

University of Wisconsin Milwaukee

UWM Digital Commons

Theses and Dissertations

May 2021

Chapter 1: Part A: A Unique Approach of Preparing 3,3-Disubstituted Oxindoles from Acyclic Tetrasubstituted Aldehydes: Total Synthesis of (-)-Coerulescine and (-)-Coixspirolactam A, Chapter 1: Part B: Synthetic Scope of Brønsted Acid Catalyzed Reactions of Carbonyl Compounds and Ethyl Diazoacetate,

Md Shahnawaz Ali

University of Wisconsin-Milwaukee

Follow this and additional works at: <https://dc.uwm.edu/etd>

 Part of the [Organic Chemistry Commons](#)

Recommended Citation

Ali, Md Shahnawaz, "Chapter 1: Part A: A Unique Approach of Preparing 3,3-Disubstituted Oxindoles from Acyclic Tetrasubstituted Aldehydes: Total Synthesis of (-)-Coerulescine and (-)-Coixspirolactam A, Chapter 1: Part B: Synthetic Scope of Brønsted Acid Catalyzed Reactions of Carbonyl Compounds and Ethyl Diazoacetate," (2021). *Theses and Dissertations*. 2638.
<https://dc.uwm.edu/etd/2638>

This Dissertation is brought to you for free and open access by UWM Digital Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of UWM Digital Commons. For more information, please contact scholarlycommunicationteam-group@uwm.edu.

**CHAPTER 1: PART 1: A UNIQUE APPROACH OF PREPARING 3,3-DISUBSTITUTED
OXINDOLES FROM ACYCLIC TETRASUBSTITUTED ALDEHYDES: TOTAL SYNTHESIS
OF (-)-COERULESCINE AND (-)-COIXSPIROLACTAM A**

**CHAPTER 1: PART 2: SYNTHETIC SCOPE OF BRØNSTED ACID CATALYZED
REACTIONS OF CARBONYL COMPOUNDS AND ETHYL DIAZOACETATE**

**CHAPTER 2: INVESTIGATION OF THE C2-ALKYLATION OF 1-(1H-INDOL-3-YL)-N,N-
DIMETHYLMETHANAMINE**

by

Md Shahnawaz Ali

A Dissertation Submitted in
Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy
in Chemistry

at

The University of Wisconsin-Milwaukee

May 2021

ABSTRACT

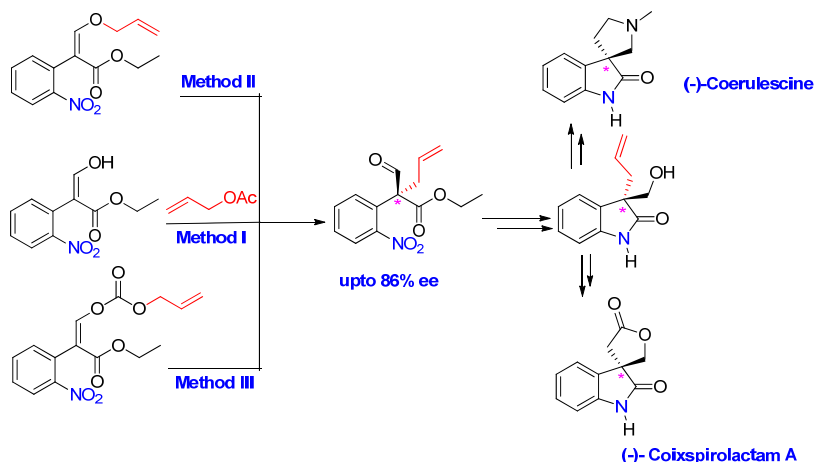
CHAPTER 1: PART A: A UNIQUE APPROACH OF PREPARING 3,3-DISUBSTITUTED OXINDOLES FROM ACYCLIC TETRASUBSTITUTED ALDEHYDES: TOTAL SYNTHESIS OF (-)-COERULESCINE AND (-)-COIXSPIROLACTAM A

by

Md Shahnawaz Ali

The University of Wisconsin-Milwaukee, 2021
Under the Supervision of Professor M. Mahmun Hossain

(-)-Coerulescine and (-)-coixspirolactam A, two naturally occurring compounds characterized with an all-carbon quaternary center containing a spirooxindole, have been synthesized asymmetrically. The key feature of their total synthesis involves



a novel rational construction of the chiral 3,3-disubstituted oxindole core from the acyclic chiral tetrasubstituted aldehyde. The later scaffold was prepared in high enantioselectivity (up to 86%) from the ethyl 3-hydroxy-2-(2-nitrophenyl)acrylate **1** by exploring both intermolecular and intramolecular Pd-mediated asymmetric

allylic allylations (Pd-AAA). A through optimization of these approaches is described in this thesis.

CHAPTER 1: PART B: SYNTHETIC SCOPE OF BRØNSTED ACID CATALYZED REACTIONS OF CARBONYL COMPOUNDS AND ETHYL DIAZOACETATE

The comprehensive study of the reactions of carbonyl compounds and ethyl diazoacetate in the presence of a Brønsted acid catalyst is described. In this, a broad range of 3-oxo esters were synthesized from a variety of ketones, specifically benzophenones and aliphatic ketones. For the diaryl ketones, we have characterized two inseparable products of migration by two-dimensional nuclear magnetic resonance spectroscopy (2D-NMR) and calculated the ratio of their relative migratory tendencies. However, the symmetric and nonsymmetrical aliphatic ketones provided the higher migration for relatively longer alkyl chains length. In case of the aliphatic aldehydes, we got exclusively the expected β -keto ester by a 1,2- hydride shift.

CHAPTER 2: INVESTIGATION OF THE C2-ALKYLATION OF 1-(1H-INDOL-3-YL)-N,N-DIMETHYLMETHANAMINE

Indole derivatives can be conveniently alkylated at the C2 position by choosing appropriate N-protecting group and appropriate base. However, 1-(1*H*-indol-3-yl)-

N,N-dimethylmethanamine (commercially named as gramine) is also limited to that restricted choice of a protecting group for such alkylation. Herein we explore a the lithiation of gramine with different protecting groups (such as Ms, Ts, Me, TIPS etc.) on the N-heteroatom and investigate the alkylation at the C-2 position by trapping the C-2 lithio species with a variety of electrophiles such as methyl iodide, benzyl bromide, prenyl bromide, allyl bromide, etc.

© Copyright by Md Shahnawaz Ali, 2021
All Rights Reserved

**To
my parents
my wife
and especially my son**

TABLES OF CONTENTS

	Page No
ABSTRACT	ii
TABLE OF CONTENTS	vii
LIST OF TABLES	xi
LIST OF SCHEMES	xii
LIST OF FIGURES	xvii
ACKNOWLEDGEMENTS	xix

CHAPTER 1: A UNIQUE APPROACH OF PREPARING 3,3-DISUBSTITUTED OXINDOLES FROM ACYCLIC TETRASUBSTITUTED ALDEHYDES USING Pd-AAA: TOTAL SYNTHESIS OF (-)-COERULESCINE AND (-)-COIXSPIROLACTAM A (PART- A)

1.1	Part 1: Introduction	1
1.1.1	Importance of 3,3-disubstituted oxindoles and their asymmetric synthesis	1
1.1.2	Useful synthesis of natural and bioactive compounds containing the 3,3-disubstituted oxindole	3
2.1	Strategies for the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles	5
2.1.1	Intramolecular Heck Coupling/modified coupling	7
2.1.2	Direct functionalization	10
2.1.2.1	Organocatalytic functionalization of C3-H	12
2.1.2.2	Halogenation	14
2.1.2.2.a	Fluorination	14
2.1.2.2.b	Chlorination	16
2.1.2.3	Sulfenylation	18
2.1.2.4	Hydroxylation	20
2.1.3	Nucleophilic addition to the Isatin moiety	22
2.1.4	Other approaches	26
2.1.4.1	1,4-Michael addition	26
2.1.4.2	Metal carbenoid assisted C-C bond formation	28
2.1.4.3	Asymmetric Strecker reaction	30
2.1.4.5	Desymmetrization of diyne	32

3.1	Part 2: Introduction (Pd-AAA)	33
3.1.1	General mechanism of regio and stereospecific Pd-catalyzed asymmetric allylation	35
3.1.2	General consideration for optimizing reaction procedure for Pd-AAA	38
3.1.3	Approaches involved in stereocontrol interactions of Pd-AAA	40
3.1.3.1	Stereo control on prochiral electrophiles	41
3.1.3.2	Stereo control on prochiral nucleophiles in Pd-AAA	46
3.1.3.2.1	Intermolecular alkylation of prochiral nucleophiles	49
3.1.3.2.2	Intramolecular alkylation of prochiral nucleophiles	56
3.1.3.2.2. A	Pd-Catalyzed decarboxylative asymmetric allylic alkylation (Pd-DAAA)	56
3.1.3.2.2. B	Asymmetric Claisen rearrangement as a route to quaternary stereocenter	64
3.1.4	Other approaches	69
4.1	Part 3: Introduction to Spirooxindole pyrrolidine	70
4.1.1	Synthesis of (-)-Coerulescine: (by Denishefsky et al)	72
4.1.2	Synthesis of (-)-Coerulescine: (by Hayashi et al)	73
4.1.3	Synthesis of (-)-Coerulescine: (by Hayashi et al)	75
4.1.4	Synthesis of (-)-Coerulescine: (by Park et al)	77
4.2.1	Part 4: Introduction to Spirooxindole lactone	79
4.2.2	Different approaches for the synthesis of spirooxindole lactone	80
4.2.3	Previous synthesis Coixspirolactam A	83
1.2	Results and Discussion	85
1.2.1	Optimization study of intermolecular Pd -AAA of prochiral 2-nitro-3-hydroxy phenyl acrylate	85
1.2.2	Optimization study of intramolecular Pd mediated decarboxylative asymmetric allylation (Pd-DAAA)	101
1.2.3	Optimization study of intramolecular Pd- mediated Claisen rearrangement	105
1.2.4	Optimization of synthetic steps involving chiral 3,3-disubstituted oxindole	109
1.3	General methods and experimental	119
1.3.1	General procedure for the intermolecular asymmetric allylation	120
1.3.2	General procedure for the O-allylation of prochiral enol acrylate	122
1.3.3	General procedure for the Pd-mediated rearrangement of O-allylated enol acrylate	124
1.3.4	General procedure for the O-allylation of prochiral enol acrylate	125
1.3.5	General procedure for the Pd-mediated rearrangement of O-carboxy allylated enol acrylate	127

CHAPTER 1: SYNTHETIC SCOPE OF BRØNSTED ACID CATALYZED REACTIONS OF CARBONYL COMPOUNDS AND ETHYL DIAZOACETATE (PART- B)

5.1	Introduction	160
5.1.1	Synthetic approaches for the preparation of 3-hydroxy aryl acrylates	161
5.1.1.1	Iron Lewis acid catalyzed reactions	161
5.1.1.2	Bronsted acid catalyzed reactions	164
5.1.1.3	Organic base catalysed reaction	166
5.2	Application of hydroxy acrylates from the present synthetic point of view	167
5.2.1	Synthesis of 2-and 4-quinolinone derivatives	167
5.2.2	Synthesis of pyrimidine/pyrimidinone type compounds	168
5.2.3	Synthesis of uracil type compounds	169
5.2.4	Synthesis of Vinyl derivatives	170
5.2.5	Synthesis of chromenone crown ether	171
5.3	Results and discussion	173
5.3.1	Development of benzophenone derived acrylates	173
5.3.2	Development of aliphatic carbonyl derived acrylates	178
5.4	General methods and experimental	180
5.4.1	General Procedure for the one-pot synthesis of 3-oxo-esters	183
5.5	References	188

CHAPTER 1: EXPLORING 18-CROWN-6-ETHER COMPLEX AS A BRONSTED ACID CATALYST (PART- C)

6.1	Introduction	197
6.2	Results and Discussion	200
6.3	General procedure for the synthesis of 3-hydroxy arylacrylates	203
6.4	References	204

CHAPTER 2: INVESTIGATION OF C2-ALKYLATION OF N-PROTECTED GRAMINE

7.1	Introduction	206
7.1.1	Concepts on the C2-alkylation of Indole/ phenothiazine/N-carboxy protected indole	207
7.1.2	Precedence for C2-alkylation of BOC-protected gramine	210
7.2	Results and discussion	211
7.3	General methods and experimental	216
7.3.1	General procedure for the N-protection of gramine	216
7.3.2	General procedure for preparing N-protected 1H-indole-3-carbaldehyde	219

7.3.3	General procedure for the reductive amination of N-protected 1H-indole-3-carbaldehyde	221
7.3.4	General procedure for C2 alkylation of gramine	222
7.4	References	226
	APPENDICES	229
	Appendix A: HPLC, HRMS and NMR data	229
	Curriculum vitae	352

LIST OF TABLES

Entry	Title of the table	Page No
Table 1	Solvent optimization studies for the Pd-AAA reaction on 3-hydroxy-2-nitro phenyl acrylate 1	88
Table 2	Optimization of ligands for intermolecular Pd-AAA reaction of compound 1	91
Table 3	Optimization of catalyst, ligand, and their loading for the intermolecular Pd-AAA reaction of compound 1	93
Table 4	Optimization of solvents with bases for the intermolecular Pd-AAA reaction of 1	94
Table 5	Optimization of additives for the intermolecular Pd-AAA reaction of compound 1	96
Table 6	Screening additives for intermolecular Pd-AAA reaction of 1 in different solvents	97
Table 7	Screening electrophile for intermolecular Pd-AAA reaction of 1	99
Table 8	Optimization studies for Pd-DAAA of O-carboxy alkylated Product 10	102
Table 9	Optimization studies for Claisen rearrangement of O-alkylated product 9	106
Table 11	Optimization reaction conditions for the oxidation of oxindole 4	112
Table 12	Optimization for the oxidation of Ms-protected oxindole 5	114
Table 13	Optimization of one-pot reductive amination cyclization of Ms-protected oxindole aldehyde 6	115
Table 14	Optimization results of effectivity of crown-ether complex A and B on promoting coupling between EDA and carbonyl compounds	200

LIST OF SCHEMES

Scheme no		Page no
Scheme 1	Enantioselective Heck coupling of butenylanilide	7
Scheme 2	Enantioselective tandem Heck cyclization of anilide	8
Scheme 3	Intramolecular coupling using NHC and modified NHC ligand-Pd catalyst pair	8
Scheme 4	Palladium catalyzed asymmetric intramolecular arylation of α -keto amides	9
Scheme 5	Iridium-catalyzed asymmetric intramolecular direct hydroarylation of α -keto amide	9
Scheme 6	First asymmetric PTC mediated alkylation of a 3-substituted oxindole	10
Scheme 7	Chiral triazolium salt catalyzed asymmetric alkylation of oxindoles	11
Scheme 8	Organocatalytic amination of oxindole with DIAD	12
Scheme 9	Hydroamination of oxindoles with nitrosobenzene	13
Scheme 10	Organocatalyzed fluorination of oxindoles	14
Scheme 11	Proposed catalytic cycle for the catalytic asymmetric organocatalyzed fluorination of oxindoles	15
Scheme 12	Organocatalytic chlorination of oxindoles using N-chlorosuccinimide (NCS)	16
Scheme 13	Sulfenylation (trifluoromethylthiolation) of 3-substituted oxindole using Bronsted base Catalysis	18
Scheme 14	Asymmetric hydroxylation of oxindole using various phase-transfer catalyst	20
Scheme 15	Pd catalyzed asymmetric allylation for the synthesis of 3-hydroxy oxindole	22
Scheme 16	Catalytic asymmetric allylation of the Isatin derivatives with arylboronic acid	23
Scheme 17	Decarboxylative addition of β -ketoacids to the Isatin derivatives catalyzed by Ytterbium	24

Scheme 18	Allylation, crotylation and reverse prenylation of Isatin derivatives using Ir catalyst	24
Scheme 19	Diastereoconvergence for different substrates of N-protected oxindoles	26
Scheme 20	Three component cascade reaction for the enantioselective synthesis of 3,3-disubstituted oxindole	28
Scheme 21	Preliminary study of the Strecker reaction for N-aryl Isatin ketimines	30
Scheme 22	Direct cyanidation using thiourea driven Cinchona mediated alkaloid catalyst	31
Scheme 23	Asymmetric CuAAC reactions for the preparation of 3,3-disubstituted oxindole	32
Scheme 24	Formation of stereocenters by Pd-AAA reaction	34
Scheme 25	Mechanism of regio and stereospecific Pd-catalyzed asymmetric allylation	35
Scheme 26	Modes of asymmetric induction by electrophile	36
Scheme 27	Pd-AAA strategy for the synthesis of acyclic tetrasubstituted building blocks by using electrophilic isoprene monoepoxide	41
Scheme 28	Mechanism of dynamic kinetic transformation (DYKAT) of isoprene monoepoxide	42
Scheme 29	Cartoon model for wall and flap concept inducing regio and stereoselective AAA	42
Scheme 30	Mechanistic pathways for Pd-AAA of isoprene monoepoxide	43
Scheme 31	Synthesis of tertiary ether through the Pd-AAA of prochiral electrophile isoprene monoepoxide	44
Scheme 32	Catalytic recognition of prochiral nucleophile (enolates)	46
Scheme 33	Potential mechanism for the erosion of enolate stereochemistry	47
Scheme 34	Reaction example shows the enolate erosion mechanism	47
Scheme 35	Asymmetric allylation of a 1,3-diketone and an α -nitro ester by counterion recognition of a chiral phosphine ligand	49

Scheme 36	Pd/BINAP-catalyzed allylation of alpha-acetamido-beta-keto ester	50
Scheme 37	Pd Catalyzed Asymmetric Allylation of beta keto ester	51
Scheme 38	Direct alpha arylation of α -arylpropanals with allylic alcohols	52
Scheme 39	Typical features related to the triple catalytic activation	53
Scheme 40	Chiral counterion strategy for the cinnamylation of α -nitro esters	54
Scheme 41	Enantiocontrol synthesis of acyclic quaternary carbon atoms from unprotected enol and its synthetic scope	55
Scheme 42	Pd-catalyzed Carroll rearrangement by Tsuji	56
Scheme 43	Palladium-catalyzed enantioselective decarboxylative asymmetric allylic alkylation of stereodefined acyclic enolates (by Marek et al)	57
Scheme 44	Synthesis of stereocontrolled carboxy allyl enolate	58
Scheme 45	Synthetic scope of the stereoconfined Pd-DAAA	59
Scheme 46	Pd-DAAA for carboxyallyl substrates (with selective scope) by Brian Stoltz	60
Scheme 47	Effect of enolate geometry on the asymmetric induction during Pd-DAAA	61
Scheme 48	Pd-DAAA of carboxy-allyl enol using the Trost ligand	62
Scheme 49	Pd-DAAA of N-acyl indole derived enol carbonate by using the Ty-PHOX ligand	63
Scheme 50	Remote stereo-control of the diastereoselective reaction	64
Scheme 51	First catalytic conversion of allyl amidates to carbamates	65
Scheme 52	Rare metal induced O-allylation and their further rearrangement	66
Scheme 53	Aluminum and Boron catalyzed O-allyl rearrangement for acyclic quaternary carbon formation	67
Scheme 54	Pd catalyzed rearrangement of O-allyl ether using the DACH-naphthyl Trost ligand	68
Scheme 55	Recent approaches for asymmetric induction using Rh, Cr and B	69
Scheme 56	Danishefsky synthesis of (S)-(-)-coerulescine	72

Scheme 57	Hayashi synthesis of (R)-(-)-Coerulescine	73
Scheme 58	Basai total synthesis of (+)-Coerulescine	75
Scheme 59	Park total synthesis of (S)-(+)-Coerulescine using PTC	77
Scheme 60	Different successful approaches for preparing lactone derivatives	81
Scheme 61	Synthesis of coixspirolactam A and the elucidation of its absolute configuration	83
Scheme 62	Retention of structural information during the asymmetric induction	86
Scheme 63	Screening the previously optimized reaction conditions	87
Scheme 64	Synthesis of carboxyallyl acrylate and the Pd-DAAA to form compound 2	101
Scheme 65	Synthesis of O-allylated enol 9 and the Pd induced rearrangement to form compound 2.	105
Scheme 66	Intermolecular vs intramolecular Pd-AAA	108
Scheme 67	Asymmetric synthesis of chiral 3,3-disubstituted oxindole	109
Scheme 68	Formation of 3,3-disubstituted indoline	111
Scheme 69	Proposed synthesis of (-)-coerulescine	112
Scheme 70	Attempted oxidation of 4 after TIPS protection and reductive amination cyclization	113
Scheme 71	Attempted oxidation of 4 after tosyl protection and reductive amination cyclization	113
Scheme 72	Attempted oxidation of 4 after mesityl protection	114
Scheme 73	One pot reductive amination cyclization to synthesize (-)-coerulescine	115
Scheme 74	Total Synthesis of (-)-coerulescine and (-)-coixspirolactam A	117
Scheme 75	Iron Lewis catalysed synthesis of 3-hydroxy aryl acrylate by Hossain et al	161
Scheme 76	Iron Lewis acid catalyzed synthesis of 3-hydroxy-2-aryl acrylate by Kirchner et al	162

Scheme 77	Role of commercially available Bronsted acid for the decomposition of 6	164
Scheme 78	First Bronsted acid catalyzed coupling of aromatic aldehydes and EDA by Hossain et al	165
Scheme 79	Organic base catalyzed formation of 3-hydroxy aryl acrylate by Wang et al	166
Scheme 80	Synthesis of 2-and 4-Quinolinone derivatives from 3-hydroxy arylacrylate	167
Scheme 81	Synthesis of pyrazolopyrimidinones from 3-hydroxyarylacrylate 2	168
Scheme 82	Synthetic application of 3-hydroxy arylacrylate 2 for preparing uracil derivatives	169
Scheme 83	Synthesis of thio vinyl derivatives from 3-hydroxy arylacrylate	170
Scheme 84	Synthesis of Chromenone-Crown Ethers from 3-hydroxy arylacrylate	171
Scheme 85	Formation of 3-hydroxy aryl acrylate/3-oxo-esters in presence of HBF ₄ .OEt ₂ catalyst by 1,2-migration	172
Scheme 86	Synthetic scope and migratory aptitude of aryl-phenyl groups	173
Scheme 87	Migratory aptitude of alkyl-hydride Groups	178
Scheme 88	Preparation of 3-hydroxy-2-aryl acrylates from the reaction of aromatic aldehydes and EDA catalyzed by complex A and complex B	200
Scheme 89	Stabilization of the indole ring due to resonance	207
Scheme 90	C2 alkylation of the indole moiety after carboxy induce lithiation assistance	208
Scheme 91	C2 alkylation at the β -aliphatic position from the heteroatom (nitrogen)	208
Scheme 92	Precedence of C2-prenylation of BOC-protected gramine	210
Scheme 93	Protection of heteroatom nitrogen of gramine	211
Scheme 94	Two-step alternative route to prepare N-protected gramine	213
Scheme 95	C2-alkylation of N-protected gramine	214
Scheme 96	Deuteration study of N-tosyl and N-Me protected gramine	215

LIST OF FIGURES

Figure no		Page no
Figure 1	Privileged heterocyclic motifs contain oxindole core	1
Figure 2	Examples of some natural and nonnatural moieties synthesized from 3,3-disubstituted oxindoles	3
Figure 3	Strategies for the synthesis of 3,3-disubstituted oxindoles	6
Figure 4	Simplified working model of Ni-catalyst with oxindole framework	27
Figure 5	Examples of the variety of ligands widely used in Pd -AAA	37
Figure 6	Examples of some commercially source of Pd(0) as a catalyst	38
Figure 7	Examples for the structure of spirooxindole containing natural products	71
Figure 8	Representative natural products and bioactive molecules containing the spirooxindole lactone and lactams	79
Figure 9	Selected ligands for Pd-AAA of prochiral 2-nitro-3-hydroxy phenyl acrylate, 1	90
Figure 10	Synthetic scope of ketone derived acrylates for both natural and synthetic drug candidates	160
Figure 11	Newman projections of six possible rotamers (A-F) and the predicted intermediates	175
Figure 12	HMBC cross peak spectra for the products of <i>para</i> -methyl benzophenone	176
Figure 13	HMBC cross peak spectra for the products of <i>para</i> -methoxy benzophenone	177
Figure 14	Commercially available predominant isomers of dicyclohexyl-18-crown-6-ether complexes	198
Figure 15	Application of acrylate for the preparation of pharmaceutically important compounds	202

Figure 16 Important biologically active natural products containing C2-substituted indole moiety

206

ACKNOWLEDGEMENTS

At first, I would like to express my sincere gratitude to my supervisor, Professor M. Mahmud Hossain for his exceptional guidance, boundless support, and immense encouragement during the course of this work. He never left me unattended and pursued me to make things happen. He taught me how to learn and made me an independent researcher.

My heartfelt appreciation and respect go to my PhD committee members Professor James M. Cook, A. Andy Pacheco, Professor Mark Dietz, and Professor Xiaohua Peng for their careful observations, suggestions, and motivation during my research. I would also like to thank Dr. F. Holger Foersterling and Dr. Anna Banko for their continuous support with NMR and HRMS analyses. I would also like to thank Dr. Mizzanoor Rahaman, Dr. S. A. Asad, Marcus Jellen and my current group members Khorshada Jahan, Jawad Bin Belayet, AFM Tawheedur Rahman and Tye Seideman for their critical help and participation in fruitful discussions.

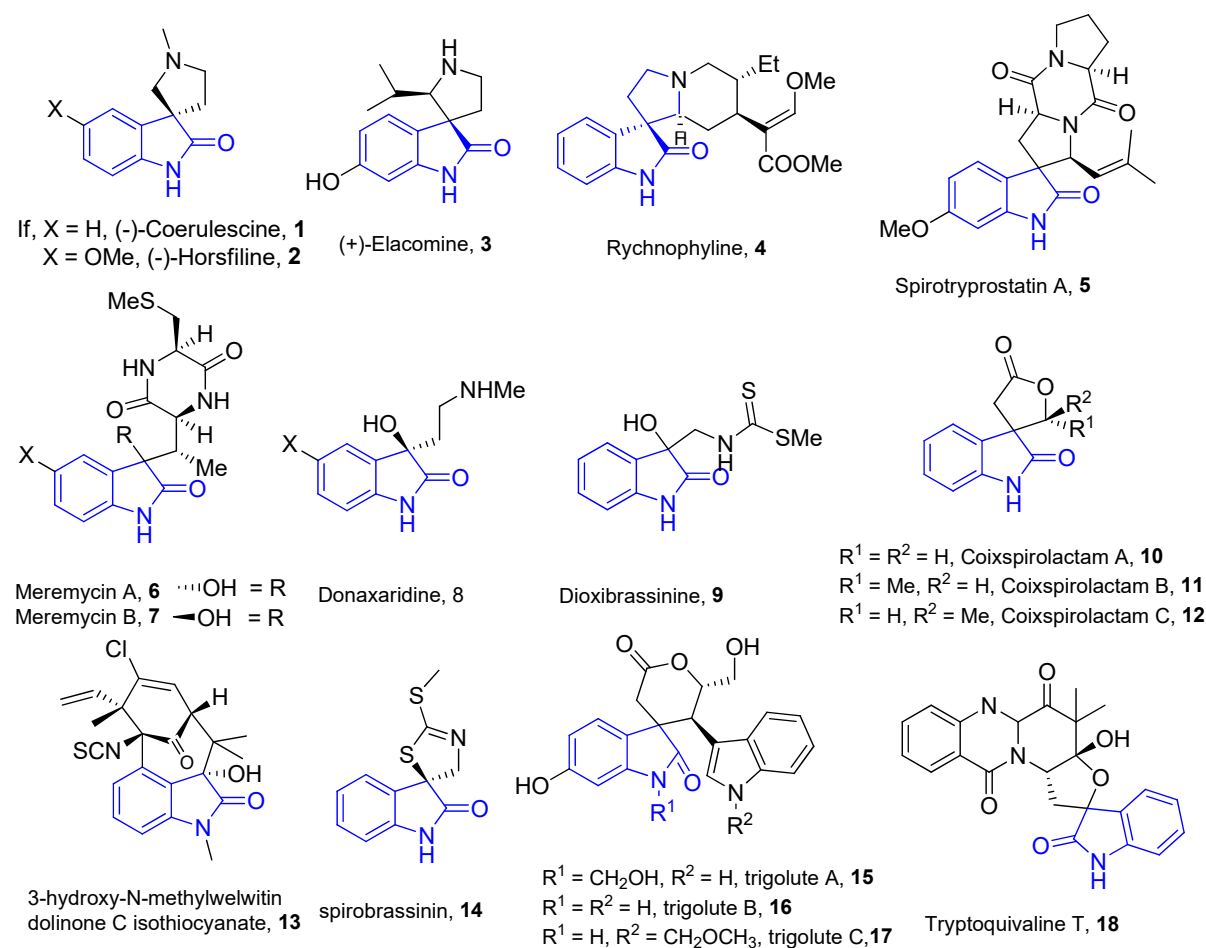
Finally, I wish to thank the Graduate School (UWM) for financial support and the office staff of the Department of Chemistry and Biochemistry (UWM) for their assistance during this work. Last but not least, my wholehearted thanks go to my family members without whom it would have been impossible for me. My parents, wife and my son who have supported me from every direction beyond their ability and helped me achieve Ph.D.

1.1 Introduction

1.1.1 Importance of 3,3-disubstituted oxindoles and their asymmetric synthesis

The Chiral 3,3-disubstituted-2-oxindole frameworks carrying a tetrasubstituted carbon stereocenter at the 3-position are present in several alkaloid natural products. This privileged heterocyclic motif makes up the core of a large family of bioactive natural products and a series of pharmaceutically active compounds (**Figure 1**). [1,2] One specific molecular architecture of this class of compounds encompasses the spiro[pyrrolidine-3,3'-oxindole] ring system that exists

Figure 1 Privileged heterocyclic motifs contain oxindole core



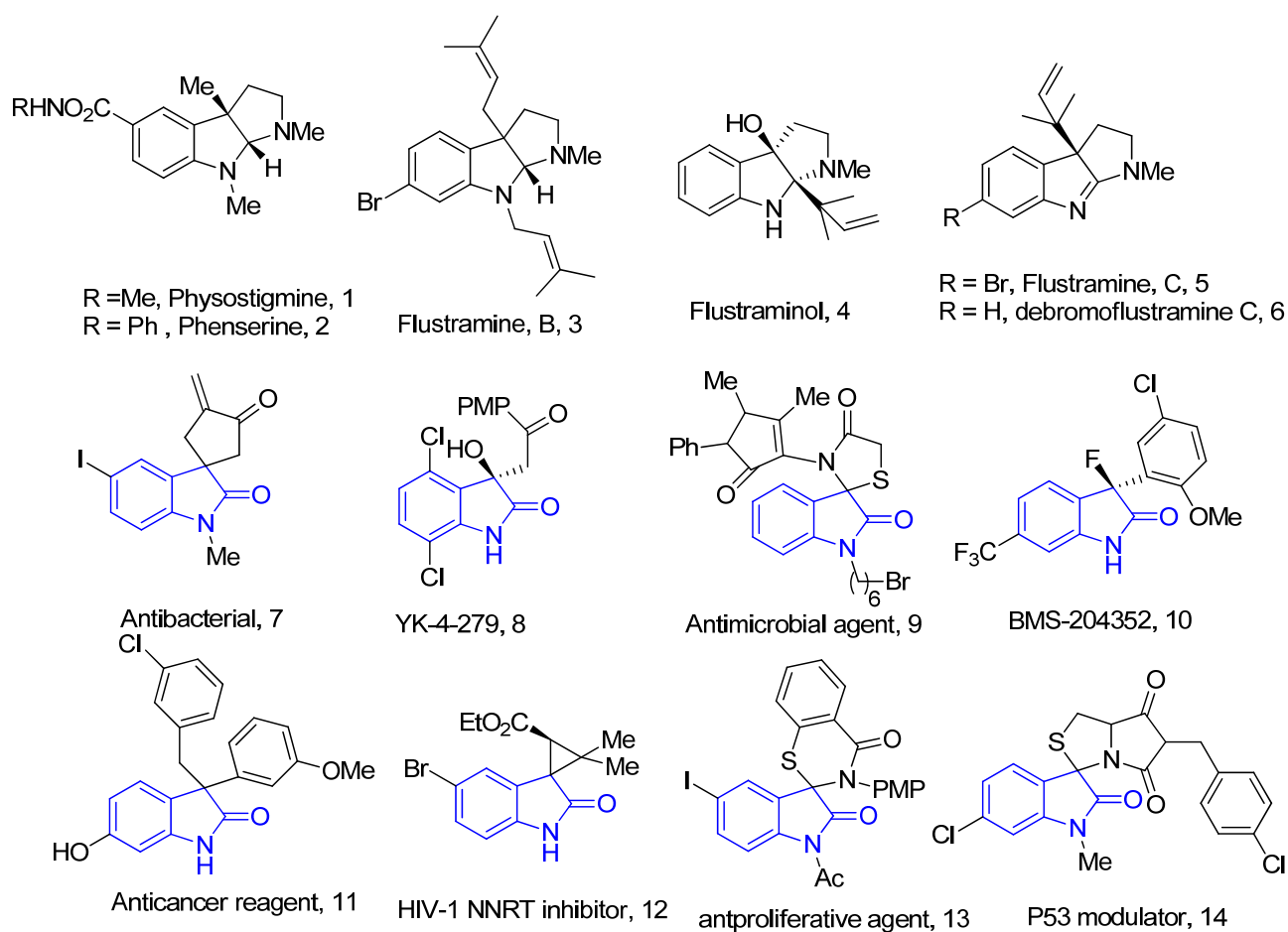
in a number of spirooxindole alkaloids such as **1–5**. Such oxindoles were first isolated from the family of plants termed the Apocynaceae and Rubiaceae and characterized by a spirofusion to a pyrrolidine ring at the 3-position of the oxindole core. Another significantly explored family of 3-substituted 3-hydroxyoxindole units covers a large variety of alkaloids and natural products exemplified by **6-9** (**Figure 1**). Moreover, 3-substituted 3-amino oxindoles are very useful because of the presence of this structure in pharmaceutical candidates, [3a, 3b] such as the potent gastrin/CCK-B receptor antagonist AG-041R 12 and the vasopressin V1b receptor antagonist SSR-149415. The existence of sulfur-containing tetrasubstituted carbon stereocenter was first discovered in Spirobrassinin **14** oxindole.

An extension of the importance added with the previous discussion of spiropyrolidine moiety is the γ -lactone scaffold. A recent isolation of natural product like Coixspirolactam (A/B/C), **10-12** from the traditional Chinese medicine adlay bran exhibit potent anti-proliferative effects on human lung cancer cells (A549), human colorectal carcinoma cells (HT-29 and COLO205), and human breast cancer cell lines (MCF-7, T-47D and MDA-MB-231).[4] Out of many other scopes of obtaining 3,3-disubstituted oxindole a couple of them has been added to the **Figure 1** numbered from **13-18**.

1.1.2 Useful synthesis of natural and bioactive compounds containing the 3,3-disubstituted oxindole

Based on the broad natural availability of such oxindoles, it is evident that the 3,3-disubstituted oxindole framework can be utilized to synthesize pyrrolidinoindolines bearing a carbon substituent at C-3a of the hexahydropyrrolo-[2,3-b]indole ring system, which exists in a number of natural products such as 1-6 with strong bioactivity (**Figure 2**). [5] Some other agents with this pivotal

Figure 2 Examples of some natural and nonnatural moieties synthesized from 3,3-disubstituted oxindoles

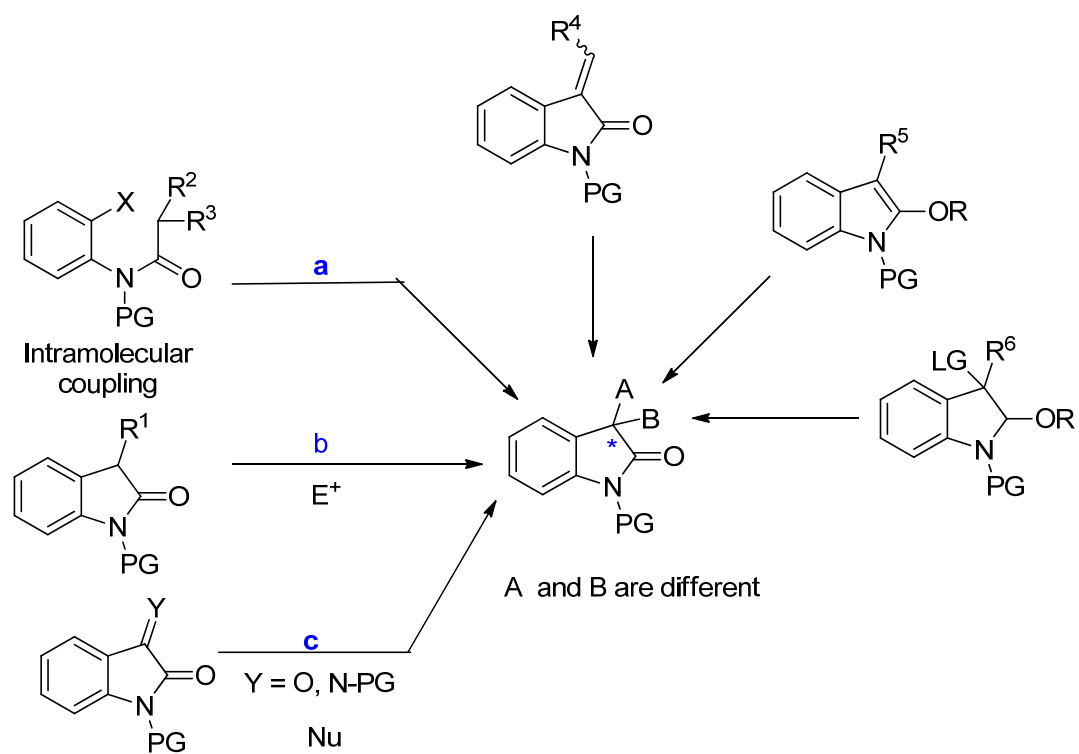


core has already been explored for the synthesis of unnatural drug candidates shown in **Figure 2**, compounds **7-14**. Owing to its importance and versatility in the synthesis of these natural products, drugs and related analogues, much effort has naturally gone into the asymmetric synthesis of the 3,3-disubstituted oxindole framework. The aim is to facilitate the synthesis of sufficient quantities of the desired natural, unnatural products and related analogues for biological evaluation and studies on structure-activity relationships. The overreaching goal is the development of new therapeutic agents or important biological tools.

2.1 Strategies for the catalytic asymmetric synthesis of 3,3-disubstituted oxindoles

Although the development of the strategies for chiral 3,3-disubstituted oxindole core is quite recent but the importance of its impact attracted a lot of chemists to develop dozens of catalytic asymmetric reactions. These reactions could be categorized into the following categories based on the substrates employed for the reaction design: 1) intramolecular coupling reactions 2) direct functionalization of 3-substituted oxindoles 3) nucleophilic additions to Isatins and 4) others (**Figure 3**). Intriguingly, to realize the impact of each and individual component of a reaction a detail study of use of chiral metal catalysts or organocatalyst are both reported in some cases.. Most of the approaches avoided the formation of oxindole ring by using commercially available oxindoles because the ring formation is the critical step to optimize. But the problem is there are only very limited number of substituted oxindole and thus somehow limited the expansion of the scope for putting different substituent on the aromatic ring. Idea of putting different substituent on the benzene ring oxindole selectively is still an elusive challenge. It should be mentioned that there is no single example of inducing chirality before the for the formation of oxindole so far observed from the literature survey. In the following sections, we summarize these exciting results in each category, and briefly discuss the scope, advantages, and limitations of each method.

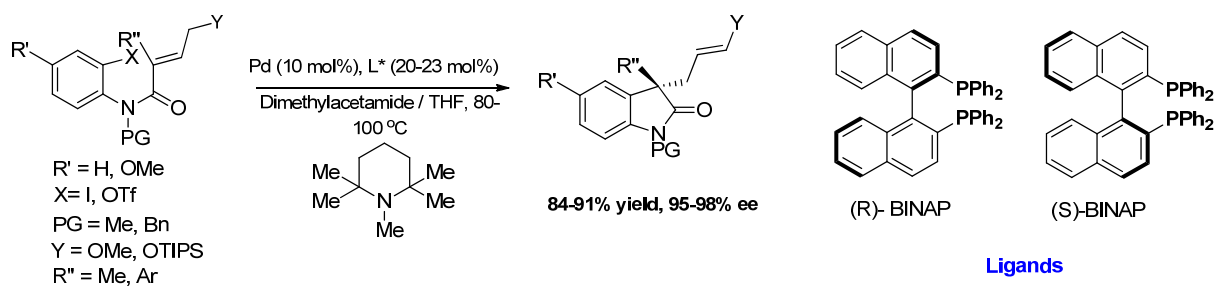
Figure 3 Strategies for the synthesis of 3,3-disubstituted oxindoles



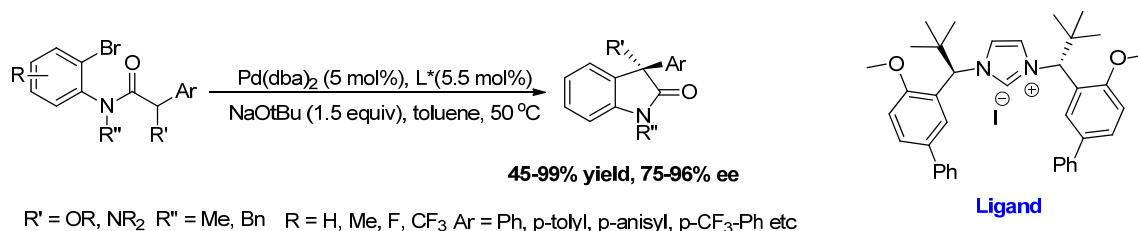
2.1.1 Intramolecular Heck Coupling/modified coupling

The palladium-catalyzed asymmetric synthesis of 3,3-disubstituted oxindoles by intramolecular amide α -arylation has received much attention. The first practical catalytic asymmetric method for the enantioselective synthesis of chiral oxindoles was developed in the past decade of the past century by Overman and coworkers in the context of the total syntheses of the alkaloids (-)-physostigmine and (-)-physovenine. [6] A couple of other methods reported the formation of disubstituted oxindole by modified Heck coupling strategies such as intramolecular amide α -arylation and cyanomidation reaction. [7] Overman's approach relied on the intramolecular Heck reaction of the (Z)-(2-methyl)-2-butenanilide, which was catalyzed by a palladium (0) complex formed in situ from commercially available (S)-BINAP and $\text{Pd}_2(\text{dba})_3$ to afford the 3,3-disubstituted oxindole **2** with excellent enantioselectivity (**Scheme 1**). Subsequently, Overman's group found that this approach could also be applied to the enantioselective synthesis of 3-alkyl-3-aryloxindoles (**Scheme 2** for a representative example). [8]

Scheme 1. Enantioselective Heck cyclization of anilide

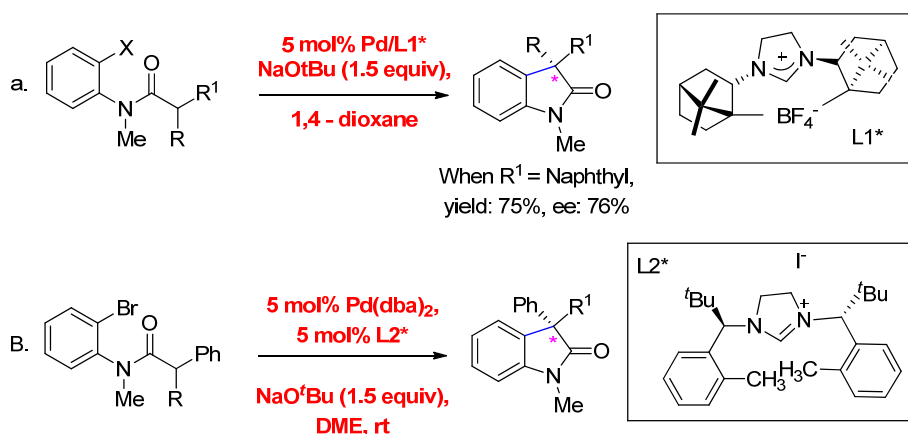


Scheme 2: Enantioselective tandem Heck cyclization of anilide



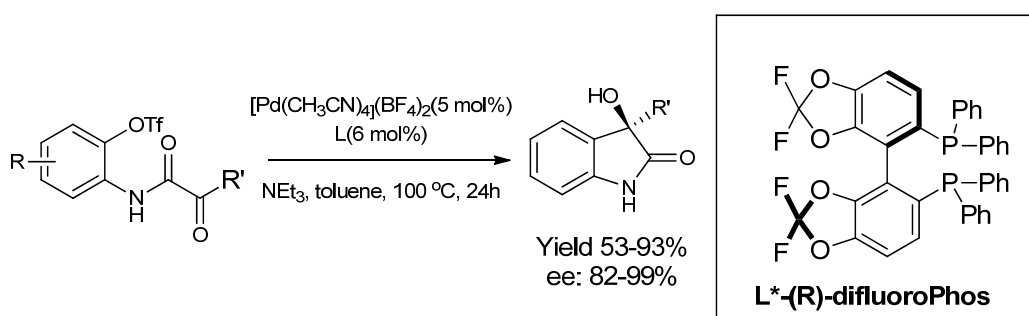
Following the seminal work of Hartwig and coworkers, which discovered that by using chiral NHC ligands they could perform this reaction at room temperature with moderate enantioselectivities (40–76% ee) [9], subsequent research focused on modifying the structure of the NHC ligand L_1^* in order to upgrade the stereoselectivity of the process (**Scheme 3a**). [10] In 2007, Kundig and coworkers modified the NHC ligand using a strategy that (i) instead of using alkyl system an aromatic ring can be introduced and (ii) ortho position of the ligand can be made more sterically hindered by putting methyl/methoxy substituent. They were able to achieve high enantioselectivities (up to 95% ee) in the cyclization of *o*-bromo(α -aryl)propanilides by means of the sterically hindered NHC ligand L_2^* (**Scheme 3b**). [11]

Scheme 3 Intramolecular coupling using NHC and modified NHC ligand-Pd catalyst pair



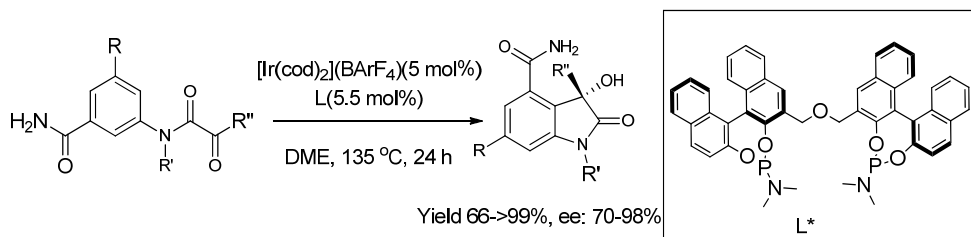
Moreover, the use of palladium has also proven to be a very useful [12] for intramolecular asymmetric arylation of α -keto amides introduced by Shibasaki et al during the optimization study of 3-hydroxy-3-alkyl oxindole synthesis. The catalyst $[\text{Pd}(\text{CH}_3\text{CN})_4](\text{BF}_4)_2/(\text{R})$ -difluoroPhos (5 mol%/6 mol% - chiral ligand L^*)(**Scheme 4**) could generate chiral 3-hydroxy-2-oxindole derivatives in moderate to good yields and excellent stereoselectivity (up to 95% ee). [13]

Scheme 4 Palladium catalyzed asymmetric intramolecular arylation of α -keto amides



Additionally, Yamamoto's group used Iridium catalyst to prepare 3-hydroxy-3-substituted-oxindole derivatives. They promoted an asymmetric intramolecular direct hydroarylation of α -ketoamides using cationic iridium ($[\text{Ir}(\text{cod})_2](\text{BARF}_4)$) and chiral ligand L^* to afford the desired products in high to excellent yields and enantioselectivities (**Scheme 5**). [14] Further studies indicated that the turnover-limiting step in the catalytic cycle was the carbonyl insertion step into the aryl-iridium bond. [15]

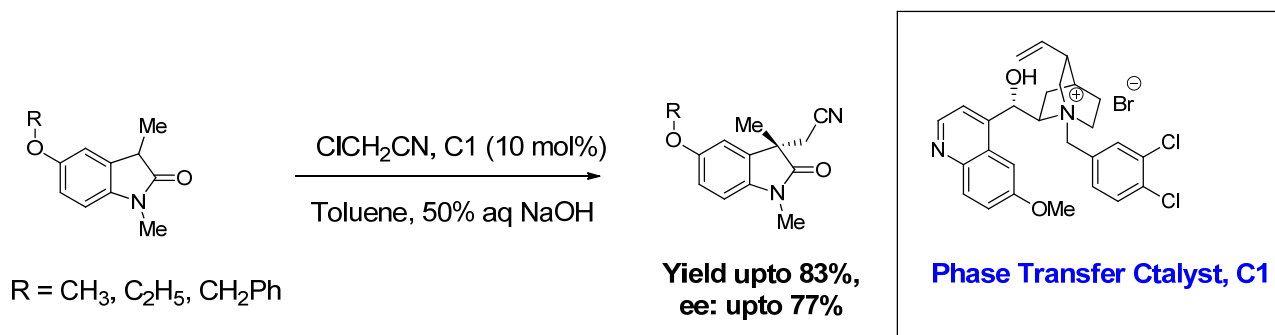
Scheme 5: Iridium-catalyzed asymmetric intramolecular direct hydroarylation of α -keto amide



2.1.2. Direct functionalization

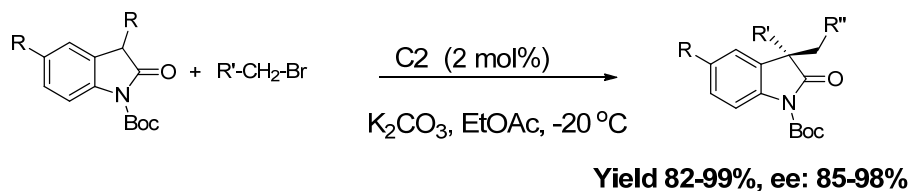
In 1991, Wong group reported the first known example of asymmetric C-H functionalization of a 3-prochiral oxindole to generate the C-3 quaternary stereocenter *via* phase-transfer catalysis (Scheme 6). [16] The catalytic asymmetric alkylation of a 3-substituted oxindole was achieved by means of phase-transfer catalysis (PTC), in the context of a formal total synthesis of (-)-esermethol. The alkylation of the 3-Me-oxindole with chloroacetonitrile was performed under PTC conditions with the aid of the quinidine-derived quaternary ammonium salt catalyst, C and furnished the 3,3-disubstituted oxindole with excellent yield 83% and moderate enantioselectivity of 77%.

Scheme 6 First Asymmetric PTC mediated alkylation of a 3-substituted oxindole



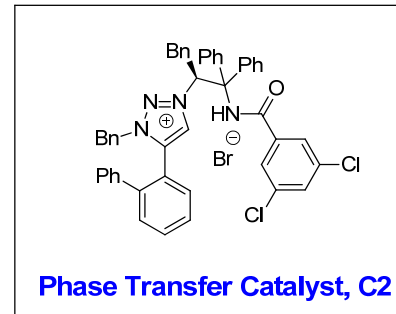
Remarkably, one more example of the application of PTC catalysis to the asymmetric alkylation of oxindoles by alkyl halides has been reported up to now. In 2010, Ooi and coworkers synthesized and tested the chiral triazolium salt. Under PTC conditions, this compound catalyzed the asymmetric alkylation of a series of 3-substituted N-Boc oxindoles with reactive alkyl bromides with excellent yield up to 99% and enantioselectivity up to 98% (Scheme 7). [17]

Scheme 7 Chiral triazolium salt catalyzed asymmetric alkylation of oxindoles



Where, R = H, Me, OMe, R' = Me, Et, *i*Pr, allyl

R'' = Ph, *p*-Br-Ph, *p*-tolyl, *m*-anisyl, CH₂=CH, CH₂=CMe etc

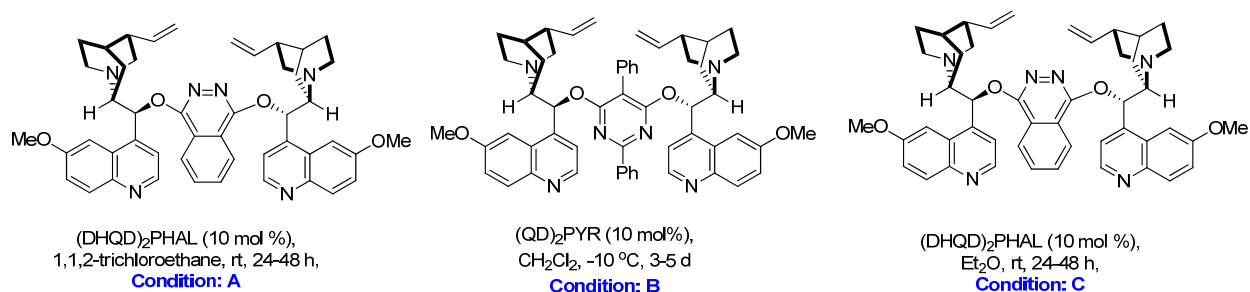


Additionally, some other protocols have also been established based on acid induced catalysis, direct fluorination / hydroxylation, asymmetric Michael addition, asymmetric Mannich reaction and aldol reaction that would be described briefly in the following discussion. [18]

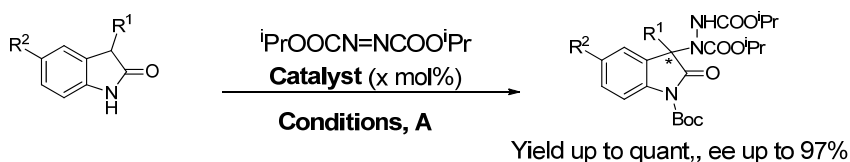
2.1.2.1 Organocatalytic functionalization of C3-H

In 2009 three independent research groups reported, almost at the same time, the organocatalytic enantioselective electrophilic α -amination reaction involving 3-substituted oxindoles as nucleophile. All three-group used azodicarboxylates as a source of nitrogen and a cinchona alkaloid as an organocatalyst. Chronologically, the group of Liu and Chen reported high yields and enantioselectivities ranging from good to high when the amination of unprotected oxindoles

Scheme 8 Organocatalytic Amination of oxindole with DIAD

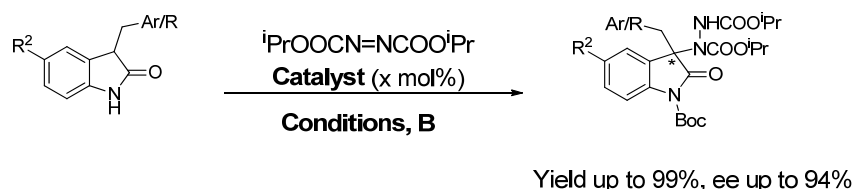


Chen et al



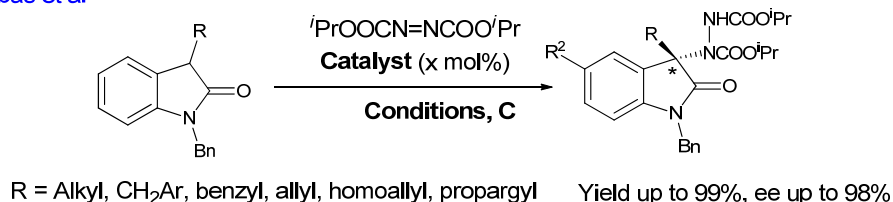
$\text{R}^1 = \text{Me}, \text{Ar}, \text{CH}_2\text{Ar}; \text{R}^2 = \text{H}, \text{Hal}, \text{MeO}$

Zhou et al



Ar = Ph, *p*-ClC₆H₄, *p*-BrC₆H₄, *o*-FC₆H₄, *o*-FC₆H₄, 2-Naphthyl, 2-thienyl.
R = isobutyl, prenyl, isopropyl

Barbas et al

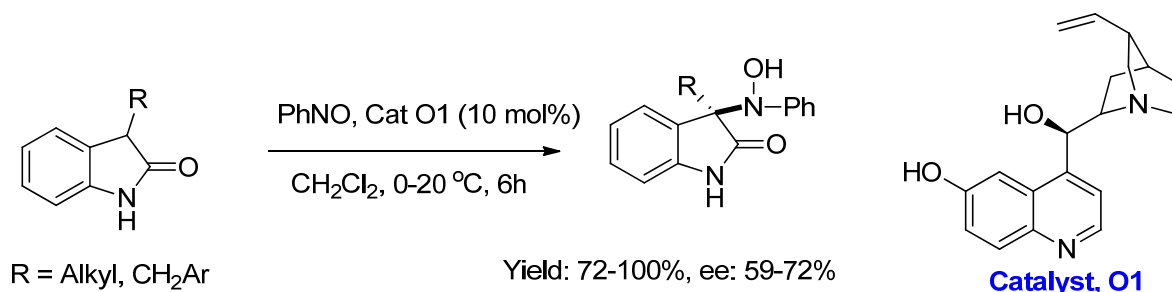


R = Alkyl, CH₂Ar, benzyl, allyl, homoallyl, propargyl

was performed using dimeric dihydroquinidine-derived (DHQD)₂PHAL as an organocatalyst and diisopropyl azodicarboxylate (DIAD) as amination reagent. [19] The results obtained by the group has presented in **Scheme 8** (condition A). Moreover, performing a fine tuning of reaction variables (solvent, temperature etc.) and more sterically hindered C3 substituent, Zhou and co-workers obtained slightly better yield and enantiobenefit (**Scheme 8**, condition B). Thus, in this case dimeric quinidine derived (QD)₂PYR and CH₂Cl₂ were the preferred organocatalyst and solvent, respectively (**Scheme 8**). [20]

Shortly after, Barbas and co-workers reported the asymmetric C3- amination of N-benzyl protected oxindoles, using dimeric cinchona-derived organo-catalyst **1** and diethyl azodicarboxylate (DEAD) as electrophilic aminating reagent (**Scheme 8**. Condition C). The protection of the nitrogen allowed broadening the scope of oxindoles used, obtaining slightly better results than when the unprotected analogues were employed. [21] However, using nitrosobenzene and unprotected oxindoles, Liu and Chen could obtain the corresponding hydroxyamination products with high yields and good enantioselectivities by employing cinchona organocatalyst **O1** (**Scheme 9**). [22]

Scheme 9 Hydroamination of oxindoles with nitrosobenzene



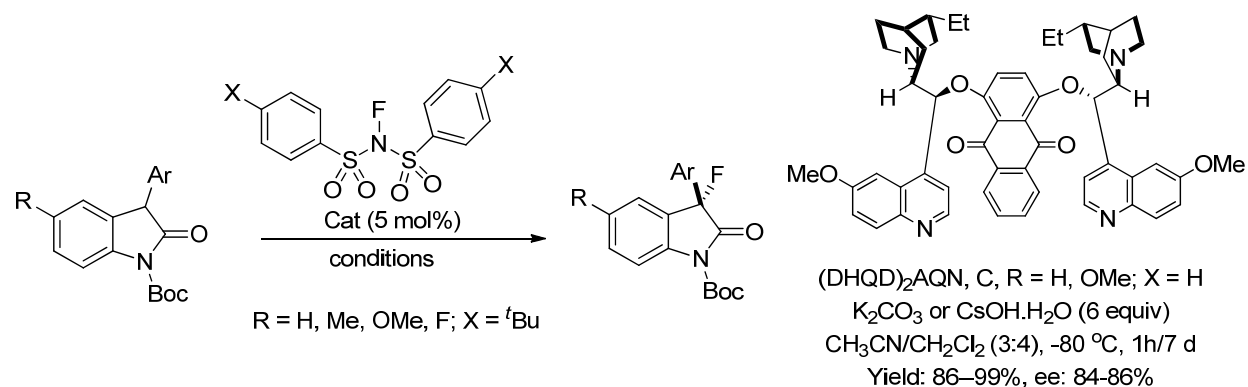
2.1.2.2 Halogenation:

The exchange of the 3-hydrogen of oxindoles by halogens is a challenging practice of improving the biological activity of these molecules for drug discovery. Benefit in bioavailability, metabolic stability and increasing protein-ligand interactions are the three main reason for the popularity of fluorinated drugs nowadays compare to the nonfluorinated parents. [23] Thus 3-substituted 3-fluorooxindoles can be referred as an interesting medicinally potential target. [24]

2.1.2.2.a Fluorination:

At the beginning of this century, a pioneering work by Shibata and co-workers described a new method for the asymmetric enantioselective C3-fluorination of oxindoles. The main problem associated with fluorine is the stable source of obtaining that, unstable sources of fluorine lead to multistep procedures. [25] Initially in 2001, Shibata's group used a stoichiometric combination of various cinchona alkaloid derivatives and Selectfluor® in their procedure using indanones and tetralones as model substrate. However, in 2008 when they established a successful procedure

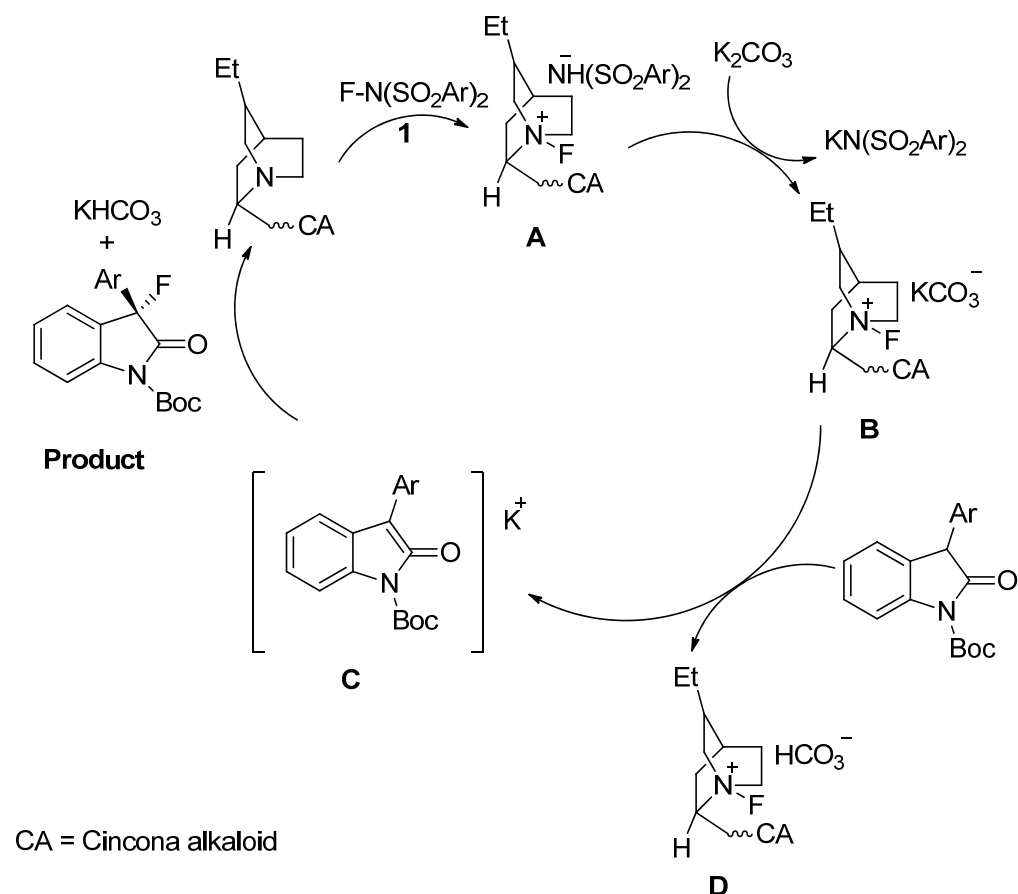
Scheme 10 Organocatalyzed fluorination of oxindoles



for the organocatalytic enantioselective C3-fluorination of oxindoles, by using a catalytic amount of bis-cinchona-derived alkaloid (DHQD)₂AQN, C and N-fluorobenzenesulfonimide (NFSI) as a source of electrophilic fluorine (**Scheme 10**). [26]

Some years later, another work was reported by Zhang et al in which (DHQD)₂PHAL (**1**) was used as an organocatalyst instead of (DHQD)₂AQN and added a tertiary butyl substituent on the para position of NFSI's phenyl ring. The authors reported slight increase of *ee* from 86-88% the

Scheme 11 Proposed catalytic cycle for the catalytic asymmetric organocatalyzed fluorination of oxindoles

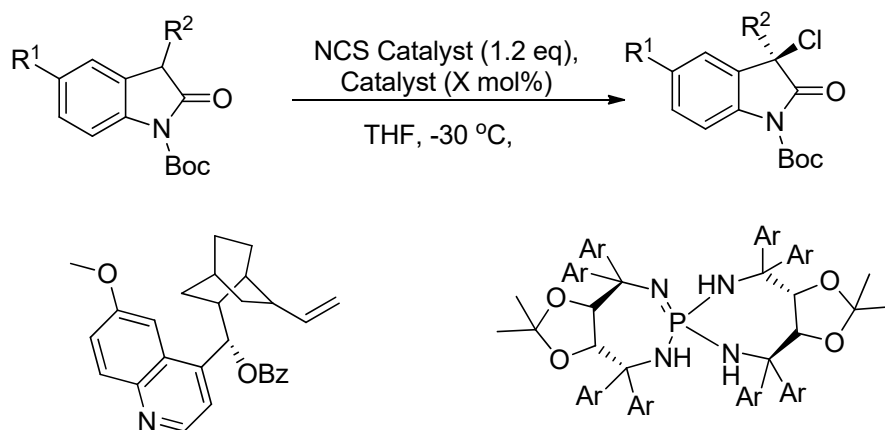


previous reported enantioselectivities. [27] In both articles, a similar catalytic cycle for this reaction was proposed (**Scheme 11**). The researchers hypothesized that the NFSI analogues react with the quinuclidine ring of the cinchona derived organo-catalyst to afford intermediate A. This species moves the inorganic base to the organic phase by acting as phase-transfer catalyst, affording intermediate B, which then promotes the enolization of the oxindole to form enolate C and intermediate D. Then either intermediates A or B or NFSI, can fluorinate the enolate generating the final product.

2.1.2.2.b Chlorination

The organocatalytic asymmetric chlorination of oxindoles is a rare reaction. [28] There are very few examples, mainly based on the use of Brønsted bases as organocatalysts. One example is the enantioselective C3-chlorination of 3-aryloxindoles using the cinchona alkaloid derivative as an

Scheme 12 Organocatalytic chlorination of oxindoles using N-chlorosuccinimide (NCS)



Condition A: Catalyst: 20 mol%

$R^1 = \text{H, Me, F}; R^2 = \text{Me, Ar, Bn}$

THF, $-30\text{ }^{\circ}\text{C}$, 2-5 h,

Yield: 81-99%, ee: 7-93%

Condition B: Catalyst 5 mol%

$\text{Ar} = 4\text{-}^t\text{BuC}_6\text{H}_4$

$R^1 = \text{H, Me, OMe, F}; R^2 = \text{Me, Ar, Bn}$

Et_2O , $-30\text{ }^{\circ}\text{C}$, 1 h

Yield: 93-99%, ee: 90-99%

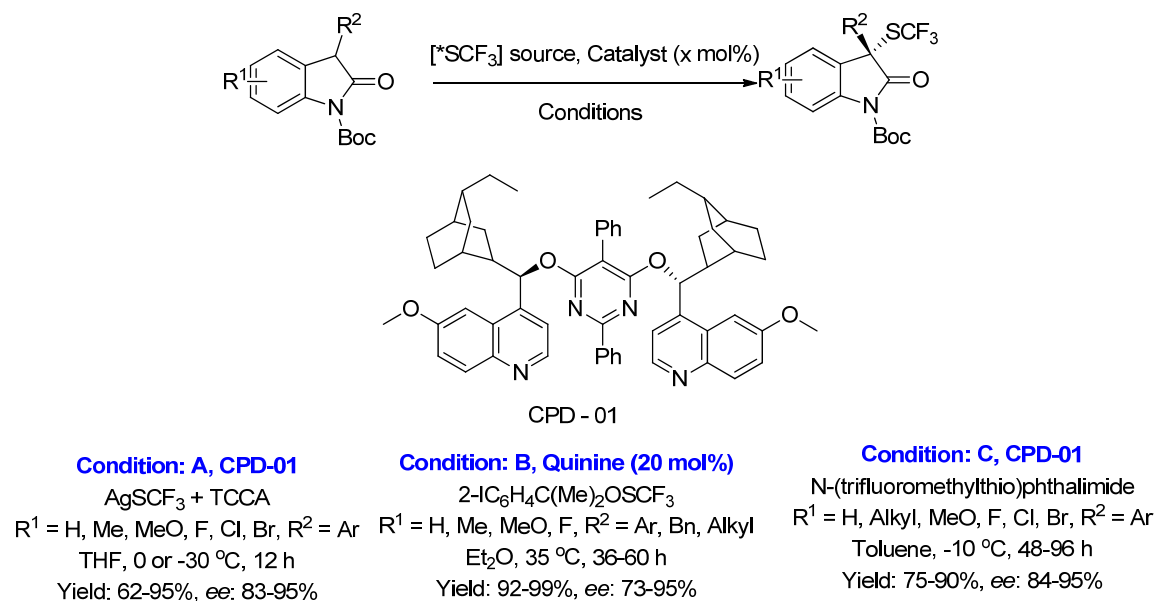
organocatalyst (condition 1) and N-chlorosuccinimide (NCS) as the chlorine source (**Scheme 12**).
[29]

The procedure gave rise to the corresponding 3-aryl-3-chlorooxindoles in high yields and moderate to high enantioselectivities under mild reaction conditions. However, the use of 3-alkyl and 3-benzyl-substituted oxindoles rendered the chlorination product in low optical purity. In addition, a similar chlorination procedure by using an iminophosphorane base organocatalysts has been proven to be more advantageous (**Scheme 12**, condition B). [30] Higher conversions and enantioselectivities were achieved even with lower catalyst loadings and short reaction time at room temperature. Furthermore, alkyl and benzyl substituents at C3 were well tolerated and excellent results were also achieved. Finally, it is worth mentioning that the catalyst could be recycled up to six times after chromatographic purification with almost no decrease in efficiency.

2.1.2.3 Sulfenylation:

The presence of a trifluoromethylthio (SCF_3) functionality in the structure of bioactive compounds gives rise to some important properties, such as a reduced hydrophilicity and higher electron-withdrawing ability, which helps to enhance their transmembrane permeation bioavailability. [31] Therefore, the addition of SCF_3 to oxindoles may lead to interesting developments for pharmacological applications. The trifluoromethylthiolation of oxindoles can be carried out by using Brønsted base catalysts, particularly cinchona alkaloid-derived organocatalysts (**Scheme 13**).

Scheme 13 Sulfenylation (trifluoromethylthiolation) of 3-substituted oxindole using Brønsted base Catalysis



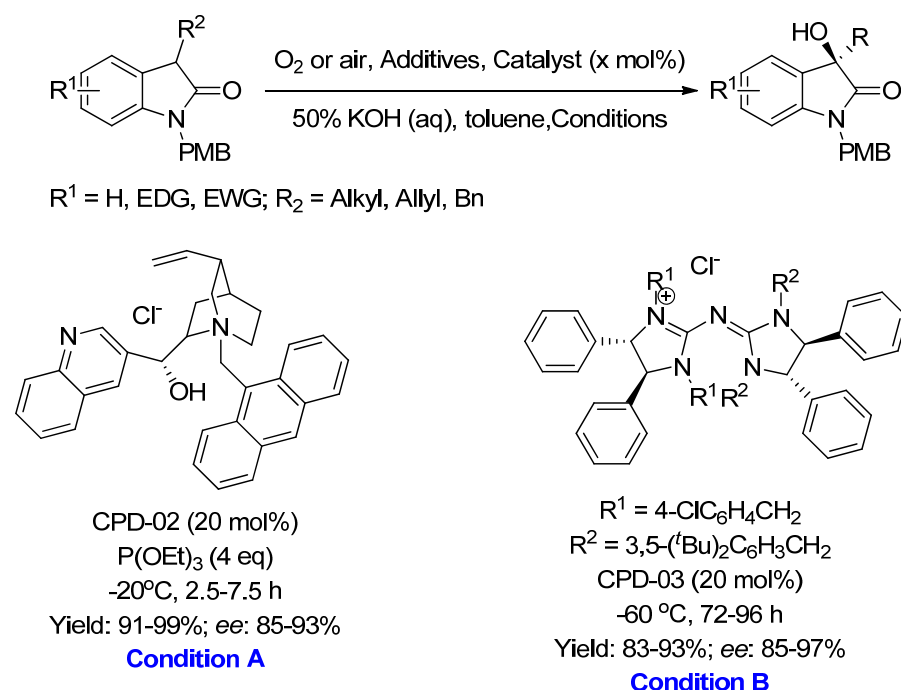
A precedence of such activation was first established in 2014 by Tan's group. They have executed that the asymmetric trifluoromethylthiolation of 3-arylated oxindoles could be achieved via in situ generation of an active electrophilic trifluoromethylthio species from AgSCF₃ and trichloroisocyanuric acid (TCCA) in presence of dimeric cinchona alkaloid organocatalysts such

as (DHQD)₂PYR (**CPD-01**) (**Scheme 13**, Condition A). [32] The scope of this reaction is broad as both electron-donating and electron-withdrawing substituents on the oxindole can afford high yields and enantioselectivities of the final products. The main advantage of this procedure is the fact that the starting materials are cheap and there is no need for the isolation of the SCF₃ reagent, saving time and money. Moreover, Chin et al initiated the asymmetric trifluoromethylthiolation of oxindoles using trifluoromethyl-substituted thioperoxide as the electrophilic reagent and quinine as organocatalysts, affording 3-substituted-3-SCF₃ oxindoles (**Scheme 13**, Condition B). [33] When exploring the scope of this reaction, an exchange of the N-protecting group from Boc to less hindered groups, caused any noticeable change in the enantioselectivity. It was also observed that the 3-trifluoromethylthiolated reaction products from 3-arylated oxindoles had lower optical purity than those from 3-alkylated ones. In addition, the same organocatalyst can be used for the enantioselective synthesis of 3-aryl-3-SCF₃-substituted oxindoles using N-(trifluoromethylthio)phthalimide with good results (**Scheme 13**, Condition C). [34]

2.1.2.4 Hydroxylation

Itoh et al developed a convenient protocol of hydroxylation for 3-substituted oxindoles in presence of molecular oxygen, using cinchonidine derived phase-transfer catalyst CPD-02. (**Scheme 14**, Condition A). [35] However, reduction using 4 equivalents of $(\text{EtO})_3\text{P}$ turned out to be vital for achieving high yields and *ee* when *N*-*p*-methoxybenzyl (PMB)- protected oxindoles were employ-

Scheme 14 Asymmetric hydroxylation of oxindole using various phase-transfer catalyst



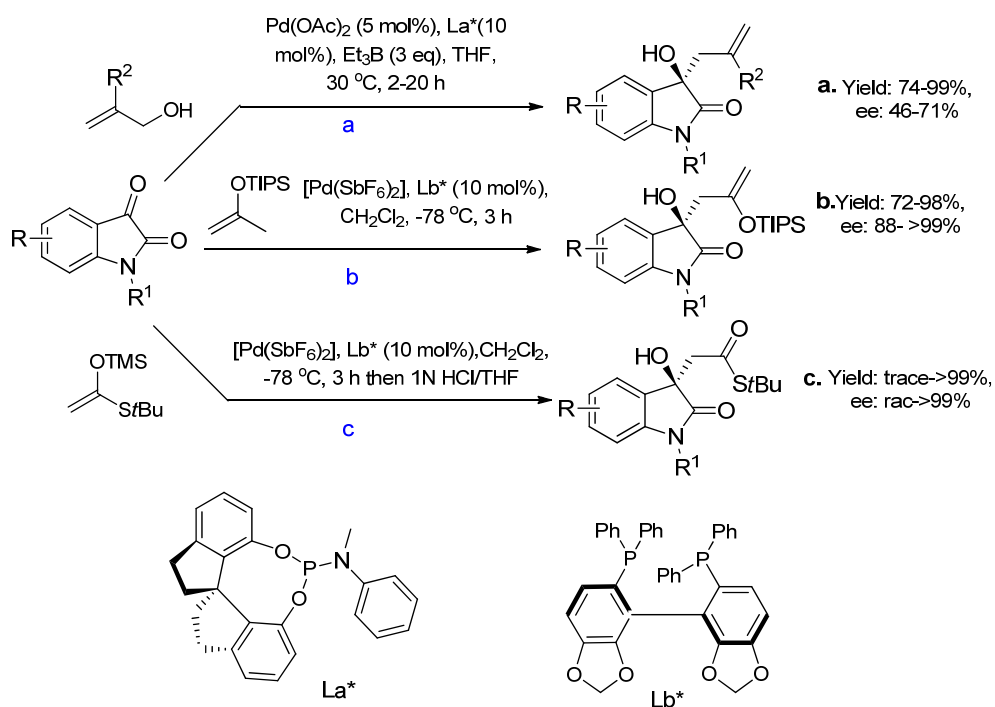
ed. In subsequent studies, pentanidium-based phase-transfer catalyst CPD-03 was employed in presence of molecular oxygen, they achieved slightly better enantiobenefit than in the previous case (**Scheme 14**, Condition B). [36] What is significant about this procedure is that there is no need for an additional reducing agent. According to the authors, this reaction proceeds via a kinetic

resolution of the hydroperoxyl oxindole intermediate by means of its reduction by the in situ generated enolate of the 3-substituted oxindole. Finally, it is worth mentioning that, only phase-transfer catalysis has been used to achieve the asymmetric electrophilic hydroxylation of oxindoles.

2.1.3 Nucleophilic addition to Isatin moiety

A direct but challenging approach of introducing various functionality in the prochiral moiety using metal catalyst is asymmetric allylation. The idea is to put the allyl group at first and later convert it to the required functionality by additional steps. Such a commercially available oxindole moiety is known as Isatin. Qiao and coworkers published the asymmetric allylation of Isatin analogues with allylic alcohols using the catalyst $[\text{Pd}(\text{OAc})_2] / \text{La}^*$ (5 mol% / 10 mol%) (**Scheme 15a**). During screening different ligands of chiral spiro phosphoramidite family La^* proved to be the best to access tertiary homoallylic alcohols 3-allyl-3-hydroxy-oxindole derivatives. Although the process resulted in very high yields with moderate enantioselectivities (up to 71% ee). [37]

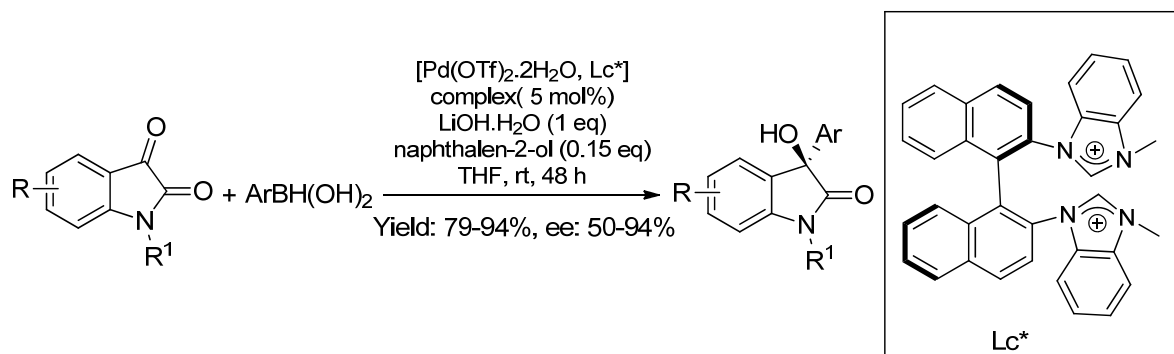
Scheme 15 Pd Catalyzed asymmetric allylation for the synthesis of 3-hydroxy oxindole



Moreover, Aikawa et al., also focused on the synthesis of tertiary alcohol, studied ene reactions of N-protected Isatins along with isopropenyloxy(triisopropyl)-silane (**Scheme 15b**) and aldol reaction using isopropenyloxy(tert-butyldimethyl)-silane trimethylsilyl ketene thioacetal (**Scheme 15c**). In both the cases they have used $[\text{Pd}(\text{SbF}_6)_2]$ and the chiral ligand L_b^* in 10 mol% as an optimized quantity. The chiral 3-hydroxy-3-substituted-oxindole derivatives were isolated in high yields and with remarkable ee in some cases (>99% ee). [38]

Use of arylboronic acids to the N-substituted Isatins for nucleophilic addition allowed the formation of 3-aryl-3-hydroxyoxindole derivatives with moderate to good yields and enantioselectivities. A pair of C2-symmetric cationic N-heterocyclic carbene-Pd $_2$ μ -diaqua complex, prepared from the chiral ligand L_c^* was incorporated as a catalyst (**Scheme 16**). [39]

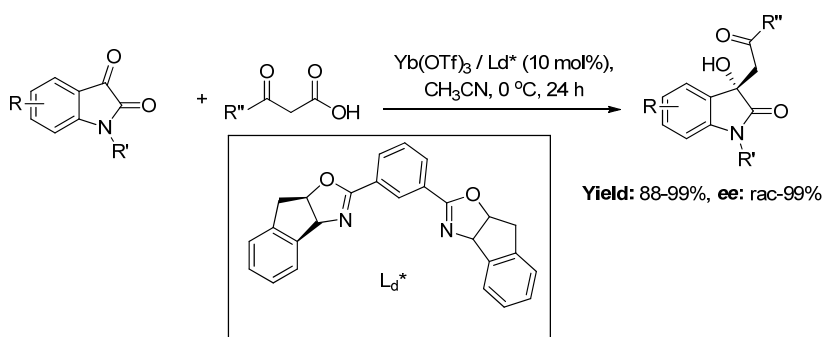
Scheme 16 Catalytic asymmetric allylation of isatin derivatives with arylboronic acid



Lanthanides have also been described for their potential application in asymmetric catalysis. [40-42] Among them, ytterbium was applied in the enantioselective decarboxylative addition of β -ketoacids to Isatins. The author mentioned that the use of N-substituted Isatins is crucial for the

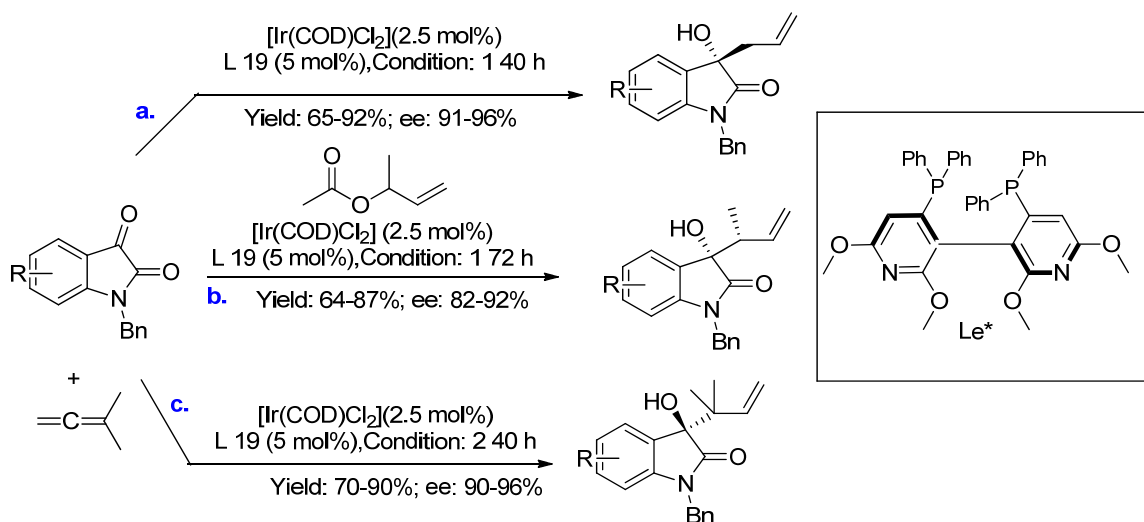
reaction yield and enantioselectivity, in the presence of the catalytic system $\text{Yb}(\text{OTf})_3/\text{Ld}^*$. As a result, chiral 1-benzyl-3-hydroxy-3-substituted-oxindole derivatives were obtained in very good yields (88-95%) and moderate to excellent enantioselectivities (65-98% ee) (**Scheme 17**). [43]

Scheme 17 Decarboxylative addition of β -ketoacids to isatin derivatives catalyzed by ytterbium



Iridium is a transition-metal from period 6 of the periodic table that presents a wide range of

Scheme 18 Allylation, crotylation and reverse prenylation of Isatin derivatives using Ir catalyst



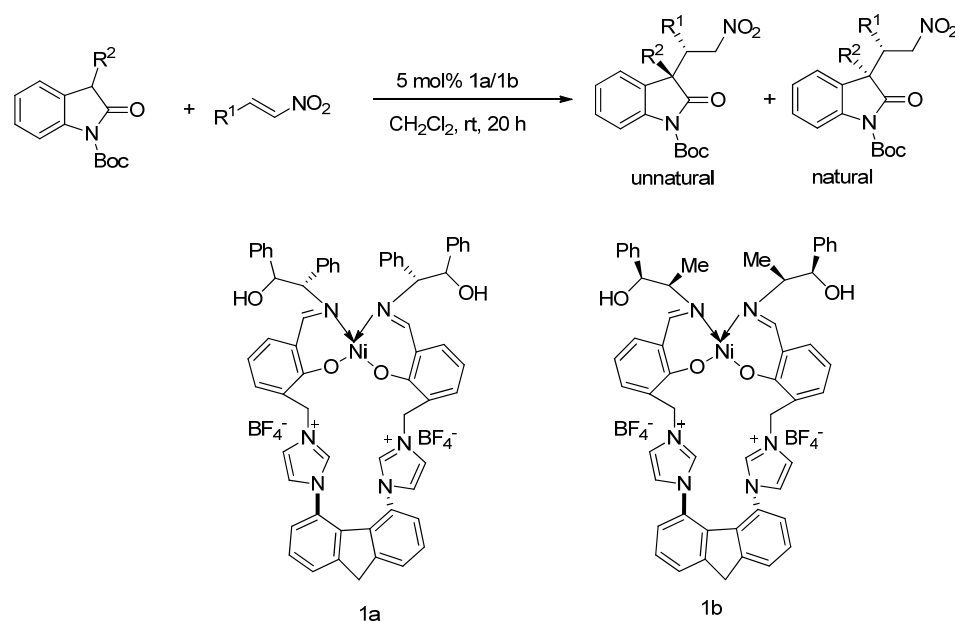
applications in synthesis. [44] Itoh et al. reported the first asymmetric allylations (**Scheme 18a**), crotylations (**Scheme 18b**) and prenylations (**Scheme 18c**). N-benzyl-isatin derivatives, using an isopropanol mediated transfer hydrogenation, in the presence of the catalyst $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.5 mol%) and the ligand (R)-*p*-phos L_e^* ((R)-(p)-2,2,6,6-tetramethoxy-4,4-bis(diphenylphosphino)-3,3'-bipyridine - 5 mol%), achieving moderate to good yields and good to excellent enantioselectivities (up to 96% ee). [45]

2.1.4 Other approaches:

2.1.4.1. 1,4-Michael addition:

Mechler and Peters developed a polyfunctional, readily available novel Ni^{II} -bis(phenoxyimine) type catalyst which can overwrite the inherent diastereoselectivity in direct 1,4-additions of oxindoles to nitroolefins to give rise to the epimeric product series (**Scheme 19**). Crucial for the switch in diastereoselectivity is the interplay of a Lewis acid, free hydroxy groups, and an axially chiral bisimidazolium linker in combination with the appropriate arrangement of the different chirality elements. The axially chiral bisimidazolium determines the configuration of the stereocenter generated at the nitroolefin, while the constitution as well as the relative.

Scheme 19 Diastereoconvergence for difference substrates of N-protected oxindoles

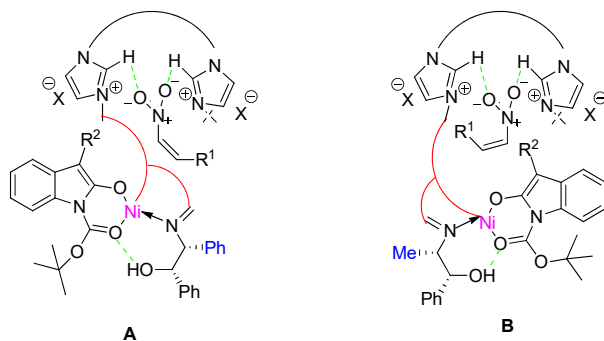


and absolute configuration of the iminoalcohol side arms mainly control the stereocenter generated at the oxindole. [46] The group has reported a novel polyfunctional catalyst type in which a Ni^{II} -

bis(phenoxyimine) unit, free hydroxy groups, and an axially chiral bisimidazolium entity participate in the stereocontrol of the direct 1,4-addition of oxindoles to nitroolefins. Both epimers of the 1,4-adduct are accessible in excess on demand by changes to the ligand constitution and configuration.

The observed diastereodivergency might be explained by a mechanism in which the Ni centers, OH group, and the bisimidazolium moieties cooperate (**Figure 4**). A control experiment with an N-methyloxindole resulted in no 1,4- adduct. We thus suggest a scenario in which oxindole enolization is triggered by bidentate coordination of the carbonyl group to Ni(II). As shown above, changes within the iminoalcohol side arms have an influence on the preferred configuration of the stereocenter at the oxindole. The orientation of the oxindole in the C-C bond-forming transition state might thus be dictated by the iminoalcohol moieties. Whereas. the preferred configuration

Figure 4 Simplified working model of Ni-catalyst with oxindole framework



Simplified proposed working model

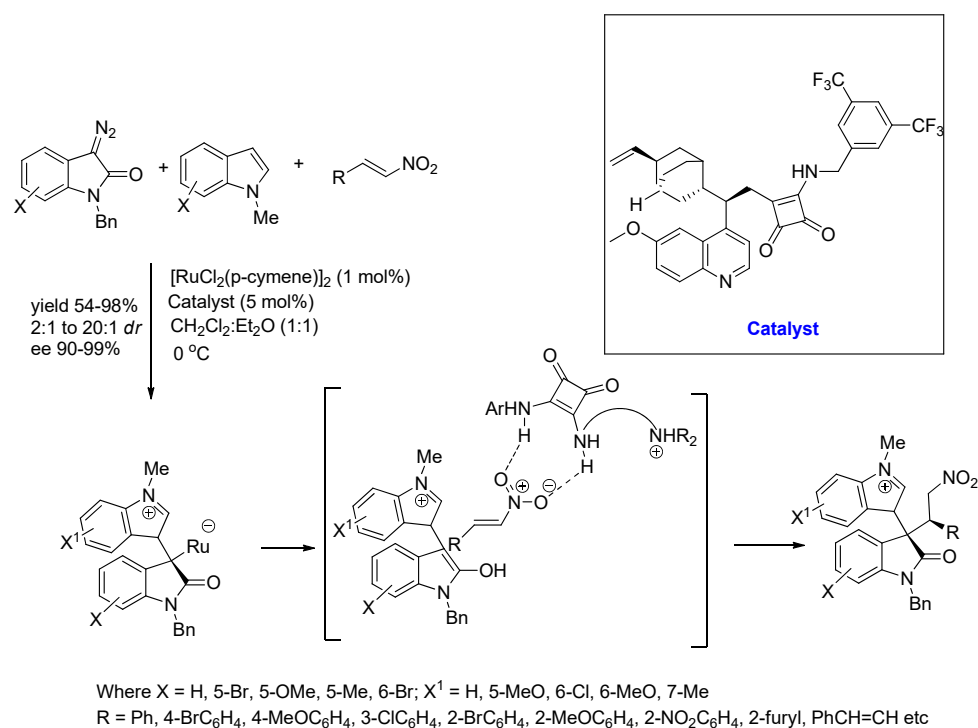
of the generated stereocenter in the nitroalkane chain is always identical when using the *R_a*-configured bisimidazolium linker. For that reason, we suggest that the nitroolefin is activated by hydrogen bonds/electrostatic interactions with the bisimidazolium groups, whereas the free hydroxy groups might be important to control the reactive conformation of the oxindole-Ni(II) adduct (**Figure 4**). It should be noted that the iminoalcohol side chains can be symmetrically

inequivalent after substrate coordination. The flexibility of an axially chiral bisimidazolium linker might be beneficial to readily adopt the optimal positions of both reacting centers

2.1.4.2 Enantioselective Michael Addition Cascade: Metal carbenoid assisted C-C bond formation

The first practically highly enantioselective synthesis of indolyl-indanes through a combination of either ruthenium (II) or Rhodium(II) complexes and quinine-derived squaramide enables 3-diazooxindoles, indoles, and nitroalkenes to undergo highly efficient asymmetric three-component reactions, thus affording optically active 3,3'-bis(indole)s through a consecutive C-C bond-forming sequence, (**Scheme 20**). It should be noted that an early attempt by Enders group

Scheme 20 Three component cascade reaction for the enantioselective synthesis of 3,3-disubstituted oxindole

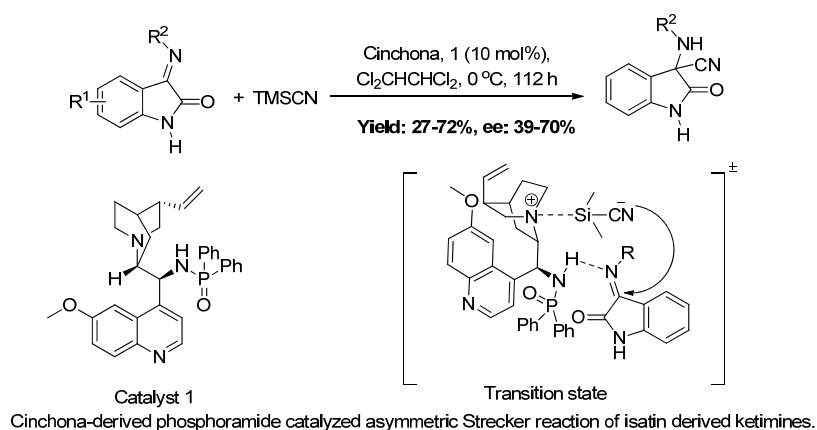


back on 2013 reported the formation of 3-methyloxindole (R=Me) with only 39% yield and 33% ee and oxindole (R=H) gave 44% yield and 73% ee although the same group later in 2015 reported a one pot scalable triple domino asymmetric synthesis of fully substituted cyclopentane-oxindoles through an organocatalytic triple Michael domino reaction. [47-48] In fact, N-benzyl-3-diazooxindoles, N-methylindoles and nitroalkenes reacted under $[\text{RuCl}_2(\text{p-cymene})]_2$ and quinine-based squaramide catalysis.

2.1.4.3 Asymmetric Strecker reaction:

Zhou et al first applied safe cyanide source, trimethylsilyl cyanide (TMSCN) in the Strecker reaction [49] of N-aryl Isatin ketimines (**Scheme 21**). At that time, the bifunctional tertiary-amine catalyzed Strecker reaction was undeveloped. [50] Although Deng had reported a highly enantioselective chiral tertiary-amine mediated ketone cyanosilylation, [51] the breakthrough was achieved by a newly developed phosphoramidate derived from the Cinchona alkaloid.

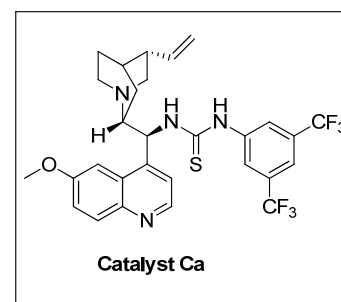
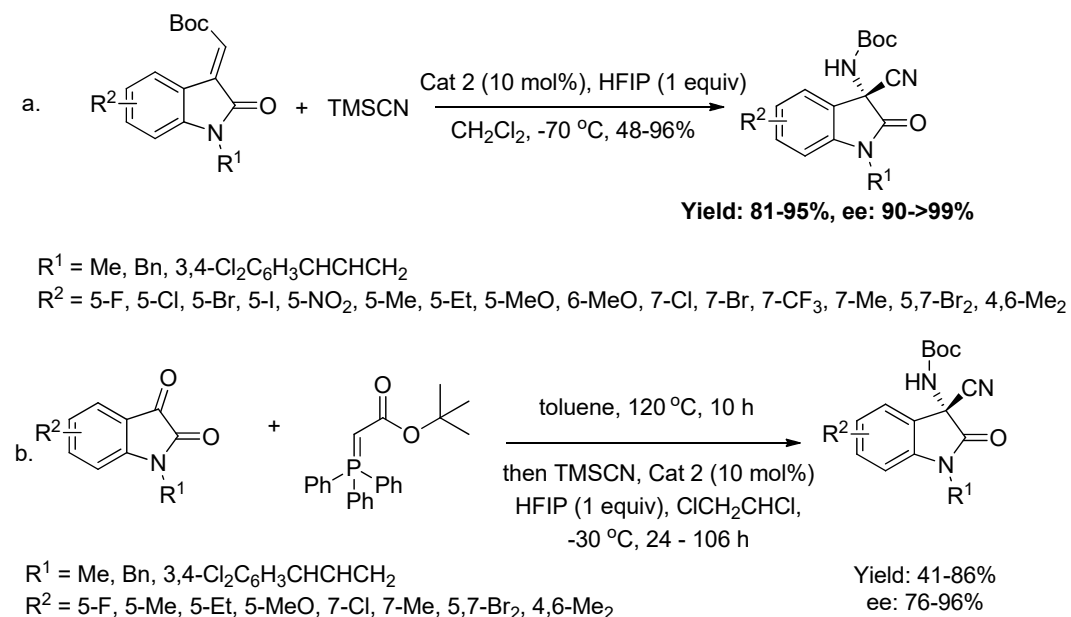
Scheme 21 Preliminary study of the Strecker reaction for N-aryl isatin ketimines



Preliminary studies indicated that 10 mol % phosphinamide catalyst C1 afforded oxindole based aminonitrile with moderate *ee*. [52] However, the best results of enantioselectivity were obtained whenever they used phosphinamide catalyst with amide or thiourea as the H-bond donor (**Scheme 21**). These results encouraged the Chouhan group to examine their potency in other reactions and triggered subsequent research on catalytic enantioselective addition of nucleophiles to Isatin ketimines for the synthesis of chiral 3-substituted 3-aminooxindoles. [53] The same group furnished an asymmetric synthesis with thiourea driven cinchona alkaloid and ended up with

excellent results (**Scheme 22a**). The catalyst **Ca** they developed was proved useful later for Zhou et al who perused another approach using Isatin a starting material with same catalyst and found an excellent outcome as well (**Scheme 22b**)

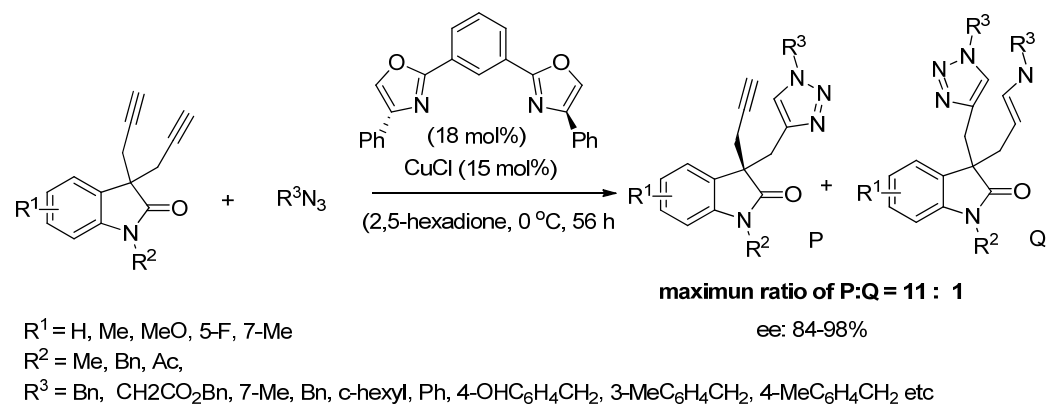
Scheme 22 Direct cyanidation using thiourea driven Cinchona alkaloid



2.1.4.4 Desymmetrization of diyne:

The Cu-catalyzed alkyne-azide cycloaddition (CuAAC) reaction has been applied in many areas of research; however, applying this strategy to the asymmetric synthesis remain still undeveloped. [54] Zhou group reported a strategy to develop enantioselective CuAAC, namely, desymmetrization of prochiral diynes (**Scheme 23**). [55] The key idea was to develop a highly enantioselective desymmetric CuAAC of oxindole-based 1,6- heptadiynes, furnishing quaternary oxindoles (**Scheme 23**) bearing a 1,2,3-triazole-containing moiety with 84–98% ee. This research also revealed that suppressing achiral diazole formation while achieving excellent enantioselectivity was very difficult, although they were fortunate to identify 2,6-hexadione as a solvent that could solve this problem in this case.

Scheme 23 Asymmetric CuAAC reactions for the preparation of 3,3-disubstituted oxindole



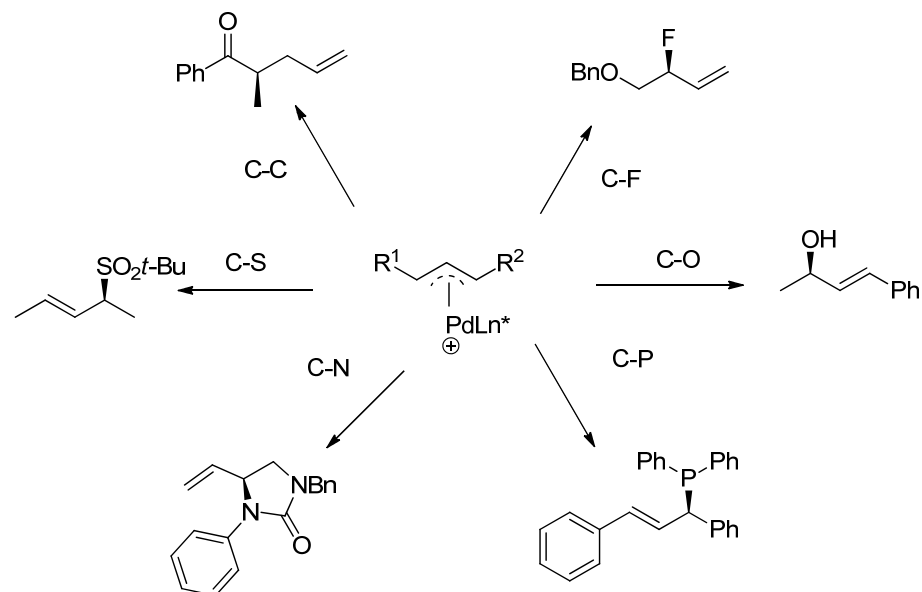
3.1 Introduction:

Part: II Palladium Catalyzed Asymmetric Allylic Alkylation

Palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) stands as a unique reaction due to the high number of stereocenters that can be created by this process. [56] Arguably, few transition-metal-catalyzed reactions offer the synthetic chemist the ability to form C–C, C–N, C–O, C–F, and C–S bonds by such a variety of mechanisms for asymmetric induction (**Scheme 24**). The development of Pd-AAA has been reviewed extensively; however, a specific aspect of Pd-AAA has not significantly matured over the past 20 years, namely the synthesis of acyclic quaternary stereocenters. [57] Unfortunately, the term “quaternary center” is a confusing terminology, because it is also used to mean “quaternary-substituted carbon”, that includes tri-carbon-substituted carbon such as occurs in tertiary alcohols. The term “all-carbon quaternary centers” is also found in the literature. Thus the ‘Quaternary substituted carbons’ and ‘quaternary carbons’ in the full sense must be distinguished carefully. Thus, in this chapter we are using the term “quaternary carbon” to designate those carbon centers that are substituted with four carbon substituents.

Pd-AAA has been shown to be successful for inducing asymmetry on both electrophilic and nucleophilic partners. Consequently, the discussion can be divided mainly into these two classes of reactions, with an emphasis on vinyl epoxides as electrophiles and enolates as prochiral nucleophiles. Possibility of using cyclic pronucleophiles that are readily converted into acyclic tetrasubstituted stereocenters after the alkylation reaction is also less explored as well.

Scheme 24 Formation of stereocenters by Pd-AAA

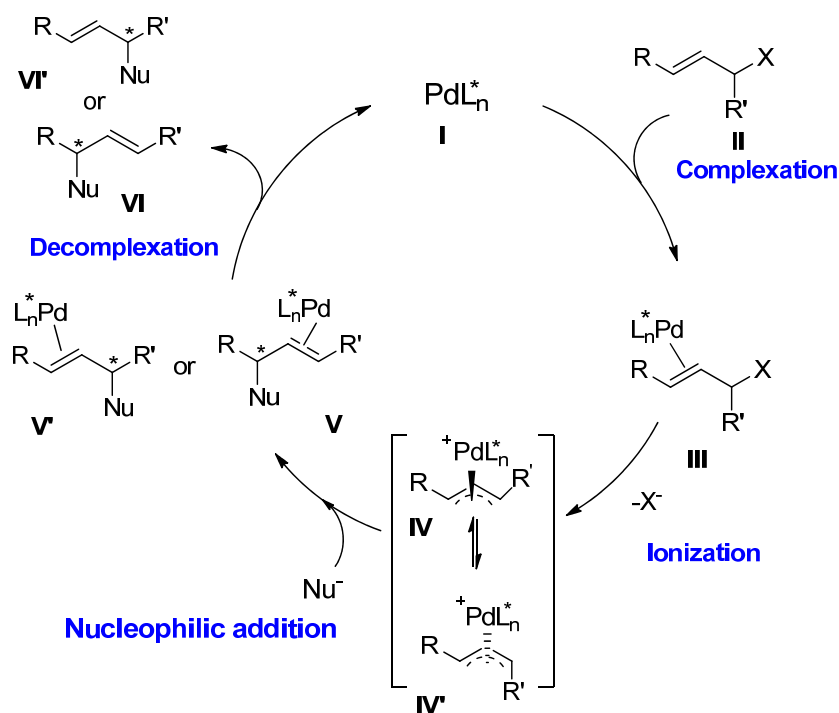


Asymmetric induction can be done by two different methods either by stereo control of the prochiral electrophile or the prochiral nucleophile. The process proceeds with different type of mechanism and can be described by considering different examples introduced by different group of researchers. A details discussion on the asymmetric induction for the synthesis of cyclic tetrasubstituted stereocenter is more common practice. [58] But the formation of acyclic quaternary stereocenter is still limited due to their conformation mobility. [59] Our focus in this part of chapter is to elaborate the idea of exploring the less accessible acyclic quaternary molecules using asymmetric allylic alkylation.

3.1.1 General mechanism of regio and stereospecific Pd-catalyzed asymmetric allylation

In the case of Pd-allylic alkylation, the most common mechanism operative involves an initial coordination of a chiral Pd(0) catalyst with an olefin bearing a leaving group at the allylic position (Scheme 25). Ionization occurs with inversion, where the η^2 - π -allyl-Pd(II) complex is situated on the opposite face to the leaving group. Alkylation of the η^3 - π -allyl-Pd(II) complex occurs with inversion of the stereochemistry about Pd(II), with simultaneous regeneration of the chiral Pd(0) catalyst. Because both the ionization and nucleophilic addition occur with inversion, the nucleophilic substitution occurs with net retention of the stereochemistry of the leaving group. An outer-sphere attack of a nucleophile is the most common pathway for soft nucleophiles ($\text{pK}_a <$

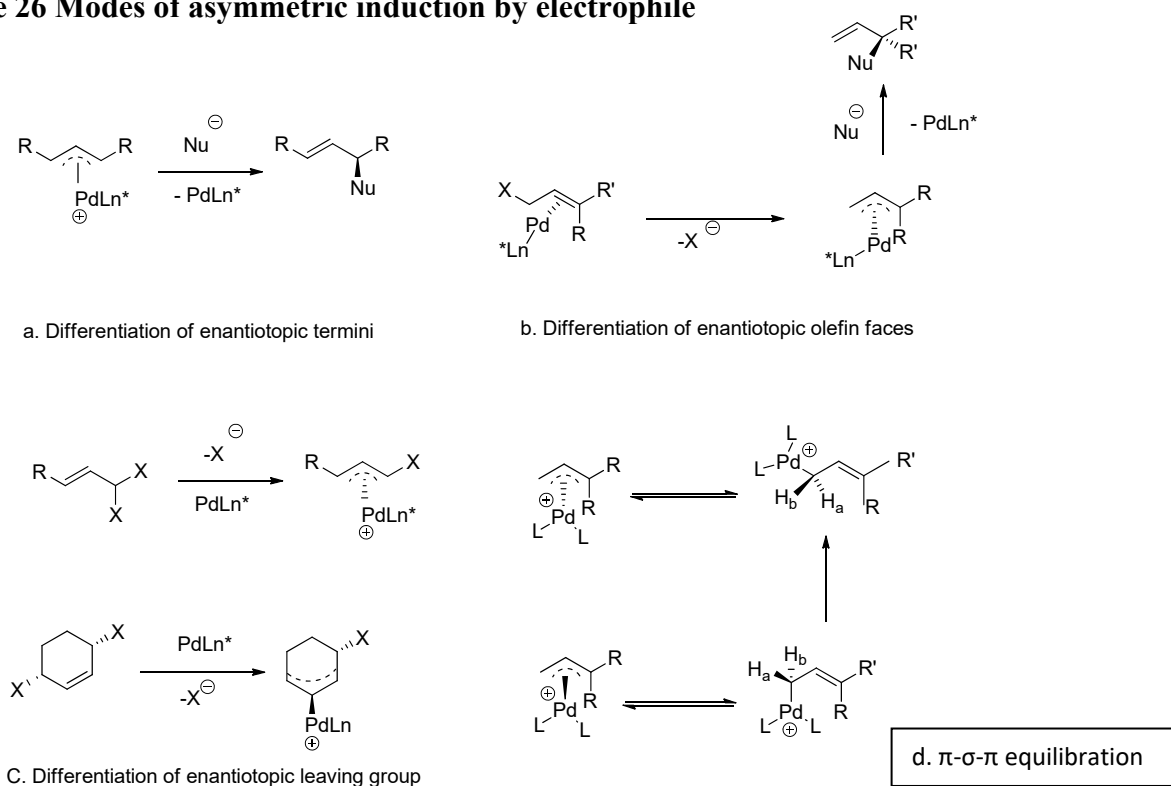
Scheme 25 Mechanism of regio and stereospecific Pd-catalyzed asymmetric allylation



25). For hard nucleophiles, the nucleophile attacks the metal directly and undergoes an inner-sphere reductive elimination with retention of stereochemistry about Pd(II), and overall net inversion of stereochemistry.

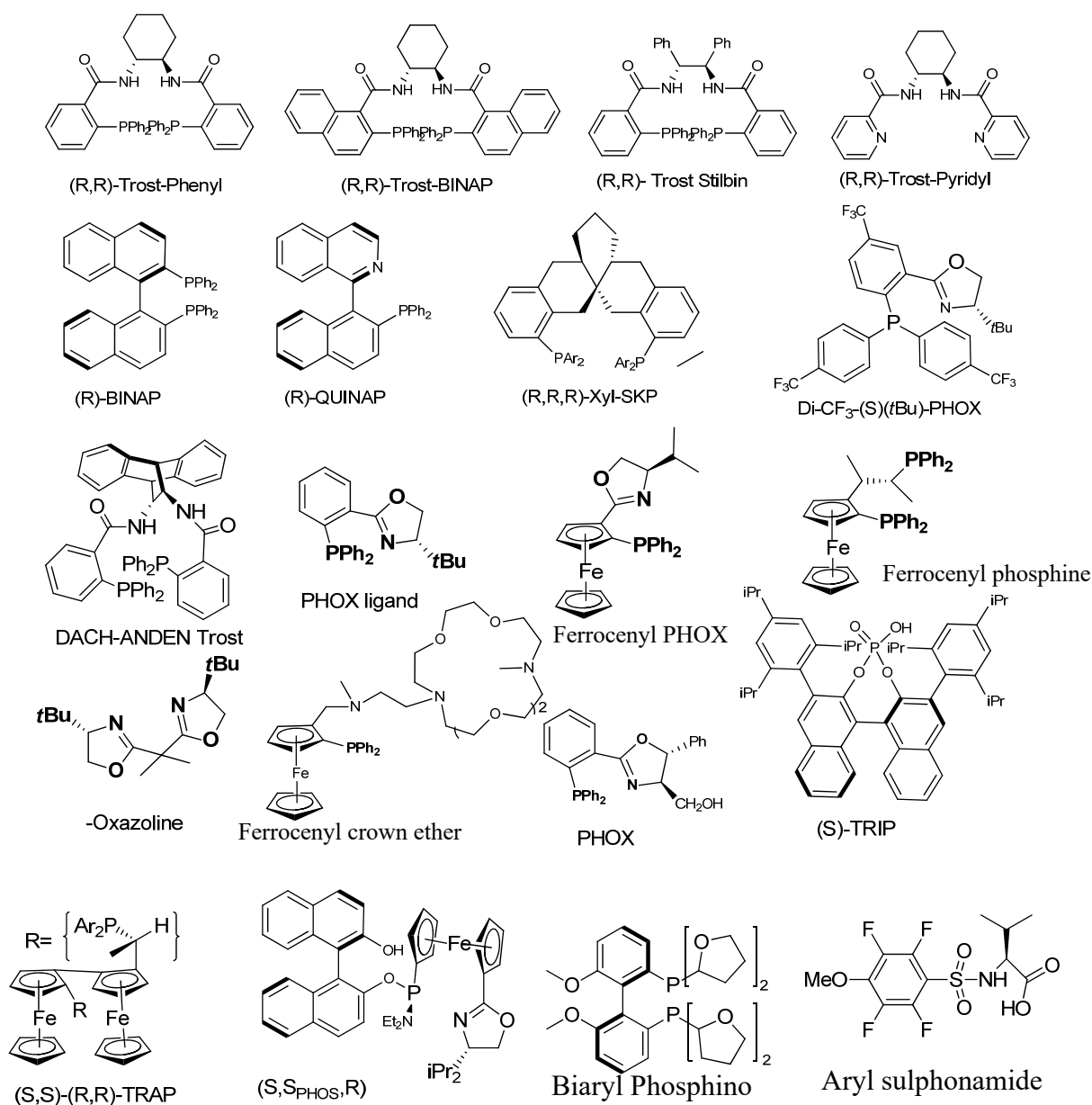
Nucleophiles such as ketone enolates alkylate at the α - carbon, producing a stereocenter on the nucleophile. In this case, asymmetric induction can be difficult to achieve since the C–C bond forming event most commonly occurs via an outer-sphere mechanism and the nucleophile remains distal to the chiral information about the metal–ligand environment. Alkylation of allyl electrophiles bearing substituents, although typically much easier substrates for obtaining asymmetric induction, operate via more complicated mechanisms involving π – σ – π equilibration of the π -allyl intermediate (**Scheme 26d**). Additionally, the enantio-determining step of the reaction may occur during any step of the catalytic cycle, save for dissociation of the alkylation product. In Pd-AAA, only two mechanisms are likely to be operative in the synthesis of acyclic

Scheme 26 Modes of asymmetric induction by electrophile



tetrasubstituted stereocenters on the electrophile, namely differentiation of enantio-topic olefin faces (**Scheme 26b**) and π - σ - π equilibration (**Scheme 26d**). In most cases, the chiral ligands employed in Pd-AAA are phosphines, and a variety of scaffolds have arisen from the many creative approaches toward acyclic stereocontrol in allylic alkylation (**Figure 5**). [60]

Figure 5 Examples of the variety of ligands widely used in Pd -AAA

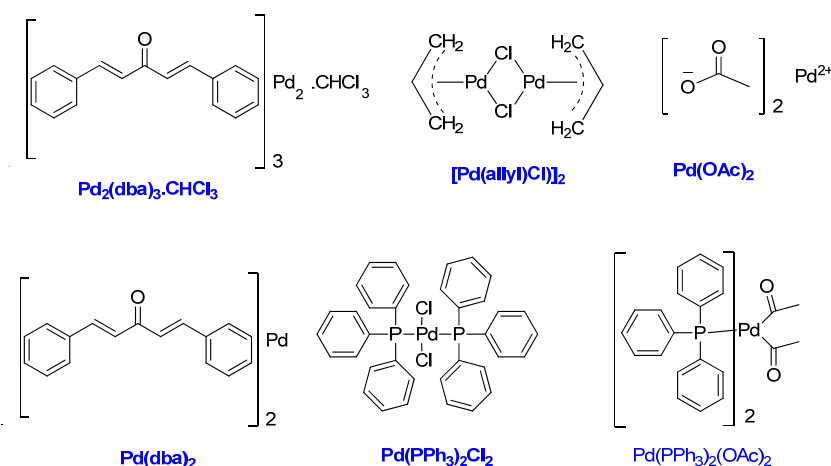


A feature that is unique to transition-metal catalyzed asymmetric allylic alkylation reaction is the ability to convert different types of starting materials such as chiral racemic, meso and achiral to enantiomerically pure compound. Therefore, several factors are primarily considered during the optimization study of the reaction conditions.

3.1.2 General consideration for optimizing reaction procedure for Pd-AAA

- Choice of appropriate solvent system that effect the formation of stable catalyst-ligand complex with solvent cage sometimes ion pair interaction
- Choice of appropriate source of metal to reduce the interaction of the leaving ligand in the reaction system. Such as a leaving ligand can act as a base and influence the reaction rate of the incoming electrophile/nucleophile and a bulky substituent attach to the catalyst stable complex may act on formation of desire geometry of the Catalyst-Ligand complex. Some of the commonly used Pd(0) source widely used in Pd-AAA or Pd-DAAA have shown in **Figure 6**.

Figure 6 Examples of some commercially source of Pd(0) as a catalyst



- iii. Choice of ligand that hinder one site of the electrophile (during inner sphere reaction mechanism) and exposed another site for the nucleophilic
- iv. attack selectively. For the outer sphere mechanism, the metal directly interacts with the substrate. The types of ligands to effect the site selective transformation have followed three general concepts in design: (1) creating chiral space with an array of groups whose conformational bias originates from primary stereogenic centers [61] (2) desymmetrization of electron density on the donor atoms of the ligand where different bond lengths on each side of the chiral space promote differential reactivity at each terminus [62] (3) attaching a tethering agent to the main skeletal symmetry which can coordinate with the incoming nucleophile. [63] **Figure 5** lists those ligands which are most prevalent in AAA-driven natural product total synthesis.
- v. Tuning the reaction temperature controls the kinetics of the reaction and thus influence the preferential formation of thermodynamic and kinetic products.
- vi. Addition order of the reactant may control the availability of the substrate to the catalyst-ligand system.
- vii. Choice of proper electrophile based on the lability of the leaving group and steric hindrance of the attacking site by the catalyst-ligand complex or toward the nucleophile
- viii. Controlling the concentration of the substrate on selected solvent system increases the interaction of the reactant molecules and thus control the rate of reaction
- ix. Use of different additives participate in some way such as formation of H-bonding, works as a linker, increase the availability of the rapid molecular interactions may

affect the reaction outcomes. [64]

- x. Consistency of the required reaction environment such as inert atmosphere, controlled increase or decrease of temperature and pressure.

Therefore, a fine tuning of all the different factors mentioned earlier can introduce an excellent outcome of getting one optically pure compound. Some other techniques of getting one selective isomer such as kinetic resolution, dynamic kinetic resolution, chiral derivatization is limited due to the additional step or the reduced yield because of the separation. Therefore, the significance of an enantiomer selectively is utmost goal for the organic chemist.

3.1.3 Approaches involved in stereocontrol interactions of Pd-AAA

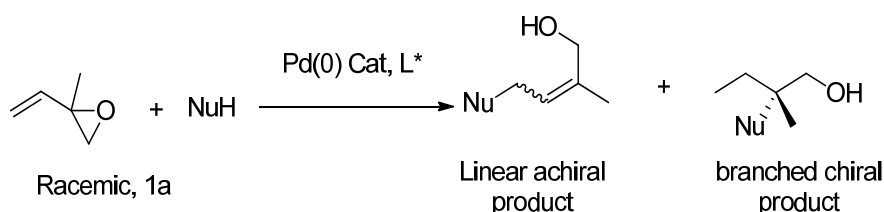
Herein our discussion of the asymmetric induction will be based on two different approach:

1. Stereocontrol of the prochiral electrophile and
2. Stereocontrol of the prochiral nucleophile

3.1.3.1 Stereocontrol on prochiral electrophiles

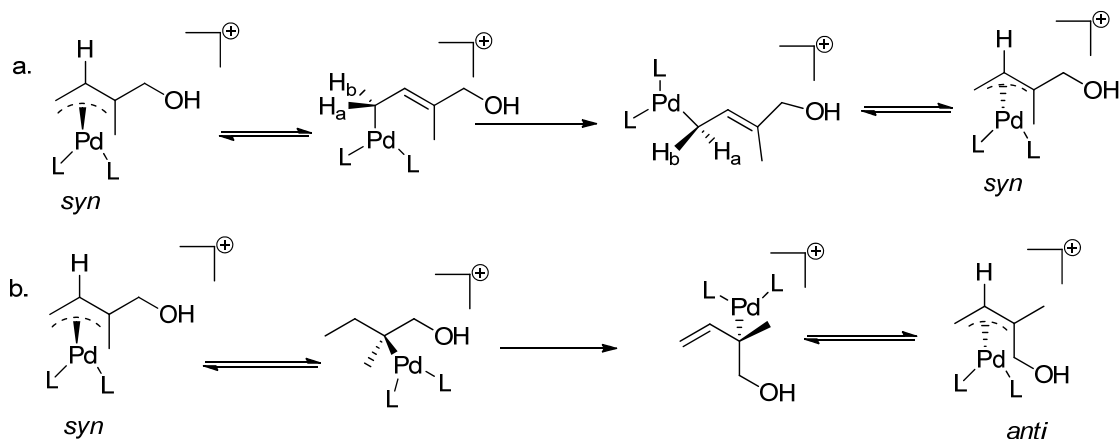
An ideal example of the Pd-AAA of prochiral electrophile was introduced by the Trost group using isoprene monoepoxide back in 1998. The success of this novel approach was due to the alkylation at the branched position for carbon, [65] oxygen [66] and nitrogen [67] nucleophiles to afford acyclic tetrasubstituted building blocks (**Scheme 27**).

Scheme 27 Pd-AAA strategy for the synthesis of acyclic tetrasubstituted building blocks by using electrophilic isoprene monoepoxide



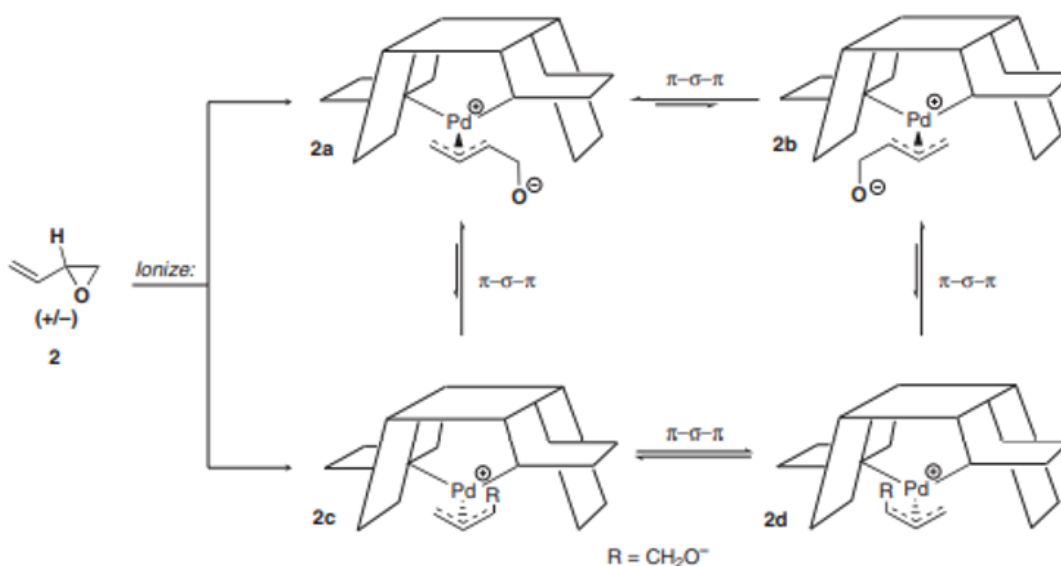
Their approach was basically a dynamic kinetic asymmetric transformation (DYKAT), whereby they choose the racemic isoprene monoepoxide which is ionized by a palladium catalyst, with the initially formed π -allyl species bearing an opposite sense of chirality or opposite syn/anti configuration (**Scheme 28**). Since π -allyl contains two hydrogen substituents on the unbranched terminus, the η^1 - σ -Pd(II) complex allows for rotation from one stereoisomer to the other without syn/anti isomerization (**Scheme 28a**). They have considered the π -allyl complex that places the higher priority group cis to the central hydrogen as the syn isomer. But the π -allyl stereochemistry and the syn/anti configuration have isomerized at the branched carbon because of the π - σ - π equilibration (**Scheme 28b**). An important structural consideration for this reaction can be represented by flap and wall model involving the equilibrium between syn and anti-isomers (**Scheme 29**).

