ORGANOCATALYTIC RESOLUTION OF RACEMIC ALPHA AZIDO KETONES

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ABSTRACT

ORGANOCATALYTIC RESOLUTION OF RACEMIC ALPHA AZIDO KETONES

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Chiral cyclic alpha azido ketones are very important compounds in organic chemistry. Because, the reduced forms of them are amino alcohols and these amino alcohols are interesting compounds for their biological activities. They have some pharmaceutical activities such as: potassium channel open up properties, treatment of central nervous system, antihypertensive properties, the agent of dopamin receptor activator, hypolipemic agent and dopamine agonist. These types of compounds have highly acidic alpha-protons, and many kinds of reactions can be performed with them. In this study, mainly, selective protonation of racemic compounds was performed with a new practical method and there are not so many examples related to deracemization in the literature. Alpha-azido derivatives of tetralone, indanone, chromanone, and thiochromanone structures are chosen as starting materials because of their importance for biological activities arising from their cyclic structures. Firstly, these α-azido compounds were synthesized according to literature. The acidic alpha-protons do not require strong bases. Their enantioselective deracemization and deracemization processes were screened by using Cinchona derivatives as organocatalysts. This screening process was monitored by chiral HPLC columns. The parameters such as catalyst loading, solvent, temperature, reaction time and additives were optimized to obtain high enantioselectivities up to 98%.

In addition to deracemization reactions, Michael addition reactions were also performed by starting from α-azido chromanones. In these reactions different type of urea catalyst was used to activate the electrophilic part of *trans*-β-nitrostyrene compound. Again by controlling the temperature, time and catalyst loading, two diastereomers were formed and the screening process was monitored by chiral HPLC columns again. The Michael products were obtained in up to 94% ee and 75% yield.

Keywords: Chiral synthesis, α-azido ketones, amino alcohols, deracemization, cinchona catalysts, Michael addition reactions, urea catalysts.

ÖZ

RASEMİK ALFA AZİDO KETONLARIN ORGANOKATALİTİK ÇÖZÜNÜRLÜĞÜ

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Halkalı α-azido ketonlar organik kimyada çok önemlidirler çünkü bu maddeler amino alkollerin başlangıç maddeleridir ve bu malzemeler biyolojik aktivite açısından oldukça önemlidir. Bu türde ürünler potasyum kanal açıcı özellikleri, merkezi sinir sistemi tedavi özelliği, antihipertansif özelliği Dopamin reseptör aktivasyonu ajanı, hipolipemik ajan ve dopamin agonist özelliği göstermeleri açısından önemli yapılardır. Sentezlenen bu alfa azido ketonlar alfa konumlarında oldukça asidik bir hidrojenine sahiptirler ve bu yüzden birçok reaksiyon denemesi yapılmaya müsaittirler. Bu çalışmada literatürde çok fazla örneği olmayan Pratik ve yeni bir metodla özellikle rasemik bileşiklerin seçici protonasyonu gerçekleştirilmiştir. Aktivite açısından önemli olması nedeniyle tetralon, indanon, kromanon ve tiyokromanon yapısında bileşikler ile bunların türevleri başlangıç ürünü olarak alınmıştır. Bu türde bileşikler önce literatürde bilinen yöntemlerle α-azido türevlerine çevrilmiştir. Elde edilen α-azidoketonların α-konumlarında bulunan protonların asidikliklerinin yüksek olması koparılmaları için çok fazla kuvvetli baz gerektirmemektedir ve bu nedenle seçilmiştir. Daha sonra deprotonasyon ve derasemizasyon işlemlerinin enansiyoseçici olması için uygun kinkona türevleri kiral katalizör taraması için kullanılmış ve bu işlem kiral kolonlu HPLC ile takip edilmiştir. Bu deneyler sırasında katalizör, solvent, sıcaklık, süre, katkı maddeleri (aditifler) gibi parametreler değiştirilerek yaklaşık 98% enansiyoseçicilik gösteren ürünler elde edilmeye çalışılmıştır.

Asimetrik deprotonasyon reaksiyonlarına ek olarak, sentezlenen α-azido khromanonlar kullanılarak Michael reaksiyonları denenmiştir. Bu tür reaksiyonlar için, *trans*-β-nitro stirenin elektrofilik olarak aktivitesini artırmak amacıyla farklı türde bir üre katalizörü kullanılmıştır. Yine aynı şekilde sıcaklık, katalizör gibi parametreler göz önünde bulundurularak bu yolla elde edilen iki diastereomerin kiral yapıları yine kiral kolonlu HPLC ile takip edilmiş ve ürünler yaklaşık 94% ee; 75% verim ile elde edilmiştir.

Anahtar Kelimeler: Kiral sentez, α-azido ketonlar, amino alkoller, derasemizasyon, cinchona katalizörleri, Michael katılma reaksiyonları, üre katalizörleri.

To My Grandmother and Prof. Dr. Ayhan Sıtkı Demir…

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TABLE OF CONTENTS

ABSTRACT.....iv
ÖZ.....v
ACKNOWLEDGEMENTS.....vii
TABLE OF CONTENTS.....viii
LIST OF TABLES.....x
LIST OF FIGURES.....xi
ABBREVIATIONS.....v

CHAPTERS

1 INTRODUCTION.....1
1.1 Asymmetric Synthesis.....1
1.1.1 The importance and Definition of Asymmetric Synthesis.....2
1.1.2 Stoichiometric asymmetric synthesis.....4
1.1.3 Catalytic asymmetric synthesis.....4
1.2 Organocatalysis in Asymmetric Synthesis.....5
1.2.1 Chiral urea as organocatalyst 5
1.2.2 Cinchona catalysts in asymmetric synthesis.....8
1.3 Asymmetric synthesis via deracemization.....19
1.4 Alpha Azido Ketones; Synthesis and Application in Organic Synthesis 21
1.5 Aim of the Work.....22

2 RESULTS AND DISCUSSION.....23
2.1 Synthesis of α-bromo ketones 23
2.2 Synthesis of α-azido ketones 25
2.3 Deracemization of α-azido ketones.....27
2.4 Michael Addition Reactions with α-azido ketones.....34

3 EXPERIMENTAL.....36
3.1 Materials and Methods.....36
3.2 General procedures for the preperation of alpha bromo ketones.....36
3.2.1 Synthesis of 3-Bromochroman-4-one (4).....36
3.2.2 Synthesis of 3-Bromo-1-thiochroman-4-one (5).....37
3.2.3 Synthesis of 3-6-Dibromochroman-4-one (6).....37
3.2.4 Synthesis of 3-Bromo-7-methylchroman-4-one (7).....37
3.2.5 Synthesis of 3-Bromo-6-fluorochroman-4-one (8).....37
3.2.6 Synthesis of 3-Bromo-6-chlorochroman-4-one (9).....38
3.2.7 Synthesis of 2-Bromo-alpha tetralone (10).....38
3.2.8 Synthesis of 2-bromo-6-methoxy-tetralone (11).....38
3.2.9 Synthesis of 2-bromo-7-fluoro-tetralone (12).....38
3.2.10 Syntheis of 2-bromo-6, 8-dimethyl-tetralone (13).....39
3.2.11 Synthesis of 2-bromo-5, 8-dimethoxy-tetralone (14).....39
3.2.12 Synthesis of 2-bromo-indanone (15).....39
3.2.13 Synthesis of 2-bromo-4-fluoro-indanone (16).....39
3.2.14 Synthesis of 2-bromo-5-fluoro-indanone (17).....40
3.2.15 Synthesis of 2-bromo-5-methoxy-indanone (18).....40
3.3 General procedures for the preperation of alpha azido ketones.....40
3.3.1 Synthesis of Synthesis of 3-Azidochroman-4-one (19).....40
3.3.2 Synthesis of 3-Azido-1-thiochroman-4-one (20).....41

3.3.3 Synthesis of 3-Azido-6-Bromochroman-4-one (21)…….....41
3.3.4 Synthesis of 3-Azido-7-methylchroman-4-one (22)…….....41
3.3.5 Synthesis of 3-Azido-6-fluorochroman-4-one (23)…….…41
3.3.6 Synthesis of 3-Azido-6-chlorochroman-4-one (24)…….....42
3.3.7 Synthesis of 2-Azido -alpha tetralone (25)…….....42
3.3.8 Synthesis of 2-Azido-6-methoxy-tetralone (26)…….....42
3.3.9 Synthesis of 2-Azido-7-fluoro-tetralone (27)…….....43
3.3.10 Synthesis of 2-Azido-6, 8-dimethyl-tetralone (28)…….....43
3.3.11 Synthesis of 2-Azido-5, 8-dimethoxy-tetralone (29)..…….....43
3.3.12 Synthesis of 2-Azido- indanone (30)…….....44
3.3.13 Synthesis of 2-Azido-4-fluoro-indanone (31)…….....44
3.3.14 Synthesis of 2-Azido-5-fluoro-indanone (32)…….....44
3.3.15 Synthesis of 2-Azido-5-methoxy-indanone (33)…….....45
3.4 General procedures for deracemization of alpha azido ketones…..…….....45
3.5 General procedures for Michael addition reaction products…….....47
3.5.1 Synthesis of 3-azido-3-(2-nitro-1-phenylethyl) chroman-4-one (39)……. ……..……..47
3.5.2 Synthesis of 3-azido-6-bromo-3-(2-nitro-1-phenylethyl) chroman-4-one(40)…….....47

4 CONCLUSION……...…48

REFERENCES…….……...……...49

APPENDICIES

A - NMR DATA…….……...…....51

B - HPLC DATA……...…....83

LIST OF TABLES

TABLES

Table 1 Enantiometric excess results of deracemization reactions of chromanones..……..31
Table 2 Enantiometric excess results of deracemization reactions of tetralones ……..32
Table 3 Enantiometric excess results of deracemization reactions of indanones ……..…..33

LIST OF FIGURES

FIGURES

Figure 1 Enantiomers of limonene and carvone……..……..1
Figure 2 Enantiomers of thalidomide ……..…..2
Figure 3 Additions to heterotopic faces of an aldehyde ……..3
Figure 4 Conversion of A into B and C under kinetic control ……..…3
Figure 5 Mechanism of catalysis (Ea and Ea' are the energies of activation of the uncatalyzed and catalyzed reaction. ΔG is the free energy change of the reaction)……..……..5
Figure 6 Dual H-bond interaction in thiourea-catalyzed enantioselective Strecker reaction……..……...6
Figure 7 C-C bond formation reaction N-Boc imine catalyzed by thiourea…….....6
Figure 8 Nitroaldol reaction with dual activation ……..…7
Figure 9 Enantioselective acyl-mannich reaction …….....7
Figure 10 Claisen rearrangement of allyl vinyl ethers……..……....8
Figure 11 Thiourea catalyzed Diels-Alder Reaction…….……8
Figure 12 Cinchona alkaloids with their functional groups…….……9
Figure 13 Activation parts of quinidine and quinine.....9
Figure 14 Interphase mechanism in the presence of a cinchonidine derived quaternary ammonium salt…….....10
Figure 15 Bifunctional cinchona catalysis in the asymmetric addition of *β*-ketoesters to N-phenyl maleimide 11
Figure 16 Asymmetric synthesis of indanone by direct alkylation …….....11
Figure 17 Michael addition of nitromethane to chalcone ……..…….....12
Figure 18 Asymmetric aldol reaction…….....12
Figure 19 Asymmetric Morita-Bayllis-Hilmann reaction……...12
Figure 20 Enantioselective Diels-Alder reaction…….……...…13
Figure 21 Formation of β-Lactones asymmetrically…….....13
Figure 22 Formation of β-Lactams asymmetrically ……..13
Figure 23 Asymmetric cyanation reaction……..…..…14
Figure 24 Asymmetric trifluoromethyl alcohol formation…….....14
Figure 25 Enantioselective Horner-Wadsworth-Emmons reaction……..…….....15
Figure 26 Asymmetric Ireland-Claisen rearrangement …….....15
Figure 27 Asymmetric epoxidation…….....15
Figure 28 Asymmetric dihydroxylation of olefins…….……....16
Figure 29 Asymmetric aminohydroxylation reactions…….……...16
Figure 30 Asymmetric aziridination reaction……..……..…16
Figure 31 Asymmetric sulfination reaction ……....17
Figure 32 Asymmetric chlorination reaction …….....17
Figure 33 Heterogeneous asymmetric hydrogenation reaction ……..……17
Figure 34 Enantioselective decarboxylation of α-aminomalonates ……..……..……...18
Figure 35 Enantioselective desymmetrization of anhydrides…….……..…18
Figure 36 Kinetic resolution of racemic anhydrides ……..18
Figure 37 Origin of stereoselectivity of cinchona derivatives as phase transfer catalyst…….……19
Figure 38 $MHCO_3$ using as both nucleophilic activator and proton source combined with a chiral Brønsted base…….....….20
Figure 39 Trapping of the anions generated from α-azido ketones by electrophiles.....21
Figure 40 Bromination of chroman-4-one, alpha tetralone and 1-indanone…….....23
Figure 41 Brominated chromanone, tetralone and indanone derivatives …….....24

Figure 42 Formation of alpha azido chromanone, tetralone and indanone……..25
Figure 43 Alpha azido chromanone, tetralone and indanone derivatives ……..…..26
Figure 44 Cinchona Alkaloids Used in Deracemization Reactions……..……27
Figure 45 Suggested mechanism of deracemization reaction……28
Figure 46 Change of enantiomeric excess of 3-Azidochroman-4-one day by day……29
Figure 47 HPLC Chromatograms of 3-Azidochroman-4-one from 2nd day to 6th day……30
Figure 48 Michael addition of β-nitro styrene to azido chromanone derivatives……...34
Figure 49 1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-(6-methoxyquinolin-4yl)((1S,2S,4S,5R)5vinylquinuclidin-2-yl)methyl)urea.....…...…….....……..35
Figure 50 Suggested mechanism of Michael addition reaction……..35

Figure A. 1 ^{1}H-NMR spectrum of **(114)**……..51
Figure A. 2 ^{13}C-NMR spectrum of **(144)**……..51
Figure A. 3 ^{1}H-NMR spectrum of **(117)**……52
Figure A. 4 ^{13}C-NMR spectrum of **(117)**……..52
Figure A. 5 ^{1}H-NMR spectrum of **(118)**……..53
Figure A. 6 ^{13}C-NMR spectrum of **(118)**……..53
Figure A. 7 ^{1}H-NMR spectrum of **(119)**……54
Figure A. 8 ^{13}C-NMR spectrum of **(119)**……54
Figure A. 9 ^{1}H-NMR spectrum of **(120)**……55
Figure A. 10 ^{13}C-NMR spectrum of **(120)**……55
Figure A. 11 ^{1}H-NMR spectrum of **(121)**……56
Figure A. 12 ^{13}C-NMR spectrum of **(121)**……56
Figure A. 13 ^{1}H-NMR spectrum of **(115)**……57
Figure A. 14 ^{13}C-NMR spectrum of **(115)**……57
Figure A. 15 ^{1}H-NMR spectrum of **(122)**……58
Figure A. 16 ^{13}C-NMR spectrum of **(122)**……58
Figure A. 17 ^{1}H-NMR spectrum of **(123)**……59
Figure A. 18 ^{13}C-NMR spectrum of **(123)**……59
Figure A. 19 ^{1}H-NMR spectrum of **(124)**……60
Figure A. 20 ^{13}C-NMR spectrum of **(124)**……60
Figure A. 21 ^{1}H-NMR spectrum of **(125)**……61
Figure A. 22 ^{13}C-NMR spectrum of **(125)**……61
Figure A. 23 ^{1}H-NMR spectrum of **(116)**……62
Figure A. 24 ^{13}C-NMR spectrum of **(116)**……62
Figure A. 25 ^{1}H-NMR spectrum of **(126)**……63
Figure A. 26 ^{13}C-NMR spectrum of **(126)**……63
Figure A. 27 ^{1}H-NMR spectrum of **(127)**……64
Figure A. 28 ^{13}C-NMR spectrum of **(127)**……64
Figure A. 29 ^{1}H-NMR spectrum of **(128)**……65
Figure A. 30 ^{13}C-NMR spectrum of **(128)**……65
Figure A. 31 ^{1}H-NMR spectrum of **(129)**……66
Figure A. 32 ^{13}C-NMR spectrum of **(129)**……66
Figure A. 33 ^{1}H-NMR spectrum of **(132)**……67
Figure A. 34 ^{13}C-NMR spectrum of **(132)**……67
Figure A. 35 ^{1}H-NMR spectrum of **(133)**……68
Figure A. 36 ^{13}C-NMR spectrum of **(133)**……68
Figure A. 37 ^{1}H-NMR spectrum of **(134)**……69
Figure A. 38 ^{13}C-NMR spectrum of **(134)**……69
Figure A. 39 ^{1}H-NMR spectrum of **(135)**……70
Figure A. 40 ^{13}C-NMR spectrum of **(135)**……70
Figure A. 41 ^{1}H-NMR spectrum of **(136)**……71
Figure A. 42 ^{13}C-NMR spectrum of **(136)**……71
Figure A. 43 ^{1}H-NMR spectrum of **(130)**……72

Figure A. 44 ^{13}C-NMR spectrum of **(130)**.....72
Figure A. 45 ^{1}H-NMR spectrum of **(137)**.....73
Figure A. 46 ^{13}C-NMR spectrum of **(137)**.....73
Figure A. 47 ^{1}H-NMR spectrum of **(138)**.....74
Figure A. 48 ^{13}C-NMR spectrum of **(138)**.....74
Figure A. 49 ^{1}H-NMR spectrum of **(139)**.....75
Figure A. 50 ^{13}C-NMR spectrum of **(139)**.....75
Figure A. 51 ^{1}H-NMR spectrum of **(140)**.....76
Figure A. 52 ^{13}C-NMR spectrum of **(140)**.....76
Figure A. 53 ^{1}H-NMR spectrum of **(131)**.....77
Figure A. 54 ^{13}C-NMR spectrum of **(131)**.....77
Figure A. 55 ^{1}H-NMR spectrum of **(141)**.....78
Figure A. 56 ^{13}C-NMR spectrum of **(141)**.....78
Figure A. 57 ^{1}H-NMR spectrum of **(142)**.....79
Figure A. 58 ^{13}C-NMR spectrum of **(142)**.....79
Figure A. 59 ^{1}H-NMR spectrum of **(143)**.....80
Figure A. 60 ^{13}C-NMR spectrum of **(143)**.....80
Figure A. 61 ^{1}H-NMR spectrum of **(150)**.....81
Figure A. 62 ^{13}C-NMR spectrum of **(150)**.....81
Figure A. 63 ^{1}H-NMR spectrum of **(151)**.....82
Figure A. 64 ^{13}C-NMR spectrum of **(151)**.....82

Figure B. 1 Racemic HPLC chromatogrom of **(129)**.....83
Figure B. 2 Chiral HPLC chromatogrom of **(129)**.....83
Figure B. 3 Racemic HPLC chromatogrom of **(132)**.....84
Figure B. 4 Chiral HPLC chromatogrom of **(132)**.....84
Figure B. 5 Racemic HPLC chromatogrom of **(133)**.....85
Figure B. 6 Chiral HPLC chromatogrom of **(133)**.....85
Figure B. 7 Racemic HPLC chromatogrom of **(134)**.....86
Figure B. 8 Chiral HPLC chromatogrom of **(134)**.....86
Figure B. 9 Racemic HPLC chromatogrom of **(135)**.....87
Figure B. 10 Chiral HPLC chromatogrom of **(135)**.....87
Figure B. 11 Racemic HPLC chromatogrom of **(136)**.....88
Figure B. 12 Chiral HPLC chromatogrom of **(136)**.....88
Figure B. 13 Racemic HPLC chromatogrom of **(130)**.....89
Figure B. 14 Chiral HPLC chromatogrom of **(130)**.....89
Figure B. 15 Racemic HPLC chromatogrom of **(137)**.....90
Figure B. 16 Chiral HPLC chromatogrom of **(137)**.....90
Figure B. 17 Racemic HPLC chromatogrom of **(138)**.....91
Figure B. 18 Chiral HPLC chromatogrom of **(138)**.....91
Figure B. 19 Racemic HPLC chromatogrom of **(139)**.....92
Figure B. 20 Chiral HPLC chromatogrom of **(139)**.....92
Figure B. 21 Racemic HPLC chromatogrom of **(140)**.....93
Figure B. 22 Chiral HPLC chromatogrom of **(140)**.....93
Figure B. 23 Racemic HPLC chromatogrom of **(131)**.....94
Figure B. 24 Chiral HPLC chromatogrom of **(131)**.....94
Figure B. 25 Racemic HPLC chromatogrom of **(141)**.....95
Figure B. 26 Chiral HPLC chromatogrom of **(141)**.....95
Figure B. 27 Racemic HPLC chromatogrom of **(142)**.....96
Figure B. 28 Chiral HPLC chromatogrom of **(142)**.....96
Figure B. 29 Racemic HPLC chromatogrom of **(143)**.....97
Figure B. 30 Chiral HPLC chromatogrom of **(143)**.....97
Figure B. 31 HPLC chromatogrom of **(150)**.....98
Figure B. 32 HPLC chromatogrom of **(151)**.....98

ABBREVIATIONS

TrocCI	2,2,2-Trichloroethyl chloroformate
QN	Quinine
DMF	Dimethyl formamide
$(DHQD)_2AQN$	Hydroquinidine (anthraquinone-1,4-diyl) diether
$(DHQD)_2PYR$	Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether
Me_3SiCF	Trifluoromethyltrimethylsilane
LHMDS	Lithium Bis(trimethylsilyl)amide
$Al(O^iPr)_3$	Aluminum Isopropoxide
KOCI	Potassium hypochlorite
DHQD	Hydroquinidine
DHQ	Hydroquinine
^{t}BuOCI	Tert-buthyl hypochlorite
18-crown-6	Crown ether
HPLC	High Performance Liquid Chromatography
TLC	Thin Layer Chromatography
DCM	Dichloromethane
THF	Tetrahydrofuran
NMR	Nuclear magnetic resonance
ppm	parts per million (in NMR)
Ph	phenyl
IR	infrared
mL	mililiter(s)
mmol	milimole(s)
nm	nanometer
s	singlet (spectral)
t	triplet (spectral)
q	quartet (spectral)
m	multiplet (spectral)

CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

Most of the compounds that occur in nature are optically active, because living organisms tend to facilitate only a single enantiomer of a given molecule. The asymmetry of these molecules arises from the inherent chirality of the enzymes that are responsible for their usage. Receptor sites in biological systems, which are chiral, have the ability to differentiate between two enantiomers of a specific molecule [1].

Synthesis of chiral compounds has very important applications in wide variety of places such as food, industries, preparation of therapeutic compounds and asymmetric synthesis. Stereochemistry has to be considered when studying xenobiotics like drugs, agrochemicals, food additives, flavours and fragrances [2] since different enantiomers have different biological effects, smell, taste, etc.; due to the fact that all biochemical reactions taking place in organisms are governed by chiral catalysts or enzymes, which are highly selective with respect to the chirality of the molecule.

Chiral molecules can determine their different properties in many ways. For instance, one enantiomeric form of a compound called limonene which is a monoterpene with isoprene units linked in rings **1** is responsible for the odor of oranges and the other enantiomeric form is **2** responsible for the odor of lemons. Another example can be seen in carvone. *(R)*-form **3** of it is responsible for the fundamental nature of caraway smell and the *(S)*-form of it **4** is responsible for spearmint smell [Figure 1].

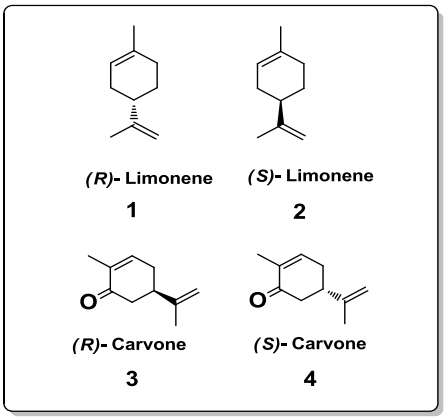


Figure 1: Enantiomers of limonene and carvone

Differences in biological activities of enantiomers are not always responsible for the differences in taste, smell, etc.; they can lead to very serious and tragic consequences as in thalidomide [Figure 2]. With molecules including one or more asymmetric centers, opposing toxicologic properties can be attributed to one enantiomer and not the other [1].

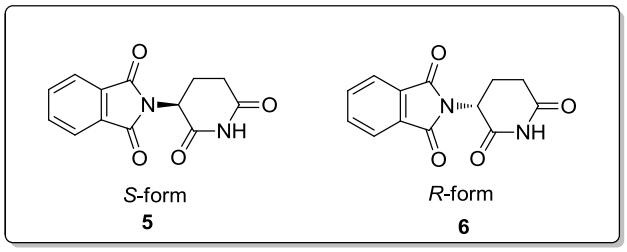


Figure 2: Enantiomers of thalidomide

(R)-form of Thalidomide **6** was used for morning sickness on pregnant woman, whereas the *(S)*-form of thalidomide **5** is highly teratogenic. So it is very important to prepare molecules in enantiomerically pure form for meaningful studies on their physical or biological properties [1].

There are two ways to synthesize enantiomerically pure compounds: The molecules can either be synthesized in racemic form and then resolved into their enantiomers, or the synthesis can be performed in an enantioselective way to produce chirally enriched products. The resolution method can have major disadvantage because half of the mixture is the undesired enantiomer. The remaining undesired enantiomer is usually wasted [1]. So using chiral catalysts or enzymes is very important to get enantiomerically pure compounds in asymmetric synthesis.

1.1.1 The Importance and Definition of Asymmetric Synthesis

The definition of asymmetric synthesis is a reaction sequence that selectively produces one configuration of one or more new stereogenic centers by the action of a chiral reagent or auxiliary, by acting on heterotopic faces, atoms, or groups of a substrate. The stereoselectiviy is primarly achieved by chiral catalyst, reagent or auxiliary [3].

Asymmetric synthesis produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials.

For the synthetic planning, there are some important factors that affect the reaction and the environment. One of the most important variables is the cost of the process relative to the value of the product. The cost of product must be valuable according to used reactants. It is also important to consider the availability of either enantiomer of the chiral reagent. The most important part is that if the reaction is environmentally friendly or not. In addition to these results there are some expectations from asymmetric synthesis. For example [3];

1. The synthesis must be highly stereoselective.
2. If the chiral auxiliary is an integral part of the starting material, the chiral center that is generated in the asymmetric synthesis must be readily separable from that auxiliary without racemization of newly generated chiral center.
3. The chiral reagent must be recoverable in good yield and again without racemization.

Enantioselective syntheses have importance, particularly in the pharmaceutical industry, and are currently the subject of intense research in academic and industrial laboratories around the world [4].

Stereoselective synthesis creates new stereogenic units in a controlled way. Such processes may be enantioselective or diastereoselective or both of them. And so they may give rise to enantiopure products, with control of relative stereochemistry [4].

The addition of a nuchleophile to a carbonyl group is one of the important reactions in asymmetric synthesis. The faces of unsymmetric carbonyls are heterotopic; either enantiotopic or diastereotopic. If there are no stereocenters in the molecule **7**, it is enantiotopic; but, if there are stereocenters in the molecule **8** it is diastereotopic. In order to achieve one stereoisomer in excess, the transition states resulting from attack from the heterotopic *Re* or *Si* faces must be diastereomeric [Figure 3]. Either the carbonyl compound or the reagent (e.g: catalyst) or both of them must be chiral [5].

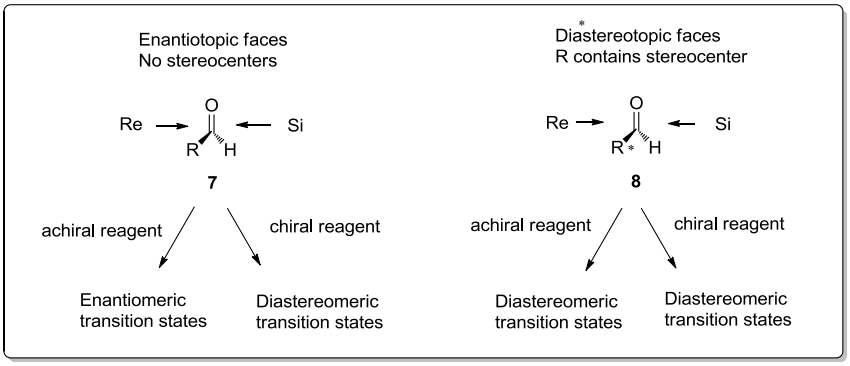


Figure 3: Additions to heterotopic faces of an aldehyde

Two types of selectivity may be used to establish new stereogenic units in a molecule as mentioned above: diastereoselectivity and enantioselectivity. In diastereoselective reactions, either kinetic or thermodynamic control is possible, but in enantioselective reactions, the products are so energetic and only kinetic control is possible. It can be understood with a reaction that is shown below [Figure 4];

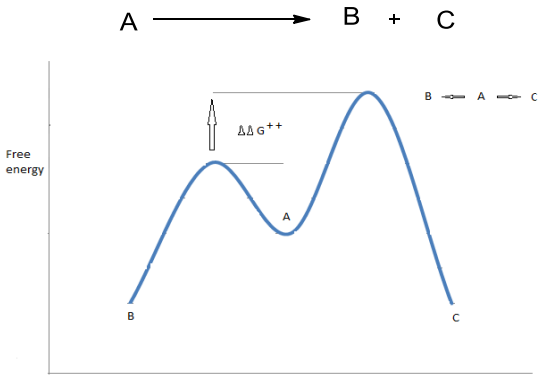


Figure 4: Conversion of A into B and C under kinetic control

At lower temperatures, the selectivity increases. Thus for a given process, foxy changes in the stereochemical control elements will usually have a greater influence, if the other reaction is carried out at low temperature. But, of course, this not allways means that lowering the temperature of a

reaction will result in increased selectivity in all cases [3]. But asymmetric syntheses are capable of giving rise to enantiopure products.

1.1.2 Stoichiometric Asymmetric Synthesis

A prochiral substrate or functional group is converted into an enantiopure product in a reaction mediated by a chiral auxiliary, either in a stoichiometric or catalytic fashion [4].

The first applied asymmetric method in asymmetric synthesis is stoichiometric asymmetric synthesis. Stoichiometric asymmetric synthesis is widely used in the academic and industrial sectors for the synthesis of chiral molecules of biological importance. Because, the use of catalytic amounts of chirality provides high selectivities over a wider range of substrates, without extensive modifications of reaction conditions [6].

It must be considered that, the relationship between stereogenic structures and the functional groups of the target molecule will determine which centers are best made by asymmetric induction and by diastereoselective later steps. Several chiral centers can be formed in a single reaction step, so the features of the target structure should not be considered in isolation. There can be some important effects of stoichiometric asymmetric synthesis.

1. A stoichiometric chiral auxiliary is covalently attached to the substrate before chirality impart is performed. Chirality in the auxiliary controls the orientation, and the chiral auxiliary can be reused once more.
2. When a stoichiometric chiral reagent affects asymmetric induction, the inducing chirality is not part of the substrate and it is not determined directly in the planning process by the structure of the target molecule. Efficient asymmetric induction is the only concern. The use of chiral reagent must be controlled in some ways.

1.1.3 Catalytic Asymmetric Synthesis

In catalytic asymmetric synthesis, the chiral reagent is used in fewer amounts than stoichiometric quantities. When a chiral catalyst is involved, a tiny amount of the chiral auxiliary can produce a large amount of enantiopure product, so catalytic processes are more cost-effective than stoichiometric processes. They have another advantage of decreasing the environmental pollution of byproducts produced in stoichiometric quantities [5].

In the modern context of the synthesis of complex molecules, the search for new and versatile methods in stereoselective synthesis remains a major challenge. Chiral reagents and catalysts that show good to best efficiency for model compounds often fail to give good results. In some reactions the enantioselectivity is slightly higher, but only when the modifier is applied in a stoichiometric amount.

Catalytic modifications must be considered about planning asymmetric synthesis. In these modifications, the chiral auxiliary can become covalently attached to the substrate in an intermediate in the catalytic cycle or might act in an intermolecular fashion, inducing asymmetry in a single step.

As a consequence, the mission for new methods, new reagents, and new concepts in asymmetric synthesis is still a growing importance. Among the different approaches in asymmetric synthesis, generally catalytic methods are used in recent years because of its advantages [6].

1.2 Organocatalysis in Asymmetric Synthesis

Organocatalysis is a developing area in the asymmetric synthesis. Enantioselective organocatalysis has had a major impact on chemical synthesis and has brought about an increase in the development of new asymmetric catalytic methodology that is being applied in many areas of chemistry. Organocatalysis have several significant advantages over conventional metal catalysis. It is an attractive method to synthesize complex structures i.e.; the operational simplicity, readily availability of catalysts and low toxicity associated with organocatalysis. In this thesis we will mainly focus on chiral urea and cinchona alkaloid derivatives as organocatalysis. As any catalysts, organocatalysis accelerate a reaction by reducing the energy barrier without being altered as a consequence of the reaction they promote [Figure 5] [7].

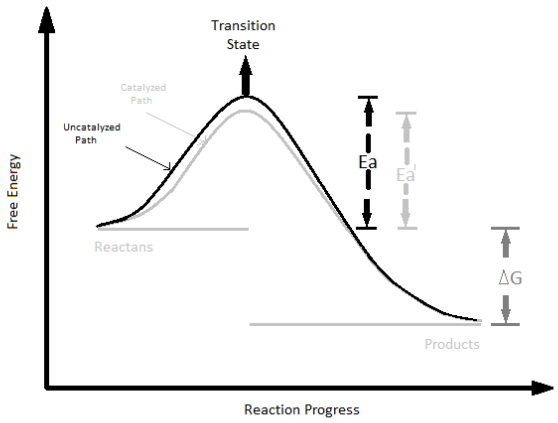


Figure 5: Mechanism of catalysis (Ea and Ea' are the energies of activation of the uncatalyzed and catalyzed reaction. ΔG is the free energy change of the reaction)

1.2.1 Chiral urea as organocatalyst

Enantioselective synthesis with small-molecule chiral hydrogen-bond donors is an important research area in the field of asymmetric catalysis. They can catalyze C-C and C-heteroatom bond-forming reactions with high enantioselectivity and broad substrate scope. In the suggested mechanisms, the key role for hydrogen bonding is in electrophile activation [7]. The ability to activate electrophiles with Hydrogen bonding is related with Lewis acid activation. It is much more usefull to use urea instead of using metals to coordinate the lone pair of a carbonyl. Because, urea catalysis relies on a hydrogen bond to enhance activation and generate a chiral environment around the electrophilic species [8].

Chiral ureas and thioureas are used most commonly to activate imines through hydrogen bonding to the nitrogen atom. In addition to this, they have been used as small-molecule catalysts for acyl transfer reactions [7].

The key activation mechanism of these small molecule chiral catalysts is the presence of H-bonding. One of the first asymmetric reactions are the urea-and thiourea-catalyzed asymmetric Strecker reactions [9]. Studies showed that the urea and thiourea functionality are responsible for catalytic

activity and that the imine substrate interacts with the catalyst via a dual H-bond interaction to the urea protons **9** as shown in Figure 6. This helped to establish that simple H-bond donors could serve as useful asymmetric catalysts [10].

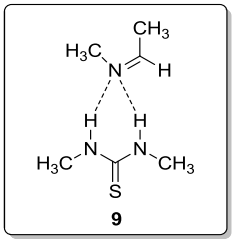


Figure 6: Dual H-bond interaction in thiourea-catalyzed enantioselective Strecker reaction.

There are several important organic transformations performed with chiral ureas and thioureas. They have the ability to perform the reactions of nitroalkenes, aldehydes, ketones, and carboxylic acid derivatives. İ.e. hydrophosphorylation, Mannich reactions are all possible. In addition, the cyanosilylation of ketones has also performed in high yields and enantiomeric excesses. Jacobsen's work has showed indole and malonate additions to nitroalkenes with good enantiomeric excesses by using thiourea catalysis [11].

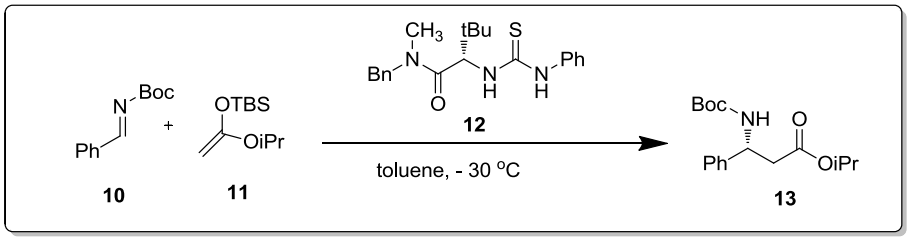


Figure 7: C-C bond formation reaction N-Boc imine catalyzed by thiourea

In addition to this a thiourea-catalyzed **12** acyl Piclet–Spengler reaction has been developed that forms imines **13** starting from imines **10** and protected aldehydes **11** in good yields and enantiomeric excesses [12] [Figure 7].

Interestingly, the bifunctional cinchona alkaloid-thiourea catalysts **16** are used for many reactions such as nitroaldol reaction starting from an aldehyde **14** and nitromethane **15** to form nitropropane-2-ol **17** [Figure 8]. Synthesis of flavanone and chromanone derivatives and malonate addition is epimeric at C^9 from the naturally occurring alkaloid structure and generates the product in higher enantiomeric excess [8].

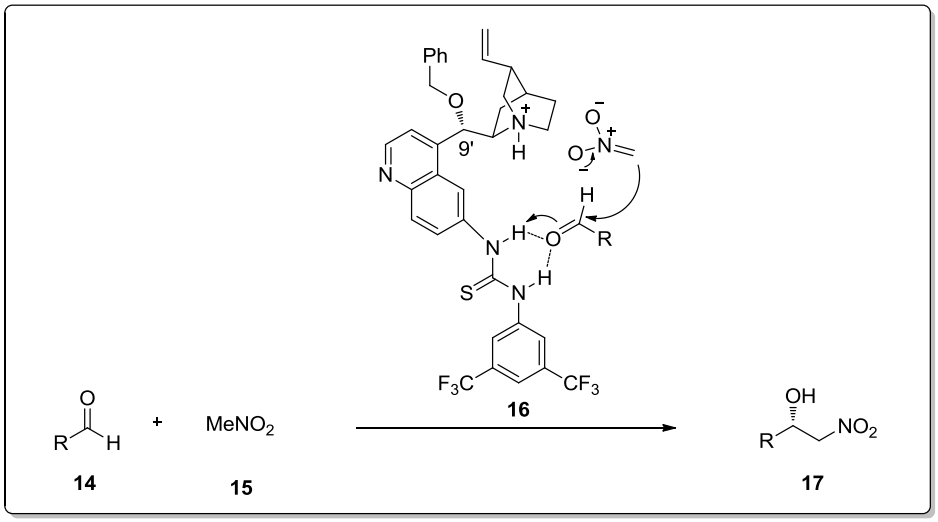


Figure 8: Nitroaldol reaction with dual activation

The unsymmetrically substituted thioure derivative **19** is used for obtaining high enantioselectivity in both the acyl-Pictet–Spengler and acyl-Mannich reactions. In the solid-state structure of this catalyst, the phenyl substituent is positioned to interact closely with isoquinoline **18** substrate as it undergoes H-bonding to the acidic thiourea protons as shown in Figure 9. The protected aldehyde **11** attack to that activated imine [13].

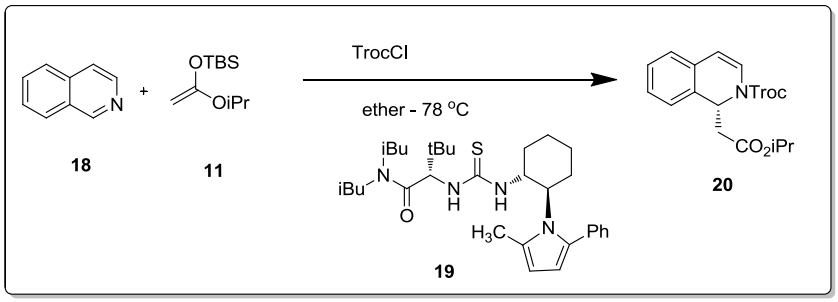


Figure 9: Enantioselective acyl-mannich reaction

In addition to these Curran and co-workers studied radical allylations of sulfoxides and Claisen rearrangements of allyl vinyl ethers **21** by using electron-poor urea **22** as catalyst [Figure 10] to form rearrangement products **23** [14].

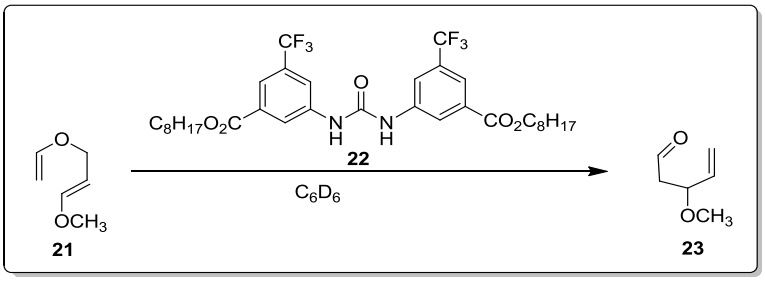


Figure 10: Claisen rearrangement of allyl vinyl ethers

The thiourea shown in Figure 11 is used to catalyze Diels–Alder and dipolar cycloaddition reactions of α,β-unsaturated carbonyl compounds **24** with dienes **25.** By using urea and thiourea derivatives with strongly electron-withdrawing groups in the 3- and 5-positions **26**, maximum rate acceleration is observed to form cycloaddition products **27** [15].

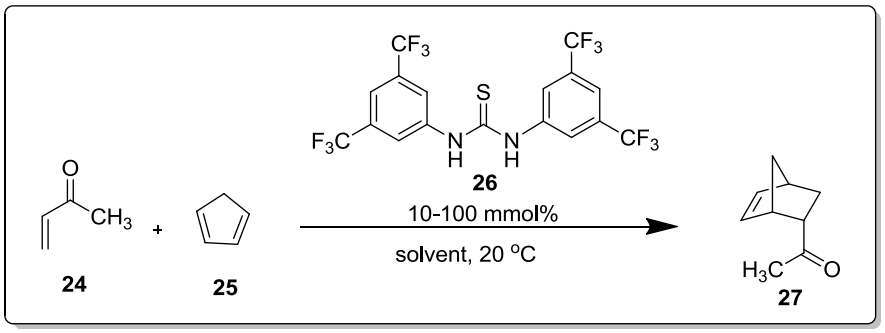


Figure 11: Thiourea catalyzed Diels-Alder Reaction

Ureas are both easily prepared and highly effective catalysis. The choice of urea or thiourea provides a method with H-bond-donating ability, and in addition to this, nitrogen substituents permits a high degree of fine-tuning of catalyst steric and electronic properties. The urea structure also lends itself readily to the preparation of bifunctional catalysts, using amine coupling partners incorporating additional acidic or basic groups.

