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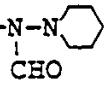
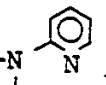
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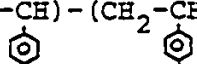
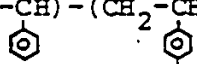
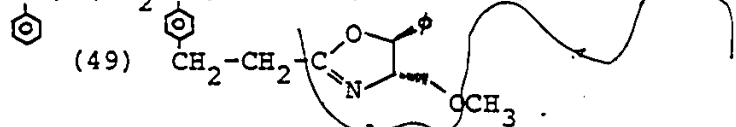
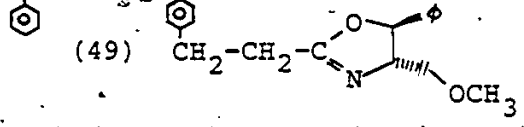
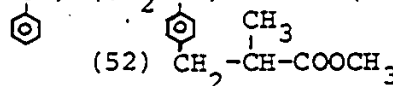
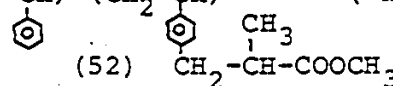
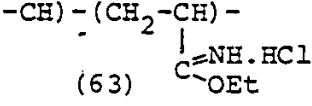
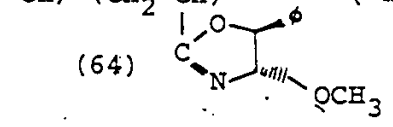
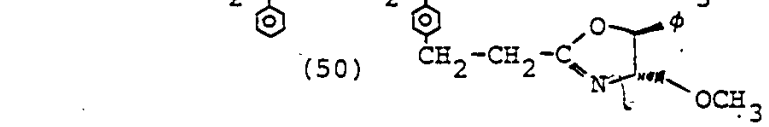
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ABBREVIATIONS

- Ⓟ - Crosslinked polystyrene resin
- Ⓟ - X - Crosslinked polystyrene resin substituted on some or all of its aromatic rings by functional group X.
- IR - Infrared
- NMR - Nuclear magnetic resonance
- DMF - Dimethyl formamide
- THF - Tetrahydrofuran
- DMSO - Dimethyl sulfoxide
- TMEDA - Tetramethylethylenediamine
- ppm - parts per million
- Hz - Hertz
- J - coupling constant
- M.P. - melting point
- n-BuLi - n-Butyllithium
- Ph - Phenyl
- Ø - Phenyl
- D.F. - Degree of functionalization

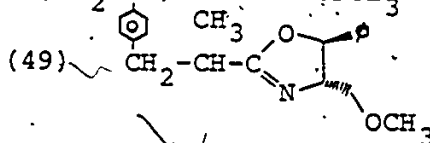
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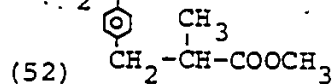
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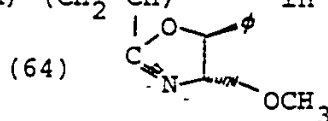
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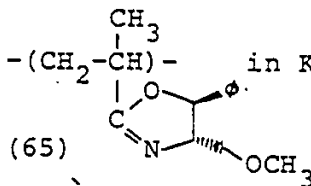
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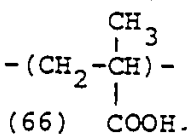
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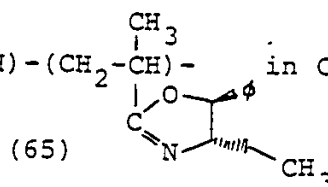
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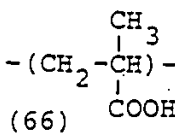
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Abstract

The preparation and applications of reactive polymers as supports and reagents in organic synthesis are reviewed, as is the preparation of polymers possessing main chain chirality.

A new polymeric reducing agent, bis(polystyryldiphenylphosphine) copper tetrahydroborate has been prepared on a crosslinked polystyrene backbone by chemical modification of ring-brominated polystyrene using a reaction sequence involving phosphination followed by copper binding through a ligand exchange process, and reaction with sodium borohydride. The polymeric reagent has a high capacity and is useful in the reduction of acid chlorides to aldehydes. Essentially quantitative yields can be obtained using the reagent, which can also be recycled efficiently without apparent loss of activity.

The role of chelation in the formylation of Grignard reagents and alkyl lithium compounds with N-formamides has been studied. A number of new reagents have been prepared and the importance of the presence of additional nitrogen ligands in the reagent has been clearly demonstrated. An attempt was made to extend these results to analogous polymer-supported reagents but the polymers generally exhibited a lower reactivity than their low molecular weight counterparts. Interestingly, chelation seemed to play no important role in the reaction of the polymer-bound reagents.

An attempt was made to improve the chemical and optical yields in the asymmetric synthesis of α - substituted alkanolic acids using a polymer supported chiral reagent.

A new route to the preparation of polymers possessing main chain chirality by chemical modification with asymmetric induction has been explored in the transformation of a copolymer containing acrylonitrile units into a copolymer containing methacrylic acid groups. The approach involved a variation of Meyer's oxazoline synthesis and was also applied to the preparation of a polymer with chiral groups in the side chain. In both cases optically active polymers were obtained, indicating that the chemical modification had proceeded with asymmetric induction.

CHAPTER I

1. INTRODUCTION

Synthetic reactive macromolecules have become increasingly popular since the mid 1960s. In 1963, Merrifield¹ introduced his solid phase method for the synthesis of peptides, where an insoluble crosslinked macromolecule was used as a support for a growing polypeptide chain.¹ Since then, functional polymers have found a wide range of applications in organic synthesis and related fields. They have been used as supports for polypeptide², polynucleotide^{3,4} and polysaccharide synthesis^{5,6}, as reagents, as catalysts, as substrate carriers in ion exchange and many other applications.⁷⁻¹⁷

A reaction or a sequence of reactions, when carried out using a reactive polymer, benefits from several advantages.

i) Ease of processing.

This is one of the main considerations in any organic reaction. Purification of the product in any polymer-assisted reaction is easy and often reduced to simple filtrations.

ii) Recovery and recyclability of the polymer.

In most reactions the functional polymer can be designed so that the spent material can be recovered quantitatively and regenerated in a simple fashion without appreciable loss of activity.¹⁴

iii) Ease of handling.

Certain functionalities, when present in low molecular weight compounds, are associated with significant toxicities and noxious odors. Odorless polymers containing the same functional groups can be made which have reduced toxicities.

iv) Influence of the polymer backbone and of the local environment within the polymer.¹⁴

Reactions between species attached to the same polymer backbone may be enhanced or reduced considerably depending on the local environment; reaction kinetics and stereoselectivity are also affected.

1.1. Preparation and characterization of functional polymers.

1.1.1. Choice of the physical form of the polymer.

Polymers are available in two different physical forms.

i) Linear polymers.

These are soluble polymers which can be dissolved in appropriate solvents.

ii) Crosslinked gels or macroreticular resins.

These are totally insoluble in all solvents.

Each type possesses its own distinct advantages and disadvantages. Therefore in any application of a polymer as a reagent, a protecting group, etc., it is necessary to consider carefully all the factors involved before deciding on the physical form of the polymer. This will help to maximize the advantages of the polymer system and minimize any potential problems.

1.1.1.1. Linear vs. crosslinked polymers.

Reactions associated with linear soluble polymers will usually be carried out in solution with few diffusion problems. Therefore this will allow the other reactants to have equal accessibility to all the functional groups of the polymer. This may be very important in a reaction which involves bulky substrates that may not be able to diffuse into the pores of a crosslinked polymer. Although high conversions are possible, it may be difficult in some cases to effect the separation of the polymer from low molecular weight impurities, and thus the primary advantage associated with the use of a polymer may be partially lost. Another difficulty that one has to face is the occurrence of side reactions which give rise to unwanted crosslinks during reaction and may result in the formation of gels which are difficult to process.

On the other hand the processing will become much easier if crosslinked polymers are used; they can be made in the form of insoluble spherical beads which will not coalesce when placed in organic solvents. The separation of the polymer from low molecular weight contaminants is by simple filtration and washing with various solvents. Polymer beads with low degrees of crosslinking will swell extensively in suitable solvents, and inner reactive groups become accessible to the soluble reagents. The beads are highly solvated and will react much as if they were in solution. Highly crosslinked polymers having very porous structures which allow the solvents and reagents to penetrate without

prior swelling can also be made. Except for the case where large substrates are involved, the reactions in both cases can be expected to occur fairly homogeneously throughout the beads. Large substrates, being unable to diffuse freely into the pores of the polymer, will react at a slower rate, or they may only be able to react at some of the more accessible sites, located on the surface of the beads or within the larger pores.

1.1.2. Preparation of functional polymers.

Two approaches are possible for the preparation of functional polymers..

i) Polymerization or copolymerization of monomers containing the desired functional group.

ii) Chemical modification of preformed polymers.

In the first approach, to obtain a good yield of the polymer in a suitable form requires a considerable manipulation of the polymerization procedure, which may be somewhat difficult. The chemical modification approach seems to be more simple and straightforward. A commercially available resin of high quality is normally used and the functional groups are introduced by using standard organic synthesis procedures. Reactions carried out on small molecules and reactions on insoluble polymers have two major differences. The first is the limited number of reactive sites available in the polymer, due to inaccessibility of some of the reactive sites which will often necessitate the use of more drastic reactive conditions. The second difference is the purification; crosslinked polymers can be purified only by washing which will not remove

any unwelcome material attached to the polymer. In contrast in the case of low molecular weight materials, techniques such as crystallization, distillation, chromatography etc. are available for purification after the reaction. Therefore the functionalized polymer will sometimes have some unchanged functionalities and impurities resulting from side reactions. The amount of these impurities will depend on the type of reaction.

1.1.2.1. Chemical modification of polystyrene.

Crosslinked polystyrene resins are widely used for the preparation of functional polymers as they meet many of the requirements of a solid support such as;

- i) They are available in bead form with good mechanical stability and well defined physical characteristics.
- ii) The aliphatic polymer backbone is stable and is not overly susceptible to degradative chain scission.
- iii) The aromatic rings are very reactive and can be functionalized easily.

Chloromethylated polystyrene $\text{(P)-CH}_2\text{Cl}$, ring-lithiated polystyrene (P)-Li and ring-brominated polystyrene (P)-Br are the three intermediates that are almost always used in the preparation of polymeric reagents, catalysts, supports etc. Among them $\text{(P)-CH}_2\text{Cl}$, also referred to as Merrifield's resin, has been used most extensively, both as a support and as a precursor to numerous other functional polymers.^{14,16}

Chloromethylation can be carried out according to two different routes; reaction of styrene-divinylbenzene copolymer with paraformaldehyde and hydrogen chloride¹⁷, or by reaction of styrene-divinylbenzene copolymer with chloromethyl methyl ether¹⁸, chloromethyl ethyl ether¹⁹, or bis(1,4-chloromethoxy) butane²⁰ in the presence of a Friedel-Craft catalyst such as AlCl_3 , ZnCl_2 or SnCl_4 .²¹ The degree of substitution depends on the catalyst and reagent concentrations, reaction time and temperature.

The versatility of this functional polymer is due to the ease with which its chlorine atoms can be replaced in nucleophilic substitutions.²²

Formylated polystyrene (P)-CHO , which is a useful intermediate in the synthesis of other functional polymers, can be obtained in good yield by DMSO oxidation of $\text{(P)-CH}_2\text{Cl}$.^{5,23,24} (P)-CHO can be oxidized with $\text{K}_2\text{Cr}_2\text{O}_7$ to give (P)-COOH .^{23,25} By reaction of $\text{(P)-CH}_2\text{Cl}$ with KCN in DMSO the cyano derivative $\text{(P)-CH}_2\text{CN}$ has been made.²³ The reaction is often accompanied by partial oxidation of $\text{(P)-CH}_2\text{Cl}$ to (P)-CHO . As will be seen elsewhere in this introduction this problem can be solved through the use of a different solvent such as DMF or by phase transfer catalysis. Polymeric acid $\text{(P)-CH}_2\text{COOH}$ can be obtained by acid hydrolysis of cyano polymer $\text{(P)-CH}_2\text{CN}$,²³ or by reacting $\text{(P)-CH}_2\text{Cl}$ with an organolithium compound containing a protected carboxylic acid group followed by acid hydrolysis.²⁶

Hydroxymethyl polystyrene $(P)-CH_2OH$ can be produced by saponification of polymeric esters^{23,27,28} and also by reduction of $(P)-COOH$.²⁴ The polymeric sulfonium salt $(P)-CH_2S^+(CH_3)_2Cl^-$, used as an ion exchange resin and a protecting group in peptide synthesis, is made by addition of dimethyl sulfide to $(P)-CH_2Cl$.²⁹⁻³¹

Polymers useful as ligands in the formation of supported transition metal catalysts have been synthesized. Polymeric phosphines belong to this category and are prepared by reaction of $(P)-CH_2Cl$ with $LiP(Ph)_2$.³² Another polymer that can be included in this group is $(P)-CH_2-$  which has been synthesized by reacting $(P)-CH_2Cl$ with the cyclopentadienyl anion.³³

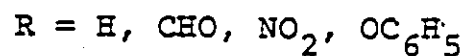
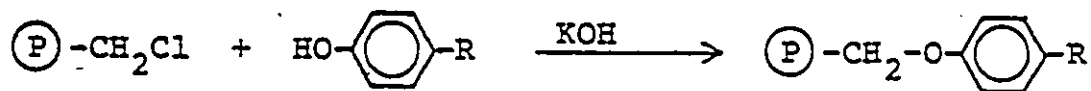
$(P)-CH_2Cl$ has also been used to make the methyl chloroformate resin $(P)-CH_2-O\overset{O}{\parallel}CCl$ which is used as a solid support in peptide synthesis, by first converting to $(P)-CH_2OH$ ^{24,34} and then reacting with excess phosgene.³⁵

One of the major applications of $(P)-CH_2Cl$ is for the preparation of the anion exchange polymers of the type

$(P)-CH_2N^+R_3Cl^-$. Some of these widely used resins are commercially available and their synthesis has been reviewed.³⁶ Another useful class of ion exchange resin of the type $(P)-CH_2-P\overset{O}{\parallel}(OH)_2$ is prepared by reacting $(P)-CH_2Cl$ with trialkyl phosphite and then hydrolysing the product.³⁷

Gibson and Bailey³⁸ in their study of chemical modification of polymers, were able to prepare several structurally different polymers and copolymers successfully using soluble $(P)-CH_2Cl$. Polymeric phenol ethers have been made in a manner analogous

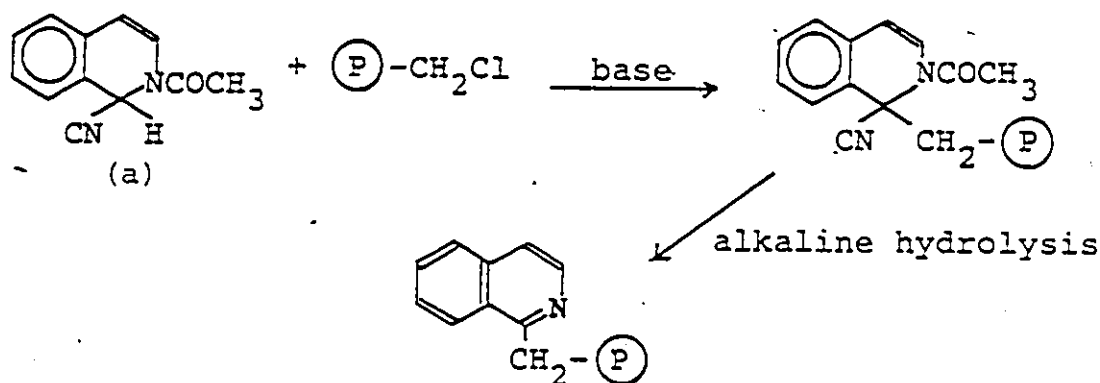
to the reaction of monomeric benzyl chlorides with phenols in the presence of a base. (Scheme (1)).



Scheme (1)

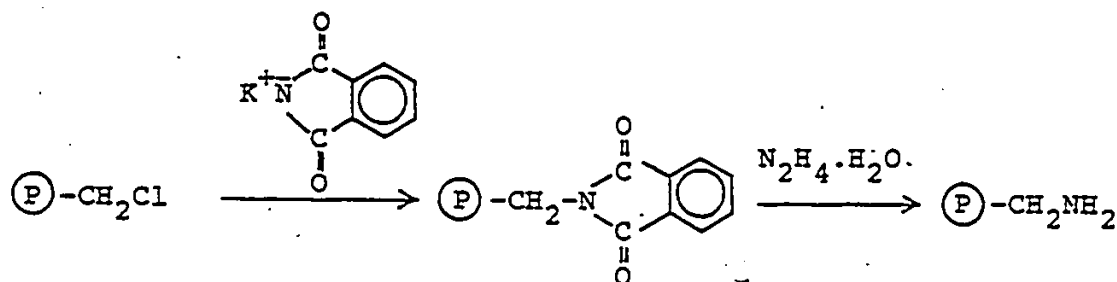
The reaction is efficient when R is electron withdrawing. When amino phenols are used, crosslinking takes place by alkylation of the amino functions with unreacted chloromethyl groups.

Alkylation of Reissert compound (a) has been done using soluble $\textcircled{\text{P}}-\text{CH}_2\text{Cl}$ and the conversion is found to be essentially quantitative. (Scheme (2)).^{39,40}



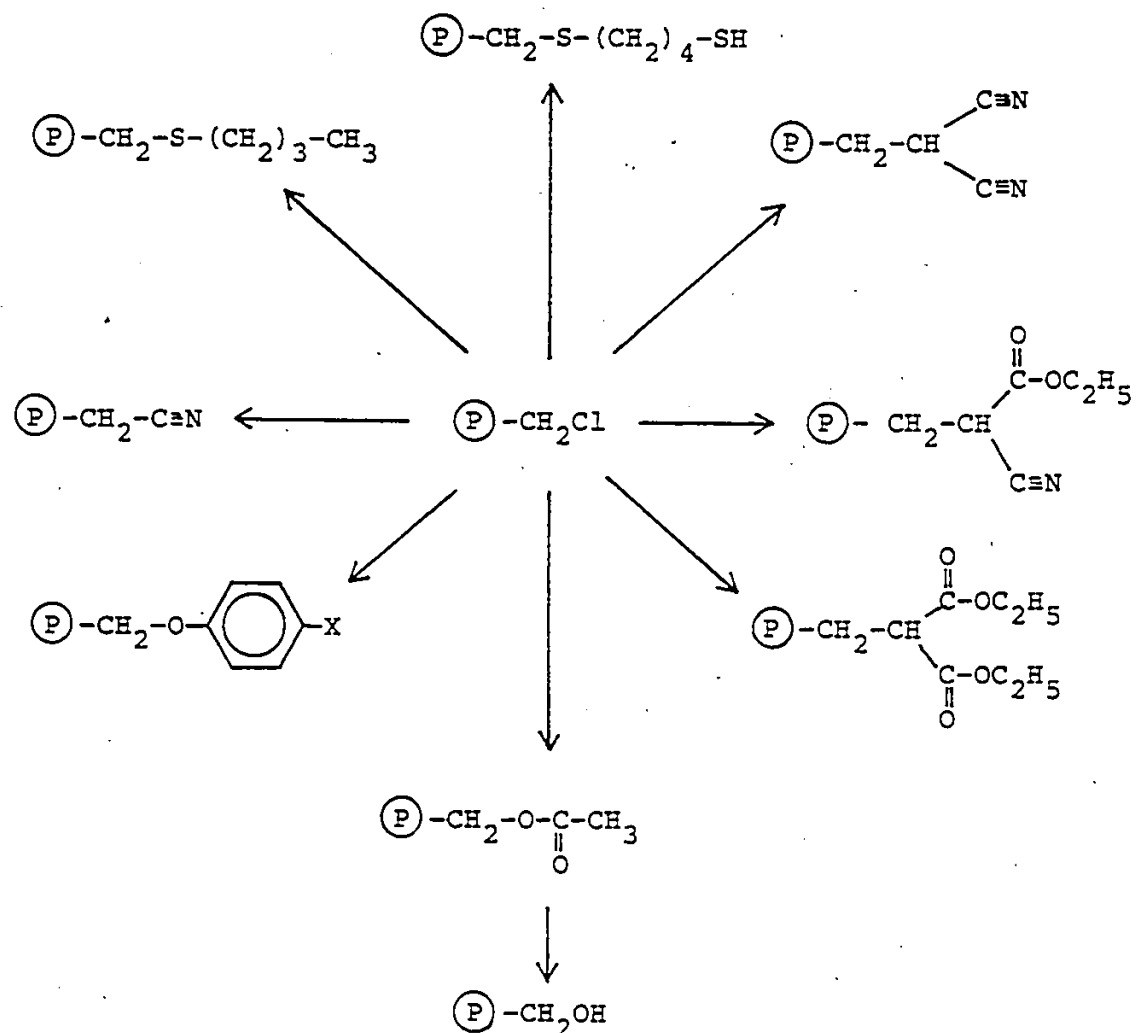
Scheme (2)

$\textcircled{\text{P}}\text{-CH}_2\text{Cl}$ has also been used to synthesize polymers of the type $\textcircled{\text{P}}\text{-CH}_2\text{NH}_2$ by reaction with potassium phthalimide followed by reaction with hydrazine.⁴¹ (Scheme (3)).



Scheme (3)

Because it is impossible to remove any impurities introduced to the polymer, it is important to choose reactions with very high yields and few side products. Improvements can be made using phase transfer conditions. Fréchet et. al. have generated reactive intermediates on insoluble polymers using this method and have demonstrated that reactions involving such three phase systems occur in a remarkably clean fashion to give excellent yields of products without appreciable formation of side products.^{42,45} Nucleophilic substitution on $\textcircled{\text{P}}\text{-CH}_2\text{Cl}$ using variety of carbon, sulphur and oxygen nucleophiles has been done under phase transfer conditions with excellent results. (Scheme (4))



Chemical modification of $\text{P}-\text{CH}_2\text{Cl}$ by phase transfer catalysis.⁴²

Scheme (4)

The reaction involves a three phase system consisting of two liquid phases, an organic swelling agent and an aqueous solution of the nucleophile, and the solid polymer in the presence of a phase transfer catalyst.

$(P)-CH_2OH$ has been prepared from $(P)-CH_2Cl$ by successive addition of acetate and hydroxide ions under phase transfer conditions.^{45,51} This reaction is interesting as OH^- alone is almost unreactive.

Nucleophilic displacement of chloride from $(P)-CH_2Cl$ by oxygen nucleophiles under phase transfer conditions has been tested by reaction with phenolate ions derived from p-hydroxy benzaldehyde and p-nitrophenol. In both cases complete displacement of chloride by the phenolate was observed.^{42,45}

Various carbon nucleophiles have also been used to displace chloride in $(P)-CH_2Cl$ under phase transfer conditions with excellent results^{42,43} while conventional techniques lead to low functional yields. For example, the preparation of $(P)-CH_2CH(CN)_2$ using malononitrile in DMF and ethoxide ion as the base results in the transformation of only 30% of the chloromethyl groups into the dinitrile.⁴⁶ On the other hand, phase transfer catalysis gave complete conversion after 2-3 days of reaction at 80 °C.^{42,43,45}

The preparation of cyanomethyl polymer $(P)-CH_2CN$ from $(P)-CH_2Cl$ has been done by using cyanide ion²³ in DMSO. Oxidation of $(P)-CH_2Cl$ to $(P)-CHO$ also occurred as a side reaction. The transformation, when done under phase transfer

conditions or in DMF as a solvent, gave excellent yields.⁴²

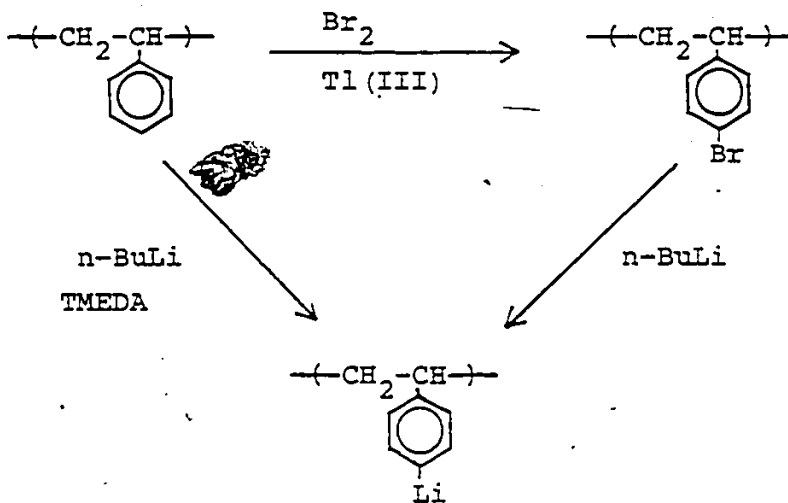
The reaction of S-nucleophiles with $\text{(P)}-\text{CH}_2\text{Cl}$ under phase transfer conditions gave results comparable to those obtained with C-nucleophiles. Displacement of chloride with butanethiol or methanethiol in the presence of aqueous hydroxide ion using $(\text{n-Bu})_4\text{N}^+\text{OH}^-$ as phase transfer catalyst, was complete and the polymeric sulphides $\text{(P)}-\text{CH}_2\text{S}(\text{CH}_2)_3\text{CH}_3$ and $\text{(P)}-\text{CH}_2\text{SCH}_3$ were obtained in quantitative yields. They can be used as oxidizing agents when converted to sulfoxides with hydrogen peroxide.⁴⁷

The second important intermediate in the chemical modification of polystyrene, ring lithiated polystyrene, $\text{(P)}-\text{Li}$ (Polystyryllithium)²², can be made in one of two ways.

- i) Direct lithiation of the aromatic rings using n-butyllithium and N,N,N',N'-tetramethylethylenediamine (TMEDA).
- ii) The metal-halogen exchange reaction between halogenated polystyrene, and n-butyllithium.

The first procedure, developed by Chalk,⁴⁸ was applied to the lithiation of soluble polystyrene. The reaction was best carried out in a nonpolar solvent such as cyclohexane. The reaction was extended to crosslinked polystyrene by Leznoff and Fyles⁴⁹ and results in the substitution of the aromatic rings in the meta and the para positions.^{49,52} Kinetic studies have shown that 1:1 TMEDA:n-BuLi complex is the active species in the metalation reaction.⁵⁰ n-BuLi used alone is completely unreactive.

The direct lithiation of insoluble polystyrene by the complexes of $n\text{-BuLi}$ with various amines was also studied by Farrall and Fréchet.^{52,53} The procedure involved the reaction of an amine- $n\text{-BuLi}$ complex with a 1% crosslinked resin at 65-70 °C in a nonpolar solvent. The best results have been obtained using TMEDA complexes in a nonpolar hydrocarbon solvent such as cyclohexane or heptane. Aromatic solvents such as benzene or polar solvents such as THF were unsuitable for this reaction. The maximum degree of functionalization achieved was 0.23 which is far better than the 0.11 value obtained by other workers.⁴⁹ The relatively low functional yields are probably due to the fact that the solvents which must be used for the reaction are unable to swell the resin and the penetration of the relatively bulky TMEDA- $n\text{-BuLi}$ in the pores of the resin is restricted to only the most accessible sites of the polymer.



Scheme (5)

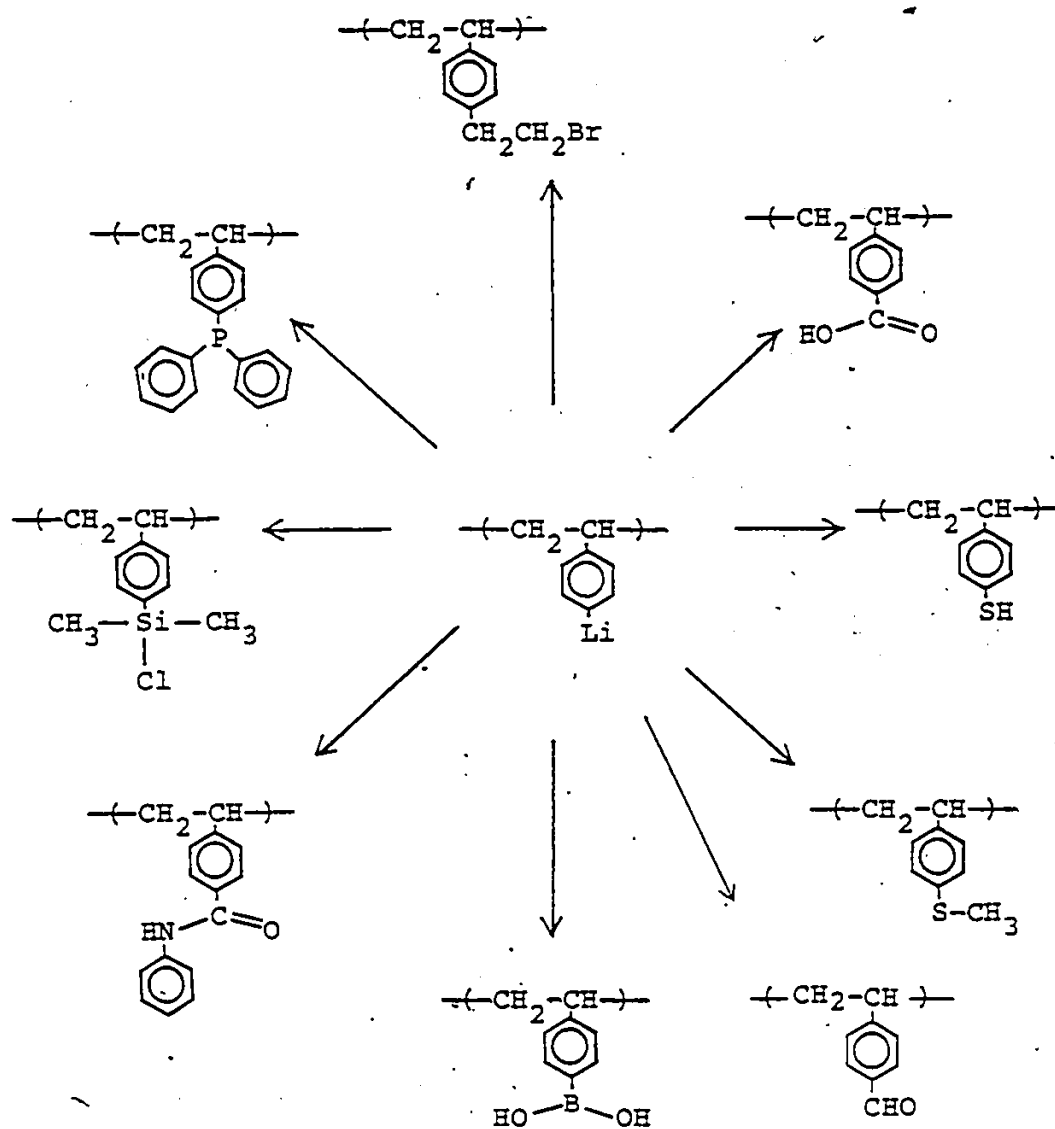
The second procedure,^{22,53,54} although requiring an additional step, is advantageous when a good control of the degree and the position of lithiation is required. It is also useful in cases where high loadings are required.