Scheme 28 Mechanism of dynamic kinetic asymmetric transformation (DYKAT) of Isoprene monoepoxide



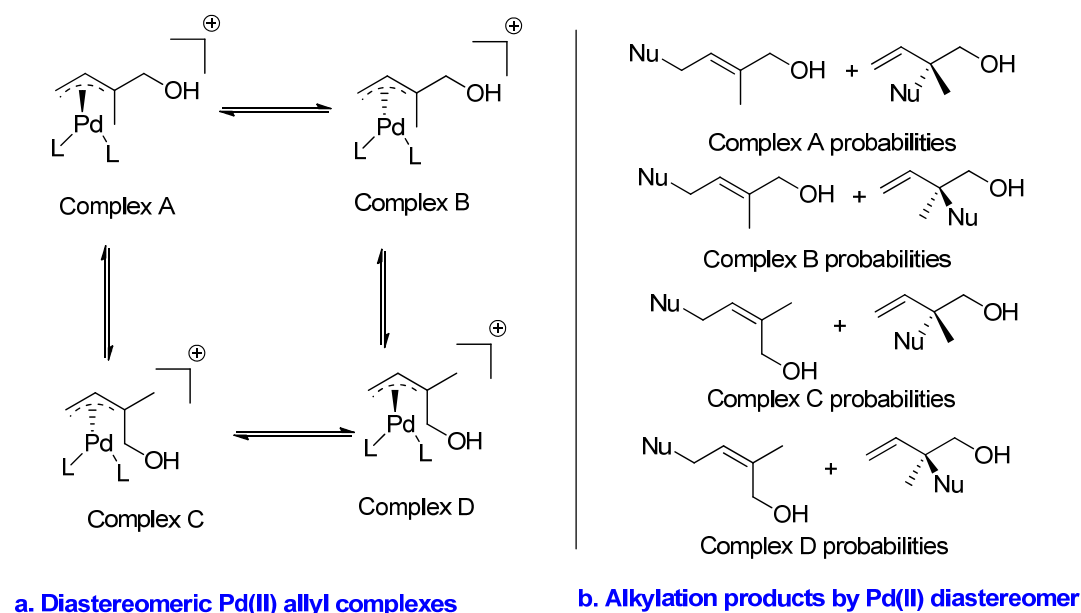
A pair of diastereomeric π -allyl complexes are formed due to the ionization of butadiene monoepoxide (**2**). The presence of more sterically hindered hydroxymethylene substituent compared to the hydrogen substituent favors complex **2a** due to the least amount of steric clash with the ligand (flap-wall) environment. The regioselectivity of such nucleophilic addition shows

Scheme 29 Cartoon model for wall and flap concept inducing regio and stereoselective AAA



an opposite idea of typically observed for Pd-AAA, where the branched isomer is formed in high selectivity mostly. Therefore, ‘wall and flap model’ becomes an attractive design to represent the approximate chiral environment about each terminus of the electrophile based on chelation of a C2-symmetric ligand bearing diarylphosphines (i.e., Trost ligand, BINAP). In fact, if we compare the case of isoprene monoepoxide (**1a** as shown in **Scheme 27**), the methyl and hydroxymethylene substituents they are sterically very similar but the presence of an alkoxide from the epoxide opening improvise the electronically dissimilarity (**Scheme 30a**). As a result, we can dictate three factors for the alkylation at the branched terminus, namely: 1. The alkoxide group present in the molecule behaves more like a leaving group often acts as a base for the pronucleophile 2. They are also engaged in hydrogen bond directed alkylation of the nucleophile. 3. Ligand and additive effects can alter the most favorable trajectory of the incoming nucleophile toward the branched

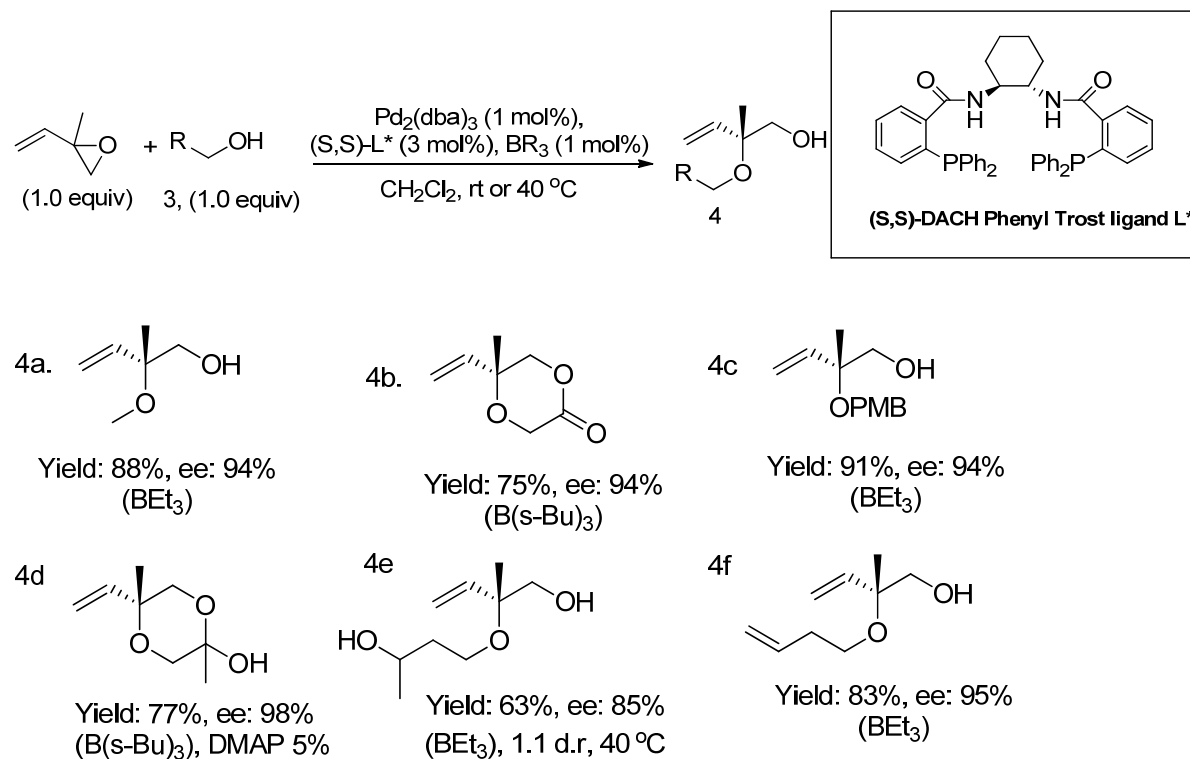
Scheme 30 Mechanistic pathways for Pd-AAA of isoprene monoepoxide



product. [68] The outer-sphere nucleophilic attack occurs with inversion of the stereochemistry of the π -allyl, and each enantiomer of product can be obtained from two of the stereoisomeric complexes (**Scheme 30b**).

Later in 2004, it was observed by the same group that, primary alcohol can be alkylated at the branched carbon with high enantioselectivity in the Pd-AAA of isoprene monoepoxide (**Scheme 31**). [65] The reaction introduced the useful interaction of the alkyl boron substance during exploring the scope of several primary alcohols **3** as competent nucleophilic partners in this

Scheme 31 Synthesis of tertiary ether through the Pd-AAA of prochiral electrophile isoprene monoepoxide

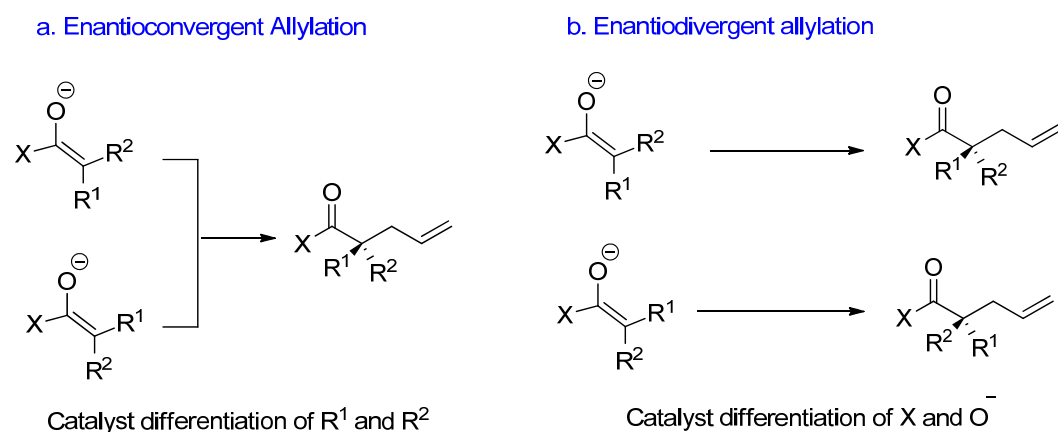


reaction. For substrates with low enantioselectivity using triethylborane as catalyst, it was reasoned that etherification was occurring faster than the required π -allyl equilibration. Use of the relatively bulky tri-sec-butylborane proved useful for solving this problem (**4b** and **4d**). With a hampered rate of etherification, the products were formed with higher enantioselectivity. Spontaneous cyclization to a hemiketal (**4d**) or lactone (**4b**) occurred when the nucleophilic alcohol contained a pendant ketone or methyl ester respectively. The etherification product due to the addition of 4-methoxybenzyl alcohol is a particularly useful synthetic precursor due to the ubiquity of PMB-protected alcohols in synthetic sequences.

3.1.3.2 Stereocontrol on prochiral nucleophiles in Pd-AAA reaction

Achieving high enantiocontrol on nucleophiles remains fundamentally more difficult than getting enantiocontrol on the electrophilic partner, due to the change of mechanism from inner sphere to outer sphere mechanism for nucleophilic addition. For this type of approach, the chiral environment created by the metal catalyst-ligand is distal from the isolated nucleophile. Therefore, the nucleophilic attack of specific site selective face is challenging. This problem is combined by the presence of enantioconvergent and enantiodivergent allylation pathways (**Scheme 32**).

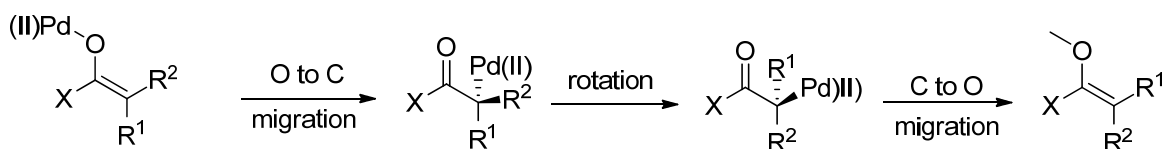
Scheme 32 Catalytic recognition of prochiral nucleophile (enolates)



In the case of enantioconvergent allylation (**Scheme 32a**), the chiral catalyst recognizes the substituents at the site of reaction. Although the restriction of controlling the enolate geometry has been removed, R¹ and R² are limited to sterically differentiable substituents (i.e., alkyl vs. aryl). When an enantiodivergent pathway is operative (**Scheme 32b**), the catalyst recognizes the substituents vicinal to the site of reaction. This pathway is desirable if R¹ and R² are of limited steric differentiation; however, the enolate geometry must be strictly controlled to observe high

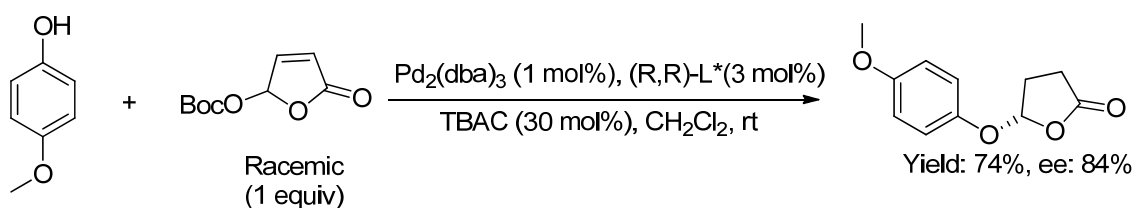
enantioselectivity. The enantiodivergent pathway has an important advantage over the enantioconvergent pathway since the identity of X can be exploited as an achiral auxiliary and a tunable parameter for reaction optimization. As will be seen, both the α -substituents and the enolate geometry are commonly recognized by the catalyst in the allylation event. In this case, the presence of match-mismatch effects will be apparent when both enolate isomers can be synthesized in geometrically pure form. The stereo fidelity of the enolate is assumed to remain intact during enantio-divergent allylations; however, oxygen-to-carbon migration may provide a mechanism for erosion of the enolate geometry if palladium enolates are formed as intermediates (**Scheme 33**). A potential example was summarized by the isomerization of palladium enolates which has been

Scheme 33 Potential mechanism for the erosion of enolate stereochemistry

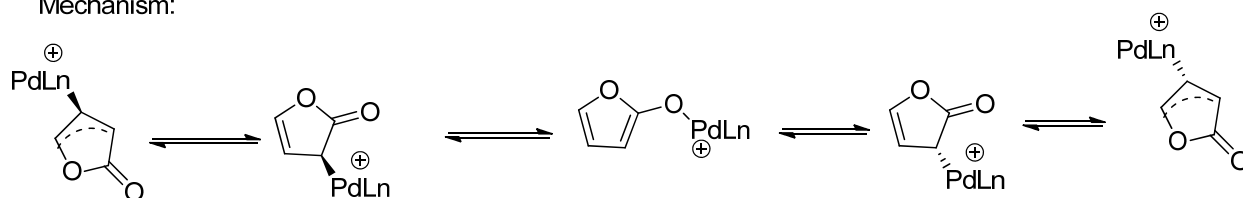


Scheme 34 Reaction example shows the enolate erosion mechanism

Example reaction:



Mechanism:

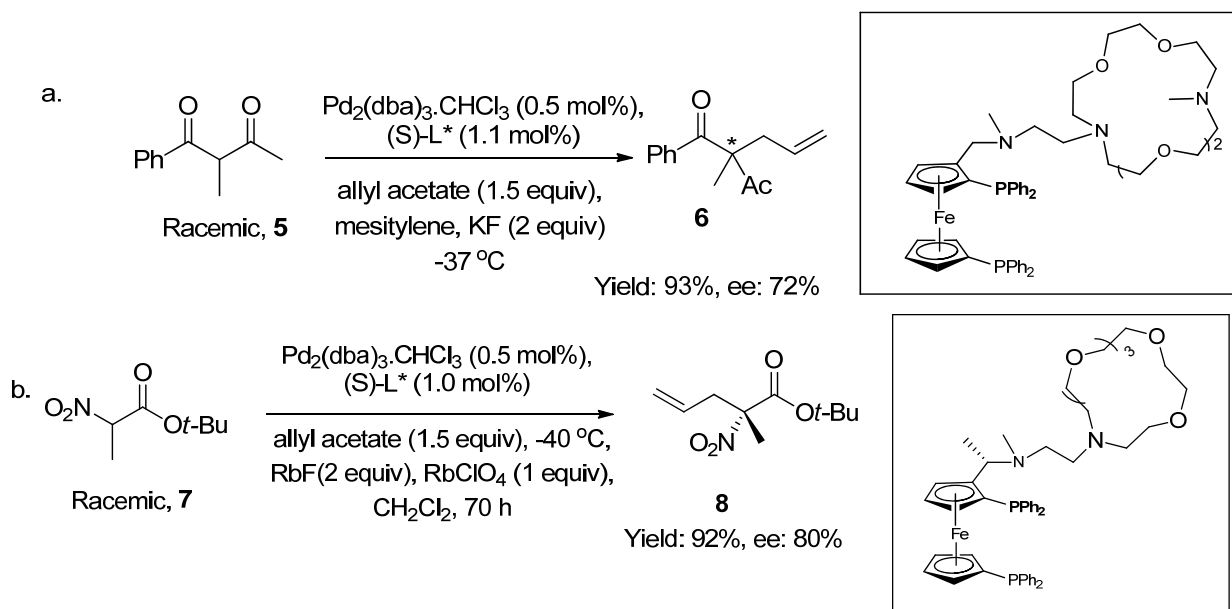


exploited for the Pd-AAA DYKAT of butenolide electrophiles with phenolic nucleophiles (**Scheme 34**). [69] In this scenario, the palladium enolate is formed on the butenolide electrophile and the mechanism for isomerization of the π -allyl species involves carbon-to oxygen migration. Another complicity of inducing asymmetry has been so far explored quite a bit based on the accomplishing control of enolate geometry. In situ formation of enolate using external base/additives or the intentional synthesis of O-allyl/O-carboxy allyl in control E/Z geometry (of course sometimes racemic) using control equivalence of base are two most popular approach. As a result, there are two different approach namely intermolecular asymmetric allylation and intramolecular asymmetric allylation has been introduced so far.

3.1.3.2.1 Intermolecular alkylation of prochiral nucleophiles

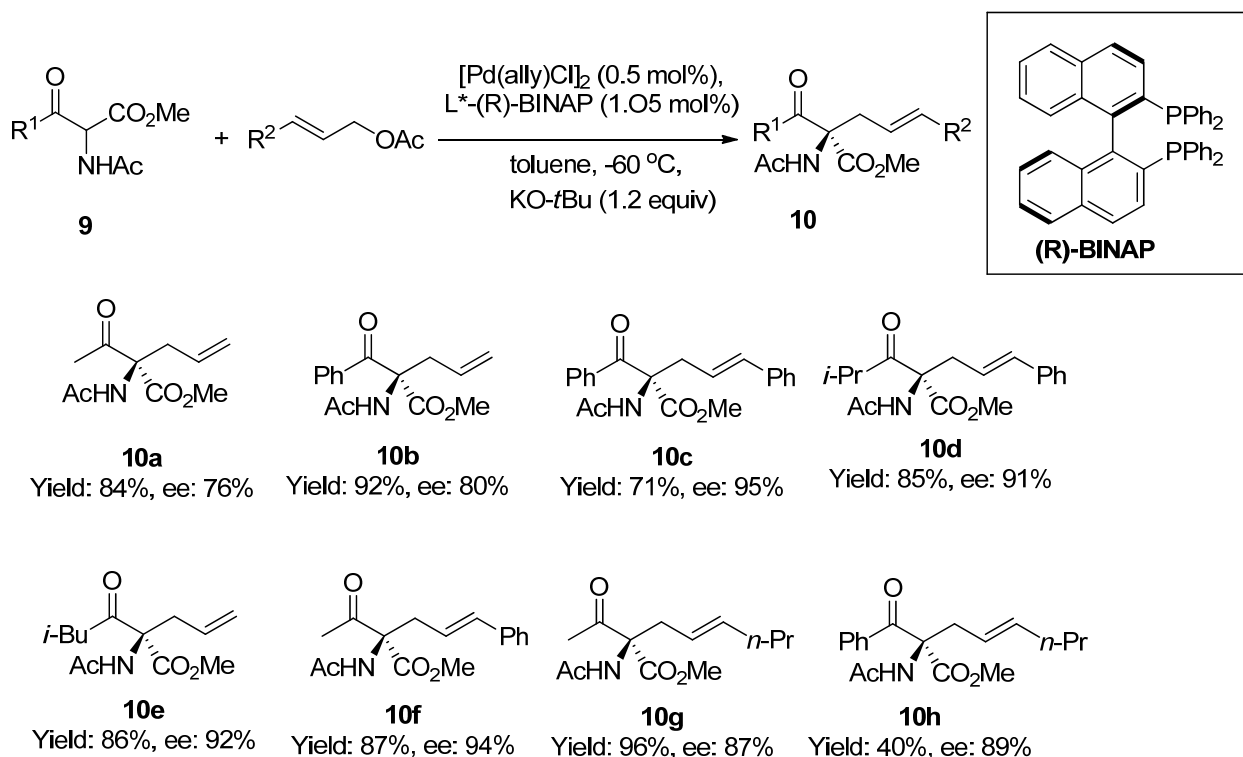
Many of the first syntheses of acyclic tetrasubstituted stereocenters by reactions of prochiral nucleophiles were discovered by the Ito group. In 1992, Ito et al reported the allylation of an acyclic 1,3-diketone **5** (**Scheme 35a**) in modest enantioselectivity by employing Ferrocenyl ligand (point and planar chiral) scaffold bearing an aza-crown ether. [70] Later in 1996, the same group established allylation of a challenging aliphatic α -nitro ester **7** by utilizing the similar strategy mentioned earlier (**Scheme 35b**). [71] In order to enhance enantioselectivity upon nucleophilic attack of a π -allyl Palladium (II) complex, it was envisioned that linking a crown ether to chiral phosphine ligands would allow for recognition of the nucleophile counterion. In this case, the chiral information of the catalyst could be relayed distal the site of the reaction, thus solving the problem of poor selectivity when using prochiral nucleophiles in Pd-AAA. In both cases, significant optimization of the crown ether and counterion was required to obtain the enantioselectivity.

Scheme 35 Asymmetric allylation of a 1,3-diketone and an alpha nitro ester by counterion recognition of a chiral phosphine ligand



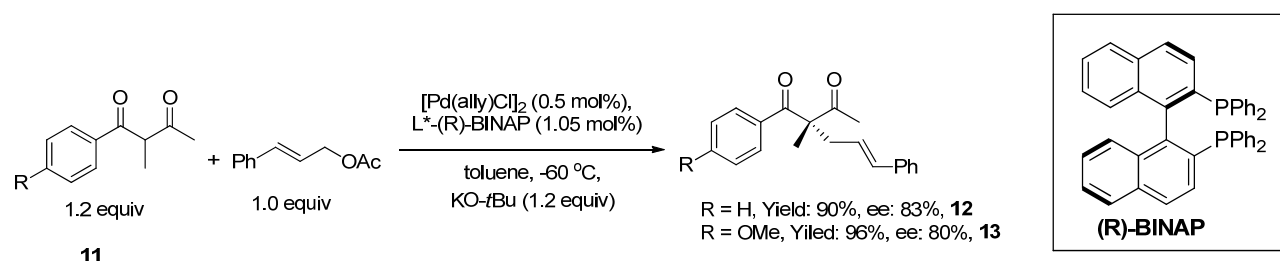
An early report on asymmetric induction utilizing acyclic prochiral nucleophiles was provided [72] on α -acetamido- β -keto esters **9** using Pd(0)/BINAP-catalyzed Pd-AAA (**Scheme 36**). High levels of enantioselectivity were reported when using potassium tert-butoxide as base. Additionally, high geometric control of the resulting olefinic products **10** was reported, even for commonly difficult allylic acetates as an electrophile such **10g** and **10h**. The highest enantioselectivities were observed for cinnamylation reactions mostly for electron stabilized cinnamyl acetate (**10c**, **10d** and **10f**), simple allylations proceeded in good enantioselectivity as well.

Scheme 36 Pd/BINAP-catalyzed allylation of α -acetamido- β -keto ester



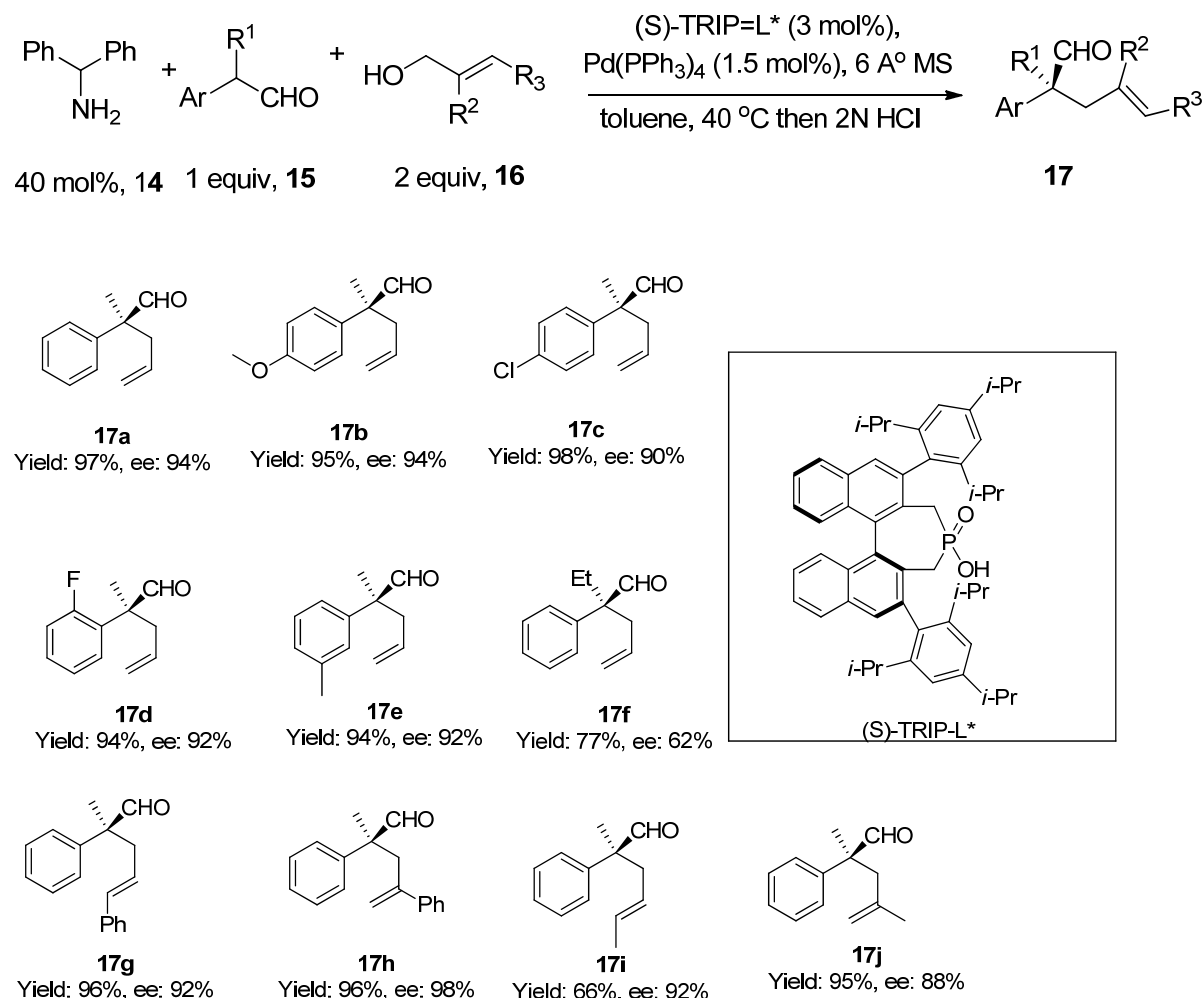
Other work by the Ito group demonstrated acyclic control in the cinnamylation of 1,3-diketones (**Scheme 37**). [73] They have demonstrated the cinnamylation of acyclic 1,3- diketones in good enantioselectivity. Cryogenic temperatures were required for high enantiocontrol in this reaction, however, in conjunction with their work on α -acetamido- β -keto esters and α -acetamido- β -ketophosphonates, these reactions serve as some of the earliest examples of Pd-AAA with stereocontrol on acyclic nucleophiles under simple catalyst conditions.

Scheme 37 Pd-Catalyzed asymmetric allylation of β -keto ester



In 2011, List and Jiang were able to demonstrate the asymmetric α -allylation of α -arylpropanals, **15** under three-way catalysis using chiral acid, enamine, and palladium (**Scheme 38**). [74] Surprisingly, they optimized the reaction using an achiral source of palladium, Palladium tetrakis, by achiral amine catalyst, **14** in the presence of (S)-TRIP phosphoric acid L^* . In addition to allyl alcohol, more substituted alcohols **16** were effective in the reaction. The limitation of this protocol is that elongation of the aliphatic aldehyde side chains of α -arylpropanals diminishes the enantioselectivity albeit with reduced yield **17f** even though the reaction showed impressive display of control for asymmetric quaternary carbon synthesis.

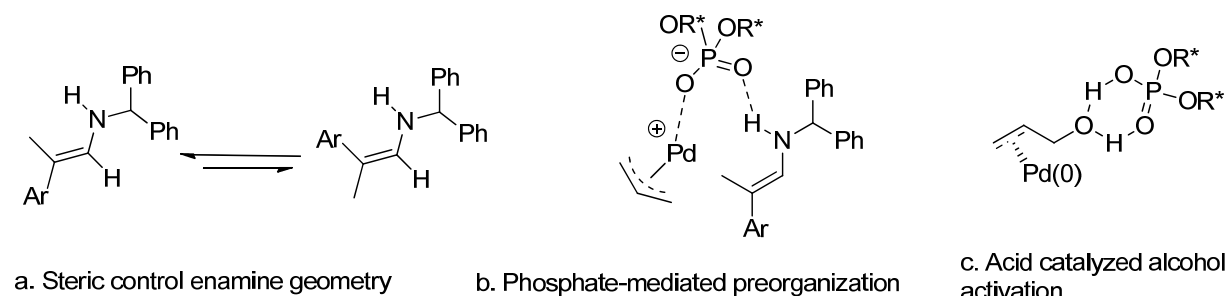
Scheme 38 Direct α -arylation of α -arylpropanals with allylic alcohols



In the discussion they stated that the geometry was highly controlled firstly due to the in situ transiently formed chiral enamine due to their steric elements (**Scheme 39a**), and then the chiral information is transferred by hydrogen bonding by the enamine to the chiral phosphate (**Scheme 39b**). The chiral phosphoric acid also acts as a ligand to the π -allyl-Pd(II) species. The resulted complex is counterion-paired with the cationic π -allylpalladium(II) species, asymmetric induction can be realized in the alkylation event. Interestingly, under the reaction conditions, allyl alcohols

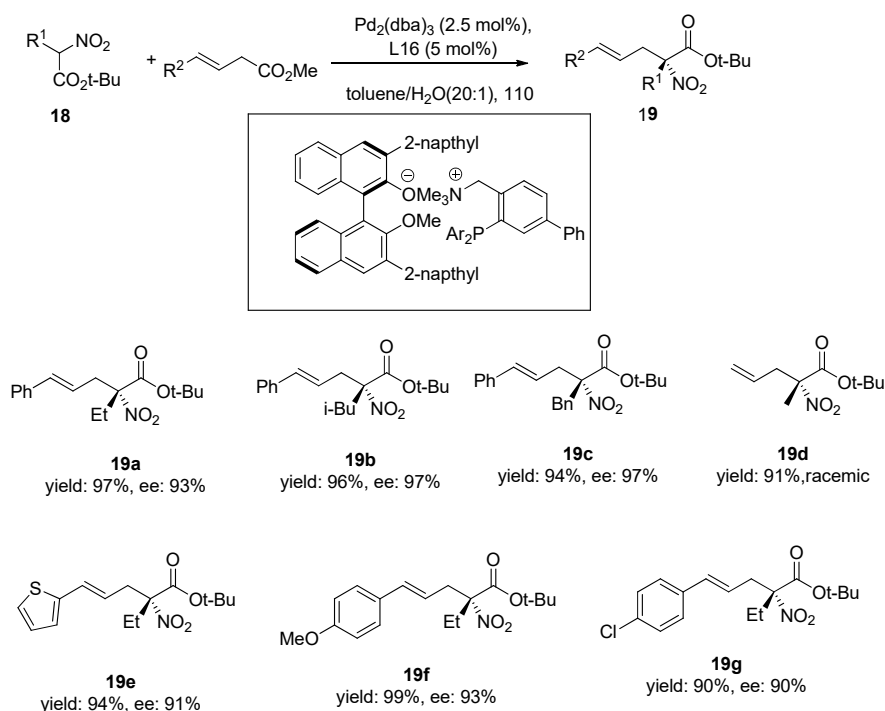
can be used directly, due to the activation of the hydroxyl leaving group by the phosphoric acid (Scheme 39c).

Scheme 39 Typical features related to the triple catalytic activation



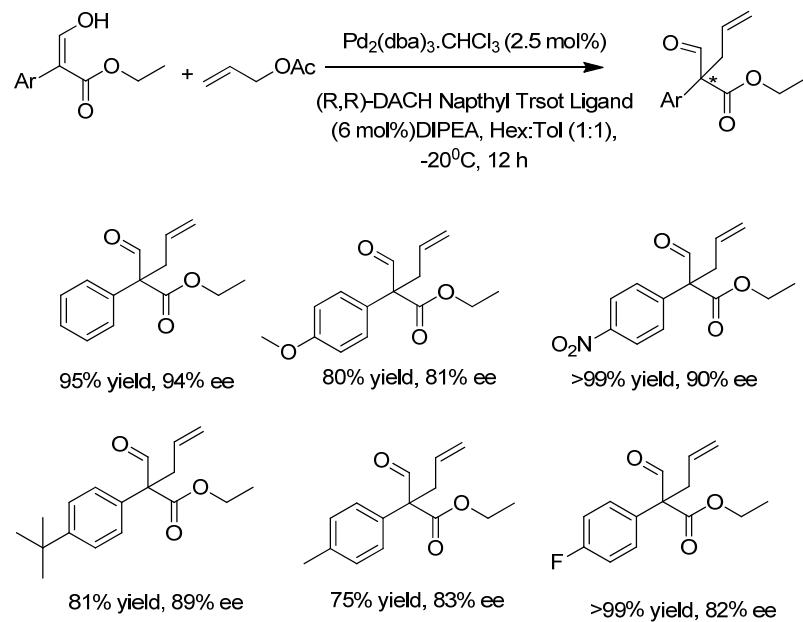
A dual-catalytic approach was showed by Ooi's group for the α -cinnamylation of α -nitro esters shown in (Scheme 40). [75] They have also employed the achiral phosphine like system developed by List and Jiang. A Pd/ligand ratio of 1:2 was used, as it was believed that a C2- symmetric palladium complex would form upon cis-complexation of the phosphine ligands. An interesting finding about this synthesis is the use of a linked cationic ammonium functionality with the chiral BINOL counterion. Excellent yields and enantioselectivities were observed for the reaction when using cinnamyl carbonate electrophiles (Scheme 40) although no enantioselectivity was observed for the simple allyl system (19d).

Scheme 40 Chiral counterion strategy for the cinnamylation of α -nitro esters



In 2015, Hossain et al published the first unprecedented example of the Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-hydroxy aryl acrylates for the synthesis of all-carbon α -aryl quaternary aldehydes. [76] The formation of servocontrolled enol/ protection of enol with bulky protecting group are the common practices but the use of unprotected enol as a nucleophilic counterpart with a thorough optimization ligands, solvents, temperatures was not established before, the group published an excellent enantiocontrol by a fine tuning of variables and resulted ee up to 94% with quantitative yield. Both the electron donating and electron withdrawing substituents resulted from good to excellent enantio-discriminations as shown in Scheme 41.

Scheme 41 Enantiocontrol synthesis of acyclic quaternary carbon from unprotected enol and its synthetic scope

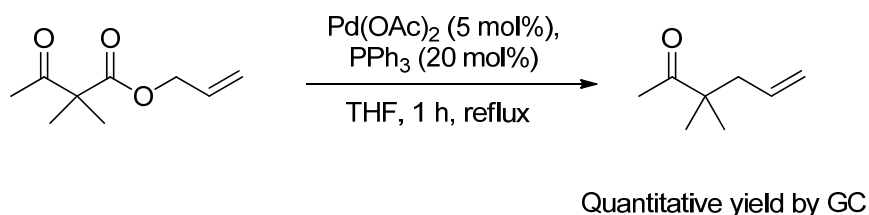


3.1.3.2.2 Intramolecular Pd-mediated asymmetric allylic alkylation

A. Pd-Catalyzed Decarboxylative Asymmetric Allylic Alkylation (Pd-DAAA)

The intention of inserting allylic groups into the α -position of carbonyl-containing compounds was first reported by Carroll in 1940. [77] In this version of the Carroll rearrangement, $\text{Pd}(\text{OAc})_2$ in the presence of triphenylphosphine, was employed as the catalyst (**Scheme 42**). However, the reaction only found limited scope in organic synthesis due to the harsh conditions required to induce the [3,3]-sigmatropic rearrangement. The limitation was overcome by Tsuji-Trost reaction through the development of mild synthetic route to the formation of allylic compounds via π -allyl palladium complexes. [78] The unique idea involves the reaction of activated nucleophiles such as enolates, amines and phenols with allylic compounds such as allyl acetates and allyl halides, allyl carbonates and allyl mesylate/tosylates. In 1980 Tsuji and Saegusa independently reported the decarboxylative allylation of β -keto allyl esters (**Scheme 42**). [79] Here the electrophile and nucleophile are generated in situ eliminating the requirement to prepare preformed enolate equivalents.

Scheme 42 Pd-catalyzed Carroll rearrangement by Tsuji

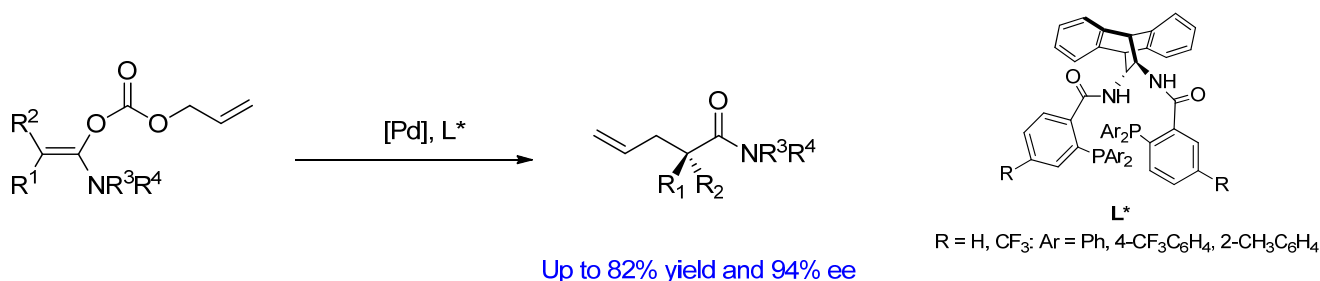


During the 1980s other groups extended the substrate scope to allyl enol carbonates, silyl enol ethers and enol acetates. [80] Although regioselectivity was excellent for the above transformation, it was a further 20 years before the reaction was performed enantioselectively. Several methods to

address their synthesis have been developed, particularly in cyclic systems. [81] In acyclic systems, however, the synthesis of this motif is less explored. [82] This is in part due to additional problems that often arise in acyclic systems such as reduced rigidity of substrates leading to lower levels of selectivity. Additionally, selectively controlling the formation of fully substituted olefins/enolates is required for high selectivity in many catalytic processes. In the case of electrophilic functionalization of fully substituted enolates, the general and selective formation of such enolates as pure geometric isomers is highly challenging and has slowed progress. Although selective enolizations have been reported, these typically require highly specialized substrates, often incorporating chiral auxiliaries to impart selectivity in the enolate formation step. [83]

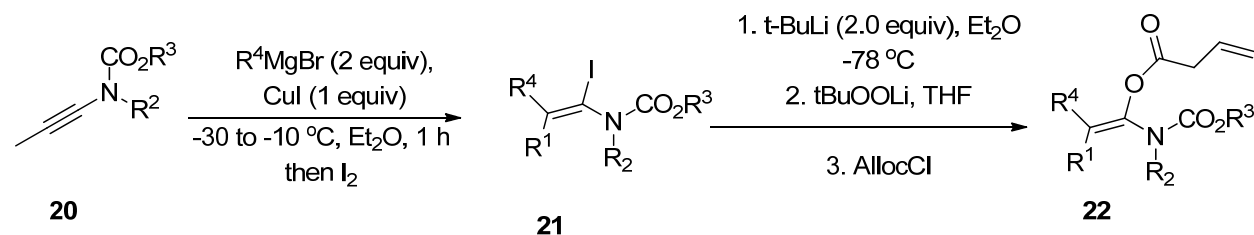
Recently a practical approach of Pd-DAAA for the formation of acyclic quaternary carbon was introduced by Marek et al in 2004 involving the use of achiral acyclic amide enolates in combination with enantioselective palladium-catalyzed decarboxylative allylic alkylation technology (**Scheme 43**). They have synthesized the carboxy allyl enolate species in two steps.

Scheme 43 Palladium-catalyzed enantioselective decarboxylative asymmetric allylic alkylation of stereo defined acyclic enolates (by Marek)



[84] A copper-promoted carbomagnesiation reaction using Normant-type reagent (RMgBr/CuI in a 2:1 ratio) provided highly regioselective formation of compound **21** in diethyl ether as solvent.

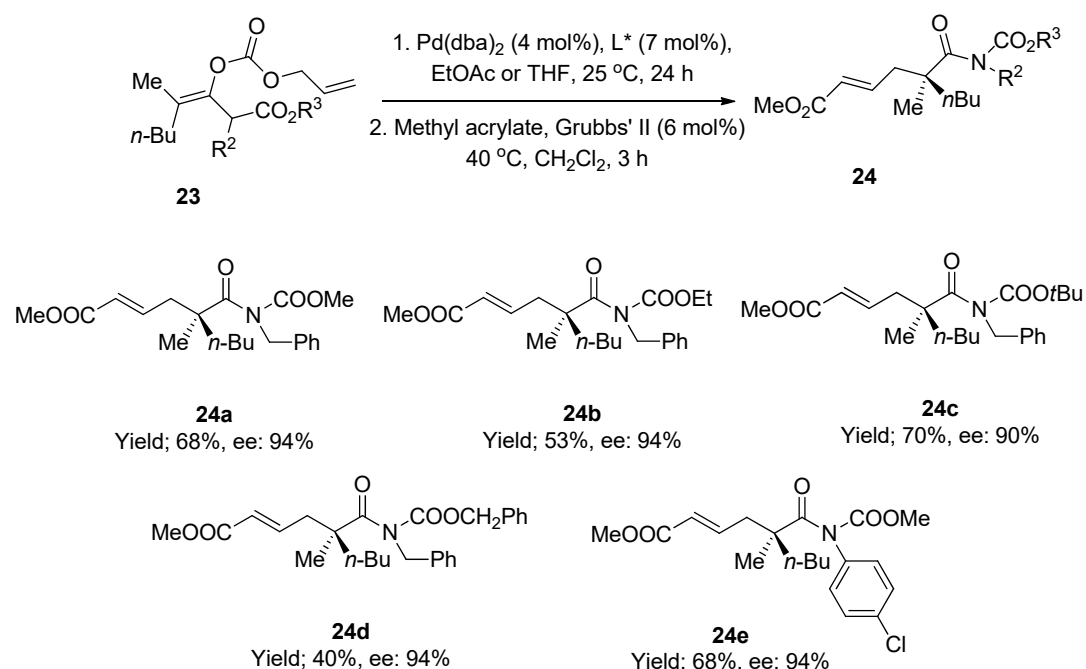
Scheme 44 Synthesis of stereocontrolled carboxy allyl enolate



Then the resulting vinyl magnesium species with molecular iodine leads to the formation of fully substituted vinyl iodide **21** in excellent yields as a single constitutional isomer (**Scheme 44**). The vinyl iodide is then directly converted to the corresponding vinyl lithium species by iodine–lithium exchange. Finally the oxidation with an externally prepared oxenoid (t -BuOOLi) retained the stereoselectivity. The resulting stereodefined fully substituted enolate is then reacted with AllocCl to deliver well-diversified products **22** in excellent yields as single isomers as shown in **Scheme 44**.

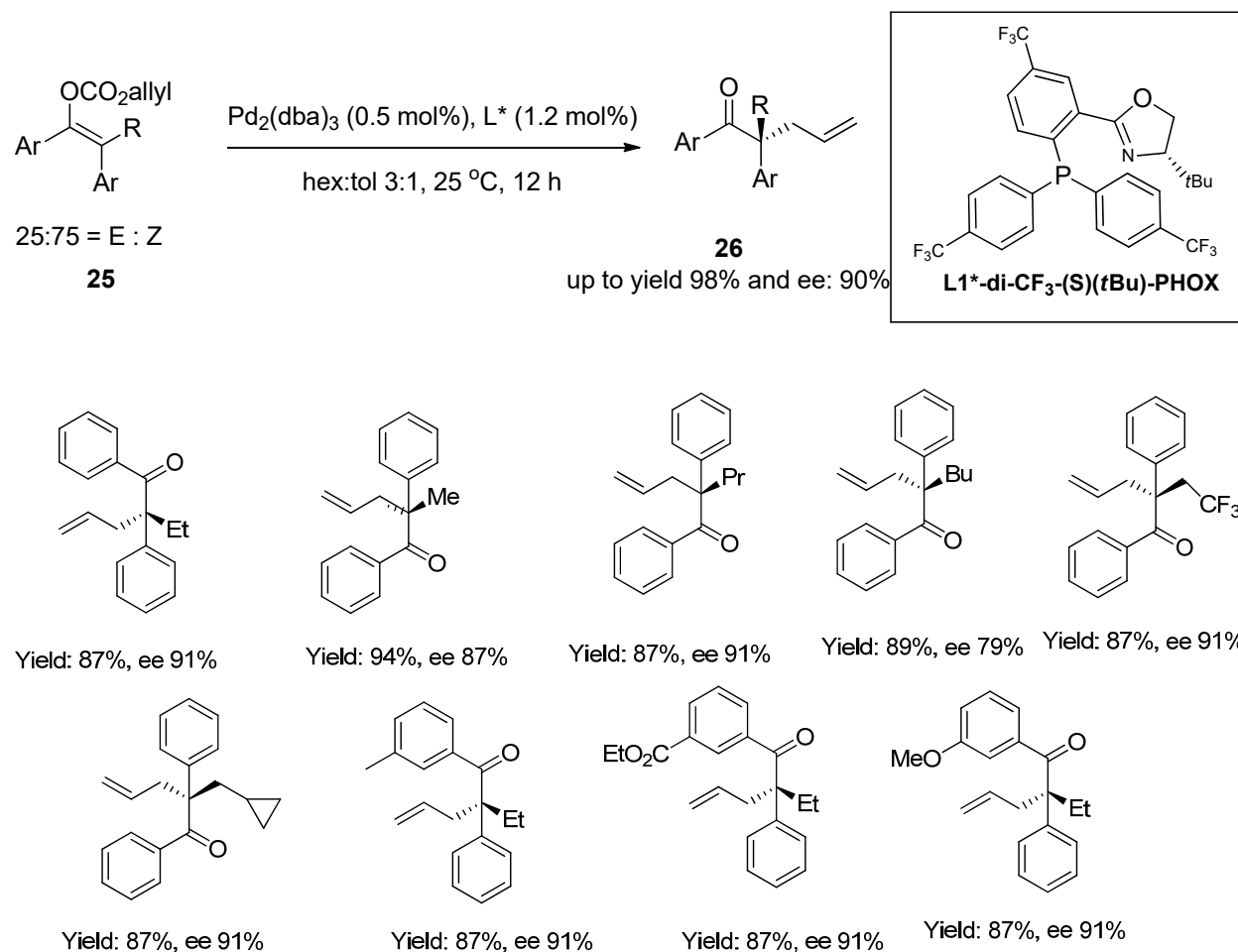
Later they reported an excellent outcome of the asymmetric induction using chiral Trost ligand by a thorough optimization of ligands, solvents, catalyst loading. During the study they realized the enolate geometry plays the vital roles for the conservation of enantioselectivity and therefore the syn position of small substituent to the allyloxycarbonyl group concluded as a favorable enolate structure for getting high optical purity of the desired compound. [85] Gratifyingly, the scope of the reaction process appears to be fairly broad with respect to the R^3 substituent on the carbamate group ($COOR^3$ where $R^3 = Me, Et, t-Bu$ and Bn ; **23a–c**, respectively) and produced reaction products **24a–c** of uniformly high enantiomeric excess.

Scheme 45 Synthetic scope of the stereoconfined Pd-DAAA



Recently, Stoltz group has become interested in preparing fully substituted acyclic enolates and applying them toward the synthesis of acyclic quaternary stereocenters, particularly via transition-metal catalyzed allylic alkylation (**Scheme 46**). [86] While palladium-catalyzed allylic alkylation has been employed in the synthesis of acyclic tertiary stereocenters, the formation of all-carbon quaternary stereocenters has proven more challenging. Using the allylating agent consistently they found a huge impact of solvent especially non-polar solvents such as 3:1 mixture of hexane/toluene for providing highest and most reproducible yields. In this solvent system, using ligand L1^* gave the desired product obtained in 98% isolated yield and 90% ee. They have also reduced

Scheme 46 Pd-DAAA for carboxyallyl substrate (with selective scopes) by Brian Stoltz

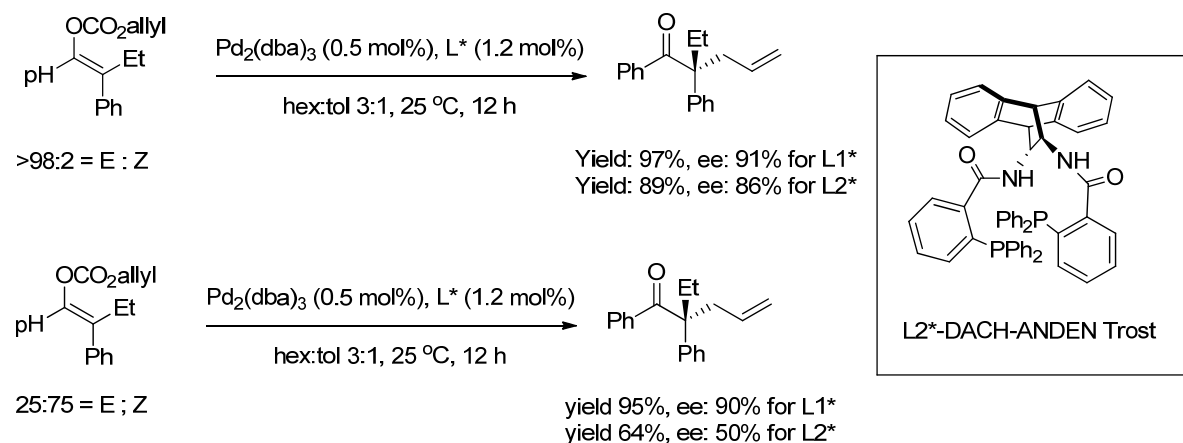


the catalyst loading from 1.0 mol% to 0.5 mol % and found similar yield and selectivity without significantly increasing reaction time. Some of the selective substrate scope of the reaction has been presented in the **Scheme 46**.

After optimizing the reaction conditions, they tried to examine the importance of enolate geometry on the transformation (**Scheme 47**). Whenever they used ligand L1^* , for E/Z ratio of enolates from >98:2 and 25:75 they have isolated the desired product in excellent ee of 91 and 90% respectively. Surprisingly, the 25:75 E/Z ratio of enolates provides the product in a diminished 64% yield and

50% ee (compared to 89% yield and 86% ee) whenever using ligand L2*.

Scheme 47 Effect of enolate geometry on the asymmetric inductions during Pd-DAAA

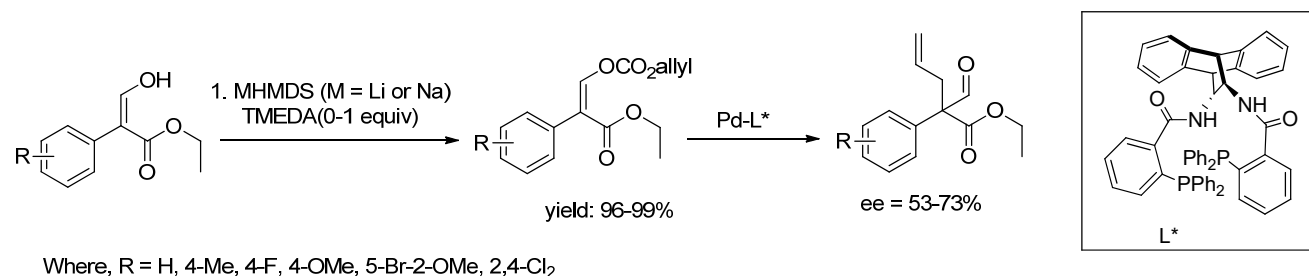


They mentioned that a dynamic kinetic resolution of the two enolate geometries and different facial selectivity between the two enolates occurs in the reaction when L2 is used as the ligand, possibly due to facile equilibration between O-bound and C-bound palladium enolates. Therefore, the enolate geometry along with right kind of ligand is a major tunable area along with other general parameters of these type of reactions. In fact, an analogous phenomenon regarding different enolate geometries was observed by the Trost lab when forming acyclic tertiary stereocenters via palladium-catalyzed allylic alkylation. [87]

In 2014 Hossain's group reported a synthesis of chiral aldehydes bearing all carbon quaternary stereocenters via the decarboxylative asymmetric allylic alkylation (DAAA) (Scheme 48). [88] At first, they were able to develop a stereoselective synthesis for the formation of both E- and Z-allyl carbonate by optimizing the choice of base and screening temperature along with solvent. Then a

fine tuning of solvent with number of different ligands resulted the formation of desired quaternary aldehyde up to 73% enantioselectivity and 96% conversion. A general trend of getting better enantiobenefit for electron donating group was observed compared to the electron withdrawing groups.

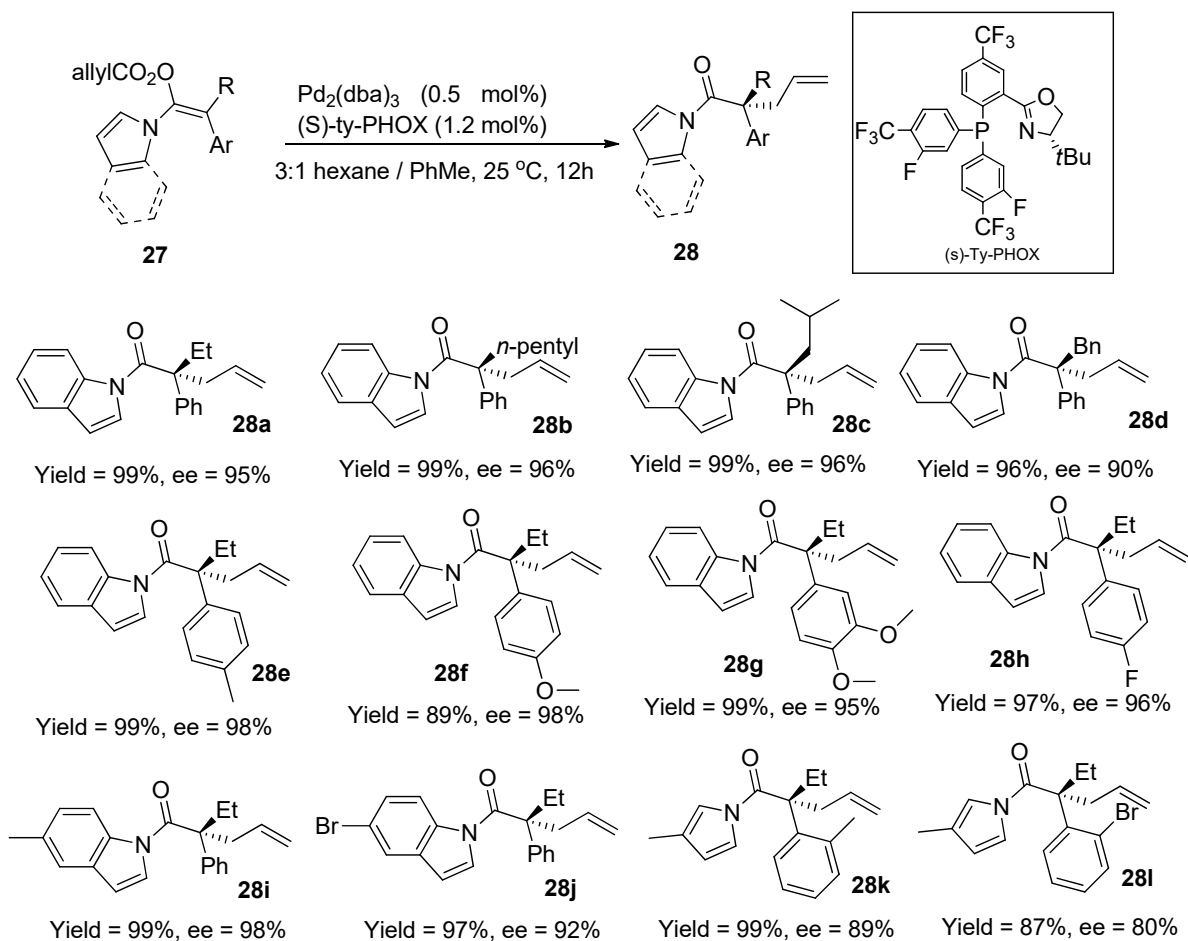
Scheme 48 Pd-DAAA of carboxy-allyl enol using Trost ligand



A recent approach of the first enantioselective palladium-catalyzed decarboxylative allylic alkylation of fully substituted N-acyl indole-derived enol carbonates forming acyclic all-carbon quaternary stereocenters is reported by Stoltz group in 2019 (**Scheme 49**). [89] Use of a novel electron deficient phosphinoxazoline (PHOX) ligand namely (S)-Ty-PHOX yielded up to 99% and ee up to 98%.

After getting an optimized ratio of E/Z for the enolate they have agreed that the control of substrate enolate geometry is crucial for high selectivity. They have examined the scope of the transformation for accessing various acyclic all-carbon quaternary stereocenters (**Scheme 49**). The presence of electron-rich aryl groups resulted in a slight increase in selectivity, with both *p*-Me (**28e**) and *p*-OMe (**28f**) substrates yielding the desired products in 98% ee each, and the bis-OMe

Scheme 49 Pd-DAAA of N-acyl indole derived enol carbonate by using Ty-PHOX ligand

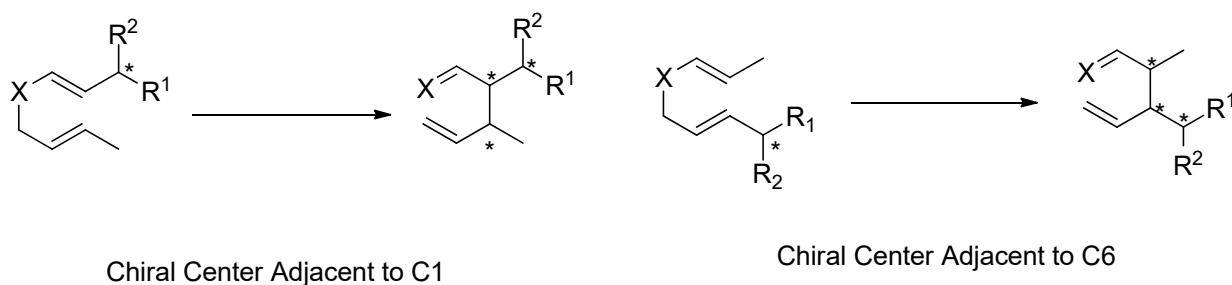


substrate (**2g**) in 95% ee. Notably, both methoxy containing substrates **28f** and **28g** required longer reaction times to reach full conversion (i.e., **24h**). An examination of electron-poor aryl groups demonstrated that, while *p*-Cl (**28h**), *p*-Br (**28i**), and *p*-F (**28j**) groups were well tolerated (94–96% ee), a *p*-CF₃ (**28k**) containing substrate provided the product in a diminished 72% ee, believed to result from increased stabilization of the resultant enolate.

B. Asymmetric Claisen rearrangement as a route to quaternary stereocenter

To make chiral Claisen rearrangement products using an asymmetric route there are several possibilities. If no external asymmetric induction is applied, the enantiomers can be separated via resolution, but this method suffers from the disadvantage of losing half of the unwanted enantiomer, which is highly undesirable. The first option is to transfer chirality from either the allylic or vinylic fragment of the allyl enol ether to the chiral carbon through a complete [1,3]-chirality transfer (remote stereocontrol), although other positions in the allyl enol ether substrate have also been used to transfer the chirality. Alternatively, more than one chiral center can be used to transfer the stereochemical information. The chiral allylic fragment can be obtained by such well known processes like the Sharpless asymmetric epoxidation, [90] enantioselective reduction of carbonyl compounds⁶ and enzymatic processes. [91] In the diastereoselective reaction proceeding through remote stereocontrol the chiral center is usually present to position one and six (Scheme 50).

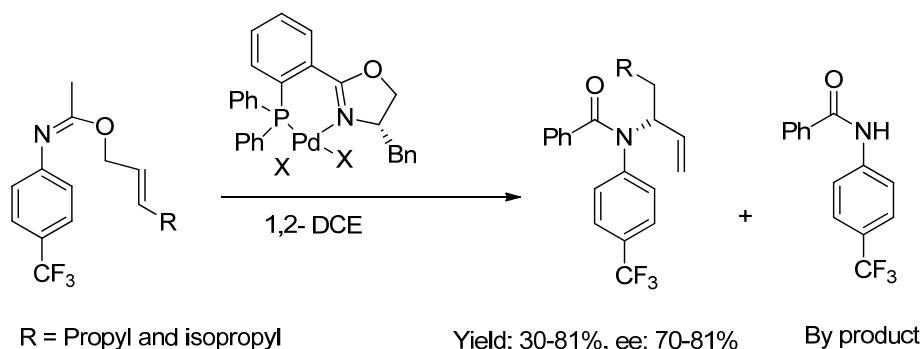
Scheme 50 Remote stereo-control of the diastereoselective reaction



Overman et al. reported the first examples of a truly catalytic reaction of the conversion of allyl amidates into the corresponding carbamates employing chiral palladium catalysts. [92] A series of chiral oxazoline substituted ligands were tested by Uozumi and Hayashi in the palladium (II)-

catalyzed rearrangement of a N-(4- (trifluoromethyl) phenyl) substituted allyl imidate (**Scheme 51**).

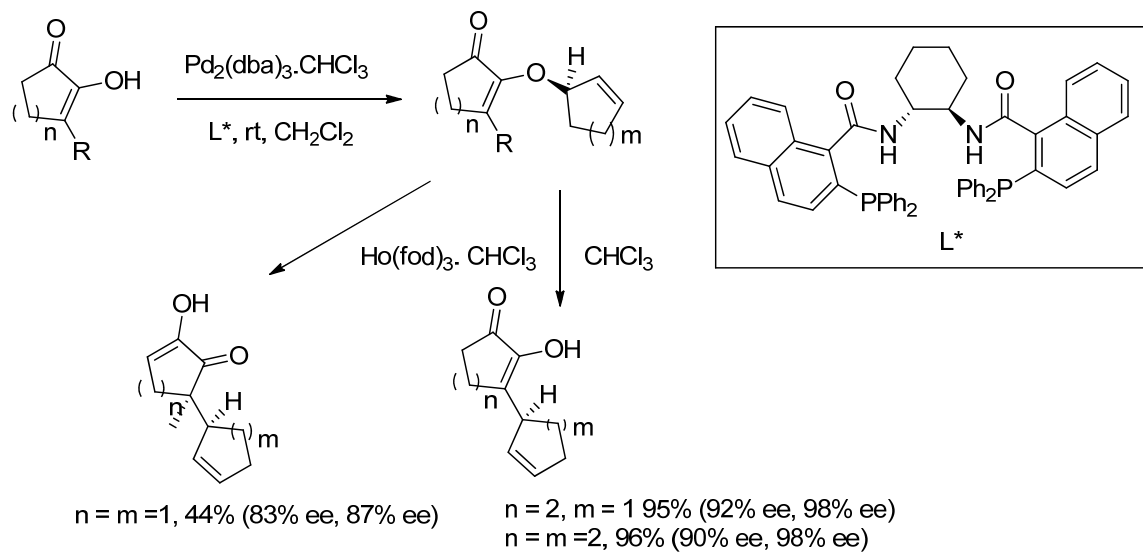
Scheme 51 First catalytic conversion of allyl amidates to carbamates



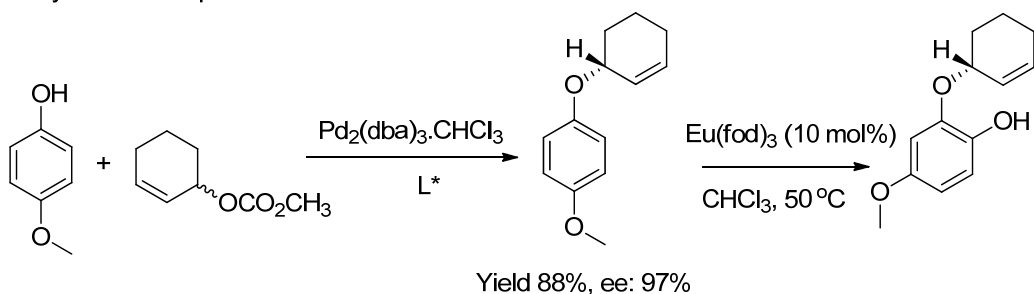
The most conventional approach of using Palladium usually being used for the primary O-allylation and the 1,2-Claisen type rearrangement is usually conveyed out by using other rare metals like Europium, Holmium etc. Some of the examples has shown in the **Scheme 52**. [93] Beside the use of rare metal with Pd catalyst, the use of achiral Al (III) Lewis acids are able to accelerate the aliphatic Claisen rearrangement as well. However, their applicability as catalysts is mainly prevented by product inhibition. [94] Al (III), B (III), and Mg (II) chiral Lewis acid complexes have been efficient for the asymmetric reaction but have not found applicability for a catalytic version of the reaction. However, the Lewis acid catalysts are substrate specific, (**Scheme 53**) if one metal Lewis acid is found to catalyze the Claisen rearrangement of a specific allyl enol ether substrate, this does not make it suitable as a catalyst for a varied range of allyl enol ether substrates.

Scheme 52 Rare metal induced O-allylation and their further rearrangement

(a) O-allylation of enolic cyclic substrate

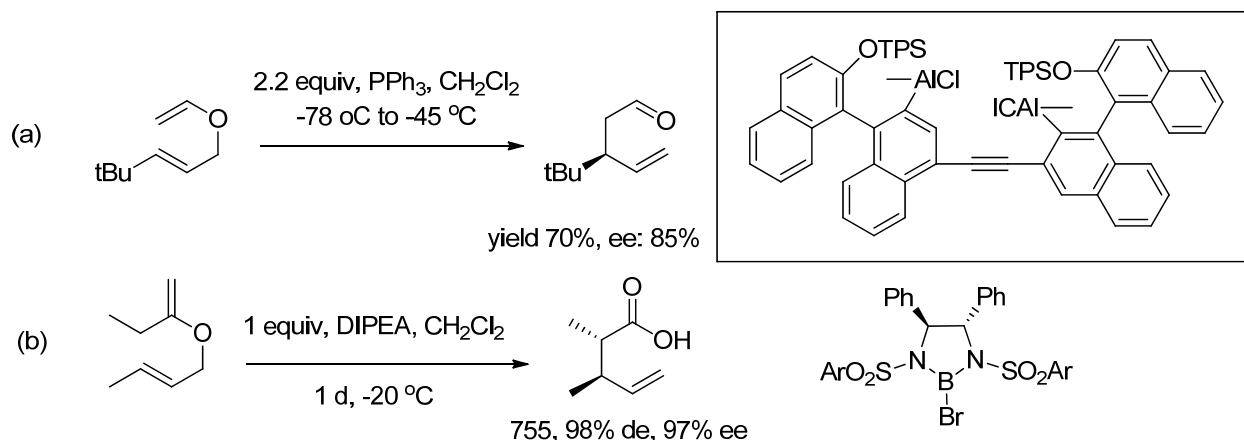


(b) O-allylation of the phenolic substrate



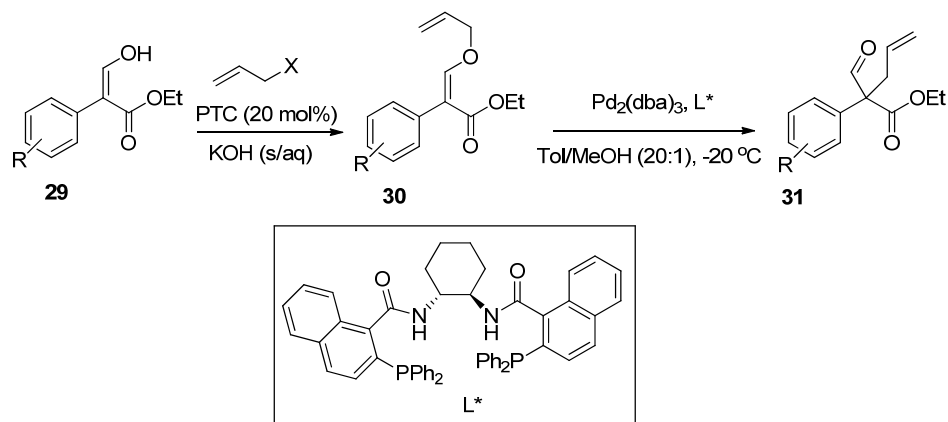
The following example shows some of the metal induced O-allyl rearrangement where the catalyst used in stoichiometric or more amount of the aluminum and boron catalyst.

Scheme 53 Aluminum and Boron catalyzed O-allyl rearrangement for acyclic quaternary carbon formation



But the use of Pd-L* for the rearrangement is quite rare and little complicated because of the reaction condition. A representative study has been shown by Hossain et al. [95] They have shown the first Palladium (0)-catalyzed asymmetric allylic alkylation (AAA) of O-allyl enol ether rearrangement of via π -allylpalladium intermediate using Trost chiral diphosphine (**Scheme 54**). This unprecedented reaction produced very rare α -aryl quaternary aldehydes with multi-functional groups. The main novelty in the chemistry demonstrates the formation of enol, **30** from the unprotected enol **29** using $n\text{Bu}_4\text{NI}$ as a phase transfer catalyst (PTC) in presence of KOH base. Therefore, they have used the ethers as a precursor for π -allylpalladium intermediates, to the best of the knowledge, perhaps without prior precedent. Chiral ligand (R,R)-L* was found to be optimal in this Pd-AAA reaction and provided good to excellent yield (80–95%) and enantioselectivity (70–90%) with a range of analogs.

Scheme 54 Pd catalyzed rearrangement of O-allyl ether 30 using DACH-naphthyl Trost ligand



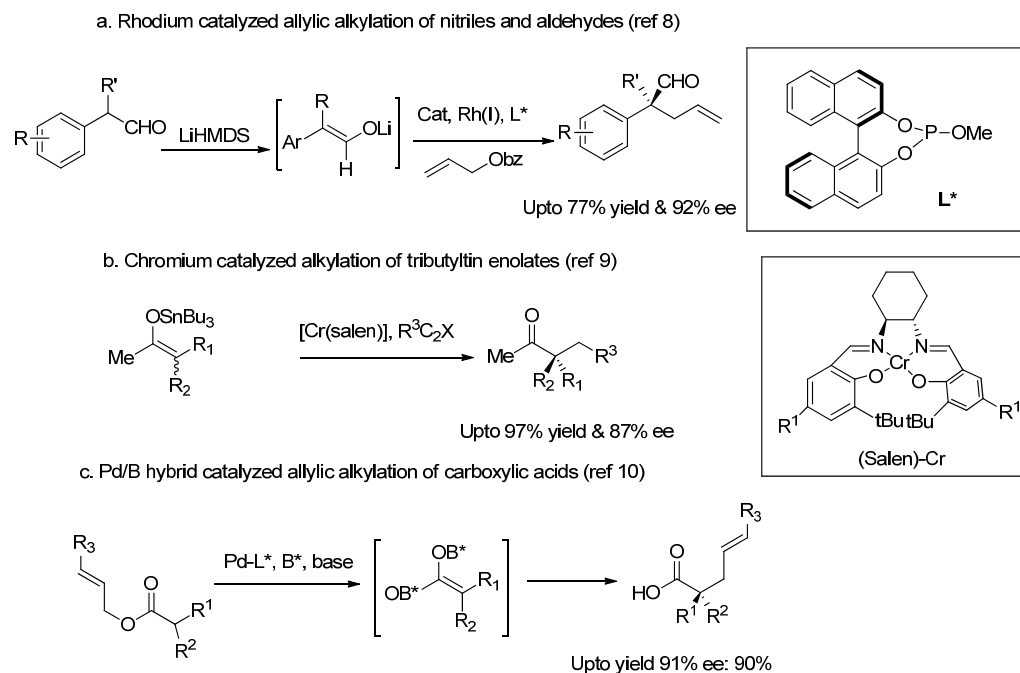
In fact A small number of catalytic achiral metal catalysts that speed up the Claisen rearrangement have been reported, for example Pd(II) complexes, lanthanide (III) complexes and TiCl_4 . [96-98]

In both metal promoted and metal catalyzed Claisen rearrangement reaction, substituents on allyl enol ether have a dramatic effect on the rate of rearrangement briefly.

3.1.4 Some Other recent approaches for the synthesis of achiral quaternary center

Additionally, the Evans lab has reported the use of rhodium-catalyzed allylic alkylation to furnish acyclic α -quaternary nitriles and aldehydes (**Scheme 55a**). [99] In the later work, they showed that both enolate geometries (E/Z) result similar enantiomeric excess of the product, which they have predicted as a consequence of substrate selectivity and not the result of an enolate equilibration event. In contrast, a dynamic equilibration of tributyltin enolates has been invoked by the Jacobsen group to directly alkylate fully substituted acyclic enolates with alkyl halides catalyzed by a [Cr(salen)] complex, affording α -quaternary ketones in high enantioselectivity starting with mixtures of enolates (**Scheme 55b**). [100a] Recently, Shimizu and Kanai demonstrated the preparation of acyclic α -quaternary carboxylic acids via allylic alkylation utilizing a hybrid boron-palladium catalytic system (**Scheme 55c**). [100b]

Scheme 55 Recent approaches for asymmetric induction using Rh, Cr and B



Part 3: Introduction

Introduction to Spirooxindole pyrrolidine

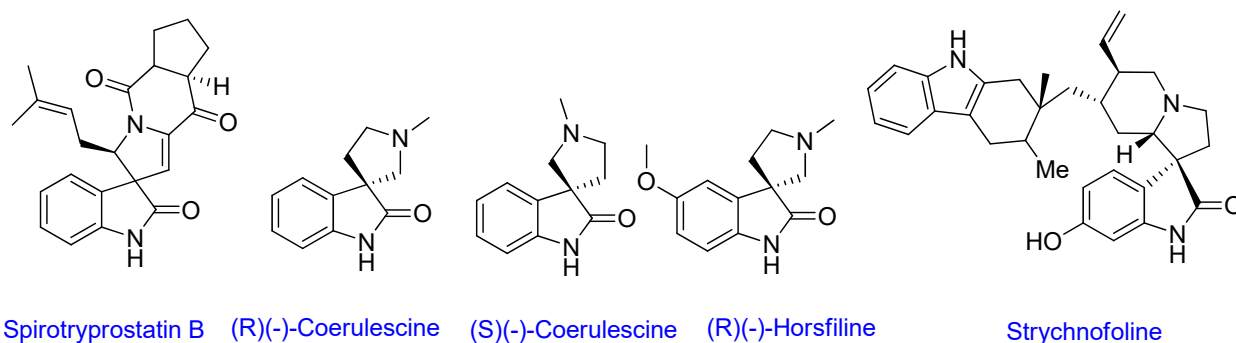
Phalaris coerulescens, a lesser-known species of *Phalaris*, is a winter growing perennial with rapid germination, vigorous seedling growth and high production in its seedling year. Trials in Australia in the late 1950s and the 1960s produced conflicting reports on persistence and productivity. [101] The introduced strains were not commercialized but it has become volunteer species in higher rainfall areas, particularly in the state of Victoria, where it has also been circumstantially associated with horse fatalities.

P. coerulescens has recently reintroduced to Australia to provide a more persistent and productive grass, other than the traditional perennial veldt grass (*Ehrharta calycina*), for low water-holding, acid soils. Trials of *P. coerulescens* accessions were established in the south east of South Australia already. Because of the known potential toxicity of *Phalaris* and of a suspected association of *P. coerulescens* with horse fatalities on a farming property in Victoria in the late 1980s, it was considered necessary to investigate the accessions for alkaloid content before further agronomic development was pursued. [102] In the process of evaluating the alkaloid content of the various *P. coerulescens* accessions by TLC, HPLC and GC-mass spectrometry methods a new alkaloid was identified and isolated.

Thereafter a detail phytochemical study of various accessions of *Phalaris coerulescens* for the presence of toxic phenylethylamines, indoloamines and tetrahydro- β -carboline revealed the presence of oxindoles previously not reported to occur in *Phalaris* species. One of the oxindoles,

the structure of which was elucidated by spectroscopic methods (in fact a spirooxindole), has not been reported to occur naturally and has been given the trivial name coerulescine.

Figure 7 Examples for the structure of spirooxindole containing natural products

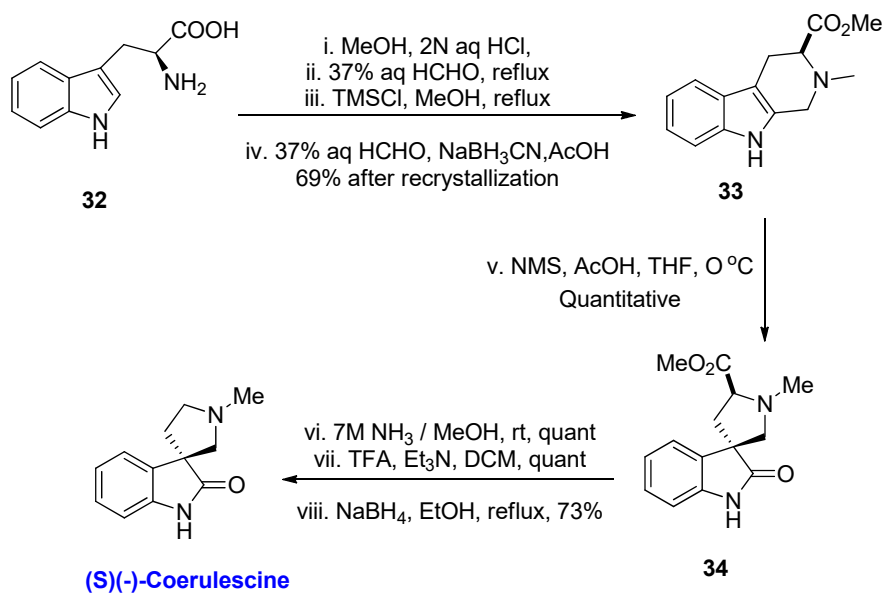


A spirooxindole is a key structure of coerulescine, horsfiline, elacomine, spirotryprostatin B, and strychnofoline can exhibit various biological activities. [103-104] Among the spirooxindole alkaloids, the relatively simple structure of coerulescine has become attractive to many medicinal chemists as a new pharmaceutical skeleton (**Figure 7**). It was first isolated in 1998 from *Pharalis coerulescens* by Colegate et al. [102]. The construction of the quaternary stereogenic center of (–)-coerulescine has been quite challenging, and until now, only four synthetic methods have been reported for the synthesis of enantiomerically enriched coerulescine.

4.1.1 Synthesis of (-)-Coerulescine: (by Danishefsky et al)

The first reported synthesis of natural product (-)-coerulescine was introduced during the investigation on the oxidative diastereoselective rearrangement of chiral tetrahydro- β -carboline precursors, for the targeted synthesis of Phalarine which is a natural product isolated from Phalaris Coerulescine (blue canary grass) by Danishefsky group in 2010. [105] They have reported the synthesis of (s)-coerulescine with excellent enantioselectivity (94%) but not as a final product rather a metabolic intermediate. The synthesis of the intermediate has shown in **Scheme 56**. L-tryptophan has used as the starting material and 4 step functional modification of the substrate produced compound **32** after recrystallization (**Scheme 56**), Then the subsequent rearrangement of the six (6) member ring and decarboxylation resulted the coerulescine as an intermediate.

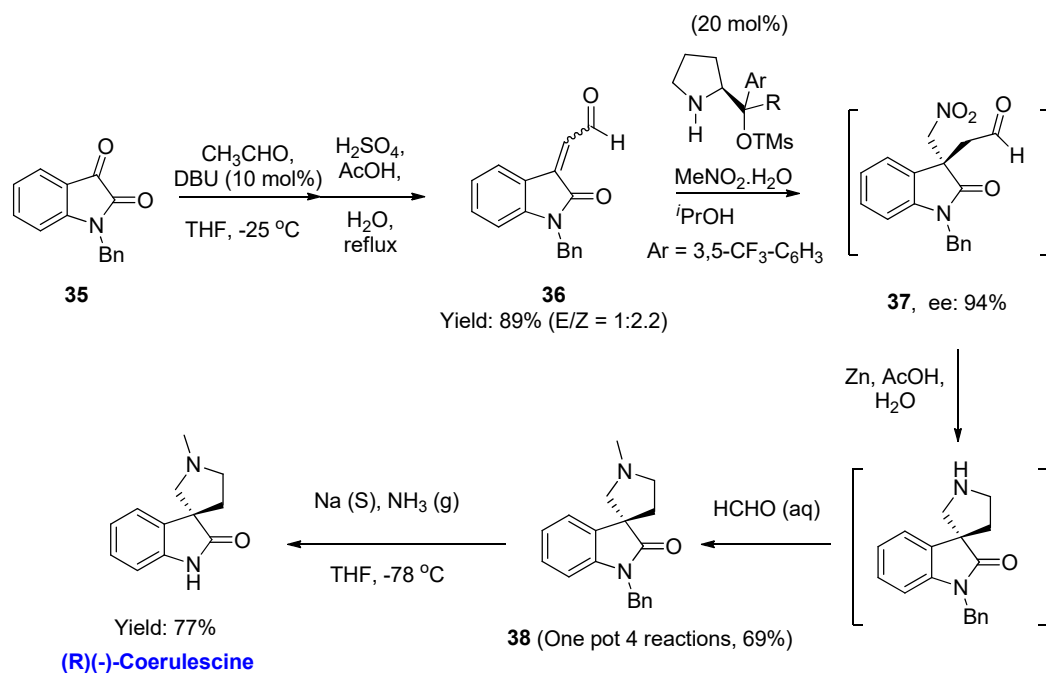
Scheme 56 Danishefsky synthesis of (S)-(-)-coerulescine



4.1.2 Synthesis of (-)-Coerulescine: (by Hayashi et al)

Later in 2014, Hayashi et al report the three one-pot sequential synthesis of (-)-coerulescine by employing two key reactions, namely 1) the synthesis of a 2-oxoindoline-3-ylidene acetaldehyde from acetaldehyde and an Isatin derivative and 2) the organocatalyzed Michael addition of nitromethane to the 2-oxoindoline-3-ylidene acetaldehyde to construct the all-carbon quaternary stereogenic centers with excellent enantioselectivity (**Scheme 57**). [106] Furthermore, they also synthesized (-)-coerulescine according to the route of Danishefsky and co-workers to verify the small optical rotation of coerulescine and to define the solvent for optical rotation comparison. [105] In this way they concluded the absolute configuration of (-)-coerulescine to be R which is not analogous to the experimental outcome earlier done by Danishefsky's group.

Scheme 57 Hayashi synthesis of (R)-(-)-Coerulescine

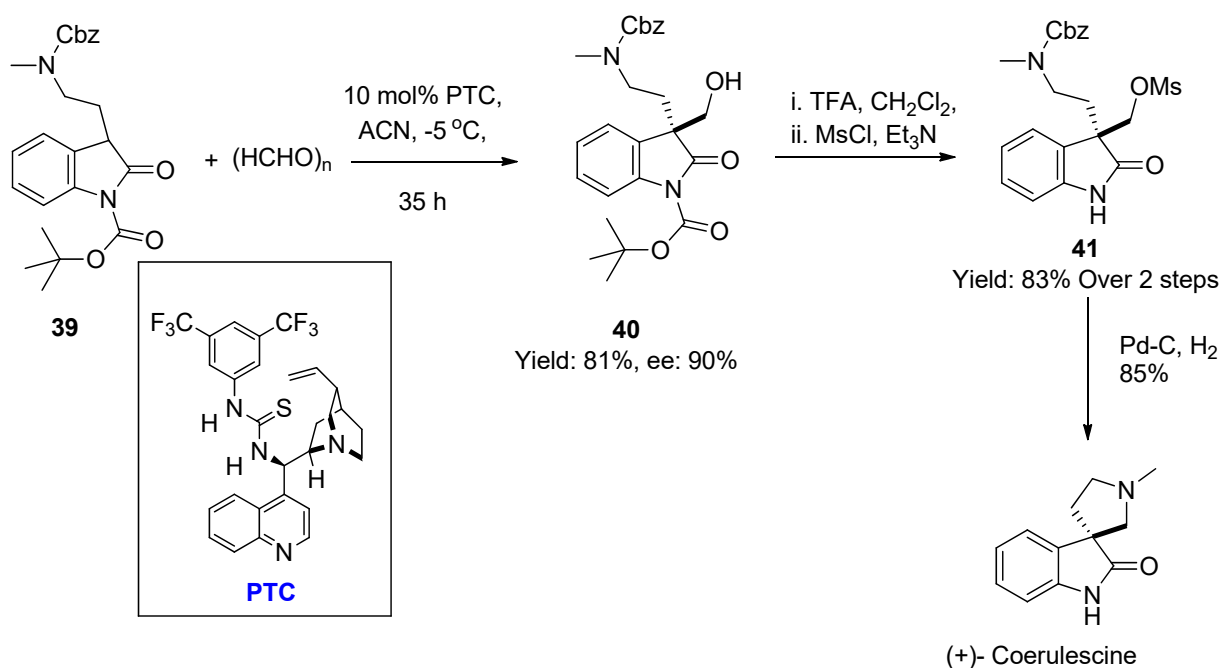


The aldol addition of Isatin derivatives **35** with acetaldehyde generated the β -hydroxyaldehyde and dehydration under acidic conditions provided **36** directly as a mixture of *E/Z* isomers (**Scheme 57**). The interesting outcome is the one pot formation of the enals **36** from Isatins **35** in excellent yield. This method was found to be higher yielding and more convenient than reported methods; for example, enal **36** has been produced in 27% over 3 steps by the reduction of the 3-position on **35** to form an alcohol, alkylation with bromoacetaldehyde diethyl ether, and acetal deprotection to afford **36**. Therefore, the approach was to start with an aldol reaction of the commercially available isatin derivatives **35** with acetaldehyde, followed by dehydration under acidic conditions to give 2-oxoindoline-3-ylidene acetaldehydes **36** as *E/Z* mixtures in excellent yields. The enantioselective conjugate addition of nitromethane to **36** generated aldehydes **37** with excellent enantioselectivity in the construction of the all-carbon quaternary stereogenic centers. Zn, AcOH, and water were added to the same reaction vessel to reduce the nitro group into an amine. At the same time, an intramolecular reductive amination proceeded to form the pyrrolidino spirocycle. Formaldehyde was then added to the reaction mixture sequentially to install the N-methyl group by an intermolecular reductive amination. The four reactions from aldehydes **36** were performed in the same reaction vessel and afforded **38** in 69% yield over 4 steps. Removal of the benzyl group under Birch conditions furnished (R)-horsfiline (**1**) and (R)-coerulescine in good yields. They understood that the spirooxyindole may tends to racemize under acidic conditions; [107-108] therefore, the optical purity was checked by HPLC analysis over a chiral phase. This showed the ee values of the prepared coerulescine was 94%, which indicated that racemization did not occur during their synthesis. Hence, the three one-pot sequential syntheses of (R)-coerulescine were developed in good total yield.

4.1.3 Synthesis of (-)-Coerulescine: (by Basai et al)

In 2015, Basai et al. also constructed the quaternary stereogenic center of coerulescine via an α -hydroxymethylation of α -(aminoalkyl)oxindole using cinchona-derived thiourea bifunctional organocatalysts as shown in the Scheme 58 starting from compound **39** as a potential starting material.[109]

Scheme 58: Basai total synthesis of (+)-Coerulescine



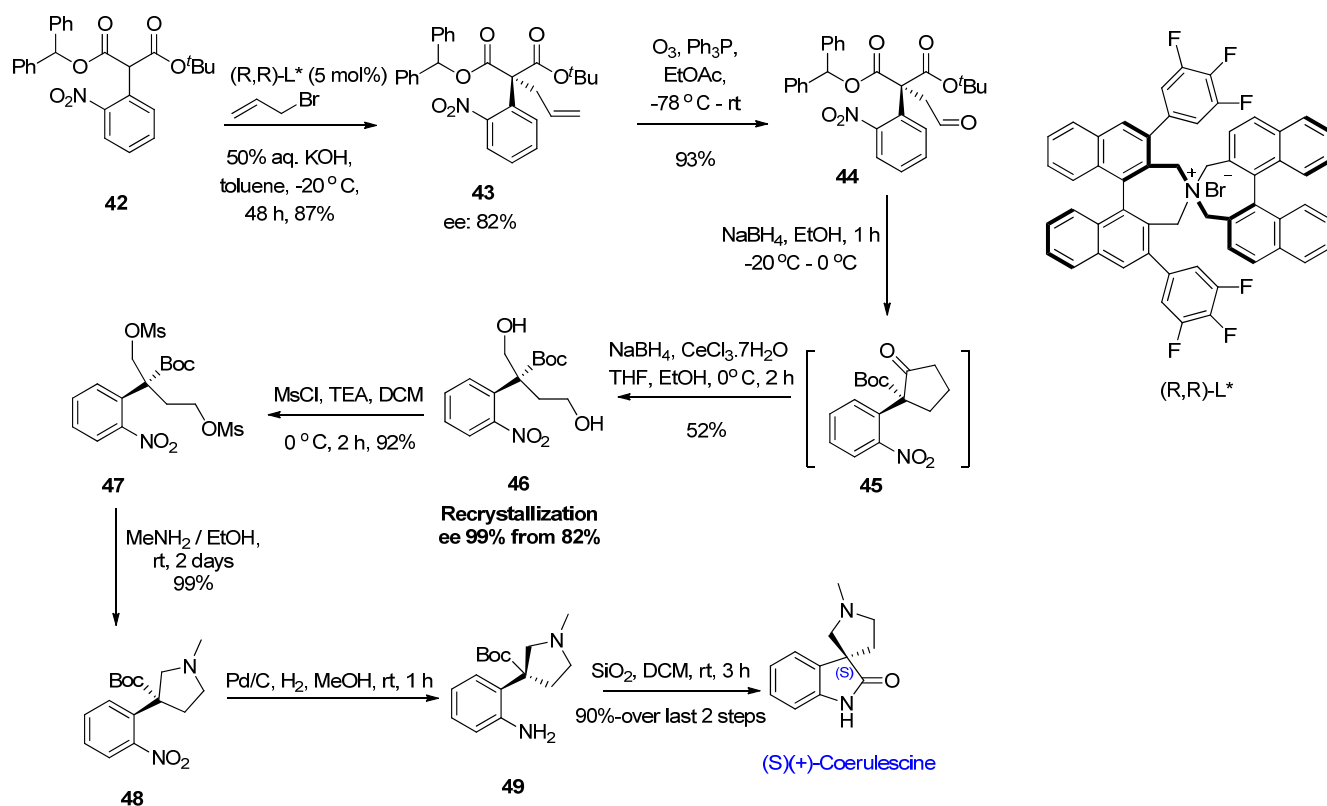
Compound **39** was potentially attached to a primary alcohol on the C3 position to form **40** with very good yield and enantioselectivity. Compound **40** was then treated with trifluoroacetic acid to get oxindole which was further reacted with methanesulfonyl chloride to afford mesylate **41** in 83% yield over 2 steps (**Scheme 58**). The latter was then converted to naturally occurring (+)-

coerulescine in 85% yield when subjected to catalytic Pd–C in ethanol (1 atm of H₂). This protocol is a newer approach, but the overall yield and the number of steps is not comparable to the other established protocol especially the formation of the starting material add 4 more steps to the overall consideration of the synthetic feasibility.

4.1.4 Synthesis of (-)-Coerulescine: (by Park et al)

Recently a practical enantioselective synthetic method for preparing (S)-(+)-coerulescine is reported through the use of diphenylmethyl tert-butyl α -(2-nitrophenyl)malonate (16% overall yield, 7 steps) by Park et al. [110] Allylation is the key step under phase-transfer catalytic conditions (82% ee). Then the compound was recrystallized and the enantiobenefit was raised up to >99% (**Scheme 59**).

Scheme 59: Park total synthesis of (s)(+)-Coerulescine using PTC



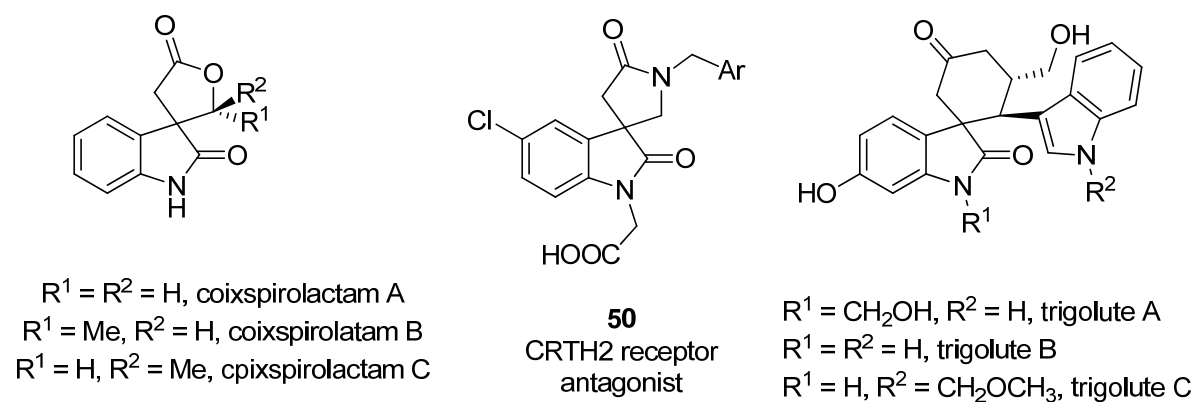
For the first step, the enantioselective allylation of **42** was performed under the reported PTC conditions with allyl bromide (10.0 equiv.), 50 mol% KOH (s) and (R, R)-L* at 0 °C in toluene to produce the allylated product (S)-**43** (yield 83%, ee: 82%). A reduction using sodium borohydride, afforded lactone **45** (95%) via the oxidative cleavage of the terminal allylic double bond was done ozonolysis which resulted compound **44**. Without purifying **45**, the treatment of additional sodium borohydride with cerium (III) trichloride heptahydrate and tetrahydrofuran as a co-solvent at 0 °C selectively reduced **45** to the corresponding diols **46** (52% from **44**) in situ. Diol **46** was purified as a single stereoisomer (>99% ee) with a 45% yield by recrystallizing (86% ee) using ethyl acetate and hexane (1:5). Dimesylation of **47** (94%) followed by N-alkylation in the presence of excess methylamine successfully produced N-methylpyrrolidines **48** retaining the enantiobenefit. The reduction of the nitro group on **48** by a catalytic hydrogenation under Pd/C and atmospheric H₂ afforded amine **49**. Finally, the prepared amine **49** was directly cyclized to (+)-coerulescine {observed [α] 20 D = 3.08 (c=1, MeOH); literature [α] 20 D = 1.0 (c=2.4, MeOH) (Mukaiyama et al., 2014)} by stirring with silica gel (SiO₂) in CH₂Cl₂ with no racemization (90% from **49**, >99% ee).

Part 4: Introduction

4.2.1 Introduction to spirooxindole lactone

A 2-oxindole spirofused with either a lactone or lactam moiety is a privileged three-dimensional framework existing across a large family of alkaloid natural products with diverse biological profiles. [1] For example, coixspirolactam A–C, isolated from the traditional Chinese medicine adlay bran, [5] exhibit potent anti-proliferative effects on human lung cancer cells A549, human colorectal carcinoma cells HT-29, and COLO 205 (**Figure 8**). [4] Although their optical rotations were reported, the absolute configuration of the spiro-carbon center was not elucidated. Another oxindole containing moiety namely, Trigolutes A–C are extracted from the twigs of *trigonostemon lutescens* and show promising activity in the treatment of hemorrhagic fever with renal syndrome. [111] Lactam derivatives such as compound **50** of spirooxindole are antagonists on the mouse CRTH2 receptor and may directly mediate the recruitment of inflammatory cells

Figure 8 Representative natural products and bioactive molecules containing the spirooxindole lactone and lactams

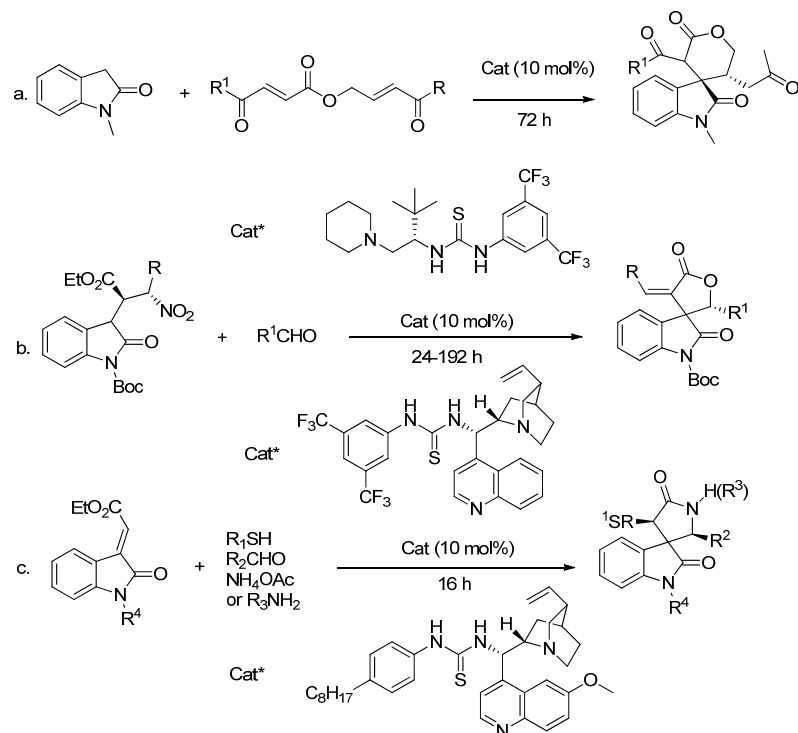


in allergic diseases such as asthma, allergic rhinitis, and atopic dermatitis. [112] The S enantiomer, which is separated by preparative chiral-phase HPLC is about 52 times more active than the R isomer. Therefore, highly enantioselective assembly of these spirooxindole lactones/lactams is of great interest in medicinal chemistry. [113] Although stereoselective construction of the spirooxindole has been well established, asymmetric synthesis of allcarbon spirooxindoles containing either a lactone or lactam moiety has had limited success. [114-115]

4.2.2 Different approaches for the synthesis of spirooxindole lactone

In 2014, Liang and Xu developed a novel approach to chiral spirooxindole δ -lactones through bifunctional thiourea catalyzed [5+1] annulation of oxindoles with ester-linked bisenones (**Scheme 60a**). [115a] An enantioselective synthesis of spirooxindole alkylidene- γ -lactones was successfully developed by Quintavalla and co-workers through organocatalytic aldol reaction of C3-alkylated oxindoles with aldehydes (**Scheme 60b**). [115b] The first asymmetric synthesis of spirooxindole γ -lactams was accessed by an oxoindolin-3-ylidene involving a four-component reaction promoted by a recyclable fluorous bifunctional cinchona alkaloid/thiourea organocatalyst (**Scheme 60c**). [115c] Each of these reactions must start from either oxindoles or their derivatives to deliver a specific skeleton after a long reaction time (up to 8 days). Therefore, a general and highly enantioselective approach, applicable to all spirooxindole γ - and δ -lactones/lactams, starting from non-oxindole-based materials, under mild reaction conditions is highly desirable.

Scheme 60 Different successful approaches for preparing lactone derivatives



Out of many known and unknown natural spiro lactone one very recent study on the extract of Adlay (Chinese pearl barley, soft-shelled Job's tears, *Coixlachryma-jobi* L. var. *ma-yuen* Stapf) grass crop that has long been described by Kuo et al in 2008 is our focus of discussion. [116-117]

The adlay seeds are used in traditional Chinese medicine and as a 'nourishing' food. It is mainly planted in Taiwan, China, and Japan, where it is considered a health food supplement. According to the ancient Chinese medical book *Pen-Tsao-Kang-Mu*, Li (1596), the seed of adlay was used in China for the treatment of warts, chapped skin, rheumatism, and neuralgia, and as an anti-inflammatory or anti-helminthic agent. Numerous recent reports have indicated that the consumption of adlay seed is beneficial to the human body. [118-119]

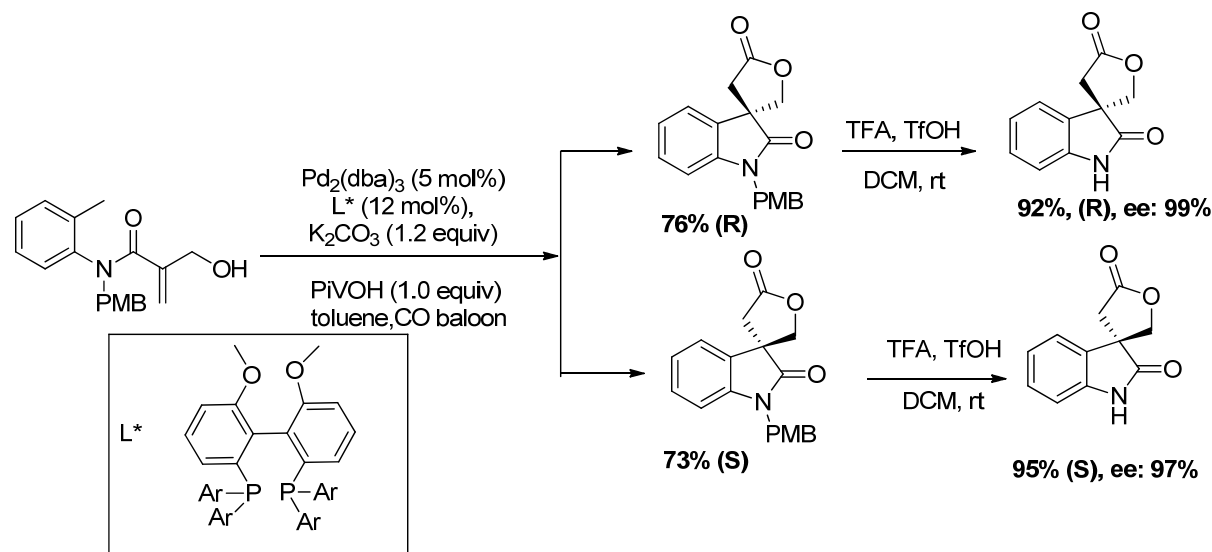
Takahashi et al. (1986) reported that coixans A, B, and C isolated from adlay seeds have hypoglycemic activity in rats. [120] Coixenolide was isolated from adlay seeds, and it exhibited anti-tumor activity towards Ehrlich ascites sarcoma in mice. [121] The anti-tumor constituents of adlay include α -monolinolein, and free fatty acids such as palmitic, stearic, oleic, and linoleic acids. [122-123] In addition, recent studies indicate that adlay has antitumor effects. Chiang et al found that adlay inhibited sarcoma-180 tumor in mice. [118] Kuo et al. indicated that a methanolic extract of adlay hull has antiproliferative activity against human histolytic lymphoma U937 monocytic cells via apoptosis. Chang et al reported that a methanolic extract of adlay has an anti-proliferative effect on A549 lung cancer cells by inducing cell cycle arrest and apoptosis. [116] Feeding mice a diet containing adlay reduced the number of surface lung tumors in mice. Shih et al showed that dehulled adlay suppressed early events in colon carcinogenesis and it also reduced COX-2 protein expression. [117]

4.2.3 Previous synthesis Coixspirolactam A

Recently the natural product coixspirolactam A was conveniently synthesized asymmetrically and absolute configuration was elucidated for the first time by Zhu et al. The key achievement of this finding is an efficient one-pot assembly of all-carbon spiro-oxindole compounds from non-oxindole-based materials through a palladium-catalyzed asymmetric Heck/carbonylative lactonization and lactamization sequence. [124] They have also reported the formation of diversified spirooxindole γ - and δ -lactones/lactams in high yields with good to excellent enantioselectivities (up to 99% ee) under mild reaction conditions.

The N-(2-iodophenyl)-N-methylacrylamide derivative 1, bearing a branched homoallylic alcohol, was investigated in Pd-catalyzed carbonylation (Scheme 58). When PPh₃ was used as a ligand in

Scheme 61 Synthesis of coixspirolactam A and the elucidation of its absolute configuration



the presence of balloon pressure of CO, intramolecular carbopalladation followed by carbonylative

lactonization occurred to give a racemic spirooxindole δ -lactone in excellent yield. Encouraged by this result, several chiral bidentate phosphine ligands were then screened and ligand (R)- L* delivered the product with good enantioselectivity (91% ee) with excellent chemical yield 92%. The optimized result was obtained using PivOH was used as an additive and K₂CO₃ as a base.

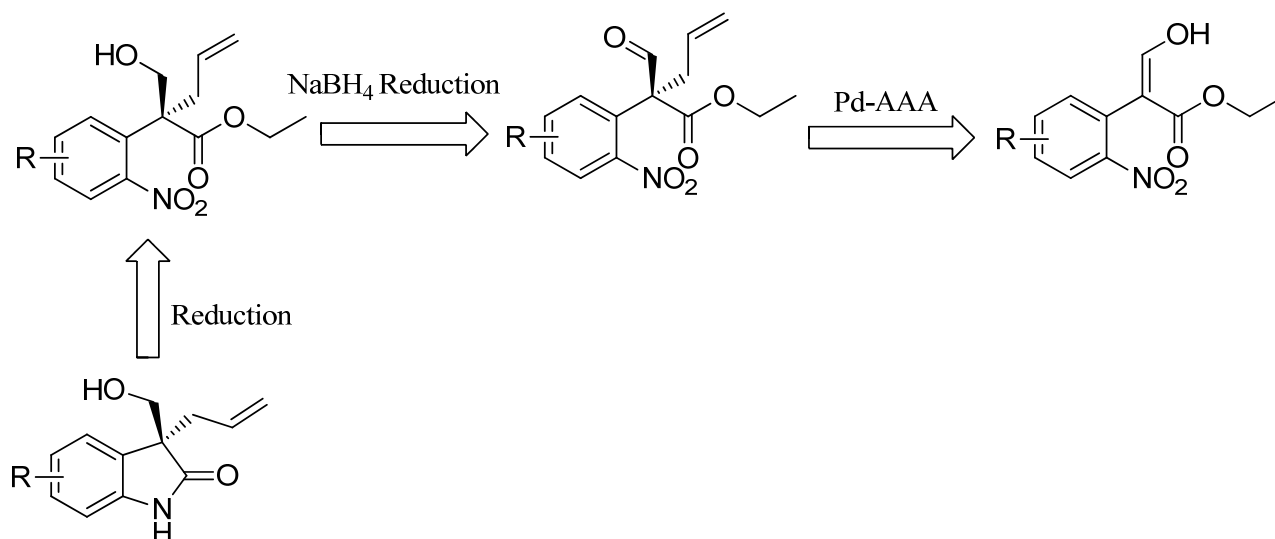
To elucidate the absolute stereochemistry of coixspirolactam A, both enantiomers R and S were synthesized conveniently through a two-step sequence with 99% and 97% ee, respectively (Scheme 58). By comparing their optical rotations with the reported value, ($c = 0.70$, MeOH at 27 °C), the structure of coixspirolactam A was confirmed as R. [125]

1.2 Results and Discussion

1.2.1 Optimization study of Pd -AAA of prochiral 2-nitro-3-hydroxy phenyl acrylate

The formation of all carbon quaternary stereocenter [126] by catalytic enantioselective manner has proven to be a challenge for the organic chemist since they are working on developing concise and facile synthetic route for drug designing and development of new synthetic route for the targets with proven potency. From the synthetic point of view a considerable number of such bioactive compounds contains a moiety namely 3,3-disubstituted oxindole. Therefore, we envisioned a retrosynthetic route as a primary goal which is achievable through the formation of all carbon quaternary center shown in retrosynthetic plan 1.

Retrosynthetic Plan 1:



Out of many different metal (such as Rh, Pt, Ni, Cr and Ru etc.) catalyzed approach, Pd-AAA that has played a key role in creating such stereocenter and allowed researchers to synthesize numerous biologically potent natural products. [127-129] However, synthetic methodologies to access

acyclic quaternary carbon center is still rare due to the conformational mobility of the structures. The existence of such aryl quaternary stereocenters in a growing number of biologically active natural products and pharmaceutical agents [130] demands a pressing need for the ability to construct this important motif enantioselectivity. Our group has first reported the synthesis of 3-hydroxy aryl acrylate with an outstanding scope of the reaction in 1998 which was then modified to a facile reaction protocol in 2004 by introducing a Brønsted acid $\text{HBF}_4 \cdot \text{OEt}_2$ in place of Iron Lewis acid catalyst. [131,132] But the scope was somehow limited to the electron withdrawing *o*-nitro group due to the complexity of work up procedure. We have recently sorted out a convenient work

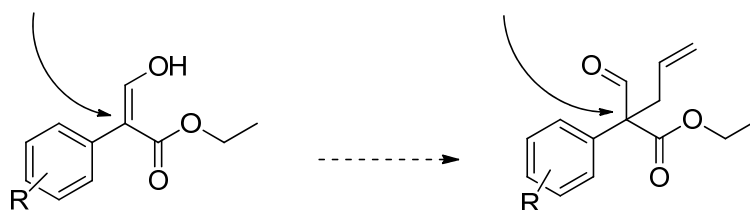
Scheme: 62 Retention of structural information during asymmetric induction

Aryl bound tertiary

All-carbon α -aryl quaternary

Prochiral α -carbon

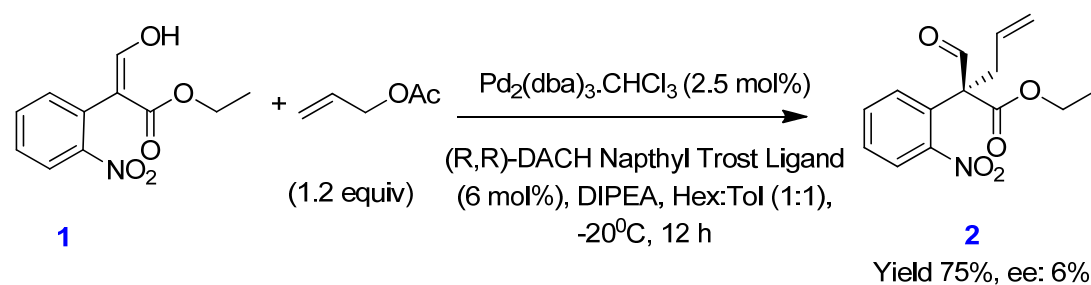
center



up protocol for 2-nitro-3-hydroxy phenyl acrylate and isolated the desired compound with 78% yield. Due to the presence of aryl bound tertiary α -prochiral carbon centers in 3-hydroxyaryl acrylates, these compounds should allow us to synthesize chiral all-carbon α -aryl quaternary stereocenters (**Scheme 62**). The necessity of having nitro group is the potential planning of forming an oxindole ring after preparing the *o*-nitro containing quaternary aldehyde **2**. One of the most convenient practice is Pd- AAA that can introduce an alkyl group by nucleophilic attack. To prove

this hypothesis, we first attempted allylation (as alkyl group) of a nitro containing substrate **1** which in fact demands a thorough investigation to prepare the challenging unprecedented formation of the quaternary chiral aldehyde, (ethyl 2-formyl-2-(2-NO₂-phenyl)pent-4-enoate **2**. The screening has initiated based on our previous success with Pd-AAA using a chiral Trost modular ligand mediated enantioselective synthesis. [133] To our disappointment, the attempt failed to result better enantiomeric excess (*ee*) may be because of the steric hindrance of the α -prochiral center due to the presence of nitro group at *ortho*-position (**Scheme 63**).

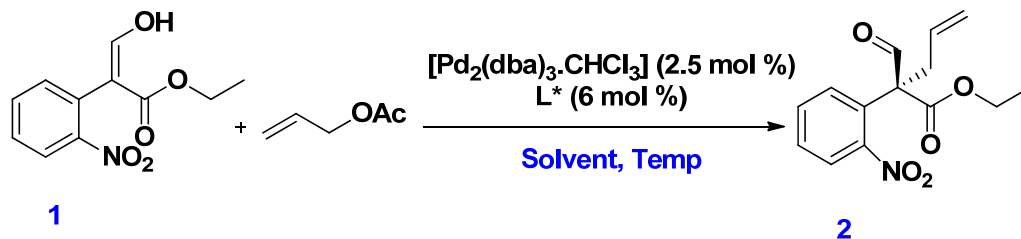
Scheme 63 Screening the previously optimized reaction condition



Even though the results were dissatisfactory, it might be only because of the optimized condition, which is not good enough for *ortho*-substituted analogs specially the electron withdrawing group like nitro and fluoro. We must optimize the reaction variables and find out a different condition for this class of analogs. Therefore we started with screening the solvent along with temperature at first by keeping the exact same ligand and Pd₂(dba)₃·CHCl₃ as a source of Pd(0).

Initially, we have studied variable polarity solvents of both protic and aprotic classes, namely DCM, DME, ether, toluene, MeOH, EtOH, *i*PA, *t*BuOH, Acetonitrile, DMF, HMPA, and THF. Surprisingly, we did not observe any O-allylation with any of these single solvents or the mixture

Table 1 Solvent optimization studies for the Pd-AAA of 3-hydroxy-2-nitro phenyl acrylate **1**



Entry ^[a]	Solvents	Temp, [°C]	Conv. [%] ^[b]	ee [%] ^[c]
1	DCM	rt	90	5
2	DME	-10	47	11
3	MeOH	-10	100	10
4	<i>i</i> PA	-10	100	24
5	Acetonitrile	rt	85	20
6	THF	rt	99	38
7	THF	-10	92	46
8	<i>t</i> -Butanol	rt	80	42
9	toluene	rt	95	11
10	toluene	-10	70	33
11	DMF	rt	82	20
12	HMPA	rt	100	31
13	CF ₃ CH ₂ OH	-10	20	n.d.
14	1,4-dioxane	rt	47	27
15	Cyclohexane	rt	40	53 ^[d]
16	Cyclohexane : toluene (3:1)	rt	38	53
17	Cyclohexane : THF (3:1)	rt	20	10
18	THF: <i>t</i> -BuOH (1:1)	rt	90	21
19	THF : toluene (1:1)	rt	75	33
20	THF : 1,4-dioxane (1:1)	rt	100	30
21	THF: 1,4-dioxane (1:1)	10	75	racemic
22	THF: <i>t</i> -BuOH (1:1)	-10	47	11
23	THF: toluene (1:1)	-10	99	21
24	Tol : Hex : <i>t</i> BuOH (1 : 1 :1)	rt	99	30
25	Tol : Hex : THF (1 : 1 :1)	-10	33	25
26	Amyl alcohol	rt	65	11

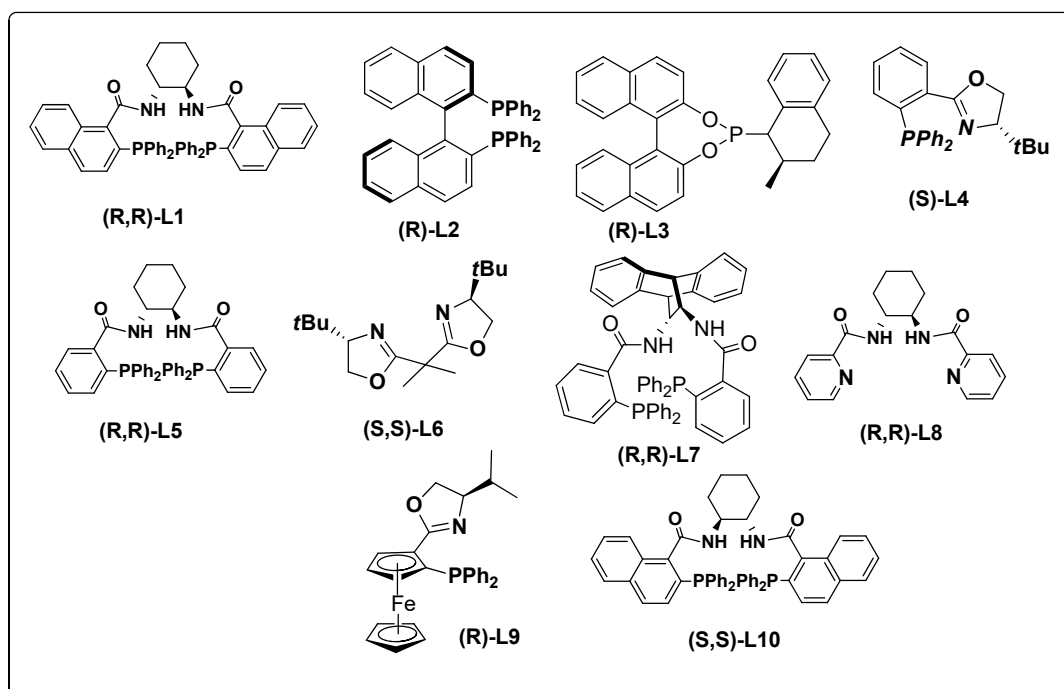
[a] Reaction conditions **1** (0.105-0.210 mmol), THF (2-5 mL). [b] Conversions were calculated from NMR. [c] Enantiomeric excess determined by chiral HPLC analysis. [d] Inversion of configuration.

of solvents. Conversion is good at room temperature in most of the cases (**Table 1**, entry 1, 5, 6, 8, 9, 11, 12, 18, 20 and 24) except 1,4-dioxane and cyclohexane (entry 14 and 15) and even at low temperature in some cases (entry 3, 4, and 7) for the single solvent system. However, for some cases at low temperature, the conversion was low (entry 2, 11, 14 and 27). We did not find a patterned correlation of enantioselectivity with the change in polarity of solvents. For example, toluene (nonpolar) provided 11% ee (entry 9) and increasing the polarity seemed like decreasing ee as with DCM (entry 1) but the most polar protic alcohols relatively increased the ee value (entry 8). The order of increasing ee obtained from primary to tertiary alcohol (entry 3, 4, and 8) at different temperature especially *t*-BuOH provided a promising ee but we could not go further lowering the temperature due to high freezing point of the solvent. However, polar aprotic solvent THF and HMPA proved to be relatively better class of solvent, as among acetonitrile, DMF, nitromethane, HMPA and THF (entry 5, 6, 11 and 12), HMPA provided 31% (entry 13) and THF provided maximum 38% ee at rt (entry 6). On the other hand, temperature does have an effect on ee in some cases (entry 7 vs 6; entry 9 vs 10). Surprisingly the solvent cyclohexane provided the best result of enantioselectivity, but the conversion was too low (entry 15) and we saw an inversion of configuration which was confirmed by chiral HPLC analysis. We have therefore planned to explore this solvent later so that we can make both enantiomer of our targeted compounds. From the screening of different solvents, we found best conditions (ee 46%) with THF at $-10\text{ }^{\circ}\text{C}$ (entry 7). It seems like the reaction goes to completion without any base in THF at as low as $-10\text{ }^{\circ}\text{C}$ without affecting %conversion or % ee. The use of binary or ternary solvent system provided no interesting result to explore furthermore (entry 16 to 25).

Whenever we achieved an enantiomeric excess from 6% to 46% by tuning the solvents, we then

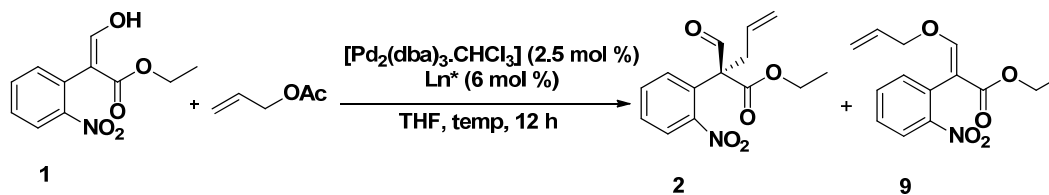
turned our investigation of different ligands on enantiodiscrimination. We have selected five C2-symmetric ligands namely Trost modular (diphenylphosphino)benzoic acid (DPPBA), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and bioxazoline (BOX) ligand; two nonsymmetrical

Figure 9 Selected ligands for Pd-AAA of prochiral 2-nitro-3-hydroxy phenyl acrylate, 1



ligands such as a mixed P/N-type phosphinooxazoline (PHOX); ferrocenyl oxazoline and phosphoramidite for the investigation (**Figure 9**). For this optimization, we kept the solvent constant to THF that provided maximum ee of 46% and studied the effect of ligands. It should be mentioned that such a diverse selection of ligands may lead the formation of both C-alkylation and O-alkylation products at the same time. It has been observed that the DPPBA ligand class, including **L1**, **L5**, **L7**, **L10** and nonsymmetrical PHOX ligand **L4** showed better enantioselectivity

Table 2 Optimization of ligands for intermolecular Pd-AAA of compound 1 (Method A)



Entry ^[a]	Ligand	Temp [°C]	Conv.[%] ^[b] , 2	Conv.[%] ^[b] , 9	ee[%] ^[c]
1	L1	rt	99	0	38
2	L1	0	95	0	42
3	L1	-10	92	0	46
4	L1	-20	nr	-	-
5	L2	-10	99	0	11
6	L3	-10	60	0	16
7	L4	-10	80	20	34
8	L5	-10	100	0	30
9	L6	-10	99	0	10
10	L7	-10	30	70	36
11	L8	-10	nr	nr	n.d.
12	L9	-10	29	71	n.d.
13	L10	-10	90	0	41 ^[d]

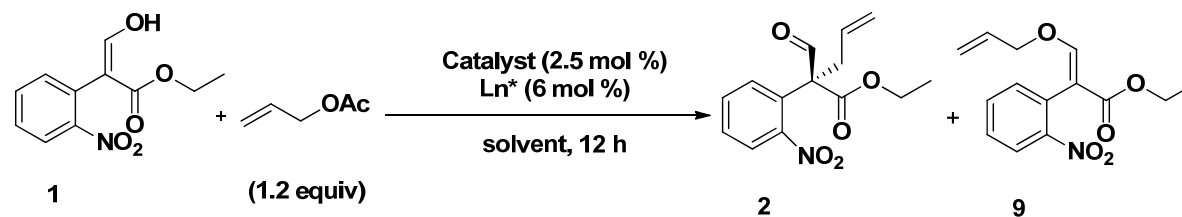
[a] Reaction conditions **1** (0.105-0.210 mmol), THF (2-5 mL). [b] Conversions were calculated from NMR. [c] Enantiomeric excess determined by chiral HPLC analysis [d] Inversion of conversion.

(Table 2). But ligands **L4** and **L7** formed C-allylated product **2** along with O-allylated product ethyl 3-(allyloxy)-2-(2-nitrophenyl)acrylate **9**. Although both ligands **L1** (46% ee) and **L5** (30% ee) regio-selectively provided the C-allylated product **2**, we selected ligand **L1** to explore further for its promising optical selectivity. The Ferrocenyl ligands **L9** has also been employed, which ensued the O-allylated product **9** with very poor yield of desired compound **2** (entry 12). One BOX ligand **L6** has been tried as well without much success (entry 7). The (S,S)-**L10** was used which

gave the product similar to the results obtained from **(R,R)-L1** (entry 13 vs entry 1-3) and also confirmed the identifying peaks for the inversion of conversion during HPLC analysis. The preliminary result prompted us to study the influence of the reaction parameters such as solvent, temperature and additive.

Achieving a result of 46% ee for the L1 ligand using THF as a choice of solvent driven us to explore the source of different Pd(0) which sometimes ensure the better selectivity of the nucleophilic attack [134]. That is the reason researcher explored different source of catalyst. We have achieved a low enantioselectivity compare to Pd₂(dba)₃.CHCl₃ (**Table 3**). Whenever screening that we didn't find an alternative source of palladium to explore as shown in Table 3. Basically, the conversion was almost in good range whenever screening the alternative palladium source such as [Pd(C₃H₅)Cl]₂, (entries 1-6, 8-11) but stereoselectivity was not satisfactory and the other sources proved to be unproductive (entries 7 and 12). But We got an idea that the catalyst Pd₂(dba)₃.CHCl₃ might be the right choice along with the (R,R)-L1 (DACH-Naphthyl Trost ligand) considering THF as a choice of solvent based on the results we obtained so far. increase of enantioselectivity for using BSA (Bis(trimethyl silyl) acetamide) (entry 17) but the conversion was low (20%).

Table 3. Selected optimization of catalyst, ligand, and their loading for the Pd-AAA of compound 1



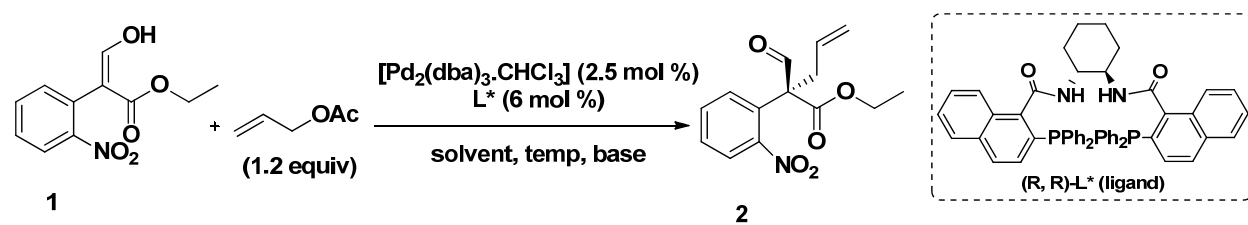
entry ^a	Solvent	Ligand (mol%)	catalyst	temp [°C]	conv. ^c [%]	ee ^d [%]
1 ^e	toluene	(R,R)-L1(7.5 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	95	35
2	toluene	(R,R)-L1(6.0 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	72	29
3 ^e	THF	(R,R)-L1(7.5 mol%)	$[Pd(C_3H_5)_2Cl]_2$	rt	90	27
4	THF	(R,R)-L1(6.0 mol%)	$[Pd(C_3H_5)_2Cl]_2$	rt	81	22
5	THF	(R,R)-L1(5.0 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	70	15
6	THF	(R,R)-L1(6.0 mol%)	$[Pd(C_3H_5)_2Cl]_2$	0	69	22
7	THF	(R,R)-L1(6.0 mol%)	$Pd(OAc)_2Cl_2$	rt	<10	n.d.
8 ^g	toluene	(R,R)-L1(6.0 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	72	29
9 ^g	toluene	(R,R)-L1(7.5 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	95	35
10 ^h	THF	(R,R)-L1(7.5 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	27	11
11 ⁱ	THF	(R,R)-L1(7.5 mol%)	$[Pd(C_3H_5)_2Cl]_2$	-10	34	13
12	THF	(R,R)-L1(6.0 mol%)	$[Rh(COD)Cl]_2$	rt	<10	n.d

^aAll reactions have carried out in 0.105-0.210 mmol scale. ^bConversions were calculated from NMR. ^cEnantiomeric excess calculated by chiral HPLC. ^e7.5 mol% of ligand used. ^g1,2 equiv of DIPEA, ^h2 equiv of *t*BuOH added. ⁱ3 equiv of *t*BuOH added, n.d.-Not Determined

Then we thought to explore different bases which may help to deprotonate the enolic proton to form the enolate and accelerate the attack of the nucleophile to the Pd-L*-electrophile complex. Another idea is the in-situ formation of the salt (such as the TEA can form a salt with the enolate

geometry) that sterically benefit the attack of the nucleophile from one site compared to the other site towards the electrophile. Screening the most widely used organic bases such as DIPEA

Table 4 Optimization of solvents with bases for the intermolecular Pd-AAA of 3-hydroxy-2-nitro phenyl acrylate 1



entry ^a	solvent	base ^b	temp. [°C]	conv. ^c [%]	ee ^d [%]
1	DCM	DIPEA	rt	100	rac
2	DCM	CsF	-20	100	20
3	toluene	CsF	rt	100	38
4	toluene	DIPEA	-10	81	36
5	THF	DIPEA	-20	100	53
6	THF	CsF	-20	99	55
7	THF	CsF	-10	100	57
8	THF	CsCl	-10	52	29
9	THF	quinine	-20	100	50
10	THF	(DHQ) ₂ AQN	-10	40	60
11	THF	(DHQ) ₂ AQN	rt	81	40
12	THF	KOtBu	-20	100	45
13	THF	DPG	-10	99	48
14	THF	TMG	-10	75	24
15	THF	TMG	0	67	23
16	THF	TEA	rt	40	17
17	THF	BSA	-10	20	87

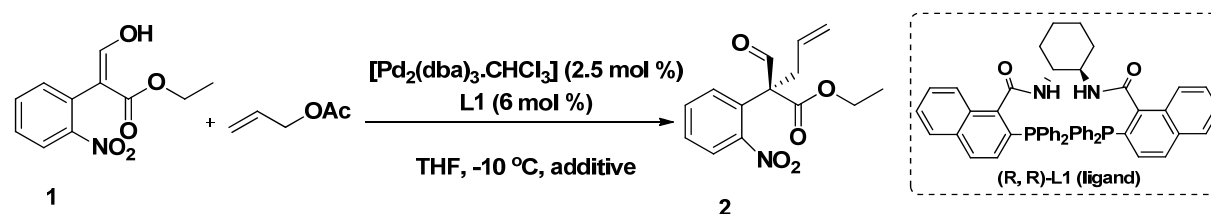
^aAll reactions have carried out in 0.105-0.210 mmol scale, ^b Used in 2-3 equiv, ^cConversions were calculated from NMR ^dEnantiomeric excess calculated by chiral HPLC.

provided the racemic formation of the compound using DCM solvent (entry 1, **Table 4**). During the study we saw that the other based like CsF, DIPEA and DPG (diphenyl guanidine), quinine, (DHQ)₂AQN (Hydroquinine anthraquinone-1,4-diyl diether) delivered decent percentage of ee (entries 5, 6, 7, 9, 10 and 13) at lower temperature. We have considered that the effect of getting better enantiobenefit is because of Cs⁺ counterion with the carbonyl group of the ligand but the maximum we managed is 57% ee with quantitative conversion (entry 7). Though the ee using (DHQ)₂AQN was high but the use of chiral auxiliaries (like quinine containing bases) in stoichiometric amount limited the scope of further exploring that. Moreover, bases like CsCl, K^tOBu, TMG (tetramethyl guanidine) and TEA (entries 8, 12, 14-16) could not add any value to achieving our targeted results. An attempt to tune the solvent with base using toluene and DCM remain unsuccessful (entries 2-4).

