Stereoselective C-C Bond Forming Reactions using Titanium Reagents: Synthesis of Chiral β-Amino Esters, β-Lactams, 3-Aryl Amides, 1,2-Diamines and Coumarin Derivatives

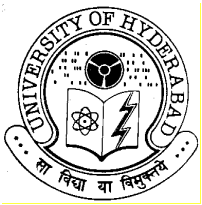
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

SURISETTI SURESH



SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD
HYDERABAD 500 046
INDIA

October 2005

To the loving memory of my father

Late Sri S. Nageswara Rao

School of Chemistry
University of Hyderabad
Central University P. O.,
Hyderabad 500 046
India

Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of **Professor M. Periasamy**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

SURISETTI SURESH

School of Chemistry
University of Hyderabad
Central University P. O.,
Hyderabad 500 046
India

Certificate

Certified that the work embodied in this thesis entitled "**Stereoselective C-C bond forming reactions using titanium reagents: Synthesis of chiral β-amino esters, β-lactams, 3-aryl amides, 1,2-diamines and coumarin derivatives"** has been carried out by Mr. **Surisetti Suresh** under my supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

DEAN
SCHOOL OF CHEMISTRY

Acknowledgements

With high regards and profound respect, I wish to express my deep sense of gratitude and indebtedness to my mentor **Prof. M. Periasamy** for his inspiring guidance and constant encouragement throughout my tenure here.

I extend my heartfelt thanks to Prof. G. R. Desiraju, Prof. E. D. Jemmis and Prof. M. Periasamy, Deans, School of Chemistry, for providing all facilities to carry out my work. I thank Prof. D. Basavaiah for his generous help in many ways. I would like to place on record my appreciation and gratitude to the faculty members of the School of Chemistry for their help and inspiring teaching.

I would like to thank the Director, IICT, Hyderabad and Dr. M. Vairamani, Mass Spectroscopy group, IICT, for providing mass spectra for some of the compounds.

I would like to thank my colleague Mr. S. Selva Ganesan, for his timely help and extreme cooperation for carrying out some of the experiments during my thesis work. I extend my heartfelt thanks to my past and present labmates Dr. P. Bharathi, Dr. L. V. Raman, Dr. C. R. Ramanathan, Dr. C. Ramesh Kumar, Dr. T. Rajesh, Dr. V. Dharma Rao, Dr. G. Srinivas, Dr. S. Sivakumar, Dr. N. Sampath Kumar, Dr. K. N. Jayakumar Mr. G. V. Karunakar, Dr. A. Mukkanti, Dr. M. Seenivasa Perumal, Mr. M. Narsi Reddy, Mr. N. Kishore Babu, Mrs. M. Padmaja, Mr. D. Shyam Raj, Mr. P. Vairaprakash, Mr. G. P. Muthukumara Gopal, Mr. Shaik Anwar, Mr. S. Satish Kumar, Mr. M. Nagaraju and Mr. B. Mallesh for creating a pleasant work atmosphere.

All the research scholars of the School of Chemistry have been extremely helpful and I thank them all. Abik, Balaraman, Balu, Bandaru, Basavoju, Bhuvan, Devendar, Gupta, Joseph, Pavan, Prabhakar, Pradeep, Prasad, Rajesh, Raju, Satyanarana Pal, Senthil, K. Senthil, Tin, Vamsee and Yadaiah are a few to mention. I also thank all of my friends in this campus that made my stay a memorable one.

A special note of thanks to all of my alchemie ‘99 friends for their extreme cooperation, affection and thoughtful discussion throughout my stay here. Shekar, Satish, Seenu, Koti, Bhaskar, Satti, Jaggu, Pushparaj, Battina, Ram, Phani, Kedar, Bharath, Venu, Chandu and Richard are some of them to mention.

I thank Mr. Raghavaiah for his help in X-ray data collection. All the non-teaching staff of the School has been helpful, I thank them all. Mr. Shetty, Mr. S. Satyanarayana, Mrs. Vijaya Lakshmi, Mr. V. Bhaskar Rao, Mrs. Asia Parwez, Mr. Vijaya Bhaskar, Mr. K. R. B. V. Prasad, Mr. Ramana, Mr. Joseph, Mr. Santosh, Mr. Sambasiva Rao, Mr. Nayak and Mr. Rangaiah are a few to mention.

I should thank all of my teachers for their constant encouragement and moral support throughout my academic carrier.

I wish to thank all my friends from Chinnapa Reddy Palli. I specially thank my childhood friends Anuradha, Riaz, Chandra, Subramanyam, Chandramohan, Gopal, Subbareddy, Shravan, Sam and Seenu for making my school education a memorable one. I thank all my Intermediate and BSc classmates for creating a very friendly atmosphere at Vidyanagar. Muni Subramanyam, Rajashekar, Tirupal, Giri, Srinivas, Muni, Venu, Penchalaiah, Hari, Vangarla, Sunkara, Ravi and Janardhan are a few to mention.

I wish to express my profound gratitude to my parents, my sister, my brother and all the relatives for their constant encouragement and moral support throughout my carrier.

I take this opportunity to gratefully acknowledge my uncle, Sri S. Sudhakar who is responsible for whatever I am today. I am at loss of words to express my indebtedness to my '*margadarsi*'.

I specially thank my uncle, Mr. B. Ayyalu, aunt, brothers and sisters at Gummidipundi. I extend my heartfelt thanks to Neelakantam uncle and Jayalakshmi aunt and other family members.

I wish to extend my sincere thanks to the University authorities for providing all the necessary facilities for this work. The X-ray crystallographic data were collected in the National Single Crystal X-ray facility funded by DST, New Delhi.

Finally I would like to thank the UGC and CSIR, New Delhi and ACRHEM, University of Hyderabad for the financial support during my tenure.

Surisetti Suresh

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
Ac	acyl
aq.	aqueous
Ar	aryl
BINAM	1,1'-binaphthyl-2,2'-diamine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi(2-naphthol)
Bn	benzyl
Boc	*tertiary*-butoxycarbonyl
br	broad (spectral)
Bu	butyl
Bz	benzoyl
cat.	catalytic
Cbz	benzyloxycarbonyl
d	doublet (spectral)
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact (in mass spectrometry)
equiv.	equivalent
er	enantiomeric ratio
Et	ethyl
HPLC	high-performance liquid chromatography
i	iso
J	coupling constant (in NMR spectroscopy)

LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
lit.	literature
m	multiplet (spectral)
MALDI-tof	matrix assisted laser desorption/ionization--time-of-flight
Me	methyl
MO	molecular orbital
mp	melting point
Ms	methanesulfonyl
n	primary
Nu	nucleophile
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
Phth	phthalyl
PMP	*para*-methoxyphenyl
Pr	propyl
Py	pyridyl
q	quartlet (spectral)
rt	room temperature
t	triplet (spectral)
t	tertiary
s	singlet (spectral)
TADDOL	α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxalan-4,5-dimethanol
TBDMS	*tertiary*-butyldimethylsilyl
TBS	tributylsilyl
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	tolyl
TS	transition state
Ts	toluenesulfonyl
X	halide

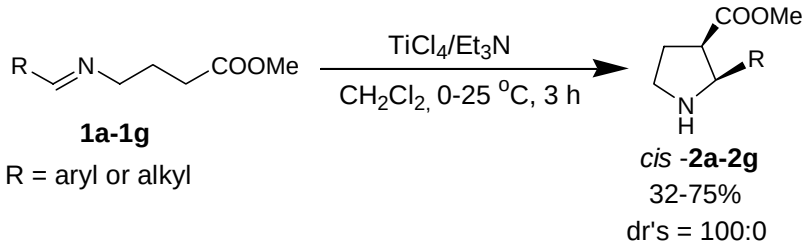
Abstract

This thesis entitled "**Stereoselective C-C bond forming reactions using titanium reagents: Synthesis of chiral β-amino esters, β-lactams, 3-aryl amides, 1,2-diamines and coumarin derivatives**" comprises of four chapters. Each chapter is subdivided into four sections namely **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**. The work described in this thesis is exploratory in nature and is arranged in the order the investigations were executed.

The first chapter describes the studies on the synthesis of cyclic and acyclic β-amino esters by the titanium enolate-mediated intramolecular Mannich-type reactions of γ-imino esters and intermolecular Mannich-type reactions of esters and imines. Applications of titanium enolates in the stereoselective C-C bond forming reactions are briefly reviewed in the introductory section.

Synthesis of *cis*-methyl 2-substituted-3-pyrrolidine carboxylates **2a-2g** was achieved in good yields and with excellent diastereoselectivity, by the intramolecular Mannich-type reactions of γ-imino esters **1a-1g** by using the $TiCl_4/Et_3N$ reagent system (Scheme 1).

Scheme 1



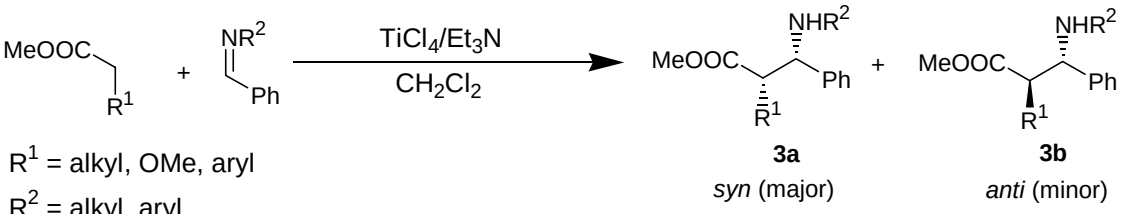
1a-1g
R = aryl or alkyl

cis -**2a-2g**
32-75%
dr's = 100:0

The structure and stereochemistry of the compound **2a** (R = Ph) was elucidated by the single crystal X-ray data of its oxalic acid complex.

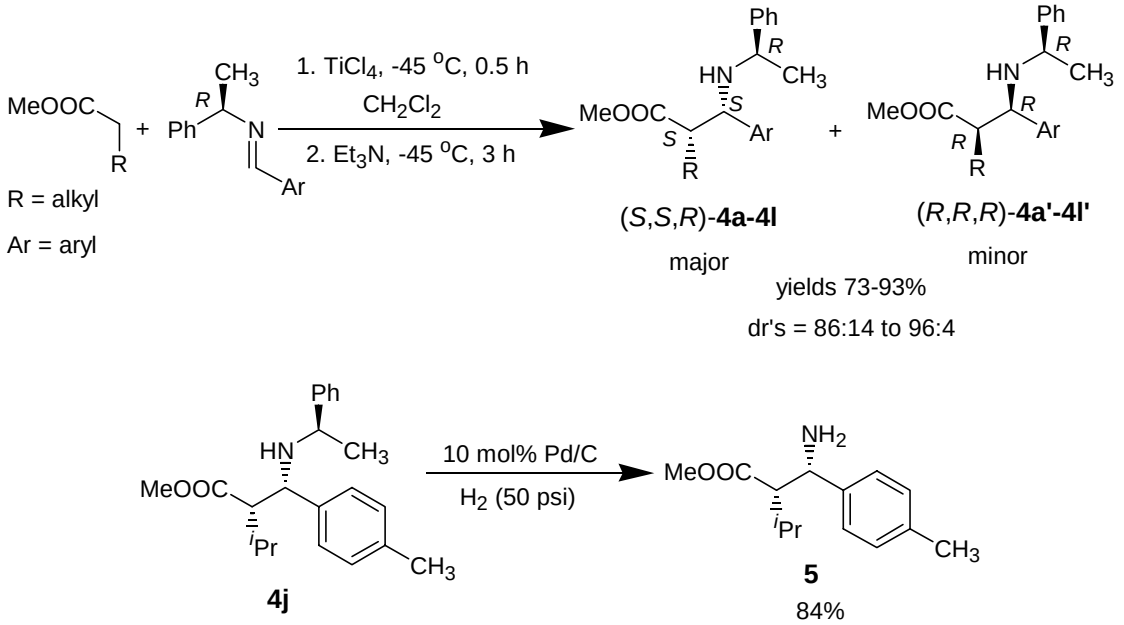
A titanium enolate-mediated intermolecular Mannich-type reaction of esters and imines was developed for the stereoselective synthesis of *syn*-β-amino esters **3a**. The β-amino esters **3** were obtained in good yields with high selectivity. In some cases, the reactions are >99% diastereoselective (Scheme 2).

Scheme 2



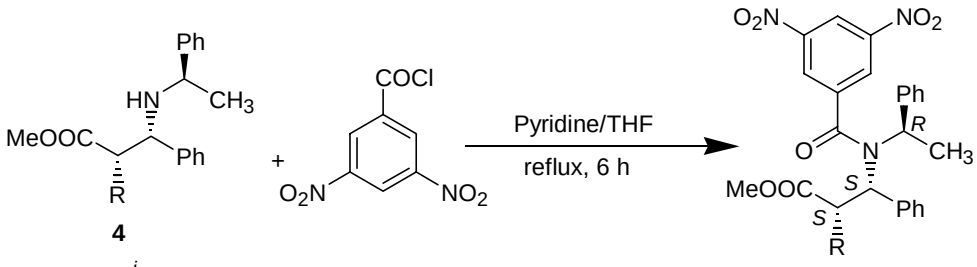
Mannich-type reactions of esters with chiral imines, prepared using optically pure α-methylbenzylamine and aldehydes, in the presence of $TiCl_4/Et_3N$ reagent system furnished the chiral *syn*-β-amino esters **4** with high diastereoselectivity (Scheme 3).

Scheme 3



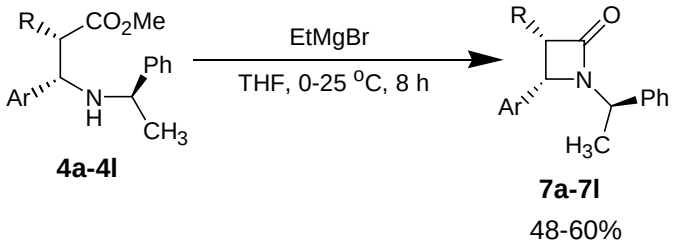
The structures of the 3,5-dinitrobenzamide derivatives **6** (Scheme 4) prepared from the chiral *syn*-β-amino esters **4**, were analyzed by single crystal X-ray studies. It was found that the 3,5-dinitrobenzamide derivatives **6** containing the (*R*)-α-methylbenzylamine moiety have the absolute configuration (*S*,*S*,*R*).

Scheme 4



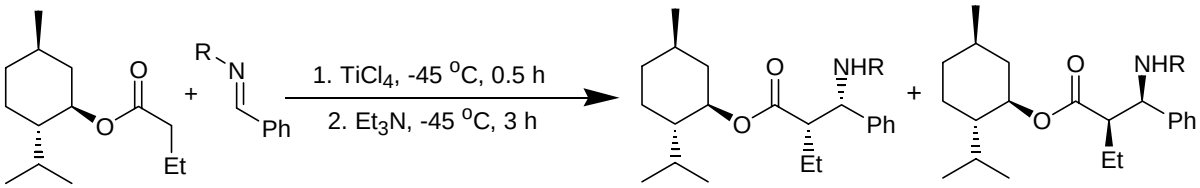
Chiral *cis*-β-lactams **7a-7l** were synthesized from the corresponding *syn*-β-amino esters **4a-4l** using the Grignard reaction (Scheme 5). The absolute configuration of the β-lactam **7l** (R = ^{i}Pr, Ar = *p*-Cl-C_6H_4) was assigned as (*S*,*S*,*R*) by X-ray structure analysis.

Scheme 5



The chiral *syn*-β-amino esters **9a-9c** containing (*L*)-menthyl moiety were also prepared by the Mannich-type reactions of the titanium enolate of the chiral ester **8** with achiral and chiral imines (Scheme 6).

Scheme 6



(*L*)-**8**

R = Bn, ^{n}Bu, *CH(Me)Ph

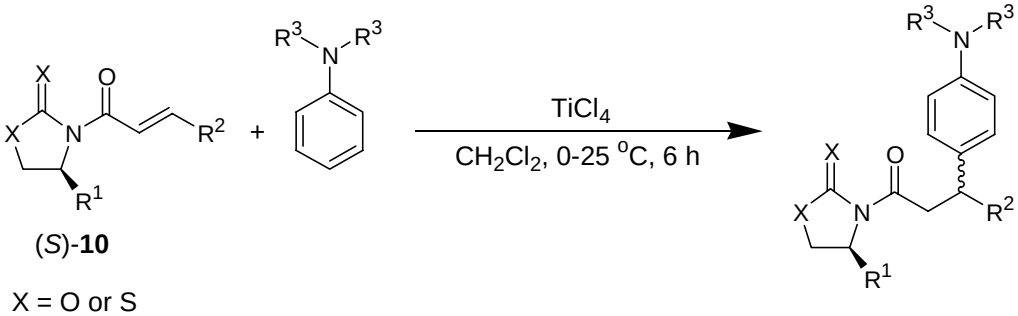
9a-9c

69-72%

dr = 56:44 to 97:3

Studies on the asymmetric 1,4-conjugate arylation (Michael-type reaction) of chiral oxazolidinone- or thiazolidinethione-derived enones **10** using *N*,*N*-dialkylarylamines and $TiCl_4$ are described in Chapter 2 (Scheme 7). The 1,4-addition products **11** were obtained in low yields and with good diastereoselectivity in some cases.

Scheme 7



(*S*)-**10**

X = O or S

R^1 = Bn or ^{i}Pr

R^2 = Ph or Me

R^3 = Me or Et

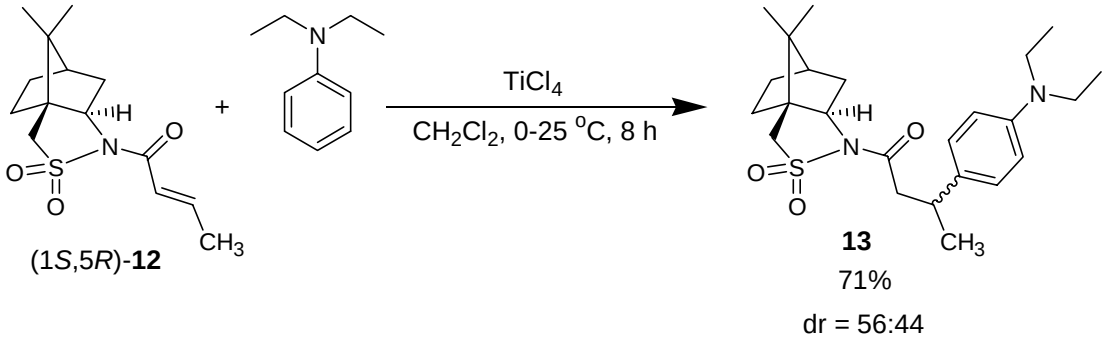
11

26-38%

dr's = 62:38 to >99:<1

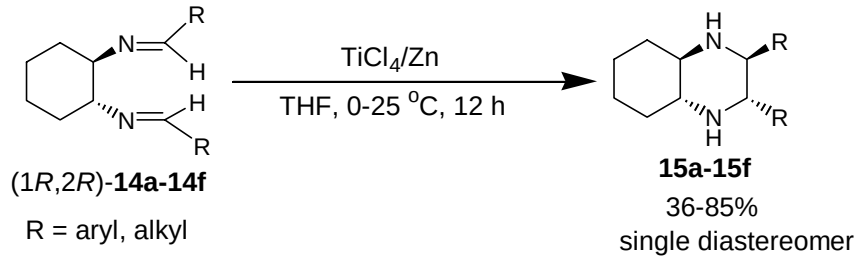
However, the conjugate addition of chiral *N*-crotonoylcamphorsultam (1*S*)-**12** using $TiCl_4$ and *N*,*N*-diethylaniline gave the corresponding 1,4-addition product **13** in good yields with poor selectivity (Scheme 8).

Scheme 8



In Chapter 3, the investigations on the intramolecular reductive coupling of diimines using low-valent titanium reagents are described. Intramolecular reductive coupling of optically active imines **14a-14f** containing *trans*-1,2-cyclohexyl moiety to the corresponding C_2-symmetric diamines **15a-15f** was achieved using the $TiCl_4$/Zn reagent system (Scheme 9). The reactions are highly diastereoselective. Variable temperature ^{13}C-NMR analyses of the products **15** revealed interesting conformational equilibria. X-Ray crystal structure studies of the compounds **15b** (R = *o*-OHC_6H_4) and **15e** (R = 1-naphthyl) were carried out.

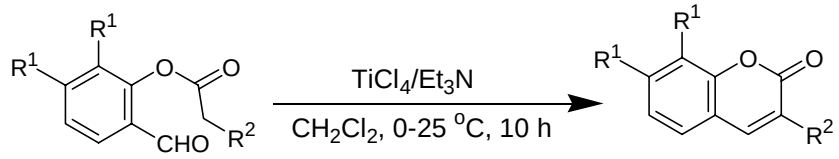
Scheme 9



Chiral oligomeric amides were prepared by the reaction of the chiral diamine **15a** (R = Ph) with adipoyl chloride. The chiral oligomeric amides were reduced to the corresponding oligomeric amino alcohols by using the $NaBH_4/I_2$ reagent system.

Studies on the synthesis of 3-substituted coumarins **17** by the reaction of the corresponding *ortho*-(*O*-alkanoyl)-arylaldehydes **16** with the $TiCl_4/R_3N$ reagent system are described in Chapter 4 (Scheme 10).

Scheme 10



16

R^1,R^1 = H,H or CH=CH-CH=CH

R^2 = H, Me, Et, Ph

17

37-63%

Mechanisms and intermediates involved in these transformations are discussed.

Note: Scheme numbers and compound numbers given in this abstract are different from those given in the Chapters. Also, different set of numbers for Schemes, Tables, compounds, Figures and references etc. are given in different Chapters.

Contents

Chapter 2

Asymmetric conjugate additions of aryltitanium reagents to chiral oxazolidinone-, thiazolidinethione- and camphorsultam-derived enones

Chapter 3

Synthesis of chiral C_2-symmetric diamines using titanium reagents and their utility in the synthesis of chiral polymers

Chapter 4

Intramolecular condensation of *ortho*-*O*-acyl aryl aldehydes using the $TiCl_4/R_3N$ reagent system: Synthesis of 3-substituted coumarins

Chapter 1

Stereoselective synthesis of β-amino esters via the reactions of γ-imino esters or esters and imines using the $TiCl_4/R_3N$ reagent system

1.1 Introduction

Titanium reagents have been used in a multitude of reactions in organic, inorganic and polymer chemistry. Several titanium reagents have become very much popular in organic synthesis due to their availability, inexpensiveness, the possibility of adjusting reactivity and selectivity by ligands, and the relative inertness toward redox processes.[1] With the exception of a structurally narrow group of cytotoxic titanocenes[2] and bis-β-diketonato complexes,[3] the toxicity effects, if any, of titanium compounds are related to the ligands. The widespread applications of titanium reagents are due to their unique ability in functional group transformations and also in attaining better chemo-, regio- and stereoselectivities.

Several titanium reagents have been extensively used in organic transformations. The Ziegler-Natta catalysis using $TiCl_4$ along with $AlEt_3$, is an important polymerization process.[4] Also, $TiCl_4$/R(Li)MgX, Cp_2TiCl_2/R(Li)MgX or $LiAlH_4$,[5] $TiCl_4$/KO^{t}Bu/Na/naphthalene,[6] $TiCl_4$/Li/TMSCl[7] and several titanium compounds in combination with other reagents are useful in fixing molecular nitrogen.[8-10] In 1973/74, it was observed that the low-valent titanium reagents ($TiCl_4$/Zn,[11] $TiCl_3$/Mg[12] and $TiCl_3$/$LiAlH_4$[13]) dimerize aldehydes or ketones to give olefins. The Cp_2TiCl_2/$(CH_3)_3Al$[14] (Tebbe's reagent) and $TiCl_4$/CH_2X_2/Zn[15] reagent systems have been used for the Wittig-type olefination of carbonyl compounds. The Reetz reagent,[16] Me_2TiCl_2, has been employed in *gem*-dimethylation of carbonyl compounds. The Sharpless epoxidation uses the Ti(O^{i}Pr)$_4$ in combination with chiral tartaric acid esters and a hydroperoxide for the asymmetric epoxidation of allylic alcohols.[17] The

Kulinkovich hydroxycyclopropanation reaction[18] allows esters to react with the $RMgX/Ti(O^iPr)_3X$ (X = O^iPr, Cl and Me) reagent system to yield the valuable organic compounds, cyclopropanols. Several organotitanium reagents prepared by the transmetalation of organoalkali metal reagents have been used in achieving chemo-, regio-, and stereoselectivities.

Carbon-carbon bond forming reactions are the most fundamental reactions in organic synthesis. The most versatile approach for this transformation is the nucleophilic additions of metal enolates of α-hydrogen containing carbonyl compounds to various kinds of electrophiles. The metal ion associated with the enolate has pronounced effect on stereoselectivity.[19] Titanium enolates have been very successfully applied in this respect and still interest is growing in this field. The titanium enolates are generally prepared by the transmetalation of the corresponding lithium enolates or silyl enol ethers. The enolates can also be prepared directly by treating the α-hydrogen containing carbonyl compounds with the $TiCl_4$/tertiary amine reagent system. We have undertaken research efforts on the development of directly prepared titanium enolates for stereoselective C-C bond forming reactions. Accordingly, it is of interest to briefly review the literature reports on the stereoselective C-C bond forming reactions mediated by titanium enolates.

1.1.1 Stereoselective aldol reactions mediated by titanium enolates:

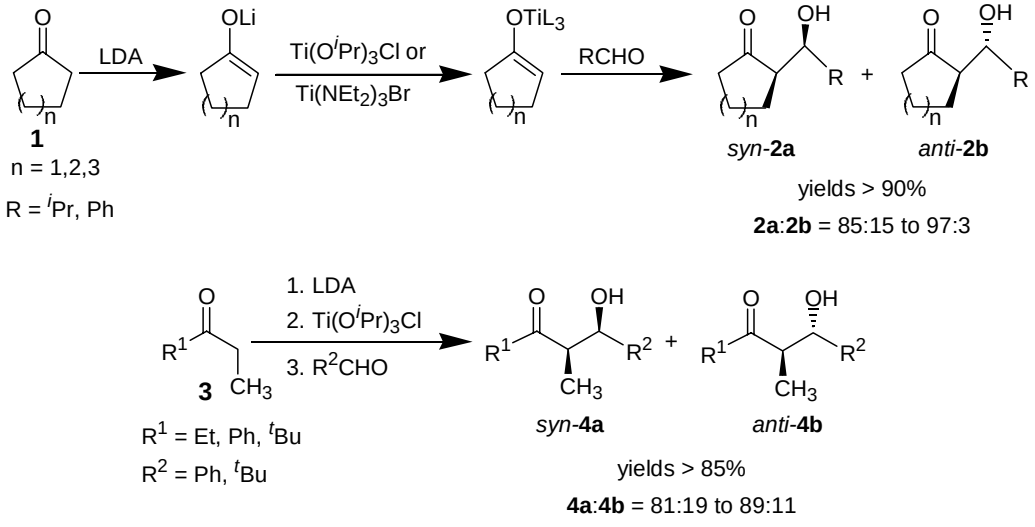
Stereoselective aldol reaction is a powerful tool for the construction of C-C bonds in organic synthesis, used in key steps in the syntheses of several complex and bioactive natural products.[20] Numerous titanium enolate-based asymmetric aldol transformations have provided convenient access to aldol products in enantiomerically

pure form. The titanium enolate-mediated aldol reaction has tremendous synthetic potential, since the titanium reagents are readily accessible and inexpensive.[21]

1.1.1.1 Aldol reactions of titanium enolates prepared by the transmetalation of lithium enolates:

In 1980/81 Reetz *et al*.[22] reported that the titanium enolates of cyclic ketones **1** or acyclic ketones **3**, prepared by the transmetalation of the corresponding lithium enolates using $Ti(O^iPr)_3Cl$ or $Ti(NEt_2)_3Br$, react with aldehydes to give *syn* adducts **2a** or **4a**, respectively with high diastereoselectivity (Scheme 1). In general, *Z*-enolates furnish *syn* aldol products under kinetic conditions. Formation of *syn* aldols from cyclic enolates seems to be difficult due to the reason that cyclic ketones can form only *E*-enolates. Interestingly, these authors reported high levels of *syn* selectivity by utilizing the titanium enolates of cyclic ketones in the aldol reaction. It was suggested that the *syn* aldol product preference occurred almost independently of enolate configuration in the case of acyclic ketones.[22]

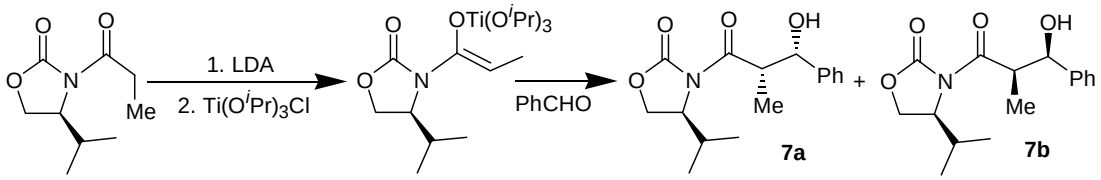
Scheme 1



Later, this methodology was extended by using the titanium enolates of aldehyde-derived *N*,*N*-dimethylhydrazones to obtain aldol type products in good yields with excellent selectivity.[22c]

Titanium enolate **6** of *N*-propanoyloxazolidinone **5** was prepared by the transmetalation of the corresponding lithium enolate with $Ti(O^iPr)_3Cl$ for use in the aldol reaction with benzaldehyde. The selectivities realized depended on the amount of the titanium reagent used (Scheme 2).[23]

Scheme 2



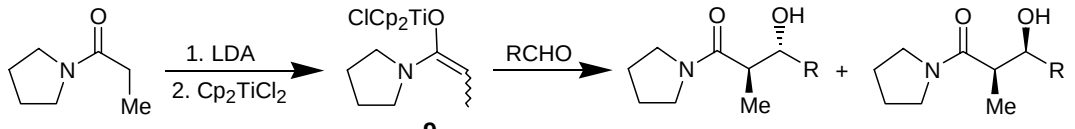
5 **6** **7a** **7b**

1 equiv. $Ti(O^iPr)_3Cl$ **7a**:**7b** = 77:16

3 equiv. $Ti(O^iPr)_3Cl$ **7a**:**7b** = 3:92

Murphy *et al*.[24] reported that an *anti*-selective aldol process using titanium enolate **9**, generated by the transmetalation of the corresponding lithium enolate of *N*-propionylpyrrolidine **8** with Cp_2TiCl_2, furnished the corresponding aldol adducts **10** in good yields with good to excellent selectivity (Scheme 3).

Scheme 3



8 **9** *anti*-**10a** *syn*-**10b**

R = Et, ^{i}Pr, Ph, MeCH=CH

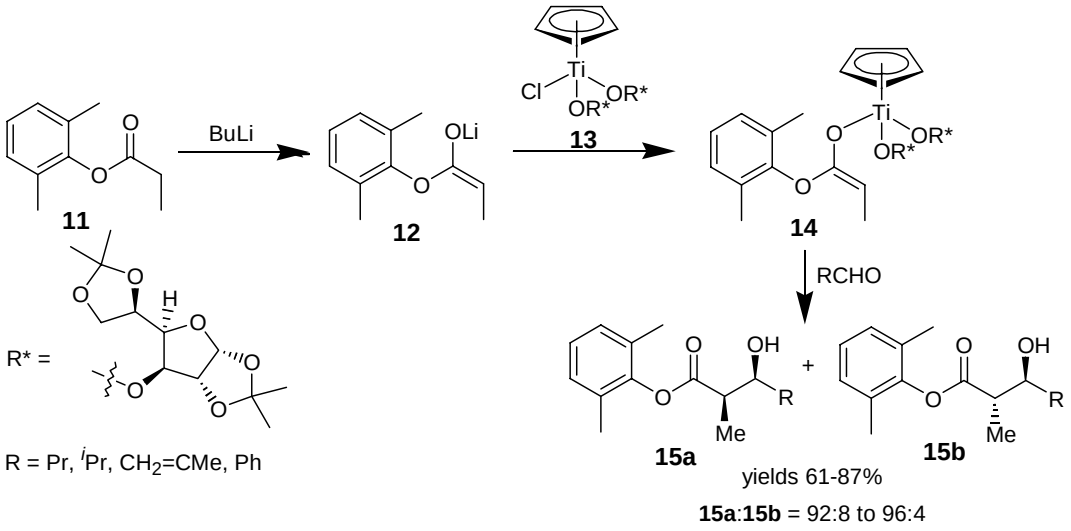
yields 64-77%

10a:**10b** = 79:21 to 98:2

Duthaler and coworkers[25] demonstrated that stereoselectivity in the titanium enolate-mediated aldol reaction could also be induced by chiral ligands on titanium. For

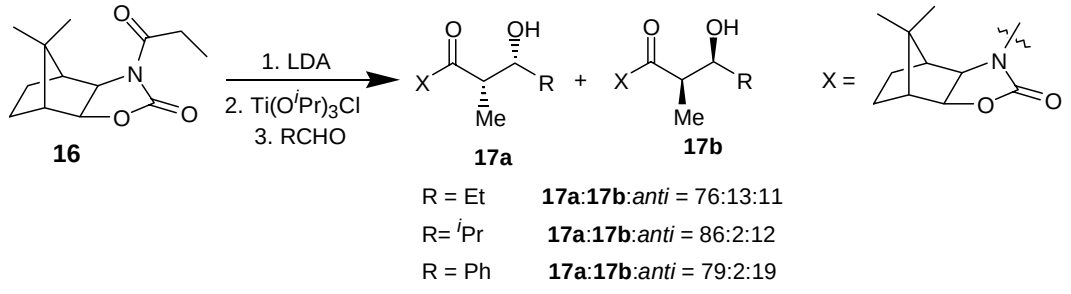
example, the cyclopentadienylbis-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose-3-*O*-yl)-chlorotitanate **13** was used in the preparation of titanium enolate **14** from the corresponding lithium enolate **12** of the ester **11**. The titanium enolate **14** upon reaction with aliphatic and unsaturated aldehydes provided the corresponding aldol adducts **15** in moderate to good yields with excellent enantioselectivity (Scheme 4).

Scheme 4



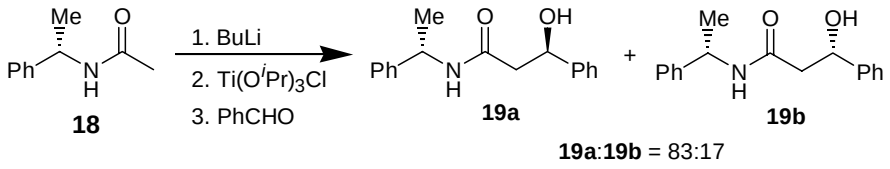
Moderate to good selectivity was observed for aldol reactions with a variety of aldehydes using camphorquinone-derived *N*-propanoyloxazolidinone **16** based titanium enolate. The enolate was generated by transmetalation of the corresponding lithium enolate with chlorotriisopropoxytitanium (Scheme 5).[26]

Scheme 5



The titanium enolate of a chiral acetamide **18** was employed in the aldol reaction with benzaldehyde to obtain the aldol product **19** with moderate selectivity. The enolate was generated from the chiral acetamide by transmetalation of the corresponding lithium enolate with triisopropoxytitanium chloride (Scheme 6).[27]

Scheme 6

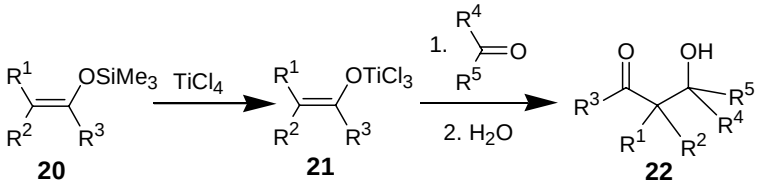


1.1.1.2 Aldol reactions of titanium enolates prepared by the transmetalation of enol silanes (Mukaiyama aldol reaction):

The discovery of the Lewis acid-mediated addition of enol silanes to aldehydes and acetals by Mukaiyama and coworkers[28] provides a useful route for the construction of molecules via the crossed-aldol reaction. Typically, enol silanes derived from esters, thioesters and ketones are not reactive towards aldehydes at ambient temperatures. However, stoichiometric quantities of Lewis acids like $TiCl_4$, $SnCl_4$, $AlCl_3$, BCl_3, $BF_3{\cdot}OEt_2$ and $ZnCl_2$ were found to promote aldehyde addition to give β-hydroxycarbonyl compounds. The titanium-mediated addition of enol silanes to aldehydes or acetals attracted considerable interest in the field of aldol reactions.

In 1973/74, Mukaiyama *et al.*[29] reported that in the presence of $TiCl_4$, trimethylsilyl enol ethers **20** react smoothly with aldehydes or ketones to give β-hydroxy carbonyl compounds **22** in good yields (Scheme 7).

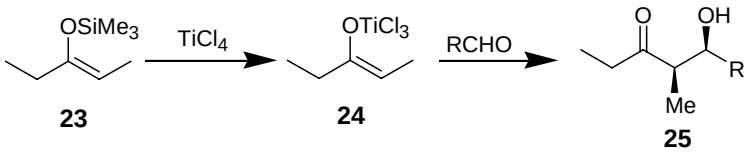
Scheme 7



R^1, R^2, R^3, R^4, R^5 = alkyl, H

Addition of titanium enolate **24**, generated in the reaction of trimethylsilyl enol ether **23** of 3-pentanone and $TiCl_4$, to aldehydes delivered the corresponding *syn* aldol adducts **25** in good yields with moderate selectivity (Scheme 8).[30]

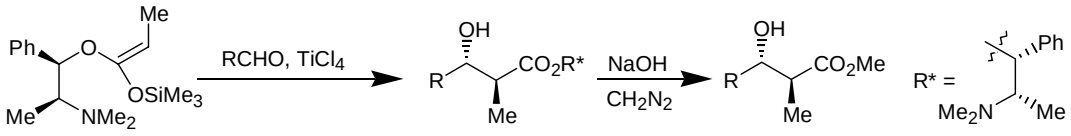
Scheme 8



R = Ph	yield 75%	*syn*:*anti* = 81:19
R = ^{i}Pr	yield 63%	*syn*:*anti* = 75:25

Gennari *et al.*[31] reported an enantioselective synthesis of *anti*-α-methyl-β-hydroxy esters **28** through $TiCl_4$-mediated aldol reactions between silylketene acetal **26** of (1*R*,2*S*)-*N*-methylephedrine propionate and aldehydes (Scheme 9).

Scheme 9



R = Ph, ^{n}C$_5$H$_{11}$, ^{n}C$_3$H$_7$, (*E*)-CH$_3$CH=CH, (*E*)-PhCH=CH

yields 60-88%

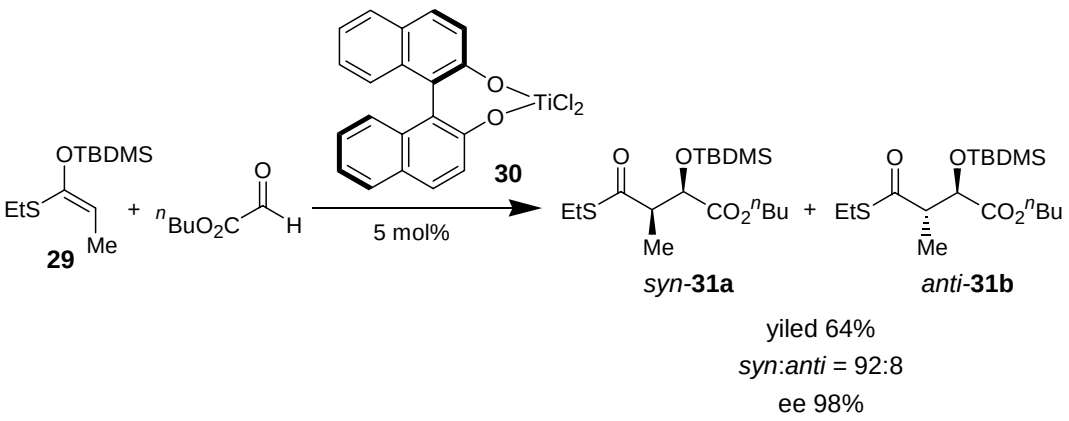
anti:*syn* = 75:25 to 85:15

yields 52-66%

ee's 91-94%

Aldol reaction of ethyl thiopropionate-derived (*E*)-enol silane **29** delivered *syn*-1,2-disubstituted aldol adduct **31a** in useful yield with excellent selectivity in presence of chiral BINOL:$TiCl_2$ complex **30**. Also, switch-over in the stereoselectivity was observed with the use of (*Z*)-configured enol silanes in this process (Scheme 10).[32]

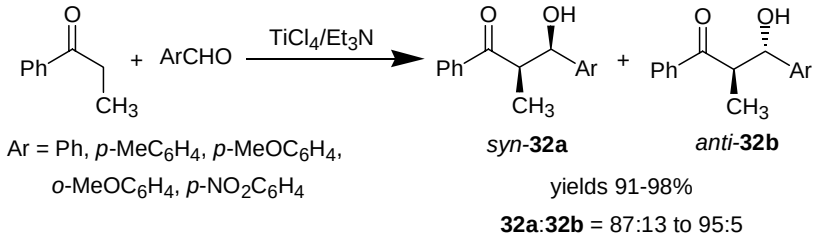
Scheme 10



1.1.1.3 Aldol reactions of titanium enolates prepared directly by using the chlorotitanium and tertiary amine combination:

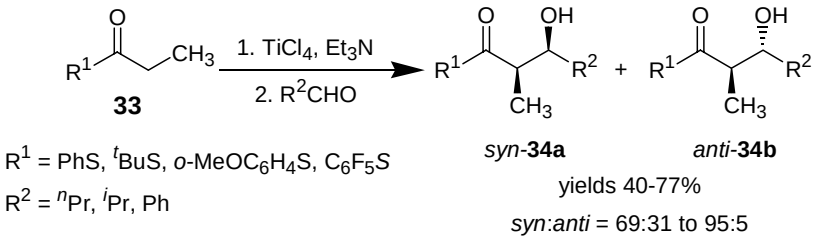
Harrison *et al*.[33] reported the first instances of stereoselective aldol reactions mediated by titanium enolates, generated directly by the reaction of carbonyl compounds using $TiCl_4$ and tertiary amine. It was reported that the reaction of propiophenone-derived titanium enolates with aromatic aldehydes afforded the corresponding *syn* aldol adducts **32a** with excellent selectivity and yields (Scheme 11).

Scheme 11



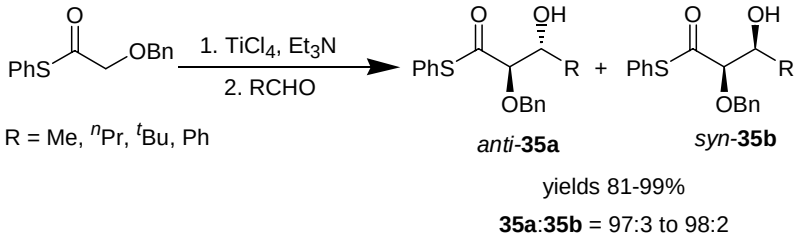
Syn-selective aldol reactions involving directly generated thioester **33** based titanium enolates were reported to give aldol adducts **34** in moderate yields with moderate to good selectivity (Scheme 12).[34]

Scheme 12



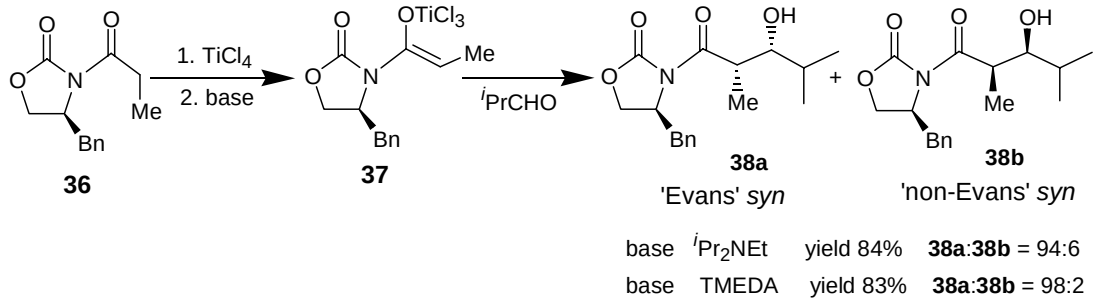
α-Benzyloxythioester-derived titanium enolates were employed in the synthesis of *anti*-α-benzyloxy-β-hydroxy thioesters **35a**. The products were obtained in excellent yields with high level of selectivity (Scheme 13).[35]

Scheme 13



Evans *et al*.[36] reported the addition of enantiomerically pure oxazolidinone **36**-derived titanium enolate **37** to isobutyraldehyde for obtaining the corresponding 'Evans' *syn* aldol product **38a** in good yield with excellent selectivity (Scheme 14).

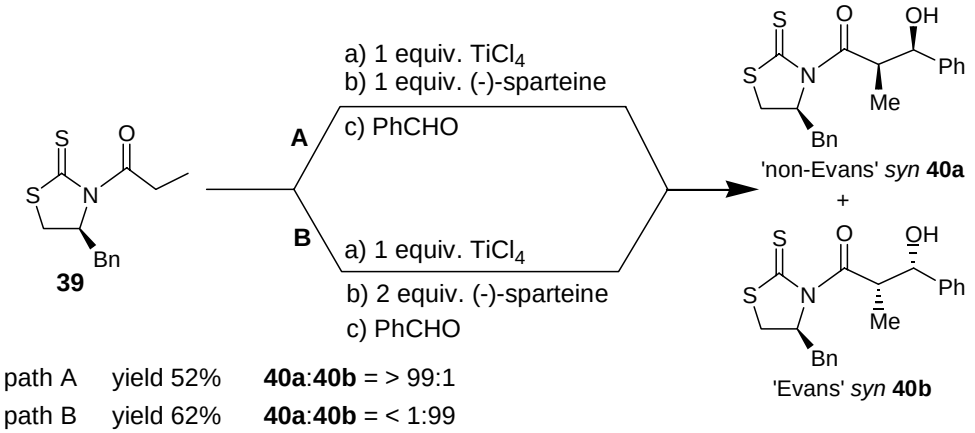
Scheme 14



It was also found that the amount of base has tremendous effect in the titanium-mediated aldol reaction of *N*-propanoylthiazolidinethione **39** with benzaldehyde. For

example, use of 1 equiv. of (-)-sparteine afforded 'non-Evans' *syn* aldol product **40a**, whereas 2 equiv. of (-)-sparteine delivered 'Evans' *syn* aldol product **40b** (Scheme 15).[37]

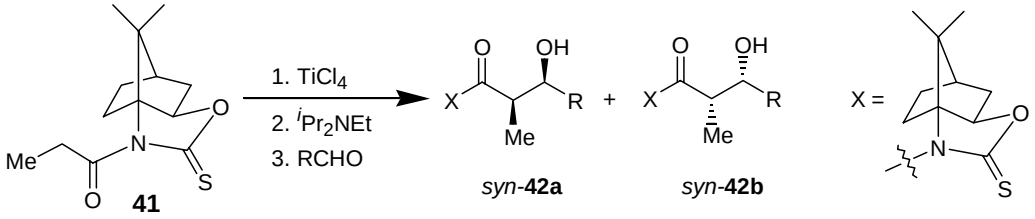
Scheme 15



Evans and several other research groups[38] studied the asymmetric aldol processes by utilizing the reactions of several oxazolidinone-, oxazolidinethione-, oxazolidineselone-, thiazolidinethione-derived titanium enolates (generated directly by treating the respective carbonyl compound with chlorotitanium reagents and tertiary amines) with different aldehydes. The selectivities realized in these reactions depend on the substrates, reagents and reaction conditions.

Yan and coworkers[39] developed titanium enolate mediated aldol reaction as an extension of their boron enolate methodology. Good yields and *syn* diastereoselectivity were reported using the camphor-derived *N*-acyloxazolidinethione **41** (Scheme 16). The high selectivities were attributed to additional chelation afforded by the thiocarbonyl of the chiral auxiliary. The reactions with the corresponding *N*-bromoacyl derivatives also provided the products in excellent isolated yields and stereoselectivity.[39c,d]

Scheme 16



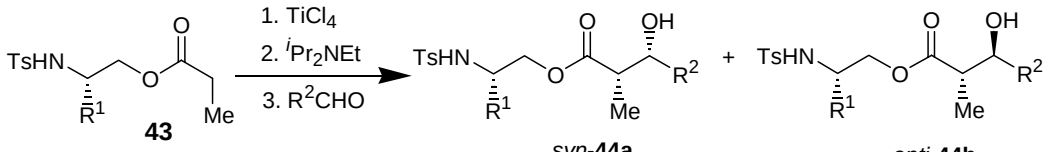
R = MeCH=CH yield 85% **42a**:**42b** = >99:1

R= ^{i}Pr yield 84% **42a**:**42b** = 98:2

R = Ph yield 85% **42a**:**42b** = 97:3

Excellent *syn* selectivity was realized in the titanium enolate-mediated asymmetric aldol reactions by utilizing the chiral auxiliaries **43** derived from enantiomerically pure 1,2-amino alcohols (Scheme 17).[40]

Scheme 17



R^1 = Bn, ^{i}Pr

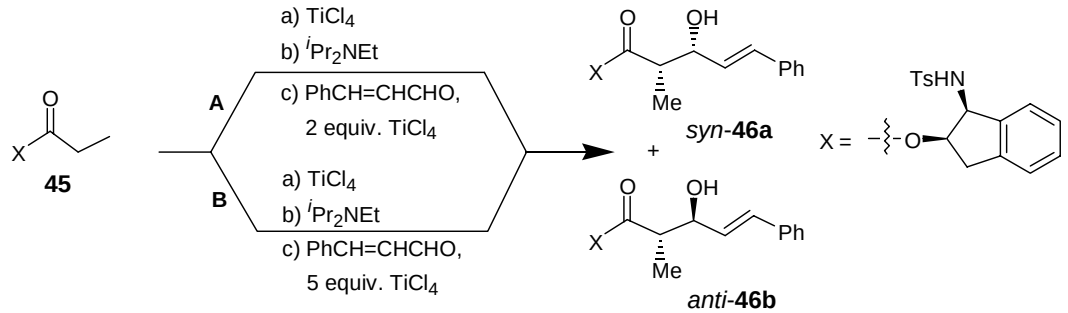
R^2 = $BnOCH_2$, $BnO(CH_2)_2$, ^{i}Bu, PhCH=CH

yields 80-93%

syn:*anti* = 95:5 to 98:2

Ghosh and coworkers[41] studied the asymmetric aldol reactions utilizing the titanium enolates generated by the reaction of enantiomerically pure *cis*-1-toluenesulfonamido-2-indanol-derived esters **45** with $TiCl_4$ and diisopropylethylamine. High levels of both *syn*- and *anti*-selectivities were observed in the aldol reactions of these titanium enolates with a range of aldehydes. A switch-over in the selectivity was observed when the stoichiometry of $TiCl_4$ was increased from 2 equiv. to 5 equiv. for pre-complexation with cinnamaldehyde (Scheme 18).[41e]

Scheme 18



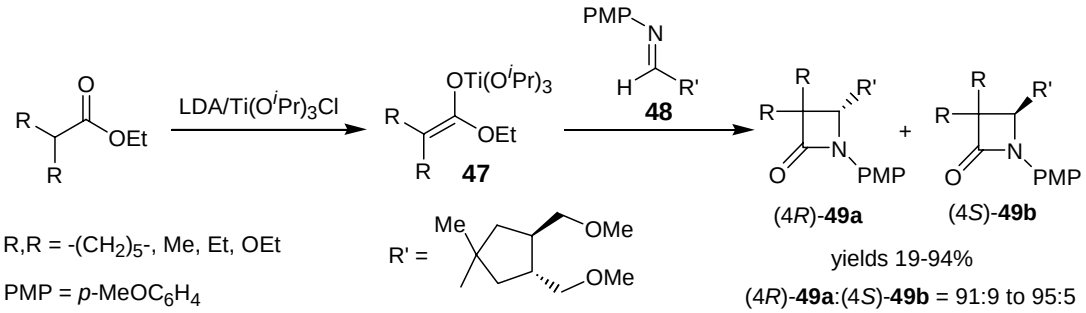
1.1.2 Stereoselective additions of titanium enolates to imines (Mannich-type reactions):

Mannich-type reactions provide convenient routes for the synthesis of β-amino carbonyl compounds.[42] Addition of titanium enolates to imines is a useful method to access the β-amino carbonyl compounds with one or two stereogenic centers depending upon the choice of enolate substituent and imine. Use of titanium enolates in the Mannich-type reactions gives high levels of selectivities with interesting features of reactivities.

1.1.2.1 Titanium enolates prepared by the transmetalation of lithium enolates (Mannich-type reactions):

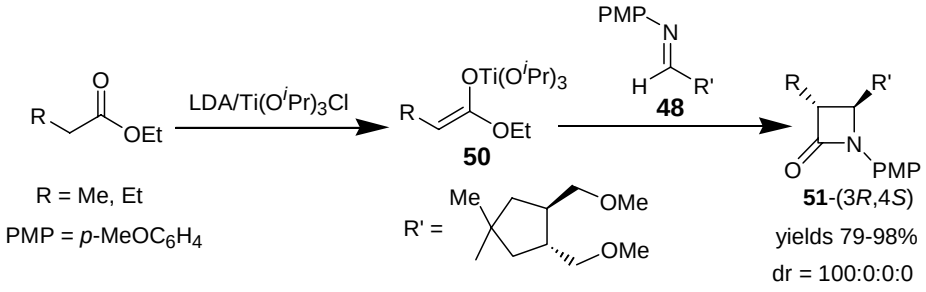
Fujisawa *et al.*[43] reported a diastereoselective addition of titanium enolates **47** of esters, prepared by the transmetalation of the corresponding lithium enolates with the chlorotriisopropoxytitanium, to a chiral imine **48** that provided (4*R*)-β-lactams **49a** as major diastereomers while the use of lithium enolates gave (4*S*)-β-lactams **49b** as major products (Scheme 19).

Scheme 19



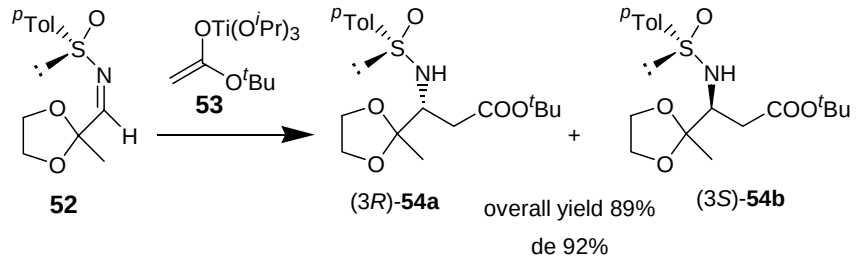
Later, two new stereogenic centers were introduced via the condensation reaction of the titanium enolates **50** of prochiral esters with the chiral imine **48** to afford (3*R*,4*S*)-β-lactams **51** exclusively.[44] Whereas the use of lithium enolates gave the corresponding (3*S*,4*S*)-β-lactams stereoselectively (Scheme 20).[44]

Scheme 20



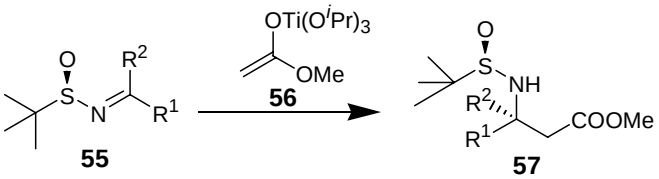
A similar strategy was employed in the addition reaction of the titanium enolate **53** of ^{t}butyl acetate, generated by the transmetalation of the corresponding lithium enolate with Ti(O^{i}Pr)$_3$Cl, to the chiral imine **52**, which resulted in the formation of chiral β-amino ester **54a** with 92% de (Scheme 21).[45]

Scheme 21



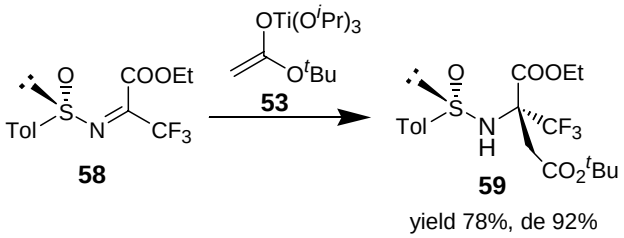
Ellman and coworkers[46] reported the addition of titanium ester enolate **56**, prepared by the transmetalation of the corresponding lithium ester enolate, to enantiomerically pure *t*butanesulfinyl aldimines or ketimines **55** that provided optically active β-amino esters **57** in good yields with high level of diastereoselectivity (Scheme 22).

Scheme 22



It was reported that the reaction of the titanium acetate enolate **53**, produced by the $Ti(O^iPr)_3Cl$/LDA reagent system and acetate, with enantiomerically pure sulfinimine **58**, exhibited high stereocontrol among the several metal enolates used (Scheme 23).[47]

Scheme 23

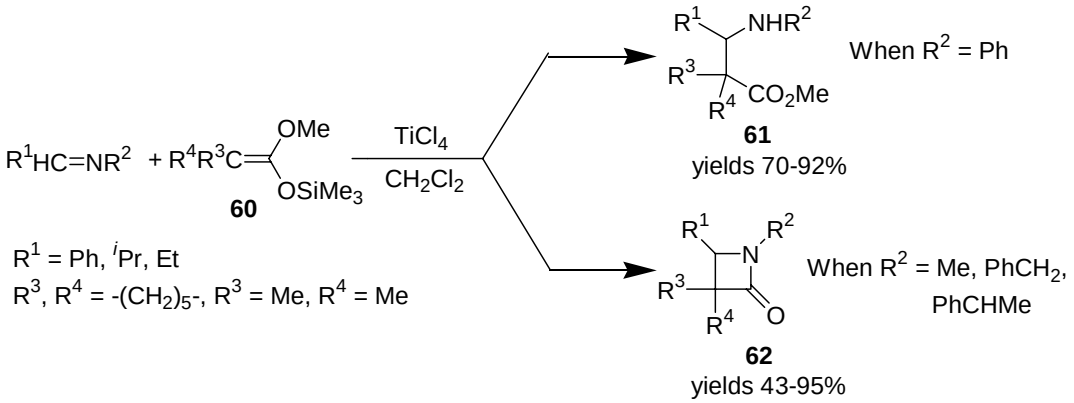


1.1.2.2 Titanium enolates prepared by the transmetalation of enol silanes (Mannich-type reactions):

First instances for the synthesis of β-amino esters via $TiCl_4$-mediated reaction of enol silanes with imines, was reported by Ojima and coworkers[48] in 1977. These authors showed that *O*-methyl-*O*-trimethylsilyl ketene acetals **60** react with imines in the presence of $TiCl_4$ to afford β-amino esters or β-lactams depending on the nature of

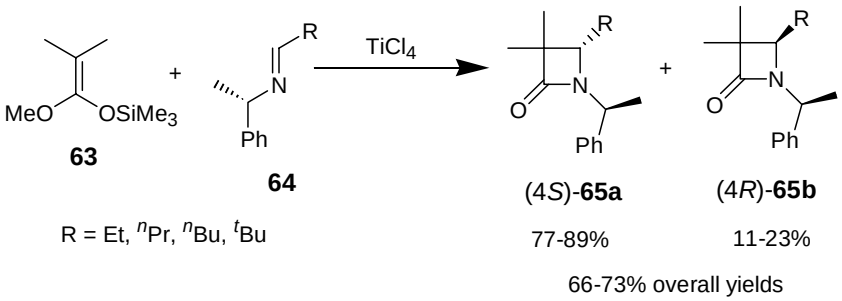
imine: *N*-arylimines afforded β-amino esters **61**, while *N*-alkylimines gave β-lactams **62** (Scheme 24).

Scheme 24

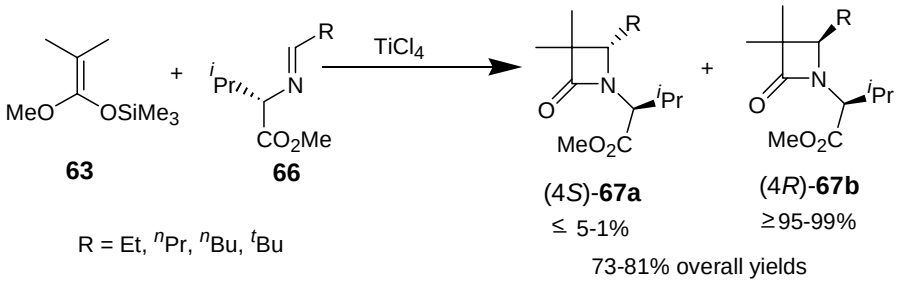


It was reported that the $TiCl_4$ mediated addition of dimethylketene methyl trimethylsilyl acetal **63** to chiral imines gave β-lactams directly with high diastereoselectivity. In the case of imines **64**, the diastereomeric excesses were in the range of 54-78%, and the (*S*) configuration was induced at the C-4 position of the resulting β-lactams **65a** (Scheme 25a). High diastereomeric ratios (up to > 99:1) were obtained using imines **66**, derived from (*S*)-valine methyl ester. It was suggested that the high level of diastereoselectivity resulted in this transformation is due to the formation of a chelated complex of the imino ester **66** with $TiCl_4$ (Scheme 25b).[49]

Scheme 25a

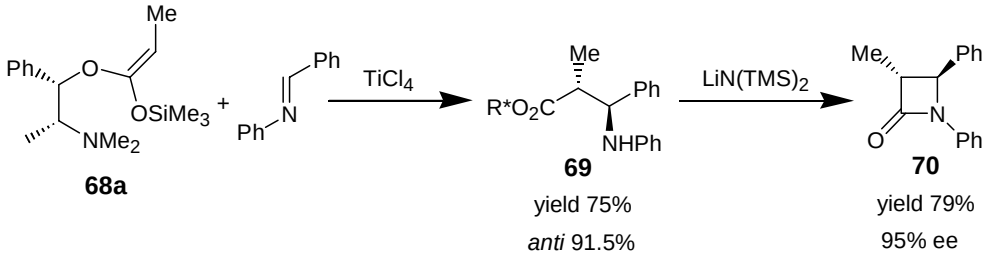


Scheme 25b

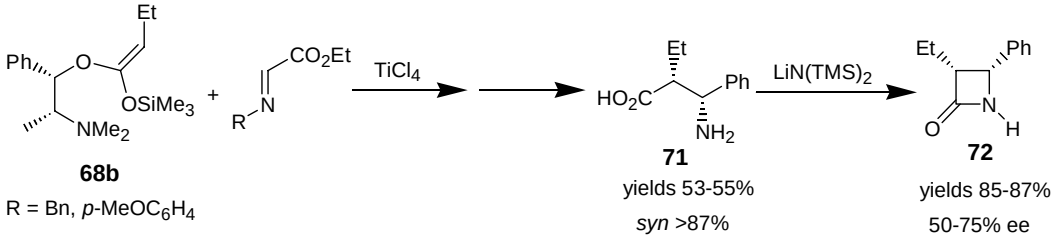


Gennari and coworkers[50] reported that the chiral *N*-methylephedrine-derived silyl ketene acetal **68a** react with *N*-benzylideneaniline to afford *anti*-β-amino esters **69** with high diastereoselectivity in the presence of $TiCl_4$ (Scheme 26a). While **68b** and imino esters gave the *syn*-β-amino ester and obtained the corresponding acid **71** in steps. The authors rationalized that the *syn* diastereoselectivity is due to the chelation of imino esters with $TiCl_4$ (Scheme 26b).

Scheme 26a



Scheme 26b

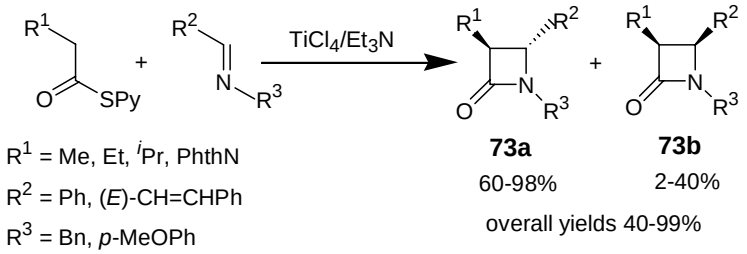


1.1.2.3 Titanium enolates generated directly from chlorotitanium reagents and tertiary amines (Mannich-type reactions):

In 1991 Cinquini and coworkers[51] reported that the reaction of titanium enolates, generated by the treatment of 2-thiopyridyl esters using triethylamine and $TiCl_4$, with

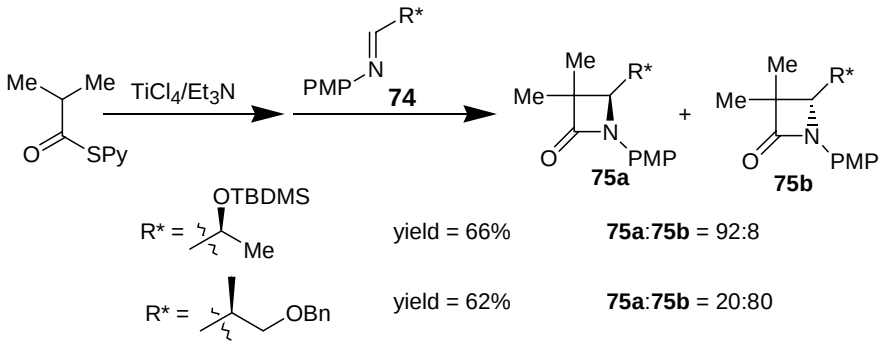
imines afforded *trans*-β-lactams **73a** in good to excellent yields with moderate to good stereoselectivity (Scheme 27).

Scheme 27



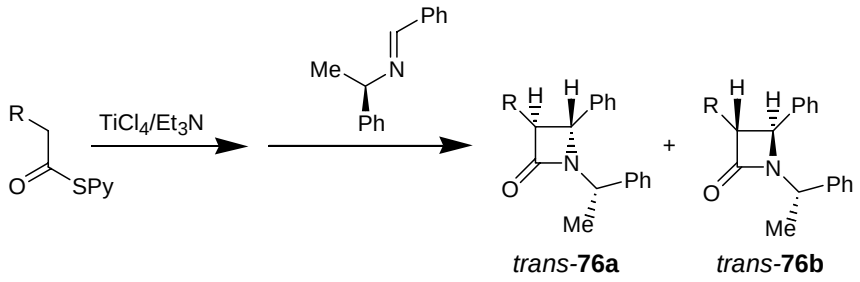
Asymmetric synthesis of β-lactams **75a** by the condensation of titanium enolates of 2-pyridyl thioesters with chiral imines **74**, derived from enantiomerically pure aldehydes, was also reported.[52] The selectivities depend on the chiral imines used (Scheme 28).

Scheme 28



The *N*-benzylidene-(*R*)-α-methylbenzylamine was also employed in the stereo-selective synthesis of *trans*-β-lactams **76** using titanium enolates of 2-pyridyl thioesters (Scheme 29).[53] The absolute configuration at C3 and C4 of the major isomer *trans*-β-**76a** was established as 3*S*,4*R*.

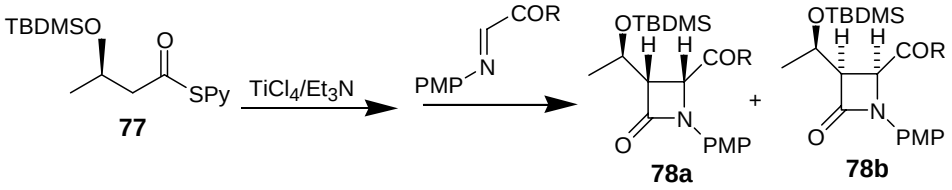
Scheme 29



R = ^{i}Pr	yield = 62%	*trans*:*cis* = 93:7	**76a:76b =** 91:9
R = OSi(^{i}Pr)$_3$	yield = 90%	*trans*:*cis* = 62:38	**76a:76b =** 90:10

Later, it was reported that the titanium enolate of a chiral 2-pyridyl thioester **77** reacted with imines to give the corresponding *cis*-β-lactams **78a** with high selectivity (Scheme 30).[54]

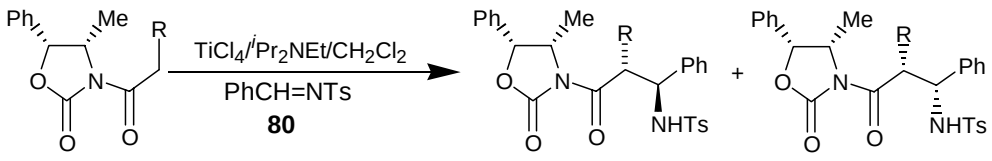
Scheme 30



R = OMe	yield = 21%	**78a**:**78b** = 91:9	
R = OCH=CH$_2$	yield = 82%	**78a**:**78b** = 94:6	

Titanium enolates of *N*-acyloxazolidinones **79**, generated by treating *N*-acyloxazolidinones with $TiCl_4$ and $^{i}Pr_2NEt$, were employed in the Mannich-type reactions of activated imines **80** to obtain the corresponding β-amino carbonyl compounds **81** in moderate yields with fairly good selectivities (Scheme 31).[55]

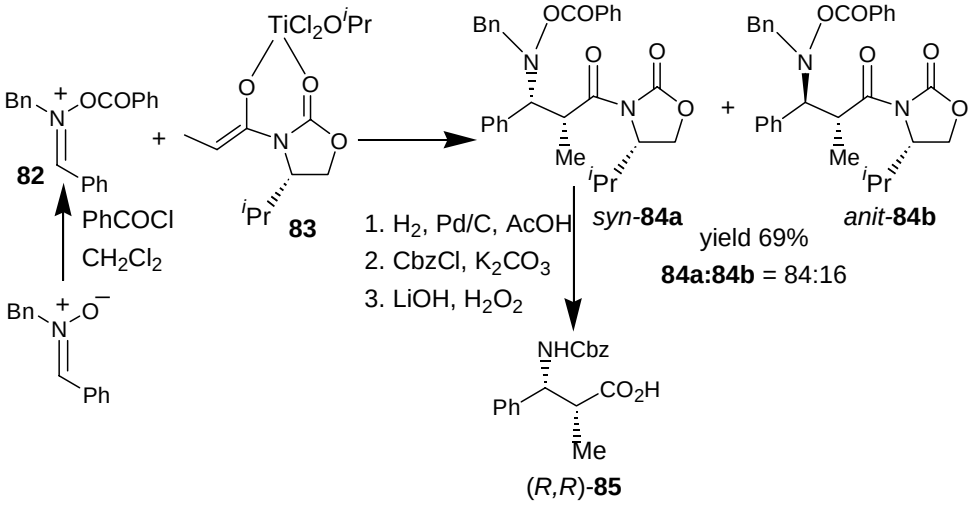
Scheme 31



R = Me	66%	12.5%
R = Et	74%	8%
R = Ph	22.5%	74%

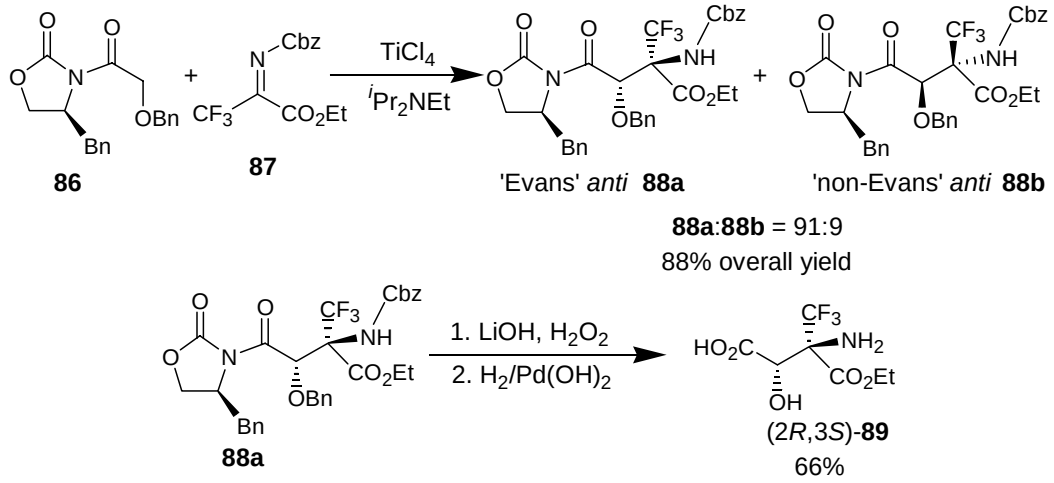
It was reported that the reaction of *N*-acyloxyiminium ion **82**, generated from nitrone and benzoyl chloride, with titanium enolate **83** of *N*-acyloxazolidinone gave *syn*-β-amino carbonyl compound **84a** with good selectivity (Scheme 32).[56] Whereas the use of boron enolate gave the *anti* isomer **84b** predominantly.[56]

Scheme 32



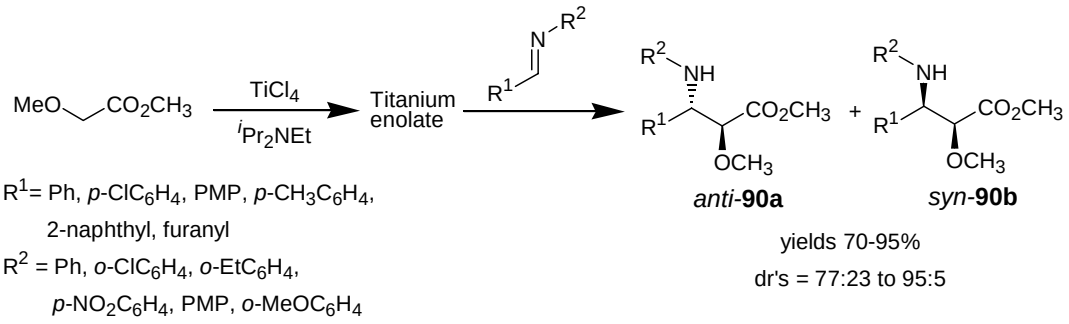
Mannich-type reaction of a ketimine **87** with the titanium enolate of *N*-acyloxazolidinone **86** was disclosed, optimized and exploited for the synthesis of densely functionalized (2*R*,3*S*)-α-trifluoromethyl-β-hydroxy-aspartic units **89** (Scheme 33).[57]

Scheme 33



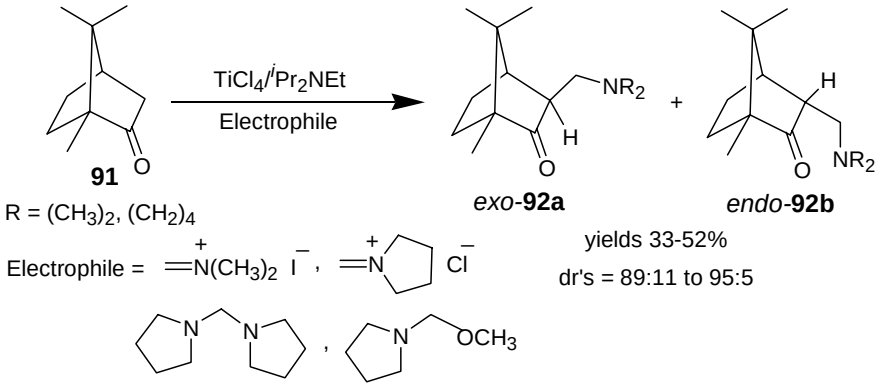
Andrian *et al.*[58] reported an *anti* selective synthesis of α-methoxy-β-substituted-β-amino esters **90** by the reaction of the titanium enolate of methyl methoxyacetate with imines (Scheme 34).

Scheme 34



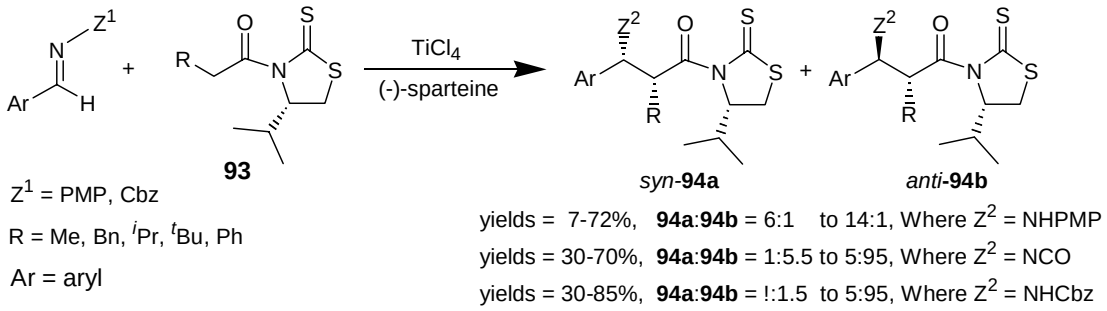
The reaction of the *D*-camphor **91**-based titanium enolate with different electrophiles proceeded with high level of stereoselectivity to give the corresponding *exo* adducts **92a** (Scheme 35).[59]

Scheme 35



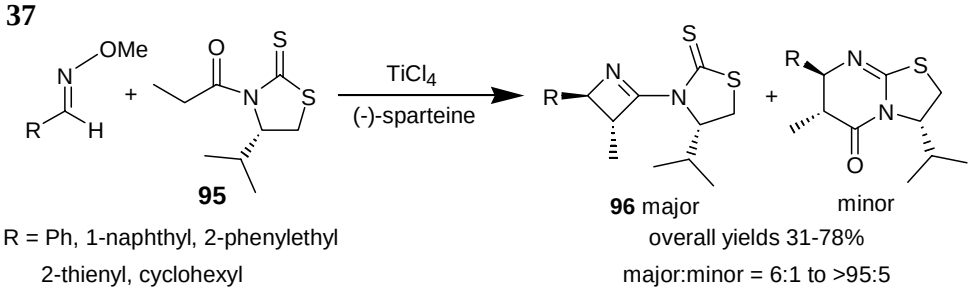
The addition of titanium enolates, generated by treating *N*-acylthiazolidine-2-thione **93** with $TiCl_4$ and *S*-(-)-sparteine, to imines afforded the corresponding *syn*- or *anti*-β-amino carbonyl compounds (**94a** or **94b**) stereoselectively depending on the nature of the imines (Scheme 36).[60]

Scheme 36



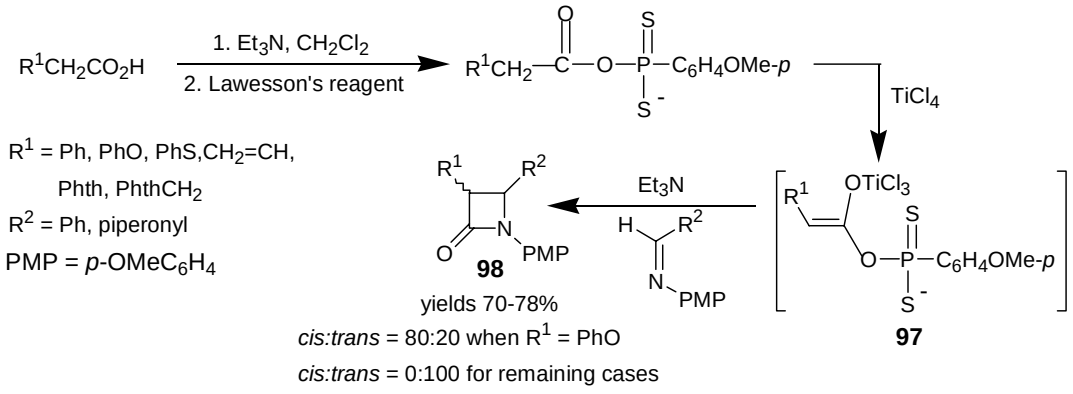
A highly diastereoselective synthesis of azetinyl thiazolidine-2-thiones **96** was reported by Liotta and coworkers[61] in the reaction of chlorotitanium enolate of *N*-acylthiazolidine-2-thione **95** with *O*-methyl aldoximes (Scheme 37).

Scheme 37



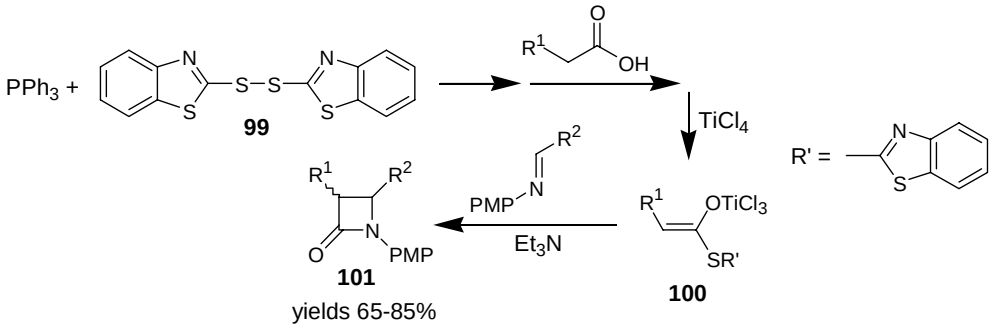
The process involving the formation of a titanium enolate **97** of a mixed anhydride, generated by the reaction of acetic acids with Lawesson's reagent and $TiCl_4$, provided a convenient route for the stereoselective synthesis of β-lactams **98** (Scheme 38).[62]

Scheme 38



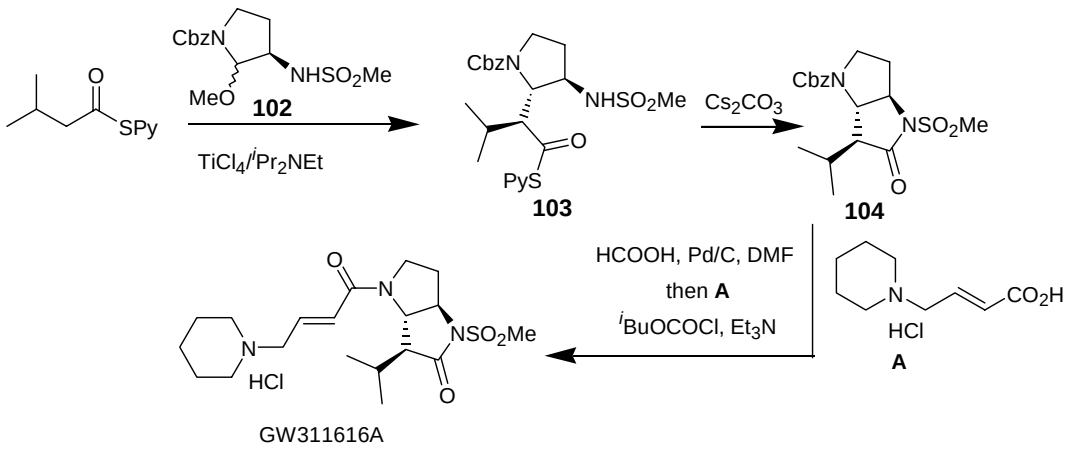
Condensation of titanium enolates **100** of thioesters, generated in the reaction of 2,2'-dibenzothiazolyl disulfide **99** with acetic acids in the presence of $TiCl_4$, with imines afforded β-lactams **101** stereoselectively (Scheme 39).[63]

Scheme 39



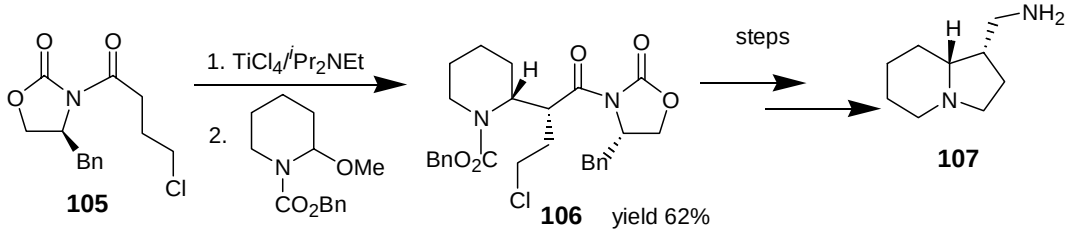
The key step in the synthesis of GW311616A, a compound with potential for the treatment of respiratory disease such as chronic bronchitis, was the addition of titanium enolate of a 2-pyridyl thioester to iminium ion formed from compound **102**. Enantiomerically pure bicyclic-*trans*-β-lactam GW311616A was obtained in two steps from the Mannich-adduct **103** (Scheme 40).[64]

Scheme 40



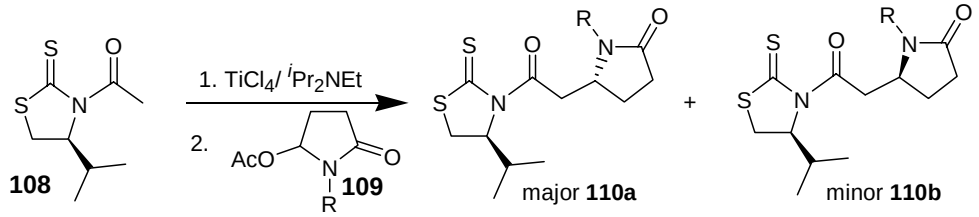
A crucial step in the synthesis of (1*S*,8a*R*)-1-aminomethyl indolizine **107**, the heterocyclic core of stelletamides, is the stereoselective addition of the preformed titanium enolate from *N*-4-chlorobutyryl-2-oxazolidinone **105** to *N*-acyliminium ion derived from 2-methoxy piperidine. A similar strategy was also exploited in the total synthesis of (+)-isoretronecanol (Scheme 41).[65]

Scheme 41



Addition of the chlorotitanium enolate of *N*-acetyl-4-isopropyl-1,3-thiazoline-2-thione **108** to *N*-acyliminium ions prepared from **109**, furnished the corresponding Mannich-type addition products **110** in good yields with good diastereoselectivity (Scheme 42).[66]

Scheme 42



R = Ph, Bn, *p*-$CH_2C_6H_4Br$, $(CH_2)_2CH_3$,
trans-CH_2CH=$CHPh$, *trans*-CH_2CH=$CHCH_3$

yields 58-84%
dr's = 73:27 to 88:12

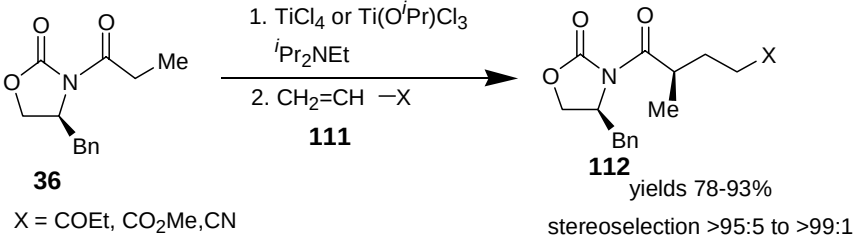
1.1.3 Titanium enolates in Michael-type reactions:

The Michael-type conjugate addition to α,β-unsaturated carbonyl systems has been recognized as one of the versatile functionalization methods in organic synthesis.[67] Generally, these reactions are promoted by strong bases such as alkali metal alkoxides or hydroxides or organoalkali meal reagents. But there are some limitations due to the

side reactions in the strongly basic media. In order to circumvent strongly alkaline conditions, several alternatives have been developed. The application of transition metal compounds as catalysts is a mild and efficient alternative to base catalysis of the Michael reaction.[68] Accordingly, the utility of titanium enolates or titanium enolate complexes attracted considerable interest in the Michael-type reactions.

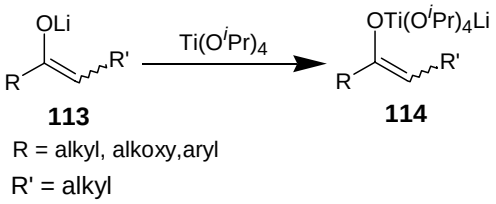
Evans *et al.*[69] reported the diastereoselective addition of chlorotitanium enolate of chiral *N*-acyloxazolidinone **36** to Michael acceptors of the type **111** to afford the corresponding Michael adducts **112** in good yields with good selectivity (Scheme 43).

Scheme 43



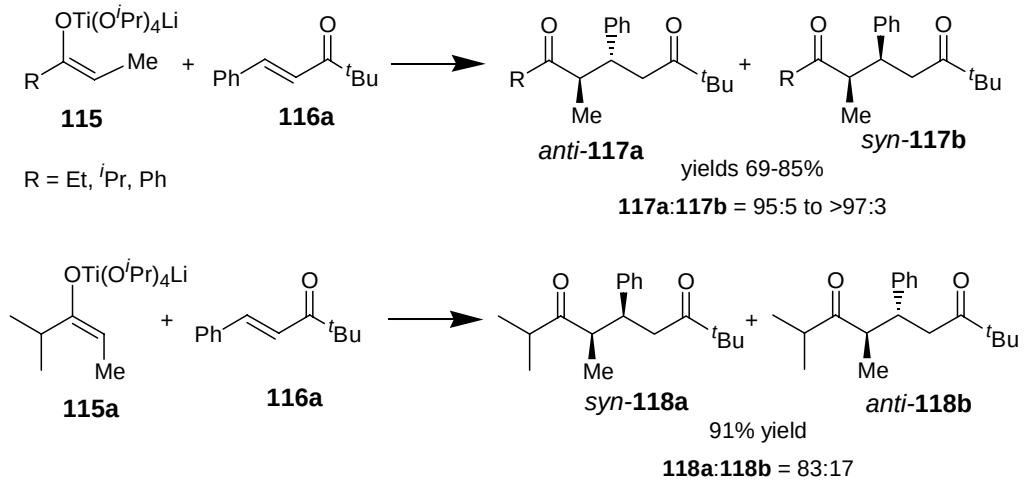
Bernardi and coworkers[70] introduced the utilization of titanium enolate complexes of lithium in the Michael-type reactions. These species gave better regio- and stereoselectivities compared to the lithium enolates. The titanium enolate complexes **114** were prepared by treating the corresponding lithium enolates **113** of carbonyl compounds with titanium(IV) isopropoxide (Scheme 44). Conjugate additions of the titanium ate complexes **114**, prepared from esters and ketones, to a variety of α,β-unsaturated carbonyl compounds were reported.

Scheme 44



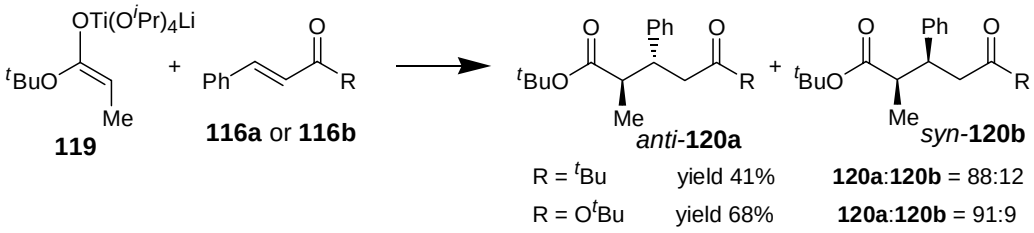
Michael-type reactions between *Z*-titanium ate complexes **115** of ketones and benzalpinacolone **116a** afforded the corresponding *anti*-Michael adducts **117a** in moderate to good yields with high selectivity. Whereas the addition of the *E*-titanium ate complex **115a** of isopropyl ethyl ketone furnished the *syn* adducts **118a** selectively (Scheme 45).[71]

Scheme 45



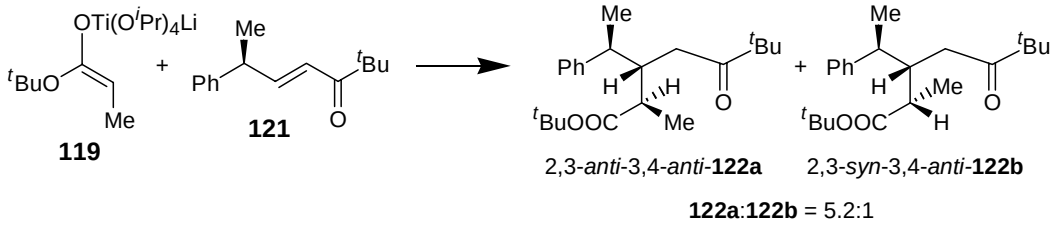
The ^{t}butyl propionate derived *E*-titanium ate complex **119** was reacted with *E*-configured benzalpinacolone **116a** or ^{t}butyl *E*-cinnamate **116b** to give the respective Michael adducts **120a** with *anti*-selectivity (Scheme 46).[70,71]

Scheme 46



The Michael-type reaction between *t*-butyl propionate-derived *E*-titanium ate complex **119** and *E*-configured chiral enone **121** was reported to give Michael adducts **122** with good stereoselectivity (Scheme 47).[72]

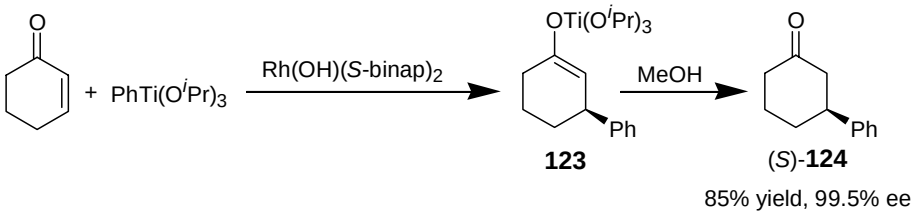
Scheme 47



Diversity of regio- and stereoselectivities was observed in the addition reactions of titanium dialkylamide or dialkylthioamide enolates and their lithium complexes with *E* or *Z* enones.[73] In these reactions, the regio- and stereochemical outcome depend on several factors such as the stoichiometry of the reagents, configurations of the substrates, and solvents.

