Organocatalytic Approaches Towards the Synthesis of Alpha-Amino Acids and Poly(lactic acid)

A thesis submitted in partial fulfillment for the degree of

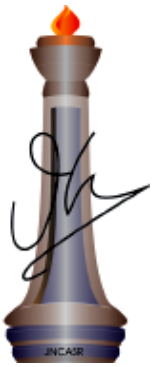
MASTER OF SCIENCE

as a part of the

Integrated Ph.D. Programme (Chemical Science)

by

Ms. Debopreeti Mukherjee



New Chemistry Unit

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March 2014

Dedicated to the memory of my grandmother

Declaration

I hereby declare that the matter embodied in the thesis entitled "**Organocatalytic Approaches Towards the Synthesis of Alpha-Amino Acids and Poly(lactic acid)**" is the result of investigations carried out by me at the New Chemistry Unit and International Centre of Materials Sciences, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India under the supervision of Dr. Sridhar Rajaram and that it has not been submitted elsewhere for the award of any degree or diploma.

In keeping with the general practice in reporting scientific observations, due acknowledgement has been made whenever the work described is based on the findings of other investigators. Any omission that might have occurred by oversight or error of judgment is regretted.

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Debopreeti Mukherjee

Certificate

I hereby certify that the matter embodied in this thesis entitled "**Organocatalytic Approaches Towards the Synthesis of Alpha-Amino Acids and Poly(lactic acid)**" has been carried out by Ms. Debopreeti Mukherjee at the New Chemistry Unit and International Centre of Materials Sciences, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India, under my supervision and that it has not been submitted elsewhere for the award of any degree or diploma.

_____

Dr. Sridhar Rajaram

(Research Supervisor)

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Next, I would like to thank my research supervisor Dr. Sridhar Rajaram for his mentorship and guidance.

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I want to take this opportunity to acknowledge all my Professors in NCU. Their advice, support and guidance have been invaluable. On the same note, I would also like to thank all my course instructors in JNC and my teachers from Presidency College for their love and support.

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I know that I have mentioned only a few names in my acknowledgement, but that does not mean I have forgotten the others. I would like to express my heartfelt gratitude to all who have been there for me. They made my stay in JNC worthwhile. Thank you all.

SYNOPSIS

The thesis consists of two chapters.

The first chapter deals with the synthesis of precursors required for the preparation of α-amino acids. α-amino acids are extremely significant in our day to day lives, owing to their importance as building blocks for proteins, peptides and their roles as chiral auxiliaries and chiral reactants in organic chemistry. However, an environmentally benign method encompassing the synthesis of all kinds of natural and non-natural alpha amino acids has eluded organic chemists till now. This chapter describes the advent of such a method, which has the potential to overcome the limitations of the existing ones. It also delineates in detail the importance of some of the precursors needed for this method and the experimental methods needed for their synthesis.

The second chapter depicts the polymerization reaction of O-carboxy anhydride derivatives of lactic acid. Poly(lactic acid) or PLA has a diverse array of applications in various fields. It can be used as a packaging material, in tissue engineering and in the release of drugs in a controlled manner. Poly(lactic acid) has been mainly prepared by the ring-opening polymerization (ROP) of six-membered lactide derivatives using organometallic and organocatalytic pathways. Here, the stereochemistry of the synthesized polymer has often been controlled by the chiral information present in the catalyst. However, the change in free energy behind this ROP is not significantly negative. On the other hand, the process involving the ring-opening polymerization of five-membered O-carboxy anhydride derivatives giving rise to PLA as the product is much more spontaneous in nature. This kind of polymerization has not been explored much till date. Thus, this chapter deals with the polymerization of the racemic O-carboxy anhydride derivative of lactic acid, using two different categories of organocatalysts.

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CHAPTER 2

Polymerization of O-carboxy anhydrides of lactic acid

Chapter 1

Precursors for the synthesis of α-amino acids

1.1 Introduction

Amino acids, a class of biologically important organic compounds, consist of functional groups like amine ($-NH_2$) and carboxylic acid (-COOH), along with various side chains (organic groups), which are specific for different amino acids. Amino acids mostly exhibit a zwitter-ionic structure, arising as a result of intramolecular acid base reaction.

1.1.1 Classification of amino acids:

Amino acids can be classified according to different parameters. Some of these parameters are as follows-

- The position of the functional groups (α-amino acids, ß-amino acids, γ-amino acids etc.)
- pH (whether acidic or basic groups are present in the side chains)
- Polarity (whether the side chains are polar or hydrophobic)
- Nature of side chains (whether they are aromatic or aliphatic, acyclic or cyclic etc.)

- Proteinogenic or Non-proteinogenic (whether they serve as building blocks of proteins or not)
- Natural or Non-natural (whether they exist naturally or are artificially synthesized)
- Essential or Non-essential (depending on the effects caused due to the deficiency of these amino acids; essential amino acids cannot be synthesized in human body)

Out of the three hundred amino acids that are known to exist, twenty two are found to combine and form polypeptides, the building blocks for protein synthesis. These amino acids are proteinogenic as well as natural. Again, out of these twenty two amino acids, twenty are found to be encoded by the triplet codon, directly into the genetic code. These are referred to as standard amino acids. The names and structures of these amino acids are shown below-

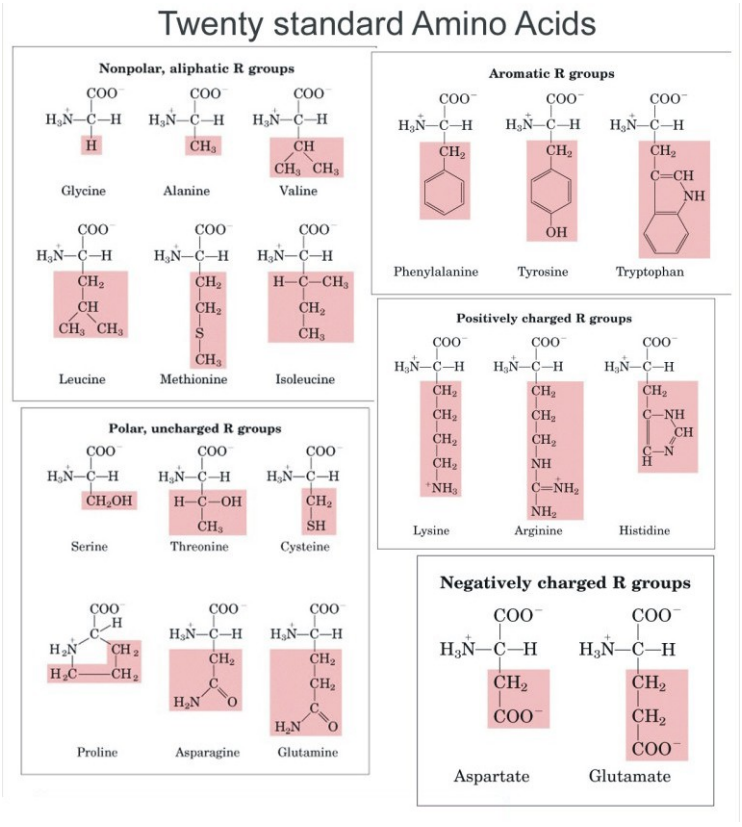


Fig.1.1: Standard Amino Acids (Adapted from http://strength-health-alliance.com/eating-for-strength-and-health-part-ii-protein-biochemistry-public-health-and-athletic-performance-part-a/)

In all the amino acids mentioned above, the amine and the carboxylic acid functional groups are attached to the same carbon (α-carbon). Thus, these amino acids are referred to as alpha amino acids. The α-carbon atom of these compounds also serves as chiral centre (Glycine being the only exception) and these amino acids are of L-configuration.

Besides, non-standard amino acids like selenocysteine, 4-hydroxy proline, pyrrolysine and artificial amino acids like- tert-leucine, selenomethionine etc. are also examples of alpha amino acids.

1.1.2 Alpha amino acids:

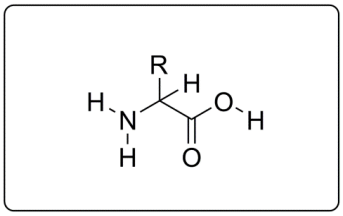


Fig.1.2: α-amino acids (Adapted from Wikipedia)

Proteinogenic and non-proteinogenic α-amino acids comprise an important family of natural products and can serve as building blocks for peptides, proteins and other pharmaceutical target molecules.[1-3] They are ubiquitous to all living organisms on Earth. Chiral alpha amino acids are used as chiral auxilliaries, chiral starting materials and as catalysts in organic synthesis. [4,5] There are four main approaches for the preparation of optically active amino acids, namely- biotechnological methods, chemical synthesis using compounds from chiral pool, resolution of racemic mixture and asymmetric synthesis. [1]

Again, asymmetric synthesis of α-amino acids can be carried out either by using chiral reagents, auxiliaries or by using catalysts, like organocatalysts, organometallic catalysts and phase transfer catalysts.

The historical background involving the synthesis of enantiomerically enriched alpha amino acids can be briefly classified into three periods-

- The classical methods involving synthesis of amino acids from natural sources were extensively used till 1980s.
- Synthesis of alpha amino acids mediated by chiral auxiliaries or chiral templates derived from glycine or alanine derivatives were used for the next two decades.
- The last 15 years have seen a surge in the development of catalytic asymmetric synthesis, thus making it the most powerful tool for the preparation of enantiopure alpha amino acids, till date. [6]

The next section will comprise brief descriptions of some of the well-known existing catalytic asymmetric methods used for the preparation of alpha amino acids. It will also include the drawbacks of each of these methods, thereby emphasizing the need to come up with an entirely new, environmentally benign concept for synthesizing this class of organic compounds.

1.1.3 Existing methods for the preparation of alpha amino acids:

Optically enriched α-amino acids can be prepared by using the following strategies[6] -

- (a) Enantioselective introduction of the α-hydrogen (C-H bond formation)
- (b) Enantioselective introduction of the α-amino group (C-N bond formation)
- (c) Enantioselective introduction of the α-side chain (C-C bond formation)
- (d) Enantioselective introduction of the α-carboxy group (C-C bond formation)

These strategies can be very well illustrated with the help of the following figure-

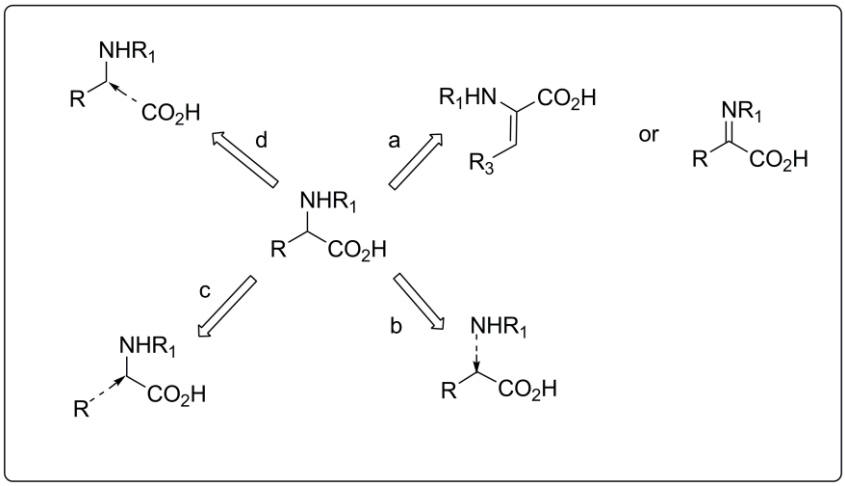


Fig.1.3: Strategies for preparation of α-amino acids (Adapted from Ref. 1)

1.1.3.1 Enantioselective introduction of α-hydrogen:

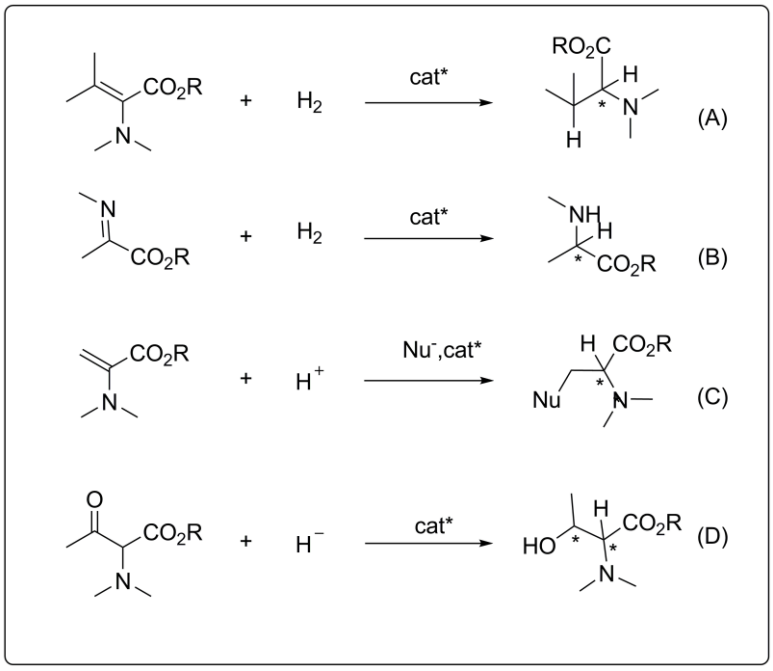


Fig.1.4: Introduction of α-hydrogen (Adapted from Ref. 6)

Figure 1.4 depicts the various methods of incorporating α-hydrogen to prepare optically active alpha amino acids.

This includes metal catalyzed dehydrogenation of alkenes[6], reductive amination of α-keto esters[6], protonation of acrylates[7] and reductive hydrogenation using Dynamic Kinetic Resolution.[3,6,8]

Among all these methods, the most widespread method is the metal catalyzed carbon-carbon double bond hydrogenation of the α,ß-dehydro-α-amino acid (DAA) derivatives (eqn.(a)). Here, I will briefly describe this reaction, it's mechanistic aspects and it's limitations.

1.1.3.1.1 Metal catalyzed dehydrogenation of alkenes:

Reaction:

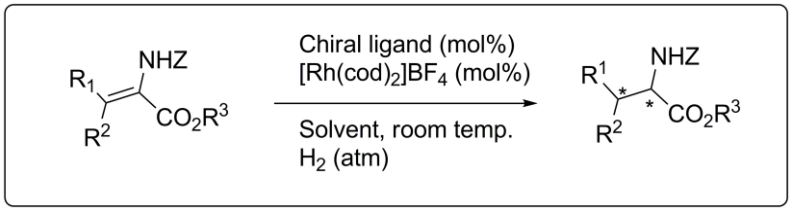


Fig.1.5: Dehydrogenation of alkenes (Adapted from Ref. 6)

Here, generally Rh-complexes like $Rh(cod)_2BF_4$ are taken along with monodentate chiral ligands such as- aminophosphinites, phosphonites, phosphoramidites and phosphites. [6] Bidentate chiral ligands are also used and ligands like 1, 1-bisphosphines often yield products with better enantioselection than their monodentate counterparts. [6]

Mechanism:

The general mechanism for alkene hydrogenation reaction can be best explained with the help of the following schematic diagram-

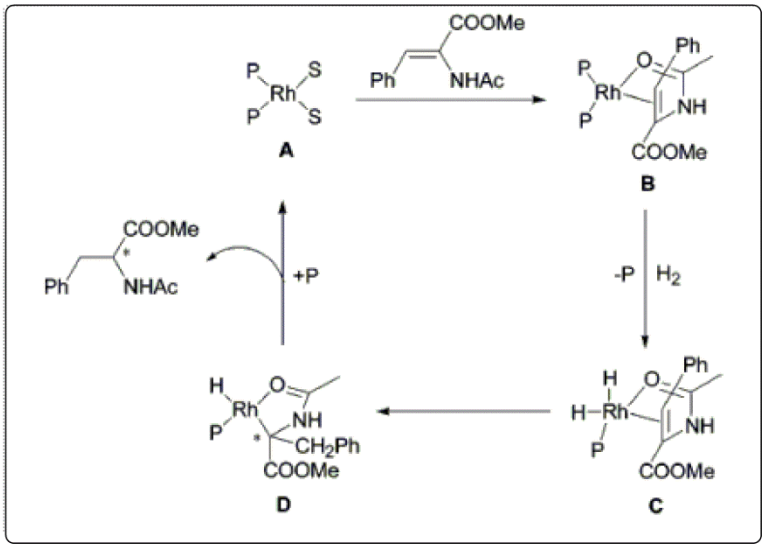


Fig.1.6: Mechanism for dehydrogenation (Adapted from Ref. 9)

In the figure, α-acetamidocinnamate is taken as the substrate and a monodentate ligand belonging to the spiro-indanyl phosphoramidite family is used. [9] Here, S refers to the solvent molecules present.

The reaction rate was found to increase on taking [Rh]:ligand in the ratio of 1:1 instead of 1:2, thereby making it evident that in the active catalytic intermediate only one monophosphorus ligand is bonded to Rhodium. [9]

Limitations of the method:

- Often, when ligands such as 1,3 diphosphines, phosphoramidites and aminophosphinites are used, high pressure of hydrogen (60-100 atm) is required in order to increase the enantioselectivity as well as the rate of the reaction. [6]
- Besides, amino acids bearing α-aryl and quarternary α-alkyl substituents cannot be prepared using this method.
- Toxic metal residues are used as catalysts.
- Regeneration of catalytic system is quite difficult. Can only be done if ionic liquids and water comprise the reaction medium or if polymer supported dehydroamino acid derivatives are taken. [10,11]

1.1.3.2 Enantioselective introduction of the α-amino group:

The figure below depicts the various ways by which the amino group is introduced at the α-position to generate optically active α-amino acids.

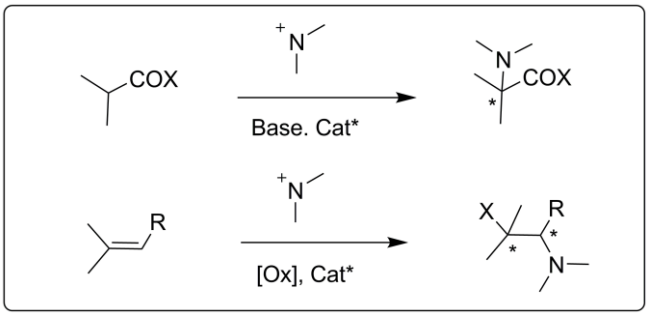


Fig.1.7: Introduction of α-amino group (Adapted from Ref. 6)

These methods and their drawbacks are briefly described in the following pages.

1.1.3.2.1 Electrophilic aminations:

These reactions involve an 'umpolung'methodology, (i.e. a methodology involving inverse polar behavior) where amination is carried out by using electrophilic nitrogenated moieties. These kinds of reactions also have a very high catalytic turnover number. [6]

Reaction:

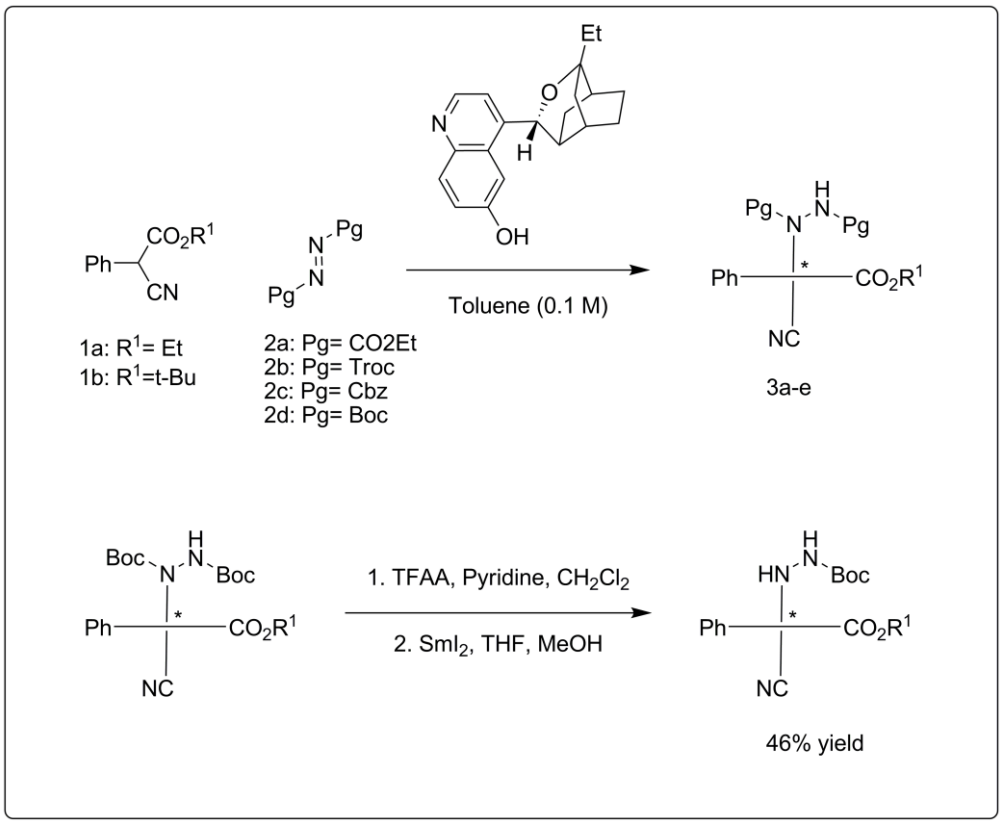


Fig.1.8: Electrophilic amination (Adapted from Ref. 12)

Initially, α-substituted α-cyano acetates are made to react with diethyl azodicarboxylates using catalytic amounts of chiral bases belonging to the cinchona alkaloid family. [12] This reaction was followed by trifluoroacetyl activated N-N bond cleavage of the resulting hydrazine giving rise to optically active quaternary α-amino acid derivatives. [13]

Limitation of this method:

- Toxic metal residue like SmI_2 is used for the cleavage of the N-N bond.
- Very few species contain an electrophilic nitrogen atom.

1.1.3.2.2 Aminohydroxylation reactions:

Reaction:

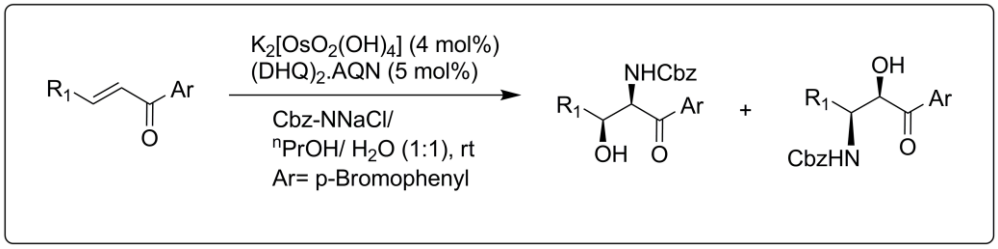


Fig.1.9: Aminohydroxylation (Adapted from Ref. 14)

The main interesting aspect of this reaction is that the starting material upon undergoing amino hydroxylation can give rise to two products, namely- the ß-amino α-hydroxy ester and the α-amino ß-hydroxy ester (precursor for α-amino acids). However, it is possible to produce the latter as the major product by using cinnamates and it is assumed that the interaction between the aromatic group of the cinnamate ester and the alkaloid ligand governs the regiochemistry of the reaction. [14]

The mechanism for this reaction is shown with the following schematic diagram-

Mechanism:

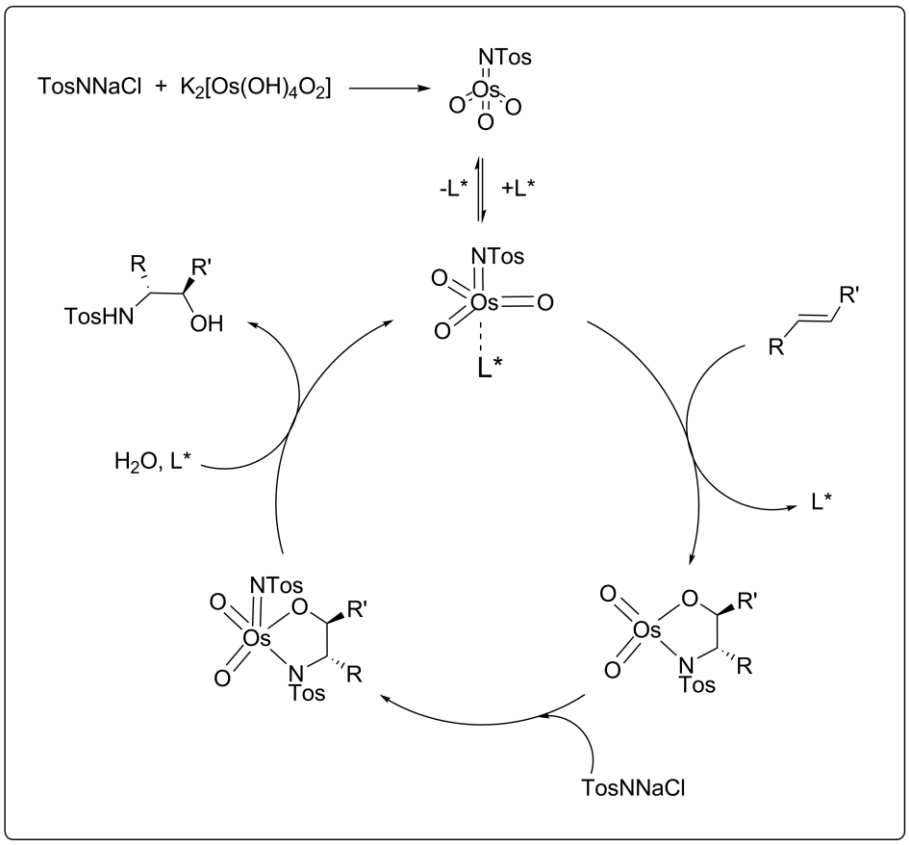


Fig.1.10: Mechanism for amino hydroxylation (Adapted from Ref. 14)

Limitations of the method:

- Toxic metal residues are involved and thus reactions are not environment friendly.

1.1.3.3 Enantioselective introduction of α-side chain:

In this methodology, a large number of strategies have been employed. Among all these strategies, the most common strategy involves electrophilic alkylation of glycine derivatives. This method will be briefly described.

1.1.3.3.1 Electrophilic alkylations of glycine derivatives:

Reaction:

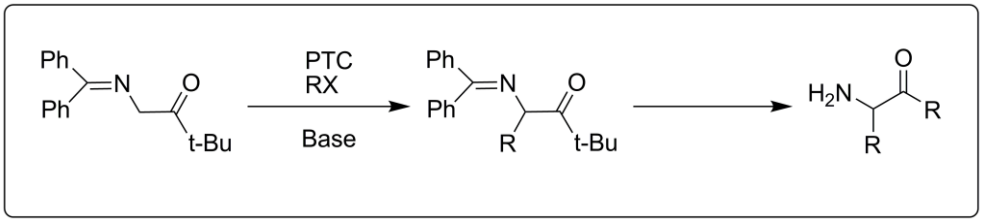


Fig.1.11: Electrophilic alkylations of glycine derivatives (Adapted from Ref. 1)

The most common methodology in this strategy involves the use of dimeric cinchona alkaloid ammonium salts as efficient phase transfer catalysts (PTC), to carry out enantioselective alkylations of glycinate derivatives. These imino esters can be further hydrolyzed to give rise to the desired α-amino acid derivatives. [15]

This method delineates a nucleophilic approach to derivatize glycine, as an α-anion equivalent of glycine is involved in the process.

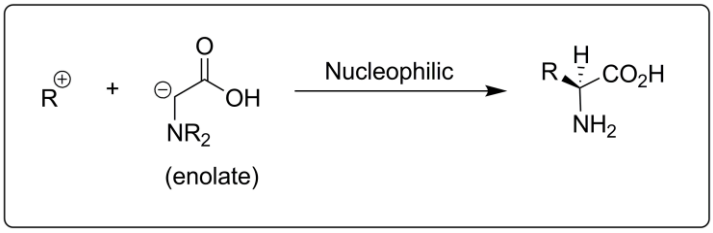


Fig.1.12: Nucleophilic approach for glycine derivatization (Adapted from Ref. 1)

The following catalysts are mostly used to for high enantioselection.

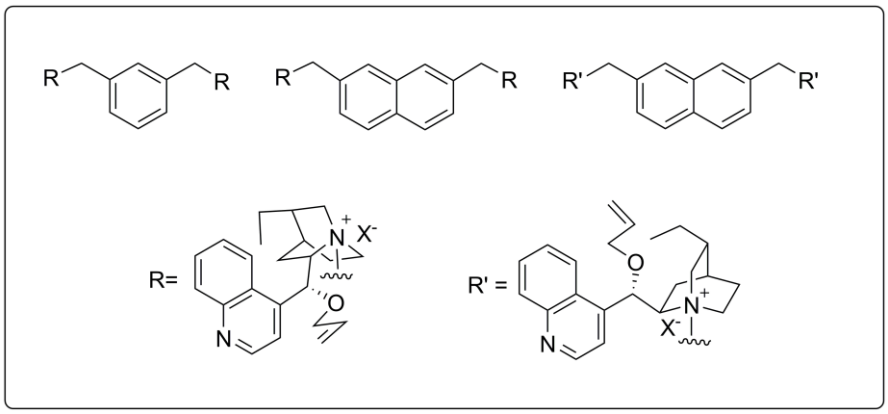


Fig.1.13: Catalysts used for electrophilic alkylation of glycines (Adapted from Ref. 15)

Limitations of the method:

- Reaction follows an S_N2 mechanism, and as a consequence, tertiary halides cannot be used to carry out the reaction. Thus, non-natural amino acids like- tert-leucine cannot be prepares using this method.
- Under basic reaction conditions, the ß- hydrogen containing quarternary ammonium salts of these phase transfer catalysts can be degraded in-situ to give Hofmann elimination product.
- To eliminate the second possibility, Maruoka et al. came up with a different catalyst design, where they used a spiro quarternary ammonium salt, bearing a simple chiral binaphthyl moiety and an achiral biphenyl substituent [1]

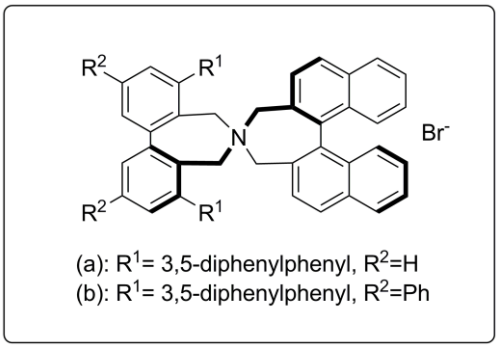


Fig.1.14: Maruoka's catalysts (Adapted from Ref. 1)

1.1.3.4 Enantioselective introduction of carboxy group:

The two important approaches that highlight this strategy are shown with the help of a schematic diagram below-

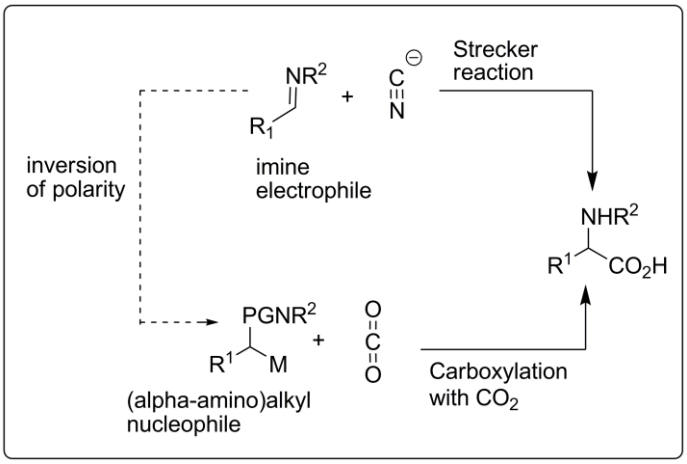


Fig.1.20: Enantioselective introduction of carboxy group (Adapted from Ref. 18)

One of them represents the well-known Strecker reaction and its modified versions. The other one portrays an umpolung (polarity inversion) strategy, where instead of using the electrophilic imine, nucleophilic α-amino alkyl anion equivalents are used. This two strategies and their limitations will be delineated in the next few pages.

1.1.3.4.1 Strecker reaction:

The original Strecker reaction involved a condensation reaction between an aldehyde, ammonia and a cyanide source and its subsequent hydrolysis of the resultant α-amino nitrile.[17]

In order to increase the enantioselectivity of the product obtained from this reaction, the Strecker reaction has been modified many times over the course of time.

The original Strecker reaction and its modified catalyzed versions are illustrated with the help of the following figures-

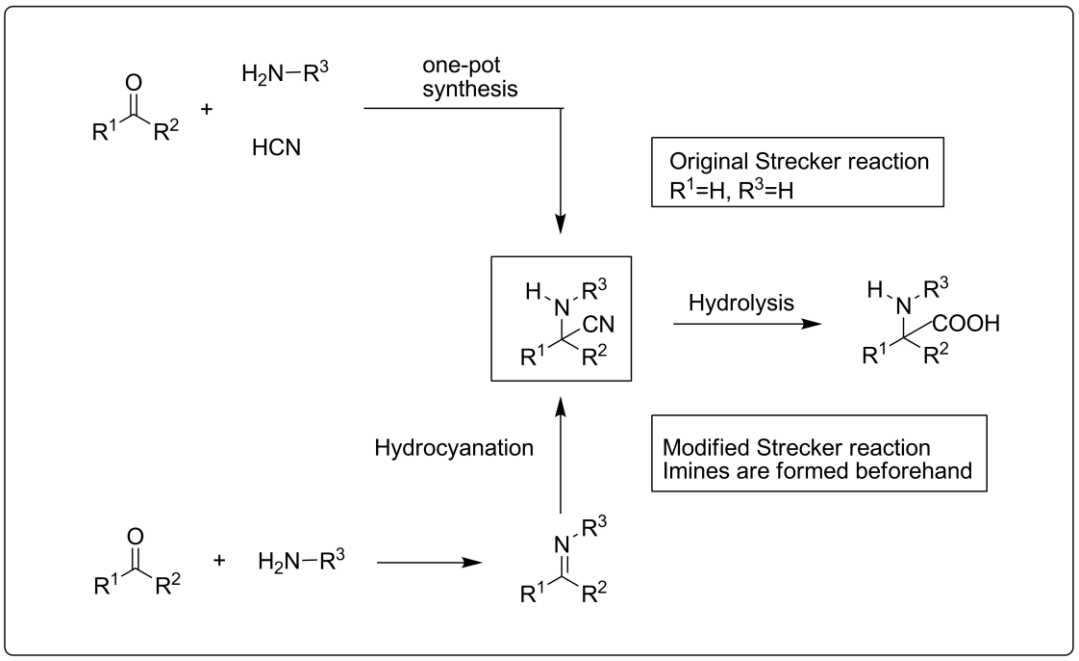


Fig.1.21: Original and modified versions of Strecker Reaction (Adapted from Ref. 17)

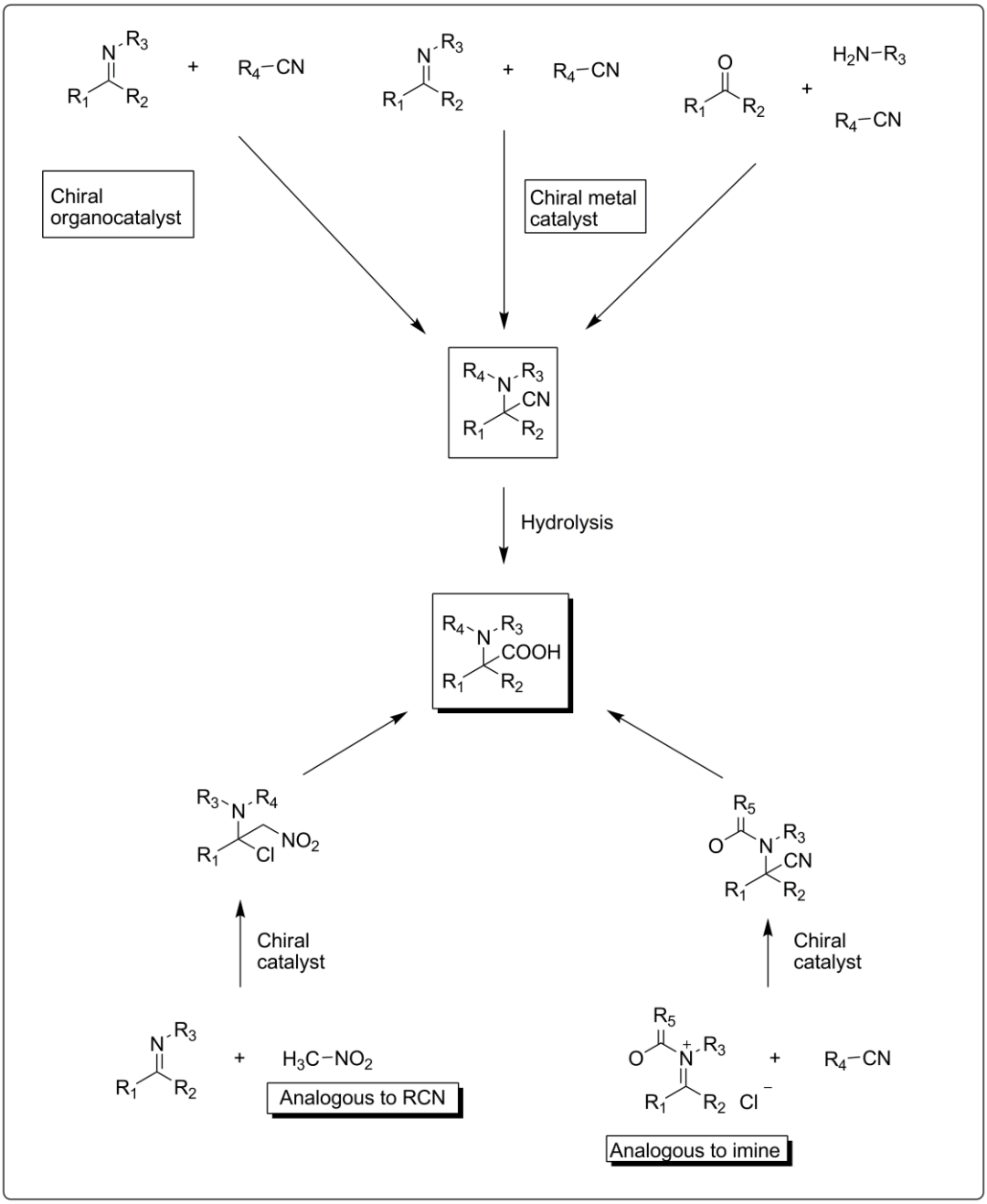


Fig.1.22: Asymmetric versions of Strecker Reaction (Adapted from Ref. 17)

Often chiral Gadolinium complexes and PyBOX-lanthanide complexes are used as organometallic catalysts for this reaction.