The lithiation of halogenated polystyrene with n-BuLi was first studied by Braun by using soluble poly(iodostyrene) (P)-I.^{55,56} A number of polystyrene derivatives have been prepared using soluble (P)-Li.^{55,57}

The lithiation of halogenated polystyrene has been widely applied to insoluble crosslinked polystyrenes using mainly brominated polystyrenes. A number of methods are available for the preparation of a suitable brominated polystyrene precursor.^{1,22,53,59,61,62} Satisfactory results can be obtained by the method developed by Heitz and Michels⁶¹ which involves the reaction of polystyrene with bromine in the presence of ferric chloride as the catalyst. Farrall and Fréchet^{22,53} have also investigated the bromination of crosslinked polystyrene with the aim of obtaining a reliable procedure for the preparation of a clean and homogeneous polymer with a predictable degree of substitution of the aromatic ring. The best procedure involves the use of bromine in carbon tetrachloride in the presence of a catalytic amount of thallium(III) salt. It has also been shown that it is possible to control the degree of functionalization accurately by regulating the amount of bromine available.

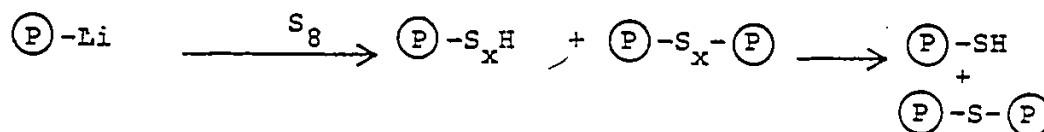
An extensive study of the preparation and chemical modification of crosslinked (P)-Li was carried out by Fréchet and Farrall^{22,53} who optimized conditions for the lithiation of

crosslinked polystyrene resins and prepared a large number of functional derivatives of polystyrene by quenching $\text{P}^{\ominus}\text{-Li}$ with appropriate electrophiles. (Scheme (6)).



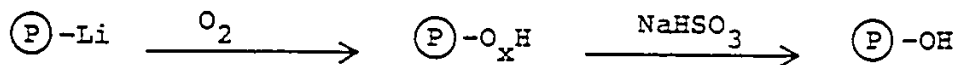
Scheme (6)

Two functional polymers $\textcircled{\text{P}}\text{-OH}$ and $\textcircled{\text{P}}\text{-SH}$, which should be very useful as polymeric supports in view of their ability to generate powerful nucleophiles which could react with various substrates under very mild conditions, have been made using $\textcircled{\text{P}}\text{-Li}$ by Fréchet and Farrall.⁵¹⁻⁵⁴ $\textcircled{\text{P}}\text{-SH}$ has been prepared either via the direct lithiation or via the bromination-lithiation procedure followed by reaction of the resulting $\textcircled{\text{P}}\text{-Li}$ with elemental sulfur. The resulting polymer is reduced with LiAlH_4 in order to cleave di- and poly-sulfides to the desired thiol. (Scheme (7)).



Scheme (7)

Hydroxy polystyrene $\textcircled{\text{P}}\text{-OH}$ is prepared by adding oxygen to a suspension of $\textcircled{\text{P}}\text{-Li}$ in dry benzene or cyclohexane at room temperature. (Scheme (8)).



Scheme (8)

Unfortunately, this reaction results in the formation of additional crosslinks in the polymer as a few ether linkages are formed between adjacent aromatic rings. A new procedure for the preparation of $\textcircled{\text{P}}\text{-OH}$ resins has been described recently by Fréchet et. al.⁵⁸

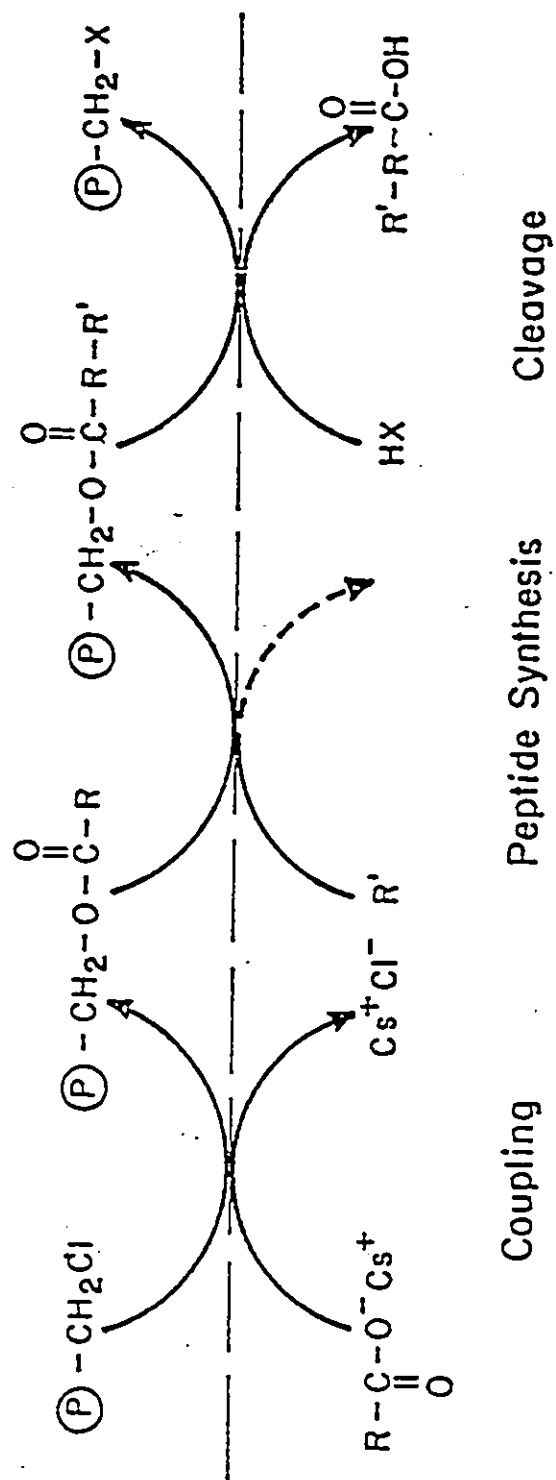
I.2. Polymers as supports and protecting groups

The advantages previously described for polymers are especially important in their application as supports and protecting groups in organic synthesis. As the desired product is attached to the insoluble support it can be fished out of a complex mixture of reactants and byproducts even though it may represent only a tiny fraction of the total mixture. This can be critical in such areas as peptide synthesis, where purification of the product is traditionally the main stumbling block.

The first polymer support was developed by Merrifield¹ for the preparation of peptides. In Merrifield's reaction scheme the carboxyl group of the carboxyl terminal amino acid was attached to $\text{P}-\text{CH}_2\text{Cl}$ to give resino-benzyl ester. This type of linkage was selected because the coupling reaction is simple and the resino-benzyl ester is resistant to the conditions of the sequential synthesis while still being susceptible to cleavage once the synthesis is complete. (Scheme(9)).^{12,63,64}

One of the shortcomings of this synthesis is that during the removal of the α -amino acid protecting group (t-butyloxycarbonyl) by treatment with acid, about 1% of the resino-benzyl ester is also cleaved, reducing the overall yield of the final product. This may also cause side reactions at later stages of the synthesis.

Another similar carboxyl protecting group which has been used in peptide synthesis can be prepared by Friedel-Craft's acylation of polystyrene with bromoacetyl chloride. The bromoacetyl resin can be esterified readily by reacting it with a carboxylate.⁶⁵ A variety of nucleophiles like ammonia, thiophenoxide etc. are available to cleave the resino-phenacyl ester linkage once the synthesis



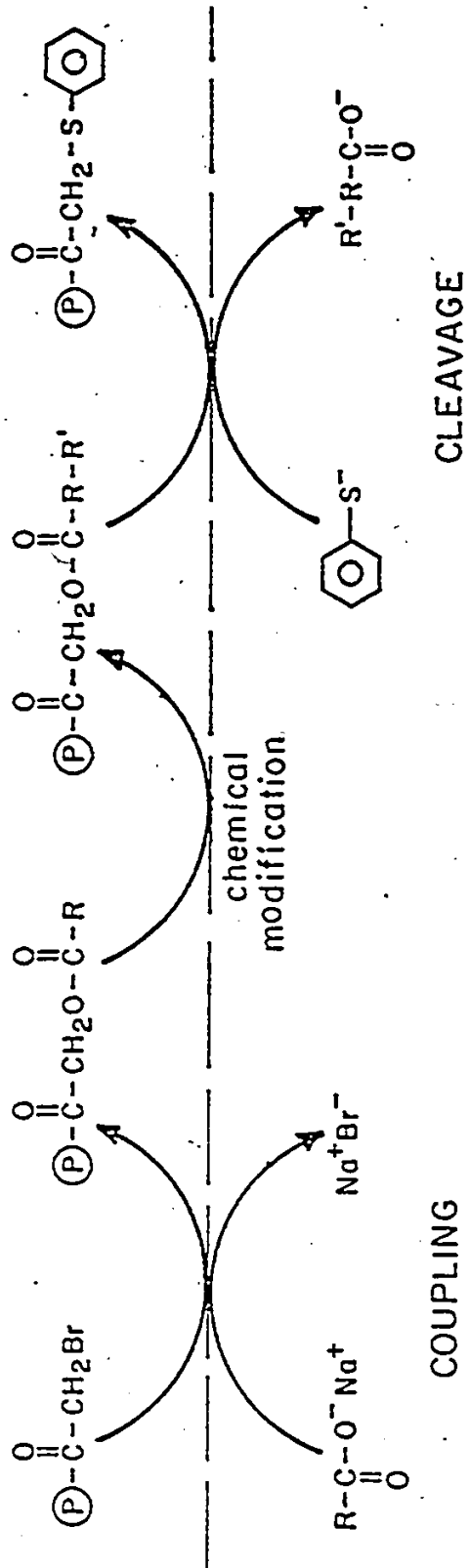
Scheme (9)

is over. (Scheme (10))

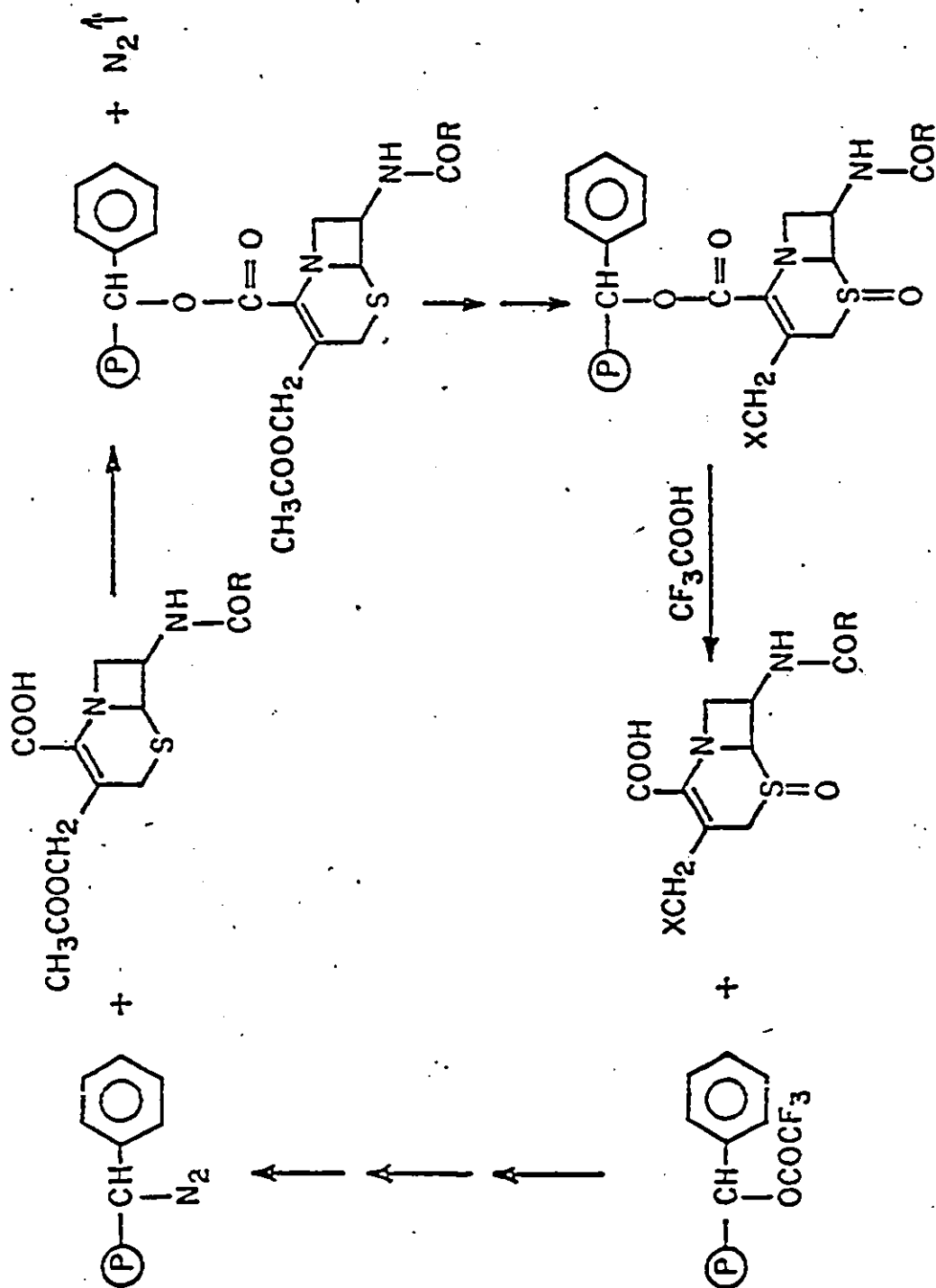
An effective polymeric protecting group was developed and used by Chapman and Walker⁶⁶ for the protection of the free carboxylic acid end groups of some penicillins and cephalosporins. The polymer which contains a diazo group is made by benzylation of a polystyrene resin followed by reaction with excess hydrazine and oxidation of the resulting polymer with peracid in the presence of iodine. Both the diazo polymer and its hydrazone precursor could be used to protect the free carboxylic acid group of penicillin G-1(S)-oxide. The polymer supported penicillin could be converted into the corresponding cephalosporin by a simple thermal rearrangement in the solid phase. In a similar reaction this polymer has been used to attach cephalosporin, which was then subjected to a series of transformations involving reactions such as oxidations and nucleophilic substitutions. (Scheme (11)). The polymer recovered after treatment with trifluoroacetic acid could be regenerated, but this would not be of great practical value as it requires more than four steps.

Polymers having chiral groups have been used in an asymmetric synthesis by Kawana and Emoto.⁶⁷ The support they used was a polymer bound xylofuranose derivative in which all but one of the hydroxyls were substituted. (Scheme (12)). Using this procedure, atrolactic acid was obtained with higher chemical and optical yields than those from similar reactions done under homogeneous conditions by a similar method

(20)



Scheme (10)



Scheme (11)

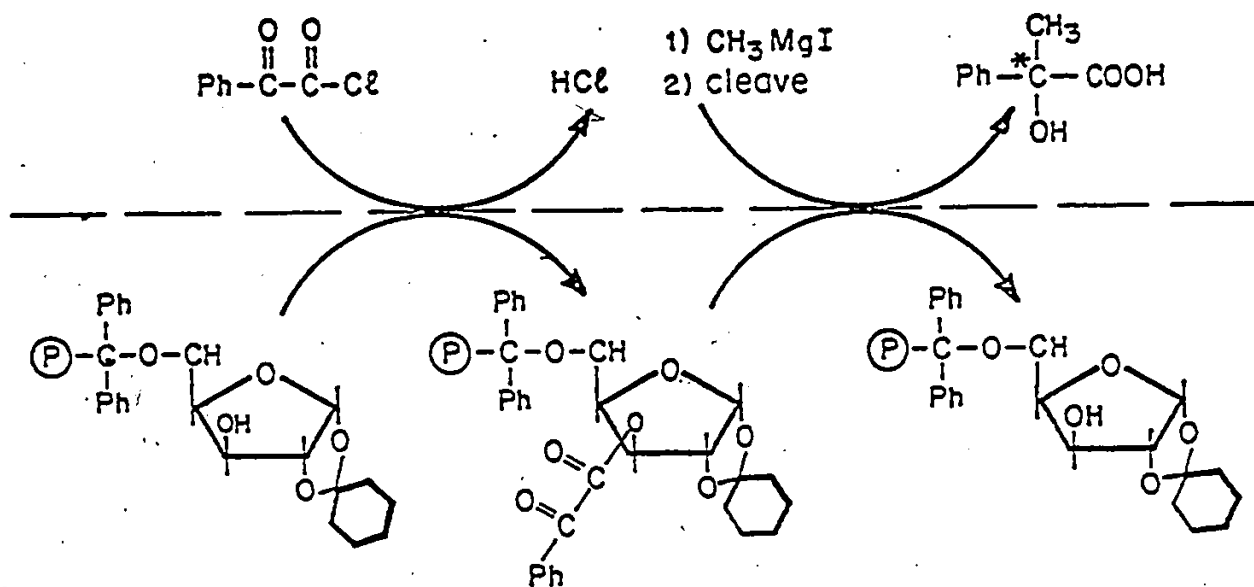
using phenylglyoxyl chloride. The recovered polymer could be used again but was slightly less effective in the second reaction cycle. The increase in stereoselectivity was probably due to a decrease in the conformational mobility of the polymer supported intermediate.

A versatile polymer supported diol protecting group has been synthesized by reacting (P)-Li with trimethylborate, followed by hydrolysis.⁶⁸⁻⁷¹ This polymer is extremely selective and is regenerated in the cleavage step, and thus can be reused repeatedly without requiring a separate regeneration step and without loss of activity. The selectivity is demonstrated by its reaction with a 1:1 mixture of cis- and trans-1,2-cyclohexane-diols.⁶⁸ A boronate is formed exclusively with the cis diol which can be removed later from the polymer by addition of a moist solvent or a solvent containing some methanol (Scheme (13)).

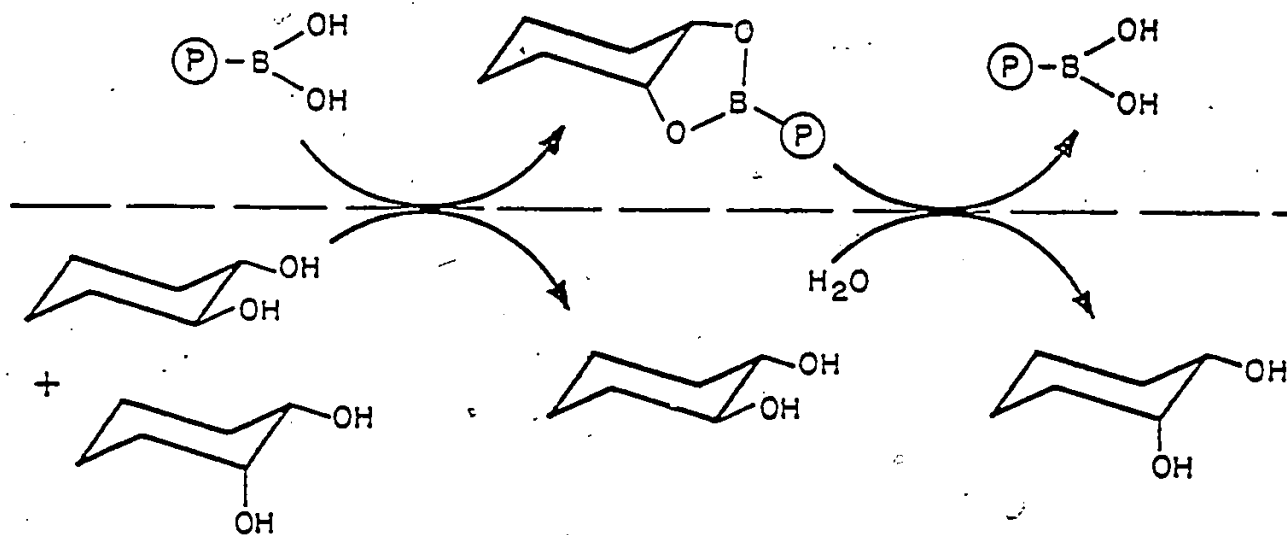
This polymer's successfulness was further demonstrated by its use in the selective protection of glycosides and other polyols.^{14,68,70}

Other protected diols bound to polymers have been used in the synthesis of insect sex attractants and carotenoids.⁷²⁻⁷⁷ (Scheme (14)). This method has been used to make gram quantities of insect sex attractants and the work has been reviewed.⁹

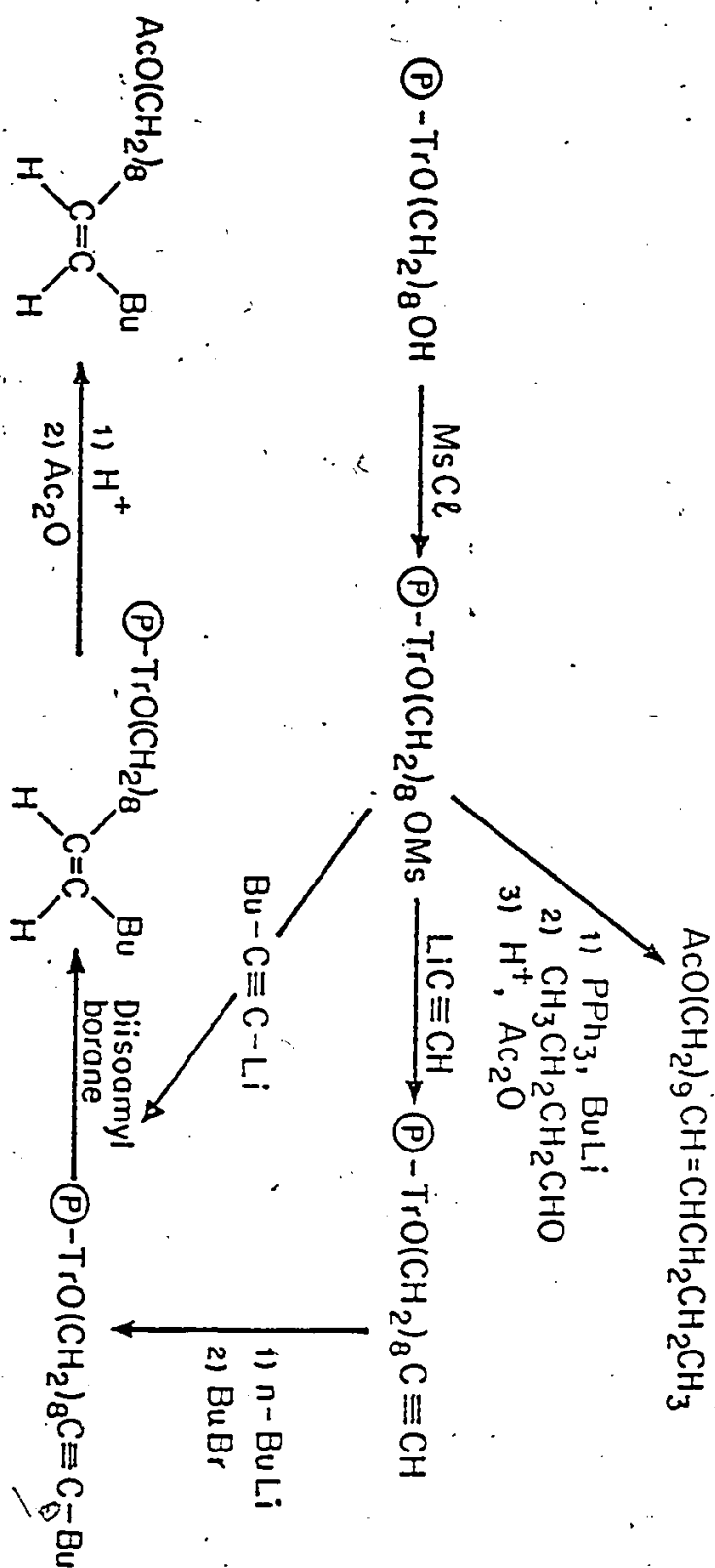
(23)



Scheme (12)



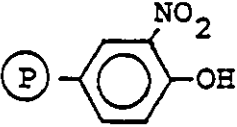
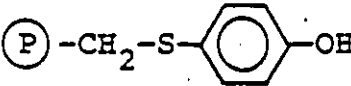
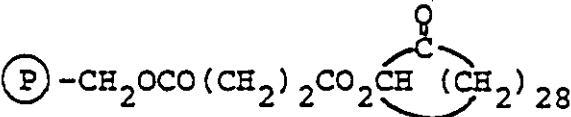
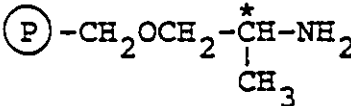
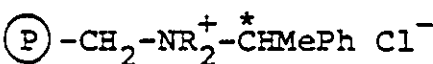
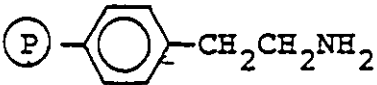
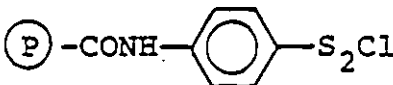
Scheme (13)



Scheme (14)

Some other polymers used as supports and protecting groups and their applications are shown in Table (1) and they have been reviewed recently.¹⁶

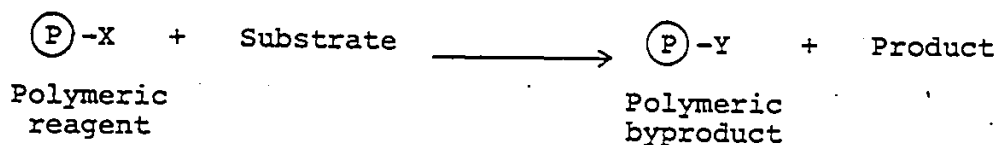
Table (1) : Selected polymeric supports and their applications.

Polymer Support	Application	Ref.
	Synthesis of cyclic peptides	78,79 80,81
	Synthesis of cyclic peptides	82, 83,84
	Synthesis of threaded macrocycles	85
	Asymmetric synthesis of 2-allylcyclohexanones	86
 R = H, Me	Resolution of mandelic acid	87
	Separation of sugar anomers	88
	Removal of allergenic substances from natural oils	89,90
	Selective separation of tryptophan and tryptophan containing peptides	91

1.3. Polymeric Reagents

A polymeric reagent is a reactive organic group bound to a polymer support which is used in stoichiometric quantities to achieve the chemical modification of a given substrate.

(Scheme (15)).



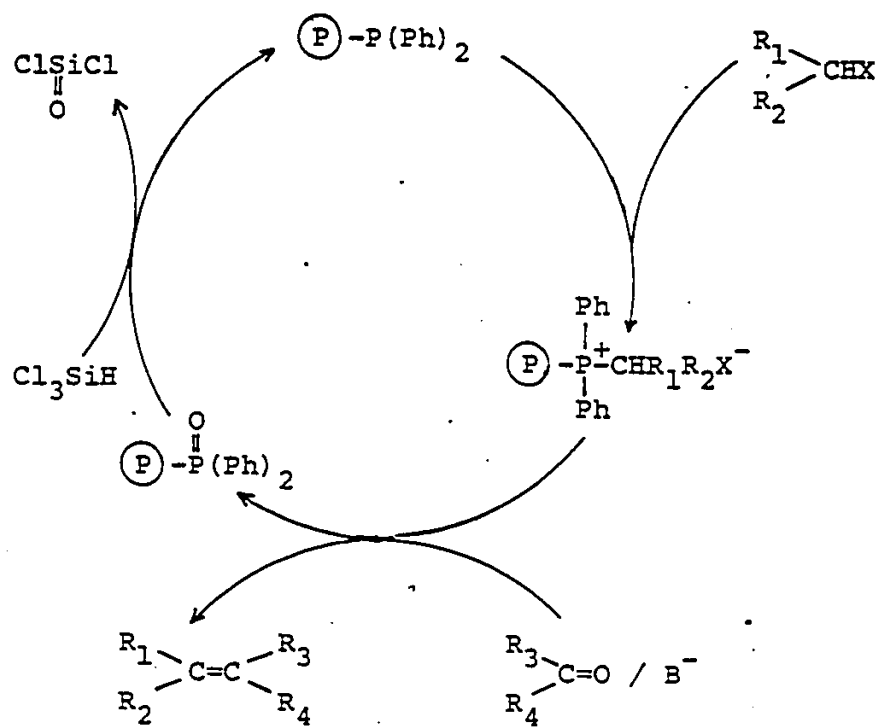
Scheme (15)

The main advantage associated with the use of polymeric reagents is the ease of isolation of the product from the reaction mixture. The product will remain in the liquid phase while the excess reagent and the byproducts stay bound to the solid polymer.