An enantioselective rhodium catalyzed asymmetric 1,4-addition using chiral titanium enolate **123** of cyclohexenone was reported (Scheme 48).[74]

Scheme 48

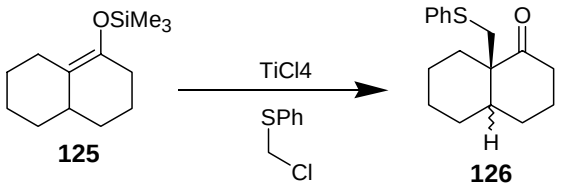


Titanium enolates derived from methyl phenylselenoacetate and other acetates bearing a selenium chiral auxiliary have been employed to bring about 1,4-addition reactions to enones.[75]

1.1.4 Titanium enolate-based alkylation reactions:

The TiX_4 (X = Cl, Br) promoted phenylthiomethylation to *O*-silylated enolate **125** of a cyclic ketone gave the corresponding thiomethylated product **126** in good yield with moderate stereoselection (Scheme 49).[76]

Scheme 49



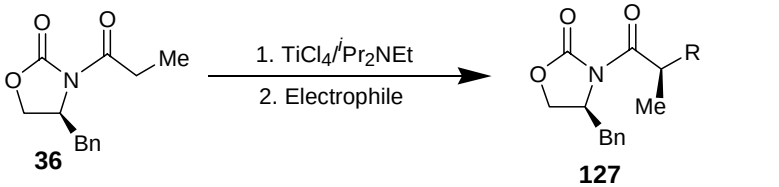
125 **126**

yield 80%

cis:*trans* = 4:1

Diastereoselective C-C bond formations between titanium enolates of *N*-acyl-oxazolidinone **36** and various electrophiles were reported by Evans and coworkers[77] (Scheme 50).

Scheme 50



36

Electrophile = $BnOCH_2Cl$, $(MeO)_3CH$, *s*-trioxane

R = CH_2OBn, $CH(OMe)_2$, CH_2OH

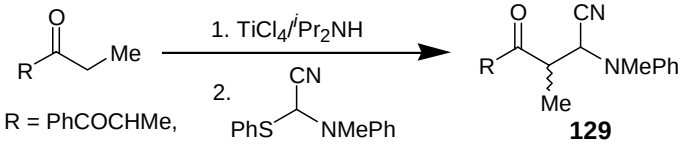
127

yields 89-99%

stereoselection >98:2 to >100:1

Reaction of 2-(*N*-methylanilino)-2-phenylsulfanylacetonitrile **128** and titanium enolates of ketones afforded the corresponding alkylated products **129** in moderate yields with low diastereoselectivity (Scheme 51).[78]

Scheme 51



R = PhCOCHMe, EtCOCHMe

128

129

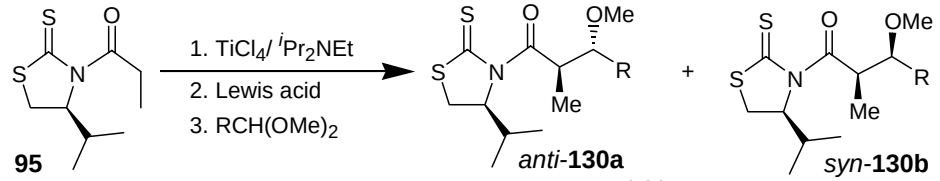
yields 80% and 65%

dr's = 68:32 and 60:40

High level of selectivity was achieved in the Lewis acid-mediated cross-coupling reactions of dimethyl acetals to a chiral 1,3-thiazolidine-2-thione **95**-derived

titanium enolate.[79] These reactions afforded enantiopure *anti*-α-methyl-β-alkoxy carbonyl compounds **130a** in a wide range of acetals (Scheme 52).

Scheme 52

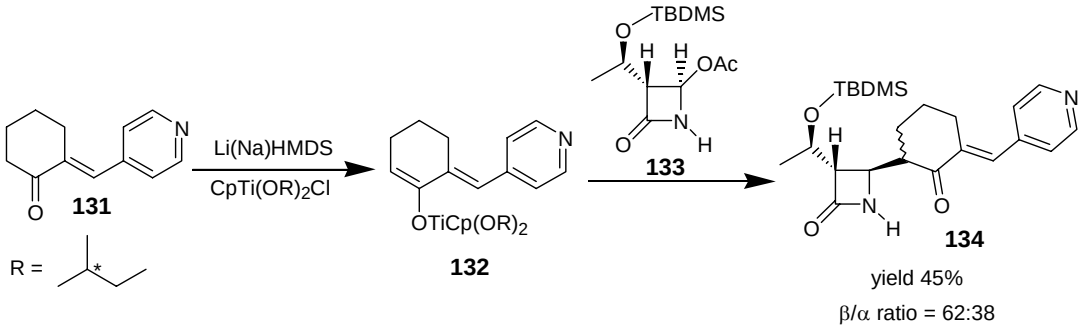


Lewis acid = BF_3:OEt_2, $SnCl_4$

R = Ph, *p*-$MeOC_6H_4$, *m*-$MeOC_6H_4$, *p*-ClC_6H_4, (*E*)-PhCh=CHMe, *p*-$NO_2C_6H_4$, ^{n}Pr, ^{i}Pr, $(CH_3)_2CHCH_2$ and $Co_2(CO)_6$

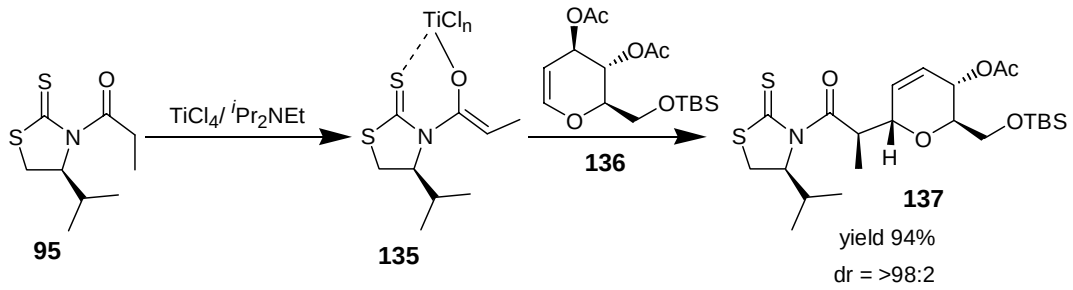
Reaction of titanium enolate **132**, derived from the corresponding lithium enolate of pyridylenone **131**, with chiral 4-acetoxyazetidinone **133** delivered the product **134** with high selectivity.[80] The product **134**, obtained in this reaction is a key intermediate in the synthesis of GV143253A which is a broad-spectrum injectable β-lactam belonging to the class of trinem antibiotics (Scheme 53).

Scheme 53



A highly stereoselective approach was reported to provide enantiomerically pure C-glycoside **137**, based on the Lewis acid mediated cross-coupling reaction of glycal **136** to chiral titanium enolate **135** derived from (*S*)-4-isopropyl-4-propanoyl-1,3-thiazolidine-2-thione **95** and its enantiomer (Scheme 54).[81]

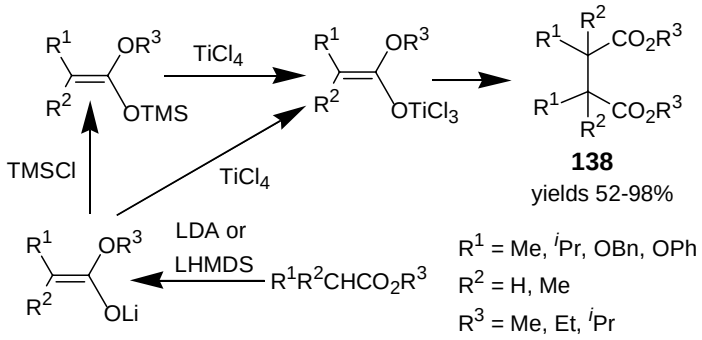
Scheme 54



1.1.5 Titanium enolate-mediated oxidative coupling reactions:

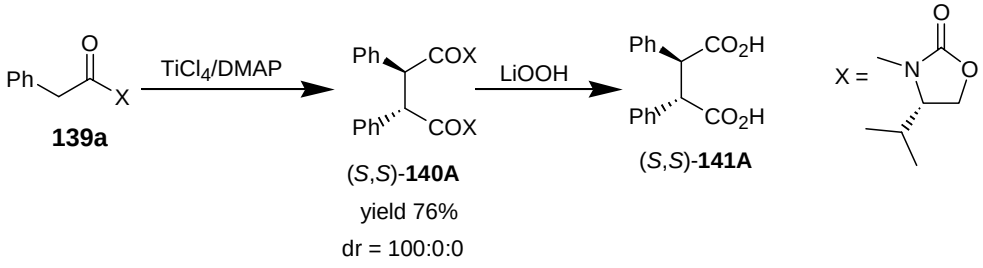
Ojima *et al.*[82] observed that the oxidative coupling of lithium ester enolates is effectively promoted by the use of $TiCl_4$ (Scheme 55). The homocoupled product **138** was obtained in this reaction in moderate to good yields.

Scheme 55

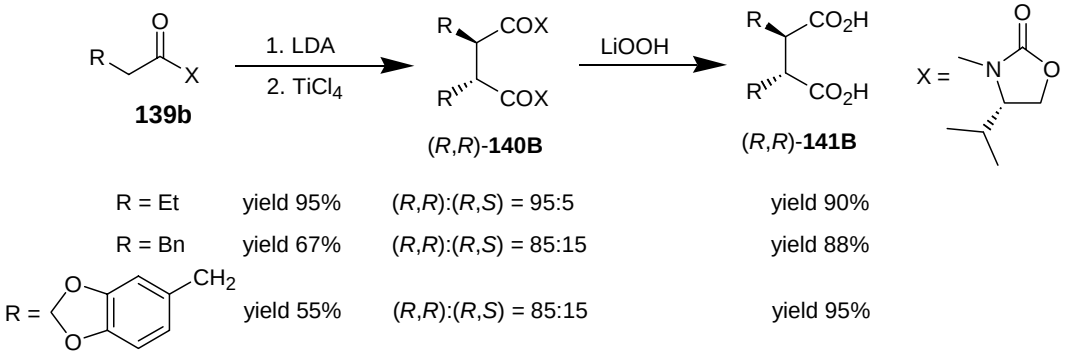


Enantioselective synthesis of 2,3-disubstituted succinic amides **140** and 2,3-disubstituted succinic acids **141** was achieved by the titanium promoted oxidative homocoupling of chiral *N*-acyloxazolidinones **139** (Schemes 56a and 56b).[83]

Scheme 56a

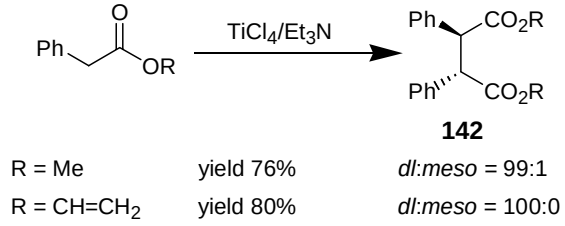


Scheme 56b



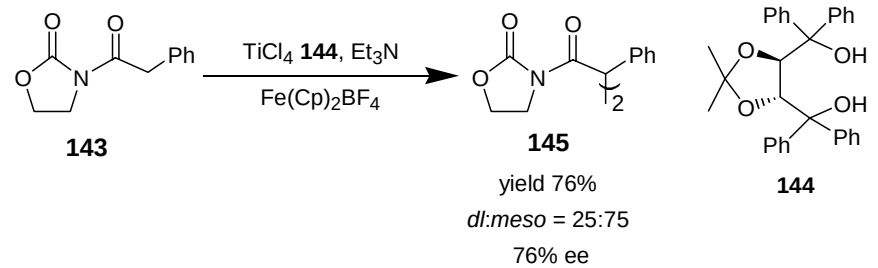
Titanium enolates of phenylacetic acid esters were used in the oxidative homocoupling to obtain 2,3-disubstituted succinic acid esters **142** in good yields with excellent diastereoselectivity (Scheme 57).[84]

Scheme 57



Enantioselective oxidative coupling of titanium enolates of *N*-phenylacetyl-oxazolidinones **143**, in presence of a chiral ligand **144** and an oxidant, afforded homodimer **145** (Scheme 58).[85]

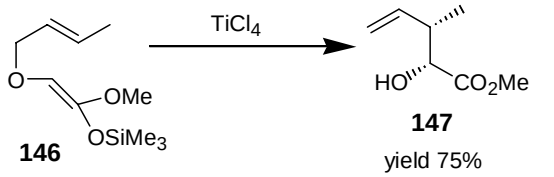
Scheme 58



1.1.6 Other transformations using titanium enolates:

Mikami *et al.*[86] found that the titanium enolate, generated by the transmetalation of silyl enol ether **146** of α-alkoxy ester, gives the 2-hydroxy-4-alkenoic ester **147** via a highly *erythro*-selective [2,3]-Wittig rearrangement (Scheme 59).

Scheme 59



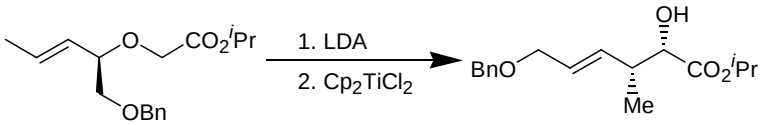
146 **147**

yield 75%

erythro selectivity 91%

It was shown that the titanium enolate-mediated Wittig rearrangement of chiral isopropyl[2(*E*)-2-alkenyloxy] acetate **148** proceeded with high *syn*-Z-selectivity to afford the rearranged product **149**, which was used as a starting material in the stereoselective synthesis of (+/-)-ireland alcohol (Scheme 60).[87]

Scheme 60



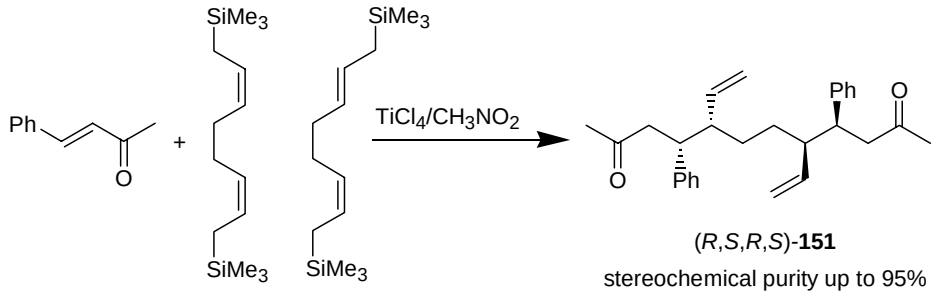
(*R*)-**148** 79% ee

yield 72%

(2*S*,3*R*)-**149** 79% ee

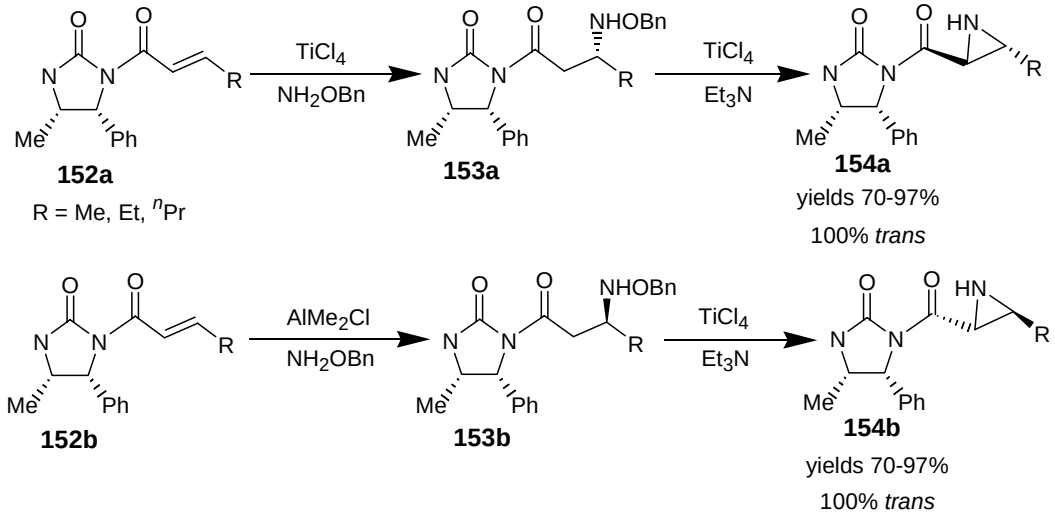
A titanium mediated Sakurai addition of 1,8-bis(trimethylsilyl)-2,6-octadiene **150** to α,β-enones resulted in one-step control of four stereogenic carbon centers to give the product **151**. It was suggested that the reaction goes through a titanium enolate intermediate (Scheme 61).[88]

Scheme 61



Enantiomerically pure aziridine-2-imides **154** were prepared by cyclization of chiral 3'-benzyloxyamino imide **153** enolates of titanium. Both the *trans*-isomers of aziridines were prepared selectively in this process (Scheme 62).[89]

Scheme 62

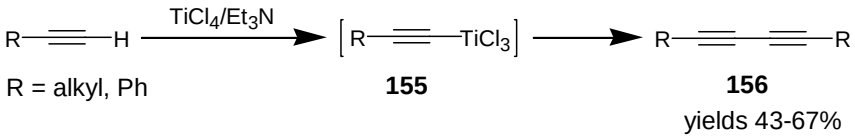


1.1.7 Reports on titanium reagents from this laboratory:

The titanium reagents were used for several organic transformations in this laboratory. Some of the transformations developed are described here.

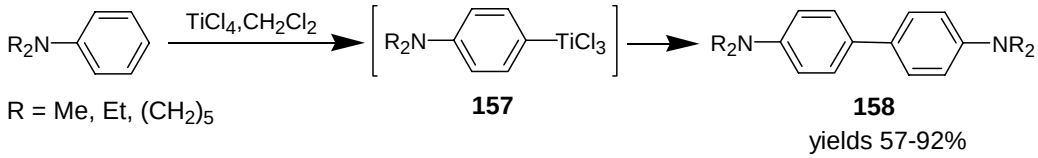
1,3-Diynes **156** were prepared by the reaction of terminal alkynes with the $TiCl_4/Et_3N$ reagent system. The reaction was suggested to go through a alkynyl titanium intermediate **155** (Scheme 63).[90]

Scheme 63



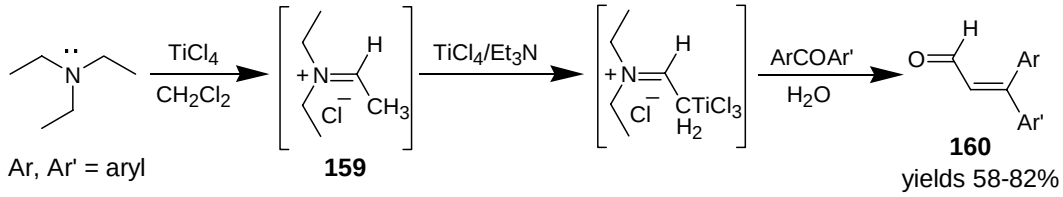
The reaction of *N,N*-dialkylarylamines with $TiCl_4$ gave the oxidative coupled *N,N,N′,N′*-tetraalkylbenzidines **158** through the intermediacy of the corresponding aryl-titanium species **157** (Scheme 64).[91]

Scheme 64



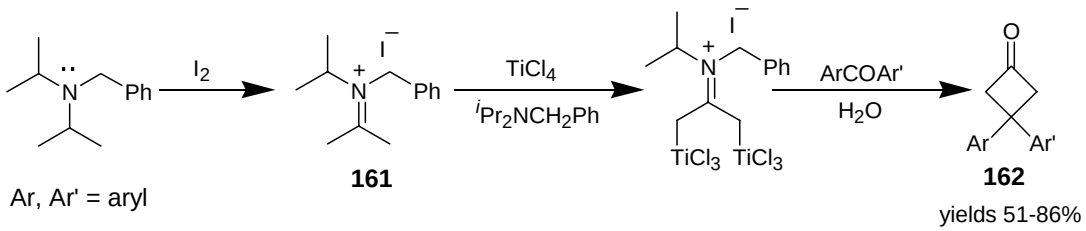
It was also reported from this laboratory that the trialkyl amines react with the $TiCl_4$ to give iminium ions **159**, which undergo metalation followed by reaction with diaryl ketones to produce the corresponding α,β-unsaturated aldehydes **160** (Scheme 65).[92]

Scheme 65



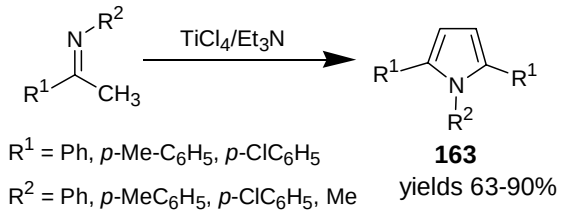
Recently, an interesting cyclobutanone synthesis was reported from this laboratory. The iminium ion **161** prepared using I_2 and diisopropylbenzylamine, upon reaction with $TiCl_4$ and excess amine produced the corresponding 3,3-diarylcyclobutanones **162** in moderate to good yields (Scheme 66).[93]

Scheme 66



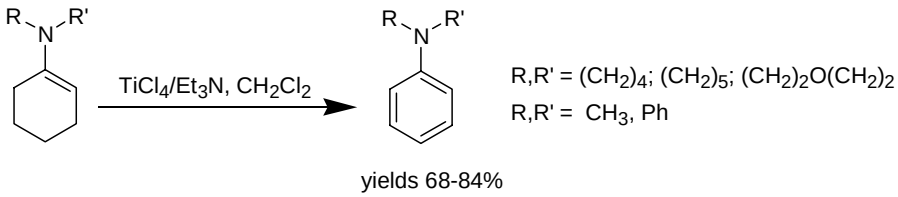
The reaction of ketimines with the $TiCl_4/Et_3N$ reagent system afforded the 1,2,5-trisubstituted pyrroles **163** in moderate to good yields (Scheme 67).[94]

Scheme 67



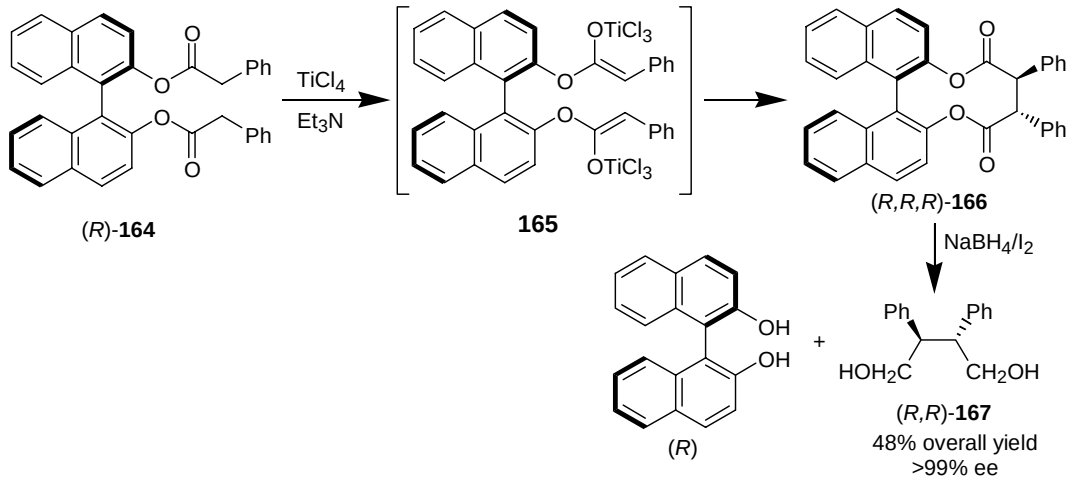
Aromatization of enamines with the $TiCl_4/Et_3N$ reagent system was reported (Scheme 68).[95]

Scheme 68



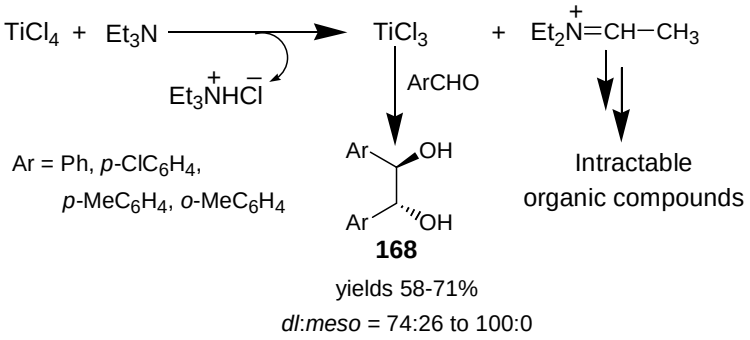
Intramolecular oxidative coupling of phenylacetic acid esters **164** of enantiomerically pure 1,1'-bi-2-naphthol was achieved by preparing the corresponding titanium ester enolates **165** *in situ* with the $TiCl_4/Et_3N$ reagent system. The corresponding coupled product **166** was reduced with the $NaBH_4/I_2$ reagent system to furnish the enantiomerically pure 2,3-diphenyl-1,4-butanediol **167** in good yields (Scheme 69).[96]

Scheme 69



In the absence of electrophiles, $TiCl_4$ oxidizes trialkyl amines to intractable organic compounds and Ti(III) species. The Ti(III) species prepared in this way is useful for the pinacol coupling of aryl aldehydes. The 1,2-diols **168** were obtained in moderate to good yields with moderate to excellent *dl*-selectivity (Scheme 70).[97]

Scheme 70

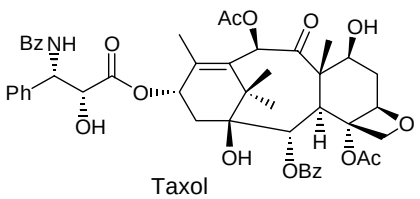


We have undertaken research efforts towards the stereoselective C-C bond construction by exploiting the titanium enolates of esters prepared *in situ* using the $TiCl_4/R_3N$ reagent system. The results are described in this Chapter.

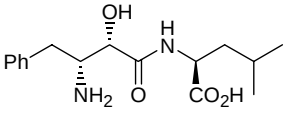
1.2 Results and Discussion

β-Amino acids and esters are useful building blocks for the synthesis of β-lactams and β-peptides that are present in several potent drugs.[98] Also, β-amino acid moiety is an integral part in numerous biologically and pharmacologically important compounds. For example, one of the best-known molecules that contain β-amino acid moiety is taxol, which is composed of a polyoxygenated diterpene and (2*R*,3*S*)-phenylisoserine. Although the role of the phenylisoserine side chain has not been fully determined, it plays an important role in the biological function of this antitumor agent.[99] Bestatin, another β-amino acid moiety containing molecule, is an immunological response modifier. Also, numerous biologically active molecules such as dolastins, astins, onchidin, jasplakinolide, motuporin, kynostatins, scytonemyn A and microginin contain β-amino acid moieties.[98]

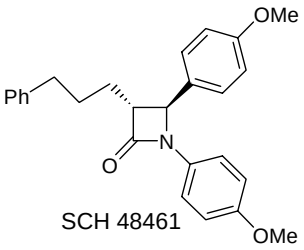
β-Lactam antibiotics are readily accessible from β-amino acid derivatives. These molecules have gained significance in clinical practice in the last few years.[100] Recent clinical trials and extensive epidemiological studies support the reduction of low-density plasma lipoproteins (LDL) as a major goal in the treatment and prevention of coronary heart disease (CHD). The pharmacological reduction of LDL levels has been achieved in man by the use of a β-lactam, SCH 48461.[101]



Taxol



Bestatin



SCH 48461

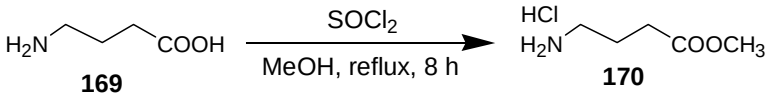
Accordingly, there has been immense interest in accessing the β-amino acid moiety from readily available starting materials.

1.2.1 Synthesis of *cis*-2-substituted-3-pyrrolidine carboxylic esters via diastereo-selective cyclization of γ-imino esters using $TiCl_4/Et_3N$ reagent:

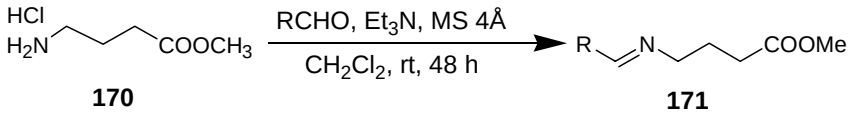
During the course of investigations on the synthetic utility of the $TiCl_4/R_3N$ reagent system,[90-97,102] we have examined the reaction of the γ-imino esters, which are readily accessible from the γ-aminobutyric esters.

The γ-imino esters were prepared in two steps. Inexpensive and readily available γ-aminobutyric acid **169** was reacted with thionyl chloride in methanol to give the corresponding methyl 4-aminobutyrate hydrochloride **170** in quantitative yields (Scheme 71). Then, the product **170** was reacted with aldehydes in the presence of triethylamine and molecular sieves to afford the corresponding γ-imino esters **171** in very good yields (Scheme 72).

Scheme 71



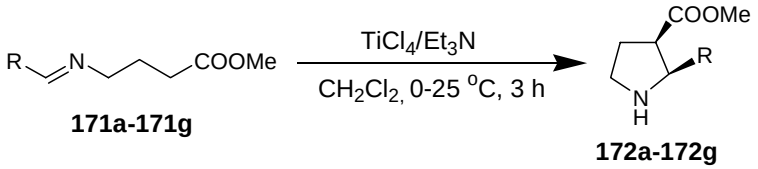
Scheme 72



These γ-imino esters react with $TiCl_4$ and Et_3N in CH_2Cl_2 to furnish the methyl-2,3-disubstituted pyrrolidine carboxylates **172** in good yields (Scheme 73). Interestingly, only one stereoisomer was formed in the reaction. Comparison of the ^{1}H-NMR and ^{13}C-NMR spectral data of the product **172a** with the previously reported data

for **172a** indicated that the phenyl and ester groupings are placed in *cis*-configuration in this compound.[103]

Scheme 73



171a-171g **172a-172g**

To confirm the stereochemistry, we have prepared the salt of the amino ester **172a** using oxalic acid. The amino ester **172a** was reacted with oxalic acid in acetone at room temperature for 6 h and the salt was filtered off. The salt was obtained in very good yields. It was crystallized from acetonitrile to obtain the crystals suitable for X-ray structure analysis. X-Ray data of the salt revealed that the starting amino ester has the *cis* configuration at C1 and C2 chiral centers (Figure 1). The ORTEP diagram of the complex of oxalic acid and compound **172a** is shown in Figure 1. The crystal structure data of the oxalic acid complex of **172a** are summarized in Table 1 and Table A1 (Appendix II).

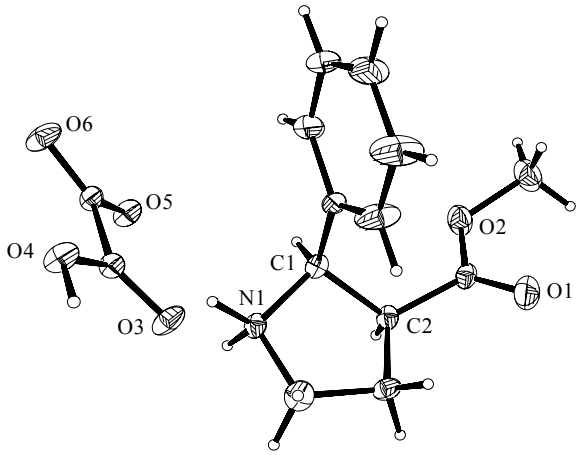


Figure 1 ORTEP representation of the crystal structure of the complex of **172a** with oxalic acid (Of two complexes only one is shown for clarity. Thermal ellipsoids are drawn at 25% probability)

Table 1 X-ray data collection and structure refinement for the oxalic acid salt of the pyrrolidine ester **172a**

Empirical formula	$C_{24}H_{28}NO_{6.5}$
Formula weight	304.29
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.7341(9) Å, α = 90°
	b = 30.789(5) Å, β = 106.63(2)°
	c = 8.577(2) Å, γ = 90°
Volume	1450.9(5) Å ^{3}
Z	4
Calculated density	1.393 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	644
Crystal size	0.56 X 0.52 X 0.40 mm
θ range for data collection	1.32 to 27.47°
Limiting indices	$-7 \leq h \leq 7$; $-39 \leq k \leq 39$; $-11 \leq l \leq 11$
Reflections collected/unique	3410 / 3391 [R(int) = 0.0000]
Completeness to θ = 27.47	100%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	3391 / 10 / 422
Goodness-of-fit on F^2	1.062
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0384$, $wR_2 = 0.0883$
R indices (all data)	$R_1 = 0.0515$, $wR_2 = 0.1028$
Largest diff. Peak and hole	0.225 and -0.176 eÅ^{-3}

We have examined this transformation using various imino esters prepared from substituted aromatic aldehydes. The products were obtained in 64-76% yields (Table 2). The isobutyraldehyde imino ester **171g** gave the corresponding product **172g** only in poor yield (32%). Comparison of the ^{1}H-NMR spectral data obtained for the substituted derivatives **172b**-**172g** with that obtained for **172a** indicated that all these products **172b**-**172g** have the same *cis* stereochemistry.

Table 2 Reaction of γ-imino esters **171** with $TiCl_4/Et_3N$ to give the *cis*-2,3-disubstituted pyrrolidines **172**

Entry	R	Substrate	Product[a]	Yield of **172**[c] (%)
1	C_6H_5	**171a**	**172a**[b]	75
2	*p*-$H_3CC_6H_4$	**171b**	**172b**	64
3	*p*-$H_3COC_6H_4$	**171c**	**172c**	76
4	*p*-ClC_6H_4	**171d**	**172d**	71
5	*p*-$O_2NC_6H_4$	**171e**	**172e**	69
6	1-naphthyl	**171f**	**172f**	66
7	$(CH_3)_2CH$	**171g**	**172g**	32

a All the products were confirmed spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass).

b *cis* Stereochemistry was assigned for the pyrrolidine carboxylate **172a** based on X-ray analysis of its oxalic acid complex and comparison with reported data.[103]

c Yields are for isolated products. *cis* Stereochemistry was assigned for compounds **172b-172g** by the comparison of their spectral data with those of **172a**.

The high level of stereoselectivity observed in this transformation can be tentatively explained by postulating the formation of a pseudo six-membered chair-like transition state **TS-1** (Figure 2), assuming that the geometry of the titanium enolate is

Z[104] and that the imine has an *E* configuration.[105] The chelated six-membered titanocycle **TS-1** would then undergo ring closure leading to *cis* stereochemistry at the 2,3-positions of the newly constructed pyrrolidine ring (Figure 2).

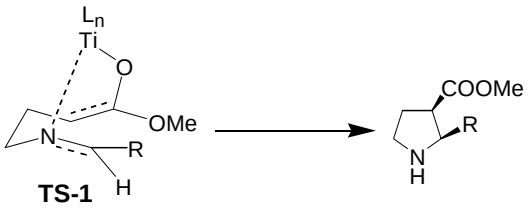
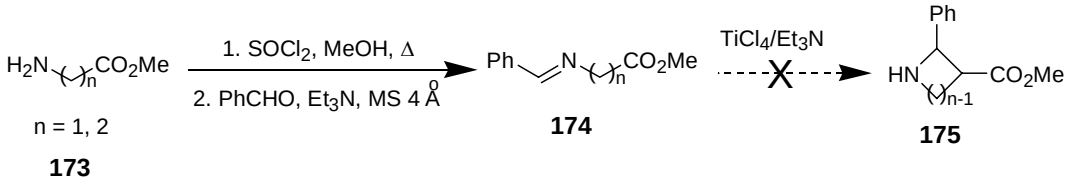


Figure 2 Proposed pathway for the *cis* diastereoselectivity

It was observed that neither $TiCl_4$ nor Et_3N alone could effect this transformation under the reaction conditions. Since $TiCl_4$ is known to mediate the formation of imines, it was thought that pyrrolidines **172** could be obtained directly by the reaction of the amino ester hydrochloride **170** and aldehydes with the $TiCl_4/Et_3N$ reagent system. To examine this possibility, methyl 4-aminobutyrate hydrochloride **170** and benzaldehyde were reacted with Et_3N followed by the addition of $TiCl_4$. To the resultant reaction mixture, additional amounts of $TiCl_4$ and Et_3N were added. It was observed that this reaction was not clean and neither γ-imino ester **171a** nor pyrrolidine derivative **172a** could be isolated from the crude product mixture in this reaction.

Attempts to prepare aziridine carboxylates or azetidine carboxylates **175** from the corresponding imino esters **174** by using this strategy were not successful under the reaction conditions (Scheme 74).

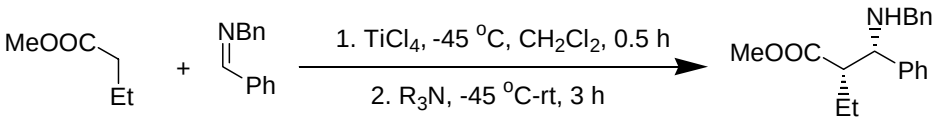
Scheme 74



1.2.2 Stereoselective synthesis of *syn*-β-amino esters using the $TiCl_4/R_3N$ reagent system:

We have observed that certain esters and imines react with the $TiCl_4$/tertiary amine reagent system to give the corresponding *syn*-β-amino esters in good yields. Initially, the experiments were carried out using methyl butyrate **176a**, *N*-benzylidene-benzylamine **177a** and $TiCl_4$ in combination with different tertiary amines such as Et_3N, $^{i}Pr_2NEt$, $^{n}Bu_3N$ and TMEDA. Titanium ester enolate of methyl butyrate was prepared *in situ* by adding $TiCl_4$ to the ester at –45 ^{o}C followed by the addition of the 3^{o} amine. It was observed that the $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino ester **178a** in excellent yields (Scheme 75). Interestingly, only one of the possible diastereomers was formed as the major product.

Scheme 75

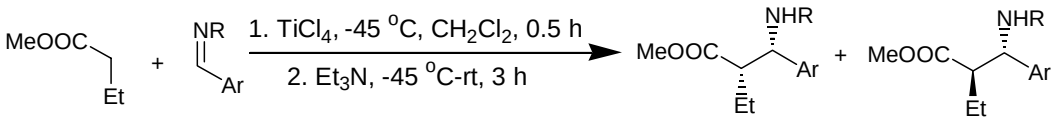


176a **177a** **178a**

R_3N (3^{o} amine)	Yield of product **178a** (%)
Et_3N	87
$^{n}Bu_3N$	33
$^{i}Pr_2NEt$	21
TMEDA	0

Then, we have examined this transformation using different imines (Scheme 76 and Table 3).

Scheme 76



176a **177a-177e** **178a-178e** *syn* (major) **178a-178e** *anti* (minor)

Table 3 Reactions of methyl butyrate and imines with the $TiCl_4/Et_3N$ reagent system

Entry	R	Ar	Imine	Yield of product[a] (%)	*syn*:*anti*[d] (dr)
1	Bn	Ph	**177a**	(**178a**) 87	100:0[e]
2	^{n}Bu	Ph	**177b**	(**178b**) 78	95:5[e]
3	*CH(Ph)CH_3	Ph	**(*R*)-177c**	(**178c**) 82[b,c]	92:8[c]
4	Ph	Ph	**177d**	(**178d**) 38	55:45[e]
5	OMe	Ph	**177e**	(**178e**) 85	100:0[e]

a The structures of the products were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and elemental analyses. Yields are for isolated products.

b The *syn* stereochemistry was assigned to the major diastereomer of the product **178c** based on the crystal structure of its derivative **180**.

c The imine **177c** was prepared from (*R*)-α-methylbenzylamine and benzaldehyde. The absolute configurations of the new chiral centers in the compound **178c** were assigned as (*S,S*) on the basis of crystal structure analysis of its derivative **180**. The diasteromeric ratio for the compound **178c** may be the ratio of both the *syn* isomers.

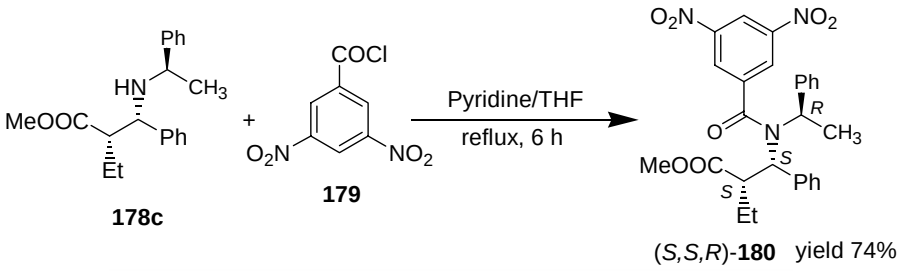
d The stereochemistry of the major products **178a**, **178b**, **178d** and **178e** was assigned as *syn* by comparison of ^{1}H-NMR data with those of **178c**.

e The *syn*/*anti* ratios were estimated using ^{13}C-NMR (50 MHz) data.

In the reaction of methyl butyrate and imines derived from alkyl amines and benzaldehyde, the selectivities as well as the yields were high (Table 3, entries 1, 2 and 3). Whereas the imine derived from aniline and benzaldehyde gave poor yield (Table 3, entry 4). However, the reaction of methyl butyrate and *O*-methyl benzaldoxime gave the corresponding β-amino ester **178e** in good yield (Table 3, entry 4) with excellent *syn* selectivity.

The imine **177c**, prepared using (*R*)-α-methylbenzylamine and benzaldehyde, reacted with methyl butyrate to afford the chiral β-amino ester **178c** in 82% yield (Table 3, entry 3). Reaction of the β-amino ester **178c** with 3,5-dinitrobenzoyl chloride **179** in the presence of pyridine gave the corresponding 3,5-dinitrobenzamide derivative **180** in 74% yield (Scheme 77). Crystals suitable for X-ray single crystal structure analysis were obtained by crystallizing the compound **180** from DMF. X-Ray data of the compound **180** revealed that the major isomer possesses *syn* stereochemistry and the new chiral centers, C2 and C3, have the absolute configuration *S*,*S* (using PLATON[106] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **180** is shown in Figure 3. The crystal structure data of the compound (*S*,*S*,*R*)-**180** are summarized in Table 4 and Table A2 (Appendix II).

Scheme 77



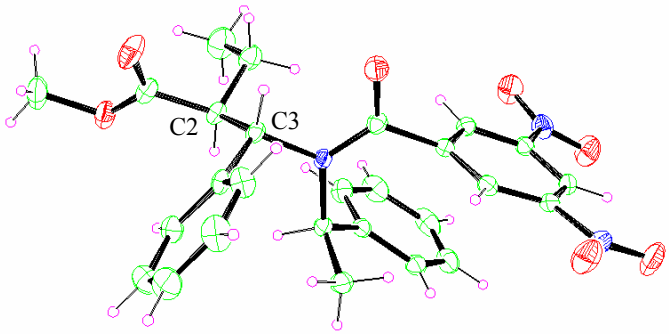


Figure 3 ORTEP representation of the crystal structure of compound **180** (Thermal ellipsoids are drawn at 20% probability)

Table 4 X-ray data collection and structure refinement for the compound (*S*,*S*,*R*)-**180** (the 3,5-dinitrobenzamide derivative of the β-amino ester **178c**)

Empirical formula	$C_{27}H_{27}N_3O_7$
Formula weight	505.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.3587(8) Å, α = 90˚
	b = 6.7522(5) Å, β = 107.5420(10)˚
	c = 17.6162(12) Å, γ = 90˚
Volume	1288.26(16) Å ^{3}
Z	2
Calculated density	1.303 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	532
Crystal size	0.40 X 0.21 X 0.09 mm
θ range for data collection	1.21 to 28.27˚
Limiting indices	$-15 \leq h \leq 15$; $-8 \leq k \leq 8$; $-23 \leq l \leq 23$
Reflections collected/unique	15055 / 5792 [R(int) = 0.0385]
Completeness to θ = 28.27	94.2%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	5792 / 1 / 337
Goodness-of-fit on F^2	0.922
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0491$, $wR_2 = 0.0820$
R indices (all data)	$R_1 = 0.0777$, $wR_2 = 0.0907$
Largest diff. peak and hole	0.169 and -0.195 eÅ^{-3}

The stereochemical configurations of the major products **178a**, **178b**, **178d** and **178e** were assigned as *syn* by comparison of their ^{1}H-NMR data with those obtained for the compound **178c**.

We have also examined the Mannich-type reactions of a few more esters such as methyl phenylacetate, methyl naphthylacetate and ibuprofen methyl ester. Reaction of methyl phenylacetate **181** with imines **177** in the presence of the $TiCl_4/Et_3N$ reagent system, proceeded at 0 ^oC to give the corresponding β-amino esters **182** in good yields and with moderate selectivity. Trace amounts of oxidative homocoupled product **183** and the Claisen condensation product **184** of methylphenyl acetate were also obtained (Scheme 78, Table 5).

Scheme 78

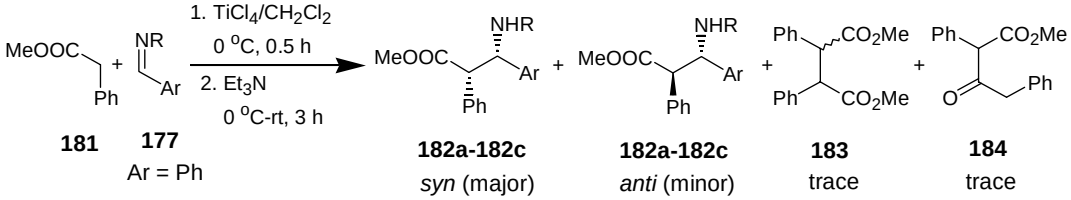


Table 5 Reactions of methyl phenylacetate and imines with the $TiCl_4/Et_3N$ reagent system

Entry	R	Ar	Imine	Yield of product[a] (%)	*syn*:*anti*[a]
1	Bn	Ph	**177a**	(**182a**) 78[b]	73:27
2	^{n}Bu	Ph	**177b**	(**182b**) 80[c]	66:34
3	Ph	Ph	**177d**	(**182c**) 41[c]	67:33

a The structures of the products were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and elemental analyses. Yields are for isolated products. The *syn/anti* ratios were the ratios of the diastereomers separated using column chromatography.

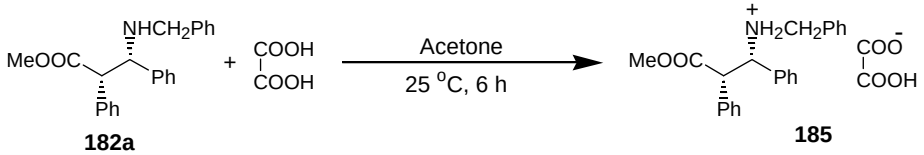
b The *syn* stereochemistry was assigned to the major diastereomer of the product **182a** based on the crystal structure of its derivative **185**.

c The stereochemistry of the major products **182b** and **182c** was assigned as *syn* by comparison of ^{1}H-NMR data with those of **182a**.

In the case of β-amino esters prepared from methyl phenylacetate, the diastereomers were separable by column chromatography. We have observed that the imines prepared from alkyl amines and benzaldehyde gave good yields (Table 5, entries 1 and 2) with moderate selectivity and the imine prepared from aniline and benzaldehyde gave poor yield (Table 5, entry 3, 41%).

The major isomer of the β-amino ester **182a**, separated using column chromatography, was reacted with oxalic acid in acetone at room temperature to obtain the complex **185** of amino ester and oxalic acid (Scheme 79). X-ray analysis of the complex **185** revealed that the product has the *syn* stereochemistry at the newly formed chiral centers, C2 and C3. The ORTEP and packing diagrams of the complex **185** are shown in Figure 4. The crystal structure data of the complex **185** are summarized in Table 6 and Table A3 (Appendix II). The stereochemistry of the major isomers of products **182b** and **182c** was assigned as *syn* by comparison of ^{1}H-NMR data with those of compound **182a**.

Scheme 79



182a **185**

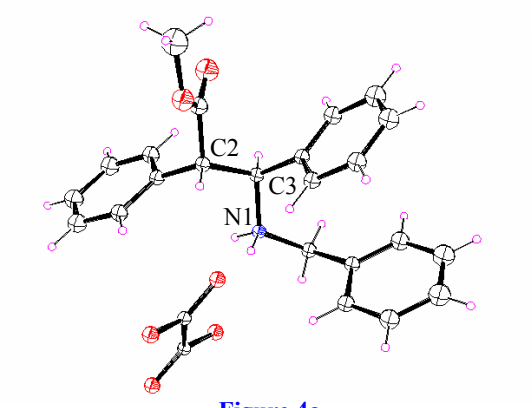


Figure 4a

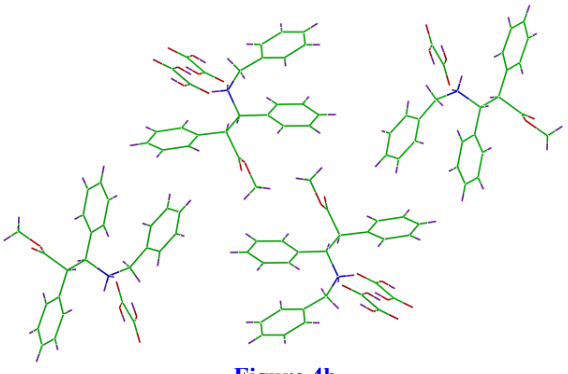


Figure 4b

Figure 4 ORTEP (Fig. 4a) and packing ((Fig. 4b) representations of the crystal structure of the complex of **182a** with oxalic acid (thermal ellipsoids are drawn at 20% probability)

Table 6 X-ray data collection and structure refinement for the complex **185** (complex of methyl phenylacetate-derived β-amino ester **182a** and oxalic acid)

Empirical formula	$C_{25}H_{28}NO_6$
Formula weight	438.48
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 6.0118(6) Å, α = 90°
	b = 15.7611(16) Å, β = 96.979(2)°
	c = 21.550(2) Å, γ = 90°
Volume	2026.8(3) $Å^3$
Z	4
Calculated density	1.437 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F(000)	932
Crystal size	0.37 X 0.22 X 0.10 mm
θ range for data collection	1.60 to 28.25°
Limiting indices	$-7 \le h \le 7$; $-20 \le k \le 20$; $-28 \le l \le 28$
Reflections collected/unique	23352 / 4878 [R(int) = 0.0728]
Completeness to θ = 28.25	97.5%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	4878 / 0 / 263
Goodness-of-fit on F^2	0.916
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0517$, $wR_2 = 0.1085$
R indices (all data)	$R_1 = 0.1012$, $wR_2 = 0.1242$
Largest diff. peak and hole	0.184 and -0.177 $eÅ^{-3}$

The *syn* stereoselectivity for the transformation can be tentatively explained on the basis of the stereochemical model shown in Figure 5. The configuration of the imine is expected to be *E*.[105] The results can be explained considering that the *E*-titanium ester enolate would be in equilibrium with the *Z*-titanium ester enolate. The reaction of the *E*-titanium ester enolate would give a low-energy transition state **TS-2** leading to the major *syn* product, whereas the *Z*-titanium ester enolate would result in a high-energy transition state **TS-3** leading to the minor *anti* product.

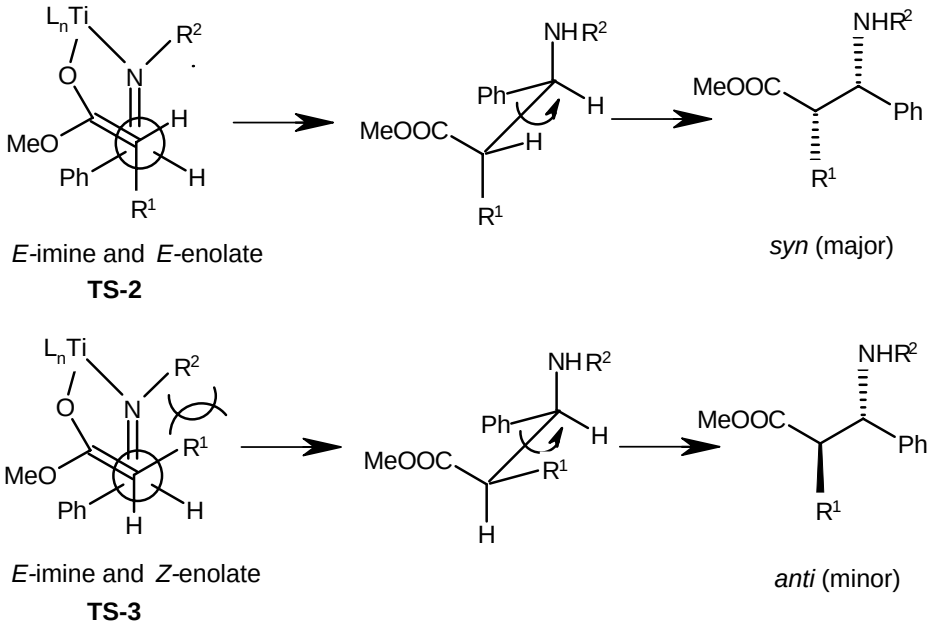
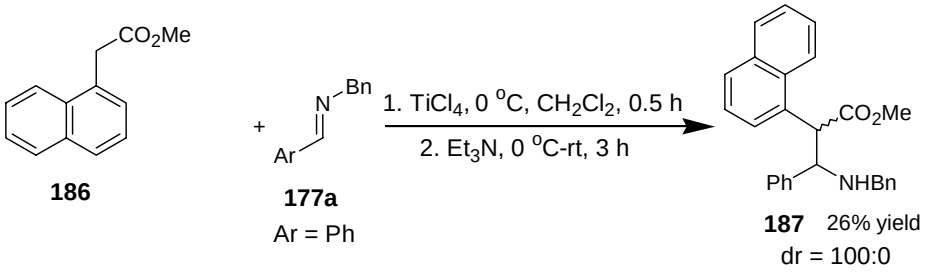


Figure 5 Stereochemical models

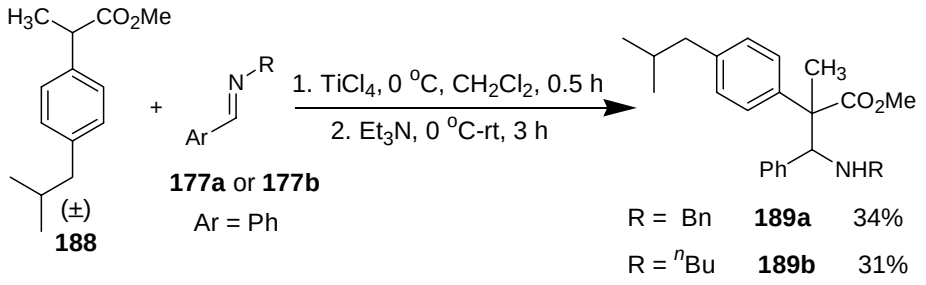
However, the Mannich-type reaction between methyl 1-naphthylacetate **186** and *N*-benzylidenebenzylamine **177a** gave the corresponding β-amino ester **187** in poor yield (26%) with excellent stereoselectivity under the reaction conditions (Scheme 80). Use of an excess amount of the $TiCl_4/Et_3N$ reagent had no effect in this reaction. The titanium enolate of methyl 1-naphthylacetae **186** formed in this case may not be able to attack the imine **177a** efficiently due to steric reasons. It was also observed that the

reaction of ibuprofen methyl ester **188** with *N*-benzylidenebenzylamine **177a** and *N*-benzylidene-*n*-butylamine **177b** with the $TiCl_4/Et_3N$ reagent system gave the corresponding β-amino esters **189a** and **189b,** respectively in poor yields (Scheme 81). In these cases, poor yields may be due to the difficulty in the formation of enolate.

Scheme 80



Scheme 81

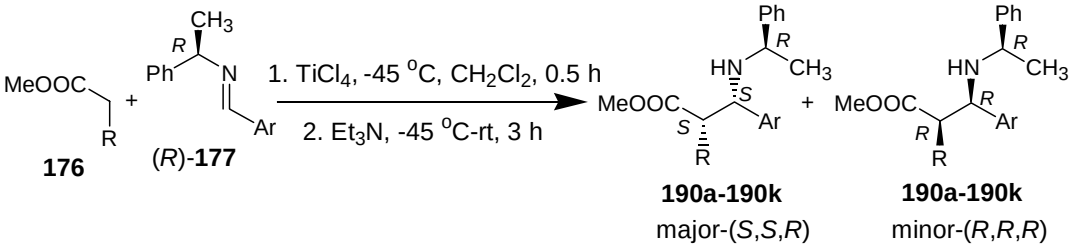


1.2.3 Asymmetric synthesis of β-amino esters from the reactions of esters with optically pure *N*-arylidene-α-methylbenzylamines:

As discussed in the section **1.2.2**, the reaction of methyl butyrate and *N*-benzylidene-(*R*)-α-methylbenzylamine **177c** with $TiCl_4/Et_3N$ reagent system furnished the corresponding β-amino ester **178c** in very good yields and with excellent *syn* selectivity (Scheme 76). The amino ester obtained in this case has an $[\alpha]_D$ value of $+40.0^o$ (*c* 1, $CHCl_3$). Furthermore, the crystal structure analysis of its derivative **180** revealed that the two newly formed chiral centers possess *S*,*S* absolute configurations.

As discussed in the section **1.2.2**, the Mannich-type reactions of esters with imines are *syn*-stereoselective. We became interested to explore whether asymmetric induction could result in the Mannich-type reactions of esters with chiral imines. Accordingly, we have examined the Mannich-type reactions between different esters and optically active α-methylbenzylamine-derived imines in the presence of the $TiCl_4/Et_3N$ reagent system (Scheme 82). The results are summarized in Table 7.

Scheme 82



It was observed that the Mannich-type reaction of methyl butyrate and *N*-benzylidinebenzylamine is 100% *syn*-selective (Table 3, entry 1 in Section 1.2.2). We expected that the Mannich-type reactions of esters with *N*-arylidene-(*R*)-α-methylbenzylamines would be also 100% *syn*-selective. All possible optical isomers of the β-amino esters should be diastereomers due to the presence of α-mehtylbenzylamine moiety with fixed configuration. The ^{13}C-NMR data of the product mixture revealed that only two diasteromers are formed, one as major and another as minor product.

In the reactions of methyl butyrate **176** with chiral imines **177f-177h**, the corresponding chiral β-amino esters **190a-190c** were obtained in good yields with high level of selectivity. The stereochemical configuration for the β-amino esters **190a-190c** was assigned as *syn* by comparing the ^{1}H-NMR data with those of **178c**. The absolute configuration of the new chiral centers in the β-amino ester **178c** was assigned as *S*,*S* based on the X-ray data (Figure 3, Section 1.2.2).

Table 7 Mannich-type reactions of esters and imines of (*R*)-(α)-methylbenzylamine

Entry	R (Ester)	Ar (Imine)	Yield of product[a] (%)	Diaster-eomeric ratio[f]	$[\alpha]_D$ of diastereo-meic mixture (*c* 1, $CHCl_3$)
1	(**176a**) C_2H_5	(**177f**) *p*-MeC_6H_4	(**190a**) 79[b]	93:7	+44.9°
2	(**176a**) C_2H_5	(**177g**) *p*-$MeOC_6H_4$	(**190b**) 81[b]	96:4	+44.3°
3	(**176a**) C_2H_5	(**177h**) *p*-ClC_6H_4	(**190c**) 76[b]	89:11	+39.6
4	(**176b**) Bn	(**177c**) C_6H_5	(**190d**) 79[c]	86:14	+17.8°
5	(**176b**) Bn	(**177f**) *p*-MeC_6H_4	(**190e**) 84[d]	91:9	+24.4°
6	(**176b**) Bn	(**177g**) *p*-$MeOC_6H_4$	(**190f**) 81[d]	95:5	+22.4°
7	(**176b**) Bn	(**177h**) *p*-ClC_6H_4	(**190g**) 80[d]	94:6	+23.3°
8	(**176c**) ^{i}Pr	(**177c**) C_6H_5	(**190h**) 93[c]	93:7	+49.0°
9	(**176c**) ^{i}Pr	(**177f**) *p*-MeC_6H_4	(**190i**) 90[e]	88:12	+55.9°
10	(**176c**) ^{i}Pr	(**177g**) *p*-$MeOC_6H_4$	(**190j**) 85[e]	90:10	+53.1°
11	(**176c**) ^{i}Pr	(**177h**) *p*-ClC_6H_4	(**190k**) 73[e]	86:14	+57.5°

a The structures of the products were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and elemental analyses. Yields are for isolated products.

b The *syn* stereochemistry was assigned for the products **190a-190c** by comparison of ^{1}H-NMR data with those of **178c**.

c The *syn* stereochemistry and *S,S,R* absolute configurations were assigned to the major diastereomers of the products **190d** and **190h** based on the crystal structures of their derivatives **191** and **192**, respectively.

d The *syn* stereochemistry for the products **190e-190g** was assigned by comparison of ^{1}H-NMR data with those of **190d**.

e The *syn* stereochemistry for the products **190i-190k** was assigned by comparison of ^{1}H-NMR data with those of **190h**.

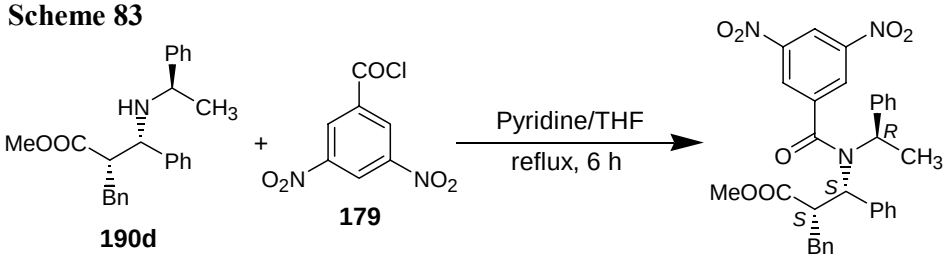
f The diastereomeric ratios (dr's) were estimated by ^{13}C-NMR (100 MHz) data.

The $[\alpha]_D$ values obtained for all methyl butyrate derived-β-amino esters (**178c**, **190a-190c)** were in the range of 40-45°. Though there is no relation between the value of $[\alpha]_D$ and absolute configuration, change of the substituent at the remote position from

the chiral centers may not have much effect on the sign and magnitude of rotation, $[\alpha]_D$. Accordingly, configurations at the new chiral centers for the major products of β-amino esters **190a-190c** may be assigned as *S*,*S*.

To assign the configurations of the β-amino ester **190d**, we have prepared the corresponding 3,5-dinitrobenzamide derivative **191** (Scheme 83). X-ray structure analysis of the compounds **191** revealed that the new chiral centers, C2 and C3, possess the absolute configurations as *S*,*S* (using PLATON[106] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **191** is shown in Figure 6. The crystal structure data of the compound (*S*,*S*,*R*)-**191** are summarized in Table 8 and Table A4 (Appendix II). The de (96%) of the compound **191** was estimated by HPLC analysis using Chiralcel OD-H column (hexanes:^{i}PrOH = 90:10)

Scheme 83



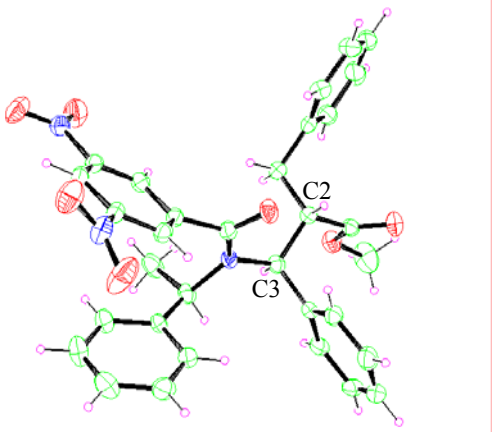


Figure 6 ORTEP representation of the crystal structure of compound **191**

(Thermal ellipsoids are drawn at 20% probability)

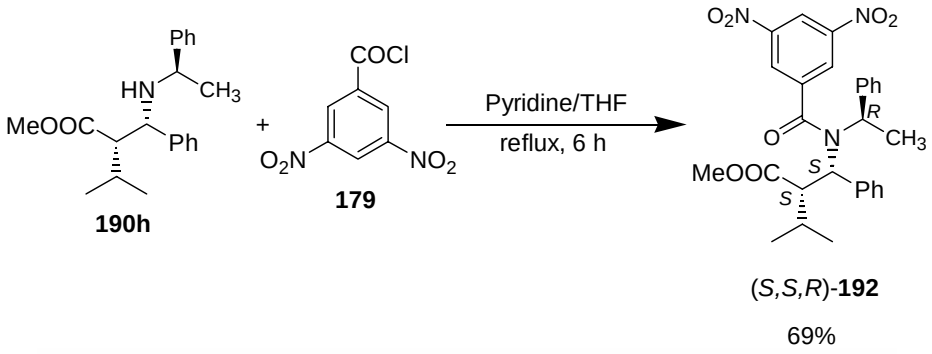
Table 8 X-ray data collection and structure refinement for the compound (*S*,*S*,*R*)-**191** (the 3,5-dinitrobenzamide derivative of the β-amino ester **190d**)

Empirical formula	$C_{32}H_{29}N_3O_7$
Formula weight	567.60
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	$P4_3$
Unit cell dimensions	a = 9.1861(2) Å, α = 90°
	b = 9.1861(2) Å, β = 90°
	c = 34.6903(13) Å, γ = 90°
Volume	2927.32(14) $Å^3$
Z	4
Calculated density	1.288 Mg/m^3
Absorption coefficient	0.092 mm^{-1}
F(000)	1192
Crystal size	0.39 X 0.30 X 0.10 mm
θ range for data collection	2.22 to 24.99°
Limiting indices	$-10 \le h \le 10$; $-10 \le k \le 10$; $-41 \le l \le 40$
Reflections collected/unique	28207 / 5119 [R(int) = 0.0720]
Completeness to θ = 24.99	99.8%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	5119 / 1 / 381
Goodness-of-fit on F^2	1.068
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0582$, $wR_2 = 0.0803$
R indices (all data)	$R_1 = 0.1116$, $wR_2 = 0.0947$
Largest diff. peak and hole	0.125 and -0.105 $eÅ^{-3}$

In the reaction using methyl hydrocinnamate, the corresponding β-amino esters **190e-190g** were obtained in good yields with high selectivity. The *syn* stereochemistry was assigned for the β-amino esters **190e-190g** by the comparison of the ^{1}H-NMR data with those of **190d**. In these cases, the absolute configurations of the new chiral centers may be assigned tentatively as *S*,*S*. This assignment was made on the basis of the $[\alpha]_D$ values, which are comparable. The stereochemical configurations of the minor diastereomers in these cases also may be assigned as *syn* with *R*,*R* absolute configuration.

Furthermore, the Mannich-type reaction of methyl isovalerate **176c** with chiral imines **177c** and **177f-177h** in the presence of the $TiCl_4/Et_3N$ reagent system proceeded in the same way to furnish the corresponding β-amino esters **190h-190k** in excellent yields with good selectivity. The 3,5-dinitrobenzamide derivative **192** of the β-amino ester **190h** was prepared (Scheme 84). The de (94%) of the compound **192** was estimated by HPLC analysis using Chiralcel OD-H column (hexanes:^{i}PrOH = 90:10). The crystal structure of the derivative **192** was analyzed using single crystal X-ray data. The data revealed that the stereochemistry and absolute configurations are in the same lines as it was found in the earlier cases; *i. e. syn* stereochemistry and absolute configurations *S*,*S* for the newly formed chiral centers, C2 and C3. The ORTEP diagram of the compound (*S*,*S*,*R*)-**192** is shown in Figure 7. The crystal structure data of the compound (*S*,*S*,*R*)-**192** are summarized in Table 9 and Table A5 (Appendix II).

Scheme 84



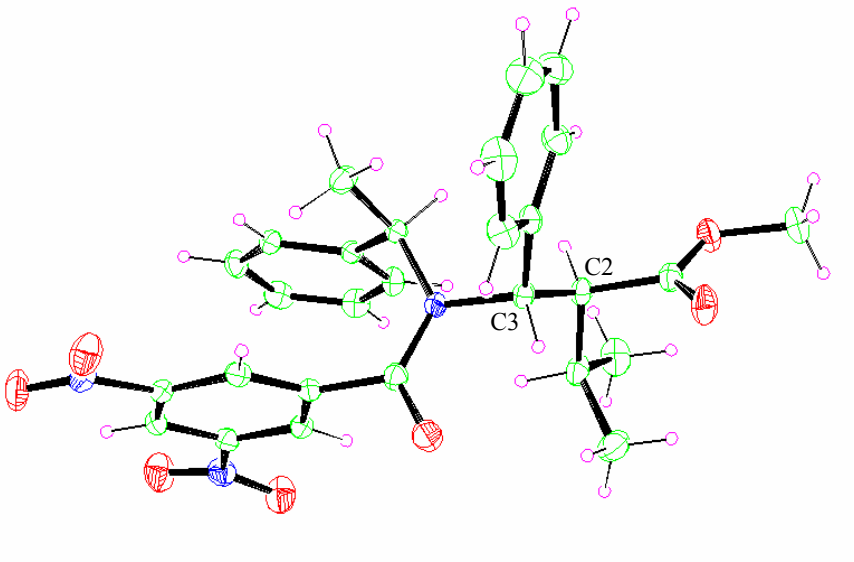


Figure 7 ORTEP representation of the crystal structure of compound **192**

(Thermal ellipsoids are drawn at 20% probability)

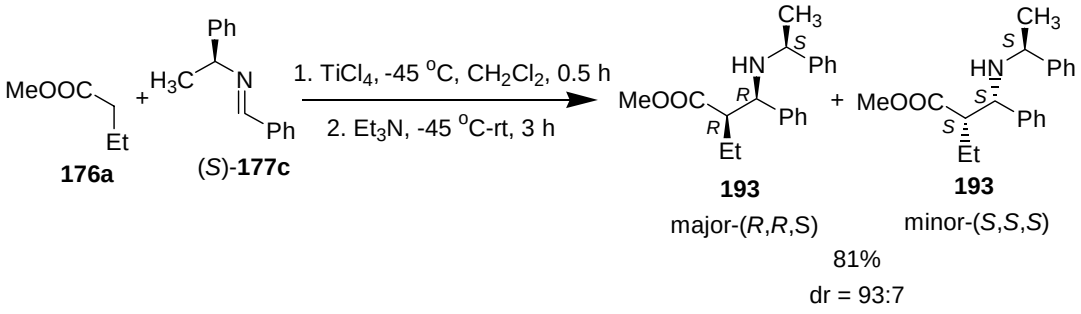
Further, configurations for other β-amino esters **190i-190k** were assigned as *syn* by the comparison of the ^{1}H-NMR data with those of **190h**. Here also, a tentative assignment of absolute configurations as *S*,*S* for the new chiral centers can be made by comparison of the $[\alpha]_D$ values. The stereochemical configurations for the minor diastereomers in these cases may be tentatively assigned as *syn* with *R*,*R* absolute configuration.

Table 9 X-ray data collection and structure refinement for the compound (*S*,*S*,*R*)-**192** (the 3,5-dinitrobenzamide derivative of the β-amino ester **190h**)

Empirical formula	$C_{28}H_{29}N_3O_7$
Formula weight	519.54
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.3739(7) Å, α = 90˚
	b = 6.7949(5) Å, β = 106.3300(10)˚
	c = 17.7374(12) Å, γ = 90˚
Volume	1315.52(15) Å ^{3}
Z	2
Calculated density	1.312 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	548
Crystal size	0.40 X 0.20 X 0.16 mm
θ range for data collection	1.20 to 28.26˚
Limiting indices	$-14 \leq h \leq 14$; $-8 \leq k \leq 8$; $-23 \leq l \leq 23$
Reflections collected/unique	15427 / 5986 [R(int) = 0.0363]
Completeness to θ = 28.26	95.2%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	5986 / 1 / 347
Goodness-of-fit on F^2	0.893
Final *R* indices [I> 2σ (I)]	R_1 = 0.0439, wR_2 = 0.0758
R indices (all data)	R_1 = 0.0689, wR_2 = 0.0826
Largest diff. peak and hole	0.131 and -0.184 eÅ^{-3}

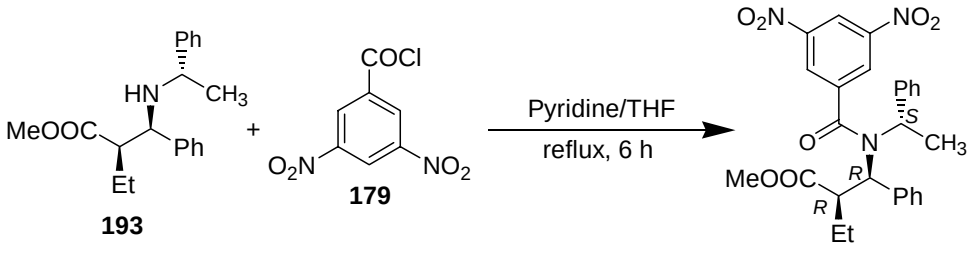
We have also carried out the Mannich-type reaction of methyl butyrate **176a** and *N*-benzylidene-(*S*)-α-methylbenzylamine (*S*)-**177c** in the presence of the $TiCl_4/Et_3N$ reagent system. The corresponding β-amino ester **193** was formed in excellent yields with good selectivity (Scheme 85). The product **193** would be the enantiomer of the β-amino ester **178c** derived from *N*-benzylidene-(*R*)-α-methylbenzylamine and methyl butyrate.

Scheme 85



The $[\alpha]_D$ value of the β-amino ester **193** was found to be -39.7^o (*c* 1, $CHCl_3$), which is almost same in magnitude and opposite in sign to that of the β-amino ester **178c**, suggesting that the amino esters **178c** and **193** are enantiomers. Therefore, in this case, the configuration of the new chiral centers should be *R,R*. To confirm this further, the corresponding 3,5-dinitrobenzamide derivate was prepared (Scheme 86) and analyzed by the single crystal X-ray data.

Scheme 86



X-ray structure analysis of the compounds **194** revealed that the new chiral centers, C2 and C3, have the absolute configuration *R*,*R* (using PLATON[106] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **194** is shown in Figure 8. The crystal structure data of the compound (*R*,*R*,*S*)-**194** are summarized in Table 10 and Table A6 (Appendix II).

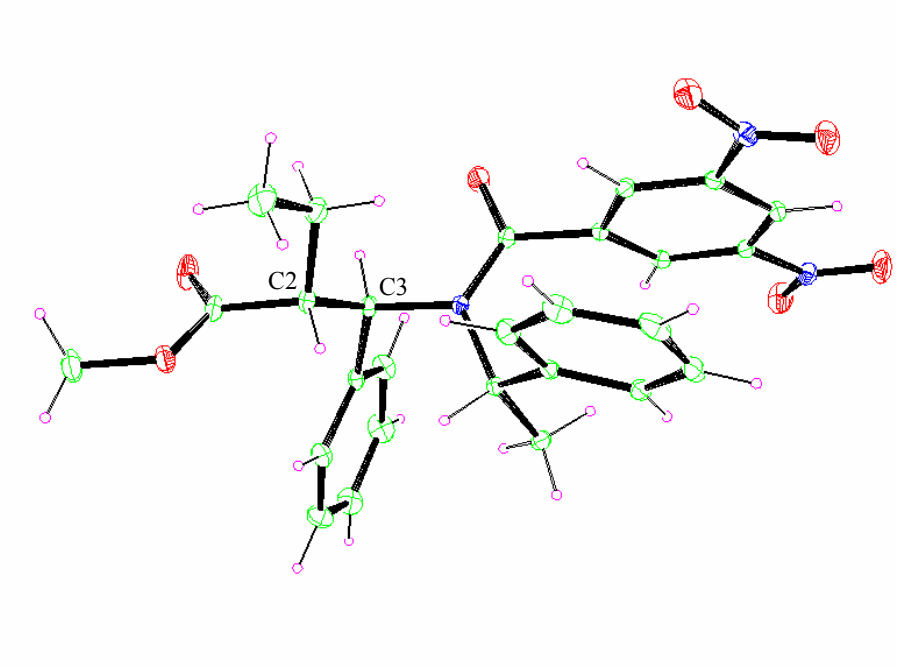


Figure 8 ORTEP representation of the crystal structure of compound **194**

(Thermal ellipsoids are drawn at 20% probability)

It is obvious, from the $[\alpha]_D$ values, that the 3,5-dinitrobenzamide derivatives **180** and **194** are enantiomers. HPLC analyses of the compounds **180** and **194,** were carried out on Chiralcel OD-H column using hexanes/^{i}PrOH mixture (90:10) as eluent. The diastereomeric excess (de) of the compound **180** is >98% with the retention time 27 min. for the major isomer (*S*,*S*,*R*)-**180**. Whereas the de of the compound **194** is >99% with the retention time 25 min for the major isomer (*R*,*R*,*S*)-**194**.

Table 10 X-ray data collection and structure refinement for the compound (*S*,*S*,*R*)-**194** (the 3,5-dinitrobenzamide derivative of the β-amino ester **193**)

Empirical formula	$C_{27}H_{27}N_3O_7$
Formula weight	505.52
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.365(3) Å, α = 90°
	b = 6.7529(19) Å, β = 107.620(4)°
	c = 17.633(5) Å, γ = 90°
Volume	1289.8(6) $Å^3$
Z	2
Calculated density	1.302 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	532
Crystal size	0.40 X 0.23 X 0.10 mm
θ range for data collection	1.21 to 28.29°
Limiting indices	$-14 \leq h \leq 14$; $-8 \leq k \leq 8$; $-22 \leq l \leq 22$
Reflections collected/unique	15071 / 5937 [R(int) = 0.0291]
Completeness to θ = 28.29	95.8%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	5937 / 1 / 337
Goodness-of-fit on F^2	1.069
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0557$, $wR_2 = 0.1130$
R indices (all data)	$R_1 = 0.0705$, $wR_2 = 0.1198$
Largest diff. peak and hole	0.177 and -0.196 $eÅ^{-3}$

The stereochemical models shown in Figure 11 may explain the origin of the asymmetric induction realized for the β-amino esters formed in the reactions of aldimines of chiral α-methylbenzylamines and esters using the $TiCl_4/Et_3N$ reagent system. The model depicted in the Figure 5 (Section **1.2.2**), for explaining *syn* diastereoselectivity could be adopted here also. The asymmetric induction observed in the Mannich-type reactions described in this Section **1.2.3** could be explained with the aid of the stereochemical models depicted in Figure 11.

The following informations are considered for explaining the origin of asymmetric induction in these Mannich-type reactions: (i) The geometry of titanium enolate is expected to be *E*, and that of imine is *E*.[105] (ii) Ab initio DFT calculations (at $B_3LYP/6\text{-}31$ G* level) of the conformations **A-E** of the imine (*R*)-**178c** revealed that the conformation **C** is more stable (Figure 9).

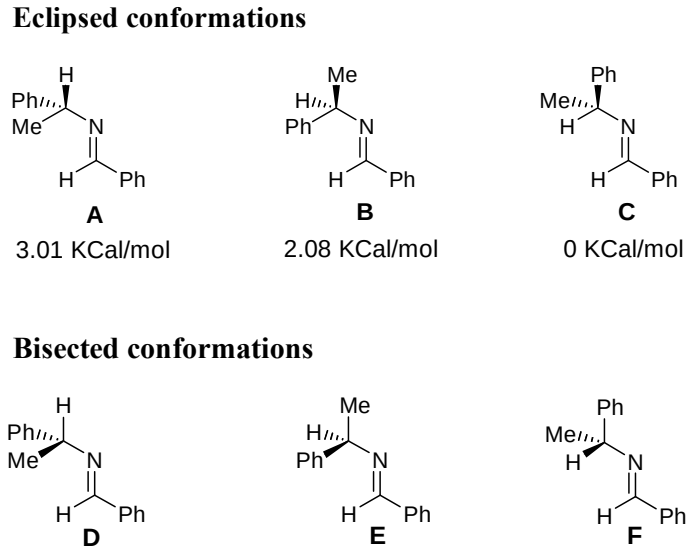


Figure 9 Conformations of the imine (*R*)-**178c**

Previous theoretical calculations also predicted that the conformer **C** is more stable.[107a] Also the *syn* arrangement of 'H' atoms, H-C-N-C-H of the imine is the most stable based on the 1,3-allylic strain model.[107]

It is well-documented that the bisected conformations are less stable than the corresponding eclipsed conformations in the case of olefins and carbonyl compounds (eg. propene and acetaldehyde) (Figure 10).[108]

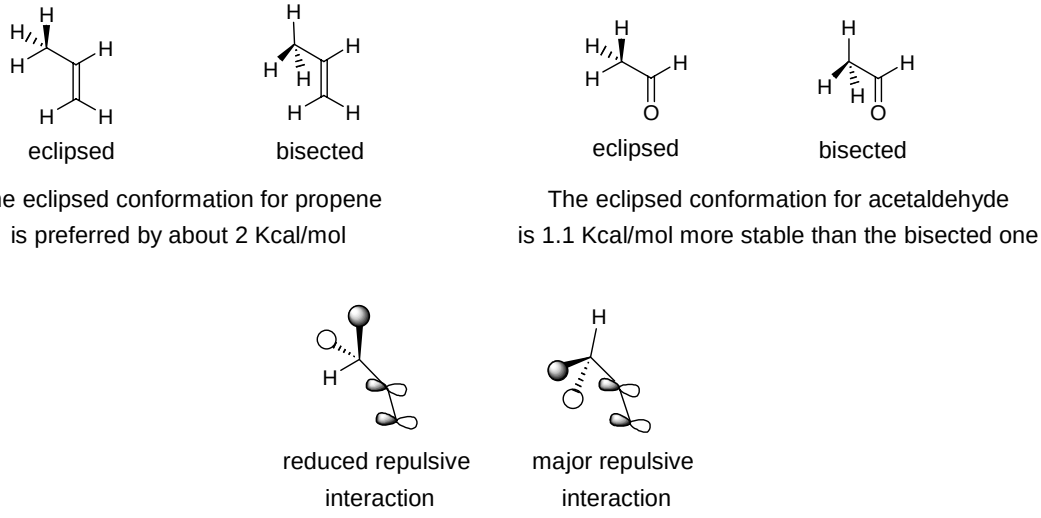


Figure 10 Conformations of propene and acetaldehyde

Accordingly, the origin of the preference for the eclipsed conformations (**A-C**) can be explained in similar MO terms by considering the interaction between the filled π-orbitals of the double bond and the filled orbitals associated with the α-methylbenzyl group. Presumably, the eclipsed conformations **A**, **B** and **C** are more stable compared to the bisected conformations **D**, **E** and **F** because of such filled orbital interactions (Figure 9). Further, among the conformations **A**, **B** and **C** the conformation **C** is most stable due to the least steric interactions (Figure 9). The stereochemical outcome can be

readily explained by considering the interaction of the conformation **C** with the titanium ester enolate.

Then, the *Si* face attack of ester enolate onto imine (conformer **C**) in **TS-4** would be more favorable because in this, the large phenyl group is positioned far away from the C-C bond forming side (Figure 11). Hence, the low-energy transition state **TS-4** would give the major isomer, with (*R*,*S*,*S*) absolute configuration. Whereas the *Re* face attack of the enolate onto imine would experience greater repulsions from the large phenyl substituent on the chiral imine, which is positioned in C-C bond forming side, leading to the high-energy transition state **TS-5** and hence the formation of the (*S*,*R*,*R*)-isomer is not favorable (Figure 11).

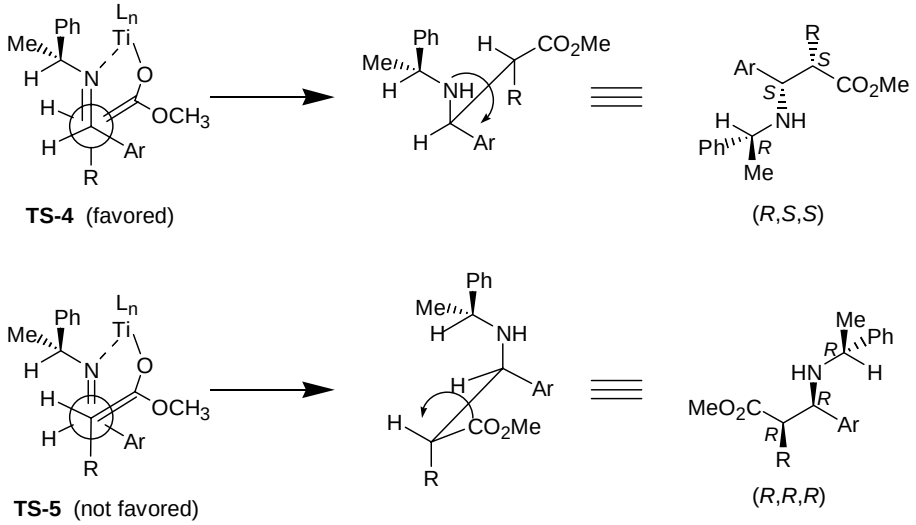
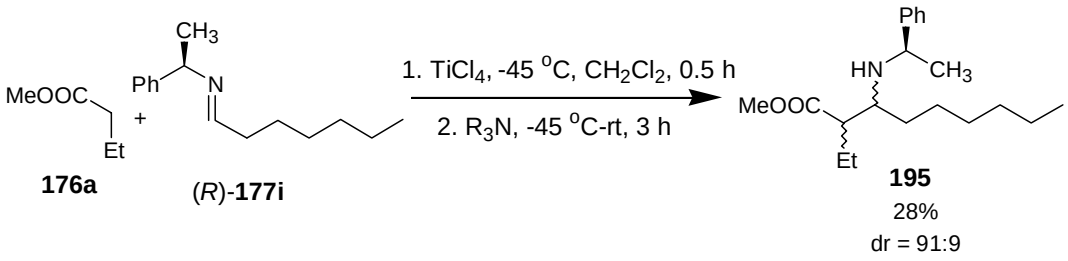


Figure 11 Stereochemical models

It was observed that the Mannich-type reaction of methyl butyrate **176a** with chiral imine **177i**, prepared from heptaldehyde and (*R*)-α-methylbenzylamine, resulted in the formation of the corresponding β-amino ester **195** in poor yield (28%) but with good diastereoselectivity (dr = 91:9) (Scheme 87).

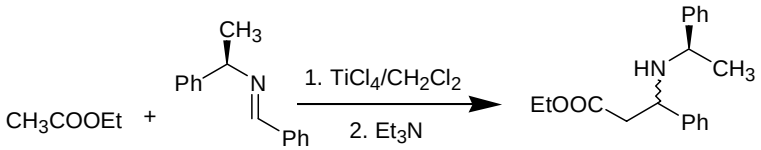
Scheme 87



176a (*R*)-**177i** **195** 28% dr = 91:9

We have also examined the reaction of ethyl acetate with the chiral imine **177c** in the presence of the $TiCl_4/Et_3N$ reagent system. The corresponding β-amino ester **196** was formed in 28% yield under the reaction conditions with good selectivity (dr = 82:18) (Scheme 88). The dr was estimated by both NMR and HPLC analysis (Chiralcel OD-H column and hexanes/^{i}PrOH mixture (95:5) as eluent).

Scheme 88



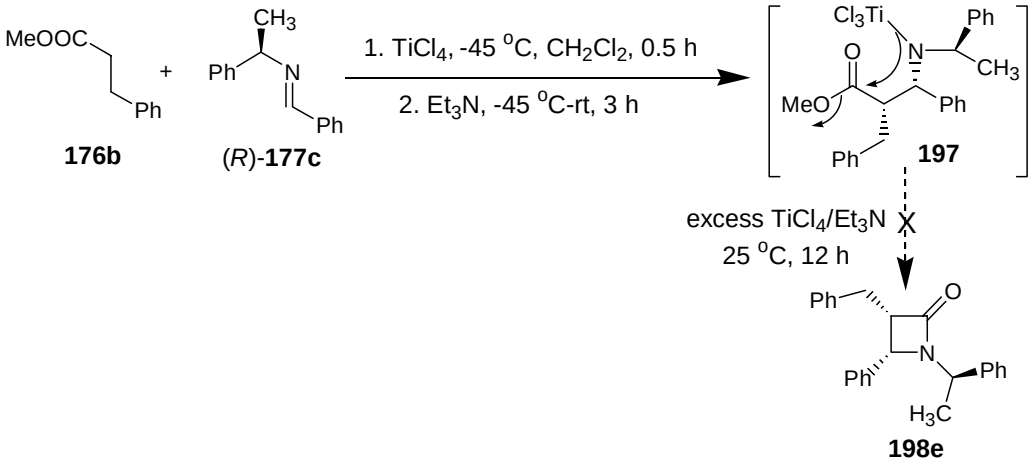
(*R*)-**177c** **196** 28%

1.2.4 Synthesis of chiral β-lactams from the corresponding β-amino esters containing α-methylbenzylamine moiety:

β-Lactams are important structural motifs that are present in numerous biologically and pharmacologically important compounds. Accordingly, we have examined the possibility of synthesizing chiral β-lactam derivatives. Initial attempts made to synthesize β-lactams by using excess amounts of $TiCl_4$ and Et_3N reagents in the Mannich-type reaction between methyl hydrocinnamate **176b** and *N*-benzylidene-(*R*)-α-

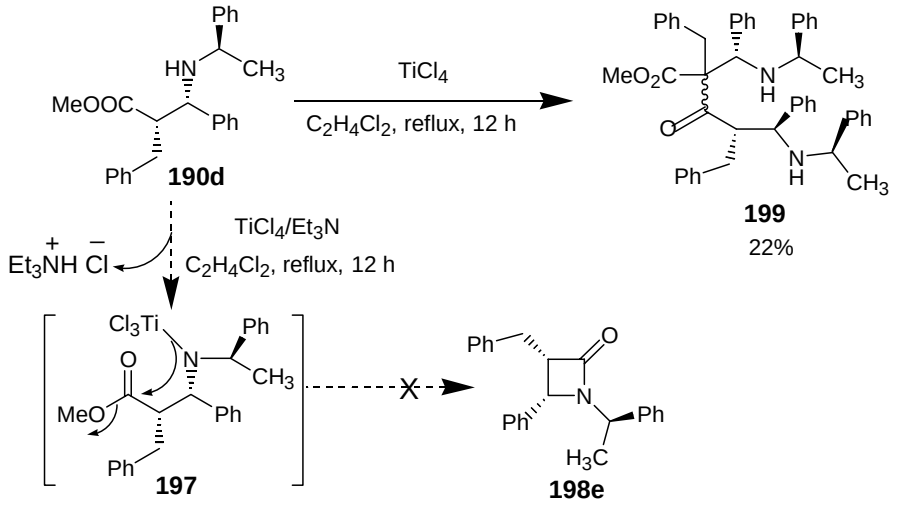
methylbenzylamine **177c** were not successful. The reaction was expected to go through the intermediate **197** to give the β-lactam **198e** (Scheme 89).

Scheme 89



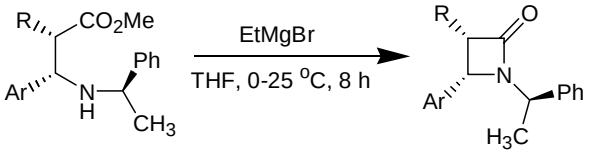
We have then carried out the reaction of β-amino ester **190d** with $TiCl_4$ and Et_3N in dichloroethane under reflux condition. In this run, the reaction yielded the corresponding Claisen condensation product **199** (22%) instead of the β-lactam **198e** (Scheme 90).

Scheme 90



We have then carried out the synthesis of β-lactams by utilizing the Grignard reagents. It was found that the addition of EtMgBr to β-amino esters **178c** and **190a-190k** afforded the β-lactams **198a-198l** in moderate yields (Scheme 91). The results are summarized in Table 11.

Scheme 91



178c & 190a-190k → **198a-198l**

In the reactions of methyl butyrate derived chiral β-amino esters **178c** and **190a-190c** with the ethylmagnesium bromide, the corresponding β-lactams **198a-198d** were obtained in moderate yields (50-56%) (Table 11, entries 1-4). In these cases, it was observed that the diasteromeric ratios were higher than those noted for the starting β-amino esters. In some cases, the dr's are 100:0 (Table 11, entries 1 and 3). This may be due to the loss of the minor diasteromer during the transformation (Scheme 91) and further purification of the β-lactam during column chromatography.

The Grignard reaction of EtMgBr with the chiral β-amino esters **190d-190g** gave the corresponding β-lactams **198e-198h** in 48-55% yields and with very good diastereoselectivity (Table 11, entries 5-8). In these cases also, the diastereomeric ratios were found to be higher than those observed for the starting β-amino esters.

The β-lactams **198i-198l** were isolated in 40-60% yields with excellent diasteromeric ratios (Table 11, entries 9-12) from the Grignard reactions of the

corresponding chiral β-amino esters **190h-190k**. Again, the diastereomeric ratios of the β-lactams were found to be higher than the corresponding starting β-amino esters.

