ENANTIOSELECTIVE SYNTHESIS OF BIOACTIVE MOLECULES *via* METAL-CATALYZED ASYMMETRIC REDUCTIONS, OXIDATIONS OF ALKENES AND ADDITION BY NUCLEOPHILES ONTO IMINES

A THESIS

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in

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By

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dedicated to my beloved parents

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Enantioselective Synthesis of Bioactive Molecules *via* Metal-Catalyzed Asymmetric Reductions, Oxidations of Alkenes and Addition by Nucleophiles onto Imines**" was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(Dr. A. Sudalai)

Research Supervisor

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ABSTRACT

The thesis entitled **"Enantioselective Synthesis of Bioactive Molecules *via* Metal-Catalyzed Asymmetric Reductions, Oxidations of Alkenes and Addition by Nucleophiles onto Imines"** is divided in to four chapters.

The title of the thesis clearly indicates the objective, which is to synthesize optically pure drugs and to interface synthetic organic chemistry with transition-metal chemistry for the development of synthetic methodologies. Chapter 1 **describes the asymmetric synthesis of three important drugs namely (*R*)-Baclofen, (*R*)-Rolipram and (*R*)-4-(4-fluorophenyl)piperidin-2-one (intermediate for (-)-Paroxetine) *via* $CoCl_2$ catalyzed asymmetric reductions using $NaBH_4$ as reducing agent.** Chapter 2 **deals with an enantioselective synthesis of (-)-Cytoxazone *via* Sharpless asymmetric epoxidation.** Chapter 3 **presents Cu-catalyzed multicomponent strategy for high yield synthesis of dihydropyrimidinones, dihydropyridines and dihydrooxazinones.** Chapter 4 **examines the Lewis acid and organic base as catalysts for nucleophilic addition of CN^- and $P(OMe)_3$ as nucleophiles onto imines.**

CHAPTER 1

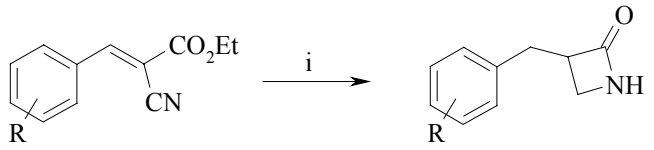
Co(II)-Catalyzed Asymmetric Reduction of α, β-Unsaturated Esters: Enantioselective synthesis of (R)-Baclofen, (R)-Rolipram, and (R)-4-(4-fluorophenyl)piperidin-2-one

The $CoCl_2$ catalyzed asymmetric reduction of olefins using sodiumborohydride as hydrogen source is a powerful method, which replaces the hazardous hydrogen gas and costly Rh and Ru complexes[1]. This chapter is divided into three sections.

SECTION I: Co-Catalyzed reduction of α-cyano ethyl cinnamates: One pot synthesis of 3-substituted azetidin-2-ones

3-substituted azetidin-2-ones (β-lactams) are useful intermediates in organic synthesis[2]. We have developed a new method for the synthesis of β-lactams in a single step, the results of which are presented in this section. Thus, cyanoesters 1**, readily obtained in high yields from the corresponding aldehydes by condensation with ethyl**

cyanoacetate, were subjected to Co(II)-catalyzed reduction using $NaBH_4$ to afford 3-substituted β-lactams 2 **in high yields and enantioselectivity (**Scheme 1**).**



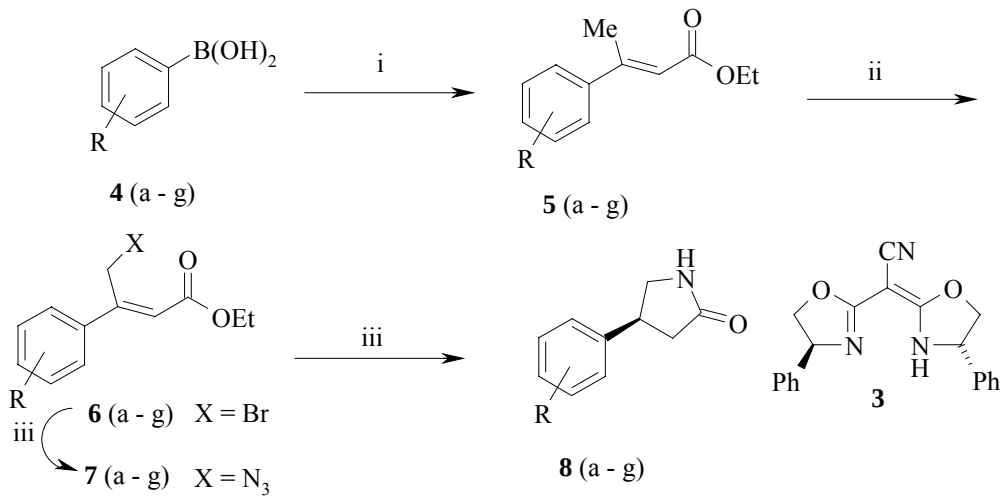
1 **2**

R = H, 4-OMe, 4-Cl, 3,4(OMe)$_2$, etc. 70 - 99 %

Scheme 1: **i cat. $CoCl_2.6H_2O$, $NaBH_4$, dry DMF:EtOH (1:1), 25 ^{0}C, 24 h, 70 – 99%.**

SECTION II: Co-catalyzed reductive cyclization of γ-azido-α,β-unsaturated esters: Enantioselective Synthesis of (R)-Baclofen and (R)-Rolipram

Baclofen, [γ-amino-β-(p-chlorophenyl) butyric acid], 8b**, plays an important role as an inhibitory neurotransmitter in central nervous system of mammalians[3]. Rolipram, [4-(3-cyclopentyloxy-4-methoxy phenyl)-2-pyrrolidinone],** 8g**, has been shown to be a potent and selective inhibitor of phosphodiesterase type IV (PDE IV)[4], inhibition of PDE IV is rapidly becoming recognized as a promising therapeutic target for treatment of a number of disorders such as asthma, atopy and multiple sclerosis[5]. Although both baclofen (**8b**) and rolipram (**8g**) are commercialized in their racemic forms, it has recently been disclosed that their biological activities reside exclusively in (R)–(-)-enantiomers. This section provides the asymmetric synthesis of variety of 4-aryl pyrrolidinones (**8a-g**) from readily available substituted aryl boronic acids (**4a-g**). Thus, boronic acids (**4a-g**) were arylated with ethyl crotonate in the presence of $Pd(OAc)_2$ as catalyst to afford the arylated products** 5a-g **in high yields. Allylic bromination of (**5a-g**) with NBS gave the bromo derivatives** 6 **which were transformed into the corresponding azido derivatives** 7 **in good yields. One-pot asymmetric reduction of azido esters** 7 **with catalytic $CoCl_2/NaBH_4$/oxazolidine system afforded the corresponding 4-arylpyrrolidinones** 8a-g **in excellent yields and high enantioselectivity (**Scheme 2**).**

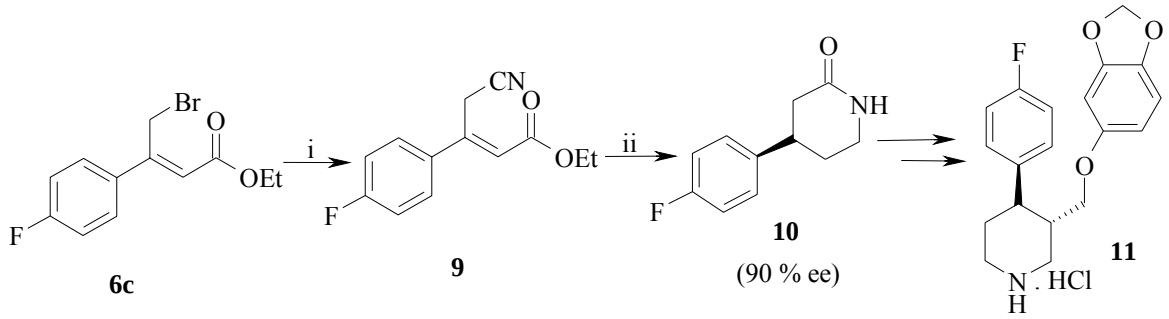


8	R	Yield (%)	%ee	Config.
a	**H**	**86**	**--**	
b	**4-Cl**	**82**	**89**	**R**
c	**4-F**	**80**	**--**	
d	**2-OMe**	**91**	**--**	
e	**4-OMe**	**93**	**--**	
f	***t*-C_4H_9**	**77**	**--**	
g	**3-OCp-4-OMe**	**90**	**92**	**R**

Scheme 2: **i cat. $Pd(OAc)_2$, K_2CO_3, Ethyl crotonate, DMF, O_2, 70 ^{0}C; ii cat. AIBN, NBS, CCl_4, reflux; iii cat. $CoCl_2.6H_2O$, Ligand (3), $NaBH_4$, dry DMF:EtOH (1:1), 25 ^{0}C, 24 h, 70–99 %.**

SECTION III: Co-catalyzed reductive cyclization of γ-cyano-α,β-unsaturated esters: Enantioselective Synthesis of (*R*)-4-(4-fluorophenyl)piperidin-2-one

(-)-Paroxetine hydrochloride (11**) is a selective serotonin reuptake inhibitor in the treatment of depression, obsessive compulsive disorder and panic disorder[6]. This section describes the enantioselective synthesis of (*R*)-4-(4-fluorophenyl)piperidin-2-one** 10 **(intermediate for (-)-paroxetine** 11**)[7] from readily available bromoester** 6c**. Thus, the exchange of bromide ion in** 6c **with CN^- was achieved to afford cyano derivative** 9 **in good yields. One-pot asymmetric reduction of cyanoester** 9 **with catalytic amount of $CoCl_2$/oxazolidine with $NaBH_4$ as hydrogen source gave the 4-aryl piperidinone** 10 **in 99 % yield and 86 % ee (**Scheme 3**).**



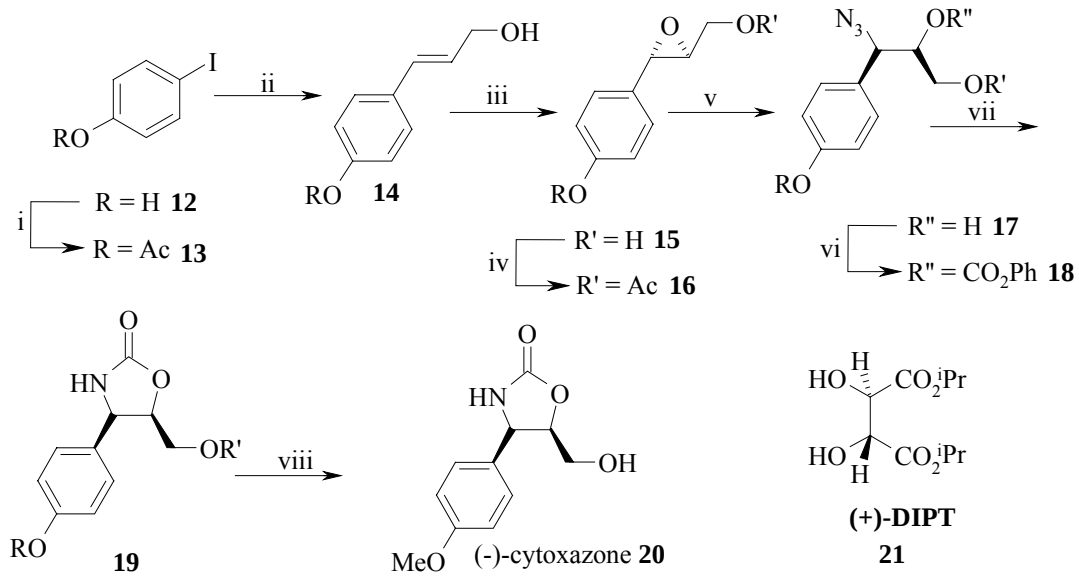
6c **9** **10** (90 % ee) **11**

Scheme 3: i NaCN, dry DMF, 25 ^{0}C, 80%; ii cat. $CoCl_2.6H_2O$, Ligand (**3**), $NaBH_4$, dry DMF:EtOH (1:1), 25 ^{0}C, 24 h, 86% ee, 99 %.

CHAPTER 2

Enantioselective Synthesis of (-)-Cytoxazone, a Novel Cytokine Modular *via* Sharpless asymmetric epoxidation

Cytoxazone 20**, produced by *Streptomyces sp.*, is a novel cytokine modular, which interferes with the cytokine IL-4, IL-10 and IgG production by selective inhibition of the signaling pathway of Th2 cells[8]. The structure of** 20 **includes a 4, 5-disubstituted 2-oxazolidinone ring, which is rare in microbial metabolites. This chapter describes the enantioselective synthesis of cytoxazone** 20 **by making use of Sharpless asymmetric epoxidation of allylic alcohol** 14 **as the key step in introducing stereogenicity into the molecule. Thus, 4-acetoxyiodobenzene** 13 **was arylated with allyl alcohol to produce the arylated product** 14 **in 70% yield. Allylic alcohol** 14 **was epoxidized using $Ti(OiPr)_4$/(+)-DIPT(**21**)/TBHP system to afford the chiral epoxy alcohol** 15 **in high yield and enantioselectivity. Compound** 16 **was subjected to nucleophilic epoxide ring opening with N_3 to provide azido alcohol** 17 **in a highly regio and diastereoselective manner. Compound** 17 **was subsequently converted into cytoxazone** 20 **by following known protocol[9] (**Scheme 4**).**



Scheme 4: i AcCl, Et_3N, CH_2Cl_2, 0 to 25^{0}C, 6h, 95%. ii Allyl alcohol (3 equiv), AgOAc (1 equiv), cat. $Pd(OAc)_2$, cat. PPh_3, DMF, 70^{o}C, 16h, 81%. iii anhyd. 5.4 M TBHP in CH_2Cl_2, 4Å MS, cat. $Ti(O^iPr)_4$, cat. (+)-DIPT (**21**), CH_2Cl_2, -20^{o}C, 20h, 78%. iv AcCl, Et_3N, cat. DMAP, CH_2Cl_2, 25^{0}C, 87%. v) NaN_3, cat. NH_4Cl, THF:H_2O (2:1), 50^{0}C, 3h, 79%. vi PhOCOCl, pyridine, CH_2Cl_2, -5 to 25^{0}C, 1h, 93%. vii PPh_3 (4 equiv), THF:H_2O (10:1), 50^{0}C, 2h, 87%. viii (a) aq. $NaHCO_3$, MeOH, reflux, 1h; (b) NaH, MeI, THF, 0 to 25^{0}C, 3h, 69%.

CHAPTER 3

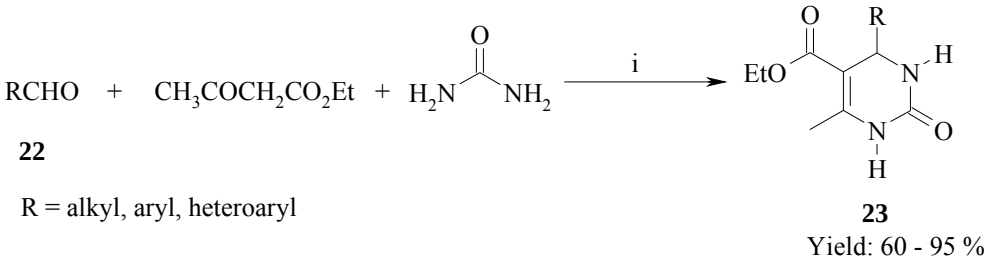
Cu(OTf)$_2$ catalyzed multicomponent reactions: High yield synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones, 3,4-dihydropyridines and 3, 4-dihydro-(*2H*)1,3-oxazin-2-(1*H*)-ones

Multicomponent reactions (MCRs) are of increasing importance in organic synthesis and medicinal chemistry as they offer significant advantages such as speed, diversity and efficiency in the drug discovery process over the conventional linear-type synthesis[10]. In this chapter three such MCRs (Biginelli, Hantzsch and Biginelli-type reactions) catalyzed by copper triflate are discussed. This chapter is divided into three sections.

SECTION I: Cu-catalyzed three-component synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

Biginelli reactions are simple one-pot condensations of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of acids to produce 3,4-dihydropyrimidin-2-(1*H*)-ones. In recent years, interest in this reaction has

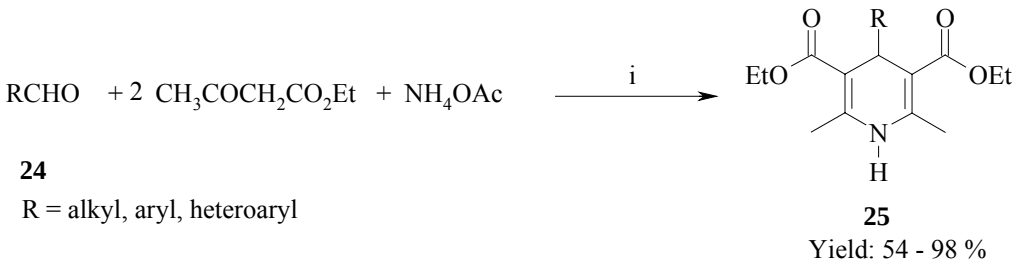
increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported[11]. This section describes a simple but effective procedure for Biginelli's three-component cyclocondensation producing high yields of 3,4-dihydropyrimidin-2(1*H*)-ones 23 **by employing $Cu(OTf)_2$ as a *reusable* catalyst. After the reaction was complete the product was isolated by simple filtration and filtrate containing soluble catalyst was *reused* several times. Both electron-donating as well as electron-withdrawing substituent on aldehydes underwent Biginelli reaction to give 3,4-dihydropyrimidin-2(1*H*)-ones** 23 **in good to excellent yields[12] (**Scheme 5**).**



Scheme 5: i $Cu(OTf)_2$ (1 mol%), CH_3CN, 25 ^{0}C, 6-12 h, 60-95%.

SECTION II: Cu-catalyzed three-component synthesis of 1,4-dihydropyridines

Hantzsch reaction is simple one-pot condensations of β-dicarbonyl compounds with aldehydes and ammonia in the presence of catalytic amount of acids to produce 1,4-dihydropyridines.[13] Interest in this reaction has increased rapidly because 1, 4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers and several modified procedures aimed at improving the efficiency of the 1,4-DHP synthesis have been reported.[14] This section describes a simple but effective procedure for Hantzsch three-component cyclocondensation producing high yields of 1,4-dihydropyridines 25 **by employing $Cu(OTf)_2$ as a catalyst. (**Scheme 5**).**



24

R = alkyl, aryl, heteroaryl

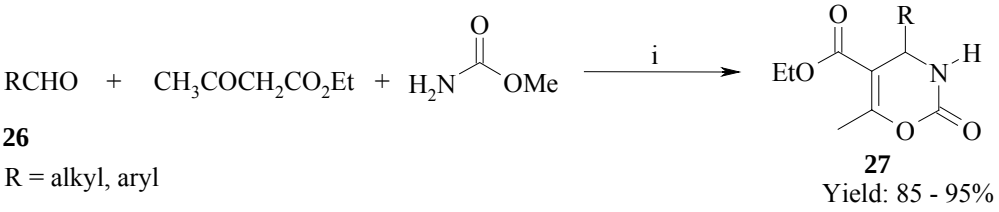
25

Yield: 54 - 98 %

Scheme 6: i $Cu(OTf)_2$ (1 mol%), CH_3CN, 25 ^{0}C, 4-24 h, 54 – 98%.

SECTION III: Cu-catalyzed three-component synthesis of 3,4-dihydro[1,3]oxazin-2-ones

This section describes, for the first time, the high yield synthesis of new class of dihydro-1,3-oxazin-2-ones (27**), resembling structurally with 3,4-dihydropyrimidin-2(1*H*)-ones (**23**). The synthesis of oxazinones** 27 **catalyzed by $Cu(OTf)_2$ was achieved in a single step by following MCRs strategy wherein aldehydes, ethyl acetoacetate and methyl carbamate were employed as condensation agents (**Scheme 7**).**



26

R = alkyl, aryl

27

Yield: 85 - 95%

Scheme 7: i $Cu(OTf)_2$ (1 mol%), CH_3CN, 25- 80 ^{0}C, 6-12 h, 62-82%.

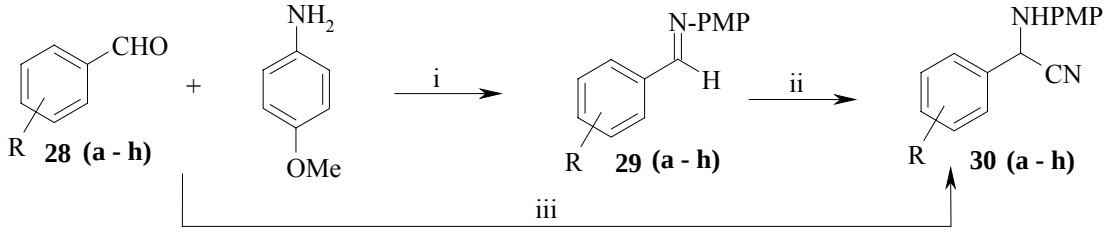
CHAPTER 4

$Cu(OTf)_2$ and Et_3N-catalyzed Cyanide and Phosphite additions onto Imines

The Strecker amino acid synthesis, which involves treatment of aldehydes with ammonia and HCN (or equivalents) followed by hydrolysis of the intermediate α-aminonitriles to provide α-aminoacids, was first reported in 1850.[15] The catalytic asymmetric Strecker-type reaction offers one of the most direct and viable methods for the asymmetric synthesis of α-aminoacid derivatives.[16] This chapter is divided into two sections.

SECTION I: $Cu(OTf)_2$ and Et_3N-catalyzed addition of CN^- onto imines: Synthesis of α-aminonitriles

α-Aminonitriles are valuable intermediates for the synthesis of amino acids, amino alcohols, etc. and one of the most convenient preparative methods to make these compounds is the nucleophilic addition reaction of CN^- onto imines catalyzed by several Lewis acids.[17] This section describes new catalytic methods for the addition of CN^- onto imines generated in situ. Thus, addition of CN^- onto imines was achieved by catalytic amount of $Cu(OTf)_2$ or catalytic amount of Et_3N to afford the corresponding α-aminonitriles (30a-h**) in high yields (**Scheme 8**). It is remarkable that the addition takes place at room temperature using CH_3CN as solvent employing 1 mol % of the catalyst ($Cu(OTf)_2$ or Et_3N).**

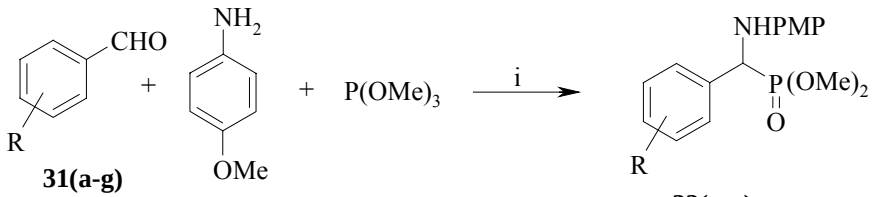


Entry	R	Yield (%)	
		$Cu(OTf)_2$	Et_3N
a	**H**	**95**	**93**
b	**4-Cl**	**90**	**85**
c	**4-OMe**	**99**	**95**
d	**4-CN**	**88**	**90**
e	**4-OH**	**85**	**88**
f	**2-OH**	**82**	**85**
g	**4-NO_2**	**78**	**73**
h	**3-NO_2**	**81**	**72**

Scheme 8: i dry MgSO4, CH_2Cl_2, 25 ^{0}C, 1 h. ii cat. Et_3N (5 mol%), CH_3CN, 25 ^{0}C, 5 h. iii cat. $Cu(OTf)_2$ (1 mol%), CH_2Cl_2, , 25 ^{0}C, 5 h

SECTION II: Cu(II) catalyzed one pot addition of $P(OMe)_3$ onto imines: Synthesis of α-aminophosphonates

α-Aminophosphonates (32a-g**) have major roles to play in peptidomimetics, hapten design in antibody generation and also enzyme inhibitory activity.[18] Such compounds have been prepared by using several Lewis acids as catalysts.[19] This section describes a new catalytic method for the preparation of α-aminophosphonates (**32**) in a single step by treating several aldehydes (**31**) with *p*-anisidine and trimethyl phosphite performing the reaction at ambient conditions (**Scheme 9**).**



31(a-g) **32(a-g)**

Entry	R	Yield (%)
a	**H**	97
b	**4-Cl**	92
c	**4-OMe**	95
d	**4-CN**	82
e	**4-OH**	88
f	**2-OH**	79
g	**3-NO_2**	75

Scheme 9: **i cat. $Cu(OTf)_2$ (1 mol %), CH_3CN, 25 ^{0}C. , 5 h**.

CONTENTS

SECTION I:

Co-Catalyzed reduction of α-cyano ethyl cinnamates: One pot synthesis of 3-substituted azetidin-2-ones

1.0.1 Introduction

Azetidin-2-one (β-lactam), a four membered cyclic amide, is a basic structure of many biologically important antibiotics. The unique structural feature and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of synthetic chemists, as they provide variety of synthetic challenges. Although the first synthesis of β-lactam ring was reported way back in 1907[1] by Staudinger, β-lactams as a class acquired immense importance only after the discovery of penicillin by Fleming in 1928[2] and its structural confirmation by X-ray crystallography[3] which unambiguously confirmed the presence of 4-membered amide ring (β-lactam). The azetidin-2-one ring was identified as the key structural unit responsible for the antibiotic activity.

Until 1970, penicillin (**1**) and cephalosporins[4] (**2**) were the only examples of naturally occurring β-lactam antibiotics. The discovery of 7-α-methoxycephalosporins[5] (**3**) from "*Streptomyces*" in 1971 stimulated the search for novel antibiotics like carbapenem (**4**).

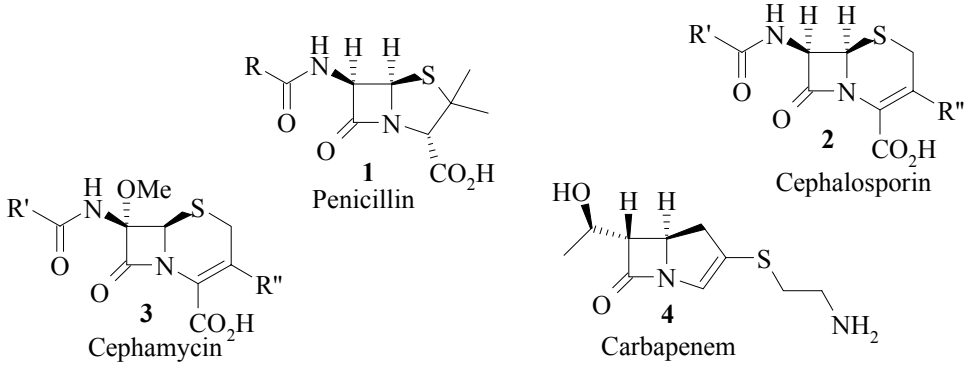


Fig. 1: Some of the important biologically active β-lactam units

1.0.2 Pharmacology of β-lactams

The biological activity of β-lactam antibiotics is mainly due to the presence of the azetidin-2-one ring (β-lactam ring). The Structure Activity Relationship[6] studies have shown that the main requirement for the antibiotic is that it should be able to penetrate the outer spheres of the bacterial cell-wall and then bind in active form to the targets, which are the inner membrane enzymes. These are responsible for the biosynthesis of the cell wall, thereby inactivating one or more enzymes involved in the cell-wall synthesis. Penicillin binds to the so-called 'penicillin-binding proteins' (PCBs), which are specific molecules on the inner membrane of the cell-wall. The binding of penicillin to the PCBs causes termination of the peptide chain linking and inhibits the formation of normal peptidoglycan structure. This leads to the weakening of cell wall and lysis.[7]

1.0.3 Transition metal boride catalyzed reduction

Since the pioneering discovery of nickel-catalyzed hydrogenation by Paul Sabatier, for which he won the Nobel Prize in 1912, Organic Chemists have been fascinated with transition metals and their compounds as promoters for other synthetically important reductions. In the past 40 years, metal hydrides, particularly sodium borohydride and lithium aluminum hydride, have emerged as preeminent reducing agents in modern organic chemistry.[8] These are extraordinarily versatile reagents capable of reducing most functional groups. Moreover by attaching organic ligands at boron or aluminum or changing the metal counter ion, one can modulate the scope, regio, and stereoselectivity of such reductions. Literally hundreds of substituted boron and aluminum hydrides have been described in the chemical literature and dozens are now commercially available.[9]

More recently, transition metal salts have been used as catalysts or additives in conjunction with $NaBH_4$ and $LiAlH_4$, to modify or enhance the properties of these reagents. Nearly every conceivable combination of salt and hydride has been investigated with the concomitant development of many useful new synthetic methods.[10] The resulting systems are complex, however, and in most cases virtually nothing is known about mechanism or reactive intermediates. Boron and aluminum hydrides may combine with metal halides in several different ways: (1) simple metathesis (e.g., LiCl + $NaBH_4$, $LiBH_4$, + NaCl), (2) reduction of the metal halide to the metal, (3) conversion of metal halide to metal hydride: (4) some combination of (2) and (3), viz., $FeC1_3$, + $LiBH_4$ = $Fe(BH_4)_2$, or (5) formation of a boride or aluminide.[11] Furthermore, it is often unclear whether the metal salt serves a true catalytic function or whether some transient, metalloidal complex formed *in situ* is the actual reducing agent.

Historically, borides were first produced by the combination of boron with metallic or metalloidal elements less electronegative than itself. For the most part, borides are very hard, high-melting, refractory substances whose structures and stoichiometries do not conform to the ordinary concepts of valence. A much simpler synthesis was discovered by H. I. Schlessinger in his pioneering work on borohydrides. Combinations of cobalt or nickel (or other metal salts) with aqueous $NaBH_4$ deposit finely divided black precipitates of Co_2B and Ni_2B (eq 1).

$$4NaBH_4 + 2CoC1_2 + 9H_2O = Co_2B + 3H_3BO_3 + 4NaC1 + 12.5H_2 \quad (1)$$

Because they actively catalyzed the decomposition of borohydride, these borides have been commonly used as a practical, controlled source of hydrogen (eq 2).

$$NaBH_4 + 2H_2O = NaBO_2 + 4H_2 \quad (2)$$

The actual composition of borides prepared from inorganic salts depends to a great extent on the specific mode of preparation. Maybury, Mitchell, and Hawthorne analyzed nickel and cobalt borides prepared in ethanol under N_2 using excess $NaBH_4$, and concluded that the stoichiometries Ni_2B and Co_2B inadequately represented their constitution.[12]

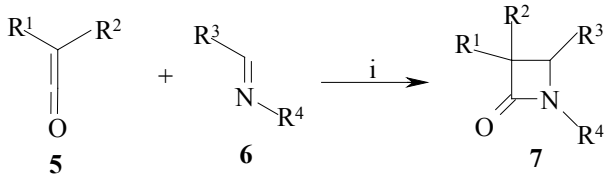
In dimethylformamide (DMF) reduction of $CoC1_2$ or $NiC1_2$ with $NaBH_4$, produced dark brown/black solutions[13] which comprised quite efficient systems for hydrogenation of alkenes, alkynes, azides, nitriles, alkyl halides, nitro compounds, amides, oximes, etc.[14] Simple reaction procedures and excellent yields of products coupled with high catalytic efficiency makes this method much more impressive and practical.

1.0.4 Review of Literature

Literature search revealed that over the past few decades, there are several methodologies[15] have been developed for the construction of the β-lactam ring. However, there is no report exist on reductive cyclization of α-cyano esters producing β-lactams. Some of the important methods on the synthesis of β-lactams known in the literature are described below.

Staudinger *et al.*[16]

Staudinger and coworkers achieved the first chemical synthesis of β-lactam ring in 1907 by [2+2] cycloaddition of ketenes **5** with imines **6** in CH_2Cl_2 at room temperature producing required product **7** in 30-75 % yield. This reaction is referred to as Staudinger reaction or ketene-imine cycloaddition reaction[16] (**Scheme 1**). Later it was modified, wherein acid chlorides or activated carboxylic acids were used in presence of a base as ketene precursor.

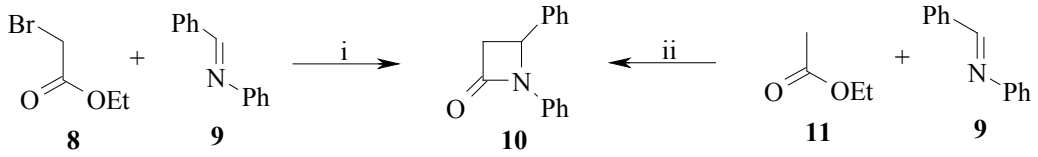


Yield = 30 - 75 %

Scheme 1: i Ketene (1 equiv.), imine (1equiv.), CH_2Cl_2, 25^0C, 12h, 30-75 %.

Gilman *et al.*[17]

Gilman and Speeter first reported a reaction,[17] in which they constructed a β-lactam ring **10** by condensation of Zn enolate (Reformatsky reagent) generated from ethyl bromoacetate **8** with imines **9** in 45 – 88 % yield. Later on, other metal enolates generated from ethyl acetate **11** have also been used in the enolate imine condensation reaction to achieve good selectivities and yields in β-lactam formation[18] (**Scheme 2**).

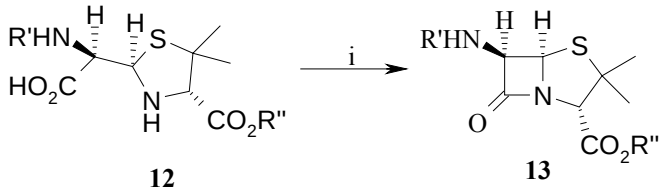


Yield = 60 - 88 %

Scheme 2: i Zn (1 equiv.), toluene, 100^0C, 6h, 60 %. ii LDA, THF, -78 ^{0}C, 88%.

Formation of N-C2 bond:

This approach was first reported by Staudinger, Klever and Kober in 1910.[19] Sheehan and Henery-Logan have used this method for their landmark synthesis of penicillin[20] by cyclization of β-amino acid **12** using dicyclohexylcarbodiimide (DCC) as condensing reagent yielding 54 % required product **13** (**Scheme 3**).

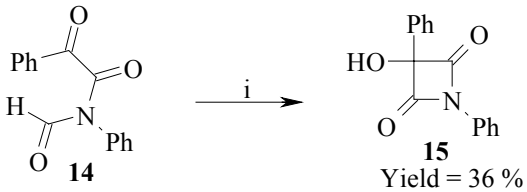


Yield = 54 %

Scheme 3: i DCC (1.2 equiv.), CH_2Cl_2, RT, 6h, 54 %.

Formation of C2-C3 bond:

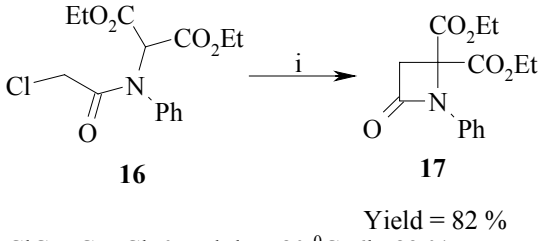
Compared to the amide (N-C2) bond formation, azetidinone formation at the C2-C3 position is complicated by the difficulty in forming a C-C bond versus an amide bond. Hence this method is least used. A photochemical approach leading to formation of 4-keto-β-lactams **15** has been developed[21] from the corresponding dicarbonyl compound **14** (**Scheme 4**).



Scheme 4: i hυ, *t*-BuOH, argon, 25^{0}C, 6h, 36 %.

Formation of C3-C4 bond:

This involves formation of a nucleophilic center at C3 and an electrophilic center at C4 or *vice versa*. The first example of such an Intramolecular nucleophilic displacement reaction was reported by Sheehan and Bose[22] wherein haloacylamino malonate **16** was cyclized in an intramolecular fashion in the presence of Et_3N at 0 and then 80 ^{0}C in $ClCH_2CH_2Cl$ for 6 h producing required product **17** in 82 % yield (**Scheme 5**).

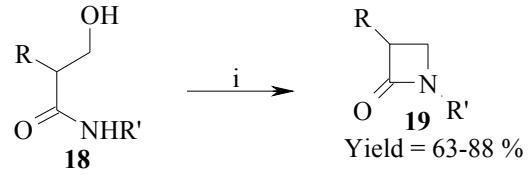


Scheme 5: i Et_3N, $ClCH_2CH_2Cl$, 0 and then 80 ^{0}C, 6h, 82 %.

Formation of C4 -N bond:

This is the route selected by nature for the biosynthesis of azetidinone containing antibiotics.[23] The essential strategy involved in the synthesis of β-lactams through C4 –N bond is the intramolecular displacement of a leaving group attached to C4 with an appropriately activated nitrogen. Miller and coworkers[24] have made significant contribution to this

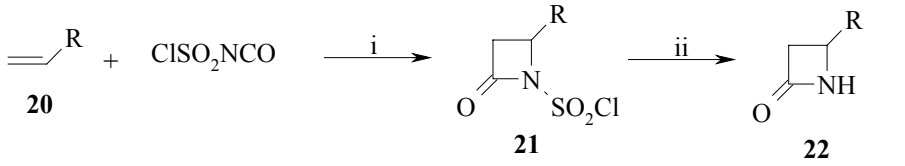
methodology. The key feature of the Miller's hydroxamate approach is the intramolecular cyclization of β-hydroxy amides **18** under Mitsunobu reaction conditions[25] which afforded 3-substituted-β-lactams **19** (**Scheme 6**).



Scheme 6: i PPh_3 (1.1 equiv.), DEAD (1.1 equiv.), THF, 25^0C, 12h, 63-88 %.

Isocyanate addition to alkenes:

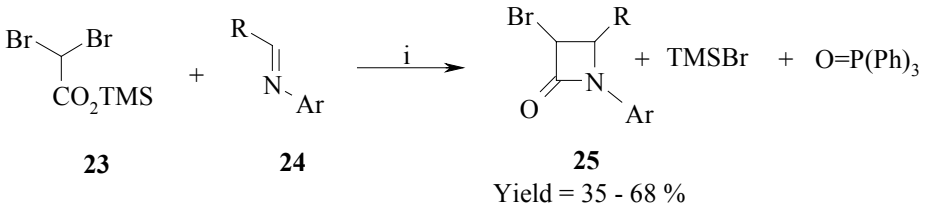
Graf[26] reported the cycloaddition of N-chlorosulfonyl isocyanate (CSI) with alkenes **20** to get 1-chlorosulfonyl azetidin-2-ones **21**. Subsequent removal of the chlorosulfonyl group gave the NH β-lactam **22**. The cycloaddition is promoted by activated alkenes like vinyl acetates (**Scheme 7**).



Scheme 7: i CH_2Cl_2, 0 – 25 ^{0}C, 8h, 29 – 57 %.

Manhas *et al.*[27]

Manhas *et al.*[27] have developed this approach, which involves condensation of halo ester **23** with imines **24** in presence of triphenyl phosphine at 100 ^{0}C in toluene to produc 3-halo-β-lactams **25** in 35 – 68 % yield (**Scheme 8**).



Scheme 8: i PPh_3, toluene, 100 ^{0}C, 3h, 35 – 68 %.

1.0.5 Present Work

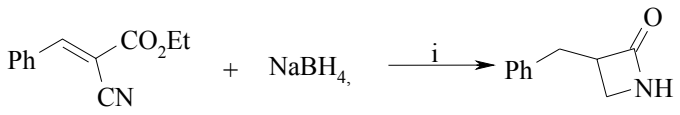
1.0.5.1 Objective

Although several methodologies[28] have been developed for the construction of the β-lactam ring, no report exists on reductive cyclization of α-cyano esters producing β-lactams. Further, the existing methods suffer from the following drawbacks: (i) use of stoichiometric amount of reagents; (ii) difficulties in getting starting materials; (iii) difficulties in generating unstable intermediates (ketene); (iv) lower yields of the product. In order to overcome these difficulties, there is a definite need to develop a convenient method for the construction of the β-lactam ring.

Inspired by the catalytic activity of cobalt-sodium borohydride system,[14] we became interested to subject multi reducible groups such as various α-cyano ethyl cinnamates to reduction. We observed that reduction of C=C, CN groups had occurred simultaneously followed by cyclization to produce azetidin-2-ones (**27a-i**). The results of this methodology are presented in this section.

1.0.6 Results and Discussion

When α-cyano ethyl cinnamate **26a** was treated with $NaBH_4$ (3 equiv) in the presence of catalytic amount of $CoCl_2.6H_2O$ (1 mol%) in DMF:EtOH (1:1) at room temperature, the corresponding reductively cyclized product **27a** (azetidin-2-one) was obtained in 67 % yield. When we increased the amount of $NaBH_4$ to 4 equiv, yield the of desired product (**27a**) was also increased from 67 % to 95 % (**Scheme 9**).

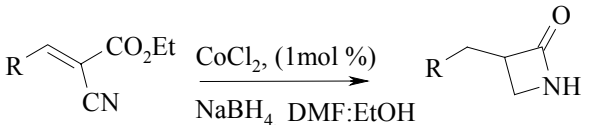


26 a **27 a**

Scheme 9: i $CoCl_2.6H_2O$ (1 mol %), $NaBH_4$ (4 equiv.), DMF:EtOH (1:1), 25^0C, 24h, 95 %.

We then turned our attention to systematically explore the utility of this catalytic system for the synthesis of various 3-substituted azetidin-2-ones **27**. Variety of α-cyano ethyl cinnamates **26(a-i)** were successfully screened to afford the corresponding 3-substituted azetidin-2-ones **27(a-i)** in excellent yields. The results of these reactions are summarized in **Table 1**.

Table 1: $CoCl_2$-catalyzed reductive cyclization of α-cyano-α, β-unsaturated esters with $NaBH_4$[a]



26 (a - i) **27(a - i)**

Entry	R	Yield of (%)[b]
a	C_6H_5	95
b	4-ClC_6H_4	90
c	4-$MeOC_6H_4$	97
d	4-MeC_6H_4	92
e	3-$F_3CC_6H_4$	85
f	3-$O_2NC_6H_4$	80
g	3,4-$(MeO)_2C_6H_3$	96
h	3,4-(-O-CH_2-O-)C_6H_3	99
i	n-C_8H_{17}	70

a = Conditions: Cyano ester (2 mmol), $CoCl_2$ (1 mol %), $NaBH_4$ (8 mmol), DMF:EtOH (1:1), 25 ^{0}C, 24h, 70 - 99%.
b = Isolated yield after chromatographic purification.

As can be seen from **Table 1,** a variety of α-cyano ethyl cinnamates **26a-i** underwent reductive cyclization smoothly with sodium borohydride in the presence of 1 mol % $CoCl_2.6H_2O$ as catalyst in DMF:EtOH (1:1) at room temperature to afford the corresponding 3-substituted azetidin-2-ones **27a-i** in excellent yields and selectivity. Particularly, nitro substituted α-cyano ethyl cinnamate **26f** underwent chemoselective reductive cyclization to afford β-lactam **27f** as the only product without affecting the nitro group.

The formation of 3-substituted azetidin-2-ones **27a-i** was confirmed by spectroscopic techniques such as ^{1}H and ^{13}C-NMR, IR and GC-MS. Thus, the IR spectrum of all 3-substituted azetidin-2-ones **27a-i** showed bands in the region of 1520 – 1610 and 3435-3450 cm^{-1} due to C=O and NH stretching vibrations, typically of cyclic amide functionality in the molecule.

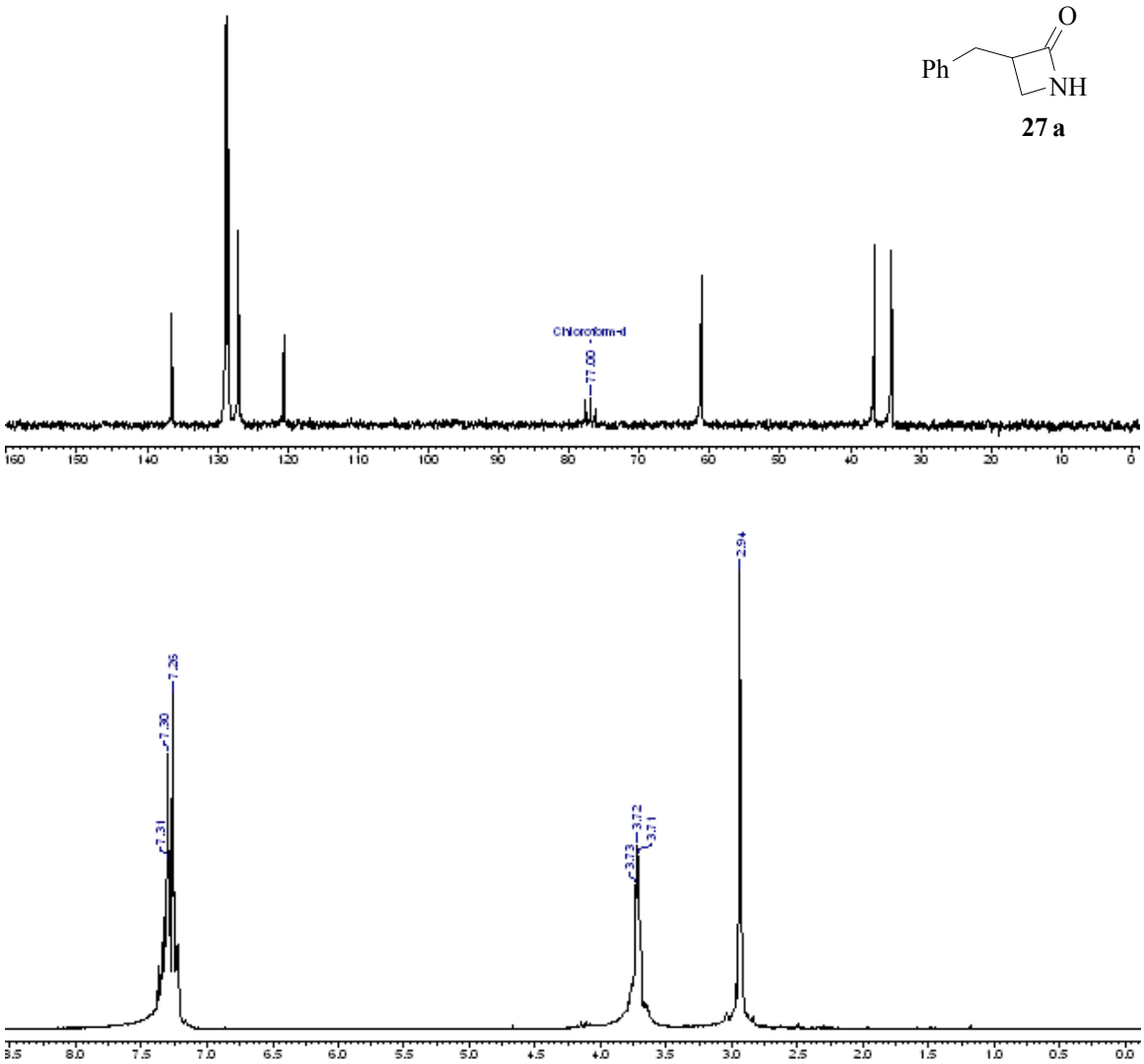


Fig. 2: ^{13}C and ^{1}H -NMR spectrum of 27a

The ^{1}H-NMR spectrum of **27a** showed two multiplets at δ 2.94 and δ 3.71 for 3 protons corresponding to the presence of benzyl group and CH_2 and CH protons of azetidin-2-one ring in the molecule. Its ^{13}C-NMR showed signals at δ 34.14, 36.60 and 61.19 for benzylic carbon, C-4 and C-3 carbons of azetidin-2-one ring respectively. Its IR spectrum also showed a strong absorption band at 3421 cm^{-1} confirming the presence of imide functionality in the molecule. Its mass spectrum showed molecular ion peak at m/z 161 (8%) the formation of azetidin-2-one **27a** (**Fig. 2**).

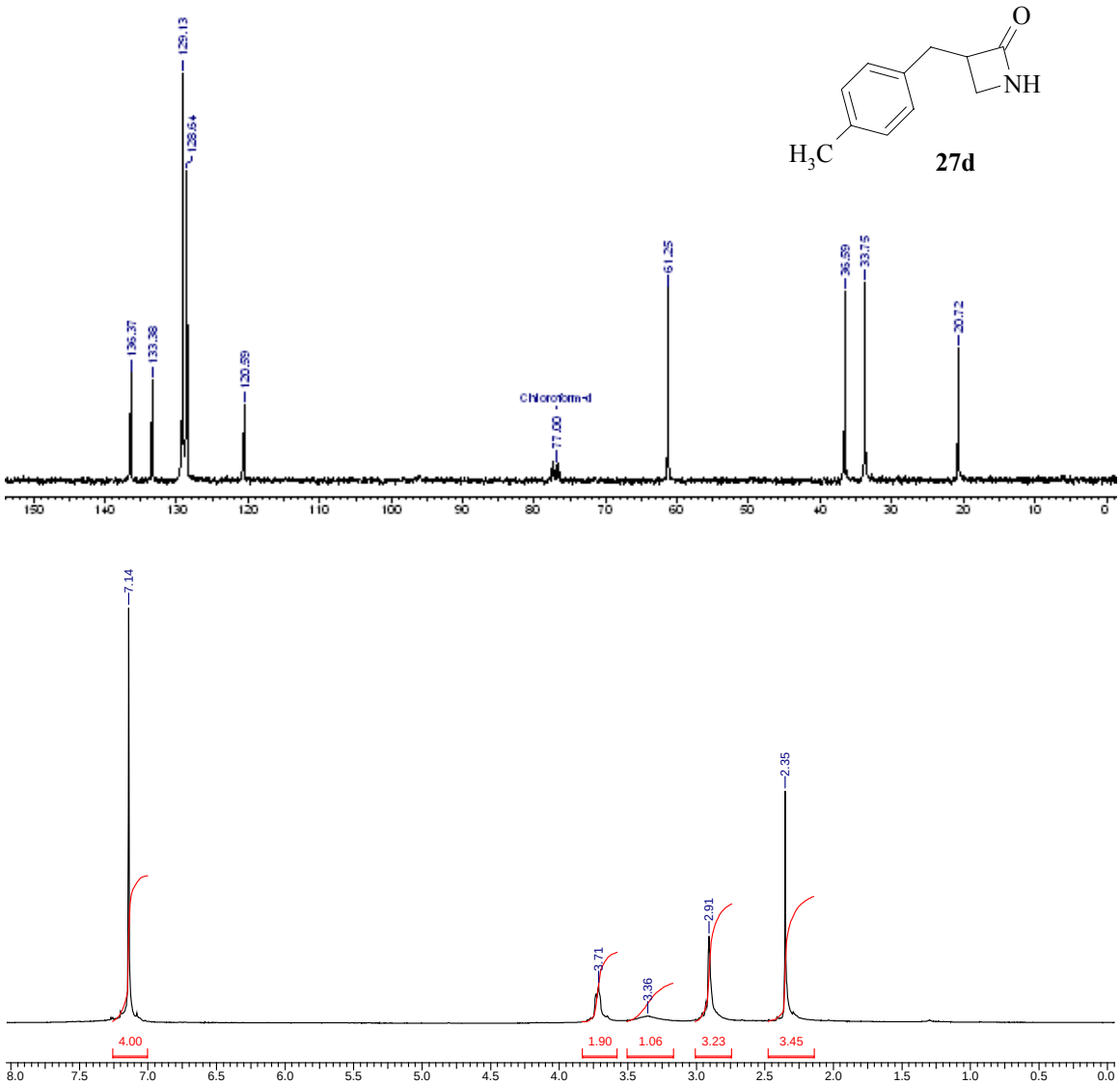
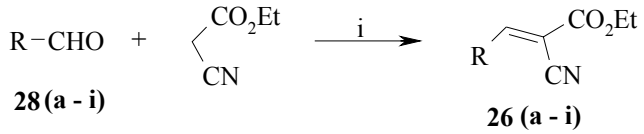


Fig. 3: ^{13}C and ^{1}H -NMR spectrum of 27d

The ^{1}H-NMR spectrum of **27d** showed two singlets at δ 2.35 and 2.91 corresponding to 3 and 2 protons, a multiplet at δ 3.71 for one α proton to the carbonyl and a multiplet at δ 7.14 for phenyl ring confirming the presence of β-lactam moiety and phenyl ring in the molecule. Its ^{13}C-NMR spectrum also showed specific signals at δ 20.72 and 33.75 due to the presence of aromatic methyl and benzylic carbons and at δ 36.59 and 61.25 due to presence of α and β carbons of β-lactam ring respectively. Its IR spectrum exhibited strong absorption bands at 1516, 1625 and 3444 cm^{-1} for amide functionality. Its mass spectrum showed molecular ion peak at m/z 175 (10%) confirming the formation of azetidin-2-one **27d** (**Fig. 3**).

In order to develop asymmetric version of this methodology for synthesis of chiral β-lactams, we employed various chiral oxazolidinones and chiral salen-based ligands, but the asymmetric induction did not take place.

The starting materials, α-cyano ethyl cinnamates **26a-i** were prepared following the literature procedures from the corresponding aldehydes (**Scheme 10**)[29] and the results are presented in **Table 2**.



Scheme 10: i NH_4OAc (10 mol %), toluene, Dean-Stork, reflux, 12h, 69 – 86 %.

Thus, the mixture containing various aldehydes **28a-i** and ethyl cyano acetate in the presence of 10 mol % NH_4OAc in toluene was refluxed using Dean-Stork apparatus for 12 h. The reaction mixture was then poured onto crushed ice to obtain white α-cyano ethyl cinnamates **26a-i** in good to excellent yield. It was further purified by column chromatography and used for subsequent reactions.

Table 2: NH_4OAc-catalyzed Knoevenagel condensation between aldehydes and ethyl cyano acetate[a]

Entry	R	Yield of (%)[b]
a	C_6H_5	84
b	4-ClC_6H_4	80
c	4-$MeOC_6H_4$	86
d	4-MeC_6H_4	75
e	3-$F_3CC_6H_4$	76
f	3-$O_2NC_6H_4$	72
g	3,4-$(MeO)_2C_6H_3$	78
h	3,4-(-O-CH_2-O-)C_6H_3	83
i	n-C_8H_{17}	69

a = Conditions: Aldehydes (4 mmol), ethyl cyano acetate (4.4 mmol), NH_4OAc (10 mol %), toluene, Dean-Stork, 110 ^{0}C, 12h, 69 – 86 %.
b = Isolated yield after chromatographic purification.

1.0.7 Conclusion

In conclusion, we have developed, for the first time, a general method involving simultaneous reductions of C=C and CN functions followed by cyclization of α-cyano ethyl cinnamates in a single step by using $CoCl_2$ as catalyst and $NaBH_4$ as a reducing agent to prepare azetidin-2-ones (**27a-i**) in 70-99% yield. This method provides an efficient and high yield synthesis of 3-substituted β-lactams as compared to other protocols known in the literature.[28]

1.0.8 Experimental Section

Typical experimental procedure for the synthesis of azetidin-2-ones (27a-g)

To 2.01 g (10 mmol) of cyano ester **26a** in a 10 ml RB flask was added a solution of $CoCl_2.6H_2O$ (0.024 g, 0.11 mmol) in 2 ml of ethanol under nitrogen balloon. After dilution with 2 ml of DMF, the clear, dark blue solution was degassed by three freeze-thaw cycles. The solution, which was kept under nitrogen, was then added solid sodium borohydride (1.51g, 40 mmol) resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze-thaw cycles. The evacuated flask containing the yellow, slightly turbid solution was stirred at room temperature. In the beginning, slow H_2-evolution was observed which gradually ceased after 1h. Towards the end of the reaction, solid precipitate and brown-yellow foam began to form. After completion of reaction (as monitored by TLC), the reaction mixture was transferred to a separatory funnel with 50 ml of EtOAc and 50 ml of water, diluted with 25 ml of ice water and extracted with EtOAc. The organic layer was washed three times with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vaccum. Column chromatographic purification (EtOAc/pet. ether 3: 1) afforded 1.53 g (95 %) of azetidin-2-one **27a** as a colorless solid. Recrystallization from $CHCl_3$ provided 1.46 g of azetidin-2-one **27a** (91 %, m.p. 75-78^{0}C).

3-Benzylazetidin-2-one (27a):

Yield: 95%; colorless solid; **mp:** 75-78^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 700.11, 750.26, 1070.42, 1218, 1454, 1496, 1602, 1641, 1718, 1955, 2245, 2887, 2935, 3028, 3064, 3421; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.71 (m, 3H), 7.26 (m, 5H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 34.14, 36.60, 61.19, 120.56, 127.03, 128.53, 128.83, 136.44; **MS** (m/z, % relative intensity): 161 (M^+, 8), 143 (10), 130 (7), 116 (5), 104 (10), 91 (100), 78 (10), 65 (15), 51 (10); **Analysis:** $C_{10}H_{11}NO$ requires C, 74.51; H, 6.88; N, 8.69; found C, 74.50; H, 6.85; N, 8.70%.

3-(4-Chlorobenzyl)azetidin-2-one (27b):

Yield: 90%; colorless solid; **mp:** 118-120^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 757, 1215, 1492, 2400, 3020, 3433; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.98 (s, 3H), 3.78 (m, 3H), 7.47 (d, J = 8.72 Hz, 2H), 7.75 (d, J = 7.12 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 34.15, 36.65, 61.20, 120.16, 122.28, 123.62, 128.16, 128.53, 134.12, 136.04, 140.25; **MS**

(m/z, % relative intensity): 195 (M^+, 10), 177 (3), 164 (3), 138 (5), 125 (100), 112 (5), 101 (5), 89 (15), 75 (10), 63 (10), 51 (8); **Analysis:** $C_{10}H_{10}ClNO$ requires C, 61.39; H, 5.15; N, 7.16; found C, 61.42; H, 5.11; N, 7.21%.

3-(4-Methoxylbenzyl)azetidin-2-one (27c):

Yield: 97%; grey color solid; **mp:** 122-124^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 667, 756, 837, 1033, 1068, 1111, 1180, 1249, 1301, 1442, 1463, 1514, 1612, 1660, 2244, 2837, 2935, 3014, 3448; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.09 (t, *J* = 6.9 Hz, 3H), 2.24 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 5.14 (d, *J* = 3.6 Hz, 1H), 7.22 (m, 5H), 7.73 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **MS** (m/z, % relative intensity): 191 (M^+, 10), 173 (3), 160 (5), 145 (3), 134 (2), 121 (100), 108 (5), 91 (10), 77 (15), 63 (10), 51 (8); **Analysis:** $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found C, 69.10; H, 6.80; N, 7.28%.

3-(4-Methylbenzyl)azetidin-2-one (27d):

Yield: 92%; colorless solid; **mp:** 100-101^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 667, 757, 1070, 1214, 1381, 1446, 1516, 1625, 1903, 2245, 2887, 2927, 3018, 3444; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.91 (s, 3H), 3.35 (s, 2H), 3.71 (m, 1H), 7.14 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.72, 33.75, 36.59, 61.25, 120.59, 128.64, 129.13, 133.38, 136.37; **MS** (m/z, % relative intensity): 175 (M^+, 10), 156 (2), 142 (5), 130 (5), 115 (7), 105 (100), 91 (8), 77 (10), 65 (7), 51 (8); **Analysis:** $C_{11}H_{13}NO$ requires C, 75.40; H, 7.48; N, 7.99; found C, 75.32; H, 7.35; N, 8.00%.

3-(3-(Trifluoromethyl)benzyl)azetidin-2-one (27e):

Yield: 85%; colorless solid; **mp:** 105-108^{0}C (crystallized from $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.00 (s, 3H), 3.54 (brs, 1H), 3.76 (m, 2H), 7.44 – 7.53 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 33.93, 36.47, 61.27, 120.21, 121.18, 124.05, 125.57, 129.21, 131.18, 132.44, 137.41; **MS** (m/z, % relative intensity): 229 (M^+, 2), 211 (15), 202 (5), 191 (3), 179 (2), 159 (100), 151 (5), 119 (5), 109 (10), 91 (5), 75 (6), 63 (5), 40 (8); **Analysis:** $C_{10}H_{10}F_3NO$ requires C, 57.64; H, 4.40; N, 6.11; found C, 57.50; H, 4.45; N, 6.10%.

3-(4-Nitrobenzyl)azetidin-2-one (27f):

Yield: 80%; yellowish solid; **mp:** 182-184^{0}C (crystallized from mixture of EtOH and $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.10 (s, 3H), 3.84 (m, 3H), 7.54 – 7.59 (d, *J* = 8.72 Hz, 2H),

8.13 – 16 (d, *J* = 6.19 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 33.84, 36.29, 61.34, 119.79, 122.43, 123.90, 129.81, 135.41, 138.50, 148.31; **Analysis:** $C_{10}H_{10}N_2O_3$ requires C, 58.25; H, 4.89; N, 13.59; found C, 58.22; H, 4.85; N, 13.60%.

3-(3, 4-Dimethoxylbenzyl)azetidin-2-one (27g):

Yield: 96%; brown color solid; **mp:** 170-171^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 765, 812, 858, 1026, 1072, 1141, 1157, 1238, 1263, 1336, 1421, 1465, 1515, 1591, 1724, 2243, 2837, 2937, 3494; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.11 (s, 3H), 3.48 (brs, 1H), 3.71 (m, 2H), 3.81 (s, 6H), 6.58 – 6.72 (m, 3H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 33.71, 36.38, 56.32, 61.19, 114.70, 115.70, 132.28, 132.60, 138.28, 144.52, 147.18; **MS** (m/z, % relative intensity): 221 (M^+, 10), 203 (3), 190 (2), 176 (3), 152 (10), 151 (100), 135 (5), 116 (5), 107 (10), 91 (7), 77 (10), 65 (10), 40 (15); **Analysis:** $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33; found C, 65.11; H, 6.80; N, 6.35%.

3-((Benzo[*d*][1,3]dioxol-5-yl)methyl)azetidin-2-one (27h):

Yield: 99%; colorless solid; **mp:** 190-192^{0}C (crystallized from $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 771, 813, 864, 927, 1039, 1091, 1193, 1247, 1365, 1444, 1510, 1608, 1728, 1843, 2245, 2781, 2893, 3452; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.97 (s, 3H), 3.44 (brs, 1H), 3.62 (m, 2H), 5.87 (s, 2H), 6.53 – 6.62 (m, 3H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 34.12, 35.32, 61.19, 91.12, 115.30, 115.93, 132.34, 132.84, 138.44, 145.16, 146.85; **MS** (m/z, % relative intensity): 189 (M^+, 10), 135 (100), 105 (5), 89 (3), 77 (15), 63 (5), 51 (20); **Analysis:** $C_{11}H_{11}NO_3$ requires C, 64.38; H, 5.40; N, 6.83; found C, 64.43; H, 5.36; N, 6.70%.

3-Decylazetidin-2-one (27i):

Yield: 70%; colorless solid; **mp:** 50-53^{0}C (crystallized from $CHCl_3$); **mp:** 200-202^{0}C; **IR** (KBr, cm^{-1}): 667, 757, 1047, 1215, 1377, 1465, 1670, 1730, 2200, 2854, 2925, 3018, 3386; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.66 Hz, 3H), 1.27 – 1.57 (m, 16H), 3.88 (m, 2H), 4.49 (m, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **MS** (m/z, % relative intensity): 221 (M^+, 5), 154 (7), 140(7), 127 (10), 110 (12), 97 (20), 83 (10), 69 (9), 54 (50), 41 (100); **Analysis:** $C_{13}H_{25}NO$ requires C, 73.88; H, 11.92; N, 6.63; found C, 73.98; H, 11.95; N, 6.60%.

Typical experimental procedure for the synthesis of α-cyano ethyl cinnamates (26a-i):

To a 25 ml flask with Dean-Stork apparatus attached was charged with aldehydes **28a-i** (20 mmol), ethyl cyano acetate (2.5 g, 22 mmol), catalytic amount of NH_4OAc (0.154 g, 10 mol %) and toluene (15 ml) under nitrogen atmosphere. The flask was allowed to reflux for 12 hours. When water stoped coming out from reaction mixture, it was poured on onto 100 g of crushed ice. Precipitate would form which was filtered through Buckner funnel and dried in vacuum. The crude material, was then purified by column chromatography, eluting the column with 10% ethyl acetate in petroleum ether to get the cyano ester **26a-i** (86-69%).

SECTION II:

Co-catalyzed reductive cyclization of γ-azido-α,β-unsaturated esters: Enantioselective Synthesis of (R)-Baclofen and (R)-Rolipram

1.1.1 Introduction

The γ-butyrolactam (pyrrolidin-2-one or γ-lactam) skeleton exists throughout nature and is present in many bioactive natural products.[30] It also serves as a key intermediate in the synthesis of biologically and pharmaceutically useful molecules such as (R)-baclofen **29**, (R)-rolipram **31**.[31] For example, Ennis and co-workers[32] used a chiral polycyclic lactam **32** to prepare *cis*-fused bicyclic pyrrolidine U-93385, a potent serotonin 1A agonist. Recently, Snider and his team[33] finished the total synthesis of racemic martinellic acid **33**, a novel non-peptide antagonist for the bradykinin (BK) B_1 and B_2 receptor (**Fig. 4**).

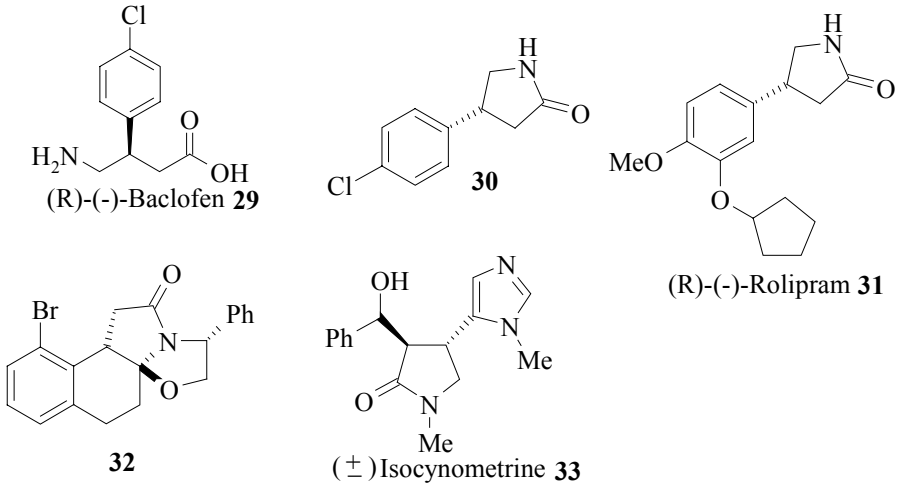


Fig. 4: Some biologically important pyrrolidin-2-ones

Reduction of the pyrrolidinone to amino alcohol, was achieved by careful selection of the reducing agent. Duan and co-workers[34] reported development of a new series of selective TACE inhibitors based on a γ-lactam scaffold. These compounds may have potential use in the treatment of rheumatoid arthritis.

The γ-butyrolactam skeleton **30** can be viewed as the dehydration product of γ-aminobutyric acid (GABA) **29**,[35] one of the most abundant inhibitory neurotransmitters. Several successful pharmaceutical products and drug candidates such as Neurontin, (*R*)-Baclofen **29**, and CI-1008 (Pregabalin) are γ-amino acids.[36] The γ-lactams such as (R)-Rolipram **31** and Rolicyprine are antidepressant agents.[37] Generally, γ-amino acids serve as precursors to γ-lactams,[38] but in some cases γ-lactams can be transformed into the corresponding γ-amino acid.[39] Furthermore, the γ-butyrolactam can be converted to pyrrolidine by reduction.[40]

Pyrrolidines are ubiquitous structural motifs in drugs and potential drug candidates such as antidepressants,[41] antimicrobials,[42] antihypertensives,[43] antiarthritics,[44] antivirals,[45] and antinociceptive agents.[46] Singaram and co-workers recently reported the facile reduction of *N*-alkyl lactams to the corresponding pyrrolidines in excellent yields using lithium aminoborohydrides.[47]

Considering the close relationship among γ-lactams, γ-amino acids, and pyrrolidine and their potential benefit in drug discovery and development, we set out to develop a method for preparing 4-aryl-pyrrolidin-2-ones.

1.1.2 The Pharmacology of (R)-Baclofen and (R)-Rolipram

Bowery *et al.*[48,49] has demonstrated that Baclofen (**29**) helps to decrease the neurotransmitter release in mammalian central nervous system by action at the GABA-

receptor. This effect is associated with the stereospecificity of (*R*)-(–)-baclofen (**29**) isomer being 100-fold more active in producing neural depression than (*S*)-(+)-baclofen isomer. The $GABA_B$ receptors of peripheral and central nervous systems are associated with many biological processes including analgesia, muscle relaxation, hypertension, increased gastric mutility and inhibition of the liberation of corticotropin releasing hormone. There are only few agonist and antagonists available concerning these factors. Baclofen (**29**) is one of them and used in treatment of spasticity, a serious disease characterized by increase muscle tone, usually perceived muscle tightness or achiness in the limbs.[50] These symptoms are normally associated with multiple sclerosis. Although baclofen is commercially available in its racemic form, only the (*R*)-enantiomer (**29**) shows entire medicinal activity.[48,51]

The antidepressant potential of rolipram[52] **31** and inhibitors of phosphodiesterase (PDE) which are selective for cyclic AMP[53] has been known to enhancement of central noradrenergic transmission by the combination of two mechanisms of action: increase of synthesis of noradrenaline and release (presynaptic component) and concomitant potentiation of noradrenaline signals due to inhibition of phosphodiesterase (postsynaptic component).[54] The antihypothermic and antihypokinetic action of rolipram was not prevented by blockade of central β-adrenergic or dopaminergic receptors.[55] It is concluded that an action of Rolipram **31**, beyond postsynaptic receptors, essentially contributes to its antidepressant effect. The postsynaptic adenylate cyclase/cyclic AMP phosphodiesterase system is thought to be the most likely target. The unique properties of rolipram to stimulate both presynaptic and postsynaptic components of central neurotransmission should enable more efficient transduction of postsynaptic signals by circumventing presynaptic inhibitory feedback

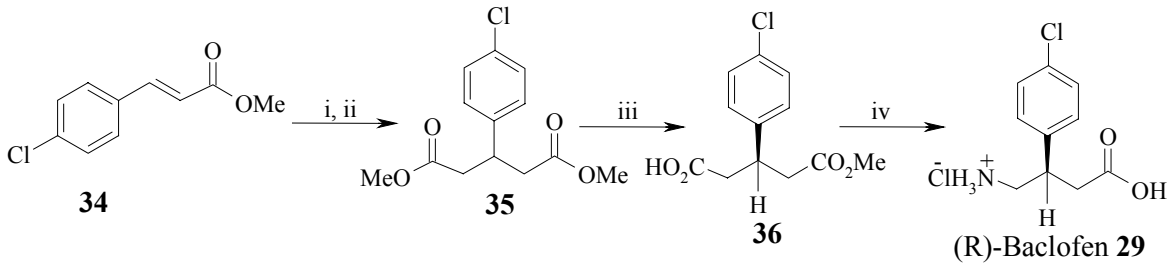
mechanisms, responsible for the delay in the therapeutic action of conventional antidepressant drugs.[56]

1.1.3 Review of Literature

Literature search revealed that there are several reports available on the synthesis of (*R*)-(–)-baclofen (**29**) and (R)-(-)-rolipram (**31**).[57-77] They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis, which are described below.

Chenevert's approach (1991)[57]

Chenevert *et al.* have achieved the synthesis of both (*R*)- and (*S*)-baclofen by enantioselective hydrolysis of intermediate **35** using *Chymotrypsin* enzyme (**Scheme 11**). Michael addition of dimethyl malonate with **34** followed by demethoxycarbonylation afforded the key intermediate **35**. It was then subjected to enantioselective hydrolysis with *Chymotrypsin* enzyme to afford chiral monoester **36** in 98% ee and 85% yield. The chiral monoester **36** upon Curtius rearrangement followed by acid hydrolysis gave (*R*)-(–)-baclofen (**29**).

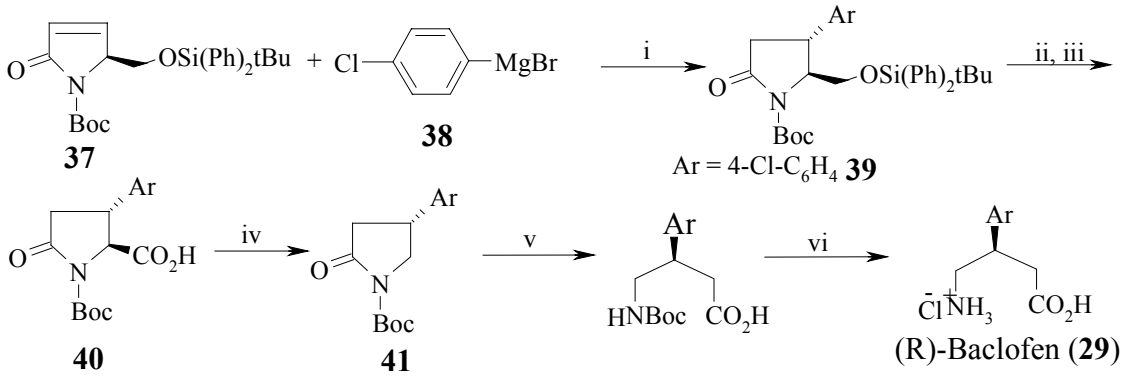


34 **35** **36** (R)-Baclofen **29**

Scheme 11: (i) Dimethyl malonate, CH_3ONa, THF, reflux; (ii) NaCl, H_2O, DMSO, 160°C; (iii) *α-Chymotrypsin*, phosphate buffer, pH 7.7, 25°C; (iv) a: Ethyl chloroformate, Et_3N, acetone, 0°C; b: NaN_3, H_2O, acetone; c: toluene, reflux; d: HCl, H_2O.

Hubmann's approach (1992)[58]

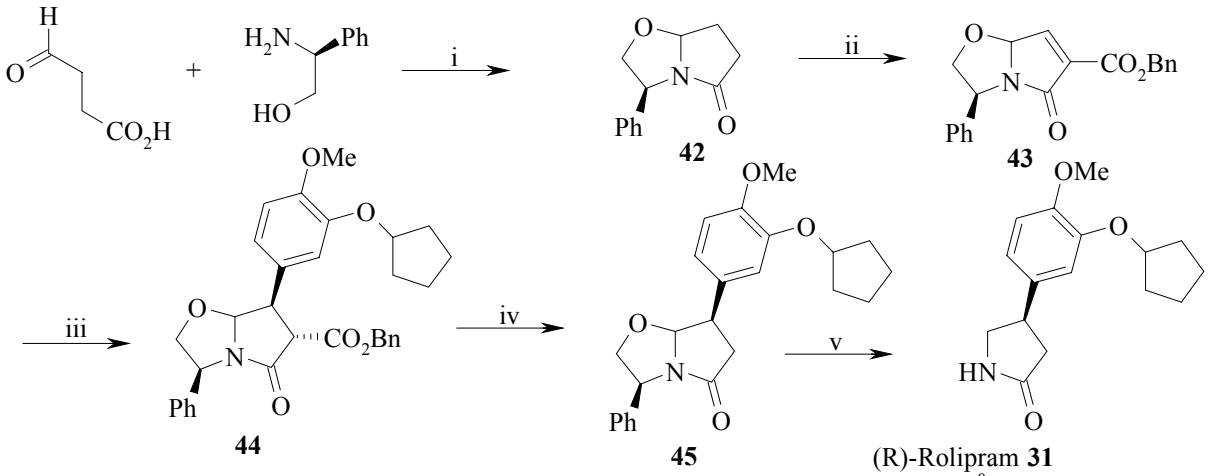
Hubmann's strategy to synthesize (*R*)-baclofen (**29**) involved stereoselective Michael addition of (*S*)-pyroglutamic acid derivative **37** with Grignard reagent **38** (**Scheme 12**).



Scheme 12: (i) $CuBr.SMe_2$, Et_2O, -35°C, 20 min; -78°C, TMS-Cl, NH_4Cl; (ii) Et_3NHF, THF, RT, 4-5 days; (iii) $RuCl_3$, $NaIO_4$, CH_3CN:CCl_4 (2:1), H_2O; (iv) N-methylmorpholine, isobutyl chloroformate, –15°C, N-hydroxy-2-thiopyridone, Et_3N, THF, 2 h; (v) aq. 1M LiOH, 1.5 h, (vi) 6M HCl, reflux, 3 h.

Meyers's approach (1993)[59]

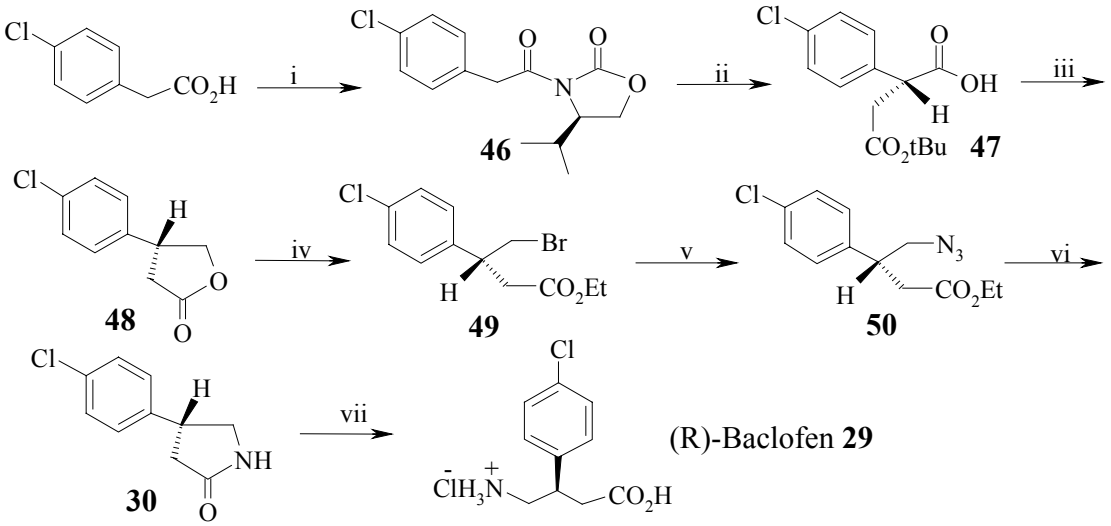
Bicyclic lactam generated from aminoalcohol is a chiral precursor for pyrrolidin-2-one synthesis. Enone **43** was subjected for conjugate addition of cuprates inducing chirality at C4 position **44**. After removal of chiral auxiliary and ester group generates required rolipram **31** in 60 % ee and 73 % yield (**Scheme 13**).



Scheme 13: i *p*-TSA, toluene, reflux, 3h, 70 %.; ii (a) LDA, $ClCO_2Bn$, THF, -78 °C; (b) LDA, PhSeBr, THF, H_2O_2, rt, 60 %.; iii 3-(cyclopentyloxy)-4-OMe-C_6H_3-CuCNLi, THF, -78 °C, 1h, 84 %.; iv 5 % Pd/C (2 mol %), H_2 (1 atm), MeOH, reflux, 98 % ee, 73 %.; v (a) Ca-NH_3, THF, -78 °C, 4h, 84 %.; (b) $NaCNBH_3$, MeOH, rt, 3h, 60 % ee, 73 %.

Schoenfelder's approach (1993)[60]

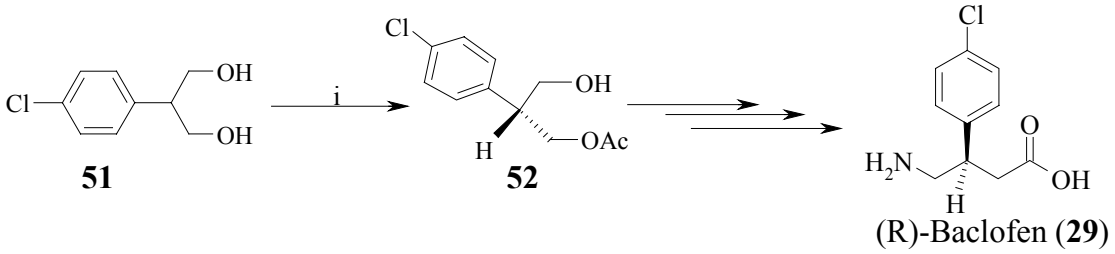
This strategy makes use of enantioselective alkylation of chiral 2-(4-chlorophenyl) acetyl oxozolidone (**46**). The oxozolidone **46** was prepared from 2-(4-chlorophenyl)acetic acid. It was then converted to chiral *t*-butyl-2-(4-chlorophenyl)succinate **47** in two steps. Chemoselective reduction of the acid functionality of **47** followed by dehydration gave *γ*-butyrolactone **48**. The lactone **48** was then converted to azidoester **50**, which on reduction followed by cyclization gave lactam **30**. Lactam **30** was then hydrolyzed with HCl to afford (*R*)-baclofen (**29**) hydrochloride salt (**Scheme 14**).



Scheme 14: (i) a) $ClCO^tBu$, Et_3N; b) Li-oxazolidine, THF, -78°C; (ii) a) NaHMDS, $BrCH_2CO_2{}^tBu$, -78°C; b) H_2O_2-LiOH; (iii) a) BH_3.DMS; b) *p*-TSA, toluene, reflux; (iv) EtOH, HBr; (v) NaN_3, DMSO; (vi) a) PPh_3, H_2O; b) DMAP, toluene, reflux; (vii) 6N HCl, reflux.

Desjardins's approach (1994)[61]

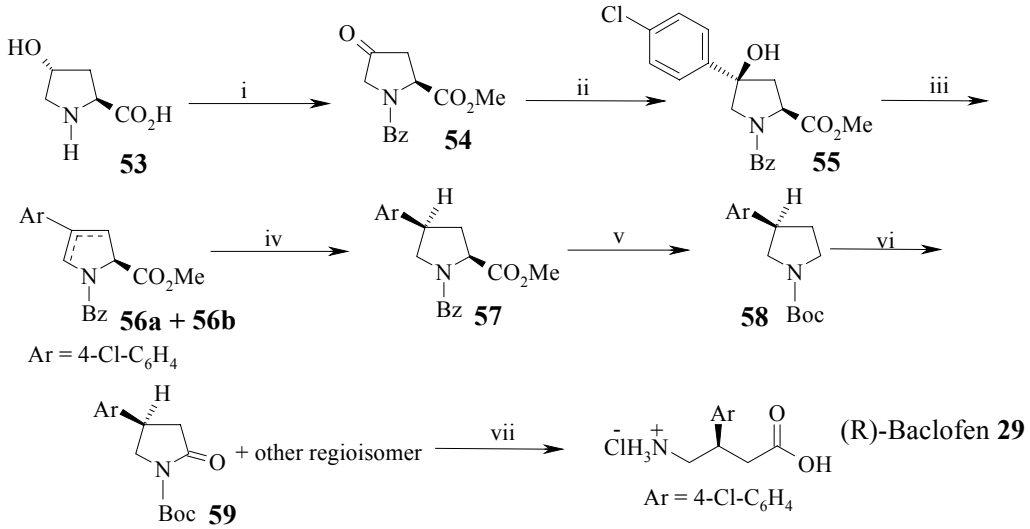
In this approach *lipase* was used to carry out the desymmetrization of 2-(4-chlorophenyl)-1,3-propane diol (**51**) to give optically active mono acetate **52** as a key intermediate. The mono acetate **52** was further converted to (*R*)-baclofen (**Scheme 15**).



Scheme 15: i *lipase*, Ac_2O.

Yashifuji's approach (1995)[62]

This approach consists of chiral *trans*-4-hydroxy-L-proline (**53**) as a chiral precursor for the synthesis of both (*R*)- and (*S*)- baclofen (**Scheme 16**). The strategy is based on the following two key steps (i) a stereoselective hydrogenation of dehydroproline derivatives **56a** and **56b**, controlled by C_2-carboxyl functionality (ii) an effective Ru-catalyzed oxidation of pyrrole **58** to pyrrolidone **59**.

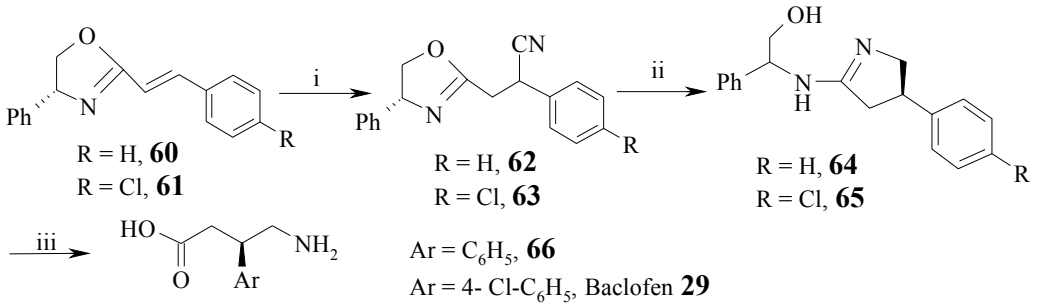


Scheme 16: (i) a) MeOH; b) benzoyl chloride, Et_3N; $COCl_2$, DMSO, Et_3N, -78°C, 92%; (ii) 4-Cl-Ph-Br, Mg, $CeCl_3$, Et_2O, RT, 78%; (iii) $SOCl_2$, pyridine, RT, 79%; (iv) Pt, H_2 (1 atm), RT, 6N HCl AcOH, 110°C; (v) a) cyclohexanol, 2-cyclohexen-1-one, 155°C; b) *tert*. Butoxylchloride; (vi) RuO_2, aq. $NaIO_4$, AcOEt : H_2O, RT, 3 h; (vii) 6N HCl, reflux, 18 h.

Langlois's approach (1997)[63]

Using this method, both (*R*)-4-amino-3-phenylbutyric acid (**66**) and (*R*)-baclofen (**29**) have been synthesized in 50% ee. The chiral precursors, α,β-unsaturated oxazolines **60** and

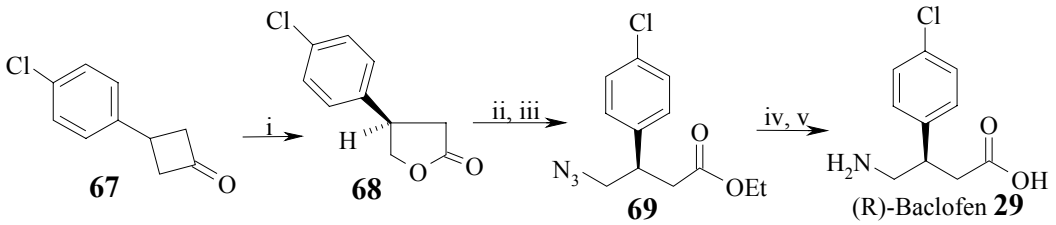
61, were derived from the reaction of (*R*)-phenylglycinol with the corresponding cinnamic acids and these were subjected to hydrocyanation reaction to afford cyanooxazolines **62** and **63**. Subsequently, these were reduced to imides **64** and **65** respectively. Finally, imides **64** and **65** were hydrolyzed to give (*R*)-(**66**) and (*R*)-baclofen (**29**) respectively (**Scheme 17**).



Scheme 17: (i) $AlEt_2CN$, DCM, -30°C, RT, 48 h, 30-40%, 50% de; (ii) $NaBH_4$, $NiCl_2$, THF:H_2O (2:1); (iii) 2N NaOH:EtOH, 100°C, 14 h, 97%.

Mazzini's approach (1997)[64]

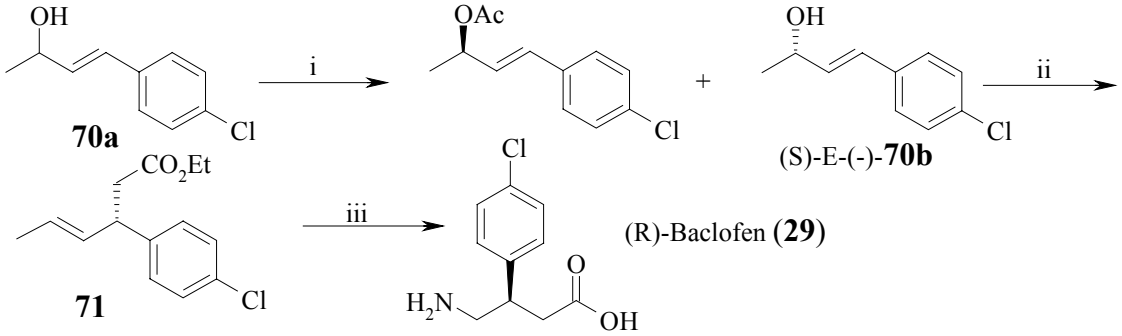
Mazzini *et al.*[16] have synthesized (*R*)-baclofen *via* chemoenzymatic Baeyer-Villiger oxidation as a key step (**Scheme 18**). 3-(4-Chlorophenyl)cyclobutanone (**67**) was subjected to enantioselective Baeyer-Villiger oxidation in presence of *Cunninghamell echinulata* (NRLL 3655) enzyme to obtain (*3R*)-chlorophenyl-γ-butyrolactone **68** in 30% yield and >99% ee which was further converted to azidoester **69**. Subsequently, hydrolysis with NaOH and Pd-catalyzed hydrogenation afforded (*R*)-baclofen (**29**).



Scheme 18: (i) culture *C. echinulata*; (ii) Me_3SiI, EtOH, DCM, 0°C to RT, 95%; (iii) NaN_3, DMF, 75°C, 95%;(iv) 2M NaOH, conc. HCl, RT, 95%; (v) Pd-C, H_2, Et_2O/EtOH, RT.