1.2.2 Cinchona catalysts in asymmetric synthesis

Phase-transfer catalysis is one of the most useful organocatalysts for practical synthesis because of its operational simplicity and mild reaction conditions. Cinchona alkaloids are very popular organocatalysts due to mainly their unique structure, commercial availability at very low prices, simple operation, mild reaction conditions and environmentally friendly chemical reactions. These properties allows them to be used in many applications especially in asymmetric synthesis.

Cinchona comes from the family of Rubiaceae tree, originally native to tropical South America. Bark extracts of these trees have been used as a herbal medicine to treat various diseases [20].

Depending on their pseudoenantiomeric stereo-structure and functional groups, there exist four kinds of Cinchona alkaloids at present as shown below [Figure 12]. These are quinine **28**, quinidine**31**, cichonine **29** and cinchonidine **30**.

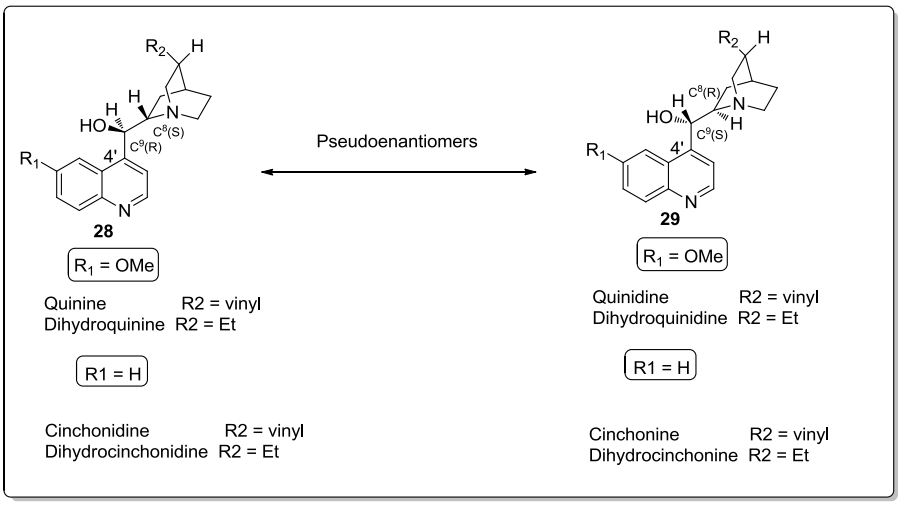


Figure 12: Cinchona alkaloids with their functional groups

Cinchona alkaloids have a unique structure that involves a sterically hindered tertiary amino alcohol group with different functional groups. They have a quite sterically hindered tertiary amine that can be derivatized to provide a variety of quaternery ammonium salts. In addition to this; there are rotational freedom around the C8-C9 and C4'-C9 bonds in some kinds of cinchona alkaloids that makes them effective chiral organic catalysts [16]. All of these functional groups play critical roles in chirality-creating steps. Either themselves or in chemically modified forms of them are used in many kinds of asymmetric reactions.

The reaction between a nucleophile and an electrophile is one of the most viable mechanism in organic synthesis. So catalytic asymmetric synthesis mainly focus on enantioselective nucleophile-electrophile reactions. Since the electrophile and the nucleophile can be activated by an acid and a base, to give an enantioselective reaction [17]. As shown in the Figure 13 the cinchona derivatives can activate both a nucleophile and an electrophile from the tertiary amine and the hydroxyl groups [18].

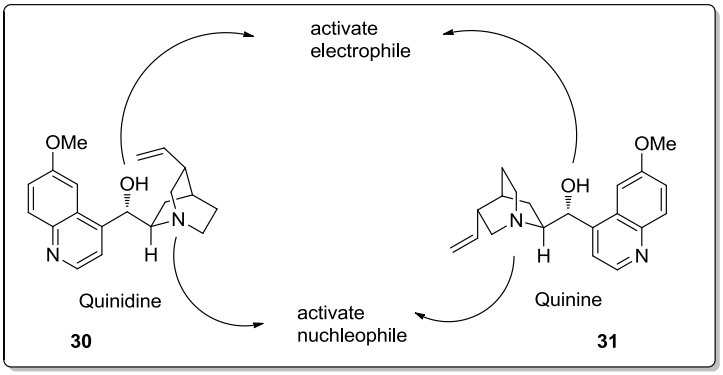


Figure 13: Activation parts of quinidine and quinine

Cinchona alkaloids can be used as phase transfer catalysis as shown below [Figure 14]. The quaternary ammonium cation forms a nucleophilic ionic complex. This complex, $N^{+\cdots}Nu^{-}$, then reacts with the electrophile, to provide the resulting products as Nu–E. Finally, the quaternary ammonium salt returns to the interface for catalyst recycling. During the catalytic phase-transfer reaction, the Cinchona-derived quaternary ammonium salt generates a chiral environment in the stage of the nucleophilic ionic complex, $N^{+\cdots}Nu^{-}$, and the electrophile attacks the least sterically hindered face to provide the chiral product [19].

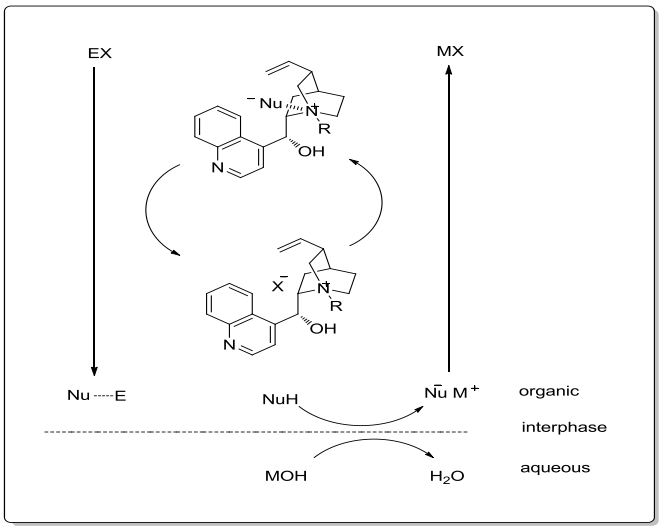


Figure 14: Interphase mechanism in the presence of a cinchonidine derived quaternary ammonium salt

The cinchona alkaloids behave as bifunctional catalyst with the help of -OH group attached to C^9. In some of the cinchona derivatives, while the N part deprotonates a pronucleophile and coordinates the resulting anion through the quinuclidinium proton, the -OH group forms hydrogen bonding with the electrophile, and it increases the reactivity and orients the electrophile for the nucleophilic addition [Figure 15]. This activation step can be understood by the enantioselective addition of *β*-ketoesters **32** to N-substituted maleimides **33** [20]. (*R*)-tert-butyl 2-((*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-methyl-3-oxobutanoate **34** was formed at the end of this reaction.

Although the N part is the most basic atom of the Cinchona derivatives, it shows nucleophilic behavior. In addition, the reaction of Cinchona alkaloids with most alkylating agents takes place at the N part.

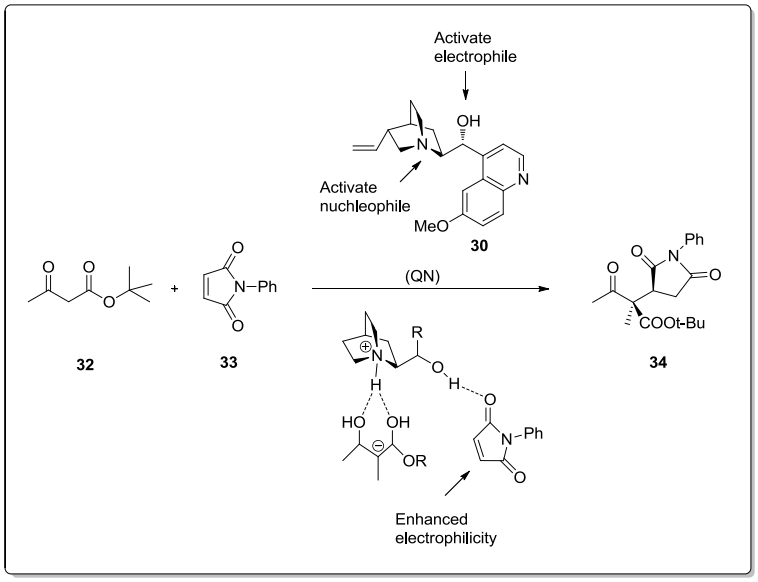


Figure 15: Bifunctional cinchona catalysis in the asymmetric addition of *β*-ketoesters to N-phenyl maleimide.

Cinchona alkaloids are versatile catalysts that can be used principally in four types of reactions: (i) C-C bond formation, (ii) C-O bond formation, (iii) C-Heteroatom bond formation, and (vi) miscellaneous reactions.

(i) carbon-carbon bond formation reactions are mainly alkylation, Michael and aldol reactions, Baylis-Hilman, Diels-Alder, cyanation reactions and synthesis of β-lactams and lactons. These reactions can be shown below with one example for each of them.

Sharpless firstly studied asymmetric synthesis of indanone **35, 37** by direct alkylation by the use of *N*-(*p*-(trifluoromethyl)-benzylcinchonidinium bromide **36** and cinchona derivatives with the product of ee 92% [Figure 16] [21].

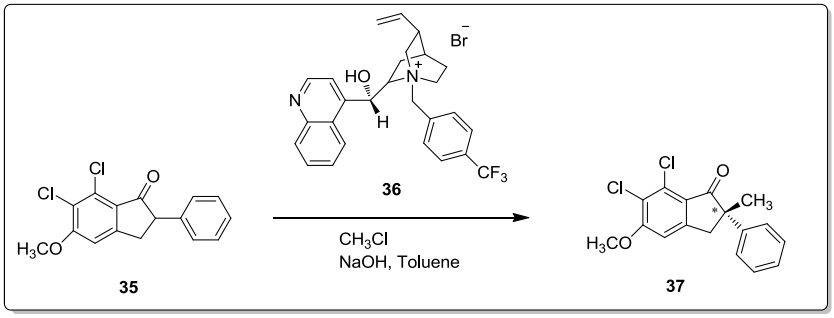


Figure 16: Asymmetric synthesis of indanone by direct alkylation

The first asymmetric Michael addition of nitromethane **15** to chalcone **38** was catalyzed by the chiral quaternary ammonium salt **39** by Wynberg group to form 1,4 addition product **40** [Figure 17]. In

addition to this intramolecular and intermolecular Michael additions have been performed by Gaunt and co-workers with high ee's [18].

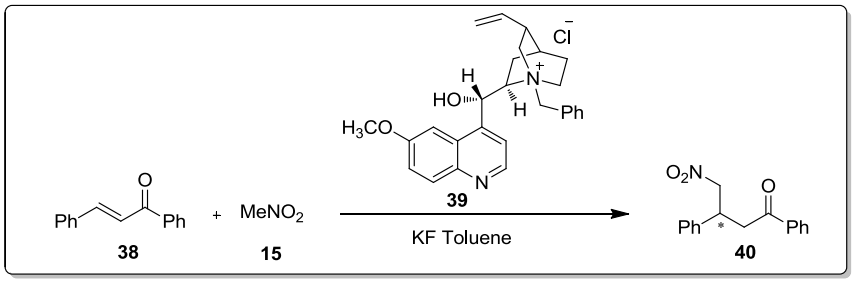


Figure 17: Michael addition of nitromethane to chalcone

The cinchona alkaloids were firstly used in asymmetric Henry reactions by Shibasaki and his group by using cinchona derivatives **42.** But only moderate yields and low enantioselectivities (up to 23% ee) **43** were obtained for addition of nitromethane **15** to highly substituted aldehyde **41** derivative[Figure 18] [22].

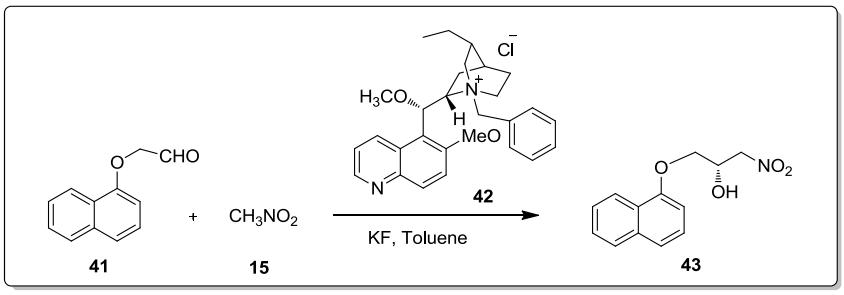


Figure 18: Asymmetric Henry reaction

The first Morita-Baylis-Hillmann reaction (MBH), was performed with moderate ee's by Drewes and Markó's groups [Figure 19]. Then Hatakeyama and co-workers got highly enantioselective MBH product **47** as the major one by using cinchona derivative **45** and less amount of minor product **46** [23]. In this reaction the hydroxyl group at C-6' on the catalyst, plays an important role. It stabilizes the oxy anion intermediate by an intramolecular hydrogen bonding. Aromatic aldehydes as well as aliphatic aldehydes **14** can be employed in this reactions with acrylates **44** in equal efficiency.

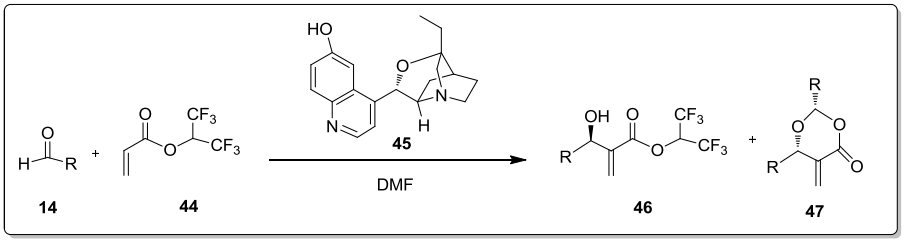


Figure 19: Asymmetric Morita-Baylis-Hillmann reaction

Anthrone reacts with *N*-methylmaleimide **49** in the presence of catalytic amounts of quinidine **50** as the first example of enantioselective Diels-Alder reaction [24]. In the proposed mechanism of the reaction, the anthranone dienolate **48** forms an ion-pair with the quaternized nitrogen of the catalyst to form cycloadduct **51**. *N*-methylmaleimide as the dienophile makes hydrogen-bond with the hydroxyl group of the catalyst as shown below [Figure 20].

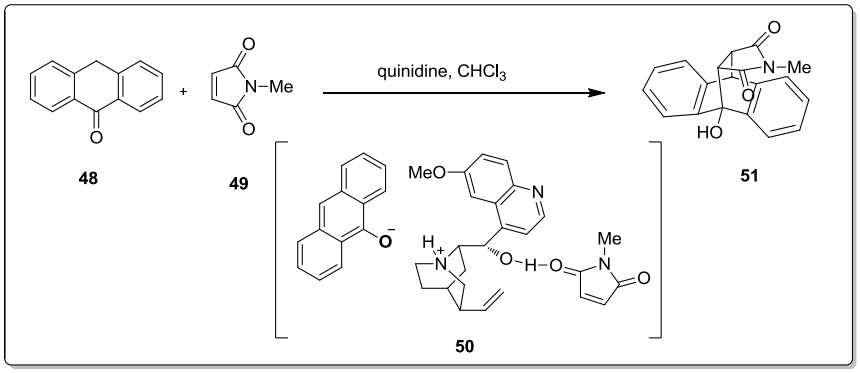


Figure 20: Enantioselective Diels-Alder reaction

Wynberg firstly tried enantioselective [2+2] cycloaddition by using catalytic amount of quinidine with activated aldehydes and ketenes **52, 53** to form β-Lactones **54**, and 98% ee was observed [Figure 21] [25].

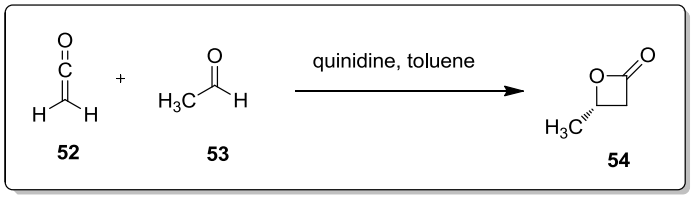


Figure 21: Formation of β-Lactones asymmetrically

Asymmetric [2+2] cycloaddition of ketenes **55** with *N*-tosylimines **56**, catalyzed by quinine ester **57** gives the formation of β-lactams **58** up to 99% ee [Figure 22] [26].

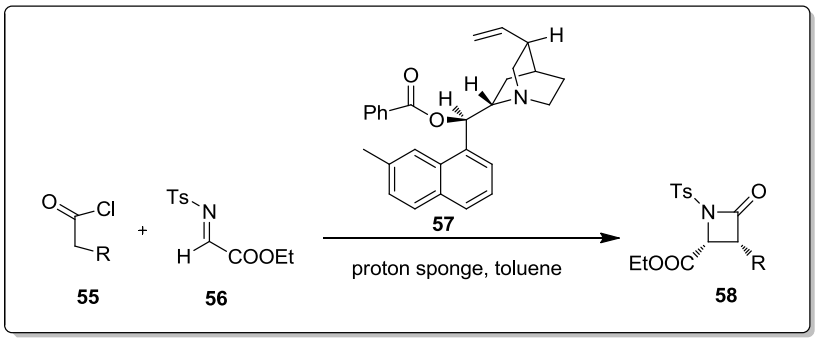


Figure 22: Formation of β-Lactams asymmetrically

The asymmetric cyanation reaction was firstly tried by Deng's group. Cinchona alkaloids were used in this reaction as chiral Lewis bases [27]. (DHQD)PHN and $(DHQD)_2AQN$ **60** gave the best results up to 97% ee [Figure 23]. In the suggested mechanism the ion pair is said to be responsible, in the transition state, for the enantioselectivity of the reaction.

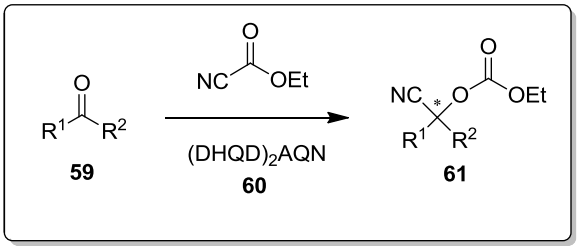


Figure 23: Asymmetric cyanation reaction

There are many other additional reactions that can be catalyzed by cinchona derivatives **36**. For example, addition of trifluoromethylsilane to aldehydes and ketones **59** to form trifluoromethyl alcohols **62** gives moderate ee's [Figure 24]. Furthermore, enantioselective Horner-Wadsworth-Emmons reactions of a phosphonate **64** with cyclohexanone **63** derivatives give up to 54% ee [Figure 25]. Moreover, the asymmetric Ireland-Claisen rearrangement of *N*-protected glycine allyl esters **67** gives γ,δ- unsaturated amino acids **68** in up to 93% ee [Figure 26] [28].

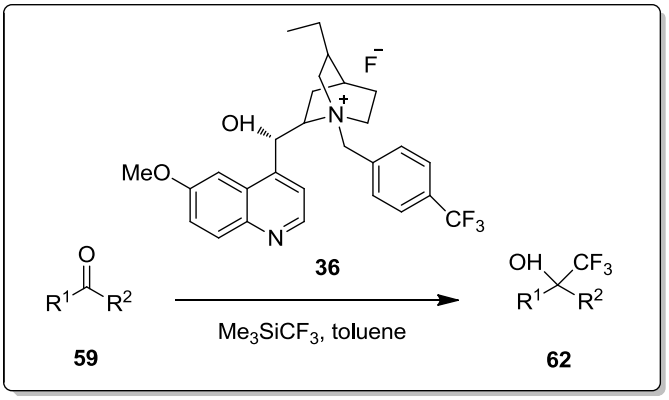


Figure 24: Asymmetric trifluoromethyl alcohol formation

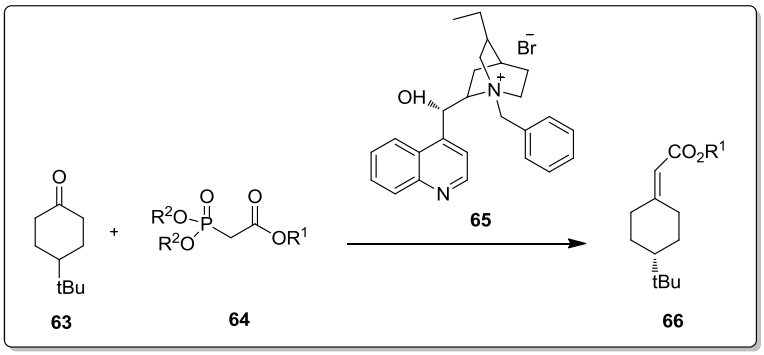


Figure 25: Enantioselective Horner-Wadsworth-Emmons reaction

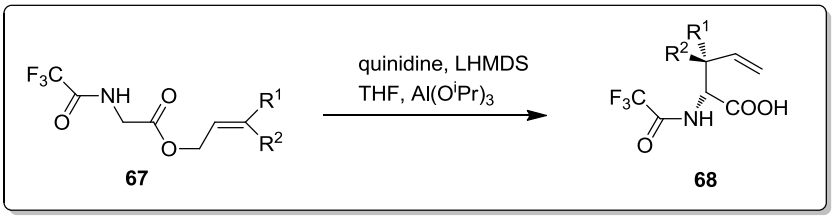


Figure 26: Asymmetric Ireland-Claisen rearrangement

(ii) carbon-oxygen bond formation reactions can be classified with the examples of epoxidation and dihydroxylation reactions.

Since the first example of asymmetric epoxidation of enones **69** were performed up to 98% ee by using -OH protected cinchona derivative **70** to form epoxide **71** [Figure 27].

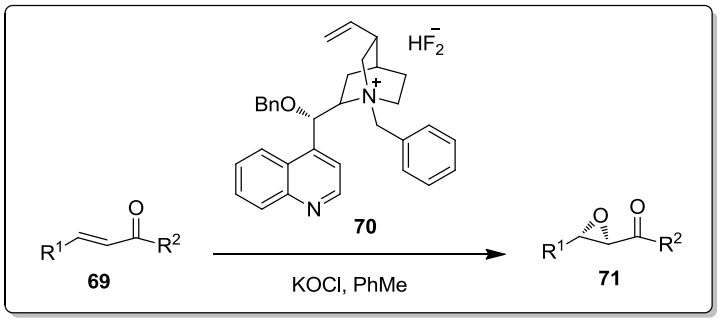


Figure 27: Asymmetric epoxidation

In addition to epoxidation reactions asymmetric dihydroxylation of olefins **72** was performed by using cinchona-based ligands by Sharpless and Hentges [29]. Products **73,74** with high enantioselectivities were obtained by using functionalized and non-functionalized olefins [Figure 28].

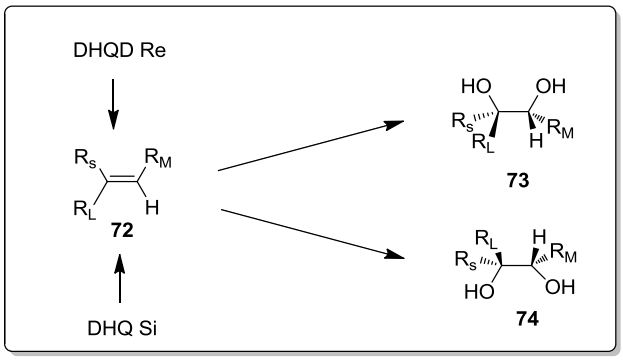


Figure 28: Asymmetric dihydroxylation of olefins

Catalytic asymmetric aminohydroxylation is similar to dihydroxylation. In these type of asymmetric conversion of alkenes **75** into N-protected amino alcohols **76,77**, nitrogen sources were used to carry out the asymmetric aminohydroxylation of alkenes. They also functions as oxidant [Figure 29] [30].

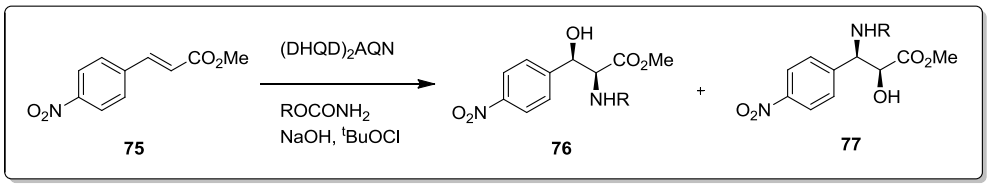


Figure 29: Asymmetric aminohydroxylation reaction

(iii) carbon- heteroatom bond formation reactions are another important part of the Cinchona catalyzed reactions. These type of reactions can be classified as aziridination, chlorination or sulfination reactions.

Catalytic enantioselective aziridination **80** of α,β-unsaturated esters **79** by *N*-acyl-*N*-arylhydroxylamines **78** was obtained firstly with 61% ee and 12% yield [Figure 30] [31].

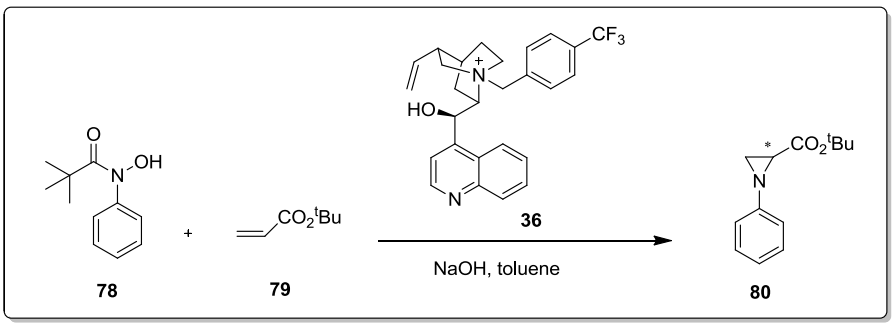


Figure 30: Asymmetric aziridination reaction

In the Shibata's asymmetric sulfination reaction of alcohols, the alkaloid reacts with the sulfinyl chloride **81** to form a complex **82** that acts as an asymmetric sulfinating agent of achiral alcohols [32]. It was catalysed by 9-acetoxyquinine and the arenesulfinate **83** was isolated with up to 95% ee [Figure 31].

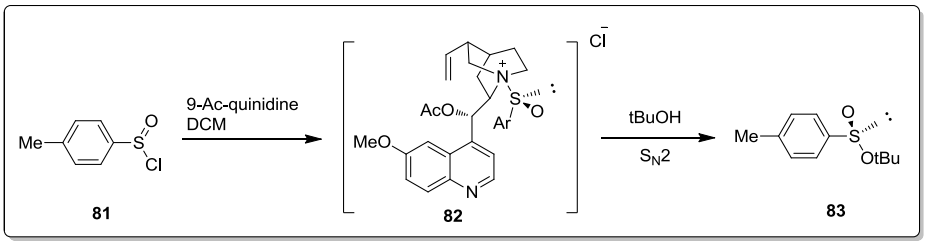


Figure 31: Asymmetric sulfination reaction

In catalytic enantioselective **chlorination/esterification** reactions α-chloroesters **86** can be generated from acid halides by using benzoylquinine and polychloroquinone **85** derivatives with ketones **84** to form tandem esterification sequence **87, 88, 89** [Figure 32] [33].

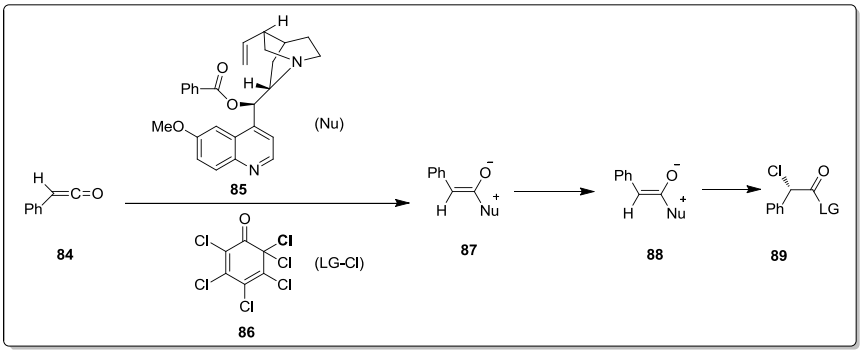


Figure 32: Asymmetric chlorination reaction

(vi) miscellaneous reactions are important reactions that can be performed by cinchona derivatives. They can be classified as hydrogenation reactions, reduction, decarboxylation, desymmetrization and kinetic resolution.

Orito tried the first heterogeneous asymmetric hydrogenation. The catalytic reaction involves Pt as an achiral activator responsible for the reduction **91** of keto ester **90** and a cinchona alkaloid as a chiral promotor, responsible for the enantioselectivity [Figure 33] [34].

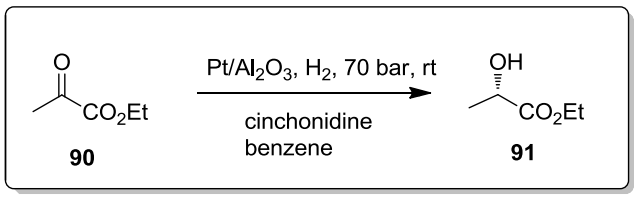


Figure 33: Heterogeneous asymmetric hydrogenation reaction

Homogeneous Reduction of α,β-unsaturated ketones with $LiAlH_4$ was performed in the presence of cinchona alkaloids but low enantioselectivities were obtained [35].

The enantioselective decarboxylation of α-aminomalonates **92** was used as an efficient way to synthesize α-amino acids **94** in the presence of quinidine catalyst **93**, but only led up to 52% ee [Figure 34] [36].

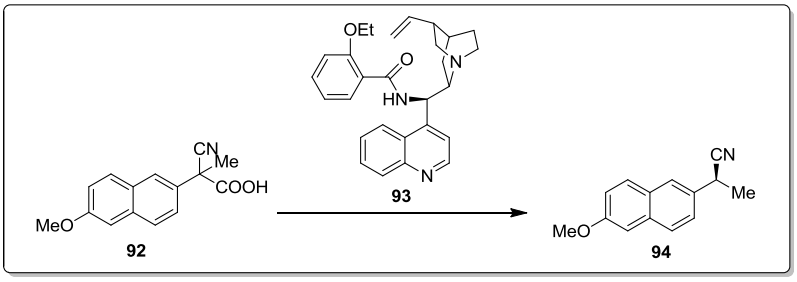


Figure 34: Enantioselective decarboxylation of α-aminomalonates

Desymmetrization of prochiral and meso cyclic anhydrides **95** was tried by Aitken and the enantioselective results **96, 97** was increased by using catalytic amounts of cinchonidine or quinidine as catalysts with methanol [Figure 35] [37].

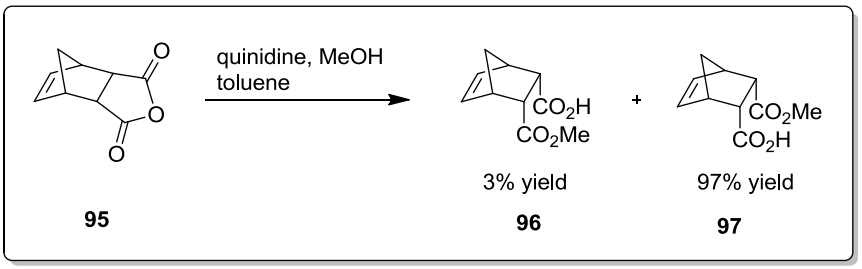


Figure 35: Enantioselective desymmetrization of anhydrides

Deng showed anhydride opening **99, 100** way by kinetic resolution of racemic monosubstituted anhydrides. The reaction of racemic 2-substituted succinic anhydrides **98** with an alcohol was carried out in the presence of catayltic amount of $(DHQD)_2AQN$ [Figure 36].

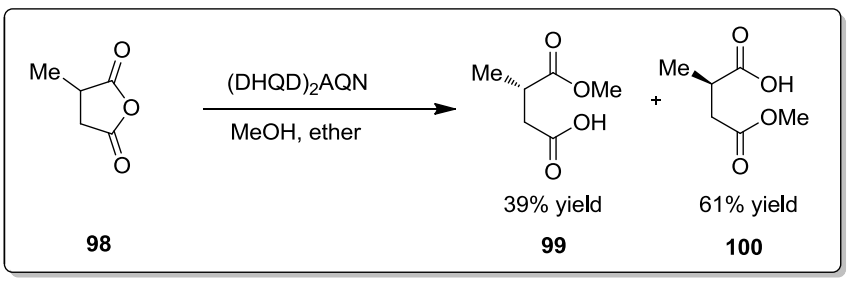


Figure 36: Kinetic resolution of racemic anhydrides

Using chiral organocatalysts, especially chiral cinchona derivatives is one of the powerful and efficient methods to synthesize interesting organic compounds in optically active form. As mentioned above cinchona alkaloids have played a very important role in the history of development of catalytic asymmetric organic transformations in many kinds of reactions.

1.3 Asymmetric Synthesis via Desymmetrization

Desymmetrization by enantioselective protonation is a common process in biosynthetic sequences. Chiral organocatalysis are able to control both the steric atmosphere around the proton acceptor (typically an enolate) and the proton donor (typically a thiol). Several chemical methods for achieving enantioselective protonation have been developed in different mechanisms by using different organocatalysis [38].

One of the most useful method of achieving an enantioselective protonation is to use a chiral proton donor. The acidic proton often comes from an oxygen, nitrogen, or carbon atom in the proton donor. The other important method is enantioselective protonation by a chiral Brønsted base. Different techniques have been used for enolate generation as simple deracemizations, pericyclic reactions, decarboxylations and dehalogenations [38]. The synthesis of the specific enolate precursor is required for a protonation protocol. Although several successful chiral Bronsted base protonation protocols have been developed, substrate scope remains a significant problem. In addition, a π–π-stacking interaction between the substrate and rigid proton source can be possible as the chiral controlling interaction during the protonation event.

Desymmetrization process was firstly examined by Deng based on the alcoholysis of meso cyclic anhydrides by the use of a cinchona alkaloid-derived primary amine catalyst. Conformationally rigid cinchona alkaloid derivatives were synthesized to perform these kind of reactions [39].

The enantioselective desymmetrization by protonation of prochiral enolates is one of the simplest and most useful method to obtain optically active α-substituted carbonyl compounds [40]. The most challenging step of this process is the development of a catalytic enantioselective protonation of enolates **101**, for which the substrate scope is relatively limited [Figure 37] [41].

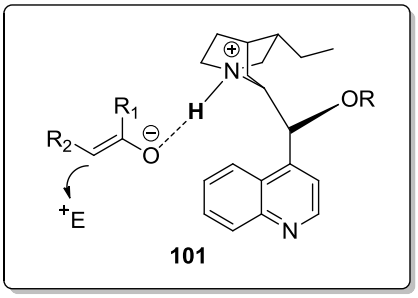


Figure 37: Origin of stereoselectivity of cinchona derivatives as phase transfer catalyst

The enantioselective protonation of prochiral intermediates to afford high enantio-pure chiral products is a useful technique in asymmetric organic synthesis. This method involves the complete generation of a deprotonated prochiral intermediate, typically an enolate, followed by irreversible protonation in a chiral environment to afford the desired enantiomer. On the other hand, a similar concept for the enantiomeric enrichment of racemic molecules via a reversible deracemization and protonation by a

chiral catalyst has been assumed impossible by thermodynamics. Principally enantioselective protonations are necessarily kinetic processes, because under thermodynamic control a racemate would be formed. For example, if the *S* enantiomer would be preferentially formed by virtue of an energetic advantage, it would also be preferentially deprotonated to re-form the prochiral enolate. As a consequence, this system cannot provide for overall enantiomeric enrichment [42].
This thesis will mainly focus on the simple use of hydrogenocarbonates **102** providing not only the protonating agent but also serving as a nucleophilic activator to release the transient enolate **103**. The presence of a chiral Brønsted base is expected to act as a chiral proton shuttle to ensure the asymmetric proton transfer as shown below **104** [Figure 38].

These types of useful transformations allow the synthesis of valuable chiral materials including natural products such as α- and β-amino acids.

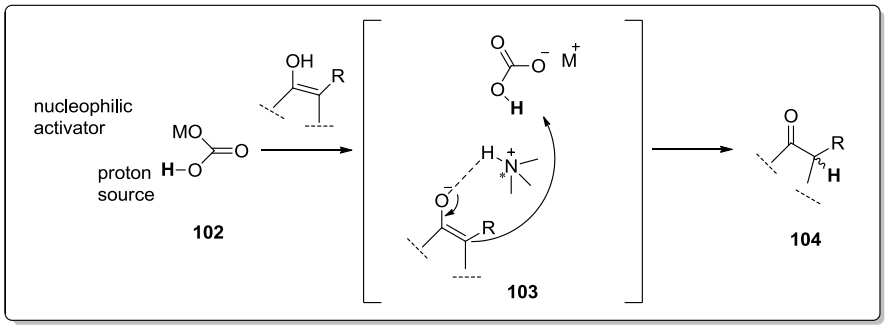


Figure 38: $MHCO_3$ using as both nucleophilic activator and proton source combined with a chiral Brønsted base

1.4 Alpha Azido Ketones; Synthesis and Application in Organic Synthesis

The ability of α-azido ketones to undergo different reactions **(105)** under basic conditions have been known for a long time [43]. α-Azido ketones with at least one α-hydrogen atom are highly base-sensitive and they can undergo different types of reactions. For example by the loss of nitrogen from carbanion **(106)**, followed by protonation of imino anion **(108)** to give α-imino ketone **(109)** or tautomeric α-amino enone **(110)** or it can be open to electrophilic attacs by the loss of α-hydrogen **(107)** as shown in below [Figure 39].

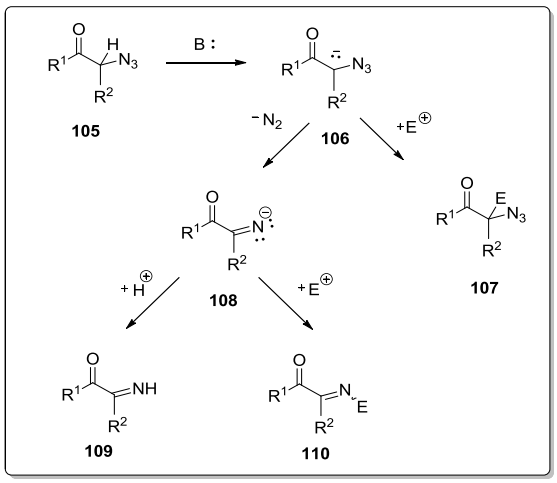


Figure 39: Trapping of the anions generated from α-azido ketones by electrophiles [44].

Number of methods to synthesize α-azido ketones have been developed. The most frequently used method is the nucleophilic substitution of a ketone containing a good leaving group, such as halogen or sulfonyloxy group, at the α-position. The main difficulty of this method is the unstability of the formed azide under basic conditions; substrates with α-hydrogen atoms, and in particular with a conjugating group at the α-position, give α-azido ketones in low yields and the major product is the tautomerized form of the imine [44]. New preparative methods to overcome this difficulty have been developed, but these approaches also suffer from lack of regioselectivity. Another solution is to enhance nucleophilic substitution, increasing the rate of displacement under less basic conditions. The use, in acetone solution, of α-nosyloxy ketones with a leaving group of greater nucleophilicity has been demonstrated.

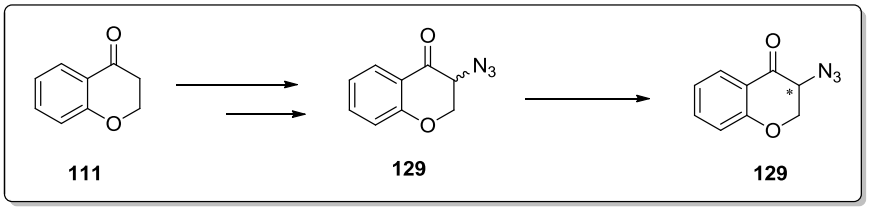
In the literature, Patonay and his group demonstrated that anions generated from azides by treatment with amines, could be trapped with aldehydes or ketones to yield 2-azido-3-hydroxy ketones or 2,5-dihydro-5-hydroxyoxazoles, depending on the conditions and techniques [44].

Asymmetric α-functionalization is very important prosess in organic chemistry. Patonay and his group studied on aldol reactions of α-azido ketones. But there aren't any study and publications about the chiral forms of these α-azido ketones.

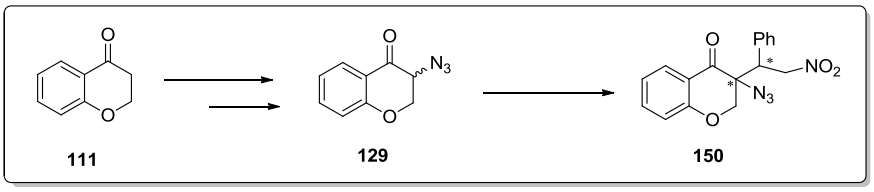
1.5 Aim of the Work

The main objective of this thesis is to synthesize chiral α-azido ketone derivatives by using different methods and different chiral catalysts. These kinds of compounds have very acidic alpha-protons and they can undergo many kinds of reactions without requiring strong bases. As an example, can be used in enantioselective reactions to form chiral, biologically active compounds. In this work, firstly alpha-azido ketones will be synthesized by using chromanone **111**, tetralone and indanone derivatives. Selective mono bromination reactions will be applied to obtain alpha bromo ketones. Then the reactions will be completed by addition of sodiumazide to alpha bromo ketones to obtain alpha azido ketones **129**. The chiral forms of them will be controlled in the deracemization and Michael addition reactions by the use of chiral cinchona alkaloids and bifunctional urea derivatives. The main objective to choose these kinds of cyclic azido ketones is because of their polyfunctional structure. There are carbonyl and azido groups that can be reduced to chiral amines and amino alcohols that can be used in many drug intermediates by further modifications.

By this way, mainly desymmetrizetion reactions will be performed by the use of C_2-symmetrical cinchona alkaloids. They will be used as potential chiral proton donors for the enantioselective deracemization **129** of alpha azido ketones derived from chromanone, tetralone and indanone derivatives.



As a part of this study in addition to desymmetrization reactions, Michael addition reactions will be performed by using a bifunctional urea derivative as catalyst to test the ability of forming Michael product **150** in highly enantiomericaly enriched forms.



CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of alpha bromo ketones

Bromination reactions of chromanone, tetralone and indanones were performed according to literature procedure [35].

Chromanone, tetralone and indanone derivatives **111**, **112**, **113** were brominated to **114**, **115**, **116** by using elemental bromine [Figure 40]. Fifteen different types of alpha bromo ketones were synthesized with good to high yields [Figure 41]. The yields of these reactions vary between 55- 70%. It is difficult to brominate selectively with high yields due to the formation of dibrominated products as side products. To prevent these side reactions less than stoichiometric amounts of bromine was used in these reactions. The ^{1}H and ^{13}C NMR spectra of these products were in aggrement with the reported values as shown in experimental part. The typical value of α-proton in ^{1}H NMR spectra can be seen in each compound at ca. 5 ppm as doublet of doublet as shown in Figure 40.

