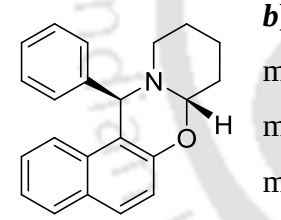


washing (10 X 1 mL of cold EtOAc : Hexane, 1 : 30) to afford **4.11h**[7] as white solid (94 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 – 7.60 (m, 2H), 7.27 – 7.21 (m, 5H), 6.94 – 6.90 (m, 2H), 6.63 (s, 1H), 5.33 (s, 1H), 5.13 – 5.09 (m, 1H), 3.61 (s, 3H), 3.38 – 3.29 (m, 1H), 2.97 – 2.91 (m, 1H), 2.16 – 1.92 (m, 4H).

***rac*-(7a*S*,12*R*)-3-bromo-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11i):** According to GP 6: Pyrrolidine (20 µL, 0.24 mmol), (6-bromo-2-hydroxynaphthalen-1-yl)(phenyl)methanone (95 mg, 0.29 mmol) in 1 mL of toluene at 145 °C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11i**[7] as brown solid (70 mg, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.89 – 7.87 (m, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.28 – 7.20 (m, 6H), 7.08 (d, *J* = 9.0 Hz, 1H), 5.40 (s, 1H), 5.07 – 5.06 (m, 1H), 3.35 – 3.32 (m, 1H), 2.91 – 2.87 (m, 1H), 2.11 – 1.98 (m, 4H).



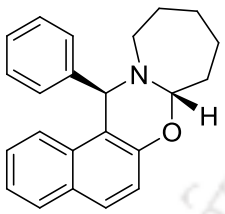
***rac*-(7a*S*,13*R*)-13-phenyl-7a,8,9,10,11,13-hexahydronaphtho[1,2-*e*]pyrido[2,1-*b*][1,3]oxazine (4.11j):** According to GP 6: Piperidine (30 µL, 0.30 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (90 mg, 0.36 mmol) in 1 mL of toluene at 145°C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11j**[6,7] as white solid (43 mg, 45%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.28 – 7.23 (m, 7H), 7.14 – 7.12 (m, 1H), 5.17 (s, 1H), 4.90 – 4.88 (m, 1H), 2.87 – 2.83 (m, 2H), 1.98 – 1.95 (m, 1H), 1.81 – 1.72 (m, 3H), 1.60 – 1.97 (m, 2H).



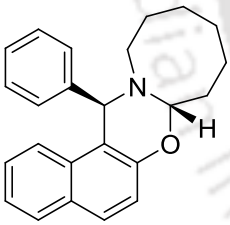
Oxazine (4.11k): According to GP 6: 1,2,3,4-tetrahydroisoquinoline (42 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene 20 min 145 °C under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11k** as white solid (81 mg, 66%). FTIR (KBr): $\tilde{\nu}$ = 2921, 2855, 1621, 1597, 1463, 1402, 1257, 1235, 1137, 1091, 1067, 985, 878, 857, 748, 725, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.43 – 7.41 (m, 1H), 7.31 – 7.30 (m, 7H), 7.24 – 7.18 (m, 4H), 7.11 (d, *J* = 9.0 Hz,

1H), 5.65 (s, 1H), 5.43 (s, 1H), 3.40 – 3.24 (m, 2H), 3.11 – 3.08 (m, 1H), 2.89 – 2.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.2, 142.6, 135.2, 133.3, 132.6, 129.5, 129.3, 129.1, 129.0, 128.98, 128.96, 128.8, 128.5, 127.6, 126.8, 126.4, 123.3, 122.9, 119.1, 111.1, 82.4, 62.9, 45.6, 29.6. HRMS (ESI) exact mass calculated for $C_{26}H_{22}NO^+$ ($[M+H]^+$): 364.1696; Found: 364.1684.

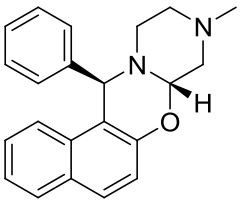
***rac*-(7a*S*,13*R*)-13-Phenyl-7a,8,9,10,11,12-hexahydro-13*H*-7-oxa-12a-aza-cyclohepta [*b*]phenanthrene (4.11l):** According to GP 6: Hexamethyleneimine (30 µL, 0.26 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (79 mg, 0.32 mmol) in 1 mL of toluene 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 40) to afford **4.11l**[6,7] as white solid (57 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.75 – 7.74 (m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.33 (m, 1H), 7.28 – 7.24 (m, 6H), 7.22 – 7.19 (m, 1H), 7.10 (dd, *J* = 8.9, 2.0 Hz, 1H), 5.29 (s, 1H), 4.87 – 4.85 (m, 1H), 3.26 – 3.22 (m, 1H), 2.69 – 2.67 (m, 1H), 2.22 – 2.17 (m, 1H), 1.89 – 1.82 (m, 2H), 1.78 – 1.71 (m, 2H), 1.67 – 1.64 (m, 1H), 1.50 – 1.44 (m, 1H), 1.43 – 1.35 (m, 1H).



Oxazine (4.11m): According to GP 6: Heptamethyleneimine (40 µL, 0.31 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (94 mg, 0.37 mmol) in 1 mL of toluene first 40 min 100 °C then another 10 min at 145 °C under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 60) to afford **4.11m**[6] as light yellow solid (41 mg, 38%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.76 – 7.75(m, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.34 – 7.33 (m, 1H), 7.29 – 7.21 (m, 7H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.28 (s, 1H), 4.70 – 4.67 (m, 1H), 3.28 – 3.23 (m, 1H), 2.59 – 2.55 (m, 1H), 1.98 – 1.87 (m, 5H), 1.55 – 1.51 (m, 2H), 1.48 – 1.43 (m, 3H).

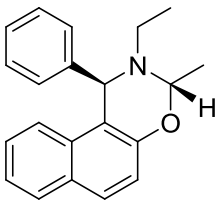


***rac*-(7a*S*,12*R*)-9-Methyl-12-(3-nitro-phenyl)-8,9,10,11-tetrahydro-7a*H*,12*H*-7-oxa-9,11adiaza-benzo [*a*]anthracene(4.11n):** According to GP 6: *N*-methyl piperazine (30µL, 0.27 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.13 g, 0.54 mmol) in 1.5 mL of toluene at 145 °C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 8) to afford **4.11n**[6] as white solid (24 mg, 20%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.77 – 7.76 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H),



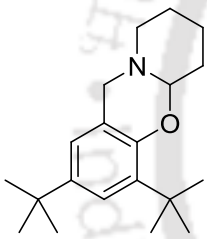
7.35 – 7.33 (m, 1H), 7.28 – 7.25 (m, 3H), 7.24 – 7.21 (m, 5H), 5.23 (s, 1H), 4.83 – 4.81 (m, 1H), 3.21 – 3.17 (m, 1H), 3.11 – 3.09 (m, 1H), 2.89 – 2.88 (m, 2H), 2.45 – 2.39 (m, 1H), 2.34 (s, 3H), 2.21 – 2.17 (m, 1H).

***rac*-(1*R*,3*S*)-2-ethyl-2,3-dihydro-3-methyl-1-phenyl-1*H*-naphtho[1,2-*e*][1,3]oxazine**



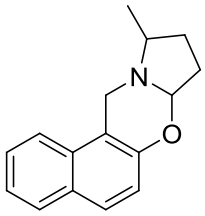
(4.11o): According to GP 6: Diethylamine (35 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(4-methoxyphenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene at 145 ^{o}C under microwave irradiation for 40 min and SiO_2-column chromatography (EtOAc : Hexane 1 : 80) to afford **4.11o**[6] as brown solid (22 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.71 (m, 2H), 7.33 – 7.07 (m, 9H), 5.40 (s, 1H), 4.94 (m, 1H), 3.09 (m, 1H), 2.46 (m, 1H), 1.46 – 1.42 (m, 3H), 1.27 (m, 3H).

2,4-di-tert-butyl-5a,6,7,8,9,11-hexahydrobenzo[*e*]pyrido[2,1-*b*][1,3]oxazine (4.11p):



According to GP 6: Piperidine (35µL, 0.36 mmol), 3,5-di-*tert*-butyl salicylaldehyde (0.10 g, 0.43 mmol) in 1.5 mL of toluene at 145 ^{o}C under microwave irradiation for 30 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 25) to afford **4.11p** as yellow oil (51 mg, 47%). FTIR (KBr): $\tilde{\nu}$ = 2949, 2865, 1652, 1641, 1479, 1449, 1360, 1226, 1128, 1103, 1069, 879, 870, 758 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.15 (s, 1H), 6.81 (s, 1H), 4.85 – 4.83 (m, 1H), 4.30 (d, *J* = 16.1 Hz, 1H), 3.61 (d, *J* = 16.1 Hz, 1H), 2.94 – 2.90 (m, 1H), 2.54 – 2.51 (m, 1H), 2.01 – 1.98 (m, 1H), 1.87 – 1.83 (m, 1H), 1.78 – 1.70 (m, 3H), 1.61 – 1.57 (m, 1H), 1.40 (s, 9H), 1.29 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.3, 142.0, 136.4, 121.9, 121.7, 118.3, 86.3, 54.7, 48.2, 35.1, 34.4, 31.8, 30.7, 29.9, 25.5, 19.4. HRMS (ESI) exact mass calculated for $C_{20}H_{32}NO^+$ ([M+H]$^+$): 302.2478; Found : 302.2478.

10-methyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine (4.11q):



According to GP 6: 2-Hydroxy naphthaldehyde (86 mg, 0.50 mmol), 1-methyl pyrrolidine (20 µL, 0.19 mmol) in 1 mL of toluene at 130 ^{o}C under microwave irradiation for 20 min and SiO_2-column chromatography (EtOAc : Hexane, 1 : 20) to afford inseparable regio-isomeric mixture (~5:1) of **4.11q** as brown solid (22 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2920, 2853, 1635, 1516, 1467, 1434, 1396, 1261, 1228, 1095, 1074, 1016, 860, 811, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.63 (d,

J = 8.8 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.36 – 7.32 (m, 1H), 6.99 (d, *J* = 8.9 Hz, 1H), 5.26 – 5.25 (m, 1H), 4.58 (d, *J* = 17.4 Hz, 1H), 4.27 (d, *J* = 17.5 Hz, 1H), 3.15 – 3.10 (m, 1H), 2.29 – 2.03 (m, 4H), 1.23 (d, *J* = 6.0 Hz, 3H). HRMS (ESI) exact mass calculated for $C_{16}H_{18}NO^+$ ($[M+H]^+$): 240.1383; Found: 240.1381.

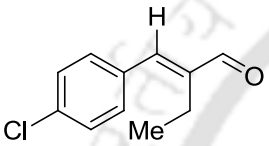
7a-methyl-12-phenyl-8,9,10,12-tetrahydro-7a*H*-naphtho[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazine(4.11r): According to GP 6: 2-Methyl pyrrolidine (34 µL, 0.33 mmol), (2-hydroxynaphthalen-1-yl)(phenyl)methanone (0.10 g, 0.40 mmol) in 1.5 mL of toluene at 145 ^oC for 20 min under microwave irradiation and SiO_2-column chromatography (EtOAc : Hexane, 1 : 30) to afford inseparable regio-isomeric mixture (~4:1) of **4.11r** as yellowish oil (85 mg, 82%). FTIR (KBr): $\tilde{\nu}$ = 2935, 2850, 1623, 1599, 1514, 1462, 1380, 1241, 1109, 1065, 972, 811, 746, 702, 623 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.78 (m, 1H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.31 – 7.19 (m, 8H), 7.09 (d, *J* = 8.9 Hz, 1H), 5.50 (s, 1H), 3.52 – 3.47 (m, 1H), 3.02 – 2.96 (m, 1H), 2.28 – 2.22 (m, 1H), 2.10 – 2.07 (m, 1H), 1.96 – 1.87 (m, 2H), 1.04 (s, 3H). HRMS (ESI) exact mass calculated for $C_{22}H_{22}NO^+$ ($[M+H]^+$): 316.1696; Found: 316.1685.

7.5 Syntheses of Conjugated Aldehydes, Chromenes, Chromene 2-ol Through Direct *β*-C(sp³)-H Functionalization of Aliphatic Amines

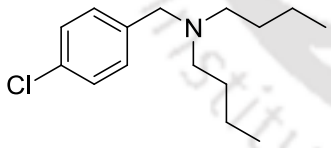
General Procedure (GP 7):

Aldehyde (0.71 mmol) and secondary amine (1.77 mmol) was dissolved in xylene (2 mL). After stirring for 5 minutes, 3,5-dinitrobenzoic acid (0.43 mmol) was added to the mixture and the reaction mixture was allowed to reflux for 26 h. Then the mixture was cooled to room temperature and concentrated under vacuum. Then the crude mixture was subjected to neutral alumina column chromatography to get the analytically pure 2-alkyl Cinnamaldehyde.

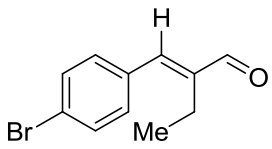
(*E*)-2-(4-chlorobenzylidene)butanal (5.21a): According to GP 7: 4-Chlorobenzaldehyde (0.10 g, 0.71 mmol), dibutylamine (0.30 mL, 1.78 mmol) and 3,5-dinitrobenzoic acid (98 mg, 0.46 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21a**[1,2] as yellow oil (69 mg, 50%). FTIR (KBr): $\tilde{\nu}$ = 2970, 2934, 1682, 1621, 1488, 1396, 1277, 1179, 1091, 1057, 1013, 894, 805, 783, 569, 505 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 7.43 (br. s, 4H), 7.16 (s, 1H), 2.54 (q, *J* = 7.4 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.4, 148.0, 144.9, 135.7, 133.5, 131.0, 129.3, 18.2, 12.9. LRMS (ESI): Exact mass calculated for $C_{11}H_{12}ClO^+$ ($[M+H]^+$): 195.0571; Found: 195.0504.



***N*-butyl-*N*-(4-chlorobenzyl)butan-1-amine (5.21aa):** The product **5.21aa** (14 mg, 8%) was isolated from the same reaction for the preparation of **5.21a.** ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (br. s 4H), 3.49 (s, 2H), 2.37 (t, *J* = 7.2 Hz, 4H), 1.44 – 1.40 (m, 4H), 1.31 – 1.26 (m, 4H) 0.87 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 139.2, 132.3, 130.2, 128.4, 58.2, 53.8, 29.5, 20.8, 14.3. HRMS (ESI): Exact mass calculated for $C_{15}H_{25}ClN^+$ ($[M+H]^+$): 254.1670. Found: 254.1677.



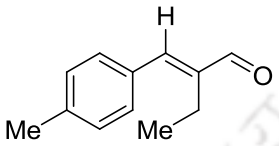
(*E*)-2-(4-bromobenzylidene)butanal (5.21b): According to GP 7: 4-Bromobenzaldehyde (85 mg, 0.46 mmol), dibutylamine (0.31 mL, 1.83 mmol) and 3,5-dinitrobenzoic acid (63 mg, 0.30 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral



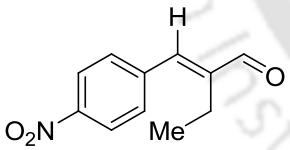
[1] Eljabour, S.; Unterhalt, B. *Arch. Pharm.* **1986**, *319*, 666.
[2] Ram, R. N.; Charles, I. *J. Chem. Res. (S)* **2000**, 540.

alumina column chromatography (EtOAc : Hexane, 1 : 200) to afford **5.21b** as yellow oil (49 mg, 43 %)**.** FTIR (KBr): $\tilde{\nu}$ = 2967, 2931, 2714, 1683, 1627, 1584, 1486, 1391, 1280, 1180, 1074, 1056, 1008, 821, 803, 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.14 (s, 1H), 2.53 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.4, 148.1, 145.1, 133.9, 132.2, 131.2, 124.1, 18.2, 12.9. HRMS (APCI): Exact mass calculated for $C_{11}H_{12}BrO^+$ ($[M+H]^+$): 239.0066; Found: 239.0056.

(*E*)-2-(4-methylbenzylidene)butanal (5.21c): According to GP 7: 4-Methyl benzaldehyde (0.10 mL, 0.84 mmol), dibutylamine (0.35 mL, 2.11 mmol) and 3,5-dinitrobenzoic acid (0.12 g, 0.55 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 75) to afford **5.21c**[2] as brown gum (73 mg, 49%). FTIR (KBr): $\tilde{\nu}$ = 2967, 2933, 2870, 2703, 1683, 1628, 1609, 1465, 1182, 1057, 803, 583 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.07 (s, 1H), 2.48 (q, *J* = 7.5 Hz, 2H), 2.31 (s, 3H), 1.05 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.8, 150.0, 143.6, 140.2, 132.2, 129.9, 129.7, 21.6, 18.1, 12.9. HRMS (APCI): Exact mass calculated for $C_{12}H_{15}O^+$ ($[M+H]^+$): 175.1117; Found: 175.1111.



(*E*)-2-(4-nitrobenzylidene)butanal (**5.21d):** According to GP 7: 4-Nitrobenzaldehyde (0.10 g, 0.66 mmol), dibutylamine (0.28 mL, 1.65 mmol) and 3,5-dinitrobenzoic acid (91 mg, 0.43 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 20) to afford **5.21d**[2] as deep brown oil (47 mg, 35 %)**.** FTIR (KBr): $\tilde{\nu}$ = 2973, 2720, 2356, 1683, 1626, 1593, 1512, 1345, 1298, 1181, 1106, 1054, 911, 866, 852, 836, 782, 751, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 8.31 (d, *J* = 7.1 Hz, 2H), 7.65 (d, *J* = 7.0 Hz, 2H), 7.29 (s, 1H), 2.58-2.51 (m, 2H), 1.16 (t, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.9, 147.9, 147.4, 146.0, 141.3, 130.2, 124.1, 18.4, 13.1. HRMS (APCI): Exact mass calculated for $C_{11}H_{12}NO_3^+$ ($[M+H]^+$): 206.0812; Found: 206.0816.



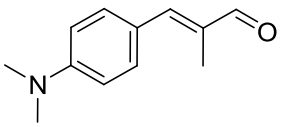
(*E*)-2-(3-nitrobenzylidene)butanal (**5.21e):** According to GP 7: 3-Nitro benzaldehyde (0.10 g, 0.66 mmol), dibutylamine (0.28 mL, 1.65 mmol) and 3,5-dinitrobenzoic acid (91 mg, 0.43 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 30) to afford **5.21e** as deep brown oil (69 mg, 50 %). FTIR (KBr): $\tilde{\nu}$ = 2967, 2939, 1685, 1631, 1530, 1352, 1183, 1056, 826, 806, 735, 707, 679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 8.27 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 2.47 (q, *J* = 7.5 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.9, 148.6, 146.7, 146.0, 136.6, 135.1, 130.0, 124.1, 124.0, 18.3, 13.0. HRMS (APCI): Exact mass calculated for $C_{11}H_{12}NO_3^+$ ($[M+H]^+$): 206.0812; Found: 206.0815.

(*E*)-2-(4-(dimethylamino)benzylidene)butanal (**5.21f):** According to GP 7: 4-*N*,*N*-Dimethyl benzaldehyde (0.15 g, 1.00 mmol), dibutylamine (0.42 mL, 2.50 mmol) and 3,5-dinitrobenzoic acid (0.14 g, 0.65 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 6) to afford **5.21f** as brown gum (60 mg, 29%)**.** FTIR (KBr): $\tilde{\nu}$ = 2970, 2931, 2817, 1676, 1600, 1524, 1444, 1361, 1196, 1183, 1058, 816, 803, 786 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.04 (s, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 3.04 (s, 6H), 2.60 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.6, 151.4, 151.0, 139.9, 132.3, 122.8, 111.9, 40.2 (2C), 18.1, 12.7. HRMS (APCI): Exact mass calculated for $C_{13}H_{18}NO^+$ ($[M+H]^+$): 204.1383; Found: 204.1386.

(*E*)-2-(pyren-1-ylmethylene)butanal (5.21g): According to GP 7: Pyrene 1-carboxaldehyde (0.10 g, 0.43 mmol), dibutylamine (0.18 mL, 1.08 mmol) and 3,5-dinitrobenzoic acid (60 mg, 0.28 mmol) were mixed and refluxed for 48 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 50) to afford **5.21g** with as yellow solid (42 mg, 34%). The product was isolated as mixture of *E/Z* isomers with 6 : 1 ratio. FTIR (KBr): $\tilde{\nu}$ = 2965, 2927, 2850, 1679, 1620, 1462, 1254, 1235, 1184, 1074, 1049, 846, 714 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.85 (s, 1H), 8.26 – 8.22 (m, 4H), 8.21 – 8.14 (m, 6H), 2.55 – 2.50 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 195.6, 148.3, 146.9, 132.1, 131.5, 131.0, 129.4, 129.2, 128.6, 128.5,

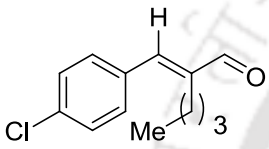
127.5, 126.5, 126.3, 126.1, 126.1, 125.0, 124.8, 124.8, 123.6, 18.9, 13.5. HRMS (ESI): Exact mass calculated for $C_{21}H_{17}O^+$ ($[M+H]^+$): 285.1274; Found: 285.1277.

(*E*)-3-(4-(dimethylamino)phenyl)-2-methylacrylaldehyde (5.21h): According to GP 7: 2-



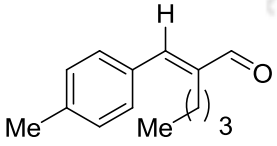
Bromo benzaldehyde (0.120 g, 0.648 mmol), dipropylamine (0.22 mL, 1.62 mmol) and 3,5-dinitrobenzoic acid (89 mg, 0.424 mmol) were mixed and refluxed for 26 h in 2 mL benzene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21h**[3] as brownish oil (40 mg, 27%). 1H NMR (600 MHz, $CDCl_3$) δ = 9.48 (s, 1H), 7.52 – 7.50 (m, 2H), 7.13 (s, 1H), 6.74 – 6.72 (m, 2H), 3.05 (s, 6H), 2.10 (s, 3H).

(*E*)-2-(4-chlorobenzylidene)hexanal (5.21i): According to GP 7: 4-Chlorobenzaldehyde



(0.10 g, 0.71 mmol) dihexylamine (0.41 mL, 1.78 mmol) and 3,5-dinitrobenzoic acid (99 mg, 0.47 mmol) were mixed and refluxed for 60 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21i** light yellow oil (65 mg, 47%). FTIR (KBr): $\tilde{\nu}$ = 2957, 2928, 2862, 1685, 1625, 1591, 1490, 1462, 1177, 1092, 1012, 818, 569, 508, 470 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 7.42 (br. s, 4H), 7.15 (s, 1H), 2.53 – 2.47 (m, 2H), 1.50 – 1.42 (m, 2H), 1.39 (dd, *J* = 15.0, 7.5 Hz, 2H), 0.92 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.6, 148.3, 143.9, 135.7, 133.6, 131.0, 129.3, 30.5, 24.7, 23.2, 14.0. HRMS (APCI): Exact mass calculated for $C_{13}H_{16}ClO^+$ ($[M+H]^+$): 223.0884; Found: 223.0889.

(*E*)-2-(4-methylbenzylidene)hexanal (5.21j): According to GP 7: 4-Methyl benzaldehyde

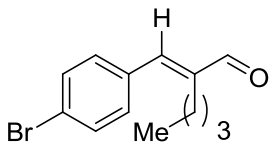


(0.12 mL, 0.99 mmol), dihexylamine (0.58 mL, 2.49 mmol) and 3,5-dinitrobenzoic acid (0.14 g, 0.65 mmol) were mixed and refluxed for 60 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21j** light yellow oil (0.10 g, 50%). FTIR (KBr): $\tilde{\nu}$ = 2957, 2927, 2863, 2705, 1682, 1624, 1607, 1456, 1376, 1207, 1177, 1082, 1019, 810, 565, 508 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.52 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.17 (s, 1H), 2.57 – 2.50 (m, 2H), 2.40 (s, 3H), 1.49 – 1.38 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz,

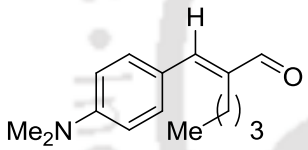
[3] Smith, M. R.; Jang, Y. J.; Kim, J. Y.; Ciufolini, M. A. *Tetrahedron* **2013**, *69*, 10139.

$CDCl_3$): δ = 196.0, 150.2, 142.7, 140.2, 132.4, 130.0, 129.8, 30.5, 24.7, 23.3, 21.7, 14.1. HRMS (APCI): Exact mass calculated for $C_{14}H_{19}O^+$ ([M+H]$^+$): 203.1430; Found: 203.1430.

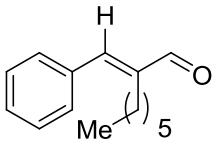
(*E*)-2-(4-bromobenzylidene)hexanal (**5.21k):** According to GP 7: 4-Bromo benzaldehyde (0.10 g, 0.54 mmol), dihexylamine (0.31 mL, 1.35 mmol) and 3,5-dinitrobenzoic acid (74 mg, 0.35 mmol) were mixed and refluxed for 48 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 200) to afford **5.21k** as yellow oil (77 mg, 44%). FTIR (KBr): $\tilde{\nu}$ = 2960, 2931, 2867, 1684, 1587, 1487, 1427, 1399, 1261, 1069, 1012, 851, 803, 757 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.54 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 2.52 – 2.47 (m, 2H), 1.48 – 1.42 (m, 2H), 1.38 (dt, *J* = 14.9, 7.1 Hz, 2H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.6, 148.3, 144.1, 134.1, 132.3, 131.2, 124.1, 30.5, 24.7, 23.2, 14.1. HRMS (APCI): Exact mass calculated for $C_{13}H_{16}BrO^+$ ([M+H]$^+$): 267.0379; Found: 267.0378.



(*E*)-2-(4-(dimethylamino)benzylidene)hexanal (5.21l): According to GP 7: 4-*N*,*N*-dimethylbenzaldehyde (0.10 g, 0.67 mmol), dihexylamine (0.39 mL, 1.67 mmol) and 3,5-dinitrobenzoic acid (92 mg, 0.44 mmol) were mixed and refluxed for 86 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 20) to afford **5.21l** brown oil (59 mg, 38%). FTIR (KBr): $\tilde{\nu}$ = 2955, 2927, 1670, 1595, 1524, 1365, 1192, 1170, 1082, 813 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.43 (s, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.04 (s, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 3.05 (s, 6H), 2.61 – 2.54 (m, 2H), 1.47 (ddd, *J* = 17.9, 8.0, 4.6 Hz, 4H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.9, 151.4, 151.3, 138.9, 132.3, 122.9, 111.9, 40.3 (2C), 30.3, 24.7, 23.3, 14.2. HRMS (ESI): Exact mass calculated for $C_{15}H_{22}NO^+$ ([M+H]$^+$): 232.1696; Found: 232.1688.



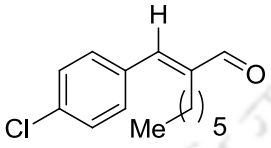
(*E*)-2-benzylideneoctanal (5.21m): According to GP 7: Benzaldehyde (0.10 mL, 0.98 mmol), dioctaylamine (0.38 mL, 1.25 mmol) and 3,5-dinitrobenzoic acid (0.14 g, 0.64 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21m**[4] as yellow oil



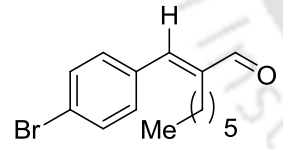
[4] Limnios, D.; Kokotos, C. G. *RSC Adv.* **2013**, *3*, 4496.

(80 mg, 43%). FTIR (KBr): $\tilde{\nu}$ = 2956, 2927, 2856, 1683, 1624, 1458, 1200, 1091, 1018, 801, 755, 697 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.55 (s, 1H), 7.51 – 7.48 (m, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.42 – 7.38 (m, 1H), 7.20 (s, 1H), 2.55 – 2.51 (m, 2H), 1.52 – 1.46 (m, 2H), 1.38 (p, *J* = 7.3 Hz, 2H), 1.29 (td, *J* = 7.1, 6.0, 3.7 Hz, 4H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.9, 149.9, 143.6, 135.2, 129.8, 129.7, 128.9, 31.7, 29.7, 28.4, 25.0, 22.8. 14.2. HRMS (APCI): Exact mass calculated for $C_{15}H_{21}O^+$ ($[M+H]^+$): 217.1587; Found: 217.1589.

(*E*)-2-(4-chlorobenzylidene)octanal (5.21n): According to GP 7: 4-Chloro benzaldehyde (0.10 g, 0.71 mmol), dioctaylamine (0.27 mL, 0.91 mmol) and 3,5-dinitrobenzoic acid (99 mg, 0.47 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.21n** as yellow oil (90 mg, 50 %). FTIR (KBr): $\tilde{\nu}$ = 2956, 2927, 2855, 1739, 1865, 1623, 1592, 1491, 1466, 1093, 1013, 817 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.53 (s, 1H), 7.42 (br. s, 4H), 7.14 (s, 1H), 2.51 – 2.47 (m, 2H), 1.49 – 1.43 (m, 2H), 1.36 (dt, *J* = 14.4, 7.1 Hz, 2H), 1.28 (dt, *J* = 7.5, 3.6 Hz, 4H), 0.89 – 0.85 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.5, 148.3, 144.0, 135.7, 133.6, 131.0, 129.3, 31.7, 29.7, 28.4, 24.9, 22.8, 14.2. HRMS (APCI): Exact mass calculated for $C_{15}H_{20}ClO^+$ ($[M+H]^+$): 251.1196; Found: 251.1197.



(*E*)-2-(4-bromobenzylidene)octanal (5.21o): According to GP 7: 4-Bromo benzaldehyde (40 mg, 0.21 mmol), dioctaylamine (0.19 mL, 0.64 mmol) and 3,5-dinitrobenzoic acid (29 mg, 0.14 mmol) were mixed and refluxed for 86 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 200) to afford **5.21o** as yellow oil (26 mg, 41%). FTIR (KBr): $\tilde{\nu}$ = 2955, 2927, 2856, 1684, 1625, 1585, 1487, 1465, 1391, 1163, 1088, 1009, 892, 814, 506 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 9.53 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.13 (s, 1H), 2.51 – 2.45 (m, 2H), 1.46 (p, *J* = 8.0, 7.5 Hz, 2H), 1.36 (p, *J* = 7.1 Hz, 2H), 1.31 – 1.25 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 195.5, 148.3, 144.1, 134.0, 132.2, 131.2, 124.0, 31.7, 29.7, 28.4, 25.0, 22.8, 14.3. HRMS (APCI): Exact mass calculated for $C_{15}H_{20}BrO^+$ ($[M+H]^+$): 295.0692; Found: 295.0692.



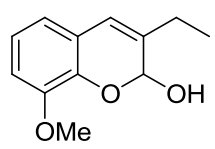
(*E*)-2-benzylidenedecanal (5.21p): According to GP 7: Benzaldehyde (0.15 mL, 1.47 mmol), didecylamine (0.52 g, 1.76 mmol) and 3,5-dinitrobenzoic acid (0.20 g, 0.96 mmol) were mixed and refluxed for 26 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 80) to afford **5.21p** as reddish oil (56 mg, 43%). FTIR (KBr): $\tilde{\nu}$ = 2955, 2925, 2854, 1684, 1625, 1466, 1376, 1190, 1094, 1028, 858, 858, 754, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.55 (s, 1H), 7.52 – 7.48 (m, 2H), 7.47 – 7.42 (m, 2H), 7.42 – 7.37 (m, 1H), 7.21 (s, 1H), 2.55 – 2.50 (m, 2H), 1.53 – 1.44 (m, 2H), 1.37 (dt, *J* = 14.4, 7.2 Hz, 2H), 1.34 – 1.26 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 195.9, 149.9, 143.6, 135.2, 129.8, 129.7, 128.9, 32.0, 30.1, 29.5, 29.4, 28.5, 24.9, 22.8, 14.3. HRMS (APCI): Exact mass calculated for $C_{17}H_{25}O^+$ ($[M+H]^+$) 245.1900; Found: 245.1907.

(*E*)-2-ethyl-5,5-diphenylpenta-2,4-dienal (5.21q): According to GP 7: *β*-Phenyl cinnamaldehyde (50 mg, 0.24 mmol), dibutylamine (0.10 mL, 1.21 mmol) and 3,5-dinitrobenzoic acid (34 mg, 0.32 mmol) were mixed and refluxed for 80 h in 2 mL *m*-xylene and preparative TLC separation (EtOAc : Hexane, 1 : 65) to afford **5.21q** as brown oil (29 mg, 46%)**.** The product was isolated as mixture of *E/Z* isomer with 6 : 1 ratio. FTIR (KBr): $\tilde{\nu}$ = 2967, 2930, 2848, 1674, 1610, 1446, 1276, 1201, 1055, 767, 701 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 9.29 (s, 1H), 7.46 – 7.42 (m, 3H), 7.37 – 7.33 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 11.7 Hz, 1H), 6.89 (d, *J* = 11.7 Hz, 1H), 2.50 (q, *J* = 7.6 Hz, 2H), 1.09 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.9, 151.9, 146.0, 144.8, 141.7, 138.8, 130.7, 129.2, 128.8, 128.7, 128.6, 128.5, 122.3, 17.9, 14.1. HRMS (APCI): Exact mass calculated for $C_{19}H_{19}O^+$ ($[M+H]^+$): 263.1430; Found: 263. 1418.

(*E*)-2-(3,3-diphenylallylidene)hexanal (5.21r): According to GP 7: *β*-Phenyl cinnamaldehyde (80 mg, 0.39 mmol), dihexylamine (0.22 mL, 0.97 mmol) and 3,5-dinitrobenzoic acid (53 mg, 0.25 mmol) were mixed and refluxed for 80 h in 2 mL *m*-xylene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 120) to afford **5.21r** brown oil (44 mg, 39%). The product was isolated as mixture of *E/Z* isomer with 4 : 1 ratio. FTIR (KBr): $\tilde{\nu}$ = 3050, 2953, 2927, 2858, 1673, 1608, 1446, 1277, 1195, 1075, 767, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1H), 7.81 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.45 (dd, *J* = 5.1, 1.8 Hz, 2H), 7.36 – 7.35

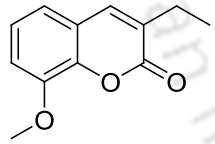
(m, 4H), 7.13 (d, *J* = 11.7 Hz, 1H), 6.93 (d, *J* = 11.7 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 1.46 – 1.34 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.1, 151.8, 146.5, 143.4, 138.7, 132.6, 130.7, 130.2, 128.7, 128.6, 128.5, 128.4, 122.5, 31.7, 24.3, 23.0, 14.2. HRMS (APCI): Exact mass calculated for $C_{21}H_{23}O^+$ ($[M+H]^+$): 291.1744. Found: 291.1734.

3-ethyl-8-methoxy-2*H*-chromen-2-ol (5.33a) and 3-ethyl-8-methoxy-2*H*-chromen-2-one



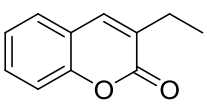
(5.34a): According to GP 7: *o*-Vanillin (0.10 g, 0.66 mmol), dibutylamine (0.27 mL, 1.64 mmol) and 3,5-dinitrobenzoic acid (91 mg, 0.43 mmol) were mixed and refluxed for 12 h. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 10) to afford **5.33a** as colorless solid (64 mg, 47%) and **5.34a** as colourless solid (11 mg, 8%). **5.33a:** FTIR (KBr): $\tilde{\nu}$ = 3465, 2966, 2839, 1610, 1583, 1484, 1460, 1435, 1273, 1208, 1170, 1098, 1046, 994, 947, 908, 768, 736, 722, 669, 503 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.90 (t, *J* = 7.8 Hz, 1H), 6.18 (dd, *J* = 7.2 Hz, 1.2 Hz, 1H), 6.75 (dd, *J* = 6.6, 1.2 Hz, 1H), 6.40 (s, 1H), 5.92 (s, 1H), 3.86 (s, 3H), 2.42 – 2.36 (m, 1H), 2.33 – 2.27 (m, 1H), 1.2 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 148.4, 138.8, 136.6, 121.83, 121.55, 119.3, 118.9, 111.3, 92.8, 56.2, 25.8, 12.0. HRMS (APCI): Exact mass calculated for $C_{12}H_{15}O_3^+$ ($[M+H]^+$) 207.1016; Found: 207.1008.

5.34a: FTIR (KBr): $\tilde{\nu}$ = 2961, 2934, 2873, 1718, 1670, 1611, 1580, 1481, 1461, 1440, 1276,



1182, 1109, 1039, 945, 734 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (s, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.96 (s, 3H), 2.61 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.4, 147.3, 142.9, 137.8, 131.8, 124.3, 120.5, 118.9, 112.7, 56.4, 24.1, 12.5. HRMS (APCI): Exact mass calculated for $C_{12}H_{13}O_3^+$ ($[M+H]^+$): 205.0859; Found: 205. 0858.

3-ethyl-2*H*-chromen-2-one (5.34b): According to GP 7: Salicylaldehyde (0.10 mL, 0.95

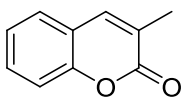


mmol), dibutylamine (0.40 mL, 2.37 mmol) and 3,5-dinitrobenzoic acid (0.13 g, 0.62 mmol) were mixed and refluxed for 26 h. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 75) to afford **5.34b**[5] as light yellow solid (75 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.24 (m,

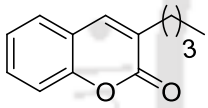
[5] Shi, M.; Gross, U.; Gross, P. J.; Brase, S. *Synlett* **2011**, 635.

1H), 2.61 (q, *J* = 7.4 Hz, 2H), 1.27 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 153.2, 137.7, 131.5, 130.6, 127.3, 124.4, 119.8, 116.6, 24.1, 12.5.

3-methyl-2*H*-chromen-2-one (5.34c): According to GP 7: Salicylaldehyde (0.10 mL, 0.950 mmol), dipropylamine (0.32 mL, 2.37 mmol) and 3,5-dinitrobenzoic acid (0.13 g, 0.62 mmol) were mixed and refluxed for 26 h in 2 mL benzene. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.34c**[6] as colorless solid (59 mg, 38%). FTIR (KBr): $\tilde{\nu}$ = 2951, 2923, 2854, 1706, 1635, 1610, 1463, 1450, 1371, 1257, 1194, 1076, 1004, 918, 754 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.53 (s, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 162.4, 153.4, 139.4, 130.7, 127.1, 126.0, 124.5 (CH, aromatic), 119.8, 116.7, 17.4. HRMS (APCI): Exact mass calculated for $C_{10}H_9O_2^+$ ([M+H]$^+$) 161.0597; Found: 161.0590.



3-butyl-2*H*-chromen-2-one (5.34d): According to GP 7: Salicylaldehyde (74 μL, 0.70 mmol), dihexylamine (0.41 mL, 1.76 mmol) and 3,5-dinitrobenzoic acid (97 mg, 0.46 mmol) were mixed and refluxed for 20 h. The crude mixture was subjected to neutral alumina column chromatography (EtOAc : Hexane, 1 : 100) to afford **5.34d** as light yellow solid (50 mg, 46%). FTIR (KBr): $\tilde{\nu}$ = 2952, 2929, 2868, 1724, 1612, 1576, 1457, 1255, 1171, 1070, 1044, 997, 867, 759, 711 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 7.47 – 7.42 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 2.60 – 2.54 (m, 2H), 1.66 – 1.58 (m, 2H), 1.42 (h, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.3, 138.5, 130.6, 130.3, 127.3, 126.2, 124.4, 119.8, 116.6, 30.8, 30.3, 22.6, 14.1. HRMS (APCI): Exact mass calculated for $C_{13}H_{15}O_2^+$([M+H]$^+$): 203.1067; Found: 203.1067.



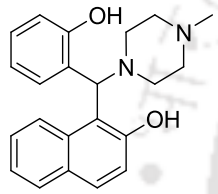
[6] Olomola, T. O.; Klein, R.; Kaye, P. T. *Synth. Commun.* **2012**, *42*, 251.