Recently, thiourea-based organocatalysts are used as bifunctional organocatalysts in order to carry out the asymmetric version of Strecker reaction. [6]

Limitations of Strecker reaction:

- Potassium cyanide or hydrogen cyanide which are used as cyanide sources for these reactions are extremely toxic.

1.1.3.4.2 Reductive carboxylation of imines with carbon dioxide:

Reaction:

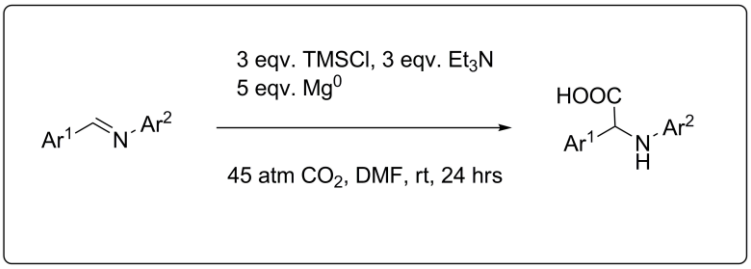


Fig.1.23: Reductive decarboxylation (Adapted from Ref. 18)

In this reaction, α-amino alkyl metal reagents generated by the reductive metallation of aryl imines are made to undergo reductive carboxylation with carbon dioxide to produce α-amino acids. [18]

Mechanism:

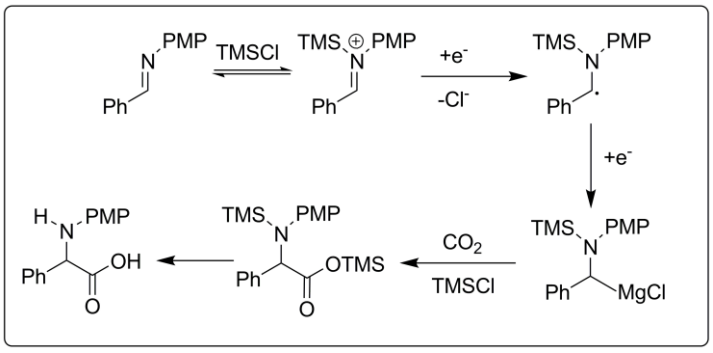


Fig.1.24: Mechanism for reductive decarboxylation (Adapted from Ref. 18)

The reaction proceeds by means of two single electron transfer events, followed by the incorporation of CO_2 to the resultant α-aminobenzyl magnesium chloride intermediate. [18]

Limitations of the method:

- Reaction cannot be performed with alkyl aldimines or ketimines. [18]
- Mesityl derivative of the imine gives a very low yield of the corresponding product, (20%) owing to steric reasons. [18]
- High pressure of CO_2 (45 atm) is needed to avoid the formation of side products. [18]
- α,α- disubsituted α-amino acids cannot be prepared.

1.1.4 Basis for the project:

Thus, the different approaches presented herein justify the importance of preparing chiral amino acids. However, the methods described above either affect the environment in an adverse way or they are restricted to the synthesis of only a certain class of amino acids. Hence, coming up with an environment friendly and holistic approach was deemed necessary in this regard.

In that respect, preparation of α-nitroesters was considered as a possible alternative, as they can be easily reduced to give rise to the corresponding α-amino acids.

However, using one of the procedures reported in literature where Pd-catalyzed cross coupling takes place between ethyl nitroacetates and aryl bromides, only preparation of α-aryl nitroesters was possible. [19]

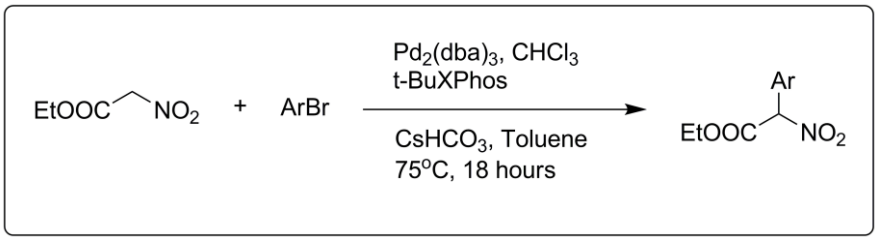


Fig.1.25: Preparation of aryl nitroesters

Besides, toxic organometallic catalysts and expensive biphenyl phosphine ligands were used for the reaction.[19]

In another procedure, nitroalkane was first treated with two equivalents of a strong base like LDA to generate a dianion, which was in turn esterified using methyl chloroformate. [20]

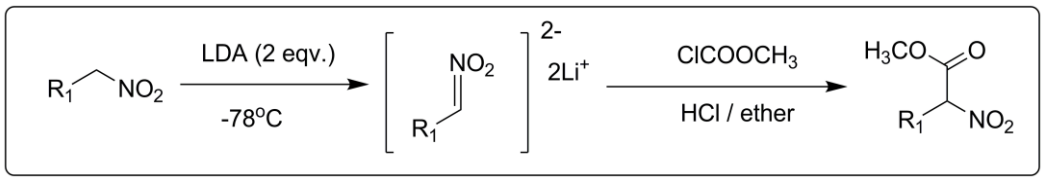


Fig.1.26: Preparation of α-nitroester derivatives using strong base

Here, though nitroester is produced (C-acylation takes place), yet this reaction also has serious limitations. These are as follows:

- Toxic reagent like methyl chloroformate has been used.
- Reaction takes place at very low temperature.
- Two equivalents of a very strong base have been used.

It has been previously reported in literature that nitroalkanes on treatment with ethyl chloroformate and a base, undergoes O-acylation instead of C-acylation and in turn forms nitrile oxide derivatives instead of α-nitroesters. [21]

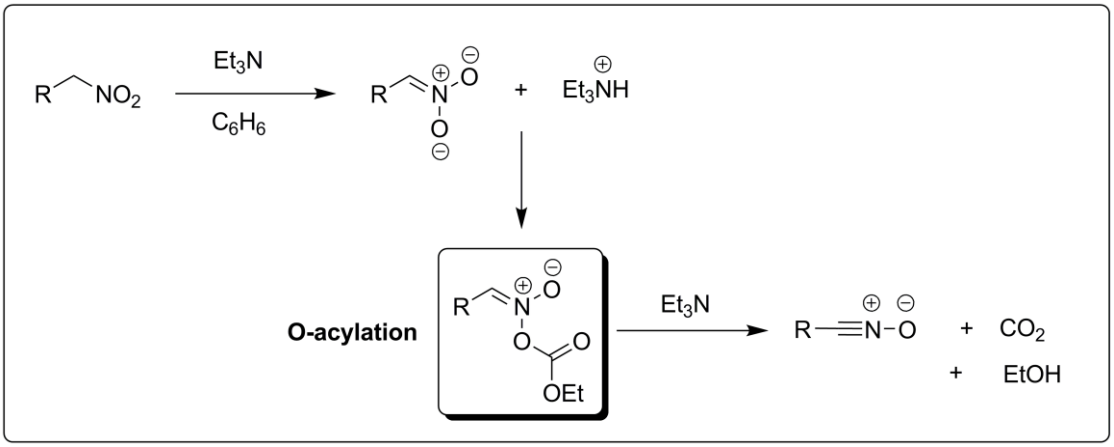


Fig.1.27: Formation of O-acylated product

It has also been shown that di tert-butyl carbonate on reacting with nitroalkanes in presence of a nucleophilic catalyst like DMAP (N,N-dimethyl aminopyridine), gives rise to nitrile oxides. [22]

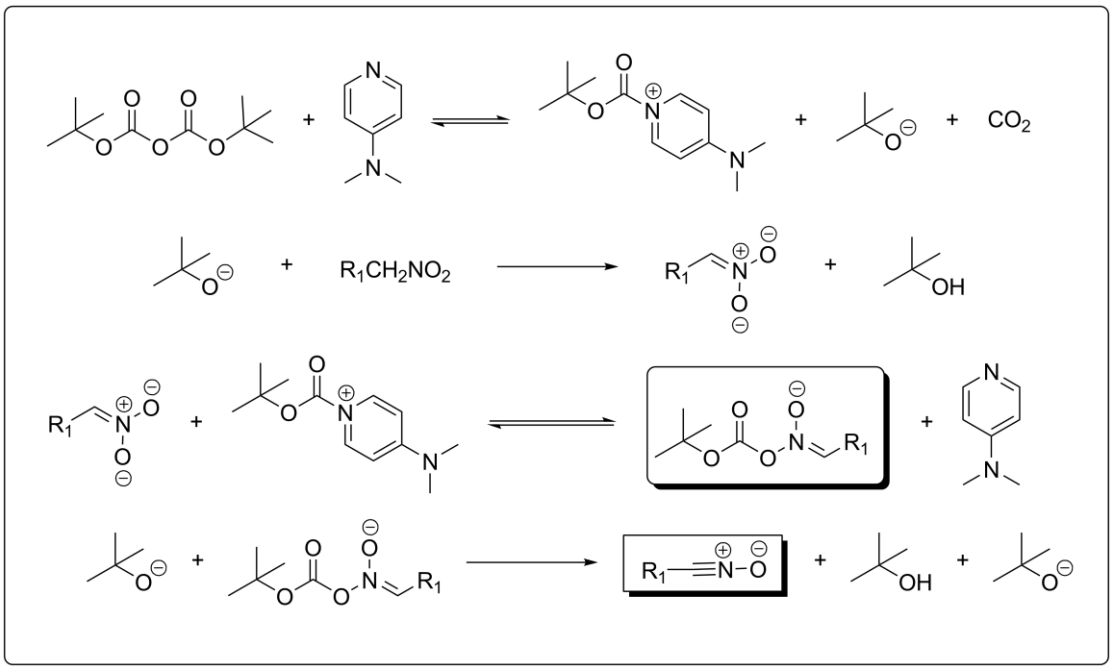


Fig.1.28: Preparation of nitrile oxides from di tert-butyl carbonate

The above examples clearly highlight the fact that the mononitronate ion, derived from the nitroalkane derivatives upon treatment with a base, forms the O-acylated product

(nitrile oxides), while the dinitronate ion forms the C-acylated product (α-nitro esters).Thus, keeping all these details in mind, a completely new methodology has been developed for the preparation of α-nitroesters. Here it has been shown that, even the mononitronate ion on reacting with phenyl benzyl carbonate, in presence of a nucleophilic catalyst like DABCO (1,4-diazabicyclo[2.2.2]octane), is capable of giving the C-acylated product.

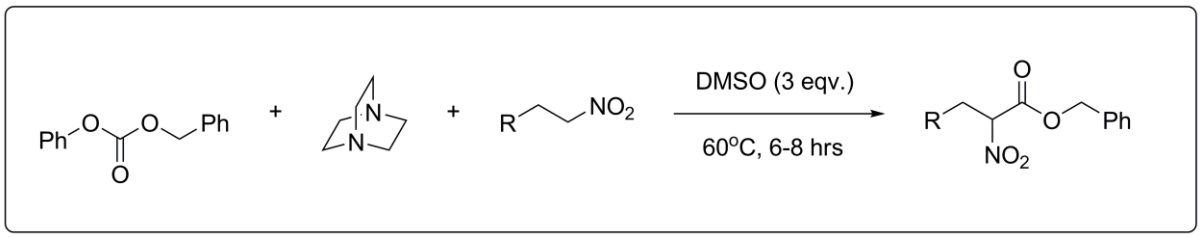


Fig.1.29: Preparation of α-nitroesters from phenyl benzyl carbonate

Taking into account the pKa values of phenol, nitroalkanes and protonated DABCO, the following mechanism has been proposed for the reaction.

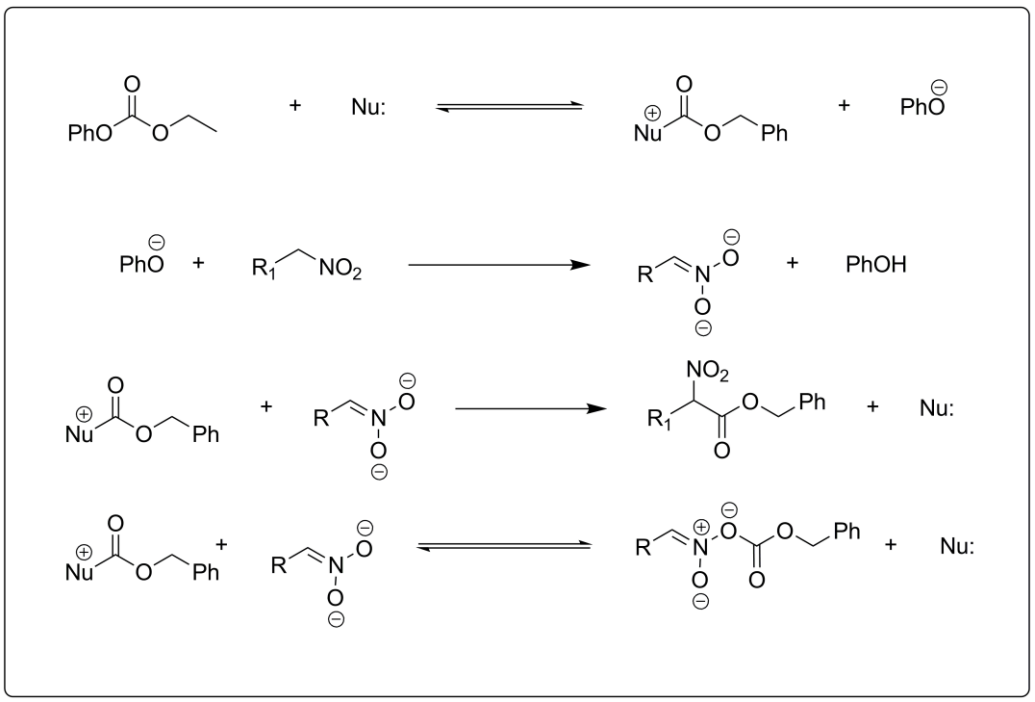


Fig.1.30: Mechanism of α-nitroester formation

Initially, phenyl benzyl carbonate reacts with DABCO and liberates the phenoxide ion. Phenoxide then serves as a base to deprotonate the nitroalkane and generates the mononitronate anion. Now, it is possible for the mononitronate anion to undergo C-acylation as well as O-acylation. However, only the C-acylated product is isolated. The following explanation is thus provided to account for the above observation.

DABCO (protonated DABCO has a pKa value of 8.9) can easily deprotonate the nitroester derivative, having a pKa value around 9. As a consequence, the C-acylation step is driven towards the forward direction, making it irreversible in nature. The O-acylation step, which is reversible in nature, also lies more towards the left hand side in order to facilitate the deprotonation of the nitroester derivative.

Hence, the C-acylated product (nitroester) gets formed in good yields.

My role in this project was to synthesize the nitroalkene and the corresponding nitroalkane derivatives. Apart from that, I have also prepared phenyl benzyl carbonate. Preparation of α-nitroesters and the α-amino acid derivatives have been done by my labmate, Mr. G. Ramana Reddy.

1.1.5 My role in the project: Preparation of nitroalkane derivatives:

Preparation of a diverse array of nitroalkane derivatives using a simple methodology is the most essential part of this project as these derivatives serve as the precursors for α-nitroesters, the most crucial intermediate needed for the synthesis of α-amino acids.

When we think about the preparation of nitroalkanes, it is easy to envisage a reaction between a nitronate anion and an alkyl or aromatic halide.

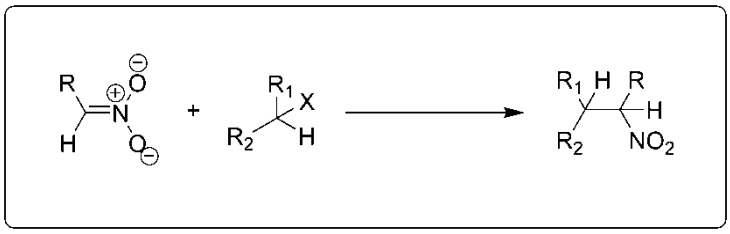


Fig.1.31: Reaction between nitronate anion and alkyl halide (Adapted from Ref. 23)

However, on drawing the resonance structure of a nitronate anion (ambident species), it immediately becomes evident that two modes of alkylation are actually present. [23]

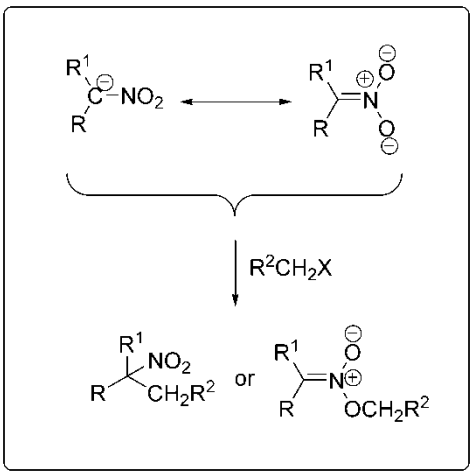


Fig.1.32: Two possible modes of alkylation (Adapted from Ref. 23)

Though the C-alkylation product is stable, the O-alkylation product i.e. the nitronic ester has never been isolated. Instead, the nitronic ester decomposes to aldehydes and oximes. [23]

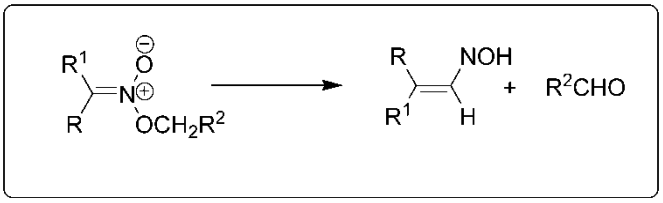


Fig.1.33: Decomposition of nitronic ester (Adapted from Ref. 23)

Haas and Bender in 1949 had observed that only p-nitrobenzyl chloride on reacting with sodium salt of 2-nitropropane yields the C-alkylated product. All the other benzylic halides resulted in the formation of aldehydes, obtained from the decomposition of the O-alkylated product as the major product.[24]

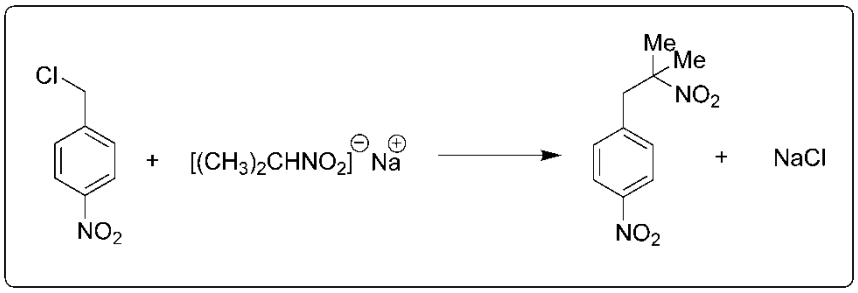


Fig.1.34: Formation of C-alkylated product from p-nitrobenzyl chloride

In order to explain this observation, Kornblum and co-workers came up with the following mechanism-

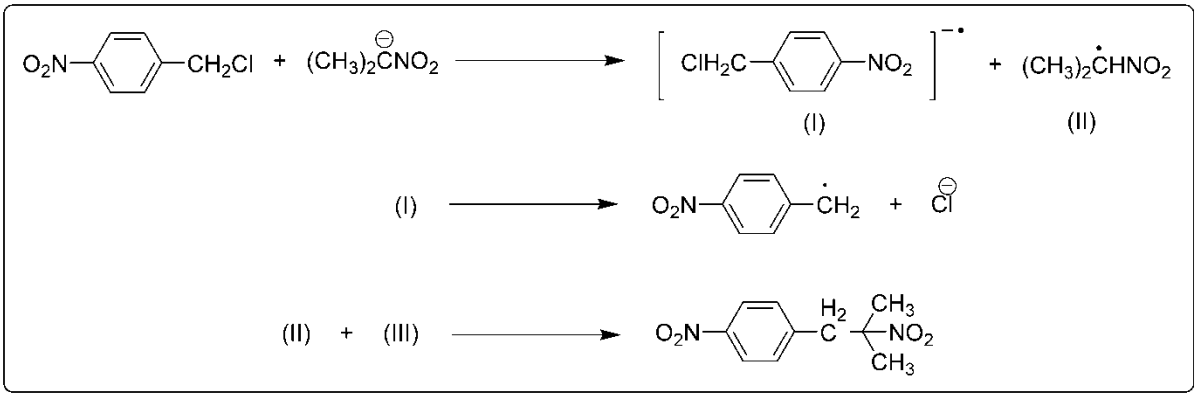


Fig.1.35: Mechanism involved (Adapted from Ref. 23)

They hypothesized that loss of chloride ion by an internal elimination from p-nitrobenzyl chloride radical anion produces an aromatic olefin, which is stable owing to its aromaticity. This sets p-nitrobenzyl chloride apart from the rest of the substrates. [23]

Apart from benzylic halides, reactions of allylic and aliphatic halides with nitro compounds also results in the formation of the O-alkylated product. [25] Thus, it is evident that this method is not at all a versatile one for the purpose of synthesis of nitroalkanes.

There are several other methods used for the synthesis of nitroalkenes. Some are metal-catalyzed while the others are devoid of toxic metal residues. Here, I will briefly describe few important methods used for nitroalkene synthesis, their drawbacks and the reason behind me choosing one particular method for preparing my substrates. Nitroalkenes once prepared, can be easily reduced using reducing agents such as sodium borohydride to give rise to the corresponding nitroalkane derivatives.

1.1.5.1 From olefins:

Nitroalkanes can be prepared from olefins, where one of the olefinic hydrogens is replaced by the nitro group. [26]

Reaction:

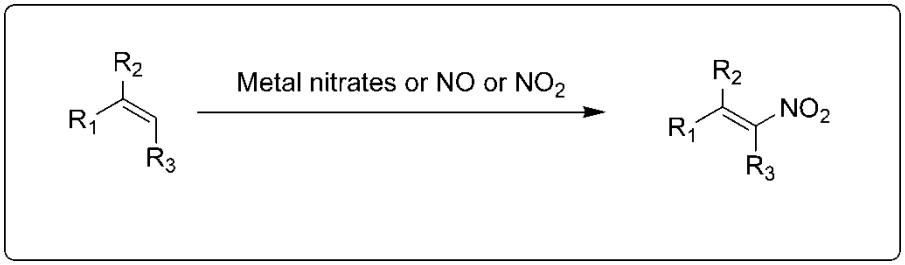


Fig.1.36: Preparation of nitroalkanes from olefins

1.1.5.1.1 Metal catalyzed reactions:

1.1.5.1.1.1 Using silver nitrate:

Here, silver nitrate was used as a catalyst for the preparation of nitroolefins.

Mechanism:

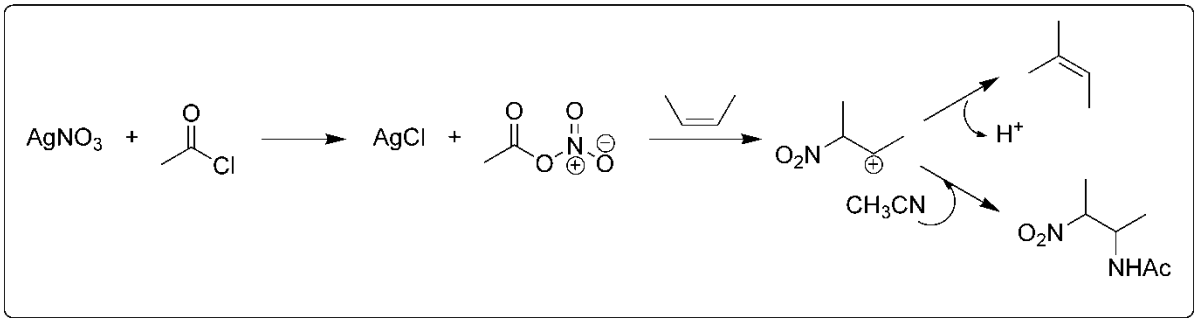


Fig.1.37: Mechanism involved

Here, acetyl chloride reacts with silver nitrate to generate acetyl nitrate, which can serve as an excellent source of nitronium ion. This species on reacting with an olefin and subsequently losing a proton generates the corresponding nitroalkane. The reaction takes place at room temperature.[27]

Limitations:

- Metal residues are used.
- Since, acetonitrile is used as a solvent system, it reasct with the secondary cation to generate nitroacetamides instead of nitroolefins. [27]

1.1.5.1.1.2 Using Silver nitrite and radical initiator (TEMPO):

Reaction:

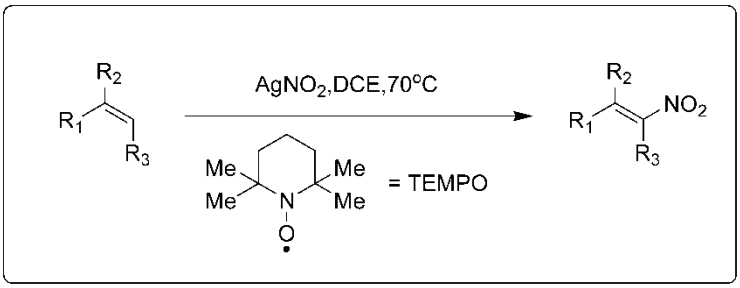


Fig.1.38 (Adapted from Ref. 23)

Here, silver nitrite is used in combination with a radical initiator, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to generate nitroolefins. [28]

Mechanism:

The possible mechanisms are shown in the next page-

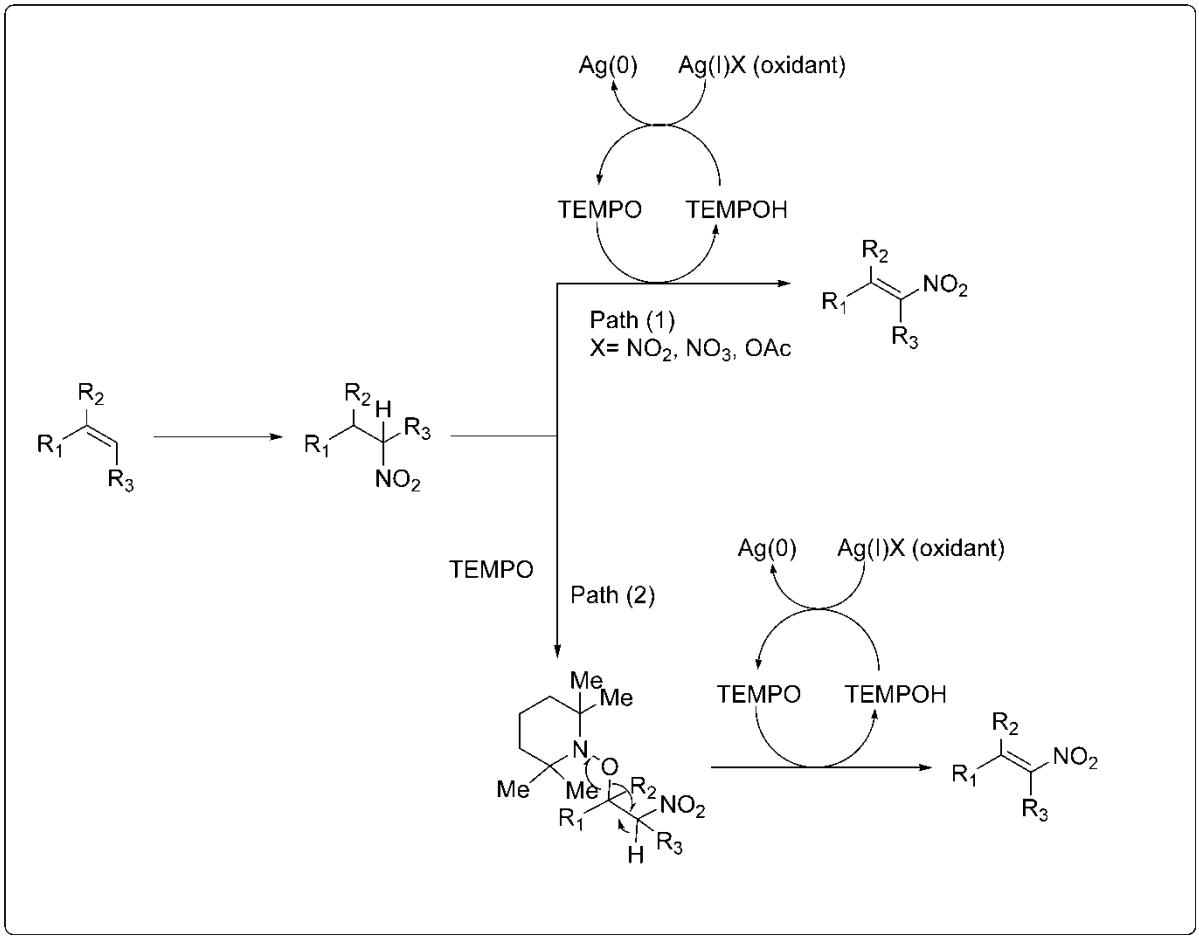


Fig.1.39: Mechanisms involved (Adapted from Ref. 23)

Limitations:

- Toxic metal residues involved.
- High temperature (70^{o}C) is needed. [28]

1.1.5.1.2 Reactions without metals:

1.1.5.1.2.1 Using nitrous oxide:

Here, nitroalkenes are prepared from nitrous oxides (2 atm pressure) and olefins at room temperature under aerobic conditions. [29]

Reaction:

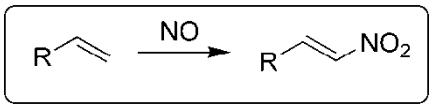


Fig.1.40: Preparation of nitroalkene from nitrous oxide

Mechanism:

The mechanism of the reaction is as follows-

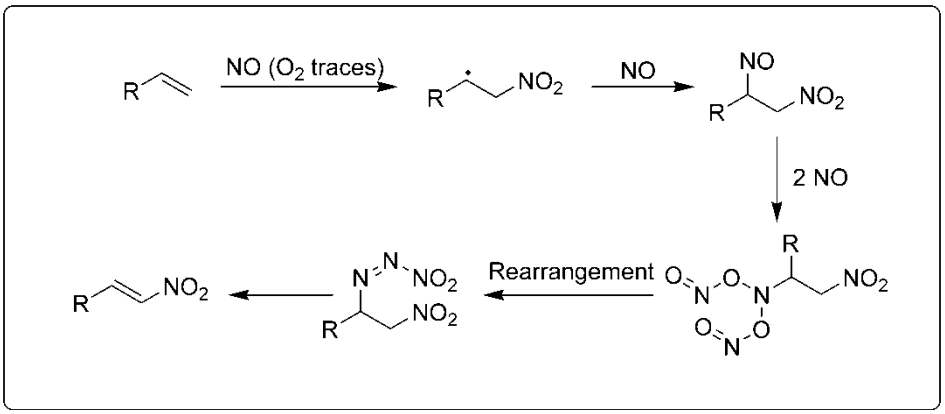


Fig.1.41: Mechanism involved (Adapted from Ref. 29)

Limitations:

- Nitrous oxide which is used in the reaction can interact with Vitamin B_{12} present in the human body and thus inhibit the action of methionine synthase, a key enzyme in folate metabolism. As a consequence, long-term exposure to nitrous oxide can cause bone-marrow depression and neurological problems. [30]

- The reaction is extremely temperature and pressure sensitive. Increasing the temperature and varying the pressure drastically reduces the yield of the product. [29]

1.1.5.1.2.2 Using tert-butyl nitrite and TEMPO:

Reaction:

Here, tert-butyl nitrite reacts with olefins in presence of catalytic amounts of TEMPO and under aerobic conditions to give nitroolefins. Here, harsh reaction conditions are not used. [26]

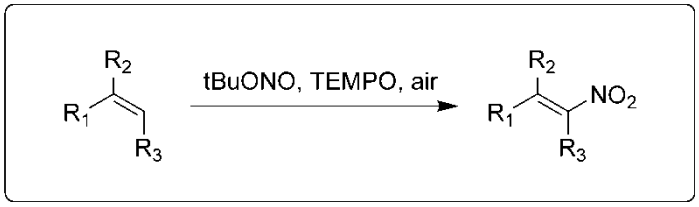


Fig.1.42: Reaction with t-butyl nitrite

Mechanism:

The mechanism is shown with the help of the following schematic diagram-

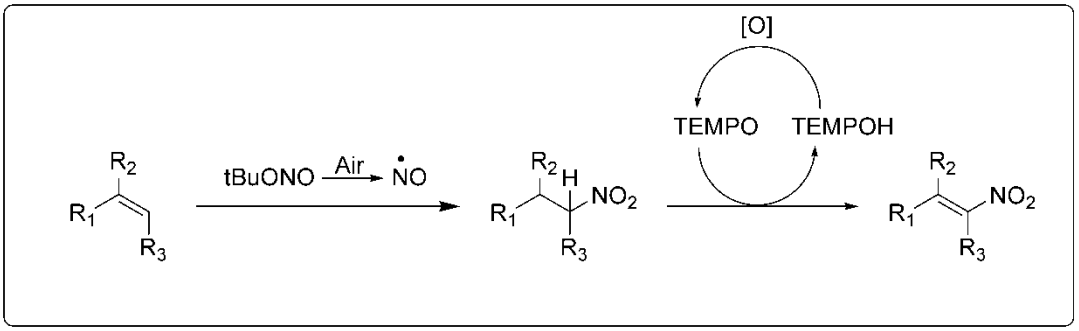


Fig 1.43: Mechanism involved

Limitations:

- Though this method is metal-free and has a wide substrate scope, yet, it is not without limitations. The radical initiator TEMPO that is used in this reaction is highly corrosive to skin.
- Elevated temperatures (90^oC) are required for this reaction to occur. [26]

1.1.5.2 From carbonyl compounds:

The main reaction of this type involves an Aza-Henry reaction (nitroaldol reaction) between a carbonyl compound and a nitroalkane followed by dehydration to give the nitroolefin.

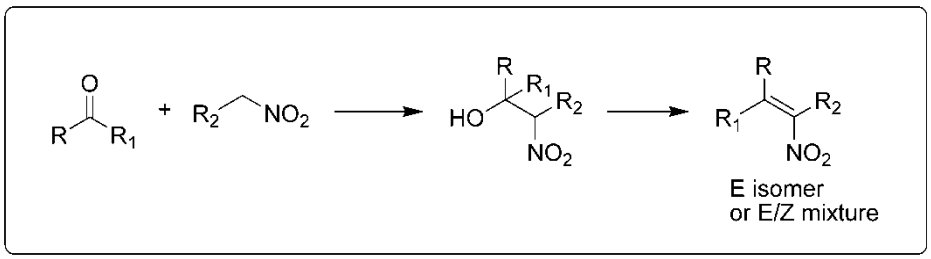


Fig.1.44: Aza-Henry reaction

The asymmetric versions of the nitroaldol reaction are very popular, as it is possible to selectively prepare one stereoisomer over the other with certain catalysts. There are metal-catalyzed as well as organocatalyzed versions of this reaction, involving Copper and Zinc based catalysts on one hand and bifunctional catalysts like Guanidine or thiourea based catalysts on the other. [31]

The resultant ß-nitroalcohol derivative is then subjected to dehydration conditions to obtain the nitroolefins as a mixture of (E) and (Z) isomers. [32]

There are methods to prepare either (E) or (Z) isomers in a stereoselective way as well [32], but that is not our concern.

In any case, it is the (E)-isomer which is formed as a major product, upon dehydration of nitroalcohols. [33]

Thus, upon considering the pros and cons of all the procedures related to the formation of nitroolefins, we decided to follow the protocol involving the Aza-Henry reaction, as it has the largest substrate scope and it deals with inexpensive, commercially available, non-toxic starting materials. The reaction conditions are also mild enough.

1.2 Results and Discussions

1.2.1 Synthesis of Nitroalkanes:

I have prepared the following nitroalkanes. Preparations of these nitroalkanes comprise a two-step process. The first step involves the synthesis of nitroalkenes from the corresponding aldehydes and the second step involves the reduction of the nitroalkene derivatives to give the desired nitroalkanes. In this section, briefly I will describe the methods of preparation of these compounds, the limitations of some of the reported procedures and the measures that I had taken to overcome those problems. A detailed description of the methods is given in the next section.

1.2.1.1 Preparation:

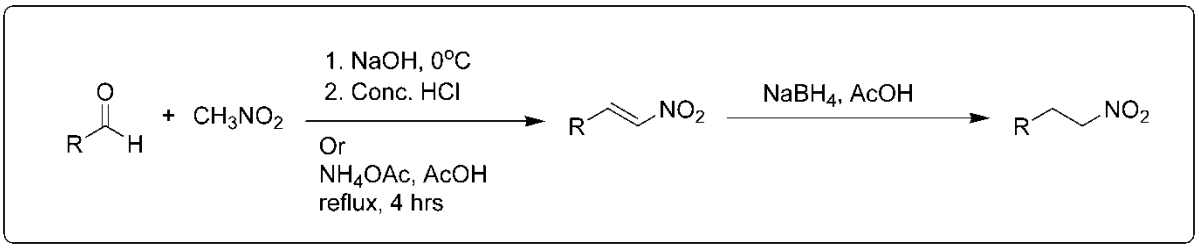


Fig.1.45: General methods for synthesis of nitroalkanes

NH_4OAc: Ammonium acetate; NaOH: Sodium hydroxide; AcOH: Acetic acid; $NaBH_4$: Sodium borohydride

1.2.1.1.1 2-(nitroethyl)benzene:

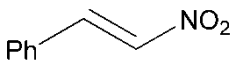


Fig.1.46

For 2-(nitroethyl)benzene, commonly known as ß-phenyl nitroethane, a reported procedure has been followed. The commercially available trans ß-nitrostyrene has been reduced by sodium borohydride in DMSO (dimethyl sulphoxide) in presence of acetic acid to give the nitroalkane in good yield.[34] No modification was required for this procedure.

1.2.1.1.2 2-(2-nitroethyl)naphthalene:

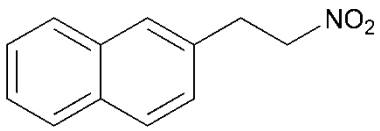


Fig.1.47

For preparing the nitroalkene derivative of 2-naphthaldehyde, the reported procedure involved refluxing a reaction mixture containing 2-naphthaldehyde, ammonium acetate, acetic acid and nitromethane for 4 hours. Since, boiling point of acetic acid is 118^{o}C and reluxing nitromethane at this temperature may lead to an explosion, hence, this procedure was abandoned. [35] Nitroalkene was thus prepared by taking 2-naphthaldehyde, nitromethane and methanol in a round bottom flask and then adding sodium hydroxide to this mixture at 0^{o}C. Preparation of nitroalkane was then performed in a way analogous to the one mentioned for 2-(nitroethyl)benzene.

1.2.1.1.3 2-(2-nitroethyl)thiophene:

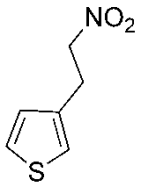


Fig.1.48

In order to prepare the nitroalkene derivative for thiophene-3-carboxaldehyde, a reported procedure has been followed, which is similar to the preparation of the nitroalkene derivative of naphthaldehyde .[36] However, in literature, the reduction reaction had been performed using catalytic amounts of Rhodium complexes by means of a transfer hydrogenation mechanism. [37] In order to avoid the presence of toxic metal based catalyst, the reduction reaction was performed using sodium borohydride, acetic acid and DMSO. Here, only 40% yield was observed for the reduction, while the reported yield was 84%. [37] Thus, though the yield has been compromised to a great extent, yet this method offers an environmentally benign way of reducing the nitroalkane derivative as compared to its metal-catalyzed counterpart.