Polymeric phosphines have been made and successfully used in Wittig reactions to synthesis olefins.⁹² The polymeric phosphine can be readily recycled and after regeneration reused in further Wittig reactions. (Scheme (16)).

In conventional Wittig reactions the lithium ions complex with the threo form of the betaine, which leads to the formation of the trans olefin.¹⁶ With polymeric phosphonium reagents, the lithium salts could be removed by filtration before the addition of the carbonyl compound. This leads to the formation of cis olefins in high yields.⁹²

A large number of polymeric reagents have been developed and used successfully for reactions such as oxidation, epoxidation,



Scheme (16)

reduction, acylation, halogenation etc. and some of these are shown in Table (2).

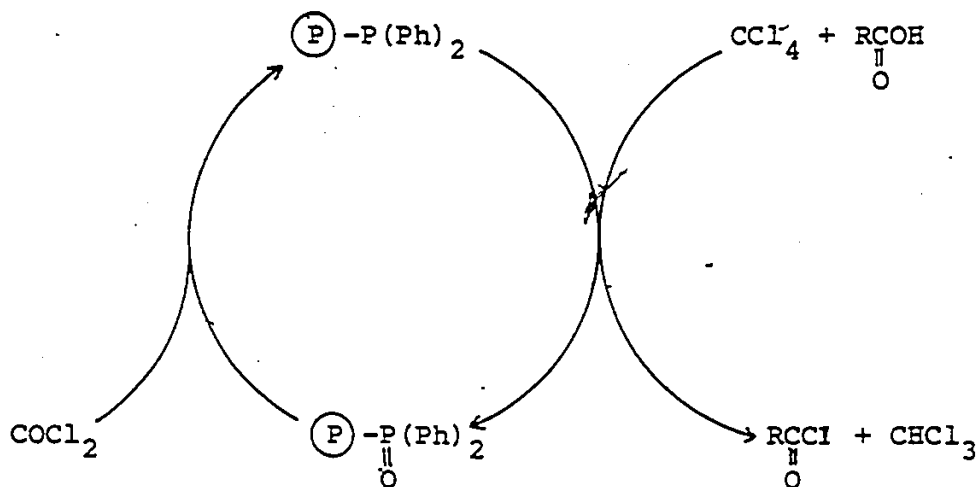
A polymeric analogue of perbenzoic acid $(P)-COOOH$ has been made and used successfully to convert olefins to epoxides and to oxidize diimines to N-oxides,^{25,93,94} and sulfides to sulfoxides or sulfones.^{93,95} The spent resin is regenerated efficiently by treatment with hydrogen peroxide in the presence of sulfonic acid as a catalyst.

$(P)-N^+(Me)_3)^+CrO_4^-$ has been used to oxidize alcohols to aldehydes and ketones in good yields.⁴⁷ Another very efficient mild oxidizing agent is poly(vinylpyridinium dichromate) $(P)-\text{C}_5\text{H}_5\text{NH}^+)_2Cr_2O_7^{2-}$. It has been used to oxidize alcohols to

aldehydes and ketones without any overoxidation.⁹⁶ Another important factor with this reagent is that unlike the more classical soluble CrO_3 /pyridine analogues it could be used safely in larger scale oxidation of alcohols under mild conditions.⁹⁶ The polymer has been regenerated several times without loss of activity. Another useful polymeric oxidizing agent is $(\text{P})-\text{CH}_2\overset{\text{O}}{\underset{|}{\text{N}}^+}(\text{CH}_3)_2$ which has been used to oxidize alkyl bromides and iodides to aldehydes.⁹⁷ The polymeric reagent is found to give better yields than the monomeric reagent and is easily regenerated by reaction with H_2O_2 .

Several polymer-supported reducing agents are known although only few of them are recyclable. Reducing agents for converting aldehydes and ketones to alcohols could be made by complexing sodium borohydride with poly(4-vinyl pyridine)⁹⁸ or ion exchange resins $(\text{P})-\text{CH}_2-\text{N}(\text{Me})_3\text{BH}_4$,⁹⁹ or by reacting diborane with $(\text{P})-\text{SnH}_2\text{Bu}$. The latter also reduces alkyl halides to alkanes. The first reagent is recyclable^{98,99} while the second is not.^{106,107} Most of these reagents had lower reactivities than their monomeric counterparts and have found little application.

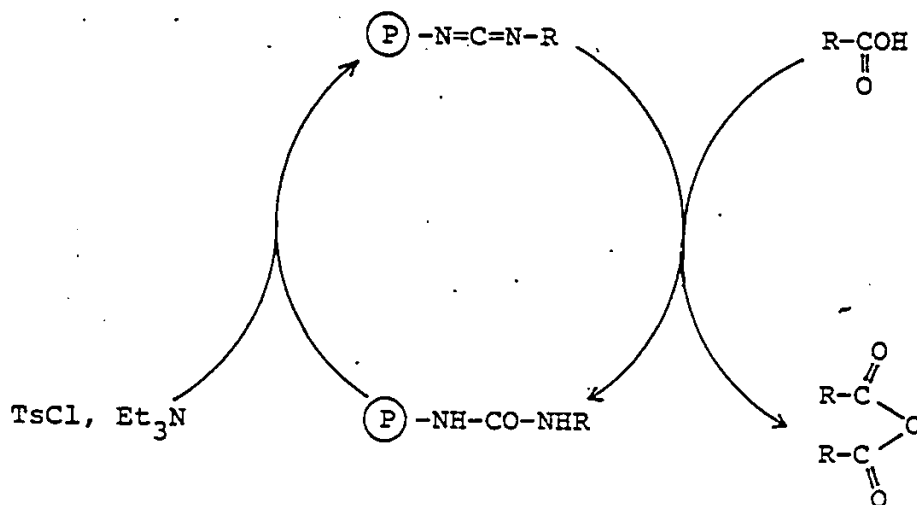
$(\text{P})-\text{P}(\text{Ph})_2/\text{CCl}_4$ and $(\text{P})-\text{P}(\text{Ph})_2\text{Cl}_2$ have been used to make alkyl chlorides from alcohols in excellent yields.^{60,100,101} The $(\text{P})-\text{P}(\text{Ph})_2$ produced is regenerated by using phosgene.⁶⁰ The same reagents have been used to convert primary amides and aldoximes to nitriles,^{60,102} and carboxylic acids into acid chlorides.^{60,103} (Scheme (17)).



Scheme (17)

Polymer supported carbodiimide derivatives have been prepared and used as condensing agents in the synthesis of peptides.^{104,105} They have also been used for the conversion of carboxylic acids to their anhydrides¹⁰⁶ and in the Moffat oxidation of highly sensitive alcohols.¹⁰⁷ These polymeric reagents have the advantage that the byproduct, urea, remains attached to the polymer and can be easily separated from the reaction mixture by filtration and regenerated back into the polymeric carbodiimide.^{105,106} However, side reactions on the polymer reduce its usefulness and recyclability. (Scheme (18)).

A number of polymeric halogenating agents have been developed and used efficiently in reactions such as bromination of olefins, ketones, allylic and aromatic compounds, conversion of acids into acid chlorides etc.^{108,109,110}

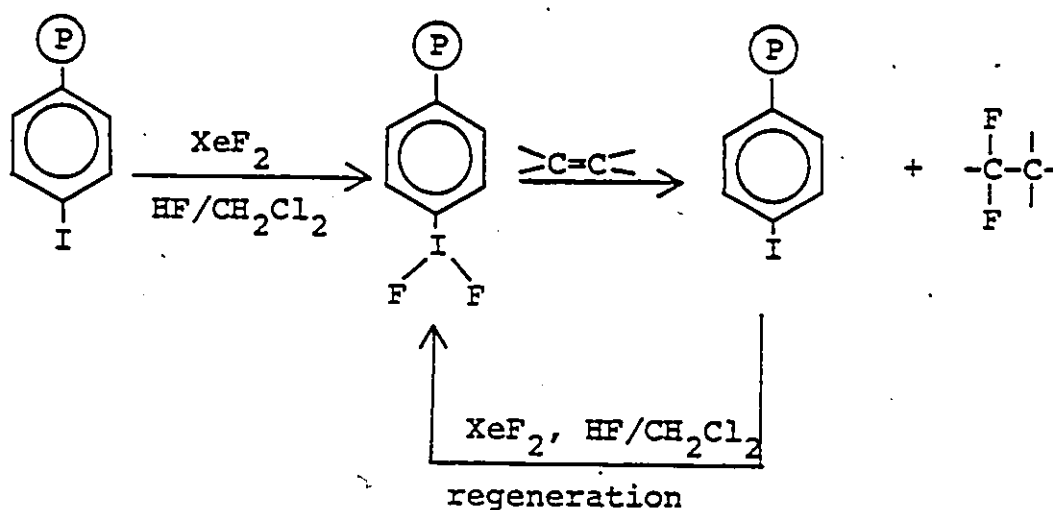


Scheme (18)

Poly(vinyl pyridinium hydrobromide perbromide) $\text{P}-\text{C}_5\text{H}_4\text{N}^+\text{HBr}_3^-$ has been used by Frechet and co-workers¹⁰⁸ for bromination of alkenes and ketones. The brominated products were obtained in excellent yields. The spent polymeric reagent has been regenerated without loss of activity. The polymeric reagent was made by reaction of 4-vinyl pyridine-styrene-divinyl benzene copolymer with hydrogen bromide and bromine. Attempts have been made to use a similar polymer containing chiral groups in asymmetric synthesis;¹⁰⁹ however these were generally not successful.

A polymeric aryl iodine (III) difluoride (Scheme (19)) has been prepared by first iodinating crosslinked polystyrene and then reacting it with XeF_2 in the presence of HF in CH_2Cl_2 at 25 °C.¹¹⁰ This reagent has been used to fluorinate several phenyl substituted olefins to their difluorides in high yields under mild conditions. The spent reagent has been reused several times.

(31),



Scheme (19)

A selected list of other polymeric reagents and their applications are shown in Table (2).

Table (2) : Selected polymeric reagents and their applications.

Functional Polymer	Application as a reagent	Ref.
(P)- $\text{S}^+\text{Me.Et FSO}_3^-$	Epoxidation of aldehydes	111
(P)- ICl_2	Chlorination of olefins	112,113
(P)- $\text{CH}_2\text{N}^+\text{Me}_3 \text{Br}^-$	α -bromination of carbonyl compounds, additions of bromine to alkenes and alkynes	114,115
(P)- C(Ph)=NBr	Allylic bromination	116
(P)- COCl	Conversion of acids to acid chlorides	117
(P)- $\text{C=CN}^+\text{Et}_2$	Conversion of acids to mixed esters anhydrides, and amides	118

Table (2) (Cont'd)

Functional Polymer	Application as a reagent	Ref.
$\text{P}-\text{C}_6\text{H}_4\text{N}-\text{BH}_3$	Reduction of carbonyl compounds	119
$\text{P}-\text{SnH}_2(\text{n-Bu})$	Reduction of carbonyl compounds, selective monoreduction of dials, reduction of alkyl halides to ketones	120
$\text{P}-\text{Se-R}$ R = Na, Cl	α, β -dehydrogenation of carbonyl compounds	121,122
$\text{P}-\text{Se}-\text{Ph}$ O	Oxidation of α -methylnaphthalene to α -naphthaldehyde	121,122
$\text{P}-\text{C}_6\text{H}_4\text{N}-\text{Br}_2$	Oxidation of thiols to sulphides	123

1.4. Optically active polymers

Optically active polymers are drawing a great deal of attention presently, especially in biomimetic chemistry in which they are used as backbones for models of the active sites of enzymes. Their study also represents a new approach to the problems of polymeric structures and polymerization mechanisms. Another potential application associated with these polymers is as chiral resolving agents for racemic mixtures.

Optically active polymers are of two types.

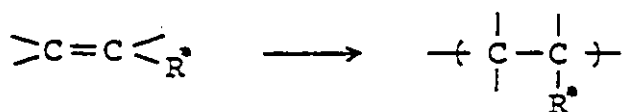
- i) Polymers having chiral substituents in the side chain.
- ii) Polymers with optical activity due to the chiral structure of the main chain.

1.4.1. Polymers with chiral substituents in the side chain

A considerable amount of work has been done on the synthesis of optically active polymers with chiral substituents in the side chain. Although a number of methods are available for the preparation of these polymers, two methods have been studied most extensively. They involve the direct polymerization of monomers with chiral side chains and the stereoselective or stereoelective polymerization of racemic monomers.

1.4.1.1. Polymerization of monomers having optical activity

The simplest method of producing polymers with side chains consists of polymerizing the corresponding optically active monomer.

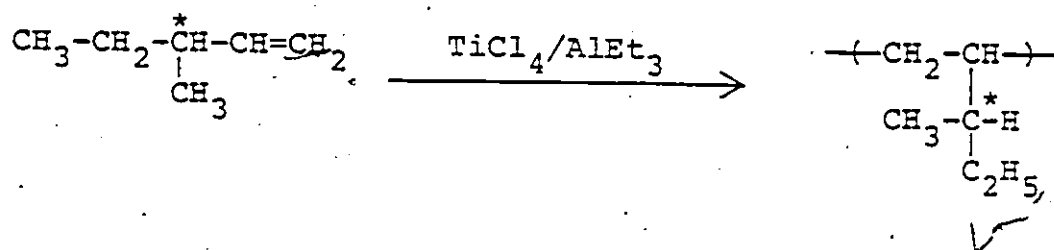


The first polymer of this type, a poly(isoamyl itaconic-acid) was prepared by Walder.¹²⁴ Since that time polymers derived from optically active α -olefins, vinyl ethers, vinyl ketones, acrylic or methacrylic esters, acrylic amides and aldehydes have been widely investigated. One of the utilities of these polymers is as a probe of conformational equilibria of the polymer chains in solution. If the chirality of the side chains induces a chiral conformation in the polymer chains, a marked change in optical activity on going from the monomer to the polymer would

be seen.

Murahashi , Nozakura et. al.¹²⁵

polymerized two optically active α -olefins, l-4-methyl-1-hexene and d-3-methyl-1-pentene, using a Ziegler-Natta catalyst (titanium tetrachloride/triethyl aluminum) (Scheme (20)) and the nature of the polymer was examined in anticipation that the asymmetric substituent might induce preferentially one helical configuration in the polymer chain. Both the polymers, poly(l-4-methyl-1-hexene) and poly(d-3-methyl-1-pentene), showed optical activity with very large optical rotations compared to those of the monomers. The large optical rotation seemed to be caused not only by the neighbouring groups around the asymmetric carbon atom of the side group but also by the molecular asymmetry of the helical configuration of the main chain, more particularly by a predominant concentration of either right- or left-handed helix in the solution. However, the optical rotation of the polymer in solution did not change with the concentration, the temperature or the addition of poor solvents. This strongly suggests that the optical rotation of this polymer can only be attributed to one species, the asymmetric carbon atom of the substituent group, at least in solution.



Scheme (20)

Optically active poly-(α -methyl benzyl methacrylate) PMBMA has been made using optically active α -methyl benzyl methacrylate by Ullman and co-workers.¹²⁷ In these studies a substantial enhancement of optical activity (about 30%) was found for the polymer by comparison with a monomeric analogue.

Menthyl methacrylate has been polymerized with different catalysts such as phenyl magnesium bromide, n-BuLi, benzoyl peroxide etc.¹²⁷ The poly (menthyl methacrylates) obtained have shown strong optical activity in most cases.^{127,128}

Optically active vinyl polymers from (S)-1-(methylpropyl) vinyl ether and (S)-2-(methyl butyl) vinyl ether have been synthesized with different stereoregularities and their optical activity has been investigated by Pino and co-workers.¹²⁹⁻¹³¹ These results show that when the asymmetric carbon atoms of the lateral chains are in the β -position with respect to the main chain of the macromolecules, (Figure (1)), the relationship between optical activity and polymer structure are quantitatively the same in the polyvinyl ether and in the corresponding poly- α -olefin. In fact poly[(S)-1-methyl propyl vinyl ether], like poly[(S)-4-methyl-1-hexene], has a very high positive optical activity strongly dependent on the stereoregularity of the polymer chain. On the other hand when the asymmetric carbon atoms of the lateral chains are in the γ -position with respect to the main chain of the macromolecule, (Figure (1)), the optical activity of the polyvinyl ether was much lower than that of the corresponding poly- α -olefin.

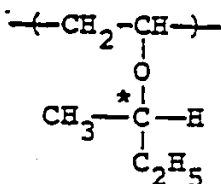
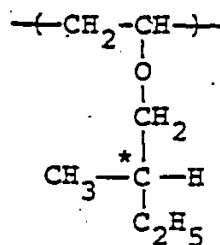
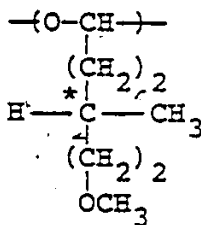
Poly [(S)-1-methyl propyl
vinyl ether]Poly [(S)-2-methylbutyl
vinyl ether]

Figure (1)

Goodman and Abe¹³² studied the polymerization of optically active aldehyde monomers and were able to prepare successfully a number of optically active polyaldehydes. (R)(-)-2-methyl butanal , (S)(+)-2-methyl butanal , (R)(+)citronellal and (R)(+)-6-methoxy-4-methyl hexanal have been polymerized using an aluminum triisobutyl catalyst.



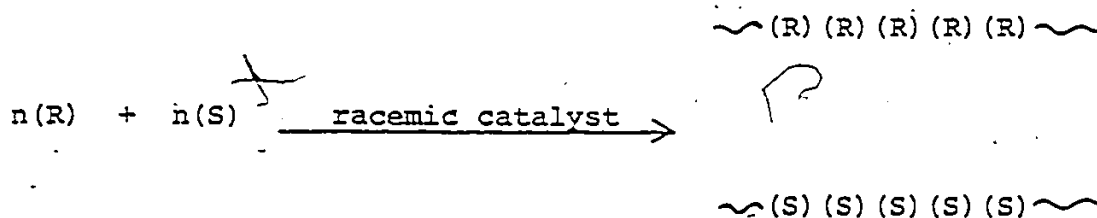
Poly ((R)(+)-6-methoxy-4-methyl hexanal)

Figure (2)

1.4.1.2. Stereoselective or stereoelective polymerization of racemic monomers

The second approach to synthesizing optically active polymers having chiral side chains involves the polymerization of sterically inhomogeneous monomers (eg., racemic monomers or a mixture of diastereomers) with polymerization catalysts which are able to discriminate between the enantiomeric or diastereomeric forms of the monomer. Two versions of these enantioselective polymerizations are known; stereoselective polymerization and stereoelective polymerization.

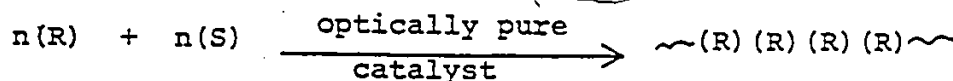
A stereoselective polymerization is a polymerization involving a racemic monomer which gives rise to a polymer containing macromolecules in which R or S monomeric units exist in a larger percentage than that calculated for a random copolymer of the two antipodes. The occurrence of this polymerization can be proved experimentally when it is possible to separate the obtained polymer into fractions having optical activity of opposite sign. (Scheme (21)).



The stereoselective polymerization of racemic monomers

Scheme (21)

The stereoselective polymerization of a racemic monomer is a polymerization process in which one of the monomeric antipodes is preferentially polymerized. This is achieved by using an optically active catalyst. In the ideal case, with an optically pure catalyst, only one of the enantiomeric monomers should polymerize. (Scheme (22)).



Ideal stereoselective polymerization of the monomer (R) from a racemic monomer (R) and (S)

Scheme (22)

This process is also known as "asymmetric selective" polymerization. If the conversion of monomer to polymer is not complete, both polymer and recovered monomer will be optically active. This kind of polymerization corresponds to a kinetic resolution of a racemic mixture.

The polymerization of racemic 3,7-dimethyl-1-octene and 3-methyl-1-pentene has been investigated by Pino and co-workers¹³³ using an optically active catalyst prepared from $TiCl_4$ and bis (S)-2-methyl butyl zinc. The recovered unpolymerized monomer showed measurable optical activity and the sign of its optical rotation indicates that, in both cases, the monomeric antipode preferentially polymerized is the one having the same absolute

structure as the optically active 2-methylbutyl groups present in the catalyst mixture. Different soluble fractions extracted with organic solvents show varying optical activity.

Racemic 1-methylpropyl vinyl ether has been copolymerized with several optically active vinyl ethers all having an asymmetric carbon atom directly bound to the oxygen atom, in the presence of heterogeneous catalyst systems such as $\text{Al}(\text{O-i-C}_3\text{H}_7)_3\text{-H}_2\text{SO}_4$.¹³⁴ When (S)-1-phenyl ethyl vinyl ether, (R)-1-phenyl ethyl vinyl ether, or (-)-menthyl vinyl ether was used as optically active comonomer the recovered unpolymerized 1-methylpropyl vinyl ether was optically active indicating that the process was stereoelective. The chemical composition and the optical rotations of the fractions obtained by extracting the polymeric product with boiling solvents, showed that the antipode of 1-methyl propyl vinyl ether, which according to the stereoelective character of the process was polymerized at a higher rate, gives preferentially a copolymer with the optically active comonomer. The other antipode gives the homopolymer which renders the process stereoselective.

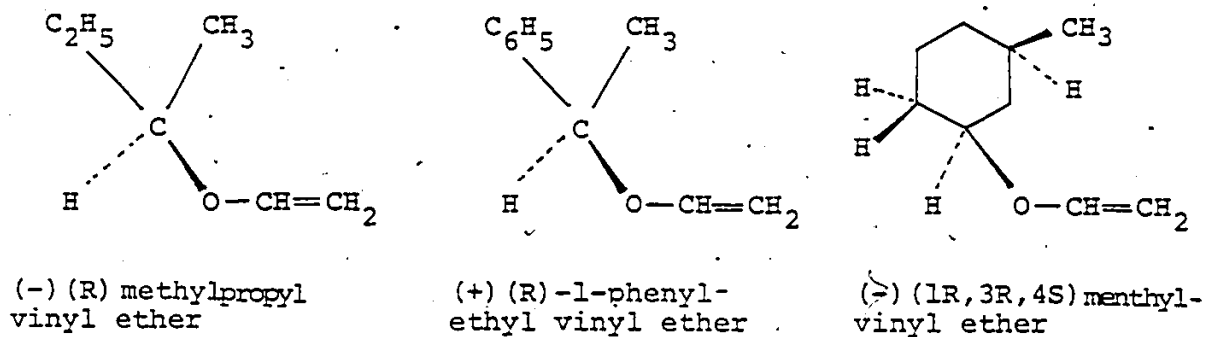


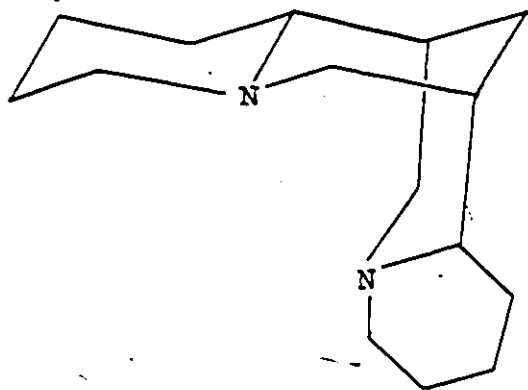
Figure (3)

It has also been shown that stereoelective polymerizations of racemic α -olefins are possible with Ziegler-Natta catalysts modified by additional of an optically active third component.¹³⁵ Chiral internal olefins, monomeric and polymeric aromatic hydrocarbons, amines and esters have been used for these polymerizations. The stereoelective polymerization of α -olefins has been done using (-) (α)pinene as an optically active component. In fact both polymer and unreacted monomer were optically active with opposite sign of rotation. No stereoelection has been observed when (-) (α)-pinene was removed from the catalyst before the addition of the racemic monomer. This indicates that the reaction of TiCl_4 and AlR_3 (Ziegler-Natta catalyst) in the presence of (-) (α)pinene does not yield active sites with a predominant absolute configuration. The preferential polymerization of the (-) (R) antipodes of the α -olefin observed when (-) (α)pinene is present during polymerization must therefore be attributed to an asymmetric perturbation of the catalyst sites.

α -methyl- α -n-propyl- β -propiolactone has been polymerized at room temperature using typical anionic initiators (spartein, Na, tetrahexylammonium benzoate) and a "stereoelective" initiator made from a 1:1 mixture of diethyl zinc and (R) (-)-3,3-dimethyl-1,2-butanediol.¹³⁶ The anionic initiators lead to racemic polymers while the "stereoelective" initiator gave an optically active polymer.

The stereoelective polymerization of (RS)- α -methylbenzyl methacrylate (RS)MBMA with homogeneous cyclohexyl magnesium

chloride and bromide-(-)-spartein system has been studied by Ohta and co-workers.¹³⁷ The system polymerized preferentially (S)-MBMA over (R)-MBMA. The optical purity of the monomer which was polymerized in the early stage of the polymerization was greater than 90% and the optical purity of the unreacted monomer was nearly 100% at about 65% polymer yield. This high asymmetric selectivity was ascribed to the non-simultaneous existence of two different active centers. One of them, produced exclusively in the initiation reaction, polymerizes (S)-MBMA preferentially and disappears at approximately 45-65% polymer yield. The other is then formed and polymerizes only (R)-MBMA. The existence of these two centers was supported by the studies of optical rotation, molecular weight and tacticity of the polymers as well as by kinetic data.



(-) Spartein

Figure (4)

The same catalyst systems have also been tested in the polymerization of methacrylic esters which have an asymmetric

center at the more remote δ -position from the carbon-carbon double bond.¹³⁸ A monomer such as 2,3-epoxypropyl methacrylate (EPMA), when polymerized using cyclohexyl magnesium-chloride(bromide)-(-)-spartein system, gave a highly isotactic, optically active polymer which had not been obtained with typical anionic catalysts such as n-BuLi and Grignard reagents.¹³⁹

1.4.2. Polymers with optical activity due to the chiral structure of the main chain

In the polymerization of monosubstituted vinyl monomers a chiral center is formed from a prochiral center in each step of the polymerization. However the final polymer which is obtained is not optically active due to internal compensation.¹⁴⁰⁻¹⁴⁵ In a polymerization of this nature three types of polymer chains can be formed, (Figure (5)).

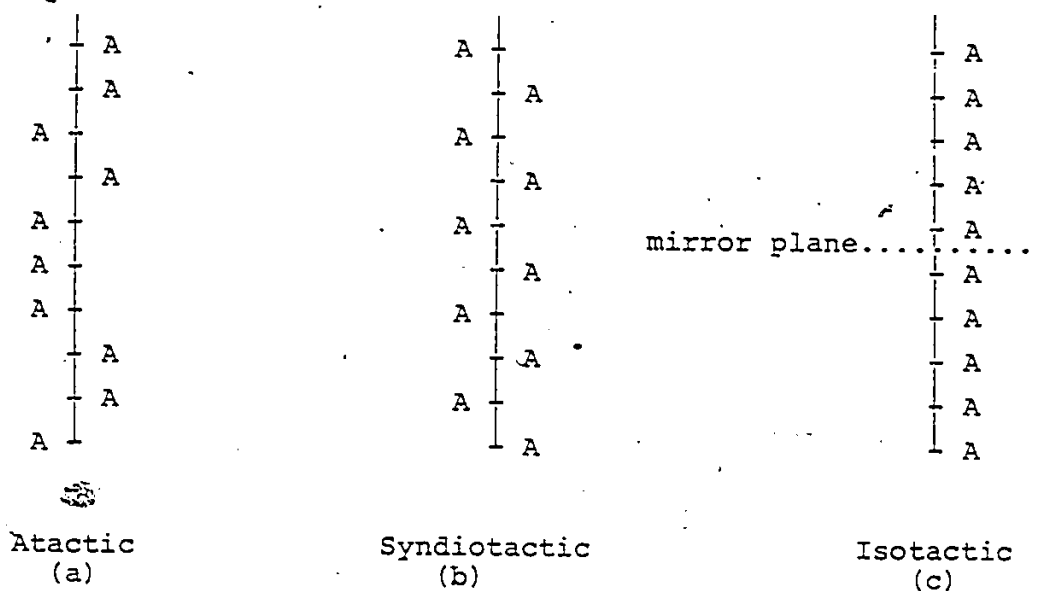


Figure (5)

Atactic polymers with an irregularly alternating R and S configuration (Figure (5) (a)) and syndiotactic polymers with regularly alternating R and S configuration (Figure (5) (b)) can indeed be chiral, but the optical activity is intramolecularly compensated and therefore not measurable. Isotactic polymers (Figure (5) (c)) could give two enantiomorphous chains beginning with either an R or S configuration. If the difference in the end groups is neglected, which is permissible in the case of long chains, the molecule possesses a mirror plane and therefore does not show any optical activity.