7.6 Synthesis, *In silico* Studies and *In vitro* Evaluation for Antioxidant and Antibacterial Properties of Diarylmethylamines

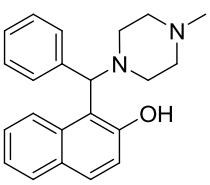
General procedure (GP 8):

2-Naphthol or sesamol was added to a solution of secondary amine and aldehyde in benzene or ethanol and the mixture was refluxed for 16 h. After the disappearance of the starting material indicated by TLC, the solvents were allowed to evaporate under ambient condition to obtain the solid residue. The solid was washed with hexane and binary solvent mixture (EtOAc and hexane) to afford analytically pure diarylmethylamine derivatives. Compounds **6.1a**, **6.1b**, **6.1d**, **6.1e**, **6.1g**, **6.1h**, **6.1i**, **6.1j** and **6.1n** were synthesized following the reported literature procedure.[1,2]

1-((2-hydroxyphenyl)(4-methylpiperazin-1-yl)methyl)naphthalen-2-ol (**6.1c**): According to GP 8: 2-Napthol (0.20 g, 1.39 mmol), salicylaldehyde (0.17 mL, 1.66 mmol), *N*-methyl piperazine (0.18 mL, 1.66 mmol) in benzene 2 mL for 16 h, slow evaporation under ambient condition and washing (50 mL; EtOAc : hexane; 1 : 15) the resulting solid gave **6.1c** (0.42 g, 90%) as white powder. FTIR (KBr): $\tilde{\nu}$ = 3458, 3061, 3045, 2956, 2806, 1622, 1601, 1577, 1517, 1459, 1332, 1283, 1239, 1152, 1139, 1096, 997, 949, 832, 813, 760, 754, 746, 636, 533 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 13.87 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.30 – 7.26 (m, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.15 (m, 1H), 7.04 – 7.00 (m, 1H), 6.68 (t, *J* = 8 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 1H), 3.32 – 3.29 (m, 1H), 3.12 – 3.09 (m, 1H), 3.04 – 2.91 (m, 3H), 2.69 – 2.66 (m, 1H), 2.60 – 2.56 (m, 1H), 2.53 (s, 3H), 2.38 – 2.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.2, 155.2, 133.2, 130.6, 129.5, 129.3, 128.8, 128.7, 126.8, 125.3, 122.7, 121.9, 120.3, 119.9, 116.1, 114.9, 62.5, 55.9, 55.3, 52.7, 47.1, 45.8. HRMS (ESI) exact mass calculated for $C_{22}H_{25}N_2O_2^+$ ($[M + H]^+$): 349.1911; Found: 349.1904.



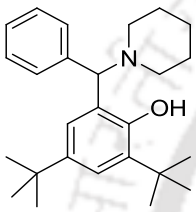
1-((4-methylpiperazin-1-yl)(phenyl)methyl)naphthalen-2-ol (**6.1f**): According to GP 8: 2-Napthol (1.0 g, 6.94 mmol), benzaldehyde (0.84 mL, 8.32 mmol), *N*-methylpiperazine (0.92 mL, 8.32 mmol) in benzene 2 mL in reflux condition for 18 h, slow evaporation under ambient condition, washing the



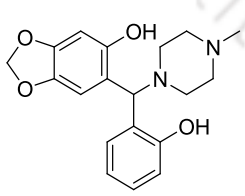
[1] Mahato, S.; Haldar, S.; Jana, C. K. *Chem. Commun*. **2014**, *50*, 332.
[2] Mahato, S.; Haque, M. A.; Dwari, S.; Jana, C. K. *RSC Adv*. **2014**, *4*, 46214.

solid residue (60 mL; EtOAc : hexane; 1 : 10) gave **6.1f** as yellowish solid (1.82 g, 80%). FTIR (KBr): $\tilde{\nu}$ = 3439, 3061, 2970, 2839, 2798, 1620, 1598, 1581, 1520, 1473, 1452, 1415, 1265, 1238, 1154, 1136, 1083, 1016, 999, 949, 834, 817, 748, 698, 637, 514, 497 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 13.34 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.64 (t, *J* = 8.6 Hz, 1H), 7.55 – 7.53 (m, 2H), 7.35 – 7.31 (m, 1H), 7.24 – 7.20 (m, 3H), 7.18 – 7.14 (m, 3H), 5.10 (s,1H), 3.62 – 2.43 (br. m, 8H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.0, 139.2, 132.3, 129.6, 128.9, 128.8, 128.1, 126.5, 122.6, 121.1, 119.9, 115.6, 71.6, 55.1, 53.3, 51.0, 45.7. HRMS (APCI) exact mass calculated for $C_{22}H_{25}N_2O^+$ ($[M + H]^+$): 333.1961; Found: 333.1954.

2,4-di-tert-butyl-6-(phenyl(piperidin-1-yl)methyl)phenol (6.1k): According to GP 8: 2,4-Di-*tert*-butyl phenol (0.15 g, 0.73 mmol), benzaldehyde (88 µL, 0.87 mmol), piperidine (86 µL, 0.87 mmol) in benzene 2 mL in reflux condition for 16 h. SiO_2-column chromatography (EtOAc : Hexane; 1 : 200) gave product **6.1k** as white solid (0.20 g, 72%). FTIR (KBr): $\tilde{\nu}$ = 3458, 2964, 2947, 2859, 1483, 1453, 1434, 1357, 1261, 1236, 1199, 1158, 1035, 953, 871, 790, 708, 651 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 12.56 (s, 1H), 7.43 (br. s, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.25 – 7.23 (m,1H), 7.14 (s, 1H), 6.74 (s, 1H), 4.44 (s, 1H), 3.29 – 1.63 (br. m, 10 H), 1.45 (s, 9H), 1.19 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 153.8, 140.2, 140.1, 136.0, 129.2, 128.7, 127.7, 124.7, 124.2, 122.6, 52.4, 35.2, 34.3, 31.8, 29.8, 26.2, 24.4. HRMS (APCI) exact mass calculated for $C_{26}H_{38}NO^+$ ($[M + H]^+$): 380.2948; Found: 380.2950.



6-((2-hydroxyphenyl)(4-methylpiperazin-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (**6.1l**): According to GP 8: Sesamol (0.20 g, 1.45 mmol), salicylaldehyde (0.18 mL, 1.74 mmol), *N*-methyl piperizine (0.19 mL, 1.74 mmol) in ethanol 2 mL in reflux condition for 16 h, slow evaporation under ambient condition, washing the solid residue (50 mL; EtOAc : hexane; 1 : 10), and recrystallization from ethanol gave **6.1l** (0.36 g, 72%) as whitish solid. FTIR (KBr): $\tilde{\nu}$ = 3453, 2856, 2809, 1607, 1586, 1500, 1476, 1463, 1282, 1257, 1214, 1183, 1164, 1134, 1041, 987, 936, 875, 759, 571 cm^{-1}.^1H NMR (400 MHz, CD_3OD) δ = 7.00 – 6.94 (m, 2H), 6.68 – 6.66 (m, 1H), 6.62 (t, *J* = 7.5 Hz, 1H), 6.51 (s, 1H), 6.25 (s, 1H), 5.68 (s, 2H), 5.01 (s, 1H) 2.81– 2.23 (br. 8H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 155.7, 150.4, 146.6, 139.9, 128.6, 128.0, 126.2, 119.2, 117.3, 116.0, 107.5, 100.7, 97.9, 64.8, 54.8 (2C), 50.4 (2C),



45.4. HRMS (ESI) exact mass calculated for $C_{19}H_{23}N_2O_4^+$ ([M + H]$^+$): 343.1652; Found: 343.1646.

6-((2-hydroxy-3-methoxyphenyl)(4-methylpiperazin-1-yl)methyl)benzo[d][1,3]dioxol-5-ol (6.1m): According to GP 8: Sesamol (0.10 g, 0.72 mmol), *o*-vanillin (0.13 g, 0.87 mmol), *N*-methyl piperazine (0.10 mL, 0.87 mmol) in ethanol 2 mL in reflux condition for 16 h, slow evaporation under ambient condition, washing the solid residue (30 mL; EtOAc : Hexane; 1 : 10), and recrystallization from ethanol gave **6.1m** (0.18 g, 67%) as whitish solid. FTIR (KBr): $\tilde{\nu}$ = 3453, 2989, 2961, 1632, 1500, 1480, 1460, 1281, 1139, 1068, 1058, 1037, 994, 934, 864, 789, 730 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.70 – 6.67(m, 2H), 6.59 (t, *J* = 7.9 Hz, 1H), 6.44 (s, 1H), 6.21 (s, 1H), 5.66 (d, *J* = 3.0 Hz, 2H), 5.01 (s, 1H), 3.73 (s, 3H), 2.91 – 2.27 (br. m, 8H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 150.4, 147.7, 146.6, 145.0, 139.9, 126.5, 120.2, 118.8, 117.3, 110.5, 107.4, 100.7, 97.8, 64.8, 55.5, 54.8, 50.4, 45.5. LRMS (APCI) exact mass calculated for $C_{20}H_{25}N_2O_5^+$([M + H]$^+$): 373.1758; Found: 373.1788.

Materials and Methods for Biological Assays

i) Antibacterial studies

a) Bacterial strains

The antibacterial activities of synthesized compounds were evaluated against two bacteria: *Listeria monocytogenes*, LM (ATCC 19115) and *Escherichia coli* enterotoxic, ETEC (MTCC 723). All the tested bacteria were grown and maintained on nutrient agar (NA) as described earlier by Kesari et al.[3]

b) Determination of MIC

Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial agent that will inhibit the visible growth of a microorganism. The MIC was determined using the microdilution method, in 96 wells microtitre plates according to protocol described by Ghosh et al.[4] Compounds were dissolved in dimethyl sulfoxide (DMSO) at concentration of 2 mg/mL and this concentration was further used to make compound with concentration up to 1.95 µg/mL by two fold dilution method. Controls

[3] Kesari, V.; Das, A.; Rangan, L. *Biomass Bioenergy* **2010**, *34*,108.
[4] Ghosh, S.; Indukuri, K.; Bondalapati, S.; Saikia, A. K.; Rangan, L. *Eur. J. Med. Chem.* **2013**, *66*, 101.

(growth, compound and negative control) were also included. Microtitre plates containing different concentration of compound (1.95 µg/mL - 1 mg/mL) were incubated at 37 ºC for 24 h and MIC was recorded spectrophotometrically at 600 nm (concentration at which there is sharp decline in the absorbance value). In addition, colour based assay were performed using resazurin (HiMedia) solution prepared in distilled water as described by Sarker et al.[5] Change in colour from purple to pink and colourless was recorded as positive and the lowest concentration at which colour change occurs was recorded as MIC. Kanamycin (5 mg/mL) was used as standard drug for the comparison.

c) FC analysis

The ability to distinguish different physiological states is very important for assessing and validating the survival and virulence of any pathogenic microorganisms. To determine the antibacterial action, the mid log phase culture of most susceptible bacteria, i.e., LM was treated with compound **6.1l** at its MIC and subsequently incubated for 24 h along with the vehicle control (cells treated with 1% DMSO). Bacterial suspensions were centrifuged at 10,000 rpm and cells resuspended in phosphate buffer saline (PBS) to maintain the cell density of approximately 10^4cells/mL. Heat killed cells (95 ºC for 15 min) were taken as negative control. Samples were first singly stained by adding 10 µL carboxyfluorescein diacetate (cFDA) (0.25 mM, Sigma Aldrich) or 10 µL propidium iodide (PI) (100 µg/mL, Sigma Aldrich) and incubated at 37 ºC for 30 min in the dark. All the stained samples were subsequently washed with PBS to remove residual dye. Samples were also double stained following the protocol described by Amor et al.[6] Multicolour flow analysis was carried out by fully integrated and multiparamatric BD FACSCalibur (Becton Dickinson) system equipped with an air-cooled argon ion laser emitting 15mW blue light at 488 nm and with standard filter set up. The FC analysis of the cell samples was performed using FACS Flow solution (BD) as the sheath fluid. Samples were kept at low flow rate (12 µL/min ± 3 µL/min) up to a total of 5,000 events per sample. Bacterial cells were analyzed by forward (FSC) and side (SSC) light scatter. Viability in term of membrane integrity and functional cytoplasmic enzymes was examined by staining with cFDA detected by FL1 channel, having 530 nm bandpass filter. Red fluorescence signal of PI was collected in the FL3 channel with >600 nm long pass filter for membrane permeability. The fluorescence signals of individual cells were collected in biexponential mode. Gating was done in dot-plot of FSC-SSC to discriminate

[5] Sarker, S. D.; Nahar, L.; Kumarasamy, Y. *Methods* **2007**, *42*, 321.
[6] Amor, K. B.; Breeuwer, P.; Verbaarschot, P.; Rombouts, F. M.; Akkermans, A. D. L.; De Vos, W. M.; Abee, T. *Appl. Environ. Microb.* **2002**, 5209.

bacteria from noise and artifacts. Data were acquired by BD CellQuest Pro software and were analyzed and refined by FloJo software (Tree Star, Stanford, USA).

d) Statistical analysis

All experiments were set up in a completely randomized design and repeated thrice with a minimum of three replicates. The statistical analysis was carried out using SPSS Statistics 17.0. The MFI values of FC data were subjected to analysis of variance (ANOVA) followed by Tukey's test (Post-hoc analysis) to detect significant difference between the treatments and vehicle control for bacterial strain. Differences were considered significant at a value of $p < 0.05$.

e) FESEM study

Field emission scanning electron microscopy (FESEM) was used to visualize the changes in the morphology of the LM cells before and after treatment with compound **6.1l**. Untreated bacterial cells were used as negative control. The bacterial samples were gently washed with freshly prepared 50 mM phosphate buffer solution (pH 7.2), fixed with 2.5% glutaraldehyde in PBS and rinsed with the same buffer solution. The specimen was dehydrated using sequential exposure for each ethanol concentrations ranging from 30% to 100%. Finally, the specimens were coated with gold and analyzed through FESEM (Carl Zeiss, Ultra 55).

ii) Antioxidant activity

The free radical scavenging efficacy of all the compounds **6.1a-6.1n** were estimated using DPPH (2,2-diphenyl-1-picrylhydrazyl) assay according to the method described by Park et al.[7] DPPH is known as a stable free radical and strong scavenger for other radicals, which loses its purple colour on accepting an electron from an antioxidant molecule available in a reaction system.[8] DPPH free radical scavenging activity of the compounds were determined using colorimetric assay. First 80 µL of DPPH solution (0.2 mM DPPH in absolute ethanol) was mixed thoroughly with 20 µL of the compound (concentrations ranging from 1.95 µg/mL to 1 mg/mL), and incubated for 30 min in dark at 25 ºC. Butylated hydroxyl toluene (BHT) (Sigma Aldrich, USA) and ascorbic acid were used as positive controls and ethanol as solvent control. The absorbance was recorded at 517 nm in multimode microplate reader (Tecan, Infinite M-200, Switzerland). The ability to scavenge the DPPH radical was calculated as % radical scavenging activity (RSA) using the following equation:

$$RSA\ (\%) = (1 - A/B) \times 100$$

[7] Park, Y. S.; Leontowicz, H.; Leontowicz, M.; Namiesnik, J.; Suhaj, M.; Cvikrová, M.; Martincová, O.; Weisz, M.; Gorinstein, S. *J. Food Comp. Anal.* **2011**, *24*, 963.
[8] Zou, Y.; Lu, Y.; Wei, D. *J. Agric. Food. Chem.* **2004**, *52*, 5032.

where, A was the absorbance of test compound and B was the absorbance of the DPPH dye. Linear graph of concentration and percentage inhibition was prepared and inhibitory concentration 50% (IC_{50}) values were calculated.

iii) *In silico* studies

Physico-chemical properties by OSIRIS

Physico-chemical properties like lipophilicity, aqueous solubility, molecular weight, etc of a bioactive molecule are important parameters to be considered for the drug discovery and development. Therefore, *in silico* studies were carried out to calculate the above mentioned parameter for all the synthesized compounds and the results were summarized in **Table 3**. For most of the compounds, the parameters were within the standard range. The calculated logP has been shown to be one of the key parameters in quantitative structure activity/property

Table 3: *In silico* studies of the compounds **6.1a-n**

Compounds	Mutagenic	Tumorigenic	Irritant	Reproductive effective	cLogP	LogS	Molecular weight	TPSA	Drug likeness	Drug score
6.1a	Red	Red	Green	Green	3.0	-3.73	377	72.53	-1.06	0.17
6.1b	Red	Red	Green	Green	4.29	-4.09	319	43.7	0.33	0.19
6.1c	Red	Red	Green	Green	3.58	-2.97	348	46.94	4.15	0.28
6.1d	Red	Red	Red	Green	4.64	-4.39	303	23.47	0.64	0.15
6.1e	Red	Red	Green	Green	4.06	-5.12	362	69.29	-7.42	0.1
6.1f	Red	Red	Green	Red	3.93	-3.27	332	26.71	5.69	0.22
6.1g	Red	Red	Green	Green	3.69	-3.62	304	36.36	1	0.24
6.1h	Red	Red	Green	Green	1.95	-3.46	365	91.41	-6.63	0.15
6.1i	Red	Red	Green	Green	5.27	-5.02	353	23.47	1.4	0.16
6.1j	Green	Green	Red	Green	3.44	-2.78	253	23.47	3.66	0.67
6.1k	Green	Green	Red	Green	6.95	-5.37	379	23.47	-9.78	0.11
6.1l	Green	Green	Green	Green	2.5	-2.08	342	65.4	5.58	0.87
6.1m	Red	Green	Red	Green	2.43	-2.10	372	74.63	4.45	0.41
6.1n	Green	Green	Red	Green	5.23	-4.11	303	23.47	-9.99	0.18

relationship (QSAR/QSPR) studies.[9,10] Potential antibacterial agents **6.1f, 6.1l** and **6.1m** showed to have logP value of 3.93, 2.5 and 2.43, respectively, which are well below the maximum acceptable value (5). The aqueous solubility is also an important parameter which significantly affects the absorption and distribution characteristics of bioactive molecules. More than 80% of the drugs in the market have aqueous solubility values greater than -4.[11] It is also known that the total sum of all polar regions of a molecule's surface correlates well with various bioavailability related properties, such as intestinal absorption and blood brain barrier penetration. The solubility parameters for compounds **6.1f** (-3.27), **6.1l** (-2.08) and **6.1m** (-2.10) were found to be in the acceptable range. Positive value of drug likeness and drug score state that **6.1l** and **6.1m** contains predominant fragments which are frequently present in commercial drugs. The analysis also suggested that compound **6.1l** may have low risk to human health considering the four main parameters (mutagenic, tumorigenic, irritant, and reproductive effectiveness). Overall, with highly desirable physico-chemical parameters and nontoxic behaviour, the structure of compound **6.1l** disclosed its potential as a promising therapeutic agent.

Lipinski's rule

Lipinski's rule of 5 evaluates whether a given compound can be administered as orally active drug.[12] The analysed data showed that most of the synthesized compounds (**6.1a-6.1c** and **6.1f-6.1h**, **6.1j**, **6.1l**, **6.1m**) meet the Lipinski's rules of the five, suggesting that the compound theoretically would not have problems with oral bioavailability (**Table 4**). Compounds **6.1d**, **6.1e**, **6.1i**, **6.1k** and **6.1n** with high partition coefficient log P are violating the Lipinski's rule where permeability could be a barrier for their transport in biological system. The methyl groups of **6.1k** and **6.1n** contributes to its high lipophilicity, therefore unsuitable for oral consumption.

[9] Alves, C. N.; Pinheiro, J. C.; Camargo, A. J.; Ferreira, M. M. C.; Silva, A. B. F. *J. Mol. Struc-Theochem.* **2000**, *530*, 39.
[10] Bayat, Z.; Nassab, S. Q. *J. Chem. Pharm. Res.* **2010**, *2*, 306.
[11] Sander, T.; Freyss, J.; Korff, M. v.; Reich, J. R.; Rufener, C. *J. Chem. Inf. Model.* **2009**, *49*, 232.
[12] Lipinski, C. A.; Lombardo, F.; Dominy, B.W.; Feeney, P. J. *Adv. Drug Deliv. Rev.* **1997**, *23*, 4.

Table 4. Drug likeness property of compounds (**6.1a-n**) by Lipinski's rule.

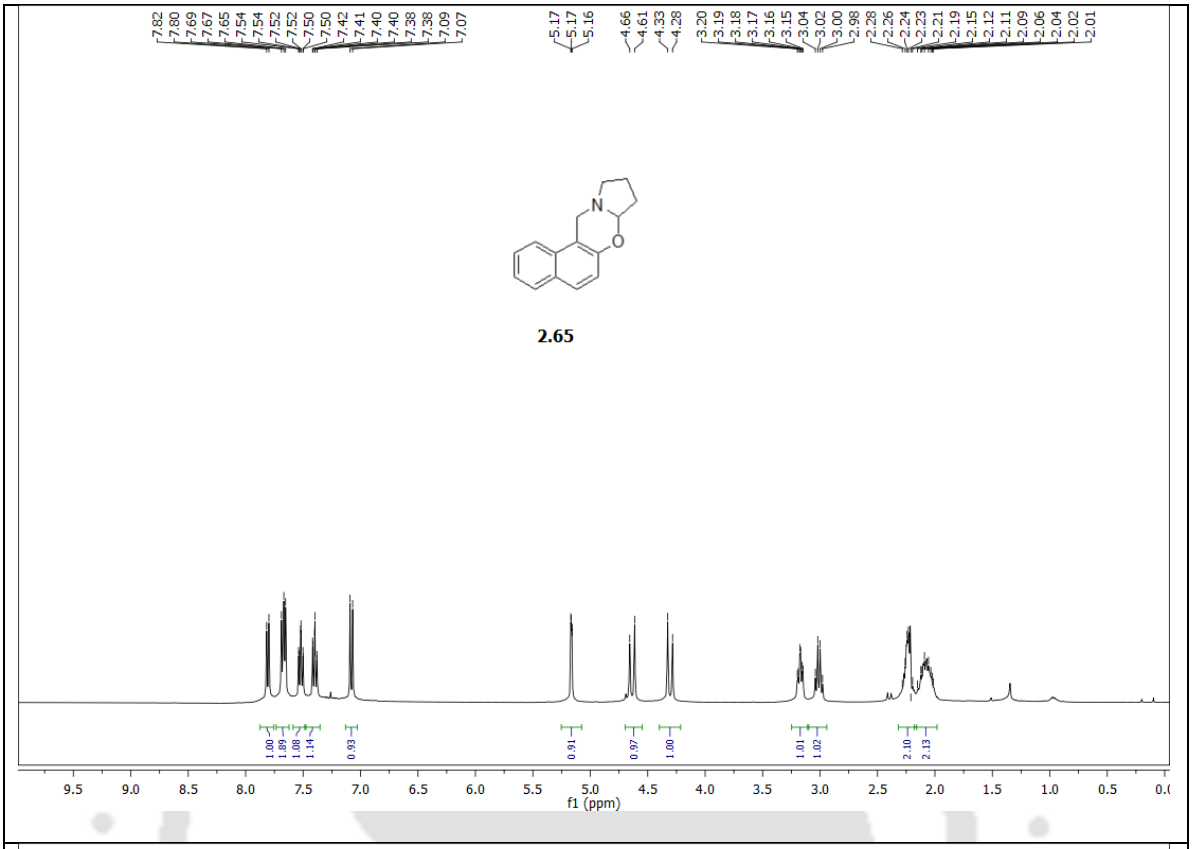
Compounds	Log P	Number of hydrogen bonds donors	Number of hydrogen bond acceptors	Molecular weight	Violation
6.1a	4.45	6	1	377.44	0
6.1b	4.65	3	2	319.40	0
6.1c	4.45	4	2	348.45	0
6.1d	5.02	2	1	303.40	1
6.1e	5.46	5	1	362.43	1
6.1f	4.51	3	1	332.45	0
6.1g	3.85	3	1	304.39	0
6.1h	4.40	6	1	364.40	0
6.1i	6.02	2	1	353.46	1
6.1j	3.86	2	1	253.34	0
6.1k	7.48	2	1	379.59	1
6.1l	3.16	6	2	342.39	0
6.1m	2.76	7	2	372.42	0
6.1n	5.70	2	1	303.49	1

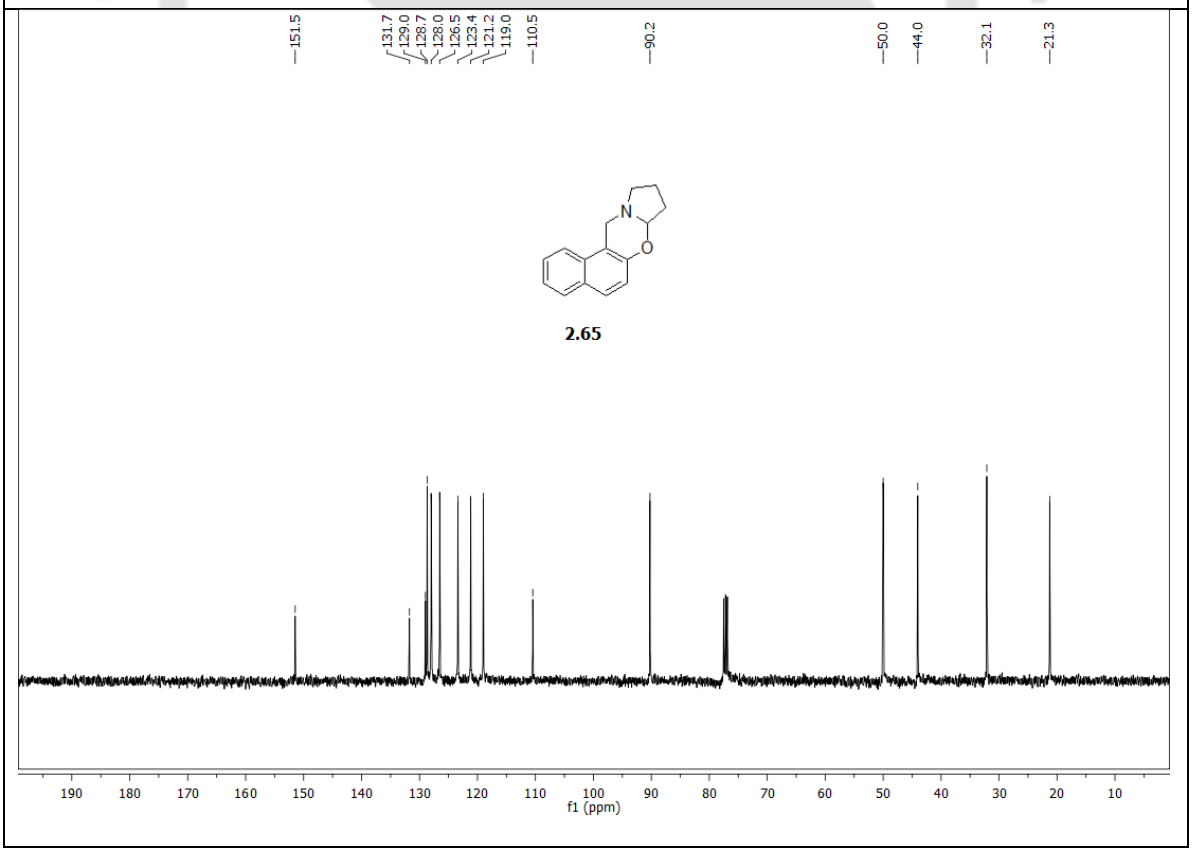
भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

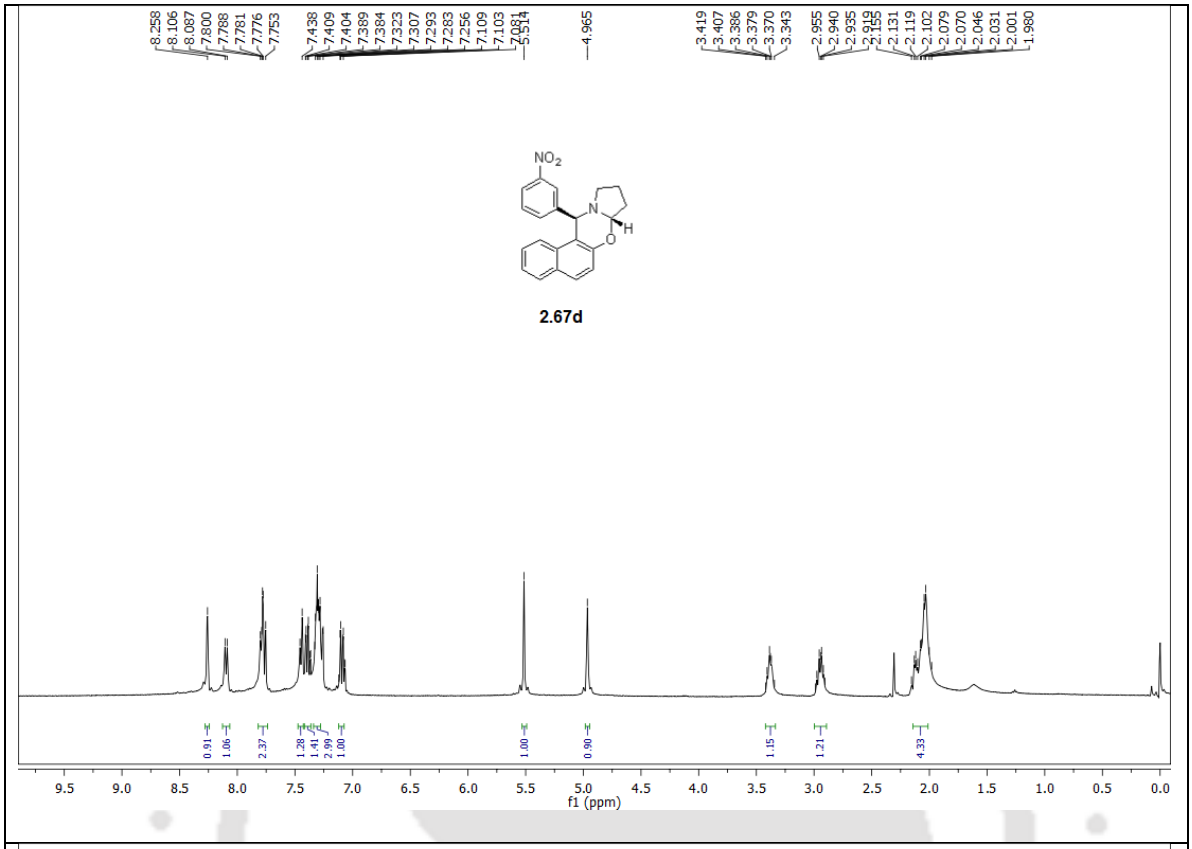
Chapter 8

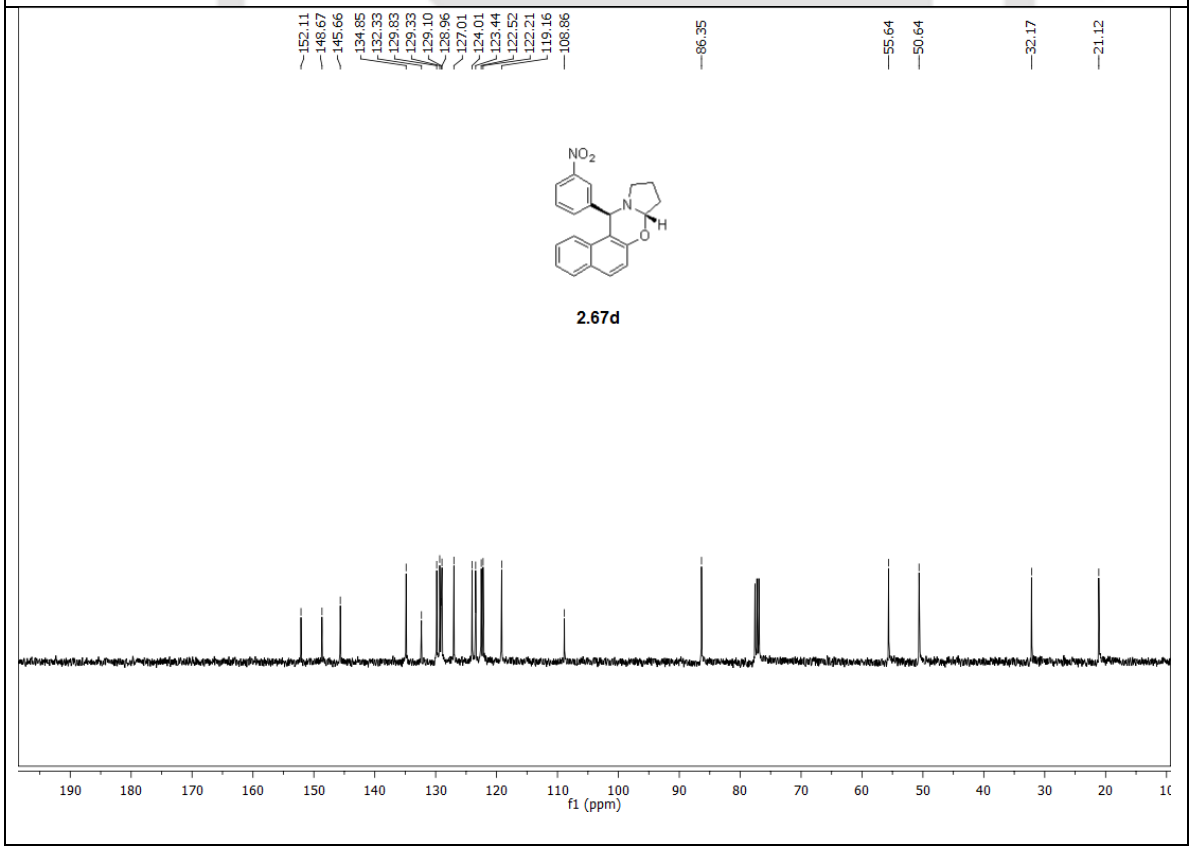
^{1}H and ^{13}C Spectra of New Compounds

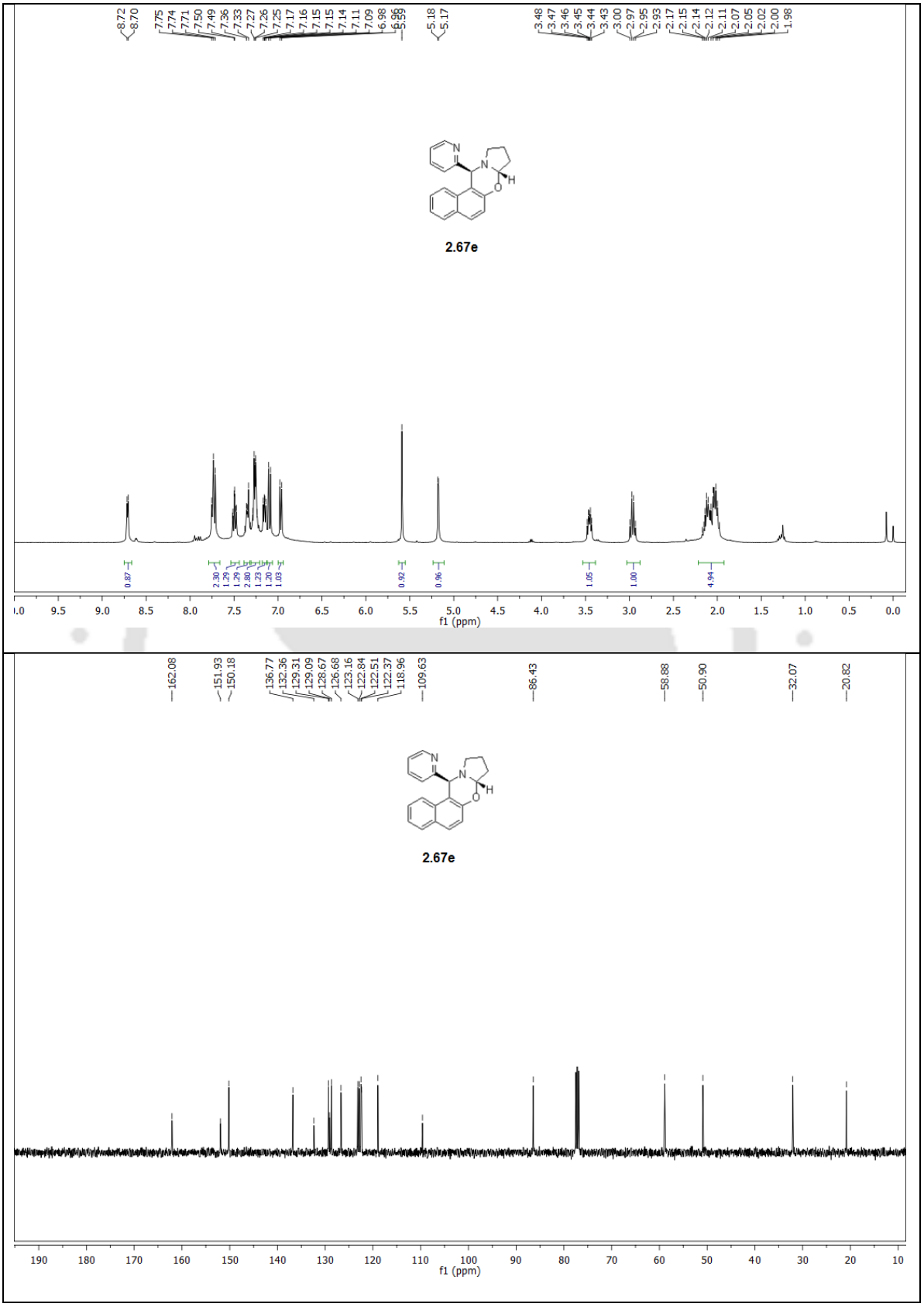
भारतीय प्रौद्योगिकी संस्थान गुवाहाटी
Indian Institute of Technology Guwahati

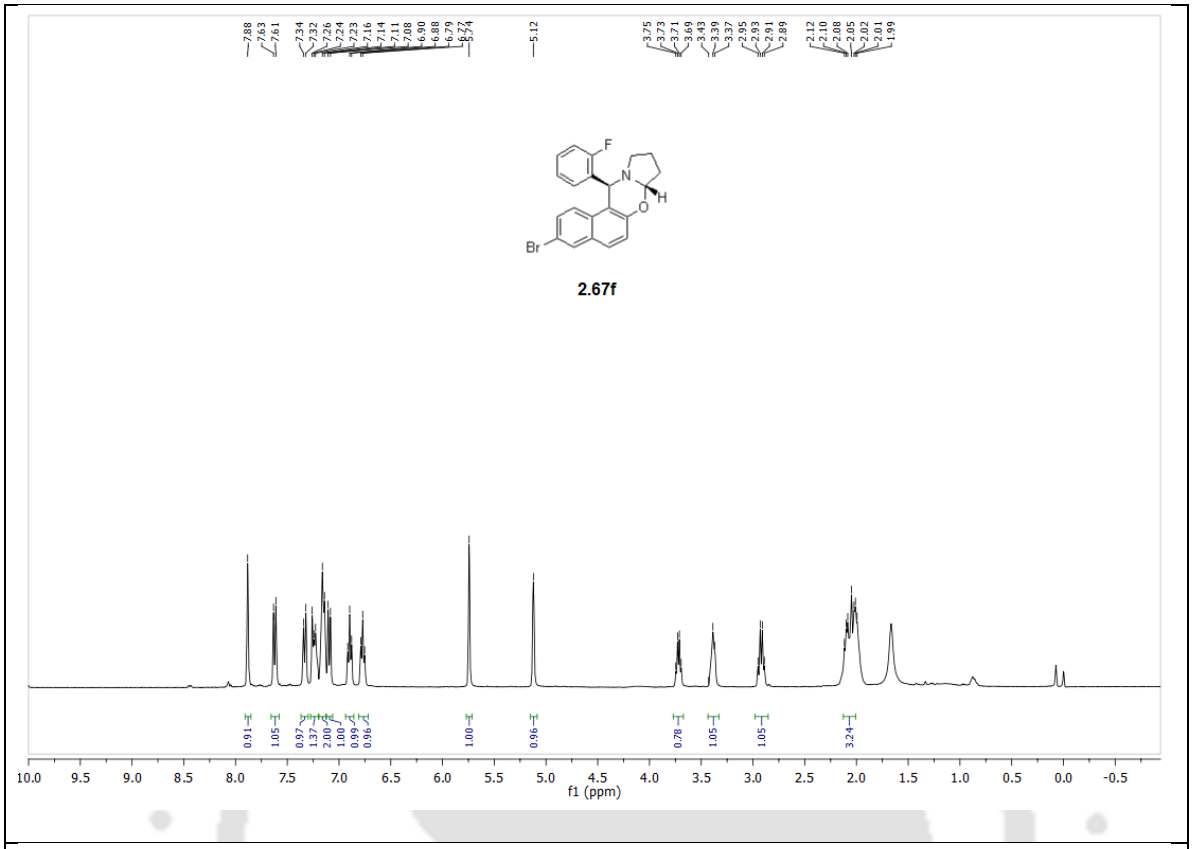

7.82
7.80
7.69
7.67
7.65
7.54
7.54
7.52
7.52
7.50
7.50
7.42
7.41
7.40
7.40
7.38
7.38
7.09
7.07
5.17
5.17
5.16
4.66
4.61
4.33
4.28
3.20
3.19
3.18
3.17
3.16
3.15
3.04
3.02
3.00
2.98
2.28
2.26
2.24
2.23
2.21
2.19
2.15
2.12
2.11
2.09
2.06
2.04
2.02
2.01
N
O
2.65
1.00
1.89
1.08
1.14
0.93
0.91
0.97
1.00
1.01
1.02
2.10
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