1.2.1.1.4 1-methyl-4-(2-nitroethyl)benzene:

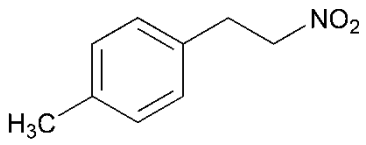


Fig.1.49

Again, the synthesis of the nitroolefin derivative of tolualdehyde has been carried out either by using a metal-catalyzed pathway [38] or by refluxing the aldehyde, ammonium acetate, acetic acid and nitromethane for 4 hours [39]. In these two cases, 94% yield and 44% yield have been obtained respectively. [38,39] Since, both the methods have shortcomings, one involving the usage of toxic metal-based catalyst and the other involving the refluxing of nitromethane at high temperatures, hence, 1-Methyl-4-(2-nitrovinyl)benzene has been prepared by using tolualdehyde, nitromethane and sodium hydroxide (NaOH) followed by the addition of 6(N) HCl (hydrochloric acid).

The problem that I had encountered while doing this reaction is that, on adding NaOH to the reaction mixture at 0^{o}C, white solid (most likely tolualdehyde) used to crash out. Thus, as the amount of aldehyde in the solution decreased, poor yields were obtained

(23%) as compared to the reported procedures. Besides, on performing column chromatography using

DCM/hexane (15:85) as the eluent, quite a few fractions were obtained which contained a mixture of the unreacted aldehyde and the nitroalkene derivative. This resulted in a further decrease of yield.

According to literature, reduction of the nitroolefin derivative has been carried out by using organometallic reagents like tributyltin hydride [40] or by using a combination of organocatalysts like Hantzsch esters and S-benzyl isothiouronium chloride [41]. As these compounds are either toxic or they are not easily available, hence, reduction of the nitroolefin was done by using sodium borohydride and acetic acid in DMSO.

1.2.1.1.5 1,2-dimethoxy-4-(2-nitroethyl)benzene:

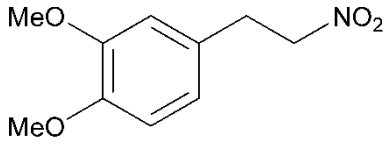


Fig.1.50

While preparing the nitroalkene derivative of 3,4-dimethoxybenzaldehyde, lots of problems were encountered. A procedure where refluxing of nitromethane was involved, was not followed because of reasons mentioned before. [42] However, when nitroolefin was synthesized using sodium hydroxide, veratraldehyde (3,4-dimethoxybenzaldehyde) and nitromethane, as reported in the literature [36], the prepared nitroalkene was found to be impure, as a small shoulder was found to be present in the proton NMR spectrum of the compound along with a singlet peak corresponding to three methyl protons. Another shoulder was also found to be present in two of the multiplets present in the aromatic region of the ^{1}H NMR spectrum.

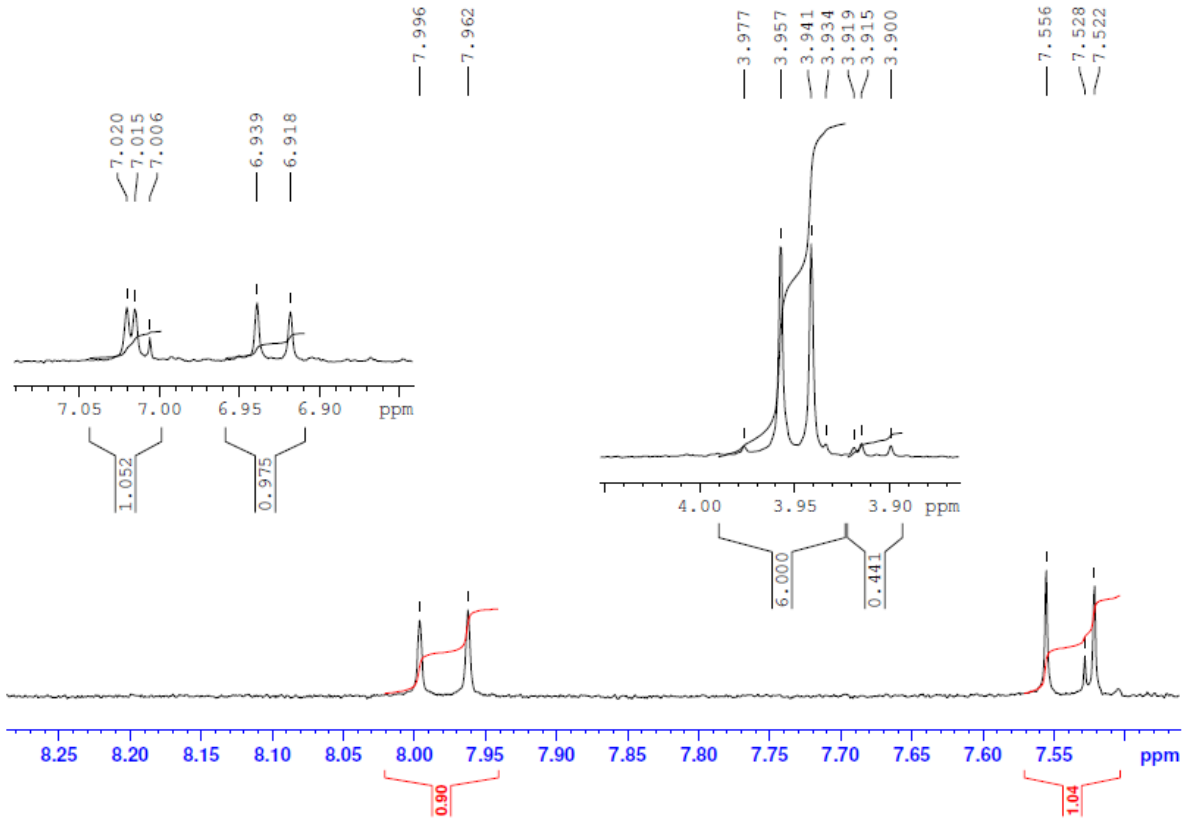


Fig.1.50

After recrystallizing the nitroalkene derivative from ethanol and toluene successively, the intensities of these shoulder peaks were found to decrease, but they did not vanish entirely. Finally, when the nitroalkene was dissolved in minimum volume of toluene and recrystallization was performed using vapour diffusion method taking hexane as the solvent with lower boiling point, then the impurity peaks completely disappeared. Reduction reaction was then performed according to the reported procedure by taking sodium borohydride as the reducing agent. Here, methanol:DCM (1:1) was used as the solvent system instead of dimethyl sulphoxide (DMSO). [43]

1.2.1.1.6 1-chloro-2-(2-nitroethyl)benzene:

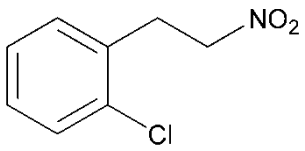


Fig.1.51

The nitroalkene derivative of 2-chlorobenzaldehyde was synthesized in the same way as the other nitroalkene derivatives. [36] However, as the boiling point of this compound is quite less, hence, it cannot be kept under vaccum for the complete removal of solvent. Reduction with sodium borohydride, isopropanol and silica gel resulted in the formation of nitroalkanes with very less yields. [44] Thus, reduction was performed in the same way as mentioned before.

1.2.1.1.7 3-(2-nitroethyl)indole:

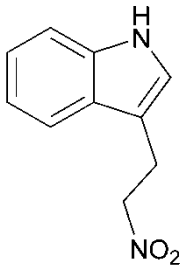


Fig.1.52

For the synthesis of the nitroolefin of indole-3-carboxaldehyde, the procedure involving sodium hydroxide and nitromethane did not work out. So, a procedure dealing with the refluxing of aldehyde, ammonium acetate, acetic acid and nitromethane for 45 minutes at 105^{o}C was followed. [45] The purification of the nitroalkene derivative was performed using flash column chromatographic technique on silica gel and it was found that the produced nitroolefin has a tendency of getting decomposed on silica. Thus, flash column for the compound was finished within 20 minutes, to ensure minimum decomposition.

Reduction of the nitroalkene derivative was performed in a way similar to the ones mentioned previously.

1.2.2 Synthesis of carbonates:

I had prepared three carbonates namely- phenyl benzyl carbonate, 2-methyl propyl phenyl carbonate, 1,1-dimethylethyl phenyl carbonate.

1.2.2.1 Preparation:

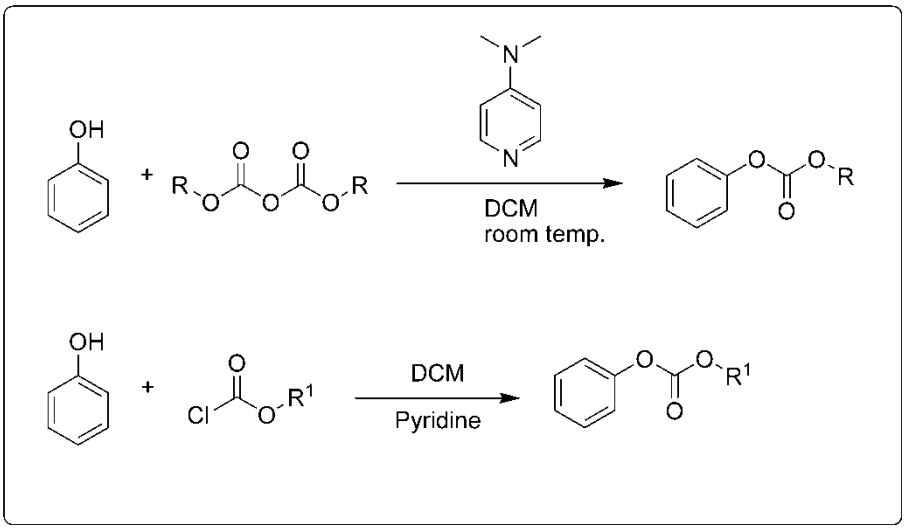


Fig.1.53: General methods for the synthesis of carbonates

1.2.2.1.1 Phenyl benzyl carbonate:

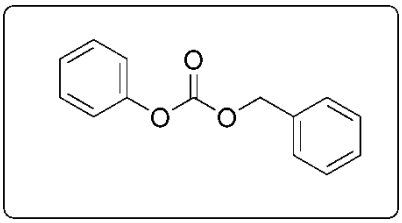


Fig.1.54

Phenyl benzyl carbonate was prepared according to a procedure reported in literature. [46] However, in literature, a combination of phenyl chloroformate and benzyl alcohol was used, while I used a combination of benzyl chloroformate (1 equiv.) and phenol (1 equiv.). Both the combinations yielded the same product. Pyridine (1.1 equiv.) was used as a base for the

reaction. I used copper sulphate solution to remove the excess pyridine during workup, as otherwise it has to be removed through column chromatography and that is not advisable owing to the toxic nature of pyridine. In the reported procedure, this step was not mentioned.

1.2.2.1.2 2-methyl propyl phenyl carbonate:

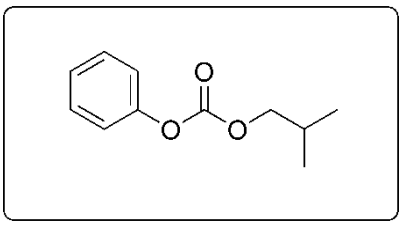


Fig.1.56

2-methyl propyl phenyl carbonate, commonly known as isobutyl phenyl carbonate was also prepared in a manner analogous to the preparation of phenyl benzyl carbonate.

1.2.2.1.3 1,1-dimethylethyl phenyl carbonate:

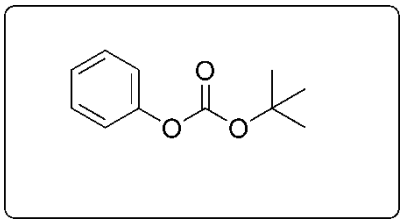


Fig.1.57

1,1-dimethylethyl phenyl carbonate was prepared from ditert-butyl carbonate and phenol in presence of N,N-dimethylaminopyridine at room temperature, according to a previously reported procedure [47] 1,1-dimethylethyl phenyl carbonate is commonly known as tert-butyl phenyl carbonate.

1.2.3 Future Directions:

- It remains to be seen whether α-nitroesters can be prepared from isobutyl phenyl carbonate and ditert-butyl carbonate. The role of solvent in the preparation of nitroesters also needs to be studied, as it was seen that on using ethyl acetate as a solvent, α-nitroesters could not be generated from these two carbonates.
- Substrate scope for nitroalkanes should be increased. At present, my labmate Mr. G. Ramana Reddy is trying to prepare the nitroalkane derivative of pyridine-3-carboxaldehyde.
- Acylation of phenyl nitromethane needs to be carried out. Preparation of phenyl nitromethane was found to be exceedingly difficult, as the reaction between benzaldehyde oxime and oxone (in presence of phosphate buffer) produces phenyl nitromethane in only 11% yield. [48]
- Preparations of α-nitroesters from substituted phenyl benzyl carbonates need to be carried out.
- Preparation of α-amino phosphonic acids is also an interesting prospect.

1.3 Experimental section:

1.3.1 General Experimental Methods:

All the reactions were performed under a positive pressure of Argon, using oven dried glassware equipped with magnetic stirbar. Moisture sensitive reagents were handled using standard Schlenk techniques. Solvents were dried and distilled prior to use.

Progress of the reactions was monitored using thin layer chromatography using commercial Aluminium-backed silica gel plates. TLC spots were viewed under Ultraviolet light and by heating the TLC plate after immersing it in potassium permanganate stain. Products were purified using flash column chromatographic techniques using silica gel of mesh size 200-400.

^{1}H NMR spectra were recorded on a 400 MHz Fourier transform NMR spectrometer with $CDCl_3$ as solvent. Chemical shift values were reported in δ ppm (parts per million) values, using the residual solvent protons as internal standard (δ = 7.2700 for $CDCl_3$ in Proton NMR). Coupling constants were reported as J values in Hertz (Hz).The following abbreviations were used while reporting ^{1}H NMR spectra- brs: broad singlet; s: singlet; d: doublet; t: triplet; m: multiplet; dt: doublet of triplet; dd: doublet of doublet.

1.3.2 Preparation of nitroalkanes:

1.3.2.1 Detailed synthetic procedures:

Since, all these nitroalkane derivatives have been previously reported and the spectral data of the synthesized compounds are found to match with those reported in literature, hence only the ^{1}H NMR spectra of the nitroalkanes have been delineated here.

1.3.2.1.1 2-(nitroethyl)benzene:

Fig.1.58

A 25 mL round bottom flask was charged with 1.2385g (8.3037 mmol; 1 equiv.) of commercially available ß-nitrostyrene, under Argon atmosphere. To this flask, 7 mL of DMSO (dimethyl sulphoxide) was added followed by the addition of 950 µL (16.5953 mmol; 1.9985 equiv.) of acetic acid. The reaction mixture was then kept in water bath and 505 mg (13.289 mmol; 1.6 equiv.) of sodium borohydride was added to it in five portions. The reaction mixture was then stirred at room temperature for 30 mins. Progress of the reaction was monitored using TLC. The reaction mixture was diluted with 50 mL of ethyl acetate and the organic layer was washed successively with 50 mL water, 50 mL of saturated solution of sodium bicarbonate and 50mL brine solution. The organic layer was then dried over sodium sulphate. It was concentrated and product was purified by flash column chromatography on silica gel using ethyl acetate/hexane (2:98) as an eluent to afford 666.5 mg of yellow oil. (53% yield). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.37-7.28 (m, 3H), 7.23-7.21 (m, 2H), 4.62 (t, J=7.4Hz, 2H), 3.33 (t, J= 7.4Hz, 2H).

1.3.2.1.2 2-(2-nitroethyl)naphthalene:

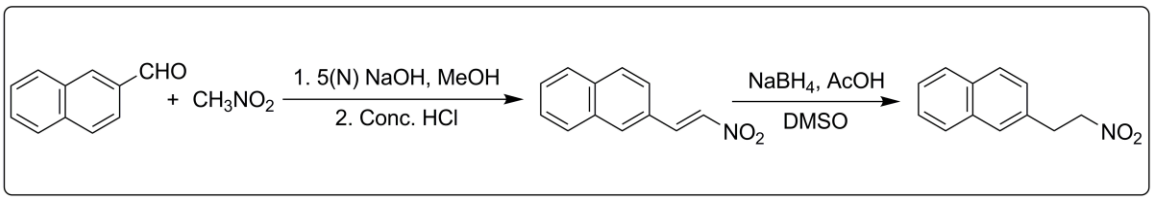


Fig.1.59

A 10 mL round bottom flask was charged with 1.5g of 2-naphthaldehyde (9.604 mmol; 1.0 equiv.) and 520 µL of nitromethane (9.687 mmol; 1.0086 equiv.) under Argon atmosphere. Then 2.5 mL of methanol was added to the reaction mixture. The mixture was cooled to 0^{o}C and 2.5 mL of 5(N) NaOH (sodium hydroxide) was added dropwise. Progress of the reaction was monitored using TLC. Reaction was stopped after 3 hours as further consumption of naphthaldehyde was not observed. The contents of the flask were then poured into a 100 mL beaker containing 10 mL water and 12 mL of 12(N) HCl. Formation of yellow precipitate was observed. The entire reaction mixture was then transferred to a 500 mL separating funnel using water and dichloromethane (DCM). The aqueous layer was then washed with (50X3 mL) of DCM and the combined organic layers were dried over sodium sulphate transferred to a 25mL flask and was concentrated. Upon performing column chromatography using DCM-hexane (20:80) as the eluent, mostly a mixture of nitroalkene and naphthaldehyde was obtained and the bottom impurities were removed. This mixture was then directly reduced to give the corresponding nitroalkane without further purification.

A 25 mL round bottom flask was charged with 3.5815g (17.80 mmol (approx.); 1 equiv.) of the mixture containing nitroalkene and naphthaldehyde, under Argon atmosphere. To this flask, 19 mL of DMSO was added followed by the addition of 2.2 mL (38.43 mmol; 2.159 equiv.) of acetic acid. The reaction mixture was then kept in water bath and 1.69g (44.47 mmol; 2.5 equiv.) of sodium borohydride was added to it in ten portions. The reaction mixture was then stirred at room temperature for 30 mins. Progress of the reaction was monitored using TLC. Then, the reaction mixture was diluted with 50 mL of ethyl acetate and the organic layer was washed successively with 50 mL water, 50 mL of saturated solution of sodium bicarbonate and 50mL brine solution (workup procedure). The organic layer was dried over sodium sulphate. It was concentrated and product was purified by flash column chromatography on silica gel using DCM/hexane (20:80) as an eluent to afford 753.9 mg of white solid. (39% yield; here the yield is a combined yield obtained after performing two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.79 (m, 3H), 7.6798 (brs, 1H), 7.53-7.46 (m, 2H), 7.34-7.32 (m, 1H), 4.72 (t, J=7.4Hz, 2H), 3.50 (t, J= 7.4Hz, 2H).

1.3.2.1.3 2-(2-nitroethyl)thiophene:

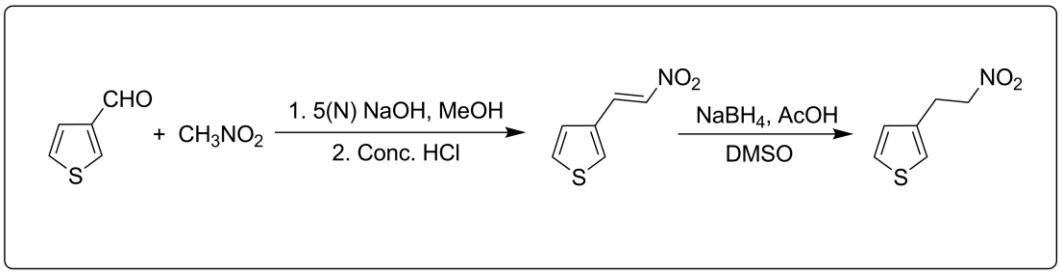


Fig.1.60

The procedure followed is exactly the same as the one mentioned for the preparation of 2-(2-nitroethyl)naphthalene, except for the fact that while preparing the nitroalkene derivative , the reaction mixture was stirred for 4 hours instead of 3 hours. Here, 920mg (8.203 mmol) of thiophene-3-aldehyde was taken as the starting material and 1.3608 g of a mixture of the nitroalkene derivative and the aldehyde was obtained, which was directly reduced without further purification. Flash column chromatography was performed on silica gel for the purification of the nitroalkane product. Ethyl acetate/hexane (2:98) was used as an eluent to afford 449.2 mg of yellow oil. (35% yield; here the yield is a combined yield obtained after performing two steps). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.33-7.31 (m, 1H), 7.09-7.08 (m, 1H), 6.97-6.95 (dd, 1H), 4.72 (t, J=7.4Hz, 2H), 3.50 (t, J= 7.4Hz, 2H).

1.3.2.1.4 1-methyl-4-(2-nitroethyl)benzene:

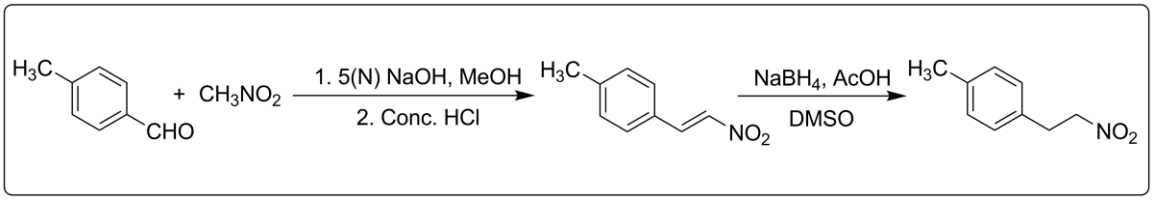


Fig.1.61

The procedure for the synthesis of 1-methyl-4-(2-nitroethyl)benzene is also the same as the above two procedures. The first reaction involving the synthesis of the nitroalkene derivative was stopped after 1hour. 520 µL (12.552 mmol) of tolualdehyde was taken as the starting material. 2.4188 g of a mixture of the nitroalkene derivative and the aldehyde was obtained, and it was directly reduced without further purification. On obtaining the crude nitroalkane derivative from the sodium borohydride reduction reaction, flash column chromatography was performed on silica gel using DCM/hexane (15:85) as the eluent. 479.1 mg of the pure nitroalkane was obtained (23% yield; here the yield is a combined yield obtained after performing two steps). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.16-7.09 (m, 4H), 4.72 (t, J=7.4Hz, 2H), 3.50 (t, J= 7.4Hz, 2H), 2.338 (s, 3H).

1.3.2.1.5 1,2-dimethoxy-4-(2-nitroethyl)benzene:

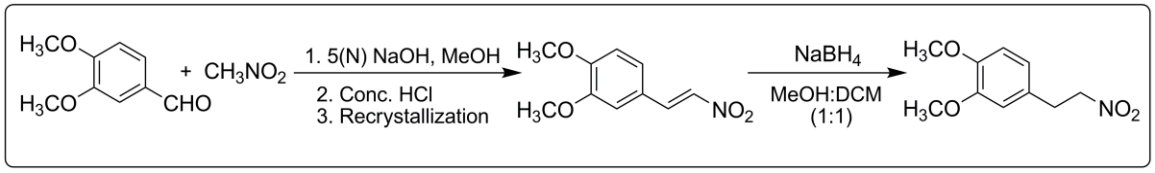


Fig.1.62

A 10 mL round bottom flask was charged with 3g of 3,4-dimethoxybenzaldehyde (18.05mmol; 1.0 equiv.) and 1 mL of nitromethane (18.629 mmol; 1.032 equiv.) under Argon atmosphere. Then 18 mL of methanol was added to the reaction mixture. The mixture was cooled to 0^{o}C and 18 mL of 5(N) NaOH (sodium hydroxide) was added dropwise. Progress of the reaction was monitored using TLC. Reaction was stopped after 3 hours as further consumption of aldehyde was not observed. The contents of the flask were then poured into a 100 mL beaker containing 20 mL water and 24 mL of 12(N) HCl. Formation of yellow precipitate was observed. Instead of extracting with DCM, the precipitate was dissolved in minimum volume of toluene. It was then made to undergo

recrystallization using hexane as the low boiling solvent system. The recrystallization setup was kept aside for two days and after that the solution was filtered and the residue

(yellow crystals) was washed with ethanol. The crystals were then dried under vacuum and upon checking the corresponding proton NMR, the formation of the pure nitroalkene derivative was confirmed.

808.4 mg (3.864 mmol) of nitroalkene was obtained, which was subjected to sodium borohydride reduction using 1:1 methanol:DCM as the solvent system instead of DMSO. After workup, flash column chromatography was performed using DCM/hexane (80:20) as the eluent to afford 520.1 mg of yellow oil as the product. (Yield of the first step: 28%; Yield of the second step: 63.7%)

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 6.83-6.82 (m, 1H), 6.77-6.71 (m, 2H), 4.59 (t, J=7.4Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.28 (t, J= 7.4Hz, 2H).

1.3.2.1.6 1-chloro-2-(2-nitroethyl)benzene:

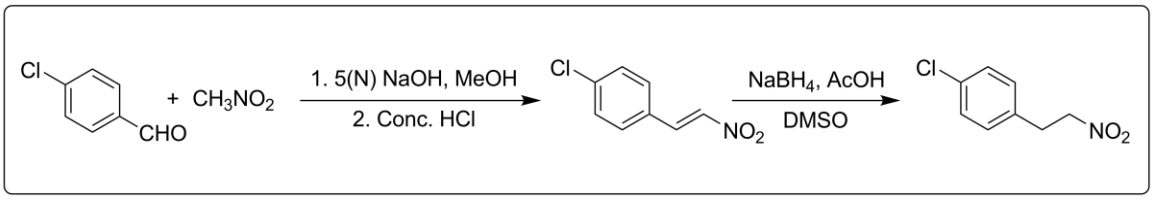


Fig.1.63

The procedure for the preparation of the above nitroalkane is analogous to the procedures used for the preparation of the nitroalkane derivatives of naphthaldehyde and thiophene-3-carboxaldehyde. Here, 1.5 g (9.64 mmol) of 2-chlorobenzaldehyde was used as starting material. Finally, after reduction with sodium borohydride and purification by means of column chromatography, 1.0123g of the nitroalkane derivative in the form of an yellowish oil, was obtained. (Overall yield from the two step process: 67.4%)

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 7.415-7.37 (m, 1H), 7.28-7.23 (m, 3H), 4.66 (t, J=7.28Hz, 2H), 3.46 (t, J= 7.3Hz, 2H).

1.3.2.1.7 3-(2-nitroethyl)indole:

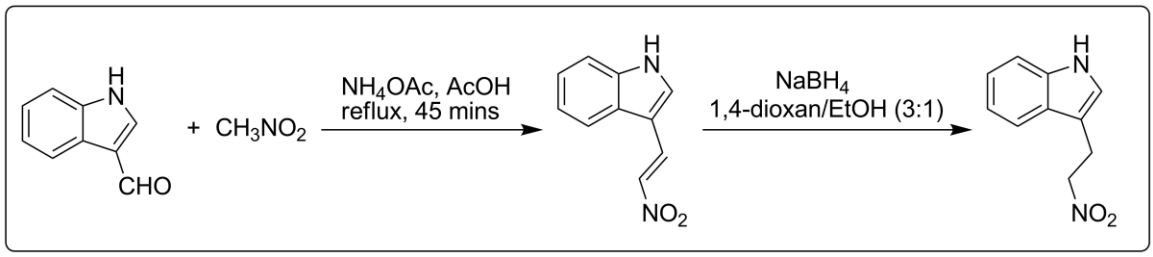


Fig.1.64

A 100 mL round bottom flask equipped with a magnetic stirbar and a reflux condenser was charged with 1.6 g (11.022 mmol) of Indole-3-carboxaldehyde, 2.12g of ammonium acetate (NH_4OAc) and 22 mL of acetic acid (AcOH) under inert atmosphere. To this reaction mixture, 1.8 mL (33.53 mmol) of nitromethane was added at room temperature and the mixture was then refluxed at 60^oC for 45 minutes. The contents of the round bottom flask were then transferred to a 500 mL separating funnel using water and DCM. The aqueous extract was extracted with (4X50 mL) of DCM. For the purpose of purification of the nitroalkene derivative, flash column chromatography on silica gel was performed using DCM/hexane (70:30) as the eluent. This afforded 484.7mg of the nitroalkene derivative, the purity of which was confirmed using ^1H NMR spectroscopy. (Yield: 23.4%)

The nitroalkene was then reduced using sodium borohydride and 1,4 dioxan/Ethanol (3:1) was used as the solvent system. The reduction reaction was allowed to run for 1 hour at 0^oC and the excess sodium borohydride was quenched using a saturated solution of ammonium acetate. 220.8mg of the desired nitroalkane in the form of a brownish-white solid was obtained. (Yield: 45%)

^1H NMR (400 MHz, *$CDCl_3$*) δ 7.60-7.58 (m, 1H), 7.41-7.38 (m, 1H), 7.26-7.22 (m, 1H), 7.19-1.15 (m, 1H), 4.66 (t, J=7.2Hz, 2H), 3.46 (t, J= 7.2Hz, 2H).

1.3.3 Preparation of carbonates:

I have prepared three carbonates, namely- phenyl benzyl carbonate, isobutyl phenyl carbonate and tert-butyl phenyl carbonate. Here, I will briefly describe the methods of preparation of these carbonates. Since, these carbonates are already reported in literature, hence like the previous case, I will only report the proton NMR spectra of these compounds.

1.3.3.1 Detailed synthetic procedures:

1.3.3.1.1. Phenyl benzyl carbonate:

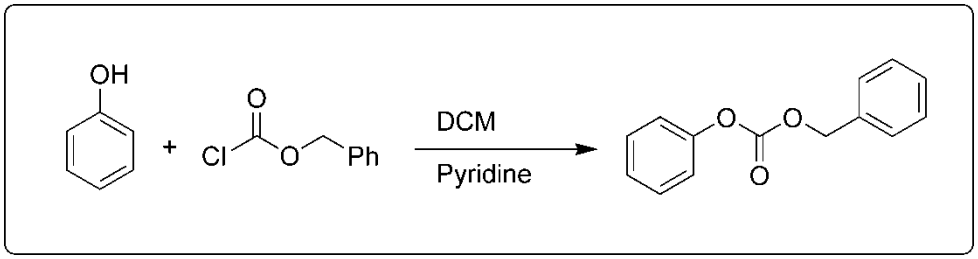


Fig.1.65

A 100 mL round bottom flask was charged with 1.14 mL (12.96 mmol, 1.005 equiv.) of phenol. To this, 40 mL of DCM was added followed by the addition of 1.23 mL (14.22 mmol, 1.103 equiv.) of pyridine. The reaction mixture was then cooled to 0^{o}C and at this temperature 4.4 mL (12.89 mmol, 1.0 equiv.) of benzyl chloroformate was added in a dropwise manner. The reaction mixture was stirred at this temperature for 15 minutes and then it was kept stirring at room temperature overnight. Next, the reaction mixture was transferred to a 250 mL separating funnel and the organic layer was washed successively with water, 5% NaOH and saturated brine solution. The organic layer was then washed with 100mL 1(M) copper sulphate solution to remove pyridine, dried over sodium sulphate and concentrated. Flash column chromatography was performed with this extract

using DCM/hexane (20:80) as the eluent to afford 1.2432g of product in the form of a pale yellow oil (yield= 43%).

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.47-7.36 (m, 7H), 7.27-7.18 (m, 3H), 5.287 (brs, 2H)

1.3.3.1.2. 2-methylpropyl phenyl carbonate:

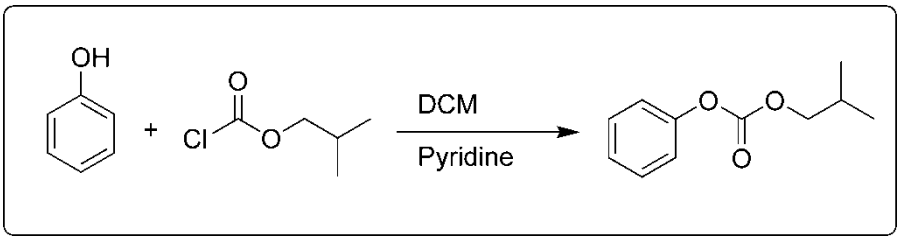


Fig.1.66

1.5 mL (11.477 mmol; 1 equiv.) was taken in a 25 mL round bottom flask under inert atmosphere. To this flask, 1.5 mL (17.0545 mmol; 1.486 equiv.) of phenol previously dissolved in 3.5 mL of DCM, was added. The mixture was then stirred at room temperature for 15 mins and 1.7 mL (21.6 mmol; 1.88 equiv.) of pyridine was added very slowly to this mixture. The solution was then stirred at room temperature for 2 hours. The progress of the raction was monitored using TLC. Then the contents of the flask were transferred to a 500 mL separating funnel using DCM and workup was done in exactly the same manner as mentioned in the previous procedure. Flash column chromatography was performed on silica gel using DCM/hexane (25:75) as the eluent system to isolate 1.4759g of product in the form of a pale yellow oil. (Yield: 88%)

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.42-7.37 (m, 2H), 7.27-7.17 (m, 3H), 4.051 (d, 2H), 2.12-2.02 (m, 1H), 1.02 (d, 6H)

1.3.3.1.3. 1,1-dimethylethyl phenyl carbonate:

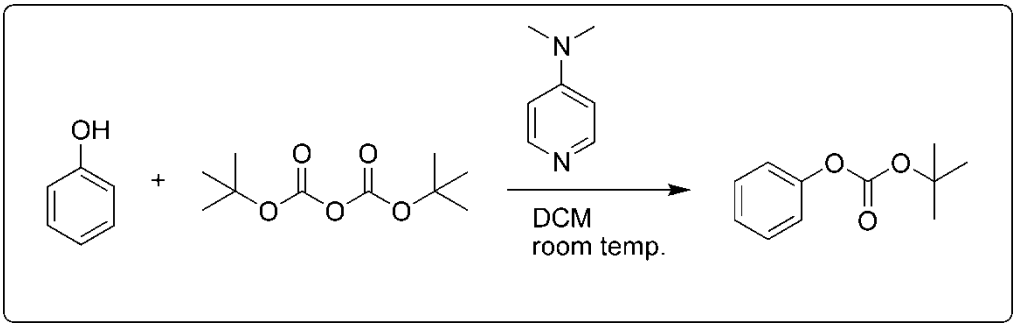


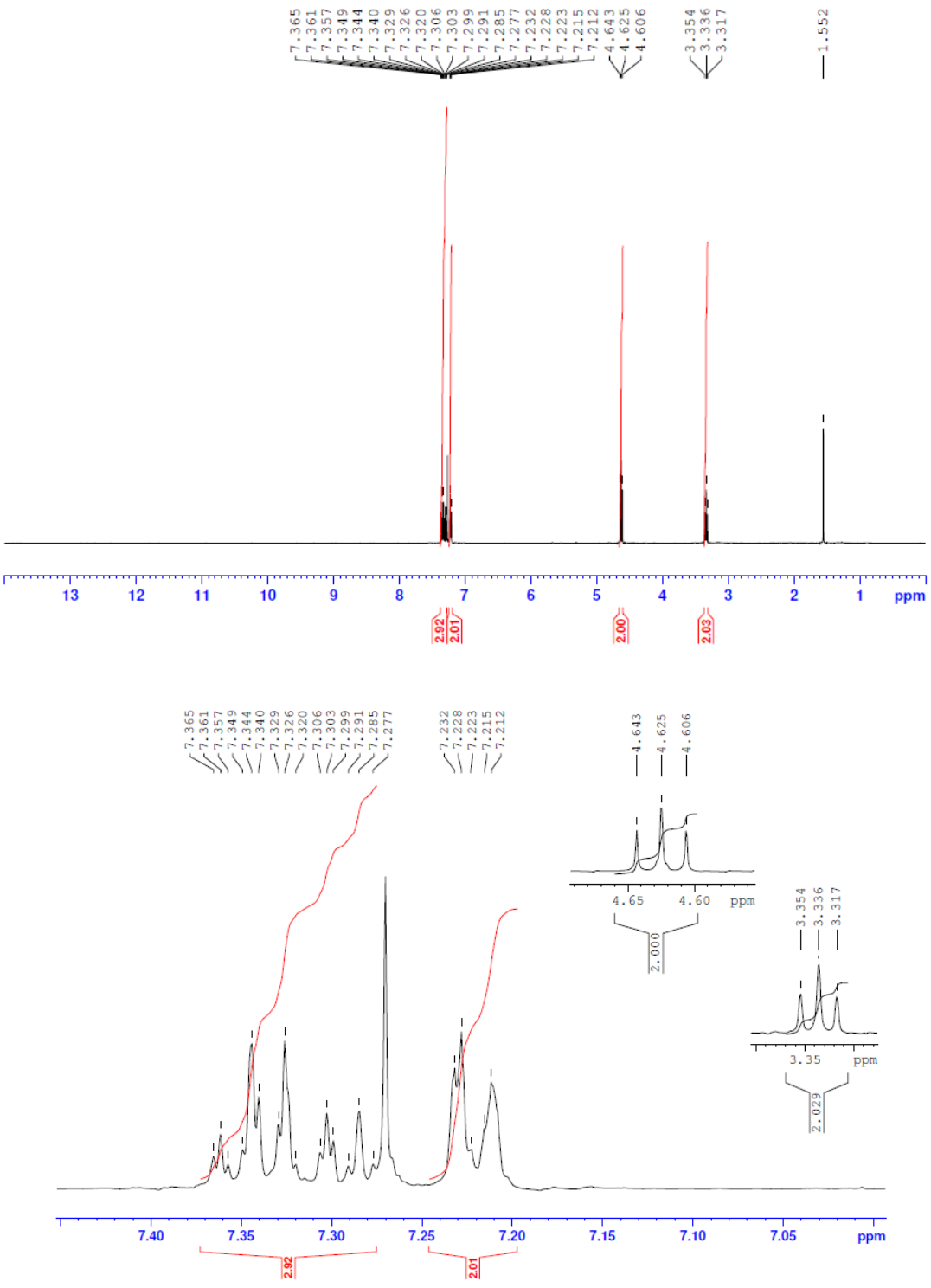
Fig.1.67

A 25 mL round bottom flask was charged with 810 µL (9.209 mmol, 1.005 equiv.) of phenol and 112 mg of DMAP (0.9618 mmol, 0.1 equiv.) i.e. N,N-dimethylamino pyridine under inert atmosphere. To this mixture, 2g (9.163 mmol, 1 equiv.) of ditert-butyldicarbonate was added at room temperature. The progress of the reaction was monitored using TLC and the reaction mixture was stirred for 2 hours. For purification of the product, flash column chromatography on silica gel was performed using DCM/hexane (20:80) as the eluant. 1.4757g of product was obtained (Yield: 83.57%).