Brenna's approach (1997)[65]

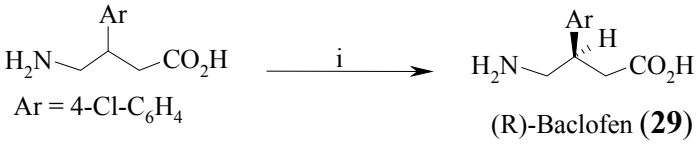
This approach involves enzymatic resolution of substituted allyl alcohol **70a** in presence of *Porcine pancreas lipase* (PPL, Sigma type II) to yield optically active allylic alcohol **70b** in >99% ee as key step (**Scheme 19**). Subsequently, it was transformed to ester **71** *via* Claisen orthoester rearrangement, which on ozonolysis followed by reductive amination afforded (*R*)-baclofen (**29**).



Scheme 19: (i) *PPL*, *t*-butylmethyl ether, vinyl acetate; (ii) $CH_3C(OEt)_3$, propanoic acid, 120-130°C; (iii) O_3, CH_2Cl_2:MeOH (1:1), NH_4OAc, $NaBH_3CN$, -78°C, 12 h, 2N NaOH, HCl, RT, 2 h.

Levadoux's approach (1998)[66]

Levadoux *et al.*[66] have developed a process for obtaining optically active baclofen and its analogues by *Streptomyces micro organism*-mediated resolution (**Scheme 20**).

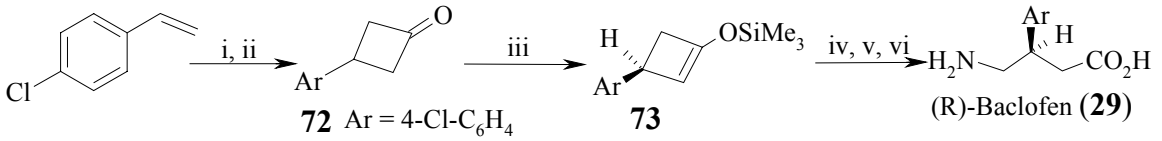


Scheme 20: (i) *Streptomyces micro organism.*

Resende's approach (1999)[67]

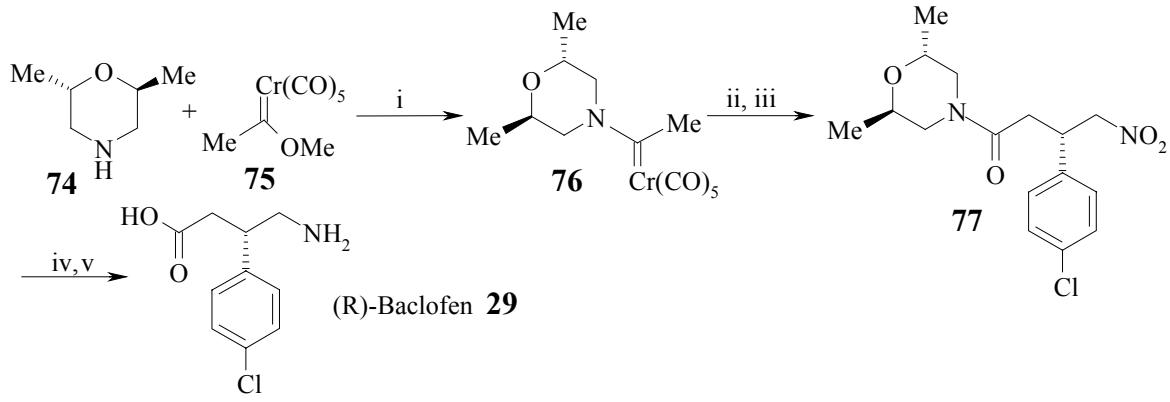
Resende's approach involves enantioselective deprotonation of **72** with lithium (*S, S'*)-α,α'-dimethylbenzylamide followed by silylation affording the chiral silylenol ether **73** in

70% yield and 98% ee. Finally, it was transformed to (*R*)-baclofen (**29**) in three steps (**Scheme 21**).



Scheme 21: (i) Zn-Cu, $POCl_3$, CCl_3COCl, Et_2O, RT, 12 h, 91%; (ii) Zn/AcOH, RT, 14 h, 93%; (iii) Lithium (S,S')-α,α'-dimethylbenzylamide, THF, TMSCl, -100°C, 15 min 70%; (iv) O_3, DCM, -78°C, 40 min; (v) Me_2S, –78°C to RT, 12 h; (vi) $NaBH_3CN$, NH_4OAc, 12 h, 6N HCl (one pot sequence)

Licandro's approach (2000)

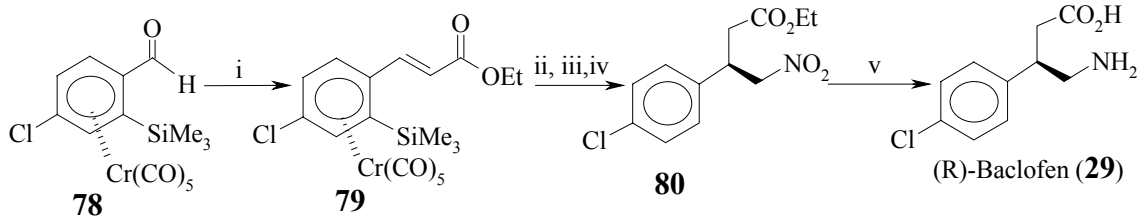


Scheme 22: (i) aminolysis (ii) *n*-BuLi, THF, -97°C, *p*-Cl-PhCH=$CHNO_2$; (iii) CAN, acetone, RT, 4 h; (iv) Raney-Ni, dry-MeOH, 5 atm, 1 h; (v) 6M HCl, reflux, 8 h.

Licandro *et al.*[68] have achieved the synthesis of (*R*)-baclofen (**29**) using diastereoselective Michael addition of enantiopure Cr-carbene complex **76** to *p*-chloronitrostyrene to give **77** (**Scheme 22**). The optically active chromium-carbene complex **76** was obtained by condensation of (*S,S*)-2,6-dimethylmorpholine (**74**) with pentacarbonyl(methoxymethylcarbene)chromium (**75**). The nitro group in **77** was then reduced with Raney-Ni and finally hydrolyzed with 6M HCl to afford (*R*)-baclofen (**1a**).

Baldoli's approach (2000)[69]

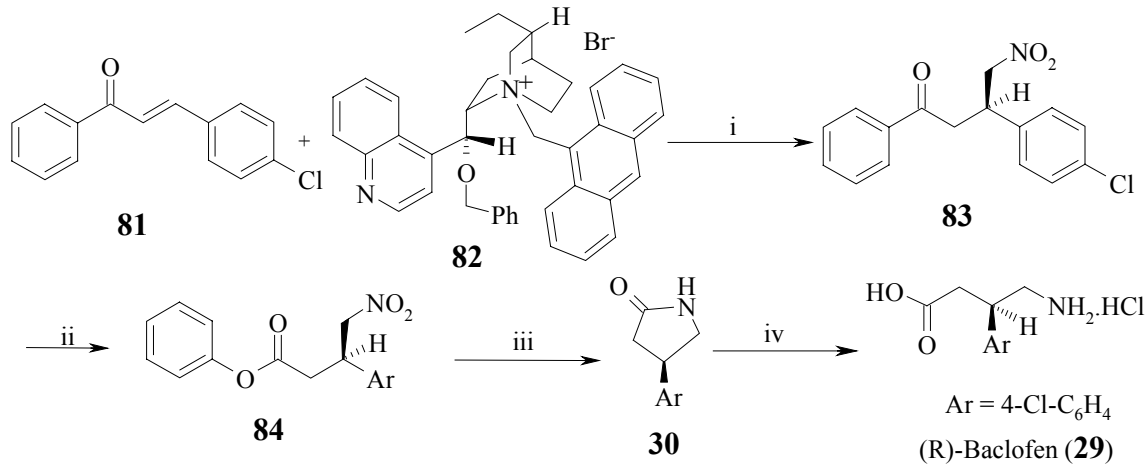
This approach involves stereoselective Michael addition of nitromethane to chiral chromium (0) complex **79** as a key step. The chiral aldehyde **78** was obtained by resolution of its diastereoisomeric-semioxamazone derivative. Aldehyde **78** was subjected to Wittig-Horner reaction to obtain ester **79** (**Scheme 23**). The Michael addition of nitromethane onto ester **79** followed by desilylation and de-complexation yielded nitroester **80**. Finally, hydrogenation of nitroester **80** followed by hydrolysis afforded (*R*)-baclofen (**29**).



Scheme 23: (i) $(EtO)_2OPCH_2CO_2Et$, $(Me_3Si)_2NLi$, THF, RT; (ii) CH_3NO_2, K_2CO_3, TEBA, RT; (iii) Bu_4NF, CH_2Cl_2, RT; (iv) hν, air, CH_2Cl_2; (v) a. PtO_2, H_2, MeOH, RT; b. 6N HCl reflux.

Corey's approach (2000)[70]

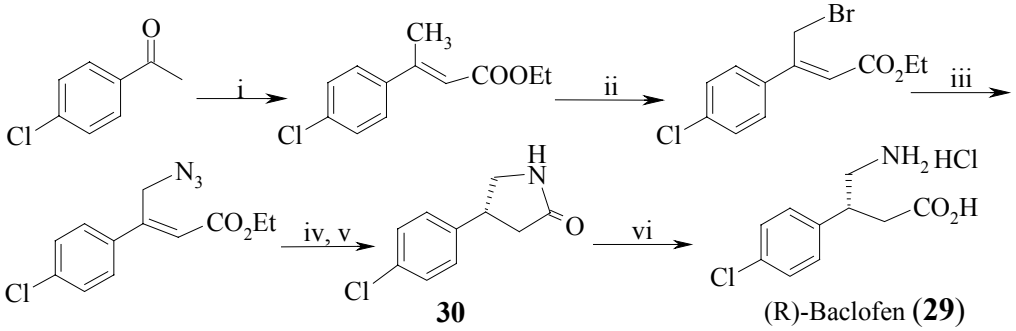
In this approach chiral quaternary ammonium salt **82** was used as a chiral catalyst for the enantioselective Michael addition of nitromethane to α,β-enone **81** to afford nitroketone **83**. Nitroketone **83** was converted to nitroester **84** followed by reduction of nitro group in **84** to give lactam **30**, which was hydrolyzed to afford (*R*)-baclofen (**29**) as a hydrochloride salt (**Scheme 24**).



Scheme 24: (i) CH_3NO_2, CsF, toluene, –40°C, 36 h; (ii) *m*-CPBA, EDC, reflux, 36 h; (iii) $NaBH_4$, $NiCl_2$, MeOH, 23°C, 10 min; (iv) 5N HCl, reflux, 4 h.

Sudalai's Approach (2002)[71]

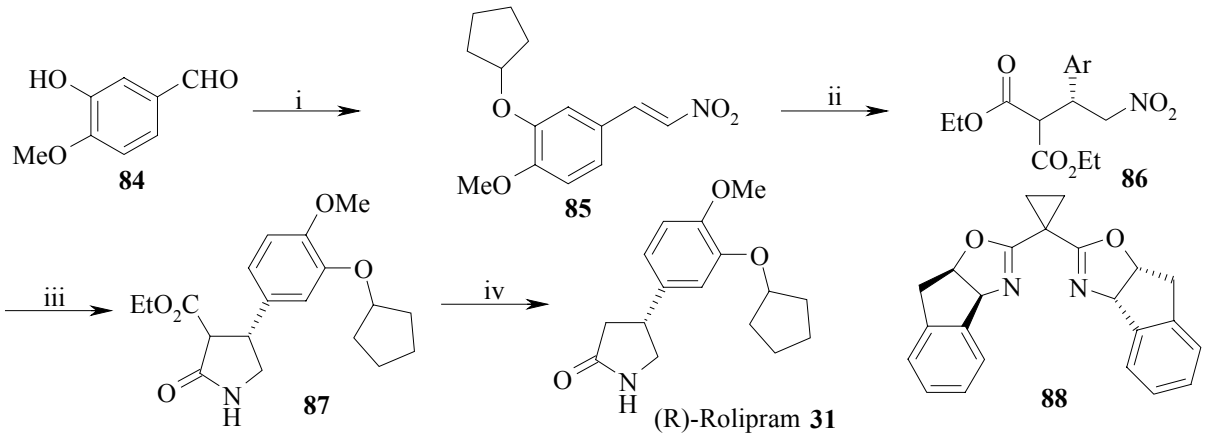
Our group has developed a simple method for the enantioselective synthesis of (*R*)-baclofen (**29**) using asymmetric reduction of azido ester using Ru (II)- (*S*)-BINAP complex to give lactam **30** which on hydrolysis gave (*R*)-baclofen (**Scheme 25**).



Scheme 25: i) Br-CH_2CO_2Et, Zn, benzene, reflux, *p*-TSA, toluene, 120°C, 78%; ii) NBS, AIBN, CCl_4, reflux, 10 h, 92%; ii) NaN_3, EtOH:H_2O (80:20), 80°C, 8 h, 78%; iv) Ru (II)-(S) BINAP, H_2 (200 *psi*), MeOH, 50°C, 20 h, 68%; v) $CoCl_2$, $NaBH_4$, H_2O, 25°C, 30 min, 80%; vi) 20% HCl, 100°C, 3 h, 76%.

Barnes's approach (2002)[72]

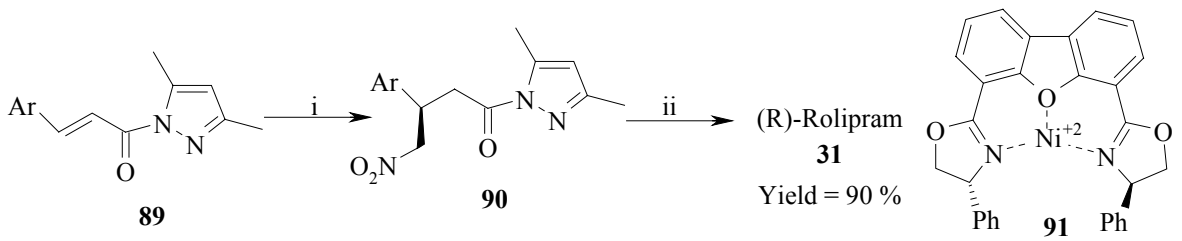
In Barnes's approach enantioselective synthesis of rolipram **31** has been accomplished via a highly selective catalytic asymmetric conjugate addition of ketoesters to nitroolefins **85**. Employing 4 mol % bis(oxazoline)-$Mg(OTf)_2$ **88** complex with an amine cocatalyst, producing nitroester **86** 94% yield with 97% ee. Hydrogenation of nitroester **86** with 1 equiv of Raney-Ni in the presence of 10 mol % H_3PO_4 in THF at 50-60 ^{0}C under H_2 (40 psi) gave lactam **87**. Without purification, lactam **87** was saponified with NaOH in EtOH/THF (1/1), then decarboxylated using TsOH in refluxing i-PrOAc producing (R)-Rolipram **31** in 92% yield (**Scheme 26**).



Scheme 26: i (a) Cyclopentyl bromide, K_2CO_3, DMF, RT, 97 %; (b) $MeNO_2$, NH_4OAc, MeOH, reflux, 90 %; ii $Mg(OTf)_2$ (5 mol %), **88** (5.5 mol %), NMM (6 mol %), 40 MS, RT, 3h, 97 % ee, 95 %; iii Raney-Ni, H_3PO_4, H_2 (40 psi), THF, 60 ^{0}C, 92 %; iv (a) NaOH, EtOH:THF (1:1), RT; (b) TsOH, *i*PrOAc, reflux, 90 %.

Kanemasa's approach (2002)[73]

Using chiral nickel based catalyst **91** for asymmetric Michael addition of nitromethane onto enone **89** provided (R)-rolipram in 89 % ee. The desired starting substrate was synthesized by Wittig-Horner olefination of the substituted benzaldehyde, followed by transformation to the pyrazole amide in two steps. Michael product was converted to rolipram **31** after its reductive cyclization (**Scheme 27**).

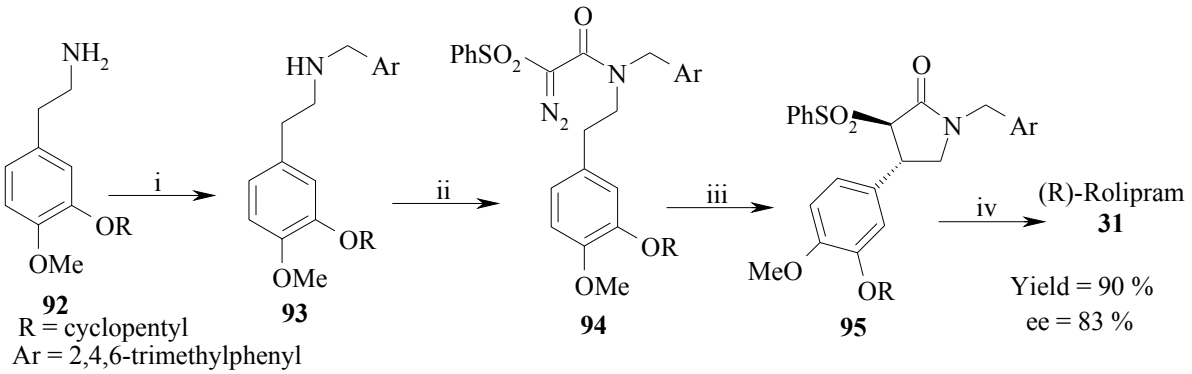


Ar = 3-(*c*-C_5H_9O)-4-$MeOC_6H_3$

Scheme 27: i *R,R*-DBFOX/Ph (**91**) - $Ni(ClO_4)_2$,$6H_2O$ (10/10 mol %), TMP (10 mol %), $MeNO_2$/THF (1:1 v/v, 0.1 M), -20 °C, 168 h, 91%. ii (a) H_2 Raney Ni, EtOH/CH_2Cl_2 (3:2 v/v (0.06 M), 1 atm, RT, 96 h.; (b) $(Boc)_2O$ (2 equiv.), DMAP (2 equiv.), Et_3N (1 equiv), RT, 12 h, 90 %.

Jung's approach (2003)[74]

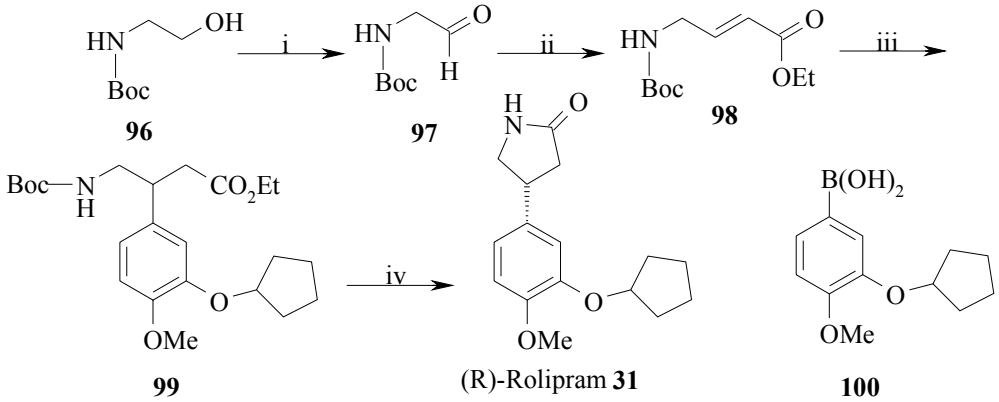
Jung's approach involves intramolecular C-H insertion of α-diazo-α-(phenylsulfonyl)acetamides, producing rolipram. The insertion precursor **94**, was obtained from compound **93**, which in turn was derived from isovaniline. Thus reductive benzylation of **92** with 2,4,6-trimethylbenzaldehyde afforded secondary amine **93**. N-Acylation of **93** with bromoacetyl bromide followed by the treatment with sodium benzenesulfinate provided the R-phenylsulfonylacetamide. Diazo transfer using *p*-ABSA and DBU yielded diazo compound **94**, which underwent C-H insertion with $Rh_2(OAc)_4$ in dichloroethane to give γ-lactam **95** as a single isomer. The phenylsulfonyl and *N*-benzyl groups of **95** were cleaved simultaneously with Li/NH_3 to afford rolipram (**31**) in 83 % ee and 90 % yield (**Scheme 28**).



Scheme 28: i (a) ArCHO, $ClCH_2CH_2Cl$, $MgSO_4$; (b) $NaBH_4$, MeOH, 75 % (for two steps); ii (a) $BrCH_2COBr$, Et_3N, CH_2Cl_2; (b) $PhSO_2Na$, DMF, 70 % (for two steps); (c) *p*-ABSA, DBU, CH_3CN, 70 %; iii $Rh_2(OAc)_4$, $ClCH_2CH_2Cl$, 80 ^{0}C, 75 %; iv Li, NH_3, -78 ^{0}C, 83 % ee, 90 %.

Helmchen's approach (2003)[75]

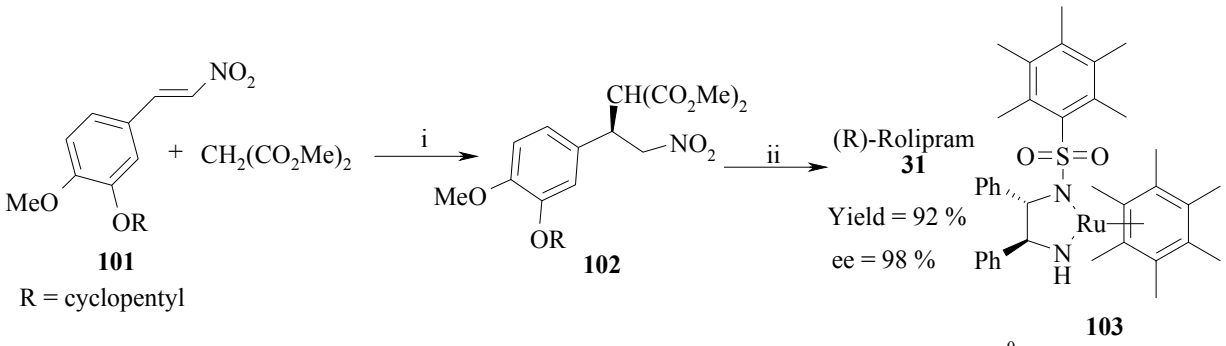
The substrates (*E*)-**98** was prepared from 2-aminoethanol **96** by oxidation followed by Horner–Wadsworth–Emmons (HWE) olefination. The 1,4-addition of aryl boronic acid **100** in the presence of 3 mol% of $[Rh(acac)(C_2H_4)_2]$ and 4.5 mol% of (*R*)-BINAP and Na_2CO_3 at 100 °C for 48 hours followed by Boc deprotection affords (R)-rolipram **31** (**Scheme 29**).



Scheme 29: i IBX, DME, 80 ^{0}C, 1h.; ii $(EtO)_2P(O)CHC(OLi)OEt$, THF, -78 ^{0}C, 1h, 57 %.; iii **100** (2 equiv.), $[Rh(acac)(C_2H_4)_2]$ (3 mol %), (R)-BINAP (4.5 mol %), Cs_2CO_3, dioxane:H_2O (10:1), 100 ^{0}C, 84 % ee, 73 %.; iv TFA:CH_2Cl_2 (1:1), Et_3N, toluene, reflux, 6h, 90 % ee, 78 %.

Ikaria's approach (2004)[76]

Ikaria's approach utilizes asymmetric Michael addition of dimethyl malonate onto nitrostyrene **101** using chiral Ruthenium catalyst **103** for the enantioselective synthesis of rolipram **31**. Further Michael product **102** was smoothly converted to (R)-Rolipram by decarboxylation and reductive cyclization in 94 % yield with 95 % ee (**Scheme 30**).

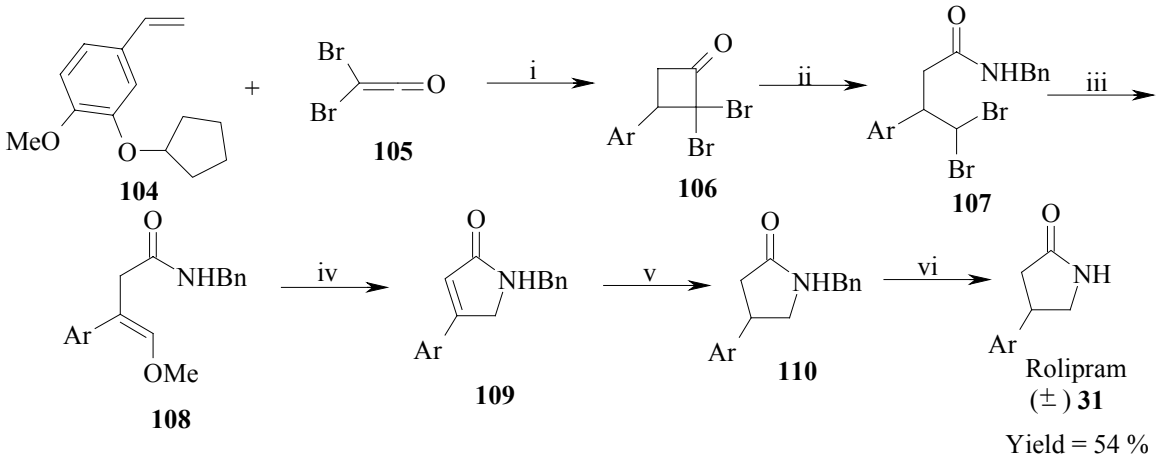


Scheme 30: i **101** (1 equiv.), $CH_2(CO_2Me)_2$ (1.2 equiv.), **103** (1mol %), toluene, -20 ^{0}C, 48h, 95 % ee, 98 %.; ii (a) Raney-Ni, H_3PO_4, H_2 (40 psi), THF, 60 ^{0}C, 90 %; (b) NaOH, EtOH:THF (1:1), RT; (c) TsOH, *i*PrOAc, reflux, 98 % ee, 92 %.

Kimpe's approach (2004)[77]

Kimpe's approach utilizes cyclobutanones **106** for the synthesis of 4-aryl-3-pyrrolin-2-ones from 3-aryl-2,2-dihalocyclobutanones **106** via an amine-induced ring opening of the

cyclobutanone ring and subsequent ring closure. Further C=C reduction and debenzylation leads to racemic 4-aryl-3-pyrrolin- 2-ones such as **31** (**Scheme 31**).



Scheme 31: i $CHBr_2COCl$, Et_3N, CH_2Cl_2, 0 – 25 ^{0}C, 50 %.; ii $BnNH_2$ (2 equiv.), Et_2O, 0 – 25 ^{0}C, 8h, 70 %.; iii aq. 2 M HCl, reflux, 69 %.; iv 5 % Pd-C (10 mol %), H_2 (4 bar), EtOH, 50 ^{0}C, 20h, 54 %.

1.1.4 Present Work

1.1.4.1 Objective

Although racemic baclofen and rolipram are commercially available in bulk quantities, their entire biological activity is associated only with the (*R*)-enantiomer. Various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed to synthesize 4-substituted-pyrrolidin-2-ones such as (*R*)-baclofen (1a) and (R)-rolipram (2) (*vide supra*).[57-77] However, these methods suffer from disadvantages such as low overall yields, the need for separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of 4-substituted-pyrrolidin-2-ones such as (*R*)-baclofen (1a) and (R)-rolipram (2) is highly desirable.

Retrosynthetic analysis (**Fig. 5**) of (*R*)-4-substituted pyrrolidin-2-ones (**111**), reveals that α, β-unsaturated ester **113** can be visualized as a key intermediate. Thus, Reformatsky

reaction of ketones **114**, with ethyl bromoacetate followed by dehydration of alcohols with *p*-TSA is expected to produce **113** (**Route 1**). Alternately, the synthesis of the intermediate, i.e. the aryl substituted α, β-unsaturated ester **113,** can be achieved by arylation of Pd-catalyzed C-C bond formation between aryl boronic acids **115** and ethyl crotonate. (**Route 2**).

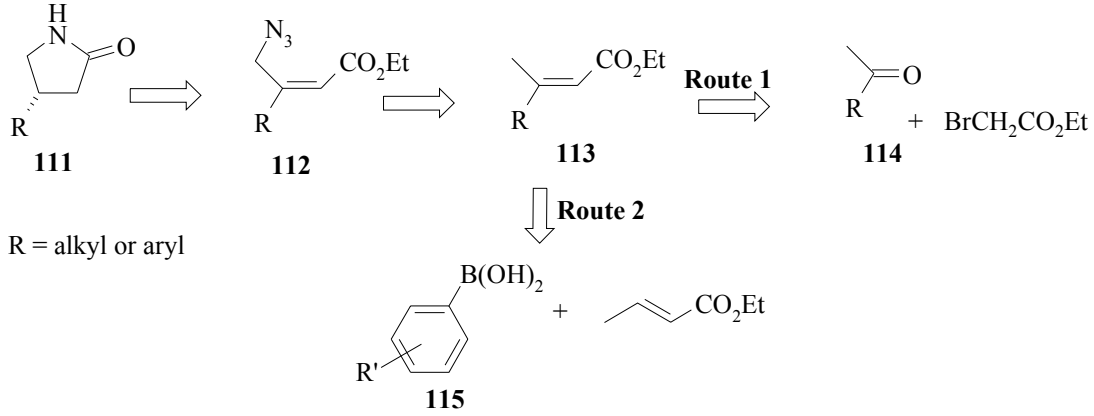


Fig. 5: Retrosynthetic analysis of 4-aryl-pyrrolidin-2-ones

Thus, the key intermediate **112** was successfully synthesized by the allylic bromination of olefin **113** followed by exchange of bromide with azide. This chapter describes the asymmetric synthesis of 4-substituted pyrrolidin-2-ones such as (*R*)-baclofen (**29**) and (R)-rolipram (**31**) from intermediate **112** by employing asymmetric hydrogenation method (AH) (**Table 4**).

Since this chapter deals with an important asymmetric reaction i.e. asymmetric hydrogenation (AH), which introduces stereogenicity into the prochiral molecule, a brief account of same is presented in the following sections.

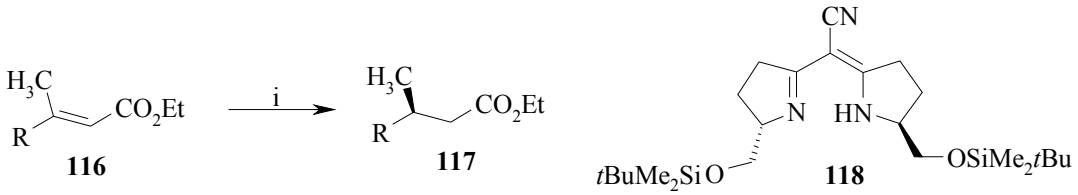
1.1.4.2 Asymmetric Hydrogenation

In recent years much attention has been focused on the catalytic asymmetric synthesis. There are several methods to obtain enantiomerically pure compounds that include classical optical resolution, chromatographic separation of enantiomer, enzymatic resolution and

asymmetric synthesis.[78] It often has significant economic advantages over stoichiometric asymmetric synthesis for industrial-scale production of enantiomerically pure compounds.

Among all these reactions, catalytic asymmetric reduction (AH) of C=C bond is one of the most important practical and widely used reaction in organic synthesis. It has become the most general method for the preparation of optically active saturated hydrocarbons from activated as well as inactivated olefins.[79] As a consequence the asymmetric hydrogenation of functionalized as well as unfunctionalized olefins catalyzed by chiral transition metal complexes has attracted much interest. In our previous section of this chapter, we have discussed about $CoCl_2.6H_2O$ in combination with $NaBH_4$, as an effective reducing system, capable of selectively reducing variety of functional groups.

Recently Pfaltz's *et al.* reported enantioselective conjugate reduction of α, β-unsaturated esters **116** with semicorrin **118** cobalt catalyst giving the corresponding saturated esters with enantiomeric excess exceeding 98%. The Co-semicorrin complex is prepared *in situ* at 25^0C by their stirring for 1 h (**Scheme 32**).[80]



116 **117** **118**

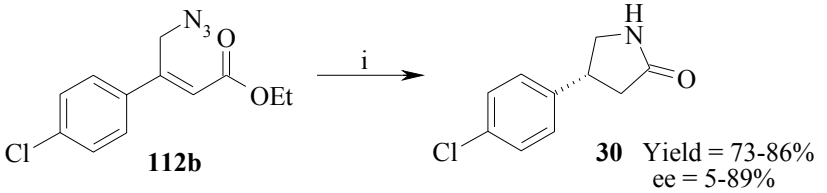
Scheme 32: i $CoCl_2.6H_2O$ (1 mol %), **118** (1.2 mol %), $NaBH_4$ (2 equiv.), EtOH:DMF (1:1), 25^0C, 24h, 95 – 98.7 % ee, 88 – 98 %.

Clean reaction procedures, easily attainable experimental conditions and excellent optical purity of resulting products coupled with low cost of catalyst makes this method much more impressive and practical.

In order to further improve and extend this methodology to the one pot enantioselective conjugate reduction of α, β-unsaturated esters followed by cyclization containing other reducible groups such as azide and nitrile, we employed commercially available chiral oxazolidine **119** with cobalt as catalyst using $NaBH_4$ as reducing agent. This improved protocol has allowed for an efficient synthesis of 4-substituted pyrrolidin-2-ones.

1.1.5 Results and Discussion

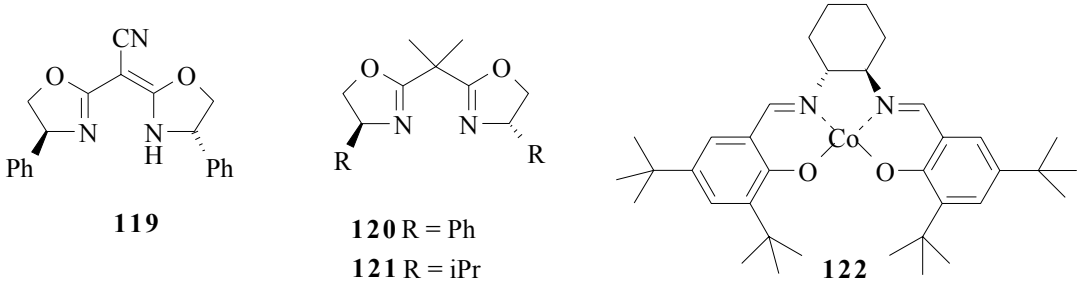
Initially, we were interested in obtaining chiral γ-amino esters by subjecting γ-azido olefinic esters **112b** to asymmetric reduction in the presence of oxazolidine (**119-121**) and salen-based (**122**) ligands. Thus when azido ester **112b** was subjected to Co-catalyzed asymmetric reduction with Co-$NaBH_4$–oxazolidine system at 25^0C, the corresponding chiral γ-lactam **30** was obtained in 73 – 84 % yield and 5 – 89 % ee. It may be noted that the azido group and C-C double bond were reduced simultaneously and the resulting amine underwent cyclization instantaneously to afford lactam **30** in a single step (**Scheme 33**).



112b **30** Yield = 73-86%
ee = 5-89%

Scheme 33: i azido ester (1 mmol), $CoCl_2$ (1 mol %), Ligand **119-122** (1.1 mol %), $NaBH_4$ (4 mmol), DMF:EtOH (1:1), 25 ^{0}C, 24h, 73 - 86%.

Among various chiral ligands and complexes screened, only (4S)-(+)-phenyl-α-[(4S)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile **119** (**Fig. 6**) was found to be good in inducing chirality in the product (**Table 3**).



119

120 R = Ph

121 R = iPr

122

Fig. 6: Chiral ligands and complex employed for asymmetric pyrrolidin-2-one synthesis

Table 3: $CoCl_2$-catalyzed reductive cyclization of γ-azido-α, β-unsaturated ester **112b** by using various chiral ligands[a]

Entry	Ligand	Yield (%)[d]	$[\alpha]_D$	% ee[e]
a	**119**[b]	84	-34.82	89
b	**120**[b]	86	-01.95	05
c	**121**[b]	80	-04.69	12
d	**122**[c]	73	--	--

a = Conditions: azido ester (1 mmol), $CoCl_2$ (1 mol %), Ligand **119-122** (1.1 mol %), $NaBH_4$ (4 mmol), DMF:EtOH (1:1), 25 ^{0}C, 24h, 73 - 86%.
b = Co-complex was generated *in situ* by reported methods.
c = Co-complex was prepared before use.
d = Isolated yield after chromatographic purification.
e = Determined by comparison of $[\alpha]_D$ with the reported values.

γ-Lactam **30** was thoroughly characterized by spectral analysis. The disappearance of 2104 cm^{-1} band in IR spectrum of *γ*-lactam **30** indicates the absence of azide group, while carbonyl absorption band observed at 1692 cm^{-1} indicates the formation of cyclic amide. Due to the presence of chiral center, the ^{1}H-NMR spectrum of **30** exhibited characteristic signals in the region of δ 2.39-3.84. Thus, the protons of *α*-CH_2 and *γ*-CH_2 groups of **30** are diastereotopic and thereby show ABX coupling pattern and each proton (H_A and H_B) of these CH_2 groups appearing as a two doublets, while H_X shows multiplet. In a similar way the protons of *γ*-CH_2 group represent another ABX pattern. Its ^{13}C-NMR spectrum shows signals at δ 49.51, 38.22 and 40.13 corresponding to *α*-CH_2, *γ*-CH_2 and *β*-CH carbons respectively (**Fig. 7**).

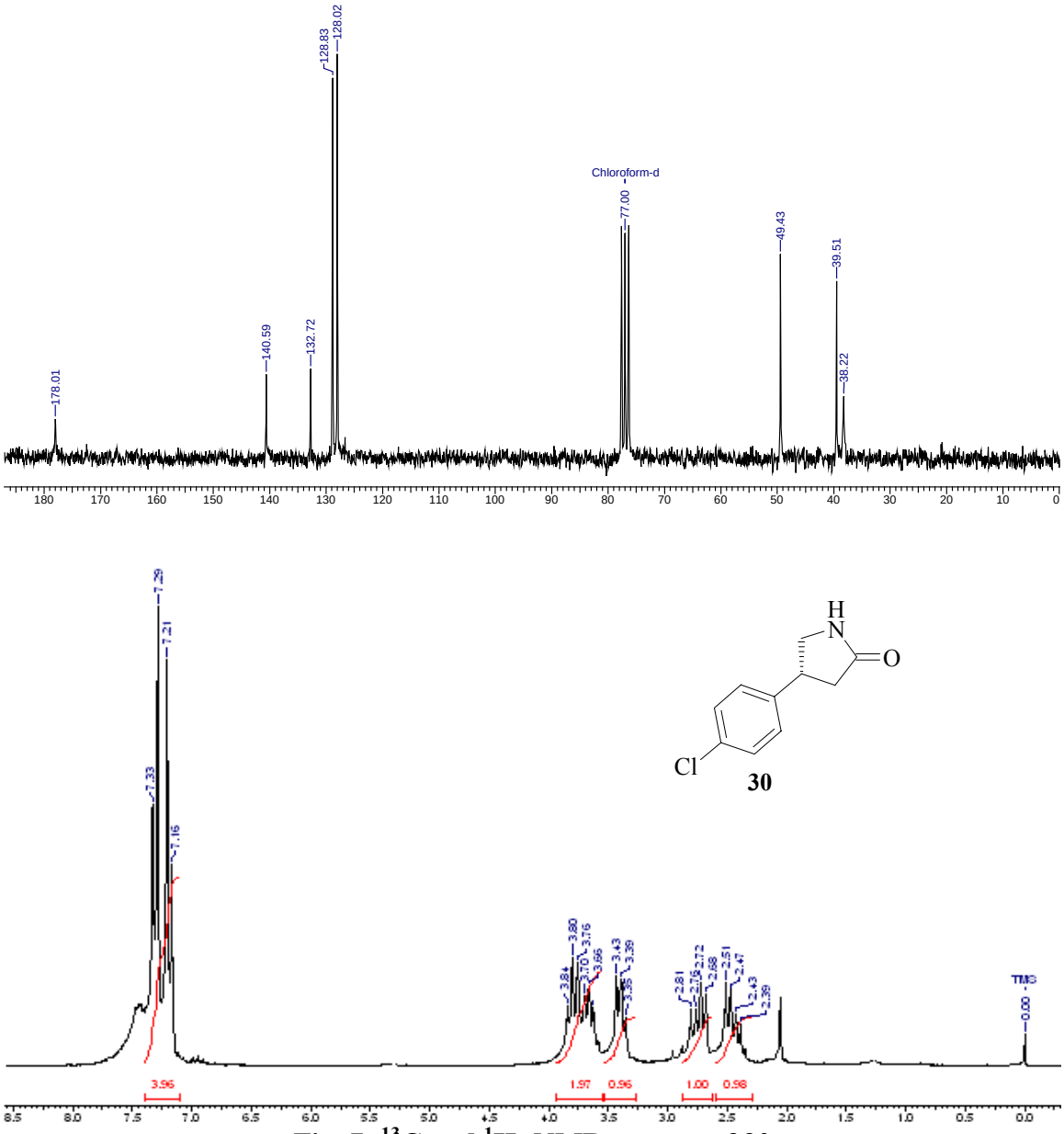
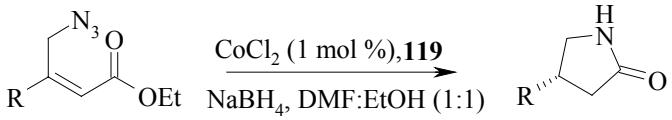


Fig. 7: ^{13}C and ^{1}H -NMR spectra of 30

The ee of γ-lactam **30** was found to be 89% based on comparison of its optical rotation with that of reported value {$[\alpha]^{25}_{D}$: – 34.82 (c 1.0, EtOH); Lit.[64] $[\alpha]^{25}_{D}$: – 39.0 (c 1.0, EtOH)}.

Table 4: $CoCl_2$-catalyzed reductive cyclization of γ-azido-α, β-unsaturated esters with $NaBH_4$[a]



112 (a-g) **111 (a-g)**

Entry	R	Yield (%)[b]	$[\alpha]_D$	% ee[c]
a	Ph	86	-18.90 (0.91, $CHCl_3$)	
b	4-ClPh	84	-34.82 (1.03, EtOH)	89[d]
c	4-FPh	80	-27.54 (1.12, MeOH)	
d	2-MeO Ph	91	-27.62 (1.10, MeOH)	
e	4-MeO Ph	93	-21.00 (1.00, MeOH)	
f	3-cpO-4-MeO Ph[e]	92	-30.10 (1.06, EtOH)	92[d]
g	*t*-C_4H_9	77	-6.17 (0.74, $CHCl_3$)	

a = Conditions: azido ester (1 mmol), $CoCl_2$ (1 mol %), oxazoline **119** (1.2 mol %), $NaBH_4$ (4 mmol), DMF:EtOH (1:1), 25 ^{0}C, 24h, 77 - 93%.
b = Isolated yield after chromatographic purification.
c = Determined by comparison of $[\alpha]_D$ with the reported values.
d = Using oxazoline (**119**) as the chiral ligand.
e = cp = Cyclopentyl.

In order to systematically explore the utility of this catalytic system for the synthesis of various 4-substituted pyrrolidin-2-ones, a variety of γ-azido olefinic esters **112(a-g)** were successfully screened to afford the corresponding 4-substituted pyrrolidin-2-ones **111(a-g)** in good to excellent yields. **Table 4** shows the results of several azido esters which smoothly underwent reductive cyclization.

In this way, (R)-rolipram **31** was obtained in 92 % yield and 92 % ee when 3-cyclopentyloxy-4-methoxy substituted azido ester (**112f**) was subjected to reductive cyclization in the presence of oxazolidine ligand **119**. The ^{1}H-NMR spectrum of **31** showed presence of typical ABX pattern in the region of δ 2.50 - 3.77 indicating diastereotopic nature of α-CH_2 and γ-CH_2 protons of **31**. Its ^{13}C-NMR spectrum showed characteristic peaks at δ 38.20, 39.77, 49.97 and 178.61 (**Fig. 8**). The methodology also works for aliphatic azido ester **112g** producing lactam **111g** in 77% yield.

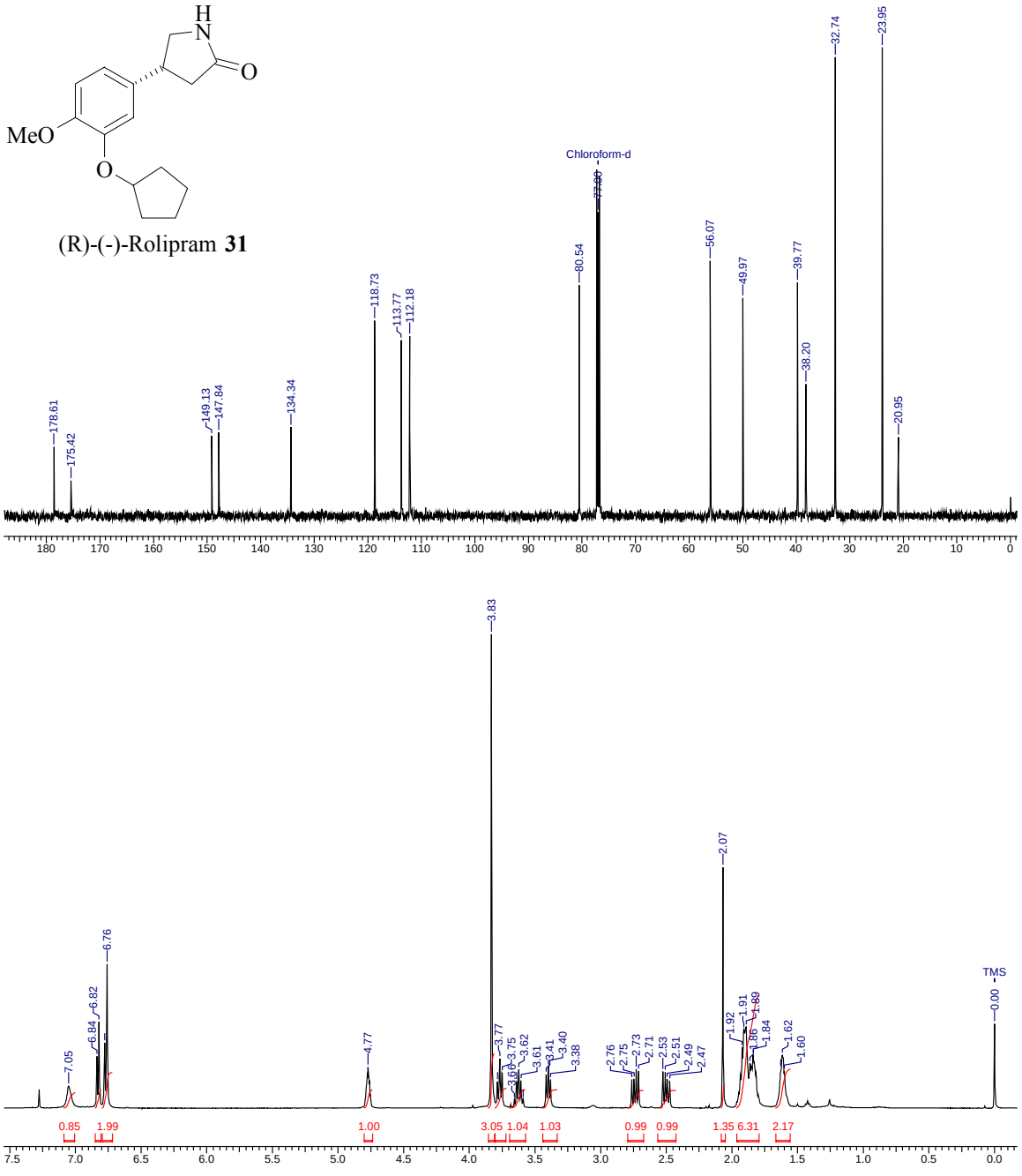
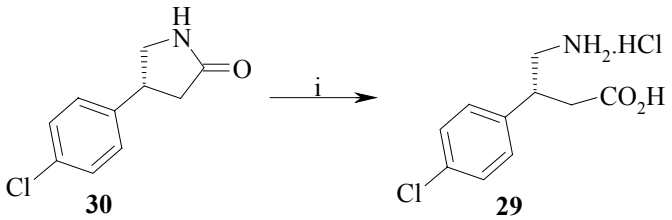


Fig. 8: ^{13}C and ^{1}H -NMR spectra of 31

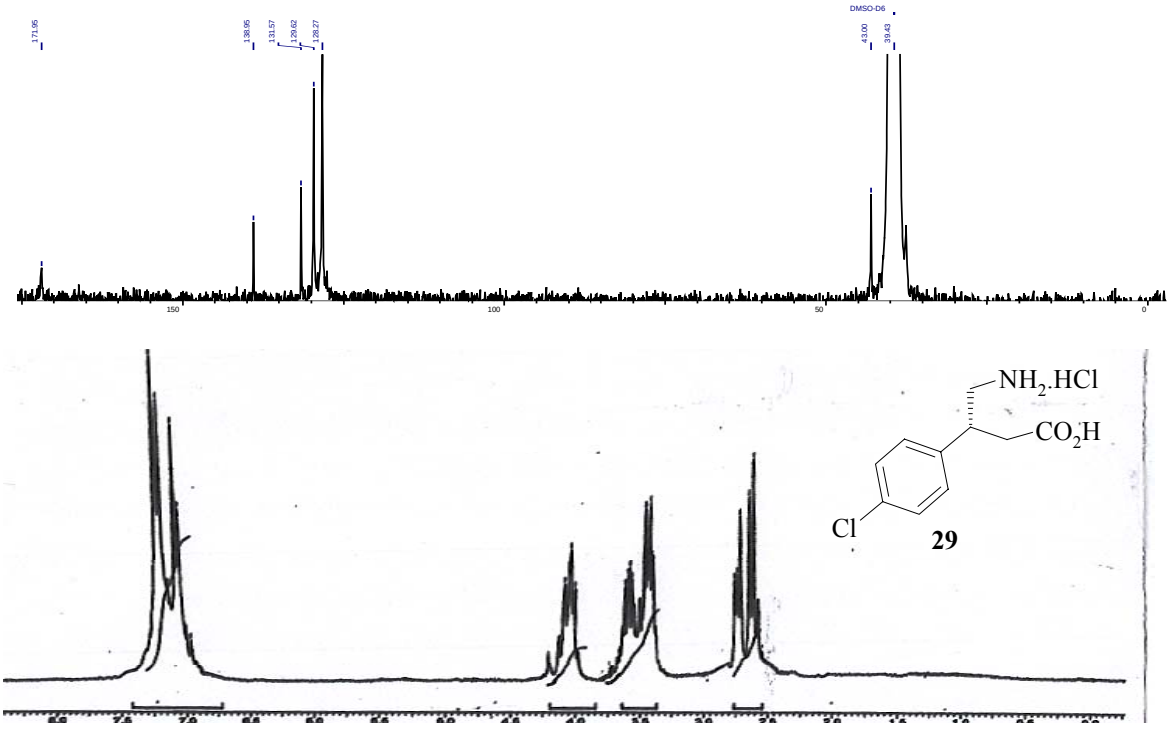
Further, chiral *γ*-lactam **30** was subjected to hydrolysis with 6N HCl to give optically active (*R*)-baclofen (**29**) as its hydrochloride salt in 73% yield and 88% ee (**Scheme 34**). The absolute configuration of **29** was confirmed to be "R" by comparison with the literature values

of its optical rotation. Hence, the prediction of stereochemical outcome of asymmetric hydrogenation has been found to be correct. The IR, ^{1}H-NMR and ^{13}C-NMR spectral data of **29** matched very well with that of the published values (**Fig. 9**).



30 **29**

Scheme 34: i 6N HCl, reflux, 16 h, 73%, 88% ee.

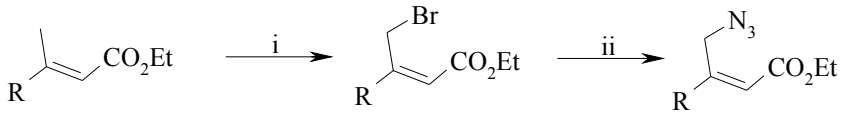


29

Fig. 9: ^{13}C and ^{1}H -NMR spectra of 29

The precursors, azido esters **112(a-g)**, were prepared in two steps as shown in **Scheme 35** from the corresponding olefins **113(a-g)** by allylic bromination of methyl group with NBS

producing γ-bromo-α, β-unsaturated esters **123(a-g)**. The results of bromination and azide exchange are summarized in **Table 5**.



113 (a-g) **123 (a-g)** **112 (a-g)**

Scheme 35: i AIBN (10 mol %), NBS, CCl_4, reflux, 12h, 72 – 90 %; ii NaN_3, EtOH:H_2O (2:1), 60 ^{0}C, 6h, 77 – 99 %.

Table 5: Allylic bromination[a] followed by bromide displacement with azide[b]: Synthesis of γ-azido olefinic esters (**112a-g**).

Entry	R	Yield of **123 (a-g)** (%)[c]	Yield of **112 (a-g)** (%)[c]
a	Ph	72	86
b	4-ClPh	88	77
c	4-FPh	84	80
d	2-MeO Ph	80	90
e	4-MeO Ph	86	95
f	3-cp-4-MeO Ph[d]	90	99
g	*t*-C_4H_9	76	91

a = Allylic bromination conditions: olefinic ester (1 mmol), NBS (1.2 mmol), AIBN (1 mol %), CCl_4, 80 ^{0}C, 24h, 72 - 90%.
b = Bromide displacement with azide conditions: bromo ester (1 mmol), NaN_3 (3 mmol), EtOH:H_2O (1:1), 50 ^{0}C, 12h, 86 - 99%.
c = Isolated yield after chromatographic purification.
d = cp = Cyclopentyl.

The IR spectrum of azido ester **112b** showed an intense peak at 2101 cm^{-1} indicative of N_3 group. Its ^{1}H-NMR showed a signal at δ 4.74 indicating a slight change in the chemical shift of the CH_2-N_3 protons. This signal is slightly upfield compared to CH_2-Br group of the bromoester **123b** (**Fig. 10**). However, in ^{13}C-NMR spectrum the signal of CH_2-N_3 moiety appeared at δ 48.03, whereas for CH_2-Br it has displayed at δ 26.13 (**Fig. 10**).

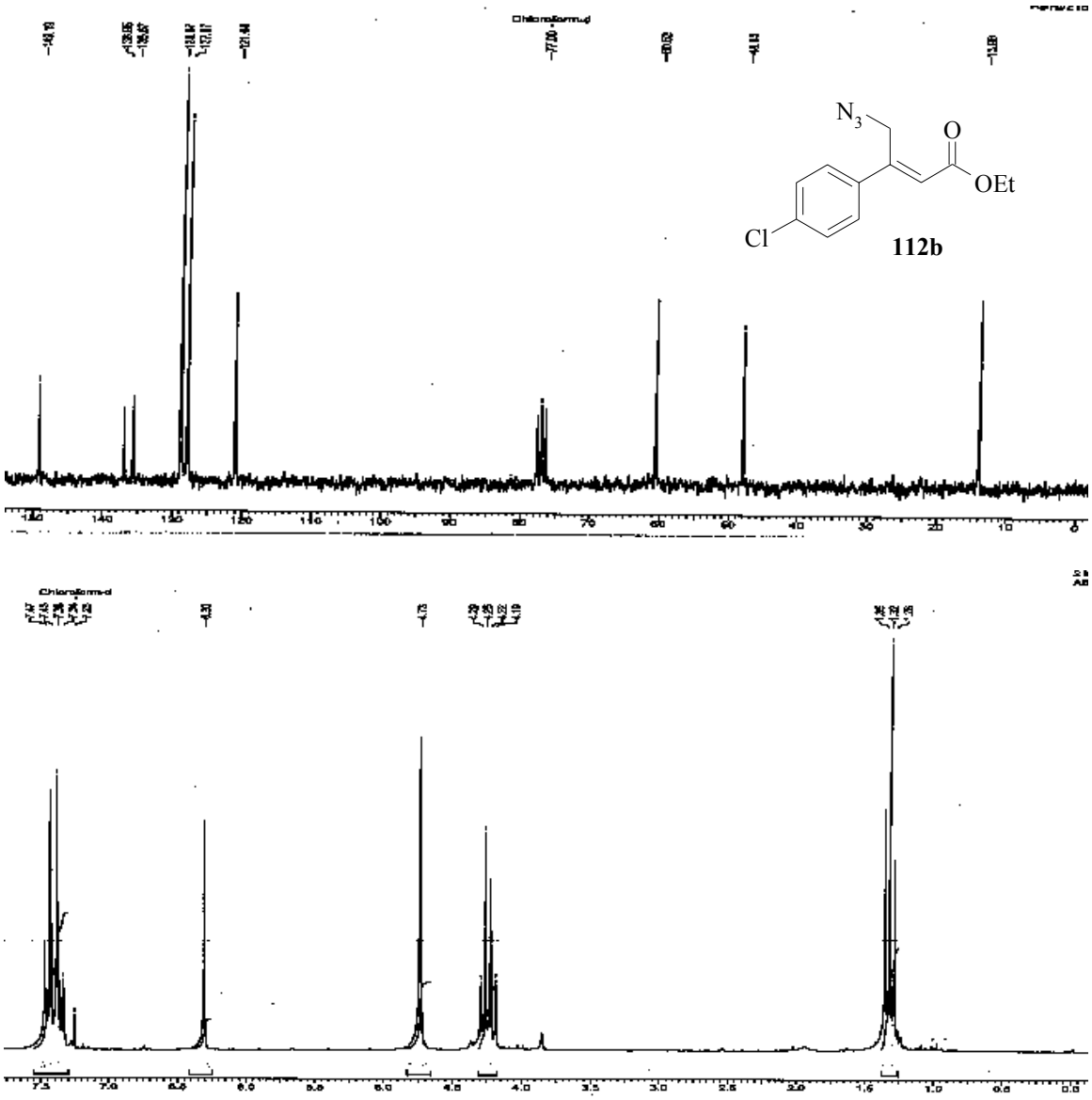


Fig. 10: ^{13}C and ^{1}H -NMR spectra of 112b

The ^{1}H-NMR of azidoester **112f** showed a downfield shift for C_2 and C_3 protons while its ^{13}C-NMR spectrum showed up-field shift for C_3 carbon signal (at δ 47.48) (**Fig 11**).

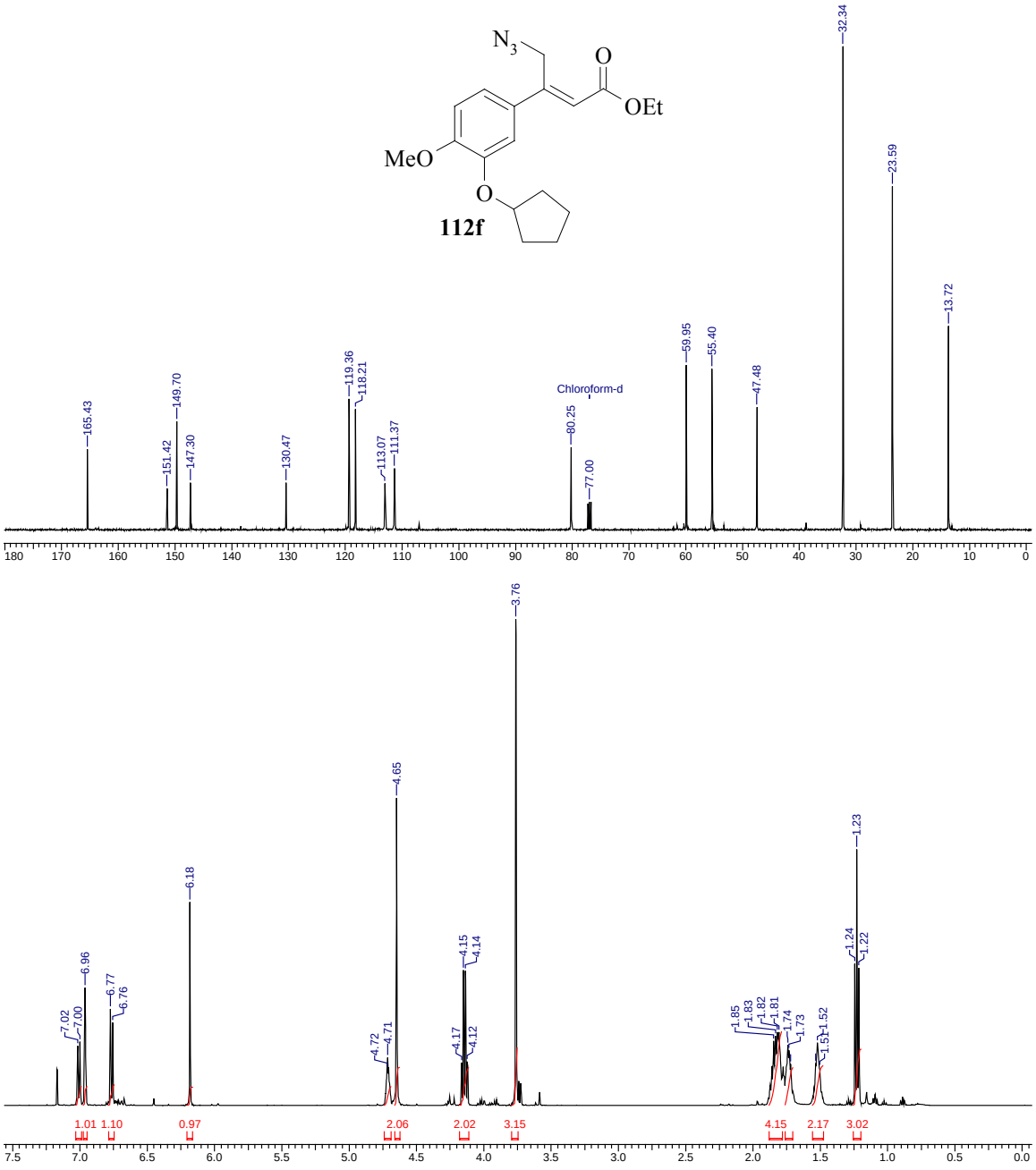


Fig. 11: ^{13}C and ^{1}H -NMR spectra of 112f

The bromo esters (**123a-g**) were prepared by allylic bromination of the corresponding olefinic esters **113(a-g)** with *N*-bromosuccinimide (NBS) in the presence of 2, 2'-azobisisobutyronitrile (AIBN) in 50–60 % yield. The ^{1}H-NMR spectrum of **123b** showed the absence of β-methyl group and appearance of methylene signal at δ 4.94 corresponding to

CH_2Br moiety. The ^{13}C-NMR spectrum showed a signal at δ 26.13 confirming the presence of CH_2-Br moiety. Its mass spectrum showed the molecular ion peak at m/e 304 confirming the formation of **123b** (**Fig. 12**).

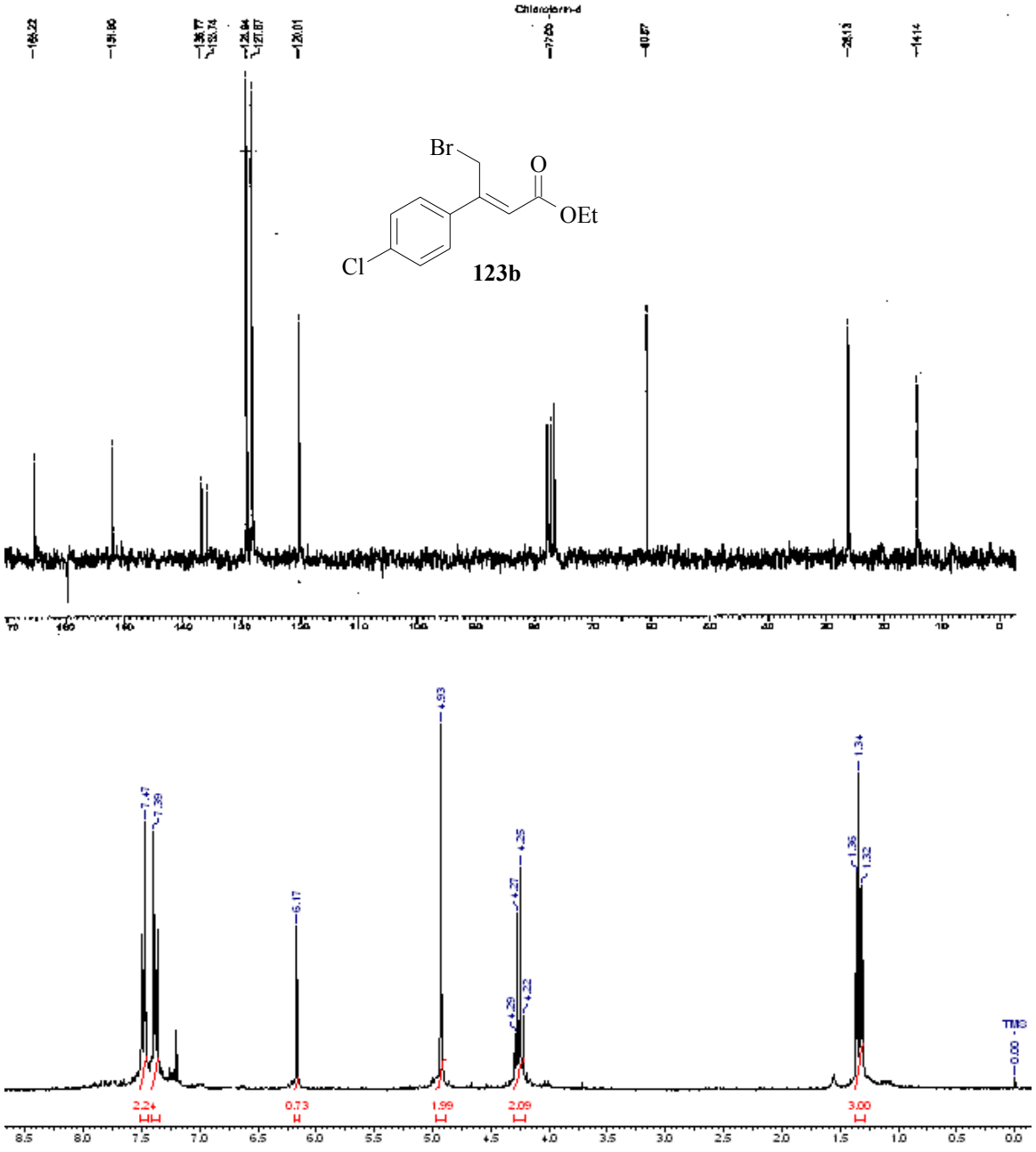


Fig. 12: ^{13}C and ^{1}H -NMR spectra of 123b

The ^{1}H and ^{13}C-NMR spectra of **123f** showed upfield shifts for proton and carbon signals of CH_2Br moiety (**Fig. 13**).

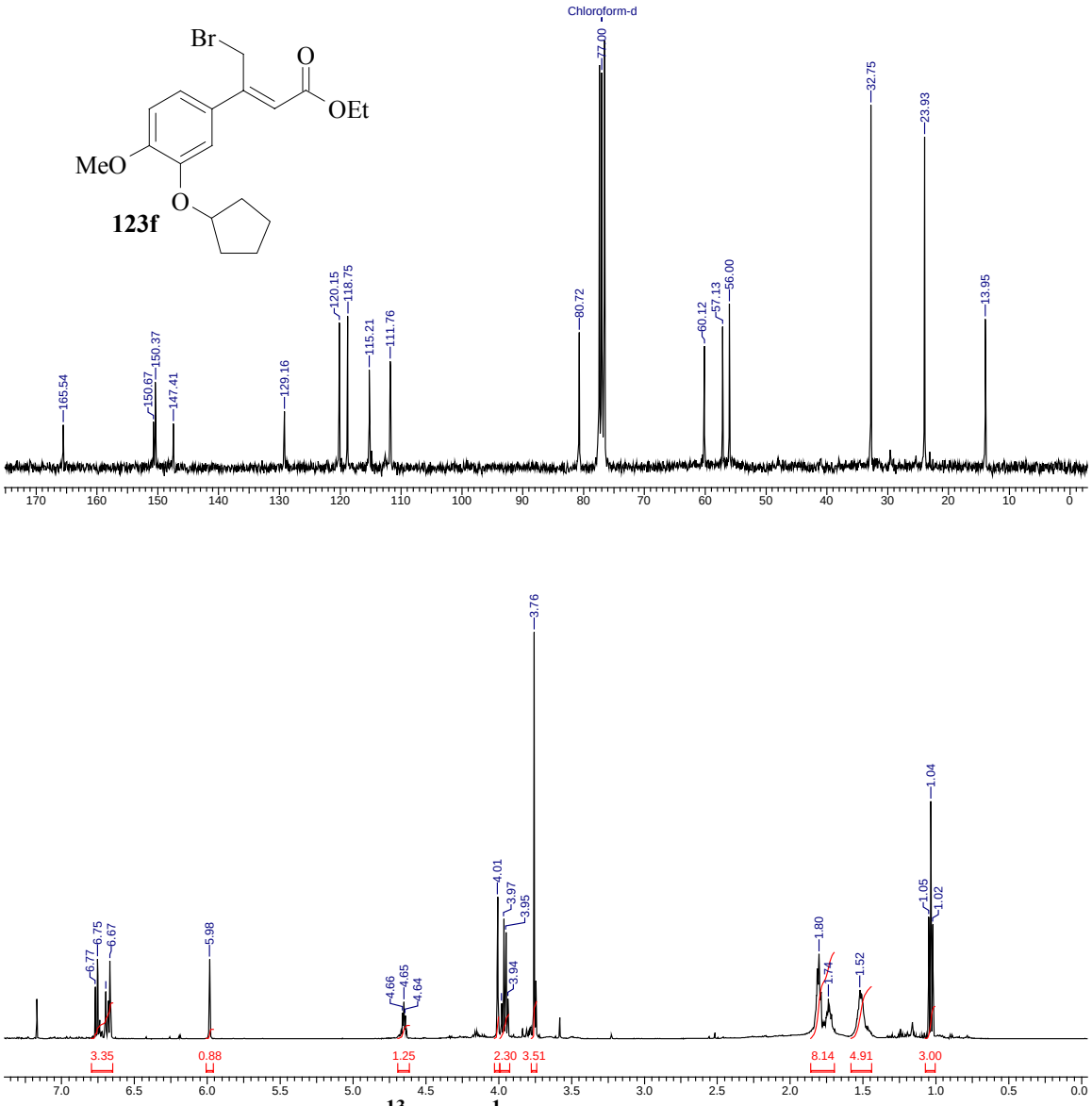
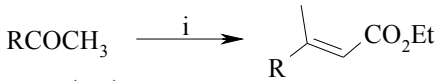


Fig. 13: ^{13}C and ^{1}H -NMR spectra of 123f

The olefins **113(a–g)** were prepared by Reformatsky reaction of the corresponding ketones **114(a–g)** with ethyl bromoacetate followed by dehydration of the alcohols generated *in situ* with *p*-TSA producing the required olefins **113(a–g)** in 80 – 93% (**Scheme 36**).



114 (a-g) **113 (a-g)**

Scheme 36: i a) Ethyl bromo acetate (12 mmol.), $ArCOCH_3$ (10 mmol), Zn dust (12 mmol), dry benzene, 80 ^{0}C , 6 h; b) *p*-TSA (10 mol %), benzene, Dean-Stark, 80 ^{0}C, 12h, 80 – 93 %.

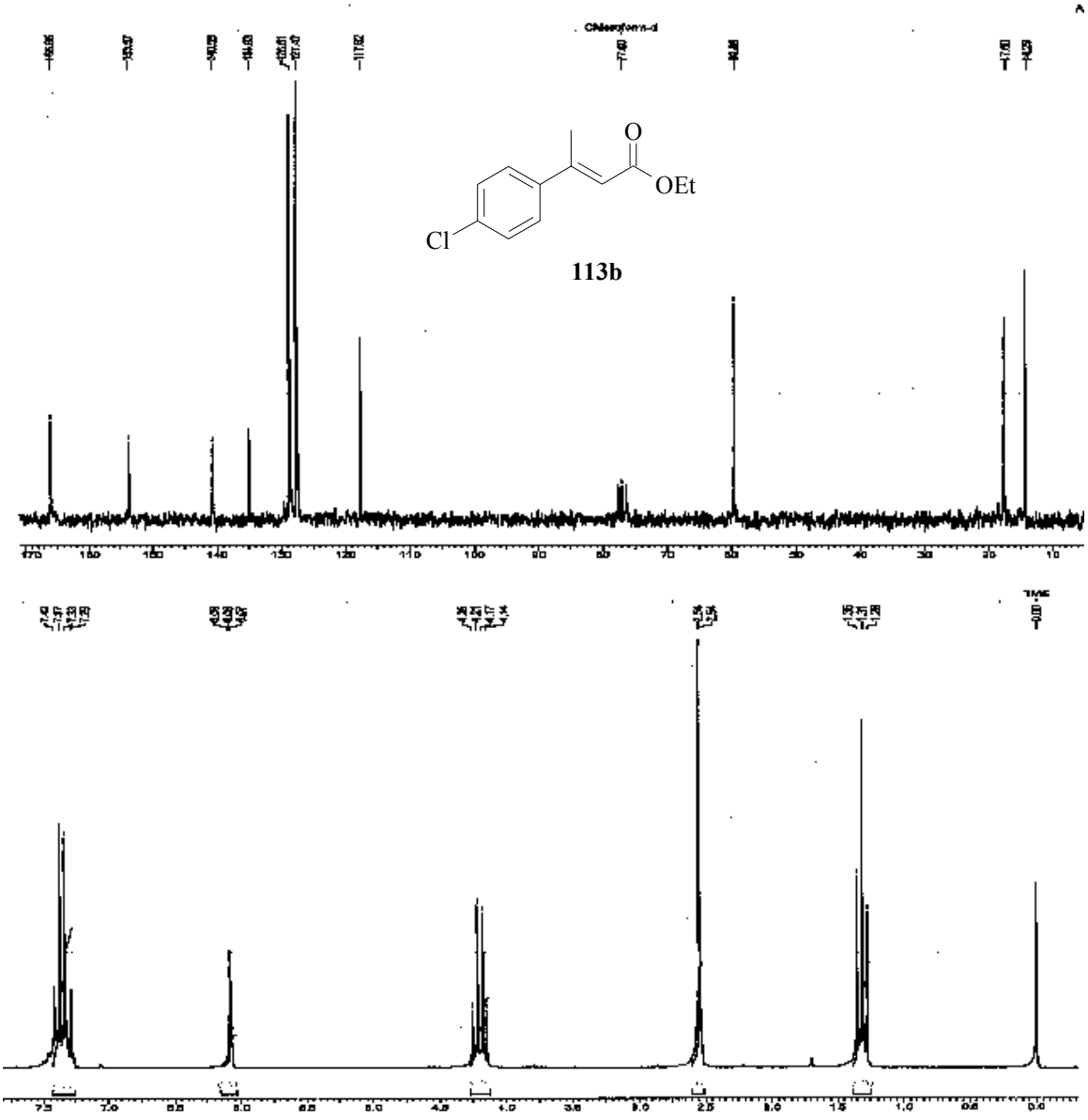
Results on the synthesis of α, β-unsaturated esters **113(a-g)** are presented in **Table 6**.

Table 6: Reformatsky[a] followed by dehydration[b]: Synthesis of α, β-unsaturated esters **113(a-g)**

Entry	R	Yield (%)[c]
a	Ph	80
b	4-ClPh	82
c	4-FPh	80
d	2-MeO Ph	91
e	4-MeO Ph	93
f	3-CpO-4-MeO Ph[d]	88
g	*t*-C_4H_9	82

a = Reformatsky conditions: Ethyl bromo acetate (1.2 equiv.), $RCOCH_3$ (1 equiv.), Zn dust (1.2 equiv.), dry benzene, 80 ^{0}C, 6 h.
b = Dehydration conditions: *p*-TSA (10 mol %), benzene, Dean-Stark, 80 ^{0}C, 12h.
c = Isolated yield after chromatographic purification.
d = cp = cyclopentyl.

The IR spectrum of **113b** showed strong bands at 1725 and 1641 cm^{-1} indicating the presence of ester and olefin group functionalities. Its ^{1}H-NMR spectrum showed characteristic singlets at δ 2.54 and 6.08 due to presence of vinylic-methyl group and olefinic proton (=CH) respectively (**Fig. 14**). The ^{13}C-NMR showed characteristic carbon signals at δ 153.57 and 117.62 corresponding to that of *β*-quaternary carbon and CH carbon of the *α, β*-unsaturated ester respectively. The signal at δ 165.95 confirms the presence of ester carbonyl. The mass spectrum of **113b** indicated intense molecular ion peak at m/z 224 (96%).



113b

Fig. 14: ^{13}C and ^{1}H -NMR spectra of 113b

The ^{1}H-NMR spectra of **124f** showed singlets for vinylic-methyl group and olefinic proton (**Fig. 15**).

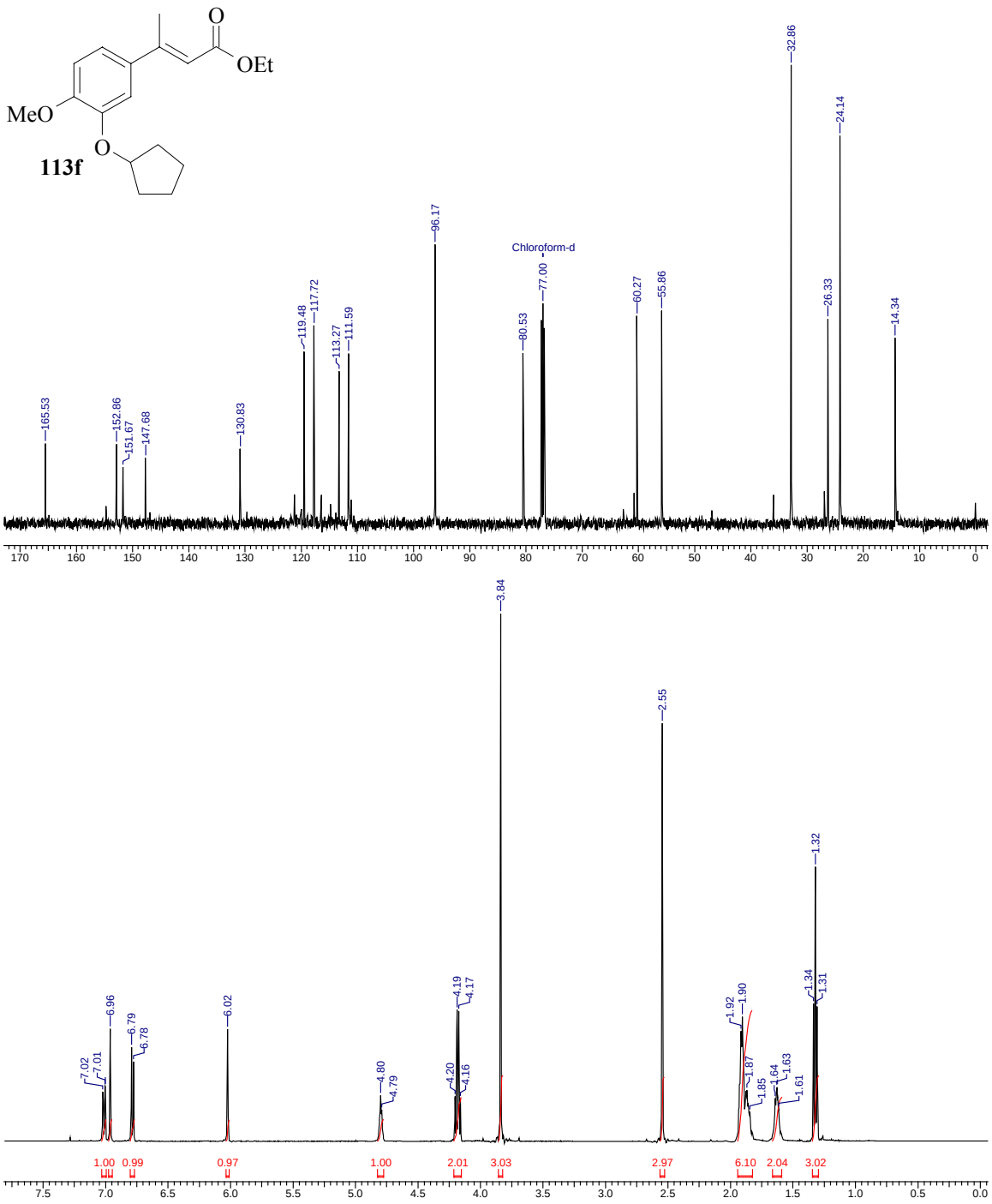
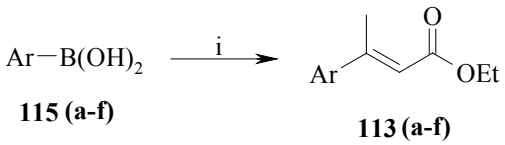


Fig. 15: ^{13}C and ^{1}H -NMR spectra of 113f

In order to circumvent the difficulties associated with the multistep synthesis of aryl α, β-unsaturated esters **113(a-f)** (**Scheme 36**), we have employed Pd-catalyzed arylation of ethyl

crotonate with the corresponding commercially available aryl boronic acids **115(a-f)** to produce the required *trans*-olefinic esters **113(a-f)** in one step in 80 – 93 % yield (**Scheme 37**).[81]



115 (a-f) **113 (a-f)**

Scheme 37: i Ethyl crotonate (2 mmol), boronic acid (1 mmol), cat. $Pd(OAc)_2$ (1 mol %), Na_2CO_3 (1.5 mmol), O_2 (1 atm), DMF, 50 ^{0}C, 12 h, 80 – 93 %.

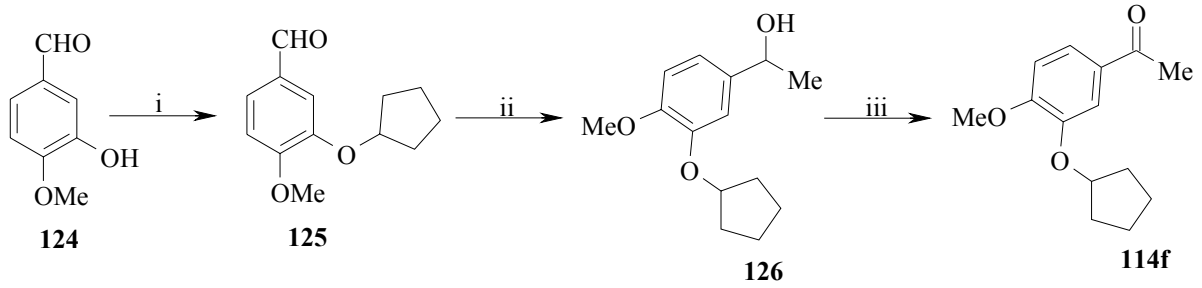
The results of these arylation reactions are depicted in **Table 7**.

Table 7: Arylation of ethyl crotonate[a]: Synthesis of α, β-unsaturated esters **113(a-f)**

Entry	Ar	Yield (%)[b]
a	Ph[c]	86
b	4-ClPh[c]	82
c	4-FPh[c]	80
e	4-MeO Ph[c]	93
f	3-Cp-4-MeO Ph[d, e]	92

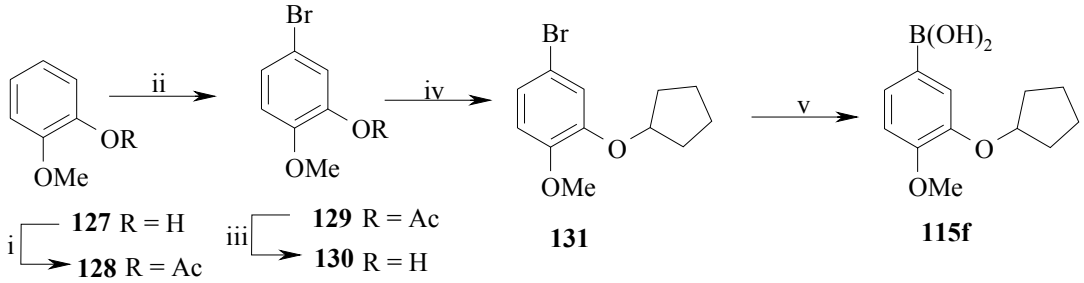
a = Conditions: Ethyl crotonate (2 mmol), boronic acid (1 mmol), cat. $Pd(OAc)_2$ (1 mol %), Na_2CO_3 (1.5 mmol), O_2 (1 atm), DMF, 50 ^{0}C, 12 h, 80 – 93 %.
b = Isolated yield after chromatographic purification.
c = Commercially available boronic acids are used as it is.
d = Boronic acid was prepared as shown in **Scheme 38**.
e = Cp = Cyclopentyl.

The ketone **114f** employed in (R)-rolipram synthesis was prepared from isovanillin **124** as shown in **Scheme 38**. O-Alkylation of phenolic OH of aldehyde **124** was achieved using cyclopentyl bromide in the presence of anhyd. K_2CO_3 in DMF. Grignard reaction of aldehyde gave alcohol **126** in 76 % yield. The oxidation of alcohol **126** with chromic acid produced the required ketone **114f** in 75 % yield.



Scheme 38: i Cyclopentyl bromide (1.5 equiv.), K_2CO_3 (1.2 equiv.), DMF, 60 ^{0}C, 12h, 85 %.; ii MeMgBr (1.3 equiv.), Et_2O, 0 – 25 ^{0}C, 1h, 76 %.; iii $H_2Cr_2O_7$, Et_2O, 0 – 25 ^{0}C, 4 h, 75%

Boronic acid **115f** utilized in (R)-rolipram synthesis was prepared in 5 steps from guaiacol **127** as depicted in **Scheme 39**. Acetyl protection of phenolic OH has facilitated the selective bromination with NBS at the *para* position to methoxy group. Deprotection of acetyl group and cyclopentylation of OH generated bromoether **131**. Bromoether **131** was further transformed to boronic acid **115f** by lithiation followed by reaction with $B(OMe)_3$ following literature conditions.[82]



Scheme 39: i Ac_2O, conc. H_2SO_4 (5 mol %), 100 ^{0}C, 7h, 97 %.; ii NBS (1.2 equiv.), CH_3CN, 50 ^{0}C, 4h, 99 %.; iii aq. 10 % $NaHCO_3$ (3 equiv.), MeOH, reflux, 6h, 95 %.; iv Cyclopentyl bromide (1.5 equiv.), K_2CO_3 (1.2 equiv.), DMF, 60 ^{0}C, 12h, 89 %.; v (a) BuLi (2 equiv.), $B(OMe)_3$ (2 equiv.), -78 ^{0}C, 3h.; (b) aq. HCl (10 %), reflux, 6h, 15%.

1.1.6 Conclusion

In conclusion, we have developed a simple and practical method of asymmetric conjugate reductive cyclization of aliphatic and aromatic substituted γ-azido-α, β-unsaturated esters producing the corresponding chiral 4-substituted pyrrolidin-2-ones **111(a-g)** in excellent yields and enantioselectivities. The methodology was successfully applied for the

enantioselective synthesis of two antidepressant drugs: (*R*)-(-)-rolipram (**31**) with 92% ee [eight steps with 12% overall yield starting from aldehyde **124** and nine steps with 5% overall yield starting from guaiacol **127**] and (*R*)-(-)-baclofen (**29**) with 89% ee [five steps with 14% overall yield starting from ketone **114b** and four steps with 15% overall yield starting from boronic acid **115b**].

1.1.7 Experimental Procedure

Typical experimental procedure for enantioselective synthesis of 4-substituted pyrrolidin-2-ones (111a-g).

To a 2.30 g (10 mmol) of azido ester **112b** in a 25 ml RB flask was added a solution of $CoCl_2.6H_2O$ (0.021 g, 0.1 mmol) in 2 ml of ethanol, followed by a solution of (4S)-(+)-phenyl-α-[(4S)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile **119** (0.039 g, 0.12 mmol) in 1 ml EtOH under nitrogen atmosphere. After dilution with 1 ml of DMF, the clear, dark blue solution was degassed by three freeze-thaw cycles. To this mixture, which was kept under nitrogen, was added sodium borohydride solution (1.514 g, 40 mmol) in 1 ml DMF which resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze-thaw cycles. The evacuated flask containing the yellow, slightly turbid solution was stirred at 25^0C. In the beginning, slow H_2-evolution was observed which gradually ceased after 1h. Towards the end of the reaction, solid precipitate along with brown-yellow foam began to form. After completion of reaction (monitored by TLC), the reaction mixture was transferred to a separatory funnel containing 50 ml of EtOAc and 75 ml of water, and extracted with EtOAc. The organic layer was washed three times with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Column chromatographic purification (EtOAc/pet. ether 4: 1) afforded 1.63 g (84 %) of (R)-4-chlorophenylpyrrolidin-2-one **111b** as a colorless solid.

4-phenylpyrrolidin-2-one (111a):

Yield: 86%; colorless solid; **mp**: 112°C; **$[\alpha]^{25}_{D}$**: - 18.90 (c 0.91, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 665, 703, 756, 1092, 1218, 1373, 1490, 1697, 2100, 3211, 3422; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.35-2.47 (dd, *J* = 16.04 Hz and 8.00 Hz, 1H), 2.65-2.77 (dd, *J* = 16.04 Hz and 8.00 Hz, 1H); 3.32-3.41 (m, 1H), 3.60-3.82 (m, 2H), 7.25 – 7.36 (m, 5H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 38.22, 39.51, 49.43, 126.28, 128.40, 132.00, 136.65, 175.53; **Analysis:** $C_{10}H_{11}NO$ requires C, 64.60; H, 6.19; N, 10.76; found C, 64.53; H, 6.11; N, 10.69%.