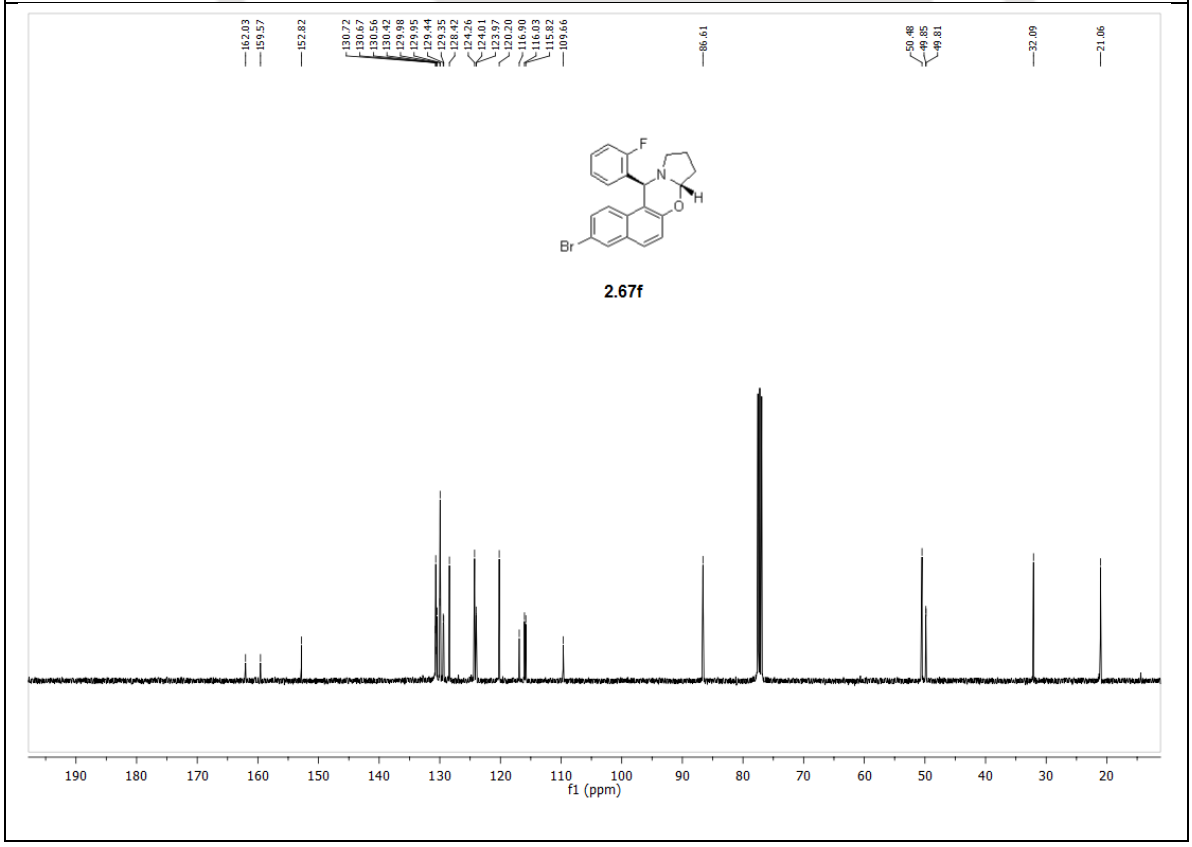

151.5
131.7
129.0
128.7
128.0
126.5
123.4
121.2
119.0
110.5
90.2
50.0
44.0
32.1
21.3
N
O
2.65
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

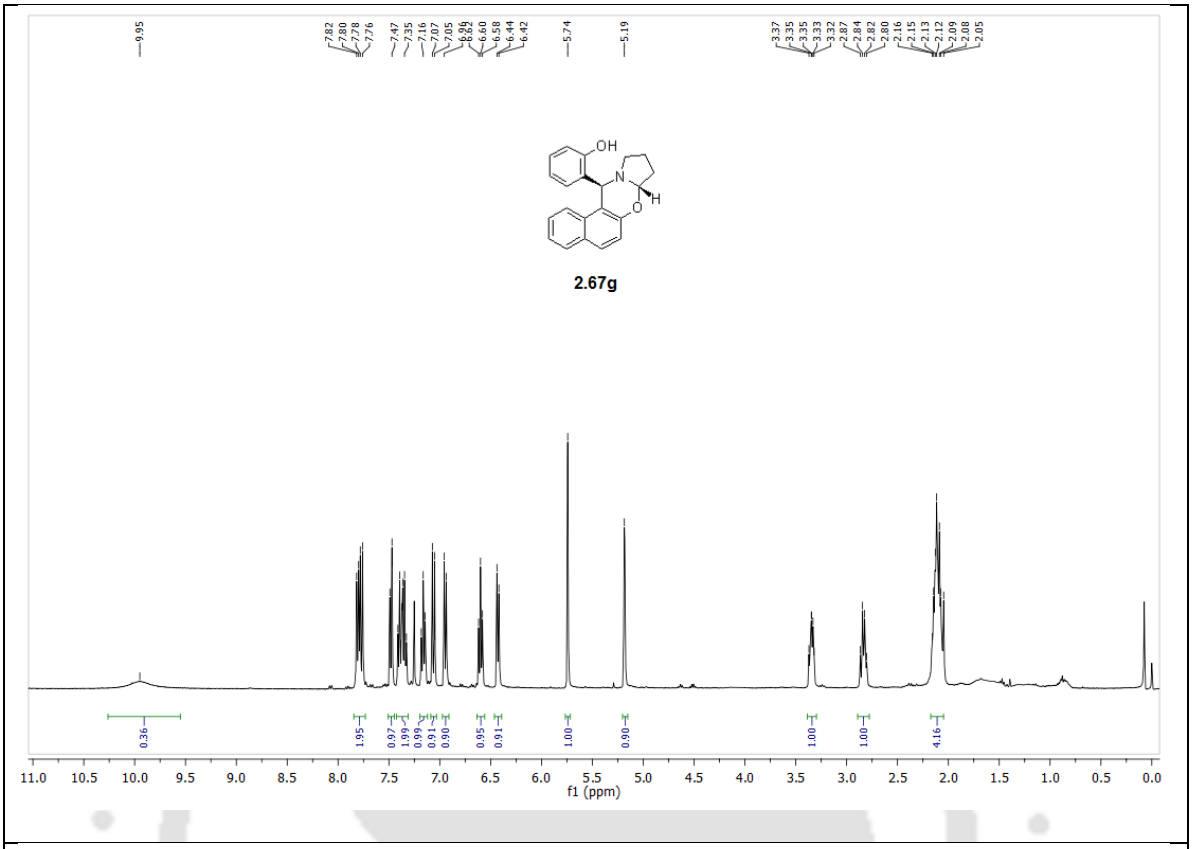

8.258
8.106
8.087
7.800
7.788
7.781
7.776
7.753
7.438
7.409
7.404
7.389
7.384
7.323
7.307
7.293
7.283
7.256
7.109
7.103
7.081
5.514
4.965
3.419
3.407
3.386
3.379
3.370
3.343
2.955
2.940
2.935
2.919
2.155
2.131
2.119
2.102
2.079
2.070
2.046
2.031
2.001
1.980
NO2
N
O
H
2.67d
0.91
1.06
2.37
1.28
1.41
2.99
1.00
1.00
0.90
1.15
1.21
4.33
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)

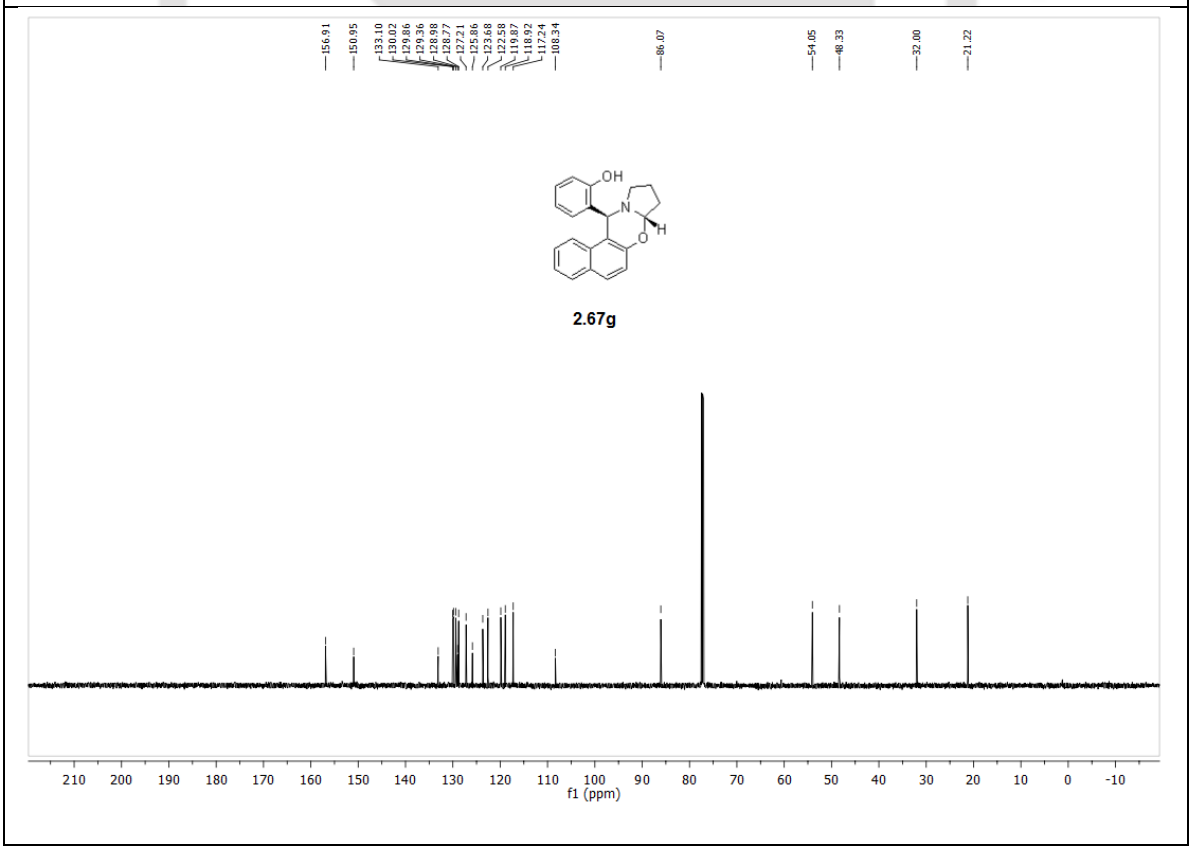

152.11
148.67
145.66
134.85
132.33
129.83
129.33
129.10
128.96
127.01
124.01
123.44
122.52
122.21
119.16
108.86
86.35
55.64
50.64
32.17
21.12
NO2
N
O
H
2.67d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

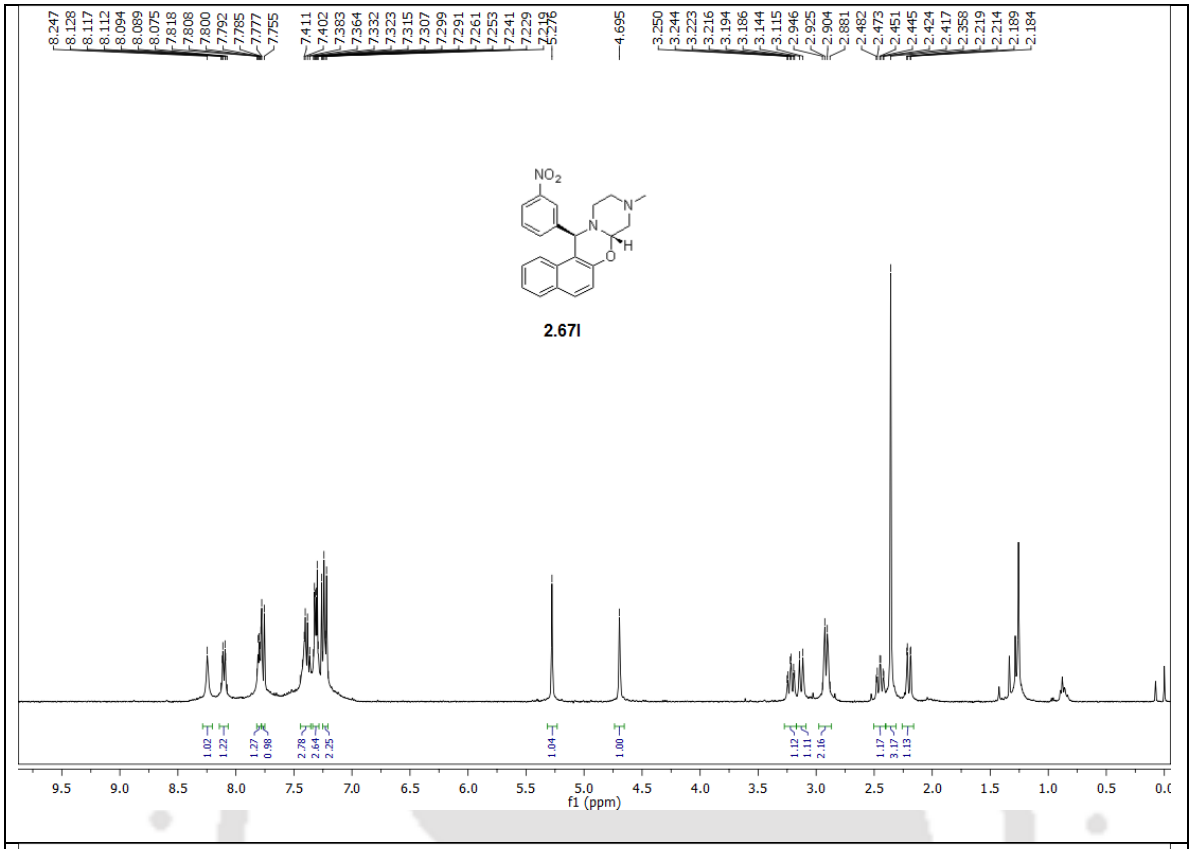

8.72
8.70
7.75
7.74
7.71
7.50
7.49
7.36
7.33
7.27
7.26
7.25
7.17
7.16
7.15
7.15
7.14
7.11
7.09
6.98
6.96
6.95
5.18
5.17
3.48
3.47
3.46
3.45
3.44
3.43
3.00
2.97
2.95
2.93
2.17
2.15
2.14
2.12
2.11
2.07
2.05
2.02
2.00
1.98
2.67e
0.87
2.30
1.29
1.29
2.80
1.23
1.20
1.03
0.92
0.96
1.05
1.00
4.94
f1 (ppm)
162.08
151.93
150.18
136.77
132.36
129.31
129.09
128.67
126.68
123.16
122.84
122.51
122.37
118.96
109.63
86.43
58.88
50.90
32.07
20.82
2.67e
f1 (ppm)

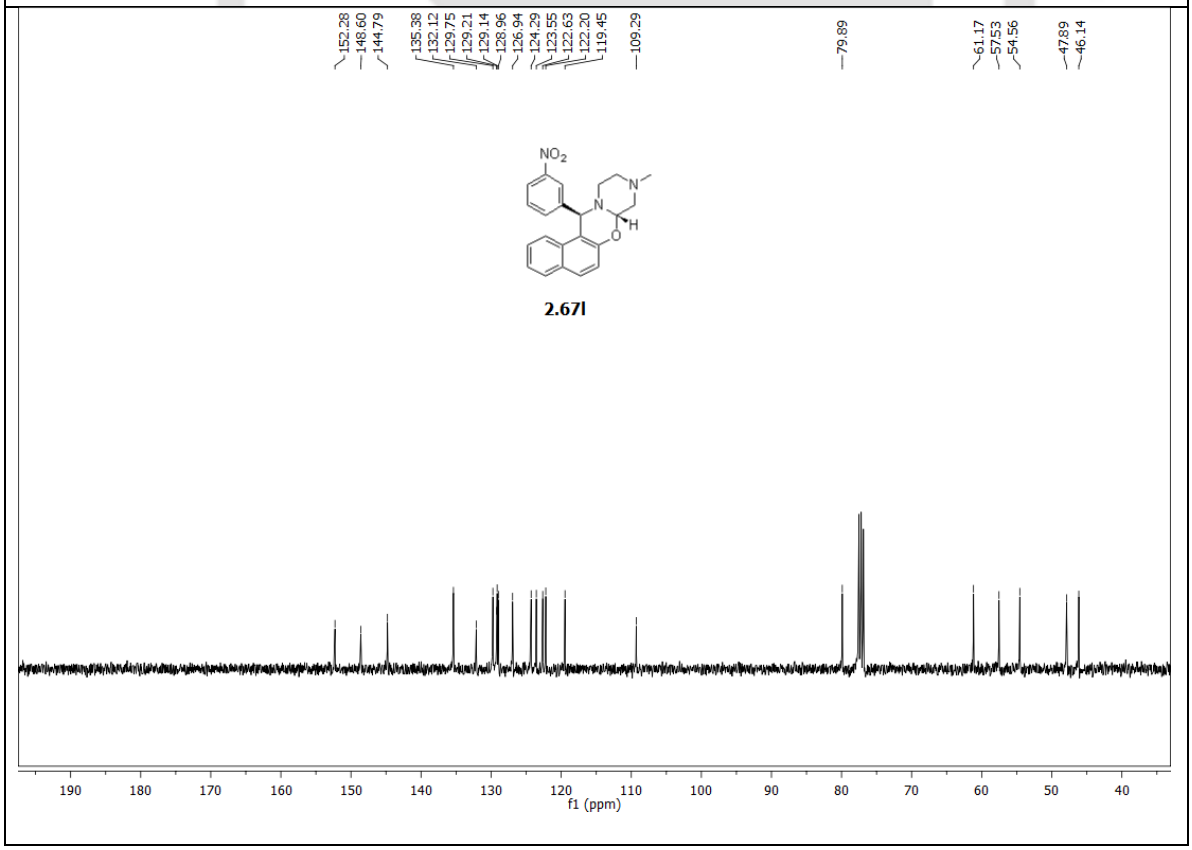

7.88
7.63
7.61
7.34
7.32
7.26
7.24
7.23
7.16
7.14
7.11
7.08
6.90
6.88
6.79
6.77
6.74
5.12
3.75
3.73
3.71
3.69
3.43
3.39
3.37
2.95
2.93
2.91
2.89
2.12
2.10
2.08
2.05
2.02
2.01
1.99
F
N
H
O
Br
2.67f
0.91
1.05
0.97
1.37
2.00
1.00
0.99
0.96
1.00
0.96
0.78
1.05
1.05
3.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 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)

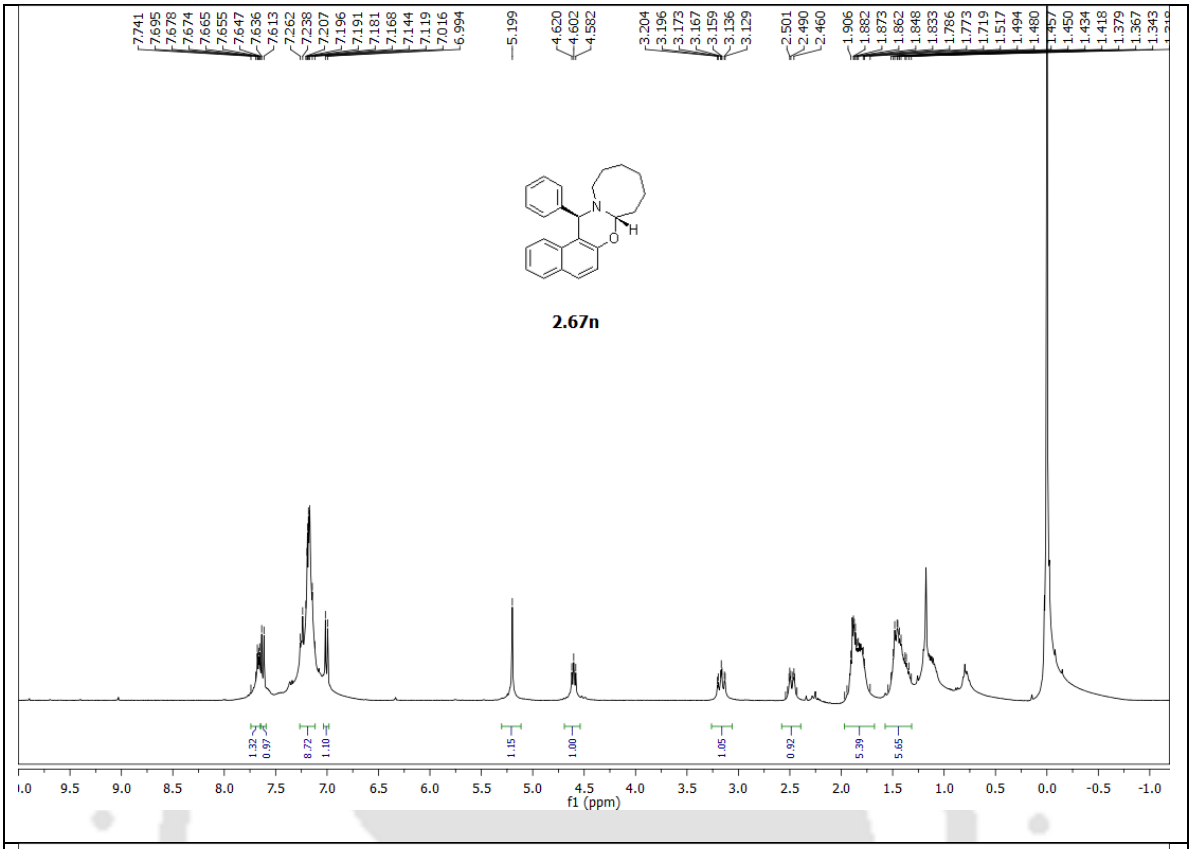

162.03
159.57
152.82
130.72
130.67
130.56
130.42
129.98
129.95
129.44
129.35
128.42
124.26
124.01
123.97
120.20
116.90
116.03
115.82
109.66
86.61
50.48
49.85
49.81
32.09
21.06
F
N
H
O
Br
2.67f
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
f1 (ppm)

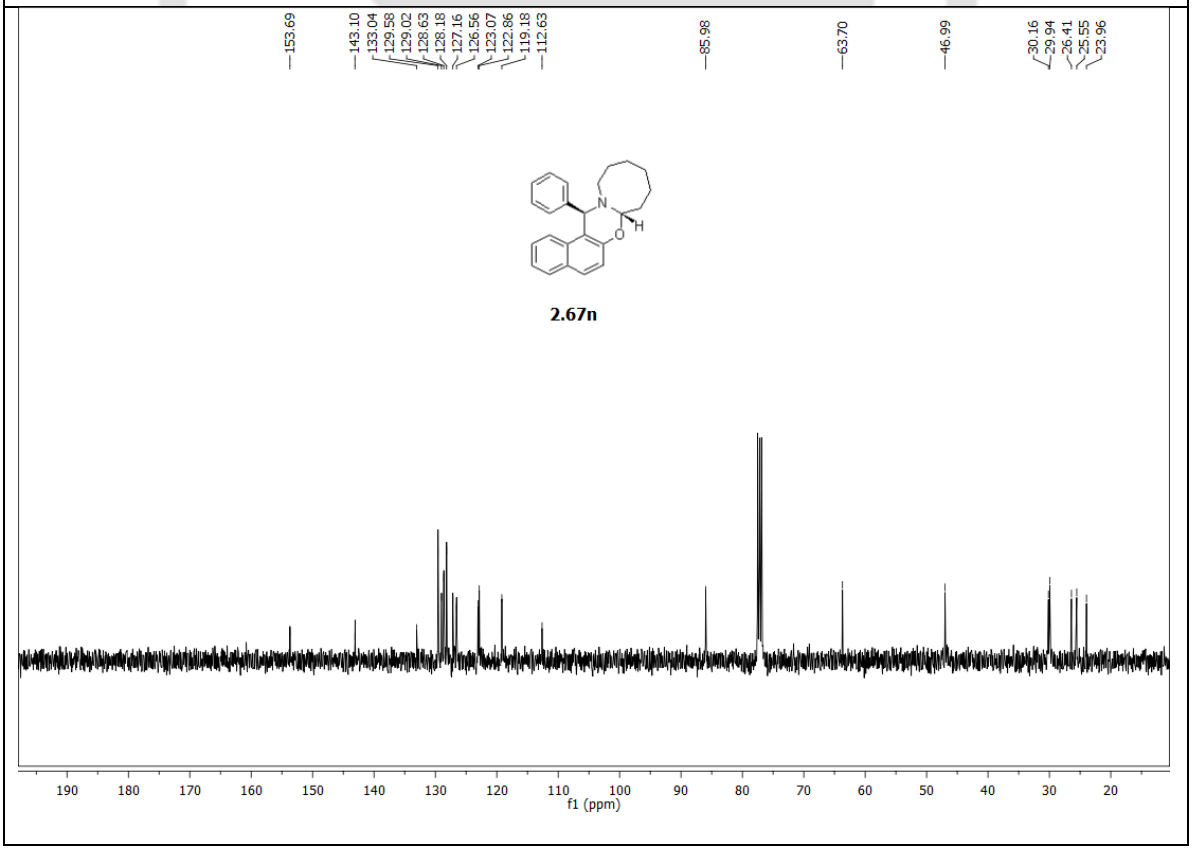

9.95
7.82
7.80
7.78
7.76
7.47
7.35
7.16
7.07
7.05
6.60
6.58
6.44
6.42
5.74
5.19
3.37
3.35
3.35
3.33
3.32
2.87
2.84
2.82
2.80
2.16
2.15
2.13
2.12
2.09
2.08
2.05
OH
N
O
H
2.67g
0.36
1.95
0.97
1.99
0.99
0.91
0.90
0.95
0.91
1.00
0.90
1.00
1.00
4.16
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

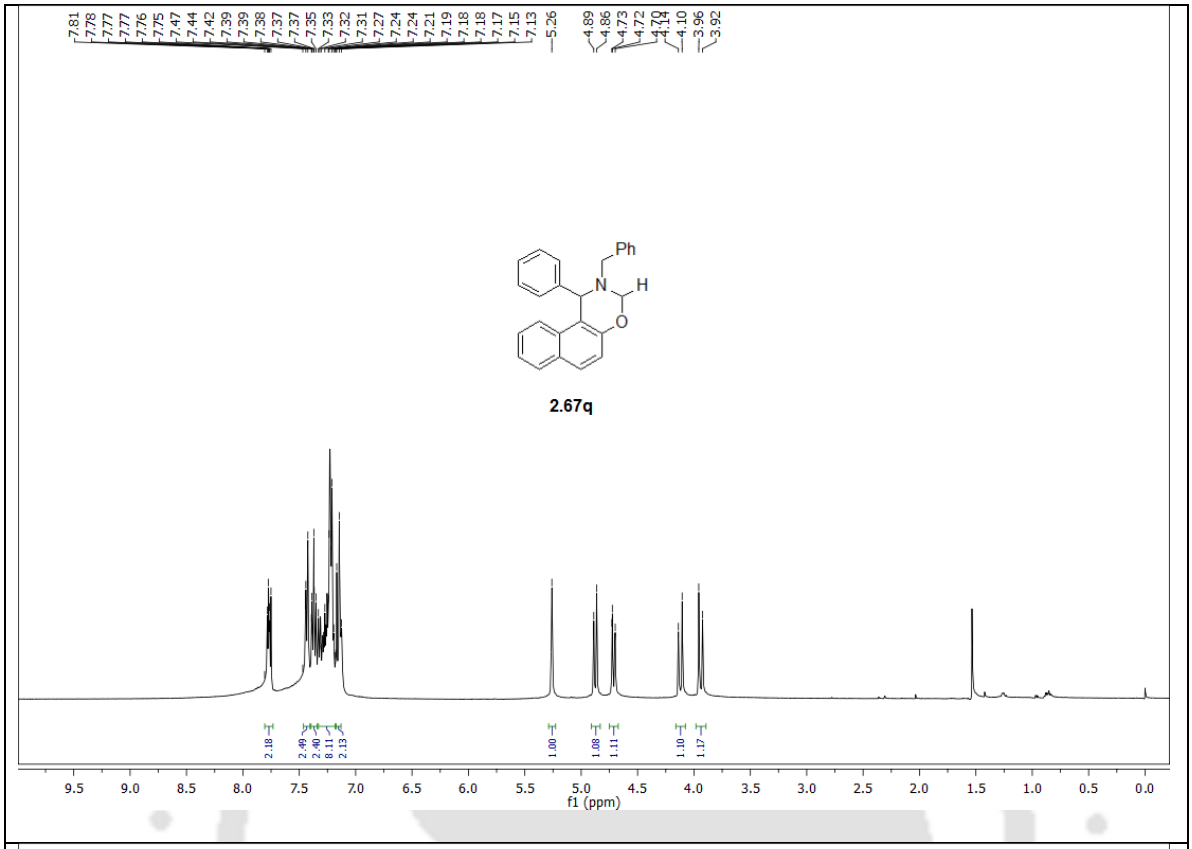

156.91
150.95
133.10
130.02
129.86
129.36
128.98
128.77
127.21
125.86
123.68
122.58
119.87
118.92
117.24
108.34
86.07
54.05
48.33
32.00
21.22
OH
N
O
H
2.67g
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

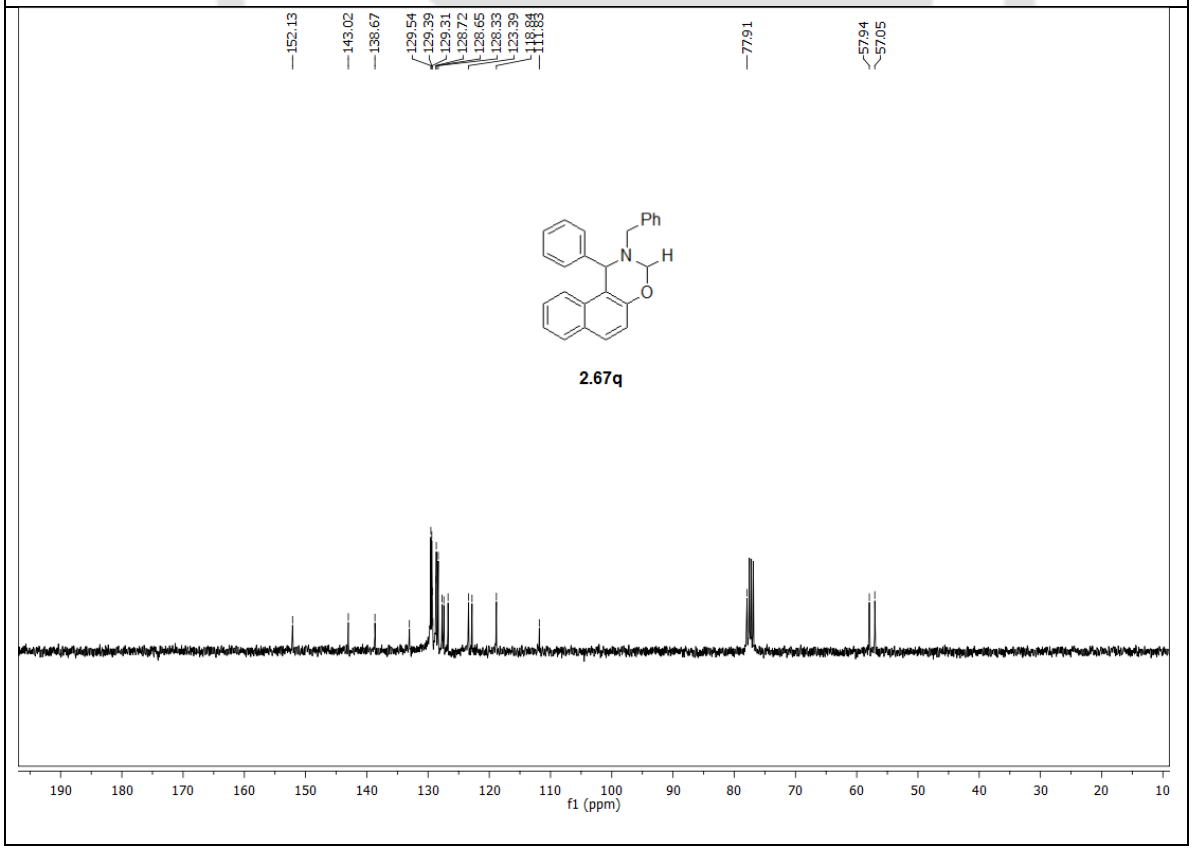

8.247
8.128
8.117
8.112
8.094
8.089
8.075
7.818
7.808
7.800
7.792
7.785
7.777
7.755
7.411
7.402
7.383
7.364
7.332
7.323
7.315
7.307
7.299
7.291
7.261
7.253
7.241
7.229
7.219
5.276
4.695
3.250
3.244
3.223
3.216
3.194
3.186
3.144
3.115
2.946
2.925
2.904
2.881
2.482
2.473
2.451
2.445
2.424
2.417
2.358
2.219
2.214
2.189
2.184
NO2
N
N
H
O
2.67l
1.02
1.22
1.27
0.98
2.78
2.64
2.25
1.04
1.00
1.12
1.11
2.16
1.17
3.17
1.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

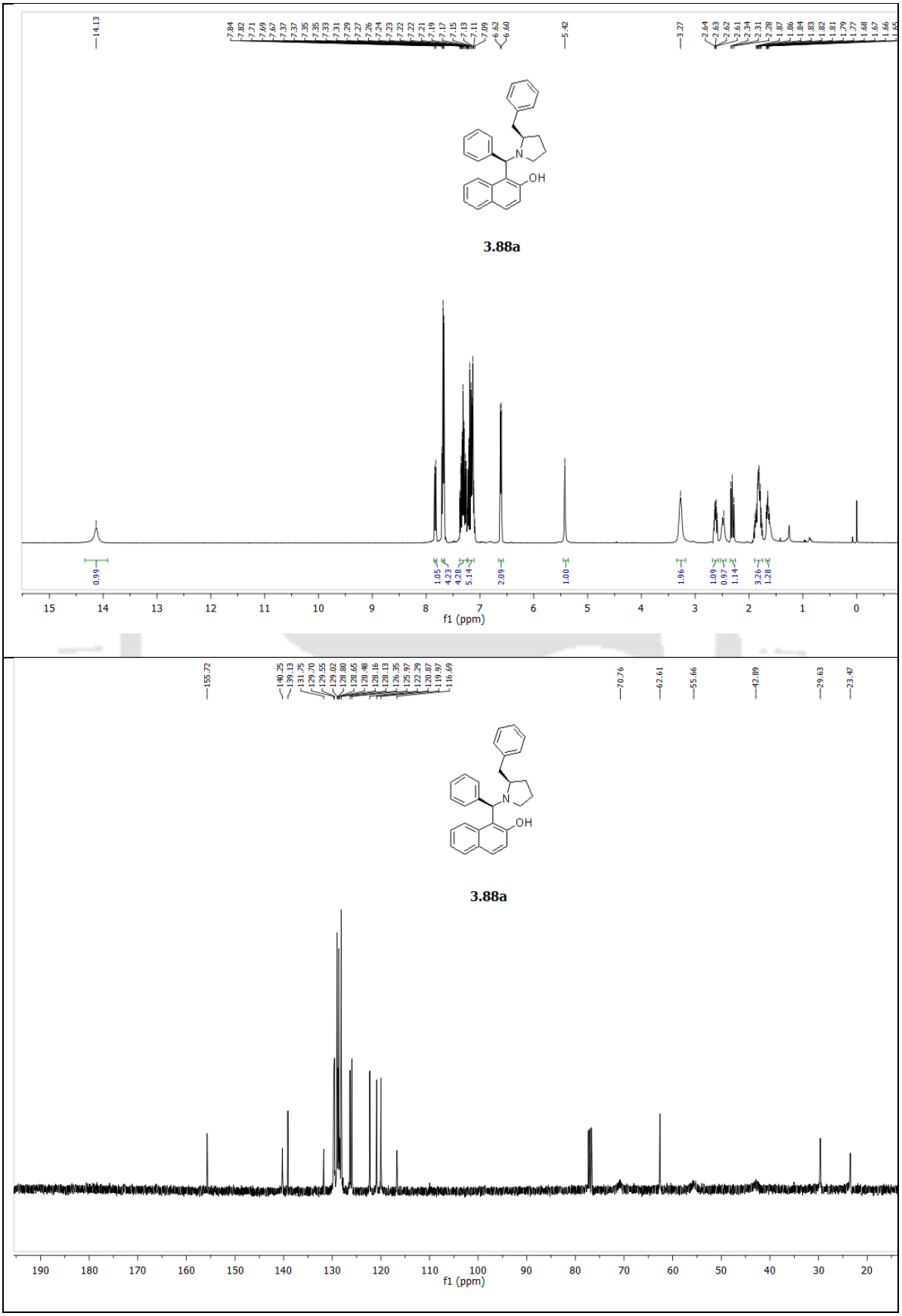

152.28
148.60
144.79
135.38
132.12
129.75
129.21
129.14
128.96
126.94
124.29
123.55
122.63
122.20
119.45
109.29
79.89
61.17
57.53
54.56
47.89
46.14
NO2
N
N
H
O
2.67l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)

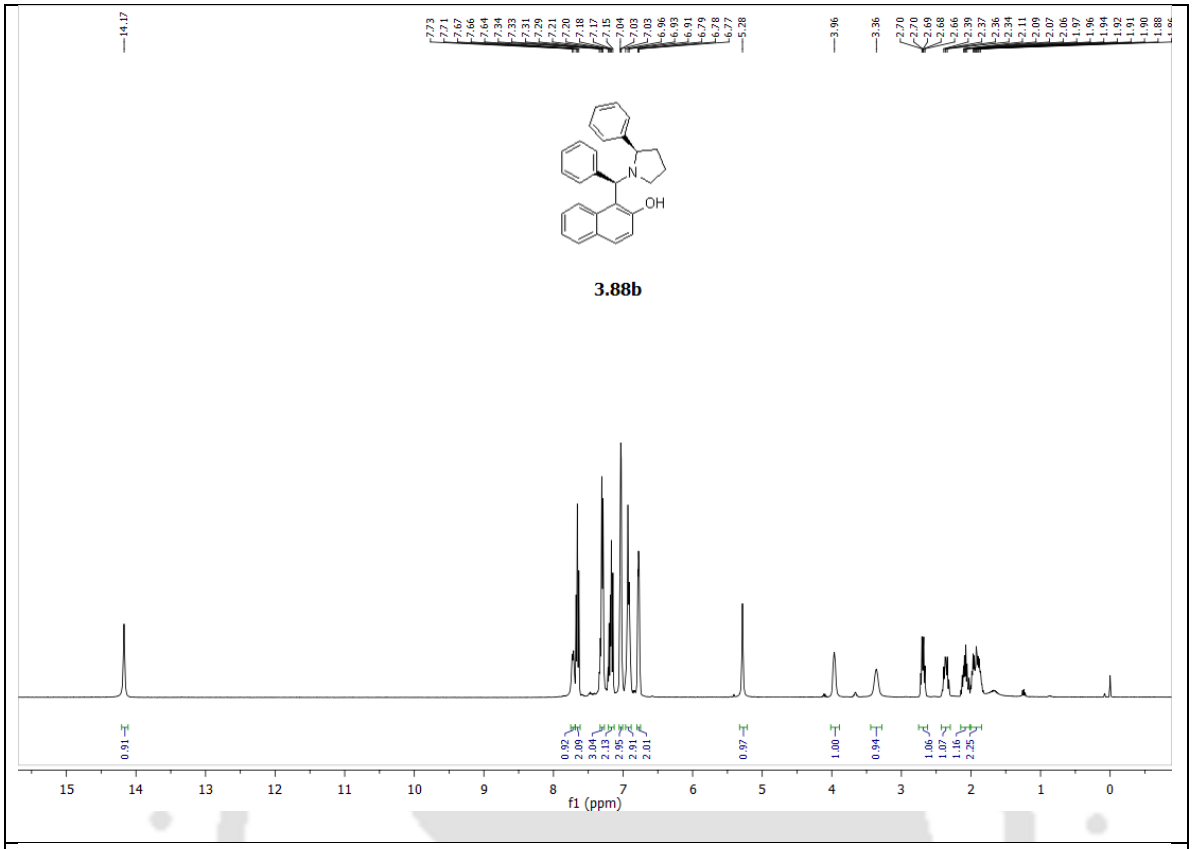

7.741
7.695
7.678
7.674
7.665
7.655
7.647
7.636
7.613
7.262
7.238
7.207
7.196
7.191
7.181
7.168
7.144
7.119
7.016
6.994
5.199
4.620
4.602
4.582
3.204
3.196
3.173
3.167
3.159
3.136
3.129
2.501
2.490
2.460
1.906
1.882
1.873
1.862
1.848
1.833
1.786
1.773
1.719
1.517
1.494
1.480
1.457
1.450
1.434
1.418
1.379
1.367
1.343
1.32
0.97
8.72
1.10
1.15
1.00
1.05
0.92
5.39
5.65
f1 (ppm)
2.67n


153.69
143.10
133.04
129.58
129.02
128.63
128.18
127.16
126.56
123.07
122.86
119.18
112.63
85.98
63.70
46.99
30.16
29.94
26.41
25.55
23.96
f1 (ppm)
2.67n