Table 11 Synthesis of β-lactams from the β-amino esters upon the reaction of EtMgBr

Entry	R	Ar	Yield of product[a] (%)	dr[b]	$[\alpha]_D$ of diastereo-meic mixture (c 1, $CHCl_3$)
1	C_2H_5	(**178c**) C_6H_5	(**198a**) 56	100:0	-135.2°
2	C_2H_5	(**190a**) *p*-MeC_6H_4	(**198b**) 54	89:11	-108.3°
3	C_2H_5	(**190b**) *p*-$MeOC_6H_4$	(**198c**) 55	100:0	-125.7°
4	C_2H_5	(**190c**) *p*-ClC_6H_4	(**198d**) 50	91:9	-122.7°
5	Bn	(**190d**) C_6H_5	(**198e**) 53	100:0	-43.4°
6	Bn	(**190e**) *p*-MeC_6H_4	(**198f**) 55	100:0	-36.7°
7	Bn	(**190f**) *p*-$MeOC_6H_4$	(**198g**) 55	100:0	-40.3°
8	Bn	(**190g**) *p*-ClC_6H_4	(**198h**) 48	85:15	-23.4°
9	^{i}Pr	(**190h**) C_6H_5	(**198i**) 56	100:0	-97.8°
10	^{i}Pr	(**190i**) *p*-MeC_6H_4	(**198j**) 60	100:0	-107.5°
11	^{i}Pr	(**190j**) *p*-$MeOC_6H_4$	(**198k**) 40	100:0	-124.3°
12	^{i}Pr	(**190k**) *p*-ClC_6H_4	(**198l**)[c] 55	100:0	-125.6°

a The structures of the products were confirmed by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and elemental analyses. Yields are for isolated products.

b The *cis* stereochemistry was assigned to the major diastereomers of all the products based on their corresponding substrates, β-amino esters those were assigned as *syn* (see Table 4). The diastereomeric ratios (dr's) were determined by ^{13}C-NMR (50 & 100 MHz) data.

c The ORTEP representation of the crystal structure for the compound **198l** is shown in Figure 12.

The starting β-amino esters (**178c** and **190a-190k**) used for the preparation of β-lactams **202a-202l** have *syn* stereochemistry. The absolute configurations of the major diastereomers for these β-amino esters (**178c** and **190a-190k**) were assigned as (*S*,*S*,*R*) (Section 1.2.3). Obviously, the β-lactams **198a-198l**, prepared using these β-amino esters (**178c** and **190a-190k**), should have the *cis*- and (*S*,*S*,*R*) configurations, if the configurations are retained. This was confirmed by the X-ray crystal structure analysis of the compound **198l**. X-ray data revealed that the β-lactam **198l** has *cis* stereochemistry. Further, the absolute configurations at the chiral centers C2, C3 and C13 were assigned as *S*, *S* and *R*, respectively (using PLATON[106] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **198l** is shown in Figure 12. The crystal structure data of the compound (*S*,*S*,*R*)-**198l** are summarized in Table 12 and Table A7 (Appendix II).

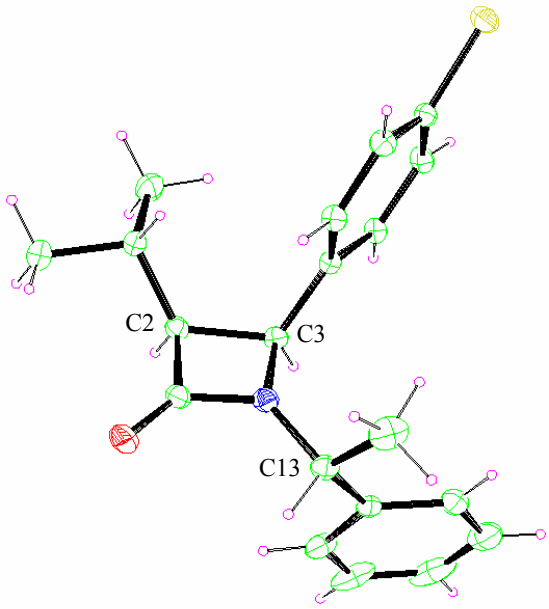


Figure 12 ORTEP representation of the crystal structure of the β-lactam **198l**

(Thermal ellipsoids are drawn at 20% probability)

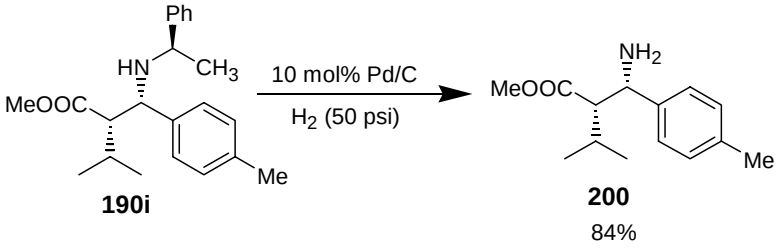
Table 12 X-ray data collection and structure refinement for β-lactam (*S*,*S*,*R*)-**198l**

Empirical formula	$C_{20}H_{22}ClNO$
Formula weight	327.84
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 10.2855(14) Å, α = 90°
	b = 11.5173(16) Å, β = 90°
	c = 15.530(2) Å, γ = 90°
Volume	1839.7(4) $Å^3$
Z	4
Calculated density	1.184 Mg/m^3
Absorption coefficient	0.212 mm^{-1}
F(000)	696
Crystal size	0.50 X 0.40 X 0.20 mm
θ range for data collection	2.20 to 28.31°
Limiting indices	$-12 \le h \le 13$; $-14 \le k \le 12$; $-20 \le l \le 20$
Reflections collected/unique	11714 / 4222 [R(int) = 0.0436]
Completeness to θ = 28.31	95.2%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	4222 / 0 / 211
Goodness-of-fit on F^2	0.920
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0463$, $wR_2 = 0.1014$
R indices (all data)	$R_1 = 0.0710$, $wR_2 = 0.1120$
Largest diff. peak and hole	0.162 and -0.180 $eÅ^{-3}$

1.2.5 Selective cleavage of the α-methylbenzyl moiety from the chiral β-amino esters containing α-methylbenzylamine:

We have observed that the α-methylbenzyl moiety is selectively cleaved from the β-amino ester **190i** with H_2 using Pd/C catalyst (Scheme 92).

Scheme 92

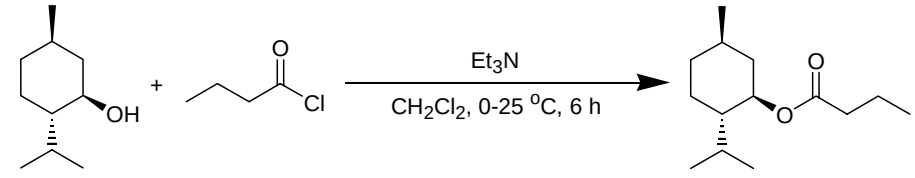


190i **200** 84%

1.2.6 Synthesis of *L*-(-)-menthol-based β-amino esters:

We have also examined the Mannich-type reactions between chiral esters and imines. Accordingly, we have prepared menthyl butyrate (1*R*,2*S*,5*R*)-**202** by treating *L*-(-)-menthol **201** with butyryl chloride in the presence of Et_3N (Scheme 93).

Scheme 93

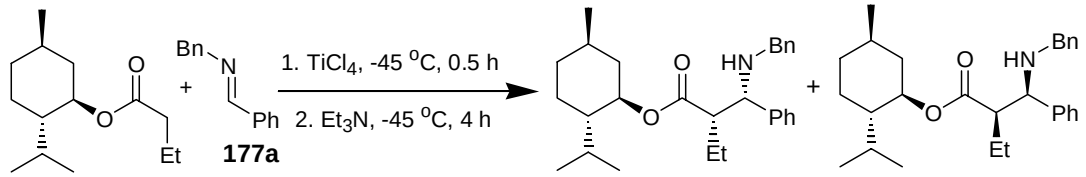


(1*R*,2*S*,5*R*)-**201** *L*-(-) (1*R*,2*S*,5*R*)-**202** 89%

The Mannich-type reaction of the menthyl butyrate (1*R*,2*S*,5*R*)-**202** with *N*-benzylidenebenzylamine **177a** in the presence of $TiCl_4/Et_3N$ reagent system afforded the corresponding β-amino ester **203a** in good yields (72%) (Scheme 94). The

selectivity resulted in this case was high (dr = 97:3). The *syn* stereochemistry was assigned for the diastereomers of the compound **203a** by comparison of the ^{1}H-NMR data with those of compound **178c**.

Scheme 94

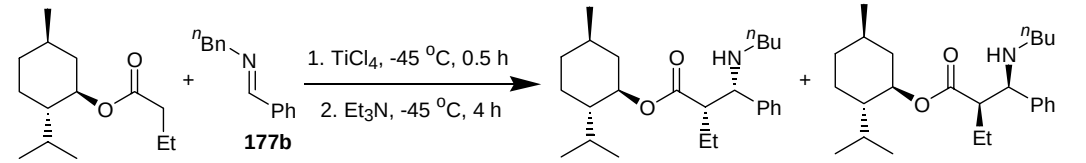


(1*R*,2*S*,5*R*)-**202**

203a
72%
dr = 97:3

We have then carried out the reaction of the menthyl butyrate (1*R*,2*S*,5*R*)-**202** and *N*-benzylidene-*n*-butylamine **177b** with the $TiCl_4/Et_3N$ reagent system. The corresponding β-amino ester **203b** was isolated in good yields and the selectivity realized in this case was also good (dr = 83:17) (Scheme 95). The *syn* stereochemistry was assigned for these diatereomers by comparison of ^{1}H-NMR data with those of compound **178c**.

Scheme 95

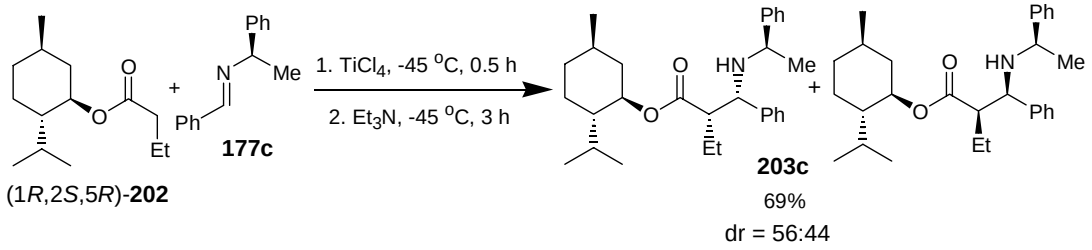


(1*R*,2*S*,5*R*)-**202**

203b
71%
dr = 83:17

The reaction of the menthyl butyrate (1*R*,2*S*,5*R*)-**202** with the *N*-benzylidene-(*R*)-α-methylbenzylamine **177c** gave the corresponding β-amino ester **203c** in good yield, but the selectivity realized here was very poor (dr = 56:44) (Scheme 96).

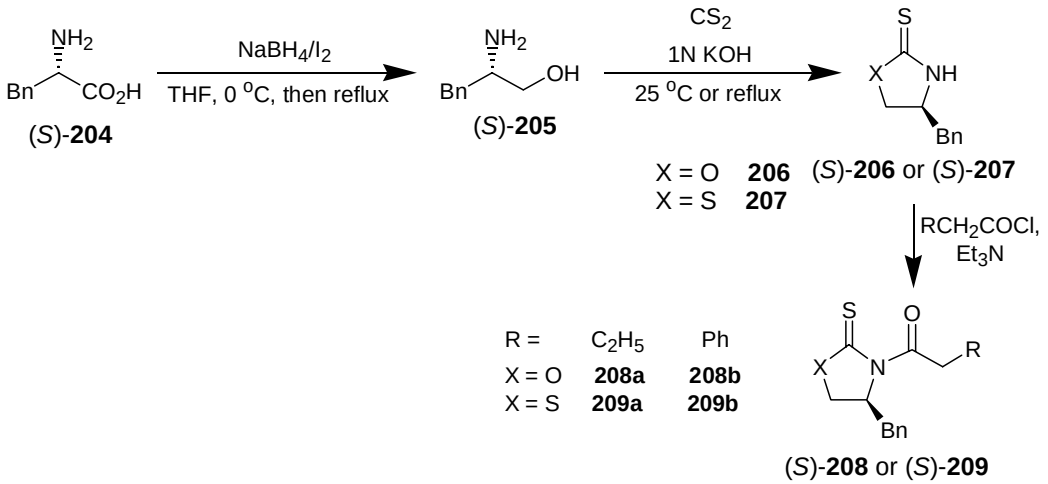
Scheme 96



We have also undertaken efforts to use the *N*-acyloxazolidinethione **208** or *N*-acylthiazolidinethione **209** as chiral auxiliaries in the Mannich-type reactions with imines **177**. Accordingly, we have prepared the corresponding chiral auxiliaries starting from (*S*)-phenylalanine **204** following reported procedures.[109,110] (*S*)-Phenylalanine **208** was reduced to give (*S*)-phenylalaninol **205** using the $NaBH_4/I_2$ reagent system.[109] The amino alcohol (*S*)-**205** was then reacted with CS_2 in 1N KOH to obtain the corresponding 5-membered cyclic product. It was found that the oxazolidinethione (*S*)-**206** was formed at room temperature and under reflux condition the thiazolidinethione (*S*)-**207** was obtained (Scheme 97).[110]

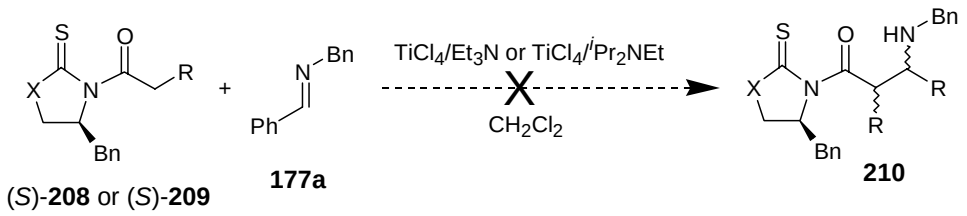
The chiral heterocycles (*S*)-**206** or (*S*)-**207** were reacted with acid chlorides (*n*-butyryl chloride or phenylacetyl chloride) in the presence of Et_3N to obtain the corresponding *N*-acyloxazolidinethiones (*S*)-**208** or *N*-acylthiazolidinethiones (*S*)-**209** (Scheme 97).[111]

Scheme 97



The Mannich-type reactions of (*S*)-**208** or (*S*)-**209** with imine **177a** were run using $TiCl_4/Et_3N$ or $TiCl_4/^iPr_2NEt$ reagent systems (Scheme 98). Unfortunately, the reactions were not clean and the corresponding β-amino carbonyl compounds **210** were not formed under the reaction conditions. Accordingly, we did not pursue these efforts further.

Scheme 98



(*S*)-**208** or (*S*)-**209**

X = O or S

R = Et or Ph

1.3 Conclusions

A highly stereoselective synthesis of *cis*-2-substituted-3-pyrrolidine carboxylates was achieved through the intramolecular Mannich-type reactions of γ-imino esters with the $TiCl_4/Et_3N$ reagent system.

Titanium enolate-mediated intermolecular Mannich-type reactions of esters and imines were developed for the stereoselective synthesis of *syn*-β-amino esters. Mannich-type reactions of esters with chiral imines, derived from optically pure α-methylbenzylamine and aldehydes, in the presence of $TiCl_4/Et_3N$ reagent system furnished the chiral *syn*-β-amino esters with good diastereoselection (dr's = 86:14 to 94:6).

The structures of the 3,5-dinitrobenzamide derivatives of prepared from the chiral *syn*-β-amino esters were analyzed by single crystal X-ray analyses: (i) compounds **180**, **191** and **192**, derived from (*R*)-α-methylbenzylamine, were found to have same absolute configurations i.e. *S*,*S*,*R* (ii) whereas the 3,5-dinitrobenzamide derivative **194** of *syn*-β-amino ester **193**, derived from (*S*)-α-methylbenzylamine, possesses absolute configurations as *R*,*R*,*S*.

Chiral *cis*-β-lactams were synthesized from the corresponding chiral *syn*-β-amino esters using the Grignard reaction. The absolute configurations of the β-lactam **198l** were determined by X-ray analysis as *S*,*S*,*R*.

(*L*)-Menthy butyrate derived chiral *syn*-β-amino esters **203** were also prepared in good yields and with good selectivities (dr's = 83:17 to 97:3) by the reactions of the titanium enolate of the chiral ester with imines. However, use of chiral imine, *N*-bezylidene-(*R*)-α-methylbenzylamine, gave the corresponding β-amino ester with poor selectivity (56:44).

1.4 Experimental Section

1.4.1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Superfit capillary point apparatus. IR (KBr) spectra were recorded on JASCO FT-IR spectrophotometer Model 5300. The neat IR spectra were recorded on JASCO FT-IR spectrophotometer Model 5300 and SHIMADZU FT-IR spectrophotometer Model 8300 with polystyrene as reference. ^{1}H-NMR (200 MHz), ^{13}C-NMR (50 MHz)) and ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) spectra were recorded on Bruker-AC-200 and Bruker-Avance-400 spectrometers, respectively with chloroform-d as solvent and TMS as reference (δ = 0 ppm). The chemical shifts are expressed in δ downfield from the signal of internal TMS. Liquid Chromatography (LC) and mass analysis (LC-MS) were performed on SHIMADZU-LCMS-2010A. The mass spectral analyses were carried out using Chemical Ionization (CI) or Electrospray Ionization (ESI) techniques. Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240C and Thermo Finnigan analyzer series Flash EA 1112. Mass spectral analyses for some of the compounds were carried out on VG 7070H mass spectrometer using EI technique at 70 eV. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01^{o}$) and AUTOPOL-IV (readability $\pm 0.001^{o}$) automatic polarimeters. The condition of the polarimeter was checked by measuring the optical rotation of a standard solution of (*R*)-(+)-α-methylbenzylamine {$[\alpha]_{D}^{25}$ = +30.2 (*c* 10, EtOH)} supplied by Fluka.

Analytical thin layer chromatographic tests were carried out on glass plates (3 x 10 cm) coated with 250mμ acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's silica gel (100-200 mesh) and neutral alumina.

All the glassware were pre-dried at 140 ^{o}C in an air-oven for 4 h, assembled in hot condition and cooled under a stream of dry nitrogen. Unless otherwise mentioned, all the operations and transfer of reagents were carried out using standard syringe-septum technique recommended for handling air sensitive reagents and organometallic compounds. Reagents prepared *in situ* in solvents were transferred using a double-ended stainless steel (Aldrich) needle under a pressure of nitrogen whenever required.

In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler was connected to the atmosphere by a long tube. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were washed with saturated sodium chloride solution (brine) and dried over anhydrous $MgSO_4$ or Na_2SO_4 or K_2CO_3 and concentrated on Heidolph-EL-rotary evaporator. All yields reported are of isolated materials judged homogeneous by TLC, IR and NMR spectroscopy.

Dichloromethane, dichloroethane and chloroform were distilled over CaH_2 and dried over molecular sieves. Methanol and ethanol supplied by Ranbaxy were distilled over CaO before use. Toluene and THF supplied by E-Merck, India were kept over sodium-benzophenone ketyl and freshly distilled before use. Titanium tetrachloride

was supplied by E-Merck, India. Triethylamine was distilled over CaH_2 and stored over KOH pellets. Aniline, benzylamine, *n*-butylamine, *N,N*-diisopropylethylamine, *n*-tributylamine, *N,N,N',N'*-tetramethylethylenediamine and pyridine, supplied by Lancaster Synthesis, Ltd., England were used as purchased. *(R)*-(+)-α-Methylbenzylamine, *(S)*-(-)-α-methylbenzylamine, (*L*)-(-)-menthol and (*S*)-phenyl-alanine were supplied by Aldrich, USA. Iodine and γ-aminobutyric acid were supplied by Spectrochem, India. Thionyl chloride, butyryl chloride, methyl butyrate and ethyl bromide were supplied by E-Merck (India) and were distilled before use. All aldehydes, supplied by Loba Chemicals (P), Ltd., India were distilled or recrystallized from the appropriate solvents before use. $NaBH_4$ and carbon disulfide were supplied by E-Merck (India). Methyl esters of phenylacetic acid, isovaleric acid were prepared by refluxing the corresponding acid in dry methanol in presence of H_2SO_4 catalyst. Methyl 3-phenylpropionate was prepared from *E*-cinnamic acid using hydrogenation followed by esterification of the acid in methanol. The Pd/C catalyst was supplied by Aldrich, USA. Hydrogenation was carried out on Parr hydrogenation apparatus.

The X-ray diffraction measurements for the respective compounds were carried out at 293 K on an automated Enraf-Nonius MACH3 difractometer using graphite monochromated, Mo-Kα (λ = 0.71073 Å) radiation with CAD4 software. Primary unit cell constants were determined with a set of 25 narrow frame scans. Intensity data were collected by the ω scan mode. Measuring the intensity of the three standard reflections after every one and half hour intervals monitored stability of the crystal during the measurement. No appreciable variation of the crystal was detected. X-ray diffraction measurements for the respective compounds were carried out at 293 K on Bruker-Nonius SMART APEX CCD area detector system. The data were reduced using XTAL 3.4 (or)

SAINT program,[112] without applying absorption correction. The refinement for structure was made by full-matrix least squares on F^2 (SHELX 97 or SHELXTL).[113]

1.4.2 General procedure for the synthesis of γ-imino esters 171 derived from γ-aminobutyric acid:

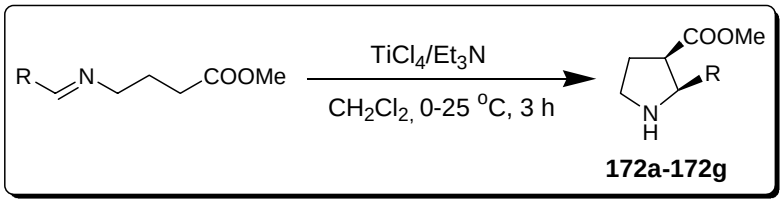
To a suspension of γ-aminobutyric acid **169** (1.24 g, 12 mmol) in methanol (40 mL) was added freshly distilled thionyl chloride (3.57 g, 2.19 mL, 30 mmol) at 0 ^oC slowly under N_2 atmosphere. Then the contents were brought to room temperature and heated under reflux for 8 h. The solvent was evaporated and the crude reaction mixture was evacuated under vacuum (1 mm of Hg). Methyl γ-aminobutyrate hydrochloride **170** was obtained in quantitative yield.

The amino ester hydrochloride (1.53g, 10 mmol) **170** was suspended in dichloromethane (30 mL) and triethylamine (1.21 g, 1.67 mL, 12 mmol) was added slowly. The reaction mixture was stirred for 1 h. Molecular sieves (10 g) and the aldehyde (10 mmol) were added successively and the reaction mixture was allowed to stir at room temperature for 48 h. Molecular sieves were filtered off and the crude reaction mixture was washed with water (30 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous K_2CO_3. The solvent was evaporated and the residue was distilled under vacuum to furnish the pure γ-imino ester **171**.

1.4.3 General procedure for the synthesis of *cis*-2,3-disubstituted pyrrolidines 172:

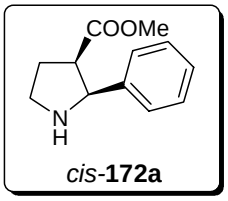
To the imino ester **171** (5 mmol) and triethylamine (0.51 g, 0.70 mL, 5 mmol) in CH_2Cl_2 (40 mL), $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in

CH_2Cl_2 (15 mL) was added dropwise at 0 ^{0}C under N_2 during 15 min. The reaction mixture was allowed to stir at room temperature for 3 h. It was quenched with saturated aq. K_2CO_3 (15 mL) and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous K_2CO_3, filtered and concentrated. The crude residue was purified by column chromatography on silica gel using $CHCl_3$/MeOH (99.5/0.5) as eluent.



172a-172g

Yield 0.77 g (75%)



cis-**172a**

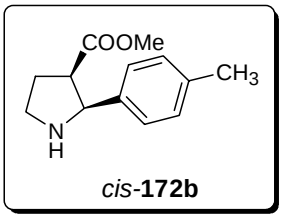
IR (Neat) (cm^{-1}) 3342, 3028, 2949, 1732

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 2.07-2.22 (m, 2H), 2.26 (s, br, NH), 2.96-3.12 (m, 2H), 3.21 (s, 3H), 3.27-3.43 (m, 1H), 4.34-4.38 (d, 1H, *J* = 8 Hz), 7.23-7.27 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 29.6, 46.6, 49.6, 50.9, 66.3, 126.7, 127.2, 128.0, 139.6, 174.3

MS (EI) m/z 205 (M^+)

Yield 0.70 g (64%)



cis-**172b**

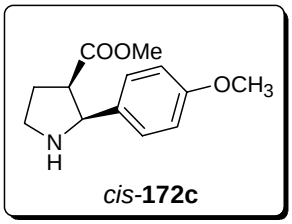
IR (Neat) (cm^{-1}) 3348, 3055, 2954, 1720

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 2.11 (s, NH), 2.18-

2.26 (m, 2H), 2.31 (s, 3H), 2.94-3.07 (m, 2H), 3.25 (s, 3H), 3.36-3.46 (m, 1H), 4.31-4.35 (d, 1H, *J* = 8 Hz), 7.07-7.27 (m, 4H) **(Spectrum No. 1)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 20.1, 29.6, 46.5, 49.5, 50.9, 66.0, 126.5, 128.6, 129.1, 139.5, 174.2 **(Spectrum No. 2)**

MS (EI) m/z 205 (M^+)



cis-**172c**

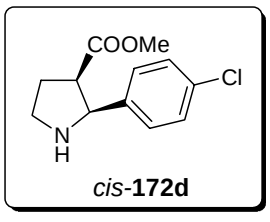
Yield 0.89 g (76%)

IR (Neat) (cm^{-1}) 3338, 3060, 2950, 1732

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 2.06-2.26 (m, 2H), 2.93-3.07 (m, 2H), 3.19 (s, br, NH), 3.26 (s, 3H), 3.38-3.47 (m, 1H), 3.78 (s, 3H), 4.30-4.34 (d, 1H, *J* = 8 Hz), 6.80-6.85 (d, 2H, *J* = 10 Hz), 7.17-7.22 (d, 2H, *J* = 10 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 29.5, 46.4, 47.5, 51.1, 55.1, 66.7, 113.4, 127.5, 131.4, 158.7, 174.4

MS (EI) m/z 235 (M^+)



cis-**172d**

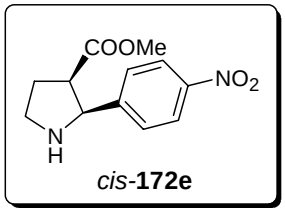
Yield 0.85 g (71%)

IR (Neat) (cm^{-1}) 3332, 3058, 2954, 1730

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.94-2.00 (m, 2H), 2.08-2.22 (m, 2H), 3.26 (s, 3H), 3.32 (s, br, NH), 3.36-3.46 (m, 1H), 4.32-4.36 (d, 1H, *J* = 8 Hz), 7.20-7.30 (m, 4H) **(Spectrum No. 3)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 29.5, 46.5, 49.4, 51.1, 65.4, 128.1, 128.2, 132.8, 138.4, 174.0 **(Spectrum No. 4)**

MS (EI) m/z 239 (M^+), 241 (M+2)



cis-**172e**

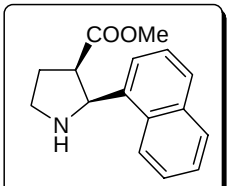
Yield 0.86 g (69%)

IR (Neat) (cm^{-1}) 3419, 3061, 2956, 1742

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.89 (s, br, NH), 2.09-2.31 (m, 2H), 3.02-3.25 (m, 1H), 3.27 (s, 3H), 3.34-3.52 (m, 2H), 4.47-4.51 (d, 1H, *J* = 8 Hz), 7.47-7.52 (d, 2H, *J* = 10 Hz), 8.14-8.19 (d, 2H, *J* = 10 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 29.4, 46.5, 49.4, 51.1, 65.1, 123.0, 127.8, 147.1, 148.1, 173.3

MS (EI) m/z 250 (M^+)



cis-**172f**

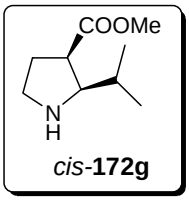
Yield 0.84 g (66%)

IR (Neat) (cm^{-1}) 3336, 3049, 2947, 1732

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.88 (s, br, NH), 2.23-2.34 (m, 2H), 2.87 (s, 3H), 3.08-3.14 (m, 1H), 3.48-3.57 (m, 2H), 5.06-5.10 (d, 1H, *J* = 8 Hz), 7.27-8.06 (m, 7H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 29.7, 46.3, 48.9, 50.7, 62.6, 122.9, 123.1, 125.1, 125.3, 125.9, 127.7, 128.7, 131.4, 133.5, 135.2, 174.2

MS (EI) m/z 255 (M^+)



cis-**172g**

Yield 0.27 g (32%)

IR (Neat) (cm^{-1}) 3342, 2964, 1726

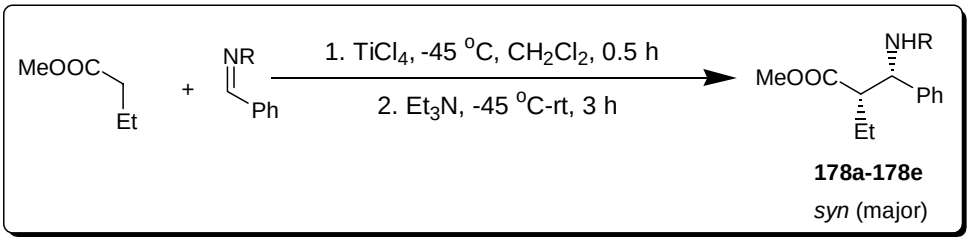
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.80-1.32 (m, 6H), 1.37-1.51 (m, 1H), 1.76-2.01 (m, 2H), 2.10-2.22 (m, 1H), 2.27-2.43 (m, 1H), 3.27-3.48 (m, 2H), 3.68 (s, 3H), 3.92 (s, br, NH)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 20.9, 21.6, 30.1, 30.9, 46.1, 46.3, 51.1, 71.7, 175.7

MS (EI) m/z 171 (M^+)

1.4.4 General procedure for the synthesis of β-amino esters 178 from the reaction of methyl butyrate with imines in presence of $TiCl_4/Et_3N$:

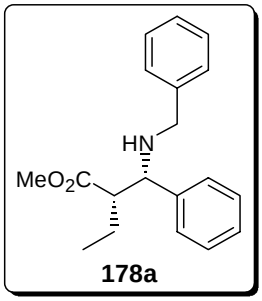
Imine (5 mmol) and methyl butyrate (0.53 g, 0.59 mL, 5.2 mmol) were taken in dichloromethane (40 mL) and $TiCl_4$ (12 mmol, 2.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (15 mL) was added at -45 ^{0}C dropwise over 15 min under N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.51 g, 0.70 mL, 5 mmol) was added and the mixture was stirred for further 3 h. It was quenched with saturated aq. K_2CO_3 (15 mL), brought to room temperature and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on neutral alumina using hexanes/EtOAc (99/1) as eluent.



Yield 1.29 g (87%)

syn:*anti* 100:0

mp 42-44 ^{o}C



IR (KBr) (cm^{-1}) 3331, 3026, 2968, 1722

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.87 (t, 3H, *J* = 8 Hz), 1.75-1.82 (m, 2H), 2.60 (s, br, NH), 3.46 (s, 3H), 3.50 (s, 2H), 3.65-3.72 (m, 1H), 3.84 (d, 1H, *J* = 8 Hz), 7.28-7.32 (m, 10H) **(Spectrum No. 5)**

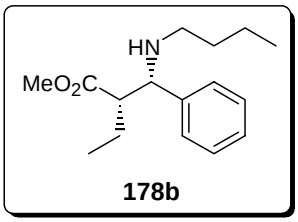
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 12.2, 21.7, 51.2, 51.4, 55.0, 63.5, 126.9, 127.4, 127.7, 128.3, 140.5, 141.6, 174.6 **(Spectrum No. 6)**

MS m/z 298 (M+1)

Analytical data calculated for $C_{19}H_{23}NO_2$: C-76.74%, H-7.79%, N-4.71%

Found: C-77.01%, H-7.44%, N-4.36%

Yield 1.03 g (78%)



178b

syn:*anti* 95:5

IR (Neat) (cm^{-1}) 3341, 3028, 2962, 1732

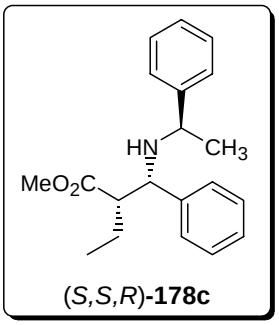
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.83-0.91 (m, 6H), 1.23-1.44 (m, 4H), 1.54 (s, br, NH), 1.68-1.77 (m, 2H), 2.36-2.43 (m, 2H), 2.52-2.63 (m, 1H), 3.47 (s, 3H), 3.78 (d, 1H, *J* = 8 Hz), 7.19-7.41 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): for major *syn* isomer: 12.1, 13.9, 20.4, 21.8, 32.3, 47.3, 51.1, 55.0, 64.5, 127.1, 127.5, 128.1, 128.4, 142.0, 174.7. Additional signals for minor *anti* isomer: 11.8, 23.1, 46.8, 65.0

MS m/z 264 (M+1)

Analytical data calculated for $C_{16}H_{25}NO_2$: C-72.97%, H-9.57%, N-5.32%

Found: C-73.25%, H-9.36%, N-5.55%



(*S,S,R*)-**178c**

Yield 1.03 g (82%)

dr 92:8

IR (Neat) (cm^{-1}) 3329, 3028, 2966, 1732

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.90 (t, 3H, *J* = 7 Hz), 1.30 (d, 3H, *J* = 7 Hz), 1.69 (s, NH), 1.75-1.81 (m, 2H), 2.54-2.65 (m, 1H), 3.45 (s, 3H), 3.56-3.62 (m, 1H), 3.96 (d, 1H, *J* = 8 Hz), 7.21-7.30 (m, 10 H) **(Spectrum No. 7)**

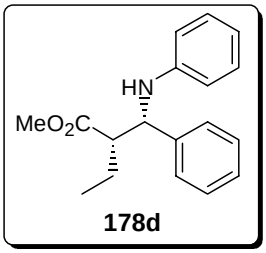
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.2, 22.1, 22.2, 51.1, 54.7, 55.1, 61.7, 126.6, 126.9, 127.2, 127.5, 128.2, 128.4, 142.0, 146.4, 174.6. Additional signals for minor diastereomer: 11.2, 21.5, 25.2, 47.5, 51.5, 61.3 **(Spectrum No. 8)**

MS m/z 312 (M+1)

$[\alpha]_D^{25}$ +40.0 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{20}H_{25}NO_2$: C-77.14%, H-8.09%, N-4.50%

Found: C-77.03%, H-8.07%, N-4.61%



178d

Yield 0.54 g (38%)

syn:*anti* 55:45

mp 90-92 ^oC

IR (KBr) (cm^{-1}) 3333, 3022, 2966, 1723

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.85-0.94 (m, 3H), 1.72 (s, NH), 1.77-1.82 (m, 2H), 2.64-2.74 (m, 1H), 3.60 (s, 3H), 4.55-4.64 (m, 1H), 6.49-6.65 (m, 5H), 7.03-7.29 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): for major *syn* isomer: 12.0, 23.7, 51.5, 54.6, 59.3, 113.5, 117.4, 126.7, 127.4, 128.6, 141.1, 147.0, 174,0. Additional signals for minor *anti* isomer: 12.3, 21.0, 23.7, 54.8, 59.7, 113.8, 117.7, 127.0, 128.5, 129.1, 141.7, 147.3, 175.0

MS m/z 284 (M+1)

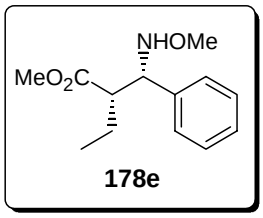
Analytical data calculated for $C_{18}H_{21}NO_2$: C-76.30%, H-7.47%, N-4.94%

Found: C-76.30%, H-7.48%, N-5.37%

Yield 0.54 g (85%)

syn:*anti* 100:0

IR (Neat) (cm^{-1}) 3270, 3030, 2954, 1736



178e

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.92 (t, 3H, *J* = 8 Hz), 1.72-1.76 (m, 2H), 2.77-2.79 (m, 1H), 3.48 (s, 3H), 3.53 (s, 3H), 4.21 (d, 1H, *J* = 8 Hz), 6.00 (s, br, NH), 7.28-7.35 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.1, 21.9, 51.2, 51.3, 61.9, 66.3, 127.7, 127.8, 128.0, 128.1, 139.9, 174.1

MS m/z 238 (M+1)

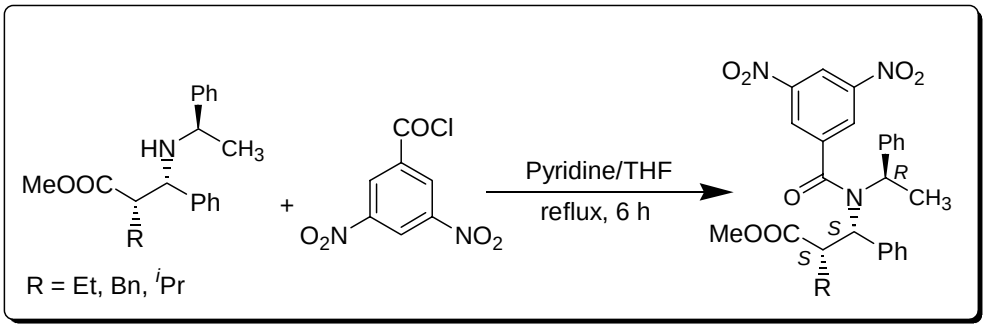
Analytical data calculated for $C_{13}H_{19}NO_3$: C-65.80%, H-8.07%, N-5.90%

Found: C-65.34%, H-8.66%, N-5.62%

1.4.5 Procedure for the synthesis of 3,5-dinitrobenzamide derivative 180 of β-amino ester 178c:

To a solution of β-amino ester **178c** (0.93 g, 3 mmol) in THF (20 mL) was added freshly prepared 3,5-dinitrobenzoyl chloride (0.69 g, 3.2 mmol) at 0 ^{o}C under N_2

atmosphere. Then, pyridine (0.28 g, 0.28 mL, 3.5 mmol) was added slowly and the contents were brought to 25 °C and refluxed gently for 6 h. Then the reaction mixture was cooled to room temperature and water (10 mL) was added. Organic solvent was evaporated and the crude was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was subjected to column chromatography on silica gel using hexanes/EtOAc (90:10) as eluent.

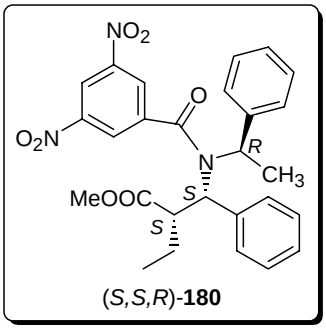


Yield 1.12 g (74%)

mp 138-140 °C

IR (KBr) (cm^{-1}) 3063, 2962, 1734, 1622

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.85 (t, 3H, J = 7 Hz), 1.15-1.28 (m, 1H), 1.40 (d, 3H, J = 7 Hz), 1.58-1.70 (m, 2H), 3.39 (s, 3H), 3.72-4.08 (m, 1H), 4.69-4.74 (m, 1H), 7.00-7.40 (m, 10H), 7.60 (s, 1H), 8.31 (s, 1H), 8.99 (s, 1H) **(Spectrum No. 9)**



^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 11.8, 18.6, 24.1, 51.4, 58.8, 60.4, 64.5, 118.7, 126.1, 127.6, 128.5, 128.8, 129.0, 138.6, 140.5, 140.8, 141.7, 148.3, 167.9, 174.6 **(Spectrum No. 10)**

MS m/z 528 (M+23)

$[\alpha]_D^{25}$ +64.3 (*c* 1, $CHCl_3$)

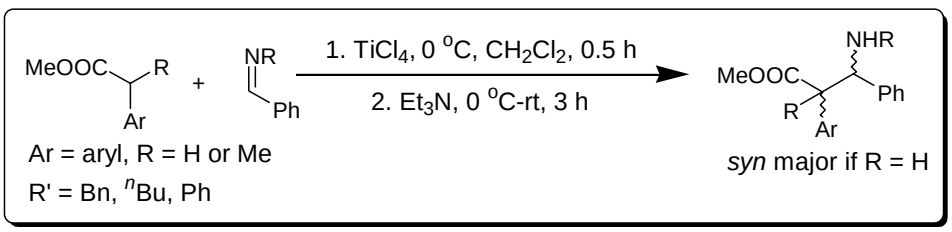
Analytical data calculated for $C_{27}H_{27}N_3O_7$: C-64.15%, H-5.38%, N-8.31%

Found: C-64.22%, H-5.34%, N-8.04%

de >98% (using HPLC, Chiralcel OD-H, hexanes/^{i}PrOH = 90:10, flow = 0.5 mL/min, t_{r1} = 25.3 min and t_{r2} = 27.0 min)

1.4.6 General procedure for the synthesis of β-amino esters from the reactions of α-arylacetic acid esters with imines in presence of $TiCl_4/Et_3N$:

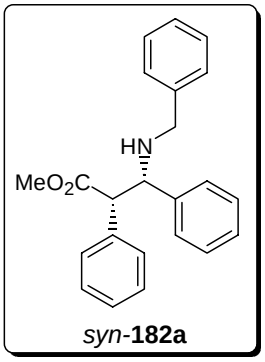
Imine (5 mmol) and ester (5.2 mmol) were taken in dichloromethane (40 mL) and $TiCl_4$ (12 mmol, 2.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (15 mL) was added at 0 ^{0}C dropwise over 15 min under N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.51g, 0.70 mL, 5 mmol) was added and the mixture allowed stirring for a further 3 h. It was quenched with saturated aq. K_2CO_3 (15 mL), brought to room temperature and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on neutral alumina using hexanes/EtOAc (99/1) as eluent.



Yield 0.54 g (78%)

syn:*anti* 73:27

For major *syn* isomer of 182a



syn-**182a**

mp 110-112 °C

IR (KBr) (cm^{-1}) 3319, 3059, 2951, 1723

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 3.34 (s, 3H), 3.53 (s, 2H), 3.65 (s, NH), 3.83 (d, 1H, *J* = 10 Hz), 4.23 (d, 1H, *J* = 10 Hz), 6.95-7.00 (m, 5H), 7.21-7.26 (m, 5H), 7.33-7.48 (m, 5H) **(Spectrum No. 11)**

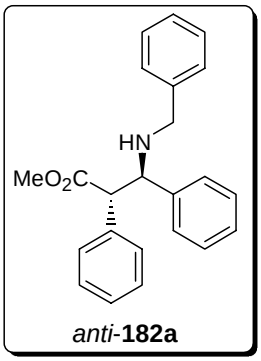
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 50.8, 51.6, 59.9, 63.9, 126.8, 127.7, 128.0, 128.3, 128.9, 135.9, 140.1, 141.0, 172.2 **(Spectrum No. 12)**

MS m/z 346 (M+1)

Analytical data calculated for $C_{23}H_{23}NO_2$: C-79.97%, H-6.71%, N-4.05%

Found: C-80.04%, H-6.65%, N-4.07

For minor *anti* isomer of 182a



anti-**182a**

IR (Neat) (cm^{-1}) 3310, 3063, 2945, 1721

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 3.59 (d, 1H, *J* = 12 Hz), 3.68 (s, NH), 3.70 (s, 3H), 3.85 (s, 2H), 4.24 (d, 1H, *J* = 12 Hz), 7.04-7.44 (m, 15H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 51.4, 52.0, 59.8, 65.7, 126.9, 127.2, 127.9, 128.2, 128.3, 128.8, 136.2, 140.4, 173.6

MS m/z 346 (M+1)

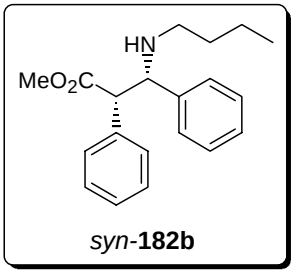
Analytical data calculated for $C_{23}H_{23}NO_2$: C-79.97%, H-6.71%, N-4.05%

Found: C-80.03%, H-6.41%, N-3.81%

Yield 0.54 g (80%)

syn:*anti* 66:34

For major *syn* isomer of 182b



syn-**182b**

mp 64-66 ^oC

IR (KBr) (cm^{-1}) 3317, 3060, 2952, 1726

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.73 (t, 3H, J = 7 Hz), 1.03-1.25 (m, 4H), 1.44 (s, NH), 2.20-2.34 (m, 2H), 3.36 (s, 3H), 3.80 (d, 1H, *J* = 10 Hz), 4.25 (d, 1H, *J* = 10 Hz), 7.12-7.54 (m, 10H)

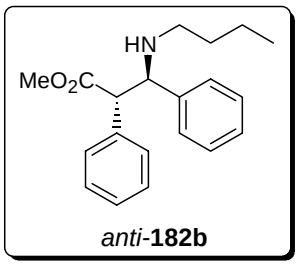
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 13.8, 20.1, 31.8, 47.0, 51.5, 59.9, 65.4, 127.5, 128.0, 128.2, 128.8, 136.2, 141.5, 172.3

MS m/z 312 (M+1)

Analytical data calculated for $C_{20}H_{25}NO_2$: C-77.14%, H-8.09%, N-4.50%

Found: C-77.20%, H-7.94%, N-4.70%

For minor *anti* isomer of 182b



anti-**182b**

IR (Neat) (cm^{-1}) 3335, 3062, 2955, 1732

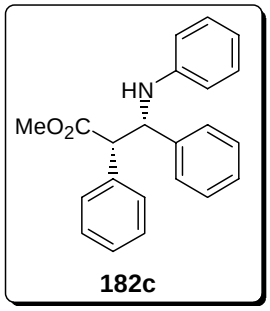
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.86 (t, 3H, J = 7 Hz), 1.27-1.40 (m, 4H), 1.79 (s, NH), 2.41 (t, 2H, *J* = 7 Hz), 3.72 (s, 3H), 3.79 (d, 1H, *J* = 11 Hz), 4.20 (d, 1H, *J* = 11 Hz), 7.01-7.27 (m, 10H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 13.9, 20.6, 31.9, 47.2, 51.5, 59.7, 65.2, 127.1, 128.1, 128.9, 129.6, 136.0, 141.7, 172.3

MS m/z 312 (M+1)

Analytical data calculated for $C_{20}H_{25}NO_2$: C-77.14%, H-8.09%, N-4.50%

Found: C-76.61%, H-7.86%, N-4.13%



182c

Yield 1.03 g (41%)

mp 100-102 °C

syn:*anti* 67:33

IR (KBr) (cm^{-1}) 3344, 3059, 2951, 1732

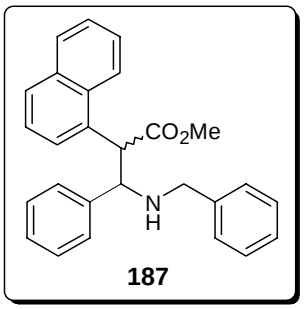
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.56 (s, NH), 3.69 (s, 3H), 3.96 (d, 1H, *J* = 8 Hz), 4.95 (d, 1H, *J* = 8 Hz), 6.54-6.65 (m, 5H), 7.00-7.26 (m ,10H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): for major *syn* isomer: 52.2, 54.8, 58.9, 114.1, 117.9, 127.0, 127.4, 127.6, 127.7, 128.5, 128.9, 129.2, 135.7, 140.7, 146.9, 173.7. Additional signals for minor *anti* isomer: 52.4, 61.3

MS m/z 332 (M+1)

Analytical data calculated for $C_{22}H_{21}NO_2$: C-79.73%, H-6.39%, N-4.23%

Found: C-79.78%, H-6.36%, N-3.79%



187

Yield 0.51 g (26%)

mp 92-94 °C

dr 100:0

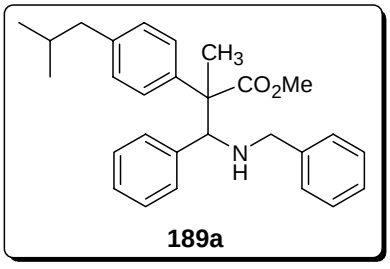
IR (KBr) (cm^{-1}) 3433, 3061, 2949, 1736

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 1.65 (s, br, NH), 3.60 (d, 1H, *J* = 8 Hz), 3.68 (s, 3H), 3.72 (d, 1H, *J* = 8 Hz), 4.56 (d, 1H, *J* = 8 Hz), 4.85 (d, 1H, *J* = 8 Hz), 6.99-7.15 (m, 5H), 7.17-7.48 (m, 8H), 7.55-7.62 (m, 1H), 7.68-7.72 (m, 1H), 794-8.00 (m, 1H), 8.03-8.06 (m, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 50.4, 51.5, 52.2, 62.9, 122.9, 123.5, 124.0, 125.5, 125.8, 126.1, 126.9, 127.8, 128.0, 129.1, 131.7, 132.3, 132.8, 133.6, 134.0, 142.0, 140.2, 140.4, 173.7, 173.9

MS m/z 396 (M+1)

Yield 0.68 g (34%)



189a

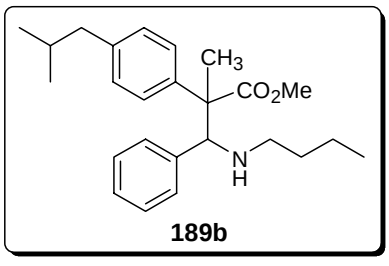
IR (Neat) (cm^{-1}) 3343, 3061, 2953, 1723

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.78-0.90 (m, 6H), 1.54 (s, 3H), 1.78-1.84 (m, 1H), 2.05 (s, br, NH), 2.40-2.43 (m, 2H), 3.51 (d, 1H, *J* = 12 Hz), 3.63 (d, 1H, *J* = 12 Hz), 3.70 (s, 3H), 4.38 (s, 1H), 6.89-6.91 (m, 2H), 6.95-7.03 (m, 5H), 7.06-7.13 (m, 2H), 7.23-7.30 (m, 5H) **(Spectrum No. 13)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 16.9, 22.2, 30.0, 44.8, 52.0, 55.6, 69.0, 126.4, 126.7, 126.8, 127.1, 128.3, 128.6, 129.3, 138.5, 140.3, 140.6, 176.1 **(Spectrum No. 14)**

MS m/z 400 (M-1)

Yield 0.57 g (31%)



189b

IR (Neat) (cm^{-1}) 3347, 3026, 2955, 1726

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.84-0.92

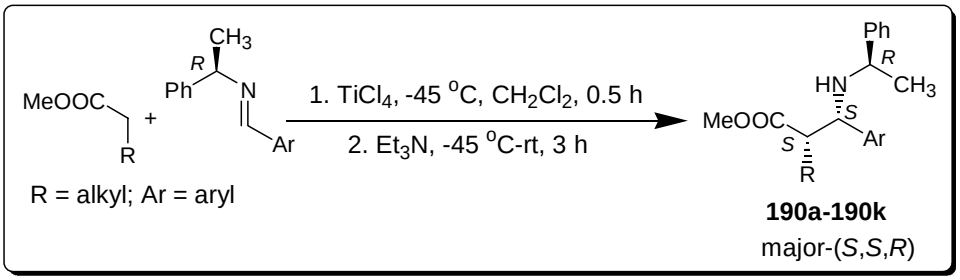
(9H), 1.24-1.32 (m, 2H), 1.39-1.43 (m, 2H), 1.53 (s, 3H), 1.77 (s, NH), 1.79-1.90 (3H), 2.38-2.42 (m, 2H), 3.72 (s, 3H), 4.36 (s, 1H), 6.80-6.82 (m, 2H), 6.94-7.08 (7H)

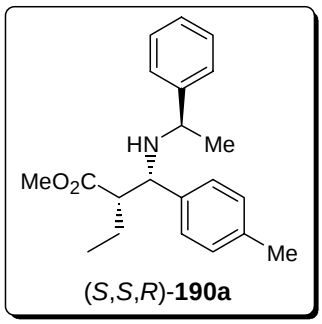
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 14.0, 16.2, 20.4, 22.3, 30.2, 32.3, 44.9, 48.0, 52.2, 55.6, 69.6, 126.4, 126.7, 127.0, 128.7, 129.2, 130.5, 138.9, 140.3, 176.4

MS m/z 368 (M+1)

1.4.7 General procedure for the synthesis of chiral β-amino esters from esters and imines of optically pure α-methylbenzylamine:

Chiral imine (5 mmol) and ester (5.2 mmol) were taken in dichloromethane (40 mL) and $TiCl_4$ (12 mmol, 2.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (15 mL) was added at -45 ^{0}C dropwise over 15 min under N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.51 g, 0.70 mL, 5 mmol) was added and the mixture was stirred further for 3 h. It was quenched with saturated aq. K_2CO_3 (15 mL), brought to room temperature and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on neutral alumina using hexanes/EtOAc (99/1) as eluent.





(*S*,*S*,*R*)-**190a**

Yield 1.28 (79%)

dr 93:7

IR (Neat) (cm^{-1}) 3329, 3026, 2967, 1734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.88 (t, 3H, *J* = 7.6 Hz), 1.28 (d, 3H, *J* = 6.4 Hz), 1.57 (s, br, NH), 1.66-1.88 (m, 2H), 2.32 (s, 3H), 2.52-2.59 (m, 1H), 3.47 (s, 3H), 3.58-3.63 (m, 1H), 3.92 (d, 1H, *J* = 7.6 Hz), 7.03-7.10 (m, 4H), 7.20-7.27 (m, 5H)

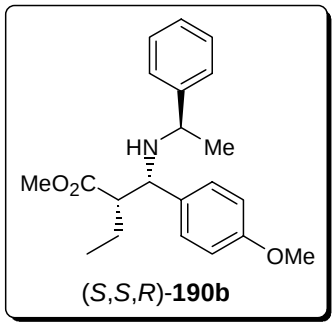
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.2, 21.1, 22.0, 22.2, 51.2, 54.4, 55.0, 61.2, 126.7, 126.9, 127.3, 127.4, 128.4, 129.0, 136.7, 138.7, 146.4, 174.7. Additional signals for minor diastereomer: 21.5, 25.2, 54.8, 55.1, 60.8

MS m/z 326 (M+1)

$[\alpha]_D^{25}$ +44.9 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{21}H_{27}NO_2$: C-77.50%, H-8.36%, N-4.30%

Found: C-77.68%, H-8.37%, N-3.98%



(*S*,*S*,*R*)-**190b**

Yield 1.38 g (81%)

dr 96:4

IR (Neat) (cm^{-1}) 3329, 3063, 2966, 1736

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.91 (t, 3H, *J* = 8 Hz), 1.31(d, 3H, *J* = 6.4 Hz), 1.60 (s, br, NH), 1.68-1.76 (m, 2H), 2.55-2.60 (m, 1H), 3.48 (s, 3H), 3.62 (q, 1H, *J*

= 6 Hz), 3.82 (s, 3H), 3.91 (d, 1H, *J* = 8 Hz), 6.84 (d, 2H, *J* = 8 Hz), 7.13 (d, 2H, *J* = 8 Hz), 7.21-7.31 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.1, 21.9, 22.4, 51.2, 54.4, 55.1, 55.2, 61.0, 113.6, 126.6, 126.9, 128.3, 128.4, 133.8, 146.4, 158.6, 174.7. Additional signal for minor diastereomer: 60.5

MS m/z 342 (M+1)

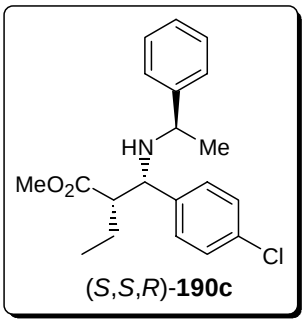
$[\alpha]_D^{25}$ +44.3 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{21}H_{27}NO_3$: C-77.87%, H-7.97%, N-4.10%

Found: C-77.76%, H-7.91%, N-3.58%

Yield 1.31 g (76%)

dr 89:11



(*S*,*S*,*R*)-**190c**

IR (Neat) (cm^{-1}) 3331, 3061, 2967, 1736

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.91 (t, 3H, *J* = 8 Hz), 1.31 (d, 3H, *J* = 7 Hz), 1.58 (s, br, NH), 1.68-1.76 (m, 1H), 1.83-1.92 (m, 1H), 2.53-2.61 (m, 1H), 3.49 (s, 3H), 3.58-3.61 (m, 1H), 3.94 (d, 1H, *J* = 8 Hz), 7.11-7.18 (m, 2H), 7.22-7.32 (7H)

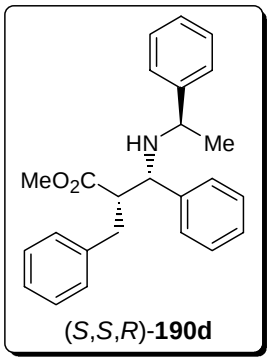
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.1, 22.1, 22.2, 41.4, 51.3, 54.8, 61.1, 126.6, 127.0, 128.4, 128.8, 132.8, 140.5, 146.0, 174.4. Additional signals for minor diastereomer: 11.1, 21.4, 25.1

MS m/z 346 (M+1)

$[\alpha]_D^{25}$ +38.5 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{20}H_{24}ClNO_2$: C-69.45%, H-6.99%, N-4.05%

Found: C-69.62%, H-6.76%, N-4.46%



(*S*,*S*,*R*)-**190d**

Yield 1.47 g (79%)

dr 86:14

IR (Neat) (cm^{-1}) 3327, 3061, 2851, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.34 (d, 3H, *J* = 6.4 Hz), 1.80 (s, br, NH), 2.98-3.01 (m, 2H), 3.24-3.27 (m, 1H), 3.64-3.69 (m, 1H), 4.06 (d, 1H, *J* = 6.8 Hz), 7.13-7.20 (m, 5H), 7.24-7.35 (m, 10H) **(Spectrum No. 15)**

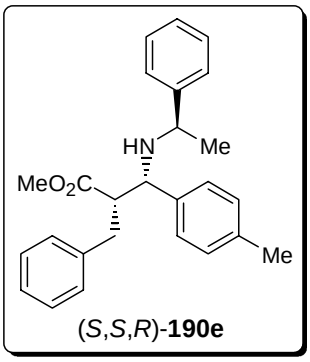
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 21.1, 35.3, 51.2, 54.6, 55.3, 61.8, 126.2, 126.7, 127.0, 127.4, 128.3, 128.6, 128.8, 139.8, 141.4, 146.2, 174.0. Additional signals for minor diastereomer: 25.2, 34.1, 52.5, 55.0, 55.5, 60.6 **(Spectrum No. 16)**

MS m/z 374 (M+1)

$[\alpha]_D^{25}$ +17.8 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{25}H_{27}NO_2$: C-80.40%, H-7.29%, N-3.75%

Found: C-79.50%, H-7.31%, N-3.58%



(*S*,*S*,*R*)-**190e**

Yield 1.62 g (84%)

dr 91:9

IR (Neat) (cm^{-1}) 3323, 3026, 2957, 1734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.30 (d, 3H, *J* = 6.4 Hz), 1.73 (s, NH), 2.33 (s, 3H), 2.96 (d, 2H, *J* = 7.2 Hz), 3.18-3.23 (m, 1H), 3.33 (s, 3H), 3.62-3.67 (m, 1H), 4.01 (d, 1H, *J* = 6.8 Hz), 7.10-7.15 (m, 4H), 7.17-7.30 (m, 10H)

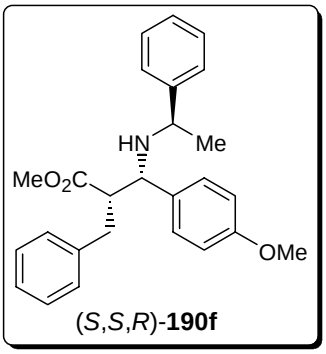
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 21.2, 22.1, 35.3, 51.1, 54.5, 55.2, 61.4, 126.1, 126.7, 127.0, 127.3, 128.3, 128.4, 128.8, 129.1, 136.9, 138.2, 139.9, 146.3, 174.0. Additional signals for minor diastereomer: 25.3, 34.5, 54.9, 55.6, 61.1

MS m/z 388 (M+1)

$[\alpha]_D^{25}$ +24.4 (*c* 1, $CHCl_3$)

Yield 1.63 g (81%)

dr 95:5



(*S*,*S*,*R*)-**190f**

IR (Neat) (cm^{-1}) 3325, 3061, 2953, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.33 (d, 3H, *J* = 6 Hz), 1.62 (s, br, NH), 2.97-3.02 (m, 2H), 3.24-3.26 (m, 1H), 3.35 (s, 3H), 3.62-3.67 (m, 1H), 3.82 (s, 3H), 4.01 (d, 1H, *J* = 6.4 Hz), 6.86 (d, 4H, *J* = 9 Hz), 7.11-7.20 (m, 5H), 7.24-7.31 (m, 5H)

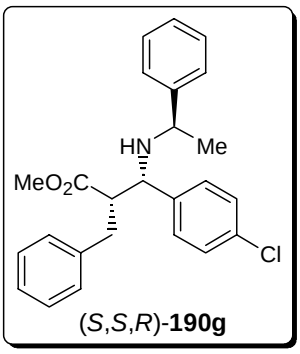
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 22.2, 35.5, 51.2, 54.6, 55.2, 55.4, 61.2, 113.7, 126.2, 126.7, 127.0, 128.4, 128.5, 128.9, 133.4, 139.9, 146.3, 158.8, 174.1. Additional signals for minor diastereomer: 22.7, 34.7, 51.8, 54.9, 55.7, 60.8

MS m/z 404 (M+1)

$[\alpha]_D^{25}$ +22.4 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{26}H_{29}NO_3$: C-77.39%, H-7.24%, N-3.47%

Found: C-77.34%, H-7.24%, N-3.60%



(*S*,*S*,*R*)-**190g**

Yield 1.63 g (80%)

dr 94:6

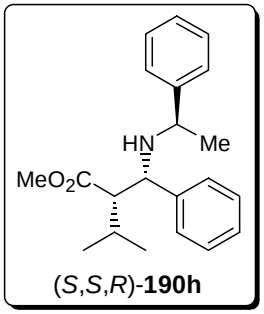
IR (Neat) (cm^{-1}) 3024, 2964, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.31 (d, 3H, *J* = 6.8 Hz), 1.73 (s, br, NH), 2.94-3.00 (m, 2H), 3.14-3.19 (m, 1H), 3.33 (s, 3H), 3.58-3.61 (m, 1H), 4.01 (d, 1H, *J* = 6.8 Hz), 7.11 (d, 2H, *J* = 7.6 Hz), 7.15 (d, 2H, *J* = 7.2 Hz), 7.18-7.31 (10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 22.2, 35.3, 51.3, 54.9, 55.1, 61.3, 126.3, 126.7, 127.1, 128.5, 128.8, 128.9, 129.0, 133.0, 139.5, 140.1, 145.9, 173.8. Additional signals for minor diastereomer: 22.7, 34.4, 55.3, 60.1

MS m/z 408 (M+1)

$[\alpha]_D^{25}$ +23.3 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**190h**

Yield 1.51 g (93%)

dr 93:7

IR (Neat) (cm^{-1}) 3321, 3063, 2962, 1732

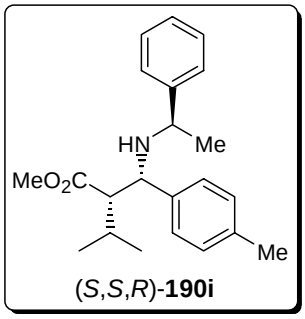
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.02 (d, 3H, *J* = 7.2

Hz), 1.12 (d, 3H, *J* = 6.8 Hz), 1.34 (d, 3H, *J* = 6.8 Hz), 1.55 (s, br, NH), 2.45-2.51 (m, 1H), 2.64-2.68 (m, 1H), 3.37 (s, 3H), 3.55-3.60 (m, 1H), 4.08 (d, 3H, *J* = 9.6 Hz), 7.22-7.33 (10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 17.5, 21.6, 21.7, 27.1, 50.7, 54.2, 58.9, 126.7, 127.0, 127.2, 127.6, 128.2, 128.4, 142.1, 146.5, 173.2. Additional signals for minor diastereomer: 17.2, 21.9, 26.8, 50.6, 54.6, 59.0

MS m/z 326 (M+1)

$[\alpha]_D^{25}$ +49.0 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**190i**

Yield 1.52 g (90%)

dr 88:12

IR (Neat) (cm^{-1}) 3319, 3926, 2962, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.8 Hz), 1.30 (d, 3H, *J* = 6.4 Hz), 1.47 (s, br, NH), 2.31 (s, 3H), 2.39-2.44 (m, 1H), 2.59-2.63 (m, 1H), 3.37 (s, 3H), 3.52-3.57 (m, 1H), 4.02 (d, 1H, *J* = 10 Hz), 7.03-7.08 (m, 4H), 7.19-7.24 (m, 5H)

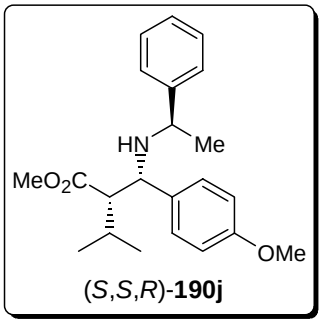
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 17.6, 21.1, 21.6, 21.6, 27.1, 50.7, 54.1, 58.5, 58.9, 126.7, 126.9, 127.2, 127.4, 127.6, 128.3, 128.9, 136.6, 139.0, 146.6, 173.2. Additional signals for minor diastereomer: 17.3, 31.9, 26.8, 50.6, 54.5, 59.1

MS m/z 340 (M+1)

$[\alpha]_D^{25}$ +55.9 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{22}H_{29}NO_2$: C-77.84%, H-8.61%, N-4.13%

Found: C-77.70%, H-8.59%, N-4.88%



(*S*,*S*,*R*)-**190j**

Yield 1.51 g (85%)

dr 90:10

IR (Neat) (cm^{-1}) 3320, 3061, 2963, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, 3H, *J* = 6.8 Hz), 1.08 (d, 3H, *J* = 6.6 Hz), 1.30 (d, 3H, *J* = 6.4 Hz), 1.43 (s, br, NH), 2.38-2.42 (m, 1H), 2.52-2.62 (m, 1H), 3.37 (s, 3H), 3.52-3.57 (m, 1H), 3.80 (s, 3H), 4.00 (d, 1H, *J* = 9.6 Hz), 6.81 (d, 2H, *J* = 8 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 7.21-7.28 (m, 5H) **(Spectrum No. 17)**

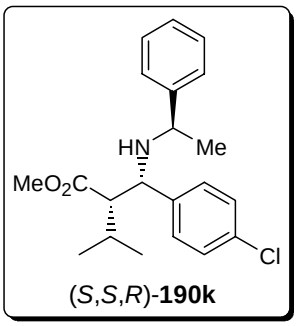
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 17.5, 21.6, 27.1, 50.7, 54.1, 58.2, 59.0, 113.5, 128.3, 128.6, 128.8, 134.2, 146.5, 158.6, 173.3. Additional signals for minor diastereomer: 17.2, 21.8, 26.8, 54.5, 59.2 **(Spectrum No. 18)**

MS m/z 356 (M+1)

$[\alpha]_D^{25}$ +53.1 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{22}H_{29}NO_3$: C-74.33%, H-8.22%, N-3.94%

Found: C-74.37%, H-8.49%, N-4.61%



(*S*,*S*,*R*)-**190k**

Yield 1.31 g (73%)

dr 86:14

IR (Neat) (cm^{-1}) 3324, 3061, 2965, 1732

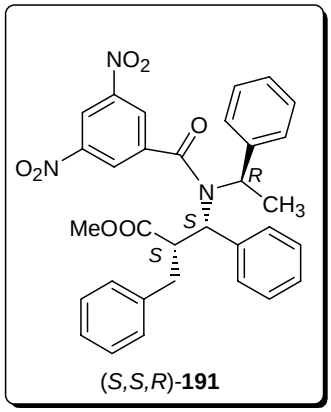
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (d, 3H, *J* = 6.8 Hz), 1.07 (d, 3H, *J* = 6.8 Hz), 1.30 (d, 3H, *J* = 6.4 Hz), 1.49 (s, br, NH), 2.37-2.44 (m, 1H), 2.57-2.61 (m, 1H), 3.38 (s, 3H), 3.49-3.54 (m, 1H), 4.02 (d, 1H, *J* = 9.6 Hz), 7.14 (d, 2H, *J* = 8 Hz), 7.19 (d, 2H, *J* = 8 Hz), 7.22-7.27 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 17.5, 21.5, 21.7, 27.1, 54.4, 58.5, 58.7, 126.6, 127.0, 128.4, 129.0, 129.2, 132.8, 140.8, 146.1, 173.0. Additional signals for minor diastereomer: 17.2, 21.9, 26.8, 54.6, 58.2, 58.9

MS m/z 360 (M+1)

$[\alpha]_D^{25}$ +57.5 (*c* 1, $CHCl_3$)

The compound **191** was prepared form the β-amino ester **190d** by following the procedure given in the Section **1.4.5**.



(*S*,*S*,*R*)-**191**

Yield 1.21 g (71%)

mp 90-92 °C

IR (KBr) (cm^{-1}) 3030, 2949, 1732, 1641

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.51 (d, 3H, *J* = 7 Hz), 2.12 (s, br, 1H), 2.88-2.91 (m, 1H), 3.11 (s, 3H), 4.39 (s, br, 1H), 4.69 (s, br, 1H), 4.96 (s, br, 1H), 7.09-7.40

(13H), 7.68 (s, br, 2H), 8.44 (s, br, 2H), 9.06 (s, br, 1H) **(Spectrum No. 19)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 18.5, 37.3, 51.3, 52.6, 59.6, 64.5, 119.0, 126.1, 126.6, 127.9, 128.4, 128.7, 128.8, 129.1, 138.2, 140.4, 141.6, 148.5, 167.5, 174.1 **(Spectrum No. 20)**

MS m/z 566 (M-1)

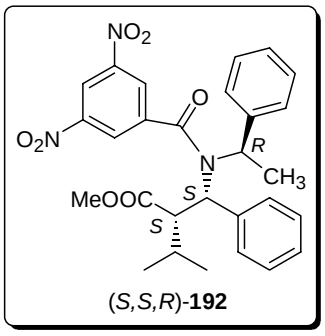
$[\alpha]_D^{25}$ +66.4 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{32}H_{29}N_3O_7$: C-67.72%, H-5.15%, N-7.40%

Found: C-67.71%, H-5.16%, N-7.50%

de >96% (using HPLC, Chiralcel OD-H, hexanes/^{i}PrOH = 90:10, flow = 0.5 mL/min, t_{r1} = 26.9 min and t_{r2} = 33.7 min)

The compound **192** was prepared form the β-amino ester **190h** by following the procedure given in the Section **1.4.5**.



(*S*,*S*,*R*)-**192**

Yield 1.07 g (69%)

mp 204-206 ^oC

IR (KBr) (cm^{-1}) 3067, 2961, 1730, 1620

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.55-0.56 (m, 3H), 1.06 (s, br, 3H), 1.27 (s, 1H), 1.39-1.40 (m, 3H), 2.18 (s, 1H), 3.45 (s, 3H), 4.86 (s, br, 2H), 6.96 (s, br, 2H), 7.26-7.28 (m, 4H), 7.38-7.40 (m, 2H), 7.68 (s, br, 2H), 8.26 (s, br, 2H), 8.98 (s, br, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 17.4, 18.9, 22.2, 27.4, 51.0, 53.9, 58.1, 62.2, 118.5, 126.2, 127.5, 128.3, 128.9, 139.1, 140.6, 141.9, 148.1, 168.4, 172.0

MS m/z 518 (M-1)

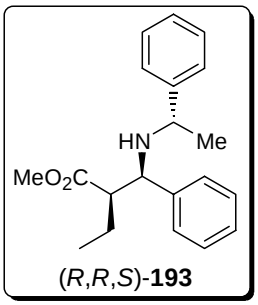
$[\alpha]_D^{25}$ +47.1 (*c* 1, $CHCl_3$)

de >96% (using HPLC, Chiralcel OD-H, hexanes/^{i}PrOH = 90:10, flow = 0.5 mL/min, t_{r1} = 26.0 min and t_{r2} = 35.1 min)

The compound **193** was prepared by following the procedure given in the Section **1.4.4**, starting from *N*-benzylidene-(*S*)-α-methylbenzylamine (*S*)-**177c**.

Yield 1.25 g (81%)

dr 93:7



(*R*,*R*,*S*)-**193**

IR (Neat) (cm^{-1}) 3329, 3062, 2966, 1732

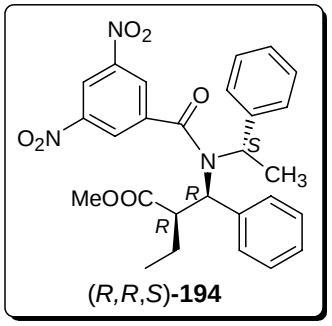
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.91 (t, 3H, *J* = 7 Hz), 1.29 (d, 3H, *J* = 7 Hz), 1.67 (s, NH), 1.74-1.81 (m, 2H), 2.52-2.63 (m, 1H), 3.46 (s, 3H), 3.57-3.61 (m, 1H), 3.95 (d, 1H, *J* = 8 Hz), 7.20-7.28 (10 H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.2, 22.1, 22.3, 51.1, 54.7, 55.1, 61.7, 126.7, 126.9, 127.2, 127.5, 128.3, 128.4, 141.9, 146.4, 174.6. Additional signals for minor diastereomer: 11.3, 21.5, 25.2, 47.5, 51.5, 61.2

MS m/z 312 (M+1)

$[\alpha]_D^{25}$ -39.7 (*c* 1, $CHCl_3$)

The compound **194** was prepared from the β-amino ester **193** by following the procedure given in the section **1.4.5**.



(*R*,*R*,*S*)-**194**

Yield 1.09 g (72%)

mp 140-142 °C

IR (KBr) (cm^{-1}) 3061, 2965, 1732, 1626

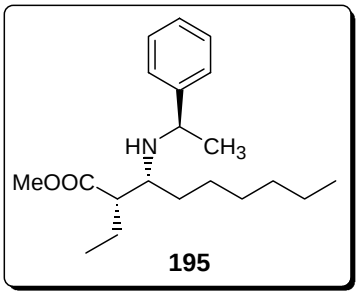
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.84 (t, 3H, *J* = 7 Hz), 1.17-1.29 (m, 1H), 1.42 (d, 3H, *J* = 7 Hz), 1.60-1.70 (m, 1H), 3.38 (s, 3H), 3.69-4.06 (m, 1H), 4.70-4.76 (m, 1H), 6.69-7.41 (m, 10H), 7.61 (s, 1H), 8.30 (s, 1H), 9.00 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 11.8, 18.7, 24.2, 51.4, 58.8, 64.6, 118.7, 126.2, 127.7, 128.5, 128.8, 129.0, 141.8, 148.3, 167.9, 174.5

MS m/z 506 (M+1)

$[\alpha]_D^{25}$ -65.0 (*c* 1, $CHCl_3$)

de >99% (using HPLC, Chiralcel OD-H, hexanes/^{i}PrOH = 90:10, flow = 0.5 mL/min, t_r = 25.2 min)



195

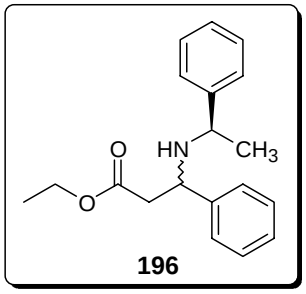
Yield 0.45 g (28%)

dr 91:9

IR (Neat) (cm^{-1}) 3441, 3030, 2959, 1738

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.4, 14.1, 21.5, 22.5, 27.8, 29.1, 29.9, 31.8, 32.5, 51.0, 52.1, 54.6, 63.6, 126.7, 128.2, 129.0, 137.9, 175.1. Additional signals for minor diastereomer: 51.0, 51.8, 63.2

MS m/z 320 (M+1)



196

Yield 0.52 g (28%)

dr 82:18

IR (Neat) (cm^{-1}) 3331, 3063, 2876, 1732

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.21 (t, 3H, *J* = 7.2 Hz), 1.37 (d, 3H, *J* = 6.4 Hz), 1.76 (s, br, NH), 2.61-2.78 (m, 2H), 3.68 (q, 1H, *J* = 6.4 Hz), 4.11 (q, 2H, *J* = 7.0 Hz), 4.23 (t, 1H, J = 7.2 Hz), 7.21-7.37 (m, 10H) **(Spectrum No. 21)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 14.2, 22.3, 42.8, 54.6, 56.9, 60.4, 126.6, 126.9, 127.0, 127.3, 128.4, 128.5, 142.8, 146.0, 171.7. Additional signals for minor diastereomer: 25.1, 43.4, 54.9 **(Spectrum No. 22)**

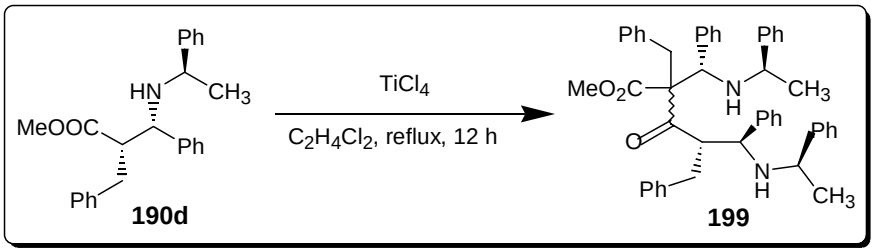
MS m/z 298 (M+1)

$[\alpha]_D^{25}$ +31.0 (*c* 1, $CHCl_3$)

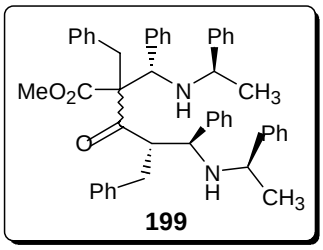
1.4.8 Formation of the product 199 in the reaction of β-amino ester 190d with $TiCl_4$ under reflux condition:

To a $C_2H_4Cl_2$ (30 mL) solution of β-amino ester **190d** (1.87 g, 5 mmol) was added $TiCl_4$ (1.1 mL, 1.90 g, 10 mmol) at 0 ^oC under N_2 atmosphere. The reaction mixture was brought to room temperature and then refluxed for 12 h. The contents were cooled to 0 ^oC and quenched with saturated aqueous K_2CO_3 solution (15 mL). The reaction mixture was filtered through a Buchner funnel and the organic extract was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was successively washed with water (30 mL) and brine (10 mL). The

organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude reaction mixture was subjected to column chromatography on silica gel using hexanes/EtOAc mixture (90:10) as eluent to obtain pure product.



Yield 0.79 g (22%)



IR (Neat) (cm^{-1}) 3381, 3061, 3028, 2951, 1742, 1690

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.61-2.75 (m, 2H), 2.88-3.07 (5H), 3.15-3.33 (4H), 3.66 (s, 2H), 3.72 (s, 2H), 3.78 (s, 3H), 3.80-3.86 (m, 1H), 4.13-4.21 (m, 1H), 6.82-6.86 (m, 2H), 7.11-7.34 (22H), 7.46-7.51 (m, 3H), 7.63-7.70 (m, 2H), 7.74-7.81 (m, 1H)

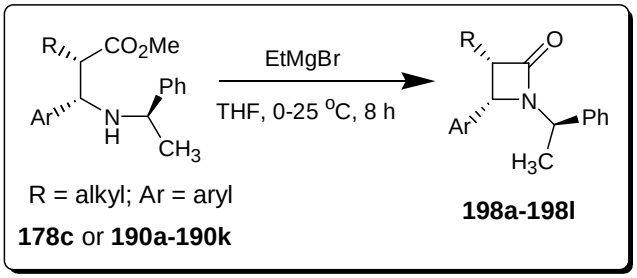
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 29.4, 30.9, 34.2, 34.5, 41.6, 44.5, 51.9, 52.53, 59.3, 60.6, 64.1, 119.0, 124.3, 126.7, 128.4, 128.6, 128.8, 128.9, 129.0, 130.9, 134.3, 135.9, 138.0, 138.4, 144.6, 169.8, 193.5

$[\alpha]_D^{25}$ -27.4 (*c* 1, $CHCl_3$)

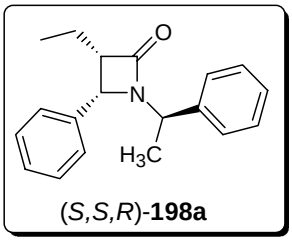
1.4.9 General procedure for the synthesis of chiral β-lactams 198a-198l from the β-amino esters containing from (*R*)-α-methylbenzylamine moiety:

Chiral β-amino ester **178c** or **190** (4 mmol) were taken in THF (20 mL). To this a solution of ethylmagnesium bromide (0.67 g, 5 mmol) in THF (10 mL) was added slowly at 0 ^oC under N_2 atmosphere over 10 min. The reaction mixture was stirred at

25 ^{o}C for 8 h and then quenched with saturated NH_4Cl solution. The crude reaction mixture was diluted with ether (20 mL), organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on silica gel using hexanes/EtOAc (95/5) as eluent.



Yield 0.61 g (56%)



dr 100:0

IR (Neat) (cm^{-1}) 3063, 2966, 1743

^{1}H-N MR (400 MHz, $CDCl_3$, δ ppm): 0.65 (t, 3H, *J* = 7.4 Hz), 1.06-1.17 (m, 1H), 1.43 (d, 3H, *J* = 7 Hz), 1.51-1.58 (m, 1H), 3.14-3.19 (m, 1H), 4.49 (d, 1H, *J* = 5.4 Hz), 5.00 (q, 1H, *J* = 7 Hz), 7.23-7.27 (m, 5H), 7.29-7.33 (m, 5H) **(Spectrum No. 23)**

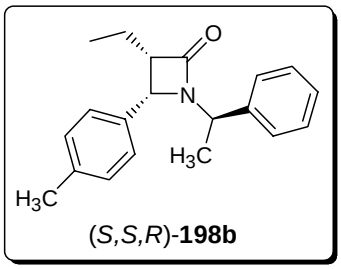
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 18.7, 19.5, 52.5, 56.3, 58.1, 127.3, 127.7, 127.8, 128.1, 128.2, 128.6, 137.0, 140.4, 171.2 **(Spectrum No. 24)**

MS m/z 302 (M+1)

$[\alpha]_D^{25}$ -135.2 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{19}H_{21}NO$: C-81.68%, H-7.58%, N-5.01%

Found: C-81.66%, H-7.58%, N-4.86%



(*S*,*S*,*R*)-**198b**

Yield 0.63 (54%)

dr 89:11

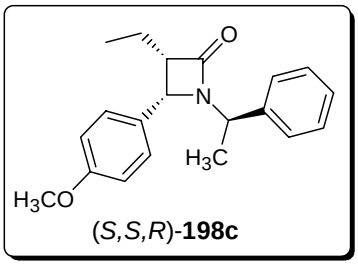
IR (Neat) (cm^{-1}) 3061, 2978, 1747

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.67 (t, 3H, *J* = 7.1 Hz), 1.12-1.18 (m, 1H), 1.43 (d, 3H, *J* = 7 Hz), 1.53-1.61 (m, 1H), 2.38 (s, 3H), 3.13-3.18 (m, 1H), 4.48 (d, 1H, *J* = 4.8 Hz), 5.00 (q, 1H, *J* = 6.8 Hz), 7.12-7.24 (m, 4H), 7.26-7.40 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 11.8, 18.7, 19.5, 21.2, 52.4, 56.3, 57.9, 126.3, 127.3, 127.6, 127.7, 128.6, 128.9, 129.1, 133.9, 137.8, 140.4, 171.3. Additional signals for minor diastereomer: 13.6, 21.8, 50.0

MS m/z 294 (M+1)

$[\alpha]_D^{25}$ -108.3 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**198c**

Yield 0.68 g (55%)

dr 100:0

IR (Neat) (cm^{-1}) 3063, 2966, 1739

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.67 (t, 3H, *J* = 7.4 Hz), 1.12-1.15 (m, 1H), 1.43 (d, 3H, *J* = 7.3 Hz), 1.54-1.59 (m, 1H), 3.11-3.17 (m, 1H), 3.84 (s, 3H), 4.46 (d, 1H, *J* = 5.5 Hz), 5.00 (q, 1H, *J* = 7.2 Hz), 6.88 (d, 2H, *J* = 8.6 Hz), 7.18 (d, 2H, *J* = 8.6 Hz), 7.25-7.40 (m, 5H)

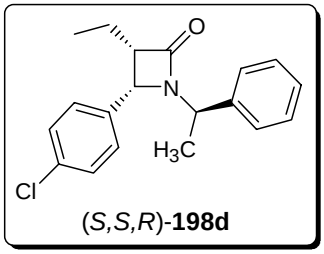
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.8, 18.6, 19.5, 52.3, 55.2, 56.3, 57.6, 113.6, 127.3, 127.6, 128.6, 128.7, 129.0, 140.4, 159.4, 171.3

MS m/z 310 (M+1)

$[\alpha]_D^{25}$ -125.7 (*c* 1, $CHCl_3$)

Yield 0.63 g (50%)

dr 91:9



(*S*,*S*,*R*)-**198d**

IR (Neat) (cm^{-1}) 3063, 2974, 1741

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.68 (t, 3H, *J* = 7.3 Hz), 1.07-1.16 (m, 1H), 1.45 (d, 3H, *J* = 7 Hz), 1.52-1.61 (m, 1H), 3.16-3.21 (m, 1H), 4.47 (d, 1H, *J* = 5.5 Hz), 4.99 (q, 1H, *J* = 7.1 Hz), 7.08-7.39 (9H)

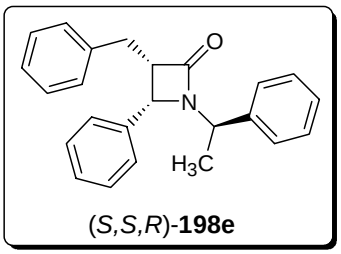
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 11.7, 18.6, 19.5, 52.6, 56.3, 57.5, 127.2, 127.8, 128.4, 128.7, 129.1, 133.8, 135.7, 140.2, 170.6. Additional signals for minor diastereomer: 13.4, 21.2, 21.7, 49.0, 54.3, 57.1

MS m/z 314 (M+1)

$[\alpha]_D^{25}$ -122.7 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{19}H_{20}ClNO$: C-72.72%, H-6.42%, N-4.46%

Found: C-72.24%, H-6.42%, N-4.36%



(*S*,*S*,*R*)-**198e**

Yield 0.72 g (53%)

dr 100:0

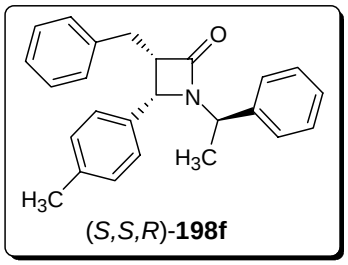
IR (Neat) (cm^{-1}) 3063, 2926, 1748

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.47 (d, 3H, *J* = 7 Hz), 2.43-2.49 (m, 1H), 2.97-3.01 (m, 1H), 3.61-3.62 (m, 1H), 4.53 (d, 1H, *J* = 5.5 Hz), 5.06 (q, 1H, *J* = 7.1 Hz), 6.66 (s, 1H), 7.07 (s, 2H), 7.21-7.34 (12H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 19.5, 30.9, 52.6, 55.9, 58.3, 126.0, 127.3, 127.8, 128.1, 128.3, 128.5, 128.7, 136.7, 138.6, 140.3, 170.3

MS m/z 342 (M+1)

$[\alpha]_D^{25}$ -43.4 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**198f**

Yield 0.78 g (55%)

dr 100:0

IR (Neat) (cm^{-1}) 3061, 2962, 1723

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.46 (d, 3H, *J* = 7 Hz), 2.41 (s, 3H), 2.43-2.50 (m, 1H), 2.95-3.00 (m, 1H), 3.56-3.60 (m, 1H), 4.51 (d, 1H, *J* = 5.6 Hz), 5.06 (q, 1H, *J* = 7.2 Hz), 6.70-6.71 (m, 2H), 7.08-7.17 (8H), 7.27-7.34 (4H) **(Spectrum No. 25)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 19.5, 21.3, 30.9, 52.5, 55.9, 58.2, 125.9, 127.3, 127.7, 128.1, 128.5, 129.0, 133.6, 138.0, 138.9, 140.4, 170.4 **(Spectrum No. 26)**

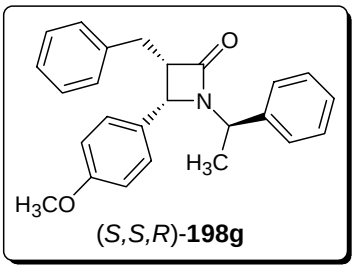
MS m/z 356 (M+1)

$[\alpha]_D^{25}$ -36.7 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{19}H_{21}NO$: C-84.47%, H-7.09%, N-3.94%

Found: C-84.58%, H-7.10%, N-4.06%

Yield 0.82 g (55%)



(*S,S,R*)-**198g**

dr 100:0

IR (Neat) (cm^{-1}) 3030, 2932, 1743

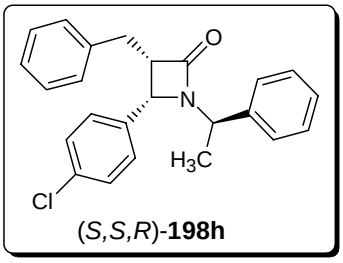
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.45 (d, 3H, *J* = 7.1 Hz), 2.46-2.52 (m, 1H), 2.98-3.04 (m, 1H), 3.57-3.62 (m, 1H), 3.86 (s, 3H), 4.49 (d, 1H, *J* = 5.4 Hz), 5.04 (q, 1H, *J* = 7.2 Hz), 6.68-6.71 (m, 2H), 6.86-6.88 (m, 2H), 7.07-7.13 (m, 5H), 7.25-7.33 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 19.6, 21.2, 31.5, 52.8, 57.7, 58.9, 114.1, 127.5, 128.0, 128.5, 128.9, 129.0, 129.6, 133.6, 138.4, 140.9, 158.5, 170.1

MS m/z 372 (M+1)

$[\alpha]_D^{25}$ -40.3 (*c* 1, $CHCl_3$)

Yield 0.72 g (48%)



(*S,S,R*)-**198h**

dr 85:15

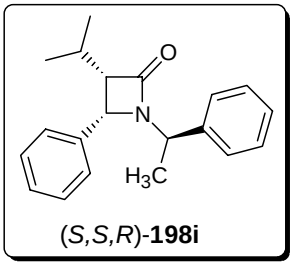
IR (Neat) (cm^{-1}) 3061, 2980, 2932, 1748

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.47 (d, 3H, *J* = 7.3 Hz), 2.38-2.44 (m, 1H), 2.98-3.02 (m, 1H), 3.62-3.66 (m, 1H), 4.48 (d, 1H, *J* = 5.6 Hz), 5.03 (q, 1H, *J* = 7.1 Hz), 6.68-6.70 (m, 2H), 7.04-7.12 (m, 5H), 7.24-7.35 (7H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 19.4, 30.8, 52.8, 55.7, 57.6, 126.1, 127.3, 127.9, 128.2, 128.3, 128.5, 128.8, 129.3, 134.0, 135.4, 138.2, 140.1, 170.1. Additional signals for minor diastereomer: 21.8, 33.4, 49.1

MS m/z 374 (M-1)

$[\alpha]_D^{25}$ -23.4 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**198i**

Yield 0.66 g (56%)

mp 114-116 °C

dr 100:0

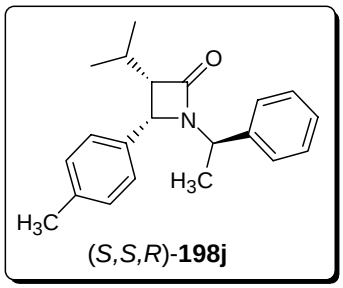
IR (KBr) (cm^{-1}) 3026, 2955, 1734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.28 (d, 3H, *J* = 6.1 Hz), 1.12 (d, 3H, *J* = 6.3 Hz), 1.39 (d, 3H, *J* = 7.3 Hz), 1.72-1.84 (m, 1H), 2.90-2.94 (m, 1H), 4.45 (d, 1H, *J* = 5.7 Hz), 5.05 (q, 1H, *J* = 7.3 Hz), 7.23-7.29 (m, 5H), 7.31-7.35 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 19.2, 20.5, 20.7, 25.5, 52.2, 58.1, 62.2, 127.3, 127.6, 128.1, 128.5, 137.3, 140.3, 170.0

MS m/z 294 (M+1)

$[\alpha]_D^{25}$ -97.8 (*c* 1, $CHCl_3$)



(*S*,*S*,*R*)-**198j**

Yield 0.74 g (60%)

mp 82-85 °C

dr 100:0

IR (KBr) (cm^{-1}) 3030, 2953, 1734

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.29 (d, 3H, *J* = 6.1 Hz), 1.12 (d, 3H, *J* = 6.4 Hz), 1.38 (d, 3H, *J* = 7 Hz), 1.75-1.80 (m, 1H), 2.28 (s, 1H), 2.87-2.91 (m, 1H), 4.42 (d, 1H, *J* = 5.3 Hz), 5.04 (q, 1H, *J* = 7.1 Hz)), 7.11-7.23 (m, 5H), 7.25-7.35 (m, 4H)

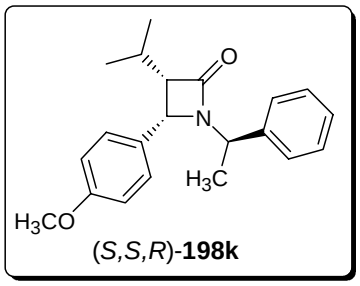
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 19.3, 20.6, 20.7, 21.1, 25.5, 52.1, 57.9, 62.1, 127.3, 127.6, 128.1, 128.5, 128.8, 134.1, 137.8, 170.6

MS m/z 308 (M+1)

$[\alpha]_D^{25}$ -107.5 (*c* 1, $CHCl_3$)

Yield 0.52 g (40%)

dr 100:0



(*S*,*S*,*R*)-**198k**

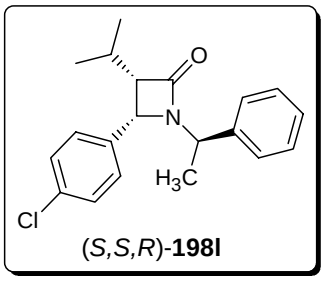
IR (Neat) (cm^{-1}) 3031, 2965, 1742

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.30 (d, 3H, *J* = 6.4 Hz), 1.12 (d, 3H, *J* = 6.5 Hz), 1.38 (d, 3H, *J* = 7.1 Hz), 1.75-1.80 (m, 1H), 2.85-2.88 (m, 1H), 3.84 (s, 3H), 4.41 (d, 1H, *J* = 5.4 Hz), 5.02 (q, 1H, *J* = 7.1 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 7.20-7.33 (7H) **(Spectrum No. 27)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 19.3, 20.5, 20.7, 25.5, 52.0, 55.2, 57.5, 62.1, 113.5, 126.8, 127.3, 127.6, 128.5, 129.0, 129.2, 140.4, 159.5, 170.6 **(Spectrum No. 28)**

MS m/z 324 (M+1)

$[\alpha]_D^{25}$ -124.3 (*c* 1, $CHCl_3$)

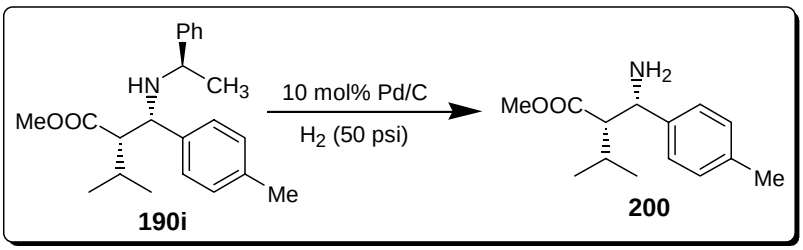


(*S*,*S*,*R*)-**198l**

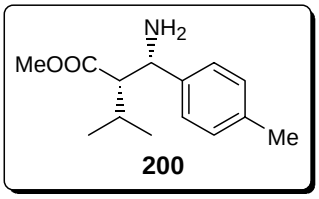
Yield	0.72 g (55%)
mp	94-96 ^{o}C
dr	100:0
IR (KBr)	(cm^{-1}) 3030, 2955, 1740
^{1}H-NMR	(400 MHz, $CDCl_3$, δ ppm): 0.30 (d, 3H, *J* = 6.5 Hz), 1.12 (d, 3H, *J* = 6.6 Hz), 1.39 (d, 3H, *J* = 7.3 Hz), 1.70-1.77 (m, 1H), 2.90-2.95 (m, 1H), 4.41 (d, 1H, *J* = 5.3 Hz), 5.02 (q, 1H, *J* = 7 Hz), 7.11-7.33 (9H)
^{13}C-NMR	(50 MHz, $CDCl_3$, δ ppm): 19.2, 20.5, 20.6, 25.4, 52.4, 57.5, 62.2, 127.3, 127.7, 128.4, 128.6, 129.4, 133.9, 1.36.0, 140.2, 170.3
MS	m/z 328 (M+1)
$[\alpha]_D^{25}$	-125.6 (*c* 1, $CHCl_3$)

1.4.10 Procedure for selective cleavage of α-methylbenzyl moiety from the chiral β-amino ester 190i:

A methanol (30 mL) solution of the β-amino ester **190i** (1.70 g, 5 mmol) was taken in a hydrogenation flask. To this, Pd/C reagent (0.5 mmol) was added. Then, the contents were shaken under H_2 pressure (50 psi) for 3 h. The contents were filtered through a Buchner funnel and methanol was evaporated. The crude residue was purified by column chromatography on neutral alumina using hexanes/EtOAc (95/5) as eluent.