(*R*)-4-(4-chlorophenyl)pyrrolidin-2-one (111b):

Yield: 84%; colorless solid; **mp**: 115-117°C; **$[\alpha]^{25}_{D}$**: – 34.82 (c 1.0, EtOH), 89% ee, {Lit.[12,21] **$[\alpha]^{25}_{D}$** = – 39 (c 1.0, EtOH)}; **IR** ($CHCl_3$, cm^{-1}): 486, 550, 625, 676, 829, 1015,1106, 1168, 1273, 1297, 1410, 1460, 1488, 1666, 1763, 1911, 2228, 2840, 2898, 2952, 3106, 3197, 3443; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.39-2.51 (dd, *J* = 16.90 Hz and 8.41 Hz, 1H), 2.68-2.81 (dd, *J* = 16.90 Hz and 8.72 Hz, 1H); 3.35-3.43 (m, 1H), 3.62-3.84 (m, 2H), 7.18 (d, *J* = 9.12 Hz, 2H), 7.31 (d, *J* = 9.12 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 38.22, 39.51, 49.43, 128.02, 128.83, 132.72, 140.59, 178.01; **MS** m/z (% rel. intensity): 195 (M^+, 15), 140 (24), 138 (100), 75 (5); **Analysis**: $C_{10}H_{10}ClNO$, requires C, 61.39; H, 5.15; N, 7.16; found: C, 61.30; H, 4.10; N, 7.19%

4-(4-fluorophenyl)pyrrolidin-2-one (111c):

Yield: 80%; colorless solid; **mp**: 98-99°C; **$[\alpha]^{25}_{D}$**: -27.54 (c 1.12, MeOH); **IR** ($CHCl_3$, cm^{-1}): 669, 704, 760, 1095, 1210, 1375, 1493, 1695, 2105, 3209, 3417; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.53-2.69 (m, 2H); 3.37-3.46 (m, 1H), 3.61-3.82 (m, 2H), 7.06 (d, *J* = 8.61 Hz, 2H), 7.51 (d, *J* = 9.00 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 38.12, 39.68, 49.51, 115.31, 128.74, 134.14, 151.22, 178.00; **Analysis**: $C_{10}H_{10}FNO$, requires C, 67.03; H, 5.62; N, 7.82; found: C, 67.00; H, 5.58; N, 7.79%.

4-(2-methoxyphenyl)pyrrolidin-2-one (111d):

Yield: 91%; colorless solid; **mp**: 118°C; **$[\alpha]^{25}_{D}$**: -27.62 (c 1.10, MeOH); **IR** ($CHCl_3$, cm^{-1}): 664, 673, 685, 731, 1046, 1250, 1441, 1542, 1694, 2405, 2977; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.56-2.60 (d, *J* = 8.00 Hz, 2H), 3.40-3.46 (m, 1H); 3.69-3.77 (m, 2H), 6.84 – 6.95 (m, 2H), 7.17 – 7.25 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 35.17, 48.22, 55.17, 110.49, 117.84,

120.67, 127.36, 128.06, 129.89, 157.21, 175.00; **Analysis:** $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found C, 69.10; H, 6.80; N, 7.20%.

4-(4-methoxyphenyl)pyrrolidin-2-one (111e):

Yield: 93%; colorless solid; **mp**: 121-123^{o}C; **$[\alpha]^{25}_{D}$**: -21.00 (c 1.00, MeOH); **IR** ($CHCl_3$, cm^{-1}): 495, 516, 546, 564, 604, 641, 685, 772, 829, 884, 926, 1030, 1059, 1080, 1112, 1161, 1184, 1247, 1298, 1316, 1352, 1413, 1458, 1516, 1558, 1611, 1680, 1889, 1957, 2021, 2051, 2430, 2515, 2840, 2905, 2959, 3090, 3200; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.85 (s, 1H), 2.41-2.54 (d, *J* = 7.2 Hz, 1H), 2.67-2.79 (d, *J* = 8.61 Hz, 1H); 3.37-3.45 (m, 1H), 3.63-3.80 (m, 2H), 3.83, (s, 3H), 6.88 (d, *J* = 8.60 Hz, 2H), 7.19 (d, *J* = 8.61 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 38.44, 39.43, 49.80, 54.95, 113.98, 127.54, 134.05, 158.38, 178.19; **Analysis:** $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32; found C, 69.00; H, 6.72; N, 7.30%.

(*R*)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one: (R)-(-)-Rolipram (111f):

Yield: 92%; colorless solid; **mp:** 133-134^{0}C (recrystallized from $CHCl_3$); **$[\alpha]^{25}_{D}$**: – 27.80 (c 1.01, MeOH), 92% ee, {Lit.[12] **$[\alpha]^{25}_{D}$** = – 30.2 (c 1.0, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 508, 601, 619, 641, 686, 772, 816, 877, 973, 1002, 1025, 1060, 1145, 1164, 1236, 1250, 1272, 1310, 1438, 1513, 1592, 1686, 1701, 1868, 2042, 2575, 2942, 3098, 3200; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.62 (m, 2H), 1.82 – 1.93 (m, 6H), 2.07 (s, 1H), 2.50 (d, *J* = 8.71 Hz, 1H), 2.74 (d, *J* = 8.71 Hz, 1H), 3.40 (t, *J* = 8.00 Hz, 1H), 3.62 (q, *J* = 8.71 Hz, 1H), 3.77 (t, *J* = 9.00 Hz, 1H), 3.83 (s, 3H), 4.77 (m, 1H), 6.76 (d, 2H), 6.82 (d, 1H), 7.05 (brs, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.95, 23.95, 32.74, 38.20, 39.77, 49.97, 56.07, 80.54, 112.18, 113.77, 118.73, 134.34, 147.84, 149.13, 175.42, 178.61; **MS** (m/z, % relative intensity): 275 (10), 208 (5), 207 (80), 196 (5), 168 (5), 151 (10), 150 (100), 135 (15), 125 (20), 93 (15), 77 (10), 65 (15); **Analysis:** $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09; found C, 69.63; H, 7.67; N, 5.03%.

4-*tert*-butylpyrrolidin-2-one (111g):

Yield: 77%; colorless solid; **mp**: 81^{o}C; **$[\alpha]^{25}_{D}$**: -6.17 (c 0.74, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.98-2.32 (m, 1H), 2.22-2.59 (m, 2H**),** 3.31-3.56 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 23.82**,** 33.46**,** 35.20**,** 41.18, 41.63**,** 176.30; **Analysis:** $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92; found C, 68.00; H, 10.72; N, 9.78%.

(*R*)-(–)-Baclofen hydrochloride (29):

Yield: 73%; colorless solid; **mp**: 196-197°C; **$[\alpha]^{25}_{D}$**: – 1.76 (c 0.5, H_2O) 88% ee {Lit.[19] **$[\alpha]^{25}_{D}$** = – 2.00 (c 0.6, H_2O)}; **IR** ($CHCl_3$, cm^{-1}): 698, 704, 758, 1090, 1490, 1550, 1620, 2955, 2092, 3200; **^{1}H-NMR** (200 MHz, DMSO-d_6 + $CDCl_3$): 2.51-2.71 (m, 2H), 3.42-3.65 (m, 2H), 4.15-4.21 (m, 1H), 7.01-7.21 (m, 4H); **^{13}C-NMR** (50 MHz, DMSO-d_6): δ 37.57, 38.88, 43.00, 128.27, 129.62, 131.57, 138.95, 171.95; **MS** m/z (% rel. intensity): 195 (10), 140 (61), 138 (100), 125 (6), 115 (10), 103 (45), 89 (9), 77 (29); **Analysis**: $C_{10}H_{13}Cl_2NO_2$ requires C, 48.02; H, 5.24; N, 5.60; found C, 48.24; H, 5.15; N, 5.49 %.

Typical experimental procedure for the synthesis of γ-azido-α, β-unsaturated esters (112a-g):

A solution of bromoester **123b** (1.85 g, 6.1 mmol) and sodium azide (0.594 g, 9.14 mmol) in ethanol: water (80:20, 15ml) mixture was taken in 50ml RB and refluxed for 8h. The resulting yellow color solution was concentrated under reduced pressure to yield crude azidoester **112b**, which was purified by column chromatography packed with silica gel to give pure azidoester **112b** (1.24g) as colorless viscous liquid.

(Z)-ethyl 4-azido-3-phenylbut-2-enoate (112a):

Yield: 86%; gum; **IR** ($CHCl_3$, cm^{-1}): 443, 669, 698, 757, 1035, 1182, 1215, 1371, 1448, 1710, 1845, 2104, 2343, 2360, 3018, 3421; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.4 Hz, 3H), 4.17 (q, *J* = 7.4 Hz, 2H), 4.69 (s, 2H), 6.25 (s, 1H), 7.33 – 7.43 (m, 5H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 13.73, 47.79, 60.12, 120.40, 126.29, 128.39, 129.28, 138.28, 150.16, 165.23; **Analysis:** $C_{12}H_{13}N_3O_2$ requires C, 62.33; H, 5.67; N, 18.17; found C, 62.28; H, 5.65; N, 18.09%.

(Z)-ethyl 4-azido-3-(4-chlorophenyl)but-2-enoate (112b):

Yield: 77%; colorless liquid; **IR** ($CHCl_3$, cm^{-1}): 415, 427, 435, 457, 478, 1179, 1350, 1591, 1713, 2101, 2982; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.0 Hz, 3H), 4.24 (q, *J* = 8 Hz, 2H), 4.74 (s, 2H), 6.30 (s, 1H), 7.34 (d, *J* = 8 Hz, 2H), 7.43 (d, *J* = 8 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.96, 48.03, 60.53, 121.04, 127.87, 128.87, 135.67, 136.95, 149.19, 165.33;

Analysis: $C_{12}H_{12}ClN_3O_2$ requires C, 54.25; H, 4.55; N, 15.82; found 54.12; H, 4.48; N, 15.80%.

(Z)-ethyl 4-azido-3-(4-fluorophenyl)but-2-enoate (112c):

Yield: 80%; gum; **IR** ($CHCl_3$, cm^{-1}): 730, 830, 910, 1014, 1090, 1185, 1250, 1372, 1453, 1495, 1590, 1630, 1710, 2104, 2991; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.04 Hz, 3H), 4.22 (q, *J* = 8 Hz, 2H), 4.72 (s, 2H), 6.29 (s, 1H), 7.09 (d, *J* = 8.62 Hz, 2H), 7.54 (d, *J* = 9 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.13, 47.86, 61.13, 115.31, 119.42, 128.27, 131.63, 134.21, 151.54, 164.75; **Analysis:** $C_{12}H_{12}FN_3O_2$ requires C, 57.83; H, 4.85; N, 16.86; found C, 57.82; H, 4.88; N, 16.80%.

(Z)-ethyl 4-azido-3-(2-methoxyphenyl)but-2-enoate (112d):

Yield: 90%; gum; **IR** ($CHCl_3$, cm^{-1}): 650, 755, 821, 836, 887, 941, 1030, 1094, 1120, 1177, 1250, 1293, 1371, 1425, 1478, 1515, 1581, 1611, 1703, 1888, 2100, 2548, 2830, 2900, 2930, 2984, 3337; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.05 Hz, 3H), 3.85 (s, 3H), 4.22 (q, *J* = 7.05 Hz, 2H), 4.79 (s, 2H), 6.00 (s, 1H), 6.86 – 6.99 (m, 2H), 7.17 - 7.38 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.03, 49.98, 55.24, 60.28, 110.56, 120.74, 121.88, 128.53, 129.67, 130.34, 152.83, 156.40, 165.55; **Analysis:** $C_{13}H_{15}N_3O_3$ requires C, 59.76; H, 5.79; N, 16.08; found C, 59.75; H, 5.80; N, 16.10%.

(Z)-ethyl 4-azido-3-(4-methoxyphenyl)but-2-enoate (112e):

Yield: 95%; gum; **IR** ($CHCl_3$, cm^{-1}): 666, 758, 810, 834, 885, 937, 1029, 1096, 1115, 1174, 1254, 1291, 1369, 1421, 1462, 1513, 1574, 1604, 1712, 1891, 2101, 2550, 2831, 2906, 2937, 2981, 3332; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.05 Hz, 3H), 3.83 (s, 3H), 4.24 (q, *J* = 7.20 Hz, 2H), 4.77 (s, 2H), 6.31 (s, 1H), 6.93 (dd, *J* = 7.05 Hz, 2H), 7.49 (dd, *J* = 9.00 Hz, 2H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 13.96, 47.56, 55.06, 60.20, 113.98, 118.39, 127.87, 130.34, 149.63, 160.77, 165.77; **MS** m/z (% rel. intensity): 261 (10), 253 (10), 225 (5), 219 (100), 204 (5), 191 (70), 173 (5), 163 (80), 145 (30), 131 (35), 115 (15), 103 (40), 83 (30), 77 (35), 55 (40), 40 (55); **Analysis:** $C_{13}H_{15}N_3O_3$ requires C, 59.76; H, 5.79; N, 16.08; found C, 59.63; H, 5.72; N, 16.10%.

(Z)-ethyl 4-azido-3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (112f):

Yield: 99%; light yellow liquid; **IR** ($CHCl_3$, cm^{-1}): 667, 756, 1045, 1166, 1216, 1253, 1373, 1442, 1514, 1598, 1734, 2104, 2966, 3019, 3403; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 6 Hz, 3H), 1.52 (m, 2H), 1.72 – 1.85 (m, 6H), 3.76 (s, 3H), 4.14 (q, *J* = 6 Hz, 2H), 4.65 (s, 2H), 4.72 (s, 1H), 6.18 (s, 1H), 6.76 (d, *J* = 3.00 Hz, 1H), 6.96 (s, 1H), 7.00 (d, *J* = 4.00 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.72, 23.59, 32.34, 47.48, 55.40, 59.95, 80.25, 111.37, 113.07, 118.21, 119.36, 130.47, 147.30, 149.70, 151.42, 165.43; **Analysis:** $C_{18}H_{23}N_3O_4$ requires C, 62.59; H, 6.71; N, 12.17; found C, 62.63; H, 6.54; N, 12.10%.

(Z)-ethyl 3-(azidomethyl)-4,4-dimethylpent-2-enoate (112g):

Yield: 91%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.14 (s, 9H), 1.29 (t, *J* = 7.05 Hz, 3H), 4.17 (q, *J* = 7.04 Hz, 2H), 4.27 (s, 2H), 6.00 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.95, 24.12, 29.00, 36.55, 59.75, 117.52, 163.00; **Analysis:** $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.11; N, 19.89; found C, 56.73; H, 8.10; N, 19.90%.

Typical experimental procedure for the synthesis of γ-bromo-α, β-unsaturated esters (123a-g):

A solution of α, β-unsaturated ester **113b** (3.5 g, 15.62 mmol), NBS (2.81 g, 17.2 mmol) and AIBN (0.102 g, 0.62 mmol) in dry CCl_4 (35 ml) was refluxed under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature and then filtered through a sintered funnel to separate succinimide formed during the reaction. The filtrate was concentrated under reduced pressure to obtain bromoester **123b**. It was then purified by column chromatography packed with silica gel to give pure 4.25 g of pale yellow color gum, bromoester **123b**.

(Z)-ethyl 4-bromo-3-phenylbut-2-enoate (123a):

Yield: 72%; gum; **IR** ($CHCl_3$, cm^{-1}): 447, 460, 696, 767, 881, 960, 1020, 1047, 1095, 1176, 1218, 1286, 1344, 1367, 1448, 1492, 1577, 1596, 1623, 1710, 1766, 1890, 1955, 2345, 2935, 2979, 3058, 3537; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.4 Hz, 3H), 4.25 (q, *J* = 7.4 Hz, 2H), 4.95 (s, 2H), 6.18 (s, 1H), 7.38 – 7.53 (m, 5H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 14.04, 26.34, 60.24, 119.55, 126.36, 128.53, 129.47, 138.19, 152.90, 165.18; **Analysis:** $C_{12}H_{13}BrO_2$ requires C, 53.55; H, 4.87; found C, 53.63; H, 4.81%.

(Z)-ethyl 4-bromo-3-(4-chlorophenyl)but-2-enoate (123b):

Yield: 88%; yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): 649, 734, 908, 1012, 1095, 1182, 1288, 1340, 1369, 1490, 1625, 1710, 2982, 3060; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.0 Hz, 3H), 4.26 (q, *J* = 8 Hz, 2H), 4.94 (s, 2H), 6.19 (s, 1H), 7.36 (d, *J* = 9 Hz, 2H), 7.47 (d, *J* = 9 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.14, 26.13, 60.57, 120.01, 127.87, 128.94, 135.74, 136.77, 151.80, 165.22; **MS** m/z (% rel. intensity): 304 (M^+, 5), 289 (5), 224 (8), 179 (10), 152 (100), 137 (55), 115 (92), 101 (48), 91 (22), 75 (15); **Analysis:** $C_{12}H_{12}BrClO_2$ requires C, 47.48; H, 3.98; found C, 47.50; H, 3.83%.

(Z)-ethyl 4-bromo-3-(4-fluorophenyl)but-2-enoate (123c):

Yield: 84%; gum; **IR** ($CHCl_3$, cm^{-1}): 742, 912, 1214, 1090, 1185, 1283, 1332, 1363, 1495, 1622, 1715, 2980, 3055; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.04 Hz, 3H), 4.25 (q, *J* = 7.05 Hz, 2H), 4.94 (s, 2H), 6.14 (s, 1H), 7.08 (d, *J* = 8.61 Hz, 2H), 7.52 (d, *J* = 8.99 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.86, 25.97, 60.03, 115.24, 119.36, 128.30, 130.41, 134.19, 151.56, 164.62; **Analysis:** $C_{12}H_{12}BrFO_2$ requires C, 50.20; H, 4.21; found C, 50.16; H, 4.20%.

(Z)-ethyl 4-bromo-3-(2-methoxyphenyl)but-2-enoate (123d):

Yield: 80%; gum; Yield**: 75%**; **IR** ($CHCl_3$, cm^{-1}): 682, 754, 806, 883, 933, 950, 1022, 1041, 1112, 1176, 1240, 1269, 1298, 1340, 1367, 1434, 1461, 1488, 1579, 1598, 1631, 1710, 2042, 2837, 2937, 2977, 3060; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.43 Hz, 3H), 3.84 (s, 3H), 4.26 (q, *J* = 7.05 Hz, 2H), 5.03 (s, 2H), 5.95 (s, 1H), 6.92 (d, *J* = 8.22 Hz, 1H), 6.99 (t, *J* = 7.40 Hz, 1H), 7.21 - 7.27 (m, 1H), 7.33 - 7.41 (m, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.89, 28.26, 55.09, 59.98, 110.52, 120.34, 121.66, 128.09, 130.08, 130.30, 153.82, 156.03, 164.96; **Analysis:** $C_{13}H_{15}BrO_3$ requires C, 52.19; H, 5.05; found C, 52.20; H, 5.10%.

(Z)-ethyl 4-bromo-3-(4-methoxyphenyl)but-2-enoate (123e):

Yield: 86%; gum; **IR** ($CHCl_3$, cm^{-1}): 412, 428, 667, 757, 810, 833, 879, 950, 1024, 1031, 1047, 1095, 1174, 1217, 1253, 1288, 1342, 1369, 1438, 1461, 1514, 1573, 1604, 1708, 1890, 2057, 2430, 2549, 2839, 2904, 2937, 2981, 3014, 3398, 3568; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.20 Hz, 3H), 3.73 (s, 3H), 4.14 (q, *J* = 7.04 Hz, 2H), 4.86 (s, 2H), 6.05 (s, 1H), 6.80 (d, *J* = 8.79 Hz, 2H), 7.40 (d, *J* = 9.40 Hz, 2H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 13.93,

26.07, 54.98, 59.97, 113.86, 117.25, 127.67, 152.16, 160.67, 165.28; **MS** m/z (% rel. intensity): 300 (10), 298 (10), 254 (60), 252 (60), 239 (3), 228 (5), 219 (40), 191 (60), 174 (8), 163 (10), 145 (100), 131 (15), 115 (12), 103 (60), 91 (10), 77 (70), 63 (30), 40 (80); **Analysis:** $C_{13}H_{15}BrO_3$ requires C, 52.19; H, 5.05; found C, 52.13; H, 5.11%.

(Z)-ethyl 4-bromo-3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (123f):

Yield: 90%; crystalline solid; **mp:** 167-169^{0}C (recrystallized from pet. ether); **IR** ($CHCl_3$, cm^{-1}): 666, 756, 808, 858, 990, 1024, 1095, 1164, 1218, 1256, 1299, 1348, 1367, 1440, 1513, 1578, 1597, 1619, 1708, 2038, 2572, 2872, 2961, 3331; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.37 (t, *J* = 8 Hz, 3H), 1.66 (m, 2H), 1.89 – 1.95 (m, 6H), 3.89 (s, 3H), 4.27 (q, *J* = 6 Hz, 2H), 4.84 (s, 1H), 4.96 (s, 2H), 6.15 (s, 1H), 6.86 (d, *J* = 3 Hz, 1H), 7.11 (s, 1H), 7.13 (dd, *J* = 4 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.34, 24.14, 26.33, 32.86, 55.86, 60.27, 80.53, 111.59, 113.27, 117.72, 119.48, 130.83, 147.68, 151.67, 152.86, 165.53; **Analysis:** $C_{18}H_{23}BrO_4$ requires C, 56.41; H, 6.05; found C, 56.33; H, 6.00%.

(Z)-ethyl 3-(bromomethyl)-4,4-dimethylpent-2-enoate (123g):

Yield: 76%; **IR** ($CHCl_3$, cm^{-1}): 412, 430, 460, 688, 707, 730, 745, 877, 962, 1033, 1095, 1155, 1193, 1267, 1338, 1371, 1469, 1631, 1720, 1755, 2358, 2873, 2908, 2968, 3417; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.19 (s, 9H), 1.28 (t, *J* = 7.04 Hz, 3H), 4.15 (q, *J* = 7.04 Hz, 2H), 4.53 (s, 2H), 5.87 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.96, 24.18, 28.96, 37.60, 59.83, 117.73, 163.56; **MS** (m/z, % relative intensity): 248 (5), 235 (3), 205 (10), 189 (3), 169 (5), 155 (50), 141 (10), 127 (30), 123 (20), 109 (15), 95 (45), 79 (20), 57 (50), 41 (100); **Analysis:** $C_{10}H_{17}BrO_2$ requires C, 48.21; H, 6.88; found C, 48.13; H, 6.73%.

Typical experimental procedure for the synthesis of α, β-unsaturated esters from ketones (8a-g):

A 100 ml two-necked RB flask was charged with activated zinc (3.40 g, 44 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80^{o}C (oil bath temp.). A solution of ethyl bromoacetate (7.25 g, 44 mmol) and 4-chloroacetophenone **114b** (5.52 g, 40 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was

refluxed for 6 h, cooled to 25^0C and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether, evaporated under reduced pressure and then was subjected to dehydration using Dean-Stork apparatus with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. Water generated during the dehydration was separated azeotropically and then toluene was distilled off. The crude olefinic ester **113b** was purified by column chromatography packed with silica gel, eluting with EtOAc:pet. ether (1:10) to give 8.08 g (82%) of **113b**.

(E)-ethyl 3-phenylbut-2-enoate (113a):

Yield: 80%; gum; **IR** ($CHCl_3$, cm^{-1}): 428, 694, 756, 871, 950, 1000, 1026, 1045, 1076, 1170, 1215, 1242, 1272, 1344, 1365, 1377, 1448, 1492, 1575, 1600, 1627, 1656, 1710, 1959, 2360, 2979, 3031, 3058, 3028, 3303, 3398; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.4 Hz, 3H), 2.58 (s, 3H), 4.20 (q, *J* = 7.4 Hz, 2H), 6.11 (s, 1H), 7.33 – 7.54 (m, 5H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 14.10, 18.47, 59.29, 116.99, 121.71, 125.96, 127.96, 128.18, 132.05, 154.92, 166.14; **MS** m/z (% rel. intensity): 190 (70), 175 (5), 161 (50), 145 (100), 131 (5), 115 (90), 102 (10), 91 (40), 77 (20), 57 (20), 51 (30); **Analysis:** $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42; found C, 75.70; H, 7.36%.

(E)-ethyl 3-(4-chlorophenyl)but-2-enoate (113b):

Yield: 82%; viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 840, 887, 1056, 1109, 1182, 1288, 1493, 1578, 1594, 1641, 1725, 1915, 2116, 3001; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.31 (t, *J* = 7.0 Hz, 3H), 2.54 (s, 3H), 4.19 (q, *J* = 8 Hz, 2H), 6.08 (s, 1H), 7.29 (d, *J* = 8.74 Hz, 2H), 7.37 (d, *J* = 9.00 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.29, 17.60, 59.58, 117.62, 127.47, 128.61, 134.93, 140.55, 153.57, 165.95; **MS** m/z (% rel. intensity): 224 (M^+, 96), 209 (8), 195 (55), 179 (100), 152 (32), 115 (92); **Analysis:** $C_{12}H_{13}ClO_2$ requires C, 64.15; H, 5.83; found 64.12; H, 5.80%.

(E)-ethyl 3-(4-fluorophenyl)but-2-enoate (113c):

Yield: 90%; Yellow color viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 696, 770, 878, 1045, 1175, 1280, 1345, 1366, 1445, 1577, 1620, 1710, 2988, 3062; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.04 Hz, 3H), 2.56 (s, 3H), 4.22 (q, *J* = 7.04 Hz, 2H), 6.09 (s, 1H), 7.05 (d, *J* = 8.61 Hz, 2H), 7.45 (d, *J* = 9 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.25, 17.56, 59.52, 116.21, 118.13,

127.73, 130.66, 138.52, 153.47, 162.43, 165.78; **Analysis:** $C_{12}H_{13}FO_2$ requires C, 69.22; H, 6.29; found C, 69.12; H, 6.21%.

(E)-ethyl 3-(2-methoxyphenyl)but-2-enoate (113d):

Yield: 80%; gum; Yield**: 75%**; **IR** ($CHCl_3$, cm^{-1}): 754, 806, 883, 1026, 1112, 1163, 1228, 1247, 1274, 1369, 1434, 1461, 1490, 1579, 1598, 1639, 1712, 1726, 2837, 2937, 2977, 3072, 3452; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.72 Hz, 3H), 2.39 (s, 3H), 3.72 (s, 3H), 4.10 (q, *J* = 7.70 Hz, 2H), 5.77 (s, 1H), 6.77 (d, *J* = 8.25 Hz, 1H), 6.81 (t, *J* = 7.33 Hz, 1H), 7.02 (d, *J* = 7.79 Hz, 1H), 7.16 (d, *J* = 7.79 Hz, 1H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 13.90, 19.38, 54.90, 59.16, 110.73, 118.88, 120.19, 128.35, 129.09, 132.73, 156.02, 166.14; **Analysis:** $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.80; H, 7.30%.

(E)-ethyl 3-(4-methoxyphenyl)but-2-enoate (113e):

Yield: 93%; gum; **IR** ($CHCl_3$, cm^{-1}): 589, 668, 701, 759, 840, 928, 978, 1018, 1040, 1083, 1123, 1184, 1215, 1272, 1411, 1509, 1572, 1606, 1672, 1695, 1736, 2400, 3019, 3617; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.00 Hz, 3H), 2.47 (s, 3H), 3.72 (s, 3H), 4.11 (q, *J* = 7.05 Hz, 2H), 6.02 (s, 1H), 6.79 (d, J = 8.71 Hz, 2H), 7.35 (d, J = 8.70 Hz, 2H); **^{13}C-NMR** (500 MHz, $CDCl_3$): δ 14.13, 17.34, 54.99, 59.40, 113.65, 115.13, 127.41, 134.08, 154.52, 160.31, 166.73; **MS** m/z (% rel. intensity): 220 (90), 205 (3), 191 (10), 175 (100), 161 (5), 148 (90), 131 (15), 115 (20), 103 (15), 91 (25), 77 (20), 63 (10), 51 (12); **Analysis:** $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.72; H, 7.26%.

(E)-ethyl 3-(3-(cyclopentyloxy)-4-methoxyphenyl)but-2-enoate (113f):

Yield: 88%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.32 (t, *J* = 7.15 Hz, 3H), 1.61 – 1.64 (m, 2H), 1.85 – 1.92 (m, 6H), 2.55 (s, 3H), 3.84 (s, 3H), 4.18 (q, *J* = 6 Hz, 2H), 4.79 – 4.80 (m, 1H), 6.02 (s, 1H), 6.78 (d, *J* = 10 Hz, 1H), 6.96 (s, 1H), 7.00 (d, *J* = 3.72 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.27, 17.67, 23.93, 32.74, 55.94, 59.60, 80.63, 111.51, 113.31, 115.37, 119.22, 134.59, 147.36, 151.13, 155.04, 166.93; **Analysis:** $C_{18}H_{24}O_4$ requires C, 71.03; H, 7.95; found C, 71.00; H, 7.90%.

(E)-ethyl 3,4,4-trimethylpent-2-enoate (113g):

Yield: 82%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.26 (t, *J* = 7.05 Hz, 3H), 2.14 (s, 3H), 4.10 (q, *J* = 7.04 Hz, 2H), 5.68 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.92, 28.08,

37.34, 58.66, 115.66, 166.10; **Analysis:** $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66; found C, 70.52; H, 10.52%.

Typical experimental procedure for the synthesis of α, β-unsaturated esters from aryl boronic acids:

A 25 ml flask with reflux condenser attached was charged with 4-choro-phenylboronic acid **115b** (0.156 g, 1 mmol), ethyl crotonate (.228 g, 0.25 ml, 2 mmol), Na_2CO_3 (0.159 g, 1.5 mmol), catalytic amount of $Pd(OAc)_2$ (0.022 g, 0.1 mmol) and DMF (5 ml) under oxygen atmosphere (1 atm.). The flask was heated at 50^0C for 12 h. After completion of reaction (monitored by TLC), the reaction mixture was allowed to come to 25^0C. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 10ml). The combined organic extracts were washed with water (5 ml) followed by brine (10ml) and concentrated under reduced pressure to give crude product. The crude material, which was then purified by column chromatography eluting 10% ethyl acetate in petroleum ether to get the (0.183 g, 82%) olefinic esters **113b**.

Preparation of 3-(Cyclopentyloxy)-4-methoxybenzaldehyde (125):

To a mixture of isovaniline 124 (3.04 g, 20 mmol) and K_2CO_3 (1.76 g, 20 mmol) in DMF (40 ml) was added cyclopentyl bromide (3.73 g, 25 mmol) through syringe at 50 ^{0}C with vigorous stirring. After completion of reaction (monitored by TLC), the reaction mixture was allowed to come to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford ether 125 (3.74 g).

Yield: 85%; yellow solid; **mp:** 107-110^{0}C (recrystallized from EtOAc); **IR** ($CHCl_3$, cm^{-1}):426, 446, 452, 590, 742, 868, 902, 936, ,968, 1022, 1238, 1362, 2038, 2360, 2606, 2720, 3078, 3354, 3624; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.63 – 2.00 (m, 8H), 3.93 (s, 3H), 4.86 (m, 1H), 6.65 (d, *J* = 8 Hz, 1H), 7.41 – 7.45 (m, 2H), 9.84 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 23.66, 32.30, 55.64, 80.01, 110.45, 111.74, 125.85, 129.60, 147.80, 155.04, 190.47; **MS** (m/z, % relative intensity): (M^+ 220, 10), 177 (5), 151 (100), 137 (10), 122 (12), 108 (15), 95

(8), 79 (20), 65 (20); **Analysis:** $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32; found C, 70.63; H, 7.25%.

Preparation of 1-(3-(Cyclopentyloxy)-4-methoxyphenyl)ethanol (126):

A dry, argon flushed 100 ml round-bottom flask, equipped with a magnetic stirring (bar, reflux water condenser and dropping funnel, was charged with 2-3 crystals of iodine, and magnesium turnings (0.675 g, 28 mmol) in dry diethyl ether (20 ml) at 25^0C. Then methyl iodide (3.8 g, 2.12 ml, 28 mmol) was added dropwise at RT in diethyl ether. After stirring for 3-4 hours, the dropping funnel was replaced by a rubber septum. The reaction flask was cooled in crushed ice water, followed by slow addition of aldehyde **125** (5.0 g, 23 mol) in ether over a period of 10 minutes. Then it was allowed to stir over night. The reaction mixture was quenched with saturated solution of NH_4Cl, poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic fractions were washed with brine, then dried over Na_2SO_4 and concentrated under reduced pressure to afford crude alcohol **126**. The crude alcohol **126** was purified by column chromatography packed with silica gel, eluting with pet ether: EtOAc (5:1) gave 4.12 g of **126**.

Yield: 76%; grey solid; **mp**: 123-125^{0}C (recrystallized from EtOAc + pet. ether); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.43 (d, J = 6 Hz), 1.86 – 1.99 (m, 8H), 3.81 (s, 3H), 4.75 – 4.84 (m, 2H), 6.76 – 6.92 (m, 3H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 22.93, 23.85, 24.51, 24.91, 32.74, 56.23, 69.98, 74.10, 74.43, 80.49, 112.47, 113.46, 117.65, 118.57, 118.72, 137.28, 138.83, 147.98, 149.38; **MS** (m/z, % relative intensity): (M^+ 236, 20), 218 (5), 196 (5), 168 (40), 153 (100), 135 (10), 125 (40), 107 (5), 93 (17), 77 (10), 65 (12); **Analysis**: $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53; found C, 71.13; H, 8.51%.

Preparation of 1-(3-(Cyclopentyloxy)-4-methoxyphenyl)ethanone (114f):

To a mixture of alcohol **126** (3.54 g, 15 mmol) in diethyl ether (40 ml) was added drop wise through addition funnel freshly prepared chromic acid solution (15 ml) under ice-cold condition with vigorous stirring. The reaction mixture was allowed to come to room temperature and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (3 x 15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under

reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford cyclopentyl acetophenone **114f** (2.63 g).

Yield: 75%; brown colored solid; **mp:** 127-129^{0}C (crystallized from EtOAc); **IR** ($CHCl_3$, cm^{-1}): 408, 430, 442, 456, 466, 472, 588, 642, 668, 776, 808, 878, 898, 1076, 1132, 1178, 1216, 1356, 1584, 1676, 2360, 2870, 2960; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.72 – 1.91 (m, 8H), 2.56 (s, 3H), 3.91 (s, 3H), 4.81 – 4.90 (m, 1H), 6.85 (d, *J* = 10 Hz, 1H), 7.53 – 7.57 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 23.92, 26.05, 32.63, 55.94, 80.42, 110.38, 113.54, 122.84, 130.30, 147.54, 154.23, 196.68; **Analysis:** $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74; found C, 71.75; H, 7.68%.25^{0}C

Preparation of 2-Methoxyphenyl acetate (128):

To a mixture of guaiacol **127** (2.48 g, 20 mmol) and acetic anhydride (40 ml) was added three drops of conc. H_2SO_4 with vigorous stirring. The reaction mixture was heated at 100^{0}C for 6h and then allowed to come to 25^{0}C and stirring continued for 3 h (monitored by TLC). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford acetate **128** (3.22 g).

Yield: 97%; colorless liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.78 (s, 3H), 6.89 – 7.14 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.28, 55.57, 112.32, 120.52, 122.62, 126.62, 151.03, 168.64; **MS** (m/z, % relative intensity): (M^+ 166, 5), 124 (100), 109 (90), 95 (8), 91 (4), 81 (60), 77 (18), 64 (15); **Analysis:** $C_9H_{10}O_3$ requires C, 65.05; H, 6.07; found C, 64.93; H, 6.11%.

Preparation of 5-Bromo-2-methoxyphenyl acetate (129):

A solution of guiacolic ester **128** (2.59 g, 15.62 mmol) and NBS (2.81 g, 17.2 mmol) in dry CH_3CN (35 ml) was heated at 60 ^{0}C under nitrogen atmosphere for 10 h. The resulting reaction mixture was cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 ml). The combined organic extracts were

washed with saturated solution of sodium sulfite (15 ml), water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford pure 3.75 g of pale yellow color gum, bromoester **129**.

Yield: 99%; pale yellow color gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.75 (s, 3H), 6.77 (d, *J* = 10 Hz, 1H), 7.18 (d, *J* = 3 Hz, 1H) 7.24 – 7.29 (dd, *J* = 10 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.21, 55.79, 111.66, 113.54, 125.78, 129.34, 140.19, 150.41, 168.23; **MS** (m/z, % relative intensity): (M^+ 244, 10), 204 (100), 187 (60), 173 (3), 161 (10), 143 (4), 123 (5), 108 (5), 94 (7), 79 (20), 71 (3), 63 (8); **Analysis**: $C_9H_9BrO_3$ requires C, 44.11; H, 3.70; found C, 44.00; H, 3.65%.

Preparation of 5-Bromo-2-methoxyphenol (130):

A 25 ml flask was charged with ester **129** (3.66 g, 15 mmol), 10% $NaHCO_3$ (2.5 g, 22 mmol) and MeOH (15 ml) under nitrogen atmosphere. The flask was allowed to reflux for 3 hours. Then EtOAc (25 ml) was added to reaction mixture. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (3:1) as eluent to phenol **130** (2.85 g).

Yield: 95%; yellow solid; **mp**: 102-105^{0}C (recrystallized from EtOAc); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.77 (s, 3H), 6.58 (d, *J* = 10 Hz, 1H), 6.83 – 6.89 (dd, *J* = 10 Hz, 1H), 6.97 (d, *J* = 2 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 56.05, 111.88, 113.39, 117.95, 122.76, 145.88, 146.58, 159.74; **MS** (m/z, % relative intensity): (M^+ 204, 20), 202 (20), 189 (20), 160 (20), 131 (5), 116 (3), 107 (7), 91 (5), 79 (900), 62 (100) ; **Analysis**: $C_7H_7BrO_2$ requires C, 41.41; H, 3.48; found C, 41.38; H, 3.52%.

Preparation of 4-Bromo-2-(cyclopentyloxy)-1-methoxybenzene (131):

To a mixture of phenol **130** (2.04 g, 10 mmol) and K_2CO_3 (1.2 g, 20 mmol) in DMF (40 ml) was added cyclopentyl bromide through syringe at 50 ^{0}C with vigorous stirring. After completion of reaction (monitored by TLC), the reaction mixture was allowed to come to room temperature. The organic layer was separated and the aqueous layer was extracted with

EtOAc (2 x 15 ml). The combined organic extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude product, which was further purified by column chromatography on silica gel using pet. ether: EtOAc (9:1) as eluent to afford ether **131** (2.42 g).

Yield: 89%; yellowish liquid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.59 – 1.87 (m, 8H), 3.79 (s, 3H), 4.71 (m, 1H) 6.67 (d, *J* = 10 Hz, 1H), 6.96 – 7.00 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 23.55, 32.27, 55.53, 80.20, 112.14, 112.91, 117.54, 122.80, 148.13, 148.97; **MS** (m/z, % relative intensity): (M^+ 272, 10), 270 (10), 202 (100), 187 (60), 173 (5), 159 (10), 142 (5), 123 (7), 108 (7), 94 (20), 79 (70), 63 (40); **Analysis:** $C_{12}H_{15}BrO_2$ requires C, 53.15; H, 5.58; found C, 53.10; H, 5.50%.

Preparation of 3-(Cyclopentyloxy)-4-methoxyphenylboronic acid (115f):

To a mixture of Bromo ether **131** (4.56 g, 20 mmol) in diethyl ether (40 ml) was added drop wise through syringe 1 M n-BuLi solution in hexane (15 ml) at -78^{0}C with vigorous stirring. The reaction mixture was stirred for 1 h and then was added $B(OMe)_3$ (2 ml). After stirring for 1 more h, the reaction mixture was quenched with sat. NH_4Cl solution (10 ml) and organic layer was separated and the aqueous layer was extracted with ether (2 x 15 ml). The combined ethereal extracts were washed with water (15 ml) followed by brine (15 ml) and concentrated under reduced pressure to give crude boronic acid **115f** (0.236 g), which was used as it is further reactions.

Yield: 15%; grey color solid; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.82 (m, 8H), 3.95 (s, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 24.25, 33.01, 55.94, 80.59, 121.34, 129.66, 147.21, 153.90; **Analysis:** $C_{12}H_{17}BO_4$ requires C, 61.05; H, 7.26; found C, 61.10; H, 7.20%.

SECTION III:

Co-catalyzed reductive cyclization of γ-cyano-α,β-unsaturated esters: Enantioselective Synthesis of (*R*)-4-(4-fluorophenyl)piperidin-2-one

1.2.1 Introduction

Chiral drugs have long been used as therapeutic agents, but in most cases only in racemic form. Over the last 20 years, however, great advances in production technology and quality control techniques have made chirality an important issue. In the development process of a new drug, differentiation due to chirality is now an integral part of preclinical and clinical investigations. The choice of racemate must be justified and the criteria for this will become more demanding in the future. [83]

The members of a pair of enantiomers often show different pharmacological and metabolic characteristics. The synthesis of homochiral drugs has become a key issue not only in academic research but also in the pharmaceutical industry.[84] Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will exhibit different responses. Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. It has been shown for many pharmaceuticals that only one enantiomer contains all the desired activity, and the other is either totally inactive or highly toxic.

Six-membered nitrogen-containing heterocycles are abundant in nature and exhibit diverse and important biological properties.[85] Alkaloids that contain the piperidine ring continue to be the targets of extensive synthetic interest, partly because there are many

biologically active natural products of this type.[86] Accordingly, the development of a general method for the preparation of piperidine derivatives has been the subject of considerable synthetic efforts.[87] δ-Lactams have been generally regarded as the precursors of the corresponding piperidines.

4-Arylpiperidine is an important structural element in a number of biologically active compounds, possibly due to the similarity to aryl alkylamine pharmacophore common to neurotransmitters like serotonin [5-hydroxytryptamine (5-HT)], dopamine (DA), noradrenaline (NA) and to antagonists of opiate receptors. Drugs that modulate the physiological and pathophysiological actions of 5-HT are useful or potentially useful in the treatment of a variety of human diseases, including depression, anxiety, alcoholism, chronic pain, emesis and eating disorders such as obesity and bulimia.[88] Such compounds can be exemplified by the antipsychotic 5-HT- and DA-antagonists, preclamol **134**, haloperidol **135**,[89] the analgesic opioid agonist, meperidine **136**,[90] and the selective serotonin reuptake inhibitor (SSRI), paroxetine **132** [Paxil®, Seroxat®], femoxetine **133** (**Fig. 16**).[91]

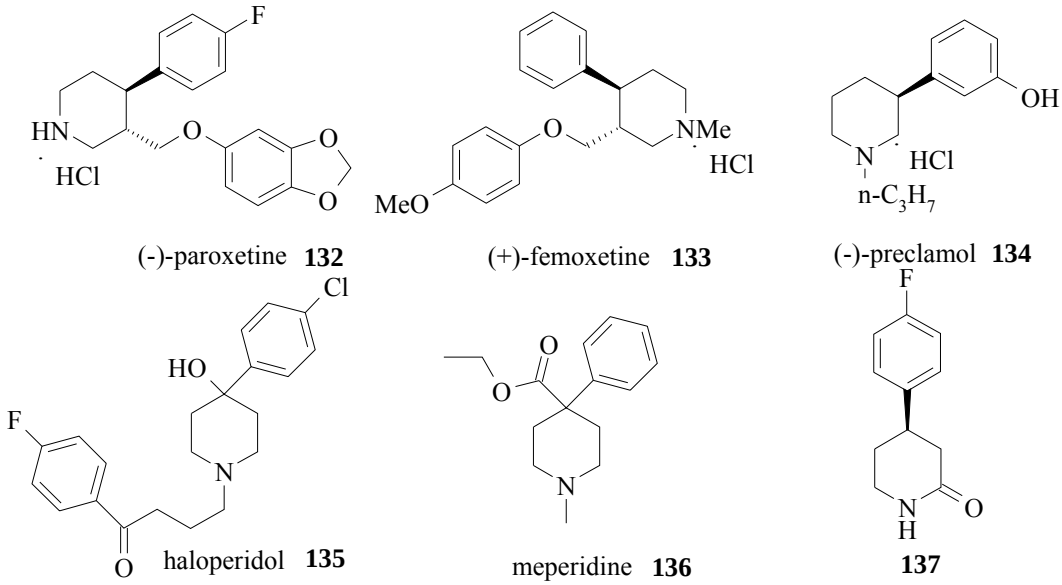


Fig. 16: Biologically important piperidines and piperidin-2-ones

1.2.2 The Pharmacology of (-)-paroxetine

Paroxetine is a potent and selective inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine; 5-HT), which was previously reviewed as an antidepressant drug in 1991.[92] Paroxetine has also been studied in several other disorders with a presumed serotonergic component, primarily obsessive compulsive disorder (OCD) and panic disorder.[93] In short term clinical trials in patients with depression, paroxetine produced clinical improvements that were significantly greater than those with placebo and similar to those achieved with other agents including tricyclic antidepressants (TCAs), maprotiline, nefazodone and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine and sertraline.[94] Long term data suggest that paroxetine is effective in preventing relapse or recurrence of depression in patients treated for up to 1 year. In the elderly, the overall efficacy of paroxetine was at least as good as that of comparator agents. In short term clinical trials involving patients with OCD or panic disorder, paroxetine was significantly more effective than placebo and of similar efficacy to clomipramine. Limited long term data show that paroxetine is effective in maintaining a therapeutic response over periods of 1 year (OCD) and up to 6 months (panic disorder). Preliminary data suggest that paroxetine has potential in the treatment of social phobia, premenstrual dysphoric disorder and chronic headache. Like the other SSRIs, paroxetine is better tolerated than the TCAs, causing few anticholinergic adverse effects. Serious adverse effects associated with paroxetine are very rare.

With adjustment for the number of previous suicide attempts, paroxetine showed significant efficacy in the prevention of recurrent suicidal behavior. Paroxetine was also significantly more effective in patients who met fewer than 15 criteria for cluster B personality disorders than in those who met more than 15 criteria. Overall, paroxetine was not

significantly different from placebo in its effect on depressive mood, hopelessness, and anger. However, the data suggest that paroxetine may have some temporary effect in reducing anger.

Social phobia, also known as social anxiety disorder, is a highly prevalent disorder with significant morbidity. Patients with social phobia frequently develop co-morbid psychiatric disorders such as depression and substance abuse, and the disorder impacts significantly on social and occupational functioning. It has been suggested that the selective serotonin reuptake inhibitors (SSRIs) are useful in the management of this disorder, but few controlled trials have been undertaken in this regard.

In conclusion, paroxetine is effective and well tolerated, and suitable as first-line therapy for depression. It also appears to be a useful alternative to other available agents for the treatment of patients with OCD or panic disorder.

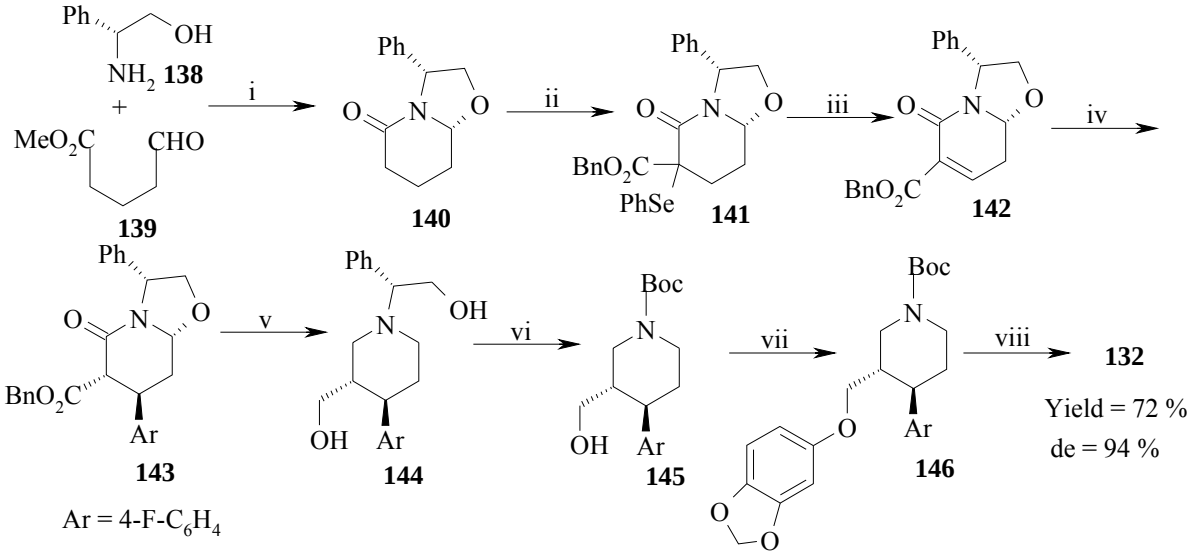
1.2.3 Review of Literature

Literature search revealed that due to biological importance of (-)-paroxetine **132**, several enantiocontrolled synthetic approaches have been reported,[95-106] which are described below.

Amat's approach(2000)[95]

Amat's approach consists of reaction of (*R*)-phenylglycinol **138** with methyl 5-oxopentanoate to give bicyclic lactam *cis*-**140,** which was converted to the unsaturated lactam **142**. On treatment with lithium alkyl (or aryl) cyanocuprates, this chiral building block underwent conjugate addition to give enantiopure *trans*-3,4-substituted 2-piperidone derivative **142**. Synthesis starts with bicyclic lactam generation of (*R*)-phenylglycinol **138** and methyl 5-oxopentanoate **139** at reflux temperature for 36 h under neutral conditions, with azeotropic removal of water, in 86% yield. Acylation and selenation of **140** at -78 ^{0}C gave **141** in 77 % yield. Deselenation with O_3 yielded olefin **142**. Olefin is further subjected to aryl

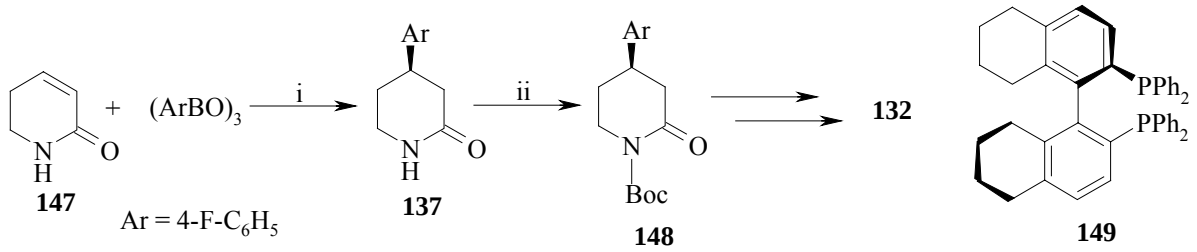
cyano cuptrate conjugate addition producing arylated product **143** in 64 % yield. Reductive cleavage of arylated bicyclic lactam **143** produced diol **144** in 75 % yield. After debenzylation of **144** with $Pd(OH)_2$ was protected with Boc yielding **145** in 57 % yield. Further Boc protected piperidine **145** was mesylated and etherified affording **146** in 66 % yield. Deprotection of Boc with TFA generated (-) paroxetine **132** in 72 % yield (**Scheme 40**).



Scheme 40: i Toluene, 110 ^{0}C, azeotropic water removal, 36h, 86 %; ii LiHMDS, $ClCO_2Bn$, PhSeBr, THF, -78 °C, 77%; iii O_3, CH_2Cl_2, -78 °C; then O_2, 25 °C; iv ArCu(CN)Li, THF, -78 °C, 64%; v (a) HCO_2NH_4, Pd-C, MeOH, 25 °C, then toluene, reflux, 85%; (b) $AlCl_3$, $LiAlH_4$, THF, -78 °C to 25 °C, 50%; vi H_2, (*t*-BuOCO)$_2$O, 20% $Pd(OH)_2$-C, AcOEt, 25 °C, 57%; vii MsCl, pyr, 10 °C, then NaH, sesamol, THF, reflux, 66%; viii TFA, CH_2Cl_2, RT, 72%.

Hayashi's approach (2001)[96]

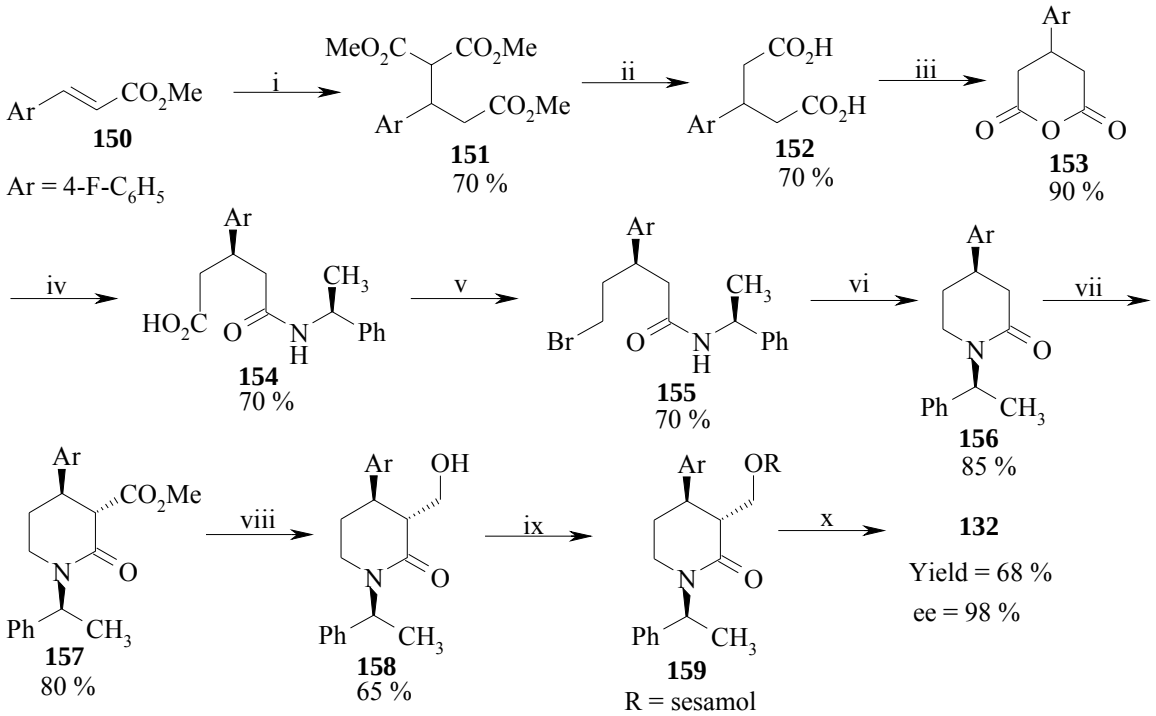
Hayashi's approach consists of catalytic asymmetric synthesis of 4-aryl-2-piperidinone by asymmetric 1, 4-addition of arylboron reagent to 5,6-dihydro-2(1*H*)-pyridinone **137** in the presence of a chiral bisphosphine ligand **149** with rhodium catalyst. For introducing 4-fluorophenyl group, the use of 4-fluorophenylboroxine and 1 equiv (to boron) of water was employed at 40 °C to give 70 % yield of the arylation product **137** with 98% ee. (*R*)-4-(4-fluorophenyl)-2-piperidinone **137** was protected with Boc. The product **148** obtained here is the key intermediate for the synthesis of (-)-Paroxetine **132** (**Scheme 41**).



Scheme 41: i $Rh(acac)(C_2H_4)_2$ (3 mol %), **149** (3.3 mol %), dioxane:H_2O (10:1), 40 °C, 3 h, 98 % ee, 70 %. ii $(Boc)_2O$, DMAP, CH_3CN, reflux, 82 %.

Liu's approach (2001)[97]

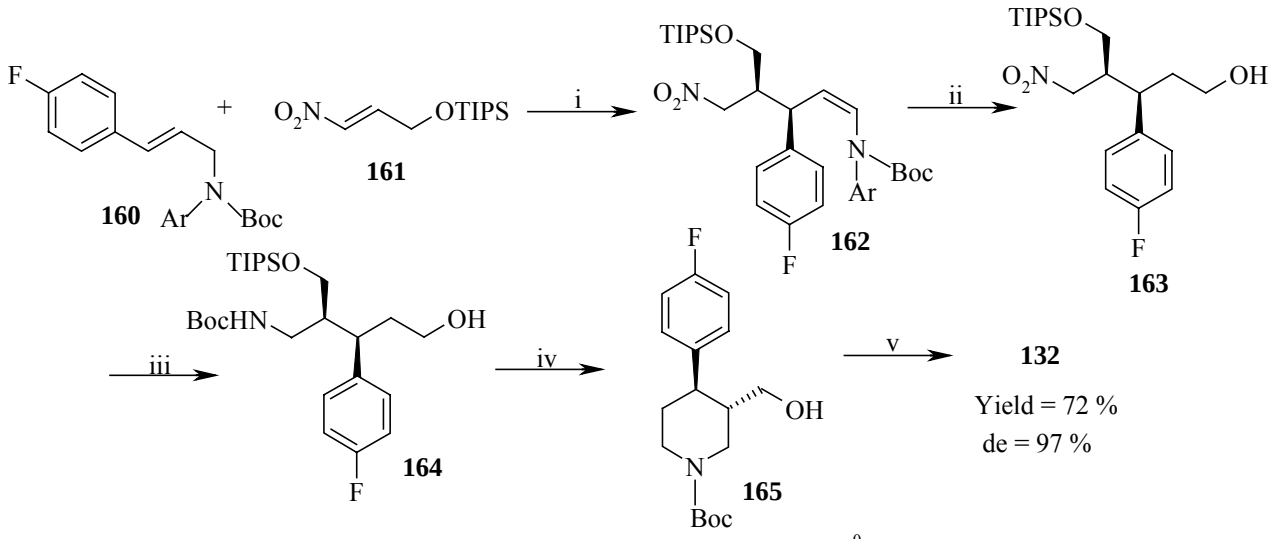
Diacid **152** was prepared from 4-fluorocinnamic acid methyl ester **150** in three steps (Michael addition to ester **150**, hydrolysis of triester **151**, and decarboxylation of acid). The prochiral 3-substituted glutaric anhydride **153** was then obtained by dehydration of **152** in acetyl chloride. Desymmetrisation of *meso*-3-substituted glutaric anhydride **153** with (*S*)-methylbenzylamine was effected in toluene at -78°C generating acid **154** which was further reduced and brominated leading to piperidin-2-one moiety **156**. After acylation the piperidin-2-one moiety was reduced with lithium aluminum hydride providing 3-hydroxymethyl piperidine **158**. Further mesylation, etherification, deprotection, leads to (-)-paroxetine **132** (**Scheme 42**).



Scheme 42: i NaOMe, $CH_2(CO_2Me)_2$, MeOH, reflux, 20 h, 70%; ii (a) 1N NaOH, reflux, 20 h; (b) conc. HCl, reflux, 20 h, 70% (two steps); iii AcCl, reflux, 20 h, 90%; iv (*S*)-methylbenzylamine, EtN_3, toluene, -78°C, 10h, 25^{0}C, 10h, 70%; v (a) Et_3N, isobutyl chloroformate, THF, -78 to 0°C, 20 h; (b) $NaBH_4$, H_2O, 0–25°C, 20 h, 86%; (c) PBr_3, conc. HBr, 0–25°C, 4 days, 70%; vi NaH, THF, reflux, 20 h, 85%; vii LDA, MeO_2CCN, THF, -78^{0}C, 4h, 80 %; viii $LiAlH_4$, THF, reflux, 72 h, 65%; ix (a) MsCl, CH_2Cl_2, RT, 20 h; (b) sesamol, Na, *n*-PrOH, reflux, 36 h; (c) HCl, 64%; x H_2, Pd–C, MeOH, 68%.

Beak's approach (2001)[98]

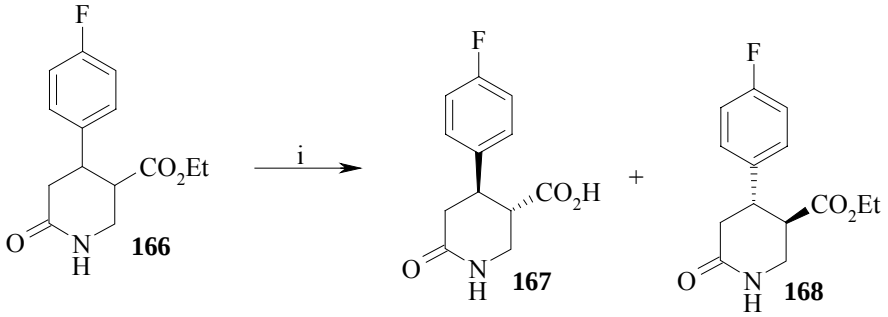
Treatment of **160** with *n*-BuLi in the presence of (-)-sparteine under standard conditions followed by conjugate addition to nitroalkene **161** provided the desired enecarbamate (*S*,*S*)-**162** in 83% yield as a single diastereomer. Hydrolysis and reduction of the resulting aldehyde provided nitro alcohol **163** in 88% yield. Reduction of the nitro functionality by transfer hydrogenation and subsequent Boc-protection afforded **164** in 95% yield. Cyclization and deprotection afforded **165** in 83% yield. Mesylation followed by displacement with sesamol and subsequent deprotection provided **132** in 72% yield and 97 % de (11 steps, 41% from **160**) (**Scheme 43**).



Scheme 43: i n-BuLi (1 equiv.), (-) sparteine (1.2 equiv.), toluene, -78 ^{0}C, de 99 %, 83 %; ii (a) HCl, $CHCl_3$, 25^{0}C.; (b) $NaBH_4$, MeOH, 25^{0}C, 86 %; iii (a) cat. Pd/C, HCO_2NH_4, MeOH, 25^{0}C.; (b) $(Boc)_2O$, CH_2Cl_2, 25^{0}C, 95 %; iv (a) MsCl, Et_3N, CH_2Cl_2, 25^{0}C.; (b) KO*t*-Bu, THF, reflux, 12h.; (c) TBAF, MeOH, 25^{0}C, 83 %.; v (a) MsCl, Et_3N, CH_2Cl_2, 25^{0}C.; (b) NaH, sesamol, DMF, 100 ^{0}C, 6h.; (c) TFA, MeOH, 25^{0}C, 3h, 97 % de, 72 %.

Guisan's approach (2002)[99]

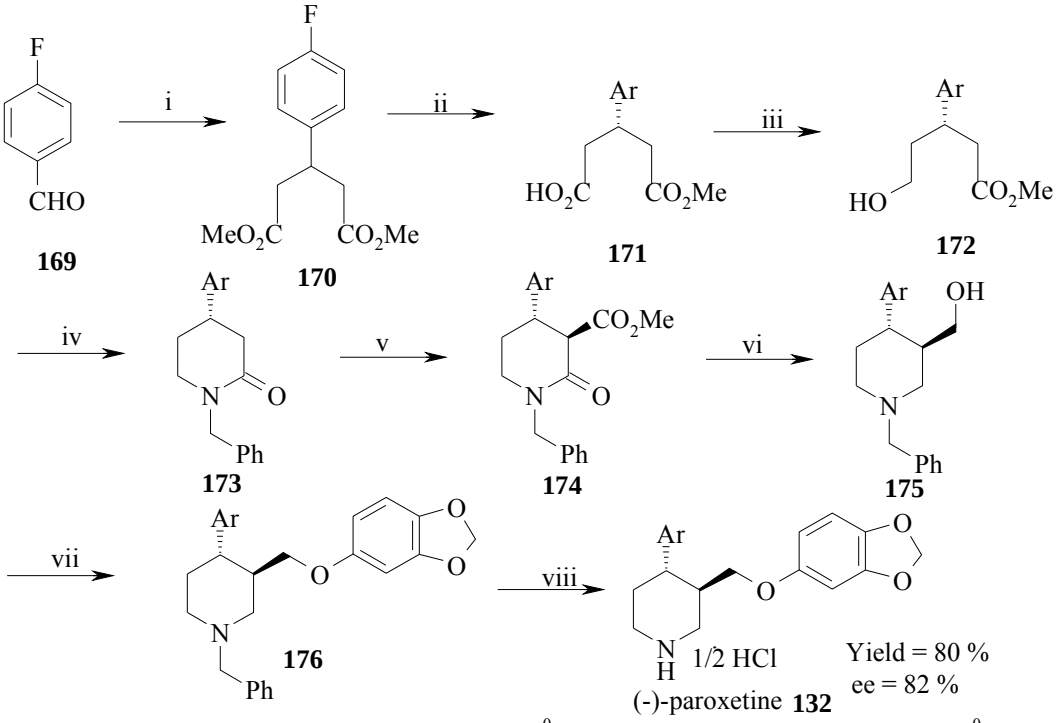
Guisan's approach contains formal synthesis of (-) paroxetine by enantioselective hydrolysis of racemic piperidin-2-one **166** using a commercially available lipase from *C. antarctica A* (CAL-A). Resolution was performed using a racemic mixture with a substrate concentration of 50 mM. The acid **167** was separated and further transformed to (-)-paroxetine **132** (**Scheme 44**).



Scheme 44: i CAL-A, $NaPO_4$ (5 ml, 10mM, pH 7), 45 ^{0}C, substrate concentration 2mM, 50h, 45 %.

Yu's approach (2003)[100]

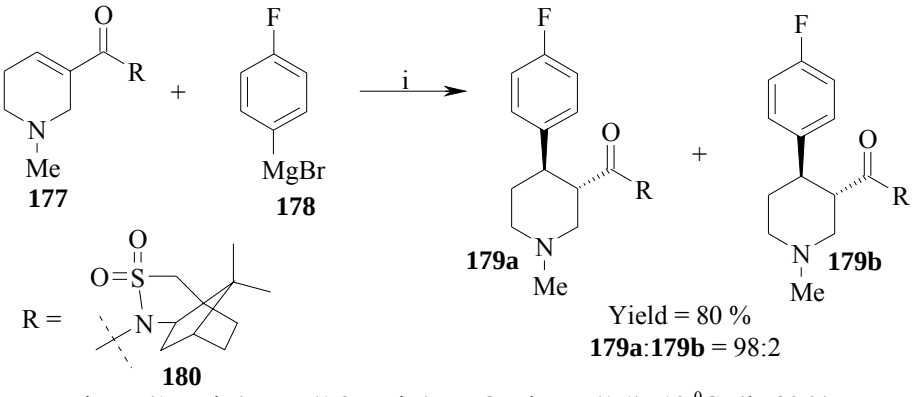
(-)-Paroxetine was produced in eight steps starting from 4-Fuorobenzaldehyde. The synthesis (**Scheme 45**) begins with the preparation of bis ester **170**. Enzymatic hydrolysis of **170** with *pig liver esterase* afforded optically active acid ester **171** in 86% yield and 95% ee. Reduction of the acid functionality of **171** with borane provided alcohol **172** which was further mesylated and treated with benzylamine to provide lactam **173** in 82% yield and 99% ee. Acylation of **173** afforded **174** (88%). Reduction of **174** with either LAH (71%) or BH_3.THF in refluxing THF (92%) gave amino alcohol **175**. Etherification with sesamol (80%) and hydrogenolysis of the benzyl group (93%) completed the synthesis of (-)-paroxetine **132** (**Scheme 45**).



Scheme 45: i (a) Ethyl acetoacetate, NaOH, 150 ^{0}C, 75 %; (b) aq. 10 % HCl, MeOH, 60 ^{0}C, 75 %; ii PLE (pig liver esterase) (p^H 7.0), 10 % aq. acetone, 95 % ee, 86 %; iii BH_3-DMS, THF, 94 %; iv (a) MsCl, Et_3N, toluene; $BnNH_2$, Et_3N, toluene, 99 % ee, 82 %; v NaH, NaOMe, $(MeO)_2CO$, toluene, 100 ^{0}C, 88 %; vi (a) BH_3-THF, 93 %; vii MsCl, Et_3N, toluene; (b) sesamol, NaH, DMF, 60 ^{0}C, 80 %; vii (a) cat. 5 % Pd/C, H_2 (70 psi), iPrOH, AcOH; (b) HCl gas.

Murthy's approach (2003)[101]

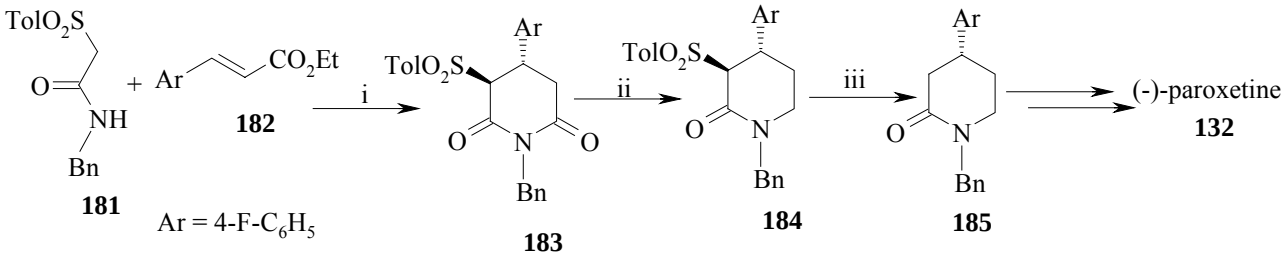
Keshava Murthy's approach deals with the synthesis of 3, 4 disubstituted piperidine, a key intermediate in the (-)-paroxetine synthesis by the asymmetric conjugate addition of 4-fluorophenylmagnesium bromide **178** with chiral α, β-unsaturated ester **177**. The most selective auxiliary was found to be Oppolzer's (1*S*)-(-)-camphorsultam **180** (**Scheme 46**).



Scheme 46: i **177** (1 equiv.), **178** (1.3 equiv.), Et_2O:toluene (1:1) -10 ^{0}C, 4h, 80 %.

Chang's approach (2003)[102]

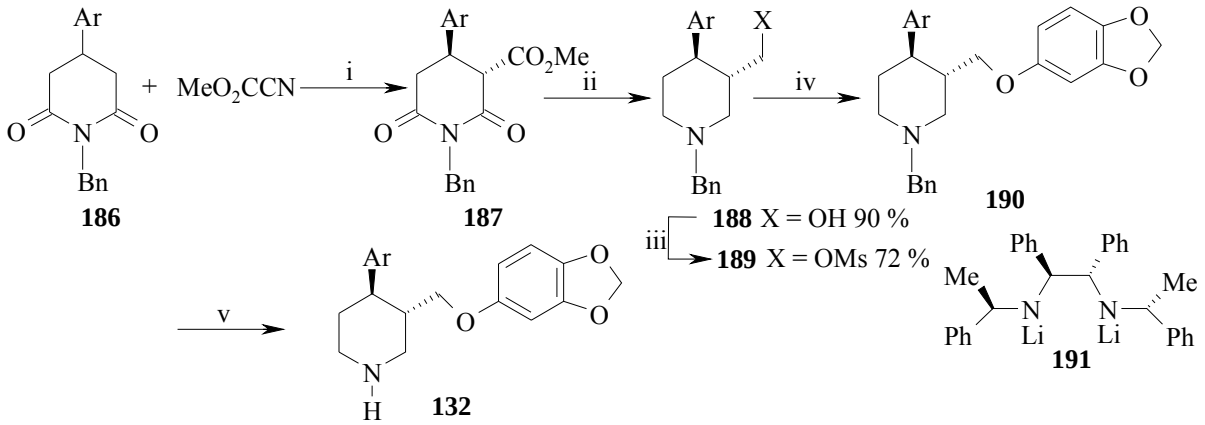
Chang's approach provides method for the preparation of 4-substituted 3-sulfonyl-δ-lactams **184** *via* regioselective reduction of N-alkyl-3-sulfonyl glutarimide **183**. Reduction of δ-lactams **184** by desulfurization with Na-Hg and $NaPO_4$ leads to **185**, an important intermediate in (-)-paroxetine **132** synthesis (**Scheme 47**).



Scheme 47: i NaH, THF, 80 ^{0}C, 1h, 75 %; ii Et_3N, $LiAlH_4$, THF, 80 ^{0}C, 3h, 76 %; iii Na-Hg, $NaPO_4$, MeOH, 25 ^{0}C, 2h, 90 %.

Simpkins's approach (2003)[103]

Simpkins's approach involves asymmetric desymmetrisation of prochiral imide **186** by a chiral lithium amide base **191**. A short reaction sequence, starting with a desymmetrisation of a 4-arylglutarimide **186**, by use of **191** in its bis-lithiated form enabled the formation of the desired imide **187** in 71 % yield, with 97 % of ee, and as a single diastereoisomer. Reduction of imide **187** (97% ee) gave piperidine alcohol **188**, to which the appropriate sesamol side-chain was introduced by conventional means, *via* the intermediate mesylate **189**. Deprotection of the piperidine nitrogen then gave the desired drug substance **132** as the free amine after base treatment in 54 % yield (**Scheme 48**).

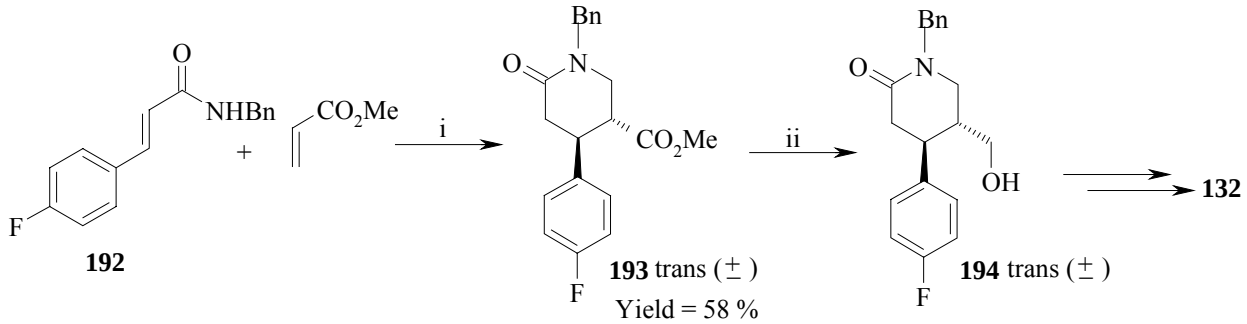


Scheme 48: i n-BuLi (1 equiv.), (-) sparteine (1.2 equiv.), toluene, -78 ^{0}C, 97 % ee, 71 %; ii $LiAlH_4$ (5 equiv.), THF, reflux, 12h, 90 %; iii MsCl, pyridine, CH_2Cl_2, 72 %; iv sesamol (5 equiv.), NaOMe (5 equiv.), MeOH, 12h, 55 %; v (a) $CH_3CHClOCOCl$, 0 to 25^{0}C and then reflux 3h; (b) MeOH, NaOH, reflux, 2h, 54 %.

Takasu's approach (2003)[104]

Takasu's approach for recemic paroxetine synthesis makes use of intermolecular aza-double Michael reaction leading to functionalized piperidin-2-ones **193**. The method allows to utilize α, β-unsaturated amides as a synthon of piperidine nucleus. The synthesis begins with reaction of the unsaturated amide **192** with acrylate in the presence of TBSOTf, Et_3N (0.7 equiv.) and *t*BuOH (0.25 equiv.) in dichloroethane. This provides a mixture of *trans*- and *cis*-3,4-disubstituted piperidinones which without purification is treated with NaOMe to afford

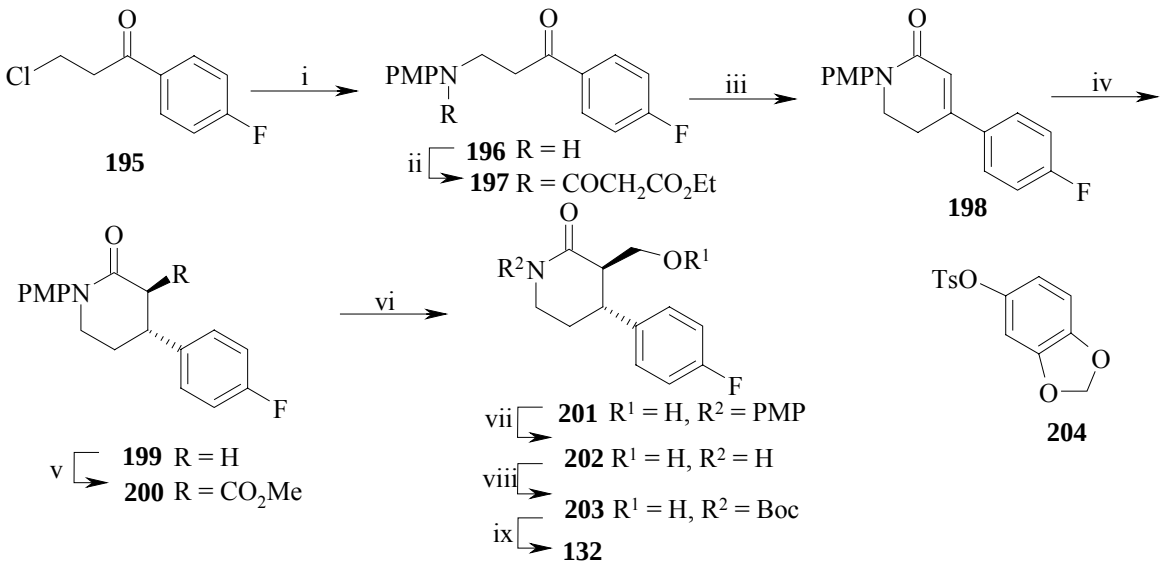
trans-**193** in 58% overall yield (for two steps). Reduction of **193** with $LiAlH_4$ quantitatively furnishes the known piperidinol **194**, transformation of which into (-)-paroxetine (**132**) has been reported[100] (**Scheme 49**).



Scheme 49: i (a) **192** (1.0 equiv.), TBSOTf (1.2 equiv.), Et_3N (0.7 equiv.), *t*BuOH (0.25 equiv.), $ClCH_2CH_2Cl$, RT; (b) NaOMe, MeOH–toluene, reflux (58% for two steps); ii $LiAlH_4$ (2 equiv.), THF, reflux, 56 %.

Buchwald's approach (2003)[105]

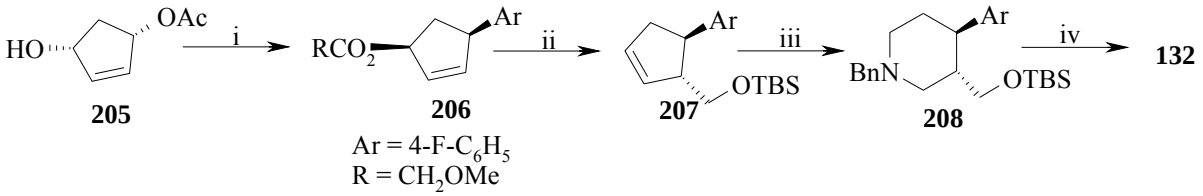
Buchwald *et al.* have employed Cu(I)/*p*-tolBINAP catalyst for the enantioselective 1,4-reduction of lactams, which is outlined in **Scheme 50**. 4-Fluoro-3-chloropropiophenone was converted to **196** in 75% yield. The amidation product **197** on treatment with NaOEt produced lactam **198** in 76% yield. The product **198** was subjected to asymmetric reduction using Cu(I)/*p*-tolBINAP as catalyst with 16 equiv. each of PMHS and *t*-AmOH affording **199** in 90% yield and 90% ee. This intermediate was converted to **201** in two steps (81% overall yield) using previously reported conditions.[100] The oxidative removal of the PMP functionality and protecting with $(Boc)_2O$ afforded **203** in 75% yield. Etherification is achieved by treating **203** with tosylate **204** in the presence of Cs_2CO_3 at 130 ^{0}C in xylene. Removal of the Boc group gave **132** in 52% yield from **203** (**Scheme 50**).



Scheme 50: i $PMPNH_2$ (1.1 equiv), Et_3N (1.2 equiv), THF, reflux, 75%; ii $ClCOCH_2CO_2Et$ (1.1 equiv), Na_2CO_3 (sat), CH_2Cl_2. iii NaOEt (4 equiv), EtOH, reflux, 74% (two steps). iv PMHS (16 equiv), *t*-AmOH (16 equiv), (*S*)-*p*-tol-BINAP (0.5 mol %), $CuCl_2$ (2.5 mol %), *t*-BuONa (5 mol %), C_6H_5F, air, 23 ^{0}C 90%, 90% ee. v NaH (6 equiv), MeOH (3 equiv), $(MeO)_2CO$ (3 equiv), toluene, reflux, 86%. vi BH_3,THF, reflux, 97%. vii CAN (4 equiv), CH_3CN:H_2O (3:1). viii $(Boc)_2O$ (2.0 equiv), NaOH (1.5 equiv), toluene, H_2O, 75% (two steps). ix (a) **204** (1.3 equiv), Cs_2CO_3 (1.5 equiv), xylene, 130 ^{0}C; (b) TFA, CH_2Cl_2, 52% (two steps).

Kobayashi's approach (2004)[106]

In Kobayashi's approach, *trans*-cyclopentene derivative **207**, was prepared from monoacetate **205** by a sequence of reactions: (1) 4-C_6H_5MgCl/CuCN (cat.) to produce **206**, 87%; (2) AcOH, DIAD, PPh_3, 90%; (3) (*i*-PrO)$Me_2SiCH_2Cu.MgICl$ (3 equiv), THF, 2h, 90 %. Ozonolysis of **207** proceeded well in *n*-PrOH to afford diol in 85% yield after reductive workup with $NaBH_4$. Subsequently, diol was converted into iodide and finally, on treatment with $BnNH_2$ at 115^{0}C for 2h in dioxane produced *trans* piperidine **208** in 54% overall yield from *trans*-**207**. Piperidine **208** was subjected to deprotection followed by etherification to produce (-)-paroxetine **132** in 70 % yield and 80 % ee (**Scheme 51**).



Scheme 51: i (a) *p*-F–C_6H_4MgCl (3 equiv), CuCN (0.3 equiv), THF, 25°C, 87 %; (b) $MeOCH_2CO_2H$, DIAD, PPh_3,-78^{0}C, 90 %; ii (a) (*i*-PrO)$Me_2SiCH_2Cu.MgICl$ (3 equiv), THF, 2h, 90 %; (b) H_2O_2, KF, $KHCO_3$, 60–65^{0}C; iii (a) O_3, -70^{0}C then Me_2S; (b) $NaBH_4$, 0^{0}C; (c) I_2, imidazole, PPh_3; (d) $BnNH_2$, dioxane, 115^{0}C, 60 %; v (a) TFA, CH_2Cl_2, 25°C; (b) H_2, (*t*-BuOCO)$_2$O, 20% Pd(OH)$_2$-C, EtOAc, 25°C, 50%; (b) MsCl, pyr, 10 °C, then NaH, sesamol, THF, reflux, 70%; (c) TFA, CH_2Cl_2, 25°C, 70%.

1.2.4 Present Work

1.2.4.1 Objective

Literature search revealed that various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed for the synthesis of (-)-paroxetine (**132**) (*vide supra*).[95-106] However, these methods suffer from disadvantages such as low overall yields, the need for separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of (-)-paroxetine (**136**) is highly desirable.

Retrosynthetic analysis (**Fig. 17**) of (-)-paroxetine (**132**) reveals that piperidin-2-one **137** could be visualized as a key intermediate. In order to prepare this piperidin-2-one **137** in optically pure form, Co-catalyzed-reductive cyclization of the corresponding cyano ester **209** was envisaged. Thus, the cyanoester **209** was successfully synthesized in four steps from the corresponding ketone by a sequence of reactions: Reformatsky reaction of the corresponding ketone with ethyl bromoacetate, dehydration of alcohols with *p*-TSA producing **113c**, allylic bromination of methyl group with NBS followed by bromide displacement with cyanide; overall yield being 54 % (**Schemes 52**).

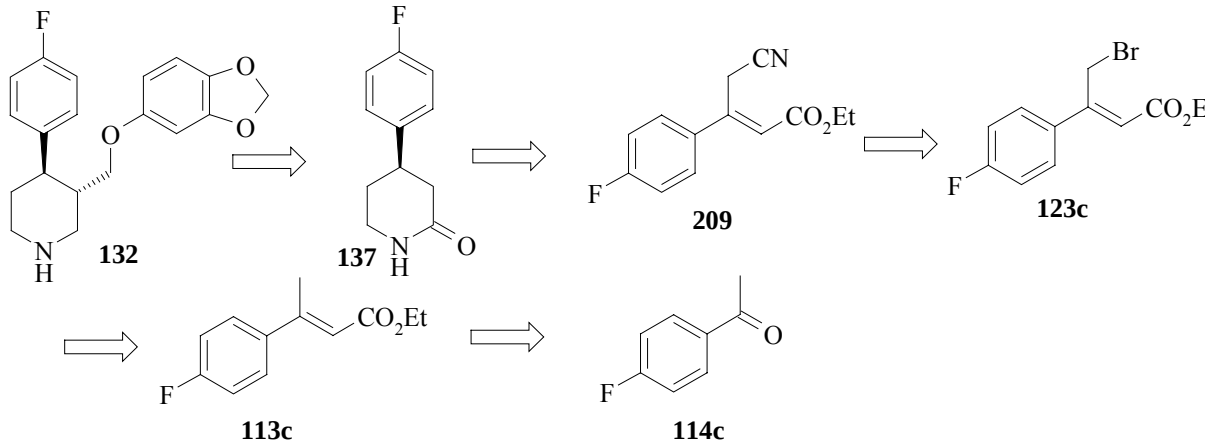
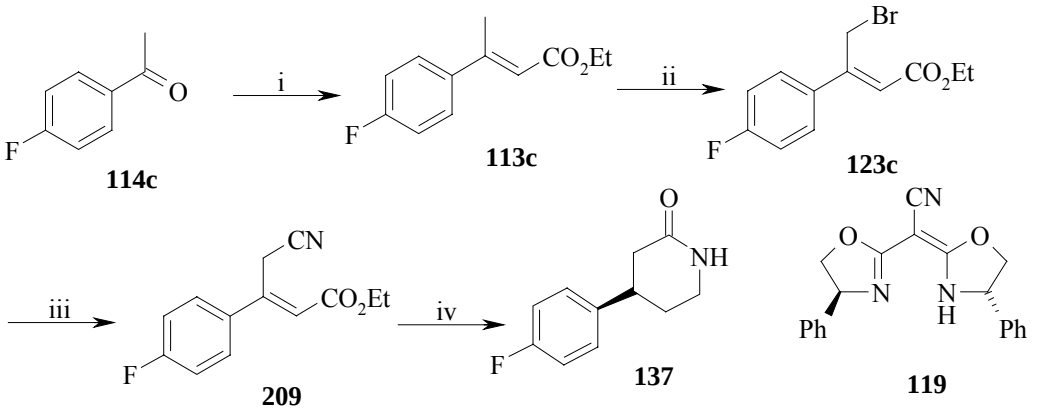


Fig. 17: Retrosynthetic analysis of (-)-paroxetine (132)

1.2.5 Results and Discussion

The synthetic strategy for (*R*)-4-(4-fluorophenyl)piperidin-2-one (**137**), key intermediate for (-)-paroxetine, is shown in **Scheme 52** wherein Co-catalyzed asymmetric reduction (AH) constitutes a key step in introducing chirality into the molecule.[80]



Scheme 52: i a) Ethyl bromo acetate (12 mmol.), $ArCOCH_3$ (10 mmol), Zn dust (12 mmol), dry benzene, 80 ^{0}C , 6 h; b) *p*-TSA (10 mol %), benzene, Dean-Stark, 80 ^{0}C, 12h, 80 %. ii AIBN (10 mol %), NBS, CCl_4, reflux, 12h, 84 %; iii NaCN, dry DMF, 25 ^{0}C, 81%; iv cyano ester (1 mmol), $CoCl_2$ (1 mol %), Ligand **119** (1.1 mol %), $NaBH_4$ (4 mmol), DMF:EtOH (1:1), 25 ^{0}C, 24h, 99 %, 86 % ee.

The α,β-unsaturated ester **113c** was prepared by the Reformatsky reaction of 4-fluorobenzaldehyde **114c** with ethyl bromoacetate followed by *p*-TSA catalyzed dehydration of the resulting alcohol, producing the required olefinic ester **113c** in 80 % yield. The IR

spectrum of **113c** showed strong bands at 1710 and 1620 cm^{-1} indicating the presence of ester and olefin functionalities. Its ^{1}H-NMR spectrum showed characteristic singlets at δ 2.56 and 6.09 due to presence of vinylic-methyl group and olefinic proton (=CH) respectively (**Fig. 18**). The ^{13}C-NMR showed characteristic carbon signals at δ 153.47 and 118.13 corresponding to that of β-quaternary carbon and CH carbon of the α, β-unsaturated ester respectively. The signal at δ 165.78 confirms the presence of ester carbonyl carbon.