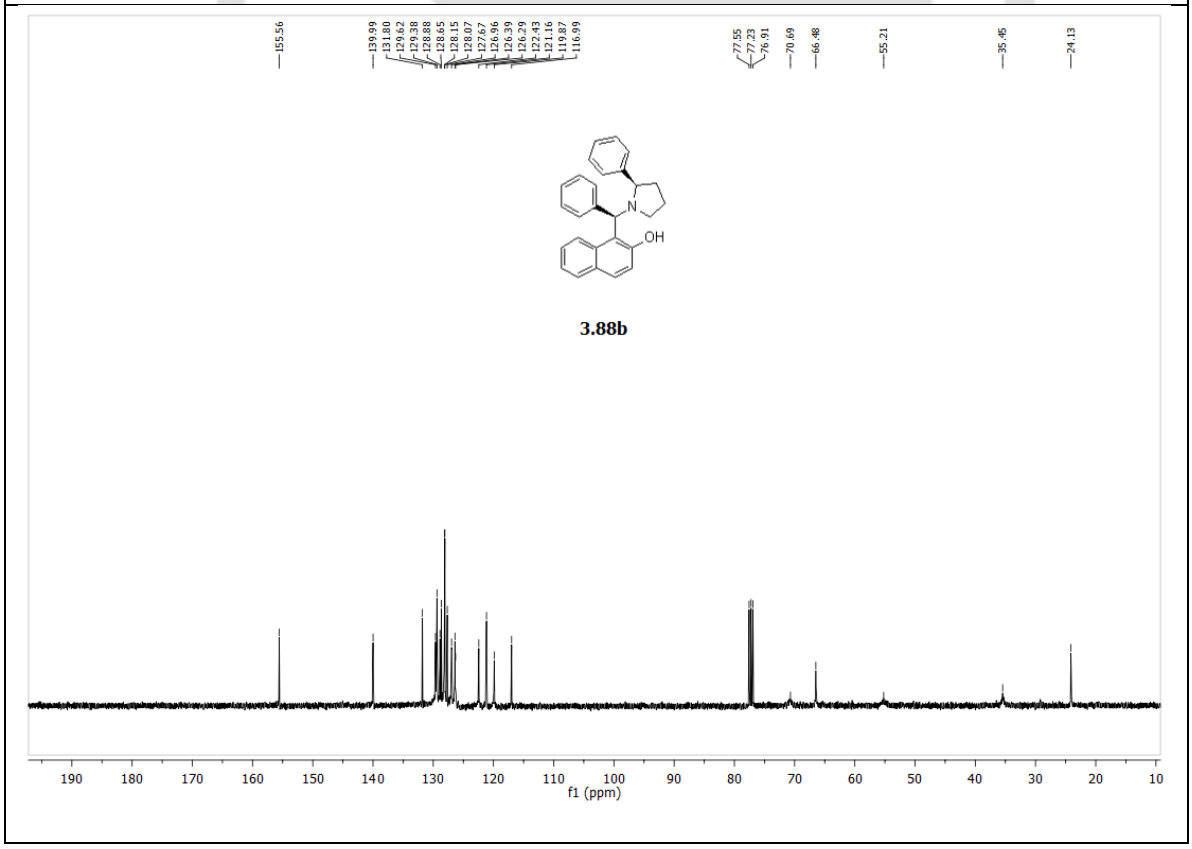

7.81
7.78
7.77
7.77
7.76
7.75
7.47
7.44
7.42
7.39
7.39
7.38
7.37
7.37
7.35
7.33
7.32
7.31
7.27
7.24
7.24
7.21
7.19
7.18
7.18
7.17
7.15
7.13
5.26
4.89
4.86
4.73
4.72
4.70
4.10
3.96
3.92
Ph
N
H
O
2.67q
2.18
2.49
2.40
8.11
2.13
1.00
1.08
1.11
1.10
1.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


152.13
143.02
138.67
129.54
129.39
129.31
128.72
128.65
128.33
123.39
118.84
111.83
77.91
57.94
57.05
Ph
N
H
O
2.67q
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

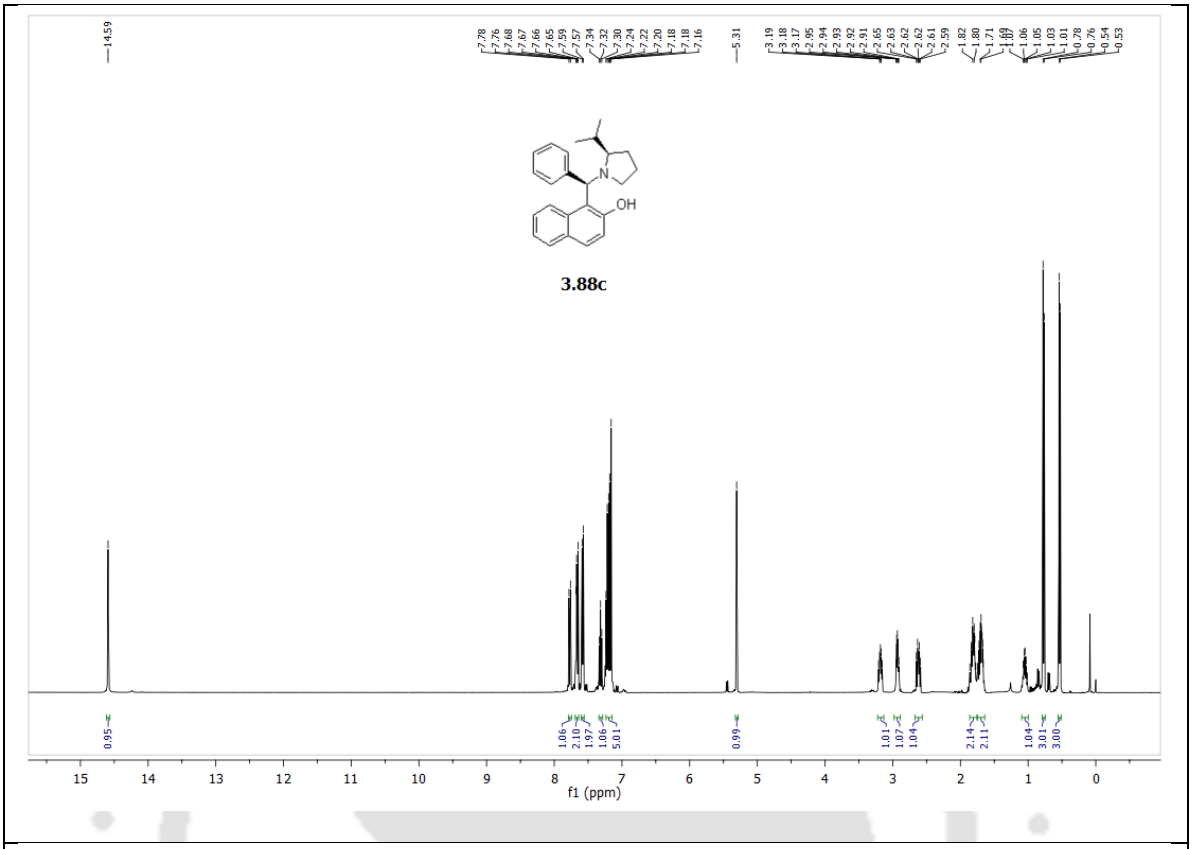

3.88a
f1 (ppm)
3.88a
f1 (ppm)

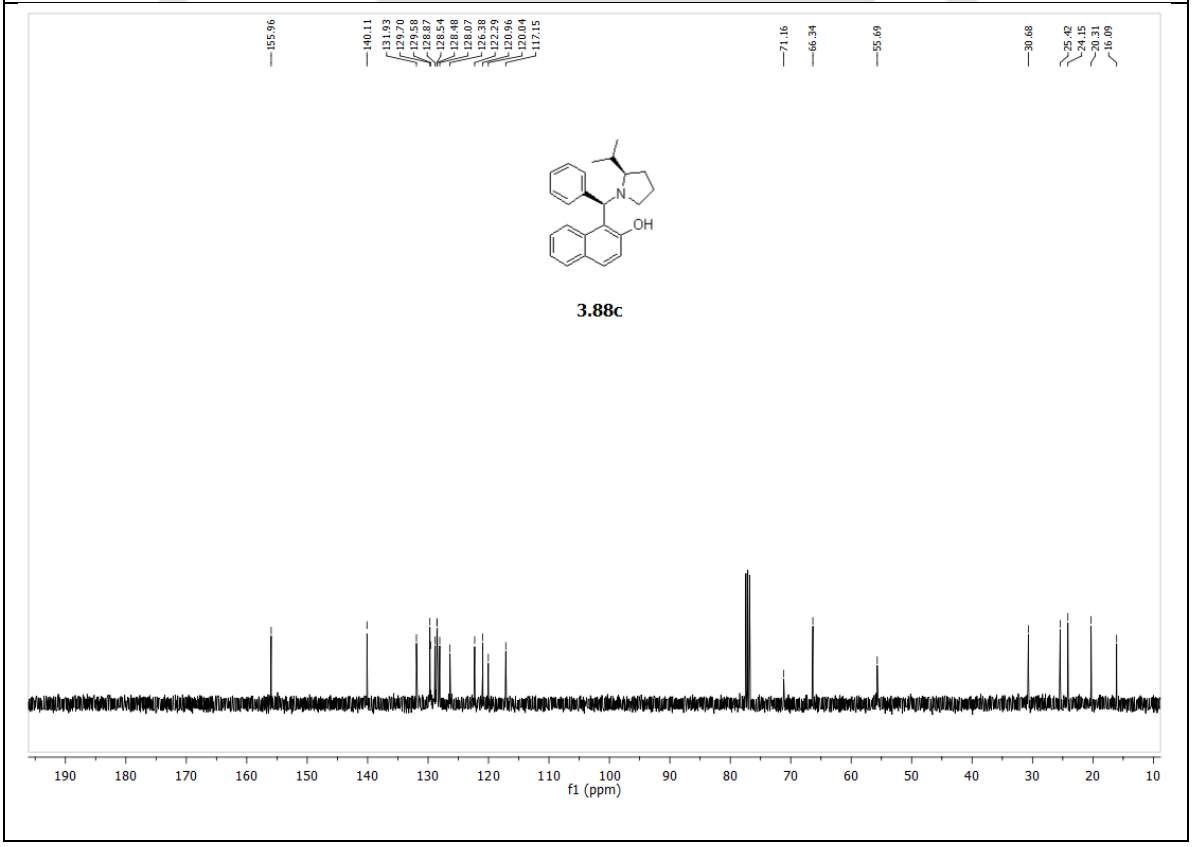

14.17
7.73
7.71
7.67
7.66
7.64
7.34
7.33
7.31
7.29
7.21
7.20
7.18
7.17
7.15
7.04
7.03
7.03
6.96
6.93
6.91
6.79
6.78
6.77
5.28
3.96
3.36
2.70
2.70
2.69
2.68
2.66
2.39
2.37
2.36
2.34
2.11
2.09
2.07
2.06
1.97
1.96
1.94
1.92
1.91
1.90
1.88
N
OH
0.91
0.92
2.09
3.04
2.13
2.95
2.91
2.01
0.97
1.00
0.94
1.06
1.07
1.16
2.25
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

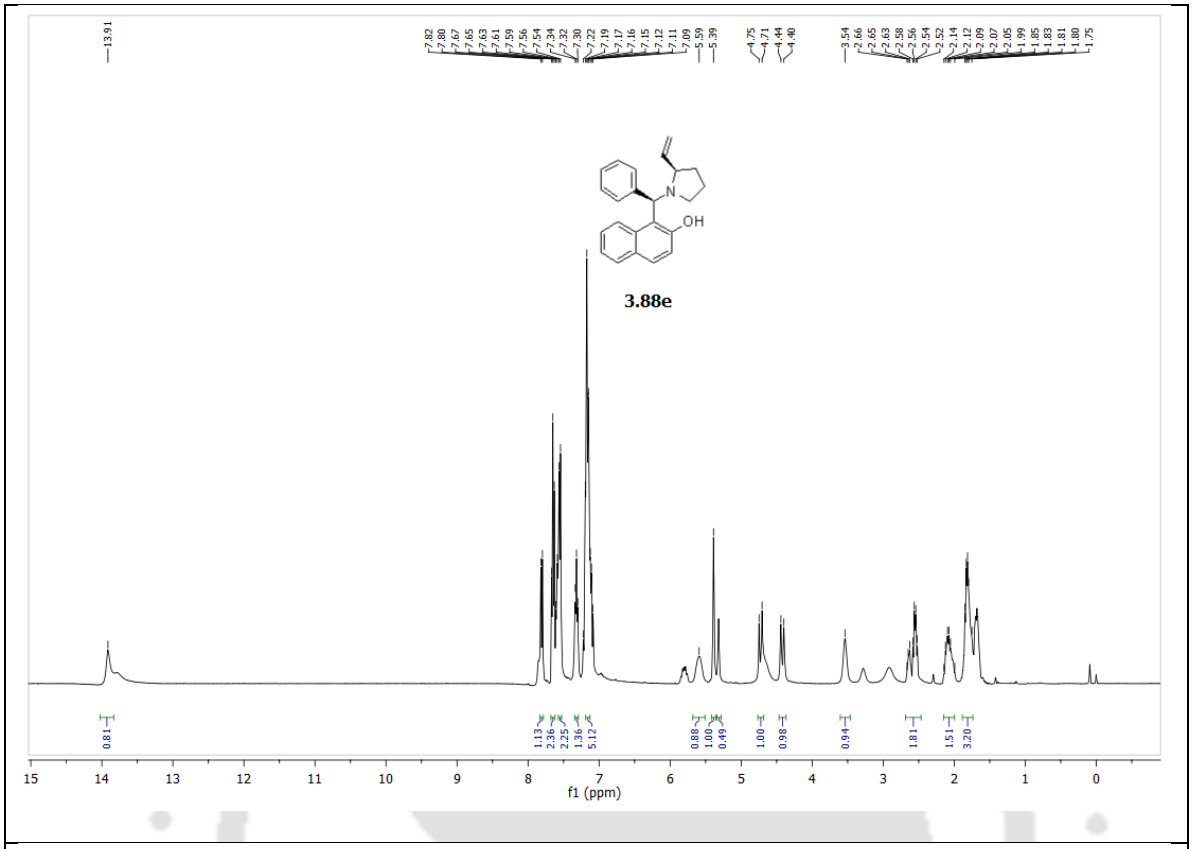
3.88b

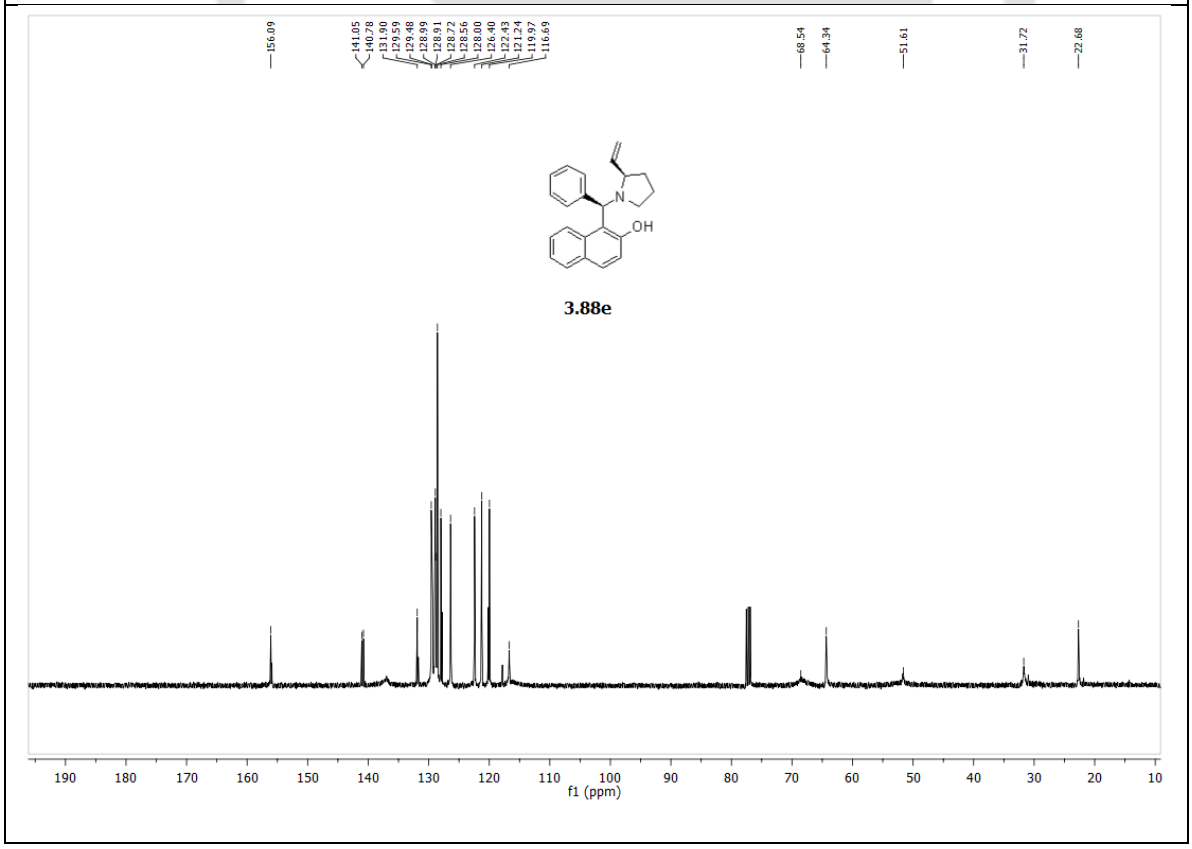

155.56
139.99
131.80
129.62
129.38
128.88
128.65
128.15
128.07
127.67
126.96
126.39
126.29
122.43
121.16
119.87
116.99
77.55
77.23
76.91
70.69
66.48
55.21
35.45
24.13
N
OH
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

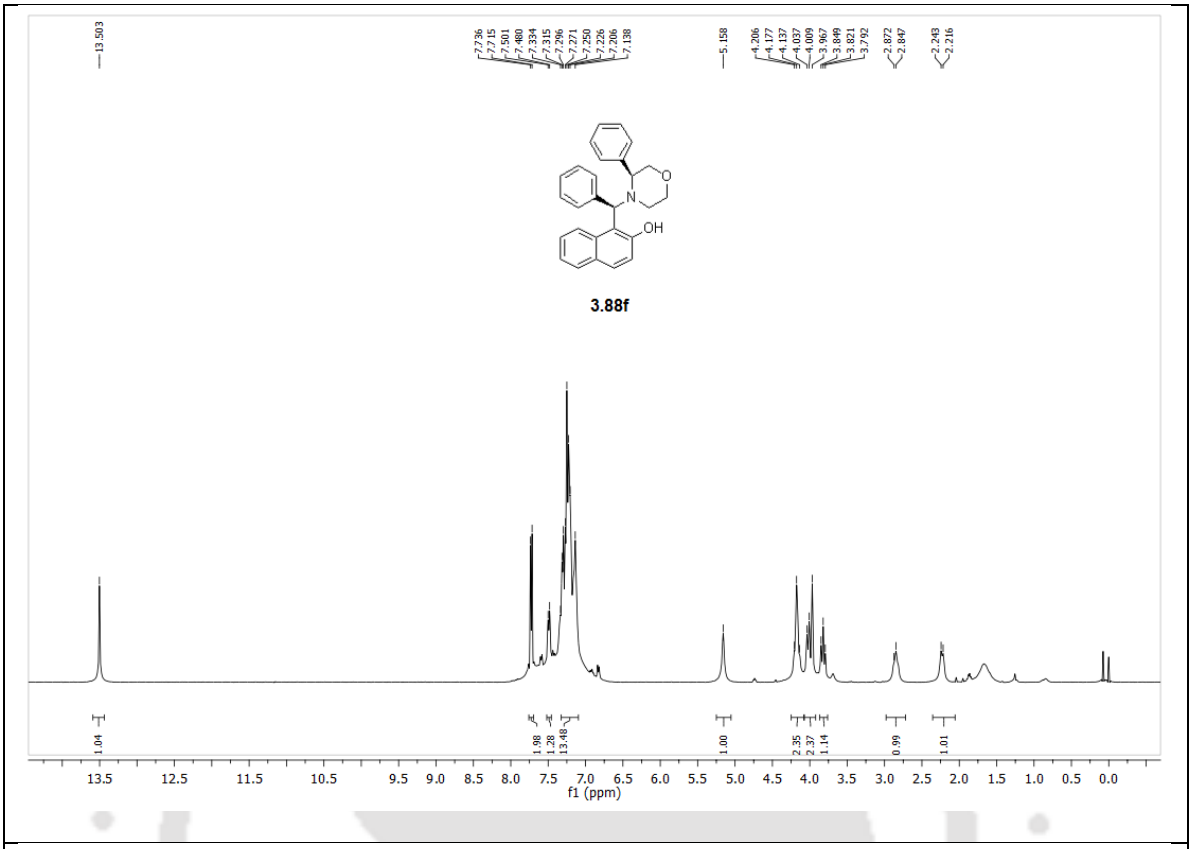
3.88b

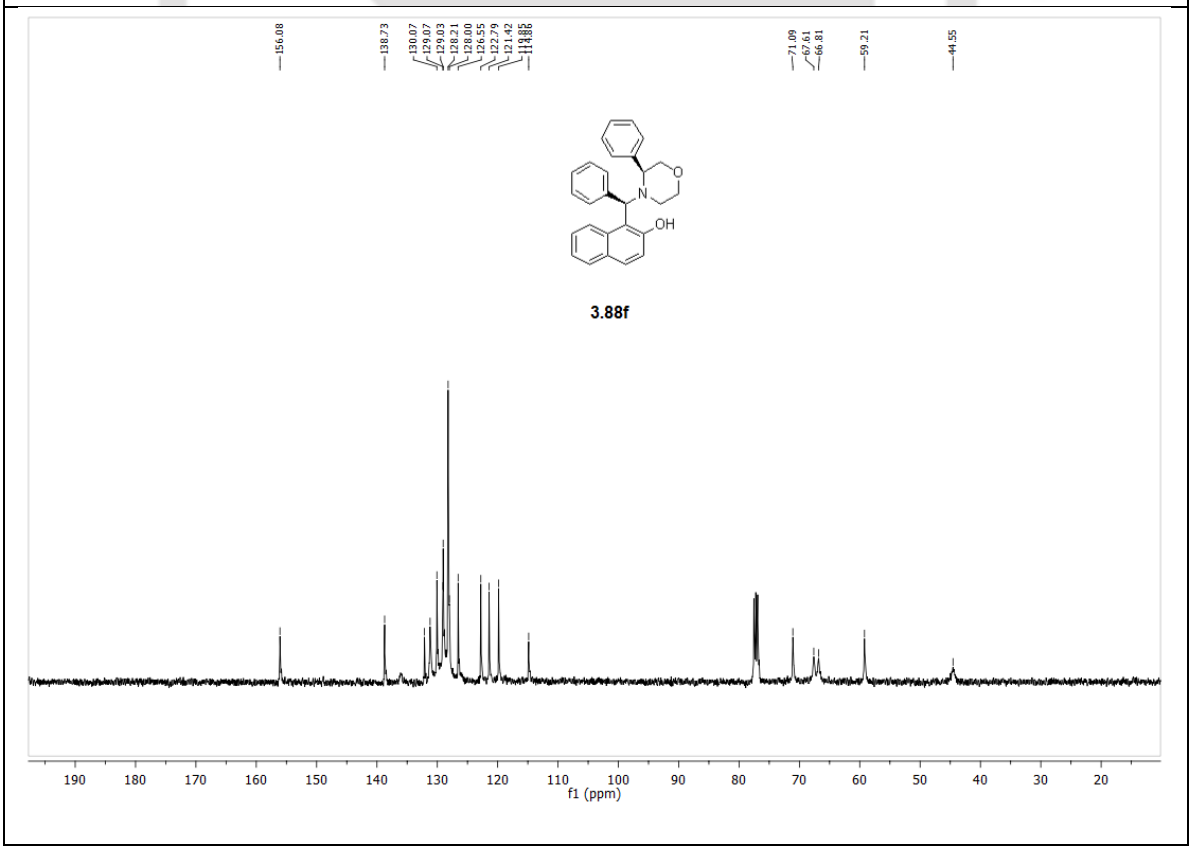

14.59
7.78
7.76
7.68
7.67
7.66
7.65
7.59
7.57
7.34
7.32
7.30
7.24
7.22
7.20
7.18
7.18
7.16
5.31
3.19
3.18
3.17
2.95
2.94
2.93
2.92
2.91
2.65
2.63
2.62
2.62
2.61
2.59
1.82
1.80
1.71
1.69
1.69
1.06
1.05
1.03
1.01
0.78
0.76
0.54
0.53
N
OH
3.88c
0.95
1.06
2.10
1.97
1.06
5.01
0.99
1.01
1.07
1.04
2.14
2.11
1.04
3.01
3.00
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

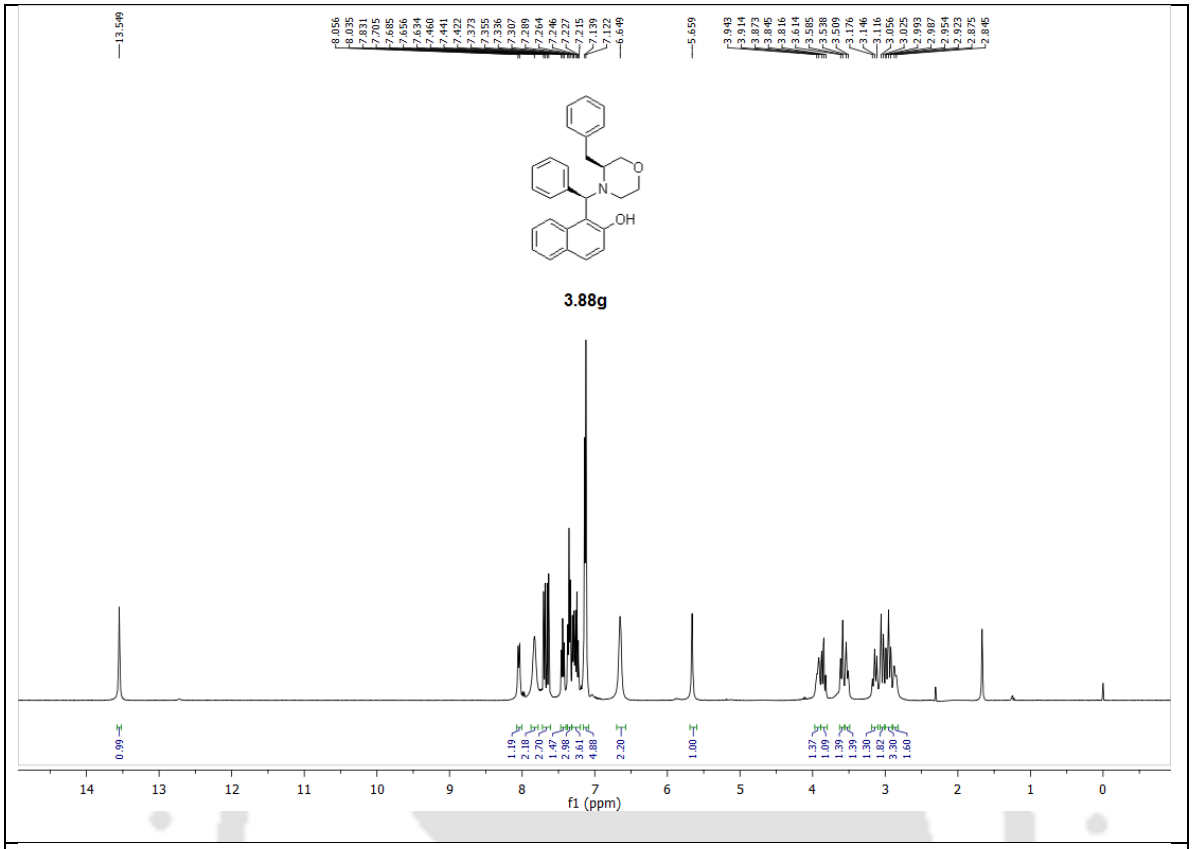

155.96
140.11
131.93
129.70
129.58
128.87
128.54
128.48
128.07
126.38
122.29
120.96
120.04
117.15
71.16
66.34
55.69
30.68
25.42
24.15
20.31
16.09
N
OH
3.88c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

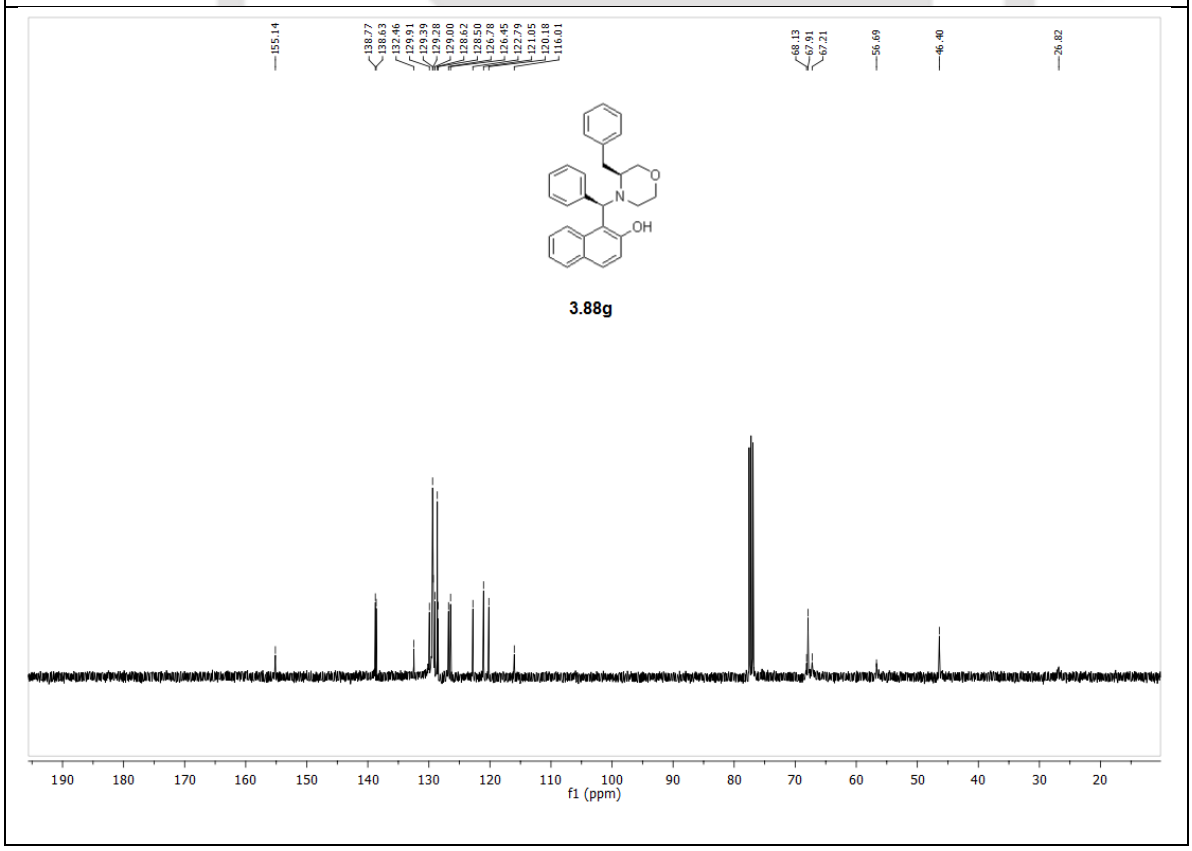

OH
3.88e
f1 (ppm)

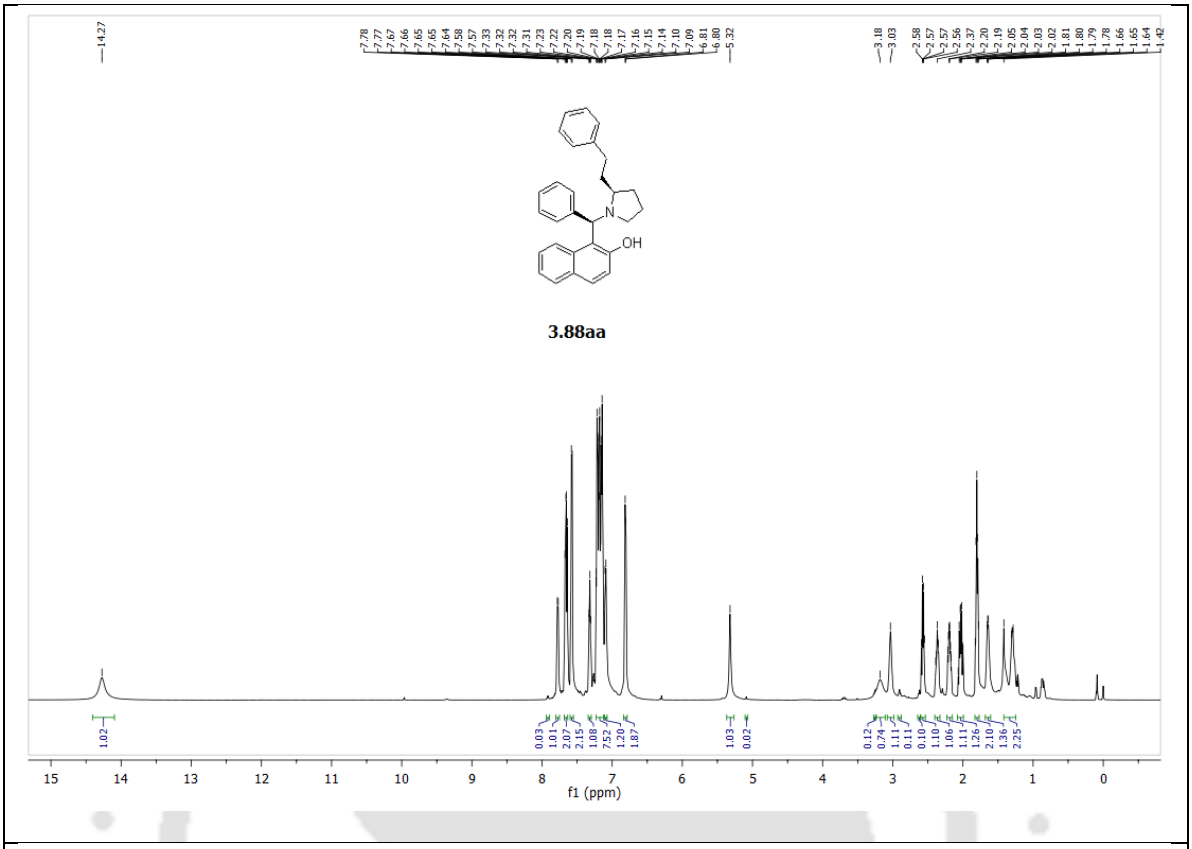

OH
3.88e
f1 (ppm)

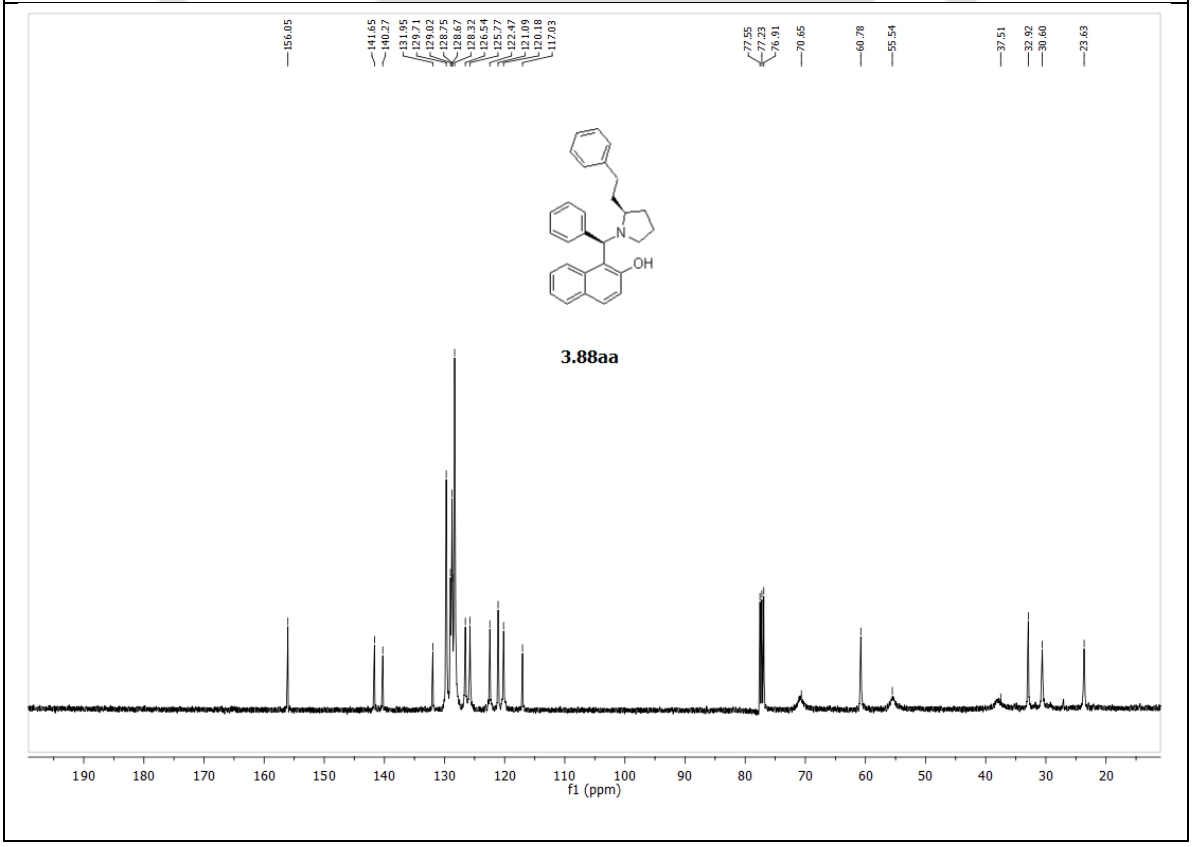

13.503
7.736
7.715
7.501
7.480
7.334
7.315
7.296
7.271
7.250
7.226
7.206
7.138
5.158
4.206
4.177
4.157
4.037
4.009
3.967
3.949
3.871
3.792
2.872
2.847
2.243
2.216
OH
3.88f
1.04
1.98
1.28
13.48
1.00
2.35
2.37
1.14
0.99
1.01
f1 (ppm)

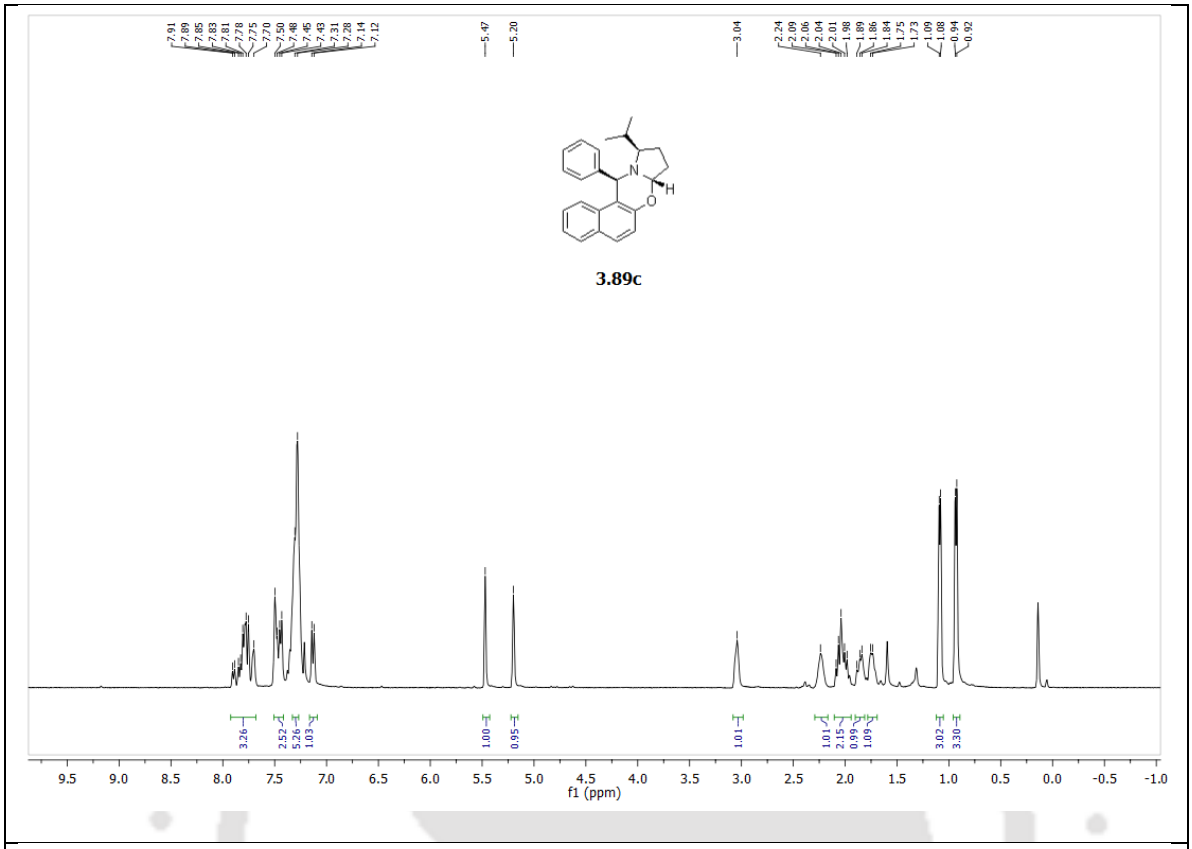

156.08
138.73
130.07
129.07
129.03
128.21
128.00
126.55
122.79
121.42
71.09
67.61
66.81
59.21
44.55
OH
3.88f
f1 (ppm)