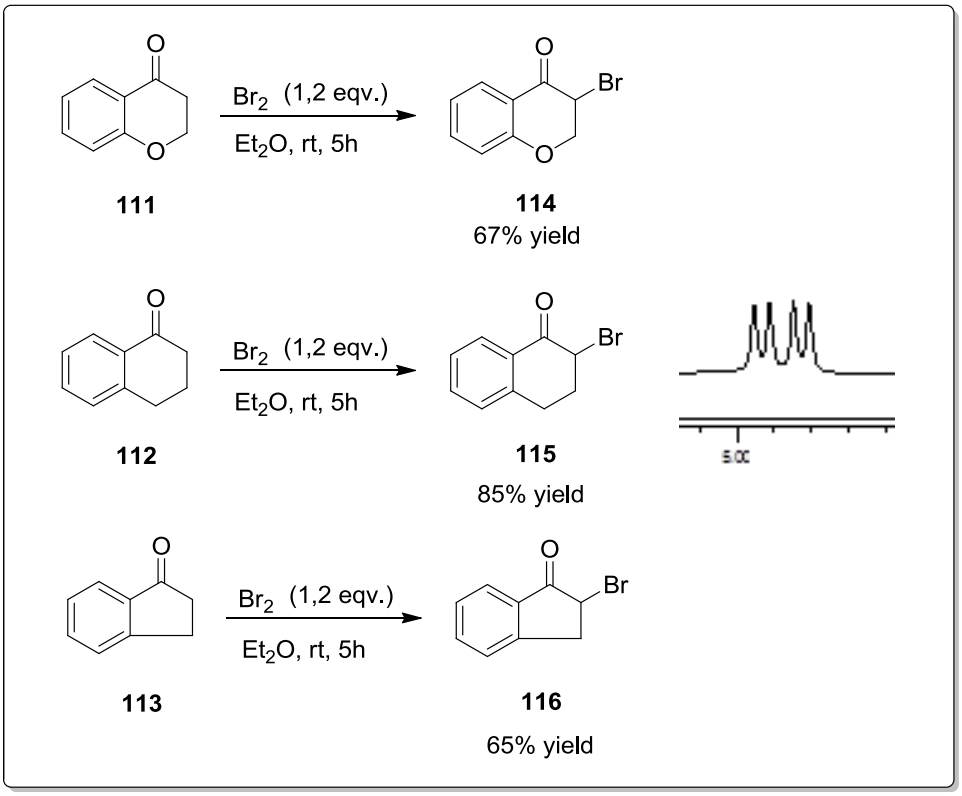


Figure 40: Bromination of chroman-4-one, alpha tetralone and 1-indanone

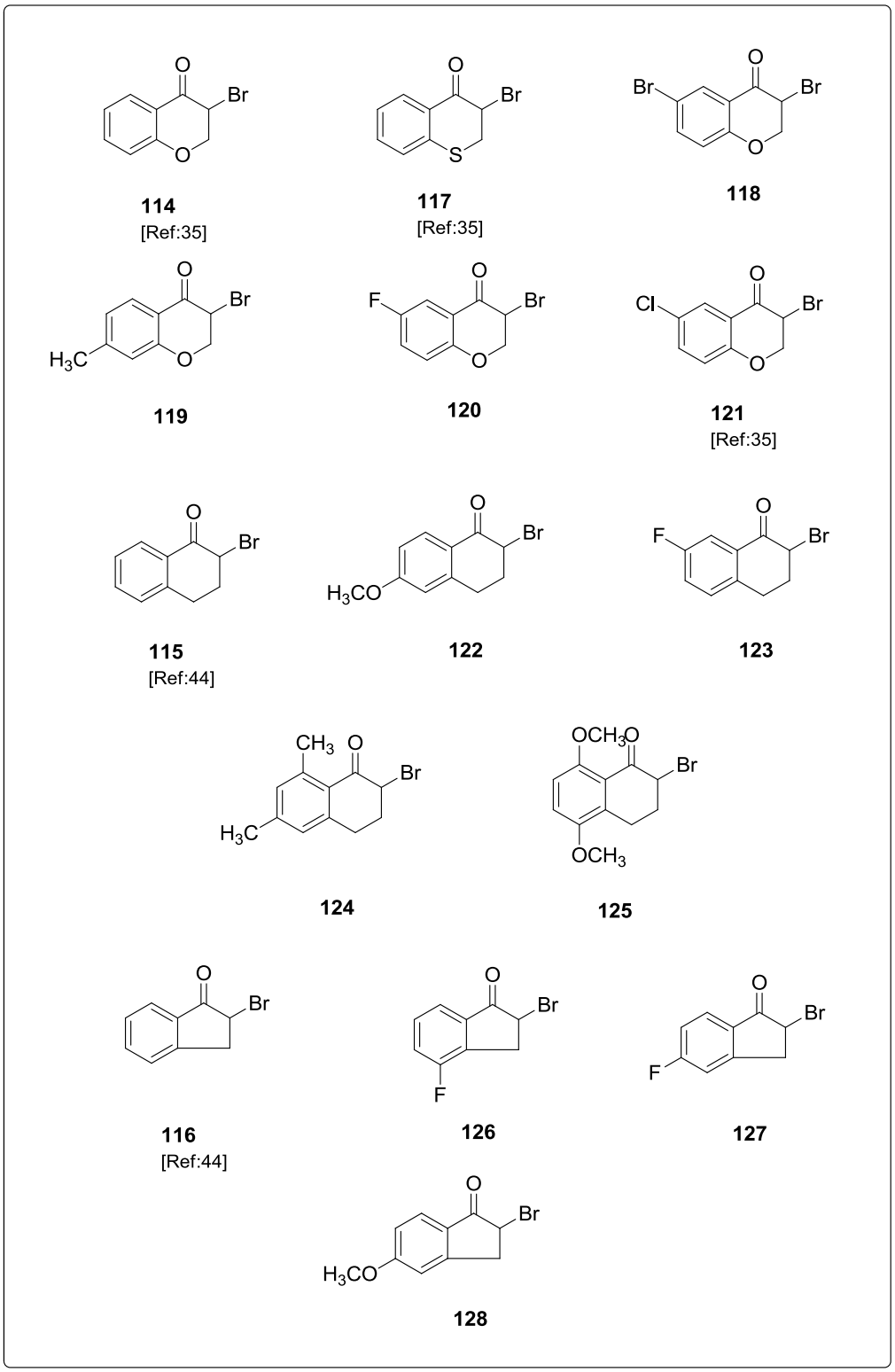


Figure 41: Brominated chromanone, tetralone and indanone derivatives

2.2 Synthesis of alpha azido ketones

The importance of the alpha azido ketones in biological activity and multifunctionalities enables us to use them in different reactions. Imediately after alpha bromo compoundsin hand, S_N2 reactions with sodium azide in the presence of 18-crown-6 were carried out on the compounds [Figure 42] [35]. Fifteen different types of racemic alpha azido ketones were obtained in good to high yields [Figure 43]. In these reactions sodium azide was used as azide source, the crown ether was used as phase transfer catalyst as well as to break the ion pairing. The yields of these reactions changed between 60-80%. Azides are known to be relatively unstable compounds in the presence of light and heat [44]. In our case, we do have azides at a very reactive positions i.e; alpha positions of ketones. With this information in mind, the lower yield in these reactions could be explained by the relative unstabilities of the alpha azido compouns. The ^{1}H and ^{13}C NMR spectra of these products were given in the experimental part. The chemical shift values of the alpha protons in alpha azido compounds shifted to high fields compared to the precersors. Therefore, the alpha protons in the azides showed up between 4-5 ppm. These compounds were analyzed by HPLC with a chiral column, the compounds appear as stable under these conditions (in HPLC columns under high pressure). Furthermore, we observed two peaks in the chromatograms corresponding to each enantiomers.

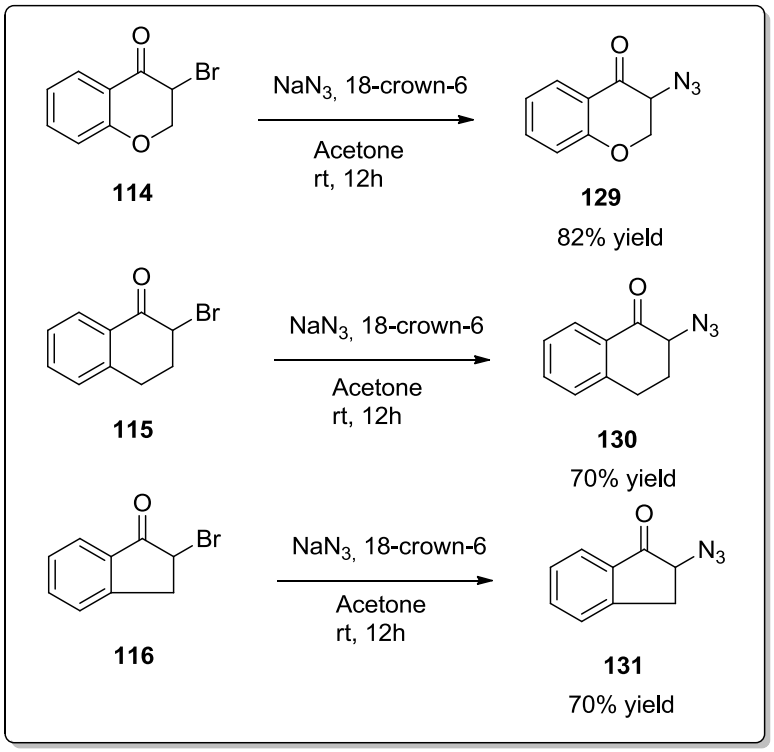


Figure 42: Formation of alpha azido chromanone, tetralone and indanone

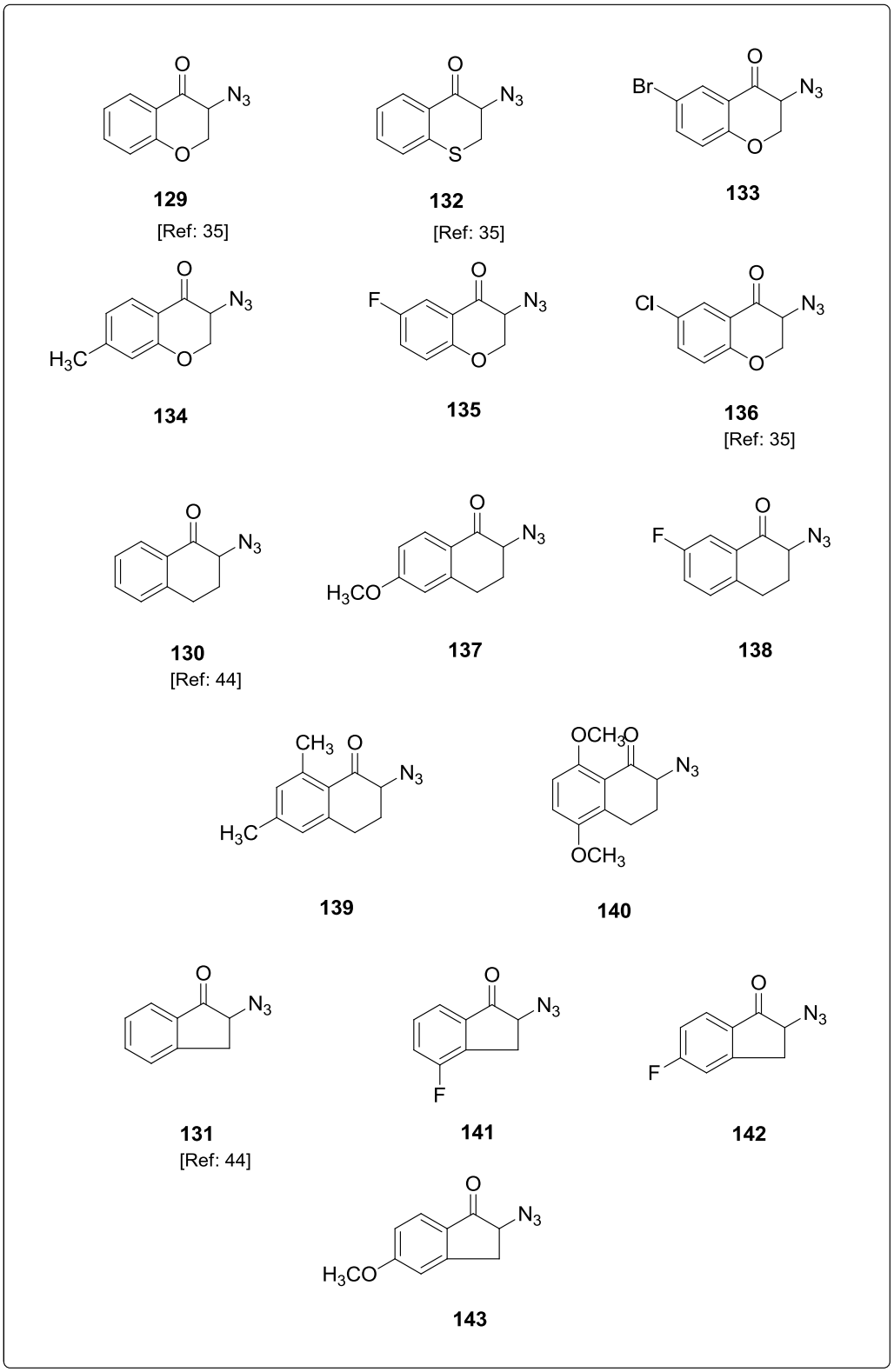


Figure 43: Alpha azido chromanone, tetralone and indanone derivatives

2.3 Deracemization of alpha azido ketones

Cinchona alkaloids were used in deracemization reactions for numereous alpha substituted ketones as mentioned in the introduction part (*cf*. pages 17-18). With this in mind, we performed deracemization reactions of alpha azido ketones with cinchona alkaloids. Therefore, we could obtain chiral alpha azido ketones in one step. To perform these kinds of reactions, four different types of cinchona bases were employed. Two of these were commercially available [(1S,2R,4S,5R)-5-ethyl-2-((S)-&&6-((S)-((1R,2S,4R,5S)-5-ethylquinulidin-2-yl)(6-methoxyquinolin-4-yl)methoxy)-5-phenylpyrimidin-4-yl)oxy)(6-methoxyquinolin-4-yl)methyl)quinuclidine], $(DHQD)_2PYR$ **144**, 1-((1R)-((2S)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methoxy)-4-((1S)-((2R,5S)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methoxy)anthracene-9,10(4aH,9aH)-dione, $(DHQD)_2AQN$ **145**, and two of these were synthesized in our laboratory for a different research [Mehmet Göllü and Ayhan Sıtkı Demir's unpublished results]; [1-((1R)-((2S)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methoxy)-4-((1S)-((2R,5S)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methoxy)anthracene-9,10(4aH,9aH)-dione], [1S,2S,4S,5R)-2-((6-methoxyquinolin-4-yl)((trimethylsilyl)oxy)methyl)-5-vinylquinuclidine] **146** and [N-((7-methoxynaphthalen-1-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)-4-methylbenzenesulfonamide] **147** [Figure 44].

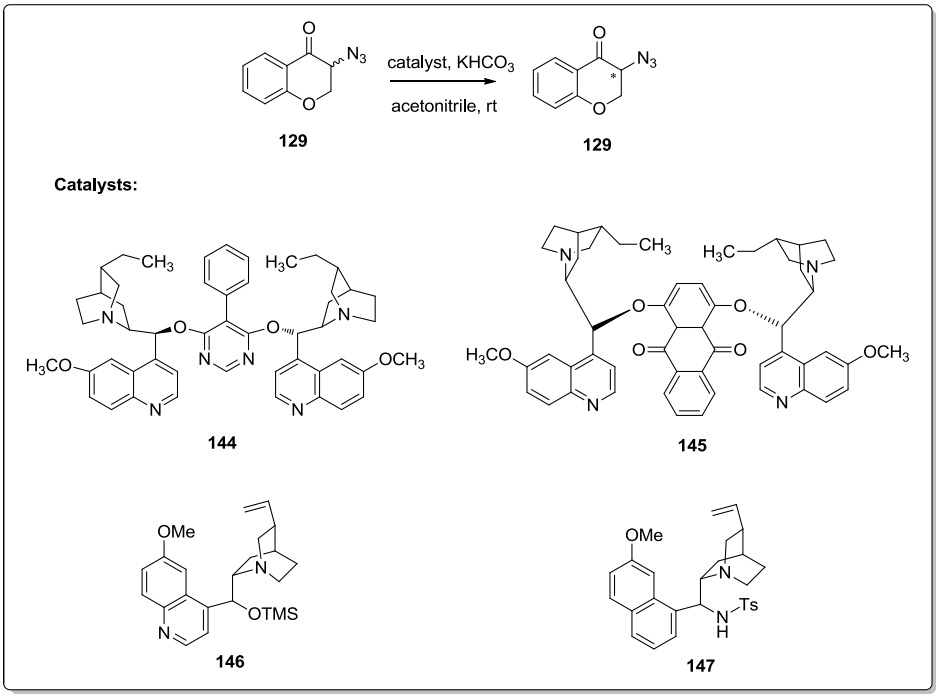


Figure 44: Cinchona Alkaloids Used in Deracemization Reactions

To perform deracemization reactions, first, the alpha azido ketones were dissolved in acetonitrile and the catalsts and $KHCO_3$ was added to the solution. This heterogeneous mixture was stirred at room temperature. The reaction was monitored day by day by HPLC with a chiral column. We first choose to use **144** and **145** due to their relatively big sizes. The initial hypothesis was that the large molecular surface could induce a steric hindrance, which, in turn, increases the *ee*. Although we obtained good *ee*'s with the bulky catalsts, hypothesis still needed to be proved. Therefore, we employed **146** and **147** as catalyst. In these cases, we again obtained products with compareable yields and *ee*s. With this in mind, we conclude that the sizes of the bases were not that influencial in these reactions.

As mentioned earlier, chromanone, tetralone or indanone derivatives were dissolved in dry acetonitrile in a reaction tube. To these solutions, catalytic amount of cinchona bases were added slowly at room temperature. The change of enantiomeric excess was monitored day by day by using the HPLC. Before we add any $KHCO_3$ there were not any changes of enantiomeric excess for each derivative of α-azido ketones. After ten days the α-azido ketones were started to decompose. To obtain the enantiomerically enriched products, the parameters were changed. For example, the temperature was decreased from 0 ^oC to -78 ^oC, increased up to 20 ^oC from 0 ^oC. However, we could not see any observable changes in the reaction products. The α-azido ketones decomposed at temperatures over 20 ^oC. In addition to temperature changes, different solvents were tested. Dichloromethane, tetrahydrofurane and acetonitrile were used. But no changes were observed. The products were racemic in any condition so far. When there is no change in HPLC chromatograms from one day to another, the reaction was eased. This required different times for different compounds as summarized in table 1, 2, 3. With the optimized reaction conditions in hand, we changed solvents and temperature and observed that the parameters do not affect the *ee*'s but increase the reaction time. As we increase the reaction time, we again observed the decomposition of the alpha azido ketones, which, in turn, reduced the yield. Then, an additional base was added to the reaction medium. The changes in enantiomeric excesses were monitored by identical methods used before. After 3 days, the formation of the products started to appear in the HPLC. Therefore the optimized way to synthesize chiral alpha azido ketones is using acetonitrile as solvent at room temperature. The products were purified by using column chromatography in which silica gel as filling material. The yields of these reactions were changing between 70-85%.

The suggested mechanism of these reactions is shown in Figure 45. According to this mechanism, highly acidic alpha hydrogen is abstracted by the cinchona base and a quaternary ammonium salt was formed. Then the alpha azido ketone form an enolate and this formed enolate's oxygen forms a hydrogen bonding with proton that is now on the nitrogen **148**. The abstraction of the proton from $KHCO_3$ became easier by this interaction. In addition to these interactions there are π-π stacking interactions between aromatic parts of the catalyst and starting material. At the end of these reactions the starting material and the product were same, but the only difference was enantiomerically enriched compounds were in hand.

The HPLC chromatogram of products are shown in Appendix B and the enantiomeric excess ratios are given in tables **1**, **2**, and **3** for chromanone, tetralone and indanone derivatives.

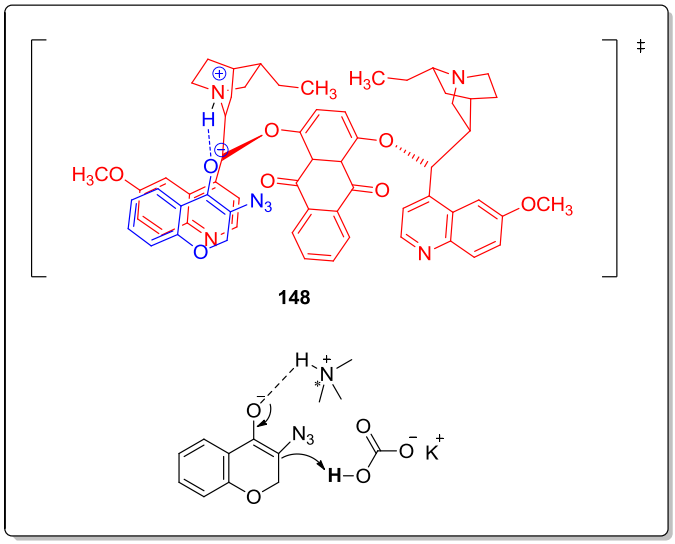


Figure 45: Suggested transition state of deracemization reaction

The best enantiomeric excesses were obtained with the trial of chromanone derivatives. Nearly 99% *ee* were obtained for each derivative but it was not same for the thiochromanone derivative. The *ee* of that one was in between 18-39%. This means high polarity and the lone pairs of oxygen on chromanone derivatives have an important effect on these deracemization reactions. The enantiomeric excesses of tetralones and indanones were not as good as chromanones.

The enantiomeric excess change versus time graph for 3-azidochroman-4-one derivative is shown in Figure 46. This graph was produced using the HPLC chromatograms shown in Figure 47. There was a rapid increase of enantiomeric excess after 3 days. It was proposed that initially, $KHCO_3$ salt had low solubility in CH_3CN. Later, the salt became more solubile after 2 days, so it could increase the enantiomeric excesses.

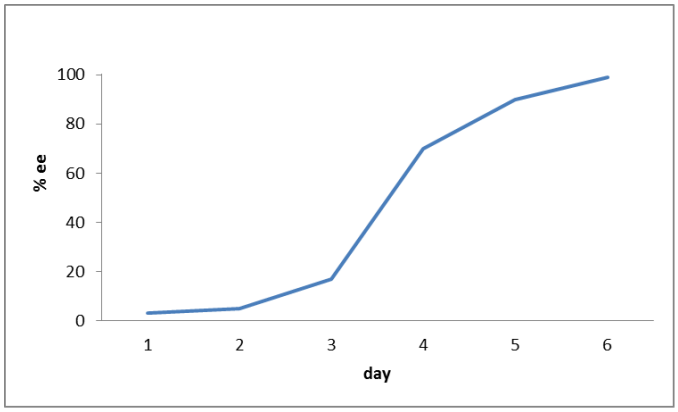


Figure 46: Change of enantiomeric excess of 3-Azidochroman-4-one day by day

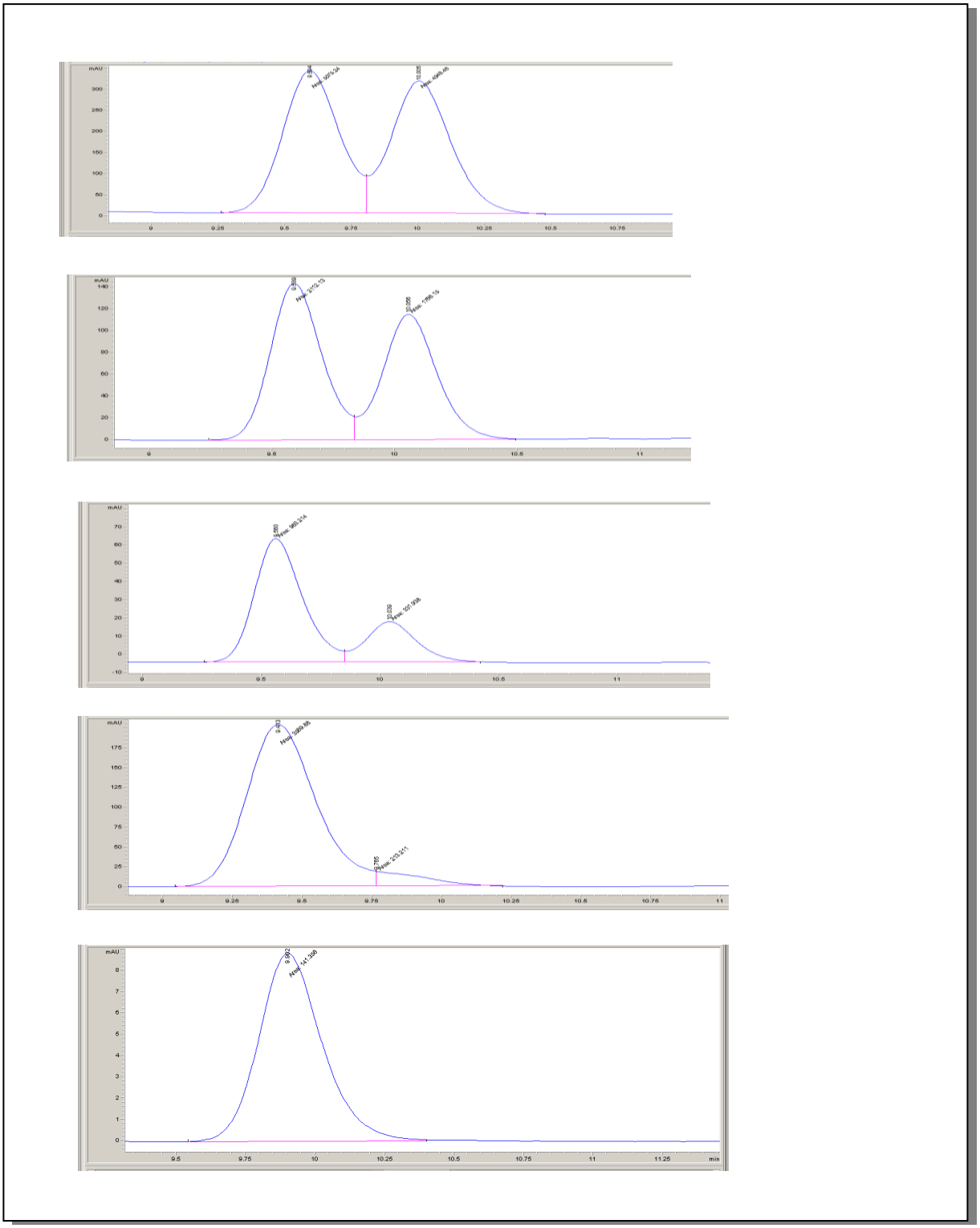


Figure 47: HPLC Chromatograms of 3-Azidochroman-4-one from 2nd day to 6th day

Table 1: Enantiometric excess results of deracemization reactions of chromanones

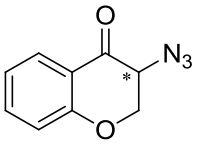
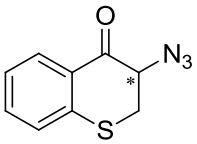
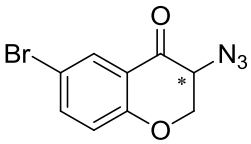
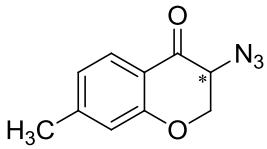
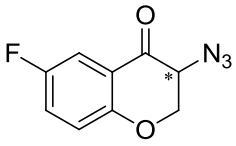
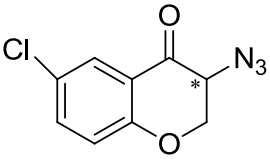
CHROMANONES	$(DHQD)_2AQN$ **144**	$(DHQD)_2PYR$ **145**	BULKY BASE **146**	BULKYBASE **147**
 80-90 % yield	99% ee After 5 days	99% ee After 5 days	99% ee After 5 days	99% ee After 5 days
 70-80 % yield	18% ee After 5 days	35% ee After 6 days	-	39%ee After 5 days
 80-90 % yield	99% ee After 5 days	99% ee After 4 days	99% ee After 3 days	99% ee After 4 days
 80-90 % yield	65%ee After 3 days	99% ee After 6 days	97%ee After 5 days	15%ee After 6 days
 70-80 % yield	70% ee After 3 days	99% ee After 6 days	40% ee After 3 days	99% ee After 5 days
 80-90 % yield	99% ee After 5 days	99% ee After 5 days	99% ee After 6 days	99% ee After 3 days

Table 2: Enantiometric excess results of deracemization reactions of tetralones

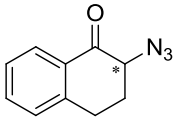
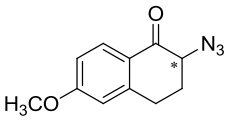
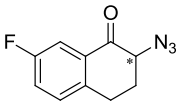
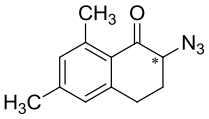
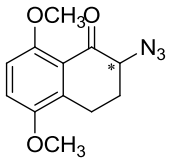
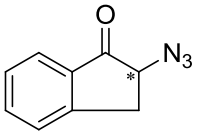
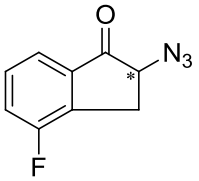
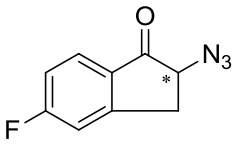
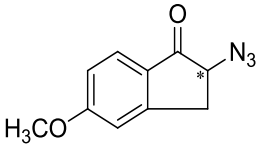
TETRALONES	$(DHQD)_2AQN$ **144**	$(DHQD)_2PYR$ **145**	BULKY BASE **146**	BULKY BASE **147**
 70-80 % yield	19% ee After 5 days	18% ee After 5 days	Racemic	19% ee After 6 days
 70-80 % yield	42% ee After 6 days	70% ee After 5 days	56% ee After 5 days	Decomposition
 70-80 % yield	Racemic	10% ee After 5 days	26% ee After 5 days	4% ee After 7 days
 60-70 % yield	35% ee After 5 days	70% ee After 4 days	40% ee After 6 days	55% ee After 6 days
 70-80 % yield	4% ee After 5 days	Racemic	48% ee After 4 days	Racemic

Table 3: Enantiometric excess results of deracemization reactions of indanones

INDANONES	$(DHQD)_2AQN$ **144**	$(DHQD)_2PYR$ **145**	BULKY BASE **146**	BULKY BASE **147**
 60-70 % yield	99% ee After 5 days	90% ee After 5 days	99% ee After 5 days	30% ee After 5 days
 70-80 % yield	98% ee After 5 days	70% ee After 4 days	60% ee After 4 days	37% ee After 4 days
 70-80 % yield	89% ee After 4 days	5% ee After 6 days	99% ee After 4 days	10% ee After 5 days
 60-70 % yield	93% ee After 4 days	24% ee After 4 days	73% ee After 3 days	15% ee After 5 days

2.4 Michael Addition Reactions of Alpha Azido Ketones

The results with deracemization reactions encourged us to try reactions other than deracemization proceses. In this context, since the deracemization reactions involved formation of enolate, we could run many reactions going through the same mechanism. Therefore, the next reaction was the addition of α-azido ketones to β-nitrostyrene **(149)** because the products of the reaction can afford multifunctional molecules that can be converted to several biologically important products. Michael addition to β-nitrostyrene was performed with two derivatives of chromanones as 3-azidochroman-4-one **(129)** and 3-azido-6-bromochroman-4-one **(133)**. The same procedure was applied for two derivatives of chromanones. By this way, Michael adduct with two chiral centers were formed. These formed diastereomers were separated from each other by using column chromatography and the enantiomeric excesses of the products are determined by HPLC with chiral OD-H column.

In these reactions, mainly one diastereomer formation was observed, small amount of the other diastereomer was detected. The diastereomeric excess for **150** was about 1:11 and the enantiomeric excess for the major diastereomer was 94%. The diastereomeric excess for **151** was about 1:12 and the enantiomeric excess for the major diastereomer was 86%. Diastereomeric excesses were determined by crude NMR for each derivative. The reactions are shown in Figure 48.

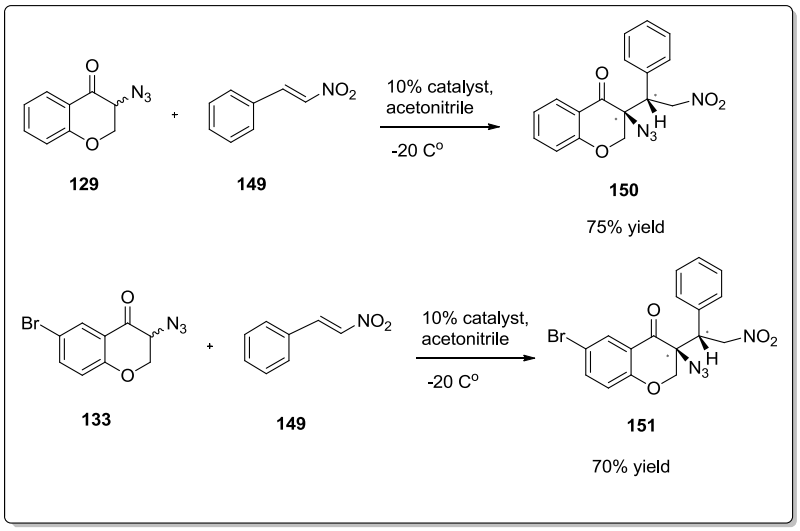


Figure 48: Michael addition of β-nitro styrene to azido chroman derivatives

To perform these reactions, bifunctional thiourea derivative [Figure 49] **(152)** was used synthesized in our laboratory for a different research by Mehmet Göllü. In the suggested mechanism the thiourea part is activating the electrophile (β-nitrostyrene) by forming Hydrogen bonding and the cinchona part (quinuclidine ring) of it is activating the alpha-azido ketone as a Brønshted base by forming quaternary ammonium salt. The suggested mechanism **153** is shown in Figure 50.

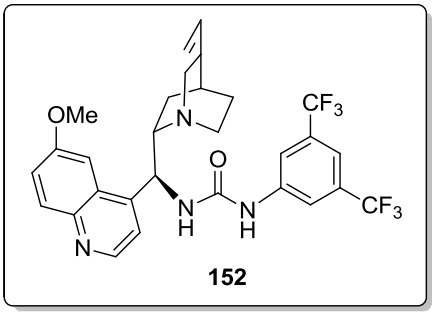


Figure 49: 1-(3,5-bis(trifluoromethyl)phenyl)-3-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)urea

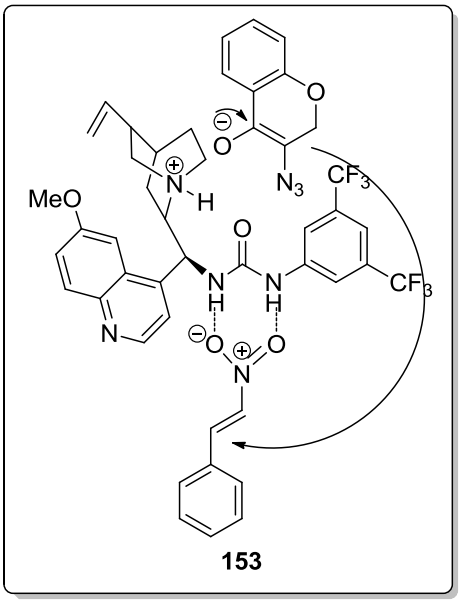


Figure 50: Suggested mechanism of Michael addition reaction

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature in $CDCl_3$ solutions at 400 MHz and 100 MHz respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. All reactions were monitored by TLC on silica gel 60 F_{254}. TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm). Column chromatography was performed on silica gel 60 with a particle size of 0.063–0.200 mm. Evaporation refers to the removal of solvent under reduced pressure.

NMR spectra were recorded on a Bruker DPX 300. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: δ=7.27), $CDCl_3$ (^{13}C: δ=77.0) and CCl_4 (^{13}C: δ=96.4) as internal standards. ^{1}H and ^{13}C NMR spectra of products are given in appendix A.

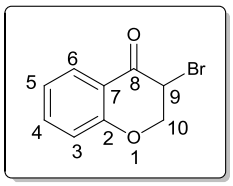
HPLC chromatograms were recorded on an Agilent 1100 Series. OD-H chiral column was used with different solvent systems. HPLC chromatograms of chiral products and racemic forms of them were given in appendix B.

3.2 General Procedure A for Preparation α-Bromo Ketones

3.2.1 Synthesis of 3-Bromochroman-4-one (114)

4-Chromanone (889mg, 6 mmol) was dissolved in of diethyl ether (20 mL) in a (100 mL) flask. To this solution, bromine (0.37 mL, 7.2 mmol) was added slowly at room temperature. The resulting solution was monitored by TLC every 2 hours. After 5 hours the reaction was completed and the solvent was evaporated using Rotary Evaporator. After evaporation of the solvent the residue is dissolved in ethyl acetate and extracted with brine (25 mL) and the organic layer is dried over $MgSO_4$ and concentrated in vacuo.

After evaporation of the solvent the residue is dissolved in a minimum amount of CH_2Cl_2 for column chromatography on silica gel. The clomun is eluted with hexane: ethylacetate (95: 5) and the residue is collected from as the second band. After the combination of all parts, (908 mg) pure product **114** (67% yield, white crystals) was obtained after drying [35].



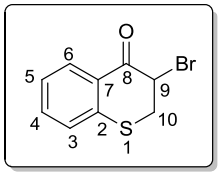
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (dd, $J_{5,6}$ = 7.9, $J_{4,6}$ =1.7 Hz, 1H, H-6), 7.46 (ddd, $J_{3,4}$= 8.8, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.8 Hz, 1H, H-4), 7.12-7.07 (m, 1H, H-5), 7.04 (dd, $J_{3,4}$ = 8.3, $J_{3,5}$=0.6 Hz, 1H, H-3), 4.72-4.41 (m, 3H, H-9,10).

^{13}C NMR (100 MHz, $CDCl_3$): 185.2, 160.7, 136.8, 128.3, 122.4, 118.8, 117.9, 71.3, 45.4.

The same procedure is applied for each derivative of chromanone, tetralone and indanones as general procedure A.

3.2.2 Synthesis of 3-Bromo-1-thiochroman-4-one (117)

General procedure A afforded pure and yellowish product up to 55% yield [35].

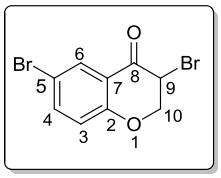


^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, $J_{5,6}$ = 8.0, $J_{4,6}$ = 1.5 Hz, 1H, H-6), 7.44 (ddd, $J_{3,4}$ = 8.1, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.55 Hz, 1H, H-4), 7.34-7.17 (m, 2H, H-3,5), 4.98 (dd, $J_{9,10}$ = 8.5, $J_{9,10}$ = 3.4 Hz, 1H, H-9), 3.59 (ddd, J_1 = 22.6, J_2 = 14.1, J_3 = 5.9 Hz, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 187.0, 141.1, 133.9, 130.7, 127.3, 125.6, 98.3, 49.7, 35.1.

3.2.3 Synthesis of 3-6-Dibromochroman-4-one (118)

General procedure A afforded pure and yellow crystals as product up to 75% yield.

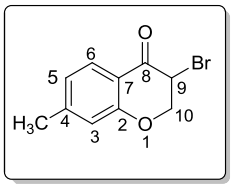


^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, $J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.62 (dd, $J_{4,3}$= 8.9, $J_{4,6}$ = 2.5 Hz, 1H, H-4), 6.96 (d, $J_{3,4}$ = 8.8 Hz, 1H, H-3), 4.71-4.57 (m, 3H, H-9,10);

^{13}C NMR (100 MHz, $CDCl_3$): 184.0, 159.5, 139.4, 130.6, 120.1, 120.0, 115.0, 71.3, 44.5.

3.2.4 Synthesis of 3-Bromo-7-methylchroman-4-one (119)

General procedure A afforded pure and white solid particals up to 75% yield.

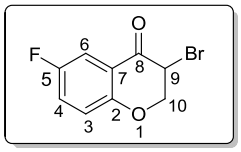


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (m, 1H, H-6) 7.39 (dd, $J_{5,6}$ = 8.5, $J_{5,3}$ = 2.2 Hz, 1H, H-5), 6.96 (d, $J_{3,5}$ = 8.5 Hz, 1H, H-3), 4.69 (broad s, 3H, H-9,10), 2.35 (s, 3H, CH3);

^{13}C NMR (100 MHz, $CDCl_3$): 184.4, 157.7, 136.9, 130.9, 126.7, 117.4, 116.7, 70.3, 44.6, 19.4.

3.2.5 Synthesis of 3-Bromo-6-fluorochroman-4-one (120)

General procedure A afforded pure and yellowish solid particals up to 65% yield.

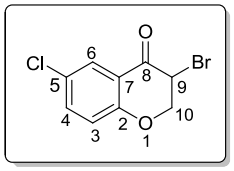


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (dd, $J_{4,3}$ = 8.1, $J_{4,6}$ = 3.2 Hz, 1H, H-4), 7.31-7.25 (m, 1H, H-6), 7.04 (dd, J_1 = 9.1, J_2= 4.2 Hz, 1H, H-3), 4.74-4.53 (m, 3H, H-9,10).

^{13}C NMR (100 MHz, $CDCl_3$): 184.5, 157.6 (d, J_{CF}= 243.3 Hz, C-5), 156.4 (d, J = 1.7 Hz, C-2), 124.5 (d, J = 24.6 Hz,C-7), 119.8 (d, J = 7.4 Hz,C-4), 119.2 (d, J = 6.9 Hz,C-6), 112.9 (d, J = 23.7 Hz,C-3), 71.4, 44.8.

3.2.6 Synthesis of 3-Bromo-6-chlorochroman-4-one (121) [35]

General procedure A afforded pure and white crystals up to 60% yield.

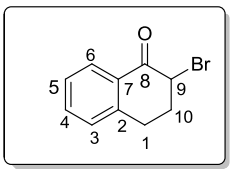


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (d, $J_{6,4}$ = 2.7 Hz, 1H, H-6), 7.49 (dd, $J_{4,3}$ = 8.9, $J_{4,6}$ = 2.7 Hz, 1H, H-4), 7.02 (d, $J_{3,4}$ = 8.86 Hz, 1H, H-3), 4.71-4.55 (m, 3H, H-9,10).

^{13}C NMR (100 MHz, $CDCl_3$): 184.1, 159.1, 136.6, 127.9, 127.4, 119.7, 119.6, 71.3, 44.6.