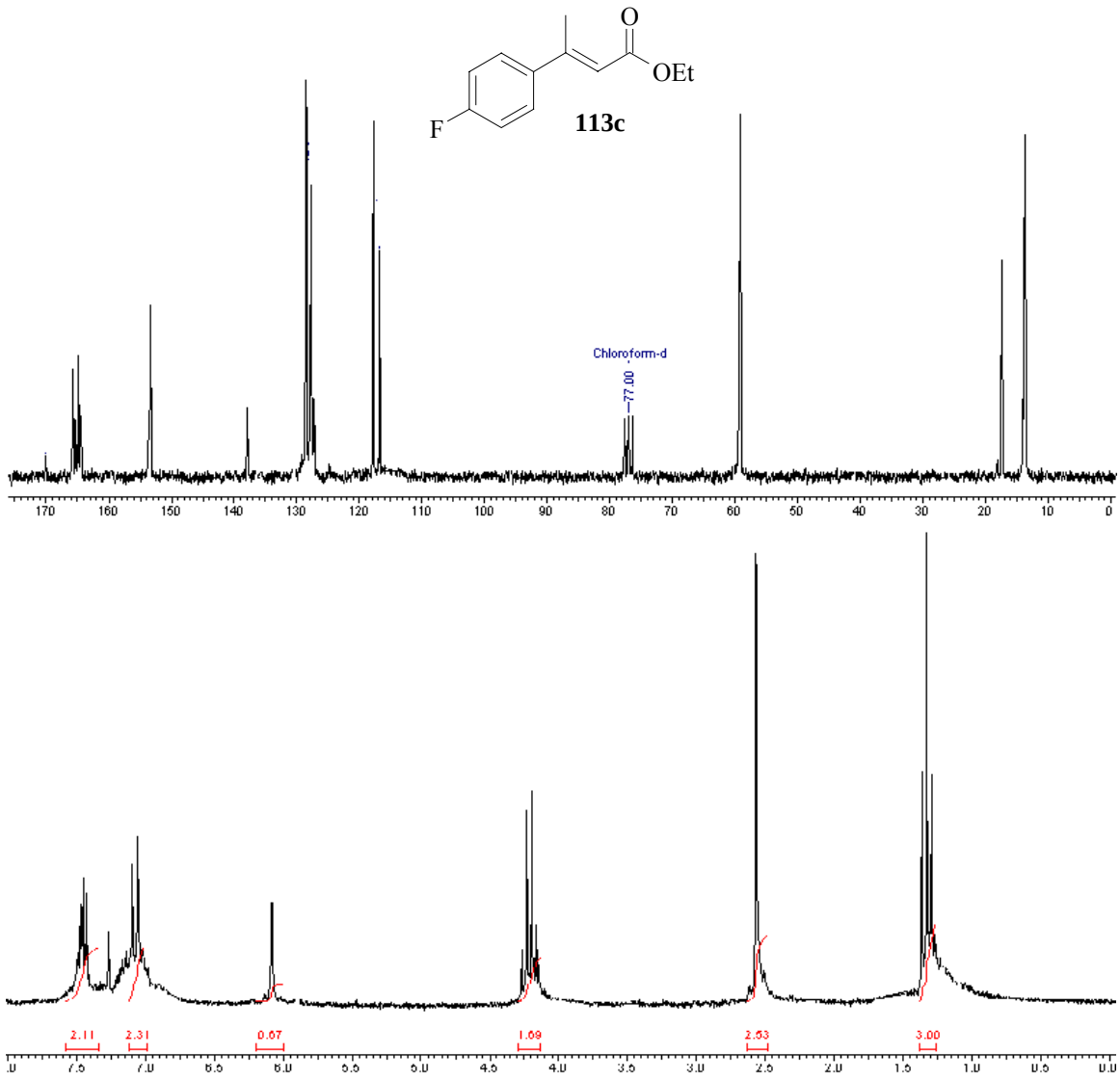


Fig. 18: ^{13}C and ^{1}H NMR spectra of olefinic ester (113c)

The bromo ester **123c** was prepared by allylic bromination of olefinic ester (**113c**) with N-bromosuccinimide (NBS) in the presence of 2, 2'-azobisisobutyronitrile (AIBN) in 84 % yield. The ^{1}H-NMR spectrum of **123c** showed the absence of β-methyl group and appearance of signal at δ 4.93 corresponding to CH_2Br moiety. The ^{13}C-NMR spectrum showed a signal at δ 25.97 confirming the presence of CH_2-Br moiety. Its mass spectrum showed the molecular ion peak at m/e 288 (5%) confirming the formation of **123c** (**Fig. 19**).

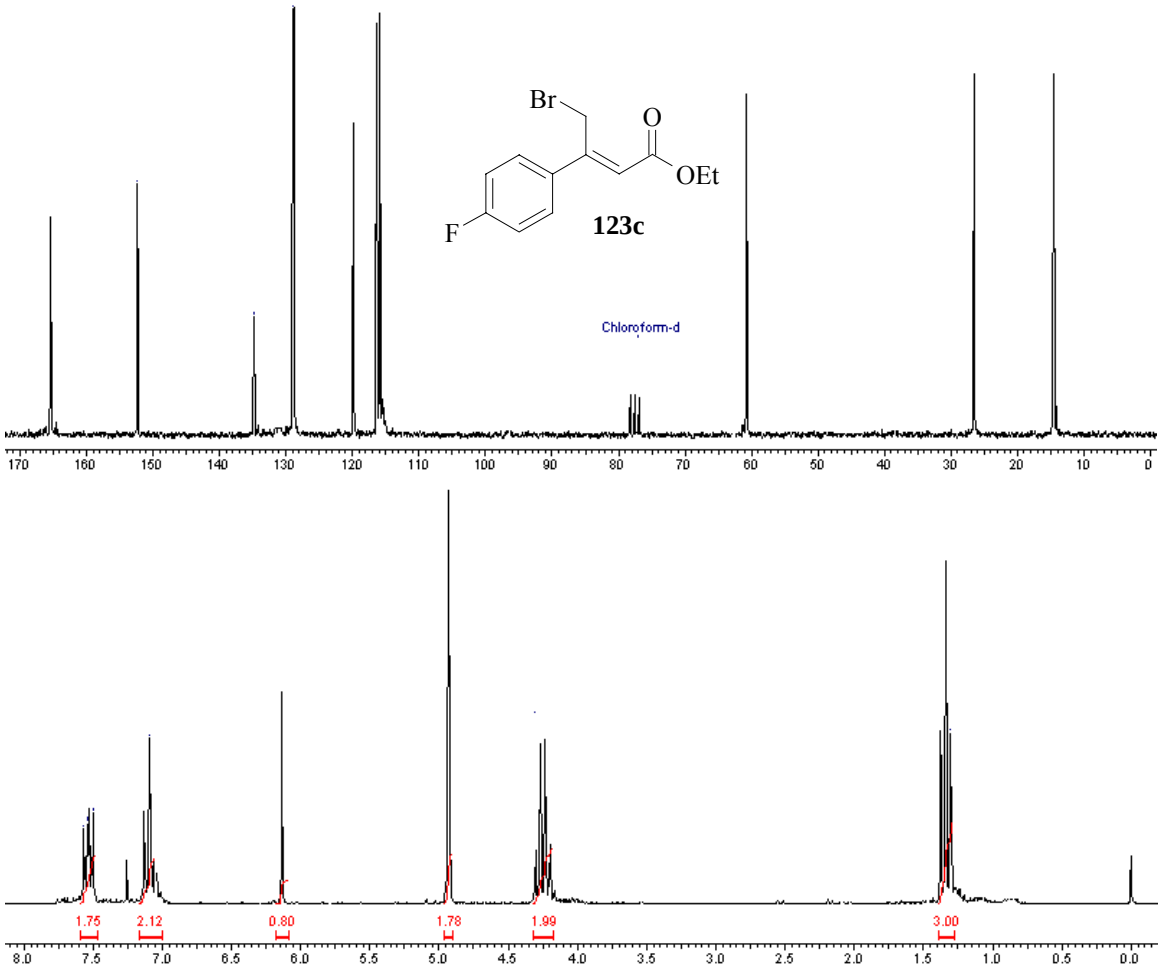


Fig. 19: ^{13}C and ^{1}H NMR spectra of bromo olefinic ester (123c)

The β-bromo ester **123c** underwent S_N2 nucleophilic displacement using NaCN in DMF at 70^{0}C to afford the γ-cyanoester **209** in 81% yield. The IR spectrum of γ-cyanoester **209** showed an intense band at 2216 cm^{-1} indicative of CN group. Its ^{1}H-NMR showed a

signal at δ 3.88 indicating a slight change in the chemical shift of the CH_2-CN protons. This signal is slightly upfield compared to CH_2-Br linkage (δ 4.93) of the bromoester **123c** (**Fig. 19**). However, in ^{13}C-NMR spectrum the signal of CH_2-CN moiety appeared at δ 39.32, whereas for CH_2-Br at δ 25.97. Its ^{1}H and ^{13}C-NMR spectra showed upfield shifts for both proton and carbon signals (**Fig. 20**). Its mass spectrum showed the molecular ion peak at m/e 233 (25%) confirming the formation of **209**.

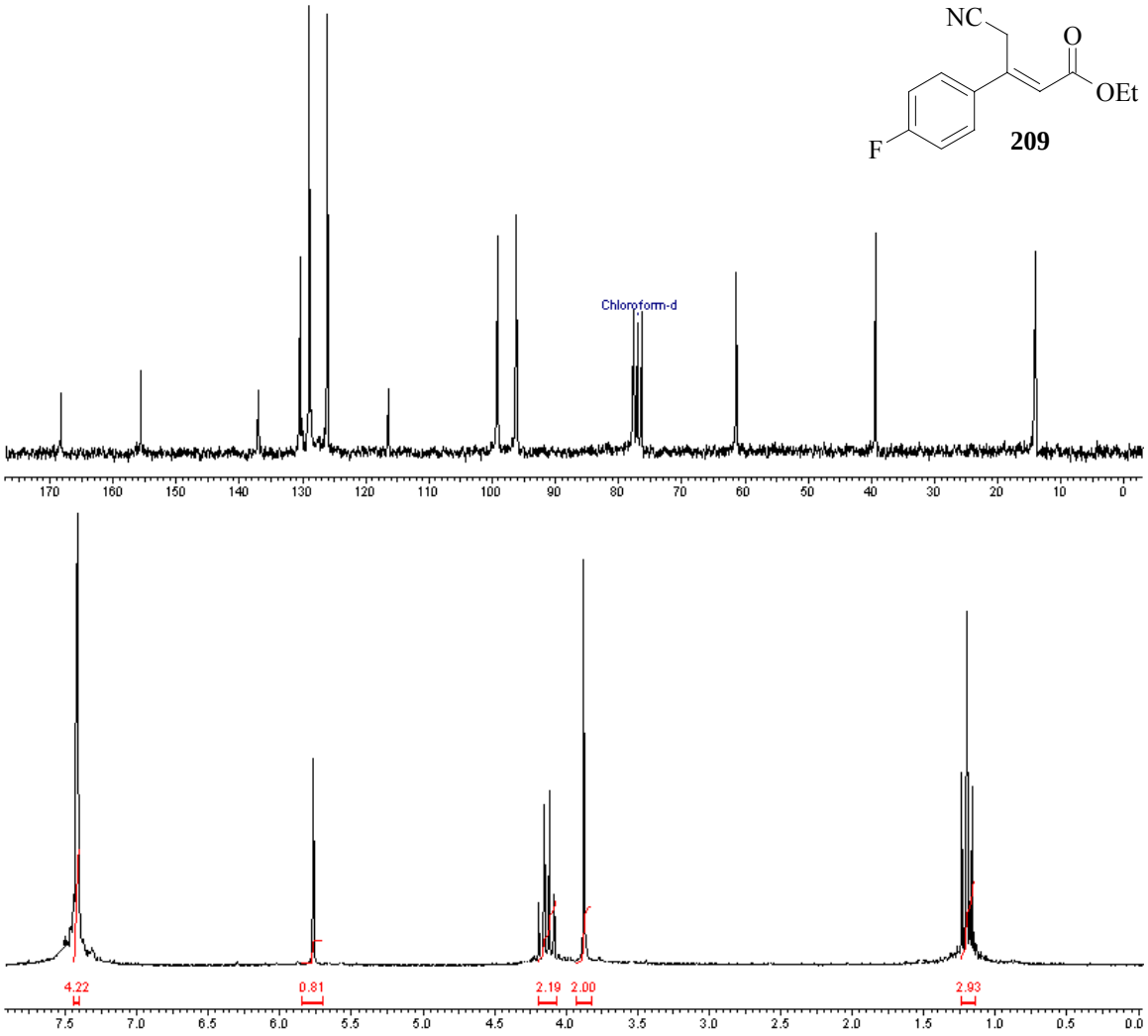


Fig. 20: ^{13}C and ^{1}H NMR spectra of cyano olefinic ester (209)

In earlier sections of this chapter, we have already discussed application of Co-$NaBH_4$ system for obtaining β- and γ-lactams from the corresponding β-cyano olefinic ester and γ-

azido olefinic ester respectively. Now, we are interested in obtaining chiral δ-lactam by subjecting γ-cyano olefinic ester **209** to asymmetric reduction in the presence of (4S)-(+)-phenyl-α-[(4S)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile (**119**). Thus when cyano ester **209** was subjected to Co-catalyzed asymmetric reduction with Co-$NaBH_4$–oxazolidine system at 25^0C, the corresponding chiral δ-lactam **137** was obtained in 99 % yield and 86 % ee. It may be noted that the cyano group and C-C double bond were reduced simultaneously and amine underwent cyclization instantaneously to afford the lactam **137** in a single step (**Scheme 52**). The disappearance of 2216 cm^{-1} band in IR spectrum of *γ*-lactam **137** indicates the absence of cyano group, while carbonyl absorption band observed at 1685 cm^{-1} indicating the formation of cyclic amide carbonyl group. Due to the presence of chiral center, the ^{1}H-NMR spectrum of **137** shows characteristic signals at δ 1.78-3.43. The protons of α-CH_2 and γ-CH_2 groups of **137** are diastereotopic and thereby shows ABX coupling pattern and each proton (H_A and H_B) of these CH_2 groups appearing as a two doublets, while H_X shows multiplet. The proton of δ-CH_2 group shows a multiplet at δ 3.37. In a similar way the protons of γ-CH_2 group represent another ABX pattern. Its ^{13}C-NMR spectrum shows a signal at δ 41.20 due to α-CH_2 group, while the signal at δ 29.48 is due to γ-CH_2 group and the signal at δ 37.90 corresponds to β-CH carbon (**Fig. 21**). The ee of lactam **137** was found to be 86% based on comparison of its data on optical rotation with the literature values. {$\mathbf{[\alpha]^{25}_D}$: + 16.63 (c 1.00, $CHCl_3$), 86% ee, {Lit.[96] $\mathbf{[\alpha]^{25}_D}$ = + 19.0 (c 1.02, $CHCl_3$)}.

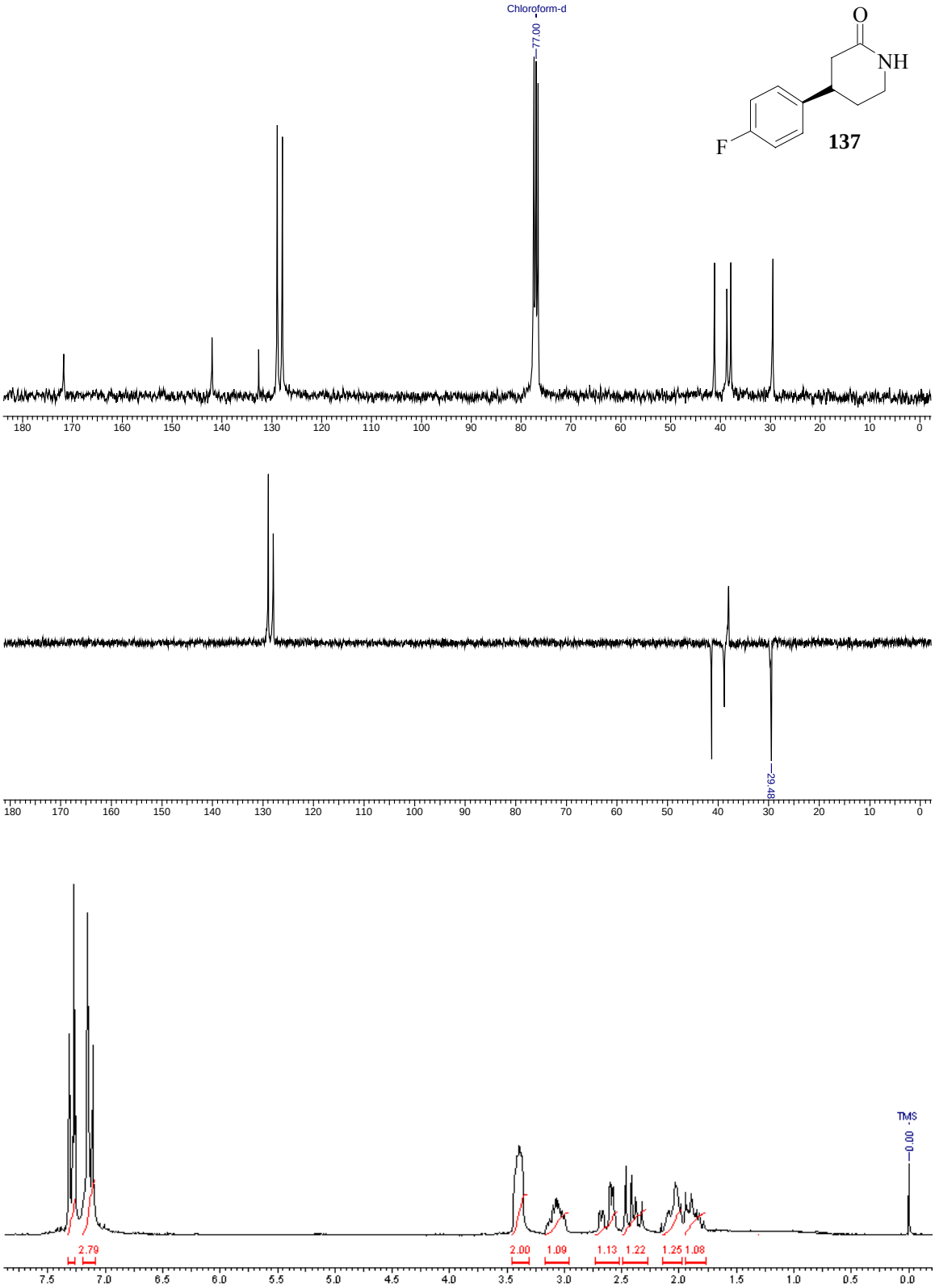


Fig. 21: ^{13}C, DEPT and ^{1}H NMR spectra of piperidin-2-one (137)

The piperidin-2-one **137** can be further transformed to (-)-paroxetine **132** by a sequence of reactions already reported in literature.[96,100]

1.2.6 Conclusion

In conclusion, we have successfully developed a simple and practical method for the synthesis of chiral 4-fluorophenyl-piperidin-2-one **137**, an important intermediate in the synthesis of anti-depressant drug, (-)-paroxetine **132**) [53 % overall yield, 86% ee] in overall four steps starting from 4-fluoroacetophenone **114c**. The method employs asymmetric reduction strategy as the key reaction.

1.2.7 Experimental Procedure

Preparation of (*E*)-ethyl 3-(4-fluorophenyl)but-2-enoate (113c):

A 100 ml two-necked RB flask was charged with activated zinc (2.32 g, 35.7 mmol), and kept under N_2 atmosphere. Dry benzene (30 ml) was introduced and the reaction mixture was heated to 80^{o}C (oil bath temp.). A solution of ethyl bromoacetate (5.88 g, 35.7 mmol) and *p*-fluoroacetophenone **114c** (4.14 g, 30 mmol) in dry benzene (20 ml) was added dropwise to the reaction mixture. After completion of the addition, the resulting reaction mixture was refluxed for 6 h, cooled to 25^{0}C and quenched by adding ice cold 4N H_2SO_4 (30 ml). The crude hydroxyester was extracted with diethyl ether, evaporated under reduced pressure and then was subjected to dehydration using Dean-Stork apparatus with *p*-toluenesulphonic acid (0.7 g, 3.68 mmol) in toluene at reflux. Water generated during the dehydration was azeotropically separated and then toluene was distilled off. The crude olefinic ester **113c** was purified by column chromatography packed with silica gel, eluting with EtOAc:pet. ether (1:10) to give 8.15 g (80%) of **113c**.

Yield: 80%; Yellow color viscous liquid; **IR** ($CHCl_3$, cm^{-1}): 667, 685, 836, 1043, 1177, 1280, 1345, 1366, 1444, 1509, 1630, 1707, 2405, 2977, 3022; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.04 Hz, 3H), 2.56 (s, 3H), 4.22 (q, *J* = 7.04 Hz, 2H), 6.09 (s, 1H), 7.05 (d, *J* = 8.61 Hz,

2H), 7.45 (d, *J* = 9 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.25, 17.56, 59.52, 116.21, 118.13, 127.73, 130.66, 138.52, 153.47, 162.43, 165.78; **Analysis:** $C_{12}H_{13}FO_2$ requires C, 69.22; H, 6.29; found 69.12; H, 6.21%.

Preparation of (*Z*)-ethyl 4-bromo-3-(4-fluorophenyl)but-2-enoate (123c):

A 100 ml RB flask fitted with reflux condenser was charged with olefinic ester **113c** (4.16 g, 20 mmol), NBS (3.52 g, 20 mmol), AIBN (2, 2'-azobisisobutyronitrile, 8 mg, 0.048 mmol) and CCl_4 (55 ml). The reaction mixture was heated for 8 h at 80^0C (as monitored by TLC). The reaction was cooled and quenched with saturated solution of sodium sulfite (10g in 20 ml water) and extracted with ethyl acetate (3 x 60 ml). The organic layer was washed with brine (50 ml), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using EtOAc: pet. ether (1:3) as eluent to yield **123c** as a yellow oil (4.8 g, 84%).

Yield: 84%; gum; **IR** ($CHCl_3$, cm^{-1}): 837, 885, 1014, 1020, 1097, 1163, 1180, 1230, 1340, 1369, 1446, 1510, 1602, 1710, 2360, 2981, 3051; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.04 Hz, 3H), 4.25 (q, *J* = 7.05 Hz, 2H), 4.93 (s, 2H), 6.13 (s, 1H), 7.08 (d, *J* = 8.61 Hz, 2H), 7.52 (d, *J* = 8.99 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.86, 25.97, 60.03, 115.24, 116.36, 128.30, 130.41, 134.19, 151.56, 164.62; **MS** m/z (% rel. intensity): 288 (M^+, 5), 260 (3), 241 (5), 207 (10), 179 (40), 162 (5), 151 (15), 133 (100), 123 (10), 109 (8), 83 (7), 75 (9), 57 (12); **Analysis:** $C_{12}H_{12}BrFO_2$ requires C, 50.20; H, 4.21; found C, 50.16; H, 4.20%.

Preparation of (*E*)-ethyl 4-cyano-3-(4-fluorophenyl)but-2-enoate (209):

In a 25 ml flask were added γ-bromo ester **123c** (2.87 g, 10 mmol), NaCN (0.735 g, 15 mmol) and dry DMF (20 ml) under argon atmosphere. The reaction mixture was heated at 50^0C for 6 h (monitored by TLC). After completion of the reaction it was diluted with water (5 ml) and extracted with EtOAc (4 x 15 ml) combined organic extracts were washed with brine (10 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product. The crude product was further purified by column chromatography on silica gel using EtOAc:pet. ether (2:8) as eluent to afford cyanoester **209** (1.88 g, 81%).

Yield: 81%; yellow colored liquid; **IR** ($CHCl_3$, cm^{-1}): 827, 1027, 1103, 1164, 1240, 1317, 1369, 1427, 1512, 1602, 1735, 2216, 2360, 2983, 3066; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.0 Hz, 3H), 3.88 (s, 2H), 4.14 (q, *J* = 8 Hz, 2H), 5.77 (s, 1H), 7.41 (m, 4H); **^{13}C-NMR**

(200 MHz, $CDCl_3$): δ 14.14, 39.32, 61.38, 99.20, 116.48, 126.11, 128.98, 130.41, 137.04, 155.63, 168.27; **MS** m/z (% rel. intensity): 233 (M^+, 25), 218 (5), 205 (8), 188 (10), 174 (7), 161 (100), 133 (55), 121 (8), 96 (40), 75 (20), 57 (15); **Analysis:** $C_{13}H_{12}FNO_2$ requires C, 66.94; H, 5.19; N, 6.01; found C, 67.00; H, 5.20; N, 6.00%.

Preparation of (R)-4-(4-fluorophenyl)piperidin-2-one (137):

To a 1.01 g (4.33 mmol) of cyano ester **209** in a 15 ml RB flask was added a solution of $CoCl_2.6H_2O$ (0.009 g, 0.04 mmol) in 4 ml of ethanol, followed by a solution of (4S)-(+)-phenyl-α-[(4S)-phenyloxazolidin-2-ylidine]-2-oxazoline-2-acetonitrile (**119**) (0.016 g, 0.048 mmol) in 2 ml ethanol under nitrogen balloon. After dilution with 2 ml of DMF, the clear, dark blue solution was degassed by three freeze-thaw cycles. The solution, which was kept under nitrogen, was then added sodium borohydride solution (0.64, 17 mmol) in 2 ml DMF resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze-thaw cycles. The evacuated flask containing the yellow, slightly turbid solution stirred at room temperature. In the beginning, slow H_2-evolution was observed which gradually ceased after 1h. Towards the end of the reaction, solid precipitated and brown-yellow foam began to form. After completion of reaction (as monitored by TLC), the reaction mixture was transferred to a separatory funnel with 50 ml of EtOAc and 50 ml of water, diluted with 25 ml of ice water and extracted with EtOAc. The organic layer was washed three times with brine solution, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Column chromatographic purification (EtOAc/pet. ether 4: 1) afforded 0.828 g (99 %) of piperidin-2-one **137** in 86 % ee as a colorless solid.

Yield: 99%; crystalline solid; **mp:** 158^{0}C (recrystallized from $CHCl_3$); **$[\alpha]^{25}_D$**: + 16.63 (c 1.00, $CHCl_3$), 86% ee, {Lit.[96] **$[\alpha]^{25}_D$** = + 19.0 (c 1.02, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 627, 675, 832, 1013,1102, 1159, 1275, 1300, 1414, 1458, 1476, 1685, 1756, 1910, 2231, 2842, 2895, 2950, 3100, 3201, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.78-1.95 (m, 1H), 2.02-2.10 (m, 1H), 2.40 (dd, *J* = 17.56, 10.74 Hz, 1H), 2.64 (dd, *J* = 17.56, 5.30 Hz, 1H), 3.00-3.31 (m, 1H), 3.37-3.43 (m, 2H), 7.11 (d, *J* = 8.46 Hz, 3H), 7.27 (d, *J* = 8.46 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 29.48, 37.90, 38.70, 41.20, 127.88, 128.91, 132.64, 141.98, 171.76; **Analysis:** $C_{11}H_{12}FNO$ requires C, 68.38; H, 6.26; N, 7.25; found C, 68.33; H, 6.20; N, 7.23%.

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Enantioselective Synthesis of (-)-Cytoxazone, a Novel Cytokine Modular *via* Sharpless asymmetric epoxidation

2.0.1 Introduction

In 1998, Osada and co-workers reported the isolation of (4*R*,5*R*)-5-(hydroxymethyl)-4-(4-methoxyphenyl)-1,3-oxazolidine-2-one [(–)-**1a**, generic name cytoxazone],[1] which was shown to possess high cytokine modulator activity by acting on the Th2 cells.[2] Because of these biological properties, several total syntheses of (-)-**1a** and of its *trans*-diastereoisomer (4-*epi*-cytoxazone **1b**) (**Fig 1)** have been published in the last three years.[3, 10-20]

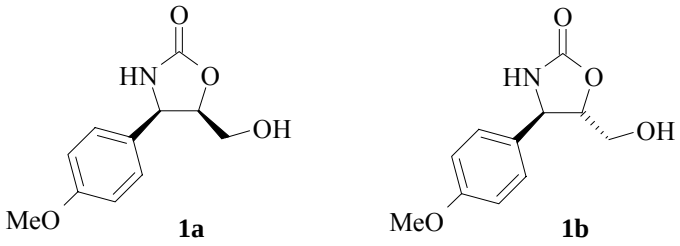


Fig. 1: Structure of cytoxazone and 4-epi-cytoxazone

Prompted by the first positive biological results, many researchers also reported the preparation of *cis*- and *trans*-isocytoxazones **2a**,**b**, structural isomers of cytoxazone **1a** and its *trans* epimer **1b** (**Fig 1**).[3]

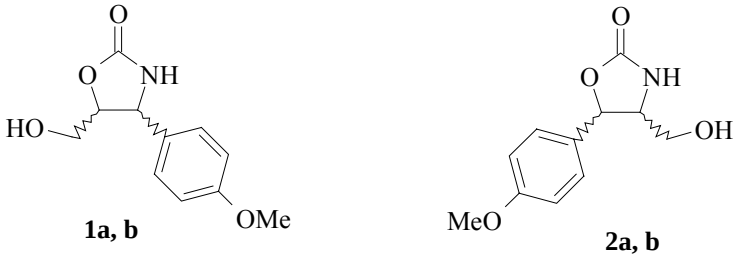


Fig. 2: Structural isomers of cytoxazone

There are several methods to obtain enantiomerically pure materials, which include classical resolution *via* diastereomers, chromatographic separation of enantiomers, enzymatic

resolution, chiral kinetic resolution and asymmetric synthesis. L-proline catalyzed one pot Mannich reaction,[4] $Ti(OiPr)_4$-catalyzed asymmetric epoxidation (AE) and further opening of epoxide with amine or N_3, OsO_4-catalyzed asymmetric aminohydroxylation (AA), developed by Sharpless *et al*.[5] are simple, efficient and the most reliable methods for asymmetric synthesis of chiral vicinal aminoalcohols.[6]

2.0.2 The Pharmacology of Cytoxazone

It is well established that the induction of humoral or cellular response is influenced by the development of distinct subsets of $CD4^+$ T cells.[7] The Th1 cell subset produces predominately IL-2, GM-CSF, INF-γ, and TNF-β, (type 1 cytokines) and is involved in delayed-type hypersensitivity reactions, whereas the Th2 cell subset secretes IL-4, IL-5, IL-6, IL-10, and IL-13 (type 2 cytokines), which are important factors for B cell growth and differentiation to Ig secretion. The imbalance of cytokine production by $CD4^+$ T cells leads to a wide variety of immunological disorders, i.e. allergy, progressive lymphoproliferation, and severe immunodeficiency.[8] Skin and lung biopsies from allergic patients indicate that the pivotal cells in the allergic site are the Th2 cells.[9] Treatments effectively suppressing the function or the differentiation of these allergen-specific Th2 cells will most likely provide efficient ways to intervene in Ig-mediated allergic diseases.

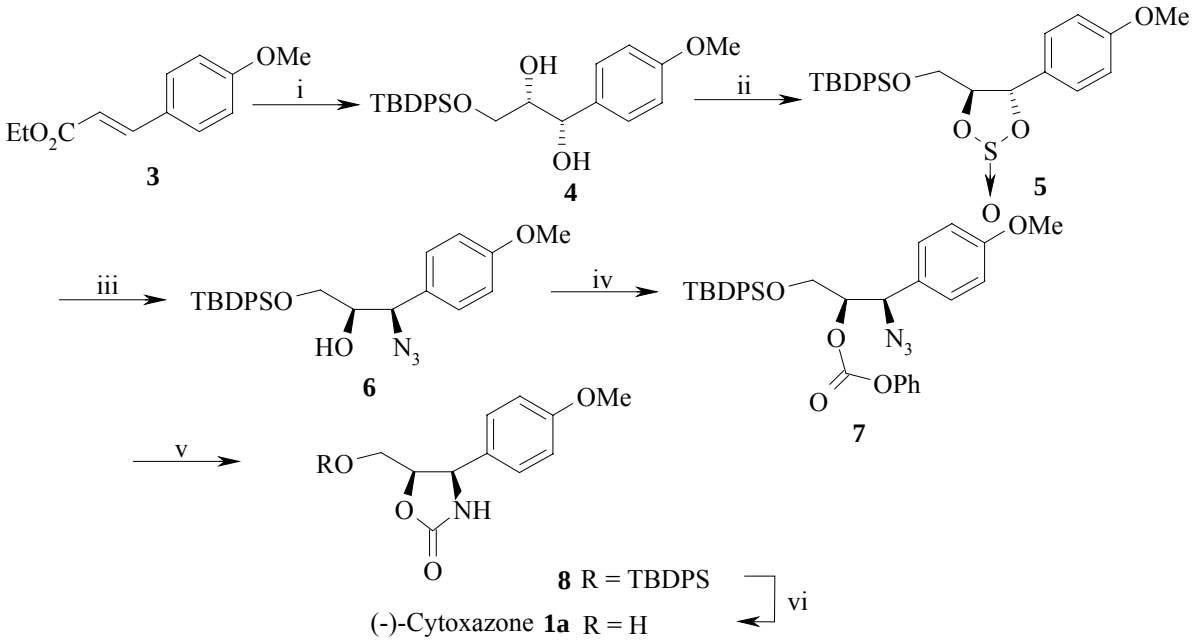
In the course of screening for chemical immunomodulators that inhibit the type 2 cytokine production in Th2 cells, it was found that cytoxazone (**1a**) containing a 2-oxazolidinone ring, which is rare in microbial metabolites, as a novel cytokine modulator produced by *Streptomyces* sp. Cytoxazone (**1a**) shows a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells, but not Th1 cells.[1]

2.0.3 Review of Literature

Literature search revealed that there are several reports available for the synthesis of cytoxazone (**1**).[10-20] They are concerned mostly with resolution, chemo-enzymatic or enantioselective synthesis, which are described below.

Nakata's approach (1999)[10]

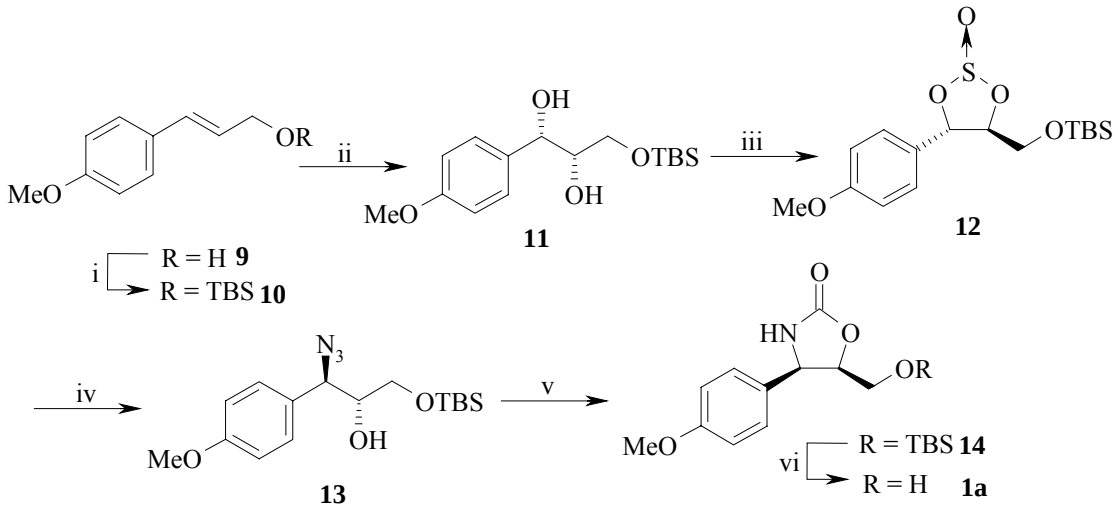
Nakata *et al.* have achieved synthesis of (-)-cytoxazone from the corresponding azido alcohol (**6**). The construction of the 2-oxazolidinone ring in **8** was achieved from azide carbonates **7** by reduction of azide to amine function and subsequent cyclization using PPh_3. The regio and stereoselective introduction of an azide group is achieved by cyclic sulfite (**5**) ring opening by using LiN_3 in 74 % yield. The cyclic sulfite **5** was obtained from ethyl p-methoxycinnamate by the Sharpless catalytic asymmetric dihydroxylation followed by its treatment with $SOCl_2$ (**Scheme 1**).



Scheme 1: i) (a) AD-mix-α, t-BuOH: H_2O (1:1), RT, 93 % (99%ee); (b) $NaBH_4$, THF, 0 °C, 66%; (c) TBDPSCI, imidazole, DMF, 0 °C, 99%, ii) $SOCI_2$, Et_3N, CH_2CI_2, 0 °C, 99%; iii) LiN_3, DMF, 70 °C, 74 %; iv) $CICO_2Ph$, Py, CH_2CI_2, RT, 96%; v) PPh_3, THF/ H_20, 50 °C, 90%; vi) n-Bu_4NF, THF, 0 °C, 89 % ee, 96%.

Mori's approach (1999)[11]

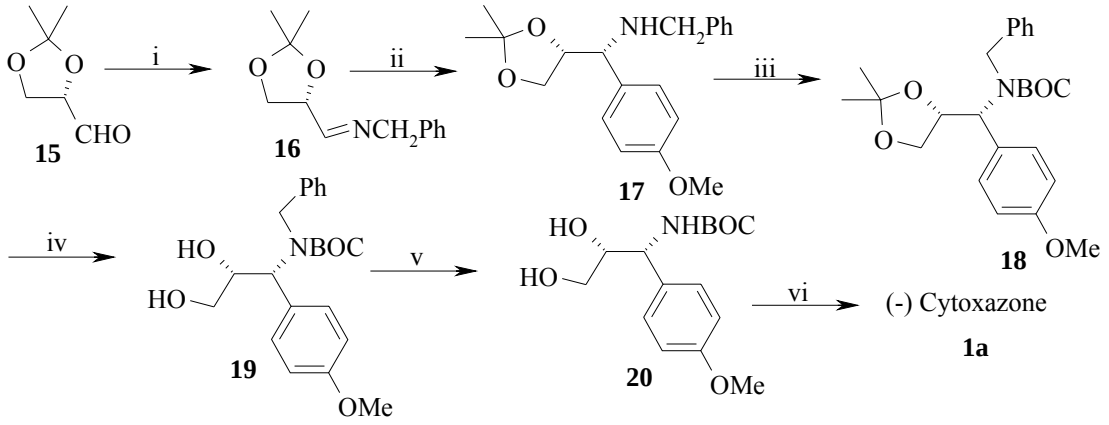
Mori *et al.* synthesized cytoxazone starting from *p*-methoxycinnamyl alcohol (**9**) employing the Sharpless asymmetric dihydroxylation as the key reaction in 26% overall yield (7 steps). *p*-Methoxycinnamyl alcohol (**9**) was converted into the corresponding *tert*-butyldimethylsilyl (TBS) ether **10**, which was dihydroxylated to give (2*S*,3*S*)-**11** (99.6% *ee*) in 99% yield. 1,2-Glycol **11** was further converted to an azido alcohol **13** *via* cyclic sulfite **12** in 60 % yield. The azide **6** was then reduced and the 2-oxazolidinone ring was achieved by treatment with diethyl carbonate to furnish **14**. Removal of the TBS protective group of **14** with TBAF yielded (4*R*,5*R*)-cytoxazone (**1a**) (**Scheme 2**).



Scheme 2: i TBSCl, imidazole, DMF, 97%; ii AD mix-·α[$(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3], $MeSO_2NH_2$, *t*BuOH/H_2O, 99%; iii $SOCl_2$, Et_3N, CH_2Cl_2, 88%; iv LiN_3, DMF, 100^0C, then H_2O at 0^0C (61%); v (a) HCO_2NH_4, Pd/C, MeOH, 50^0C, 87%; (b) $CO(OEt)_2$, K_2CO_3, 66%; vi TBAF, THF, 89%.

Rao's approach (2001)[12]

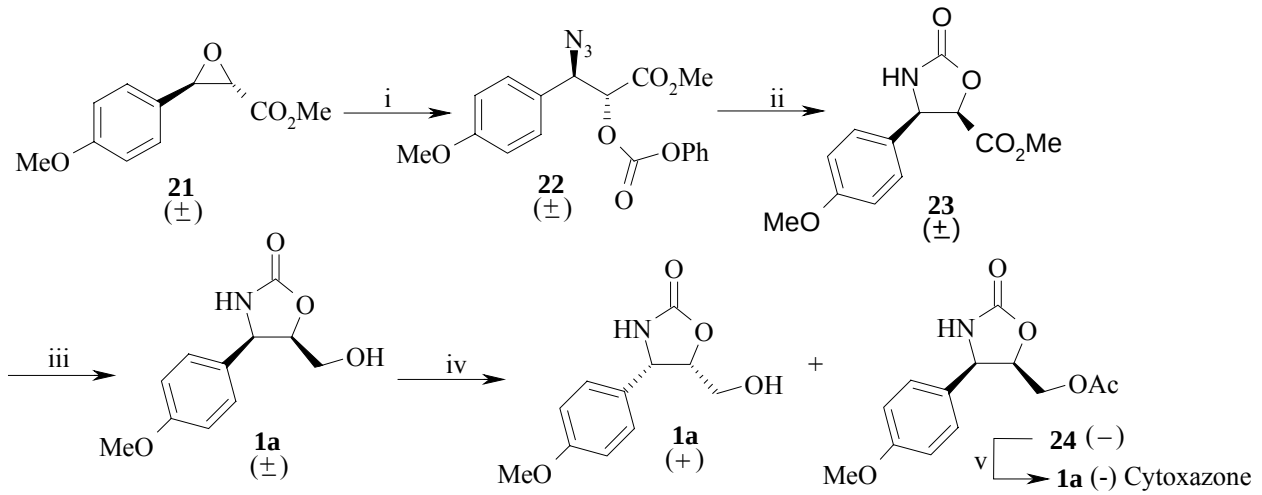
Grignard addition of *p*-methoxyphenylmagnesium bromide to *N*-benzylimine derived from (*S*)-2,3-*O*-isopropylidene glyceraldehydes **15**, followed by a single step regioselective conversion of the *N*-BOC amino diol **20** afforded the (-)-cytoxazone (**1a**) (**Scheme 3**).



Scheme 3: i) $PhCH_2NH_2$, dry ether, 0°C; ii) p-Methoxyphenyl magnesium bromide dry ether; iii) $(BOC)_2O$, Et_3N, dry ethanol; iv) PTSA (cat), MeOH; v) Pd/C (cat), conc.HCl (a drop), EtOH; vi) NaH, dry THF.

Sunjic's approach (2001)[13]

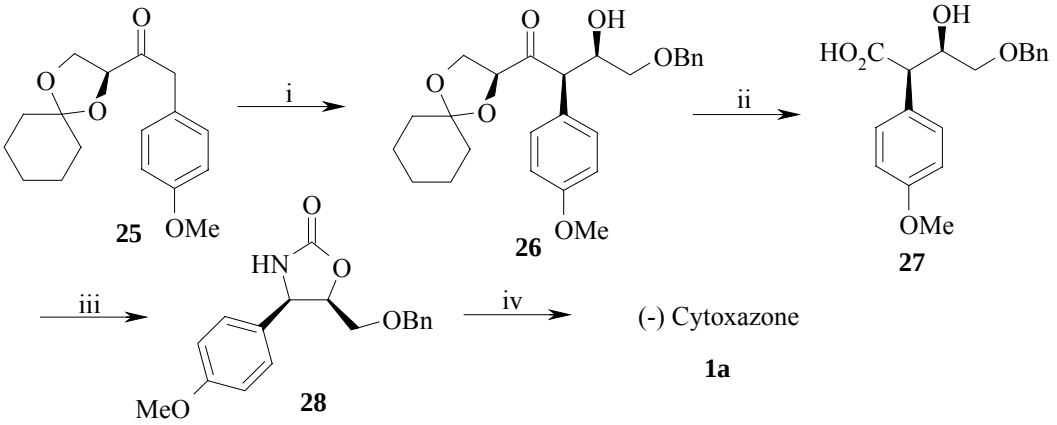
Racemic cytoxazone (**1a**) was synthesized starting from glycidic ester **21** by nucleophilic epoxide ring opening, followed by construction of 2-oxazolidinone ring and reduction of the intermediary ester **22**. Kinetic resolution of recemic **1a** was performed by acetylation using *Penicillium camemberti lipase* (PcamL) afforded, (-)-cytoxazone **1a** in 33% overall yield and 88.2% ee (**Scheme 4**).



Scheme 4: i) aq NaN_3, dioxane, 50 °C, 3 h, 56%; ii) $ClCO_2Ph$, CH_2Cl_2, –5 °C, 1 h, 100%; iii) (a) Ph_3P, aq THF, 50 °C, 90 min, 88%; (b) $NaBH_4$, $CaCl_2$, absolute EtOH, RT, 20 min, 79%; iv) *Penicillium camemberti lipase* (PcamL), vinyl acetate, 30 °C; v) KOH, MeOH, RT, 1 h.

Carda's approach (2002)[14]

The key steps of Carda's approach are; (i) *syn*-stereoselective aldol addition of a chiral ketone mediated by chlorodicyclohexylborane; (ii) Curtius rearrangement. Thus, aldol additions of ketone **25** with benzyl protected glycolic aldehyde furnished the expected *syn* aldol adduct **26**. Oxidative cleavage of the acetonide ring gave the corresponding β-hydroxy acids **27**. Curtius rearrangement of the latter furnished oxazolidinones **28**. Removal of benzyl group by hydrogenolysis of **28** led to cytoxazone (-)-**1a** (**Scheme 5**).

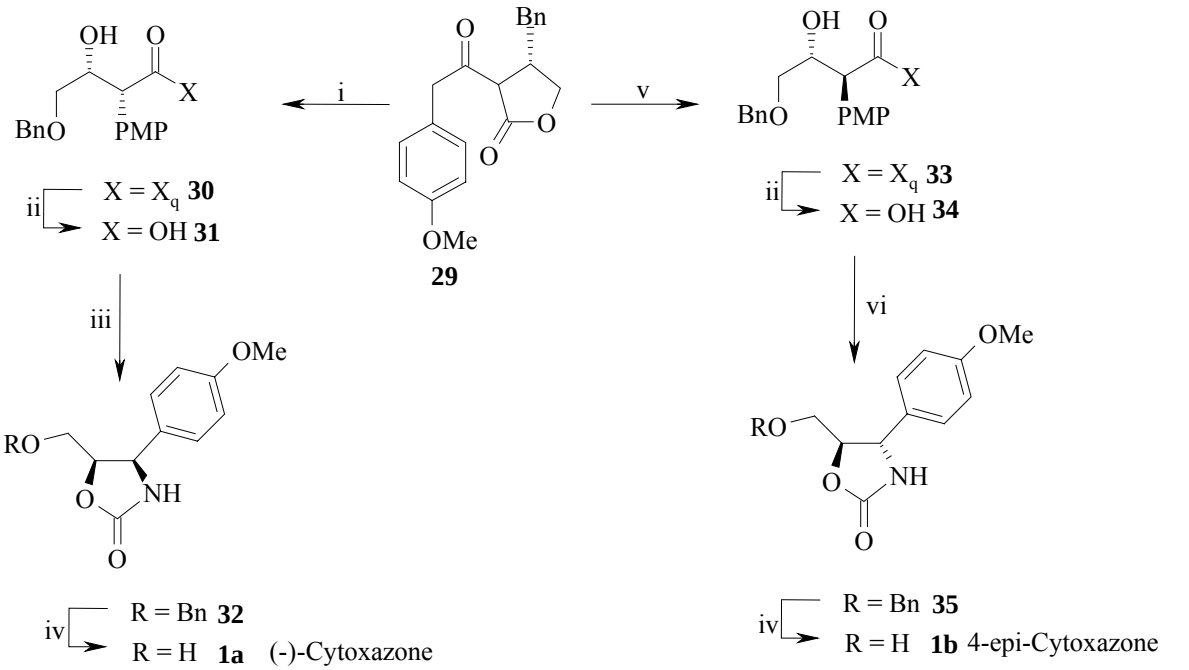


Scheme 5: i) Chx_2BCl, Et_3N, Et_2O, $BnOCH_2CHO$, -78^{0}C to RT, 79%; ii) H_5IO_6, Et_2O-EtOAc, 70 %; iii) Et_3N, 4 A^o MS, DPPA, toluene, reflux, 12 h, 68%; iv) EtOH, cat. $Pd(OH)_2$, H_2 500 psi, 24h, 78%.

Carter's approach (2003)[15]

The reaction of dibutylboron enolate **29** with the benzyloxyacetaldehyde provided the aldol **30** in good *syn*-diastereoselectivity. Removal of the chiral auxiliary from **30** using lithium hydroperoxide provided the acid **31** in good yield. Acid **31** was transformed into the oxazolidinone **32** in a one-pot, three-step (acyl azide formation, Curtius rearrangement, isocyanate trapping) procedure using diphenylphosphoryl azide (toluene, 23-110 ^{0}C, 3 h). Ether **32** was directly debenzylated using Pearlman's catalyst to provide

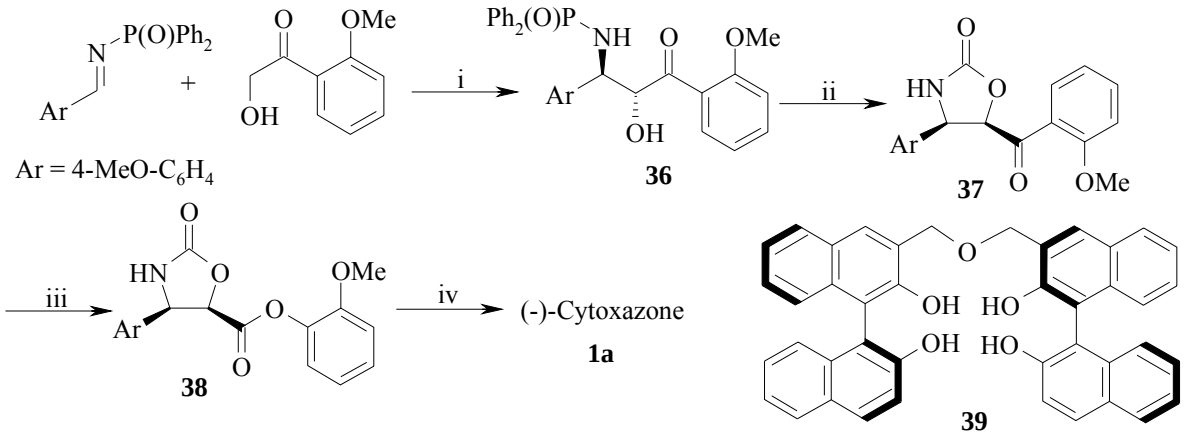
(-)-cytoxazone **1a**. The same sequence of reaction was used to synthesize 4-epi-cytoxazone (**1b**) (**Scheme 6**).



Scheme 6: i Bu_2BOTf, i-Pr_2EtN, -78 ^{0}C, 20min; $BnOCH_2CHO$, -78 ^{0}C to 0 ^{0}C, 1.5 h, 51%; ii 4:1 THF:H_2O, H_2O_2, LiOH, 0 ^{0}C, 1 h; $NaHSO_3$, 99%; iii $(PhO)_2PON_3$, $PhCH_3$, 23^{0}C, 40min; 110 ^{0}C, 3h, 77%; iv 1 atm H_2, $Pd(OH)_2$, MeOH, 23 ^{0}C, 24 h, 84%; v Bu_2BOTf, i-Pr_2EtN, 0 ^{0}C, 30min; add $BnOCH_2CHO$ precomplexed w/0.5 equiv $SnCl_4$, -78 ^{o}C, 3 h, 64%; vi $(PhO)_2PON_3$, CH_2Cl_2, 23 ^{0}C, 40min; 45 ^{0}C, 12 h, 61%.
Note: PMP = para-methoxyphenyl; Xq = (R)-4-benzyloxazolidin-2-one

Shibasaki's approach (2004)[16]

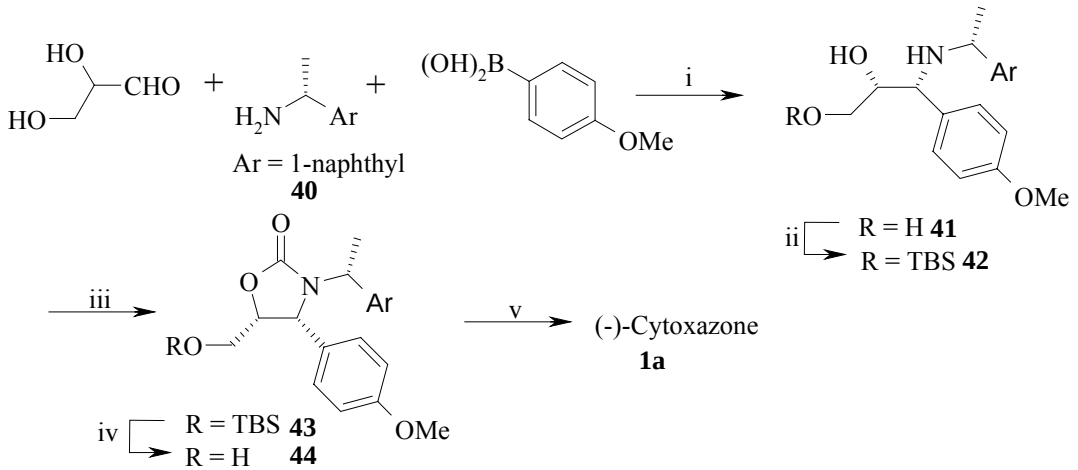
A direct catalytic asymmetric Mannich-type reaction of hydroxyketone with N-diphenylphosphinoyl (Dpp) imine using a 0.05 mol % Et_2Zn/(S, S)-linked-BINOL complex gave *anti*-amino alcohol in 98 % de, 99% yield, and 99.5% ee. Mannich adduct **36** was readily converted to cyclic carbamate **37** in 84% yield (two steps) after removal of the *N*-Dpp group under acidic conditions, followed by Baeyer-Villiger oxidation of **37** to afford ester **38** in 88% yield. Successive treatment of **38** with $NaBH_4$/ AcOH gave (-)-cytoxazone **1a** in 88% yield (**Scheme 7**).



Scheme 7: i) Et_2Zn/(S, S)-linked-BINOL (**1**) complex, MS 3 ^{o}A, THF/CH_2Cl_2, -20 ^{0}C *anti/syn*: 95/5, e.e. (anti): 99% ; ii) (a) concentrated HCl(aq)/THF, 25^{0}C, 1 h; (b) triphosgene, pyridine, CH_2Cl_2, -78 ^{0}C, 0.5 h, yield 84% (two steps); iii) *m*CPBA, NaH_2PO_4, $Cl(CH_2)_2Cl$, 60 ^{0}C, 3 h, yield 88%; iv) $NaBH_4$, AcOH, THF, 25 ^{0}C, 2 h, yield 88%.

Sugiyama's approach (2004)[17]

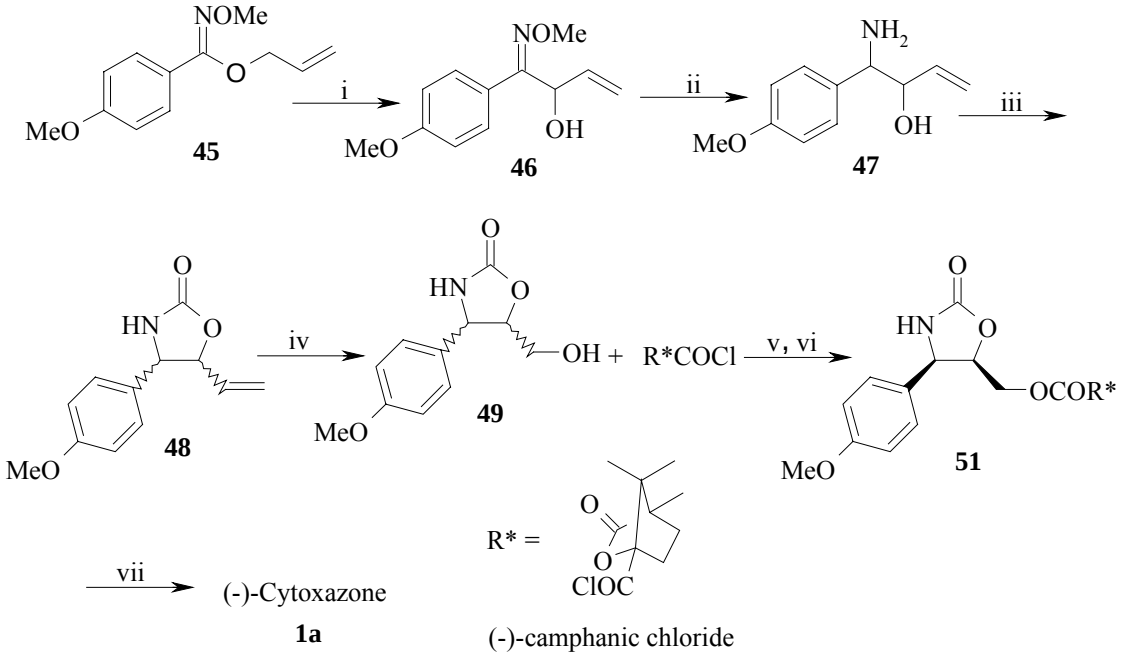
Sugiyama *et al.* synthesized (-)-cytoxazone **1a** using the Petasis three-component coupling reaction of DL-glyceraldehyde, 4-methoxyphenylboronic acid and (R)-1-(1-naphthyl)ethylamine **40**, after formation of an oxazolidin-2-one ring **43**. After separation of the diastereomers using column chromatography and the acidic removal of 1-naphthylethyl groups produced (-)-cytoxazone in 13 % overall yield (**Scheme 8**).



Scheme 8: i) EtOH, reflux, three days (50%); ii) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, RT, 5h; iii) *N,N'*-succinimidyl carbonate (DSC), Et_3N, MeCN, RT, 6h, 66%; iv) TBAF, THF, RT, 63h and SiO_2 column chromatographic separation 59%; v) MsOH, anisole, $MeNO_2$, 50 ^{0}C, 6h.

Naito's approach (2004)[18]

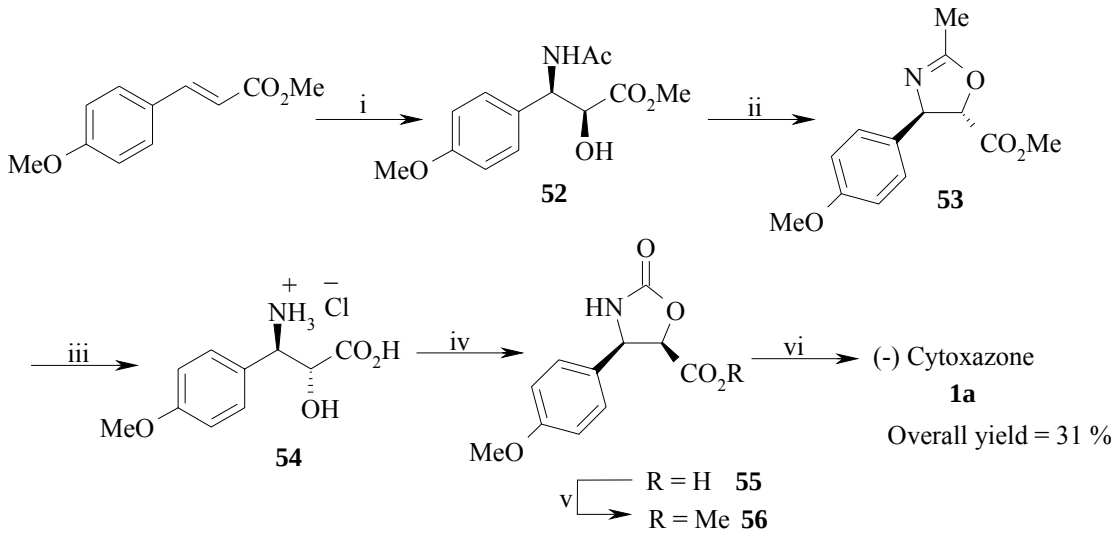
Naito's approach utilizes imino 1,2-Wittig rearrangement for the construction of 2-hydroxyoxime ether (**46**), which was converted into amino alcohol **47** by LAH reduction. Oxazolidinone ring was constructed by $(Boc)_2O$ treatment. Reductive ozonolysis of **48** generated racemic cytoxazone **49** which was resolved using (-)-camphanic chloride **50** in 42 % yield (**Scheme 9**).



Scheme 9: i) 2 equi. LDA, THF, -23 ^{0}C; ii) LAH, diethyl ether, 25 ^{0}C; iii) (a) 2.2 equi. $(Boc)_2O$, DMAP; (b) TFA, CH_2Cl_2, 25 ^{0}C; iv) (a) O_3, CH_2Cl_2, -78 ^{0}C, 2h; (b) MeOH, $NaBH_4$ v) (-)-camphanic chloride, CH_2Cl_2, Et_3N, DMAP, 0 ^{0}C; vi) column chromatographic separation of diastereoisomers; vii) KOH, MeOH, 25^{0}C.

Saicic's approach (2004)[19]

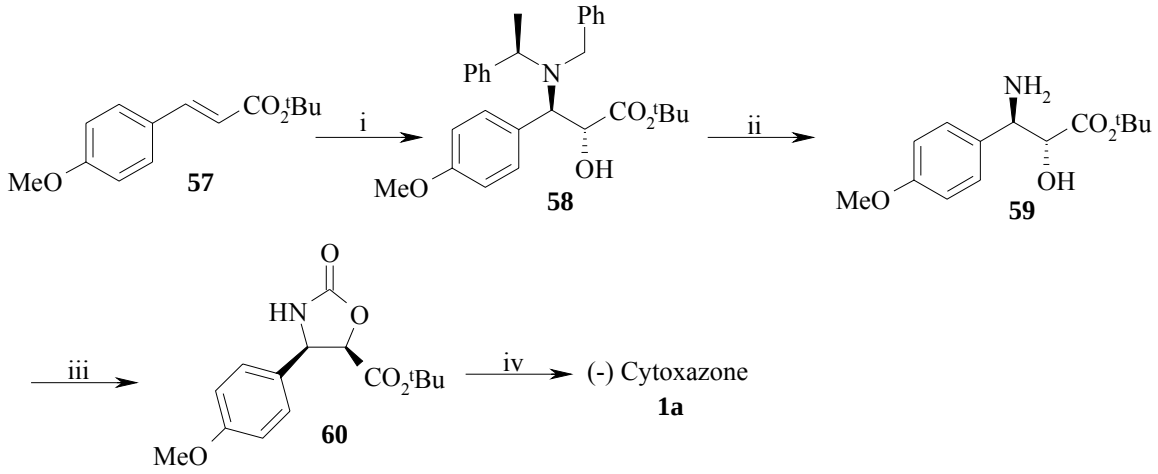
Saicic's approach is based on the Sharpless asymmetric aminohydroxylation reaction protocol, starting from methyl p-methoxycinnamate, in six steps and in 31% overall yield. The required *anti*-aminoalcohol **54** was established by combining Sharpless asymmetric aminohydroxylation with the configurational inversion of the intermediate amidoalcohol **52** via an oxazoline **53** (**Scheme 10**).



Scheme 10: i) $K_2[OsO_2(OH)_4]$ (4 mol %), BrNHAc, $(DHQD)_2PHAL$ (1 mol %), LiOH, H_2O, t-BuOH, 4 ^{0}C, 20 h, 72%; ii) Tf_2O, DMAP, CH_2Cl_2, 80%; iii) 12% HCl, RT, 1.5 h; iv) $ClCO_2CCl_3$, NaOH, H_2O, 0 ^{0}C; v) CH_2N_2, THF, 72%; (vi) $NaBH_4$, THF, 0 ^{0}C, 75%.

Davies's approach (2004)[20]

Davies's approach consist of conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to olefinic ester (**57**) and subsequent *in situ* diastereoselective enolate oxidation with (-)-(camphorsulfonyl)oxaziridine gave amino alcohol **58** in 98% de. Subsequent benzyl deprotection, oxazolidinone (**60**) formation by treatment with diphosgene and ester reduction furnished (-)-cytoxazone **1a** in 61% yield (**Scheme 11**).



Scheme 11: i) lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, -78 ^{0}C; then (-)-CSO [(-)-(camphorsulfonyl)oxaziridine], THF, -78 ^{0}C to RT; ii). $Pd(OH)_2$ on C, H_2 (5atm.), MeOH; iii) (a) CDI, DMAP, THF, rt; (b). $Cl_3COCOCl$, activated charcoal, toluene, RT (1 hour) then reflux (4 h); iv) DIBAL-H, CH_2Cl_2, 0 ^{0}C to RT.

2.0.4 Present Work:

2.0.4.1 Objective

Literature search revealed that various methods such as resolution, chemo-enzymatic or enantioselective synthesis have been developed to synthesize cytoxazone (**1**).[3, 10-20] However, these methods suffer from disadvantages such as low overall yields, the need for separation of diastereoisomers and the use of expensive reagents. In this context, a more practical approach for the synthesis of cytoxazone (**1a**) is highly desirable.

Retrosynthetic analysis (**Fig. 3**) of cytoxazone (**1**) reveals that amino alcohol **61** could be visualized as a key intermediate. In order to prepare optically pure amino alcohol **61**, Os-catalyzed asymmetric aminohydroxylation of the corresponding *cis*-olefin **62** was attempted (Route 1). However, the desired chiral amino alcohol **61** was not obtained. Further, L-proline catalyzed three-component Mannich reaction between aromatic aldehyde, p-anisidine and ketone was also attempted for the synthesis of 4-*epi*-cytoxazone (**1b**) *via* chiral amino ketone **63**. However, we could not oxidize the methyl ketone **63** to the corresponding carboxylic acid in order to achieve 4-*epi*-cytoxazone (**1b**) (Route 2).

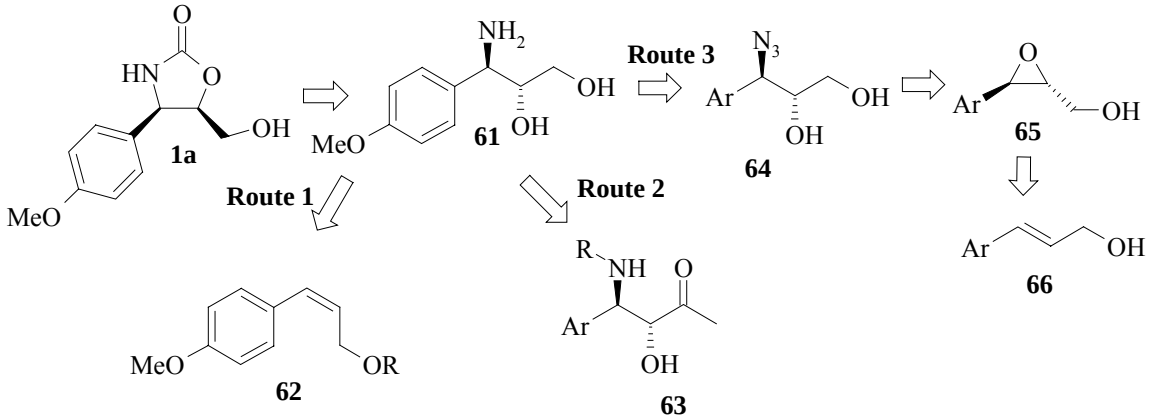


Fig 3: Retrosynthetic analysis of (-)-Cytoxazone (1)

Sharpless asymmetric epoxidation of the allyl alcohol **66** was also attempted. However, the desired chiral epoxide **65** was not obtained. Finally, the key intermediate **61** was successfully synthesized when electron donating OMe group was replaced with OAc group in the aromatic nucleus, using asymmetric epoxidation its transormation to azido alcohol **64** (Route 3). This chapter describes novel strategies for the asymmetric synthesis of (-)-cytoxazone (**1a**) and its *trans* analogue, 4-*epi*-cytoxazone (**1b**) by employing the proline-catalyzed Mannich reaction, asymmetric aminohydroxylation and asymmetric epoxidation (**Schemes 12**, **13** and **15**).

Since this chapter deals with three important asymmetric reactions such as asymmetric epoxidation, asymmetric aminohydroxylation and asymmetric Mannich reaction, which introduce stereogenicity into the prochiral molecule, a brief account of each is presented in the following sections.

2.0.4.2 Asymmetric Epoxidation (AE)

Asymmetric epoxidation of allylic alcohols was one of the leading areas of investigation in synthetic organic chemistry, mainly due to the fact that very high enantioselective induction for a wide range of substrates is possible using several classes of reagents. Today, the most successful asymmetric epoxidation reaction is the titanate-mediated epoxidation of allylic alcohols, or Sharpless epoxidation, which enables the achievement of an enantiomeric excess of over 90% in most cases.[21] The Sharpless epoxidation is a popular laboratory and industrial process due to its both enantioselective and catalytic nature. Not only does it employ inexpensive reagents and involve various important substrates (allylic

alcohols) and products (epoxides) in organic synthesis, but it also demonstrates unusually wide applicability because of its insensitivity to many aspects of substrate structure.

Selection of the proper chirality in the starting tartrate esters and proper geometry of the allylic alcohols allows one to establish both the chirality and relative configuration of the product (**Fig. 4**).

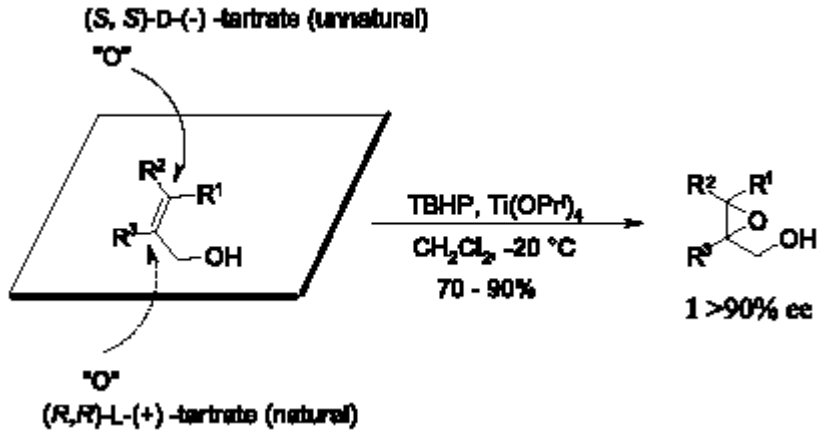


Fig. 4: The Sharpless epoxidation reaction

Since its discovery in 1980,[21] the Sharpless expoxidation of allylic alcohols has become a benchmark classic method in asymmetric synthesis. A wide variety of primary allylic alcohols have been epoxidized with over 90% optical yield and 70-90% chemical yield using TBHP (t-BuOOH) as the oxygen donor and titanium isopropoxide-diethyl tartrate (DET, the most frequently used dialkyl tartrate) as the catalyst. One factor that simplifies the standard epoxidation reaction is that the active chiral catalyst is generated *in situ*, which means that the pre-preparation of the active catalyst is not required.

The wide scope application of this transformation arises not only from the utility of epoxide compounds but also from the subsequent regiocontrolled and stereocontrolled nucleophilic substitution (ring-opening) reactions of the derived epoxy alcohol. These,

through further functionalization, allow access to an impressive array of target molecules in enantiomerically pure form.

It is believed that the species containing equal moles of Ti and tartrate is the most active catalyst. It promotes the reaction much faster than Ti(IV) tetraalkoxide alone and exhibits selective ligand-accelerated reaction.[22] Sharpless suggested that epoxidation was catalyzed by a single Ti center in a dimeric complex with a C2 symmetric axis (**Fig. 5**).[23]

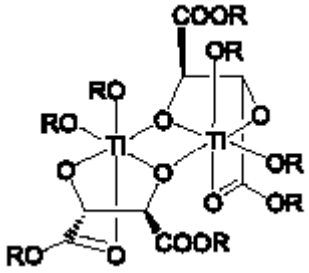


Fig. 5: Structure of dinuclear Ti-tartrate complexes

As shown in **Fig. 6**, the reaction proceeds via a Ti(IV) mixed-ligand complex **A** bearing allyl alkoxide and TBHP anions as ligands. The alkyl peroxide is electrophilically activated by bidentate coordination to the Ti(IV) center. Oxygen transfer to the olefinic bond occurs to provide the complex **B**, in which Ti(IV) is coordinated by epoxy alkoxide and *t*-butoxide. In complex **B**, alkoxide products are replaced by allylic alcohol and TBHP to regenerate **A** and complete the catalytic cycle. It seems clear that enantioselectivity is controlled by the chiral ligands on Ti(IV), which determines the conformation of the coordinated allylic alcohol.

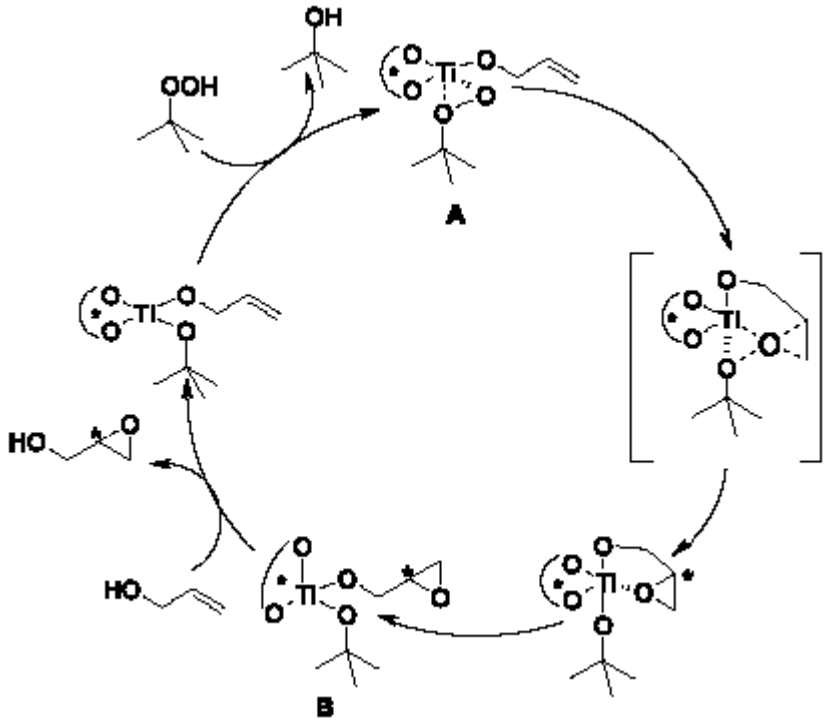


Fig. 6: Mechanism of Ti-catalyzed Sharpless Epoxidation

2.0.4.3 Asymmetric Aminohydroxylation (AA)

The Sharpless asymmetric aminohydroxylation (AA), first reported in 1996,[24] allows for the catalytic and enantioselective synthesis of protected vicinal aminoalcohols, in a single step, from a wide range of simple alkene starting materials.[25] AA reaction provides straightforward access to the aminoalcohol array present in a wide variety of biologically active agents and natural products.[6] As a result, the reaction rapidly gained the prominence of its forerunners, the asymmetric epoxidation (AE) and asymmetric dihydroxylation (AD) processes, and belongs to the significant body of work developed by Sharpless for which he was awarded the 2001 Nobel Prize in Chemistry.

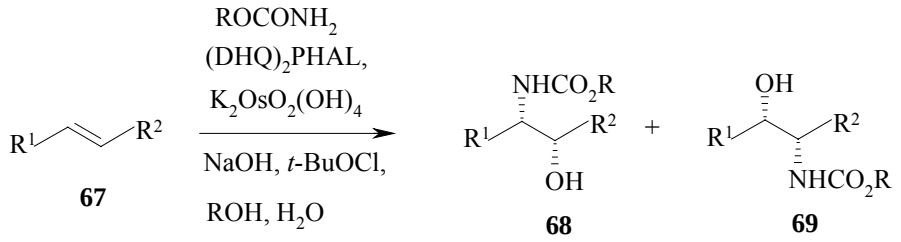
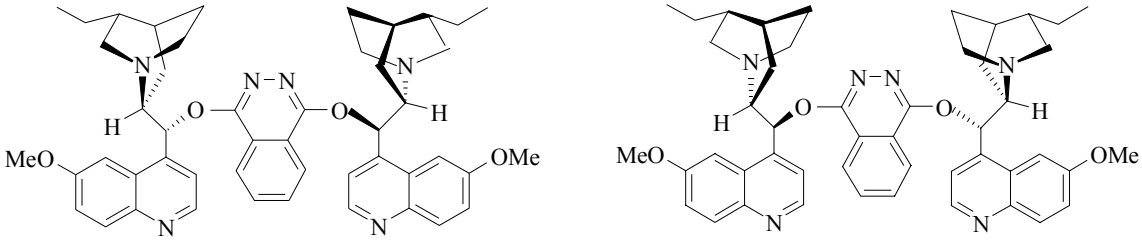


Fig. 7: Enantioselectivity mnemonic scheme

The reaction, typified by the conversion shown in **Fig. 7**, employs a catalyst consisting of *Cinchona* alkaloid derived ligands (**Fig. 8**) and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.



$(DHQ)_2$-PHAL (70) **$(DHQD)_2$-PHAL (71)**

Fig. 8: Ligands for asymmetric aminohydroxylation reaction

A wide range of nitrogen sources are available that differ in the *N*-substituent and therefore give rise to differently protected aminoalcohol products, most of which correspond to commonly used and synthetically useful protecting groups, such as sulfonamides, carbamates and amides.[26] The chiral ligands give rise to the observed enantioselectivity by favouring addition to one enantiotopic face of the prochiral alkene substrate. In this way, the $(DHQ)_2PHAL$ ligand directs addition to the α-face of an alkene **67** to form aminoalcohol products such as **68** or **69** (**Fig. 7**). Alternatively the $(DHQD)_2PHAL$ ligand directs addition to the β-face of **67**.[27]

2.0.4.4 L-proline-catalyzed asymmetric Mannich reaction

Asymmetric catalysis with proline was first realized in the Hajos-Parrish-Eder-Sauer-Wiechert reaction,[28] an enantiogroup-differentiating aldol cyclization. The basis of proline-catalysis in these reactions is the facile *in situ* generation of chiral enolate equivalents (enamines) from ketones and aldehydes. This particular type of catalysis, *enamine catalysis*, represents a way of merging enolization and enantioselective bond construction in enolate-electrophile-type reactions.[29]

List *et al.* recently discovered proline-catalyzed Mannich reactions as direct three-component reactions of ketones (**74**), aldehydes (**72**) and amines (**73**) without prior imine formation (**Fig. 9**).[4] The proline-catalyzed Mannich reactions with hydroxyacetone (**74**) furnished *syn*-1,2-amino alcohols (**76**) in high diastero- and enantioselectivities and in good yields. Thus, proline-catalyzed Mannich reaction can be considered a regiospecific alternative to the Sharpless asymmetric aminohydroxylation. The high diastero- and enantioselectivities can be explained by proposed transition state as shown in **Fig. 9**.

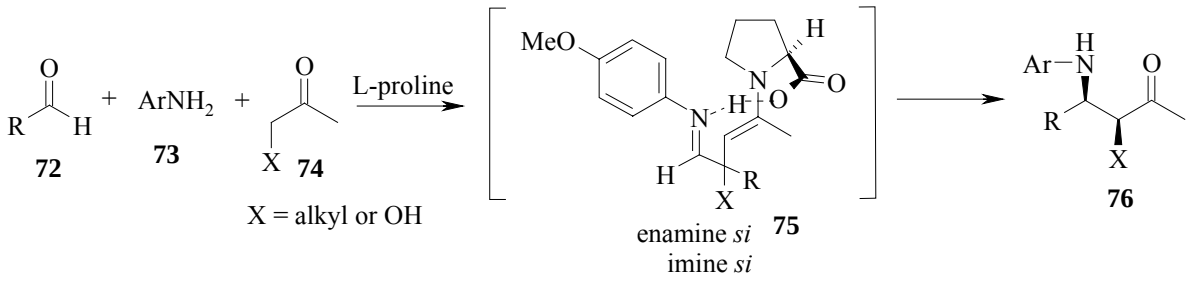


Fig. 9: Trasition State for L-proline-catalyzed Mannich reaction

In the transition state (**75**) it is assumed that the *si*-face of the imine is selectively attacked by the enamine to allow for protonation of its lone pair and compensation of negative charge formation. Attack of the imine *re*-face would result in unfavorable steric interactions between the pyrrolidine and aromatic ring.

The most plausible mechanism of the proline-catalyzed three-component Mannich reaction is depicted in **Fig. 10**. Accordingly, ketone reacts with proline to give an enamine. In a second preequilibrium between the aldehydes and the aniline, an imine is formed. Imine and enamine then react to give after hydrolysis the enantiomerically enriched Mannich product (**76**).

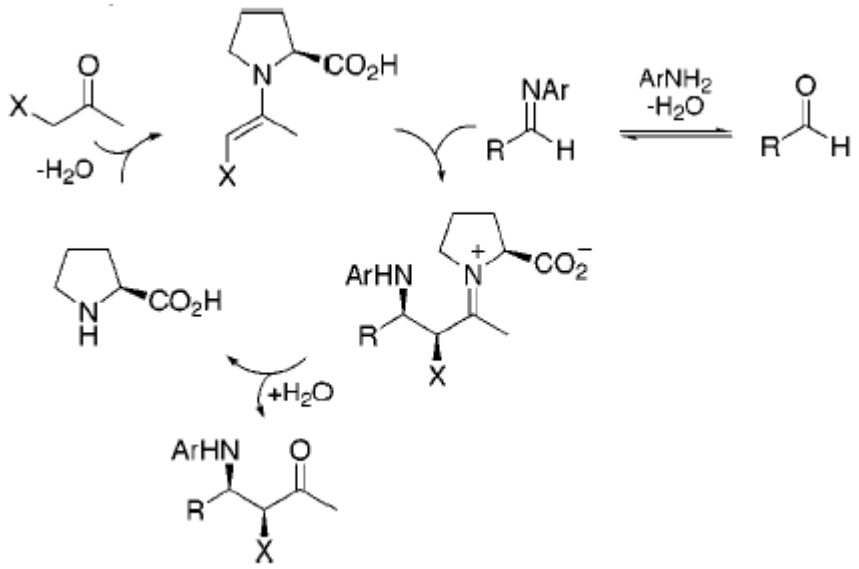
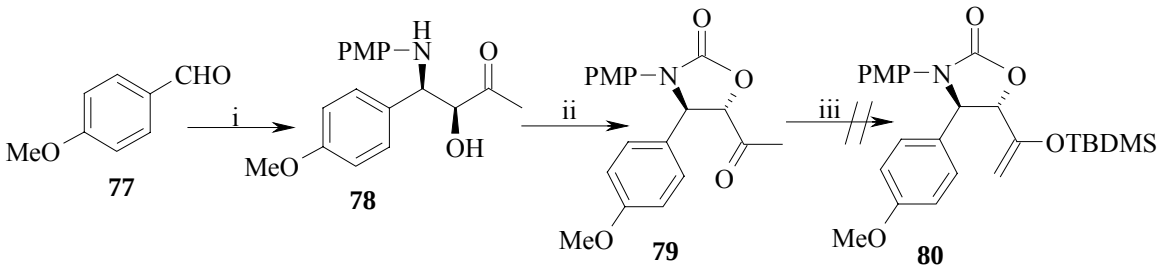


Fig. 10: Mechanism of proline-catalyzed Mannich reaction

2.0.5 Results and Discussion

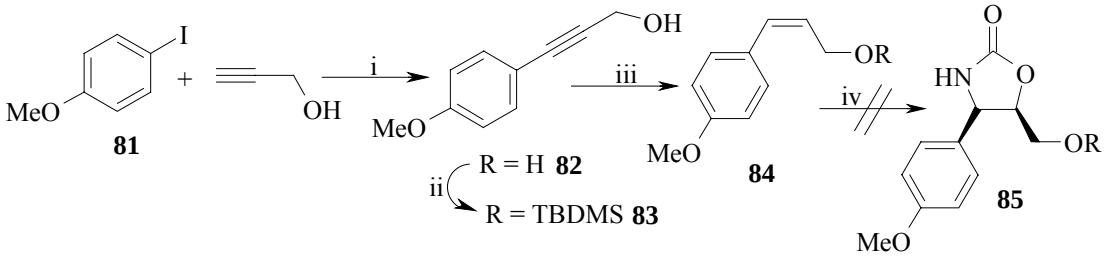
The retrosynthetic analysis envisaged for 4-*epi*-cytoxazone (**1b**) is shown in **Fig. 3**. Route 2 envisaged a L-proline-catalyzed asymmetric one-pot Mannich reaction which constitutes a key step in introducing chirality into the molecule (**Scheme 12**).[4] Thus, when 4-methoxybenzaldehyde was condensed with hydroxyacetone and *p*-anisidine catalyzed by L-proline, we obtained aminoalcohol **78** in 76% yield with low *syn/anti* ratio (2:1). Efforts to improve diastereomeric ratio were not successful even after replacing electron-donating OMe with electron-withdrawing groups such as OAc and OMs on the aromatic nucleus. Amino alcohol **78** was then protected with triphosgene to give oxazolidinone **79** in 82% yield. Attempts to convert methyl ketone **79** to the corresponding carboxylic acid *via* haloform

reaction were not successful. Alternately, we tried to prepare kinetically controlled silyl enol ether **80** from oxazolidinone **79**, so that **80** could be further easily converted to 4-epi-cytoxazone (**1b**) by ozonolysis. However, all attempts (using LDA with TMSCl and TBDMSCl at –78^{0}C) to isolate kinetically controlled product silyl enol **80** ether failed.



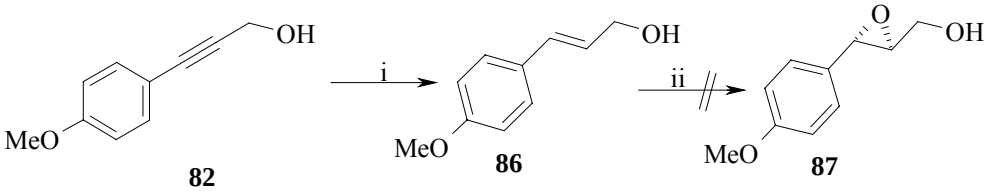
Scheme 12: i *p*-anisidine (1.1 equiv), hydroxyacetone (10 equiv), cat. L-proline, DMSO, 25 ^{o}C, 24 h, 76 %; ii Triphosgene, Et_3N, cat. DMAP, CH_2Cl_2, -10 to 25 ^{o}C, 82 %; iii LDA, TMSCl or TBDMSCl, THF, -78 ^{o}C.

We then turned our attention to another approach (Route 1) in which we employed Os-catalyzed asymmetric aminohydroxylation (AA) as a key step in introducing chirality into the molecule (**Scheme 13**) **Fig. 3**. The key intermediate (Z)-olefinic ether was obtained in two steps: (i) Sonogashira coupling of iodo compond **81** with propargyl alcohol gave acetylenic compound **82** in 96% yield; (ii) Acetylenic compond **82** was stereospecifically reduced to (Z)-olefin **84** in 99% yield with Lindlar catalyst. However, when (Z)-olefinic ether **84** was subjected to Os-catalyzed asymmetric aminohydroxylation (AA) under various reaction conditions,[26] we recovered back all (Z)-olefinic ether **84** without any functionalization. Interestingly, even we did not get any dihydroxylated side product.



Scheme 13: i) cat. $Pd(PPh_3)_4$, cat. CuI, Et_2NH, 25 ^{0}C, 96 %; ii) TBDMSCl, cat. DMAP, Et_3N, CH_2Cl_2, 0 to 25 ^{0}C, 98 %; iii) Lindlar catalyst (5 % Pd on $CaCO_3$ with Pb poisoned), dry hexane, H_2 (1 atm), 25 ^{0}C, 99 %; iv) cat. K_2OsO_6, $(DHQD)_2PHAL$, Urethane, *tert*-BuOCl, aq. 10 % NaOH, n-PrOH, 25 ^{0}C, 24h.

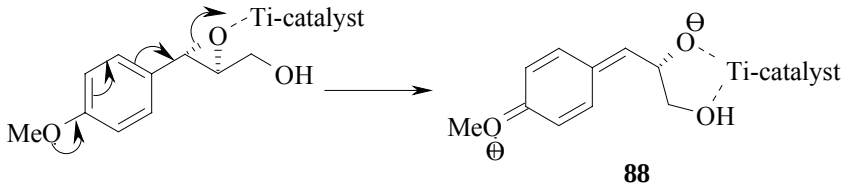
After failing to aminohydroxylate (Z)-olefinic ether **84**, we then turned our attention to functionalize (E)-olefin **86**. The synthetic strategy using this approach is shown in **Fig. 3** (Route 3), wherein Ti-catalyzed asymmetric epoxidation (AE) becomes a key step in introducing chirality into the molecule (**Scheme 14**).



82 **86** **87**

Scheme 14: i LAH, THF, 0^0C, 3h, 90%. ii $Ti(OiPr)_4$, (+)-DIPT, anhydrous TBHP, CH_2Cl_2, -20^0C, 24h.