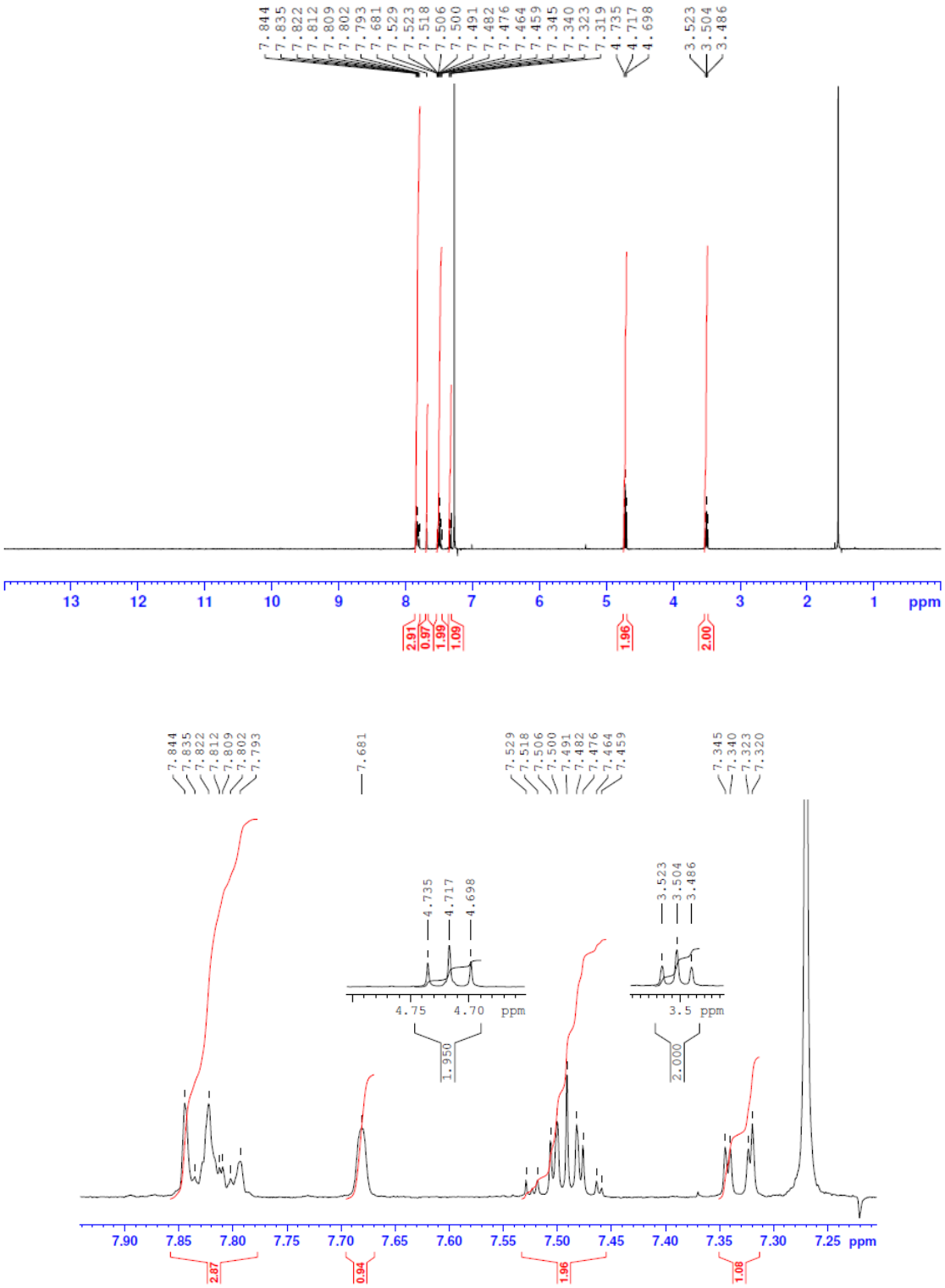
^{1}H NMR (400 MHz, *$CDCl_3$*) δ 7.4-7.36 (m, 2H), 7.25-7.17 (m, 3H), 1.57 (s, 9H)

1.3.4 Characterization Data (^{1}H NMR Spectra):

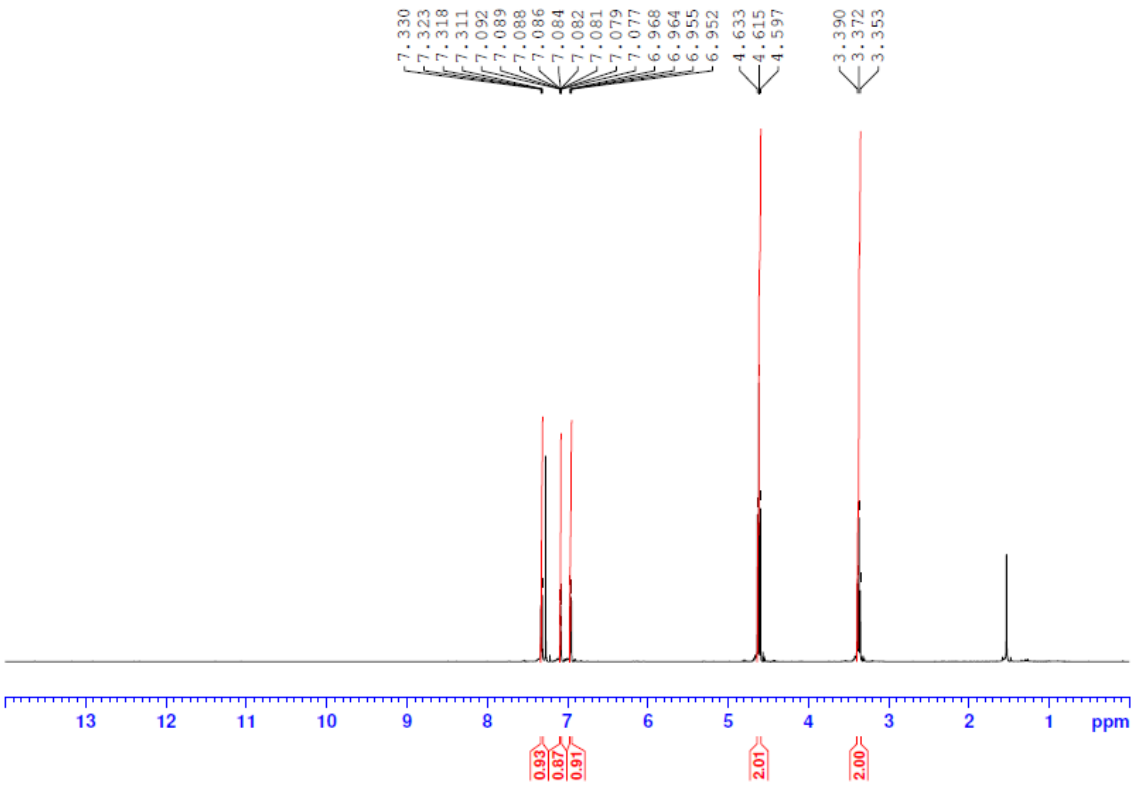
2-(nitroethyl)benzene

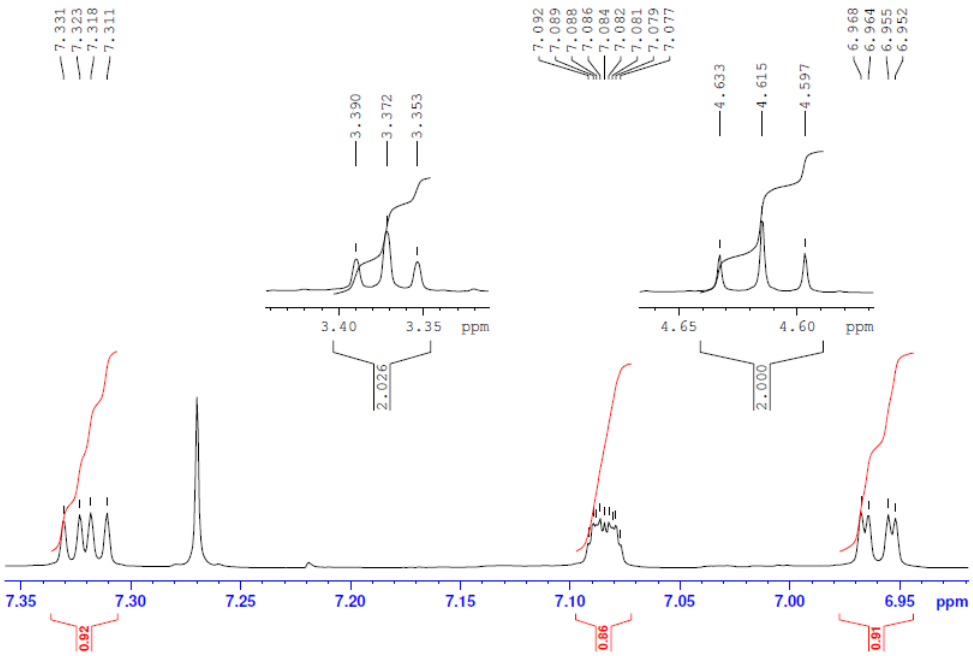


2-(2-nitroethyl)naphthalene

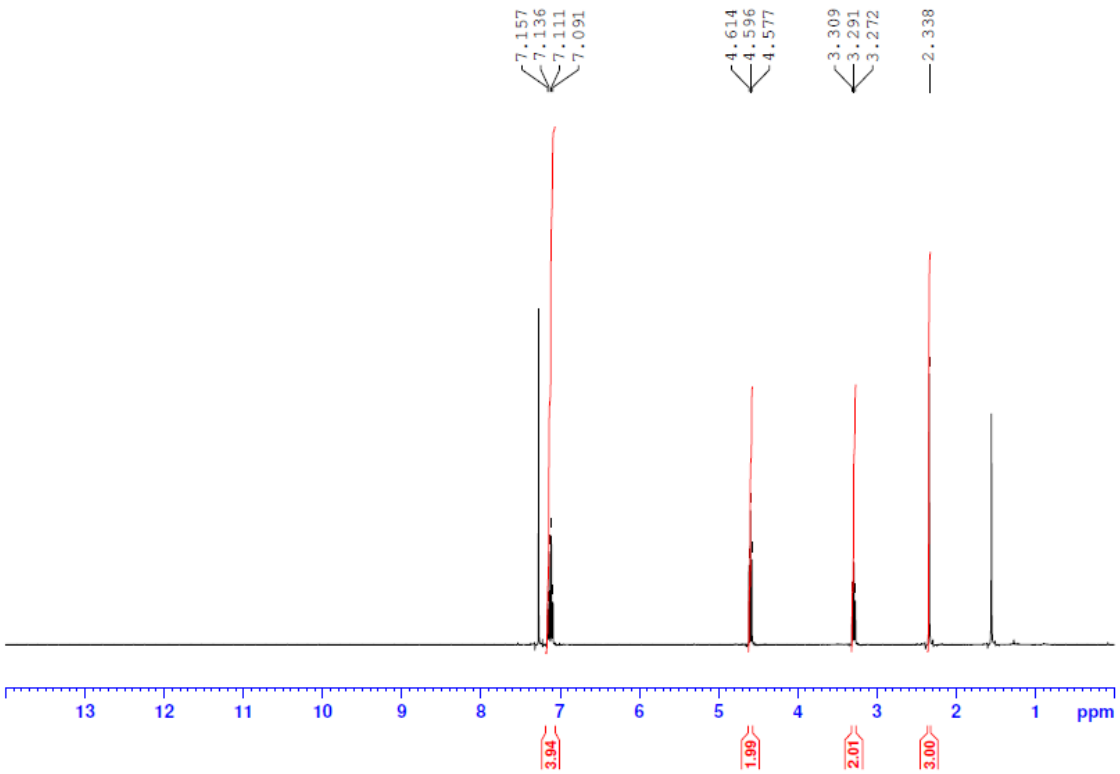


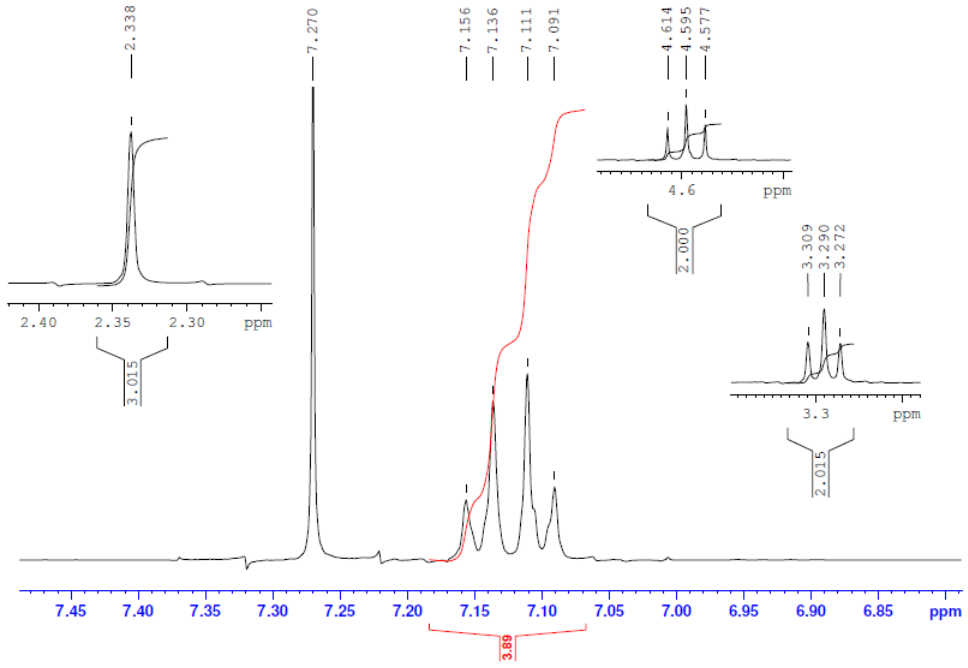
2-(2-nitroethyl)thiophene



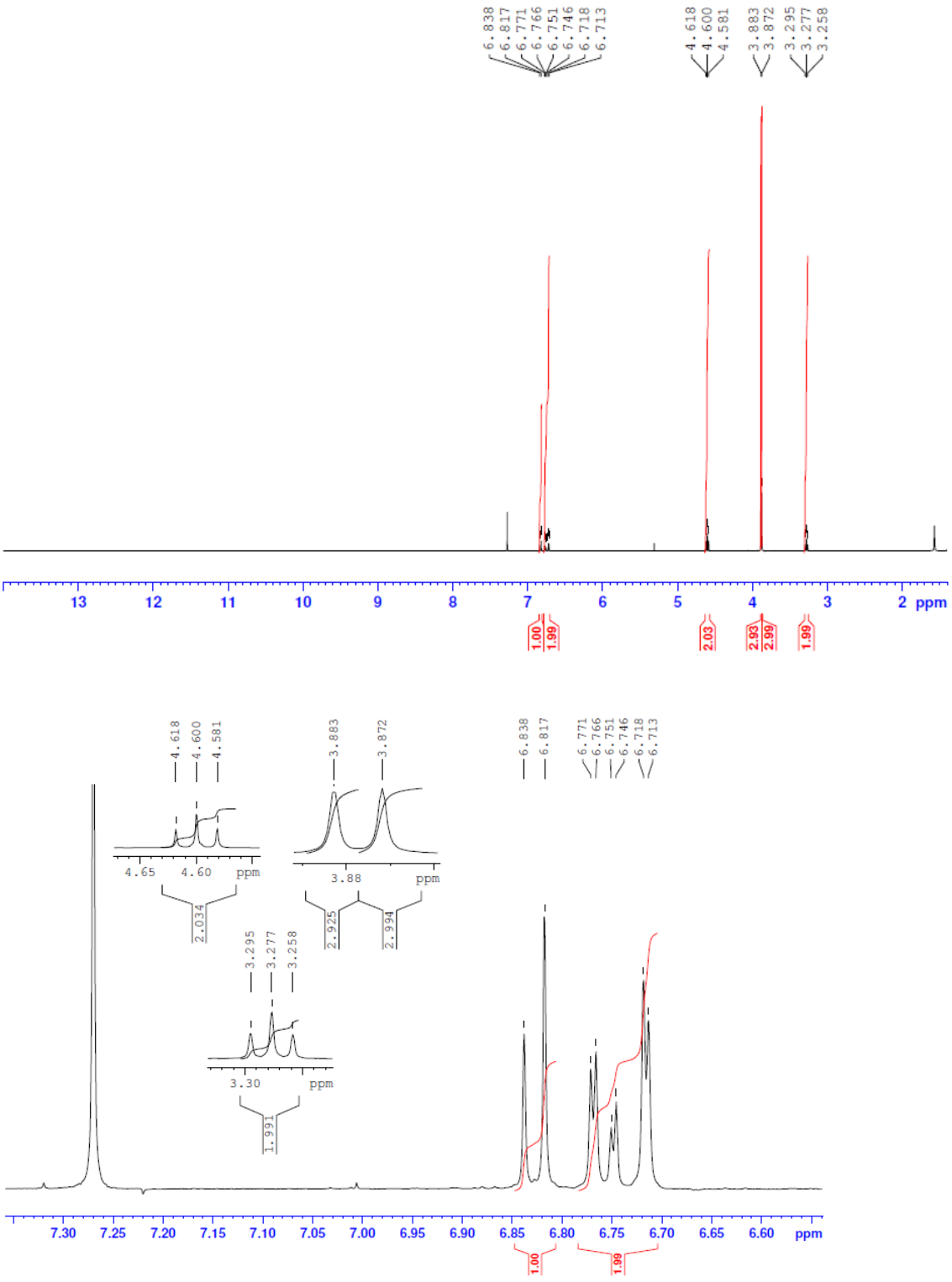


1-methyl-4-(2-nitroethyl)benzene

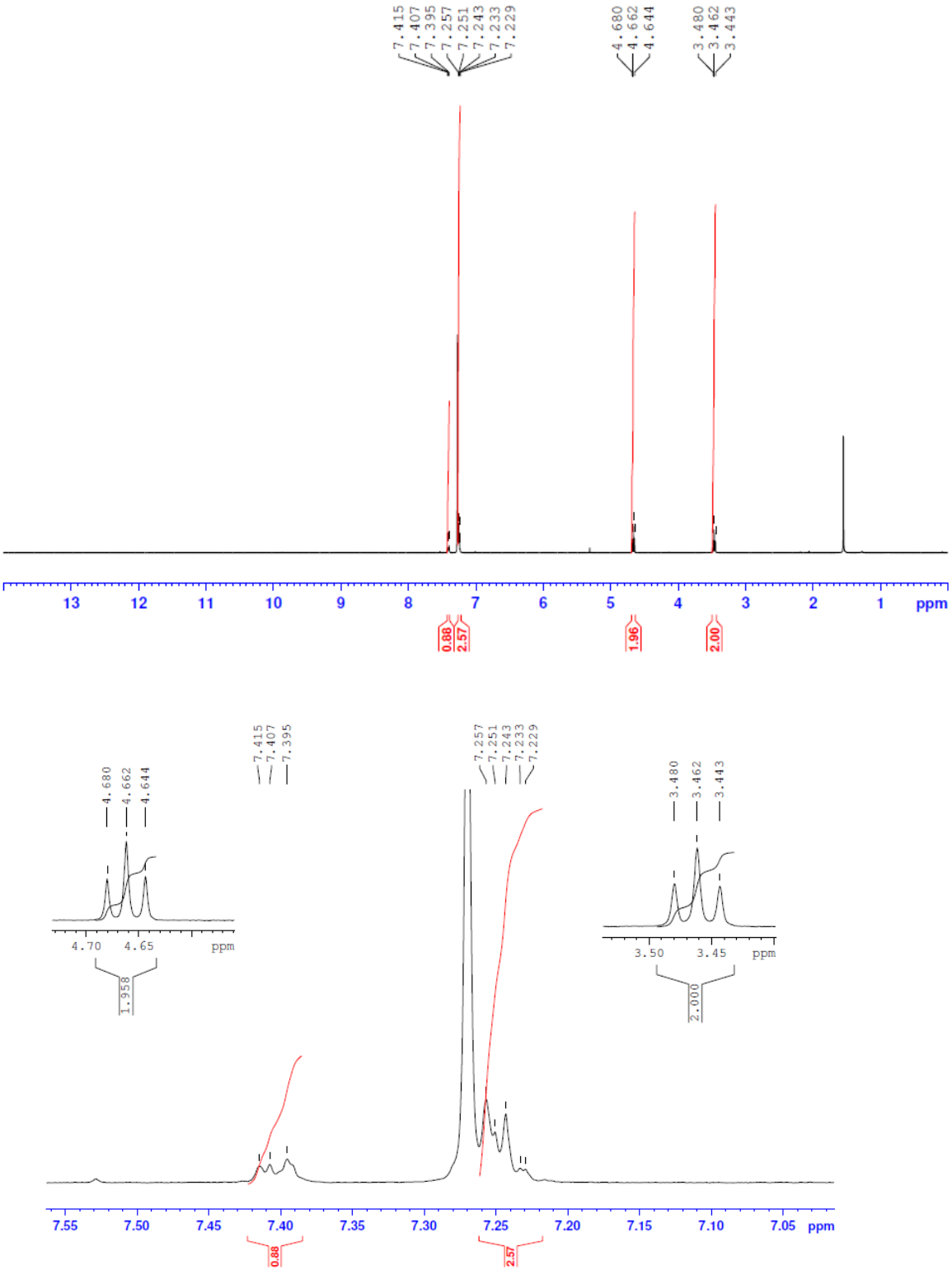




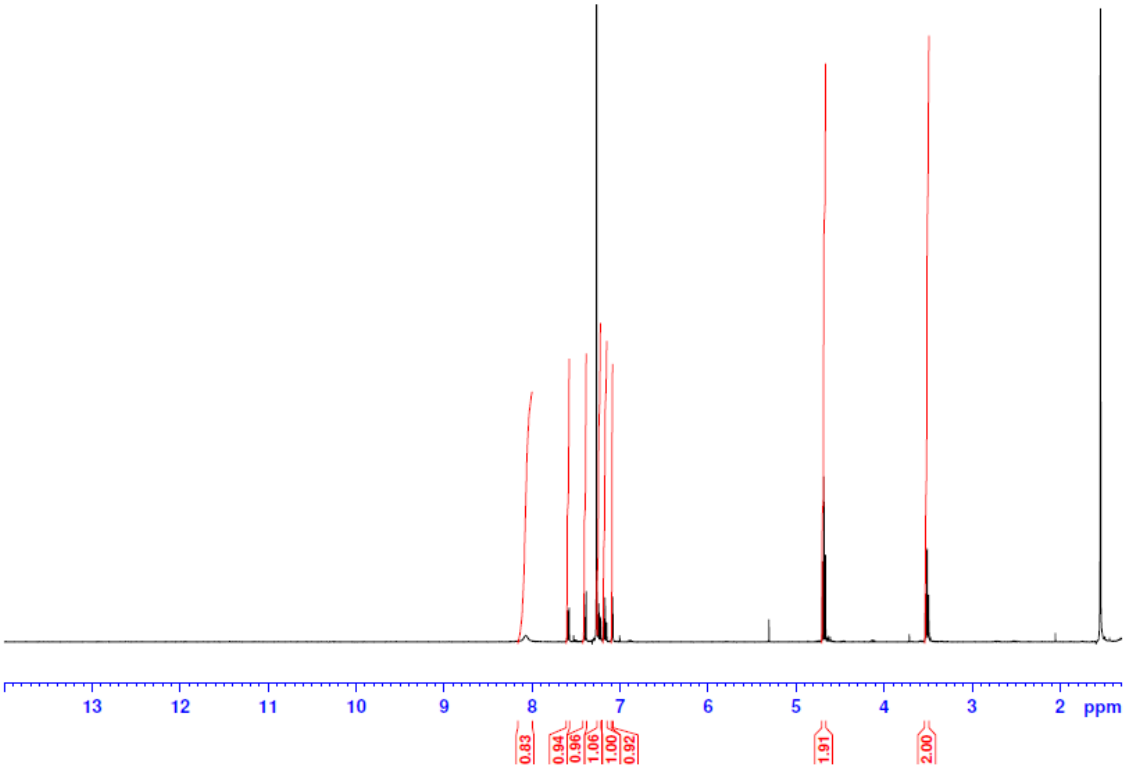
1,2-dimethoxy-4-(2-nitroethyl)benzene

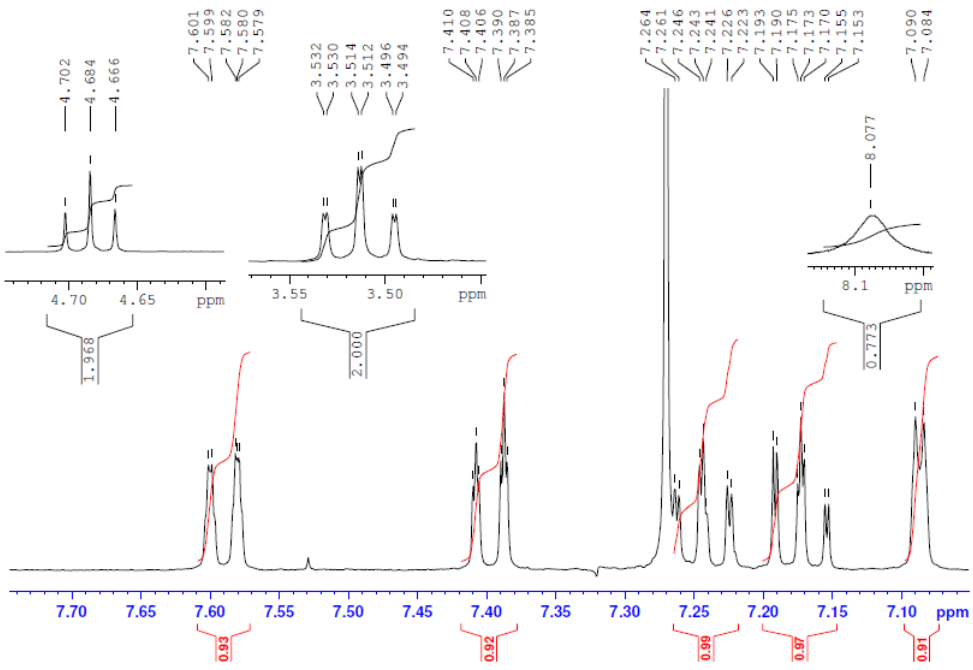


1-chloro-2-(2-nitroethyl)benzene

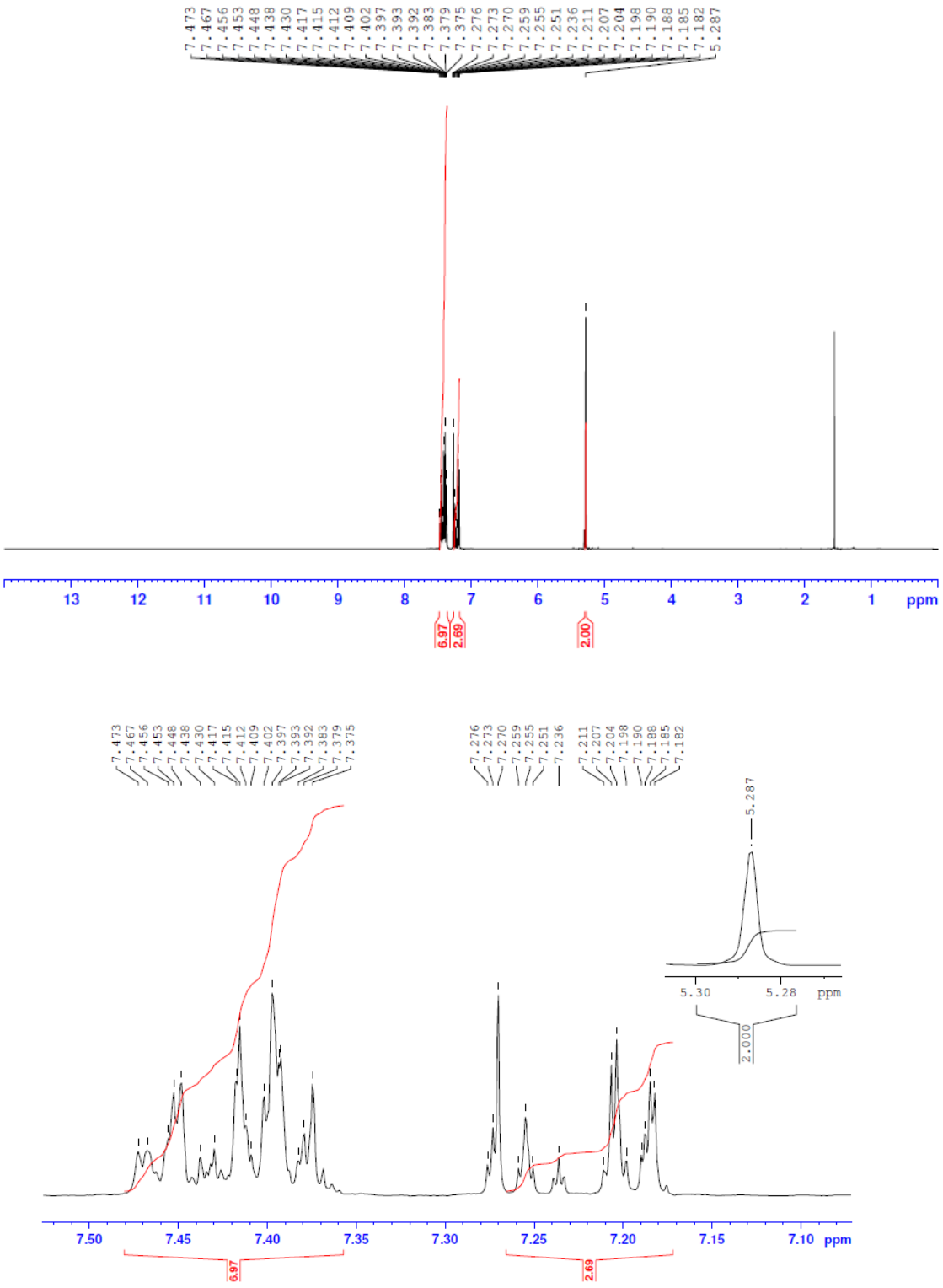


3-(2-nitroethyl)indole

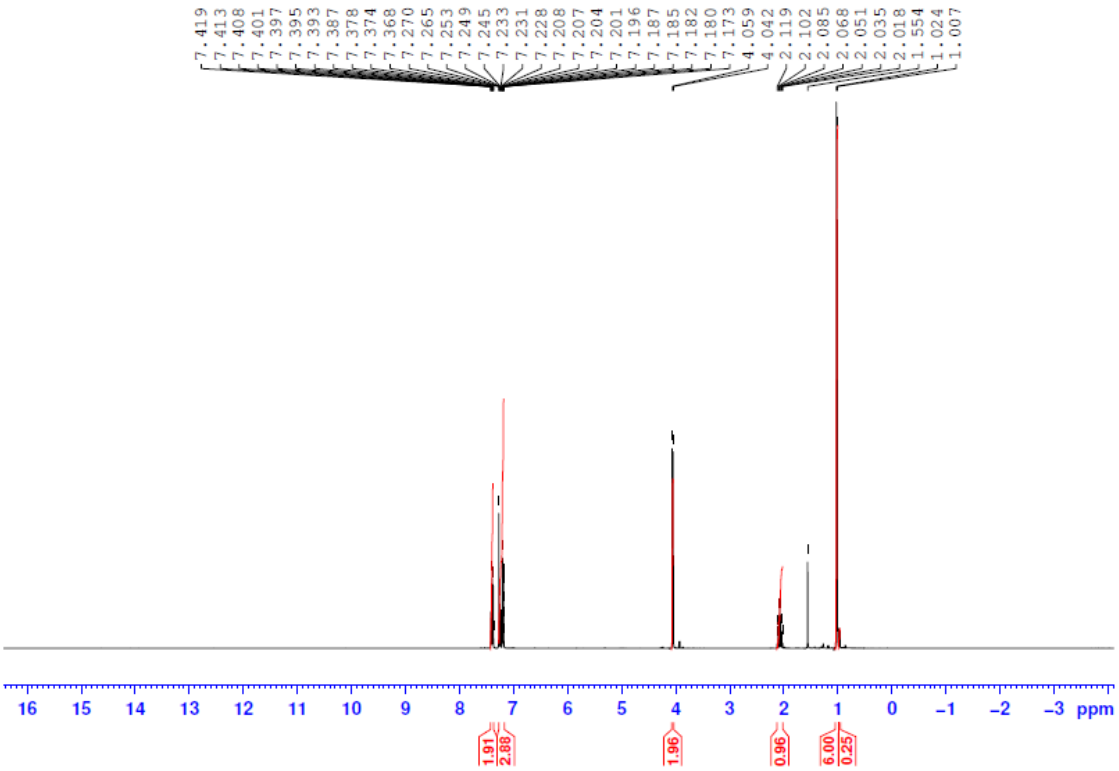


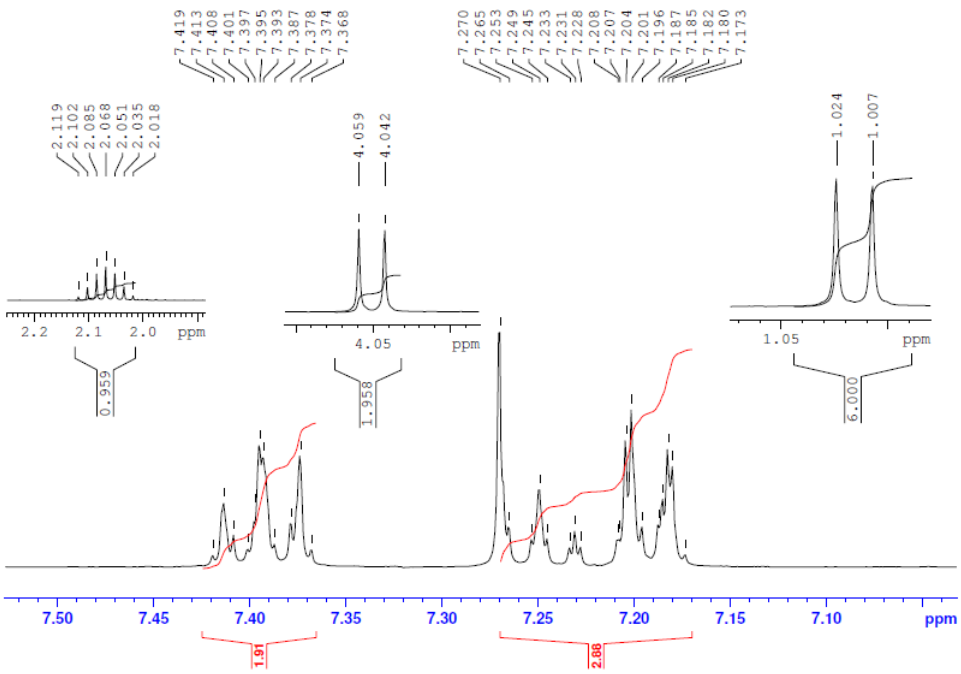


Phenyl benzyl carbonate

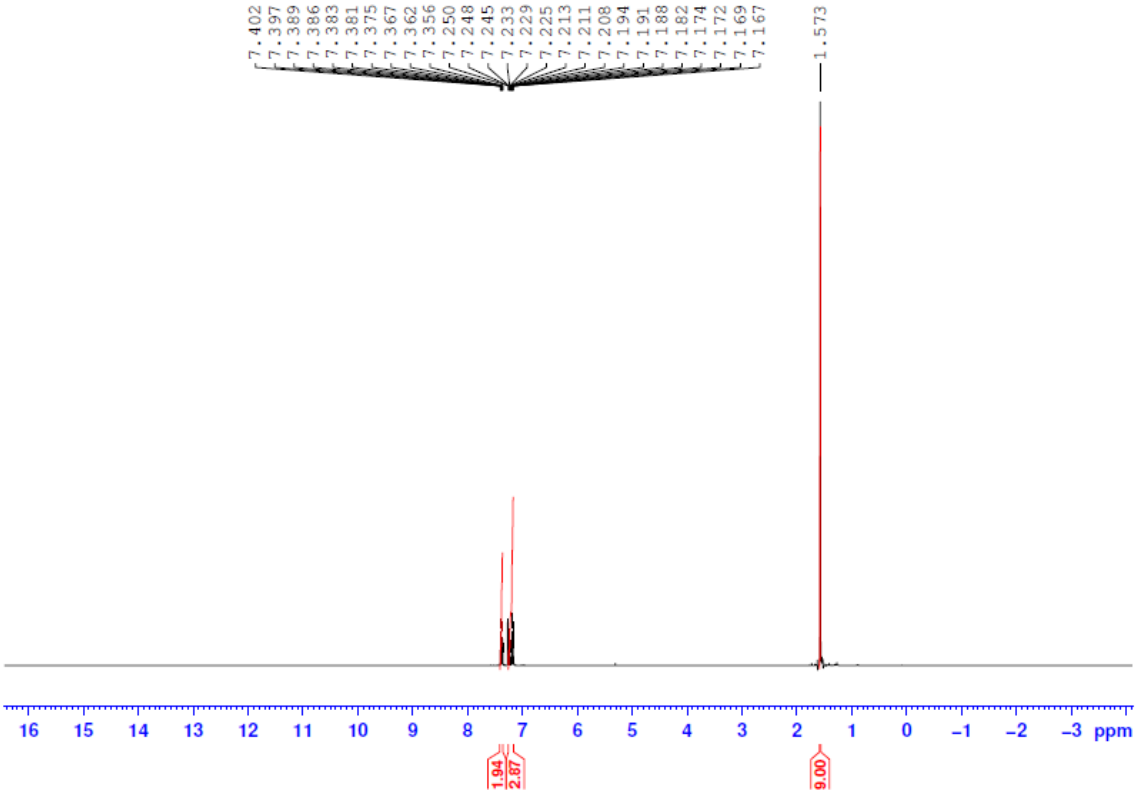


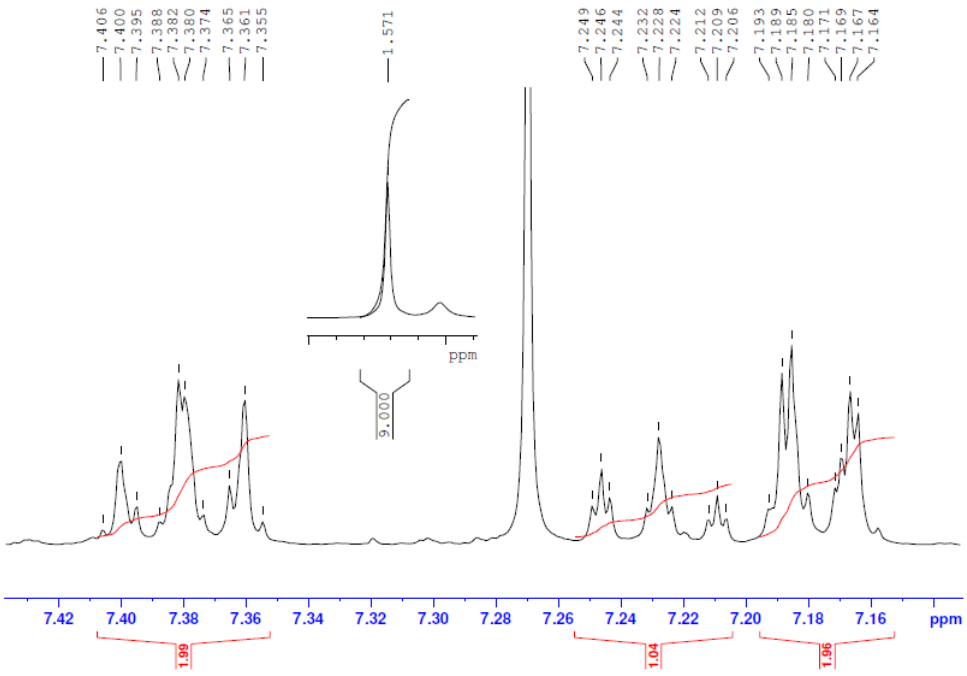
2-methylpropyl phenyl carbonate





1,1-dimethylethyl phenyl carbonate





Abbreviations:

- COD: 1,5-cyclooctadiene
- BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
- Chiraphos: (2*S*,3*S*)-(–)-Bis(diphenylphosphino)butane
- Pg: Protecting group
- Troc: 2,2,2-Trichlorethoxycarbonyl chloride
- Cbz: Carboxybenzyl
- Boc: Di-*t*-butyl dicarbonate
- TFAA: Trifluoroacetic anhydride
- Tos: 4-toluenesulfonyl
- THF: Tetrahydrofuran
- $(DHQ)_2AQN$: Hydroquinine anthraquinone-1,4-diyl diether
- PYBOX: bis(oxazoline) ligand with pyridine linker
- dba: Dibenzylideneacetone
- XPhos: 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
- tBuONO: tert-butyl nitrite

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Chapter 2

Polymerization of O-carboxyanhydride of lactic acid

2.1 Introduction

This chapter deals with the synthesis of Poly(lactic acid) from the O-carboxy anhydride derivative of lactic acid.