3.2.7 Synthesis of 2-Bromo-alpha tetralone (115)

General procedure A afforded pure and black oily product up to 85% yield.

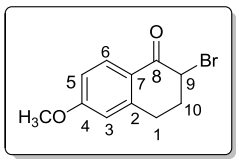


^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (dd, $J_{5,6}$ = 33.8, $J_{4,6}$ = 7.9 Hz, 1H, H-6), 7.57-7.47 (m, 1H, H-5), 7.41-7.30 (m, 1H, H-4), 7.27 (dd, $J_{3,4}$ = 7.0, $J_{3,5}$ = 4.6 Hz, 1H, H-3), 4.74-4.70 (m, 1H, H-9), 3.36-3.23 (m, 1H, H-1), 2.91 (td, J_1=17.13, J_2 = 4.41, J_3 = 4.41 Hz, 1H, H-1), 2.58-2.40 (m, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 190.5, 143.1, 134.2, 129.9, 128.8, 128.6, 127.1, 50.6, 31.9, 26.2.

3.2.8 Synthesis of 2-bromo-6-methoxy-tetralone (122)

General procedure A afforded pure and brown solid product up to 78% yield.

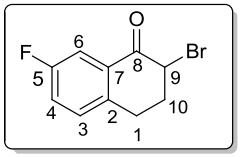


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J=7.86 Hz, 1H, H-6), 7.32 (t, J = 8.01Hz, 1H, H-5), 7.06 (d, J=8.03 Hz, 1H, H-3), 4.71 (t, J = 4.36 Hz, 1H, H-9), 3.88 (s, 3H, OCH_3), 3.02 (dd, J_1= 8.72, J_2= 4.24 Hz, 2H, H-1), 2.48 (dd, J_1=10.53, J_2=5.76 Hz, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 193.9, 156.6, 143.6, 132.1, 127.3, 120.1, 114.8, 55.7, 50.3, 31.1, 19.9.

3.2.9 Synthesis of 2-bromo-7-fluoro-tetralone (123)

General procedure A afforded pure and light brown solid product up to 88% yield.

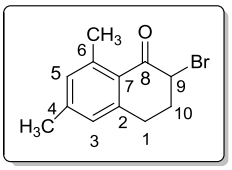


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73 (dd, $J_{3,4}$ = 8.98, $J_{4,6}$ = 2.71 Hz, 1H, H-4), 7.31-7.20 (m, 2H, H-3,6), 4.72 (t, J = 4.2 Hz, 1H, H-9), 3.32-3.21 (m, 1H, H-10), 2.91 (td, J_1=17.06, J_2=4.35, J_3=4.35 Hz, 1H, H-10), 2.66-2.31 (m, 2H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): 189.6, 161.7 (d, J_{CF} = 247.13 Hz,C-5), 138.7 (d, J = 2.83 Hz,C-2), 131.51 (d, J = 6.44 Hz,C-7), 130.7 (d, J = 7.08 Hz,C-3), 121.6 (d, J = 22.41 Hz, C-4), 114.3 (d, J = 22.24 Hz, C-6), 49.6, 31.8, 25.4.

3.2.10 Syntheis of 2-bromo-6,8-dimethyl-tetralone (124)

General procedure A afforded pure and brown solid product up to 67% yield.

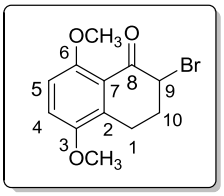


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (s, 1H, H-5), 7.23 (s, 1H, H-3), 4.70 (t, *J* = 4.2 Hz, 1H, H-9), 3.10-2.95 (m, 1H, H-1), 2.88-2.78 (m, 1H, H-1), 2.56-2.42 (m, 2H, H-10), 2.33 (s, 3H, CH_3), 2.30 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 191.3, 138.3, 138.4, 136.7, 136.3, 129.8, 126.5, 50.3, 31.2, 23.0, 20.8, 19.4.

3.2.11 Synthesis of 2-bromo-5,8-dimethoxy-tetralone (125)

General procedure A afforded pure and black product with the lowest yield as up to 40%.

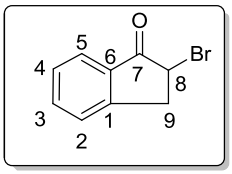


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, $J_{5,4}$ = 9.0 Hz, 1H, H-5), 6.83 (d, $J_{4,5}$ = 9.0 Hz, 1H, H-4), 4.63 (t, *J* = 4.1 Hz, 1H, H-9), 3.86 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.06-2.98 (m, 2H, H-1), 2.63-2.26 (m, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 189.9, 150.1, 150.0, 133.4, 120.0, 116.1, 110.3, 56.4, 55.9, 52.3, 25.4, 20.5.

3.2.12 Synthesis of 2-bromo-indanone (116)

General procedure A afforded pure and white crystals up to 65% yield.

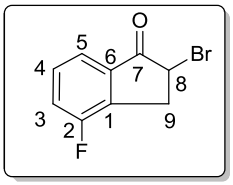


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, *J*=7.6 Hz, 1H, H-5), 7.67 (dt, $J_{3,4}$ = 7.7, $J_{3,2}$ = 7.6, $J_{3,5}$ = 1.2 Hz, 1H, H-3), 7.51-7.37 (m, 2H, H-2,4), 4.66 (dd, J_1 = 7.5, J_2 = 3.22 Hz, 1H, H-8), 3.83 (dd, J_1=18.1, J_2=7.5 Hz, 1H, H-9), 3.42 (dd, J_1 = 18.1, J_2 = 3.1 Hz, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 199.5, 151.2, 136.0, 133.5, 128.3, 126.5, 124.9, 44.3, 37.97.

3.2.13 Synthesis of 2-bromo-4-fluoro-indanone (126)

General procedure A afforded pure and light white crystals up to 70%.

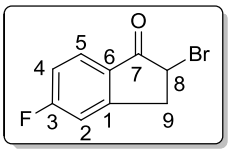


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.66 (d, *J* =7.57 Hz, 1H, H-5), 7.50-7.42 (m, 1H, H-3), 7.39-7.33 (m, 1H, H-4), 4.67 (dd, J_1=7.5, J_2=3.1 Hz, 1H, H-8), 3.86 (dd, J_1=18.4, J_2=7.5 Hz, 1H, H-9), 3.43 (dd, J_1=18.4, J_2=3.0 Hz, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 197.4, 158.61 (d, J_{CF} = 251.43 Hz,C-2), 135.99 (d, *J* = 19.33 Hz,C-6), 135.17 (d, *J* = 4.69 Hz,C-5), 129.31 (d, *J* = 6.29 Hz,C-4), 120.99 (d, *J* = 19.91 Hz, C-1), 119.86 (d, *J* = 4.03 Hz,C-3), 43.3, 33.9.

3.2.14 Synthesis of 2-bromo-5-fluoro-indanone (127)

General procedure A afforded pure light yellow product up to 60%.

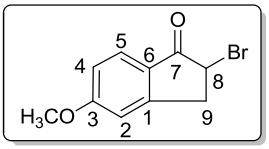


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87-7.59 (m, 1H, H-5), 7.14-6.91 (m, 2H, H-2,4), 4.71-4.47 (m, 1H, H-8), 3.76 (dd, J_1=18.36, J_2=7.51 Hz, 1H, H-9), 3.38-3.23 (m, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 197.6, 167.8 (d, J_{CF}= 258.42 Hz, C-3), 154.1 (d, J = 10.47 Hz,C-1), 129.9 (broad s,C-6), 127.4 (d, J = 10.55 Hz, C-5), 116.6 (d, J = 23.82 Hz,C-2) , 113.3 (d, J = 22.73 Hz,C-4), 43.9, 37.8.

3.2.15 Synthesis of 2-bromo-5-methoxy-indanone (128)

General procedure A afforded pure and white crystal up to 70% yield.



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, J=8.6 Hz, 1H, H-5), 6.89 (dd, $J_{4,5}$ = 8.6, $J_{4,2}$ = 1.9 Hz, 1H, H-4), 6.81-6.77 (m, 1H, H-2), 4.57 (dd, J_1=7.5, J_2=3.1 Hz, 1H, H-8), 3.83 (s, 3H, OCH_3), 3.72 (dd, J_1=18.1, J_2 = 7.5 Hz, 1H, H-9), 3.31 (dd, J_1 = 18.1, J_2=2.9 Hz, 1H, H-9).

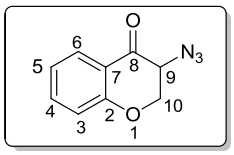
^{13}C NMR (100 MHz, $CDCl_3$): 196.9, 165.6, 153.4, 126.1, 125.9, 115.6, 108.8, 55.1, 43.9, 37.3.

3.3 General Procedure B for Preparation α-Azido Ketones

3.3.1 Synthesis of Synthesis of 3-Azidochroman-4-one (129) [35]

(908 mg) 3-bromochroman-4-one **(114)** (3.9 mmol) was dissolved in acetone (20 mL) in a (100 mL) flask. To this solution, sodium azide (513 mg, 7.9 mmol) and 18-crown-6 (208 mg, 0.79 mmol) were added respectively at room temperature. The resulting solution was stirred overnight at room temperature. After evaporation of the solvent the residue was dissolved in ethyl acetate and extracted with brine (25 mL), and the organic layer was dried over $MgSO_4$ and concentrated in vacuo. After evaporation of the solvent the residue was dissolved in a minimum amount of CH_2Cl_2 for column chromatography on silica gel.

The column was eluted with hexane: ethylacetate (95: 5) and the residue was collected. After the combination of all parts 600mg (82%) of product (yellow crystals) was obtained after drying. Melting point of this compound was 86 ^{o}C according to literature data. IR (ATR) spectra showed the azide peak at 2110 cm^{-1}.



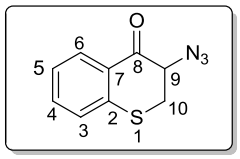
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94-7.89 (m, 1H, H-6), 7.56-7.49 (m, 1H, H-5), 7.11-7.05 (m, 1H, H-4), 7.01-6.97 (m, 1H, H-3), 4.51 (ddd, J_1 = 11.2, J_2 = 4.9, J_3 = 1.5 Hz, 1H, H-10), 4.39 (ddd, J_1 = 10.4, J_2 = 4.9, J_3 = 1.2 Hz, 1H, H-10), 4.28-4.20 (m, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 188.6, 161.4, 136.8, 127.7, 122.2, 119.4, 117.9, 68.9, 60.1.

3.3.2 Synthesis of 3-Azido-1-thiochroman-4-one (132) [35]

According to general procedure B; starting from 3-bromo-1-thiochroman-4-one **(117)** afforded pure product **(132)**. (70% yield, yellow crystals). (m.p.: 85-86 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



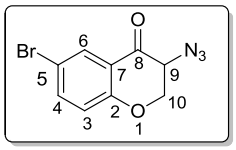
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (dd, $J_{6,5}$ = 8.0, $J_{6,4}$ = 1.3 Hz, 1H, H-6), 7.48-7.40 (m, 1H, H-4), 7.29-7.21 (m, 2H, H-3,5), 4.53 (dd, J_1 = 12.7, J_2 = 4.3 Hz, 1H, H-9), 3.38 (t, J = 12.9, 1H, H-10), 3.15 (dd, J_1 = 13.14, J_2 = 4.27 Hz, 1H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 186.3, 154.9, 130.2, 127.3, 126.6, 125.6, 112.4, 63.7, 30.9 ppm.

3.3.3 Synthesis of 3-Azido-6-Bromochroman-4-one (133)

According to general procedure B; starting from 3-6-dibromo-chroman-4-one **118** afforded pure product **133**. (75% yield, light yellow crystals). (m.p.: 93 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2110 cm^{-1}.



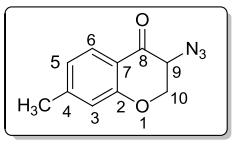
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (d, J = 2.5 Hz, 1H, H-6), 7.60 (dd, $J_{3,4}$ = 8.8, $J_{4,6}$ = 2.5 Hz, 1H, H-4), 6.91 (d, J = 8.8 Hz, 1H, H-3), 4.57-4.19 (m, 3H, H-9,10).

^{13}C NMR (100 MHz, $CDCl_3$): 187.4, 160.3, 139.4, 130.0, 120.7, 120.0, 114.9, 68.9, 59.8.

3.3.4 Synthesis of 3-Azido-7-methylchroman-4-one (134)

According to general procedure B; starting from 3-bromo-7-methylchroman-4-one (**119)** afforded pure product (**134)**. (85% yield, dark yellow crystals). (m.p.: 86 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2080 cm^{-1}.



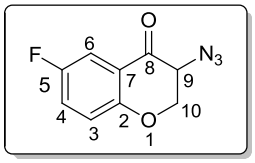
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, $J_{5,3}$ = 1.3 Hz, 1H, H-3), 7.34 (dd, $J_{5,6}$ = 8.4, $J_{5,3}$ = 2.1 Hz, 1H, H-5), 6.90 (d, $J_{5,6}$ = 8.5 Hz, 1H, H-6), 4.48 (dd, J_1 = 11.1, J_2 = 4.8 Hz, 1H, H-10), 4.36 (dd, J_1 = 10.2, J_2 = 4.8 Hz, 1H, H-10), 4.23 (dd, J_1 = 10.9, J_2 = 10.4 Hz, 1H, H-9), 2.33 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): 188.4, 158.8, 137.2, 131.1, 127.0, 126.4, 117.1, 68.3, 59.5, 19.7.

3.3.5 Synthesis of 3-Azido-6-fluorochroman-4-one (135)

According to general procedure B; starting from 3-bromo-6-fluorochroman-4-one **120** afforded pure product **135**. (75% yield, yellow crystals). (m.p.: 76 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2118 cm^{-1}.



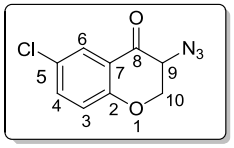
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (dd, $J_{4,3}$ = 8.0, $J_{4,6}$ = 3.2 Hz, 1H, H-4), 7.29-7.23 (m, 1H, H-6), 6.99 (dd, J_1 = 9.1, J_2 = 4.14 Hz, 1H, H-3), 4.57-4.15 (m, 3H, H-9,10).

^{13}C NMR (100 MHz, $CDCl_3$): 187.9, 157.62 (d, J_{CF} = 243.39 Hz,C-5), 157.69 (d, J = 1.32 Hz,C-2), 124.48 (d, J = 24.91 Hz,C-7), 119.88 (d, J = 7.77 Hz, C-4), 119.75 (d, J = 7.49 Hz, C-3), 112.57 (d, J = 23.61 Hz, C-6), 69.1, 59.9.

3.3.6 Synthesis of 3-Azido-6-chlorochroman-4-one (136) [35]

According to general procedure B; starting from 3-bromo-6-chlorochroman-4-one (**121)** afforded pure product (**136)**. (80% yield, light yellow crystals). (m.p.: 85 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



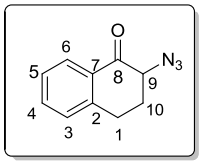
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, $J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.47 (dd, $J_{4,3}$ = 8.9, $J_{4,6}$ = 2.6 Hz, 1H, H-4), 6.97 (d, $J_{3,4}$ = 8.8 Hz, 1H, H-3), 4.52 (dd, J_1 = 11.3, J_2 = 4.8 Hz, 1H, H-10), 4.39 (dd, J_1 = 10.2, J_2 = 4.8 Hz, 1H, H-10), 4.26 (dd, J_1 = 11.0, J_2 = 10.4 Hz, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 187.5, 159.8, 136.7, 127.9, 126.9, 120.2, 119.7, 69.0, 59.8.

3.3.7 Synthesis of 2-Azido -alpha tetralone (130)

According to general procedure B; starting from 2-bromo-alpha tetraloneone (**115)** afforded pure product (**130)**. (70% yield, dark green oily).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



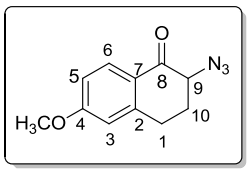
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (dd, $J_{5,6}$ = 7.9, $J_{4,6}$ = 1.01 Hz, 1H, H-6), 7.51 (dt, J_1=7.5, J_2=1.4 Hz, 1H, H-4), 7.34 (t, J = 7.6, 1H, H-5), 7.30-7.22 (m, 1H, H-3), 4.75-4.68 (m, 1H, H-9), 3.36-3.25 (m, 1H, H-1), 3.00-2.85 (m, 1H, H-1), 2.58-2.40 (m, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 190.6, 143.0, 134.2, 129.9, 128.8, 128.6, 127.13, 50.5, 31.9, 26.2.

3.3.8 Synthesis of 2-Azido-6-methoxy-tetralone (137)

According to general procedure B; starting from 2-bromo-6-methoxy-tetralone **122** afforded pure product (**137)**. (70% yield, dark brown solid particles). (m.p.: 58-60 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.

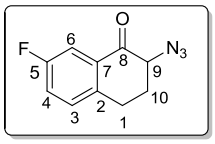


^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70 (dd, $J_{5,6}$ = 7.9, $J_{3,6}$ = 0.8 Hz, 1H, H-6), 7.31 (t, J = 8.0 Hz, 1H, H-3), 7.06 (dd, $J_{6,5}$ = 8.1, $J_{5,3}$ = 0.9 Hz, 1H, H-5), 4.71 (t, J = 4.4 Hz, 1H, H-9), 3.88 (s, 3H, OCH_3), 3.06-2.98 (m, 2H, H-1), 2.50-2.45 (m, 2H, H-10).
^{13}C NMR (100 MHz, $CDCl_3$): 190.8, 156.6, 132.1, 127.3, 120.1, 114.9, 114.8, 55.7, 50.3, 31.1, 19.9 ppm.

3.3.9 Synthesis of 2-Azido-7-fluoro-tetralone (138)

According to general procedure B; starting from 2-bromo-7-fluoro-tetralone **123** afforded pure product (**138)**. (65% yield, dark brown crytals). (m.p.: 43-45 ^oC).

IR (ATR) spectra showed the azide peak at around 2110 cm^{-1}.



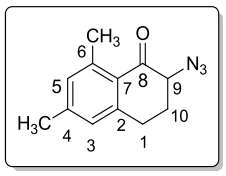
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (dd, $J_{3,4}$ = 8.9, $J_{4,6}$ = 2.6 Hz, 1H, H-4), 7.32-7.19 (m, 2H, H-3,6), 4.72 (t, J = 4.1 Hz, 1H, H-9), 3.35-3.17 (m, 1H, H-1), 2.91 (td, J_1 = 17.0, J_2 = 4.2 Hz, 1H, H-1), 2.58-2.39 (m, 2H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 189.6, 161.6 (d, J_{CF} = 247.07 Hz, C-5), 138.76 (d, J = 2.84 Hz, C-2), 131.5 (d, J = 6.33 Hz,C-7), 130.7 (d, J = 7.20 Hz,C-3), 121.6 (d, J = 22.11 Hz, C-4), 114.3 (d, J = 22.13 Hz,C-6), 49.7, 31.7, 25.4 .

3.3.10 Synthesis of 2-Azido-6,8-dimethyl-tetralone (139)

According to general procedure B; starting from 2-bromo-6,8-dimethyl-tetralone **124** afforded pure product (**139)**. (70% yield, brown solid particles). (m.p.: 66-68 ^oC).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



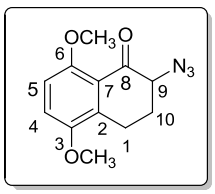
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (s, 1H, H-3), 7.23 (s, 1H, H-5), 4.21 (dd, J_1 = 12.5, J_2 = 4.6 Hz, 1H, H-9), 3.00 (td, J_1 = 17.3, J_2 = 4.4, Hz, 1H, H-1), 2.90-2.76 (m, 1H, H-1), 2.43-2.35 (m, 1H, H-10), 2.34 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.19-2.04 (m, 1H, H-10).

^{13}C NMR (100 MHz, $CDCl_3$): 196.6, 138.7, 136.6, 136.5, 136.3, 136.2, 125.9, 64.0, 28.7, 24.6, 20.8, 19.2.

3.3.11 Synthesis of 2-Azido-5,8-dimethoxy-tetralone (140)

General procedure B; starting from 2-bromo-5,8-dimethoxy-tetralone **125** afforded pure product **140.** (60% yield, dark brown oily product.

IR (ATR) spectra showed the azide peak at around 2080 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (dd, J_1=9.06, J_2=4.70 Hz, 1H, H-4), 6.83 (d, $J_{4,5}$ = 8.9 Hz, 1H, H-5), 4.70-4.07 (m, 1H, H-9), 3.87 (d, J = 3.51 Hz, 3H, OCH_3), 3.83 (d, J = 5.5 Hz, 3H, OCH_3), 3.23-2.69 (m, 2H, H-1), 2.54-1.92 (m, 2H, H-10).

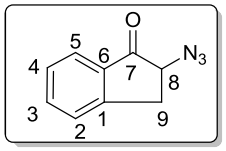
^{13}C NMR (100 MHz, $CDCl_3$): 196.1, 155.6, 155.2, 150.1, 133.4, 116.1, 110.4,

64.9, 56.4, 55.9, 53.4, 20.5.

3.3.12 Synthesis of 2-Azido- indanone (131)

General procedure B; starting from 2-bromo-indanone **(116)** afforded pure product (**131).** (70% yield, light white crytals). (m.p.: 45-47 ^{o}C)

IR (ATR) spectra showed the azide peak at around 2084 cm^{-1}.



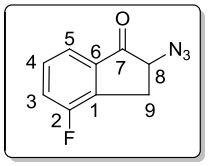
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, J=7.62 Hz, 1H, H-5), 7.60 (t, J_1=7.45, J_2=7.45 Hz, 1H, H-3), 7.48-7.29 (m, 2H, H-2,4), 4.59 (dd, J_1 = 7.5, J_2 = 3.2 Hz, 1H, H-8), 3.77 (dd, J_1 = 18.1, J_2 = 7.5 Hz, 1H, H-9), 3.35 (dd, J_1 = 18.1, J_2 = 3.0 Hz, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 203.2, 151.2, 136.1, 134.2, 128.3, 126.6, 124.7, 62.0, 33.0.

3.3.13 Synthesis of 2-Azido-4-fluoro-indanone (141)

General procedure B; starting from 2-bromo-4-fluoro-indanone **126** afforded pure product **141.** (70% yield, light yellow crytals). (m.p.: 61-63 ^{o}C)

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



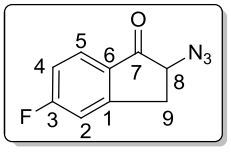
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, J=7.51 Hz, 1H, H-5), 7.43-7.33 (m, 1H, H-3), 7.31-7.24 (m, 1H, H-4), 3.17 (m, 1H, H-8), 2.77-2.71 (m, 2H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 205.58, 160.22 (d, J_{CF} = 250.25 Hz, C-2), 140.84 (d, J = 19.43 Hz, C-4), 139.99 (d, J = 4.95 Hz, C-6), 129.31 (d, J = 6.36 Hz, C-1), 120.63 (d, J = 19.95 Hz, C-3), 119.50 (d, J = 3.80 Hz, C-5), 35.9, 21.6.

3.3.14 Synthesis of 2-Azido-5-fluoro-indanone (142)

General procedure B; starting from 2-bromo-5-fluoro-indanone **127** afforded pure product **142.** (60% yield, white oily product).

IR (ATR) spectra showed the azide peak at around 2110 cm^{-1}.



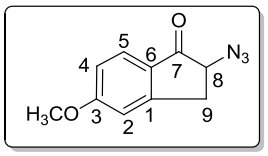
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (dd, $J_{4,5}$ = 9.0, $J_{2,4}$ = 5.3 Hz, 1H, H-4), 7.20-7.04 (m, 2H, H-2,5), 4.34 (dd, J_1 = 8.1, J_2 = 4.5 Hz, 1H, H-8), 3.50 (dd, J_1 = 17.4, J_2 = 8.1 Hz, 1H, H-9), 2.92 (dd, J_1 = 17.4, J_2 = 4.4 Hz, 1H, H-9)

^{13}C NMR (100 MHz, $CDCl_3$): 199.8, 167.9 (d, J_{CF} = 256.28 Hz,C-3), 154.2 (d, J = 10.71 Hz, C-1), 130.6 (d, J = 1.37 Hz,C-6), 127.2 (d, J = 10.70 Hz, C-5), 116.7 (d, J = 23.91 Hz, C-2), 113.4 (d, J = 22.70 Hz,C-4), 61.9, 32.9 .

3.3.15 Synthesis of 2-Azido-5-methoxy-indanone (143)

General procedure B; starting from 2-bromo-5-methoxy-indanone **128** afforded pure product **143.** (65% yield, yellow solid particles). (m.p.: 78 ^{o}C).

IR (ATR) spectra showed the azide peak at around 2100 cm^{-1}.



^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76-7.66 (m, 1H, H-4), 6.93 (d, $J_{4,5}$ = 8.4 Hz, 1H, H-5), 6.86 (s, 1H, H-2), 4.46-4.08 (m, 1H, H-8), 3.89 (d, J = 2.1 Hz, 3H, OCH_3), 3.44 (dd, J_1 = 17.1, J_2 = 8.0 Hz, 1H, H-9), 2.93-2.78 (m, 1H, H-9).

^{13}C NMR (100 MHz, $CDCl_3$): 199.6, 166.4, 154.3, 127.3, 126.5, 116.3, 109.7, 62.1, 55.8, 33.1.

3.4 General Procedure C for Deracemization of Alpha Azido Ketones

The same general procedure C was applied for fifteen derivatives of α-azido ketones.

(19 mg) 3-azidochroman-4-one (0.1 mmol) was dissolved in (0.5 mL) of dry acetonitrile in a reaction tube. To this solution, 10% mmol of cinchona base was added slowly at room temperature. Then (12mg) 0.12 mmol of potassium bicarbonate an additional base is added in the reaction medium.The resulting solution was stirred at room temperature. The changes in enantiomeric purity were monitored by using OD-H and AD-H chiral HPLC columns. Hexane/2-propanol mixture was used as column solvent. Minimum amount of sample was taken from the reaction medium day by day and dissolved in hexane/2-propanol (90/10) to analyze by using chiral HPLC. And after 3 days the formation of desired products were seen. The racemic starting materials were started to be changed as enantiomerically pure products. The reactions were completed in different times and each one was monitored by using chiral columns. After completing the reactions the solvent was removed *in vacuo*. The residue was dissolved in a minimum amount of CH_2Cl_2 for column chromatography on silica gel. The column was eluted with hexane: ethylacetate (95: 5) and the residue was collected. The starting material and the product were same in these deracemization reactions so; only the HPLC results were get. For these deracemization reactions, the yields were changed between 60-90 % and the yields were shown in table **1,2,3** for each derivative.

The chiral form of 3-Azidochroman-4-one **(129)** was obtained up to 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 9.93 for major and t_R: 11.48 for minor peaks. $[\alpha]_D$: +2.67.

The chiral form of 3-Azido-1-thiochroman-4-one **(132)** was obtained up to 39 % ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R:10.15 for major and t_R: 9.84 for minor peaks. $[\alpha]_D$: -1.3.

The chiral form of 3-Azido-6-Bromochroman-4-one **(133)** was obtained in a maximum of > 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 13.17 for major peak. $[\alpha]_D$ +17.5.

The chiral form of 3-Azido-7-methylchroman-4-one **(134)** was obtained up to 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 8.89 for major and t_R:8.46 for minor peaks. $[\alpha]_D$ +5.25.

The chiral form of 3-Azido-6-fluorochroman-4-one **(135)** was obtained up to 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 14.35 for major and t_R: 15.19 for minor peaks. $[\alpha]_D$ +3.75.

The chiral form of 3-Azido-6-chlorochroman-4-one **(136)** was obtained up to 99% ee. The optical purity was determined by HPLC on chiralpak AD-H chiral column [hexane/2-propanol 99:1]; flow rate 0.5 mL/min. t_R: 42.55 for major and t_R: 46.95 for minor peaks. $[\alpha]_D$ -5.89.

The chiral form of 2-Azido -alpha tetralone **(130)** was obtained up to 19% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 9.46 for major and t_R: 8.84 for minor peaks. $[\alpha]_D$ -0.074.

The chiral form of 2-Azido-6-methoxy-tetralone **(137)** was obtained up to 70% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 15.16 for major and t_R: 14.44 for minor peaks. $[\alpha]_D$ +12.7.

The chiral form of 2-Azido-7-fluoro-tetralone **(138)** was obtained up to 26% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 15.33 for major and t_R: 14.58 for minor peaks. $[\alpha]_D$ +6.5.

The chiral form of 2-Azido-6,8-dimethyl-tetralone **(139)** was obtained up to 70% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 8.14 for major and t_R: 7.55 for minor peaks. $[\alpha]_D$ +6.7.

The chiral form of 2-Azido-5,8-dimethoxy-tetralone **(140)** was obtained up to 48% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 99:1]; flow rate 1 mL/min. t_R: 28.2 for major and t_R: 31.5 for minor peaks. $[\alpha]_D$ -1.34.

The chiral form of 2-Azido- indanone **(131)** was obtained in a maximum of > 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 12.08 for major peak. $[\alpha]_D$ -6.1.

The chiral form of 2-Azido-4-fluoro-indanone **(141)** was obtained up to 98% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min. t_R: 12.09 for major and t_R: for minor peaks. $[\alpha]_D$ +4.23.

The chiral form of 2-Azido-5-fluoro-indanone **(142)** wasobtained in a maximum of > 99% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min.. t_R: 11.33 for major peak. $[\alpha]_D$ +7.5.

The chiral form of 2-Azido-5-methoxy-indanone (**143)** was obtained up to 93% ee. The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 98:2]; flow rate 1 mL/min.t_R: 17.85 for major and t_R: 16.95 for minor peaks. $[\alpha]_D$ +2.5.

The HPLC chromatograms of products are shown in Appendix B. The enantiomeric ratios, yields and the times that the reactions were performed with different bases are given in tables 1, 2, and 3.

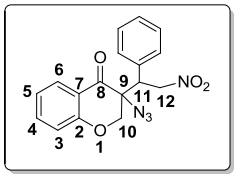
3.5 General Procedure D for Addition of β-Nitrostyrene to Chromanones

3.5.1 Synthesis of 3-azido-3-(2-nitro-1-phenylethyl) chroman-4-one (150)

90 mg (0.5mmol) of 3-azido-chroman-4-one was dissolved in dry acetonitrile at -20 ^{o}C. Then 29 mg (0.05 mmol, 10%) of urea catalyst was added to the mixture. To this solution, 150 mg (1 mmol) of β-nitrostyrene was added slowly at same temperature. The reaction is monitored by TLC after 1 day and 2 days. Formation of desired products was completed after 2 days. Two diastereomers were formed in the reaction medium. The remaining solvent was removed by rotary.

The residue was dissolved in a minimum amount of CH_2Cl_2 for column chromatography on silica gel. The clomun was eluted with hexane: ethylacetate (95: 5) and the residue was collected. Nearly one diastereomer was obtained at the end of this reaction. The diastereometic ratio was up to 11:1. Yield of this reaction is 75% and the enantiometric excess of it is 94%. The enantiomeric excess was monitored by using chiral HPLC columns. Minimum amount of sample was taken from the product and dissolved in hexane/2-propanol (90/10) to analyze by using chiral HPLC. The column solvent was arranged to 97/3 (hexane/2-propanol) for analysis. IR (ATR) spectra showed the azide peak at around 2110 cm^{-1}.

The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 97:3]; flow rate 0.5 mL/min. t_R: 19.50 for major and t_R: 14.02 for minor peaks. $[\alpha]_D$ -24.1.



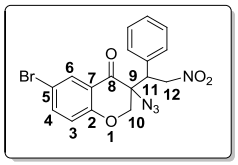
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J_1 = 7.9, J_2 = 1.7 Hz, 1H, H-5), 7.65-7.60 (m, 1H, H-4), 7.44-7.36 (m, 5H, Ph ring), 7.21-7.15 (m, 1H, H-6), 7.07 (dd, J_1 = 8.4, J_2 = 0.6 Hz, 1H, H-3), 5.02-4.78 (m, 2H, H-10), 4.08 (dd, J = 71.6, 11.8 Hz, 2H, H-12), 4.07-3.94 (m, 1H, H-11).

^{13}C NMR (100 MHz, CDCl3) 189.5, 160.9, 137.5, 133.2, 132.7, 129.5, 129.0, 128.9, 128.6, 122.9, 118.8, 118.0, 75.4, 70.6, 67.1, 44.3.

3.5.2 Synthesis of 3-azido-6-bromo-3-(2-nitro-1-phenylethyl) chroman-4-one (151)

General procedure D afforded pure yellow product. At the end of the reaction two diastereomers were obtained and its ratio was 12:1. Yield of this reaction is up to 70% and the enantiometric excess of it is 86%. IR (ATR) spectra showed the azide peak at around 2099 cm^{-1}.

The optical purity was determined by HPLC on chiralpak OD-H chiral column [hexane/2-propanol 97:3]; flow rate 0.5 mL/min. t_R: 29.50 for major and t_R: 8.38 for minor peaks. $[\alpha]_D$ -35.7.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, $J_{6,4}$ = 2.5 Hz, 1H, H-6), 7.70 (dd, $J_{3,4}$ = 8.8, $J_{4,6}$ = 2.5 Hz, 1H, H-4), 7.39 (s, 5H, Ph), 6.99 (d, $J_{3,4}$ = 8.8 Hz, 1H, H-3), 4.97-4.82 (m, 2H, H-10), 4.08 (dd, J_1 = 59.9, J_2 = 11.8 Hz, 2H, H-12), 4.04-3.95 (m, 1H, H-11).

^{13}C NMR (100 MHz, CDCl3) 197.7, 158.7, 139.2, 131.9, 129.8, 128.5, 128.1, 128.0, 119.1, 118.9, 74.3, 69.7, 63.4, 28.7.

CHAPTER 4

CONCLUSION

In this study new deracemization method is developed starting from α-azido ketones by using cinchona alkaloids, up to 98% enantiomeric excesses. In addition to this study Michael addition reactions are carried out with nitrostyrene and α-azido ketones by using cinchona alkaloid-urea derived catalyst in high diastereomeric excesses and enantiomeric excesses. The products are interesting for further modification. Fifteen different types of α-azido ketones were synthesized as the starting materials for deracemization and Michael addition reactions. Firstly chromanone, tetralone and indanone derivatives were brominated and then α-azido ketones were formed. Some of these starting materials were known and some of them were firstly synthesized. The first part of the study is enantioselective deracemization reactions of α-azido ketones by using commercially available or synthesized cinchona alkaloid derivatives. To perform these kinds of reactions firstly cinchona alkaloids were used only in the reaction medium. Much more bulky bases were used because it was thought that base covers one side of ketone and the remaining side is free to make attack. By this way chiral azido ketones were synthesized that are not exist in the literature.

In the second part of the study is asymmetric addition of α-azido ketones to *trans* β-nitro styrene. In this reaction carbonyl group is activated by thiourea catalyst and the acidity of α-proton increases. The diastereomeric ratios are very high for these reactions (1:11, 1:12 de).With the help of cinchona-urea derived catalyst highly enantioselectivities were obtained (94-86% ee).