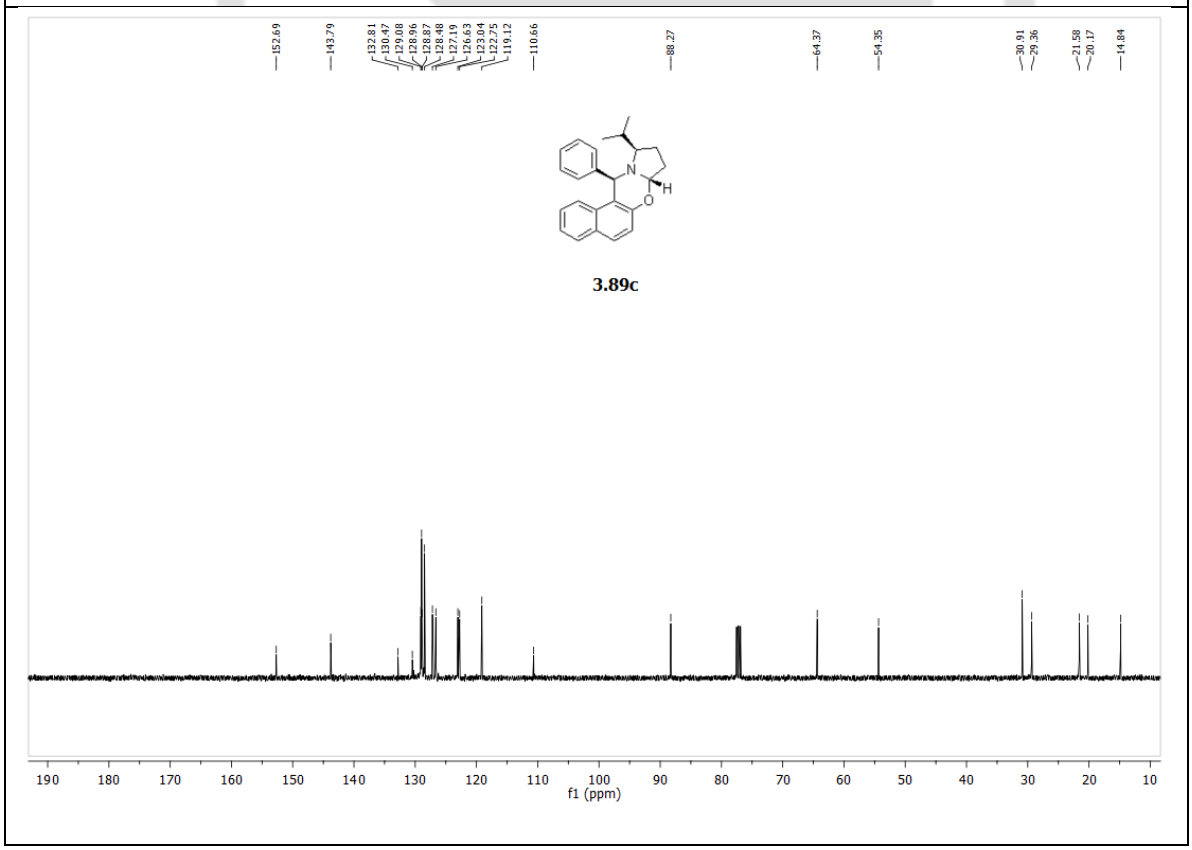

13.549
8.056
8.035
7.831
7.705
7.685
7.656
7.634
7.460
7.441
7.422
7.373
7.355
7.336
7.307
7.289
7.264
7.246
7.227
7.215
7.139
7.122
6.649
5.659
3.943
3.914
3.873
3.845
3.816
3.614
3.585
3.538
3.509
3.176
3.146
3.116
3.056
3.025
2.993
2.987
2.954
2.923
2.875
2.846
OH
3.88g
0.99
1.19
2.18
2.70
1.47
2.98
3.61
4.88
2.20
1.00
1.37
1.09
1.39
1.30
1.82
3.30
1.60
f1 (ppm)

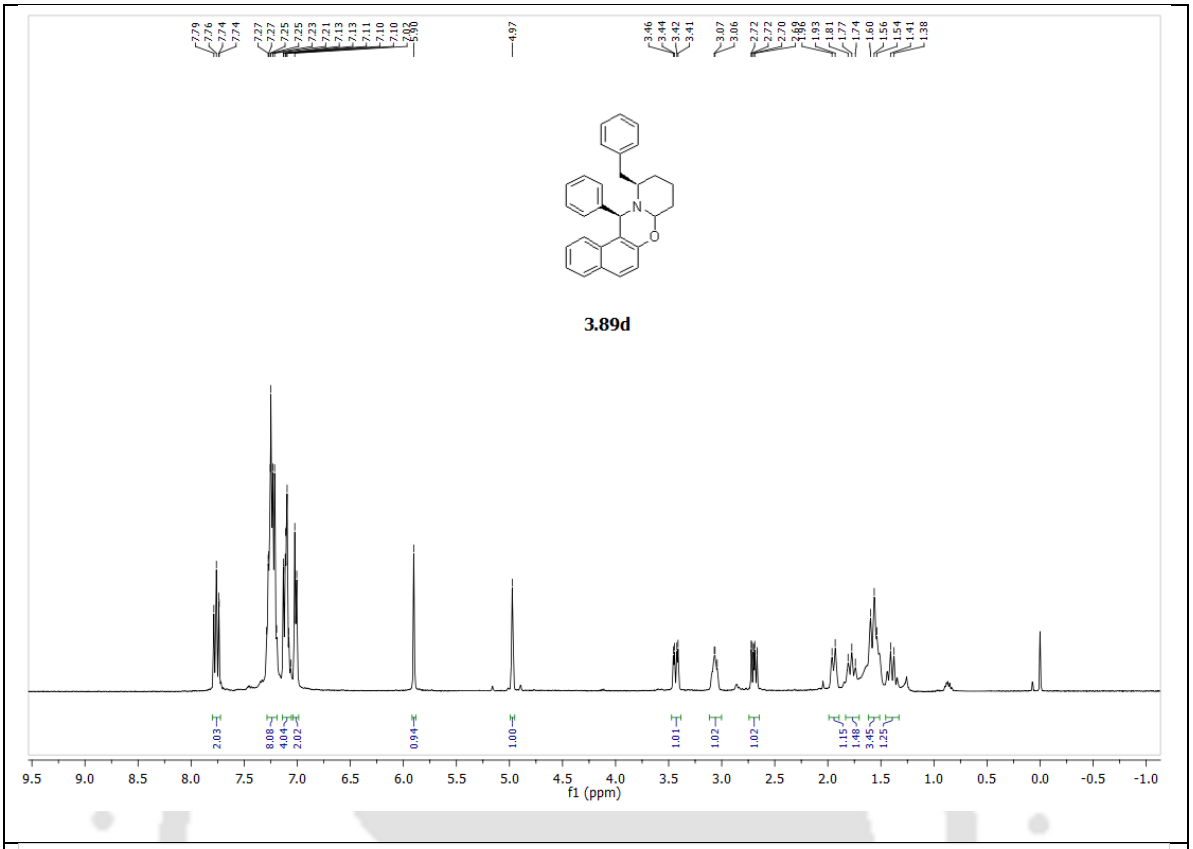

155.14
138.77
138.63
132.46
129.91
129.39
129.28
129.00
128.62
128.50
126.78
126.45
122.79
121.05
120.18
116.01
68.13
67.91
67.21
56.69
46.40
26.82
OH
3.88g
f1 (ppm)

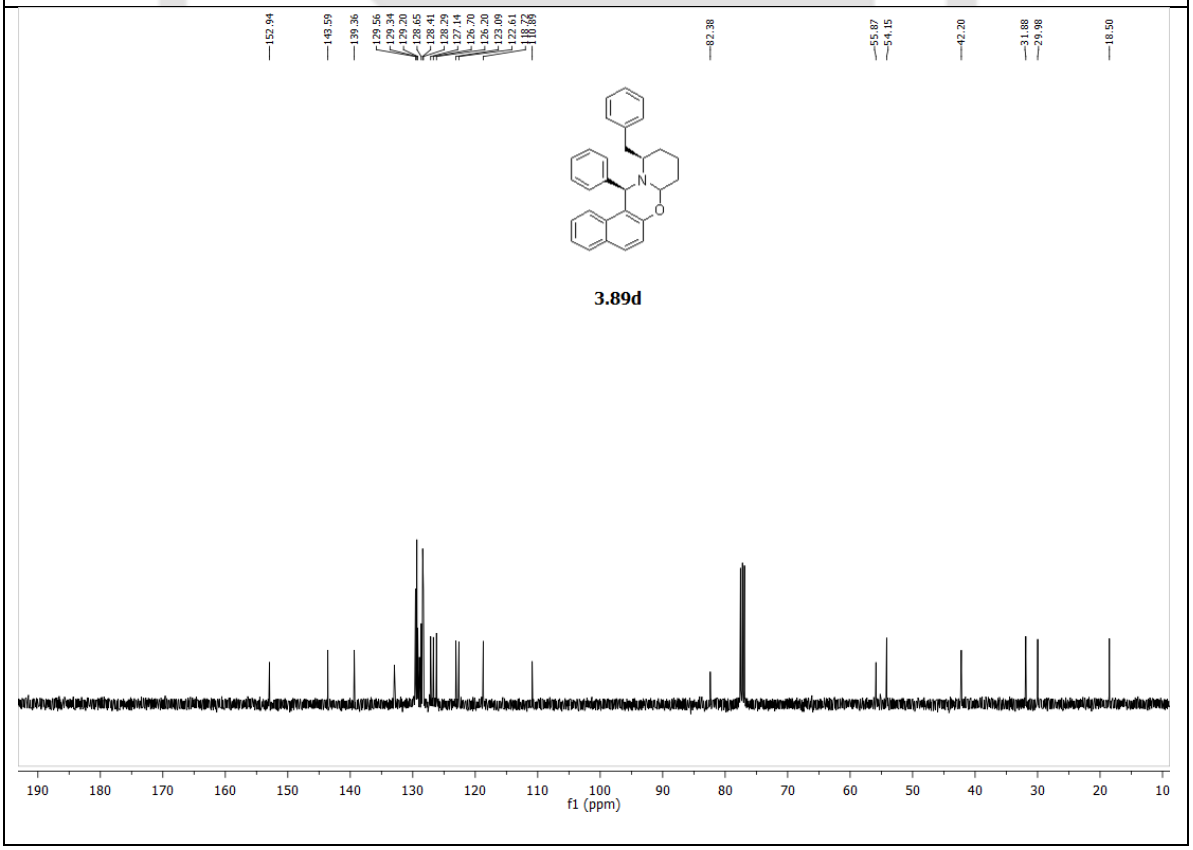

OH
3.88aa
f1 (ppm)

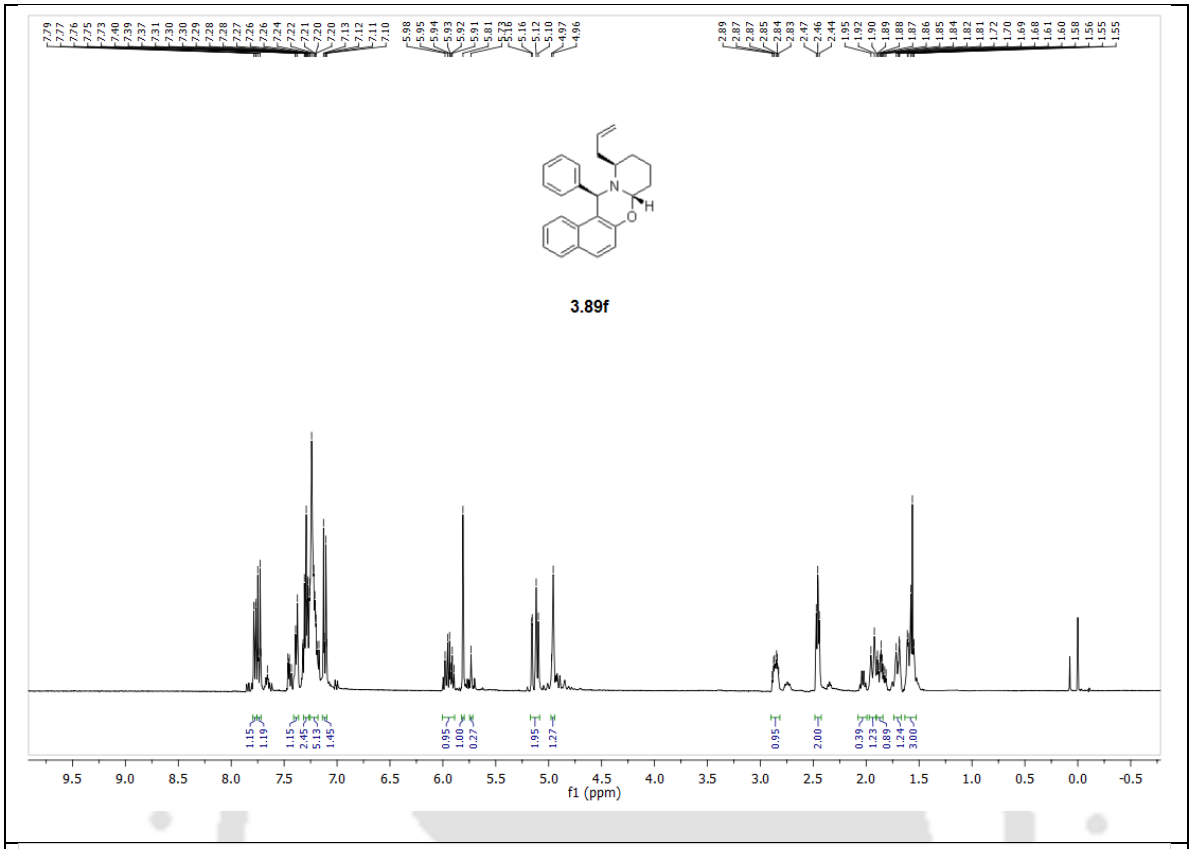

OH
3.88aa
f1 (ppm)

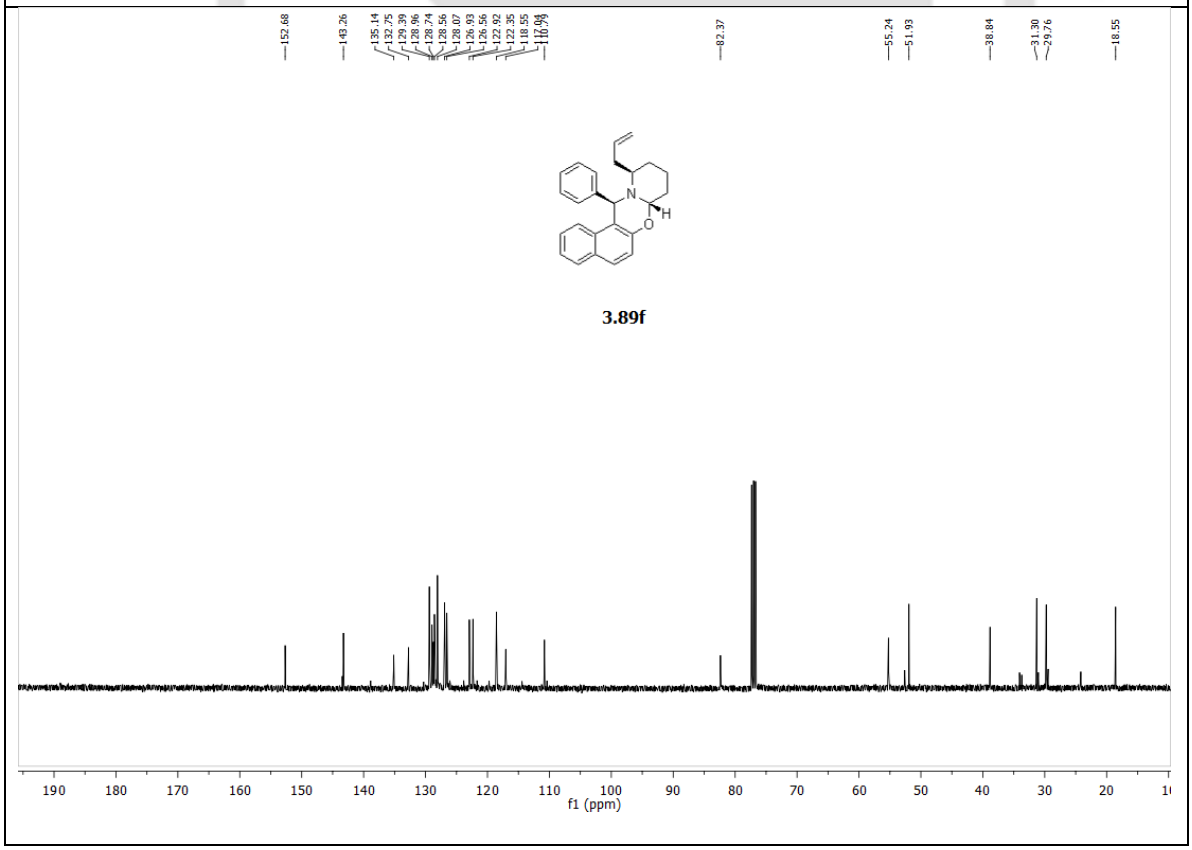

7.91
7.89
7.85
7.83
7.81
7.78
7.75
7.70
7.50
7.48
7.46
7.45
7.31
7.28
7.14
7.12
5.47
5.20
3.04
2.24
2.09
2.06
2.04
2.01
1.98
1.89
1.86
1.84
1.75
1.73
1.09
1.08
0.94
0.92
N
O
H
3.89c
3.26
2.52
5.26
1.03
1.00
0.95
1.01
1.01
2.15
0.99
1.09
3.02
3.30
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

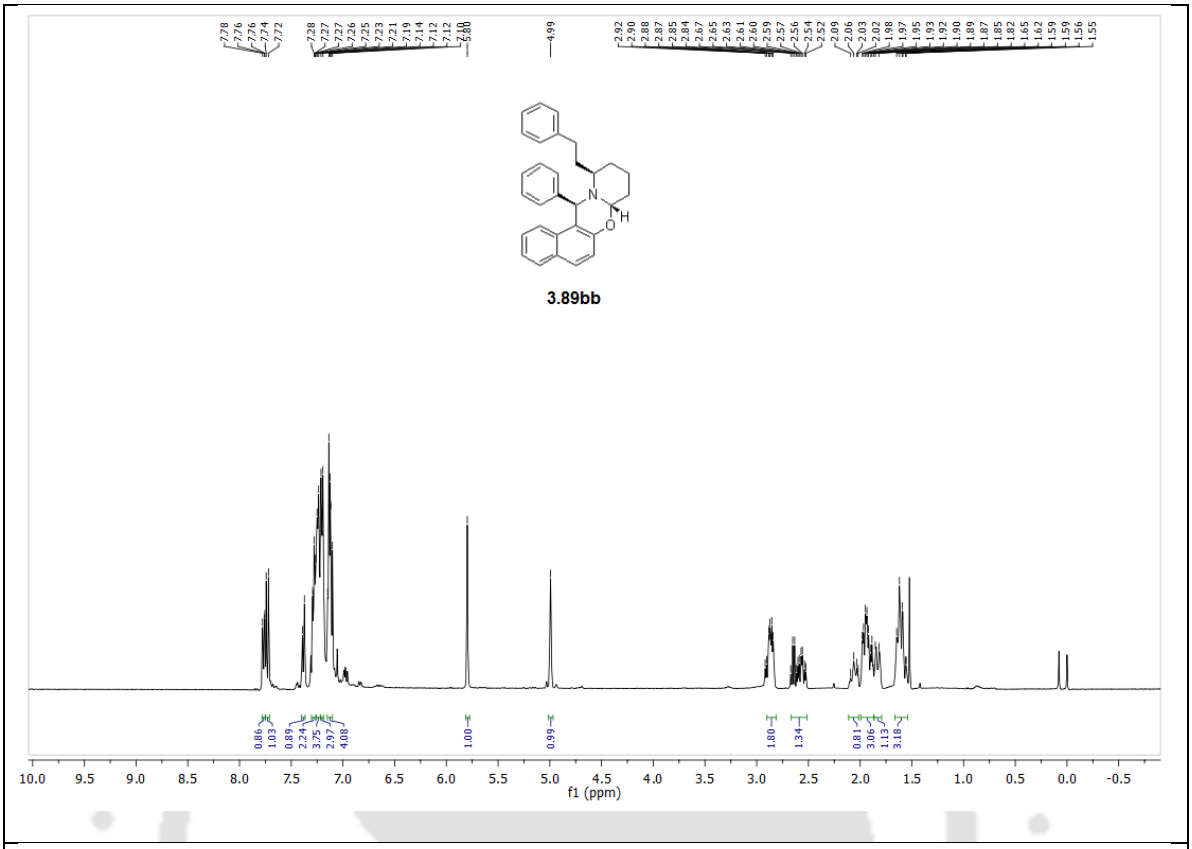

152.69
143.79
132.81
130.47
129.08
128.96
128.87
128.48
127.19
126.63
123.04
122.75
119.12
110.66
88.27
64.37
54.35
30.91
29.36
21.58
20.17
14.84
N
O
H
3.89c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

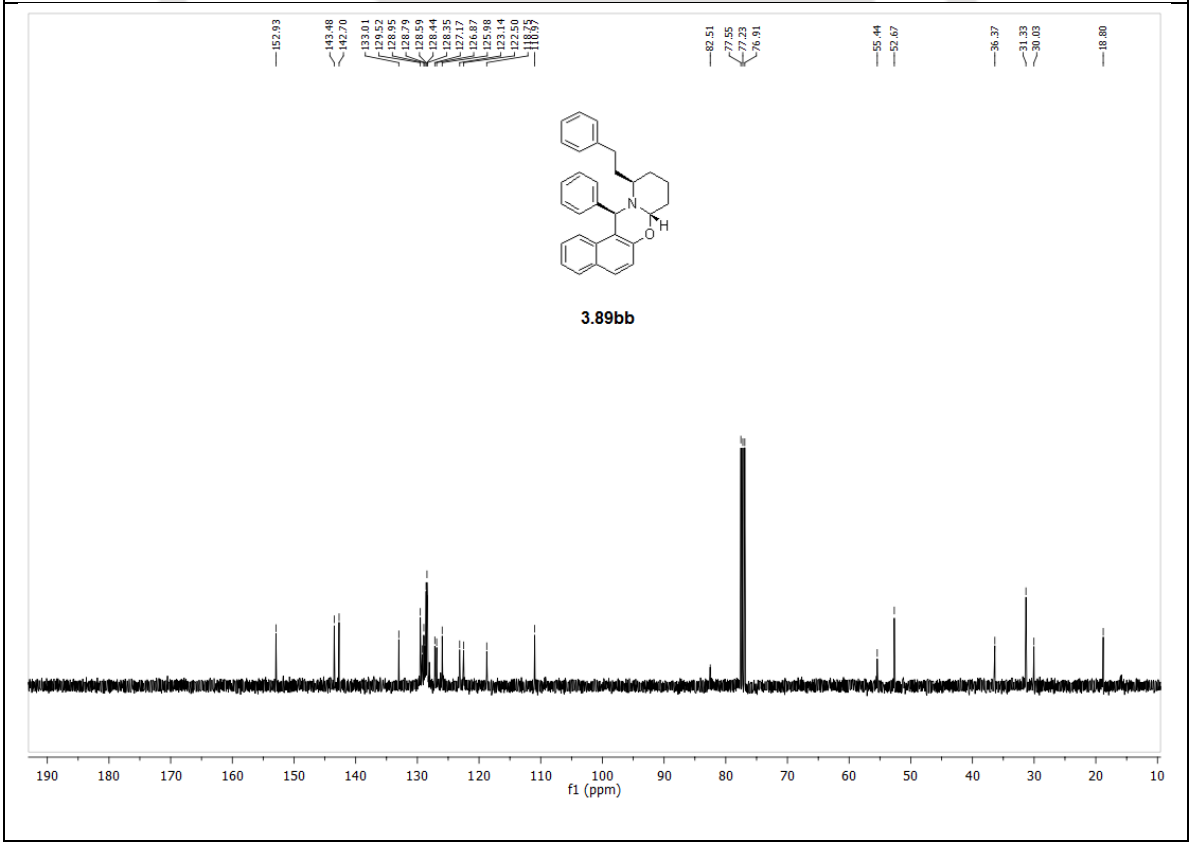

7.79
7.76
7.74
7.74
7.27
7.27
7.25
7.25
7.23
7.21
7.13
7.11
7.10
4.97
3.46
3.44
3.42
3.41
3.07
3.06
2.72
2.72
2.70
1.93
1.81
1.77
1.74
1.60
1.56
1.54
1.41
1.38
3.89d
2.03
8.08
4.04
2.02
0.94
1.00
1.01
1.02
1.02
1.15
1.48
3.45
1.25
f1 (ppm)

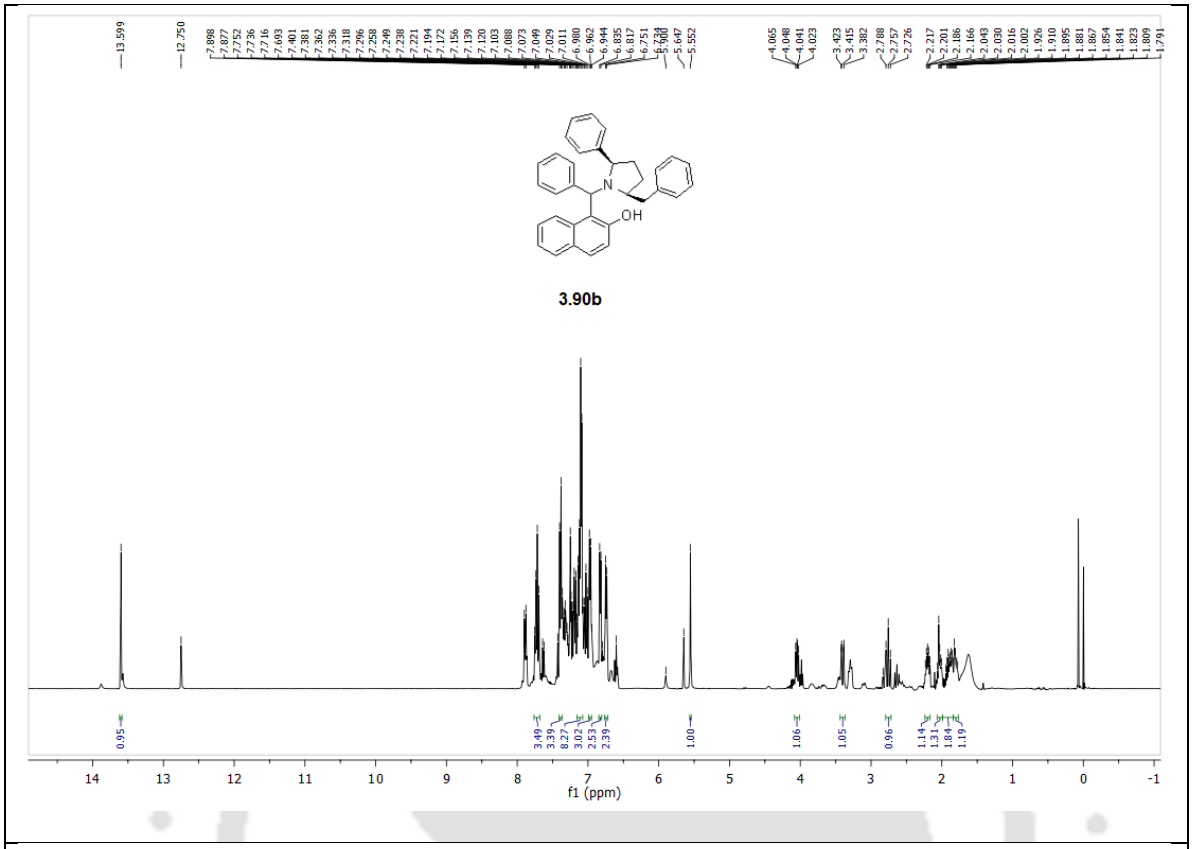

152.94
143.59
139.36
129.56
129.34
129.20
128.65
128.41
128.29
127.14
126.70
126.20
123.09
122.61
118.72
110.89
82.38
55.87
54.15
42.20
31.88
29.98
18.50
3.89d
f1 (ppm)

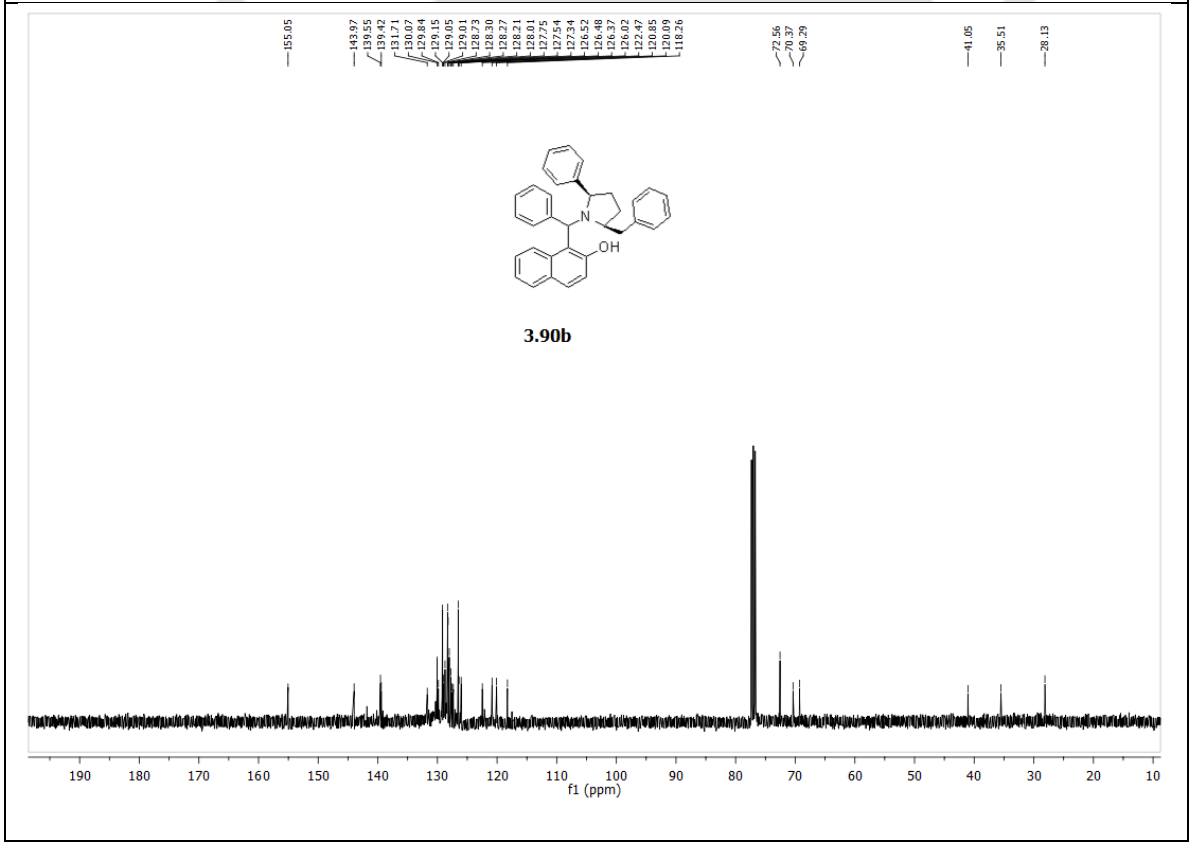

7.79
7.77
7.76
7.75
7.73
7.40
7.39
7.37
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.26
7.24
7.21
7.21
7.20
7.20
7.13
7.12
7.11
7.10
5.98
5.95
5.94
5.93
5.92
5.91
5.81
5.18
5.16
5.12
5.10
4.97
4.96
2.89
2.87
2.87
2.85
2.84
2.83
2.47
2.46
2.44
1.95
1.92
1.90
1.89
1.88
1.87
1.86
1.85
1.84
1.82
1.81
1.72
1.70
1.69
1.68
1.61
1.60
1.58
1.56
1.55
1.55
N
O
H
3.89f
1.15
1.19
1.15
2.45
5.13
1.45
0.95
1.00
0.27
1.95
1.27
0.95
2.00
0.39
1.23
0.89
1.24
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
-0.5
f1 (ppm)

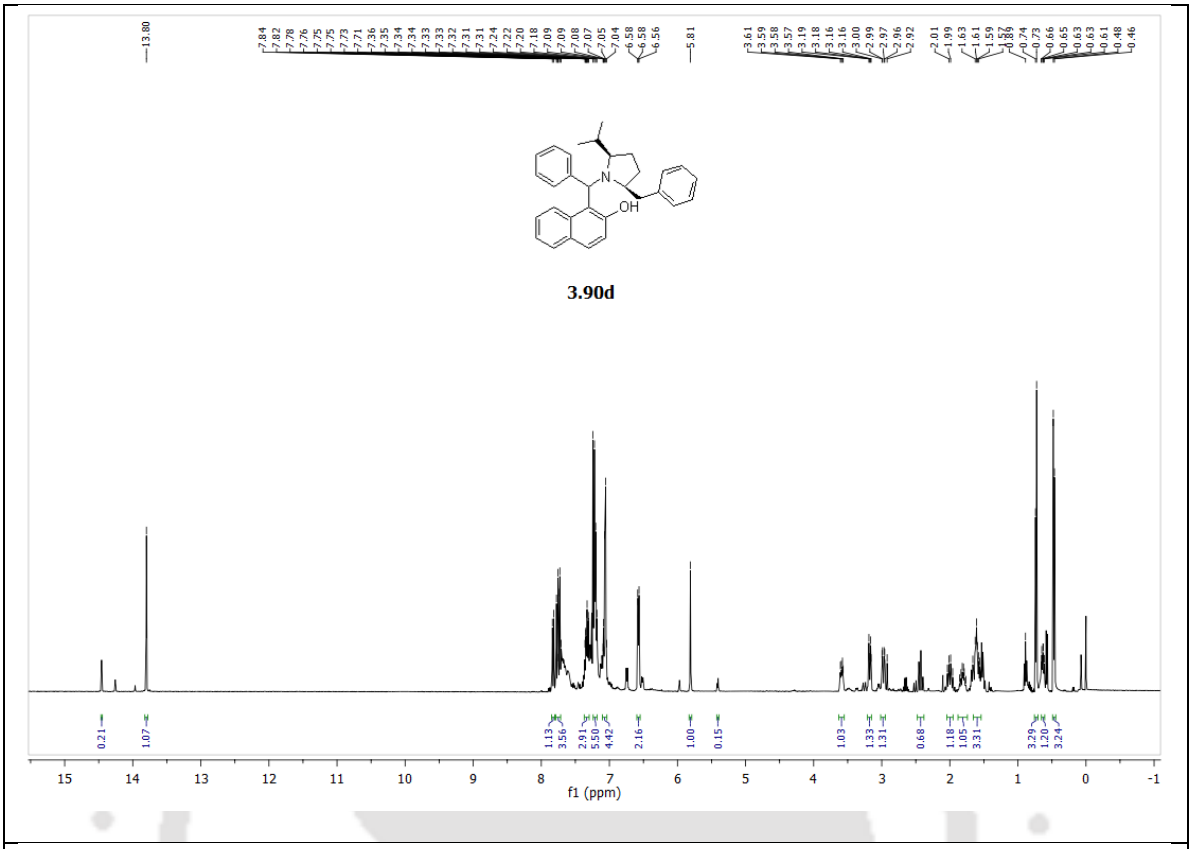

152.68
143.26
135.14
132.75
129.39
128.96
128.74
128.56
128.07
126.93
126.56
122.92
122.35
118.55
110.94
82.37
55.24
51.93
38.84
31.30
29.76
18.55
N
O
H
3.89f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

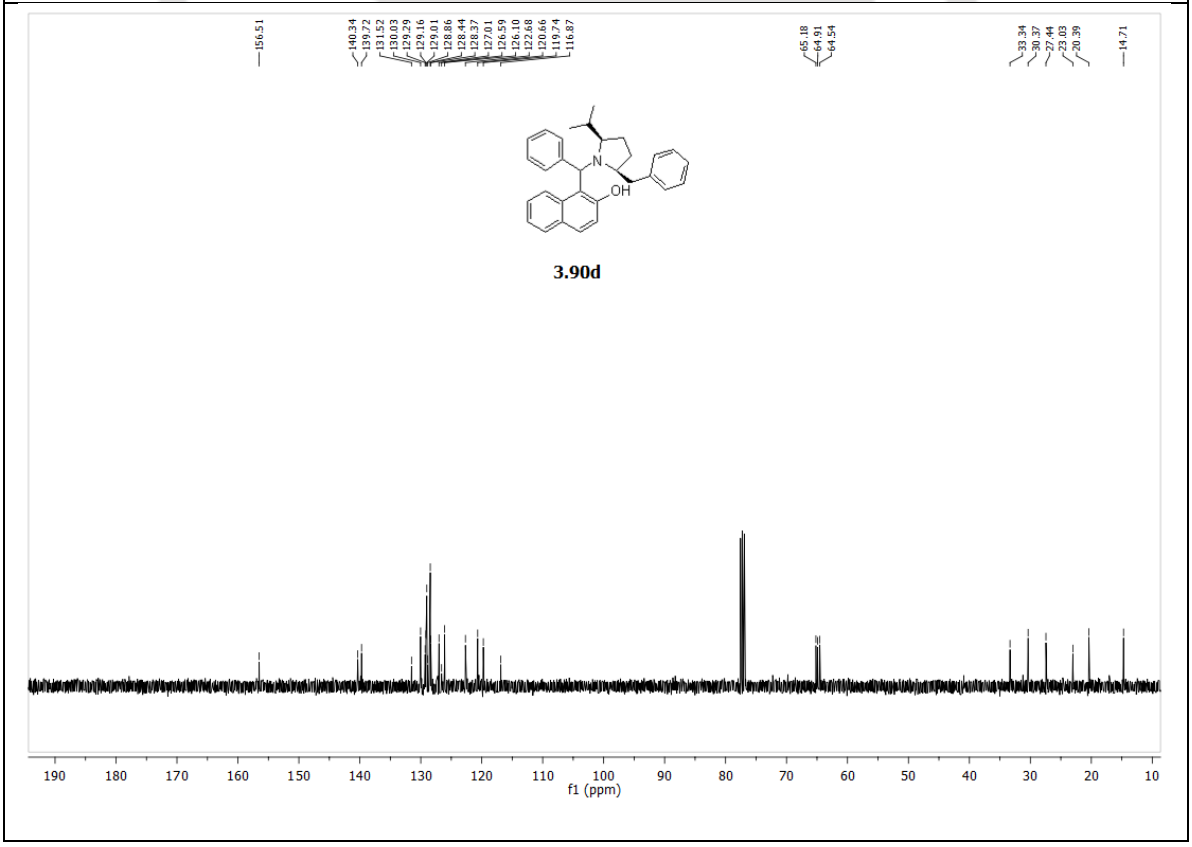

3.89bb
f1 (ppm)

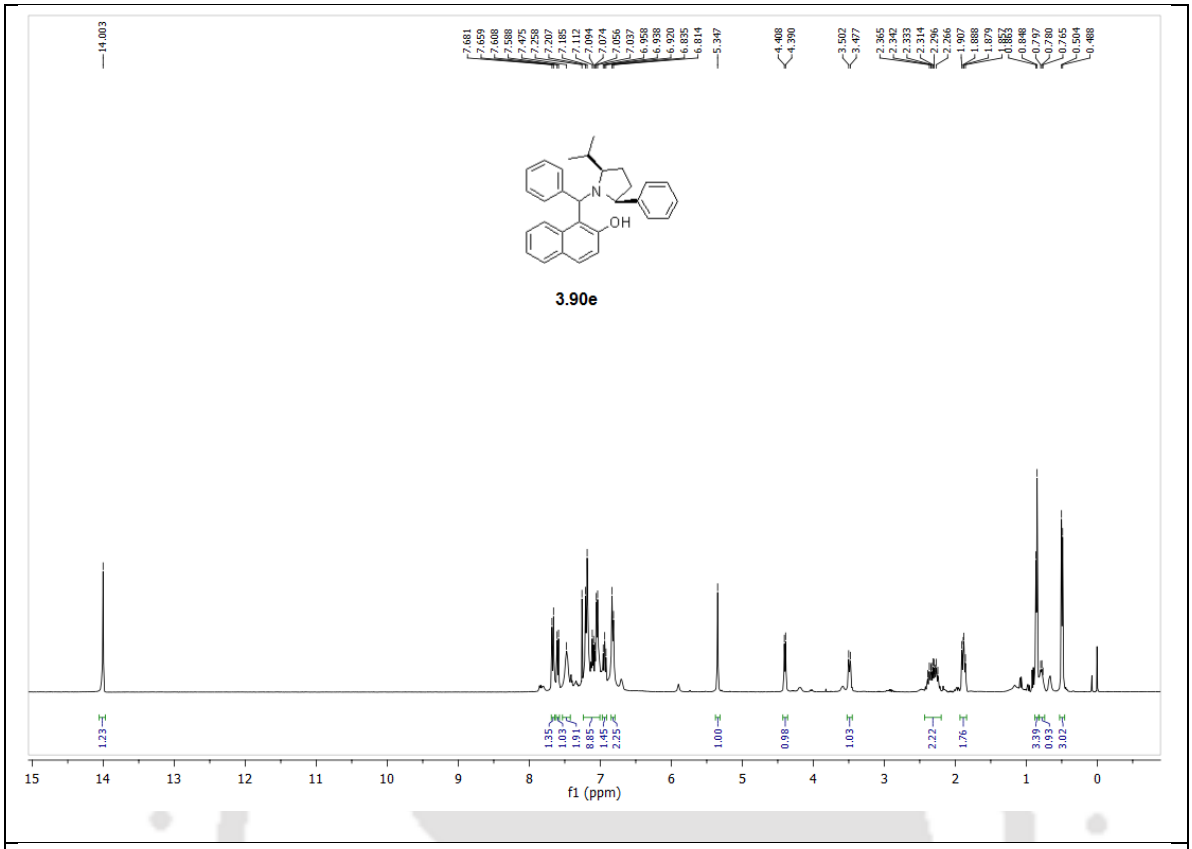

3.89bb
f1 (ppm)