190i **200**



200

Yield 0.99 g (84%)

IR (Neat) (cm^{-1}) 3379, 3312, 3060, 2961, 1732, 1610

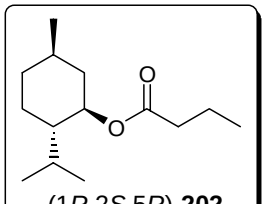
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.03 (d, 3H, *J* = 7 Hz), 1.07 (d, 3H, *J* = 6.9 Hz), 2.23-2.30 (m, 1H), 2.33 (s, 3H), 2.56 (s, br, NH_2), 2.69-2.72 (m, 1H), 3.42 (s, 3H), 4.20 (d, 1H, *J* = 9.8 Hz), 7.12 (d, 2H, *J* = 7.9 Hz), 7.22 (d, 2H, *J* = 7.9 Hz) **(Spectrum No. 29)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 17.3, 20.9, 21.7, 27.0, 50.5, 55.0, 59.1, 126.8, 128.9, 136.8, 140.6, 172.8 **(Spectrum No. 30)**

$[\alpha]_D^{25}$ -6.3 (*c* 1, $CHCl_3$)

1.4.11 Procedure for the synthesis of (*L*)-menthyl butyrate:

To a solution of (*L*)-menthol (1.56 g, 10 mmol) in CH_2Cl_2 (30 mL) was added butyryl chloride (1.12 g, 1.14 mL, 11 mmol) at 0 ^oC under N_2 atmosphere, followed by slow addition of triethylamine (1.31 g, 1.81 mL, 13 mmol) in CH_2Cl_2 (10 mL) using a dropping funnel over 10 min. The reaction mixture was stirred for 6 h. Then, it was diluted with CH_2Cl_2 (50 mL) and washed successively with 5% $NaHCO_3$ (20 mL), water (20 mL) and brine solution (10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was distilled under reduced pressure to isolate pure (*L*)-menthyl butyrate.



(1*R*,2*S*,5*R*)-**202**

Yield 2.01 g (89%)

IR (Neat) (cm^{-1}) 2959, 1732

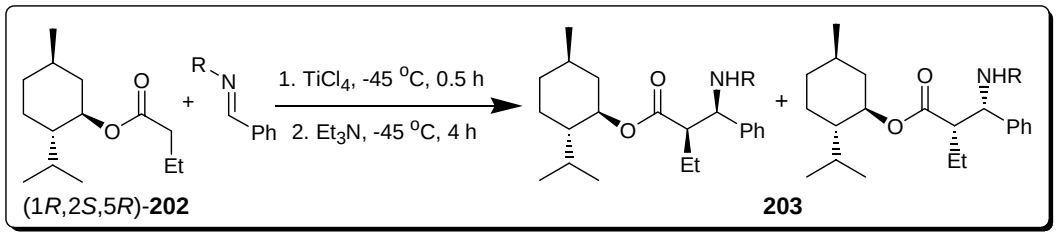
^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.76 (d, 3H, J = 8 Hz), 0.86-1.14 (14H), 1.55-1.78 (m, 4H), 1.85-2.05 (m, 2H), 2.26 (t, 2H, *J* = 8 Hz), 4.62-4.75 (m, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 13.5, 16.2, 18.5, 20.6, 21.9, 23.5, 26.2, 31.3, 34.3, 36.5, 40.9, 45.0, 73.7, 173.0

$[\alpha]_D^{25}$ -71.8 (*c* 1, $CHCl_3$)

1.4.12 General procedure for the synthesis of chiral β-amino esters derived from menthyl butyrate (1*R*,2*S*,5*R*)-202 and imines:

Imine (5 mmol) and menthyl butyrate (1*R*,2*S*,5*R*)-**202** (1.18 g, 5.2 mmol) were taken in dichloromethane (40 mL) and $TiCl_4$ (12 mmol, 2.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (15 mL) was added at -45 ^{0}C dropwise over 15 min under N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.70 mL, 5 mmol) was added and the mixture was stirred at -45 ^{0}C for a further 4 h. It was quenched with saturated aq. K_2CO_3 (15 mL), brought to room temperature and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by column chromatography on neutral alumina using hexanes/EtOAc (99/1) as eluent.

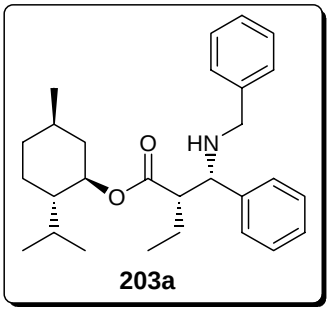


(1*R*,2*S*,5*R*)-**202** **203**

Yield 1.51 g (72%)

mp 118-120 °C

dr 97:3



203a

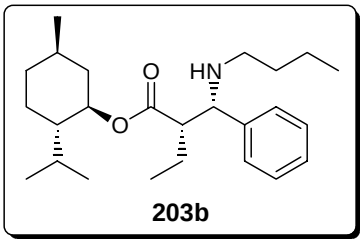
IR (KBr) (cm^{-1}) 3321, 3061, 2962, 1712

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.46 (d, 3H, *J* = 6 Hz), 0.73 (d, 6H, *J* = 6 Hz), 0.78-0.87 (m, 4H), 0.90-0.92 (m, 3H), 1.23-1.31 (m, 2H), 1.36-1.39 (m, 1H), 1.64 (t, 2H, *J* = 15 Hz), 1.76 (s, NH), 1.79-1.85 (m, 1H), 1.99-2.02 (m, 1H), 2.62-2.68 (m, 1H), 3.49 (d, 1H, *J* = 13 Hz), 3.65 (d, 1H, *J* = 13 Hz), 3.86 (d, 1H, *J* = 8 Hz), 4.52-4.59 (m, 1H), 7.27-7.37 (10H) **(Spectrum No. 31)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 15.9, 20.9, 22.1, 22.7, 23.0, 25.4, 31.4, 34.2, 40.9, 46.7, 51.4, 55.0, 63.6, 73.9, 126.9, 127.3, 128.0, 128.2, 128.3, 140.5, 141.9, 173.9. Additional signals for minor diastereomer: 11.8, 25.9, 29.7, 51.3 **(Spectrum No. 32)**

MS m/z 422 (M+1)

$[\alpha]_D^{25}$ -18.6 (*c* 1, $CHCl_3$)



203b

Yield 1.37 g (71%)

mp 76-78 ^oC

dr 83:17

IR (KBr) (cm^{-1}) 3322, 3030, 2955, 1711

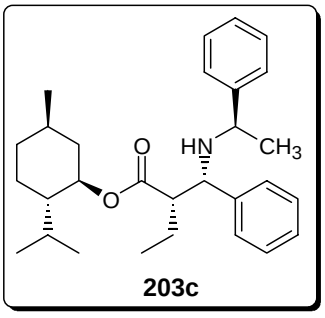
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.49 (d, 3H, *J* = 7 Hz), 0.75 (d, 6H, *J* = 7 Hz), 0.83-0.93 (m, 6H), 1.28-1.30 (m, 4H), 1.36-1.42 (m, 4H), 1.58-1.65 (m, 1H), 1.71-1.73 (m, 1H), 1.80-1.83 (m, 3H), 2.19 (s, NH), 2.33-2.37 (m,

2H), 2.56-2.60 (m, 1H), 3.76 (d, 1H, J = 8 Hz), 4.51-4.58 (m, 1H), 7.25-7.35 (m, 5H) **(Spectrum No. 33)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.0, 13.9, 15.8, 20.4, 20.8, 22.4, 22.9, 25.3, 31.3, 32.3, 34.2, 40.9, 46.7, 47.3, 55.0, 64.3, 73.8, 127.0, 127.7, 128.1, 128.3, 142.2, 174.0. Additional signals for minor diastereomer: 11.7, 15.9, 21.8, 23.0, 23.5, 34.3, 46.9, 47.0, 55.5, 65.6, 74.0 **(Spectrum No. 34-** DEPT-135 and DEPT-90 spectra are also shown**)**

MS m/z 388 (M+1)

$[\alpha]_D^{25}$ -27.4 (*c* 1, $CHCl_3$)



203c

Yield 1.50 g (69%)

mp 70-72 ^{o}C

dr 56:44

IR (KBr) (cm^{-1}) 3325, 3063, 2957, 1732

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 11.1; 11.8, 12.2; 15.9; 20.9; 21.7, 22.0; 22.6, 23.3; 25.3, 25.9; 31.3, 31.4; 34.2, 34.3; 40.1, 40.8; 46.7, 46.9; 54.5, 54.7; 55.1, 55.2; 60.1, 62.0; 77.8, 74.4; 125.1; 126.6, 126.8; 127.2; 127.8, 127.9; 128.1, 128.2; 130.0; 142.0, 142.3; 145.4, 146.4; 173.7, 174.0

MS m/z 436 (M+1)

$[\alpha]_D^{25}$ -27.4 (*c* 1, $CHCl_3$)

1.5 References

1. Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807 and references cited therein.
2. (a) Köpf, H.; Köpf-Maier, P. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 477 (b) McLaughlin, M. L.; Cronan, J. M., Jr.; Schaller, T. R.; Snelling, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 8949.
3. Bischoff, H.; Berger, M. R.; Keppler, B. K.; Schmähl, D. *J. Cancer Res. Clin. Oncol.* **1987**, *113*, 446.
4. (a) Ziegler, K.; Holzkamp, E.; Breil, H.; Martin, H. *Angew. Chem.* **1955**, *67*, 541 (b) Ziegler, K. *Angew. Chem.* **1964**, *76*, 545 (c) Natta, G. *Angew. Chem.* **1956**, *68*, 393 (d) Bochmann, M. *J. Chem. Soc.*, *Dalton Trans.* **1996**, 255.
5. Vol'pin, M. E.; Shur, V. B. *Nature* **1966**, *209*, 1236.
6. (a) vanTamelen, E. E.; Boche, G.; Ela, S. W.; Fechter, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 5707 (b) vanTamelen, E. E. *Acc. Chem. Res.* **1970**, *3*, 361.
7. Hori, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 1480.
8. (a) Mori, M.; Uozumi, Y.; Shibasaki, M. *J. Organomet. Chem.* **1990**, *395*, 255 (b) Uozumi, Y.; Mori, E.; Mori, M.; Shibasaki, M. *J. Organomet. Chem.* **1990**, *399*, 93.
9. (a) Shruzer, G. N.; Guth, T. D. *J. Am. Chem. Soc.* **1977**, *99*, 7189 (b) Hoshino, K.; Inui, M.; Kitamura, T.; Kokado, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 2509 (c) Hoshino, K.; Kitamura, T. *Chem. Lett.* **2000**, 1120 (d) Hoshino, K. *Chem. Eur. J.* **2001**, *7*, 2727 (e) Ogawa, T.; Kitamura, T.; Shibuya, T.; Hoshino, K. *Electrochem. Commun.* **2004**, *6*, 55.
10. (a) vanTamelen, E. E.; Fechter, R. B.; Schneller, S. W.; Boche, G.; Greeley, R. H.; Akermark, B. *J. Am. Chem. Soc.* **1969**, *91*, 1551 (b) Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651.
11. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.
12. Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147.
13. McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708.

14. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611 (b) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Strauss, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55,* 1733 (c) Meinhardt, J. D.; Anslyn, E. V.; Grubbs, R. H. *Organometallics* **1989**, *8*, 583 (d) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72.

15. (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698 (b) Minicione, E.; Pearson, A. J.; Bovicelli, P.; Chandler, M.; Heywood, G. C. *Tetrahedron Lett.* **1981**, *22,* 2929 (c) Snowden, R. L.; Sonnay, P.; Ohloft, G. *Helv. Chim. Acta* **1981**, *64*, 25 (d) Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293 (e) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25,* 1067 (f) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26,* 5579.

16. Reetz, M. T.; Westermann, J.; Steinbach, R. *J. Chem. Soc., Chem. Commun.* **1981**, 237.

17. (a) Johnson, R.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH: Weinheim, 1993, 103 (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis I-III;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999, Vol. II, Chapter 18.1 and references cited therein.

18. (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244; *J. Org. Chem. USSR* (*Engl. Transl.*) **1989**, *25*, 2027 (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234.

19. (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737 (b) Mukaiyama, T. *Israel J. Chem.* **1984**, *24*, 162 (c) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181 (d) Burkhardt, E. R.; Doney, J. J.; Slough, G. A.; Stack, J. M.; Heathcock, C. H.; Bergman, R. G. *Pure Appl. Chem.* **1988**, *60*, 1 (e) Fujisawa, T.; Makoto, S. *Rev. Heteroatom Chem.* **1996**, *15*, 203 (f) Saito, S.; Yamamoto, H. *Chem. Eur. J.* **1999**, *5*, 1959 (g) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis I-III;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999, Vol. III, Chapter 34.2 (h) Benaglia, M.; Cinquini, M.; Cozzi, F. *Eur. J. Org. Chem.* **2000**, 563 (i) Schmittel, M.; Haeuseler, A. *J. Organomet. Chem.* **2002**, *661,* 169 (j) Denissova, I.;

Barriault, L. *Tetrahedron* **2003**, *59*, 10105 (k) Hiyashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13 (l) Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715.

20. *Modern Aldol Reactions;* Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co.: KgaA, Germany, 2004; Vol. 1 & 2.
21. Ghosh, A. K.; Shelvin, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co.: KgaA, Germany, 2004; Vol. 1, Chapter 2.
22. (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett*. **1981**, *22*, 4691 (b) Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986 (c) Reetz, M. T.; Steinbach, R.; Kesseler, K. *Angew. Chem. Int. Ed. Engl.* **1982**, *21,* 864.
23. Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897.
24. Murphy, P. J.; Procter, G.; Russell, A. T. *Tetrahedron Lett.* **1987**, *28*, 2037.
25. Duthaler, R. O.; Herold, P.; Wiler-Helfer, S.; Riediker, M. *Helv. Chim. Acta* **1990**, *73*, 659.
26. Bonner, M. P.; Thornton, E. A. *J. Am. Chem. Soc.* **1991**, *113*, 1299.
27. Devant, R.; Braun, M. *Chem. Ber.* **1986**, *119*, 2191.
28. (a) Mukaiyama, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5590 (b) Carreira, E. M. In *Comprehensive Asymmetric Catalysis I-III;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999, Vol. III, Chapter 29.1.
29. (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011 (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
30. Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.
31. Gennari, C.; Bernardi, A.; Colombo, L.; Scolastico, C. *J. Am. Chem. Soc.* **1985**, *107*, 5812.
32. Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*,7039.
33. Harrison, C. *Tetrahedron Lett.* **1987**, *28*, 4135.
34. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Coslandi, E. *Tetrahedron* **1991**, *47*, 7897.
35. Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339.

36. Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am Chem. Soc.* **1991**, *113*, 1047.

37. Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775.

38. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127 (b) Evans, D. A.; Clark, J, S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866 (c) Phillips, A. J.; Guz, N. R. *Org. Lett.* **2002**, *4*, 2253 (d) Cosp, A.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **2001**, *42*, 4629 (e) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883 (f) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III. *J. Am. Chem. Soc.* **2000**, *122*, 386 (g) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591.

39. (a) Yan, T.; Lee, H.; Tan, C. *Tetrahedron Lett.* **1993**, *34*, 3559 (b) Yan, T.; Tan, C.; Lee, H.; Lo, H.; Huang, T. *J. Am. Chem. Soc.* **1993**, *115*, 2613 (c) Wang, Y.; Su, D.; Lin, C.; Tseng, H.; Li, C.; Yan, T. *Tetrahedron Lett.* **1999**, *40*, 3577 (d) Wang, Y.; Su, D.; Lin, C.; Tseng, H.; Li, C.; Yan, T. *J. Org. Chem.* **1999**, *64*, 6495.

40. Ghosh, A. K.; Kim, J. *Tetrahedron Lett.* **2002**, *43*, 5621.

41. (a) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527 (b) Ghosh, A. K.; Fidanze, S.; Onishi, M.; Hussain, K. A. *Tetrahedron Lett.* **1997**, *38*, 7171 (c) Ghosh, A. K.; Kim, J. *Tetrahedron Lett.* **2001**, *42*, 1227 (d) Ghosh, A. K.; Kim, J. *Org. Lett.* **2003**, *5*, 1063 (e) Ghosh, A. K.; Shelvin, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH, 2004, Vol. 1, Chapter 2, p 90.

42. (a) Tramontini, M.; Angiolini, L. In *Mannich-Bases: Chemistry and Uses;* CRC: Boca Raton, FL, 1994; *Tetrahedron* **1990**, *46*, 1791 (b) Tramontini, M. *Synthesis* **1973**, 703 (c) Overmann, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, p 1007 (d) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044 (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069 (f) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817 (g)

Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221 (h) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895 (i) Lui, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.

43. Fujisawa, T.; Ukaji, Y.; Noro, T.; Date, K.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 7563.
44. Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307.
45. Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881.
46. Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.
47. Lazzaro, F.; Crucianelli, M.; DeAngelis, F.; Frigerio, M.; Malpezzi, L.; Volonterio, A.; Zanda, M. *Tetrahedron*: *Asymmetry* **2004**, *15*, 889.
48. Ojima, I.; Inaba, S. –i.; Yoshida, K. *Tetrahedron Lett.* **1977**, *18*, 3643.
49. (a) Ojima, I.; Inaba, S. –i. *Tetrahedron Lett.* **1980**, *21*, 2077 (b) Ojima, I.; Inaba, S. –i. *Tetrahedron Lett.* **1980**, *21*, 2081.
50. (a) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227 (b) Gennari, C.; Schimperna, G.; Venturini, I. *Tetrahedron* **1988**, *44*, 4221.
51. Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767.
52. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155.
53. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1993**, *34*, 6921.
54. Cozzi, F.; Annunziata, R.; Cinquini, M.; Poletti, L.; Perboni, A.; Tamburini, B. *Chirality* **1998**, *10*, 91.
55. Abramhams, I.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1994**, *50*, 12755.
56. Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S. –I. *Chem. Lett.* **1999**, 795.
57. Bravo, P.; Fustero. S.; Guidetti, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1999**, *64*, 8731.

58. Andrian, J. C., Jr.; Barkin, J. L.; Fox, R. J.; Chick, J. E.; Hunter, A. D.; Nicklow, R. A. *J. Org. Chem.* **2000**, *65*, 6264.

59. Pinheiro, S.; Greco, S. J.; Veiga, L. S.; deFarias, F. M. C.; Costa, P. R. R. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1157.

60. Ferstl, E. M.; Venkatesan, H.; Ambhaikar, N. B.; Snyder, J. P.; Liotta, D. C. *Synthesis* **2002**, 2075.

61. Ambhaikar, N. B.; Snyder, J. P.; Liotta, D. C. *J. Am. Chem. Soc.* **2003**, *125*, 3690.

62. Sharma, S. D.; Kanwar, S. *Org. Process Res. Dev.* **2004**, *8*, 658.

63. Sharma, S. D.; Kanwar, S. *Synlett* **2004**, 2824.

64. Cooke, J. W. B.; Berry, M. B.; Caine, D. M.; Cardwell, K. S.; Cook, J. S.; Hodgson, A. *J. Org. Chem.* **2001**, *66*, 334.

65. Pilli, R. A.; Zanotto, P. R.; Böckelmann, M. A. *Tetrahedron Lett.* **2001**, *42*, 7003.

66. Barragán, E.; Olivo, H. F.; Romero-Ortega, M.; Sarduy, S. *J. Org. Chem.* **2005**, *70*, 4214.

67. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Tetrahedron Organic Chemistry Series, Pergamon Press: Oxford 1992 (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227 (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771 (d) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176 (e) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186 (f) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236 (g) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

68. Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259.

69. Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.

70. Bernardi, A. *Gaz. Chim. Italiana* **1995**,*125*, 539.

71. (a) Bernardi, A.; Dotti, P.; Poli, G.; Scolastico, C. *Tetrahedron* **1992**, *48*, 5597 (b) Viteva, L. Z.; Gospodova, T. S.; Stefanovsky, Y. N. *ibid.* **1994**, *50*, 7193.

72. Bernardi, A.; Marchionni, C.; Pilati, T. G.; Scolastico, C. *Tetrahedron Lett.* **1994**, *34*, 6357.

73. Viteva, L. Z.; Gospodova, T. S.; Stefanovsky, Y. N. *Tetrahedron* **1994**, *50*, 7193.

74. Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 12102.

75. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A. *Eur. J. Org. Chem.* **2005**, 543.

76. Peterson, I. *Tetrahedron* **1988**, *44*, 4207.

77. Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M.T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.

78. Chen, C. –C.; Chen, S. –T.; Chuang, T. –H.; Fang, J. –M. *J. Chem. Soc. Perkin Trans.* 1, **1994**, 2217.

79. Cosp, A.; Romea, P.; Talavera, P.; Urpí, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2001**, *3*, 615.

80. Maragni, P.; Mattioli, M.; Pachera, R.; Perboni, A.; Tamburini, B. *Org. Process Res. Dev.* **2002**, *6*, 597.

81. Larrosa, I.; Romea, P.; Urpí, F.; Balsells, D.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. *Org. Lett.* **2002**, *4*, 4651.

82. Ojima, I.; Brandstadter, S. M.; Donovan, R. J. *Chem. Lett.* **1992**, 1591.

83. Kise, N.; Tokioka, K.; Aoyama, Y. *J. Org. Chem.* **1995**, *60*, 1100.

84. Matsumura, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809.

85. Nguyen, P. Q.; Schäfer, H. J. *Org. Lett.* **2001**, *3*, 2993.

86. Mikami, K.; Takahashi, O.; Fujimoto, K.; Nakai, T. *Synlett* **1991**, 629.

87. Ikegami, S.; Okamura, H.; Kuroda, S.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1841.

88. Pellissier, H.; Toupet, L.; Santelli, M. *J. Org. Chem.* **1998**, *63*, 2148.

89. Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148.

90. Bharathi, P.; Periasamy, M. *Organometallics* **2000**, *19*, 5511.

91. Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2000**, *65*, 3548.

92. Bharathi, P.; Periasamy, M. *Org. Lett.* **1999**, *1*, 857.

93. (a) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *Chem. Commun.* **2001**, 1728 (b) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2005**, *70*, 5420.

94. Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem*. **1999**, *64*, 4204.

95. Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* **2002**, *43*, 2785.

96. Rao, V. D.; Periasamy, M. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1151.

97. Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577.

98. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996,** 117 and references cited therein.

99. Nicolaou, K. C.; Dai, W. –M.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15 and references cited therein.

100. (a) vanderSteen, F. H.; vanKoten, G. *Tetrahedron* **1991,** *47,* 7503 (b) Hart, D. J.; Ha, D. -C. *Chem. Rev.* **1989,** *89,* 1447 (c) Tzouvelekis, L. S.; Bonomo, R. A. *Current Pharm. Design* **1999**, *5*, 847 (d) Massova, I.; Mobashery, S. *Current Pharm. Design* **1999**, *5*, 929 (e) Mascaretti, O. A.; Danelon, G. O.; Laborde, M.; Mata, E. G.; Setti, E. L. *Current Pharm. Design* **1999**, *5*, 939 (f) Garau, G.; Garcia-Saez, I.; Bebrone, C.; Anne, C.; Mercuri, P.; Galleni, M.; Frere, J. –M.; Dideberg, O. *Antimicrobial Agents and Chemotherapy* **2004**, *48*, 2347 and references cited therein.

101. Rosenblum, S. B.; Huynh, T.; Afonso, A.; Davis, H. R., Jr.; Yumibe, N.; Clader, J. W.; Burnett, D. A. *J. Med. Chem.* **1998,** *41,* 973.

102. Periasamy, M. *ARKIVOC* **2002**, 151.

103. Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1987,** *35,* 593.

104. (a) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118,* 2527 (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57,* 4155.

105. (a) McCarty, C. G. In *The Chemistry of the Carbon-Nitrogen Double Bond;* Patai, S., Ed.; Wiley: New York, 1970, Chapter 9 (b) Curtin, D. Y.; Grubbs, E. J.; McCarty, C. G. *J. Am. Chem. Soc.* **1966**, *88,* 2775.

106. A. L. Spek, *PLATON, A Multipurpose Crystallographic Tool*, Utrecht University, Utrecht, The Netherlands, 2002.

107. (a) Nancy; Ghosh, S.; Singh, N.; Nanda, G. K.; Venugopalan, P.; Bharatam, P. V.; Trehan, S. *Chem. Commun.* **2003**, 1420 (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841 (c) Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119,* 826.

108. (a) Hehre, W. J.; Pople, J. A.; Devaquet, A. J. P. *J. Am. Chem. Soc.* **1976**, *98*, 664 (b) Wiberg, K. B.; Martin, E. *J. Am. Chem. Soc.* **1985**, *107*, 5035 (c) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113,* 5006 (d) Dorigo, A. E.; Pratt, D. W.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 6591 (e) Kondo, S.; Hirota, E.; Morino, Y. *J. Mol. Spectrosc.* **1968**, *28*, 471 (f) Shimanouchi, T.; Abe, Y.; Kuchitsu, K. *J. Mol. Struct.* **1968**, *2*, 82 (g) Kilb, R. W.; Lin, C. C.; Wilson, Jr., E. B. *J. Chem. Phys.* **1957**, *26*, 1695.

109. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58,* 3568.

110. Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60,* 6604.

111. Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

112. (a) Hall, S. R., King, G. S. D., Stewart, J. M., Eds.; *Xtal 3.4 User's manual;* Xtal system, University of Western Australia, 1995 (b) *SAINT* Version 6.2.

113. (a) Sheldrick, G. M. *SHELX-97*, University of Göttingen, Göttingen, Germany, 1997 (b) *SHELXTL* Version 6.14, Bruker AXS.

Chapter 2

Asymmetric conjugate additions of aryltitanium reagents to chiral oxazolidinone-, thiazolidinethione- and camphorsultam-derived enones

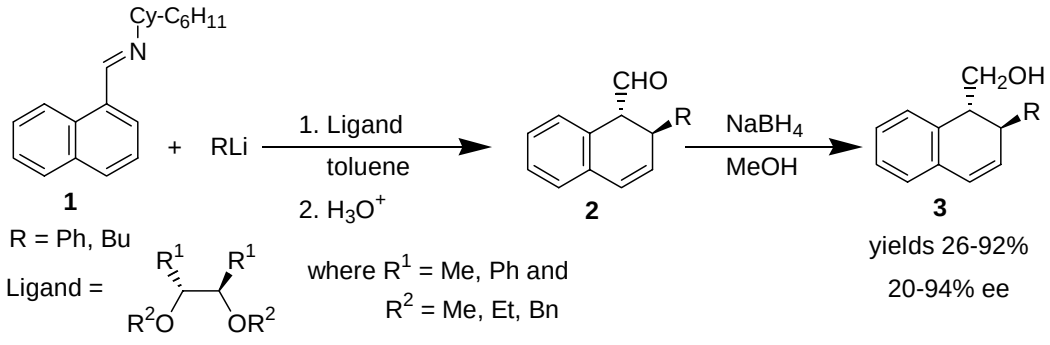
2.1 Introduction

The conjugate addition (1,4-addition) reaction is one of the most important carbon-carbon bond forming reactions in organic synthesis.[1] Basically, the conjugate additions involve the reaction of nucleophiles (donors) with alkenes or alkynes attached to electron withdrawing groups (acceptors). Generally, carbon or heteroatom based anions are used as nucleophiles.[1] Two major classes of carbon nucleophiles used as donors in these reactions are enolates of carbonyl compounds and organometallic reagents. We have undertaken efforts on the asymmetric conjugate addition reactions using organotitanium reagents. Accordingly, it will be of interest to review some of the literature reports on the asymmetric conjugate additions using organometallic reagents.

2.1.1 Additions of organolithium reagents:

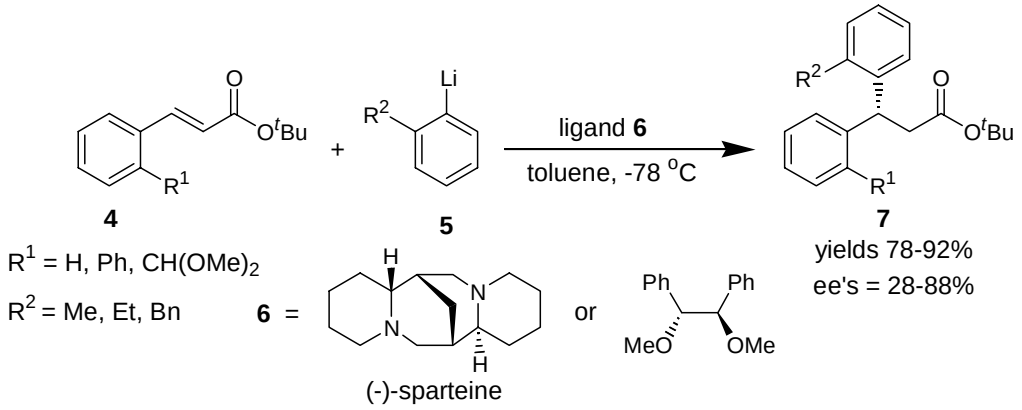
Tomioka and coworkers[2] found that α,β-unsaturated aldimine **1** undergoes either 1,2- or 1,4-addition depending on whether the substituent on the imine is an alkyl (1,2-addition) or an aromatic (1,4-addition) group. The 1,4-addition products were hydrolyzed to give the corresponding aldehydes **2**, which on subsequent reduction afforded the chiral alcohols **3**. Good enantioselection was achieved in this reaction by using the diol-based chiral ligands (Scheme 1).[2]

Scheme 1



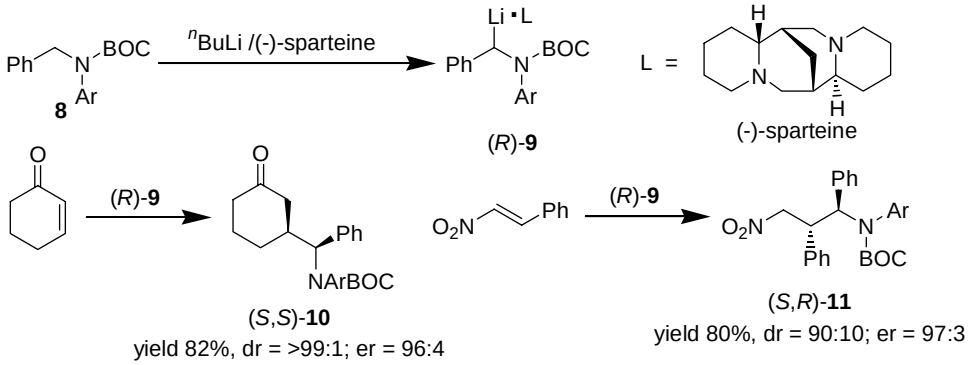
Asymmetric conjugate additions of aryllithium reagents **5** to α,β-unsaturated ^{t}butyl esters **4** were reported using the chiral ligands **6**. The corresponding 1,4-addition products **7** were obtained in good yields with moderate enantioselectivity (Scheme 2).[3]

Scheme 2



Conjugate addition of chiral organolithium compound of the type **9** to cyclohexenone and nitroalkene delivered the corresponding 1,4-addition products **10** and **11**, respectively in good yields with good selectivity (Scheme 3).[4]

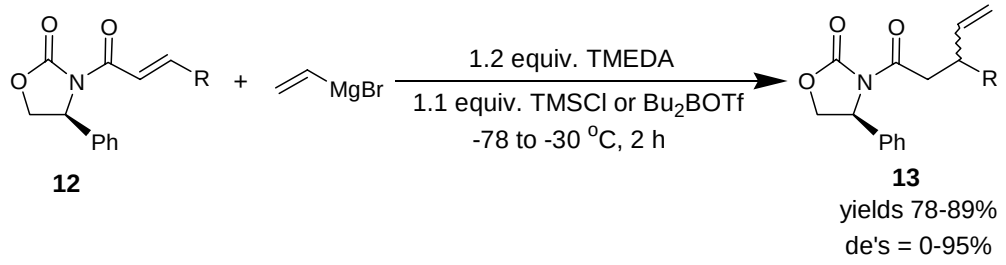
Scheme 3



2.1.2 Additions of Grignard reagents:

Lewis acid promoted conjugate additions of vinylmagnesium bromide to chiral α,β-unsaturated *N*-acyloxazolidinones **12** afforded the corresponding addition products **13** in good yields with excellent selectivity (Scheme 4).[5]

Scheme 4



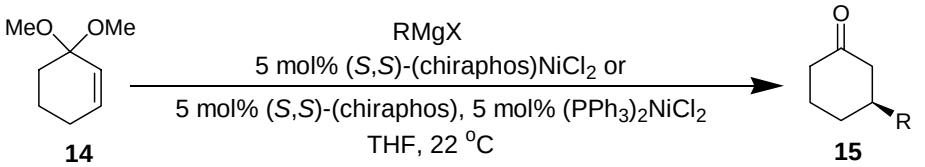
12 **13**

yields 78-89%

de's = 0-95%

It was found that the addition of the Grignard reagents to acetals **14** in the presence of chiraphos and $(PPh_3)_2NiCl_2$ gave the corresponding adducts **15** in good yields with good enantioselectivity (Scheme 5).[6]

Scheme 5



14 **15**

R = Et, ^{n}Bu, ^{t}Bu, Ph, $Ph(CH_2)_2$

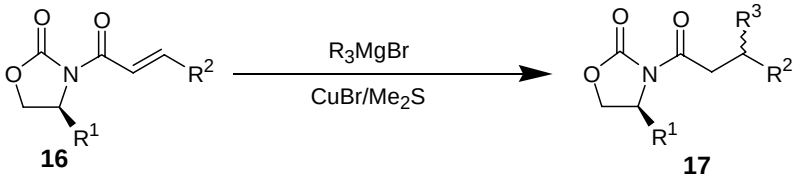
yields 50-90%

ee's = 0-85%

2.1.3 Additions of organocuprate reagents:

Nicolás *et al.*[7] reported an asymmetric 1,4-conjugate addition of organocuprates, prepared using the Grignard reagents and CuBr/Me_2S reagent combination, to chiral α,β-unsaturated *N*-acyloxazolidinones **16**. The reactions gave the 1,4-addition products **17** in good yields with good selectivity (Scheme 6).[7]

Scheme 6



16

R^1 = Bn, Ph

R^2 = Me, Ph

R^3 = Me, Ph, 4-$MeOC_6H_4$, 2-Me-4-$MeOC_6H_3$

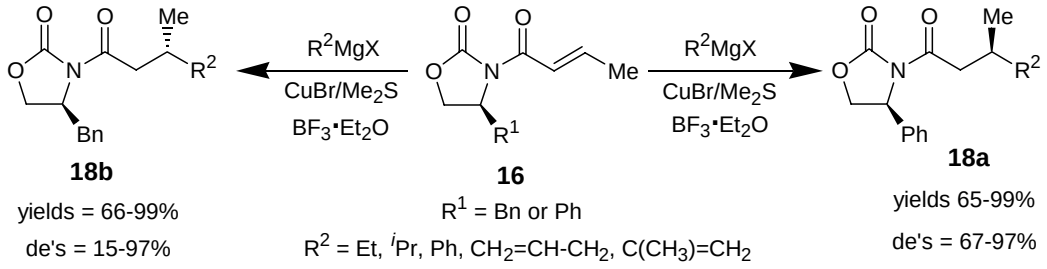
17

yields 85-96%

de's = 10-98%

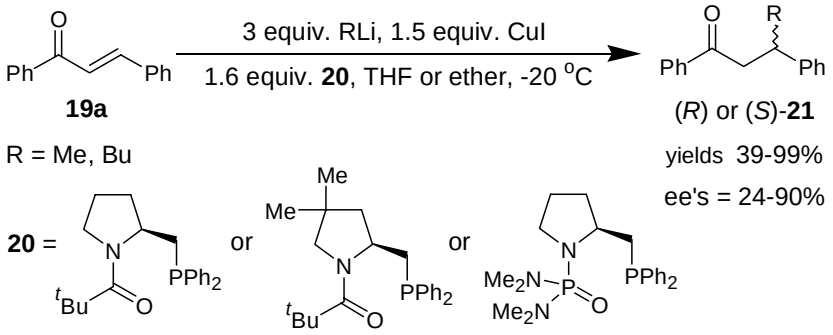
Williams *et al.*[8] reported a diastereoselective conjugate addition of the organocopper reagents to the oxazolidinone-derived enones **16**. The corresponding addition products **18** were obtained in good yields with good stereoselection (Scheme 7).[8]

Scheme 7



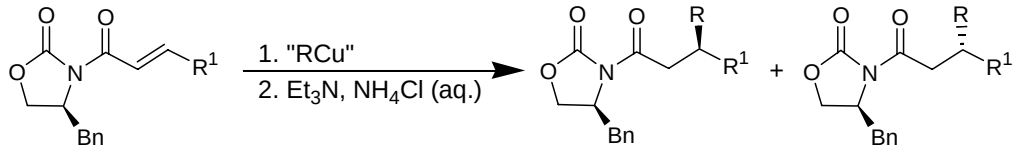
The conjugate addition of the lithium organocuprate to a chalcone **19a** in the presence of chiral amidophosphines **20** provided the 1,4-addition products **21** in good yields with good enantioselection (Scheme 8).[9]

Scheme 8



Diastereoselective conjugate additions to α,β-unsaturated *N*-acyloxazolidinones **22** using various monoorganocuprate reagents, Li[RCuI], were reported (Scheme 9).[10] The addition products **23** were obtained in excellent yields with good diastereoselectivity.

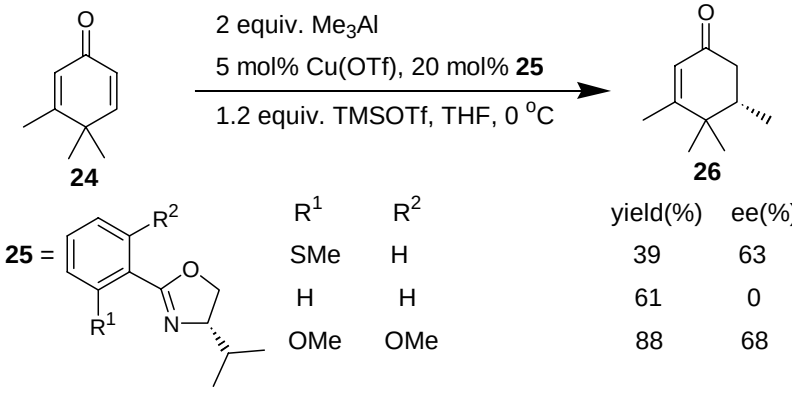
Scheme 9



2.1.4 Additions of organoaluminium reagents:

Iwata *et al.*[11] reported that trimethylaluminium adds to cyclohexa-2,5-dienone **24** in the presence of Cu(OTf) and chiral ligand **25**. The addition took place at the less substituted double bond in the presence of 1.2 equiv. of TMSOTf and the product **26** was obtained with moderate enantioselectivity (Scheme 10).[11]

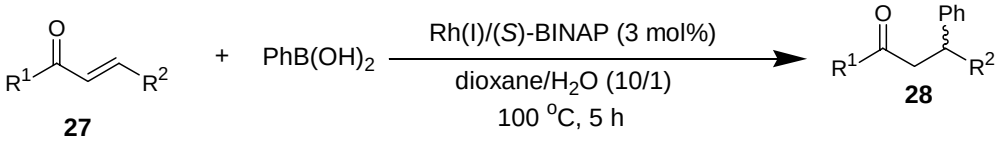
Scheme 10



2.1.5 Additions of organoboron reagents:

It was found that the phenylboronic acid adds to the enones **27** in the presence of chiral BINAP and a rhodium catalyst to give the conjugate addition products **28** in very good yields with high enantioselectivity (Scheme 11).[12]

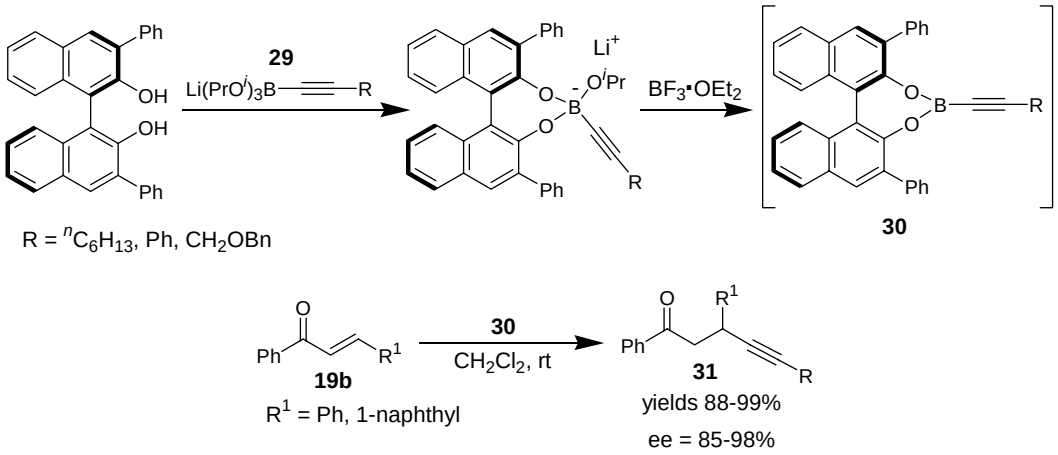
Scheme 11



enone (**27**)	yield(%) **28**	ee(%)
2-cyclohexenone	99	97 (*S*)
2-cyclopentenone	93	97 (*S*)
(*E*)-5-methyl-2-hexenone	82	97

Chiral alkynyl boronates of the type **30**, prepared from chiral BINOL and alkynyl boronate **29**, were reported to add to conjugate enones **19b**. The corresponding adducts **31** were obtained in high yields with high ees (Scheme 12).[13]

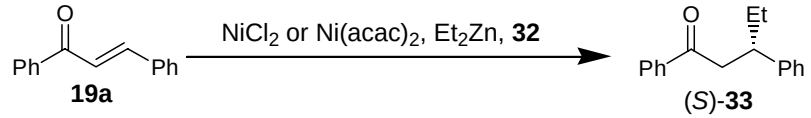
Scheme 12



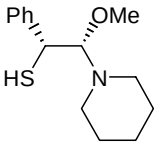
2.1.6 Additions of organozinc reagents:

The conjugate addition of diethylzinc to chalcone **19a** in the presence of various chiral amine-based ligands **32** was studied. The reaction was catalyzed by $NiCl_2$ or $Ni(acac)_2$ (Scheme 13).[14a-c]

Scheme 13

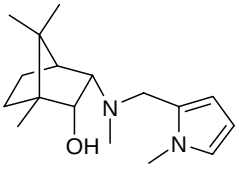


Ligand **32** =



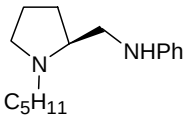
32a

,



32b

,

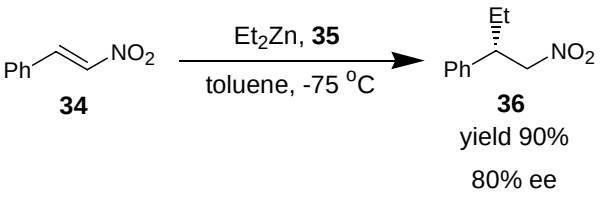


32c

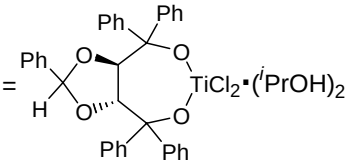
ligand	yield of **33** (%)	ee (%)
32a	77	62
32b	83	83
32c	75	82

An asymmetric conjugate addition of diethylzinc to *trans*-β-nitrostyrene **34** in the presence of titanium TADDOLate **35** was reported. The corresponding adduct **36** was obtained in good yield with good enantioselectivity (Scheme 14).[15]

Scheme 14



35 =



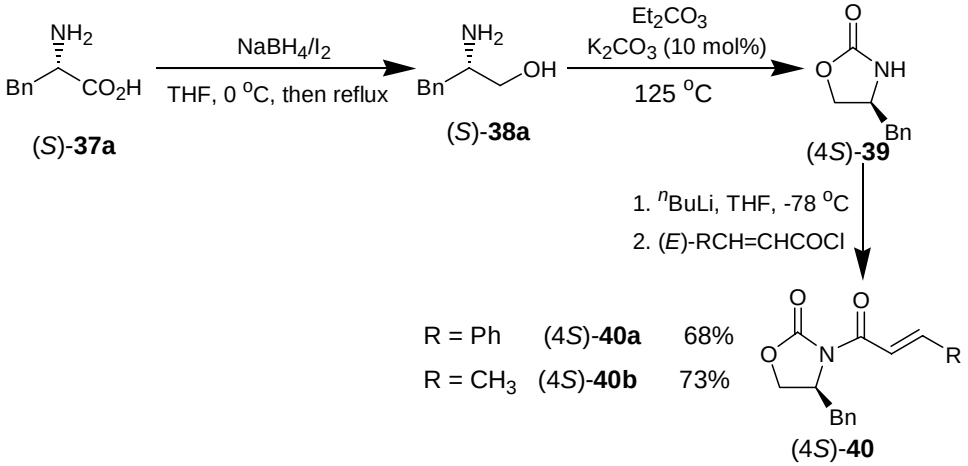
We have examined the asymmetric conjugated additions of aryltitanium reagents to chiral auxiliary-derived enones. The results are described in this Chapter.

2.2 Results and Discussion

2.2.1 Asymmetric 1,4-conjugate arylations (Michael-type reactions) of chiral oxazolidinone-derived enones with *N,N*-dialkylanilines mediated by titanium:

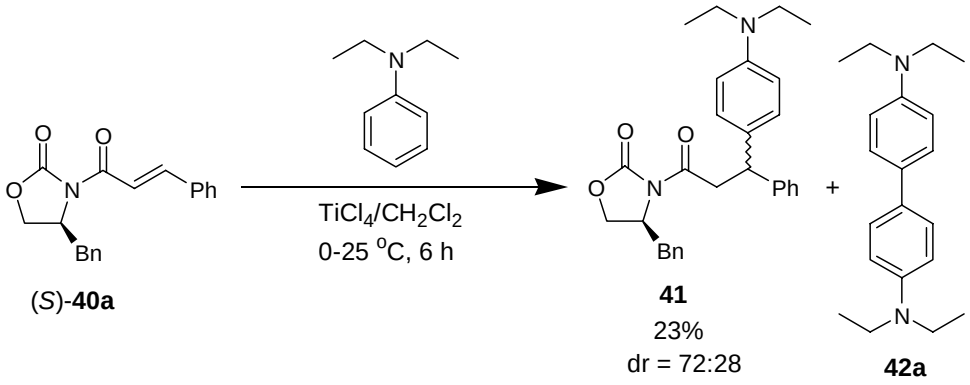
We have undertaken efforts to develop a method for asymmetric 1,4-conjugate arylation (Michael-type reaction) mediated by aryltitanium species generated *in situ* in the reaction of *N,N*-dialkylanilines and $TiCl_4$ (Scheme 64, Chapter 1, Section 1.1.7).[16] Chiral oxazolidinone-derived enones were chosen as substrates. Accordingly, α,β-unsaturated *N*-acyl-(4*S*)-benzyl-2-oxazolidi-nones **40** were prepared by following the literature procedures. (*S*)-Phenylalanine **37a** was reduced to give (*S*)-phenylalaninol **38a** using the $NaBH_4/I_2$ reagent system.[17] The reaction of (*S*)-phenylalaninol **38a** with diethyl carbonate in the presence of catalytic amount of K_2CO_3 resulted in the formation of the corresponding oxazolidinone (4*S*)-**39** in good yields.[18a] The product (4*S*)-**39** was reacted with (*E*)-cinnamoyl chloride or (*E*)-crotonoyl chloride in the presence of *n*-butyllithium to obtain the corresponding α,β-unsaturated *N*-acyl-(4*S*)-benzyl-2-oxazolidinones (4*S*)-**40a** or (4*S*)-**40b**, respectively (Scheme 15).[18b]

Scheme 15



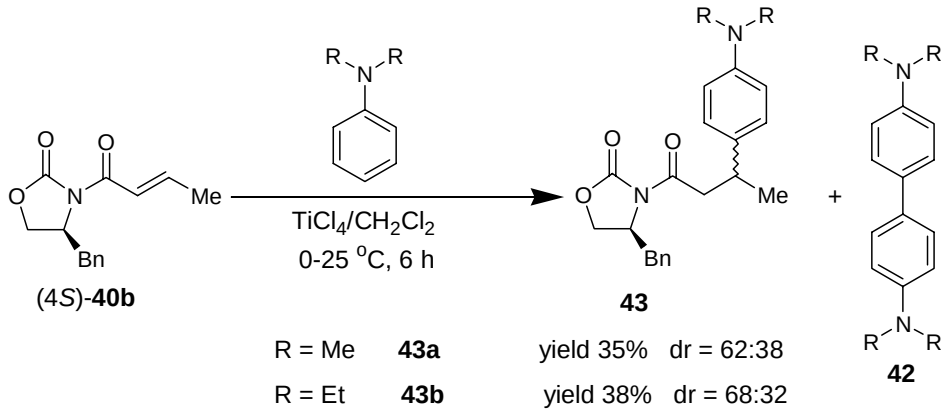
The oxazolidinone (4*S*)-**40a** was treated with $TiCl_4$ and *N,N*-diethylaniline in CH_2Cl_2 at 0 ^oC and stirred at room temperature for 6 h to obtain the corresponding 1,4-addition product **41** in 23% yield besides the benzidine **42a** (Scheme 16) formed through coupling of $ArTiCl_3$ produced *in situ* (see Scheme 64, Chapter 1, Section 1.1.7).[16] Though the yield of the conjugate addition product **41** was poor, the diastereomeric ratio was moderate (dr = 72:28). The diastereomeric ratio was estimated by ^{13}C-NMR spectral analysis of the product.

Scheme 16



However, the use of *N*-crotonoyloxazolidinone (4*S*)-**40b** has improved the yields slightly in the reaction with *N,N*-dialkylaniline in presence of $TiCl_4$ under the reaction conditions. Unfortunately, the diastereomeric ratios (dr's) realized in these cases were poor. For example, the reaction of *N,N*-dimethylaniline with *N*-crotonoyl-oxazolidinone (4*S*)-**40b** gave the 1,4-addition product **43a** in 35% yield with 62:38 diastereomeric ratio. Whereas the reaction of *N,N*-diethylaniline with *N*-crotonoyl-oxazolidinone (4*S*)-**40b** gave the corresponding adduct **43b** in 32% yield (dr = 68:32) (Scheme 17). Also, the corresponding benzidines **42** were obtained as side products in these reactions.[16]

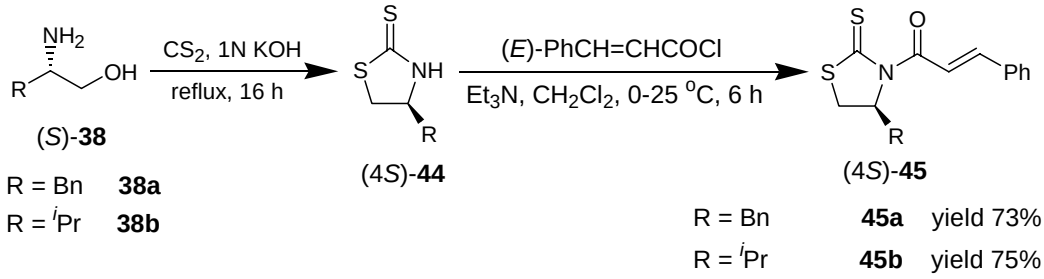
Scheme 17



2.2.2 Asymmetric 1,4-conjugate arylations (Michael-type reactions) of chiral thiazolidinethione-derived enones with *N*,*N*-dialkylaniline mediated by $TiCl_4$:

It was of interest to us to examine the use of *N*-cinnamoylthiazolidinethione as an electrophile in this transformation. Accordingly, *N*-cinnamoylthiazolidinethiones (4*S*)-**45a** and (4*S*)-**45b** were prepared from the corresponding (*S*)-phenylalaninol[17] **38a** and (*S*)-valinol[17] **38b**, respectively by following the literature procedures (Scheme 18).[19,20]

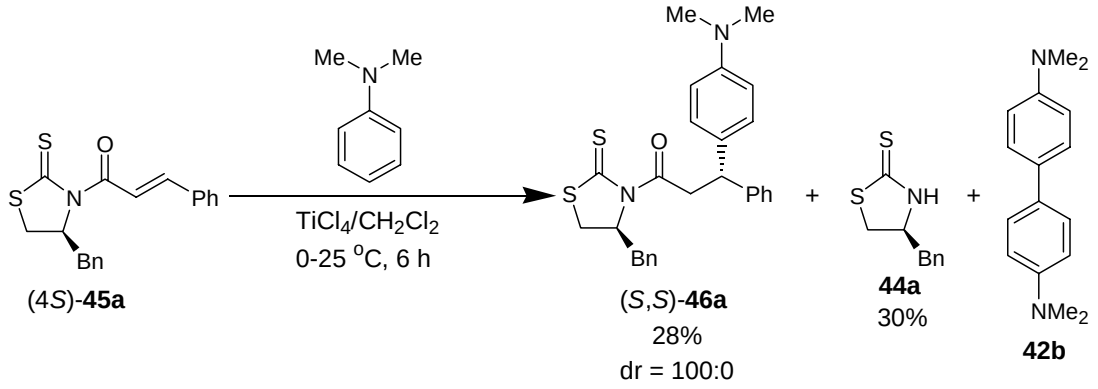
Scheme 18



The chiral enone (4*S*)-**45a** was reacted with *N*,*N*-dimethylaniline in the presence of $TiCl_4$. In this reaction, the corresponding 1,4-addition product **46a** was isolated only in 28% yield besides the homocoupled benzidine product **42b**.[16] Interestingly, only one

of the diastereomers of the product **46a** was formed in this reaction. The thiazolidinethione **44a** (30%) was also isolated from the reaction mixture (Scheme 19).

Scheme 19



X-ray structure analysis of the compounds **46a** revealed that the new chiral center has the absolute configuration *S* (using PLATON[21] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **46a** is shown in Figure 1. The crystal structure data of the compound (*S*,*S*)-**46a** are summarized in Table 1 and Table A8 (Appendix II).

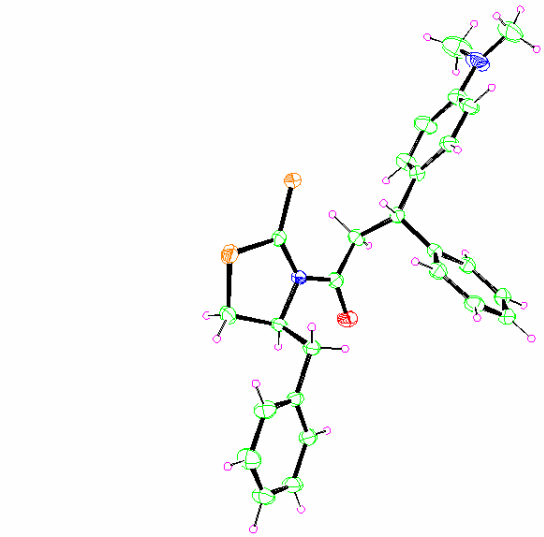


Figure 1 ORTEP representation of the crystal structure of the compound **46a**

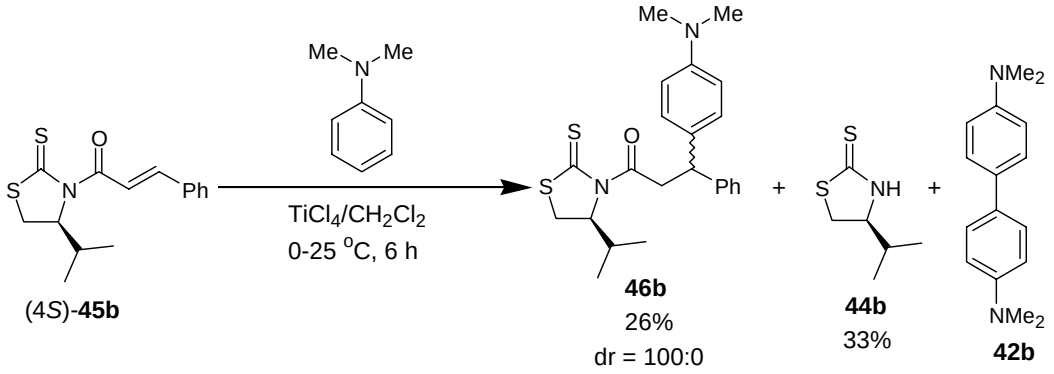
(Thermal ellipsoids are drawn at 20% probability)

Table 1 X-ray data collection and structure refinement for the thiazolidinethione derivative (*S*,*S*)-**46a**

Empirical formula	$C_{27}H_{28}NOS_2$
Formula weight	460.63
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 14.4320(11) Å, α = 90˚
	b = 5.7087(5) Å, β = 107.2470(10)˚
	c = 15.2966(12) Å, γ = 90˚
Volume	1203.59(17) $Å^3$
Z	2
Calculated density	1.271 Mg/m^3
Absorption coefficient	0.243 mm^{-1}
F(000)	488
Crystal size	0.40 X 0.27 X 0.13 mm
θ range for data collection	1.39 to 28.23˚
Limiting indices	$-18 \le h \le 19$; $-7 \le k \le 7$; $-20 \le l \le 20$
Reflections collected/unique	14086 / 5574 [R(int) = 0.0335]
Completeness to θ = 28.23	96.2%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	5574 / 1 / 291
Goodness-of-fit on F^2	0.945
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0454$, $wR_2 = 0.0953$
R indices (all data)	$R_1 = 0.0599$, $wR_2 = 0.1016$
Largest diff. peak and hole	0.319 and -0.156 $eÅ^{-3}$

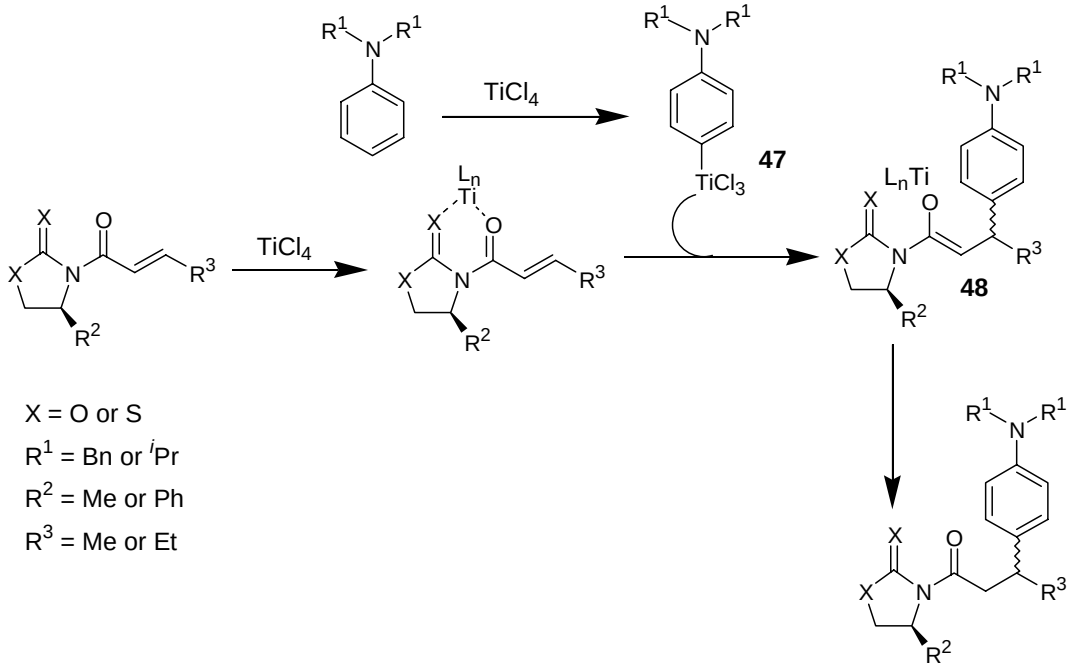
The reaction of (S)-valinol-derived enone (4*S*)-**45b** with $TiCl_4$ and *N*,*N*-dimethylaniline afforded the corresponding 1,4-addition product **46b** in 26% yield along with the homocoupled benzidine product **42b** and the thiazolidinethione **44b** (33%). In this case also, only one of the diastereomers of the addition product **46b** was isolated from the reaction mixture (Scheme 20).

Scheme 20



A tentative mechanism is given in the **Scheme 21** for the 1,4-conjugate addition reaction of α,β-unsaturated carbonyl compound with *N,N*-dialkylaniline. Initially, the aryltitanium species **47** is expected to form in the reaction of *N,N*-dialkylaniline with $TiCl_4$.[16] The aryltitanium species formed in this way would then add to the α,β-unsaturated carbonyl compound activated by $TiCl_4$, in a 1,4-conjugate fashion to give the corresponding 1,4-addition product. The reaction is expected to go through a titanium enolate intermediate **48** (Scheme 21).

Scheme 21



A cyclic six-membered transition state **TS-1** shown in Figure 2 may explain the asymmetric induction resulted in the 1,4-conjugate addition reaction of α,β-unsaturated carbonyl compound with *N,N*-dialkylaniline. In the transition state, the benzyl group of the chiral oxazolidinone is likely to be positioned far away from the new C-C bond. The aryl group is expected attack on the *Si* face of the unsaturated bonding to give the diastereomer (*S*,*S*)-**46a**.

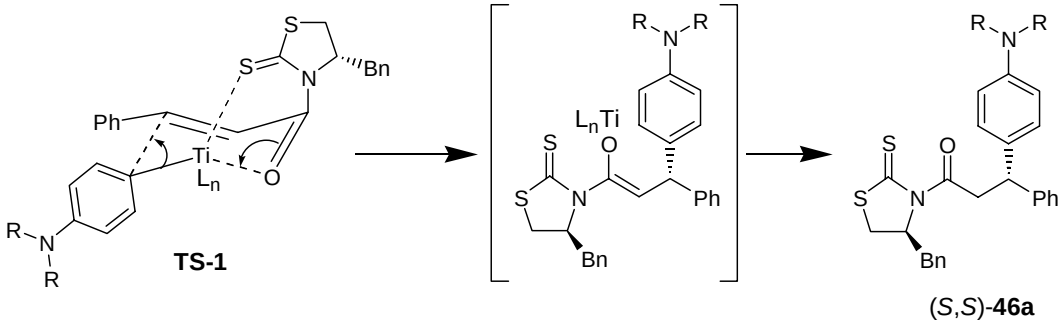
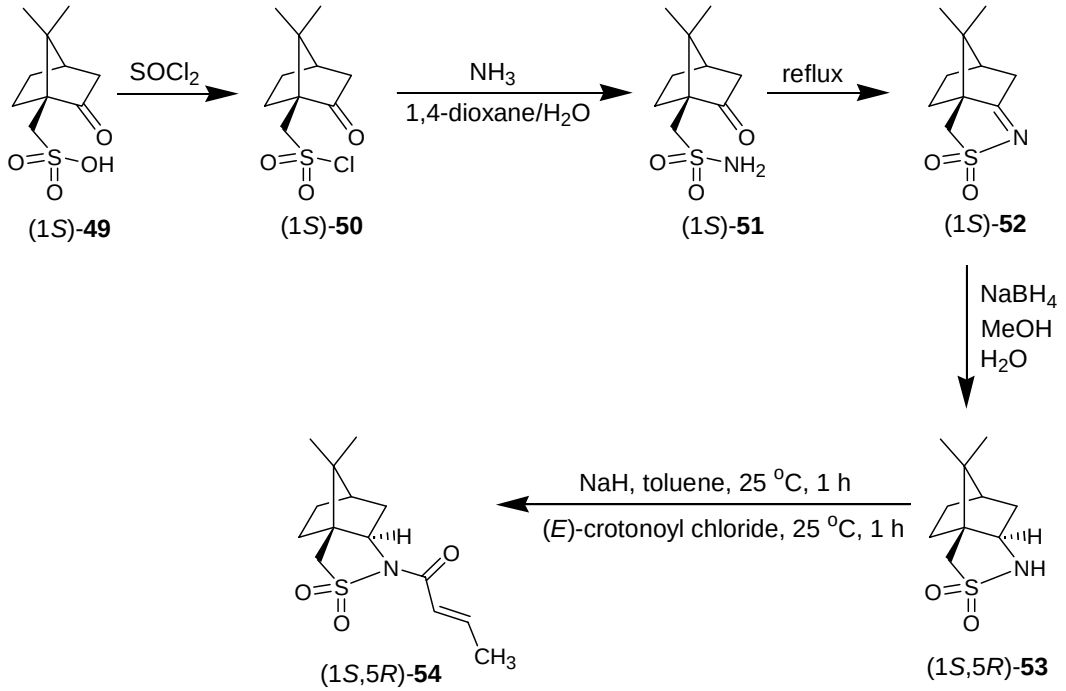


Figure 2 Six-membered transition state model to account for asymmetric induction

2.2.3 Asymmetric 1,4-conjugate arylation (Michael-type reaction) of chiral camphorsultam-derived enones with *N*,*N*-diethylaniline mediated by $TiCl_4$:

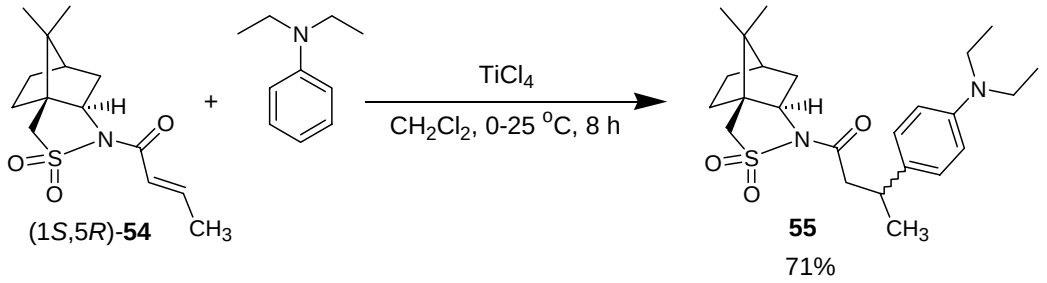
The Oppolzer camphorsultam **53** is a versatile chiral auxiliary that is known to mediate several diastereoselective C-C bond forming reactions.[22] We became interested to carry out investigations on the asymmetric conjugate additions of camphorsultam-derived enones, using aryltitanium reagents. Accordingly, we have prepared the *N*-crotonoylcamphorsultam **54** by following the literature reports.[23,24] The synthetic protocol followed for the preparation of *N*-crotonoylcamphorsultam (1*S*,5*R*)-**54** is given in the Scheme 22.

Scheme 22



The *N*-crotonoylcamphorsultum (1*S*,5*R*)-**54** was then reacted with $TiCl_4$ and *N*,*N*-diethylaniline in CH_2Cl_2. Though, the 1,4-addition product **55** was obtained in good yields (71%), the selectivity realized in this case was very poor (dr = 54:46) (Scheme 23).

Scheme 23



Though, excellent to moderate selectivities are realized in the 1,4-addition reactions described in this Chapter, the chemical yields are poor in most cases. However, the results may be helpful in screening for the appropriate reaction conditions for the asymmetric 1,4-conjugate arylation of the chiral auxiliary-derived enones using organotitanium reagents.

2.3 Conclusions

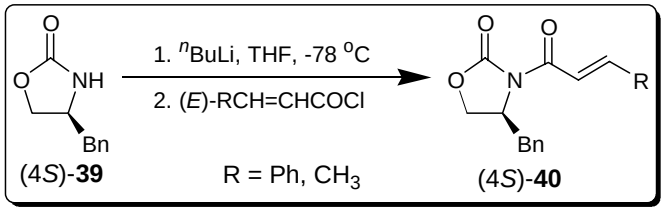
Asymmetric 1,4-conjugate arylations (Michael-type reactions) of chiral oxazolidinone- or thiazolidinethione-derived enones (*S*)-**40** and (*S*)-**45** using *N*,*N*-dialkylanilines in the presence of titanium tetrachloride gave the corresponding 1,4-addition products (**41**, **43** and **46**) in moderate to excellent diastereomeric ratios (62:38 to 100:0). The crystal structure analysis of **46a** revealed that the absolute configurations of the chiral centers are *S*,*S*. The conjugate addition of chiral *N*-crotonoylcamphorsultam (1*S*,5*R*)-**54** using $TiCl_4$ and *N*,*N*-diethylaniline gave the corresponding adduct **55** in 71% yield with poor diastereoselectivity (dr = 56:44).

2.4 Experimental Section

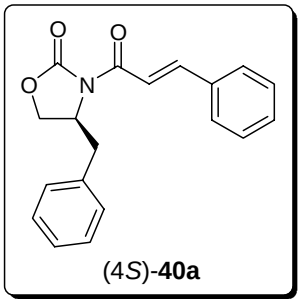
Several informations given in the section **1.4** are also applicable to the experiments outlined in this section. (*S*)-Phenylalanine, (*S*)-valine and (*1S*)-camphorsulfonic acid were purchased from Lancaster Synthesis Ltd., UK. Crotonoyl chloride (*E*:*Z* = 90:10) was supplied by Aldrich, USA. Sodium borohydride, diethyl carbonate, carbon disulfide, ^{n}butyllithium (1.6 M in hexane), *N*,*N*-dimethylaniline, *N*,*N*-diethylaniline and sodium hydride (60% dispersion in mineral oil) were obtained from E-Merck, India. (*E*)-Cinnamoyl chloride was prepared from the reaction of thionyl chloride with (*E*)-cinnamic acid, supplied by Loba Chemie (P) Ltd., India.

2.4.1 Procedure for the synthesis of *N*-cinnamoyl-(4*S*)-benzyl-2-oxazolidinone (*S*)-40a or *N*-crotonoyl-(4*S*)-benzyl-2-oxazolidinone (*S*)-40b:

To a solution of oxazolidinone (4*S*)-**39** (1.77 g, 10 mmol) in anhydrous THF (30 mmol) was added *n*-butyllithium (6.2 mL, 1.6 M solution in hexane, 10 mmol) at –78 ^{o}C under N_2 atmosphere. After 15 min, freshly distilled cinnamoyl chloride or crotonoyl chloride (11 mmol) was added. The reaction mixture was stirred at –78 ^{o}C for 30 min and at 0 ^{o}C for 15 min. It was quenched with excess saturated aqueous ammonium chloride (15 mL), and the resultant slurry was concentrated in vacuum. The residue was diluted with ether (60 mL) and washed successively with saturated aqueous sodium bicarbonate (20 mL) and then saturated aqueous sodium chloride (15 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified on a silica column using hexanes/EtOAc (90:10) mixture as eluent.



Yield 2.09 g (68%)


(4*S*)-**40a**

mp 106-108 °C

IR (KBr) (cm^{-1}) 3028, 1780, 1672, 1618

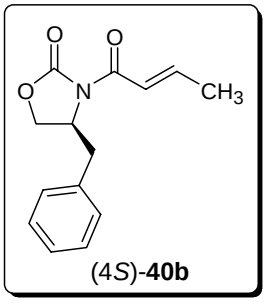
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.85-2.91 (m, 1H), 3.38-3.43 (m, 1H), 4.22-4.30 (m, 2H), 4.80-4.85 (m, 1H), 7.18-7.44 (10H), 7.66-7.68 (m, 1H), 7.90-7.99 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 38.3, 56.2, 66.8, 122.1, 127.8, 128.2, 128.6, 128.9, 131.2, 132.7, 135.42, 144.4, 146.1, 153.6, 165.0

MS m/z 308 (M+1)

$[\alpha]_D^{25}$ +47.3 (*c* 1, $CHCl_3$)

Yield 1.84 g (73%)


(4*S*)-**40b**

mp 82-86 °C (lit.[17] mp: 85-86 °C)

IR (KBr) (cm^{-1}) 3022, 1778, 1665, 1614

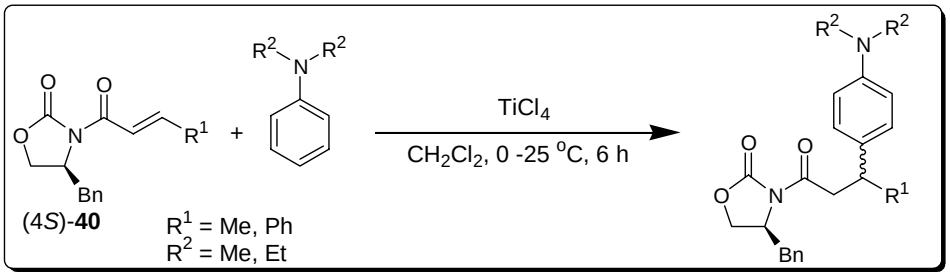
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.60-2.03 (m, 3H), 2.32-2.94 (m, 1H), 3.30-3.41 (m, 1H), 4.13-4.29 (m, 2H), 4.28-4.32 (m, 1H), 7.09-7.40 (7H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 18.55, 37.83, 55.24, 66.10, 121.89, 127.28, 128.92, 129.47, 135.42, 146.87, 153.44, 164.93

$[\alpha]_D^{25}$ +70.0 (*c* 2, $CHCl_3$) {lit.[17] $[\alpha]_D^{25}$: +77.9 (*c* 2, $CHCl_3$)}

2.4.2 Procedure for conjugate arylation of α,β-unsaturated *N*-acyl-(4*S*)-benzyl-2-oxazolidinones 40 using *N*,*N*-dialkylaniline and $TiCl_4$:

N,*N*-Dialkylaniline (4 mmol) and α,β-unsaturated *N*-acyl-(4*S*)-benzyl-2-oxazolidinone **40a** or **40b** (2 mmol) were taken in CH_2Cl_2 (15 mL) at 0 °C under N_2 atmosphere. $TiCl_4$ (6 mmol) was added to the reaction mixture and stirred vigorously at 0 °C for 0.5 h and stirred further at 25 °C for 6 h. A saturated K_2CO_3 solution (10 mL) was added and stirred for 0.5 h. The contents were filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The desired 1,4-addition product was isolated using hexanes/EtOAc (90:10) as eluent.



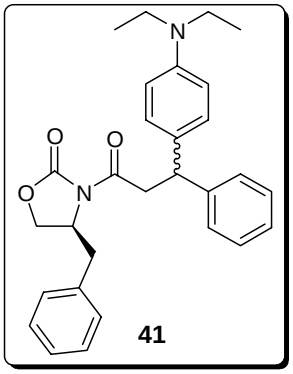
Yield 0.20 (23%)

dr 72:28

mp 98-100 °C

IR (KBr) (cm^{-1}) 3026, 2954, 1780, 1685, 1614

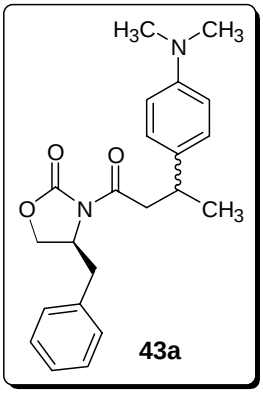
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.23 (t, 6H, *J* = 7.8 Hz), 2.62-2.81 (m, 2H), 3.00-3.16 (m, 2H), 3.26-



3.39 (m, 1H), 3.68 (q, 4H, *J* = 8 Hz), 3.99-4.20 (m, 2H), 4.55-4.66 (m, 1H), 6.66-6.74 (m, 2H), 7.19-7.27 (m, 2H), 7.35-7.70 (10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 20.9, 30.1, 32.9, 38.5, 44.7, 53.2, 65.3, 117.5, 126.4, 127.1, 127.9, 128.8, 129.0, 129.5, 130.6, 136.4, 144.9, 149.1, 154.5, 170.3. Additional signals for minor diastereomer: 20.1, 30.5, 32.4, 37.9, 44.4, 53.6, 66.0

$[\alpha]_D^{25}$ +40.1 (*c* 1, $CHCl_3$)



43a

Yield 0.31 (35%)

dr 62:38

mp 128-130 ^{o}C

IR (KBr) (cm^{-1}) 3031, 2957, 1786, 1691, 1615

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.33-1.36 (m, 3H), 2.60-2.75 (m, 1H), 2.93 (s, 6H), 3.04-3.18 (m, 2H), 3.26-3.48 (m, 2H), 4.05-4.22 (m, 2H), 4.53-4.67 (m, 1H), 6.71-6.75 (m, 2H), 7.11-7.35 (7H)

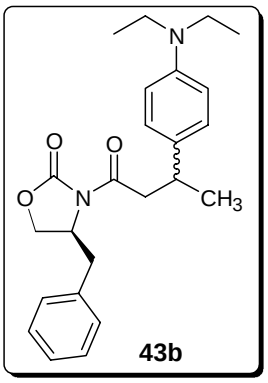
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 22.3, 35.3, 37.9, 40.8, 43.6, 55.2, 66.1, 112.8, 127.3, 127.7, 129.0, 129.5, 133.7, 135.5, 149.4, 153.2, 172.2. Additional signals for minor diastereomer: 22.2, 35.2, 37.6, 43.6, 55.0, 66.0, 112.9, 127.3, 135.3, 172.3

MS m/z 367 (M+1)

$[\alpha]_D^{25}$ +65.8 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{22}H_{26}N_2O_3$: C-72.11%, H-7.15%, N-7.64%

Found: C-72.21%, H-7.16%, N-7.15%



43b

Yield 0.30 g (38%)

dr 68:32

IR (Neat) (cm^{-1}) 3033, 2952, 1788, 1693, 1610

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.12 (t, 6H, *J* = 7.2 Hz), 1.32 (d, 3H, *J* = 6.8 Hz), 2.56-2.72 (m, 1H), 3.00-3.14 (m, 2H), 3.25-3.47 (6H), 4.04-4.22 (m, 2H), 4.59-4.67 (m, 1H), 6.60-6.64 (m, 2H), 7.09-7.32 (7H) **(Spectrum No. 35)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): for major diastereomer: 12.6, 22.1, 35.2, 37.7, 43.6, 44.4, 55.0, 65.9, 112.1, 127.2, 127.8, 128.9, 129.4, 132.3, 135.5, 153.4, 172.4. Additional signals for minor diastereomer: 22.3, 35.3, 37.9, 55.3 **(Spectrum No. 36)**

MS m/z 395 (M+1)

$[\alpha]_D^{25}$ +49.4 (*c* 1, $CHCl_3$)

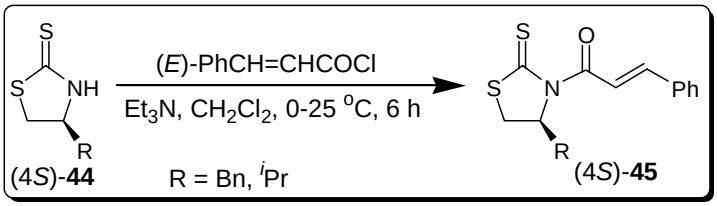
Analytical data calculated for $C_{24}H_{30}N_2O_3$: C-73.07%, H-7.66%, N-7.10%

Found: C-73.03%, H-7.68%, N-7.22%

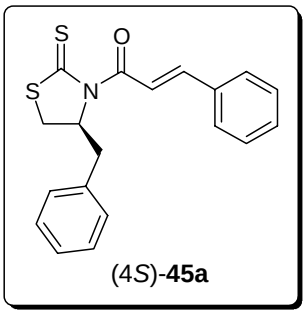
2.4.3 Procedure for the synthesis of *N*-cinnamoylthiazolidinethiones (4*S*)-45:

To a solution of thiazolidinethione (4*S*)-**44** (10 mmol) in CH_2Cl_2 (30 mL) was added freshly distilled cinnamoyl chloride (1.83 g, 11 mmol) at 0 ^oC under N_2 atmosphere. Triethylamine (1.2 g, 1.7 mL, 12 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 10 min at 0 ^oC and the reaction was stirred at 25 ^oC for 6 h. The contents were diluted with CH_2Cl_2 (40 mL) and washed successively with saturated aq. sodium bicarbonate (20 mL) and then brine (15 mL). The organic layer was dried over

anhydrous Na_2SO_4, filtered and concentrated in vacuum. The crude product was purified on a silica column using hexanes/EtOAc (90:10) mixture as eluent.



Yield 2.48 g (73%)



mp 114-116 °C

IR (KBr) (cm^{-1}) 2952, 1674, 1622, 1493

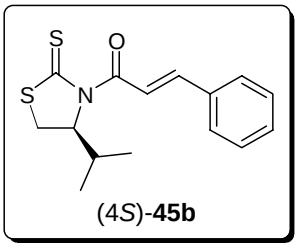
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.97-3.00 (m, 1H), 3.08-3.14 (m, 1H), 3.39-3.50 (m, 2H), 5.27-5.32 (m, 1H), 6.44-6.56 (m, 1H), 7.29-7.60 (m, 10H), 7.91-7.95 (m, 1H) **(Spectrum No. 37)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 32.8, 36.8, 69.0, 120.0, 127.3, 128.4, 128.6, 129.0, 129.5, 130.6, 134.8, 136.7, 144.2, 166.7, 201.3 **(Spectrum No. 38)**

MS m/z 340 (M+1)

$[\alpha]_D^{25}$ -220.4 (*c* 1, $CHCl_3$)

Yield 2.18 g (75%)



IR (Neat) (cm^{-1}) 2956, 1671, 1620, 1495

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.02 (d, 3H, *J* = 7 Hz), 1.07 (d, 3H, *J* = 7 Hz), 2.49-2.56 (m, 1H), 3.11-3.14 (m, 1H), 3.53-3.58 (m, 1H), 5.07-5.11 (m, 1H), 7.35-7.47 (m, 3H), 7.50-7.61 (m, 2H), 7.66 (d, 1H, *J* = 16 Hz), 7.93 (d, 1H, *J* = 16 Hz)

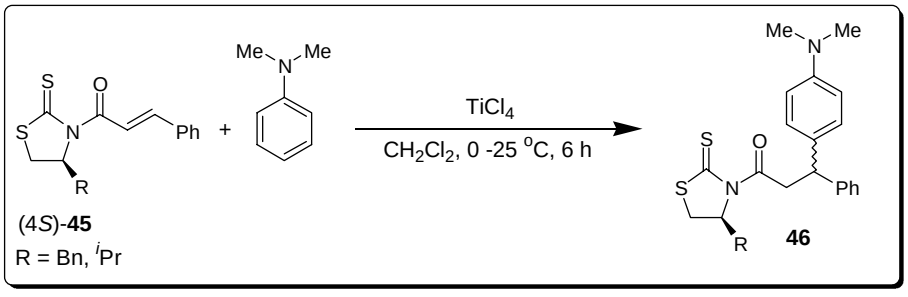
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 17.3, 19.1, 30.8, 30.9, 72.1, 120.2, 128.5, 128.9, 130.4, 134.9, 143.9, 166.9, 202.7

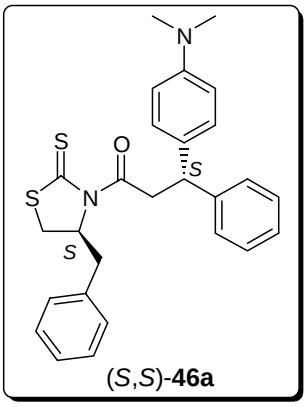
MS m/z 292 (M+1)

$[\alpha]_D^{25}$ +58.3 (*c* 0.58, $CHCl_3$)

2.4.4 General procedure for conjugate arylation of *N*-cinnamoylthiazolidine-thiones using *N,N*-dimethylaniline and $TiCl_4$:

To a stirred solution of chiral enone (4*S*)-**45a** or (4*S*)-**45b** (1 mmol) and *N,N*-dialkylaniline (3 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (4 mmol) slowly at 0 ^oC under N_2 atmosphere. The contents were allowed to stir at 0 ^oC for 0.5 h and then at 25 ^oC for 6 h. Then the reaction was quenched with saturated K_2CO_3 (10 mL) solution and stirred for 0.5 h. The reaction mixture was filtered using a Buchner funnel and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was subjected to column chromatography on silica gel using hexane/EtOAc (90:10) as eluent to obtain the pure compound **46**.





Yield 0.13 g (28%)

dr 100:0

mp 130-132 ^{o}C

IR (KBr) (cm^{-1}) 3027, 2922, 1693, 1614

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.75 (d, 1H, *J* = 10 Hz), 2.89 (s, 6H), 2.95 (d, 1H, *J* = 10 Hz), 3.06-3.13 (m, 2H), 3.77-3.83 (m, 1H), 4.29-4.36 (m, 1H), 4.57-4.61 (m, 1H), 4.96-5.02 (m, 1H), 6.67 (d, 2H, *J* = 8 Hz), 7.14 (d, 2H, *J* = 8 Hz), 7.20-7.32 (10H) **(Spectrum No. 39)**

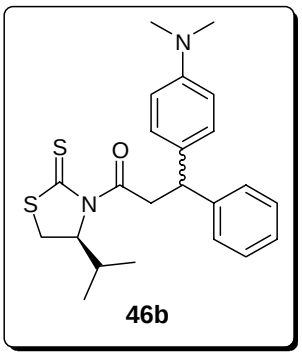
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 32.1, 36.6, 40.7, 44.2, 46.7, 68.8, 112.8, 126.4, 127.2, 127.7, 128.4, 128.5, 128.9, 129.5, 136.5, 144.2, 149.3, 172.9, 201.4 **(Spectrum No 40)**

MS m/z 461 (M+1)

$[\alpha]_D^{25}$ +177.8 (*c* 1, $CHCl_3$)

Analytical data calculated for $C_{27}H_{28}N_2OS_2$: C-70.40%, H-6.13%, N-6.08%, S-13.92%

Found: C-70.47%, H-6.05%, N-6.42%, S-13.98%



Yield 0.11 g (26%)

dr 100:0

IR (Neat) (cm^{-1}) 3062, 2952, 1690, 1617

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.89 (d, 3H, *J* = 7 Hz), 0.98 (d, 3H, *J* = 7 Hz), 2.19-2.26 (m, 1H), 2.92 (s, 6H), 3.21-3.26 (m, 1H), 3.83-

3.88 (m, 1H), 4.27-4.33 (m, 1H), 4.57-4.61 (m, 1H), 4.81-4.85 (m, 1H), 6.67 (d, 2H, *J* = 9 Hz), 7.15 (d, 3H, *J* = 9 Hz), 7.27-7.30 (m, 5H) **(Spectrum No. 41)**

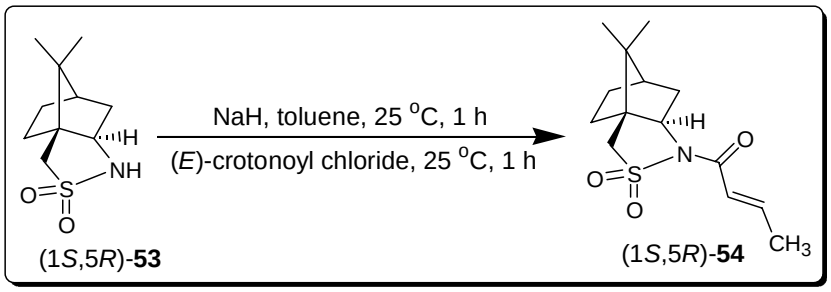
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 17.7, 19.0, 30.5, 30.7, 40.7, 43.8, 46.7, 71.9, 112.8, 126.2, 127.7, 128.3, 128.5, 131.6, 144.2, 149.3, 172.7, 203.0 **(Spectrum No. 42)**

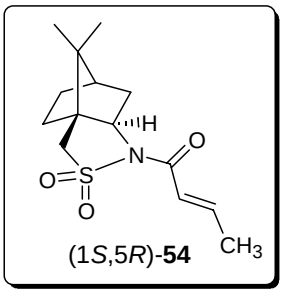
MS m/z 435 (M+23)

$[\alpha]_D^{25}$ +7.0 (*c* 0.15, $CHCl_3$)

2.4.5 Procedure for the synthesis of (1*S*,5*R*)-*N*-crotonoylcamphorsultam 54:

A solution of camphorsultam (1*S*,5*R*)-**53** (0.86 g, 4 mmol) in toluene (20 mL) was added dropwise at 25 ^oC to a stirred suspension of NaH (0.24 g, 60% dispersion in mineral oil, 6 mmol). After 1 h a solution of crotonoyl chloride (0.84 g, 0.77 mL, 8 mmol) in toluene (20 mL) was added slowly and the mixture was stirred at room temperature for 3 h. The reaction was quenched with water and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extract was dried over Na_2SO_4, filtered and concentrated. The crude product was purified on a silica column using hexanes/EtOAc (85:15) mixture as eluent.





(1*S*,5*R*)-**54**

Yield 0.96 g (85%)

mp 186-188 °C (lit.[24] mp = 187-188 °C)

IR (KBr) (cm^{-1}) 3012, 2864, 1678, 1614, 1443, 1327, 1298, 1216, 1136

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.98 (s, 3H), 1.17 (s, 3H), 1.35-1.45 (m, 2H), 1.86-1.98 (6H), 2.06-2.16 (m, 2H), 3.42-3.53 (m, 2H), 3.90-3.98 (m, 1H), 6.59 (d, 1H, *J* = 8 Hz), 7.05-7.13 (m, 1H) **(Spectrum No. 43)**

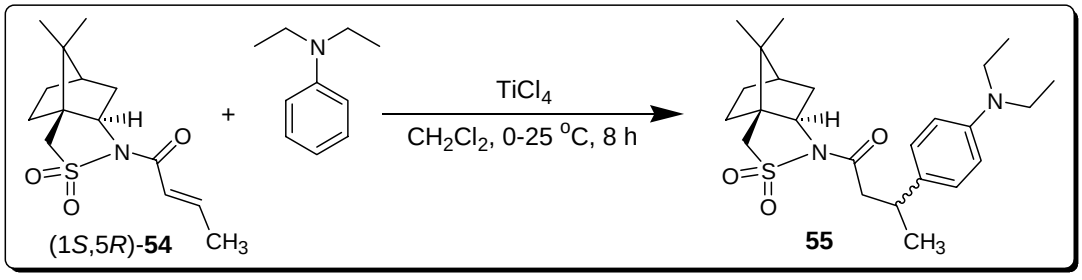
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 18.3, 19.9, 20.8, 26.5, 32.8, 38.5, 44.7, 47.8, 48.4, 53.1, 65.1, 112.3, 146.0, 163.9 **(Spectrum No. 44)**

MS m/z 284 (M+1)

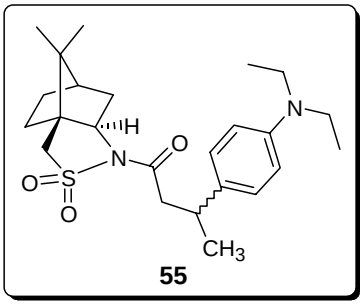
$[\alpha]_D^{25}$ +103.1 (*c* 3.7, $CHCl_3$) {lit.[24] $[\alpha]_D^{25}$: +103.9 (*c* 3.7, $CHCl_3$)}

2.4.6 Procedure for asymmetric conjugate arylation of *N*-crotonoylcamphorsultam (1*S*)-54 using *N*,*N*-diethylaniline and $TiCl_4$:

The reaction was performed with (1*S*,5*R*)-*N*-crotonoylcamphorsultam by following the procedure given in the Section 2.4.2.