2.1.1 Poly(lactic acid):

Poly(lactic acid), also known as PLA is a biodegradable, aliphatic polyester that provides an alternative to petroleum-based polymers for uses such as plastics, fibers, coatings and sutures in biomedical applications. [1] [2]Owing to its versatility, PLA has occupied the second highest consumption volume among the bioplastics in the world. It is also environment friendly as it is an easily hydrolysable polymer, which can be degraded by various microorganisms present in the environment. The versatility of PLA can be exemplified with the help of the schematic diagram in the following page-

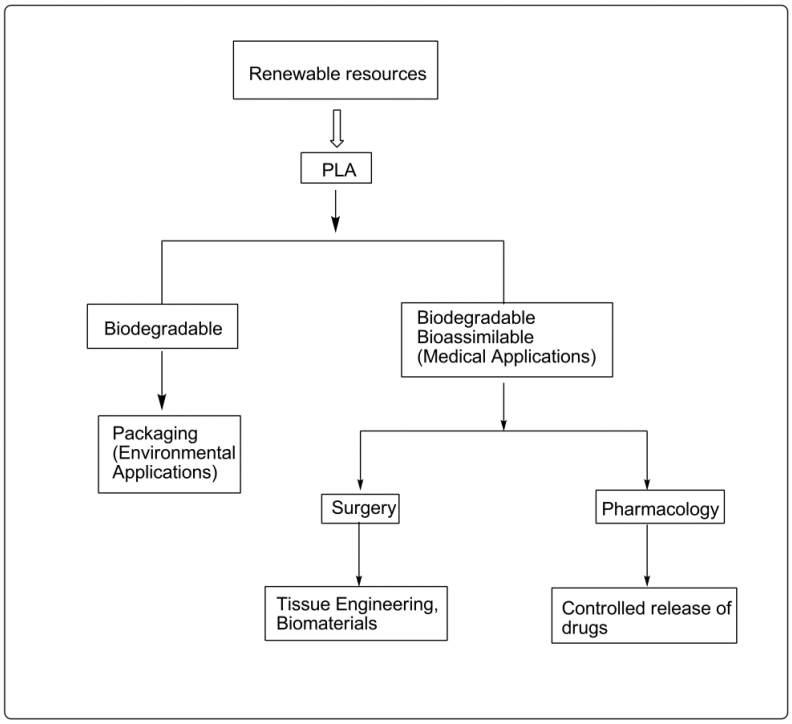


Fig.2.1: Applications of PLA (Adapted from Ref. 7)

PLA can be obtained either from the polycondensation of D or L-lactic acid (Step-Growth mechanism) or by performing Ring-Opening Polymerization (ROP) of lactide, the cyclic diester of lactic acid (Chain-Growth mechanism). [1]

However, as polycondensation process involves an equilibrium reaction, people face problems regarding the removal of the last traces of water during the final stages of polymerization. Thus, the polymer cannot attain its maximum possible molecular weight as small quantities of water can lead to the hydrolysis of the ester bonds present in it. [1]

The Ring-Opening Polymerization (ROP) of lactides on the other hand, involves an atom-economical, thermodynamically favorable process, which is driven in the forward direction due to a relief in the angle strain. With the advent of Living Ring Opening Polymerization reactions, poly (lactic acid) derivatives with polydispersity values close to 1 can also be synthesized. [3]

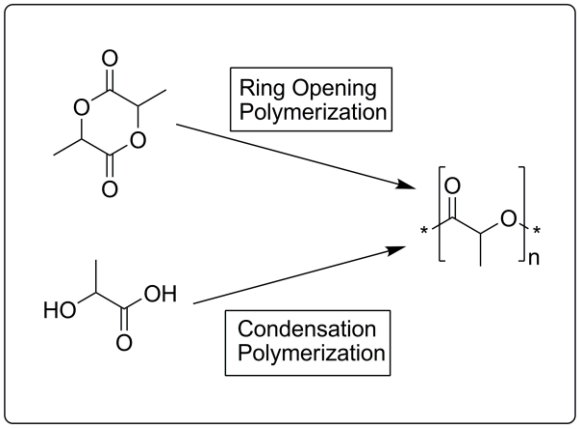


Fig.2.2: Synthesis of PLA (Adapted from Ref. 3)

As three stereoisomers of lactide are present, namely- L-lactide, D-lactide and meso-lactide (as shown in the figure below), hence different stereoisomers of PLA can also be formed with varying regions of stereohomogeneity.

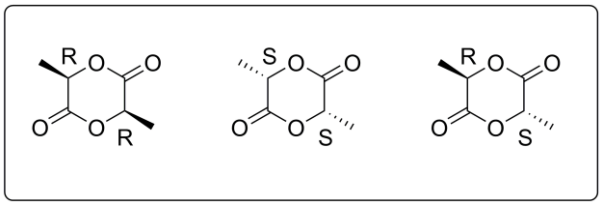


Fig.2.3: Stereoisomers of lactide (Adapted from Porter, Keith A., *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois, 2 Mar. 2006)

Depending on the extent of stereohomogeneity present, the properties of the PLA derivatives also change.

The stereochemistry in polymers like PLA can be best described with the help of tacticity. Tacticity delineates the relative stereochemistry of the adjacent chiral centres present in a polymer. The four different stereoisomers of PLA are shown in the following page-

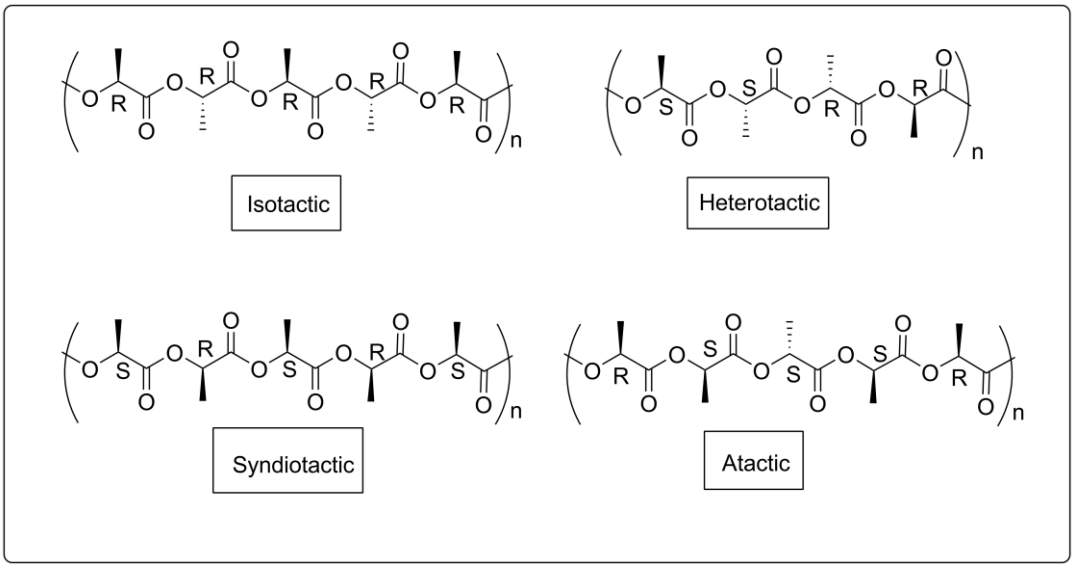


Fig.2.4: Stereoisomers of PLA (Adapted from Porter, Keith A., comp. *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois, 2 Mar. 2006)

In isotactic PLA all the carbons forming stereocentres have the same absolute configuration. In case of syndiotactic PLA, the consecutive stereogenic centres have alternating configuration. Heterotactic PLA includes specific regions of stereohomogeneity, while the atactic polymer bears a random distribution of configurations about the chiral centres.

Tacticity can also be expressed by the terms- diad, triad, tetrad and so on.

A diad consists of two consecutive structural units in a molecule. If the two units in a diad have the same stereochemical orientation then it comprises a meso diad (represented by ‘i’ or ‘m’). A racemo diad (represented by ‘r’or ‘s’) on the other hand, bears two units which have the opposite orientation.

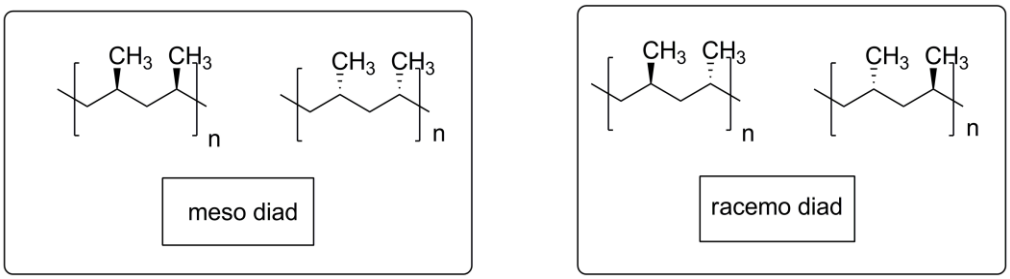


Fig.2.5: Meso and Racemo diads (Adapted from Wikipedia)

Two adjacent diads comprise a triad. Isotactic triads consist of two meso diads (ii or mm), syndiotactic diads consist of two racemo diads (ss or rr), while heterotactic triads are made up of one meso diad followed by a racemo diad (is or mr).

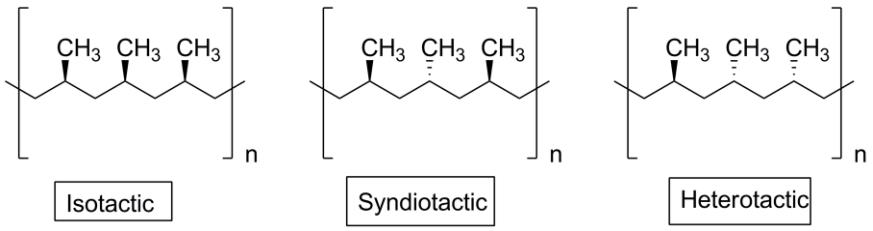


Fig.2.6: Isotactic, Syndiotactic, Heterotactic triads (Adapted from Wikipedia)

In an analogous manner, tetrads, pentads etc. are also defined to depict the stereochemistry of a macromolecule in a more precise way. To determine the distribution of stereosequence in PLA, proton decoupled ^{1}H NMR analysis of the methine hydrogen has been taken into account. [4 5]

Like other polymers, the morphology of PLA can also be determined by observing two main transition temperatures. One is the crystalline melting temperature T_m, above which the crystalline domains of the polymer start melting. The other one is the glass transition temperature T_g, the temperature at which the amorphous domains of the polymer reaches a brittle, rigid glassy state. Below this temperature, the long-range motions of the polymer segments are totally nonexistent. These two temperatures can be determined by means of Differential Scanning Calorimetry (DSC).

Poly L-lactide, having a left-handed helical structure and Poly D-lactide forming a right handed helix can come together in solution and form a stereocomplex, which is stabilized by the dipole-dipole interactions of the two lactide derivatives. When the number of stabilizing interactions increase, an improvement is also observed in the mechanical and thermal properties of the polymer. [6]

2.1.2 Existing methods for preparation of Poly (lactic acid):

Polymer catalysis is a fundamental concept that addresses the issue of synthesis of polymers like PLA in an efficient manner. Apart from tackling problems related to general catalysis such as- increment in turnover number, promoting selectivity etc., polymer catalysis has to deal with additional problems like- the molecular weight distribution of the polymer, the nature of the end groups present, the topology of the polymer, the sequence and functionality of the monomers added along the polymer chain and so on. [3] Generally, polymerization of lactides can be classified according to the different kinds of catalytic systems used, namely- organometallic catalytic system, the enzymatic catalytic system and the organocatalytic system. This classification is illustrated in the next page-

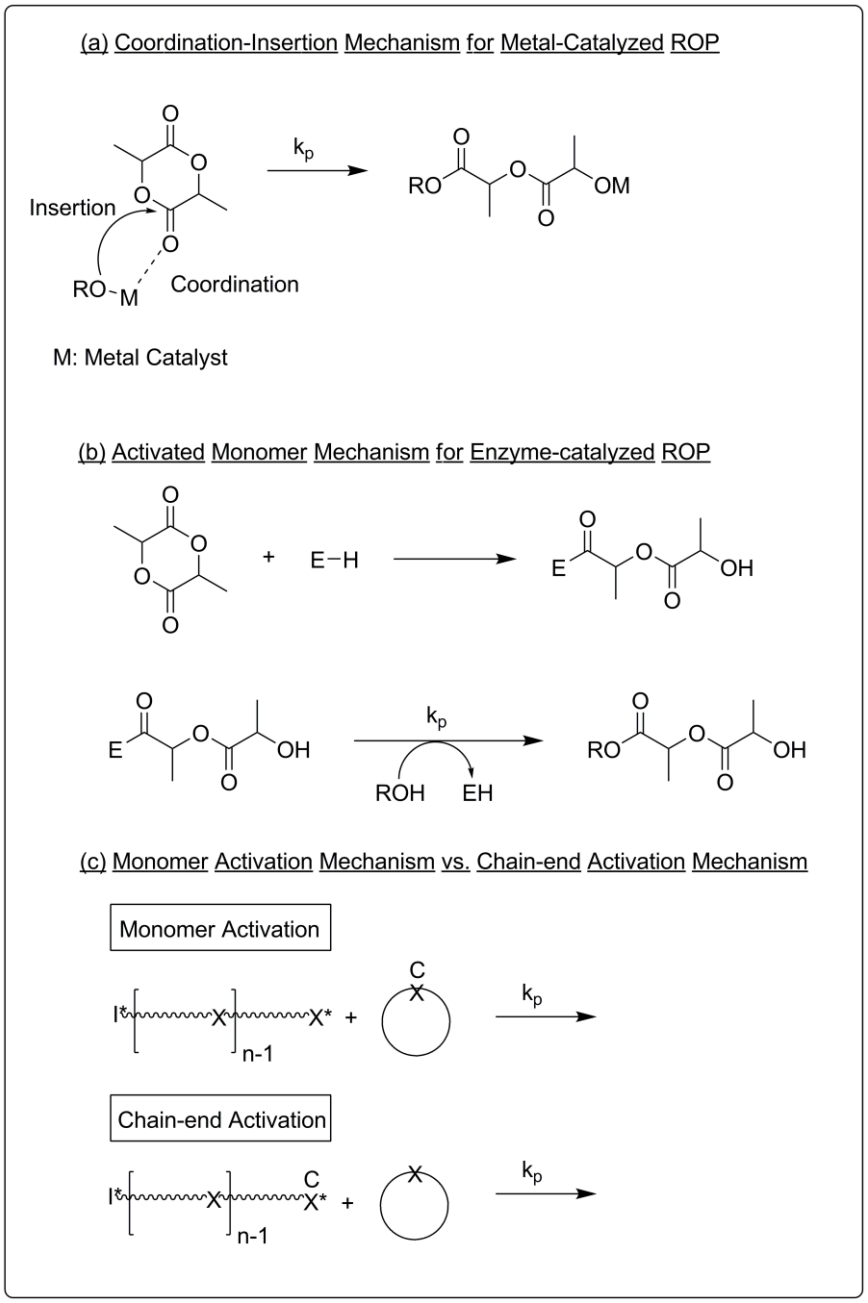


Fig.2.7: Different catalytic systems used for synthesis of PLA (Adapted from Ref. 3)

Here, I will be talking about the organometallic catalytic pathway (considering both chiral and achiral organometallic catalysts) and the organocatalytic pathway.

2.1.2.1 Using common organometallic catalysts:

Some of the organometallic catalysts commonly used are chiral in nature, while some are achiral. Since achiral catalysts are less expensive than their chiral counterparts, hence it is more recommendable to achieve stereocontrolled polymerization using achiral catalysts. A few examples of lactide polymerization reactions using common organometallic catalysts are shown below-

2.1.2.1.1. Preparation of Poly (lactic acid) using optically active lactides:

Generally, isotactic PLA can be synthesized using enantiomerically pure D or L-lactide, in presence of an organometallic catalyst. The most widely used organometallic catalyst is Tin (II) octanoate, owing to its commercial availability, high reaction rates and excellent solubility in common organic solvents and monomer melts. [7] Besides, the catalyst is highly active and high molecular weight polymers can be prepared with its aid. A coordination-insertion mechanism is involved in the process. Molecular modelling suggests that two equivalents of an alcohol (the initiator) initially get exchanged with the octoate ligand and this is followed by the coordination of the enantiopure lactide to the metal centre. Subsequent steps include insertion of the alcohol, ring opening and polymer propagation. [5 7]

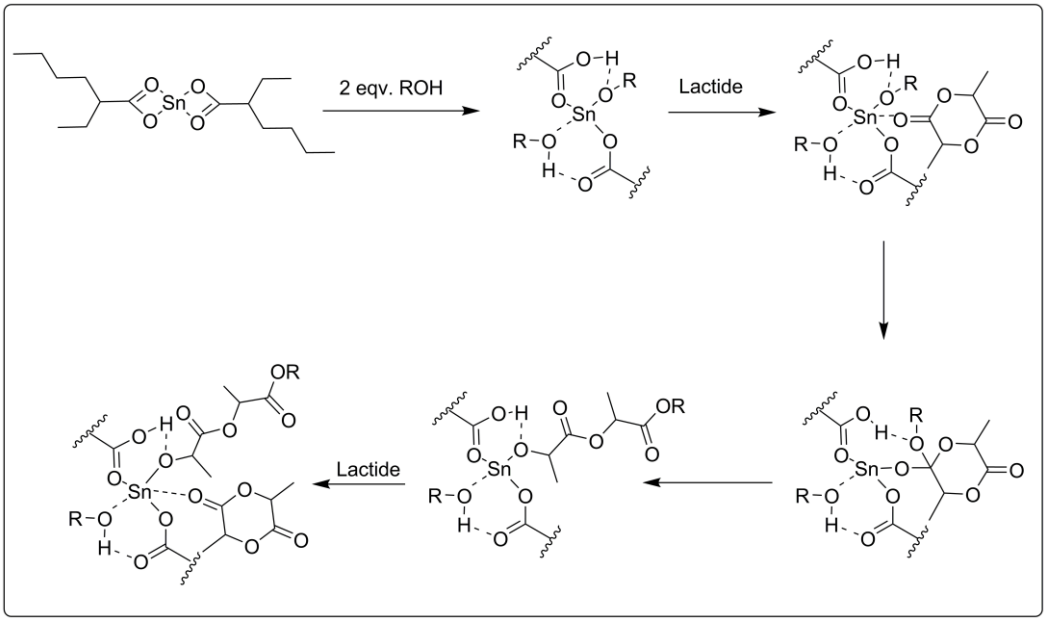


Fig.2.8: ROP of lactide using Tin(II) octanoate (Adapted from Porter, Keith A., *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*., State of Illinois)

The major drawback of using the tin catalyst lies in the incorporation of the toxic metal residue at the end of the polymer chain. This in turn imposes a restriction on the use of the synthesized polymer in biomedical applications.

Apart from Tin (II) octanoate, aluminium alkoxides are also used as catalysts for the Ring-Opening Polymerization reactions of lactides.

The prototypical example is obviously Aluminium Isopropoxide. [8] However, the activity of this catalyst is found to be considerably lower than the tin catalyst. [7] The polymerization reaction in this case also proceeds via a similar coordination-insertion mechanism as shown below-

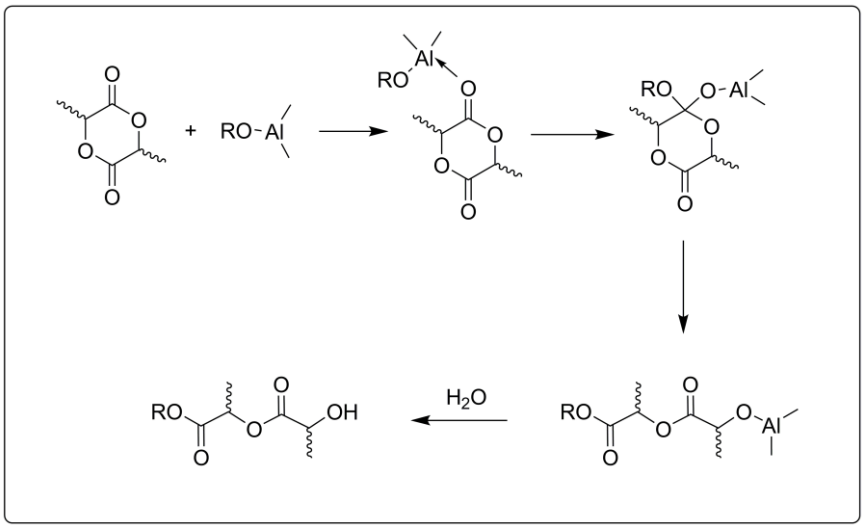


Fig.2.9: ROP of lactide using Aluminium Isopropoxide (Adapted from Ref. 7)

The molecular weight of the PLA synthesized using these catalysts can be improved by reducing the possibility of side reactions like transesterification. [7] Transesterification in general, occurs according to the following schematic diagram-

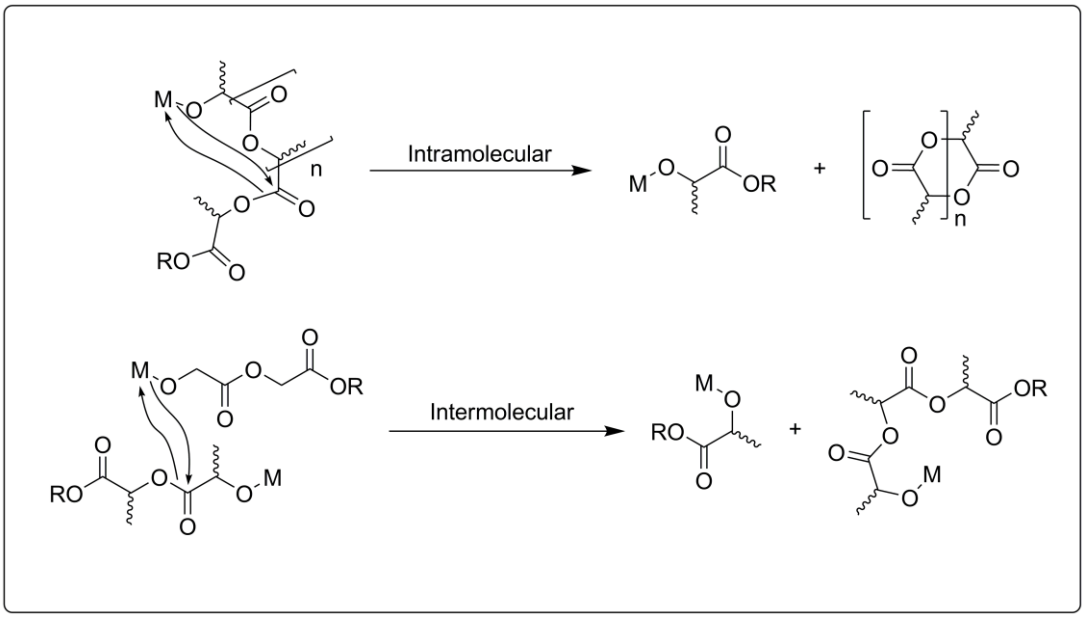


Fig.2.10: Mechanism of transesterification (Adapted from Ref. 7)

In order to prevent this reaction from occurring, an equimolar amount of a lewis base like- 4-picoline is added to the reaction mixture. This compound activates the Al-OiPR bond towards monomer insertion and also decreases the rate of transesterification by creating steric hindrance. [8]

2.1.2.1.2 Preparation of Poly (lactic acid) using racemic lactide:

The polymerization reactions of poly(lactic acid) from racemic lactide derivatives using various chiral and achiral initiators are described in the following pages.

2.1.2.1.2.1 Preparation of heterotactic PLA from rac-lactide using Zinc diiminate complexes:

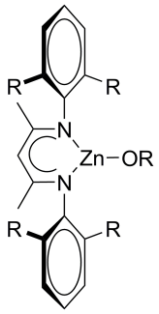


Fig.2.11: Zinc diiminate complex (Adapted from Porter, Keith A., *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois)

The above catalyst, an achiral ß-diiminate zinc complex bearing bulky ligands, was used as a single-site catalyst to carry out the polymerization of rac-lactide by means of a chain-end control mechanism. [9]

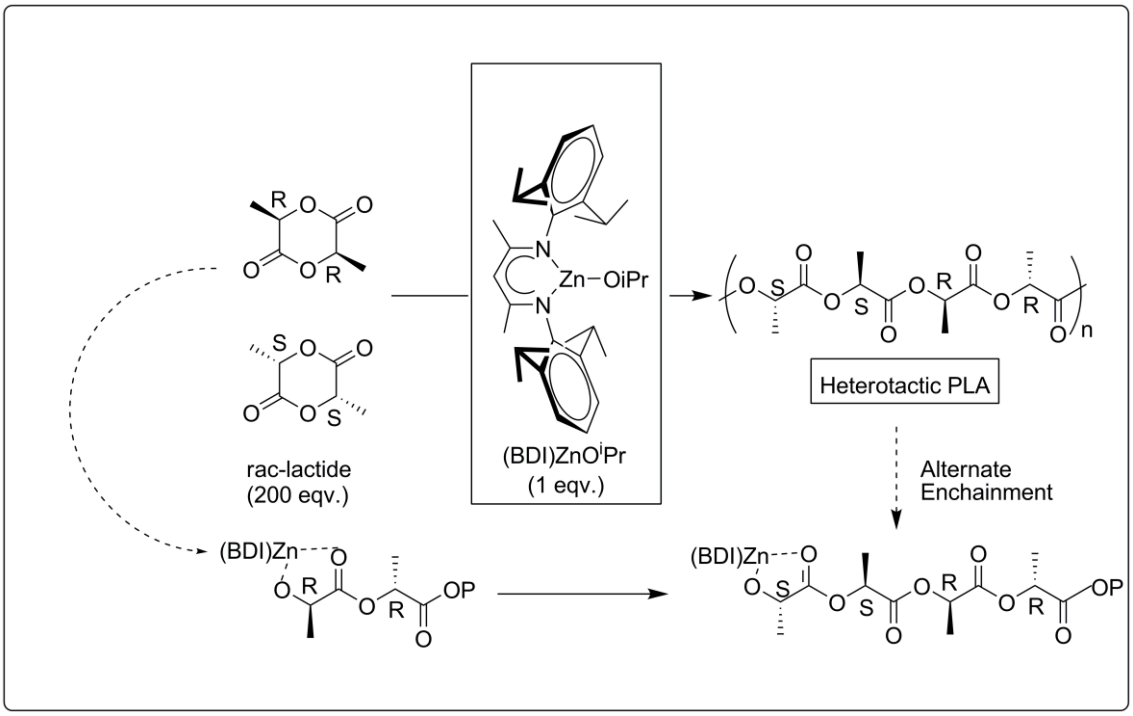


Fig.2.12: Preparation of heterotactic PLA from zinc complex (Adapted from Ref. 9)

Here, the bulky nature of the achiral catalyst increased the influence of the stereochemistry of the last inserted monomer, which then determined the type of lactide that will get enchained.

Thus, two cases were possible. If meso enchainment would take place i.e. chain end of (R) stereochemistry selected (R,R)-lactide, then isotactic PLA would be formed. On the other hand, if racemic enchainment would take place, i.e. chain end of (R) stereochemistry selected (S,S)-lactide, then heterotactic PLA would be formed.

It was found that the achiral zinc catalyst was highly active and resulted in the formation of heterotactic PLA with a molecular weight of 37900 g/mol and a polydispersity index of 1.1. The reaction was monitored by ^{1}H NMR. The polymer was amorphous in nature and had a Tg of 49^{o}C. [9]

It was also seen from the mass spectrometric analysis, that the ß-diiminate ligand did not undergo any reaction with the lactide and it was the isopropoxide group that initiated the polymerization reaction.[9]

2.1.2.1.2.2 Preparation of heterotactic PLA using ß-diiminate magnesium complex from racemic lactide derivatives:

The achiral ß -diiminate magnesium complex used to carry out the heterotactic polymerization can be prepared in a manner shown below-

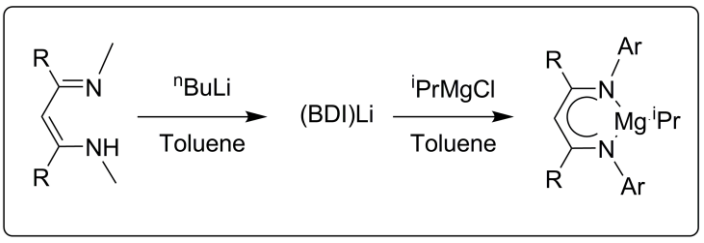


Fig.2.13: Preparation of ß-diiminate magnesium complex (Adapted from Lecture 7: Biorenewable polymers 1: Stereoselective polymerization of lactide by Dr. Ed Marshall, Imperial College, London)

From X-ray crystallographic analysis, it was found that the Mg-complex was not monomeric.[10] In fact, it was an isopropoxide-bridged dimer as shown in the following figure-

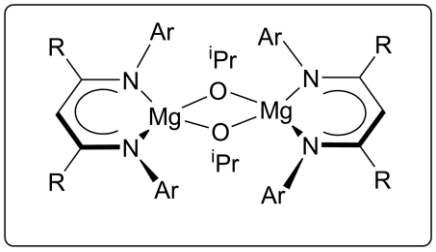


Fig.2.14: Structure of ß-diiminate magnesium complex (Adapted from Ref. 10)

This complex resulted in the formation of a heterotactic polymer only when a co-ordinating solvent like THF was used. On using non co-ordinating solvents like dichloromethane, atactic polymer was obtained. [11]

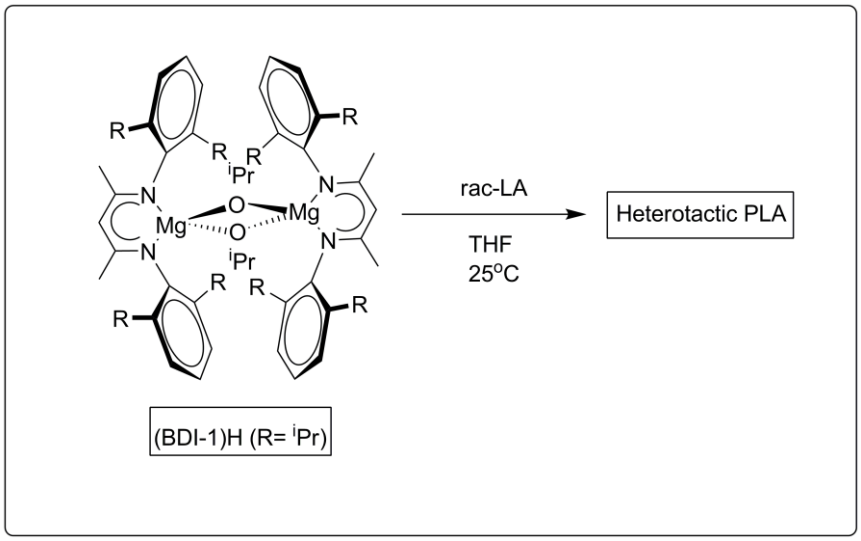


Fig.2.15: Preparation of heterotactic PLA from Mg complexes (Adapted from Ref.11)

From NMR analysis at low temperature, it was clear that in a co-ordinating solvent the propagating species of both magnesium and zinc complexes are monomeric in nature. The structure of these species are shown below-

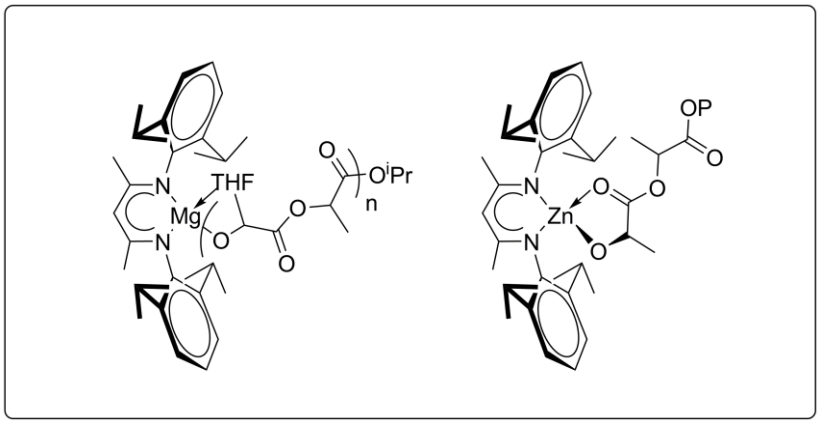


Fig.2.16: Actual structure of the complexes (Adapted from Lecture 7: Biorenewable polymers 1: Stereoselective polymerization of lactide by Dr. Ed Marshall, Imperial College, London)

From the above figure, it is quite clear that the magnesium species is a monomer, as THF occupies one co-ordination site of the metal. The zinc species on the other hand is monomeric as the growing polymer chain chelates to the metal centre in a way as shown above.

It was observed that the involvement of a monomeric species is generally responsible for the heterotacticity of PLA.

Thus, in presence of co-ordinating solvents, both magnesium and zinc complexes form heterotactic PLA, while in presence of non-coordinating solvents only the zinc complex forms heterotactic PLA. [11]

In order to delineate the reason behind the stereocontrol observed during the formation of heterotactic PLA, the ring opening polymerization of PLA catalyzed by magnesium diiminate complex was investigated using theoretical studies (Density Functional Procedure). [12]

2.1.2.1.2.3 Preparation of isotactic stereoblocks using enantiopure organometallic initiators:

In 1997, Spassky and his group used a chiral enantiopure Schiff's base aluminium alkoxide complex as initiator to achieve a stereocontrol over PLA. The catalyst, Al(O^iPr)[(R)-(SalBINAP)], exhibited a 20:1 preference for the polymerization of the D-lactide over that of

the L-lactide. This resulted in a kinetic resolution mediated polymerization. At 60% conversion, the product was found to be isotactic PLA with a T_m (melting temperature) of 170^{o}C. However, at 100% conversion, the T_m of the polymer was found to be 187^{o}C, thereby indicating that an isotactic stereoblock has been produced. [13]

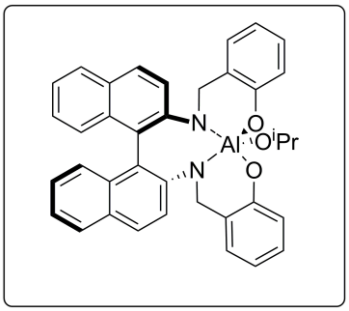


Fig.2.17: Initiator used to prepare stereoblock polymer (Adapted from Porter, Keith A., comp. *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois)

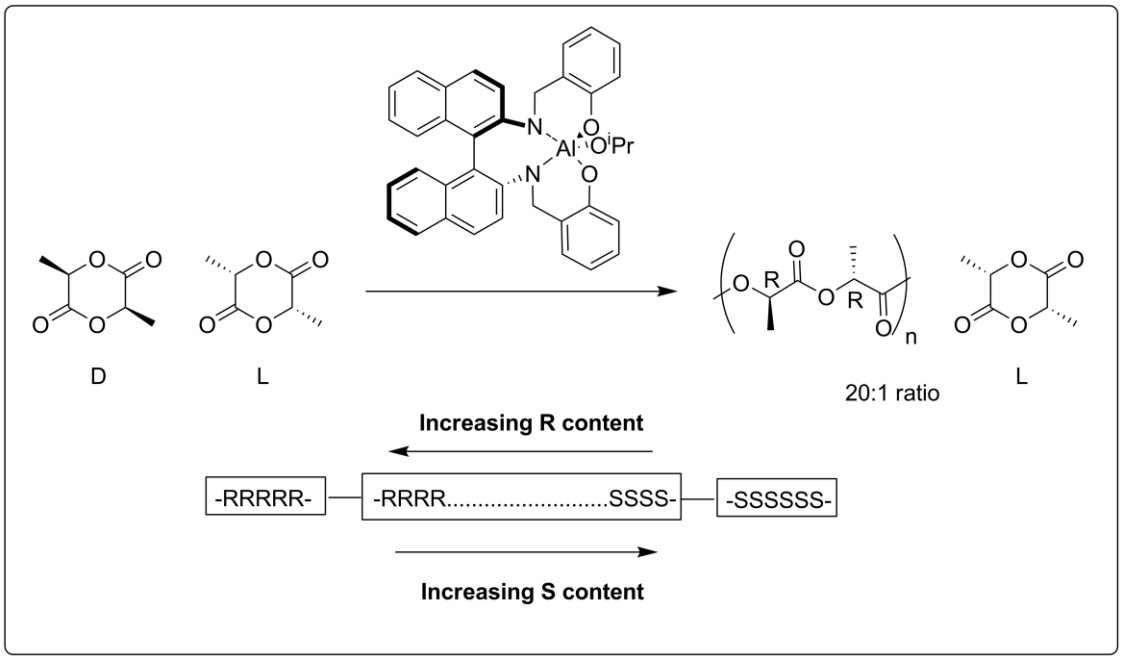


Fig.2.18: Preparation of stereoblock polymer(Adapted from Porter, Keith A., comp. *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois)

The usage of this reaction to generate pure L-lactide, i.e. the separation of racemic lactide to give the enantiomerically pure counterparts, is quite evident from the above illustration.