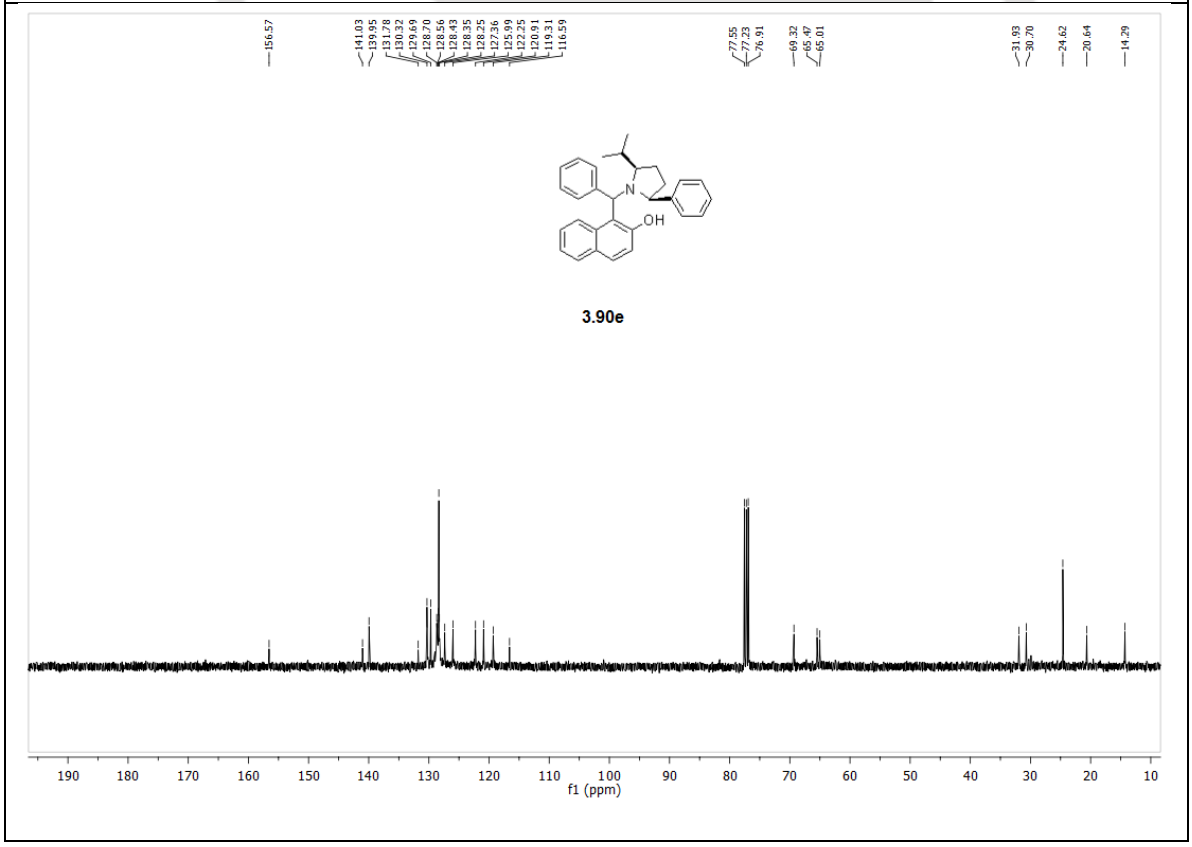

13.599
12.750
7.898
7.877
7.732
7.726
7.716
7.693
7.401
7.381
7.362
7.336
7.318
7.296
7.258
7.249
7.238
7.221
7.194
7.172
7.156
7.139
7.120
7.103
7.088
7.073
7.049
7.029
7.011
6.980
6.962
6.944
6.835
6.817
6.751
5.647
5.552
4.065
4.048
4.041
4.023
3.423
3.415
3.382
2.788
2.757
2.726
2.217
2.201
2.186
2.166
2.043
2.030
2.016
2.002
1.926
1.910
1.895
1.881
1.867
1.854
1.841
1.823
1.808
1.791
N
OH
3.90b
0.95
3.49
3.39
8.27
3.02
2.53
2.39
1.00
1.06
1.05
0.96
1.14
1.31
1.84
1.19
f1 (ppm)

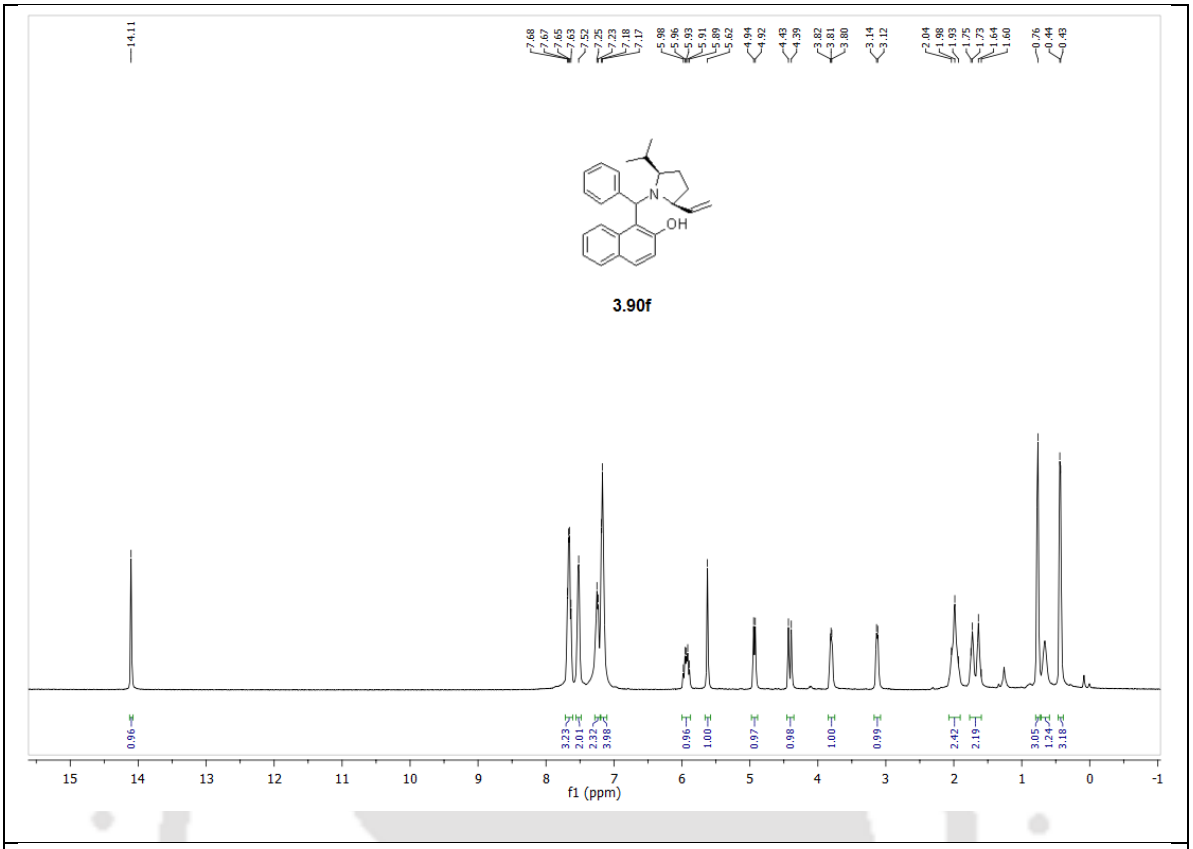

155.05
143.97
139.55
139.42
131.71
130.07
129.84
129.15
129.05
129.01
128.73
128.30
128.27
128.11
127.75
127.54
127.34
126.52
126.48
126.37
126.02
122.47
120.85
120.09
118.26
72.56
70.37
69.29
41.05
35.51
28.13
N
OH
3.90b
f1 (ppm)

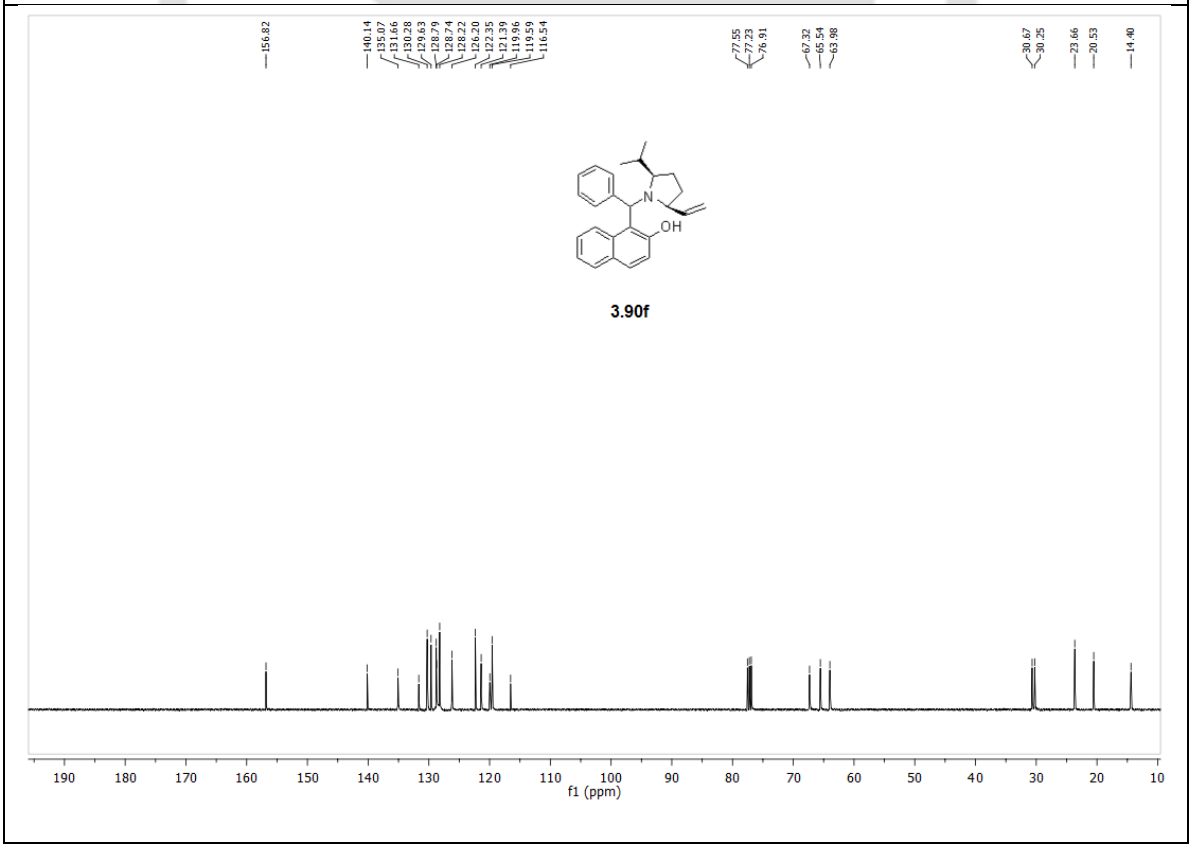

13.80
7.84
7.82
7.78
7.76
7.75
7.75
7.73
7.71
7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.24
7.22
7.20
7.18
7.09
7.09
7.08
7.07
7.05
7.04
6.58
6.58
6.56
5.81
3.61
3.59
3.58
3.57
3.19
3.18
3.16
3.16
3.00
2.99
2.97
2.96
2.92
2.01
1.99
1.63
1.61
1.59
1.57
0.89
0.74
0.73
0.66
0.65
0.63
0.63
0.61
0.48
0.46
N
OH
3.90d
0.21
1.07
1.13
3.56
2.91
5.50
4.42
2.16
1.00
0.15
1.03
1.33
1.31
0.68
1.18
1.05
3.31
3.29
1.20
3.24
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

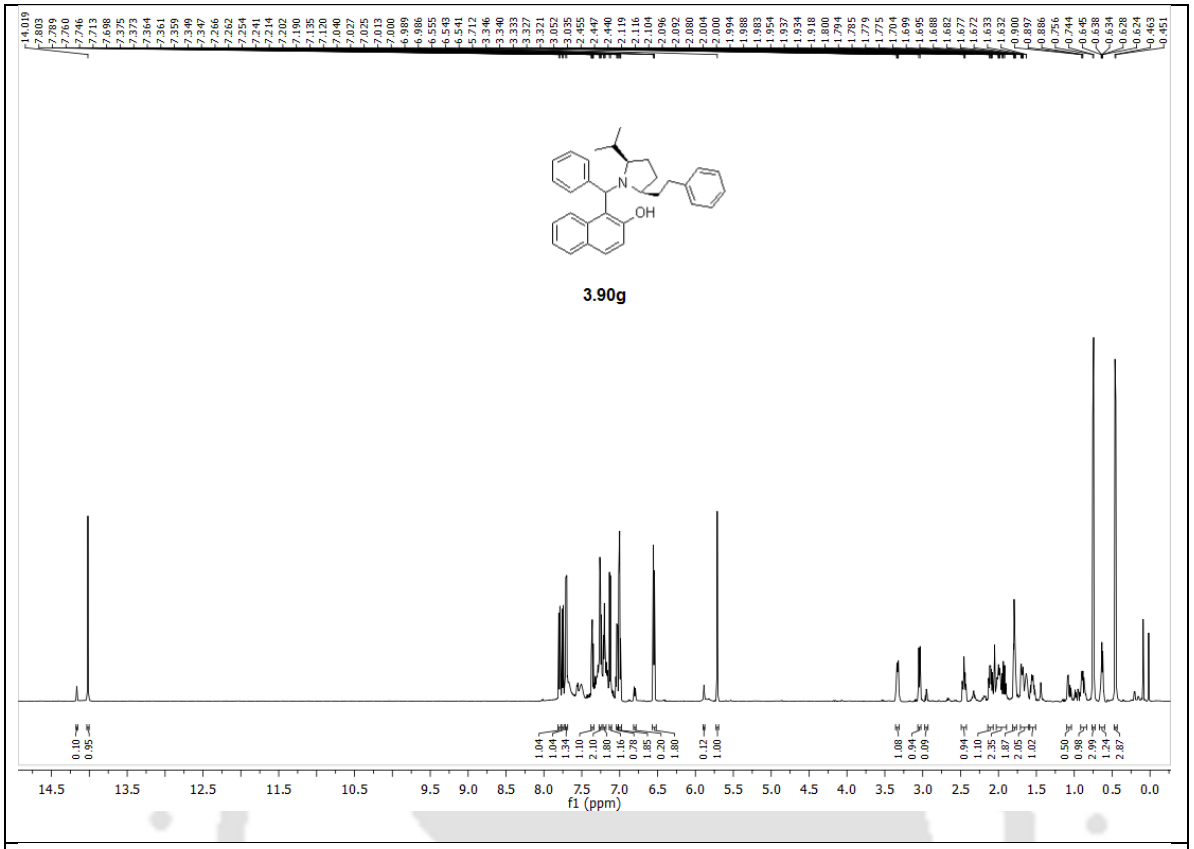

156.51
140.34
139.72
131.52
130.03
129.29
129.16
129.01
128.86
128.44
128.37
127.01
126.59
126.10
125.68
122.66
119.74
116.87
65.18
64.91
64.54
33.34
30.37
27.44
23.03
20.39
14.71
N
OH
3.90d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

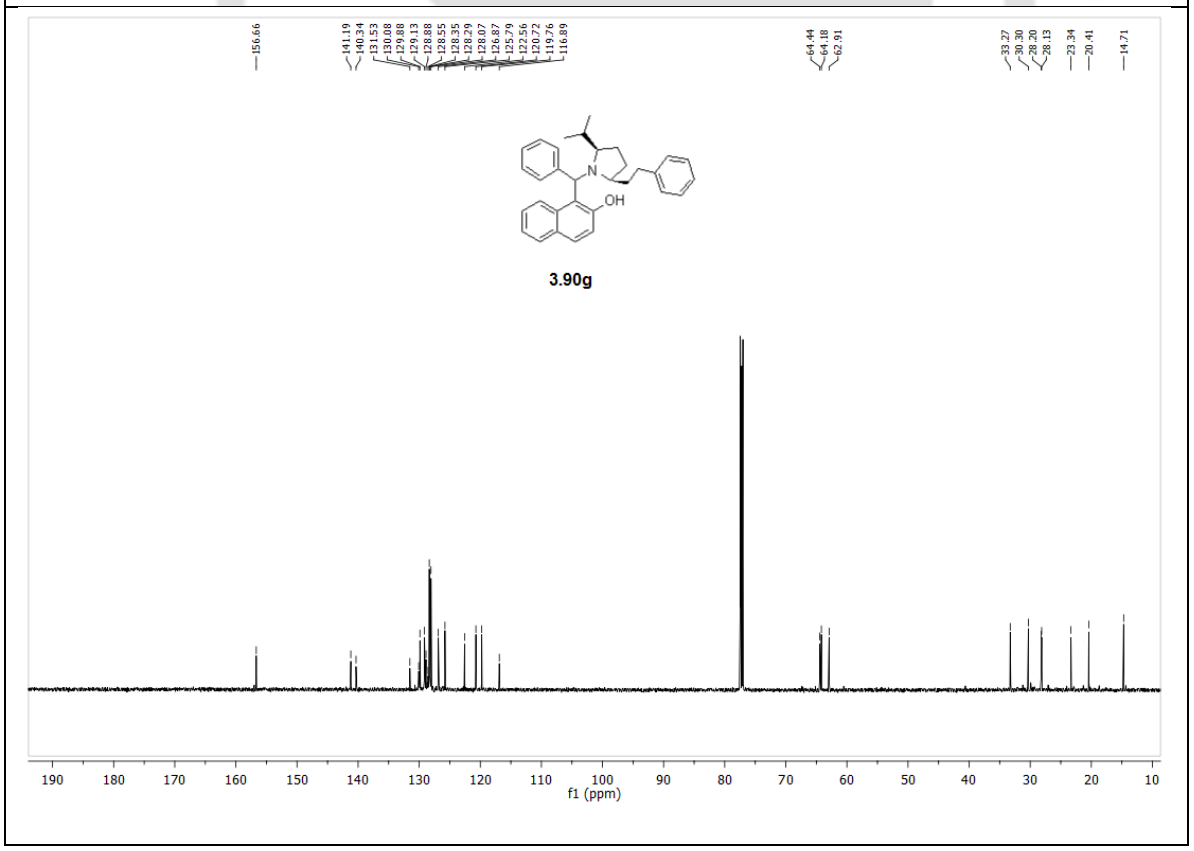

14.003
7.681
7.659
7.608
7.588
7.475
7.258
7.207
7.185
7.112
7.094
7.074
7.056
7.037
6.958
6.938
6.920
6.835
6.814
5.347
4.408
4.390
3.502
3.477
2.365
2.342
2.333
2.314
2.296
2.266
1.907
1.888
1.879
1.857
1.843
1.048
0.797
0.780
0.745
0.504
0.488
OH
3.90e
1.23
1.35
1.03
1.91
8.85
1.45
2.25
1.00
0.98
1.03
2.22
1.76
3.39
0.93
3.02
f1 (ppm)

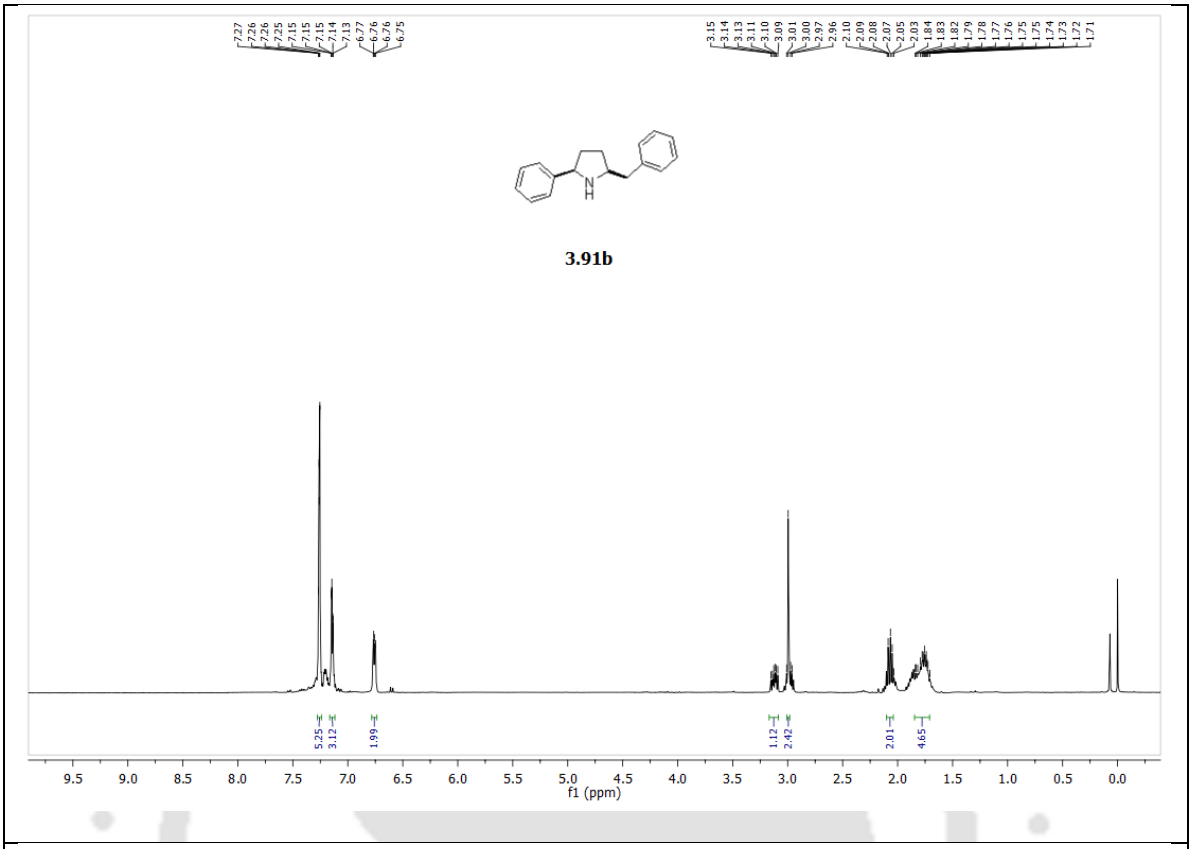

156.57
141.03
139.95
131.78
130.32
129.69
128.70
128.56
128.43
128.35
128.25
127.36
125.99
122.25
120.91
119.31
116.59
77.55
77.23
76.91
69.32
65.47
65.01
31.93
30.70
24.62
20.64
14.29
OH
3.90e
f1 (ppm)


14.11
7.68
7.67
7.65
7.63
7.52
7.25
7.23
7.18
7.17
5.98
5.96
5.93
5.91
5.89
5.62
4.94
4.92
4.43
4.39
3.82
3.81
3.80
3.14
3.12
2.04
1.98
1.93
1.75
1.73
1.64
1.60
0.76
0.44
0.43
OH
3.90f
0.96
3.23
2.01
2.32
3.98
0.96
1.00
0.97
0.98
1.00
0.99
2.42
2.19
3.05
1.24
3.18
f1 (ppm)

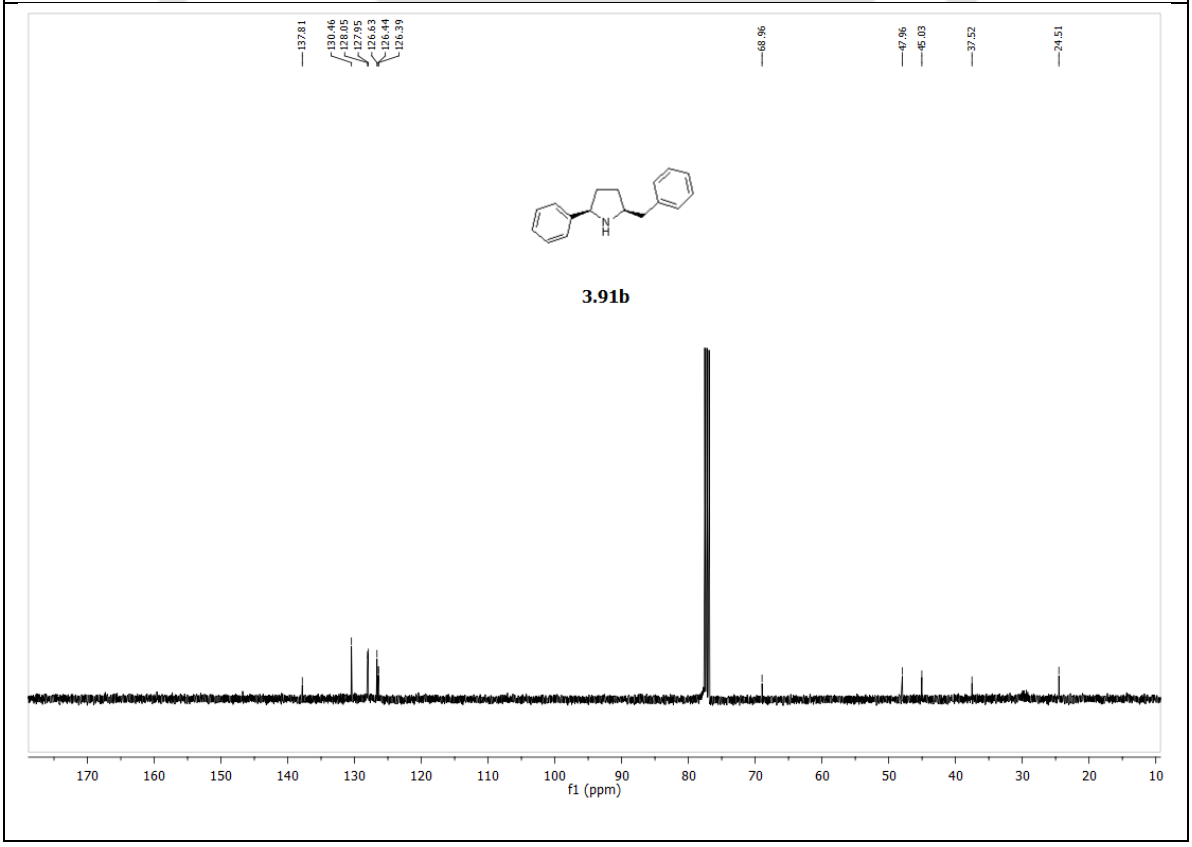

156.82
140.14
135.07
131.66
130.28
129.63
128.79
128.74
128.22
126.20
122.35
121.39
119.96
119.59
116.54
77.55
77.23
76.91
67.32
65.54
63.98
30.67
30.25
23.66
20.53
14.40
OH
3.90f
f1 (ppm)


OH
3.90g
f1 (ppm)

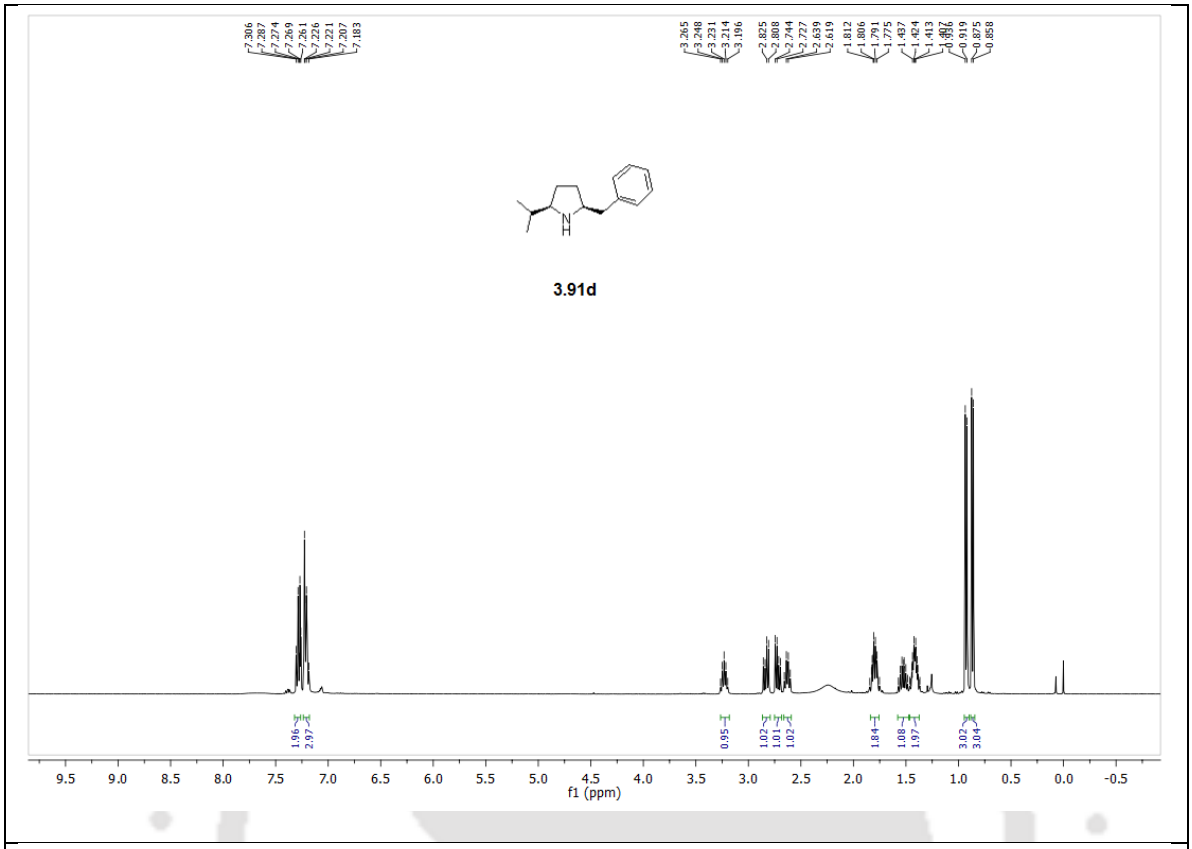

OH
3.90g
f1 (ppm)

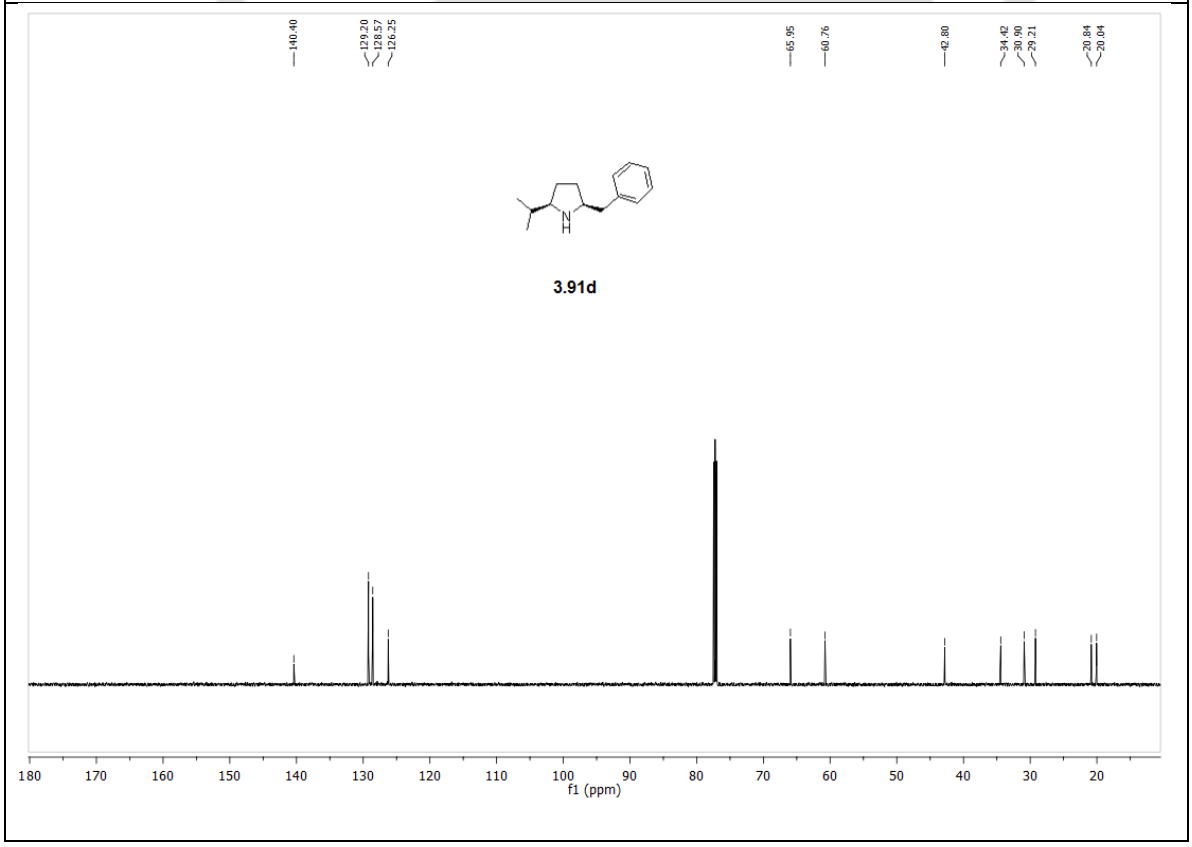

7.27
7.26
7.26
7.25
7.15
7.15
7.15
7.14
7.13
6.77
6.76
6.76
6.75
3.15
3.14
3.13
3.11
3.10
3.09
3.01
3.00
2.97
2.96
2.10
2.09
2.08
2.07
2.05
2.03
1.84
1.83
1.82
1.79
1.78
1.77
1.76
1.75
1.75
1.74
1.73
1.72
1.71
5.25
3.12
1.99
1.12
2.42
2.01
4.65
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

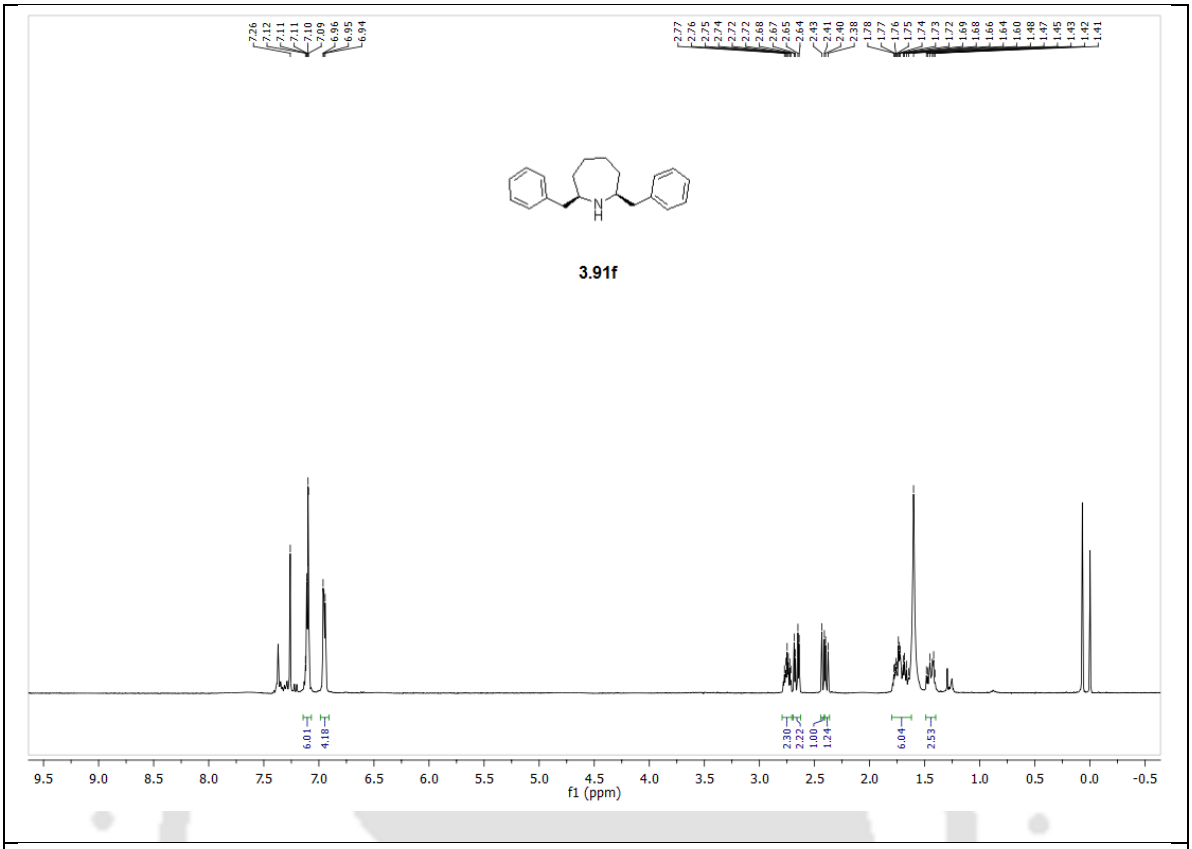
3.91b

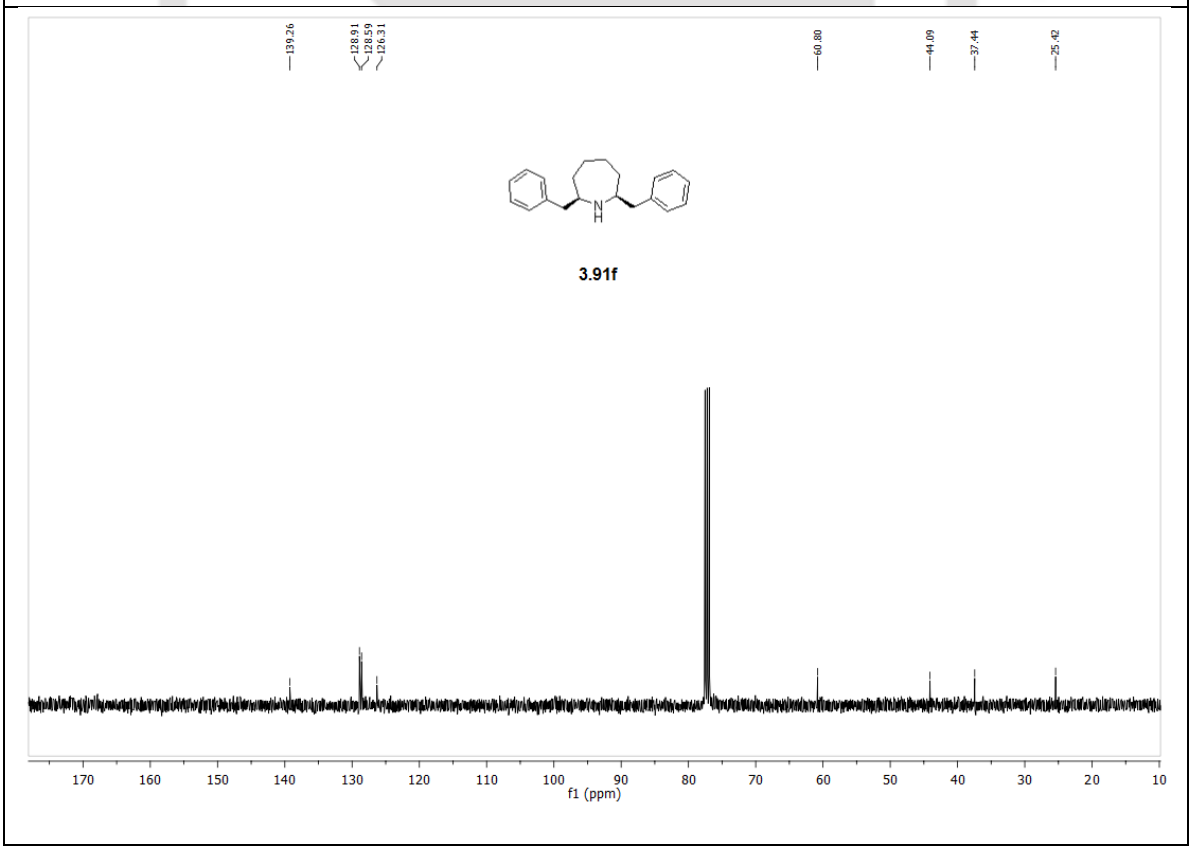

137.81
130.46
128.05
127.95
126.63
126.44
126.39
68.96
47.96
45.03
37.52
24.51
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