(1*S*,5*R*)-**54** **55**



55

Yield 0.61 g (71%)

dr 56:44

mp 124-128 ^{o}C

IR (KBr) (cm^{-1}) 2964, 1695, 1614, 1520, 1456, 1335

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.88-0.97 (5H), 1.10-1.41 (13H), 1.74-2.10 (5H), 2.71-3.12 (m, 2H), 3.27-3.51 (m, 6H), 3.79-4.86 (m, 1H), 6.57-6.62 (m, 2H), 7.06-7.10 (m, 2H) **(Spectrum No. 45)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.6, 12.7; 19.9; 20.6, 20.9; 21.8, 22.1; 26.5; 32.8, 32.9; 35.3, 35.8; 38.4, 38.6; 43.9, 44.1; 44.4, 44.4; 44.7; 47.6, 47.8; 48.3, 48.7; 53.0, 53.1; 65.0, 65.3; 112.1; 127.6, 127.8; 132.0, 132.5; 146.4; 171.0, 171.2 **(Spectrum No. 46-** signals for minor diasteromer are not shown**)**

MS m/z 433 (M+1)

2.5 References

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Tetrahedron Organic Chemistry Series, Pergamon Press: Oxford, 1992 (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227 (c) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771 (d) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1176 (e) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed. Engl.***1997**, *36*, 186 (f) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236 (g) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.
2. (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266 (b) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527 (c) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *111*, 8266.
3. Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. *Tetrahedron: Asymmetry* **1998**, *9*, 1651.
4. (a) Park, Y, S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537 (b) Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 2996.
5. Han, Y.; Hruby, V. J. *Tetrahedron Lett.* **1997**, *38*, 7317.
6. Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649.
7. Nicolás, E.; Russel, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766.
8. Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593.
9. Kanai, M.; Nakagawa, Y.; Tomioka, K. *Tetrahedron* **1999**, *55*, 3831.
10. Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett.* **2002**, *43*, 3693.
11. (a) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C. *Tetrahedron* **1996**, *52*, 14177 (b) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 993.

12. Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

13. Chong, M. J.; Shen, L.; Taylor, N. J. *J. Am. Chem. Soc.* **2000**, *122*, 1822.

14. (a) Kang, J.; Kim, J. I.; Lee, J. H.; Kim, H. J.; Byun, Y. H. *Bull. Korean Chem. Soc.* **1998**, *19*, 601 (b) deVries, A. H. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467 (c) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, 297.

15. Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305.

16. Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2000**, *65*, 3548.

17. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568.

18. (a) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830 (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

19. Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604.

20. Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

21. A. L. Spek, *PLATON, A Multipurpose Crystallographic Tool;* Utrecht University, Utrecht, The Netherlands, 2002.

22. (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603 (b) Hanessian, S.; Yang, R. –Y. *Tetrahedron Lett.* **1996**, *37*, 5273 (c) Oppolzer, W.; Rosset, S.; DeBrabander, J. *Tetrahedron Lett.* **1997**, *38*, 1593 (d) Cusk, R.; Schröder, C.; Hutter, S.; Mohr, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1411 (e) Jezewski, A. Chajewska, K.; Wielogórski, Z.; Jurczak, J.; *Tetrahedron: Asymmetry* **1997**, *8*, 1741 (f) Bond, S.; Perlmutter, P. *J. Org. Chem.* **1997**, *62*, 6397 (g) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *117*, 4317.

23. Capet, M.; David, G.; Bertin, L.; Hardy, J. C. *Synth. Commun.* **1995**, 25, 3123.

24. Vandewalle, M.; vanderEychen, J. *Tetrahedron* **1986**, *42*, 4035.

Chapter 3

Synthesis of chiral C_2-symmetric diamines using titanium reagents and their utility in the synthesis of chiral polymers

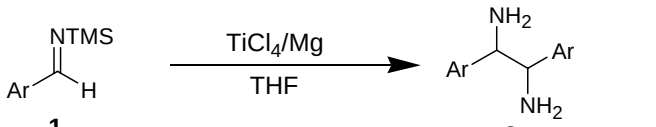
3.1 Introduction

The 1,2-diamino moiety is present in many biologically and medicinally important valuable compounds.[1] Chiral 1,2-diamines have also been increasingly used in organic synthesis especially in the preparation of chiral catalysts that are useful in asymmetric transformations in recent years. Hence, interest in these compounds brought about numerous studies aimed at the design of efficient diastereo- and enantioselective routes to access chiral 1,2-diamines.[1] One of the most practical ways to access these vicinal diamines is the reductive coupling or reductive dimerization of the corresponding imines. We have undertaken efforts on the synthesis of chiral diamines using low-valent titanium reagents and also the use of these chiral diamines in the synthesis of chiral macrocycles and polymeric compounds. Accordingly, it is of interest to present an account of literature reports on the reductive coupling of imines.

3.1.1 Reductive coupling of imines mediated by the transition metal reagents:

Seebach and coworkers[2] reported that the reductive coupling of aldimines **1** (Scheme 1a) or iminium ions **3** (Scheme 1b), prepared *in situ*, gave the corresponding vicinal diamines **2** or **4** by using a low-valent titanium reagent. It was observed that the diastereoselectivities realized in these cases are only low to moderate.

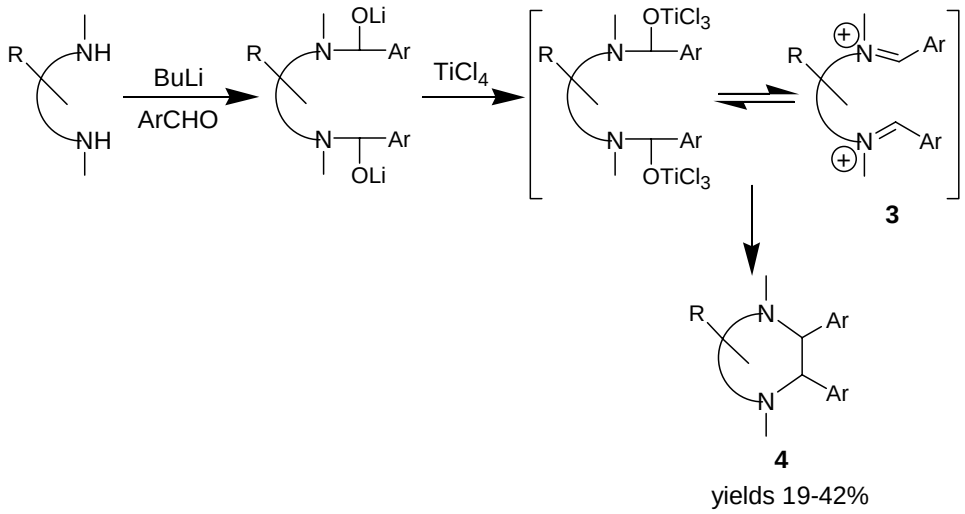
Scheme 1a



1
Ar = aryl

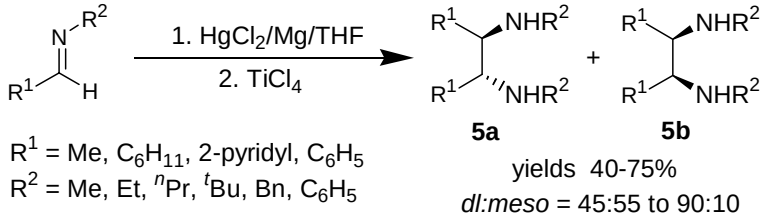
2
yields 50-79%
dl:meso = 5.5:4.5 to 6:1

Scheme 1b



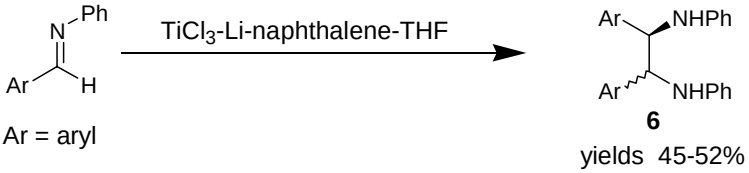
Symmetrical vicinal *dl*-diamines **5a** were prepared from the corresponding imines and the low-valent titanium species, generated by the action of $TiCl_4$ on amalgamated magnesium. The racemic diamines were obtained in moderate to good yields and good selectivity (Scheme 2).[3]

Scheme 2



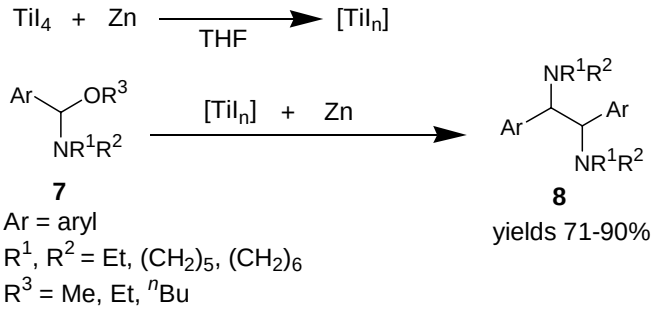
It was found that the reductive coupling of aldimines gave the corresponding vicinal diamines **6** using the low-valent titanium reagent prepared from $TiCl_3$-Li-naphthalene-THF (Scheme 3).[4]

Scheme 3



An efficient method for the preparation of vicinal tertiary diamines **8** by reductive coupling of aminoacetals **7** using a low-valent titanium iodide species was reported. However, the selectivity realized in this reaction was only very low to moderate (Scheme 4).[5]

Scheme 4



7

Ar = aryl

R^1, R^2 = Et, $(CH_2)_5$, $(CH_2)_6$

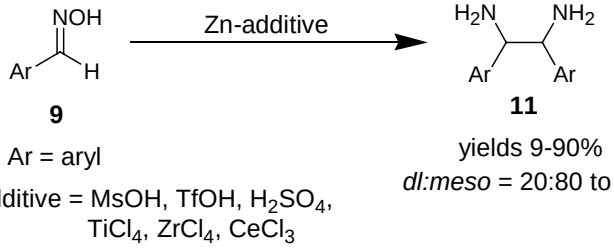
R^3 = Me, Et, ^{n}Bu

8

yields 71-90%

Kise *et al.*[6] reported that the reductive coupling of aromatic oximes **9** and azines **10** using Zn-MsOH or Zn-$TiCl_4$ reagents afforded the corresponding 1,2-diamines **11** in good yields with good selectivity. The reductive coupling with Zn-MsOH gave *meso*-1,2-diamines selectively, whereas *dl*-1,2-diamines were formed selectively by the reduction with Zn-$TiCl_4$ (Scheme 5).

Scheme 5



9

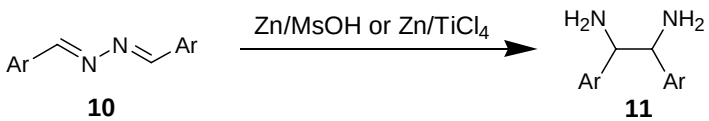
Ar = aryl

additive = MsOH, TfOH, H_2SO_4, $TiCl_4$, $ZrCl_4$, $CeCl_3$

11

yields 9-90%

dl:meso = 20:80 to 67:33



10

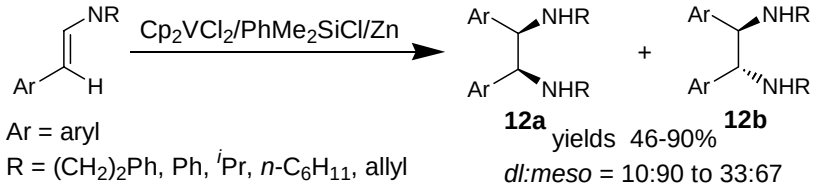
Ar = aryl

11

	Zn/MsOH	$Zn/TiCl_4$
yields of **11**	2-62%	55-73%
dl:meso	20:80 to 44:56	70:30 to 82:18

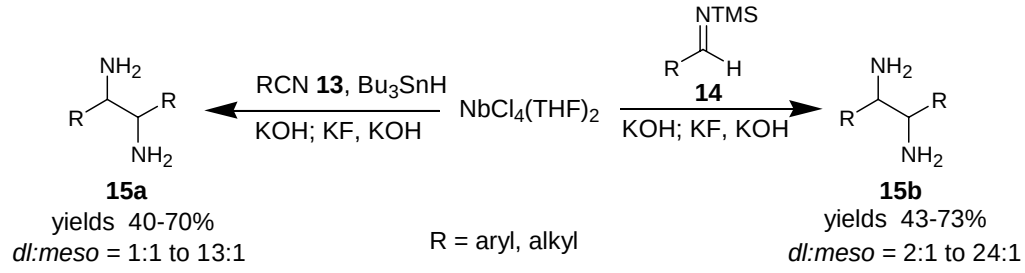
A Cp_2VCl_2-catalyzed *meso*-selective pinacol coupling reaction of aldimines in the presence of chlorosilane and zinc metal was reported (Scheme 6).[7]

Scheme 6



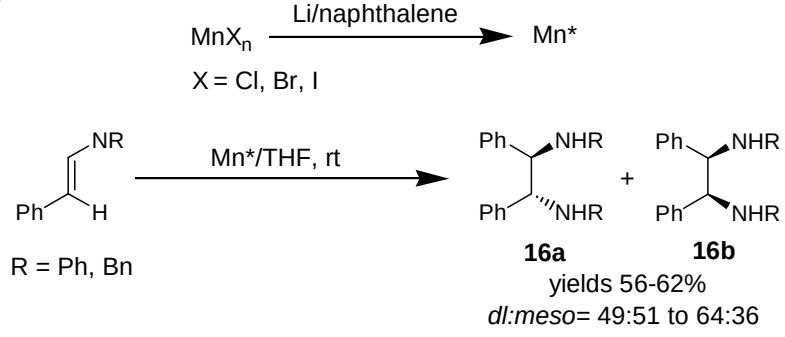
The reductive coupling of nitriles **13** or *N*-(trimethylsilyl) imines **14** gave the vicinal diamines **15a** or **15b**, respectively in the presence of the niobium reagent, $NbCl_4(THF)$. The diamines were obtained in moderate to good yields with moderate to good *dl* selection (Scheme 7).[8]

Scheme 7



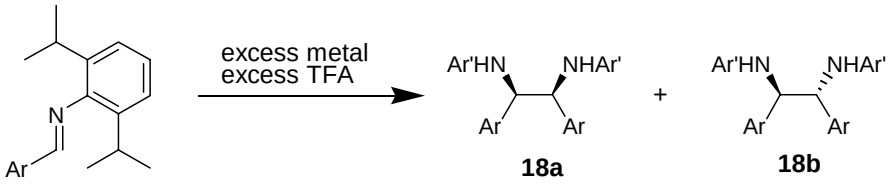
A highly reactive manganese-mediated pinacol coupling of aldimines afforded the corresponding vicinal diamines **16** in good yields and with moderate to good diastereoselection. The highly reactive manganese (Mn*) was prepared by the reduction of anhydrous manganese halides with lithium using naphthalene as an electron carrier (Scheme 8).[9]

Scheme 8



Reductive coupling of highly hindered *N*-arylimines **17** was mediated by using various metals (Mn, Mg, Zn) and trifluoroacetic acid in excess amounts (Scheme 9).[10]

Scheme 9



17 **18a** **18b**

yields 22-95%

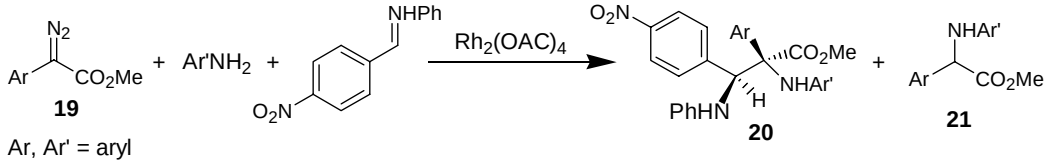
metal = Mn, Mg, Zn

TFA = trifluoroacetic acid

dl:meso = 14:86 to 49:51

Recently,[11] it was reported that the reaction of methyl phenyldiazoacetate **19** with arylamine and imine in the presence of dirhodium acetate gave the *erythro* diastereomer of methyl 1,2-diaryl-1,2-diaminopropanoate **20** with excellent stereochemical preferences (Scheme 10).

Scheme 10



19 **20** **21**

Ar, Ar' = aryl

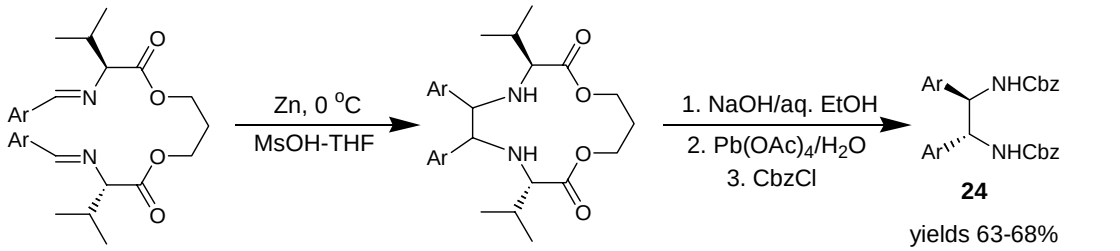
20:**21** = 40:60 to 96:4

isomer ratio of **20**

erythro:threo = 88:12 to >97:3

Shono *et al.*[12] reported a stereoselective synthesis of (1*R*,2*R*)-diarylethylene diamines **23** by the reductive intramolecular coupling of chiral aromatic diimines **22** using zinc-methanesulfonic acid reagent system as reductant (Scheme 11).

Scheme 11



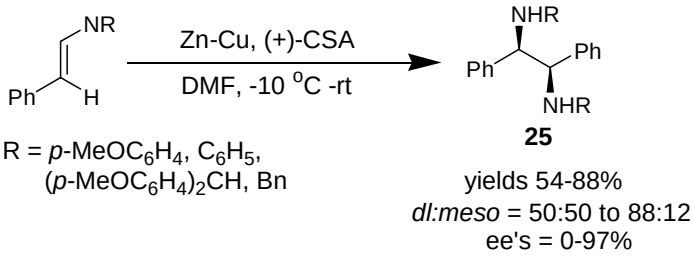
22 **23** **24**

yields 63-68%

(*R*,*R*):(*R*,*S*) = 72:28 to 97:3

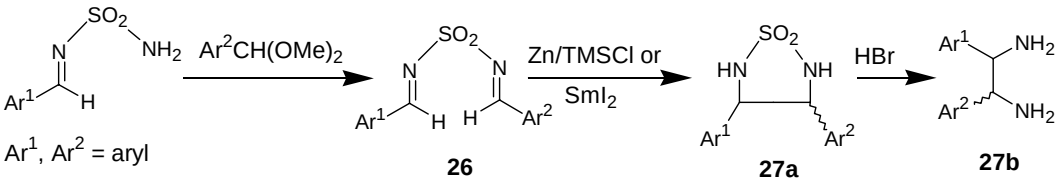
A highly enantioselective imino pinacol coupling approach for the synthesis of 1,2-diphenylethylenediamine derivatives **25** by the reaction of Zn-Cu couple with imines in the presence of (+)-camphorsulfonic acid (CSA) was reported (Scheme 12).[13]

Scheme 12



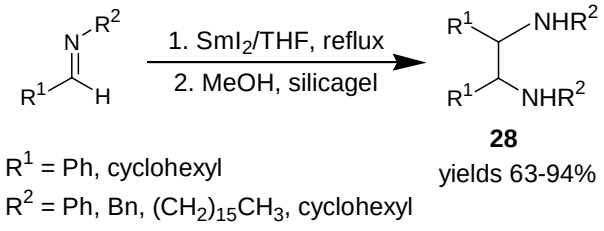
Synthesis of unsymmetrical vicinal diamines **27** by the intramolecular reductive cross coupling of unsymmetrical dibenzylidene sulfamides **26** has been reported. The reaction was promoted by the Zinc-trimethylsilyl chloride reagent system or samarium diiodide (Scheme 13).[14]

Scheme 13



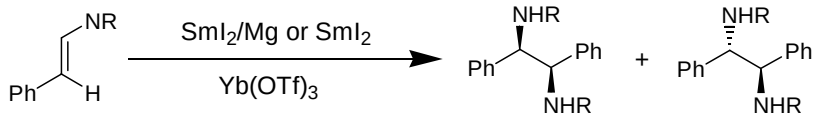
Samarium diiodide mediated reductive coupling of imines to obtain the corresponding vicinal diamines **28** was reported (Scheme 14).[15]

Scheme 14



It was reported that the reductive coupling of imines gave the 1,2-diphenyl-1,2-diaminoethanes **29** with moderate to good diastereoselection in the presence of SmI_2 and $Yb(OTf)_3$ (Scheme 15).[16]

Scheme 15



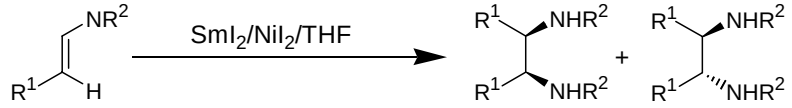
R = Bn, CH(Ph)Me
CH(1-naphthyl)Me

29a **29b**

yields 23-96%
syn:*anti* = 50:50 to >98:2

Samarium diiodide and catalytic amount of nickel diiodide reagent system was found to be efficient for the homocoupling reaction of imines (Scheme 16).[17]

Scheme 16

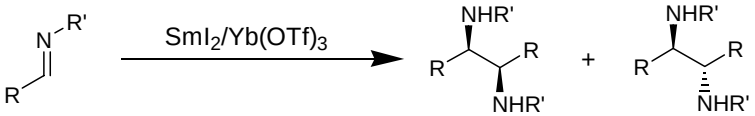


R^1 = aryl
R^2 = aryl, alkyl

yields 85-98%
dl:meso = 28:72 to 53:47

It was found that samarium(II) iodide and Lewis acid or Zn/MsOH reagent systems promoted the inter- or intramolecular reductive coupling of imines to give the corresponding C_2-symmetrical diamines **30** (Scheme 17a) or **31** (Scheme 17b) with moderate to good diastereoselection.[18]

Scheme 17a

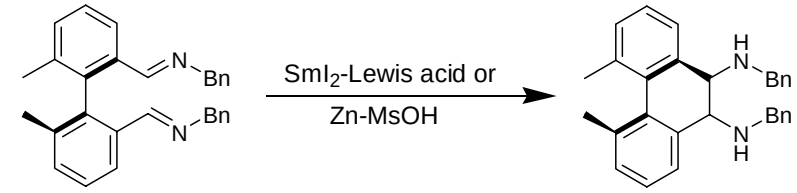


R = aryl, cyclohexyl
R' = aryl, ^{t}Bu, *CH(Me)Ph

30a **30b**

yields 14-88%
syn:anti = 55:45 to >98:2

Scheme 17b



Lewis acid = $Yb(OTf)_3$, $BF_3{\cdot}Et_2O$, HMPA

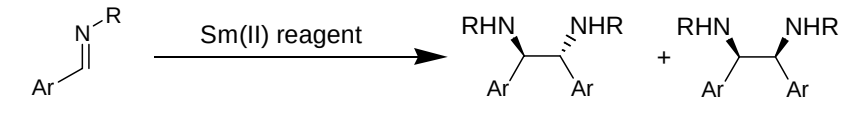
31

yields 5-51%

trans:*cis* = 70:30 to >98:2

A series of Sm(II)-based reagents were tested for the reductive coupling of aldimines and ketimines (Scheme 18).[19]

Scheme 18



Ar = aryl

R = Bn, ^{n}Bu

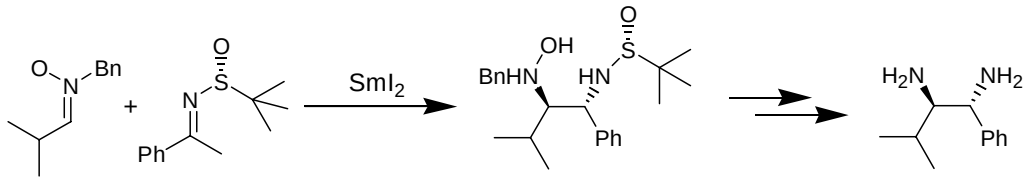
yields 65-95%

dl:*meso* = 50:50 to 84:16

Sm(II) reagent: $SmBr_2$, SmI_2, $Sm\{N(SiMe_3)_2\}_2$, SmI_2/Et_3N, SmI_2/HMPA

SmI_2-mediated reductive cross-coupling of nitrones **32** and chiral *N*-*t*-butanesulfinyl imine **33** afforded the unsymmetrical diamine **34**, which was converted into optically pure diamine **35** (Scheme 19).[20]

Scheme 19

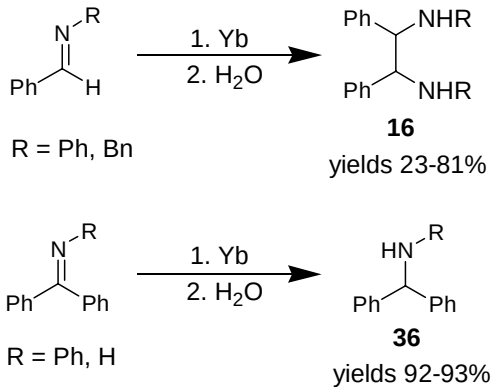


32 **33** **34** **35**

>99% ee

Reductive coupling of aldimines gave the 1,2-diaminoethane derivatives **16** in good yields by the reaction with ytterbium metal. Whereas ketimines were reduced to the corresponding amines **36** under the reaction conditions (Scheme 20).[21]

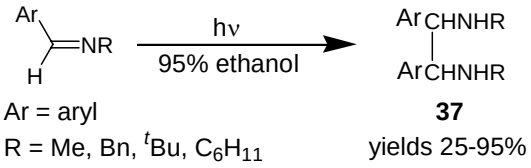
Scheme 20



3.1.2 Reductive coupling of imines by using other methods:

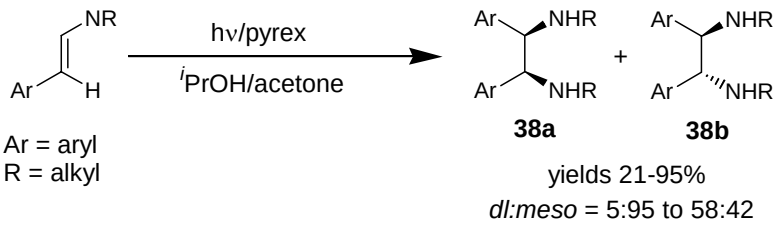
In 1969, it was reported that photoreduction of *N*-alkylimines afforded the corresponding vicinal diamines **37** in good yields (Scheme 21).[22]

Scheme 21



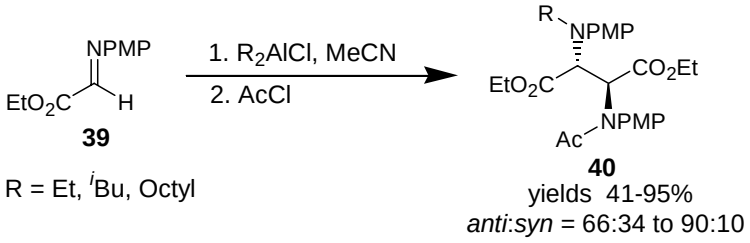
Photoreductive coupling of aldimines afforded the C_2-symmetrical diamines **38** in good yields with moderate to good *meso* selectivity (Scheme 22).[23]

Scheme 22



N-Alkylation-coupling reactions of the imines **39**, derived from glyoxalate esters, in the presence of dialkylaluminium chloride afforded the *N*-monoalkylated 1,2-diamines **40** in good yields with moderate to good *anti* selectivity (Scheme 23).[24]

Scheme 23



39

R = Et, ^{i}Bu, Octyl

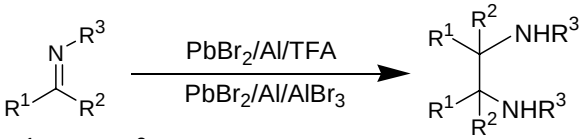
40

yields 41-95%

anti:*syn* = 66:34 to 90:10

Reductive dimerization of *N*-alkylimines into vicinal diamines **41** was performed by the action of a catalytic amount of lead(II) bromide and aluminium in THF containing trifluoroacetic acid (TFA) or aluminium(III) bromide (Scheme 24).[25]

Scheme 24



R^1 = aryl, R^2 =H

R^1,R^2 = cyclohexyl

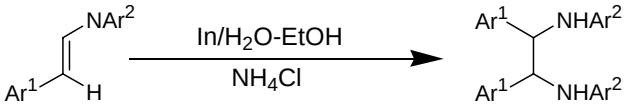
R^3 = Bn, ^{i}Pr

41

yields 62-90%

Aldimines were reductively coupled by indium to vicinal diamines **42** in aqueous ethanol in good yields (Scheme 25).[26]

Scheme 25



Ar^1, Ar^2 = aryl

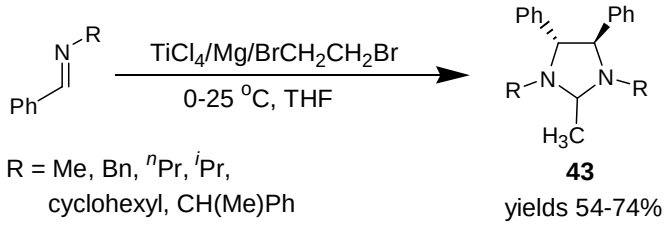
42

3.1.3 Reductive coupling of imines reported from this laboratory:

It was reported from this laboratory that the reductive coupling of imines could be achieved by the use of low-valent titanium reagents. It was found that the reaction

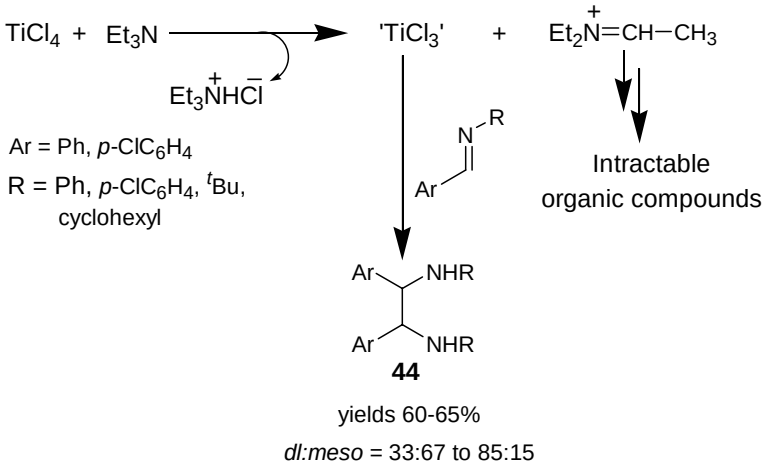
of *N*-alkylimines with the low-valent titanium reagent, prepared *in situ* using $TiCl_4/Mg/BrCH_2CH_2Br$ reagent system in THF, resulted in the synthesis of 2-mehtyl imidazolidines **43** (Scheme 26).[27]

Scheme 26



The Ti(III) species prepared using the $TiCl_4/Et_3N$ reagent system was utilized for *dl*-selective imine coupling to obtain the corresponding vicinal diamines **44** (Scheme 27).[28]

Scheme 27



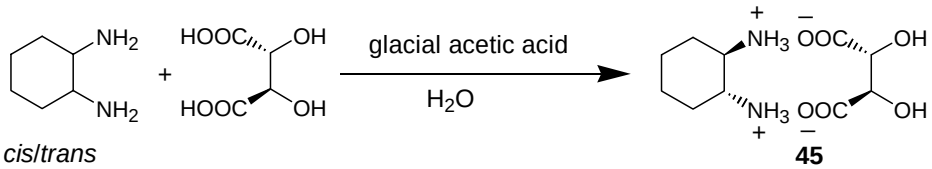
In continuation of these studies, we have undertaken efforts to synthesize C_2-symmetric chiral diamines by using low-valent titanium reagents and the corresponding chiral imines. The results are described in this Chapter.

3.2 Results and Discussion

3.2.1 Intramolecular reductive coupling of chiral diimines containing cyclohexyl moiety using low-valent titanium species:

The *cis*/*trans* mixture of 1,2-diaminocyclohexane was resolved using *L*-(+)-tartaric acid following a reported procedure (Scheme 28a).[29] The (1*R*,2*R*)-1,2-diaminocyclohexane mono-*L*-(+)-tartrate salt **45** obtained in this way was treated with aqueous saturated KOH to give (1*R*,2*R*)-1,2-diaminocyclohexane **46** in good yield with >98% ee (Scheme 28b). The optically active (1*R*,2*R*)-1,2-diaminocyclohexane **46** was then reacted with aldehydes in the presence of molecular sieves to obtain chiral diimines **47a-47g** (Scheme 29). The diimines obtained in this way, were crystallized from petroleum ether or ethanol.

Scheme 28a

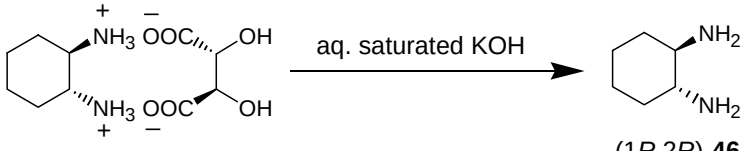


cis/*trans*

45

96% yield, >99% ee

Scheme 28b

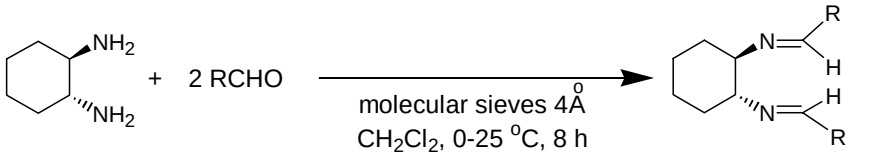


45

(1*R*,2*R*)-**46**

95% yield, >98% ee

Scheme 29



(1*R*,2*R*)-**46**

R = aryl, ^{i}Pr

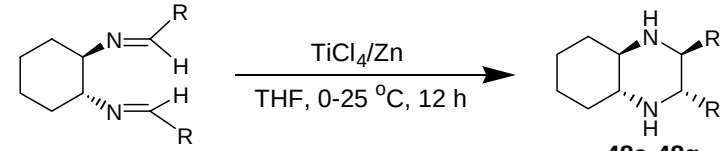
(1*R*,2*R*)-**47a-47g**

85-92%

The (*E*,*E*) configuration may be assigned for the imine double bonds comparing the stability expected for the (*E*,*E*)-, (*E*,*Z*)- and (*Z*,*Z*)-diimines.

We have examined the reactivity of different chiral diimines **47a-47g**, using the low-valent titanium species, prepared using $TiCl_4$ and Zn in THF at 0-25 ^oC. The corresponding 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes **48a-48g** were obtained (Scheme 30). The results are summarized in Table 1. The yields are in the range of 70-86% for diimines derived from aromatic aldehydes. In the case of diimine obtained from isobutyraldehyde, the yield was poor (36%).

Scheme 30

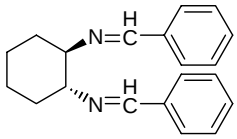
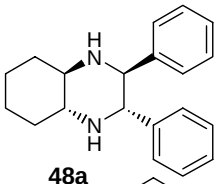
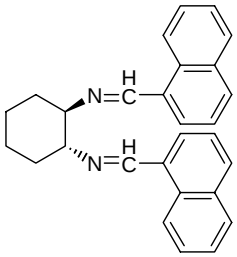
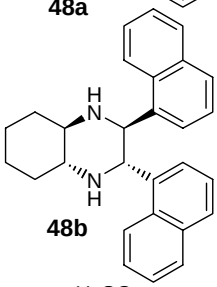
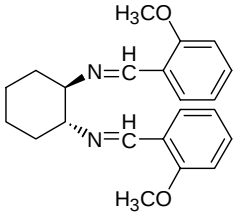
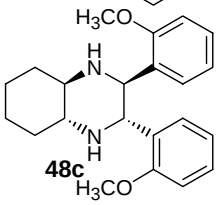
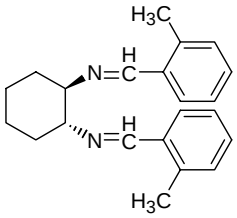
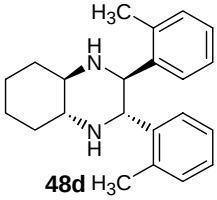
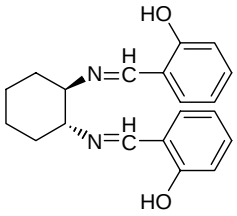
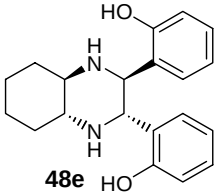
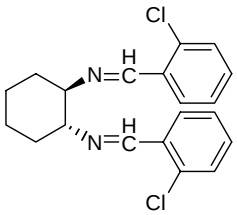
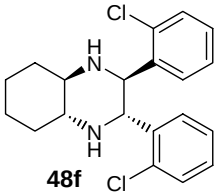
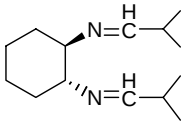
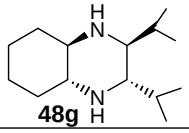


(1*R*,2*R*)-**47a-47g** **48a-48g** 75-86%

Only one of the diastereomers was obtained in this reaction. X-ray structure analysis of the compound **48b** revealed that the new chiral centers have *trans* stereochemistry. The absolute configurations at C1, C3, C4 and C6 chiral centers in the crystal structure of **48b** were found to be *R*, *S*, *S* and *R*, respectively (PLATON[30] program, A. L. Spek, version 210103). The ORTEP diagram of the compound **48b** is shown in Figure 1. The crystal structure data of the compound (1*R*,3*S*,4*S*,6*R*)-**48b** are summarized in Table 2 and Table A9 (Appendix II). The $[\alpha]_D$ value of the compound **48b** is $+200^o$ (*c* 1, $CHCl_3$).

It was of interest to assign the absolute configuration of the compound **48e**, which exhibited a negative $[\alpha]_D$ value i.e. -4^o (*c* 1, $CHCl_3$). Accordingly, the structure of the compound **48e** was also analyzed by the X-ray crystal structure data. The analysis revealed that the absolute configurations at C1, C3, C4 and C6 chiral centers in **48e** were also found to be *R*, *S*, *S* and *R*, respectively (PLATON[30] program A. L. Spek, version 210103).

Table 1 Reaction of chiral diimines with the $TiCl_4$/Zn reagent system

S. No.	Substrate	Product	Yield (%)	$[\alpha]_D^{25}$ (c, solvent)
1		 **48a**	75	-77.6 (1, $CHCl_3$)
2		 **48b**	85	+200.0 (1, $CHCl_3$)
3		 **48c**	86	+8.0 (1, $CHCl_3$) -17.0 (1, MeOH)
4		 **48d**	75	-28.0 (1, $CHCl_3$)
5		 **48e**	70	-4.0 (1, $CHCl_3$)
6		 **48f**	78	-56.4 (0.33, $CHCl_3$)
7		 **48g**	36	-28.64 (0.83, $CHCl_3$)

It was also found from the analysis that there are intramolecular hydrogen bonding between the hydroxy group of phenyl and nitrogen of heterocyclic system (O–H···N; O–H = 0.82 Å, H···N = 1.95 Å, O···N = 2.66 Å, O–H···N= 145°). The ORTEP diagram of the compound **48e** is shown in Figure 2. The crystal structure data of the compound (1*R*,3*S*,4*S*,6*R*)-**48e** are summarized in Table 3 and Table A10 (Appendix II).

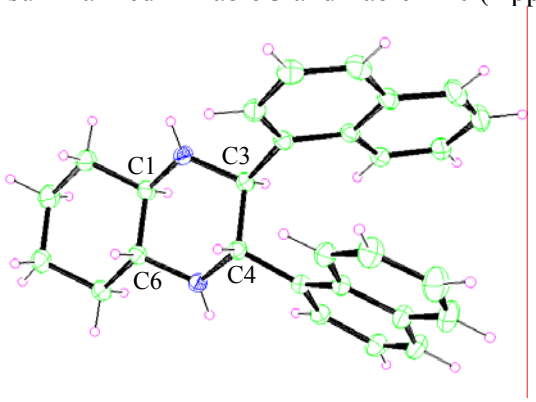


Figure 1 ORTEP representation of the crystal structure of the compound **48b**

(Thermal ellipsoids are drawn at 20% probability)

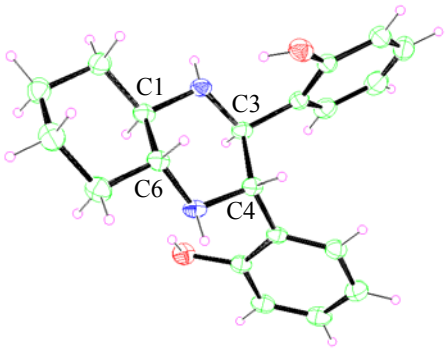


Figure 2 ORTEP representation of the crystal structure of the compound **48e**

(Thermal ellipsoids are drawn at 20% probability)

The crystal structure analysis of **48a** has been reported.[31] By comparison of ^{1}H-NMR (400 MHz) data, *trans* configurations for the aryl and isopropyl substituents for compounds **48c**, **48d**, **48f** and **48g** were assigned as they exhibit data similar to those reported for **48a**.

Table 2 X-ray data collection and structure refinement for (1*R*,3*S*,4*S*,6*R*)-3,4-dinaphthyl-2,5-diazabicyclo[4.4.0]decane **48b**

Empirical formula	$C_{28}H_{28}N_2$
Formula weight	392.55
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.0064(8) Å, α = 90˚
	b = 8.6950(7) Å, β = 101.5020(10)˚
	c = 12.6856(10) Å, γ = 90˚
Volume	1081.55(15) $Å^3$
Z	2
Calculated density	1.205 Mg/m^3
Absorption coefficient	0.070 mm^{-1}
F(000)	420
Crystal size	0.57 X 0.41 X 0.26 mm
θ range for data collection	1.64 to 28.25˚
Limiting indices	$-13 \le h \le 13$; $-11 \le k \le 11$; $-16 \le l \le 16$
Reflections collected/unique	12406 / 4926 [R(int) = 0.0408]
Completeness to θ = 28.25	95.2%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	4926 / 1 / 271
Goodness-of-fit on F^2	1.034
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0493$, $wR_2 = 0.1352$
R indices (all data)	$R_1 = 0.0599$, $wR_2 = 0.1430$
Largest diff. peak and hole	0.333 and -0.278 $eÅ^{-3}$

Table 3 X-ray data collection and structure refinement for (1*R*,3*S*,4*S*,6*R*)-3,4-bis(2-hydroxyphenyl)-2,5-diazabicyclo[4.4.0]decane **48e**

Empirical formula	$C_{20}H_{24}N_2O_2$
Formula weight	324.41
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$C2_1$
Unit cell dimensions	a = 25.608(2) Å, α = 90˚
	b = 5.1724(15) Å, β = 102.397(8)˚
	c = 13.0380(15) Å, γ = 90˚
Volume	1686.7(5) Å ^{3}
Z	4
Calculated density	1.278 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	696
Crystal size	0.50 X 0.30 X 0.24 mm
θ range for data collection	1.60 to 29.96˚
Limiting indices	$0 \le h \le 35$; $0 \le k \le 7$; $-18 \le l \le 17$
Reflections collected/unique	2748 / 2707 [R(int) = 0.0157]
Completeness to θ = 29.96	100%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	2707 / 3 / 227
Goodness-of-fit on F^2	1.021
Final *R* indices [I> 2σ (I)]	R_1 = 0.0522, wR_2 = 0.0865
R indices (all data)	R_1 = 0.1192, wR_2 = 0.1065
Largest diff. peak and hole	0.115 and -0.149 eÅ^{-3}

The mechanism depicted in the Figure 3 may explain the asymmetric induction at the newly formed chiral centers, (*S*,*S*) at C3,C4, observed for the compounds **48a**, **48b** and **48e**. The substrate chiral (*E*,*E*)-diimine **47** upon reaction with the low-valent titanium would give a diradical anion of type **TS-I** or **TS-II**. In **TS-I** the 1,3-diaxial repulsions are expected to be less to that in **TS-II**. Hence, the low-energy transition state **TS-I** would undergo ring closure to give *trans* stereochemistry and *S*,*S* absolute configurations of the newly formed chiral centers. Obviously, the less favorable high-energy **TS-II** leads to the diastereomer with *trans* stereochemistry and *R*,*R* absolute configurations at the new chiral centers. However, only one of the diastereomers was isolated in all these reactions.

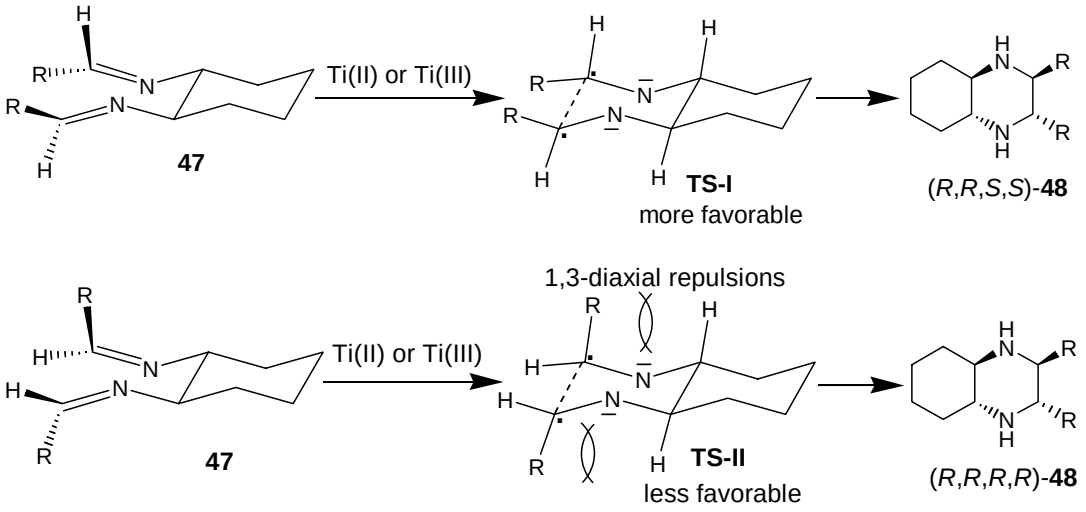


Figure 3 Mechanism to account for the diastereoselectivity

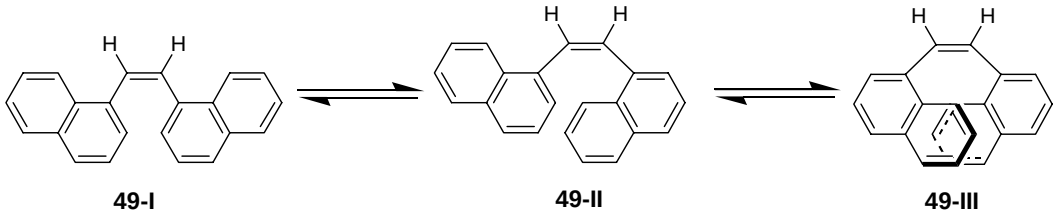
3.2.2 ^{13}C-NMR Studies of the chiral diamines containing cyclohexyl moiety 48a-48f:

We have also noticed some interesting features in the ^{13}C-NMR spectra (400 MHz) of products **48b** and **48c** containing unsymmetrical aryl groups. The C3,C4 carbons of the compound **48b** in the ^{13}C-NMR spectrum recorded at room temperature

gave a broad signal at 60.9 δ ppm. For the compound **48c**, the broad signal was observed for C3,C4 carbons at 60.0 δ ppm.

It was thought that these observations might be due to a conformational phenomenon. For example, it has been observed that the *cis*-1,2-bis-α-naphthylethylene (**49-I, 49-II** and **49-III**) can exist as three possible conformers, due to Hula twist (Scheme 31).[32]

Scheme 31

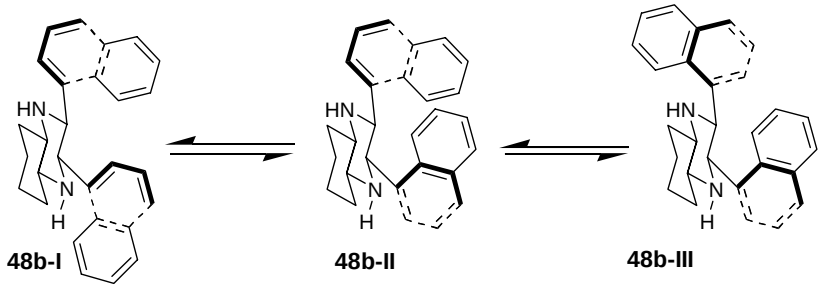


49-I **49-II** **49-III**

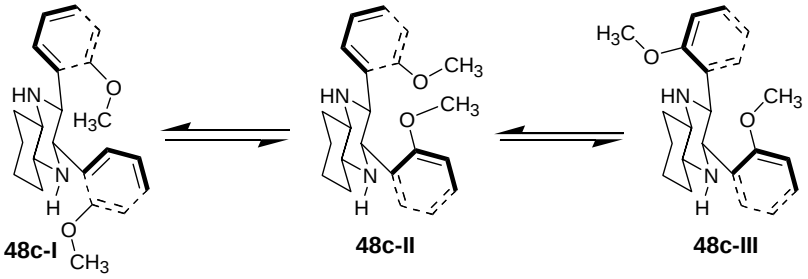
A similar probability may exist in the case of compounds **48b** and **48e**, due to barrier to rotation of the carbon-aryl bond. However, such interactions here would be expected to be present in lesser extent compared to the planar system as in **49-I, 49-II** and **49-III**.

In compound **48b**, the possibilities of the existence of rotamers with minimum energies are expected to be **48b-I**, **48b-II** and **48b-III**. Isomer **48b-II** is expected to be in lower energy compared to the degenerate isomers **48b-I** and **48b-III** (Scheme 32a). The X-ray crystal structure analysis of **48b** also revealed that it has the structure of the conformer **48b-II**. A similar explanation can be given for the spectral behavior of the compound **48c**, considering the steric requirements of the methoxy groups (Scheme 32b).

Scheme 32a



Scheme 32b



The ^{13}C-NMR spectra (400 MHz) of compounds **48b** and **48c** were recorded at different temperatures to examine this possibility (Figure 4 for **48b** and Figure 5 for **48c**).

The C3,C4 carbon atoms of compound **48b** exhibited the broadening of signals. The signals were broad at 60.9 δ ppm for C3,C4 and 62.2 δ ppm for C1,C6 at room temperature (20 ^{o}C). Broad signals were also observed for aromatic carbons at this temperature. At 0 ^{o}C, these signals became sharp with the appearance of small peaks besides the main signals. The expected structures of the conformers are depicted in Scheme 32a. Extra signals with less intensity were also obtained in the aromatic region. Then, the spectra were recorded at –20 ^{o}C, -40 ^{o}C, –60 ^{o}C and –80 ^{o}C for the compound **48b**. The spectral behavior was almost the same as it was at 0 ^{o}C, except that all the peaks were sharp at lower temperatures. However, the peaks for the carbons C7,C10 and C8,C9 were also split at these temperatures (Figure 4). The variable temperature (-80 to 20 ^{o}C) ^{13}C-NMR spectra of the compound **48b** are shown in Figure 4.

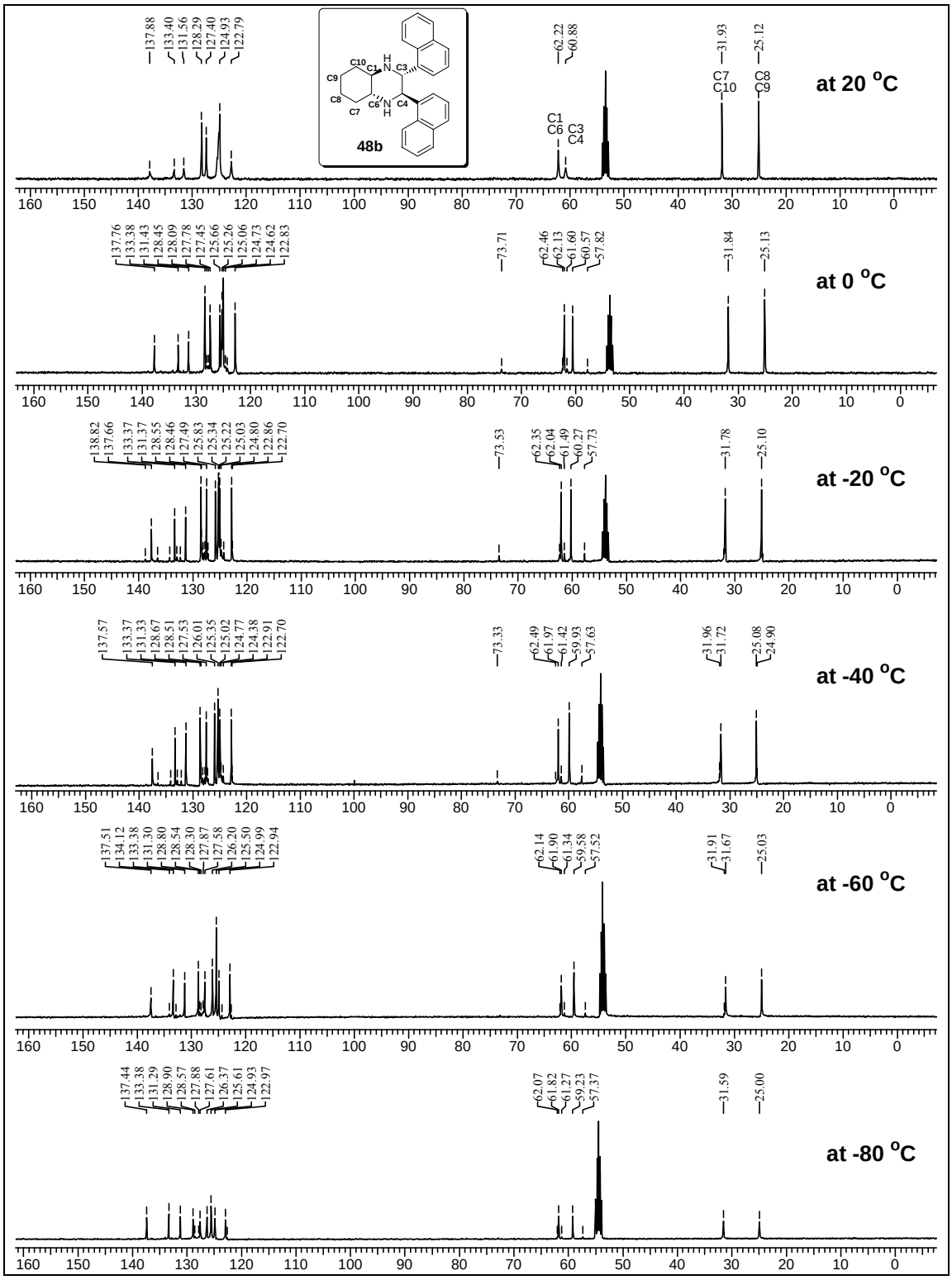


Figure 4 Variable temprature (-80 to 20 °C) ^{13}C-NMR spectra of the compound **48b**

In the case of the compound **48c** at 20 ^{o}C, a broad peak with less intensity was observed at 60.0 δ ppm for C3,C4 carbon atoms and a sharp peak at 61.9 δ ppm for C1,C6 carbon atoms. These two signals appeared with little broadening and with less intensity at 0 ^{o}C. The broadening of the peaks was also observed in the aromatic region at 129.0 δ ppm and 129.5 δ ppm. At -20 ^{o}C, the signals appeared with more broadness at 57.2, 61.7, 128.3, 129.3, 130.9 and 156.6 δ ppm. At –40 ^{o}C extra broad peaks with less intensity were obtained besides the major peak. Similar trend in the appearance of signals was also observed for aromatic carbons. The expected structures of the possible stable rotamers are depicted in Scheme 32b. When the experiment was run at –60 ^{o}C the extra peaks appeared sharper. Almost every peak was split into 2-3 peaks at this temperature, suggesting that the possibility of the existence of rotamers. However, the ^{13}C-NMR spectra obtained at +40 ^{o}C and +50 ^{o}C did not give any further information, except the peaks at +20 ^{o}C were observed with little more intensity and sharpness. The variable temperature (-60 to 50 ^{o}C) ^{13}C-NMR spectra for the compound **48c** are presented in Figure 5.

The variable temperature ^{13}C-NMR spectra (-60 ^{o}C, -40 ^{o}C, -20 ^{o}C, 0 ^{o}C, 20 ^{o}C, 40 ^{o}C, 50 ^{o}C) were also recorded for the compound **48a** containing unsubstituted phenyl group. Here, as it was expected, neither extra peaks nor broad signals were observed in the spectra at various temperatures. This is in accordance with the expectation that compounds containing unsymmetrical groups with steric hindrance to rotation would only exhibit such isomerism.

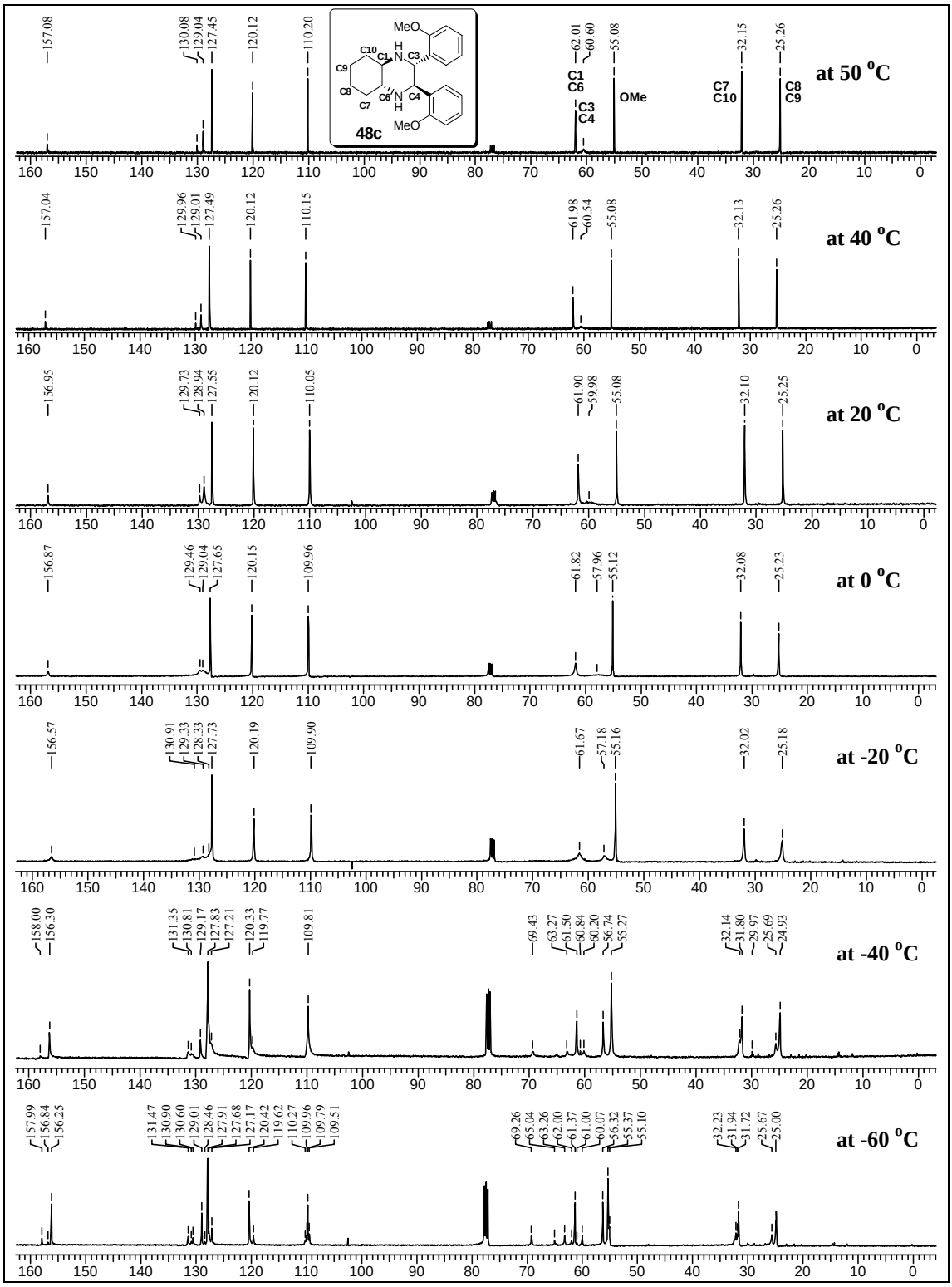


Figure 5 Variable temprature (-60 to 50 °C) ^{13}C-NMR spectra of the compound **48c**

The ^{13}C-NMR spectra were recorded for **48d**, which contains *ortho* methyl groups on the phenyl substituents at different temperatures (-60 ^{o}C, -40 ^{o}C, -20 ^{o}C, 0 ^{o}C, 20 ^{o}C, 40 ^{o}C, 50 ^{o}C). However, no extra signals were observed for this compound at all the temperatures, except that the broad peak became sharper at <0 ^{o}C. Presumably, the rotational barrier for the carbon-aryl bond may be relatively small in this case and it may be significant only with branched substituent like -OCH_3 as in **48c** or the naphthyl ring system as in **48b**.

Also, for the compound **48f**, with *ortho* chlorine substituents, no extra signal was obtained in the ^{13}C-NMR spectra recorded at different temperatures (-60 ^{o}C, -40 ^{o}C, -20 ^{o}C, 0 ^{o}C, 20 ^{o}C, 40 ^{o}C, 50 ^{o}C). Again, compound with unsymmetrical substituent like -Cl may not exhibit the phenomenon observed for –OCH_3 as the –Cl is not a branched substituent.

No broad peak was obtained for the compound **48e** in the ^{13}C-NMR spectrum (400 MHz) recorded at room temperature and no broad or extra signal was observed in the ^{13}C-NMR spectra recorded at various temperatures (-60 ^{o}C, -40 ^{o}C, -20 ^{o}C, 0 ^{o}C, 20 ^{o}C, 40 ^{o}C, 50 ^{o}C). Presumably, this compound may not exist in equilibrium with its rotamers due to restricted rotation about C-aryl bond. The hydrogen bonding between *ortho*-OH of phenyl and –NH of decalin may be the reason for the restricted rotation. X-ray single crystal structure analyses of the compound **48e** revealed that the existence of hydrogen bonding between the -OH and the –NH (O–H···N). The hydrogen of -OH participates in the hydrogen bonding (see p 171).

The observations of the ^{13}C-NMR spectra are summarized in Scheme 33 and Table 4.

Scheme 33

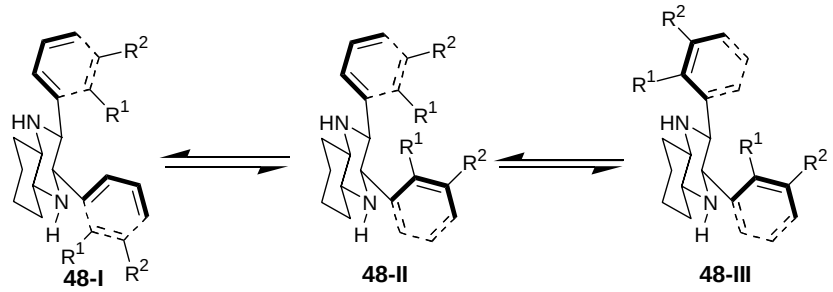


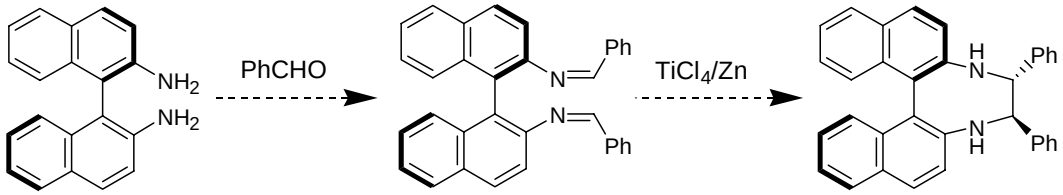
Table 4 Summary of the VT ^{13}C-NMR effects of the respective 3,4-disubstituted-2,5-diazabicyclo[4.4.0]decanes **48**

Entry	R^1, R^2	Variable temperature ^{13}C-NMR effect	Reason attributed for the effect
1	(**48a**) Ph, H	no effect	no isomers
2	(**48b**) CH=CH-CH=CH	effect was observed	high barrier of rotation
3	(**48c**) OMe, H	effect was observed	high barrier of rotation
4	(**48d**) CH_3, H	no effect	low barrier of rotation
5	(**48e**) OH, H	no effect	one stable conformation due to O–H···N bonding
6	(**48f**) Cl, H	no effect	low barrier of rotation

3.2.3 Reductive coupling of chiral 1,1'-binaphthyl-2,2'-diamine- (BINAM) derived imines:

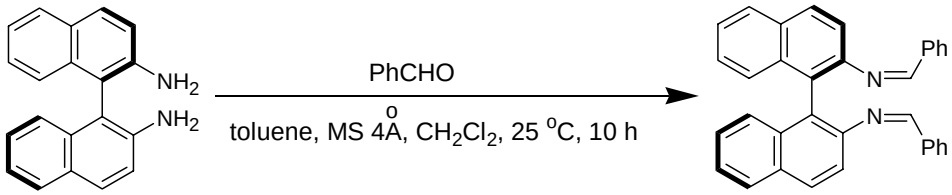
We have also examined the reactivity of chiral bisimines, prepared from optically active 1,1'-binaphthyl-2,2'-diamine (BINAM) and benzaldehyde, with the low-valent titanium reagents (Scheme 34).

Scheme 34



Accordingly, the chiral bisimine (*R*)-**51** was prepared from (*R*)-BINAM **50** and benzaldehyde in toluene in the presence of molecular sieves (Scheme 35).

Scheme 35

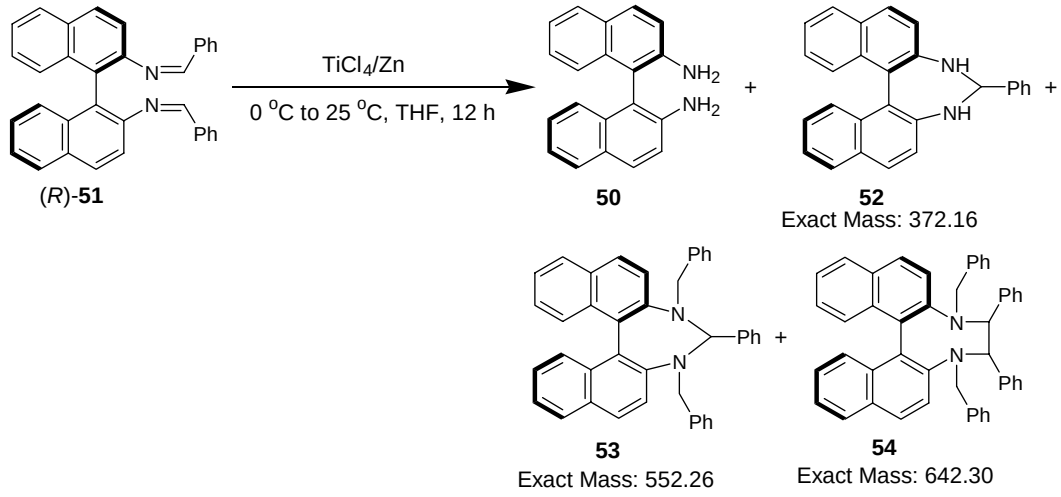


(*R*)-**50** (*R*)-**51**

The bisimine was then reacted with the low-valent titanium reagent, prepared using $TiCl_4$ and Zn in THF (Scheme 36). The desired coupled product diamine could not be isolated from the reaction mixture. The ^{1}H-NMR (400 MHz) spectrum of the reaction mixture exhibited broad peaks. The broad signals were also observed in the ^{13}C-NMR (400 MHz) spectrum. It was thought that the product would be a mixture of polymeric or macrocyclic products, formed by the intermolecular reductive coupling reaction. To examine this possibility, MALDI-tof spectrum (Figure 6) was run for the crude product. The spectrum showed major signals at 284, 373, 461, 552 and 642. The signal at 284 corresponds to BINAM **50**. The signal at 373 might have resulted from the M+1 of the product of **52**; a signal observed at 77.3 δ ppm in the ^{13}C-NMR spectra may be attributed to the tertiary carbon of **52**. The signal at 461 corresponds to the M+1 signal of the substrate **51**, bisimine of BINAM. The signal at 552 was attributed to the compound **53**; a peak at 77.4 δ ppm, which is expected for the tertiary carbon of

53, in the ^{13}C-NMR spectra supports the existence of this compound. Whereas the signal at 642 might be due to the reductively coupled product **54** (Scheme 36).

Scheme 36



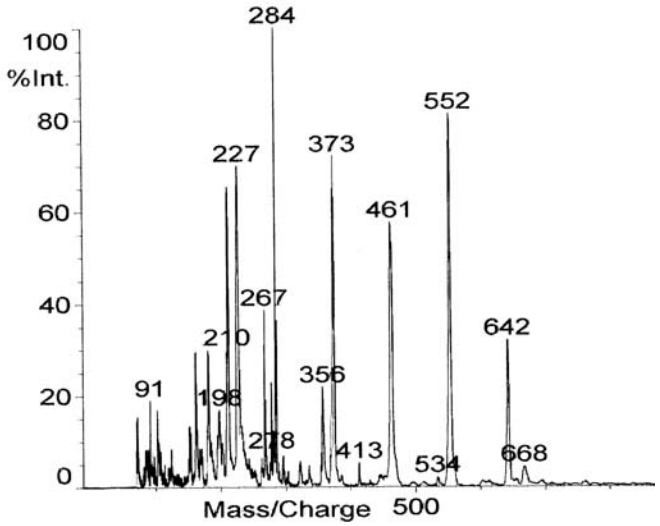


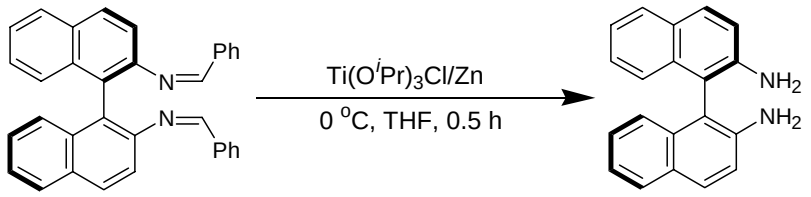
Figure 6 MALDI-tof spectrum of the mixture of the products **50-54** (Scheme 36)

The compound **52** might have formed via the hydrolysis of the starting diimine **51** during workup. The compounds **53** and **54** should have formed through reduction of the imine double bond and the mechanism of formation of these products is unclear.

As there was no macrocyclic or polymeric product observed in the above transformation, we thought of using mild conditions that may lead to the simple

intramolecular reductive coupling. Accordingly, the chiral diimine (*R*)-**51** was reacted with the less acidic $Ti(O^iPr)_3Cl$ and Zn at 0 ^oC for 0.5 h. However, the desired coupled product was not formed. Instead, the starting BINAM **50** was recovered in 78% yield (Scheme 37).

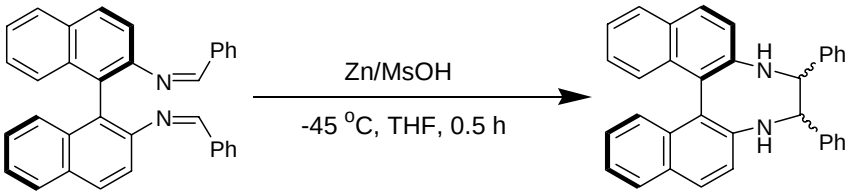
Scheme 37



(*R*)-**51** (*R*)-**50**

We have then carried out the reaction of diimine with zinc and methanesulfonic acid at –45 ^oC. The reductive coupled product **55** was obtained in 11% yield but there was no stereoselection (Scheme 38).

Scheme 38



(*R*)-**51** **55**
11%
dr = 1:1

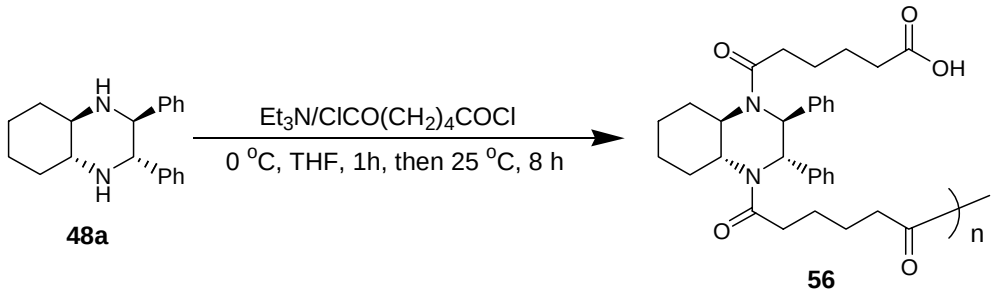
3.2.4 Synthesis of chiral polyamides and polyamines by the reaction of chiral diamines with dicarboxylic acid chloride spacers:

In recent years, synthesis of chiral polymers has been receiving growing research attention due to their potential applications.[34] Besides their structurally appealing features; chiral polymers have potential for applications in areas such as

nonlinear optics, polarized light emission, chiral sensing, chiral separation and asymmetric catalysis.[34]

We have undertaken efforts to synthesize chiral polymers and macrocycles by the reaction of the chiral diamines with achiral dicarboxylic acid chloride spacers. Initially, the reaction of chiral diamine **48a** with adipoyl chloride was studied (Scheme 39). The crude reaction mixture obtained was not soluble in common organic solvents except in CH_2Cl_2 and $CHCl_3$. The unreacted starting materials, if any, were removed by washing the crude product in ether, ethyl acetate and methanol.

Scheme 39



48a **56**

The IR, ^{1}H-NMR and ^{13}C-NMR spectral analyses of the product were carried out. The IR spectrum has shown the presence of carboxylic acid and amide functionalities: at 3478 (-OH), 1745 (C=O) and 1651 (N-C=O) cm^{-1}. However, the ^{1}H-NMR spectrum has shown only broad signals. Several signals were observed in the ^{13}C-NMR spectrum in the range 173-175 δ ppm, indicating the presence of different amide carbonyls.

The MALDI-tof spectrum (Figure 7) exhibited signals at m/z = 406, 517, 810, 920, 1323, 1727 and 2129. Clearly, no polymeric product is formed in this reaction and none of the products could be obtained in pure form.

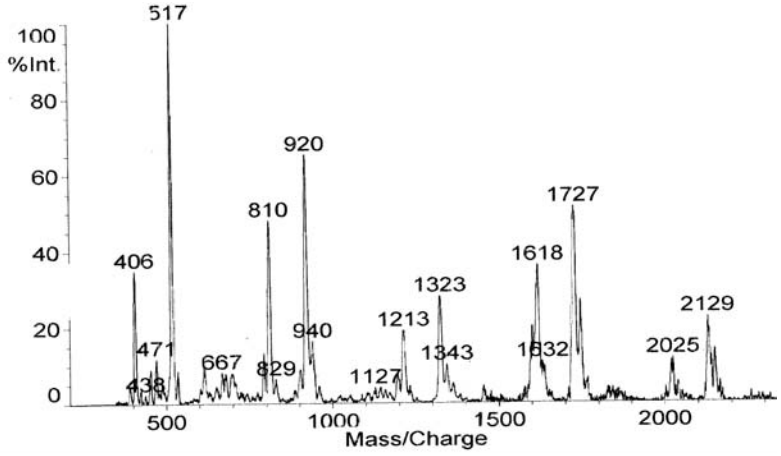
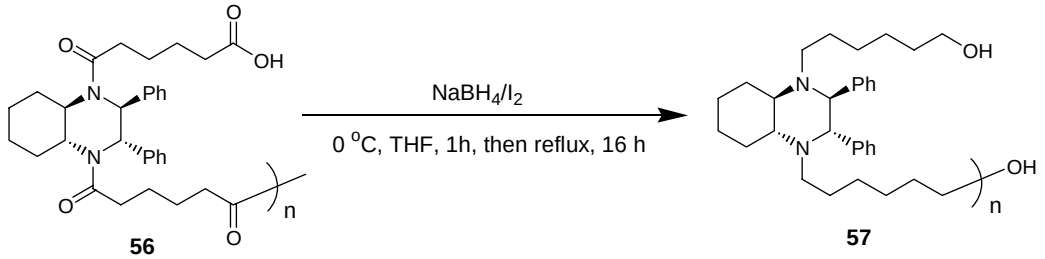


Figure 7 MALDI-tof spectrum of the mixture of oligomeric amides **56** (Scheme 39)

It was thought that it might be possible to isolate the products in pure form after reducing the crude product mixture of chiral oligomeric amides **56a-56f**, obtained in the reaction given in the Scheme 39. Accordingly, the crude product **56** was reduced using the $NaBH_4/I_2$ reagent system (Scheme 40).

Scheme 40



At this stage also no pure product could be isolated from the crude product **57**. We have then recorded the IR, ^{1}H-NMR and ^{13}C-NMR spectra for the crude product **57**. From these spectral data, it was confirmed that the product **56** was completely reduced to **57**: disappearance of IR signals for **56** in IR at 1745 (C=O) and 1651 (N-C=O) cm^{-1}. The MALDI-tof (Figure 8) spectrum was obtained for the product **57**. Major signals were observed at m/z = 490, 766, 865, 1240, 1615, 1990.

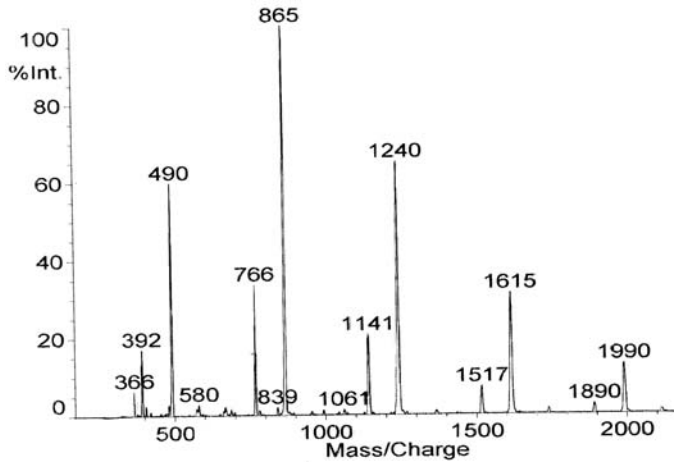
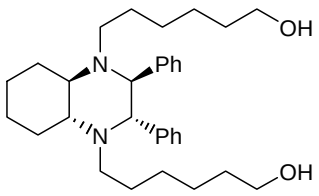


Figure 8 MALDI-tof spectrum of the mixture of oligomeric amino alcohols **57**

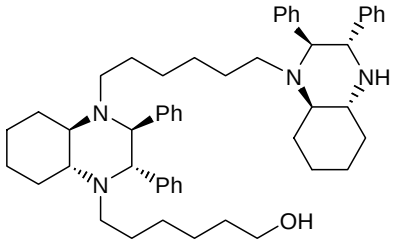
(Scheme 40 and Chart 1)

Some of the structures of the oligomeric amino alcohols **57a**-**57f**, which may be attributed to the signals observed in the MALDI-tof spectrum are depicted in the Chart 1.

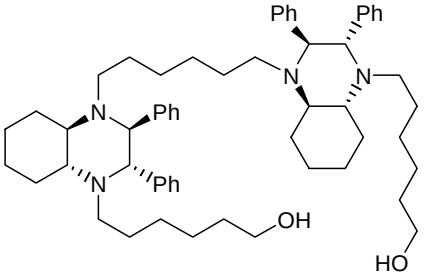
Chart 1



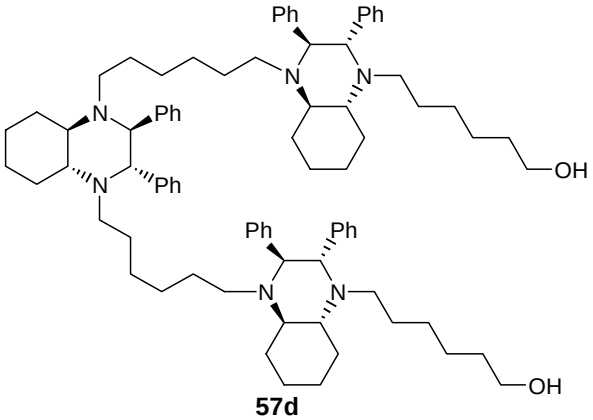
57a
Exact Mass: 492.37



57b
Exact Mass: 766.55

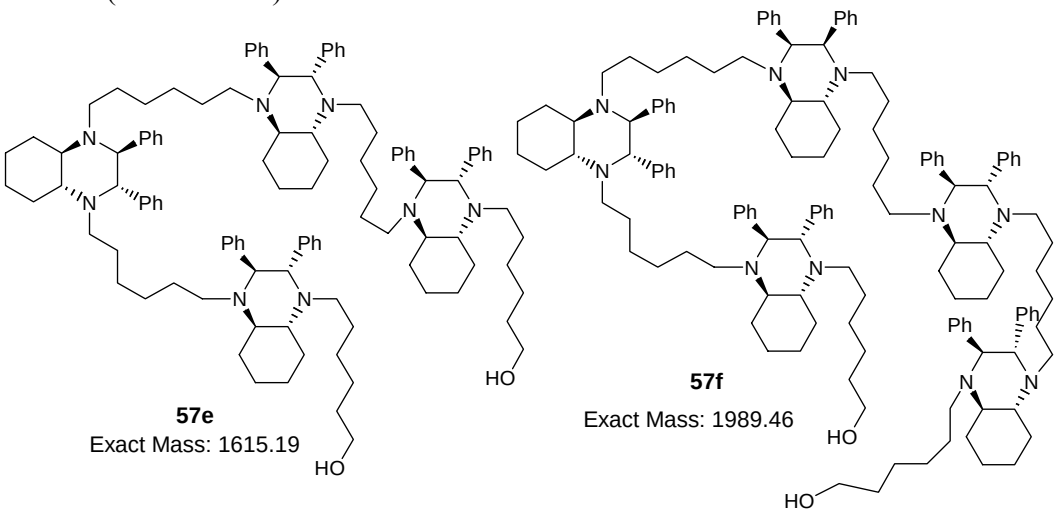


57c
Exact Mass: 866.64



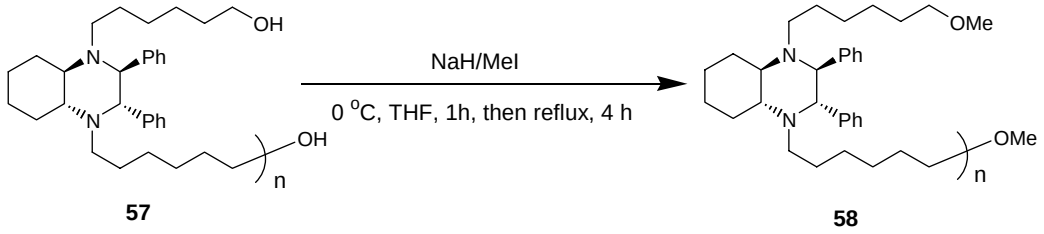
57d
Exact Mass: 1240.92

Chart 1 (….continued)



The *O*-methylated product **58** was prepared by the reaction of the chiral oligomeric amino alcohols **57** with the NaH/MeI reagent system (Scheme 41). The disappearance of the –OH stretch in the IR spectrum confirmed the formation of the product **58**.

Scheme 41



Further investigations are underway in this laboratory on the synthesis and applications of chiral oligomers and polymers containing the chiral 1,2-diaminocyclohexane and chiral binaphthyldiamine skeletons.

3.3 Conclusions

Intramolecular reductive coupling of optically active 1,2-diaminocyclohexane-derived imines to the corresponding C_2-symmetric diamines was achieved using the $TiCl_4$/Zn reagent system. The variable temperature ^{13}C-NMR spectral studies of the products **48** were carried out. The crystal structures of the compounds **48b** and **48e** were analyzed. The reaction of diimine (*R*)-**51**, derived from BINAM, with the low-valent titanium reagent system led to a mixture of coupling products **52-54**. The reductive coupling of chiral *N,N'*-dibenzylidene-BINAM to the corresponding diamine **55** (11% yield) was mediated by Zn/MsOH reagent system. Chiral oligomeric amides were prepared by the reaction of chiral diamine **48a** with adipoyl chloride. The chiral oligomeric amides were reduced to the corresponding oligomeric amino alcohols by using $NaBH_4/I_2$ reagent system. The oligomeric amino alcohols were converted to the corresponding *O*-methylated products using the NaH/MeI reagent system.

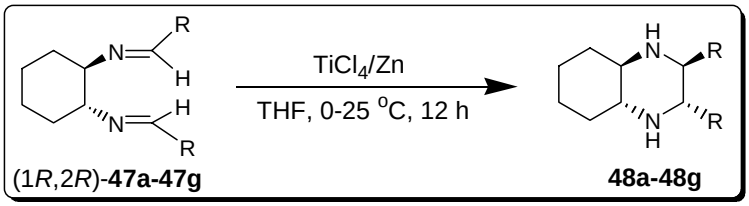
3.4 Experimental Section

Several informations given in the experimental section of Chapter 1 are also applicable for the experiments outlined here. The mixture of *cis*- and *trans*–1,2-diaminocyclohexane supplied by Aldrich, USA was used. *L*-(+)-Tartaric acid was supplied by BDH, India. Zinc dust was supplied by Ranbaxy, India. Activated Zinc dust was prepared by treating the commercial Zn dust with 1% H_2SO_4, then washing with water, acetone and drying at 150^oC for 4 h under vacuum. E-Merck, India supplied methanesulfonic acid and sodium borohydride, sodium hydride (60% dispersion in mineral oil) and methyl iodide. (*R*)-(+)-1,1'-Binaphthyl-2 2'-diamine was supplied by Gerchem laboratory (Pvt) Ltd., India. Adipoyl chloride was prepared from the reaction of thionyl chloride with adipic acid, supplied by Sisco Chem. Pvt. Ltd., India.

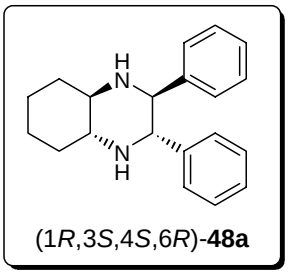
3.4.1 General procedure for the synthesis of 3,4-disubstituted 2,5-diazabicyclo-[4.4.0]decanes using diimines and low-valent titanium reagents:

In dry THF (100 mL), $TiCl_4$ (3.8 g, 2.2 mL, 20 mmol) was added under N_2 atmosphere at 0 ^oC. Zn dust (2.6 g, 40 mmol) was added with a solid addition flask for 10 min. The reaction mixture was stirred for 0.5 h at 0 ^oC and the imine (5 mmol) in 50 mL of THF was added for 15 min. The reaction mixture was stirred for 0.5 h at 0 ^oC and for 12 h at 25 ^oC. It was quenched with saturated K_2CO_3 (30 mL) and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic extract was washed with brine solution (20 mL) and dried over anhydrous K_2CO_3. The solvent was removed and the

residue was chromatographed on basic alumina column using EtOAc/hexanes mixture as eluent.



(1*R*,2*R*)-**47a-47g** **48a-48g**



(1*R*,3*S*,4*S*,6*R*)-**48a**

Yield 1.08 g (75%)

mp 60-62 °C

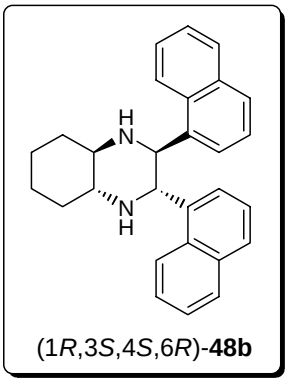
IR (KBr) (cm^{-1}) 3220, 3060, 2955

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.32-1.48 (m, 4H), 1.69-1.75 (m, 4H), 1.77 (s, br, 2NH), 2.58-2.70 (m, 2H), 3.83 (s, 2H), 7.05-7.20 (m, 10H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 24.9, 31.9, 61.6, 68.6, 127.0, 127.6, 128.1, 142.6

MS m/z 293 (M+1)

$[\alpha]_D^{25}$ -77.6 (*c* 1, $CHCl_3$)



(1*R*,3*S*,4*S*,6*R*)-**48b**

Yield 1.65 g (85%)

mp 159-161 °C

IR (KBr) (cm^{-1}) 3230, 3056, 2955

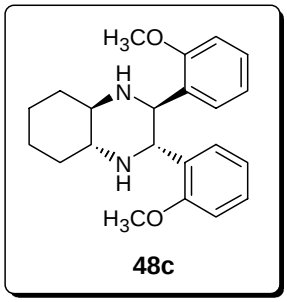
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.38-1.54 (m, 4H), 1.73-1.94 (m, 4H, 2NH), 2.80-2.90 (m, 2H), 5.13 (s, 2H), 7.18-7.40 (m, 6H), 7.47-7.78 (m, 6H), 7.92-8.10 (m, 2H)

(Spectrum No. 47)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 25.1, 31.9, 60.9, 62.2, 122.8, 124.9, 125.1, 125.4, 127.4, 128.3, 131.6, 133.4, 137.8 **(Spectrum No. 48)**

MS m/z 393 (M+1)

$[\alpha]_D^{25}$ +200 (*c* 1, $CHCl_3$)



48c

Yield 1.59 g (86%)

mp 46-48 °C

IR (KBr) (cm^{-1}) 3307, 3061, 2951

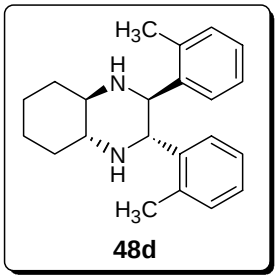
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.14-1.38 (m, 4H), 1.65-1.80 (m, 4H), 2.09-2.27 (m, 2H, 2NH), 3.27 (s, 6H), 3.90 (s, 2H), 6.39 (d, 2H, *J* = 8 Hz), 6.81-6.85 (m, 2H), 6.95-6.99 (m, 2H), 7.58 (d, 2H, *J* = 8 Hz)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 25.2, 32.1, 55.1, 60.7, 61.9, 110.1, 120.1, 127.5, 128.9, 129.7, 156.9

MS m/z 353 (M+1)

$[\alpha]_D^{25}$ -17 (*c* 1, MeOH); $[\alpha]_D^{25}$ = + 8 (*c* 1, $CHCl_3$)

Yield 1.20 g (75%)



48d

mp 120-122 °C

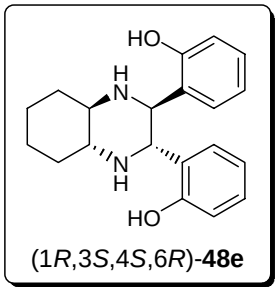
IR (KBr) (cm^{-1}) 3323, 3065, 3022, 2924

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.32-1.47 (m, 4H), 1.59 (s, 6H), 1.71-1.92 (m, 4H, 2NH), 2.56-2.68 (m, 2H), 4.21 (s, 2H), 6.83-6.85 (m, 2H), 6.98-7.02 (m, 2H), 7.08-7.12 (m, 2H), 7.66-7.76 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 19.2, 25.0, 31.9, 61.7, 62.6, 125.5, 126.8, 128.0, 129.8, 136.2, 139.7

MS m/z 321 (M+1)

$[\alpha]_D^{25}$ -28.0 (*c* 1, $CHCl_3$)



(1*R*,3*S*,4*S*,6*R*)-**48e**

Yield 1.13 g (70%)

mp 206-208 ^oC

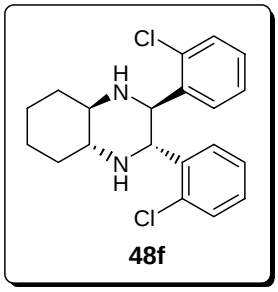
IR (KBr) (cm^{-1}) 3250, 3060, 2952

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.38-1.51 (m, 4H), 1.77-1.92 (m, 4H), 2.41 (s, br, 2NH), 2.70-2.80 (m, 2H), 4.16 (s, 2H), 6.11-6.14 (m, 2H), 6.40-6.44 (m, 2H), 6.82-6.84 (m, 2H), 7.05-7.09 (m, 2H), 10.83 (s, br, 2OH) **(Spectrum No. 49)**

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 24.4, 31.6, 59.8, 63.5, 116.6, 118.6, 123.2, 129.0, 130.1, 156.9 **(Spectrum No. 50)**

MS m/z 325 (M+1)

$[\alpha]_D^{25}$ -4.0 (*c* 1, $CHCl_3$)



48f

Yield 1.41 g (78%)

mp 98-100 ^oC

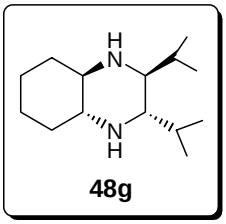
IR (KBr) (cm^{-1}) 3316, 3069, 2962

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.30-1.46 (m, 4H), 1.67-1.82 (m, 4H, 2NH), 2.61-2.72 (m, 2H), 4.63 (s, 2H), 7.02-7.06 (m, 2H), 7.09-7.18 (m, 4H), 7.55-7.69 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 23.1, 30.1, 60.9, 60.9, 124.9, 126.6, 127.2, 128.1, 131.7, 136.3

MS m/z 362 (M+1)

$[\alpha]_D^{25}$ -56.4 (*c* 0.33, $CHCl_3$)



48g

Yield 0.40 g (36%)

IR (Neat) (cm^{-1}) 3325, 2931

^{1}H-NMR (200 MHz, $CDCl_3$, δ ppm): 0.83 (d, 6H, *J* = 6 Hz), 0.95 (d, 6H, *J* = 6 Hz), 1.11 (s, br, 2NH), 1.16-1.28 (m, 4H), 1.61-1.82 (m, 4H), 1.88-1.20 (m, 2H), 2.05-2.15 (m, 2H), 2.42 (s, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 15.3, 20.7, 25.0, 27.0, 32.0, 61.8, 63.3

$[\alpha]_D^{25}$ -28.64 (*c* 0.83, $CHCl_3$)

3.4.2 Reaction of bis(*N*-benzylidene)-1,1'-binaphthyl-2,2'-diamine with the $TiCl_4$/Zn reagent system (Scheme 36, Section 3.2.3)

Experimental procedure described in the Section 3.4.1 was followed by using 1 mmol (0.46 g) of bis(*N*-benzylidene)-1,1'-binaphthyl-2,2'-diamine, 4 mmol (0.76 g, 0.44 mL) of $TiCl_4$ and 8 mmol (0.52 g) of Zn.