Now a days, the role of additive is one of the known approaches, although the mechanism of action for most of them is either unknown or not clear. Our screening of the additive was mainly based on the previously published literature for inducing high asymmetry. Few of these additives provided mentionable enantioselectivity in our case are *t*BuOH and NaHSO₃ (entries 14 and 16). *t*BuOH as additives has been employed before by Trost and co-workers with significant improvement in *ee*, which proved to be true for our case as well. [135] It participated in the enantiodiscriminative process most satisfactorily so far with 65% ee (entry 14). We assume the reason is the H-bond interaction of tertiary alcohol and its bulkiness fits one of the enol structures favorable then the other one. NaHSO₃ is another interesting additive we have found that provided us as much as 53% ee (entry 16). Since tertiary alcohol *t*BuOH provided relatively better ee, we

tried to use different alcohols such as BINOL, isopropyl alcohol, MeOH, amyl alcohol, isoamyl alcohol, CF₃CH₂OH and phenol but none of them provided further improvement of the

Table 5. Optimization of additives for the intermolecular Pd-AAA of compound 1



entry ^a	additive ^b	conv. ^f [%]	ee ^g [%]
1	HMPA ^e	83	30
2	<i>n</i> Bu ₄ NI ^{b,c}	100	0
3	<i>n</i> Bu ₄ NF ^{b,c}	100	44
4	Ph ₃ SiCl ^b	-	-
5	KHSO ₃ ^e	63	18
6	B(OMe) ₃ ^b	100	35
7	CH ₃ COOH	10	-
8	C ₆ H ₅ OH ^e	64	37
9	<i>R</i> -Binol ^d	100	30
10	MeOH ^e	60	37
11	amyl alcohol ^e	87	09
12	isoamylalcohol ^e	85	41
13	<i>i</i> PA ^e	70	13
14	<i>t</i> BuOH ^e	100	65
15	H ₂ O ^e	65	40
16	NaHSO ₃ ^e	90	53
17	<i>t</i> BuOH ^d & Zn(OAc) ₂ ^e	60	23
18	DME ^e	33	11
19	CF ₃ CH ₂ OH ^e	100	43
20	NMP ^h	100	34

^aAll reactions have carried out in 0.105-0.210 mmol scale ^b1.2 equivalent of additives, unless otherwise mentioned. ^c30 mol%. ^d10 mol%. ^e2-3 equivalent, ^fConversions calculated from NMR ^gEnantiomeric excess calculated by chiral HPLC, ^hReaction ran at rt.

Enantiomeric excess (entries 8-13, 19). Further investigation of different organic salts and acids were screened without much success (entries 1-6, 17, 18 and 20).

During screening different additives with our choice of solvent THF, we have also tried to see the impact of some selected additives with other solvents to explore the feasibility of tuning other solvents. As we expect from the previous screening that

Table 6 Screening additives for intermolecular Pd-AAA of 1 in different solvents

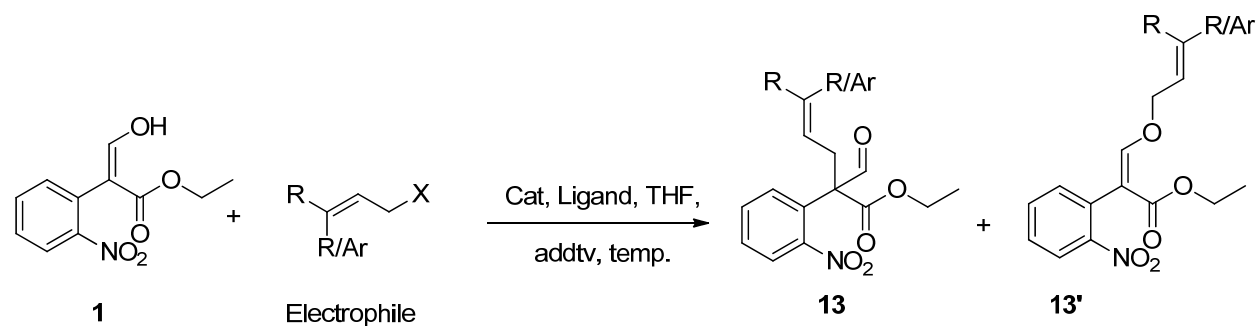
entry ^a	Solvent	Temperature [°C]	additive ^b	conv. ^c [%]	ee ^f [%]
1	Cyclohexane	rt	DIPEA	100	23
2	Cyclohexane	rt	<i>t</i> BuOH ^d	100	27
3	Cyclohexane	10	DIPEA	80	27
4	Cyclohexane	10	<i>t</i> BuOH ^d	80	25
5	Cyclohexane	10	<i>t</i> BuOH ^e	40	81
6	Cyclohexane	10	<i>t</i> BuOH	40	55
7	Cyclohexane	rt	<i>t</i> BuOH ^e	20	73
8	1,4-dioxane	rt	<i>t</i> BuOH	27	29
9	1,4-dioxane	rt	K ₂ CO ₃	25	37
10	CF ₃ CH ₂ OH	-10	LiCl	20	n.d.
11	CF ₃ CH ₂ OH	-10	<i>t</i> BuOH	10	n.d.
12	<i>t</i> BuOH	-10	NaHSO ₃	30	40
13	DME	-10	<i>t</i> BuOH	30	10
14	Hex: Tol	-10	<i>t</i> BuOH ^d	75	25
15	Toluene	rt	CsF	100	38

^aAll reactions have carried out in 0.105-0.210 mmol scale ^b1.2 equivalent of additives, unless otherwise mentioned. ^c30 mol%. ^dConversions calculated from NMR ^e2 equiv of DIPEA added, ^f1 equiv of *t*BuOH added, ^g2-3 equivalent, ^henantiomeric excess calculated by chiral HPLC.

the room temperature might not be a good choice for reaction, got the same feedback from solvent cyclohexane, 1,4-dioxane and toluene (**Table 6**, entries 1, 2, 7-9, and 15). Considering the high freezing point of cyclohexane, we had to run the reaction at 10 °C. We tried to optimize the quantity of the *t*BuOH as a choice of additive and obtained up to 81% ee but the conversion was low (entry 5 vs entries 4 and 6). Choice of dioxane with the additives proved to be a random selection. Other solvent-additive pairing could not change our obtained results so far.

Hoping to explore more to increase the enantioselectivity, we then choose different electrophiles based on the change alkyl/aryl groups (cinnamyl acetate and prenyl acetate) and leaving groups (allyl alcohol, cinnamyl mesylate). The idea is that the phenyl group might introduce a steric effect on the electrophile and help to manage lower dihedral angle compared to allyl acetate, thus susceptible to more stereoselectivity. The choice of prenyl acetate was considered based on making the allyl group more stable by forming tertiary carbocation. We thought the relatively bulky mesylate group might help to make the nucleophilic attack more selective. We have seen the same results that the cinnamyl acetate resulted the ee value of up to 70% with low conversion of 71% compare to the allyl acetate (65% ee with quantitative conversion) shown in Table 7 entry 3 using DIPEA as an additive at -10 °C. Whereas other additives like *t*BuOH, TEA and variation of temperature as well as catalyst (entries 1, 2, 4-7) could not result anything better. Formation of O-allylated 13' have also noticed during screening additives with [Pd(C₃H₅)Cl]₂ (entry 8-9). Other electrophiles resulted either racemic product (entry 10) or the lower conversion of the expected product 13 (entries 11-12).

Table 7 Screening electrophile for intermolecular Pd-AAA of 1



Where, R = H, Me, Ar = Ph, X = -OH, -I, -OAc, -OMs

Entry ^a	Ligand, L1* (mol%)	Catalyst (2.5 mol%)	Electrophile	Temp [°C]	Addtv. (2 eqv)	Conv. [%] ^b	ee [%] ^c
1	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	rt	DIPEA	55	40
2	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	0	DIPEA	99	53
3	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	-10	DIPEA	71	70
4	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	0	DIPEA ^d	69	8
5	6.0	[Pd(C ₃ H ₅)Cl] ₂	R = H, Ar = Ph, X = OAc	50	DIPEA	40	14
6	7.5	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	rt	<i>t</i> BuOH	20-30	n.d.
7	7.5	Pd ₂ (dba) ₃ .CHCl ₃	R = H, Ar = Ph, X = OAc	rt	TEA	40	34
8	6.0	[Pd(C ₃ H ₅)Cl] ₂	R = H, Ar = Ph, X = OAc	-10	DIPEA	Cpd 13' as a major product	
9	7.5	[Pd(C ₃ H ₅)Cl] ₂	R = H, Ar = Ph, X = OAc	-10	<i>t</i> BuOH		
10	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = H, R' = H, X = -OH	rt	<i>t</i> BuOH	80	racemic
11	6.0	Pd ₂ (dba) ₃ .CHCl ₃	R = CH ₃ , R' = CH ₃ , X = -OAc	rt	-	10-20	n.d.
12	7.5	[Pd(C ₃ H ₅)Cl] ₂	R = CH ₃ , R' = CH ₃ , X = -OAc	rt	-	10-20	n.d.

^aAll reactions have carried out in 0.105-0.210 mmol scale ^b Conversions calculated from NMR.

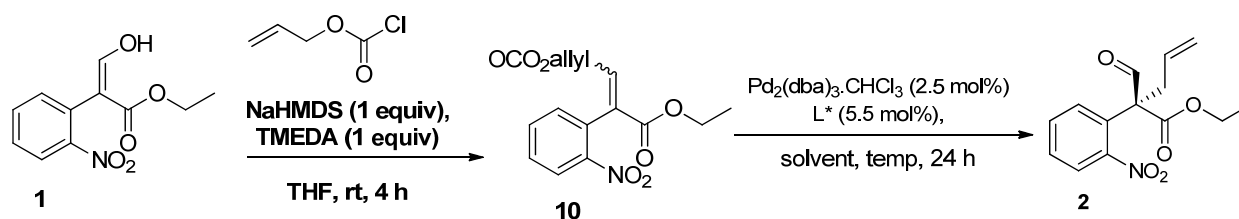
^cenantiomeric excess calculated by chiral HPLC.

Since we have achieved 65% ee (with quantitative conversion) of compound **2** using allyl acetate from the Pd-AAA reaction of **1** (see Table 5, entry 14) and 70% ee compound **13** (with 71% conversion) from the allylation using cinnamyl acetate, we went on to implement the intramolecular Pd-AAA technique for further increase the ee.

1.2.2 Optimization study of intramolecular Pd mediated decarboxylative asymmetric allylation (Pd-DAAA) reaction

At first, we tried to explore Pd catalyzed asymmetric allylic alkylation (Pd-DAAA). We therefore made the carboxy allyl enol compound **10** from compound **1** using NaHMDS/LiHMDS as a base. Optimizing the required amount of base (1 equiv) along with a activating agent TMEDA (tetramethyl ethylenediamine), we obtained the desired compound **10** with quantitative conversion. It should be mentioned that the role of the activating agent is to form chelated complex with the NaHMDS/LiHMDS base which helps to deprotonate the enolic proton in a controlled manner. Addition of more activating agent could not influence the percentage conversion.

Scheme 64 Synthesis of carboxyallyl acrylate and the Pd-DAAA to form compound **2**

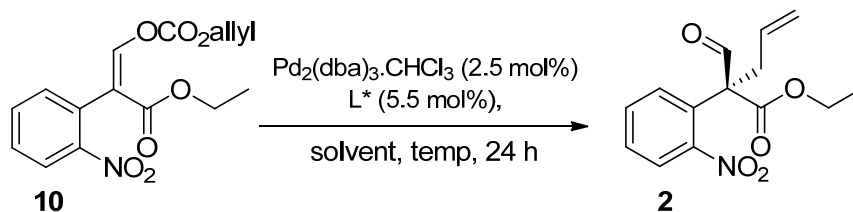
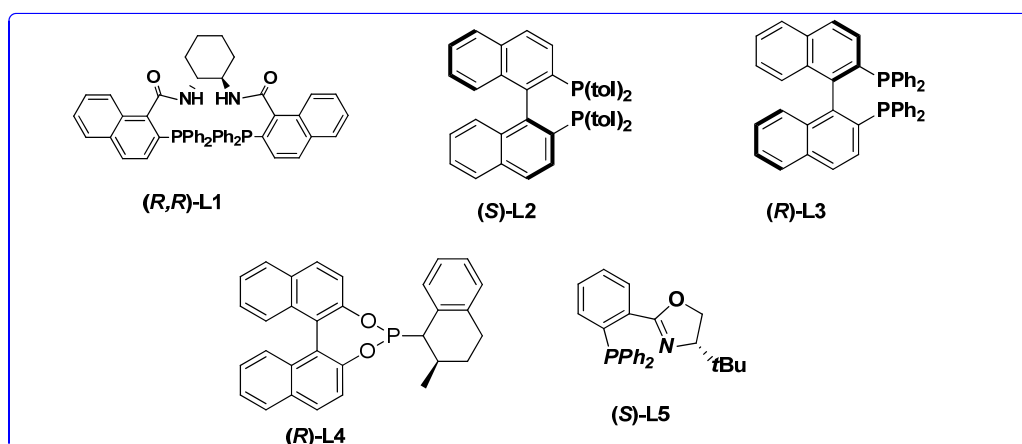


Once we obtained compound **10**, the next step was to rearrange the compound ethyl 3-(((allyloxy)carbonyl)oxy)-2-(2-nitrophenyl)acrylate **10** to form compound **2** by decarboxylative manner (loss of CO_2 as a gas). But the synthesis of compound **2** needs a systematic optimization of variables like solvents, ligands, and temperature to achieve a better optical selectivity. Therefore, we have screened the parameters as shown in Table 8.

By using our previously optimized reaction conditions i.e considering THF as a choice of solvent,

five different ligands **L1-L5** were applied for screening initially where ligand **L1** provided reasonable enantioselectivity (44% ee) providing compound **2** (Table 8, entry 1-6) at -20 °C. Later, the use of solvent DME and toluene produced the desired product with roughly similar enantiobenefit (**Table 8**, entry 7 and 8). Switching to a mixed solvent system such as THF-toluene or THF-hexane, we observed a decreasing value of both conversion and ee (Table 8, entries 9 and 10). We subsequently explored less polar solvent mixture of toluene-hexane (2:1) at different temperatures; the best results obtained at -10 °C (**Table 8**, entry 13 vs entries 11, 12 and 14). Increasing or decreasing ratio of toluene/hexane didn't

Table 8 Selected optimization studies for decarboxylative rearrangement of O-Carboxy alkylated Product 10



entry ^[a]	ligand	solvents	temp[°C]	conv. ^[b] [%]	ee ^[c] [%]
1	(<i>R,R</i>)-L1	THF	rt	99	32
2	(<i>S</i>)-L2	THF	rt	99	04 ^d
3	(<i>R,R</i>)-L3	THF	rt	99	10
4	(<i>R,R</i>)-L4	THF	rt	99	11
5	(<i>S</i>)-L5	THF	rt	50	rac
6	(<i>R,R</i>)-L1	THF	-20	>99	44
7	(<i>R,R</i>)-L1	DME	rt	>99	34
8	(<i>R,R</i>)-L1	toluene	rt	>99	35
9	(<i>R,R</i>)-L1	THF:tol (1:1)	rt	85	25
10	(<i>R,R</i>)-L1	THF:hex (1:1)	rt	90	21
11	(<i>R,R</i>)-L1	tol:hex (2:1)	rt	95	43
12	tol:hex (2:1)	(<i>R,R</i>)-L1	40	100	38
13	(<i>R,R</i>)-L1	tol:hex (2:1)	-10	>99	55
14	(<i>R,R</i>)-L1	tol:hex (2:1)	-20	>99	48
15	(<i>R,R</i>)-L1	tol:hex (1:1)	-10	67	30
16	(<i>R,R</i>)-L1	tol:hex (3:1)	-10	48	21
17	(<i>R,R</i>)-L1	Tol:hex(2:1)	40	100	38
18	(<i>R,R</i>)-L1	toluene	-78-rt	100	28
19	(<i>R,R</i>)-L1	dioxane	rt	10-20	n.d.
20	(<i>R,R</i>)-L1	THF	0	85	19
21	(<i>R,R</i>)-L1	DCM	rt	75	23
22	tol:hex (2:1)	(<i>R,R</i>)-L4	-10	99	08
23	tol:hex (2:1)	(<i>R,R</i>)-L4	rt	99	racemic
24	tol:hex (2:1)	(<i>R,R</i>)-L9	rt	nr	-
25	tol:hex (2:1)	(<i>R,R</i>)-L8	rt	<15	n.d.

^aAll reactions have carried out in 0.1-0.2 mmol scale, ^bConversions were calculated from NMR ^cenantiomeric excess calculated by chiral HPLC

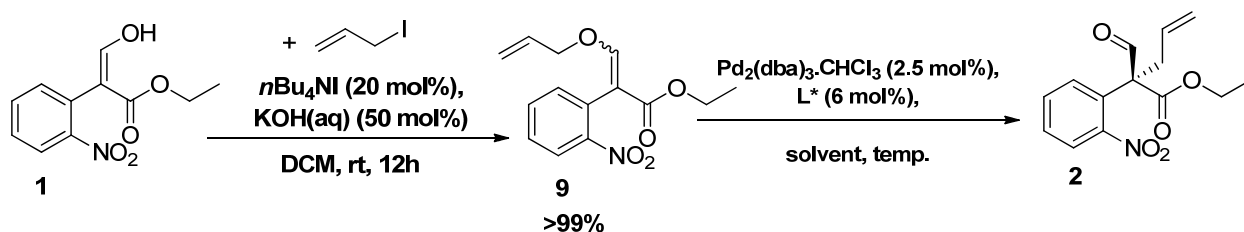
improved the enantioselectivity (**Table 8**, entry 15 and 16). Use of similar solvent mixture at different temperature resulted either low conversion or lower enantioselectivity as shown in table 9 (entries 17-21). Later, we decided to screen more ligands like **L8** and **L9** along with **L4** and ended up with either racemic or a very low enantioselectivity (entries 21-24).

We believe that the reason of getting low enantioselectivity is the non-regioselective formation of carboxy enol acrylate **10** i.e., the formation of racemic **10**.

1.2.3 Optimization study of intramolecular Pd-mediated Claisen rearrangement

As we did not achieve a higher enantiobenefit from the intermolecular approach, we embarked upon our investigation of another intramolecular Pd-AAA involving intramolecular Claisen type rearrangement of O-allylated compound **9** for preparing compound **2**. Compound **9** was prepared under alkaline conditions from the reaction of **1** and allyl bromide/allyl iodide (1.2 equiv) using $n\text{Bu}_4\text{NI}$ as a phase transfer catalyst. (Scheme 65).

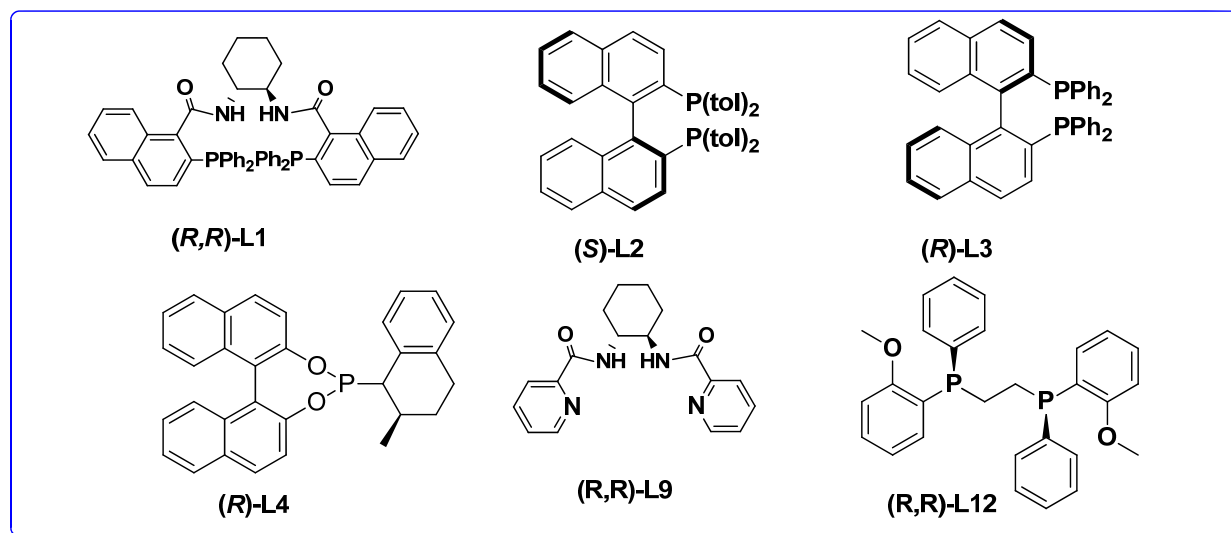
Scheme 65 Synthesis of O-allylated enol **9** and the Pd induced rearrangement to form compound **2**

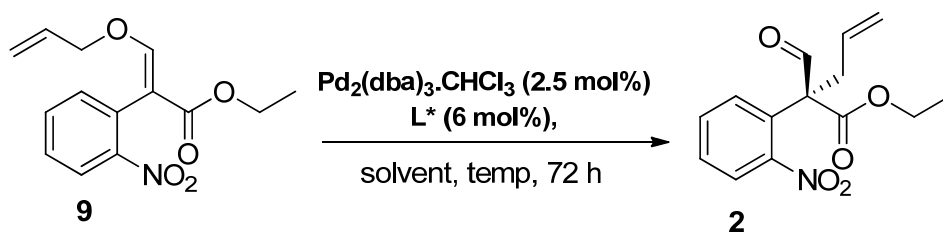


The formation of compound **9** with quantitative conversion encourage us to move towards the rearrangement approach using Pd with different ligand. This approach is very less explored and limited to the substrate scope as well. After a general screening of ligands **L1-L4**, **L9** and **L12** in toluene : MeOH (20 : 1), we found ligand **L1** was promising to achieve better enantioselectivity (32% ee) of compound **2** at -20 °C (Table 9, entry 7 vs entries 1-7). Elevation of temperature decreased the enantioselectivity for **L1** (entry 8). Increasing the percentage of toluene in MeOH (30:1) retained almost the same ee with a considerably higher conversion (entry 9) at -10 °C. Additionally, a slight improvement of selectivity was observed in pure toluene at room temperature and -20 °C (entries 10 and 11). We believe that the low polarity systems may help to improve stereinduction by helping to form tight ion pairs via the formation of “solvent cages”, and thus

bring the enolate and Pd π -allyl complex closer together.[136] Therefore, we drew our attention to a methodical decrease in polarity of toluene by adding hexane. A lower value of both conversion and ee were obtained using a 2:1 ratio of toluene-hexane solvent (entry 12). An equal volume of hexane and toluene (1:1) resulted a slight increase of ee (entry 13 vs entry 14); lowering the temperature from 25 °C to -10 °C strikingly increased the value of ee (58%) with an excellent conversion (entry 14). Higher ratio of hexane/toluene (2:1 and 3:1) at -10 °C demonstrated lower value of the obtained results (entries 15 and 16). Moreover, use of polar solvents such as DCM or THF provided inferior results compared to toluene or toluene/hexane (entries 17 and 18 vs entries 10-16). Screening similar solvent system at different temperature did not prove to be helpful for this approach as well (entries 19-22)

Table 9 Optimization studies for Claisen rearrangement of O-alkylated product 9 (Method B)



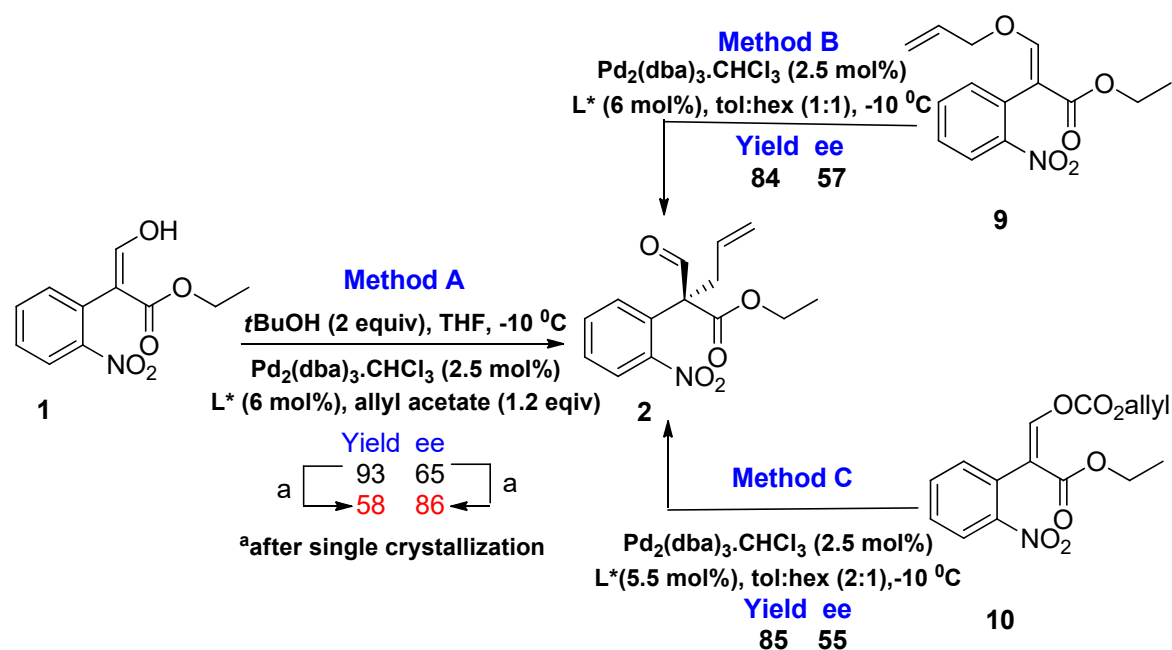


entry ^a	ligand	solvent	temp, °C	% conv. ^b	% <i>e.r.</i> ^c
1	L1	tol:MeOH (20:1)	rt	95	63:37
2	L2	tol:MeOH (20:1)	rt	67	46:54
3	L3	tol:MeOH (20:1)	rt	75	rac
4	L4	tol:MeOH (20:1)	rt	30	61:39
5	L9	tol:MeOH (20:1)	rt	n.r.	n.d.
6	L12	tol:MeOH (20:1)	rt	<10	n.d.
7	L1	tol:MeOH (20:1)	-20	80	66:34
8	L1	tol:MeOH (20:1)	40	100	67:23
9	L1	tol:MeOH (30:1)	-10	95	65:35
10	L1	toluene	rt	85	68:32
11	L1	toluene	-20	90	67:33
12	L1	tol:hex (2:1)	rt	70	61:39
13	L1	tol:hex (1:1)	rt	99	64:36
14	L1	tol:hex (1:1)	-10	99	79:21
15	L1	tol:hex (1:2)	-10	86	70:30
16	L1	tol:hex (1:3)	-10	78	69:31
17	L1	DCM	rt	99	62:38
18	L1	THF	rt	99	62:38
19	L1	THF	-10	63	60:40
20	L1	hexane	rt	10-20	n.d.
21	L1	DCM	-78-rt	99	62:38
22	L1	THF:DCM(1:1)	-10	71	59:41

^aAll reactions have carried out in 0.1-0.2 mmol scale, ^bConversions were calculated from NMR ^cenantiomeric excess calculated by chiral HPLC

From the above studies, it is noteworthy that both the yield and ee (of compound **2**) remained roughly unaffected whether the Pd-AAA reaction was performed intermolecularly or intramolecularly. However, the intermolecular approach, Method A appears to be more appealing than the intramolecular approaches, Method B and C because it requires one less step to prepare compound **2** and gave better results (**Scheme 66**). For further improvement of enantioselectivity, we decided to recrystallize compound **2** prepared by Method A. [137] Upon recrystallization from hexane, the supernatant led the enantioenriched product to 85% ee with 58% yield (**Scheme 66**).

Scheme 66 Intermolecular vs Intramolecular Pd-AAA



1.2.4 Optimization of synthetic steps involving chiral 3,3-disubstituted oxindole

Since we have achieved 86% ee of compound **2** from the Pd-AAA reaction of **1**, we went on to synthesize our targeted 3,3'-disubstituted oxindole framework **4** in order to show the application of the developed acyclic quaternary molecule **2** in the synthesis of a significantly accessible building block **4** (Scheme 67). Reduction of aldehyde using NaBH₄ of **2** provided compound **3** with more than 99% yield. Then selective reduction of nitro group of **3** has targeted through different approaches shown in Table 10. Use of reducing agent like Sn with HCl or Fe with HCl and Zn with TiCl₄ provided trace to low yielding of the product (Table 10, entries 1-3). But the Zn with NH₄Cl whenever used in the ratio of 1:1.25 yielded less product (Table 10 entry 4); increase ratio of that 1: 2.25 proved to be optimized (Table 10, entry 5). Increasing amount of NH₄Cl showed complexity of separating the compound from the crude mixture. An attempt to get rid of NH₄Cl during the reaction using a aqueous solution of surfactant to ethanol proved detrimental to the formation of the oxindole, **4**. (Table 10, entry 6).

Scheme 67 Asymmetric synthesis of chiral 3,3-disubstituted oxindole

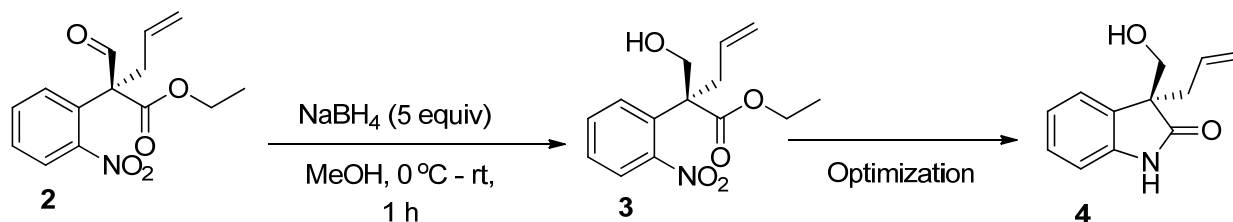


Table 10 Optimization for the formation of chiral 3,3 disubstituted oxindole from 2

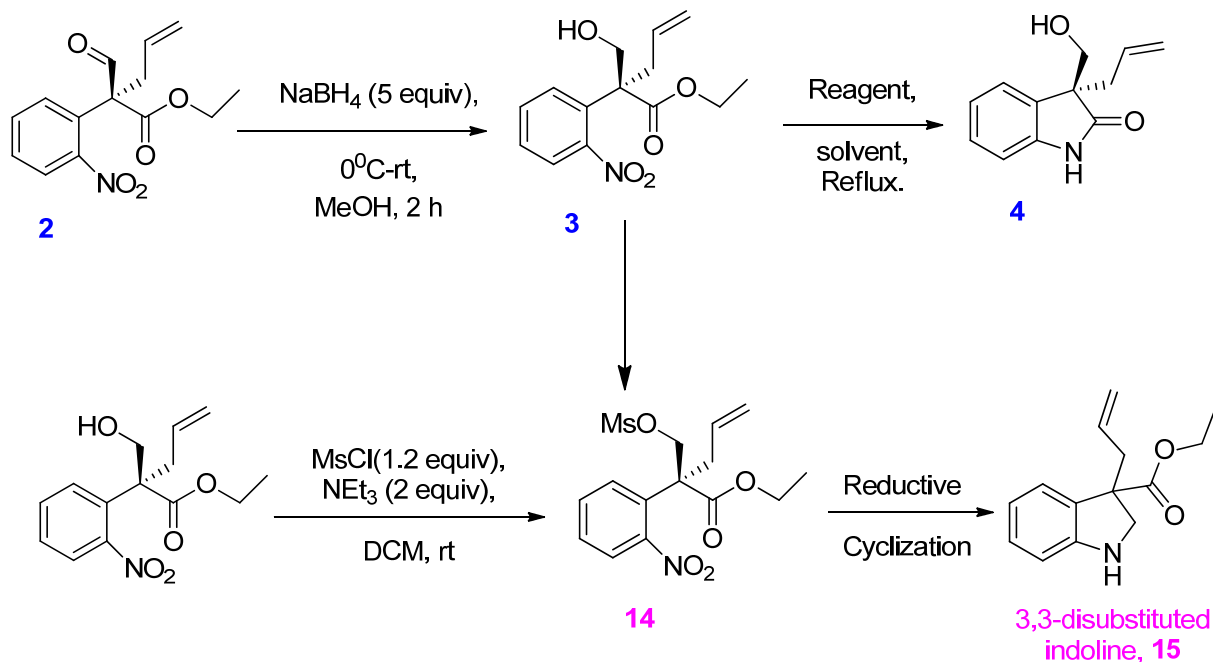
Entry ^a	Reagent	Solvent	Remarks ^d
1	Fe (4-5 equiv), HCl, NH ₄ OAc ^b	EtOH : H ₂ O (2:1)	Trace/no product
2	Sn (4-5 equiv), HCl, NH ₄ OAc ^b	EtOH : H ₂ O (2:1)	Trace/no product
3	Zn (3-4 equiv), TiCl ₄ (2 equiv)	Ether : H ₂ O (1:1)	Trace/no product
4	Zn (4 equiv), NH ₄ Cl (5 equiv)	EtOH : H ₂ O (4:1)	10-20%
5	Zn (8 equiv), NH ₄ Cl (9.5 equiv)	EtOH : H ₂ O (4:1)	85%
6	Zn (8 equiv), NH ₄ Cl (9.5 equiv)	EtOH : H ₂ O (1:1) ^c	Trace/no product

^aall reactions have conducted 1-2 mmol, ^bused for adjusting pH of the solution, ^c1 equiv of PEG surfactant had added.

^disolated yield

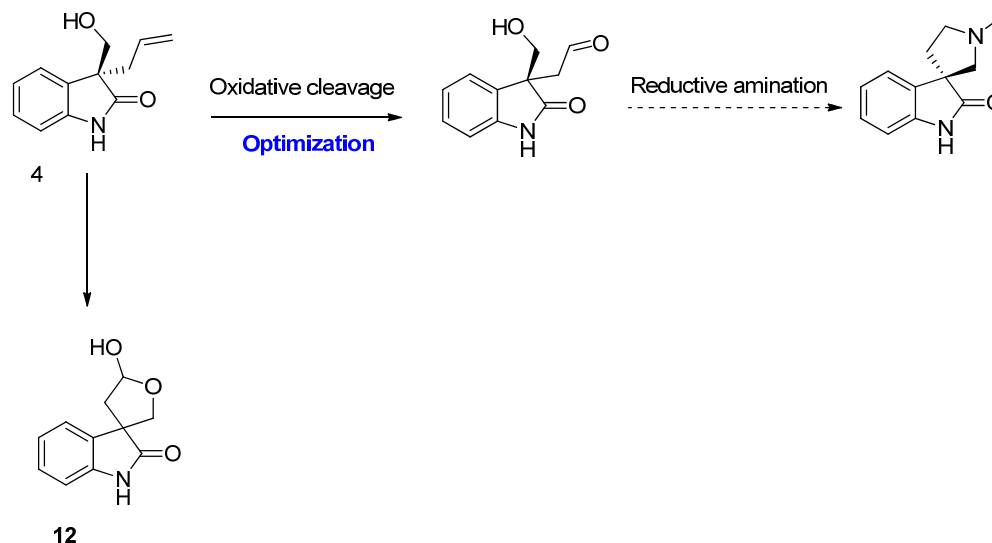
One new finding during the attempt of synthesizing oxindole, **4** from compound **3** is that whenever we tried to cyclize the Mesyl protected allyl alcohol, **14** we ended up with the formation of 3,3-disubstituted indoline, **18** instead of the expected formation of Mesyl protected oxindole (**Scheme 68**). We believe that because of the bulky mesyl group; allows the rotation of the ester functionality distant from the reduced amine to form compound **15**. This approach therefore introduces a new dimension of exploring various substrate scope of compound **15** for future research.

Scheme 68 Formation of 3,3-disubstituted indoline



However, when we get out key intermediate, **4** we therefore planned a route for the total synthesis of rarely explored (-)-coerulescine moiety. Oxidative cleavage using the conventional oxidant like $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$, OsO_4 , ozonolysis and classical $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ provided trace or no product almost each instance shown in scheme **Table 11** (entries 1-5). We therefore found the formation of lactol derivative (an acetal ring), **12** during oxidative cleavage which happened because of the cyclization of the in-situ formed aldehyde after oxidation and intramolecular cyclization with the alcoholic -OH functionality in compound **4** (**Table 11**, entries 6 and 7).

Scheme 69 Proposed synthesis of (-)-coerulescine



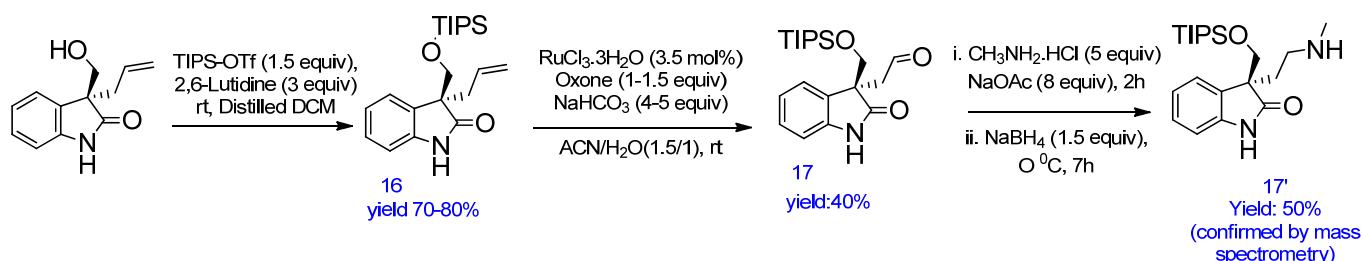
^aAll reactions have conducted 1-2 mmol scale

Table 11 Optimization reaction conditions for the oxidation of oxindole 4

entry ^a	reagent	Solvent /temp /time	remarks
1	i. OsO ₄ (2 mol%), 2,6-Lutidine (2 equiv), ii. NaIO ₄ (4 equiv),	Dioxane: H ₂ O (5:1), 25 °C, 22 h	Trace / no product
2	i. K ₂ OsO ₄ ·2H ₂ O (20 mol%), NMO (5 equiv), ii. NaIO ₄ (5 equiv),	THF : H ₂ O (3:1), rt, 12 h	Trace / no product
3	O ₃ (1 min/mmol), -78 ⁰ C, Pyridine (3 equiv),	DCM, -78 °C	Trace / no product
4	RuCl ₃ (3.5 mol%), Oxone (1.5 equiv), NaHCO ₃ (4.7 equiv),	ACN / H ₂ O (1.5/1), rt, 6-8 h	Trace / no product
5	RuCl ₃ (3.5 mol%), Oxone (1.5 equiv), NaHCO ₃ (4.7 equiv),	ACN / H ₂ O (6/1), rt, 6-8 h	Trace / no product
6	RuCl ₃ (3.5 mol%), NaIO ₄ (2.6 equiv)	ACN / H ₂ O (6/1), rt,	Small Cpd 12
7	RuCl ₃ (3.5 mol%), NaIO ₄ (2.6 equiv)	ACN / H ₂ O (6/1), rt,	15% cpd 12

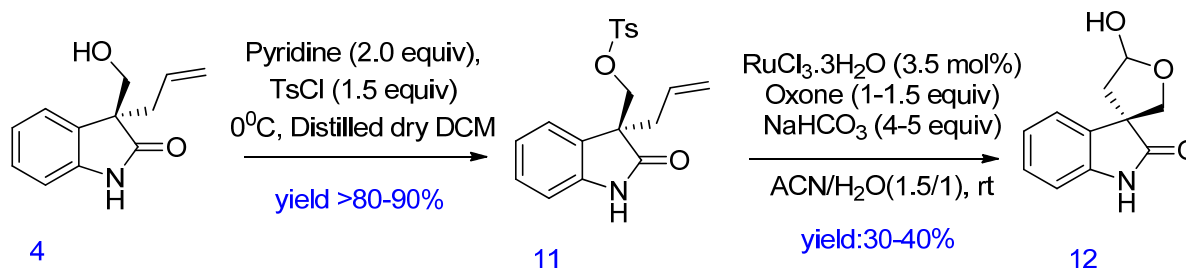
Therefore, we decided to protect the hydroxy group (which is interfering the formation of aldehyde) with various protecting groups such as TIPS, tosyl and mesyl. At first the hydroxy group was protected by TIPS group to prepare compound **16** and then the oxidation was successfully carried out using classical oxidant $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}/\text{NaIO}_4$ to prepare **17**. The following step of reductive amination cyclization could not proceed with the TIPS protected oxindole **17**. We believe that the bulky TIPS group made the oxygen more hindered; only identified the product **17'** (by mass spectrometry) rather getting the expected product **7**.

Scheme 70 Attempted oxidation of **4** after TIPS protection and reductive amination cyclization



Secondly, the attempt of oxidation followed by tosyl protection of compound **4** proceeded well but lability of tosyl group in the ACN : H_2O solvent system resulted the formation of compound **12** as shown in **Scheme 71**. After exploring TIPS and tosyl protection, we decided to mesylate group which is in fact not that bulky (like TIPS) or as labile as (Tosyl). The oxidation was optimized

Scheme 71 Attempted oxidation of **4** after tosyl protection and reductive amination cyclization



(as shown in **Table 12**) followed by the mesyl protection. The use of oxone /NMO as a co-oxidant along with NaHCO₃ resulted trace product (**Table 12**, entries 1 and 6). But NaIO₄ as terminal oxidant in a solvent system of ACN:H₂O-1.5:1 gave us 30% yield of the expected product **6** (**Table 12**, entry 2). A fine tuning of binary solvent system ACN:H₂O (6:1) provided 85% of isolated yield (**Table 12**, entries 3-5). Though we achieved an excellent outcome of desired oxidation

Scheme 72 Attempted oxidation of **4** after mesityl protection

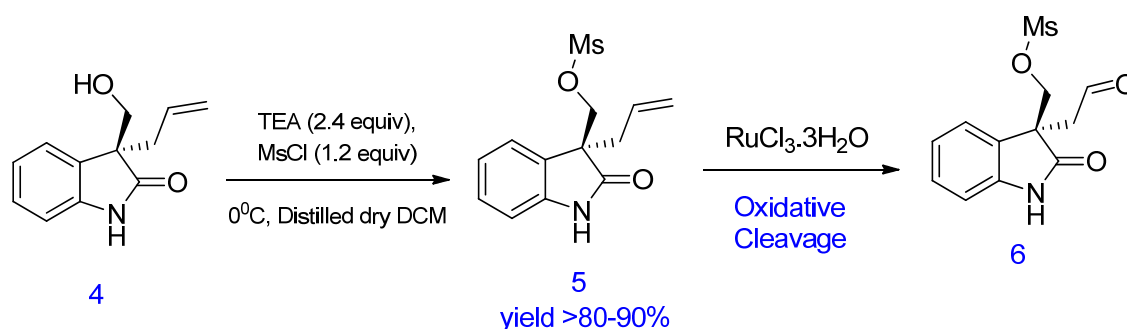


Table 12 Optimization for the oxidation of Ms-protected Oxindole 5

entry ^a	reagents	solvent	yield(%)
1	Oxone (1.5 equiv), NaHCO ₃ (4.7 equiv)	ACN:H ₂ O-1.5:1	Trace / no product
2	NaIO ₄ (2 equiv)	ACN:H ₂ O-1.5:1	30%
3	NaIO ₄ (2.6 equiv)	ACN:H ₂ O-1.5:1	35-40%
4	NaIO ₄ (2 equiv)	ACN:H ₂ O-6.0:1	50%
5	NaIO ₄ (2.6 equiv)	ACN:H ₂ O-6.0:1	85%
6	NMO (5 equiv), NaIO ₄ (5 equiv)	THF:H ₂ O-3.0:1	Trace product

^a 1-2 mmol of the compound **4** and **5** was used

(compound **6**), we needed to explore the way to form the pyrrolidine ring from **6**. Therefore, we started screening various condition of reductive amination cyclization shown in **Scheme 73**.

Scheme 73 One pot reductive amination cyclization to synthesize (-)-coerulescine

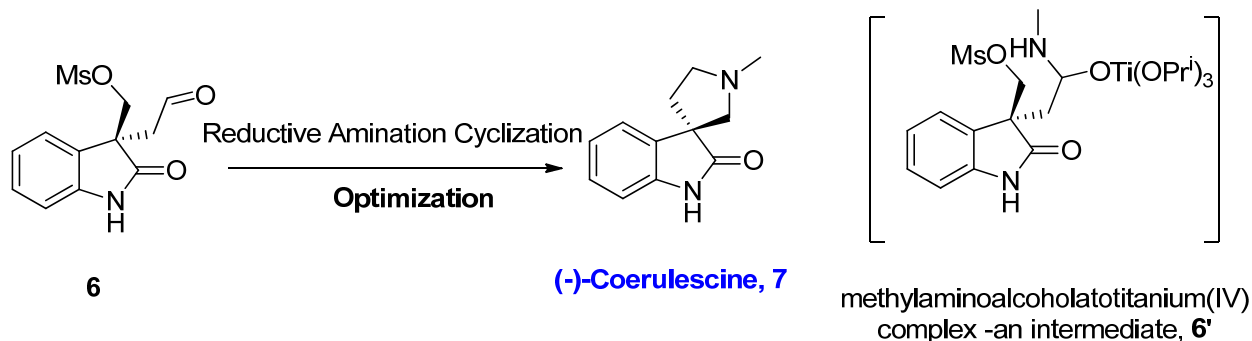


Table 13: Optimization of One-pot reductive amination cyclization of Ms-Protected oxindole aldehyde 6

entry ^a	Reaction conditions	remarks
1	i. MeNH ₂ (in EtOH) (1 equiv), DCE, rt, 2h ii. NaBH ₃ CN (1 equiv), pH= 6-7, overnight	Trace / no product
2	i. MeNH ₂ (in EtOH) (1. equiv), DCE, rt, 4A0 mol. sieve, 2h ii. NaBH ₄ (1.2 equiv), 2h	Trace / no product
3	i. MeNH ₂ .HCl (1.05 equiv), TEA (1.5 equiv), DCE, rt, 2h NaBH ₄ (1.5 equiv), 3.5 h	Trace / no product
4	MeNH ₂ (in EtOH) (1.05 equiv), Ti(OiPr) ₄ (2 equiv), EtOH, rt, 3h; NaBH ₄ (1.5 equiv), 3 h	15-20%
5	i. MeNH ₂ (in THF) (1.25 equiv), THF, rt, 3h ii. NaBH ₄ (1.5 equiv), 4 h	Trace / no product
6	i. MeNH ₂ (in THF) (1.25 equiv), THF, rt, 3h ii. NaBH ₄ (1.5 equiv), CH ₃ COOH (1 equiv), 4 h	Trace / no product
7	MeNH ₂ (in THF) (1.05 equiv), Ti(OiPr) ₄ (2 equiv), rt, 3 h NaBH ₄ (1.1 equiv), 2 h	95% product

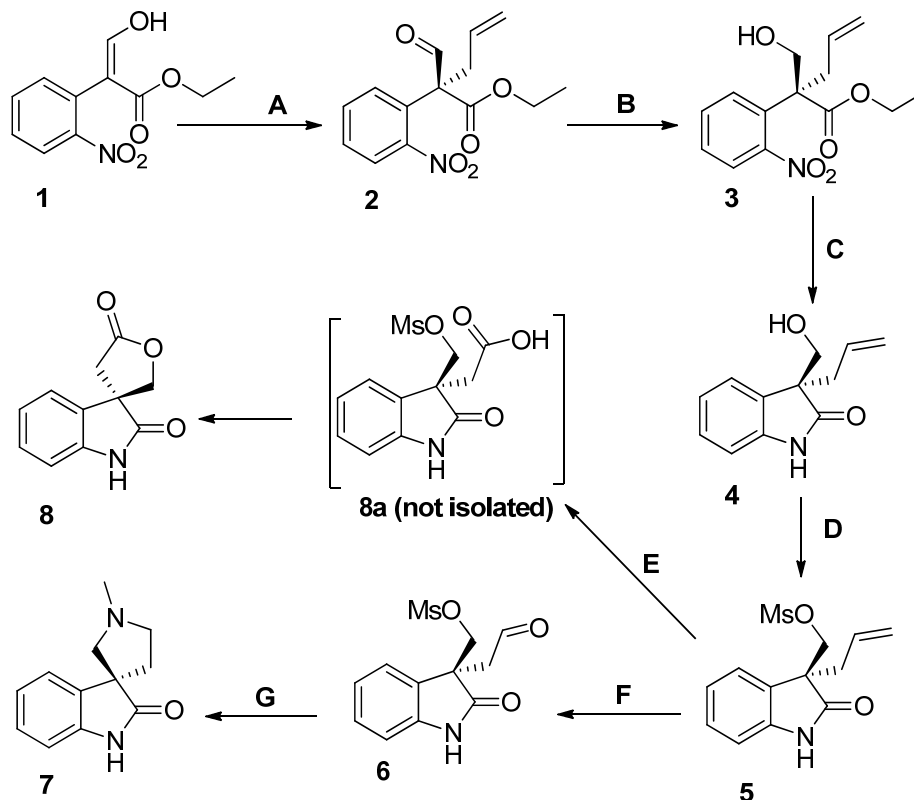
^a 1-2 mmol of the compound 6 was used for optimization study

Through the study, use of MeNH₂ (in EtOH) along with NaBH₃CN/NaBH₄ and additives (triethylamine, CH₃COOH) in 1,2-DCE as solvent did not result any considerable amount of

product for isolation (entries 1-3, 5-6). But the use of $\text{Ti}(\text{O}^i\text{Pr})_4$ with MeNH_2 in EtOH resulted 15% of the isolated product which was a promising result for further screening. Fortunately, a source of MeNH_2 in THF and $\text{Ti}(\text{O}^i\text{Pr})_4$ provided 95% of the desired compound (-)-coerulescine which exactly matches the NMR spectra and optical rotation of Hyaashi et al. We believe the cyclization was pursued by the formation of the non-isolated intermediate **6'**.

In summary, our overall synthesis can be shown by the **Scheme 74**. Our synthesis commenced with a reduction of aldehyde functionality of compound **2** by sodium borohydride in methanol to provide alcoholic product **3**. The *ortho*-nitro functional group of compound **3** was selectively reduced to afford the desired oxindole **4**. Later, the hydroxy group of the compound **4** was protected by mesyl group to prepare compound **5**. The oxidative cleavage of **5** using an optimized amount of NaIO_4 (2.4 equiv) along with $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (3.5 mol%) afforded compound **6**. Finally, one pot reductive amination-cyclization of **6** using commercially available methyl amine solution in presence of titanium isopropoxide yielded the desired product (-)-coerulescine with an overall yield of 34%. The NMR of **7** was matched with the values reported in the literature. [138]

Scheme 74 Total Synthesis of (-)-coerulescine and (-)-coixspirolactam A



Conditions: [A] Allyl acetate, $[\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3]$, L^* , -10°C , 58%. [B] NaBH_4 , MeOH, 0°C - rt, 1 h, 99%. [C] Zn, NH_4Cl , EtOH: H_2O (4:1), reflux, 2 h, 80%. [D] MsCl , NEt_3 , DCM, 0°C , 4 h, 85%. [E] (i) $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, 1,2-DCE: H_2O (2:1) (ii) NaIO_4 (3 equiv), 32 h, 68%. [F] (i) $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$, ACN: H_2O (6:1) (ii) NaIO_4 (2.4 equiv), 12-14 h, 80%. [G] (i) MeNH_2 , $\text{Ti}(\text{O}^i\text{Pr})_4$, MeOH, rt, 5 h. (ii) NaBH_4 , rt, 2 h, 95%.

In order to synthesize another targeted natural product coixspirolactam A **8**, compound **5** was oxidized with an optimized quantity of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ (3.5 mol%) with higher equivalent of NaIO_4 (3 equiv) involving prolonged reaction time (32 h). We assume that the formation of such lactone is due to intramolecular lactonization of non-isolated carboxylic acid **8a**. [139] The desired product

8 was obtained with an overall yield of 32% in five steps and NMR was matched with the values reported in the literature. [140]

In summary, we have explored different approaches of Pd-AAA for the enantioselective synthesis of acyclic all carbon quaternary aldehyde starting from a rare prochiral *ortho*-nitro arylacrylate. The efficient intermolecular Pd-AAA was forwarded to develop a unique route to synthesize chiral 3,3-disubstituted oxindole **4**. By utilizing the present methodology as a key step, the concise synthesis of spirocyclic (-)-coerulescine **7** and (-)-coixspirolactam A **8** have been described. We believe that this protocol is going to be a beneficial tool for synthetic chemists in the total synthesis of natural products and drug discovery either in academic or industrial laboratories.

1.3 General methods and experimental

Experimental procedures and tabulated characterization data

Compound **1**, (Z)-ethyl-3-hydroxy-2-nitro-phenylacrylate was synthesized by using our published procedure.¹ Isolated Yield: 78%. The identity of this compound was confirmed by ¹H, ¹³C NMR and HRMS.[141]

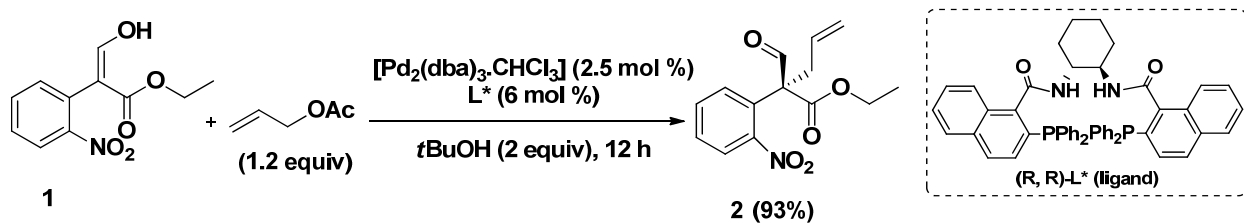
¹H NMR (CDCl₃, 300 MHz): δ 11.98 (d, J = 12.0 Hz, 1H), 7.99 (d, J = 6.0 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 6.0 Hz, 1H), 4.22 (brs, 2H), 1.15 (t, J = 7.5 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 170.0, 162.2, 149.2, 133.3, 133.2, 129.2, 128.6, 124.9, 106.6, 61.3, 13.7.

HRMS (ESI⁺): Calculated (m/z) for C₁₄H₁₆NO₅ (M-H)⁻ : 236.0564, Found 236.0562.

Melting Point: 88-90 °C

1.3.1 General procedure for the synthesis of Ethyl 2-formyl-2-(2-nitrophenyl)pent-4 enolate, **2** (Method A-Intermolecular Approach)



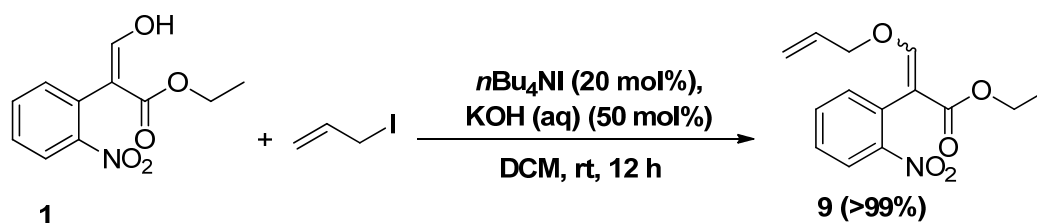
In an oven dried and desiccator-cooled sealable test tube was added $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (5.4 mg, 0.00525 mmol, 2.5 mol%) and $(R, R)\text{-L}^*$ (10.0 mg, 0.0126 mmol, 6 mol%). The test tube was then evacuated and backfilled with argon three times. Previously distilled and degassed tetrahydrofuran (THF) was added to the flask and the mixture was stirred for 15 min until it was homogeneous, and an orange color persisted. Then, allyl acetate (28 μL , 0.252 mmol, 1.2 equiv) was added to the system and the solution was stirred at room temperature for an additional 5 min. In the meantime, the other test tube was charged with 3-hydroxy 2-nitro phenyl acrylate **1** (50.0 mg, 0.210 mmol, 1.0 equiv) with the addition of 2 mL of degassed tetrahydrofuran (THF) and it was finely dissolved in solvent. Then the cat- L^* -allyl acetate mixture was added to the solution of 3-hydroxy 2-nitro phenyl acrylate **1** via cannula. Additive, $t\text{BuOH}$ (39 μL , 0.420 mmol, 2.0 equiv) was added into the reaction mixture. The mixture was stirred at room temperature and confirmed the completion of reaction by TLC monitoring. The crude was passed through a thick pad of silica (2 cm) and solvent was decanted. The crude was then purified by column chromatography on silica gel elution (hexane/EtOAc = 19/1) and 53.5 mg (93% yield) of white solid product **2** was obtained.

¹H NMR (CDCl₃, 300 MHz): δ 10.16 (s, 1H), 8.16 (d, *J* = 9.0 Hz, 1H), 7.72 (t, *J* = 10.5 Hz, 1H), 7.64 (t, *J* = 9.0 Hz, 1H), 7.54 (td, *J* = 15.0, 1.5 Hz, 1H), 5.80-5.67 (m, 1H), 5.29-5.17 (m, 2H), 4.22 (q, *J* = 9.0 Hz, 2H), 3.04 (d, *J* = 3.0 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 196.9, 169.4, 148.4, 133.7, 131.1, 130.7, 130.5, 129.0, 125.9, 120.4, 63.9, 62.0, 37.8, 14.0.

HRMS (ESI⁺): Calculated (m/z) for C₁₄H₁₆NO₅ (M+Na)⁺: 300.0842, Found 300.0834. **Melting point:** 101-103 °C

1.3.2 General procedure for the synthesis of general procedure for the O-allylation of prochiral enol acrylate: Synthesis of (*E/Z*)-ethyl 3-(allyloxy)-2-(2-nitrophenyl)acrylate, **9**



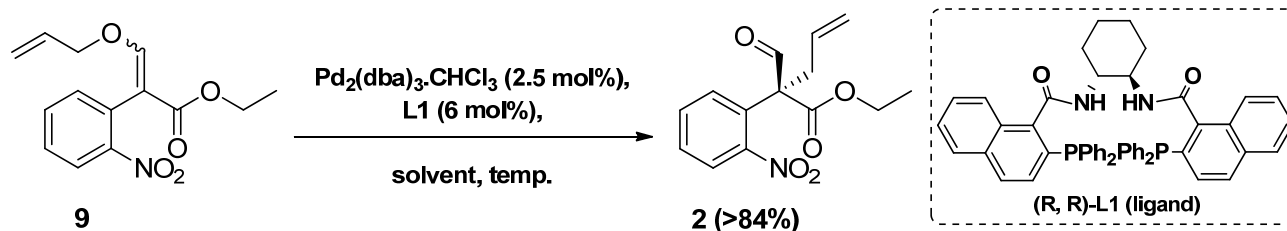
(*Z*)-Ethyl 2-nitro-3-hydroxyphenylacrylate, **1** (50.0 mg, 0.210 mmol, 1.0 equiv) was dissolved in freshly distilled dichloromethane (5 mL) under argon. $n\text{Bu}_4\text{NI}$ (7.8 mg, 0.021 mmol, 0.1 equiv), allyl bromide (22.0 μL , 0.252 mmol, 1.2 equiv), and potassium hydroxide (118.0 mg, 2.10 mmol, 10 equiv) were added, and the reaction mixture was stirred at room temperature until reaction completion was confirmed by NMR. The reaction was quenched by adding saturated NH_4Cl solution, and the aqueous layer was extracted with diethyl ether ($2 \times 25 \text{ mL}$). The organic portions were combined and dried over Na_2SO_4 . Then, the organic layer was then passed through a cotton plug and the solvent was removed by rotary evaporation. Pure product **9** was isolated by flash chromatography on silica gel elution (hexane/EtOAc= 9/1) as (58.0 mg, 99.2% yield) a light-yellow oil.

^1H NMR (300 MHz, CDCl_3): δ 8.05 (d, $J = 6.0 \text{ Hz}$, 1H), 7.65 (s, 1H), 7.61 (t, $J = 4.5 \text{ Hz}$, 1H), 7.46 (dd, $J = 6.0, 3.0 \text{ Hz}$, 2H) 5.96-5.88 (m, 1H), 5.34 (dd, $J = 9.0, 6.0 \text{ Hz}$, 2H), 4.54 (d, $J = 3.0 \text{ Hz}$, 2H), 4.18 (q, $J = 7.5 \text{ Hz}$, 2H), 1.23 (t, $J = 4.5 \text{ Hz}$, 3H);

^{13}C NMR (75 MHz, CDCl_3): δ 166.1, 157.9, 148.9, 133.3, 132.6, 132.1, 128.3, 128.2, 124.5, 119.3, 127.6, 75.3, 60.7, 14.1.

HRMS (ESI+): Calculated (m/z) for $\text{C}_{14}\text{H}_{15}\text{NO}_5$ ($\text{M}+\text{H}$) $^+$: 278.1023, Found 278.1013.

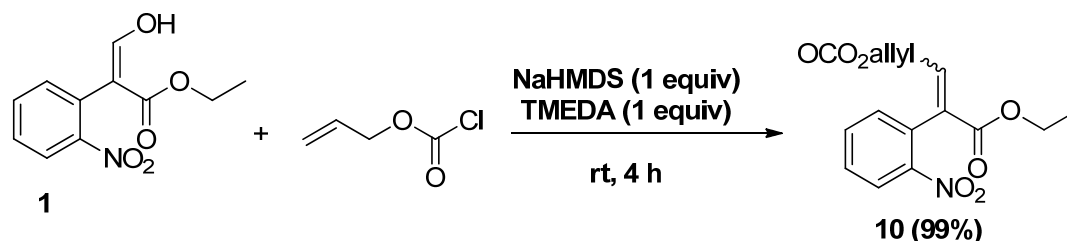
1.3.3 General procedure for the Pd-mediated rearrangement of compound **9** to prepare Ethyl 2-formyl-2-(2-nitrophenyl) pent -4 enolate, **2** (Method B)



Except for the variation in solvent, ligand and temperature, all O-allyl rearrangement reactions were carried out by the following general procedure:

In an oven dried and desiccator-cooled sealable test tube was added $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (4.7 mg, 0.0045 mmol, 2.5 mol%) and (R,R)-L1 (8.6 mg, 0.010 mmol, 6.0 mol%). The test tube was then evacuated and backfilled with argon three times. Previously degassed (1:1) hex: tol (5 mL) was added to the flask and the mixture was stirred for 15 min until it was homogeneous, and an orange color persisted. In the meantime, another test tube was charged with Ethyl-3-(allyloxy)-2-nitrophenylacrylate **9** (50.0 mg, 0.180 mmol, 1.0 equiv), evacuated and backfilled with Argon, and then degassed solvent hex: tol (1 mL: 1 mL) was added to dissolve. Both the test tubes were then put into -10 °C cooling bath and stir for another 15 min before transferring the substrate solution into the catalyst mixture via a cannula. The reaction was stirred for 24 h, unless otherwise mentioned. The reaction mixture was then passed through a thick pad of silica plug and the solvent was removed in vacuo. The pure product, **2** was isolated (42.1 mg, 84.2 % yield) by flash column chromatography eluting through silica gel (hexane / EtOAc = 10/1) as a white solid and confirmed by ^1H NMR. and ^{13}C NMR.

1.3.4 General procedure for the carboxy allylation of prochiral enolacrylate to prepare Ethyl 3-(allyloxy)carbonyloxy)-2-(2-nitrophenyl)acrylate, **10**



To a flask was added anhydrous THF (2 mL) via syringe, followed by NaHMDS (1M solution in THF); (43.0 μ L, 0.210 mmol, 1.0 equiv) and TMEDA (31.5 μ L, 0.210 mmol, 1.0 equiv), both reagents being added at room temperature. After the mixture was stirred for 5 min, 3-hydroxy-2-nitro-phenylacrylate, **1** (50.0 mg, 0.210 mmol, 1.0 equiv) was dissolved in anhydrous THF (2 mL) in a separate flask and is then transferred to the reaction flask containing the NaHMDS / TMEDA mixture via syringe at room temperature. The mixture allowed stirring at room temperature for 20 min, at which point allylchloroformate (25 μ L, 0.231 mmol, 1.1 equiv) was added dropwise via syringe at rt. The resulting solution was then allowed to stir at temperature for 45 minutes. The reaction was monitored by taking a small aliquot (0.1 mL) via syringe from the reaction flask, passing it through a small silica plug, concentrating the solvent under vacuum and taking a ^1H NMR. When the reaction completed, the crude mixture was passed through a silica plug (4 cm diameter medium porosity fritted funnel, 2 cm of silica). The silica plug was rinsed through with additional solvent (10 mL) to ensure quantitative elution of product. The solvent was then concentrated under reduced pressure at room temperature. Finally, the crude yellow powder product **10** (67 mg, 99% yield) was pure enough for next step reaction.

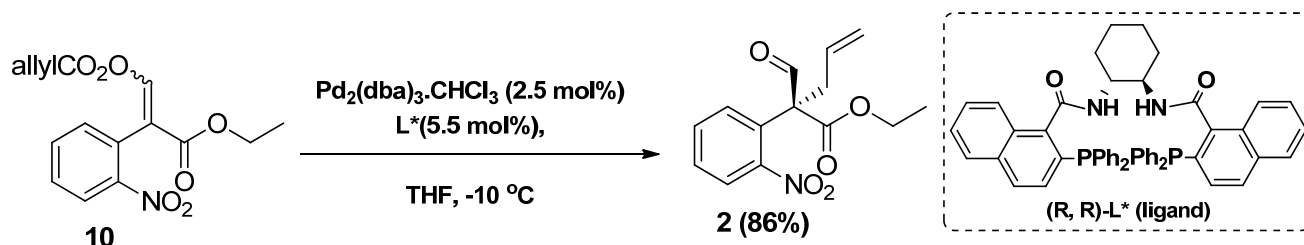
¹H NMR (300 MHz, CDCl₃): δ 8.38 (s, 1H), 8.17 (d, *J* = 3.0 Hz, 1H), 7.68 (t, *J* = 4.5 Hz), 7.55 (t, *J* = 6.0 Hz, 1H), 7.41 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 5.97-5.97 (m, 1H), 5.42 -5.32 (m, 2H), 4.73 (d, *J* = 3.0 Hz, 2 H), 4.24 (q, *J* = 3.0 Hz, 2H), 1.27 (t, *J* = 4.5 Hz, 3H)

¹³C NMR (75 MHz, CDCl₃): δ 164.8, 151.3, 148.2, 145.9, 133.3, 132.8, 130.3, 129.4, 127.1, 124.9, 120.6, 116.6, 70.1, 61.5, 14.1.

HRMS (ESI⁺): Calculated (m/z) for C₁₅H₁₅NO₇ (M+H)⁺: 322.0921, Found 322.0910.

Melting Point: 72-74 °C.

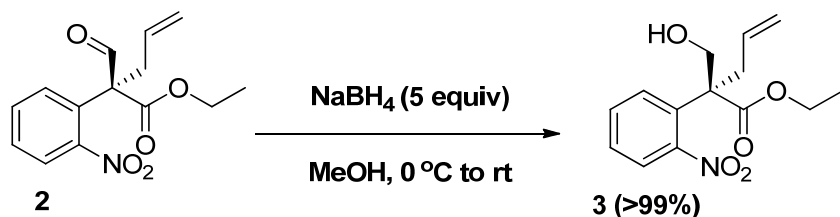
Preparation of Ethyl 2-formyl-2-(2-nitrophenyl) pent -4 enolate, **2** using DAAA: (Method C)



Except for the variation in solvent, ligand, and temperature, all DAAA reactions were carried out by the following general procedure:

To a dry flask was added $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (4.0 mg, 0.004 mmol, 2.5 mol%) followed by (R, R) -DACH-naphthyl Trost ligand **L1** (7.0 mg, 0.0088 mmol, 5.5 mol%). To the flask was added a mixture of dry and degassed THF (3 mL) at room temperature and the mixture stirred for 15 minutes. After several minutes of stirring, the mixture turned into a bright yellow color (occasionally a slight pink hue is observable) with a small amount of beige precipitate. The resulting mixture was cooled down to -10°C and was transferred via cannula to a separate flask containing compound **10** (50.0 mg, 0.16 mmol, 1.0 equiv) dissolved in THF (2 mL) which was already cooled down to -10°C . The reaction mixture stirred at this temperature until the reactant completely disappeared (monitored by TLC) and a cloudy yellow/green solution was obtained. After the reaction, the solution was passed through a silica plug (1 cm fritted funnel, 2 cm silica, medium porosity filter) which was washed through with DCM (10 mL). The solvent was concentrated under vacuum and the residue was purified with flash column chromatography on silica gel (hexane/EtOAc = 20/1) to afford compound **2** (37.0 mg, 85.7 % yield) as a white solid.

Synthesis of (Ethyl 2-(hydroxymethyl)-2-(2-nitrophenyl)pent-4-enoate (3)



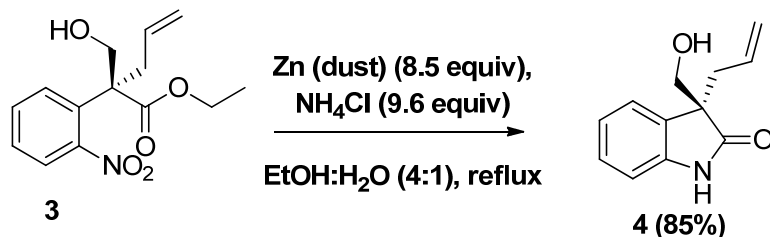
Ethyl 2-formyl-2-(2-nitrophenyl)pent-4-enoate, **2** (430.0 mg, 1.55 mmol, 1.0 equiv) was added to a 100 mL round bottom flask and placed in an argon atmosphere. 30 mL of anhydrous methanol was added, and it could dissolve through stirring. The reaction flask was then brought down to $0\text{ }^\circ\text{C}$ and NaBH_4 (294.0 mg, 7.76 mmol, 5.0 equiv) was added to the stirring mixture. Subsequently the mixture was removed from the ice for 5 min and returned to room temperature until the reaction was monitored through the end by Thin layer chromatography (TLC). 10 mL of water was added to quench the reaction and then extracted using DCM (3 x 30 mL). The organic fraction was then dried with Na_2SO_4 and concentrated in vacuo. The crude was purified by column chromatography on silica gel eluted with 20% EtOAc in hexane to afford the above-mentioned product, **3** as colorless viscous liquid (429.0 mg, $>99\%$ yield).

^1H NMR (CDCl_3 , 300 MHz): δ 7.93 (t, $J = 4.5$ Hz), 7.65 (t, $J = 4.5$ Hz, 1H), 7.57 (d, $J = 3.0$ Hz, 1H), 7.49-7.45 (m, 1H), 5.67-5.61 (m, 1H), 5.11 (dd, $J = 15.0, 6.0$ Hz, 2H), 4.36 (d, $J = 9.0$ Hz, 1H), 4.20-4.10 (m, 2H), 3.98 (d, $J = 6.0$ Hz, 1H), 3.11-2.96 (m, 2H), 2.41 (brs, 1H), 1.24 (t, $J = 4.5$ Hz);

^{13}C NMR (CDCl_3 , 75 MHz): δ 172.8, 150.2, 133.3, 132.9, 132.6, 130.4, 128.2, 125.7, 119.0, 67.2, 61.3, 55.1, 39.3, 14.0.

HRMS (ESI $^+$): Calculated (m/z) for $\text{C}_{14}\text{H}_{17}\text{NO}_5$ [$\text{M}+\text{H}$] $^+$: 280.1179, Found: 280.1173

Synthesis of 3-allyl-3-(hydroxymethyl)indolin-2-one (4)[142]



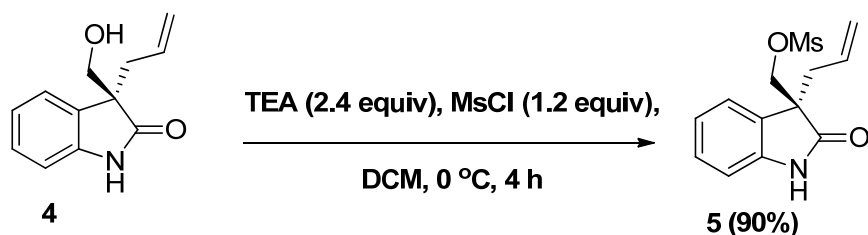
Ethyl 2-(hydroxymethyl)-2-(2-nitrophenyl)pent-4-enoate, **3** (200 mg, 0.72 mmol, 1.0 equiv) zinc powder (400 mg, 6.12 mmol, 8.5 equiv) and solid NH₄Cl (370.0 mg, 6.92 mmol, 9.6 equiv) were taken in a round bottom flask in an argon atmosphere. A degassed solvent mixture of EtOH: H₂O (4:1) mixture was added to the flask via syringe followed by vigorous stirring under reflux temperature. The mixture was then allowed to react for 2 h and monitored by TLC before cooling down to the room temperature. Then a cotton plug was used to separate the Zn dust and the solvent was removed by rotary evaporation. The crude was then extracted by ethyl acetate and finally purified via column chromatography using neutral alumina as a stationary phase with MeOH/DCM = 1/10, which yielded the desired oxindole **4**, as pale-yellow solid powder (0.13 g, 85% yield)⁷.

¹H NMR (CDCl₃, 300MHz): δ 8.40 (s, 1H), 7.41-7.22 (m, 2H), 7.10 (t, J = 7.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 5.55-5.43 (m, 1H), 5.09-4.96 (m, 2H), 3.97 (d, J = 9.0 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 2.71-2.59 (m, 2H), 1.97 (s, 1H);

¹³C NMR (CDCl₃, 75MHz): δ 180.5, 140.9, 131.6, 129.9, 128.5, 123.7, 122.7, 119.3, 109.8, 66.5, 54.6, 37.3.

HRMS (ESI⁺): Calculated (m/z) for C₁₂H₁₃NO₂ (M+H)⁺: 204.1001, Found 204.1019.

(S)-(3-allyl-2-oxoindolin-3-yl)methyl methanesulfonate (5)



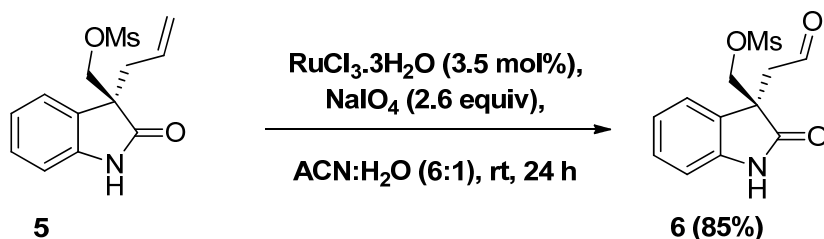
To a clean oven dried flask, DCM (6mL) was added to dissolve 3-allyl-3-(hydroxymethyl)indolin-2-one **4** (70.0 mg, 0.35 mmol, 1.0 equiv), Then triethylamine (117.1 μL , 0.84 mmol, 2.4 equiv) was added and the solution was maintained in an ice bath for 30 minutes under argon atmosphere. After that, MsCl (32.0 μL , 0.42 mmol, 1.2 equiv) was added and ran the reaction until the consumption of the starting material, as judged by TLC analysis. The mixture was neutralized by 10 mL of 1M HCl then the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic fraction was washed with NaHCO_3 (saturated) and brine (1 x 10 mL). The combined organic layer was dried over anhydrous MgSO_4 ; evaporated using rotary evaporator. The crude product was purified by silica gel column chromatography (50/50 = EtOAc/hexane) to afford **5** as a light-yellow oil (87.0 mg, 90% yield).

^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (brs, 1H), 7.32 (d, J = 5.0 Hz, 2H), 7.12 (t, J = 15 Hz, 1H), 6.93 (d, J = 5.0 Hz, 1H), 5.56-5.47 (m, 1H), 5.12 (d, J = 15 Hz), 5.05 (d, J = 10 Hz, 1H), 4.56 (d, J = 10.0 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 2.84 (s, 3H), 2.62 (d, J = 5.0 Hz, 2H);

^{13}C NMR (CDCl_3 , 125 MHz): δ 177.6, 140.8, 130.2, 129.0, 127.8, 124.2, 122.9, 120.3, 110.0, 71.8, 52.7, 37.9, 37.2.

HRMS (ESI⁺): Calculated (m/z) for $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 282.0795, Found: 282.0782.

(S)-2-oxo-3-(2-oxoethyl)indolin-3-yl)methyl methanesulfonate (6)[143]



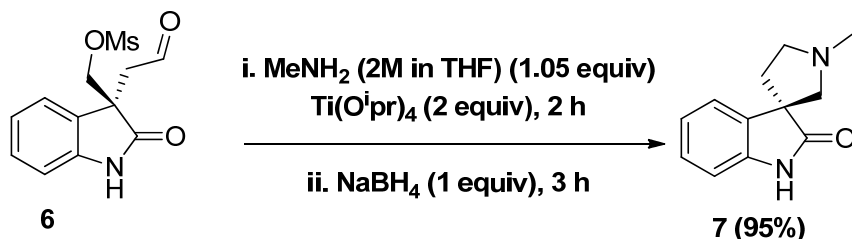
To a stirred mixture of compound **6** (30.0 mg, 0.11 mmol, 1.0 equiv) and RuCl_3 stock solution (15 μL , 0.0037 mmol, 3.5 mol%) in CH_3CN (3.0 mL) and distilled water (0.5 mL) was added in portions NaIO_4 (61.2 mg, 0.286 mmol, 2.6 equiv) over a period of 5 minutes at room temperature. The color of the mixture color changed from the black to yellowish brown. Then the reaction was monitored by TLC until the starting material disappeared completely. Adding 2 mL of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution quenched the reaction. The organic layer was then separated and extracted three times using DCM. The combined organic layer was washed with water and brine, respectively. Then it was dried over MgSO_4 and filtered through a cotton plug and finally decanted. The crude purified via column chromatography using silica gel as a stationary phase with $\text{MeOH}/\text{DCM} = 1/9$, which yielded the desired product **7**, as pale-yellow oil (25.7 mg, 85% yield).

^1H NMR (CDCl_3 , 500 MHz): δ 9.58 (s, 1H), 8.10 (s, 1H), 7.33-7.29 (m, 2H), 7.10 (t, $J = 11.40$ Hz, 1H), 6.97 (d, $J = 7.70$ Hz, 1H), 4.58 (d, $J = 9.85$ Hz, 1H), 4.32 (d, $J = 9.85$ Hz, 1H), 3.22 (d, $J = 18.0$ Hz, 1H), 3.13 (d, $J = 18.0$ Hz, 1H), 2.87 (s, 3H);

^{13}C NMR (CDCl_3 , 125 MHz): δ 197.1, 177.5, 141.3, 136.4, 129.5, 128.0, 124.0, 123.0, 110.6, 71.9, 49.3, 46.1, 37.4.

HRMS (ESI⁺): Calculated (m/z) for $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{S}$ $[\text{M}+\text{H}]^+$: 284.302, Found: 284.303.

Synthesis of (-)-Coerulescene (7) [144]



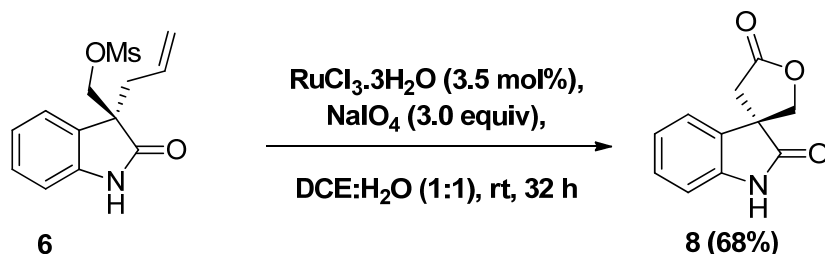
Titanium (IV) isopropoxide (128.0 μ L, 0.42 mmol, 2.0 equiv) was added to a commercially available solution of methylamine in THF (2 M) (9.0 μ L, 0.22 mmol, 1.05 equiv) followed by the addition of the compound **6** (59.1 mg, 0.21 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for 5 h, after which sodium borohydride (8.0 mg, 0.21 mmol, 1.0 equiv) was added and the resulting mixture was further stirred for another period of 2 h. The reaction was then quenched by the addition of water (2 mL), the resulting inorganic precipitate was filtered and washed with diethyl ether (10 mL). The organic layer was separated, and the aqueous part was further extracted with ethyl acetate ether (2 x 10 mL). The combined ether extracts were dried (K_2CO_3) and concentrated in vacuo and obtained (40.1 mg, 95% yield) (-)-coerulescene **7** with high purity. The proton NMR, carbon NMR and the optical rotation is exactly matched with the data reported by Hayashi et al. [145]

¹H NMR (CDCl₃, 300 MHz): δ 8.81 (s, 1H), 7.41 (d, J = 10.0 Hz, 1H), 7.20 (t, J = 7.50 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 5.0 Hz, 1H), 3.04-2.79 (m, 4H), 2.49 (s, 3H), 2.46-2.42 (m, 1H), 2.15-2.10 (m, 1H).

¹³C NMR (CDCl₃, 75 MHz): δ 182.8, 140.0, 136.2, 127.8, 123.4, 122.9, 109.5, 66.4, 56.8, 53.7, 41.9, 38.0.

HRMS (ESI+): Calculated (m/z) for C₁₂H₁₄N₂O [M+H]⁺: 203.1186, Found: 203.1179: [α]_D²⁷ +1.1 (c 2.0, CHCl₃). Enantiomeric excess = 85%

Synthesis of (-)-coixspirolactam **8** (**8**) [146]



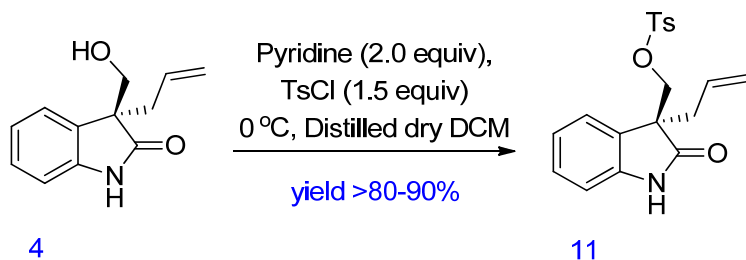
To a stirred mixture of compound **6** (61.0 mg, 0.22 mmol, 1.0 equiv) and RuCl_3 stock solution (29 μL , 0.0075 mmol, 3.5 mol%) in 1,2-dichloroethane (3 mL) and distilled water (3 mL) was added in portions NaIO_4 (141.2 mg, 0.66 mmol, 3.0 equiv) over a period of 5 minutes at room temperature. The color of the mixture changed from the black to yellowish brown. Then the reaction was monitored by TLC until the starting material disappeared completely. After 32 h the reaction was quenched by adding 2 mL of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution. The organic layer was then separated and extracted three times using DCM. The combined organic layer was washed with water and brine, respectively. Then it was dried over MgSO_4 and filtered through a cotton plug and finally decanted. The crude was eluted through silica gel using 80% EtOAc in hexane solvent mixture and the product **8** was separated as a white solid powder (29.9 mg, 68% yield). The proton NMR, carbon NMR and the optical rotation is exactly matched with the data reported by Andrade et al. [147]

^1H NMR (500 MHz, CDCl_3): δ 7.92 (s, 1H), 7.33 (d, J = 10 Hz, 2H), 7.15 (t, J = 12.5 Hz, 1H), 6.97 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 5.0 Hz, 1H), 4.42 (d, J = 10.0 Hz, 1H), 3.19 (d, J = 15.0 Hz, 1H), 2.75 (d, J = 15.0 Hz, 1H);

^{13}C NMR (125 MHz, CDCl_3): δ 177.4, 174.2, 139.8, 131.0, 129.6, 123.8, 122.8, 110.5, 74.8, 51.0, 38.4.

HRMS (ESI+): Calculated (m/z) for C₁₁H₉NO₃ [M+H]⁺: 204.0660, Found: 203.0652.

Synthesis of (S)-(3-allyl-2-oxoindolin-3-yl)methyl 4-methylbenzenesulfonate (11)

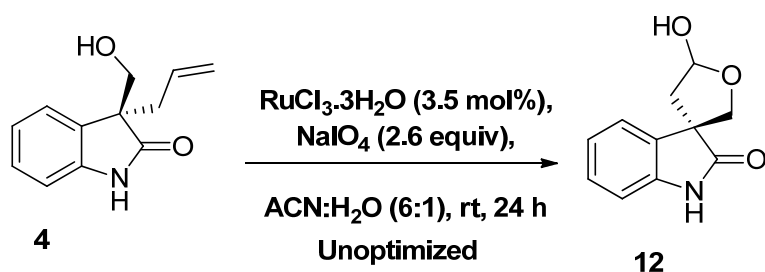


To a clean oven dried flask, DCM (6mL) was added to dissolve 3-allyl-3-(hydroxymethyl)indolin-2-one **4** (98.0 mg, 0.48 mmol, 1.0 equiv), Then pyridine (78.1 μ L, 0.96 mmol, 2.0 equiv) was added dropwise and the solution was maintained in an ice bath for 30 minutes under argon atmosphere. After that, TsCl (106.0 μ L, 0.72 mmol, 1.5 equiv) was added and ran the reaction until the consumption of the starting material, monitored by TLC analysis. The mixture was neutralized by 10 mL of 1M HCl then the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The organic fraction was washed with NaHCO₃ (saturated) and brine (1 x 10 mL). The combined organic layer was dried over anhydrous MgSO₄; evaporated using rotary evaporator. The crude product was purified by silica gel column chromatography (25/75 = EtOAc/hexane) to afford compound **11** as a yellow viscous oil (155.3 mg, 90% yield).

¹H NMR (CDCl₃, 300 MHz): δ 7.89 (brs, 1H), 7.25 (t, J = 4.5 Hz, 5H), 7.09 (t, J = 7.5 Hz, 2H), 6.91 (d, J = 6.0 Hz, 2H), 5.59-5.45 (m, 1H), 5.10-4.97 (m, 2H), 3.94 (d, J = 6.0 Hz, 1H), 3.83 (d, J = 9.0 Hz, 1H), 2.75-2.59 (m, 2H), 2.04 (s, 3H),

¹³C NMR (CDCl₃, 125 MHz): δ 177.6, 140.8, 130.2, 129.0, 127.8, 124.2, 122.9, 120.3, 110.0, 71.8, 52.7, 37.9, 37.2.

Synthesis of (3S)-5-hydroxy-4,5-dihydro-2H-spiro[furan-3,3'-indolin]-2'-one (12)



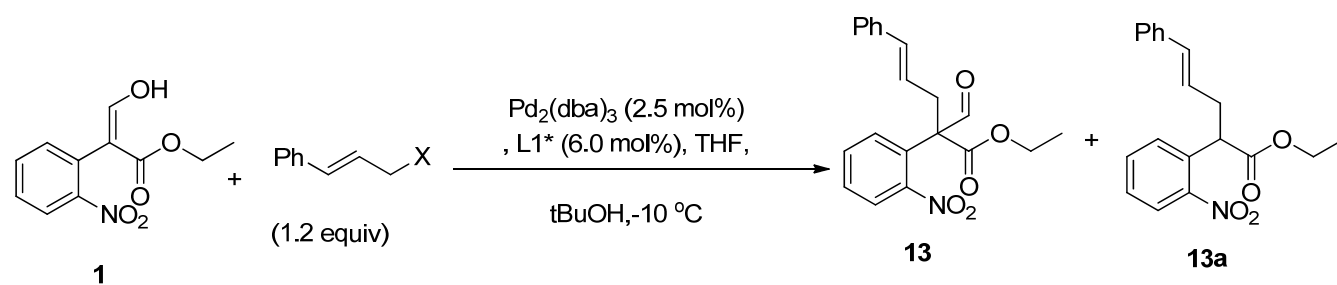
To a stirred mixture of compound **4** (100.0 mg, 0.49 mmol, 1.0 equiv), RuCl₃ stock solution (68 μL, 0.0171 mmol, 3.5 mol%) in CH₃CN (3.0 mL) and distilled water (0.5 mL) was added in portions NaIO₄ (272.6 mg, 1.28 mmol, 2.6 equiv) over a period of 5 minutes at room temperature. The color of the mixture color changed from the black to yellowish brown. Then the reaction was monitored by TLC until the starting material disappeared completely. Added 2 mL of saturated Na₂S₂O₃ solution quenched the reaction. The organic layer was then separated and extracted three times using DCM. The combined organic layer was washed with water and brine, respectively. Then it was dried over MgSO₄ and filtered through a cotton plug and finally decanted. The crude purified via column chromatography using silica gel as a stationary phase with MeOH/DCM = 1/8, which yielded the desired product **12**, as yellow oil (52.1 mg, 52 % yield).

¹H NMR (CDCl₃, 500 MHz): δ 8.31 (s, 1H), 7.32-7.25 (m, 2H), 7.10 (d, *J* = 10.0 Hz, 1H), 6.94 (d, *J* = 15.0 Hz, 1H), 4.25 (d, *J* = 3.0 Hz, 1H), 4.34 (s, -C-OH, 1H), 4.21 (d, *J* = 3.5 Hz, 1H), 4.09 (d, *J* = 14.0 Hz, 1H), 3.98 (d, *J* = 14.2 Hz, 1H), 2.61 - 2.52 (m, 1H), 2.12 - 2.11 (m, 1H)

¹³C NMR (CDCl₃, 125 MHz): δ 197.1, 177.5, 141.3, 136.4, 129.5, 128.0, 124.0, 123.0, 110.6, 71.9, 49.3, 46.1, 37.4;

MS (20:20): Calculated (m/z) for C₁₁H₁₁NO₃ [M+H]⁺: 205.21, Found: 205.16 (100%), 206.11 (17%).

General procedure for the synthesis of (E/Z)-ethyl 2-formyl-2-(2-nitrophenyl)-5-phenylpent-4-enoate (13)



In an oven dried and desiccator-cooled sealable test tube was added Pd₂(dba)₃.CHCl₃ (5.4 mg, 0.00525 mmol, 2.5 mol%) and (R, R)-L* (10.0 mg, 0.0126 mmol, 6 mol%). The test tube was then evacuated and backfilled with argon three times. Previously distilled and degassed tetrahydrofuran (THF) was added to the flask and the mixture was stirred for 15 min until it was homogeneous, and an orange color persisted. Then, cinnamyl acetate (42 μL, 0.252 mmol, 1.2 equiv) was added to the system and the solution was stirred at room temperature for an additional 5 min. In the meantime, the other test tube was charged with 3-hydroxy 2-nitro phenyl acrylate **1** (50.0 mg, 0.210 mmol, 1.0 equiv) with the addition of 2 mL of degassed tetrahydrofuran (THF) and it was finely dissolved in solvent. Then the cat-L*-allyl acetate mixture was added to the solution of 3-hydroxy 2-nitro phenyl acrylate **1** via cannula. Additive, *t*BuOH (39 μL, 0.420 mmol, 2.0 equiv) was added into the reaction mixture. The mixture was stirred at room temperature and confirmed the completion of reaction by TLC monitoring. The crude was passed through a thick pad of silica

(2 cm) and solvent was decanted. The crude was then purified by column chromatography on silica gel elution (hexane/EtOAc = 10/1) and 37.0 mg (55% yield) of clear oily liquid product **13** was obtained. During the column chromatography some decarbonylated product formed. The NMR of that compound 13a has attached.

NMR for compound 13:

¹H NMR (CDCl₃, 300 MHz): δ 10.24 (s, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 6.0 Hz, 2H), 7.58 (t, J = 4.5 Hz, 1H), 7.31-7.26 (m, 5H), 6.60 (d, 1H), 6.11 (t, J = 7.5 Hz, 1H), 4.20 (q, J = 7.5 Hz, 2H), 3.23 (d, J = 9.0 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H);

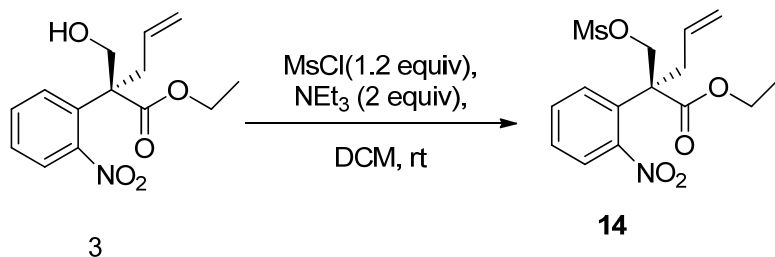
¹³C NMR (CDCl₃, 75 MHz): δ 196.8, 169.4, 148.4, 133.7, 131.1, 130.7, 130.5, 129.0, 125.9, 120.4, 63.9, 62.0, 37.8, 14.0;

NMR for compound 13a:

¹H NMR (CDCl₃, 300 MHz): δ 7.92 (d, J = 6.0 Hz, 1H), 7.61 (d, J = 3.0 Hz, 2H), 7.46 – 7.41 (m, 2H), 7.31 – 7.21 (m, 5H), 6.44 (d, J = 18 Hz, 1H), 6.22 – 6.14 (m, 1H) 4.39 (t, J = 7.5 Hz, 1H), 4.21 – 4.13 (m, 2H), 3.11 - 3.02 (m, 1H), 2.85 – 2.78 (m, 1H) 1.22 (t, J = 10.5 Hz, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 172.07, 149.5, 137.1, 133.0, 132.9, 130.0, 128.5, 128.2, 127.3, 126.2, 124.8, 61.3, 46.6, 36.3, 14.1.

Synthesis of (S)-ethyl 2-(((methylsulfonyl)oxy)methyl)-2-(2-nitrophenyl)pent-4-enoate (**14**)

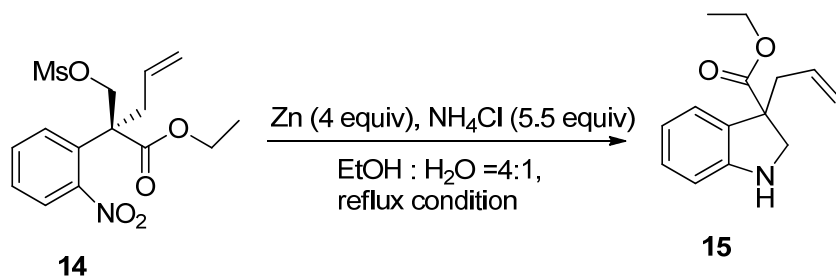


To a clean flame dried flask, DCM (6mL) was added to dissolve compound **3** (200.0 mg, 0.72 mmol, 1.0 equiv). Then triethylamine (201 μ L, 1.44 mmol, 2.0 equiv) was added and the solution was maintained in an ice bath for 30-45 minutes under argon atmosphere. After that, MsCl (66.0 μ L, 0.86 mmol, 1.2 equiv) was added and ran the reaction until the consumption of the starting material, as judged by TLC analysis. After confirming the disappearance of the starting material, the mixture was neutralized by 1M HCl (as required observed by pH paper) then the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The organic fraction was washed with NaHCO_3 (saturated) and brine (1 x 25 mL). The combined organic layer was dried over anhydrous MgSO_4 ; evaporated using rotary evaporator. The crude product was purified by silica gel column chromatography (25/75 = EtOAc/hexane) to afford **14** as a colorless oil oil (225.6 mg, 88% yield).

^1H NMR (CDCl_3 , 500 MHz): δ 7.93 (d, J = 10 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.59 (d, J = 10.0 Hz, 1H), 7.54-7.50 (m, 1H), 5.68-5.60 (m, 1H), 5.32-5.15 (m, 2H), 4.93 (d, J = 10 Hz, 1H), 4.87 (d, J = 10.0 Hz, 1H), 4.21-4.08 (m, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.84 (s, 3H), 1.24 (t, J = 7.5 Hz, 3H)

^{13}C NMR (CDCl_3 , 125 MHz): δ 169.9, 149.9, 132.7, 132.0, 131.4, 130.9, 128.8, 125.8, 120.2, 71.6, 61.7, 53.4, 39.3, 37.1, 14.0.

Synthesis of ethyl 3-allylindoline-3-carboxylate (**15**)

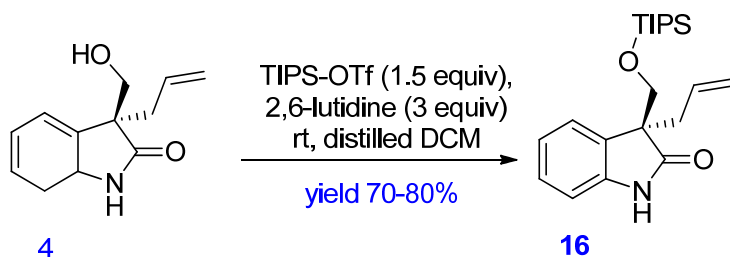


Compound **14** (220 mg, 0.62 mmol, 1.0 equiv) zinc powder (182 mg, 2.77 mmol, 4.5 equiv) and solid NH_4Cl (281.8 mg, 5.27 mmol, 8.5 equiv) were taken in a round bottom flask in an argon atmosphere. A degassed solvent mixture of EtOH: H_2O (4:1) (20 mL) mixture was added to the flask via syringe followed by vigorous stirring under reflux temperature. The mixture was then allowed to react for 3h and monitored by TLC before cooling down to the room temperature. Then a cotton plug was used to separate the Zn dust and the solvent was removed by rotary evaporation. The crude was then extracted by ethyl acetate and finally purified via column chromatography using neutral alumina as a stationary phase with MeOH/DCM = 1/20, which yielded the desired indole **15**, as colorless liquid (0.11 g, 78% yield).

^1H NMR (CDCl_3 , 500MHz): δ 7.36 (s, 1H), 7.12 (t, $J = 7.5$ MHz, 1H), 6.80 – 6.77 (m, 1H), 6.69 (d, $J = 10$ Hz) 5.73 – 5.68 (m, 1H), 5.15 – 5.10 (m, 1H), 4.23 (q, $J = 7.5$ Hz, 2H), 3.52 (d, $J = 5.0$ Hz) 2.86 (t, $J = 7.5$ Hz, 1H), 2.77 – 2.55 (m, 1H) 1.31 (t, $J = 7.5$ Hz)

^{13}C NMR (CDCl_3 , 125 MHz): δ 177.3, 150.5, 133.3, 130.1, 128.8, 124.7, 119.0, 118.7, 110.2, 61.2, 56.3, 53.5, 42.5, 29.7.

Synthesis of (S)-3-allyl-3-(((triisopropylsilyl)oxy)methyl)indolin-2-one (16)

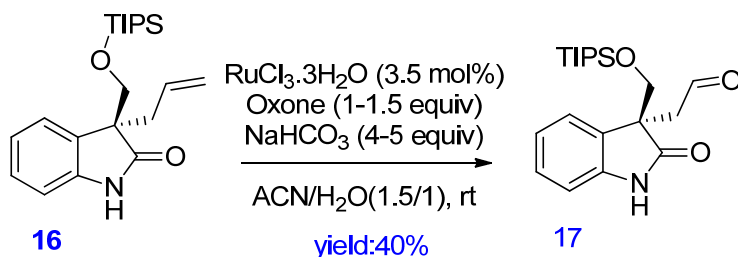


To a clean oven dried flask, DCM (6mL) was added to dissolve 3-allyl-3-(hydroxymethyl)indolin-2-one **4** (180.0 mg, 0.89 mmol, 1.0 equiv), Then the base 2,6-Lutidine (308.0 μ L, 3.0 equiv) was added and the solution was maintained at room temperature for 30 minutes under argon atmosphere. After that, TIPS-OTf (359.0 μ L, 1.5 equiv) was added and ran the reaction until the consumption of the starting material, as judged by TLC analysis. The crude mixture was then extracted 3X by using water. The combined organic layer was dried over anhydrous MgSO_4 ; evaporated using rotary evaporator. The crude product was purified by silica gel column chromatography (30/70 = EtOAc/hexane) to afford **16** as a light-yellow oil (273.0 mg, 70% yield).

^1H NMR (CDCl_3 , 500 MHz): δ 8.48 (s, 1H), 7.31-6.87 (m, 4H), 5.52-5.46 (m, 1H), 5.07-4.91 (m, 2H), 4.02-3.92 (m, 2H), 2.73-2.54 (m, 2H), 1.28-1.00 (m, 21 H).

^{13}C NMR (CDCl_3 , 125 MHz): δ 177.3, 150.5, 133.3, 130.1, 128.8, 124.7, 119.0, 118.7, 110.2, 61.2, 56.3, 53.5, 42.5, 29.7.

Synthesis of (S)-2-(2-oxo-3-(((triisopropylsilyl)oxy)methyl)indolin-3-yl)acetaldehyde, **17**



To a stirred mixture of compound **16** (70.0 mg, 0.19 mmol, 1.0 equiv) and RuCl_3 stock solution (28 μL , 0.007 mmol, 3.5 mol%) in CH_3CN (6.0 mL) and distilled water (4.0 mL) was added. Then 63.9 mg (0.76 mmol, 4 equiv) of NaHCO_3 charged to the reaction vessel all at once along with the addition of 43.37 mg (0.285 mmol 1.5 equiv). The color of the mixture color changed from the brown to dark black. Then the reaction was monitored by TLC until the starting material disappeared completely. We have added saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution quenched the reaction. The organic layer was then separated and extracted three times using ethyl acetate. The combined organic layer was washed with water and brine, respectively. Then it was dried over MgSO_4 and filtered through a cotton plug and finally decanted. The crude purified via column chromatography using silica gel as a stationary phase with $\text{EtOAc}/\text{hexane} = 6/1$, which yielded the desired product **17**, as pale-yellow oil (28.2 mg, 40% yield).

^1H NMR (CDCl_3 , 300 MHz): δ 9.40 (s, 1H), 7.43 (s, 1H), 7.27-7.22 (m, 2H), 7.02 (t, $J = 4.5$ Hz, 1H), 6.90 (d, $J = 6.0$ Hz, 1H), 4.00 (d, $J = 9.0$ Hz, 1H), 3.84 (d, $J = 9.0$ Hz, 1H), 3.22 (d, $J = 18.0$ Hz, 1H), 3.13 (d, $J = 18.0$ Hz), 0.94-0.98 (m, 21H);

^{13}C NMR (CDCl_3 , 125 MHz): δ 179.9, 141.1, 132.2, 131.4, 127.8, 124.3, 122.1, 118.7, 109.2, 55.8, 55.7, 37.3, 29.8, 17.9, 17.5, 12.5, 12.4, 12.3.

MS (ESI⁺): Calculated (m/z) for $\text{C}_{20}\text{H}_{31}\text{NO}_3\text{Si}$, Found: 339.30 (100%), 360.35(40%).

References for Chapter A

- 1 (a) C. V. Gallifor and K. A. Scheidt, *Angew. Chem. Int. Ed.*, **2007**, *46*, 8748 – 8758; (b) Z.-H. Gao, L.-M. Kong, X.-S. Zou, Y.-M. Shi, S.-Z. Shang, H.-R. Lou, C.-Q. Liang, X.-N. Li, Y. Li, X. Du, W.-L. Xiao and H.-D. Sun, *Nat. Prod. Bioprospect.*, **2012**, *2*, 249–254; (c) F.-D. Kong, S.-L. Zhang, S.-Q. Zhou, Q.-Y. Ma, Q.-Y. Xie, J.-P. Chen, J.-H. Li, L.-M. Zhou, J.-Z. Yuan, Z. Hu, H.-F. Dai, X.-L. Huang and Y.-X. Zhao, *J. Nat. Prod.*, **2019**, *82*, 3456–3463; (d) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, **2014**, *24*, 3673–3682.
- 2 (a) T. L. Pavlovska, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Divers.*, 2015, **20**, 299–344; (b) B. Yu, D.-Q. Yu and H.-M. Liu, *Eur. J. Med. Chem.*, **2015**, *97*, 673–698; (c) S. Wang, Y. Zhao, A. Aguilar, D. Bernard and C.-Y. Yang, Targeting the MDM2-p53 Protein-Protein Interaction for New Cancer Therapy: Progress and Challenges, *Cold Spring Harb Perspect Med.*, 2017, **7**, a026245. <https://doi.org/10.1101/cshperspect.a026245>; (d) N. Ye, H. Chen, E. A. Wold, P.-Y. Shi and J. Zhou, *ACS Infect Dis.*, **2016**, *2*, 382–392; (e) S. Hati, S. Tripathy, P. K. Dutta, R. Agarwal, R. Srinivasan, A. Singh, S. Singh and S. Sen, Spiro[pyrrolidine-3, 3'-oxindole] as potent anti-breast cancer compounds: Their design, synthesis, biological evaluation and cellular target identification, *Sci. Rep.*, **2016**, *6*, 32213, DOI: 10.1038/srep32213
- 3 (a) S. P. Marsden, E. L. Watson, S. A. Raw, *Org. Lett.* **2008**, *10*, 2905 – 2908; (b) M. Suchy', P. Kutschy, K. Monde, H. Goto, N. Harada, M. Takasugi, M. Dzurilla, E. Balentov, *J. Org. Chem.* **2001**, *66*, 3940 – 3947.
- 4 (a) M.-Y. Lee, H.-Y. Lin, F. Cheng, W. Chiang and Y.-H. Kuo, *Food Chem. Toxicol.*, 2008, **46**, 1933–1939; (b) C.-P. Chung, C.-Y. Hsu, J.-H. Lin, Y.-H. Kuo, W. Chiang and Y.-L. Lin, *J. Agric. Food Chem.*, 2011, **59**, 1185–1194.
- 5 A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 14043 – 14053.
- 6 (a) A. Ashimori, T. Matsuura, L.E. Overman, *J. Org. Chem.* **1993**, *58*, 6949–6951. (b) T. Matsuura, L.E. Overman, D.J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503.

- 7 a) S. Lee, F. John, J. F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415; b) Y. Yasui, H. Kamisaki, Y. Takemoto, *Org. Lett.* **2008**, *10*, 3303–3306.
- 8 A.B. Dounay, K. Hatanaka, J.J. Kodanko, M. Oestreich, L.E. Overman, L.A. Pfeifer, M.W. Weiss, *J. Am. Chem. Soc.* **2003**, *125*, 6261–6271.
- 9 S. Lee, J.F. Hartwig, *J. Org. Chem.* **2001**, *66*, 3402–3415.
- 10 (a) F. Glorius, G. Altenhoff, R. Goddard, C. Lehmann, *Chem. Commun.* **2002**, 2704–2705. (b) T. Arao, K. Kondo, T. Aoyama, *Tetrahedron Lett.* **2006**, *47*, 1417–1420.
- 11 (a) E.P. Ku"ndig, T.M. Seidel, Y.-X. Jia, G. Bernardinelli, *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 8484–8487. Full paper: (b) Y.-X. Jia, D. Katayev, G. Bernardinelli, T.M. Seidel, E.P. Ku"ndig, *Chem. Eur. J.* **2010**, *16*, 6300–6309.
- 12 (a) M. Fernandez-Ibanez, B. Maci, D. Alonso, I. Pastor, *Molecules.* **2013**, *18*, 10108. (b) K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, *Nat. Chem.* **2012**, *4*, 473. (c) J.W. Han, T. Hayashi, *Tetrahedron. Asymmetry.* **2014**, *25*, 479e484.
- 13 L. Yin, M. Kanai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *123*, 7762e7765.
- 14 T. Shirai, H. Ito, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2014**, *53*, 2658e2661.
- 15 T. Shirai, Y. Yamamoto, *Organometallics.* **2015**, *34*, 3459e3463
- 16 T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, *56*, 872–875.
- 17 K. Ohmatsu, M. Kiyokawa, T. Ooi, *J. Am. Chem. Soc.* **2011**, *133*, 1307–1309.
- 18 (a) B. M. Trost, M. U. Frederiksen, *Angew. Chem.* **2005**, *117*, 312–314; (b) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165; (c) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2007**, *119*, 8820–8823; (d) X. Tian, K. Jiang, J. Peng, W. Du, Y.-C. Chen, *Org. Lett.* **2008**, *10*, 3583–3586; (e) P. Galzerano, G. Bencivenni, F. Pesciaoli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2009**, *15*, 7846–7849.
- 19 L. Cheng, L. Liu, D. Wang, Y.-J. Chen, *Org. Lett.* **2009**, *11*, 3874–3877.

- 20 Z. Qian, F. Zhou, T. Du, B. Wang, M. Ding, X. Zhao, J. Zhou, *Chem. Comm.* **2009**, 6753-6755.
- 21 T. Bui, M. Borregan, C. F. Barbas, *J. Org. Chem.* **2009**, 74, 8935-8938.
- 22 T. Zhang, L. Cheng, L. Liu, D. Wang, Y.-J. Chen, *Tetrahedron: Asymmetry* **2010**, 21, 2800-2806
- 23 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, 116, 422-518.
- 24 P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone, J. E. Starrett, Jr., *Bioorg. Med. Chem. Lett.* **2002**, 12, 1023-1026.
- 25 a) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.* **2003**, 68, 2494-2497. b) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, 123, 7001-7009.
- 26 T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* 2008, 120, 4225-4229; *Angew. Chem. Int. Ed.* **2008**, 47, 4157-4161.
- 27 Y. Zhang, X. Yang, T. Xie, G. Chen, W. Zhu, X. Zhang, X. Yang, X. Wu, 333X. He, H. He, *Tetrahedron* **2013**, 69, 4933-4937.
- 28 M. Gómez-Martínez, D. A. Alonso, I. M. Pastor, G. Guillena, A. Baeza, *Asian J. Org. Chem.* **2016**, 5, 1428-1437.
- 29 M. Zhao, Z. Zhang, M. Chen, W. Tang, M. Shi, *Eur. J. Org. Chem.* **2011**, 3001-3008.
- 30 X. Gao, J. Han, L. Wang, *Org. Lett.* **2015**, 17, 4596-4599.
- 31 F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, 105, 827-856.
- 32 X. Zhu, J. Xu, D. Cheng, L. Zhao, X. Liu, B. Tan, *Org. Lett.* **2014**, 16, 2192-2195
- 33 M. Rueping, X. Liu, T. Bootwicha, R. Pluta, C. Merckens, *Chem. Comm.* **2014**, 50, 2508-2511.
- 34 T. Yang, Q. Shen, L. Lu, *Chin. J. Chem.* **2014**, 32, 678-680.
- 35 D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, 10, 1593-1595.

- 36 Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Jiang, C. Tan, *Org. Lett.* **2012**, *14*, 4762-4765.
- 37 X.-C. Qiao, S.-F. Zhu, Q.-L. Zhou, *Tetrahedron. Asymmetry*. **2009**, *20*, 1254e1261.
- 38 (a) K. Aikawa, S. Mimura, Y. Numata, K. Mikami, *Eur. J. Org. Chem.* **2011**, (2011) 4956 (b) P. Brandao, A.J. Burke, *Tetrahedron*, **2018**, *74*, 4927, e495762e65.
- 39 Z. Liu, P. Gu, M. Shi, P. McDowell, G. Li, *Org. Lett.* **2011**, *13*, 2314e2317.
- 40 M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187e2210.
- 41 J. Inanaga, H. Furuno, T. Hayano, *Chem. Rev.* **2002**, *102*, 2211e2226.
- 42 K. Mikami, M. Terada, H. Matsuzawa, *Angew. Chem. Int. Ed.* **2002**, *41*, 3554e3571.
- 43 Z. Duan, J. Han, P. Qian, Z. Zhang, Y. Wang, Y. Pan, *Org. Biomol. Chem.* **2013**, *11*, 6456e6459.
- 44 (a) S. Davey, *Nat. Chem.* **2010**, <https://doi.org/10.1038/nchem.669> online publication. (b) C. Yuan, B. Liu, *Org. Chem. Front.* **2018**, *5*, 106e131.
- 45 J. Itoh, S.B. Han, M. Krische, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6313e6316.
- 46 M. Mechler, R. Peters, 10442–10446; *Angew. Chem. Int. Ed.* **2015**, *54*, 10303– 10307. *Angew. Chem.* **2015**, *127*,
- 47 C. C. J. Loh, D. Hack, D. Enders, *Chem. Commun.* **2013**, *49*, 10230–10232.
- 48 L.-H. Zou, A. R. Philipps, G. Raabe, D. Enders, *Chem. Eur. J.* **2015**, *21*, 1004–1008.
- 49 Zhou et al
- 50 Liu, Y.-L.; Zhou, J. Catalytic Asymmetric Strecker Reaction: Bifunctional Chiral Tertiary Amine/Hydrogen-Bond Donor Catalysis Joins the Field. *Synthesis* **2015**, *47*, 1210–1226
- 51 Tian, S.-K.; Deng, L. A Highly Enantioselective Chiral Lewis Base-Catalyzed Asymmetric Cyanation of Ketones. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196
- 52 Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. A Facile Method for the Synthesis of Oxindole Based Quaternary. α -Aminonitriles via the Strecker Reaction. *Org. Biomol. Chem.*

2010, *8*, 3847–3850

53 (a) Chauhan, P.; Chimni, S. S. Organocatalytic Asymmetric Synthesis of 3-Amino-2-Oxindole Derivatives Bearing a TetraSubstituted Stereocenter. *Tetrahedron: Asymmetry* **2013**, *24*, 343–356.

(b) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. A Journey in the Catalytic Synthesis of 3-Substituted 3-Aminooxindoles. *Synlett* **2015**, *26*, 2491–2504

54 Brittain, W. D. G.; Buckley, B. R.; Fossey, J. S. Asymmetric Copper-Catalyzed Azide-Alkyne Cycloadditions. *ACS Catal.* **2016**, *6*, 3629–3636

55 Zhou, F.; Tan, C.; Tang, J.; Zhang, Y.-Y.; Gao, W.-M.; Wu, H.-H.; Yu, Y.-H.; Zhou, J. Asymmetric Copper(I)-Catalyzed Azide-Alkyne Cycloaddition to Quaternary Oxindoles. *J. Am. Chem. Soc.* **2013**, *135*, 10994–10997.

56 For selected general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: (a) S. F. Martin, *Tetrahedron* **1980**, *36*, 419. (b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037. (c) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (d) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (e) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105. (f) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533. (g) D. J. Ramon, M. Yus, *Curr. Org. Chem.* **2004**, *8*, 149. (h) Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; J. Christoffers, A., Baro Ed.; Wiley, Weinheim, Germany, **2005**. (i) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473. (j) P. G. Cozzi, R. Hilgraf, N. Zimmermann *Eur. J. Org. Chem.* **2007**, 5969. (k) J. T. Mohr, B. M. Stoltz *Chem. Asian J.* **2007**, *2*, 1476. (l) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295. (m) B. M. Trost, C. Jiang *Synthesis* **2006**, 369. (n) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583. (n) J. P. Das, I. Marek *Chem. Commun.* **2011**, *47*, 4593. (o) J. Douglas, L. E. Overman, *PNAS*, **2004**, *101*, 5363.

57 (a) Jiajie Feng, Michael Holmes, and Michael J. Krische, Acyclic Quaternary Carbon Stereocenters via Enantioselective Transition Metal Catalysis, *Chem. Rev.* **2017**, *117*, 12564–12580

58 (a) Christopher J. Douglas and Larry E. Overman, Catalytic asymmetric synthesis of all-carbon quaternary stereocenters, *PNAS*, **2011**, *101*, 5363–5367; (b) Hong, Allen Y.; Stoltz, Brian

M. The Construction of All-Carbon Quaternary Stereocenters by Use of Pd-Catalyzed Asymmetric Allylic Alkylation Reactions in Total Synthesis, *European Journal of Organic Chemistry*, **2013**, 14, 2013, 2745-2759; (c) Douglas, Christopher J.; Overman, Larry E. Catalytic asymmetric synthesis of all-carbon quaternary stereocenters, *Proceedings of the National Academy of Sciences of the United States of America*, **2004**, 101, 5363-5367; (d) Liu, Yiyang; Han, Seo-Jung; Liu, Wen-Bo; Stoltz, Brian M. Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules, *Accounts of Chemical Research*, **2015**, 48, 740-751 etc.

59 (a) Yury Minko and Ilan Marek, Stereodefined acyclic trisubstituted metal enolates towards the asymmetric formation of quaternary carbon stereocentres, *Chem. Commun.*, **2014**, 50, 12597; (b) B. M. Trost, J. E. Schultz, Palladium-Catalyzed Asymmetric Allylic Alkylation Strategies for the Synthesis of Acyclic Tetrasubstituted Stereocenters, *Synthesis* **2019**, 51, 1–30.

60 Trost, B. M.; Jiang, C. Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters, *J. Am. Chem. Soc.* **2001**, 123, 12907.

61 Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, 114, 9327.

62 Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, 33, 336.

63 Hayashi, T. *Pure Appl. Chem.* **1988**, 60, 7.

64 Liang Hong, Wangsheng Sun, Dongxu Yang, Guofeng Li, and Rui Wang, Additive Effects on Asymmetric Catalysis, *Chem. Rev.* **2016**, 116, 6, 4006–4123

65 Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, 120, 12702.

66 Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, 121, 8649.

67 (a) Trost, B. M.; Jiang, C.; Hammer, K. *Synthesis* **2005**, 3335. (b) Trost, B. M.; Bunt, R. C.; Lemoine, R.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, 122, 5968. (c) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, 39, 1713.

68 Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, 121, 4545.

- 69 (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090.
- 70 Sawamura, M.; Nagata, H.; Sakamoto, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2586.
- 71 Sawamura, M.; Nakayama, Y.; Tang, W.-M.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 9090.
- 72 Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3236.
- 73 Kuwano, R.; Uchida, K.; Ito, Y. *Org. Lett.* **2003**, *5*, 2177.
- 74 Jiang, G.; List, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 9471.
- 75 Ohmatsu, K.; Ito, M.; Kuriyada, T.; Ooi, T. *Nat. Chem.* **2012**, *4*, 473.
- 76 Sharif A. Asad, Joseph Ulicki, Maria Shevyrev, Nazim Uddin, Eduardo Alberch, and M. Mahmum Hossain, First Example of the Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of Hydroxyacrylates: Synthesis of All-Carbon α -Aryl Quaternary Aldehydes, *Eur. J. Org. Chem.* **2014**, 5695–5699
- 77 M. F. Carroll, *J. Chem. Soc.*, 1940, 704-706.
- 78 L. Kürti, B. Czako in Strategic Applications of Named Reactions in Organic Synthesis. Background and Detailed Mechanisms, Elsevier Academic Press, **2005**.
- 79 (a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199-3202; (b) T. Tsuda, Y. Chujo, S. Nishi, K. Tawara, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.
- 80 (a) I. Shimizu, J. Tsuji, *J. Am. Chem. Soc.* **1982**, *104*, 5844-5846; (b) J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 1793-1796; (c) B. M. Trost, C. R. Self, *J. Org. Chem.* **1984**, *49*, 468-473; (d) B. M. Trost, C. R. Self, *J. Org. Chem.* **1984**, *49*, 468-473; (e) T. Tsuda, M. Okada, S. Nishi, T. Saegusa, *J. Org. Chem.* **1986**, *51*, 421-426; (f) J. Tsuji, Y. Ohashi, I. Minami, *Tetrahedron Lett.* **1987**, *28*, 2397-2398.
- 81 Y. Liu, S. J. Han, W. B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, **2015**, *48*, 740–751. 2 (a) S. F. Martin, *Tetrahedron*, **1980**, *36*, 419–460; (b) E. J. Corey and A. Guzman-Perez, *Angew. Chem. Int. Ed.*, **1998**, *37*, 388–401; *Angew. Chem.*, **1998**, *110*, 402–415; (c) C. J. Douglas and L. E.

Overman, *Proc. Natl. Acad. Sci.*, **2004**, 101, 5363–5367; (d) I. Marek and G. Sklute, *Chem. Commun.*, 2007, 1683–1691; (e) B. M. Trost and C. Jiang, *Synthesis*, **2006**, 369–396; (f) D. C. Behenna, J. T. Mohr, N. H. Sherden, S. C. Marunescu, A. M. Harned, K. Tani, M. Seto, S. Ma, Z. Novak, M. R. Krout, R. M. McFadden, J. L. Roizen, J. A. Enquist Jr, D. E. White, S. R. Levine, K. V. Petrova, A. Iwashita, S. C. Virgil and B. M. Stoltz, *Chem.–Eur. J.*, **2011**, 17, 14199–14223; (g) B. M. Trost, J. Xu and T. Schmidt, *J. Am. Chem. Soc.*, **2009**, 131, 18343–18357.

82 For successful diastereoselective examples, see: a) D. Enders, A. Zamponi, T. SchQfer, C. NRbling, H. Eichenauer, A. S. Demir, G. Raabe, *Chem. Ber.* **1994**, 127, 1707 – 1721; b) T. Mino, K. Takagi, M. Yamashita, *Synlett* 1996, 645 – 646; c) R. K. Boeckman, D. J. Boehmler, R. A. Musselman, *Org. Lett.* **2001**, 3, 3777 – 3780; d) T. Abe, T. Suzuki, K. Sekiguchi, S. Hosokawa, S. Kobayshi, *Tetrahedron Lett.* **2003**, 44, 9303 – 9305; e) A. Arpin, J. M. Manthorpe, J. L. Gleason, *Org. Lett.* **2006**, 8, 1359 – 1362, and references therein; for a successful catalytic example, see: f) A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2005**, 127, 5604 – 5607.

83 Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*. John Wiley & Sons, Inc.; New York: **1995**. P.3. (a) Enders, D. *Asymmetric Synthesis: Stereodifferentiating Addition Reactions*, Part B. Morrison, JD., editor. Vol. 3. Academic; Orlando: **1984**. p. 275 (b) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*. John Wiley & Sons, Inc.; New York: **1995**.

84 P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz, I. Marek, *J. Am. Chem. Soc.* **2017**, 139, 9615-9620.

85 Yury Minko and Ilan Marek, Stereodefined acyclic trisubstituted metal enolates towards the asymmetric formation of quaternary carbon stereocentres, *Chem. Commun.*, **2014**, 50, 12597

86 E. J. Alexy, H. Zhang, B. M. Stoltz, *J. Am. Chem. Soc.* **2018**, 140, 10109-10112.

87 (a) Trost BM, Van Vranken DL. *Chem. Rev.* **1996**, 96, 395. [PubMed: 11848758] (b) Trost BM, Van Vranken DL. *Angew. Chem., Int. Ed. Engl.* **1992**; 31, 228, (c) Trost BM, Van Vranken DL, Bingel C. *J. Am. Chem. Soc.* **1992**, 114, 9327; (d) Trost BM, Michaelis DJ, Charpentier J, Xu

J. Angew. Chem., Int. Ed. **2012**; *51*, 204.

88 Eduardo Alberch Colin Brook Sharif A. Asad Maria Shevyrev Joseph S. Ulicki M. Mahmum Hossain, Stereoselective allyl enol carbonates for the synthesis of chiral aldehydes bearing all-carbon quaternary stereocenters via the decarboxylative asymmetric allylic alkylation (DAAA), *Synlett*. **2015**, *26*, 388–392

89 Eric J. Alexy, Tyler J. Fulton, Haiming Zhang and Brian M. Stoltz, Palladium-catalyzed enantioselective decarboxylative allylic alkylation of fully substituted N-acyl indole-derived enol carbonates, *Chem. Sci.*, **2019**, *10*, 5996.

90 (a) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (b) J.-M. Brunel, T. O. Luukas, H. B. Kagan, *Tetrahedron: Asymmetry* **1998**, *9*, 1941. (c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* 1994, *94*, 2483.

91 (a) V. Gotor, F. Rebolledo, R. Liz, *Tetrahedron: Asymmetry* **2001**, *12*, 513. (b) Enzyme Catalyst in Organic Synthesis; K. Drauz, H. Waldmann, Eds.; VCH: Weinheim, Germany, **1995**.