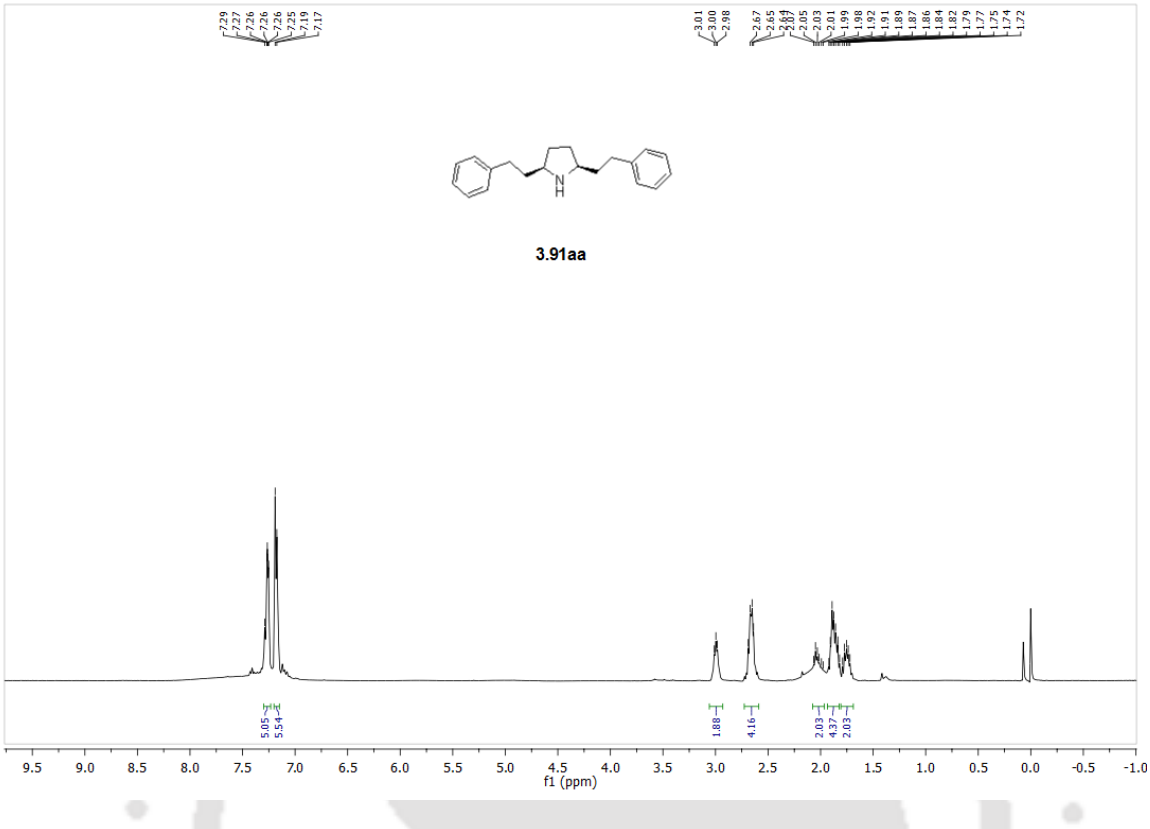
3.91b

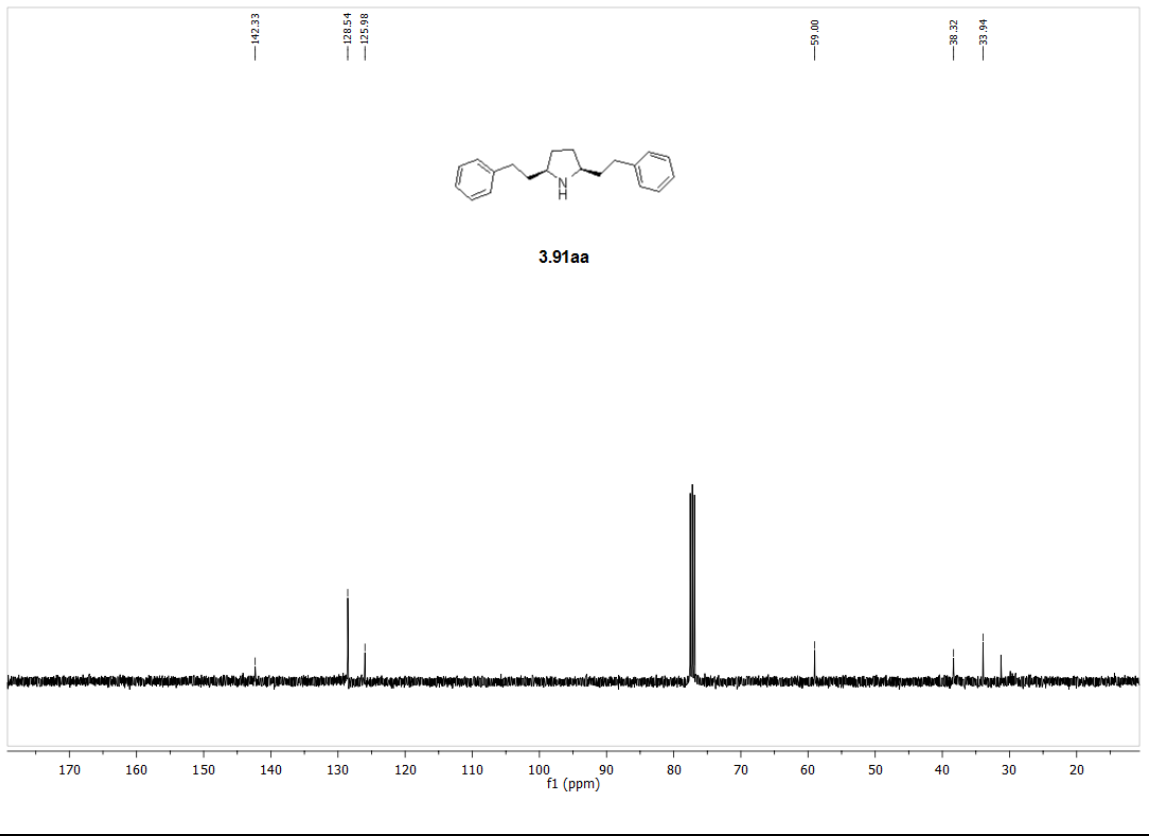

7.306
7.282
7.274
7.269
7.261
7.226
7.221
7.207
7.183
3.265
3.248
3.231
3.214
3.196
2.825
2.808
2.744
2.727
2.639
2.619
1.812
1.806
1.791
1.775
1.437
1.424
1.413
0.919
0.875
0.858
3.91d
1.96
2.97
0.95
1.02
1.01
1.02
1.84
1.08
1.97
3.02
3.04
f1 (ppm)

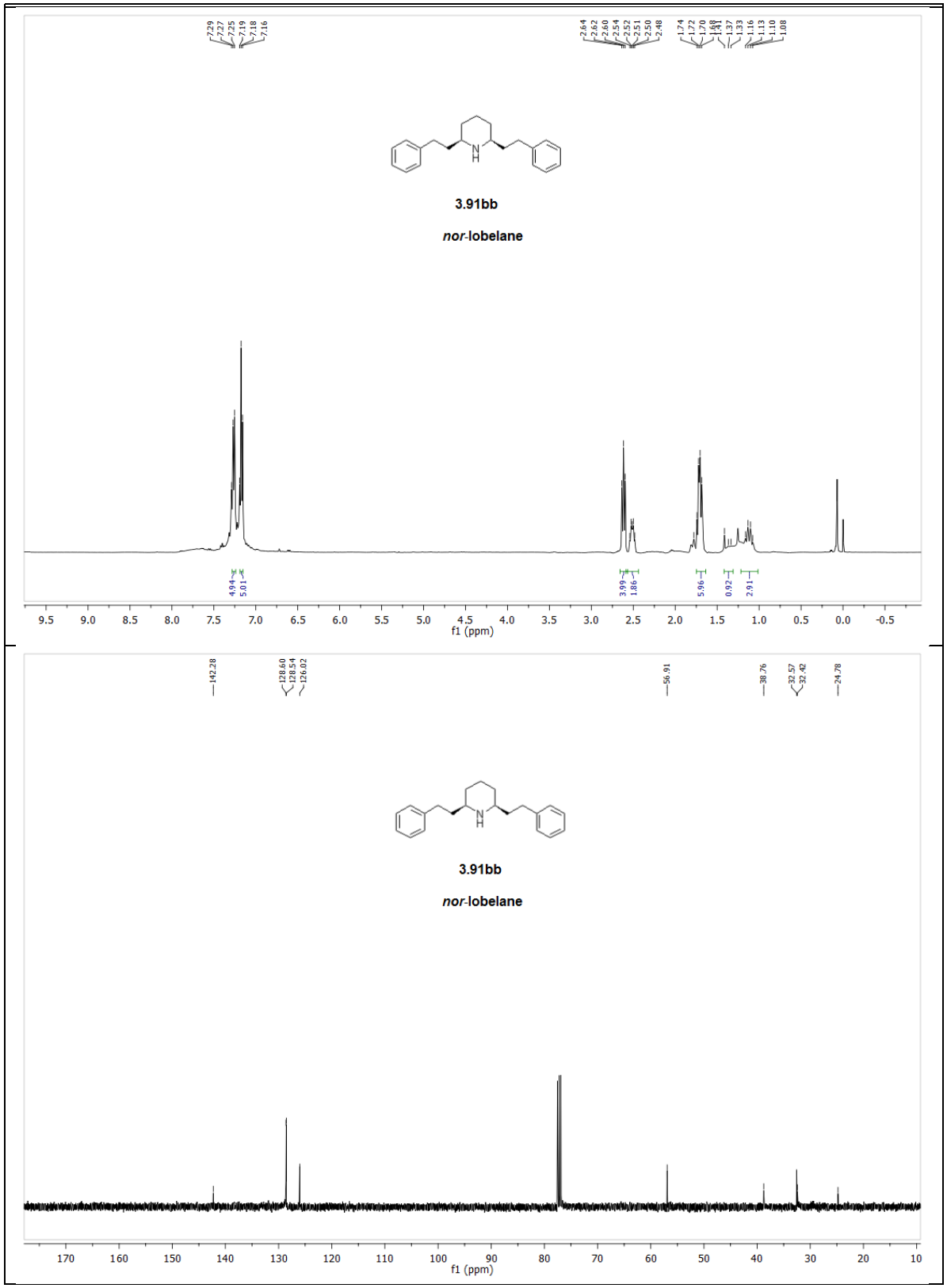

140.40
129.20
128.57
126.25
65.95
60.76
42.80
34.42
30.90
29.21
20.84
20.04
3.91d
f1 (ppm)

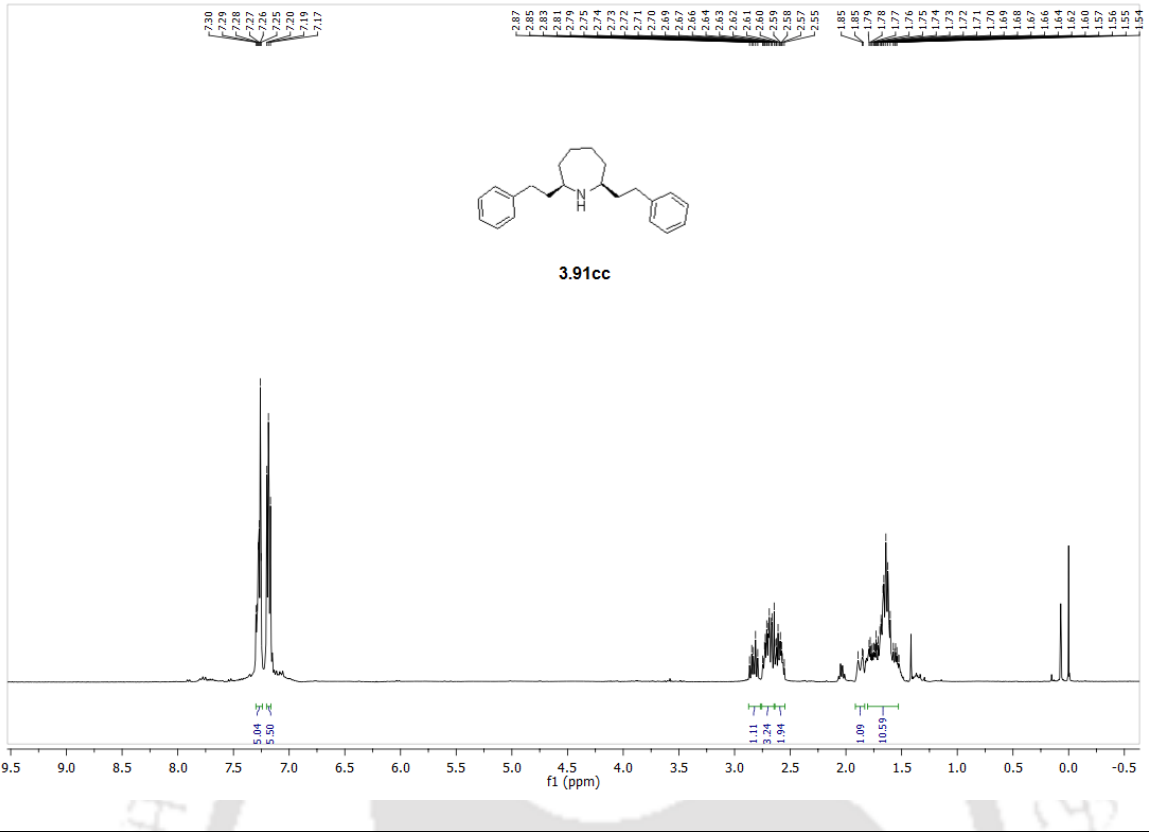

7.26
7.12
7.11
7.11
7.10
7.09
6.96
6.95
6.94
2.77
2.76
2.75
2.74
2.72
2.72
2.68
2.67
2.65
2.64
2.43
2.41
2.40
2.38
1.78
1.77
1.76
1.75
1.74
1.73
1.72
1.69
1.68
1.66
1.64
1.60
1.48
1.47
1.45
1.43
1.42
1.41
3.91f
6.01
4.18
2.30
2.22
1.00
1.24
6.04
2.53
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

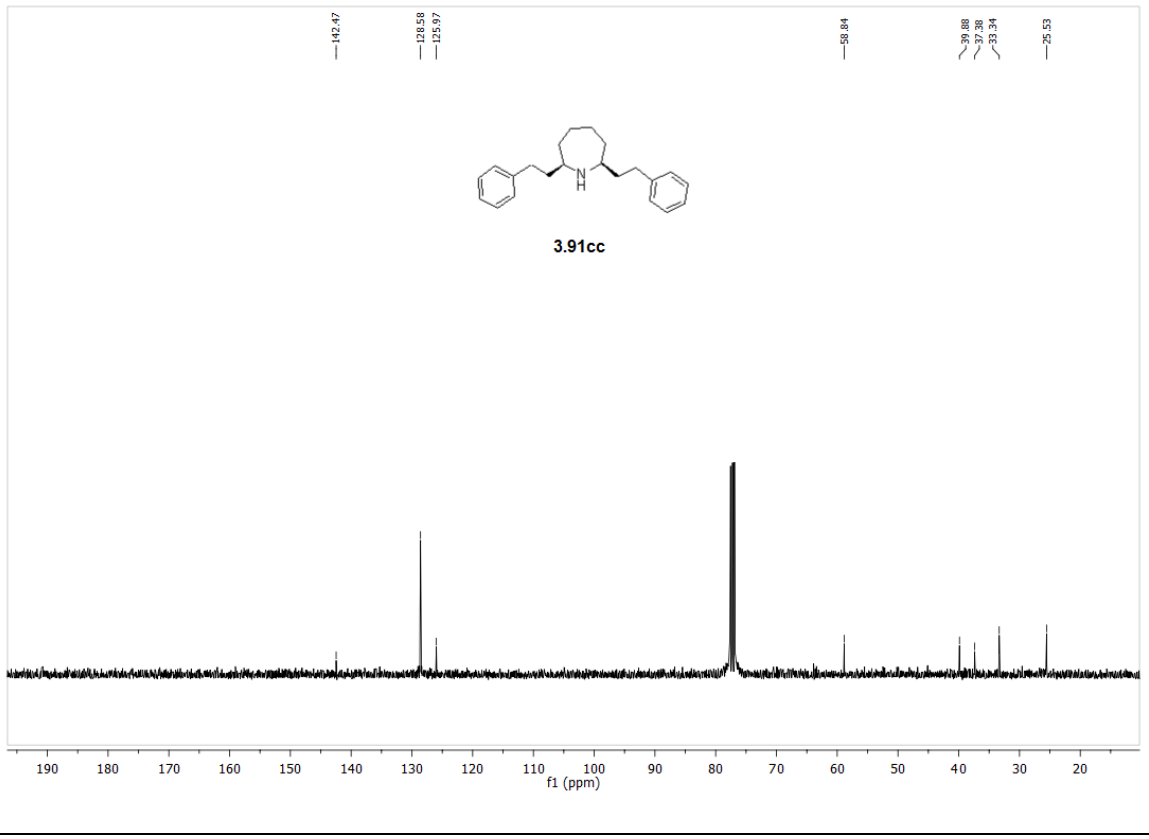

139.26
128.91
128.59
126.31
60.80
44.09
37.44
25.42
3.91f
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

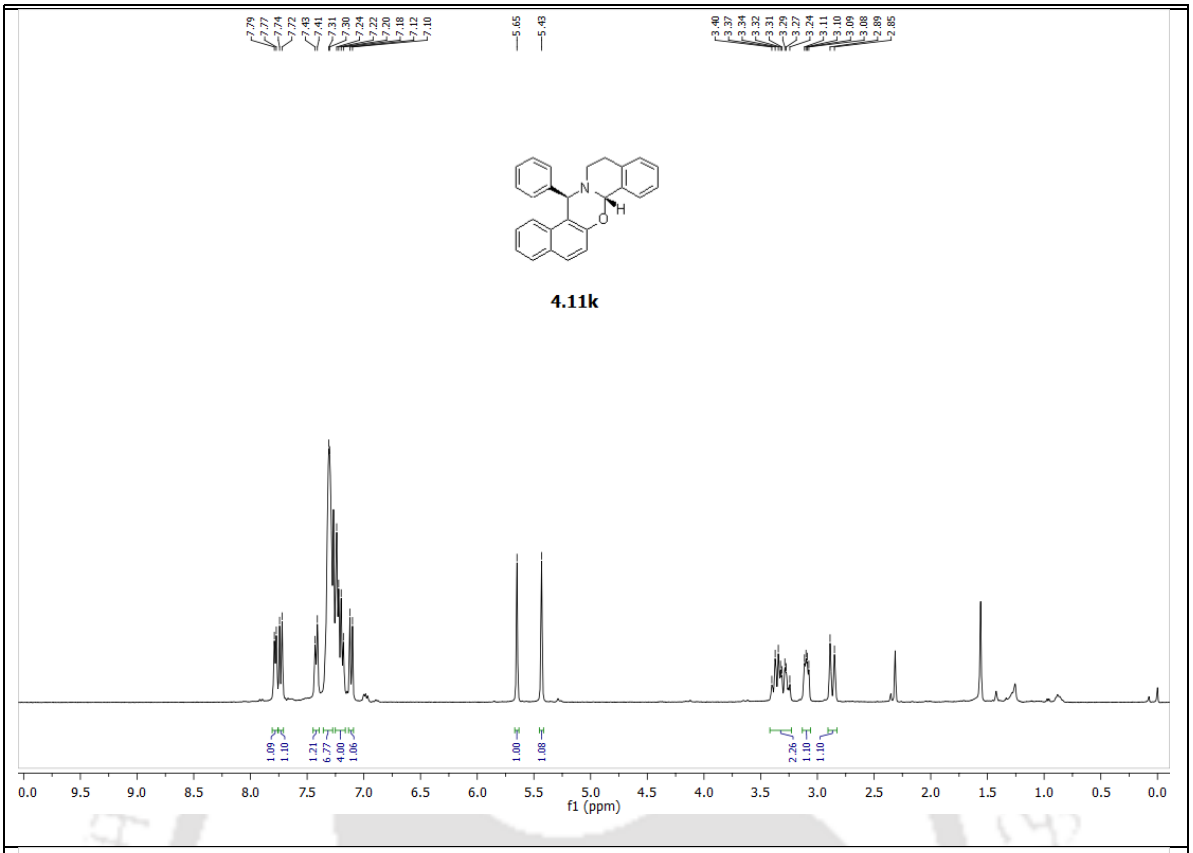

7.29
7.27
7.26
7.26
7.26
7.25
7.19
7.17
3.01
3.00
2.98
2.67
2.65
2.64
2.07
2.05
2.03
2.01
1.99
1.98
1.92
1.91
1.91
1.89
1.87
1.86
1.84
1.82
1.79
1.77
1.75
1.74
1.72
3.91aa
5.05
5.54
1.88
4.16
2.03
4.37
2.03
f1 (ppm)

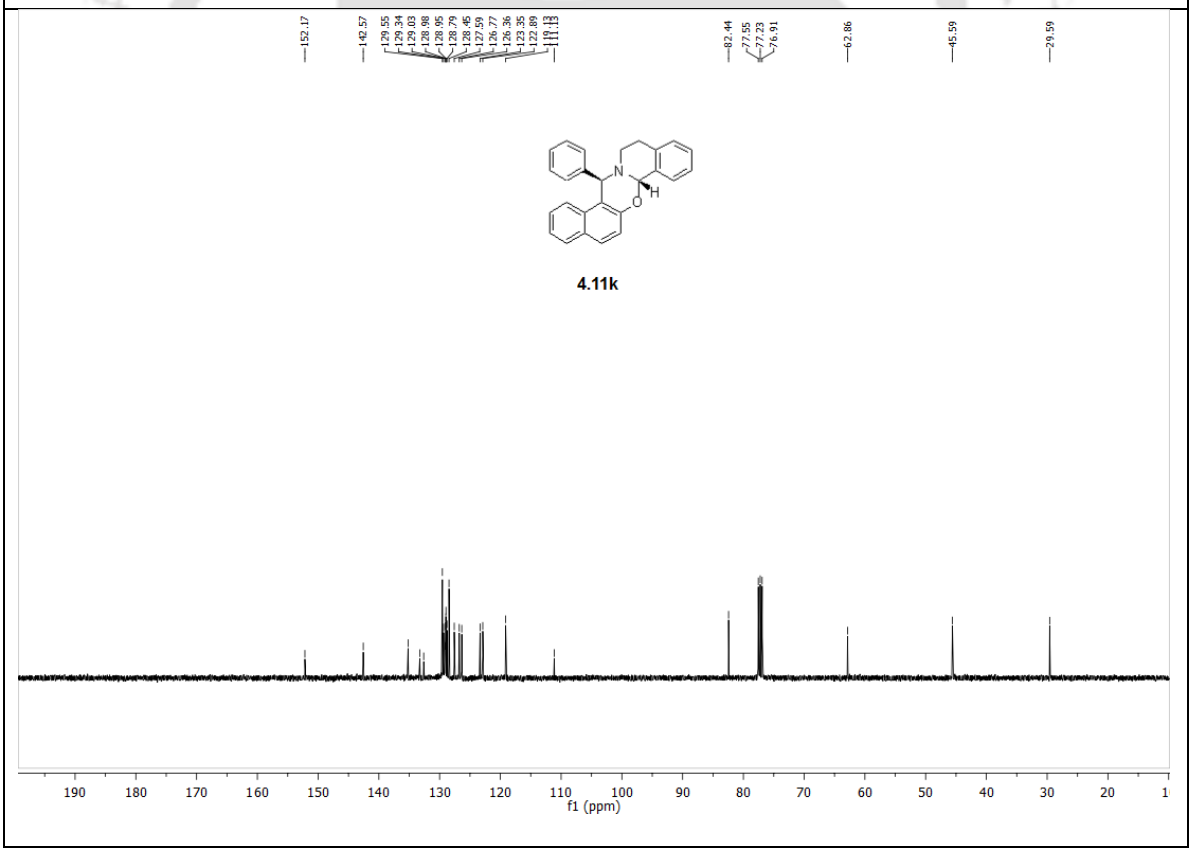

142.33
128.54
125.98
59.00
38.32
33.94
3.91aa
f1 (ppm)

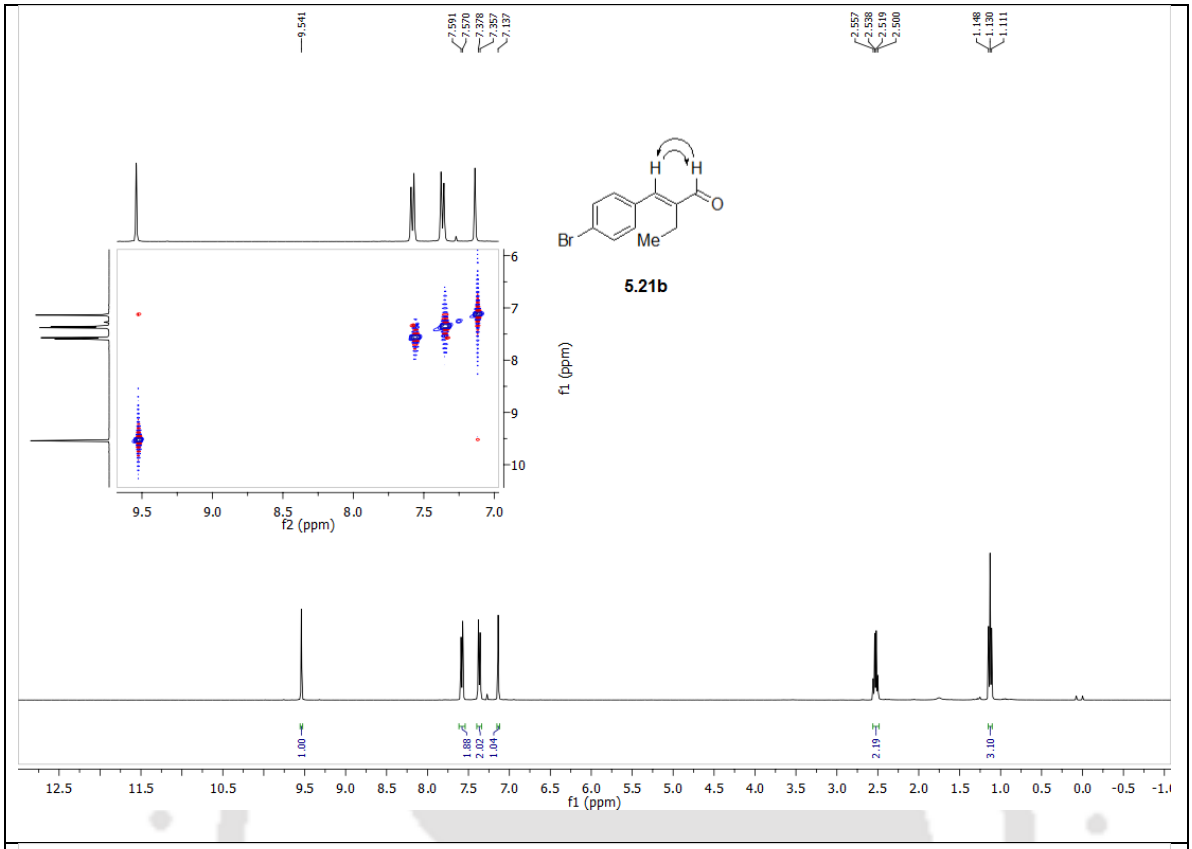

3.91bb
nor-lobelane
f1 (ppm)
3.91bb
nor-lobelane
f1 (ppm)

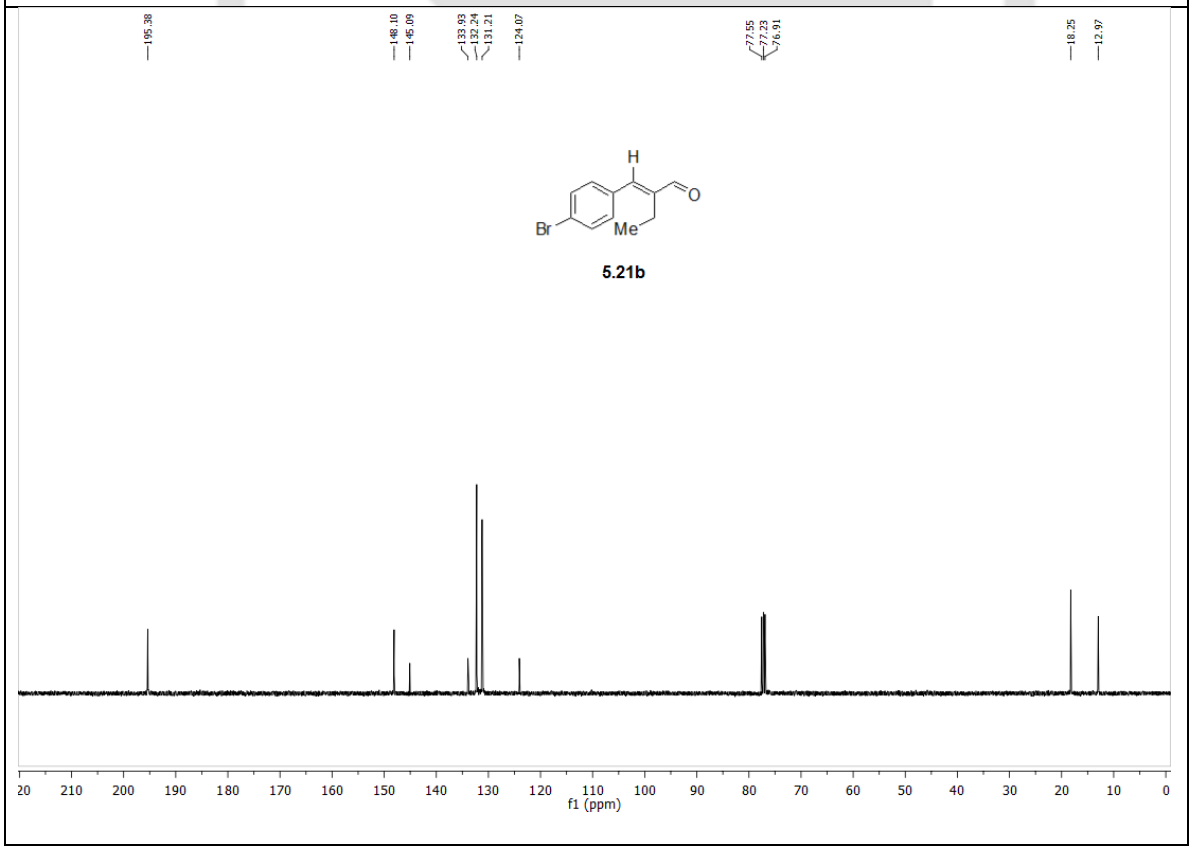

7.30
7.29
7.28
7.27
7.26
7.25
7.20
7.19
7.17
2.87
2.85
2.83
2.81
2.79
2.75
2.74
2.73
2.72
2.71
2.70
2.69
2.67
2.66
2.64
2.63
2.62
2.61
2.60
2.59
2.58
2.57
2.55
1.85
1.85
1.79
1.78
1.77
1.76
1.75
1.74
1.73
1.72
1.71
1.70
1.69
1.68
1.67
1.66
1.64
1.62
1.60
1.57
1.56
1.55
1.54
3.91cc
5.04
5.50
1.11
3.24
1.94
1.09
10.59
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)

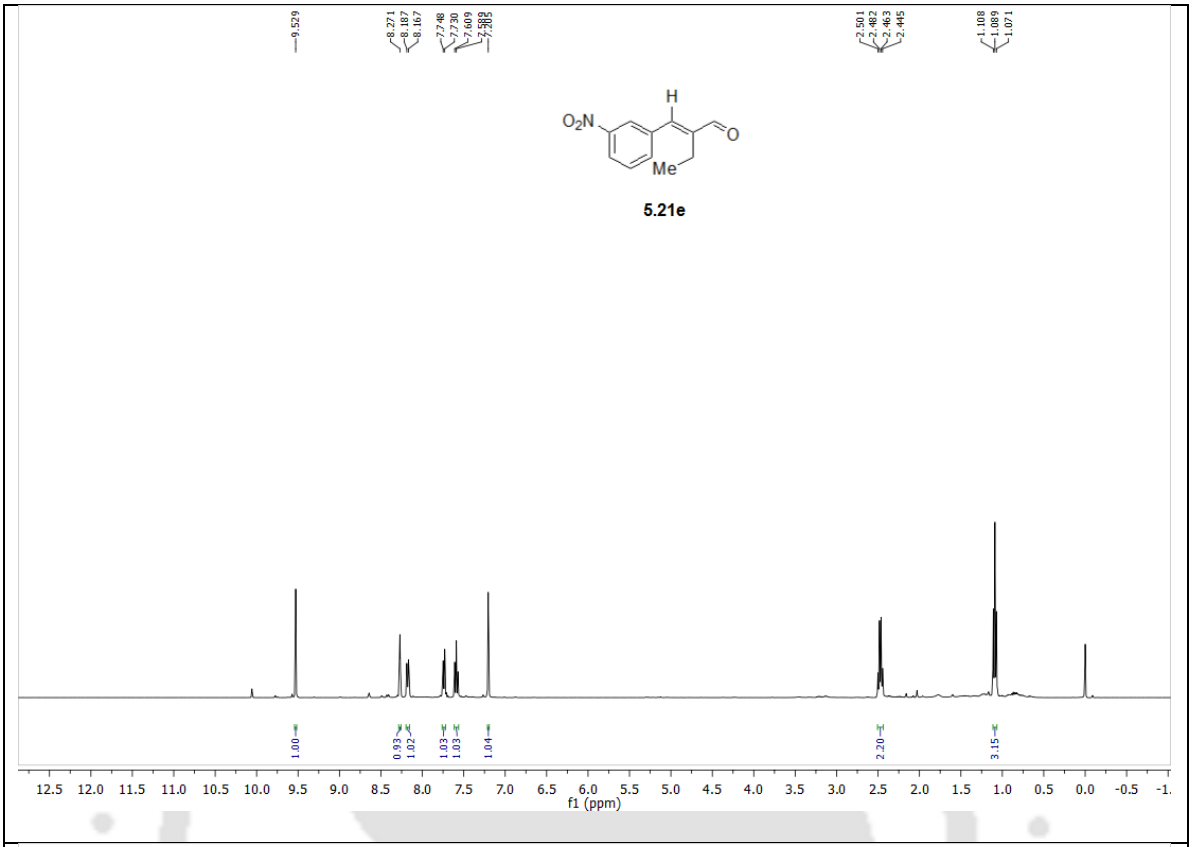

142.47
128.58
125.97
58.84
39.88
37.38
33.34
25.53
3.91cc
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

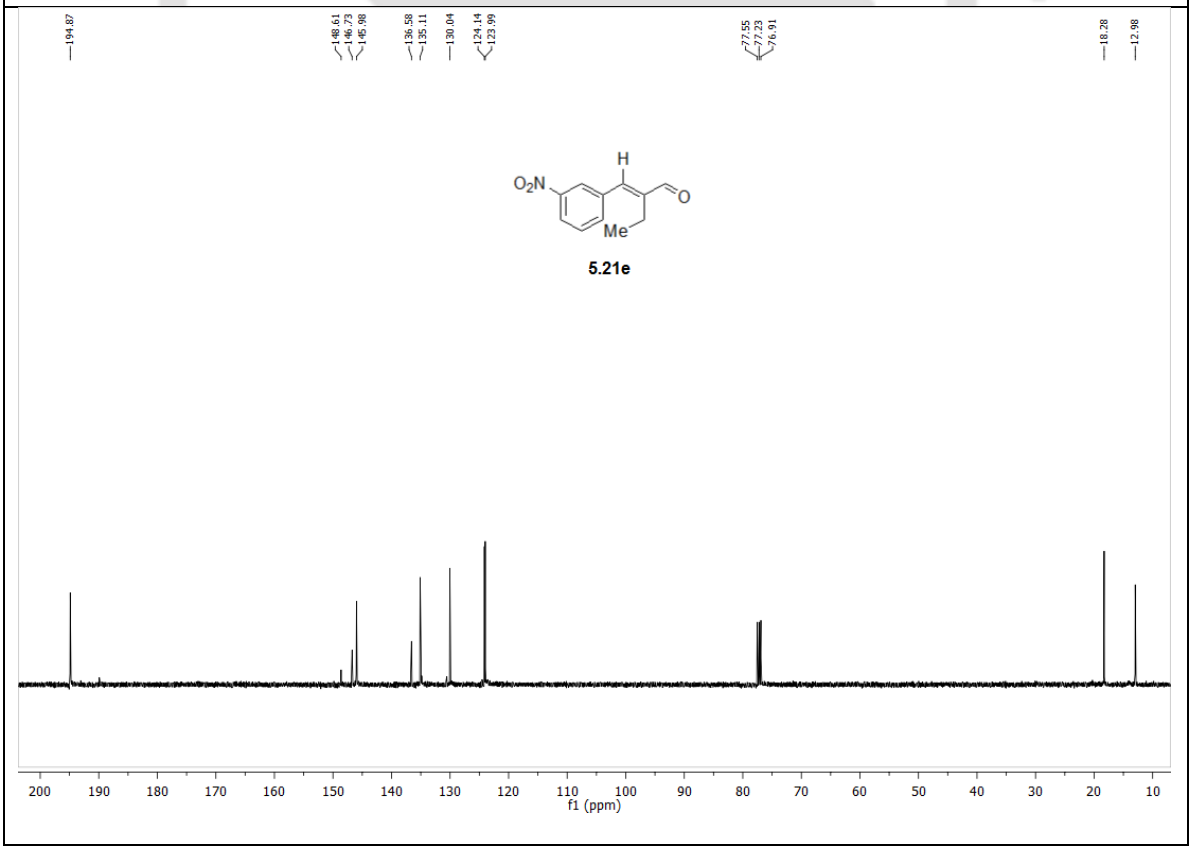

4.11k
f1 (ppm)

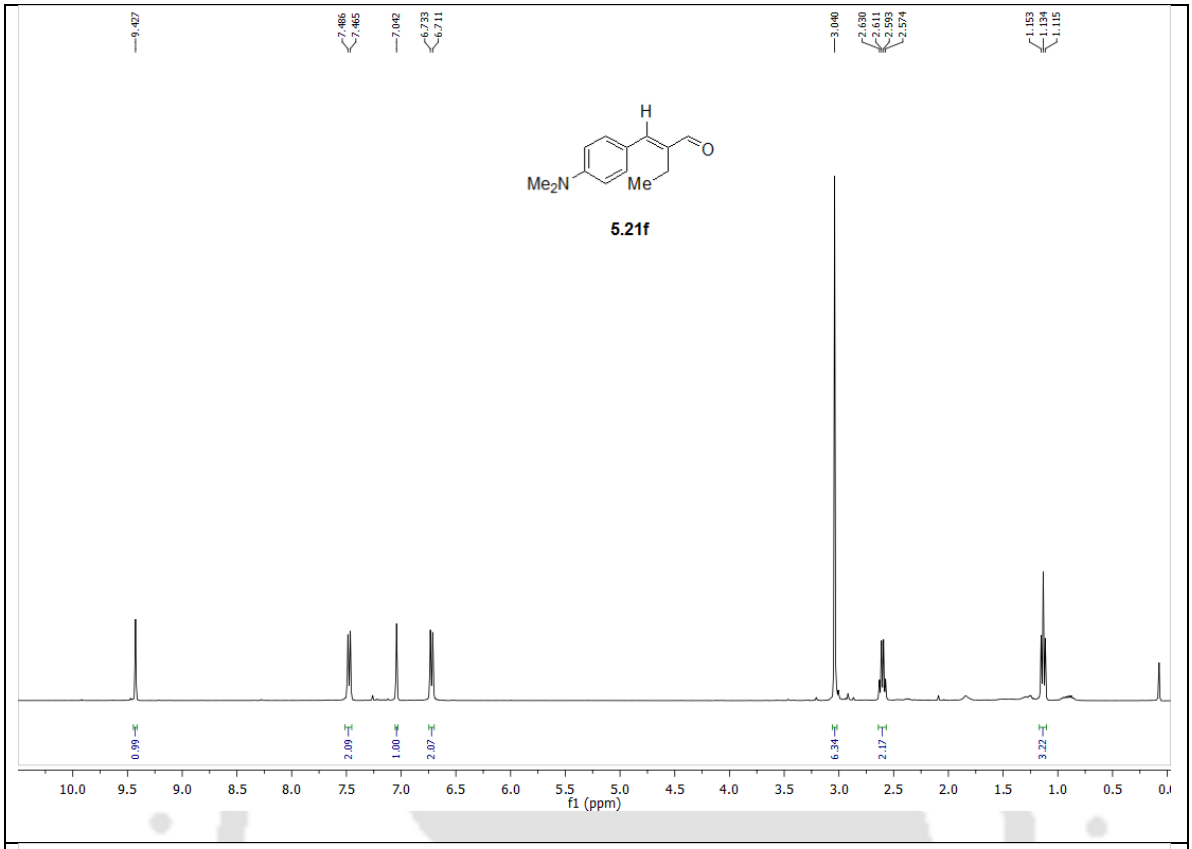

4.11k
f1 (ppm)