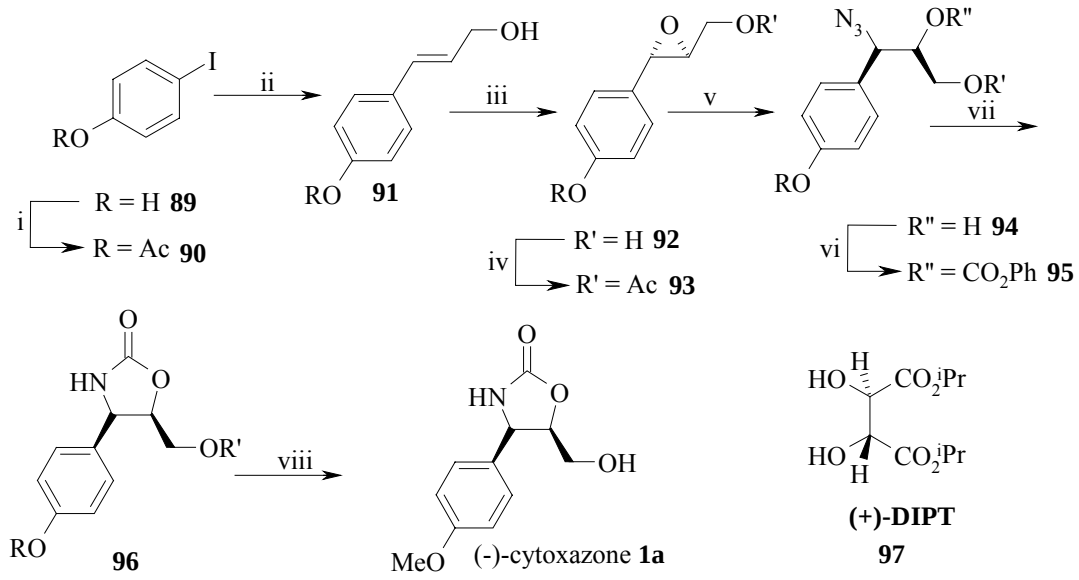
Accordingly, we subjected (*E*)-allyl alcohol **86** for Ti-catalyzed asymmetric epoxidation (AE) under standard reaction conditions; here again, all our attempts to obtain chiral epoxide **87** failed. The reason may be due to the positive inductive effect of methoxy group present on aromatic ring, which facilitates the opening of epoxide ring, thus deactivating the Ti-catalyst by forming chelate **88** (**Fig. 11**).



88

Fig. 11: Proposed mechanism for deactivation of Ti-catalyst

In order to eliminate this positive inductive effect due to OMe group, we changed our strategy by replacing electron-rich OMe group on aromatic ring with electron-deficient OAc group. This protecting group can be further deprotected easily during the course of the synthesis (**Scheme 15**).



Scheme 15: i AcCl, Et_3N, CH_2Cl_2, 0 to 25^{0}C, 6h, 95%. ii Allyl alcohol (3 equiv), AgOAc (1 equiv), cat. $Pd(OAc)_2$, cat. PPh_3, DMF, 70^{o}C, 16h, 81%. iii anhyd. 5.4 M TBHP in CH_2Cl_2, 4Å MS, cat. $Ti(O^iPr)_4$, cat. (+)-DIPT (**97**), CH_2Cl_2, -20^{o}C, 20h, 78%. iv AcCl, Et_3N, cat. DMAP, CH_2Cl_2, 25^{0}C, 87%. v) NaN_3, cat. NH_4Cl, THF:H_2O (2:1), 50^{0}C, 3h, 79%. vi PhOCOCl, pyridine, CH_2Cl_2, -5 to 25^{0}C, 1h, 93%. vii PPh_3 (4 equiv), THF:H_2O (10:1), 50^{0}C, 2h, 87%. viii (a) aq. $NaHCO_3$, MeOH, reflux, 1h; (b) NaH, MeI, THF, 0 to 25^{0}C, 3h, 69%.

Thus, 4-iodophenol **89** was acylated quantitatively using acetyl chloride and Et_3N in CH_2Cl_2 to yield 4-iodophenyl acetate **90**. The *trans*-allylic alcohol **91** was prepared in 81% yield by the Pd-catalyzed arylation of allyl alcohol with 4-iodophenyl acetate **90**. The *trans* geometry of the double bond of allyl alcohol **91** was confirmed by the ^{1}H-NMR spectrum, which showed a doublet at δ 6.57 with the coupling constant J = 15.90 Hz. The *trans*-allylic alcohol **91** was then subjected to AE reaction using catalytic amount of $Ti(O^iPr)_4$ and diisopropyl tartarate [(+)DIPT] as chiral auxiliary to give the chiral epoxide **92** in 78% yield and 92.5% ee (determined by chiral HPLC using Chiralcel OD-H® column). The formation of epoxide **92** was confirmed by the disappearance of a doublet at δ 6.57 and the appearance of proton signals in the region δ 3.78 –4.08 for methine protons in its ^{1}H-NMR spectrum. Further, its ^{13}C-NMR spectrum showed signals at δ 54.67 and 60.89 due to the two carbons of epoxy ring (**Fig. 12**).

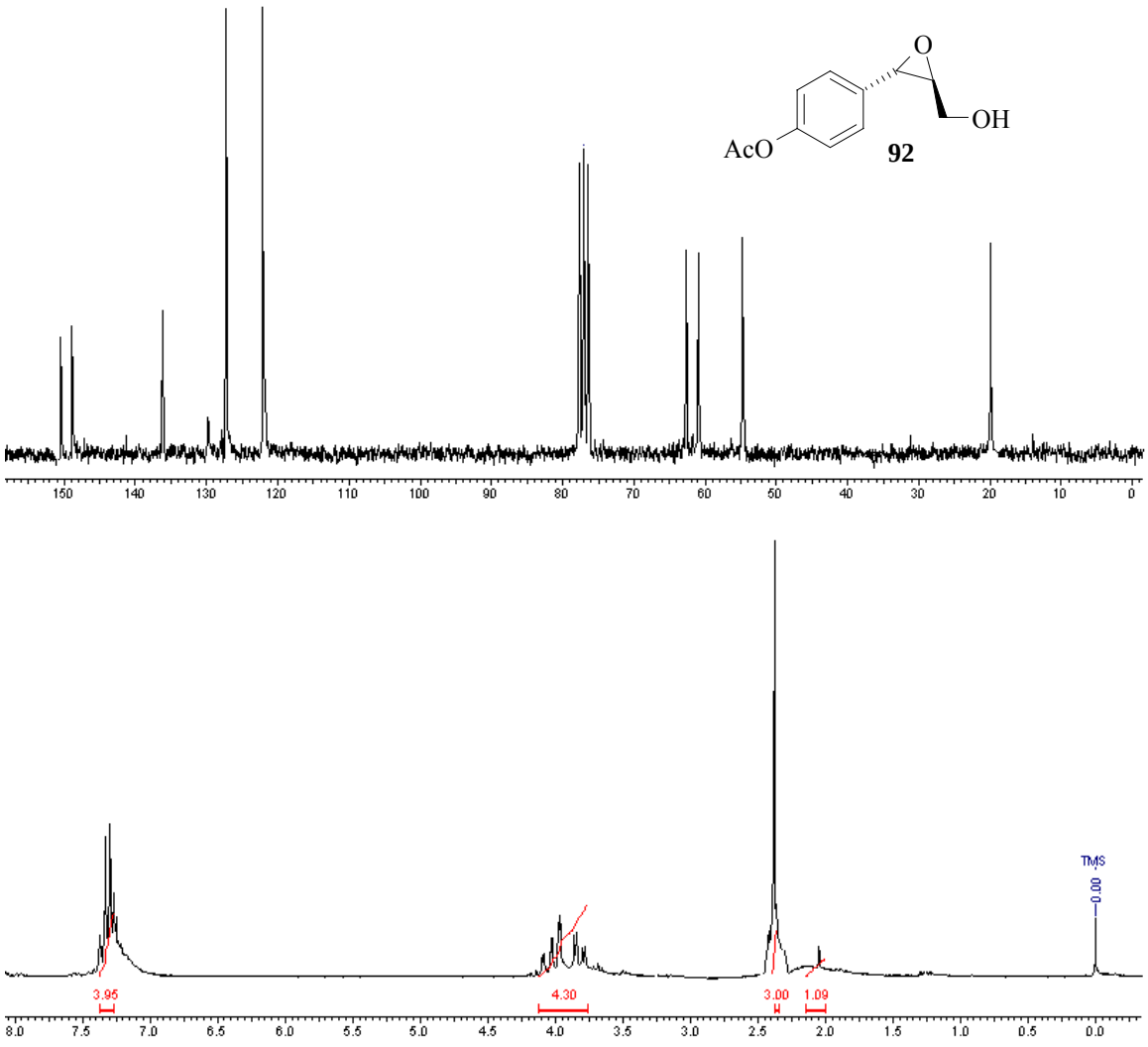


Fig. 12: ^{13}C and ^{1}H NMR spectra of epoxy alcohol 92

The primary alcohol in epoxide **92** was then protected with acyl group by treating the epoxy alcohol **92** with acetyl chloride in presence of Et_3N and catalytic amount of DMAP in CH_2Cl_2 at 25^0C for 3h to yield the epoxy acetate **93** in 86% yield. The ^{1}H-NMR spectrum of epoxy acetate **93** showed the presence of the two acyl groups as evidenced by two singlets at δ 2.12 and 2.40. Its ^{13}C-NMR spectrum also showed carbon signals at δ 20.55 and 20.76 indicating the presence of two acyl CH_3 groups (**Fig. 13**).

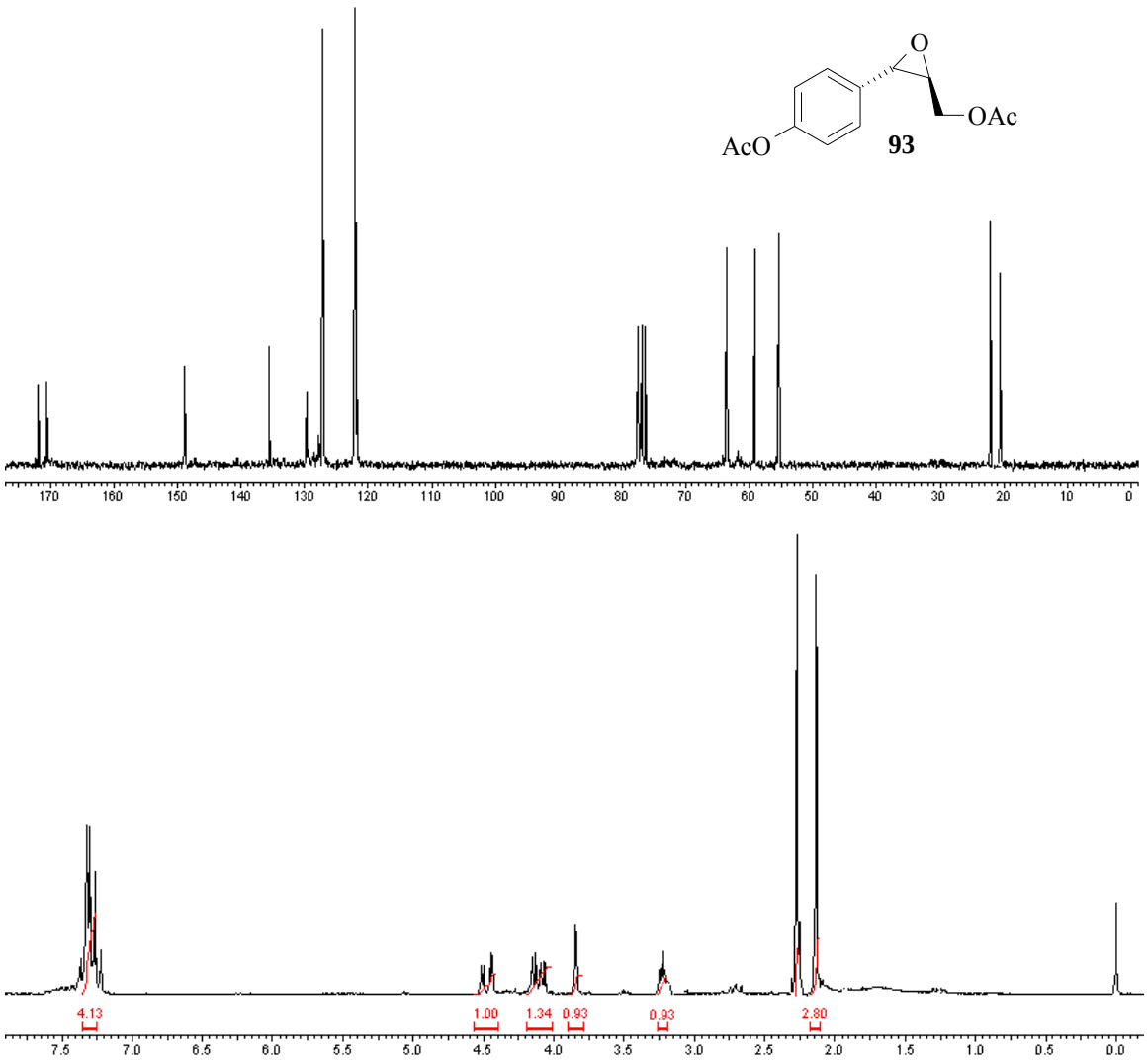


Fig. 13: ^{13}C and ^{1}H NMR spectra of epoxy ester 93

The epoxy ester **93** was then treated with aq. NaN_3 at 25^0C in CH_2Cl_2 for 12h, but all attempts to isolate azido alcohol **94** in pure form failed. To overcome this difficulty, catalytic amount of NH_4Cl was added to obtain azido alcohol **94** in 88% yield. The IR spectrum of azido alcohol **94** showed intense bands at 2108 and 3472 cm^{-1} indicative of presence of N_3 and OH groups. Its ^{1}H-NMR showed a signal at δ 4.63 indicating a change in the chemical shift of the benzylic CH-N_3 proton. This signal is slightly downfield compared to methine protons in

epoxide **93** (δ 3.85). In ^{13}C-NMR spectrum, the signal of CH-N_3 carbon appeared at δ 66.09 (**Fig. 14**).

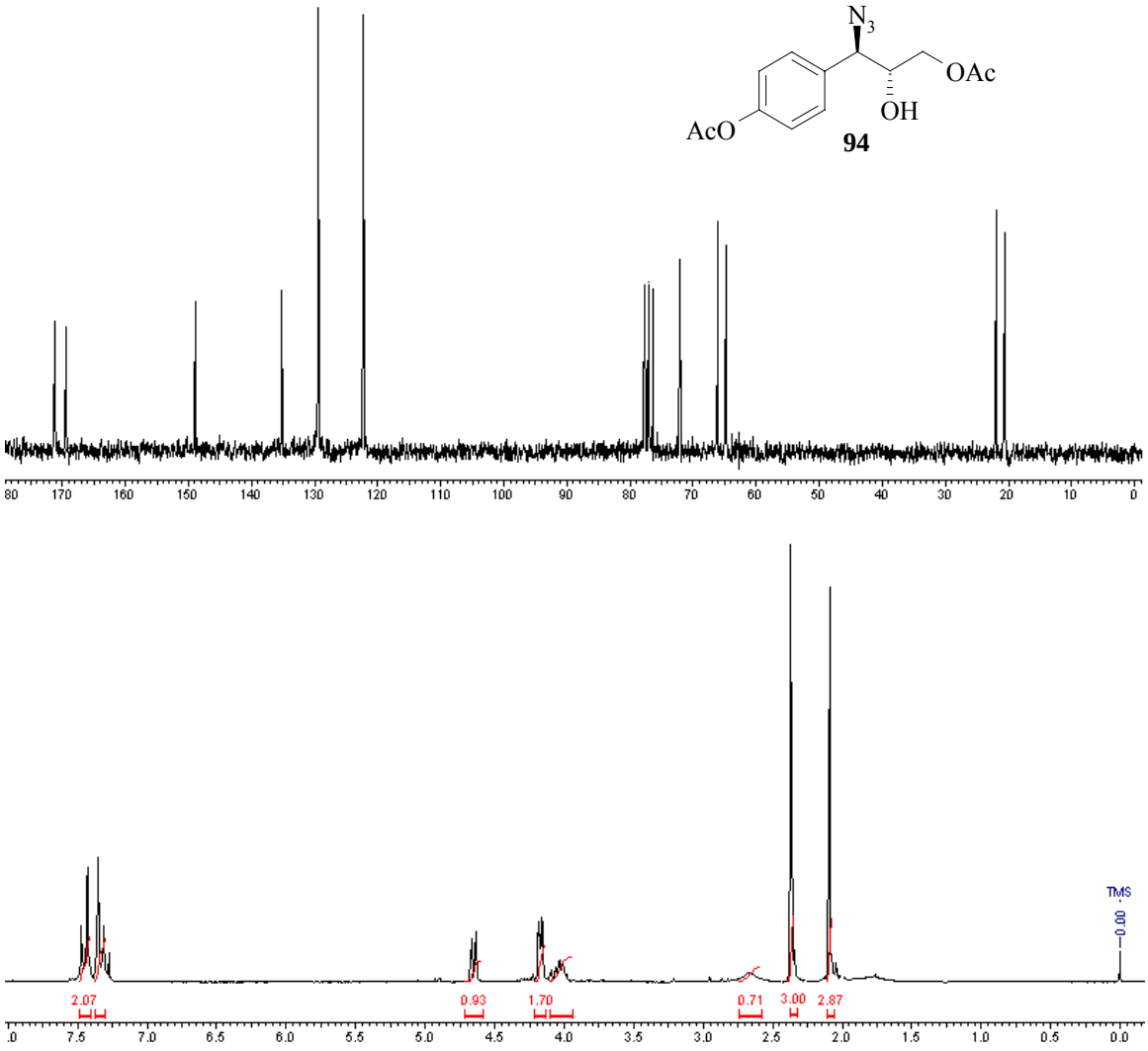
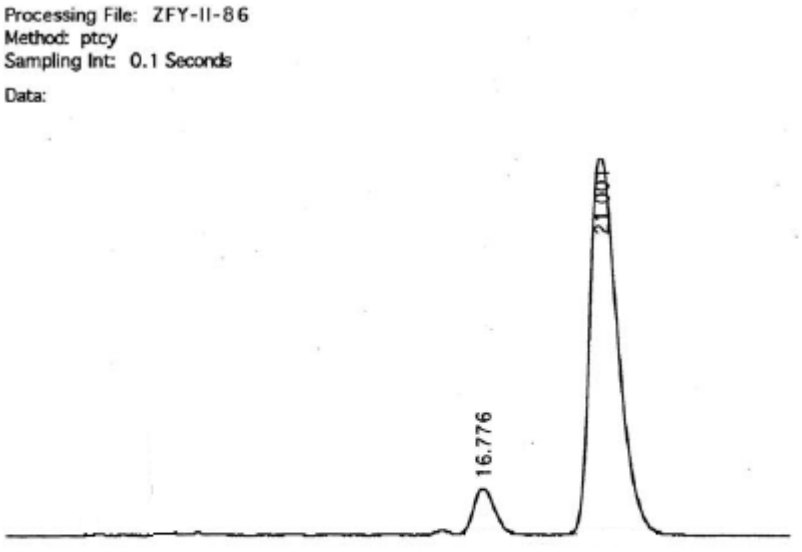


Fig. 14: ^{13}C and ^{1}H NMR spectra of azido alcohol 94

We followed standard protocol[10-13] for the conversion of azido alcohol **94** to the corresponding oxazolidinone **96**. The OH group of azido alcohol **94** was transformed to carbonate ester **95** using phenyl chloroformate, which was further reductively cyclized by treatment with PPh_3, thereby producing oxazolidinone **96**. The formation of oxazolidinone **96** was confirmed from its ^{1}H-NMR, which showed the appearance of broad peak at δ 8.11 due to

peculiar oxazolidinone ring NH proton. Hydrolysis of both acetate groups was achieved by refluxing with $NaHCO_3$ in MeOH, the deacylated oxazolidinone was directly methylated using MeI in the presence of NaH to give the required (-)-cytoxazone **1a** in 65% yield and in 83% ee [measured by both chiral HPLC using Chirasphere® column (**Fig. 15**) and $[\alpha]_D$]. The ^{1}H NMR spectrum of **1a** established the existence of an 1,4-disubstituted aromatic ring because of the presence of two doublets each of 2H at δ 6.91 and 7.15. In the aliphatic region, two methine protons attached to oxygen and nitrogen atoms were observed at δ 4.62-4.90. In addition, a singlet of a methoxy group at δ 3.75 (OCH_3), and the ABX pattern of an oxymethylene group was also observed between δ 2.95-2.97. Its ^{13}C-NMR spectrum showed signals at δ 56.82 and 61.93 due to benzylic and oxymethylene group carbons respectively (**Fig. 16**). The ^{1}H-NMR and ^{13}C-NMR spectral data of (–)-cytoxazone (**1a**) matched very well with that of the published values.[1]



Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	16.776	*N	2843	135468	8.127
2	21.001	*N	23862	1531408	91.872
Total Area				1666876	99.999

Fig. 15: HPLC chromatogram of (-)-cytoxazone (1a)

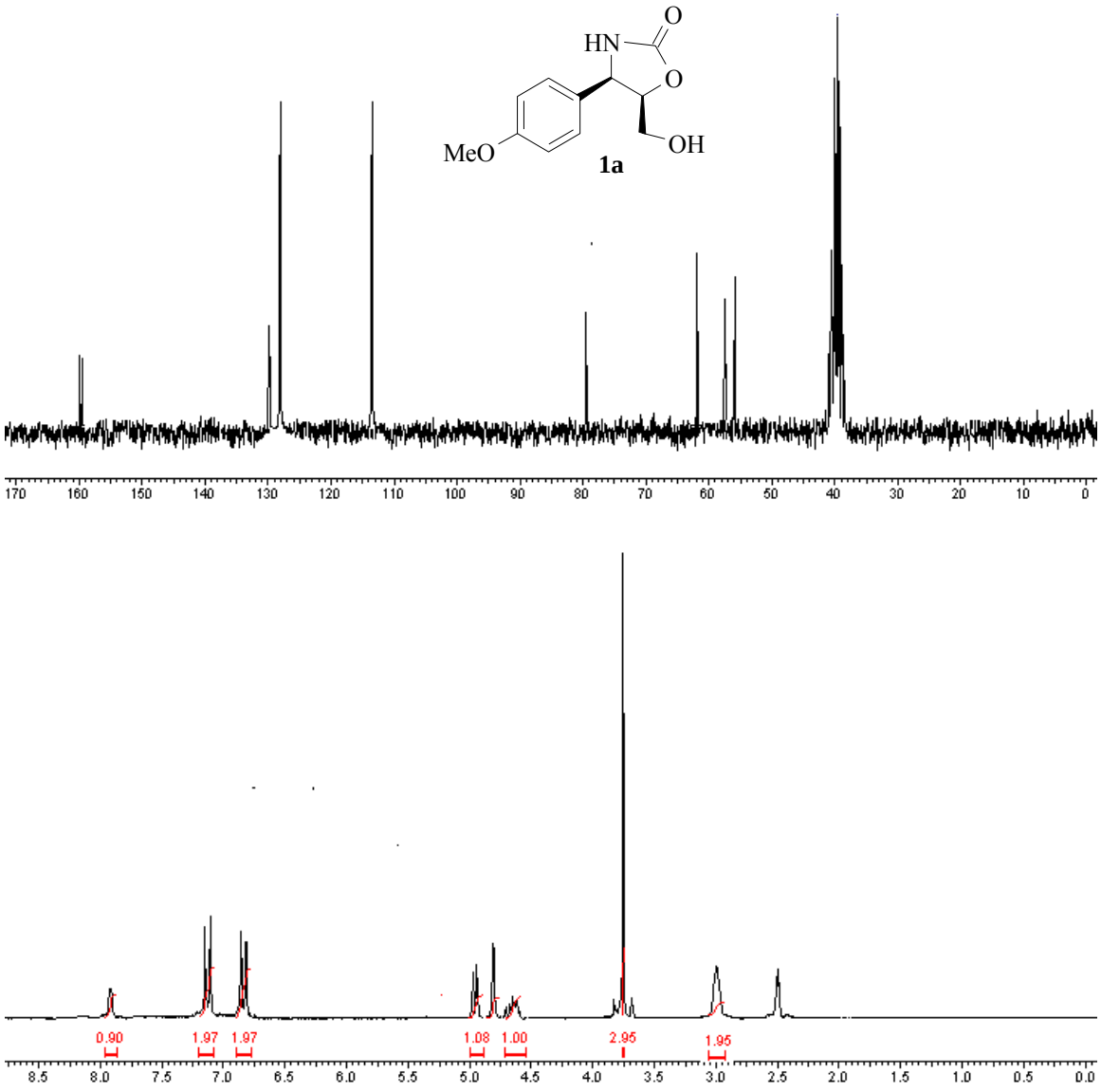


Fig. 16: ^{13}C and ^{1}H NMR spectra of (-)-cytoxazone (1a)

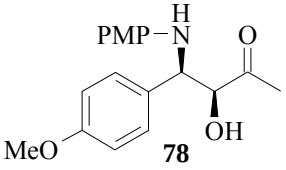
2.0.6 Conclusion

In conclusion, we have achieved for the first time a simple and efficient asymmetric synthesis of (-)-cytoxazone using asymmetric epoxidation of allylic alcohol (AE) in the presence of $Ti(OiPr)_4$ as a catalyst and (+)-DIPT as ligand with a over all yield of 23.03%, and optical purity of 83% ee (by HPLC) in eight steps starting from the readily available 4-iodophenol.

2.0.7 Experimental Section

Preparation of (3S,4R)-4-(4-methoxyphenylamino)-3-hydroxy-4-(4-methoxyphenyl)butan-2-one (78):

A mixture of L-proline (0.23 g, 2 mmol), p-anisidine (1.35 g, 11 mmol), p-anisaldehyde (1.36 g, 10 mmol) and hydroxyacetone (2ml) in DMSO (10ml), was stirred at room temperature for 24 h. After completion of reaction, aq. saturated NH_4Cl (10ml) was added and the mixture was extracted with ethyl acetate. Upon evaporation of the solvent, crude product was purified by column chromatography on silica gel (EtOAc: pet. ether, 3:4) yielding required Mannich product (**78**) 2.39 g (76%) as yellow oil.



78

Yield: 76%; yellow oil; $[\alpha]^{25}_{D}$: – 1.28 (c 1.3, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1092, 1237, 1346, 1513, 1709, 2360, 2916, 3269; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 4.42 (d, *J* = 2.20 Hz, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 6.54 (m, 2H), 6.72 (m, 2H), 6.96 (m, 2H), 7.35 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 25.79, 55.62, 56.12, 60.14, 81.32, 114.15, 115.24, 115.76, 128.60, 131.58, 140.00, 152.77, 159.44, 207.98; **Analysis:** $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44; found C, 68.50; H, 6.80; N, 4.39%.

Preparation of (4R,5S)-5-acetyl-3,4-bis(4-methoxyphenyl)oxazolidin-2-one (79):

The Mannich product **78** (0.315 g, 1 mmol), in dry CH_2Cl_2 (20 ml) was cooled to – 20^0C and to this Et_3N (506 mg, 5 mmol) and triphosgene (297 mg, 1 mmol) was added. The mixture was warmed to room temperature, stirred for 3h, and quenched with aq. NH_4Cl (10ml). After extraction with CH_2Cl_2 (20 ml), the organic layer was, dried over Na_2SO_4 and concentrated to furnish crude *trans*-oxazolidine **79** which was further purified by column chromatography (EtOAc: pet. ether, 5:3) yielding 0.28 g (82%) of white solid.

Yield: 82%; **mp:** 106-108^{0}C (crystallized from EtOH); **$[\alpha]^{25}_D$**: – 18.14 (c 0.5, $CHCl_3$); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 4.58 (d, *J* = 4.80 Hz, 1H), 5.41 (d, *J* = 4.80 Hz, 1H), 6.55 (m, 2H), 6.71 (m, 2H), 6.95 (m, 2H), 7.37 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 26.72, 55.24, 55.97, 62.43, 83.12, 114.16, 115.24, 115.76, 128.87, 129.19, 129.34, 137.77, 157.00, 204.55; **Analysis:** $C_{19}H_{19}NO_5$ requires C, 66.85; H, 5.61; N, 4.10; found C, 66.77; H, 5.56; N, 4.04%.

Preparation of 3-(4-methoxyphenyl)prop-2-yn-1-ol (82):

A two-necked 100 ml RB flask was charged with p-iodoanisole (4.68 g, 20 mmol), propargyl alcohol (1.68 g, 30 mmol), CuI (0.40 g, 2 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol) and diethylamine (50 ml). The resulting mixture was stirred at 25^{0}C for 6 h. Then the reaction was diluted with ethyl acetate (80 ml), washed with 10% HCl (10 ml), water, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give black colored thick oil. This crude product was purified on column chromatography using 20% ethyl acetate in pet. ether as eluent to afford pure **82** (3.10 g, 96%) as pale yellow colored solid.

Yield: 96%; **mp:** 74-75^{0}C; **IR** ($CHCl_3$, cm^{-1}): 669, 757, 833, 1033, 1172, 1215, 1249, 1292, 1463, 1510, 1606, 2856, 2927, 3018, 3421; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.61 (brs, 1H), 3.78 (s, 3H), 4.48 (s, 2H), 6.79 – 6.84 (d, *J* = 9.00 Hz, 2H), 7.34 – 7.39 (d, *J* = 9.00 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 51.42, 55.13, 85.38, 85.90, 113.83, 114.57, 133.06, 159.59; **MS** m/z (% rel. intensity): 162 (M+, 100), 145 (33), 131 (40), 108 (30), 102 (33), 91 (57), 77 (30), 63 (43); **Analysis:** $C_{10}H_{10}O_2$ requires C, 74.06; H, 6.21; found C, 74.17; H, 6.14 %.

Preparation of (3-(4-methoxyphenyl)prop-2-ynyloxy)(*tert*-butyl)dimethylsilane (83):

To a stirred solution of alcohol **82** (2.46 g, 15.2 mmol) in dry CH_2Cl_2 (25 mL), Et_3N (2.29 g, 22.7 mmol) and *tert*-butyldimethylsilyl chloride (2.75 g, 18.2 mmol) were added portionwise at 0^0C. This mixture was then brought to room temperature and stirred for 12h and then quenched with MeOH. It was poured into water and extracted with EtOAc. The organic phase was washed with aq. $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$ and purified over column chromatography using pet. ether as eluent to afford pure **83** (4.11 g, 98%) as yellow colored oil.

Yield: 98%; yellow color oil; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.00 (s, 6H), 0.78 (s, 9H), 3.61 (s, 3H), 4.34 (s, 2H), 6.61 (dd, *J* = 8.84 Hz, 1H), 6.66 (dd, *J* = 8.84 Hz, 1H), 7.15 (dd, *J* = 8.97 Hz, 1H), 7.20 (dd, *J* = 8.97 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ -5.23, 18.03, 25.62, 51.94, 54.64, 84.62, 86.26, 113.62, 114.90, 132.70, 159.37; **MS** m/z ((% rel. intensity): 276 (M^+, 5), 261 (3), 231 (3), 219 (65), 205 (5), 189 (80), 174 (5), 159 (5), 145 (100), 130 (15), 115 (10), 102 (20), 94 (20), 75 (15), 57 (10), 41 (12); **Analysis:** $C_{16}H_{24}O_2Si$ requires C, 69.51; H, 8.75; found C, 69.47; H, 8.70%.

Preparation of (Z)-(4-methoxycinnamyloxy)(*tert*-butyl)dimethylsilane (84):

To a 50 ml 2 neck RB flask equipped with a condenser and a balloon filled with H_2 at 1 atm. was added Lindlar catalyst (5% Pd/$CaCO_3$ poisoned with lead, 1.4g), silyl ether **83** (2.76g, 10 mmol), quinoline (2.6 g, 21 mmol) and 45 ml of dry n-hexane. The resulting mixture was stirred at room temperature under H_2 (1 atm.) for 1 h. When starting material was consumed (monitored by TLC), the reaction mixture was filtered through sintered funnel. After distilling off hexane, we obtained 2.75g (99%) of pure (Z)-olefin **84**.

Yield: 99%; yellow color oil; **IR** ($CHCl_3$, cm^{-1}): 534, 617, 650, 668, 814, 837, 909, 938, 960, 983, 1006, 1035, 1085, 1175, 1216, 1253, 1302, 1361, 1405, 1442, 1464, 1471, 1511, 1575, 1607, 1681, 2401, 2857, 2897, 2931, 2956, 3019, 3443; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.01 (s, 6H), 0.84 (s, 9H), 3.76 (s, 3H), 4.37-4.40 (d, *J* = 5.86 Hz, 2H), 5.61-5.73 (q, *J* = 5.86 Hz, 1H), 6.34-6.40 (d, *J* = 11.72 Hz, 1H), 6.79-6.84 (d, *J* = 8.79 Hz, 2H), 7.06-7.10 (d, *J* = 8.80 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 5.18, 18.25, 25.87, 55.08, 60.36, 113.51, 129.04, 129.49, 130.00, 130.76, 158.55; **MS** m/z ((% rel. intensity): 278 (M^+, 5), 222 (15), 221 (50), 205 (5), 189 (5), 175 (10), 166 (5), 147 (100), 131 (45), 115 (75), 103 (65), 91 (90), 75 (90), 57 (80), 41 (90); **Analysis:** $C_{16}H_{26}O_2Si$ requires C, 69.01; H, 9.41; found C, 69.00; H, 9.35%.

Preparation of (*E*)-3-(4-methoxyphenyl)prop-2-en-1-ol (86):

LAH (0.29 g, 7.8 mmol) was taken in THF (23 ml) and the slurry cooled to 0 ^{0}C in an ice bath under nitrogen atmosphere. To this mixture, alcohol **82** (1.60 g, 9.88 mmol) was added drop-wise and the reaction mixture was stirred at 0 ^{0}C for 30 min. After completion of reaction (monitored by TLC), ice-cold water (20 ml) was added and extracted with ether (3 x 30 ml). The ethereal layer was washed with 10% HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether : EtOAc (3:1) as eluent to furnish **86** as white solid (1.18 g). **Yield:** 73%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.60 (brs, 1H), 3.81 (s, 3H), 4.28 – 4.31 (q, *J* = 6.00 Hz, 2H), 6.17 – 6.30 (m, 1H), 6.52 – 6.60 (dd, *J* = 16 Hz, 1H), 6.84 – 6.88 (dd, *J* = 8.00 Hz, 2H), 7.31 – 7.35 (dd, *J* = 8.00 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 55.13, 63.58, 113.90, 126.29, 127.54, 129.42, 130.67, 159.15; **Analysis:** $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37; found C, 73.12; H, 7.80%.

Preparation of 4-((*E*)-3-hydroxyprop-1-enyl)phenyl acetate (91):

A mixture of 4-iodophenyl acetate **90** (7.89g, 30 mmol) and allyl alcohol (3.48g, 60 mmol) was stirred for 16 h in the presence of the AgOAc (5.01g, 30 mmol), PPh_3 (0.78g, 3 mmol), $Pd(OAc)_2$ (0.33g, 1.5 mmol) at 70^{0}C in 50 ml DMF. The reaction mixture was filtered through sintered funnel and washed with aq. HCl (15ml), water (15ml), aq. $NaHCO_3$ (15ml) and brine (15ml) sequentially. The crude allyl alcohol was purified by column chromatography using pet. ether : EtOAc (3:1) as eluent to furnish 4.65g of **91** as white solid. **Yield:** 81%; **mp:** 81-83^{0}C (crystallized from EtOH); **IR** ($CHCl_3$, cm^{-1}): 504, 524, 692, 755, 872, 970, 1016, 1087, 1151, 1196, 1332, 1414, 1503, 1600, 1677, 1714, 2869, 2939, 3029, 3366; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ δ 1.67 (brs, 1H), 2.38 (s, 3H), 4.32 – 4.34 (d, *J* = 4.92 Hz, 2H), 6.27 – 6.40 (m, 1H), 6.57 – 6.65 (d, *J* = 15.90 Hz, 1H), 7.20 – 7.25 (d, *J* = 8.72 Hz, 2H), 7.39 – 7.43 (d, *J* = 8.72 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.74, 61.84, 121.52, 127.15, 128.01, 129.76, 135.84, 147.80; **MS** m/z ((% rel. intensity): 192 (M^+, 5), 174 (3), 150 (50), 131 (10), 121 (10), 107 (100), 94 (60), 76 (30), 65 (15), 50 (20); **Analysis:** $C_{11}H_{12}O_3$ requires C, 68.74; H, 6.29; found C, 68.61; H, 6.18%.

Preparation of 4-((2S,3S)-3-(hydroxymethyl)oxiran-2-yl)phenyl acetate (92) using Sharpless asymmetric epoxidation:

A 100 ml 2-neck RB flask was charged with 4Å molecular sieves (1 g), 20 ml CH_2Cl_2 and cooled at -25^0C. Then the $Ti(O^iPr)_4$ (0.59 ml, 0.568 g, 2 mmol) and L-(+)-DIPT (0.53 ml, 0.585 g, 2.5 mmol) was added sequentially and the mixture was stirred for 10 min. before the addition of allyl alcohol **91** (3.84 g, 20 mmol). Finally a 5.4 M anhydrous TBHP solution in CH_2Cl_2 (7.6 ml, 41 mmol) was added and the resulting mixture was stirred at -20^0C for 20 h. After completion of reaction (monitored by TLC), 10% aq. tartaric acid (20 ml) was added and the aqueous layer solidifies. After 1h the reaction was brought to room temperature and stirring was continued until the aqueous layer becomes clear. The organic layer was washed with brine and dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using pet. ether: EtOAc (3:1) as eluent to furnish epoxide **92** as white solid (3.23 g).

Yield: 78%; **mp:** 96^0C (crystallized from EtOH); **$[\alpha]^{25}_D$**: + 23.59 (c 1.3, $CHCl_3$); **HPLC**: 92.5% ee, Chiralcel OD-H®, λ = 254 nm, 5% 2-propanol/hexane, 1 ml/min., Retention time: (R,R) 10.81 min. (S,S) 15.716 min.; **IR** ($CHCl_3$, cm^{-1}): 527, 605, 703, 736, 784, 872, 971, 1045, 1152, 1175, 1200, 1232, 1369, 1417, 1504, 1605, 1740, 2939, 3029, 3060, 3499; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.04 (brs, 1H), 2.39 (s, 3H), 3.78 – 4.08 (m, 4H), 7.25 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.75, 54.67, 60.89, 62.63, 122.11, 127.22, 136.13, 148.81, 149.23; **Analysis:** $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81; found C, 63.38; H, 5.78%.

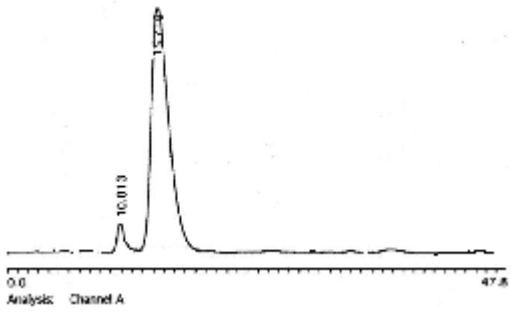


Fig. 17: HPLC chromatogram of epoxy alcohol (92)

Preparation of 4-((2S,3S)-3-(acetoxymethyl)oxiran-2-yl)phenyl acetate (93):

The mixture of epoxy alcohol **92** (2.08 g, 10 mmol), acetyl chloride (0.858g, 11 mmol), Et_3N (1.52 g, 15 mmol) and DMAP (0.122 g, 10 mol%) in dry CH_2Cl_2 (10 ml) was stirred at room temperature. After the reaction was complete (TLC), the solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (10 ml) and was extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with saturated $NaHCO_3$ (2 x 15 ml), brine (15 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to afford 2.17g (87%) of epoxy ester **93**.

Yield: 87%; **gum, IR** ($CHCl_3$, cm^{-1}): 526, 604, 702, 735, 783, 871, 970, 1016, 1044, 1109, 1152, 1175, 1200, 1232, 1369, 1418, 1504, 1605, 1740, 1913, 2939, 3029, 3062, 3499; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.40 (s, 3H), 3.20 – 3.25 (m, 1H), 3.84 – 3.85 (d, *J* = 1.89 Hz, 1H), 4.07 – 4.16 (d, *J* = 5.68 Hz, 1H), 4.44 – 4.51 (d, *J* = 3.41 Hz, 1H), 7.22 – 7.37 (dd, *J* = 9.09, 6.57 Hz, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.55, 20.76, 55.45, 59.29, 63.67, 122.09, 127.15, 129.71, 135.57, 148.93, 170.51; **Analysis:** $C_{13}H_{14}O_5$ requires C, 50.34; H, 4.93; found C, 50.28; H, 4.89%.

Preparation of (2R,3R)-3-azido-2-hydroxy-3-(4-acetoxyphenyl)propyl acetate (94):

To a solution of NaN_3 (0.29 g, 5.2 mmol) and NH_4Cl (0.054 g, 1 mmol) in water (5 ml), a solution of epoxy ester **93** (0.775 g, 3.1 mmol) in THF (10 ml) was added. The reaction mixture was stirred at 50 °C for 3 h. Cooled to RT and the solution was extracted with EtOAc and washed with water (50 ml), dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, the crude product was purified by column chromatography over silica gel (EtOAc: pet. ether, 2:8) yielding 0.717 g (79%) of azido alcohol **94**.

Yield: 79%; yellow color solid; **mp**: 61^{0}C; **$[\alpha]^{25}_D$**: – 9.16 (c 0.8, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 527, 604, 668, 757, 873, 908, 970, 1018, 1044, 1108, 1151, 1176, 1217, 1332, 1371, 1417, 1503, 1603, 1735, 2108, 2401, 2939, 3022, 3472; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.38 (s, 3H), 2.66 (brs, 1H), 3.98 – 4.09 (m, 1H), 4.15 – 4.16 (d, *J* = 2.52 Hz, 1H), 4.17 – 4.18 (d, *J* = 1.39 Hz, 1H), 4.63 – 4.67 (d, *J* = 6.31 Hz, 1H), 7.31 – 7.35 (d, *J* = 8.71 Hz, 2H), 7.43 – 7.47 (d, *J* = 8.72 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.62, 20.76, 64.79, 66.09,

72.03, 122.27, 129.40, 135.17, 148.96, 169.12, 171.21; **Analysis:** $C_{13}H_{15}N_3O_5$ requires C, 53.24; H, 5.16; N, 14.33; found C, 53.15; H, 5.10; N, 14.30%.

Preparation of (1R,2R)-3-acetoxy-1-azido-1-(4-acetoxyphenyl)propan-2-yl phenyl carbonate (95):

To a solution of azido alcohol **94** (0.469 g, 1.6 mmol) and pyridine (0.14 ml, 1.7 mmol) in CH_2Cl_2 (20 ml), a solution of phenylchloroformate (0.22 ml, 0.28 g, 1.7 mmol) in CH_2Cl_2 (1 ml) was added at -5 °C over 10 min. After stirring at –5 °C for 1 h, the reaction mixture was poured into water. The organic layer was washed with 1% H_3PO_4, then with 3% $NaHCO_3$, and dried over anhydrous Na_2SO_4. Upon evaporation of the solvent, 0.614 g of gummy azido ester **95** was obtained.

Yield: 93%; **gum**; **IR** (KBr, cm^{-1}): 602, 670, 761, 873, 1045, 1109, 1150, 1175, 1245, 1510, 1610, 1760, 2100, 2955; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.37 (s, 3H), 4.16 – 4.20 (m, 2H), 4.45 – 4.56 (m, 1H), 4.63 – 4.67 (d, *J* = 6.31 Hz, 1H), 7.12–7.48 (m, 9 H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.64, 20.75, 64.81, 66.11, 72.05, 122.32, 124.95, 129.44, 135.22, 148.98, 152.24, 159.73, 166.65, 171.37; **Analysis:** $C_{20}H_{19}N_3O_7$ requires C, 58.11; H, 4.63; N, 10.16; found C, 58.05; H, 4.60; N, 10.10%.

Preparation of ((4R,5R)-4-(4-acetoxyphenyl)-2-oxooxazolidin-5-yl)methyl acetate (96):

Azido ester **95** (0.454 g, 1.1 mmol) and Ph_3P (1.18 g, 4.5 mmol) were dissolved in THF (20 ml) and water (2 ml). The reaction mixture was heated at 50 °C for 2 h. Evolution of N_2 was observed during the first 1h of the reaction. Solvent was evaporated; the solid residue was dissolved in EtOAc (20 ml), washed with brine (10 ml), and dried over anhydrous Na_2SO_4. Crude product was purified by column chromatography and recrystallized from $CHCl_3$ to obtain 0.280 g (87%) of oxazolidinone **96**.

Yield: 87%; grey color solid; **mp:** 103^{0}C (crystallized from $CHCl_3$); **$[\alpha]^{25}_D$**: – 54.82 (c 0.8, $CHCl_3$); **IR** (KBr, cm^{-1}): 971, 1025, 1043, 1051, 1173, 1233, 1367, 1514, 1605, 1712, 1720, 1740, 2938, 3228, 3255, 3475; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.34 (s, 3H), 3.14-3.16 (m, 2H), 4.66–4.78 (m, 1H), 4.92 (d, *J* = 8.24 Hz, 1H), 7.13-7.25 (m 4H), 8.11 (brs, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 20.64, 20.75, 56.86, 67.49, 80.55, 121.51, 128.59,

132.73, 148.66, 159.92, 170.10, 171.15; **Analysis:** $C_{14}H_{15}NO_6$ requires C, 57.34; H, 5.16; N, 4.78; found C, 57.28; H, 5.12; N, 4.69%.

Preparation of (4*R*, 5*R*)-5-hydroxymethyl-4-(4-methoxyphenyl)-oxazolidin-2-one: (-)-Cytoxazone, (1a):

A mixture of oxazolidine **96** (0.237 g, 0.81 mmol), and 10% aq. $NaHCO_3$ (2 ml) in methanol (5 ml) was heated under reflux for 1h. After the reaction was complete (TLC), solvent was removed under reduced pressure to give the crude product. The residue was diluted with water (5 ml) and was extracted with ethyl acetate (2 x 5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was then added to THF (5 ml) containing NaH (60% suspension in paraffin) (0.034 g, 0.85 mmol) at 0^0C and stirred for 1h. To this mixture was further added MeI (0.12 g, 0.85 mmol) at 0^0C and then stirred at room temperature for 3h. After the reaction was complete, the reaction mixture was diluted with water (3 ml) and extracted with diethyl ether (2 x 5 ml). The organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product, which was purified by column chromatography and recrystallized from MeOH to afford the required (-)-cytoxazone **1a** in 69% (0.124 g) yield.

Yield: 69%; colorless solid; **mp:** 117-120^{0}C (crystallized from MeOH), (Lit.[1]118-121 ^{0}C); **$[\alpha]^{25}_D$**: – 60.16 (c 0.3, MeOH), {Lit.[1] **$[\alpha]^{25}_D$** = – 71 (c 0.1, MeOH)}; **HPLC**: 83% ee, Chirasphere®, λ = 254 nm, 5% 2-propanol/hexane, 1 ml/min., Retention time: (*S,S*) 16.776 min. (*R,R*) 21.001 min.; **IR** (KBr, cm^{-1}): 450, 766, 965, 997, 1026, 1041, 1050, 1177, 1215, 1236, 1254, 1398, 1514, 1615, 1712, 1720, 2948, 3228, 3255, 3352, 3476; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 2.95-2.97 (m, 2H), 3.75 (s, 3H), 4.62–4.73 (m, 1H), 4.82 (t, *J* = 5.1 Hz, 1H), 4.90 (d, *J* = 4.37 Hz, 1H), 6.91 (d, *J* = 8.76 Hz, 2H), 7.15 (d, *J* = 8.46 Hz, 2H), 7.92 (brs, 1H); **^{13}C-NMR** (200 MHz, , DMSO-d_6): δ 55.17, 56.82, 61.93, 80.48, 113.79, 128.17, 129.45, 158.81, 160.09; **Analysis:** $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27; found C, 59.17; H, 5.80; N, 6.19%.

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SECTION I:

Cu-catalyzed three-component synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

3.0.1 Introduction

In 1893, Italian chemist Pietro Biginelli reported the acid catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde, and urea.[1] The reaction was carried out by simply heating a mixture of these three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines.[2] This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold (DHPMs, "Biginelli compounds" **1** - **8**) represents a heterocyclic system of remarkable pharmacological efficiency.[3]

In the past decades, a broad range of biological effects, including antiviral (nitractin **1**), antitumor,[4] antibacterial, antiinflammatory and cardiovascular activities[3] (**2** and **3**), has been ascribed to these partly reduced pyrimidine derivatives. Most notably among them are batzelladine alkaloid **4**, which have been found to be potent HIV gp-120-CD4 inhibitors.[5] More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents[6] (**5**, **6**) or α_{1a} adrenoceptor-selective antagonists[7] (**7**). A very recent highlight in this context has been the identification of the structurally rather simple DHPM

monastrol[4] (**8**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest. Monastrol (**8**) specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs[4] (**Fig. 1**).

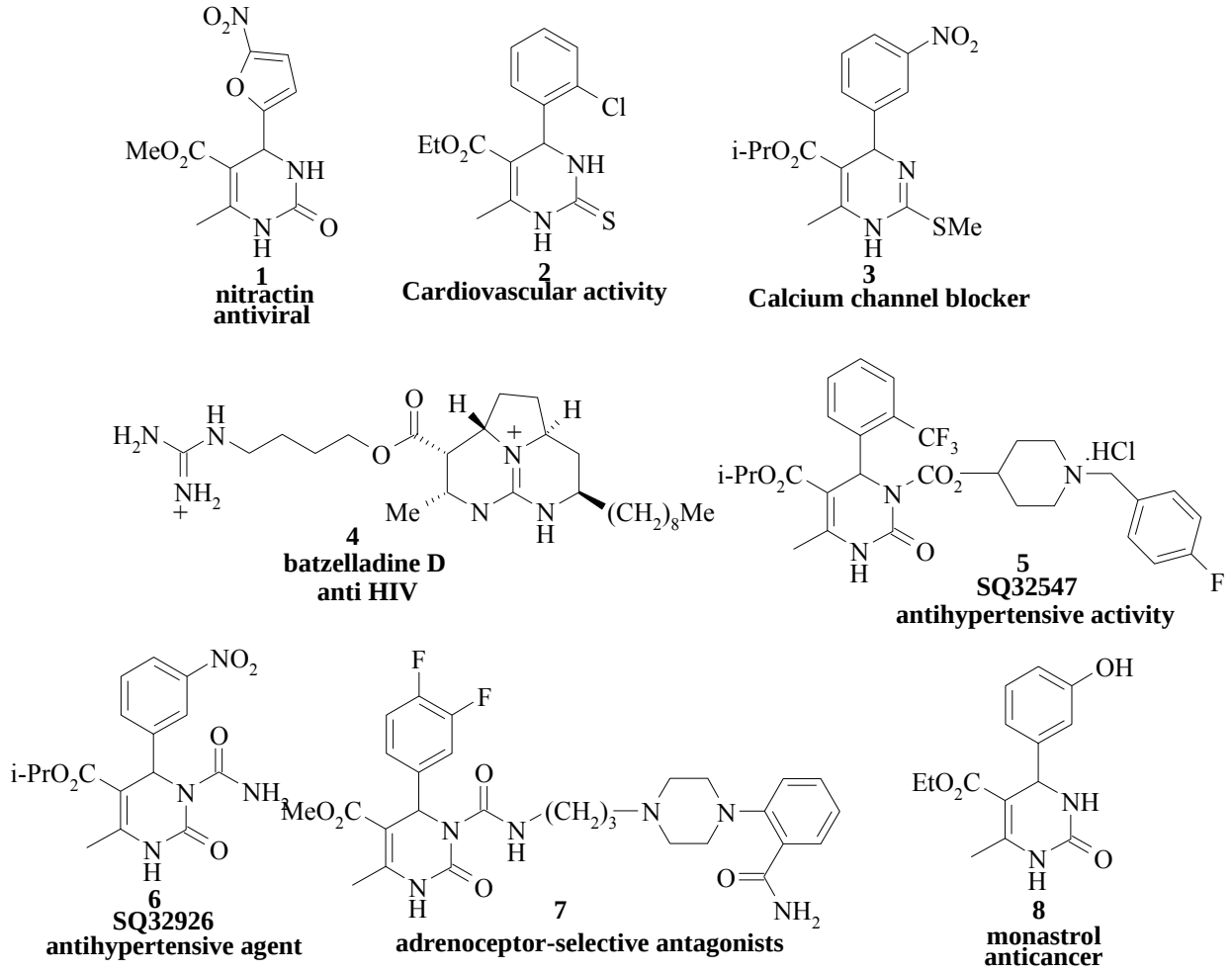


Fig. 1: Some of the drugs containing dihydropyrimidine moiety

In recent years, interest in this reaction has increased rapidly and several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis have been reported.[12-23] However, some of these procedures involve difficulties such as the use of stoichiometric amounts of catalysts, high temperatures, the use of metal halides as

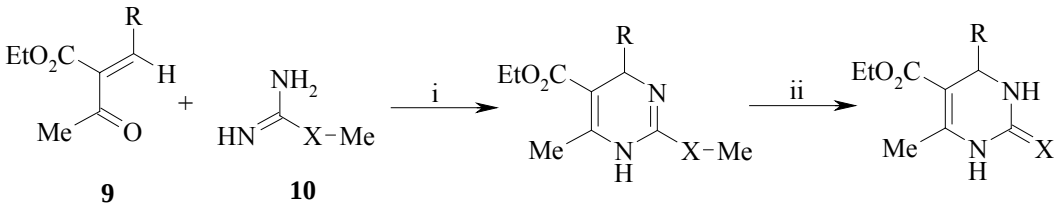
catalysts, the separation of the product from the catalyst, etc. Moreover, the recovery and reuse of catalysts in any such process offers advantages in terms of a clean and environmentally benign process.

3.0.2 Review of Literature

Literature search revealed that there are various methods of dihydropyrimidine synthesis are known in the literature. Some of the important methods so far known are described below.

Atwal *et al.*[8]

Atwal and co-workers reported a more reliable approach to Biginelli compounds. In the first step an unsaturated ketoester **9** is condensed with a suitable protected urea or thiourea derivative **10** in the presence of sodium bicarbonate. The reaction presumably proceeds through a Michael addition product and affords dihydropyrimidines **11**. Deprotection with HCl or trifluoroacetic acid/ ethanethiol leads to the desired Biginelli compounds **12** in high overall yield (**Scheme 1**).



9 R = alkyl or aryl

10 X = O or S

11

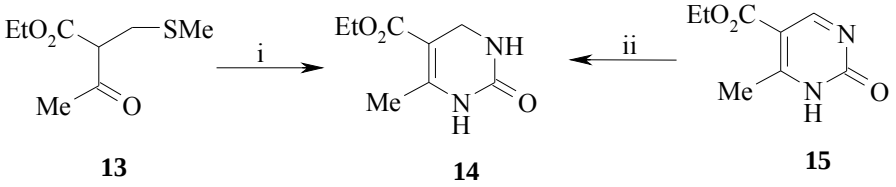
12 Yield = 40 - 87 %

Scheme 1: i $NaHCO_3$, DMF, 100 ^{0}C, 55 – 70 %; ii aq. 10 % HCl, MeOH, 60 ^{0}C or trifluoroacetic acid, ethanethiol, 60 ^{0}C, 40 – 87 %.

Apart from the procedure described in **Scheme 1** there are few other methods that leads to Biginelli compounds. Most of them however, are limited in their scope and are hardly ever

used for synthetic purposes. When substituted acetoacetate was allowed to react with urea, elimination of MeSH has occurred to furnish DHPM compound **14** (**Scheme 2**).[9]

The same compound **14** is obtained upon hydrogenation of pyrimidine **15** with H_2/Pt.

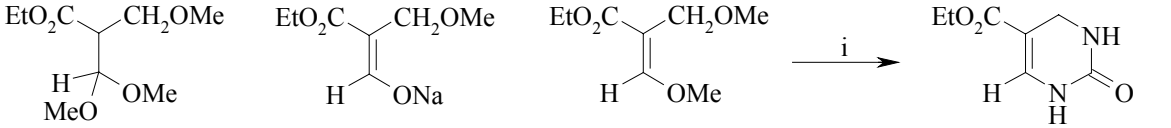


13 **14** **15**

Yield = 60 - 80 %

Scheme 2: i Urea, DMF, 100 ^{0}C, 60 %; ii 10 % Pt/C, H_2 (1 atm), MeOH, 60 ^{0}C, 80 %.

A route leading to DHPM **19** having a hydrogen atom in position 6 is the acid catalyzed condensation of urea with precursors such as **16**, **17** or **18** (**Scheme 3**).[10]

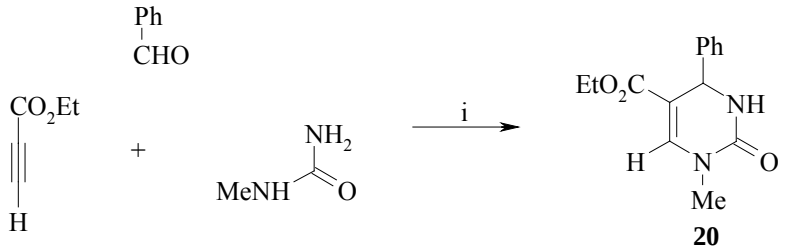


16 **17** **18** **19**

Yield = 30 - 75 %

Scheme 3: i Urea, aq. 10 % HCl, MeOH, 60 ^{0}C, 30 - 75 %

Another route leading to Biginelli compounds with a hydrogen atom in 6 position **20** is the condensation of ethyl propionate with N-methylurea and benzaldehyde (**Scheme 4**)[11].



20

Yield = 55 %

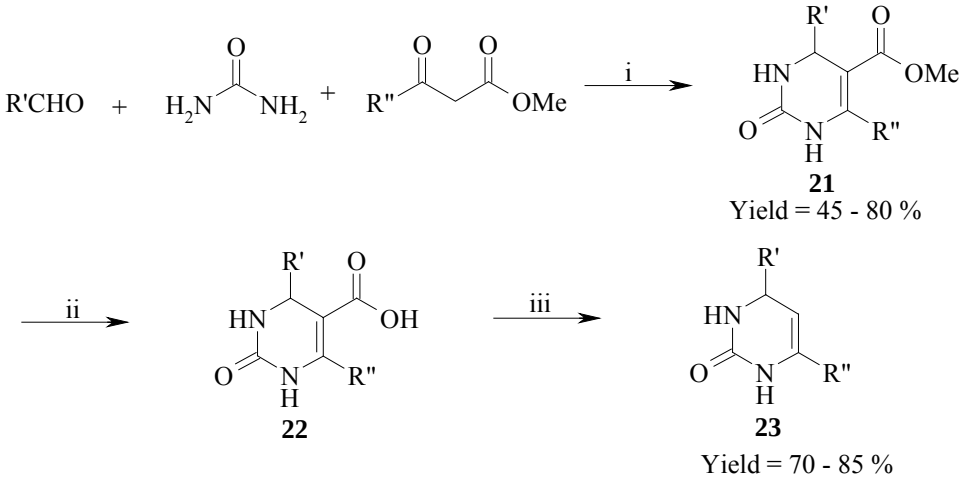
Scheme 4: i aq. 10 % HCl, EtOH, 60 ^{0}C, 55 %.

Literature search also revealed that several modified procedures aimed at improving the efficiency of the Biginelli dihydropyrimidine synthesis are known in the literature. Many

of these methods make use of transition metal based Lewis acid catalysts for Biginelli dihydropyrimidine synthesis such as $InCl_3$,[12a] $LaCl_3$,[12b] $Yb(OTf)_3$,[13] $CeCl_3$,[14] $BiCl_3$,[15] $Mn(OAc)_3$,[16] $FeCl_3$,[17] $NiCl_3$,[18] $InBr_3$,[19] $ZrCl_4$,[20] $BF_3.OEt$,[21] $LiClO_4$,[22] etc. Some of the important methods are described below.

Patane *et al.*[23]

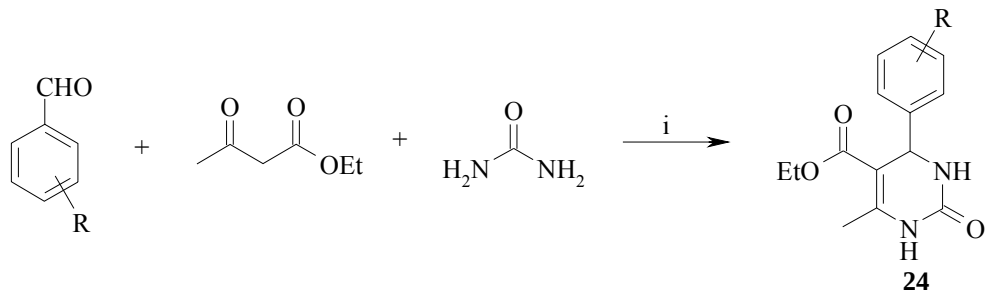
Patane's developed a new procedure for the synthesis of 5-unsubstituted 3, 4-dihydropyrimidin-2(IH)-ones which represent a significant improvement over existing methods. In this method classical Biginelli products (**21)** was further hydrolyzed with 1 N NaOH yielding corresponding acids (**22)** which are decarboxylated with sodium hydride to produce 5-unsubstituted DHPMs (**23)**. This method provides a variety of new DHPMs (**23)** ring systems accessible for inclusion into pharmacologically important agents (**Scheme 5**).



Scheme 5: i $BF_3.OEt_2$, THF, cat. AcOH, cat. CuO, reflux 45 – 80 %; ii 1 N NaOH, MeOH, 70 ^{0}C, 1h, 25 ^{0}C, 12h 60 – 70 %; iii NaH, dry MeOH, reflux, 10 min., 70 – 85%.

Sartori *et al.*[24]

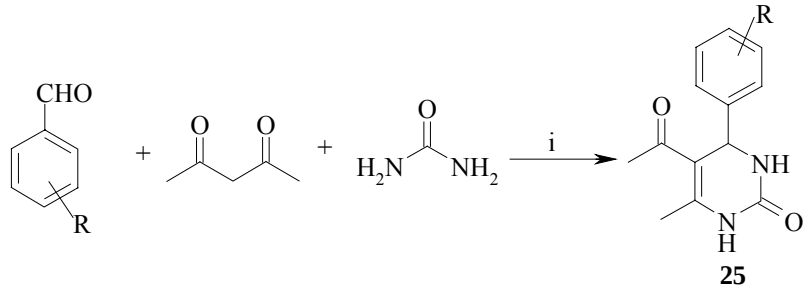
Sartori *et al.* have found that the Biginelli reaction was efficiently performed with clay catalysis (KSF) under solvent less conditions or in water, and it gives good yields of dihydropyrimidinone **24** up to 88 % at 100 ^{0}C (**Scheme 6**).



Scheme 6: i KSF, 100 ^{o}C, 74 – 88 %.

Yarim *et al.*[25]

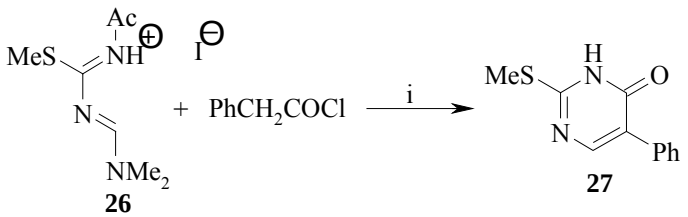
Yarim *et al.* synthesized some new 5-acetyl-3, 4-dihydro-6-methyl-4-(substituted phenyl)-2(1*H*)-pyrimidinones (**25**) and studied their biological activity. The compounds were prepared by the Biginelli reaction of acetylacetone, aromatic aldehydes and urea by employing aq. HCl in ethanol at room temperature for 6 h (**Scheme 7**).



Scheme 7: i cat. 37 % HCl, EtOH, RT, 6h.

Friot *et al.*[26]

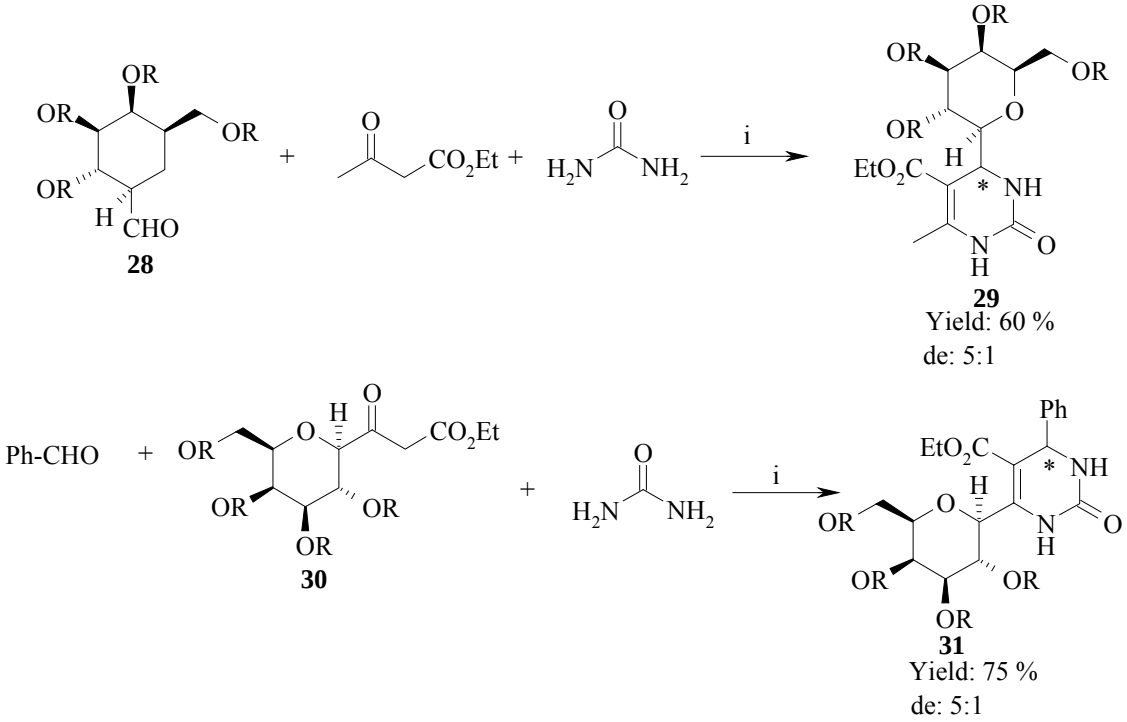
Friot *et al*. demonstrated [4+2] cycloaddition reactions of cationic 1,3-diazadienes (**26**) with benzoyl chloride in the presence of Et_3N and iodine to prepare various common heterocyclic compounds such as dihydropyrimidines, dihydropyrimidinones (**27**) (**Scheme 8**).



Scheme 8: i Et_3N, I_2, CH_2Cl_2, RT, 24h.

Dondoni *et al.*[27]

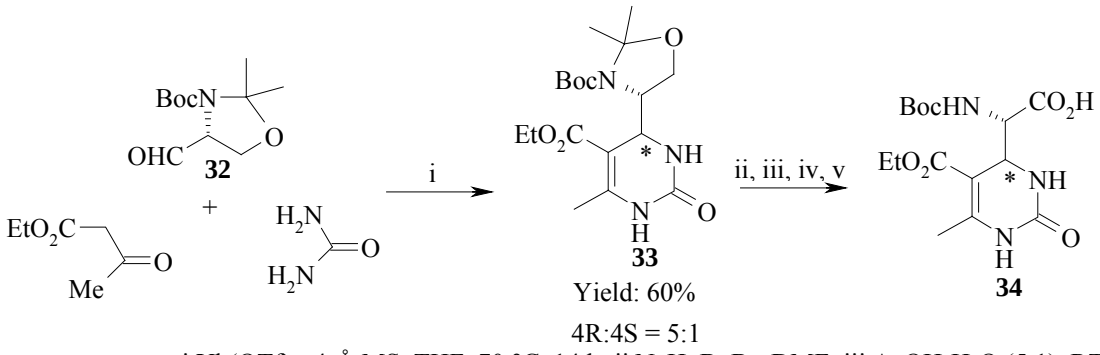
Dondoni *et al*. demonstrated that the three-component Biginelli reaction can be applied to the synthesis of different mono- and bis-*C*-glycosylated DHPMs. Given the availability of various sugar aldehydes (**28**) and keto esters (**30**), the access to a combinatorial library of glycosylated Biginelli products (**29**, **31**) with a wide range of structural and stereochemical elements of diversity for an extensive exploration of biological properties now becomes of interest (**Scheme 9**).



Scheme 9: i CuCl, $BF_3.Et_2O$, AcOH, 4ºA MS, 65 °C,12-24h.

They also demonstrated the use of aldehydes bearing a masked glycinyl moiety (**32**) as components in Biginelli reactions. The use of aldehyde bearing a masked glycinyl moiety in Biginelli cyclocondensations allowed access to the 4-dihydropyrimidinyl-R-glycines (**33**). Dihydropyrimidinylamino acids were obtained after deprotecting amino alcohol and further

oxidation with Jones reagent as a mixture of diastereoisomers due to the formation of the stereocenter at C4 of the dihydropyrimidinone ring (**34**) (**Scheme 10**).



Scheme 10: i $Yb(OTf)_3$, 4-Å MS, THF, 70 °C, 14 h; ii NaH, BnBr, DMF; iii AcOH-H_2O (5:1), RT; iv 1 M Jones reagent, 0 °C to rt, 3 h; v H2 (5 atm), $Pd(OH)_2$, AcOH-EtOH(1:1), RT, 7 d.

Deng *et al.*[28]

Deng *et al*. reported an improved method for the synthesis of Biginelli DHPMs by using room temperature ionic liquids (1-*n*-butyl-3-methylimidazolium tetrafluoroborate [0.4 mol% of $BMImBF_4$]) as catalyst under solvent-free and neutral conditions. The main advantages of this methodology are: (1) relatively simple catalyst system; (2) shorter reaction times; (3) higher yields; (4) free of organic solvent, and (5) easy synthetic procedure.

Kappe *et al.*[29]

Kappe *et al*. introduced automated sequential microwave-assisted library synthesis. For this purpose a dedicated single-mode microwave reactor with a robotics interface including a liquid handler and gripper was employed. The liquid handler allows dispensing of reagents into the Teflon sealed reaction vials, while the gripper moves each sealed vial in and out of the microwave cavity after irradiation. This technology was employed for the Biginelli three-component cyclocondensation reaction. For most building block combinations 10 min of microwave flash heating at 120 °C using AcOH/EtOH (3:1) and 10 mol % $Yb(OTf)_3$ as

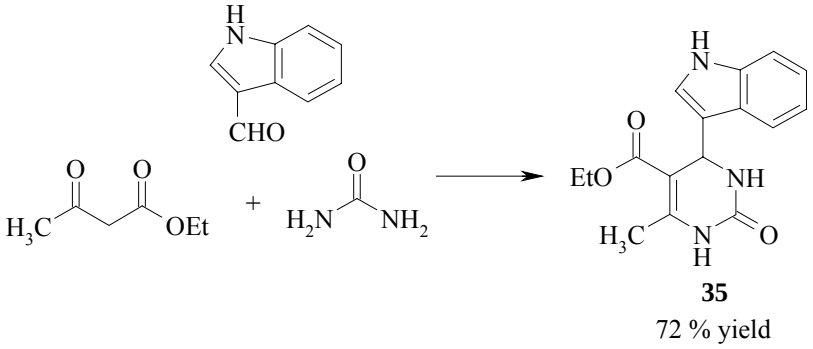
solvent/ catalyst system proved to be successful, leading to an isolated yield of 40 – 70 % of DHPMs. This flexibility is a distinct advantage of sequential over parallel microwave-assisted processes where all reactions are exposed to the same irradiation conditions.

Vallribera *et al.*[30]

Vallribera *et al*. employed iron (III)-containing silica aerogels as catalysts for Biginelli condensation reactions. The aerogels are recovered and reused without decrease of activity.

Choudhary *et al.*[31]

Choudhary *et al*. employed Si-MCM-41 and montmorillonite K 10 clay-supported onto $ZnCl_2$, $AlCl_3$, $GaCl_3$, $InCl_3$ and $FeCl_3$ heterogeneous catalysts; $FeCl_3$/Si-MCM-41 showed best performance for the microwave-assisted Biginelli reaction in the absence of any solvent. It is a promising catalyst for the microwave-assisted reaction providing product (**35**) in 70 – 89 % yield in a short period (3.0–5.0 min) (**Scheme 11**).



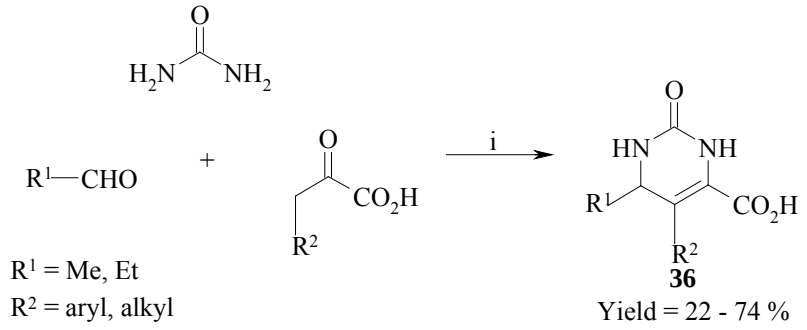
35

72 % yield

Scheme 11: i $FeCl_3$/Si-MCM-41, MWI (3 – 5 min.), 70 – 89 %.

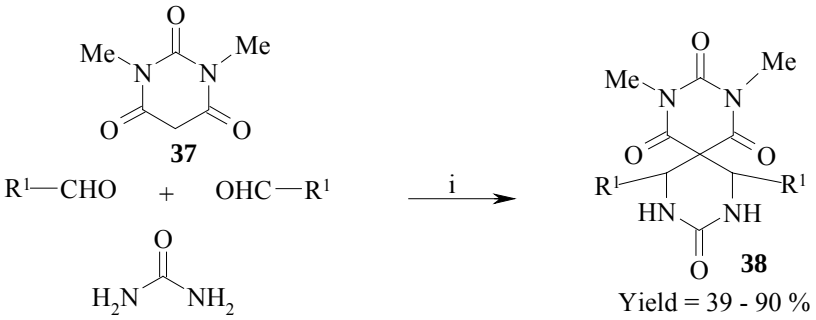
Abelman *et al.*[32]

Abelman *et al*. have expanded the synthetic scope of the multicomponent Biginelli reaction treating α- ketoacids with aldehydes and urea producing dihydropyrimidinecarboxylic acids in 22 – 74 % yield (**36**) (**Scheme 12**).



Scheme 12: i EtOH, CH_3SO_3H, reflux, 6h 22 – 74%.

In addition, spiroheterocycles (**38**) are also prepared from dimethylbarbituric acid (**37**) using a four-component condensation reaction where the aldehyde is utilized twice in the reaction (**Scheme 13**). The novel carboxylic acid scaffolds make useful functional coupling partners in amidation reactions with diverse amines providing focused, drug-like library components.



Scheme 13: i EtOH, CH_3SO_3H, reflux, 6h, 39 – 90%.

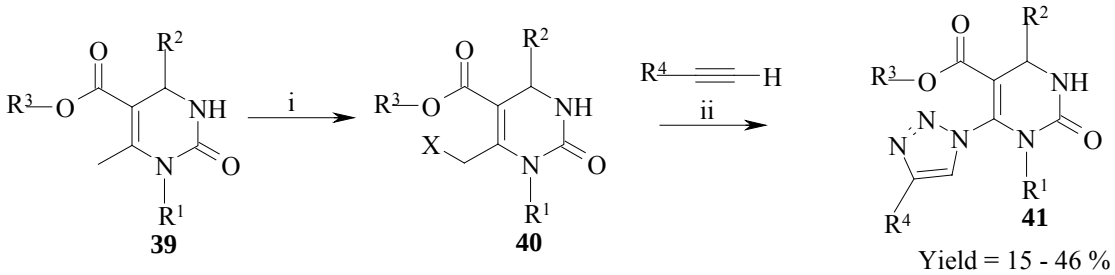
Sabitha *et al.*[33]

Sabitha *et al*. have discovered a new method for the synthesis of Biginelli dihydropyrimidinones using *in situ* generated iodotrimethylsilane at room temperature.

Khanetsky *et al.*[34]

Khanetsky *et al*. have reported the modification of dihydropyrimidone (DHPM) scaffolds at the C-6 position with a 1,2,3-triazole pharmacophore. The key step in the synthesis was the Cu(I)-catalyzed azide-acetylene ligation ("click chemistry"), reacting azide-

functionalized DHPMs (**40**) with terminal acetylenes. The required 6-azidomethyldihydropyrimidone precursors (**40**) were readily prepared using a bromination/azidation sequence that involved a polymer-supported brominating reagent under flowthrough conditions and subsequent displacement of the bromide with azide. The resulting 6-(1,2,3-triazol-1-yl)-methyldihydropyrimidones **41** (27-member library, 4 diversity points) were obtained in moderate overall yields (15 – 46 %) in three steps (**Scheme 14**).



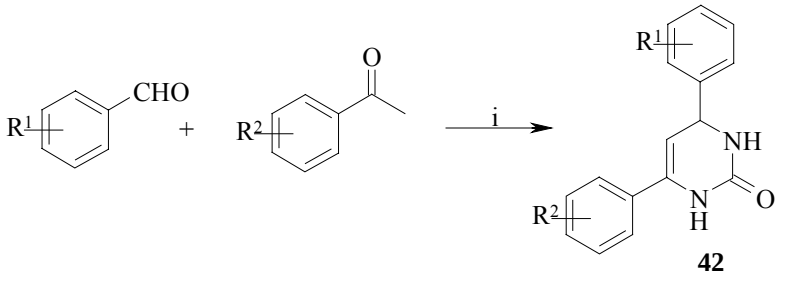
Scheme 14: i Br_2, CCl_4, 25 ^{0}C, flow condition; ii $CuSO_4$, Na ascorbate, DMF, 80^{0}C, 1 min, 15 – 46 %.

Bose *et al.*[35]

Bose et al synthesized DHPMs in 71 – 96 % yield by just grinding reactants together with small amount of PTSA as a catalyst for 3 – 5 min. They found that Biginelli reaction is exothermic reaction and grinding will generate small amount of friction energy which will initiate reaction leading to its completion.

Wang *et al.*[36]

Wang *et al*. reported a new method for the three-component Biginelli-like reactions in the presence of TMSCl (stoichiometric amount) and $FeCl_3.6H_2O$ as a catalyst expanding the synthetic scope of the multicomponent Biginelli reaction with ketones instead of activated β-dicarbonyl compounds (acetoacetate) for the synthesis of interesting 5-unsubstituted 3,4-dihydropyrimidin-2-(1*H*)-ones in 75 – 89 % yield (**42**) (**Scheme 15**).



42

Yield = 75 - 89 %

Scheme 15: i Urea, cat. $FeCl_3.6H_2O$, TMSCl (1 equiv), CH_3CN reflux, 12h, 75 – 89 %.

Karimi *et al.*[37]

Karimi *et al*. have introduced a new application for NBS as a mild, efficient and almost neutral catalyst for the preparation of dihydropyrimidinones (DHPMs) and the corresponding thio-derivatives under microwave irradiation.

Jenner *et al.*[38]

Jenner *et al*. examined the effect of high pressure on Biginelli reactions. This effect is small when moderately hindered aldehydes or ureas are involved. However, particularly in the case of bulky aldehydes, the sensitivity of the reaction to pressure increases with increasing steric congestion. The results also provide insights into the mechanism. Such a result highlights the synthetic utility of high pressure activation for the preparation of hindered Biginelli products.

3.0.3 Present Work

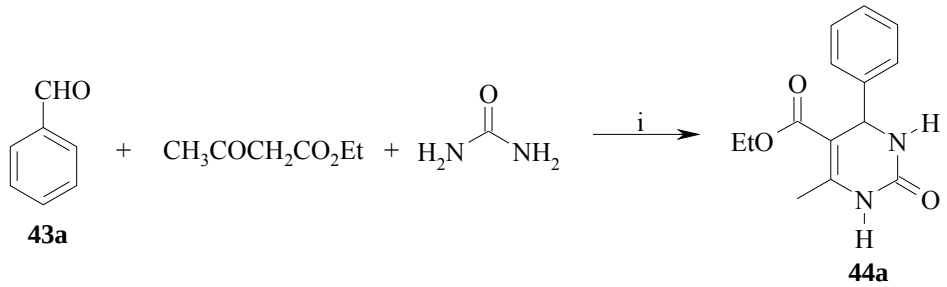
3.0.3.1 Objective

It is seen from the foregoing discussion that there are many catalytic methods available in the literature for the synthesis of dihydropyrimidinones (DHPMs). However, some of these procedures involve several difficulties such as (i) the use of stoichiometric amounts of catalysts, (ii) high temperatures, (iii) the use of metal halides as catalysts, (iv) the separation of the product from the catalyst, etc. In order to overcome these difficulties a new reusable catalytic method for the synthesis of Biginelli dihydropyrimidinones (DHPMs) is highly desirable. Moreover, the recovery and reuse of catalysts in any such processes offers advantages in terms of a clean and environmentally benign process.

Initially, we were interested in developing a simple and efficient procedure at ambient conditions for the Biginelli dihydropyrimidinones (DHPMs) synthesis using copper salts as catalysts. Subsequently, we have evaluated the use of $Cu(OTf)_2$ as a reusable catalyst for Biginelli 3,4-dihydropyrimidin-2(1*H*)-one synthesis, the results of which are presented in this section.

3.0.4 Results and Discussion

When a mixture containing benzaldehyde, ethyl acetoacetate and urea was allowed to react in the presence of $Cu(OTf)_2$ as a catalyst in CH_3CN at 25 ^{0}C, we obtained dihydropyrimidinones (DHPMs) in excellent yields (**Scheme 16**).



43a **44a**

Scheme 16: i $Cu(OTf)_2$ (1 mol %), CH_3CN, 25^{0}C, 6 h, 95%.

Among the various polar solvents screened, CH_3CN, THF and EtOH were proved to be effective but best results were obtained with CH_3CN as solvent. The results of optimized experimentation for the three-component Biginelli condensation involving benzaldehyde, urea and ethyl acetoacetate with copper salts as catalysts are presented in **Table 1.**

Table 1: Cu-catalyzed condensation of benzaldehyde, ethyl acetoacetate and urea[a]

No.	Catalyst	Catalyst mole%	Solvent	Yield of 44a (%)[b]	TON[c]
1	None	----	CH_3CN	00	----
2	$Cu(OTf)_2$	0.5	CH_3CN	85	170
		1	----	90	90
		1	CH_3CN	95, 90, 88, 85, 80[d]	95,90,88,85,80
		1	THF	62	62
		1	EtOH	83	83
		1	H_2O	05	05
		5	CH_3CN	95	19
		10	CH_3CN	94	9.4
3	CuCl	5	CH_3CN	20	04
4	CuCN	5	CH_3CN	30	06
5	$Cu(OAc)_2.H_2O$	5	CH_3CN	05	01
6	$CuSO_4.5H_2O$	5	CH_3CN	00	00

a: reaction conditions:[4] benzaldehyde (2 mmol), urea (2 mmol), ethyl acetoacetate (2 mmol), 25 ^{0}C; b: isolated yield after recrystallization; c: TON = turn over number (defined as: mmol of product/ mmol of catalyst); d: catalyst was reused at least for 5 times.

It is remarkable to note that the condensation proceeded with a low catalyst concentration [0.5 mol % of $Cu(OTf)_2$] at ambient conditions and gave 3,4-dihydropyrimidin-2(1*H*)-one **44a** in high yields. Even after increasing catalyst concentration from 1 mol % to 10 mol %, there was no significant change in product yield. After the reaction was complete as monitored by TLC, the precipitated solid product **44a** was isolated by simple filtration. When the filtrate containing the catalyst $Cu(OTf)_2$ was further treated with the reactants (benzaldehyde, urea and ethylacetoacetate), a slight decrease in the yield (from 95% to 80% after 5th time) of the 3,4-dihydropyrimidin-2(1*H*)-one **44a** was observed (**Table 1**).

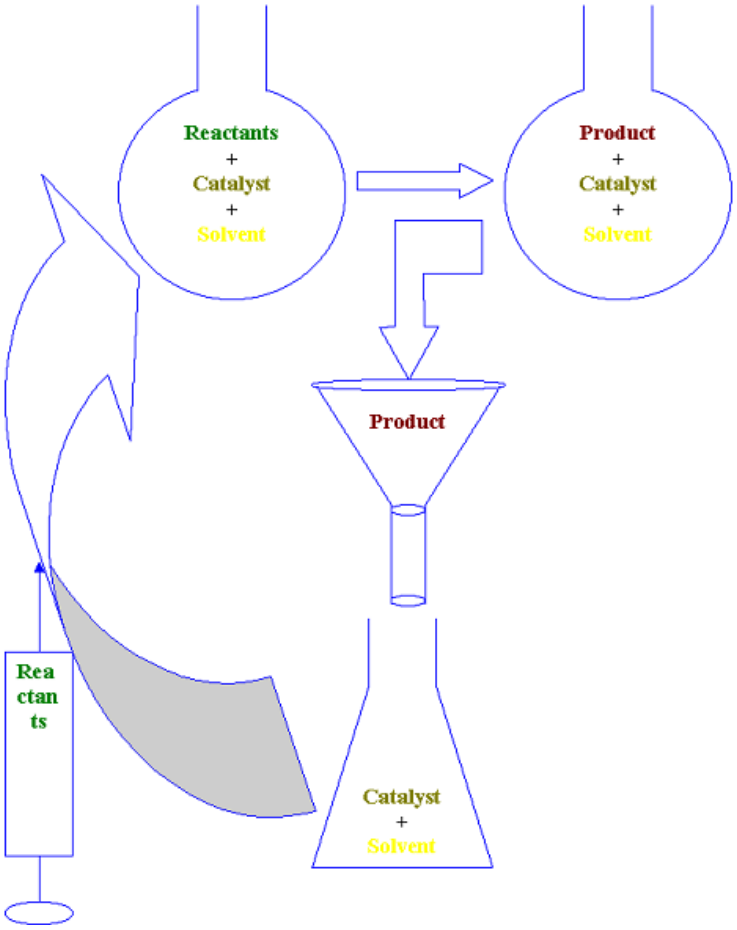
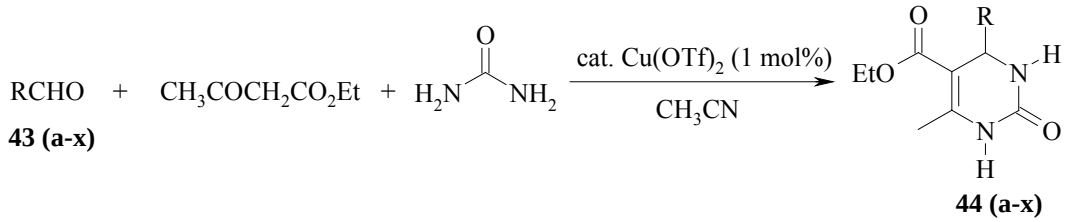


Fig. 2: Experimental setup for reusability study

In another experiment, when the filtered solution containing the catalyst was used after 6 months of storage, it was found that the catalyst was quite active (no appreciable change in the yield of the product), demonstrating that $Cu(OTf)_2$ is stable and does not undergo any deterioration. Thus, this study demonstrates that $Cu(OTf)_2$ can be effectively used as a reusable catalyst for Biginelli-type condensations. Also reactions can be conducted under "solvent free" conditions. **Fig. 2** shows the typical experimental set-up for reusability study.

In order to find the scope of these reactions, several aromatic and aliphatic aldehydes were examined under the optimized conditions using 1 mol % of $Cu(OTf)_2$ (**Scheme 17**). The results are shown in **Table 2**.



43 (a-x) **44 (a-x)**

Scheme 17: i $Cu(OTf)_2$ (1 mol %), CH_3CN, 25-70^{0}C, 6-12 h, 60-95%.

Table 2: $Cu(OTf)_2$-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [a]

No.	R	Temp. (^{0}C)	t/h	Product 44(a-x) Yield[b] (%)	mp (^{o}C)	TON[c]
a	Ph	25	6	95	200-202	95
b	2-Cl-C_6H_4	50	9	70	216-218	70
c	3-Cl-C_6H_4	60	9	80	190-193	80
d	4-Cl-C_6H_4	50	4	85	212-213	85
e	4-MeO-C_6H_4	40	5	90	200-201	90
f	2-HO-C_6H_4	50	6	80	200-202	80
g	4-HO-C_6H_4	40	5	90	199-200	90
h	3-O_2N-C_6H_4	60	9	75	226-225	75
i	4-O_2N-C_6H_4	50	6	80	207-209	80
j	4-NC-C_6H_4	70	12	60	219-222	60
k	4-Me_2N-C_6H_4	60	9	65	230-232	65
l	3-MeO-4-HO-C_6H_3	50	6	85	200-202	85
m	3-HO-4-MeO-C_6H_3	50	6	85	185-187	85
n	3,4-$(MeO)_2$-C_6H_3	50	6	85	175-177	85
o	3,4,5-$(MeO)_3$-C_6H_2	50	6	85	180-182	85
p	3,4-(O-CH_2-O)-C_6H_3	50	6	85	188-189	85
q	3-(cyclopentyloxy)-4-MeO-C_6H_3	50	6	80	185-188	80
r	2-HO-4-Cl-C_6H_3	70	9	65	240-243	65
s	2-HO-4-Br-C_6H_3	70	9	80	195-196	80
t	3-O_2N-4-Me-C_6H_3	60	9	70	218-219	70
u	1-Naphthyl	50	6	85	246-248	85
v	2-Furyl	70	6	70	203-205	70
w	c-C_6H_{11}	70	12	60	236-237	60
x	n-C_9H_{19}	70	12	60	122-124	60

a: reaction conditions: aldehyde (2 mmol), urea (2 mmol), ethyl acetoacetate (2 mmol), $Cu(OTf)_2$ (1 mol%), 25 ^{0}C; b: isolated yield after recrystallization; c: TON = turn over number (defined as: mmol of product/ mmol of catalyst).