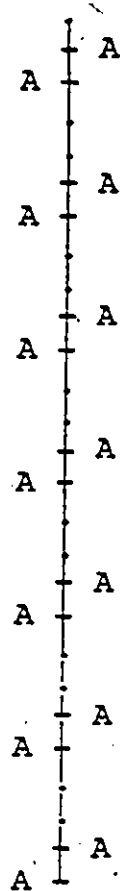
Optically active polyvinyl or polyvinylidene polymers whose optical activity depends on the chiral structure of the main chain are very rare. On the other hand, optically active polymers with main chain chirality from 1,2-disubstituted olefins have been made.¹⁴⁵ Homopolymers from benzofuran and alternating copolymers from maleic acid are some of the examples which belong to this category. Another group of polymers which shows optical activity due to the chirality of the main chain are those obtained from substituted dienes.^{140-145,147}

Recently Wulff deduced by symmetry considerations three types of structures where optical activity due to chirality is expected in vinyl and vinylidene polymers.^{148,150} One of them would be the head-to-head polymerization of the monomers which will give rise to 1,2-disubstituted chiral segments, (Figure (6)) with a structure similar to that of the copolymers obtained from 1,2-disubstituted monomers. The main chain can also become chiral

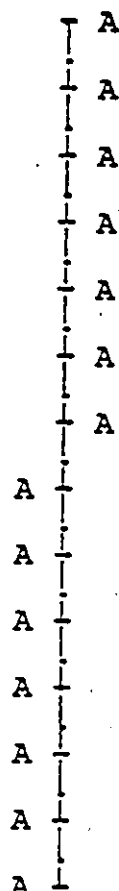
if the substituent near the center of an isotactic polymer chain changes to the other side of the main chain with respect to the Fischer projection, (Figure (6) (e)). This type of rearrangement have been named "inverse-diblock isotactic" since each part of the chain has in itself a strong isotactic structure. It is chiral as it has one two-fold symmetry axis. This type of polymer has not been synthesized yet. The third type of polymer chain with main chain chirality can occur only in copolymers and Figure (6) (f) represents one of three possibilities. In the copolymers, triad I as well as the other two possible triads is asymmetric and polymers of this type should show optical activity.

An optically active polymer of the type shown in (Figure (6) (f)) containing asymmetric triads has been successfully synthesized by Wulff and co-workers.¹⁴⁶ As can be seen in (Figure (6) (f)) a triad unit is made up of a monomeric unit with a B substituent placed between two monomers with A substituents. To prepare such triads with the appropriate stereochemistry two monomeric units were fixed stereospecifically on a chiral template molecule and then another monomer was inserted between those two diastereoselectively during polymerization. The template molecule was then removed from the polymer.

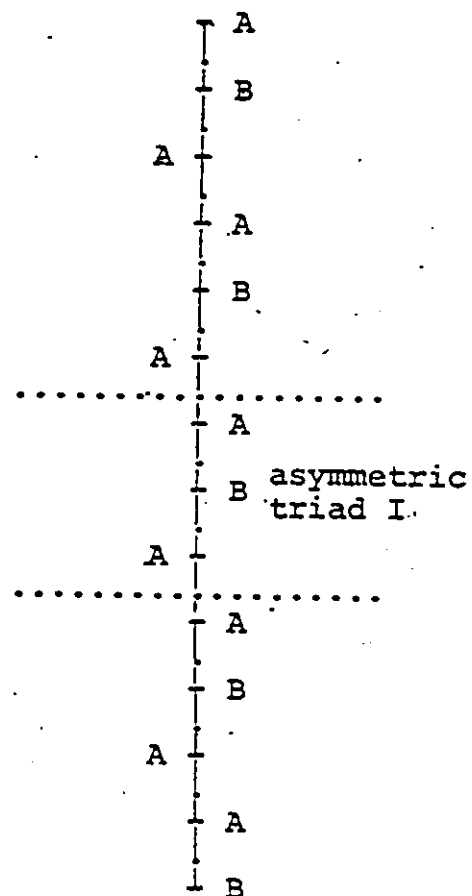
D-mannitol-1,2:3,4:5,6-tris -O-(4-vinyl phenyl)boronate (Figure (7) (g)) has been used for this synthesis. A comonomer can be easily inserted between the styrene units in the 1,2- and 5,6-positions of the mannitol derivative in the given conformation.



(d)



(e)



(f)

Figure (6)

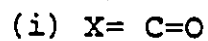
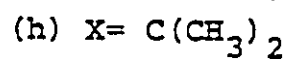
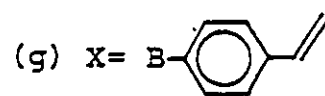
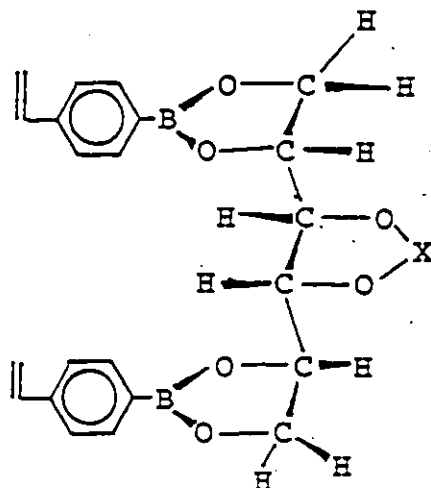


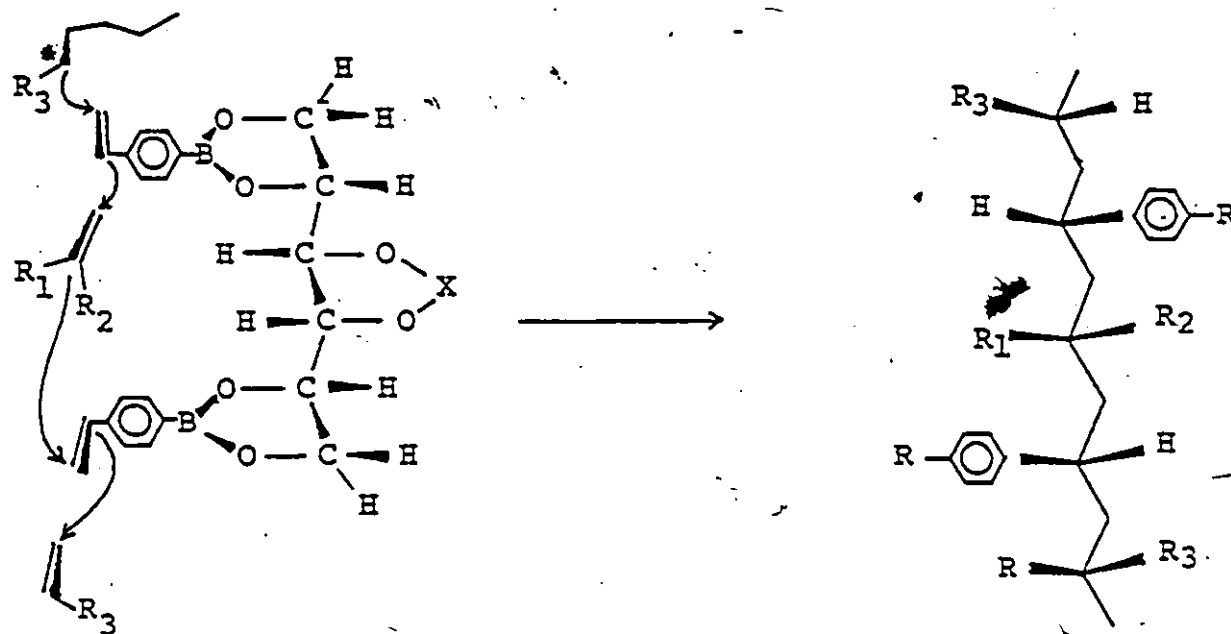
Figure (7)

The polymerization was carried out by a free radical technique using azobisisobutyronitrile as initiator. The yields were in the range of 60-90% .

The optical rotations have been measured in acetone-water (10:1) solution. Copolymers from (g), (h) and (i) have shown strong negative rotation in contrast to the strong positive rotation of the monomeric precursors, which indicates an asymmetric induction by the chiral template. From labelled studies using ^{14}C labelled D-mannitol it has been shown that the optical rotation of the polymers does not originate from the pendant template but from the chirality of the main chain of the polymer.

The mechanism for the polymerization is given in Scheme (23). Monomers (g), (h) and (i) all have C_2 symmetry and therefore radical attack of a growing chain at the (4-vinyl phenyl)boronate groups of the 1,2-position as well as the 5,6-position of the D-mannitol will result in the same product. In the proposed mechanism the growing radical first attacks one of the vinyl groups of (g), (h) or (i) predominantly from the outside conformation of the vinyl group. In the second step the newly formed radical attacks a comonomer which should be situated between the two (4-vinyl phenyl)boronate moieties. This attack yields the asymmetric induction of the triad I, induced by the chiral environment of the template molecule. In the next step the comonomer radical formed in the previous step attacks at the second (4-vinyl phenyl)boronate ester residue

which produces a pseudoasymmetric center in the resulting triad I. Then the attack of the second (4-vinyl phenyl)-boronate residue at another monomer completes the triad.



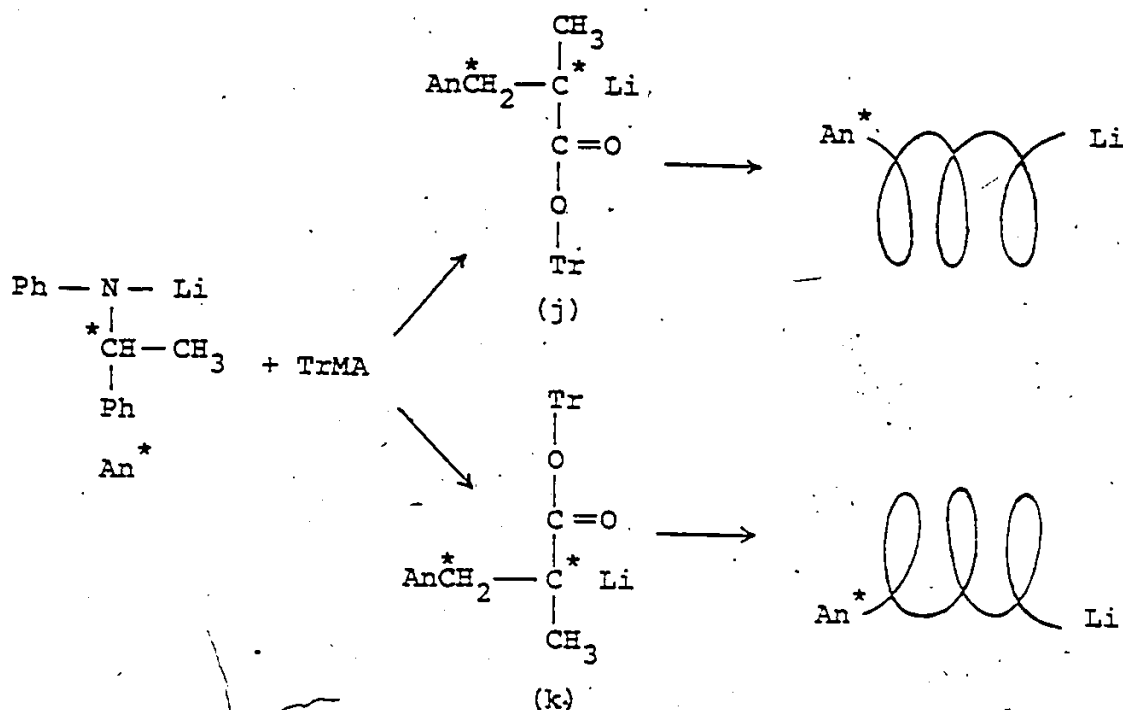
Scheme (23)

Another type of optically active polymer could be achieved if one helical conformation of the polymer chain is preferred over the other. The first attempt was by Murahashi, Nozakura et al.¹²⁵ who polymerized styrene, a prochiral monomer, with an anionic catalyst containing an optically active group such as optically active amyl sodium triamyl aluminum combined with titanium trichloride. However it was not successful.

Okamoto et al.¹⁵¹ recently described a new chiral polymer which was claimed to be the first optically active vinyl polymer in which chirality is the result of the helicity of the polymer chain. A high isotactic polymer with a large optical rotation has been obtained by polymerizing triphenylmethyl methacrylate (TrMA) using a chiral anionic catalyst such as lithium

(R)-N-(1-phenylethyl)anilide (LiAn) or (-)spartein-butyllithium complex (Sp-BuLi).

In the polymerization of TrMA using LiAn two diastereomeric anions (j) and (k) (Scheme(24)) are produced whose yields will depend on the steric effect of the (R)-N-(1-phenylethyl)anilino group. Subsequent additions of the monomer probably proceed with retention of configuration to form fully isotactic right handed and left handed polymers and one of them will be formed predominantly. (Scheme(24)).

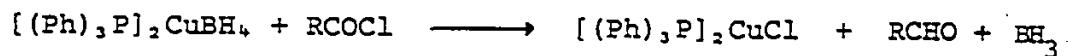


Scheme (24)

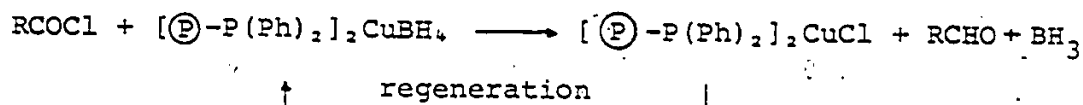
I.5.

Aims of researchI.5.1 Recyclable polystyrene-based polymeric reagent for the reduction of acid chlorides to aldehydes

Recent studies have shown that bis(triphenylphosphine) copper tetrahydroborate is a useful reagent to effect the conversion of acid chlorides into aldehydes under mild conditions - without production of side products¹⁵²⁻¹⁵⁶. Significant problems which remain in these reductions are the difficult isolation of the aldehydes from the reaction medium and the fact that the spent reagent is not readily recycled. The latter is important as the reagent, which has a molecular weight of 603, provides only one hydride equivalent per mole for the reduction.



For these reasons it was felt that the use of a polymer as a ligand for copper tetrahydroborate would help alleviate these problems, as the separation of the spent reagent from the desired product would amount to a simple filtration and regeneration of the polymer should be easily accomplished. (Scheme (25)).



Scheme (25)

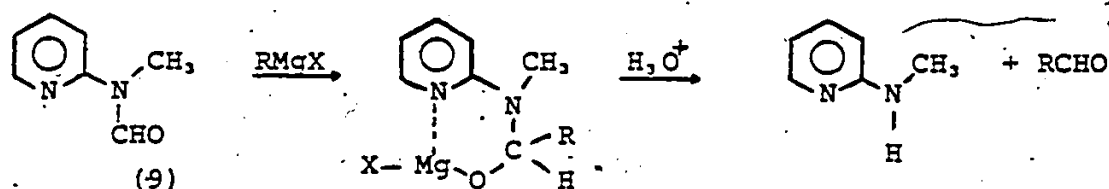
I.5.2. The role of chelation in the formylation of Grignard reagents with formamide and a recyclable polymeric formylating agent for Grignard reagents.

The preparation of aldehydes from Grignard reagents using 2-(N-formyl - N-methyl)aminopyridine has been described by Comins and Meyers¹⁵⁷ (Scheme (26)). The success of the reaction was attributed in part to the presence of an additional ligand (pyridyl nitrogen) which is thought to stabilize the reaction intermediate by the formation of a six-membered ring chelate.

It appeared that this reaction might yield better results when carried out with the polymeric reagent as an increase in chelate stability would likely be observed, which would allow the reaction to be carried out at room temperature rather than at 0°C in perhaps higher overall yield. An additional advantage would be the enhanced recyclability of the polymeric reagent.

In a more recent report, Olah and Arvanaghi¹⁵⁸ claimed that chelation played no significant role in this formylation reaction, as extremely high yields of aldehydes could be obtained in the formylation of Grignard reagents with a N-formyl piperidine reagent which possesses no additional stabilizing ligand for the intermediate.

These conflicting claims prompted us to undertake a model study to determine which type of formylation reagent would be best suited for incorporation into a polymeric reagent. The model study was used in the design of several polymeric reagents which were tested in formylation reactions.

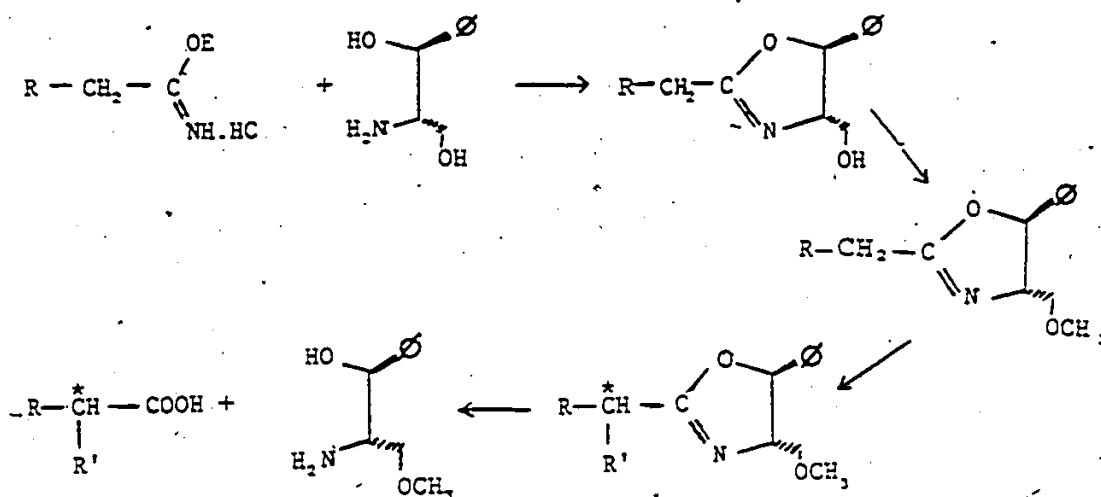


Scheme (26)

1.5.3. Chiral polymer-supported oxazolines for asymmetric synthesis

The chiral oxazoline approach¹⁵⁹ to the synthesis of optically active carboxylic acids (Scheme (27)) appeared well suited for the development of a polymeric reagent, as the decrease in conformational mobility and the increase in

stability of the reaction intermediate, which might result from binding to a polymer support, would likely lead to increased stereoselectivities. In addition, the polymeric reagent would benefit from the usual enhanced purification and recycling advantages. Thus routes for the preparation of polymer bound analogues of Meyers' oxazolines were explored.



Scheme (27)

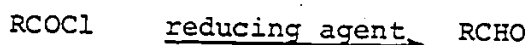
I.5.4. Synthesis of optically active polymers

The preparation of optically active polymers of 1-substituted olefins, whose optical activity depends on the chirality of the main chain, is a goal which has long remained unachieved. Our aim was to synthesize the optically active polymer of a 1-substituted olefin in which main chain chirality would be obtained by chemical modification with concurrent asymmetric induction.

II

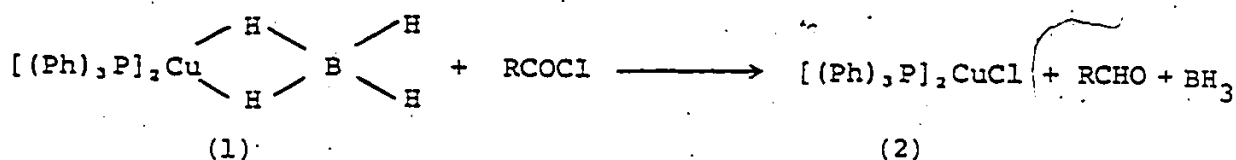
Results and DiscussionII.1. Bis(Polystyryldiphenylphosphine) Copper (I)Tetrahydroborate; recyclable polymeric reducing reagent.

Considerable interest has been shown in the application of transition metal hydrides in selective reductions. Reduction of epoxides, alkenes, alkynes and alkyl halides has been done with reagents derived from treatment of halides of titanium, other first row transition elements¹⁶⁰, and zirconium¹⁶¹ with lithium aluminum hydride. Reductions with transition metal tetrahydroborates in organic synthesis are rare. Lanthanide tetrahydroborate has been used in the reduction of α, β -unsaturated ketones to allylic alcohols¹⁶² and bis(cyclopentadienyl)chlorotetrahydroboratezirconium (IV) has been used to reduce aldehydes and ketones.¹⁶³ In the past, the selective reduction of acid chlorides to aldehydes has been done with reagents such as $\text{LiAlH}(\text{O}-t\text{Bu})$,¹⁶⁴ $\text{Na}_2\text{Fe}(\text{CO})_4$ ¹⁶⁵ and $\text{HFe}(\text{CO})_4$ ¹⁶⁶ which demand special care during their preparation and application. It can also be done by hydrogenation with Pd/BaSO_4 , known as Rosenmund reduction. Over reduction is sometimes a problem with this reagent.¹⁸⁹



A novel reagent, bis(triphenylphosphine) copper (I) tetrahydroborate, (1) (Scheme (28)) has been developed for this selective reduction and used to reduce a wide range of acid

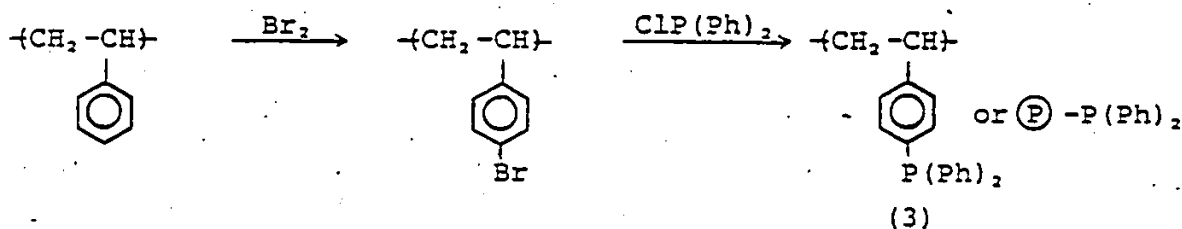
chlorides to their corresponding aldehydes under mild conditions in very high yields¹⁵²⁻¹⁵⁶, (Scheme(28)).



Scheme (28)

In their concluding study of this reaction, Fleet et al.^{155,156} indicated, however, that the major problem in this reaction is the separation of the aldehyde from the reaction mixture. Such a problem can obviously be alleviated through the use of a polymeric reagent, as both the unspent reagent and its byproduct remain firmly bound to the polymer throughout the reaction, allowing recovery of the product by a simple filtration process. This can be accomplished by replacing either one or both of the triphenyl phosphine ligands in bis(triphenylphosphine) copper(I) tetrahydroborate by analogous polystyryldiphenylphosphine ligands.

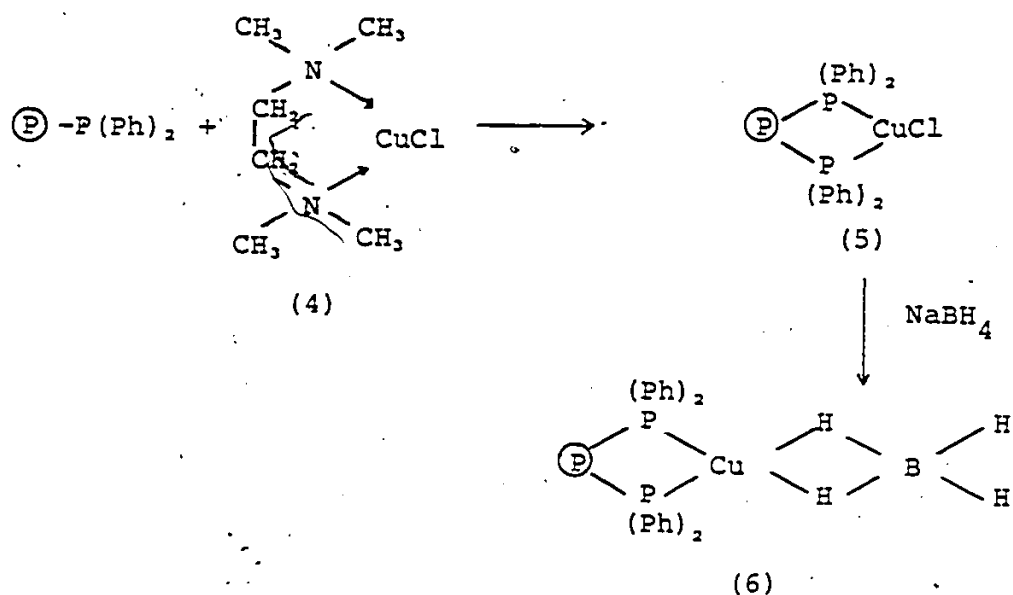
Polystyryldiphenylphosphine (3) (Scheme(29)) was prepared according to the literature^{45,60}. The crosslinked polystyrene beads were first ring brominated by treating with bromine and a catalytic amount of ferric chloride in carbon tetrachloride. The polymer obtained after the bromination showed a capacity of 5.1 mequiv/g which is close to the maximum for incorporation of one bromine atom per aromatic ring. Polystyryldiphenylphosphine was made by reacting the brominated polystyrene with chlorodiphenylphosphine in the presence of lithium metal and, in a typical reaction, the polymer obtained had a degree of functionalisation (DF) in the range of 0.8 -0.9.



Scheme (29)

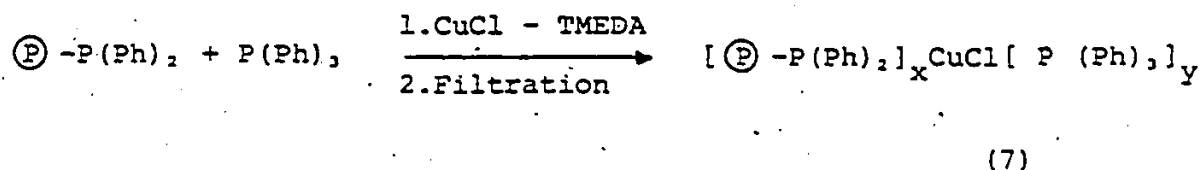
Polymeric phosphine (3) was then used to bind copper (I) chloride. Several different methods were tested to effect this binding; best results were obtained with a ligand exchange reaction involving treatment of the polystyryldiphenylphosphine (3) with cuprous chloride - N,N,N',N'-tetramethylethylenediamine

complex in acetone (Scheme(30)). This reaction can lead to essentially complete functionalization of the phosphine sites on the polymer. The polymer-bound copper tetrahydroborate reagent (6) can be obtained very easily by treatment of the polymer-CuCl complex (5) with excess sodium borohydride in ethanol, followed by washing of the polymer to remove any unbound borohydride. This reaction yields a polymeric reagent with a capacity of up to 1.6 mequiv. of boron per gram, a value which is comparable to that of the analogous monomeric reagent.



Scheme. (30)

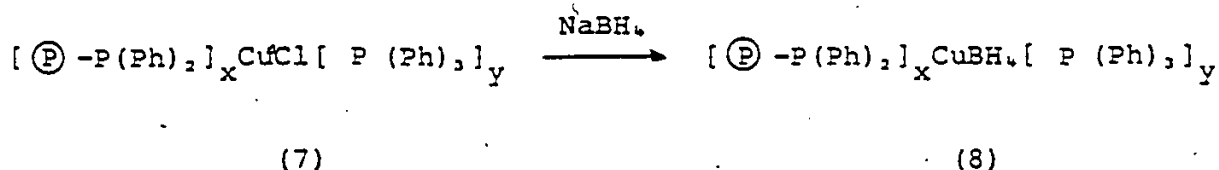
Another interesting approach was made for the preparation of the polymer supported copper (I) tetrahydroborate reagent, and it involved the use of both polymeric phosphine (3) and monomeric triphenylphosphine to bind the copper. The advantage of this procedure was that only one of the polymer's active sites was required for the binding of each molecule of cuprous chloride (Scheme (31)).



Scheme (31)

Polymer (7) was prepared by dispersing (3) in a concentrated solution of triphenylphosphine, removing most of the solvent by evaporating under reduced pressure, then adding an excess of CuCl-TMEDA complex in acetone and allowing it time to equilibrate. The polymer was filtered and washed thoroughly to remove excess CuCl-TMEDA complex and triphenyl phosphine.

Treatment of this polymer with excess sodium borohydride in ethanol at room temperature afforded the polymeric reagent (8) (Scheme (32)).



Scheme (32)

The advantage of this method was that a larger amount of polymeric reagent can be obtained from a given amount of polymeric phosphine (3). Polymer (8) also had a high capacity of 1.5-1.6 mequiv. B/g.

When using polymer (6) or (8), care has to be taken to exclude water from the reaction medium, as it would hydrolyze the acid chloride to the acid.

In order to determine the actual capacity of the polymeric reagent, a reaction was designed in which 2 mmol. of acid chloride was treated with 1 g of the polymeric reagent. The results of these reactions are shown in Table (3). Since the maximum capacity that can be achieved with this polymer is 1.5 - 1.6 mequiv/g, the yields of the aldehydes obtained for the reduction reactions were excellent and close to the calculated maximum of 75%. In addition to some unreacted acid chloride, some side product was also seen. It was found by the comparison of G.C. retention times that the side product was neither the alcohol, which could result from the over-reduction of the aldehyde, nor the acid, which could result by the hydrolysis of the starting acid chloride. This product must arise from a side reaction in which the polymeric reagent does not participate, as almost all of its reactive sites were consumed for the reduction. In order to overcome this problem, an excess of polymeric reagent was used for the reductions.

Reductions were carried out using a 50% excess of polymeric reagent with respect to acid chlorides and, in a typical reaction, 1.5 g of polymeric reagent in 5 ml. of solvent was

treated with 1 mmol. of acid chloride and the reaction was monitored by gas chromatography. The results obtained in these reactions when acetone was used as the solvent are shown in Table (4). The data also includes results obtained in reactions involving the recycled reagent. The yields were almost quantitative and no side reactions were seen. It is also apparent that the recycled reagent is just as effective as the freshly prepared reagent and that no loss of activity occurs during regeneration.

Regeneration of the spent reagent amounted to a new reaction with sodium borohydride. (Scheme (33)) No new addition of cuprous chloride was necessary as no leaching of copper salts from the polymer was observed during a typical reaction cycle.