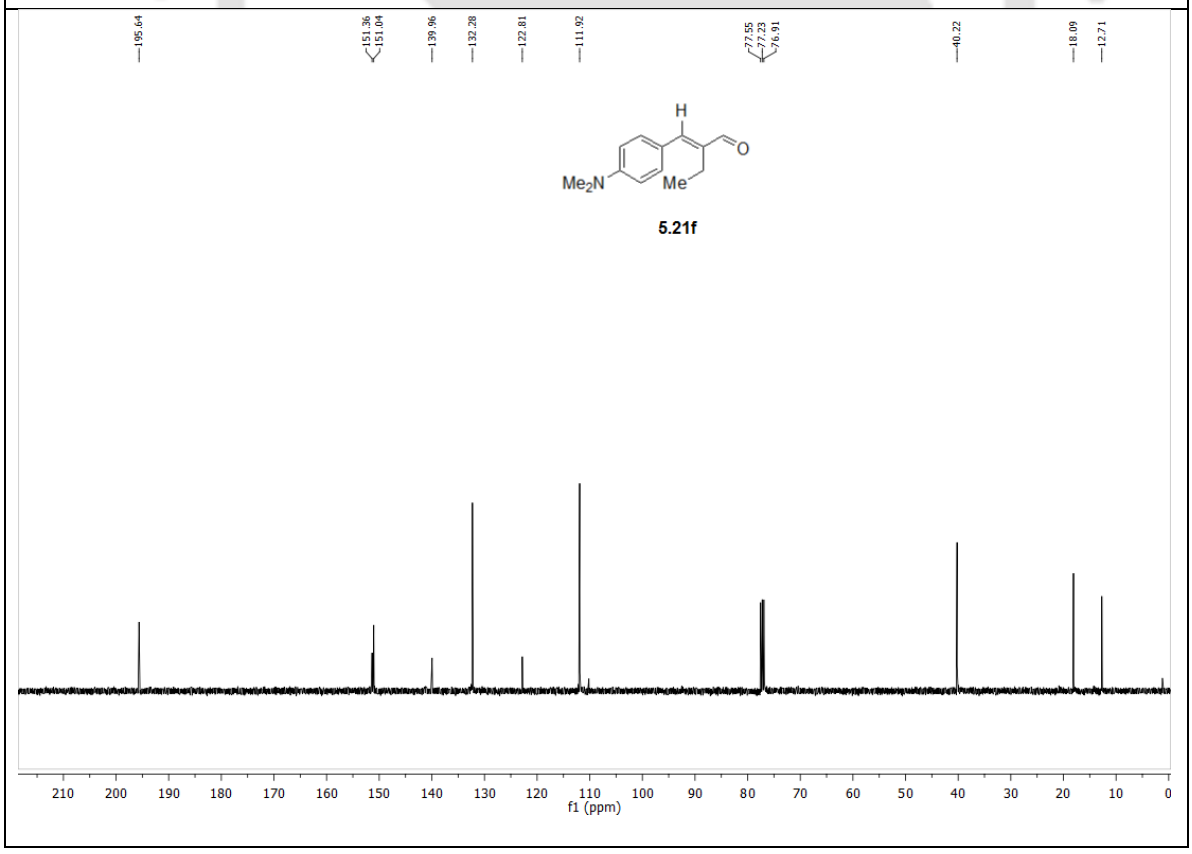

9.541
7.591
7.570
7.378
7.357
7.137
2.557
2.538
2.519
2.500
1.148
1.130
1.111
H
H
O
Br
Me
5.21b
f1 (ppm)
f2 (ppm)
1.00
1.88
2.02
1.04
2.19
3.10
f1 (ppm)

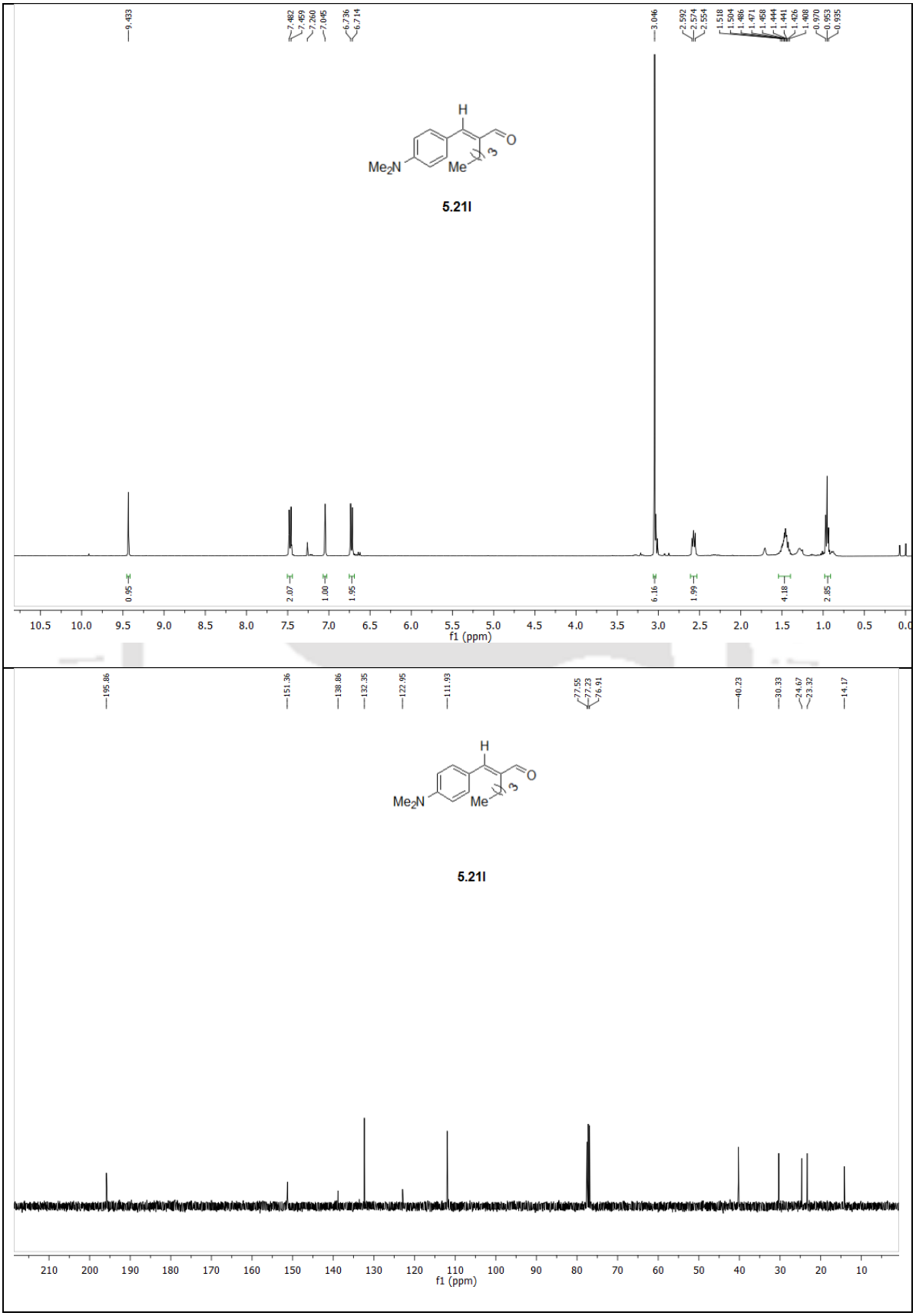

195.38
148.10
145.09
133.93
132.24
131.21
124.07
77.55
77.23
76.91
18.25
12.97
H
O
Br
Me
5.21b
f1 (ppm)

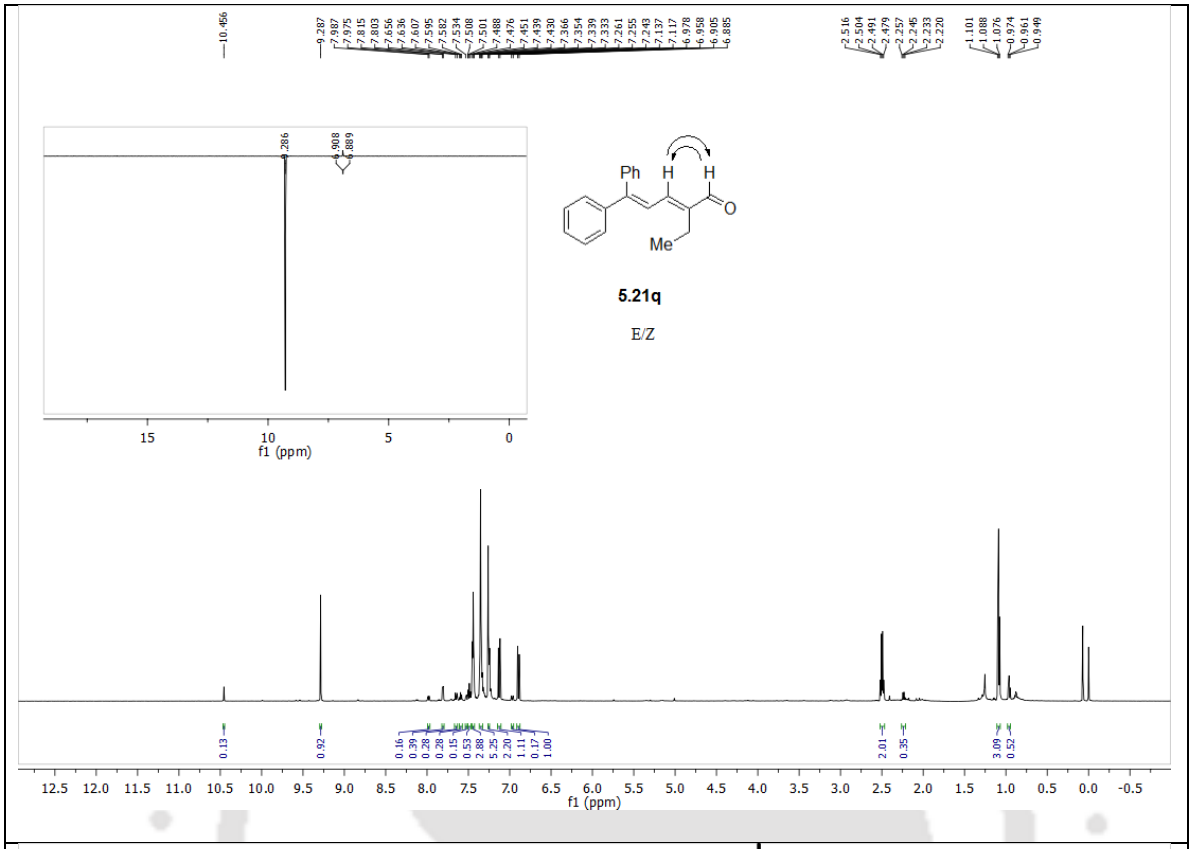

9.529
8.271
8.187
8.167
7.748
7.730
7.609
7.588
7.565
2.501
2.482
2.463
2.445
1.108
1.089
1.071
H
O2N
O
Me
5.21e
1.00
0.93
1.02
1.03
1.03
1.04
2.20
3.15
f1 (ppm)

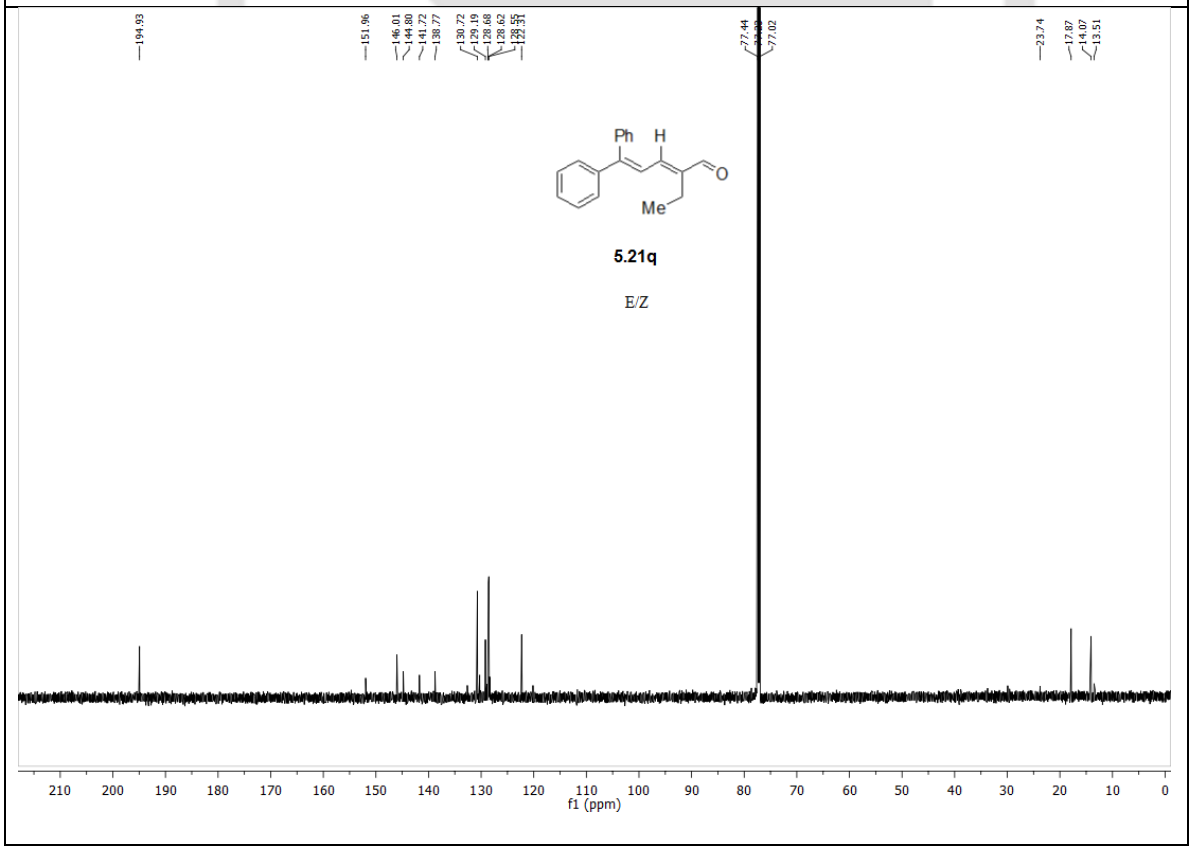

194.87
148.61
146.73
145.98
136.58
135.11
130.04
124.14
123.99
77.55
77.23
76.91
18.28
12.98
H
O2N
O
Me
5.21e
f1 (ppm)

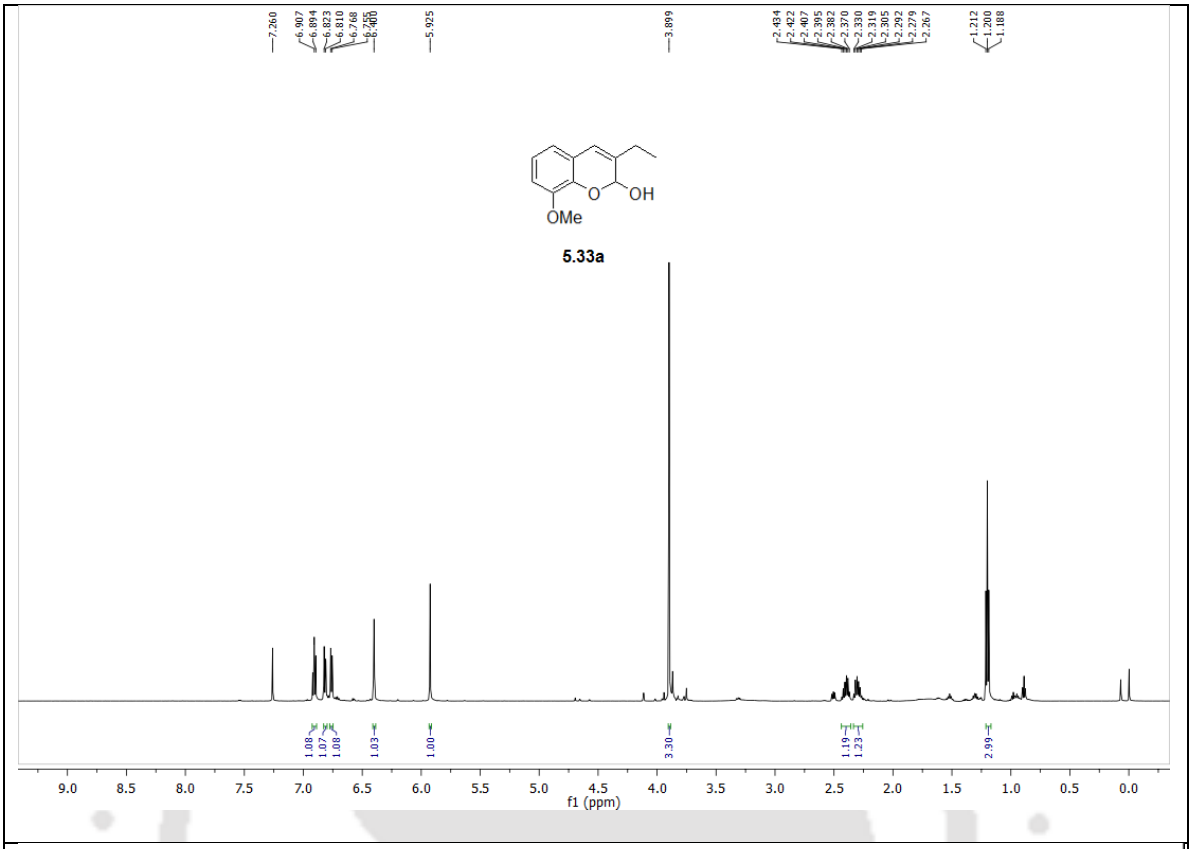

9.427
7.486
7.465
7.042
6.733
6.711
3.040
2.630
2.611
2.593
2.574
1.153
1.134
1.115
H
O
Me2N
Me
5.21f
0.99
2.09
1.00
2.07
6.34
2.17
3.22
f1 (ppm)

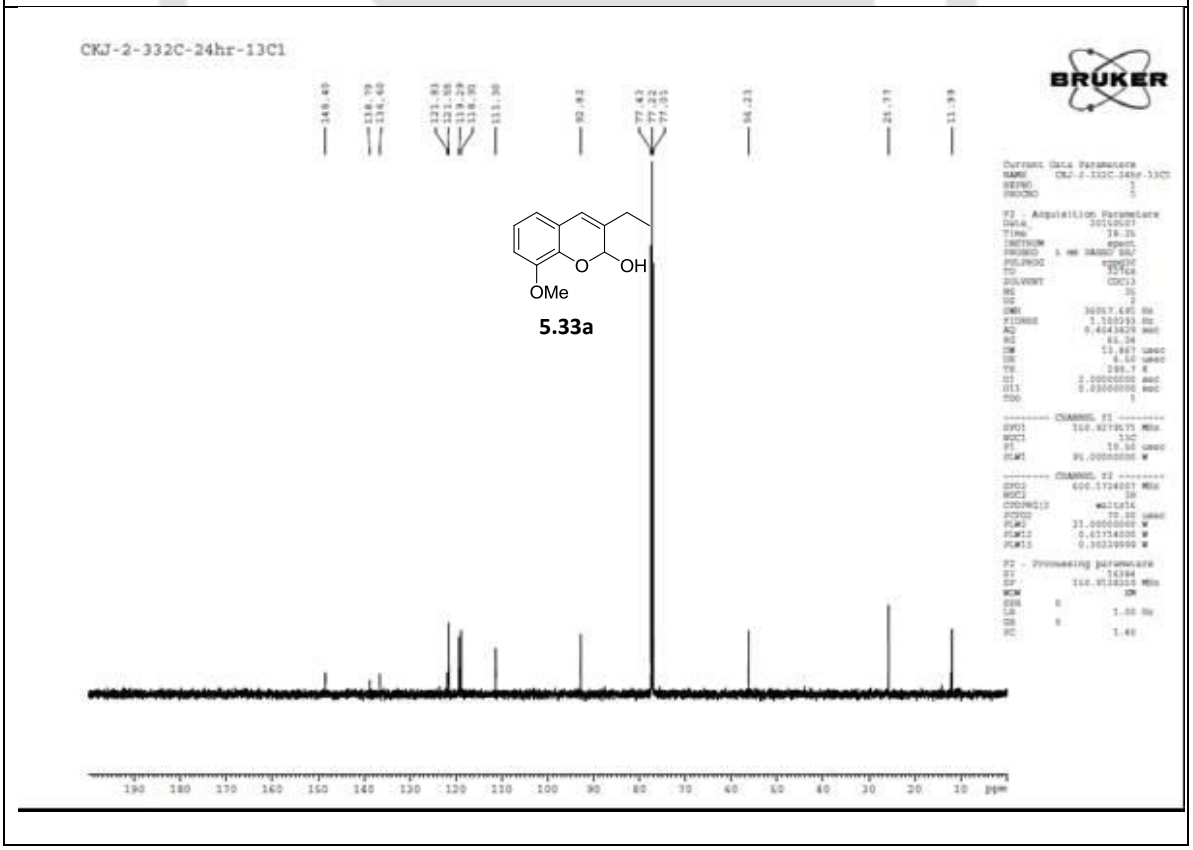

195.64
151.36
151.04
139.96
132.28
122.81
111.92
77.55
77.23
76.91
40.22
18.09
12.71
H
O
Me2N
Me
5.21f
f1 (ppm)

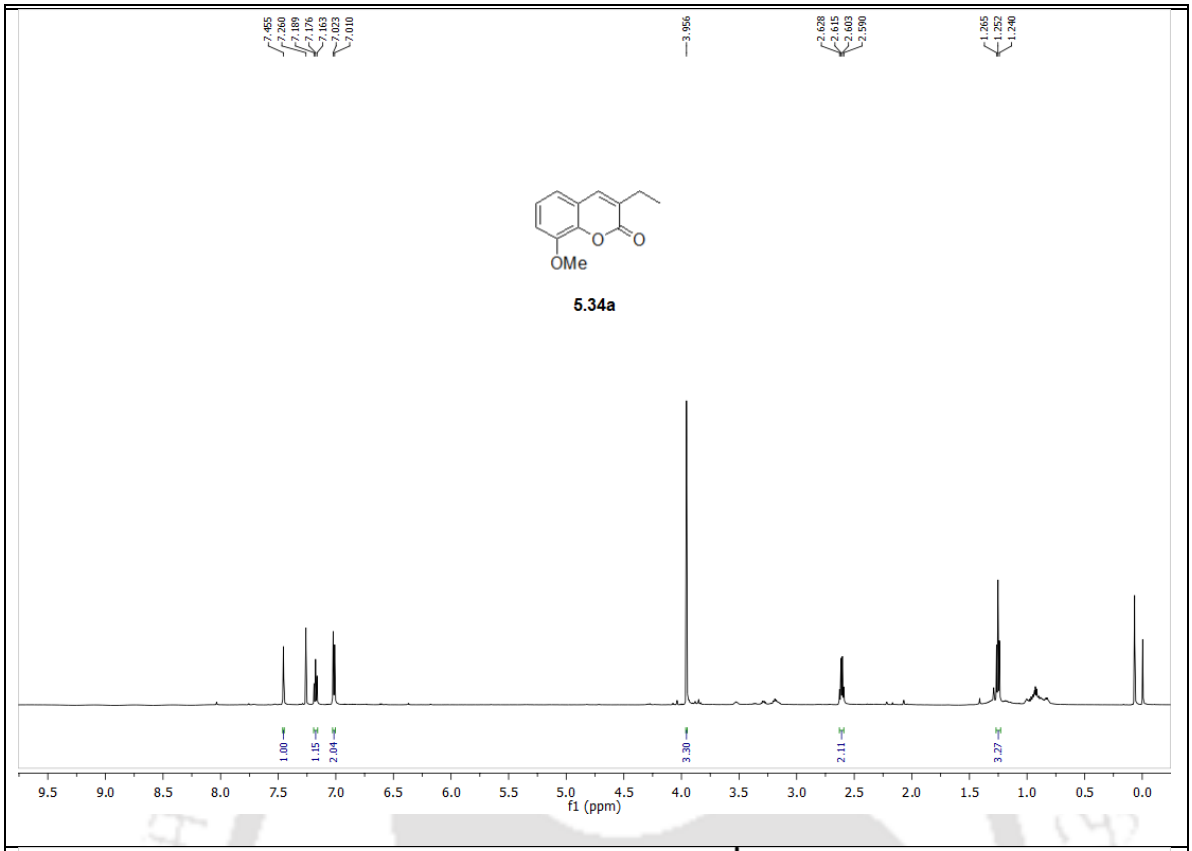

9.483
7.482
7.469
7.260
7.045
6.736
6.714
3.046
2.592
2.574
2.554
1.518
1.504
1.486
1.471
1.458
1.444
1.441
1.426
1.408
0.970
0.953
0.935
H
O
3
Me2N
Me
5.21l
0.95
2.07
1.00
1.95
6.16
1.99
4.18
2.85
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)
195.86
151.36
138.86
132.35
122.95
111.93
77.55
77.23
76.91
40.23
30.33
24.67
23.32
14.17
H
O
3
Me2N
Me
5.21l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

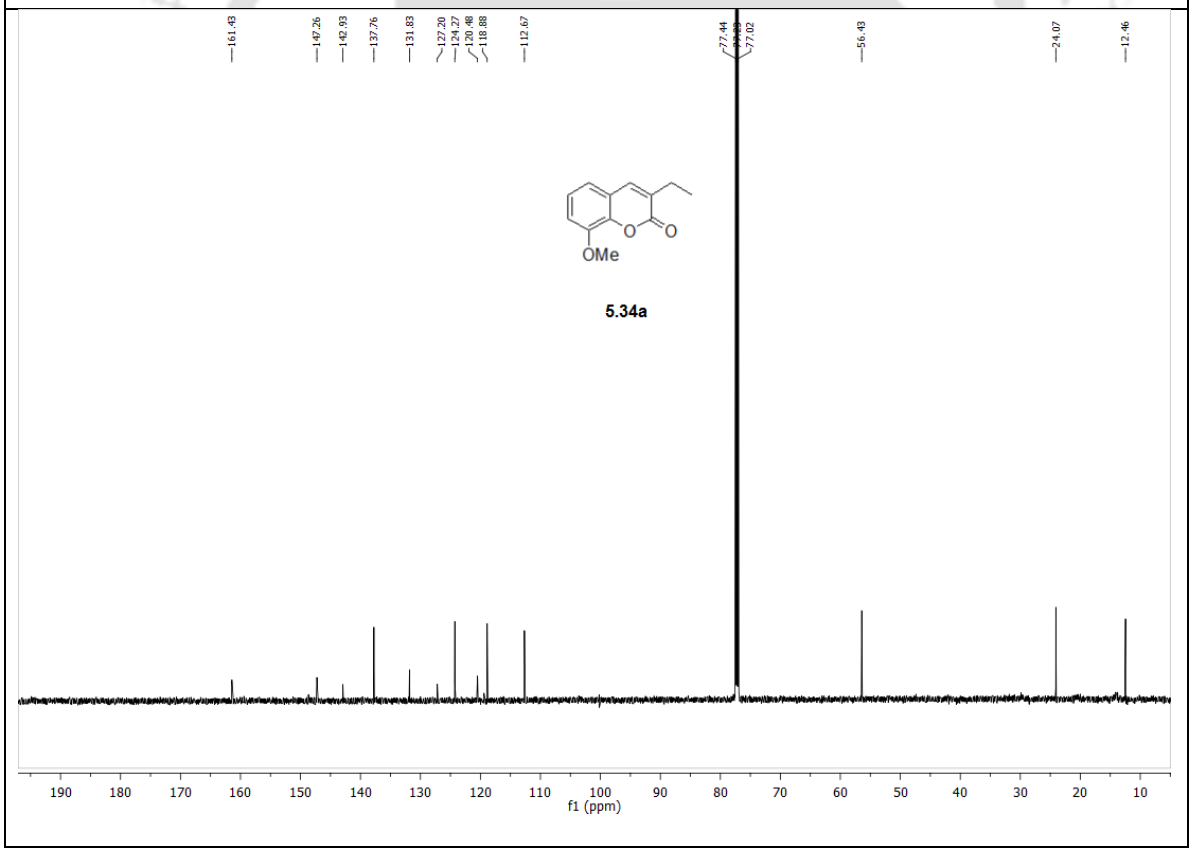

Ph
H
H
O
Me
5.21q
E/Z
f1 (ppm)

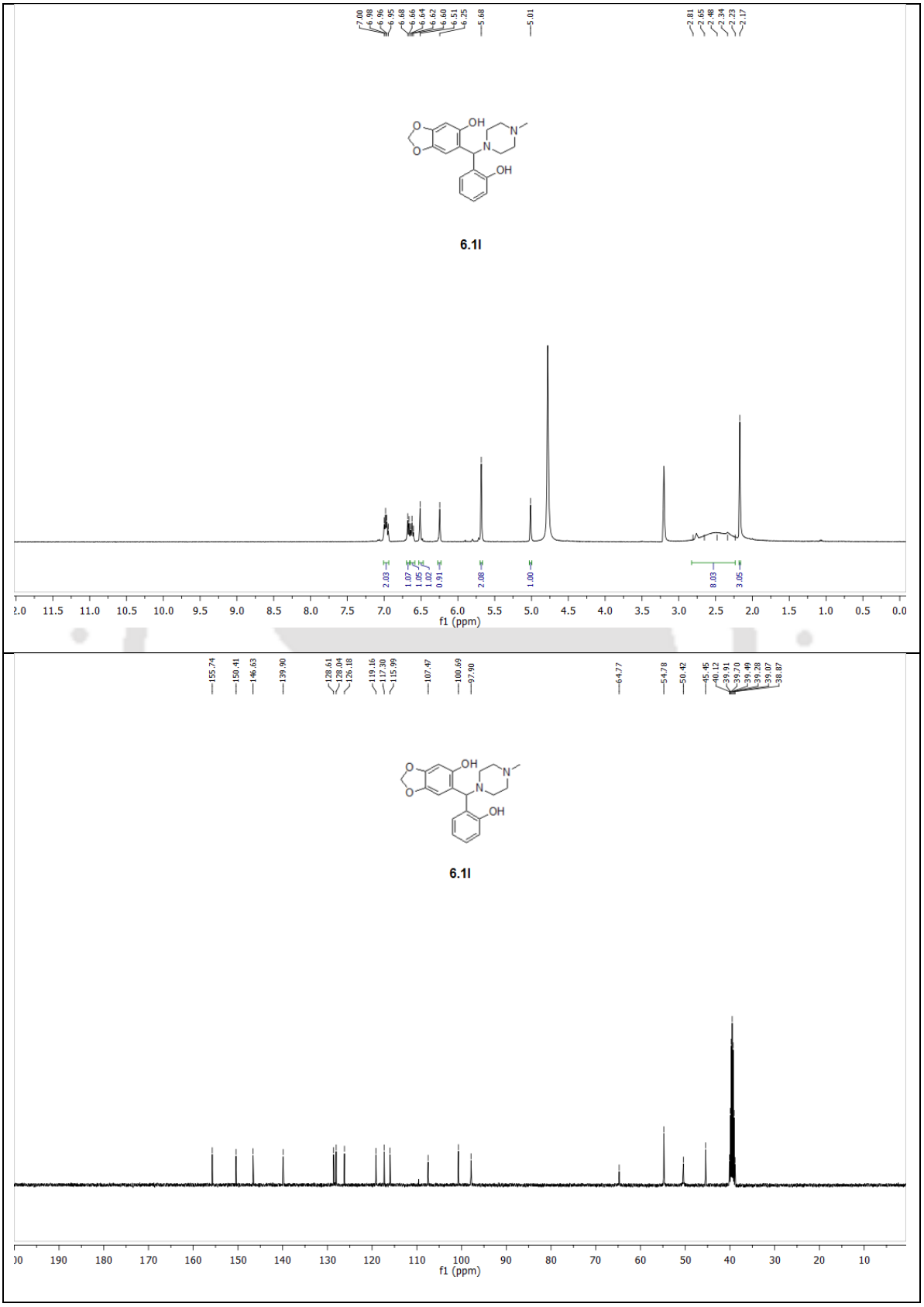

Ph
H
O
Me
5.21q
E/Z
f1 (ppm)

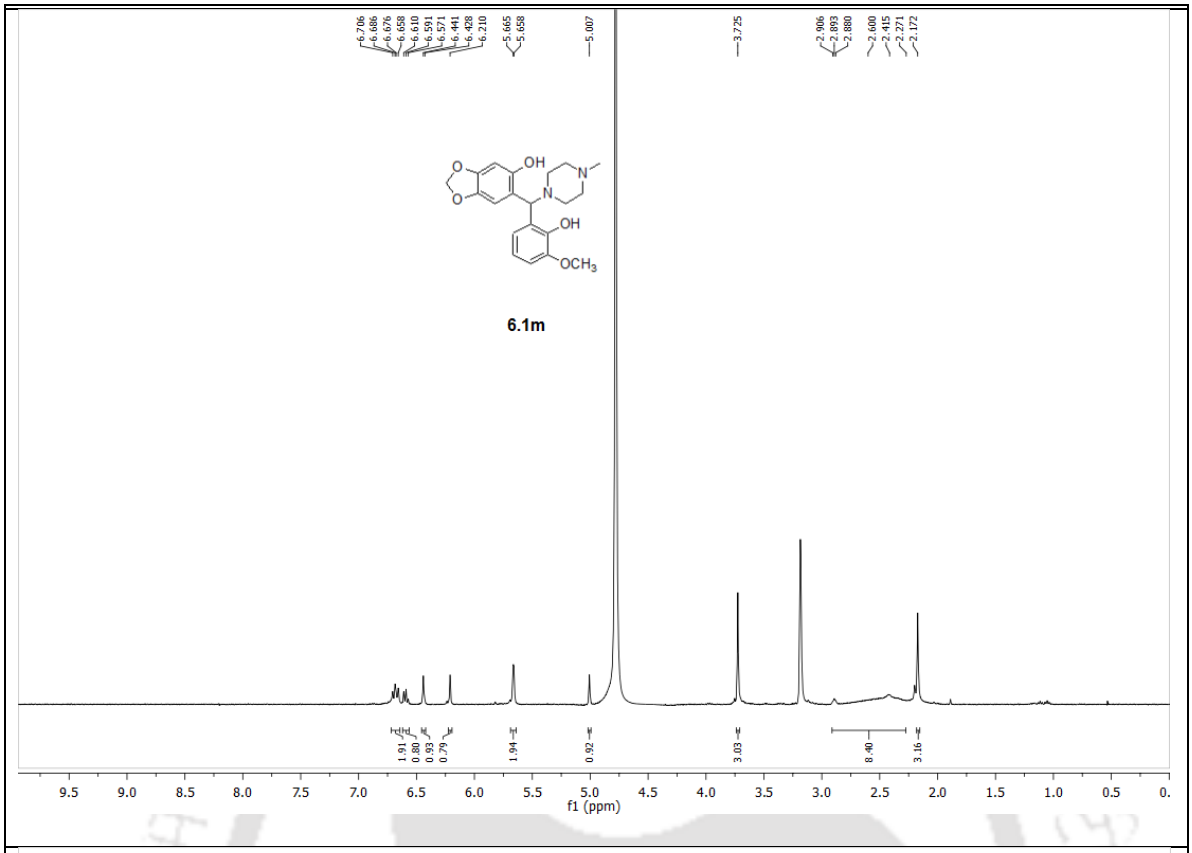

7.260
6.907
6.894
6.823
6.810
6.768
6.765
6.760
5.925
3.899
2.434
2.422
2.407
2.395
2.382
2.370
2.330
2.319
2.305
2.292
2.279
2.267
1.212
1.200
1.188
OH
OMe
5.33a
1.08
1.07
1.08
1.03
1.00
3.30
1.19
1.23
2.99
f1 (ppm)

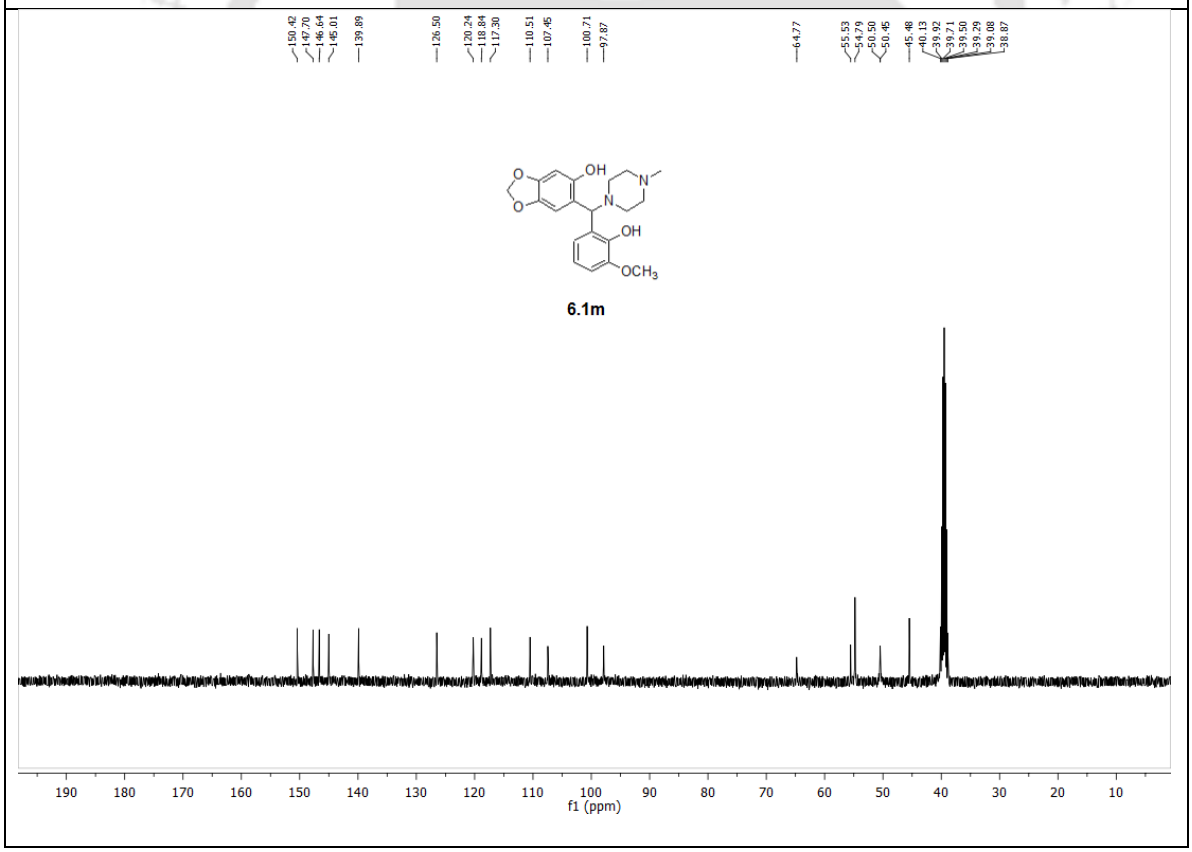

CKJ-2-332C-24hr-13C1
BRUKER
OH
OMe
5.33a
ppm


7.455
7.260
7.189
7.176
7.163
7.023
7.010
3.956
2.628
2.615
2.603
2.590
1.265
1.252
1.240
OMe
5.34a
1.00
1.15
2.04
3.30
2.11
3.27
f1 (ppm)


161.43
147.26
142.93
137.76
131.83
127.20
124.27
120.48
118.88
112.67
77.44
77.02
56.43
24.07
12.46
OMe
5.34a
f1 (ppm)


7.00
6.98
6.96
6.95
6.68
6.66
6.64
6.62
6.60
6.51
6.25
5.68
5.01
2.81
2.65
2.48
2.34
2.23
2.17
OH
N
O
O
OH
6.1l
2.03
1.07
1.05
1.02
0.91
2.08
1.00
8.03
3.05
f1 (ppm)
155.74
150.41
146.63
139.90
128.61
128.04
126.18
119.16
117.30
115.99
107.47
100.69
97.90
64.77
54.78
50.42
45.45
40.12
39.91
39.70
39.49
39.28
39.07
38.87
OH
N
O
O
OH
6.1l
f1 (ppm)


6.706
6.686
6.676
6.658
6.610
6.591
6.571
6.441
6.428
6.210
5.665
5.658
5.007
3.725
2.906
2.893
2.880
2.600
2.415
2.271
2.172
OH
OH
OCH3
6.1m
1.91
0.80
0.93
0.79
1.94
0.92
3.03
8.40
3.16
f1 (ppm)


150.42
147.70
146.64
145.01
139.89
126.50
120.24
118.84
117.30
110.51
107.45
100.71
97.87
64.77
55.53
54.79
50.50
50.45
45.48
40.13
39.92
39.71
39.50
39.29
39.08
38.87
OH
OH
OCH3
6.1m
f1 (ppm)