92 (a) M. Calter, T. K. Hollis, L. E. Overman, J. Ziller, G. G. Zipp, *J. Org. Chem.* **1997**, *62*, 1449. (b) T. K. Kollis, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8837. (c) F. Cohen, L. E. Overman, *Tetrahedron: Asymmetry* **1998**, *9*, 3213. (d) Y. Donde, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 2933. (e) For the thermal and palladiumcatalyzed racemic rearrangement see: Overman, L.

93 Ana M, Martin Castro, Claisen Rearrangement over the Past Nine Decades, *Chem. Rev.* **2004**, *104*, 2939–3002.

94 (a) K. Nonoshita, H. Banno, K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 316 – 322. (b) L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841. (c) K. Maruoka, J. Sato, H. Banno, H. Yamamoto, *Tetrahedron Lett.* **1990**, *31*, 377. (d) S. Saito, K. Shimada, H. Yamamoto, *Synlett* 1996, 720. (e) T. Ooi, M. Takahashi, K. Maruoka, *J. Am. Chem. Soc.* **1996**, *118*, 11307.

95 N. Uddin, M. Rahaman, E. Alberch, S. A. Asad, M. M. Hossain, Palladium(0)-catalyzed rearrangement of allyl enol ethers to form chiral quaternary carbon centers via asymmetric allylic

alkylation, *Tetrahedron. Lett.* **2018**, 59, 3401-3404.

96 (a) M. Sugiura, T. Nakai, *Tetrahedron Lett.* 1996, 37, 7991. (b) M. Hiersemann, *Synlett* **1999**, 1823. (c) D. J. Watson, P. N. Devine, A. I. Meyers, *Tetrahedron Lett.* **2000**, 41,1363. (d) K. Neuschütz, J.-M. Simone, T. Thyran, R. Neier, *Helv. Chim. Acta*, **2000**, 83, 2712.

97 (a) B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* 1998, 120, 815. (b) G. V. M. Sharma, A. Ilangovan, P. Sreenivas, A. K. Mahalingam, *Synlett* 2000, 615. (c) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **2000**, 122, 3785.

98 (a) G. Koch, P. Janser, G. Kottirsch, E. Romero-Giron, *Tetrahedron Lett.* **2002**, 43, 4837. (b) G. Koch, G. Kottirsch, B. Wietfeld, E. Küsters, *Org. Proc. Res. Dev.* **2002**, 6, 652.

99 Ben W. H. Turnbull and P. Andrew Evans, Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions: Discovery, Development and Applications to Target-Directed Synthesis, *J. Org. Chem.*, 2018, **83**,11463

100 (a) Abigail G. Doyle and Eric N. Jacobsen, Enantioselective Alkylation of Acyclic α,α -Disubstituted Tributyltin Enolates Catalyzed by a {Cr(salen)} Complex, *ngew. Chem. Int. Ed.* 2007, 46, 3701 –3705, (b) Rodney A. Fernandes and Jothi L. Nallasivam, Catalytic allylic functionalization *via* π -allyl palladium chemistry, *Org. Biomol. Chem.*, **2019**,17, 8647-8672

101 Rhodes, I., *Fld. Sin. Rec. Di, Pl. hid. CSIRO 6 Frs containi (no. 2)*, **1967**, 69.

102 N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit, and R. I. Willing, Oxindoles from *Phalaris Coerulescens*; *Phytochemistry*, **1998**, 48, 3, 437-439.

103 Marti, C., and Carreira, E. M. (2003). Construction of spiro[pyrrolidine-3,3'- oxindoles]-recent applications to the synthesis of oxindole alkaloids. *Eur. J. Org. Chem.* **68**, 2209–2219. doi: 10.1002/ejoc.200300050

104 Galliford, C. V., and Scheidt, K. A. (2007). Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem. Int. Ed.* **46**, 8748–8758. doi: 10.1002/anie.200701342

105 Chaomin Li, Collin Chan, Annekatrin C. Heimann, and Samuel J. Danishefsky, *Angew. Chem. Int. Ed.* **2007**, 46, 1444 –1447

- 106 Takasuke Mukaiyama, Kento Ogata, Itaru Sato, and Yujiro Hayashi*[a], *Chem. Eur. J.* **2014**, *20*, 1–7
- 107 G. Lakshmaiah, T. Kawabata, M. Shang, K. Fuji, Total Synthesis of (–)-Horsfiline via Asymmetric Nitroolefination, *J. Org. Chem.* **1999**, *64*, 1699.
- 108 E. Wenkert, J. H. Udelhofen, N. K. Bhattacharyya, 3-Hydroxymethyleneoxindole and its Derivatives, *J. Am. Chem. Soc.* **1959**, *81*, 3763.
- 109 Subhadip De, Mrinal Kanti Das, Subhajit Bhunia, and Alakesh Bisai, Unified Approach to the Spiro(pyrrolidinyl-oxindole) and Hexahydropyrrolo[2,3-b]indole Alkaloids: Total Syntheses of Pseudophrynamines, 270 and 270A, *Org. Lett.* **2015**, *17*, 5922.
- 110 Hong, S., Lee, J., Kim, M., Park, Y., Park, C., Kim, M.-H., et al. (2011). Highly enantioselective synthesis of α,α -dialkylmalonates by phase-transfer catalytic desymmetrization. *J. Am. Chem. Soc.* **133**, 4924–4929. doi: 10.1021/ja110349a
- 111 (a) S.-S. Ma, W.-L. Mei, Z.-K. Guo, S.-B. Liu, Y.-X. Zhao, D.-L. Yang, Y.-B. Zeng, B. Jiang, H.-F. Dai, *Org. Lett.* **2013**, *15*, 1492 – 1495; (b) B. Narendraprasad Reddy, C. V. Ramana, *Tetrahedron* **2017**, *73*, 888 – 899
- 112 (a) S. Crosignani, P. Page, M. Missotten, V. Colovray, C. Cleva, J.-F. Arrighi, J. Atherall, J. Macritchie, T. Martin, Y. Humbert, M. Gaudet, D. Pupowicz, M. Maio, P.-A. Pittet, L. Golzio, C. Giachetti, C. Rocha, G. Bernardinelli, Y. Filinchuk, A. Scheer, M. K. Schwarz, A. Chollet, *J. Med. Chem.* **2008**, *51*, 2227 – 2243; (b) S. Crosignani, C. Jorand-Lebrun, P. Page, G. Campbell, V. Colovray, M. Missotten, Y. Humbert, C. Cleva, J.-F. Arrighi, M. Gaudet, Z. Johnson, P. Ferro, A. Chollet, *ACS Med. Chem. Lett.* **2011**, *2*, 644 – 649
- 113 (a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209 – 2219; (b) M. M. M. Santos, *Tetrahedron* **2014**, *70*, 9735 – 9757; (c) A. Ding, M. Meazza, H. Guo, J. W. Yang, R. Rios, *Chem. Soc. Rev.* **2018**, *47*, 5946 – 5996
- 114 (a) P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou, J. Zhou, *ACS Catal.* **2019**, *9*, 1820 –

1882; (b) J.-Z. Huang, C.-L. Zhang, Y.-F. Zhu, L.-L. Li, D.-F. Chen, Z.-Y. Han, L.-Z. Gong, *Chem. Eur. J.* **2015**, *21*, 8389 – 8393; (c) L. Liu, D. Wu, S. Zheng, T. Li, X. Li, S. Wang, J. Li, H. Li, W. Wang, *Org. Lett.* **2012**, *14*, 134 – 137; (d) G.-Y. Chen, F. Zhong, Y. Lu, *Org. Lett.* **2012**, *14*, 3955 – 3957.

115 (a) S. Zhao, J.-B. Lin, Y.-Y. Zhao, Y.-M. Liang, P.-F. Xu, *Org. Lett.* **2014**, *16*, 1802 – 1805; (b) L. Cerisoli, M. Lombardo, C. Trombini, A. Quintavalla, *Chem. Eur. J.* **2016**, *22*, 3865 – 3872; (c) X. Huang, M. Liu, K. Pham, X. Zhang, W.-B. Yi, J. P. Jasinski, W. Zhang, *J. Org. Chem.* **2016**, *81*, 5362 – 5369; (d) S. De, M. Kanti Das, A. Roy, A. Bisai, *J. Org. Chem.* **2016**, *81*, 12258 – 12274.

116 Kuo, C.C., Shih, M.C., Kuo, Y.H., Chiang, W., 2001. Antagonism of freeradical-induced damage of adlay seed and its antiproliferative effect in human histolytic lymphoma U937 monocytic cells. *J. Agric. Food Chem.* **2001**, *49*, 1564–1570.

117 Shih, C.K., Chiang, W., Kuo, M.L, Effects of adlay on azoxymethane-induced colon carcinogenesis in rats. *Food Chem. Toxicol.* **2004**, *42*, 1339–1347.

118 (a) Chiang, W., Cheng, C.Y., Chiang, M.T., Chung, K.T., Effects of dehulled adlay on the culture count of some microbiota and their metabolism in the gastrointestinal tract of rats. *J. Agric. Food Chem.* **2000**, *48*, 829–832. (b) Chiang, W., Shyu, M.L., Su, J.P., Pang, V.F, Evaluation of the accessory anti-tumor effect of adlay processing food. *J. Health Sci.* **2000**, *2*, 113–122.

119 Chang, H.C., Huang, Y.C., Hung, W.C., Antiproliferative and chemopreventive effects of adlay seed on lung cancer in vitro and in vivo. *J. Agric. Food Chem.* **2003**, *51*, 3656–3660.

120 Takahashi, M., Konno, C., Hikino, H., Isolation and hypoglycemic activity of coixan A, B, C, glycans of *Coix lachryma-jobi* var. *ma-yuen* seeds. *Planta Med.* **1986**, *52*, 64–65.

121 Tanimura, A., Studies on the anti-tumor component in the seeds of *Coix lachryma-jobi* L. var. *ma-yuen* (Roman.) Stapf. II. The structure of coixenolide. *Chem. Pharm. Bull.* **1961**, *9*, 47–53.

122 Tokuda, H., Matsumoto, T., Konoshima, T., Kozuka, M., Nishino, H., Iwashima, A., Inhibitory effects on Epstein-Barr virus activation and anti-Inhibitory effects on Epstein-Barr virus

activation and anti-tumor promoting activities of coix seed. *Planta Med.* **1990**, *56*, 653– 654.

123 Numata, M., Yamamoto, A., Moribayashi, A., Yamada, H., Antitumor components isolated from the Chinese herbal medicine Coix lachryma-jobi. *Planta Med.* **1994**, *60*, 356–359.

124 Huaanzi Hu, Fan Teng, Jian Liu, Weiming Hu, Shuang Luo,* and Qiang Zhu, Enantioselective Synthesis of 2-Oxindole Spirofused Lactones and Lactams by Heck/Carbonylative Cyclization Sequences: Method Development and Applications, *Angew. Chem. Int. Ed.* **2019**, *58*, 9225 –9229.

125 M.-Y. Lee, H.-Y. Lin, F. Cheng, W. Chiang, Y.-H. Kuo, *Food Chem. Toxicol.* **2008**, *46*, 1933 – 1939.

126 For selected general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: (a) S. F. Martin, *Tetrahedron* **1980**, *36*, 419. (b) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037. (c) E. J. Corey, A. Guzman-Perez *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (d) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591. (e) I. Denissova, L. Barriault *Tetrahedron* **2003**, *59*, 10105. (f) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533. (g) D. J. Ramon, M. Yus *Curr. Org. Chem.* **2004**, *8*, 149. (h) Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; J. Christoffers, A. Baro, *Ed.*; Wiley, Weinheim, Germany, **2005**. (i) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473. (j) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969. (k) J. T. Mohr, B. M. Stoltz, *Chem. Asian J.* **2007**, *2*, 1476. (l) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295. (m) B. M. Trost, C. Jiang *Synthesis* **2006**, 369. 4 M. Bella, T. Gasperi, *Synthesis* **2009**, 1583. (n) J. P. Das, I. Marek *Chem. Commun.* **2011**, *47*, 4593. 6 J. Douglas, L. E. Overman, *PNAS*, **2004**, *101*, 5363.

127 (a) P. M. Herrinton, K. L. Klotz, W. M. Hartley, *J. Org. Chem.* **1993**, *58*, 678. (b) K. C. Nicolaou, G. Vassilikogiannakis, W. M. Ogerlein, R. Kranich, *Angew. Chem. Int. Ed.* **2001**, *40*, 2482. (c) K. C. Nicolaou, M. Bella, D. Y. K. Chen, X. Huang, T. Ling, S. A. Snyder, *Angew. Chem. Int. Ed.* **2002**, *41*, 3495. (d) A. W. G. Burgett, Q. Li, Q. Wei, P. G. Harran, *Angew. Chem. Int. Ed.* **2003**, *42*, 4961. (e) K. C. Nicolaou, P. B. Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y. K. Chen, S. A. Snyder, *Angew. Chem. Int. Ed.* **2003**, *42*, 1753. (f) R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738. (g) A. Steven, L. E. Overman, *Angew. Chem. Int. Ed.*

2007, *46*, 5488. (h) G. E. Veitch, E. Beckmann, b. j. Burke, A. Boyer, C. Ayats, S. V. Ley, *Angew. Chem. Int. Ed.* **2007**, *46*, 7633. (i) D. E. White, I. C. Stewart, R. H. Grubbs, B. M. Stoltz, *J. Am. Chem. Soc.* **2008**, *130*, 810. (j) D. E. White, I. C. Stewart, B. A. Seashore-Ludlow, R. H. Grubbs, B. M. Stoltz, *Tetrahedron*, **2010**, *66*, 4668. (k) A. Y. Hong, N. B. Bennett, M. R. Krout, T. Jensen, A. M. Harned, B. M. Stoltz *Tetrahedron* **2011**, *67*, 10234. (l) W. Lee, J.-H. Youn, S. H. Kang, *Chem. Commun.*, **2013**, *49*, 5231.

128 For a review of the synthesis of natural products bearing quaternary stereocenters via the Pd catalyzed decarboxylative allylation, see: B. M. Stoltz, A. Y. Hong, *Eur. J. Org. Chem.* **2013**, 2745. 203.

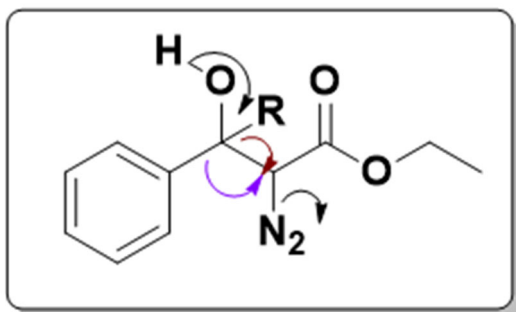
129 R. M. Marcia de Figueiredo, M. Christmann, *Organocatalytic Synthesis of Drugs and Bioactive Natural Products*, *Eur. J. Org. Chem.* **2007**, 2575.

130 (a) J. S. Bindra, *Oxindole Alkaloids in The Alkaloids-Chemistry and Physiology*, Vol. 14 (Eds: R. H. F. Manske), Academic Press: New York, **1973**, 83. (b) M. J. Kornet, A. L. Thio, *J. Med. Chem.* **1976**, *19*, 892. (c) A. Jossang, P. Jossang, H. A. Hadi, T. Sevenet, B. Bodo, *J. Org. Chem.* **1991**, *56*, 6527. (d) S. Edmondson, L. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147. (e) B. D. Dangel, K. Godula, S. W. Youn, B. Sezen, D. Sames, *J. Am. Chem. Soc.* **2002**, *124*, 11856. (f) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp, *J. Am. Chem. Soc.* **2005**, *127*, 18054. (g) B. M. Trost, Y. Zhang *J. Am. Chem. Soc.* **2006**, *128*, 4590. (h) A. Wilsily, E. Fillion, *J. Org. Chem.* **2009**, *74*, 8583. (i) V. J. Reddy, C. J. Douglas, *Tetrahedron*, **2010**, *66*, 4719. (j) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schurmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nature Chemistry*, **2010**, *2*, 735. (k) V. J. Reddy, C. J. Douglas *Org. Lett.* **2010**, *12*, 952. (l) B. Wang, Y. Q. Tu *Acc. Chem. Res.* **2011**, *44*, 1207. (m) J. E. DeLorbe, S. Y. Jabri, S. M. Mennen, L. E. Overman, F.-L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6549. (n) B. M. Trost, Y. Zhang *Chem. Eur. J.* **2011**, *17*, 2916. (o) M.-X. Wei, C.-T. Wang, J.-Y. Du, H. Qu, P.-R. Yin, X. Bao, X.-Y. Ma, X.-H. Zhao, G.-B. Zhang, C.-A. Fan, *Chem. Asian J.* **2013**, *8*, 1966. (p) J. E. DeLorbe, D. Horne, R. Jove, S. M. Mennen, S. Nam, F.-L. Zhang, L. E. Overman, *J. Am. Chem. Soc.* **2013**, *135*, 4117

- 131 S. J. Mahmood and M. M. Hossain, Iron Lewis Acid Catalysed Reactions of Aromatic Aldehydes with Ethyl Diazoacetate: Unprecedented Formation of 3-Hydroxy-2- Acid Ethyl Esters by a Unique 1,2-Aryl Shift, *J. Org. Chem.*, **1998**, *63*, 3333–3336.
- 132 M. E. Dudley, M. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M.-R. Atuu, B. Branstetter and M. M. Hossain, Acid-Catalysed Reactions of Aromatic Aldehydes with Ethyl Diazoacetate: An Investigation on the Synthesis of 3-Hydroxy-2-arylacrylic Acid Ethyl Esters, *J. Org. Chem.*, **2004**, *69*, 7599–7508.
- 133 Sharif A. Asad,[a] Joseph Ulicki,[a] Maria Shevyrev,[a] Nazim Uddin,[a] Eduardo Alberch,[a] and M. Mahmud Hossain, First Example of the Intermolecular Palladium-Catalyzed Asymmetric Allylic Alkylation of Hydroxyacrylates: Synthesis of All-Carbon α -Aryl Quaternary Aldehydes, *Eur. J. Org. Chem.* **2014**, 5695–5699.
- 134 Barry M. Trost, Metal catalyzed allylic alkylation: its development in the Trost laboratories, *Tetrahedron*, **2015**, <http://dx.doi.org/10.1016/j.tet.2015.06.044>
- 135 B. M. Trost, C. Pissot-Soldermann, I. Chen, G. M. Schroeder, An Asymmetric Synthesis of Hamigeran B via a Pd Asymmetric Allylic Alkylation for Enantiodiscrimination, *J. Am. Chem. Soc.* **2004**, *126*, 4480.
- 136 B. M. Trost, J. Xu, Schmidt, An Asymmetric Synthesis of Hamigeran B via a Pd Asymmetric Allylic Alkylation for Enantiodiscrimination, *J. Am. Chem. Soc.* **2009**, *131*, 18342
- 137 S. Hong, M. Jung, Y. Park, M. W. Ha, C. Park, M. Lee, H.-g. Park, Efficient Enantioselective Total Synthesis of (–)-Horsfiline, *Chem. Eur. J.* **2013**, *19*, 9599 – 9605.
- 138 Mukaiyama, T.; Ogata, K.; Sato, I.; Hayashi, Y. Asymmetric Organocatalyzed Michael Addition of Nitromethane to a 2-Oxoindoline-3-ylidene Acetaldehyde and the Three One-Pot Sequential Synthesis of (–)-Horsfiline and (–)-Coerulescine. *Chem. Eur. J.* **2014**, *20*, 13583–13588.
- 139 Plietker, B. Selectivity versus Reactivity - Recent Advances in RuO₄-Catalyzed Oxidations. *Synthesis*, **2005**, 2453–2472.

- 140 Vinicius R. Nascimento^a, Melissa L. S. Suenagaa and Leandro H. Andrade, An Efficient Approach for the Synthesis of New Coixspirolactams, *Org. Biomol. Chem.*, **2020**, *18*, 5458-5465
- 141 M. M. Hossain, US Patent 6,683205 B2, **2004**.
- 142 M. G. Kulkarni, A. P. Dhondge, S. W. Chavhan, A. S. Borhade, Y. B. Shaikh, D. R. Birhade, M. P. Desai, N. R. Dhattrak, *Beilstein, J. Org. Chem.* **2010**, *6*, 876–879.
- 143 D. Yang, C. Zhang, Ruthenium-Catalyzed Oxidative Cleavage of Olefins to Aldehydes, *J. Org. Chem.* **2001**, *66*, 4814-4818
- 144 H. J. Kumpaty, S. Bhattacharyya, E. W. Rehr, A. M. Gonzaleza, Selective Access to Secondary Amines by a Highly Controlled Reductive Mono-N-Alkylation of Primary Amines, *Synthesis*, **2003**, 2206–2210.
- 145 T. Mukaiyama, K. Ogata, I. Sato, Y. Hayashi, Asymmetric Organocatalyzed Michael Addition of Nitromethane to a 2-Oxoindoline-3-ylidene Acetaldehyde and the Three One-Pot Sequential Synthesis of (–)-Horsfiline and (–)-Coerulescine, *Chem. Eur. J.* **2014**, *20*, 13583-13588
- 146 E. E. Garcia, J. G. Riley, R. I. Fryer, Acylindoles. I. Synthesis and transformations of 3-(2-aminobenzoyl)indoles, *J. Org. Chem.* **1968**, *33*, 2868-2874.
- 147 V. R. Nascimento, M. L. S. Suenagaa, L. H. Andrade, An efficient approach for the synthesis of new (±)-coixspirolactam, *Org. Biomol. Chem.* **2020**, *18*, 5458–5465.

Chapter 1: Synthetic Scope of Brønsted Acid Catalyzed Reactions of Carbonyl Compounds and Ethyl Diazoacetate-Part B

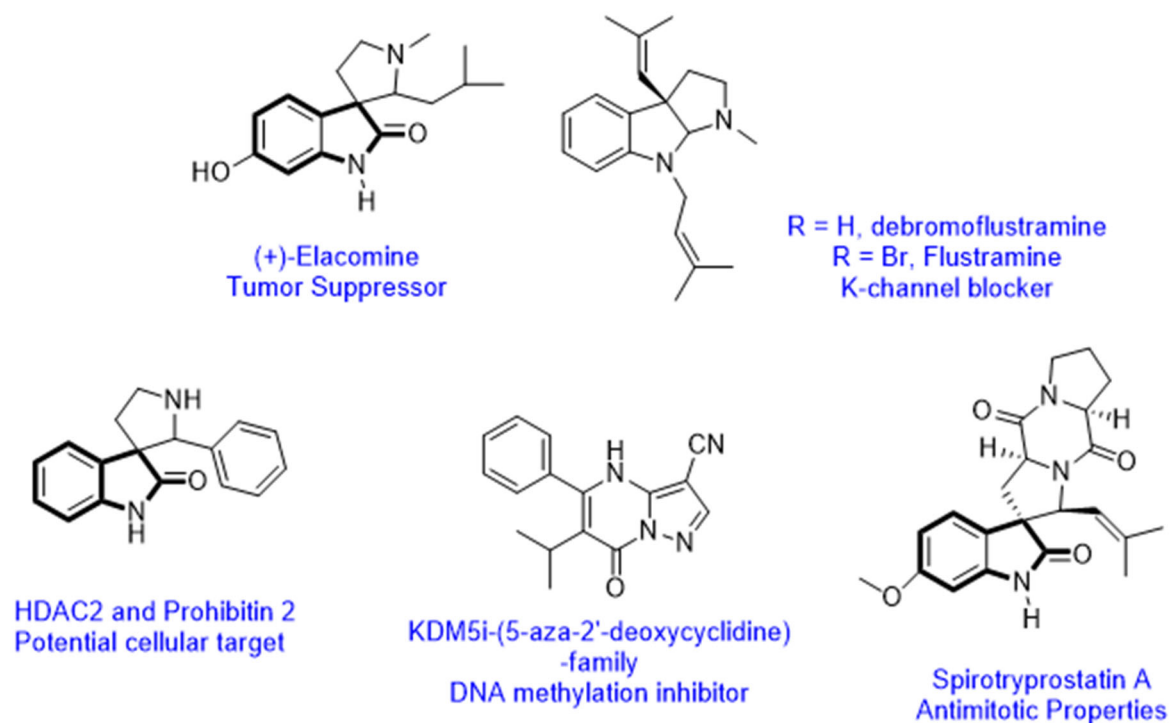


Where, R= Alkyl, Aryl

5.1 Introduction

To an intension of exploring the synthetic scope of the 3-hydroxy aryl acrylate beyond the limitations of aromatic aldehydes, we decided to work on the aromatic ketones along with the aliphatic ketone and aldehydes. Our focus was mainly the development of the quaternary ketones which can be implemented for the synthesis of natural and synthetic products like elacomine, flustramine, spirotryprostatin etc as shown in **Figure 10**.

Figure 10 Synthetic scope of ketone derived acrylates for both natural and synthetic drug candidates

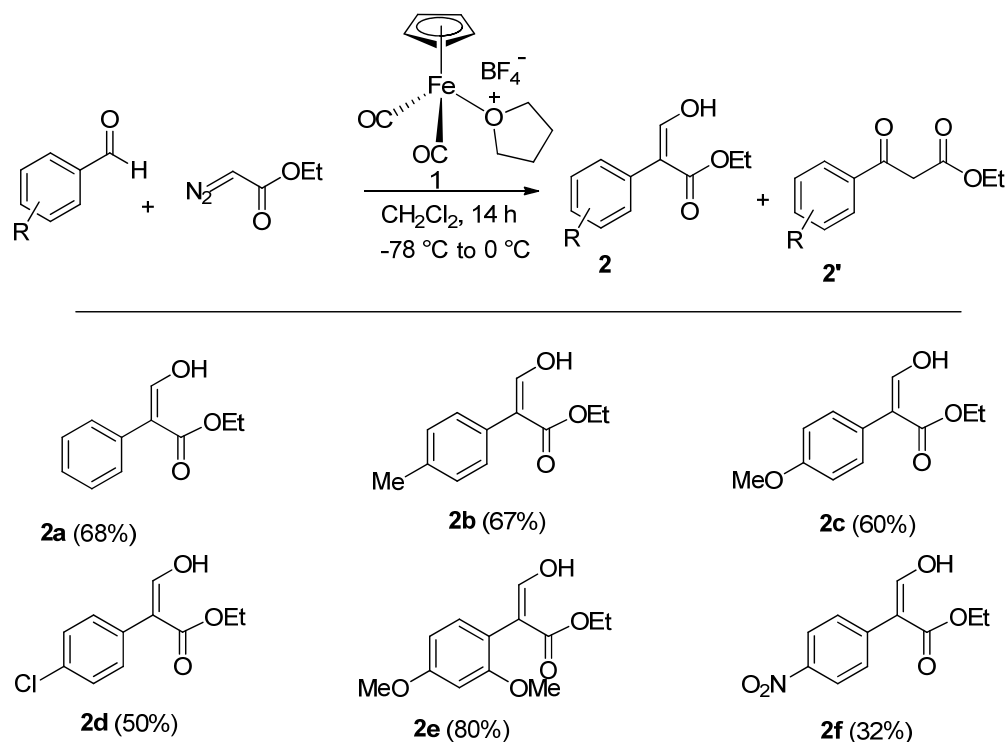


5.1.1 Synthetic approaches for the preparation of 3-hydroxy aryl acrylates:

5.1.1.1 Lewis acid catalyzed reactions

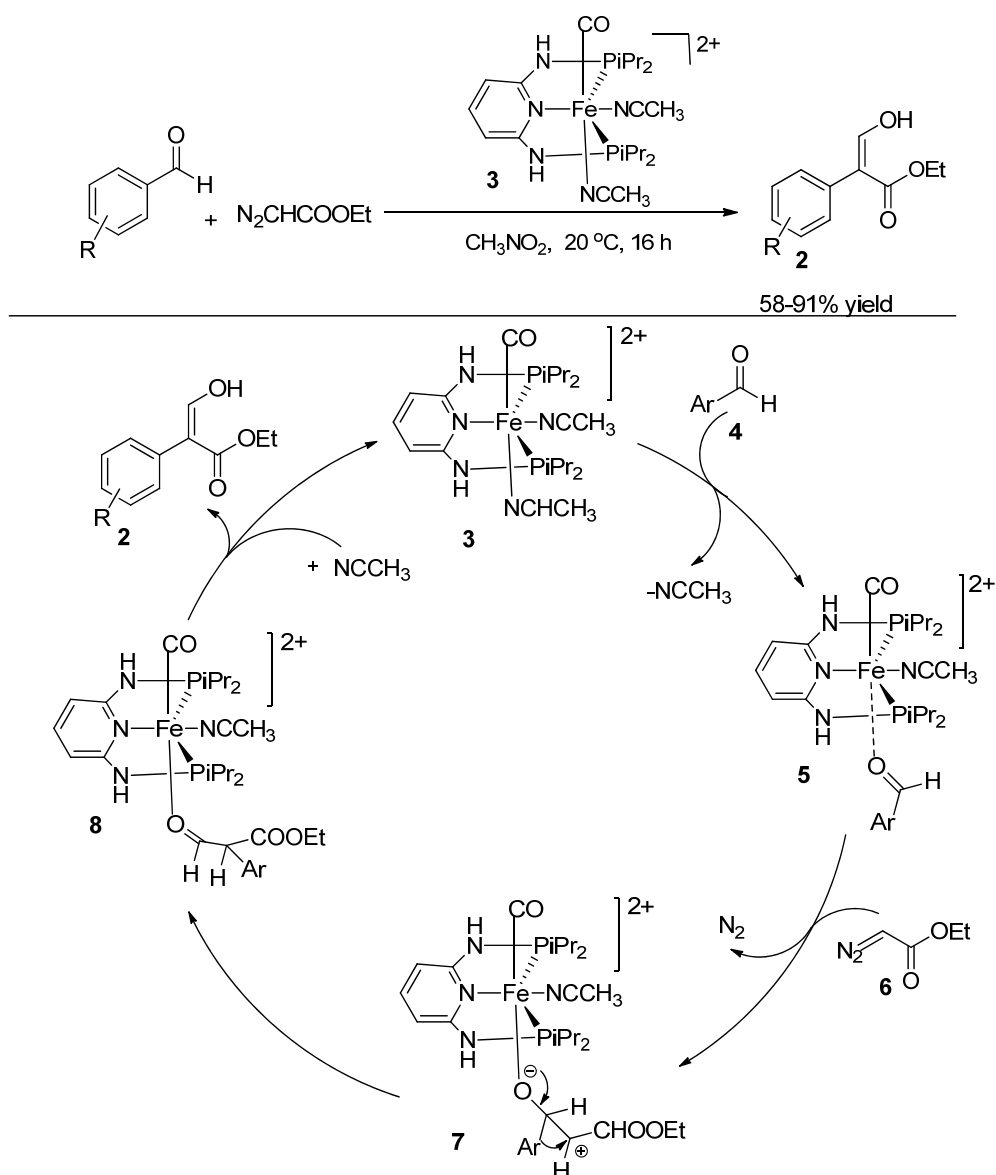
In our previous work, we reported the formation of 3-hydroxy-2-aryl acrylates by 1,2-aryl migration from the reactions of aromatic aldehydes with ethyl diazoacetate (EDA) in the presence of an iron Lewis acid catalyst. [131] The approach proceeded by iron Lewis acid catalyst, $[\eta^5\text{-(C}_5\text{H}_5)\text{Fe}^+(\text{CO})_2(\text{THF})]\text{BF}_4^-$ **1**, catalysed reaction with the formation of desired compound **2** along with β -ketoester **2'** from moderate to excellent yields (**Scheme 75**). Our group reported that

Scheme 75 Iron Lewis catalysed synthesis of 3-hydroxy aryl acrylate by Hossain et al



benzaldehyde having electron donating groups provided higher yield of product **2** (2b, 2c and 2e) compared to having electron withdrawing groups (2d and 2f). Later on, other groups also reported the similar type of reactions by using different Lewis acid catalysts. [146-151]. One of such noticeable work was published by Kirchner and coworkers. The specialty of their approach is the regioselective formation of **2** (consistently got <3% of **2'**) by using cationic iron pincer complexes such as $[\text{Fe}(\text{PNP})(\text{CH}_3\text{CN})_3](\text{BF}_4)_2$ and $[\text{Fe}(\text{PNP})(\text{CO})(\text{CH}_3\text{CN})_2](\text{BF}_4)_2$, where PNP are various

Scheme 76 Iron Lewis acid catalyzed synthesis of **2** by Kirchner et al



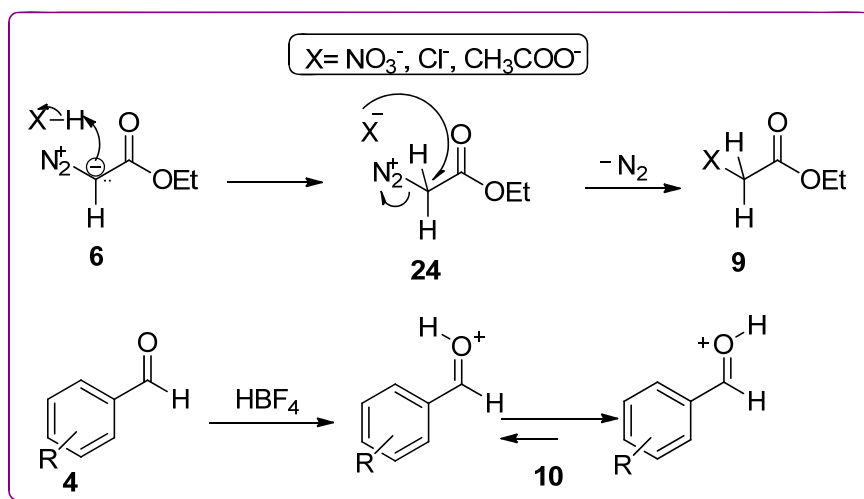
tridentate pincer-type ligands based on 2,6-diaminopyridine, and R = Ph, iPr, biphenol, Ph^{Hex}. The most effective catalyst was found to be *cis*-[Fe(PNP-*i*Pr)(CO)(CH₃CN)₂]⁺BF₄⁻ (**Scheme 76**). [145]

Based on their proposed mechanism, the presence of CO ligand makes CH₃CN more labile in the catalyst **3**, due to its stronger *trans*-effect and easily substituted by incoming aromatic aldehyde **4** to form [Fe (PNP-*i*Pr)(CO)(CH₃CN)(κ¹(O)-aldehyde)]²⁺ complex **5**. Then the ligand substituted complex **5** was attacked by **6** and formed the complex **7** by subsequent liberation of N₂. Preferential migratory tendency of the aryl group over hydride led to a κ¹O-coordinated aldehyde ester ligand **8**. Finally, the aldehyde ester ligand was easily removed from **8** by an incoming CH₃CN, and rapidly tautomerized to yield the thermodynamically more stable **2** (**Scheme 76**).

5.1.1.2 Bronsted Acid catalyzed reactions

In 2004, our group explored the catalyst scopes to produce 3-hydroxy-2-aryl acrylates and 3-oxo-esters with Brønsted type acids by using similar substrates. [152] We have screened several commercially available Brønsted acids, such as HNO₃, H₂SO₄, HClO₄, HCl besides HBF₄, to see the protonation tendency and the counterion effect on selective product formation. They found that

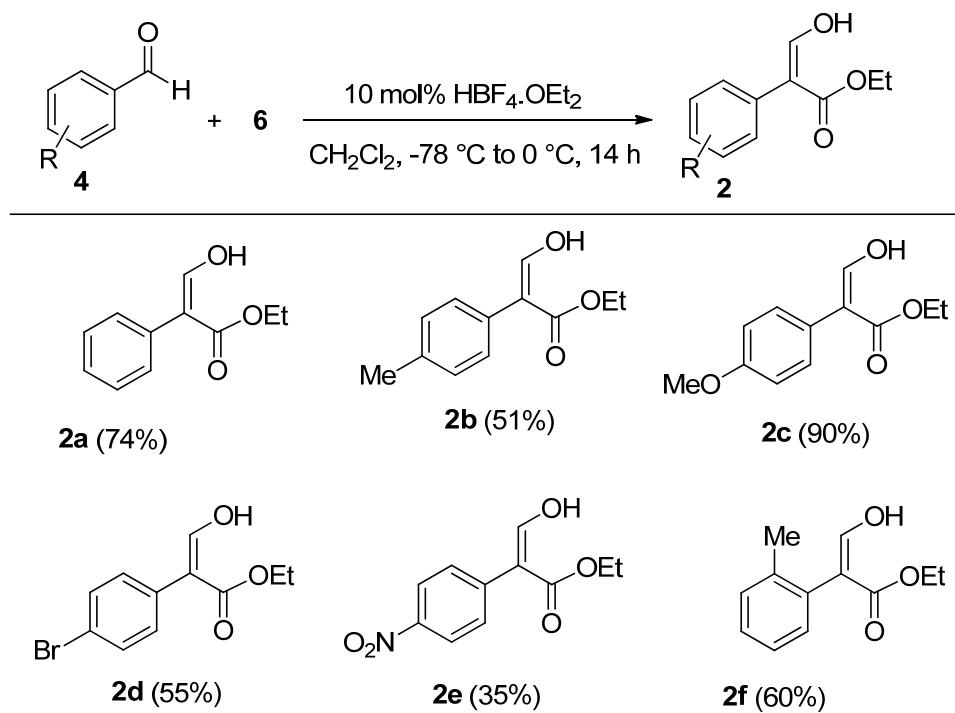
Scheme 77 Role of commercially available Bronsted acid for the decomposition of **6**



the acids with nucleophilic counterions, such as Cl⁻, AcO⁻, and NO₃⁻, provided a small amount of product **1** since these acids readily quenched by EDA **6** and formed byproduct **9** (**Scheme 77**). However, HBF₄ did not quench by EDA due to the presence of non-nucleophilic counterion (BF₄⁻) rather protonated the carbonyl oxygen to access *O*-protonated benzaldehyde **10** which initiated the reaction (**Scheme 77**). Therefore, they explored the substrate scope (**Scheme 78**) with their developed simplified protonation technique. Unfortunately, no more precedence of other Brønsted acid catalyzed approaches have been reported so far. Later Kirchner et al synthesized the acrylates following the same protocol for the computational study of the migratory tendency of aryl group

relative to the alkyl group. [153a]

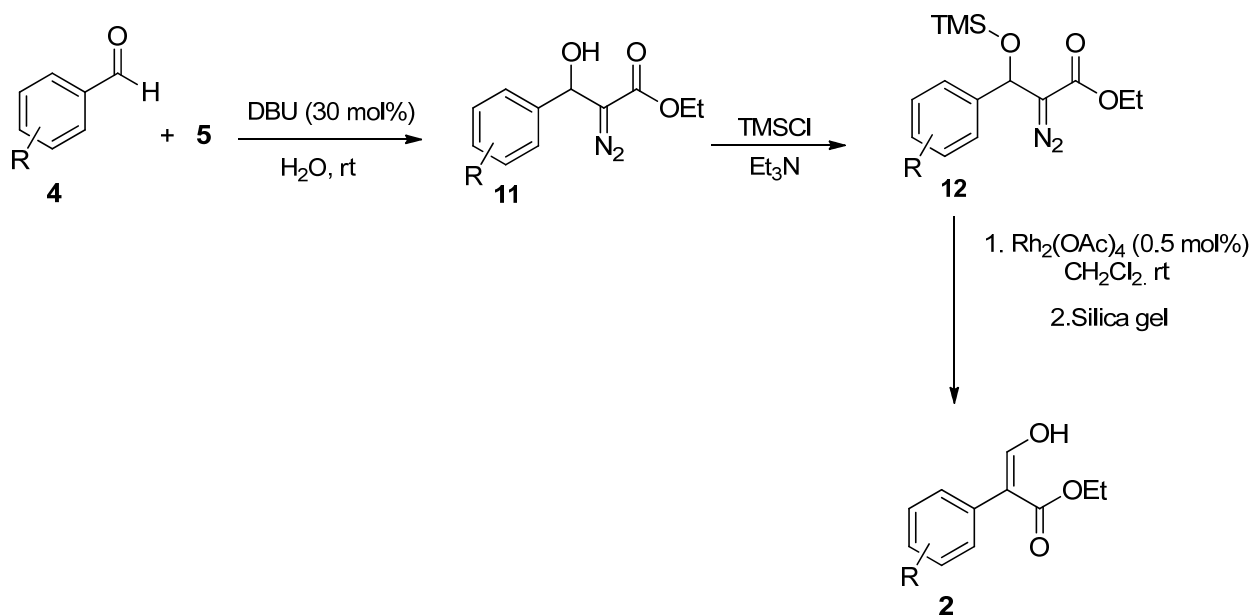
Scheme 78 First Bronsted acid catalyzed coupling of aromatic aldehyde, 4 and EDA, 6 by Hossain et al



5.1.1.3 Organic base catalysed reaction

In 2007, Wang et al. reported 1, 8-diazabicyclo [5.4.0]undec-7-ene (DBU) catalysed nucleophilic reaction between **4** and EDA **6** to synthesize **2** via β -hydroxy diazo ester **11** as an intermediate. Initially, the β -Hydroxy group of **11** was protected by trimethylsilyl chloride (TMSCl) to form compound **12**. In the presence of Rh(II)-catalyst, compound **12** underwent 1,2-aryl migration to provide the final product **1** (**Scheme 79**). [153b, 153c] The steric factors play an important role in the 1,2-migratory aptitude of Rh(II)- catalysed reaction. When the substituent was bulkier at the β -position, such as a siloxy group, aryl migration was favored over hydride migration.

Scheme 79 Organic base catalyzed formation of 3-hydroxy arylacrylate, 2 by Wang et al

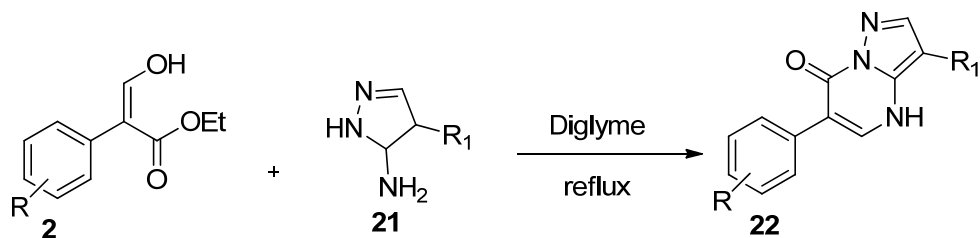


by Bisagni et al. [159] Condensation reactions between **2** and 3,5-dimethoxy aniline **13** formed non-regioselective E/Z mixture of intermediate **16** which underwent cyclization by refluxing in Dowtherm A (biphenyl/diphenyl ether mixture 26.5 : 73.5) to prepare **17**. On the other hand, by direct heating of **2** and **13** at 230 °C they obtained 3-phenyl-2-quinolone **14**. They also prepared other quinolone derivatives such as **15**, **18**, **19**, and **20** from quinolones **14** and **15** using a little far of chemical methodologies (Scheme 80).

5.2.2 Synthesis of Pyrimidine/pyrimidinone type compounds

After years of research on various neurological disorders which mainly related to the GABAergic system, it has been evident that such disorders can be treated by targeting the GABA_A-Receptors (GABA_A-Rs). [160] Moreover, development of compounds of different structural classes can modulate, directly activate or inhibit GABA_A-R subtypes. Therefore, different types of fused nitrogen-containing heterocyclic systems have been extensively investigated to synthesize GABA_A-Receptors sub-type ligands. [161] Selleri et al. described the synthesis of second-generation pyrazole-pyrimidine compound **22**, containing an aryl ring at 6-position

Scheme 81 Synthesis of pyrazolopyrimidinone from 3-hydroxyarylacrylate **2**



R = H; R₁ = Ph, 4-FPh, 3-BrPh, 3-CF₃Ph, 3-OMePh, 3-MePh, 2-Py, 3-Py, 2-thienyl, 3-thienyl, benzyl, 1-naphthalen, 2-naphthalen

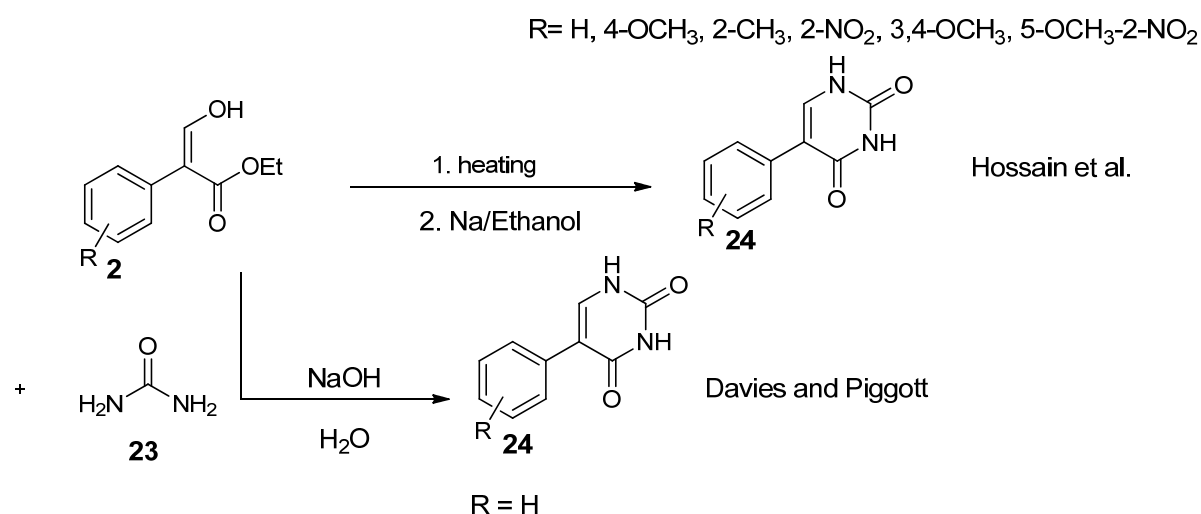
as an isostere of the thiophene ring to evaluate in vitro GABAA-receptors affinity. [162] A single step approach of preparing compound **22** has proposed by the reaction between a suitable pyrazole **21** and **2** in diglyme at reflux condition (**Scheme 81**).

5.2.3 Synthesis of Uracil type compounds

Uracil is one of the three basic pyrimidines obtained in naturally occurring nucleic acids.⁴¹ Because of structural similarities with nucleosides and nucleotides, uracil plays a pivotal role in the treatment for human immunodeficiency virus (HIV), [163] hepatitis B virus (HBV), [164] hepatitis C virus (HCV), [165] herpes simplex virus (HSV), [166] and various types of cancer. [167]

In 2007, our group has reported NaOEt catalyzed synthesis of a series of derivatives **24** using a variety of acrylates including both electron donating and electron withdrawing groups (**Scheme 82**). [168]

Scheme 82 Synthetic application of 3-hydroxy arylacrylate **2** for preparing Uracil derivatives

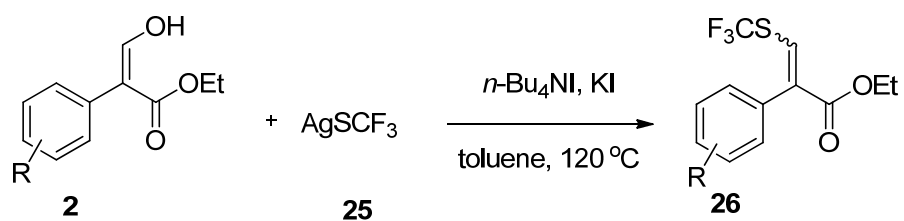


Another approach of similar synthetic approach was attempted by Davies and Piggott for the synthesis of **24** from the reaction of **1** and **68** in the presence of NaOH (Scheme 82). [169] Interestingly, whenever other amides were attempted to be used in this reaction, no product was yielded.

5.2.4 Synthesis of Vinyl derivatives

A unique idea of direct trifluoromethylthiolation of C_{sp}²-OH bond activation of **2** using silvertrifluoromethanethiol **25** has recently explained by Qing and co-workers; a variety of trifluoromethyl sulfides **26** has been synthesized thereafter. [170] The employment of both of *n*-Bu₄NI and KI activated **25** to afford the desired product **26** (Scheme 83). This convenient approach of incorporating an extremely high lipophilic [171] trifluoromethylthio group (SCF₃) might simplify the synthesis of many pharmaceutical and agrochemical compounds such as toltrazuril [172], fipronil [173] and tiflorex. [174]

Scheme 83 Synthesis of thio vinyl derivatives from 3-hydroxy aryl acrylate

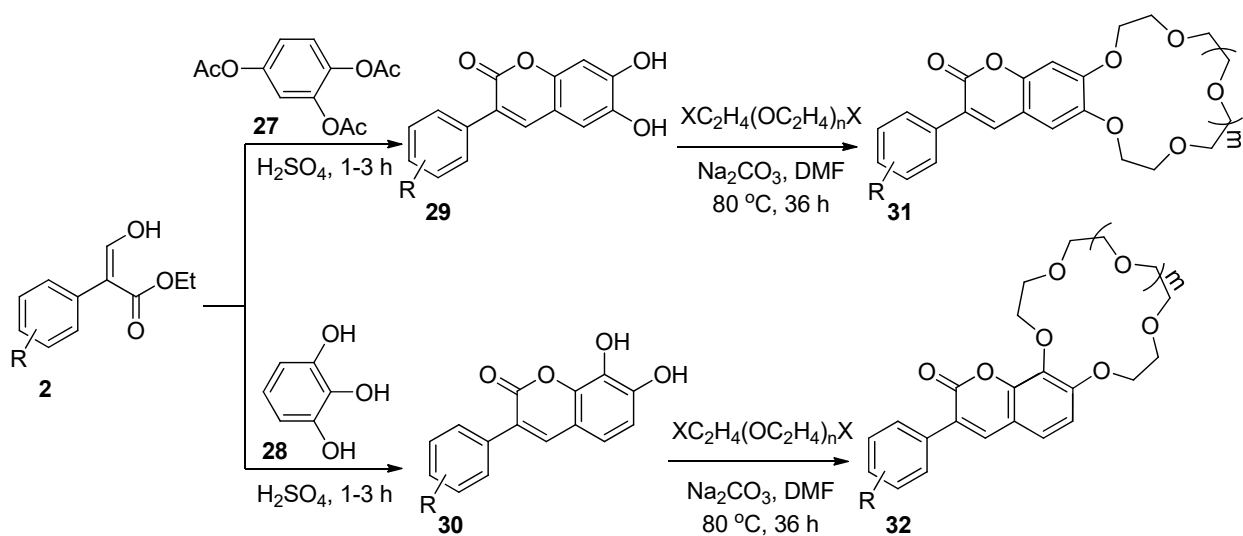


R = H, 4-Me, 4-*t*Bu, 4-NC, 4-NO₂, 4-F, 2-NO₂-3-OMe, 2,5-di-Br, 2-Br-5-CF₃, 2-Br-3-OCF₃, 4-Ph, naphthyl

5.2.5 Synthesis of Chromenone Crown ether

Macrocyclic ethers (depending on the ring size) have been used to estimate cationic recognition and selective cation binding using different physical approaches such as filtration, absorption etc. [175-177] Erk et al. reported the synthesis of various 3-phenyl chromenone-crown ether moieties **31** and **32** which was used for the detection of cations such as Li^+ , Na^+ , K^+ , and Rb^+ as well as perchlorates with fluorescence spectroscopy. [178,179] Compounds **31** and **32** were synthesized by the addition of crown ether (12-Crown-4, 15-Crown-4, and 18-Crown-6) to chromenones **29** and **30**; which was obtained from the cyclization of triacetate **27** or triol **28** with compound **2** (Scheme 84).

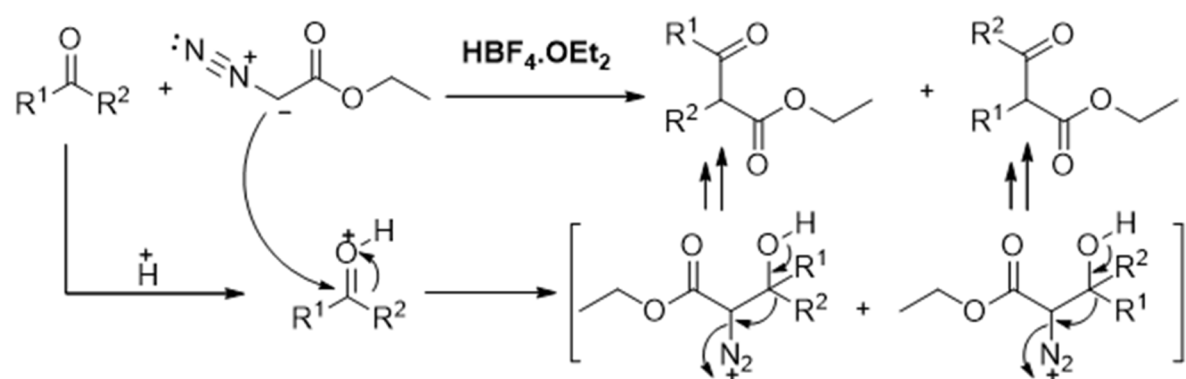
Scheme 84 Synthesis of Chromenone-Crown Ethers from 3-hydroxy arylacrylate 2



Therefore, we attempted to unfold the scope of these underdeveloped substrates. We expected to obtain product mixture of the migrated products due to the variation of migratory tendency of different alkyl/aryl groups and investigated the relative product ratios (from crude by NMR

analysis or possibly from isolated products). However, reactions of more sterically hindered and less electrophilic aromatic/aliphatic ketones or aliphatic aldehydes with EDA in the presence of a Brønsted acid catalyst are certainly rare. Before starting our investigation, we have outlined a general mechanism for the 1,2-aryl migration of carbonyl substrates considering EDA as a reaction partner with an optimized amount of $\text{HBF}_4 \cdot \text{OEt}_2$ as a catalyst (**Scheme 85**). To expand the scope of this reaction, benzophenones, aliphatic ketone (both symmetric and nonsymmetric) along with aliphatic aldehydes were employed as substrates in this transformation.

Scheme 85 Formation of 3-hydroxy aryl acrylate/3-Oxo-Esters in presence of $\text{HBF}_4 \cdot \text{OEt}_2$ catalyst by 1,2-migration.



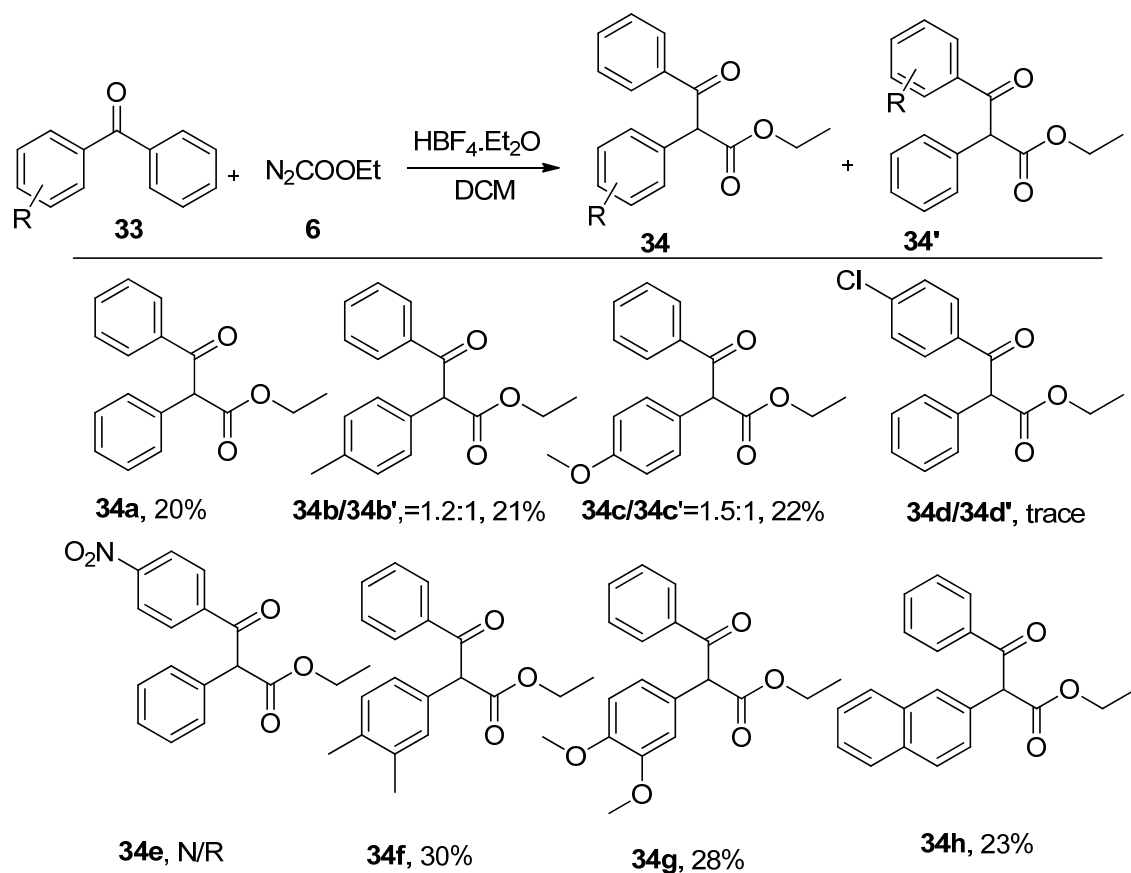
5.3 Results and Discussion

5.3.1 Development of Benzophenone derived acrylates

We first focused on the synthesis of benzophenone and substituted benzophenones (**Scheme 86**).

The result obtained from the reaction of benzophenone with EDA was encouraging; the yield is

Scheme 86 Synthetic scope and migratory aptitude of Aryl-Phenyl groups



^aReaction conditions: **33** (5.0-10.0 mmol), **6** (10.0-20 mmol), $\text{HBF}_4 \cdot \text{OEt}_2$ (1.0-2.0 mmol), CH_2Cl_2 (15-20 mL) at -78 °C to rt for 3 days. ^bThe ratios of the products are calculated from the NMR of the crude mixtures.

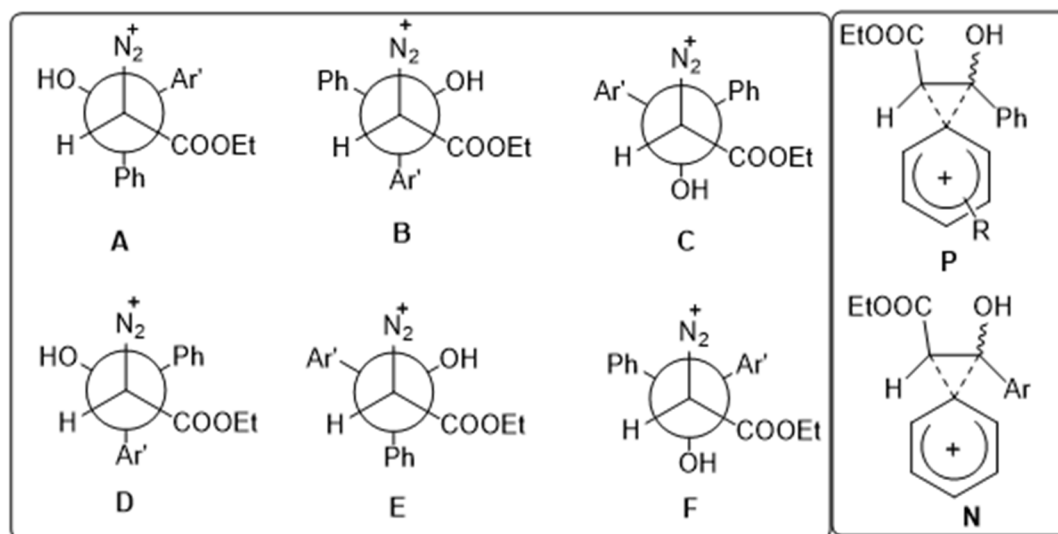
low may be because of the sterically hindered and very less reactive structure of benzophenone which does not allow the nucleophilic EDA to attack with the mild reaction conditions. Though we expected much better yield from the electron donating para substituted methyl or methoxy

group in one of the phenyl rings on the benzophenone moiety, but the yield was similar. From our enquiry, it was revealed that when an electron donating group such as methyl was present in the monosubstituted benzophenone (**34b**), both phenyl and *para*-tolyl migrated products were formed in a ratio of 1:1.2. Our result agree with the value (1.28 ± 0.09) reported by Curtin and Crew in the acid catalyzed deamination reaction of 2-amino-1-phenyl-1-*p*-tolylethanol involving carbocation intermediate.[180] Moreover, in our study the *p*-anisyl group in compound **34c** provided the relatively better migration (1.5/1) might be because of the additional interaction energy in the transition state induce by the *para*-methoxy group during carbocation formation.[161] In the case of electron rich 3,4-disubstituted benzophenone (**34f** and **34g**), we obtained exclusively the disubstituted phenyl-migrated products (**34f** and **34g**) and the yield increase a little. This type of migration was also found in naphthyl phenyl ketone (**34h**) where electron rich naphthyl group was migrated to give the product (**34h**). The exclusive formation of (34f), (34g), and (34h) may be due to the better stability of the corresponding phenonium carbocation intermediate. On the other hand, when an electron withdrawing group (**34d** and **34e**) was present in the monosubstituted benzophenone, trace or no product was observed which could be due to the instability of carbocation intermediate. [132]

The above findings could be explained with respect to six probable rotamers **A-F** (**Figure 11**) from the reaction of benzophenones and EDA in the presence of $\text{HBF}_4 \cdot \text{OEt}_2$. Rotamers **A-C** are interconvertible due to the rotation of C-C bonds and their diastereomeric form of rotamers, **D-F** are also interconvertible. In both rotamer **A** and **E**, migrating phenyl group and leaving diazonium group were anti to each other, thus the formation of 3-oxo-ester **34** was favorable. Whereas, in rotamers **B** and **D**, the aryl migrating group was anti to the leaving group could favor

the formation of aryl migrated product **34'**. However, the aryl migration from rotamer **A/E** was more favorable over phenyl from rotamer **B/D** due to its ability of the electron donating methyl and methoxy group to stabilize an intermediate arylonium ion (**Figure 11, P**) by six electron resonance participation. Whereas it is also stable for unsubstituted phenyl group (**Figure 11, N**) but relatively less compare to **P**. Therefore, during the crude NMR analysis, we saw more of **34b**, **34c** compared to **34b'** and **34c'**. In our discussion, we did not consider rotamers **C** and **F** which are prerequisite for the formation of epoxide, not observed in our reactions.

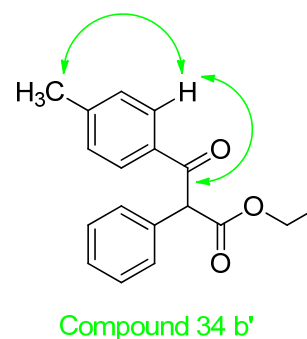
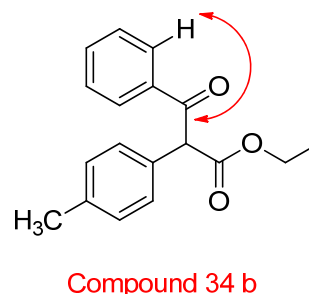
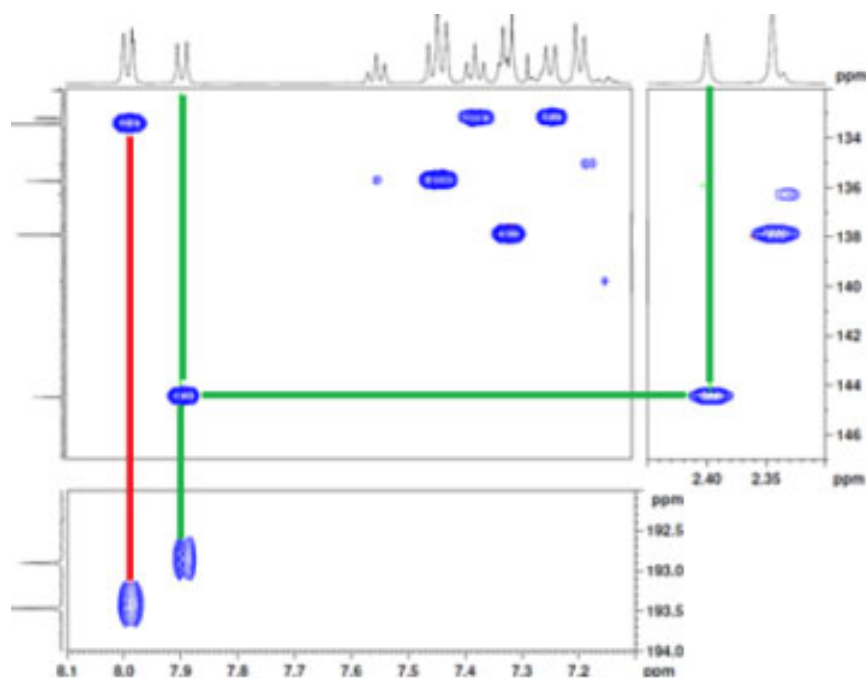
Figure 11 Newman projections of six possible rotamers (A-F) and the predicted intermediates



As we obtained mixture of products from the reactions of *para*-methyl (**33b**) and *para*-methoxy benzophenone (**33c**) and EDA, we undertook 2D NMR studies to confirm the structure of the products. After analyzing HMBC spectra, we observed a cross peak signal between the *ortho*-proton of the benzene ring (a doublet at δ 7.99) and the carbonyl carbon of ester (δ 193.7) (red line

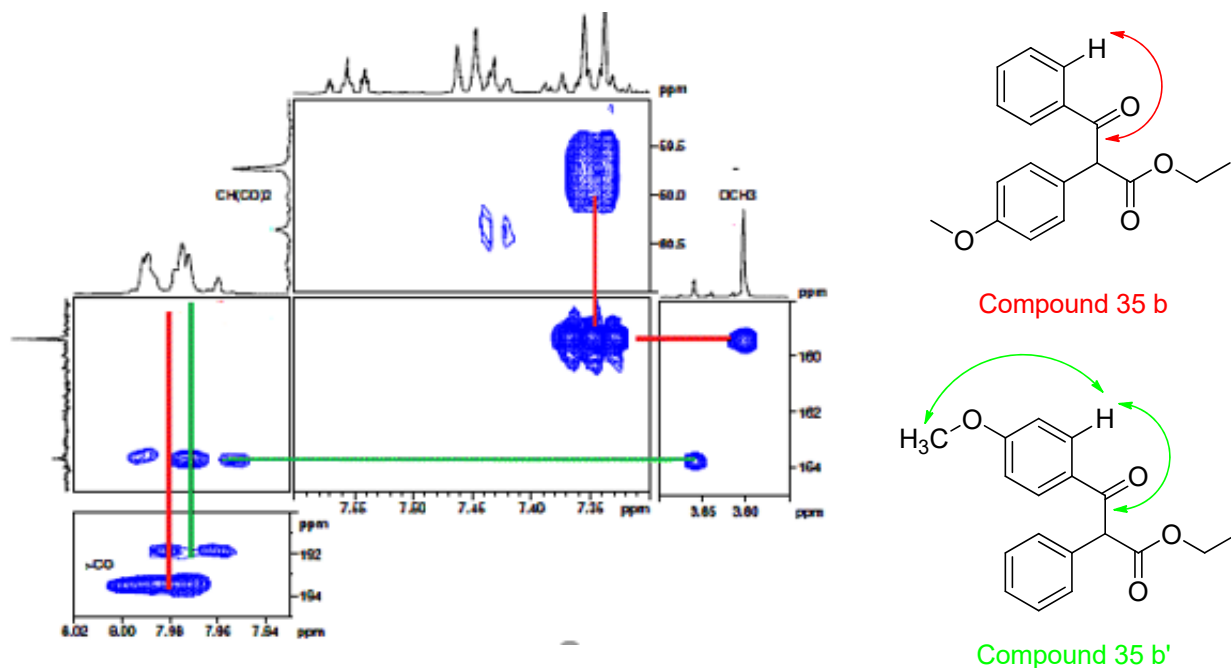
in **Figure 12**), which correlates with the structure of (**34b**) generated by *para*-methyl phenyl migration. On the other hand, a cross peak signal was identified among the *ortho*-proton (a doublet at δ 7.89) and the *para*-methyl carbon of the benzene ring (δ 2.39) as well as with the carbonyl carbon of ester (δ 192.9) (green line in Figure 12). This cross coupling nicely correlates with (**34b'**) formed by phenyl migration. By comparing the peaks at δ 7.89 and δ 7.99 in the crude mixture (see experimental section), we concluded the product (**34b**) yielded slightly more product (**34b'**) due to the favorable migration of electron donating *para*-methyl phenyl over phenyl group.

Figure 12 HMBC cross peak spectra for the products of *para*-methylbenzophenone



Similarly, we have confirmed the structure of (**34c**) by 2D NMR by comparing a cross peak signal between the *ortho*-proton of the benzene ring (a doublet at δ 7.98) and the carbonyl carbon of ester (δ 194.0) (red line in Figure 13) and the structure of **34c'** from the cross peak signal among the *ortho*-proton (a doublet at δ 7.97) and the *para*-methoxy carbon of the benzene ring (δ 3.86) with the carbonyl carbon of ester (δ 192.0) (green line in **Figure 13**) (see also experimental section).

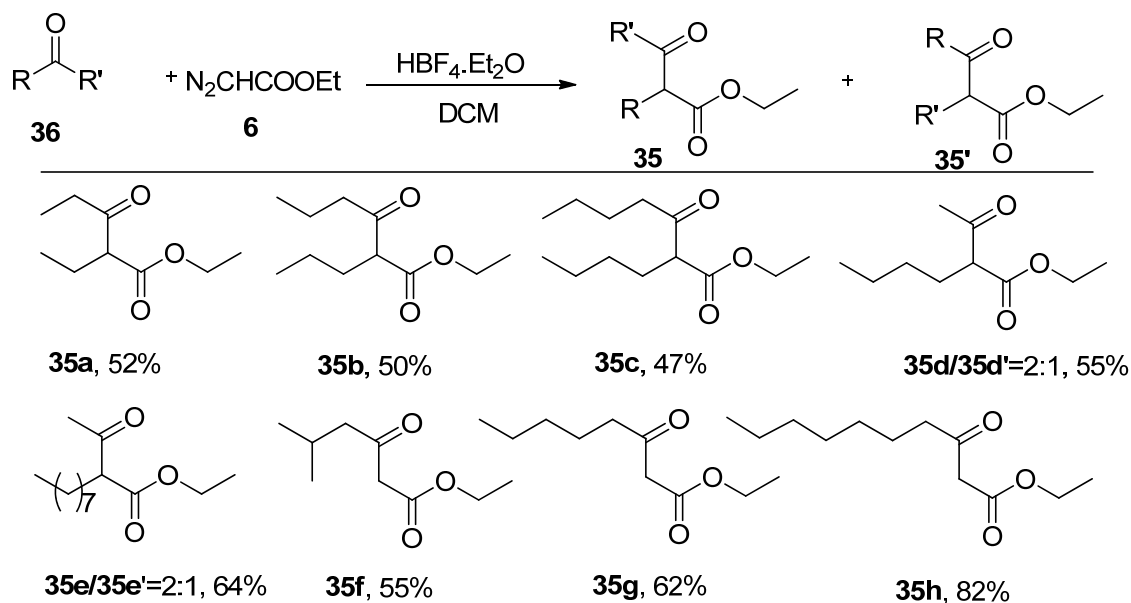
Figure 13 HMBC cross peak spectra for the products of *para*-methoxybenzophenone



5.3.2 Development of Aliphatic carbonyl derived acrylates

Lastly, to demonstrate further utility of the reaction, transformation of the aliphatic aldehydes and ketones were explored. Symmetrical ketone such as **35a-35c** provided yield up to 52% and the nonsymmetrical ketones resulted from 55-64% isolated yield. The aliphatic aldehydes with linear (**35g** and **35h**) and branched alkyl group (**20f**) yielded up to 82%. The results of these reactions are summarized in Scheme 78. For the migratory aptitude of unsymmetrical aliphatic ketones, increasing the steric bulk of the alkyl group increases its tendency to migrate. The longer alkyl chain migrated products dominated over the methyl migrated products (**35d/35d'** and **35e/35e'**=2:1) due to the hyperconjugation effect with longer chain alkyl group, triggered better stability of the carbocation intermediate. [182] In the case of aliphatic aldehydes, the hydride migrated products (**35f, 35g, and 35h**) formed exclusively as observed with aromatic aldehyde. [183]

Scheme 87 Migratory Aptitude of Alkyl-Hydride Groups^{a,b}



^aReaction conditions: **36** (2.0-8.0 mmol), **6** (4.0-16.0 mmol), $\text{HBF}_4 \cdot \text{OEt}_2$ (0.4-1.6 mmol), CH_2Cl_2 (10-15 mL) at -78 °C to rt for 3 days. ^bThe ratios of the products are calculated after isolation.

In summary, we investigated the reaction of less explored benzophenone/aliphatic ketones as well as aliphatic aldehydes with EDA employed as the reaction partner. The distinct reactivity between carbonyl compounds and EDA has allowed the incorporation of a diverse range of substituent patterns into the product formation. Depending on the migratory aptitudes of hydride, alkyl, phenyl, and aryl groups, a wide range of 3-oxo-esters are formed. We anticipate that these valuable synthons will further prove its utility in preparing important building blocks of biologically active natural and synthetic compounds.

5.4 General methods and experimental

5.4.1 General Procedure for the One-Pot Synthesis of 3-Oxo-Esters

For each experiment, carbonyl compounds (2.0-8.0 mmol, 1.0 equiv) was dissolved in 10-20 mL of freshly distilled dichloromethane under nitrogen at -78 °C. A Brønsted acid, HBF₄·OEt₂ catalyst (0.4-1.6 mmol, 0.2 equiv) was added, and the reaction mixture was stirred for 1 hour at the same temperature. Ethyl diazoacetate (EDA) (4.0-16.0 mmol, 2.0 equiv) was diluted in 5 mL of freshly distilled dichloromethane and added to the solution over a period of 0.5-1 h. Then, the reaction mixture was allowed to stir for 72 h at room temperature. After completion of the reaction, it was quenched by adding THF. The reaction mixture was filtered through a silica plug using dichloromethane as solvent and the solvent removed by rotary evaporation. Pure products were isolated by silica gel column chromatography with 0-10% ethyl acetate in hexane.

Ethyl 3-oxo-2,3-diphenylpropanoate (34a). [184a] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.37 g, 20%) from the reaction of benzophenone (1.25 g, 6.86 mmol, 1.0 equiv) and EDA (1.67 mL, 13.72 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.19 mL, 1.37 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 8.00 (d, *J* = 6.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47-7.32 (m, 7H), 5.66 (s, 1H), 4.25 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H).

Ethyl 3-oxo-3-phenyl-2-(p-tolyl)propanoate (34b) and ethyl 3-oxo-2-phenyl-3-(p-tolyl)propanoate (7b'). The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 13:1). The title product was isolated as a colorless oil (0.36 g, 21%) from the reaction of 4-methylbenzophenone (1.18 g, 6.01

mmol, 1.0 equiv) and EDA (1.45 mL, 12.02 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.17 mL, 1.20 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 7.98 (d, *J* = 10.0 Hz, 2H), 7.88 (d, *J* = 5.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.44 (q, *J* = 7.5 Hz, 4H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 10.0 Hz, 3H), 7.24 (d, *J* = 10.0 Hz, 2H), 7.18 (d, *J* = 5.0 Hz, 2H), 5.61 (s, 1H), 5.59 (s, 1H), 4.26-4.22 (m, 4H), 2.40 (s, 2H), 2.34 (s, 3H), 1.26 (t, *J* = 6.0 Hz, 6H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 193.5, 192.9, 169.0, 168.9, 144.5, 137.9, 135.8, 133.5, 133.3, 133.2, 130.0, 129.6, 129.4, 129.1, 128.9, 128.8, 128.8, 128.1, 66.1, 66.0, 61.7, 60.5, 60.2, 21.7, 21.2, 14.1, 14.0.

HRMS (ESI/Q-TOF): Calculated (m/z) for C₁₈H₁₉O₃ (M+H)⁺ : 283.1329, Found 283.1264.

Ethyl 2-(4-methoxyphenyl)-3-oxo-3-phenylpropanoate (34c) and ethyl 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanoate (34c'). [184a] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 9:1). The title product was isolated as a colorless oil (0.36 g, 22%) from the reaction of 4-methoxybenzophenone (1.15 g, 5.42 mmol, 1.0 equiv) and EDA (1.31 mL, 10.84 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.15 mL, 1.08 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 7.99-7.95 (m, 4H), 7.55 (t, *J* = 6.0 Hz, 2H), 7.44 (t, *J* = 6.0 Hz, 4H), 7.37-7.28 (m, 4H), 6.90 (d, *J* = 9.0 Hz, 4H), 5.58 (s, 1H), 5.57 (s, 1H), 4.24 (q, *J* = 7.5 Hz, 4H), 3.86 (s, 3H), 3.80 (s, 3H), 1.29-1.24 (m, 6H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 193.6, 191.8, 169.1, 169.0, 163.8, 159.4, 135.7, 133.4, 133.4, 131.3, 130.7, 129.5, 129.9, 128.8, 128.7, 128.6, 128.0, 125.0, 114.3, 113.9, 61.7, 60.3, 59.7, 55.5, 55.2, 14.1, 14.0.

Ethyl 3-(4-chlorophenyl)-3-oxo-2-phenylpropanoate (34d) and ethyl 2-(4-chlorophenyl)-3-oxo-3-phenylpropanoate (34d'). [184b] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 9:1). The title product was isolated as a colorless oil (trace amount) from the reaction of 4-chlorobenzophenone (1.21 g, 5.58 mmol, 1.0 equiv) and EDA (1.35 mL, 11.16 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.15 mL, 1.12 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 7.98-7.90 (m, 2H), 7.46-7.35 (m, 8H), 5.60 (s, 0.3H), 5.55 (s, 0.7H), 4.28-4.21 (m, 3H), 1.29-1.24 (m, 5H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 192.1, 168.5, 140.0, 134.0, 133.7, 132.7, 130.9, 130.3, 129.5, 129.1, 129.0, 128.9, 128.9, 128.8, 128.3, 128.2, 62.0, 61.9, 60.6, 59.7, 14.0.

Ethyl 2-(3,4-dimethylphenyl)-3-oxo-3-phenylpropanoate (34f). The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/dichloromethane = 1:1). The title product was isolated as a colorless oil (0.50 g, 30%) from the reaction of 3,4-dimethylbenzophenone (1.18 g, 5.61 mmol, 1.0 equiv) and EDA (1.36 mL, 10.22 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.15 mL, 1.12 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 7.49-7.31 (m, 6H), 7.15-7.07 (m, 2H), 5.24 (s, 1H), 4.38-4.24 (m, 2H), 2.24 (s, 3H), 2.28 (s, 3H), 1.21 (t, *J* = 7.5 Hz, 2H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 169.8, 168.2, 153.4, 152.2, 139.6, 138.3, 137.1, 136.9, 130.3, 130.2, 130.0, 130.0, 129.8, 129.7, 129.4, 129.2, 128.7, 128.6, 128.6, 127.1, 126.9, 126.4, 126.2, 124.8, 99.6, 99.5, 64.2, 19.8, 19.7, 13.8.

HRMS (ESI/Q-TOF): Calculated (*m/z*) for C₁₉H₂₁O₃ (M+H)⁺ : 297.1485; Found 297.1474.

Ethyl 2-(3,4-dimethoxyphenyl)-3-oxo-3-phenylpropanoate (34g). [184c] The compound was prepared according to the general procedure and purified by silica gel column chromatography (dichloromethane). The title product was isolated as a colorless oil (0.43 g, 28%) from the reaction of 3,4-dimethoxybenzophenone (1.15 g, 4.75 mmol, 1.0 equiv) and EDA (1.15 mL, 9.50 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.13 mL, 0.95 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 7.99 (d, *J* = 5.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 4H), 6.95 (d, *J* = 10.0 Hz, 2H), 6.86 (d, *J* = 10.0 Hz, 4H), 5.56 (s, 1H), 4.24 (q, *J* = 5.0 Hz, 4H), 3.89 (s, 3H), 3.87 (s, 3H), 1.27 (t, *J* = 5.0 Hz, 2H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 193.5, 169.0, 149.2, 149.0, 135.8, 133.5, 128.9, 128.7, 125.4, 122.1, 112.5, 111.2, 61.7, 60.0, 56.0, 55.8, 30.9, 14.1.

Ethyl 2-(naphthalen-2-yl)-3-oxo-3-phenylpropanoate (34h). The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 20:1). The title product was isolated as a colorless oil (0.34 g, 23%) from the reaction of 2-naphthyl phenyl ketone (1.08 g, 4.65 mmol, 1.0 equiv) and EDA (1.12 mL, 9.30 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.13 mL, 0.93 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 8.29 (s, 1H), 7.97-7.88 (m, 6H), 7.65-7.60 (m, 2H), 7.58-7.7.51 (m, 3H), 4.29-4.23 (m, 3H), 1.31 (t, *J* = 7.5 Hz, 3H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 196.7, 169.8, 137.9, 135.3, 134.8, 132.4, 132.3, 131.9, 130.1, 129.4, 128.4, 128.3, 127.8, 126.8, 125.8, 68.2, 61.1, 14.2.

HRMS (ESI/Q-TOF): Calculated (m/z) for C₂₁H₁₉O₃ (M+H)⁺ : 319.1329, Found 319.1365.

Ethyl 2-ethyl-3-oxopentanoate (35a). [184d] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.53 g, 52%) from the reaction of 3-pentanone (0.51 g, 5.92 mmol, 1.0 equiv) and EDA (1.43 mL, 11.84 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.16 mL, 1.18 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.09 (q, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 7.5 Hz, 1H), 2.49-2.42 (m, 2H), 1.78 (t, *J* = 7.5 Hz, 2H), 1.17 (t, *J* = 6.0 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H).

Ethyl 3-oxo-2-propylhexanoate (35b). The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.45 g, 50%) from the reaction of 4-heptanone (0.52 g, 4.53 mmol, 1.0 equiv) and EDA (1.43 mL, 9.06 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.13 mL, 0.91 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.15 (q, *J* = 7.5 Hz, 2H), 3.41 (t, *J* = 6.0 Hz, 1H), 2.52-2.43 (m, 2H), 1.82-1.78 (m, 2H), 1.59 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 6.0 Hz, 5H), 0.91-0.86 (m, 6H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 205.3, 169.9, 61.1, 58.9, 43.6, 30.2, 20.7, 16.9, 14.0, 13.8, 13.5.

HRMS (ESI/Q-TOF): Calculated (*m/z*) for C₁₁H₂₁O₃ (M+H)⁺ : 201.1485; Found 201.1478.

Ethyl 2-butyl-3-oxoheptanoate (35c). [184e] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.38 g, 47%) from the reaction of 5-nonanone

(0.51 g, 3.59 mmol, 1.0 equiv) and EDA (0.87 mL, 7.18 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.10 mL, 0.72 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 500 MHz): δ 4.14-4.11 (m, 2H), 3.36 (t, *J* = 7.5 Hz, 1H), 2.51-2.41 (m, 2H), 2.33 (t, *J* = 5.0 Hz, 1H), 1.78-1.75 (m, 2H), 1.51-1.47 (m, 2H), 1.27-1.24 (m, 3H), 1.22-1.18 (m, 3H), 0.85-0.81 (m, 6H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 205.3, 169.9, 61.0, 59.1, 42.4, 41.4, 29.5, 27.8, 25.9, 25.5, 22.3, 22.1, 14.0, 13.7.

Ethyl 2-acetylhexanoate (35d) and ethyl 2-methyl-3-oxoheptanoate (35d'). [184f] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.51 g, 55%) from the reaction of 2-hexanone (0.50 g, 4.99 mmol, 1.0 equiv) and EDA (1.20 mL, 9.98 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.14 mL, 1.0 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.24-4.20 (m, 4H), 3.53 (q, *J* = 7.5 Hz, 1H), 3.41 (t, *J* = 7.5 Hz, 1H), 2.63-2.48 (m, 1H), 2.25 (s, 3H), 1.85-1.81 (m, 2H), 1.61-1.57 (m, 3H), 1.36-1.28 (m, 15H), 0.94-0.91 (m, 6H).

¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 206.0, 203.4, 170.6, 169.9, 61.2, 59.9, 41.0, 29.5, 28.7, 27.9, 25.6, 22.4, 22.2, 14.1, 14.0, 13.8.

Ethyl 2-acetyldecanoate 35e [184g] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.36 g, 44%) from the reaction of 2-decanone (0.53 g, 3.39 mmol, 1.0 equiv) and EDA (0.89 mL, 6.78 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.09 mL, 0.68 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.21 (q, *J* = 7.5 Hz, 2H), 3.41 (t, *J* = 7.5 Hz, 1H), 2.23 (s, 3H), 1.85 (s, 2H), 1.31-1.27 (m, 15H), 0.89 (t, *J* = 6.0 Hz, 3H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 203.4, 170.0, 61.2, 60.0, 31.8, 29.3, 29.3, 29.2, 28.7, 28.2, 27.4, 22.6, 14.1, 14.1.

Ethyl 2-acetyldecanoate (35e'). The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.16 g, 20%) from the reaction of 2-decanone (0.53 g, 3.39 mmol, 1.0 equiv) and EDA (0.89 mL, 6.78 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.09 mL, 0.68 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 5.32 (s, 1H), 4.32-4.13 (m, 2H), 3.52 (q, *J* = 7.5 Hz, 2H), 2.24 (s, 3H), 1.62 (s, 4H), 1.38-1.36 (m, 13H), 1.38 (t, *J* = 7.5 Hz, 3H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 203.3, 170.0, 61.2, 60.0, 32.0, 29.3, 29.2, 28.7, 28.2, 27.4, 22.6, 14.1.

HRMS (ESI/Q-TOF): Calculated (m/z) for C₁₄H₂₇O₃ (M+H)⁺ : 243.1955; Found 243.1940.

Ethyl 5-methyl-3-oxohexanoate (35f). [184h] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil (0.56 g, 55%) from the reaction of 3-methylbutanal (0.51 g, 5.92 mmol, 1.0 equiv) and EDA (1.43 mL, 11.84 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.16 mL, 1.2 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.20-4.08 (m, 2H), 3.38 (s, 2H), 2.39 (d, *J* = 6.0 Hz, 2H), 2.18-2.11 (m, 1H), 1.25 (t, *J* = 6.0 Hz, 3H), 0.92-0.88 (m, 6H).

Ethyl 3-oxooctanoate (35g). [185f] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil with hexane (0.60 g, 62%) from the reaction of hexanal (0.52 g, 5.19 mmol, 1.0 equiv) and EDA (1.43 mL, 10.38 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.14 mL, 1.04 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.19 (q, *J* = 6.0 Hz, 2H), 3.42 (s, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.61-1.59 (m, 2H), 1.29-1.25 (m, 4H), 0.88-0.82 (m, 3H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 203.0, 167.3, 61.3, 49.3, 43.0, 31.9, 31.2, 29.7, 23.2, 22.7, 22.4, 14.1, 13.9.

Ethyl 3-oxodecanoate (35h). [184i] The compound was prepared according to the general procedure and purified by silica gel column chromatography (hexane/ethyl acetate = 50:1). The title product was isolated as a colorless oil with hexane (0.70 g, 82%) from the reaction of octanal (0.51 g, 3.98 mmol, 1.0 equiv) and EDA (0.96 mL, 7.96 mmol, 2.0 equiv) in the presence of HBF₄·OEt₂ (0.11 mL, 0.80 mmol, 0.2 equiv).

¹H NMR (CDCl₃, 300 MHz): δ 4.91 (q, *J* = 7.5 Hz, 2H), 3.16 (s, 1H), 2.28 (t, *J* = 7.5 Hz, 1H), 1.32 (s, 2H), 1.03-0.98 (m, 15H), 0.62 (d, *J* = 6.0 Hz, 6H).

¹³C{¹H} NMR (CDCl₃, 75 MHz): δ 201.7, 166.5, 88.2, 60.1, 48.3, 41.9, 31.0, 28.4, 28.3, 28.3, 22.7, 21.9, 13.2, 13.2.

References for Chapter 1-Part B

- 146 (a) H. J. Liu and S. P. Majumdar, On the regioselectivity of boron trifluoride catalysed ring expansion of cycloalkanones with ethyl diazoacetate, *Synth. Commun.*, **1975**, *5*, 125–130; (b) W. L. Mock and M. Hartman, Synthetic scope of the triethyloxonium ion catalysed homologation of ketones with diazoacetic esters, *J. Org. Chem.*, **1977**, *42*, 459–465; (c) V. Dave and E. W. Warnhoff, Regiospecific homologation of unsymmetrical ketones, *J. Org. Chem.*, **1983**, *48*, 2590–2598; (d) C. R. Holmquist and E. J. Roskamp, A Selective Method for Diazoacetate Catalysed the Direct Conversion of Aldehydes into β -Keto Esters with Ethyl by Tin(II) Chloride, *J. Org. Chem.*, **1989**, *54*, 3258–3260; (e) C. R. Holmquist and E. J. Roskamp, Tin (II) chloride catalysed addition of diazo sulfones, diazo phosphine oxides, and diazo phosphonates to aldehydes, *Tetrahedron Lett.*, **1992**, *33*, 1131–1134; (f) A. Padwa, S. F. Hornbuckle, Z. Zhang and L. Zhi, Synthesis of 1,3- Diketones Using α -Diazo Ketones and Aldehydes in the Presence of Tin(II) Chloride, *J. Org. Chem.*, **1990**, *55*, 5297– 5299; (g) S. G. Sudrik, B. S. Balaji, A. P. Singh, R. B. Mitra and H. R. Sonawane, Zeolite-mediated Synthesis of β -Keto Esters: Condensation of Ethyl Diazoacetate with Aldehydes, *Synlett*, **1996**, 369–370; (h) K. Nomura, T. Iida, K. Hori and E. Yoshii, Synthesis of γ -unsubstituted α -acyl- β -tetronic acids from aldehydes, *J. Org. Chem.*, **1994**, *59*, 488–490.
- 147 M. Redlich, S. J. Mahmood, M. F. Mayer and M. M. Hossain, Silica Supported Catalysis: A Practical use of an Iron Lewis Acid, *Synth. Commun.*, **2000**, *30*, 1401– 1411.
- 148 S. Kanemasa, T. Kanai, T. Araki and E. Wada, Lewis acid catalysed reactions of ethyl diazoacetate with aldehydes. Synthesis of α -formyl esters by a sequence of aldol reaction and 1,2-nucleophilic rearrangement, *Tetrahedron Lett.*, **1999**, *40*, 5055–5058.
- 149 D. Benito-Garagorri, J. Wiedermann, M. Pollak, K. Mereiter and K. Kirchner, Iron(II) Complexes Bearing Tridentate PNP Pincer-Type Ligands as Catalysts for the Selective Formation of 3-Hydroxyacrylates from Aromatic Aldehydes and Ethyldiazoacetate, *Organometallics*, **2007**,

26, 217–222. 150 L. G. Alves, G. Dazinger, L. F. Veiros and K. Kirchner, Unusual Anion Effects in the Iron–Catalysed Formation of 3–Hydroxyacrylates from Aromatic Aldehydes and Ethyl Diazoacetate, *Eur. J. Inorg. Chem.*, **2010**, 3160–3166.

151 M. R. Fructos, M. M. Díaz-Requejo and P. J. Pérez, Highly active gold-based catalyst for the reaction of benzaldehyde with ethyl diazoacetate, *Chem. Commun.*, **2009**, 5153–5155. 22 K. J. Kilpin, U. S. D. Paul, A.-L. Lee and J. D. Crowley, Gold (I) “click” 1,2,3-triazolyldienes: Synthesis, self-assembly and catalysis, *Chem. Commun.*, **2011**, 47, 328–330.

152 M. E. Dudley, M. M. Morshed, C. L. Brennan, M. S. Islam, M. S. Ahmad, M.-R. Atuu, B. Branstetter and M. M. Hossain, Acid-Catalysed Reactions of Aromatic Aldehydes with Ethyl Diazoacetate: An Investigation on the Synthesis of 3-Hydroxy-2-arylacrylic Acid Ethyl Esters, *J. Org. Chem.*, 2004, **69**, 7599–7508

153 (a) G. Dazinger and K. A. Kirchner, Acid catalysed coupling of aromatic aldehydes and methyl diazoacetate—a theoretical mechanistic study, *New J. Chem.*, **2012**, 36, 781–788, (b) F. Xiao, Y. Liu and J. Wang, DBU-catalysed condensation of acyldiazomethanes to aldehydes in water and a new approach to ethyl β -hydroxy α -arylacrylates, *Tetrahedron Lett.*, **2007**, 48, 1147–1149.

154 (a) T. Akiyama, J. Ishida, S. Nakagawa, H. Ogawara, S. Watanabe, N. Itoh, M. Shibuya and Y. Fukami, Genistein, a Specific Inhibitor of Tyrosine-Specific Protein Kinases, *J. Biol. Chem.*, **1987**, 262, 5592–5595; (b) J. Markovits, C. Linassier, P. Fossé, J. Couprie, J. Pierre, A. Jacquemin-Sablon, J.-M. Saucier, J.-B. L. Pecq and A. K. Larsen, Inhibitory Effects of the Tyrosine Kinase Inhibitor Genistein on Mammalian DNA Topoisomerase II, *Cancer Res.*, **1989**, 49, 5111–5117.

155 M. H. Cynamon and G. H. Wilcox, The Role of 4-quinolones in the Treatment of Infections, *Compr. Ther.*, **1987**, 13, 37–43.

- 156 S. Heeb, M. P. Fletcher, S. R. Chhabra, S. P. Diggle, P. Williams and M. Cámara, Quinolones: from antibiotics to autoinducers, *FEMS Microbiol. Rev.*, **2011**, *35*, 247–274.
- 157 (a) Z.-P. Xiao, P.-C. Lv, S.-P. Xu, T.-T. Zhu and H.-L. Zhu, Synthesis, Antiproliferative Evaluation, and Structure– Activity Relationships of 3–Arylquinolines, *Chem. Med. Chem*, **2008**, *3*, 1516–1519; (b) A. Monastyrskyi, D. E. Kyle and R. Manetsch, 4(1H)-Pyridone and 4(1H)-Quinolone Derivatives as Antimalarials with Erythrocytic, Exoerythrocytic, and Transmission Blocking Activities, *Curr. Top. Med. Chem.*, **2014**, *14*, 1693–1705; (c) L. Huang, M.-C. Hsieh, C.-M. Teng, K.-H. Lee and S.-C. Kuo, Synthesis and antiplatelet activity of phenyl quinolones, *Bioorg. Med. Chem.*, **1998**, *6*, 1657–1662.
- 158 S. Fiorucci, X. Lin, K. Sadoul, G. Fournet, D. Bouvard, O. Vinogradova, B. Joseph and M. R. Block, Targeting Integrin-Dependent Adhesion and Signaling with 3-Arylquinoline and 3-Aryl-2-Quinolone Derivatives: A new Class of Integrin Antagonists, *PLoS One*, **2015**, *10*, e0141205, DOI: 10.1371/journal.pone.0141205.
- 159 M. Croisy, C. Huel and E. Bisagni, Synthesis of 3-(4-methoxyphenyl)-5,7-dimethoxy-(1H)-quinolin-2- or 4-ones and derivatives, *Heterocycles*, **1997**, *45*, 683–690.
- 160 (a) J. R. Atack, GABAA Receptor Subtype-Selective Modulators. II. α 5-Selective Inverse Agonists for Cognition Enhancement, *Curr. Top. Med. Chem.*, **2011**, *11*, 1203– 1214; (b) R. W. Olsen, Chapter Seven - Allosteric Ligands and Their Binding Sites Define γ -Aminobutyric Acid (GABA) Type A Receptor Subtypes, *Adv. Pharmacol.*, **2015**, *73*, 167–202.
- 161 U. Rudolph and F. Knoflach, Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes, *Nat. Rev. Drug Discovery*, **2011**, *10*, 685–697.

- 162 G. Guerrini, G. Ciciani, S. Daniele, L. D. C. Mannelli, C. Ghelardini, C. Martini and S. Selleri, Synthesis and pharmacological evaluation of pyrazolo[1,5-a]pyrimidin-7 (4H)-one derivatives as potential GABAA-R ligands, *Bioorg. Med. Chem.*, **2017**, 25, 1901–1906.
- 163 (a) H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, N. Inouye, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq and T. Miyasaka, Synthesis and Antiviral Activity of 6-Benzyl Analogs of 1-[(2-Hydroxyethoxy)methyl]-5-(phenylthio) thymine (HEPT) as Potent and Selective AntiHIV-1 Agents, *J. Med. Chem.*, **1995**, 38, 2860–2865; (b) T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R. T. Walker, J. Balzarini and E. De Clercq, A novel lead for specific anti-HIV-1 agents: 1-[(2-hydroxyethoxy) methyl]-6-(phenylthio)thymine, *J. Med. Chem.*, **1989**, 32, 2507–2509.
- 164 C. K. Chu, F. D. Boudinot, S. F. Peek, J. H. Hong, Y. Choi, B. E. Korba, J. L. Gerin, P. J. Cote, B. C. Tennant and Y. C. Cheng, Preclinical Investigation of L-FMAU as an Anti-Hepatitis B Virus Agent, *Antiviral Ther.*, **1998**, 3, 113– 121.
- 165 A. C. Krueger, J. T. Randolph, D. A. DeGoey, P. L. Donner, C. A. Flentge, D. K. Hutchinson, D. Liu, C. E. Motter, T. W. Rockway, R. Wagner, D. W. A. Beno, G. Koev, H. B. Lim, J. M. Beyer, R. Mondal, Y. Liu, W. M. Kati, K. L. Longenecker, A. Molla, K. D. Stewart and C. J. Maring, Aryl uracil inhibitors of hepatitis C virus NS5B polymerase: Synthesis and characterization of analogs with a fused 5,6-bicyclic ring motif, *Bioorg. Med. Chem. Lett.*, **2013**, 23, 3487–3490.
- 166 Y. Sekino, S. D. Bruner and G. L. Verdine, Selective Inhibition of Herpes Simplex Virus Type-1 Uracil-DNA Glycosylase by Designed Substrate Analogs, *J. Biol. Chem.*, **2000**, 275, 36506–36508.

- 167 (a) C. H. Heidelberger, N. K. Chaudhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Plevin and J. Scheiner, Fluorinated Pyrimidines, A New Class of Tumour-Inhibitory Compounds, *Nature*, **1957**, *179*, 663–666; (b) E. De Clercq, Potential of bromovinyldeoxyuridine in anticancer chemotherapy, *Anticancer Res.*, **1986**, *6*, 549–556.
- 168 M. M. Morshed, Q. Wang, S. Islam and M. M. Hossain, Convenient Synthesis of 5-Aryl Uracils, *Synth. Commun.*, **2007**, *37*, 4173–4181.
- 169 W. H. Davies and H. A. Piggott, A novel pyrimidine synthesis. Part I. 4-Amino-5-phenylpyrimidine, *J. Chem. Soc.*, **1945**, 347–351.
- 170 Y.-L. Liu, X.-H. Xu and F.-L. Qing, Synthesis of vinyl and electron-deficient aryl trifluoromethyl sulfides via Csp²–OH bond activation with AgSCF₃ and n-Bu₄NI/KI, *Tetrahedron*, **2018**, *74*, 5827–5832.
- 171 (a) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani and E. J. Lien, Aromatic substituent constants for structure-activity correlations, *J. Med. Chem.*, **1973**, *16*, 1207–1216; (b) C. Hansch, A. Leo and R. W. Taft, A survey of Hammett substituent constants and resonance and field parameters, *Chem. Rev.*, **1991**, *91*, 165–195.
- 172 M. Diaferia, F. Veronesi, G. Morganti, L. Nisoli and D. P. Fioretti, Efficacy of toltrazuril 5% suspension (Baycox®, Bayer) and diclazuril (Vecoxan®, Janssen-Cilag) in the control of *Eimeria* spp. in lambs, *Parasitol. Res.*, **2013**, *112*, 163–168.
- 173 D. B. Gant, A. E. Chalmers, M. A. Wolff, H. B. Hoffman and D. F. Bushey, Fipronil: action at the GABA receptor, *Rev. Toxicol.*, **1998**, *2*, 147–156.
- 174 J. F. Giudicelli, C. Richer and A. Berdeaux, Preliminary assessment of flutorex, a new anorectic drug, in man, *Br. J. Clin. Pharmacol.*, **1976**, *3*, 113–121

- 175 R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, Thermodynamic and kinetic data for macrocycle interaction with cations, anions, and neutral molecules, *Chem. Rev.*, 1995, 95, 2529–2586.
- 176 J. S. Bradshaw and R. M. Izatt, Crown ethers: the search for selective ion ligating agents, *Acc. Chem. Res.*, **1997**, 30, 338–345.
- 177 G. W. Gokel, W. M. Leevy and M. E. Weber, Crown Ethers: Sensors for Ions and Molecular Scaffolds for Materials and Biological Models, *Chem. Rev.*, **2004**, 104, 2723–2750.
- 178 Ç. Erk, Cation Recognition with fluorophore crown ethers, *Ind. Eng. Chem. Res.*, **2000**, 39, 3582–3588.
- 179 M. Bulut and Ç. L. Erk, The synthesis of novel crown ethers, part IX, 3-phenyl chromenone-crown ethers, *J. Heterocycl. Chem.*, **2001**, 38, 1291–1295.
- 180 Curtin, D. Y.; Crew, M. C. Migration ratios in the rearrangement of 2-amino-1,1-diarylethanols. *J. Am. Chem. Soc.* **1954**, 76, 3719–3722.
- 181 Brown, H. C.; Kim, C. J. Structural effects in solvolytic reactions. III. Nature of the intermediate involved in the solvolysis of 3-aryl-2,3-dimethyl-2-butyl derivatives. *J. Am. Chem. Soc.* **1968**, 90, 2082–2096.
- 182 House, H.; Grubbs, E. J.; Gannon, W. F. The reaction of ketones with diazomethane. *J. Am. Chem. Soc.* **1960**, 82, 15, 4099–4106.
- 183 Holmquist, C. R.; Roskamp, E. J. A selective method for the direct conversion of aldehydes into. beta.-keto esters with ethyl diazoacetate catalyzed by tin(II) chloride. *J. Org. Chem.* **1989**, 54, 3258–3260.

- 184 (a) Zeng, L.; Lai, Z.; Cui, S. One-pot reaction of carboxylic acids and ynol ethers for the synthesis of β -keto esters. *J. Org. Chem.* **2018**, *83*, 14834–14841.
- 184 (b) Liang, Z.; Hou, W.; Du, Y.; Zhang, Y.; Pan, Y.; Mao, D.; Zhao, K. Oxidative aromatic C–O bond formation: synthesis of 3-functionalized benzo[b]furans by FeCl₃-mediated ring closure of α -aryl ketones. *Org. Lett.* **2009**, *11*, 4978–4981.
- 184 (c) Zoeller, J. R.; Ackerman, C. J. Reduction of α -diketones and α -keto esters with hydrogen iodide in acetic anhydride-acetic acid. *J. Org. Chem.* **1990**, *55*, 1354–1356.
- 184 (d) Mageswaran, S.; Sultanbawa, M. U. S. A stereospecific route to trisubstituted olefins via β -lactones. *J. Chem. Soc. Perkin Trans. 1* **1976**, 884–890.
- 184 (e) Filloux, C. M.; Rovis, T. Rh(I)–Bisphosphine-catalyzed asymmetric, intermolecular hydroheteroarylation of α -substituted acrylate derivatives. *J. Am. Chem. Soc.* **2015**, *137*, 508–517.
- 184 (f) Liu, X.; Li, X.; Wang, Z.; Zhou, J.; Fan, X.; Fu, Y. Biosynthesis of α -substituted β -ketoesters via the tandem Knoevenagel condensation–reduction reaction using a single enzyme. *ACS Sustainable Chem. Eng.* **2020**, *8*, 8206–8213.
- 184 (g) Davis, J. M.; Truong, A.; Hamilton, A. D. Synthesis of a 2,3';6',3''-Terpyridine Scaffold as an α -Helix Mimetic. *Org. Lett.*, **2005**, *7*, 5405–5408. 184 (h) Ganeshapillai, D.; Woo, L. W. L.; Thomas, M. P.; Purohit, A.; Potter, B. V. L. C-3- and C-4-Substituted bicyclic coumarin sulfamates as potent steroid sulfatase inhibitors. *ACS Omega* **2018**, *3*, 10748–10772.
- 184 (i) Galleano, I.; Schiedel, M.; Jung, M.; Madsen, A. S.; Olsen, C. A. A continuous, fluorogenic sirtuin 2 deacylase assay: substrate screening and inhibitor evaluation. *J. Med. Chem.* **2016**, *59*, 1021–1031.

Part C: Exploring 18-Crown-6-ether complex as a Bronsted Acid catalyst

6.1 Introduction

Macrocyclic ether containing scaffolds have been used to estimate cationic recognition and selective cation binding using different physical approaches such as filtration, absorption etc. [175-177] which was used for the detection of cations such as Li^+ , Na^+ , K^+ , and Rb^+ as well as perchlorates by the help of fluorescence spectroscopy. [178-179] Several crown ether complexes have been synthesized so far because of its synthetic application in different fields such as trapping metal ion in commercial waste container, as an additive in the asymmetric synthesis, to prepare soluble ionic liquids etc.

A class of commercially available 18-crown-6 ether is shown in the **Figure 14A**. As part of our ongoing research on the synthesis and reactivity of 18-crown-6 ether cationic complexes, we have recently isolated the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 as their hydronium cationic salts using Tf_2NH super acids for the first time. However, this type of complexes was separated before using K^+ and NH_4^+ as a choice of cation. The uniqueness of this isolation of such crown complexes with specific geometry of cyclohexyl group may distinctly function for synthetic applications (**Figure 14B**).

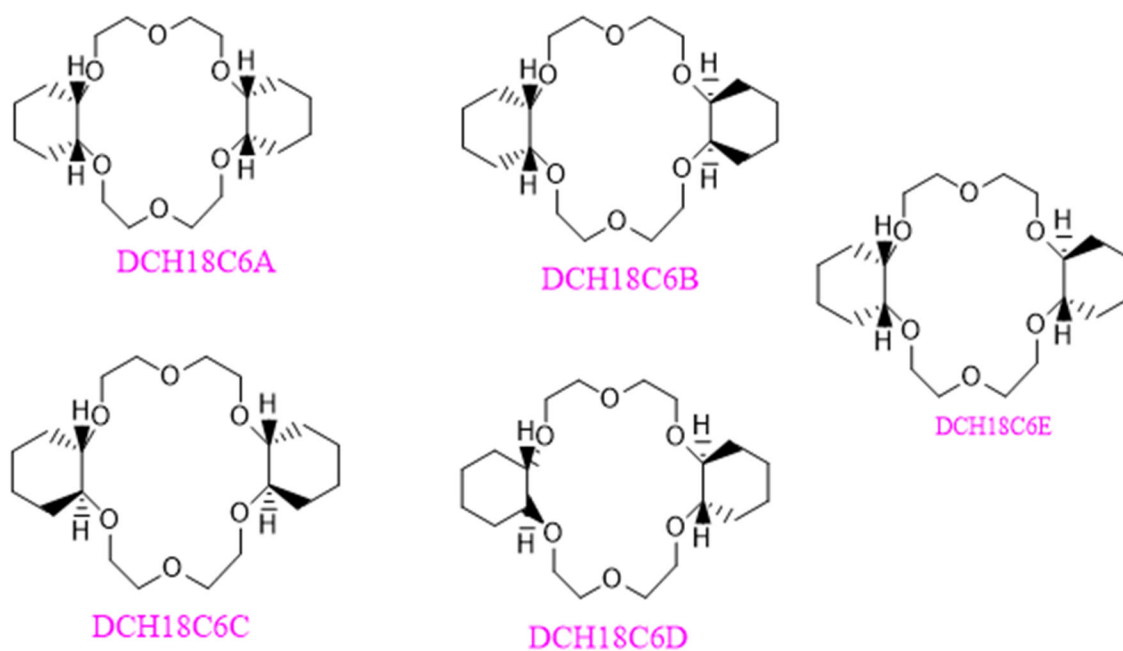
There are data in the literature for the stability constants of the *cis-syn-cis* and *cis-anti-cis* isomers of dicyclohexano-18-crown-6 with different alkali- and alkaline-earth metal cation salts in water and in methanol, [185-188] and for potassium picrate in dichloromethane (picrate = 2,4,6-trinitrophenolate). [189] However, explanation of the effect of the pendent hydronium ion as an available proton source (which is related to the association constant) instead of alkali metal has remained underdeveloped. In 1995 Bartsch et al introduced an excellent approach for more

accessibility of one form of coordinated hydrogen compared to other. [190] It should be added that host-guest association in organic media of low polarity imposes requirements different from those found for the association in polar solvents.

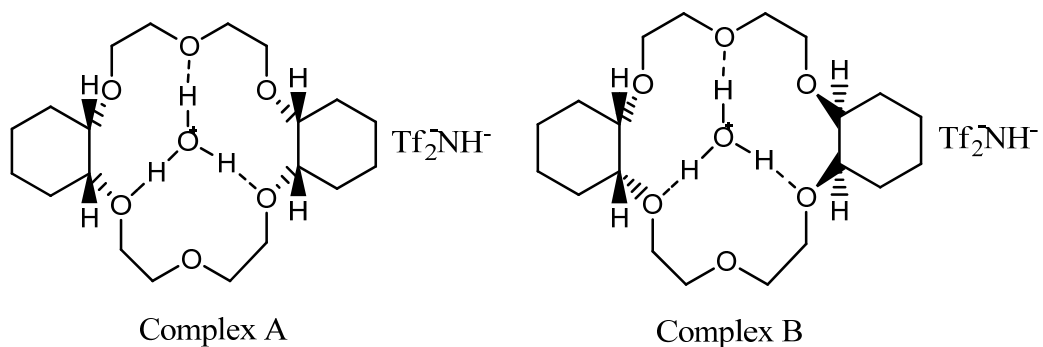
To understand the influence of stereochemical availability of proton, we decided to screen our complexes as a proton donor (Brønsted acid) catalyst in an organic reaction. In 2004, Hossain's group reported a coupling reaction of Ethyl diazoacetate (EDA) with aromatic aldehyde in presence of tetrafluoroboric acid diethyl ether complex ($\text{HBF}_4 \cdot \text{OEt}_2$) as a Brønsted acid catalyst. [132] We plan to study the same coupling reaction by replacing $\text{HBF}_4 \cdot \text{OEt}_2$ with our crown complex A/B to determine the catalytic strength and scope of this reaction in organic synthesis. In

Figure 14 Commercially available predominant isomers of Dicyclohexyl-18-crown-6-ether complexes

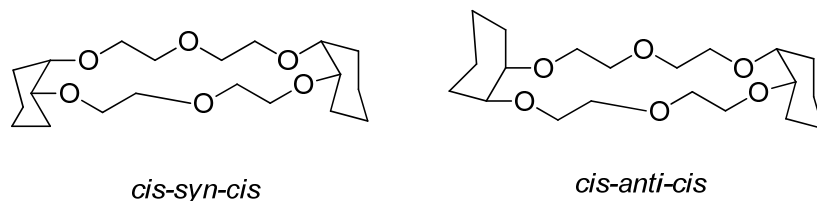
(A)



B) Isolated protonated complex having specific geometrical structures



C) Geometry of the crown ether before protonation



this regard, we investigated the reaction of EDA with different aromatic aldehydes in the presence of complex A and complex B (**Scheme 88**). We focused mainly on the accessibility of the hydrogen ion of the complex instead of optimizing the percentage yield of the reaction. Therefore different equivalent of complex A and B have been explored instead of choosing different solvent systems or coupling partners.

6.2 Results and Discussions

The results obtained from the screening of both complex A and complex B has summarized in Table 14. At room temperature, in the presence of 0.12 equiv of complex A, benzaldehyde with 2 equiv of EDA provided a decent percentage of yield (52%) of hydroxy acrylate, **1a** (Table 14,

Scheme 88 Preparation of 3-hydroxy-2-aryl acrylates from the reaction of aromatic aldehydes and EDA catalyzed by complex A and complex B

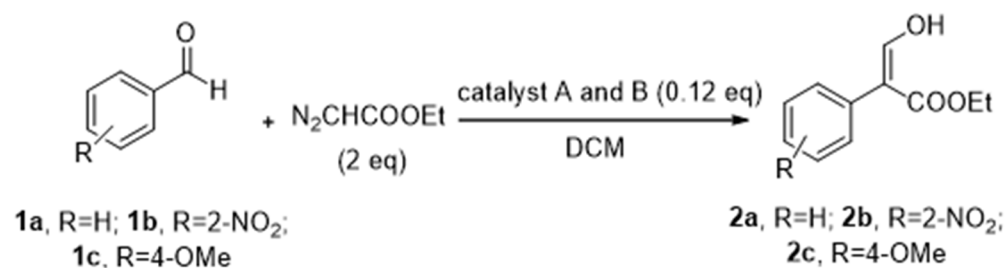


Table 14 Optimization results of effectivity of Crown-ether complex A and B on exploring coupling between EDA and Carbonyl compounds

Entry ^a	Carbonyl compound	Complex	Temp (°C)	3-hydroxyacrylate	% yield ^c
1	 1a	A	rt	 2a	52
2		A	0		28
3		A ^d	rt		51
4		A ^e	rt		10
5		B ^f	rt	2a	trace
6	 1b	A	rt	 2b	71
7		B	rt	2b	17
8 ^b	 1c	A	rt	 2c	N/R
9 ^b		B	rt	2c	N/R

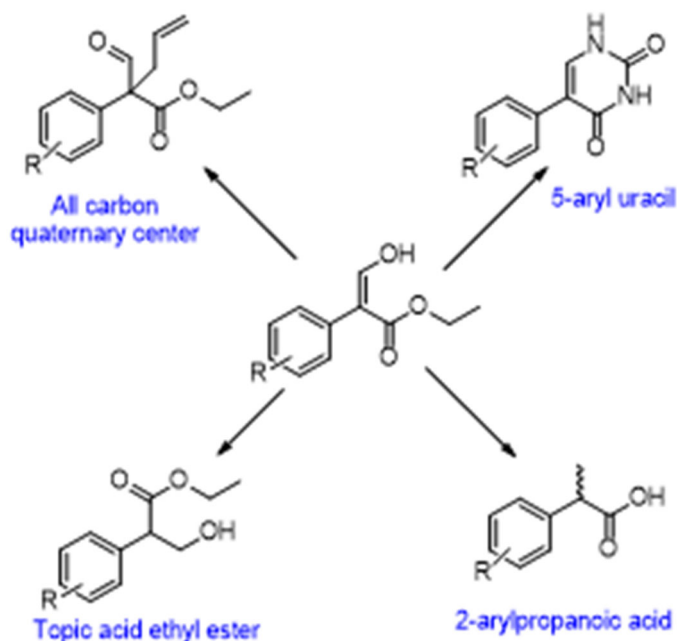
^a1 equiv of substrate was reacted with 2 equiv of EDA (added dropwise over 20-30 mins) in the presence of 0.12 equiv of catalyst complex and stirred for an additional 14h at that temperature unless otherwise stated. ^bthe reaction was allowed to stir for an additional 12h. ^c an unidentified compound was isolated about 5-10%. ^d0.25 equiv of catalyst A used. ^e0.05 equiv of catalyst A used. ^f 0.05, 0.12 & 0.25 equiv of catalyst B used.

entry 1). Lowering the temperature reduced the yield of the product to 28% (**Table 14**, entry 2). Increasing catalyst loading did not improve yield of the product (**Table 14**, entry 3 vs entry 1); whereas, decreasing amount of the catalyst loading from 0.12 equiv to 0.05 equiv significantly reduced the yield of the product (**Table 14**, entry 4 vs entry 1). Coupling reaction with benzaldehyde and EDA in the presence of Complex B resulted trace amount of **1a** (**Table 14**, entry 5). With complex A, electron rich *para*-methoxybenzaldehyde gave better yield (71%) of acrylate **2a** (**Table 14**, entry 6). We believe that happen due to formation of stable carbocation during the 1,2-aryl migration. Very poor yield of **2a** was obtained when the reaction was done with complex B (**Table 14**, entry 7). Electron deficient *ortho*-nitrobenzaldehyde provided no product of **3a** in presence of complex A or complex B (**Table 14**, entries 8-9). Compounds having electron withdrawing group might destabilized the carbocation during migration and resulted trace or no product formation. It should be added that use of benzophenone with both the complex A and B at -78-rt with the same reaction condition ended up with trace or no product.

Based on the mechanism proposed by Hossain et al, to start the reaction, protonation of carbonyl oxygen of benzaldehyde is required followed by the nucleophilic attack of EDA. [132] It is very likely that the carbonyl group of aromatic aldehydes could easily binds to the proton from the less crowded face of the *cis-syn-cis* of complex A, [190] which initiated the reaction to form the products. Whereas *cis-anti-cis* configuration of catalyst B may hinder the binding of the proton to the incoming carbonyl compounds. As a result, there was little, or trace amount of product formation was observed.

There are few catalysts known to give selective formation of 3-hydroxyacrylates from the reaction of aromatic aldehydes and EDA. [149-150] In most of the cases, the acrylates form along with β -keto esters⁴ or exclusively the latter compound. [191] Therefore, the use of crown ether complex A as a catalyst, would be an additional finding for the selective synthesis of acrylates. The possibility of preparing such prochiral molecules is pivotal for the synthesis of pharmaceutically important scaffold as shown in **Figure 15**. [192, 88]

Figure 15 Application of acrylate for the preparation of pharmaceutically important compounds



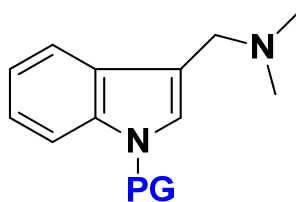
6.3 General procedure for the synthesis of 3-hydroxy arylacrylates

For each experiment, carbonyl compounds (3.5-8.0 mmol, 1.0 equiv) was dissolved in 10-20 mL of freshly distilled dichloromethane under nitrogen at -78 °C. A Brønsted acid, $\text{HBF}_4 \cdot \text{OEt}_2$ catalyst (0.18-2.0 mmol, 0.05-0.25 equiv) was added, and the reaction mixture was stirred for 1 hour at the same temperature. Ethyl diazoacetate (EDA) (7.0-16.0 mmol, 2.0 equiv) was diluted in 5 mL of freshly distilled dichloromethane and added to the solution over a period of 0.5-1 h. Then, the reaction mixture was allowed to stir for 24-72 h at room temperature (depending on the substrate- aromatic aldehydes have ran for 24 h and the ketones have run until up to 3 days). After completion of the reaction, it was quenched by adding THF and Na_2SO_4 had added to resolve the problem associated with unreacted EDA. The reaction mixture was filtered through a silica plug using dichloromethane as solvent and the solvent removed by rotary evaporation. Pure products were isolated by silica gel column chromatography with 5-20% ethyl acetate in hexane.

References

- 185 R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb and J. J. Christensen, Thermodynamic and kinetic data for cation-macrocyclic interaction, *Chem. Rev.*, **1985**, 85, 271-339.
- 186 H. K. Frensdorff, Salt complexes of cyclic polyethers. Distribution equilibria, *J. Am. Chem. Soc.*, **1971**, 93, 600.
- 187 R. M. Izatt, R. E. Terry, B. L. Haymore, L. D. Hansen, N. K. Dalley, A. G. Avondet and J. J. Christensen, Calorimetric titration study of the interaction of several uni- and bivalent cations with 15-crown-5, 18-crown-6, and two isomers of dicyclohexyl-18-crown-6 in aqueous solution at 25. °C and $\mu = 0.1$, *J. Am. Chem. Soc.*, **1976**, 98, 7620-7626.
- 188 R. M. Izatt, D. P. Nelson, J. H. Rytting, B. L. Haymore and J. J. Christensen, Calorimetric study of the interaction in aqueous solution of several uni- and bivalent metal ions with the cyclic polyether dicyclohexyl-18-crown-6 at 10, 25, and 40 °C. *J. Am. Chem. Soc.*, **1971**, 93, 1619-1623.
- 189 H. K. Frensdorff, *J. Am. Chem. Soc.*, **1971**, 93, 4684-4688
- 190 Batinic-Haberle, I.; Spasojevic, I.; Bartsch, A. R.; Alvin L. Crumbliss. Salt complexes of cyclic polyethers. Distribution equilibria, *J. Chem. Soc. Dalton Trans.* **1995**, 15, 2503-2508.
- 191 (a) Holmquist, C. R.; Roskamp, E. *J. Org. Chem.* **1989**, 54, 3258-3260. (b) Liao, M.; Jianbo Wang, *J. Tetrahedron Letters*. **2006**, 47, 8859-8861. (c) Jeyakumar, K.; Chand, D. K. *Synthesis*. **2008**, 11, 1685-1687.
- 192 (a) Atuu, M. R.; Mahmood, S. J.; Laib, F.; Hossain, M. M. *Tetrahedron Asym.* **2004**, 15, 3091-3101. (b) Mahmood, S. J.; Brennan, C. L.; Hossain, M. M. *Synthesis*. **2002**, 13, 1807-1809.

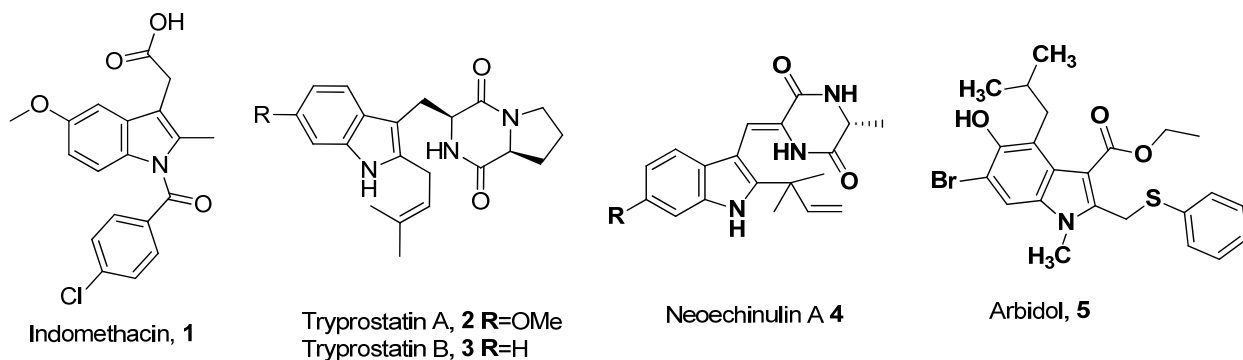
Chapter 2 Investigation of C2-alkylation of N-protected Gramine



7.1 Introduction

An indole core with an alkyl substituent in the C2-position serve as precursors for a variety of medicinally important alkaloids and their analogs.[193] Some of the representative examples are Indomethacin **1** (non-steroidal anti-inflammatory drug commonly used for the treatment of rheumatoid arthritis)[194], Tryprostatin A **2** (act as a breast cancer resistance protein inhibitor)[195] and Tryprostatin B **3** (act as a microtubule inhibitor)[196], Neoechinulin A **4** (shows anti-nitration, antioxidant and cytoprotective activity against peroxynitrite from SIN-1 in PC12 cells)[197], and Arbidol **5** (used the treatment of influenza infection)[198] (**Figure 16**). Due to the weak reactivity of the C–H bond at the C2-position of an indole and the possibility of metalation on the aromatic ring, C2–H alkylation of indoles are still challenging for chemists.[199] Therefore, strong bases like *n*BuLi, *sec*BuLi, *t*BuLi, LDA etc. was used as a deprotonation source to obtain information concerning the position of attack by this organometallic compound either on indole or some of its derivatives.

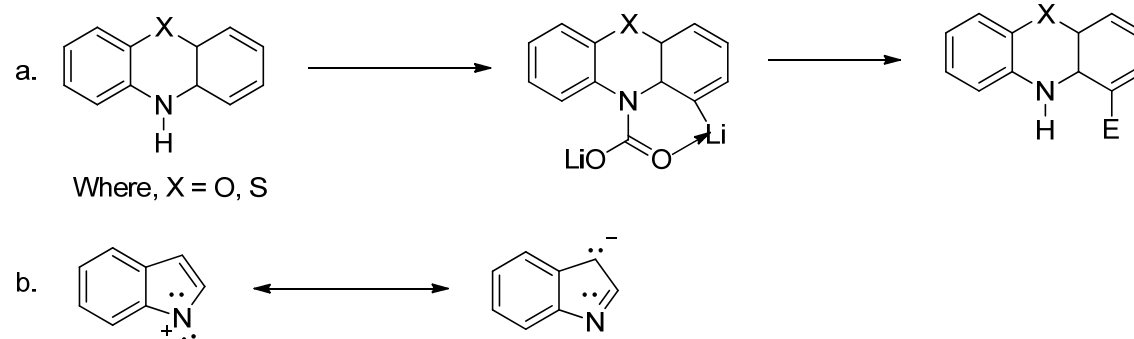
Figure 16 Important biologically active natural products containing C2-substituted indole moiety



7.1.1 Concepts on the C2-alkylation of Indole/ phenothiazine/N-carboxy protected indole

Gilman and Sengupta introduce the lithiation chemistry in hetero-cyclic nuclei, explained the way of metalation happen which is quite different from ordinary electrophilic substitution processes.[200] Treatment of the indole with excess (up to 4 equiv) of *n*-BuLi could not introduce anything next to the heteroatom nitrogen (at C2 position) which is in sharp contrast to the study based on carbazole. The reason is the more acidic proton of -N-H comes out first and thus the metalation are evident in that place. But Metalation of aromatic phenothiazine was successfully resulted due the introduction of carboxy group to the N-H to induce a lithiation on that position. As a result, they got an alkylation in C-1 position of the aromatic ring **Scheme 89a**. [201] Which means the presence of sulfur/oxygen might enhanced the acidity of the C1 proton and thus get alkylated. In case of less reactive indole, it is due to the stabilization of the anion shown in the following **Scheme 89b**.