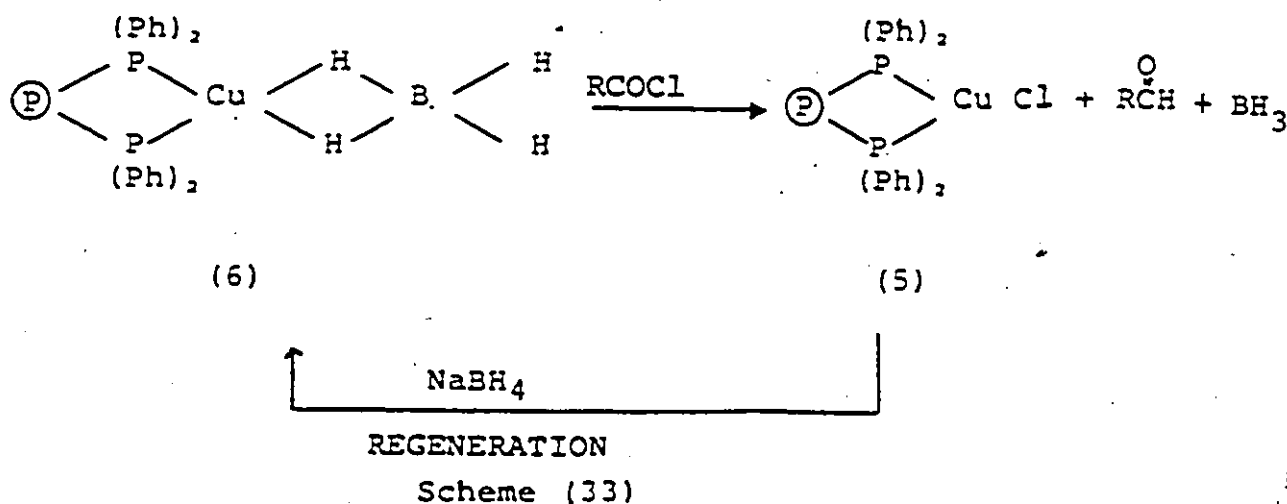


Table (3): Reduction of 2 mmol of acid chloride with 1.5 mmoles of Reagent (6)

Acid Chloride	Product Analysis %		
	Starting Material	Aldehyde	Other
$\text{CH}_3(\text{CH}_2)_5\text{COCl}$	13	68	19
$\text{C}_6\text{H}_5\text{COCl}$	7	73	20

Table (4): Reduction of acid chlorides with 50% excess of polymeric reagent (6)

Acid Chloride	Reaction cycle (Yield of aldehyde)		
	1st cycle	2nd cycle*	3rd cycle*
$\text{CH}_3(\text{CH}_2)_5\text{COCl}$	96%	91%	94%
$\text{C}_6\text{H}_{11}\text{COCl}^\#$	96%	93%	
$\text{C}_6\text{H}_5\text{COCl}$	100%		

* Regenerated reagent used in 2nd and 3rd cycles

$^\# \text{C}_6\text{H}_{11}$ = cyclohexyl

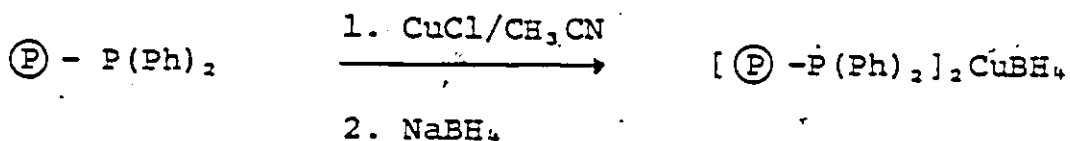
The best solvent for the reduction was found to be acetone and the reactions were very fast at room temperature, usually complete in 15 min. or less. The aldehydes were formed free from any alcohol. Ether and ether/toluene (1:1) were also found to be satisfactory solvents for the reduction. Benzene and toluene were not satisfactory; reaction rates were slow and the yields of aldehydes were very poor (30 - 40%) when the reductions were done in these solvents. This could be due to the polar copper tetrahydroborate groups present in the polymer which make the polymer more polar and thereby restrict the diffusion of reactants to the reactive sites of the polymer in less polar solvents due to reduced swelling.

During some regeneration reactions the polymer became black in colour instead of the usual brown, but the reactivity and the capacity of the polymer did not change significantly. This could be due to the reduction of some copper (I) to copper (0) which became deposited on the polymer. The black colour of the polymer was probably due to an oxidation of the copper (0) film on the polymer to copper oxide. The amount of copper used for this conversion was so small that it did not affect the reaction rates and yields.

However, this shortcoming was completely eliminated by using a very small amount of triphenylphosphine (2-3% with respect to the reagent) in the reaction of the spent reagent with sodium borohydride.

These results show that the polymeric reagent (6) is an effective and fully recyclable polymeric reagent useful in the reduction of acid chlorides to aldehydes. It had a capacity which was essentially as high as that of its low molecular weight counterpart and the two reagents have approximately the same reactivity. The polymeric reagent was easier to use and to recycle due to the ease with which it can be removed from the reaction medium once the reduction is complete.

While the work on this polymeric reagent was in progress, Sorrell and Pearlman¹⁶⁷ reported the synthesis of a similar polymeric reagent using a different route. (Scheme (34)). However, this reagent could only be prepared with a low capacity of approximately 0.5 mequiv/g; therefore much larger amounts were required to effect the reductions and in addition, yields did not exceed 70-75%.



Scheme (34)

The superior performance of the polymeric reducing reagent described in this thesis can probably be attributed to the fact that efforts were made to maximize the loading of copper on the polymeric phosphine (3). This was achieved with a ligand exchange reaction by using CuCl-TMEDA complex in acetone. In contrast, the reagent described by Sorrell and Pearlman, prepared in CH₃CN, has a low loading of copper with a capacity of only one third of the reagent described in this thesis. Therefore, this will require the use of large amounts of polymer for the reductions which could in fact increase the chances for side reactions. The large volumes of solvents which are involved will make the dry conditions required for the reactions harder to maintain. The recycling of this polymeric reagent is not a real advantage as it is far inferior to the monomeric reagent.

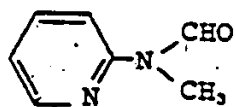
II.2.2. The role of chelation in the formylation of Grignard reagents with formamides

A number of methods are available to form aldehydes from Grignard reagents, but they involve at least two steps, the formation of an aldehyde precursor and then conversion to the aldehyde¹⁶⁸⁻¹⁷². The yields are normally low because of the number of steps involved. Formylation of aromatic rings can be done by the Vilsmeier reaction with disubstituted formamides and POCl₃.

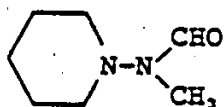
An efficient one step reaction to formylate Grignard reagents to give aldehydes using 2-(N-formyl N-methyl)aminopyridine (9), (Scheme (26)) was described recently by Comins and Meyers¹⁵⁷. A wide range of aldehydes have been prepared from their corresponding Grignard reagents under mild conditions in very good yields with this reagent. Although Grignard reagents have been reported to undergo formylation with dimethylformamide, the yields were not very high. The success of the reaction with 2-(N-formyl N-methyl)aminopyridine has been attributed in part to the presence of an additional ligand (pyridyl nitrogen) which could stabilize the incipient aldehyde through the formation of a six-membered ring chelate. (Scheme (26)).

The efficiency of the reagent, minimum side products and the easy recyclability of the spent reagent make it an ideal case to be used on an insoluble polymer support. By using a polymer support the above reaction will be benefited by all the advantages associated with supported reagents.

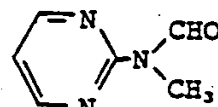
A number of alkylformamides (9)-(18) (Scheme (35)) were considered for possible grafting to a polymer support. While this work was in progress the report of Olah and Arvanaghi¹⁵⁸ appeared which suggested that no additional ligands were in fact necessary for this reaction to be successful, as N-formylpiperidine (14) also gave excellent results in the formylation of Grignard and organolithium compounds.



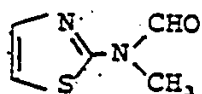
(9)



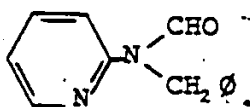
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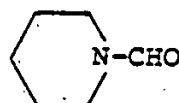
(11)



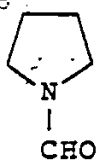
(12)



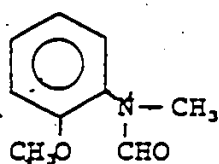
(13)



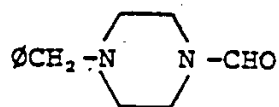
(14)



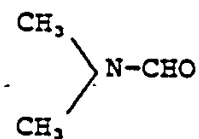
(15)



(16)



(17)



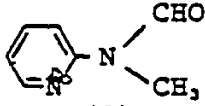
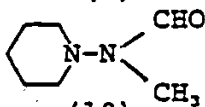
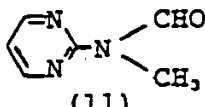
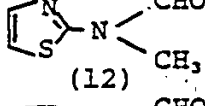
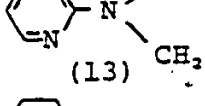
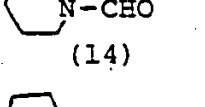
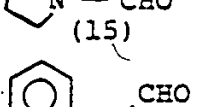
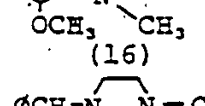
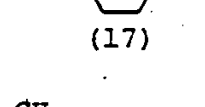
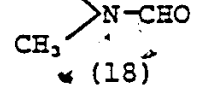
(18)

Scheme (35)

In our investigation, formylation reactions of Grignard and organolithium compounds were studied using reagents (9)-(18). For the first series of comparative studies phenyl magnesium bromide was used and its reaction with reagents (9)-(18) were studied under the conditions described by Meyers¹⁵⁷ and by Olah and Arvanaghi¹⁵⁸. In a typical reaction, the formylating reagent was reacted with phenyl magnesium bromide, in slight excess (Meyers') or in stoichiometric quantities (Olah's) at 0°C in THF. The reaction was monitored by thin layer chromatography and quenched with 5% HCl. The products were isolated by column chromatography and the results are shown in Table (5). It is clear that the yields obtained using the two methods are quite similar and can be considered identical within experimental error.

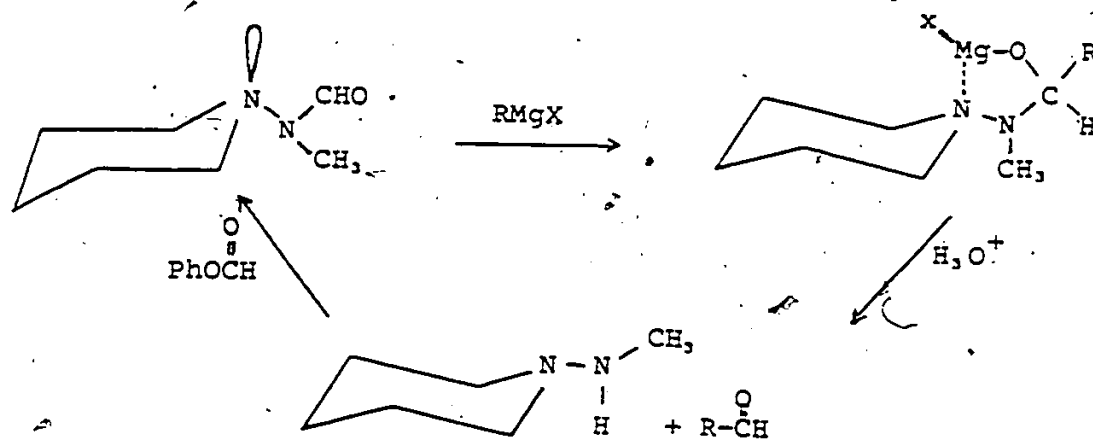
The formamide reagents 2-(N-formyl-N-methyl)aminopyridine (9), N-(N-formyl-N-methyl)aminopiperidine (10), 2-(N-formyl, N-methyl)aminopyrimidine (11) and 2-(N-formyl-N-benzyl)aminopyridine (13) all gave very high isolated yields of benzaldehyde without any side products. All the other reagents 2-(N-formyl-N-methyl)thiazole (12), N-formylpiperidine (14), N-formylpyrrolidine (15), 2-methoxy(N-formyl-N-methyl)aniline (16), (N-formyl-N'-benzyl)piperazine (17) and DMF (18) gave lower isolated yields of benzaldehyde with a significant amount of the secondary alcohol benzhydrol, which might have been produced by reaction of benzaldehyde with a second mole of the Grignard reagent.

Table (5): Reaction of PhMgBr with formamide reagents.

	Yield (Isolated)	
	PhCHO*	(Ph) ₂ CHOH
 (9)	79	0
 (10)	85	0
 (11)	84	0
 (12)	66	11
 (13)	77	0
 (14)	61 (64)	14 (15)
 (15)	63	9
 (16)	60	11
 (17)	65	9
 (18)	69 (66)	9 (9)

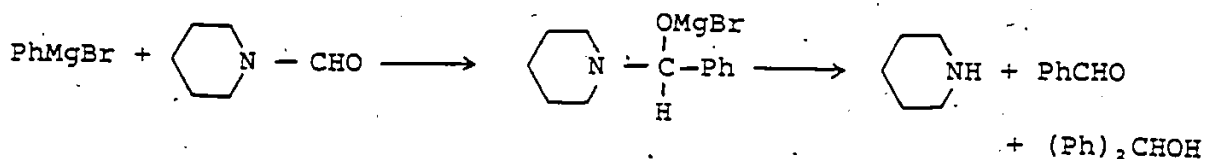
*Yields for reactions carried out under the conditions described by Meyers or by Olah for values in parenthesis.

As can be seen in Table (5), best results were obtained with the reagent (10), which affords an excellent yield of benzaldehyde without any trace of benzhydrol. This reagent can form a five membered chelate intermediate, as shown in Scheme (36), which is resistant to further reaction with the Grignard reagent.



Scheme (36)

Both reagents (14) (used by Olah) and (15) gave less satisfactory results with a significant amount of benzhydrol being produced, which indicates the poor stability of the intermediate and some attack of the liberated benzaldehyde by the Grignard reagent. (Scheme (37)).



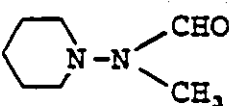
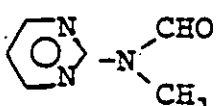
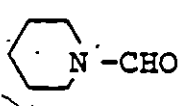
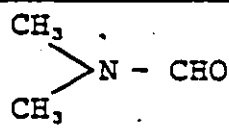
Scheme (37)

The high yield reported by Meyers for this reaction with reagent(9) was accomplished or even bettered without any difficulty during this study. Although the report in the literature by Olah claims yield of 96% for the same reaction with the reagent (14), in our hands a maximum yield of 60-64% of benzaldehyde was obtained with up to 15% of benzhydrol byproduct.

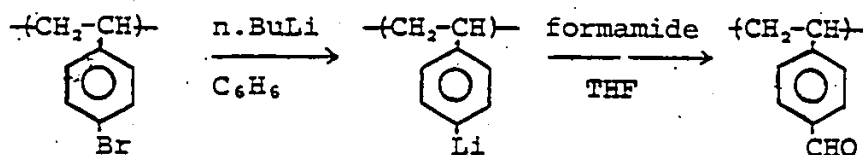
Little chelating effect was expected in the reagents (12) and (16), due to the weaker donating ability of the additional ligands present and, in fact, they gave inferior yields of benzaldehyde with some benzhydrol in their reactions with phenyl magnesium bromide. With (17) the extra ligand is located too far from the reaction center to have any chelating influence and benzhydrol formation was also observed.

Similar results were obtained in reactions with other Grignard and organolithium compounds as shown in Table (6). The influence of the reaction temperature is clearly evident, as a small amount of secondary alcohol was formed even with the reagent (10) in the reaction with the Grignard derivative of phenylacetylene or with phenyllithium at 0°C. When the temperature was lowered to -10°C the secondary alcohol was not formed. This is in agreement with the observations of Comins and Dernell¹⁷⁵ who were able to prepare unsymmetrical secondary alcohols in excellent yields by successive reaction of 2-(N-formyl-N-methyl)aminopyridine with two different Grignard reagents added at 0°C and 65°C respectively.

Table (6): Isolated yields of aldehydes (alcohols) in the reaction of selected formamide with RMgX or RLi at 0 and 10 C.

Grignard reagent	formamide						
	 (10)	 (11)	 (14)	 (18)			
	0C°	-10C°	0C°	0C°	-10C°	0C°	-10C°
PhCH ₂ CH ₂ MgBr	86 (0)		81 (0)	71 (9)		67 (14)	
Ph-C≡C-MgBr	73 (1)	80 (0)		60 (12)	68 (10)	64 (10)	
Ph-C≡C-Li	92 (0)				71 (6)		
Ph-Li	79 (5)	81 (0)	81 (0)		68 (18)	69 (9)	70 (9)
Ph-MgBr	85 (0)		84 (0)	61 (4)		69 (9)	

The formylation of a ring lithiated 1% crosslinked polystyrene has been used extensively to prepare reactive resins containing vinylbenzaldehyde units⁸³. The reagent of choice for this reaction is usually DMF, which is used in large excess to quench the lithiated resin. Further studies were carried out regarding the formylation of ring lithiated polystyrene using the reagents (10), (15) and (18). All the reactions were done under the same conditions using exactly the same proportions of reagents. (Scheme (38)).

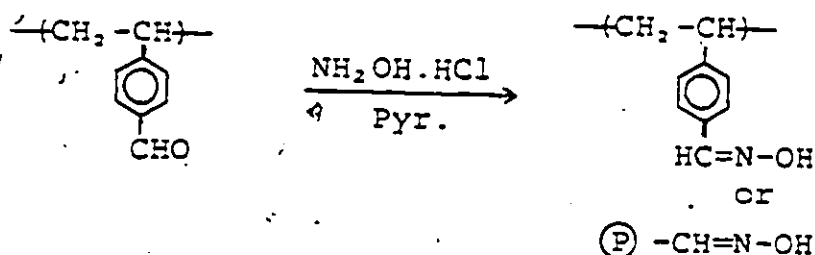


Scheme (38)

Brominated polystyrene was reacted first with n-BuLi in benzene. The excess n-BuLi was removed by washing and the lithiated polymer was then reacted with the formamide in THF. These experiments revealed that while excellent results can be obtained when a large excess of DMF (18) is used, the reaction is unsatisfactory when it is used in equimolar amounts, as interactions between the reactive sites of the polymer result in the formation of a significant amount of the polymer-bound

secondary alcohol. Even the reaction with a three-fold excess of DMF afforded a product in which only a very small amount of carbonyl could be seen in the infrared spectrum of the polymer. Similar results were observed with the reagent (15) when used in equimolar amount or three-fold excess to formylate the lithiated polystyrene. In contrast, very little alcohol was observed in the product obtained with the reagent (10) when used in equimolar amount or three fold excess. The infrared spectrum of this polymer showed a larger carbonyl absorbtion at 1701 cm^{-1} than that seen for the polymer obtained with DMF under the same conditions, indicating the presence of a significantly greater amount of aldehyde groups.

In order to have a rough estimation of the amount of carbonyl present in each of these polymers, obtained by the formylation of lithiated polystyrene with (10), (15) and (18), the polymeric aldehydes were converted to their corresponding oximes⁵ by reaction with hydroxylamine hydrochloride in pyridine. (Scheme (39)).



Scheme (39)

The polymer $\text{(P)}-\text{CHO}$, obtained by the formylation of $\text{(P)}-\text{Li}$ with a large excess of DMF (18), showed the most intense carbonyl absorption in the IR spectra and, as expected, the corresponding polymeric oxime had the highest nitrogen content of 3.61%. (Table (7)). $\text{(P)}-\text{CHO}$ obtained from the reaction of $\text{(P)}-\text{Li}$ with (10) gave a polymeric oxime with 2.38% nitrogen whereas the polymer $\text{(P)}-\text{CHO}$ resulting from the reaction $\text{(P)}-\text{Li}$ of with (15) gave a polymeric oxime having 1.92% nitrogen, (Table (7)). The polymer obtained with three fold excess of DMF was the worst of them and had only 1.23% nitrogen. The IR spectra of these polymers did not show any bands corresponding to carbonyl absorption, indicating that the oxime formation reaction was essentially quantitative.

This extensive study indicates that the presence of an additional ligand group in formamides offers a significant advantage, as the final aldehyde obtained will be free of any secondary alcohol byproduct. Reagents (9), (10) and (11) all gave excellent yields of aldehydes without any byproduct when the reactions were done at 0°C or at -10°C . All three reagents have a second nitrogen atom in the molecule which could take part in the formation of a five or six-membered ring chelated intermediate during the reactions with Grignard or organolithium compounds. The reagents without such additional ligands (14), (15), (17) and (18) or reagents having additional ligands with poor donor properties gave lower yields of aldehydes with significant amounts of the secondary alcohol. Therefore, it is quite likely that the formation of a five or six-membered ring

chelate intermediate occurs in the formylation reactions of Grignard and organolithium compounds with reagents of the type (9), (10) and (11). Reagents (12) and (16) will also belong to this category, but the ring chelated intermediate must be too weak to prevent the formation of secondary alcohol.

It was also observed that the stability of this intermediate is temperature dependent. Lower temperatures make it more stable and result in better yields of aldehydes. This is also true for the reagents without any additional ligands, but in such cases much lower temperatures may be required for the prevention of the side reaction. This may not be worthwhile as it may decrease the reactivity of the reagent which would result in longer reaction times.

Other evidence available to support the existence of these chelated intermediates was reported by Nahm and Wener¹⁷⁶ for the reactions of N-methoxy-N-methylformamide with Grignard and organolithium compounds.

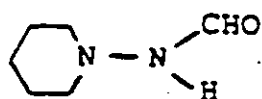
Reagent (10) is probably the reagent of choice for the clean formylation of Grignard and organolithium compounds as it gives excellent yields of aldehydes without any secondary alcohol. However, it should be noted that adequate results can be obtained with the more readily available DMF^{173,174}.

Table (7): Nitrogen analyses of various polymeric oximes

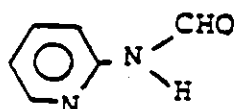
$\textcircled{\text{P}} - \text{CHO}$ from (at room temperature)	% Nitrogen in $\textcircled{\text{P}} - \text{CH}=\text{N}-\text{OH}$
$\textcircled{\text{P}} - \text{Li} + \begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{N}-\text{CHO} \end{array} (18)$ large excess	3.61
$\textcircled{\text{P}} - \text{Li} + \begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{N}-\text{CHO} \end{array} (18)$ 3 fold excess	1.23
$\textcircled{\text{P}} - \text{Li} + \begin{array}{c} \text{CHO} \\ \diagup \\ \text{N}-\text{N} \\ \diagdown \\ \text{CH}_3 \end{array} (10)$ 3 fold excess	2.38
$\textcircled{\text{P}} - \text{Li} + \begin{array}{c} \text{N}-\text{CHO} \\ \diagup \\ \text{CH}_2 \end{array} (15)$ 3 fold excess	1.92

II.2.2. Polymer-supported formylation agents for Grignard reagents

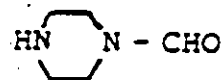
Having completed the study of monomeric formylating reagents we proceeded to apply these results to the preparation of polymer supported reagents. Three formamides were selected to bind to the polymer, (Scheme(40)).



(19)



(20)



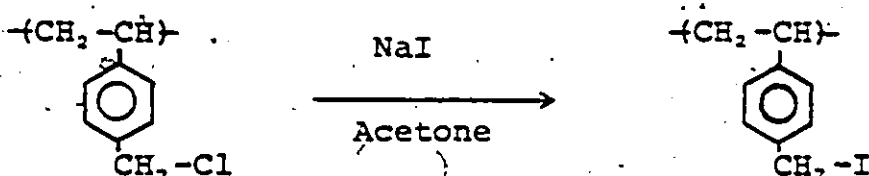
(21)

Scheme (40)

The reagents (19) and (20) were selected as their N-methyl derivatives were very successful in formylation of Grignard and organolithium compounds, giving excellent yields of aldehydes free from secondary alcohol. Compound (21) was also selected as it has an amino group remote from the formyl group and therefore may be easier to attach to the polymer support.

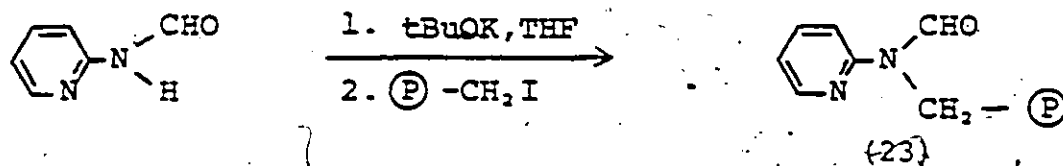
During the preparation of 2-(N-formyl-N-benzyl)amino pyridine, we found that benzyl chloride did not react with 2-(N-formyl)aminopyridine in the presence of potassium tert. butoxide and benzyl bromide had to be used. Therefore the preparation of polymeric reagents from 2-(N-formyl)amino-

pyridine and N(N-formyl)aminopiperidine cannot be achieved with the readily available $(P)-CH_2Cl$. In order to overcome this problem the more reactive $(P)-CH_2I$ was prepared by reacting $(P)-CH_2Cl$ with sodium iodide in acetone. The gain in weight of the polymer after the reaction confirmed that the replacement of chloride by the iodide was close to 100%, (Scheme (42)).



Scheme (42)

Starting with polymer $(P)-CH_2I$ having 2.9 mequiv. I/g, a polymeric reagent (23) with 3.01 mequiv. N/g was obtained as shown in (Scheme (43)).



Scheme (43)

Similarly, a polymeric reagent having N-(N-formyl)amino piperidine group (24) with 3.6 mequiv. N/g was obtained. (Figure (8)).

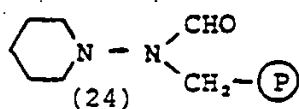
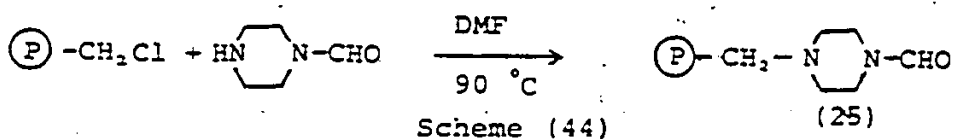


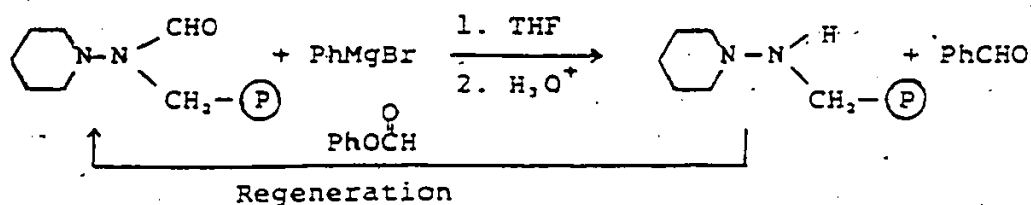
Figure (8)

In the case of N-formyl piperazine (17), the amino group has no influence from the formyl group and therefore will be nucleophilic enough for an alkylation reaction with $\text{(P)}-\text{CH}_2\text{Cl}$. The alkylation was therefore carried out directly on $\text{(P)}-\text{CH}_2\text{Cl}$ in DMF at 90°C using excess N-formyl piperazine, (Scheme (44)).



Using $\text{(P)}-\text{CH}_2\text{Cl}$ with 2.5 mequiv. Cl/g, a polymeric reagent (25) with 4.0 mequiv. N/g was obtained.

The formylation of phenyl magnesium bromide using these polymer-supported reagents was studied. In all cases the reactions were done using a 50% excess of the Grignard reagent with respect to the polymer. After hydrolysis, the aldehyde was isolated and the spent reagent was regenerated by an exchange with phenyl formate, a reaction which produces phenol as a by-product, and the formylated polymer was filtered and washed. (Scheme (45)).



Scheme (45)

The results of the formylation of phenyl magnesium bromide with polymeric reagents (23), (24), and (25) are shown in Table (8). In all cases, the yields of aldehydes isolated were lower than 65% with respect to the estimated capacities of the polymers (from N analysis). This suggests that the polymer had fewer reactive groups than calculated from the available analytical data. No Benzhydrol was found with any of the

polymeric reagents including that derived from piperazine. Although (25) has no additional ligand for chelation, this surprising finding may be attributed to a polymer "backbone effect". Although many authors have cited the occurrence of a "backbone effect"⁷⁻¹⁶ to explain the success or failure of polymer-supported reactions, this effect remains largely unexplained with few exceptions^{58,185-6}. In this instance the "backbone effect" is likely an increase in stability of the polymer-bound intermediate, which does not break down until hydrolysis, and thus, is not accessible for further reaction with the Grignard reagent.

Although the polymeric reagent, despite its recyclability, is not fully satisfactory in its performance with Grignard reagents, it is useful as a probe of this so called "backbone effect". Thus, it is expected that if the polymer does indeed contribute to an increased stability of the intermediate formed by reaction with a Grignard reagent, then, the use of higher reaction temperatures should be possible without observing the formation of secondary alcohol side product.

Formylation of phenyl magnesium bromide with polymer (25) at 60°C gave a similar yield of benzaldehyde while no benzhydrol could be detected in the reaction mixture. This finding is in sharp contrast with the results obtained using the

monomeric reagent (17) which gave a product containing a significant amount of benzhydrol even when the reaction was carried out at 0°C.