2.1.2.1.2.4 Preparation of stereoblock copolymer using racemic organometallic initiators:

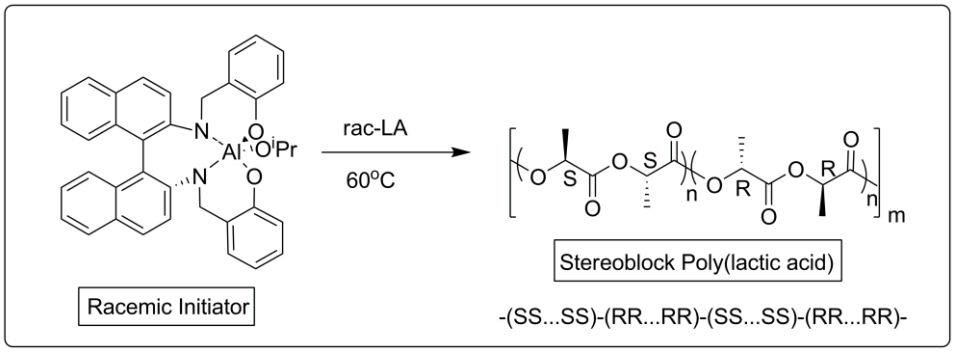


Fig.2.19: Preparation of stereoblock copolymer from rac-LA (Adapted from Lecture 7: Biorenewable polymers 1: Stereoselective polymerization of lactide by Dr. Ed Marshall, Imperial College, London)

Here, each isomer of the chiral Al-initiator reacts preferentially with one enantiomer of the lactide, gives short sequences of ….RRRRR….. and …..SSSSS….. and these sequences can then get exchanged between the metal centres according to the following mechanism-

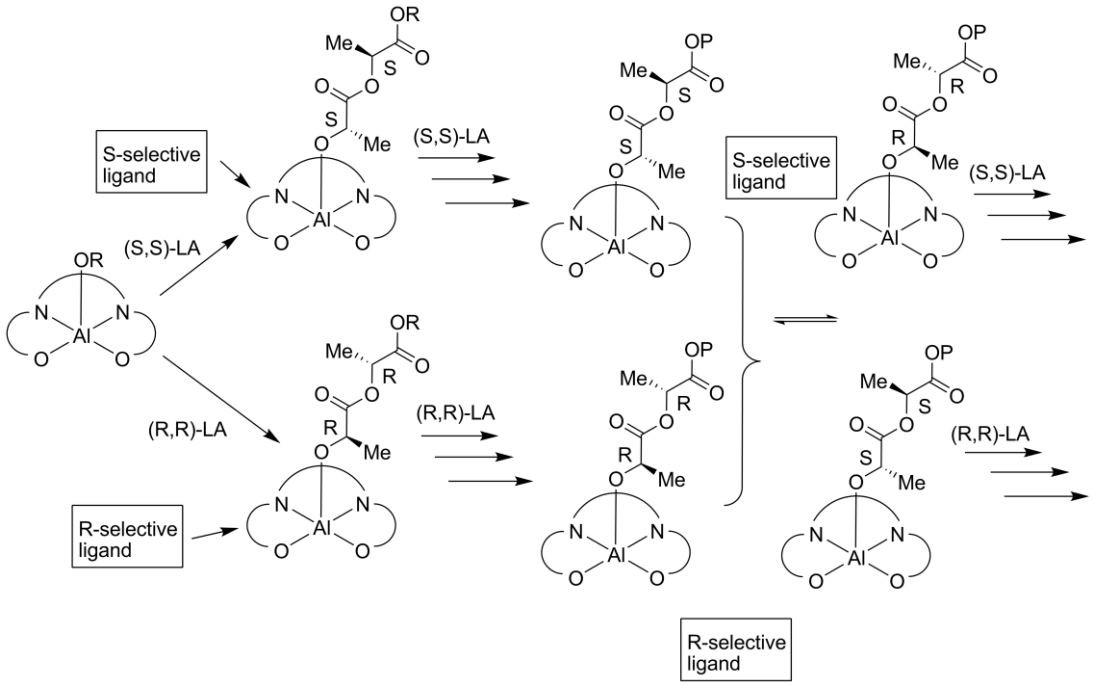


Fig.2.20: Mechanism for the preparation of stereoblock copolymer Fig.13: Preparation of stereoblock copolymer from rac-LA (Adapted from Lecture 7: Biorenewable polymers 1: Stereoselective polymerization of lactide by Dr. Ed Marshall, Imperial College, London)

Initially, it was expected that the two isotactic isomers of PLA would come together and form a stereocomplex with a very high melting temperature. [14]

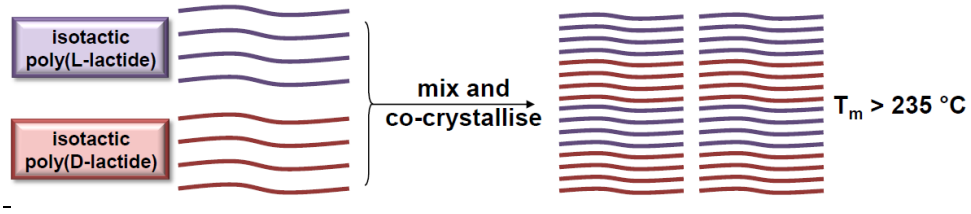


Fig.2.21: Preparation of isotactic stereocomplex (Adapted from Lecture 7: Biorenewable polymers 1: Stereoselective polymerization of lactide by Dr. Ed Marshall, Imperial College, London)

However, due to the exchange of the short isotactic domains between the metal centres, a stereoblocky copolymer having a relatively lower melting temperature was obtained. [15]

2.1.2.1.3 Preparation of Poly (lactic acid) using meso lactide:

Here, the preparation of both syndiotactic PLA and heterotactic PLA from meso-lactide are described.

2.1.2.1.3.1 Preparation of syndiotactic PLA from meso-lactides using enantiopure organometallic initiators:

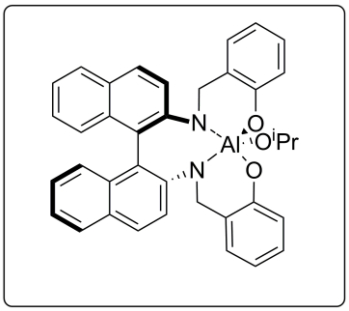


Fig.2.22: Initiator used for preparation of syndiotactic PLA (Adapted from Porter, Keith A., *Ring Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois)

The catalyst shown above was used for the preparation of syndiotactic PLA from meso-lactide. [15] This can be easily illustrated by means of the following schematic diagram-

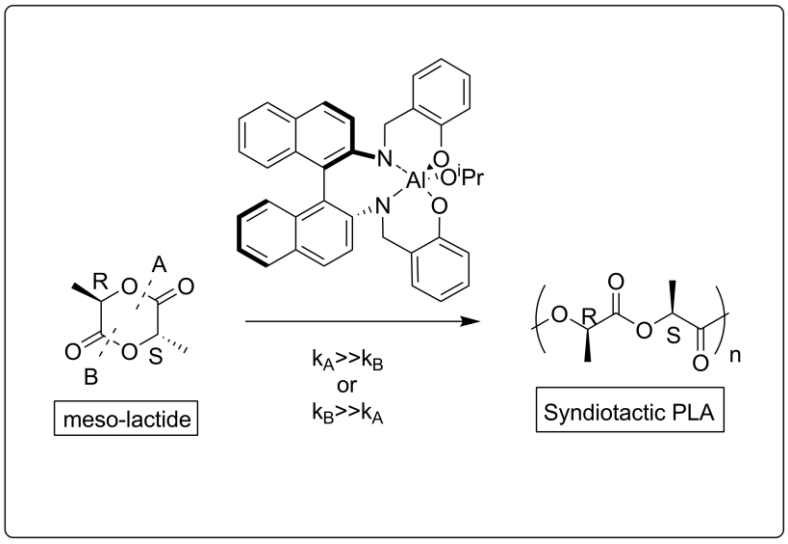


Fig.2.23: Preparation of syndiotactic PLA (Adapted from Ref. 15)

It was however not possible to determine which acyl-oxygen bond was getting cleaved by the R-enantiomer of the catalyst, but it was seen that on neglecting the end groups, cleavage of any of the acyl-oxygen bonds give rise to the same syndiotactic polymer. [15]

The syndiotacticity of the polymer was confirmed by ^{1}H NMR analysis.

The mechanical aspects for the polymerization is shown below-

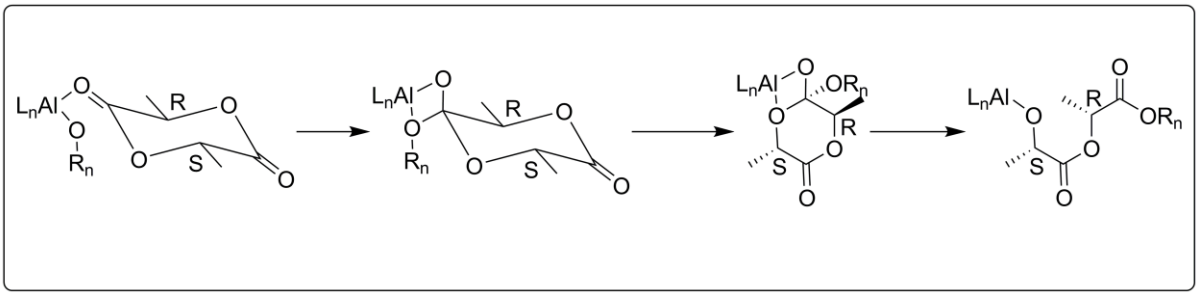


Fig.2.24: Mechanism for the formation of syndiotactic PLA (Adapted from Porter, Keith A., R*ing Opening Polymerization of Lactide for the Synthesis of Polylactic Acid*. State of Illinois)

Here, L_n refers to the chiral ligand and R_n refers to ^{i}Pr.

2.1.2.1.3.2 Preparation of heterotactic PLA from meso-lactides using racemic organometallic initiators:

When the racemic catalyst, Al(O^{i}Pr)[rac-(SalBINAP)] was used as an initiator in the Ring-Opening Polymerization reaction of meso-lactide, heterotactic PLA was obtained as a result. To explain this observation, Coates and co-workers came up with a polymer-exchange mechanism where each polymer chain shuttles between the two enantiomeric centres present in the racemic catalyst. [15] This mechanism is shown in the following figure-

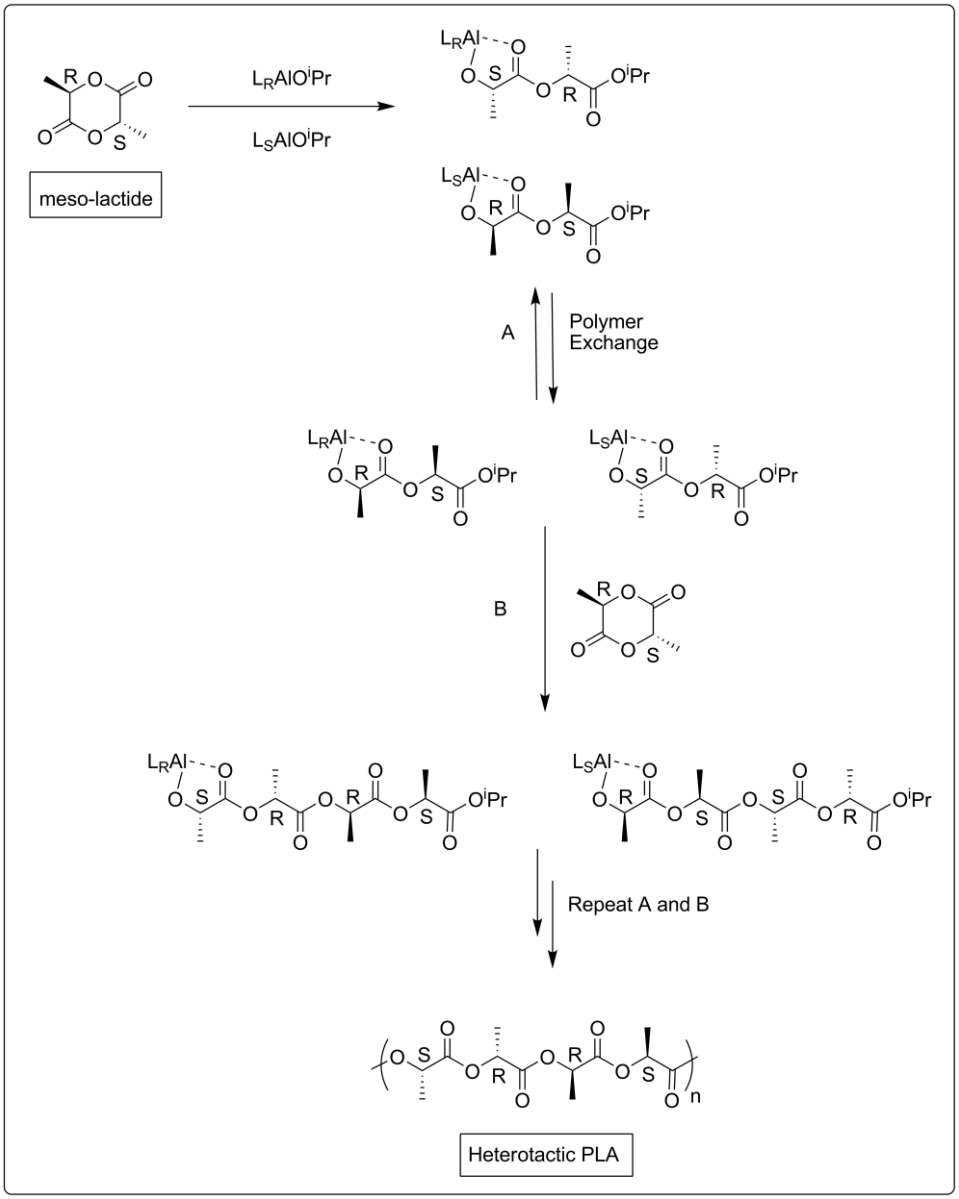


Fig.2.25: Mechanism for the preparation of heterotactic PLA (Adapted from Ref. 15)

From molecular modelling, it was also found that the (R)-enantiomer present in the racemic catalyst preferentially opens the meso-lactide at the carbonyl group adjacent to the (R) stereocentre. [15]

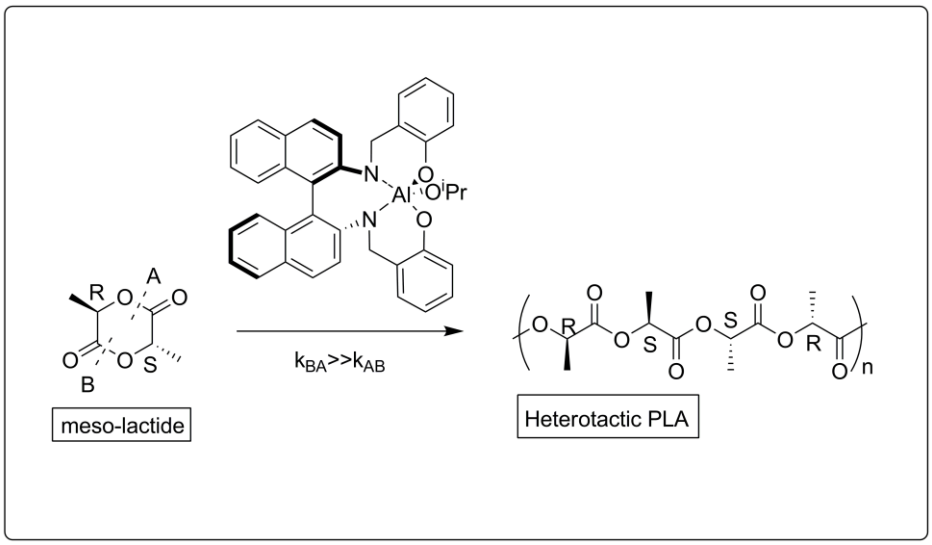


Fig.2.26: Synthesis of heterotactic PLA (Adapted from Ref. 15)

2.1.2.1.3.3 Stereochemistry of lactide polymerization from meso-lactide using (BDI)-ZnO^{i}Pr catalysts:

Analogous to the example shown above, preparation of either syndiotactic PLA or heterotactic PLA is possible from meso-lactides using achiral (BDI)-ZnO^{i}Pr catalysts. [16] This can be illustrated with the help of the following figure-

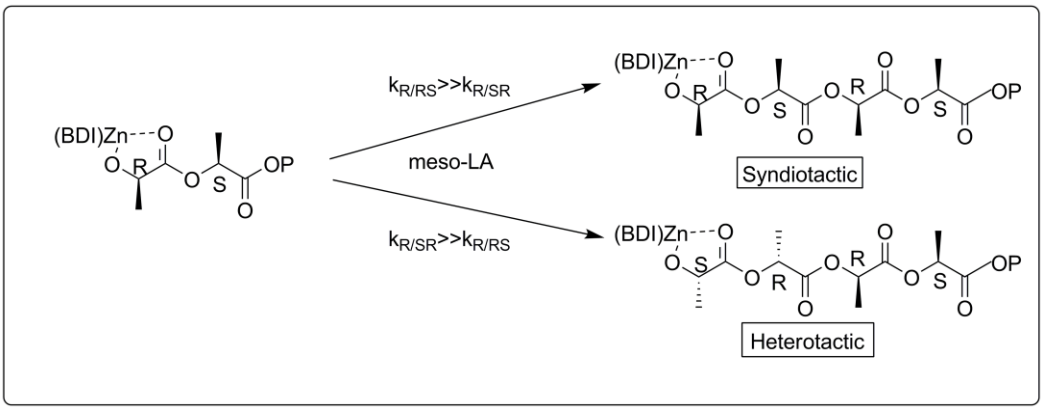


Fig.2.27: Synthesis of different stereoisomers of PLA (Adapted from Ref. 16)

It was shown by Coates and co-workers that both syndiotactic and heterotactic PLA can be separately generated from meso-lactides, by using two types of (BDI)-ZnO^{i}Pr catalysts. [16]

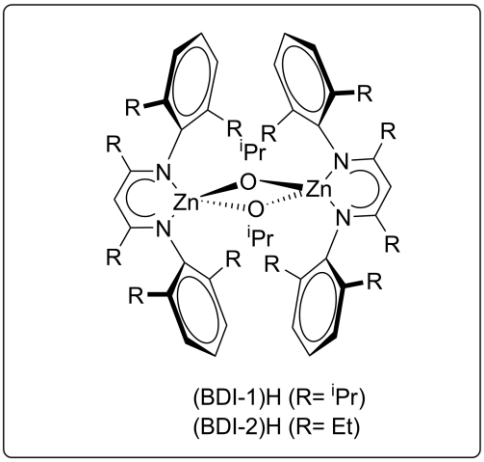


Fig.2.28: Possible structures of ß-diiminate zinc catalysts (Adapted from Ref. 16)

With [(BDI-1)Zn(μ-O^{i}Pr)$_2$], syndiotactic PLA was formed, while [(BDI-2)Zn(μ-O^{i}Pr)$_2$] resulted in the formation of heterotactic PLA. The exact reason behind this chnge of tacticity was not clear. However, it was evident that the two catalysts resulted in different modes of enchainment of the enantiomers present in the racemic lactide. [16]

2.1.2.2 Using organocatalysts:

The main problem that arises when organometallic catalysts are used for Ring Opening Polymerization of lactides is the removal of toxic metal components from the chain ends of the polymer, before these polymers are used to prepare resorbable biomaterials.[17]

One step towards preparation of PLA with high stereocontrol, in an environmentally benign way, can be taken if pure organic catalysts are used instead of organometallic ones.

The different organocatalytic pathways that are involved in the Ring Opening Polymerization of lactides and lactic acids are briefly described below.

2.1.2.2.1 Cationic Ring Opening Polymerization of lactides:

Didier Bourissou and co-workers had reported a controlled cationic ring opening polymerization of lactide derivatives using a combination of triflic acid (as catalyst) and a protic agent such as water or alcohol (as initiator), to generate isotactic PLA . [18]

Reaction was performed at room temperature and high monomer conversion was noted. [18]

The mechanism for this reaction is shown below-

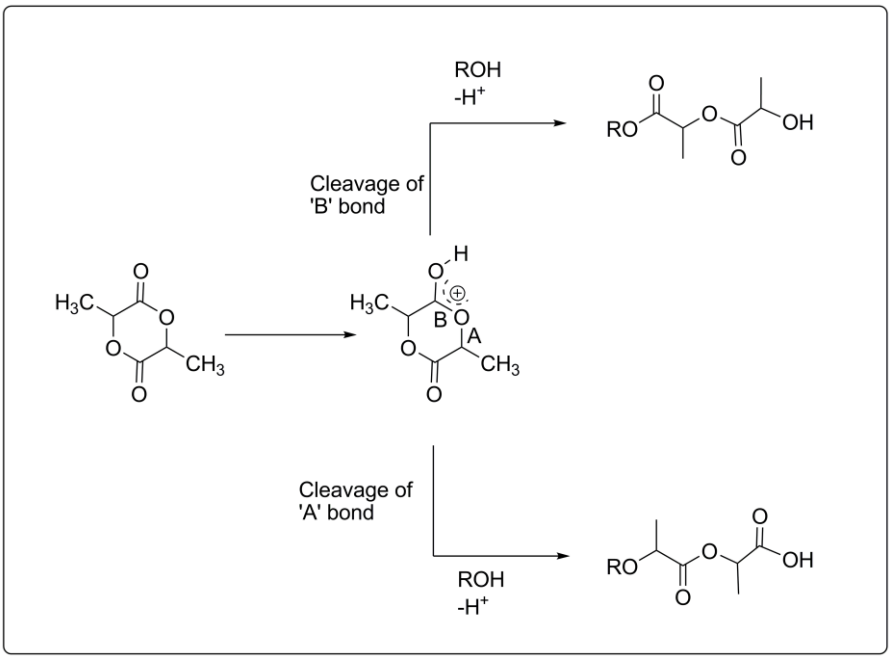


Fig.2.29: Mechanism for cationic ROP of lactides (Adapted from Ref. 3)

1.1.2.2.2 Living Anionic Ring Opening Polymerization of lactides:

Commercially available phosphazene bases such as those shown below are used to prepare isotactic PLA derivatives. 1-pyrene butanol was used as an initiator in this case.

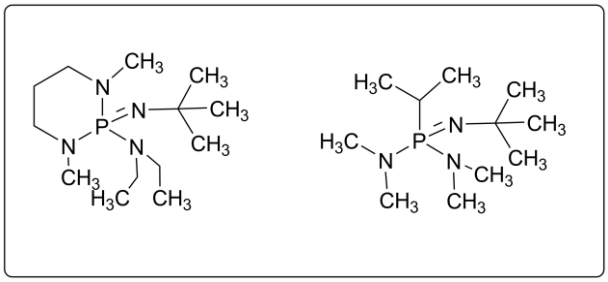


Fig.2.30: Bases used for anionic ROP of lactides (Adapted from Ref. 3)

The pKa values of the protonated phosphazene bases (1) and (2) are approximately around 27. [3]

NMR studies suggest that the intermolecular hydrogen bonding that takes place between the alcohol initiator and the phosphazene base activates the alcohol for ROP of lactides. [19]

2.1.2.2.3 Using pyridine based nucleophilic organocatalytic systems such as DMAP:

In the presence of ethanol as an initiator, DMAP was used to catalyze the Ring Opening Polymerization of lactides at 35°C in CH_2Cl_2. The polymerization was proposed to occur via a monomer-activated process. [20] The mechanism is shown in the form of the following schematic diagram-

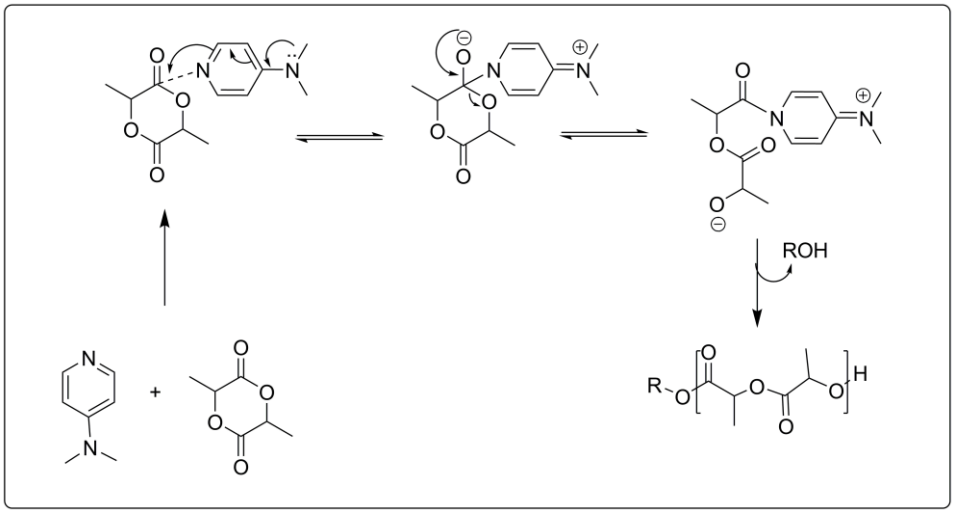


Fig.2.31: Mechanism for DMAP-catalyzed polymerization (Adapted from Ref. 3)

From NMR data it was confirmed that the α-end of PLA bears an ester group derived from the initial alcohol, while the ω-end contains a hydroxyl group. This information supports the above mechanism. [20]

2.1.2.2.4 Using N-heterocyclic carbenes as catalysts:

Hedrick and co-workers decided to use nucleophilic catalysts like- N-heteocyclic carbenes (NHC) for the Ring Opening Polymerization of PLA, as these compounds can be readily synthesized and they exhibit a wide range of structural diversity. Chiral motifs can also be introduced in these compounds. [17]

The nucleophilic monomer-activated mechanism involved in the process can be illustrated as follows-

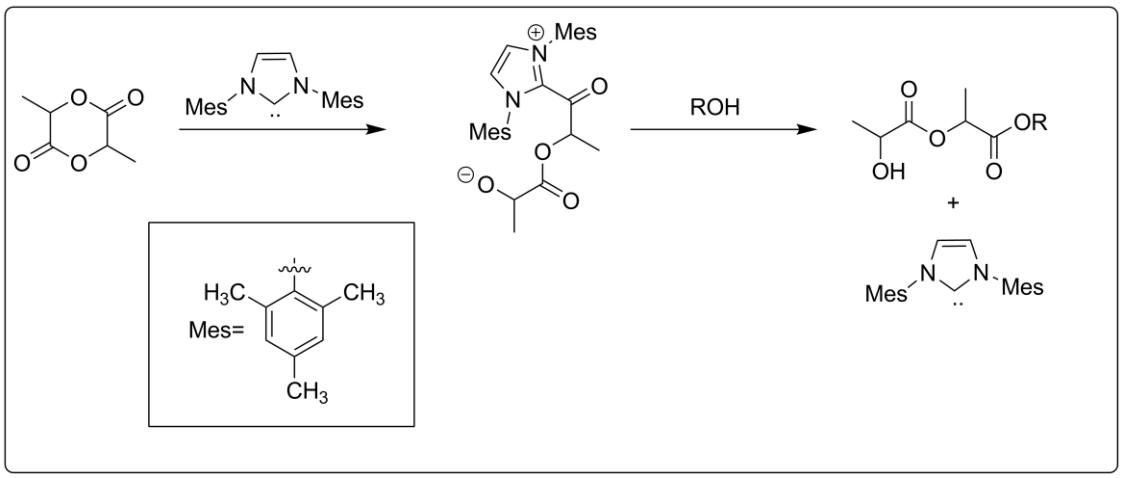


Fig.2.32: Mechanism for NHC-catalyzed polymerization (Adapted from Ref. 3)

Here, the secondary alcohol associated with the ω chain-end serves as a nucleophile for further polymerization. [17]

A wide range of structurally diverse N-heterocyclic carbenes based on thiazolylidene, triazolylidene and imidazolylidene motifs have also been used successfully for the Ring Opening Polymerization of lactides. [3]

The high activity of N-heterocyclic carbenes can be used to carry out the polymerization of racemic and meso lactides in a stereoselective manner at lower temperatures.

Polymerization of racemic lactide with a sterically hindered NHC like Ph_2IMes, results in the formation of a stereoblock polymer as the terminal alkoxide of the growing chain preferentially attacks the acyl imidazolium ion with the same stereochemistry. [21]

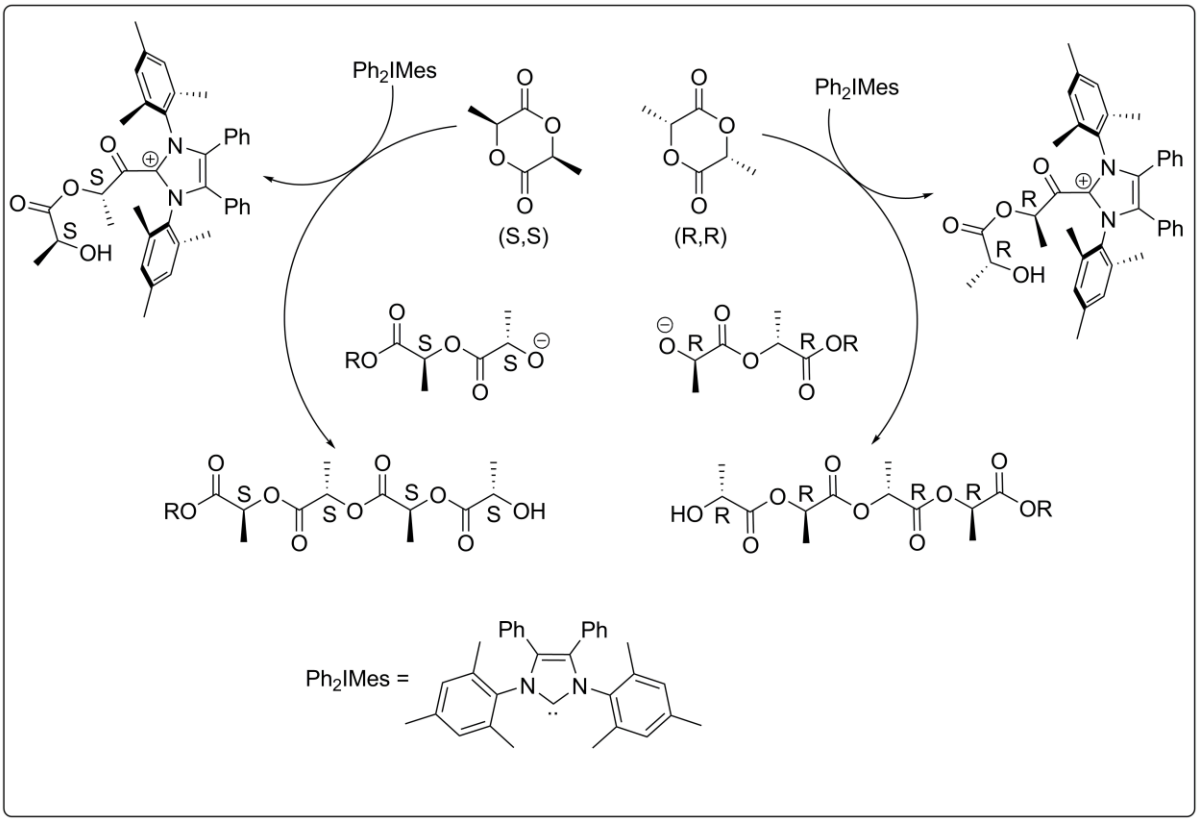


Fig.2.33: Mechanism for NHC-catalyzed polymerization of racemic lactide (Adapted from Ref. 21)

Meso-lactide also undergoes a stereocontrolled polymerization in presence of Ph_2IMes and generates a heterotactic polymer. [21]

Here, the oxygen attached to the last stereocentre of the polymer chain selectively attacks the activated monomer bearing the same stereogenic configuration. [21]

This mechanism is shown in the following figure-

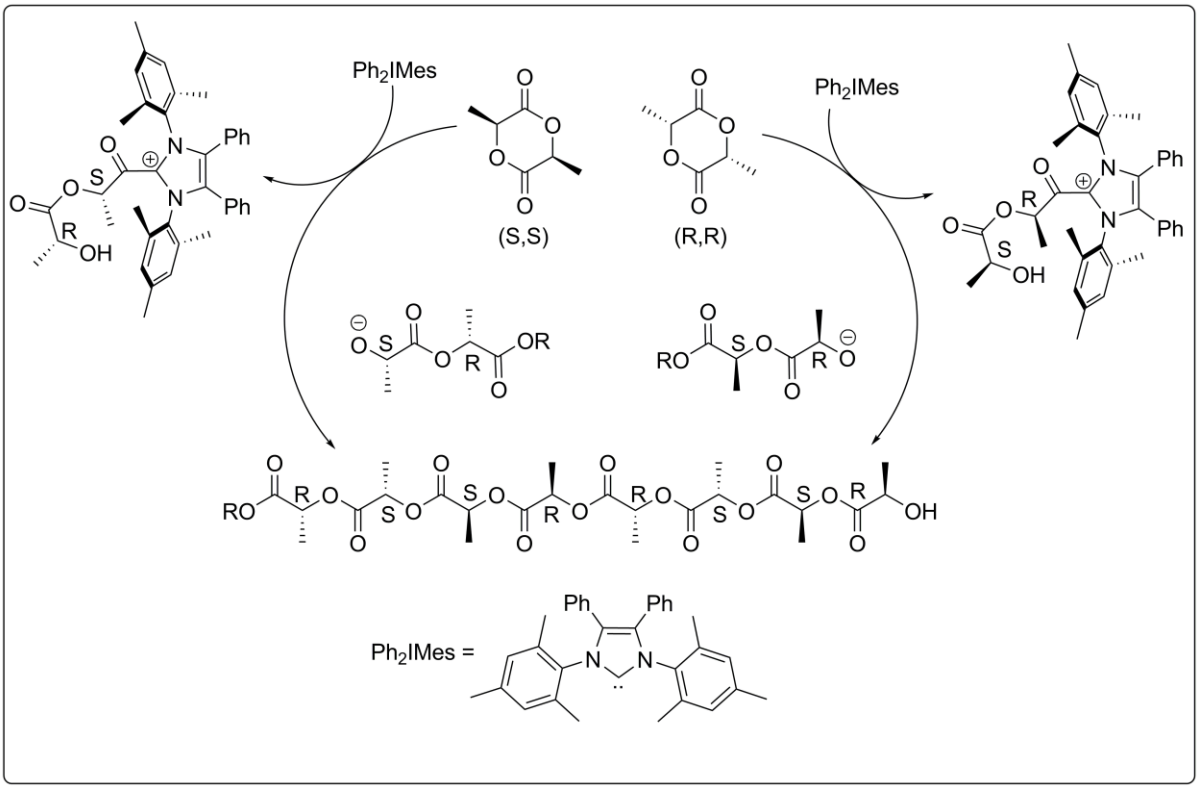


Fig.2.34: Mechanism for NHC catalyzed polymerization of meso-lactide (Adapted from Ref. 21)

2.1.2.2.5 Using bifunctional thiourea based organocatalysts:

Here, the catalytic cycle proceeds via a bifunctional mode of activation, as the lactide monomer as well as the initiator alcohol molecule are activated by the thiourea catalyst simultaneously. This can be easily illustrated with the help of the figure shown below-

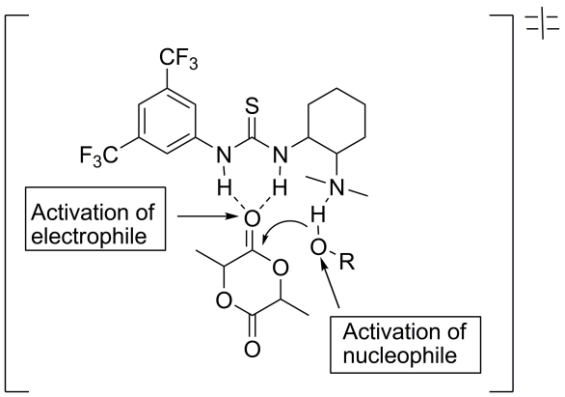


Fig.2.35: Mode of action of Bifunctional Thiourea catalysts (Adapted from Ref. 3)

This mechanistic hypothesis is supported by the following observations-

- Electron-withdrawing groups attached to the aryl group of the thiourea derivative results in an increment in the rates of catalysis. Thus, it is evident that thiourea serves as H-bond activator.
- Increasing the basicity of the amine component of thiourea increases the rate of polymerization, thereby confirming the activation of the alcohol moiety. [3]

As thiourea preferentially catalyzes the polymerization reaction over the transesterification reaction of open chain esters, hence low polydispersity and high stereocontrol is observed in the polymers obtained from thiourea catalyzed reactions. [21]

2.1.2.2.6 Using Guanidine as organocatalysts:

Superbasic Guanidine 1,4,7-triazabicyclodecene (TBD) can be used to perform Ring Opening Polymerization of lactides in non-polar solvents. [22]

TBD has two accessible nitrogen atoms. Thus, it can promote the dual activation of monomer and initiator simultaneously. It can behave as a hydrogen bond donor with respect to the monomer and as a hydrogen bond acceptor with respect to the initiator alcohol moiety. The mechanism is thus analogous to the thiourea-catalyzed one. [22]

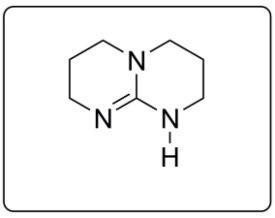


Fig.2.36: 1,4,7-triazabicyclodecene

2.1.3 Basis for the project:

Though a series of organocatalysts have been tested for the Ring Opening Polymerization (ROP) of lactides, yet the polymers obtained from these catalytic pathways have molecular weight values lesser than those obtained from organometallic catalysis.

Besides, the change in energy associated with the relief of ring strain, which is considered to be the driving force behind the ROP of lactides is also not very high. [23]As a consequence, highly active organometallic promoters are used to catalyze the polymerization reaction of lactides under mild conditions. [23]

Generally, the major problem associated with polymerization catalysis is transesterification. Hence, polymers having low molecular weights are formed.

In order to avoid these problems, it is very important to use activated equivalents of lactides where the ring strain will be more than their six-membered counterparts.