Yield 0.38 g

mp 226-230 ^{o}C

IR (Neat) (cm^{-1}) 3393, 3060, 3026, 1618

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 59.4, 59.6, 60.6, 77.32, 77.40, 111.66, 114.73, 122.12, 122.91, 122.29, 124.20, 126.85, 126.91, 127.05, 127.29, 127.37, 127.53, 127.86, 128.29, 129.34, 129.50, 129.64, 133.39, 142.63, 142.74

MALDI-tof: (m/z) 284, 373, 461, 552, 642 **(Figure 6, Section 3.2.3)**

$[\alpha]_D^{25}$ +94.6 (*c* 1, $CHCl_3$)

3.4.3 Procedure for the reductive coupling of bis(*N*-benzylidene)-(*R*)-BINAM using Zn/MsOH reagent system:

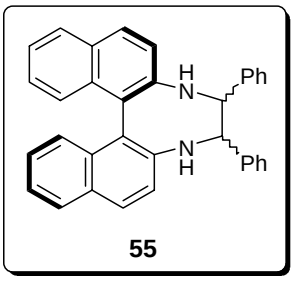
Zinc dust (0.33 g, 5 mmol) was suspended in a THF (15 mL) solution of diimine **51** (0.46 g, 1 mmol) under N_2 atmosphere. To this methanesulfonic acid (0.48 g, 0.32 mL, 5 mmol) was added at -45 ^oC. The reaction mixture was stirred for 0.5 h at this temperature. Then it was quenched with dilute aqueous K_2CO_3 (10 mL) solution and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous K_2CO_3. The solvent was removed and the residue was chromatographed on a basic alumina column using EtOAc/hexanes mixture as eluent.

Yield 0.05 g (11%)

dr 50:50

mp 172-174 ^oC

IR (KBr) (cm^{-1}) 3332, 3061, 3029, 1612



55

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.96 (br, NH), 4.72 (s, 1H), 4.80 (s, 1H), 6.88-7.00 (s, 2H), 7.16-7.28 (10H), 7.77-7.93 (6H)

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 61.93, 63.32, 112.70, 118.40, 122.11, 122.51, 124.03, 126.92, 127.06, 127.47, 127.72, 128.23, 128.57, 129.57, 129.24, 129.80, 133.80, 142.79

3.4.4 Procedure for the reaction of chiral diamine with adipoyl chloride:

A mixture of chiral diamine **48a** (1.46 g, 5 mmol) and triethylamine (0.71 g, 0.97 mL, 7 mmol) was taken in THF (15 mL). To this a THF (10 mL) solution of adipoyl

chloride (0.95 g, 0.65 mL, 5.2 mmol) was added slowly over 0.5 h under N_2 atmosphere at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 1 h and at 25 ^oC for a further 8 h. Water (25 mL) was added and the organic solvent was evaporated. The crude reaction mixture was diluted with CH_2Cl_2 (75 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product mixture was washed with ether (2 x 20 mL), EtOAc (2 x 20 mL) and toluene (2 x 20 mL) to remove the unreacted starting materials to obtain the chiral oligomeric amides **56**.

Data for a mixture of compounds (Scheme 39, Section 3.2.4)

Yield 1.2 g

mp 168-174 ^oC

IR (KBr) (cm^{-1}) 3061, 2962, 2932, 1745, 1651

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 14.9, 21.3, 24.6, 24.9, 28.1, 30.8, 31.3, 32.8, 33.6, 33.8, 38.5, 39.0, 52.3, 56.8, 57.0, 60.6, 60.9, 61.3, 62.1, 65.7, 67.1, 125.4, 125.8, 127.6, 127.9, 128.3, 128.8, 129.0, 129.1, 138.4, 139.2, 173.0, 173.5, 174.1, 174.8, 175.0, 214.4, 215.5, 216.2 **(Spectrum No. 52)**

MALDI-tof: (m/z) 406, 517, 810, 920, 1213, 1323, 1618, 1727, 2129 **(Figure 7, Section 3.2.4)**

$[\alpha]_D^{25}$ -30.8 (*c* 1, $CHCl_3$)

3.4.5 Procedure for the reduction of chiral oligomeric amides 56 to oligomeric amino alcohols 57 using $NaBH_4/I_2$ reagent system:

The mixture of chiral oligomeric amides **56** (1 g) and $NaBH_4$ (1.89 g, 50 mmol) were suspended in THF (30 mL). A THF solution (50 mL) of iodine (5.58 g, 22 mmol)

was added slowly over 1 h at 0 ^oC under N_2 atmosphere. The reaction mixture was brought to 25 ^oC and stirred for 0.5 h. It was then refluxed for 16 h, brought to room temperature and quenched carefully with water (20 mL). The organic solvent was evaporated. The crude reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product mixture was thoroughly washed with hexane (2 x 20 mL) and toluene (2 x 20 mL) to obtain the chiral oligomeric amines **57**.

Data obtained for the mixture of products isolated (Scheme 40, Section 3.2.4)

Yield 0.8 g

mp 182-193 ^oC

IR (KBr) (cm^{-1}) 3407, 3060, 3026, 2954, 2934, 2858

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 20.4, 20.7, 21.4, 21.7, 24.4, 26.3, 27.5, 28.0, 28.2, 28.7, 34.4, 40.4, 43.7, 45.6, 48.2, 50.7, 62.2, 62.8, 63.3, 64.9, 66.5, 71.1, 73.5, 74.4, 128.0, 128.2, 128.6, 129.0, 129.3, 129.7, 136.6, 136.9, 137.3, 137.8, 138.5 **(Spectrum No. 54)**

MALDI-tof: (m/z) 392, 490, 766, 865, 1240, 1615, 1990 **(Figure 8, Section 3.2.4)**

$[\alpha]_D^{25}$ -56.2 (*c* 1, $CHCl_3$)

3.4.7 Experimental procedure for *O*-methylation of oligomeric amino alcohols using the NaH/MeI reagent system:

NaH (60% dispersion in mineral oil, 2 g, 50 mmol) was washed with dry hexane (2 x 30 mL) under N_2 atmosphere and THF (30 mL) was added to the residue. To this

mixture oligomeric amino alcohols **57** (0.7 g) in 25 mL THF was added slowly over 0.5 h at 0 ^{o}C under N_2 atmosphere. Then a THF (10 mL) solution of MeI (5.68 g, 2.49 mL, 40 mmol) was added slowly over 15 min. at the same temperature. The reaction mixture was brought to room temperature and then refluxed for 4 h. Then it was cooled and water (30 mL) was added and the organic solvent was evaporated. The crude reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product mixture was thoroughly washed with hexane (2 x 20 mL) and toluene (2 x 20 mL) to obtain the chiral oligomeric amine derivatives **58**.

Data for the mixture of products isolated (Scheme 41, Section 3.2.4)

Yield 0.6 g

mp 182-193 ^{o}C

IR (KBr) (cm^{-1}) 3060, 3028, 2924,2854,1602, 1365

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 20.9, 21.7, 22.0, 22.1, 22.4, 22.6, 25.0, 25.1, 25.2, 25.3, 25.4, 25.8, 26.9, 27.0, 27.1, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 30.1, 30.3, 30.4, 30.5, 30.7, 31.9, 41.4, 42.2, 43.5, 48.7, 48.8, 54.3, 55.7, 55.9, 56.7, 58.5, 63.9, 63.4, 63.6, 64.5, 72.4, 72.5, 72.8, 73.3, 83.9, 84.4, 86.9, 87.1, 126.4, 127.2, 127.3, 127.4, 128.8, 128.9, 129.0, 129.0, 129.3, 129.5, 129.7, 141.4, 141.5, 141.7, 141.8, 141.9

$[\alpha]_D^{25}$ -66.5 (*c* 1, $CHCl_3$)

3.5 References

1. Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
2. Betschart, von C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999.
3. Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255.
4. Rele, S.; Talukdar, S.; Benerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990.
5. Yoshimura, N.; Mukaiyama, T. *Chem. Lett.* **2001**, 1334.
6. Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, *42*, 2365.
7. Hatano, B.; Ogawa, A.; Hirao, T. *J. Org. Chem.* **1998**, *63*, 9421.
8. Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.
9. Rieke, R. D.; Kim, S. –H. *J. Org. Chem.* **1998**, *63*, 5235.
10. Mercer, G. J.; Sturdy, M.; Jensen, D. R.; Sigman, M. S. *Tetrahedron* **2005**, *61*, 6418.
11. Wang, Y.; Zhu, Y.; Chen, Z.; Mi, A.; Hu, W.; Doyle, M. P. *Org. Lett.* **2003**, *5*, 3923.
12. Shono, T.; Kise, N.; Oike, H.; Yoshimoto, M.; Okazaki, E. *Tetrahedron Lett.* **1992**, *33*, 5559.
13. Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 609.
14. Pansare, S. V.; Malusare, M. G. *Tetrahedron Lett.* **1996**, *37*, 2859.
15. Enholm, E. J.; Forbes, D. C.; Holub, D. P. *Synth. Commun.* **1990**, *20*, 981.
16. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1998**, *39*, 3333.
17. Machrouhi, F.; Namy, J. -L. *Tetrahedron Lett.* **1999**, *40*, 1315.
18. Annunziata, R.; Benaglia, M.; Caporale, M.; Raimondi, L. *Tetrahedron*: *Asymmetry* **2002**, *13*, 2727.
19. Kim, M.; Knettle, B. W.; Dahlén, A.; Hilmersson, G.; Flowers, II, R. A. *Tetrahedron* **2003**, *59*, 10397.

20. Zhong, Y. –W.; Xu, M. –H.; Lin, G. –Q. *Org. Lett.* **2004**, *6*, 3953.

21. Takai, K.; Tsubaki, Y.; Tanaka, S.; Beppu, F.; Fujiwara, Y. *Chem. Lett.* **1990**, 203.

22. Padwa, A.; Bergmark, W.; Pashayan, D. *J. Am. Chem. Soc.* **1969**, *91*, 2653.

23. Campos, P. J.; Arranz, J.; Rodríguez, M. A. *Tetrahedron* **2000**, *56*, 7285.

24. Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829.

25. Tanaka, H.; Dhimane, H.; Fujita, H.; Ikemoto, Y.; Torii, S. *Tetrahedron Lett.* **1988**, *29*, 3811.

26. Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, *34*, 1647.

27. Periasamy, M.; Reddy, M. R.; Kanth, J. V. B. *Tetrahedron Lett.* **1996**, *37*, 4767.

28. Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, *40*, 7577.

29. Jay, F. L.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 1969.

30. A. L. Spek, *PLATON, A Multipurpose Crystallographic Tool;* Utrecht University, Utrecht, The Netherlands, **2002**.

31. Periasamy, M.; Srinivas, G.; Suresh, S. *Tetrahedron Lett.* **2001**, *42*, 7123.

32. Liu, R. S. H. *Acc. Chem. Res*. **2001**, *34*, 555.

33. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

34. (a) Pu, L. *Chem. Rev.* **1998**, *98*, 2405 (b) Lère-Porte, J. –P.; Moreau, J. J. E.; Serein-Spirau, F.; Wakim, S. *Tetrahedron Lett.* **2001**, *42*, 3073 (c) Zheng, L.; Urian, R. C.; Liu, Y.; Jen, A. K. –Y.; Pu, L. *Chem. Mater.* **2000**, *12*, 13 (d) Shinohara, K. –i.; Aoki, T.; Kaneko, T.; Oikawa, E. *Polymer* **2001**, *42*, 351 (e) Chen, X.; Du, D. –M.; Hua, W. –T. *Tetrahedron: Asymmetry* **2003**, *14*, 999 (f) Zhang, K.; Krishnaswami, R.; Sun, L. *Analytica Chimica Acta* **2003**, *496*, 185 (g) Zhang, H. –C.; Pu, L. *Tetrahedron* **2003**, *59*, 1703 (h) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 299 (i) Yu, H. –B.; Zheng, X. –F.; Lin, Z. –M.; Hu, Q. S.; Huang, W. -S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149.

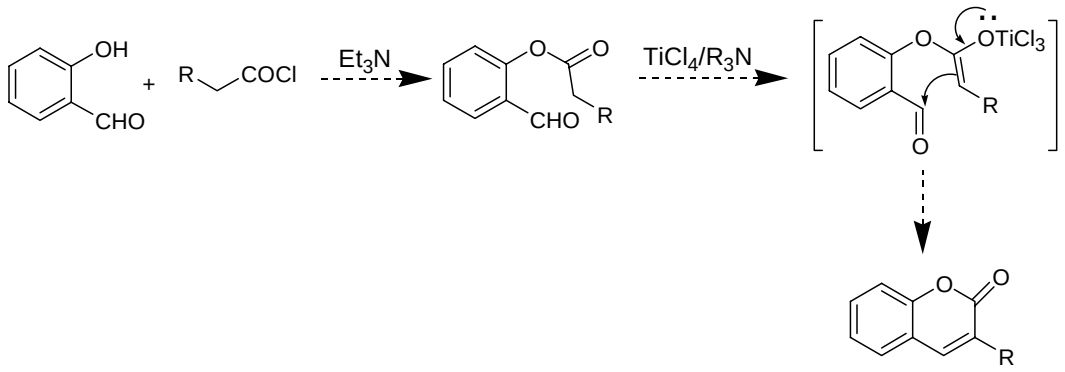
Chapter 4

Intramolecular condensation of ortho-O-acyl aryl aldehydes using the $TiCl_4/R_3N$ reagent system: Synthesis of 3-substituted coumarins

4.1 Introduction

Though, the main focus of our investigations is on the stereoselective synthesis of chiral amine derivatives via carbon-carbon bond forming reactions using titanium reagents, we became interested in the cyclization of *ortho* substituted *O*-acyl aryl aldehydes using the $TiCl_4/R_3N$ reagent system. The reaction is expected to go through the corresponding titanium enolate to give coumarin derivatives (Knoevenagel condensation -Scheme 1).

Scheme 1



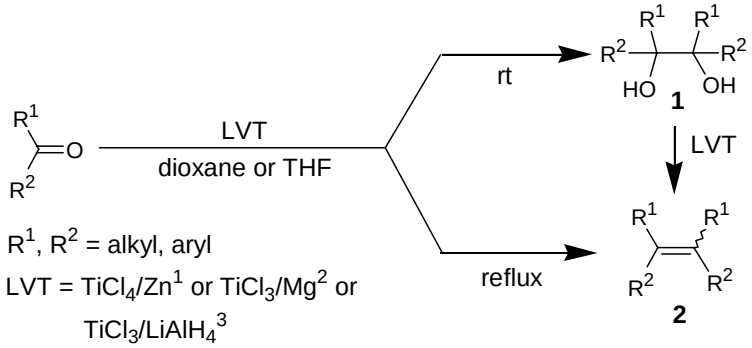
This transformation is related to the reaction of aldimines with esters mediated by the $TiCl_4/R_3N$ reagent system (Chapter 1). The common feature in these transformations *viz*. the Mannich-type reaction (described in Chapter 1) and the Knoevenagel-type condensation (Scheme 1) is that they go through the corresponding titanium enolates.

A brief review on the reactions that lead to olefinic bond formations using titanium reagents will be helpful for the discussion. The most important alkene-forming reactions involving the titanium reagents are: (i) McMurry reaction, (ii) Knoevenagel condensation, (iii) Aldol condensation, (iv) Wittig-type alkylidenations and other related reactions.

4.1.1 McMurry reaction:

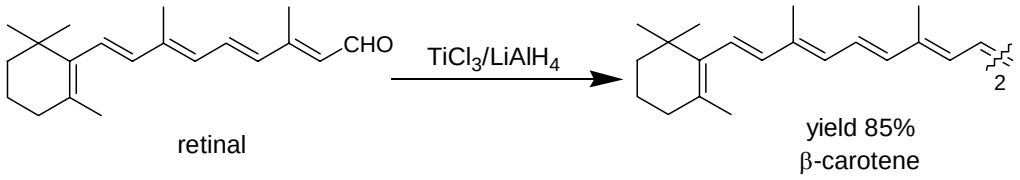
As discussed in the Section **1.1**, in 1973/74 three research groups independently observed that low-valent titanium (LVT) reagents ($TiCl_4$/Zn, $TiCl_3$/Mg and $TiCl_3$/$LiAlH_4$) dimerize aldehydes or ketones to give olefins. In 1973, Mukaiyama *et al.*[1] reported the reductive coupling of carbonyl compounds to give pinacols **1** and olefins **2** by using the LVT species, produced from $TiCl_4$ and Zn. Tyrlik *et al.*[2] reported the use of LVT species, generated in the reaction of $TiCl_3$ with Mg in THF, in the synthesis of olefins and alcohols via reductive coupling of carbonyl compounds. McMurry *et al.*[3] used the LVT prepared from $TiCl_3$-$LiAlH_4$, to effect this transformation (Scheme 2).

Scheme 2



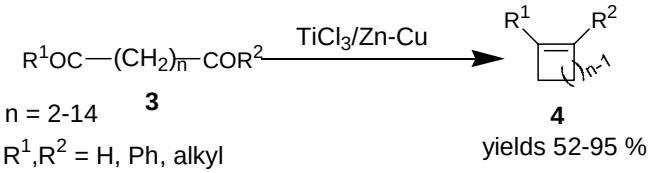
β-Carotene was synthesized from retinal by using the low-valent titanium prepared from $TiCl_3$-$LiAlH_4$ reagent combination (Scheme 3).[3]

Scheme 3



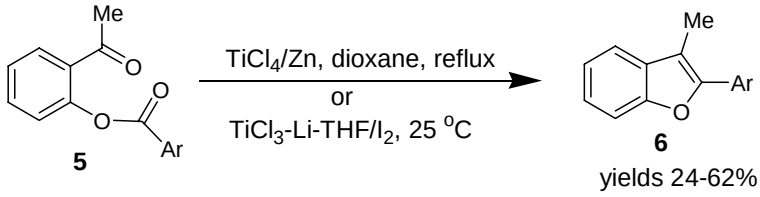
Several cycloalkenes **4** were synthesized in good yields by the treatment of dicarbonyl compounds **3** with $TiCl_3$/Zn-Cu reagent system (Scheme 4).[4]

Scheme 4



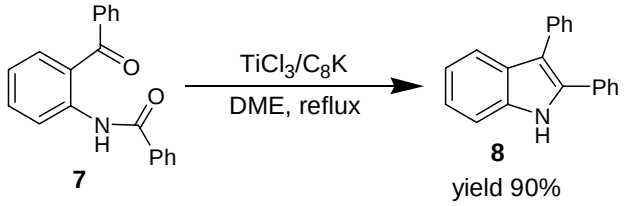
Benerji *et al.*[5a] reported the synthesis of benzofurans **6** via an intramolecular reductive deoxygenation of *O*-aroyloxyacetophenones **5** using the $TiCl_4$/Zn reagent system. A low-valent titanium reagent activated by iodine,[5b] $TiCl_3$-Li-THF/I_2 was also used to effect this transformation (Scheme 5).

Scheme 5



Fürstner *et al.*[6] reported a method for the reductive coupling of oxo amide **7** to indole **8** with a low-valent titanium reagent, prepared using $TiCl_4$ and C_8K in dimethoxyethane (DME) (Scheme 6).

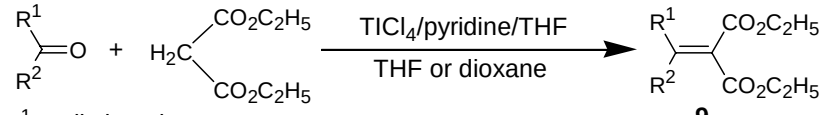
Scheme 6



4.1.2 Knoevenagel condensation:

In 1970 Lehnert *et al.*[7] reported the Knoevenagel condensation between carbonyl compounds and malonic esters mediated by the $TiCl_4$/THF/pyridine reagent combination to give olefins in good yields (Scheme 7). Later, this methodology was employed in the synthesis of different alkenes.[8-10]

Scheme 7

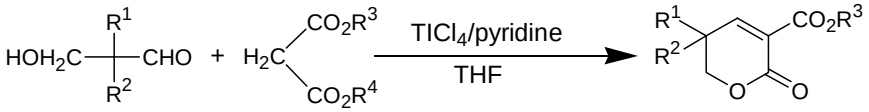


R^1 = alkyl, aryl
R^2 = H, $CO_2C_2H_5$

9
yields 75-98%

Synthesis of 3,5,5-trisubstituted 5,6-dihydro-2*H*-pyran-2-ones **10** was reported via Knoevenagel reaction in the presence of $TiCl_4$/pyridine (Scheme 8).[11]

Scheme 8

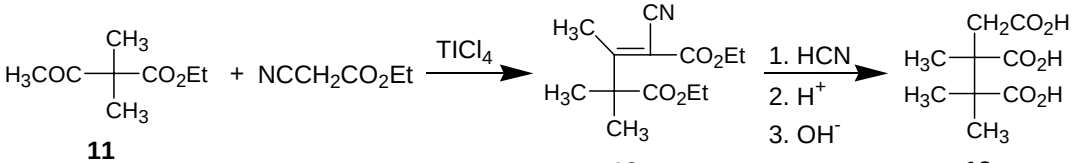


R^1 = Me, Et
R^2 = Me, Et, ^{n}Pr
R^3 = H, Me, Et, ^{t}Bu, Bn
R^4 = H, K, Me, ^{t}Bu, Bn

10
yields 69-80%

A $TiCl_4$ promoted Knoevenagel condensation of a sterically hindered ketoester **11** with ethyl cyanoacetate gave the corresponding olefin **12** in good yield. The product was converted to camphoronic acid **13** in steps (Scheme 9).[12]

Scheme 9



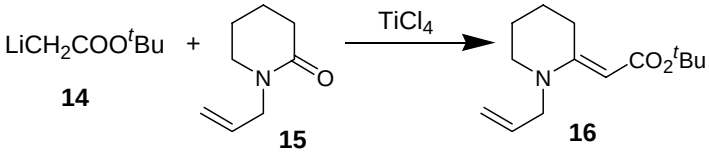
11

12
yield 96%

13
yield 39%

Reaction of *N*-allyl lactam **15** with active methylene compound **14** gave the corresponding methylidene product **16** in the presence of $TiCl_4$ (Scheme 10).[13]

Scheme 10



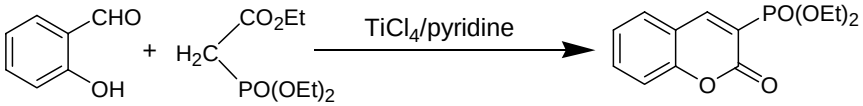
14

15

16
yield 33%

Synthesis of diethyl coumarin-3-phosphonates **18** through the reaction of salicylaldehyde with triethyl phosphonoacetate **17** mediated by $TiCl_4$/pyridine reagent system was reported (Scheme 11).[14]

Scheme 11



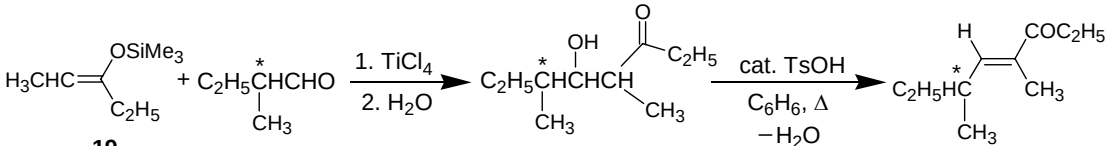
17 **18**

yield 67%

4.1.3 Aldol reaction:

Mukaiyama *et al.*[15] reported the synthesis of (+)-manicone **21**, an alarm pheromone, by a $TiCl_4$ mediated aldol reaction of silyl enol ether **19** and enantiomerically pure aldehyde (+)-**20** (Scheme 12).

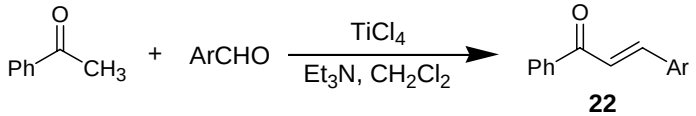
Scheme 12



19 (+)-**20** yield 92% (+)-**21** overall yield 76%

Aldol reaction of acetophenone with aromatic aldehydes afforded the chalcones **22** in the presence of $TiCl_4/Et_3N$ reagent system (Scheme 13).[16]

Scheme 13



Ar = Ph, *p*-MeC_6H_4, *p*-$OMeC_6H_4$, *o*-MeC_6H_4, *p*-$NO_2C_6H_4$,

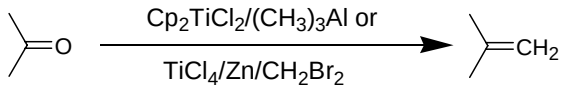
22

yields 64-96%

4.1.4 Wittig-type olefination (methylenation):

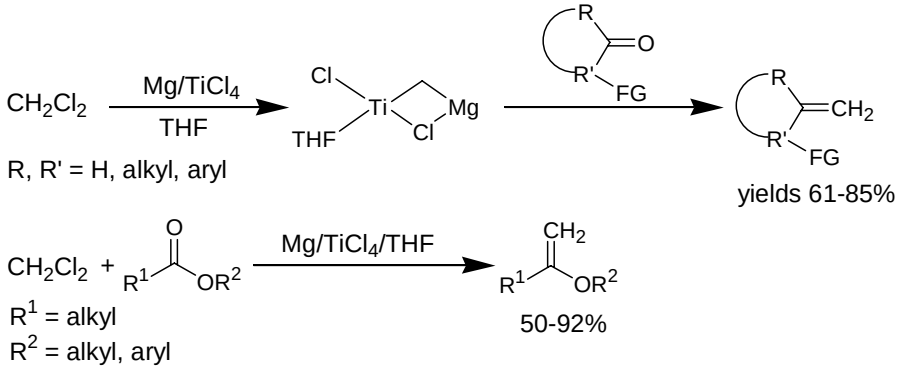
$Cp_2TiCl_2/(CH_3)_3Al$ (Tebbe reagent)[17a-d] or $TiCl_4/CH_2Br_2/Zn$ reagent combinations were used for methylenation of carbonyl compounds (Scheme 14).[17e-j]

Scheme 14



Very recently, methylenation of carbonyl compounds with CH_2Cl_2 promoted by $Mg/TiCl_4$/THF reagent combination was reported. The corresponding methylidene products were obtained in moderate to good yields (Scheme 15).[18]

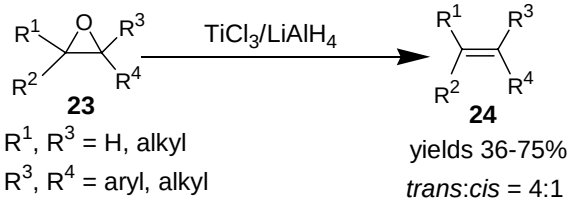
Scheme 15



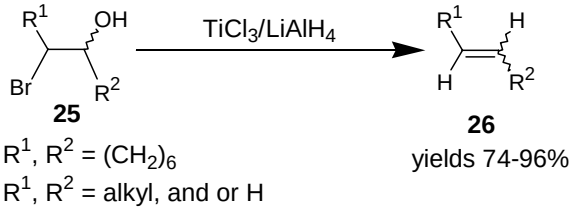
4.1.5 Other olefin-forming reactions using titanium reagents:

Low-valent titanium, produced by $TiCl_3$ and $LiAlH_4$, mediated the deoxygenation of epoxides **23** to give olefins **24** (Scheme 16). Reduction of bromohydrins **25** to olefins **26** was also reported using the low-valent titanium reagent (Scheme 17).[19]

Scheme 16

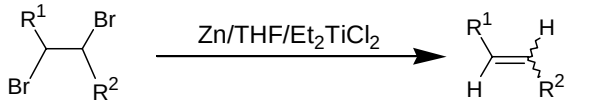


Scheme 17



It was reported that the reduction of a variety of vicinal dibromides **27** delivered olefins **28** in moderate to good yields in the presence of $Zn/THF/Et_2TiCl_2$ reagent combination (Scheme 18).[20]

Scheme 18



27 **28**

yields 68-95%

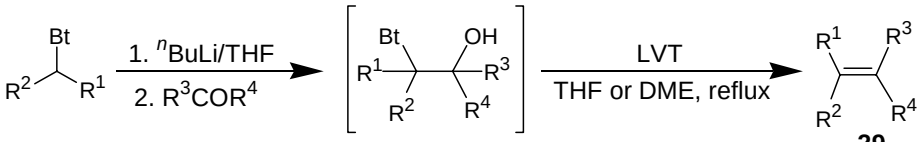
R^1, R^2 = $(CH_2)_4$, $(CH_2)_6$

R^1, R^2 = CO_2Et, Ph

R^1, R^2 = Ph or H, Ph or alkyl

Katritzky *et al.*[21] reported the *trans*-selective olefination of carbonyl compounds by low-valent titanium-mediated dehydroxybenzotriazolylation. The *E*-olefins **29** were obtained in good yields with excellent selectivity (Scheme 19).

Scheme 19



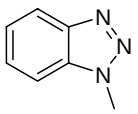
29

R^1 = Ar, R^2 = H, Me

R^3 = Ar, alkyl, R^4 = Ph, alkyl

yields 27-84%

E:*Z* = 9:1 to 100:0

Bt = 

LVT = $TiCl_3/Li$, $TiCl_3/Zn$-Cu, $TiCl_4/Zn$-Cu

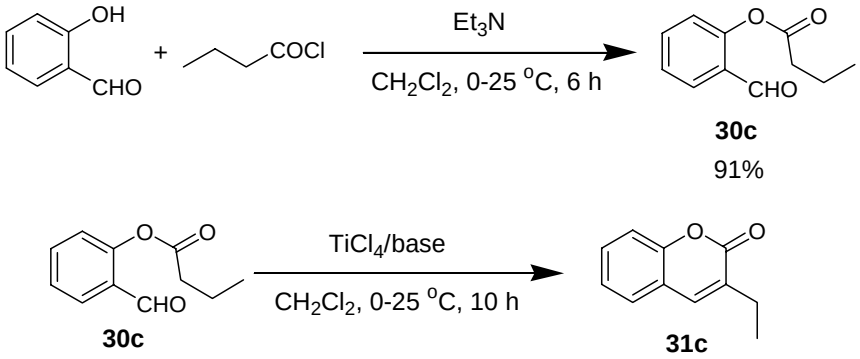
We have studied the construction of the stereoselective C-C bonds in the Mannich-type reactions mediated by the $TiCl_4/R_3N$ reagent system (Chapter 1). In this chapter, we describe our results on the formation of C=C (alkene-forming reactions) via the condensation reactions using the $TiCl_4/R_3N$ reagent system.

4.2 Results and Discussion

4.2.1 Synthesis of 3-substituted coumarins from 2-(*O*-alkanoyl)-benzaldehydes using the $TiCl_4/R_3N$ reagent system:

ortho-(*O*-Butyryl) benzaldehyde **30c** was prepared from salicylaldehyde and ^{n}butyryl chloride in the presence of Et_3N. The product **30c** was reacted with $TiCl_4$ in combination with different organic bases like Et_3N, $^{i}Pr_2NEt$, $^{n}Bu_3N$ and pyridine. 3-Ethyl coumarin **31c** was obtained in all these reactions. The $TiCl_4/Et_3N$ reagent system was found to give acceptable yields (Scheme 20).

Scheme 20



base	yield of product **31c** (%)
Et_3N	63
$^{i}Pr_2NEt$	32
$^{n}Bu_3N$	28
pyridine	38

The structure of the coumarin **31c** was confirmed by the X-ray structure analysis. The ORTEP diagram of 3-ethyl coumarin **31c** is shown in Figure 1. The crystal structure data of the compound **31c** are summarized in Table 1 and Table A11 (Appendix II).

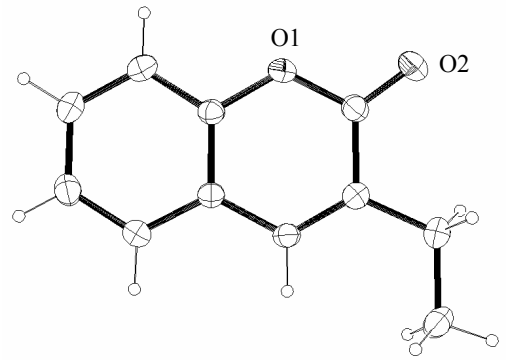
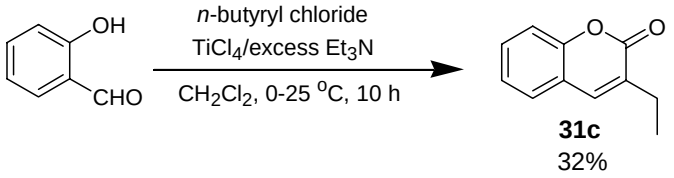


Figure 1 ORTEP representation of the crystal structure of 3-ethyl coumarin **31c** (Thermal ellipsoids are drawn at 20% probability)

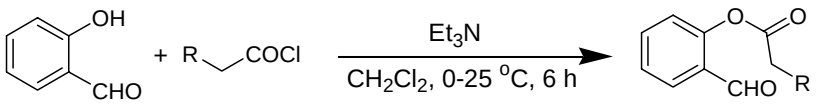
It was of interest to develop a one-pot procedure for this transformation. Accordingly, we have carried out the reaction of salicylaldehyde with ^{n}butyryl chloride in presence of $TiCl_4$ and excess Et_3N and isolated the corresponding coumarin **31c** in only 32% yield (Scheme 21).

Scheme 21



Therefore, it was decided to follow the two-stage transformation outlined in the Scheme 20 for the coumarin synthesis. Accordingly, a series of *ortho*-(*O*-acyl) benzaldehydes **30** were prepared from salicylaldehyde and acyl chlorides in the presence of Et_3N in CH_2Cl_2 (Scheme 22).

Scheme 22



yield of **30**

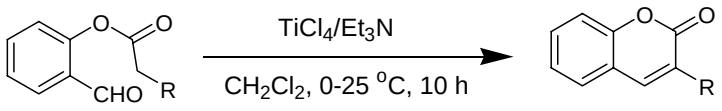
R = H	**30a**	92%
R = Me	**30b**	90%
R = Ph	**30d**	86%

Table 1 X-ray data collection and structure refinement for 3-ethyl coumarin **31c**

Empirical formula	$C_{11}H_{10}O_2$
Formula weight	174.19
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 7.3522(13) Å, α = 90˚
	b = 10.4605(18) Å, β = 102.889(3)˚
	c = 11.731(2) Å, γ = 90˚
Volume	879.5(3) $Å^3$
Z	4
Calculated density	1.316 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	368
Crystal size	0.30 X 0.29 X 0.20 mm
θ range for data collection	2.64 to 26.05˚
Limiting indices	$-8 \le h \le 9$; $-11 \le k \le 12$; $-14 \le l \le 14$
Reflections collected/unique	6244 / 1728 [R(int) = 0.0195]
Completeness to θ = 26.05	99.5%
Refinement method	Full-matrix least-square on F^2
Data / restraints / parameters	1728 / 0 / 120
Goodness-of-fit on F^2	1.069
Final *R* indices [I> 2σ (I)]	$R_1 = 0.0408$, $wR_2 = 0.1141$
R indices (all data)	$R_1 = 0.0502$, $wR_2 = 0.1220$
Largest diff. peak and hole	0.151 and -0.158 $eÅ^{-3}$

The reactions of *ortho*-(*O*-acyl) benzaldehydes **30** with the $TiCl_4/Et_3N$ reagent system resulted in the corresponding 3-substituted coumarins **31a-31d** in moderate yields (Scheme 23). The results are summarized in Table 2.

Scheme 23



30a-30d **31a-31d**

Table 2 Synthesis of coumarins **31** from *ortho*-(*O*-acyl)-benzaldehydes **30** using the $TiCl_4/Et_3N$ reagent system

Entry	R	Substrate	Product[a]	Yield of **31** (%)[c]
1	H	**30a**	**31a**	42
2	CH_3	**30b**	**31b**	61
3	C_2H_5	**30c**	**31c**[b]	63
4	C_6H_5	**30d**	**31d**	60

a All the structures of products were confirmed by spectral analyses (IR, ^{1}H-NMR, ^{13}C-NMR and mass).

b ORTEP representation of X-ray crystal structure analysis is given in Figure 1.

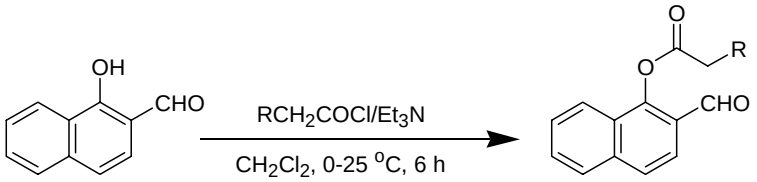
c Yields are based on the amount of the substrate **30** used. Yields are for the products isolated by column chromatography and subsequent crystallization in hexanes/EtOAc.

The reaction of **30a** with $TiCl_4/Et_3N$ reagent gave the unsubstituted coumarin **31a** only in 42% yield (entry 1). The reactions of compounds **30b-30d** containing an α-substituent gave the corresponding 3-substituted coumarins **31b-31d** in moderate yields (60-63% entries 2-4).

4.2.2 Synthesis of 3-substituted benzocoumarins from 1-(*O*-alkanoyl)-2-naphthaldehydes using the $TiCl_4/Et_3N$ reagent system:

We have also prepared 1-(*O*-acyl)-2-naphthaldehydes **32a-32d** using 1-hydroxy-2-naphthaldehyde and acyl chlorides in the presence of Et_3N in CH_2Cl_2. The products were obtained in good yields (Scheme 24).

Scheme 24

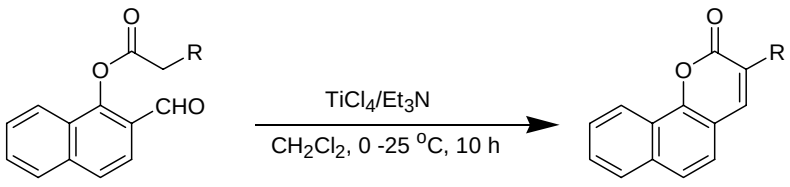


32a-32d

		yield
R = H	**32a**	82%
R = Me	**32b**	91%
R = Et	**32c**	88%
R = Ph	**32d**	80%

The reaction of 1-(*O*-acyl)-2-naphthaldehydes **32** with the $TiCl_4/Et_3N$ reagent system gave the corresponding benzocoumarins **33** (Scheme 25). The results are summarized in Table 3.

Scheme 25



32a-32d **33a-33d**

Table 3 Synthesis of benzocoumarins **33** from 1-(*O*-acyl)-2-naphthaldehydes **32** using the $TiCl_4/Et_3N$ reagent system

Entry	R	Substrate	Product[a]	Yield of **33** (%)[b]
1	H	**32a**	**33a**	37
2	CH_3	**32b**	**33b**	58
3	C_2H_5	**32c**	**33c**	55
4	C_6H_5	**32d**	**33d**	59

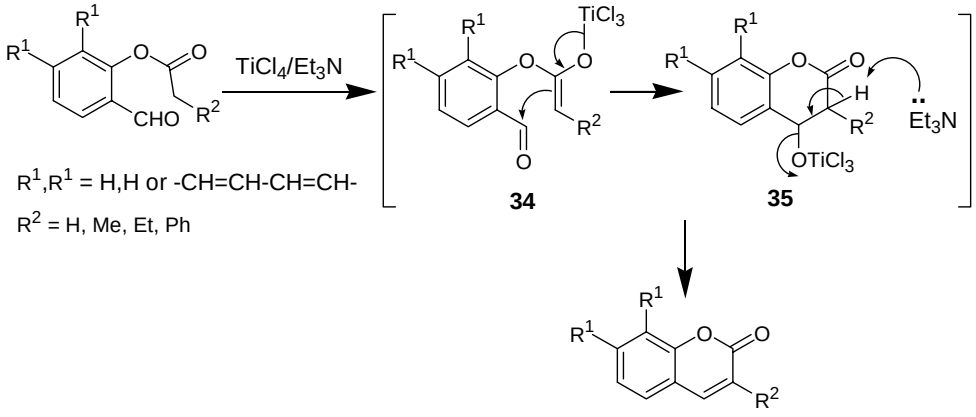
a All the structures of products were confirmed by spectral analyses (IR, ^{1}H-NMR, ^{13}C-NMR and mass).

b Yields are based on the amount of the substrate **32** used. Yields are for the products isolated by column chromatography and subsequent crystallization in hexanes/EtOAc.

The reaction of **32a**, derived from 1-hydroxy-2-naphthaldehyde and acetyl chloride, with $TiCl_4/Et_3N$ reagent gave the unsubstituted benzocoumarin **33a** in 37% yield only (entry 1). The reactions of the α-substituent containing 1-(O-alkoxy)-2-naphthaldehydes **32b-32d** delivered the corresponding benzocoumarins **33b-33d** in moderate yields (55-59% entries 2-4).

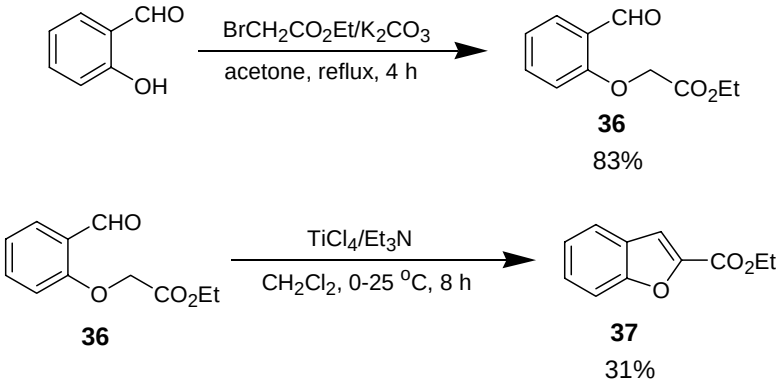
These transformations are expected to go through the titanium enolate intermediate **34**, formed by the reaction of the ester with $TiCl_4$ and Et_3N. The enolate could then attack the aldehyde functionality to give the adduct **35**, which on subsequent dehydration would give the corresponding coumarin (Scheme 26).

Scheme 26



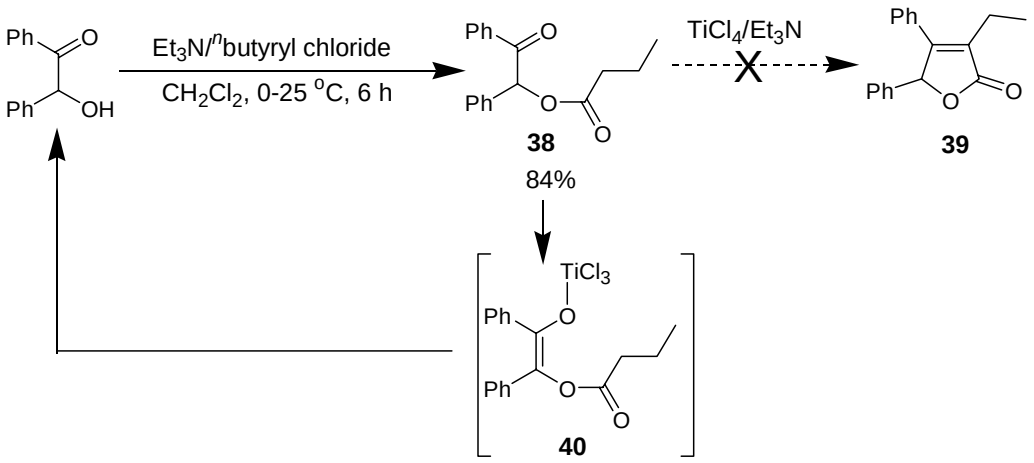
It was of interest to examine the synthesis of benzofurans via the Knoevenagel condensation of appropriate *O*-alkylated salicylaldehydes using the $TiCl_4/Et_3N$ reagent system. Accordingly, the 2-(2-formylphenoxy)acetic acid ethyl ester **36** was prepared from salicylaldehyde and 2-bromoethyl acetate in the presence of K_2CO_3 in acetone by refluxing for 4 h.[22] The product was treated with the $TiCl_4/Et_3N$ reagent system. In this case, benzofuran-2-carboxylic acid ethyl ester **37** was obtained only in 31% yield (Scheme 27).

Scheme 27



We have also examined the synthesis of 5H-furan-2-one **39** by the condensation of the appropriate substrate using the $TiCl_4/R_3N$ reagent system. Accordingly, the substrate **38** was prepared by the reaction of benzoin with ^{n}butyryl chloride in the presence of Et_3N. The compound **38** was then treated with the $TiCl_4/Et_3N$ reagent system. In this reaction, only benzoin was obtained in 52% yield (Scheme 28).

Scheme 28



Presumably, the titanium enolate may have difficulty in attacking the carbonyl group in this case. Instead, the titanium enolate **40** would be formed by enolization of the methine of the benzoin moiety, giving back the benzoin upon hydrolysis (Scheme 28).

4.3 Conclusions

An intramolecular Knoevenagel-type condensation reaction was developed for the synthesis of oxygen containing heterocycles by employing the titanium enolates prepared using the respective carbonyl compounds with the $TiCl_4/R_3N$ reagent system. 3-Substituted coumarins were prepared from the corresponding 2-(*O*-alkanoyl)-benzaldehydes using the $TiCl_4/Et_3N$ reagent system. Benzocoumarins were also prepared by the treatment of the respective substrates with the $TiCl_4/Et_3N$ reagent system.

4.4 Experimental Section

Several informations given in the section **1.4** are also applicable for the experiments outlined in this section. Acetyl chloride, propanoyl chloride and salicylaldehyde were supplied by Loba Chemie (P), Ltd., India. 1-Hydroxy-2-naphthaldehyde, 2-bromoethyl acetate and bezoin were purchased from E-Merck, India. Phenylacetyl chloride was prepared from thionyl chloride and phenylacetic acid, supplied by Loba Chemie (P) Ltd., India.

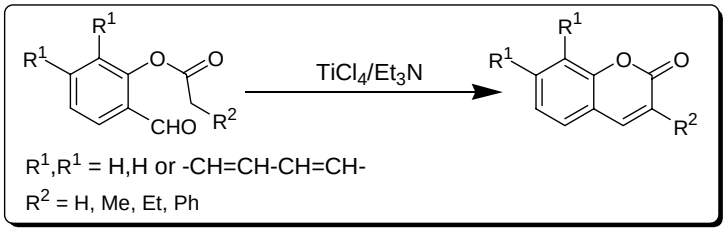
4.4.1 General procedure for the synthesis of *ortho*-*O*-acyl benzaldehydes or 1-(*O*-acyl)-2-naphthaldehydes:

Salicylaldehyde or 1-hydroxy-2-naphthaldehyde (10 mmol) was taken in CH_2Cl_2 (30 mL) and the respective acid chloride (11 mmol) was added at 0 ^oC under N_2 atmosphere. To this, Et_3N (1.2 g, 1.7 mL, 12 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 ^oC and stirred for 0.5 h. The reaction mixture was allowed to stir for further 6 h at 25 ^{o} C. Then the crude reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed successively with saturated aqueous sodium bicarbonate (25 mL) and brine (15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was distilled under reduced pressure to afford the desired *O*-acylated product.

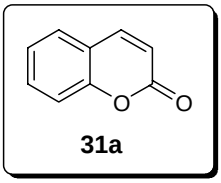
4.4.2 General procedure for the synthesis of coumarins or benzocoumarins using the $TiCl_4/Et_3N$ reagent system:

To a solution of *ortho*-*O*-acyl benzaldehyde or 1-(*O*-acyl)-2-naphthaldehyde (5 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (1.0 g, 1.4 mL, 10 mmol) at 0 ^oC. To this, a solution of $TiCl_4$ (3.8 g, 2.2 mL, 20 mmol) in CH_2Cl_2 (15 mL) was added dropwise over

15 min at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 0.5 h and then at 25 °C for 10 h. It was then quenched with saturated K_2CO_3 (20 mL) and stirred for 0.5 h. The reaction mixture was filtered through a Buchner funnel, organic extract was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was chromatographed on silica gel using hexanes/EtOAc (90:10) as eluent. Thus obtained product was further purified by crystallizing from hexanes/EtOAc (3:1) mixture.



Yield 0.31 g (42%)



31a

mp 70-72 °C (lit.[23] mp = 68-69 °C)

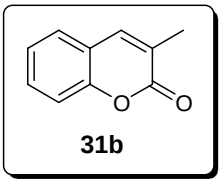
IR (KBr) (cm^{-1}) 3059, 1732, 1606

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 6.45 (d, 1H, *J* = 8 Hz), 7.28-7.37 (m, 2H), 7.50-7.58 (m, 2H), 7.73 (d, 1H, *J* = 8 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 116.5, 116.7, 118.8, 124.4, 127.9, 131.8, 143.5, 153.9, 160.6

MS m/z 147 (M+1)

Yield 0.49 g (61%)



31b

mp 68-70 °C (lit.[24] mp = 69-70 °C)

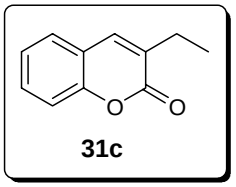
IR (KBr) (cm^{-1}) 3060, 2932, 1718

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.22 (s, 3H), 7.24-7.51 (m, 5H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 17.6, 114.5, 116.5, 118.8, 124.5, 127.9, 131.4, 143.1, 154.1, 160.6

MS m/z 161 (M+1)

Yield 0.55 g (63%)



31c

mp 66-68 ^{o}C

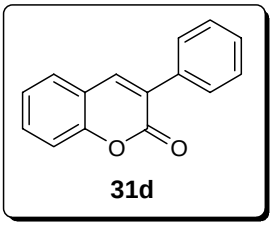
IR (KBr) (cm^{-1}) 3062, 2954, 1715

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.28 (t, 3H, *J* = 8 Hz), 2.63 (q, 2H, *J* = 8 Hz), 7.25-7.35 (m, 2H), 7.46-7.51 (m, 3H) **(Spectrum No. 55)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 12.2, 23.8, 116.3, 119.6, 124.2, 127.1, 130.4, 131.3, 137.4, 153.0, 161.7 **(Spectrum No. 56)**

MS (EI) m/z 175 (M+1)

Yield 0.67 g (60%)



31d

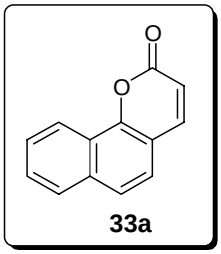
mp 134-136 ^{o}C (lit.[25] mp = 141 ^{o}C)

IR (KBr) (cm^{-1}) 3055, 2961, 1717

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.28-7.33 (m, 2H), 7.38-7.40 (m, 1H), 7.43-7.49 (m, 3H), 7.53-7.57 (m, 2H), 7.73-7.74 (m, 1H), 7.83 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 116.1, 119.4, 124.2, 127.8, 128.2, 128.3, 128.6, 131.1, 134.5, 139.6, 153.3, 160.2

MS m/z 223 (M+1)


33a

Yield 0.36 g (37%)

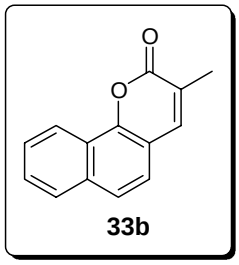
mp 118-120 ^{o}C

IR (KBr) (cm^{-1}) 3059, 1717

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 6.60 (d, 1H, *J* = 10 Hz), 7.48 (d, 1H, *J* = 9 Hz), 7.60 (t, 1H, *J* = 8 Hz), 7.72 (t, 1H, *J* = 8 Hz), 7.95 (d, 1H, *J* = 8 Hz), 8.01 (d, 1H, *J* = 8 Hz), 8.25 (d, 1H, *J* = 9 Hz), 8.51 (d, 1H, *J* = 10 Hz)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 112.9, 115.5, 116.9, 121.3, 126.0, 128.0, 128.2, 128.9, 130.2, 133.0, 138.9, 153.8, 160.8

MS m/z 197 (M+1)


33b

Yield 0.61 g (58%)

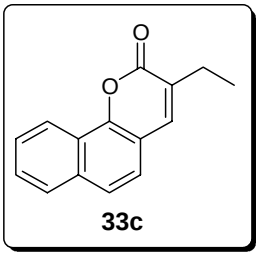
mp 148-150 ^{o}C (lit.[26] mp = 132-133 ^{o}C)

IR (KBr) (cm^{-1}) 3058, 2962, 1705

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.36 (s, 3H), 7.48 (d, 1H, *J* = 8 Hz), 7.58 (t, 1H, *J* = 8 Hz), 7.70 (t, 1H, *J* = 8 Hz), 7.92-7.96 (m, 2H), 8.26 (d, 1H, *J* = 8 Hz), 8.33 (s, 1H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 17.4, 116.5, 121.2, 124.7, 125.6, 127.6, 128.4, 128.7, 130.0, 131.3, 134.7, 152.2, 161.9

MS m/z 211 (M+1)


33c

Yield 0.62 g (55%)

mp 108-110 ^{o}C

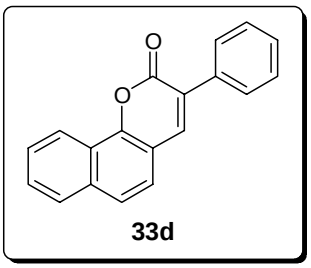
IR (KBr) (cm^{-1}) 3060, 2965, 1705

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.37 (t, 3H, *J* = 8 Hz),

2.74 (q, 2H, *J* = 8 Hz), 7.28 (s, 1H), 7.47 (d, 1H, *J* = 8 Hz), 7.58 (d, 1H, *J* = 8 Hz), 7.70 (t, 1H, *J* = 8 Hz), 7.93 (t, 1H, *J* = 8 Hz), 8.27-8.28 (m, 2H)

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 12.3, 24.1, 113.1, 116.7, 121.1, 125.5, 127.6, 128.5, 128.7, 130.0, 130.1, 131.3, 132.8, 152.0, 161.4

MS m/z 225 (M+1)



33d

Yield 0.80 g (59%)

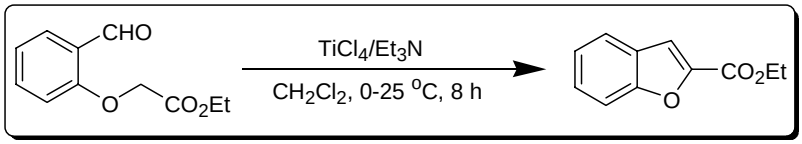
mp 214-216 °C (lit.[27] mp = 212-213 °C)

IR (KBr) (cm^{-1}) 3061, 1719

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.45-7.55 (m, 4H), 7.61 (t, 1H, *J* = 8 Hz), 7.73 (t, 1H, *J* = 8 Hz), 7.83-7.84 (m, 2H), 7.96 (d, 1H, *J* = 8 Hz), 8.02 (d, 1H, *J* = 9 Hz), 8.34 (d, 1H, *J* = 8 Hz), 8.63 (s, 1H) **(Spectrum No. 57)**

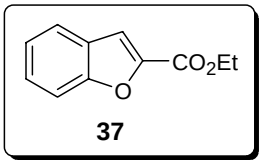
^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 113.6, 116.5, 121.3, 126.0, 126.8, 128.1, 128.5, 128.8, 129.0, 130.2, 132.5, 135.0, 135.4, 152.9, 160.4 **(Spectrum No. 58)**

MS m/z 273 (M+1)



Yield 0.29 g (31%)

IR (Neat) (cm^{-1}) 3065, 2982, 1730



37

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.46 (t, 3H, *J* = 7 Hz), 4.47 (q, 2H, *J* = 7 Hz), 7.31-7.35 (m, 1H), 7.45-7.49 (m, 1H), 7.55-7.56 (m, 1H), 7.61-7.63 (m, 1H), 7.68-7.72 (m, 1H) **(Spectrum No. 59)**

^{13}C-NMR (50 MHz, $CDCl_3$, δ ppm): 14.2, 61.3, 112.3, 113.6, 122.7, 123.7, 127.0, 127.4, 145.9, 155.8, 159.5 **(Spectrum No. 60)**

4.5 References

1. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.
2. Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147.
3. McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708.
4. McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2656.
5. (a) Benerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1990**, 150 (b) Talukdar, S.; Nayak, S. K.; Benerji, A. *J. Org. Chem.* **1998**, *63*, 4925.
6. Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215.
7. Lehnert, W. *Tetrahedron Lett.* **1970**, 4723.
8. Lehnert, W. *Tetrahedron* **1974**, *30*, 301.
9. Lehnert, W. *Synthesis* **1974**, 667.
10. Baxter, G. J.; Brown, R. F. C. *Aus. J. Chem.* **1975**, *28*, 1551.
11. Falsone, G.; Spur, B. *Liebigs Ann. Chem.* **1979**, 751.
12. Lange, J.; Kanabus-Kamińska, J. M.; Kral, A. *Synth. Commun.* **1980**, *10*, 473.
13. Yamaguchi, M.; Hirao, I. *J. Org. Chem.* **1985**, *50*, 1975.
14. Singh, R. K.; Rogers, M. D. *J. Heterocyclic Chem.* **1985**, *22*, 1713.
15. Banno, K.; Mukaiyama, T. *Chem. Lett.* **1976**, 279.
16. Harrison, C. *Tetrahedron Lett.* **1987**, *28*, 4135.
17. (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611 (b) Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clawson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Strauss, D.; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55,* 1733 (c) Meinhardt, J. D.; Anslyn, E. V.; Grubbs, R. H.

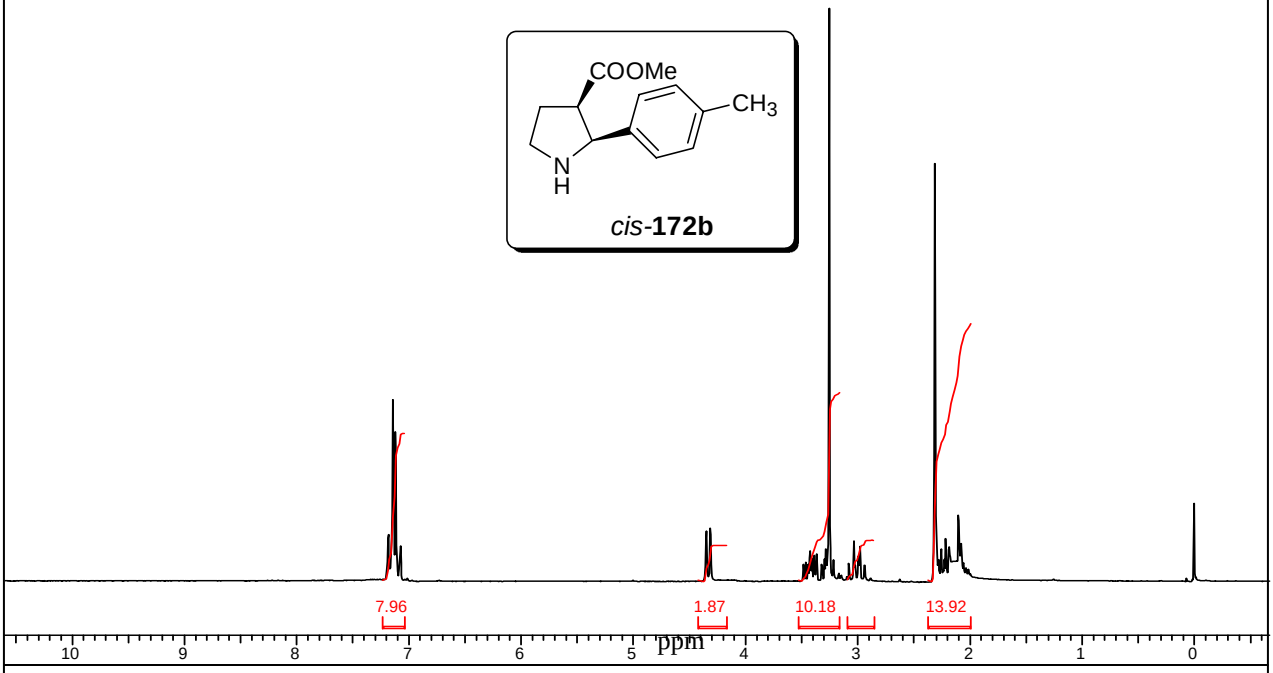
Organometallics **1989**, *8*, 583 (d) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72 (e) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698 (f) Minicione, E.; Pearson, A. J.; Bovicelli, P.; Chandler, M.; Heywood, G. C. *Tetrahedron Lett.* **1981**, *22,* 2929 (g) Snowden, R. L.; Sonnay, P.; Ohloft, G. *Helv. Chim. Acta* **1981**, *64*, 25 (h) Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, *65*, 293 (i) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25,* 1067 (j) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26,* 5579.

18. (a) Yan, T. –H.; Tsai, C. –C.; Chien, C. –T.; Cho, C. –C.; Huang, P. –C. *Org. Lett.* **2004**, *6*, 4961 (b) Yan, T. –H.; Chien, C. –T.; Tsai, C. –C.; Lin, K. –W.; Wu, Y. –H. *Org. Lett.* **2004**, *6*, 4965.
19. McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249.
20. Davies, S. G.; Thomas, S. E. *Synthesis* **1984**, 1027.
21. Katritzky, A. R.; Cheng, D.; Henderson, S. A.; Li, J. *J. Org. Chem.* **1998**, *63*, 6704.
22. Ashram, M. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1662.
23. Cartwright, G. A.; McNab, H. *J. Chem. Res. (Synopses)* **1997**, 296.
24. Sunitha, K.; Balasubramanian, K. K.; Rajagopalan, K. *J. Org. Chem.* **1985**, *50*, 1530.
25. Singer, L. A.; Kong, N. P. *J. Am. Chem. Soc.* **1966**, *88*, 5213.
26. Mali, R. S.; Yeola, S. N.; Kulkarni, B. K. *Indian J. Chem.* **1983**, *22B*, 352.
27. Brady, W. T.; Agho, M. O. *J. Org. Chem.* **1983**, *48*, 5337.

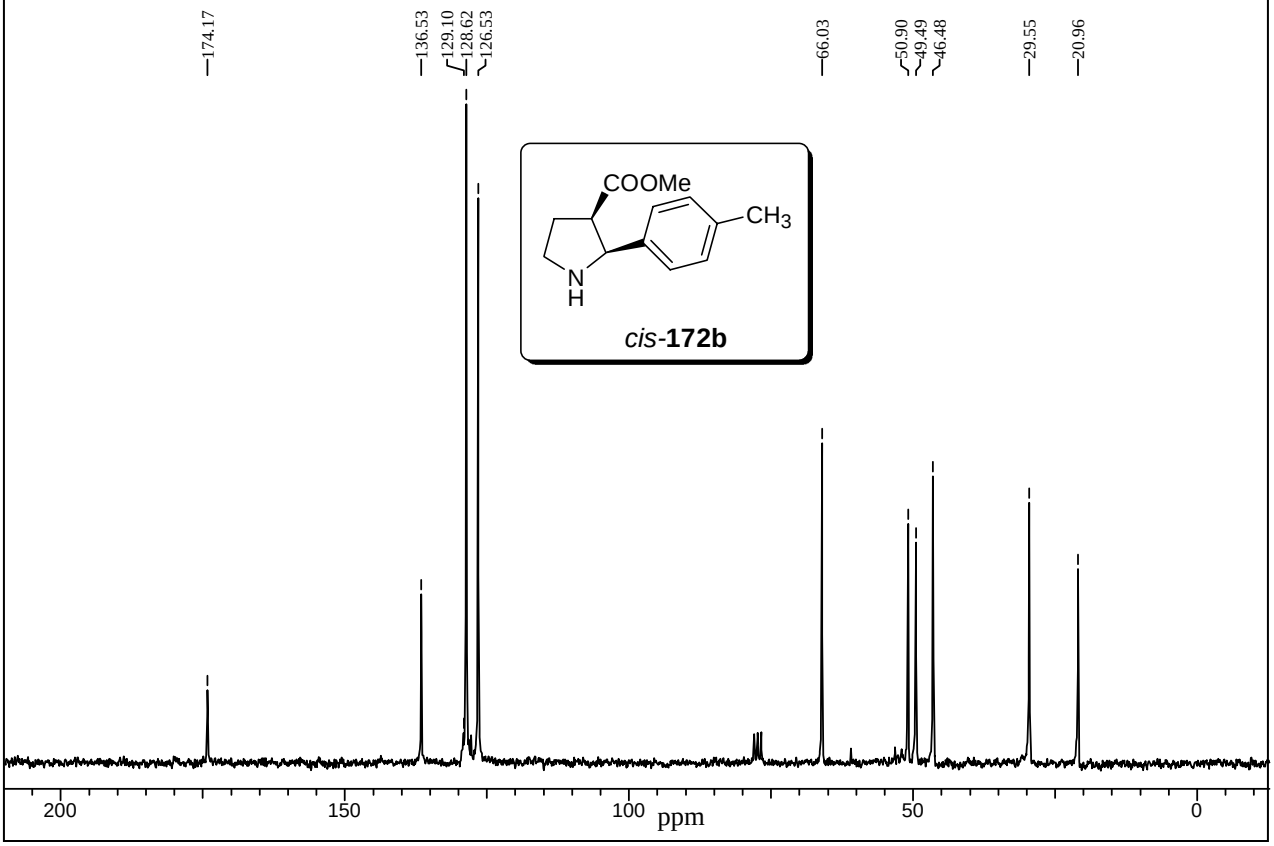
Appendix I

(Representative Spectra)

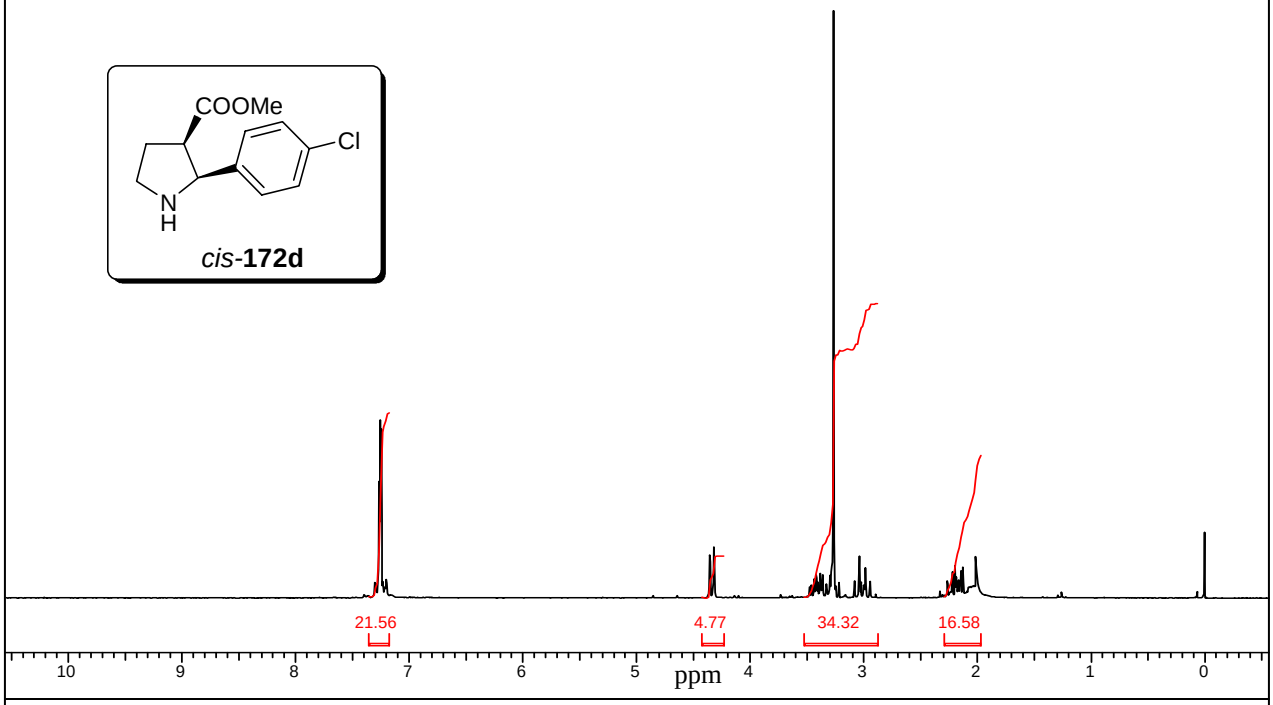
Spectrum No. 1 (Chapter 1, Section 1.4.3) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



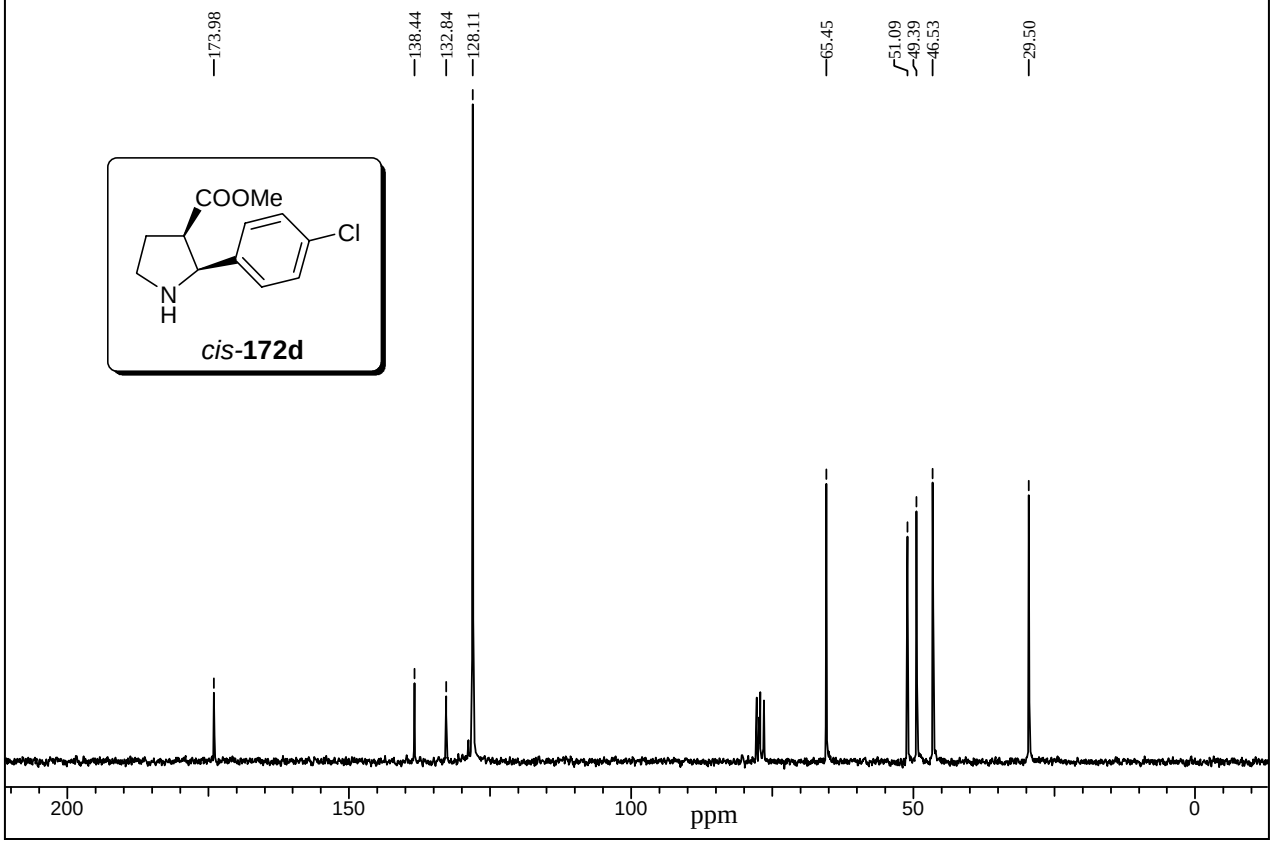
Spectrum No. 2 (Chapter 1, Section 1.4.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



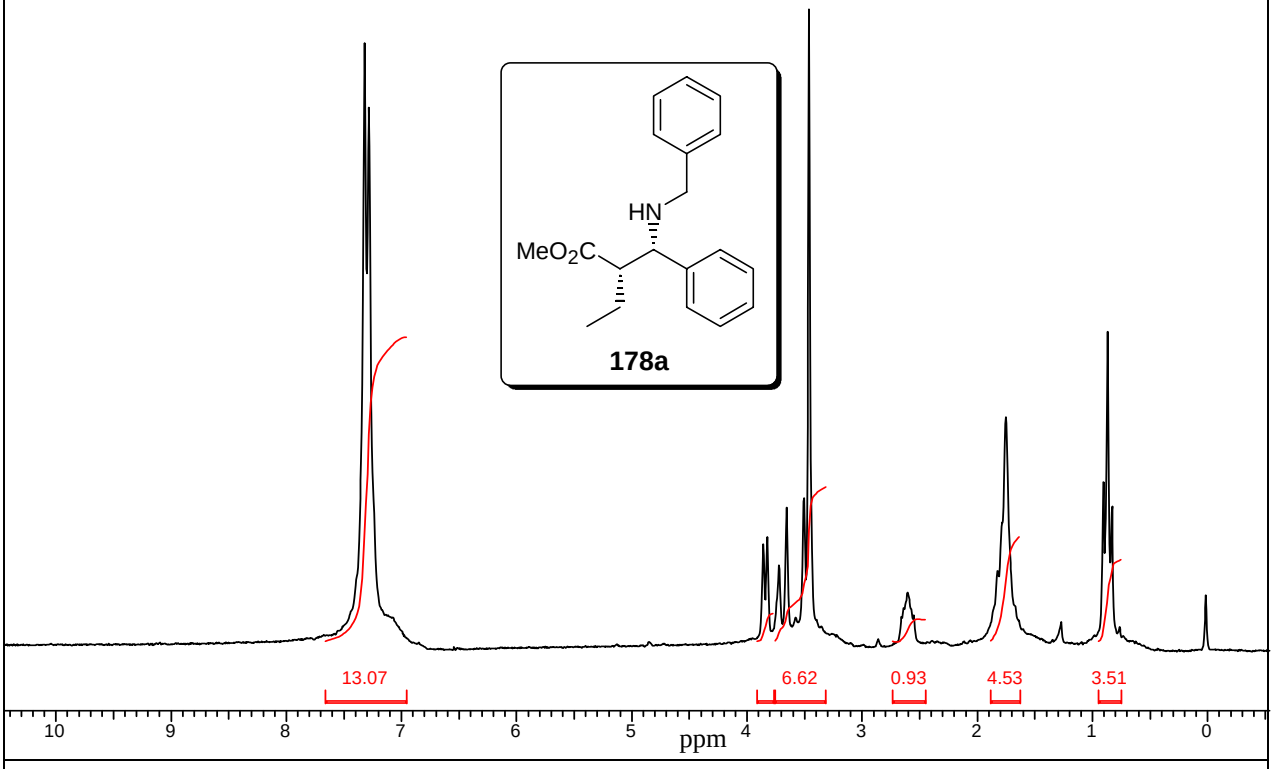
Spectrum No. 3 (Chapter 1, Section 1.4.3) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



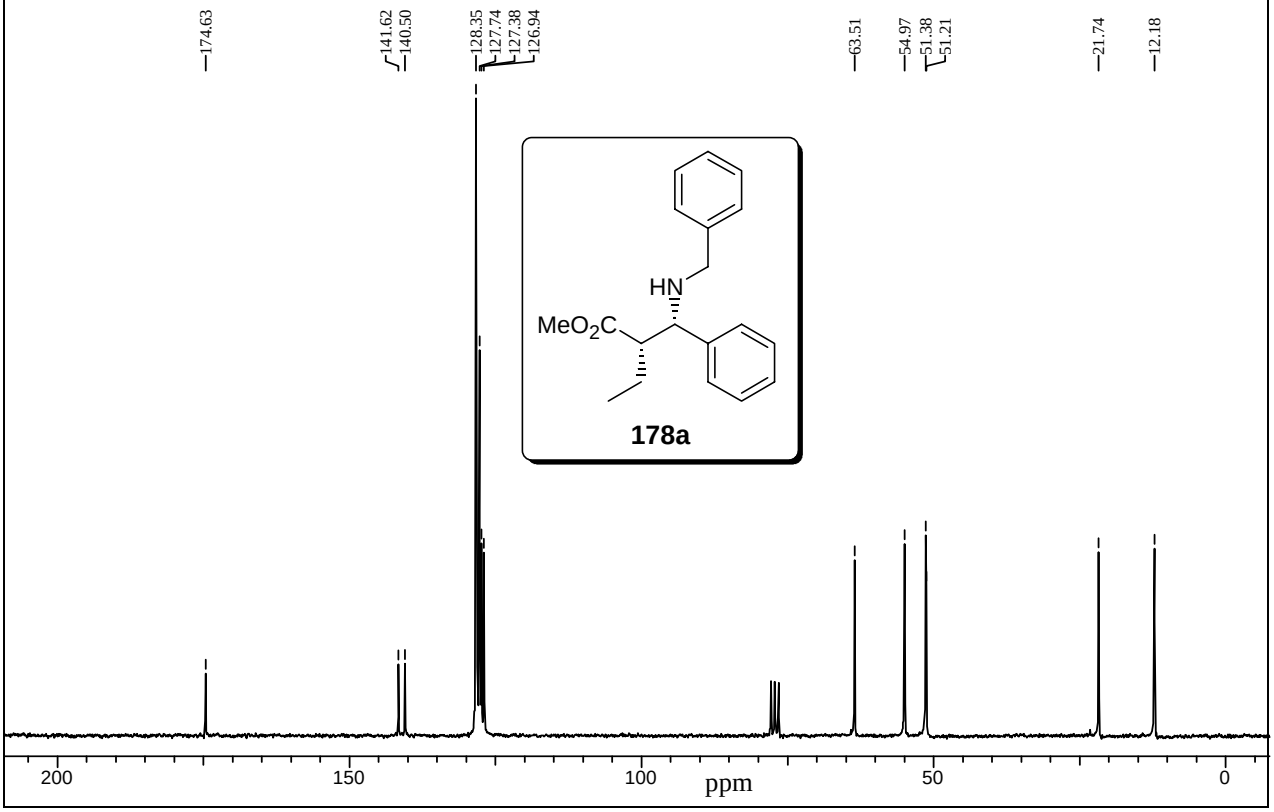
Spectrum No. 4 (Chapter 1, Section 1.4.3) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



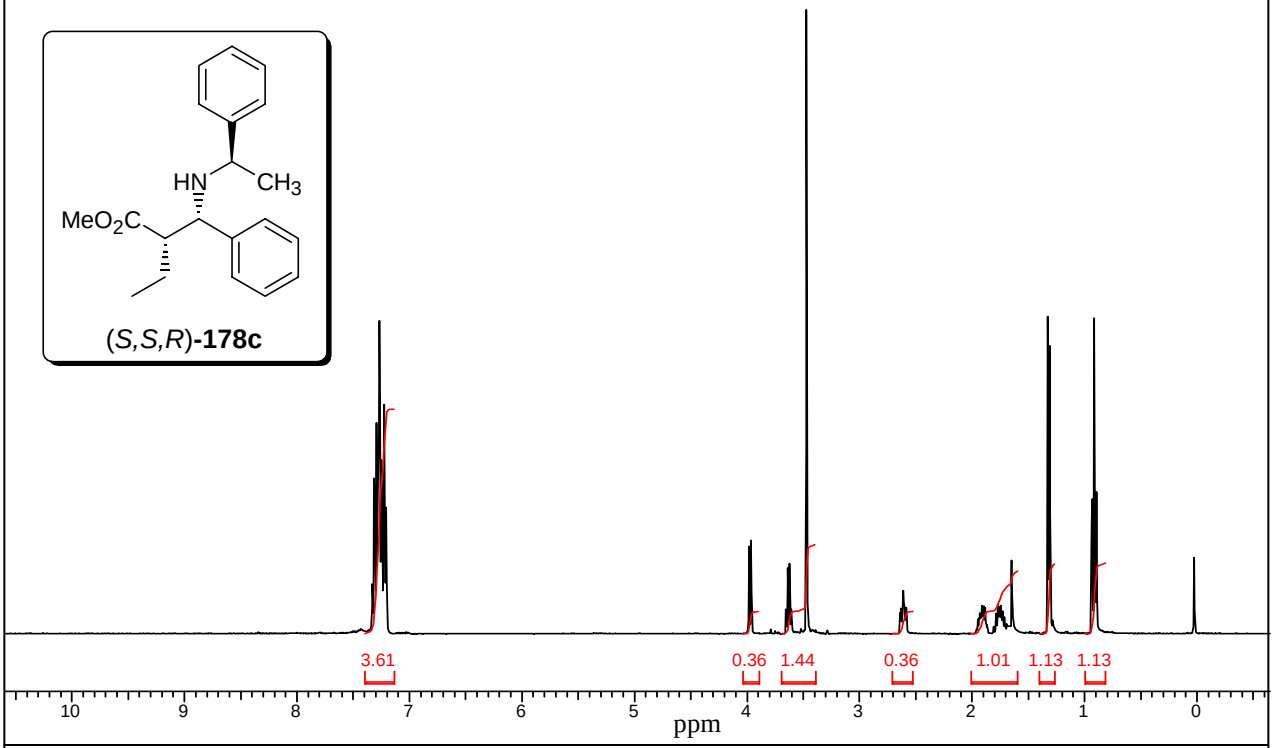
Spectrum No. 5 (Chapter 1, Section 1.4.4) ^{1}H NMR Spectrum (200MHz, $CDCl_3$)



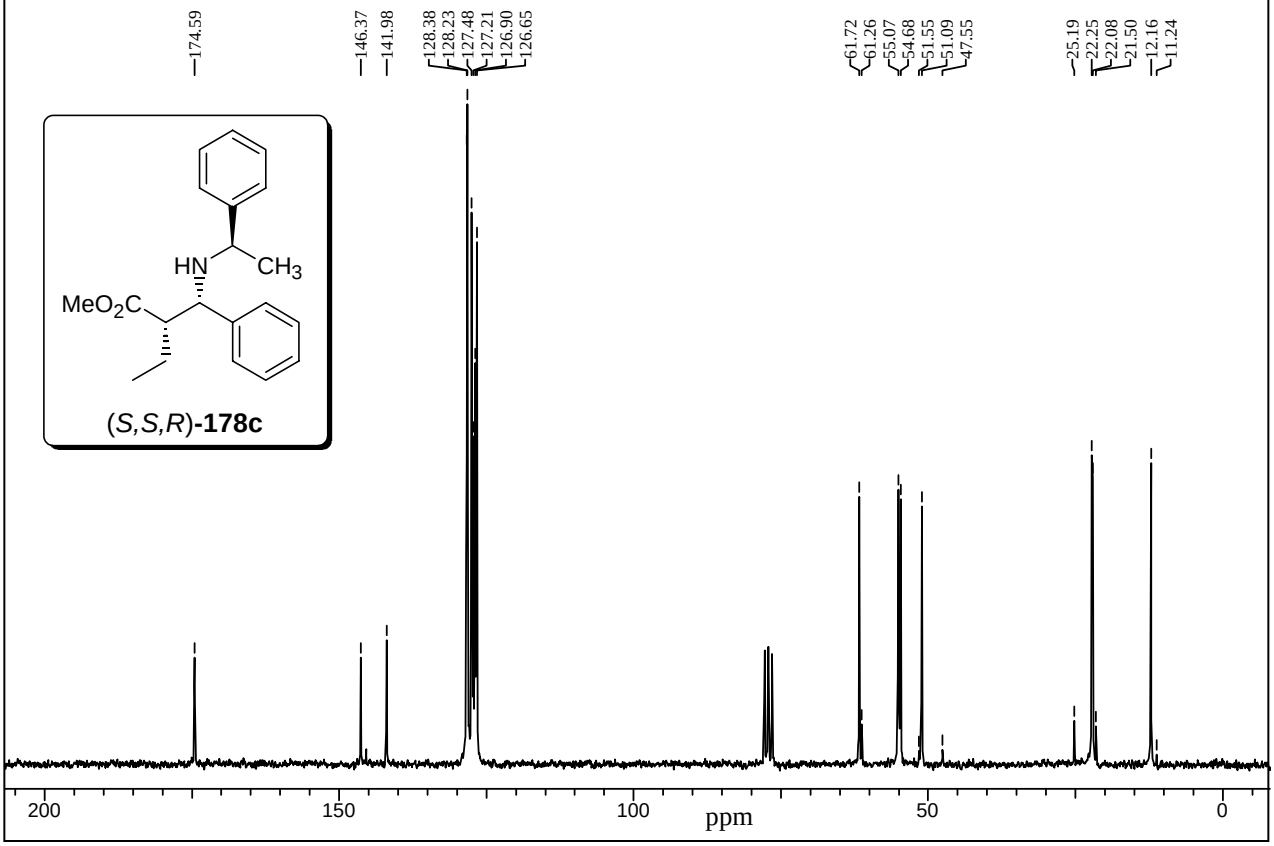
Spectrum No. 6 (Chapter 1, Section 1.4.4) ^{1}H NMR Spectrum (50 MHz, $CDCl_3$)



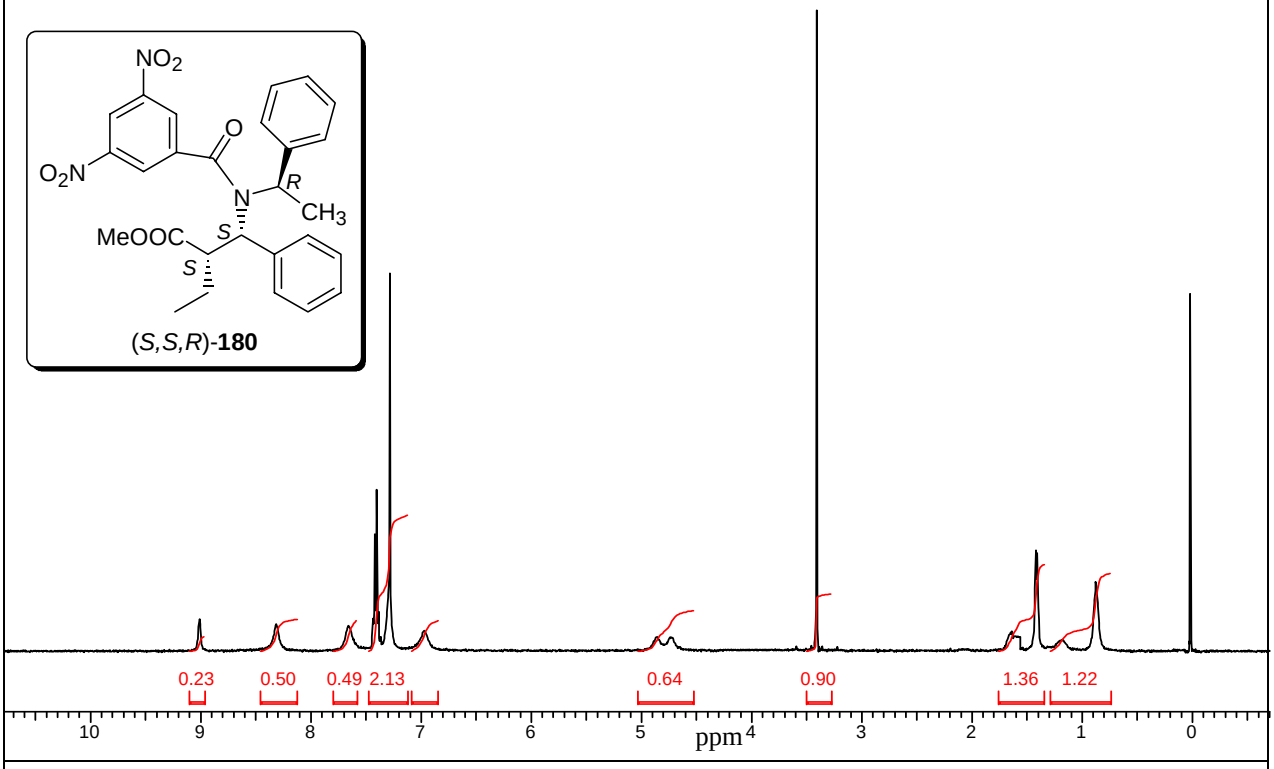
Spectrum No. 7 (Chapter 1, Section 1.4.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



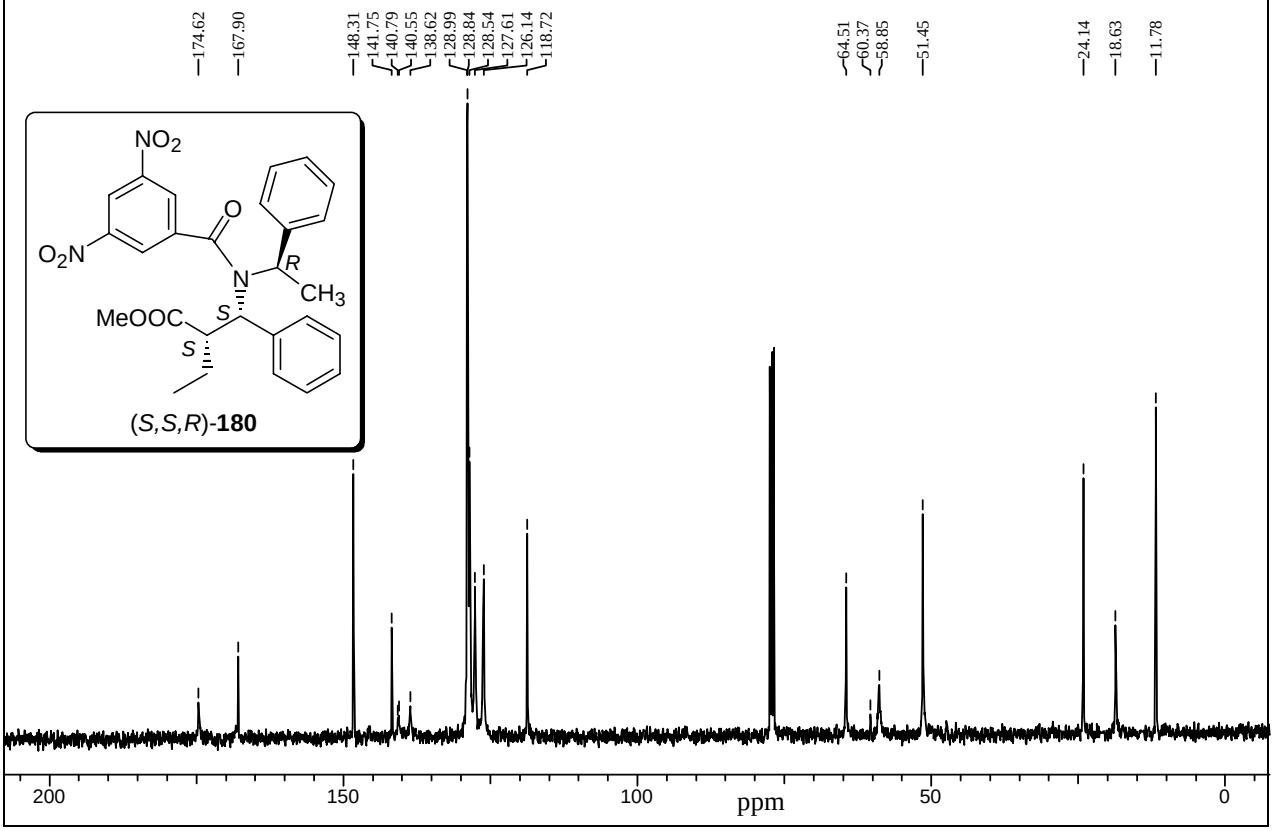
Spectrum No. 8 (Chapter 1, Section 1.4.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