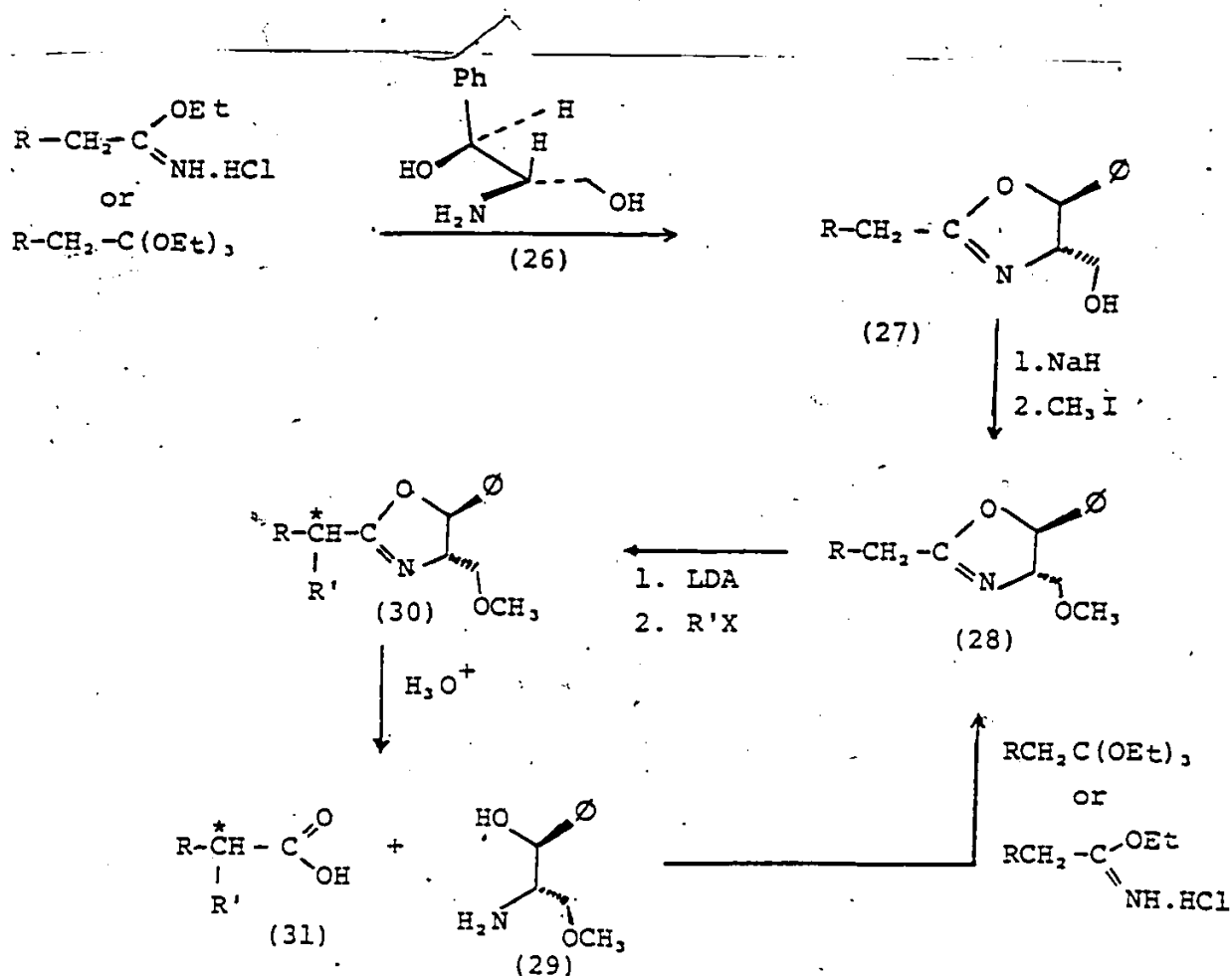
Table (8): Yield of PhCHO in the formylation of PhMgBr using polymeric reagents (23), (24) and (25) at room temperature.

Polymeric reagent	% of PhCHO			
	1st cycle	2nd cycle	3rd cycle	4th cycle
 (25)	62	59	61	63
 (24)	64	55		
 (23)	58			

II.3. Chiral polymer-supported oxazolines for asymmetric synthesis

Carbon-carbon bond-formation is a valuable tool in organic synthesis and asymmetric carbon-carbon bond formation is of even greater significance. Meyers and co-workers developed a

technique which involves carbon-carbon bond formation with the simultaneous creation of a new chiral center in their synthesis of α -substituted alkanolic acids.¹⁷⁹ In this synthesis either the R or the S enantiomer of the chiral alkanolic acid can be made in predictable manner from a single achiral substrate with high enantiomeric purity. The chiral reagent employed for this study was the oxazoline (27), (Scheme (46)) readily prepared by reacting the commercially available diol, (1S,2S)-(+)-1-phenyl-2-amino-1,3-propane diol (26), with imino ethers or orthoesters.



Scheme (46)

McManus and co-workers¹⁸³ attempted to create a polymer-supported reagent by attachment of oxazoline (27) to $\text{P}-\text{CH}_2\text{Cl}$ through the free hydroxyl group. The chemical and optical yields obtained using this polymer supported reagent were inferior to those obtained using the monomeric oxazoline.

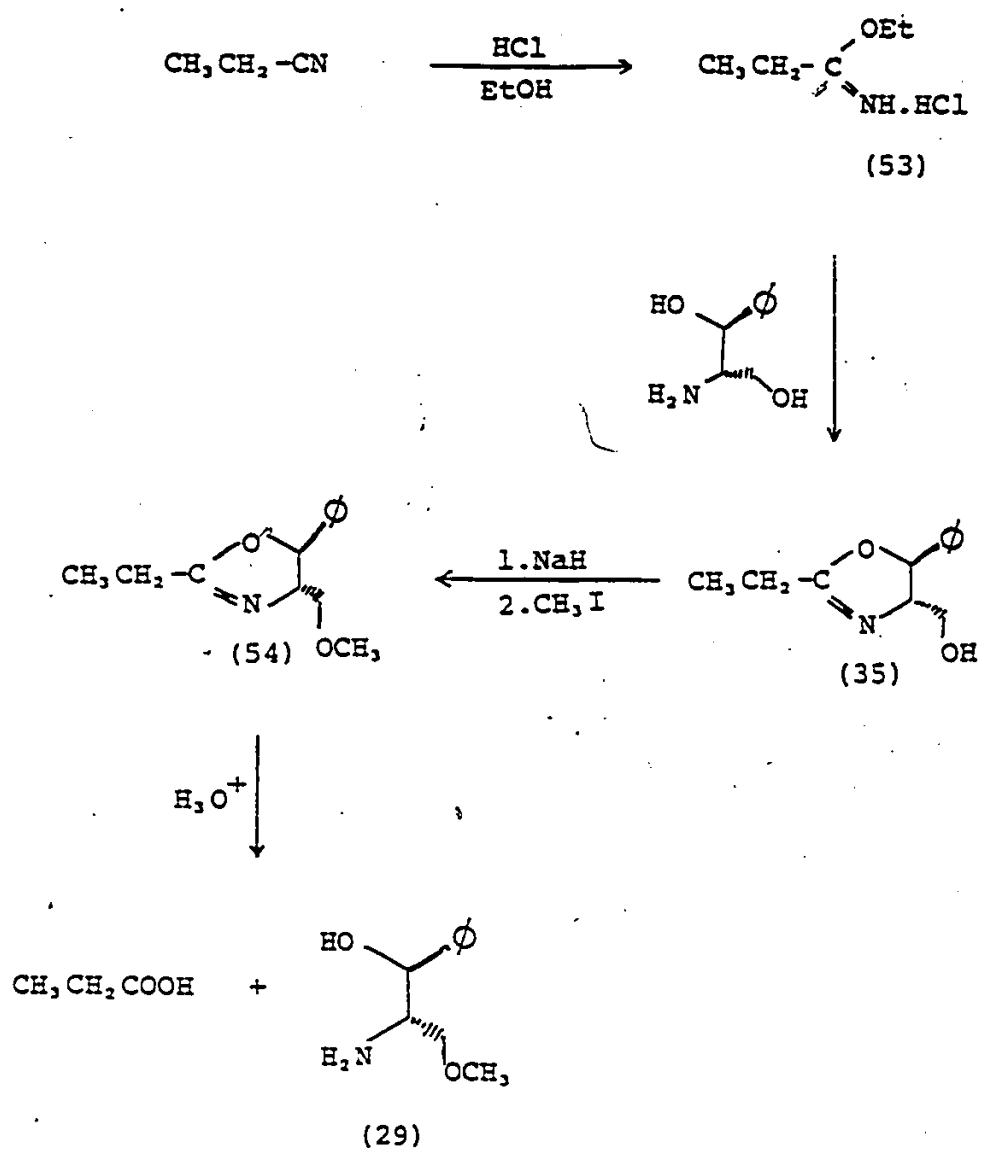
Similar results by others in this laboratory ^{57a} confirmed these observations. Earlier attempts from this laboratory⁵⁷ included several approaches to the functionalization of the aromatic ring of (26) for the eventual incorporation of a vinyl group.

Although this approach met with some limited success with the preparation of a styrene analogue of (26), the extremely low yield obtained in this synthesis made it impractical for further consideration.

The poor chemical yields observed by McManus and co-workers were due to the incomplete hydrolysis of the bulky oxazolines. When longer reaction times or more strongly acidic conditions were used to improve the chemical yields, some damaging side reactions, such as cleavage of benzylic ether linkages which results in the loss of amino alcohol residues from the polymer-support, have been observed.

In order to improve the chemical yield of the optically active carboxylic acid obtained from the polymer-supported chiral oxazolines, we thought of using a stronger linkage between the polymer and the oxazoline which would resist the strong hydrolytic conditions. The phenyl ether linkage (32)

(84)



Scheme (54)

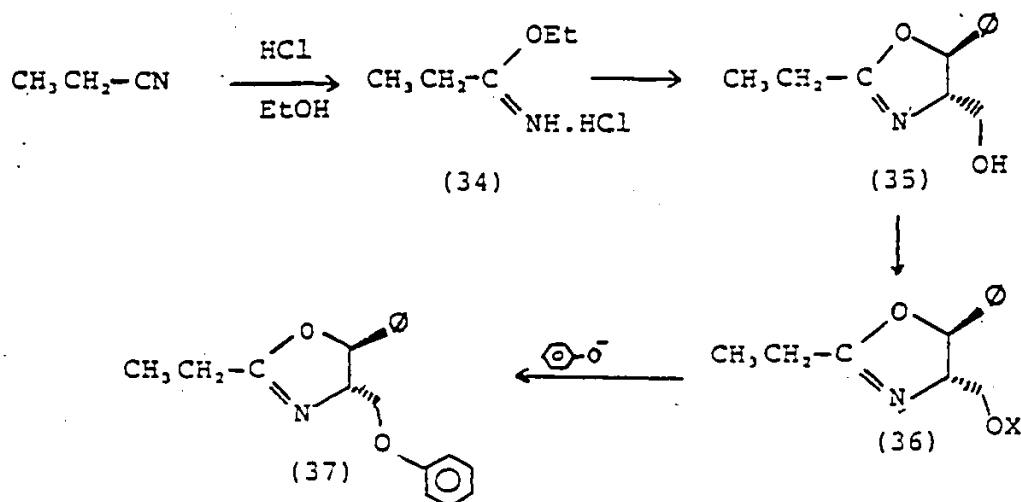
Reaction scheme for the preparation of amino alcohol¹⁵⁹

would appear to be suitable in that respect. Before attempting to develop a new polymeric reagent we undertook model studies involving compound (33). (Figure (9)).



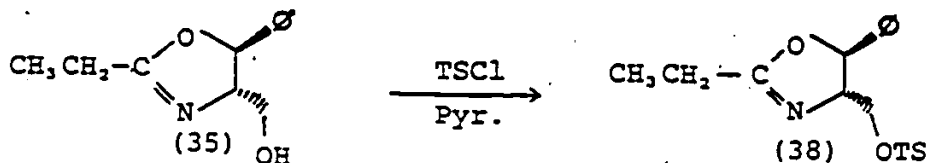
Figure (9)

Our approach to the synthesis of 4-phenoxyethyl oxazoline (33) was based on the hydroxymethyl oxazoline (35), which was obtained by reacting the imidate of propionitrile with (1S,2S)-(+)-1-phenyl-2-amino-1,3-propanediol (26) (Scheme (47)). The hydroxyl group could then be converted to a better leaving group, followed by nucleophilic displacement with phenolate anion to yield the 4-phenoxyethyl oxazoline (37).



Scheme (47)

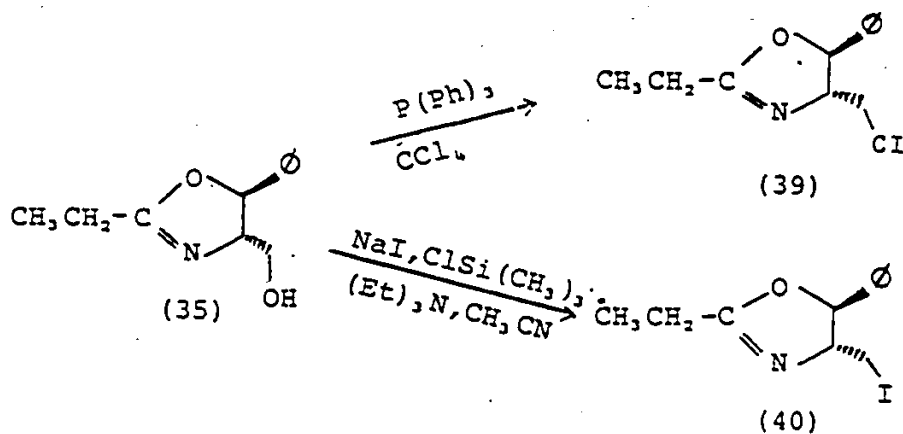
We first tried to make the oxazoline (38) by a standard procedure¹⁸⁴. (Scheme (48)).



Scheme (48)

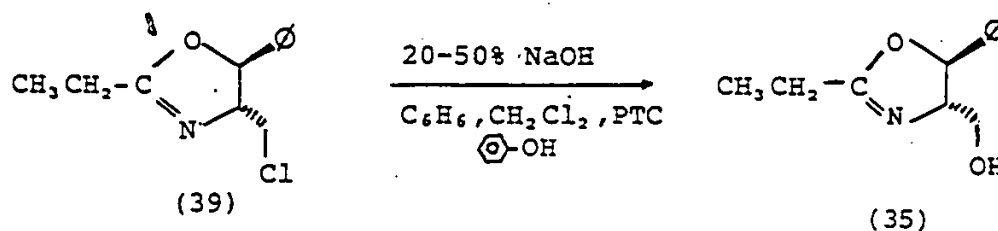
This reaction was not successful as the product decomposed to give a polymeric gum during the workup.

We then turned our attention to 4-chloromethyl oxazoline (39) which was successfully synthesized from (35) as shown in Scheme (49).



Scheme (49)

The reaction of the 4-chloromethyl oxazoline (39) with phenolate anion was then attempted under various reaction conditions. Phase transfer conditions, which are usually ideal for these types of displacement reactions, gave the starting oxazoline (35) as the only product (Scheme (50)).



Scheme (50)

To improve the reaction, the iodomethyl oxazoline (40) was prepared as shown in Scheme (49)¹⁸⁷. Unfortunately its reaction with phenolate anion under various reaction conditions only led to the starting hydroxy methyl oxazoline (35) and therefore this project was discontinued.

II.4. Preparation of optically active polymers by chemical modification with asymmetric induction

II.4.1 Optically active polymers with side chain chirality

The growing current interest in biomimetic chemistry requires the preparation of optically active synthetic polymers to be used as backbones for models of active sites of enzymes. While chiral polymers can easily be prepared by grafting optically active molecules to the side chains of a polymer, it would be more desirable to use polymers which possess main chain chirality.

Our approach to the synthesis of optically active polymers of 1-substituted olefins involved the chemical modification of polymers with creation of chiral centers in the main or side chain through the use of asymmetric induction reactions.

As a first test of this new approach, a simple system in which an optically active polymer with side chain chirality would result from a chemical modification process involving asymmetric induction on an achiral substrate was studied. The reaction sequence made use of Meyers' chiral oxazoline technique, which is known to result in high asymmetric induction¹⁷⁹⁻¹⁸². In this synthesis, an alkyl nitrile is converted to its imidate and then reacted with the amino alcohol (26) to form the chiral oxazoline (28).

(Scheme (46)). Subsequent transformations of this oxazoline (28) by treatment with diisopropylamide, followed by quenching with alkyl halide and hydrolysis of oxazoline (30) yields α -substituted alkanolic acids (31) with high asymmetric induction (70-80% ee). (Scheme (46)).

For the synthesis described in this thesis, a copolymer (47) made from styrene and p-(2-cyanoethyl)styrene was used. p-(2-Cyanoethyl)styrene was prepared using (2-chloroethyl)benzene which is available commercially. It was first subjected to Friedel-Craft acylation with acetyl chloride in the presence of aluminum chloride to obtain p-acetyl, (2-chloroethyl)benzene (43) in 90% yield, (Scheme (51)). This was reacted with sodium cyanide in dimethyl sulfoxide at 130°C to give the

cyano derivative (44) in 79% yield. The temperature here is important, since the use of a higher temperature results in a drastic decrease in yield, probably due to the oxidation of the chloroethyl group to the corresponding aldehyde. Sodium borohydride was used to reduce the acetyl groups of (44) to the secondary alcohol (45) in a very high yield (94%) without affecting the nitrile group. Dehydration of this alcohol to give p-(2-cyanoethyl)styrene was best achieved by heating it to 190°C with potassium bisulfate in the presence of tert. butyl catechol. Tert. butyl catechol acts as a radical acceptor and helps prevent polymerization of the styrene derivative during the reaction at high temperatures. Pure p-(2-cyanoethyl)styrene was obtained by subjecting the crude to column chromatography. The best yield obtained for this reaction was 32%. This low yield is the result of competing side reactions such as dimerization and polymerization, which almost always occur under the conditions used for dehydration.

In order to improve the yield of the dehydration step various other reaction conditions were tried. When the reaction was done with potassium bisulfate in refluxing benzene in the presence of tert. butyl catechol only 20% of p-(2-cyanoethyl)styrene was obtained. The water formed in the reaction was removed from the reaction mixture by an azeotropic distillation with benzene and collected in a Dean Stark trap. Similar results were obtained when the reaction was done with p-toluene sulfonic acid instead of potassium bisulfate. The

reaction was also done using iodine in refluxing xylene. The yield of p-(2-cyanoethyl)styrene was slightly lower than the previous experiments. The major product in all cases (40-60%) was the head to head dimer (41) (Figure (10)).

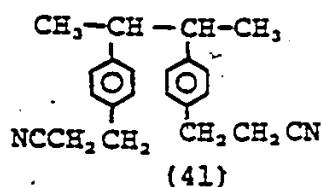
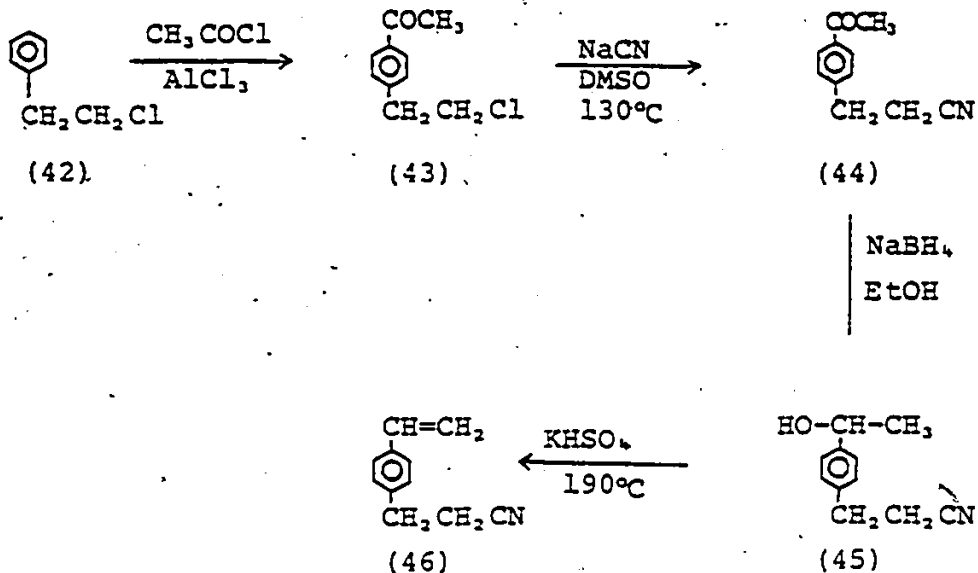


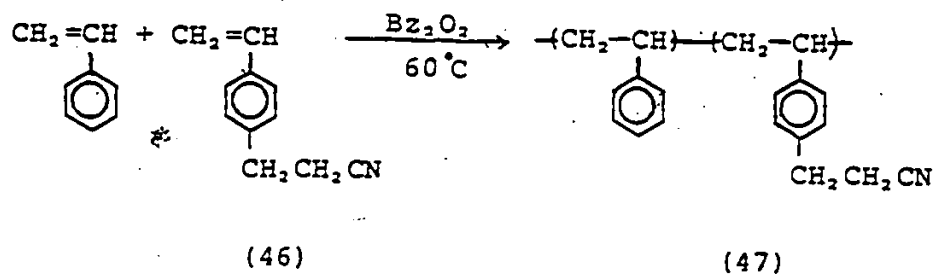
Figure (10)



Scheme (51)

The starting polymer (47) was obtained by free radical copolymerization of p-(2-cyanoethyl)styrene (46) with styrene

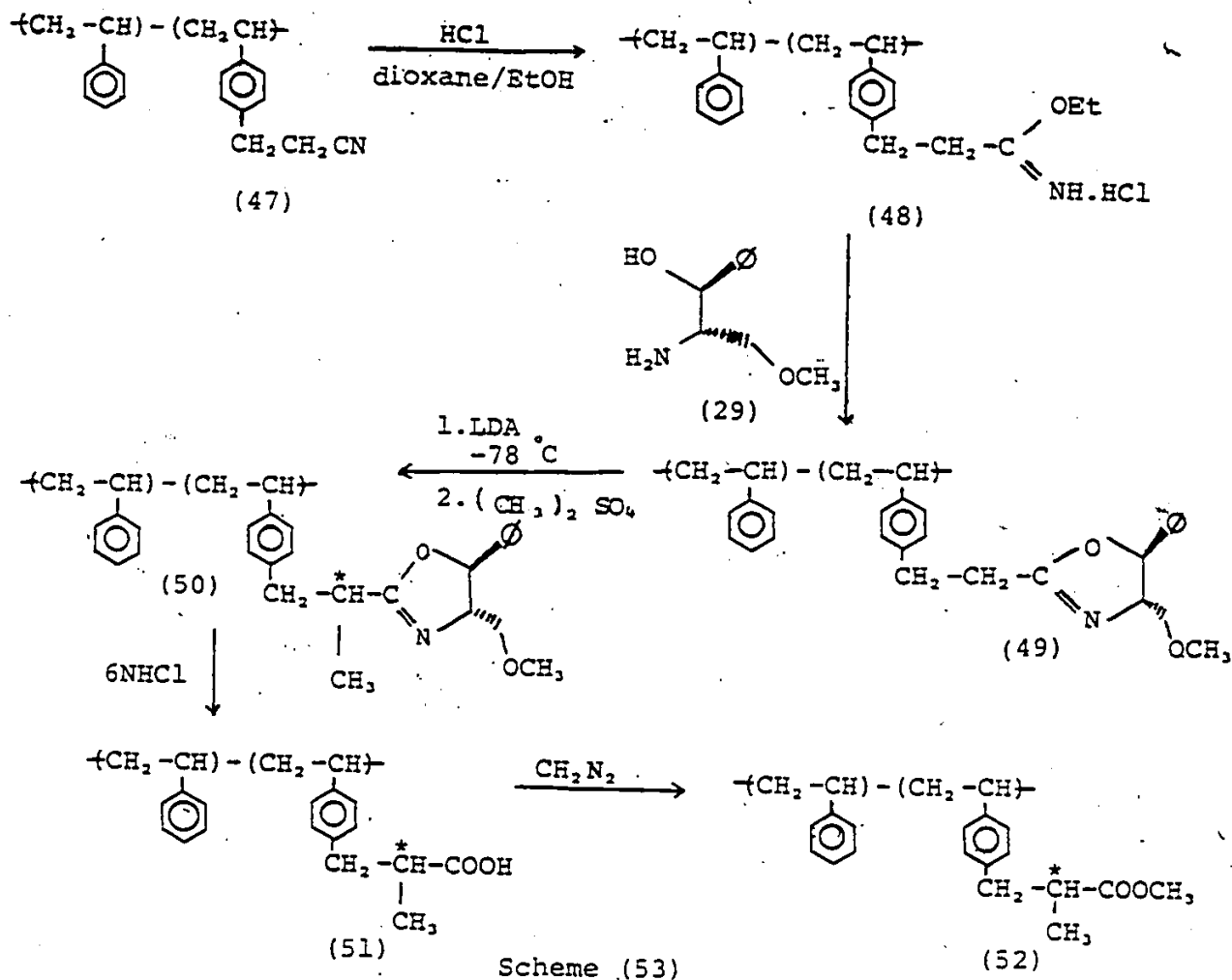
using benzoyl peroxide as the radical initiator. The bulk polymerization went smoothly at 60°C with high yields.



Scheme (52)

The nitrile copolymer (47) was transformed into its imidate (48) (Scheme (53)). This was achieved by bubbling hydrogen chloride gas through a solution of (47) in dioxane and ethanol. The polymeric oxazoline (49) was then prepared by reacting the imidate (48) with chiral (1S,2S)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol (29) in methylene chloride. Alkylation of oxazoline (49) was done according to the conditions described by Meyers¹⁵⁹ for optimum asymmetric induction. After metalation with lithium diisopropylamide at -78 °C the mixture was cooled to -98 °C in a methanol-liquid nitrogen bath and allowed to equilibrate for 30 minutes before the addition of the alkylating agent. Dimethyl sulfate was used as the alkylating agent as it has been shown to give higher optical yields than methyl iodide. Dimethyl sulfate was added to the reaction mixture very slowly, typically over a period of 30 minutes. The reaction was allowed to continue at -98 °C for 5 hrs. and

then at 78°C for 16 hrs. The resulting polymeric oxazoline (50) was hydrolyzed using 6N hydrochloric acid and gave a chiral polymeric carboxylic acid (51). This polymer (51) was found to be only partially soluble in organic solvents such as methylene chloride, chloroform, acetone, THF, etc. In order to overcome this solubility problem, the polymeric carboxylic acid (51) was transformed into its methyl ester (52) by reacting with diazomethane. (Scheme (53)).



The optical rotations of the chiral polymers (49), (50), (51) and (52) were determined in chloroform. The results of these measurements are shown in Table (9). The negative rotation of polymer (49) clearly indicates that the optical activity is actually due to the formation of the chiral oxazoline ring and not due to any impurity, as the only impurity that could be present is the chiral amino alcohol (29) which had a positive optical rotation ($[\alpha]_D^{20} = +27.5^\circ$). The polymeric oxazolines (50) also showed negative rotations which were slightly lower than the values obtained for the polymer (49). The optical rotation of the carboxylic acid polymer (51) could not be measured except for one sample, as they were only partially soluble in organic solvents. The only sample which was soluble in organic solvents was one which also contained a significant amount of ester groups formed in a side reaction, which occurred during the preparation of the imide.

The polymeric esters (52) made from insoluble carboxylic acid polymer (51) were soluble in most organic solvents and showed a positive optical rotation in chloroform. The optical activity of the final polymer was due to asymmetric induction and not to the presence of remaining impurities from the amino alcohol. This was confirmed by elemental analysis of polymeric ester (52), which indicated the absence or low level of nitrogen in the final polymer.