One such example of an activated molecule is α-lactone. However, as this molecule consists of a 3-membered ring, hence it is too reactive and cannot be used as a monomer. [23,24]

Another example of an activated lactide equivalent is 1,3-dioxolane-2,4-dione (lac-OCA). This kind of compound falls under the category of O-carboxy anhydrides (OCA).

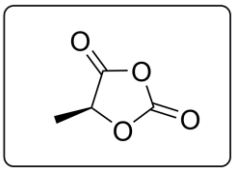


Fig.2.37: O-carboxy anhydride derivative of lactic acid (Adapted from Ref. 23)

Didier Bourissou and co-workers had computationally modelled the propagation step of the Ring Opening Polymerization using L-lac-OCA as monomer and they had found that, this step was thermodynamically more favourable than the corresponding step involving lactide as the monomer. [23]

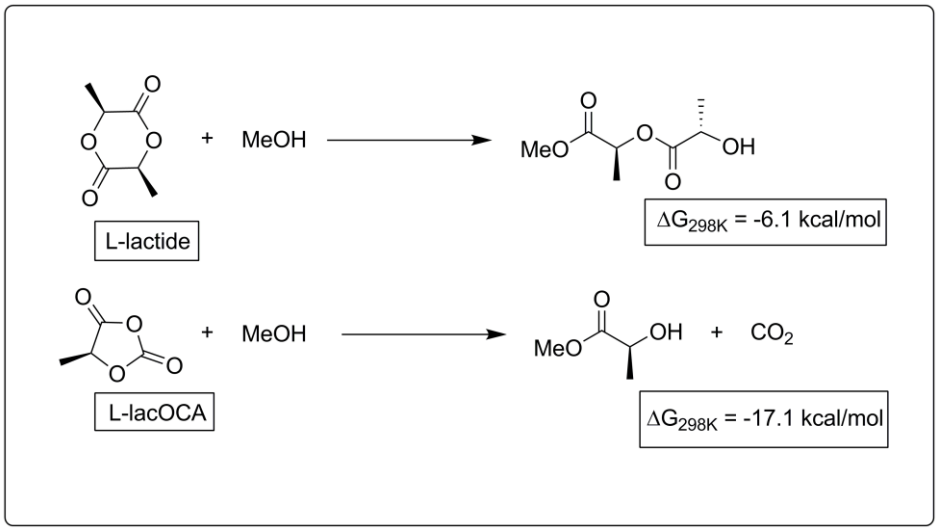


Fig.2.38: Synthesis of PLA from L-lactide and L-lacOCA (Adapted from Ref. 23)

They had also done the Ring Opening Polymerization reaction with L-lacOCA (monomer), using DMAP as the nucleophilic catalyst and isopropanol as the initiator. Complete monomer conversion was observed with a monomer: initiator: catalyst ratio of 20:1:1. [23]

Polymers with low polydispersity values (< 1.3) were observed. [23]

Keeping in mind the monomer-activation mechanism of DMAP, Bourissou proposed the following mechanism for the O-carboxy anhydride (OCA) derivative.

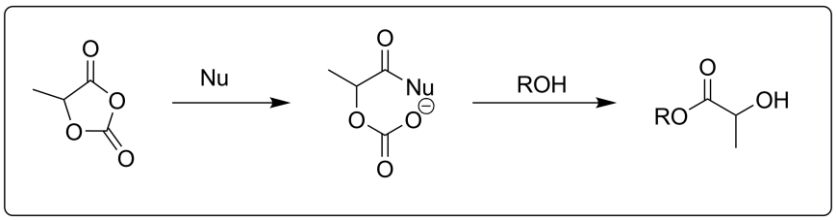


Fig.2.39: Mechanism of action of OCA derivative (Adapted from Ref. 23)

Here, the nucleophilic DMAP attacks the carbonyl carbon which is more electrophilic in nature. [23]

Bourissou and co-workers have thus reported the ROP of O-carboxy anhydride derivative of L-lactic acid using two types of catalysts, namely- DMAP (organocatalysis) [23] and lipase (enzymatic catalysis) [25].

However, till now, nobody has studied the Ring Opening Polymerization of the O-carboxy anhydride derivative of racemic lactic acid (rac-lacOCA). We decided to work on that.

Besides, the organocatalysts that have been used till date for the preparation of Poly (lactic acid) are mostly achiral in nature. Hence, we thought that if we can use a chiral organocatalyst, then we can conduct studies to find out how the chiral information present in the catalyst gets transferred to the product.

For that purpose, we chose $(DHQ)_2AQN$, a modified Cinchona alkaloid, as the catalyst.

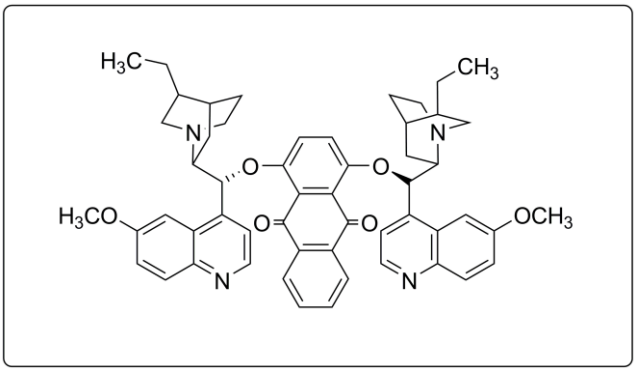


Fig.2.40: Structure of $(DHQ)_2AQN$ (Adapted from Sigma Aldrich official website)

This kind of catalyst has been previously used to carry out enantioselective alcoholysis of meso-anhydrides like succinic anhydrides and glutaric anhydrides leading to desymmetrization. The above catalyst has also been used for the desymmetrization of prochiral anhydrides like the O-carboxy anhydride derivative. [26]

$(DHQ)_2AQN$ has been used for the kinetic resolution of N-carboxy and the O-carboxy anhydrides as well. [27] The catalyst is believed to perform a dual role, catalyzing the racemization as well as the enantioselective kinetic resolution, by undergoing hydrogen bond formation with the alcohol (initiator) moiety. [27]

Hence, we thought of studying the Ring Opening Polymerization of racemic O-carboxy anhydrides, by using $(DHQ)_2AQN$ as the catalyst, in order to observe the effect of the catalyst on the stereocontrolled polymerization of rac-lacOCA.

In order to find out the extent of stereocontrol exerted by an organometallic initiator or an organocatalyst on the polymerization reaction, probability of different modes of enchainment must be taken into account. These probabilities are- P_i (probability of isotactic enchainment) and P_s (probability of syndio/heterotactic enchainment). P_i can also be written as P_m or the probability of meso linkages present between monomeric units. Similarly, P_s can also be written as P_r or the probability of having racemic linkages between monomeric units. These probability values can be obtained by analysing the tetrad level resonances occurring in the methine region of a homonuclear decoupled proton NMR spectrum and also by comparing the peak integrals with the predicted values obtained from Bernoullian statistics. [15 16 28]

Generally, organometallic initiators are found to have high P_i and P_s values, (>0.90) as compared to the organocatalysts with respect to tetrad sequences. [28] Till now, only one class of organocatalysts like sterically hindered N-heterocyclic carbenes (NHC), have been found to have P_i and P_s values close to 0.90 for diad sequences. [21] However, to achieve this P_i value, a very low temperature of -70^{o}C was required, as at room temperature a P_i value of only 0.58 was obtained. [21] The tetrad ratio of iii:(iis/isi/sii):sis obtained by using these kind of NHC catalysts is only 1:1:1.3. It is not possible to distinguish between the iis, isi, ssi tetrad sequences from the methine region of proton decoupled ^{1}H NMR spectrum. [4] This reflects the lack of long-range stereochemical order.

On the other hand, the other organocatalysts exhibit very low P_i values, that too only for diad sequences. This shows that the organocatalysts used till date are not capable of bringing about high level of stereocontrol in the prepared polymer. Thus, we wanted to use sterically encumbered organocatalysts like $(DHQ)_2AQN$, in order to see whether it is possible for these catalysts to exert stereocontrol to an extent comparable to their organometallic counterparts at room temperature.

2.2 Results and Discussions

2.2.1 Preparation of O-carboxy anhydride derivative of lactic acid:

O-carboxy anhydride derivative of racemic lactic acid (rac-LacOCA) can be synthesized from the reaction between triphosgene and the monolithium salt of lactic acid. [23] While triphosgene is commercially available, the monolithium salt for racemic lactic acid is not and it has to be synthesized. At first I will briefly describe the problems I faced while synthesizing the desired lithium salt and the measures I adopted to overcome them.

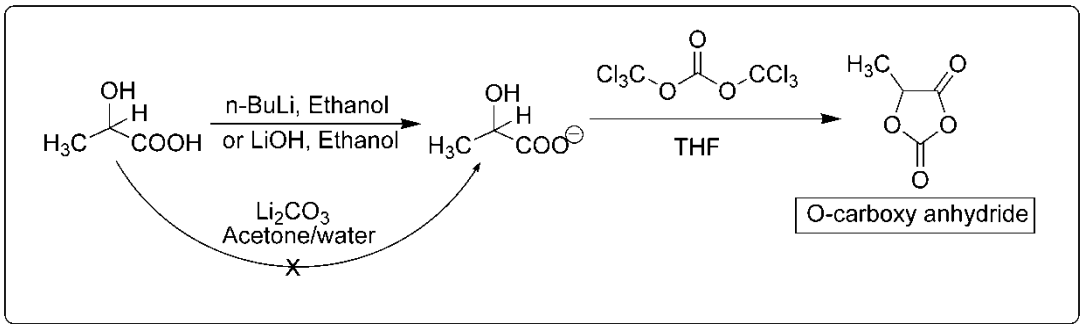


Fig.2.41: General reaction scheme for O-carboxy anhydride preparation

2.2.1.1 Preparation of monolithium salt of racemic lactic acid:

2.2.1.1.1 Using n-butyl lithium:

Initially, it was decided that the lithium salt will be generated in-situ by adding n-butyl lithium (n-BuLi) (3equiv.) to a round bottom flask containing lactic acid (3 equiv.) and triphosgene (1 equiv.) in anhydrous THF (tetrahydrofuran) at 0^{o}C. In order to find out the exact strength of butyl lithium, it was titrated with 1,10-phenanthroline and t-butanol prior to use. The reaction mixture was then stirred at room temperature for 4 hours. However, product formation was not observed (as confirmed from ^{1}H NMR spectrum). The exact reason behind this was not known. It may so happen that as the monolithium salt was not recrystallized, hence small quantities of lithium hydroxide that might have been present along with n-BuLi was somehow affecting the reaction. The presence of some other impurities in both n-butyl

lithium and lactic acid may also be responsible.

As it was not known whether the problem was arising as a result of impurities present in n-BuLi or because of bypassing the recrystallization step, hence the usage of n-butyl lithium was avoided altogether.

Besides, n-BuLi being a very strong base can result in the formation of some amount of dilithium salt of the racemic lactic acid derivative. Though the dilithium salt will also lead to the production of the O-carboxy anhydride, yet as only one equivalent of n-BuLi is used for the reaction, hence the formation of dilithium salt will indicate the presence of some amount of unreacted lactic acid in the reaction mixture. Consequently, the yield of the reaction will decrease.

As potential alternatives to n-Butyl lithium, relatively weaker bases such as- lithium hydroxide or lithium carbonate was used.

2.2.1.1.2 Using lithium carbonate:

Preparation of the monolithium salt from lactic acid and lithium carbonate using water/acetone (1:1) as the solvent system was not successful.

2.2.1.1.3 Using lithium hydroxide:

Lithium hydroxide on the other hand reacted with lactic acid in presence of ethanol, to form a white solid. Reaction mixture was stirred overnight. After that, upon sonication of the reaction mixture for 30 minutes, vapour diffusion technique was used for recrystallization of the solid and acetone was used as a solvent having a lower boiling point. The recrystallization was carried out for 2 days. Proton NMR spectrum of the recrystallized solid, suggested the presence of the monolithium salt. However, we cannot be absolutely sure of this observation, as lactic acid also has peaks in the same frequency region. The only difference lies in the fact that the proton NMR spectrum of the lithium salt does not show any broad peak

corresponding to –OH or –COOH functionalities, while lactic acid does. The recrystallized solid was thus used to carry out reaction with triphosgene and negligible amount of product was formed, as confirmed from ^{1}H NMR. The reason behind this observation can be attributed to the lower solubility of lithium hydroxide in ethanol, as compared to the monolithium salt of lactic acid. As lithium hydroxide is only sparingly soluble in ethanol, hence, unreacted lithium hydroxide may crash out along with the monolithium salt during recrystallization with acetone. As the amount of unreacted lithium hydroxide present in the reaction mixture cannot be quantified, hence it is not possible to comment on its effect on the formation of O-carboxy anhydride.

2.2.1.1.4 Again using n-butyl lithium:

As neither lithium carbonate nor lithium hydroxide yielded the desired results, hence reverting back to n-butyl lithium was deemed necessary. This time instead of generating the monolithium salt in-situ, it was decided that the monolithium salt will be prepared separately, recrystallized and then only it will be used to carry out the reaction. Thus, upon preparation of the lithium salt from n-BuLi and lactic acid, recrystallization was performed using the same vapour diffusion technique as mentioned above. IR data of the compound was also taken.

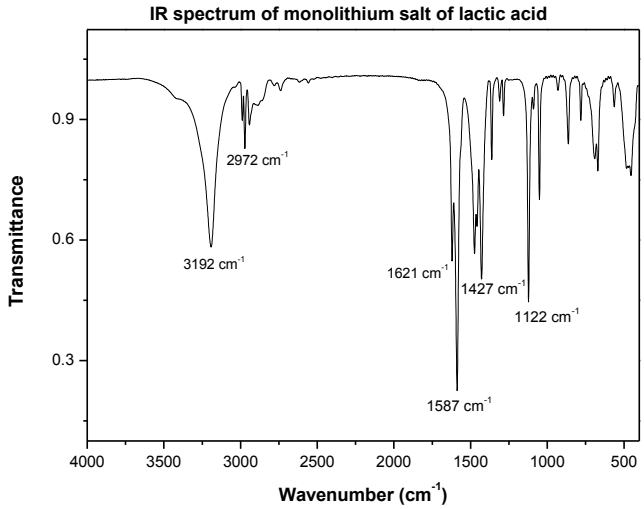


Fig.2.42: IR spectrum of monolithium salt of racemic lactic acid

In the IR spectrum, a peak is seen at 3192 cm^{-1}. As the peak is not broad enough, hence it can be said that the extent of hydrogen bonding in the molecule is low. However, if the monolithium salt gets formed, then intermolecular H-bonding is supposed to take place between the –OH groups of different molecules, leading to a broad –OH peak around 3300 cm^{-1}.But, this is not observed. As hydrogen bonded peak at this frequency will not be observed for the dilithium salt of lactic acid, hence it may so happen, that in the recrystallized material, some amount of the dilithium salt is present along with its monolithiated counterpart. The peaks at frequencies 1587 cm^{-1} and 1427 cm^{-1} confirms the presence of carboxylate anion, as these frequencies are similar to the frequencies of the antisymmetric and symmetric modes of COO^- functionality. [29]

Besides, the absence of carboxylic acid group is also confirmed by the absence of C=O stretching frequency in the range of 1700-1725 cm^{-1}.

This recrystallized compound was thus used to carry out the reactions with triphosgene. Different conditions employed for these particular reactions yielded different results. The results are discussed below.

2.2.1.2 From monolithium salt to rac-LacOCA:

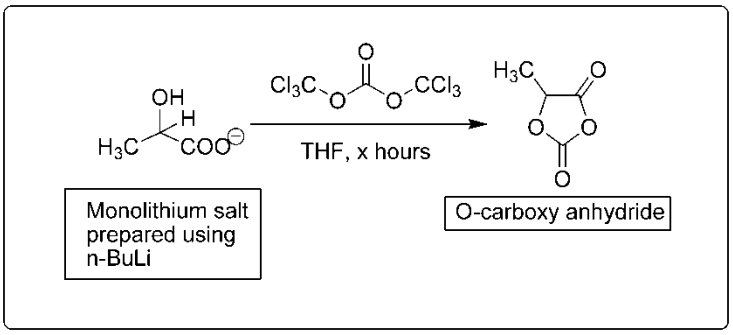


Fig.2.43: Preparation of O-carboxy anhydride

The synthesis of O-carboxy anhydride is extremely sensitive towards the time taken to carry out the reaction, the quality of the triphosgene used, the temperature of the reaction mixture and the purity of the monolithium salt prepared. As the reaction is extremely moisture sensitive, hence it is done under Argon atmosphere and THF (tetrahydrofuran) is distilled over sodium prior to use.

2.2.1.2.1 Effect of reaction time and temperature:

In the procedure reported by Boullay et al., O-carboxy anhydride of L-lactic acid has been prepared by using diphosgene and 2.5 hours were found to be sufficient for the completion of the reaction. However, on using triphosgene (bought from Avra) instead of diphosgene and using the same reaction conditions, no product formation was obtained. This observation maybe attributed to the fact that triphosgene being a solid does not liberate phosgene as easily as diphosgene and hence, reaction with triphosgene is slower. To test this hypothesis, reaction was carried out at 45^{o}C for 3 hours. Then, THF was removed under reduced pressure (vacuum pump was used) and was trapped using a slush of liquid nitrogen and acetonitrile. However, no product formation was observed.

This can be possible owing to the following reasons-

- The O-carboxy anhydride getting formed is decomposing at 45^{o}C.
- Three hours is not sufficient for the completion of the reaction.
- As the boiling point of the O-carboxy anhydride is quite less, (around 110^{o}C, as calculated by Scifinder), it might get removed along with THF under reduced pressure.

To overcome these problems, reactions were performed by varying the reaction time from 3 hours to 36 hours. Reactions were carried out at room temperature and THF was removed by purging the reaction vessel with nitrogen. After studying the outcomes of all these reactions, it was found that 9 hours was the optimum time to carry out the reaction. After 12 hours the product starts to decompose and the decomposition is complete after 24 hours.These observations will be evident upon observing the following NMR spectra.

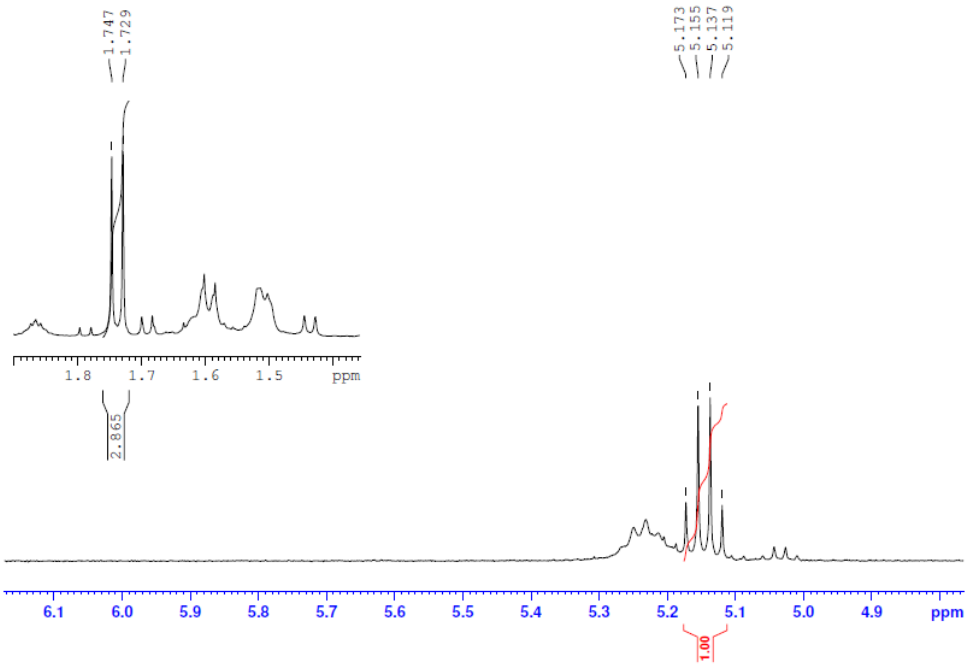


Fig.2.44: ^{1}H NMR spectrum (zoomed view) of rac-LacOCA (reaction time: 9 hours)

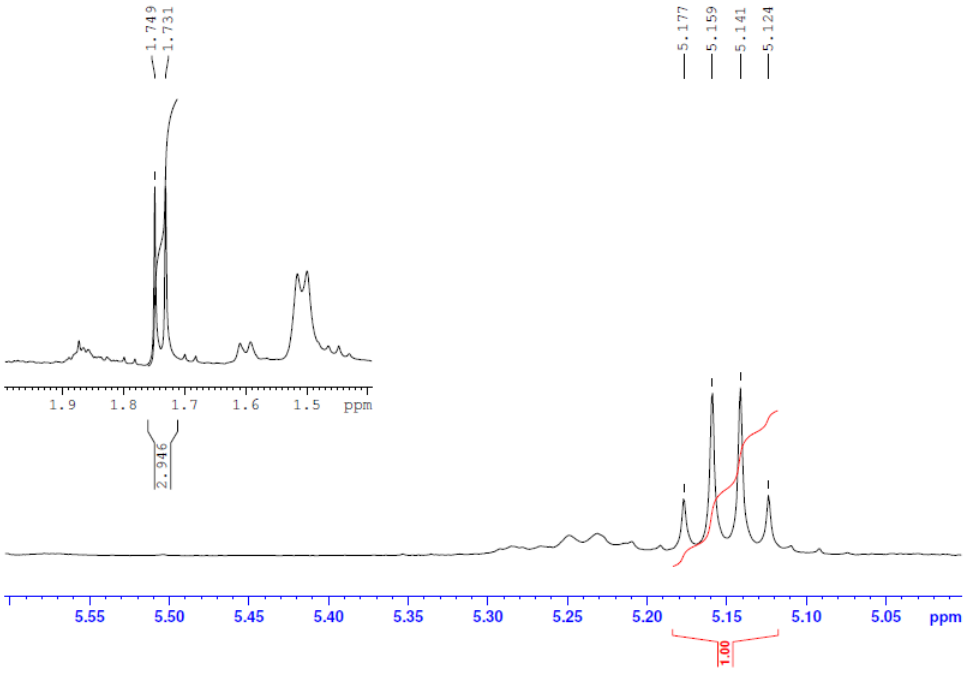


Fig.2.45 ^{1}H NMR spectrum (zoomed view) of rac-LacOCA (reaction time: 12 hours)

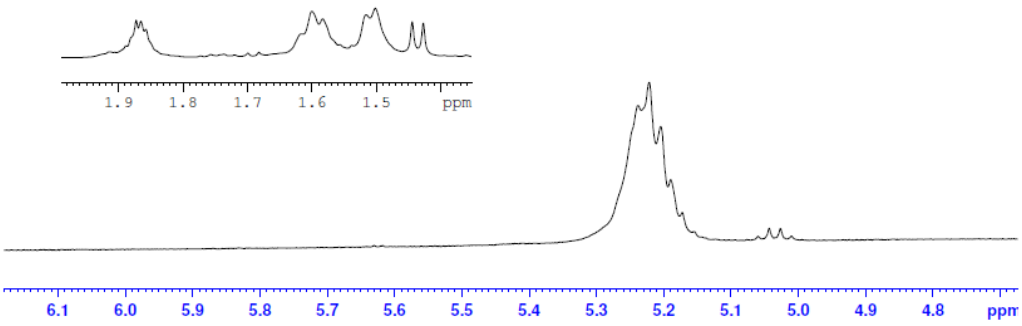


Fig.2.46: ^{1}H NMR spectrum (zoomed view) of rac-LacOCA (reaction time: 24 hours)

It is quite evident that the doublet (δ value 1.74 ppm) and the quartet (δ value 5.173-5.119 ppm) peaks that can be seen in the first NMR spectrum (reaction time: 9 hours) have completely disappeared in the third NMR spectrum (reaction time: 24 hours).

2.2.1.2.2 Effect of the quality of triphosgene:

From the NMR spectral data, it was also clear that the O-carboxy anhydride product that was obtained even after performing the reaction for 9 hours was not pure. In fact, a lot of impurities were still present. These impurities may either originate from triphosgene or the monolithium salt. However, as the NMR spectrum of the monolithium salt appeared to be clean, hence, the source of triphosgene was changed from Avra to Sigma Aldrich, in order to study the effects of the quality of triphosgene in the reaction.

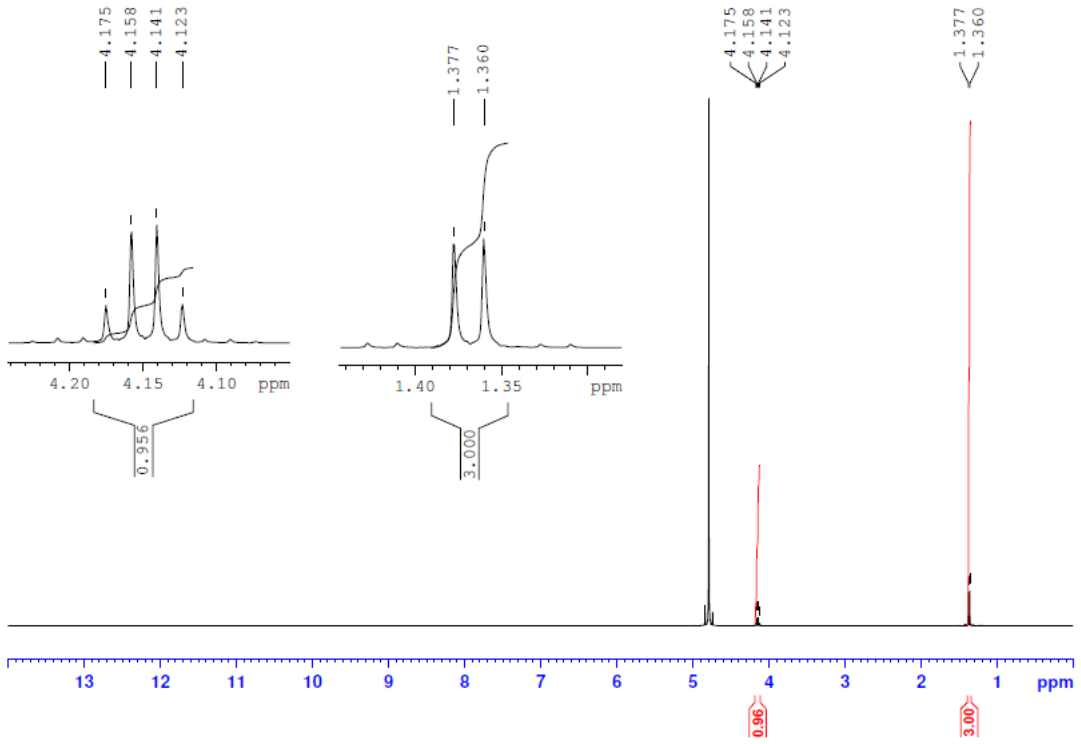


Fig.2.47: [1]H NMR spectrum of monolithium salt of rac-lactic acid

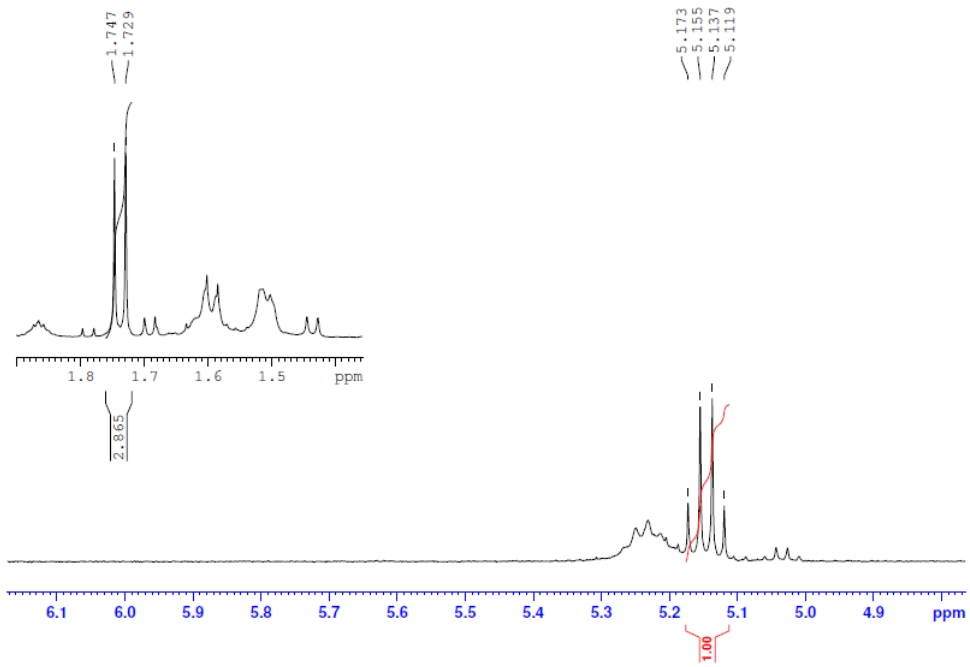


Fig.2.48: [1]H NMR spectrum (zoomed view) of rac-LacOCA (Triphosgene source: Avra)

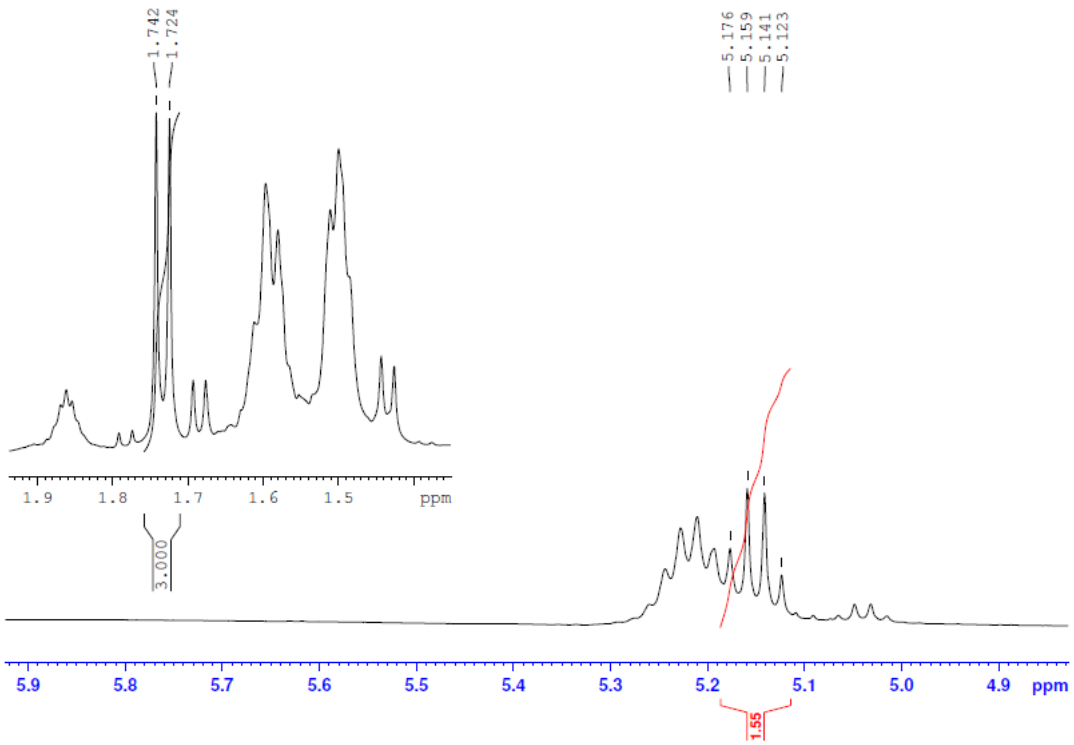


Fig.2.49: ^{1}H NMR spectrum (zoomed view) of rac-LacOCA (Triphosgene source: Sigma Aldrich)

It was seen that though triphosgene from Avra resulted in the synthesis of an O-carboxy anhydride having relatively lesser impurities than the one of Sigma Aldrich make, yet the proton NMR spectrum of that product was also not clean. The reason behind this was difficult to predict. Even after washing the product with distilled hexanes, no change was observed. Besides, product did not crash out on addition of dry, distilled hexanes. Recrystallization from methyl tert-butyl ether was also not possible. Thus, further work needs to be done in order to improve the purity of the derivative.

2.2.1.2.3 Effect of storing the O-carboxy anhydride derivative:

Not only is the O-carboxy anhydride moisture-sensitive, it is also unstable at room temperature. The O-carboxy anhydride derivative undergoes complete decomposition if it is kept for 4-5 hours at room temperature. The rate of decomposition decreases if the product is kept in the refrigerator and approximately one day is required for decomposition.

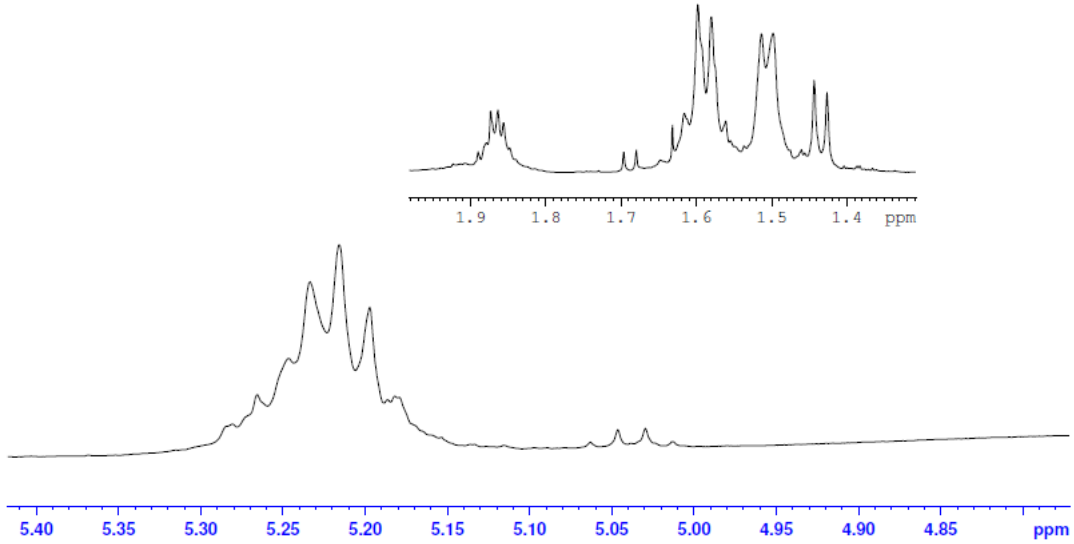


Fig.2.50: ^{1}H NMR spectra (zoomed view) after rac-LacOCA was stored for 6 hours:

2.2.1.3 Other methods for the preparation of the O-carboxy anhydride derivative:

2.2.1.3.1 With n-butyl lithium and 4-nitrophenyl chloroformate:

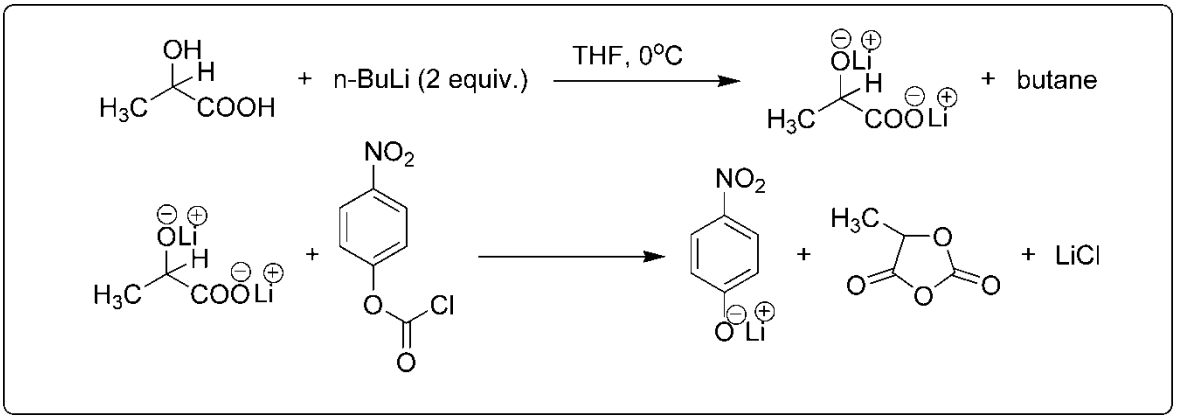


Fig.2.51: Using n-butyl lithium and 4-nitrophenyl chloroformate

Lactic acid was treated with two equivalents of n-BuLi at 0^{o}C, to generate the dilithium salt. It was expected that this dilithium salt will react with 4-nitrophenyl chloroformate to generate

the O-carboxy anhydride. However, this was not observed. Even after addition of dry, distilled hexanes to the reaction mixture nothing crashed out.

The reason behind this observation can be attributed to the insolubility of the dilithium salt in THF. Since the salt did not go into solution, hence it is very less likely to react with 4-nitrophenyl chloroformate. Thus, product might not get formed. The reaction thus needs to be carried out in polar, protic solvent like methanol where the dilithium salt will be soluble. However, the methanol has to be dried over anhydrous calcium chloride, as presence of trace amounts of water is also sufficient to decompose the produced O-carboxy anhydride.

2.2.1.3.2 With sodium hexadimethyl silazane and 4-nitrophenyl chloroformate:

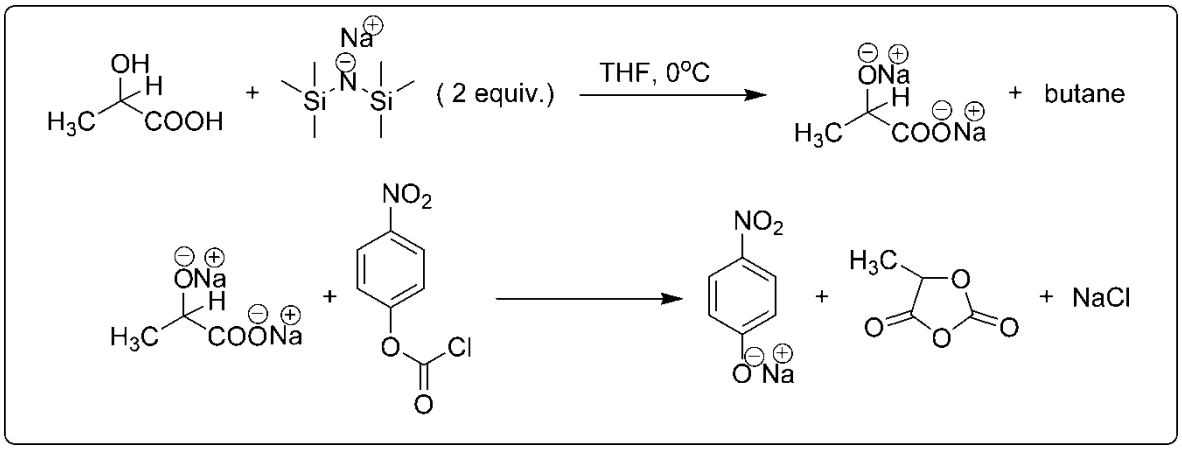


Fig.2.52: Using sodium hexadimethyl silazane and 4-nitrophenyl chloroformate

The same problem was also encountered when instead of n-butyl lithium; sodium hexadimethyl silazane was used as the base.