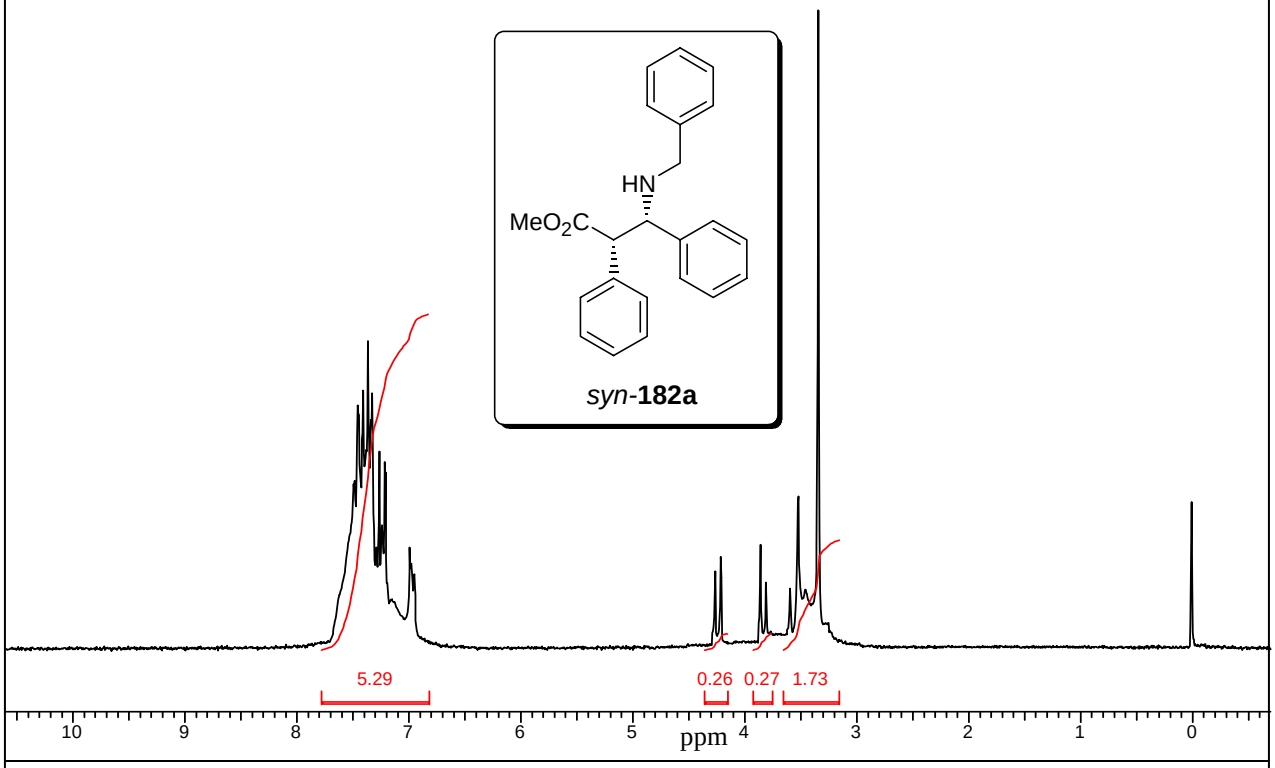
Spectrum No. 9 (Chapter 1, Section 1.4.5) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



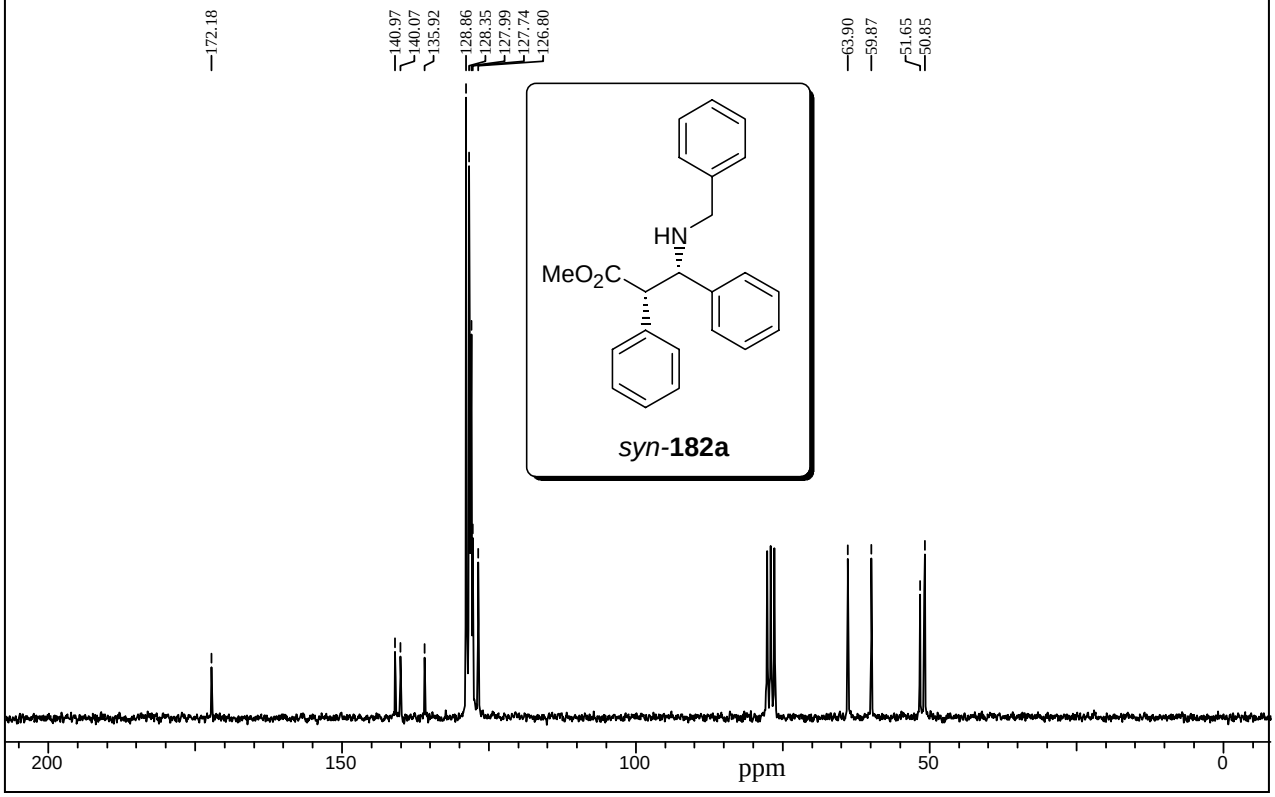
Spectrum No. 10 (Chapter 1, Section 1.4.5) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



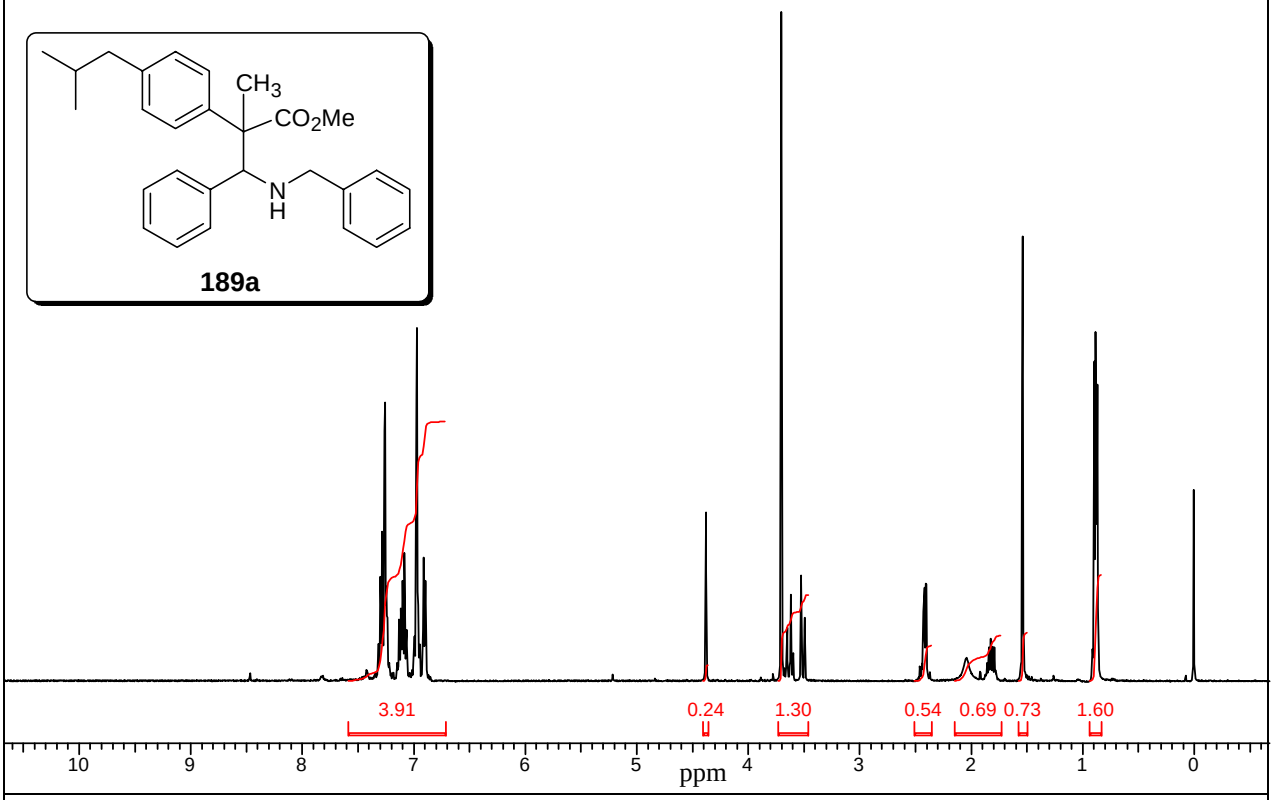
Spectrum No. 11 (Chapter 1, Section 1.4.6) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



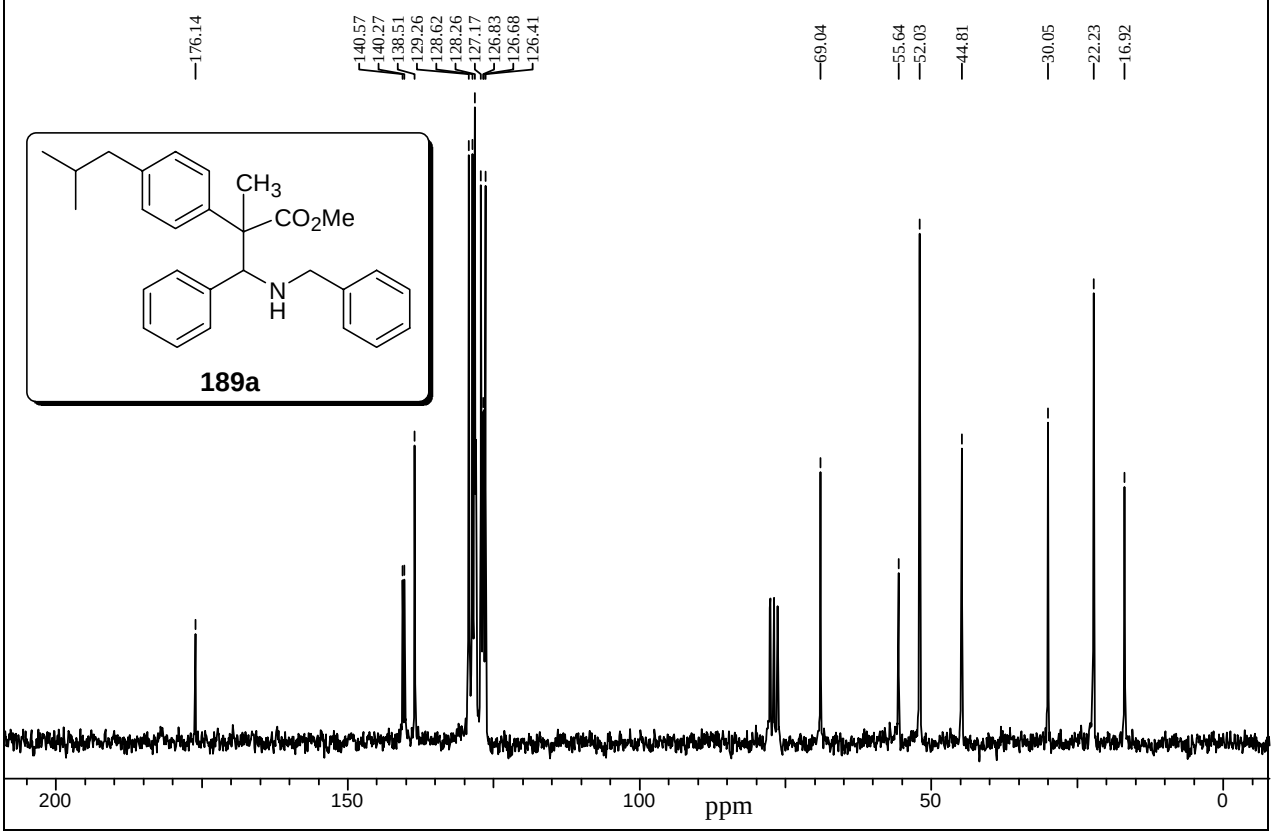
Spectrum No. 12 (Chapter 1, Section 1.4.6) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



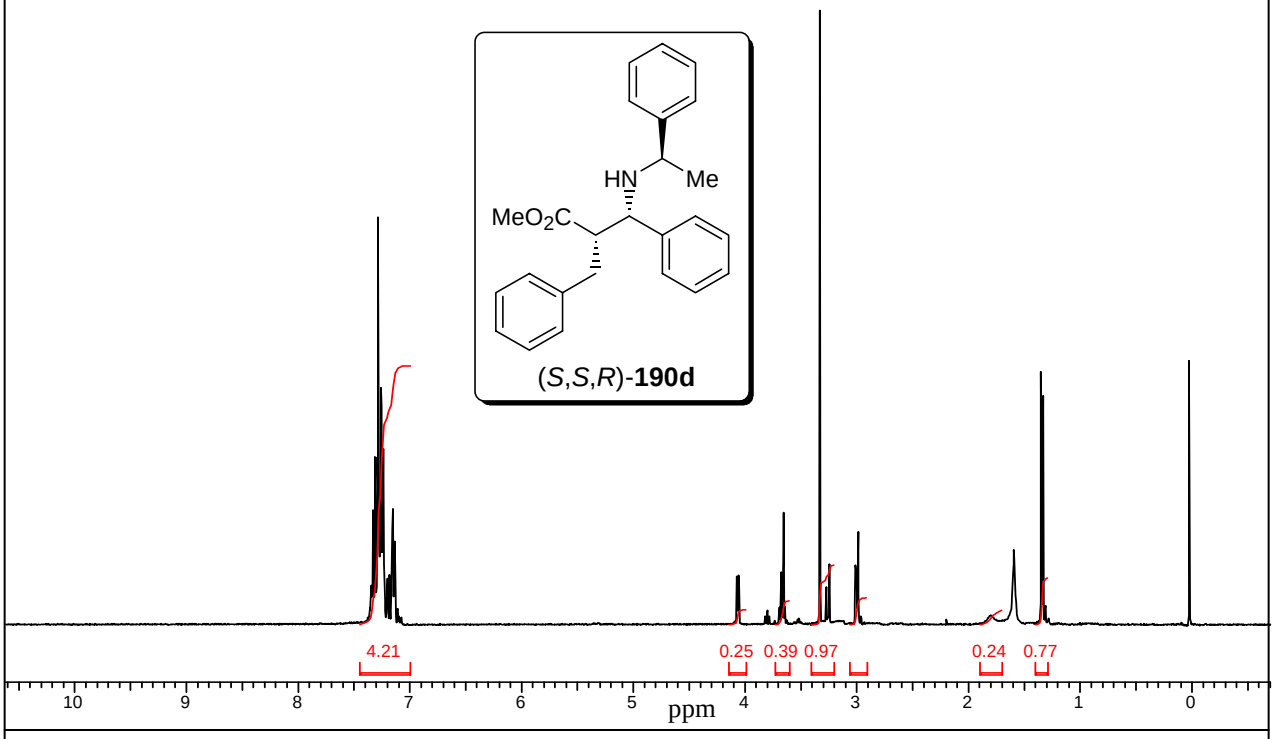
Spectrum No. 13 (Chapter 1, Section 1.4.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



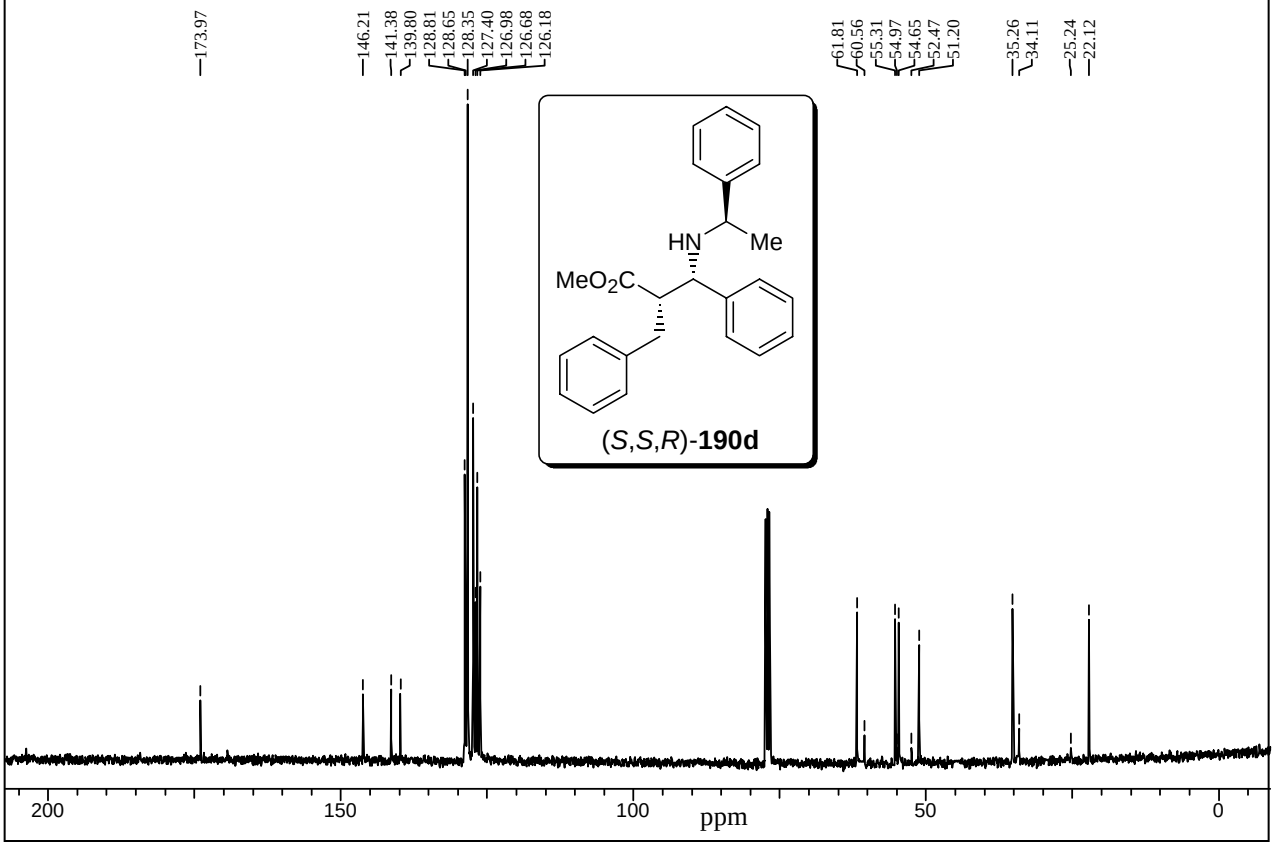
Spectrum No. 14 (Chapter 1, Section 1.4.6) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



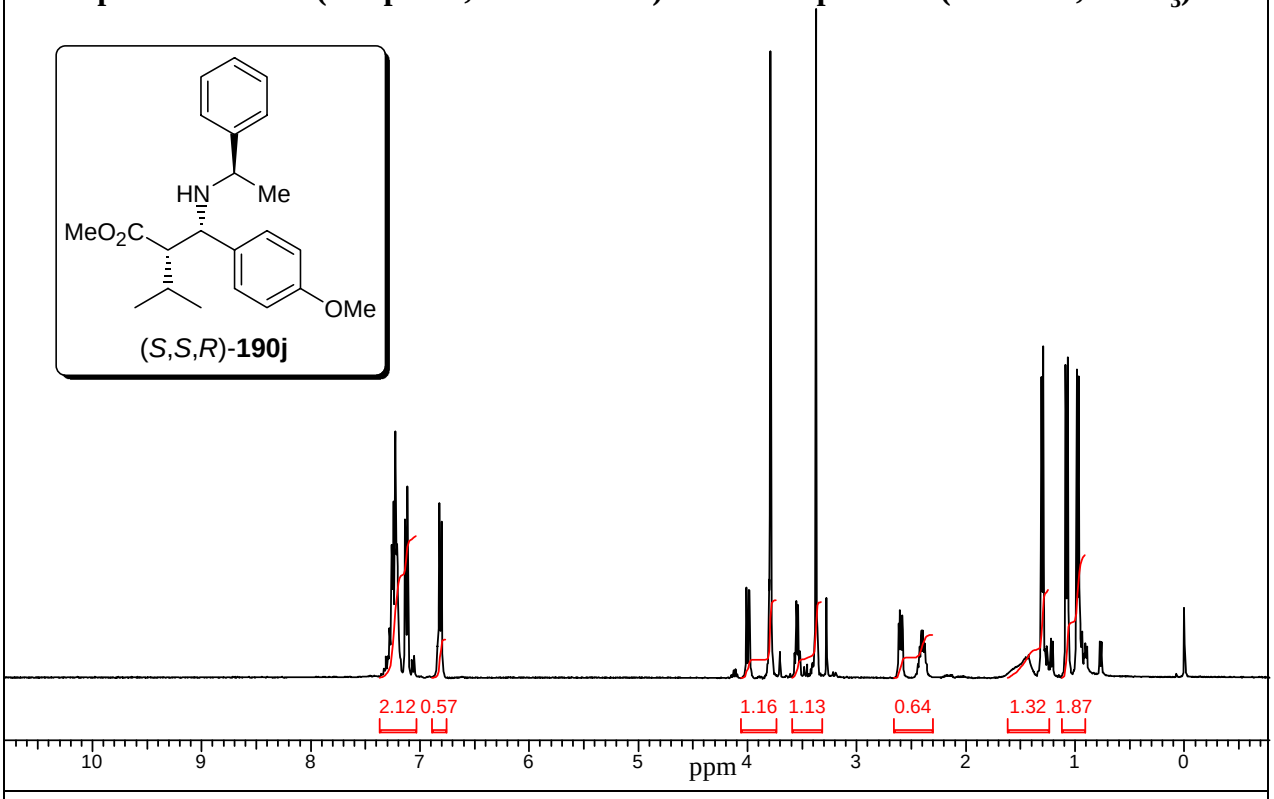
Spectrum No. 15 (Chapter 1, Section 1.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



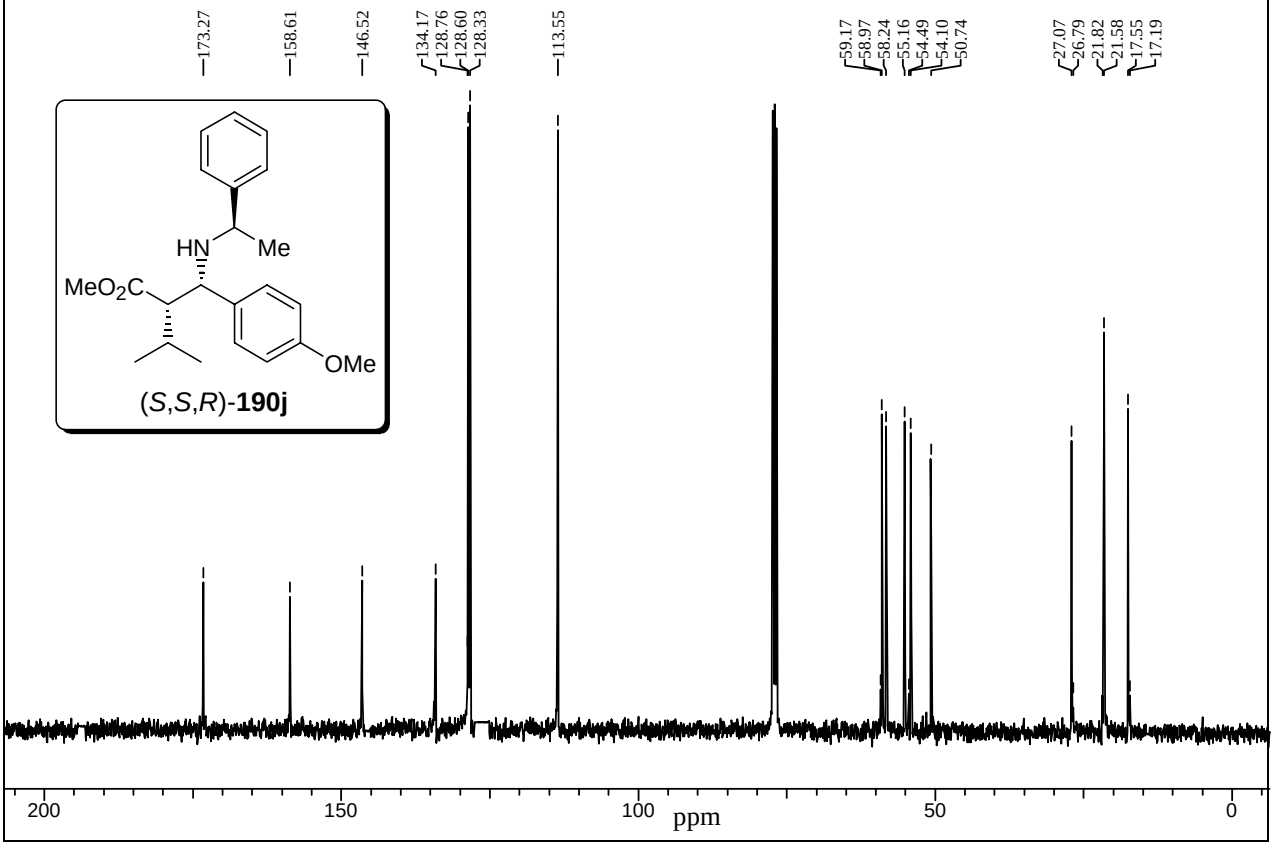
Spectrum No. 16 (Chapter 1, Section 1.4.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



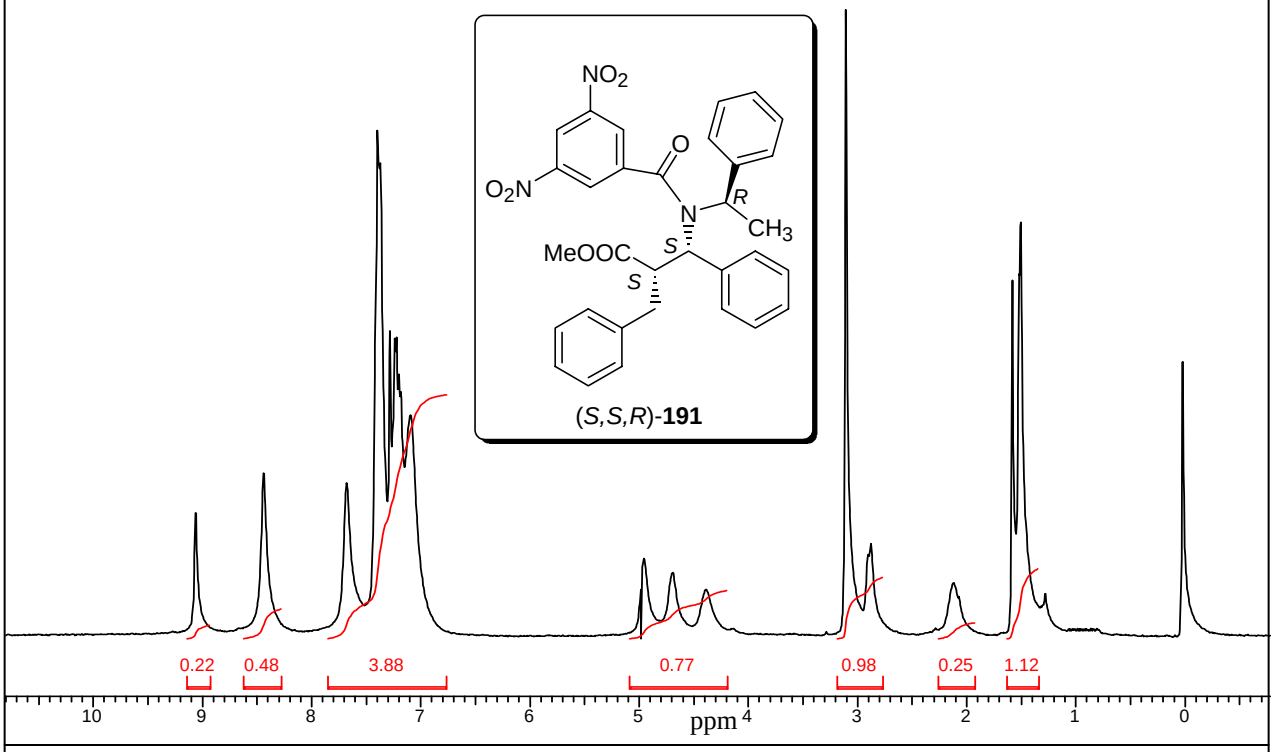
Spectrum No. 17 (Chapter 1, Section 1.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



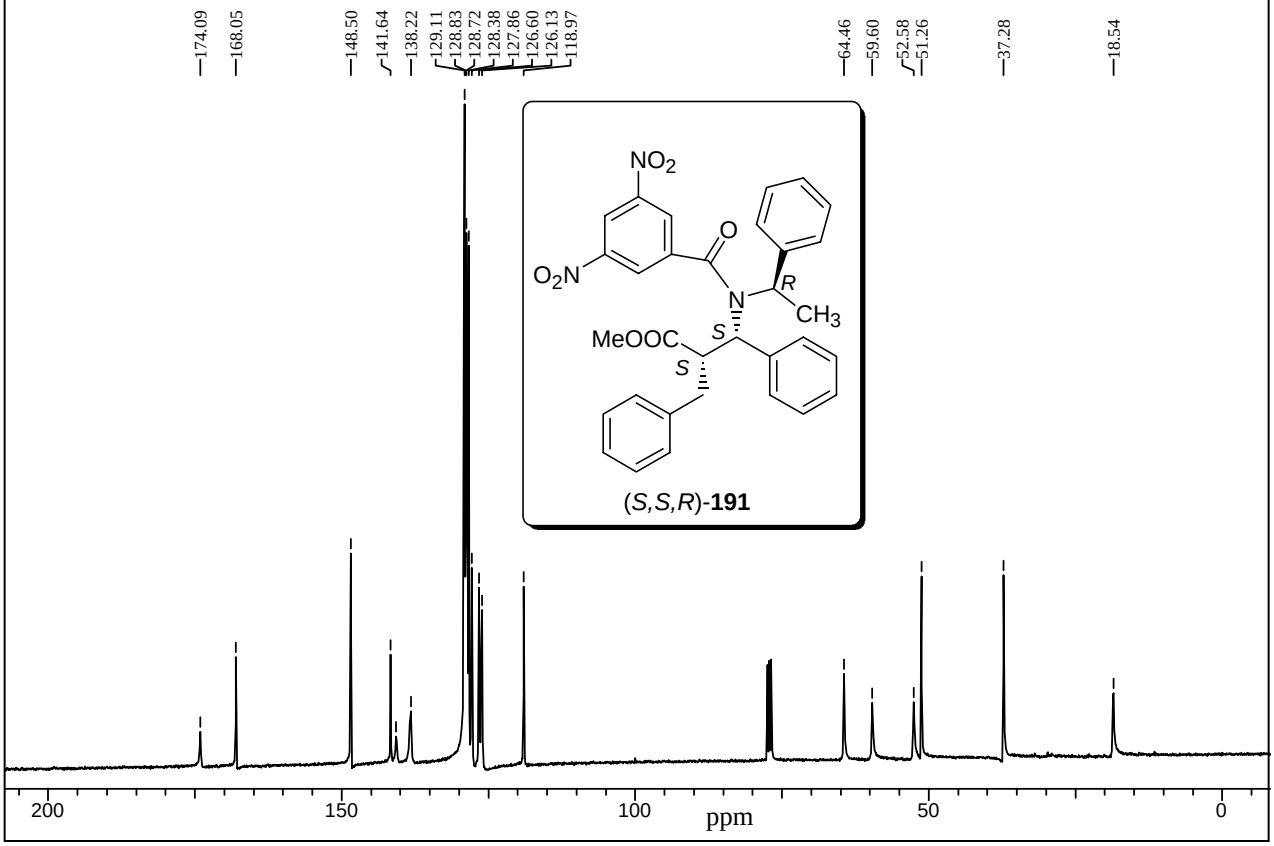
Spectrum No. 18 (Chapter 1, Section 1.4.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



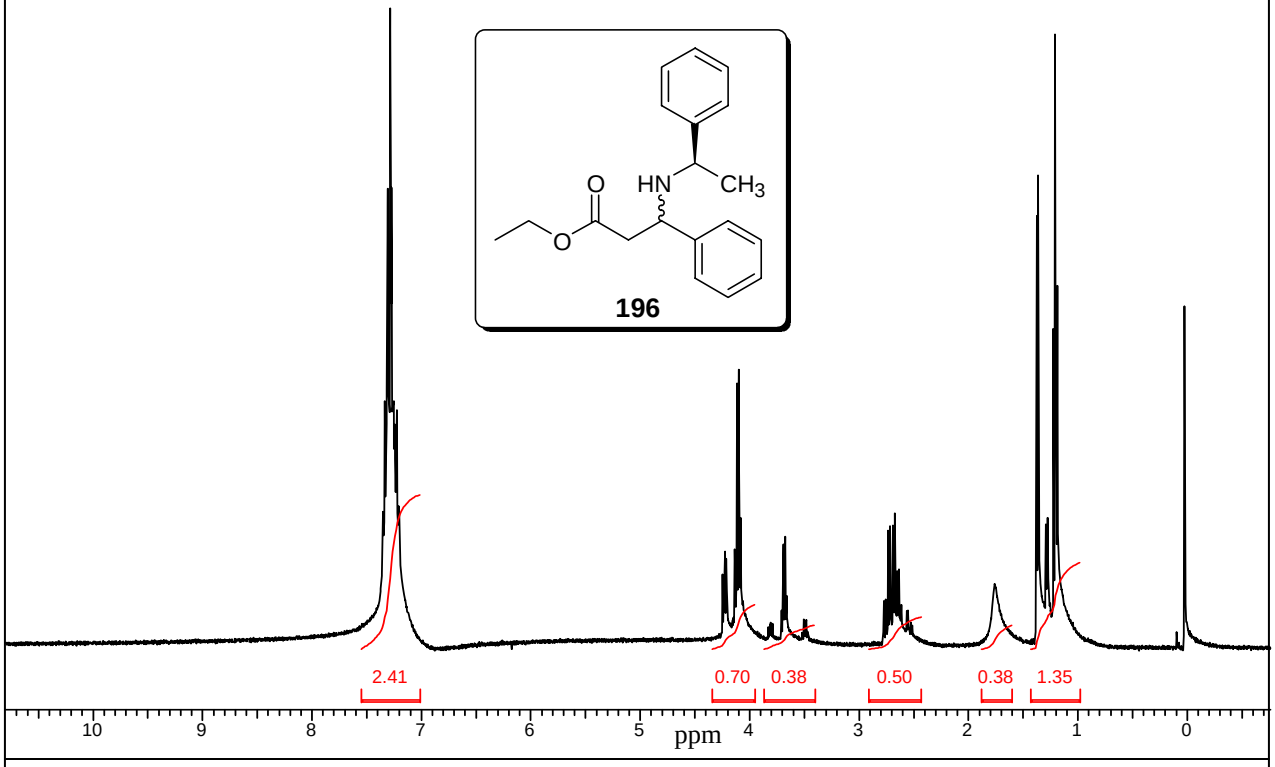
Spectrum No. 19 (Chapter 1, Section 1.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



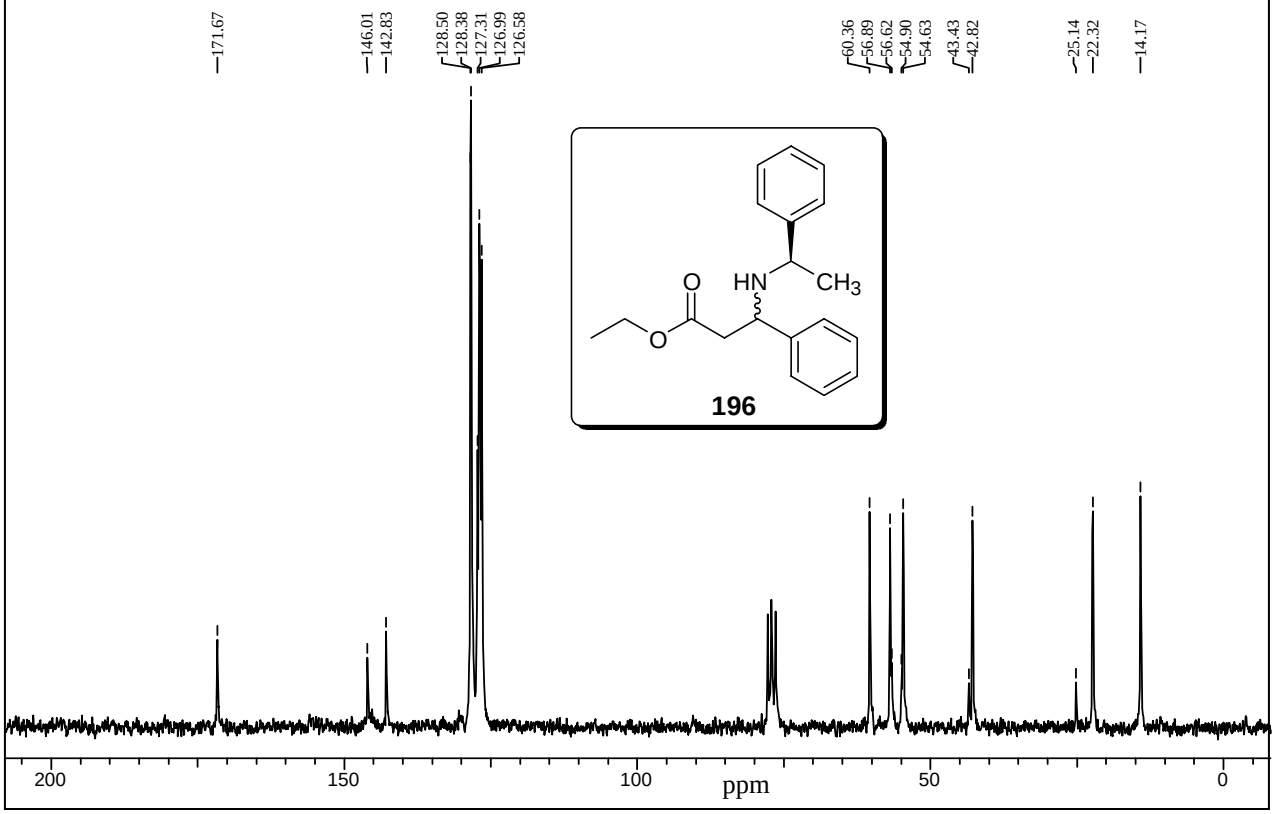
Spectrum No. 20 (Chapter 1, Section 1.4.7) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



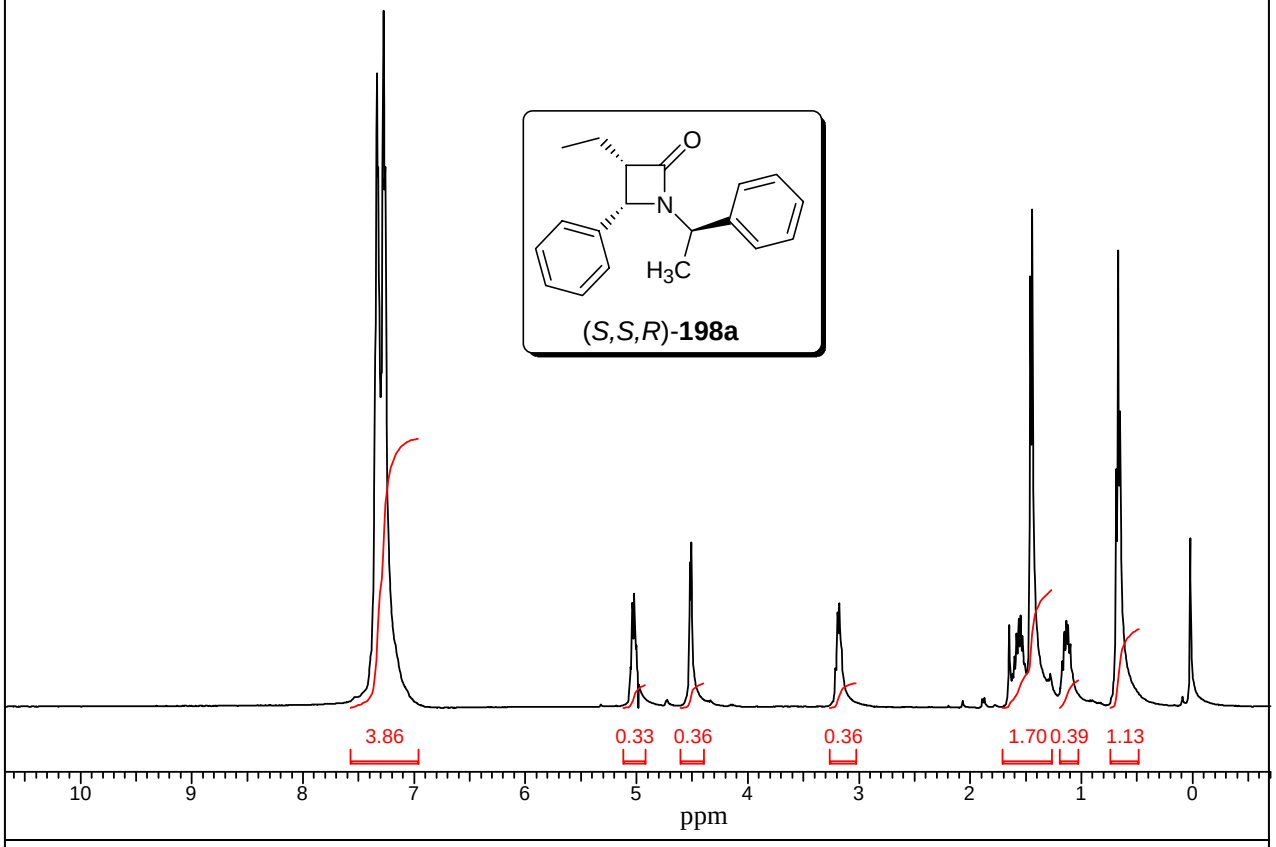
Spectrum No. 21 (Chapter 1, Section 1.4.7) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



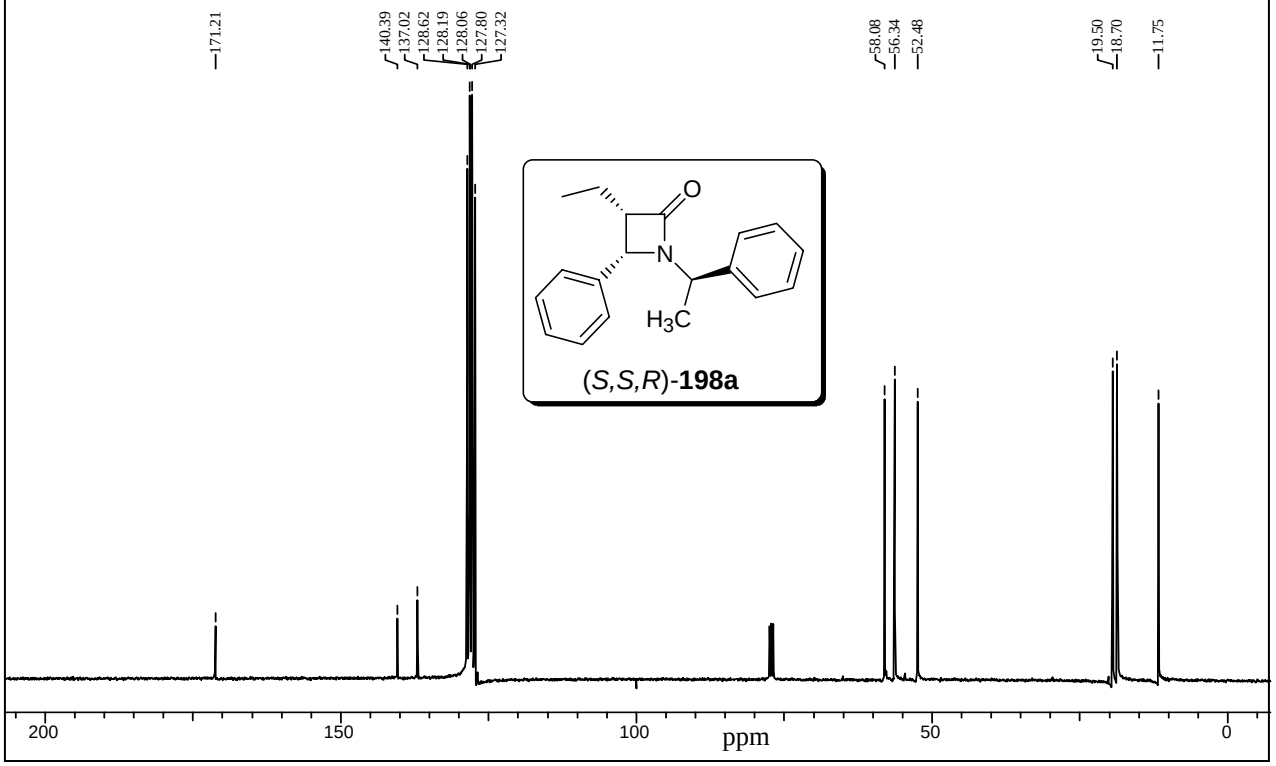
Spectrum No. 22 (Chapter 1, Section 1.4.7) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



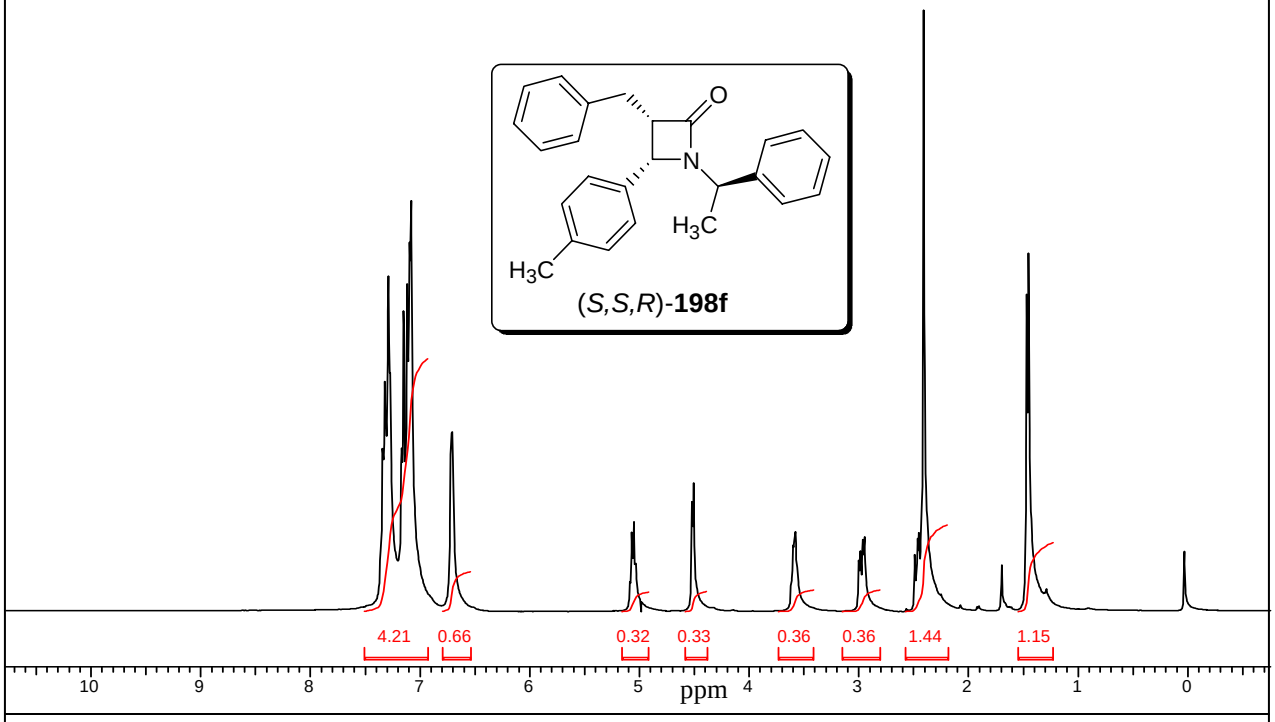
Spectrum No. 23 (Chapter 1, Section 1.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



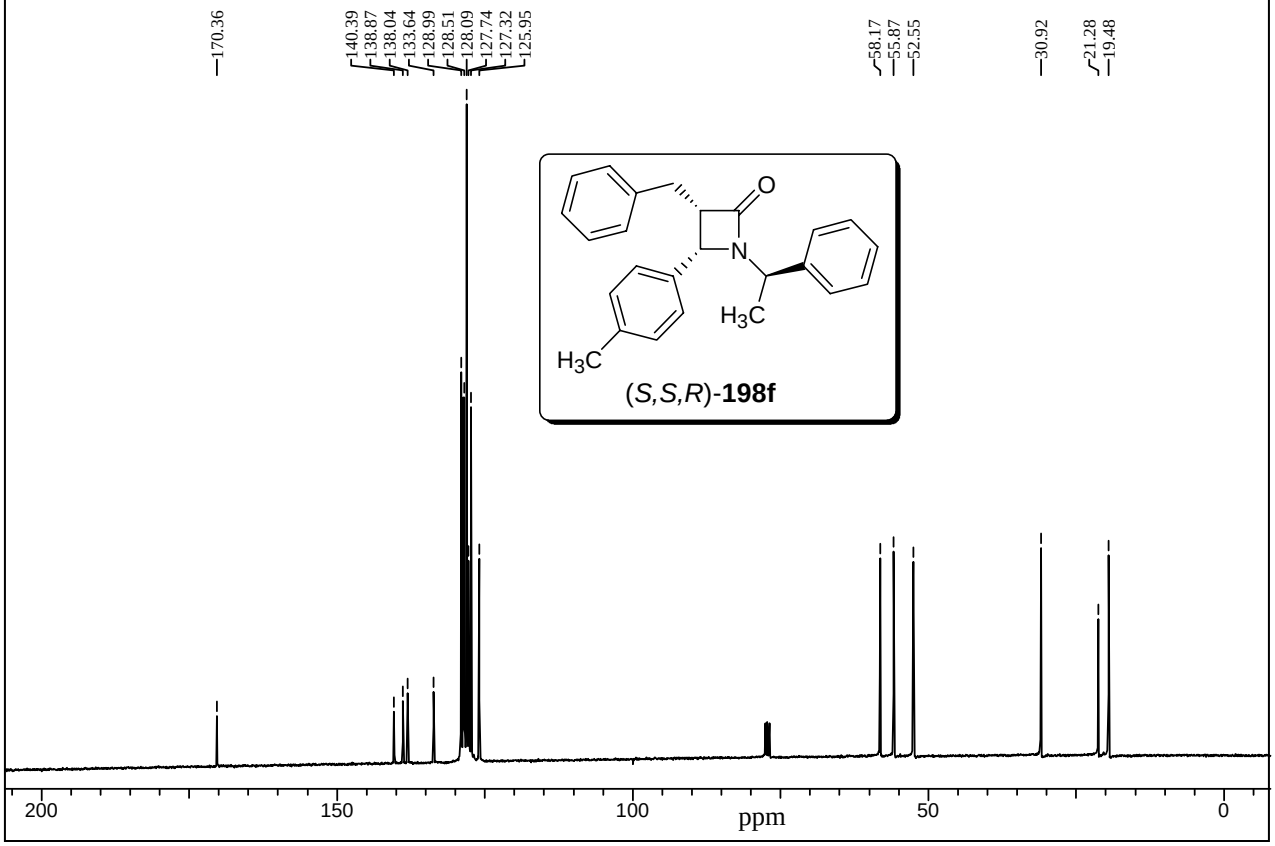
Spectrum No. 24 (Chapter 1, Section 1.4.9) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



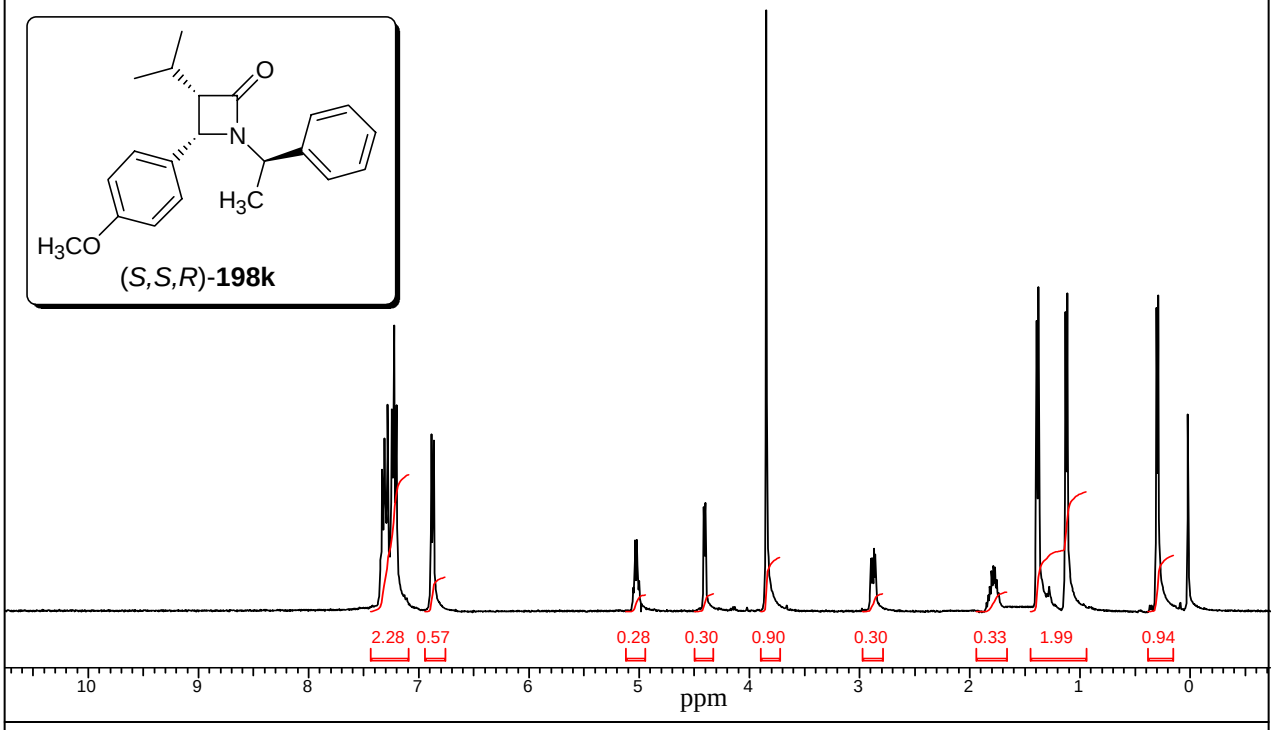
Spectrum No. 25 (Chapter 1, Section 1.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



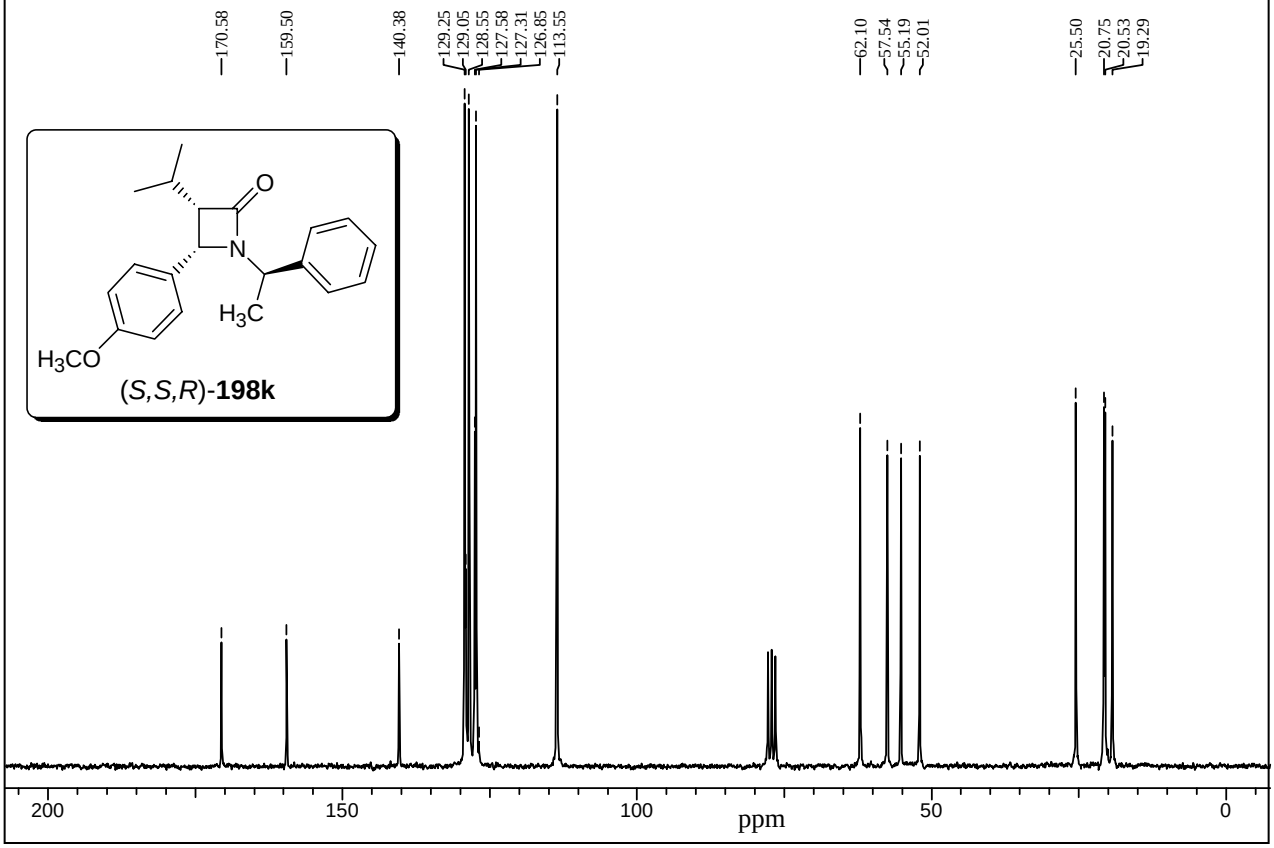
Spectrum No. 26 (Chapter 1, Section 1.4.9) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



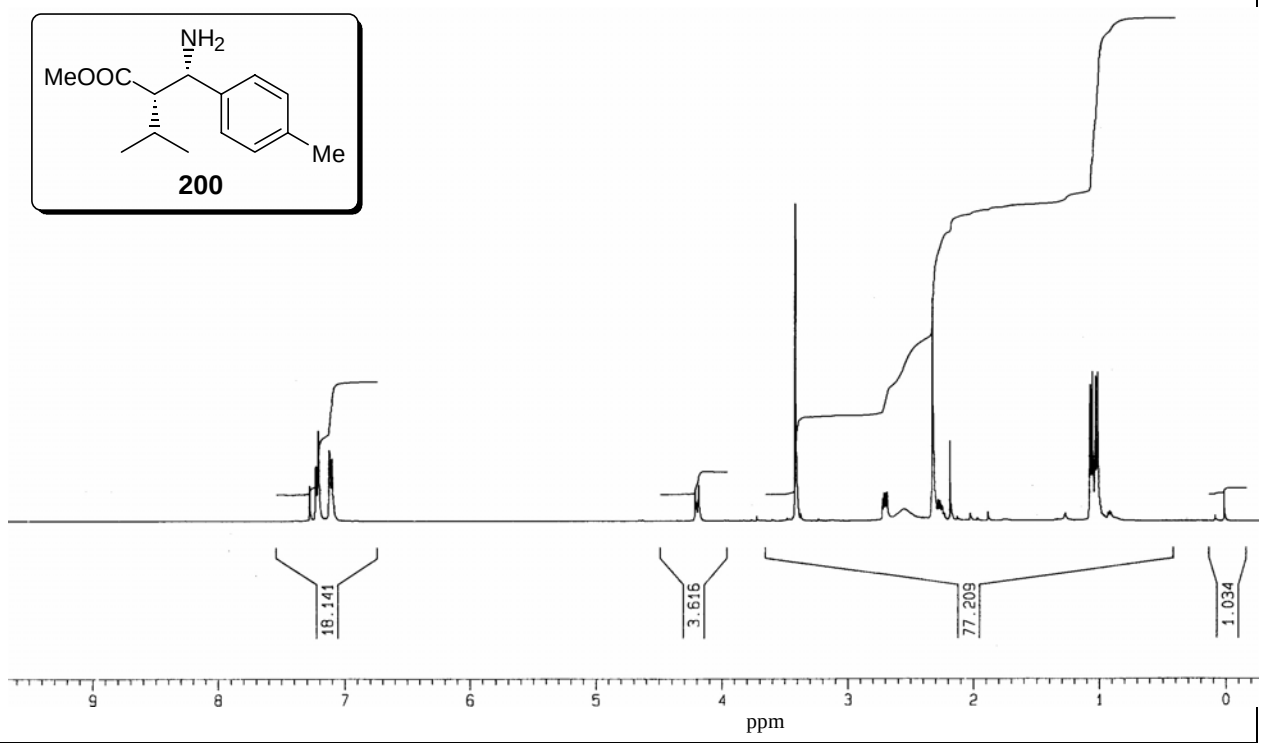
Spectrum No. 27 (Chapter 1, Section 1.4.9) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



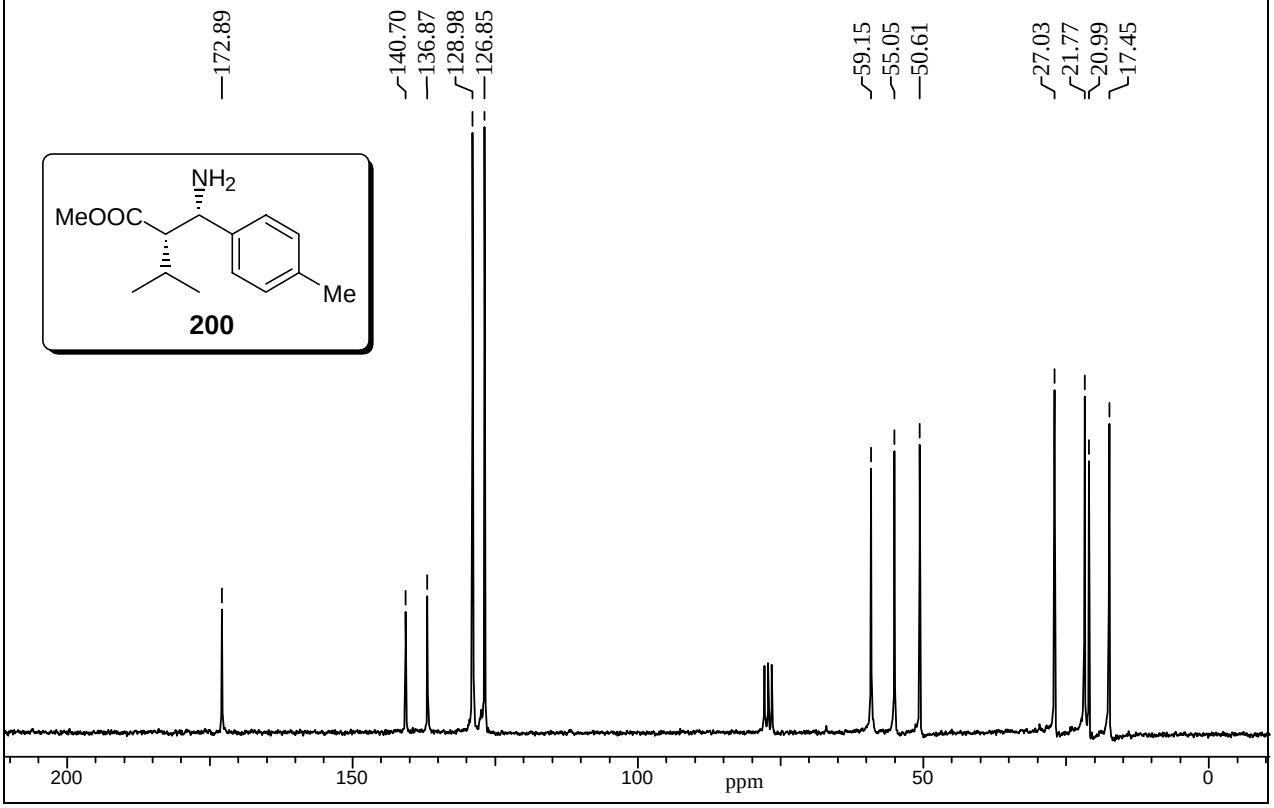
Spectrum No. 28 (Chapter 1, Section 1.4.9) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



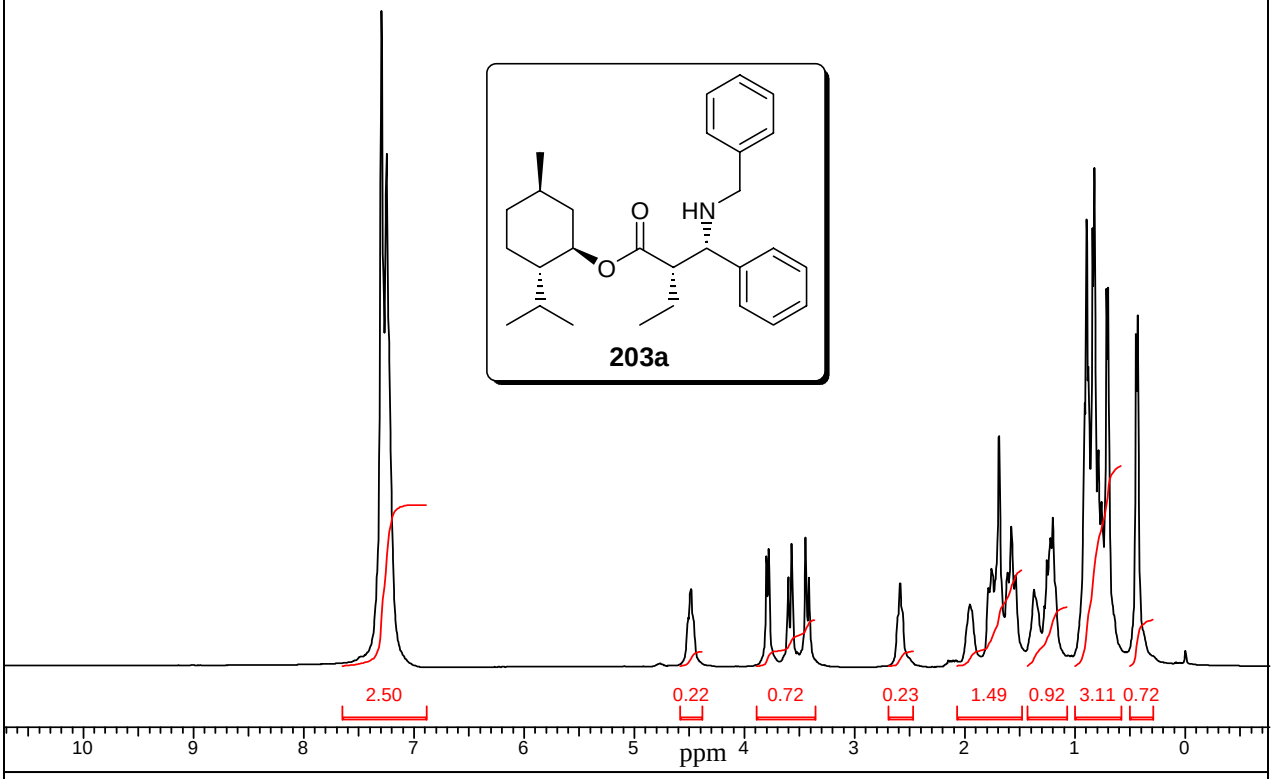
Spectrum No. 29 (Chapter 1, Section 1.4.10) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



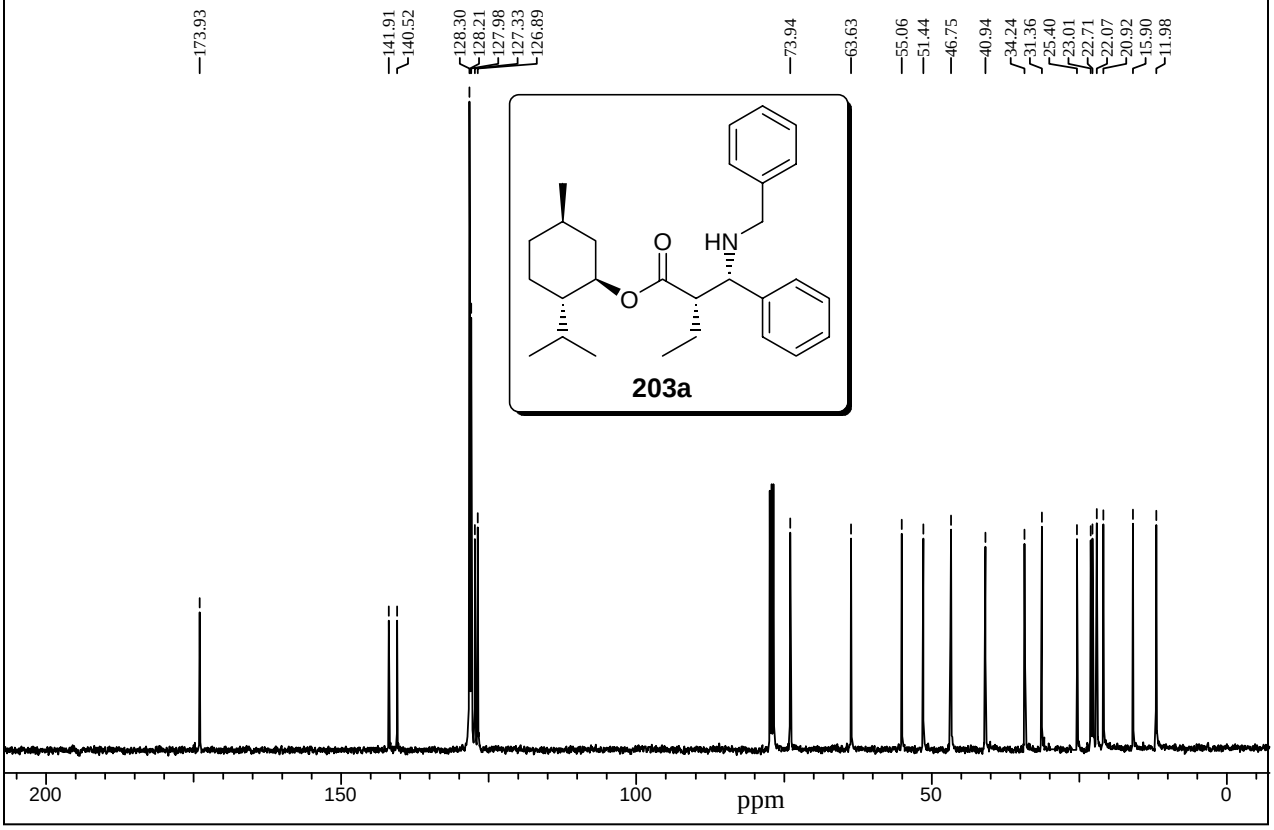
Spectrum No. 30 (Chapter 1, Section 1.4.10) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



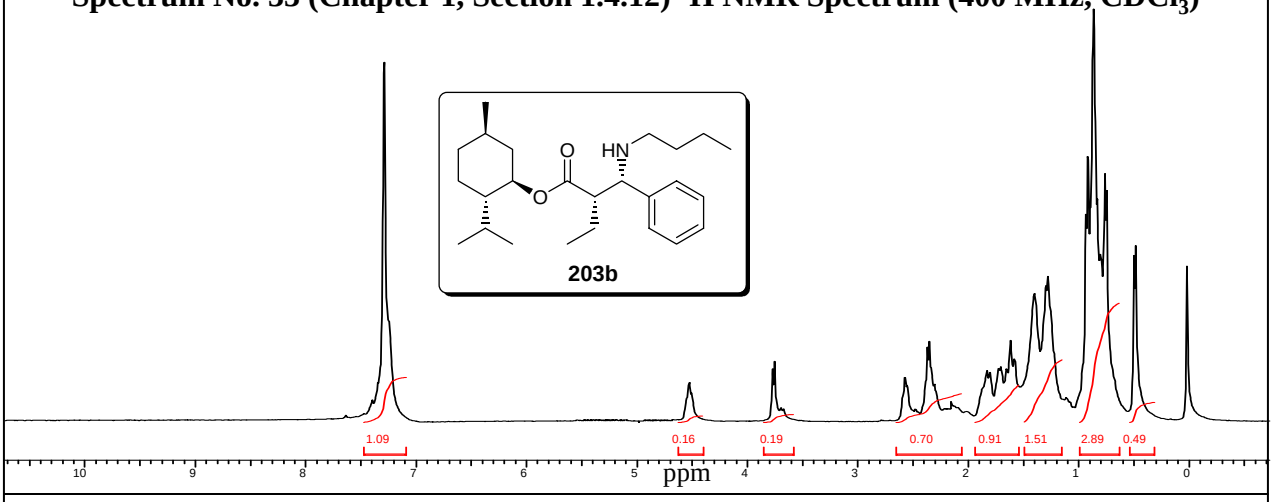
Spectrum No. 31 (Chapter 1, Section 1.4.12) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



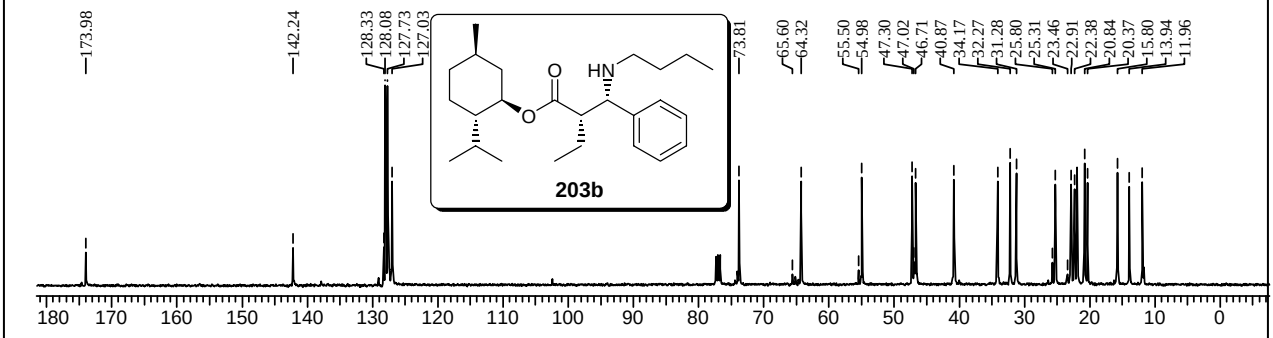
Spectrum No. 32 (Chapter 1, Section 1.4.12) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

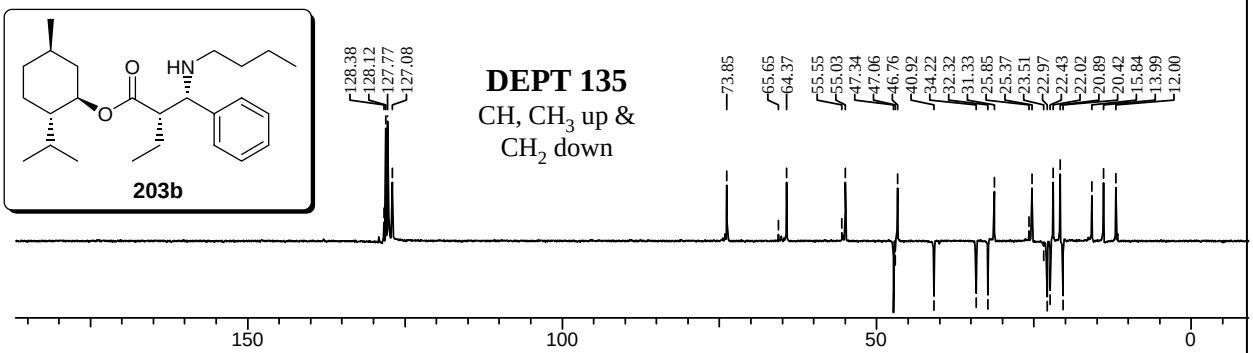


Spectrum No. 33 (Chapter 1, Section 1.4.12) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)

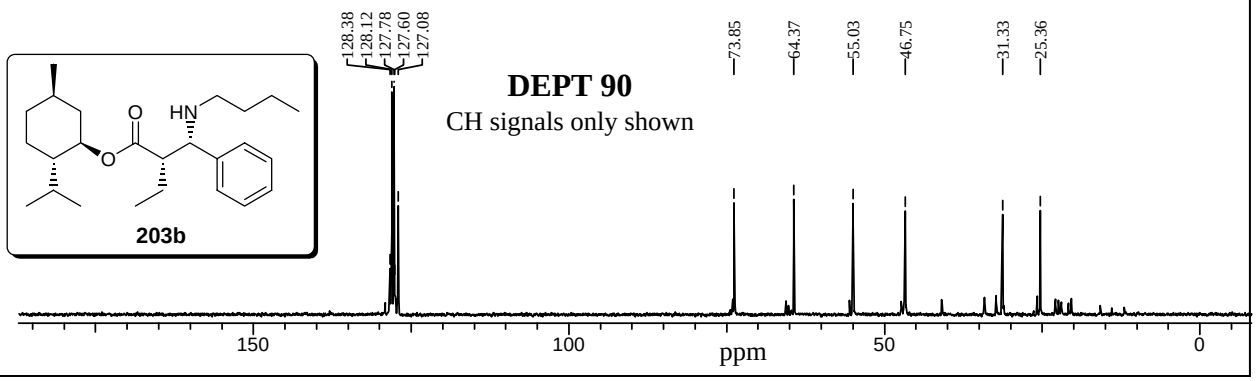


Spectrum No. 34 (Chapter 1, Section 1.4.12) ^{13}C NMR Spectra (100 MHz, $CDCl_3$)



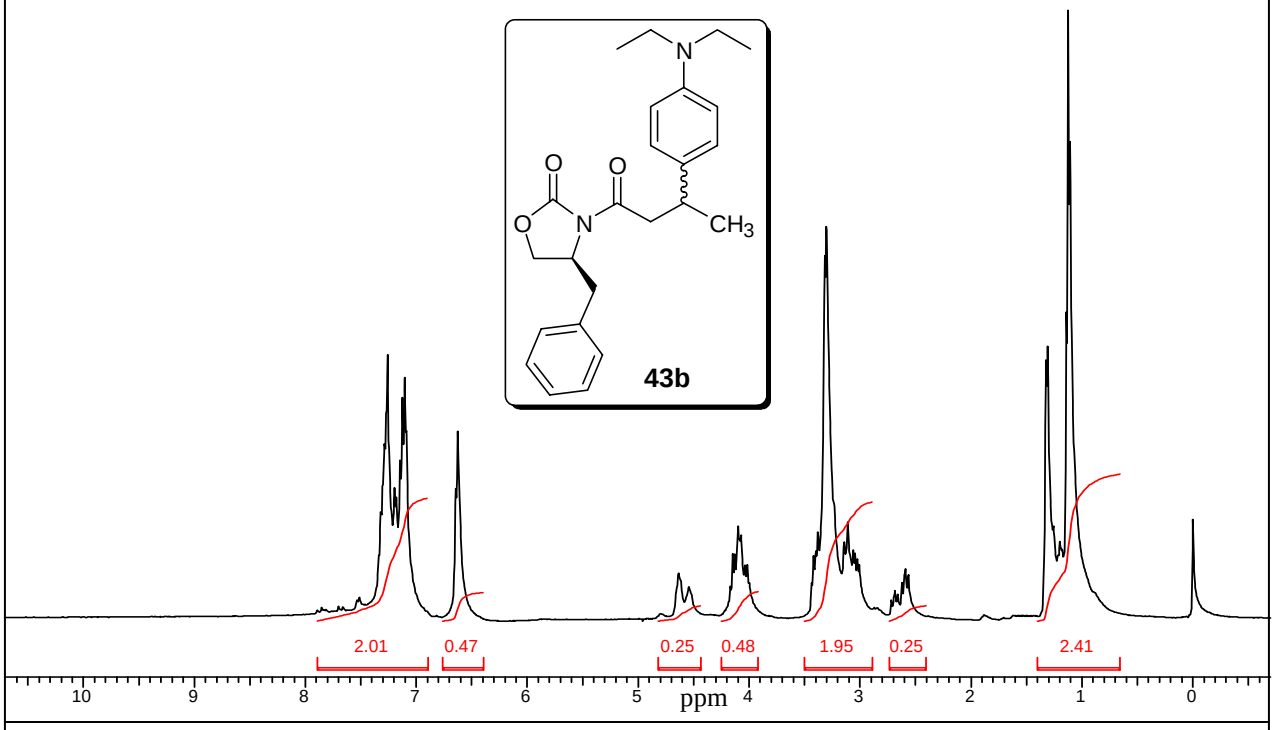


DEPT 135
CH, CH_3 up &
CH_2 down

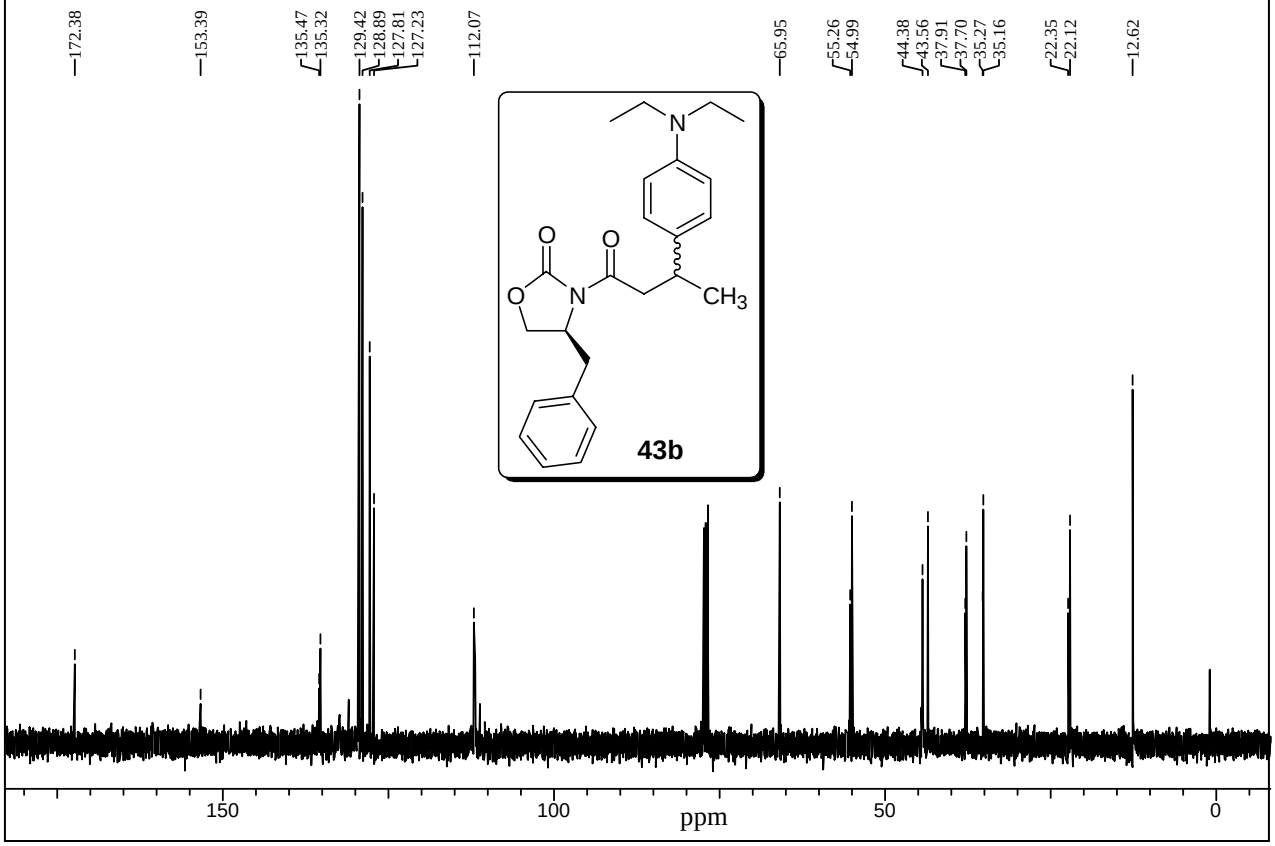


DEPT 90
CH signals only shown

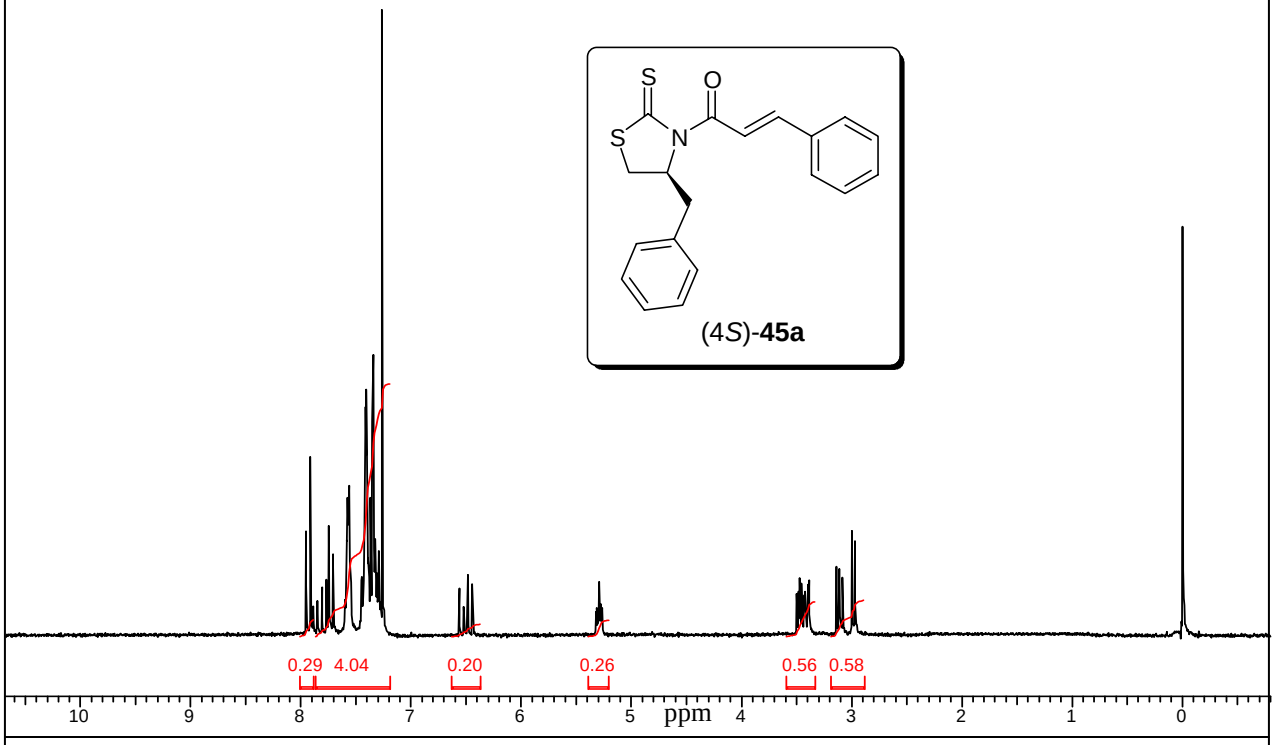
Spectrum No. 35 (Chapter 2, Section 2.4.2) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



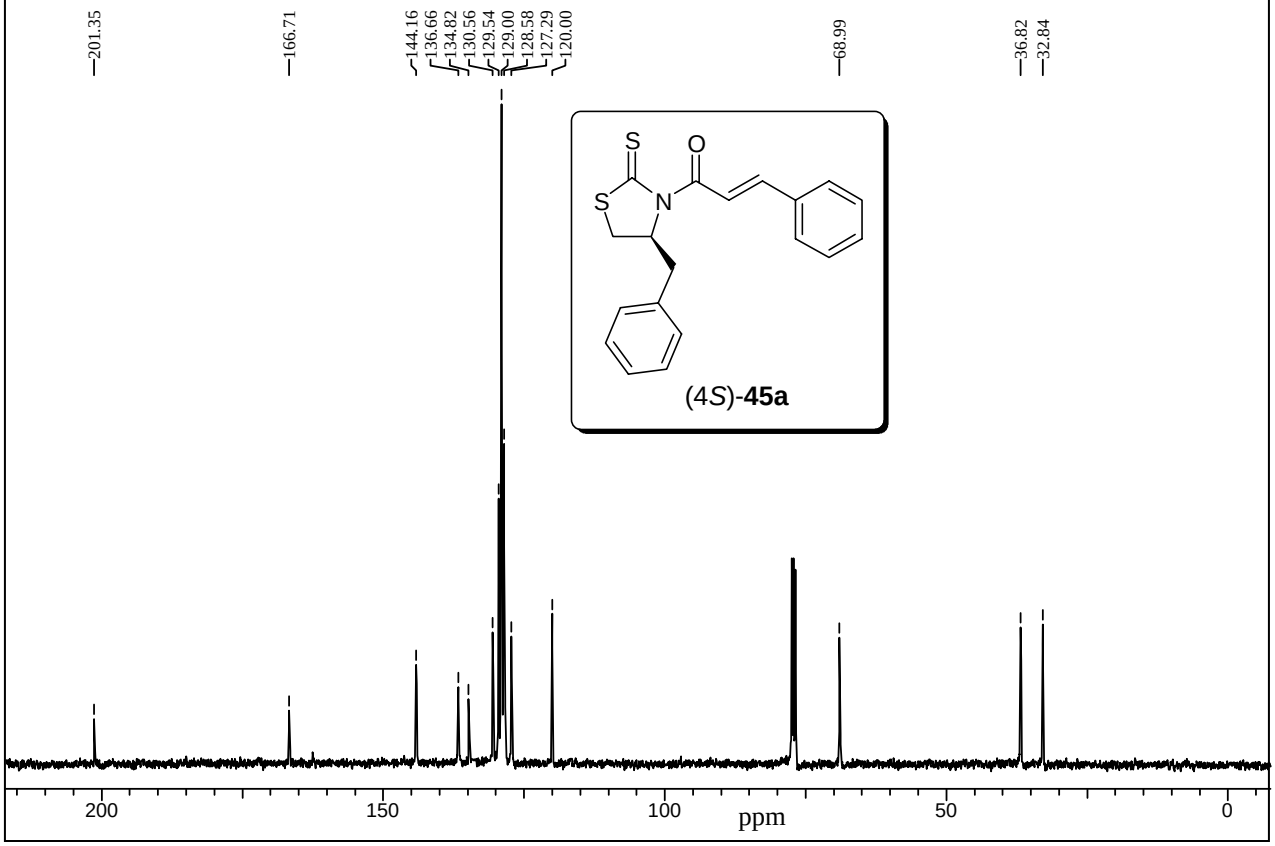
Spectrum No. 36 (Chapter 2, Section 2.4.2) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



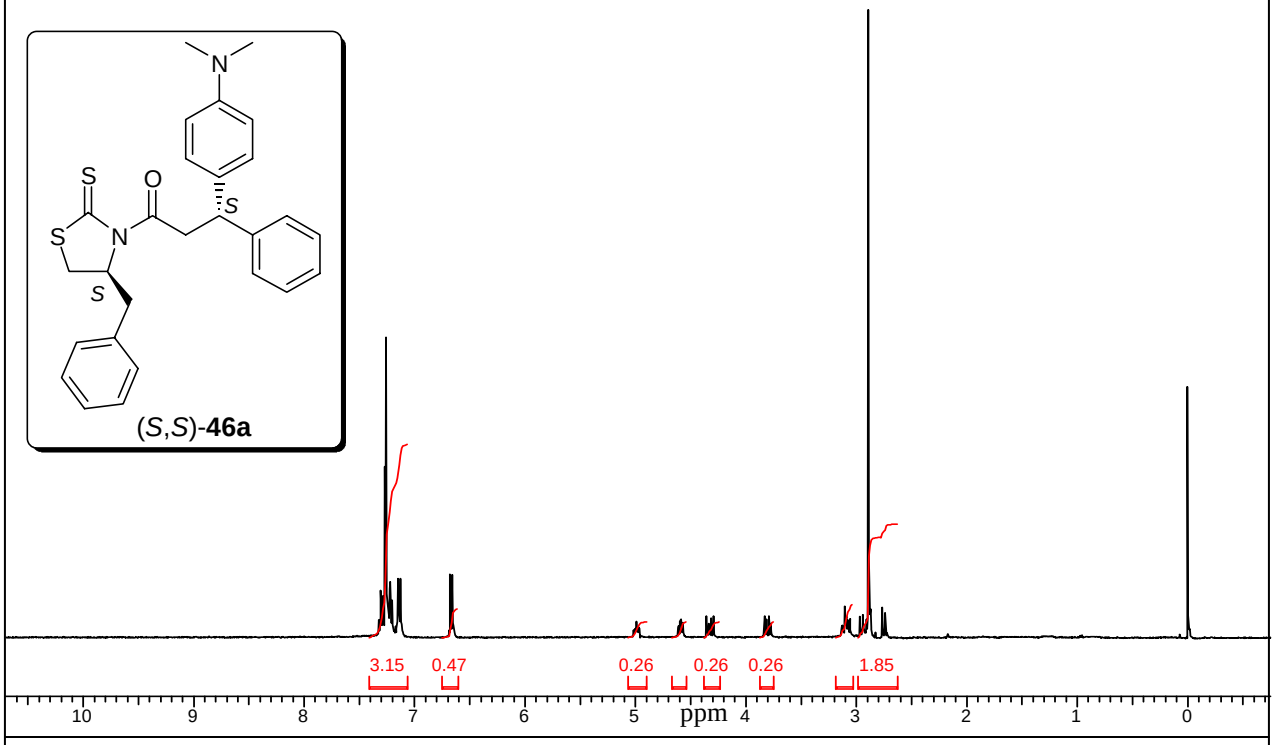
Spectrum No. 37 (Chapter 2, Section 2.4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