As can be seen from **Table 2**, for all cases studied, the three-component reaction proceeded smoothly to give the corresponding 3, 4-dihydropyrimidin-2(1*H*)-ones in high

yields. Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently giving excellent yields. Aliphatic aldehydes **43w** and **43x** in comparison to aromatic aldehydes gave lesser yields of required products **44w** and **44x**. Except parent benzaldehyde all other aldehydes needed heating preferably between 40–70^{0}C. Especially 4-cyanobenzaldehyde **43j** gave poor yield (60 %) of product **44j** even after heating at 70 ^{0}C for 12 h.

The formation of 3, 4-dihydropyrimidin-2(1*H*)-ones was confirmed by ^{1}H, ^{13}C-NMR, IR, and MS spectroscopy. The IR spectrum of the 3, 4-dihydropyrimidin-2(1*H*)-one **44o** showed typical absorption band in the region 1651 and 1713 cm^{-1} for amide and ester C=O stretching frequencies respectively. The ^{1}H-NMR spectrum exhibits benzylic proton signal at δ 5.30 and typical broad signals at δ 5.8 and 8.30 suggesting cyclic amide NH protons present in the molecule. Its ^{13}C-NMR spectra showed typical amide and ester carbonyl carbon signals at δ 152.2 and 165.4 respectively confirming the presence of 3, 4-dihydropyrimidin-2(1*H*)-ones (**Fig. 3**). As an another example, compound **44p** in its IR spectrum showed typical absorption band in the region 1642 and 1700 cm^{-1} for amide and ester C=O stretching frequencies respectively. The ^{1}H-NMR spectrum shows benzylic proton signal at δ 5.06 and typical signals at δ 7.68 and 9.18 suggesting cyclic amide NH protons present in the molecule. Its ^{13}C-NMR spectra showed typical amide and ester carbonyl carbon signals at δ 156.8 and 165.1 respectively confirming the presence of 3, 4-dihydropyrimidin-2(1*H*)-ones. Its MS spectrum also showed the molecular ion peak at m/z 304 and base peak at m/z 304 (**Fig. 4**).

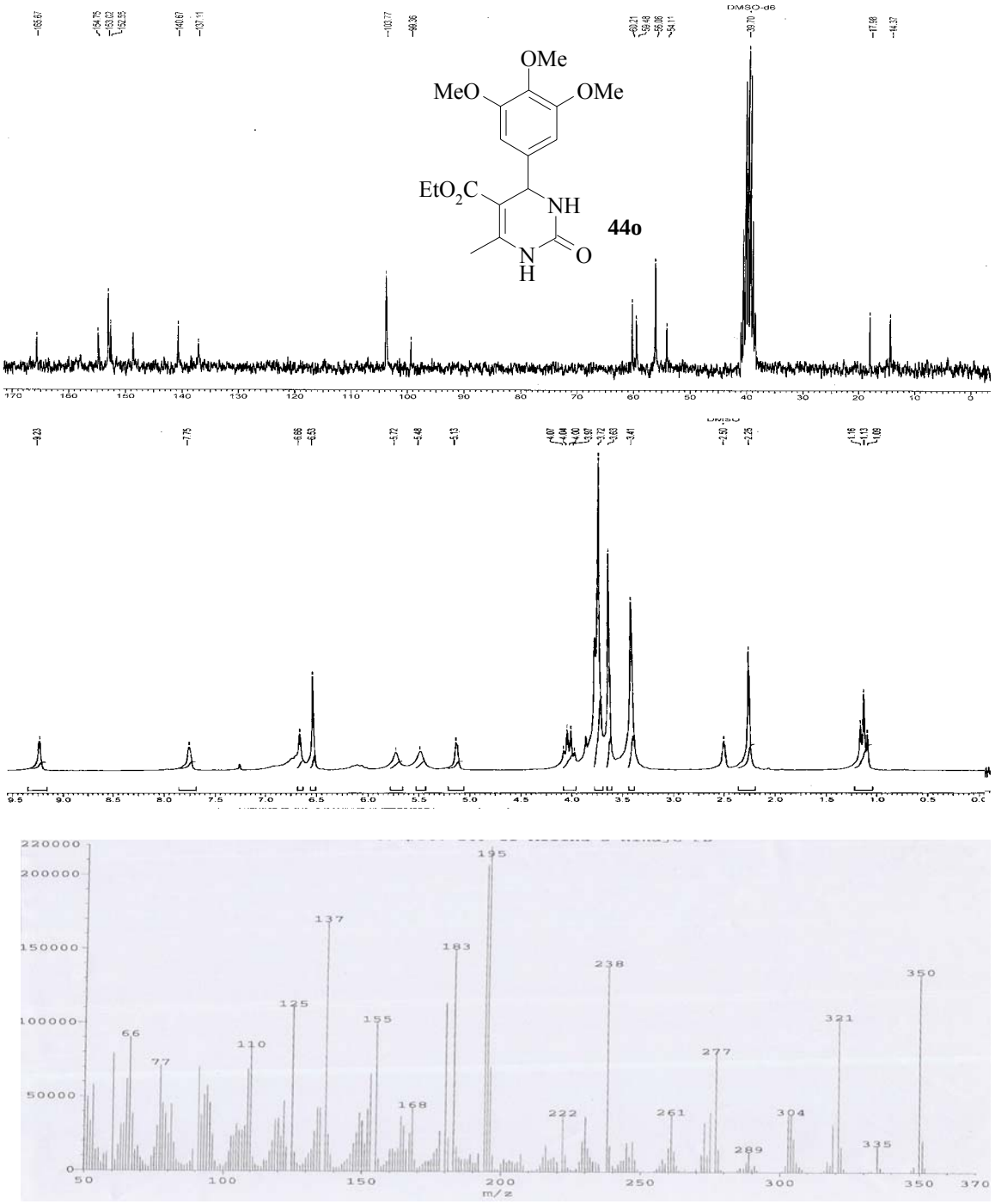


Fig. 3: ^{13}C and ^{1}H -NMR and MS of 44o

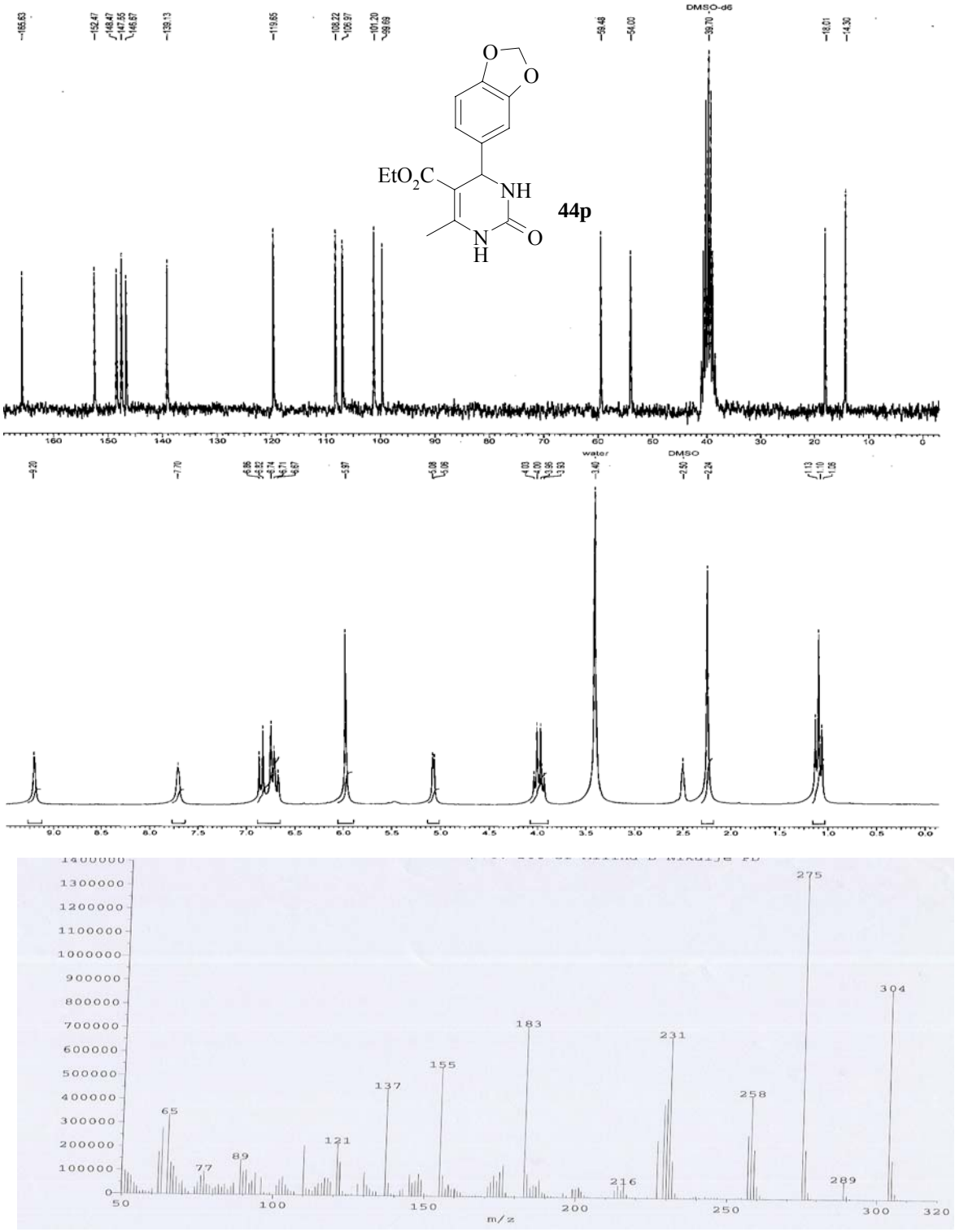


Fig. 4: ^{13}C and ^{1}H -NMR and MS of 44p

In case of DHPM **44q**, IR spectrum showed the typical absorption bands at 1682 and 1723 cm^{-1} due to amide and ester C=O stretching frequencies respectively. The signals in ^{1}H-NMR spectrum at δ 5.14, 7.73 and 9.19 are due to benzylic proton and two cyclic amide NH protons respectively. Its ^{13}C-NMR spectra showed typical amide and ester carbonyl carbon signals at δ 152.2 and 165.4 confirming the presence of 3, 4-dihydropyrimidin-2(1*H*)-ones moiety **44q** (**Fig. 5**).

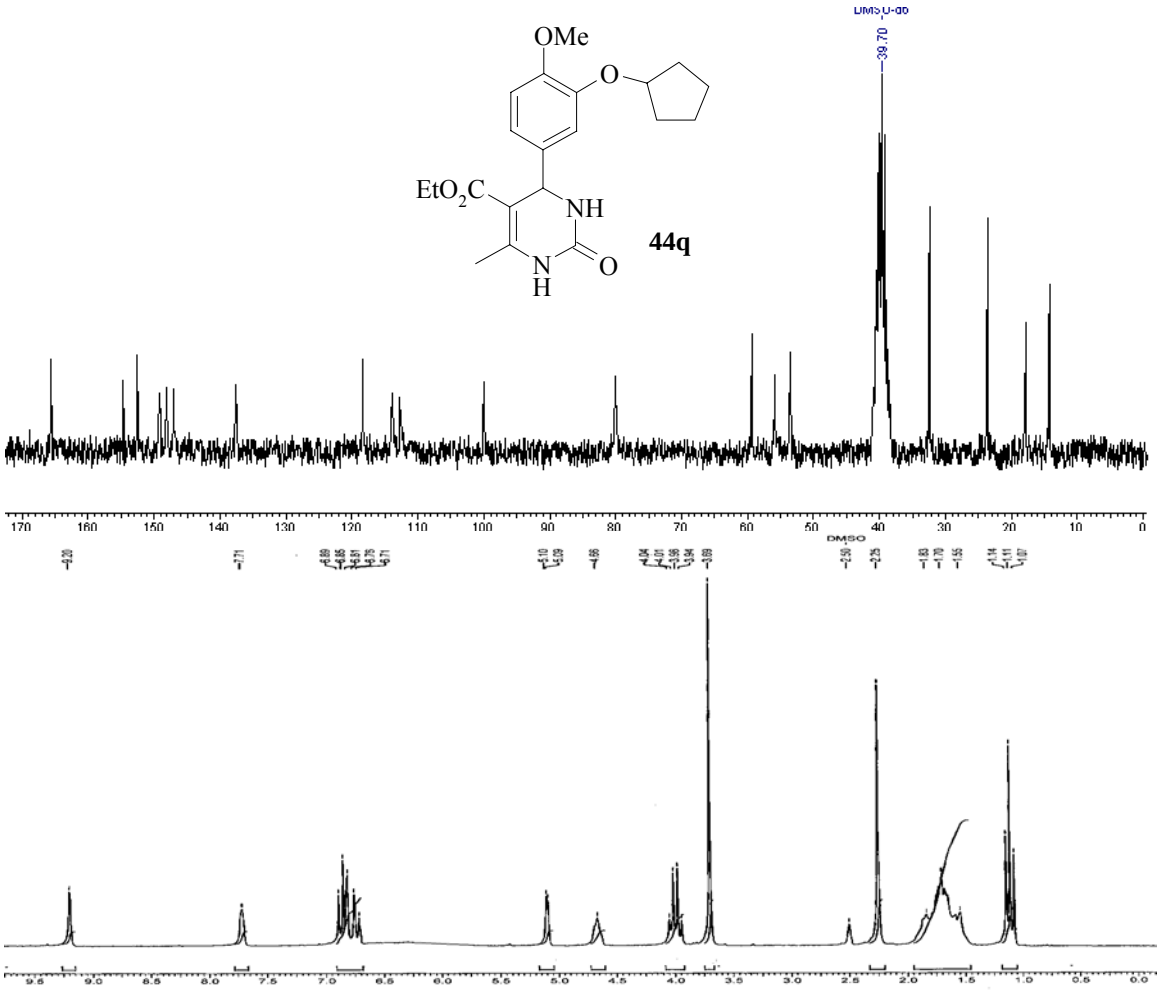
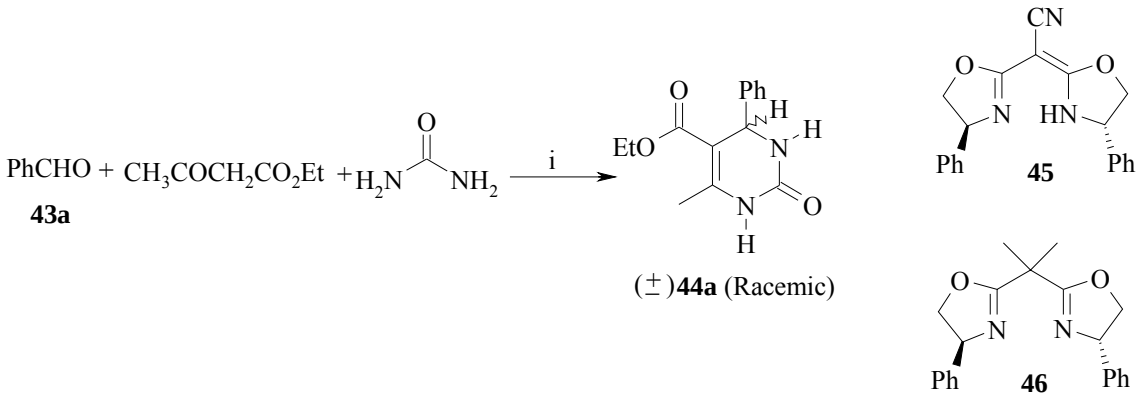


Fig. 5: ^{13}C and ^{1}H -NMR spectra of 44q

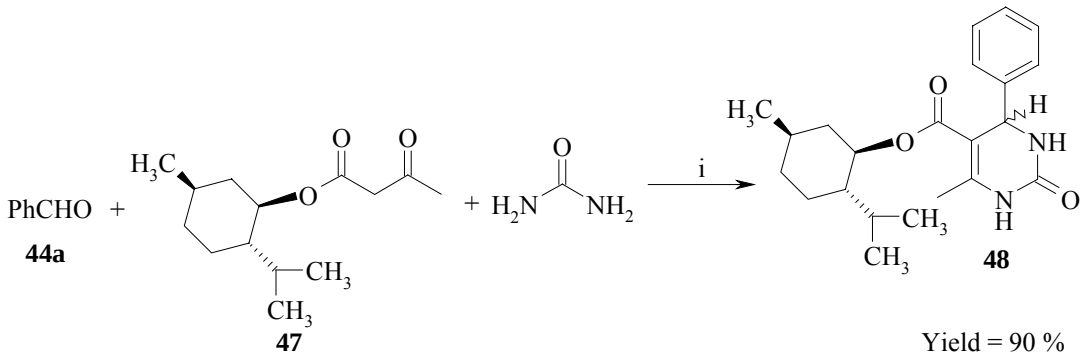
Asymmetric Biginelli reaction:

In our attempts to develop asymmetric version of Biginelli reaction, we used catalytic amount of chiral Cu-complex generated *in situ* from $Cu(OTf)_2$ and chiral oxazolidine ligands **45** and **46**. The reactions were performed at 25 ^{0}C in CH_3CN with mixture containing benzaldehyde, urea and ethyl acetoacetate in the presence of a catalyst generated *in situ* from ligands **45** and **46**[39]. However, the catalytic system failed to induce optical induction in the final product (**Scheme 18**).



Scheme 18: i $Cu(OTf)_2$ (1 mol %), **45** or **46** (1.2 mol %), CH_3CN, 25^{0}C, 12 h.

In another experiment, chiral linker attached to dicarbonyl compound (menthyl aceto acetate) is used in stoichiometric amount. The reactions were performed at 25 ^{0}C in CH_3CN with benzaldehyde, urea and menthyl acetoacetate **47** producing 90 % of both the diastereoisomers in equal ratio (**Scheme 19**). Diastereoisomeric ratio was obtained from ^{1}H-NMR signal at δ 5.35 showing two doublets of equal intensity (**Fig. 6**). It is also confirmed by single crystal X-ray crystallographic study of **48** showing the presence of both isomers in equal proportion (**Fig. 7**).



Scheme 19: i $Cu(OTf)_2$ (1 mol %), CH_3CN, 25^0C, 12 h, 90 %.

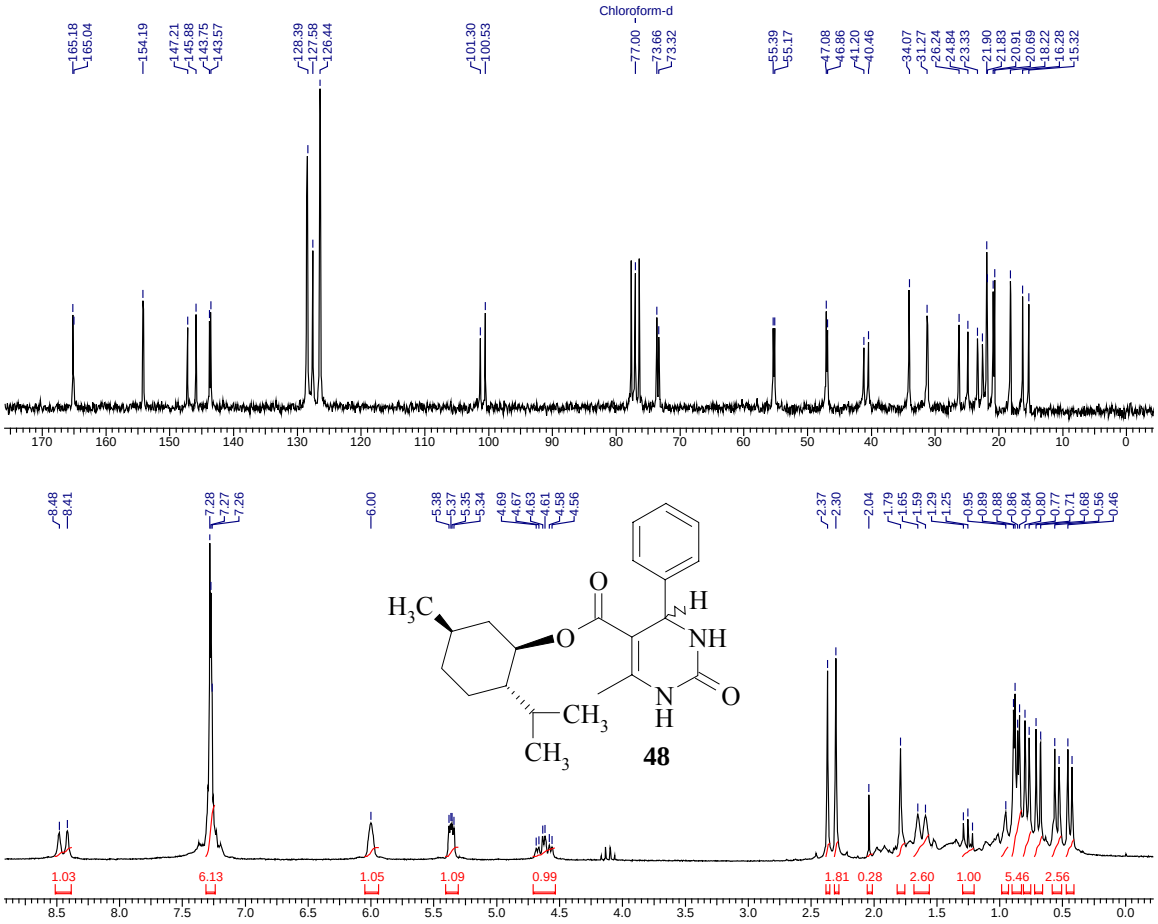


Fig. 6: ^{13}C and ^{1}H -NMR spectra of 49

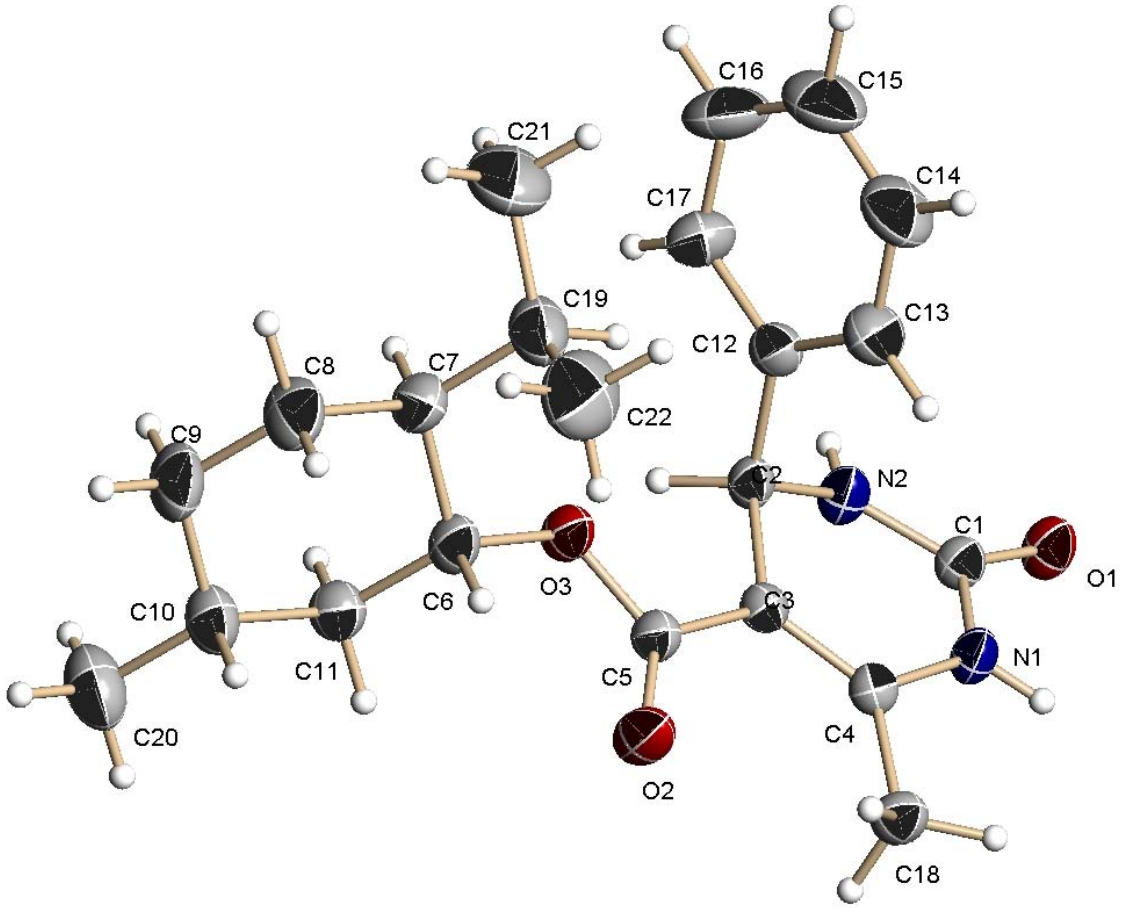


Fig. 7: Single crystal X-ray structure of DHPM 48

In conclusion, reactions employing chiral linker groups (menthyl group) also failed to induce chirality at C-4 position in the molecule

Mechanism

It has been established that the mechanism of this reaction involves, at first, the formation of acylimine **49** activated by Cu(II) salt so that addition of enolate **50** onto **49** is facilitated to afford intermediate **51** which then undergoes facile condensation

intramolecularly to give 3,4-dihydropyrimidin-2(1*H*)-ones **44** (**Fig. 8**). We have obtained spectroscopic evidence by carrying out *in situ* NMR experiments. For example, the formation of copper complex **49** was confirmed in our studies by *in situ* ^{1}H and ^{13}C-NMR experiments in CD_3OD at 25 ^{0}C. The ^{1}H-NMR of a mixture containing benzaldehyde and urea in $CD_3OD+CDCl_3$ shows aldehyde peak at δ 10.0 but just after 1 min. of addition of $Cu(OTf)_2$ (1 mol %), new peaks have emerged at δ 5.33 and 5.43 corresponding to H_2O and acylimine protons (**Fig. 9**). Its ^{13}C-NMR showed peaks at δ 193 and 103 of aldehyde and acylimine carbons respectively. After 10 min., we observed that the concentration of aldehydic proton was decreasing with respect to acylimine proton. When we further added ethyl acetoacetate into the same solution, there was sudden decrease of intensity of acylimine proton. The ^{13}C-NMR also showed the decreased intensity of peak at δ 103 (**Fig. 10**). From this NMR study we strongly believe that the mechanism of this reaction is believed to take place in stepwise manner involving intermediates **49** and **51** (**Fig. 8**).

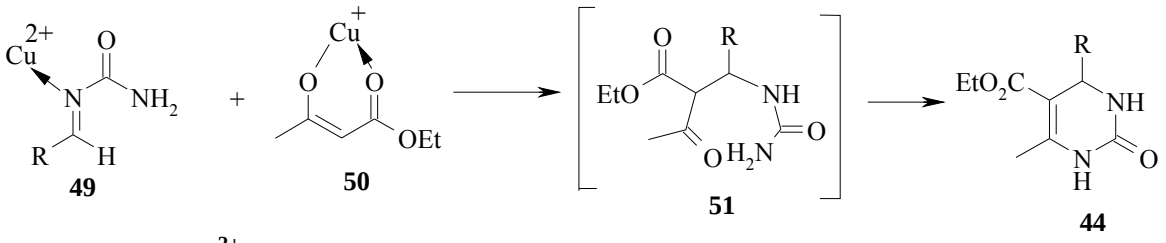


Fig. 8: Cu^{2+}- activation in three-component coupling for Biginelli reaction

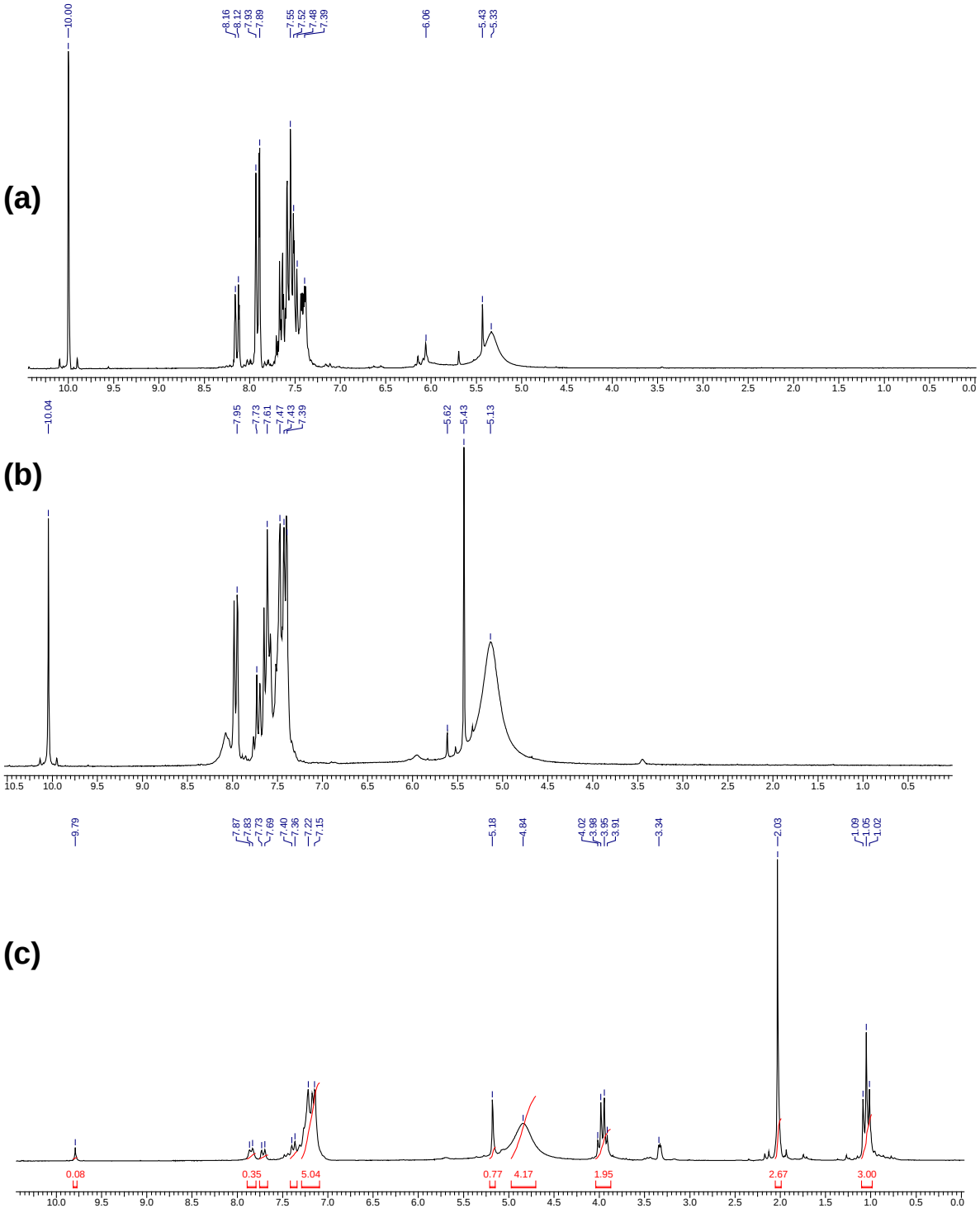


Fig. 9: *In situ* ^{1}H-NMR study (a) 1 min. after addition of $Cu(OTf)_2$ to a mixture of benzaldehyde and urea in CD_3OD+$CDCl_3$; (b) 10 min. after addition of $Cu(OTf)_2$ to a mixture of benzaldehyde and urea in CD_3OD+$CDCl_3$ (c) After addition of ethyl acetoacetate to benzaldehyde, urea, and $Cu(OTf)_2$ in CD_3OD+$CDCl_3$.

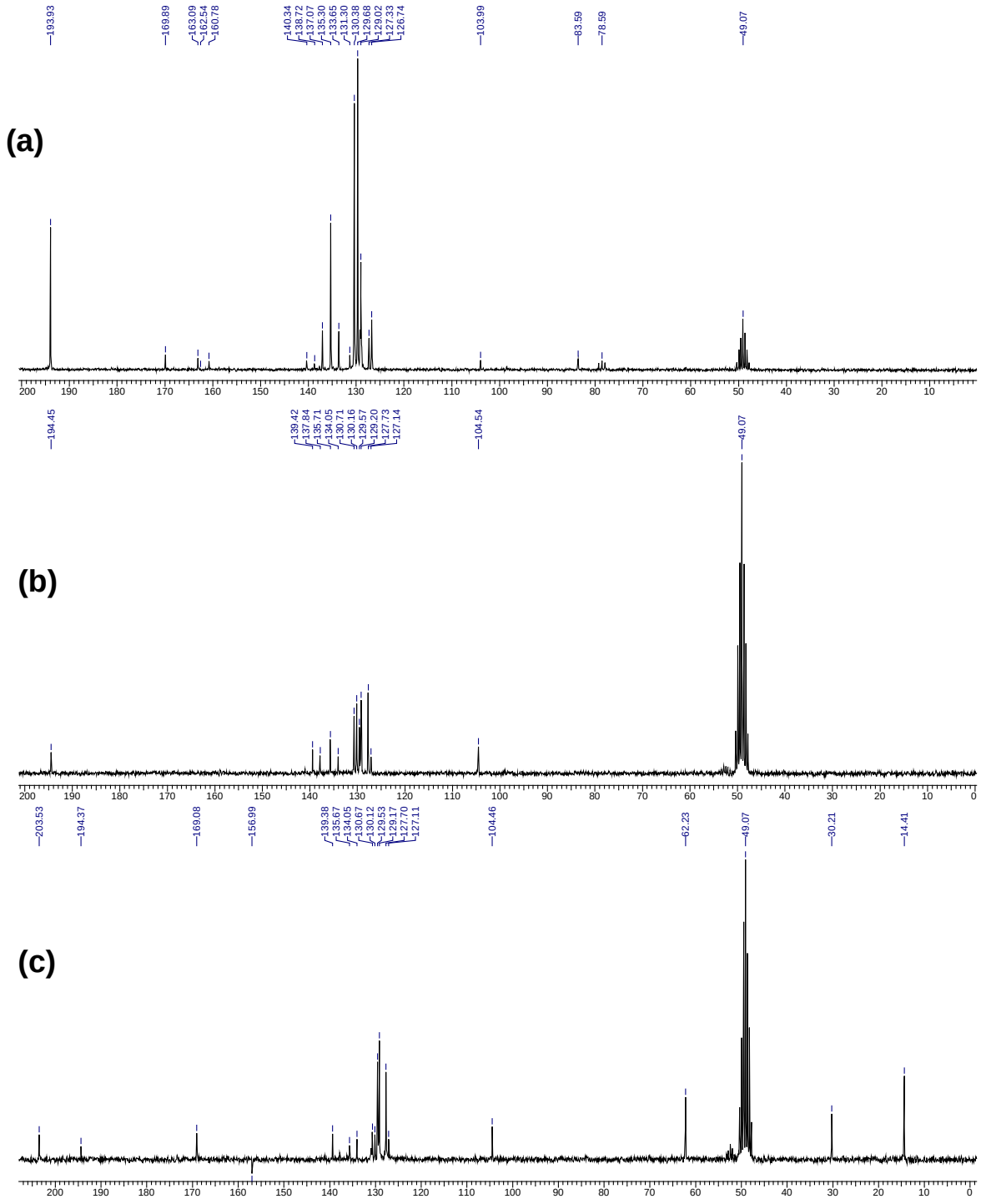


Fig. 10: *In situ* ^{13}C-NMR study (a) 1 min. after addition of $Cu(OTf)_2$ to a mixture of benzaldehyde and urea in CD_3OD+$CDCl_3$; (b) 10 min. after addition of $Cu(OTf)_2$ to a mixture of benzaldehyde and urea in CD_3OD+$CDCl_3$ (c) After addition of ethyl acetoacetate to benzaldehyde, urea, and $Cu(OTf)_2$ in CD_3OD+$CDCl_3$.

3.0.5 Conclusion

In conclusion, we have successfully demonstrated a simple modification of the Biginelli 3,4-dihydropyrimidin-2(1*H*)-one synthesis using $Cu(OTf)_2$ as a reusable catalyst. Excellent yields, recycling of the catalyst with negligible loss of activity, and the application to a variety of substituted / functionalized aryl aldehydes are some of the salient features of this reaction. We also proved that the Biginelli reaction proceeded by step-wise manner using *in situ* NMR experiments.

3.0.6 Experimental section

General procedure for the 3, 4-dihydropyrimidin-2(1*H*)-ones synthesis

A 25 ml RB flask was charged with aldehydes **43a-x** (2 mmol), urea (0.120 g, 2 mmol), ethyl acetoacetate (0.260 g, 2 mmol), $Cu(OTf)_2$ (7 mg, 1 mole %) and acetonitrile (5 ml). The resulting reaction mixture was stirred at temperature ranging from 25-70^{0}C (see **Table 2**). After the reaction was complete (monitored by TLC), the reaction mixture was cooled to room temperature and filtered through a sintered funnel. The crude product was further purified by recrystallization (EtOH or iPrOH) to afford pure 3,4-dihydropyrimidin-2(1*H*)-ones, **44a-x**.

Procedure for the catalytic asymmetric Biginelli reaction

A mixture of $Cu(OTf)_2$ and ligand **45** or **46** in acetonitrile was stirred for 6 hours at 50^{0}C to form complex. To this reaction mixture benzaldehyde (2 mmol), urea (0.120 g, 2 mmol) and ethyl acetoacetate (0.260 g, 2 mmol) were added in that order. After the reaction was complete (monitored by TLC), the reaction mixture was filtered through a sintered funnel. The residue containing the crude product was further purified by recrystallization (EtOH) to afford racemic 3, 4-dihydropyrimidin-2(1*H*)-one (0.494 g, 95 %) **44a**.

5-Ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44a):

Yield: 95%; colorless solid; **mp:** 200-202^{0}C (crystallized from EtOH), (Lit.[31]202-3 ^{0}C); **IR** (KBr, cm^{-1}): 1590, 1637, 1702, 1721, 2950, 3120, 3242; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 6.9 Hz, 3H), 2.24 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 5.14 (d, *J* = 3.6 Hz, 1H), 7.22 (m, 5H), 7.73 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **MS** m/z (% rel. intensity): 260 (M^+, 20), 245 (5), 231 (50), 214 (20), 183 (100), 172 (5), 155 (45), 144 (5), 137 (40), 110 (10), 91 (8), 85 (5), 77 (25), 67 (10); **Analysis:** $C_{14}H_{16}N_2O_3$ requires C, 64.60; H, 6.19; N, 10.76; found C, 64.63; H, 6.11; N, 10.89%.

5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44b):

Yield: 70%; colorless solid; **mp:** 216-218^{0}C (crystallized from iPrOH), (Lit.[31]215-7 ^{0}C); **IR** (Neat, cm^{-1}): 1593, 1651, 1704, 2926, 2980, 3098, 3224, 3416; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.17 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 5.40 (d, J = 3.2 Hz, 1H), 6.96 (s, 1H), 7.29–7.40 (m, 4H), 8.35 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **MS** m/z (% rel. intensity): 294 (M^+, 7), 281 (1, 259 (40), 249 (8), 221 (35), 206 (5), 183 (100), 155 (40), 137 (35), 128 (10), 110 (12), 101 (10), 91 (90), 75 (10), 65 (5); **Analysis:** $C_{14}H_{15}Cl\ N_2O_3$ requires C, 57.05; H, 5.12; N, 9.50; found C, 57.12; H, 5.16; N, 9.31 %.

5-Ethoxycarbonyl-4-(3-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44c):

Yield: 80%; colorless solid; **mp:** 190-193^{0}C (crystallized from EtOH), (Lit.[33]189-191 ^{0}C); **IR** (Neat, cm^{-1}): 1651, 1704, 2926, 2980, 3098, 3224; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 4.05 (q, J = 7.2 Hz, 2H), 5.37 (d, J = 3.2 Hz, 1H), 6.93 (s, 1H), 7.26–7.37 (m, 4H), 8.31 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.5, 18.4, 55.6, 60.2, 100.8, 125.9, 127.5, 128.2, 131.1, 134.5, 148.3, 149.1, 152.6, 166.1; **MS** m/z (% rel. intensity): 294 (M^+, 5), 265 (37), 221 (24), 183 (100), 155 (39), 137 (33); **Analysis:** $C_{14}H_{15}Cl\ N_2O_3$ requires C, 57.05; H, 5.12; N, 9.50; found C, 57.15; H, 5.18; N, 9.89 %.

5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44d):

Yield: 85%; colorless solid; **mp:** 212-213^{0}C (crystallized from iPrOH), (Lit.[31]210-3^{0}C); **IR** (Neat, cm^{-1}): 790, 1032, 1099, 1228, 1321, 1400, 1469, 1645, 1700, 2975, 3109, 3241; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, J = 6.9 Hz, 3H) 2.25 (s, 3 H), 4.00 (q, J = 7.2 Hz, 2H), 5.14 (d, J = 3.6 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.77 (s, 1H), 9.25 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.8, 53.4, 59.3, 98.8, 128.2, 128.4, 131.8, 143.8, 148.7, 151.9, 165.2; **MS** m/z (% rel. intensity): 295 (M^+, 5), 277 (61), 241 (81), 184 (90), 149 (100), 137 (50), 119 (70), 104 (40), 91 (80), 71 (75), 64 (80), 57 (90); **Analysis:** $C_{14}H_{15}Cl\ N_2O_3$ requires C, 57.05; H, 5.12; N, 9.50; found C, 56.85; H, 5.42; N, 9.43 %.

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44e):

Yield: 90%; cream color solid; **mp:** 200-201^{0}C (crystallized from EtOH), (Lit.[31]202-3 ^{0}C); **IR** (Neat, cm^{-1}): 1512, 1646, 1708, 2954, 3114, 3241, 3415; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.71 (q, *J* = 6.9 Hz, 2H), 5.08 (d, *J* = 2.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.66 (s, 1H), 9.14 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.7, 53.3, 55.0, 59.1, 99.6, 113.7, 127.4, 137.1, 148.0, 152.2, 158.4, 165.4; **MS** m/z (% rel. intensity): 290 (M^+, 5), 275 (1), 261 (10), 217 (8), 202 (1), 183 (10), 173 (2), 155 (8), 145 (1), 137 (7), 128 (5), 110 (7), 91 (100), 77 (10), 65 (10), 57 (5); **Analysis:** $C_{15}H_{18}N_2O_4$ requires C, 62.06; H, 6.25; N, 9.65; found C, 62.10; H, 6.27; N, 9.69%.

5-Ethoxycarbonyl-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44f):

Yield: 80%; colorless solid; **mp:** 200-202^{0}C (crystallized from MeOH), (Lit.[31]202-3 ^{0}C); **IR** (Neat, cm^{-1}): 1521, 1644, 1702, 1720, 2984, 3119, 3236, 3414; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.22 (t, *J* = 7.0 Hz, 3H), 1.78 (s, 3H), 3.28 (d, *J* = 2.1 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 2H), 4.53 (d, *J* = 2.1 Hz, 1H), 6.62–7.28 (m, 4H), 9.12 (br s, 1H), 9.83 (br s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.3, 23.9, 44.2, 48.0, 61.0, 83.5, 116.5, 121.0, 125.3, 128.6, 129.5, 150.5, 155.2, 168.; **MS** m/z (% rel. intensity): 276 (M^+, 62), 259 (5), 247 (81), 229 (97), 215 (5), 203 (71), 183 (100), 171 (7), 155 (40), 145 (10), 137 (20), 130 (5), 118 (15), 91 (25), 77 (20), 65 (15); **Analysis:** $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.83; N, 10.83; found C, 60.70; H, 5.56; N, 10.91%.

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44g):

Yield: 90%; colorless solid; **mp:** 199-200^{0}C (crystallized from iPrOH), (Lit.[31]198-200^{0}C); **IR** (Neat, cm^{-1}): 1512, 1649, 1687, 2984, 3120, 3241, 3417; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.08 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.97 (q, *J* = 7.2 Hz, 2H), 5.04 (d, *J* = 3.2 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.61 (s, 1 H), 9.11 (s, 1H), 9.32 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.8, 53.5, 59.1, 99.8, 115.0, 127.4, 135.5, 147.8, 152.2, 156.6, 165.4; **MS** m/z (% rel. intensity): 276 (M^+, 15), 261 (5), 247 (100), 229 (5), 212 (1), 203 (60), 183 (50), 173 (1), 155 (40), 147 (5), 137 (30), 110 (10), 91 (15), 77 (10), 65 (20); **Analysis:** $C_{14}H_{16}N_2O_4$ requires C, 60.86; H, 5.83; N, 10.83; found C, 60.89; H, 5.96; N, 10.43%.

5-Ethoxycarbonyl-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44h):

Yield: 75%; yellow color solid; **mp:** 226-225^{0}C (crystallized from EtOH), (Lit.[30]225-7^{0}C); **IR** (Neat, cm^{-1}): 666, 762, 1594, 1645, 1702, 1724, 2981, 3109, 3235; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 4.00 (m, 2H), 5.30 (d, *J* = 3.3 Hz, 1H), 7.71 (m, 2H), 7.91 (s, 1H), 8.15 (m, 2H), 9.38 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d$_6$): δ 14.1, 18.1, 54.2, 59.8, 99.1, 123.0, 128.1, 147.0, 149.6, 152.4, 152.7, 165.9; **MS** m/z (% rel. intensity): 305 (M$^+$, 5), 288 (40), 276 (15), 260 (5), 246 (1), 232 (10), 214 (2), 183 (100), 155 (50), 137 (40), 128 (10), 102 (10), 91 (80), 76 (10); **Analysis:** $C_{14}H_{15}N_3O_5$ requires C, 55.08; H, 4.95; N, 13.76; found C, 55.16; H, 5.04; N, 13.55%.

5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44i):

Yield: 75%; yellow color solid; **mp:** 207-209^{0}C (crystallized from iPrOH), (Lit.[31]208-9 ^{0}C); **IR** (Neat, cm^{-1}): 1594, 1645, 1702, 1724, 2981, 3109, 3235; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.12 (t, *J* = 6.9 Hz, 3H), 2.26 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.27 (d, *J* = 3.0 Hz, 1H), 7.52 (dd, *J* = 6.9 & 2.1 Hz, 2H), 7.90 (s, 1H), 8.23 (dd, *J* = 6.9 & 2.1 Hz, 2H), 9.36 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d$_6$): δ 14.2 18.0, 53.9, 59.7, 98.5, 124.0, 127.9, 146.9, 149.6, 152.1, 152.2, 165.3; **MS** m/z (% rel. intensity): 305 (M$^+$, 10), 290 (5), 276 (50), 259 (5), 246 (1), 232 (10), 217 (2), 183 (60), 150 (100), 137 (30), 119 (10), 103 (35), 91 (90), 76 (70), 65 (20); **Analysis:** $C_{14}H_{15}N_3O_5$ requires C, 55.08; H, 4.95; N, 13.76; found C, 54.97; H, 4.80; N, 13.80%.

5-Ethoxycarbonyl-4-(4-cyanophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44j):

Yield: 60%; dirty color solid; **mp:** 219-222^{0}C (crystallized from iPrOH), (Lit.[31]220-3 ^{0}C); **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.11 (t, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 5.25 (d, *J* = 3.0 Hz, 1H), 7.51 (dd, *J* = 6.9 & 2.1 Hz, 2H), 7.89 (s, 1H), 8.22 (dd, *J* = 6.8 & 2.0 Hz, 2H), 9.35 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d$_6$): δ 14.1, 17.8, 53.4, 59.3, 98.8, 116.5, 128.2, 128.4, 131.8, 143.8, 148.7, 151.9, 165.2; **Analysis:** $C_{15}H_{15}N_3O_3$ requires C, 63.14; H, 5.29; N, 14.72; found C, 63.23; H, 5.35; N, 15.06%.

5-Ethoxycarbonyl-4-(4-*N*,*N*-dimethylaminophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44k):

Yield: 65%; brownish color solid; **mp:** 230-232^{0}C (crystallized from MeOH), (Lit.[32]232-3 ^{0}C); **IR** (**Neat, cm^{-1}**): 1527, 1647, 1704, 2976, 3117, 3245, 3420; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.10 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 2.83 (s, 6H), 3.96 (q, *J* = 7.2 Hz, 2H), 5.02 (d, *J* = 3.2 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.57 (s, 1H), 9.07 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.7, 53.3, 59.1, 99.9, 112.2, 126.9, 132.6, 147.5, 149.7, 152.3, 165.5; **Analysis:** $C_{16}H_{21}N_3O_3$ requires C, 63.34; H, 6.97; N, 13.85; found C, 63.13; H, 7.03; N, 14.09%.

5-Ethoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44l):

Yield: 85%; colorless solid; **mp:** 204-205^{0}C (crystallized from MeOH), (Lit.[31]202-3 ^{0}C); **IR** (Neat, cm^{-1}): 1515, 1681, 1704, 1728, 2977, 2934, 3247, 3348; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.11 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 3.72 (s, 3H), 3.98 (q, *J* = 7.2 Hz, 2H), 5.05 (d, *J* = 2.8 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.80 (s, 1H), 7.66 (s, 1H), 8.95 (s, 1H), 9.15 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 17.8, 50.8, 53.6, 55.8, 99.5, 111.1, 115.4, 118.3, 135.8, 146.0, 147.5, 148.2, 152.3, 166.1; **Analysis:** $C_{15}H_{18}N_2O_5$ requires C, 58.81; H, 5.92; N, 9.14; found C, 58.63; H, 6.10; N, 9.89%.

5-Ethoxycarbonyl-4-(3-hydroxy-4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44m):

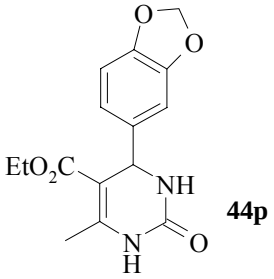
Yield: 85%; light green color solid; **mp:** 185-187^{0}C (crystallized from EtOH), (Lit.[32]187-8 ^{0}C); **IR** (Neat, cm^{-1}): 1681, 1704, 1728, 3247, 3348; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.13 (t, *J* = 7.2 Hz, 3H), 2.24 (s, 3H), 3.74 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.07 (d, *J* = 2.8 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.83 (s, 1H), 7.78 (s, 1H), 8.96 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 17.3, 51.10, 54.11, 55.9, 99.9, 111.6, 115.9, 118.8, 136.3, 146.5, 148.0, 148.7, 152.8, 166.6; **Analysis:** $C_{15}H_{18}N_2O_5$ requires C, 58.81; H, 5.92; N, 9.14; found C, 58.83; H, 6.02; N, 9.46%.

5-Ethoxycarbonyl-4-(3,4-dimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44n):

Yield: 85%; colorless solid; **mp:** 175-177^{0}C (crystallized from iPrOH), (Lit.[30]176-7 ^{0}C); **IR** (Neat, cm^{-1}): 790, 1095, 1139, 1237, 1461, 1519, 1654, 1682, 1723, 2956, 3118, 3253, 3400, 3549; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 7.2 Hz, 3H), 2.23 (s, 3H), 3.97 (q, *J* = 7.2 Hz, 2H), 5.05 (d, *J* = 3.2 Hz, 1H), 5.96 (s, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1 H), 9.16 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.7, 53.6, 59.1, 99.3, 100.9, 106.6, 107.9, 119.3, 138.8, 146.3, 147.2, 148.2, 152.0, 165.3; **Analysis:** $C_{16}H_{20}N_2O_5$ requires C, 59.99; H, 6.29; N, 8.74; found C, 60.08; H, 6.33; N, 8.67%.

5-Ethoxycarbonyl-4-(3,4,5-trimethoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44o):

Yield: 85%; creamy solid; **mp:** 180-182^{0}C (crystallized from iPrOH); **IR** (KBr, cm^{-1}): 840, 1092, 1125, 1281, 1587, 1651, 1713, 1962, 2810, 2910, 3069, 3199; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.20 (t, *J* = 6.8 Hz, 3H), 2.30 (s, 3H), 3.80 (s, 3H), 3.85 (s, 6H), 4.15 (q, *J* = 6.8 Hz, 2H), 5.30 (d, *J* = 2.7 Hz, 1H), 5.8 (s, 1H), 6.50 (s, 2H), 8.30 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 50.1, 56.3, 56.6, 59.2, 106.1, 106.3, 131.2, 136.7, 139.3, 148.4, 152.2, 165.4; **MS** m/z (% rel. intensity): 350 (M^+, 60), 335 (7), 321 (50), 304 (20), 289 (5), 277 (40), 261 (20), 238 (65), 222 (20), 195 (100), 183 (70), 168 (20), 155 (50), 137 (80), 125 (55), 110 (40), 77 (35), 66 (45); **Analysis:** $C_{17}H_{22}N_2O_6$ requires C, 58.27; H, 6.32; N, 7.99; found C, 58.23; H, 6.21; N, 8.13%.

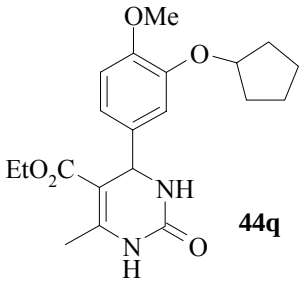


44p

5-Ethoxycarbonyl-4-(3,4-methylenedioxophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44p):

Yield: 85%; grey colored solid; **mp:** 188-189^{0}C (crystallized from iPrOH); **IR** (KBr, cm^{-1}): 795, 1093, 1225, 1490, 1642, 1700, 2975, 3222, 3356; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.11 (t, *J* = 6.9 Hz, 3H), 2.09 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.06 (d, *J* = 3.3 Hz, 1H), 5.98 (s, 2H), 6.70 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.68

(s, 1H), 9.18 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.7, 53.6, 59.1, 91.3, 106.9, 113.7, 114.9, 120.4, 135.7, 138.8, 145.3, 147.2, 148.2, 156.8, 165.1; **MS** m/z (% rel. intensity): 304 (M^+, 65), 289 (5), 275 (100), 258 (25), 231 (50), 216 (5), 183 (50), 155 (45), 137 (40), 121 (20), 89 (15), 77 (10), 65 (20); **Analysis:** $C_{15}H_{16}N_2O_5$ requires C, 59.20; H, 5.29; N, 9.20; found C, 60.63; H, 5.11; N, 9.09%.



44q

5-Ethoxycarbonyl-4-(3-cyclopentoxy-4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44q):

Yield: 80%; light yellow colored solid; **mp:** 185–188^{0}C (crystallized from iPrOH); **IR** (Neat, cm^{-1}): 790, 1095, 1139, 1237, 1461, 1519, 1654, 1682, 1723, 2956, 3118, 3253, 3400, 3549; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, J = 6.9 Hz, 3H), 2.24 (s, 3H), 3.40 (q, J = 6.9 Hz, 2H), 5.14 (d, J = 3.6 Hz, 1H), 7.22 (m, 5H), 7.73 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **Analysis:** $C_{20}H_{26}N_2O_5$ requires C, 64.15; H, 6.99; N, 7.48; found C, 64.30; H, 6.81; N, 7.85%.

5-Ethoxycarbonyl-4-(2-hydroxy-4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44r):

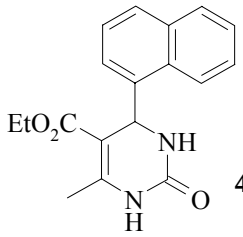
Yield: 65%; light green colored solid; **mp:** 240-243^{0}C (crystallized from MeOH), (Lit.[30]242-3 ^{0}C); **IR** (Neat, cm^{-1}): 592, 666, 762, 916, 1026, 1060, 1216, 1296, 1452, 1492, 1758, 2892, 2960, 3408; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, J = 6.9 Hz, 3H), 2.26 (s, 3H), 3.41 (q, J = 6.9 Hz, 2H), 5.0 (s, 1H), 5.17 (d, J = 3.6 Hz, 1H), 6.62 (s, 1H), 6.71 (d, J = 7.2 Hz, 1H), 6.83 (d, J = 6.8 Hz, 1H), 7.76 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 54.0, 59.2, 99.3, 115.9, 121.3, 127.2, 129.9, 133.2, 139.3, 152.2, 157.3, 165.4; **Analysis:** $C_{14}H_{15}Cl\ N_2O_4$ requires C, 54.11; H, 4.86; N, 9.01; found C, 54.14; H, 4.89; N, 9.13 %.

5-Ethoxycarbonyl-4-(2-hydroxy-4-bromophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44s):

Yield: 80%; grey colored solid; **mp:** 195-196^{0}C (crystallized from EtOH), (Lit.[33]195-6 ^{0}C); **IR** (KBr, cm^{-1}): 1651, 1704, 2926, 2980, 3098, 3224; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ δ 1.11 (t, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 4.98 (s, 1H), 5.15 (d, *J* = 3.6 Hz, 1H), 6.58 (s, 1H), 6.70 (m, 1H), 6.81 (m, 1H), 7.75 (s, 1H), 9.21 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.2 17.7, 54.1, 60.1, 101.2, 118.0, 125.5, 128.7, 130.5, 133.2, 139.3, 157.3, 158.7, 165.4; **Analysis:** $C_{14}H_{15}BrN_2O_4$ requires C, 47.34; H, 4.25; N, 7.88; found C, 47.23; H, 4.16; N, 7.45%.

5-Ethoxycarbonyl-4-(3-nitro-4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44t):

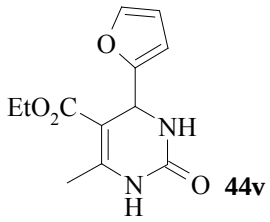
Yield: 70%; yellow colored solid; **mp:** 218-219^{0}C (crystallized from iPrOH), (Lit.[32]220-1 ^{0}C); **IR** (Neat, cm^{-1}): 1558, 1645, 1700, 2975, 3110, 3240; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.11 (t, *J* = 6.9 Hz, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 4.19 (q, *J* = 6.9 Hz, 2H), 5.54 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.87 (s, 1H), 9.20 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 12.3, 13.7, 17.2, 48.2, 59.8, 106.4, 122.1, 129.9, 130.8, 133.1, 139.3, 140.3, 148.9, 156.8, 165.3**; Analysis:** $C_{15}H_{17}N_3O_5$ requires C, 56.42; H, 5.36; N, 13.15; found C, 56.63; H, 5.21; N, 13.89%.



44u

5-Ethoxycarbonyl-4-naphthyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44u):

Yield: 85%; colorless solid; **mp:** 246-248^{0}C (crystallized from EtOH), (Lit.[31]247-9 ^{0}C); **IR** (Neat, cm^{-1}): 790, 1088, 1231, 1431, 1647, 1698, 2977, 3118, 3245; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 6.9 Hz, 3H), 2.24 (s, 3H), 3.40 (q, *J* = 6.9 Hz, 2H), 5.14 (d, *J* = 3.6 Hz, 1H), 7.22 (m, 5H), 7.73 (s, 1H), 9.19 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1 17.8, 54.0, 59.2, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **Analysis:** $C_{18}H_{18}N_2O_3$ requires C, 69.66; H, 5.84; N, 9.03; found C, 69.63; H, 5.81; N, 9.08%.



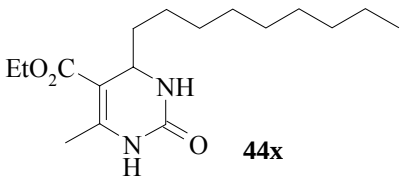
44v

5-Ethoxycarbonyl-4-furyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44v):

Yield: 70%; brown colored solid; **mp:** 203-205^{0}C (crystallized from MeOH), (Lit.[30]202-4 ^{0}C); **IR** (Neat, cm^{-1}): 1130, 1265, 1485, 1585, 1655, 1716, 2920, 3140, 3278; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.12 (t, *J* = 7.2 Hz, 3H), 2.22 (s, 3H), 4.00 (q, *J* = 7.2 Hz, 2H), 5.20 (d, *J* = 3.6 Hz, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 2.8 Hz, 1H), 7.53 (s, 1H), 7.74 (s, 1H), 9.22 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.2, 17.9, 47.8, 59.3, 96.9, 105.5, 110.6, 142.3, 149.5, 152.4, 155.9, 165.0; **Analysis:** $C_{12}H_{14}N_2O_4$ requires C, 57.59; H, 5.63; N, 11.19; found C, 57.48; H, 5.54; N, 11.21%.

5-Ethoxycarbonyl-4-cyclohexyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44w):

Yield: 60%; colorless solid; **mp:** 236-237^{0}C (crystallized from iPrOH), (Lit.[31]237-8 ^{0}C); **IR** (KBr, cm^{-1}): 789, 1095, 1230, 1450, 1647, 1702, 1726, 2850, 2920, 3118, 3236; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.15 (m, 4H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.50 (m, 3H), 1.80 (m, 4H), 2.35 (s, 3H), 4.20 (m, 3H), 6.20 (s, 1H), 8.50 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 13.7, 17.2, 25.0, 26.4, 27.4, 32.8, 48.4, 59.9, 112.7, 138.8, 156.8, 165.1; **Analysis:** $C_{14}H_{22}N_2O_3$ requires C, 63.13; H, 8.32; N, 10.51; found C, 63.15; H, 8.26; N, 10.42%.

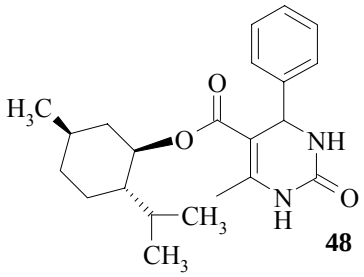


44x

5-Ethoxycarbonyl-4-nonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (44x):

Yield: 90%; colorless solid; **mp:** 156-158^{0}C (crystallized from $CHCl_3$), (Lit.[31]160 ^{0}C); **IR** (Neat, cm^{-1}): 779, 1086, 1288, 1331, 1433, 1646, 1730, 2933, 3249; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.98 Hz, 3H), 1.25 (m, 18H), 2.29 (s, 3H), 4.17(q, 3H), 4.31 (s, 1H), 5.94 (s, 1H), 8.17 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.93, 14.26, 17.72, 22.13, 23.75,

28.75, 29.0, 31.36, 36.80, 50.32, 59.11, 99.80, 148.21, 152.95, 154.64, 165.63; **Analysis:** $C_{17}H_{30}N_2O_3$ requires C, 65.77; H, 9.74; N, 9.02; found C, 65.82; H, 9.80; N, 9.07%.



48

5-(2-Isopropyl-5-methyl-cyclohexyloxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (48):

Yield: 89%; colorless solid; **mp:** 206 ^{0}C (crystallized from iPrOH); **$[\alpha]^{25}_D$**: – 19.7 (c 0.7, EtOH); **IR** (Neat, cm^{-1}): , 1637, 1702, 1721, 2950, 3120, 3242; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.42 (d, *J* = 6.65 Hz, 2H), 0.53 (d, *J* = 6.66Hz, 2H), 0.68 (d, *J* = 7.05 Hz, 2H), 0.77 (d, *J* = 6.26 Hz, 2H), 0.84-0.89 (m, 5H), 0.95 (s, 1H), 1.25 (t, J = 7.44 Hz, 1H), 1.59 (d, *J* = 12.13 Hz, 2H), 1.79 (s, 1H), 2.30 (s, 1H), 2.37 (s, 1H), 4.61 (m, *J* = 3.91 Hz, 1H), 5.35 (q, *J* = 2.74 Hz, 1H), 6.0 (s, 1H), 7.28 (m, 5H), 8.41 (d, *J* = 12.92 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 15.32, 16.28, 18.15, 18.22, 20.69, 20.91, 21.83, 21.90, 22.56, 23.33, 24.84, 26.24, 31.16, 31.27, 34.07, 40.46, 41.20, 46.86, 47.08, 55.17, 55.39, 73.32, 73.66, 100.53, 101.30, 126.44, 127.58, 128.39, 128.53, 143.57, 143.75, 145.88, 147.21, 154.12, 154.19, 165.04, 165.18; **Analysis:** $C_{22}H_{29}N_2O_3$ requires C, 71.51; H, 7.91; N, 7.58; found C, 71.53; H, 7.89; N, 7.60%.

X-ray data:

Table 3: Crystal data and structure refinement for **48**

Identification code	Sudalai
Empirical formula	C22 H30 N2 O3
Formula weight	370.48
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	MONOCLINIC, P2(1)
Unit cell dimensions	a = 9.0723(19) Å alpha = 90°. b = 17.625(4) Å beta = 92.041(8)°. c = 13.552(3) Å gamma = 90°.
Volume	2165.6(8) Å^3
Z, Calculated density	4, 1.136 Mg/m^3

Absorption coefficient	0.075 mm^{-}
F(000)	800
Crystal size	0.63 x 0.55 x 0.35 mm
Theta range for data collection	1.50 to 25.00 deg.
Limiting indices	-10<=h<=10, -20<=k<=20, -12<=l<=16
Reflections collected / unique	10403 / 6901 [R(int) = 0.0218]
Completeness to theta = 25.00	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9741 and 0.9540
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6901 / 1 / 511
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0411, wR2 = 0.1060
R indices (all data)	R1 = 0.0495, wR2 = 0.1157
Absolute structure parameter	0.0(9)
Largest diff. peak and hole	0.283 and -0.112 e. $Å^{-3}$

SECTION II:

Cu-catalyzed three-component synthesis of 1,4-dihydropyridines

3.1.1 Introduction

Hantzsch 1, 4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers, and have emerged as one of the most important classes of drugs. Examples include nifedipine **53**, nitrendipine **54**, nimodipine **55**, nicardipine **56**, amlodipine **57**, felodipine **58** and Bay K-8644 **59** used for the treatment of cardiovascular diseases, including hypertension[40] (**Fig. 1**). Recent studies have revealed that 4-methyl-1, 4-dihydropyridines, such as PCA 4248 **60**, have platelet-activating factor (PAF)-antagonistic activity[41] (**Fig. 11**).

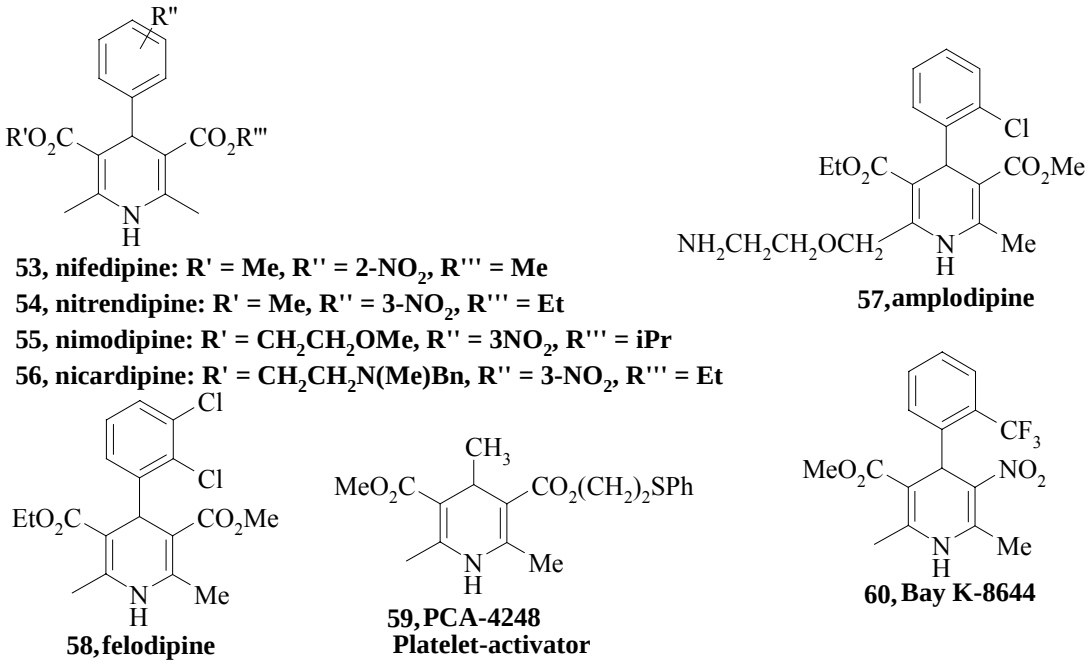


Fig. 11: Some of the important drugs containing dihydropyridine moiety.

The DHP heterocyclic ring is a common feature of various bioactive compounds such as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective and antidiabetic agents.[42]

Nifedipine **53** is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) which inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of vascular smooth muscle and cardiac muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine **53** selectively inhibits calcium ion influx across the cell membrane of vascular smooth muscle and cardiac muscle without altering serum calcium concentrations. Nifedipine **53** thus has hypotensive, antianginal properties and vasodilatory effects.[43]

These examples clearly demonstrate the remarkable potential of novel DHP derivatives as a source of valuable drug candidates. A recent computational analysis of the comprehensive medicinal chemistry database found the DHP framework to be among the most prolific chemotypes found. Thus, the synthesis of this heterocyclic nucleus is of continuing interest. The success of these calcium antagonists has led to the development of novel synthetic strategies to improve their classical methods of preparation. Microwave activation stands among the alternative routes proposed during the past decade due to the drastic reduction of reaction times.[44] More than a century ago the first 1,4-DHPs were obtained by Hantzsch.[45] This reaction involves a one-pot condensation of an aldehyde with ethyl acetoacetate, and ammonia either in acetic acid or refluxing in alcohol for a longer time. However, the yields of 1, 4-DHPs obtained by the Hantzsch method are generally low. Even though a number of modified methods under improved conditions have been reported,[46] many

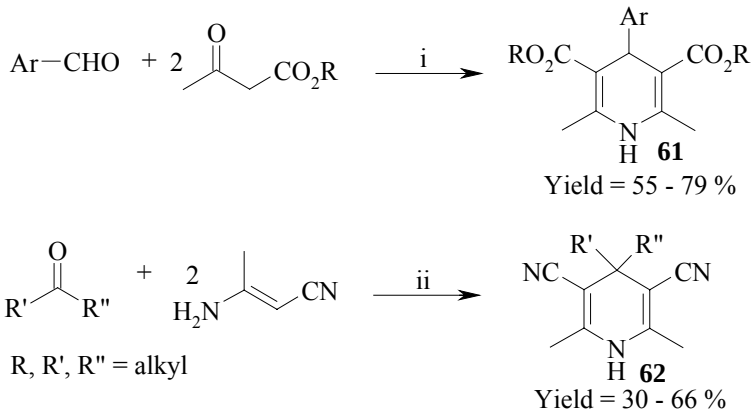
of them suffer from drawbacks such as unsatisfactory yields, high temperatures and long reaction times. Thus, the development of an efficient and versatile method for the preparation of Hantzsch 1, 4-DHPs is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and improved yields.

3.1.2 Review of Literature

Literature search revealed that there are various methods of Hantzsch dihydropyridine synthesis known in the literature. Some of the important methods so far known are described below.

Alvarez-Builla *et al.*[47]

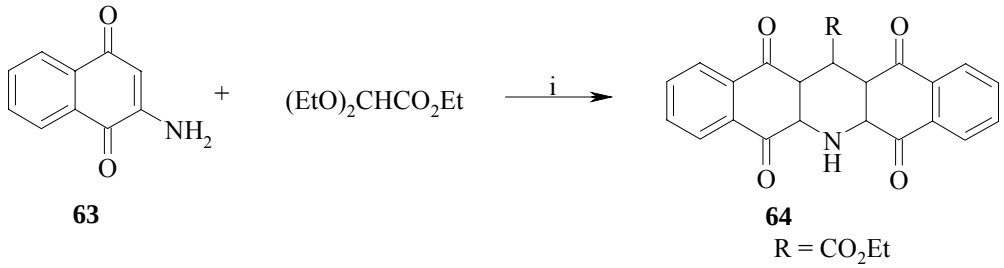
Alvarez-Builla et al. developed modified conditions for Hantzsh DHP synthesis by using domestic microwave oven to accelerate the classical Hantzsh reaction producing 4-aryl-2, 6-dimethyl-1, 4-dihydro-3, 5-pyridinecarboxylates (**61**) in 55 – 79 % yield and a variant pyridinedicarbonitriles (**62**) in 30 – 66 % yield. The above experiments show that synthesis of stericaly hindered 1, 4 DHPs **62** can be performed rapidly and safely under microwave irradiation (**Scheme 20**).



Scheme 20: i NH_4OH, EtOH, MW irradiation; ii AcOH, MW irradiation.

Marcos *et al.*[48]

One-pot annulations between 2-amino-1,4-naphthoquinone **63** and aldehydes or acetals gave **64** in 15 – 18 % yields. The acid promoted reaction (TFA, 80 ^{o}C, 15 min.) worked better than the thermal cyclization (xylene, reflux, 5h). This transformation constitutes a new example of the Hantzsch synthesis of 1,4-DHPs and has to involve a nucleophillic substitution at C-3 (**Scheme 21**).



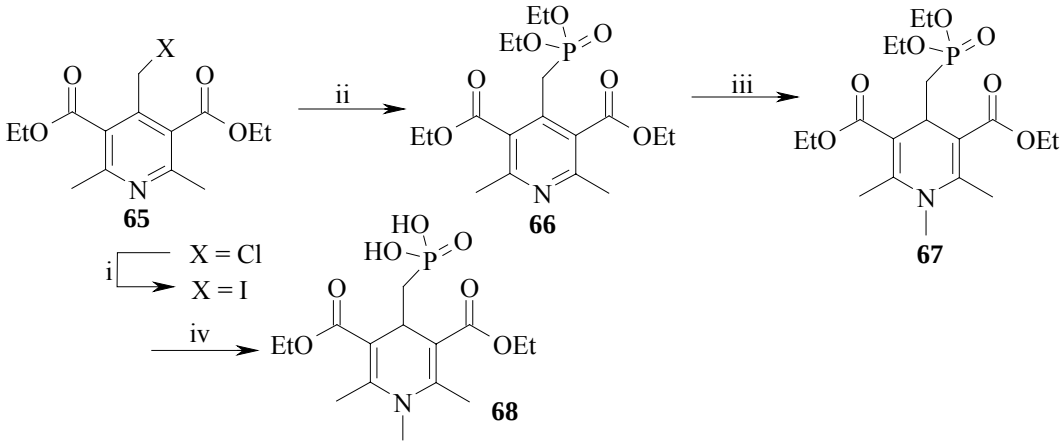
63 **64**

R = CO_2Et

Scheme 21: i TFA, 80 ^{0}C, 15min, 20%.

Maria Magdalena Cid[49]

Cid described general synthesis of C-4-substituted dihydropyridines. The route exploits a standard Hantzsch ester synthesis of **65** followed by aromatization and nucleophilic substitution. The resulting pyridine phosphonate ester **66** was reduced to dihydropyridine phosphonate ester **67**. This was further methylated and hydrolysed to give DHP phosphonic acid **68** having interesting biological properties (**Scheme 22**).

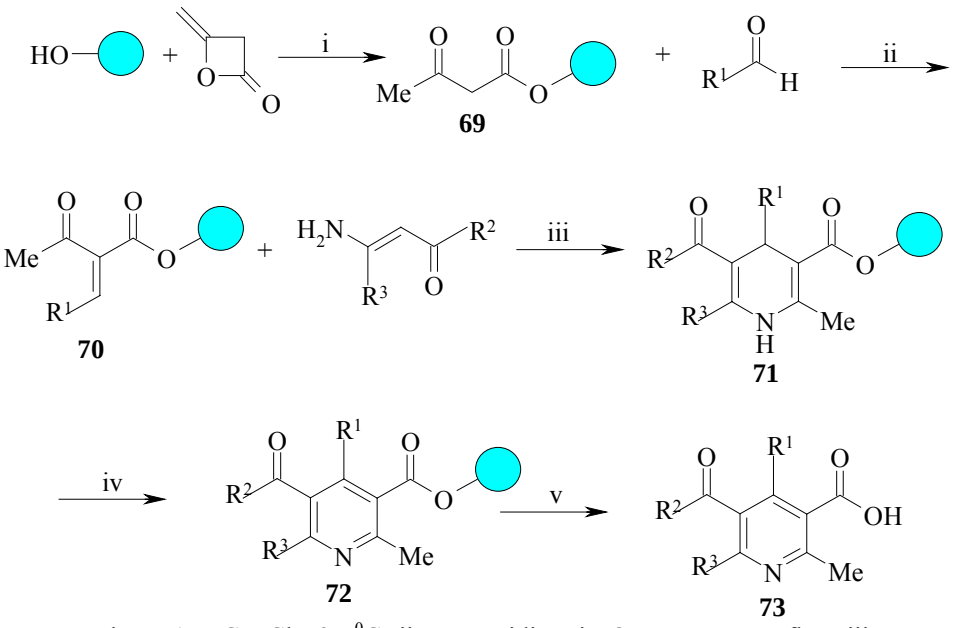


65 **66** **67** **68**

Scheme 22: i NaI, dry acetone, RT, 90%; ii $(EtO)_3P$, 130 °C; 91%; iii $(MeO)_2SO_2$, 65 °C, 5 h; iv (a) $Na_2S_2O_4$/$NaHCO_3$/water, 1 h; 46%; (d) TMSBr/dry CH_2CI_2, 2 h, RT, 87%.

Gordeev *et al.*[50]

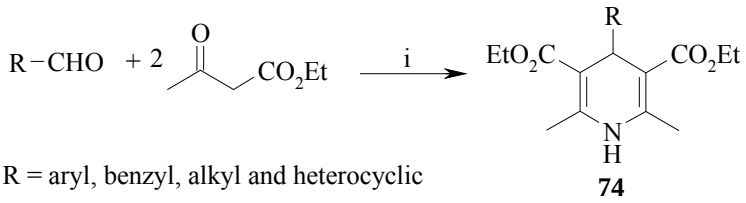
Gordeev et al. described solid phase synthesis of diverse pyridines. Immobilized keto esters **69** when refluxed with aldehydes in the presence of pyridine afforded Knoevenagel derivatives **70**. These derivatives **70** undergo Hantzsch-condensation with oxo enamines in refluxing DMF to generate 1, 4-dihydropyridines **71** in 50 – 67 % yields. Immobilized DHPs were further subjected for oxidative aromatization with ceric ammonium nitrate (CAN) in dimethyl acetamide to produce immobilized pyridines **72** in 32 – 58 % yield. The resulting heterocycles **72** are cleaved cleanly from the polymeric support with 95% aq. TFA or 3% TFA in CH_2C1_2 producing acid derivative **73** in good yield (**Scheme 23**). The course of the reaction on solid phase was studied by gel-phase ^{13}C NMR spectrosopy. The synthesis is designed to be amenable for combinatorial libraries.



Scheme 23: i DMAP, CH_2Cl_2, 25 ^0C; ii cat. Pyridine, iPrOH-Benzene, reflux; iii DMF, reflux; iv CAN, Me_2NCOMe; v TFA, CH_2Cl_2, 25 ^0C.

Yadav *et al.*[51]

DHPs **74** are synthesized in high yields by one-pot cyclocondensation of aldehyde, β-ketoester and urea on the surface of silica gel under microwave irradiation in (Pulsed irradiation [1 min with 20-s interval] operating at 2450 MHz.) solvent free conditions (**Scheme 24**).



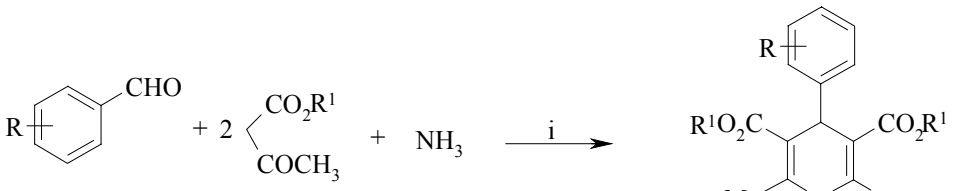
R = aryl, benzyl, alkyl and heterocyclic

74

Scheme 24: i Urea (10 mmol, 1 equi.), Silica gel 200 – 300 mesh (5 g), MWI 2-5 min at 650W.

Khadilkar *et al.*[52]

Khadilkar *et al.* reported the scaling up of clinically important dihydropyridine **75** by using a continuous microwave reactor (CMR). Scale up of DHPs is easily possible using a CMR. The construction of the reactor using a domestic microwave oven and a peristaltic pump is simple (**Scheme 25**).



75

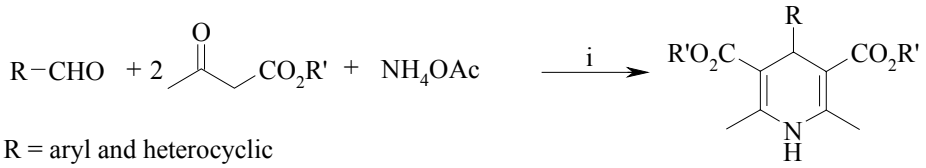
Yield = 86 - 98 %

Scheme 25: i MWI 24 min (6 x 4 cycles).

Perumal *et al.*[53]

Perumal *et al.* have described the synthesis of substituted DHPs **76** in excellent yields by the reaction of aldehydes, ethyl or methyl acetoacetic ester and ammonium acetate under microwave irradiation (MWI) within 0.75 – 3 min. This simple and convenient method for the synthesis of substituted DHPs **76** under microwave irradiation in excellent yields and shorter

reaction time as compared to previous methods which involve longer reaction times under refluxing conditions with moderate yields (**Scheme 26**).



R = aryl and heterocyclic

R' = ethyl or methyl

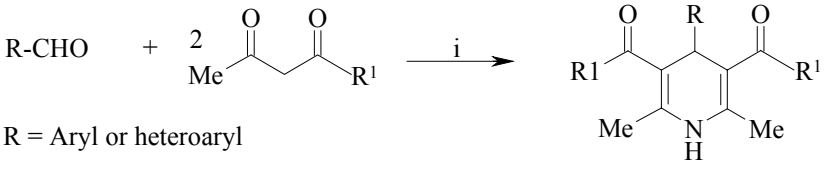
76

Yield = 66 - 96 %

Scheme 26: i EtOH, MWI 15 s pulse (0.75 – 3 min.) 580W.

Sabitha *et al.*[54]

The synthesis of various substituted Hantzsch 1, 4-dihydropyridines **77** has been achieved using the classical Hantzsch procedure with modified conditions for the first time at room temperature in the presence of iodotrimethylsilane (TMSI) generated *in situ* in CH_3CN, in good yields (**Scheme 27**).



R = Aryl or heteroaryl

R1 = OMe or OEt

77

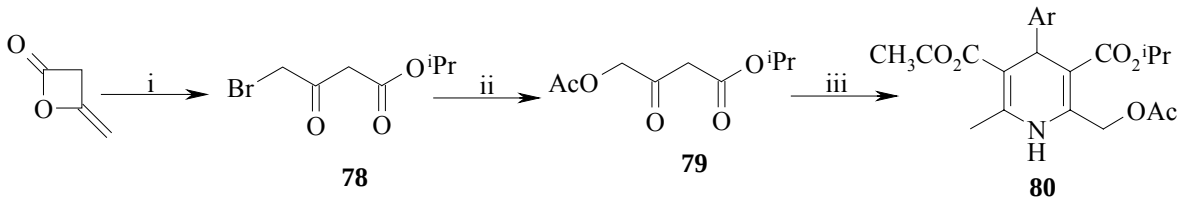
Yield = 72 - 85 %

Scheme 27: i NH_4OAc, cat. TMSCl/ NaI, CH_3CN, 25^0C, 6 – 8 h.

Achiwa *et al.*[55]

Achiwa et al. reported dissymmetric DHPs **80** synthesis from Isopropyl 4-acetoxyacetoacetate **80**. When isopropyl 4-acetoxyacetoacetate **79** with methyl 3-aminocrotonate and aryl aldehydes were refluxed in 2-propanol for 18 – 24 h, the DHP products **28** were obtained in 20 – 33 % yield. Isopropyl 4-acetoxyacetoacetate was prepared from isopropyl 4-bromoacetoacetate **78** by treatment with sodium acetate in acetic acid.

Isopropyl 4-bromoacetoacetate **78** was in turn obtained from reaction of diketene with bromine and 2-propanol in carbon tetrachloride (**Scheme 28**).



Yield = 20 - 33 %

Scheme 28: i Br_2, 2-propanol, CCl_4, 0 – 25 ^{0}C, 1h, 62 %; ii AcONa, AcOH, 25 ^{0}C, 18h, 48 %; iii methyl 3-aminocrotonate, aldehydes, 2-propanol, reflux, 18h, 20 - 33 %.

3.1.3 Present Work

3.1.3.1 Objective

Although there are many methods available in the literature for Hantzsch 1, 4-dihydropyridines synthesis, they suffer from certain drawbacks like low yields, reactions were performed under non-catalytic conditions, multi-step reaction sequences, higher temperatures, longer reaction times and low product selectivity in terms of product distribution *etc*. In order to overcome these difficulties a new catalytic method for Hantzsch 1, 4-dihydropyridines synthesis is highly desirable.

3.1.4 Results and Discussion

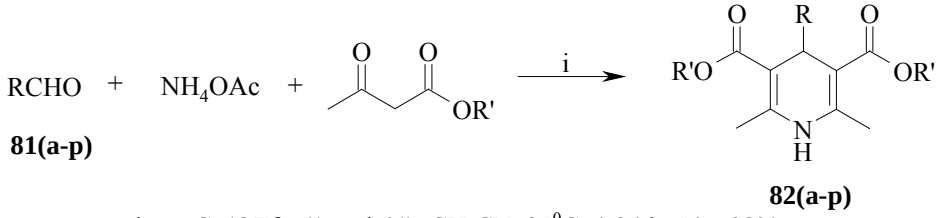
After successful demonstration of the Biginelli 3, 4-dihydropyrimidin-2(1*H*)-one synthesis using $Cu(OTf)_2$ as a reusable catalyst in the previous section of this chapter we wanted to study copper salts as catalysts for one more three-component reaction namely Hantzsch 1,4-dihydropyridines (DHP) synthesis.

Table 3: Cu-catalyzed condensation of benzaldehyde, ethyl acetoacetate and NH_4OH or NH_4OAc [a]

No.	Catalyst	Nitrogen source	Solvent	Yield of 82a (%)[b]	Time (h)
1	None	NH_4OH	CH_3CN	00	12
2	None	NH_4OAc	CH_3CN	00	12
3	$Cu(OTf)_2$	NH_4OH	CH_3CN	57	6
4		NH_4OAc	CH_3CN	98	6
5		NH_4OAc	THF	55	6
6		NH_4OAc	EtOH	89	6
7		NH_4OAc	H_2O	00	6
8		NH_4OAc	dioxane	95	6
9		NH_4OAc	$CHCl_3$	10	6
10		NH_4OAc	CH_2Cl_2	05	6
11	CuCl	NH_4OAc	CH_3CN	30	12
12	CuCN	NH_4OAc	CH_3CN	52	12
13	$Cu(OAc)_2.H_2O$	NH_4OAc	CH_3CN	15	12
14	$CuSO_4.5H_2O$	NH_4OAc	CH_3CN	00	12

a: reaction conditions: catalyst (1 mol %), benzaldehyde (2 mmol), nitrogen source (2 mmol), ethyl acetoacetate (4 mmol), 25 ^{0}C; b: isolated yield after chromatographic purification.

In our preliminary experiments, when a mixture of benzaldehyde, ethyl acetoacetate and NH_4OH in molar ratio of 1:2:1 was subjected to react at 25^{0}C in the presence of catalytic amount of $Cu(OTf)_2$ (1 mole%) in CH_3CN as solvent, the corresponding 1,4-dihydropyridine (DHP) was obtained in lower yield (57%). However, when we changed nitrogen source from NH_4OH to NH_4OAc with $Cu(OTf)_2$ (1 mole%) as catalyst in CH_3CN, we obtained the corresponding DHP (**82a**) in excellent yield (98%) and the results are summarized in **Table 3**. Among various solvents screened such as THF, CH_2Cl_2, $CHCl_3$, CH_3CN, dioxane and EtOH, only CH_3CN gave the required product in good yield. Variety of aldehydes (**81a-p**) were successfully screened for Hantzsch reaction under $Cu(OTf)_2$ conditions to afford the corresponding 1,4-dihydropyridines (**82a-p**) in good to excellent yields (**Scheme 29**).



81(a-p) **82(a-p)**

Scheme 29: i cat. $Cu(OTf)_2$ (1 mole%), CH_3CN, 25^{0}C, 4-24 h, 54 – 98%.

The results of Hantzsch reaction are summarized in **Table 4**.

Table 4: $Cu(OTf)_2$-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHP)

No.	R	R^1	Reaction time (h)	Yield %
a	Ph	Et	6	98
b	4-Cl-C_6H_4	Et	6	70
c	4-Me-C_6H_4	Et	6	80
d	4-MeO-C_6H_4	Et	4	85
e	4-NO_2-C_6H_4	Et	6	72
f	3- NO_2-C_6H_4	Et	6	77
g	4-NC-C_6H_4	Et	5	82
h	3,4-$(MeO)_2$-C_6H_3	Et	4	95
i	3,4-(O-CH_2-O)-C_6H_3	Et	4	90
j	2-O_2N-C_6H_4	Me	12	60
k	1-Naphthyl	Et	9	65
l	2-Naphthyl	Et	6	69
m	2-Furyl	Et	6	85
n	4-Me_2N-C_6H_4	Et	6	55
o	2-MeO-C_6H_4	Et	6	82
p	n-C_9H_{19}	Et	24	54

a: reaction conditions: aldehyde (2 mmol), NH_4OAc (2 mmol), ethyl or methyl acetoacetate (4 mmol), $Cu(OTf)_2$ (1 mol%), 25 ^{0}C; b: isolated yield after chromatographic purification.