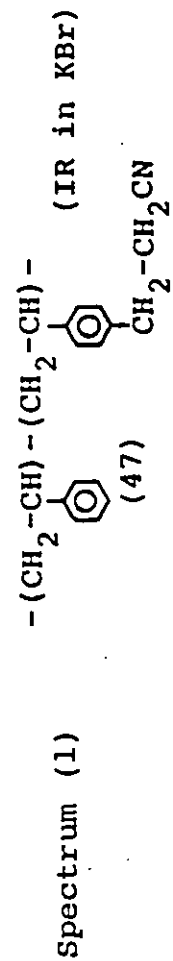
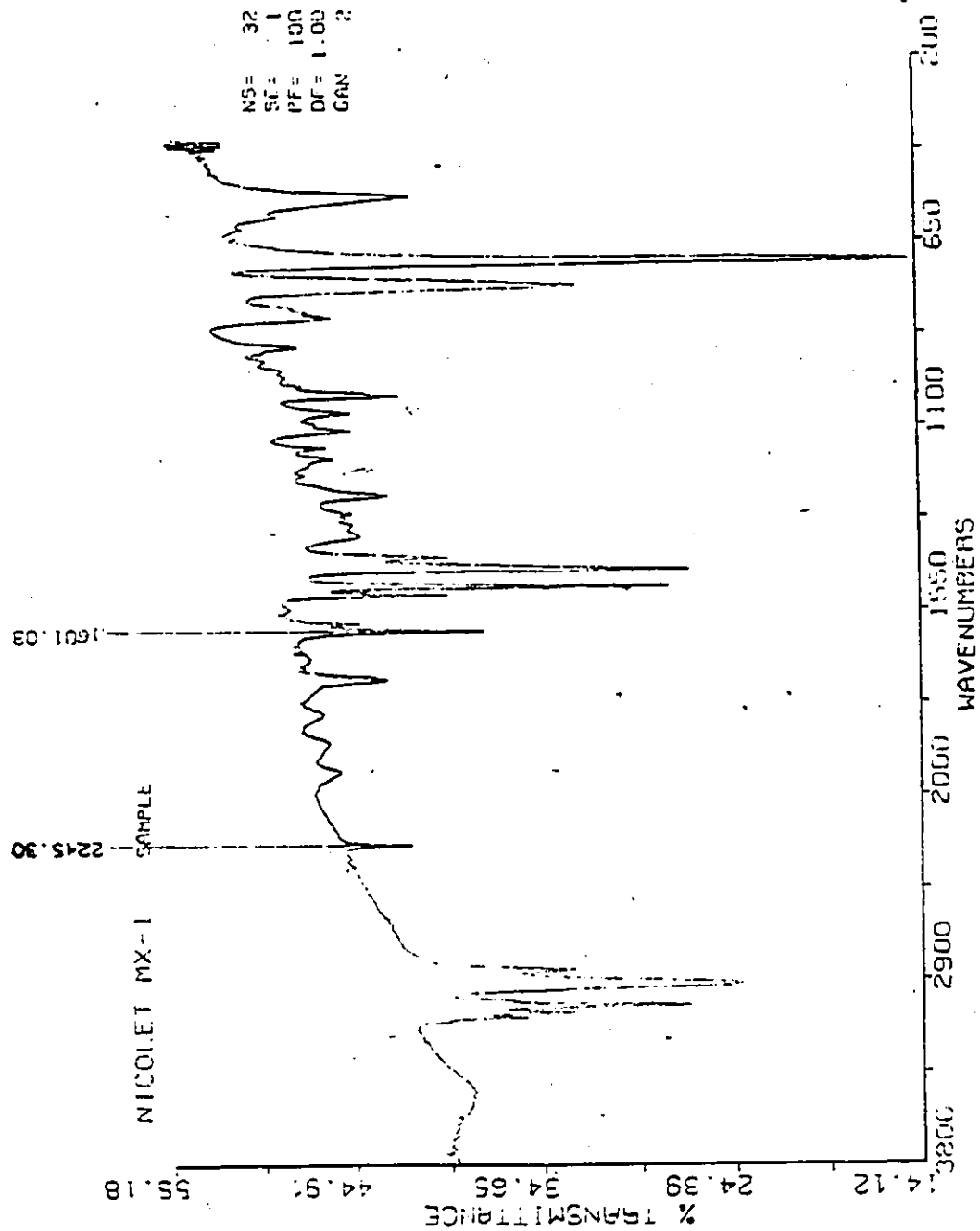
Table (9): Optical rotations of the chiral polymers (49), (50), (51)
and (52)

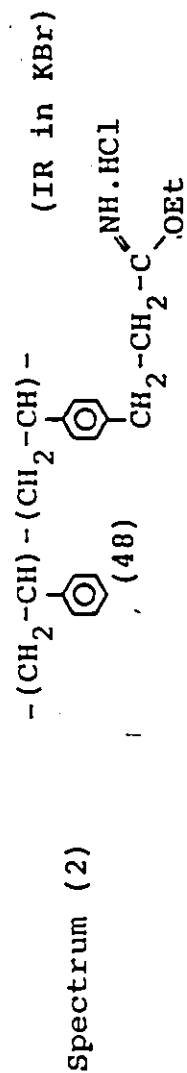
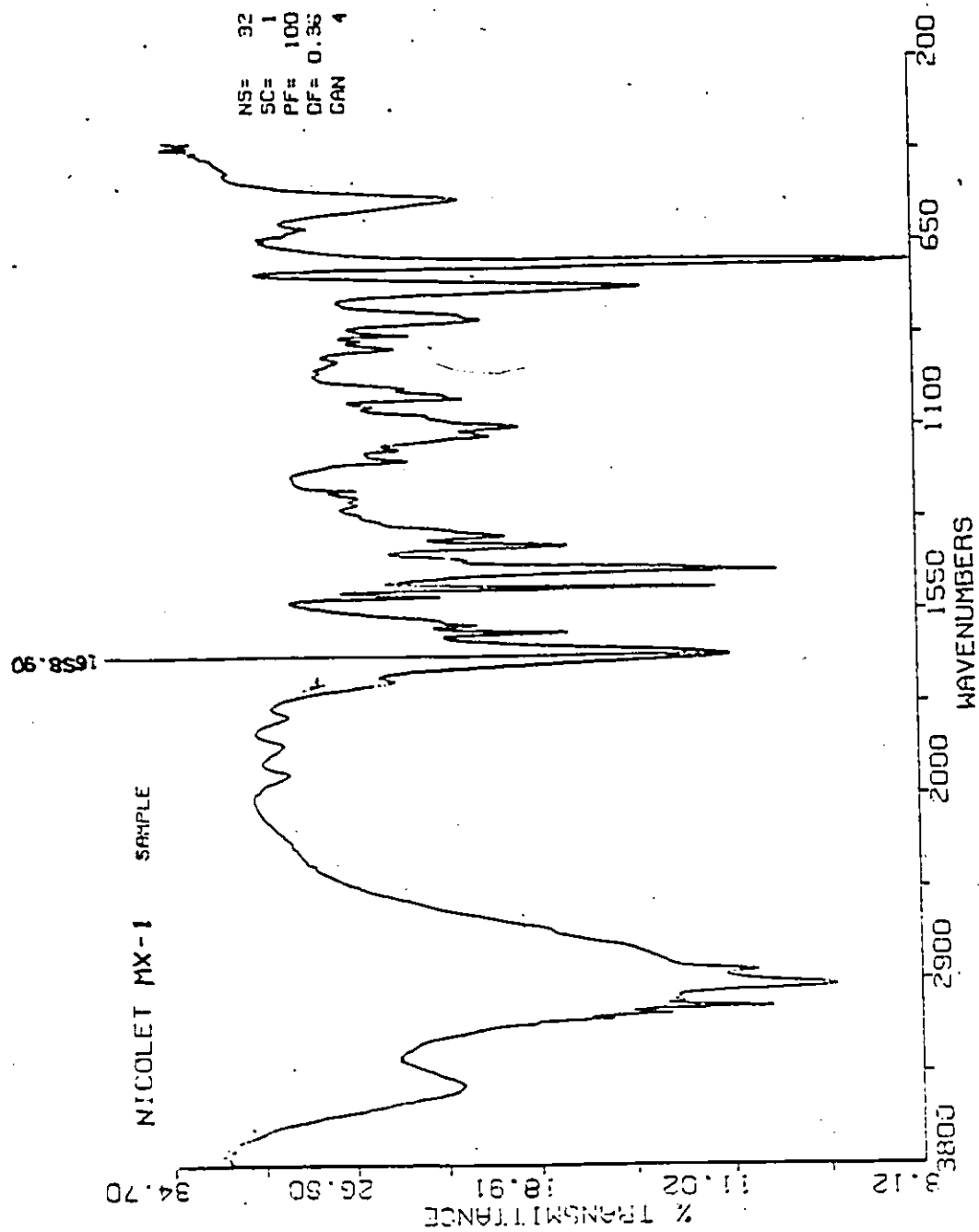
[2% solutions in chloroform were used].

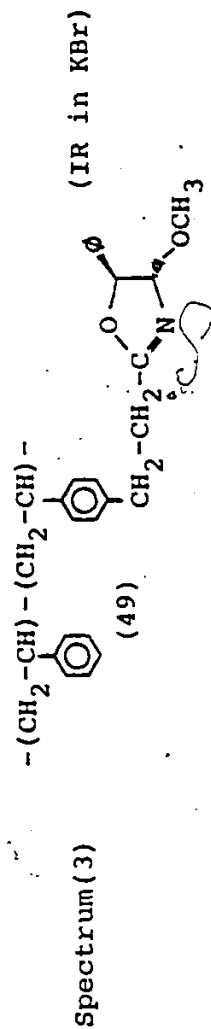
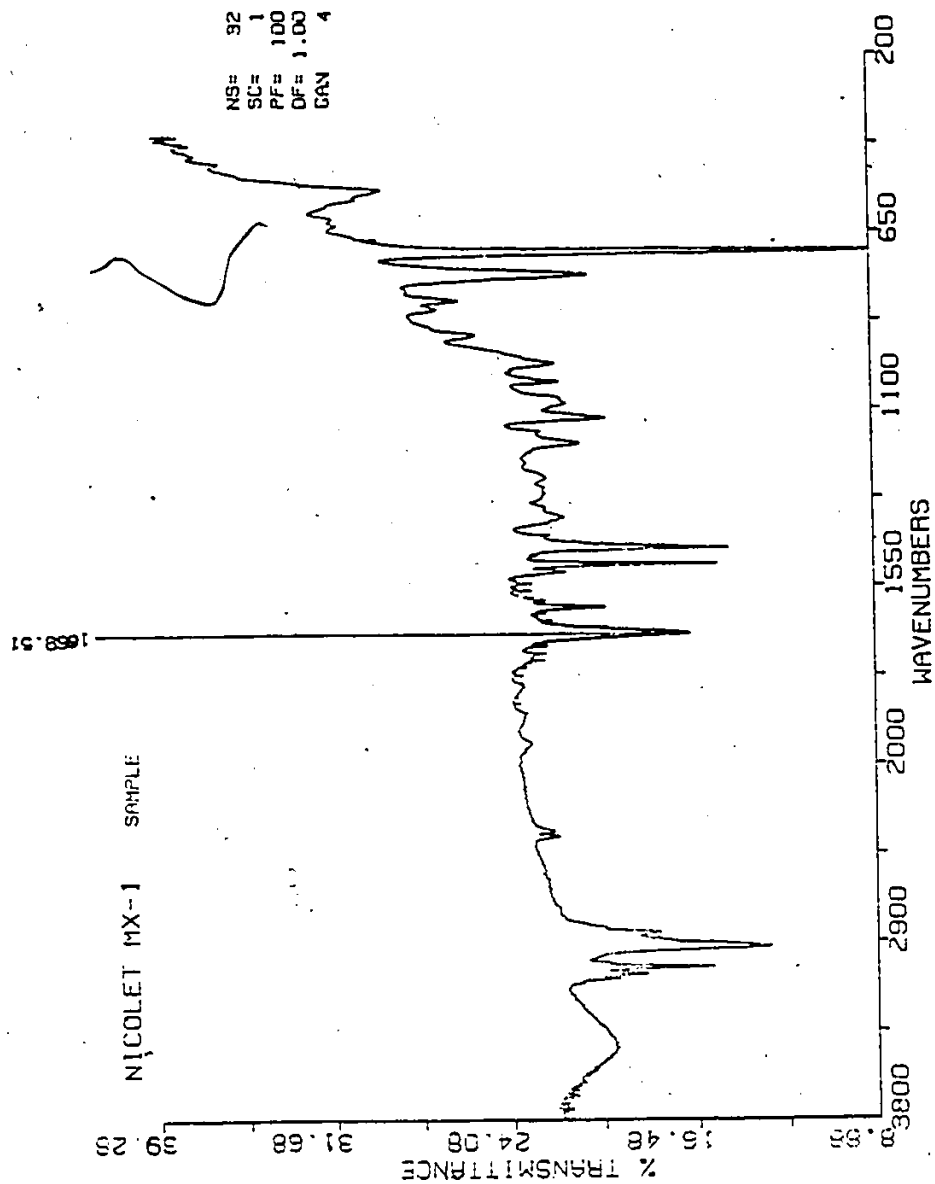
	Series 1		Series 2		Series 3	
	N%	Optical Rotation ²⁵ [α] D	N%	Optical Rotation ²⁵ [α] D	N%	Optical Rotation ²⁵ [α] D
$\begin{array}{c} \text{-(CH}_2\text{-CH)-} \\ \\ \text{C}_6\text{H}_5 \end{array} \quad \begin{array}{c} \text{-(CH}_2\text{-CH)-} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{CH}_2\text{CH}_2\text{CN} \end{array}$ (47)	3.35		2.25		3.35	
Polymeric Oxazoline (49)		-4.0°		-3.0°		-5.0°
Polymeric Oxazoline (50)		-3.6°	1.45	-2.5°		-3.0°
Polymeric Carboxylic acid (51)	0.88		0.08	+3.0°	< 0.1	
Polymeric Carboxylic ester (52)	< 0.8	+3.4°	< 0.08	+2.8°	< 0.1	+2.0°

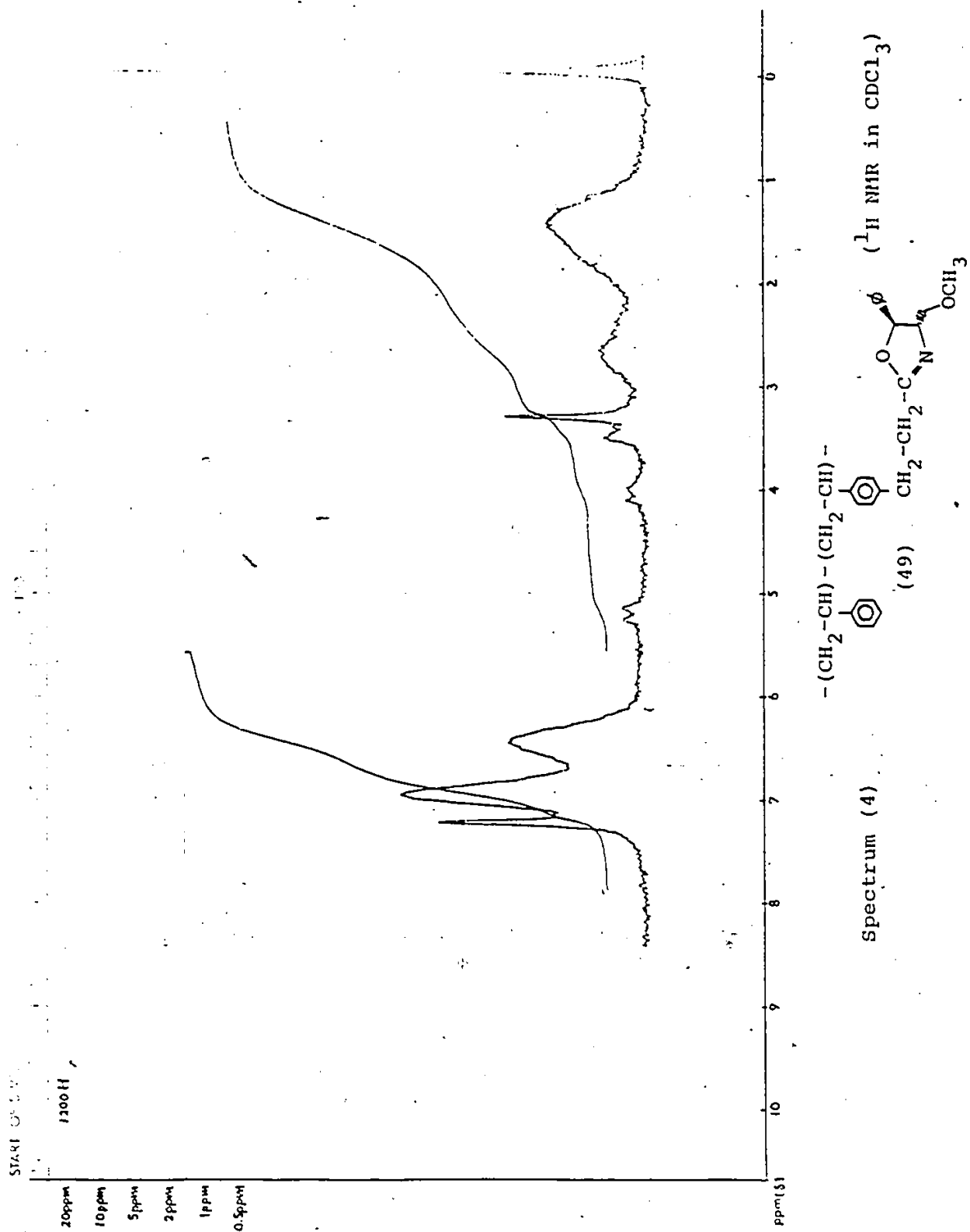
All the polymers prepared in this study were characterized with their ^1H -NMR, ^{13}C -NMR and IR spectra.

The IR spectrum of the starting nitrile polymer had a sharp weak absorption at 2245 cm^{-1} due to the nitrile group (Spectrum (1)). The polymeric imidate (48) made from polymer (47) showed a strong IR absorption band near $2700\text{--}3300\text{ cm}^{-1}$ and 1658 cm^{-1} but did not show any nitrile absorption (Spectrum (2)). The polymeric oxazoline (49) obtained from the polymer (48) had a strong sharp IR absorption at 1669 cm^{-1} indicating the presence of the oxazoline -C=N- group.¹⁵⁹ (Spectrum(3)). The proton NMR spectrum of this polymer also confirmed the presence of the oxazoline moiety in the polymer. A broad doublet near $\delta=5.1\text{--}5.3\text{ ppm}$ was due to the proton on the tert. carbon next to the oxygen of the oxazoline ring. (Spectrum (4)). A broad signal was seen near $\delta=3.8\text{--}4.2\text{ ppm}$ due to the proton on the tert. carbon next to the nitrogen in the oxazoline ring. Another broad signal at $\delta=3.3\text{--}3.6\text{ ppm}$ was due to the methylene protons next to the methoxy group of the oxazoline moiety. A sharp singlet was seen for the protons of the methoxy group around $\delta=3.33\text{ ppm}$. The signals were somewhat broad due to the high viscosities of the polymer solution. The IR spectrum of the alkylated polymer (50) was very similar to that of polymer (49), but its proton NMR indicated the presence of three additional hydrogens in the region $\delta=1.2\text{--}2.0\text{ ppm}$ due to the new methyl group introduced. The carboxylic acid polymer (51) obtained after the hydrolysis of the polymer (50), did not show an IR absorption corresponding to -C=N- of an oxazoline ring and





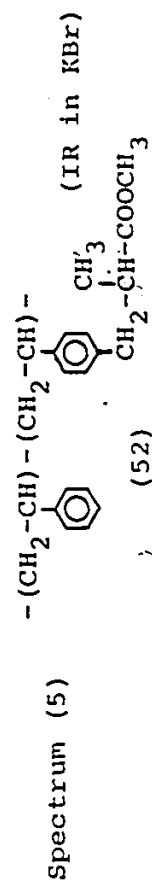
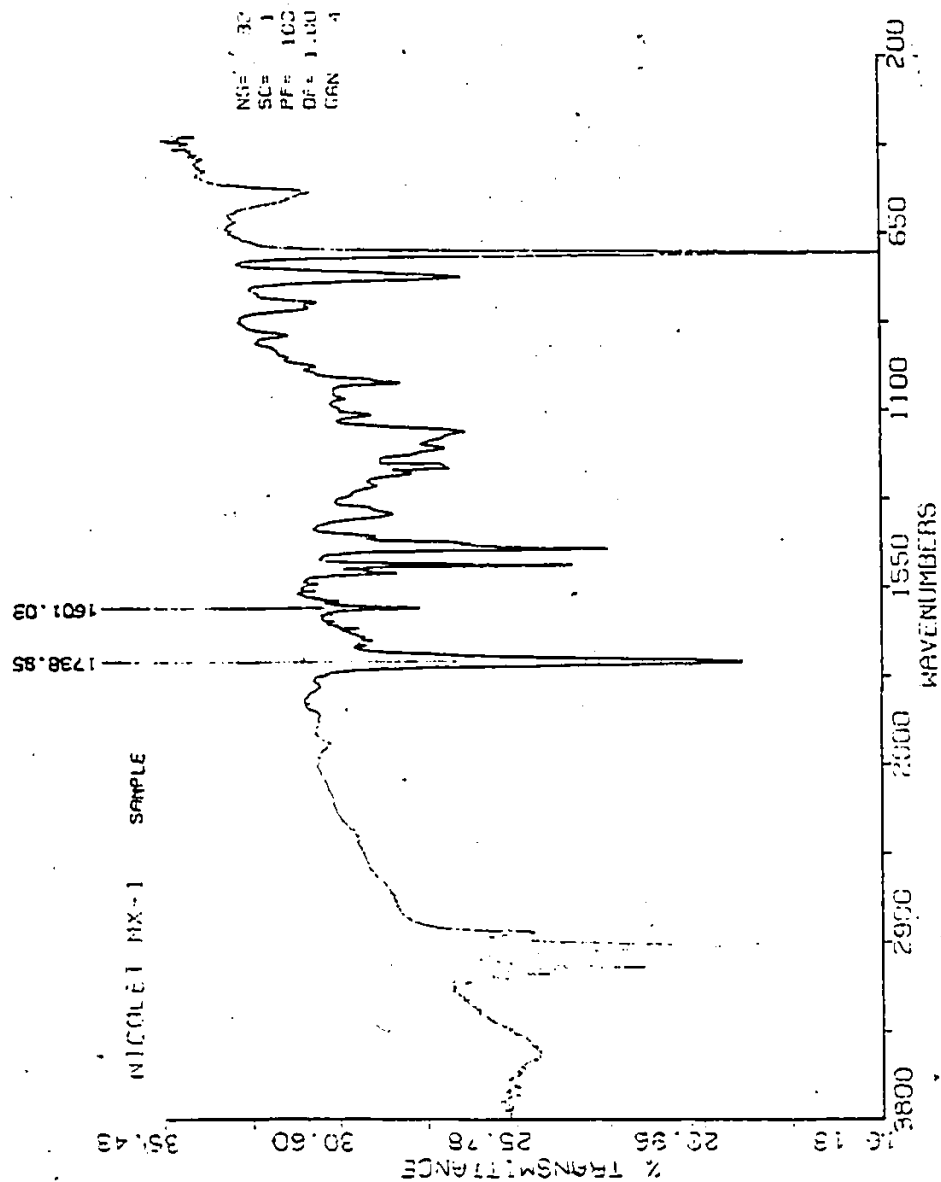


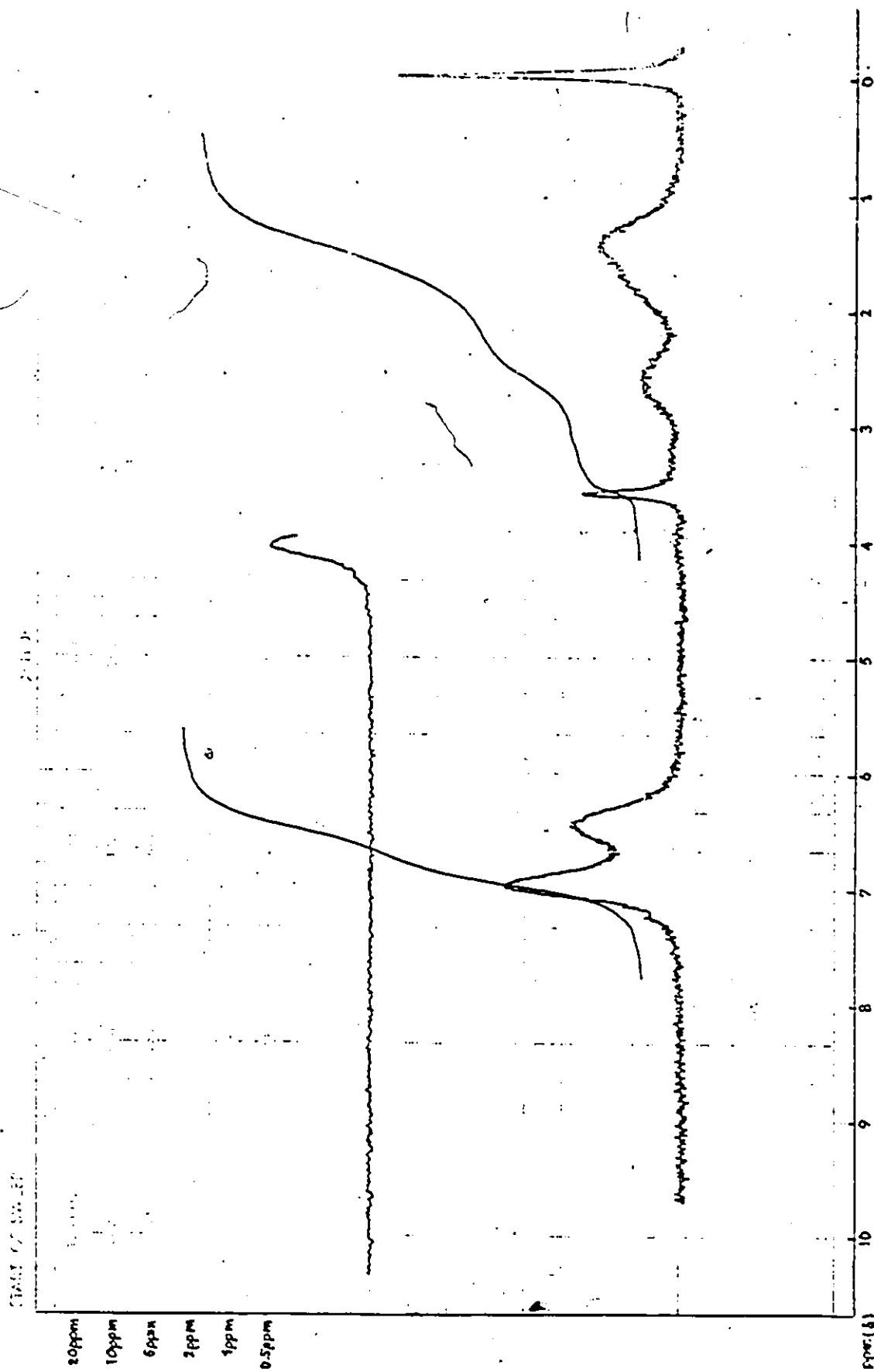


instead showed a strong sharp absorption at 1710 cm^{-1} indicating the complete hydrolysis of the oxazoline to the carboxylic acid. When the polymer (51) was converted to its carboxylic acid ester (52), the IR absorption changed from 1710 cm^{-1} to 1737 cm^{-1} . No peak was seen at 1710 cm^{-1} , indicating that the transformation was almost quantitative. (Spectrum (5)) . The proton NMR spectrum of this polymer (52) did not have the signals at $\delta=5.2-5.3\text{ ppm}$, $\delta=3.3-3.6\text{ ppm}$ and $\delta=3.33\text{ ppm}$ seen for the polymers (49) and (50), but instead had a sharp singlet at $\delta=3.6\text{ ppm}$ due to the methyl group of the carboxylic acid ester (Spectrum (6)) . The ^{13}C NMR spectra also gave some valuable information. The carbon on the $-\text{C}=\text{N}-$ group of the polymeric oxazoline (50) appeared at 167.84 ppm in the ^{13}C NMR spectrum. In the ^{13}C NMR spectrum of the polymer (52), this signal was absent and instead a new signal at 173.32 ppm was seen. This new signal was due to the carboxyl carbon on the ester group. Another important observation was that the signal at 59.28 ppm seen in the ^{13}C NMR spectra of polymers (49) and (50), due to the methoxy methyl group on the oxazoline ring, was not present in the ^{13}C NMR spectrum of the polymer (52).

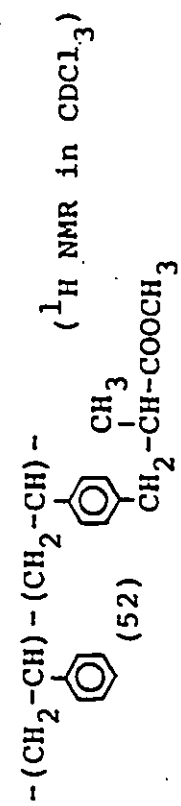
These spectral studies and optical rotation measurements indicate that the expected transformations did take place in each step of the synthesis and that the optical activity seen in the final polymer (52) was due to the asymmetric induction.

(101).





Spectrum (6)



II.4.2.

Model Studies

For comparison purposes and also to assist in the evaluation of the enantioselectivity of the reaction, the synthesis of a chiral model compound was undertaken using the same conditions as were used for the synthesis of the chiral polymeric carboxylic acid (51). The model chosen for this synthesis was 3-phenyl-2-methyl propanoic acid (55), (Figure (11)).

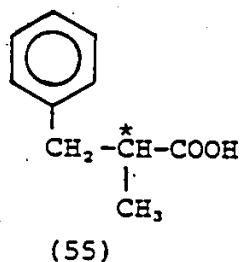
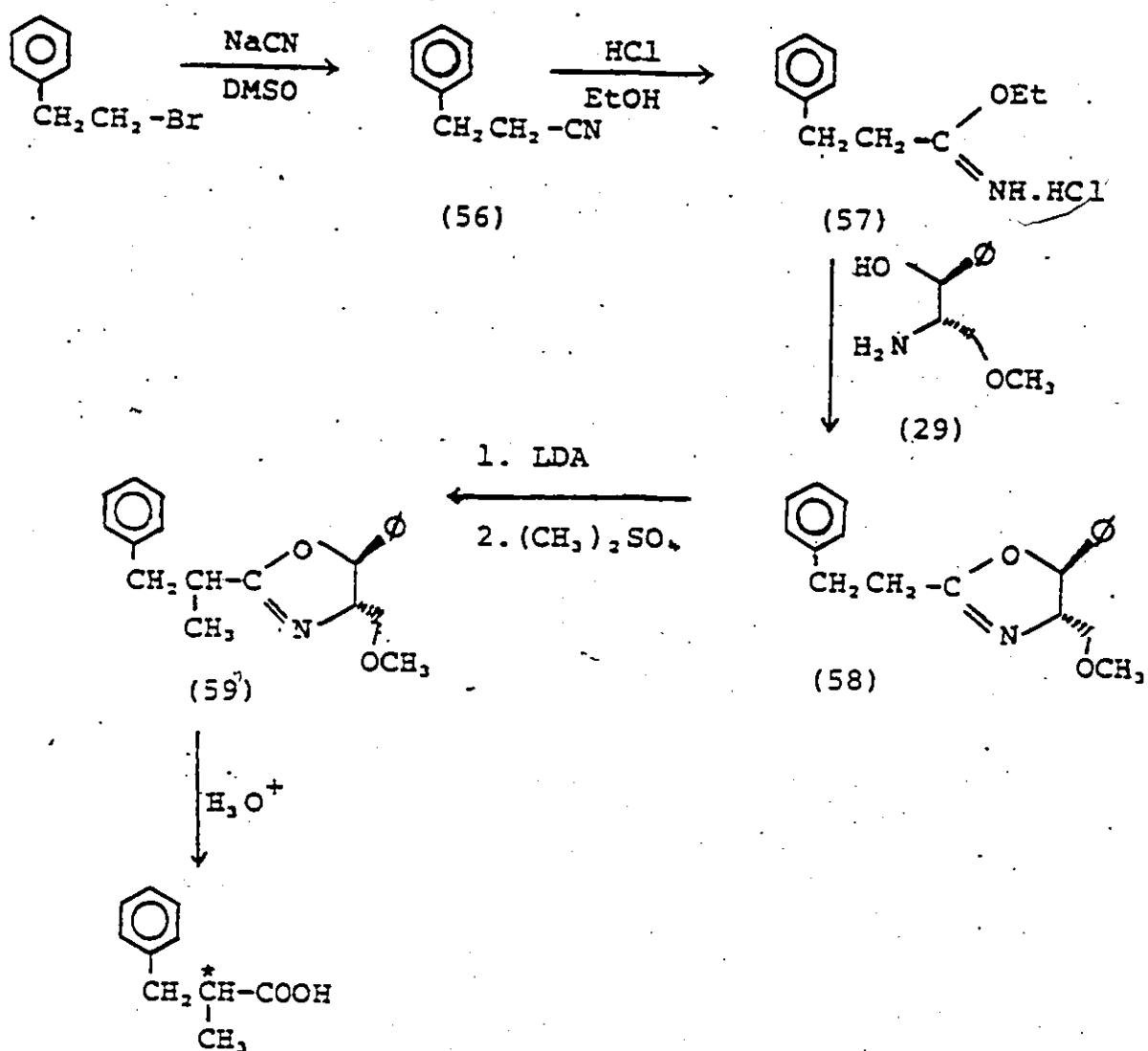


Figure (11)

The starting material, 2-bromoethylbenzene, was first converted to its cyano derivative (56) (Scheme (55)) by reacting with sodium cyanide in DMSO at 130°C. At temperatures below 130°C the reaction rates were slow, while higher temperatures were undesirable. This reaction was also carried out in DMF, but the yields were poor and the reaction was also slower. The 2-cyanoethylbenzene was converted to its imidate (57) and then

reacted with the chiral amino alcohol (29) to give the oxazoline (58) in 66% yield. Alkylation of (58) was done under the same conditions used in Scheme (53). Metalation with lithium diisopropylamide at -78°C and subsequent quenching with dimethyl sulfate at -98°C gave the oxazoline (59). Hydrolysis of the latter with 6N HCl gave 3-phenyl-2-methyl propanoic acid (55).