Scheme 89 Stabilization of the indole ring due to resonance



The early attempt of carbamate strategy shown by Akutagawa et al in 1986, was basically a one pot method of preparing 2-substituted indole derivatives. [202] Indole was first converted to the lithium carbamate by sequential treatment with *n*-BuLi in THF, followed by CO₂. Then the

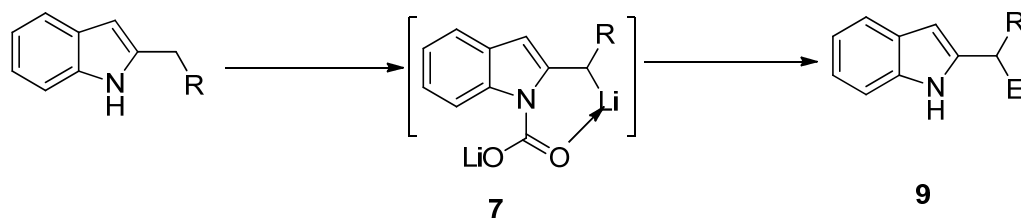
lithiation of the lithium carbamate at the C2 position was achieved with 1.2 equivalent of *t*-BuLi at -20 °C (Scheme 90). Addition of the electrophile at -70 °C and warming it up to room temperature for several hours primarily formed the crude product mixture. An aqueous acid treatment followed by gentle warming deprotected the product from CO₂ and thus gave the desired C2 substituted indoles **6** in good to excellent yield (52-86%)

Scheme 90 C2 alkylation of indole moiety after carboxy induce lithiation assistance



The interesting things to notice about the carbamate directed lithiation method is its expansion scope of alkylation to the β -aliphatic and β -aromatic carbons. Therefore, unlike other methods for directing lithiation the carbamate anion route is not restricted to those patterns where the carbanion present α to the nitrogen heteroatom and thus both the β -aliphatic and β -aromatic carbons have been successfully lithiated. For an instance when 2-alkylindoles **7** protected by lithium carbamate it can be lithiated on the α -carbon of the alkyl side chain which is β to the nitrogen to form product **9** as shown by exemplifying the following **Scheme 91**.

Scheme 91 C2 alkylation at the β -aliphatic position from the heteroatom (nitrogen)



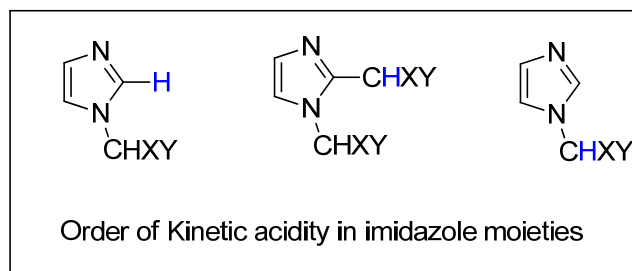
Even though the carbanion can be delocalized in to the 3-position of the indole ring to give

substitution at the C3 position, the only product observed at the aliphatic carbon. The addition of a substituent at the 3-position disfavors this delocalization and lithiation fails to occur with 2,3-dialkylindoles other than the exception of 2,3-dimethylindole. Because of the enhanced acidity of methyl groups compared to another alkyl permits deprotonation to occur.

Here the carbamate groups provide some assistance to lithiation by prior coordination to the lithiated species, but their main mode of action appears to be by dipole stabilization of the lithiated species once formed. The dipolar effect of the carbamate anions is not as strong as other systems such as nitrosamines, formamidines and oxazolidines and cannot be used for the asymmetric allylation as well. The advantage for the carbamates is their convenience (one pot procedure and available reagents) and versatility (for protection, main nucleophilic attack/reaction and deprotection) of accomplishing the completion of the reaction readily. The scope of the carbamate reaction is the electron rich heterocyclic system that can form relatively stable carbamate derivatives.

In brief a summary can be drawn from the above discussion that the formation of carbanion due to the deprotonation over the assistance of heteroatoms can occur in at least four distinct environments. One such example can be shown based on simple pyridine moiety.

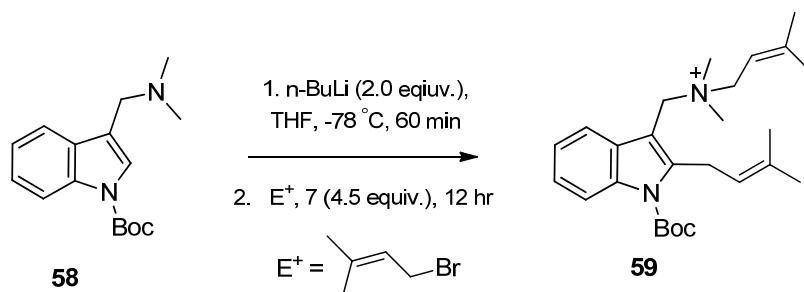
- a. A ring: CH which is α -to the heteroatom
- b. An exocyclic CHXY linkage attached α or γ to a pyridine-link nitrogen
- c. A CHXY directly attached to the pyrrole like link nitrogen atom
- d. The Ortho position of the aromatic ring α -to the ring nitrogen.



7.1.2 Precedence for C2-alkylation of BOC-protected gramine

A breakthrough came when the Hossain's group developed an unprecedented incorporation of prenyl group at the C-2 position of (3-(dimethylaminomethyl)indole) (commercially named as gramine) in 2019 during the concise total synthesis of Tryprostatin B (**Scheme 92**). [203] The idea was executed by using a BOC protection of the more acidic nitrogen of the indole ring and then by conducting the lithiation using *n*-BuLi as a base to pull out the proton from the C2 position.

Scheme 92 Precedence of C2-prenylation of BOC-protected Gramine

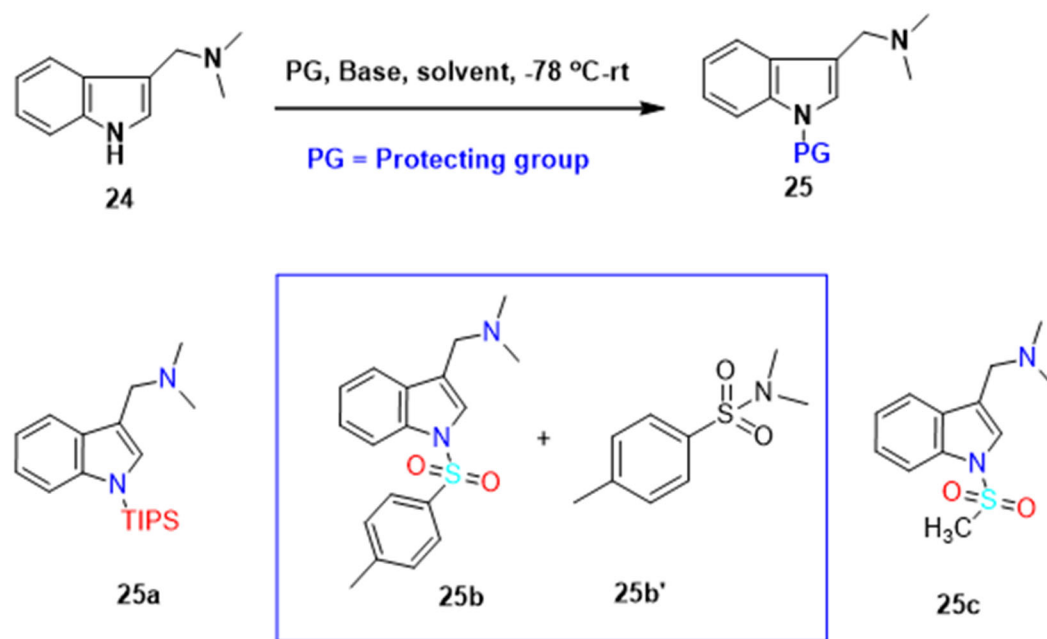


This unusual procedure opens a new window to explore a variety of N-protected gramine's to synthesize C2 substituted gramine salts by subsequent reactions with electrophiles which might be potentially effective for framing biologically and pharmaceutically important compounds. In our present research, we have examined several protecting groups and electrophiles to investigate the scope of this reaction and to probe the reaction mechanism.

7.2 Results and Discussions

At first, we decided to screen various N-protecting groups, make sure the effect of the protecting group on the C2-alkylation more precisely C-2 metalation. Our attempt of screening focused on the direct protection of the indole nitrogen of the commercially available compound **24** (**Scheme 93**). We believe there might be a directing effect of certain protecting group for inducing alkyl group exactly on the C2 position. One step protection using TIPS group resulted the desired compound **25a** with 84% yield but the product **25b** and **25c** obtained with very low yield. We therefore tried to confirm the reason why we are not getting the tosyl protection with better

Scheme 93 Protection of heteroatom nitrogen of gramine



Entry ^a	PG (1.1-1.2 equiv)	Solvent	Base (1.5-2 equiv)	Yield (%)
1	TIPS(TIPS-Cl)	DCM	NaH	84
2	Tosyl (TsCl)	ACN	NaH	18
3	Mesyl (MsCl)	ACN	NaH	21

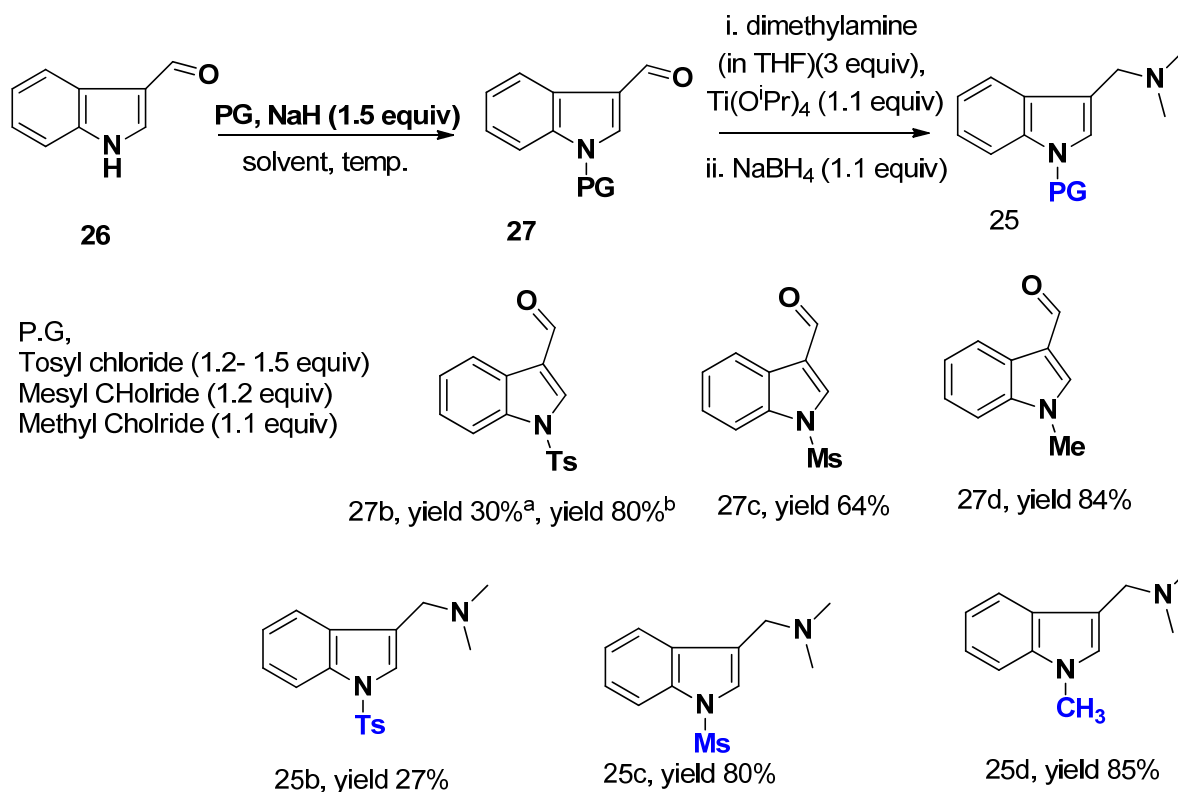
^aAll reactions have carried out from 4-8 mmol scale, NaH added at -78 °C and the protecting reagents have added after 45-60 minutes and the reactions brought to the room temperature, each reactions have done several times

conversion. We have observed that during preparing the N-tosyl gramine the reaction also forming another compound N,N-dimethyl sulfonamide **25b'** 35% of isolated yield which means compound **25b** is not stable under strong basic condition. The base NaH might pull the electron next to the tertiary amine nitrogen heteroatoms and forcing the pair of electrons throughout the aromatic system to finally retouch the tosyl group to form such byproduct **25b'**.

Therefore, we decided to explore a new route to protect the indole-3-carboxaldehyde compound **26** first and then to convert that to gramine by reductive amination reaction. It should be mentioned that commercially there are very few gramine is available with different substituent on the aromatic ring but if we can prepare gramine from Indole 3-carboxaldehyde it would be beneficial for exploring lot of gramine analogues. Initially, we considered three protecting group -Ts, -Ms and -Me (**Scheme 94**); out of that methyl gave a very good productivity of 80% isolated yield (compound **27d**). For the mesyl protection we obtained about 64% of desired product, **27c** but the tosyl protection was limited to 30% product **27a** formation. We then thought to switch the base from NaH to relatively mild organic base DIPEA for tosyl protection and successfully isolated 80% of the product **27b**. Surprisingly the reductive amination to form N-protected gramine did not work good with the tosyl protection and obtained **25b** with 27% isolated yield, but the reaction went well with mesyl and methyl protections.

After getting couple of N-protected gramine compounds in hand we started studying the C2-alkylation using prenyl bromide and benzyl bromide as electrophile in presence of *n*-BuLi as

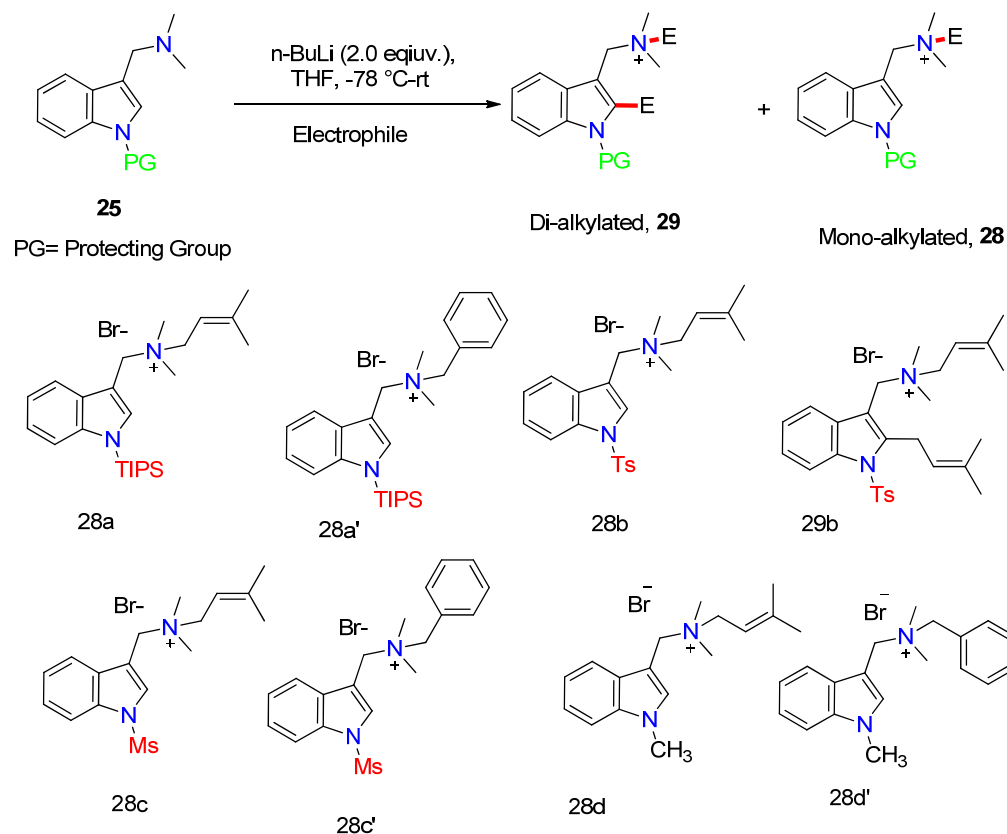
Scheme 94 Two-step alternative route to prepare N-protected gramine



^aused NaH as a base, ^bused DIPEA (1.5 equiv), DMAP (0.05 mol%) as a base

a lithiating agent (**Scheme 95**). It is expected that the monoalkylated salt would form first due to the lone pair electron of nitrogen on the amine and then the nucleophilic C2 carbon attacks the electrophile to form C-C bond by the extrusion of the leaving group. Surprisingly, we have got only monoalkylated salt (**28a**, **28c**, **28d**) for methyl and TIPS, mesityl protected gramine even we have screened different equivalent of *n*-BuLi (from 2-4 equiv). It should be mentioned that Iwao et al reported lithiation at C-2 position by using N-methyl tyramine in the presence of *t*BuLi in ether at 0 °C. [204] The anomaly of the two findings may be because of the use of stronger base and different type of electrophiles than us. However, tosyl protection gave a mixture of monoalkylated product **28b** and **28b'** which could not be separated successfully by column chromatography.

Scheme 95 C2-alkylation of N-protected gramine



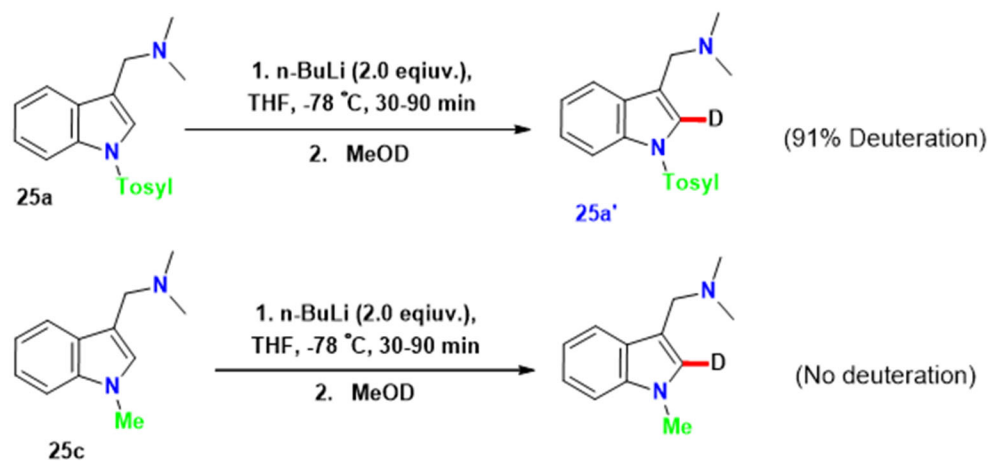
Entry ^a	PG	Electrophile	cpd 28 : cpd 29 (Overall yield%)
1	TIPS	Prenyl bromide	100 : 0 (60%)
		Benzyl bromide	100 : 0 (56%)
2	Tosyl	Prenyl bromide	65 : 35 (40%)
3	Mesityl	Prenyl bromide	100 : 0 (44%)
		Benzyl bromide	100 : 0 (35%)
4	Methyl	Prenyl bromide	100 : 0 (64%)
		Benzyl bromide	100 : 0 (52%)

^aall reactions have carried out from 2-5 mmol quantity, *n*-BuLi was added at -78 °C and the protecting reagent had added after 60-90 minutes of lithiation, overnight

Then we decided to do a deuteration study to see whether the proton from C2 had pulled out by the base or it remains intact even after introducing a strong base like *n*-BuLi. Running the study with

N-Me gramine we have seen no deuteration even after 24 h waiting after quenched with MeOD. Similar reaction was performed with the N-tosyl gramine and *n*-butyllithium in THF, quenching with MeOD, location of the deuterium incorporation was calculated by analysis of the mass spectrum and ^1H NMR (Scheme 96 and SI). In ^1H NMR, the singlet of the C-2 position for H was diminished by the incorporation of D and the percentage of D incorporation was calculated 91% based on ^1H NMR.

Scheme 96 Deuteration study of N-tosyl and N-Me protected gramine



In summary, we have so far got some idea about the assistance of the protecting group especially the tosyl group which has similar nature like CO₂ in indole protection. Therefore, the lone pair on the oxygen present in the tosyl group might help initial lithiation then the electrophilic attack on that specific position. Methyl group on the other side should show the assistance but it is not happening may be because of the less donating and non-resonating methyl group instead of the aromatic participation of the phenyl group. The idea also justified when the methyl protection did not work with the procedure. However, the bulkiness of the TIPS group could not direct the lithiation rather stopped that completely.

7.3 General methods and experimental

7.3.1 General procedure for the N-protection of gramine

20 ml of DCM was added to 1 gm (5-10 mmol, 1 equiv) 1-(1H-indol-3-yl)-N,N-dimethylmethanamine and stirred for 5 minutes to dissolve. Then the bright yellow solution brought to -78 °C using dry ice-acetone bath. By the time the solution reached the desired temperature, we have washed the NaH (containing mineral oil) by hexane and weighed 0.275-0.30 g (11.46 mmol, 2.0-2.1 equiv). Added the NaH to the reaction flask and stirred for an hour at -78 °C. Then we have added 6.876 mmol, 1.2 equiv protecting reagent all at once. The reaction was monitored by TLC for completion and the desired product 25 was isolated by column chromatography using 10-20% EtOAc in hexane as oily liquid.

Synthesis of N,N-dimethyl-1-(1-(triisopropylsilyl)-1H-indol-3-yl)methanamine (25a)

20 ml of DCM was added to 1 gm (5.73 mmol, 1 equiv) 1-(1H-indol-3-yl)-N,N-dimethylmethanamine and stirred for 5 minutes to dissolve. Then the bright yellow solution brought to -78 °C using dry ice-acetone bath. By the time the solution reached the desired temperature, we have washed the NaH (containing mineral oil) by hexane and weighed 0.275 g (11.46 mmol, 2.0 equiv). Added the NaH to the reaction flask and stirred for an hour at -78 °C. Then we have added 1.33 g (6.876 mmol, 1.2 equiv) triisopropylsilyl chloride all at once. The reaction was monitored by TLC for completion and 1.60 g of the desired product 25a was isolated by column chromatography using 10-20% EtOAc in hexane as a light beige oily liquid.

¹H NMR (CDCl₃, 500 MHz): δ 7.70 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.18 (m, s, 1H), 7.16 (dd, *J* = 10 Hz, 5 Hz, 2H), 3.66 (s, 2H), 2.30 (s, 6H), 1.78 – 1.71 (m, 3H), 1.67 (d, *J* = 10 Hz, 18H).

¹³C NMR (CDCl₃, 75 MHz): δ 141.3, 131.4, 130.5, 121.4, 119.6, 119.2, 115.1, 113.9, 54.7, 18.2, 12.9.

N,N-dimethyl-1-(1-tosyl-1H-indol-3-yl)methanamine (25b)

20 ml of acetonitrile was added to 1 gm (5.73 mmol, 1 equiv) 1-(1H-indol-3-yl)-N,N-dimethylmethanamine and stirred for 5 minutes to dissolve. Then the solution was brought to -78 °C using dry ice-acetone bath. By the time the solution reached the desired temperature, we have washed the NaH (containing mineral oil) by hexane and weighed 0.275 g (11.46 mmol, 2.0 equiv). Added the NaH to the reaction flask and stirred for an hour at -78 °C. Then we have added 1.31 g (6.876 mmol, 1.2 equiv) 4-toluenesulfonyl chloride all at once. The reaction was monitored by TLC for completion and 0.34 g of the desired product 25b was isolated by column chromatography using 20-30% EtOAc in hexane as a brown oily liquid.

¹H NMR (CDCl₃, 300 MHz): δ 8.03 (d, *J* = 9.0 Hz, 1H), 7.76 (t, *J* = 9.0 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.54 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 6.0 Hz, 2H), 3.52 (s, 2H), 2.23 (s, 6H), 2.21 (s, 3H).

N,N-dimethyl-1-(1-methyl-1H-indol-3-yl)methanamine (25c)

20 ml of acetonitrile was added to 1 gm (5.73 mmol, 1 equiv) 1-(1H-indol-3-yl)-N,N-dimethylmethanamine and stirred for 5 minutes to dissolve. Then the solution was brought to -78 °C using dry ice-acetone bath. By the time the solution reached the desired temperature, we have washed the NaH (containing mineral oil) by hexane and weighed 0.275 g (11.46 mmol, 2.0 equiv). Added the NaH to the reaction flask and stirred for an hour at -78 °C. Then we have added 0.43 ml (6.876 mmol, 1.2 equiv) methyl iodide dropwise within 5 minutes. The reaction

was monitored by TLC for completion and 0.23 g of the desired product 25a was isolated by column chromatography using 5-15% EtOAc in hexane as colorless oil.

¹H NMR (CDCl₃, 500 MHz): d 7.92 (d, *J* = 10.0 Hz, 1H), 7.76 (d, *J* = 10.0 Hz, 1H), 7.41-7.32 (m, 3H), 3.69 (s, 2H), 3.10 (s, 3H), 2.31 (s, 6H).

¹³C NMR (CDCl₃, 75 MHz): δ 135.4, 130.9, 125.0, 124.4, 123.5, 120.6, 120.1, 113.1, 54.5, 50.5, 45.6, 44.6, 40.6.

7.3.2 General procedure for preparing N-protected 1H-indole-3-carbaldehyde 26

To a 20 ml of DCM solvent, we have added 1g (6.84 -13.7 mmol, 1 equiv) of 1H-indole-3-carbaldehyde 26. After dissolving the starting material completely, we put the solution in a dry ice acetone bath to set up the temperature at -78 °C. Then 0.25-0.30 g (10.3-12.0 mmol, 1.5-1.8 equiv) of NaH was added after washing it with hexane. We let the reaction run for an hour and half and then started adding 0.47 -1.20 mL (7.52 -10.25 mmol, 1.1-1.5 equiv) of protecting reagent dropwise. The reaction left overnight for completion and quenched with water. The crude was then separated in 2 later. The organic layer was collected, and the aq. layer washed with DCM two more time. All the organic fractional gathered and rotavap. The crude was clean enough to carry out the next step.

Synthesis of 1-tosyl-1H-indole-3-carbaldehyde (27b)

To a 20 ml of DCM solvent, we have added 1g (6.84 mmol, 1 equiv) of 1H-indole-3-carbaldehyde 26. After dissolving the starting material completely, we put the solution in a dry ice acetone bath to set up the temperature at -78 °C. Then 0.25 g (10.3 mmol, 1.5-1.8 equiv) of NaH was added after washing it with hexane. We let the reaction run for an hour and half and then started adding 1.20 ml (8.20 mmol, 1.2 equiv) of Tosyl chloride dropwise. The reaction left overnight for completion and quenched with water. The crude was then separated in 2 later. The organic layer was collected, and the aq. layer washed with DCM two more time. All the organic fractional gathered and rotavap. The crude was clean enough to carry out the next step.

¹H NMR (CDCl₃, 300 MHz): δ 10.1 (s, 1H), 8.37 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H) 7.45-7.31 (m, *J* = 4H), 2.37 (s, 3H).

Synthesis of 1-(methylsulfonyl)-1H-indole-3-carbaldehyde (27c)

To a 20 ml of DCM solvent, we have added 1g (6.84 mmol, 1 equiv) of 1H-indole-3-carbaldehyde 26. After dissolving the starting material completely, we put the solution in a dry ice acetone bath to set up the temperature at -78 °C. Then 0.25 g (10.3 mmol, 1.5-1.8 equiv) of NaH was added after washing it with hexane. We let the reaction run for an hour and half and then started adding 0.64 ml (8.20 mmol, 1.2 equiv) of methyl iodide dropwise. The reaction left overnight for completion and quenched with water. The crude was then separated in 2 later. The organic layer was collected, and the aq. layer washed with DCM two more time. All the organic fractional gathered and rotavap. The crude was clean enough to carry out the next step.

¹H NMR (CDCl₃, 500 MHz): δ 10.1 (s, 1H), 8.37 (d, *J* = 10.0 Hz, 2H), 8.14 (s, 1H), 7.92 (d, *J* = 5.0 Hz, 1H) 7.53-7.46 (m, *J* = 2H), 3.31 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 186.5, 186.0, 138.3, 137.8, 125.9, 124.7, 123.6, 122.2, 122.00, 121.0, 118.7, 112.8, 111.7, 40.3.

Synthesis of 1-methyl-1H-indole-3-carbaldehyde (27d)

To a 20 ml of DCM solvent, we have added 1g (6.84 mmol, 1 equiv) of 1H-indole-3-carbaldehyde 26. After dissolving the starting material completely, we put the solution in a dry ice acetone bath to set up the temperature at -78 °C. Then 0.25 g (10.3 mmol, 1.5 equiv) of NaH was added after washing it with hexane. We let the reaction run for an hour and half and then started adding 0.47 ml (7.52 mmol, 1.1 equiv) of methyl iodide dropwise. The reaction left overnight for completion

and quenched with water. The crude was then separated in 2 later. The organic layer was collected, and the aq. layer washed with DCM two more time. All the organic fractional gathered and rotavap. The crude was clean enough to carry out the next step.

¹H NMR (CDCl₃, 500 MHz): δ 10.3 (s, 1H), 8.34 (d, J = 10.0 Hz, 2H), 7.71 (s, 1H), 7.40-7.28 (m, 3H), 3.90 (s, 3H).

¹³C NMR (CDCl₃, 75 MHz): δ 184.4, 139.1, 125.3, 124.0, 123.0, 122.1, 118.1, 108.9, 33.7.

7.3.3 General procedure for the reductive amination of N-protected 1H-indole-3-carbaldehyde 27

500 mg – 1000 mg of compound 27 (b-d) was added in 15-20 ml of MeOH solvent and brought it to 0 °C by using an ice bath. When dissolved, 3 equiv of dimethylamine (in 2M THF) solution was added all at once. The reaction ran for 3 - 4 h and added monitored by TLC until the starting material disappear. While done with the TLC monitoring 1.1 equiv. of NaBH₄ was added slowly in 3 portions within 5 minutes. The reduction then ran for 1 hour for completion. The reaction was quenched with water, methanol was removed by rotary evaporation and the organic fraction had separated by extracting with EtOAc. The crude obtained as an oily liquid then purified with MeOH: DCM (1:50) solvent mixture.

NMR for the final product 25a, 25b and 25c has attached to appendix A.

7.3.4 General procedure for C2 alkylation of Gramine

Synthesis of N,N,3-trimethyl-N-((2-(3-methylbut-2-en-1-yl)-1-tosyl-1H-indol-3-yl)methyl)but-2-en-1-aminium (**28b/28b'**)

A solution of N,N-dimethyl-1-(1-(methylsulfonyl)-1H-indol-3-yl)methanamine **25** (0.50 – 1.0 mmol) in THF (15 mL) was taken in three necked round bottomed flask and nitrogen was bubbled through the solution for 20 min. This mixture was cooled to -78 °C and n-butyl lithium (0.40–0.72 mL, 1.0 – 2.0 mmol, 2 equiv) (2.5 M in hexane) was added dropwise to the reaction mixture maintaining a temperature -78 °C over a period of 1 h under nitrogen atmosphere. Then the electrophile (2.25-6.0 mmol, 4.5-6.0 equiv) was added to the reaction dropwise through the dropping funnel over a period of 30 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. After consumption of the starting material, as judged by TLC analysis, water (5 mL) was added to the reaction mixture and THF was removed under reduced pressure. The mixture was then extracted with CH₂Cl₂ (3 x 15 mL), the combined organic layers were washed with brine solution (1 x 10 mL) and dried over anhydrous Na₂SO₄ and evaporated in vacuo to obtain crude product. The residue was purified with flash column chromatography on silica gel (DCM/MeOH = 25/1) to afford mixture of either monoalkylated product **28** or a mixture of mono/dialkylated products (**28/29**).

Synthesis of N,N,3-trimethyl-N-((1-tosyl-1H-indol-3-yl)methyl)but-2-en-1-aminium bromide 28b/ N,N,3-trimethyl-N-((2-(3-methylbut-2-en-1-yl)-1-tosyl-1H-indol-3-yl)methyl)but-2-en-1-aminium bromide 29b

A solution of N,N-dimethyl-1-(1-tosyl-1H-indol-3-yl)methanamine 25b (0.2 g, 0.61 mmol) in THF (15 mL) was taken in three necked round bottomed flask and nitrogen was bubbled through the solution for 20 min. This mixture was cooled to -78 °C and n-butyl lithium (0.47 mL, 1.22 mmol, 2 equiv) (2.5 M in hexane) was added dropwise to the reaction mixture maintaining a temperature -78 °C over a period of 1 h under nitrogen atmosphere. Prenyl bromide (0.32 mL, 2.745 mmol) was added to the reaction dropwise through the dropping funnel over a period of 30 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. After consumption of the starting material, as judged by TLC analysis, water (5 mL) was added to the reaction mixture and THF was removed under reduced pressure. The mixture was then extracted with CH₂Cl₂ (3 x 15 mL), the combined organic layers were washed with brine solution (1 x 10 mL) and dried over anhydrous Na₂SO₄ and evaporated in vacuo to obtain crude product. The residue was purified with flash column chromatography on silica gel (DCM/MeOH = 25/1) to afford mixture of 28b/29b as a brown oily liquid (27 %).

¹H NMR (CDCl₃, 300 MHz): δ 8.24 – 8.21 (m, 1H), 8.22 (d, *J* = 3.0 Hz, 1H), 8.10 (d, *J* = 3.0 Hz, 2H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 5.35 (t, *J* = 10.5 Hz, 1H), 5.17 (s, 2H), 5.10 (s, 1H), 4.49 (d, *J* = 9.0 Hz, 2H), 3.93 (s, 2H), 3.47 (s, 2H), 3.10 (s, 6H), 2.37 (s, 3H), 2.08 (d, *J* = 12 Hz, 3H), 1.87 (d, *J* = 6.0 Hz, 6H), 1.79 (s, 3H), 1.64 (s, 3H), 1.27 (s, 6H), 0.91 (d, *J* = 9.0 Hz, 3H)

Synthesis of N-benzyl-N,N-dimethyl-1-(1-(triisopropylsilyl)-1H-indol-3-yl)methanaminium bromide (28a')

A solution of N,N-dimethyl-1-(1-(triisopropylsilyl)-1H-indol-3-yl)methanamine **25a** (0.2 g, 0.61 mmol) in THF (15 mL) was taken in three necked round bottomed flask and nitrogen was bubbled through the solution for 20 min. This mixture was cooled to -78 °C and n-butyl lithium (0.47 mL, 1.22 mmol, 2 equiv) (2.5 M in hexane) was added dropwise to the reaction mixture maintaining a temperature -78 °C over a period of 1 h under nitrogen atmosphere. Prenyl bromide (0.32 mL, 2.745 mmol) was added to the reaction dropwise through the dropping funnel over a period of 30 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. After consumption of the starting material, as judged by TLC analysis, water (5 mL) was added to the reaction mixture and THF was removed under reduced pressure. The mixture was then extracted with CH₂Cl₂ (3 x 15 mL), the combined organic layers were washed with brine solution (1 x 10 mL) and dried over anhydrous Na₂SO₄ and evaporated in vacuo to obtain crude product. The residue was purified with flash column chromatography on silica gel (DCM/MeOH = 25/1) to afford mixture of **28b/29b** as a brown oily liquid (56 %).

¹H NMR (CDCl₃, 500 MHz): δ 7.93 (d, *J* = 10.0 Hz, 1H), 7.74 (s, 1H), 7.69 (d, *J* = 10.0 Hz, 2H), 7.54 (d, *J* = 10.0 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.20 (t, *J* = 7.5 Hz, 2H), 5.31 (s, 2H), 5.24 (s, 2H), 3.17 (s, 6H), 1.78-1.69 (m, 3H), 1.14 (d, 18H)

¹³C NMR (CDCl₃, 75 MHz): δ 141.2, 137.1, 133.4, 129.1, 127.8, 122.6, 121.6, 119.3, 114.5, 104.6, 67.0, 60.8, 48.2, 18.1, 12.7.

Synthesis of N,N,3-trimethyl-N-((1-methyl-1H-indol-3-yl)methyl)but-2-en-1-aminium bromide (28d)

A solution N,N-dimethyl-1-(1-methyl-1H-indol-3-yl)methanamine 25d (0.2 g, 1.06 mmol) in THF (15 mL) was taken in three necked round bottomed flask and nitrogen was bubbled through the solution for 20 min. This mixture was cooled to -78 °C and n-butyl lithium (0.82 mL, 2.12 mmol, 2 equiv) (2.5 M in hexane) was added dropwise to the reaction mixture maintaining a temperature -78 °C over a period of 1 h under nitrogen atmosphere. Benzyl bromide (0.57 mL, 4.77 mmol, 4.5 equiv) was added to the reaction dropwise through the dropping funnel over a period of 30 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. After consumption of the starting material, as judged by TLC analysis, water (5 mL) was added to the reaction mixture and THF was removed under reduced pressure. The mixture was then extracted with CH₂Cl₂ (3 x 15 mL), the combined organic layers were washed with brine solution (1 x 10 mL) and dried over anhydrous Na₂SO₄ and evaporated in vacuo to obtain crude product. The residue was purified with flash column chromatography on silica gel (DCM/MeOH = 25/1) to afford mixture of 28b/29b as a brown oily liquid (52.1 %).

¹H NMR (CDCl₃, 500 MHz): δ 7.63 – 7.34 (m, 9H), 5.35 (s, 1H), 5.05 (s, 1H), 4.52 (s, 6H), 3.73 (s, 2H), 2.55 (s, 3H)

¹³C NMR (CDCl₃, 75 MHz): δ 137.8, 137.0, 134.6, 133.3, 122.5, 121.2, 119.4, 109.9, 100.6, 66.7, 61.4, 53.5, 47.9, 33.7.

References for Chapter 2

- 193 (a) Sundberg, R. J.; Smith, F. X. *J. Org. Chem.* **1975**, *40*, 2613. (b) Sundberg, R. J.; Luis, J. G.; Parton, R. L.; Schreiber, S.; Srinivasan, P. C.; Lamb, P.; Forcier, P.; Bryan, R. F. *J. Org. Chem.* **1978**, *43*, 4859. (c) Mohan, B.; Nagarathnam, D.; Vedachalam, M.; Srinivasan, P. C. *Synthesis* **1985**, 188. (d) Hashimoto, C.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 4563. (e) Dolušić, E.; Larrieu, P.; Blanc, S.; Sapunaric, F.; Norberg, B.; Moineaux, L.; Colette, D.; Stroobant, V.; Pilotte, L.; Colau, D.; Ferain, T.; Fraser, G.; Galeni, M.; Frère, J.-M.; Masereel, B.; Eynde, B. V. D.; Wouters, J.; Frédérick, R. *Bioorg. Med. Chem.* **2011**, *19*, 1550.
- 194 Ferreira, S.; Moncada, S.; Vane, J. Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nat. New Biol.* **1971**, *231*, 237–239.
- 195 Woehlecke, H.; Osada, H.; Herrmann, A.; Lage, H. Reversal of breast cancer resistance protein-mediated drug resistance by tryprostatin A. *International journal of cancer*, **2003**, *107*, 721-728.
- 196 (a) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 527– 533. (b) Usui, T.; Kondoh, M.; Cui, C.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543– 548.
- 197 Kimoto K.; Aoki T.; Shibata Y.; Kamisuki S.; Sugawara F.; Kuramochi K.; Nakazaki A.; Kobayashi S.; Kuroiwa K.; Watanabe N.; Arai T. *The Journal of antibiotics.* **2007**, *60*, 614-21.
- 198 Leneva, I. A.; Russell, R. J.; Boriskin, Y. S.; Hay, A. J. *Antiviral Res.* **2009**, *81*, 132-140.
- 199 For regioelective Friedel–Crafts alkylation of indole at the C2-position, see: (a) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438-15439. Formal C2-alkylation by Pd-mediated Heck-type intramolecular reaction, see: (b) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904-7905. (c) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.
- 200 (a) H. Gilman, D. A. Shriley and P. R. V. Ess.-‘Progress in Heterocyclic Chemistry: A critical Review of 1988 Literature’, Chapter: New Strategies in Lithiation Chemistry (b) A. R. Katritzky, J. N. Lam and S. Sengupta –‘Some New Strategies for Protection, Activation and Direction in Lithiation Chemistry’- Chapter 1, University of Florida, Gainesville, FL, USA and G. W. Rewcastle, University of Auckland, New Zealand.

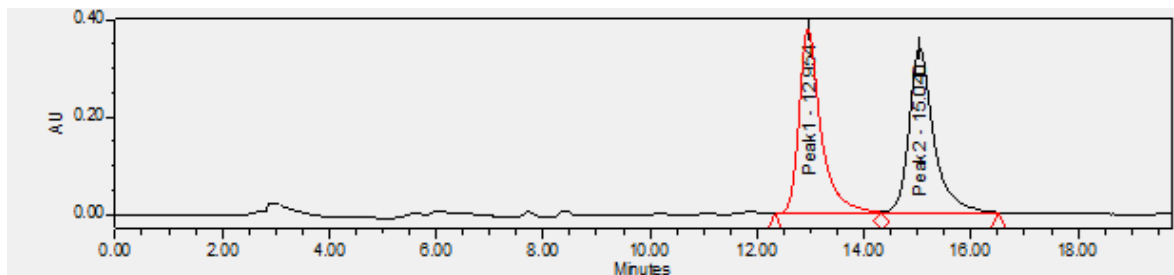
- 201 R. Katritzky, L. M. V. D. Miguel, and G. W. Rewcastle, Specific Synthesis of 1-Substituted Phenothiazines Using Carbon Dioxide Protection of the NH Group During Lithiation, *Synthesis*, 1988, 215.
- 202 A. R. Katritzky and K. Akutagawa, Carbon dioxide: a reagent for simultaneous protection of nucleophilic centers and the activation of alternative locations to electrophilic attack. V. Activation of the 2-alkyl group of a 2-alkylindole toward proton loss and subsequent electrophilic substitution, *J. Am. Chem. Soc.*, **1986**, 108, 6808.
- 203 M. Huisman, M. Rahaman, S. Asad, S. Oehm, S. Novin, A. L. Rheingold, M. M. Hossain, Total Synthesis of Tryprostatin B: Synthesis and Asymmetric Phase-Transfer-Catalyzed Reaction of Prenylated Gramine Salt, *Org. Lett.* **2019**, 21, 134–137.
- 204 Iwao, M. Directed Lithiation of 1-Triisopropylsilylgramine. A Short Access to 3,4-Disubstituted Indoles, *Heterocycles*, **1993**, 36, 29-32.

APPENDIX A
HPLC, NMR, HPLC DATA

HPLC data of compound 2 (Method A)

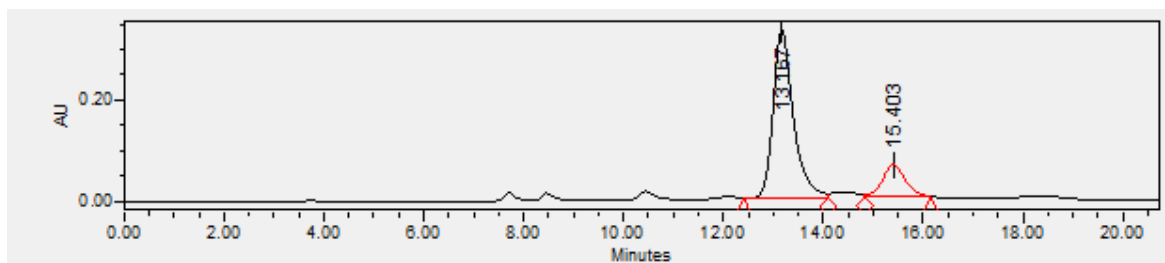
Enantiomeric excess (ee) was determined by using HPLC with a chiral stationary phase. Stationary phase (AD column, flow rate = 1.0 mL/min, eluent: hexane/EtOH = 19/1, λ = 254 nm). t_R major = 13.2 min, t_R minor = 15.4 min, e.r. = 82.7 :17.3.

Racemic:



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	Peak1	12.954	10845787	50.03	379082	BV			Found	Q20
2	Peak2	15.040	10833499	49.97	337769	VB			Found	Q20

Chiral:

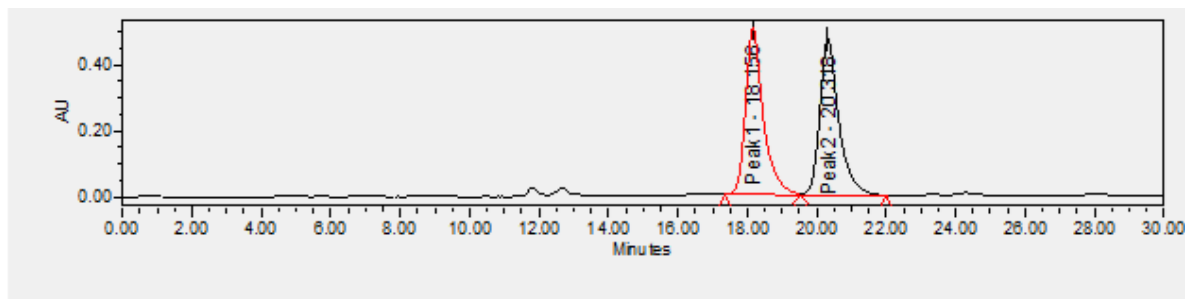


	Name	Retention Time	Area	% Area	Height	Int Type	Peak Type
1	Peak1	13.167	9263994	82.69	332254	bV	Found
2	Peak2	15.403	1938723	17.31	63495	Vb	Found
	Total		11202717	100.00	395749		

After Single Crystallization:

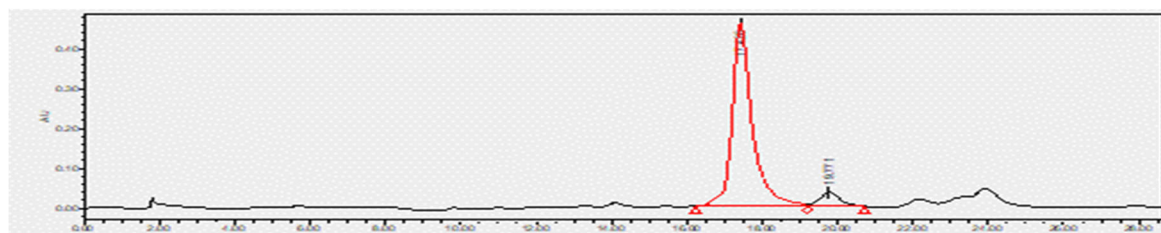
Enantiomeric excess (ee) was determined by using HPLC with a chiral stationary phase. Stationary phase (AD column, flow rate = 1.0 mL/min, eluent: hexane/EtOH = 19/1, λ = 254 nm), t_R major = 13.2 min, t_R minor = 15.4 min, e.r. = 93:7.

Racemic:



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	Peak1	18.156	17885089	49.98	503376	BV			Found	Q20
2	Peak2	20.318	17900723	50.02	472642	VB			Found	Q20

Chiral:

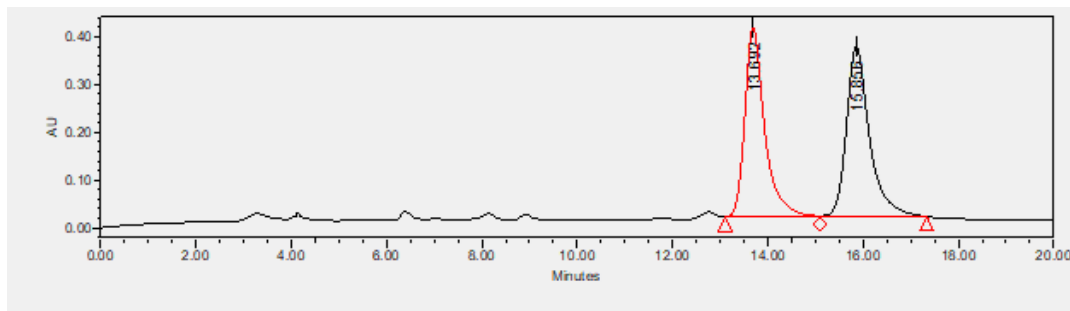


	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	Peak1	17.426	17161826	92.93	458382	bV			Unknown	
2	Peak2	19.771	1306303	7.07	34491	Vb			Unknown	

HPLC data of compound 2 (Method B):

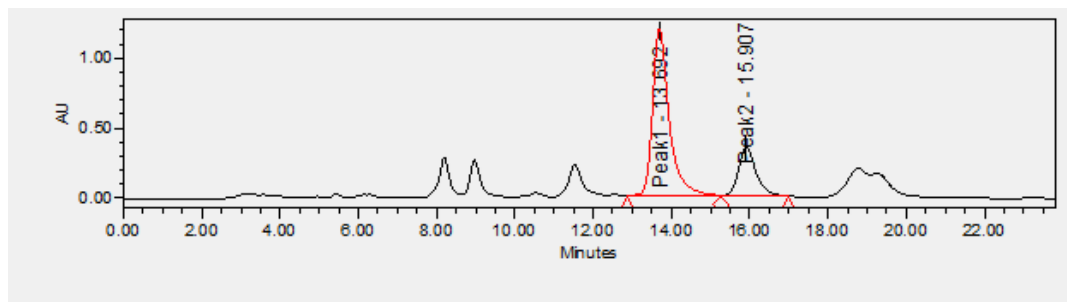
Enantiomeric excess (ee) was determined by using HPLC with a chiral stationary phase. Stationary phase (AD column, flow rate = 1.0 mL/min, eluent: hexane/EtOH = 19/1, λ = 254 nm). t_R major = 13.6 min, t_R minor = 15.6 min, e.r. = 78.5:21.5.

Racemic:



	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	Peak1	13.692	11624523	49.13	398915	BV			Found	Q20
2	Peak2	15.856	12036146	50.87	356665	Vb			Found	Q20

Chiral:

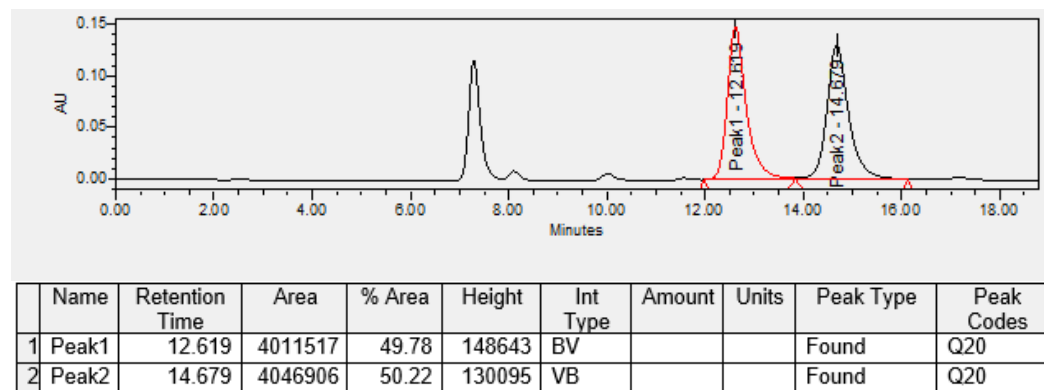


	Name	Retention Time	Area	% Area	Height	Int Type	Amount	Units	Peak Type	Peak Codes
1	Peak1	13.692	34737989	78.46	1190873	BV			Unknown	
2	Peak2	15.907	9539524	21.54	329901	Vb			Unknown	

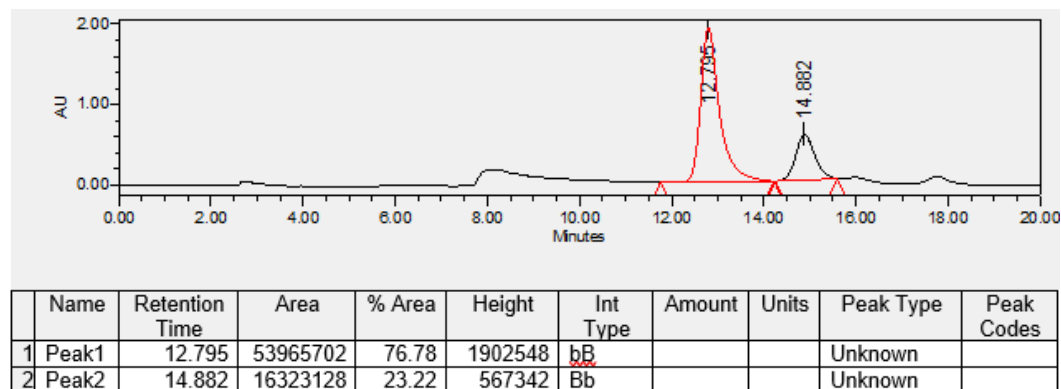
HPLC data of compound 2 (Method C):

Enantiomeric excess (ee) was determined by using HPLC with a chiral stationary phase. Stationary phase (AD column, flow rate = 1.0 mL/min, eluent: hexane/EtOH = 19/1, λ = 254 nm). t_R major = 12.8 min, t_R minor = 14.9 min, e.r. = 76.8:23.2.

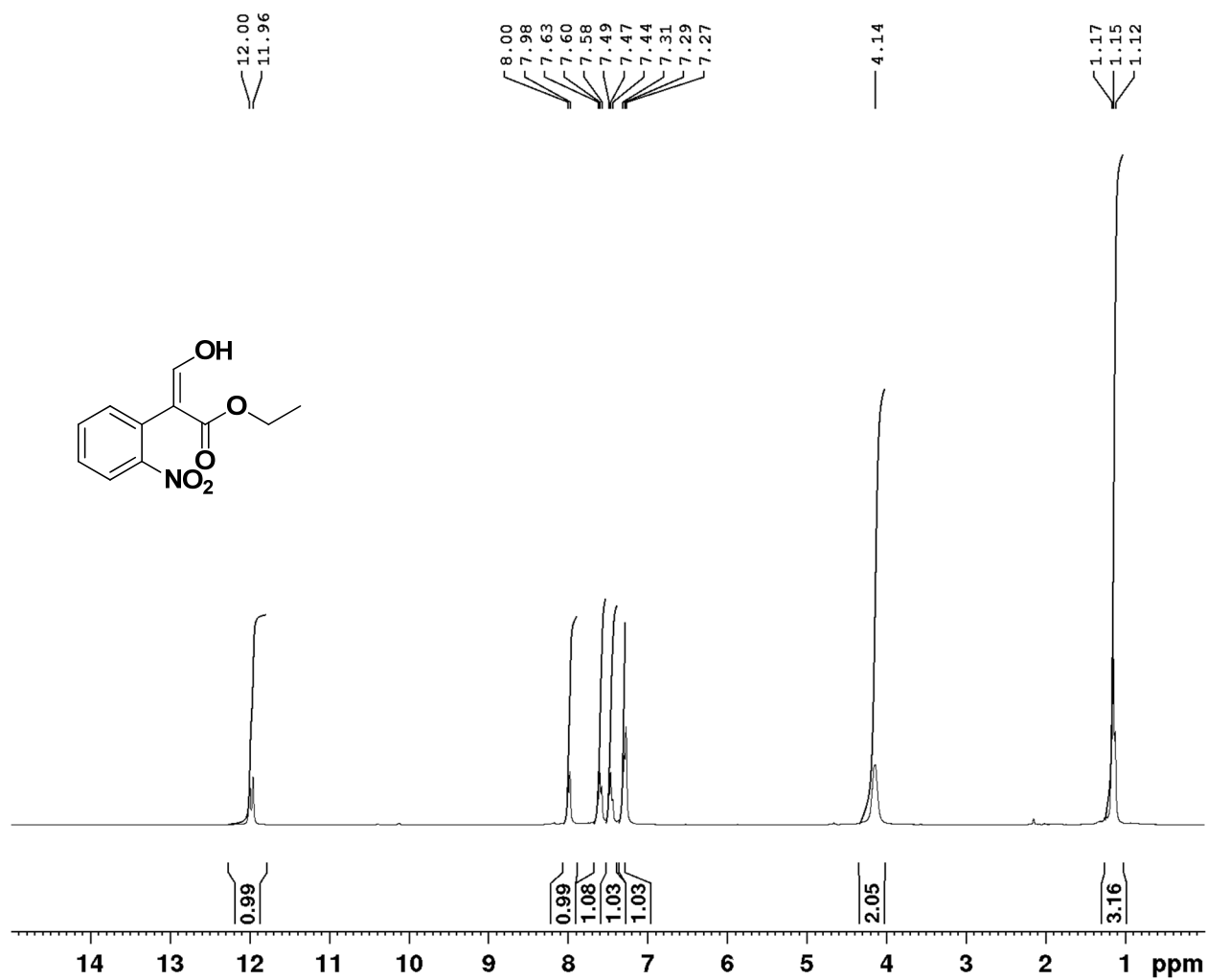
Racemic:



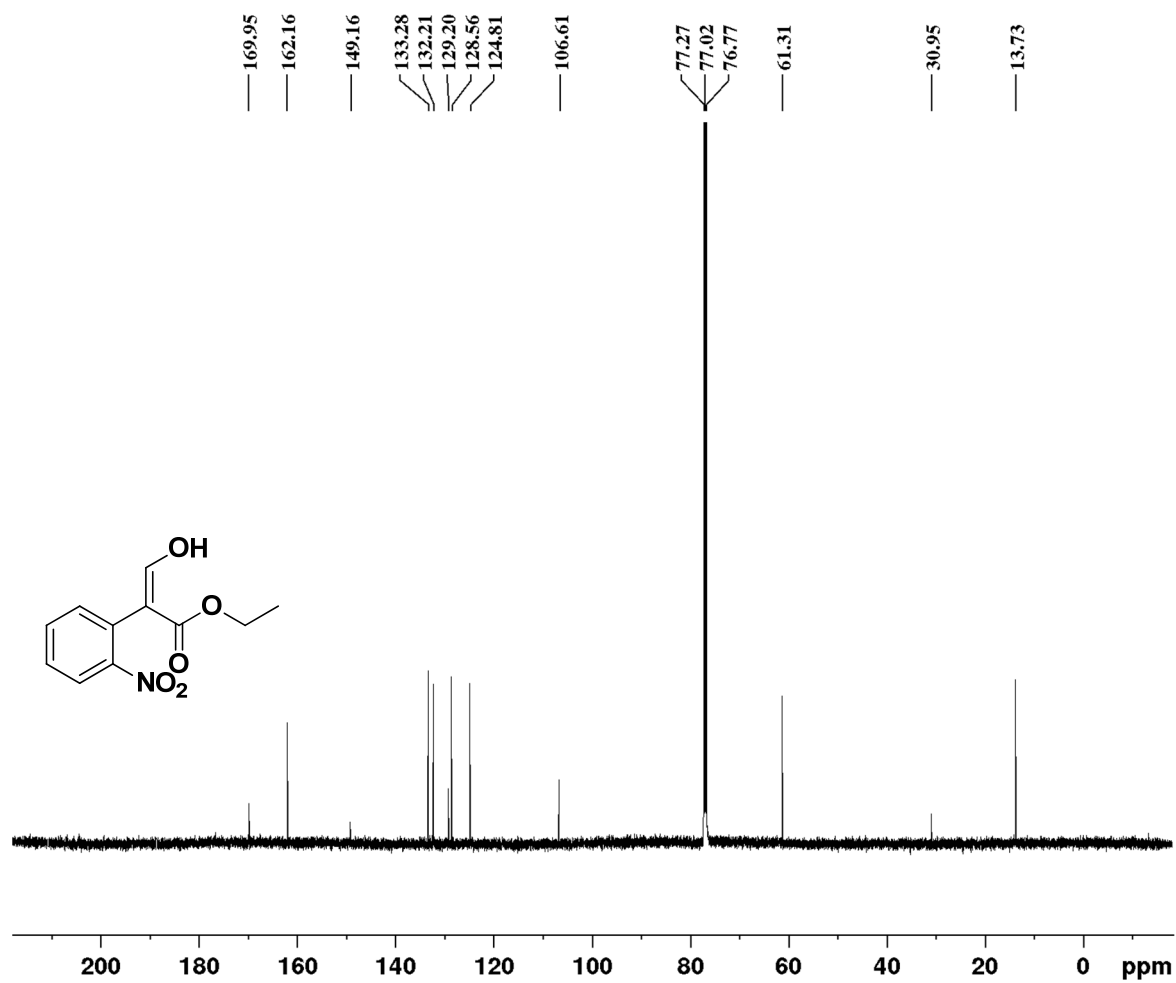
Chiral:



¹H NMR Spectrum of Compound 1 in CDCl₃

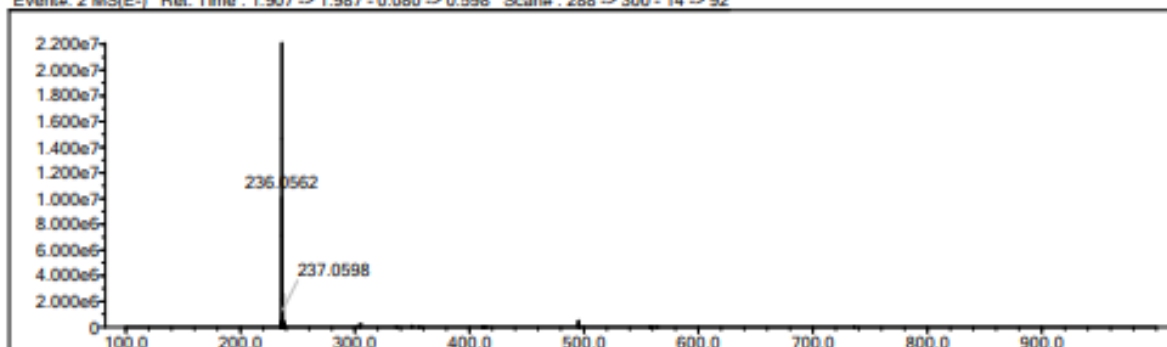


^{13}C NMR Spectrum of Compound 1 in CDCl_3

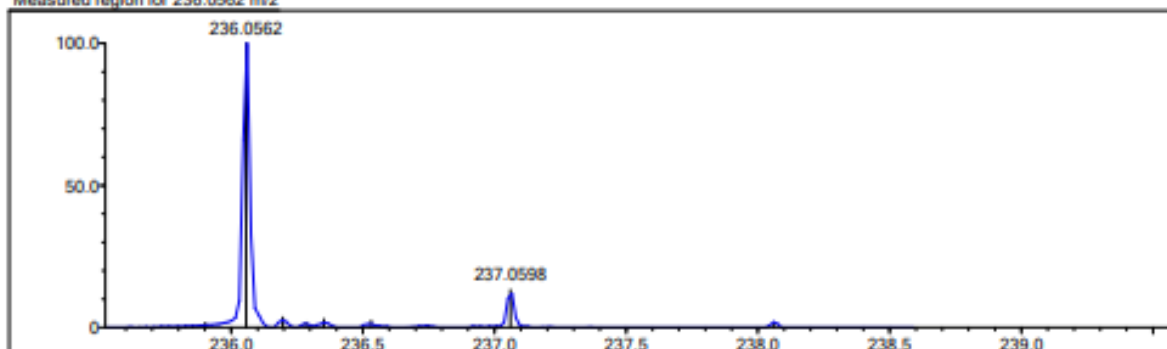


HRMS of Compound 1

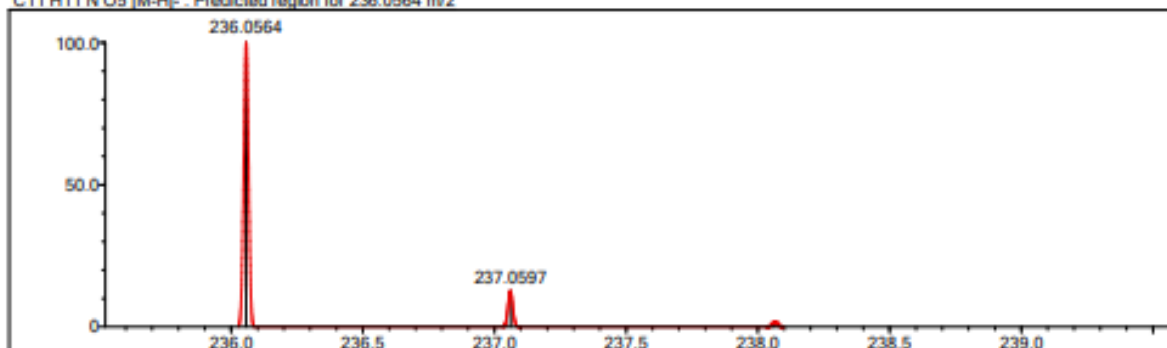
Event#: 2 MS(E-) Ret. Time : 1.907 -> 1.987 - 0.080 -> 0.598 Scan#: 288 -> 300 - 14 -> 92



Measured region for 236.0562 m/z

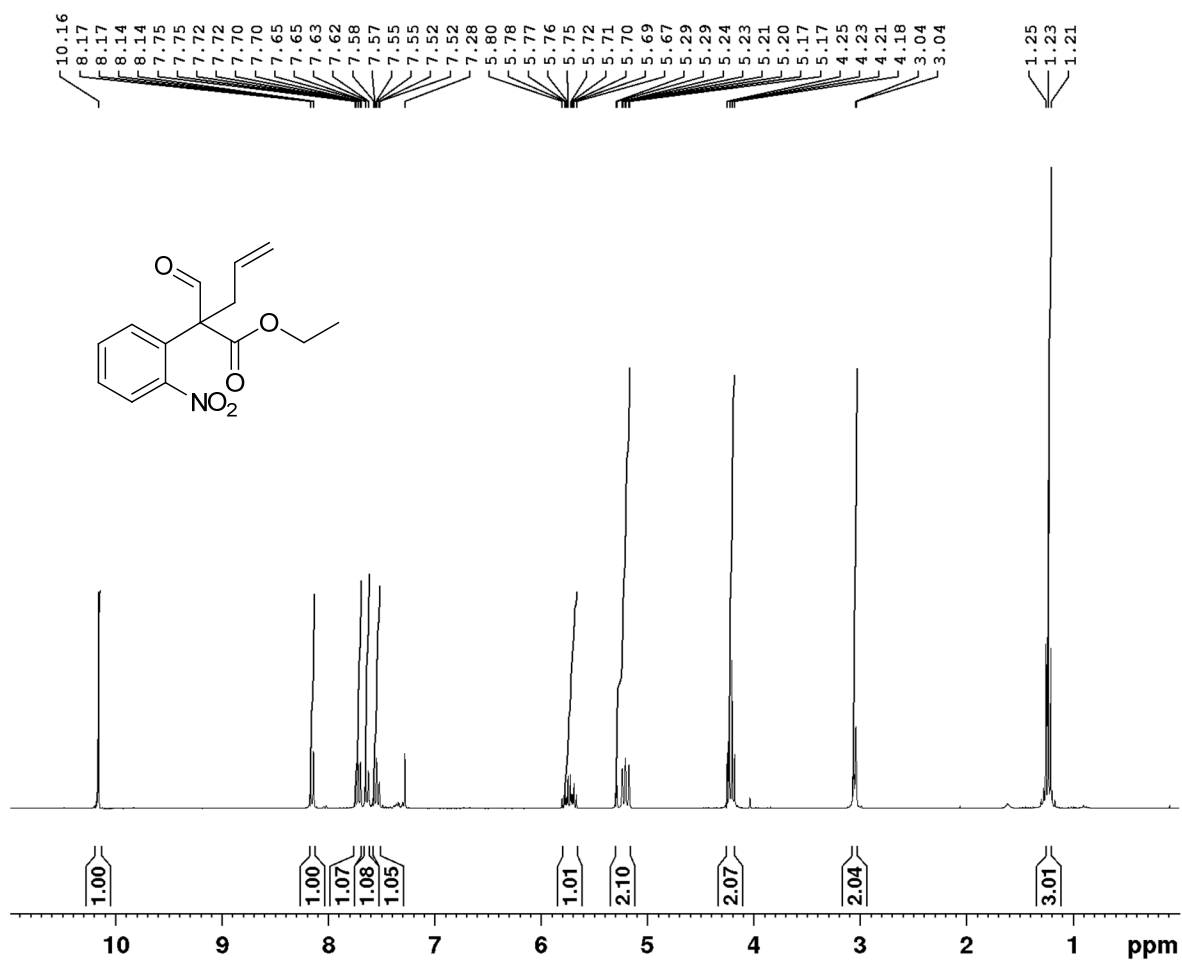


C11 H11 N O5 [M-H]- : Predicted region for 236.0564 m/z

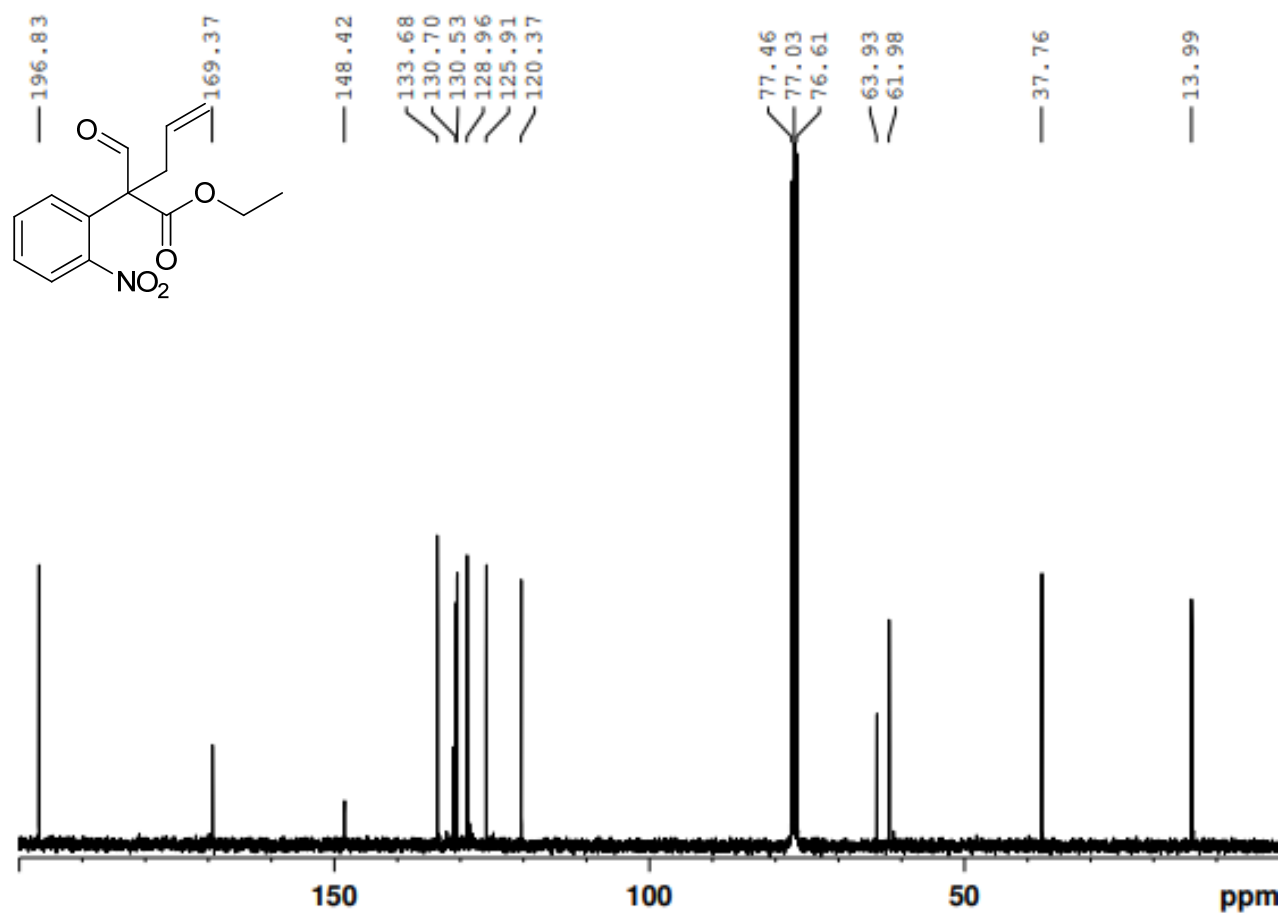


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	81.75	C11 H11 N O5	[M-H]-	236.0562	236.0564	-0.2	-0.85	81.75	7.0

¹H NMR Spectrum of Compound 2 in CDCl₃

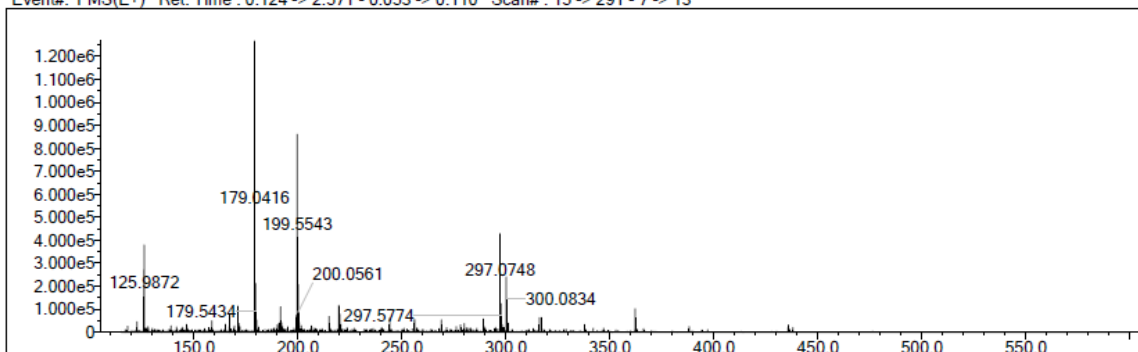


^{13}C NMR Spectrum of Compound 2 in CDCl_3

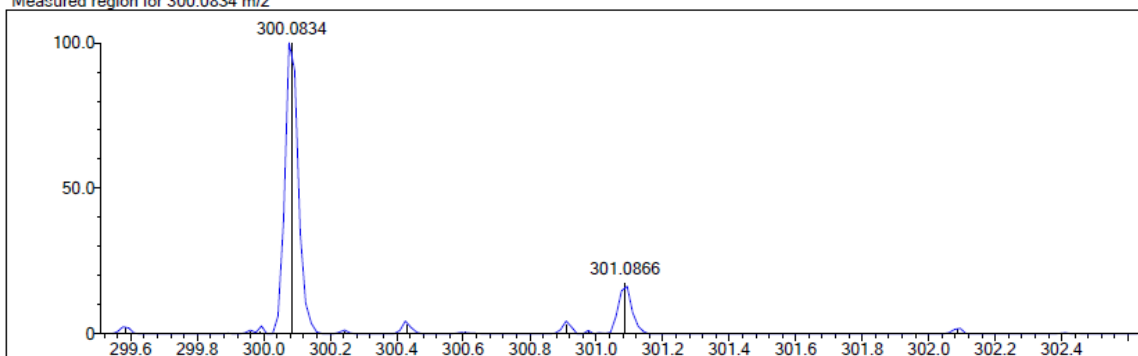


HRMS of Compound 2

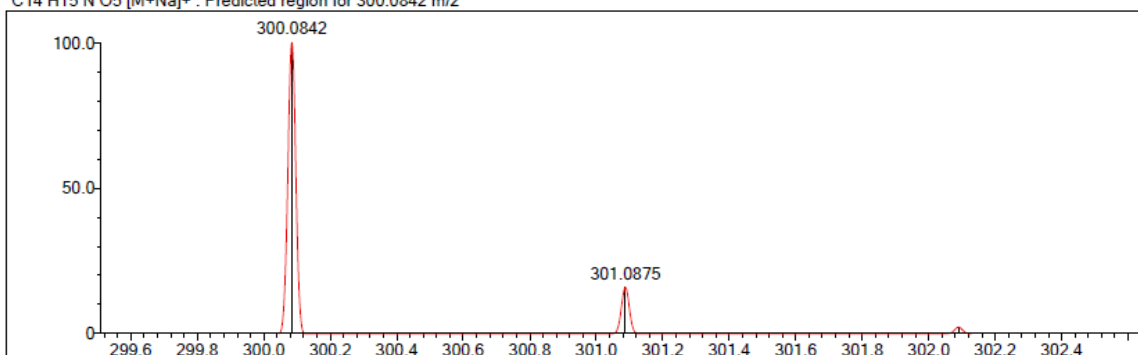
Event#: 1 MS(E+) Ret. Time : 0.124 -> 2.571 - 0.053 -> 0.110 Scan#: 15 -> 291 - 7 -> 13



Measured region for 300.0834 m/z

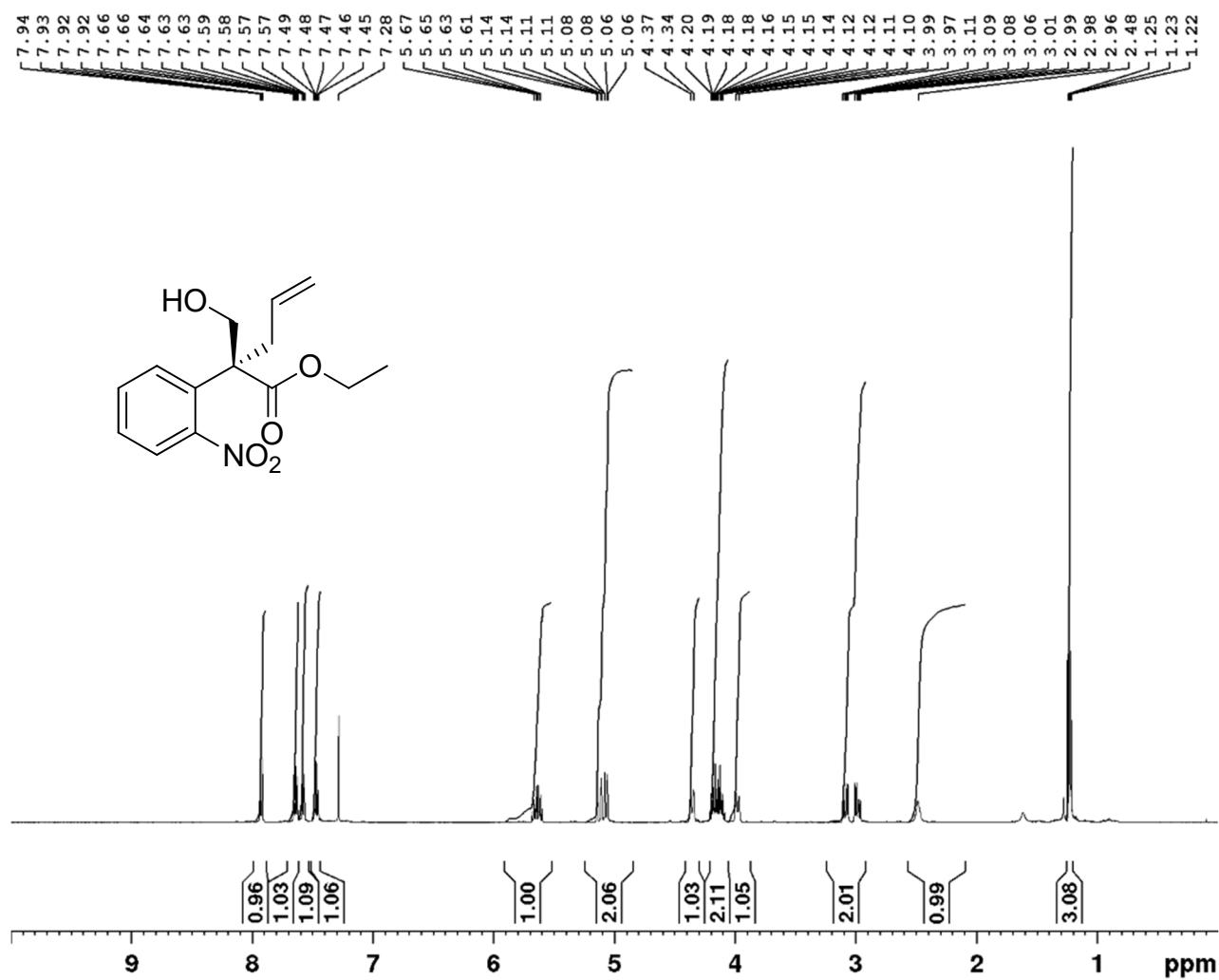


C14 H15 N O5 [M+Na]+ : Predicted region for 300.0842 m/z

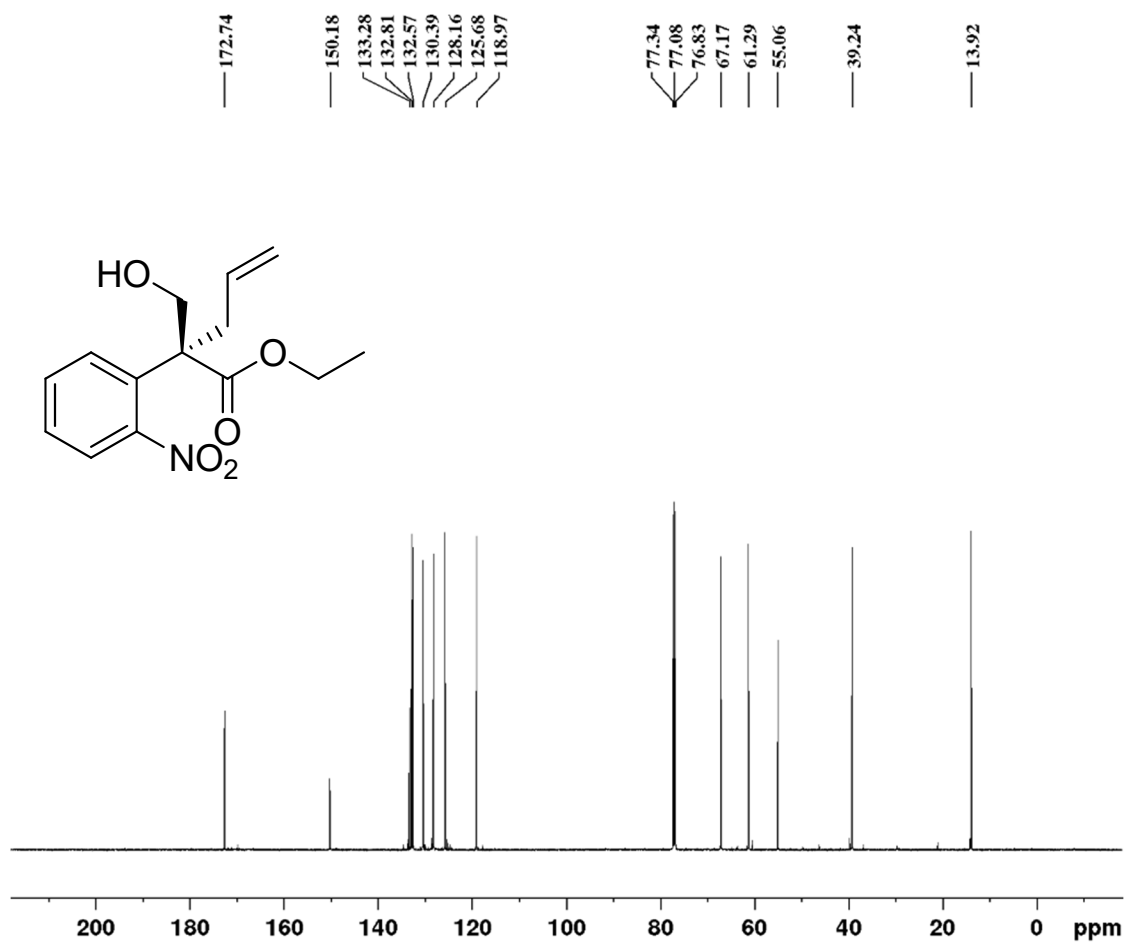


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	77.56	C14 H15 N O5	[M+Na]+	300.0834	300.0842	-0.8	-2.67	80.93	8.0

¹H NMR Spectrum of Compound 3 in CDCl₃

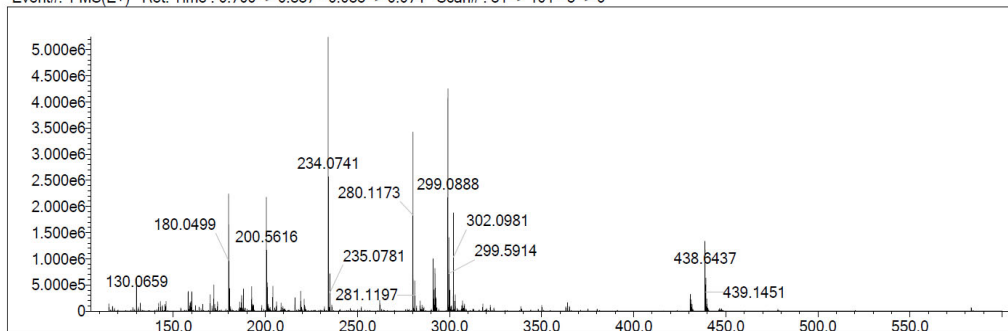


^{13}C NMR Spectrum of Compound 3 in CDCl_3

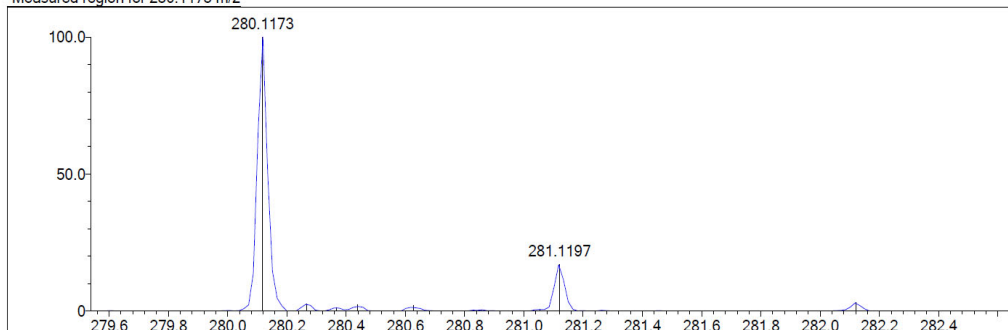


HRMS of compound 3

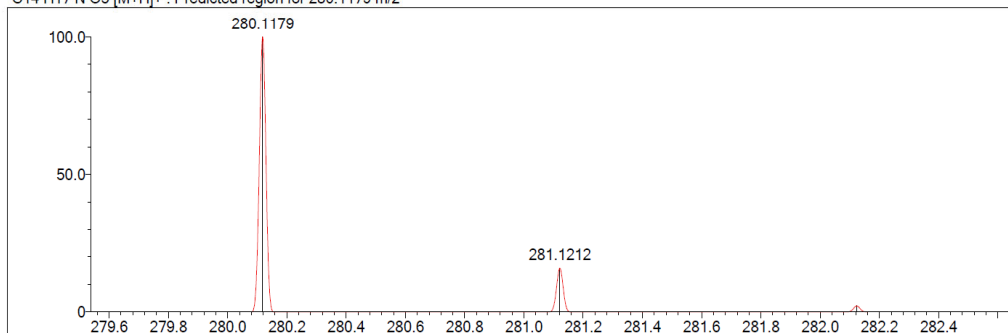
Event#: 1 MS(E+) Ret. Time : 0.709 -> 0.887 - 0.035 -> 0.074 Scan#: 81 -> 101 - 5 -> 9



Measured region for 280.1173 m/z

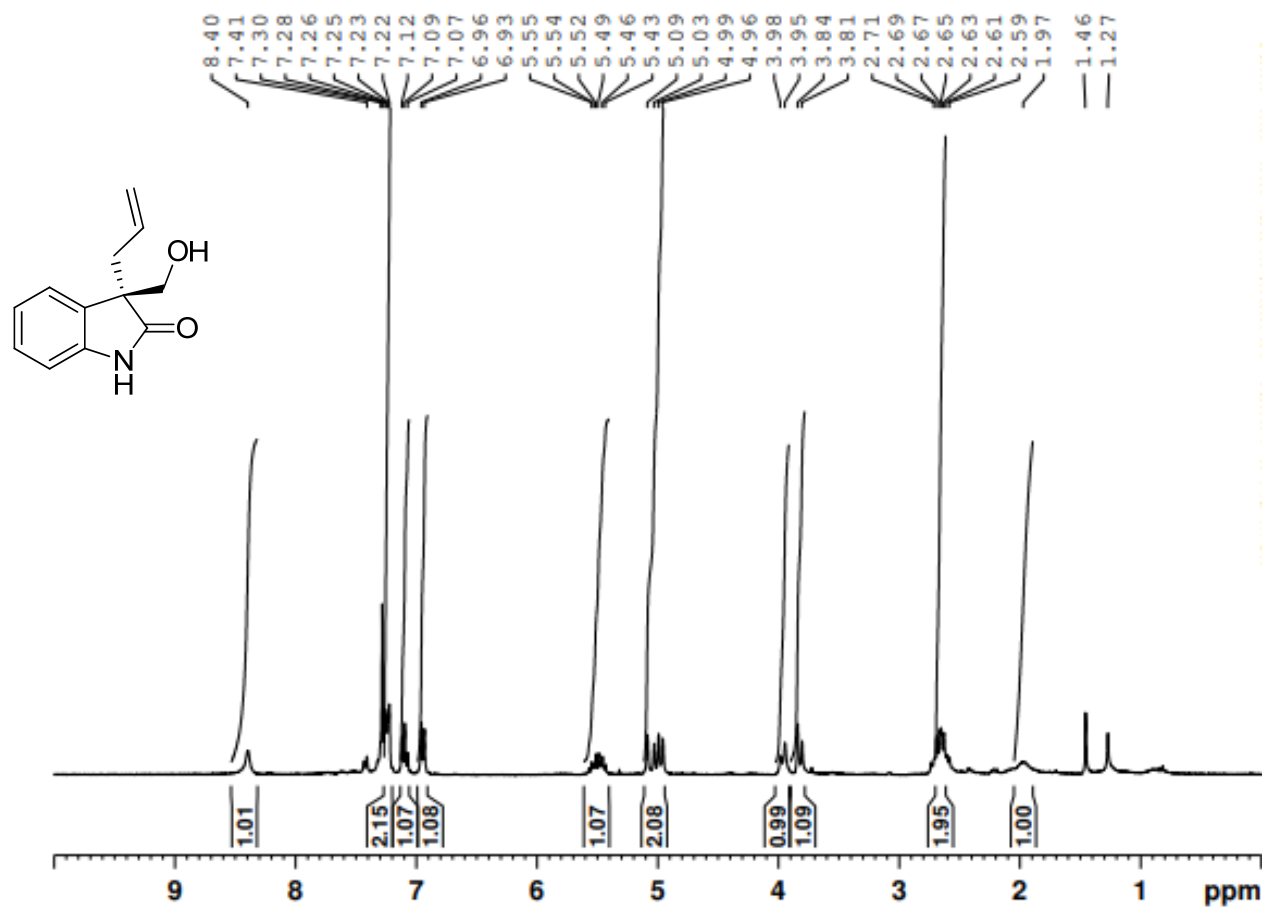


C14 H17 N O5 [M+H]⁺ : Predicted region for 280.1179 m/z

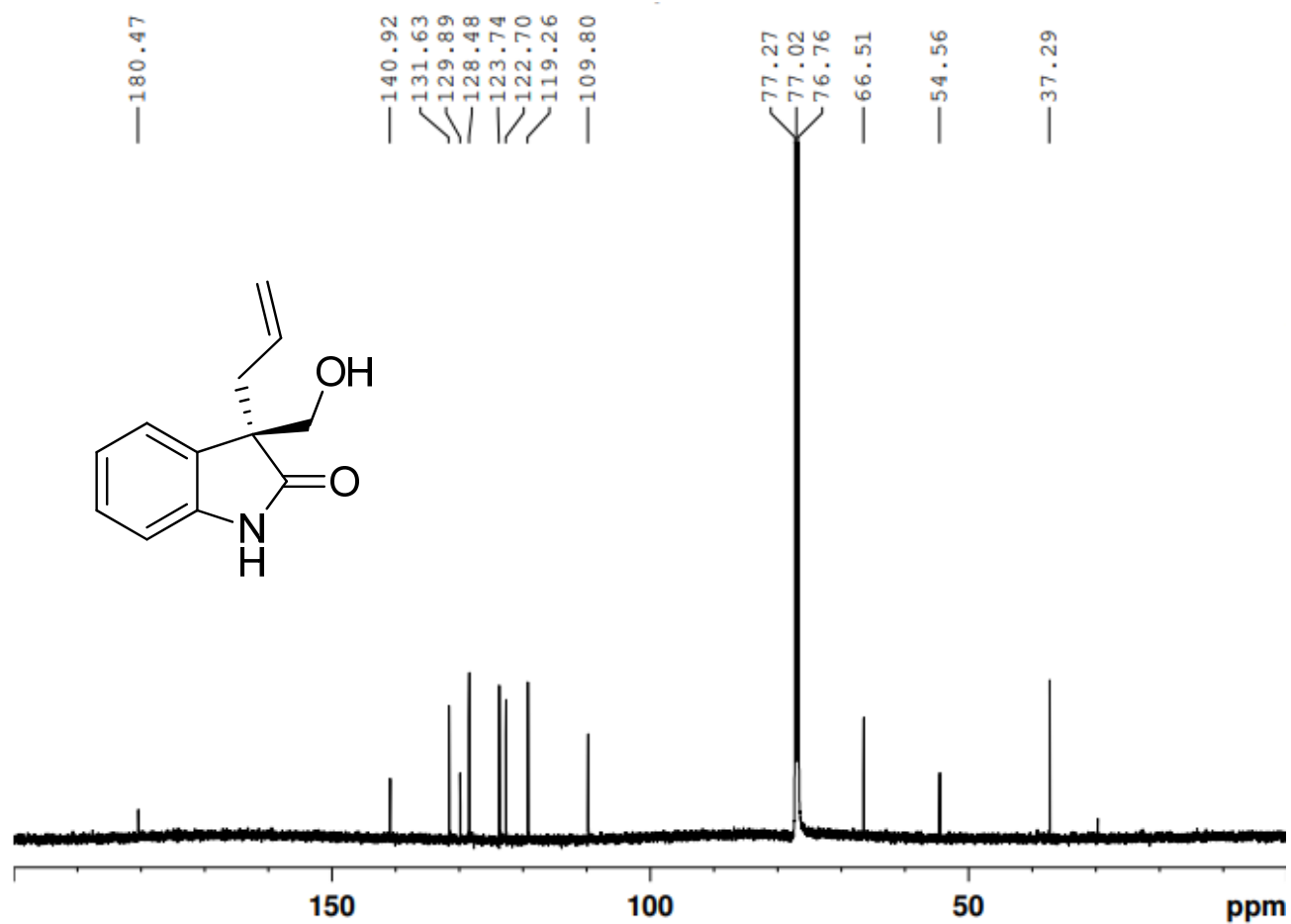


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	83.16	C14 H17 N O5	[M+H] ⁺	280.1173	280.1179	-0.6	-2.14	85.59	7.0

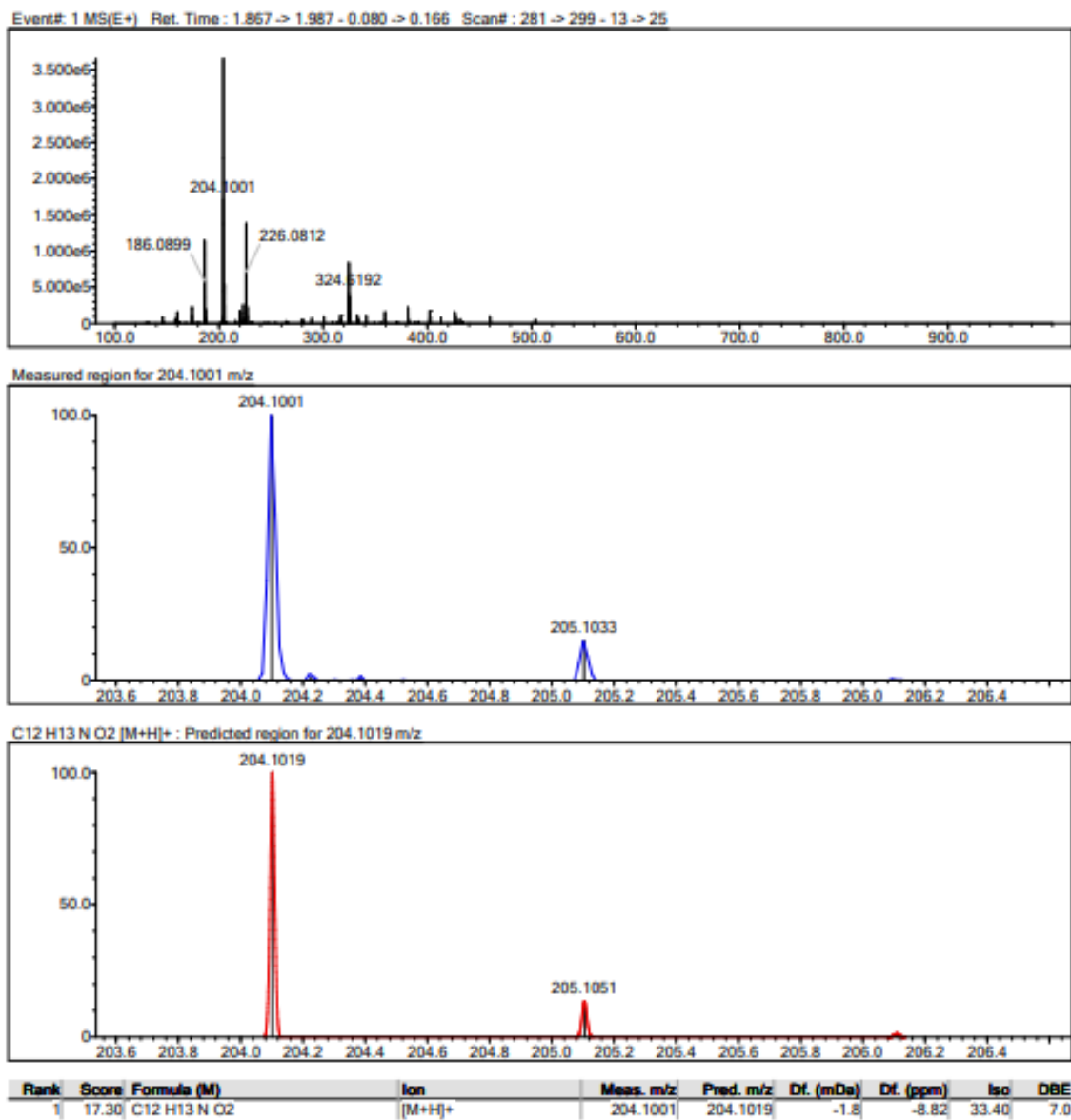
¹H NMR Spectrum of Compound 4 in CDCl₃



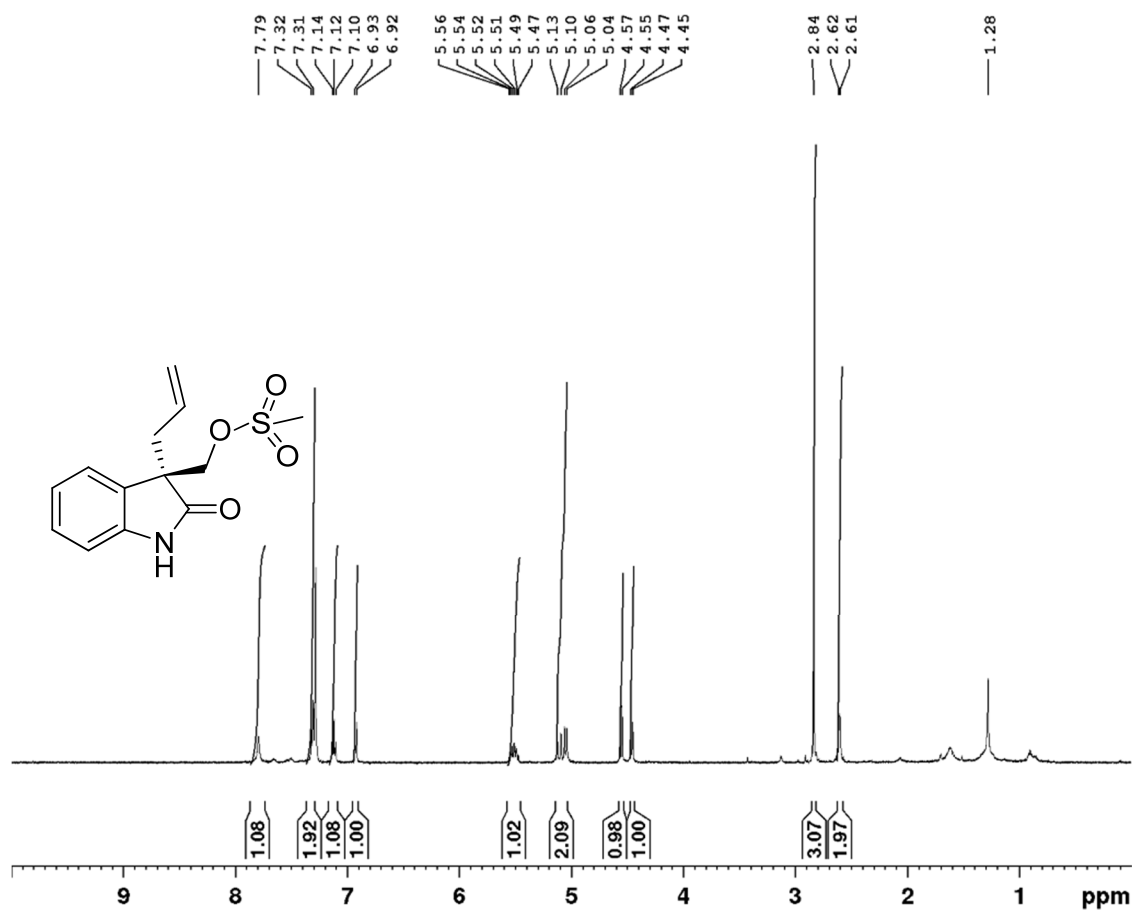
^{13}C NMR Spectrum of Compound 4 in CDCl_3



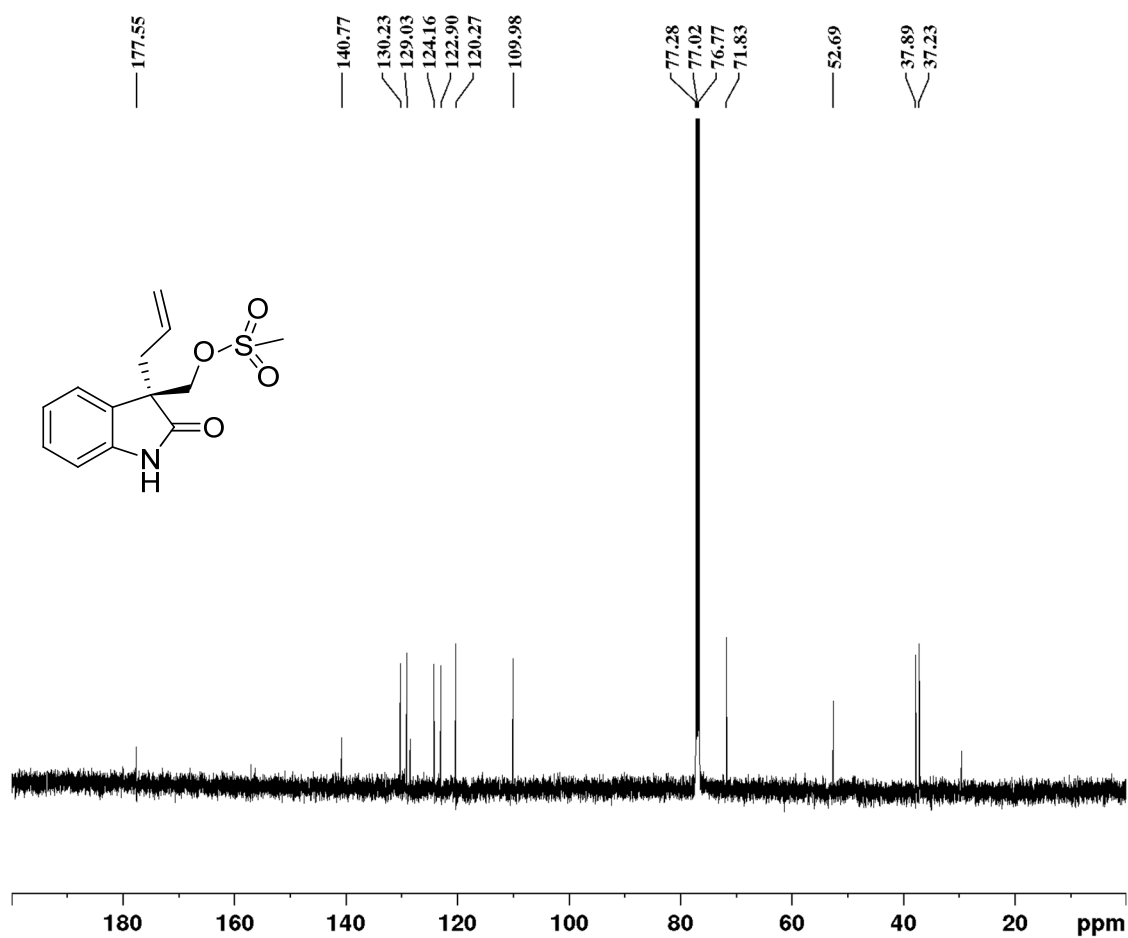
HRMS of Compound 4



¹H NMR Spectrum of Compound 5 in CDCl₃

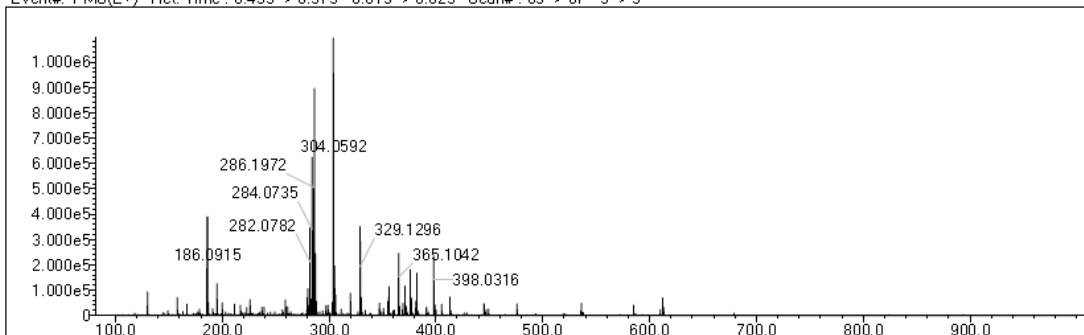


^{13}C NMR Spectrum of Compound 5 in CDCl_3

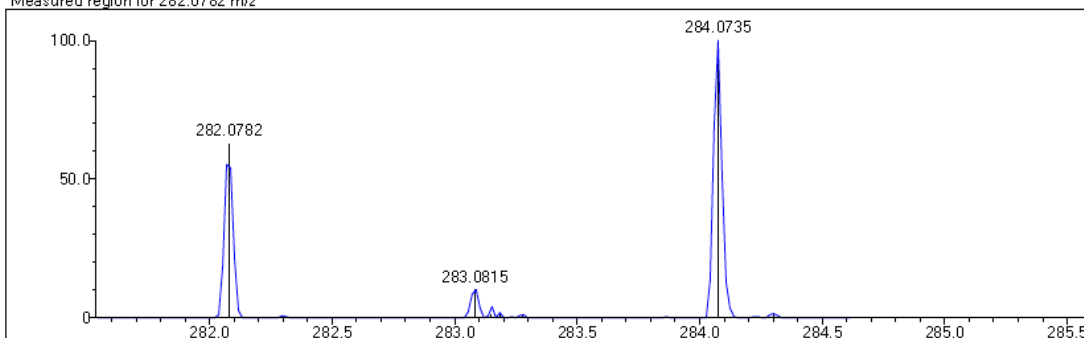


HRMS of Compound 5

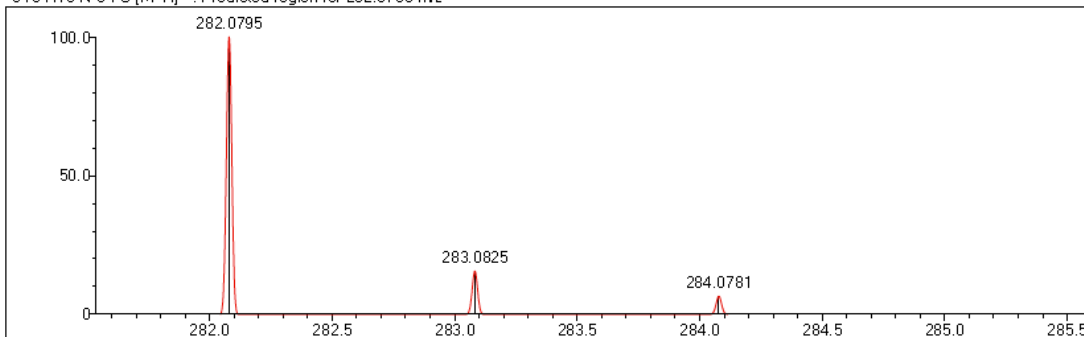
Event#: 1 MS(E+) Ret. Time : 0.453-> 0.573 - 0.013 -> 0.025 Scan#: 69 -> 87 - 3 -> 5



Measured region for 282.0782 m/z

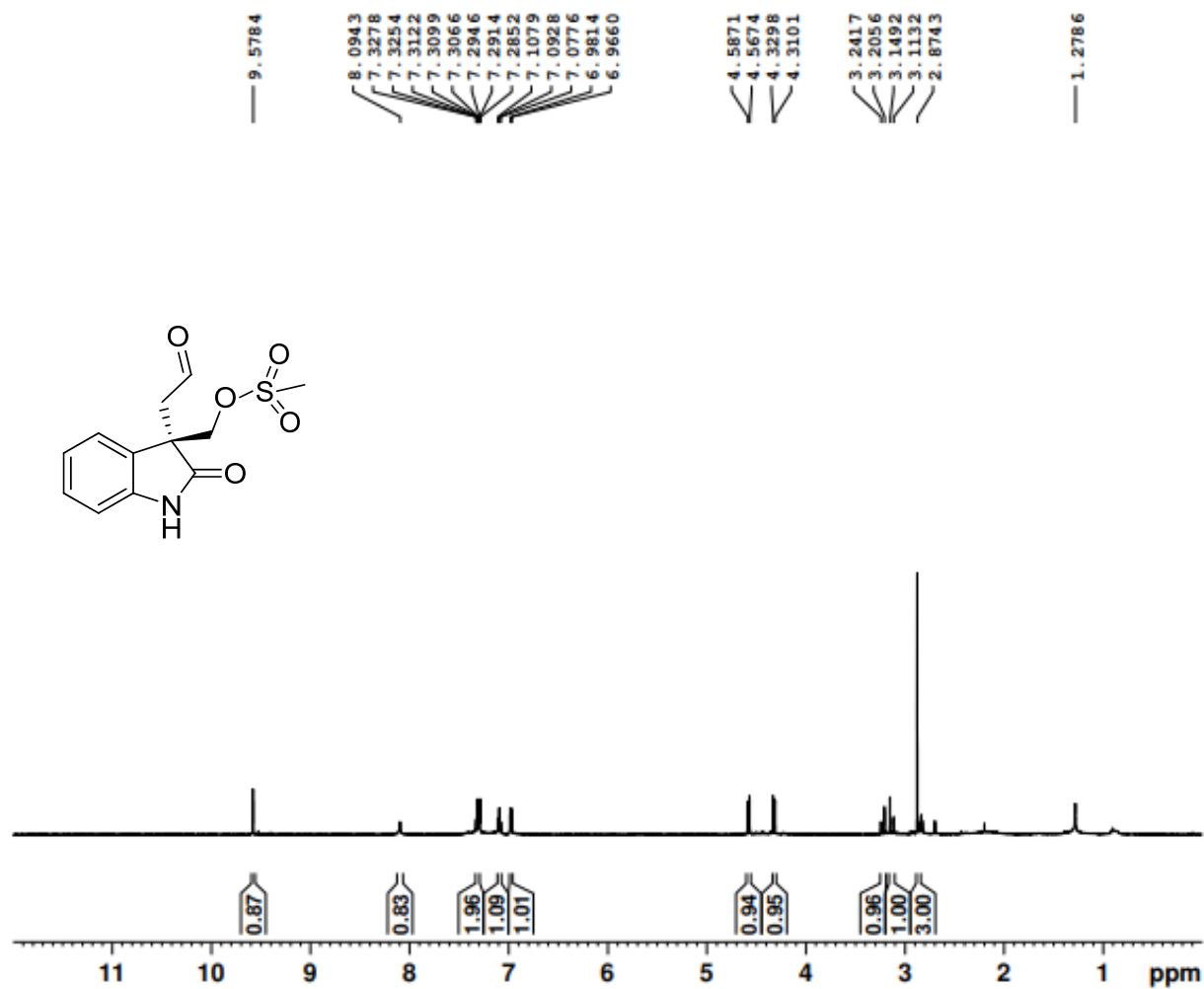


C13 H15 N O4 S [M+H]⁺ : Predicted region for 282.0795 m/z

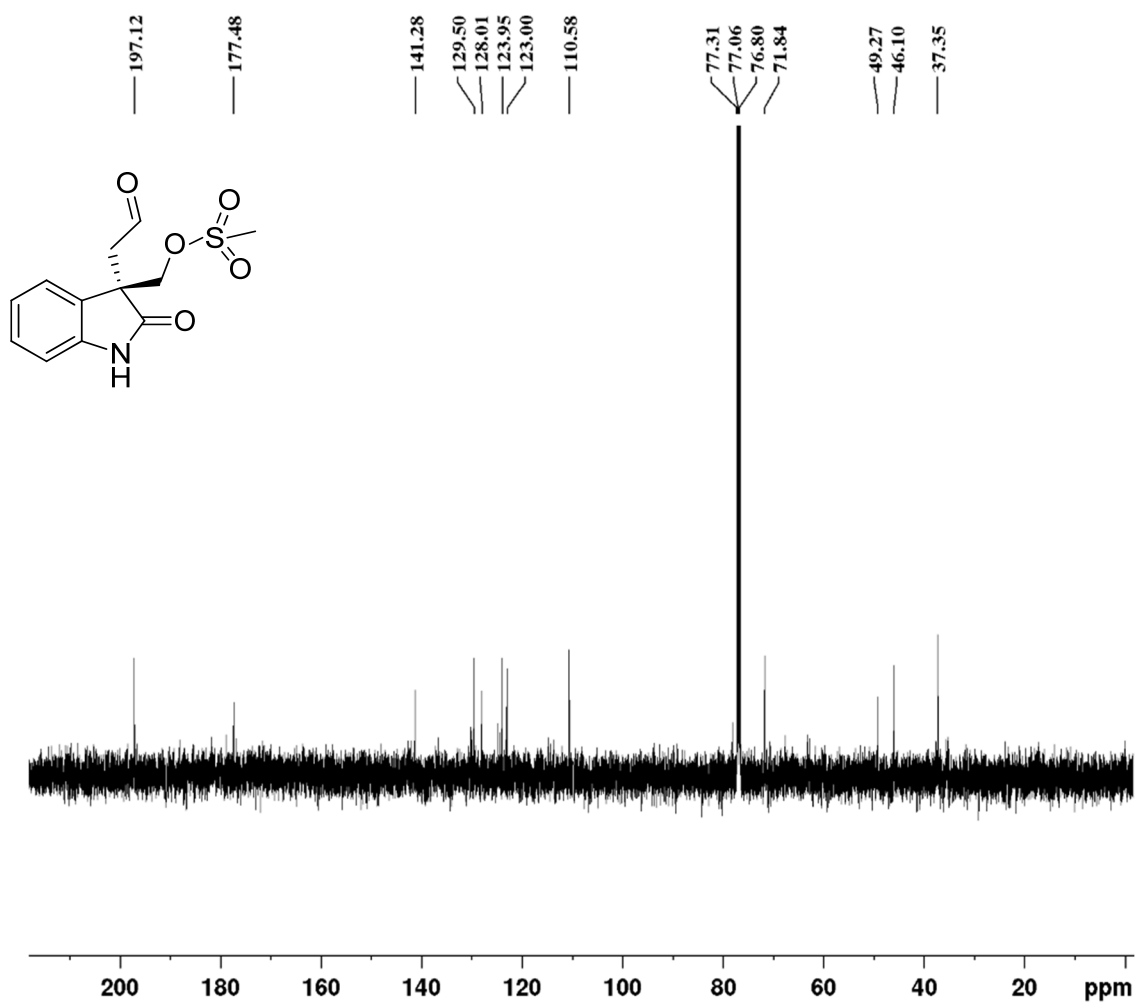


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Isot	DBE
2	37.18	C13 H15 N O4 S	[M+H] ⁺	282.0782	282.0795	-1.3	-4.61	40.87	7.0

¹H NMR Spectrum of Compound 6 in CDCl₃

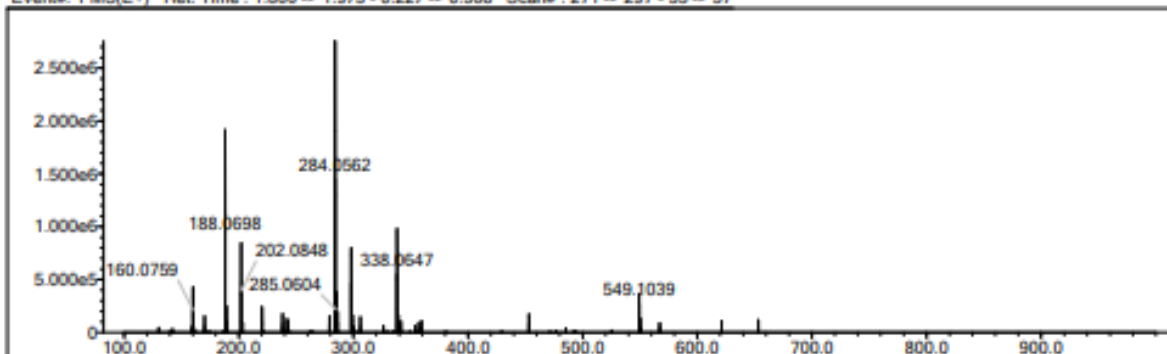


^{13}C NMR Spectrum of Compound 6 in CDCl_3

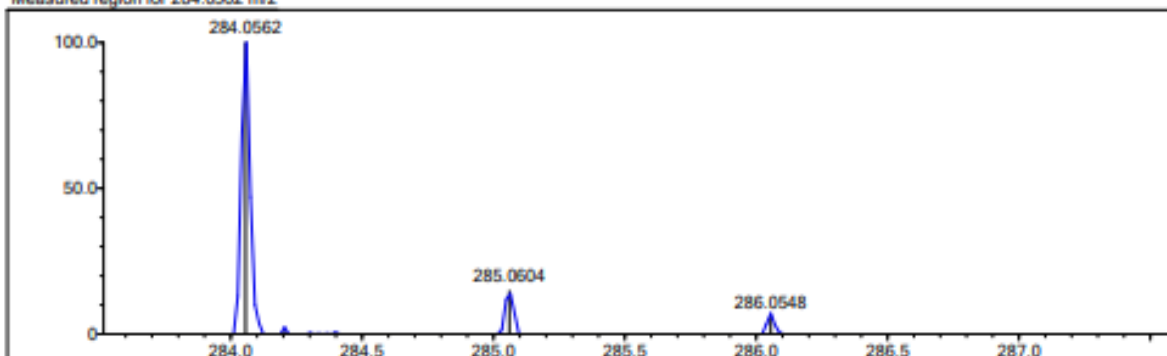


HRMS of Compound 6

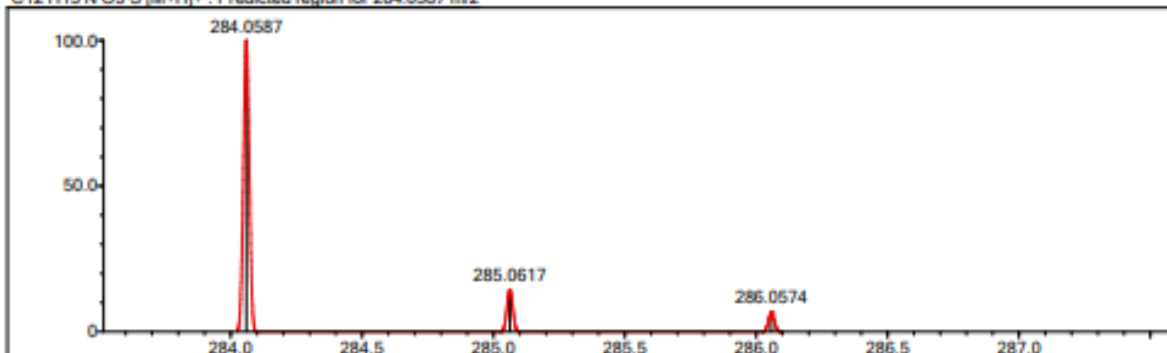
Event#: 1 MS(E+) Ret. Time : 1.800 -> 1.973 - 0.227 -> 0.368 Scan#: 271 -> 297 - 35 -> 57



Measured region for 284.0562 m/z

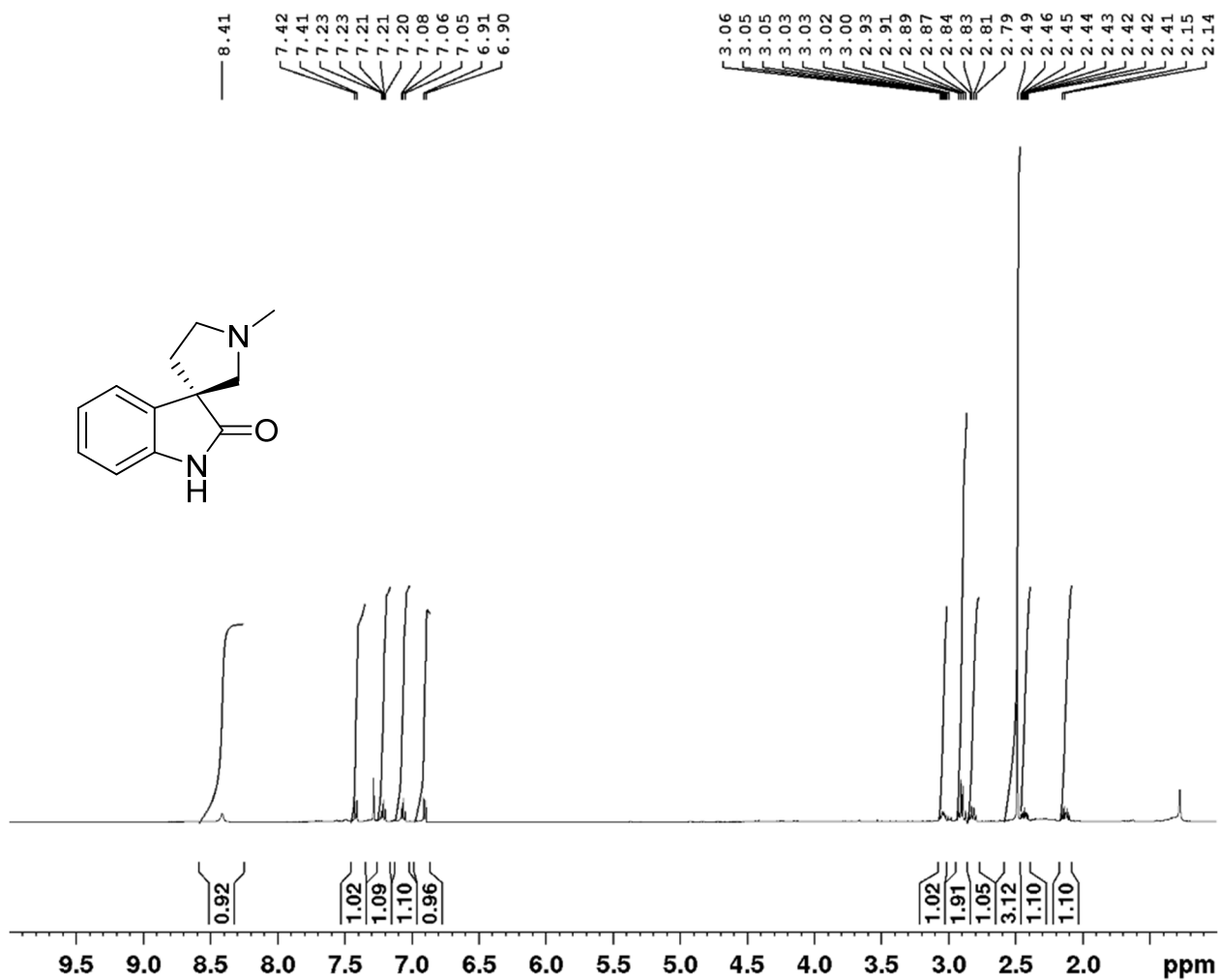


C12 H13 N O5 S [M+H]⁺ : Predicted region for 284.0587 m/z

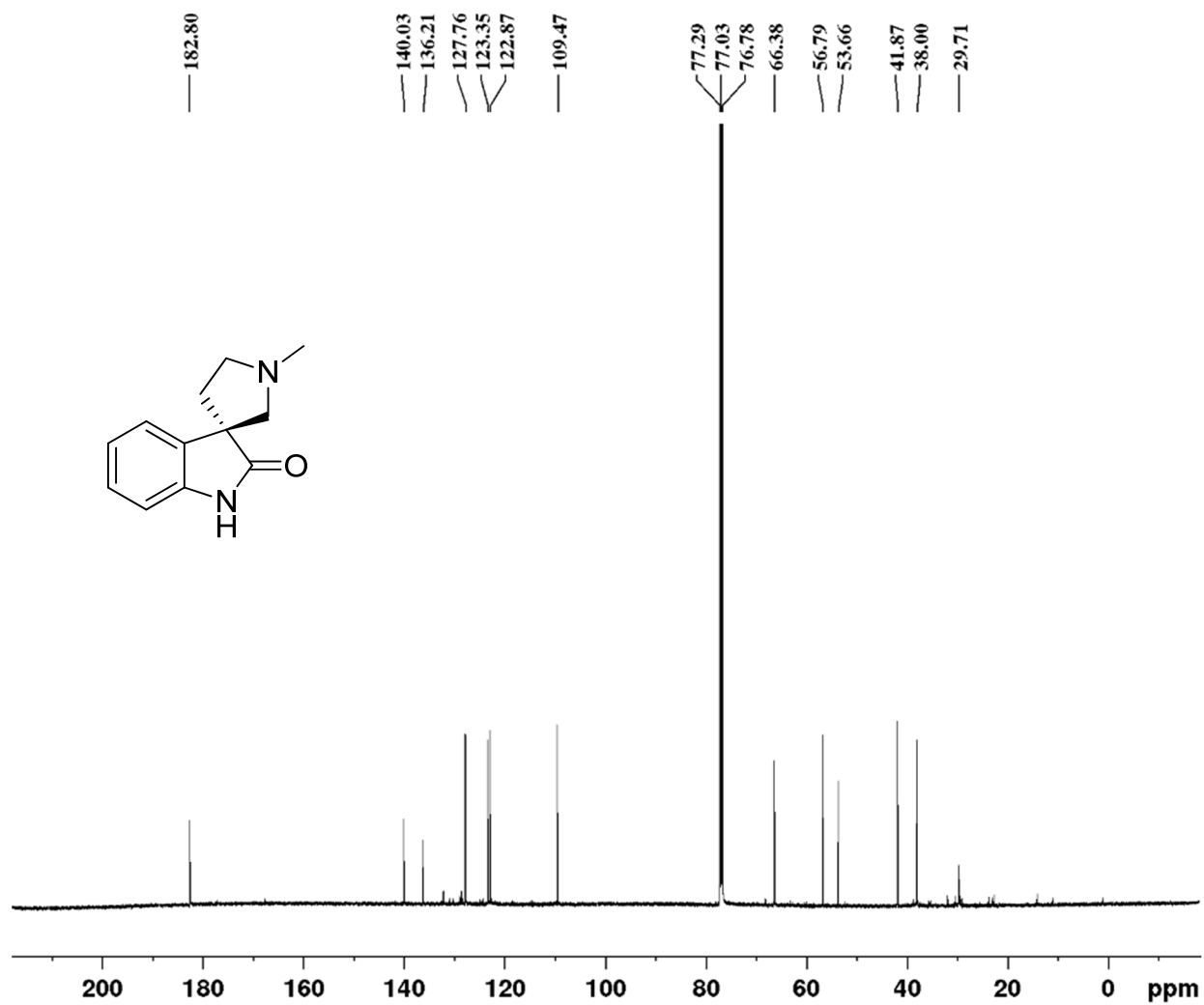


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Dt. (mDa)	Dt. (ppm)	Iso	DBE
3	50.73	C12 H13 N O5 S	[M+H] ⁺	284.0562	284.0587	-2.5	-8.80	97.56	7.0