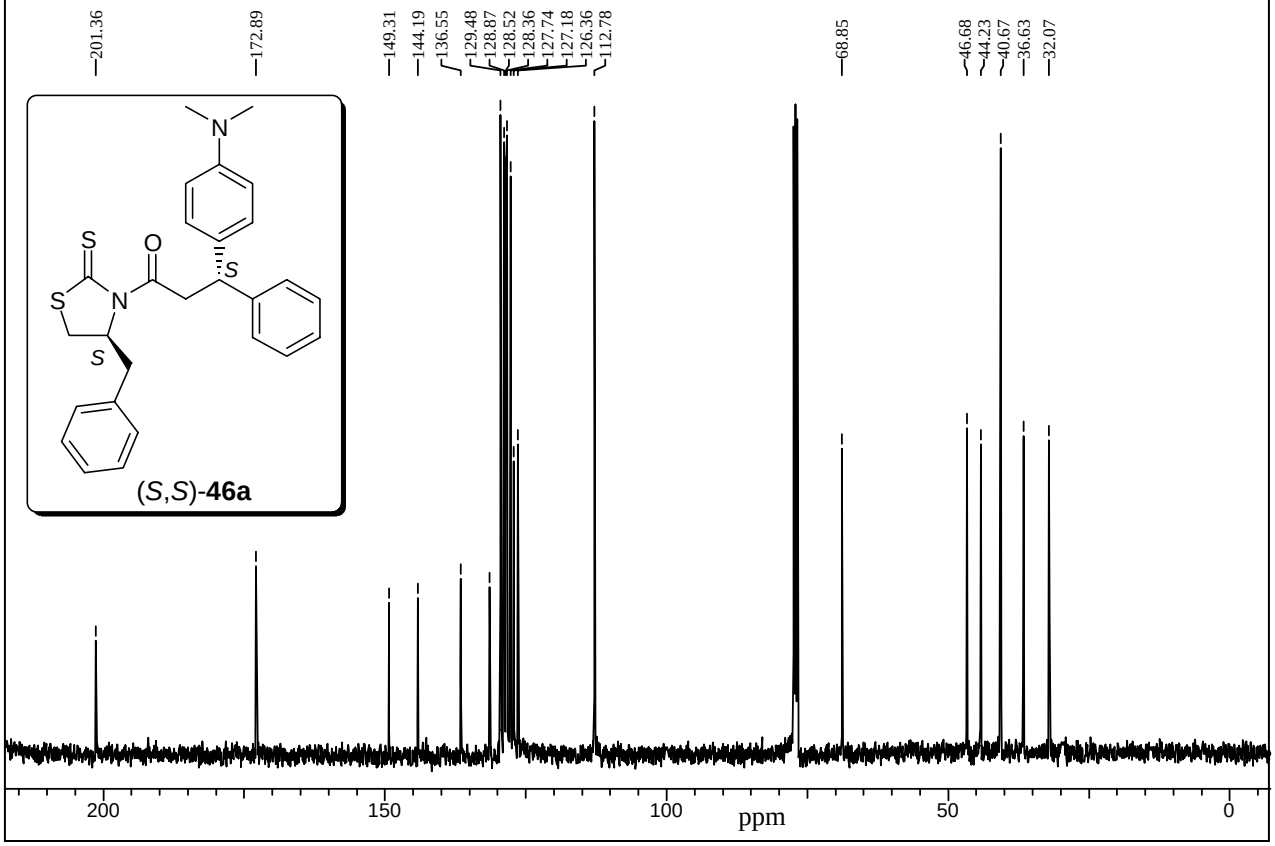
Spectrum No. 38 (Chapter 2, Section 2.4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



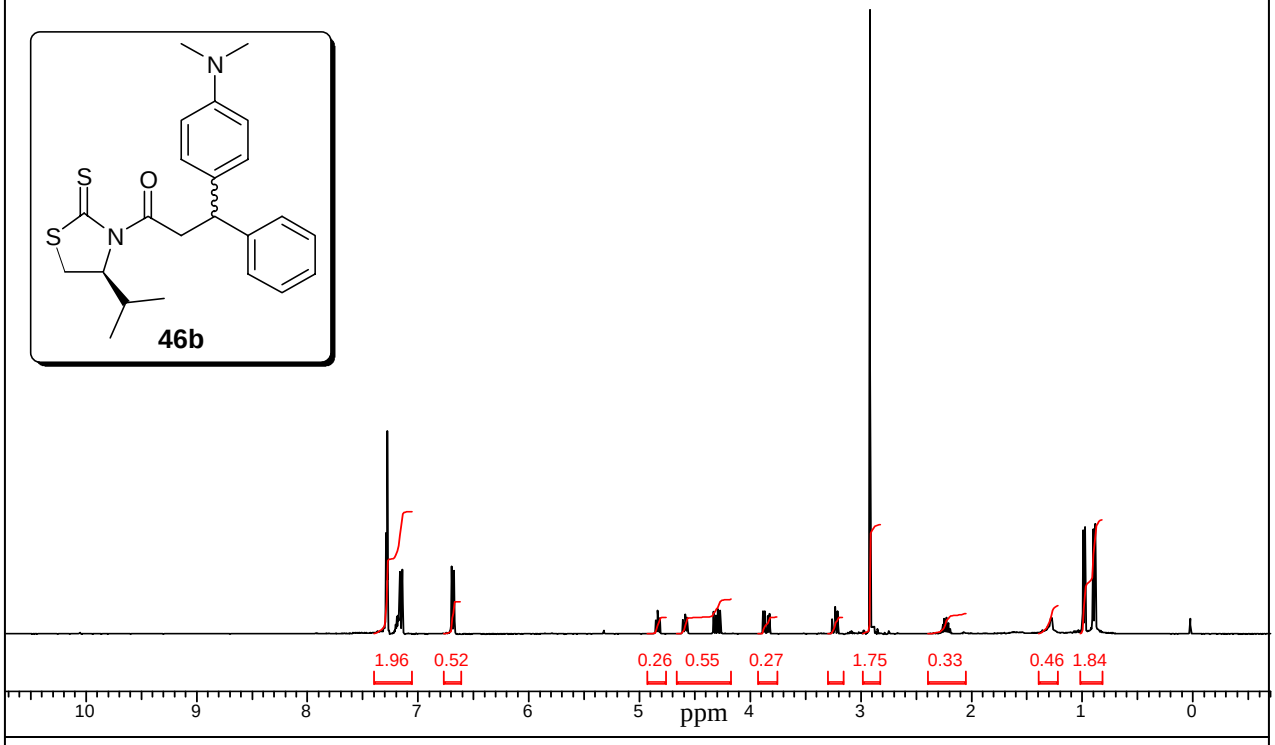
Spectrum No. 39 (Chapter 2, Section 2.4.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



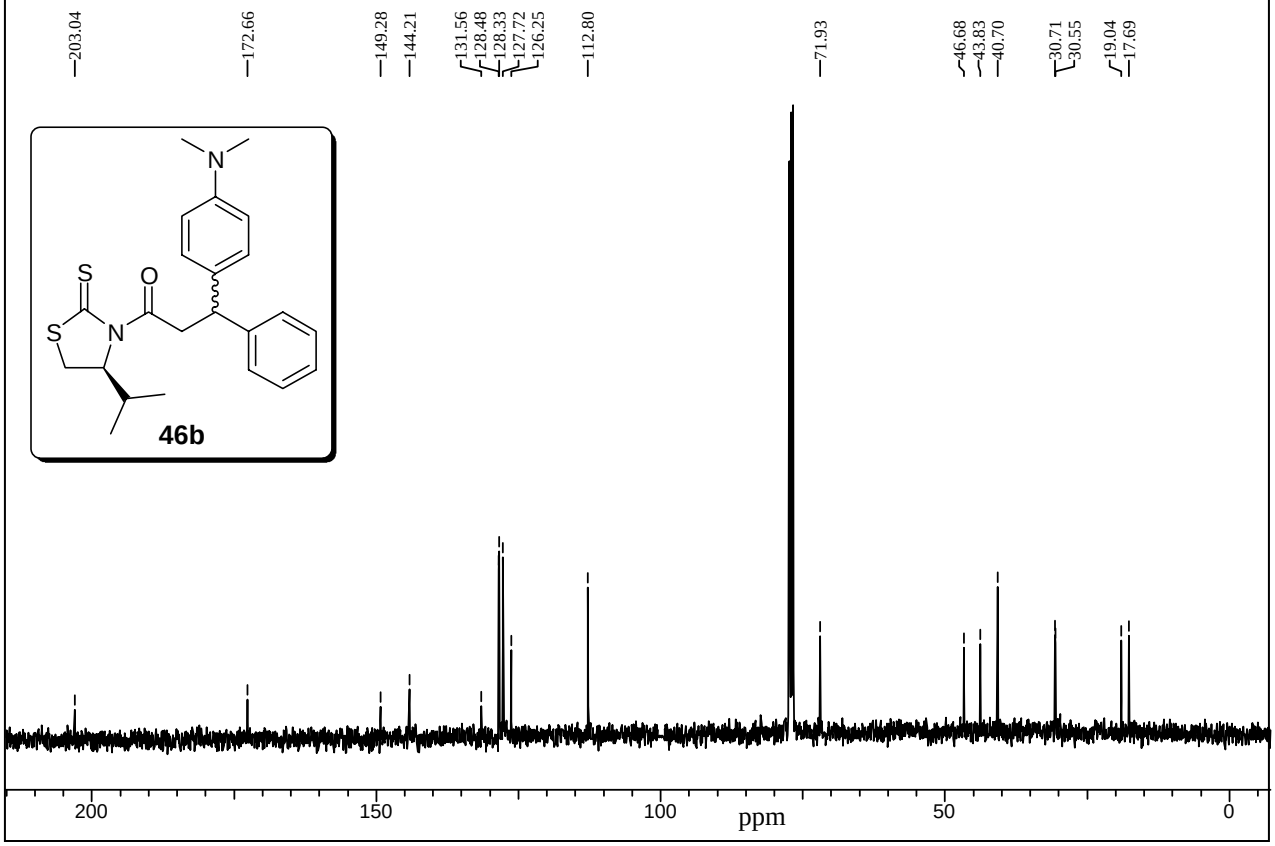
Spectrum No. 40 (Chapter 2, Section 2.4.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



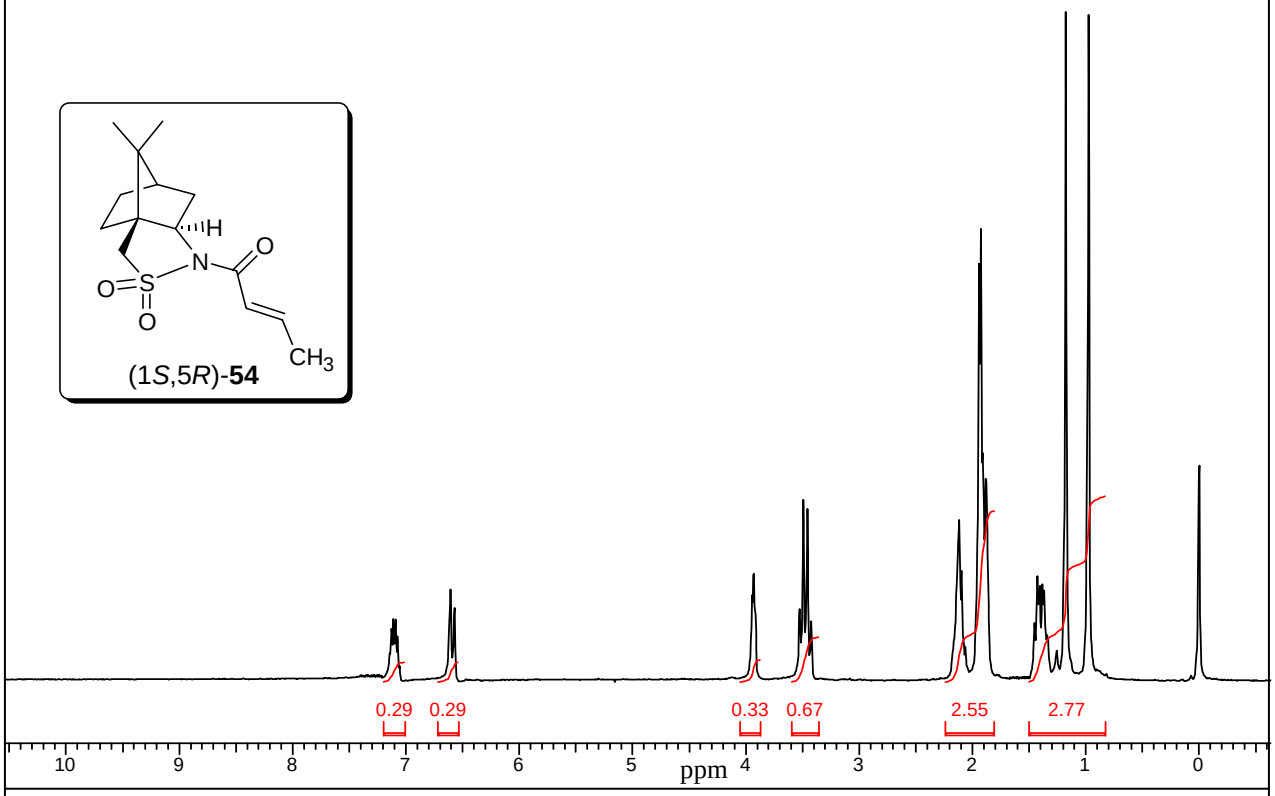
Spectrum No. 41 (Chapter 2, Section 2.4.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



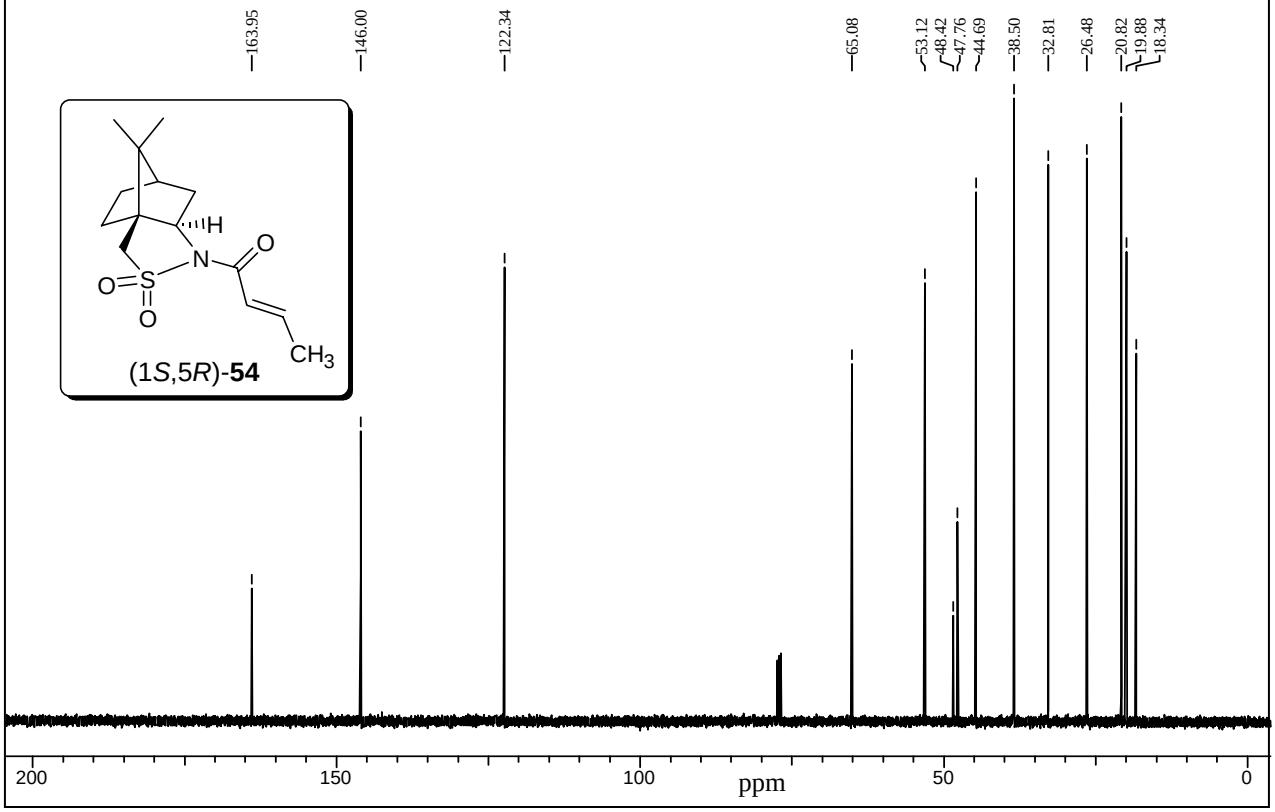
Spectrum No. 42 (Chapter 2, Section 2.4.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



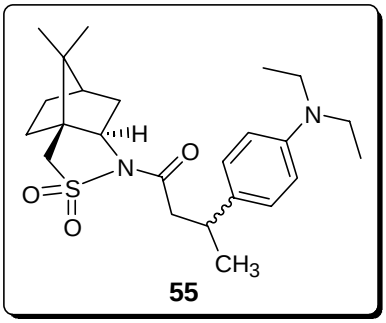
Spectrum No. 43 (Chapter 2, Section 2.4.5) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



Spectrum No. 44 (Chapter 2, Section 2.4.5) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

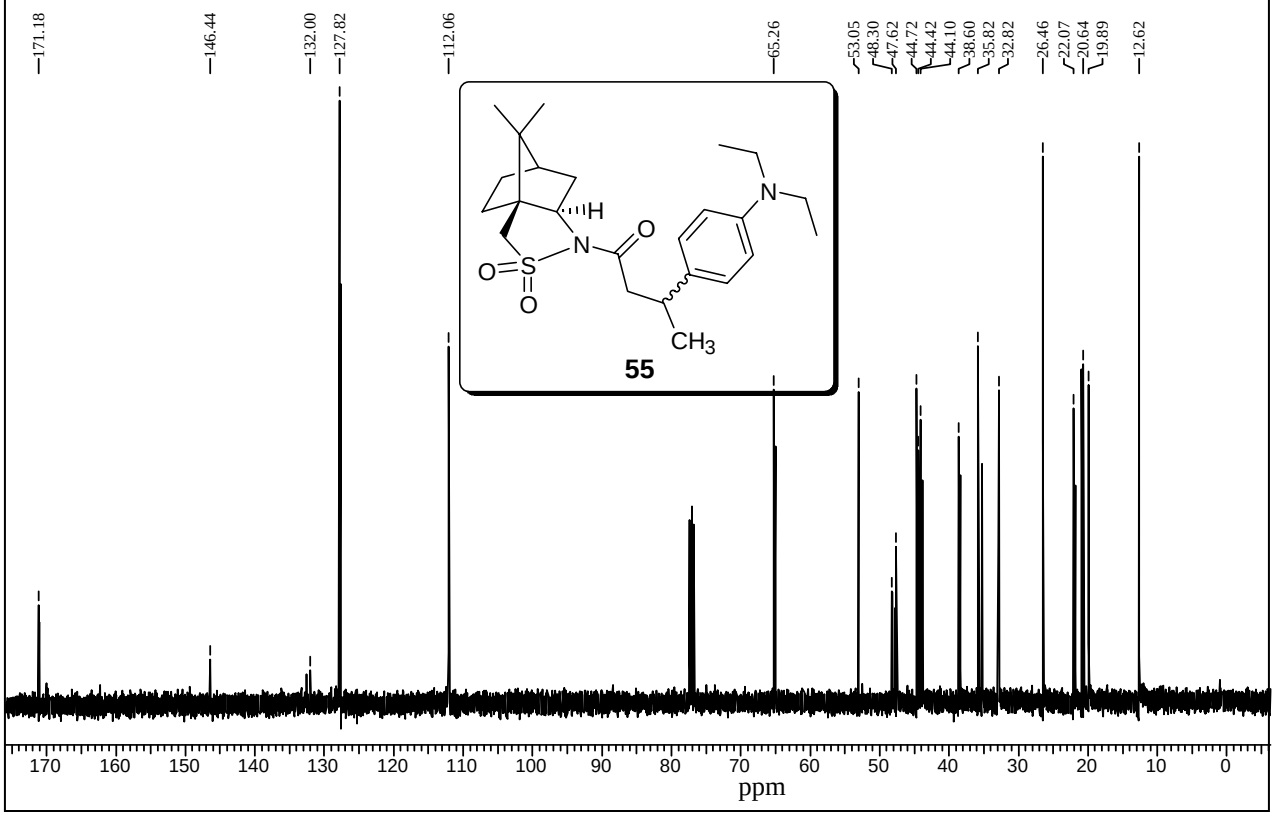


Spectrum No. 45 (Chapter 2, Section 2.4.6) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



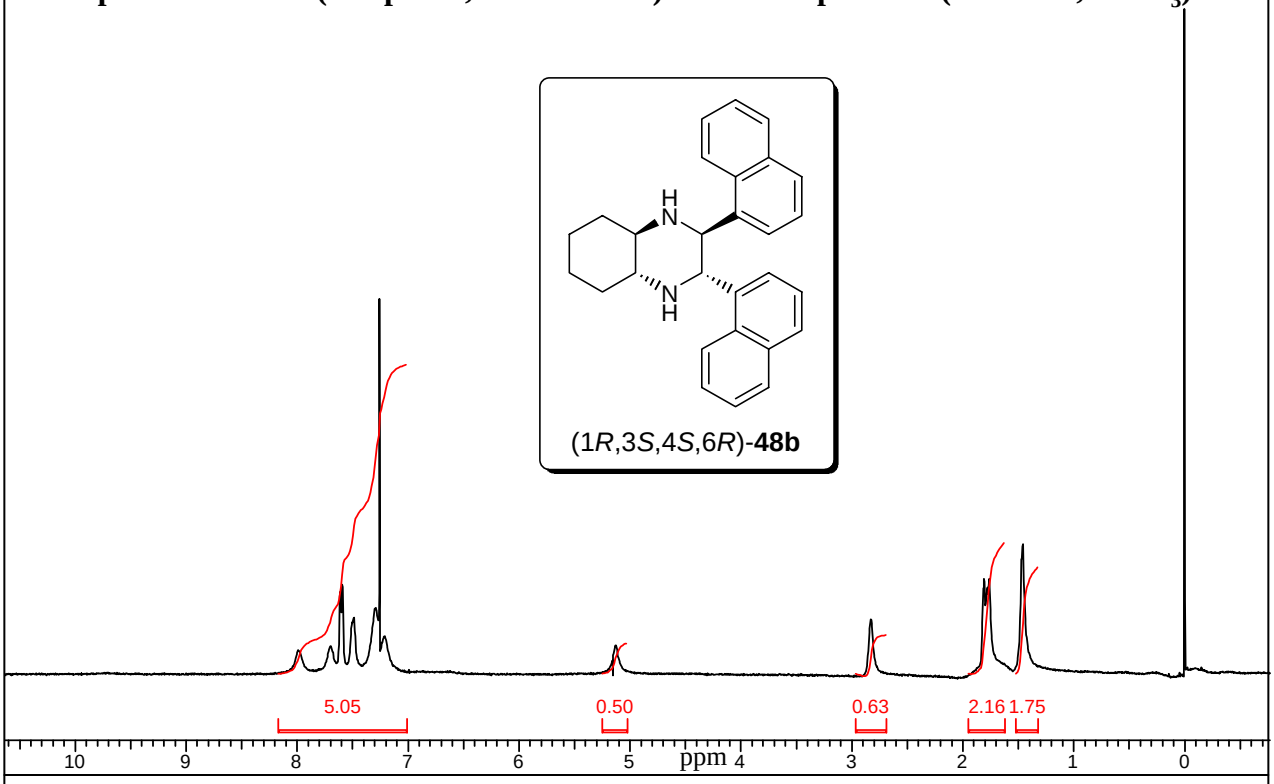
55

Spectrum No. 46 (Chapter 2, Section 2.4.6) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)

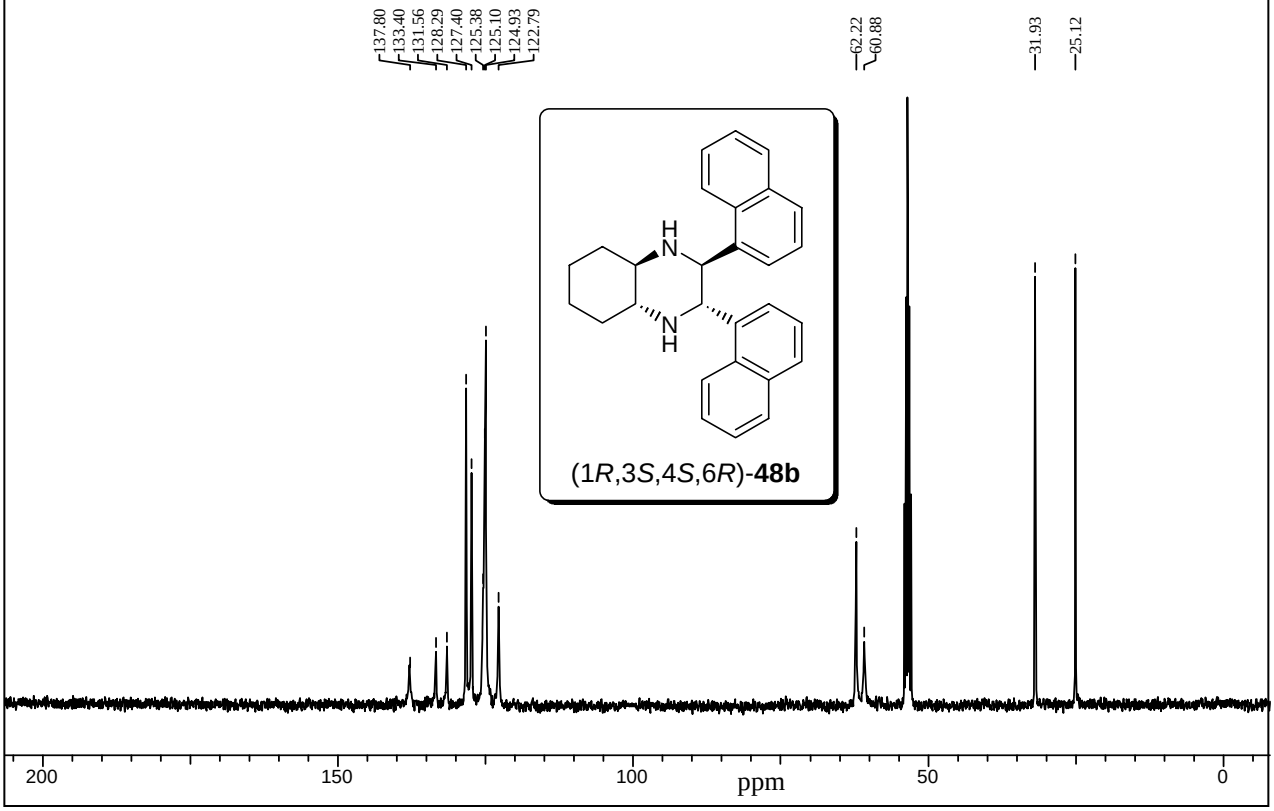


55

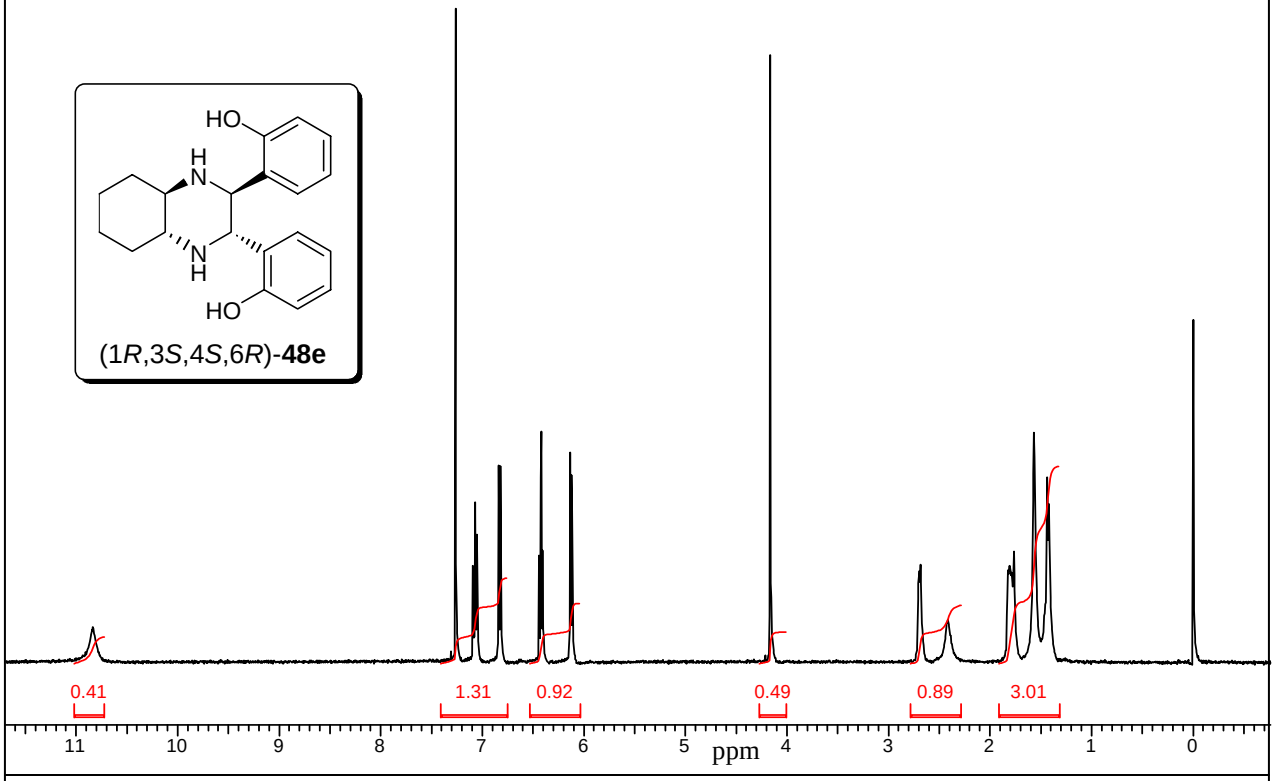
Spectrum No. 47 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



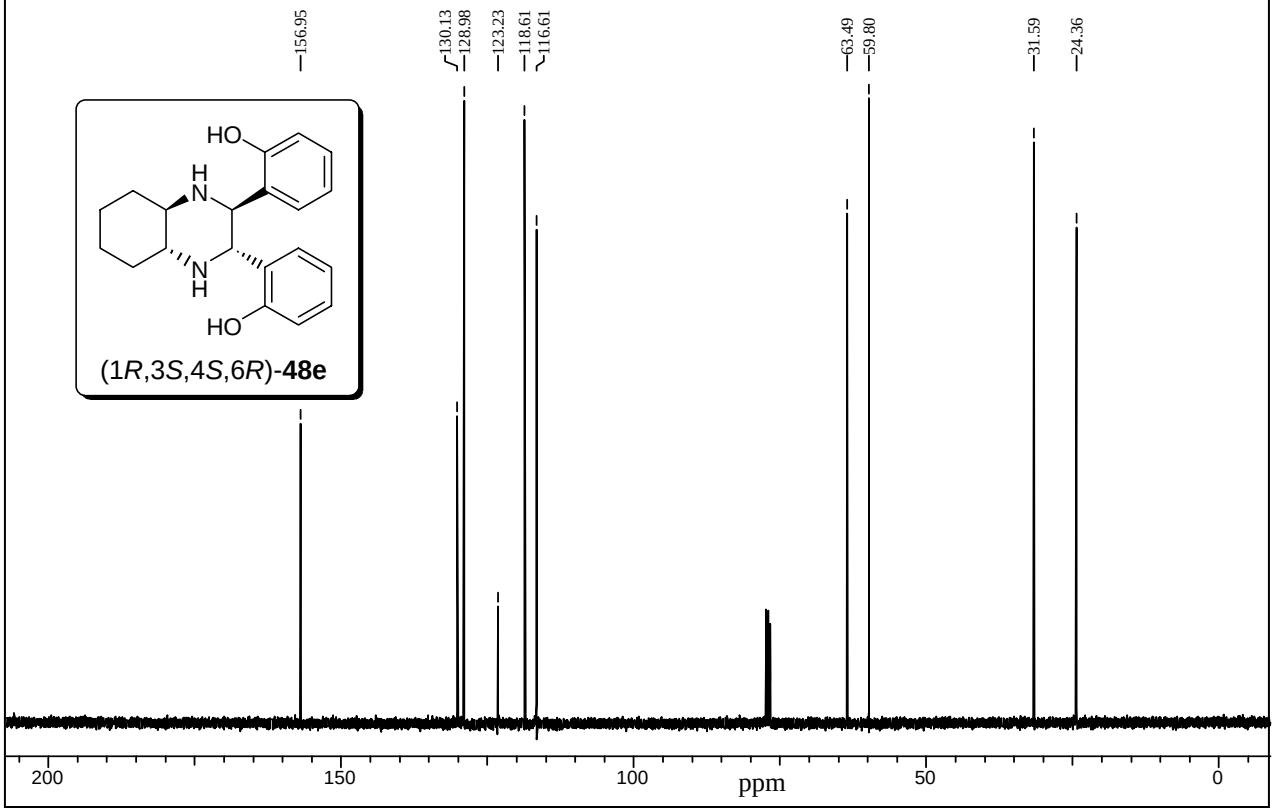
Spectrum No. 48 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



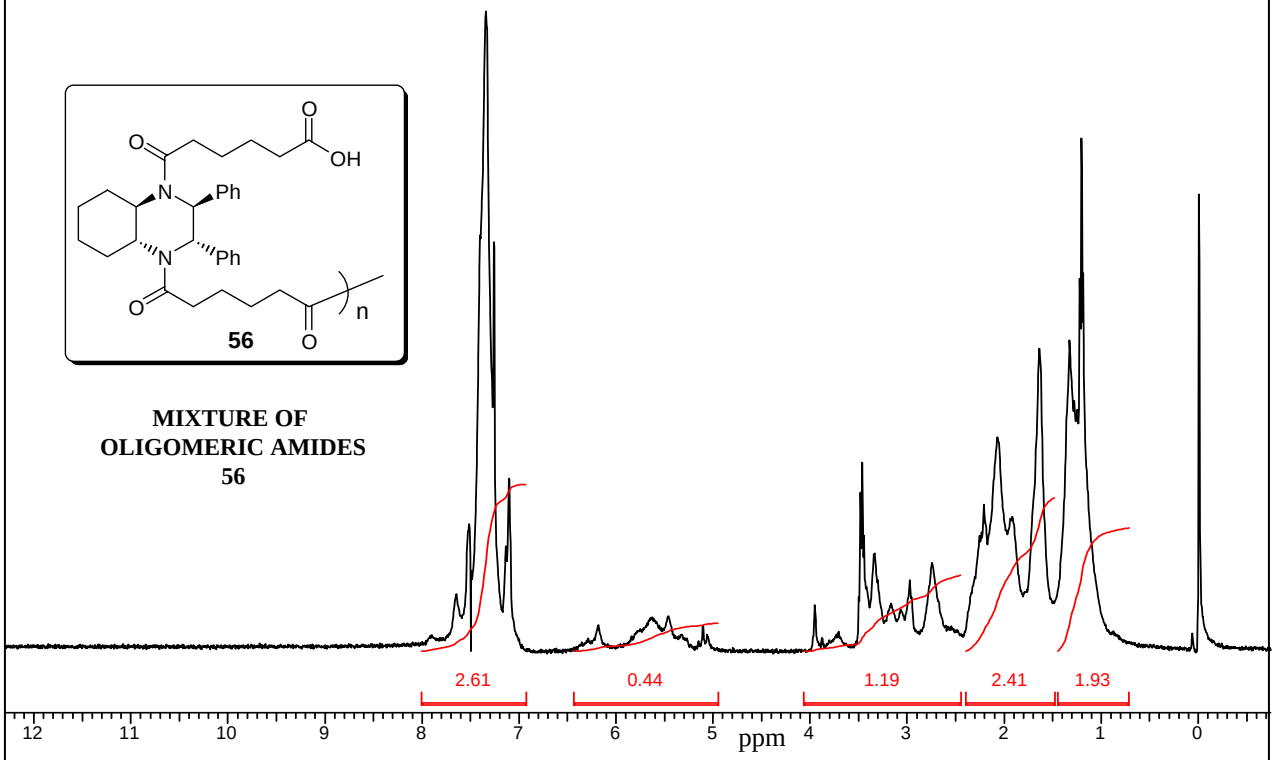
Spectrum No. 49 (Chapter 3, Section 3.4.1) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



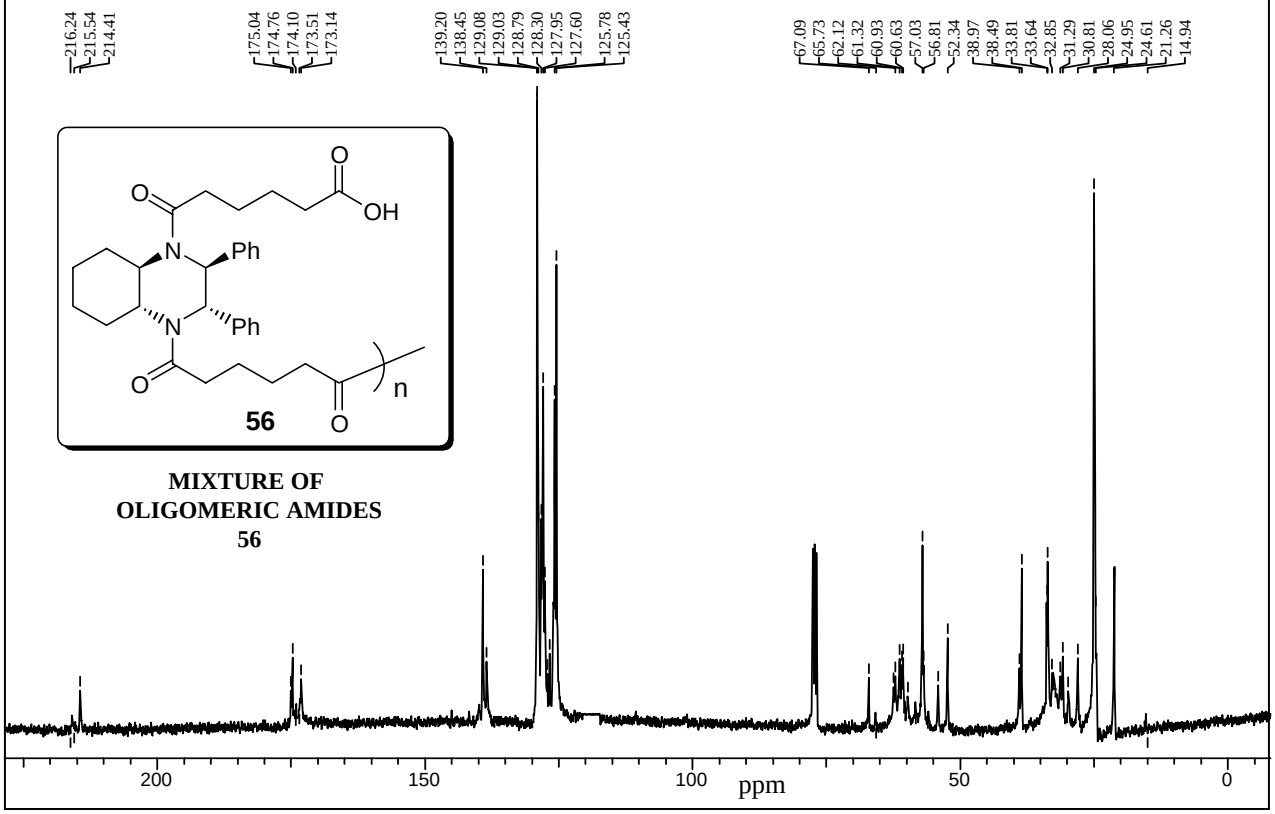
Spectrum No. 50 (Chapter 3, Section 3.4.1) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



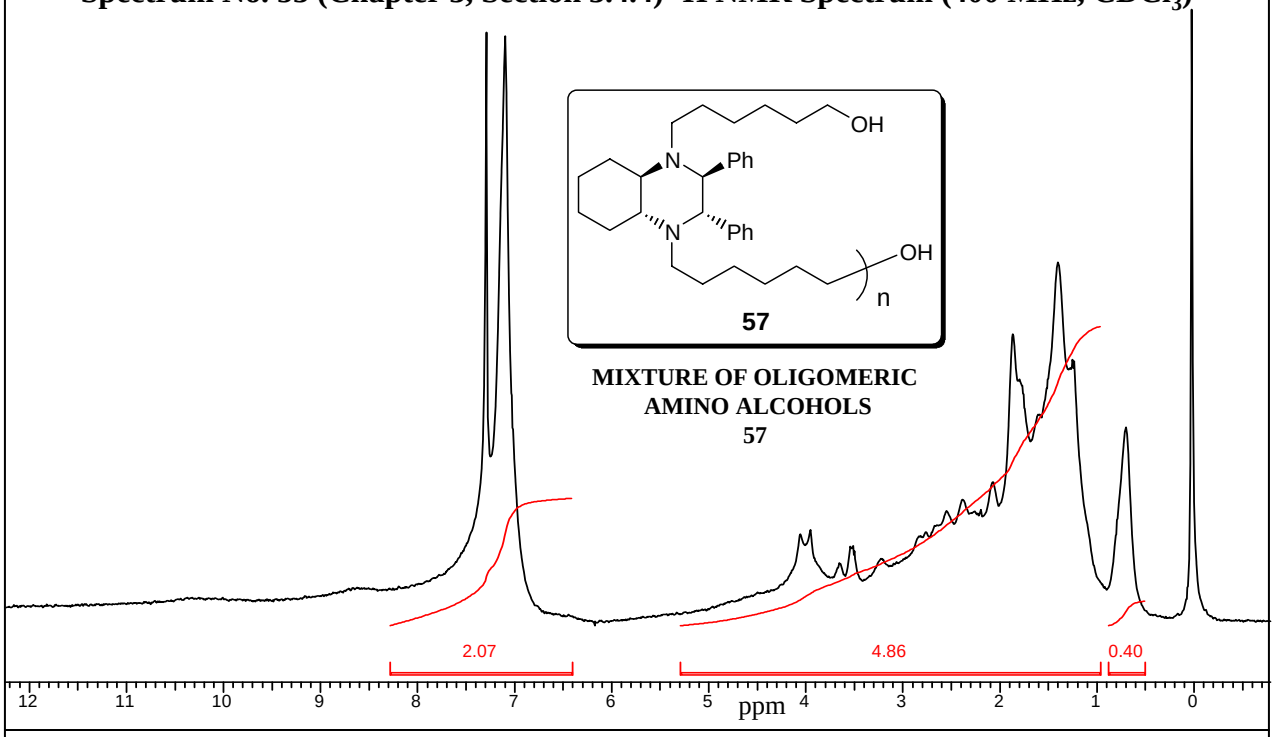
Spectrum No. 51 (Chapter 3, Section 3.4.3) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



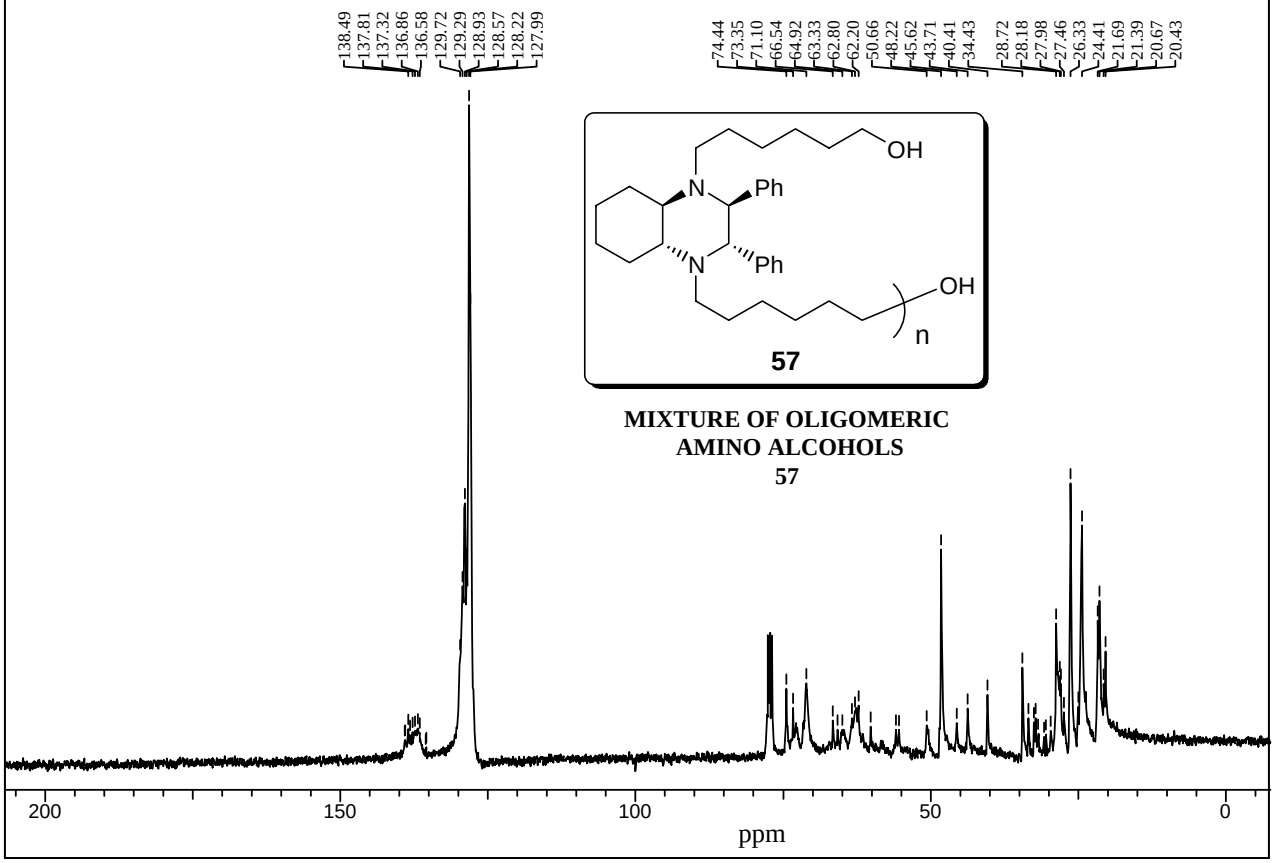
Spectrum No. 52 (Chapter 3, Section 3.4.3) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



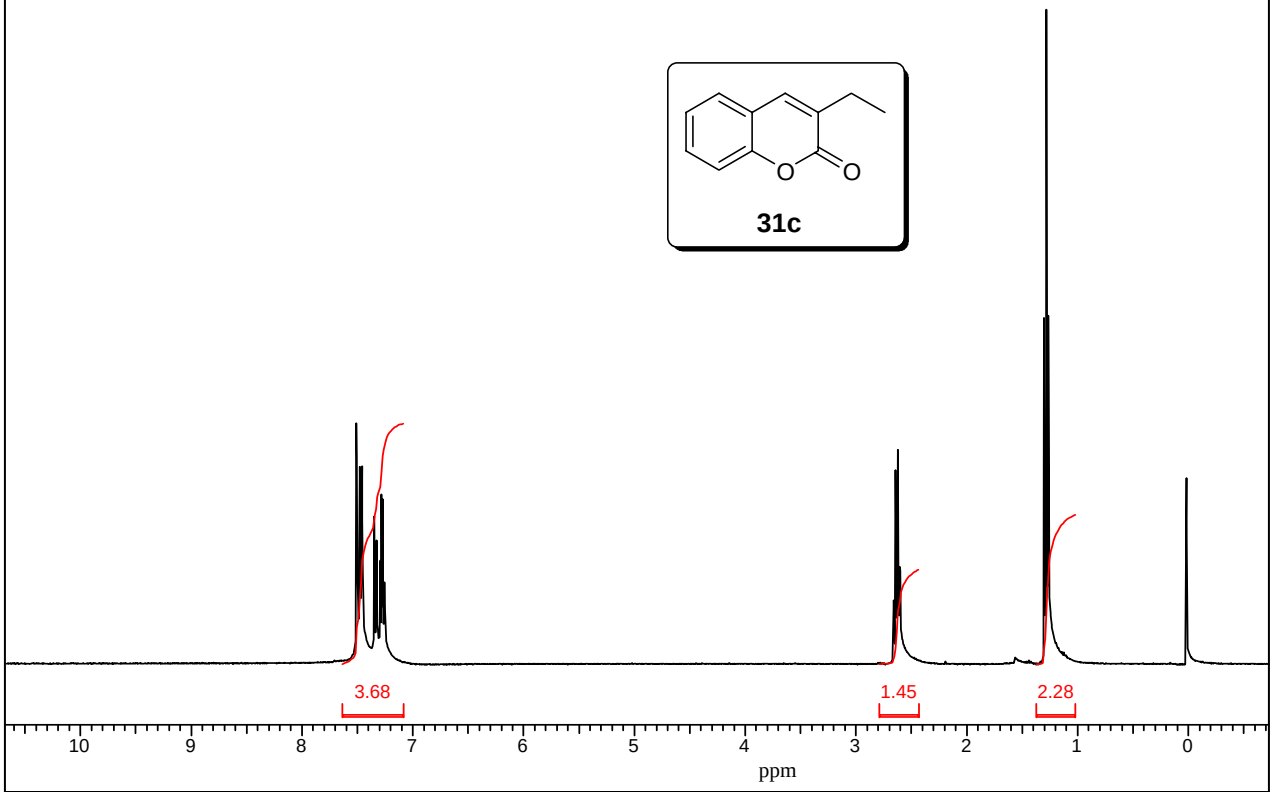
Spectrum No. 53 (Chapter 3, Section 3.4.4) ^{1}H NMR Spectrum (400 MHz, $CDCl_3$)



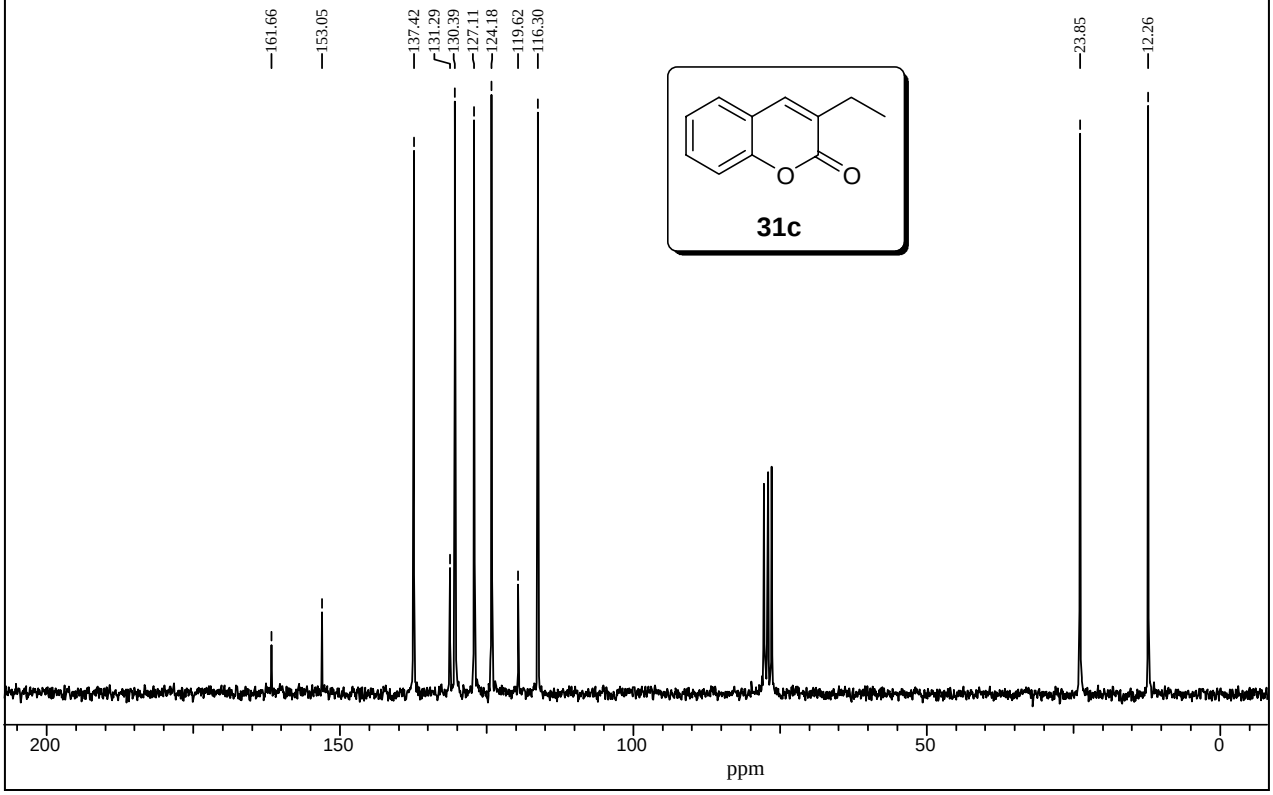
Spectrum No. 54 (Chapter 3, Section 3.4.4) ^{13}C NMR Spectrum (100 MHz, $CDCl_3$)



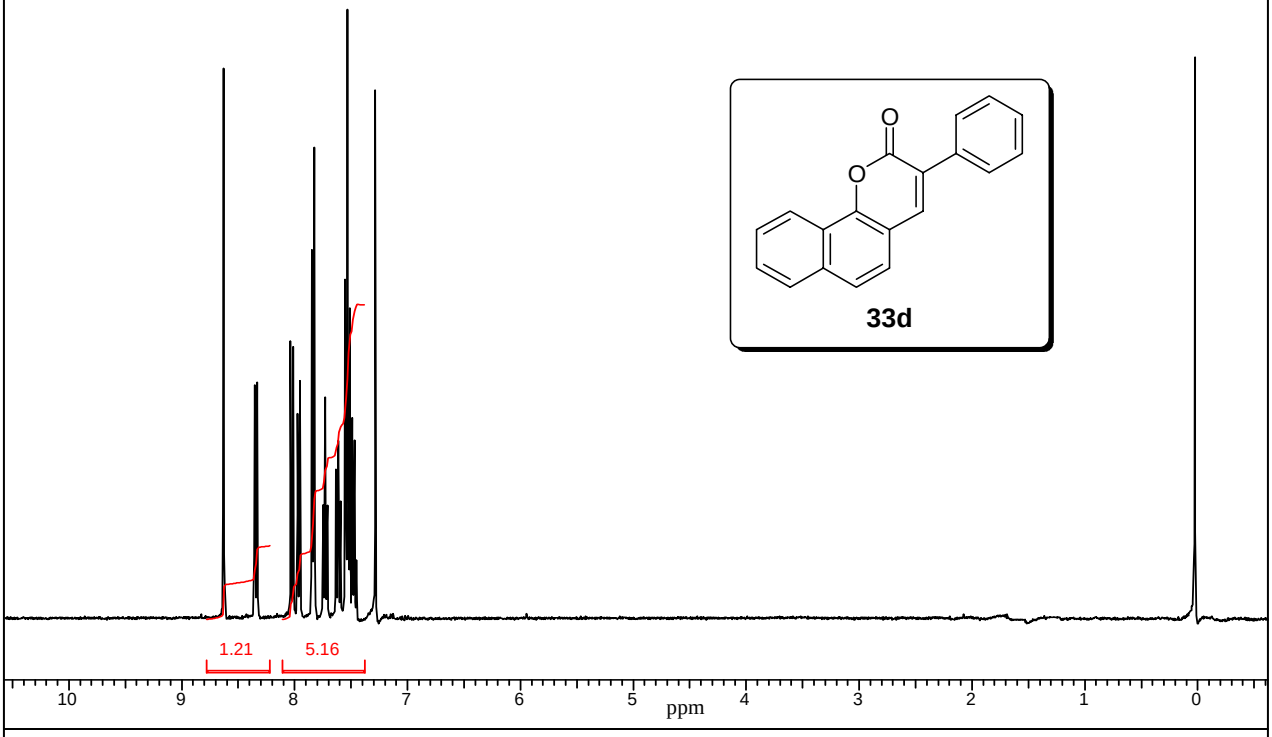
Spectrum No. 55 (Chapter 4, Section 4.4.2) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



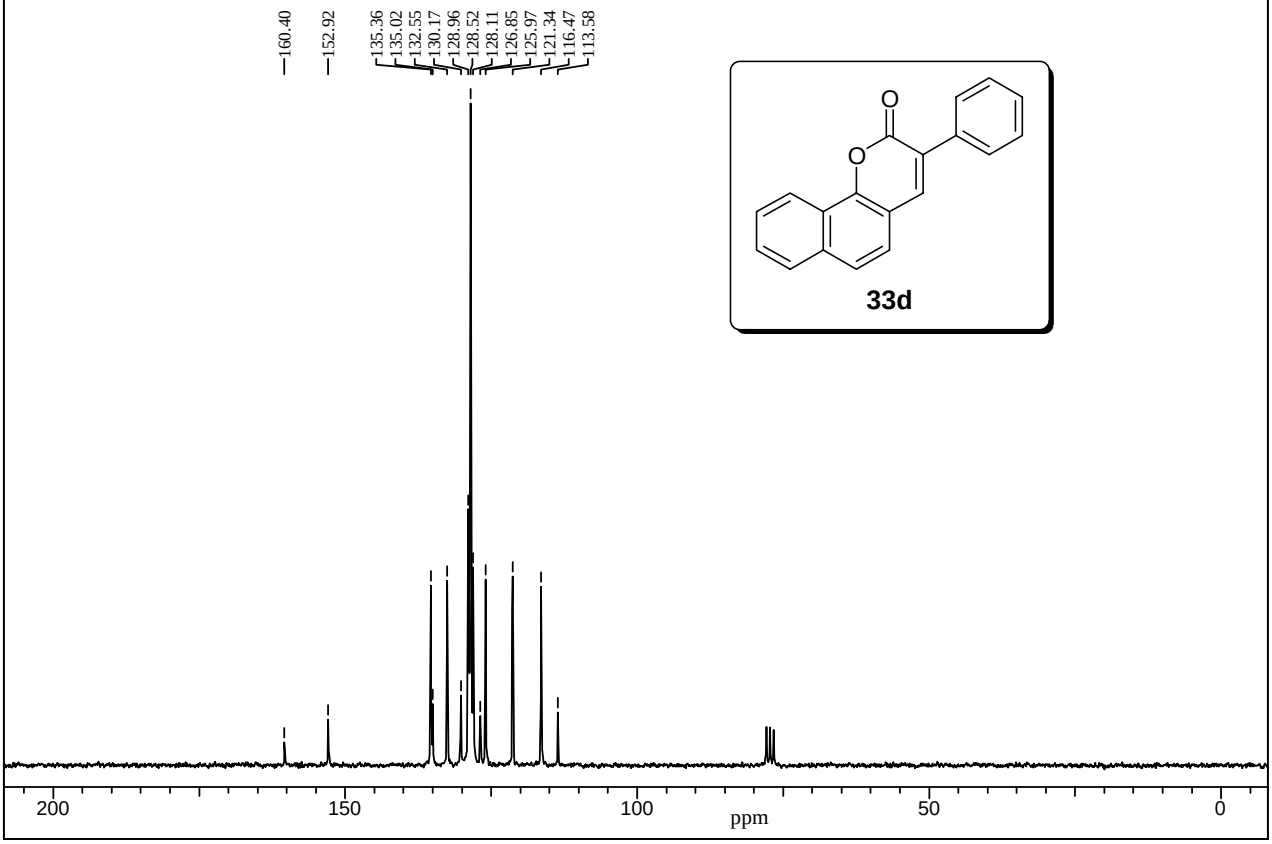
Spectrum No. 56 (Chapter 4, Section 4.4.2) ^{13}C NMR Spectrum (50 MHz, $CDCl_3$)



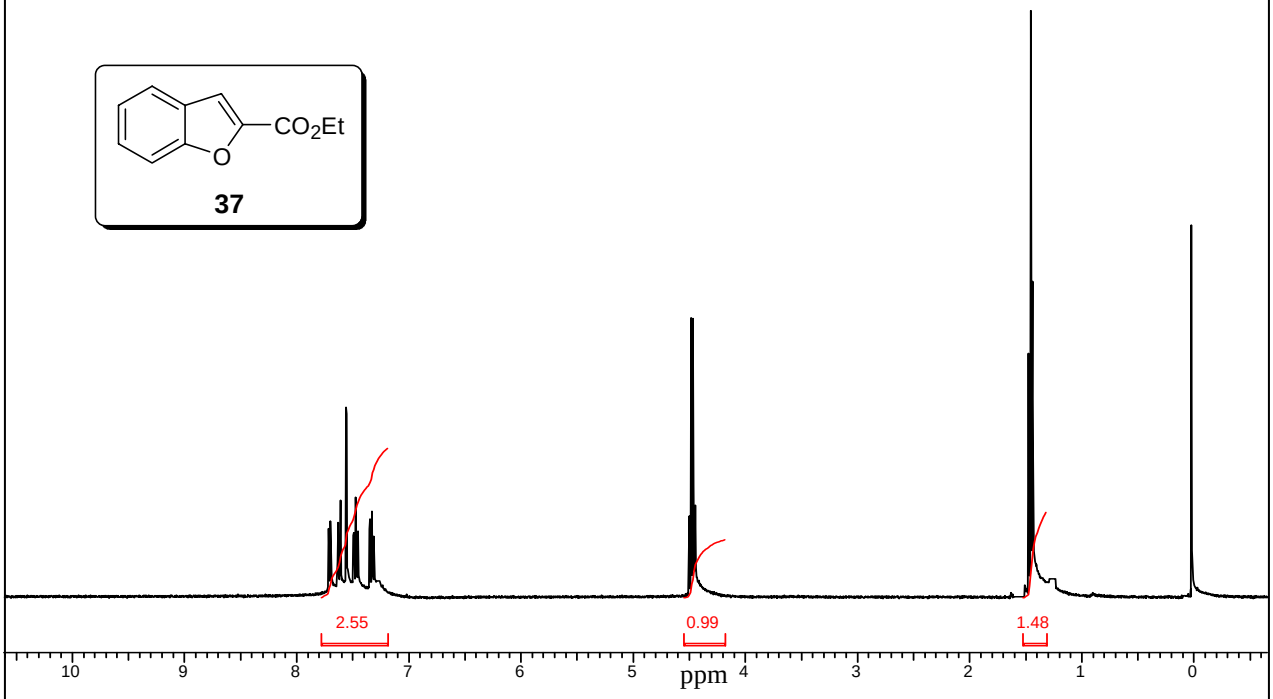
Spectrum No. 57 (Chapter 4, Section 4.4.2) ^{1}H NMR Spectrum (200 MHz,$CDCl_3$)



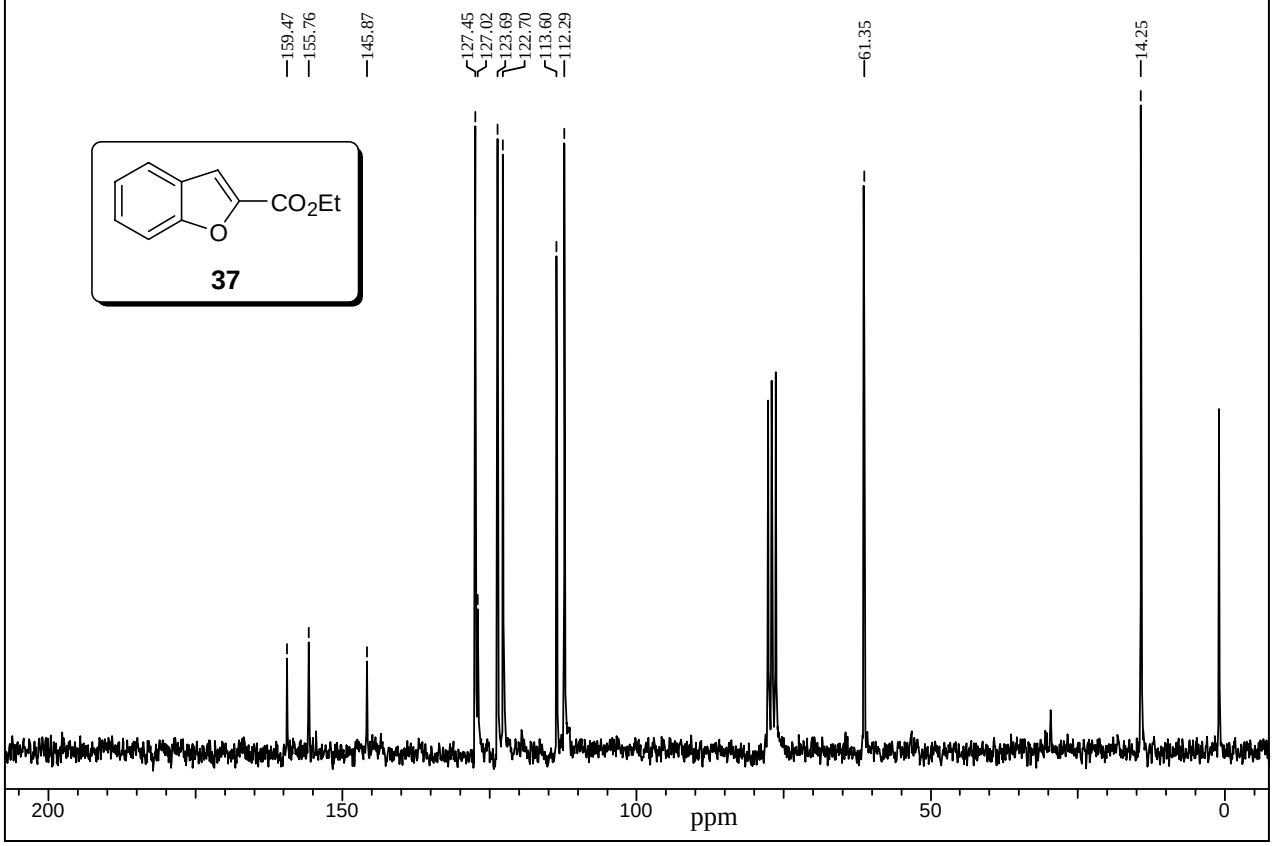
Spectrum No. 58 (Chapter 4, Section 4.4.2) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



Spectrum No. 59 (Chapter 4, Section 4.4.2) ^{1}H NMR Spectrum (200 MHz, $CDCl_3$)



Spectrum No. 60 (Chapter 4, Section 4.4.2) ^{13}C NMR Spectrum (50 MHz,$CDCl_3$)



Appendix II

(X-Ray Crystallographic Data)

Table A1 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for oxalic acid salt of the methyl 2-phenyl-3-pyrrolidine- carboxylate **172a (Chapter 1, Section 1.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O1	6983(6)	6946(1)	2029(4)	66(1)
O2	4026(5)	7115(1)	3123(4)	54(1)
O3	9545(4)	8448(1)	7886(3)	37(1)
O4	12075(4)	8461(1)	10384(3)	50(1)
O5	13407(4)	8364(1)	6691(3)	45(1)
O6	15889(4)	8490(1)	9157(3)	40(1)
O7	6841(6)	10840(1)	9676(4)	63(1)
O8	3866(5)	10665(1)	10753(4)	51(1)
O9	12989(4)	9387(1)	4128(2)	40(1)
O10	15662(4)	9341(1)	6577(3)	45(1)
O11	9389(4)	9284(1)	5464(3)	35(1)
O12	11871(4)	9476(1)	7873(3)	56(1)
O13	15483(4)	8864(1)	12660(2)	35(1)
N1	8577(5)	8245(1)	4511(3)	34(1)
N2	8430(4)	9521(1)	2018(3)	30(1)
C1	8519(6)	7525(1)	5852(4)	34(1)
C2	10561(8)	7303(2)	5753(5)	65(1)
C3	11736(9)	7011(2)	6940(7)	80(2)
C4	10913(10)	6940(2)	8256(5)	69(1)
C5	8925(11)	7160(2)	8395(5)	69(1)
C6	7706(9)	7447(1)	7189(5)	54(1)
C7	7138(5)	7841(1)	4567(4)	31(1)
C8	6532(6)	7685(1)	2785(4)	34(1)
C9	8706(7)	7819(1)	2198(4)	42(1)
C10	9964(6)	8184(1)	3294(5)	48(1)
C11	5927(6)	7206(1)	2588(4)	38(1)
C12	3316(9)	6663(1)	3069(7)	68(1)
C13	11614(5)	8453(1)	8895(3)	30(1)
C14	13752(5)	8432(1)	8122(3)	29(1)
C15	8340(6)	10232(1)	13429(4)	32(1)
C16	7438(8)	10314(1)	14740(5)	50(1)
C17	8621(11)	10604(2)	15947(5)	66(1)
C18	10673(10)	10811(2)	15856(5)	68(1)
C19	11581(8)	10732(2)	14583(6)	72(1)
C20	10432(7)	10440(2)	13363(5)	56(1)
C21	6960(5)	9923(1)	12128(4)	29(1)
C22	6292(6)	10097(1)	10339(4)	32(1)
C23	8361(6)	9951(1)	9683(4)	37(1)
C24	8925(7)	9499(1)	10387(4)	43(1)
C25	5759(6)	10574(1)	10215(4)	38(1)
C26	3173(9)	11118(1)	10745(7)	66(1)
C27	13591(5)	9368(1)	5646(3)	29(1)
C28	11507(5)	9387(1)	6472(3)	29(1)

Table A2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (*S*,*S*,*R*)-**180 (Chapter 1, Section 1.2.2)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O1	4423(2)	6807(3)	1004(1)	87(1)
O2	3498(2)	9758(3)	817(1)	68(1)
O3	2165(2)	2286(3)	2198(1)	73(1)
O4	-2908(2)	2796(3)	1284(1)	79(1)
O5	-3622(2)	2308(3)	2264(1)	84(1)
O6	-810(2)	659(4)	4819(1)	92(1)
O7	1138(2)	906(3)	5021(1)	86(1)
N1	2020(1)	5549(3)	2461(1)	38(1)
N2	-2775(2)	2526(3)	1983(1)	59(1)
N3	80(2)	1086(3)	4607(1)	59(1)
C1	3617(2)	7901(4)	1060(1)	55(1)
C2	2579(2)	7272(4)	1373(1)	46(1)
C3	3057(2)	6020(3)	2129(1)	42(1)
C4	4143(2)	6837(3)	2784(1)	44(1)
C5	4869(2)	5499(4)	3318(2)	61(1)
C6	5806(2)	6123(5)	3965(2)	78(1)
C7	6052(2)	8100(5)	4090(2)	77(1)
C8	5360(2)	9438(4)	3560(2)	70(1)
C9	4413(2)	8826(4)	2904(2)	53(1)
C10	1650(2)	6102(4)	714(1)	61(1)
C11	1015(2)	7282(6)	-23(2)	94(1)
C12	4383(2)	10486(5)	440(2)	87(1)
C13	1694(2)	3641(3)	2461(1)	43(1)
C14	632(2)	3086(3)	2778(1)	39(1)
C15	-556(2)	3033(3)	2256(1)	43(1)
C16	-1511(2)	2485(3)	2533(1)	42(1)
C17	-1337(2)	1899(3)	3305(1)	46(1)
C18	-145(2)	1862(3)	3794(1)	42(1)
C19	846(2)	2445(3)	3549(1)	43(1)
C20	1574(2)	7198(3)	2869(1)	41(1)
C21	167(2)	7385(3)	2602(1)	41(1)
C22	-450(2)	7822(4)	1812(1)	56(1)
C23	-1721(2)	7893(4)	1535(2)	73(1)
C24	-2403(2)	7548(4)	2051(2)	79(1)
C25	-1812(2)	7197(4)	2837(2)	68(1)
C26	-536(2)	7122(3)	3115(1)	52(1)
C27	2155(2)	7137(4)	3772(1)	51(1)

Table A3 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the complex **185 (Chapter 1, Section 1.2.2)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O1	9372(3)	8768(1)	-617(1)	86(1)
O2	5703(3)	8615(1)	-591(1)	74(1)
O3	2221(2)	5302(1)	9780(1)	42(1)
O8	5041(2)	6051(1)	10265(1)	41(1)
N2	9578(2)	6366(1)	415(1)	33(1)

C1	9604(3)	7286(1)	237(1)	35(1)
C2	7912(3)	7410(1)	-353(1)	38(1)
C3	9070(3)	7872(1)	755(1)	37(1)
C4	7081(3)	7804(1)	1017(1)	43(1)
C5	6621(3)	8348(1)	1485(1)	52(1)
C6	8103(4)	8976(1)	1688(1)	62(1)
C7	10044(4)	9064(1)	1423(1)	71(1)
C8	10538(3)	8514(1)	958(1)	54(1)
C9	8362(3)	6893(1)	-917(1)	39(1)
C10	6722(3)	6347(1)	-1190(1)	48(1)
C11	7035(4)	5902(1)	-1724(1)	60(1)
C12	8976(4)	5990(1)	-1990(1)	63(1)
C13	10613(4)	6523(2)	-1723(1)	64(1)
C14	10310(3)	6974(1)	-1188(1)	53(1)
C15	5338(5)	9493(1)	-782(1)	114(1)
C16	7801(4)	8344(1)	-530(1)	51(1)
C18	9881(3)	6270(1)	1607(1)	38(1)
C19	7882(3)	5896(1)	1703(1)	46(1)
C20	6995(3)	6013(1)	2257(1)	59(1)
C21	8121(5)	6492(2)	2726(1)	74(1)
C22	10114(5)	6856(1)	2641(1)	75(1)
C23	10997(3)	6748(1)	2085(1)	55(1)
C25	4206(3)	5390(1)	10012(1)	31(1)
C27	10929(3)	6121(1)	1019(1)	41(1)

Table A4 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (*S*,*S*,*R*)-**191 (Chapter 1, Section 1.2.3)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O1	6048(3)	-837(3)	7148(1)	82(1)
O2	5142(3)	-1290(3)	7733(1)	75(1)
O3	9452(3)	2277(3)	7742(1)	74(1)
O4	7440(4)	5896(4)	8985(1)	110(1)
O5	9279(4)	7156(3)	9170(1)	102(1)
O6	14396(4)	4028(4)	8408(1)	137(2)
O7	13948(3)	6247(4)	8549(1)	107(1)
N1	8687(3)	844(3)	8239(1)	52(1)
N2	8731(5)	6163(4)	8991(1)	75(1)
N3	13586(4)	4997(5)	8493(1)	82(1)
C1	6000(4)	-577(4)	7486(1)	59(1)
C2	6857(4)	589(3)	7687(1)	52(1)
C3	7806(4)	-161(3)	7995(1)	51(1)
C4	8696(4)	-1396(4)	7826(1)	53(1)
C5	9825(4)	-1125(5)	7576(1)	68(1)
C6	10573(5)	-2274(7)	7408(1)	95(2)
C7	10190(7)	-3662(7)	7487(2)	111(2)
C8	9081(7)	-3963(5)	7730(2)	100(2)
C9	8320(5)	-2820(5)	7904(1)	74(1)
C10	5841(4)	1752(4)	7855(1)	67(1)
C11	4909(5)	2467(4)	7553(1)	64(1)
C12	3504(5)	1991(5)	7485(1)	78(1)
C13	2660(6)	2659(7)	7206(2)	102(2)
C14	3187(7)	3749(6)	6986(1)	101(2)

C15	4592(7)	4217(5)	7048(1)	98(2)
C16	5443(5)	3585(5)	7329(1)	84(1)
C17	4358(6)	-2528(6)	7581(2)	133(2)
C18	9366(4)	2021(4)	8090(1)	58(1)
C19	10008(4)	3145(4)	8354(1)	52(1)
C20	9108(4)	4029(4)	8575(1)	61(1)
C21	9710(5)	5198(4)	8768(1)	58(1)
C22	11157(5)	5536(4)	8748(1)	62(1)
C23	12022(4)	4651(4)	8527(1)	59(1)
C24	11468(4)	3478(4)	8331(1)	58(1)
C25	8926(4)	279(4)	8638(1)	58(1)
C26	10485(4)	430(4)	8771(1)	54(1)
C27	10877(5)	1152(4)	9103(1)	73(1)
C28	12310(6)	1225(5)	9211(1)	93(1)
C29	13374(5)	595(5)	8997(1)	91(1)
C30	13009(5)	-150(4)	8667(1)	79(1)
C31	11569(5)	-239(4)	8560(1)	66(1)
C32	7756(4)	847(5)	8916(1)	87(1)

Table A5 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (*S*,*S*,*R*)-**192 (Chapter 1, Section 1.2.3)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O1	9669(1)	1560(2)	6188(1)	67(1)
O2	8649(1)	4377(2)	5847(1)	60(1)
O3	7259(1)	-3023(2)	7216(1)	72(1)
O4	2218(1)	-2546(3)	6283(1)	81(1)
O5	1456(1)	-3104(3)	7246(1)	84(1)
O6	4154(2)	-4861(3)	9765(1)	85(1)
O7	6101(2)	-4615(3)	9972(1)	78(1)
N1	7104(1)	213(2)	7509(1)	36(1)
N2	2310(2)	-2847(3)	6973(1)	58(1)
N3	5053(2)	-4409(3)	9561(1)	56(1)
C1	8810(2)	2603(3)	6170(1)	45(1)
C2	7728(2)	2030(3)	6463(1)	41(1)
C3	8154(2)	708(3)	7191(1)	39(1)
C4	9218(2)	1494(3)	7845(1)	42(1)
C5	9931(2)	142(4)	8366(1)	59(1)
C6	10839(2)	737(5)	9015(2)	74(1)
C7	11070(2)	2694(5)	9152(2)	75(1)
C8	10403(2)	4037(4)	8638(1)	71(1)
C9	9478(2)	3459(3)	7985(1)	54(1)
C10	6756(2)	1011(3)	5785(1)	52(1)
C11	6117(2)	2482(4)	5146(1)	77(1)
C12	7253(2)	-735(4)	5426(1)	77(1)
C13	9545(2)	5015(4)	5460(1)	78(1)
C14	6770(2)	-1704(3)	7488(1)	44(1)
C15	5697(2)	-2290(3)	7782(1)	39(1)
C16	4528(2)	-2324(3)	7260(1)	43(1)
C17	3559(2)	-2901(3)	7522(1)	42(1)
C18	3696(2)	-3535(3)	8280(1)	45(1)
C19	4869(2)	-3587(3)	8770(1)	42(1)
C20	5869(2)	-2979(3)	8537(1)	42(1)

C21	6652(2)	1802(3)	7939(1)	38(1)
C22	5253(2)	1948(3)	7714(1)	37(1)
C23	4587(2)	1610(3)	8251(1)	41(1)
C24	3325(2)	1673(3)	8021(1)	51(1)
C25	2689(2)	2054(3)	7255(1)	57(1)
C26	3335(2)	2448(3)	6721(1)	57(1)
C27	4599(2)	2428(3)	6952(1)	49(1)
C28	7248(2)	1696(3)	8830(1)	51(1)

Table A6 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (*R*,*R*,*S*)-**194 (Chapter 1, Section 1.2.3)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
O1	573(2)	-776(4)	3996(1)	83(1)
O2	1499(2)	-3727(3)	4183(1)	63(1)
O3	2837(2)	3756(3)	2808(1)	70(1)
O4	3861(2)	5136(4)	-23(1)	83(1)
O5	5808(2)	5381(4)	179(1)	89(1)
O6	8624(2)	3728(4)	2736(1)	82(1)
O7	7910(2)	3241(3)	3715(1)	75(1)
N1	2977(1)	489(3)	2540(1)	35(1)
N2	4915(2)	4949(3)	390(1)	55(1)
N3	7782(2)	3511(3)	3017(1)	55(1)
C1	1376(2)	-1866(4)	3942(1)	52(1)
C2	2422(2)	-1245(4)	3629(1)	44(1)
C3	1939(2)	10(3)	2872(1)	39(1)
C4	856(2)	-796(3)	2217(1)	42(1)
C5	125(2)	542(4)	1686(2)	60(1)
C6	-811(2)	-87(5)	1036(2)	75(1)
C7	-1051(2)	-2076(6)	914(2)	73(1)
C8	-361(2)	-3401(5)	1441(2)	67(1)
C9	587(2)	-2790(4)	2097(2)	51(1)
C10	3349(2)	-68(4)	4289(1)	58(1)
C11	3985(3)	-1253(6)	5019(2)	88(1)
C12	613(3)	-4462(6)	4562(2)	84(1)
C13	3308(2)	2406(3)	2540(1)	39(1)
C14	4366(2)	2952(3)	2226(1)	37(1)
C15	4153(2)	3592(3)	1450(1)	40(1)
C16	5150(2)	4176(3)	1205(1)	41(1)
C17	6336(2)	4142(3)	1691(1)	44(1)
C18	6513(2)	3554(3)	2467(1)	40(1)
C19	5553(2)	3006(3)	2748(1)	41(1)
C20	3424(2)	-1166(3)	2130(1)	38(1)
C21	4836(2)	-1343(3)	2402(1)	39(1)
C22	5448(2)	-1781(4)	3191(2)	54(1)
C23	6724(2)	-1861(5)	3470(2)	70(1)
C24	7402(2)	-1512(4)	2952(2)	75(1)
C25	6816(2)	-1168(4)	2167(2)	65(1)
C26	5538(2)	-1084(4)	1887(2)	50(1)
C27	2842(2)	-1102(4)	1232(1)	48(1)

Table A7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for b-lactam (*S*,*S*,*R*)-**198l (Chapter 1, Section 1.2.4)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
Cl(1)	7789(1)	10277(1)	1036(1)	95(1)
O1	-18(2)	8357(2)	2417(1)	100(1)
N1	2014(2)	8869(2)	2950(1)	65(1)
C1	1148(2)	8254(2)	2481(1)	70(1)
C2	2175(2)	7420(2)	2141(1)	65(1)
C3	3138(2)	8126(2)	2736(1)	57(1)
C4	4287(2)	8719(2)	2337(1)	54(1)
C5	5526(2)	8322(2)	2513(1)	61(1)
C6	6605(2)	8792(2)	2128(2)	70(1)
C7	6439(2)	9679(2)	1552(1)	65(1)
C8	5228(2)	10127(2)	1371(1)	68(1)
C9	4164(2)	9642(2)	1766(1)	64(1)
C10	2396(2)	7322(2)	1176(2)	77(1)
C11	3558(3)	6536(3)	985(2)	111(1)
C12	1174(3)	6875(3)	738(2)	116(1)
C13	1803(2)	9675(2)	3663(1)	73(1)
C14	2360(2)	9174(2)	4483(1)	66(1)
C15	1852(3)	8156(2)	4793(2)	93(1)
C16	2334(6)	7615(3)	5513(2)	147(2)
C17	3317(6)	8123(6)	5943(3)	165(3)
C18	3848(3)	9124(5)	5673(3)	142(2)
C19	3372(3)	9660(3)	4930(2)	103(1)
C20	2281(4)	10893(2)	3443(2)	117(1)

Table A8 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (*S*,*S*)-**46a (Chapter 2, Section 2.2.2)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
S1	9381(1)	2606(1)	8201(1)	67(1)
S2	9216(1)	1462(1)	9995(1)	75(1)
O1	7065(1)	7614(3)	8572(1)	73(1)
N1	8148(1)	4701(3)	9033(1)	48(1)
N2	8618(2)	7678(7)	3514(2)	109(1)
C1	8854(1)	3121(4)	8999(1)	51(1)
C2	8611(2)	3390(6)	10585(2)	74(1)
C3	7784(1)	4440(5)	9846(1)	54(1)
C4	7696(2)	6490(4)	8400(1)	52(1)
C5	8000(2)	6985(4)	7570(1)	53(1)
C6	7533(1)	5377(4)	6746(1)	48(1)
C7	7856(2)	6046(4)	5918(1)	52(1)
C8	8357(2)	8040(5)	5844(2)	72(1)
C9	8624(2)	8555(5)	5063(2)	84(1)
C10	8379(2)	7101(5)	4310(2)	74(1)
C11	7876(2)	5070(6)	4379(2)	79(1)
C12	7631(2)	4555(5)	5167(2)	67(1)
C13	9330(3)	9410(9)	3551(3)	142(2)
C14	8370(3)	6098(9)	2752(2)	124(1)

C15	6436(2)	5283(3)	6525(1)	46(1)
C16	5994(2)	3383(4)	6795(1)	57(1)
C17	4984(2)	3255(5)	6573(2)	64(1)
C18	4426(2)	5027(5)	6088(2)	64(1)
C19	4858(2)	6922(5)	5824(2)	62(1)
C20	5857(2)	7042(4)	6045(1)	54(1)
C21	6862(1)	2982(4)	9602(1)	54(1)
C22	6426(1)	2889(4)	10385(1)	48(1)
C23	6589(2)	1031(4)	10985(2)	66(1)
C24	6194(2)	998(5)	11709(2)	80(1)
C25	5629(2)	2798(6)	11827(2)	73(1)
C26	5468(2)	4661(5)	11247(2)	68(1)
C27	5861(2)	4709(4)	10524(2)	55(1)

Table A9 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (1*R*,3*S*,4*S*,6*R*)-**48b (Chapter 3, Section 3.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	**x**	**y**	**z**	**U(eq)**
N1	6728(1)	10813(2)	-887(1)	44(1)
N2	9248(2)	9540(2)	39(1)	50(1)
C1	7880(2)	10956(2)	-1426(1)	42(1)
C2	8821(2)	9590(2)	-1131(1)	44(1)
C3	8098(2)	9357(2)	589(1)	41(1)
C4	7124(2)	10747(2)	281(1)	40(1)
C5	7401(2)	11043(3)	-2641(1)	51(1)
C6	8617(2)	11149(3)	-3196(2)	60(1)
C7	9625(2)	9853(3)	-2865(2)	64(1)
C8	10055(2)	9734(3)	-1650(2)	55(1)
C9	8647(2)	9305(2)	1795(1)	42(1)
C10	9737(2)	10202(3)	2232(2)	51(1)
C11	10208(2)	10316(3)	3341(2)	59(1)
C12	9560(2)	9542(3)	4026(2)	59(1)
C13	8447(2)	8569(2)	3621(1)	50(1)
C14	7997(2)	8407(2)	2494(1)	43(1)
C15	6922(2)	7348(2)	2122(2)	48(1)
C16	6341(2)	6526(3)	2823(2)	59(1)
C17	6756(3)	6729(3)	3934(2)	71(1)
C18	7781(3)	7723(3)	4324(2)	67(1)
C19	5849(2)	10642(2)	766(1)	42(1)
C20	4729(2)	9887(2)	196(2)	49(1)
C21	3528(2)	9738(3)	607(2)	62(1)
C22	3463(2)	10293(3)	1581(2)	68(1)
C23	4581(2)	11075(3)	2215(2)	57(1)
C24	5790(2)	11285(2)	1794(1)	44(1)
C25	6862(2)	12111(2)	2442(2)	52(1)
C26	6785(3)	12627(3)	3442(2)	68(1)
C27	5620(3)	12371(4)	3861(2)	84(1)
C28	4550(3)	11638(4)	3250(2)	80(1)

Table A10 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for the compound (1*R*,3*S*,4*S*,6*R*)-**48e (Chapter 3, Section 3.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O1	9276(1)	5081(4)	303(2)	61(1)
O2	9169(1)	11922(4)	3958(2)	64(1)
N1	9686(1)	9299(5)	1339(2)	51(1)
N2	9631(1)	7758(5)	3375(2)	50(1)
C1	10122(1)	7459(6)	2982(2)	49(1)
C2	10139(1)	9648(6)	2227(2)	49(1)
C3	9158(1)	9414(5)	1622(2)	44(1)
C4	9133(1)	7604(6)	2555(2)	46(1)
C5	10606(1)	7439(7)	3884(2)	65(1)
C6	11125(1)	7500(8)	3491(2)	71(1)
C7	11136(1)	9756(8)	2768(3)	73(1)
C8	10657(1)	9715(7)	1851(2)	67(1)
C9	8739(1)	8644(6)	674(2)	45(1)
C10	8813(1)	6479(6)	75(2)	48(1)
C11	8422(1)	5754(7)	-782(2)	59(1)
C12	7960(1)	7169(8)	-1056(2)	67(1)
C13	7877(1)	9324(7)	-490(2)	65(1)
C14	8268(1)	10017(7)	373(2)	55(1)
C15	8671(1)	8375(6)	3040(2)	50(1)
C16	8705(1)	10513(7)	3699(2)	54(1)
C17	8279(1)	11239(8)	4116(2)	70(1)
C18	7811(2)	9882(10)	3886(3)	86(1)
C19	7764(1)	7748(9)	3250(3)	82(1)
C20	8196(1)	6985(7)	2827(2)	64(1)

Table A11 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 3-ethyl coumarin **31c (Chapter 4, Section 4.2.1)**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

atom	x	y	z	U(eq)
O1	1905(1)	-743(1)	3591(1)	59(1)
O2	874(2)	714(1)	2258(1)	79(1)
C1	2616(2)	-1111(1)	4728(1)	48(1)
C2	1494(2)	507(1)	3277(1)	54(1)
C3	1839(2)	1473(1)	4202(1)	49(1)
C4	2510(2)	1104(1)	5310(1)	50(1)
C5	2913(2)	-209(1)	5621(1)	47(1)
C6	3623(2)	-645(1)	6759(1)	59(1)
C7	4019(2)	-1917(2)	6973(1)	64(1)
C8	3720(2)	-2785(1)	6064(1)	61(1)
C9	3026(2)	-2387(1)	4936(1)	58(1)
C10	1404(2)	2822(1)	3795(1)	60(1)
C11	1853(2)	3829(2)	4734(2)	75(1)

LIST OF PUBLICATIONS

1. Intramolecular coupling of chiral diimines using low-valent titanium reagents: stereoselective synthesis of chiral 3,4-disubstituted-2,5-diazabicyclo[4.4.0] decanes; Periasamy, M.; Srinivas, G.; **Suresh, S.** *Tetrahedron Lett.* **2001**, *42*, 7123.
2. Synthesis of *cis*-2-aryl-3-pyrrolidine carboxylic esters via diastereoselective cyclization of γ-imino esters using a $TiCl_4/Et_3N$ reagent system; **Suresh, S.**; Periasamy, M. *Tetrahedron Lett.* **2004**, *45*, 6291.
3. Stereoselective synthesis of *syn*-β-amino esters using the $TiCl_4/R_3N$ reagent system; Periasamy, M.; **Suresh, S.**; Ganesan, S. S. *Tetrahedron Lett.* **2005**, *46*, 5521.
4. Stereoselective additions of titanium enolates of prochiral esters to chiral imines by the Mannich-type reactions: Asymmetric synthesis of chiral *syn*-β-amino esters; Periasamy, M.; **Suresh, S.**; Ganesan, S. S. *To be communicated*.
5. Synthesis of chiral β-lactams containing α-methylbenzyl moiety; Periasamy, M.; **Suresh, S.**; Ganesan, S. S. *To be communicated*.
6. Intramolecular Knoevenagel condensation of *ortho*-(*O*-acyl)-aryl aldehydes using the $TiCl_4/R_3N$ reagent system: Synthesis of 3-substituted coumarins; Periasamy, M.; **Suresh, S.** *To be communicated*.
7. Variable temperature ^{13}C-NMR behavior of certain 3,4-diaryl-2,5-diazabicyclo[4.4.0]decanes: Existence of rotomers with different minimum energies; Periasamy, M.; **Suresh, S.**; Srinivas, G. (*manuscript under preparation*).

POSTERS/PAPERS PRESENTED IN SYMPOSIA

1. Intramolecular coupling of chiral diimines using low-valent titanium reagents; **Suresh, S.**; Srinivas, G.; Periasamy, M. *Indo-US Conference,* IIT Madras, Chennai, December 10-12, **2003**.
2. Stereoselective cyclization of diimines and γ-imino esters using titanium reagents; **Suresh, S.**; Periasamy, M. *Chemfest 2004,* School of Chemistry, University of Hyderabad, Hyderabad, March 12, **2004**.
3. Diastereoselective synthesis of cyclic and acyclic β-amino esters using $TiCl_4/R_3N$ reagent and synthesis of β-lactams; **Suresh, S.**; Ganesan, S. S.; Periasamy, M. *Chemfest 2005,* School of Chemistry, University of Hyderabad, Hyderabad, February 19, **2005**.