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APPENDIX A

NMR DATA

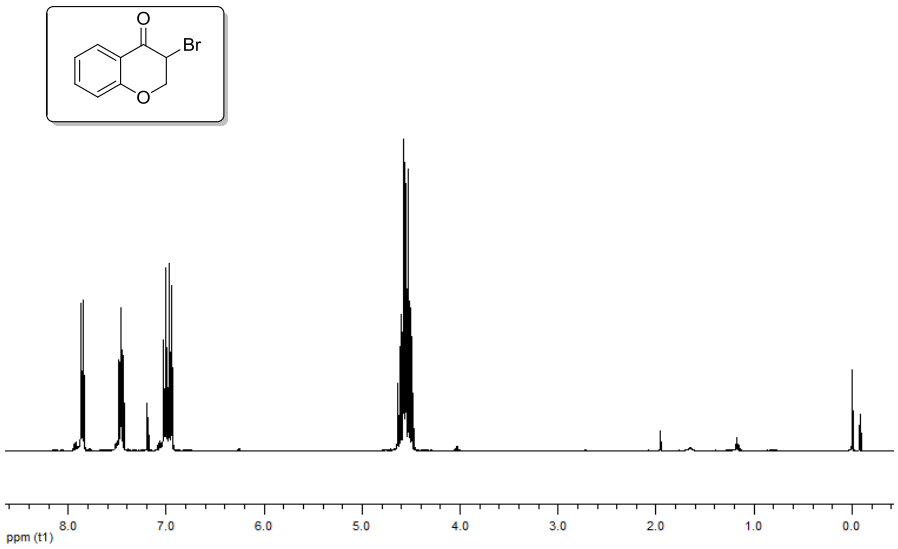


Figure A. 1 ^{1}H-NMR spectrum of **(114)**

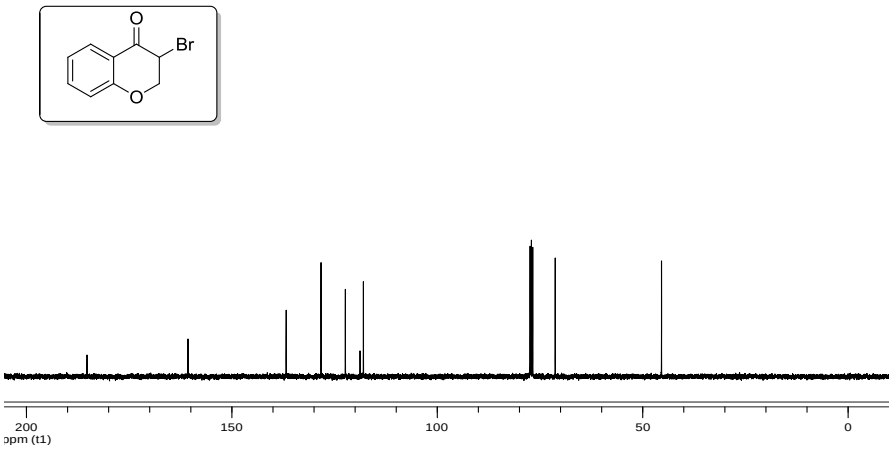


Figure A. 2 ^{13}C-NMR spectrum of **(114)**

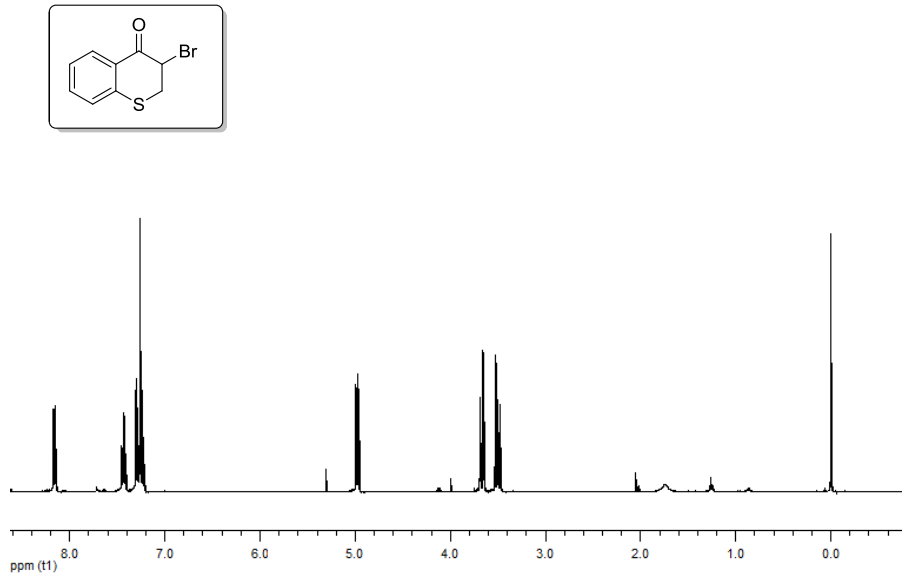


Figure A. 3 ^{1}H-NMR spectrum of **(117)**

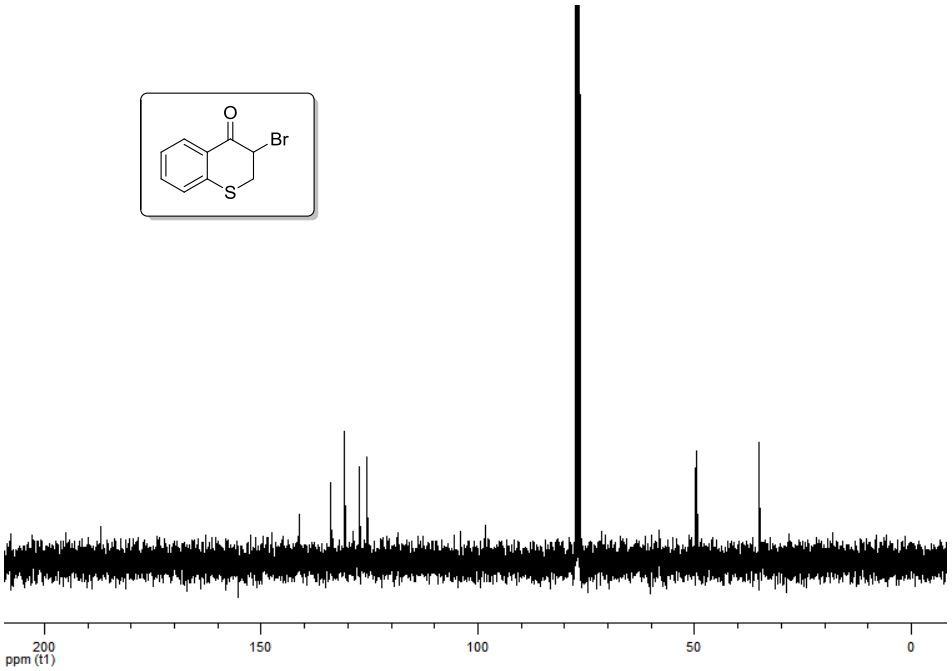


Figure A. 4 ^{13}C-NMR spectrum of **(117)**

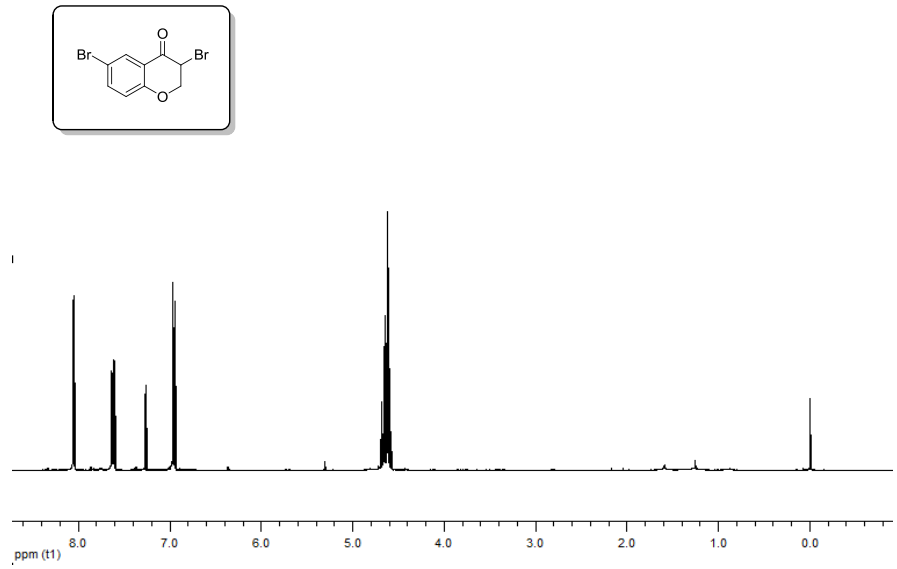


Figure A. 5 ^{1}H-NMR spectrum of **(118)**

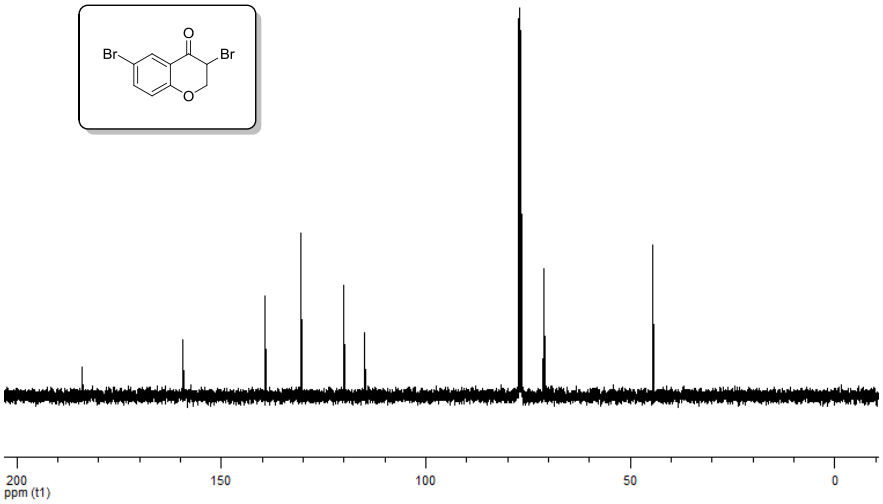


Figure A. 6 ^{13}C-NMR spectrum of **(118)**

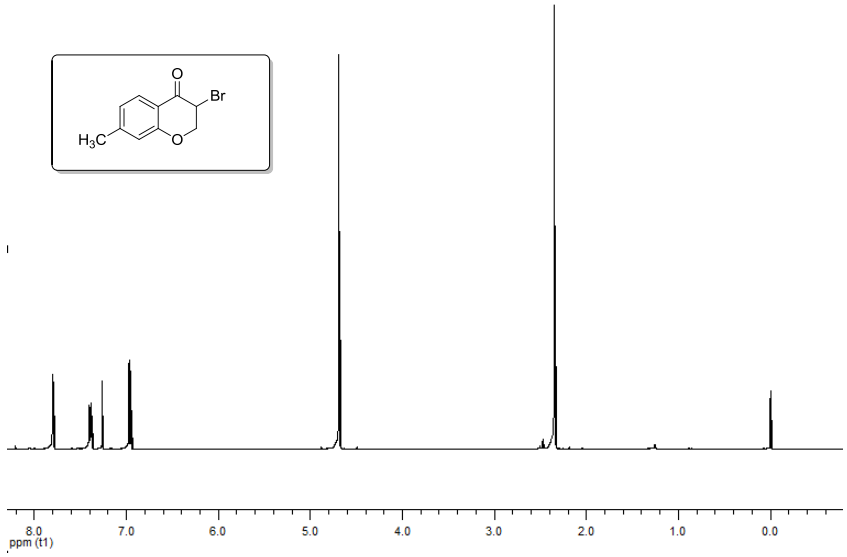


Figure A. 7 ^{1}H-NMR spectrum of **(119)**

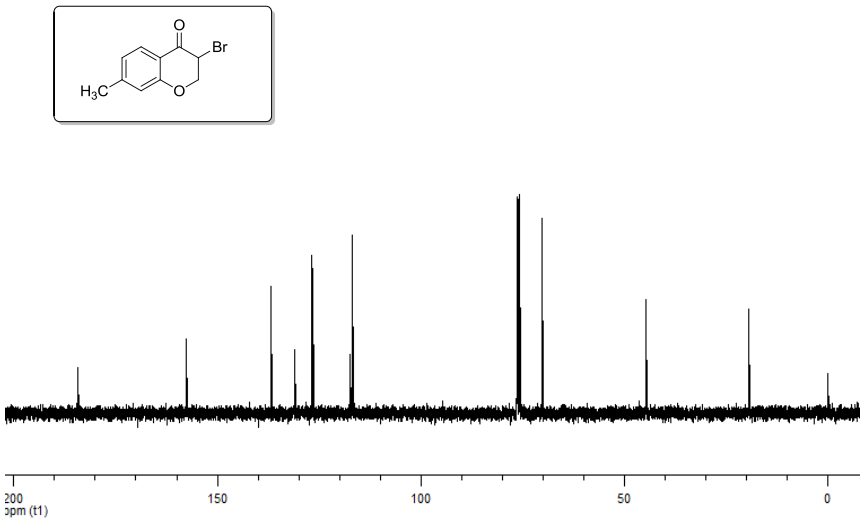


Figure A. 8 ^{13}C-NMR spectrum of **(119)**

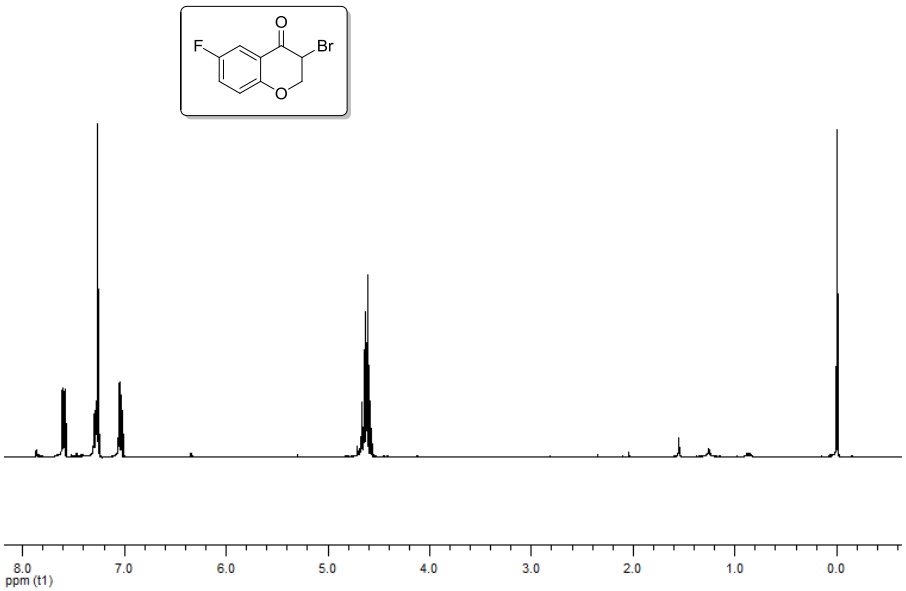


Figure A. 9 ^{1}H-NMR spectrum of **(120)**

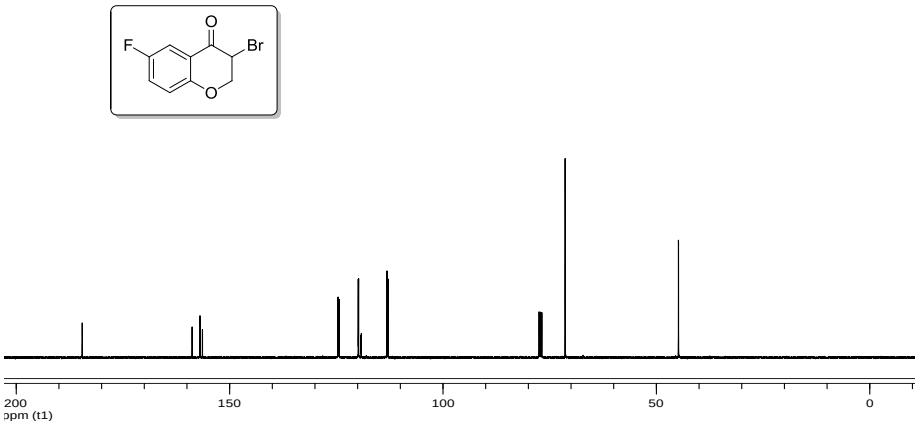


Figure A. 10 ^{13}C-NMR Spectrum of **(120)**

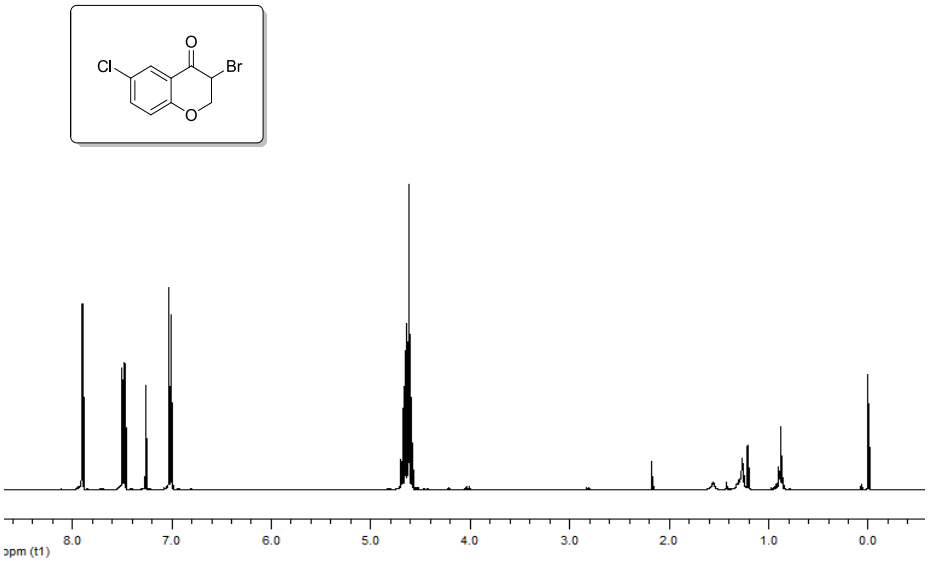


Figure A. 11 [1] H-NMR spectrum of **(121)**

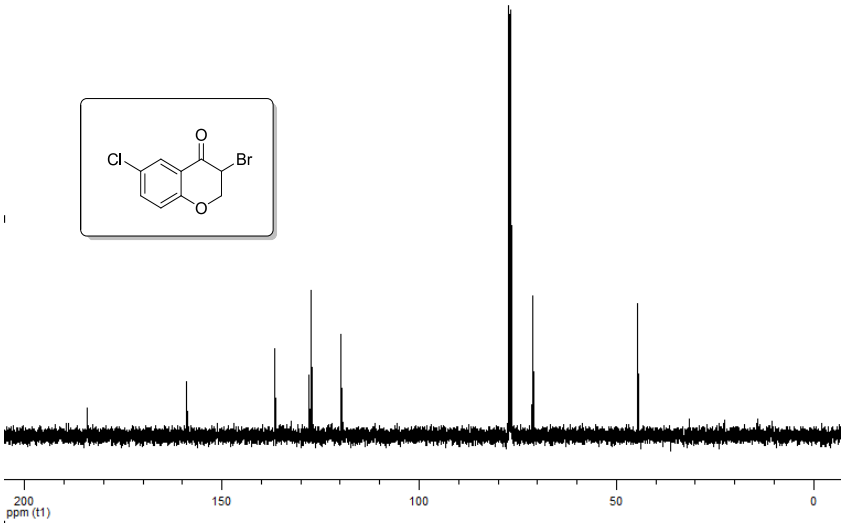


Figure A. 12 [13] C-NMR spectrum of **(121)**

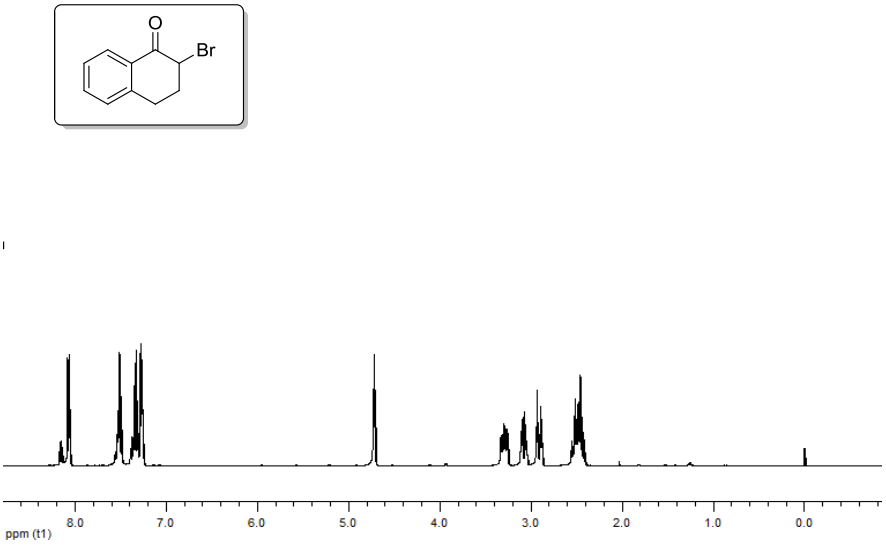


Figure A. 13 ^{1}H-NMR spectrum of **(115)**

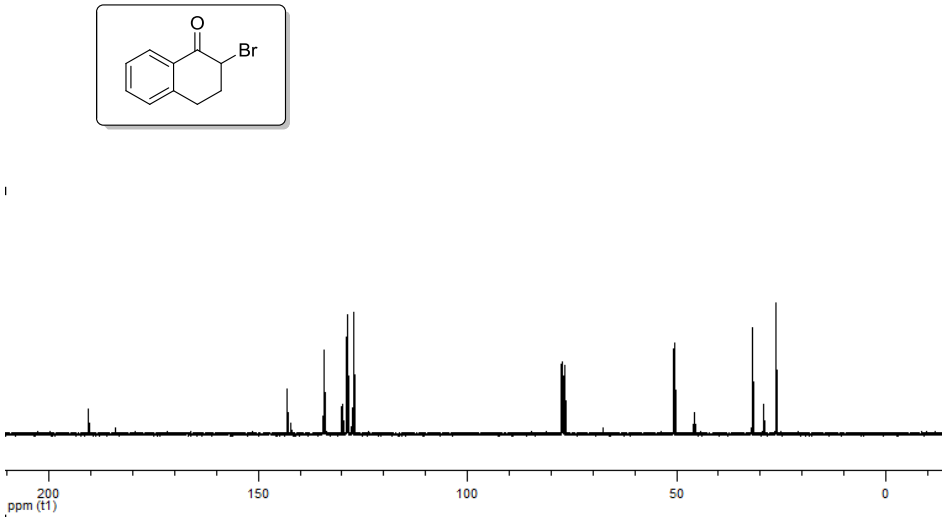


Figure A. 14 ^{13}C-NMR spectrum of **(115)**

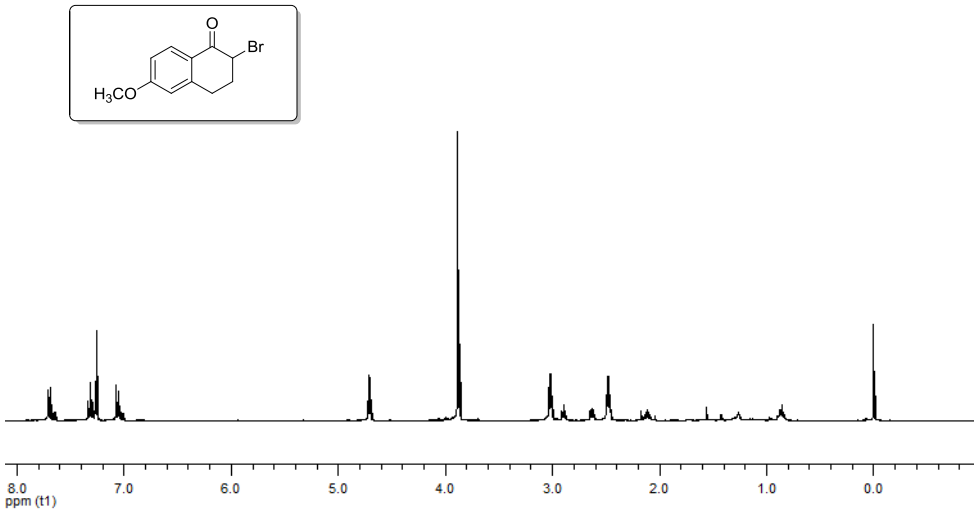


Figure A. 15 ^{1}H-NMR spectrum of **(122)**

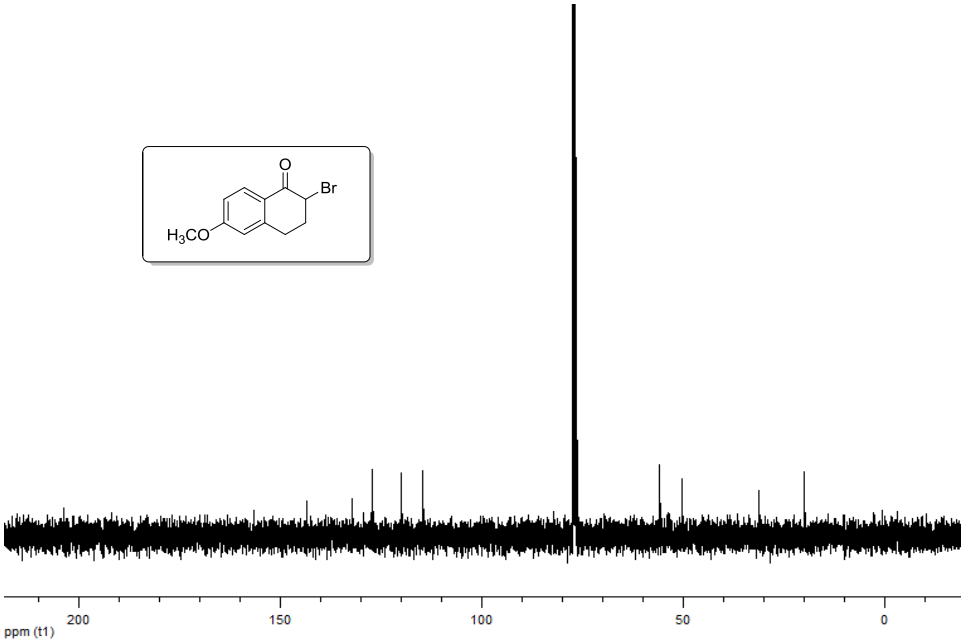


Figure A. 16 ^{13}C-NMR Spectrum of (**122)**

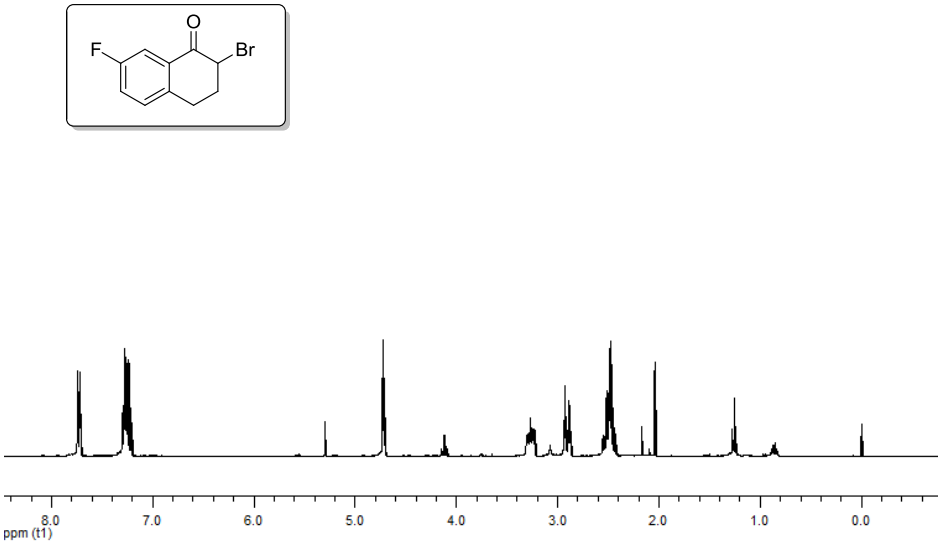


Figure A. 17 ^{1}H-NMR spectrum of **(123)**

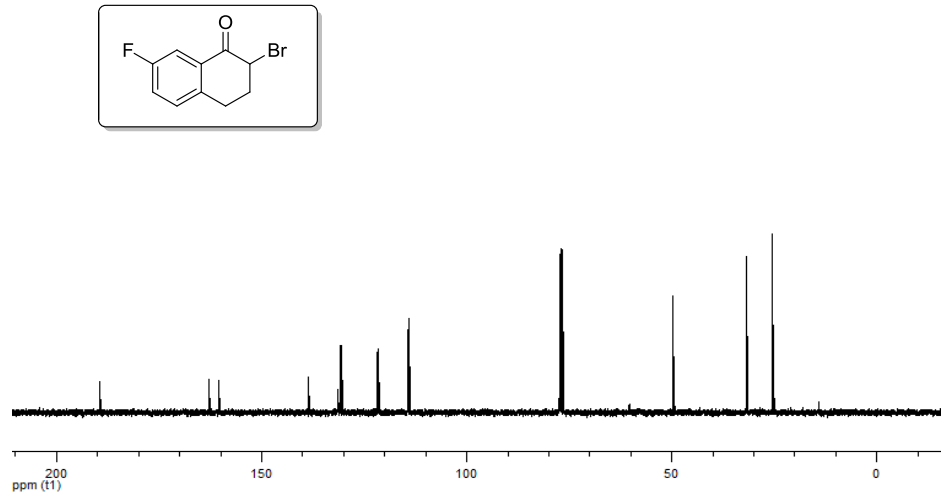


Figure A. 18 ^{13}C-NMR Spectrum of **(123)**

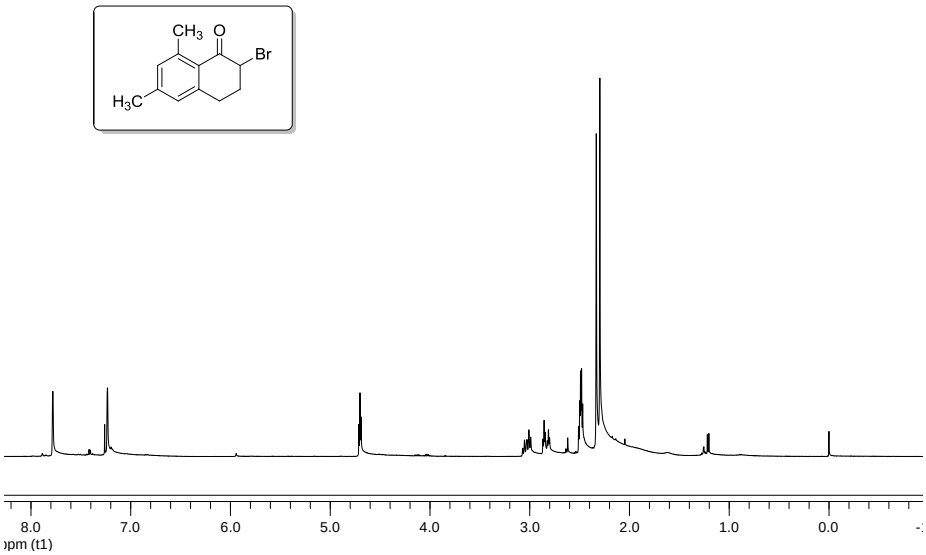


Figure A. 19 ^{1}H-NMR spectrum of **(124)**

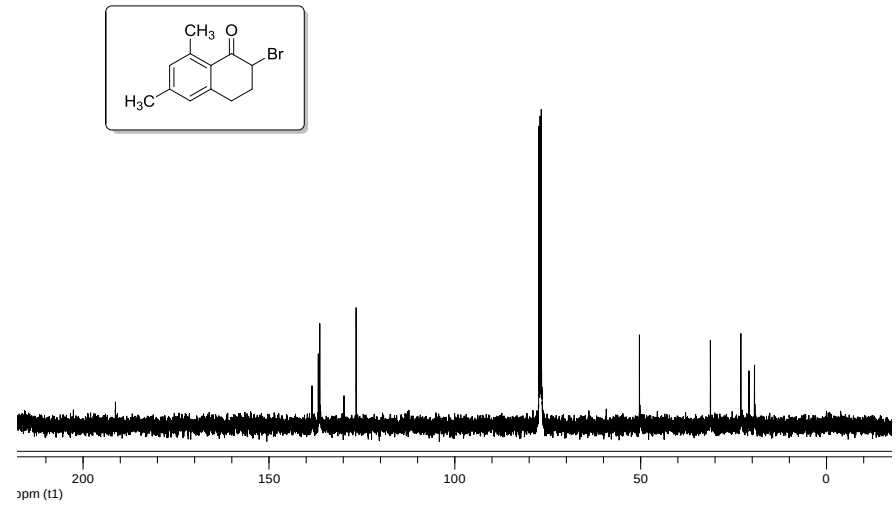


Figure A. 20 ^{13}C-NMR Spectrum of **(124)**

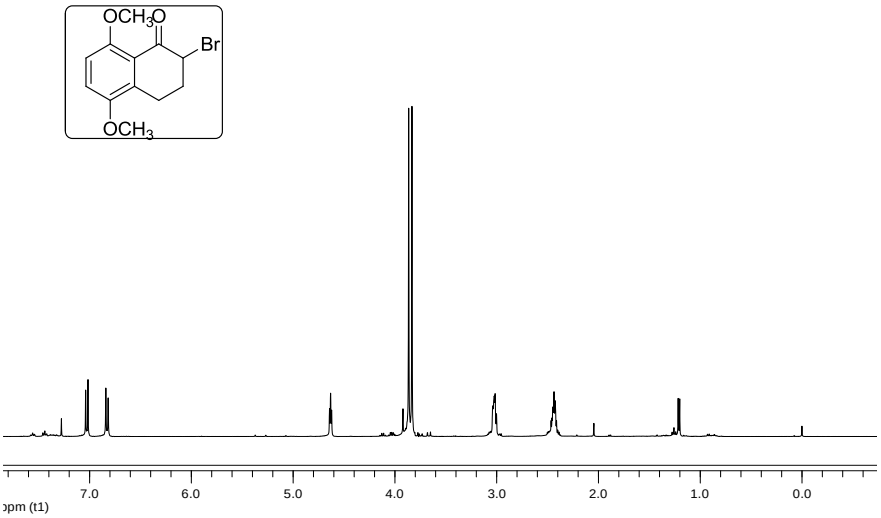


Figure A. 21 ^{1}H-NMR spectrum of **(125)**

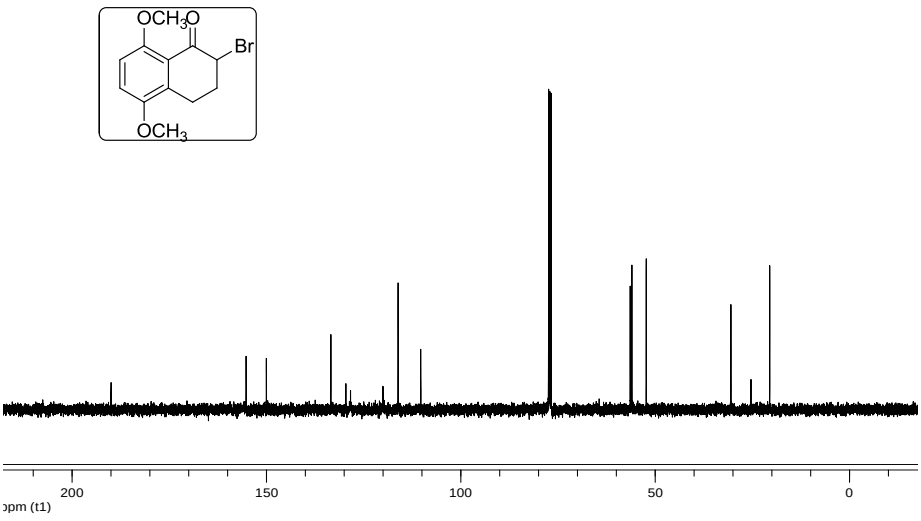


Figure A. 22 ^{13}C-NMR Spectrum of **(125)**

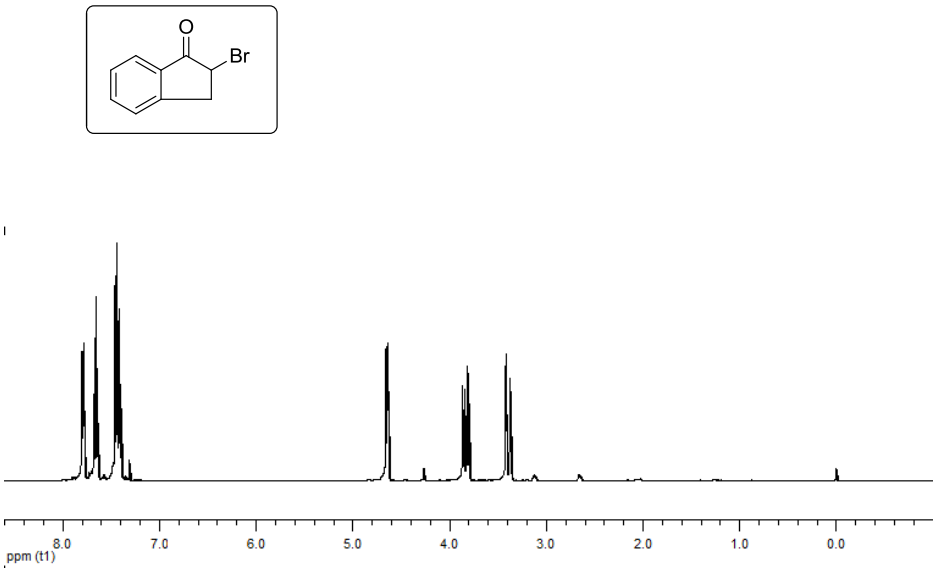


Figure A. 23 ^{1}H-NMR spectrum of **(116)**

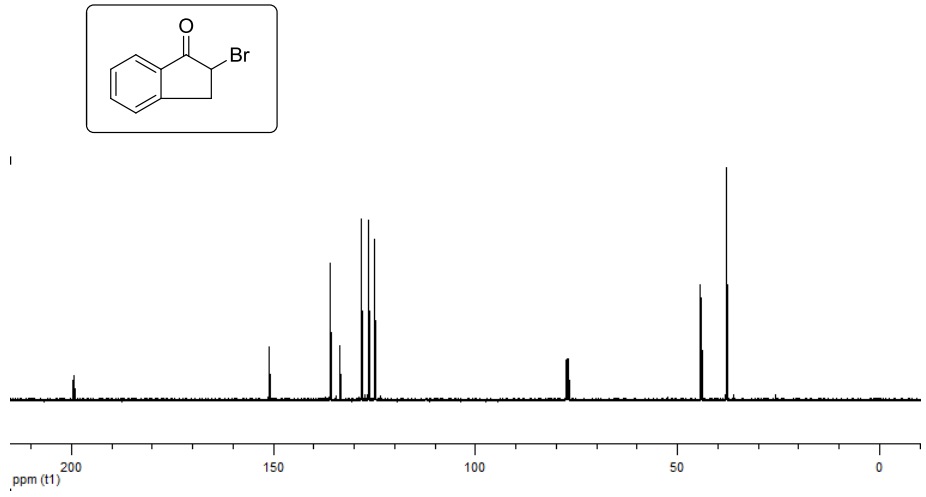


Figure A. 24 ^{13}C-NMR Spectrum of **(116)**

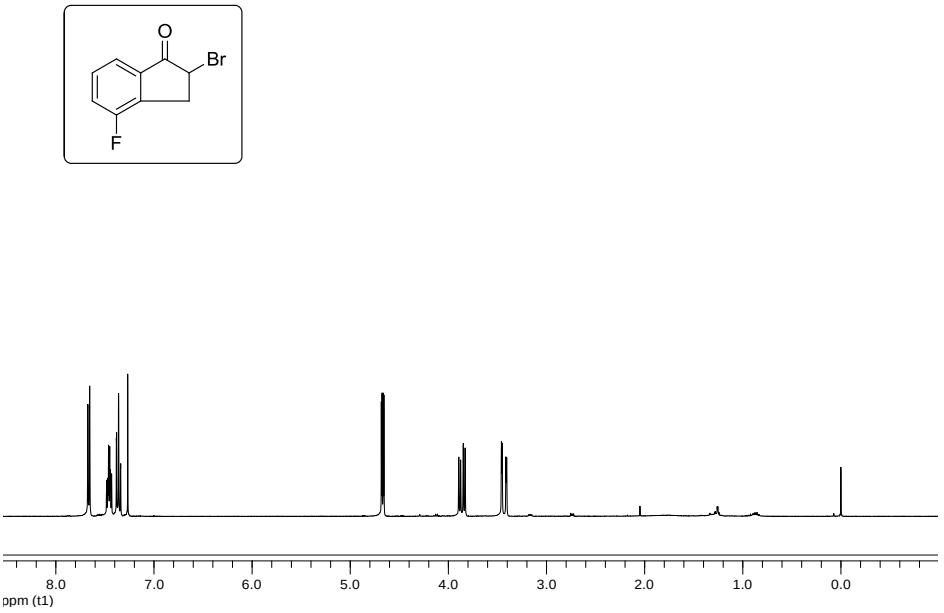


Figure A. 25 ^{1}H-NMR spectrum of **(126)**

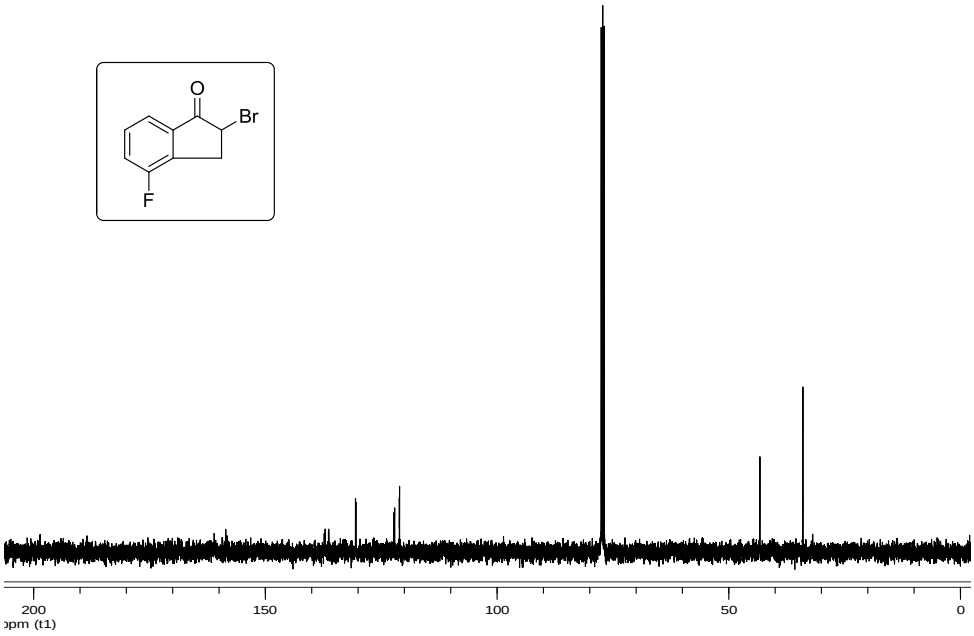


Figure A. 26 ^{13}C-NMR Spectrum of **(126)**

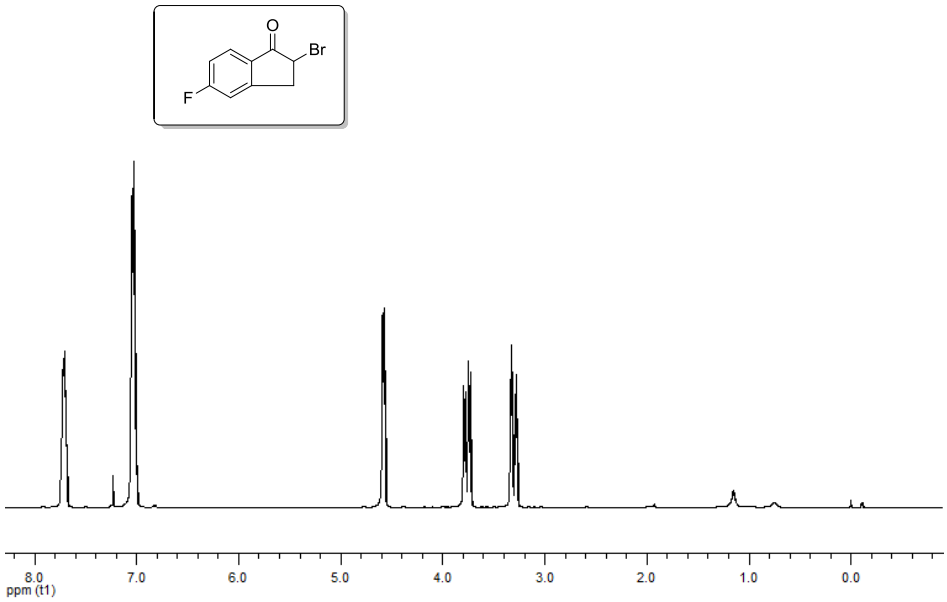


Figure A. 27 ^{1}H-NMR spectrum of **(127)**

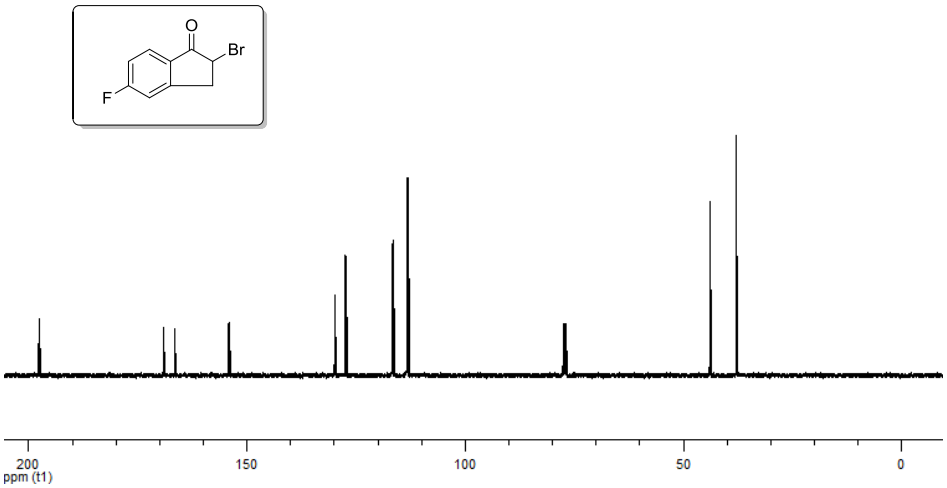


Figure A. 28 ^{13}C-NMR Spectrum of **(127)**

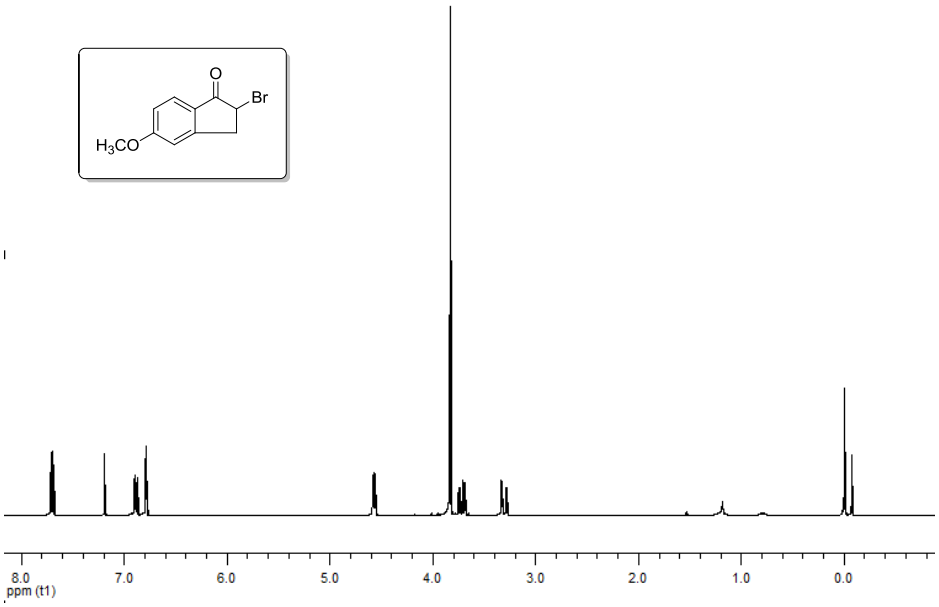


Figure A. 29 ^{1}H-NMR spectrum of **(128)**

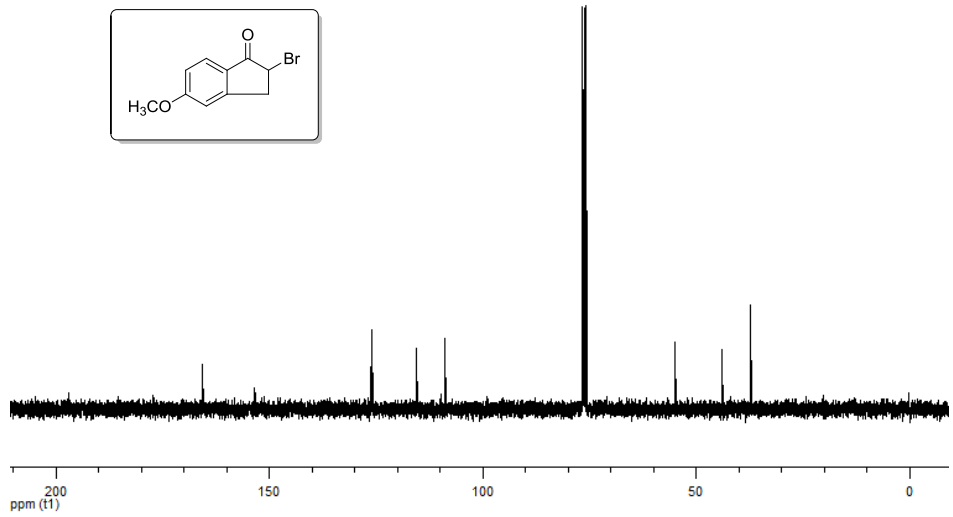


Figure A. 30 ^{13}C-NMR Spectrum of **(128)**

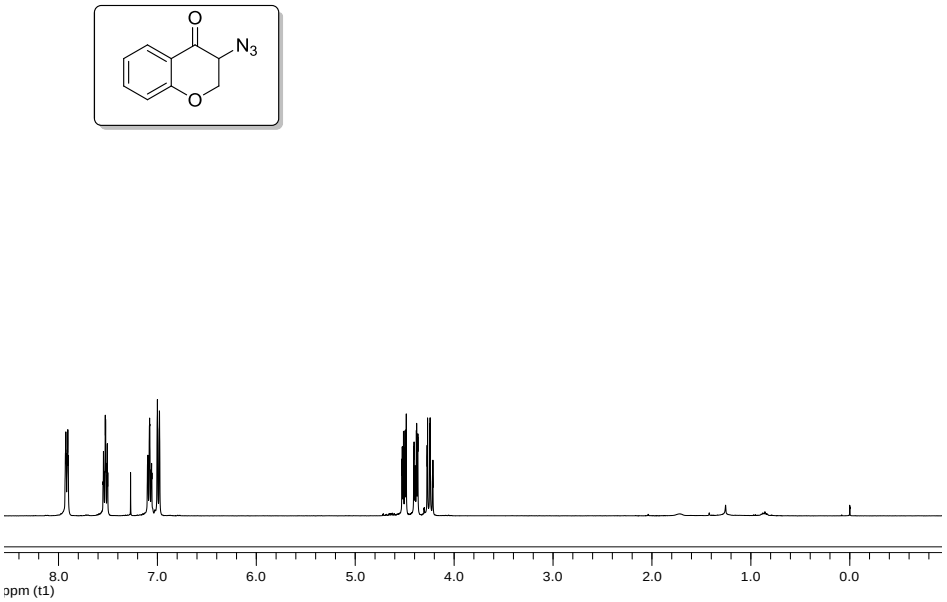


Figure A. 31 ^{1}H-NMR spectrum of **(129)**

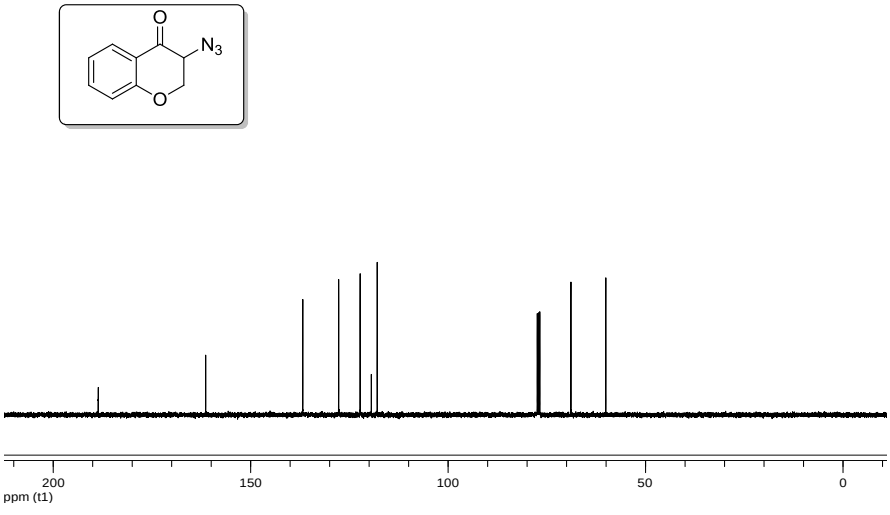


Figure A. 32 ^{13}C-NMR Spectrum of **(129)**

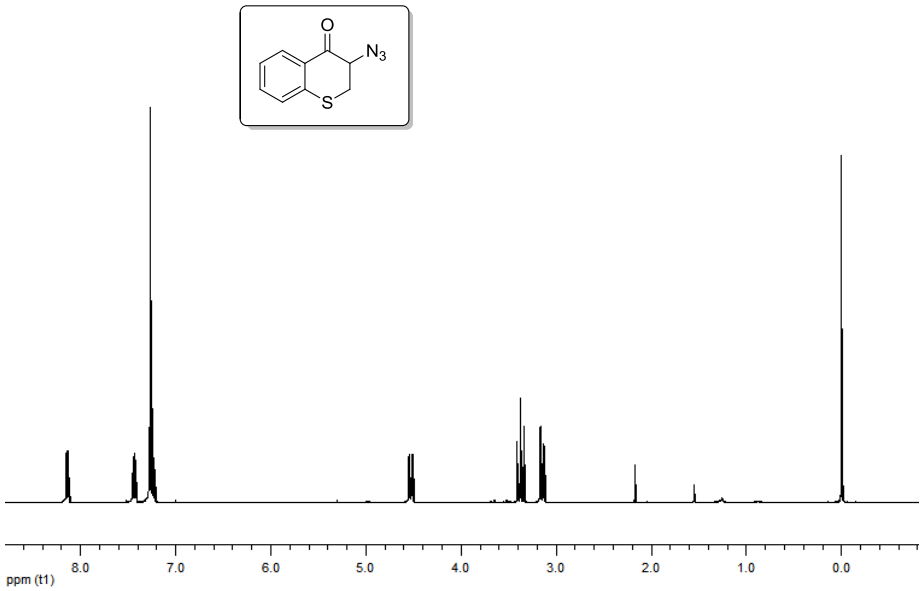


Figure A. 33 ^{1}H-NMR spectrum of **(132)**

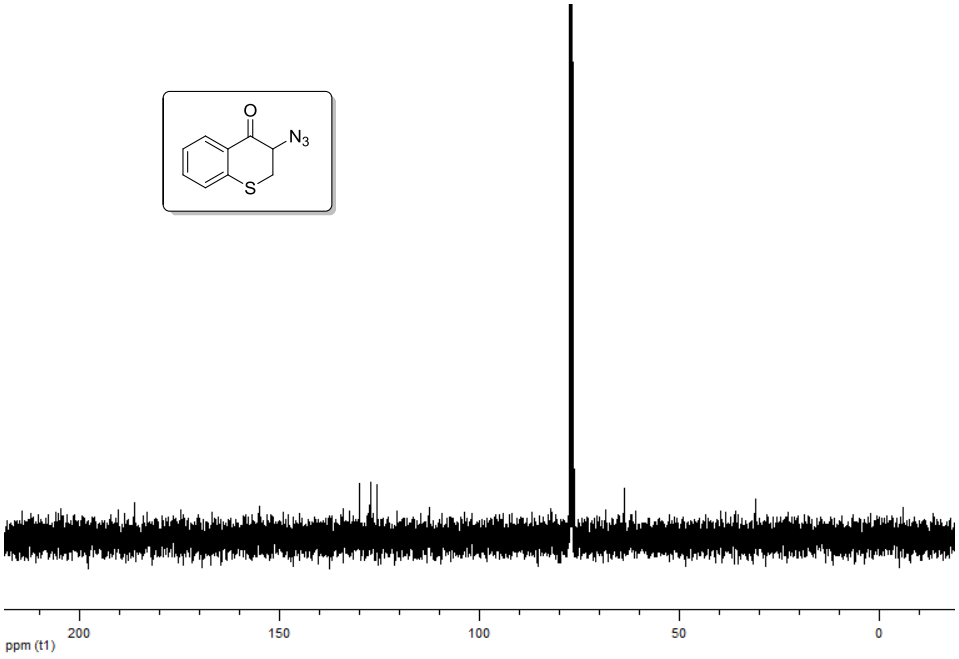


Figure A. 34 ^{13}C-NMR Spectrum of **(132)**