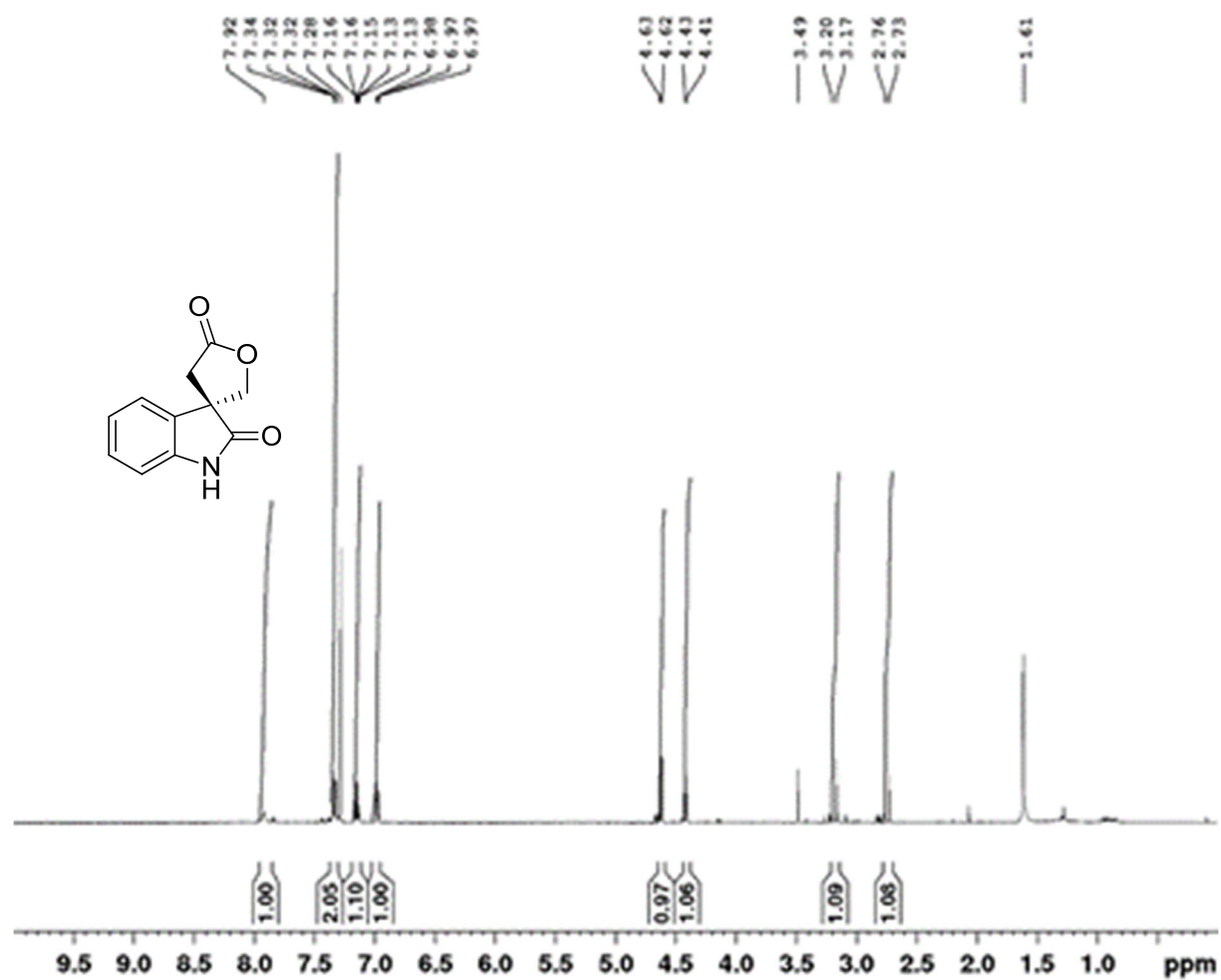
¹H NMR Spectrum of Compound 7 in CDCl₃ ((-)-Coerulescine)



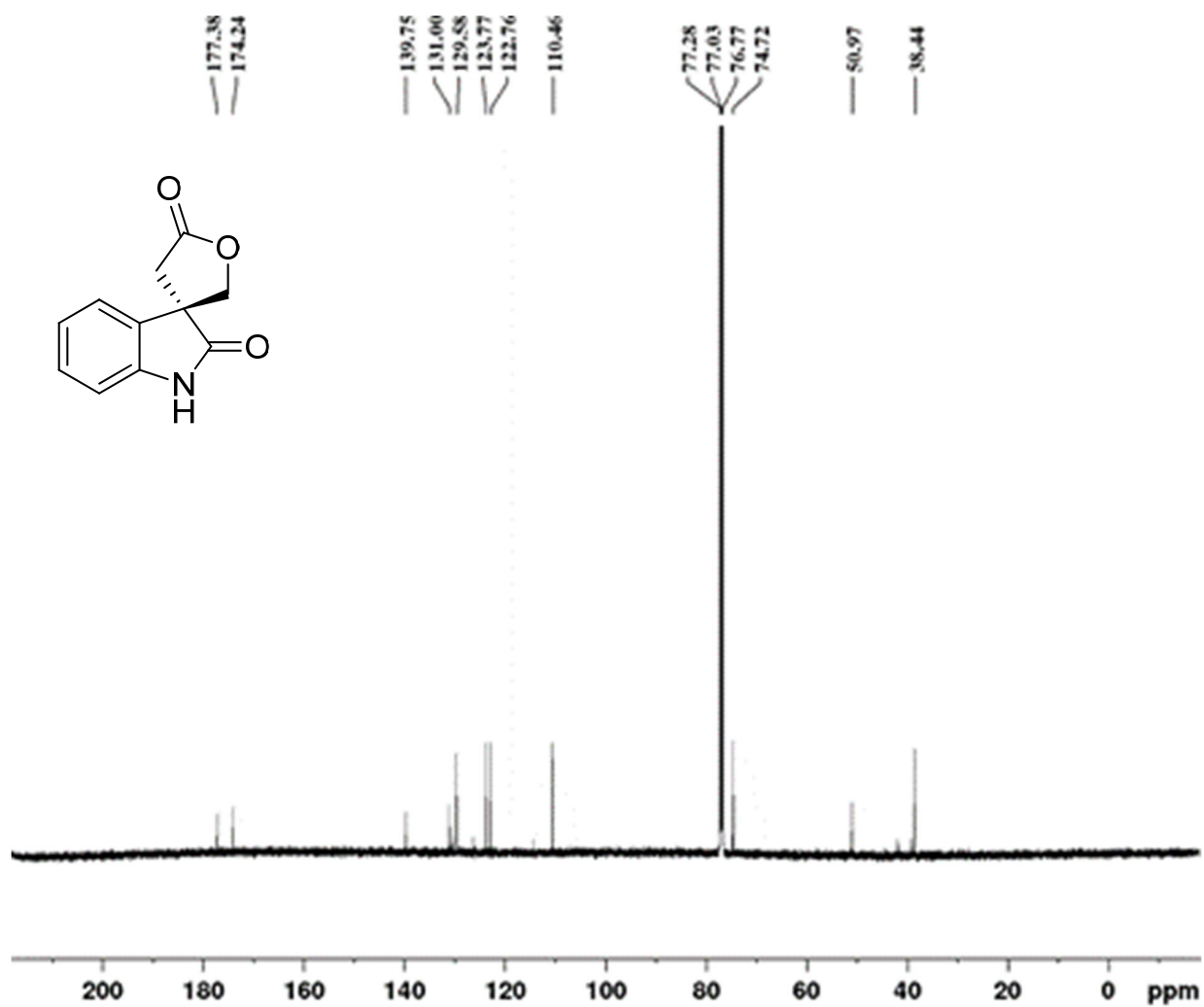
^{13}C NMR Spectrum of Compound 7 in CDCl_3 (-)-(Coerulescine)



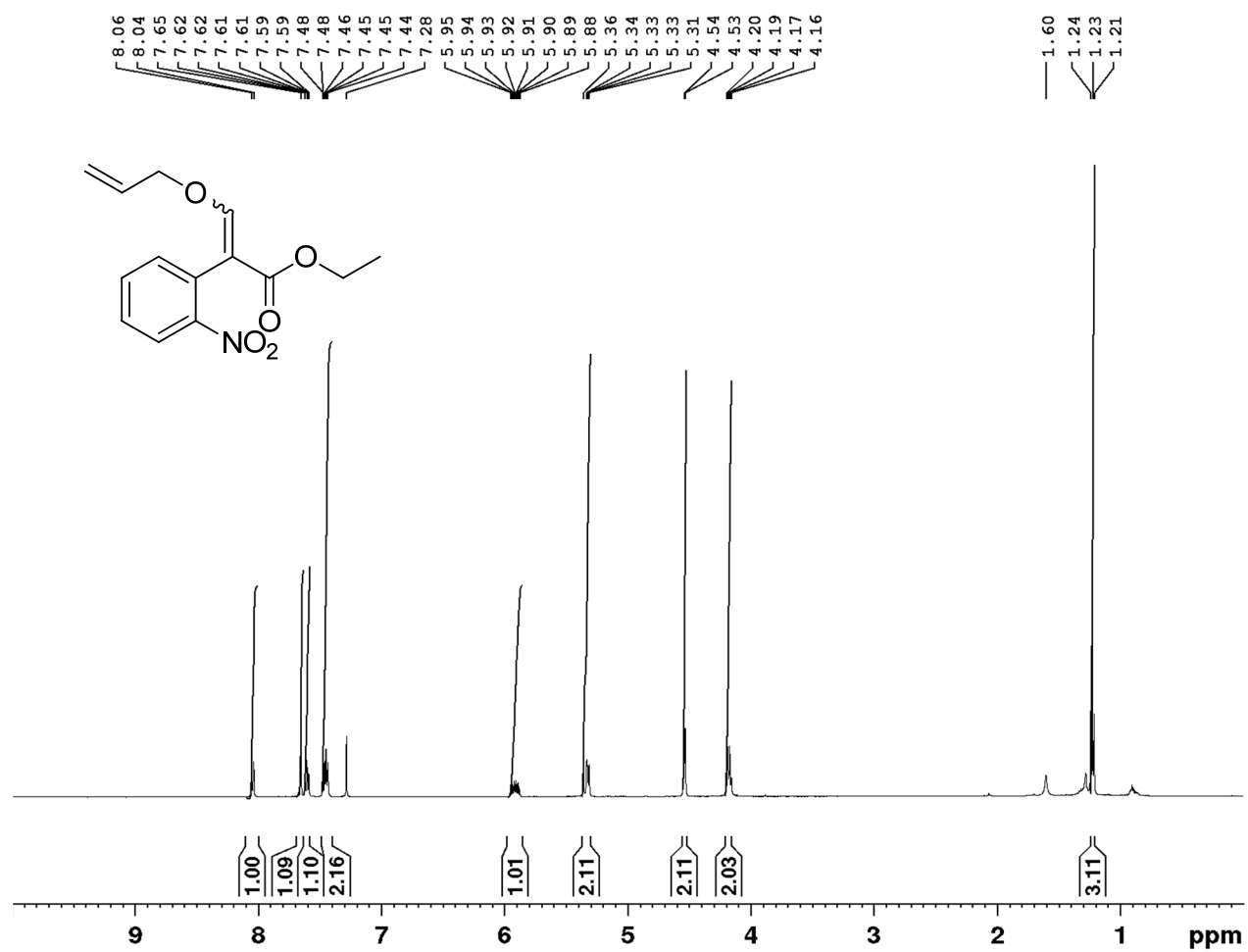
^1H NMR Spectrum of Compound 8 in CDCl_3 ((-)-Coixspirolactam A)



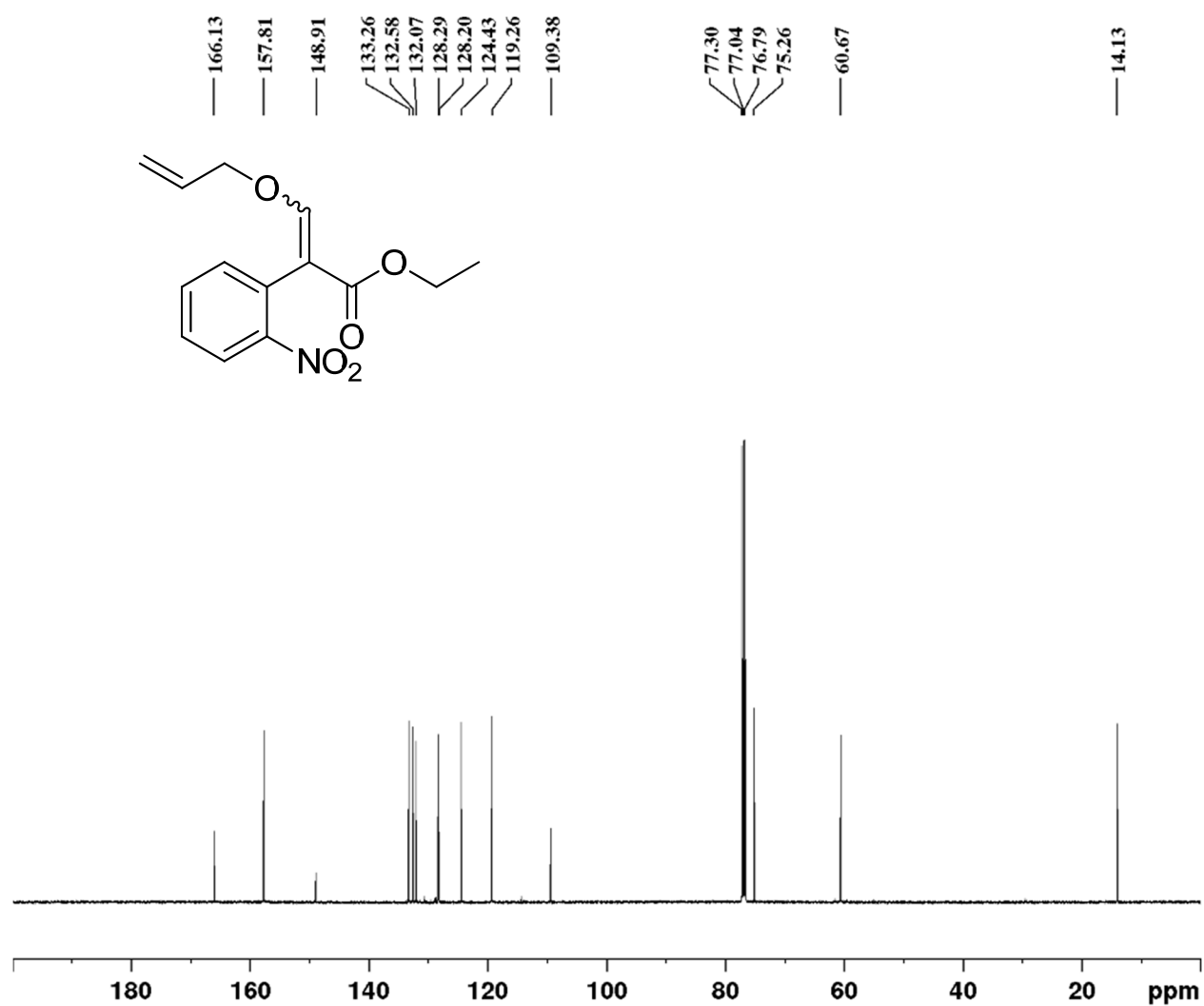
^{13}C NMR Spectrum of Compound 8 in CDCl_3 ((-)-Coixspirolactam A)



¹H NMR Spectrum of Compound 9 in CDCl₃

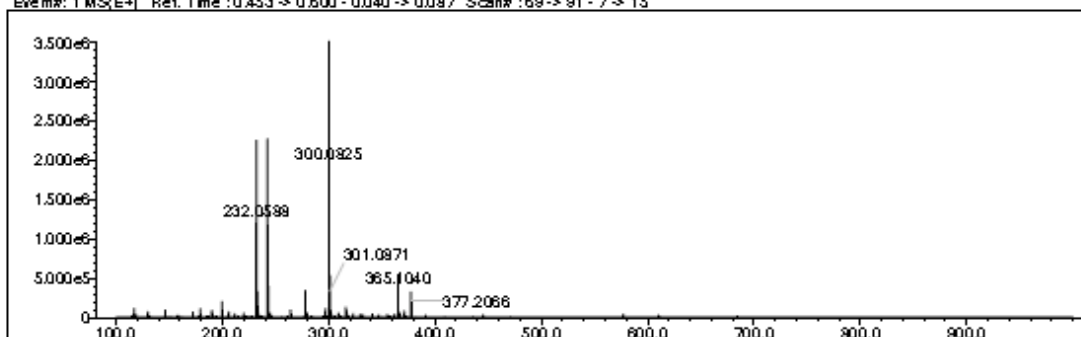


¹³C NMR Spectrum of Compound 9 in CDCl₃

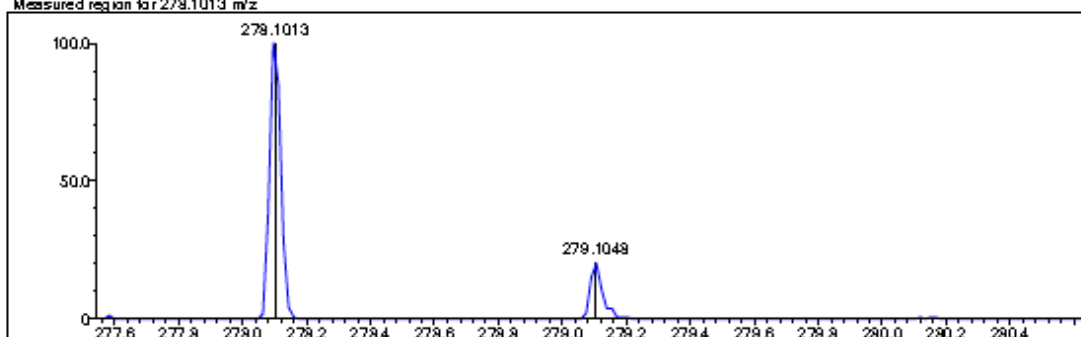


HRMS of Compound 9

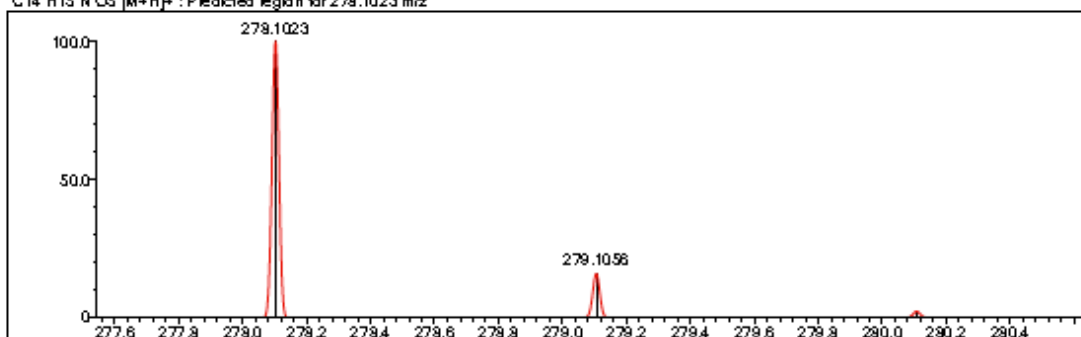
Event#: 1 MS(E+) Ret. Time : 0.453 -> 0.600 - 0.040 -> 0.087 Scan#: 69 -> 91 - 7 -> 15



Measured region for 279.1013 m/z

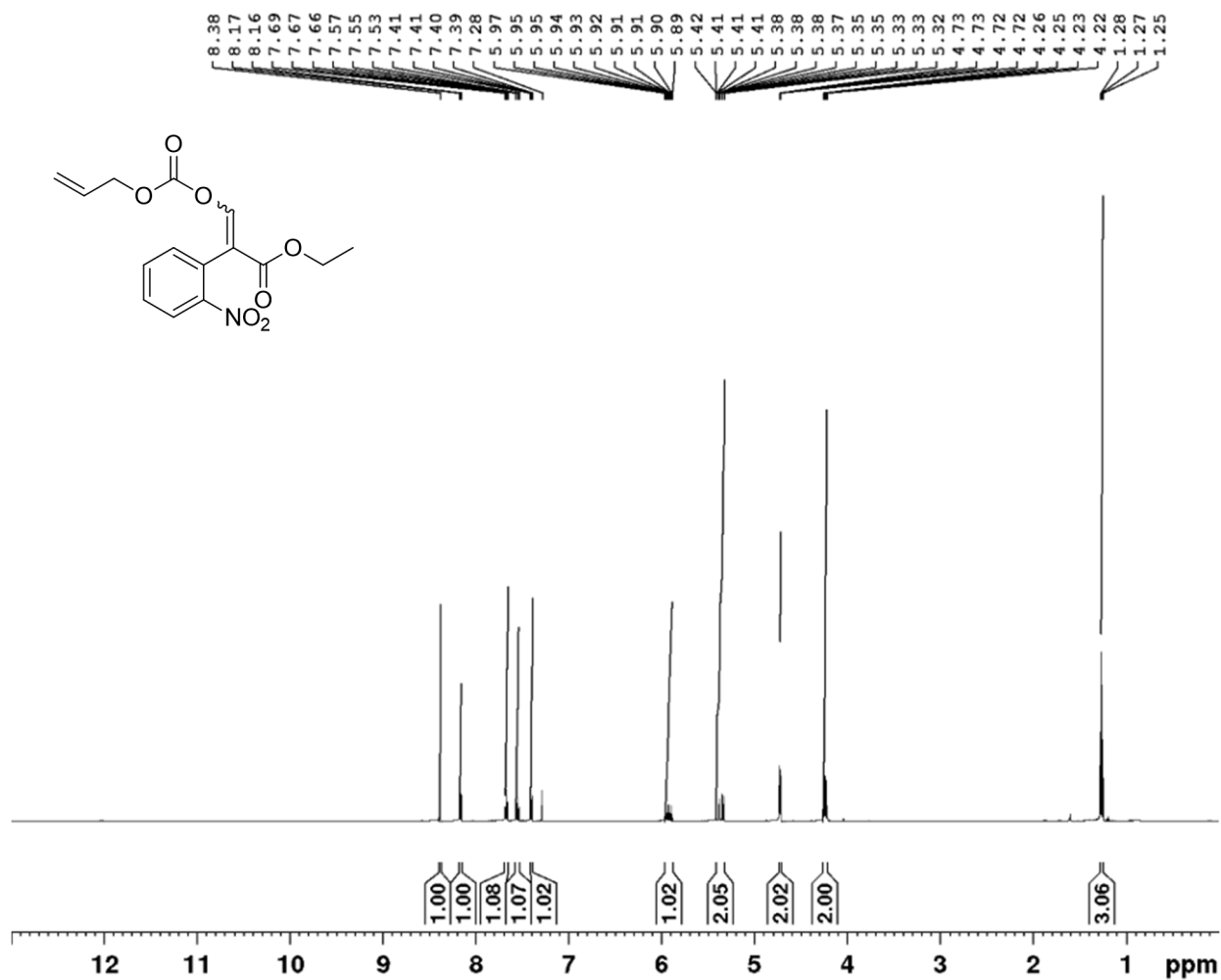


C14 H15 N O5 [M+H]⁺ : Predicted region for 279.1023 m/z

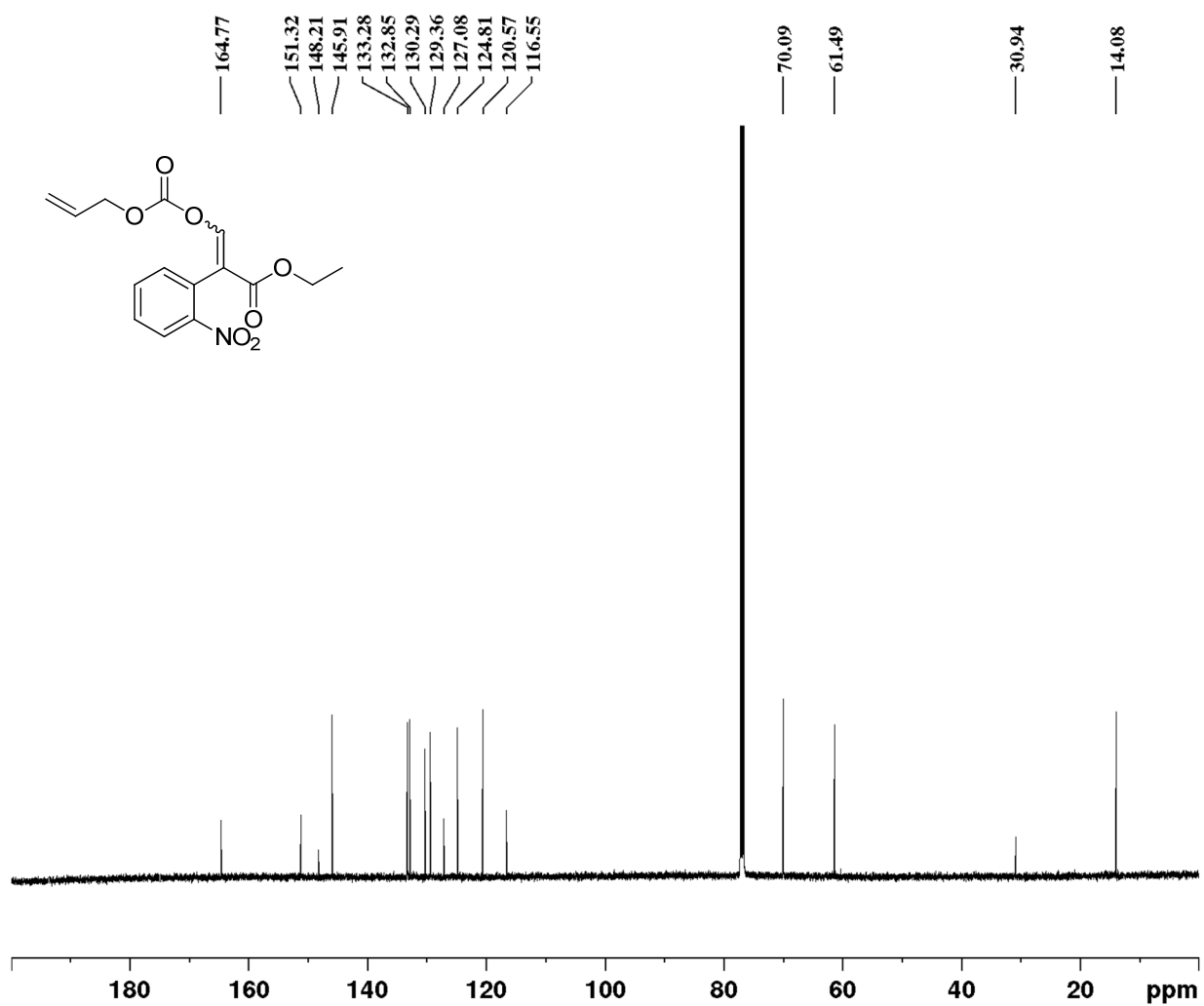


Rank	Score	Formula (M)	Ion	Mass, m/z	Pred. m/z	Diff. (mDa)	DL (ppm)	Isot	DBE
1	63.30	C14 H15 N O5	[M+H] ⁺	279.1013	279.1023	-1.0	-3.60	67.70	8.0

¹H NMR Spectrum of Compound 10 in CDCl₃

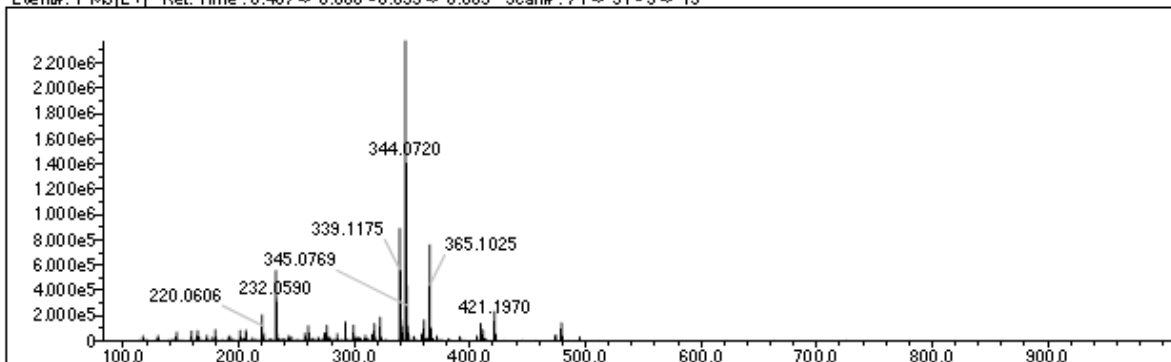


^{13}C NMR Spectrum of Compound 10 in CDCl_3

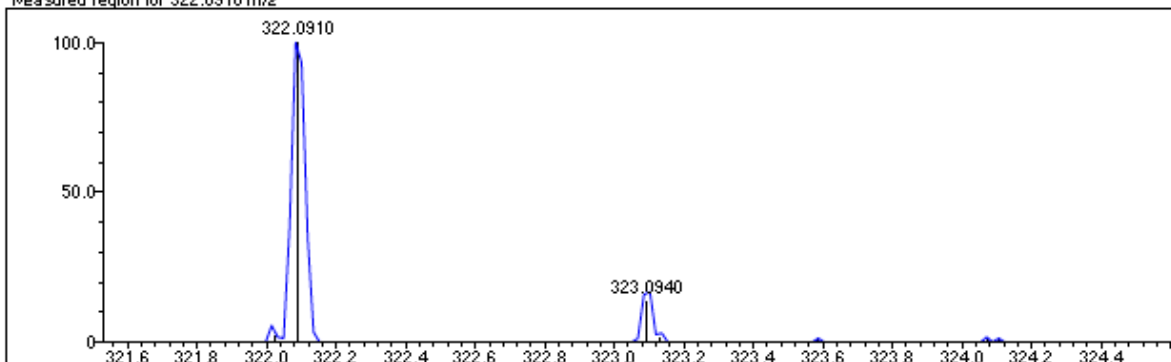


HRMS of Compound 10

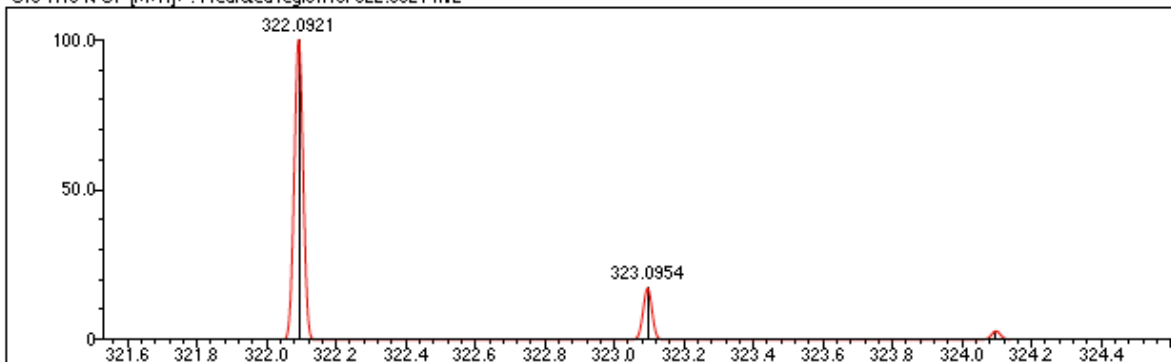
Event#: 1 MS(E+) Ret. Time : 0.467 → 0.600 -0.053 → 0.085 Scan#: 71 → 91 - 9 → 13



Measured region for 322.0910 m/z

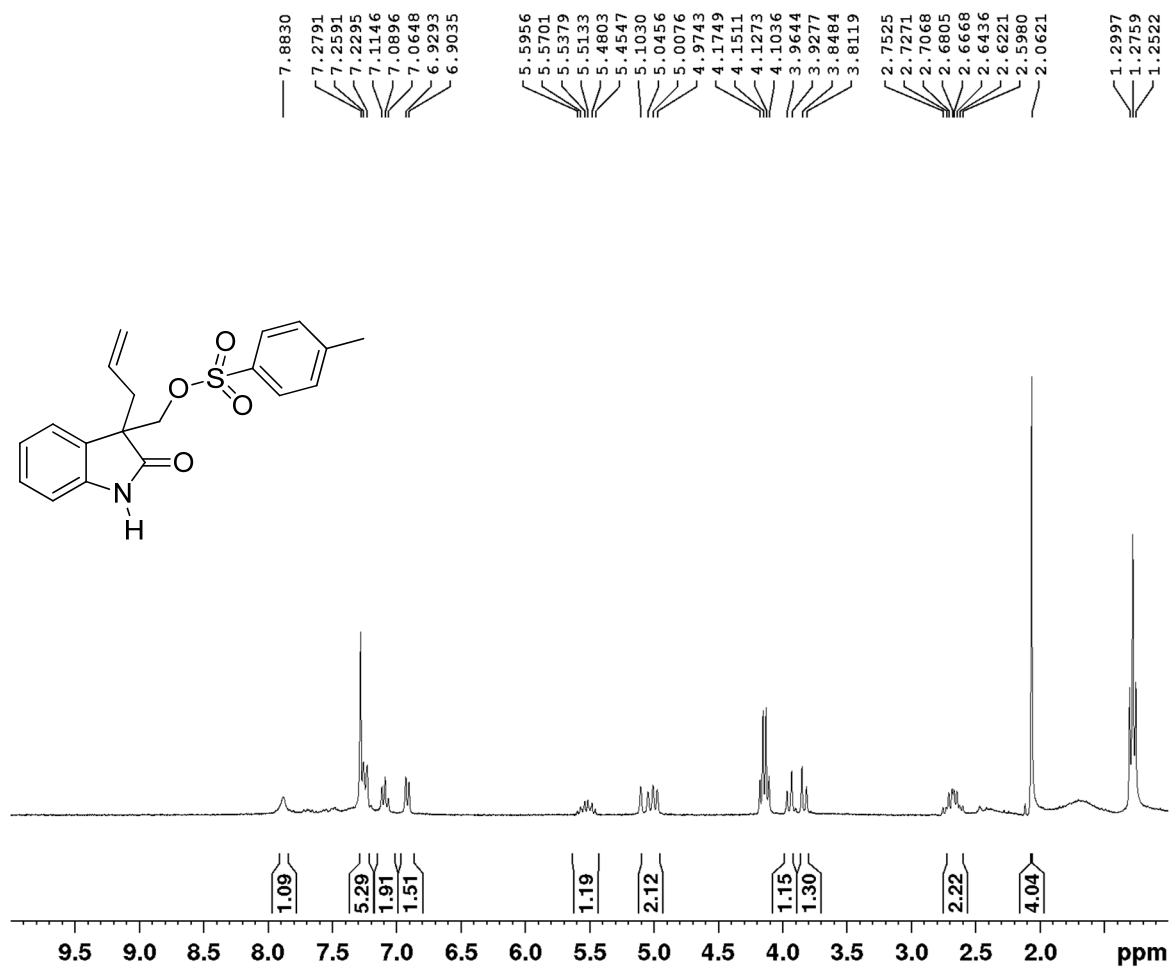


C15 H15 N O7 [M+H]⁺ : Predicted region for 322.0921 m/z

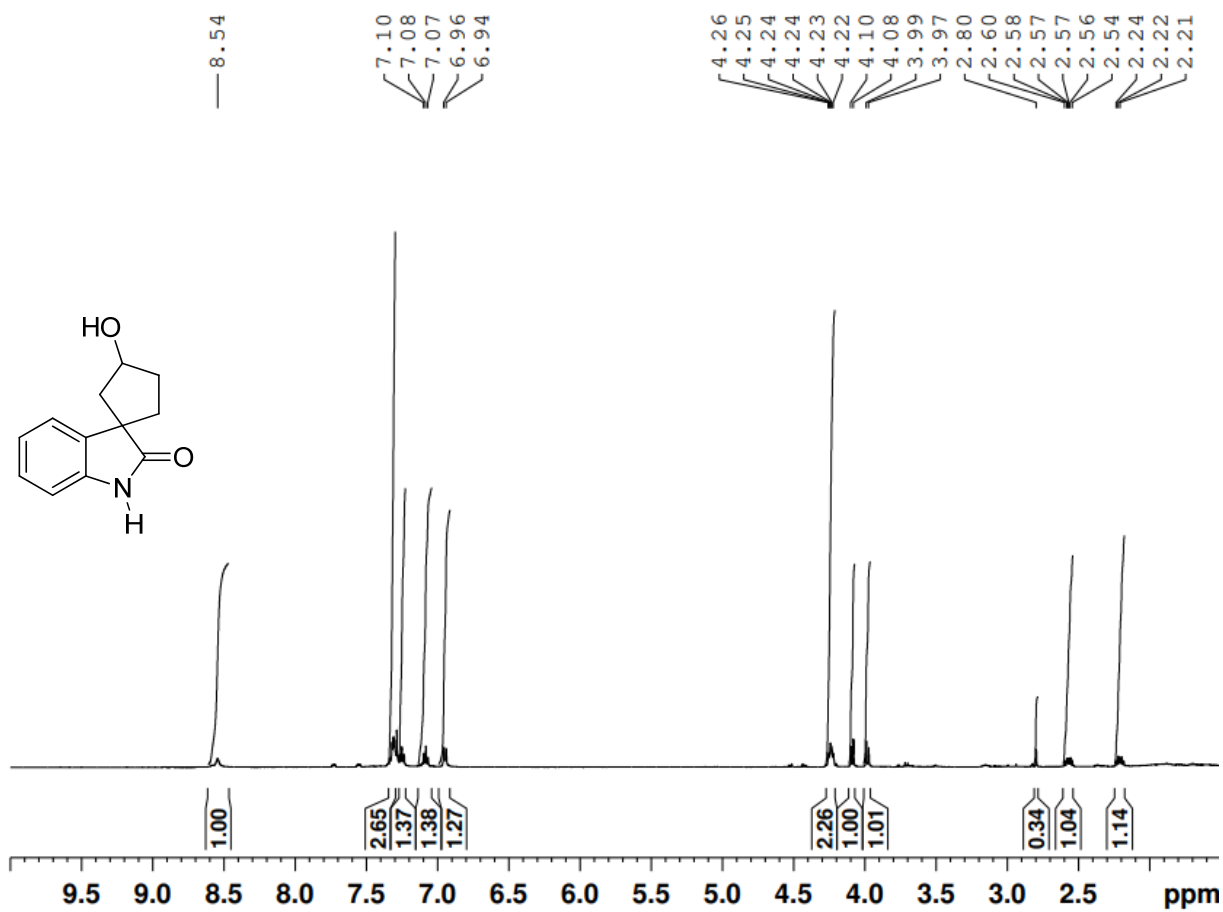


Rank	Score	Formula (M)	Ion	Mass. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Isa	DfE
2	86.87	C15 H15 N O7	[M+H] ⁺	322.0910	322.0921	-1.1	-3.42	92.47	9.0

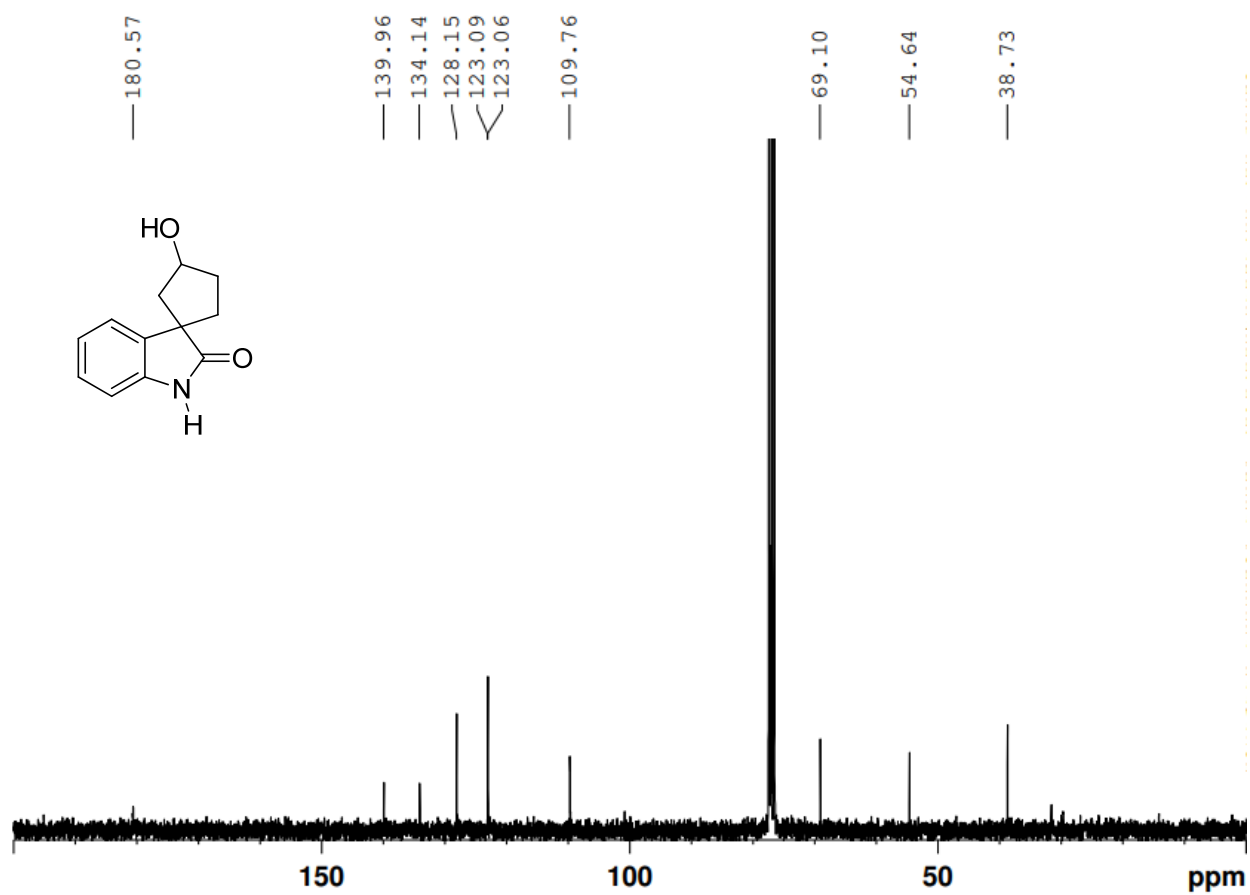
¹H NMR Spectrum of Compound 11 in CDCl₃



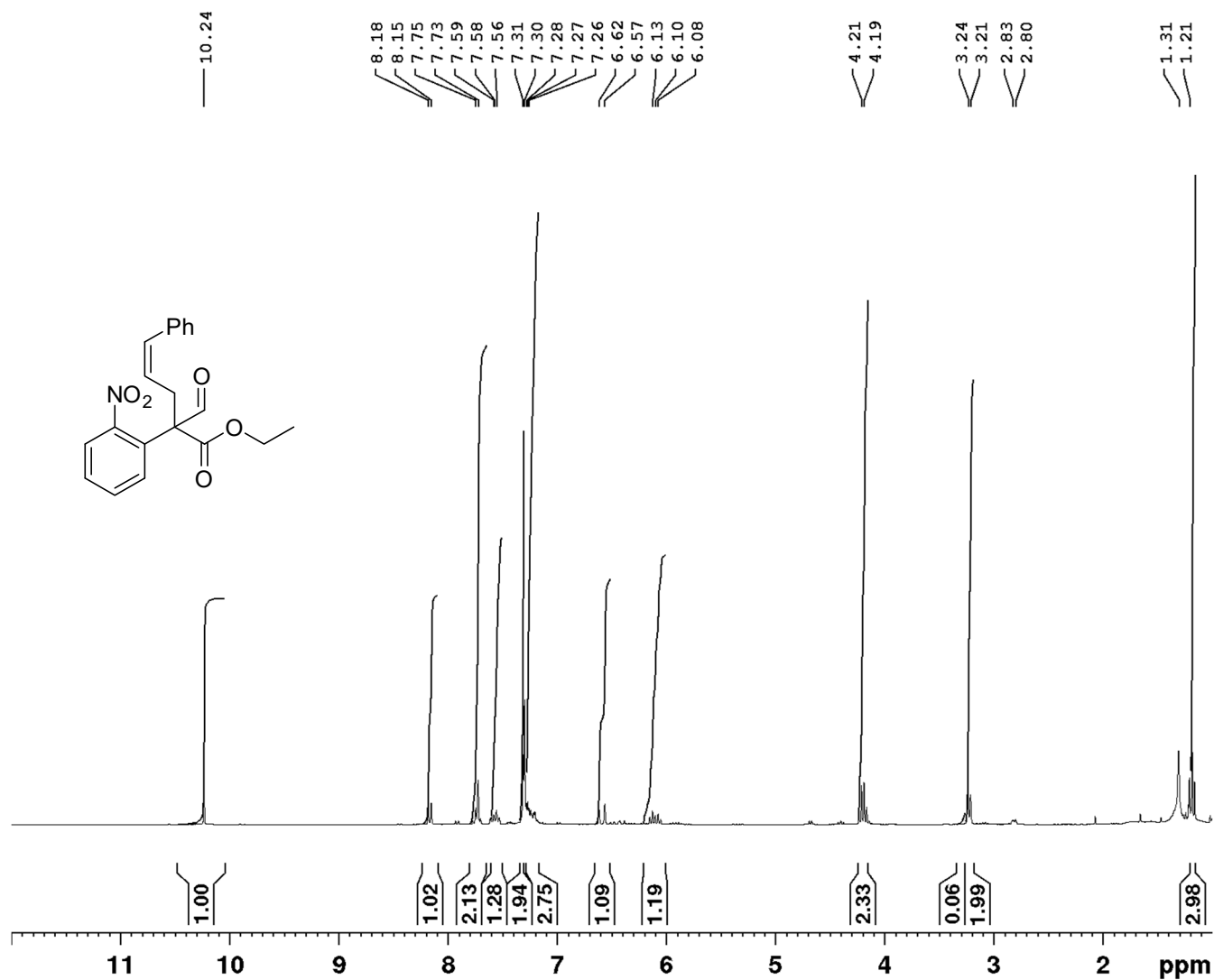
¹H NMR Spectrum of Compound 12 in CDCl₃



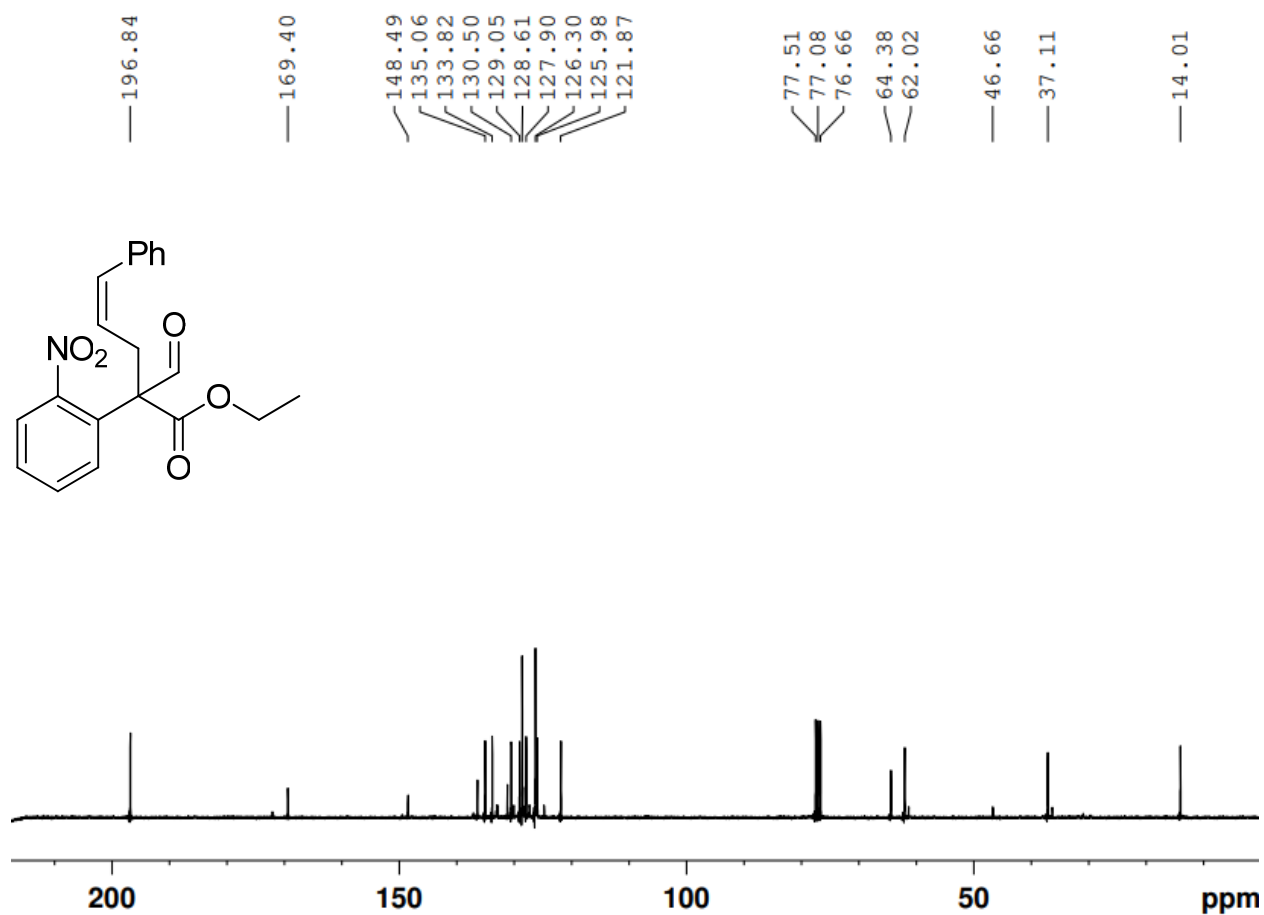
¹³C NMR Spectrum of Compound 12 in CDCl₃



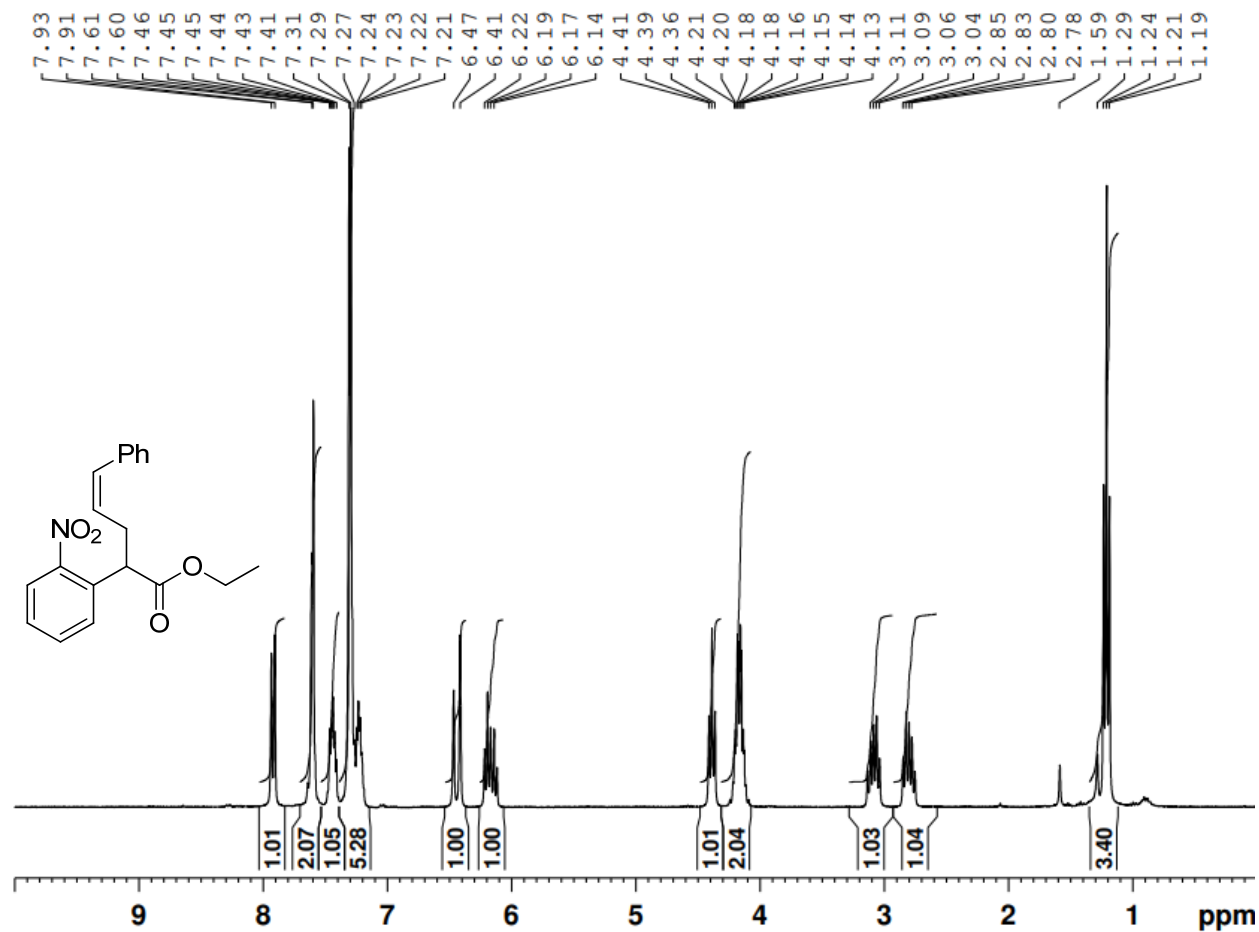
¹H NMR Spectrum of Compound 13 in CDCl₃



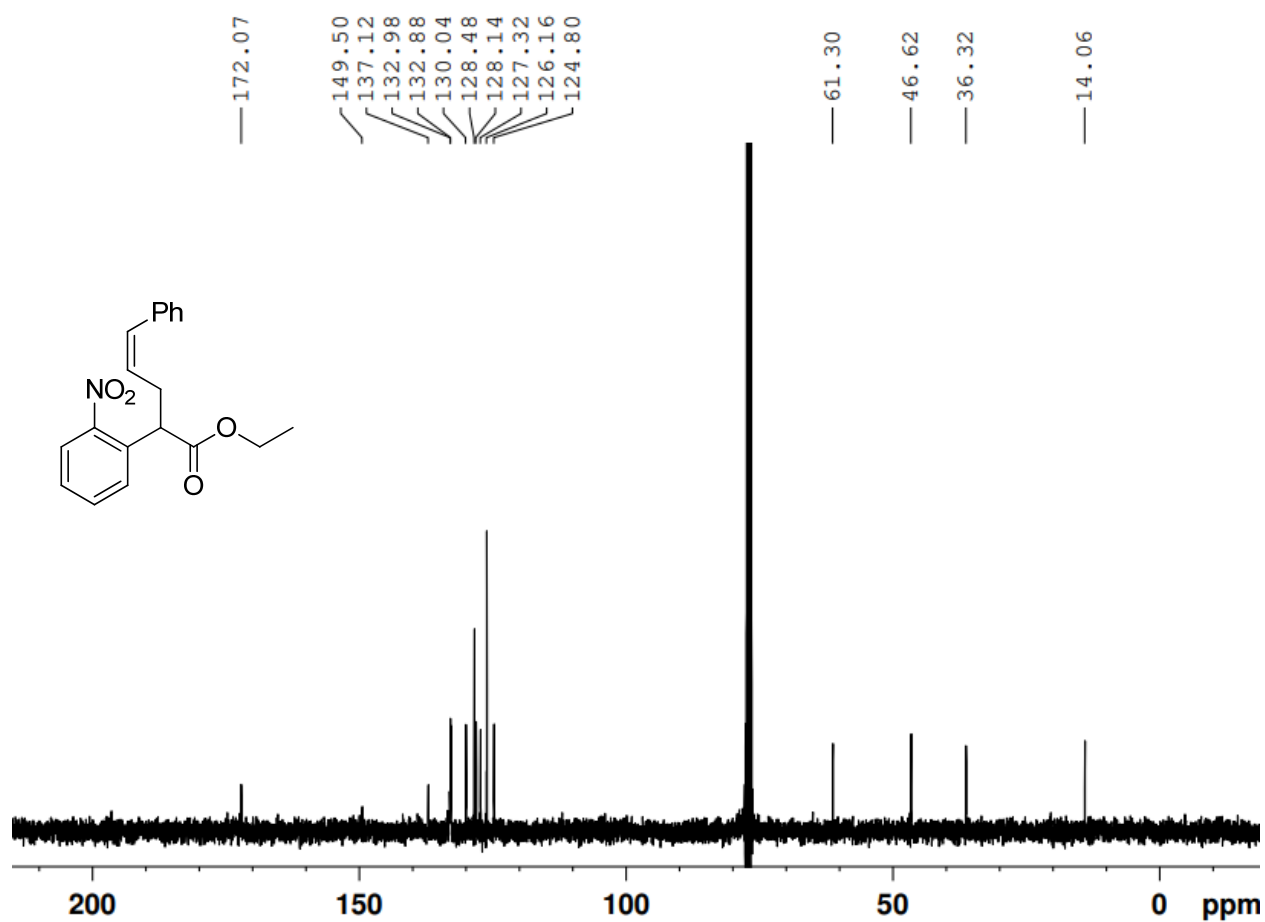
^{13}C NMR Spectrum of Compound 13 in CDCl_3



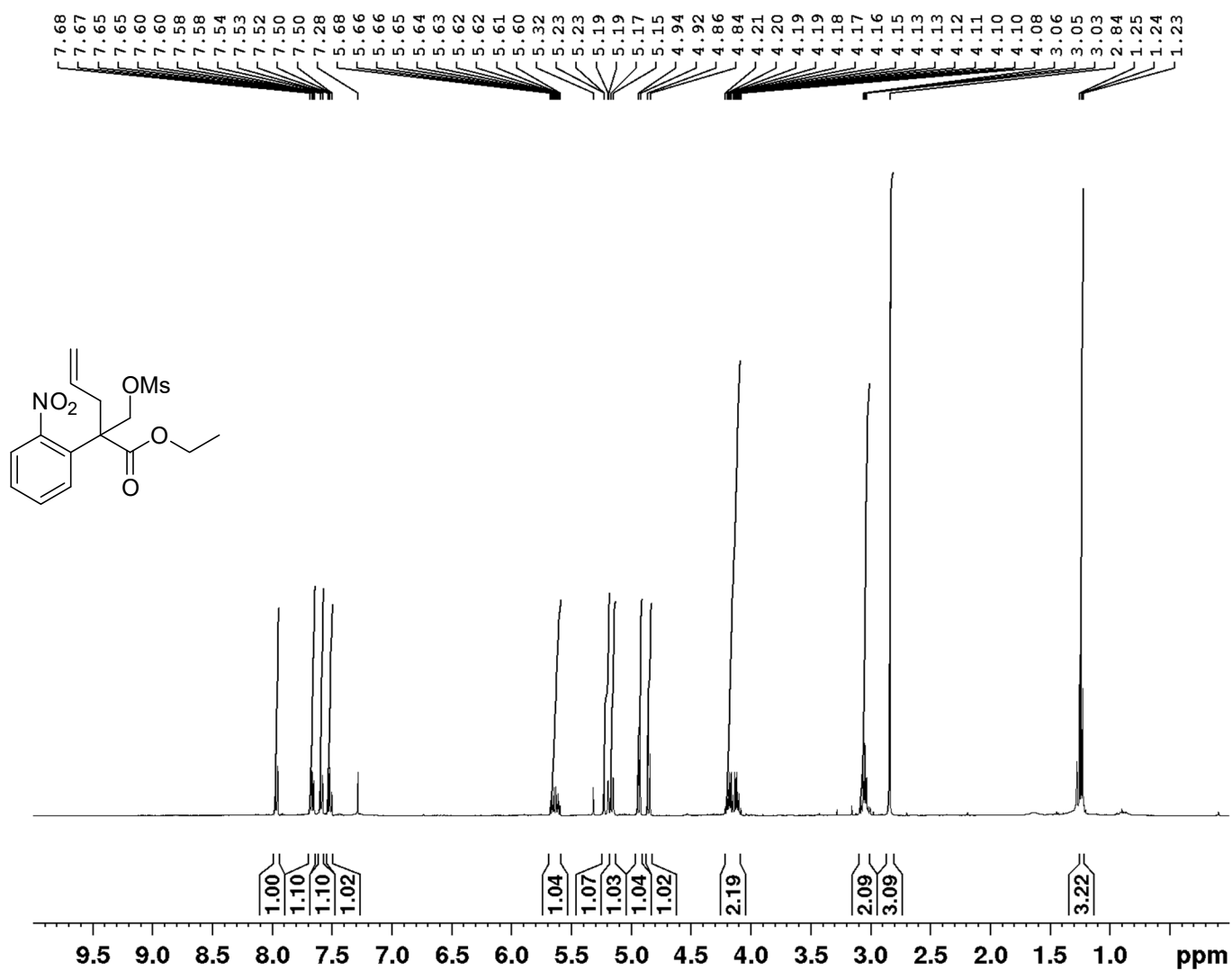
¹H NMR Spectrum of Compound 13a in CDCl₃



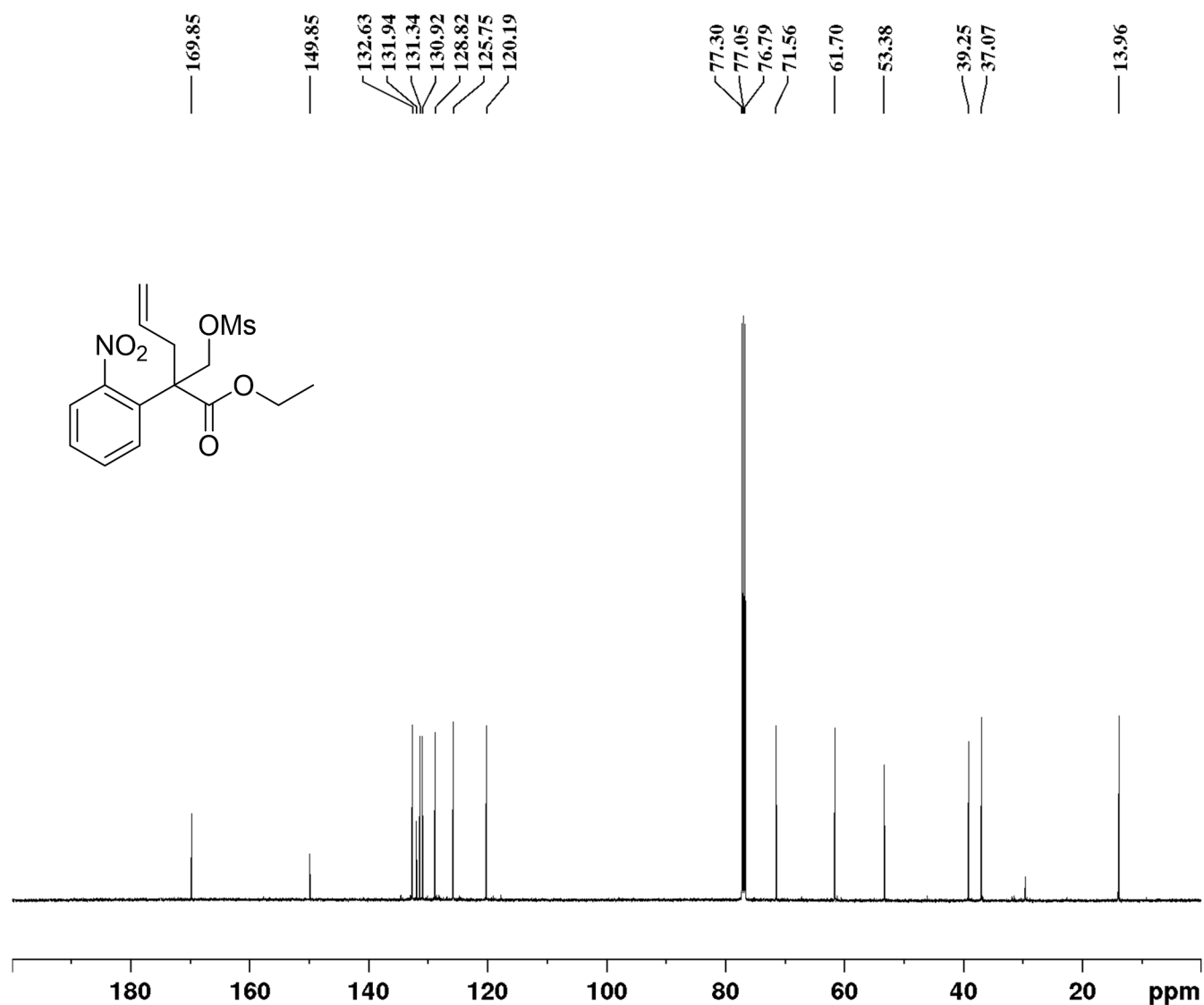
^1H NMR Spectrum of Compound 13a in CDCl_3



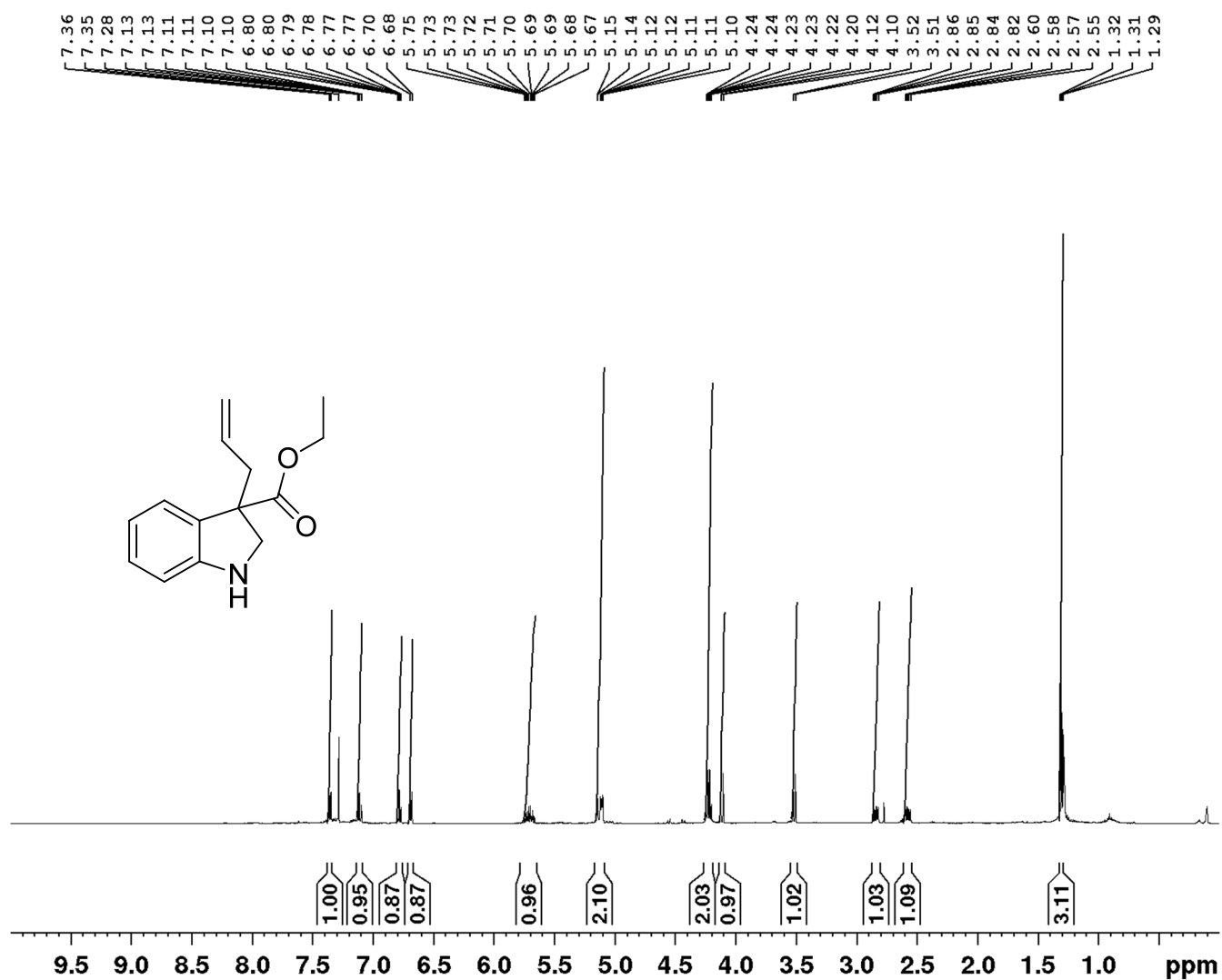
¹H NMR Spectrum of Compound 14 in CDCl₃



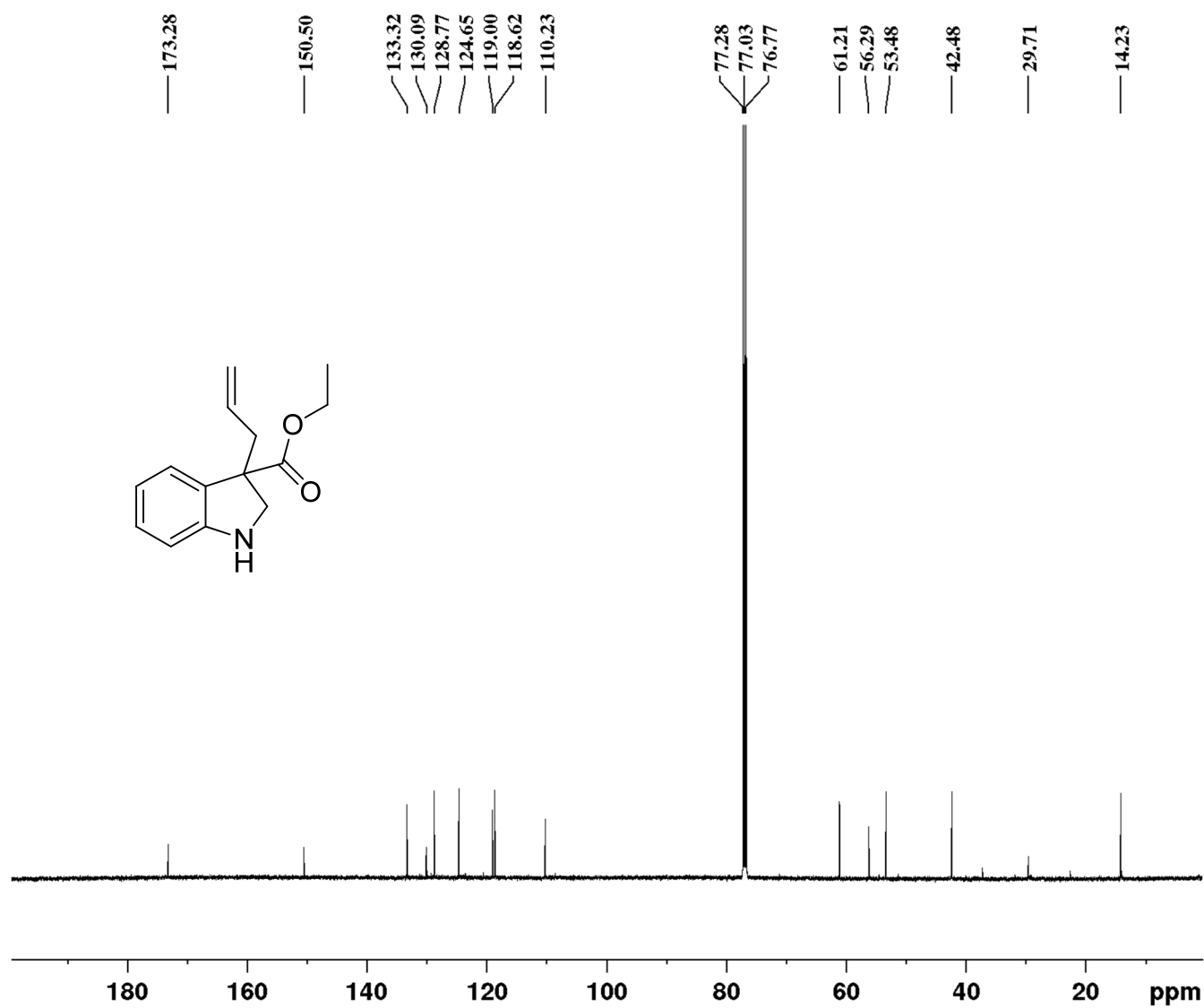
^{13}C NMR Spectrum of Compound 14 in CDCl_3



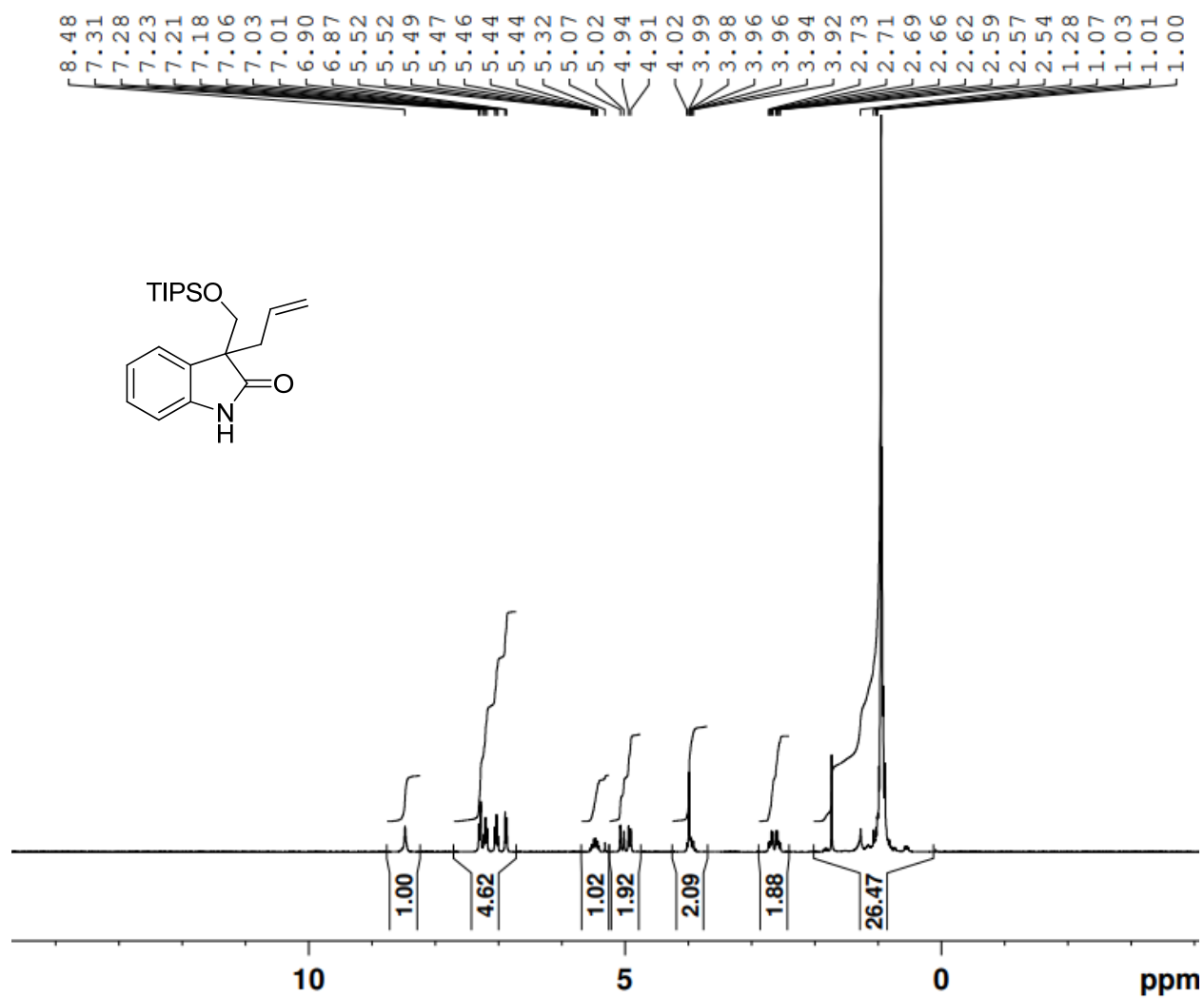
¹H NMR Spectrum of Compound 15 in CDCl₃



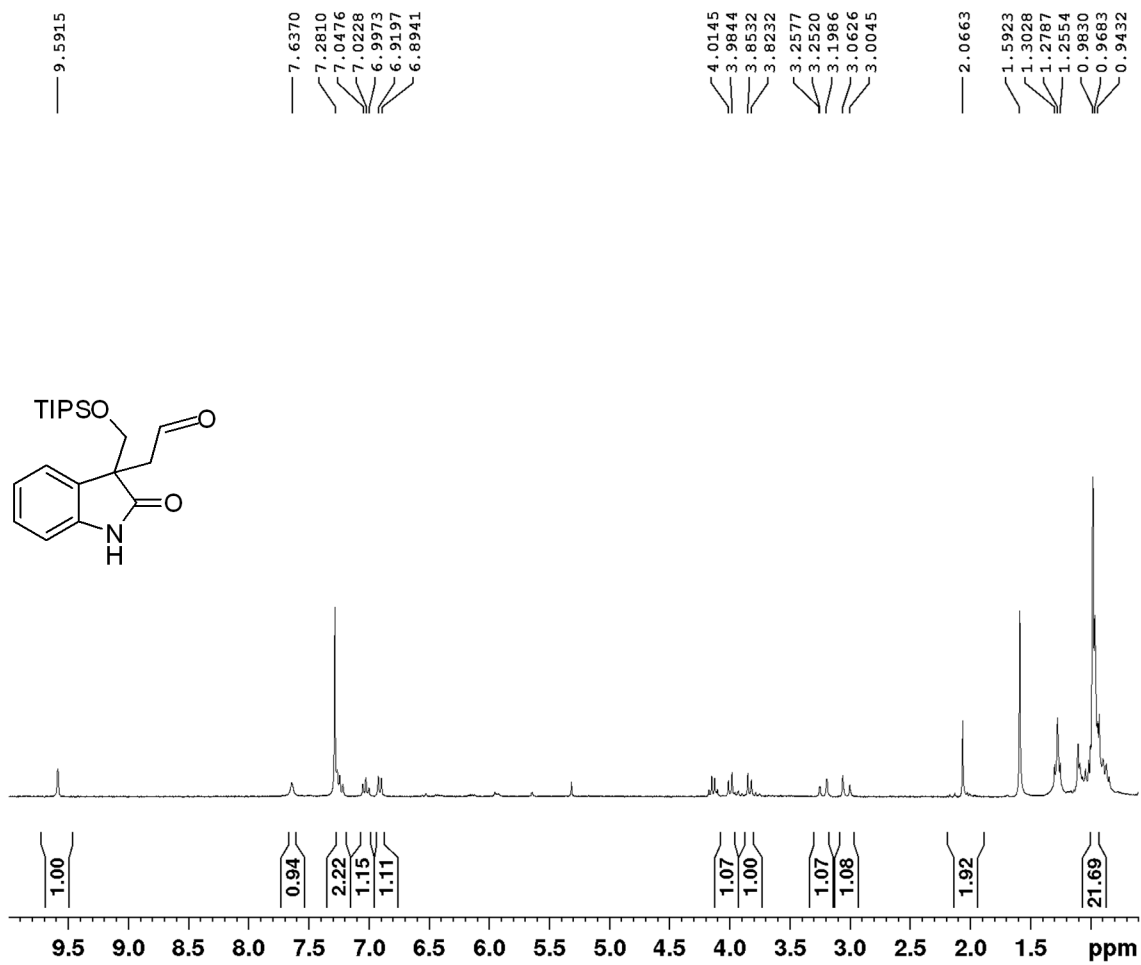
^{13}C NMR Spectrum of Compound 15 in CDCl_3



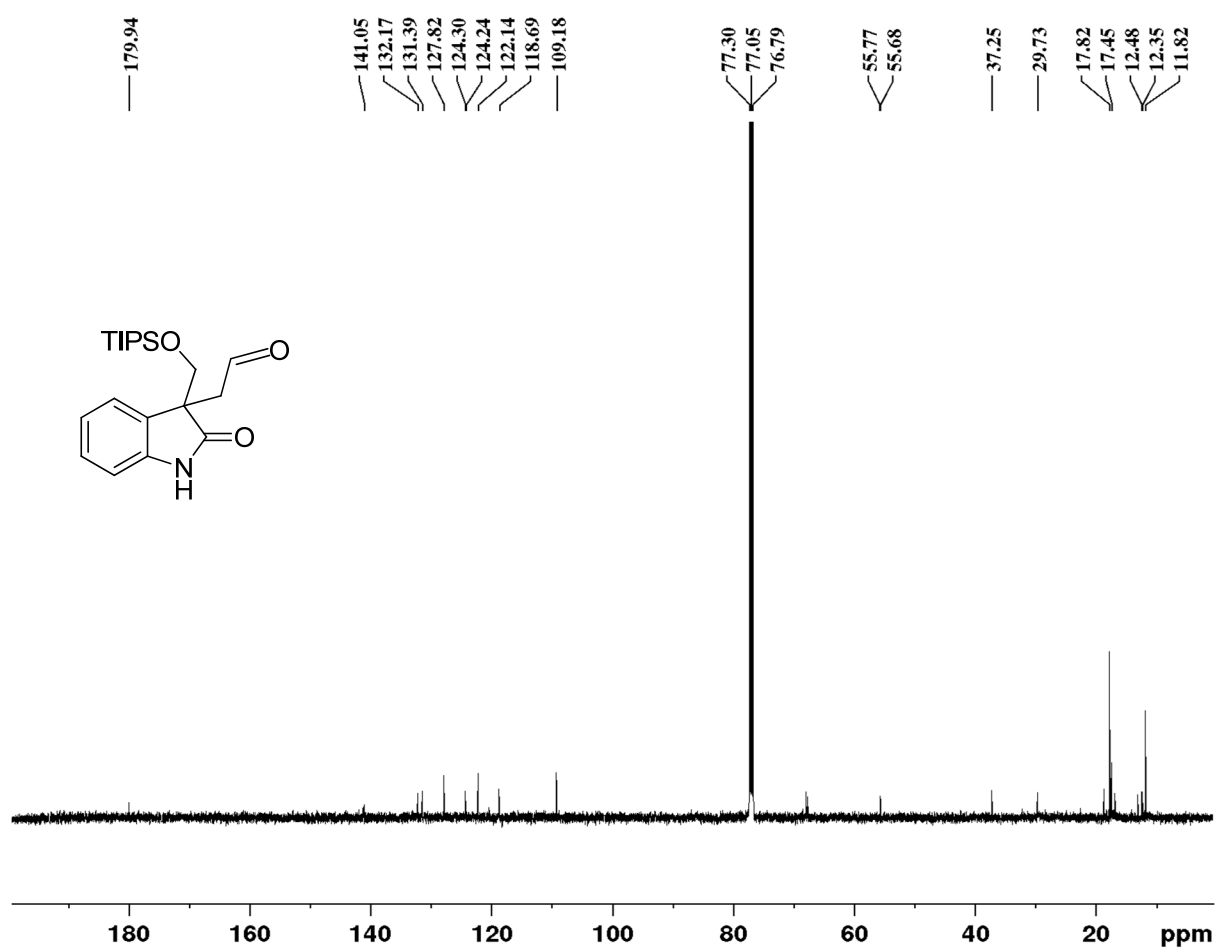
¹H NMR Spectrum of Compound 16 in CDCl₃



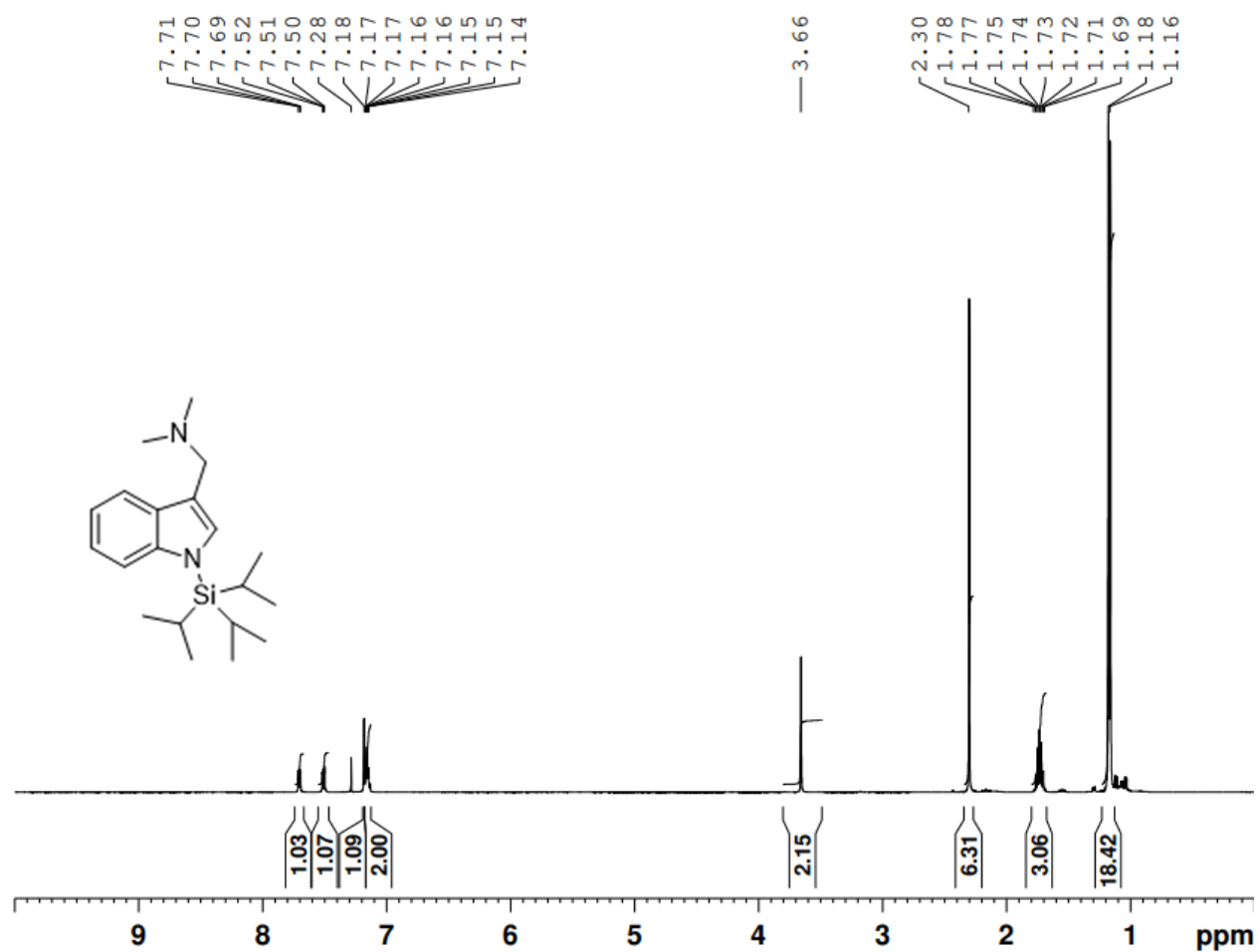
¹H NMR Spectrum of Compound 17 in CDCl₃



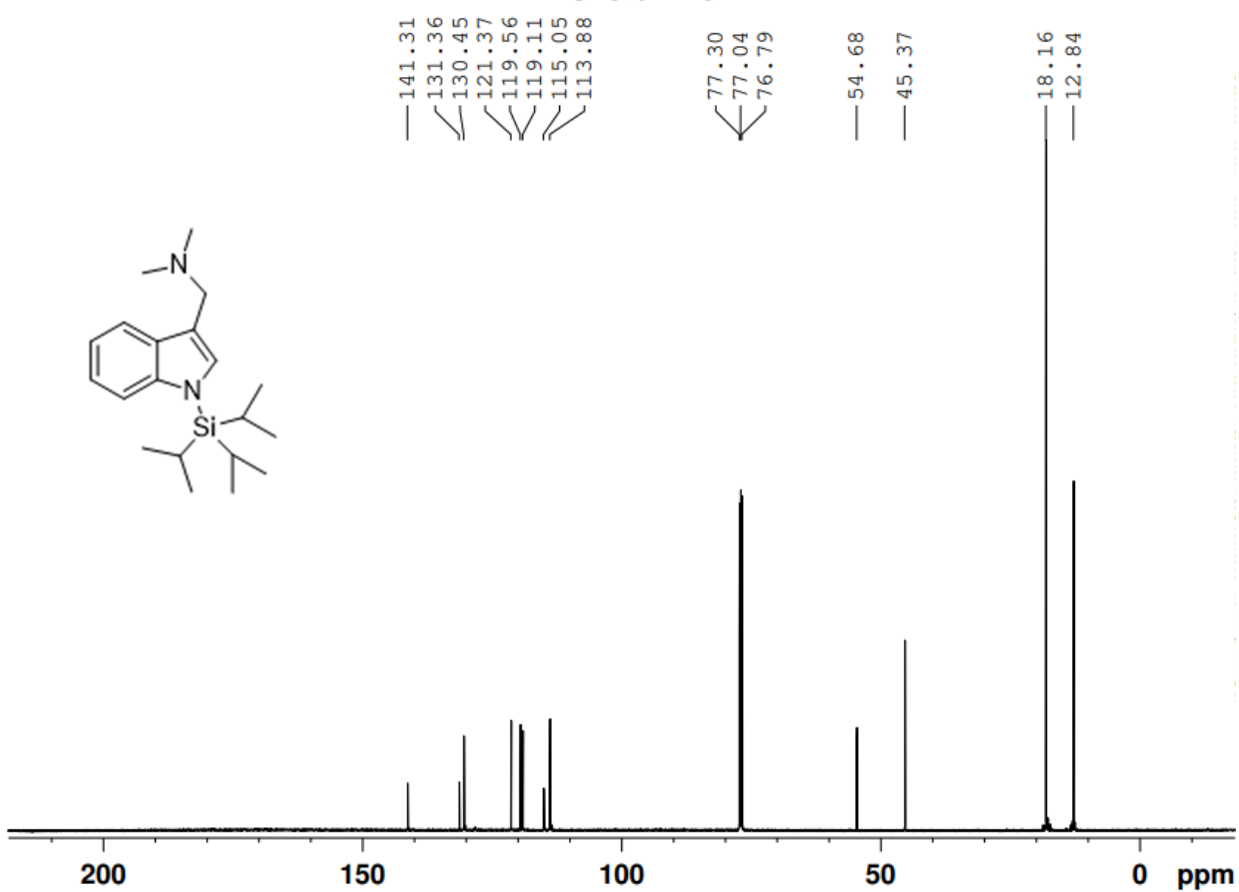
^{13}C NMR Spectrum of Compound 17 in CDCl_3



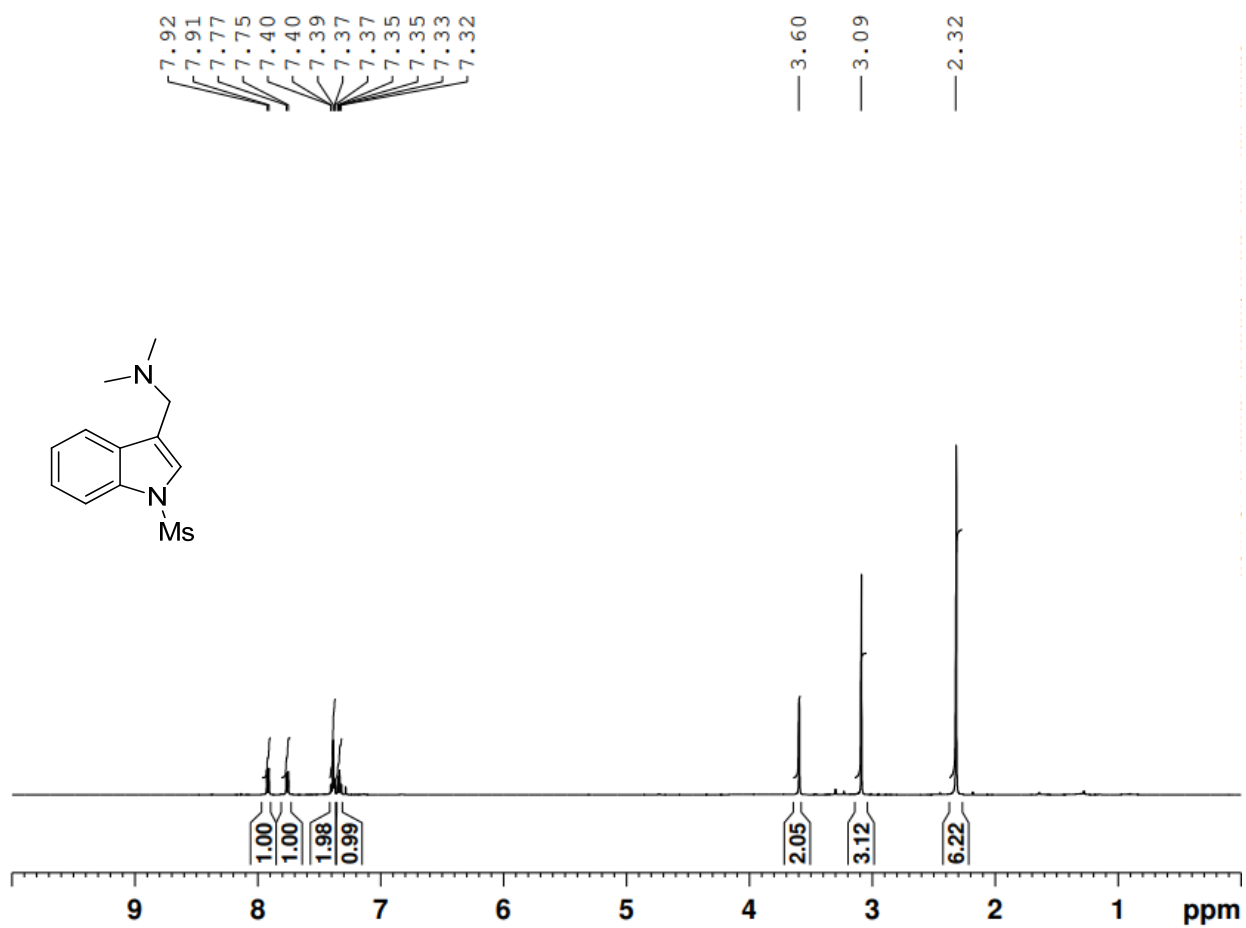
^1H NMR Spectrum of Compound 25a in CDCl_3



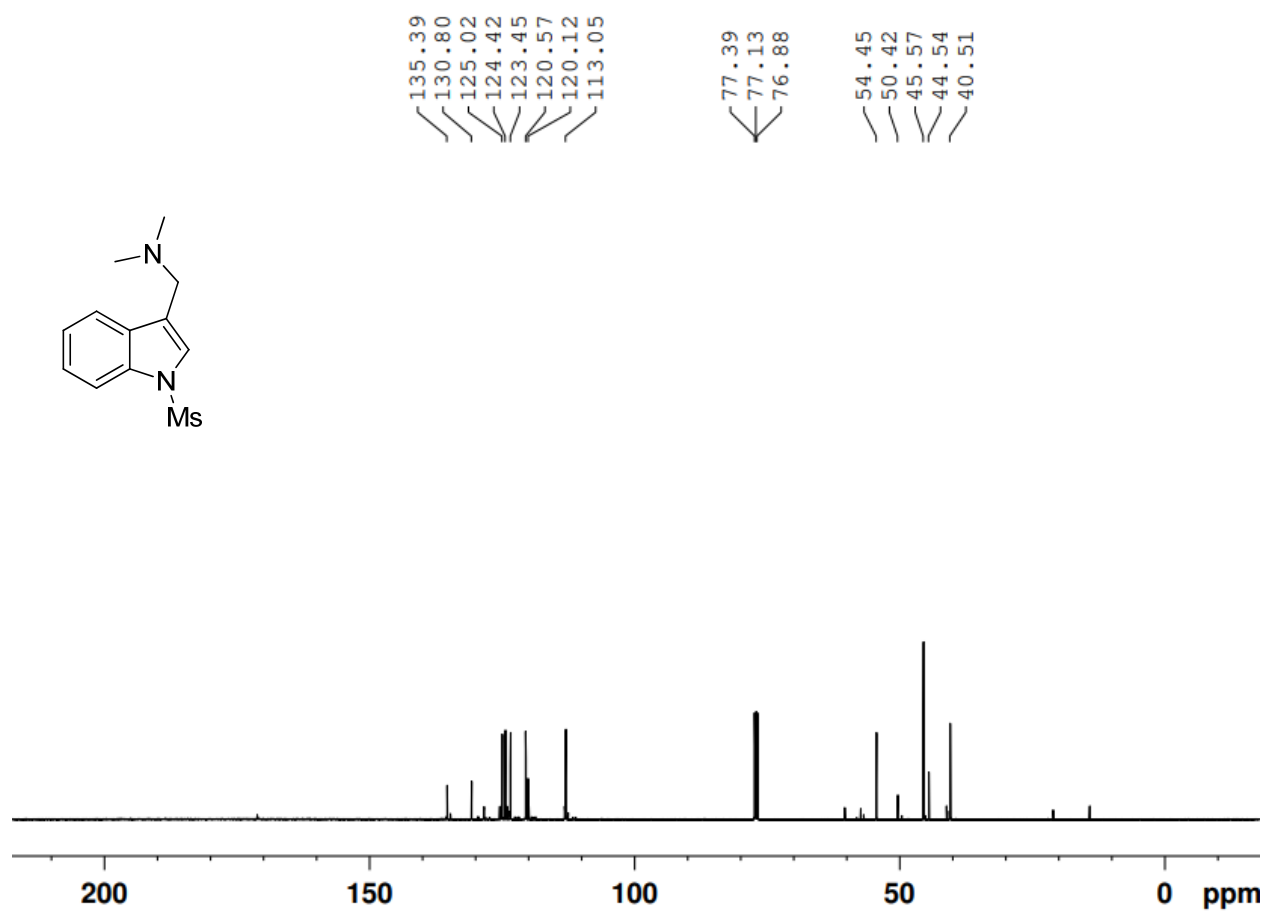
^{13}C NMR Spectrum of Compound 25a in CDCl_3



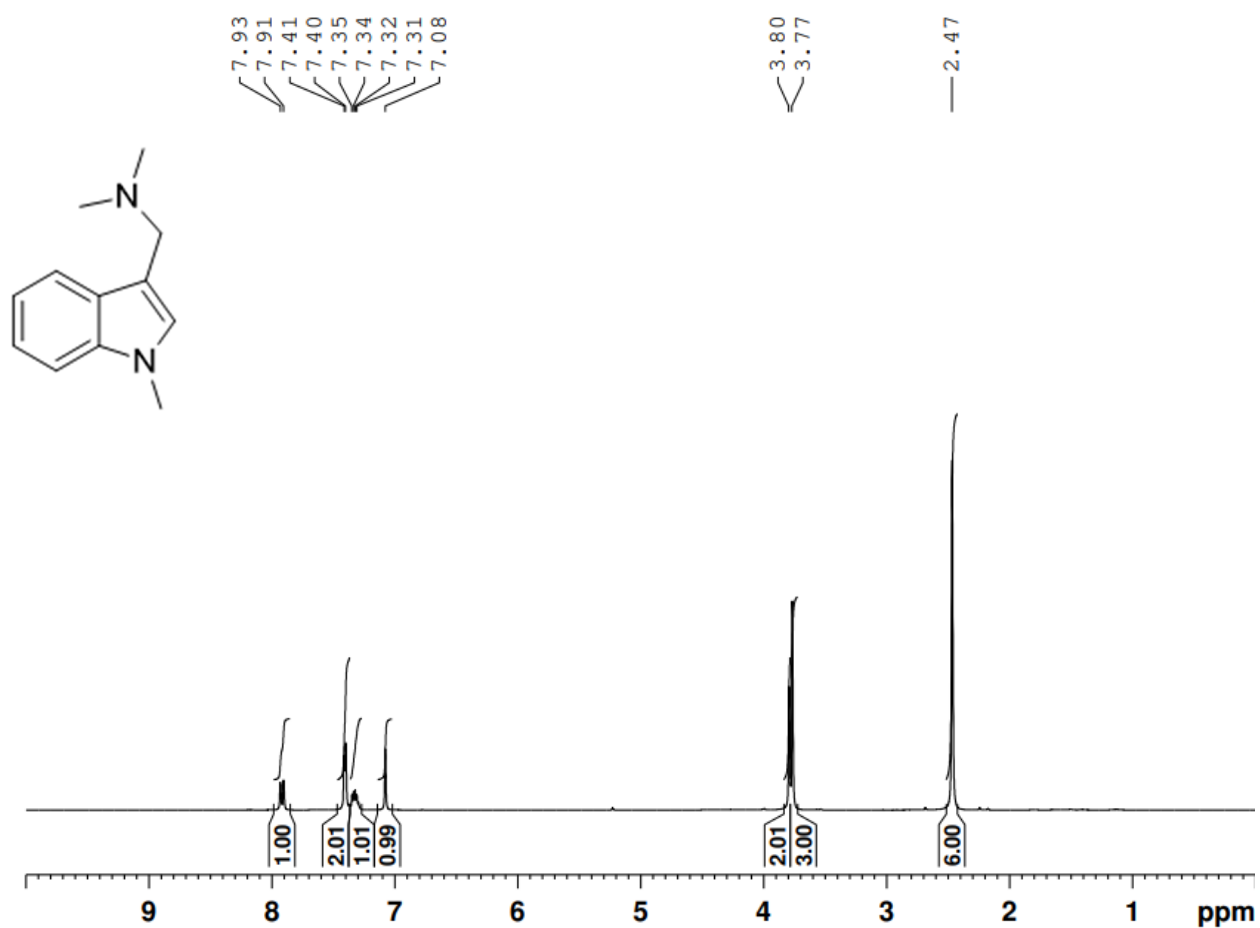
^1H NMR Spectrum of Compound 25c in CDCl_3



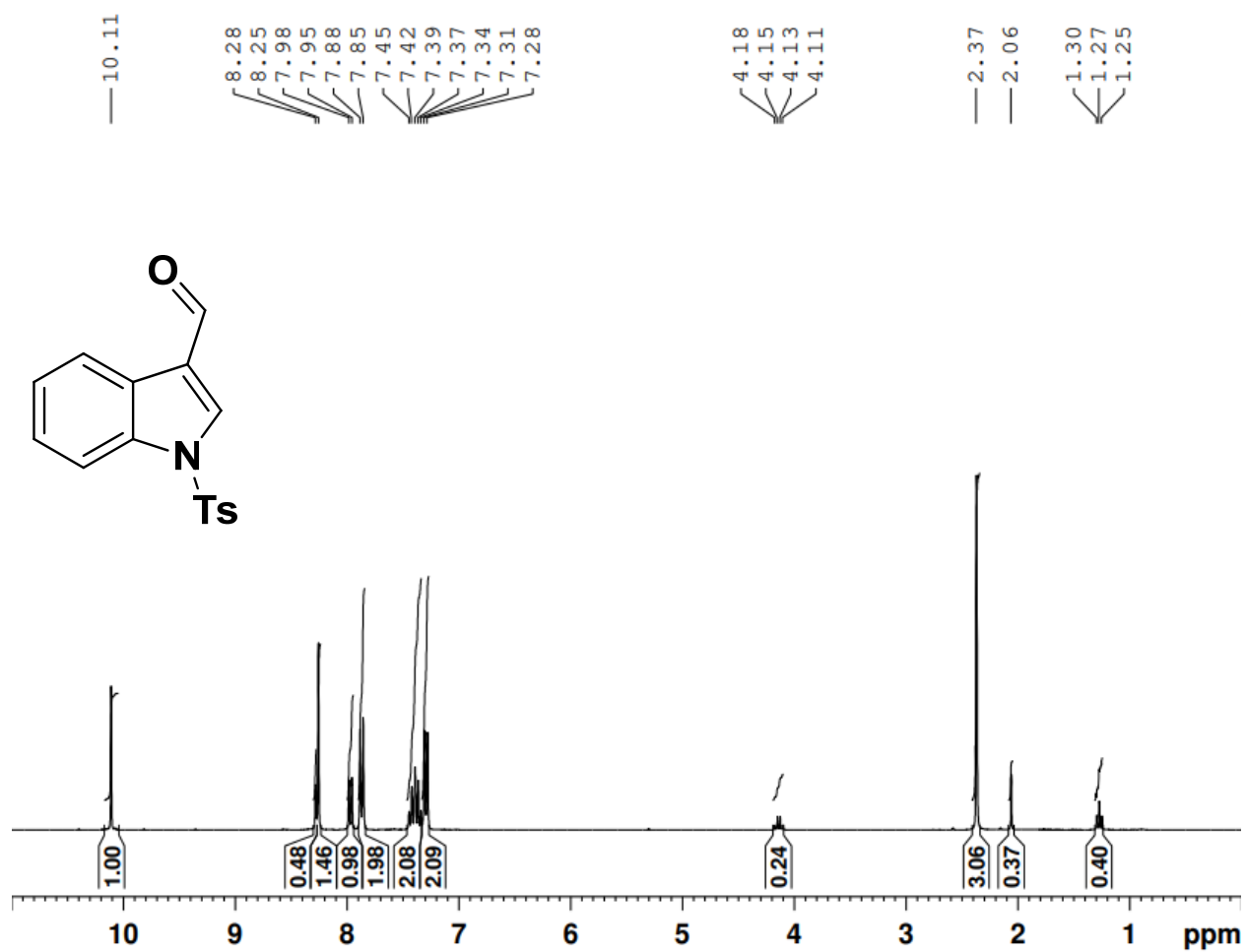
¹H NMR Spectrum of Compound 25c in CDCl₃



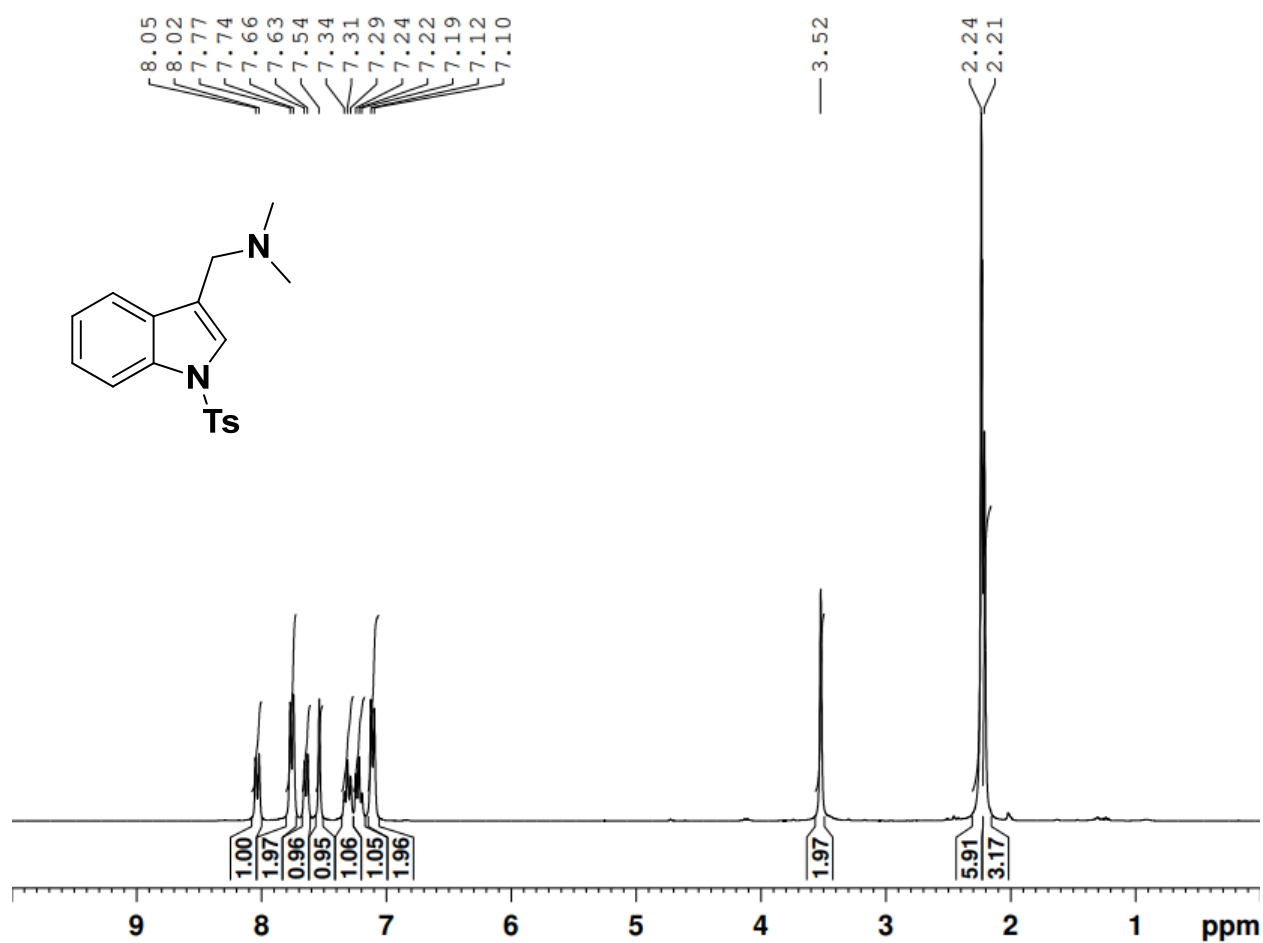
^1H NMR Spectrum of Compound 25d in CDCl_3



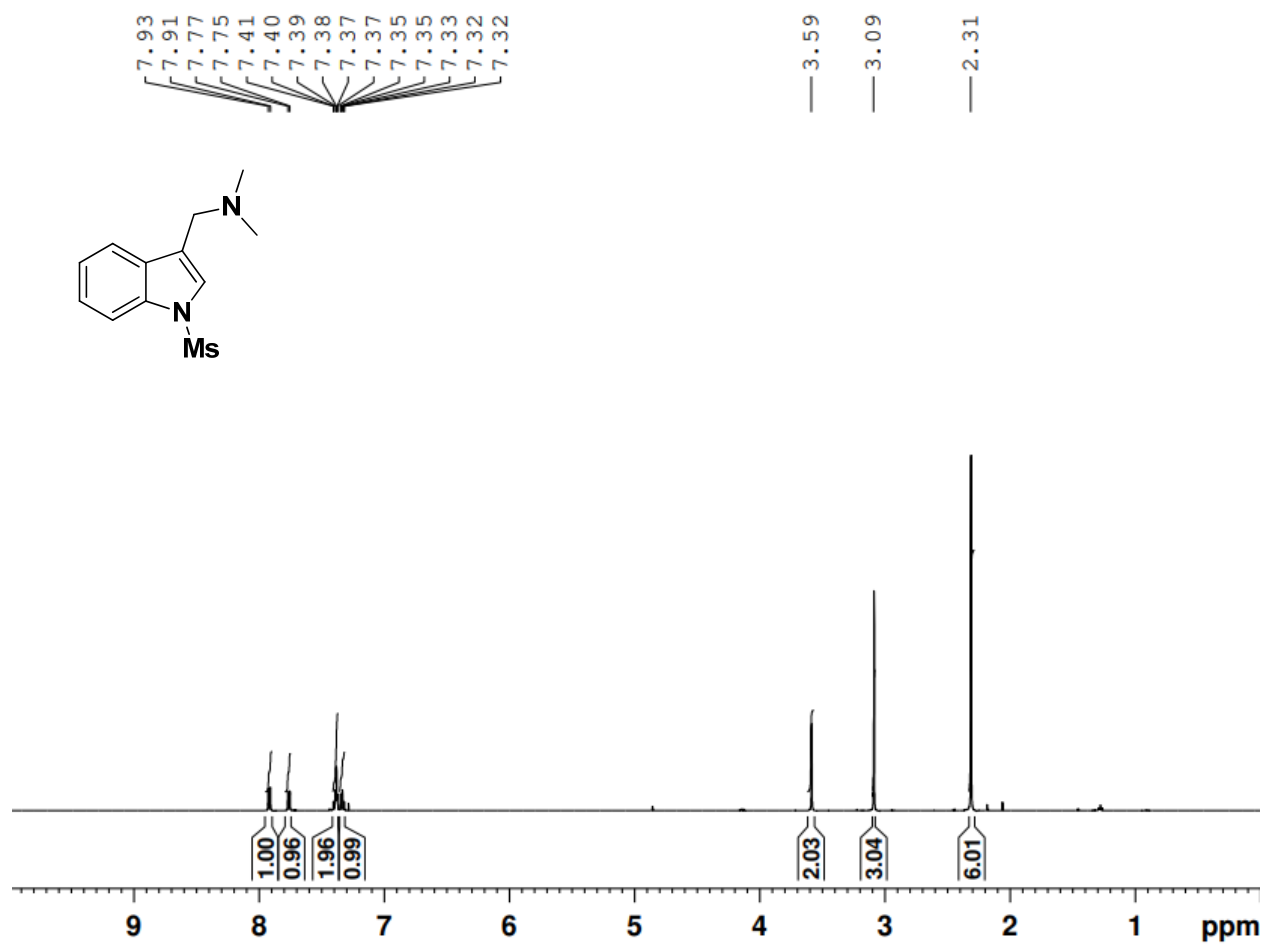
¹H NMR Spectrum of Compound 27b in CDCl₃



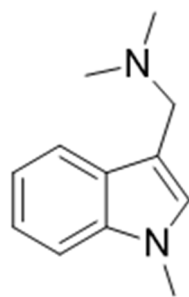
^1H NMR Spectrum of Compound 25b in CDCl_3



¹H NMR Spectrum of Compound 25c in CDCl₃



^{13}C NMR Spectrum of Compound 25d in CDCl_3



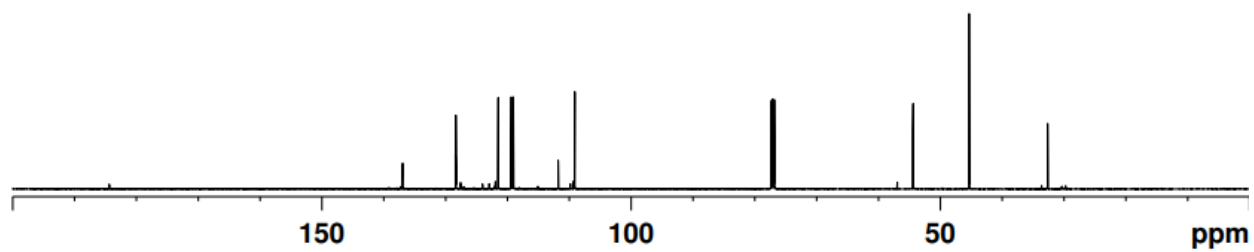
136.98
128.43
128.36
121.53
119.41
119.06
111.83
109.14

77.37
77.12
76.86

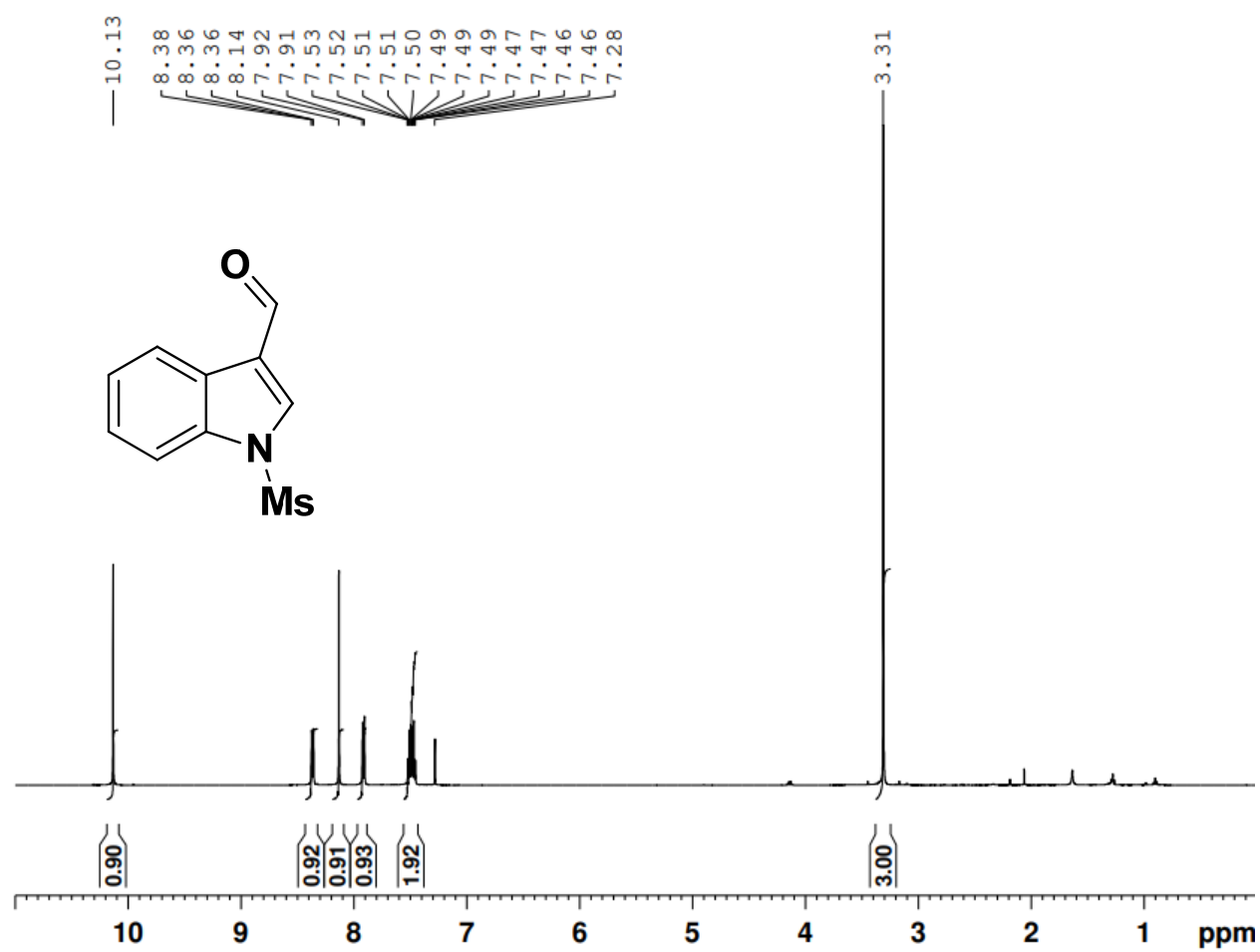
54.46

45.37

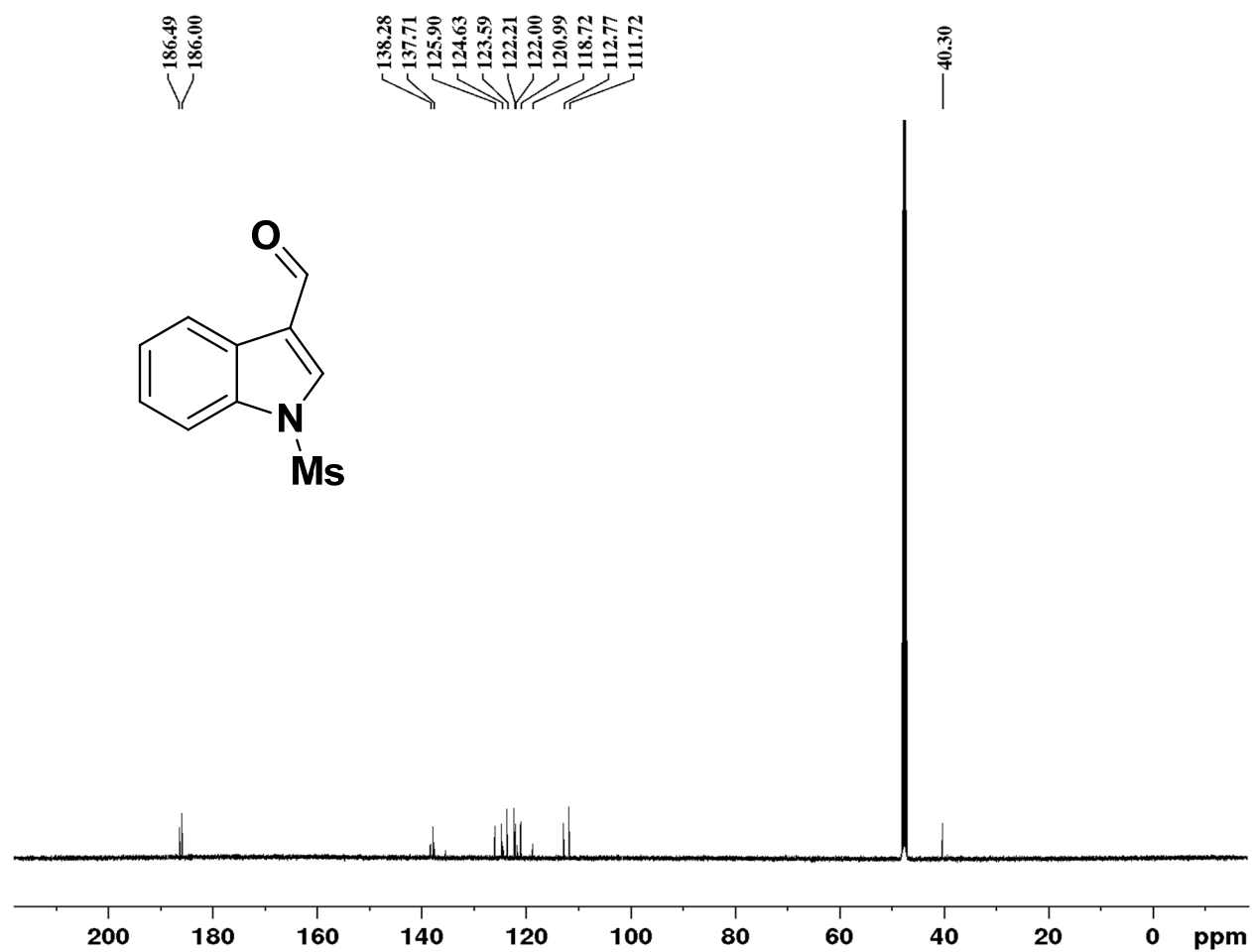
32.68



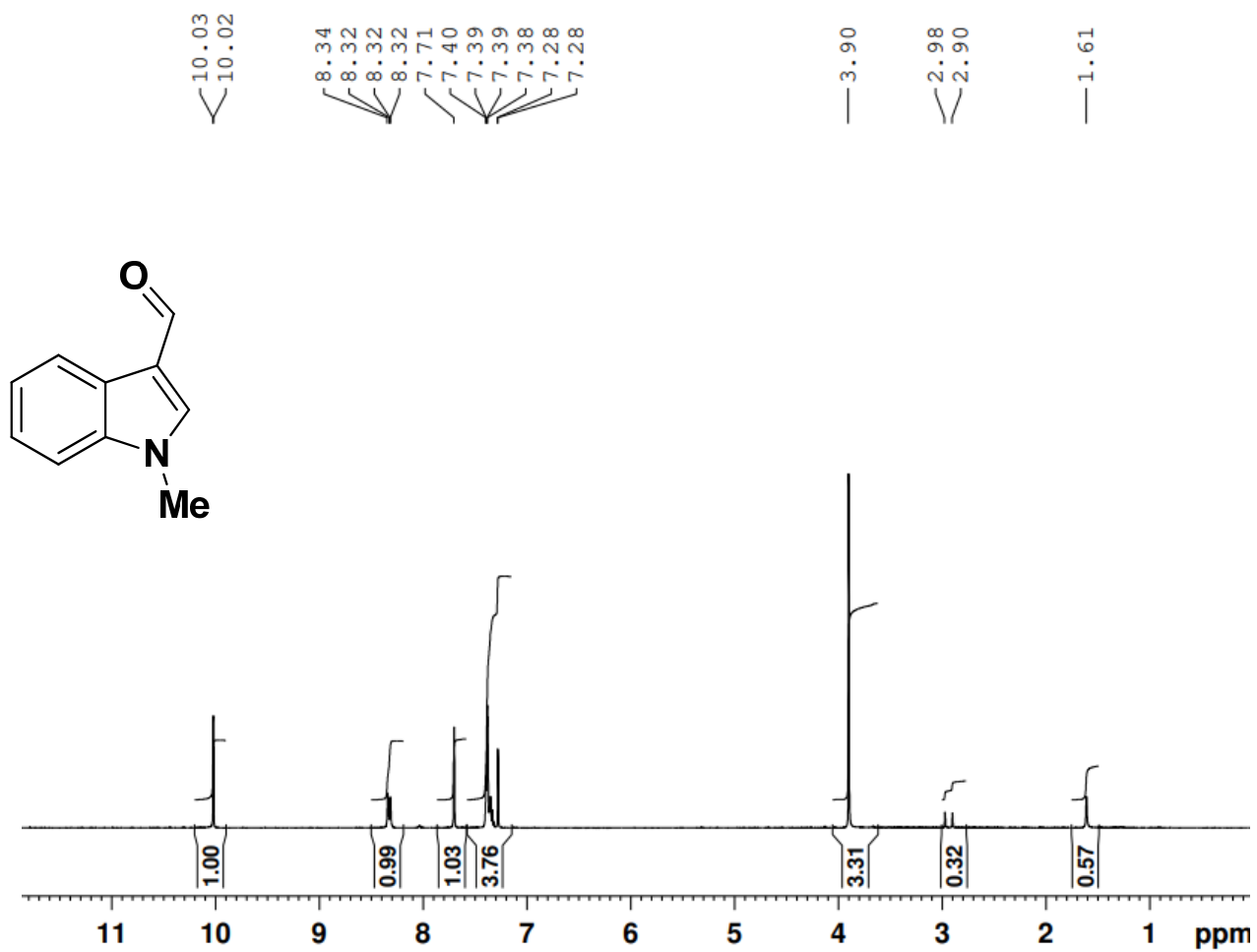
^1H NMR Spectrum of Compound 27c in CDCl_3