The formation of 1, 4-dihydropyridines **82a-p** was confirmed by ^{1}H, ^{13}C-NMR, IR, and MS spectroscopy. The IR spectrum of 1, 4-dihydropyridine showed typical absorption bands in the region 1650-1730 cm^{-1} and 3400 cm^{-1} for C=O stretching and N-H stretching frequencies respectively. For examples, the IR spectrum of the 1, 4-dihydropyridine **82a** showed typical absorption bands in the region of 1690 and 3440 cm^{-1} for ester C=O stretching and NH streching frequencies respectively. The ^{1}H-NMR shows typical benzylic proton signal at δ 4.93 and peculiar broad signals at δ 5.67 suggesting cyclic vinyl NH protons are present in the molecule. Its ^{13}C-NMR spectra showed typical ester carbonyl carbon signal at δ 167.54. Its MS spectrum also showed the molecular ion peak at m/z 329 confirming the presence of 1, 4-dihydropyridine **82a** (**Fig. 12**). In case of Nefidipine (**53**) the IR spectrum showed the typical absorption bands at 1689 and 3442 cm^{-1} corresponding to ester C=O stretching and amine NH stretching vibrations respectively. Its ^{1}H-NMR signals at δ 5.73 and 5.87 are due to benzylic proton and DHP ring NH protons respectively. Its ^{13}C-NMR spectra showed typical ester carbonyl carbon signals at δ 165.4 confirming the formation of dimethyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridine dicarboxylate (Nefidipine) **53** (**Fig. 13**).

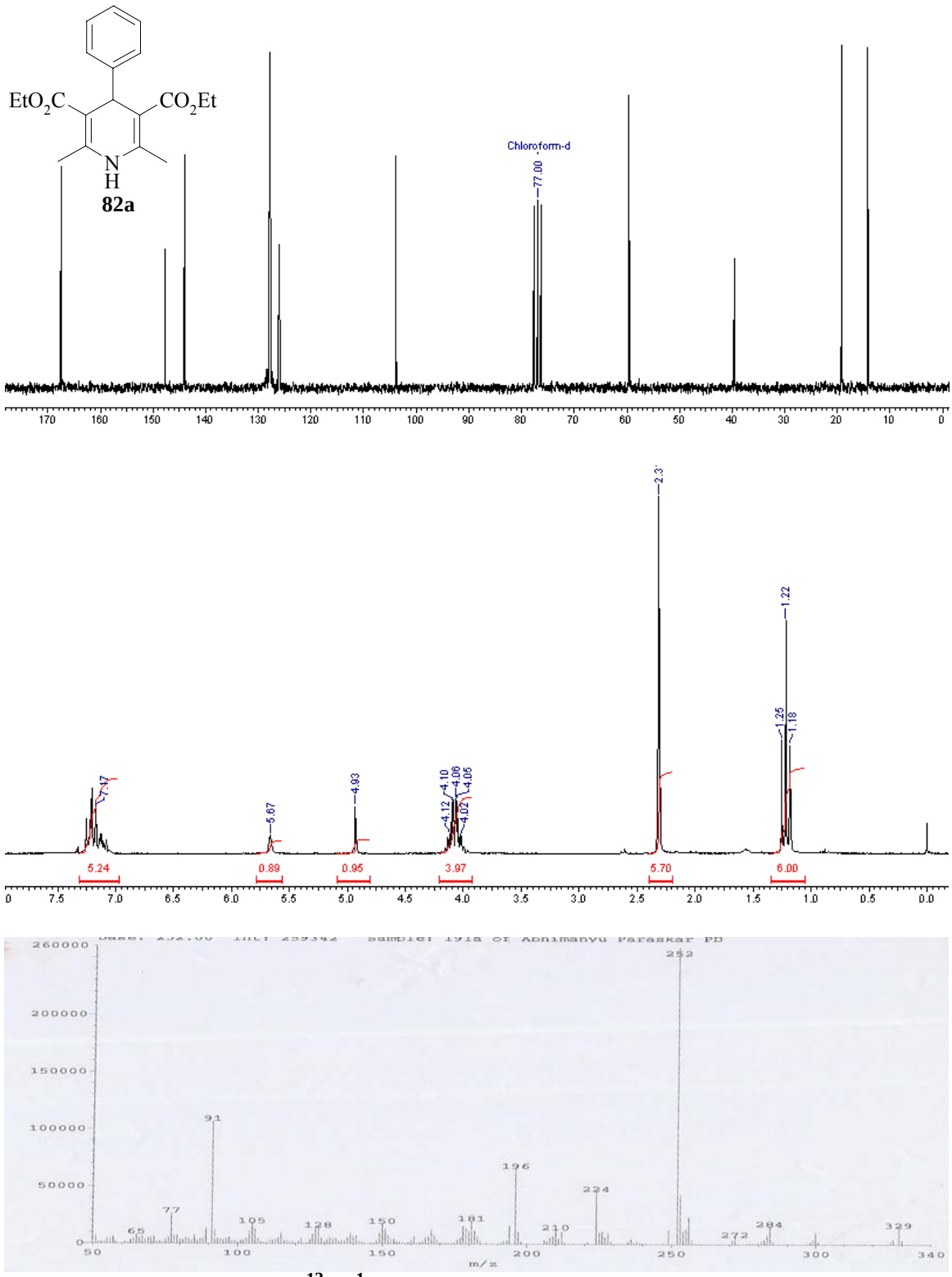


Fig. 12: ^{13}C, ^{1}H -NMR and Mass spectra of 82a

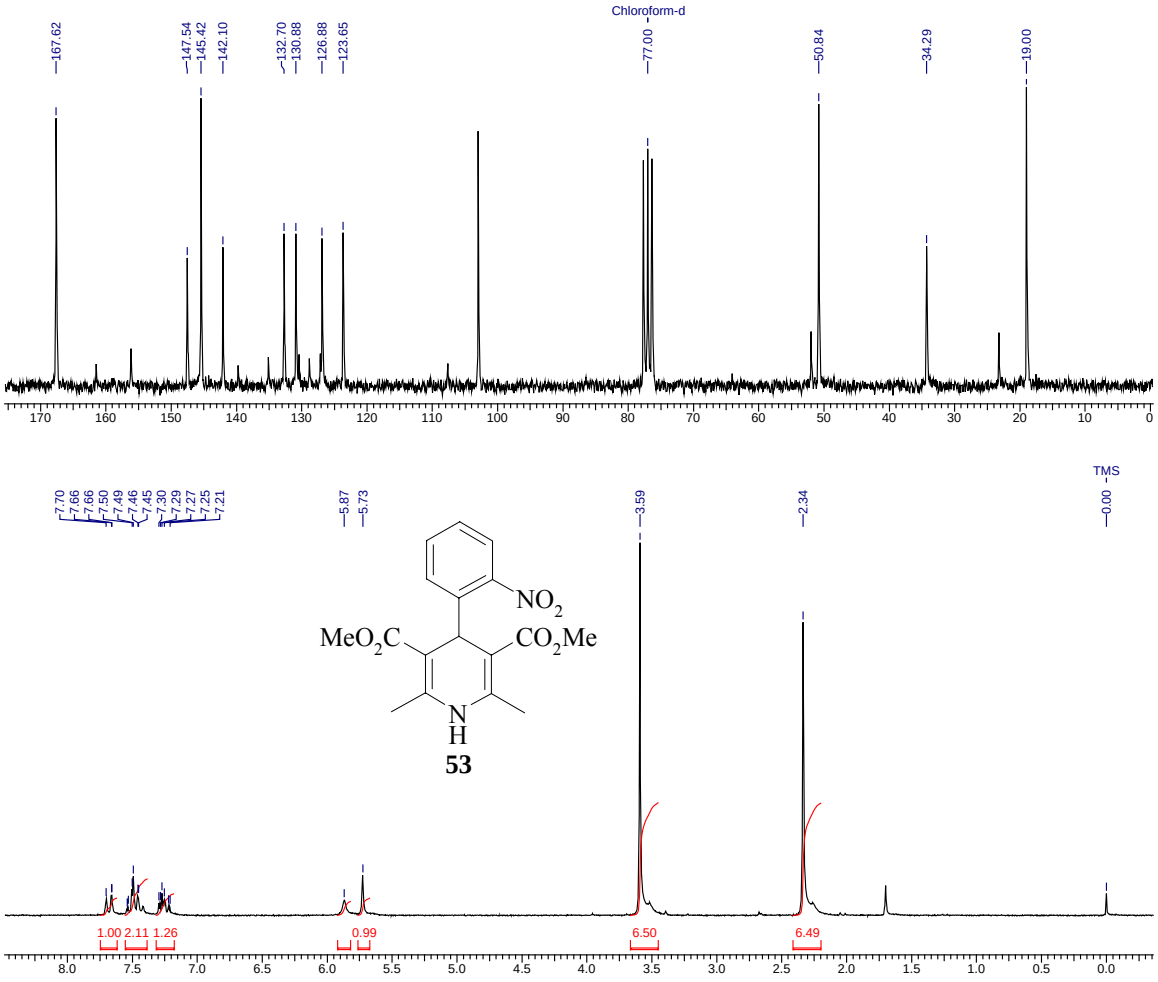


Fig. 13: ^{13}C and ^{1}H -NMR spectra of Nefidipine (53)

3.1.5 Conclusion

In conclusion, we have successfully demonstrated that $Cu(OTf)_2$ could be employed as an efficient catalyst, for the first time, to effect the three-component Hantzsch 1,4-dihydropyridine synthesis at room temperature. The method has successfully been applied for the synthesis of Nefidipine (**53**) an antihypertensive drug. The catalytic system is also very effective for the aliphatic and heterocyclic aldehydes **82m** and **82p** to give the corresponding product dihydropyridines (DHPs) in good yields.

3.1.6 Experimental section

General procedure for the Hantzsch 1, 4-dihydropyridines synthesis

A mixture of aldehydes **81a-p** (2 mmol), ethyl or methyl acetoacetate (4 mmol), ammonium acetate (2 mmol) and $Cu(OTf)_2$ as catalyst (1 mol%) in acetonitrile (5 ml) was stirred at 25^0C. After stirring for a specified time (see **Table 5**), the reaction mixture was diluted with water and extracted with ethyl acetate (3 x 15 ml). The combined organic phase was washed with aq. $NaHCO_3$ solution to remove acetic acid produced in the reaction, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then purified over column chromatography using petroleum ether and EtOAc (8:2) as eluent to afford 1,4-dihydropyridines **82a-p** in (54 – 98 %) yield.

Diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate (82a):

Yield: 98%; colorless solid; **mp:** 158-159^{0}C (crystallized from EtOH), (lit.[54] 156-7 ^{0}C); **IR** (KBr, cm^{-1}): 460, 482, 500, 620, 1011, 1050, 1100, 1180, 1200, 1209, 1500, 1667, 1690, 2350, 2867, 3440; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 6H), 2.31 (s, 6H), 4.06 (q, *J* = 7.20 Hz, 4H), 4.93 (s, 1H), 5.67 (brs, 1H), 7.08 – 7.26 (m, 5H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.28, 19.23, 39.59, 59.56, 103.92, 126.06, 127.89, 144.10, 147.61, 167.54; **MS** m/z (% rel. intensity): 329 (M^+, 5), 300 (5), 284 (5), 272 (3), 252 (100), 224 (15), 210 (10), 196 (20), 181 (10), 150 (10), 128 (7), 105 (8), 91 (40), 77 (12), 65 (5); **Analysis:** $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.03; N, 4.25; found C, 69.30; H, 7.00; N, 4.20%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-chlorophenyl)pyridine-3,5-dicarboxylate (82b):

Yield: 70%; colorless solid; **mp:** 144-145^{0}C (crystallized from EtOH), (lit.[54] 145-6^{0}C); **IR** (KBr, cm^{-1}): 500, 600, 620, 1000, 1130, 1310, 1519, 1694, 2342, 2912, 3400; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 6H), 2.30 (s, 6H), 4.09 (q, *J* = 7.2 Hz, 4H), 4.91 (s, 1H), 5.86 (s, 1H), 7.16 (s, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.22, 19.10, 39.19, 59.57, 103.58, 127.85, 129.22, 131.69, 144.20, 146.31, 167.25; **Analysis:** $C_{19}H_{22}ClNO_4$ requires C, 67.75; H, 6.58; N, 4.15; found C, 67.63; H, 6.11; N, 3.89%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate (82c):

Yield: 80%; colorless solid; **mp:** 160-161^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 500, 1040, 1150, 1200, 1300, 1390, 1450, 1700, 2400, 2460, 3300; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 6H), 2.27 (s, 3H), 2.30 (s, 6H), 4.09 (q, *J* = 7.2 Hz, 4H), 4.86 (s, 1H), 5.77 (brs, 1H), 6.95 (d, *J* = 8.09 Hz, 2H), 7.09 (d, *J* = 8.09 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.25, 19.08, 20.98, 39.03, 59.46, 103.82, 127.68, 128.44, 135.17, 144.10, 144.95, 167.59; **Analysis:** $C_{20}H_{25}NO_4$ requires C, 69.94; H, 7.33; N, 4.07; found C, 69.88; H, 7.21; N, 3.89%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (82d):

Yield: 85%; colorless solid; **mp:** 193-194^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 500, 700, 1000, 1050, 1200, 1250, 1300, 1500, 1700, 2400, 3300; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.08 Hz, 6H), 2.30 (s, 6H), 3.74 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 4H), 4.87 (s, 1H), 5.92 (s, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.59 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.68, 19.55, 39.13, 55.30, 59.85, 104.53, 113.62, 129.19, 140.79, 144.17, 158.30, 167.98; **Analysis:** $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.89; found C, 66.63; H, 7.11; N, 3.77%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (82e):

Yield: 72%; colorless solid; **mp:** 128-129^{0}C (crystallized from EtOH), (lit.[54] 129-130^{0}C); **IR** (KBr, cm^{-1}): 600, 620, 800, 850, 170, 1200, 1310, 1500, 1300, 1700, 2953, 3370; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.32 Hz, 6H), 2.34 (s, 6H), 4.09 (q, *J* = 7.33 Hz, 4H), 5.05 (s, 1H), 5.80 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.06 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.17, 20.07, 40.94, 59.75, 102.52, 124.28, 145.16, 146.09, 155.16, 166.88; **Analysis:** $C_{19}H_{22}NO_6$ requires C, 60.95; H, 5.92; N, 7.48; found C, 60.63; H, 5.91; N, 7.50%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate (82f):

Yield: 77%; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.28 Hz, 6H), 2.32 (s, 6H), 4.14 (q, *J* = 7.76 Hz, 4H), 4.98 (s, 1H), 5.97 (s, 1H), 7.32 – 8.11 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.12, 19.28, 40.17, 59.62, 102.88, 123.52, 126.78, 131.63, 132.86, 143.14, 146.27, 148.55,

168.40; **Analysis:** $C_{19}H_{22}NO_6$ requires C, 60.95; H, 5.92; N, 7.48; found C, 60.89; H, 5.80; N, 7.43%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-cyanophenyl)pyridine-3,5-dicarboxylate (82g):

Yield: 82%; colorless solid; **mp:** 200-202^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 500, 1000, 1040, 1200, 1400, 1400, 1685, 2200, 2930, 3300; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.08 Hz, 6H), 2.33 (s, 6H), 4.10 (q, *J* = 7.2 Hz, 4H), 5.99 (s, 1H), 5.91 (s, 1H), 7.34 (d, *J* = 8.46 Hz, 2H), 7.48 (d, *J* = 8.34 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.19, 19.05, 40.08, 59.66, 102.71, 109.53 118.97, 128.74, 131.61, 144.98, 153.19, 166.91; **Analysis:** $C_{20}H_{22}N_2O_4$ requires C, 73.37; H, 6.77; N, 8.55; found C, 73.33; H, 6.70; N, 8.60%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate (82h):

Yield: 95%; colorless solid; **mp:** 163-165^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 450, 1050, 1200, 1250, 1300, 1500, 1689, 2390, 2900, 3320; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.07 Hz, 6H), 2.32 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 4.11 (q, *J* = 7.07 Hz, 4H), 4.89 (s, 1H), 5.72 (s, 1H), 6.70 (m, 1H), 6.83 (m, 1H), 7.14 (m, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.26, 19.98, 38.80, 55.50, 59.37, 103.7, 110.94, 111.77, 119.68, 140.81, 143.92, 147.21, 148.06, 167.45; **Analysis:** $C_{21}H_{27}NO_6$ requires C, 64.76; H, 6.98; N, 3.59; found C, 64.63; H, 6.81; N, 3.45%.

Diethyl 4-(benzo[*d*][1,3]dioxol-6-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (82i):

Yield: 90%; colorless solid; **mp:** 200-202^{0}C (crystallized from EtOH), (lit.[54] 202-3 ^{0}C); **IR** (KBr, cm^{-1}): 858, 1108, 1530, 1595, 1630, 1670, 3325, 3406; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.24 (t, *J* = 7.2 Hz, 6H), 2.30 (s, 6H), 4.12 (q, *J* = 7.2 Hz, 4H), 4.84 (s, 1H), 5.86 (s, 1H), 6.00 (s, 2H), 6.72 (m, 3H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.25, 19.97, 38.80, 59.37, 91.3, 103.7, 110.94, 111.77, 119.68, 140.81, 143.92, 147.21, 148.06, 167.45; **Analysis:** $C_{20}H_{23}NO_6$ requires C, 64.33; H, 6.20; N, 3.75; found C, 64.16; H, 6.14; N, 3.66%.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (30j) (Nefidipine):

Yield: 60%; colorless solid; **mp:** 173-174^{0}C (crystallized from EtOH), (lit.[54] 172-4 ^{0}C); **IR** (KBr, cm^{-1}): 462, 667, 757, 831, 858, 1020, 1103, 1118, 1190, 1217, 1284, 1309, 1352, 1434, 1492, 1529, 1618, 1649, 1689, 3020, 3442; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.34 (s, 6H), 3.59 (s, 6H), 5.73 (s, 1H), 5.87 (s, 1H), 7.21 – 7.30 (m, 1H), 7.41 – 7.54 (m, 2H), 7.66 – 7.70 (m, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 19.0, 34.29, 50.84, 103.0, 123.65, 126.88, 130.88, 132.70, 142.10, 145.42, 147.54, 167.62; **Analysis:** $C_{17}H_{18}N_2O_6$ requires C, 58.95; H, 5.23; N, 8.08; found C, 58.88; H, 5.20; N, 8.00%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(1-naphthyl)pyridine-3,5-dicarboxylate (82k):

Yield: 69%; colorless solid; **mp:** 202-205^{0}C (crystallized from EtOH), (lit.[54] 202-3 ^{0}C); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 8.2 Hz, 6H), 2.29 (s, 6H), 3.92 (q, *J* = 8.2 Hz, 4H), 5.55 (brs, 1H), 5.76 (s, 1H), 7.30–7.55 (m, 4H), 7.60 (d, *J* = 8.68 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 8.55 (d, *J* = 8.6 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.7, 18.6, 28.3, 59.9, 100.6, 123.9, 125.2, 125.4, 126.2, 126.4, 126.5, 128.3, 132.5, 133.4, 134.0, 142.7, 165.0; **Analysis:** $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69; found C, 72.75; H, 6.49; N, 3.58%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-naphthyl)pyridine-3,5-dicarboxylate (82l):

Yield: 65%; colorless solid; **mp:** 196-198^{0}C (crystallized from EtOH), (lit.[54] 195-8 ^{0}C); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.95 (t, *J* = 8.2 Hz, 6H), 2.30 (s, 6H), 3.95 (q, *J* = 8.2 Hz, 4H), 5.55 (brs, 1H), 5.75 (s, 1H), 7.25 - 7.45 (m, 4H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 8.55 (s, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.7, 18.6, 30.4, 59.9, 100.5, 124.8, 125.7, 126.7, 127.2, 127.4, 127.5, 127.9, 131.6, 133.5, 135.2, 142.7, 165.0; **Analysis:** $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69; found C, 72.43; H, 6.41; N, 3.55%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-furyl)pyridine-3,5-dicarboxylate (82m):

Yield: 85%; colorless solid; **mp:** 163-165^{0}C (crystallized from EtOH), (lit.[54] 164 ^{0}C); **^{1}H-NMR** (200 MHz): δ 1.30 (t, *J* = 8.2 Hz, 6H), 2.40 (s, 6H), 4.20 (q, *J* = 8.2 Hz, 4H), 5.30 (s, 1H), 5.80 (brs, 1H), 6.80 – 7.05 (m, 3H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.7, 18.0, 31.2,

59.9, 100.6, 105.7, 110.6, 141.2, 142.7, 152.5, 165.0; **Analysis:** $C_{17}H_{21}NO_5$ requires C, 63.94; H, 6.63; N, 4.39; found C, 63.70; H, 6.45; N, 4.18%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-*N*,*N*-dimethylaminophenyl)pyridine-3,5-dicarboxylate (82n):

Yield: 55%; colorless solid; **mp:** 200-202^{0}C (crystallized from EtOH), (lit.[54] 203 ^{0}C); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 8.2 Hz, 6H), 2.35 (s, 6H), 3.10 (s, 6H), 4.15 (q, *J* = 8.2 Hz, 4H), 5.10 (s, 1H), 5.6 (brs, 1H), 7.15 – 7.75 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.7, 18.6, 30.0, 43.6, 59.9, 100.5, 113.0, 113.7, 120.1, 127.2, 130.1, 141.5, 142.7, 165.0; **Analysis:** $C_{21}H_{28}N_2O_4$ requires C, 67.72; H, 7.58; N, 7.52; found C, 67.68; H, 7.51; N, 7.26%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-methoxyphenyl)pyridine-3,5-dicarboxylate (82o):

Yield: 82%; colorless solid; **mp:** 142-143^{0}C (crystallized from EtOH), (lit.[54] 138-143^{0}C); **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.25 (t, *J* = 8.2 Hz, 6H), 2.30 (s, 6H), 3.90 (s, 3H), 4.10 (q, *J* = 8.2 Hz, 4H), 5.10 (s, 1H), 5.80 (brs, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.4 (d, *J* = 8.7 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 14.55, 19.45, 39.33, 55.32, 59.80, 104.56, 113.61, 129.20, 141.21, 144.23, 158.34, 167.77; **Analysis:** $C_{20}H_{25}NO_5$ requires C, 66.84; H, 7.01; N, 3.90; found C, 66.42; H, 6.89; N, 3.55%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-nonylpyridine-3,5-dicarboxylate (82p):

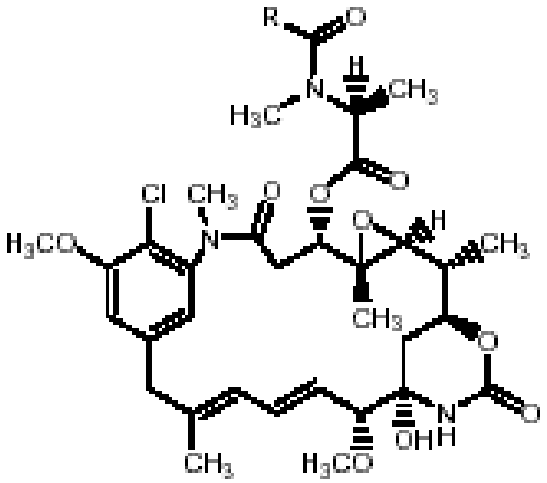
Yield: 54%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.90 (t, *J* = 8.4 Hz, 3H), 1.15 (m, 16H), 1.25 (t, *J* = 8.4 Hz, 6H), 1.45 (m, 2H), 2.30 (s, 6H), 3.85 (t, 1H), 4.15 (q, *J* = 8.6 Hz, 4H), 5.65 (brs, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 13.7, 14.0, 18.5, 23.1, 26.8, 28.3, 29.4, 30.0, 30.3, 30.8, 32.5, 59.9, 108.5, 141.2, 165.1; **Analysis:** $C_{23}H_{39}NO_4$ requires C, 72.04; H, 7.42; N, 3.65; found C, 71.86; H, 7.39; N, 3.42%.

SECTION III:

Cu-catalyzed three-component synthesis of 3,4-dihydro[1,3]oxazin-2-ones

3.2.1 Introduction

The cyclic carbamate oxazinone is an important 6-membered heterocyclic ring system which is present in many biologically important natural products like maystansine **83**, maytanbutine **84**, maystanprine **85**, maytanvaline **86** and colubrinol (**Fig**. **14**).[56]



83, Maytansine: R = CH_3
84, Maytanbutine: $CH(CH_3)_2$
85, Maytanprine: CH_2CH_3
86, Maytanvaline: $CH_2CH(CH_3)_2$

Fig. 14: Biologicaly active natural products containing 1,3-oxazinone moiety.

Recent study shows that biological activity of maystansine is mainly because of C-9 carbinolamide (**Fig**. **15**).

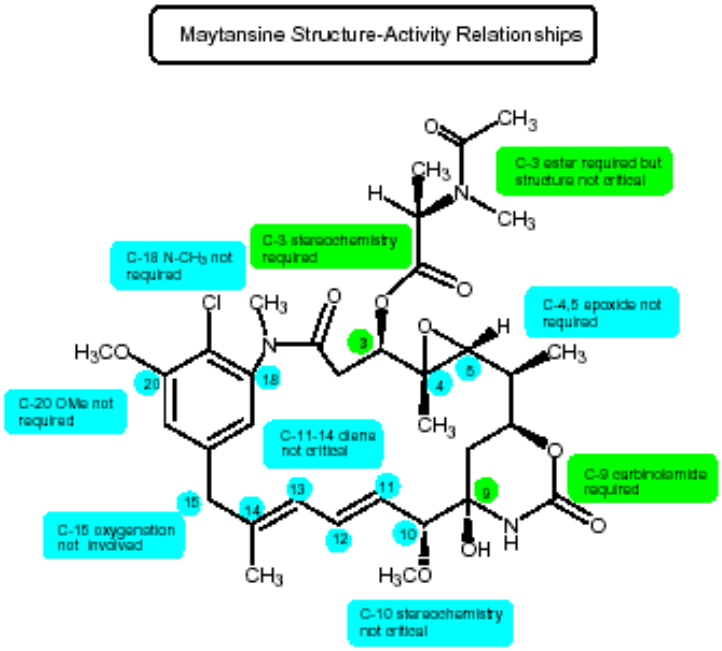


Fig. 15: Maytansine SARs showing requirement of 1,3-oxazinone moiety for biological activity.

In addition, oxazinone derivatives are known to exhibit a variety of biological activities such as antiulcer, anticonvulsant, penetration enhancer, sedative, analgesic, vasodilator, hypertensive and antidepressant.[57] 1, 3-Oxazin-2-one derivatives have also been used as key intermediates in the synthesis of several natural products such as (+) negamycin,[58] L-ristosamine,[59] and L-daunosamine[59] as well as in the synthesis of 1,3-.syn mninoalcohols.[60] Recently, oxazinones have been recognized as chiral auxiliaries in asymmetric synthesis.[61]

Multicomponent reactions (MCRs):

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[62] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. In an ideal

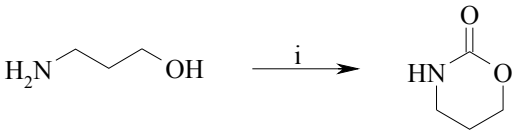
case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. Their high atom economy and simple experimental set-up make MCRs convenient tools for easy and rapid access to such large libraries of organic compounds. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. The search and discovery for new MCRs on one hand, and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. Scientific efforts focus more and more on the development of multi-component procedures for the generation of libraries of heterocyclic compounds.[62] This growing interest is stimulated by the interesting pharmaceutical properties that are associated with many heterocycles. Furthermore, the rigid well-defined structures make heterocycles ideal candidates for detailed Structure Activity Relationship (SAR)-studies.[63]

3.2.2 Review of Literature

Literature search revealed that there are various methods of construction of 1, 3-oxazin-2-one moiety are known in the literature but to the best of our knowledge no one has ever reported the synthesis of 3, 4-dihydro[1, 3]oxazin-2-ones. Some of the important methods of construction of 1, 3-oxazin-2-one so far known are described below.

Sonoda *et al.*[64]

When amino alcohols were reacted with carbon monoxide in the presence of equimolar amount of selenium at room temperature under atmospheric pressure, tetrahydro 1, 3-oxazin-2-ones (**87**) were obtained in 29 – 75 % yields (**Scheme 30**)



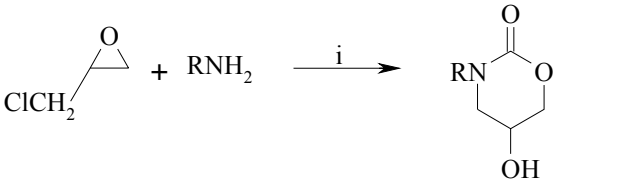
87

Yield = 29 %

Scheme 30: i Selenium, CO, O_2, DMF, 6h, 25 ^{0}C, 29 %.

Toda *et al.*[65]

Toda *et al.* reported carbon dioxide fixation *via* ammonium carbamates under mild conditions: without a catalyst, at atmospheric pressure and at ambient temperature. Intermolecular reactions between ammonium carbamates (*in situ* generated from carbon dioxide and amines) and epoxide gave hydroxy 1, 3-oxazin-2-ones (**88**) in 36 – 71 % yields (**Scheme 31**).

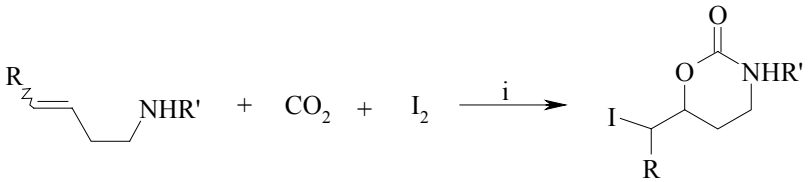


88

Yield = 36 - 71 %

Scheme 31: i CO_2 (1 atm), MeOH, 25^{0}C, 24h, 36 -71%

The authors also studied the reaction of homoallylamines **89** with carbon dioxide in MeOH, followed by treatment with I_2 at ambient temperature for 20 h, to give iodo-1,3-oxazin-2-ones (**90**) in 60 – 70 % (**Scheme 32**).



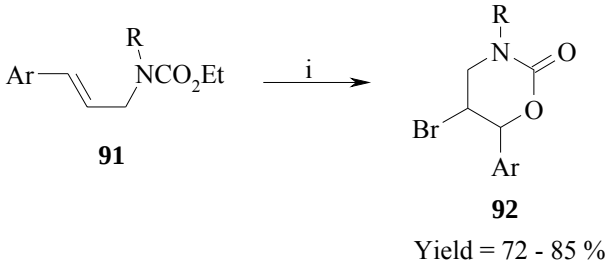
89 **90**

Yield = 60 - 70 %

Scheme 32: i Homoallyl amine, CO_2 (1 atm), I_2, MeOH, 25 ^{0}C, 20h, 60 – 70 %

Muhlstadt *et al.*[66]

Muhlstadt *et al.* studied the cyclization reaction of N-substituted allylamine **91** with bromine producing 1, 3-oxazin-2-ones (**92**) in 72 – 85 % (**Scheme 33**).



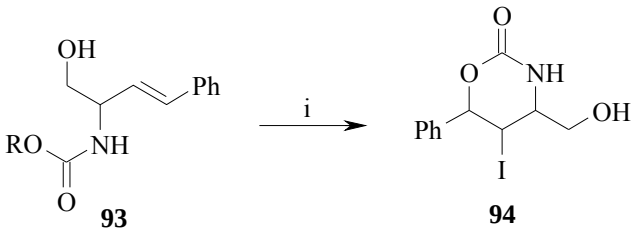
91 **92**

Yield = 72 - 85 %

Scheme 33: i Br_2, CH_2Cl_2, 25 ^{0}C, 72 – 85 %.

Orena[67]

Mario Orena studied iodocyclisation of primary homoallylic alcohols (**93**), containing a 2-*t*-butoxycarbonylamino by stirring with NIS in dichloromethane at room temperature for 24 h produce 1,3-oxazin-2-ones (**94**) in 25 – 62 % yield (**Scheme 34**).



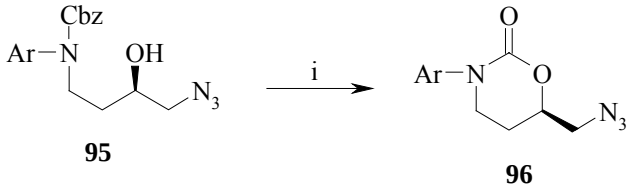
93 **94**

Yield = 25 - 62 %

Scheme 34: i NIS, CH_2Cl_2, 25 ^{0}C, 24h, 25 – 62 %.

Lohray *et al.*[68]

Lohray and coworkers synthesized 6-substituted chiral N-aryl-l,3-oxazin-2-one (**96**) derivatives starting from readily available (S)-aspartic acid in 22 – 45 % yields. (S)-aspartic acid is converted to azido alcohol **95** in 4 steps, which readily cyclizes to N-aryl-l,3-oxazin-2-ones when treated with sodium hydride in THF at 5^{0}C for 15s (**Scheme 35**).



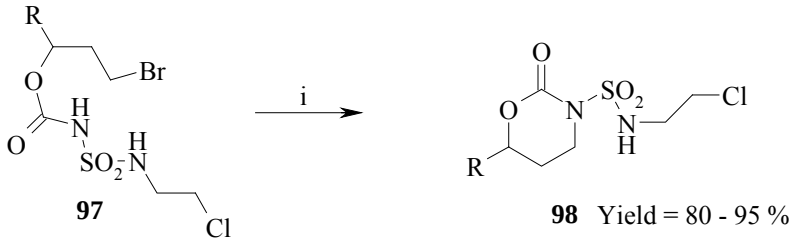
95 **96**

Yield = 76 - 86 %

Scheme 35: i NaH, THF, 5 ^{0}C, 15 s., 76 – 86 %.

Montero *et al.*[69]

Montero *et al.* observed that addition of Et_3N to carboxylsulfamides **97** in CH_2Cl_2 at 0 ^{0}C for 1h spontaneously underwent N-alkylation intramolecularly to N-sulfamoyloxazinones **98** in 80 – 95 % yield. Carboxylsulfamides were prepared from chlorosulfonyl isocyanate in 4 steps with 40 – 60 % yield. N-Sulfamoyloxazinones are pharmacologically important compounds (**Scheme 36**).

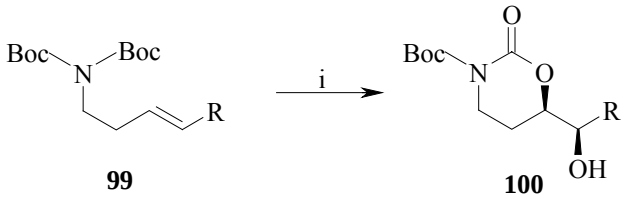


97 **98** Yield = 80 - 95 %

Scheme 36: i CSI (chlorosulfonyl isocyanate), CH_2Cl_2, Et_3N, 0 ^{0}C, 1h, 80 – 95 %.

Sharpless *et al.*[70]

Sharpless *et al.* demonstrated that asymmetric dihydroxylation of N-diBoc protected homoallylic amines **99** with *in situ* gave the corresponding 1,3-oxazin-2-one **100** in 44 – 73 % yields in a single step. The enantioselectivity is depend on the substitution pattern of the olefin and ranges from 89 – 98 %. This methodology allows selective differentiation of the hydroxyl groups formed in the AD and increases the potential applications of the resulting products (**Scheme 37**).



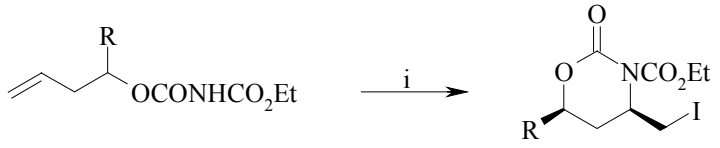
99 **100**

Yield = 44 - 73 %
ee = 89 - 98 %

Scheme 37: i AD-mix-β, H_2NSO_2Me, *tert*-BuOH:H_2O (2:1), 0 - 25 ^{0}C, 24h, 44 – 73 %.

Taguchi *et al.*[71]

Takeo Taguchi and coworkers demonstrated iodine-mediated cyclization reactions of homoallyl carbamates **101** to give 3-substituted-1,3-oxazin-2-one **102** products as single regioisomers in 58 – 86 % yield. The iodoaminocyclization reaction of the homoallyl carbamates with a chiral center at the homoallylic position was found to proceed with high 1, 3-*cis*-selectivity (**Scheme 38**).



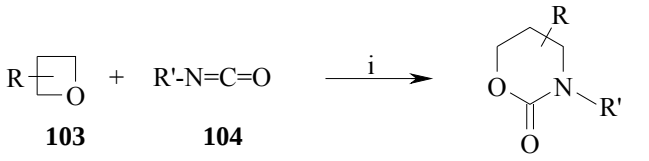
101 **102**

Yield = 58 - 86 %
cis/trans = 22 - 50 %

Scheme 38: i I_2, LiAl(O*t*-Bu)$_4$, toluene:THF (10:1), 24h, 25^{0}C, 58 – 86 %.

Baba *et al.*[72]

Baba et al. have found that cycloadditions of oxetanes **103** with isocyanates **104** were markedly accelerated by the dibutyltin diiodide-triphenylphosphine oxide complex. When oxetane **103** with aryl or alkyl isocyanate **104** in presence of dibutyltin diiodide-triphenylphosphine oxide complex was heated at 40^{0}C for 3h yielded 3-substituted-1, 3-oxazin-2-ones **105** in 11 – 87 % yield (**Scheme 39**).



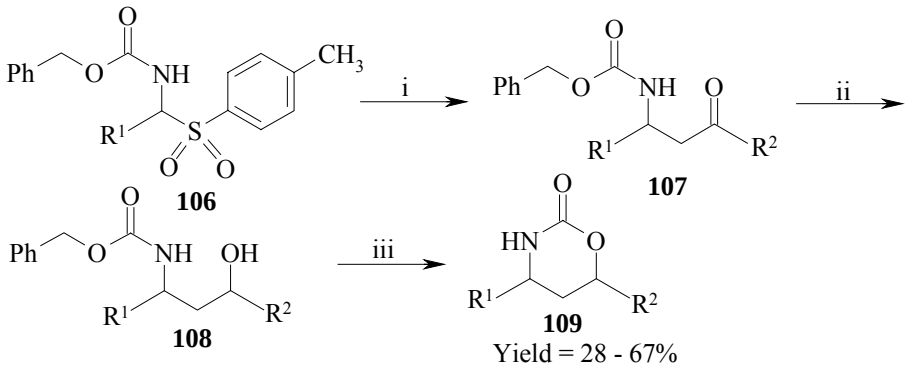
103 **104** **105**

Yield = 11 - 87 %

Scheme 39: i Bu_2SnI_2-Ph_3PO, 40 ^{0}C, 3h, 11 – 87 %.

Enders *et al.*[73]

Enders *et al.* have demonstrated the use of *N*-acylimines, which were generated from stable α-amino sulfone precursors **106**, for the synthesis of benzoyl protected β-amino ketones **107**. β-Amino ketones **107** were reduced to β-amino alcohols **108** which on further treatment with base underwent cyclization to produce 1,3-oxazinan-2-ones **109** in 28 – 67 % yield (**Scheme 40**).

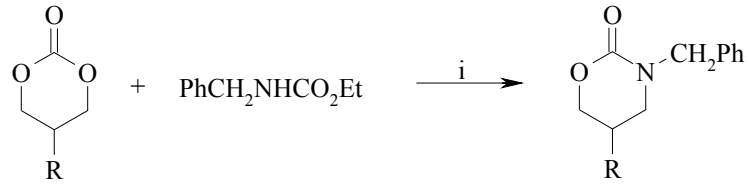


Yield = 28 - 67%

Scheme 40: i 4 equiv of H_2C=C(OLi)R_2, THF, -78 °C, 15 min, 70 - 82 %; ii 3 equiv of $LiAl[OC(CH_3)_3]_3H$, THF, -78 °C, 1 h then 0 °C to 25 °C, 14 h 20 - 67 %; iii 1 equiv of LiHMDS, THF, 25 °C, 30 min 40 – 55 %.

Renga *et al.*[74]

Renga *et al.* reported that when substituted 1,3-dioxan-2-one **110**, ethyl-N-benzyl carbamate, catalytic potassium carbonate and 18-crown-6 were combined and heated at 150 – 200 ^{0}C for 4h, carbon dioxide and ethanol were liberated producing the required product **111** in 28 – 67 % yield (**Scheme 41**).



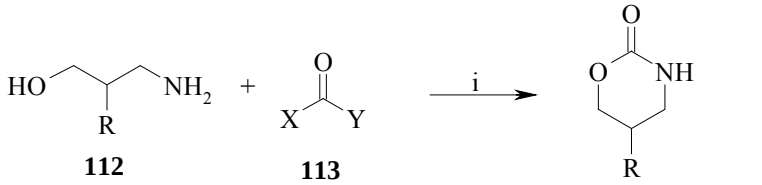
110 **111**

Yield = 74 - 82 %

Scheme 41: i cat. K_2CO_3, cat. 18-crown-6, 150 – 200 ^{0}C, 74 – 82 %.

Berichte *et al.*[75]

Phosgene, triphosgene, ethyl chloroformate, or diethylcarbonate **113** when treated with substituted 1,3-propanolamine **112** in presence of base such as triethyl amine in dichloromethane at room temperature produced 5-substituted tetrahydro-1,3-oxazin-2-ones **114** in 22 – 57 % yield (**Scheme 42**).



112 **113**

X and Y = Cl or OEt

114

Yield = 22 - 57 %

Scheme 42: i Et_3N, CH_2Cl_2, 25 °C, 22 – 57 %.

3.2.3 Present Work

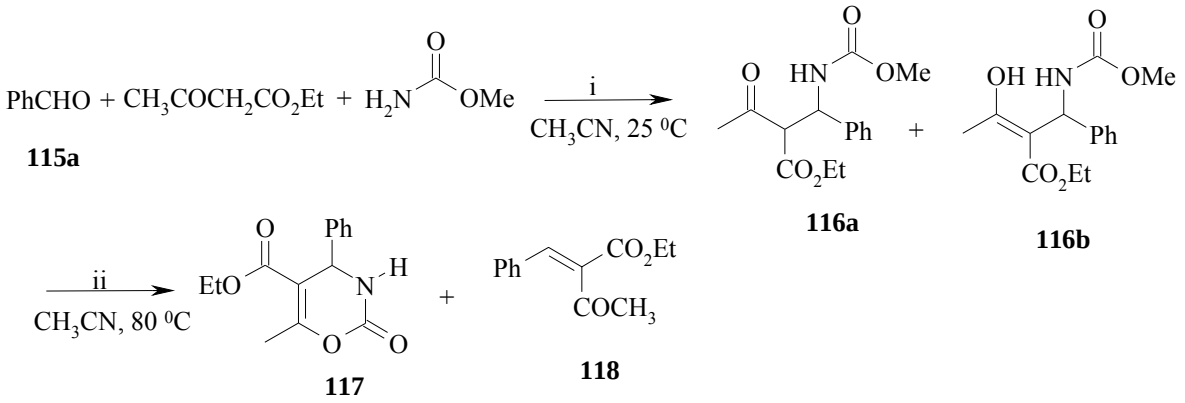
3.2.3.1 Objective

There are many catalytic methods available in the literature for the synthesis of tetrahydro 1,3-oxazin-2-ones.[64-75] However, to the best of our knowledge, synthesis of 3,4-dihydro[1,3]oxazin-2-ones are not known in the literature. For the synthesis of 1,3-oxazin-2-ones, many difficulties arise such as the use of stoichiometric amounts of catalysts, high temperatures, multistep synthesis, etc. In order to overcome these difficulties, a new catalytic multicomponent method for the synthesis of 3,4-dihydro[1, 3]oxazin-2-ones is highly desirable.

In earlier sections of this chapter, we had already discussed the application of Cu-catalyst for Biginelli dihydropyrimidinones (DHPMs) synthesis and Hantzsch 1,4-dihydropyridines (DHPs) synthesis. Now, we are interested in developing a simple and efficient procedure at ambient conditions for the synthesis of 3,4-dihydro[1,3]oxazin-2-ones using Lewis acids as catalysts. In particular, we have evaluated the use of $Cu(OTf)_2$ as catalyst for the synthesis of 3,4-dihydro[1,3]oxazin-2-ones, the results of which are discussed in this section.

3.2.4 Results and Discussion

When we subjected a mixture containing benzaldehyde, ethyl acetoacetate and methyl carbamate to react in the presence of various Lewis acid catalysts in CH_3CN at 25 ^{0}C for 3 h, we obtained carbamate ester **116**, which on further heating at 80 ^{0}C for 3 h, underwent cyclization to produce 3,4-dihydro[1,3]oxazin-2-ones **117** in 75% yield (**Scheme 43**).



Scheme 43: i Lewis acid catalyst (1 mol %), CH_3CN, 25 ^{0}C, 6h; ii Lewis acid catalyst (1 mol %), CH_3CN, 80 ^{0}C, 75 %.

When Lewis acid catalysts such as $La(OTf)_3$, $LaCl_3$, $InCl_3$ and $FeCl_3$ were employed, we obtained Knoevenagel condensation product **118** as side product in considerable quantity; whereas reactions performed with $Cu(OTf)_2$ produced dihydro[1,3]oxazin-2-one (**117**) as the exclusive product in excellent yield. Among various solvents screened (CH_2Cl_2, $CHCl_3$, benzene, CH_3CN, THF, dioxane and EtOH) best results were obtained with CH_3CN. The results for the three-component reaction leading to synthesis of 3,4-dihydro[1,3]oxazin-2-one (**117a**) using benzaldehyde, methyl carbamate and ethyl acetoacetate with Lewis acids as catalysts are presented in **Table 5**.

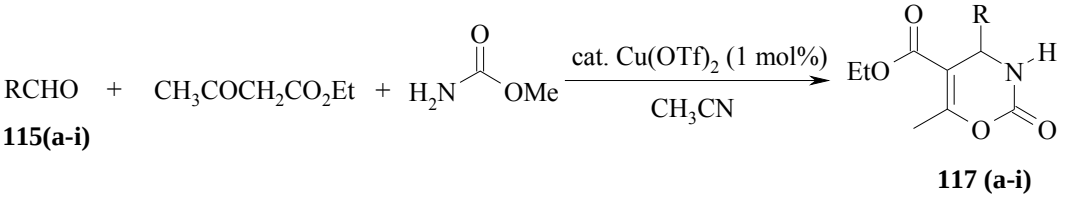
Table 5: Cu-catalyzed condensation of benzaldehyde, ethyl acetoacetate and methyl carbamate[a]

No.	Lewis acid Catalyst	Catalyst mole%	Solvent	Yield of 117a (%)[b]	Yield of 118 (%)
1.	None	----	CH_3CN	00	00
2.	$Cu(OTf)_2$	1	CH_3CN	75	05
		1	----	00	10
		1	THF	53	10
		1	EtOH	70	10
		1	H_2O	05	10
3.	$La(OTf)_3$	5	CH_3CN	50	25
4.	$LaCl_3$	5	CH_3CN	35	30
5.	$InCl_3$	5	CH_3CN	40	18
6.	$FeCl_3$	5	CH_3CN	20	40

a: reaction conditions: benzaldehyde (2 mmol), methyl carbamate (2 mmol), ethyl acetoacetate (2 mmol), 25 – 80 ^{0}C, 6h.; b: isolated yield after chromatographic purification.

A variety of aldehydes was successfully subjected to this multi-component reaction to afford the corresponding 3,4-dihydro[1,3]oxazin-2-ones (**117a-i**) in good to excellent yields. For example, several aromatic aldehydes were examined under the optimized conditions using 1 mol % of $Cu(OTf)_2$. The results are shown in **Table 6**.

Table 6: $Cu(OTf)_2$-catalyzed synthesis of 3, 4-dihydro[1, 3]oxazin-2-ones **117a-i** [a]



115(a-i) **117 (a-i)**

No.	R	t/h	Yield of 117 (%)
a	Ph	6	75
b	4-Cl-C_6H_4	6	60
c	2-HO-C_6H_4	6	76
d	4-O_2N-C_6H_4	12	62
e	3- O_2N-C_6H_4	12	67
f	4-NC-C_6H_4	12	72
g	3,4-$(MeO)_2$-C_6H_3	6	75
h	3,4-(O-CH_2-O)-C_6H_3	6	80
i	4-F_3C-C_6H_4	6	82

a: reaction conditions: aldehyde (2 mmol), methyl carbamate (2 mmol), ethyl acetoacetate (2 mmol), $Cu(OTf)_2$ (1 mol%), 25 – 80 ^{0}C, 6h; b: isolated yield after chromatographic purification.

As can be seen from **Table 6,** a variety of aldehydes **115a-i** underwent this condensation reaction smoothly with methyl carbamate and ethyl acetoacetate to give the corresponding 3, 4-dihydro[1, 3]oxazin-2-ones **117a-i** in excellent yields and selectivity. Most

importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxy groups reacted efficiently giving products **117a-i** in excellent yields.

The formation of intermediate **116** and 3,4-dihydro[1,3]oxazin-2-ones **117** was confirmed by ^{1}H, ^{13}C-NMR, and IR spectroscopy. The IR spectrum of the 3, 4-dihydro[1, 3]oxazin-2-ones **117a** showed typical absorption bands in the region 1700 and 1724 cm^{-1} for carbamate and ester C=O stretching vibrations respectively. The ^{1}H-NMR shows a typical benzylic proton signal at δ 4.89 and a broad signal at δ 8.66 suggesting cyclic carbamate NH protons present in the molecule. Its ^{13}C-NMR spectrum showed typical carbamate and ester carbonyl carbon signals at δ 152.88 and 165.74 respectively confirming the presence of 3,4-dihydro[1,3]oxazin-2-one **117a** (**Fig. 16**). The structure of **117a** was further confirmed by its single crystal X-ray studies (**Fig. 17**).

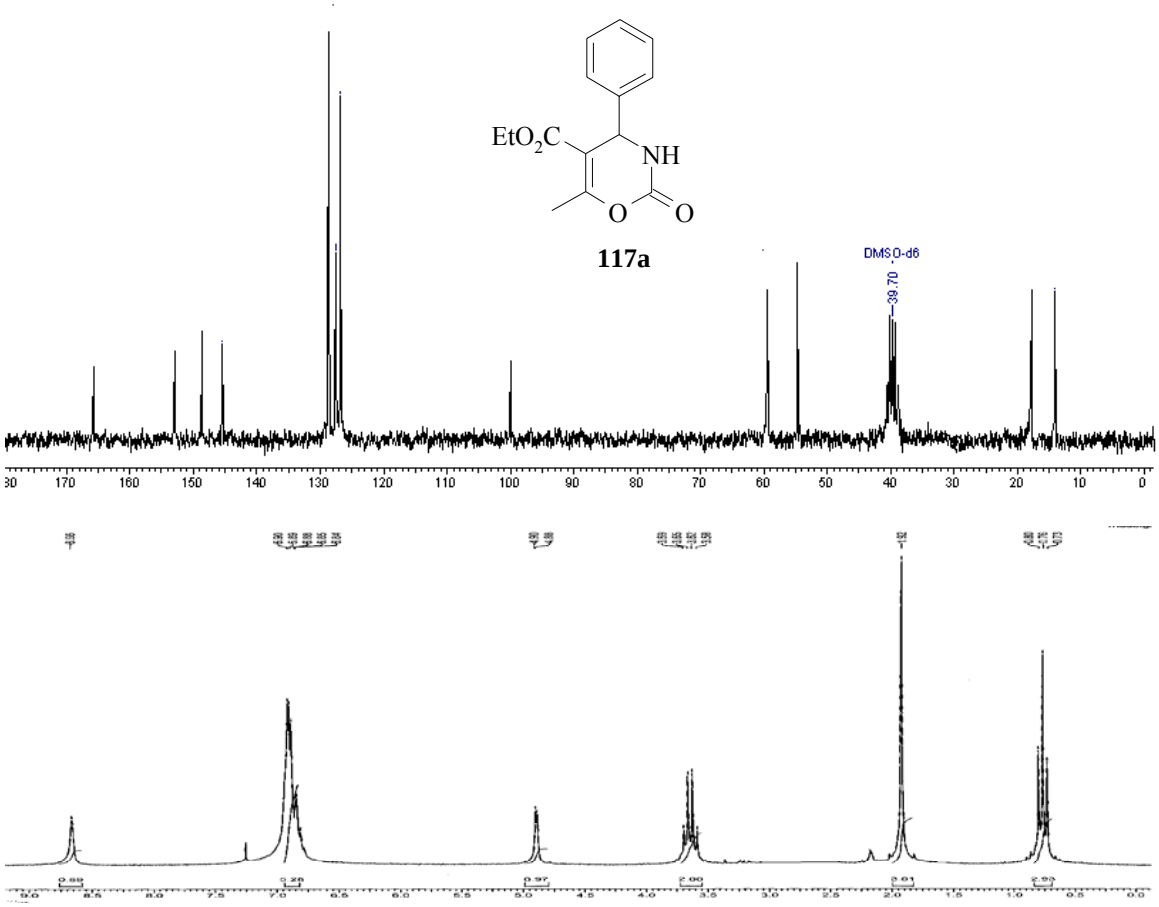


Fig. 16: ^{13}C, ^{1}H -NMR and Mass spectra of 117a

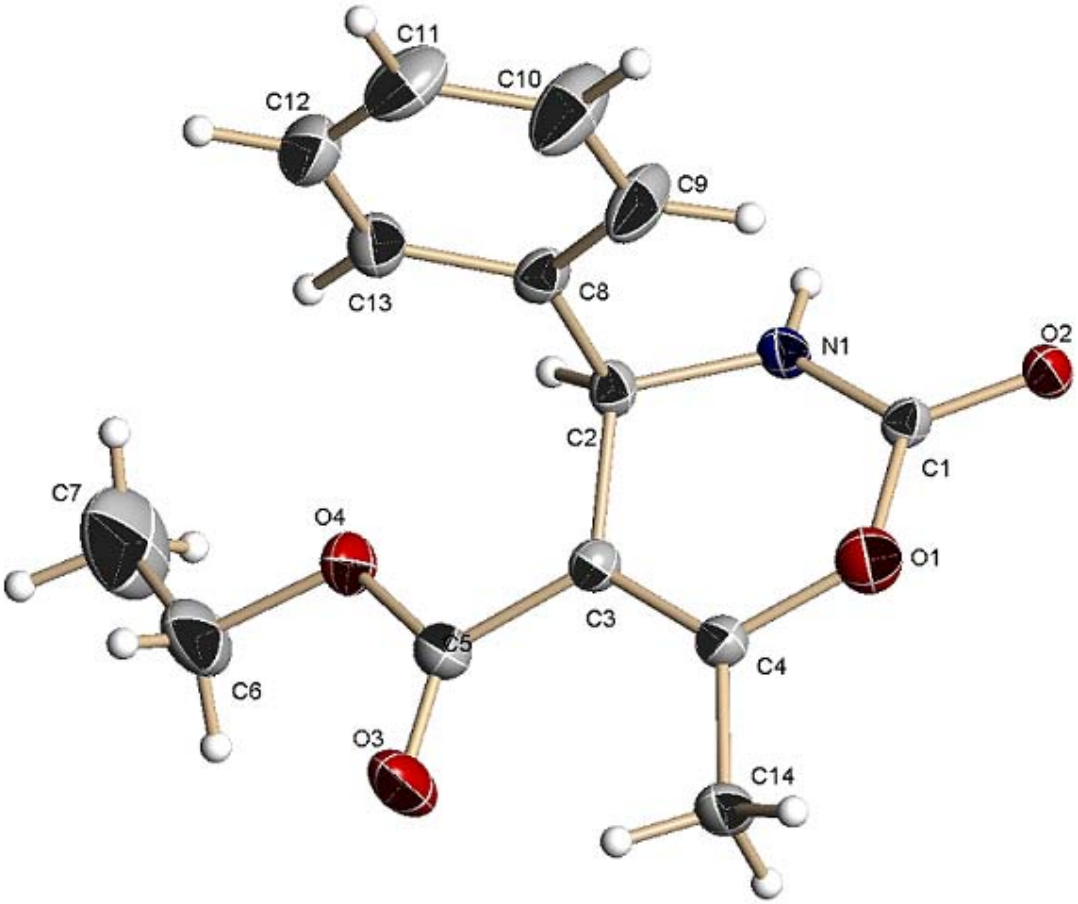


Fig. 17: Single X-ray crystal structure of 1,3-oxazin-2-one 117a

In case of 3,4-dihydro[1,3]oxazin-2-ones **117i**, the IR spectrum showed the typical absorption bands at 1646 and 1703 cm^{-1} due to carbamate and ester C=O stretching vibrations respectively. The ^{1}H-NMR signals at δ 5.28 and 9.07 are due to benzylic and cyclic carbamate NH protons respectively. Its ^{13}C-NMR spectrum showed typical carbamate and ester carbonyl carbon signals at δ 151.91 and 164.54 respectively confirming the presence of 3,4-dihydro[1,3]oxazin-2-ones moiety in the molecule (**Fig. 18**).

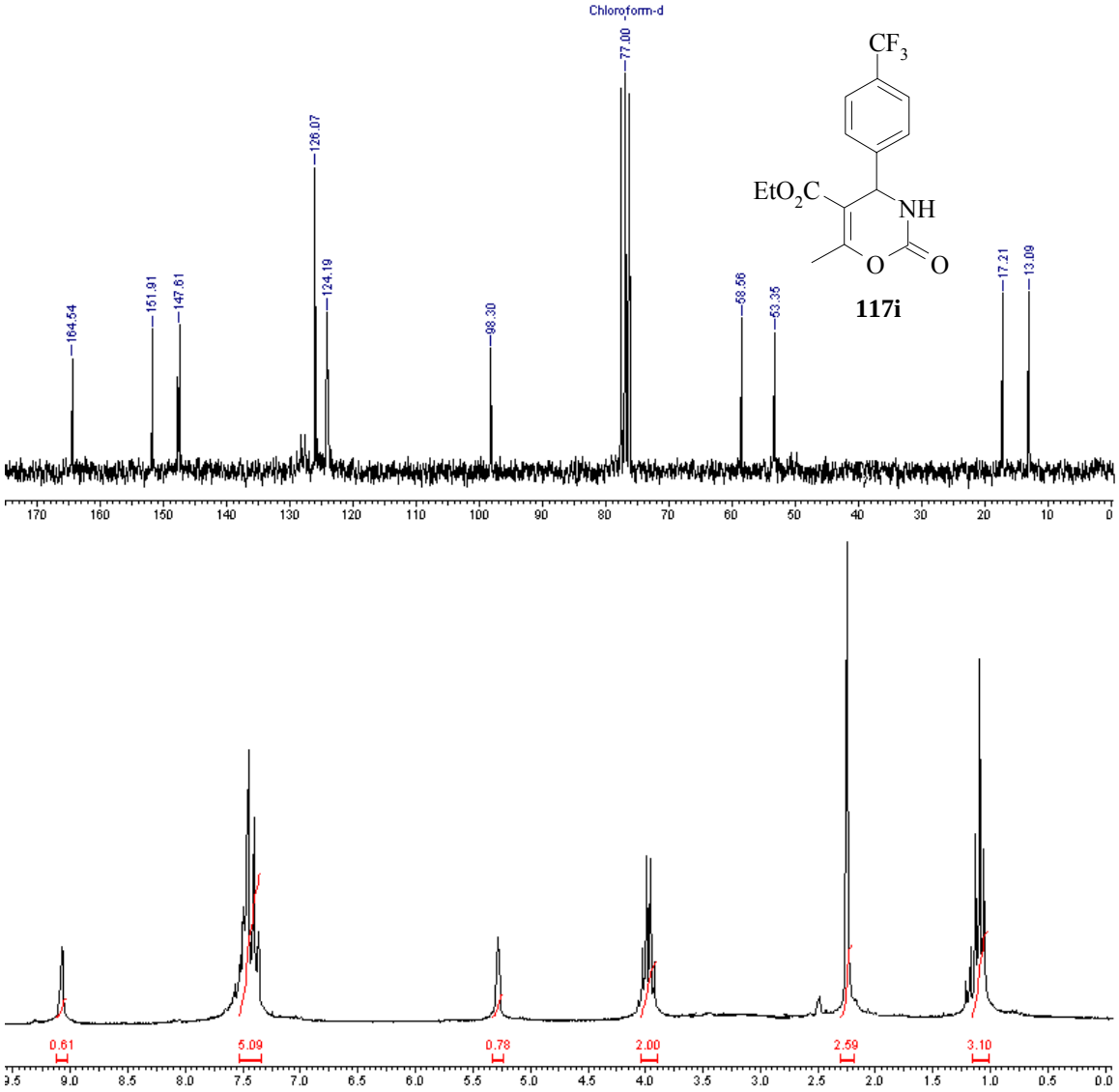


Fig. 18: ^{13}C and ^{1}H-NMR spectra of 117i

The IR spectrum of **116** showed bands at 1509 and 1719 cm^{-1} due to carbamate and ester C=O stretching vibrations respectively. The absorption at 3424 cm^{-1} is due to carbamate N-H stretching frequency. The ^{1}H-NMR signals at δ 2.15 - 2.32, 5.47 and 6.07 - 6.39 are due to $COCH_3$, benzylic and homobezylic protons respectively. Its ^{13}C-NMR spectra showed

typical carbamate ester and ketone carbonyl carbon signals at δ 156.26, 166.88 and 202.62 confirming the presence of open chain carbamate moiety (**Fig. 19**).

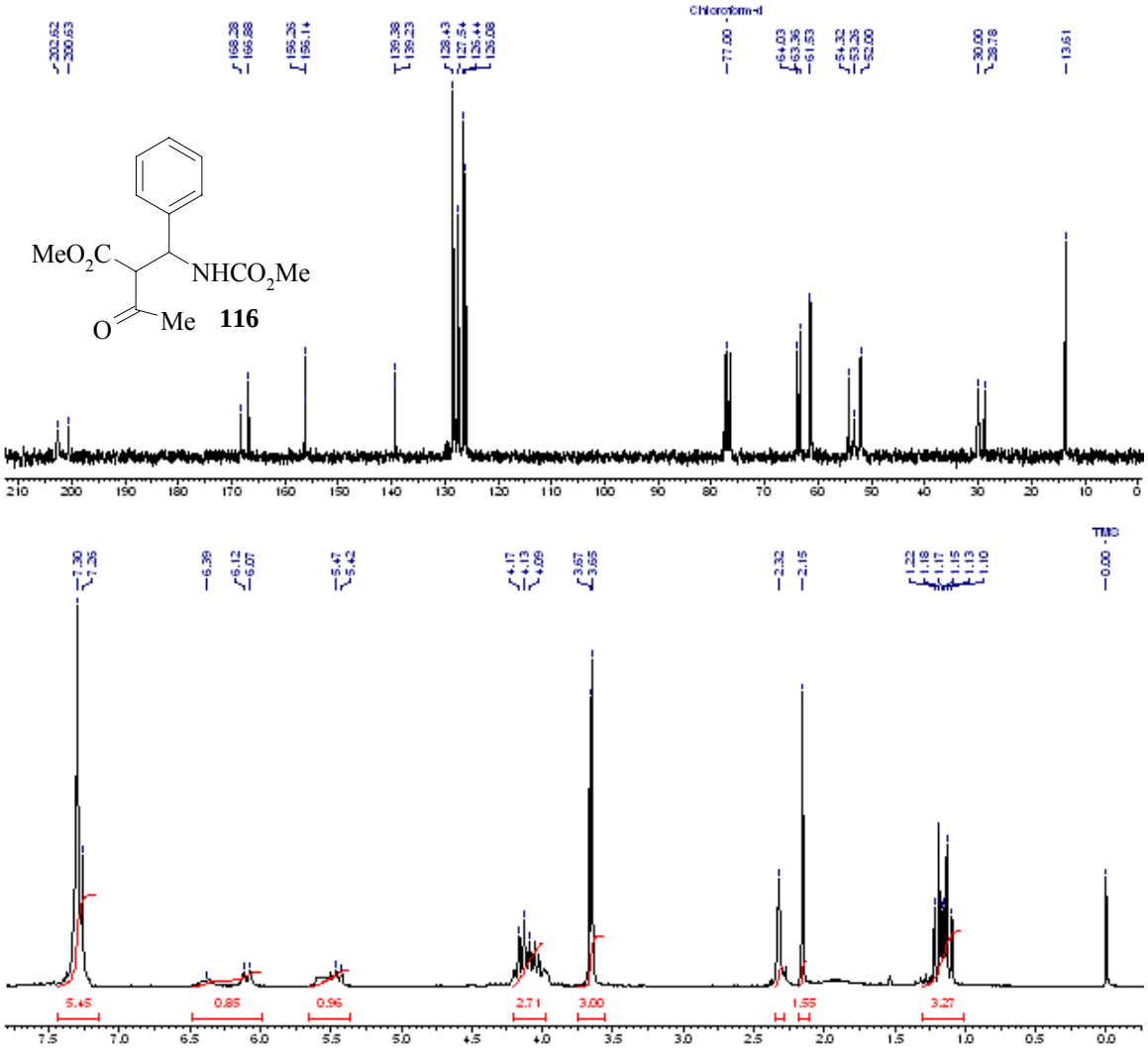


Fig. 19: ^{13}C and ^{1}H-NMR spectra of 116

Mechanism

The mechanism of this multi-component reaction is believed to involve, at first, the formation of activated acylimine **119** so that addition of enolate **120** is facilitated to afford the intermediate **116**, which enolizes and then undergoes facile condensation to give 3,4-dihydro[1,3]oxazin-2-ones **117** (**Fig. 20**) [the formation of **116** was confirmed in our studies by isolating intermediate **116** and characterizing it by spectroscopic techniques such as NMR, IR, etc].

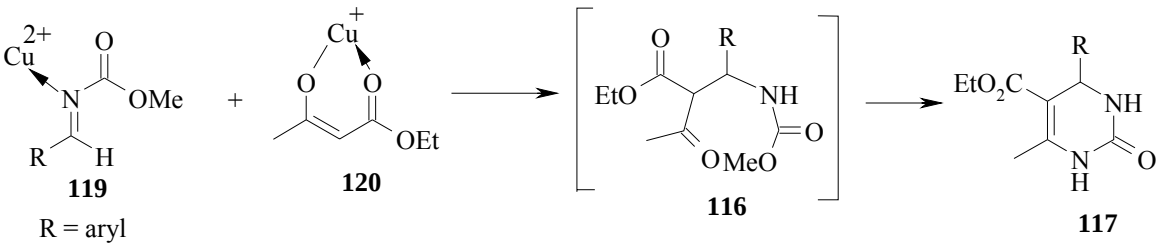


Fig. 20: Probable Cu^{2+}- activation in three-component coupling

Biological activity (High-throughput screening)

In our preliminary studies on biological testing, we have screened various 1,3 oxazin-2-ones **117(a-i)** that have been synthesized in our laboratory for inhibition activity studies. When we carried out the inhibition activity experiment on *HL-60 cancer cell line,* we found that cell morphology is changing and aggregating including death of a cell. It induced apoptosis in cell culture. The data on percentage of inhibition of growth on *HL-60 cancer cell* that occurred with various oxazinones are shown **Table 8**. Oxazinone **117b** showed better inhibition for cancer cells.

Table 8:Percentage inhibition by Oxazinones of fully grown culture[a].

Compound	Concentration (% Inhibition)	
	62.5 μg/ml	125 μg/ml
117a	56.48	57.84
117b	33.07	20.78
117c	76.86	54.78
117d	50.43	60.68
117e	54.09	75.91
117f	45.8	45.57
117g	24.43	47.5
117h	71.48	75.11
117i	62.95	62.86
116	33.07	20.78

a: Fully grown culture = 134 x 10^4 cells/ ml = 100 % growth.

3.2.5 Conclusion

In conclusion, we have successfully developed a three-component coupling method for the synthesis of 3,4-dihydro[1,3]oxazin-2-ones using $Cu(OTf)_2$ as catalyst, for the first time. The catalytic system is very effective for the aromatic aldehydes **115** to give the corresponding 3,4-dihydro[1,3]oxazin-2-ones **117** in excellent yields. Biological activity studies of these compounds have been evaluated against *HL-60 cancer cell* using *High-throughput screening*.

3.2.6 Experimental section

General procedure for the preparation of 3,4-dihydro[1,3]oxazin-2-ones (117a-i)

A 25 ml RB flask was charged with aromatic aldehyde **115a-i** (2 mmol), methyl carbamate (0.120 g, 2 mmol), ethyl acetoacetate (0.260 g, 2 mmol), $Cu(OTf)_2$ (7 mg, 1 mole %) and acetonitrile (5 ml). The resulting reaction mixture was stirred at room temperature for 3h and then heated at 80^0C for 3 more h. After the reaction was complete (monitored by TLC), the reaction mixture was cooled to 25^0C and was diluted with ethyl acetate (10 ml) and washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure 3,4-dihydro[1,3]oxazin-2-ones **117a-i**.

Ethyl 3,4-dihydro-6-methyl-2-oxo-4-phenyl-2*H*-1,3-oxazine-5-carboxylate (117a):

Yield: 75%; colorless solid; **mp:** 199-201^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 618, 662, 698, 758, 825, 1026, 1090, 1220, 1377, 1459, 1647, 1700, 1724, 2252, 2854, 2925, 3104, 3244, 3395; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 0.76 (t, *J* = 6.00 Hz, 3H), 1.92 (s, 3H), 3.63 (q, *J* = 7.00 Hz, 2H), 4.89 (d, *J* = 4.00 Hz, 1H), 6.89 (m, 5H), 8.66 (brs, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.04, 17.83, 54.66, 59.44, 126.74, 127.48, 128.58, 145.38, 148.58, 152.88, 165.74; **Analysis:** $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36; found C, 64.33; H, 5.71; N, 5.29%.

Crystal data:

Crystal data and structure refinement for **117a**

Identification code	Sudalai
Empirical formula	C14 H15 N O4
Formula weight	261.27
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	MONOCLINIC, P2(1)

Unit cell dimensions	a = 11.522(4) Å alpha = 90°. b = 7.435(2) Å beta = 104.955(6)°. c = 16.121(5)Å gamma = 90°.
Volume	1334.2(7) $Å^3$
Z, Calculated density	4, 1.301 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	552
Crystal size	0.68 x 0.08 x 0.07 mm
Theta range for data collection	1.83 to 25.00 deg.
Limiting indices	-13<=h<=13, -8<=k<=8, -19<=l<=18
Reflections collected / unique	9660 / 4680 [R(int) = 0.0251]
Completeness to theta = 25.00	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9933 and 0.9374
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4680 / 1 / 347
Goodness-of-fit on F^2	1.130
Final R indices [I>2sigma(I)]	R1 = 0.0695, wR2 = 0.1572
R indices (all data)	R1 = 0.0815, wR2 = 0.1645
Absolute structure parameter	0.1(17)
Largest diff. peak and hole	0.366 and -0.236 e. $Å^{-3}$

Ethyl 4-(4-chlorophenyl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117b):

Yield: 60%; colorless solid; **mp:** 209-210^{0}C (crystallized from EtOH); **IR** (Neat, cm^{-1}): 668, 750, 863, 929, 1041, 1097, 1215, 1242, 1299, 1369, 1446, 1488, 1504, 1643, 1698, 2400, 2898, 3019, 3234; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.18 (t, J = 7.05 Hz, 3H) 2.34 (s, 3 H), 4.09 (q, J = 7.2 Hz, 2H), 5.28 (d, J = 1.17 Hz, 1H), 6.72 – 6.78 (d, J = 8.09 Hz, 4H), 8.20 (brs, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 13.39, 17.45, 53.90, 58.77, 100.10, 106.33, 107.04, 119.04, 129.80, 137.93, 145.94, 146.78, 152.37, 165.02; **Analysis:** $C_{14}H_{14}ClNO_4$ requires C, 56.86; H, 4.77; N, 4.74; found C, 56.85; H, 4.72; N, 4.73 %.

Ethyl 3,4-dihydro-4-(2-hdroxyphenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117c):

Yield: 76%; grey color solid; **mp:** 159-163^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 667, 755, 875, 911, 1031, 1091, 1193, 1216, 1237, 1330, 1372, 1460, 1491, 1604, 1651, 1687, 2401, 2928, 3019, 3228, 3324; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.18 (t, J = 7.0 Hz, 3H),

2.29 (s, 3H), 3.98 (q, *J* = 7.0 Hz, 2H), 4.43 (s, 1H), 5.53 (s, 1H), 6.64–7.07 (m, 4H), 8.86 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.1, 17.8, 23.9, 54.0, 59.2, 83.5, 99.3, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 165.4; **Analysis:** $C_{14}H_{15}NO_5$ requires C, 64.64; H, 5.45; N, 5.05; found C, 64.63; H, 5.41; N, 5.00%.

Ethyl 3,4-dihydro-6-methyl-4-(4-nitrophenyl)-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117d):

Yield: 62%; yellow color solid; **mp:** 175-177^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 757, 890, 928, 1046, 1090, 1220, 1270, 1350, 1450, 1522, 1682, 1710, 2414, 3020, 3200, 3332; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.12 (t, *J* = 7.20 Hz, 3H), 2.30 (s, 3H), 4.00 (q, *J* = 7.07 Hz, 2H), 5.46 (d, *J* = 3.10 Hz, 1H), 7.49 – 7.60 (q, *J* = 7.88 Hz, 1H), 7.70 – 7.75 (d, *J* = 7.80 Hz, 1H), 8.09 – 8.13 (d, *J* = 8.08 Hz, 2H), 8.80 (brs, 1H) **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.4 18.5, 55.6, 60.8, 100.3, 127.7, 128.1, 128.9, 145.2, 148.9, 157.8, 165.5; **Analysis:** $C_{14}H_{14}N_2O_6$ requires C, 54.90; H, 4.61; N, 9.15; found C, 54.83; H, 4.55; N, 9.10%.

Ethyl 3,4-dihydro-6-methyl-4-(3-nitrophenyl)-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117e):

Yield: 67%; yellow color solid; **mp:** 169-170^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 669, 692, 755, 900, 928, 1045, 1091, 1215, 1265, 1316, 1349, 1455, 1526, 1690, 1708, 2400, 3020, 3219, 3326; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.19 (t, *J* = 7.46 Hz, 3H), 2.38 (s, 3H), 4.08(q, *J* = 7.07 Hz, 2H), 5.46 (d, *J* = 3.16 Hz, 1H), 7.46 – 7.57 (q, *J* = 7.84 Hz, 1H), 7.69 – 7.73 (d, *J* = 7.71 Hz, 1H), 8.09 – 8.13 (d, *J* = 8.08 Hz, 2H), 8.79 (brs, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.2 18.2, 55.0, 60.2, 99.0, 126.3, 127.3, 128.4, 144.9, 148.4, 152.2, 166.8; **Analysis:** $C_{14}H_{14}N_2O_6$ requires C, 54.90; H, 4.61; N, 9.15; found C, 54.83; H, 4.55; N, 9.10%.

Ethyl 3,4-dihydro-4-(4-cyanophenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117f):

Yield: 72%; dark brown color solid; **mp:** 190-193^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 668, 698, 758, 847, 962, 981, 1038, 1094, 1215, 1287, 1377, 1458, 1599, 1637, 1687, 2140, 2400, 2855, 2926, 3019, 3245, 3308; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.10 (t, *J* = 7.0 Hz, 3H), 2.20 (s, 3H), 4.0 (q, *J* = 7.2 Hz, 2H), 5.30 (d, *J* = 3.0 Hz, 1H), 7.53 (dd, *J* = 6.9, 2.1

Hz, 2H), 8.25 (dd, *J* = 6.8, 2.0 Hz, 2H), 9.30 (s, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 14.2, 18.0, 53.2, 60.2, 98.0, 116.2, 128.1, 128.3, 131.4, 142.1, 149.2, 153.7, 164.3; **Analysis:** $C_{15}H_{14}N_2O_4$ requires C, 62.93; H, 4.93; N, 9.79; found C, 62.83; H, 4.95; N, 9.76%.

Ethyl 3,4-dihydro-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117g):

Yield: 75%; colorless solid; **mp:** 179-182^{0}C (crystallized from ^{i}PrOH); **IR** (Neat, cm^{-1}): 759, 881, 1008, 1095, 1170, 1229, 1293, 1322, 1364, 1460, 1650, 1701, 2856, 2925, 2954, 3110, 3234; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.15 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 5.00 (d, *J* = 3.0 Hz, 1H), 5.90 (s, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 8.89 (brs, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 15.8, 18.4, 54.3, 60.2, 99.8, 101.3, 107.8, 108.4, 102.0, 139.2, 147.3, 148.2, 149.0, 156.0, 164.7; **Analysis:** $C_{16}H_{19}NO_6$ requires C, 59.81; H, 5.96; N, 4.36; found C, 60.08; H, 5.93; N, 4.27%.

Ethyl 4-(benzo[*d*][1,3]dioxol-5-yl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117h):

Yield: 80%; grey color solid; **mp:** 184-186^{0}C (crystallized from *i*PrOH); **IR** (KBr, cm^{-1}): 668, 757, 864, 954, 1012, 1091, 1170, 1216, 1290, 1322, 1367, 1422, 1462, 1490, 1575, 1646, 1704, 2980, 3019, 3115, 3240; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 7.00 Hz, 3H), 2.23 (s, 3H), 3.94 (q, *J* = 7.2 Hz, 2H), 5.18 (d, *J* = 3.14 Hz, 1H), 5.90 (s, 2H), 6.74 (m, 3H), 8.92 (brs, 1H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 12.75, 16.75, 52.91, 58.31, 98.50, 105.22, 107.18, 115.83, 119.20, 127.04, 131.33, 142.42, 147.03, 151.51, 164.33; **Analysis:** $C_{15}H_{15}NO_6$ requires C, 59.01; H, 4.95; N, 4.59; found C, 59.00; H, 4.91; N, 4.55%.

Ethyl 4-(4-(trifluoromethyl)phenyl)-3,4-dihydro-6-methyl-2-oxo-2*H*-1,3-oxazine-5-carboxylate (117i):

Yield: 82%; colorless solid; **mp:** 182-184^{0}C (crystallized from EtOH); **IR** (KBr, cm^{-1}): 668, 757, 843, 854, 873, 956, 1018, 1068, 1093, 1112, 1127, 1170, 1216, 1288, 1326, 1367, 1392, 1425, 1462, 1619, 1646, 1703, 2401, 2982, 3020, 3116, 3243; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.09 (t, *J* = 7.44 Hz, 3H), 2.25 (s, 3H), 3.98 (q, *J* = 7.00 Hz, 2H), 5.28 (d, *J* = 2.80 Hz, 1H), 7.36 – 7.41 (d, *J* = 8.21, 2H) 7.45 – 7.50 (d, *J* = 8.21, 2H), 9.07 (brs, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 13.09, 17.21, 53.35, 58.56, 98.30, 124.19, 126.07, 147.61,

151.91, 164.54; **Analysis:** $C_{15}H_{14}F_3NO_4$ requires C, 54.71; H, 4.29; N, 4.25; found C, 54.63; H, 4.21; N, 4.20%.

Methyl 2-(ethoxycarbonyl)-3-oxo-1-phenylbutylcarbamate (116):

Yield: 90%; colorless solid; **mp:** 69-71^{0}C (crystallized from $CHCl_3$); **IR** (KBr, cm^{-1}): 668, 699, 720, 928, 1029, 1044, 1215, 1359, 1456, 1509, 1719, 2400, 2856, 2927, 3020, 3424; **^{1}H-NMR** (200 MHz, DMSO-d_6): δ 1.10 – 1.22 (m, 3H), 2.15 – 2.32 (d, J = 6.74 Hz, 3H), 3.65 – 3.67 (d, J = 5.24 Hz, 3H), 4.02 – 4.20 (m, 2H), 5.47 (m, 1H), 6.07 – 6.39 (m, 1H), 7.30 (m, 5H); **^{13}C-NMR** (200 MHz, DMSO-d_6): δ 13.61, 28.78, 30.00, 52.00, 54.32, 61.53, 63.36, 64.03, 126.08, 126.44, 127.54, 128.43, 139.23, 139.38, 156.14, 156.26, 166.88, 168.28, 200.36, 202.62; **Analysis:** $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78; found C, 61.40; H, 6.51; N, 4.89%.

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SECTION I:

$Cu(OTf)_2$ and Et_3N-catalyzed addition of CN^- onto imines: Synthesis of α-aminonitriles

4.0.1 Introduction

Unnatural amino acids are expected to play key roles in improving the original properties and functions of proteins,[1] and development of efficient methods for the preparation of various types of amino acids is desired not only in the field of organic chemistry but also in many biology-related areas. Aromatic amino acids are important molecular fragments in many molecules of biological importance such as cephalecins,[2] nocardicins,[3] and glycopeptides of the vancomycin family.[4]

Aminonitriles are precursors for several amino acids and are very popular bifunctional synthons that have found numerous synthetic applications.[5] A fundamental challenge in organic chemistry is the development of catalytic C-C bond-forming reactions, which give access to this class of building blocks using simple starting materials.[6] The Strecker reaction between an aldehyde, an amine, and hydrogen cyanide is widely regarded as the first multicomponent reaction (MCR).[7] Its reliability, the ready availability of the starting materials, and the versatility of the resulting products make it a very important process for the large-scale production of amino acids, herbicides, and chelating agents, such as NTA and EDTA.

Traditionally, α-aminonitriles are prepared by the reaction with aldehyde and amine in the presence of a cyanide source (HCN, KCN, TMSCN, $(EtO)_2P(O)CN$, Et_2AlCN and Bu_3SnCN), often involving harsh reaction conditions.[7-9, 11, 15, 18] The handling of HCN gas and

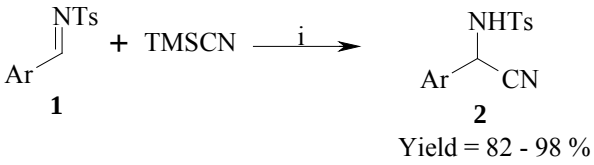
liquid Bu_3SnCN, Et_2AlCN and $(EtO)_2P(O)CN$ is cumbersome due to their hazardous nature while special equipment and care are needed for the transfer of these materials in large scale. Moreover, the use of Bu_3SnCN, Et_2AlCN and $(EtO)_2P(O)CN$ is very expensive making the process less economical.

4.0.2 Review Literature

Various modified methods of Strecker reactions are known in the literature.[8] Some of the important methods so far known are described below.

Singh *et al.*[9]

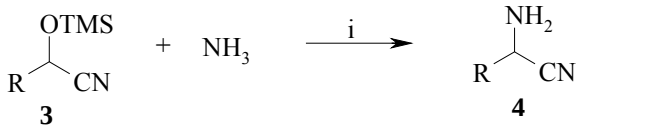
Singh *et al.* studied the addition of TMSCN to a variety of N-tosyl arylaldimines **1** in the presence of 10 mol% $LiClO_4$ or BF_3/Et_2O in acetonitrile to give the addition product, α-aminonitrile **2** in 82 – 98 % yields (**Scheme 1**). In the case of the imine derived from phenylhydrazine and benzaldehyde, the addition of TMSCN did not take place. In case of PMP-imines low yield was observed.



Scheme 1: i $LiClO_4$ or BF_3/Et_2O, CH_3CN, RT, 6h, 82 – 98 %.

Mai *et al.*[10]

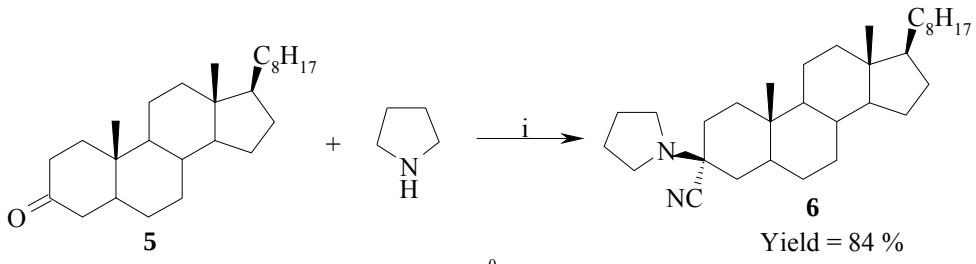
Mai *et al.* prepared α-aminonitriles **4** by reacting α-trimethylsilyloxynitriles **3** with ammonia in methanol (**Scheme 2**). The silyloxynitriles **3** were obtained by condensing various aldehydes with trimethylsilyl cyanide (TMSCN) in the presence of a catalytic amount of zinc iodide.



Scheme 2: i MeOH, 60 ^{0}C, 2h, 15 – 87 %.

Shioiri *et al.*[11]

Shioiri *et al.* showed that diethyl phosphorocyanidate (DEPC) can be efficiently used for the synthesis of α-amino nitriles from carbonyl compounds and amines. To a mixture containing 5α-cholestan-3-one **5** and DEPC in THF was added pyrrolidine and the mixture was heated at 70 ^{0}C for 6h to afforded required α-aminonitrile **6** in 84 % yield (**Scheme 3**).



Scheme 3: i $(EtO)_2P(O)CN$ (1.5 equiv.), THF, 70 ^{0}C, 6h, 84 %.

Matsumoto *et al.*[12]

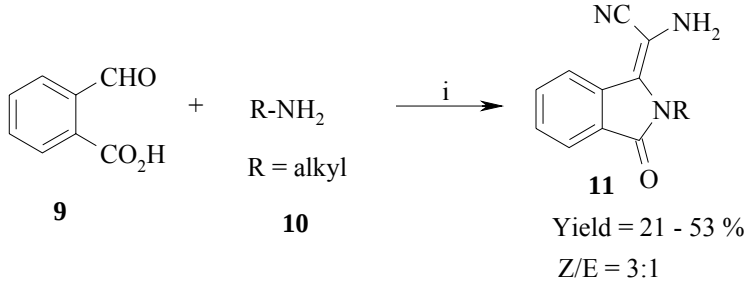
Matsumoto *et al.* studied the effect of high pressure (600 MPa) on a multicomponent reaction, in the absence of a catalyst. It was found that the pressure stimulated the three component Strecker reaction between ketones **7**, aniline and TMSCN, producing α-aminonitriles **8** in 22 – 99 % yields (**Scheme 4**).

R' and R" = alkyl or aryl

Scheme 4: i toluene, 600 MPa, 30 ^{0}C, 24h, 22 – 99 %.

Opatz *et al.*[13]

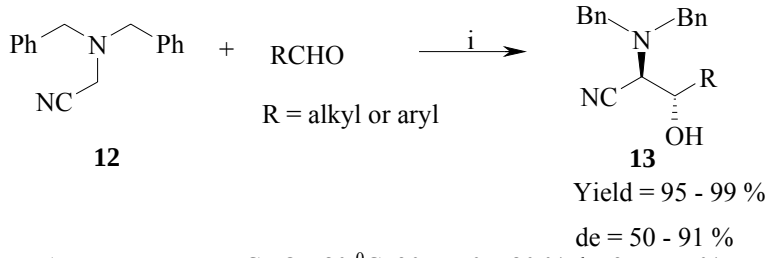
The reaction of 2-carboxybenzaldehyde **9** with primary amines **10** in the presence of potassium cyanide led to the formation of 2-substituted amino(3-oxo-2,3-dihydro-(1*H*)-isoindol-1-ylidene)acetonitriles **11** in Z/E ratio 3:1 and 21 – 53 % yield (**Scheme 5**). These compounds originate from the condensation of 2-carboxybenzaldehyde with the amine and two molecules of hydrogen cyanide.



Scheme 5: i KCN (2 equiv.), AcOH (2 equiv.), MeOH, reflux, 12h, Z/E is 3:1, 21 – 53 %.

Mangeney *et al.*[14]

Mangeney *et al.* performed aldolization by the addition of lithiated *N*-dibenzyl-aminoacetonitrile **12** to aldehydes in the presence of $MgBr_2$ at -78 ^{0}C in THF which provided *anti-β*-hydroxy-α-aminonitriles **13** in 50 – 80 % de and 37 – 75 % yield (**Scheme 1**).

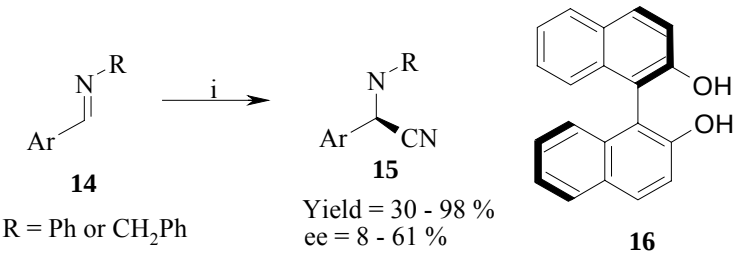


Scheme 6: i LDA, THF, $MgBr_2$, RCHO, -80 ^{0}C, 30m, 50 – 80 % de, 37 – 75 %.

Toru *et al.*[15]

Toru *et al.* described an enantioselective Strecker-type reaction of imines **14** with Et_2AlCN in the presence of chiral additives. The reaction was carried out by using Et_2AlCN as cyanide source and a chiral ligand such as (R)-BINOL **16**, in toluene at -78 ^{0}C under argon. A

solution of imine **14** was then added to give **15** in 8 – 61 % ee and 30 – 98 % yield (**Scheme 7**).



14 **15** **16**

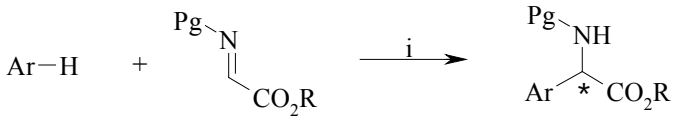
R = Ph or CH_2Ph

Yield = 30 - 98 %
ee = 8 - 61 %

Scheme 7: i Et_2AlCN, (R)-BINOL **3** (10 mol %), toluene, -78 ^{0}C, 8 – 61 % ee, 30 – 98 %.