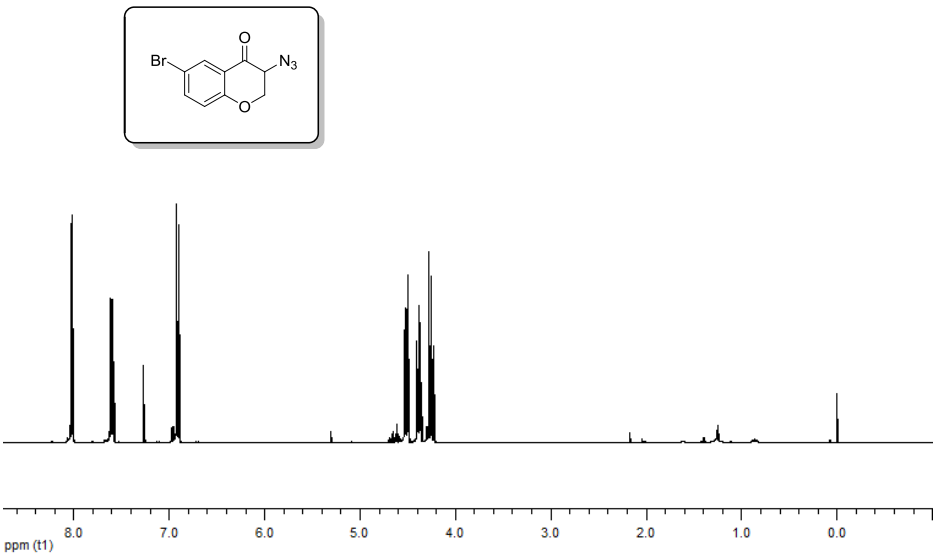


Figure A. 35 ^{1}H-NMR spectrum of **(133)**

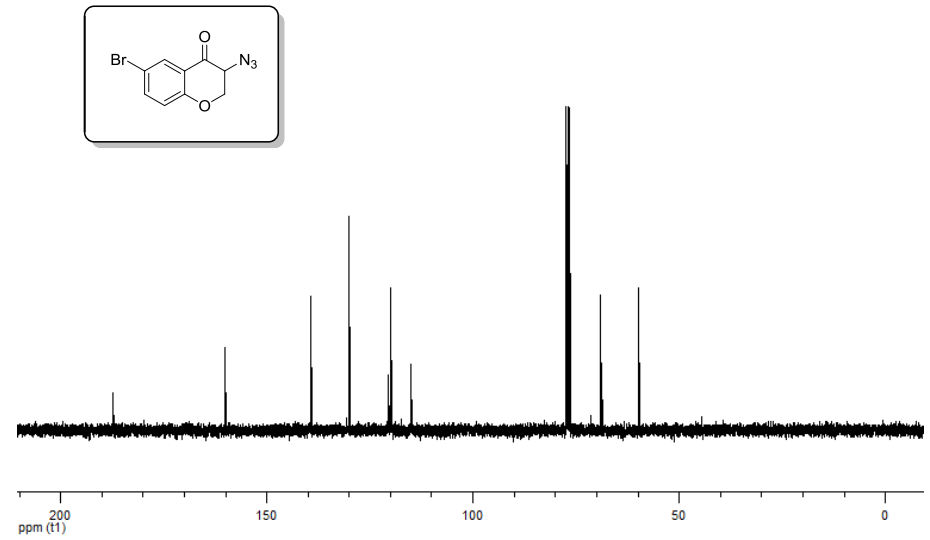


Figure A. 36 ^{13}C-NMR Spectrum of **(133)**

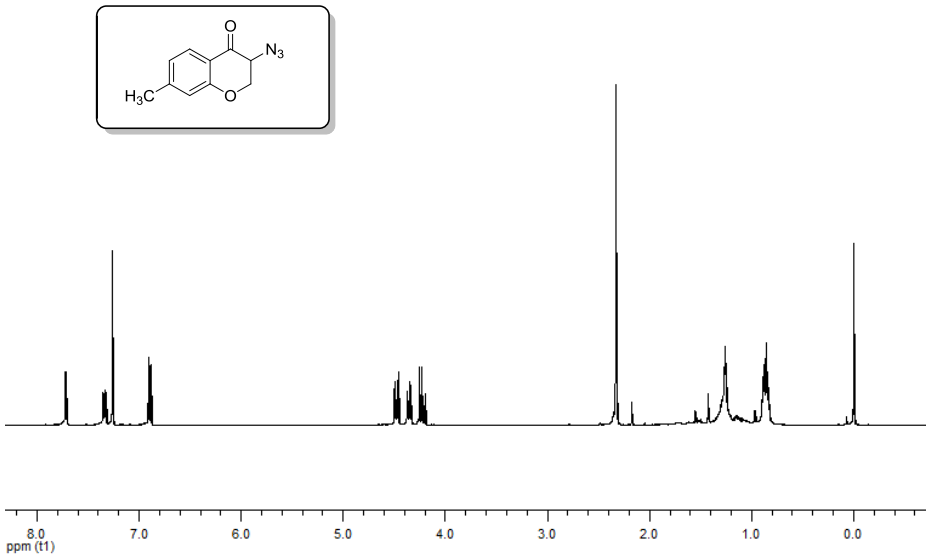


Figure A. 37 ^{1}H-NMR spectrum of **(134)**

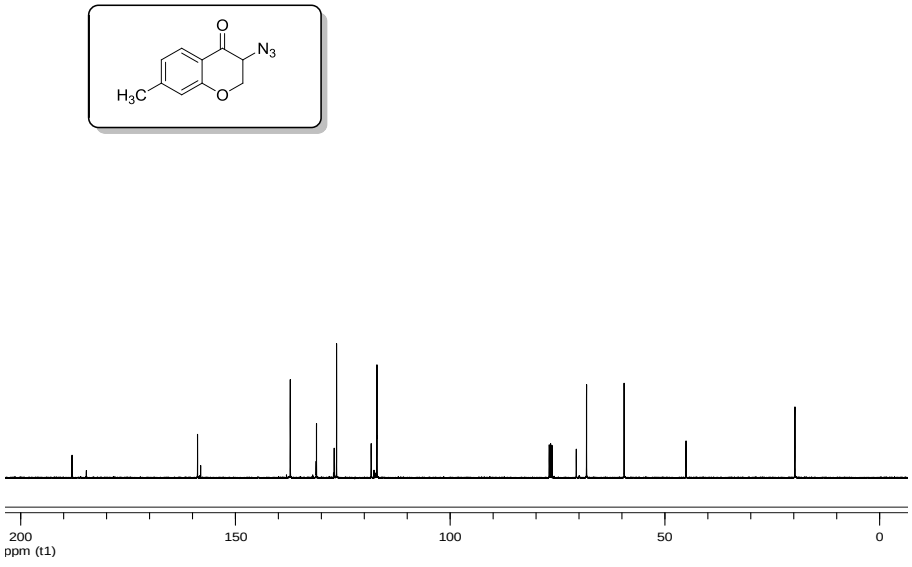


Figure A. 38 ^{13}C-NMR Spectrum of **(134)**

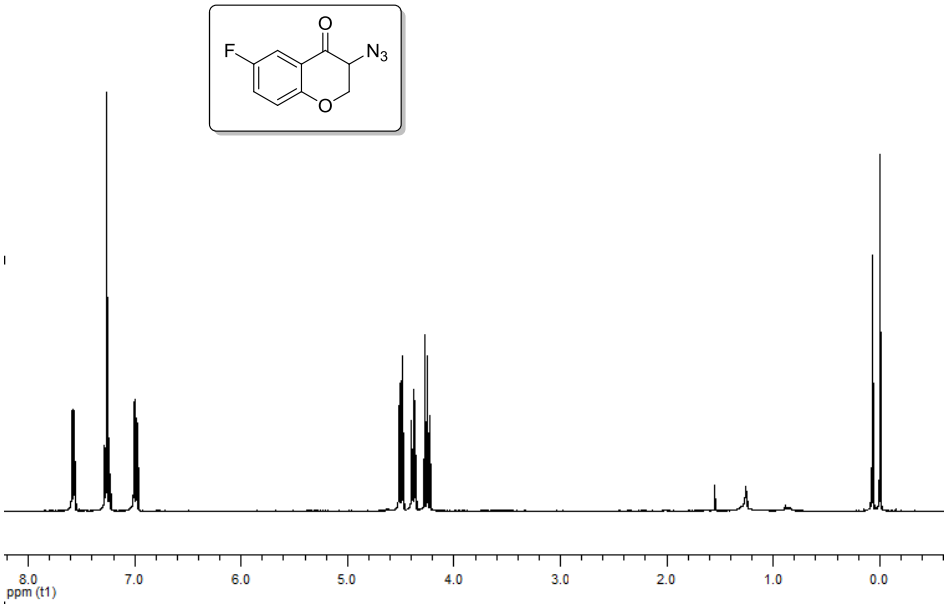


Figure A. 39 ^{1}H-NMR spectrum of **(135)**

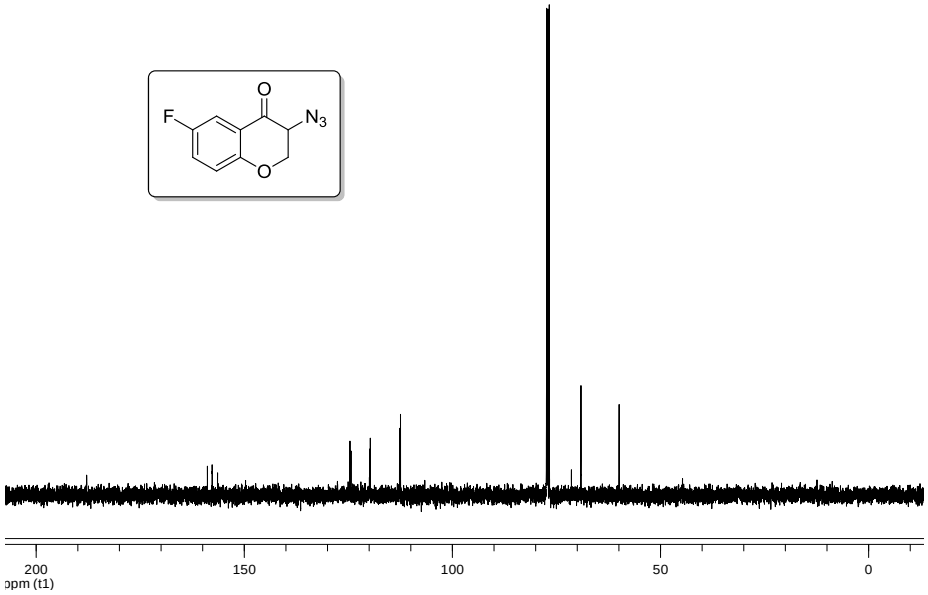


Figure A. 40 ^{13}C-NMR Spectrum of **(135)**

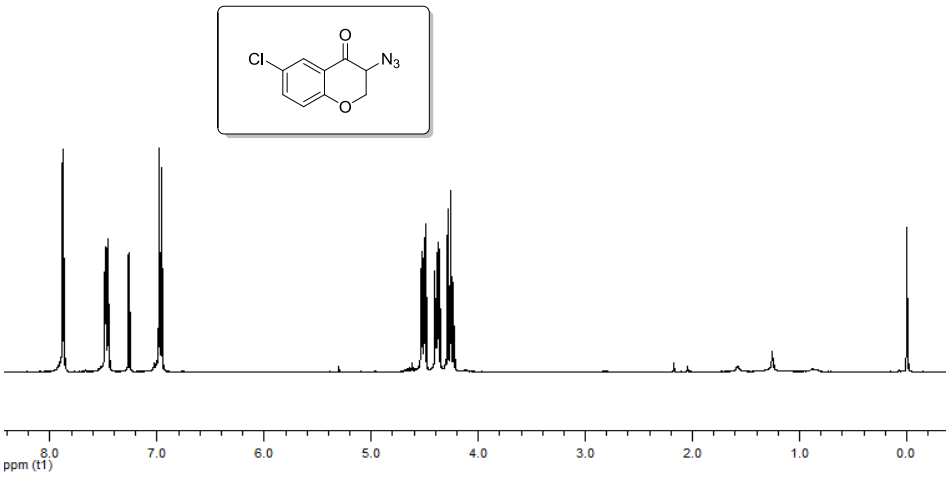


Figure A. 41 ^{1}H-NMR spectrum of **(136)**

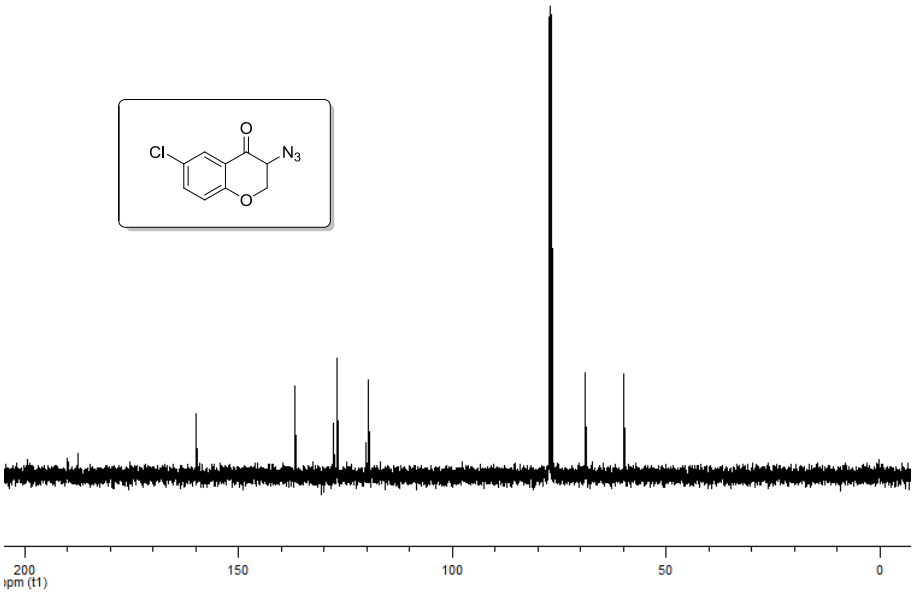


Figure A. 42 ^{13}C-NMR Spectrum of **(136)**

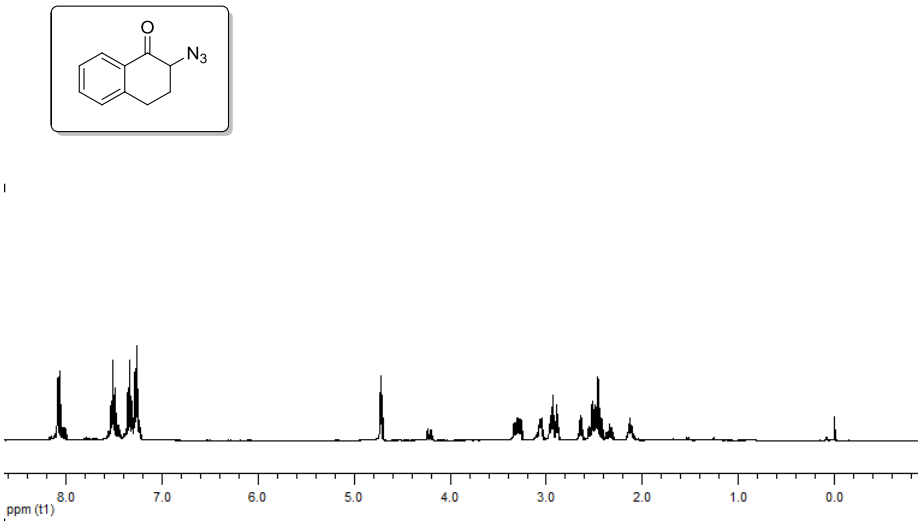


Figure A. 43 ^{1}H-NMR spectrum of **(130)**

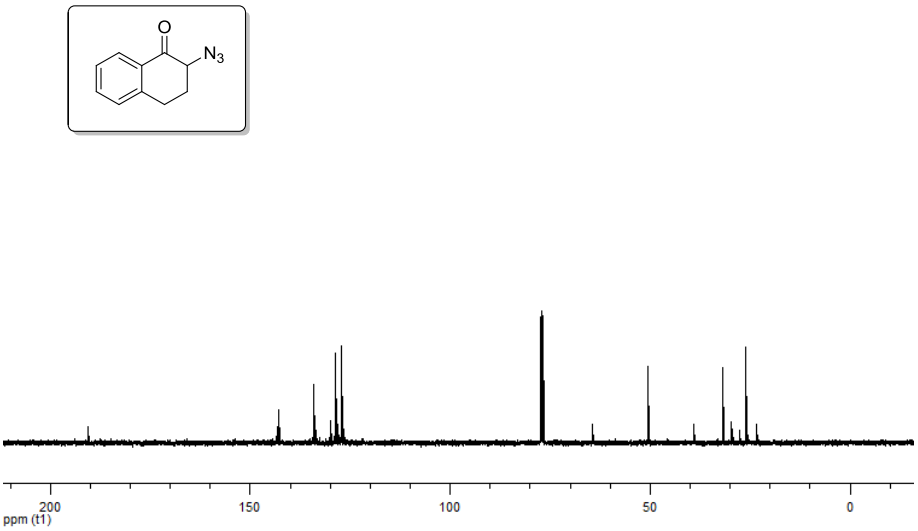


Figure A. 44 ^{13}C-NMR Spectrum of **(130)**

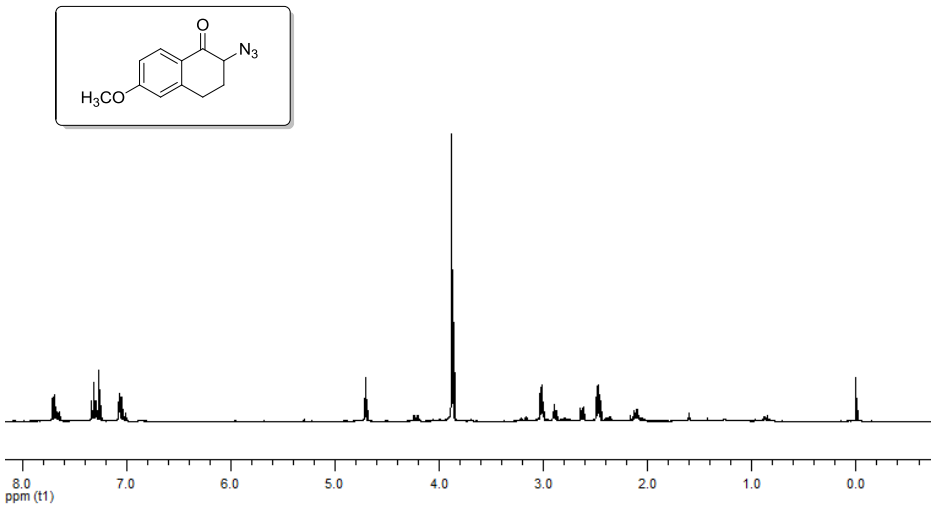


Figure A. 45 ^{1}H-NMR spectrum of **(137)**

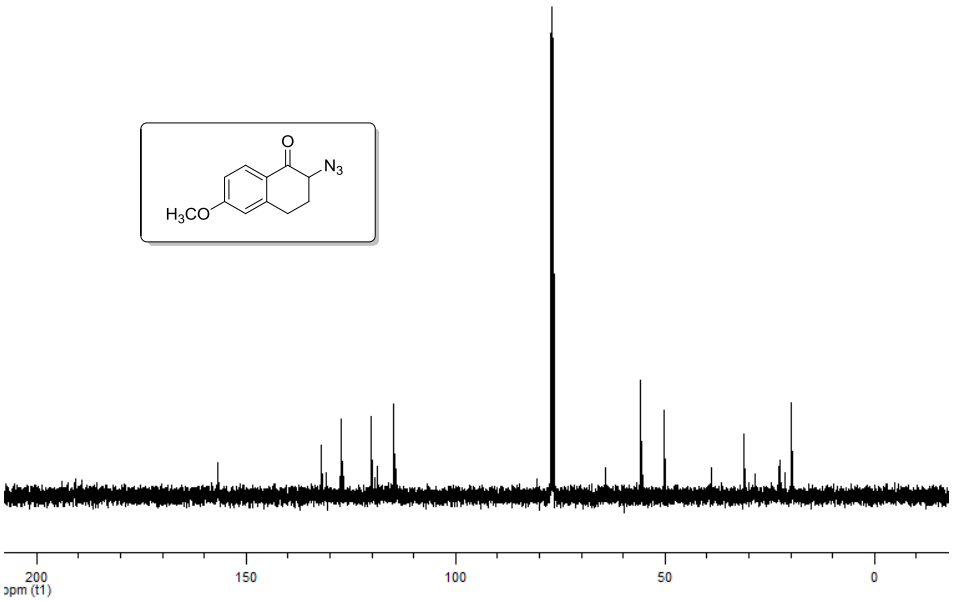


Figure A. 46 ^{13}C-NMR Spectrum of **(137)**

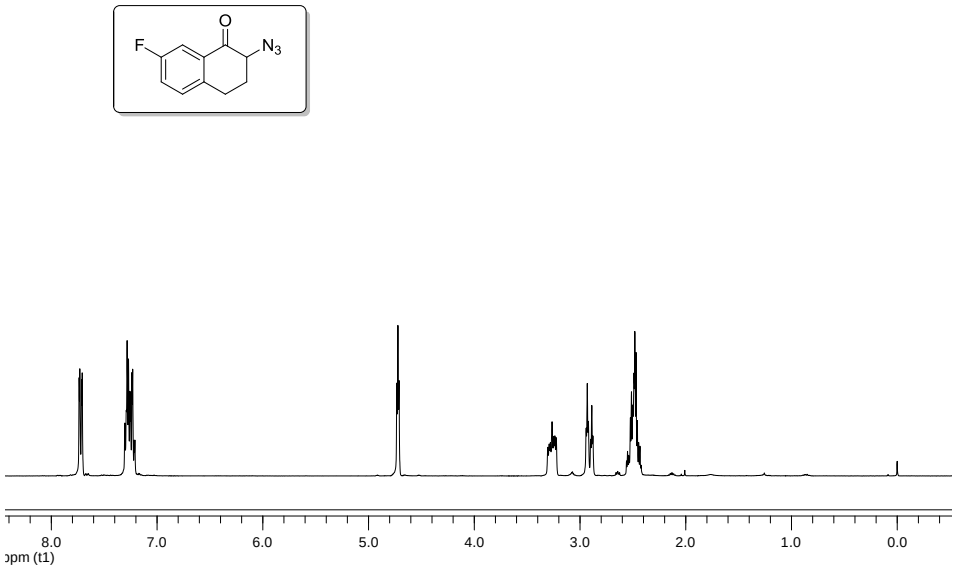


Figure A. 47 ^{1}H-NMR spectrum of **(138)**

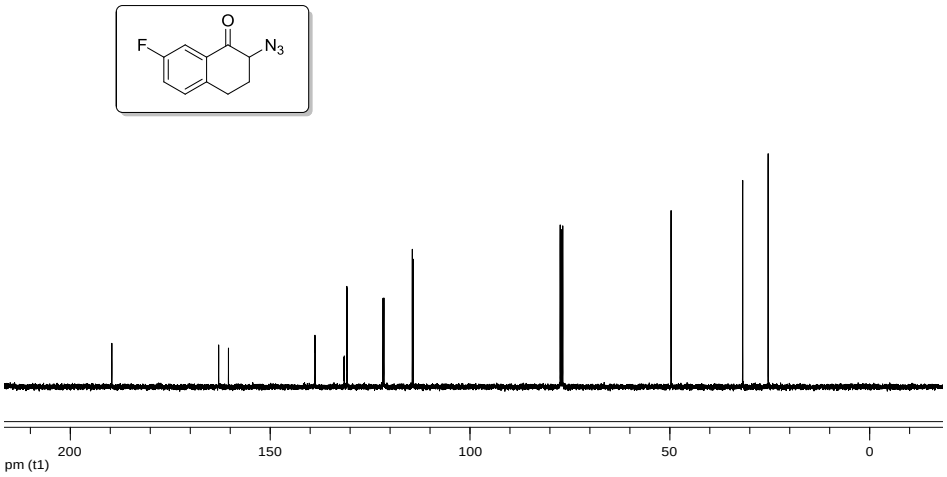


Figure A. 48 ^{13}C-NMR Spectrum of **(138)**

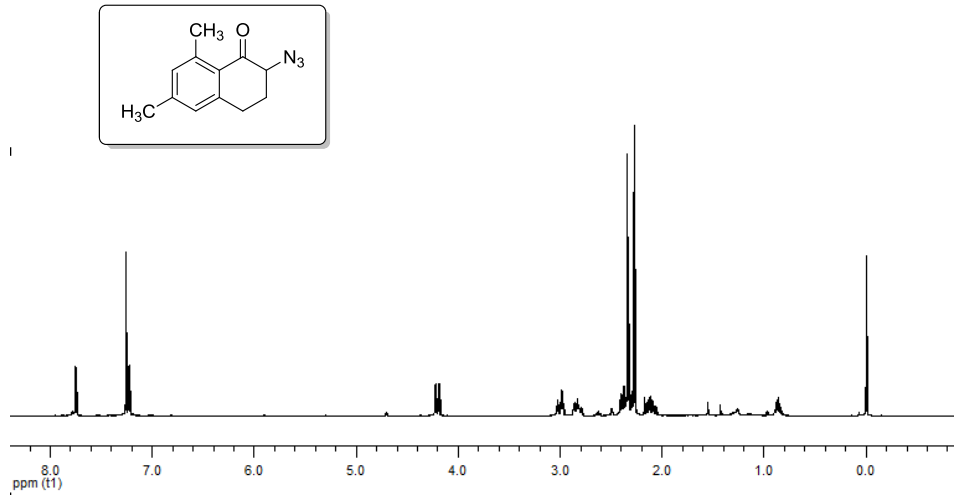


Figure A. 49 ^{1}H-NMR spectrum of **(139)**

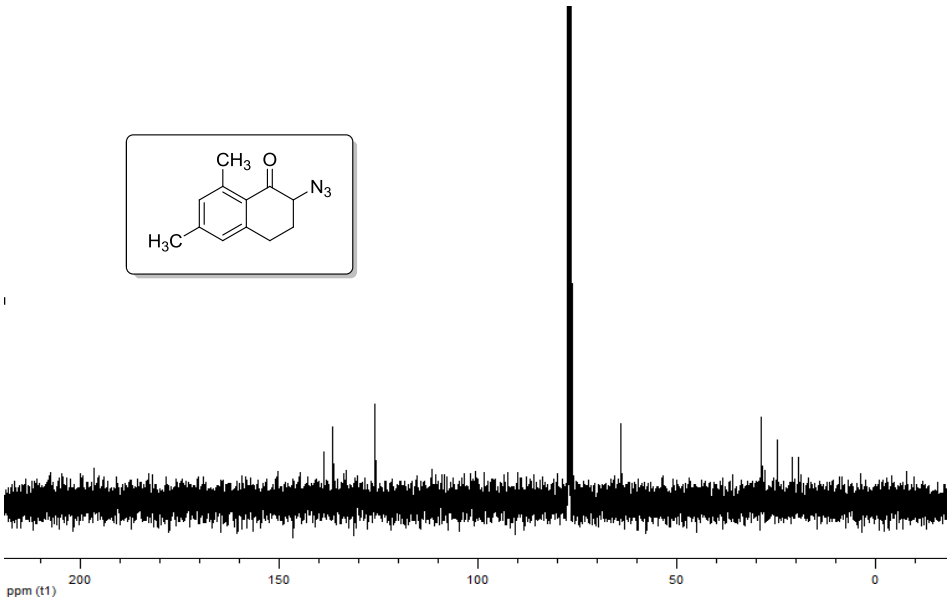


Figure A. 50 ^{13}C-NMR Spectrum of **(139)**

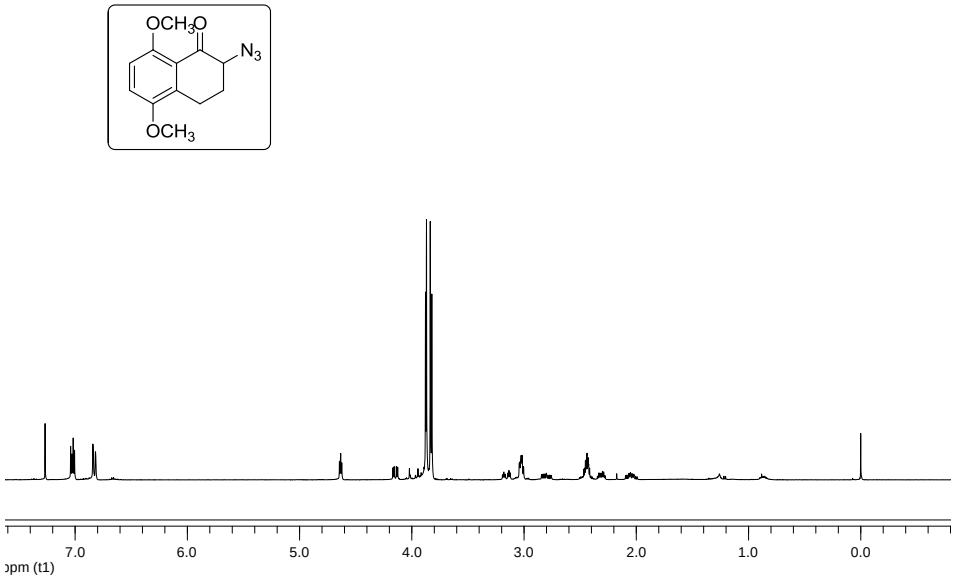


Figure A. 51 ^{1}H-NMR spectrum of **(140)**

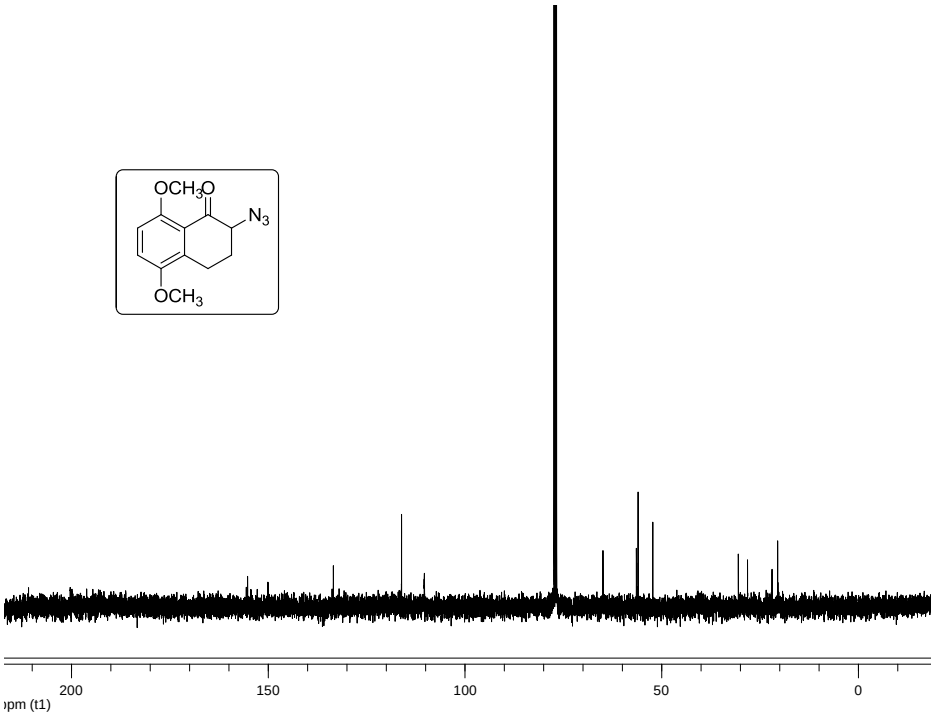


Figure A. 52 ^{13}C-NMR Spectrum of **(140)**

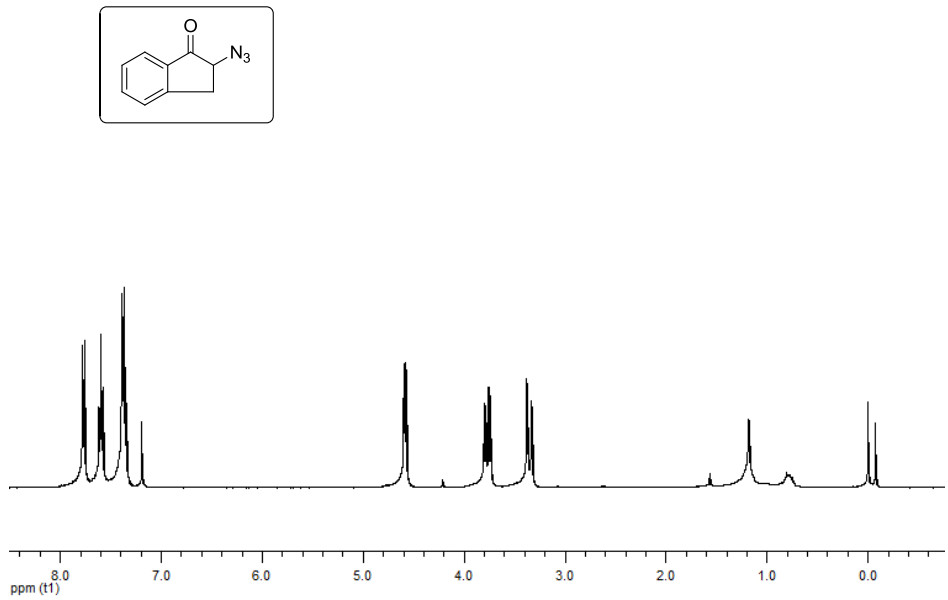


Figure A. 53 ^{1}H-NMR spectrum of **(131)**

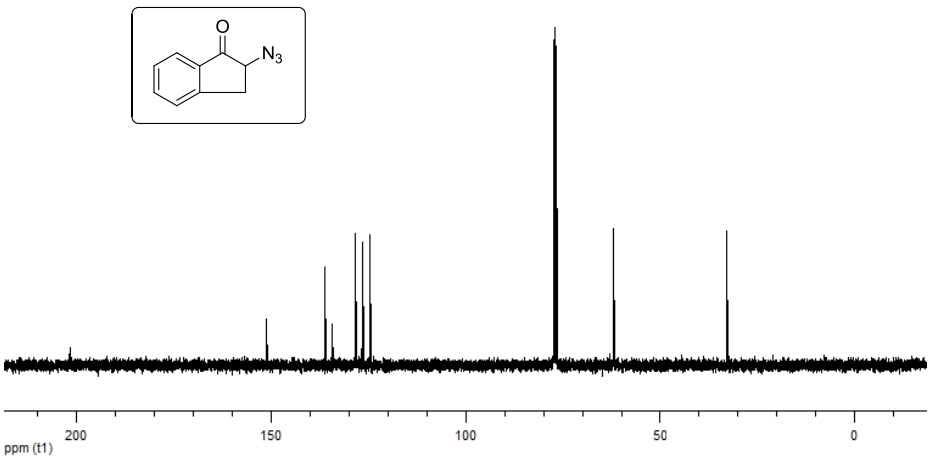


Figure A. 54 ^{13}C-NMR Spectrum of **(131)**

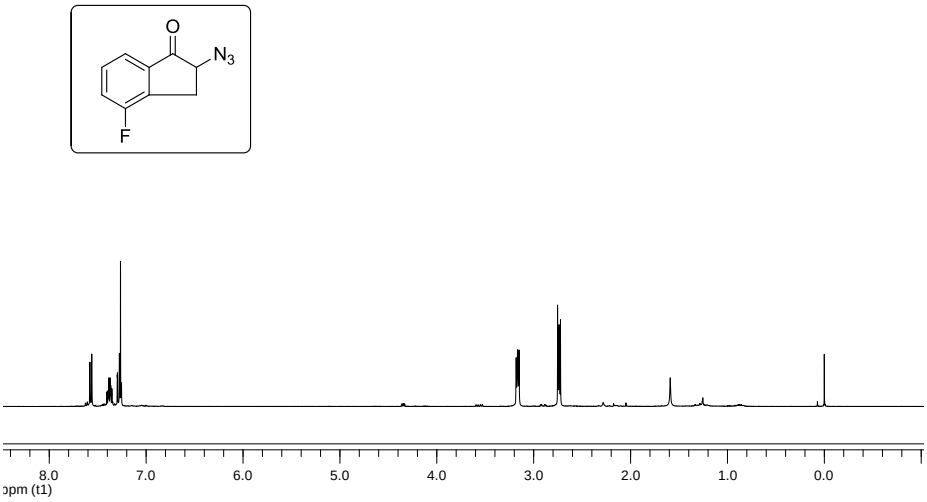


Figure A. 55 ^{1}H-NMR spectrum of **(141)**

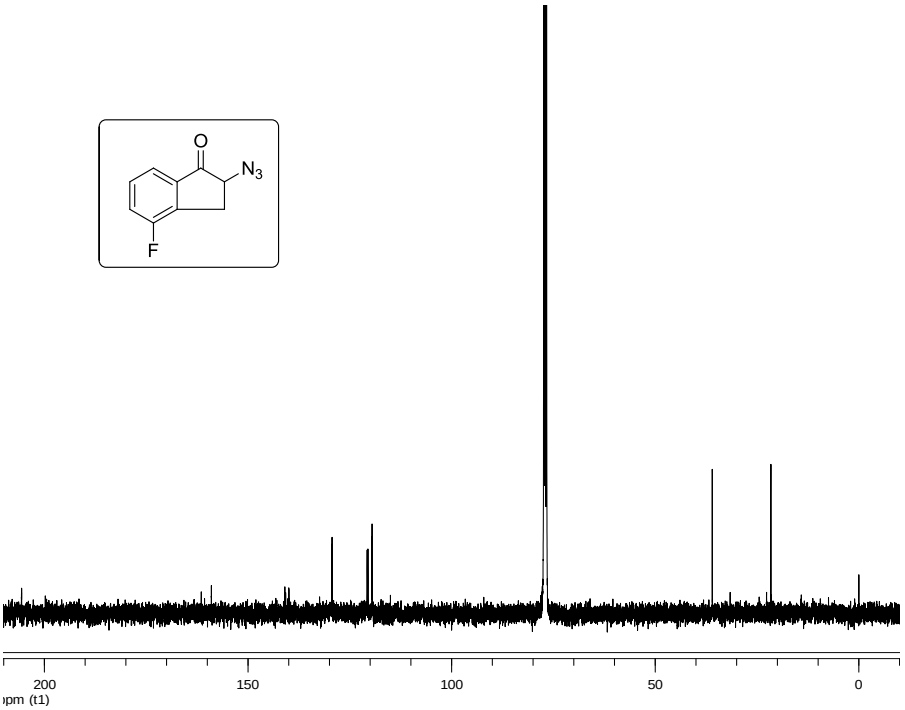


Figure A. 56 ^{13}C-NMR Spectrum of **(141)**

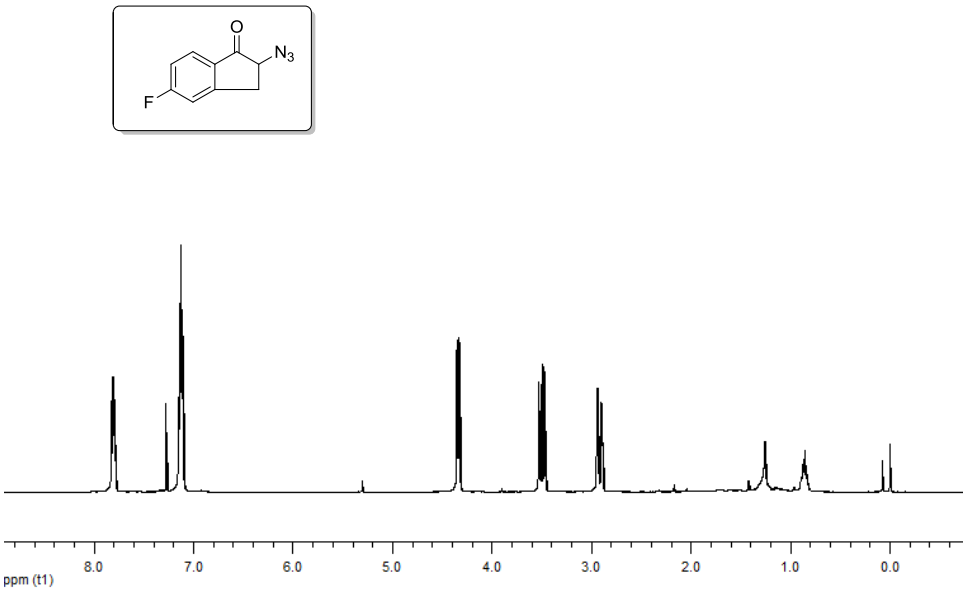


Figure A. 57 ^{1}H-NMR spectrum of **(142)**

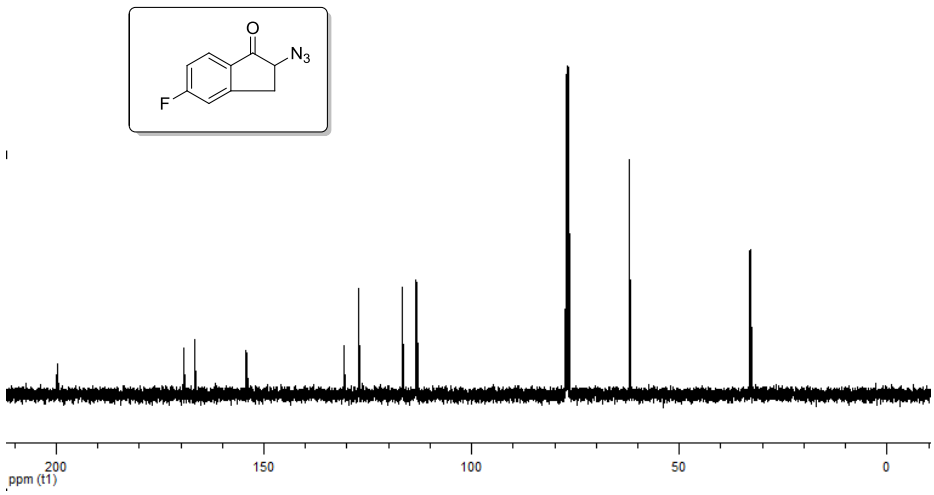


Figure A. 58 ^{13}C-NMR Spectrum of **(142)**

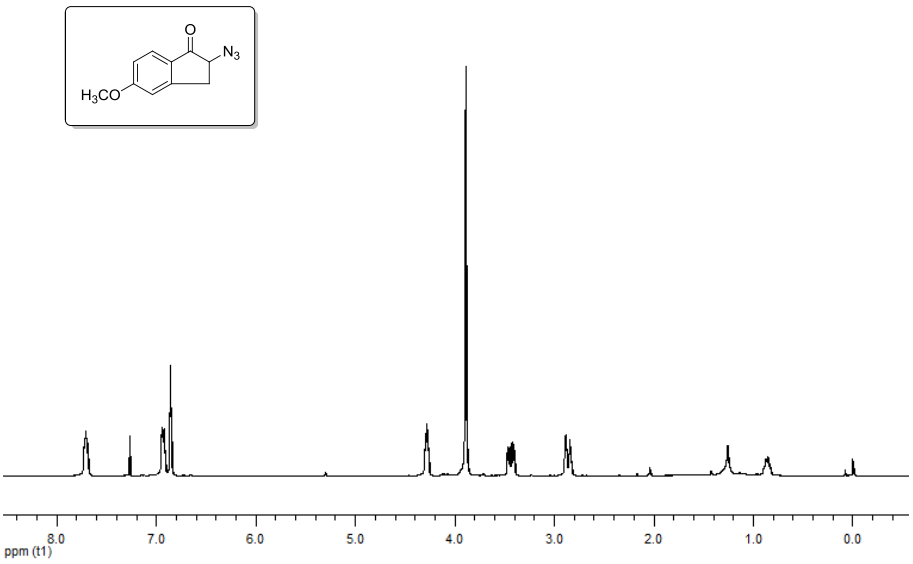


Figure A. 59 ^{1}H-NMR spectrum of **(143)**

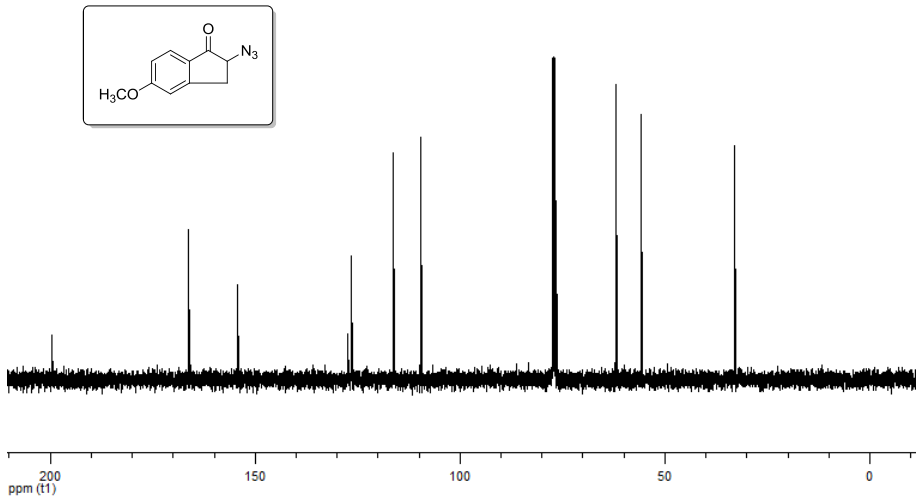


Figure A. 60 ^{13}C-NMR Spectrum of **(143)**

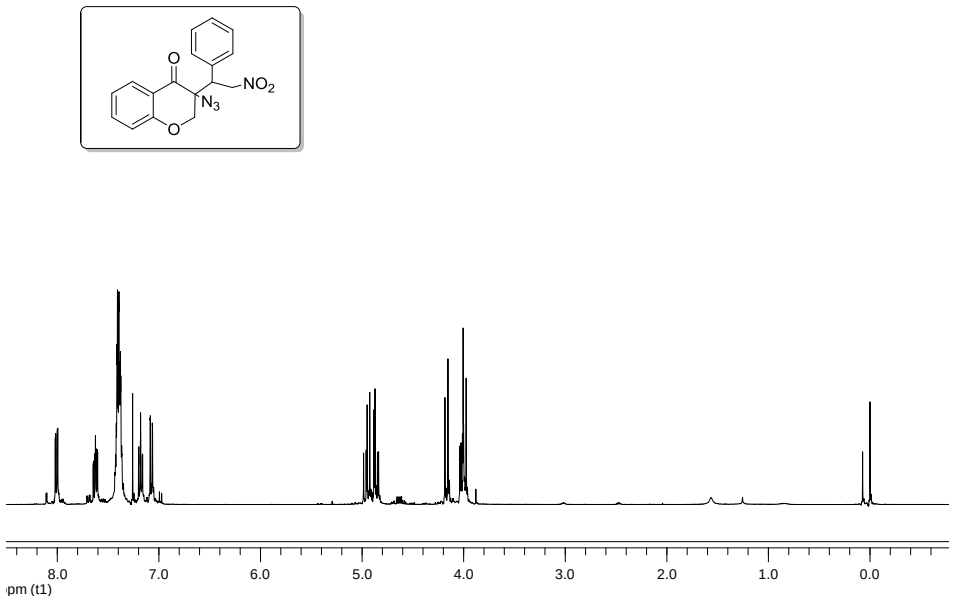


Figure A. 61 ^{1}H-NMR spectrum of **(150)**

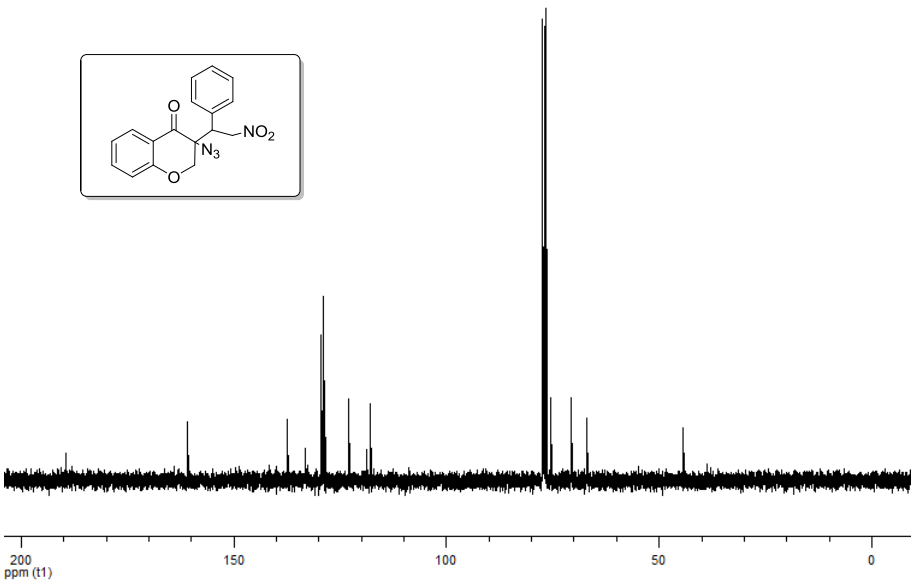


Figure A. 62 ^{13}C-NMR Spectrum of **(150)**

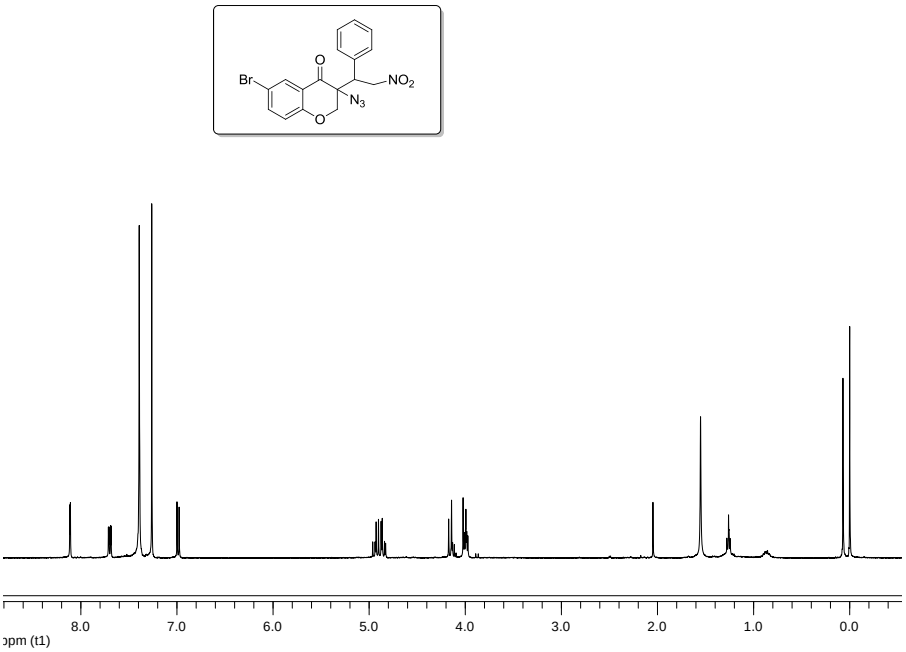


Figure A. 63 ^{1}H-NMR Spectrum of **(151)**

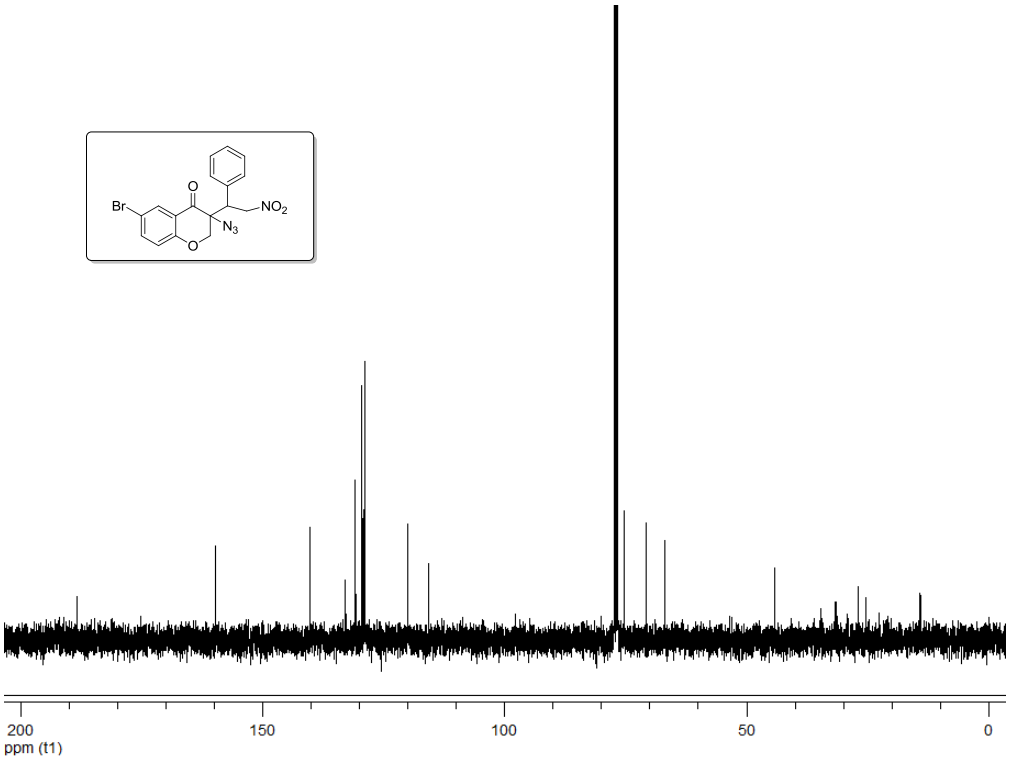
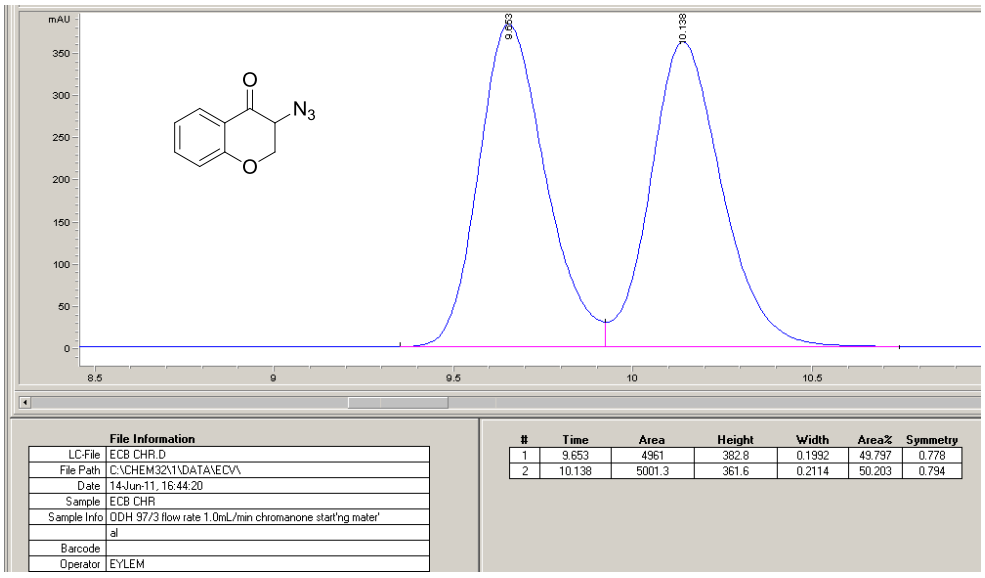


Figure A. 64 ^{13}C-NMR Spectrum of **(151)**

APPENDIX B

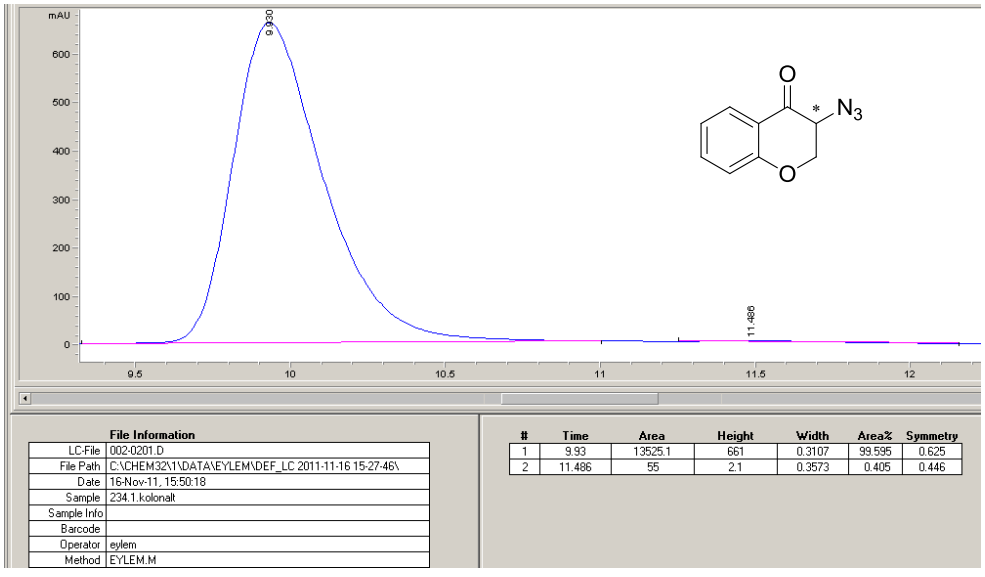
HPLC DATA



File Information	
LC-File	ECB CHR.D
File Path	C:\CHEM32\1\DATA\ECV\
Date	14-Jun-11, 16:44:20
Sample	ECB CHR
Sample Info	ODH 97/3 flow rate 1.0mL/min chromanone start'ng mater'
	al
Barcode	
Operator	EYLEM

#	Time	Area	Height	Width	Area%	Symmetry
1	9.653	4961	382.8	0.1992	49.797	0.778
2	10.138	5001.3	361.6	0.2114	50.203	0.794