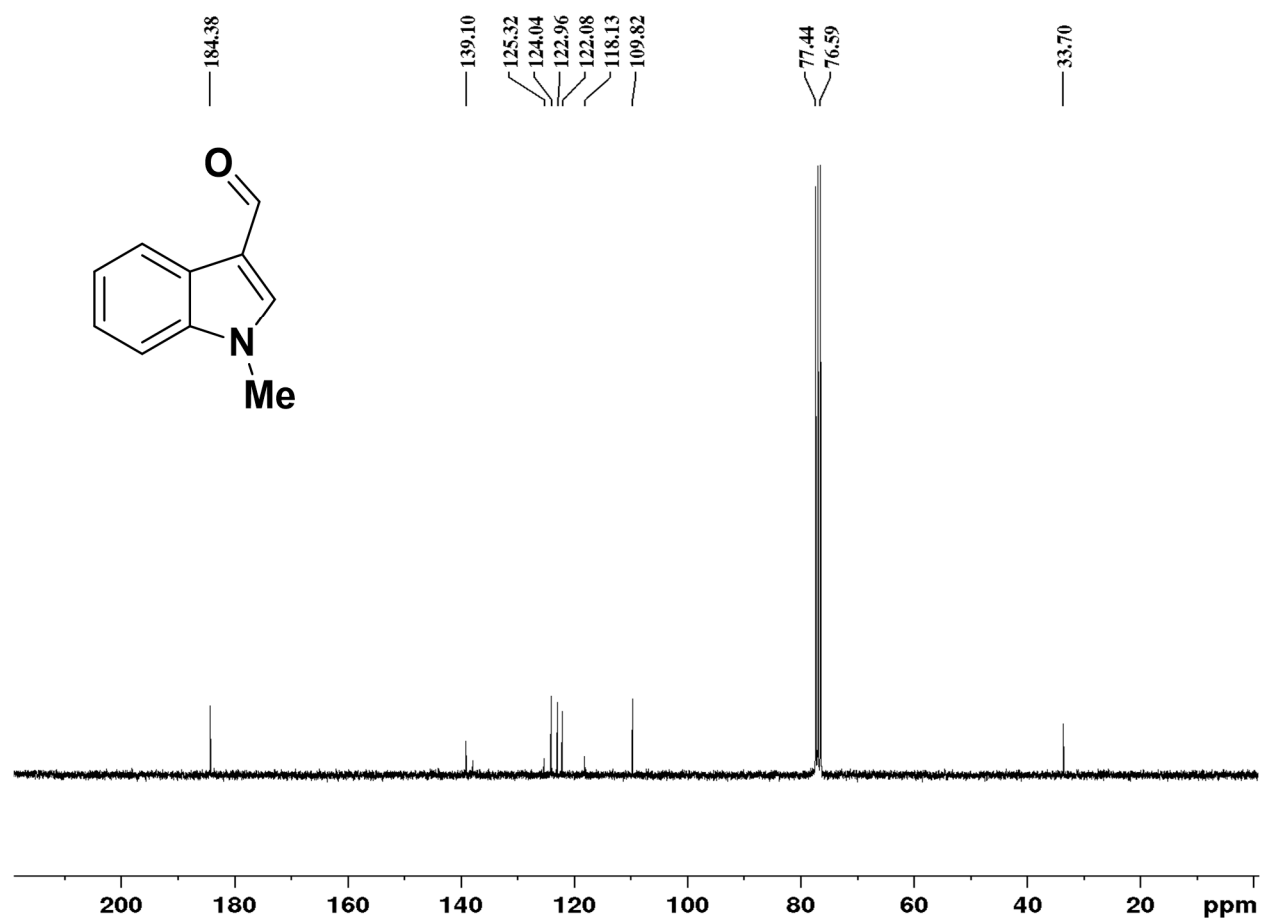
^{13}C NMR Spectrum of Compound 27c in CDCl_3



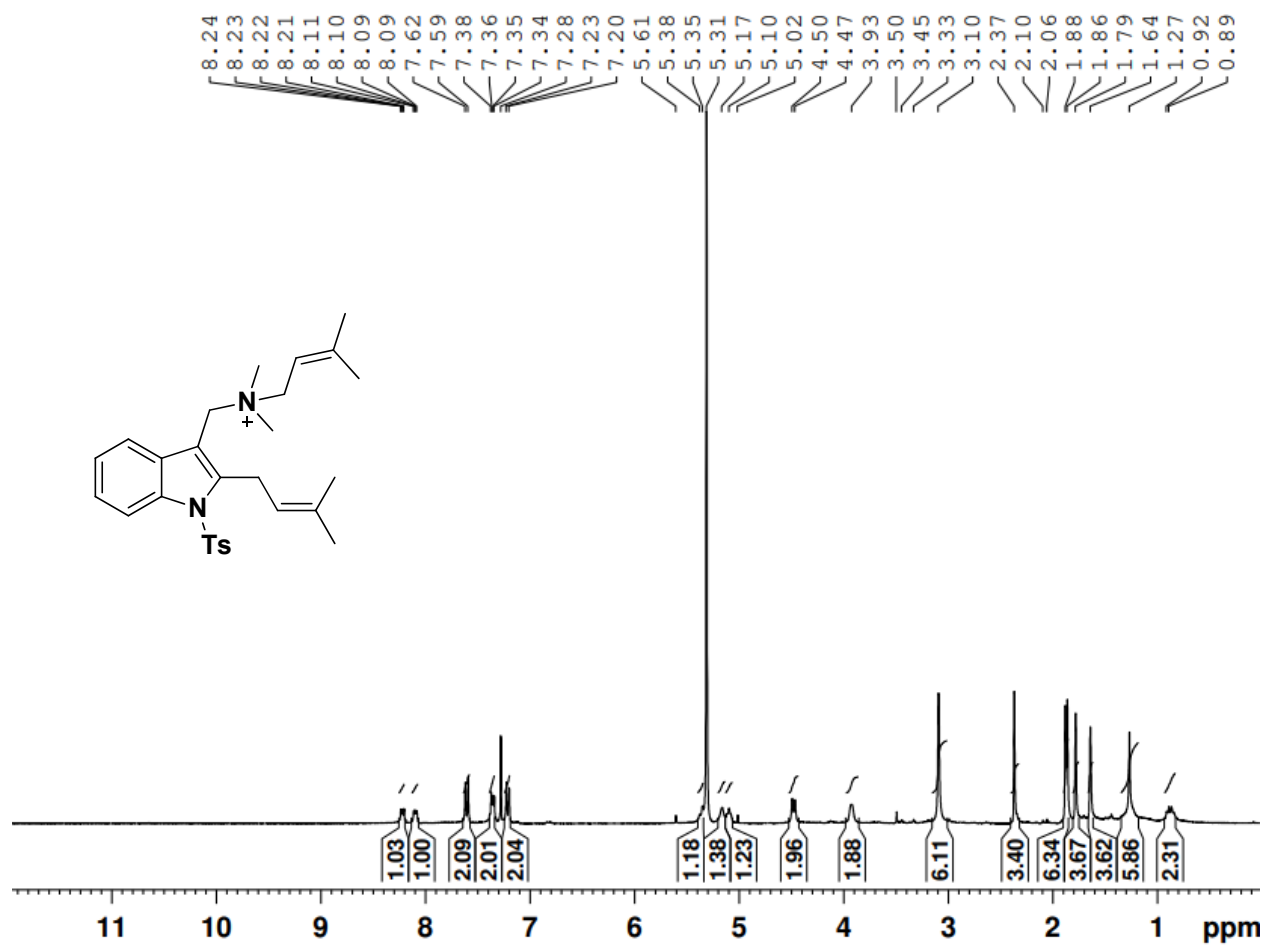
^1H NMR Spectrum of Compound 27d in CDCl_3



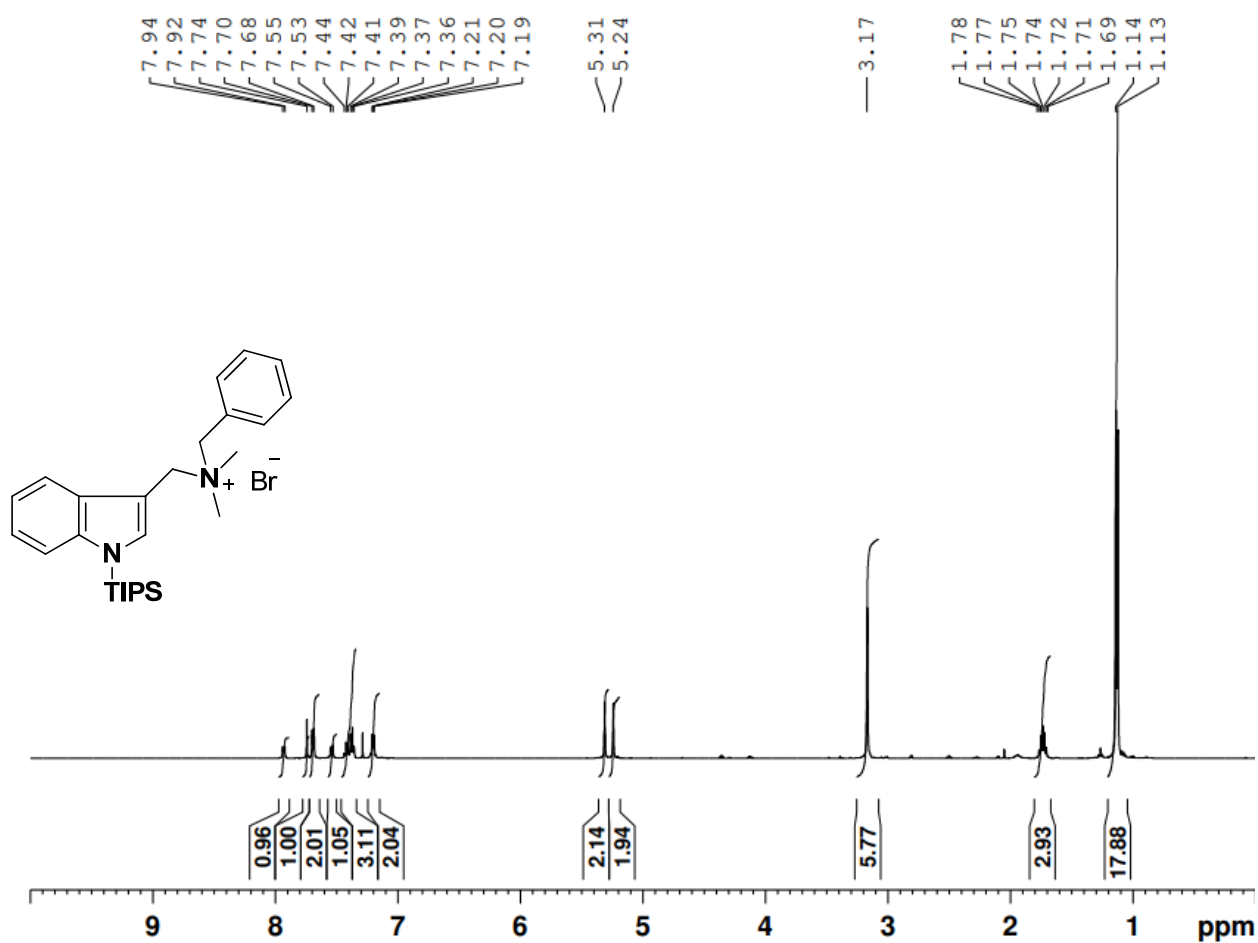
^{13}C NMR Spectrum of Compound 27d in CDCl_3



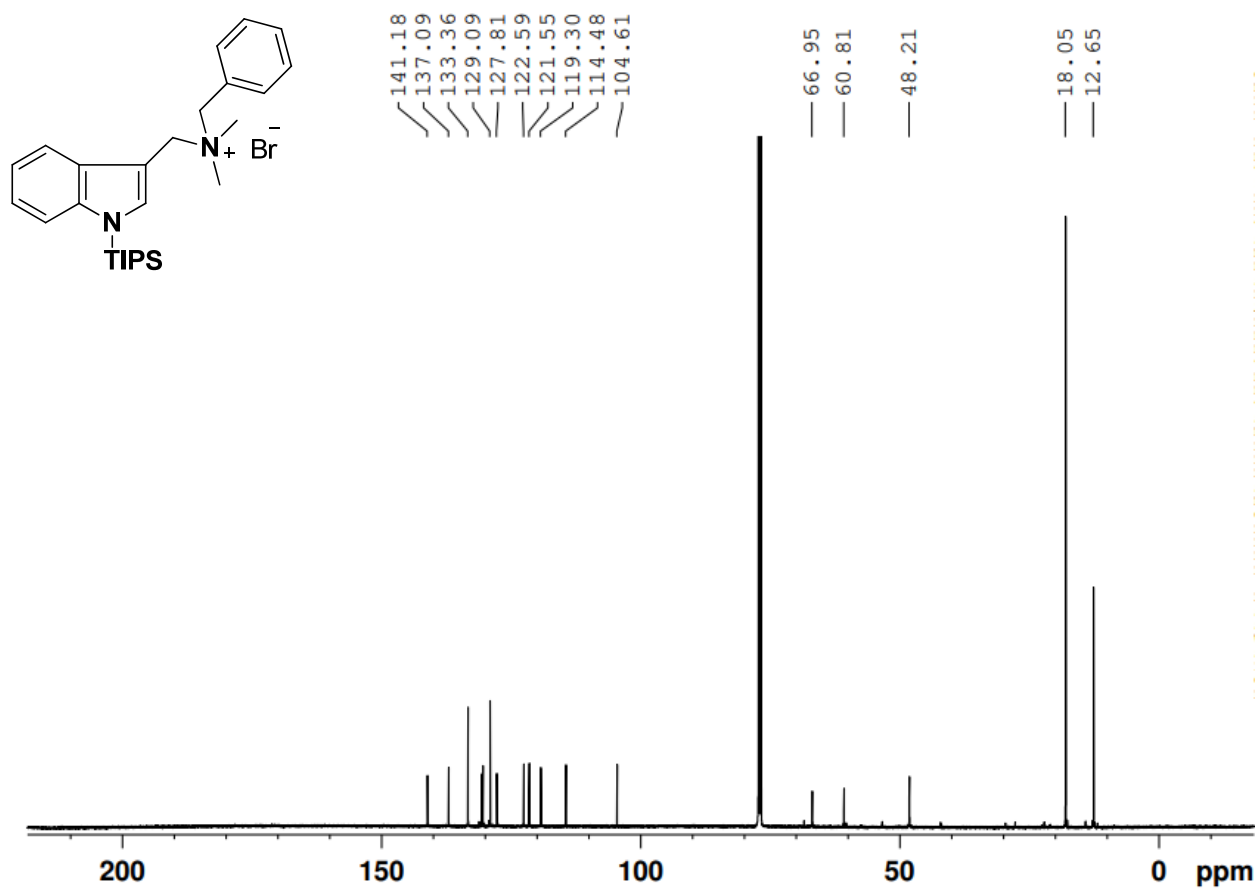
^1H NMR Spectrum of Compound 28b and 29b' in CDCl_3



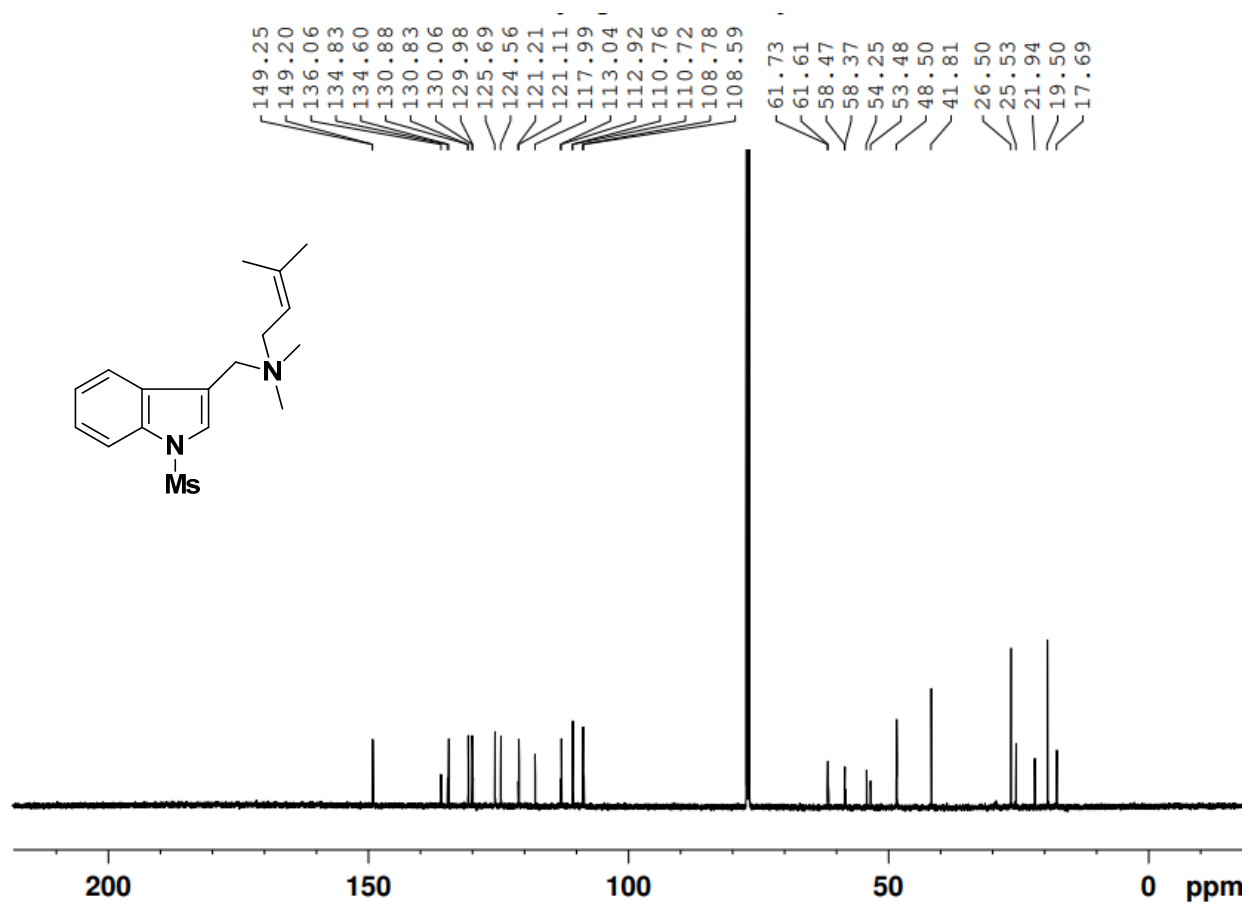
¹H NMR Spectrum of Compound 28a' in CDCl₃



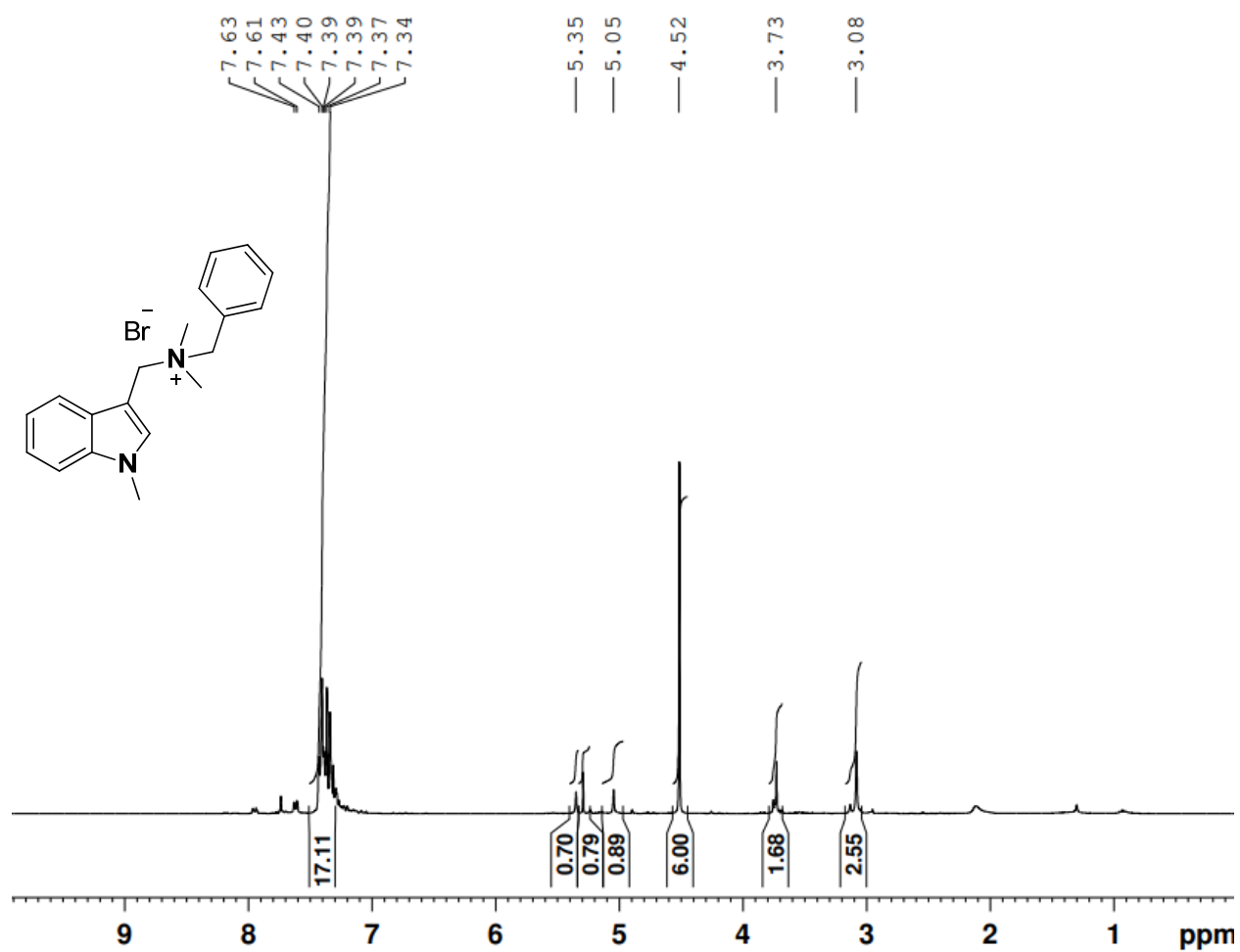
^{13}C NMR Spectrum of Compound 28a' in CDCl_3



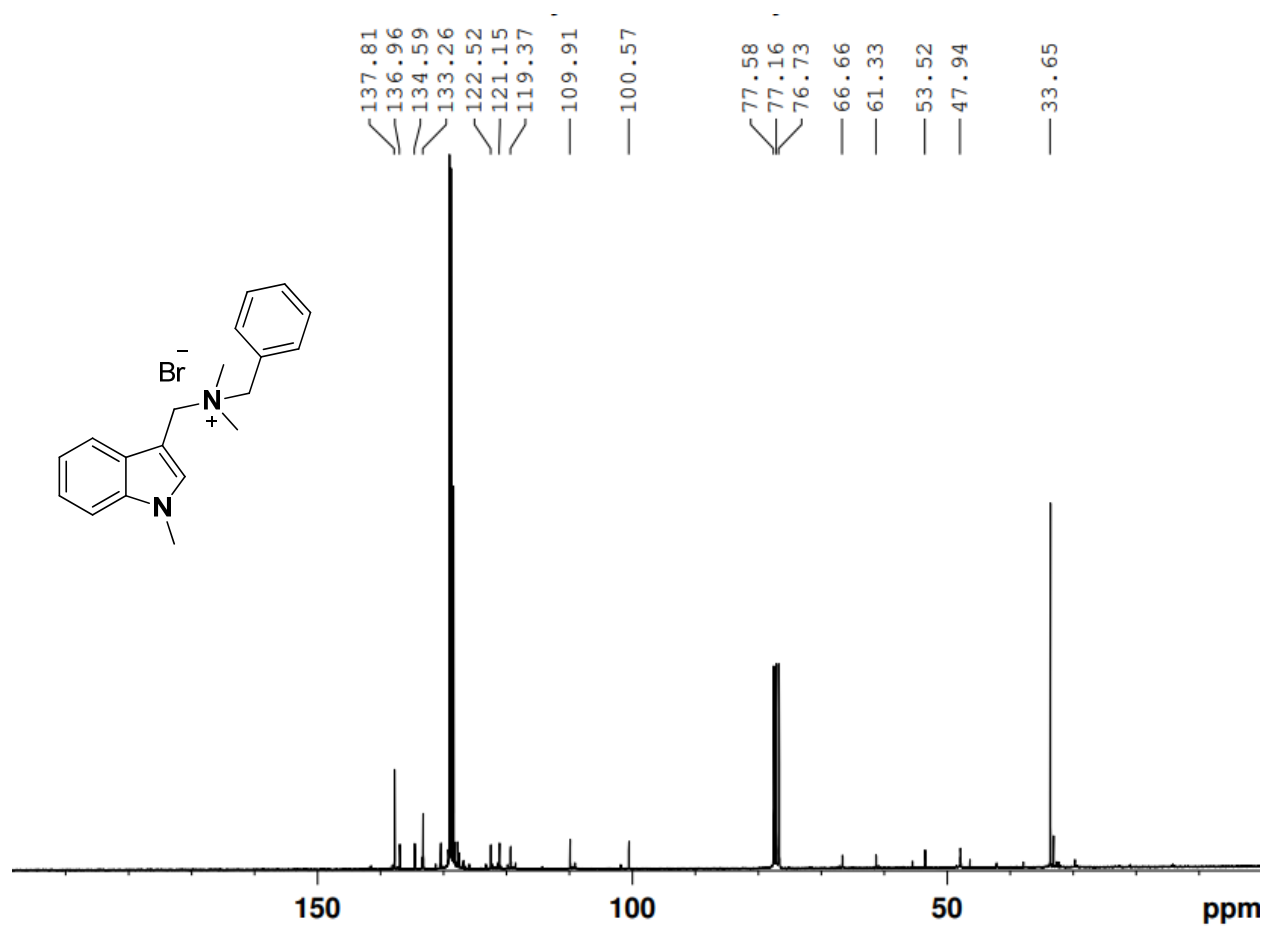
^{13}C NMR Spectrum of Compound 28c in CDCl_3



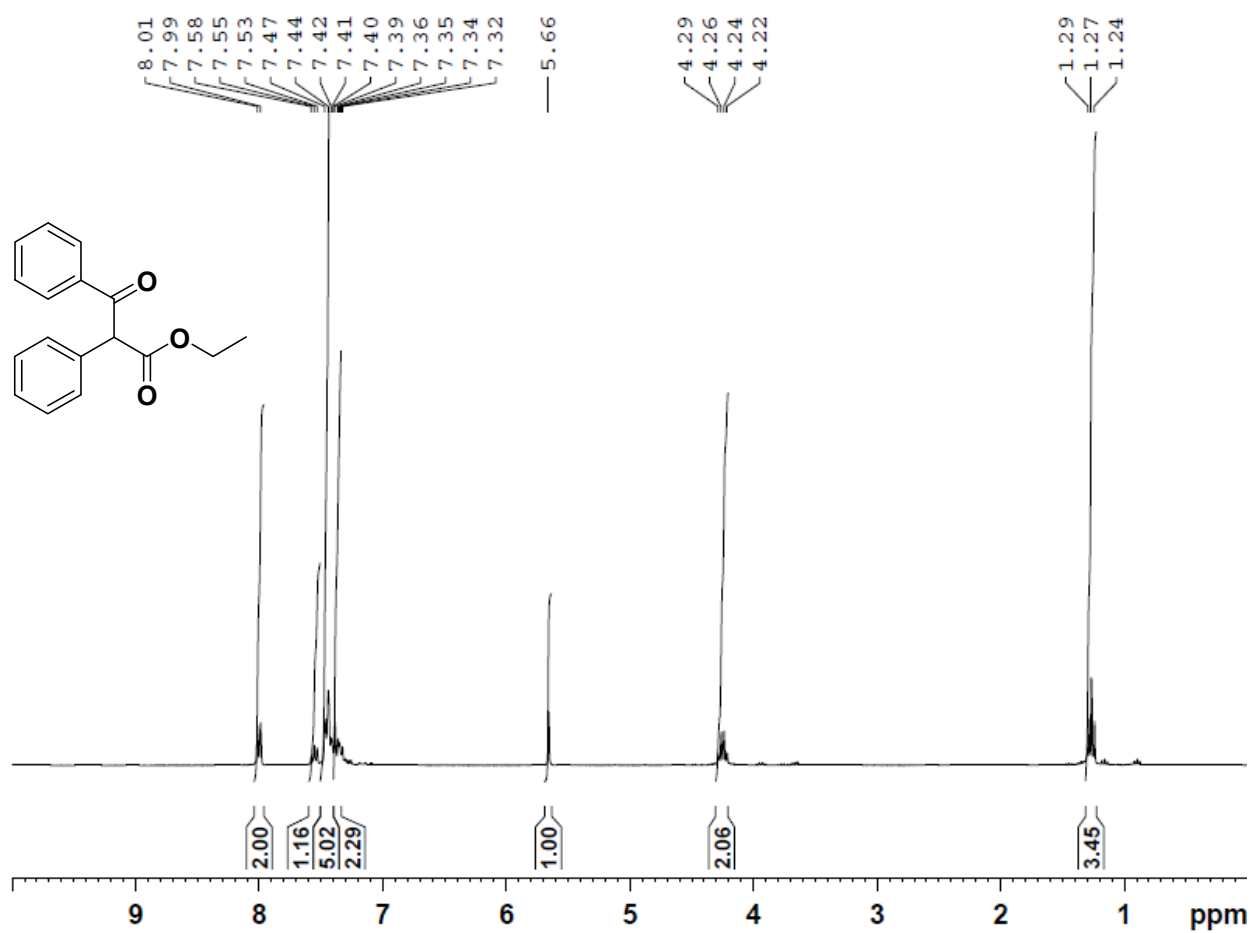
^1H NMR Spectrum of Compound 28d in CDCl_3



^{13}C NMR Spectrum of Compound 28d in CDCl_3

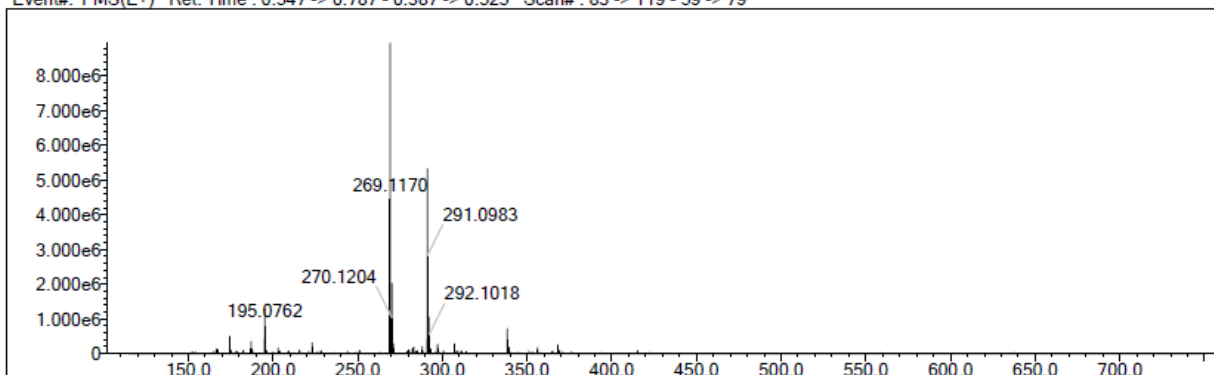


^1H NMR Spectrum of Compound 34a in CDCl_3

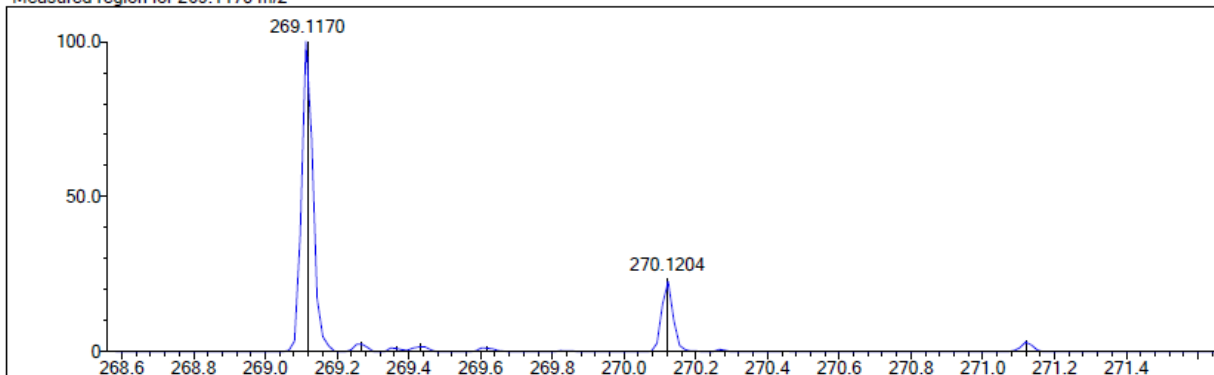


HRMS of Compound 34a

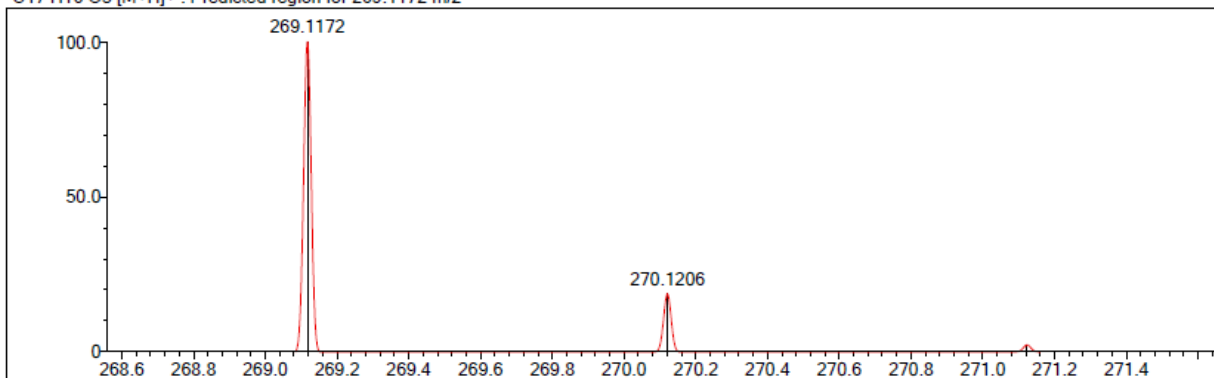
Event#: 1 MS(E+) Ret. Time : 0.547 -> 0.787 -> 0.387 -> 0.525 Scan#: 83 -> 119 - 59 -> 79



Measured region for 269.1170 m/z

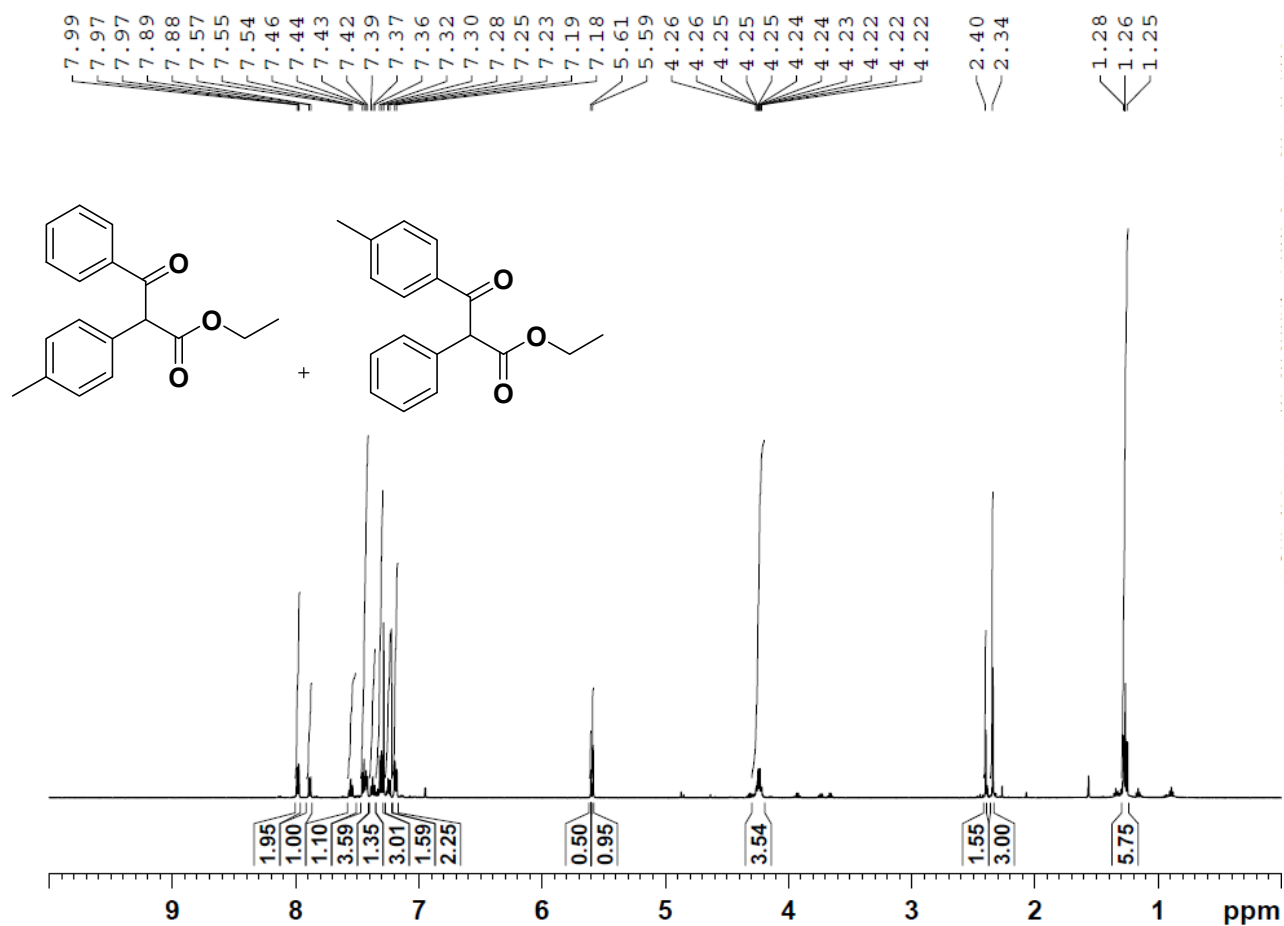


C17 H16 O3 [M+H]⁺ : Predicted region for 269.1172 m/z

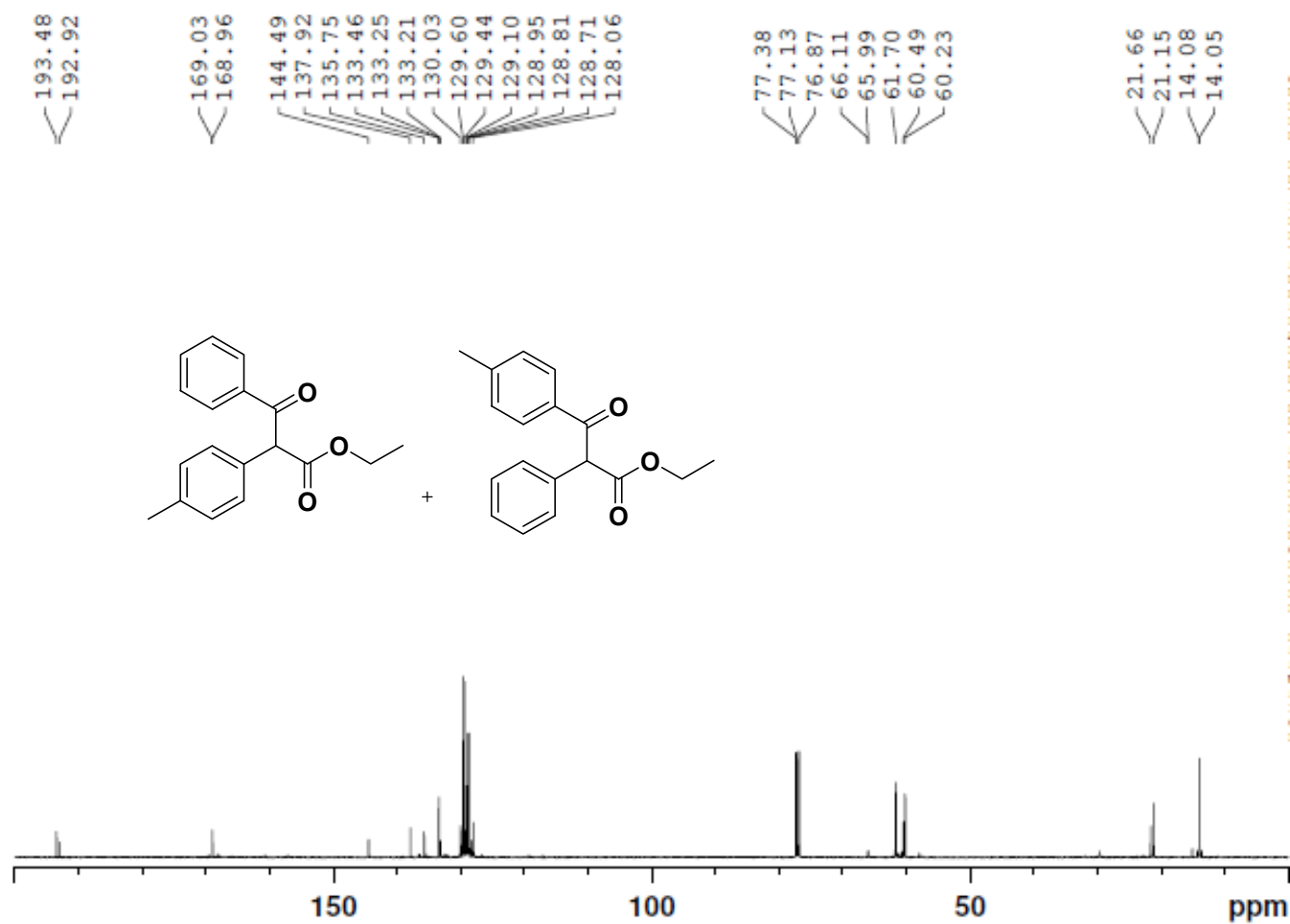


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	76.52	C17 H16 O3	[M+H] ⁺	269.1170	269.1172	-0.2	-0.74	76.52	10.0

¹H NMR Spectrum of Compound 34b and 34b' in CDCl₃

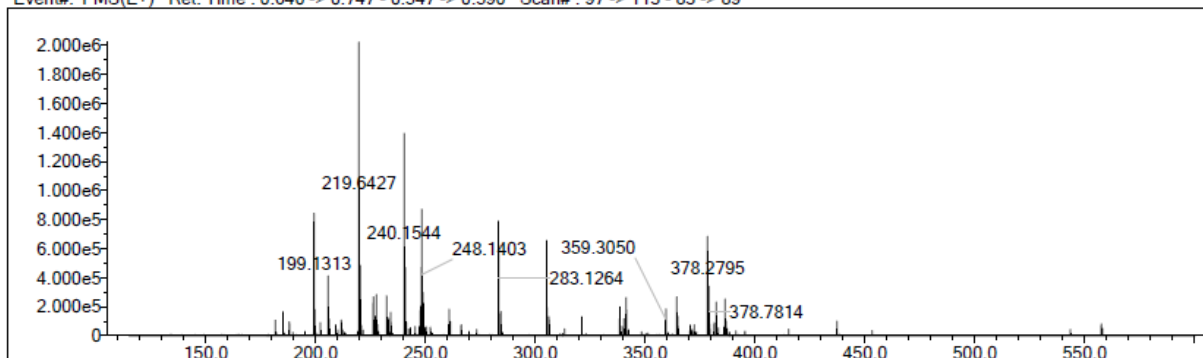


¹³C NMR Spectrum of Compound 34b and 34b' in CDCl₃

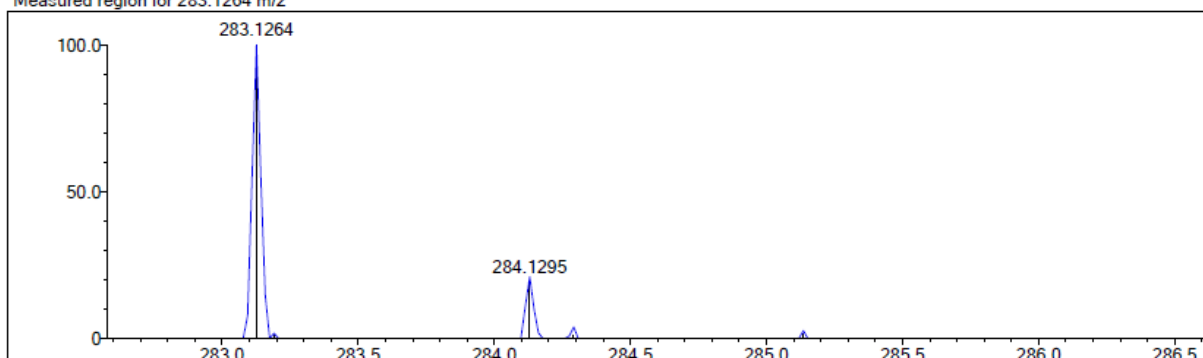


HRMS of 34b/34b'

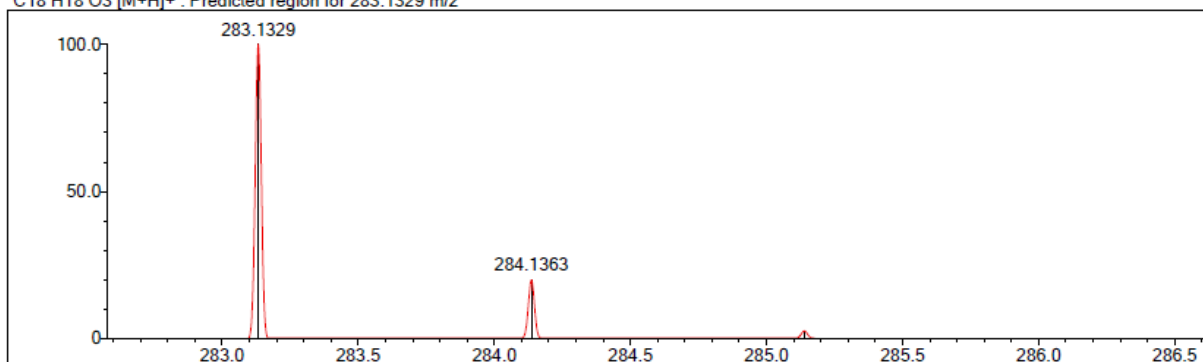
Event#: 1 MS(E+) Ret. Time : 0.640 -> 0.747 - 0.547 -> 0.590 Scan#: 97 -> 113 - 83 -> 89



Measured region for 283.1264 m/z

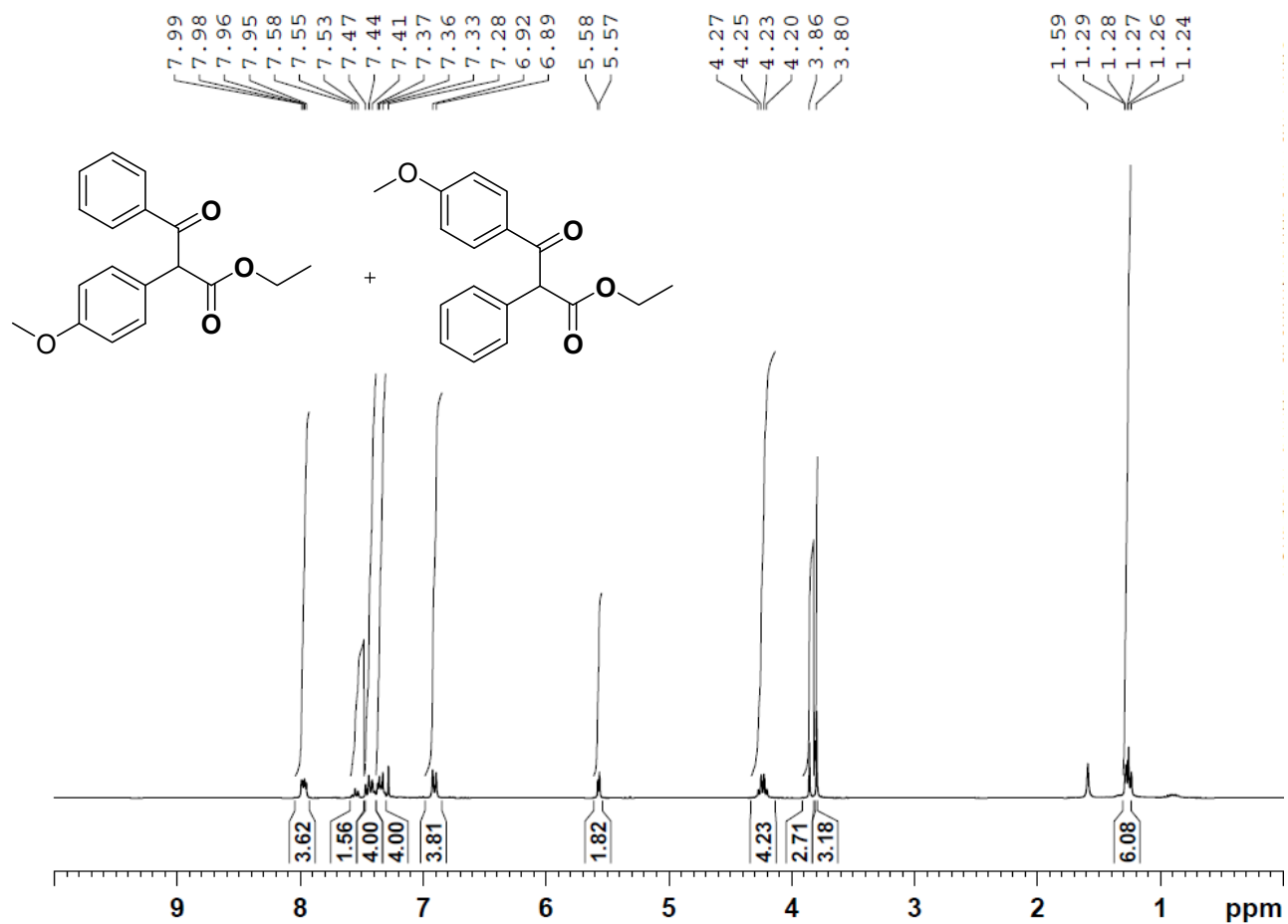


C18 H18 O3 [M+H]⁺ : Predicted region for 283.1329 m/z

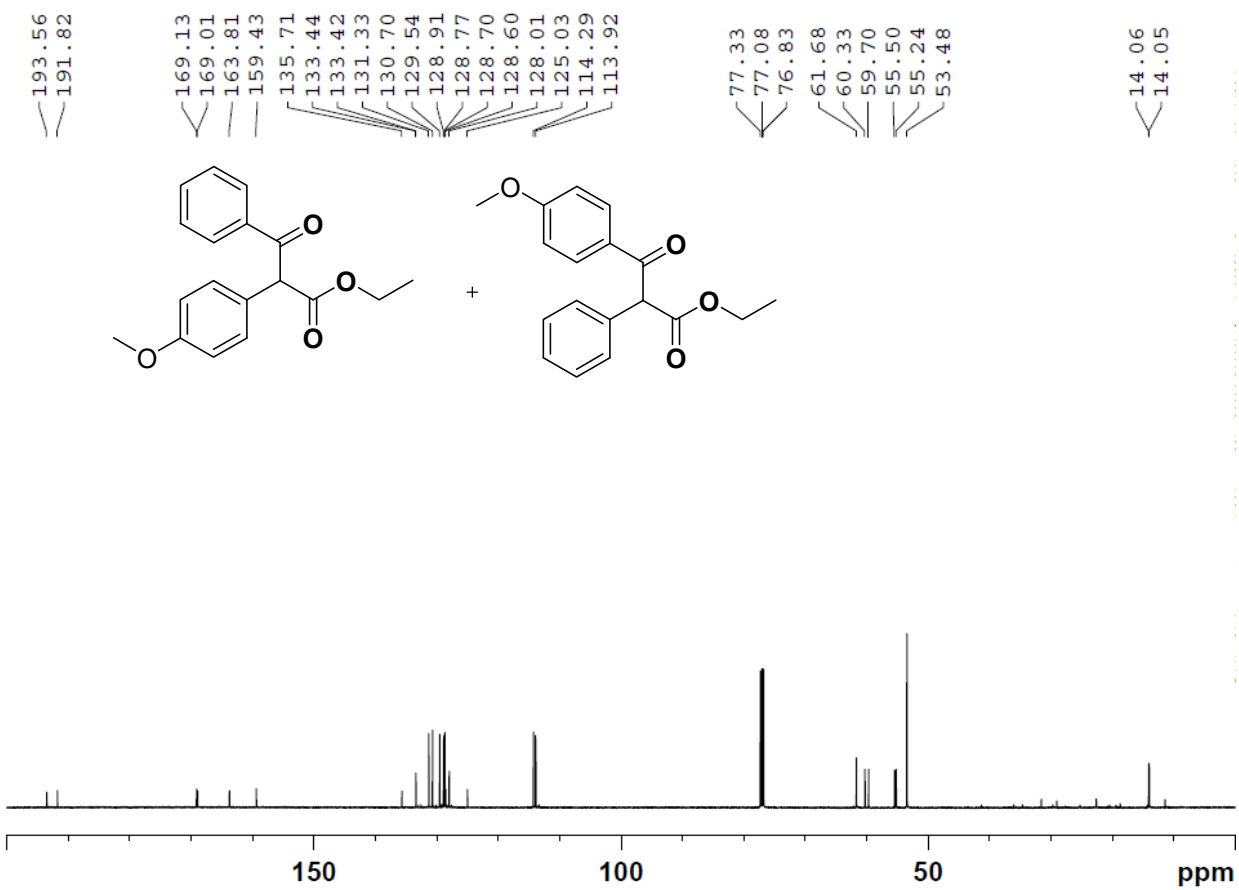


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	2.25	C18 H18 O3	[M+H] ⁺	283.1264	283.1329	-6.5	-22.96	41.40	10.0

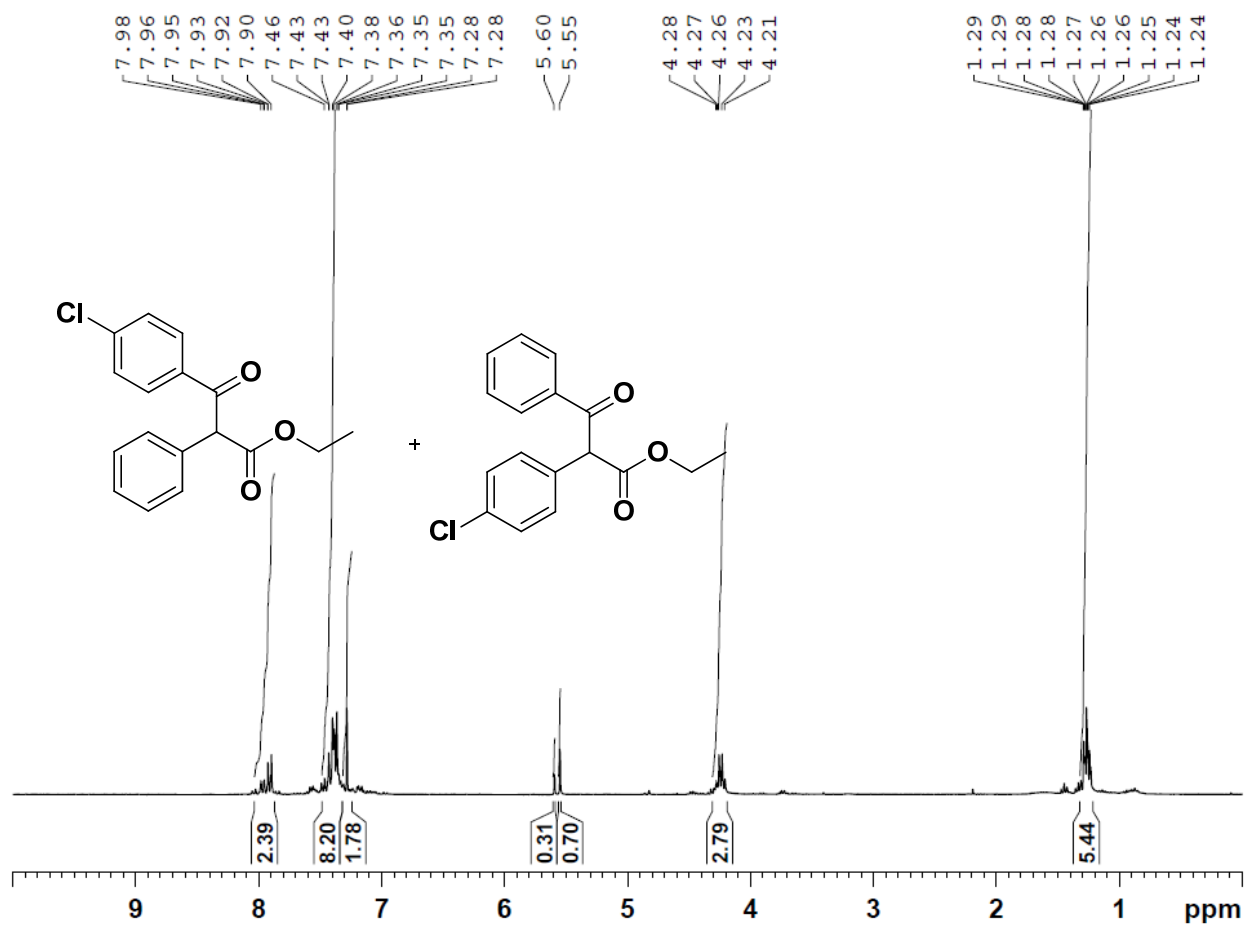
^1H NMR Spectrum of Compound 34c and 34c' in CDCl_3



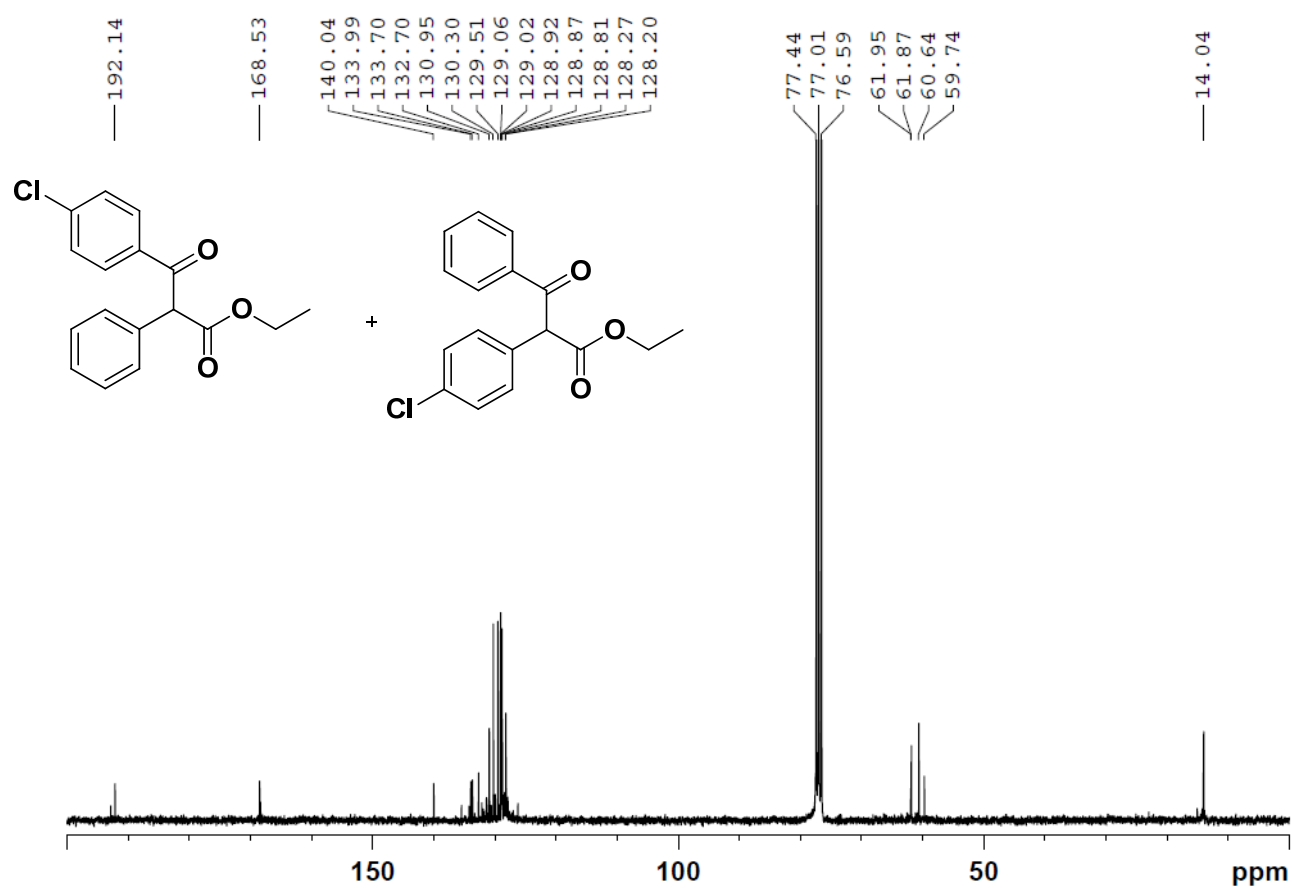
^{13}C NMR Spectrum of Compound 34c and 34c' in CDCl_3



^1H NMR Spectrum of Compound 34d and 34d' in CDCl_3

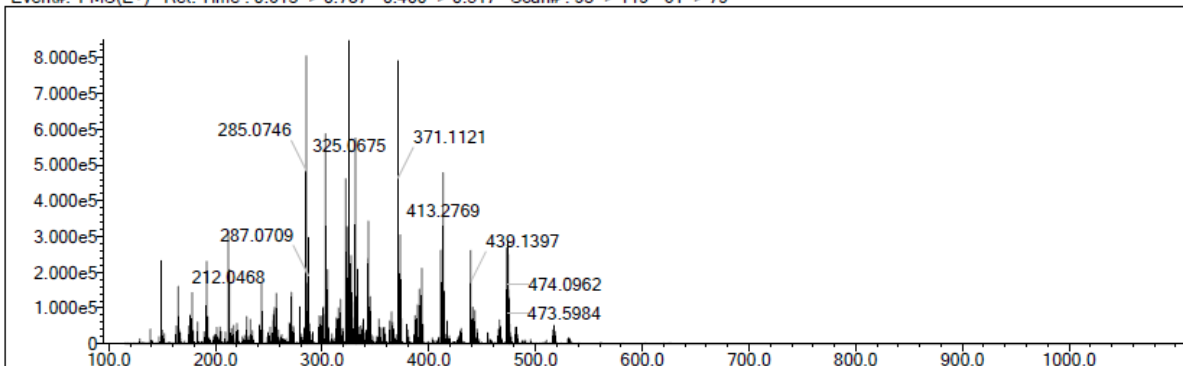


^{13}C NMR Spectrum of Compound 34d and 34d' in CDCl_3

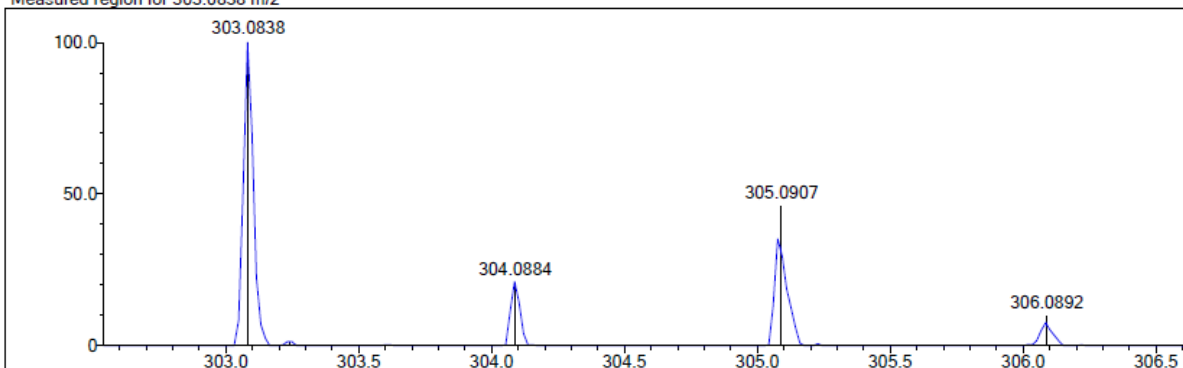


HRMS of Compound 34d and 34d'

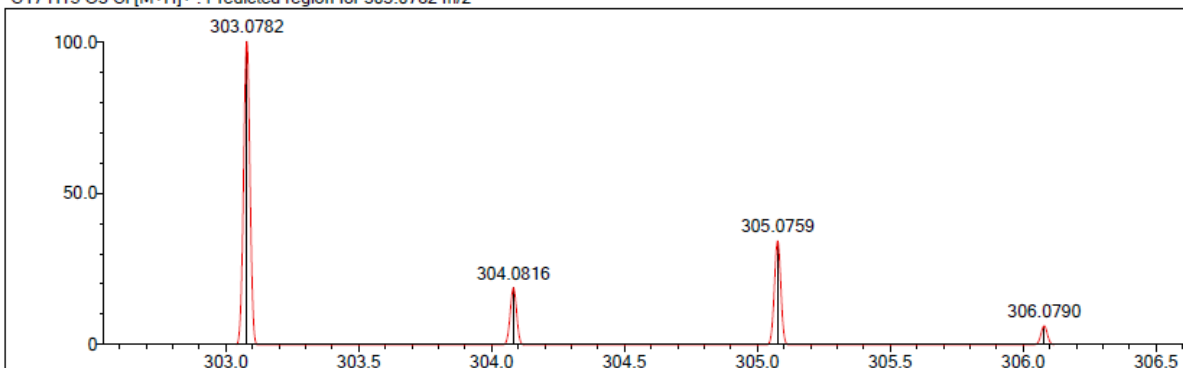
Event#: 1 MS(E+) Ret. Time : 0.613 -> 0.787 - 0.400 -> 0.517 Scan#: 93 -> 119 - 61 -> 79



Measured region for 303.0838 m/z

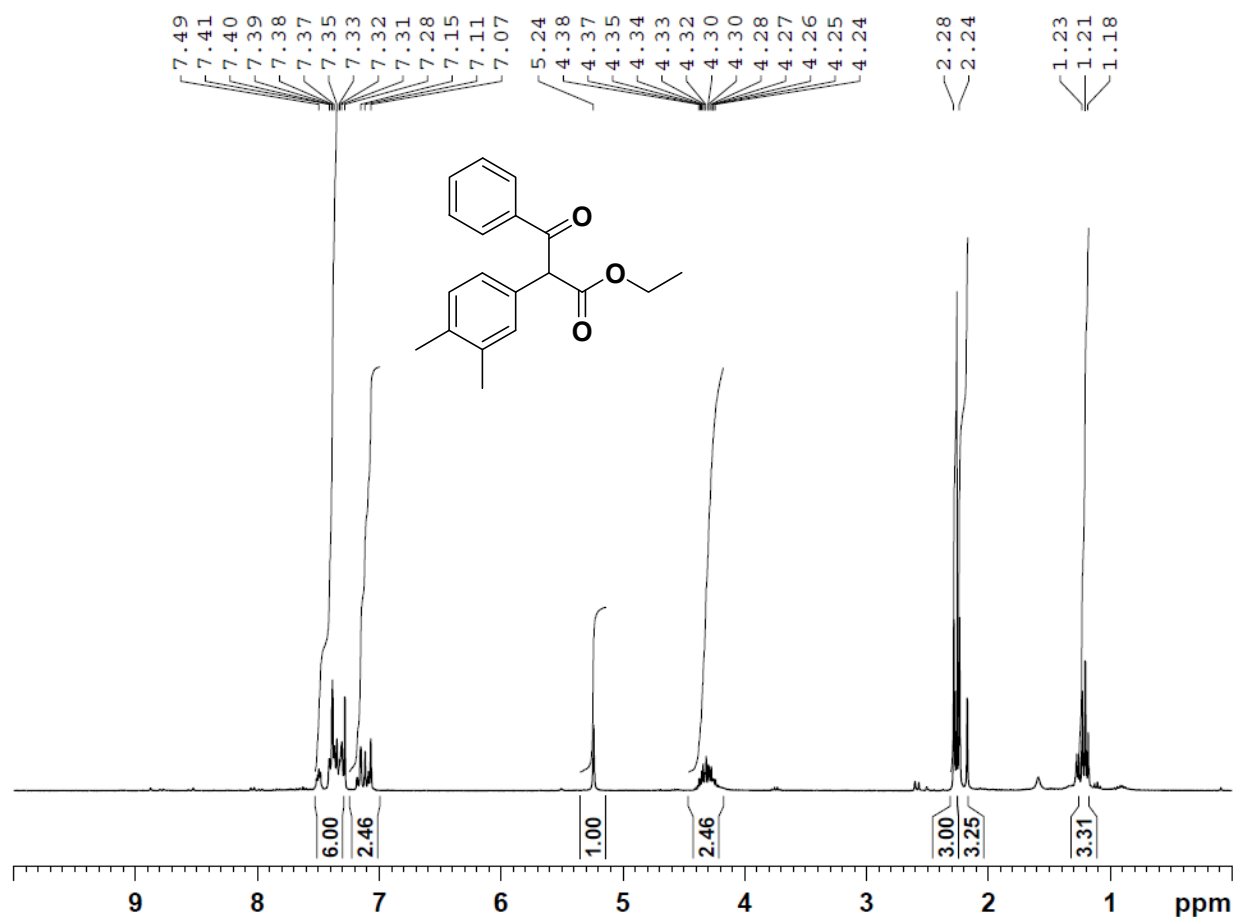


C17 H15 O3 Cl [M+H]⁺ : Predicted region for 303.0782 m/z

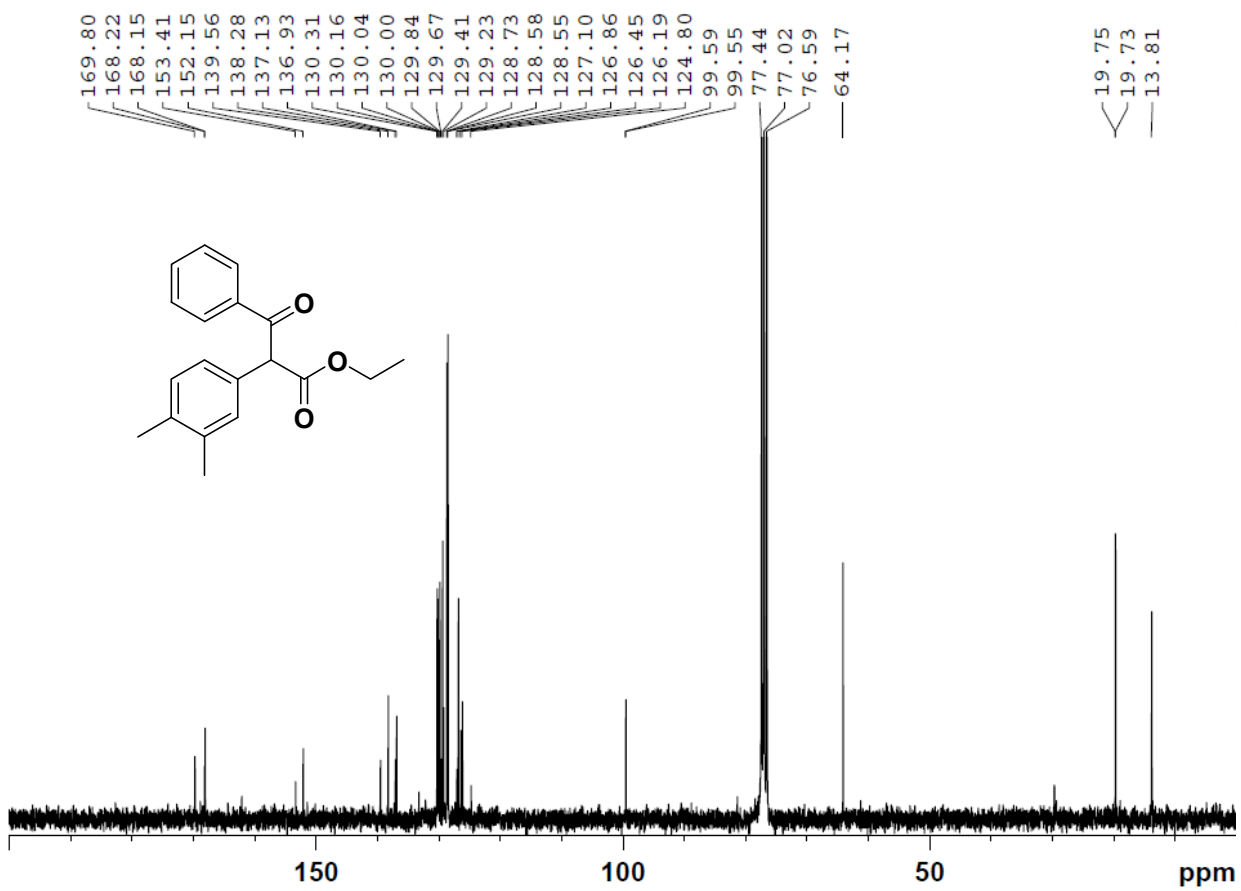


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
3	9.68	C17 H15 O3 Cl	[M+H] ⁺	303.0838	303.0782	5.6	18.48	55.68	10.0

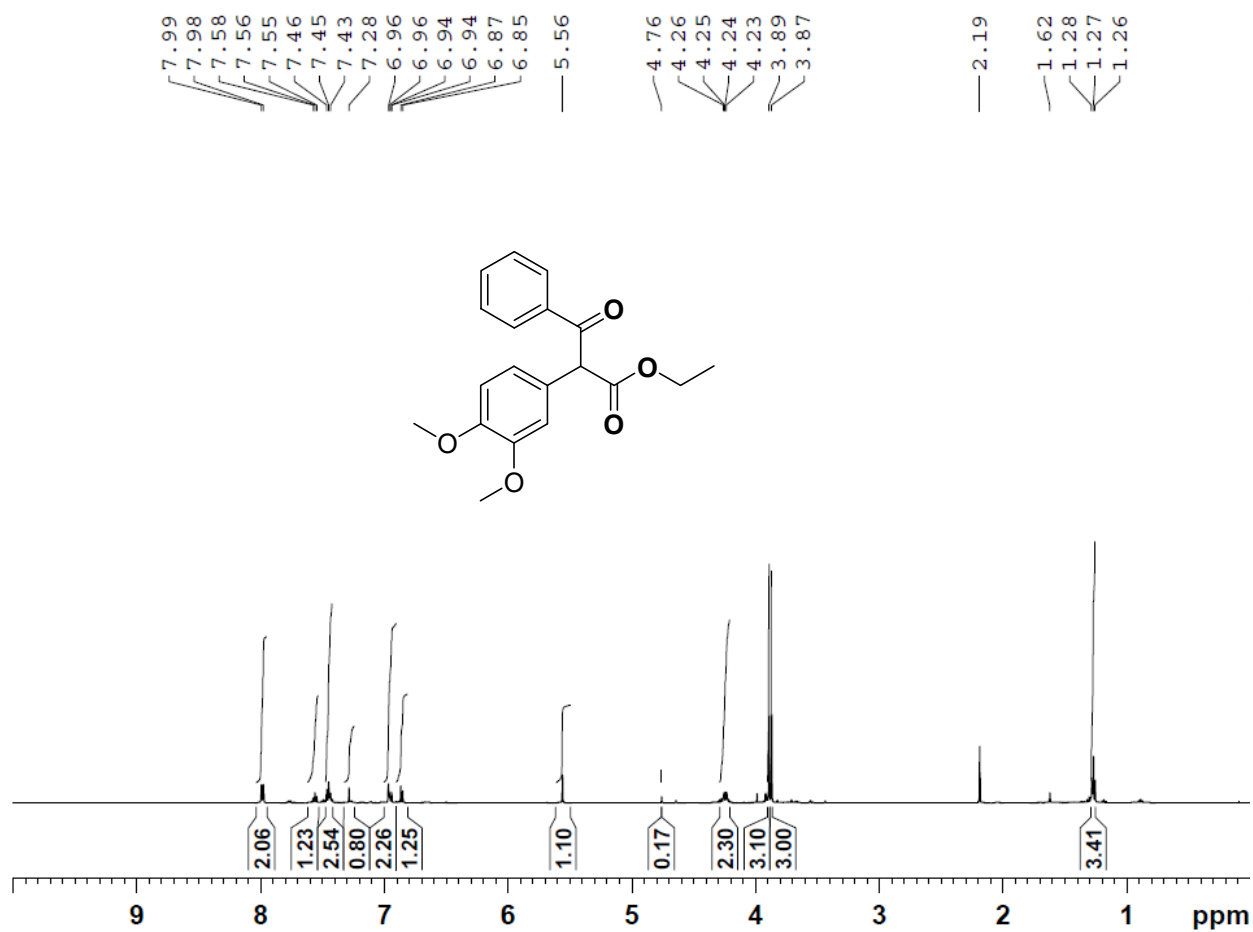
^1H NMR Spectrum of Compound 34f in CDCl_3



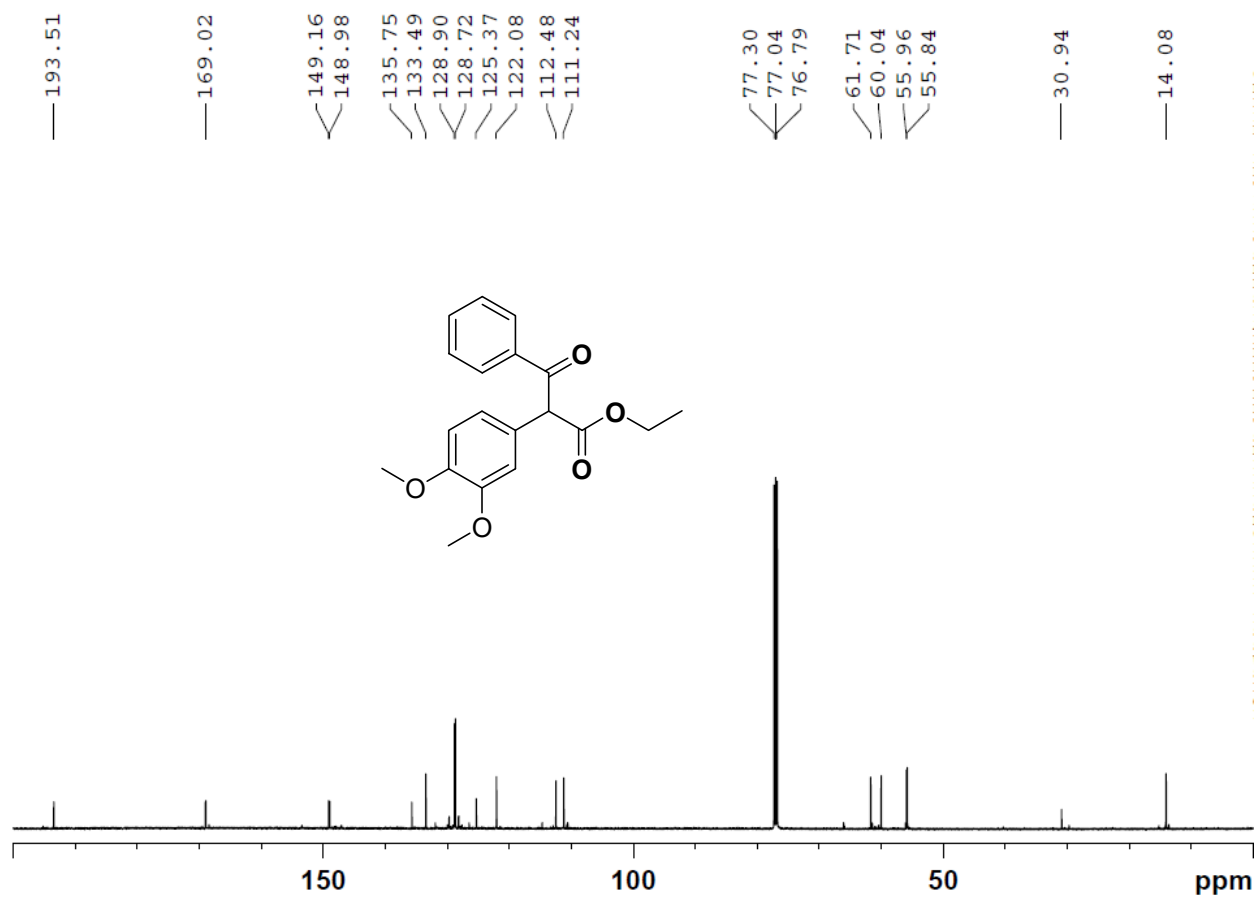
^{13}C NMR Spectrum of Compound 34f in CDCl_3



¹H NMR Spectrum of Compound 34g in CDCl₃

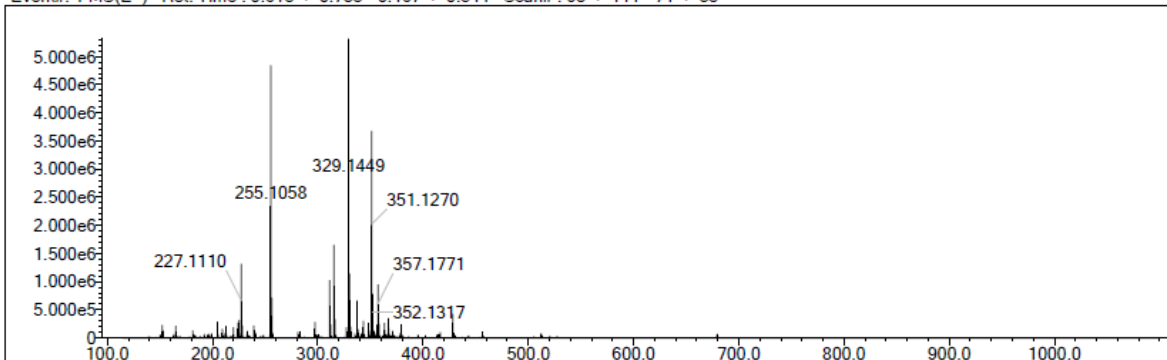


^{13}C NMR Spectrum of Compound 34g in CDCl_3

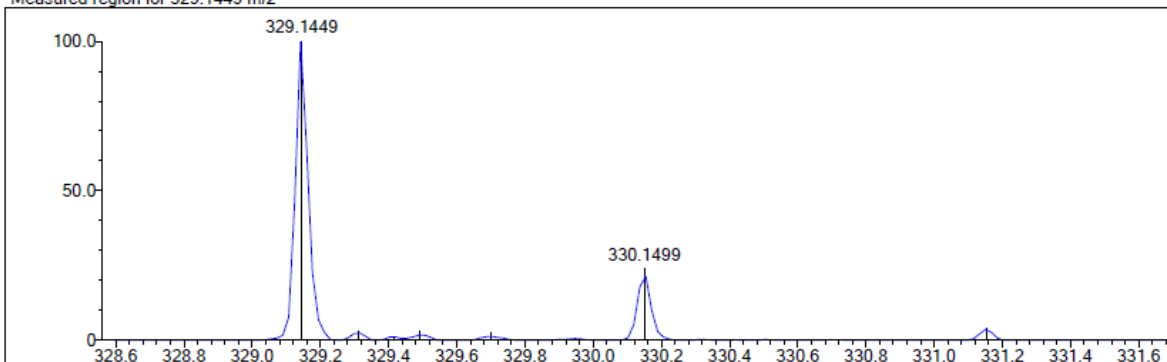


HRMS of Compound 34g

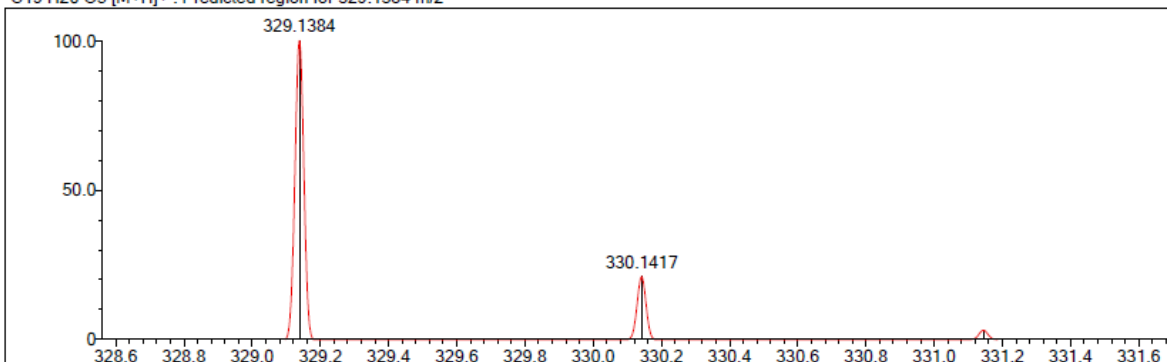
Event#: 1 MS(E+) Ret. Time : 0.613 -> 0.733 - 0.467 -> 0.544 Scan#: 93 -> 111 - 71 -> 83



Measured region for 329.1449 m/z

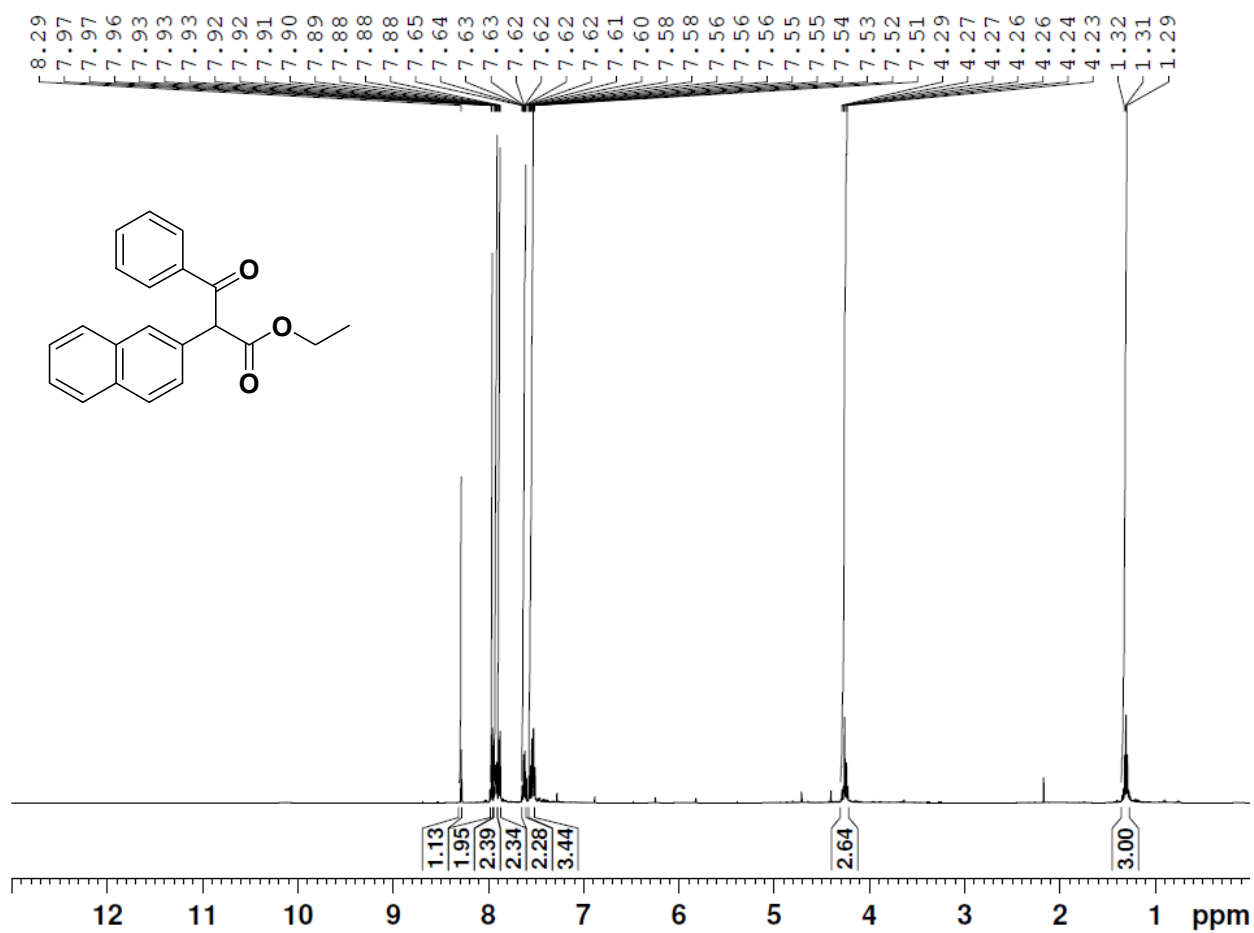


C19 H20 O5 [M+H]⁺ : Predicted region for 329.1384 m/z

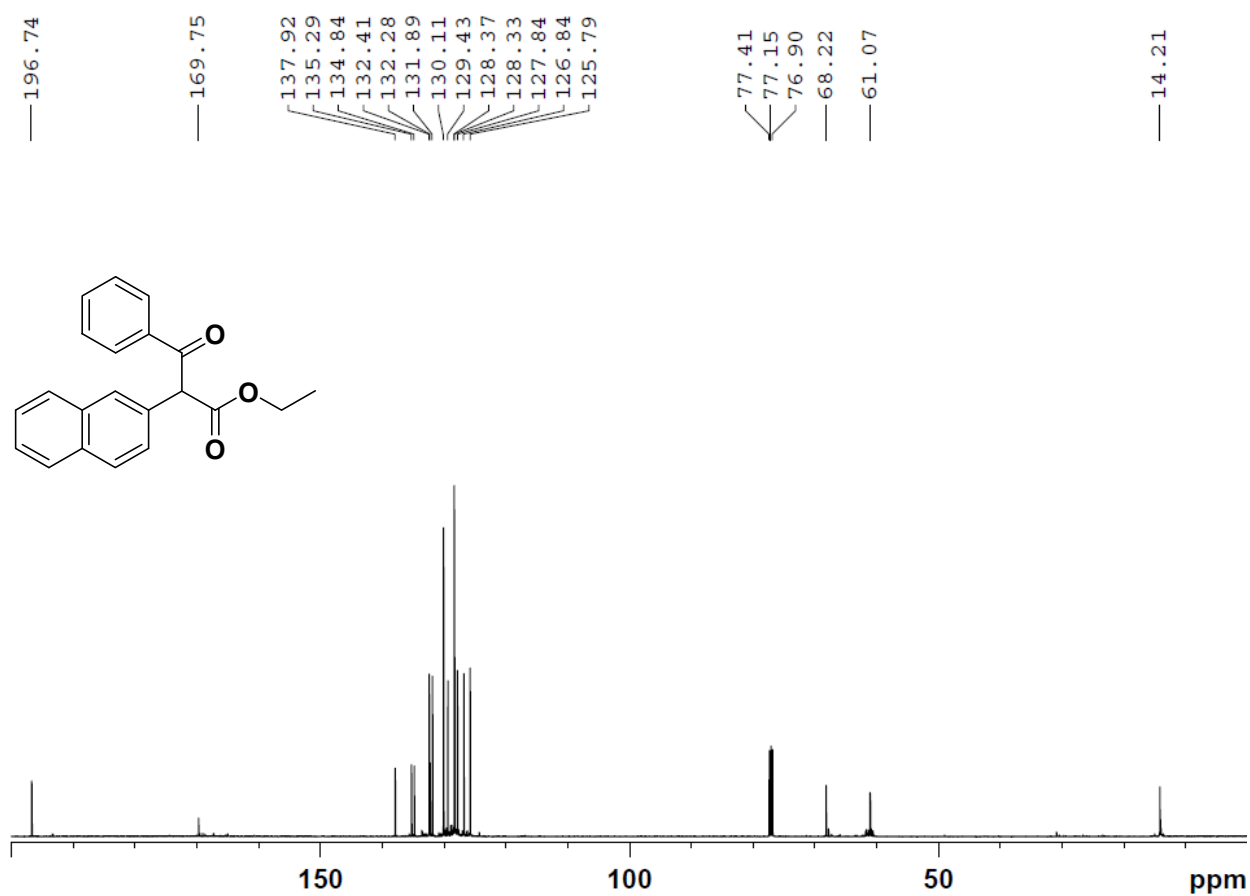


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
3	7.38	C19 H20 O5	[M+H] ⁺	329.1449	329.1384	6.5	19.75	52.71	10.0

^1H NMR Spectrum of Compound 34h in CDCl_3

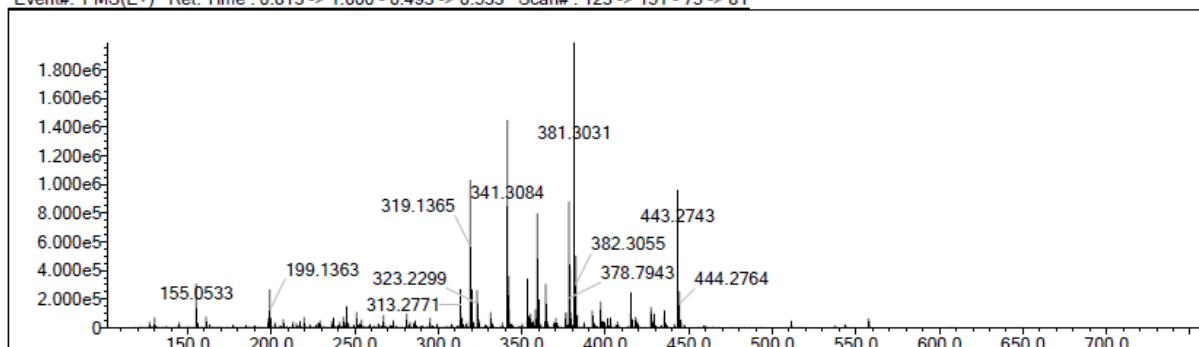


^{13}C NMR Spectrum of Compound 34h in CDCl_3

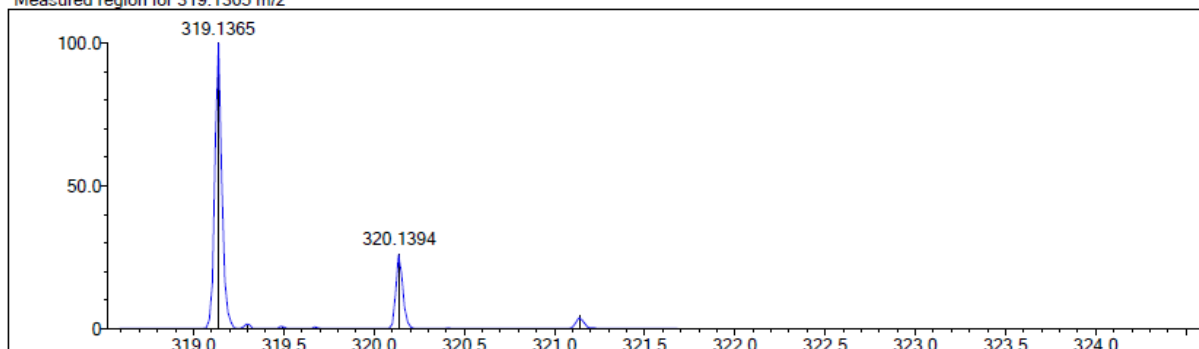


HRMS of Compound 34h

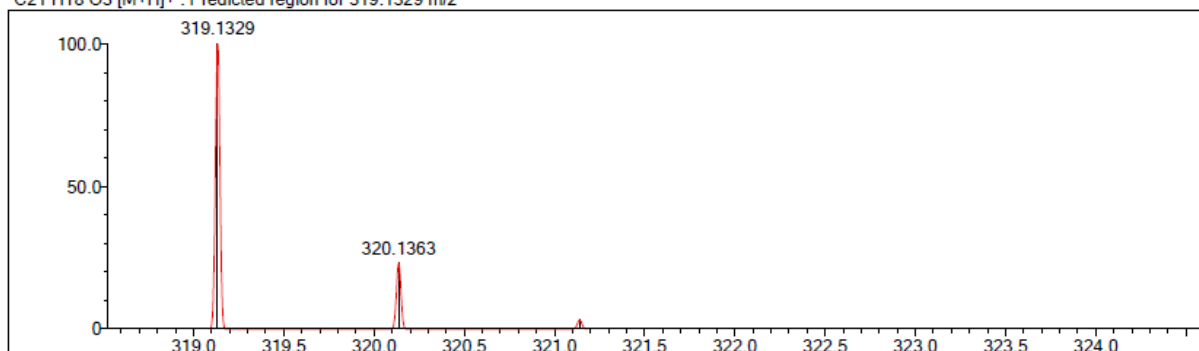
Event#: 1 MS(E+) Ret. Time : 0.813 -> 1.000 - 0.493 -> 0.533 Scan#: 123 -> 151 - 75 -> 81



Measured region for 319.1365 m/z

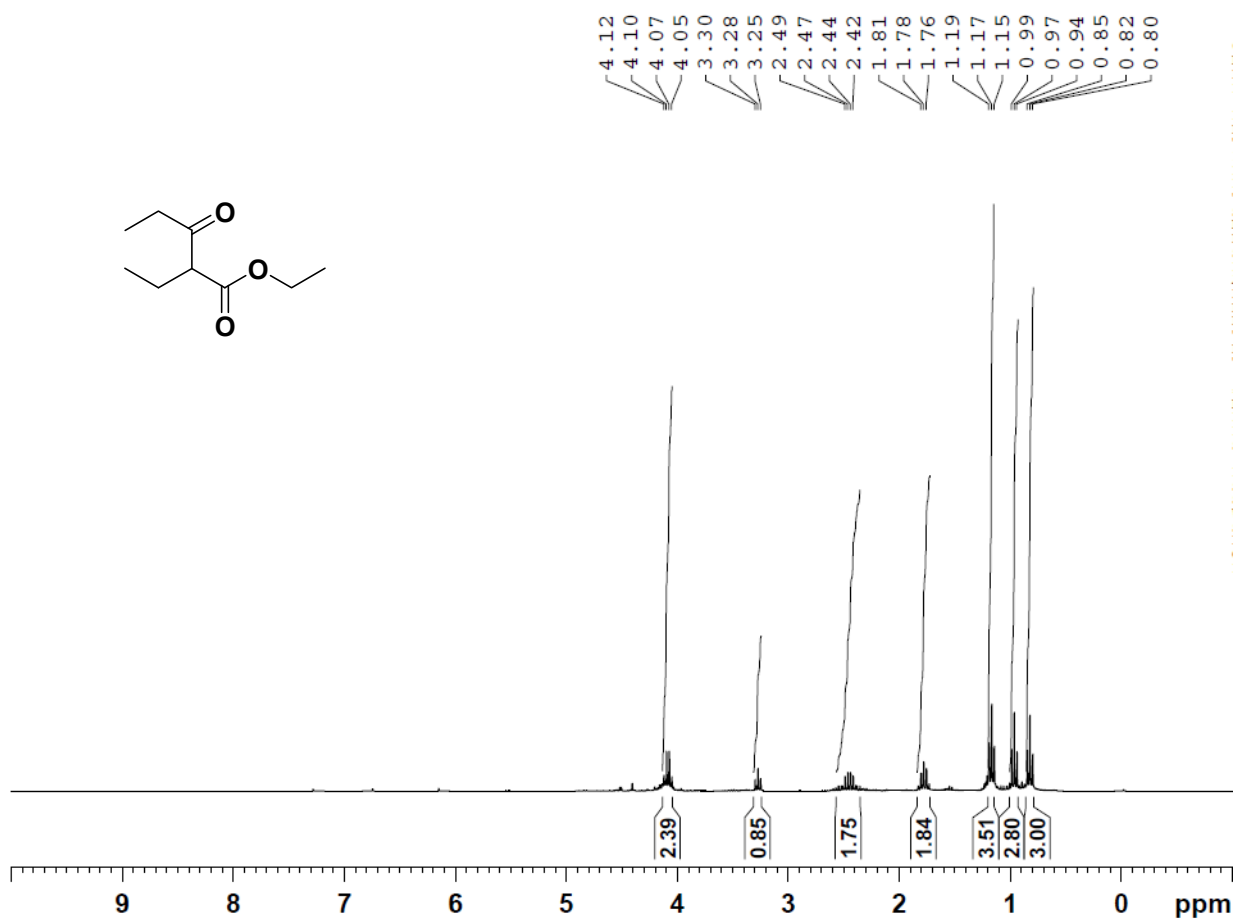


C21 H18 O3 [M+H]⁺ : Predicted region for 319.1329 m/z

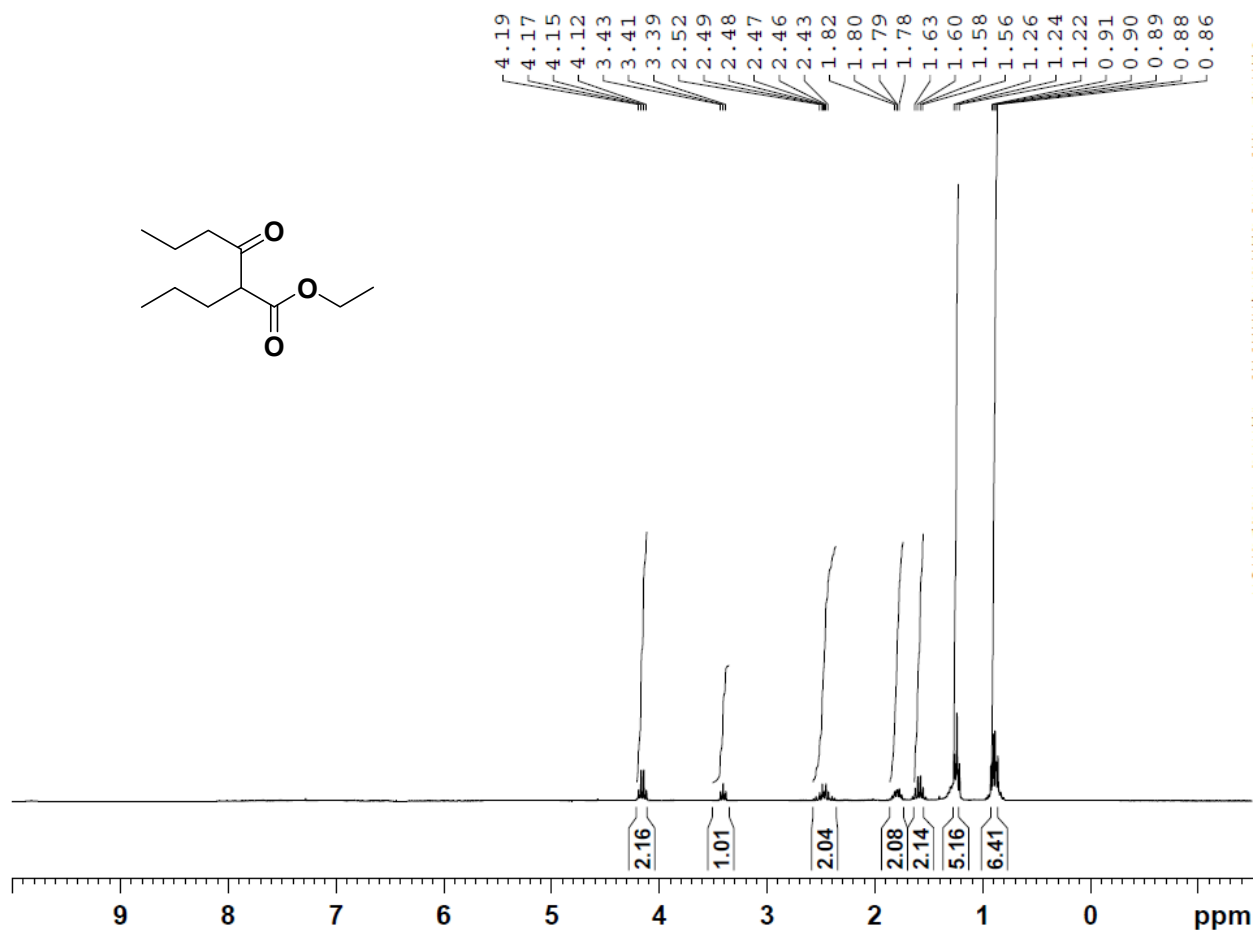
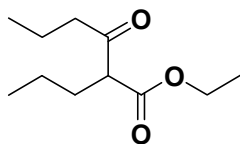


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	25.24	C21 H18 O3	[M+H] ⁺	319.1365	319.1329	3.6	11.28	69.00	13.0

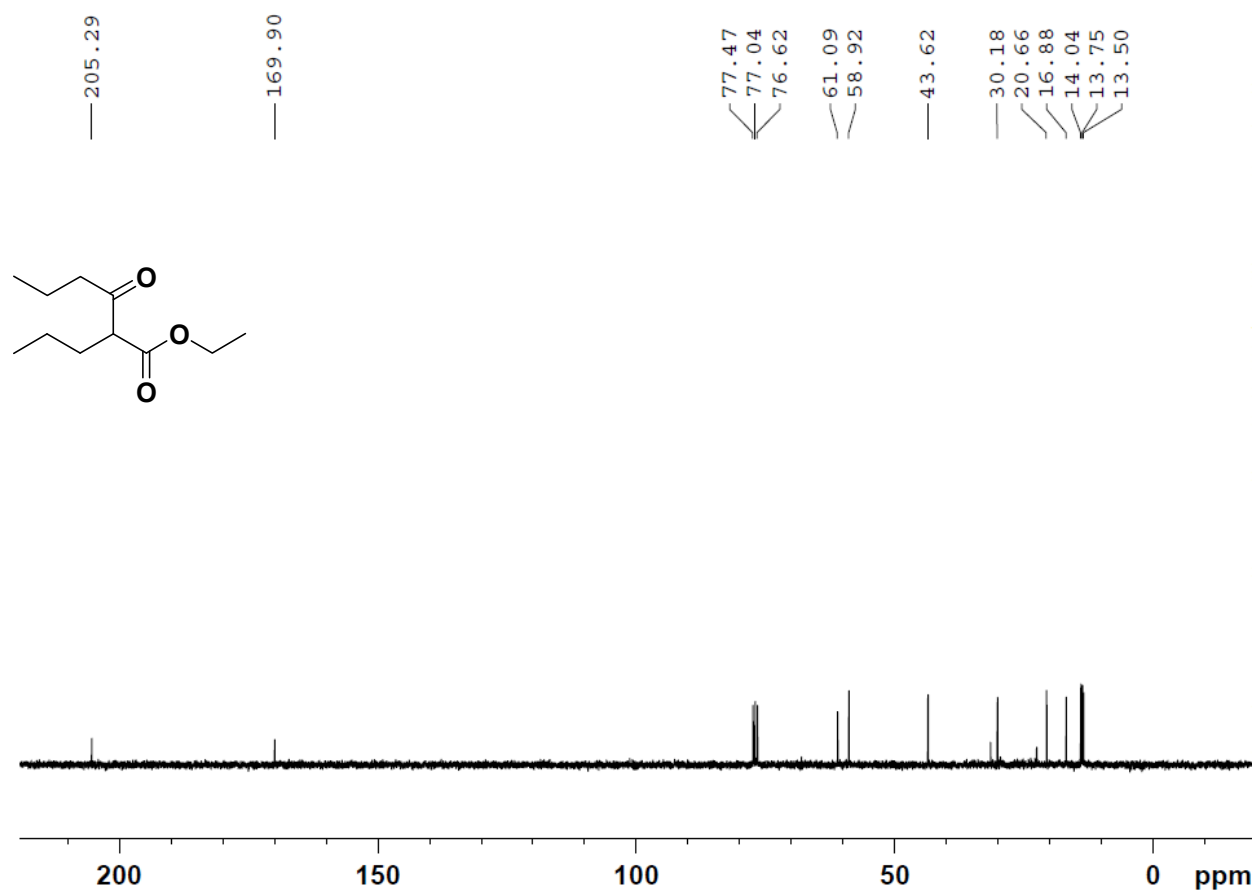
¹H NMR Spectrum of Compound 35a in CDCl₃



¹H NMR Spectrum of Compound 35b in CDCl₃

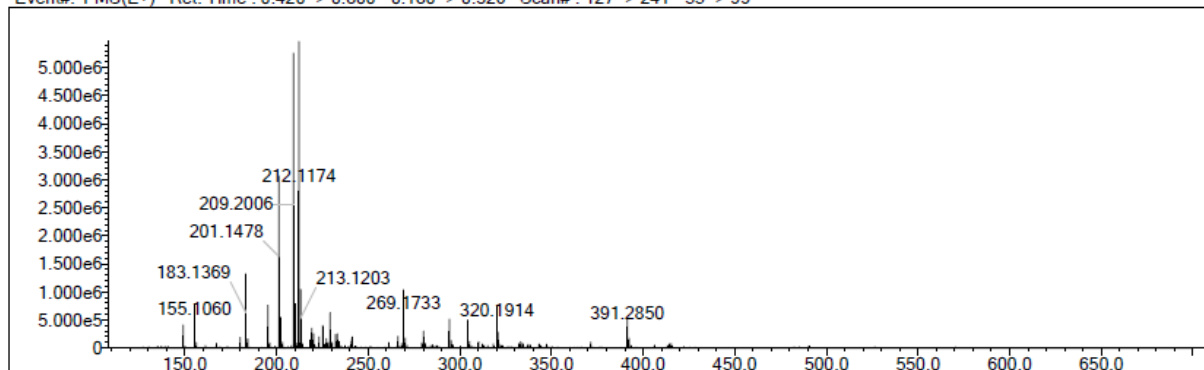


^{13}C NMR Spectrum of Compound 35b in CDCl_3

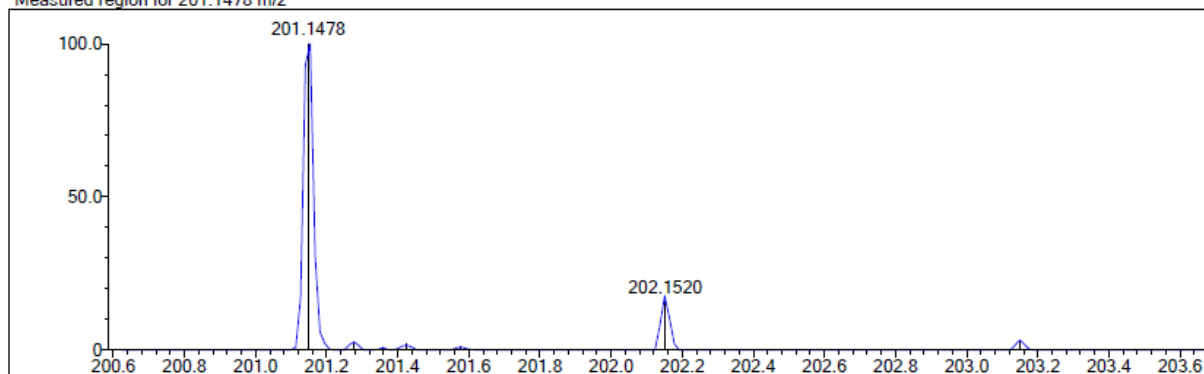


HRMS of Compound 35b

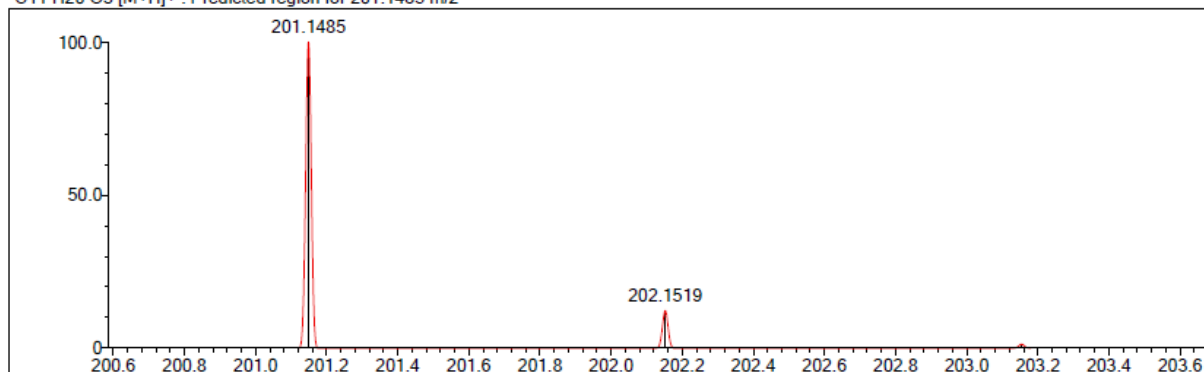
Event#: 1 MS(E+) Ret. Time : 0.420 -> 0.800 - 0.180 -> 0.326 Scan#: 127 -> 241 - 55 -> 99



Measured region for 201.1478 m/z

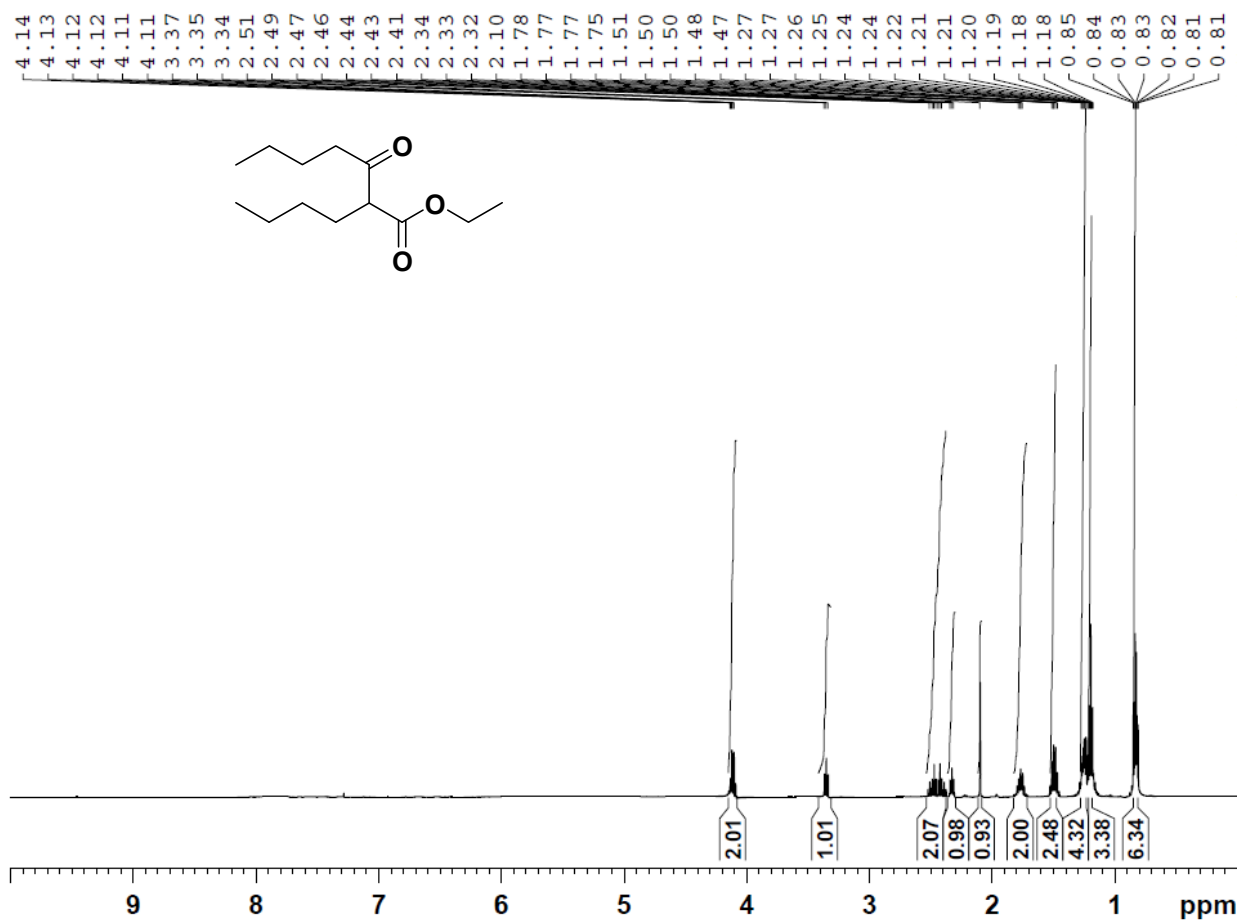


C11 H20 O3 [M+H]⁺ : Predicted region for 201.1485 m/z

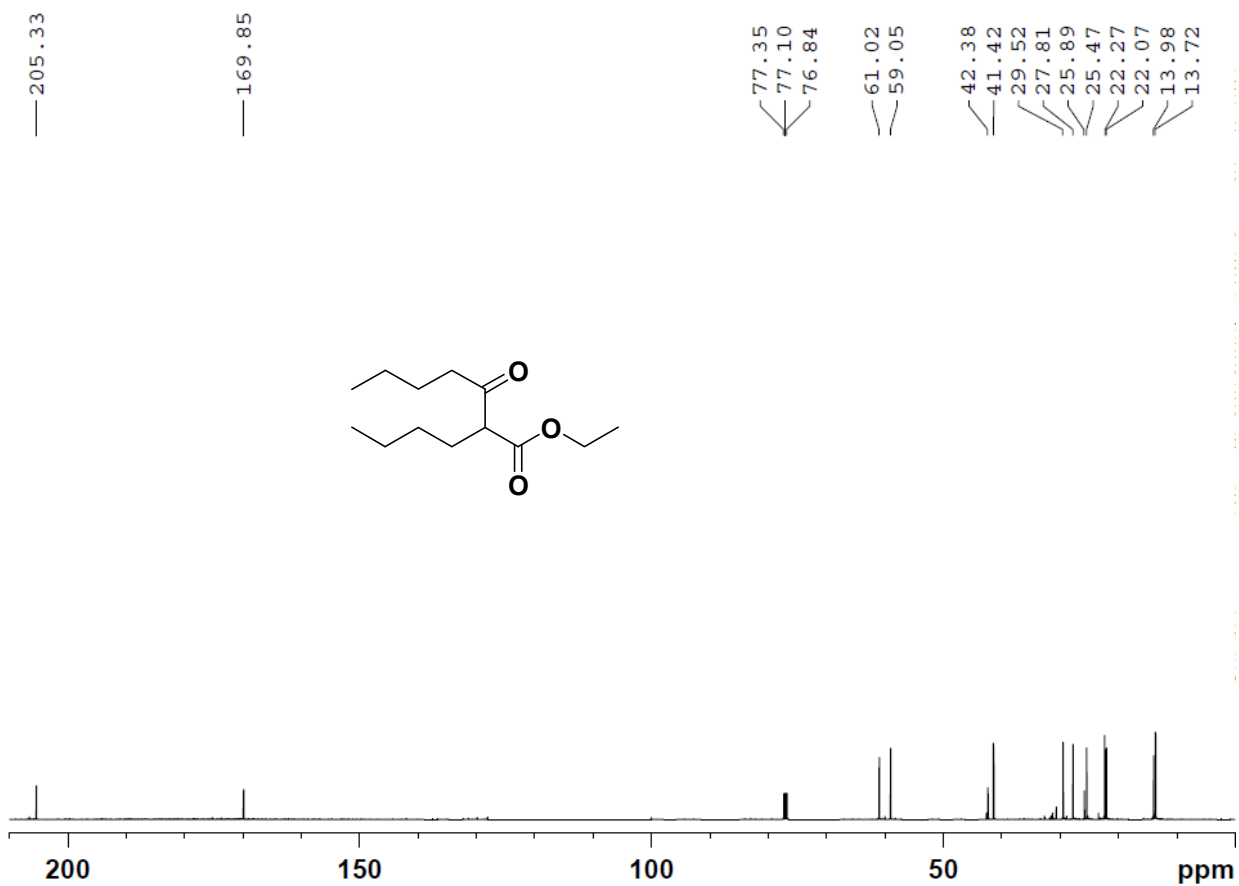


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	71.50	C11 H20 O3	[M+H] ⁺	201.1478	201.1485	-0.7	-3.48	76.23	2.0

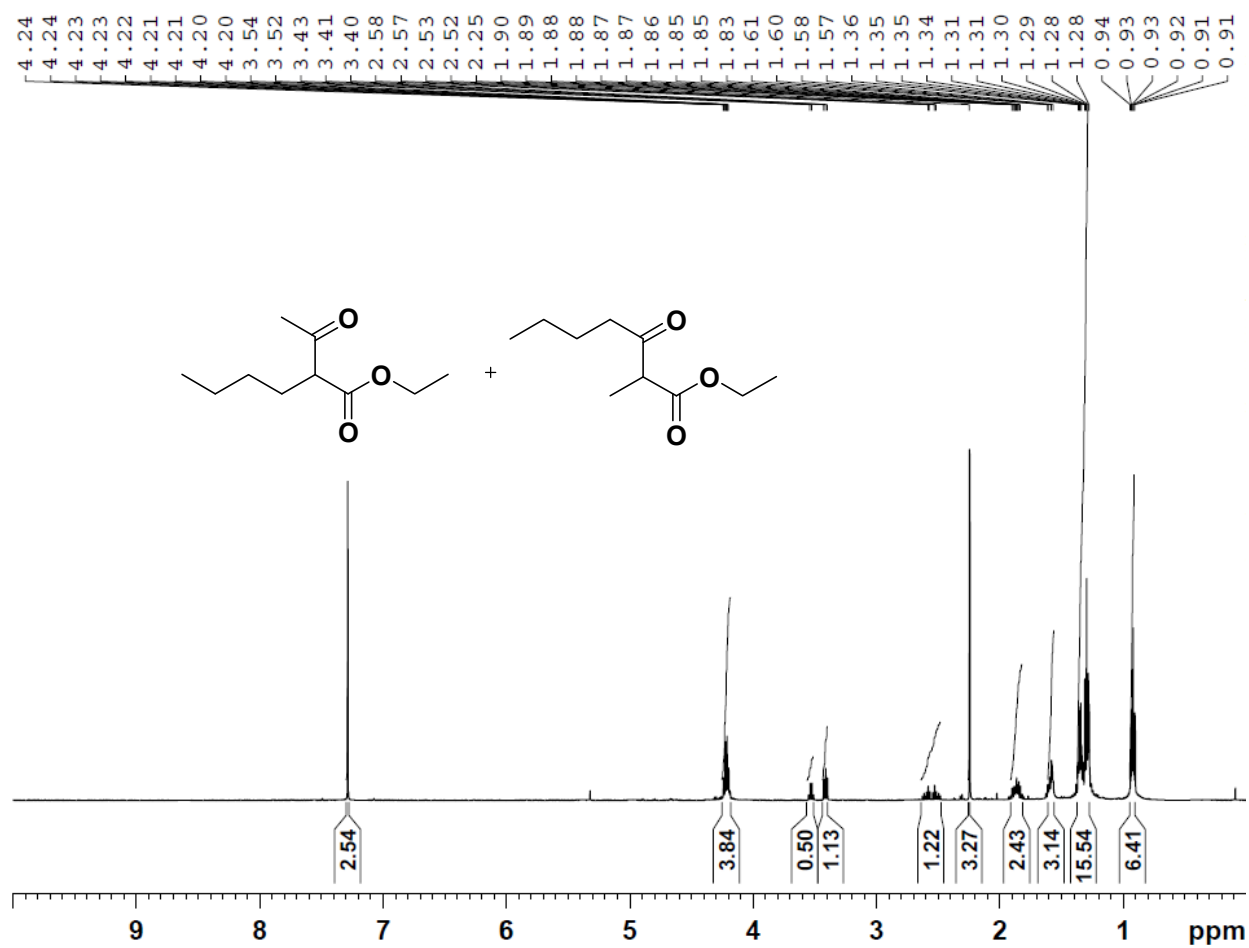
¹H NMR Spectrum of Compound 35c in CDCl₃