2.2.1.4 Polymerization of rac-LaOCA:

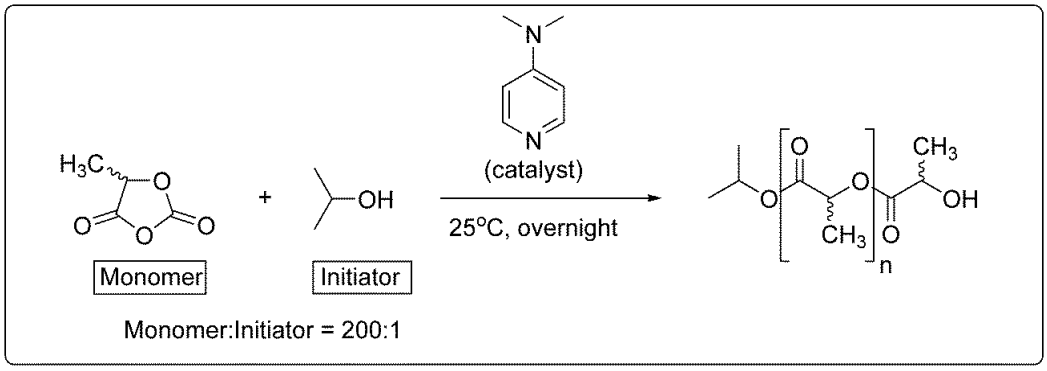


Fig.2.53: Polymerization of racemic O-carboxy anhydride

Boullay et.al had reported the living ring-opening polymerization reactions of L-LacOCA in presence of neo-pentanol (initiator) and N,N-dimethylaminopyridine or DMAP (organocatalyst) at various monomer:initiator concentrations. [23]

In order to determine the optimum conditions necessary to get a polymer of high molecular weight from rac-LacOCA, the monomer:initiator ratios were varied from 50:1 to 200:1 and the molecular weight distributions were obtained from Gel Permeation Chromatography (GPC). Polystyrene beads (Molecular weight: 10,000 g/mol) were used to calibrate the GPC instrument. Here, DMAP was used as an organocatalyst and isopropanol was used as an initiator.

Initially, when a monomer:initiator ratio of 50:1 was taken, two oligomer fragments were obtained, having number average molecular weight (M_n) values of 708 and 369 and weight average molecular weight (M_w) values of 749 and 1249 respectively.

However, the optimum condition was reached when a monomer:initiator ratio of 208:1 was taken. In that case, two polymer fragments were obtained, having an average Mn value around 44,000 and Mw value around 55,000. Polydispersity Index (PDI) value of 1.25 was obtained in this case.

These molecular weight values were even greater than the ones obtained during the polymerization of L-LacOCA, where a monomer:initiator value of 200:1 was taken and DMAP was used as an organocatalyst. [23]

However, though this result is promising, yet the problem lies in the fact that two polymer fragments were obtained instead of one. Besides, from the NMR spectrum it is also seen that, quite a bit of impurity is present along with the polymer.

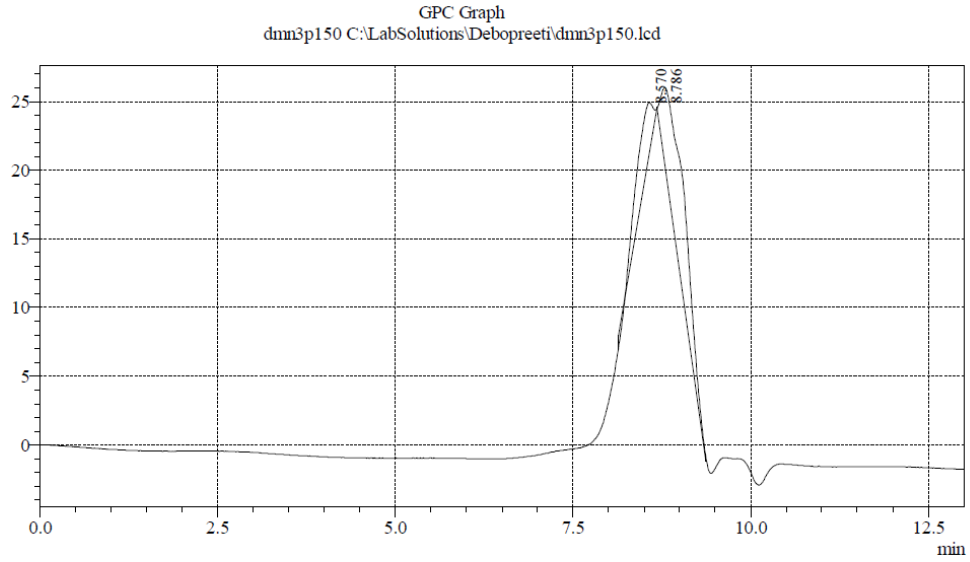


Fig.2.54: Presence of two polymer fragments (evident from GPC profile)

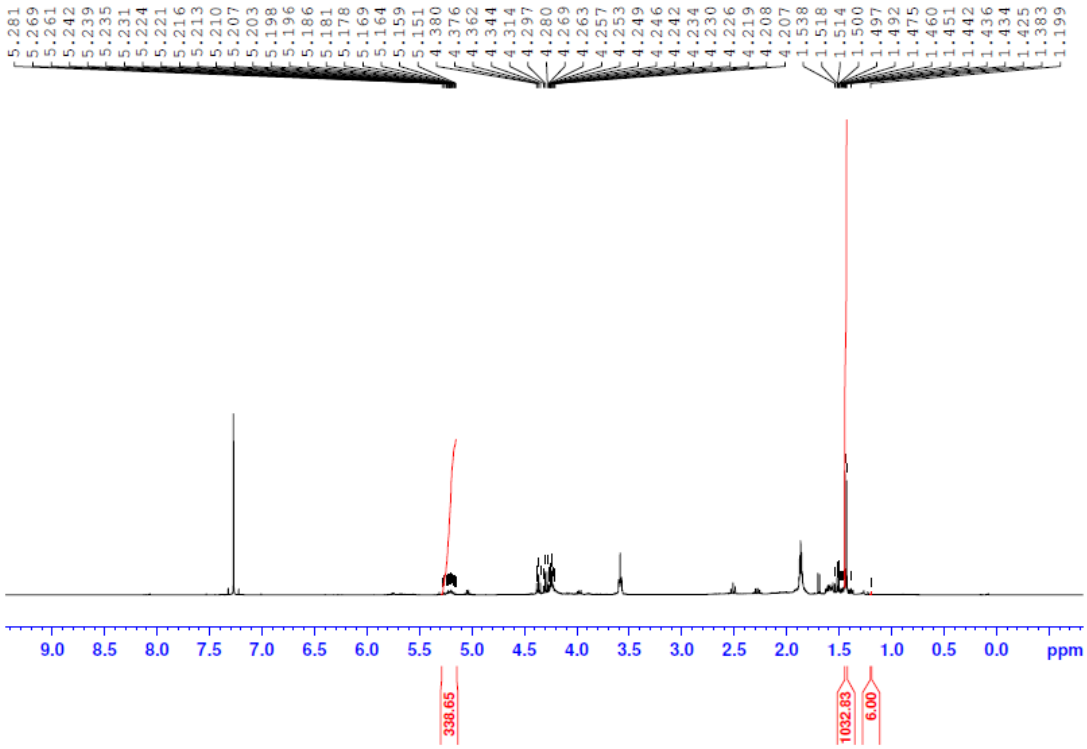


Fig.2.55: ^{1}H NMR spectrum of Poly(lactic acid).

It is quite obvious that the impurity is produced as a result of the impure rac-LaOCA sample that had been used to carry out the polymerization. Thus, in order to get a single polymer with a polydispersity index close to 1, it is absolutely necessary to carry out the polymerization reaction with a pure monomer. Further optimization of reaction conditions is thus needed to prepare the pure O-carboxy anhydride derivative.

Apart from using DMAP, the modified cinchona alkaloid, $(DHQ)_2AQN$ was also used as an organocatalyst.

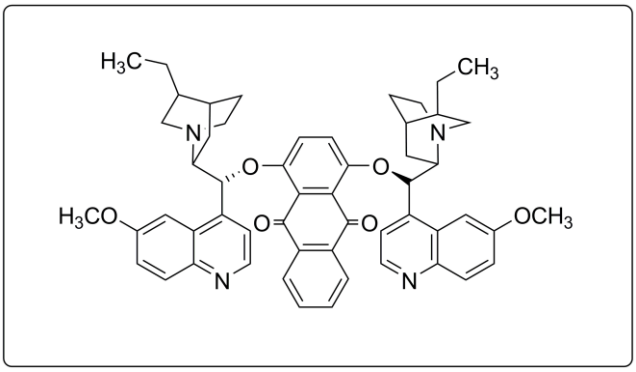


Fig.2.56: $(DHQ)_2AQN$ (Adapted from Sigma Aldrich official website)

But, even though a monomer:initiator ratio of 200:1 was used in this case, yet only oligomer fragments having M_n value around 500 and M_w value around 650 were obtained. However, it can be predicted that as oligomer fragments were obtained with this catalyst, hence, further optimization of reaction conditions and improvement in the purity of the monomer can actually give rise to high molecular weight polymers.

2.2.1.5 Future Directions:

1) Preparation of poly(mandelic acid):

Apart from polymerization reactions of natural α-hydroxy acid (lactic acid) derivatives, polymerization of derivatives of artificial α-hydroxy acids like Mandelic acid also have interesting prospects. Hence, it is worthwhile to see whether it is possible to prepare poly(mandelic acid) using the reaction conditions mentioned above and whether the prepared polymer has good solubility, processability [30] and drug delivery abilities like its lactic acid analogue [31].

The following method was used for the preparation of the O-carboxy anhydride derivative of racemic mandelic acid (rac-ManOCA). However, the method was not successful. Thus, it is necessary to come up with alternative procedures for the synthesis of rac-ManOCA.

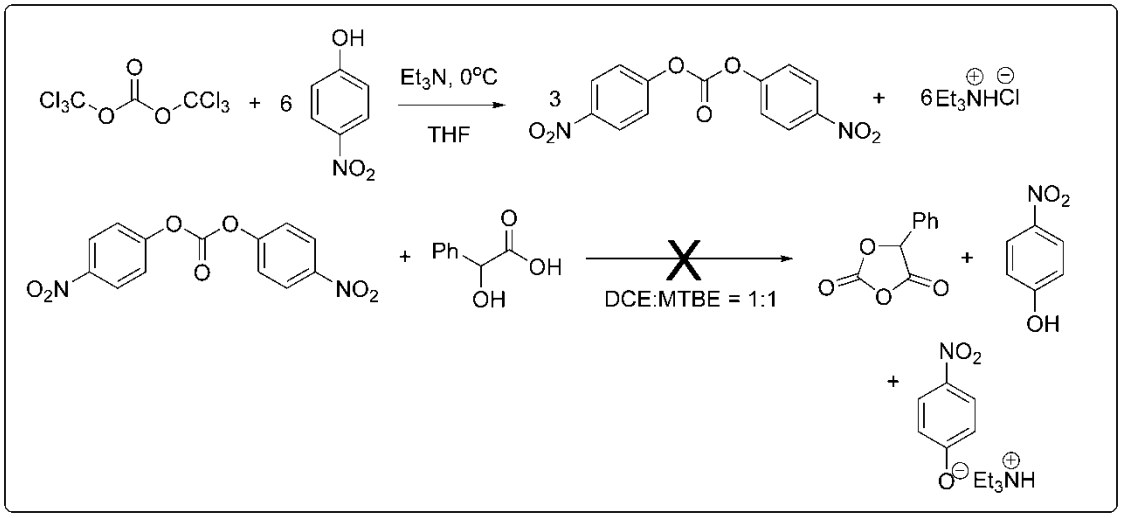


Fig.2.57: Preparation of O-carboxy anhydride of mandelic acid

2) If poly(mandelic acid) can be synthesized, this polymer can also be made to undergo copolymerization with poly(lactic acid) and the properties of this copolymer can be studied.

3) So far, the stereochemical outcome or the tacticity of the Poly(lactic acid) prepared from the racemic O-carboxy anhydride has not been studied. Besides, modified cinchona alkaloids have never been used as organocatalysts for these kinds of polymerizations before. Thus, it will be extremely interesting to study the stereochemistry of the polymer prepared from rac-LacOCA using cinchona alkaloid catalysts such as $(DHQ)_2(AQN)$.

4) The role of modified cinchona alkaloids in performing the dynamic kinetic resolution of O-carboxy anhydride derivatives, leading to the preferential formation of one stereoisomer is already well established. [27]

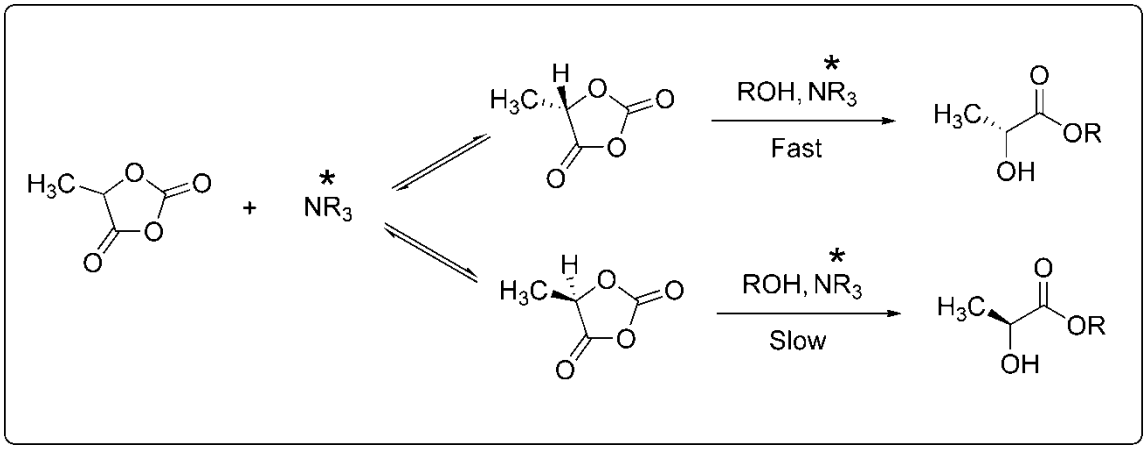


Fig.2.58: Dynamic Kinetic Resolution of O-carboxy anhydride

Hence, under polymerization conditions, it will be really intriguing to see whether this kind of kinetic resolution phenomenon can actually affect the stereochemical outcome of the poly(lactic acid) or not.

2.3 Experimental Section

2.3.1 General experimental methods:

All the reactions were performed under a positive pressure of Argon, using oven dried glassware equipped with magnetic stirbar. Moisture sensitive reagents were handled using standard Schlenk techniques. Solvents were dried and distilled prior to use. Tetrahydrofuran (THF), dithyl ether and MTBE (Methyl tert-butyl ether) were dried over sodium; Dichloromethane (DCM) and IPA (2-propanol) were dried over calcium hydride. DMAP or N,N-dimethylaminopyridine was recrystallized from dry benzene and stored in a desiccator which was kept under vacuum. To find out the exact strength of n-butyl lithium, it was titrated using 1,10-phenanthroline and dry tert-butanol prior to use.

As the O-carboxy anhydride derivatives decompose over silica, hence progress of the reactions could not be monitored using thin layer chromatography. For the same reason, flash column chromatographic techniques could not be employed for the purification of the compounds.

^{1}H NMR spectra were recorded on a 400 MHz Fourier transform NMR spectrometer with $CDCl_3$ as solvent. Chemical shift values were reported in δ ppm (parts per million) values, using the residual solvent protons as internal standard (δ = 7.2700 for $CDCl_3$ in Proton NMR). Coupling constants were reported as J values in Hertz (Hz).The following abbreviations were used while reporting ^{1}H NMR spectra- q: quartet; d: doublet; s: singlet; m: multiplet.

The degree of polymerization or DP, which depicts the number of monomeric units present in a polymer, was determined by taking into consideration the relative integration values of the proton NMR signals with respect to the chain-ends and the lactate units.

The number-average and weight-average molecular weights, M_n and M_w respectively, were obtained by performing Gel Permeation Chromatography (GPC) at 35^{o}C, with a Shimadzu LC-20AD liquid chromatograph equipped with a Shimadzu SPD-M20A Diode Array (UV) detector. THF (terahydrofuran) was used as the eluent and the flow rate was set at 0.4 mL/min. A Varian PL gel MiniMIX-C GPC column was used to perform GPC. Calibration was done by taking polystyrene beads (10,000 g/mol) as standard.

2.3.2 Detailed synthetic procedures:

2.3.2.1 Optimized procedure for the preparation of the monolithium salt of racemic lactic acid:

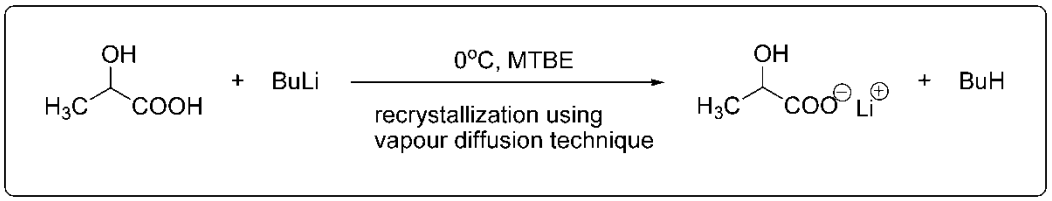


Fig.2.59: Preparation of monolithium salt

A 25 mL round bottom flask was charged with racemic lactic acid (687 mg; 7.6265 mmol; 1 equiv.) and 10 mL of dry MTBE under Argon atmosphere. The temperature of the reaction mixture was brought down to 0^{o}C and to it, 5 mL of n-BuLi (1.52475 (M); 7.62375 mmol; 1 equiv.) was added. White solid was found to crash out from the mixture. This solid was filtered, washed with dry HPLC-grade acetone, transferred to a 500 mL beaker and redissolved in minimum volume of HPLC-grade ethanol (sonication was necessary for dissolution). The contents of the beaker were then transferred to a 500 mL jar, the mouth of which was kept open. A bigger container was then taken and one-third of the volume of the container was filled with acetone. The 500 mL jar was then kept inside this bigger container containing acetone and the mouth of this container was tightly closed. This was the vapour diffusion recrystallization setup that was used and this setup was kept aside for 2 days. Here, acetone being the solvent with a lower boiling point was expected to slowly diffuse into the smaller jar, causing the pure solid to precipitate out from ethanol. Indeed, this phenomenon was observed and the recrystallized solid was collected after two days, filtered and dried using dry benzene. The solid was then used for the preparation of the O-carboxy anhydride derivative of rac-lactic acid.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ 4.175-4.123 (q, J = 6.8 Hz, 1H), δ 1.369 (d, J = 6.8 Hz).

2.3.2.2 Optimized procedure for the preparation of (rac) 5-methyl-1,3-dioxolane-2,4-dione (O-carboxy anhydride):

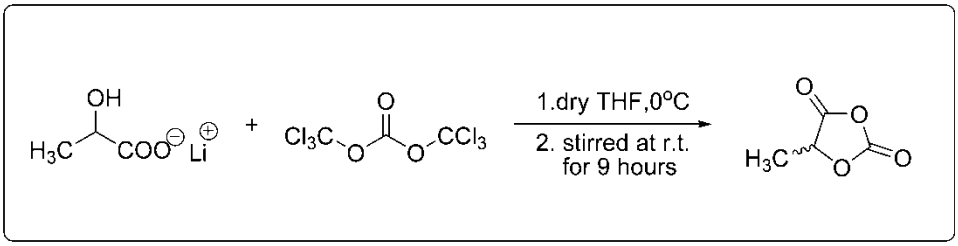


Fig.2.60: Preparation of O-carboxy anhydride

A 25 mL round bottom flask was charged with monolithium salt of lactic acid (546.0 mg; 1.893 mmol; 3equiv.) and to it 6 mL of dry THF was added under Argon. Then, the temperature of the reaction mixture was lowered to 0^{o}C. In another 10 mL round bottom flask, triphosgene (558.0 mg; 1.893 mmol; 3 equiv.) dissolved in 2 mL of dry THF was taken and this mixture was stirred for 2 minutes. The solution in the second flask was then cannulated to the first round bottom flask under positive pressure of Argon. The second flask was then further rinsed with 2 mL of dry THF and this volume of THF was again cannulated to the first round bottom flask. The reaction mixture was allowed to come to room temperature and it was stirred at this temperature for 9 hours. While the reaction was going on, the outlet coming from the Argon line was immersed in a test tube containing 5% sodium hydroxide solution. This precaution was taken in order to quench the excess phosgene gas that was liberated during the course of the reaction.

THF was then removed from the reaction vessel by applying positive pressure of Argon and the outlet was again immersed in a 250 mL beaker containing 5% sodium hydroxide solution. Formation of white solid was observed. To this solid, 10 mL of dry MTBE was added. The mixture was at first stirred for 15 minutes and then allowed to stand for another 15 minutes. The supernatant solution was then cannulated to another 50 mL flask, under positive pressure of Argon. In this case also, the outlet was immersed in a beaker containing 5% sodium hydroxide solution. The procedure was repeated with another 10 mL of MTBE. MTBE was then removed under positive pressure of Argon and resulting yellow oil was obtained. It is not advisable to dry this oil by keeping it under vacuum, as the O-carboxy anhydride has a

boiling point of only 115°C and thus it can get removed as well. To the oily liquid, 0.4 mL of dry diethyl ether was added and the mixture was kept inside the refrigerator overnight. However, recrystallization did not occur. 2 mL of dry, distilled hexane was then added to the mixture but precipitation was not observed. The organic layer containing hexane and MTBE was then cannulated and the oil was dried as much as possible using positive pressure of Argon. ^{1}H NMR spectrum of this oily liquid was taken. Yield: 60.7%

^{1}H NMR (400 MHz, *CDCl$_3$*) δ 5.173-5.119 (q, J = 7.2 Hz, 1H), δ 1.738 (d, J = 3.6 Hz, 3H).

2.3.2.3 Optimized procedure for the preparation of polylactide:

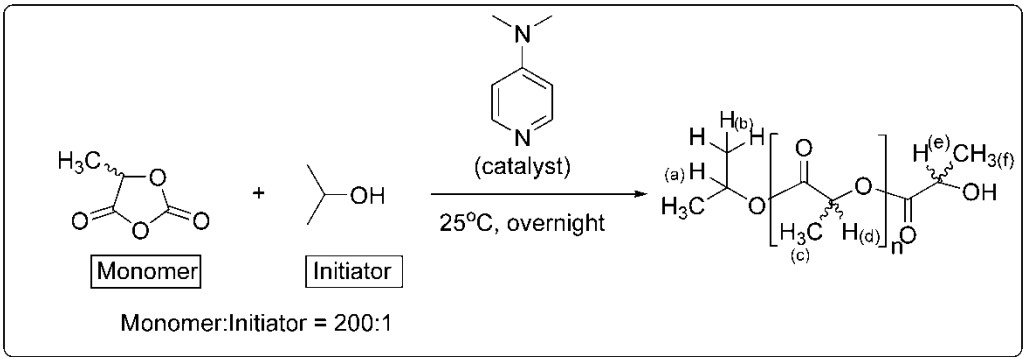


Fig.2.61: Preparation of polylactide

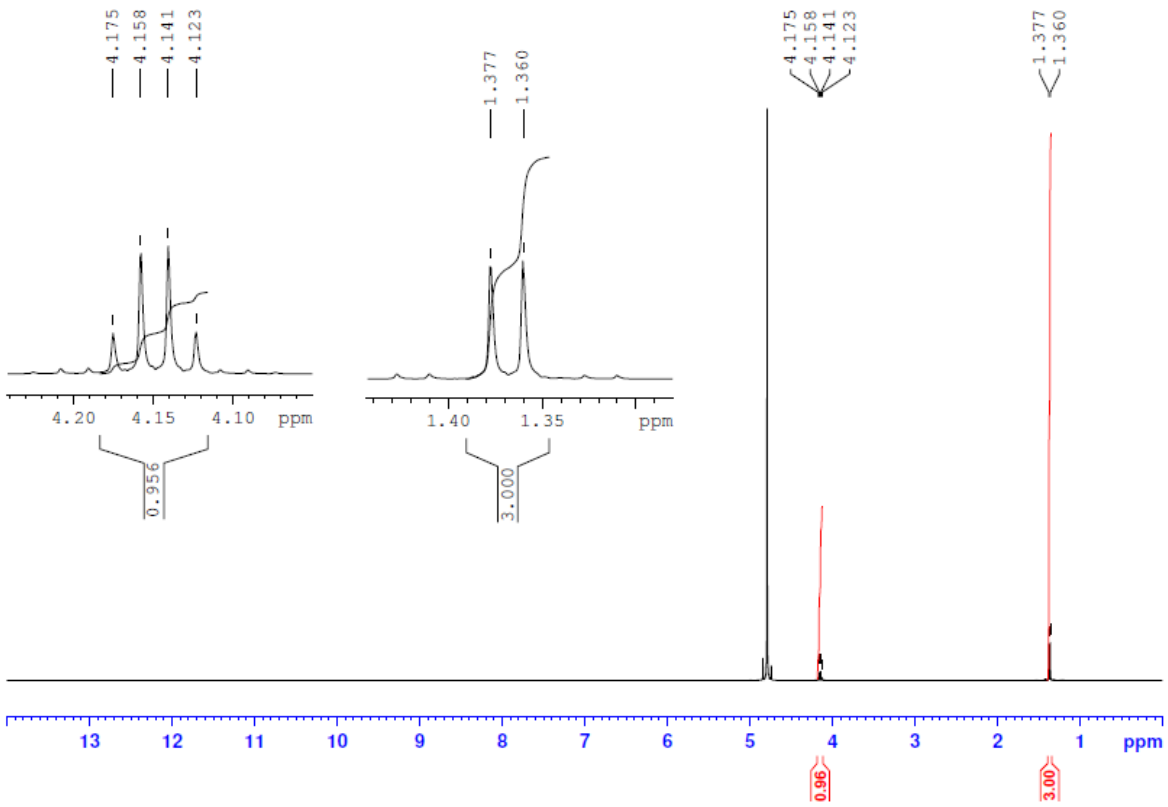
A 25 mL round bottom flask was charged with the monomer (253.1 mg; 2.1805 mmol; 208.46 equiv.) under Argon. It was then dissolved in 2 mL of dichloromethane (DCM). To this solution, 200µL of a standard solution of (IPA) and DMAP (0.0523 molL^{-1}, 1 equiv.) in DCM was added. The reaction mixture was stirred at room temperature until there was no further evolution of CO_2. It was then diluted with 10 mL of DCM and the organic layer was successively washed with cold 1(N) HCl (10X2 mL) and brine (20 mL). The organic layer was then dried over sodium sulphate and it was concentrated. Yellow oil was obtained (43 mg). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ 5.281-5.151 (m, 339 H, protons (c) and (f)), δ 1.538-1.385 (m, 1033 H, proton (d)), δ 1.195 (d, J = 3.84Hz, 6H, proton (a))

Protons of type (a) and (e) cannot be distinguished from NMR spectrum due to the presence of impurities.

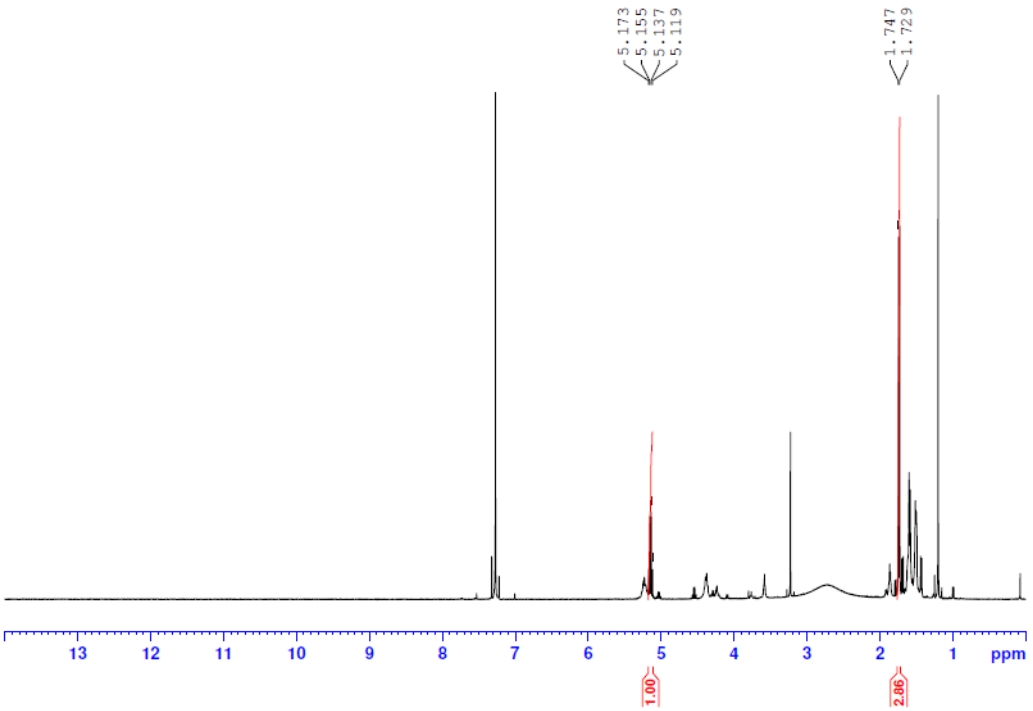
Degree of Polymerization (DP) = 340; M_n (From GPC) = 44599; M_w (From GPC) = 55825; PDI = 1.25172

2.3.3 Characterization data:

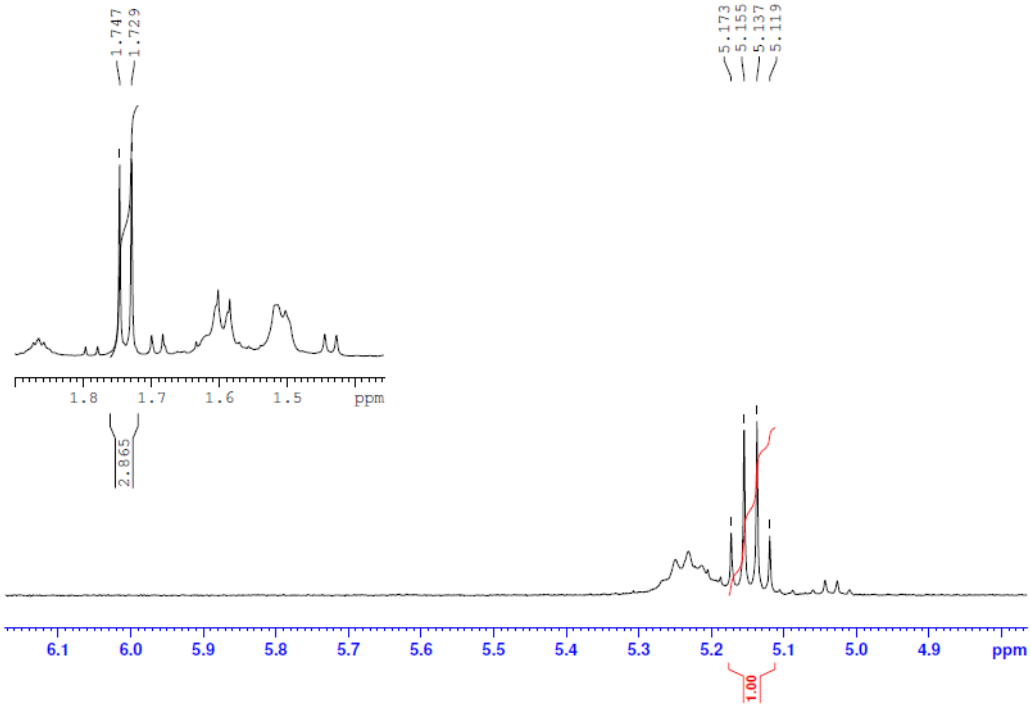
^{1}H NMR spectrum of monolithium salt of lactic acid



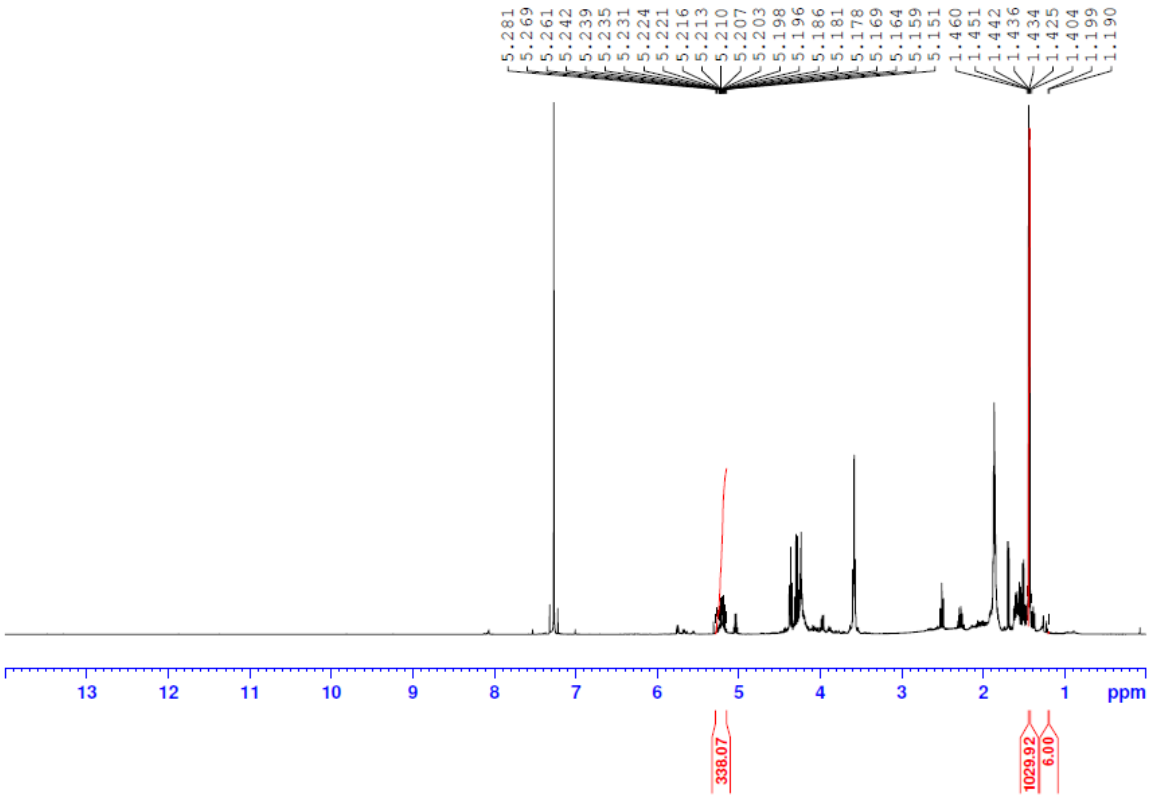
^{1}H NMR spectrum of rac-LacOCA (Reaction time: 9 hours)



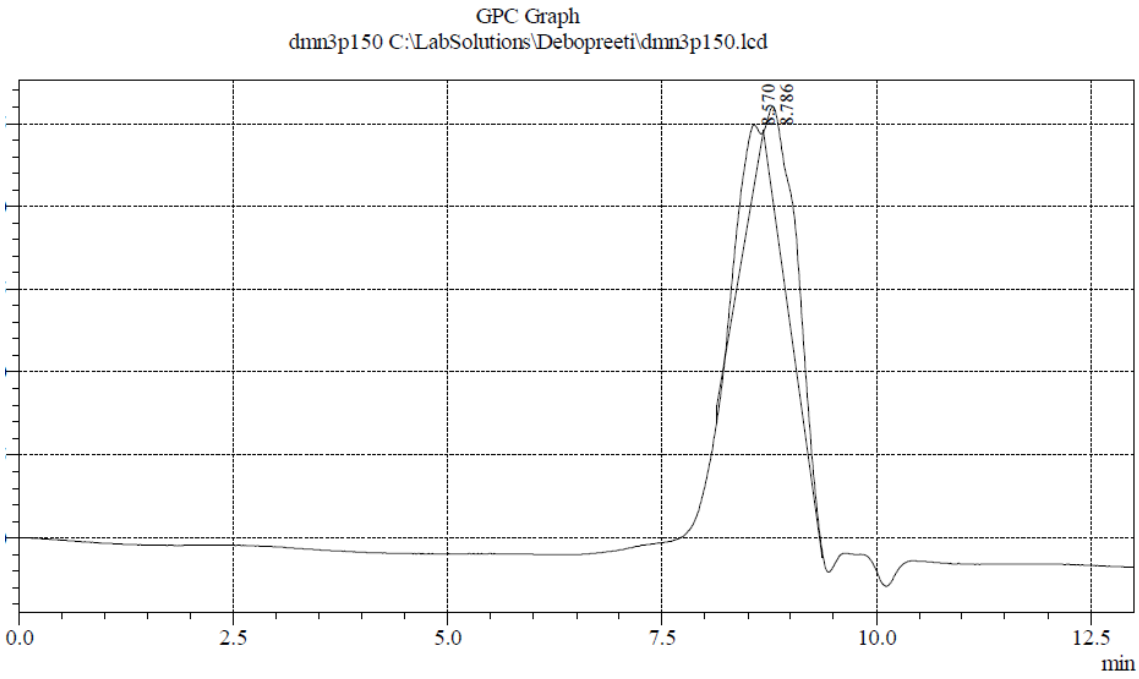
^{1}H NMR spectrum of rac-LacOCA (zoomed view) (Reaction time: 9 hours)



^{1}H NMR spectrum of polylactide (monomer:initiator= 208:1)



GPC profile of poly(lactic acid) (monomer:initiator= 208:1)



Here, a DP (degree of polymerization) value of 328 was obtained from the relative integration of the ^{1}H NMR signals of the synthesized poly(lactic acid). Ideally this DP value indicates that the prepared polymer will have a number average molecular weight (M_n) around 38000. However, in the GPC summary, a M_n value of 44,000 has been shown. This is because, the M_n value depicted in the GPC summary is an average of the M_n values of the two polymer fragments present.

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List of publications:

- **Manuscript under preparation:**

  A Reversal of Polarity Approach for the Synthesis of α-Amino Esters Using Carbonate as a One Carbon Synthon

  Golipalli Ramana Reddy, Debopreeti Mukherjee, Arjun Kumar Chittoory and Sridhar Rajaram

Title: Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Olefins Using Monodentate Spiro Phosphoramidite Ligands

Author: Yu Fu et al.

Publication: The Journal of Organic Chemistry

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