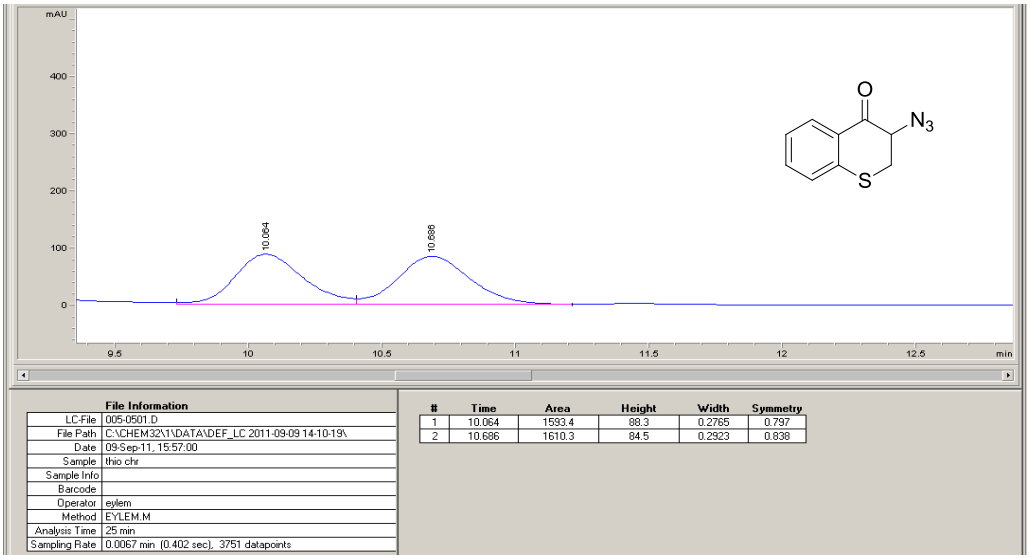
Figure B. 1 Racemic HPLC Chromatogram of **(129)**



File Information	
LC-File	002-0201.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-11-16 15-27-46\
Date	16-Nov-11, 15:50:18
Sample	234.1.kolonalt
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	9.93	13525.1	661	0.3107	99.595	0.625
2	11.486	55	2.1	0.3573	0.405	0.446

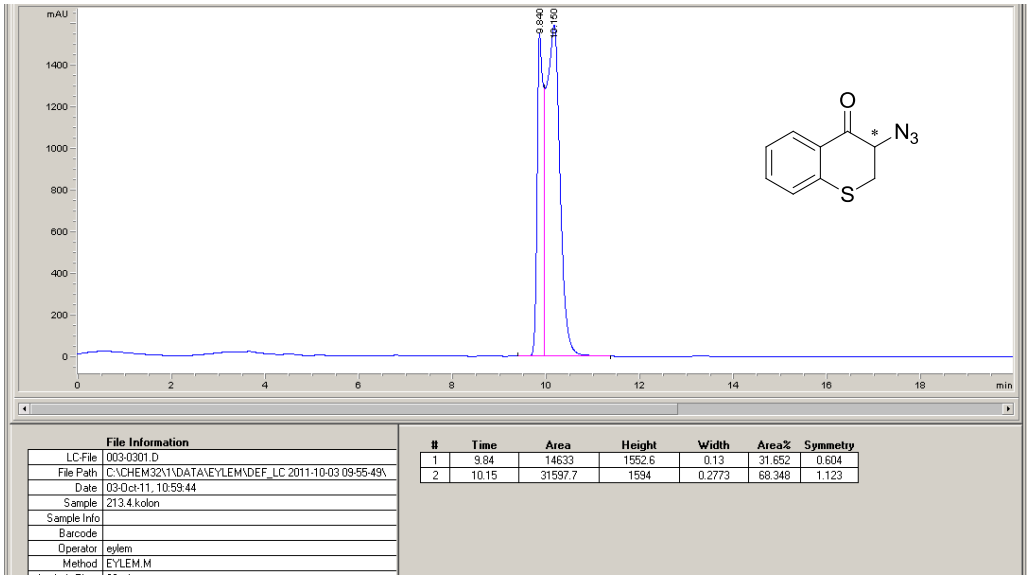
Figure B. 2 Chiral HPLC Chromatogram of **(129)**



File Information	
LC-File	005-0501.D
File Path	C:\CHEM32\1\DATA\DEF_LC 2011-09-09 14-10-19\
Date	09-Sep-11, 15:57:00
Sample	thio chr
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M
Analysis Time	25 min
Sampling Rate	0.0067 min (0.402 sec), 3751 datapoints

#	Time	Area	Height	Width	Symmetry
1	10.064	1593.4	88.3	0.2765	0.797
2	10.686	1610.3	84.5	0.2923	0.838

Figure B. 3 Racemic HPLC Chromatogram of **(132)**



File Information	
LC-File	003-0301.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-10-03 09-55-49\
Date	03-Oct-11, 10:59:44
Sample	213.4.kolon
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	9.84	14633	1552.6	0.13	31.652	0.604
2	10.15	31597.7	1594	0.2773	68.348	1.123

Figure B. 4 Chiral HPLC Chromatogram of **(132)**

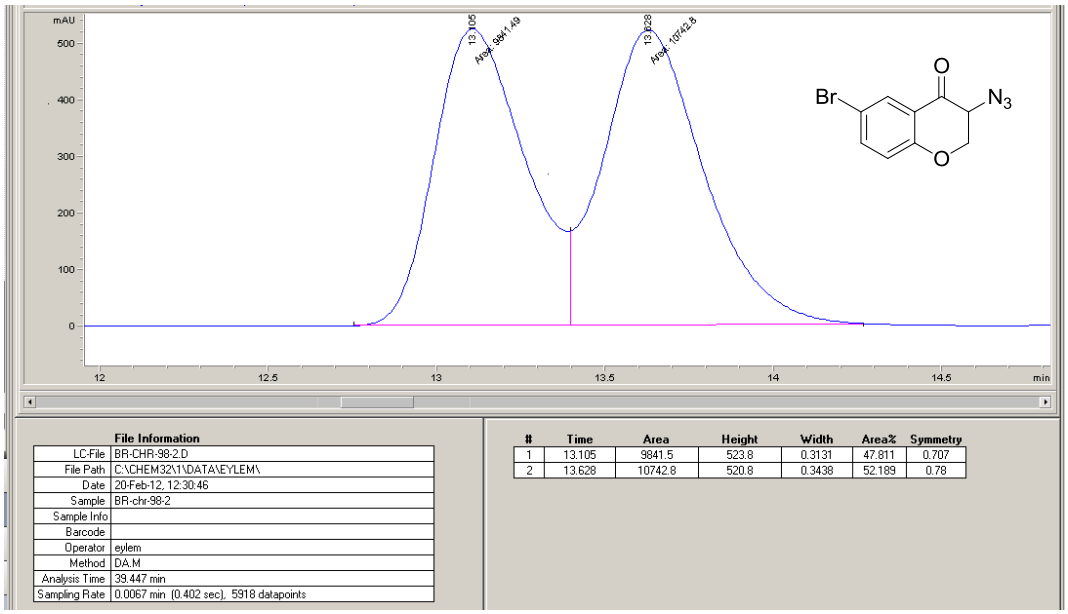


Figure B. 5 Racemic HPLC Chromatogram of **(133)**

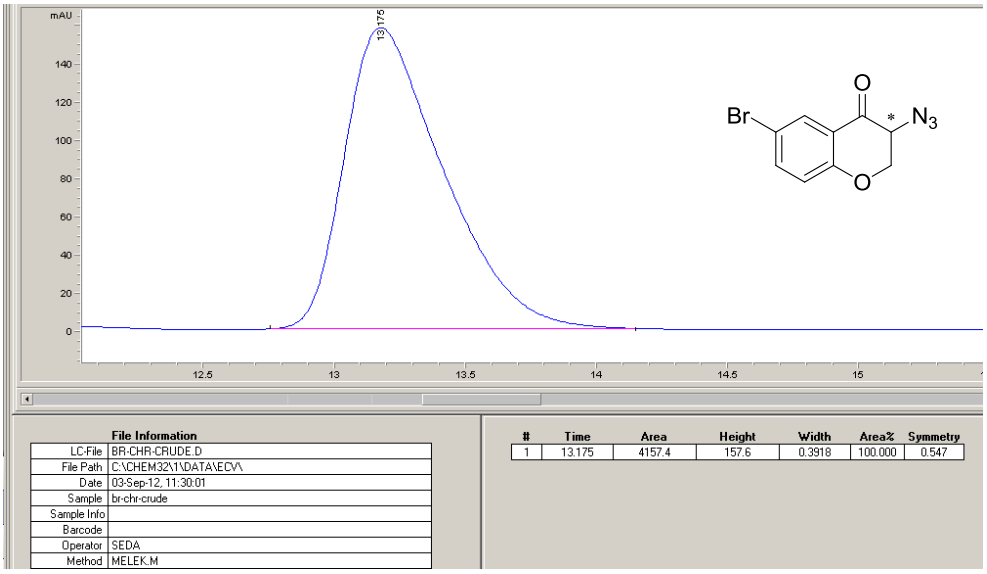
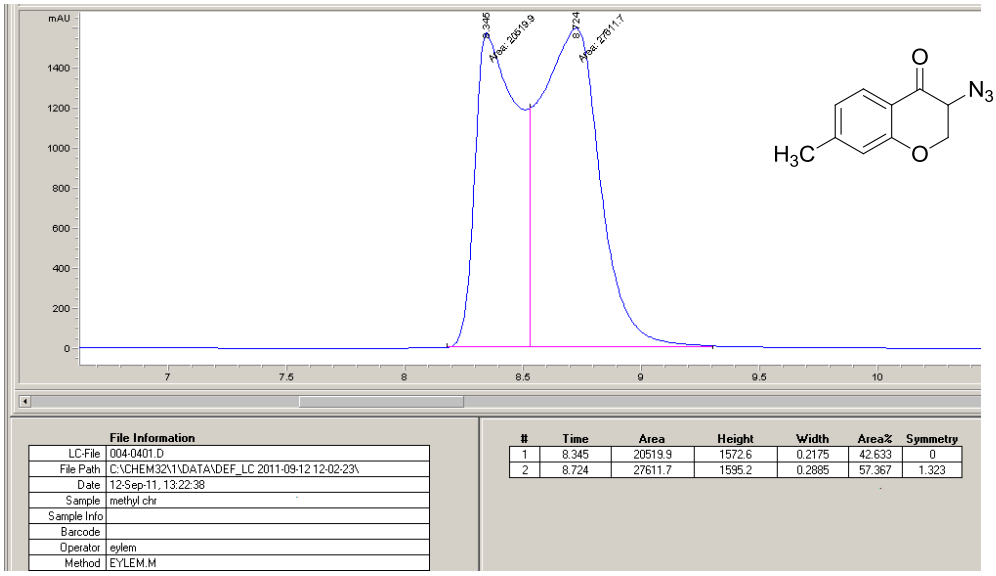


Figure B. 6 Chiral HPLC Chromatogram of **(133)**

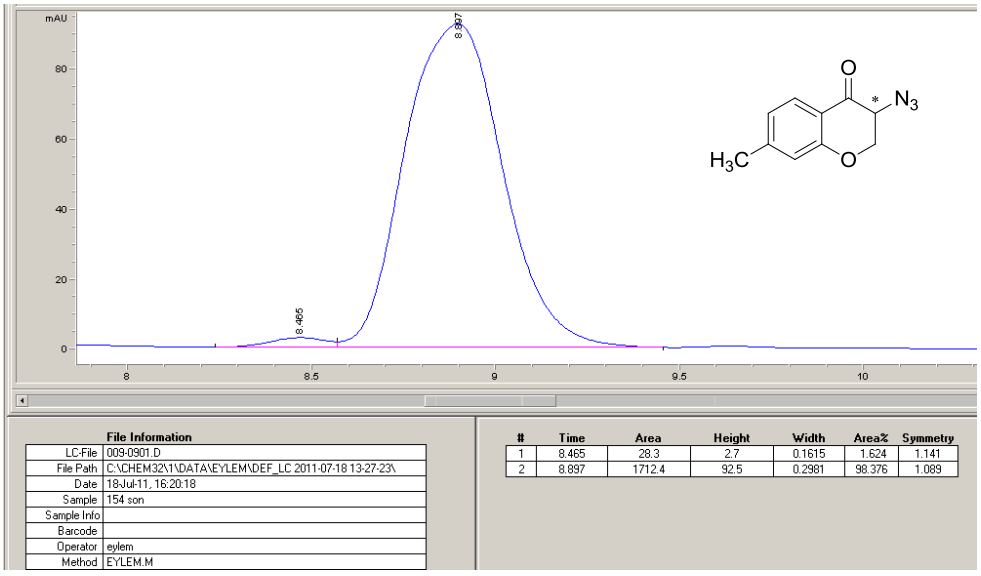


File Information

LC-File	004-0401.D
File Path	C:\CHEM32\1\DATA\DEF_LC 2011-09-12 12-02-23\
Date	12-Sep-11, 13:22:38
Sample	methyl chr
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	8.345	20519.9	1572.6	0.2175	42.633	0
2	8.724	27611.7	1595.2	0.2885	57.367	1.323

Figure B. 7 Racemic HPLC Chromatogram of **(134)**

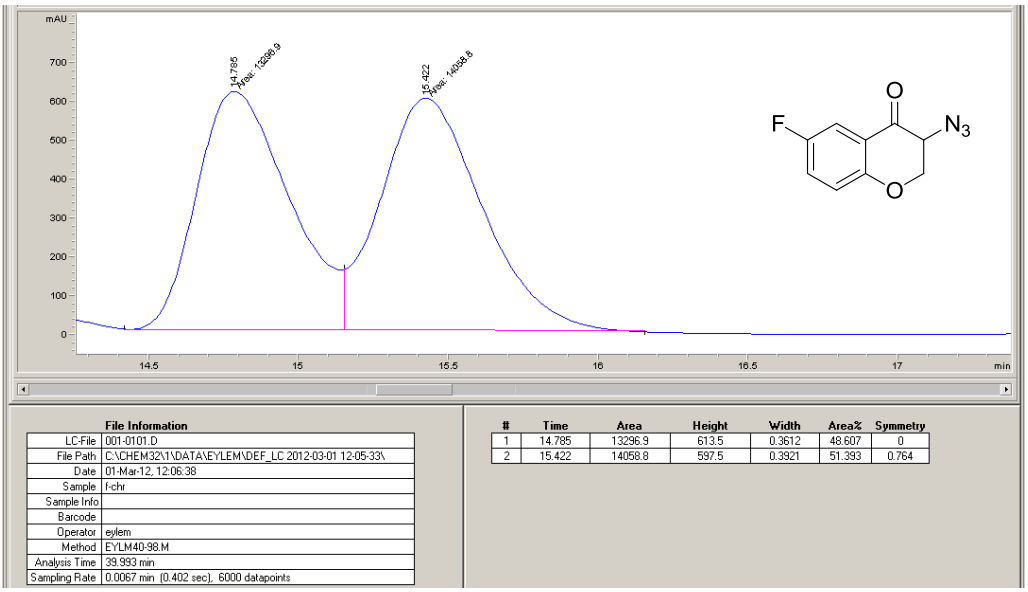


File Information

LC-File	009-0901.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-07-18 13-27-23\
Date	18-Jul-11, 16:20:18
Sample	154 son
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	8.465	28.3	2.7	0.1615	1.624	1.141
2	8.897	1712.4	92.5	0.2981	98.376	1.089

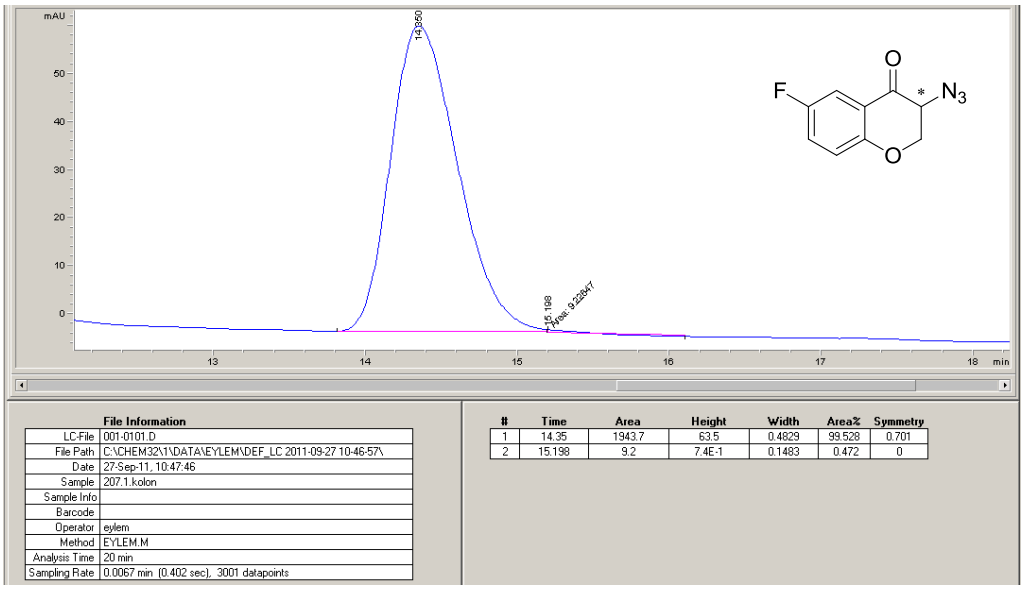
Figure B. 8 Chiral HPLC Chromatogram of **(134)**



File Information	
LC-File	001-0101.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2012-03-01 12-05-33\
Date	01-Mar-12, 12:06:38
Sample	f-chr
Sample Info	
Barcode	
Operator	eylem
Method	EYLM40-98.M
Analysis Time	39.993 min
Sampling Rate	0.0067 min (0.402 sec), 6000 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	14.785	13296.9	613.5	0.3612	48.607	0
2	15.422	14058.8	597.5	0.3921	51.393	0.764

Figure B. 9 Racemic HPLC Chromatogram of **(135)**



File Information	
LC-File	001-0101.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-09-27 10-46-57\
Date	27-Sep-11, 10:47:46
Sample	207.1.kolon
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M
Analysis Time	20 min
Sampling Rate	0.0067 min (0.402 sec), 3001 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	14.35	1943.7	63.5	0.4829	99.528	0.701
2	15.198	9.2	7.4E-1	0.1483	0.472	0