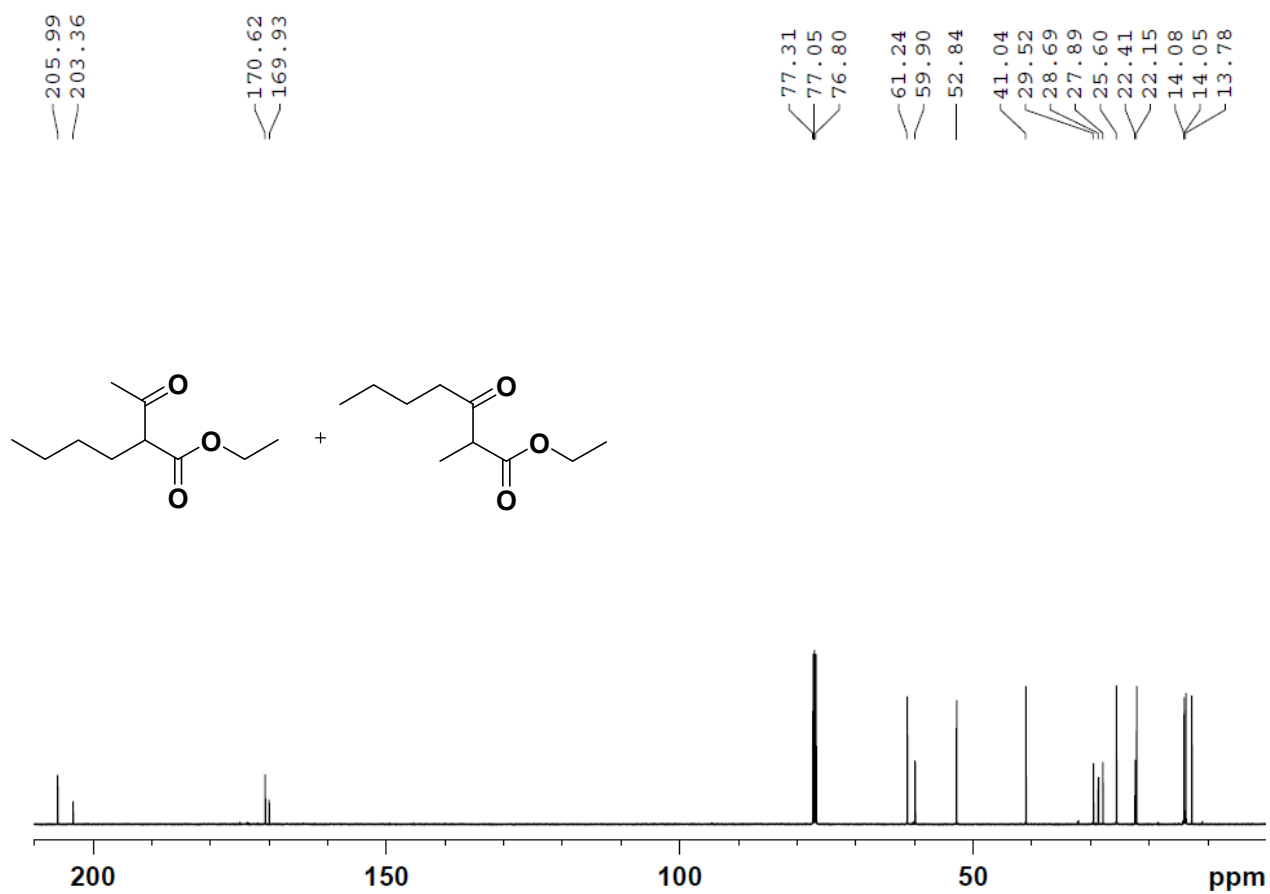
^{13}C NMR Spectrum of Compound 35c in CDCl_3



¹H NMR Spectrum of Compound 35d and 35d' in CDCl₃

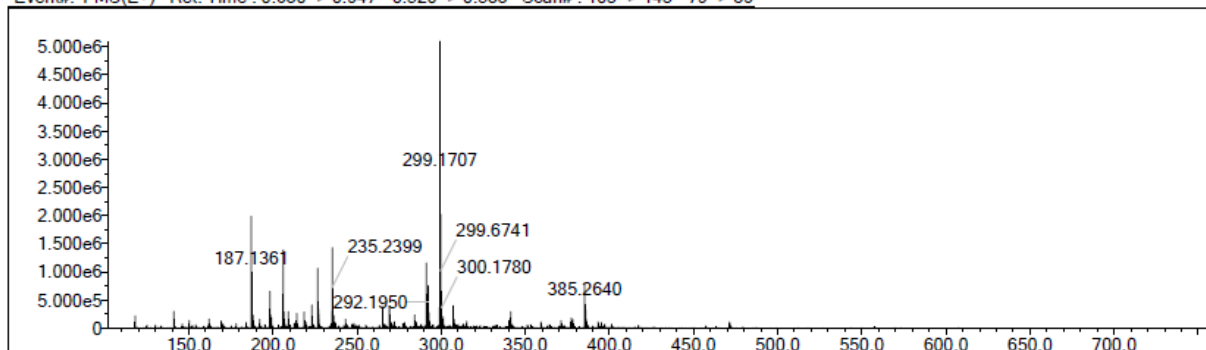


^{13}C NMR Spectrum of Compound 35d and 35d' in CDCl_3

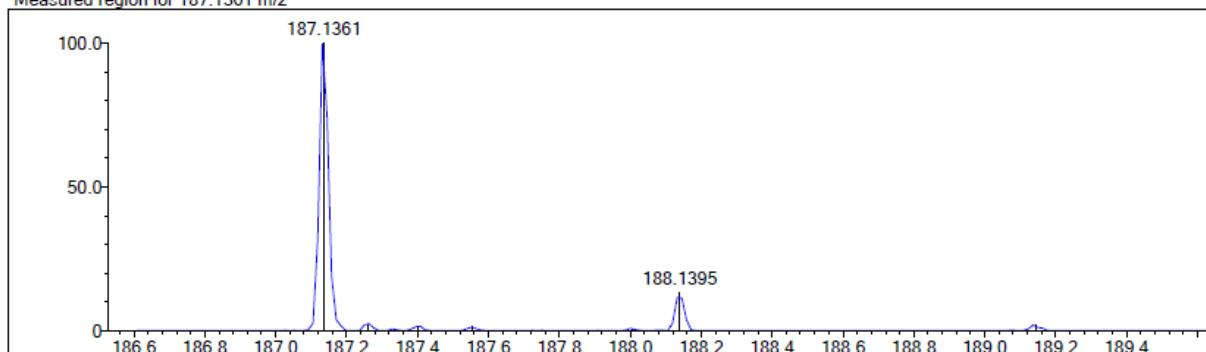


HRMS of Compound 35d

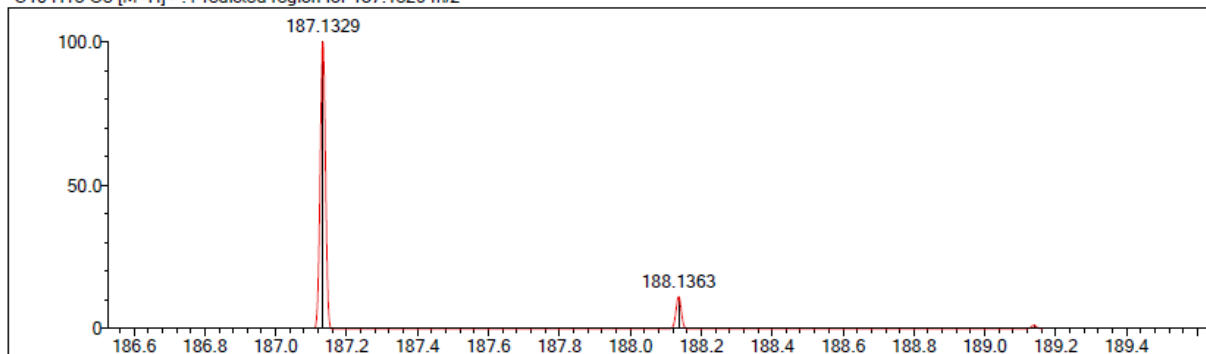
Event#: 1 MS(E+) Ret. Time : 0.680 -> 0.947 - 0.520 -> 0.588 Scan# : 103 -> 143 - 79 -> 89



Measured region for 187.1361 m/z

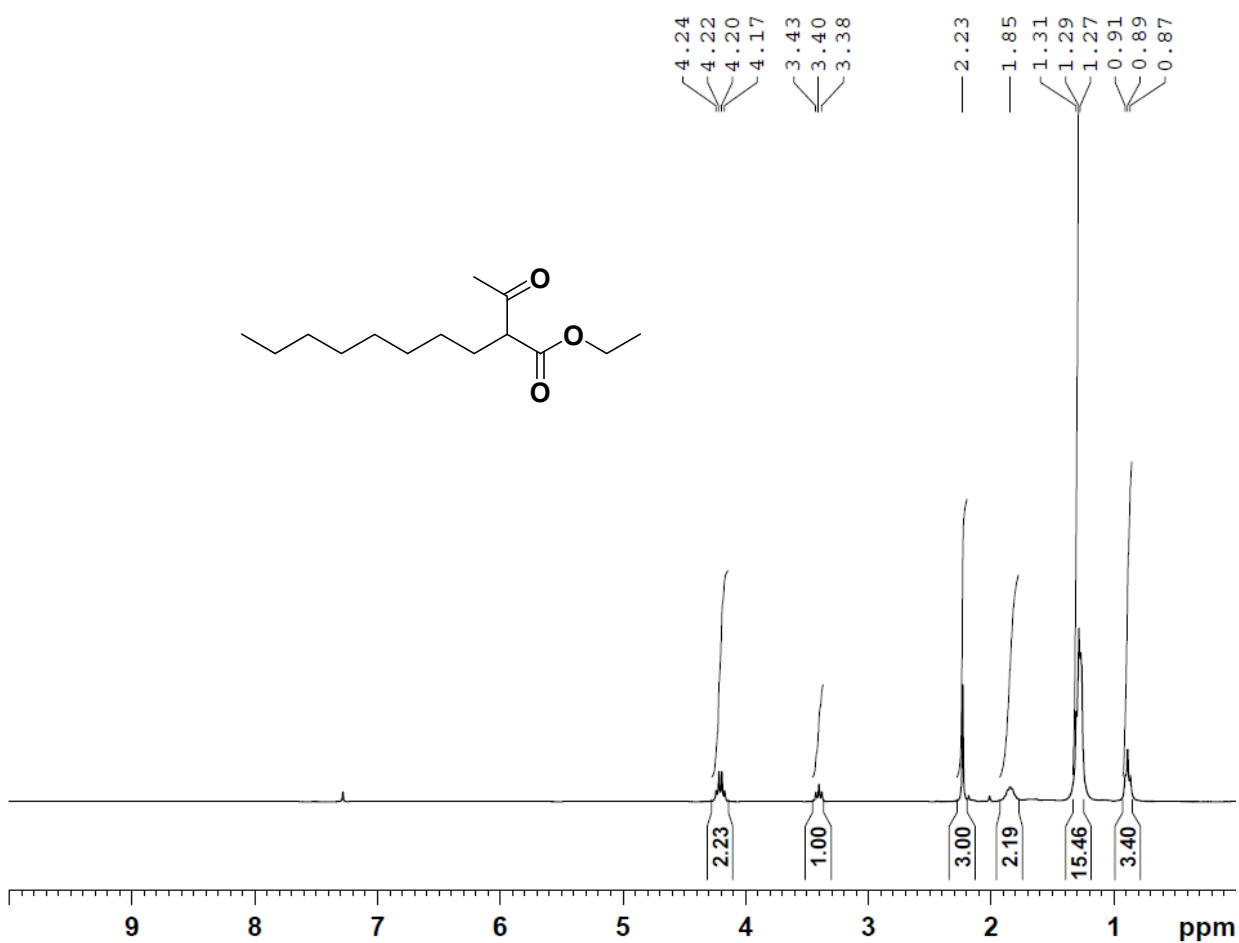


C10 H18 O3 [M+H]⁺ : Predicted region for 187.1329 m/z

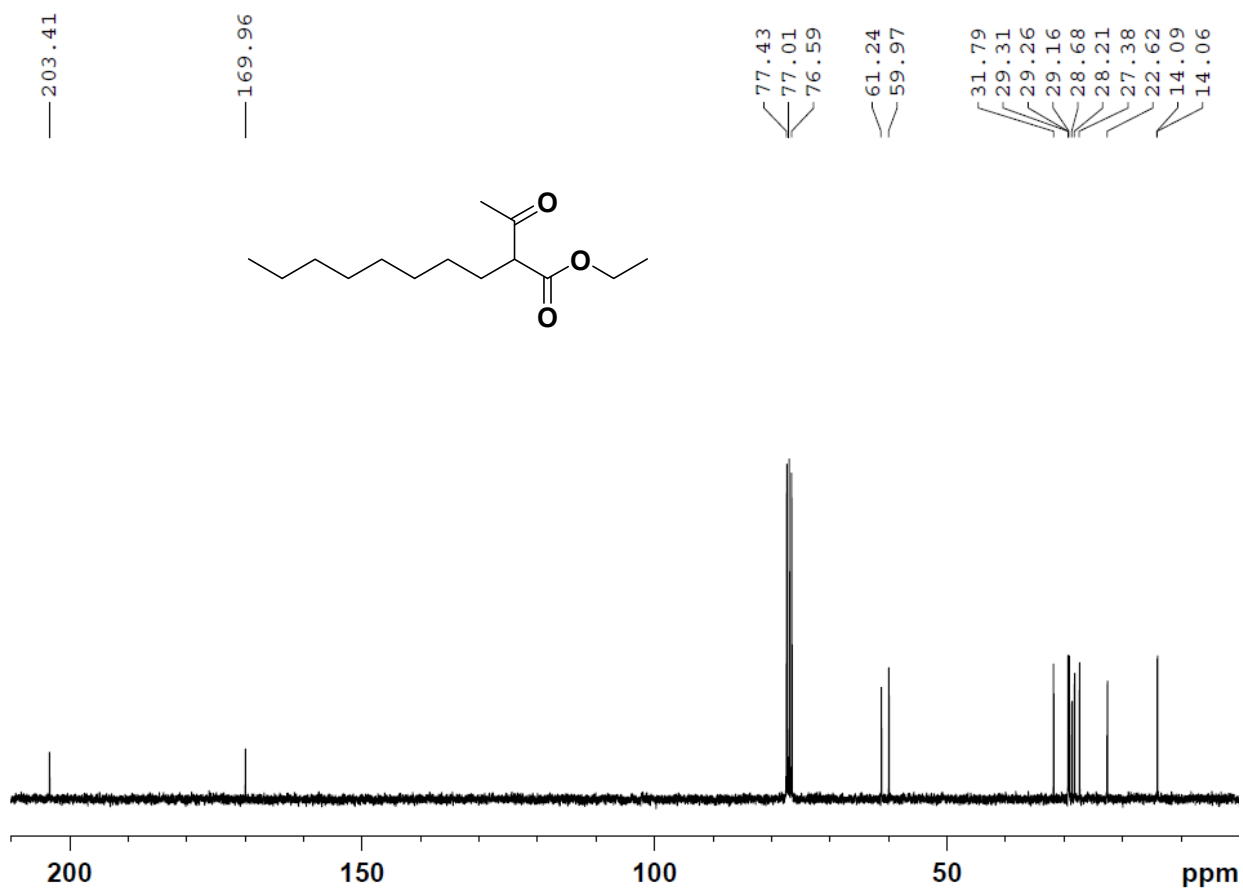


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	16.16	C10 H18 O3	[M+H] ⁺	187.1361	187.1329	3.2	17.10	76.71	2.0

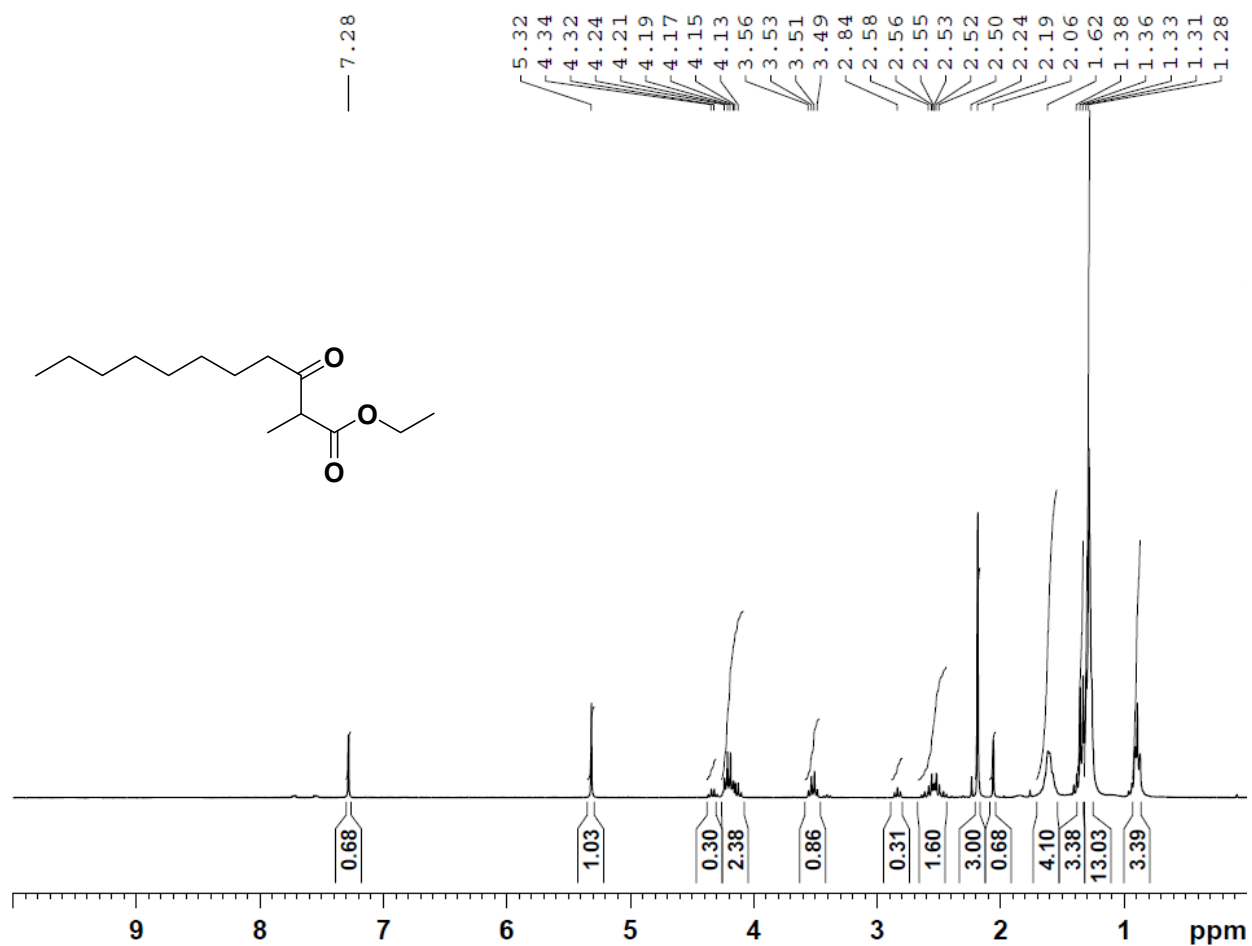
^1H NMR Spectrum of Compound 35e in CDCl_3



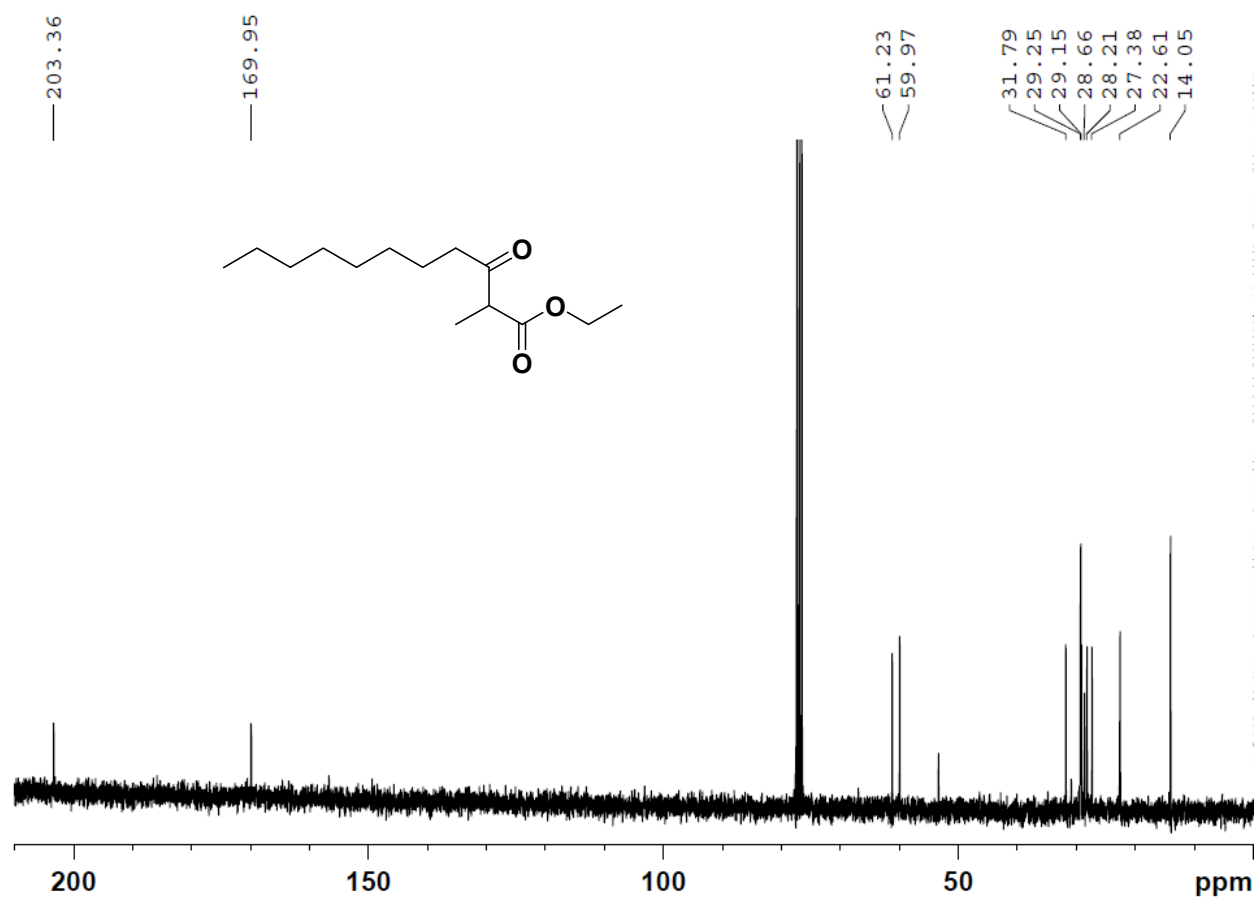
^{13}C NMR Spectrum of Compound 35e in CDCl_3



¹H NMR Spectrum of Compound 35e' in CDCl₃

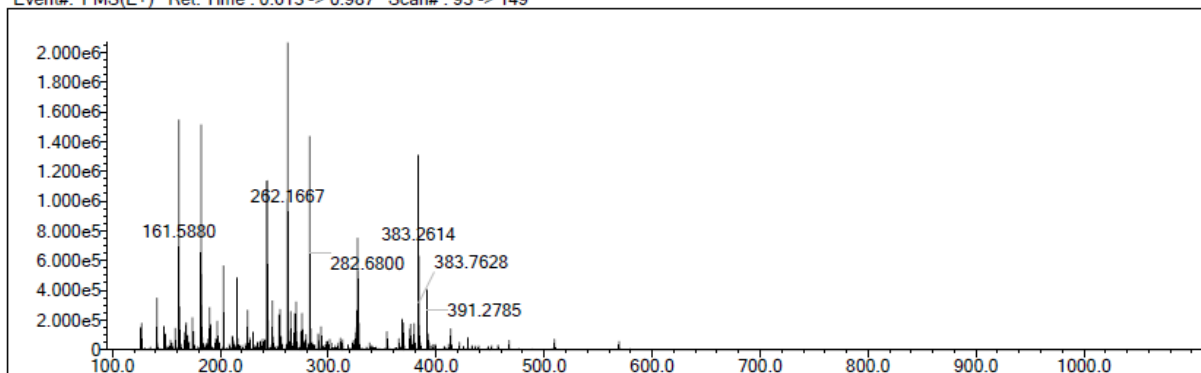


^{13}C NMR Spectrum of Compound 35e' in CDCl_3

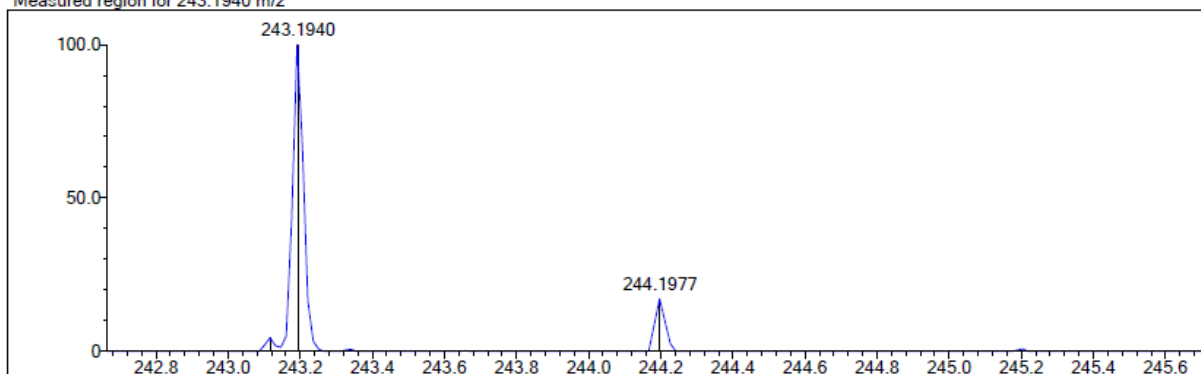


HRMS of Compound 35e'

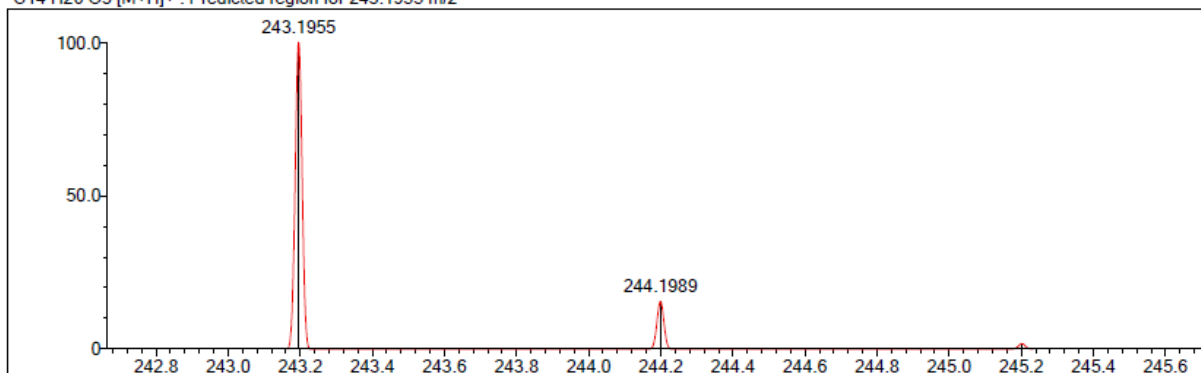
Event#: 1 MS(E+) Ret. Time : 0.613 -> 0.987 Scan#: 93 -> 149



Measured region for 243.1940 m/z

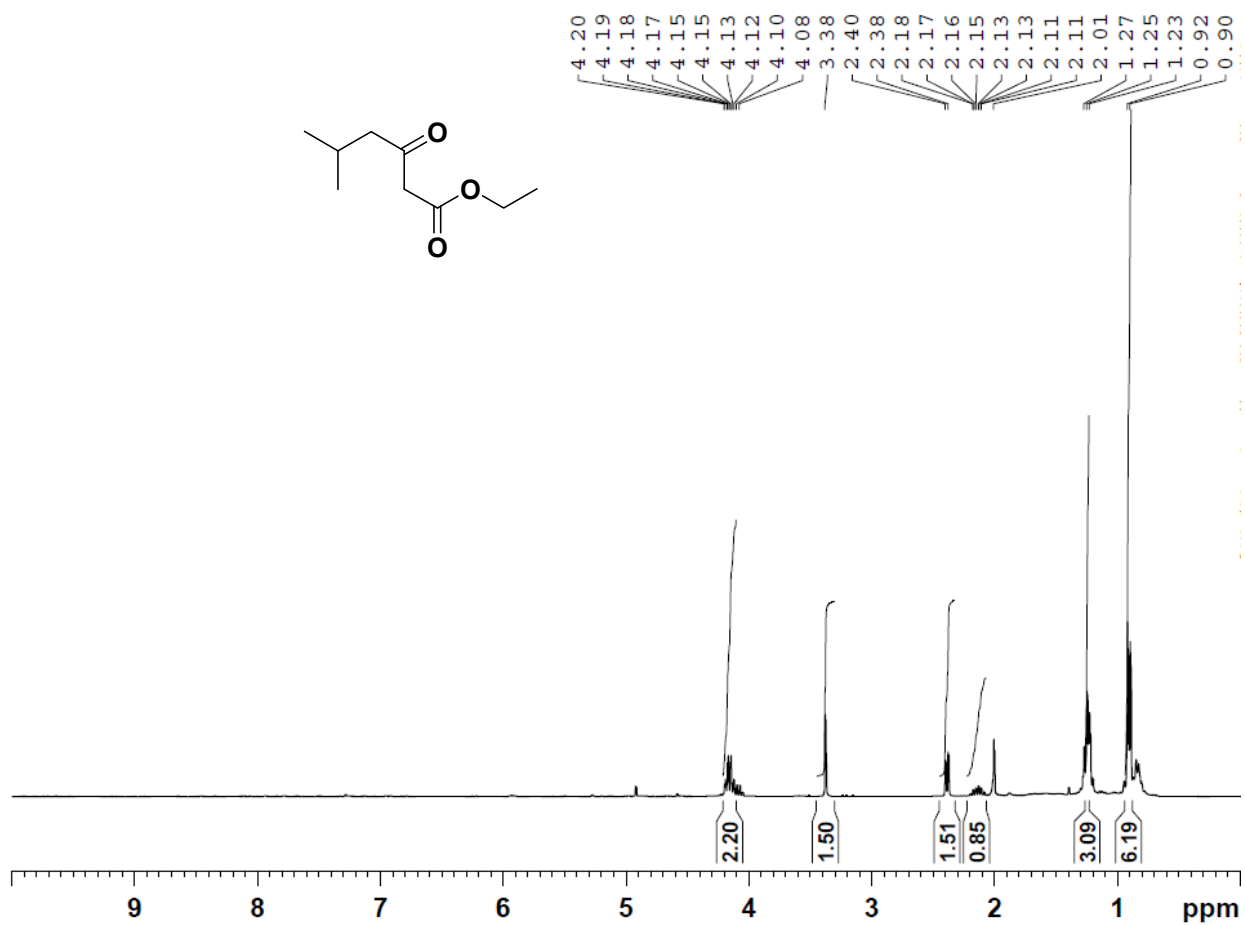


C14 H26 O3 [M+H]⁺ : Predicted region for 243.1955 m/z

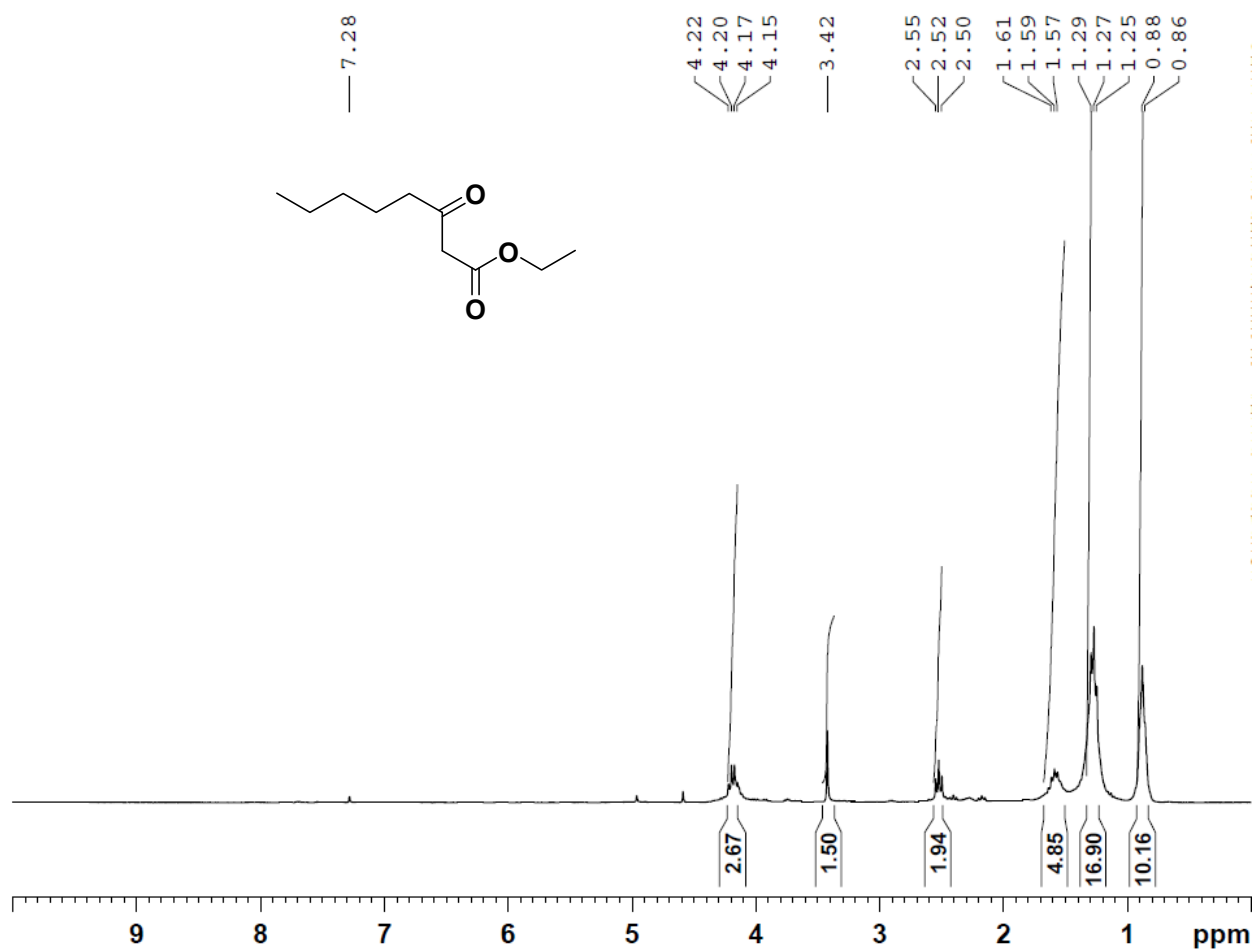


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	52.20	C14 H26 O3	[M+H] ⁺	243.1940	243.1955	-1.5	-6.17	66.67	2.0

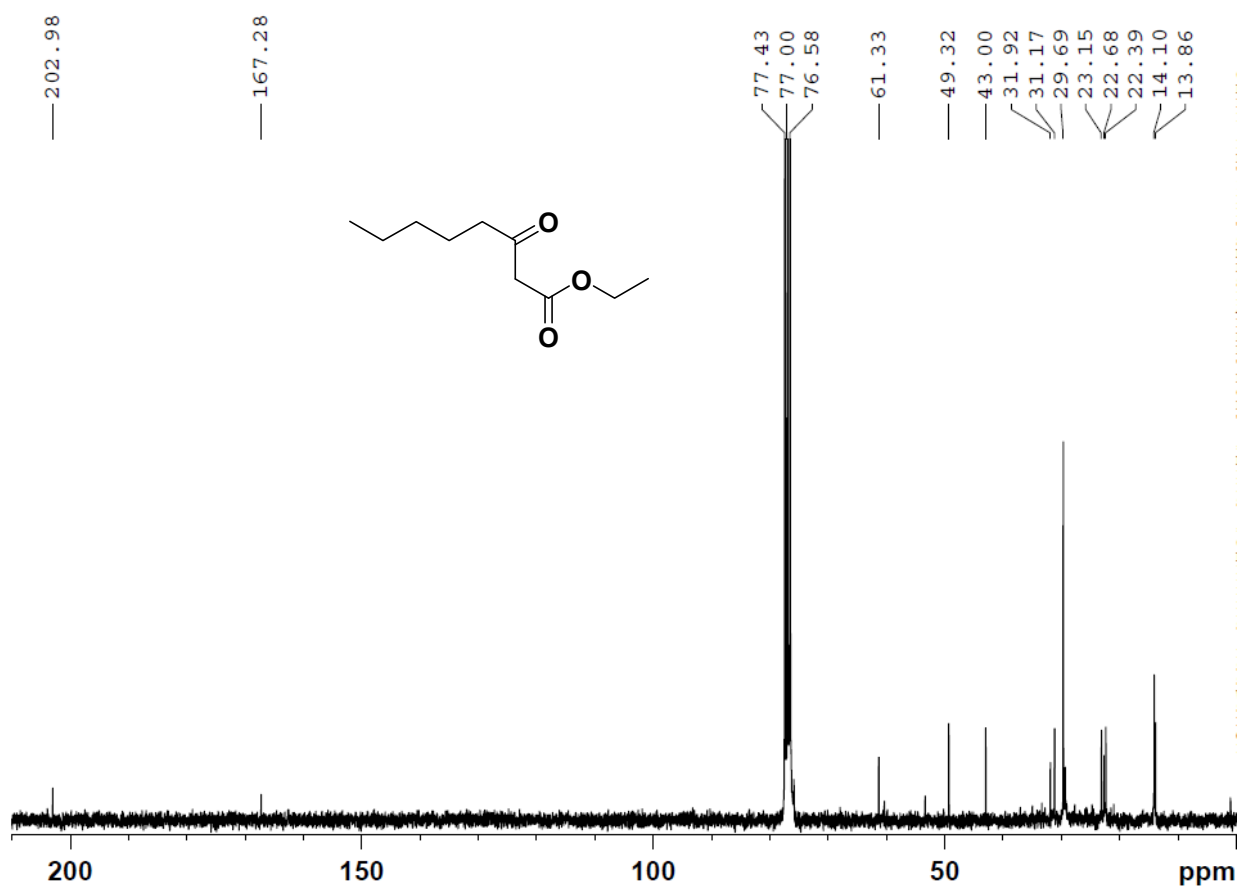
^1H NMR Spectrum of Compound 35f in CDCl_3



^1H NMR Spectrum of Compound 35g in CDCl_3

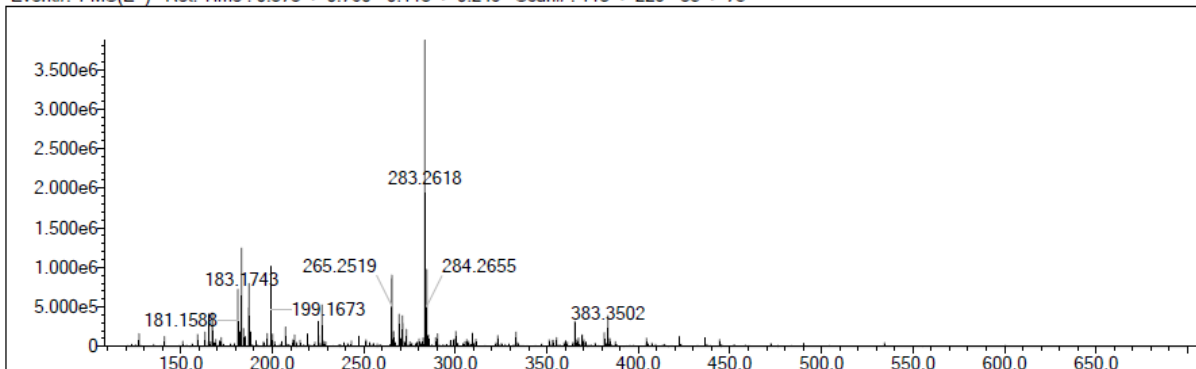


^{13}C NMR Spectrum of Compound 35g in CDCl_3

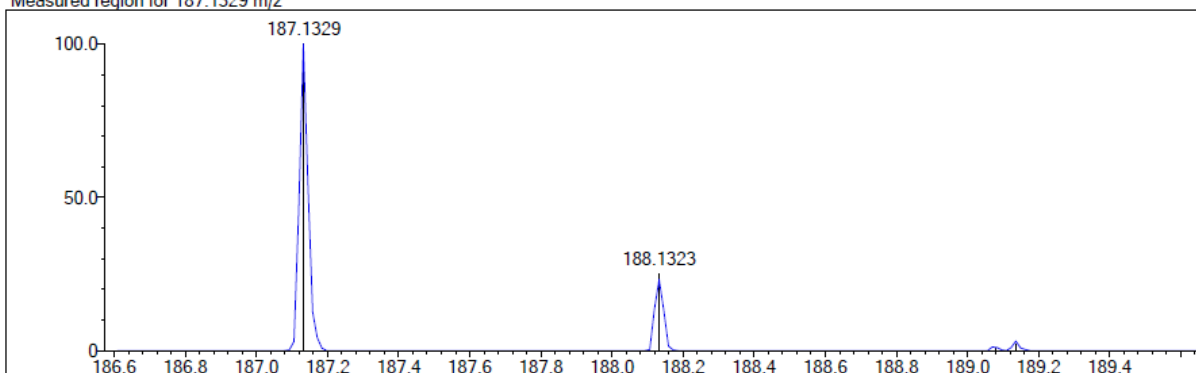


HRMS of Compound 35g

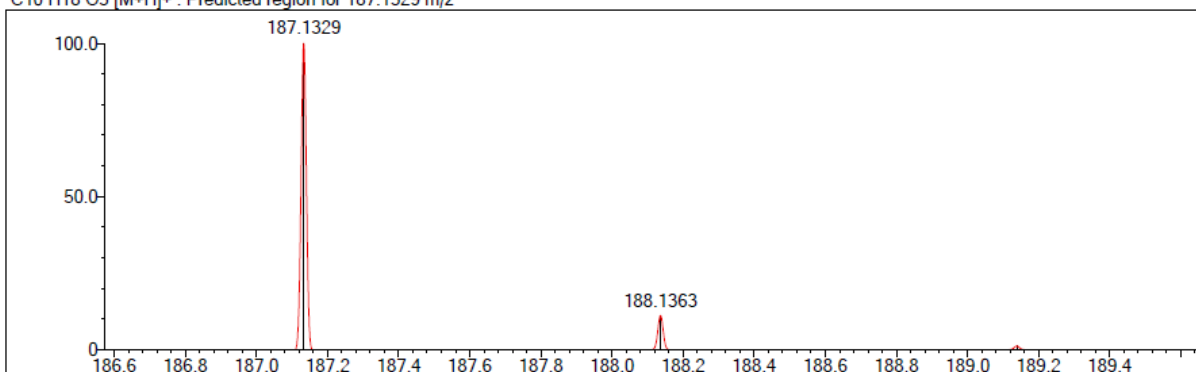
Event#: 1 MS(E+) Ret. Time : 0.373 -> 0.760 - 0.113 -> 0.249 Scan# : 113 -> 229 - 35 -> 75



Measured region for 187.1329 m/z

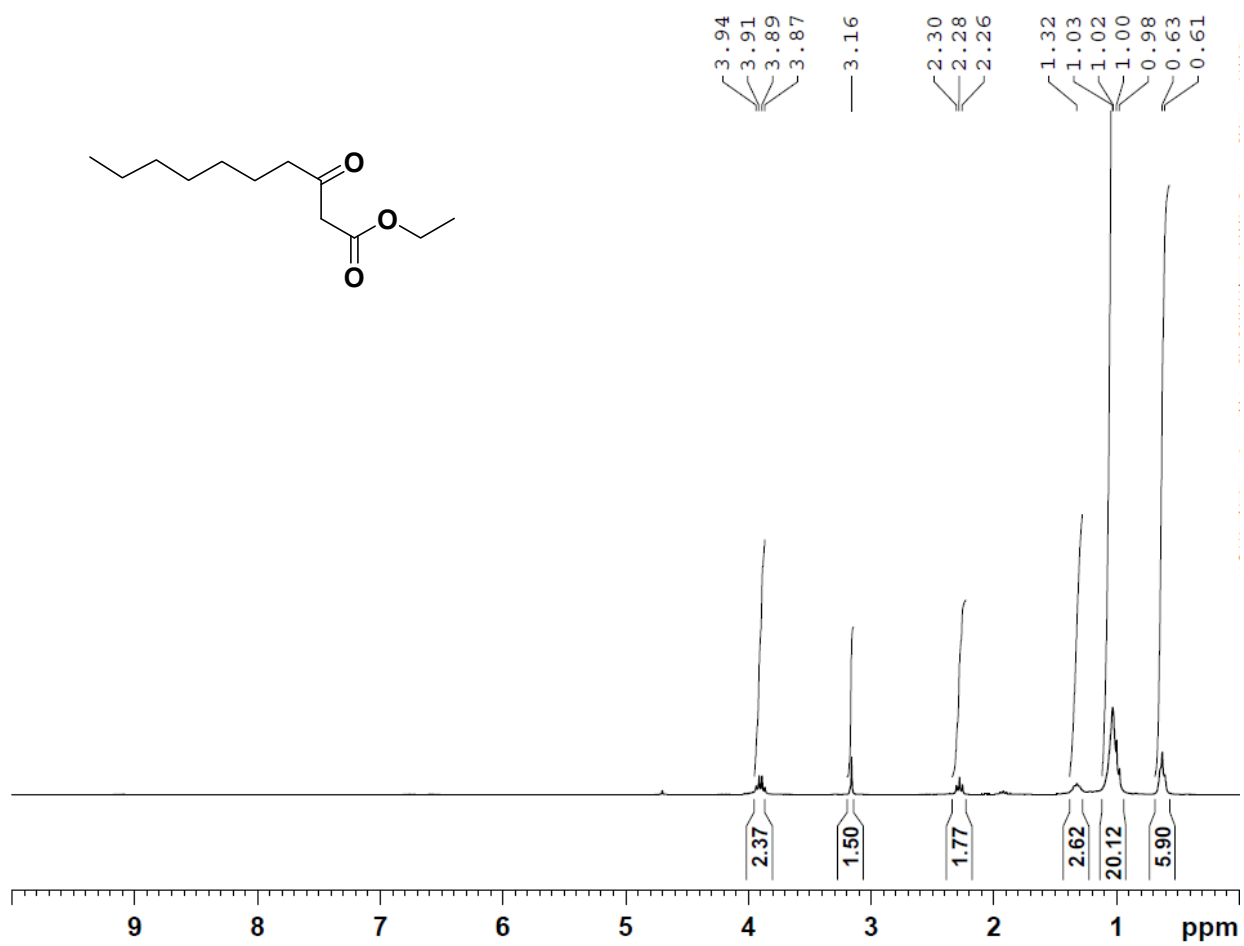


C10 H18 O3 [M+H]⁺ : Predicted region for 187.1329 m/z

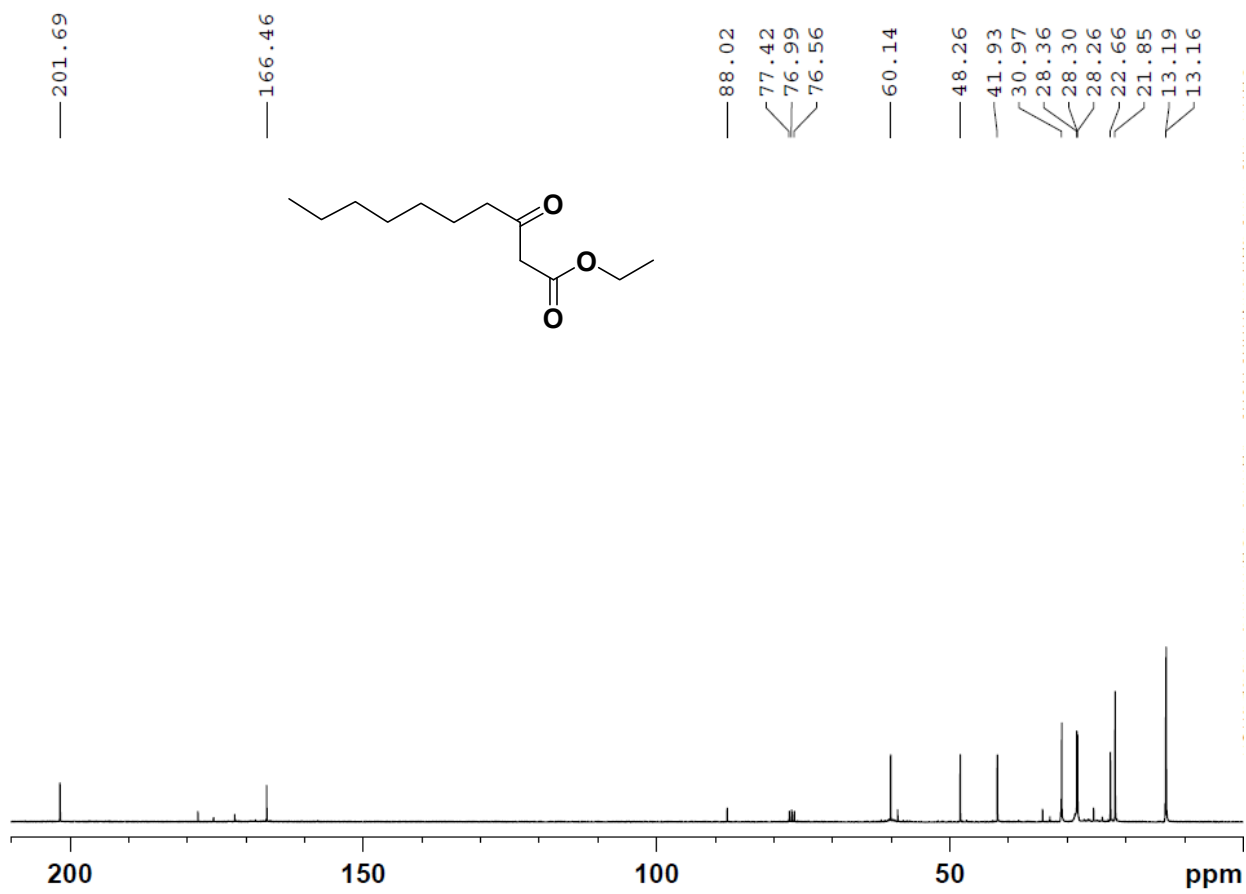


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	53.74	C10 H18 O3	[M+H] ⁺	187.1329	187.1329	0.0	0.00	53.74	2.0

^1H NMR Spectrum of Compound 9h in CDCl_3

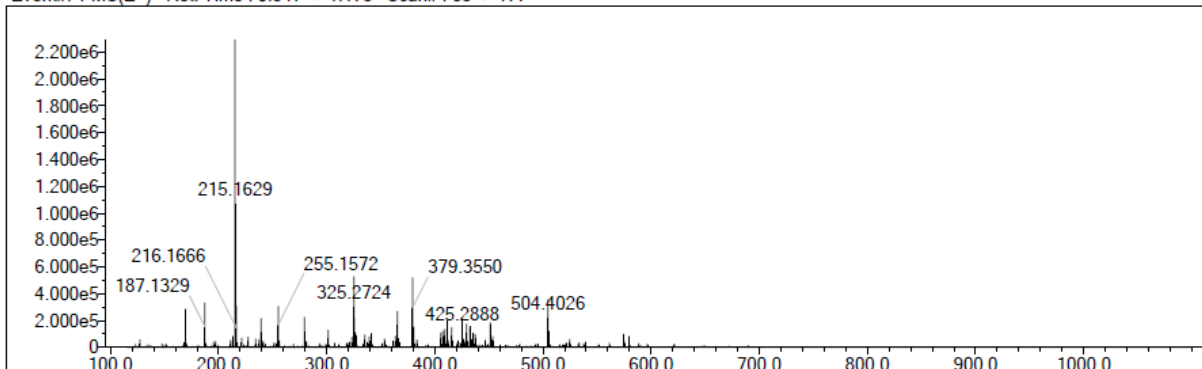


^{13}C NMR Spectrum of Compound 35h in CDCl_3

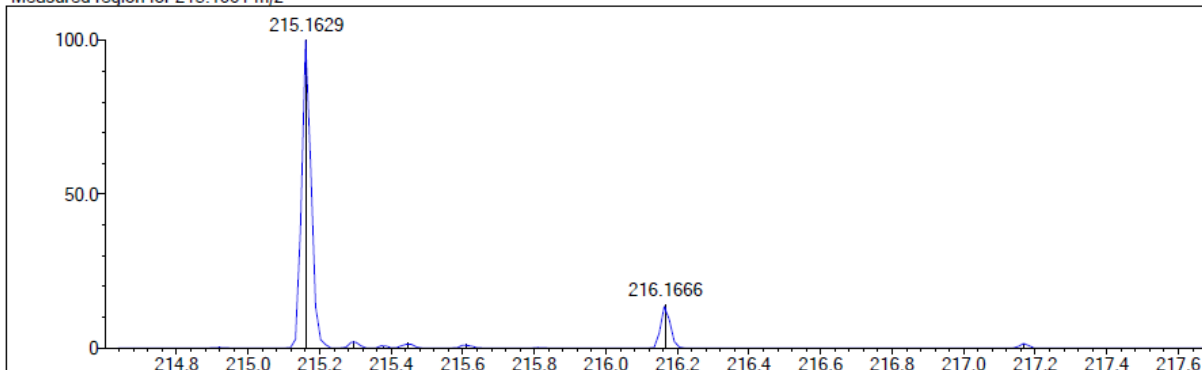


HRMS of Compound 35h

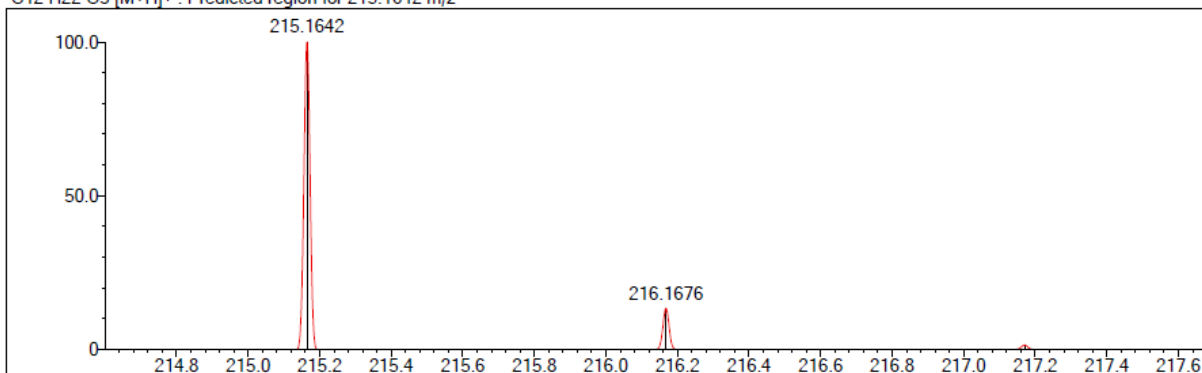
Event#: 1 MS(E+) Ret. Time : 0.547 -> 1.173 Scan#: 83 -> 177



Measured region for 215.1661 m/z

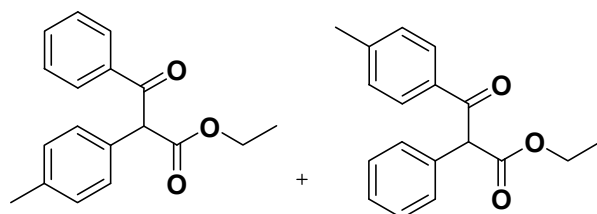


C12 H22 O3 [M+H]⁺ : Predicted region for 215.1642 m/z

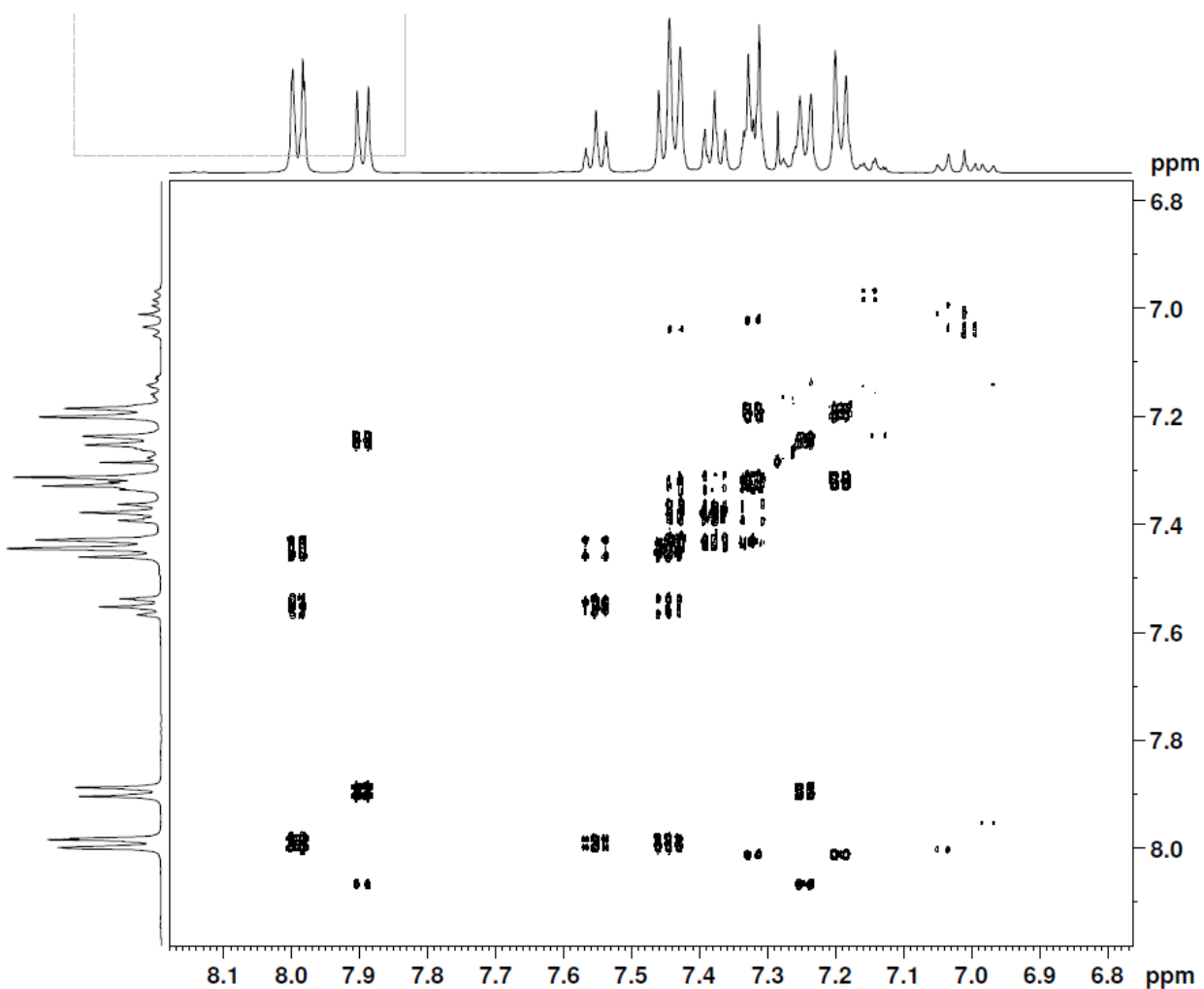


Rank	Score	Formula (M)	Ion	Meas. m/z	Pred. m/z	Df. (mDa)	Df. (ppm)	Iso	DBE
1	36.03	C12 H22 O3	[M+H] ⁺	215.1661	215.1642	1.9	8.83	69.69	2.0

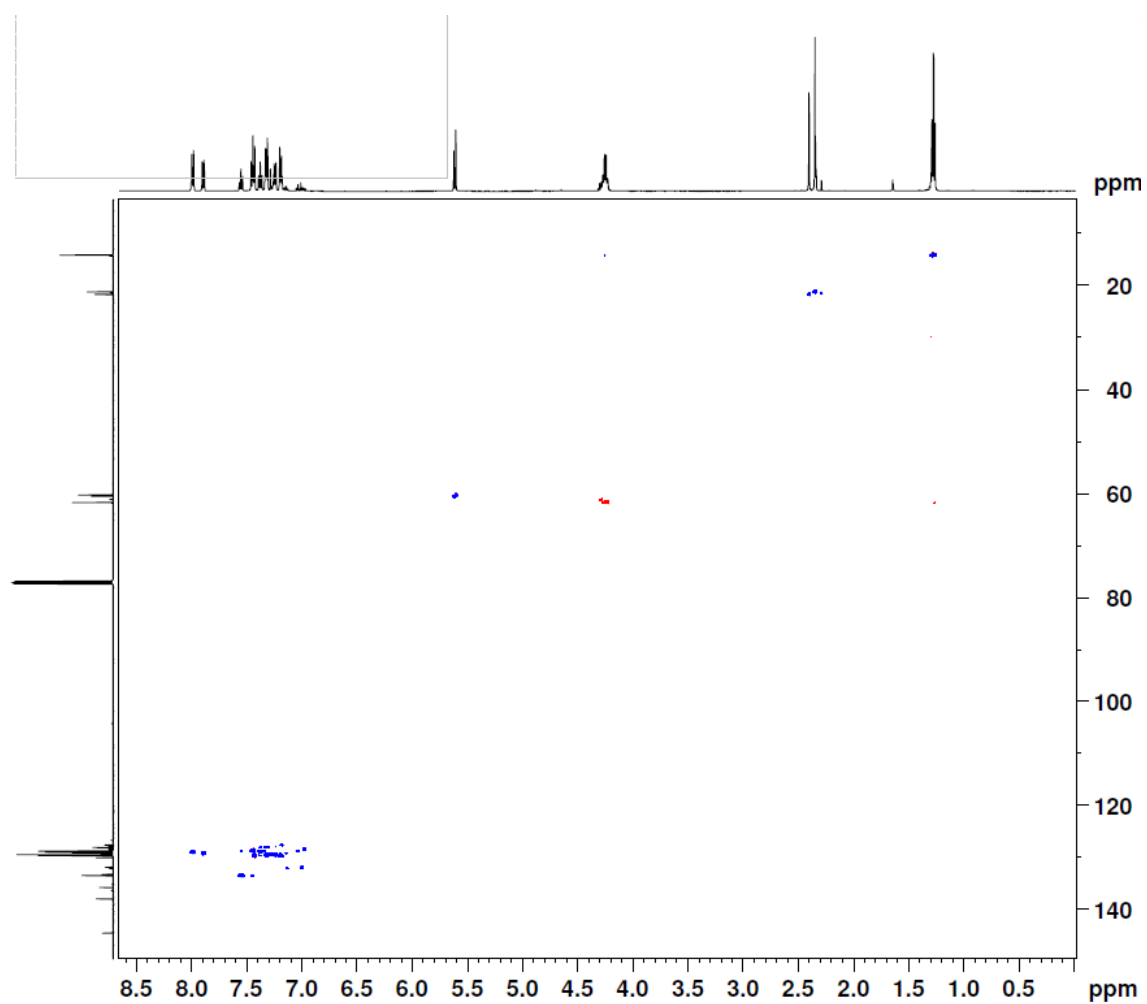
2D NMR of
Ethyl 3-oxo-3-phenyl-2-(*p*-tolyl)propanoate (34b) and
ethyl 3-oxo-2-phenyl-3-(*p*-tolyl)propanoate (34b')



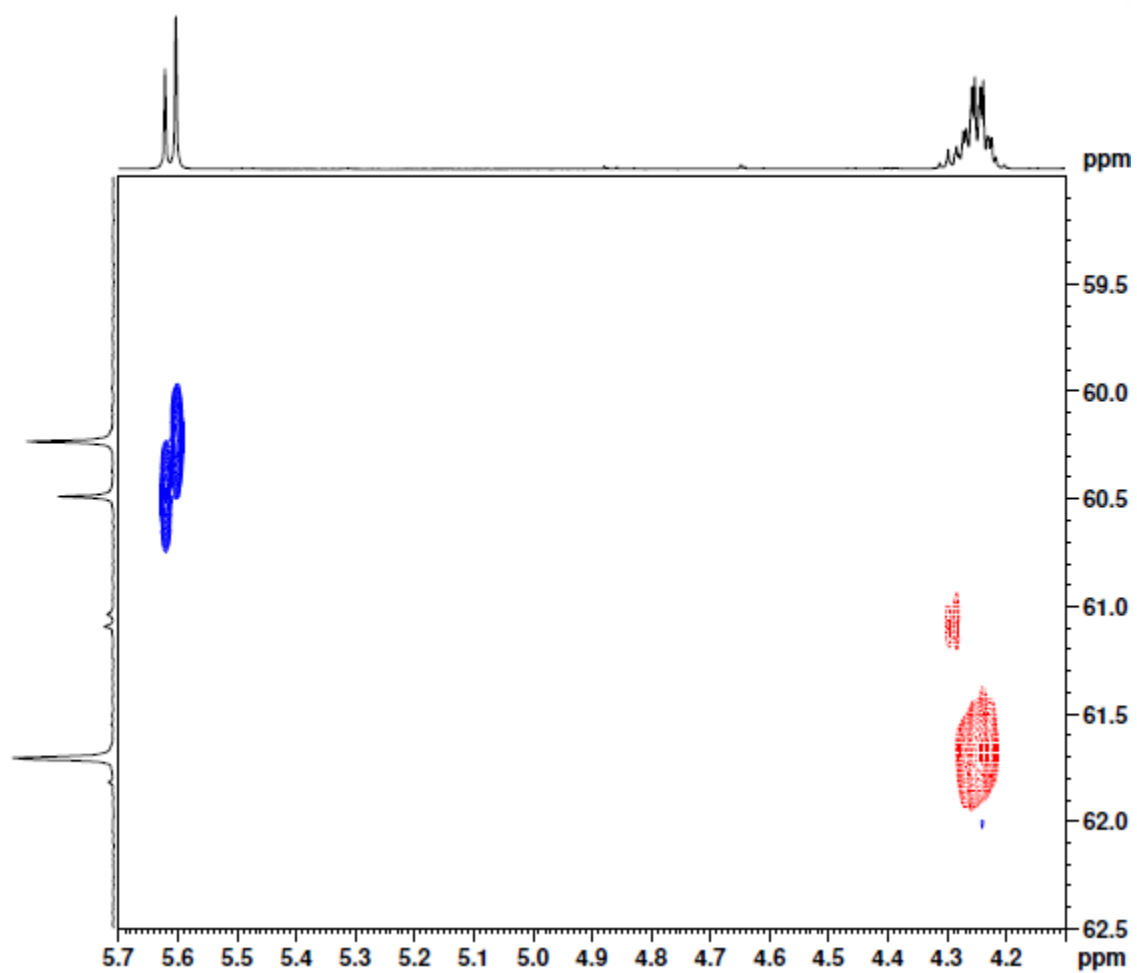
COSY Spectrum



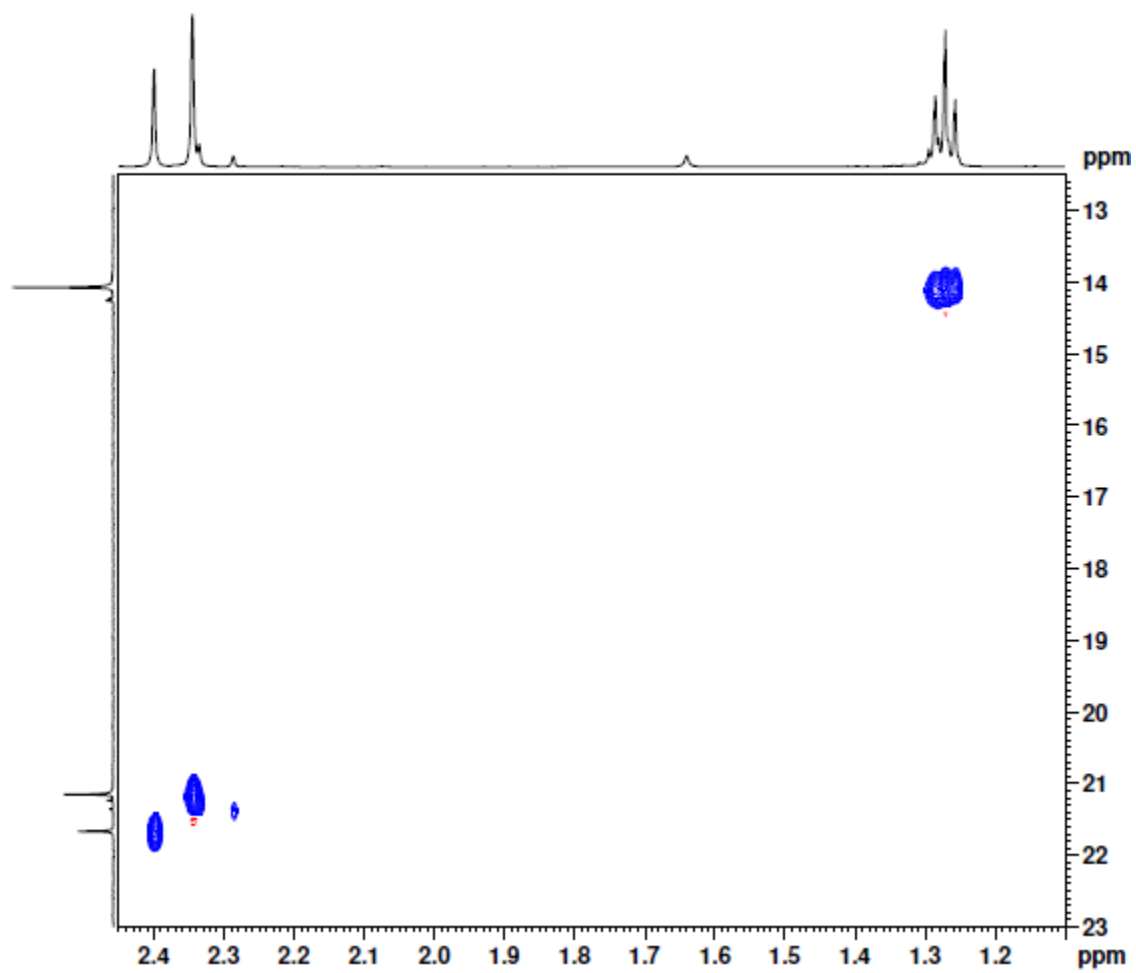
HSQC Spectrum



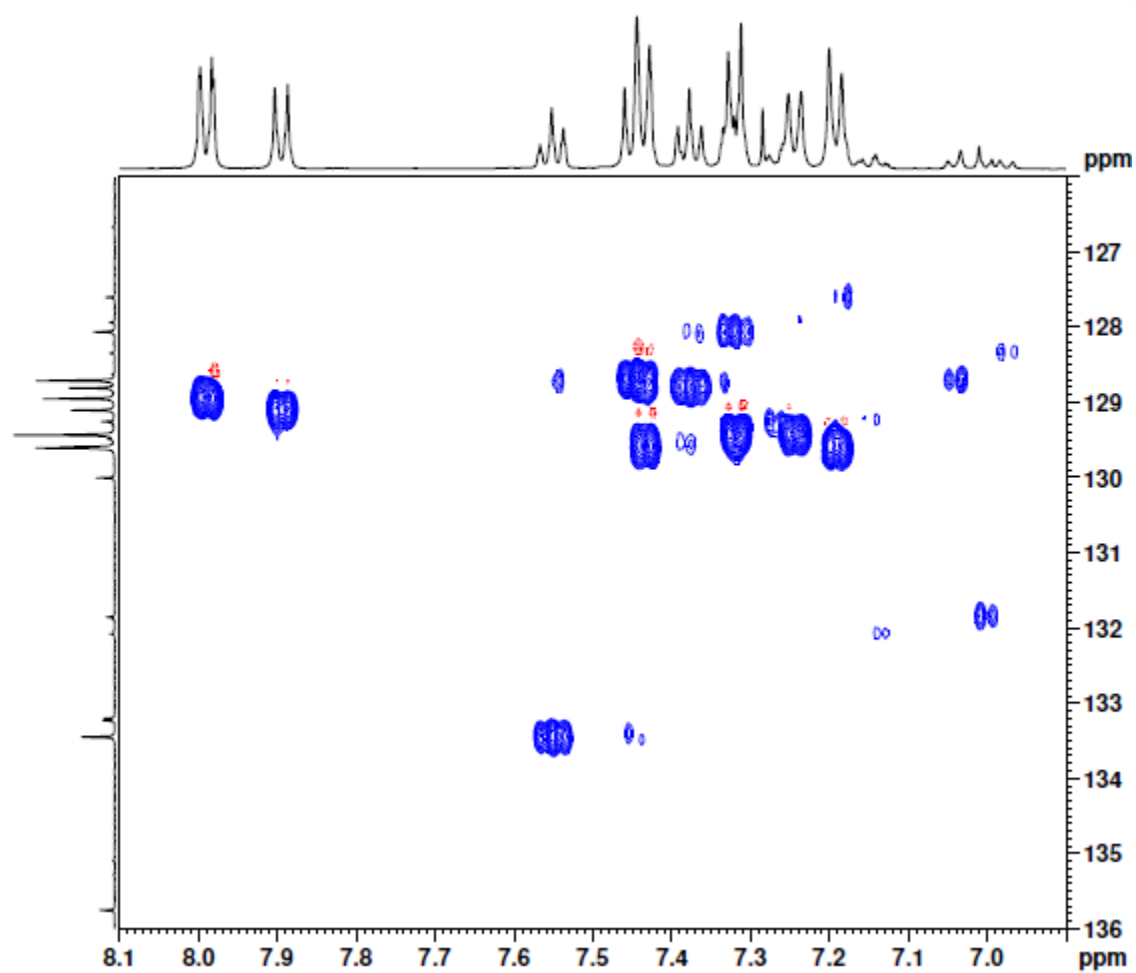
HSQC Aliphatic Down-field



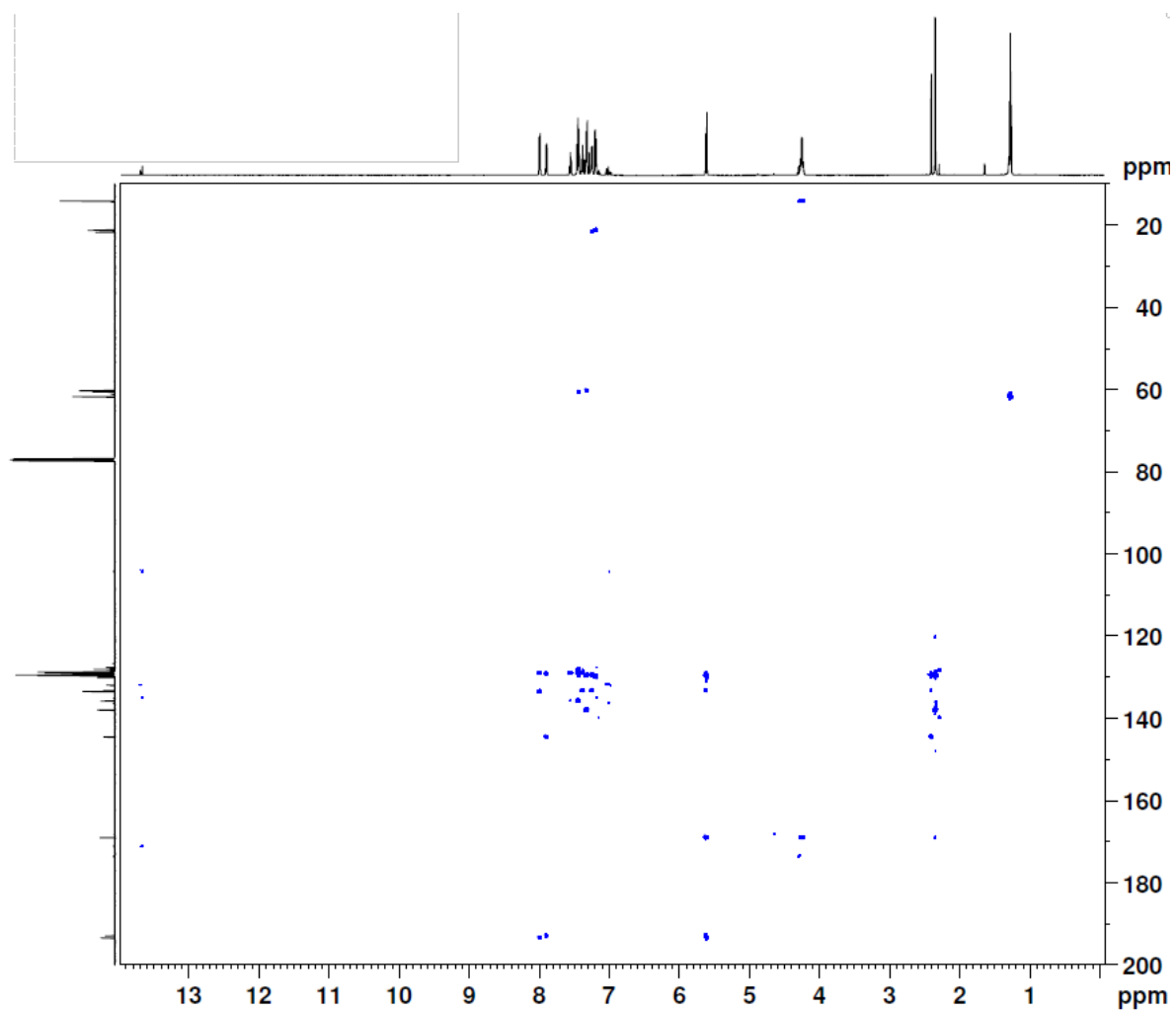
HSQC Aliphatic Up-field



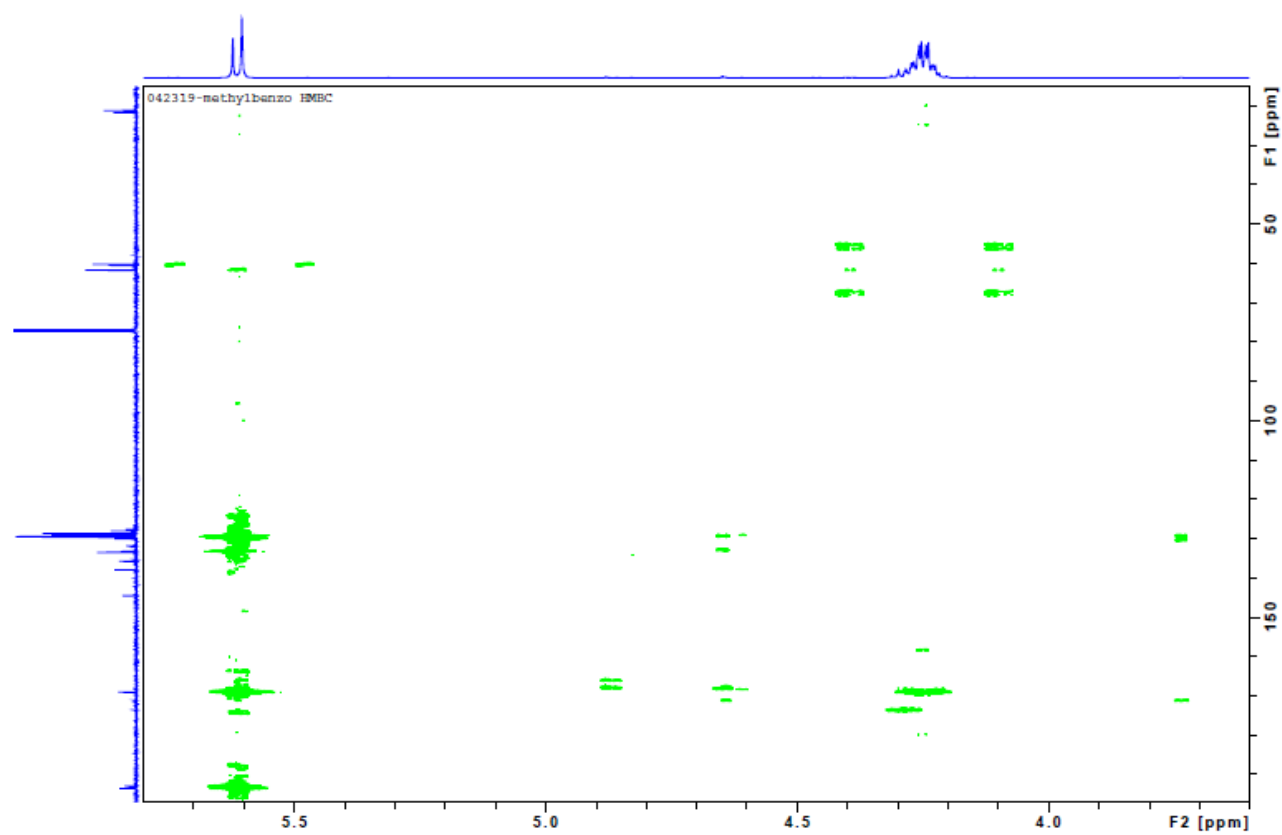
HSQC Aromatic



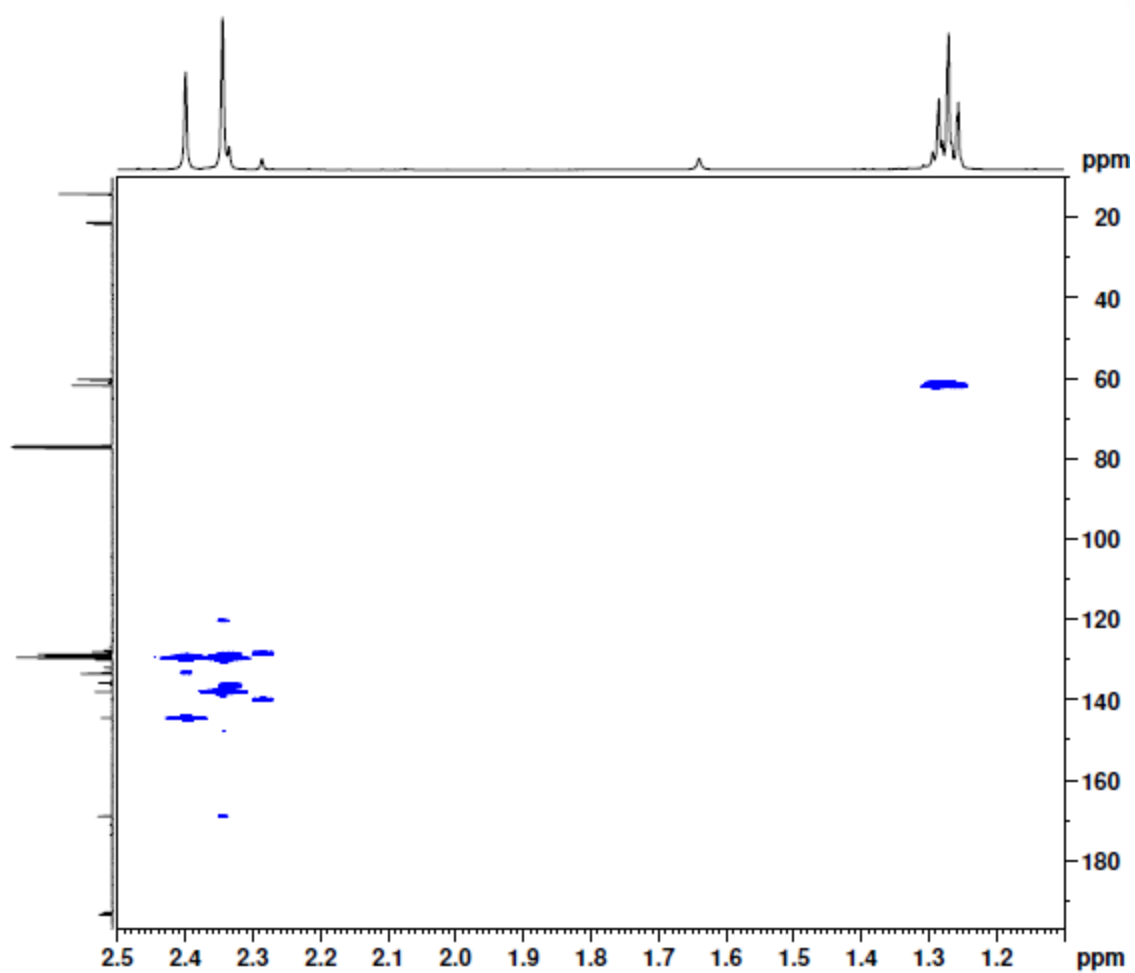
HMBC Spectrum



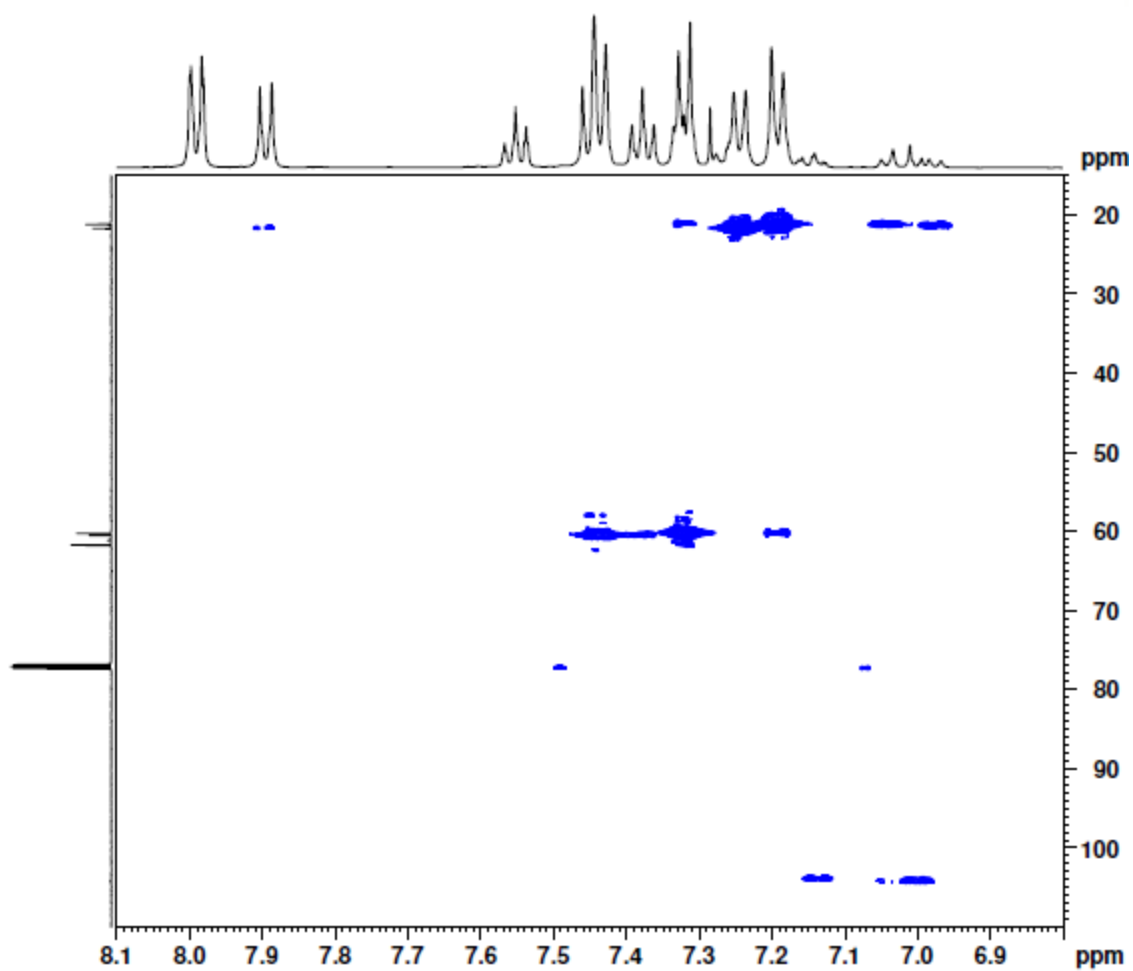
HMBC Aliphatic Down Field



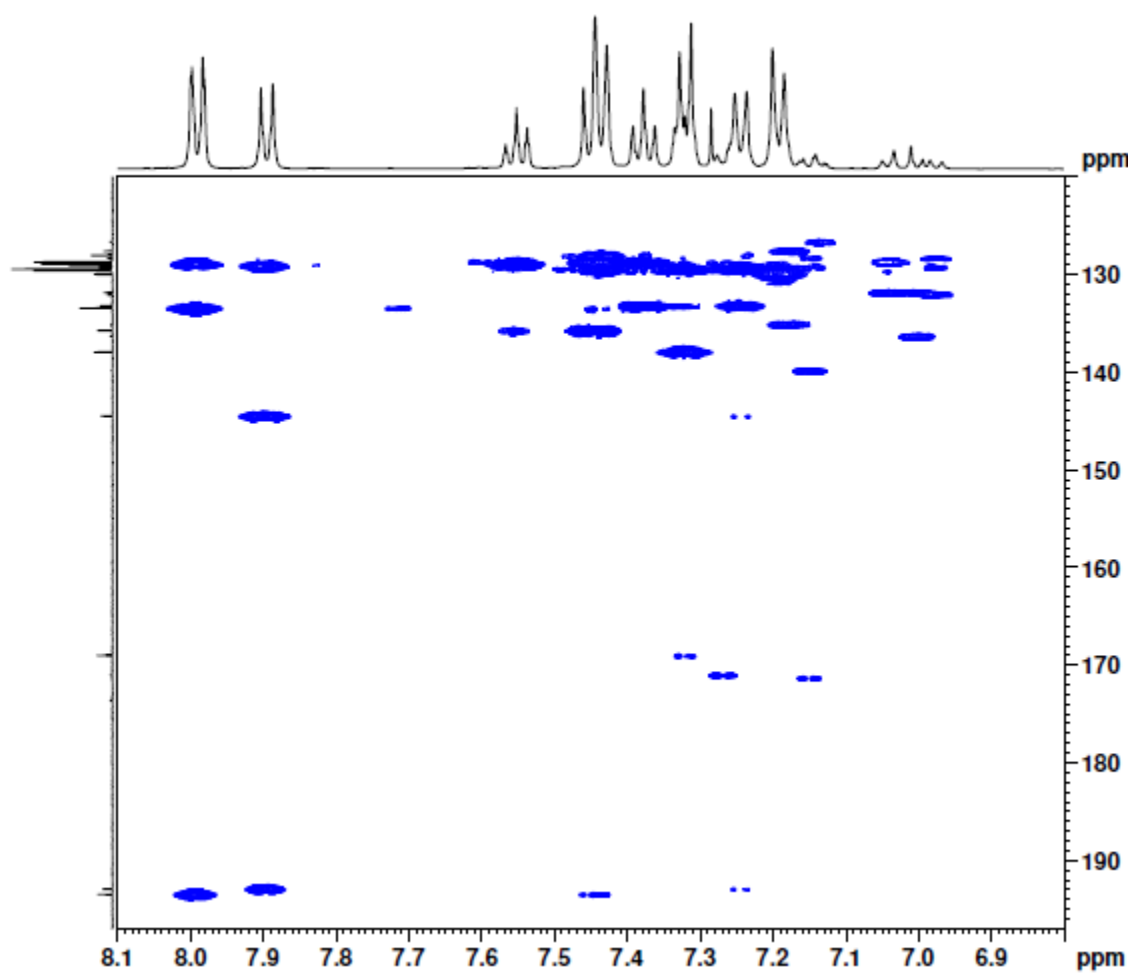
HMBC Aliphatic Up Field



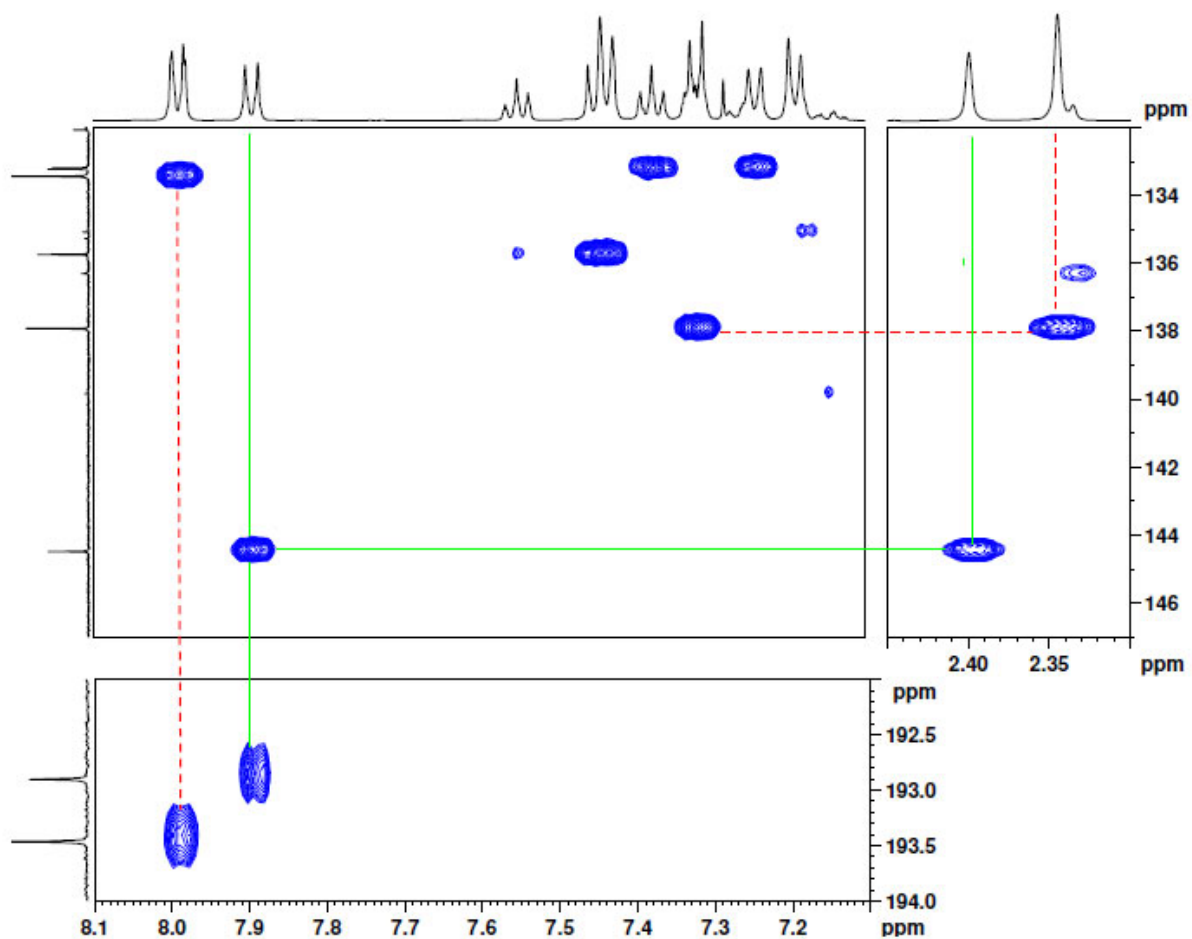
HMBC Aromatic-Aliphatic



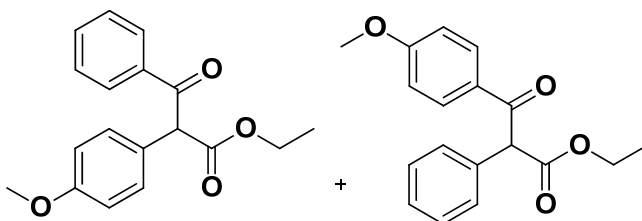
HMBC Aromatic-Aromatic



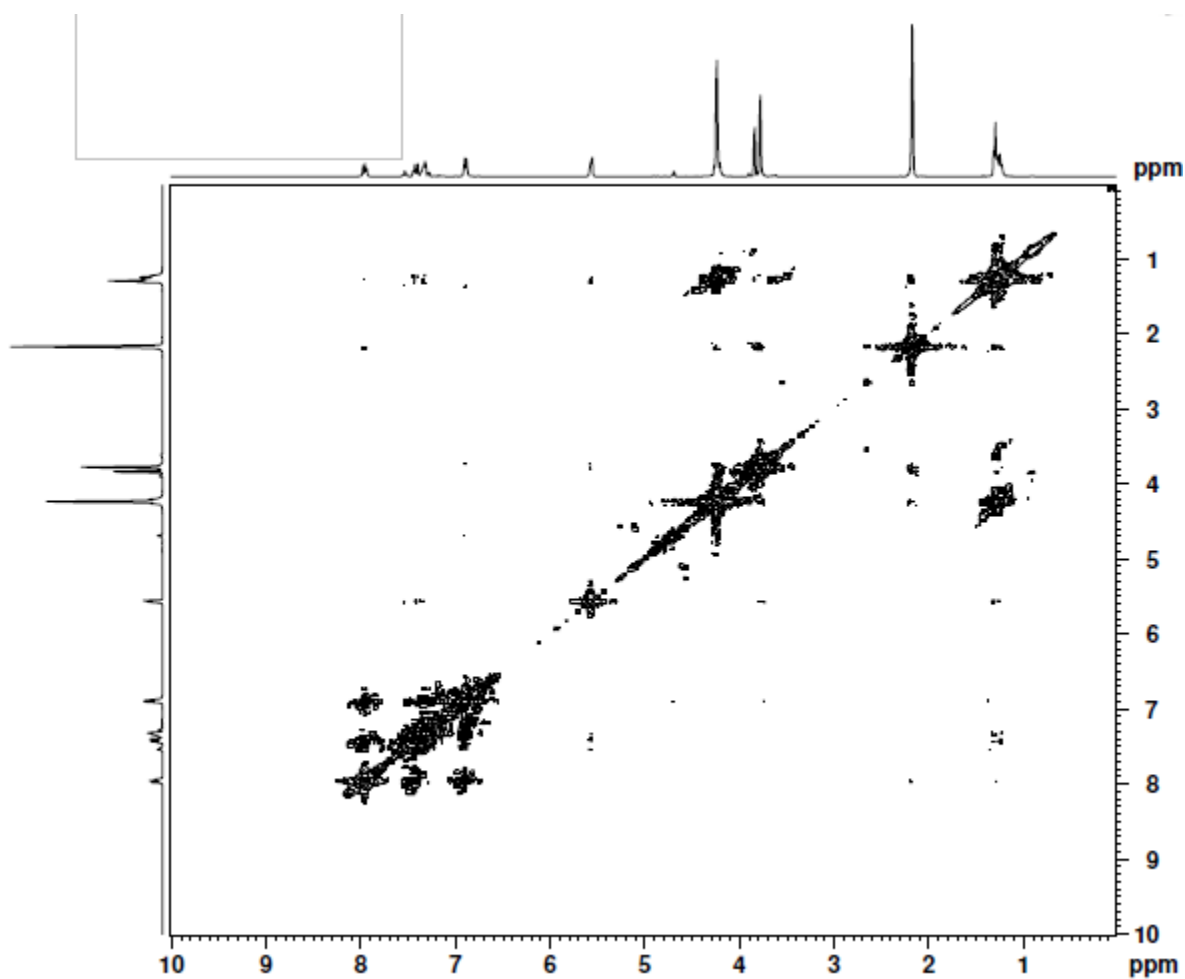
HMBC (Combination of Three Parts)



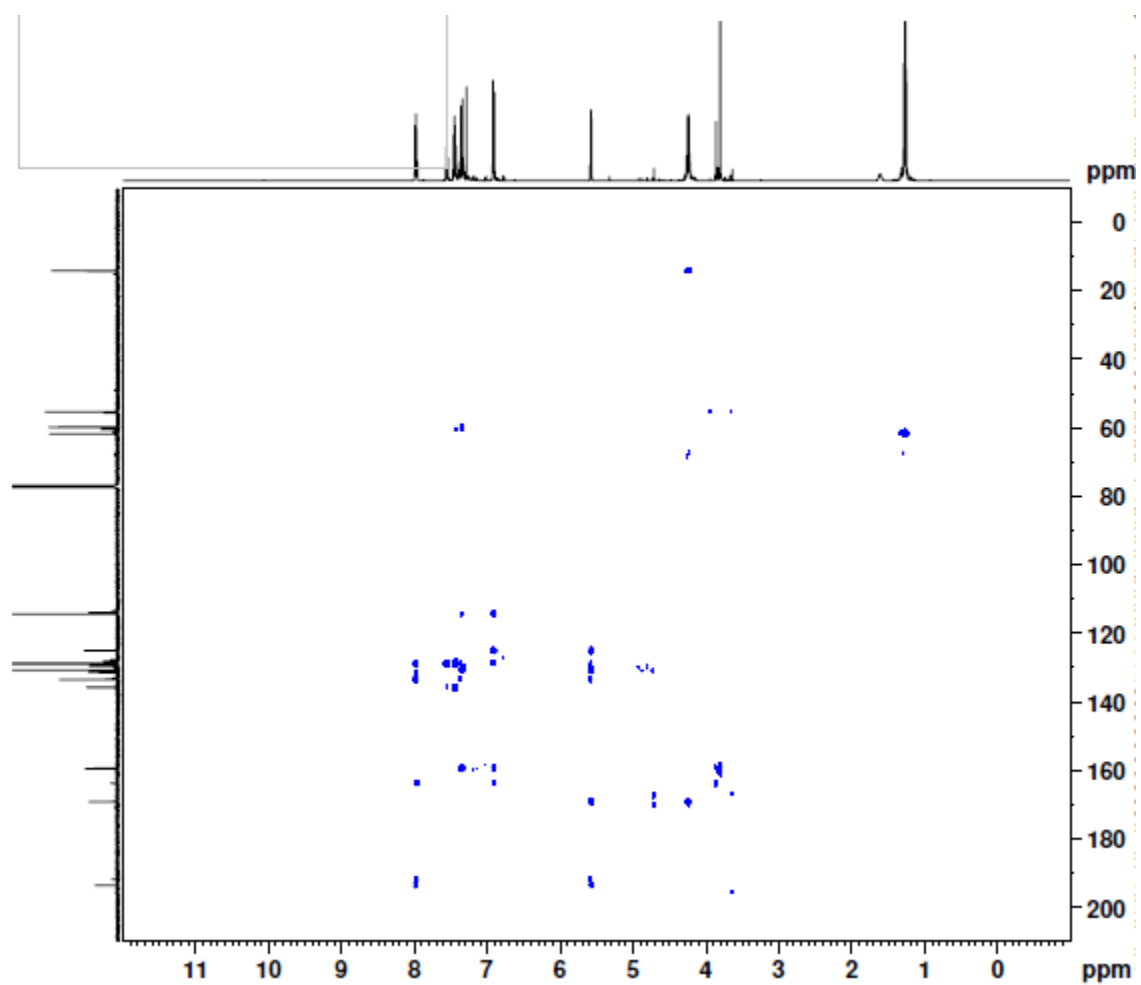
2D NMR of
Ethyl 3-oxo-3-phenyl-2-(*p*-tolyl)propanoate (34c) and
ethyl 3-oxo-2-phenyl-3-(*p*-tolyl)propanoate (34c')



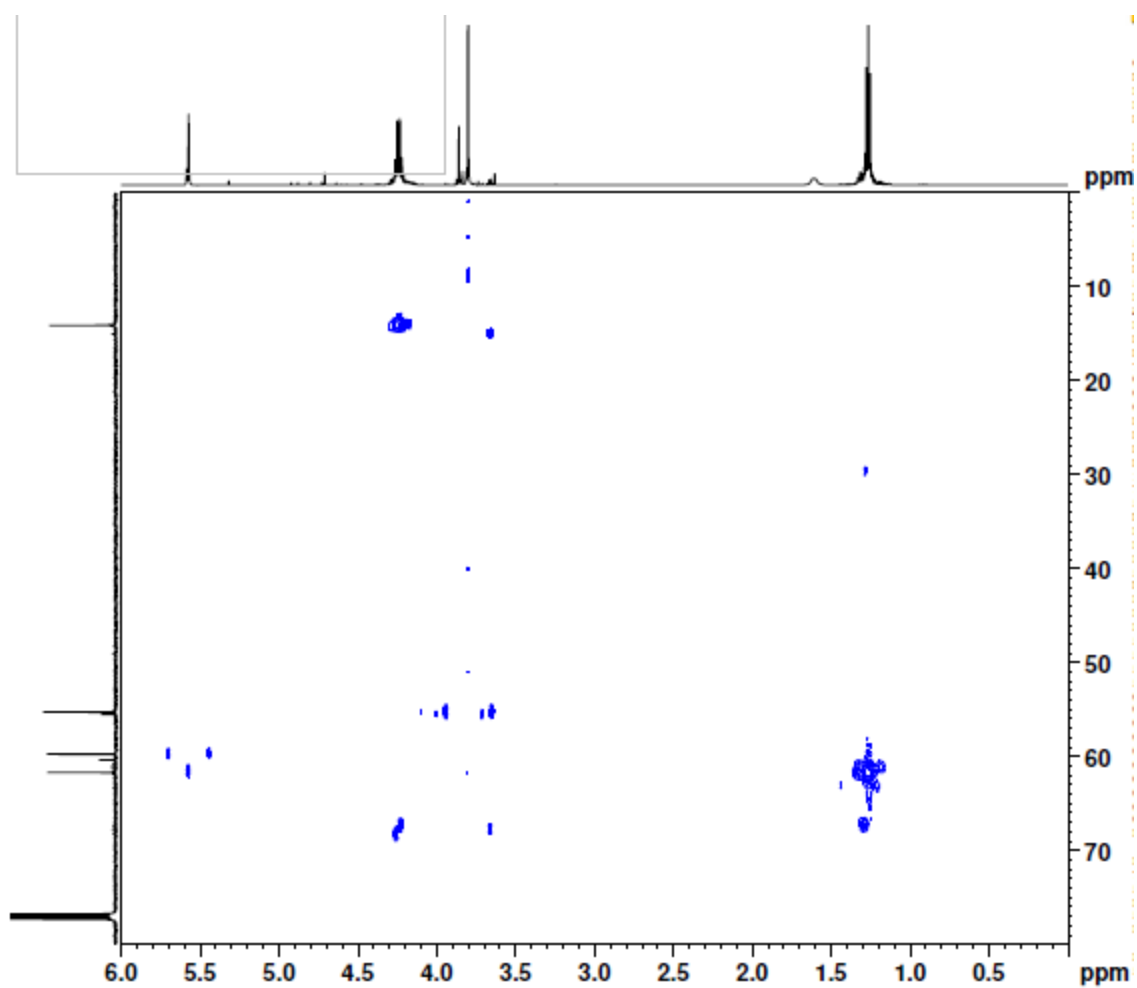
COSY Spectrum



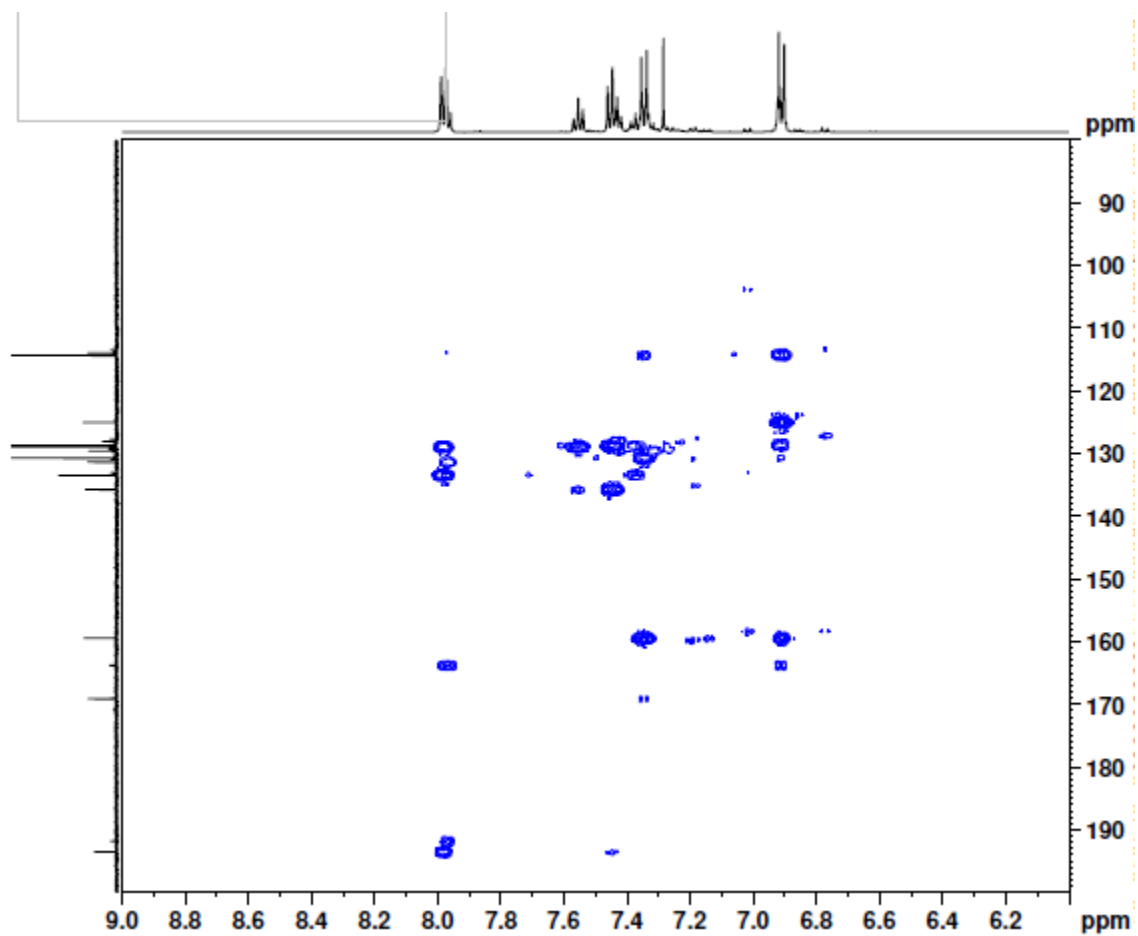
HMBC Spectrum



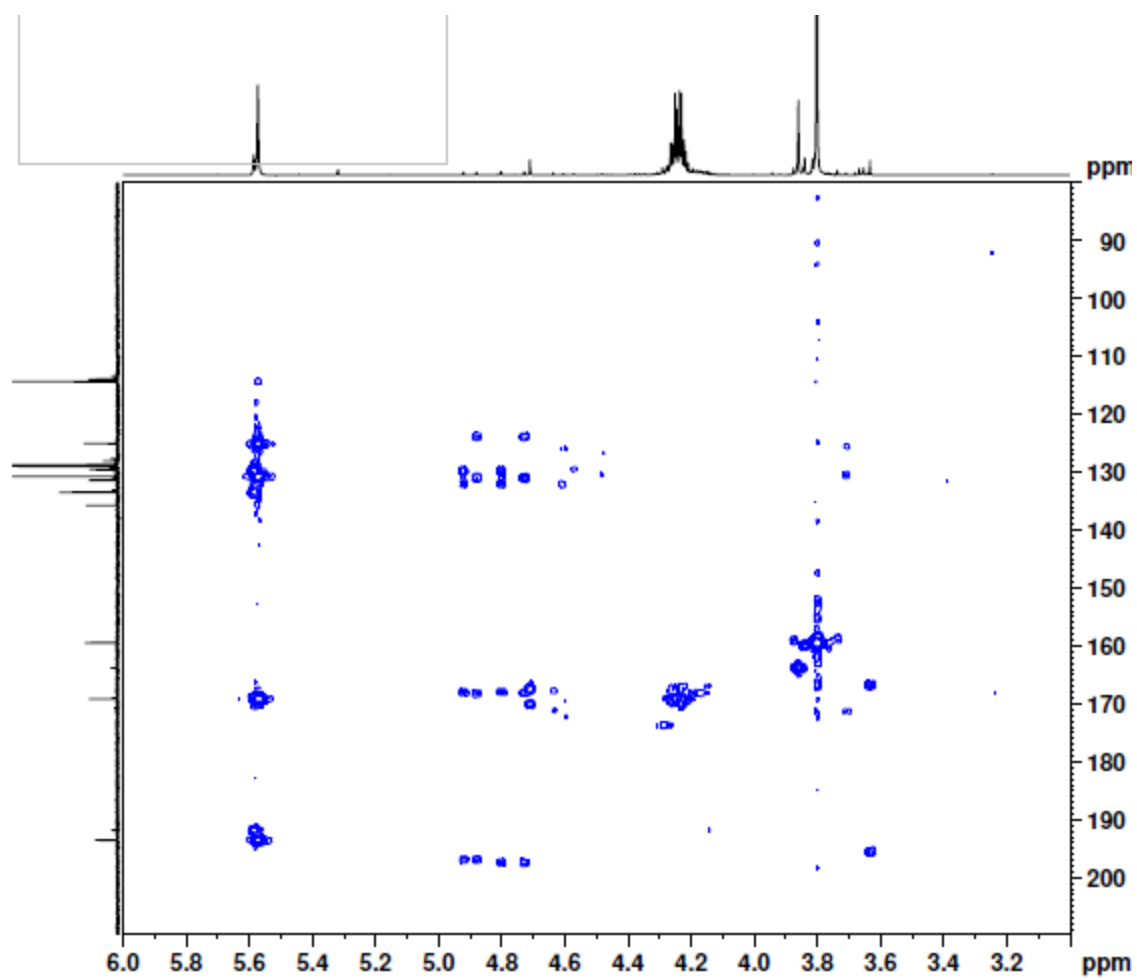
HMBC Aliphatic



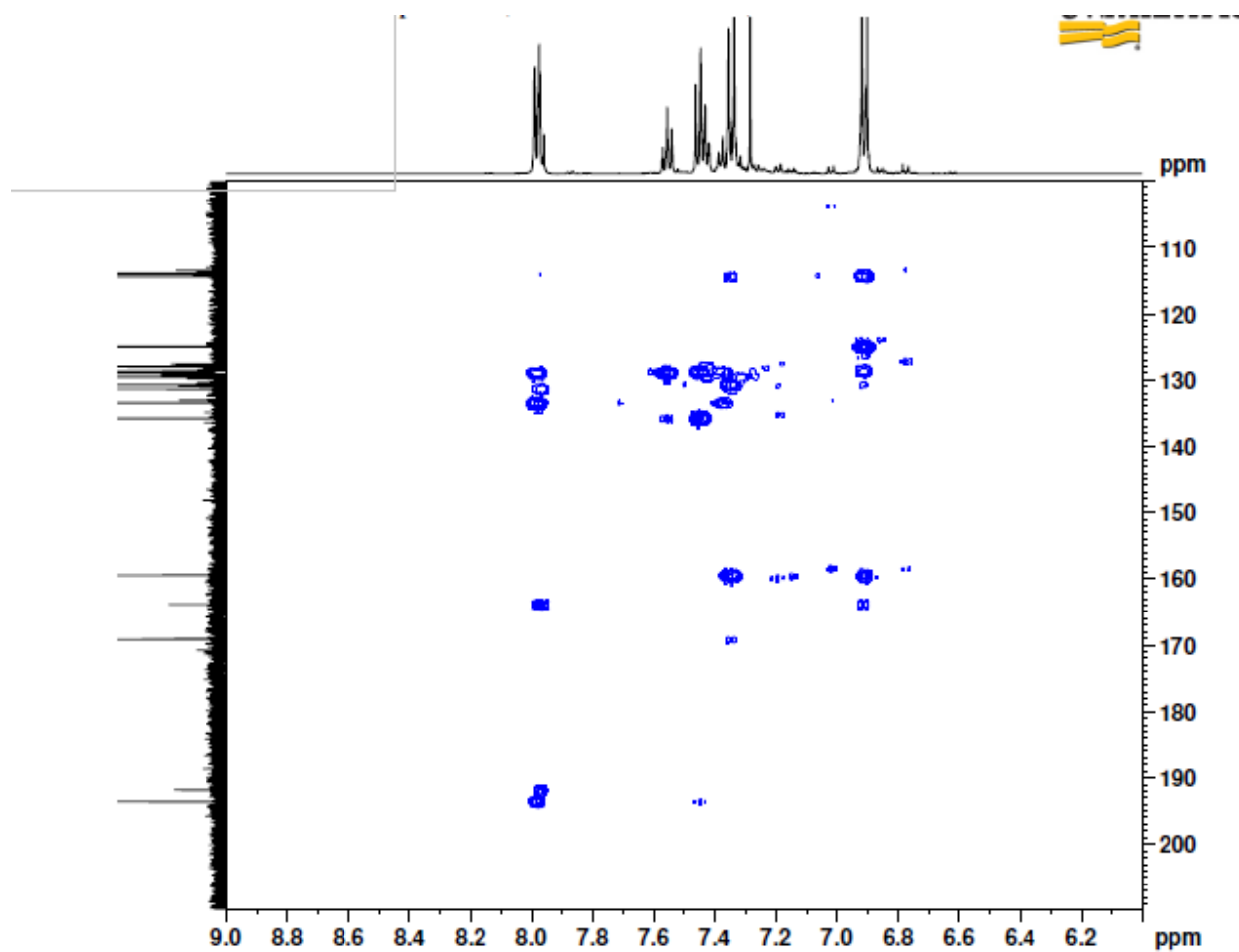
HMBC Aromatic



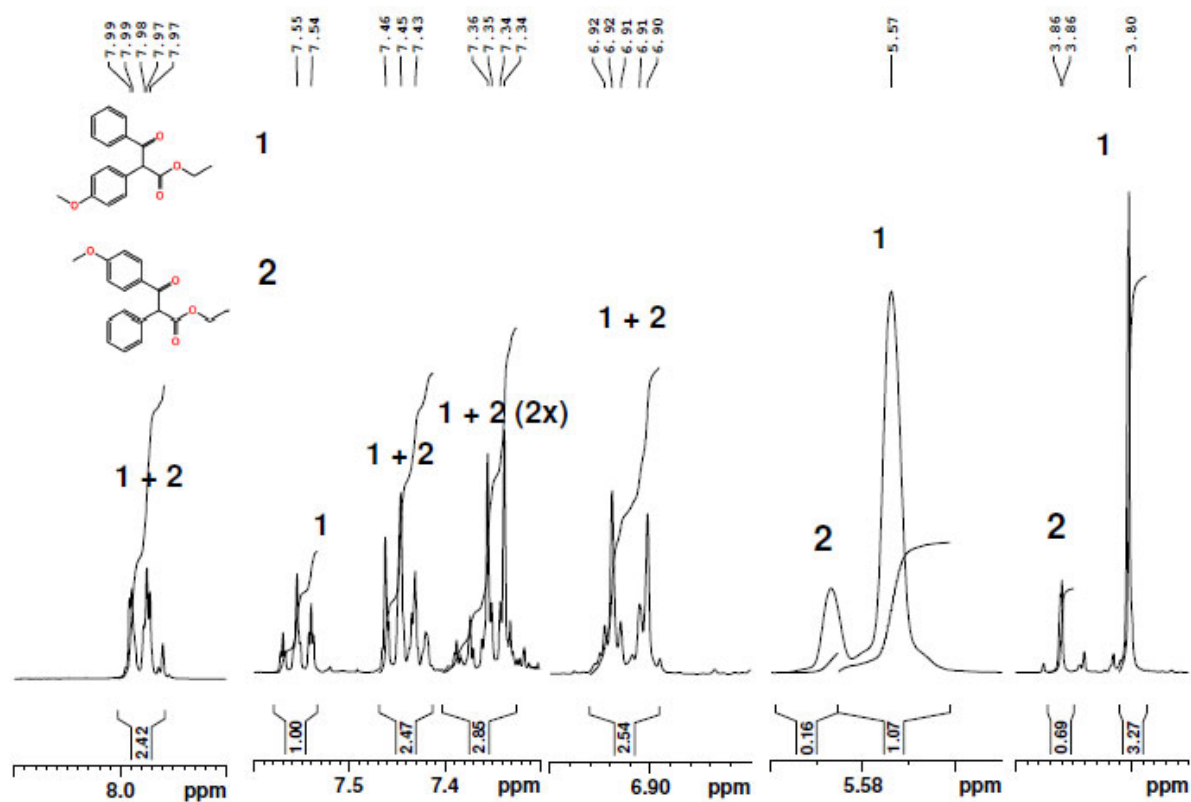
HMBC Aliphatic-Aromatic



HMBC Aromatic-Aromatic



Identifying peaks and their relative integration



Md Shahnawaz Ali

Highlights

Asymmetric Synthesis
Method Development
HPLC
Reaction Scale -up
Gas Chromatography
Hard Working

Organometallic Chemistry
Multistep Synthesis
NMR
Ligand Synthesis
Develop SOP
Writing Manuscript

Process Chemistry
Natural Product
Pd- Chemistry
FTIR
Team Worker
Leadership

EDUCATION

Ph.D. (Candidate)- Organic Chemistry

May 2021 (Anticipated)

Department of Chemistry and Biochemistry,
University of Wisconsin-Milwaukee (UWM), WI,
USA

Advisor: Dr. M Mahmum Hossain,
Professor

Master of Science

Dec 2008

Department of Applied Chemistry & Chemical
technology, University of Dhaka, Dhaka-1000,
Bangladesh

Advisor: Dr. Manoranjan Saha, Professor

Bachelor of Science

Jan 2007

Department of Applied Chemistry & Chemical
technology, University of Dhaka, Dhaka-1000,
Bangladesh

Advisor: Dr. Manoranjan Saha, Professor

RESEARCH EXPERIENCE

University of Wisconsin Milwaukee, Milwaukee, WI

Position: Teaching and Research Assistant

Sep 2015 – Present

- Five years of progressive experience in organic chemistry especially on synthesis, purification, and characterization of novel small natural products
- Extensive hands-on experience in air/moisture sensitive small-scale catalytic synthesis (using schlenk lines)

- Synthesis and optimization of metal catalyzed asymmetric allylic alkylation reactions
- Experience in design, synthesis and study of novel natural compounds and their analogues
- Development of C2 alkylated Indole products and its data driven kinetic and mechanistic study
- Hands-on large-scale multistep one pot synthesis of chiral ligands and catalysts

BANGLADESH ATOMIC ENERGY COMMISSION (BAEC)

Position: Master's Thesis Researcher (Polymer Chemistry)

Jan 2007 - Feb 2008

- Modification of physico-mechanical properties of Sodium Alginate bio-degradable polymer film
- Preparation of bio-medical grade fiber from Calcium Alginate Polymer Fiber

Teaching Experience Dept. of Chemistry & Biochemistry (UWM), Milwaukee, WI

Organic Chemistry. Teaching Assistant. Supervised and instructed students in organic chemistry laboratory techniques. Evaluating exams, preparing questions and solving problems related to the organic course and laboratory procedures. (September 2015 - present)

General Chemistry. Teaching Assistant. Carefully and sincerely taught general chemistry for both discussion and laboratory classes for almost all 100 level Chemistry courses. Assisted students individually with their lack of understanding on specific topics. (September 2009 - present)

ADDITIONAL SKILLS

- Experience in handling highly hazardous chemicals such as *n*BuLi, HF, TiCl₄, EDA etc.
- Trained on handling industrial equipment, chemicals and hazardous substances based on standard operating procedure (SOP)
- Certified training on 'Industrial Process Unit Operation & Process Control Technique' from Training Institute of Chemical Industries (TICI) in Bangladesh

CONFERENCE AND SEMINAR PRESENTATION

1. Ali, M Shahnawaz. A Unique Approach of Preparing 3,3-Disubstituted Oxindole from Acyclic Tetrasubstituted Aldehyde: Total Synthesis of (-)-Coerulescine & (-)-Coixspirolactam A.-**Oral presentation in lightening talk (organic division)**. Proceedings of ACS meetings & expositions, Virtual, USA, April 5-24, 2021.
2. Ali, M Shahnawaz. Pd-Catalyzed Asymmetric Allylic Alkylation: An Approach for the Synthesis of (-)-Coerulescine & (-)-Horsfiline. Proceedings of ACS Great lake Meeting, Chicago, Illinois, USA, April 25-29, 2019.

3. Ali, M Shahnawaz. Pd-Catalyzed Asymmetric Allylic Alkylation: An Approach for the Synthesis of (-)-Coerulescine & (-)-Horsfiline. Proceedings of H.C Brown Lectures, Purdue, Indiana, USA, June 14-15, 2019.

PUBLICATIONS

1. **Ali, M Shahnawaz**; Rahaman, Mizzanoor; Belayat, Jawad B, Asad, Sharif A; Hossain, M Mahmum. 'A Unique Approach to Preparing 3,3-Disubstituted Oxindole from Acyclic Tetrasubstituted Aldehyde: Total Synthesis of (-)-Coerulescine & (-)-Coixspirolactam A'- **Submitted.**
2. Rahaman, Mizzanoor; **Ali, M Shahnawaz**; Jahan, Khorshada; Belayat, Jawad; Hossain, M Mahmum. 'Synthetic Scope of Brønsted Acid-Catalyzed Reactions of Carbonyl 2 Compounds and Ethyl Diazoacetate- **DOI: 10.1021/acs.joc.0c03972**
3. Rahaman, Mizzanoor; **Ali, M Shahnawaz**; Jahan, Khorshada; Belayat, Jawad; Hossain, M Mahmum. 3-Hydroxy 2-aryl Acrylates: Syntheses, Mechanisms and Applications - **DOI: 10.1039/d0qo01157f.**
4. Jahan, K; **Ali, M. Shahnawaz**; Siedeman, T, Investigation of the C2 alkylation of 1-(1*H*-indol-3-yl)-*N,N*-dimethylmethanamine -manuscript in preparation.

SCHOLARSHIPS/AWARDS

- UWM Chancellor Fellowship (Fall,2015 - Spring,2020)
- Best Organic Teaching Assistant (2019 - 2020)
- UWM- Dept. of Chemistry outstanding credential award (2020)
- Graduate Student Council Award (2020).

PROFESSIONAL EXPERIENCE

Internship - R & D - Millipore Sigma, Tutonia Avenue, Milwaukee, WI, USA. (Jan,2021- now)

AFFILIATIONS

American Chemical Society (ACS)