Jørgensen *et al.*[16]

Jørgensen *et al.* developed a practical one-pot catalytic enantioselective procedure for the synthesis of non-natural aromatic and heteroaromatic R-amino acids **18**. The reaction was demonstrated by the addition of substituted furans, thiophenes, pyrroles, and aromatic compounds on to *N*-alkoxycarbonyl-imino esters **17** in the presence of a chiral BINAP-Cu(I) catalyst, the optically active products are formed with readily removable N-protecting groups to *N*-alkoxycarbonyl- R-imino esters in 20 – 61 % yields and enantioselectivities 30 – 90 % ee (**Scheme 8**).

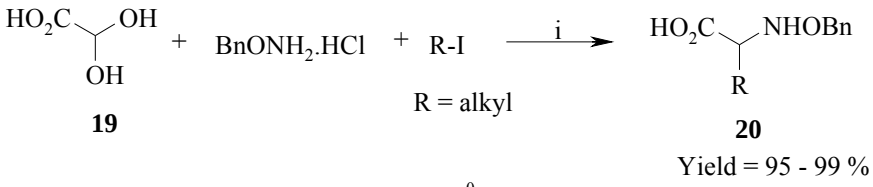


17 **18**

Scheme 8: i (R)-Tol-BINAP-Cu(I) (10 mol %), toluene:CH_2Cl_2 (9:1), -78 ^{0}C, 44h, 30 – 90 % ee, 20 – 61 %.

Naito *et al.*[17]

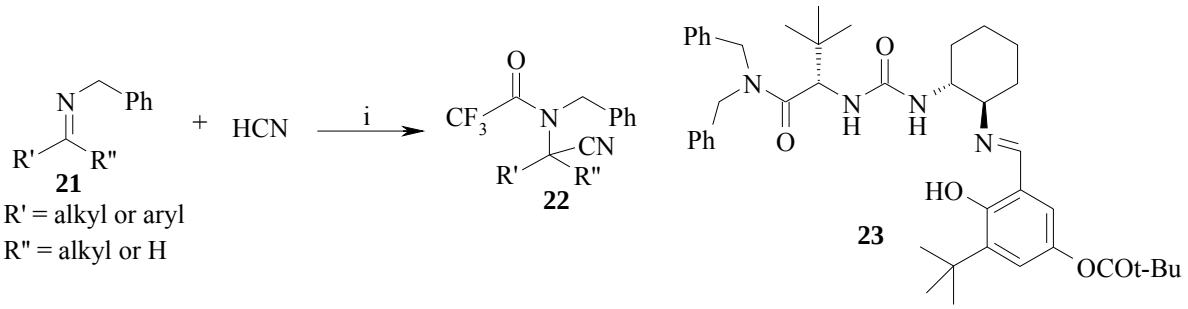
Naito *et al.* method deals with the condensation of glyoxylic acid hydrate **19** with benzyloxyamine hydrochloride and alkyl iodide in water and triethylborane affording amino acid derivatives **20** in 17 – 99 % yield (**Scheme 9**).



Scheme 9: i Et_3B in hexane, H_2O, 20 ^{0}C, 1 – 20h, 17 – 99 %.

Jacobsen *et al.*[18]

Jacobsen *et al.* utilized urea-based chiral organocatalyst **23** for asymmetric Strecker reaction. When imines **21** generated from benzyl amine and aldehydes or ketones are subjected to react with HCN at -78 ^{0}C in presence of organocatalyst **23**, α-aminonitriles **22** were obtained in 70 – 97 % ee and 22 – 99 % yield (**Scheme 10**).



Scheme 10: i **23** (1.1 mol %), toluene, -78 ^{0}C; ii TFAA, CH_2Cl_2, Et_3N, DMAP, 0 – 25 ^{0}C, 6h, 70 – 97 % ee, 85 – 99 %.

4.0.3 Present Work

4.0.3.1 Objective

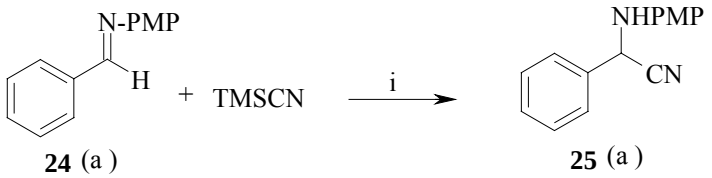
Although there are many methods available in the literature for hydrocyanation of imines,[8-15] many suffer from certain drawbacks like use of electron withdrawing groups present on imine nitrogen, low yield, separate preparation of imines, use of hazardous and expensive cyanide sources, cumbersome experimental procedures etc. In order to overcome some of these problems, a new safe and inexpensive procedure for Strecker type α-aminonitrile synthesis is highly desirable.

Our objective is to explore the catalytic activity of $Cu(OTf)_2$ and nonmetallic organic bases such as Et_3N, pyridine, etc. as catalysts for hydrocyanation of variety of imines. In our studies we explored the hydrocyanation of imines by TMSCN as well as acetone cyanohydrin using $Cu(OTf)_2$ and organic bases as catalyst, the results of which are discussed in this section.

4.0.4 Results and Discussion

After successful demonstration of the imine activation using catalytic amount of $Cu(OTf)_2$ as explained in the previous chapter, we envisioned to study Lewis acids such as $Cu(OTf)_2$ as a catalyst for Strecker's α-aminonitrile synthesis.

When benzaldimine (**24a**) was treated with TMSCN in the presence of $Cu(OTf)_2$ (1 mol%) in acetonitrile at 25 ^{0}C, the corresponding hydrocyanated product [α-aminonitrile (**25a**)] was obtained in excellent yield (**Scheme 11**).



Scheme 11: i cat. $Cu(OTf)_2$ (1 mol %), CH_3CN, 25 ^{0}C, 5 h, 89 %.

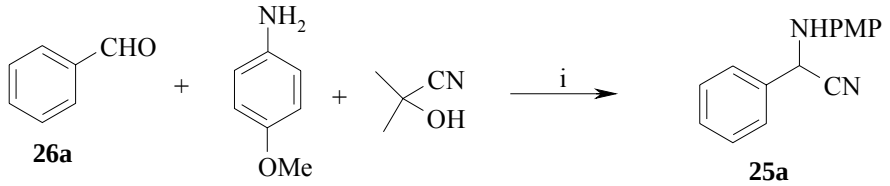
We then turned our attention to systematically study the effectiveness of cyanide sources such as TMSCN and acetone cyanohydrin, under the influence of various Lewis acid catalysts on hydrocyanation of imines. The results of Lewis acid-catalyzed Strecker-type reaction (nucleophilic addition of CN^- onto imines) are summarized in **Table 1**.

Table 1: Lewis acid catalyzed hydrocyanation of benzaldimine (**24a**)[a]

Sr. No.	Catalyst	Catalyst mol%	Cyanide source	Solvent	Yield of 25a (%)[b]
1	$Cu(OTf)_2$	10 mol%	NaCN	CH_3CN	00
2	None	--	TMSCN	CH_3CN	00
3	$Cu(OTf)_2$	0.5 mol%	TMSCN	CH_3CN	87
4	$Cu(OTf)_2$	1 mol%	TMSCN	CH_3CN	95
5	$Cu(OTf)_2$	5 mol%	TMSCN	CH_3CN	94
6	$Cu(OTf)_2$	1 mol%	TMSCN	CH_2Cl_2	91
7	$Cu(OTf)_2$	1 mol%	TMSCN	THF	84
8	$Cu(OTf)_2$	1 mol%	Acetone cyanohydrin	CH_3CN	00
9	$LaCl_3$	10 mol%	TMSCN	CH_3CN	18
10	$La(OTf)_3$	10 mol%	TMSCN	CH_3CN	48
11	CuCN	10 mol%	TMSCN	CH_3CN	23
12	$Ti(OiPr)_4$	10 mol%	Acetone cyanohydrin	CH_2Cl_2	00
13	$Ti(OiPr)_4$	10 mol%	TMSCN	CH_2Cl_2	12

a: reaction conditions: Benzaldimine **24a** (2 mmol), Cyanide source (2 mmol), CH_3CN, 25^0C, 6h; b: Isolated yield after column chromatographic purification.

Among various Lewis acid catalysts screened such as $LaCl_3$, $La(OTf)_3$, $Cu(OTf)_2$, CuCN, and $Ti(OiPr)_4$, only $Cu(OTf)_2$ in combination with TMSCN gave the required product in good yield. As acetone cyanohydrin is one of the most stable and cheap cyanide sources,[19] we employed it for Strecker-type reaction. This reagent appears to be the most practical one for scale-up studies. For hydrocyanation reactions, organic bases are used to generate free HCN from renewable sources.[20] In our preliminary experiments, benzaldimine and acetone cyanohydrin in the molar ratio of 1: 1 were subjected to react at 25^0C in the presence of catalytic amount of Et_3N (10 mol%) in CH_3CN as solvent, the corresponding α-aminonitrile (**25a**) was obtained in good yield (87%). Interestingly, when we carried out the same experiment by reacting the *in situ* generated aldimine with acetone cyanohydrin and Et_3N (5 mole%) as catalyst in CH_3CN, we obtained α-aminonitrile in excellent yield (93%) with excellent product selectivity (**Scheme 12**).



26a **25a**

Scheme 12: i cat. Et_3N (5 mol %), CH_3CN, 25 ^{0}C, 5 h, 90%.

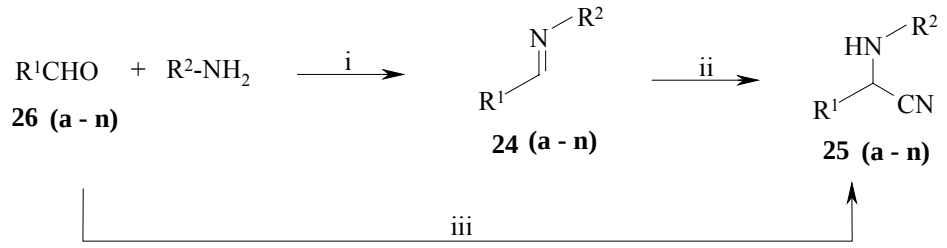
Three-component Strecker type condensation between benzaldehyde, p-anisidine and acetone cyanohydrin was conducted in the presence of various organic bases such as Et_3N, pyridine, Et_2NH, DABCO, DBU, etc. However, trace amount of Mannich reaction product (acetone addition onto imine) was obtained when L-proline is used as catalyst. As can be seen, only Et_3N in combination with acetone cyanohydrin gave the required product in excellent yield. Naturally occurring chiral organic bases (entries 10-15) was not effective in introducing chirality into the product **25a** although these are excellent catalysts for the same reaction. The results of organic base catalyzed hydrocyanation of benzaldimine are summarized in **Table 2**.

Table 2: Organic base catalyzed hydrocyanation of benzaldimines (**25a**)[a]

Entry	Catalyst	Catalyst mol %	Cyanide source	Solvent	Yield of 25a (%)[b]
1	Et_3N	10 mol%	TMSCN	CH_3CN	00
2	None	10 mol%	Acetone cyanohydrin	CH_3CN	00
3	Et_3N	5 mol%	Acetone cyanohydrin	CH_3CN	93
4	Et_3N	10 mol%	Acetone cyanohydrin	CH_3CN	95
5	Pyridine	10 mol%	Acetone cyanohydrin	CH_3CN	07
6	Pyridine	100 mol%	Acetone cyanohydrin	CH_3CN	89
7	Et_2NH	5 mol%	Acetone cyanohydrin	CH_3CN	05
8	DABCO	5 mol%	Acetone cyanohydrin	CH_3CN	88
9	DBU	5 mol%	Acetone cyanohydrin	CH_3CN	92
10	Quinine	5 mol%	Acetone cyanohydrin	CH_3CN	79[c]
11	Sparteine	10 mol%	Acetone cyanohydrin	CH_3CN	09[c]
12	L-proline[d]	20 mol%	Acetone cyanohydrin	DMSO	12[c]
13	Brucine	5 mol%	Acetone cyanohydrin	CH_3CN	67[c]
14	DHQ	5 mol%	Acetone cyanohydrin	CH_3CN	83[c]
15	Nicotine	5 mol%	Acetone cyanohydrin	Ch3CN	56[c]

a: reaction conditions: Benzaldehyde **26a** (2 mmol), p-anisidine (2mmol), cyanide source (2 mmol), CH_3CN, 25^{0}C, 5h;. b: Isolated yield after column chromatographic purification; c: No chiral induction was observed, which was determined by optical rotation. d: Mannich reaction product was observed.

It was of interest to subject various substituted imines (**26a-i)** for hydrocyanation using $Cu(OTf)_2$ coupled with TMSCN and Et_3N in combination with cheaply available and stable acetone cyanohydrin (**Scheme 12**).



Scheme 13: i dry $MgSO_4$, CH_2Cl_2, 25 ^{0}C, 1 h.; ii cat. $Cu(OTf)_2$ (1 mol %), CH_2Cl_2, 25 ^{0}C, 6 h.; ii cat. Et_3N (5 mol %), CH_3CN, 25 ^{0}C, 6 h.

As can be seen from **Table 3**, various substituted aldehydes underwent hydrocyanation with both $Cu(OTf)_2$-TMSCN and Et_3N-acetone cyanohydrin system to give the corresponding hydrocyanation products **25**(**a-n**) in good to excellent yields.

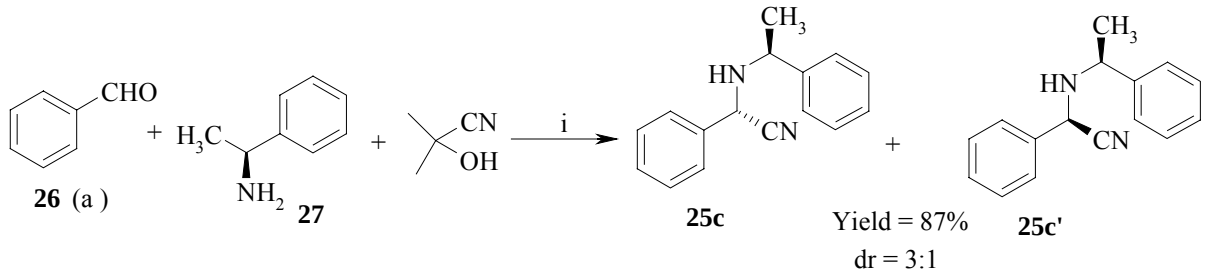
Table 3: $Cu(OTf)_2$[a] and Et_3N[b] catalyzed Strecker type synthesis of α-aminonitriles (**25**).

Entry	R^1	R^2	Yield of **25** (%)[c]	
			$Cu(OTf)_2$	Et_3N
a	C_6H_5	4-MeO-C_6H_4	95	93
b	C_6H_5	C_6H_5-CH_2	98	99
c	C_6H_5	$C_6H_5(CH_3)CH$[d]	65	87
d	C_6H_5	C_6H_5	89	74
e	4-Cl-C_6H_4	4-MeO-C_6H_4	90	85
f	4-MeO-C_6H_4	4-MeO-C_6H_4	99	95
g	4-NC-C_6H_4	4-MeO-C_6H_4	88	90
h	4-HO-C_6H_4	4-MeO-C_6H_4	85	88
i	2-HO-C_6H_4	4-MeO-C_6H_4	82	85
j	4-O_2N-C_6H_4	4-MeO-C_6H_4	78	73
k	3-O_2N-C_6H_4	4-MeO-C_6H_4	81	72
l	3,4-$(MeO)_2$-C_6H_3	4-MeO-C_6H_4	92	95
m	3,4-$(O\text{-}CH_2\text{-}O)_2$-$C_6H_3$	4-MeO-C_6H_4	90	93
n	2,4-(*tert*-Bu)$_2$-6-(MeO)-C_6H_2	4-MeO-C_6H_4	56	69
o	C_6H_5	OH	00	00

a: $Cu(OTf)_2$ catalyzed reaction conditions: aldimines **24a-o** (2 mmol), cyanide source (2 mmol), CH_3CN, 25^{0}C, 6h; b: Et_3N catalyzed reaction conditions: aldehydes **26a-o** (2 mmol), p-anisidine (2mmol), cyanide source (2 mmol), CH_3CN, 25^{0}C, 6h; c: Isolated yield after column chromatographic purification.

It is remarkable that the addition takes place at room temperature using CH_3CN as solvent employing 5 mol % of the catalyst ($Cu(OTf)_2$ or Et_3N). Aldehydes possessing both, electron-donating as well as electron-withdrawing groups underwent Strecker type reaction to afford the corresponding α-aminonitriles (**25a-n**). Even sterically hindered aldehyde (**26n**) also smoothly underwent reaction, producing the corresponding α-aminonitriles (**25n**) in 76% yield. However, the reaction failed to proceed in case of aliphatic aldehydes. The reaction also failed to proceed with acetophenone and aldoxime **24o**, under both reaction conditions.

In our attempt to obtain optically pure α-aminonitriles, we employed various chiral bases but reactions failed to induce optical induction (**Table 3**). When chiral amine such as (S)-(-)-α-methylbenzylamine (**27**) and benzaldehyde were subjected for hydrocyanation reaction in the presence of catalytic amount of Et_3N, we obtained 3:1 inseparable diastereomeric mixture of required α-aminonitrile **25c** in 87 % yield (**Scheme 14**). Diastereomeric ratio was obtained from ^{1}H-NMR spectrum by comparing peak integration of both benzylic protons as shown in **Fig. 3**.



Scheme 14: i cat. Et_3N (5 mol %), CH_3CN, 25 ^{0}C, 5 h, 87%.

The formation of α-aminonitriles (**25a-n**) was confirmed by IR, ^{1}H-NMR and ^{13}C-NMR. The IR spectrum of all α-aminonitriles showed a characteristic strong absorption peak for nitrile functionality at 2200-2240 cm^{-1}. For example, the ^{1}H-NMR spectrum of α-aminonitrile (**25m**) showed the typical singlet of benzylic C-H, methylene (O-CH_2-O) and methyl protons at δ 5.20, 6.00, and 3.76 respectively confirming the formation of α-

aminonitrile. Its ^{13}C-NMR showed signals at δ 50.60, 101.92 and 116.25 for benzylic, methylene (O-CH_2-O), and nitrile (CN) carbons of α-aminonitrile (**25m**) respectively (**Fig. 1**).

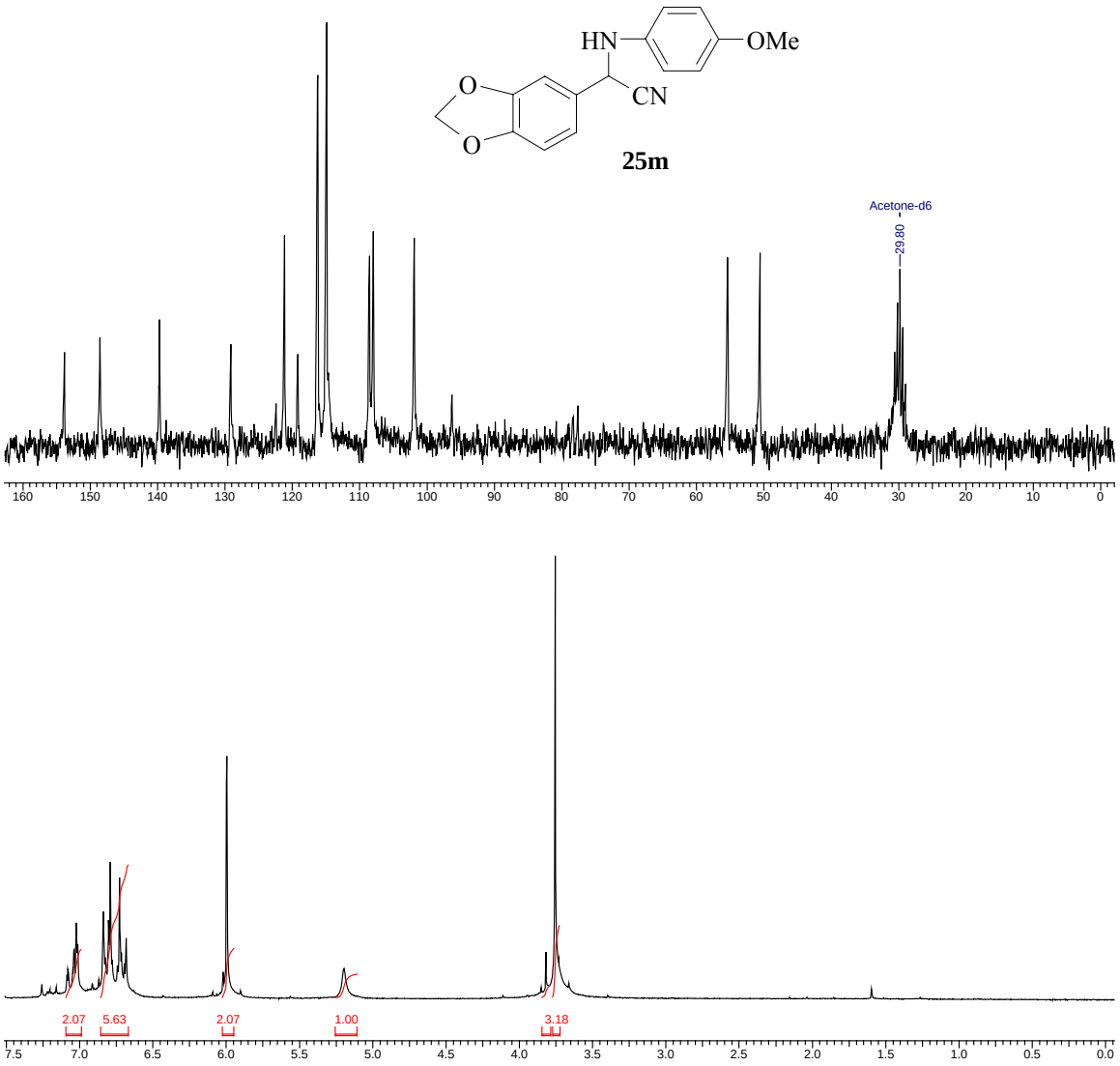


Fig. 1: ^{13}C, ^{1}H -NMR spectra of 25m

The ^{1}H-NMR spectrum of α-aminonitrile (**27n**) showed a singlet at δ 1.36, 1.41 and 5.56 for tert-butyl groups present on phenyl ring and benzylic proton. A double doublet (AB quartet) signal at δ 6.76-6.88 for four protons is due to *para* substituted phenyl ring protons. The ^{13}C-NMR spectrum also showed specific signals at δ 31.16, 31.49 and 45.90 due to

presence of *tert*-butyl groups and benzylic carbon. A typical carbon signal at δ 119.27 is due to presence of nitrile (CN) group.

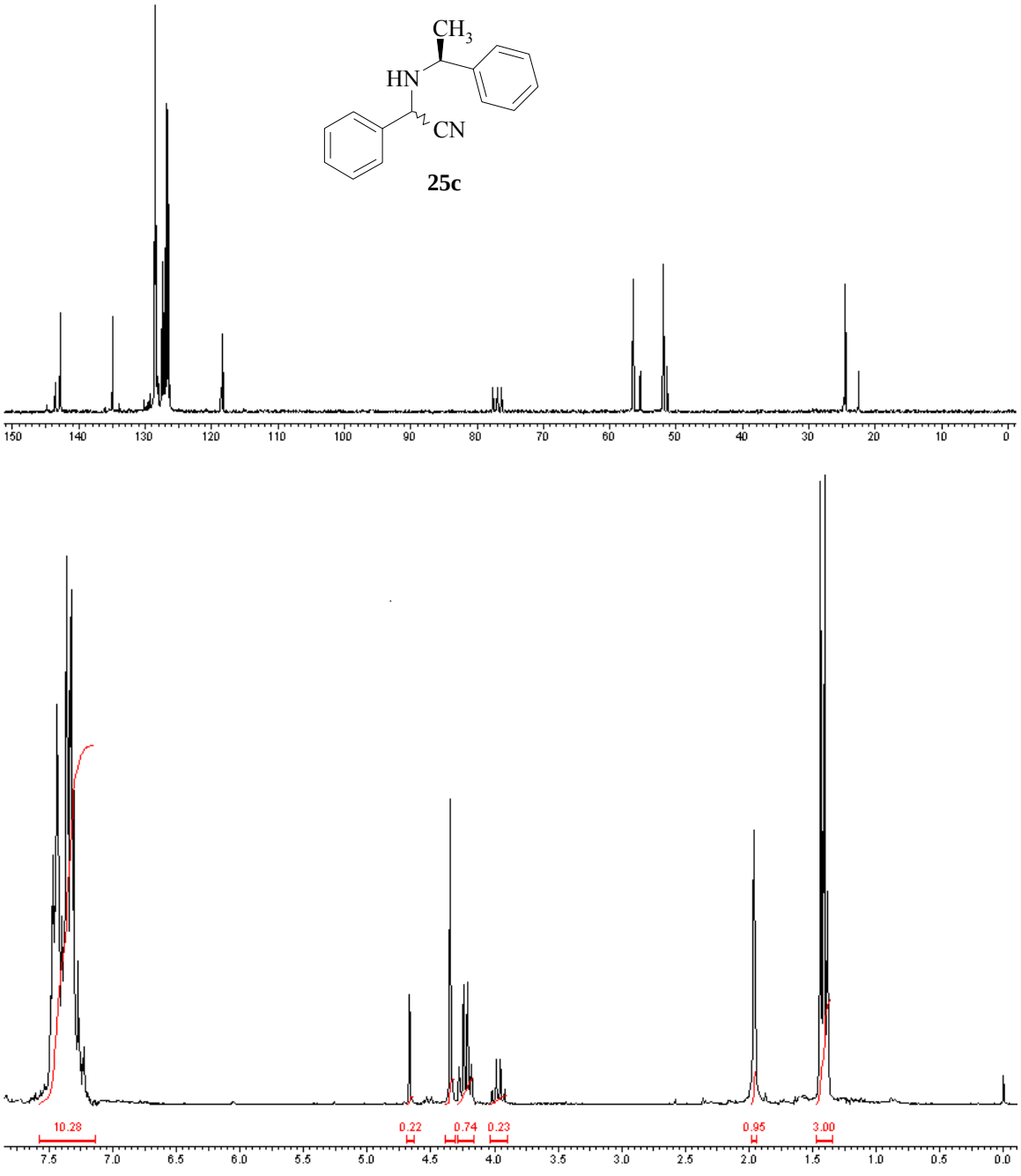


Fig. 3: ^{13}C and ^{1}H -NMR spectra of 25c

The ^{1}H-NMR spectrum of (**25c**) showed two singlets at δ 4.35 and δ 4.67 for benzylic CH proton split in 3:1 intensity due to presence of diastereoisomers. Also another benzylic CH proton adjacent to methyl group showed two quartets at δ 4.18-4.28 and δ 3.92-4.02 split in 3:1 ratio. Its β-CH_3 protons showed a doublet at δ 1.41-1.44 for 3 protons. Its ^{13}C-NMR showed signals at δ 24.52 and 22.52 for β-CH_3 carbon. Both benzylic carbons showed signals at δ 51.94, 51.40 and δ 56.49, 55.45 respectively (**Fig. 3**).

Mechanism:

We believe that the mechanism of this reaction involves, at first, the formation of Et_3N-HCN adduct **29** by reaction of acetone cyanohydrin with Et_3N. This key intermediate Et_3N-HCN adduct **29** will then transfer HCN to imine **24** to afford the required product α-aminonitrile **25** and free Et_3N (**28**) to further continue the catalytic cycle (**Fig. 4**). In order to prove the fact that the reaction is truly catalyzed by Et_3N, we carried out a hydrocyanation experiment by employing catalytic amount (10 mol %) of α-aminonitile instead of Et_3N. However, we did not observe autocatalysis, which indicates that the reaction was only catalyzed by Et_3N and not due to *in situ* generated α-aminonitile product (autocatalysis).

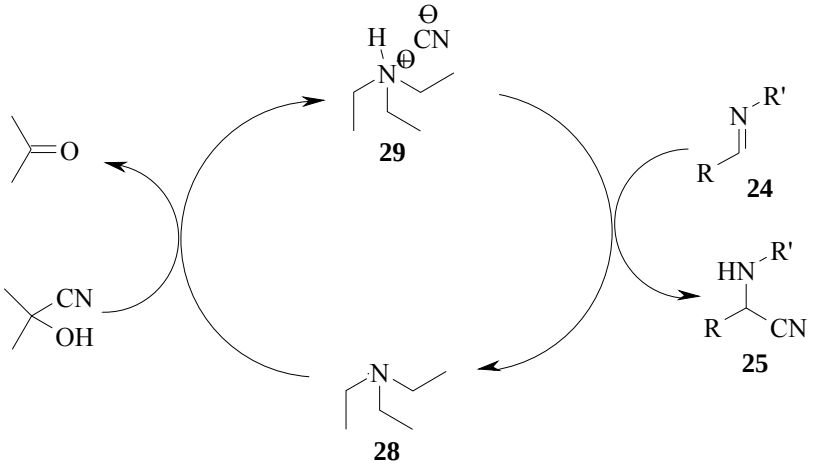


Fig. 4: Proposed catalytic cycle for Et_3N catalyzed hydrocyanation of imines

4.0.5 Conclusion

In conclusion, we have successfully demonstrated the use of both $Cu(OTf)_2$/TMSCN and Et_3N/acetone cyanohydrin as catalytic systems, for the first time, to the three-component Strecker type α-aminonitile (**25a-n**) synthesis at room temperature. Both the catalytic systems are very effective and utilize inexpensive cyanide sources giving the α-aminonitiles in excellent yields. The method also provides access to chiral aminonitriles by employing optically active imines.

4.0.6 Experimental Section

General experimental procedure for $Cu(OTf)_2$ catalyzed hydrocyanation of imines (15a-i)

A mixture of imines (10 mmol), trimethylsilyl cyanide (11 mmol) and $Cu(OTf)_2$ (1 mmol) in acetonitrile (10 ml) was stirred at 25^0C. The reaction was monitored by TLC. After completion of the reaction, it was extracted with ethyl acetate (20 ml) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure product.

General experimental procedure for Et_3N catalyzed hydrocyanation of imines (15a-i)

A mixture of aldehydes (10 mmol), p-anisidine (10 mmol), acetone cyanohydrin (11 mmol) and Et_3N (1 mmol) in acetonitrile (10 ml) was stirred at 25^0C. The reaction was monitored by TLC. After completion of the reaction, it was extracted with ethyl acetate (20 ml) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure product.

2(4-Methoxyphenylamino)-2-phenylacetonitrile (25a):

Yield: 95%; yellow colored solid; **mp:** 72-73^{0}C (crystallized from $CHCl_3$); **IR** (Neat, cm^{-1}): 682, 788, 1030, 1092, 1257, 1385, 1457, 1604, 2235, 2862, 2931, 2958, 3342; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 5.34 (s, 1H), 6.72 – 6.87 (d, J = 9.40 Hz, 2H), 7.43 – 7.48 (m, 3H), 7.58 – 7.63 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.79, 55.02, 114.53, 115.85, 118.32, 126.88, 128.76, 133.94, 138.39, 153.42; **Analysis:** $C_{15}H_{14}N_2O$ requires C, 75.61; H, 5.92; N, 11.76; found C, 75.63; H, 5.96; N, 11.79%.

2-(Benzylamino)-2-phenylacetonitrile (25b):

Yield: 99%; colorless oil, **IR** (Neat, cm^{-1}): 694, 800, 1029, 1094, 1265, 1380, 1455, 1600, 1649, 1805, 1886, 1951, 2229, 2857, 2931, 2963, 3331; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.85 (brs, 1H), 4.0 (m, 2H), 4.74 (s, 1H), 7.24 to 7.55 (m, 10H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 51.2, 53.4, 118.7, 127.2, 127.6, 128.4, 128.6, 128.9, 134.7, 138.1; **Analysis:** $C_{15}H_{14}N_2$ requires C, 81.05; H, 6.35; N, 12.60; found C, 81.12; H, 6.41; N, 12.53%.

2-((S)-1-phenylethylamino)-2-phenylacetonitrile (25c):

Yield: 87%; colorless oil, $[\alpha]^{25}_{D}$: + 15.81 (c 0.90, $CHCl_3$), dr: 3:1; **IR** (Neat, cm^{-1}): 1022, 1077, 1271, 1374, 1461, 1609, 1643, 1806, 1887, 1950, 2231, 2855, 2930, 2960, 3328; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.41-1.44 (d, *J* = 6.57 Hz, 3H), 1.96 (brs, 1H), 4.18-4.28 (q, *J* = 6.44 Hz, 1H), 4.35 (s, 1H), 7.22 to 7.47 (m, 10H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 22.52, 24.52, 51.40, 51.94, 55.45, 56.49, 118.38, 126.53, 126.64, 126.89, 127.50, 128.48, 128.60, 134.96, 142.85, 143.63; **Analysis:** $C_{16}H_{16}N_2$ requires C, 81.32; H, 6.82; N, 11.85; found C, 81.30; H, 6.77; N, 11.83%.

(2-Phenyl-2-(phenylamino)acetonitrile (25d):

Yield: 89%; yellow colored gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 5.28 (s, 1H), 6.62 – 7.04 (m, 5H), 7.18 – 7.33 (m, 5H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 51.79, 113.54, 116.82, 117.24, 127.85, 128.46, 128.90, 133.74, 151.33; **Analysis:** $C_{14}H_{12}N_2$ requires C, 80.74; H, 5.81; N, 13.45; found C, 80.63; H, 5.76; N, 13.29%.

2-(4-Methoxyphenylamino)-2-(4-chlorophenyl)acetonitrile (25e):

Yield: 90%; gum, **IR** (Neat, cm^{-1}): 1011, 1078, 1239, 1367, 1454, 1480, 1546, 1612, 1663, 1814, 1890, 1944, 2239, 2914, 2963, 2981, 3245, 3330; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.41 (s, 1H), 6.81 – 7.21 (m, 8H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.35, 55.38, 114.93, 116.36, 118.72, 129.27, 134.12, 139.45, 153.93; **Analysis:** $C_{15}H_{13}ClN_2O$ requires C, 66.06; H, 4.80; N, 10.27; found C, 66.00; H, 4.78; N, 10.22%.

2-(4-Methoxyphenylamino)-2-(4-methoxyphenyl)acetonitrile (25f):

Yield: 95%; red colored solid; **mp:** 69-71^{0}C (crystallized from $CHCl_3$); **IR** (Neat, cm^{-1}): 685, 791, 1021, 1084, 1237, 1383, 1464, 1486, 1604, 1649, 1796, 1881, 1951, 2226, 2849, 2927, 2968, 3232, 3331; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.83 (s, 3H), 5.25 (s, 1H), 6.70 – 6.84 (d, *J* = 9.00 Hz, 4H), 6.91 – 6.95 (d, *J* = 8.61 Hz, 2H), 7.46 – 7.50 (d, *J* = 8.61 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.42, 55.49, 114.71, 115.08, 116.33, 129.12, 140.15, 153.93, 160.62; **Analysis:** $C_{16}H_{16}N_2O_2$ requires C, 71.62; H, 6.01; N, 10.44; found C, 71.63; H, 6.00; N, 10.39%.

4-((4-Methoxphenylamino)(cyano)methyl)benzonitrile (25g):

Yield: 88%; gum, **IR** (Neat, cm^{-1}): 718, 1057, 1233, 1456, 1487, 1542, 1610, 1651, 1819, 1883, 1940, 2215, 2232, 2912, 2957, 2990, 3240, 3325; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.13 (brs, 1H), 5.32 (s, 1H), 6.32-6.77 (q, *J* = 9.00 Hz, 4H), 7.24-7.49 (q, *J* = 8.74 Hz,

4H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 51.71, 55.98, 111.98, 114.53, 115.16, 115.87, 116.48, 129.67, 131.12, 138.25, 151.93; **Analysis:** $C_{16}H_{13}N_3O$ requires C, 72.99; H, 4.98; N, 15.96; found C, 72.00; H, 4.87; N, 15.62%.

2-(4-Methoxyphenylamino)-2-(4-hydroxyphenyl)acetonitrile (25h):

Yield: 85%; red colored solid; **mp:** 117-120^{0}C (crystallized from EtOH); **IR** (Neat, cm^{-1}): 689, 788, 1015, 1092, 1245, 1389, 1468, 1490, 1608, 1654, 1800, 1887, 1954, 2230, 2854, 2930, 2970, 3236, 3335; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.75 (s, 3H), 5.19 (brs, 1H), 5.34 (s, 1H), 6.70 – 6.85 (d, *J* = 9.00 Hz, 2H), 7.13 – 7.30 (m, 6H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.40, 55.43, 114.70, 115.04, 115.78, 130.07, 140.12, 153.67, 158.70; **Analysis:** $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02; found C, 70.80; H, 5.50; N, 11.00%.

2-(4-Methoxyphenylamino)-2-(2-hydroxyphenyl)acetonitrile (25i):

Yield: 82%; red colored solid; **mp:** 90-92^{0}C (crystallized from $CHCl_3$); **IR** (Neat, cm^{-1}): 693, 788, 1013, 1088, 1260, 1377, 1473, 1600, 1666, 1812, 1880, 1955, 2233, 2868, 2934, 2969, 3249, 3331; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.73 (s, 3H), 5.14 (brs, 1H), 5.33 (s, 1H), 6.69 – 7.15 (m, 8H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.81, 55.11, 114.65, 115.80, 115.60, 130.04, 140.09, 153.67, 157.80; **Analysis:** $C_{15}H_{14}N_2O_2$ requires C, 70.85; H, 5.55; N, 11.02; found C, 70.83; H, 5.53; N, 10.95%.

2-(4-Methoxyphenylamino)-2-(4-nitrophenyl)acetonitrile (25j):

Yield: 78%; brown colored solid; **mp:** 104-107^{0}C; **IR** (Neat, cm^{-1}): 684, 780, 1014, 1090, 1251, 1390, 1472, 1500, 1605, 1656, 1807, 1890, 1953, 2160, 2240, 2850, 2935, 2973, 3231, 3344; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.42 (s, 1H), 6.71 – 6.85 (d, *J* = 9.00 Hz, 2H), 6.90 – 6.94 (d, *J* = 8.60 Hz, 2H), 7.31 – 7.42 (d, *J* = 8.40 Hz, 2H), 8.06– 8.17 (d, *J* = 8.14 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.46, 55.27, 114.70, 115.08, 122.18, 129.90, 135.80, 140.15, 148.84, 156.12, 160.62; **Analysis:** $C_{15}H_{13}N_3O_3$ requires C, 63.60; H, 4.63; N, 14.83; found C, 63.60; H, 4.60; N, 14.57%.

2-(4-Methoxyphenylamino)-2-(3-nitrophenyl)acetonitrile (25k):

Yield: 81%; yellow colored solid; **mp:** 95–98^{0}C (crystallized from MeOH); **IR** (Neat, cm^{-1}): 790, 1011, 1080, 1256, 1377, 1465, 1484, 1612, 1658, 1807, 1890, 1955, 2232, 2855, 2935, 2988, 3243, 3329; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.72 (s, 3H), 5.30 (s, 1H), 6.68 – 6.84 (d, *J* = 9.40 Hz, 2H), 7.45 – 8.16 (m, 6H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.82, 55.35, 113.22, 114.53, 115.85, 118.32, 122.34, 126.88, 128.76, 133.94, 138.39, 147.71, 153.42; **Analysis:** $C_{15}H_{13}N_3O_3$ requires C, 63.60; H, 4.63; N, 14.83; found C, 63.55; H, 4.61; N, 14.88%.

2-(4-Methoxyphenylamino)-2-(3,4-dimethoxyphenyl)acetonitrile (25l):

Yield: 92%; brown colored gum, **IR** (Neat, cm^{-1}): 1015, 1090, 1250, 1390, 1494, 1600, 1650, 1882, 2228, 2857, 2933, 2974, 3235, 3337; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.78 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 5.32 (s, 1H), 6.67 – 7.52 (m, 7H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 50.42, 55.06, 55.49, 114.71, 115.08, 116.33, 129.12, 140.15, 141.26, 153.93, 160.62; **Analysis:** $C_{17}H_{18}N_2O_3$ requires C, 68.44; H, 6.08; N, 9.39; found C, 68.47; H, 6.10; N, 9.40%.

2-(4-Methoxyphenylamino)-2-(benzo[*d*][1,3]dioxol-5-yl)acetonitrile (25m):

Yield: 93%; brown colored solid; **mp:** 112-114^{0}C (crystallized from EtOAc); **IR** (Neat, cm^{-1}): 692, 769, 1009, 1090, 1251, 1393, 1470, 1488, 1604, 1655, 1800, 1888, 1952, 2232, 2840, 2935, 2973, 3228, 3334; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.82 (s, 1H), 5.20 (s, 1H), 6.00 (s, 2H), 6.66–6.84 (m, 5H), 7.01–7.09 (m, 2H); **^{13}C-NMR** (200 MHz, acetone-d_6): δ 50.60, 55.42, 101.92, 107.98, 108.57, 114.93, 116.25, 119.20, 121.18, 129.16, 139.71, 148.56, 153.86; **Analysis:** $C_{16}H_{14}N_2O_3$ requires C, 68.07; H, 5.00; N, 9.92; found C, 68.00; H, 5.00; N, 10.00%.

2-(4-Methoxyphenylamino)-2-(2,4-di-*tert*-butyl-6-methoxyphenyl)acetonitrile (25n):

Yield: 69%; dark brown colored solid; **mp:** 85–88^{0}C (crystallized from EtOAc); **IR** (Neat, cm^{-1}): 560, 665, 783, 1014, 1108, 1252, 1390, 1470, 1490, 1600, 1660, 1800, 1883, 1955, 2230, 2856, 2932, 2976, 3233, 3339; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.36 (s, 9H), 1.41 (s, 9H), 3.78 (s, 3H), 3.81 (s, 1H), 5.56 (s, 1H), 6.76 – 6.88 (d, J = 9.40 Hz, 4H), 7.41 – 7.42 (d, J = 2.35 Hz, 1H), 7.48 – 7.49 (d, J = 2.35 Hz, 1H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 31.16, 31.49, 45.90, 55.46, 63.18, 115.04, 115.78, 119.27, 123.65, 126.00, 128.20, 138.61, 142.94, 147.24, 153.97, 154.74; **Analysis:** $C_{24}H_{32}N_2O_2$ requires C, 75.75; H, 8.48; N, 7.36; found C, 75.83; H, 8.50; N, 7.27%.

SECTION II:

Cu(II) catalyzed one pot addition of $P(OMe)_3$ onto imines: Synthesis of α-aminophosphonates

4.1.1 Introduction

In the recent years, α-aminophosphonates have received enormous attention because they are considered to be structural analogues of the corresponding α-amino acids and transition state mimics of peptide hydrolysis.[21] The use of α-aminoalkyl phosphonates as enzyme inhibitors,[22] antibiotics and pharmacological agents,[23] herbicides,[24] and haptens of catalytic antibodies[25] are well documented. Due to their structural analogy to α-aminoacids, they may function as inhibitors of enzymes involved in the metabolism of proteins and aminoacids. For example, the phosphonic analogue of phenylalanine is an inhibitor of phenylalanyl-5-RNA-synthetase;[26] phosphonodipeptide alafosfalin is an antimicrobial agent.[27]

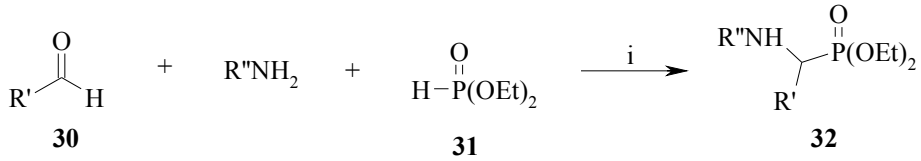
4.1.2 Review of Literature

Literature search revealed that there are various catalytic as well as non-catalytic methods available for the synthesis of α-aminophosphonates.[28] Of these methods, the nucleophilic addition of phosphites to imines, catalyzed by a base or an acid, is the most convenient.[29] Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3.Et_2O$, $ZnCl_2$, and $MgBr_2$ have been used.[30] Some of the important methods are described below.

Kaboudin *et al.*[31]

Kaboudin *et al.* developed a method for the synthesis of 1-aminoalkyl phosphonates **32** through a one-pot reaction of aldehydes **30**, amines and diethyl phosphate **31** in the presence of acidic alumina under solvent-free conditions using microwave irradiation. When the

reaction mixture in the presence of acidic alumina (10 % by weight) was irradiated by microwave for 3–6 min. using 720 W afforded the desired products in 65 – 95 % yield (**Scheme 15**).

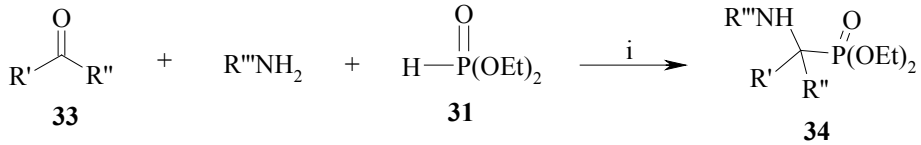


30 **31** **32**

Scheme 15: i Al_2O_3, MW (720 W), 3 – 5 min., 65 – 95 %.

Ranu *et al.*[32]

Ranu *et al.* demonstrated the synthesis of α-amino phosphonates **34** through a one-pot reaction of aldehydes and ketones **33** with amines in the presence of indium (III) chloride as a catalyst. A mixture of aldehyde or ketone, amines and diethyl phosphate **31** was added to a solution of $InCl_3$ in THF, and the mixture was stirred (11 h) at room temperature (25-30 ^{0}C) produced required product **34** in 75 – 95 % yield (**Scheme 16**).

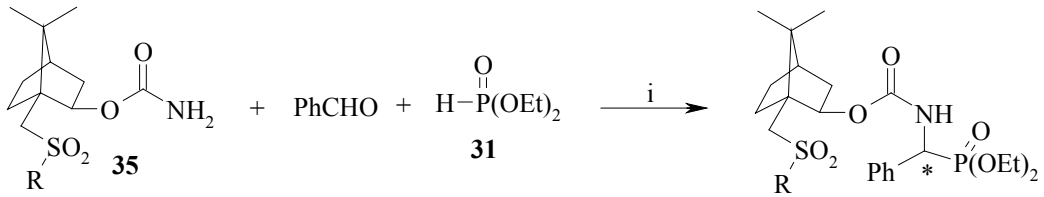


33 **31** **34**

Scheme 16: i $InCl_3$, THF, 25-30 ^{0}C, 11h, 75 – 95 %.

Chung *et al.*[33]

Chung *et al.* employed one pot three component reaction between homochiral (1S)-(+)-camphorsulfonamide-derived carbamate **35**, aldehydes and diethyl phosphate **31** in the presence of stoichiometric amount of acetyl chloride at 0°C to give protected (S)-α-aminophosphonates **36** in 14 – 96 % de and 71 – 84 % yield (**Scheme 17**).

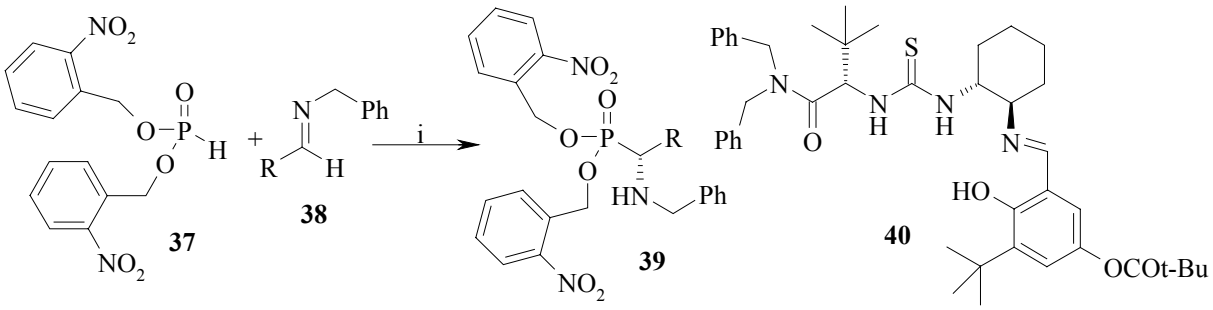


R = N(cyclohexyl)$_2$

Scheme 17: i AcCl, 0 – 25 ^{0}C, 2h, 14 – 96 % de, 71 – 84 %.

Jacobsen *et al.*[34]

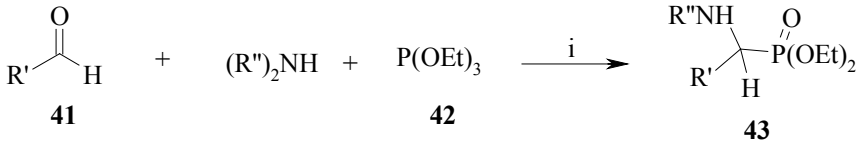
The methodology developed by Jacobsen *et al.* provides 50 – 99 % α-amino phosphonates **39** when imine **38** was subjected for hydrophosphonylation using aryl phosphate **37** in the presence of 10 mol % thiourea based ligand **40** at room temperature (**Scheme 18**).



Scheme 18: i Ligand **40** (10 mol %), HCN (gas), toluene, 25^{0}C, 1 – 24h, 43 – 90 % ee, 50 – 99 %.

Saidi *et al.*[35]

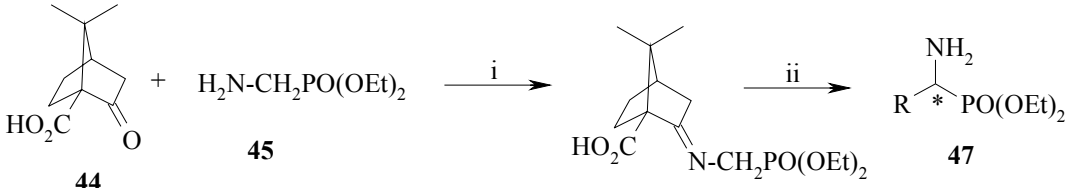
Siadi *et al.* developed a single method for the synthesis of tertiary α-aminophosphonates **43** by reaction of an aldehyde **41**, a secondary amine and trialkylphosphite **42** in ethereal solution of lithium perchlorate, at room temperature with 85 – 90 % yields (**Scheme 19**).



Scheme 19: i $LiClO_4$, Et_2O, 25^{0}C,1h, 85 – 90 %.

Cabella *et al.*[36]

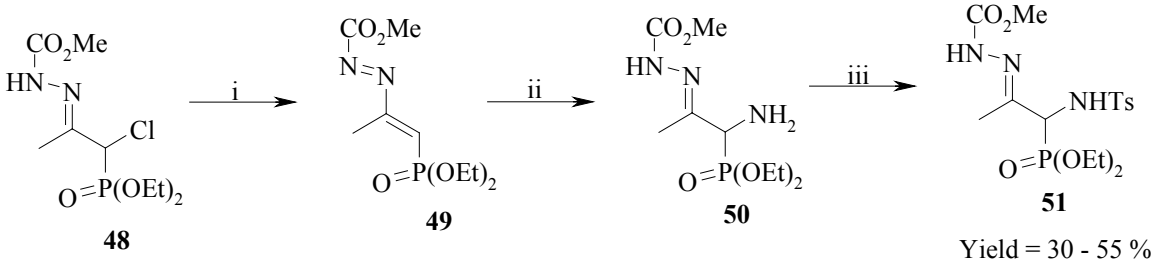
Cabella *et al.* utilized chiral imine **46** derived from ketopinic acid **44** and diethyl aminomethylphosphonate **45** in the presence of boron trifluoride as Lewis catalyst and with azeotropical removal of water for generating chiral aminophosphonates **47**. The alkylation of imine **46** was done with three equivalents of lithium diisopropylamide at -78 °C affording the required product **47** in 39 – 80 % ee and 50 – 69 % yield (**Scheme 20**).



Scheme 20: i $BF_3.Et_2O$, toluene, reflux, 6h.; ii (a) LDA (3 equiv.), alkyl halide (1 equiv.), 70 °C, 5-6h.; (b) 0.1M aq. HCl, THF, 70 °C, 4-5h, 39 – 80 % ee, 50 – 69 %.

Palacios *et al.*[37]

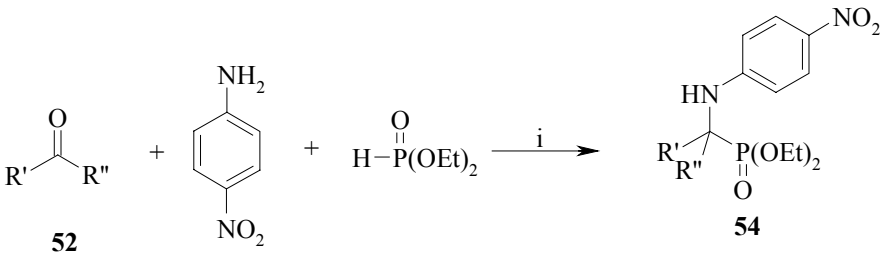
Azophosphonatealkenes **49**, generated from halophosphonateimine **48** by elimination reaction was easily transformed to aminophophonates **50** by Michael addition (1,4-addition) of ammonia producing functionalized α-aminophosphonates **51** in 30 – 55 % yield (**Scheme 21**).



Scheme 21: i Et_3N, CH_2Cl_2, 25^0C 3h.; ii (a) NH_3 (1 atm.), $CHCl_3$, 1h.; (b) TsCl, Et_3N, 25^0C, 1h, 30 – 55 %.

Chandrasekhar *et al.*[38]

Chandrasekhar *et al.* described one-pot procedure producing α-aminophosphonates **54** in 43 – 87 % yield from nitro substituted anilines **53**, aldehydes **52** and diethyl phosphite by employing 10 mol% of $TaCl_5$–SiO_2 as catalyst (**Scheme 22**).



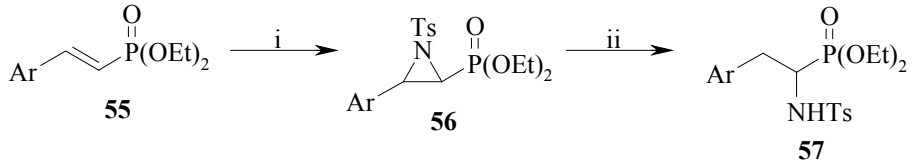
52 **53** **54**

Yield = 43 - 87 %

Scheme 22: i $TaCl_5$-SiO_2 (10 mol %), CH_2Cl_2, 24 h, 25^{0}C, 43 – 87 %.

Kim *et al.*[39]

Kim *et al.* described synthesis of aminoalkylphosphonates **57** from vinyl phosphonates **55**. It was performed by the aziridination of vinylphosphonates **55** with [N-(p-toluenesulfonyl)imino]-phenyliodonane (PhI=NTs) in the presence of copper catalyst followed by the reductive ring opening of aziridinylphosphonates **56** by using Pd/C producing aminoalkylphosphonates **57** in 81-89% yield (**Scheme 23**).



55 **56** **57**

Yield = 81 - 89 %

Scheme 23: i PhI=NTs, cat. $Cu(OTf)_2$, CH_3CN, 25^{0}C, 6h, 82 – 95 %.; ii 10 % Pd/C, MeOH, HCO_2NH_4, 25^{0}C, 24h, 81 – 89 %.

4.1.3 Present Work

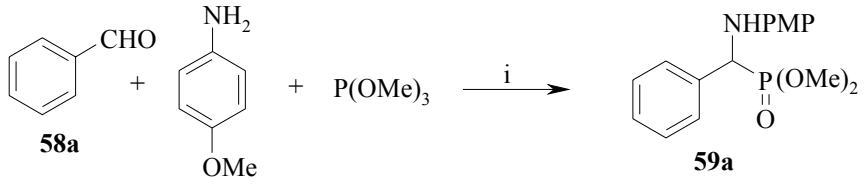
4.1.3.1 Objective

Although many methods are available in the literature for hydrophosphonylation of imines, they suffer from certain drawbacks such as use of expensive and hazardous phosphorous sources, stoichiometric amounts of catalysts, high temperatures, multistep synthesis, lower product selectivities and yields. Recently, nucleophilic addition of phosphates onto imines, catalyzed by a base or an acid, has emerged as an important alternative for the synthesis of such α-aminophosphonates derivatives.[29] Generally, Lewis acids such as $SnCl_2$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, $MgBr_2$, and $InCl_3$ have been used as catalysts. However, these reactions could not be carried out in a single step operation with the carbonyl, amine and phosphite functionalities because amines and water that are formed during imine formation can decompose or deactivate these Lewis acids.[40] So there is a need to develop one-pot synthesis of α-aminophosphonates catalyzed by a water-tolerant Lewis acid.

In the previous sections of this chapter, we had already discussed applications of Cu-catalyst for Strecker-type α-aminonitrile synthesis. Now, we are interested in developing a simple and efficient procedure at ambient conditions for the synthesis of α-aminophosphonates using Lewis acids as catalysts. Particularly, we have evaluated $Cu(OTf)_2$ as a catalyst for α-aminophosphonates synthesis, the results of which are discussed in this section.

4.1.4 Results and Discussion

When we subjected benzaldehyde, p-anisidine and $P(OMe)_3$ to react in the presence of catalytic amount of $Cu(OTf)_2$ (1 mol%) in CH_3CN at 25 ^{0}C for 3 h, we obtained α-aminophosphonate **59a** as an addition product (**Scheme 24**).

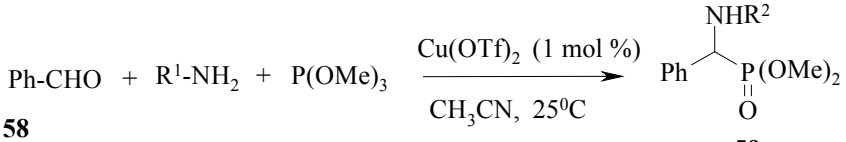


58a **59a**

Scheme 24: i cat. $Cu(OTf)_2$ (1 mol%), CH_3CN, 25 ^{0}C. , 5 h**.**

Thus, a novel operationally simple procedure for the preparation of α-aminophosphonates (**59**) using catalytic amount of $Cu(OTf)_2$ at room temperature has been established. We then became interested to investigate its synthetic utility using much economical nitrogen sources. In order to do that we subjected various cheaply available nitrogen sources such as NH_3, urea, carbamates, amide, sulphonamide, oxime, but the required α-aminophosphonates could not be produced (**Table 4**).

Table 4: $Cu(OTf)_2$-catalyzed three component condensation between benzaldehyde, trimethyl phosphite and various nitrogen sources [a]



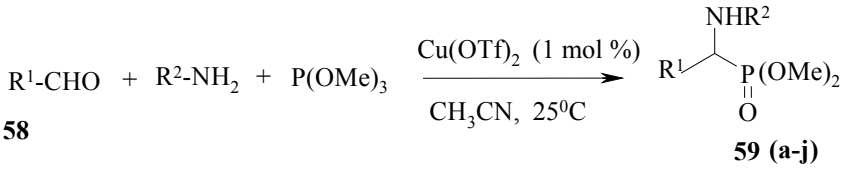
58 **59**

Entry	Amine source R^1	Catalyst (mol%)	Temp. (^{0}C)	Time (h)	Yield (%)[b]
1	4-MeO-C_6H_4	5	25	6	95
2	4-MeO-C_6H_4	1	25	6	97
3	4-MeO-C_6H_4	0.5	25	10	78
4	H	5	80	12	00
5	HO	5	80	12	00
6	NH_2CO	5	80	12	00
7	CH_3CO	5	80	12	00
8	CH_3OCO	5	80	12	00
9	4-Me-$C_6H_4SO_2$	5	80	12	00
10	$C_6H_5CH_2OCO$	5	80	12	00

a: Conditions: benzaldehyde (1 mmol), amine source (1 mmol), $P(OMe)_3$ (1mmol), $Cu(OTf)_2$ (1 mol %), CH_3CN, 25 ^{0}C, 6h.
b: Isolated yield after chromatographic purification.

After employing various amine sources, we turned our attention to screen various aldehydes **58** for one-pot nucleophilic addition of $P(OMe)_3$ onto *in-situ* generated imines in the presence of catalytic amount of $Cu(OTf)_2$ using CH_3CN as solvent to produce the corresponding α-aminophosphonates **59a-j** in excellent yields at room temperature (**Table 5**).

Table 5: $Cu(OTf)_2$-catalyzed one pot addition of $P(OMe)_3$ onto imines: Synthesis of α-aminophosphonates [a]



58 **59 (a-j)**

Entry	R^1	R^2	Yield (%)[b]
a	C_6H_5	4-MeO-C_6H_4	97
b	C_6H_5	C_6H_5	84
c	C_6H_5	$C_6H_5CH_2$	88
d	C_6H_5	$C_6H_5(CH_3)CH$	56
e	4-Cl-C_6H_4	4-MeO-C_6H_4	92
f	4-MeO-C_6H_4	4-MeO-C_6H_4	95
g	4-F_3C-C_6H_4	4-MeO-C_6H_4	80
h	4-NC-C_6H_4	4-MeO-C_6H_4	82
i	4-O_2N-C_6H_4	4-MeO-C_6H_4	75
j	4-HO-C_6H_4	4-MeO-C_6H_4	79

a: Conditions: Aldehyde (2 mmol), amine source (1 mmol), $P(OMe)_3$ (1 mmol), $Cu(OTf)_2$ (1 mol %), CH_3CN, 25 ^{0}C, 6h.
b: Isolated yield after chromatographic purification.

Several functionalities present in the aldehydes such as halogen, methoxy, nitrile, hydroxy group and nitro group were tolerated. This method did not necessitate special use of dehydrating agents and /or the technique of azeotropic removal of water. In all the cases α-aminophosphonates were obtained in good to excellent yields.

The formation of α-aminophosphonates **59a-j** was confirmed by IR, ^{1}H, ^{13}C and ^{31}P-NMR spectrum. The IR spectrum of all α-aminophosphonates **59a-j** showed a typical absorption band in the region of 3290-3350 cm^{-1} confirming the presence of amino group in the molecule. A typical P=O stretching frequency band in the region of 1220-1300 cm^{-1} was also observed. Thus, the ^{1}H-NMR spectrum of α-aminophosphonate **59b** showed a peculiar

doublet at δ 4.79-4.92 with large coupling constant (J = 24.42 Hz) for benzylic proton due to coupling with adjacent ^{31}P atom. Its ^{13}C-NMR also showed typical benzylic and methoxy carbon signals at δ 56.89 and 53.59-53.88. Its ^{31}P-NMR spectrum showed a typical phosphorus single signal at δ 25.51 due to phosphonate group (**Fig. 5**).

As an another example, the IR spectrum of α-aminophosphonate (**59g**) showed the typical absorption frequency bands in the region 3289 and 1229 cm^{-1} confirming the presence of amino and phosphonate group in the molecule. Its ^{1}H-NMR spectrum showed the signals at δ 3.54, 3.68 and 4.71 due to dimethyl phosphonate, methoxy and benzyl group protons respectively. Its ^{13}C-NMR also showed typical benzylic and methoxy carbon signals at δ 55.54 and 51.84-53.89. Its ^{31}P-NMR spectrum showed a typical phosphorus signal at δ 29.06 corresponding to phosphonate group (**Fig. 6**).

The ^{1}H-NMR spectrum of α-aminophosphonate (**59h**) showed a typical doublet at δ 4.70 for benzylic proton. Its ^{13}C-NMR also showed a benzylic carbon signal at δ 55.80. Its ^{31}P-NMR spectrum showed a typical phosphonate group signal at δ 23.88 that confirms the presence of phosphonate group in the molecule (**Fig. 7**).

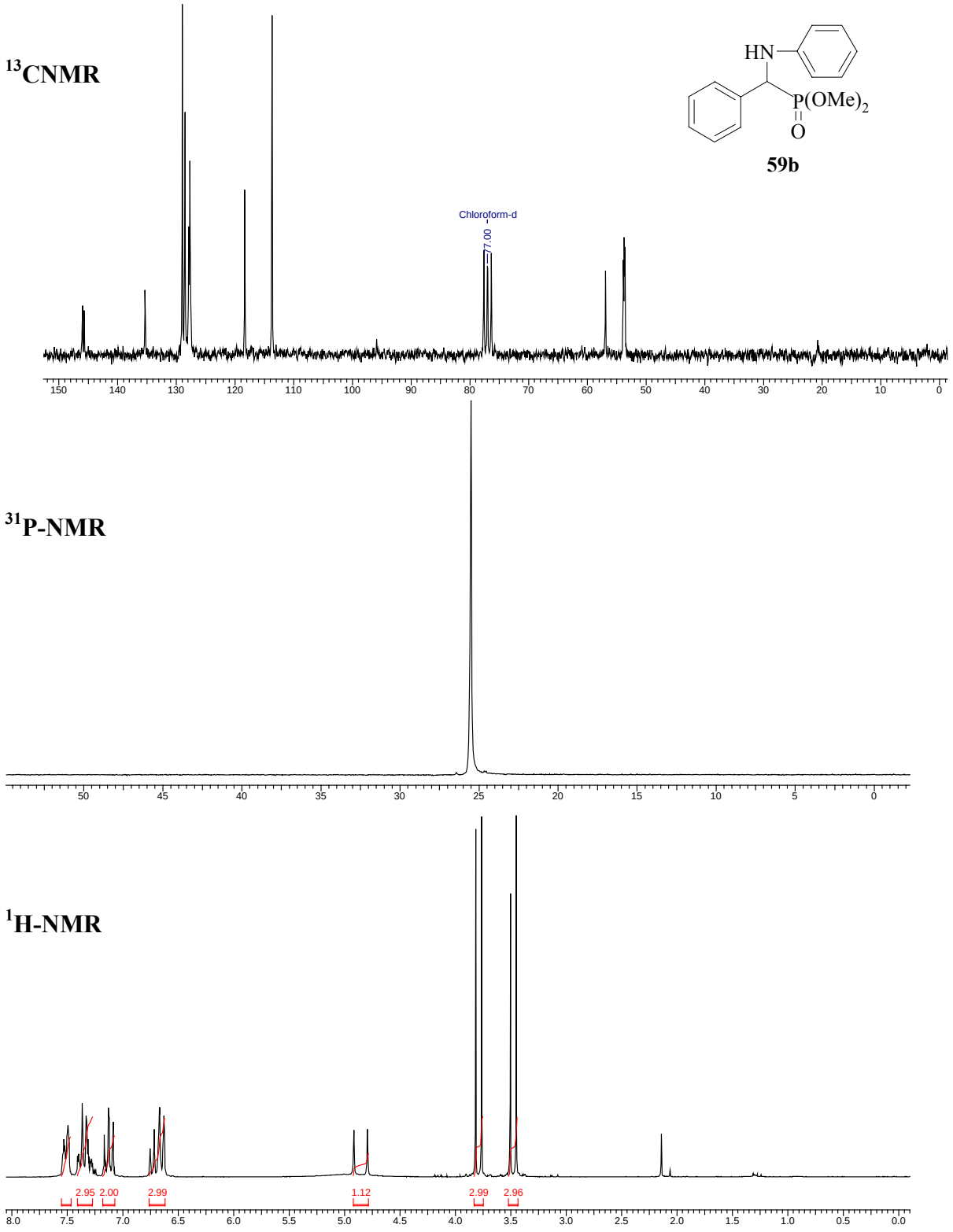


Fig. 5: ^{13}C, ^{31}P and ^{1}H -NMR of α-aminophosphonate 59b

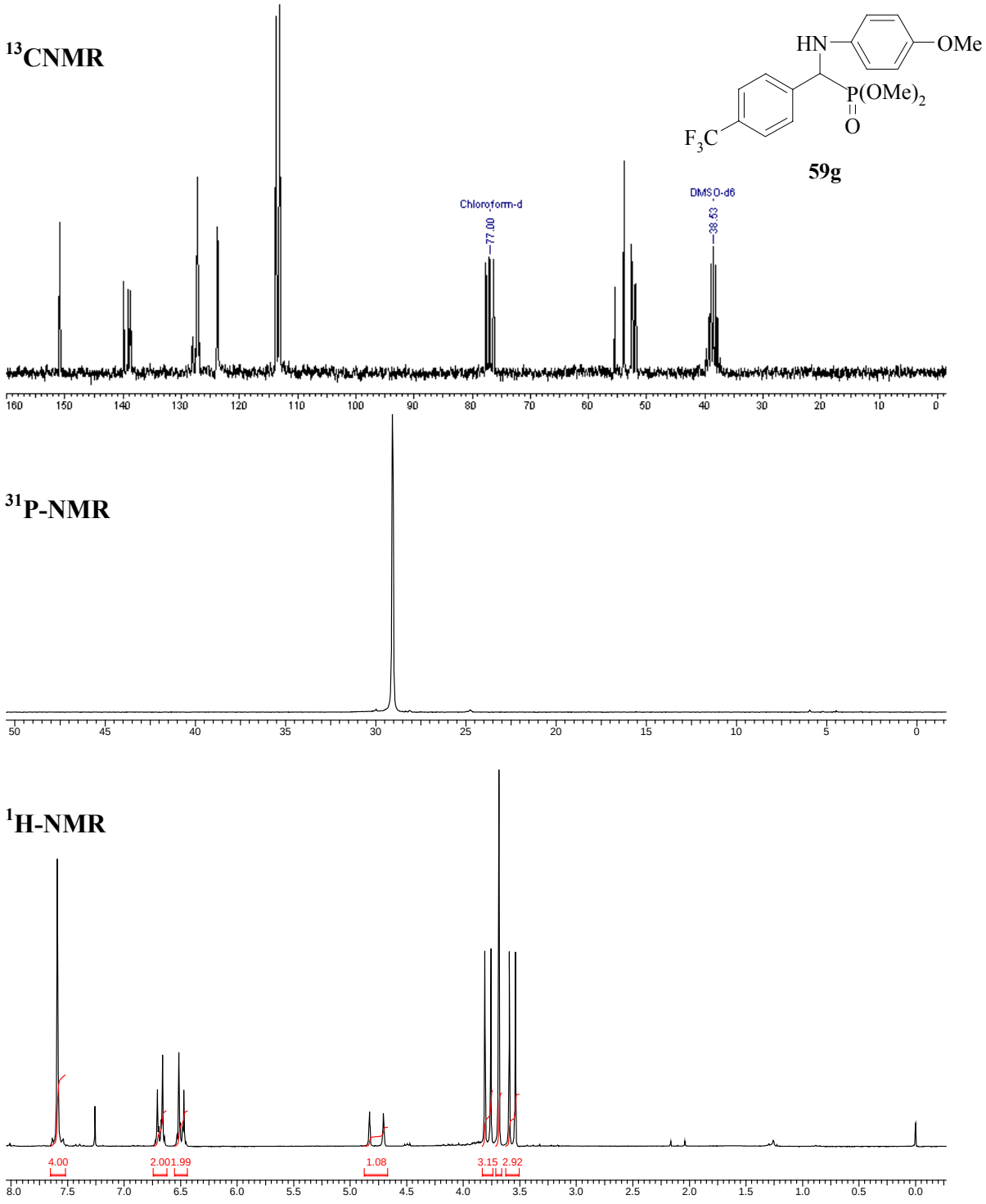


Fig. 6: ^{13}C, ^{31}P and ^{1}H -NMR of α-aminophosphonate 59g

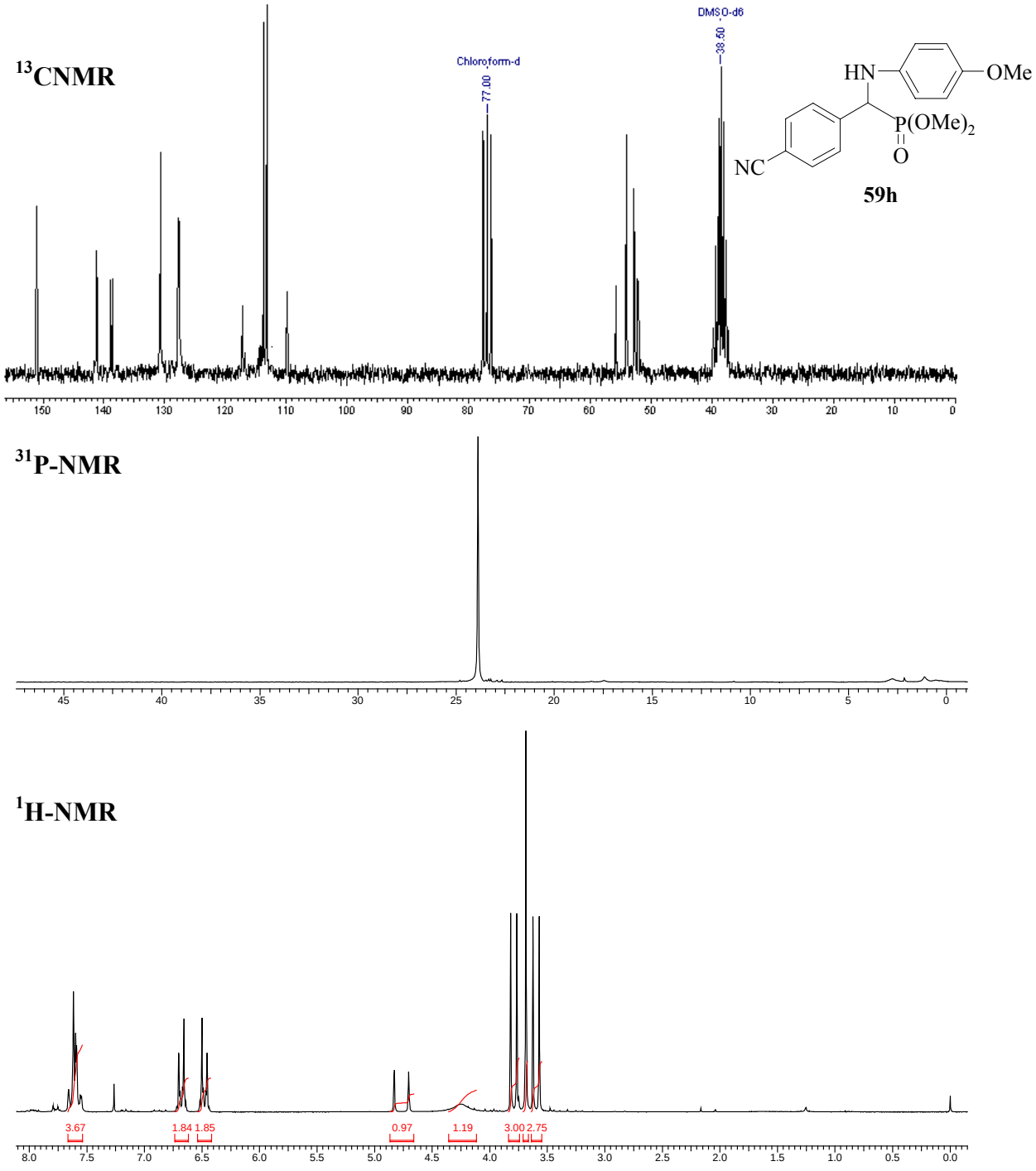


Fig. 7: ^{13}C, ^{31}P and ^{1}H -NMR of α-aminophosphonate 59h

4.1.5 Conclusion

In conclusion, we have successfully demonstrated the use of $Cu(OTf)_2$ as an efficient Lewis acid catalyst, for the first time, to the three-component high yield synthesis of α-aminophosphonates (**25a-n**) at room temperature. The $Cu(OTf)_2$ is stable and does not show any decrease in its catalytic activity due to *in-situ* generated water during the course of reaction. Finally, the present procedure appears attractive for its operational simplicity and generally high yields of products.

4.1.6 Experimental section:

General experimental procedure for hydrophosphonylation of imines:

A mixture of aldehydes (10 mmol), p-anisidine (10 mmol), $P(OMe)_3$ (11 mmol) and $Cu(OTf)_2$ (1 mmol) in acetonitrile (10 ml) was stirred at 25^0C. The reaction was monitored by TLC. After completion of the reaction, it was extracted with ethyl acetate (20 ml) and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica gel using petroleum ether as eluent to afford the pure product.

Dimethyl (4-methoxyphenylamino)(phenyl)methylphosphonate (59a):

Yield: 97%; brown colored solid; **mp:** 85–88^{0}C (crystallized from EtOAc); **IR** (Neat, cm^{-1}): 679, 995, 1032, 1100, 1230, 1382, 1452, 1609, 1805, 1879, 1948, 2855, 2932, 2960, 3294; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.28-3.34 (d, *J* = 10.61 Hz, 3H), 3.70 (s, 1H), 3.75-3.80 (d, *J* = 11.62 Hz, 3H), 4.22 (brs, 1H), 4.68-4.80 (d, *J* = 24.25 Hz, 1H), 6.54-6.59 (d, *J* = 9.09 Hz, 2H), 6.70-6.75 (d, *J* = 8.84 Hz, 2H), 7.19-7.24 (m, 5H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 51.53, 54.49, 62.51, 112.77, 113.59, 114.19, 115.42, 116.40, 121.42, 127.28, 130.04, 131.67, 152.79; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 25.19; **Analysis:** $C_{16}H_{20}NO_4P$ requires C, 59.81; H, 6.27; N, 4.36; found C, 59.63; H, 6.21; N, 4.29%.

Dimethyl phenyl(phenylamino)methylphosphonate (59b):

Yield: 84%; green colored gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 2.14 (s, 1H), 3.45-3.50 (d, *J* = 10.74 Hz, 3H), 3.76-3.82 (d, *J* = 10.75 Hz, 3H), 4.79-4.92 (d, *J* = 24.42 Hz, 1H), 6.63-6.67 (m, 3H), 7.09-7.17 (m, 2H), 7.28-7.41 (m, 3H), 7.50-7.53 (m, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$): δ 53.59, 53.73, 53.88, 56.89, 113.72, 118.35, 127.58, 127.69, 128.53, 128.98, 135.33, 145.70, 145.99; **^{31}P-NMR** (200 MHz, $CDCl_3$): δ 25.51; **Analysis:** $C_{15}H_{18}NO_3P$ requires C, 61.85; H, 6.23; N, 4.81; found C, 61.70; H, 6.12; N, 4.60%.

Dimethyl (benzylamino)(phenyl)methylphosphonate (59c):

Yield: 88%; green colored solid; **mp:** 77–78^{0}C (crystallized from $CHCl_3$); **IR** (Neat, cm^{-1}): 694, 997, 1029, 1103, 1233, 1380, 1455, 1600, 1649, 1805, 1886, 1951, 2857, 2931, 2963,

3295; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.40-3.45 (d, *J* = 10.73 Hz, 3H), 3.73-3.89 (m, 6H), 6.85-7.30 (m, 10H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 52.48, 52.57, 53.44, 54.12, 126.45, 126.72, 127.23, 127.33, 128.13, 128.58, 138.90, 129.28, 129.52, 143.60; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 23.72; **Analysis:** $C_{16}H_{20}NO_3P$ requires C, 62.94; H, 6.60; N, 4.59; found C, 63.00; H, 6.6.62; N, 4.60%.

Dimethyl (1-phenylethylamino)(phenyl)methylphosphonoate (59d):

Yield: 56%; gum; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 1.30-1.33 (d, *J* = 6.57 Hz, 3H), 2.05 (brs, 1H), 3.41-3.52 (q, *J* = 10.35 Hz, 3H), 3.76-3.82 (m, 6H), 6.82-6.89 (q, *J* = 4.67 Hz, 2H), 7.17-7.33 (m, 8H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 22.13, 24.59, 53.18, 53.57, 54.91, 58.18, 58.51, 113.87, 126.59, 126.87, 127.00, 127.12, 128.13, 128.24, 128.40, 129.28, 129.41, 129.52, 129.64, 143.60, 144.75, 159.16, 159.21; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 23.98; **Analysis:** $C_{17}H_{22}NO_3P$ requires C, 63.94; H, 6.94; N, 4.39; found C, 63.87; H, 6.82; N, 4.40%.

Dimethyl (4-methoxyphenylamino)(4-chlorophenyl)methylphosphonate (59e):

Yield: 92%; green colored solid; **mp:** 105–108^{0}C (crystallized from EtOAc); **IR** (Neat, cm^{-1}): 689, 997, 1030, 1105, 1234, 1384, 1451, 1603, 1653, 1800, 1884, 1950, 2853, 2940, 2960, 3295; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.52-3.57 (d, *J* = 10.61 Hz, 3H), 3.68 (s, 1H), 3.74-3.80 (d, *J* = 10.74 Hz, 3H), 4.61-4.74 (d, *J* = 24.25 Hz, 1H), 6.47-6.52 (d, *J* = 9.10 Hz, 2H), 6.65-6.70 (d, *J* = 9.10 Hz, 2H), 7.26-7.42 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 51.66, 51.83, 52.15, 52.28, 53.74, 54.90, 111.92, 113.52, 126.80, 128.13, 128.24, 131.38, 131.46, 133.66, 138.71, 139.03, 150.62; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 24.73; **Analysis:** $C_{16}H_{19}ClNO_4P$ requires C, 54.02; H, 5.38; N, 3.94; found C, 54.00; H, 5.52; N, 3.89%.

Dimethyl (4-methoxyphenylamino)(4-methoxyphenyl)methylphosphonate (59f):

Yield: 95%; gum; **IR** (Neat, cm^{-1}): 537, 687, 789, 994, 1014, 1093, 1237, 1369, 1459, 1611, 1652, 1802, 1883, 1950, 2864, 2930, 2962, 3294; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.53-3.58 (d, *J* = 10.73 Hz, 3H), 3.67 (s, 1H), 3.74-3.80 (d, *J* = 10.73 Hz, 3H), 4.17 (brs, 1H), 4.61-4.73

(d, *J* = 24.28 Hz, 1H), 6.43-6.48 (d, *J* = 8.90 Hz, 2H), 6.63-6.68 (d, *J* = 8.90 Hz, 2H), 6.71-6.89 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 51.12, 52.15, 52.44, 53.89, 55.72, 55.89, 112.27, 113.81, 117.27, 127.46, 127.63, 138.62, 141.36, 151.06, 158.73; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 24.89; **Analysis:** $C_{17}H_{22}NO_5P$ requires C, 58.12; H, 6.31; N, 3.99; found C, 58.10; H, 6.28; N, 4.00%.

Dimethyl (4-methoxyphenylamino)(4-(trifluoromethyl)phenyl)methylphosphonate (59g):

Yield: 80%; gum; **IR** (Neat, cm^{-1}): 994, 1011, 1029, 1087, 1107, 1229, 1378, 1457, 1805, 1886, 1951, 2860, 2930, 2965, 3289; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.54-3.59 (d, *J* = 10.74 Hz, 3H), 3.68 (s, 1H), 3.75-3.81 (d, *J* = 10.73 Hz, 3H), 4.71-4.83 (d, *J* = 24.64 Hz, 1H), 6.47-6.51 (d, *J* = 8.97 Hz, 2H), 6.66-6.70 (d, *J* = 8.97 Hz, 2H), 7.59 (s, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 51.84, 51.98, 52.44, 52.57, 53.89, 55.54, 113.14, 113.66, 123.74, 127.22, 127.32, 138.75, 139.04, 139.87, 150.92; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 29.06; **Analysis:** $C_{17}H_{19}F_3NO_4P$ requires C, 52.45; H, 4.92; N, 3.36; found C, 52.52; H, 4.98; N, 3.59%.

Dimethyl (4-methoxyphenylamino)(4-cyanophenyl)methylphosphonate (59h):

Yield: 82%; brown colored solid; **mp:** 88^{0}C (crystallized from EtOH); **IR** (Neat, cm^{-1}): 1030, 1100, 1236, 1380, 1455, 1600, 1649, 1805, 1886, 1951, 2857, 2931, 2963, 3294; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.57-3.62 (d, *J* = 10.74 Hz, 3H), 3.68 (s, 1H), 3.76-3.82 (d, *J* = 10.74 Hz, 3H), 4.23 (brs, 1H), 4.70-4.83 (d, *J* = 24.89 Hz, 1H), 6.45-6.50 (d, *J* = 8.97 Hz, 2H), 6.66-6.70 (d, *J* = 8.97 Hz, 2H), 7.55-7.66 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 52.06, 52.20, 52.80, 54.02, 55.80, 109.87, 113.24, 113.79, 117.25, 127.65, 127.74, 130.72, 138.58, 138.90, 141.21, 151.10; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 23.88; **Analysis:** $C_{17}H_{19}N_2O_4P$ requires C, 58.96; H, 5.53; N, 8.09; found C, 58.89; H, 5.55; N, 7.96%.

Dimethyl (4-methoxyphenylamino)(4-nitrophenyl)methylphosphonate (59i):

Yield: 75%; yellowish brown colored solid; **mp:** 114–117^{0}C (crystallized from MeOH); **IR** (Neat, cm^{-1}): 999, 1031, 1100, 1234, 1378, 1447, 1598, 1651, 1880, 1950, 2860, 2933, 2967, 3298; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.59-3.64 (d, *J* = 10.73 Hz, 3H), 3.67 (s, 1H), 3.80-3.86

(d, *J* = 10.74 Hz, 3H), 4.29 (brs, 1H), 4.72-4.84 (d, *J* = 24.22 Hz, 1H), 6.47-6.52 (d, *J* = 8.90 Hz, 2H), 6.71-6.75 (d, *J* = 8.87 Hz, 2H), 7.51-8.12 (m, 4H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 52.56, 52.70, 52.81, 54.28, 56.13, 113.22, 113.81, 120.25, 127.72, 127.81, 130.79, 139.61, 139.96, 148.22, 151.14; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 27.41; **Analysis:** $C_{16}H_{19}N_2O_6P$ requires C, 52.46; H, 5.23; N, 7.65; found C, 52.44; H, 5.20; N, 7.59%.

Dimethyl (4-methoxyphenylamino)(4-hydroxyphenyl)methylphosphonate (59j):

Yield: 79%; **IR** (Neat, cm^{-1}): 567, 694, 779, 994, 1012, 1021, 1078, 1103, 1231, 1385, 1456, 1602, 1653, 1806, 1951, 2857, 2937, 2971, 3296, 3386; **^{1}H-NMR** (200 MHz, $CDCl_3$): δ 3.44-3.49 (d, *J* = 10.48 Hz, 3H), 3.67 (s, 1H), 3.72-3.77 (d, *J* = 10.61 Hz, 3H), 3.92 (brs, 1H), 4.56-4.67 (d, *J* = 23.50 Hz, 1H), 6.52-6.56 (d, *J* = 8.97 Hz, 2H), 6.64-6.68 (d, *J* = 8.96 Hz, 2H), 6.77-6.81 (d, *J* = 8.21 Hz, 2H), 7.21-7.25 (d, *J* = 8.59 Hz, 2H); **^{13}C-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 51.10, 52.13, 52.41, 53.87, 55.70, 55.85, 112.32, 113.74, 117.23, 127.55, 127.62, 138.59, 141.71, 151.00, 157.68; **^{31}P-NMR** (200 MHz, $CDCl_3$ + DMSO-d_6): δ 24.36; **Analysis:** $C_{16}H_{20}NO_5P$ requires C, 56.97; H, 5.98; N, 4.15; found C, 56.82; H, 5.87; N, 4.12%.

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ABBREVATIONS

AA	Asymmetric Aminohydroxylation
AE	Asymmetric Epoxidation
AIBN	2,2'-Azobisisobutyronitrile
Ac	Acetyl
Bn	Benzyl
bp	Boiling Point
Boc	N-*tert*-Butoxycarbonyl
CAN	Ceric Ammoniumnitrate
DHQ	Dihydoquinine
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMAP	4-Dimethylaminopyridine
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
g	Grams
h	Hours
HPLC	High pressure liquid chromatography
IR	Infra red
LDA	Lithium diisopropylamide
M^+	Molecular ion
Me	Methyl
min	Minutes
ml	Milliliter
mp	Melting point
MS	Mass spectrum
NMR	Nuclear Magnetic Resonance
NBS	N-Bromosuccinimide
Pet. ether	Petroleum ether
Ph	Phenyl
PMP	*p*-Methoxyphenyl
PTSA	*p*-Toluene sulfonic acid
Py	Pyridine
RT	Room Temperature
THF	Tetrahydrofuran

TBDMS	*tert*-butyldimethylsilyl
TLC	Thin layer chromatography
TBHP	*Tert.* Butyl hydrogen peroxide
TMSCN	Trimethylsilyl cyanide

GENERAL REMARKS

1. All solvents were distilled and dried before use.
2. Petroleum ether refers to the fraction collected in the boiling range 60-80^{o}C.
3. Organic layers after every extraction were dried over anhydrous sodium sulfate.
4. Column Chromatography was performed over silica gel (60-120 mesh).
5. TLC analyses were performed by analytical thin layer chromatography plates precoated with silica gel 60 F_{254} (Merck).
6. IR spectra were recorded on a Perkin-Elmer model 683 B or 1605 FT-IR and absorptions were expressed in cm^{-1}.
7. ^{1}H, ^{13}C and ^{31}P-NMR spectra were recorded on Bruker FT AC-200, MSL-300 and 500 MHz instruments using TMS as an internal standard. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, and dd = doublet of doublet.
8. Mass spectra (MS) were recorded on an automated finnigan MAT 1020C mass spectrometer using ionization energy of 70eV.
9. Optical rotations were carried out on JASCO-181 digital polarimeter at 25^{o}C using sodium D light.
10. All melting points and boiling points are uncorrected and the temperatures are in centigrade scale.
11. Elemental analysis was done on Carlo ERBA EA 110B instrument.
12. The compounds, scheme and reference numbers given in each chapter refers to that particular chapter only.
13. The chiral ligands DHQD, $(DHQ)_2$-PHAL, Oxazolidinones were purchased from Aldrich.

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