Figure B. 10 Chiral HPLC Chromatogram of **(135)**

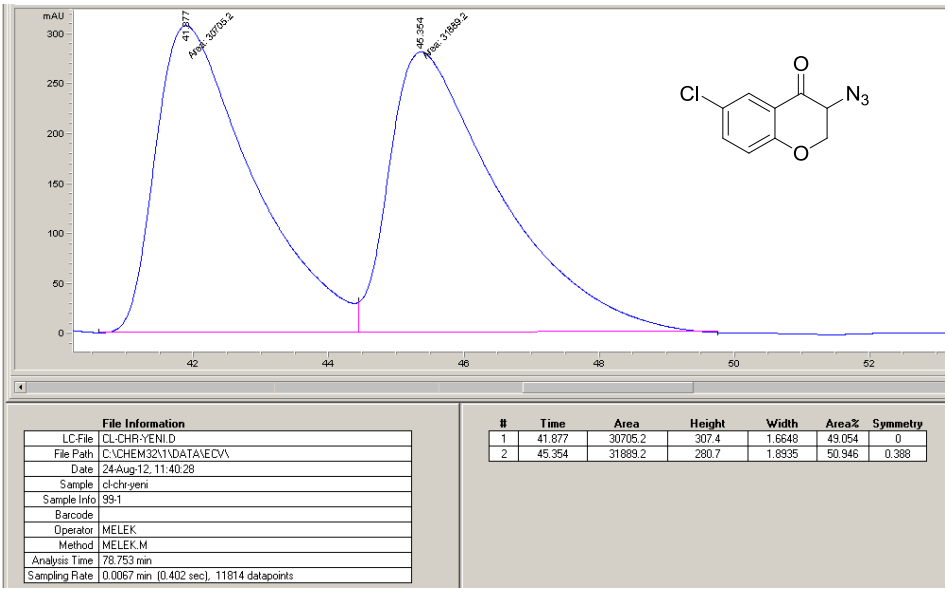


Figure B. 11 Racemic HPLC Chromatogram of **(136)**

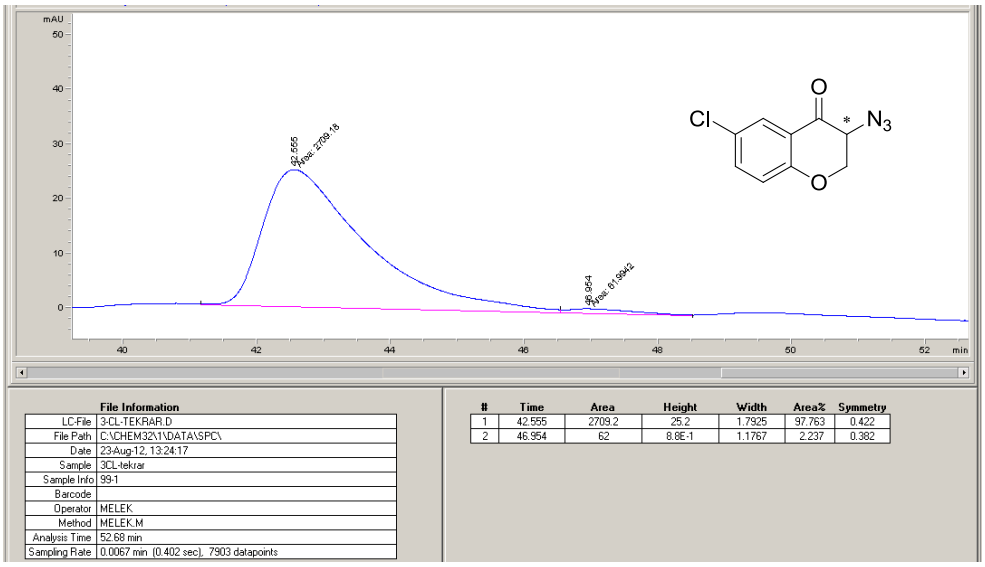
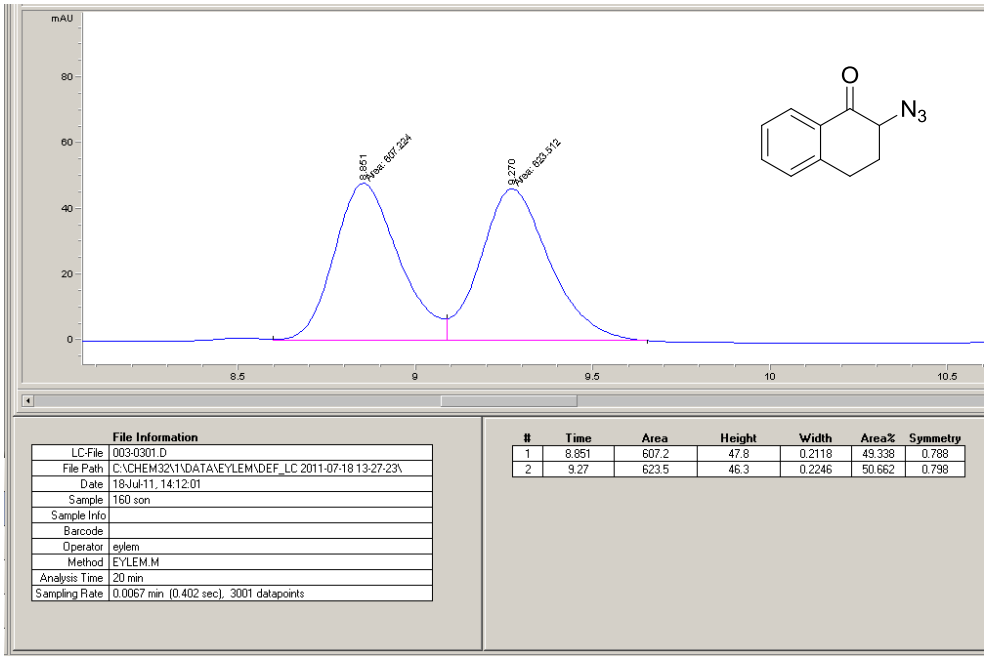


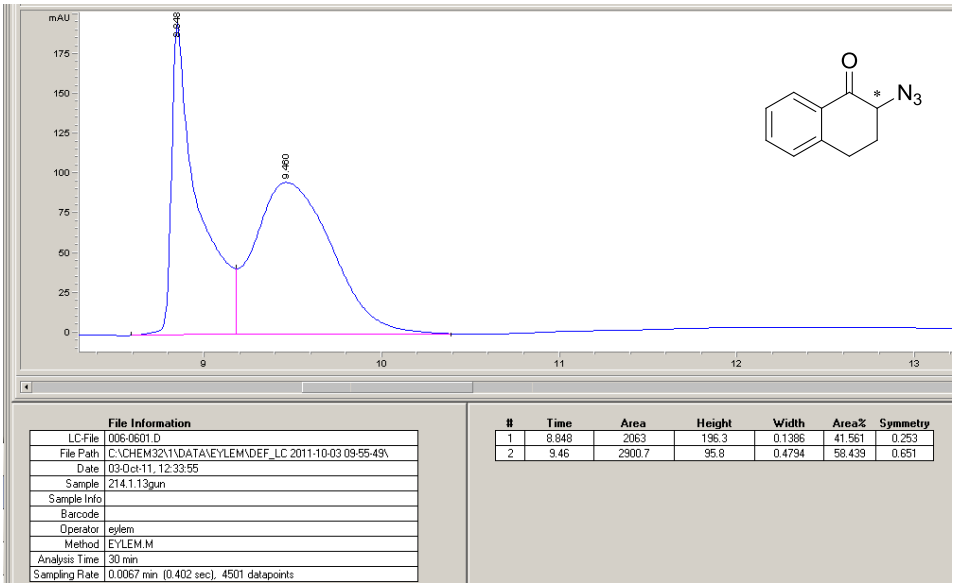
Figure B. 12 Chiral HPLC Chromatogram of **(136)**



File Information	
LC-File	003-0301.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-07-18 13-27-23\
Date	18-Jul-11, 14:12:01
Sample	160 son
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M
Analysis Time	20 min
Sampling Rate	0.0067 min (0.402 sec), 3001 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	8.851	607.2	47.8	0.2118	49.338	0.788
2	9.27	623.5	46.3	0.2246	50.662	0.798

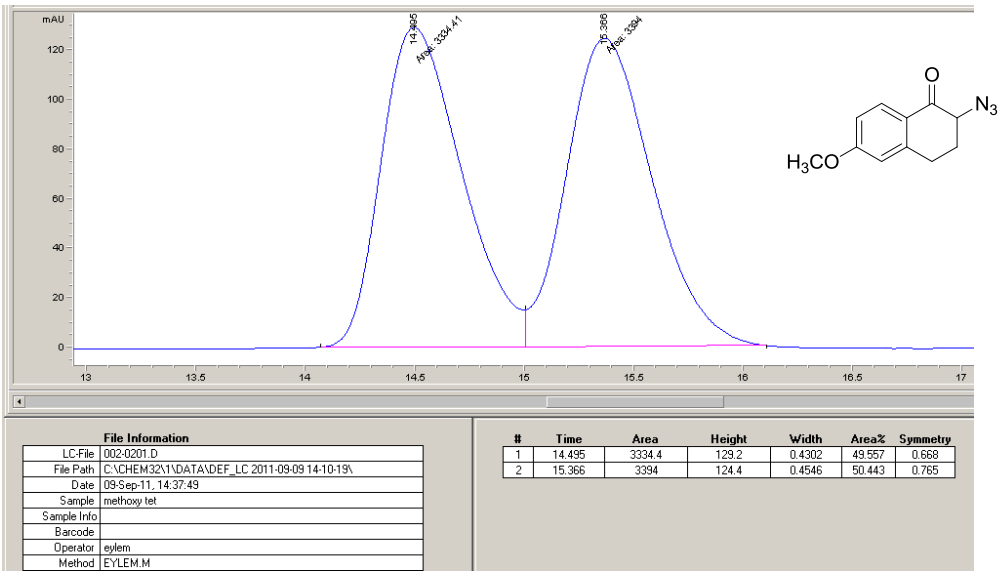
Figure B. 13 Racemic HPLC Chromatogram of **(130)**



File Information	
LC-File	006-0601.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-10-03 09-55-49\
Date	03-Oct-11, 12:33:55
Sample	214.1.13gun
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M
Analysis Time	30 min
Sampling Rate	0.0067 min (0.402 sec), 4501 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	8.848	2063	196.3	0.1386	41.561	0.253
2	9.46	2900.7	95.8	0.4794	58.439	0.651

Figure B. 14 Chiral HPLC Chromatogram of **(130)**

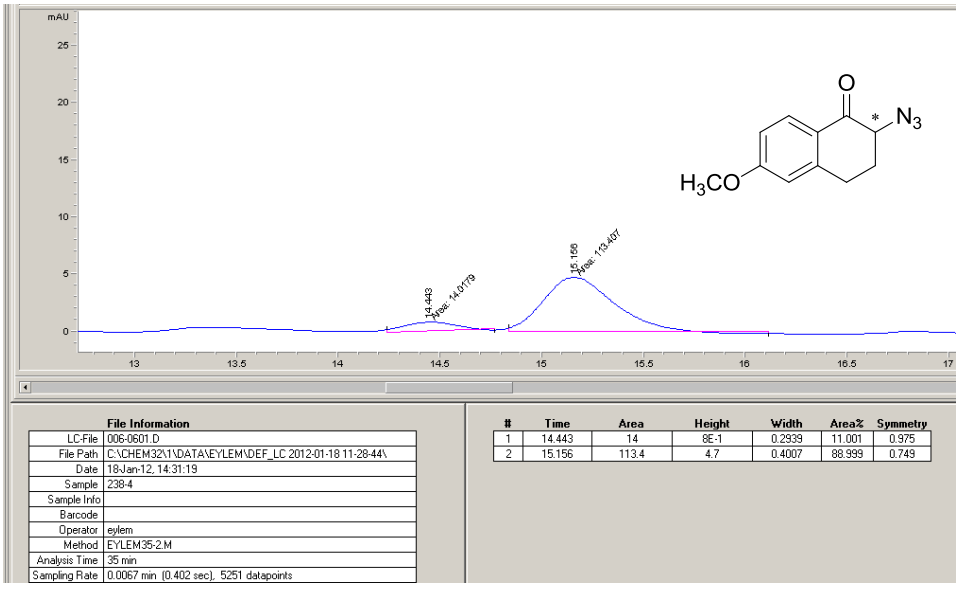


File Information

LC-File	002-0201.D
File Path	C:\CHEM32\1\DATA\DEF_LC 2011-09-09 14-10-19\
Date	09-Sep-11, 14:37:49
Sample	methoxy tet
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	14.495	3334.4	129.2	0.4302	49.557	0.668
2	15.366	3394	124.4	0.4546	50.443	0.765

Figure B. 15 Racemic HPLC Chromatogram of **(137)**



File Information

LC-File	006-0601.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2012-01-18 11-28-44\
Date	18-Jan-12, 14:31:19
Sample	238-4
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM35-2.M
Analysis Time	35 min
Sampling Rate	0.0067 min (0.402 sec), 5251 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	14.443	14	8E-1	0.2939	11.001	0.975
2	15.156	113.4	4.7	0.4007	88.999	0.749

Figure B. 16 Chiral HPLC Chromatogram of **(137)**

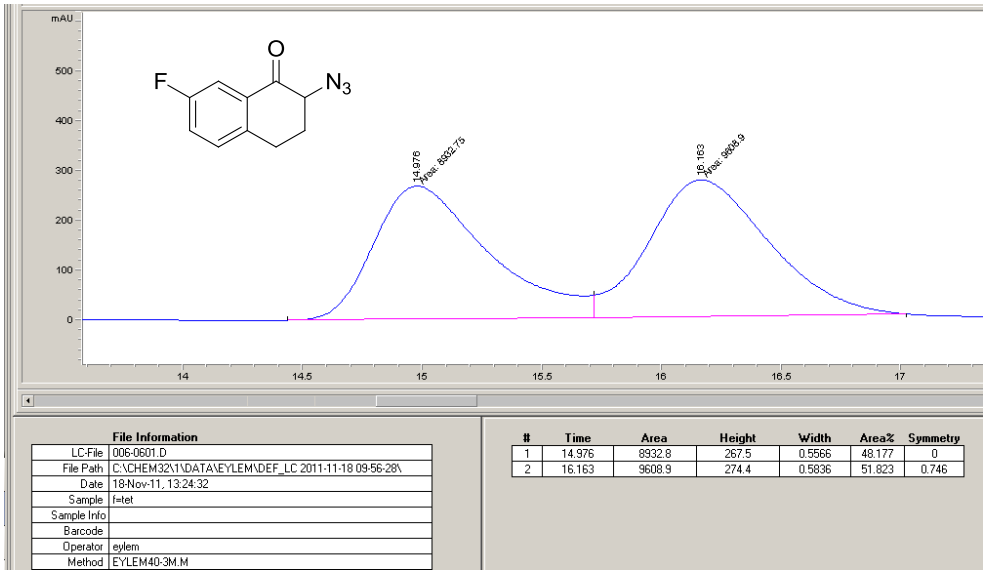


Figure B. 17 Racemic HPLC Chromatogram of (**138**)

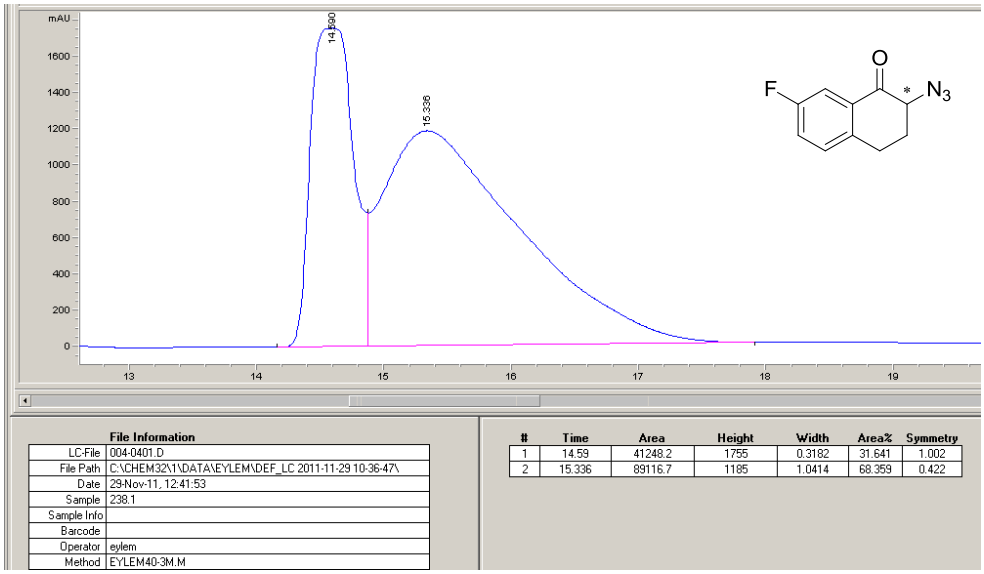


Figure B. 18 Chiral HPLC Chromatogram of **(138)**

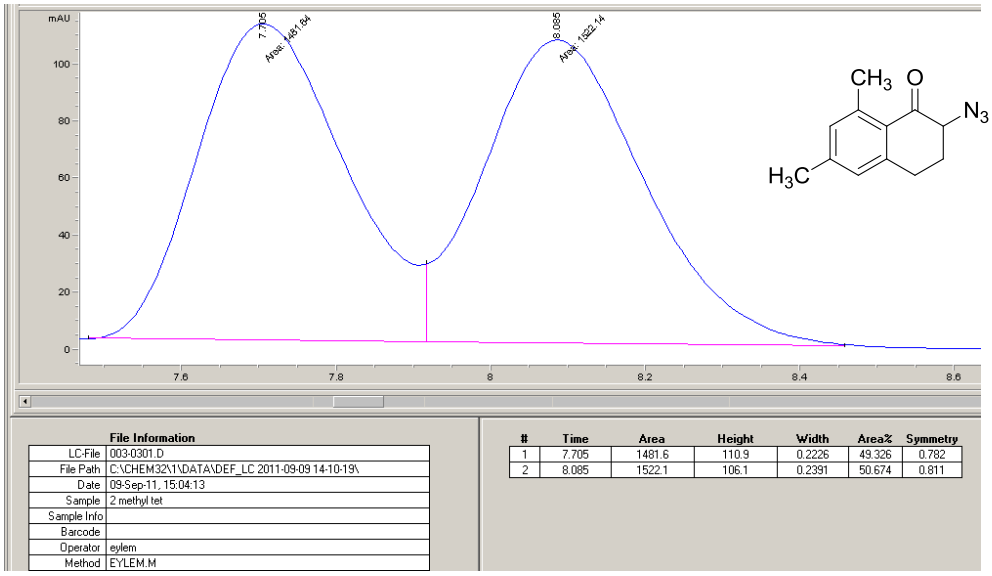


Figure B. 19 Racemic HPLC Chromatogram of **(139)**

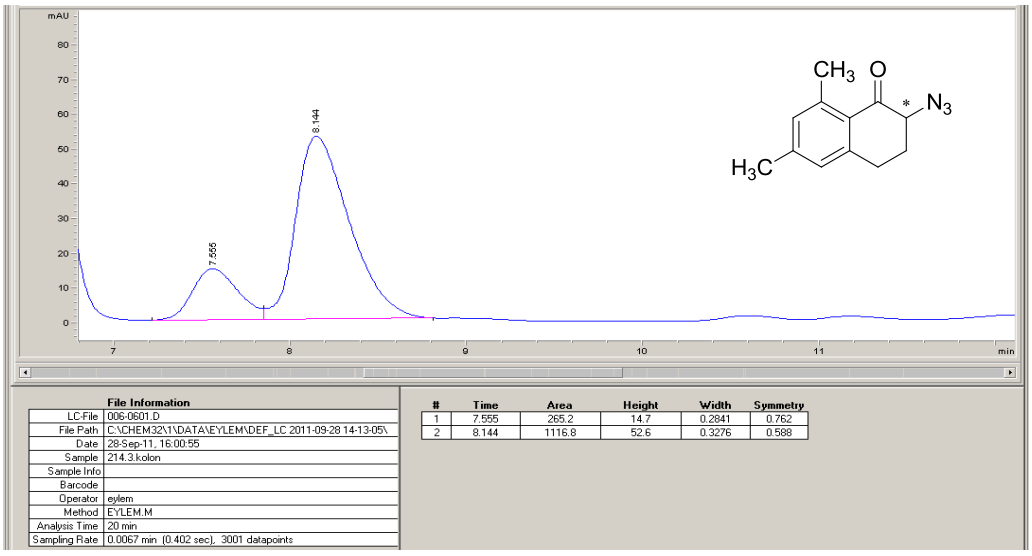
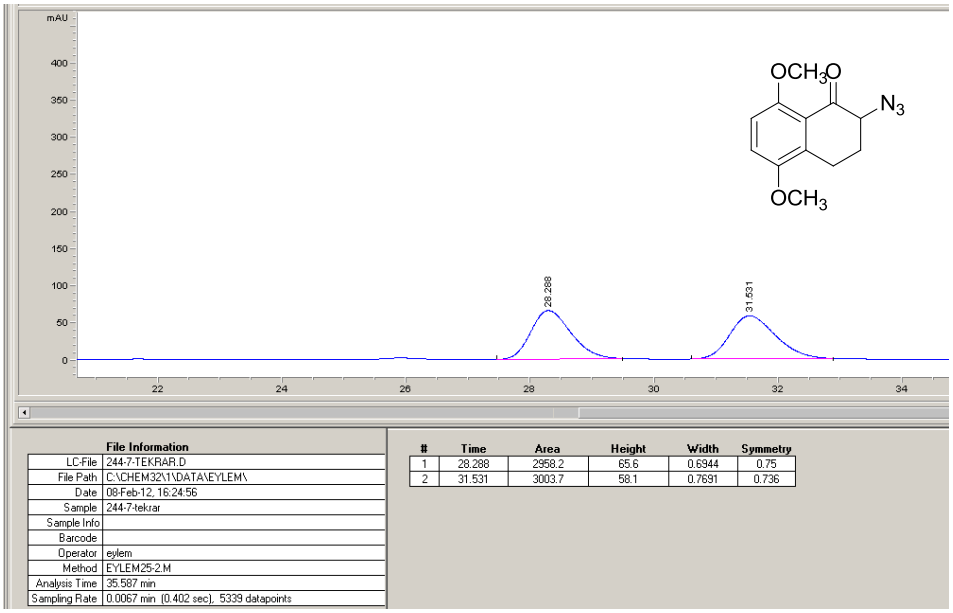


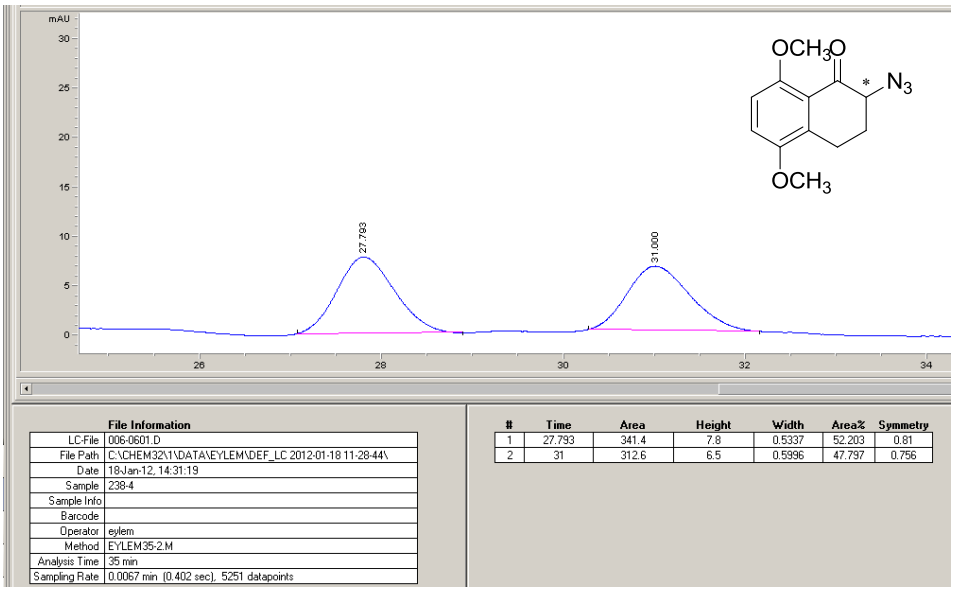
Figure B. 20 Chiral HPLC Chromatogram of **(139)**



File Information	
LC-File	244-7-TEKRAR.D
File Path	C:\CHEM32\1\DATA\EYLEM\
Date	08-Feb-12, 16:24:56
Sample	244-7-tekrar
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM25-2.M
Analysis Time	35.587 min
Sampling Rate	0.0067 min (0.402 sec), 5339 datapoints

#	Time	Area	Height	Width	Symmetry
1	28.288	2958.2	65.6	0.6944	0.75
2	31.531	3003.7	58.1	0.7691	0.736

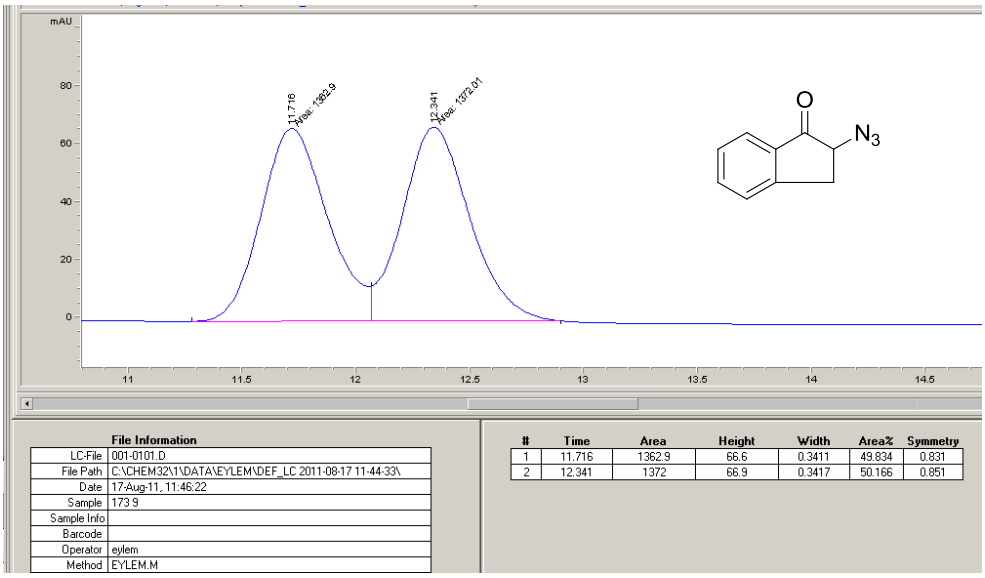
Figure B. 21 Racemic HPLC Chromatogram of **(140)**



File Information	
LC-File	006-0601.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2012-01-18 11-28-44\
Date	18-Jan-12, 14:31:19
Sample	238-4
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM35-2.M
Analysis Time	35 min
Sampling Rate	0.0067 min (0.402 sec), 5251 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	27.793	341.4	7.8	0.5337	52.203	0.81
2	31	312.6	6.5	0.5996	47.797	0.756

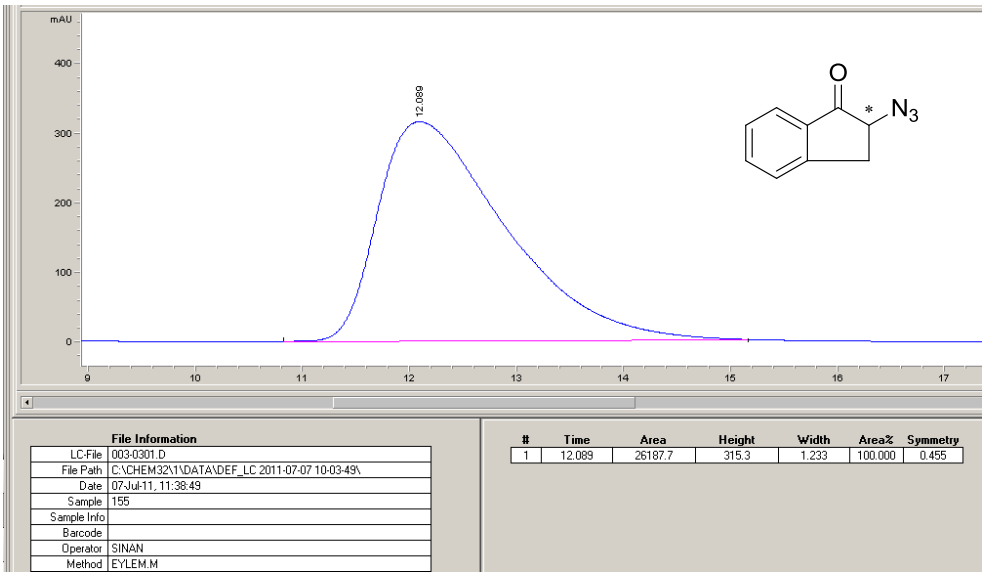
Figure B. 22 Chiral HPLC Chromatogram of **(140)**



File Information	
LC-File	001-0101.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-08-17 11-44-33\
Date	17-Aug-11, 11:46:22
Sample	173 9
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	11.716	1362.9	66.6	0.3411	49.834	0.831
2	12.341	1372	66.9	0.3417	50.166	0.851

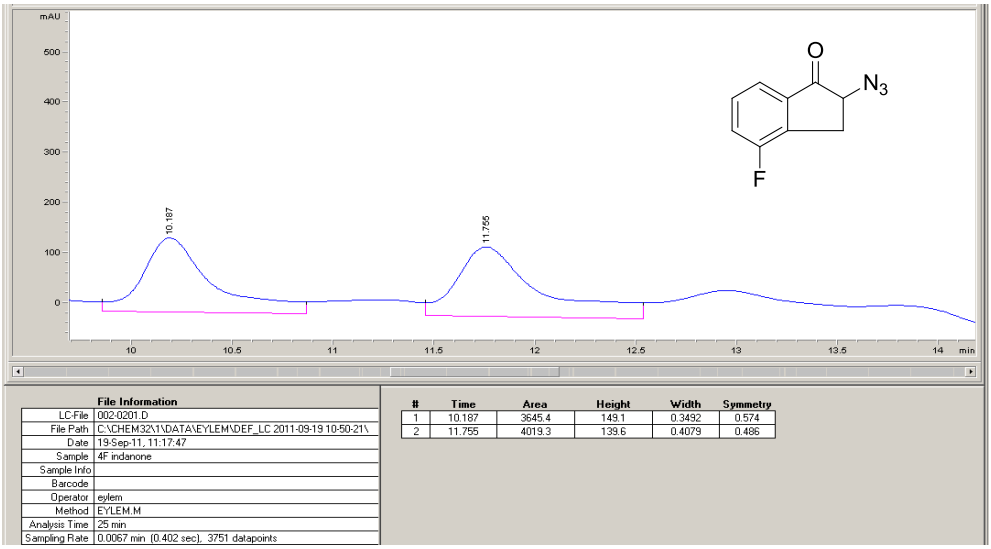
Figure B. 23 Racemic HPLC Chromatogram of **(131)**



File Information	
LC-File	003-0301.D
File Path	C:\CHEM32\1\DATA\DEF_LC 2011-07-07 10-03-49\
Date	07-Jul-11, 11:38:49
Sample	155
Sample Info	
Barcode	
Operator	SINAN
Method	EYLEM.M

#	Time	Area	Height	Width	Area%	Symmetry
1	12.089	26187.7	315.3	1.233	100.000	0.455

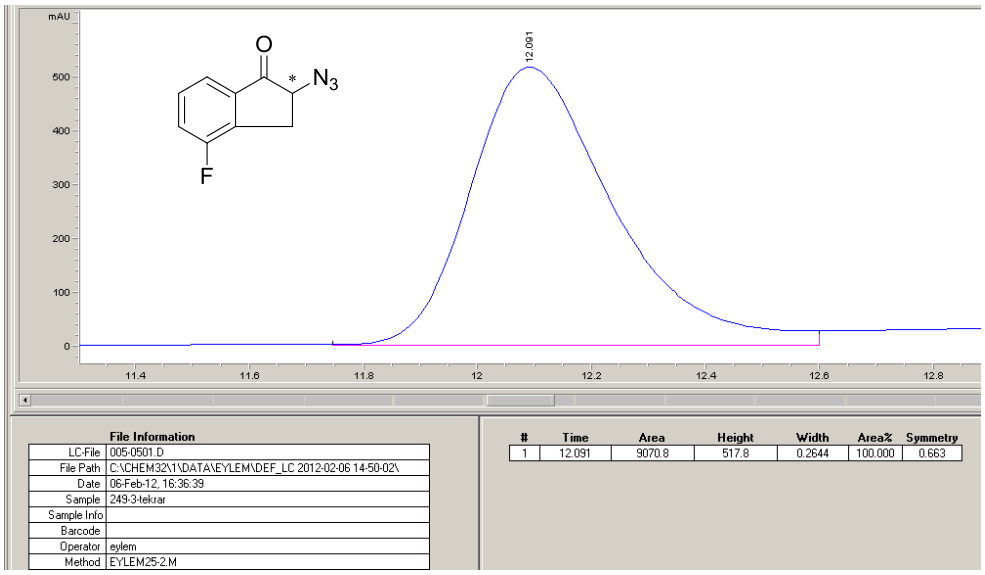
Figure B. 24 Chiral HPLC Chromatogram of **(131)**



File Information	
LC-File	002-0201.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2011-09-19 10-50-21\
Date	19-Sep-11, 11:17:47
Sample	4F indanone
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM.M
Analysis Time	25 min
Sampling Rate	0.0067 min (0.402 sec), 3751 datapoints

#	Time	Area	Height	Width	Symmetry
1	10.187	3645.4	149.1	0.3492	0.574
2	11.755	4019.3	139.6	0.4079	0.486

Figure B. 25 Racemic HPLC Chromatogram of **(138)**



File Information	
LC-File	005-0501.D
File Path	C:\CHEM32\1\DATA\EYLEM\DEF_LC 2012-02-06 14-50-02\
Date	06-Feb-12, 16:36:39
Sample	249-3-tekrar
Sample Info	
Barcode	
Operator	eylem
Method	EYLEM25-2.M

#	Time	Area	Height	Width	Area%	Symmetry
1	12.091	9070.8	517.8	0.2644	100.000	0.663

Figure B. 26 Chiral HPLC Chromatogram of **(138)**

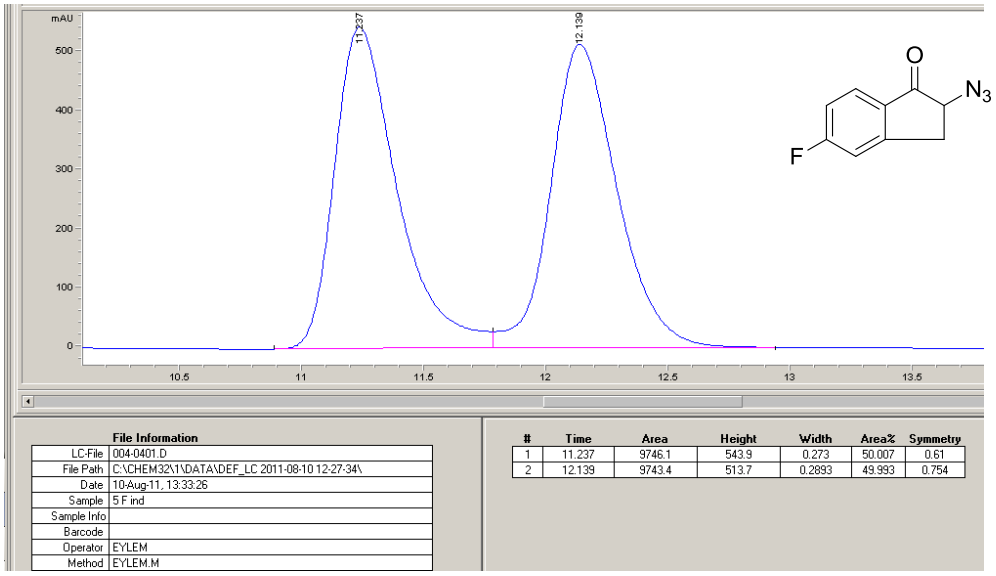


Figure B. 27 Racemic HPLC Chromatogram of **(142)**

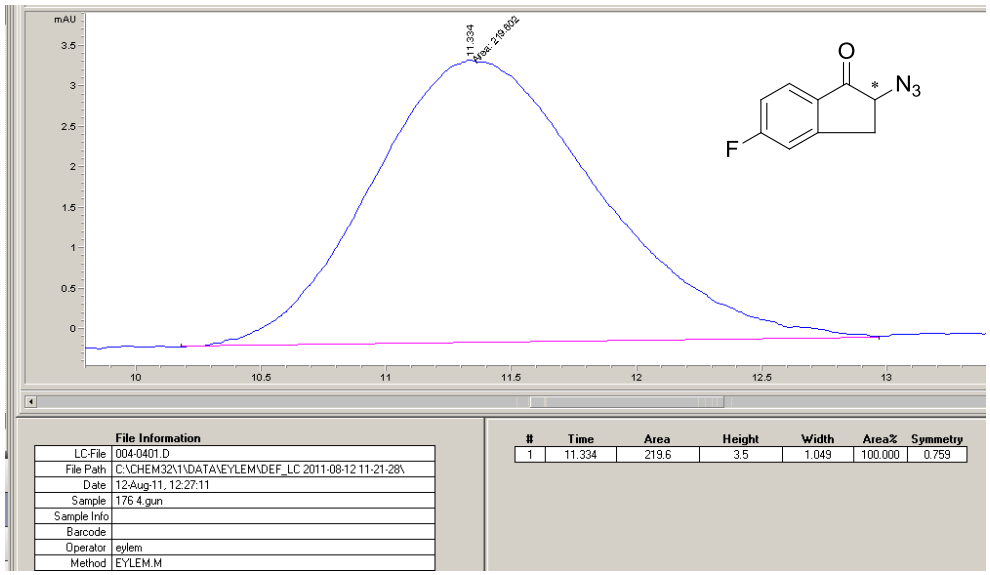


Figure B. 28 Chiral HPLC Chromatogram of **(142)**

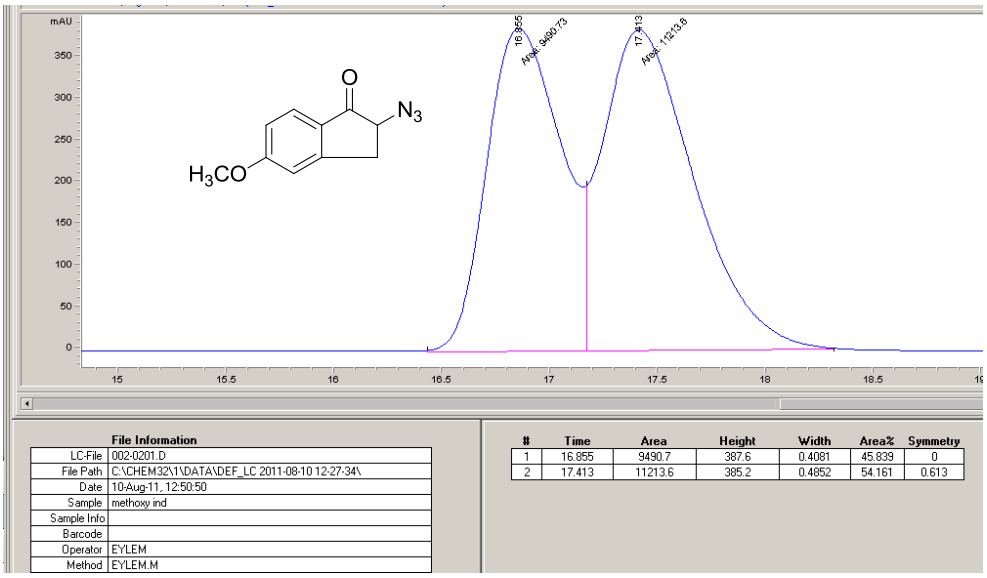


Figure B. 29 Racemic HPLC Chromatogram of **(143)**

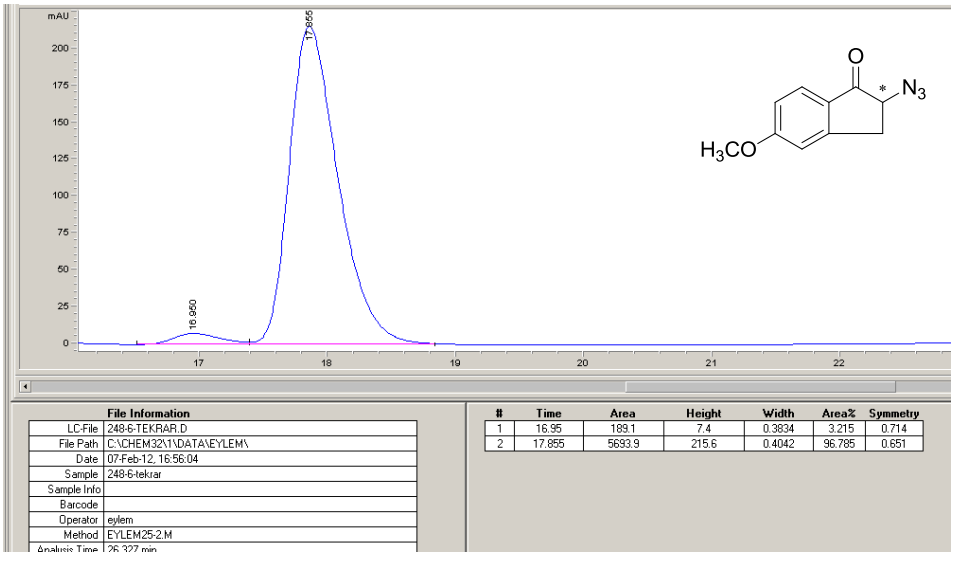


Figure B. 30 Chiral HPLC Chromatogram of **(143)**

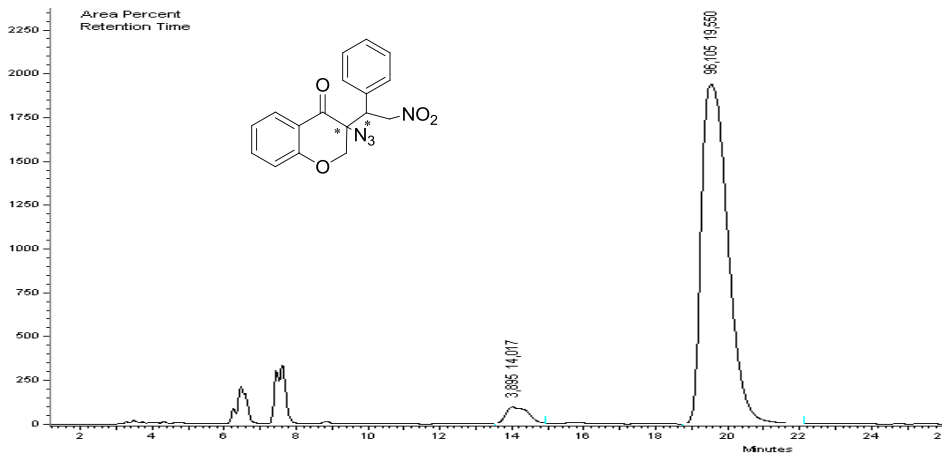


Figure B. 31 HPLC Spectrum of **(150)**

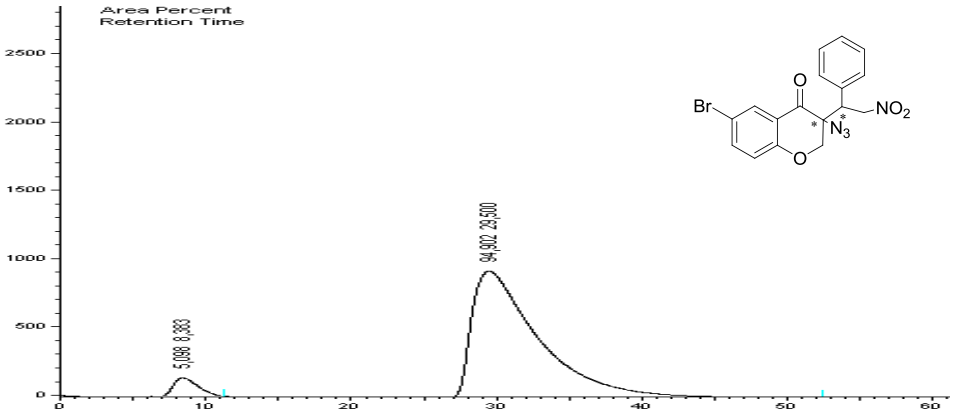


Figure B. 32 HPLC Chromatogram of **(151)**