Scheme (55)

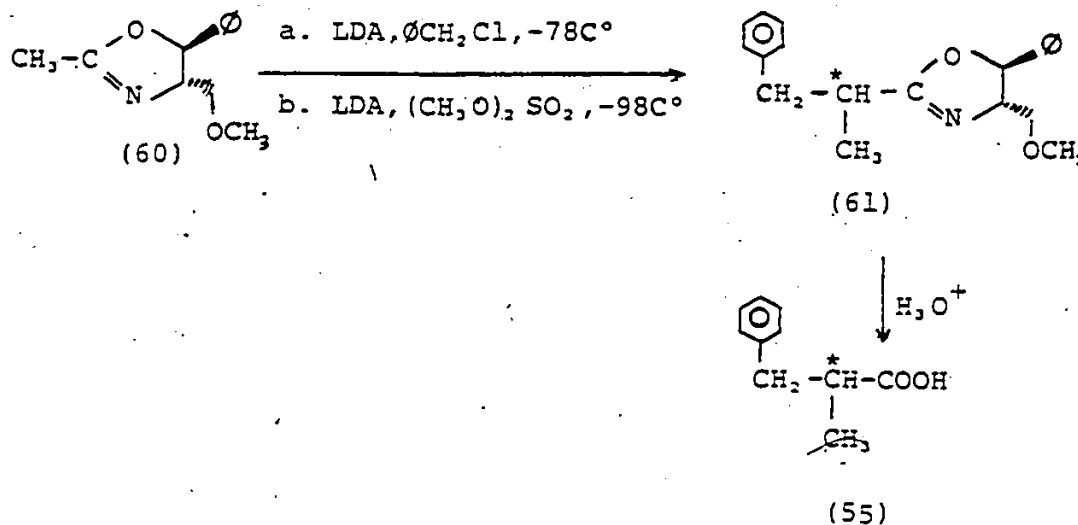
(55)

The spectral characteristics of the products were in agreement with the proposed structure and the literature values. Optical rotations of the compounds (58), (59) and (54) were measured and compared with the values cited in the literature. Oxazoline (58) had an optical rotation of $[\alpha]_D^{25} = -59.8^\circ$ ($c=2.0$, EtOH). The literature value for this compound is $[\alpha]_D^{25} = -59.1^\circ$ ($c=8.4$, EtOH)¹⁵⁹. Oxazoline (59) showed an optical rotation of $[\alpha]_D^{25} = -56.3^\circ$ ($c=2$, CHCl₃). No literature value was available for this. However, proton NMR, ¹³C NMR, IR and MS data of this compound were found to be satisfactory. Proton and ¹³C NMR spectra of (59) showed the presence of two diastereomers. The ratio of the two diastereomers could be calculated from the ¹³C NMR spectrum using the signal for the methoxy carbon. This carbon showed two signals close to each other in the ratio of 8:1 which indicates an optical purity of about 88%. The chiral carboxylic acid (55) had an optical rotation of $[\alpha]_D^{25} = 19.4^\circ$ ($c=2$, CHCl₃). By comparing this value with the value for the optically pure compound¹⁵⁹ the optical yield was found to be 83%. This value is within $\pm 5\%$ of the value obtained from the ¹³C spectral data. The chemical yield of (55) was 79%.

The good optical and chemical yields obtained in the above synthesis of the chiral model compound (55) confirms that this is a very efficient method for the synthesis of chiral compounds of this nature, and similar results should be obtained for their polymeric analogues. Another important facet in this

study was that the spectral data obtained with the model compounds could be used to assist in the analysis of the more complicated spectra of their polymeric analogues. It was also seen in this study that the ^{13}C NMR spectrum of the oxazoline (56) can be used to get valuable information about the optical purity of that particular compound and this is also an indication of the enantiomeric excess of the final product after the hydrolysis of (56). The same technique should be applicable to the measurement of the enantioselectivity of the reaction on the polymeric materials.

Meyers has also synthesized chiral 3-phenyl-2-methyl propanoic acid (55), but by a different route which involved the consecutive introduction of two alkyl groups (benzyl followed by methyl) onto oxazoline (60) to afford (61), which after hydrolysis gave the chiral carboxylic acid (55). (Scheme (56)).



Scheme (56)

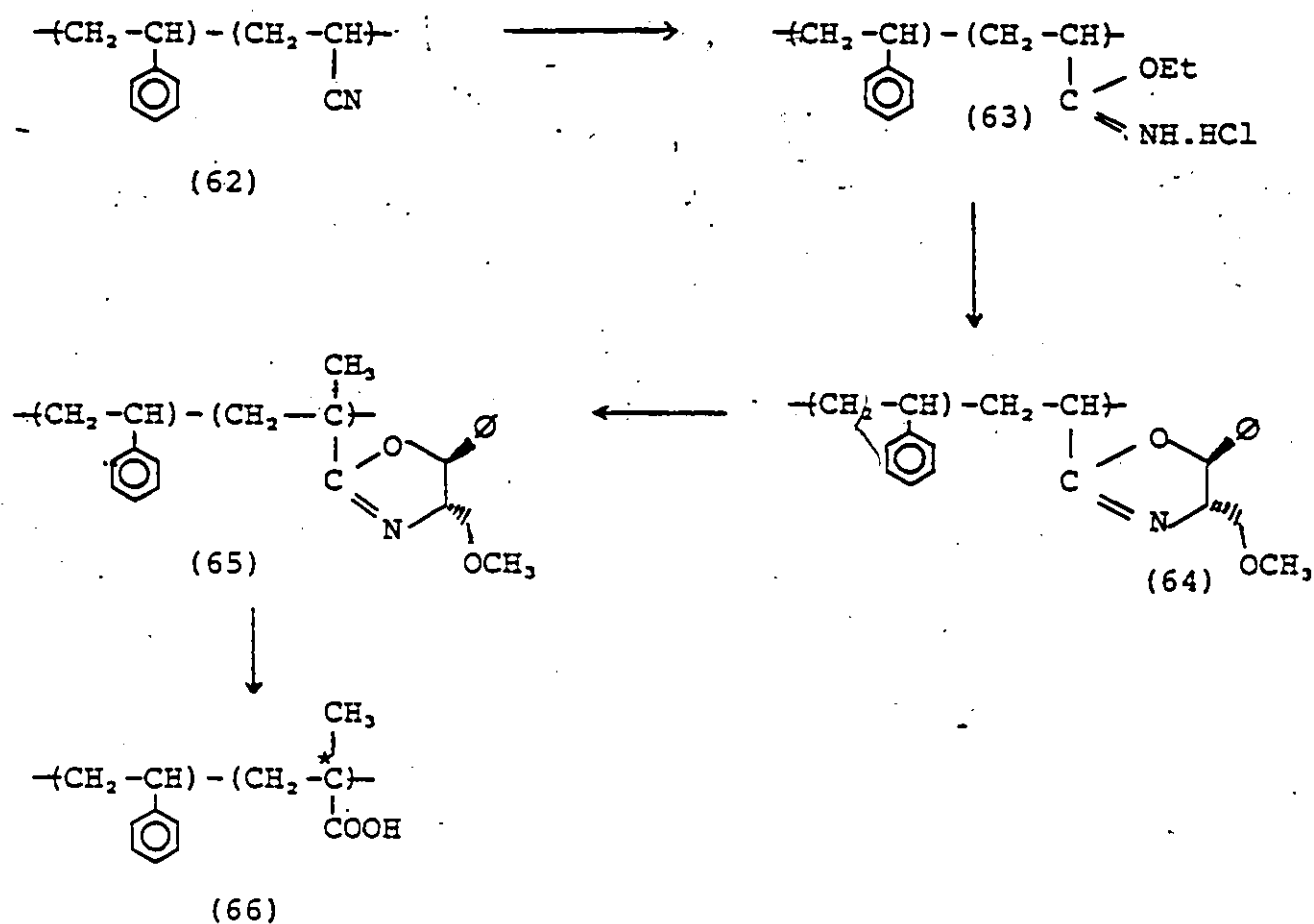
The optical yield obtained in this synthesis was 78% and the chemical yield was 75%.

II.4.3. Optically active polymers with main chain chirality

Having proved that optical induction on the side chains of polymers is possible using chiral oxazolines, asymmetric induction on the main chain of a polymer was then studied using the same technique. In order to attain this goal, the polymer selected should have nitrile groups adjacent to the main chain of a polymer with α hydrogens. The polymer should be constituted of two different vinylic units, typically one with nitrile substituent and the other with a different substituent. This requirement is important in view of the low solubility of acrylonitrile homopolymers and of the requirement for the lack of an internal plane of symmetry in the final product. In the simplest case, a polymer with asymmetric triads may be formed. A copolymer of styrene and acrylonitrile (62) was therefore chosen for this study.

The nitrile polymer (62) was first converted to its imidate (63). (Scheme (57)). This reaction was found to be harder to carry out than with the nitrile polymer (47) (Scheme (55)), mainly due to steric problems caused by the close proximity of the nitrile group and the polymer backbone. Longer reaction times had to be used and even then the conversion of nitrile to imidate was not complete. There was always a significant amount of nitrile (35-55%) left unreacted, as seen

in the IR spectrum. The imidate was converted to the oxazoline (64) by reacting with amino alcohol (29) at 0°C for 4-5 hrs. The oxazoline (64) was alkylated with lithium diisopropylamide and dimethyl sulfate and then hydrolyzed using 6N HCl to give the chiral polymeric carboxylic acid (66).



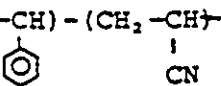
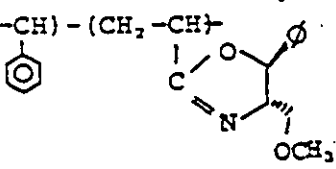
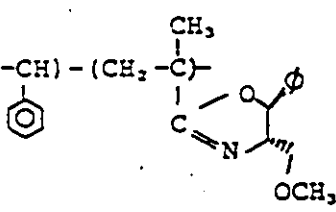
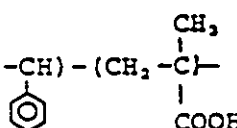
Scheme (57)

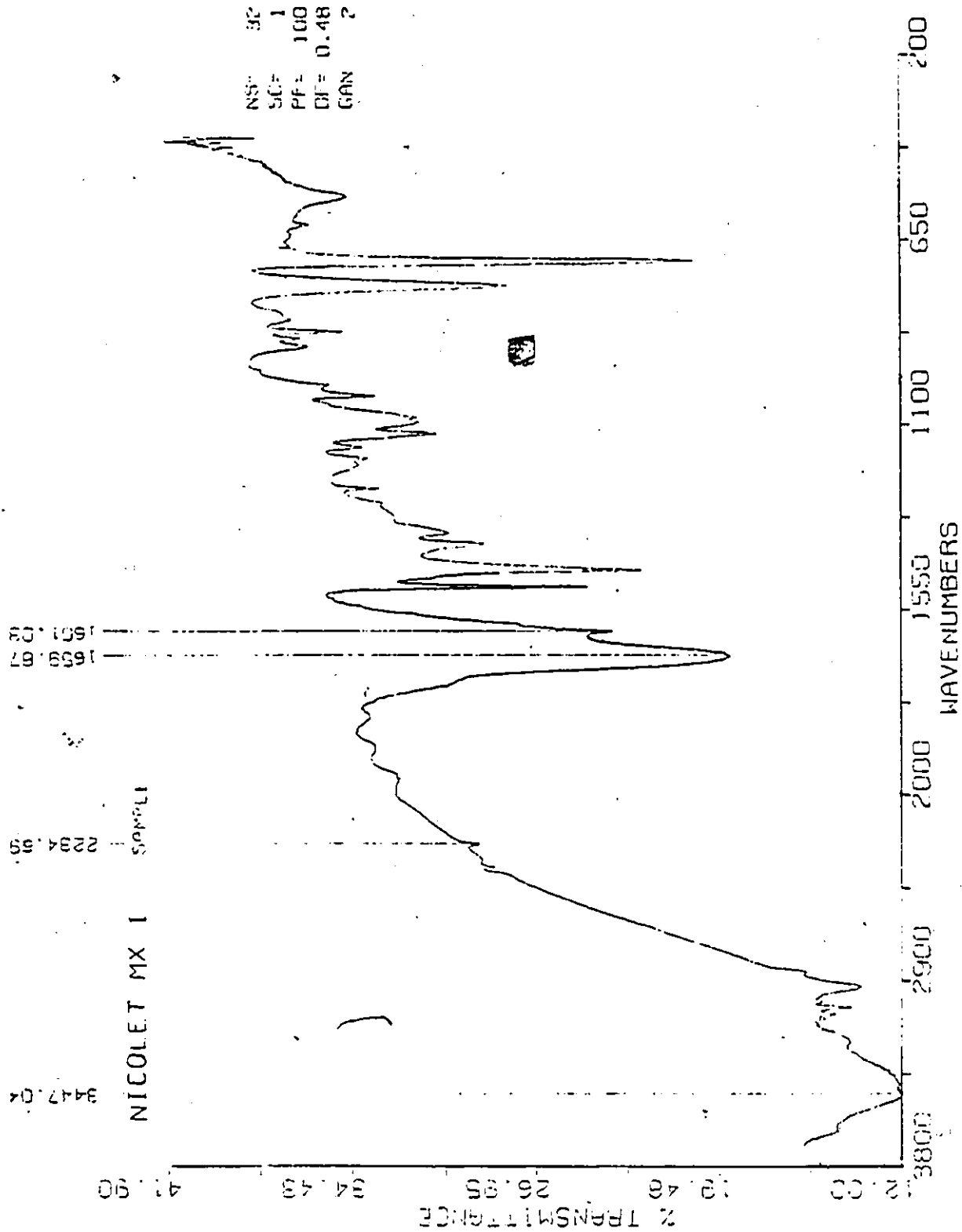
The optical rotation of polymers (64), (65), and (66) were measured and are listed in Table (10). As in the previous synthesis (Scheme (53)) the oxazolines (64) showed negative rotations while their precursor amino alcohol (29), had a positive rotation. Polymeric oxazolines (65) also showed negative rotations, but the values were slightly lower than those obtained for polymers (64). The carboxylic acid polymers (66) obtained after the hydrolysis of the polymer (65) were optically active and showed positive optical rotations.

Proton NMR, ^{13}C NMR and IR spectral studies were done on each of the polymers and valuable information was obtained. The IR spectrum of the polymeric imidate (63) showed a broad strong absorption at 1659 cm^{-1} . The absorption around $2500\text{--}3300\text{ cm}^{-1}$ was also strong (Spectrum (7)). The polymeric oxazoline (64) had a sharp strong IR absorption at 1645 cm^{-1} . The proton NMR of this polymer showed a broad signal around $\delta=6.0\text{--}6.2\text{ ppm}$ for the proton on the tert. carbon next to the oxygen of the oxazoline moiety. Another broad signal was present at $\delta=3.4\text{--}4.2\text{ ppm}$ due to the proton on the tert. carbon next to nitrogen of the oxazoline moiety and the two protons on the methylene group next to the methoxy group of the same moiety. The methoxy protons showed a broad signal at $\delta=3.2\text{--}3.4\text{ ppm}$, (Spectrum (8)). The IR spectrum of the polymer (65) was very similar to that of the polymer (64). The IR spectrum of the polymer (66) showed a sharp absorption at 1728 cm^{-1} . No signal was seen at 1645 cm^{-1} , indicating that most of the oxazoline units had undergone hydrolysis to form the

Table (10): Optical rotations of the chiral polymers (64), (65), and (66).

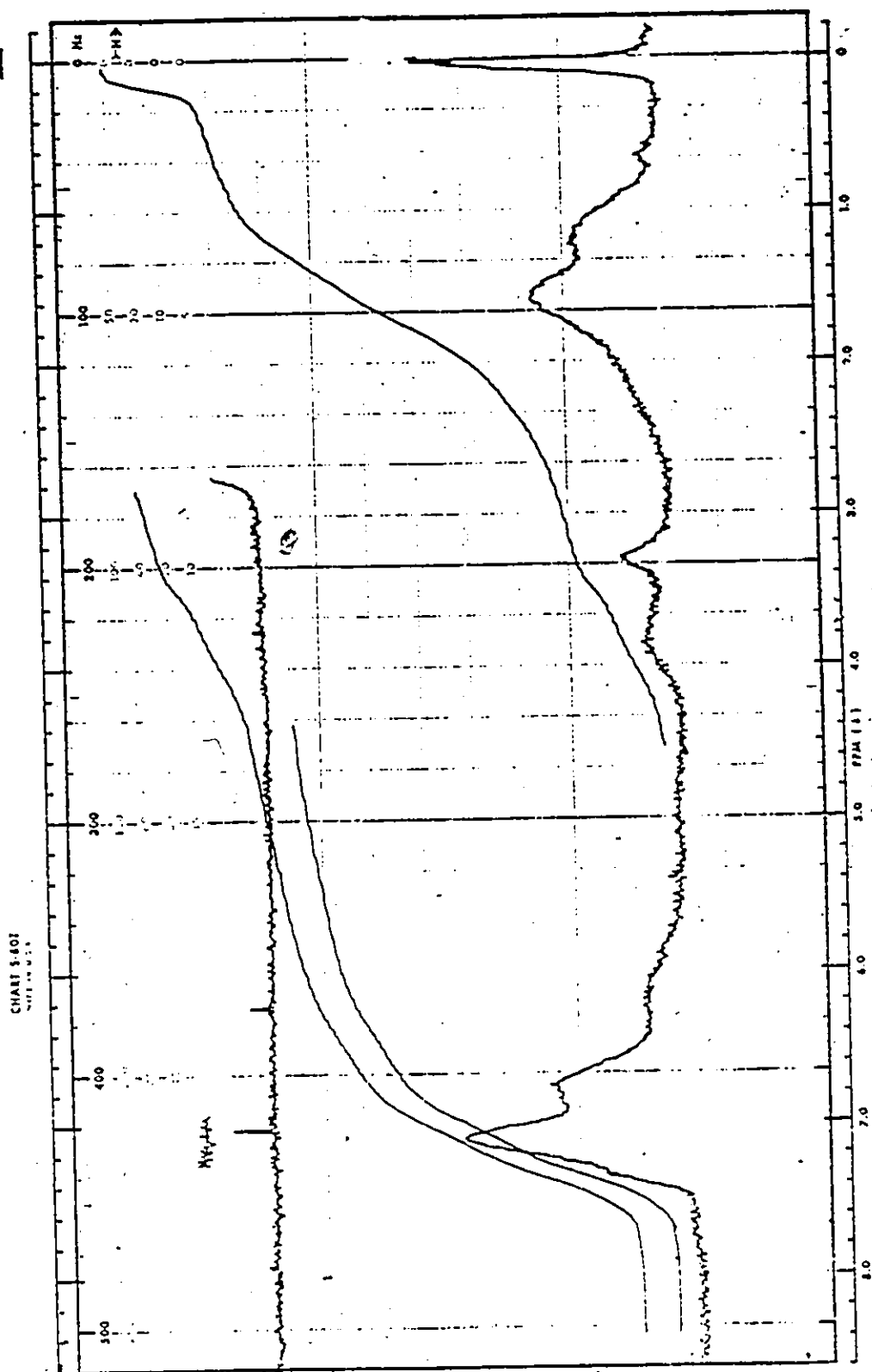
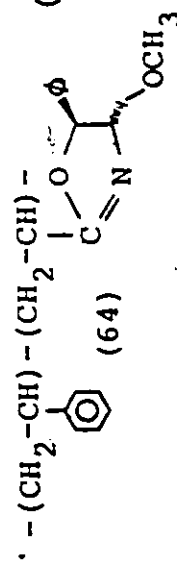
[2% solutions in chloroform were used].

	Series 1		Series 2		Series 3	
	N%	Optical Rotation $[\alpha]_D^{25}$	N%	Optical Rotation $[\alpha]_D^{25}$	N%	Optical Rotation $[\alpha]_D^{25}$
Styrene-Acrylonitrile Copolymer $\text{-(CH}_2\text{-CH)}\text{-}(\text{CH}_2\text{-CH})\text{-}$ 	6.18	0°	6.18	0°	6.18	0°
Polymeric Oxazoline (64) $\text{-(CH}_2\text{-CH)}\text{-}(\text{CH}_2\text{-CH})\text{-}$ 	-	-3.5°	4.85	-2.2°	-	-2.4°
Polymeric Oxazoline (65) $\text{-(CH}_2\text{-CH)}\text{-}(\text{CH}_2\text{-C)}\text{-}$ 	-	-2.8°	5.10	-1.6°	-	-2.0°
Polymeric Carboxylic Acid (66) $\text{-(CH}_2\text{-CH)}\text{-}(\text{CH}_2\text{-C)}\text{-}$ 	1.03	+3.0°	2.85	+1.5°	2.80	+1.4°



Spectrum (7)

$-(\text{CH}_2-\text{CH})-\text{C}_6\text{H}_4-\text{C}(\text{NH}_2)(\text{OEt})-\text{NH}_2 \cdot \text{HCl}$ (IR in KBr) •
 (63)


 $^1\text{H NMR in CDCl}_3$


Spectrum (8)

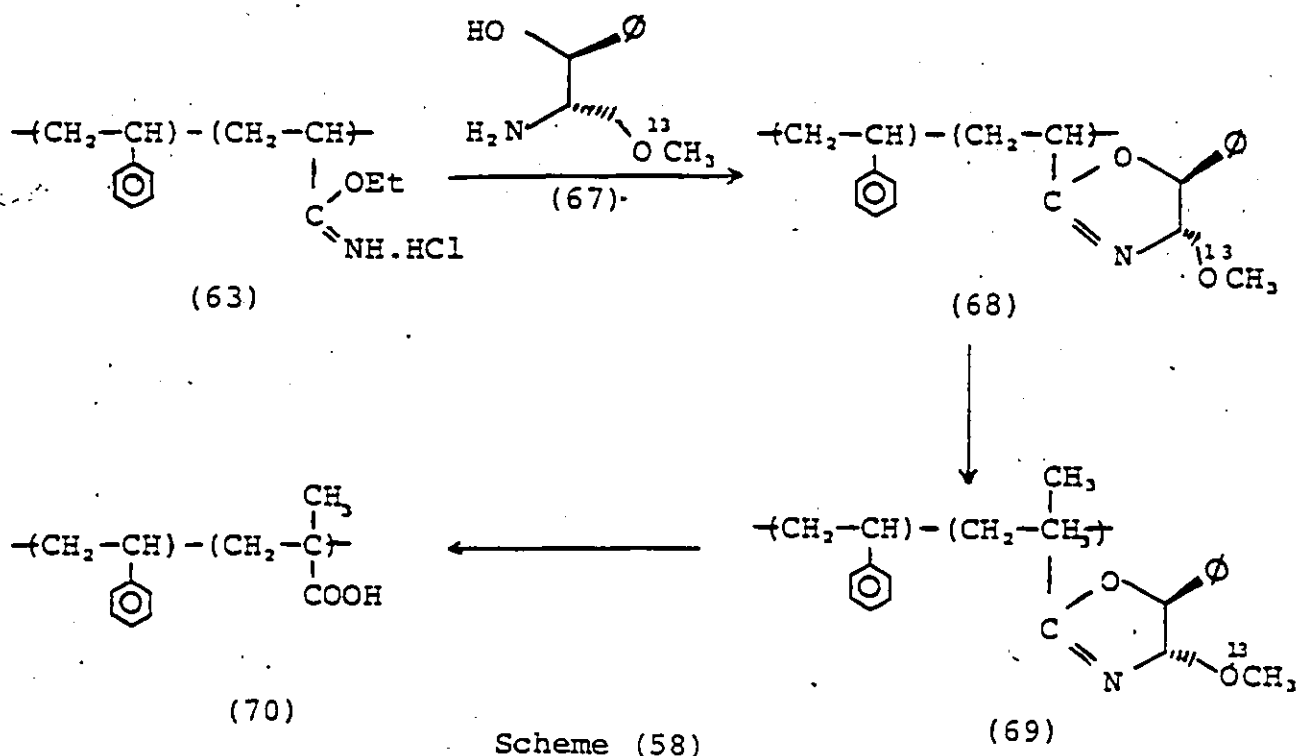
corresponding carboxylic acid. The signals at 173.78 ppm and 60.89 ppm in the ^{13}C NMR spectrum of the polymer (65), due to the carbon atoms of the $-\text{C}=\text{N}-$ and the methoxy groups respectively, were absent from the ^{13}C NMR spectrum of the polymeric carboxylic acid (66). This also indicated that the polymer (66) did not contain any significant amount of unhydrolyzed oxazoline groups. The IR spectrum of the polymer (66) showed the presence of a significant amount of unreacted nitrile. Therefore, unlike the previous synthesis (Scheme (55)), the nitrogen analysis will not be very useful.

II.4.4. ^{13}C label studies of chiral polymers

Although the polymer (66) was optically active, it was not possible to obtain any measurement of the average enantiomeric excess from either spectral data or optical rotations. In order to overcome this problem and also to confirm that the optical activity was not due to any chiral impurity but due to an asymmetric induction reaction, an experiment was designed which involved ^{13}C labeled oxazolines. In the synthesis of chiral (2-benzyl propionic acid) the ^{13}C NMR of the oxazoline (59) showed two signals close to each other for the methoxy methyl group, due to the presence of the two diastereomers and it was possible to measure the enantiomeric excess of the final product by the intensities of these two signals. Unfortunately, the band corresponding to methoxy methyl group in polymer (65) was broad, small and not clearly defined, due to the high viscosity of the polymer solutions

which led to poor resolution. This problem could be simplified by having the methoxy methyl group labeled with ^{13}C . Then the ^{13}C NMR spectrum of the polymeric oxazoline (65) would show a strong signal for the methoxy methyl group. In theory, there should be two bands in the ^{13}C NMR for this group due to the two diastereomers present. If these two bands are sufficiently separated their integration could be used to measure the enantiomeric excess. In addition, the polymeric carboxylic acid (66) will not show a signal in its ^{13}C NMR for the methoxy methyl group if all the oxazoline rings are hydrolyzed.

The synthesis involves the reaction of the polymeric imidate with the ^{13}C labeled amino alcohol (67) (Scheme (58)). The resulting ^{13}C labeled polymeric oxazoline was methylated and hydrolyzed.



The ^{13}C labeled amino alcohol (67) was made as shown in Scheme (46). Oxazoline (27) ($\text{R}=\text{CH}_3$) was methylated using sodium hydride and $^{13}\text{CH}_3\text{I}$ (90% ^{13}C enriched) and the resulting 4-methoxy methyl oxazoline (28) (with $\text{O}-^{13}\text{CH}_3$) was hydrolyzed to yield amino alcohol (67). The compounds were identified by their proton and ^{13}C NMR spectra. The proton NMR spectrum of the amino alcohol (67) showed a doublet at $\delta=3.0$ ppm with a coupling constant of 140 Hz which is typical for an $\text{O}-^{13}\text{CH}_3$ group.

The polymeric oxazoline (68), made using ^{13}C labeled amino alcohol (67), showed a sharp absorption at 1645 cm^{-1} , due to the $-\text{C}=\text{N}-$ group of oxazoline ring, in its IR spectrum. The ^{13}C NMR of this polymer had a strong peak at 59.8 ppm which corresponded to the ^{13}C of the $\text{O}-^{13}\text{CH}_3$ group. The expanded spectrum of this particular peak, (Figure (12)), was very symmetrical which indicated the presence of only one peak. The IR spectrum of the polymeric oxazoline (69), obtained after methylation of (68), also had a sharp strong absorption at 1645 cm^{-1} , but the ^{13}C NMR spectrum, when expanded around 59.8 ppm, showed a small shoulder in addition to the main peak for the $\text{O}-^{13}\text{CH}_3$ group. The same spectrum when measured with a 400 MHz spectrometer showed two separate peaks for the $-\text{O}-^{13}\text{CH}_3$ group, probably due to the two diastereomers, (Figure (13)). Although the two peaks were close to each other, it was possible to estimate the diastereomeric ratio from the 400 MHz spectral data. Thus, the ratio of diastereoisomers was approximately (75:25), in agreement with the results of similar alkylation reactions using Meyers' conditions¹⁵⁸.

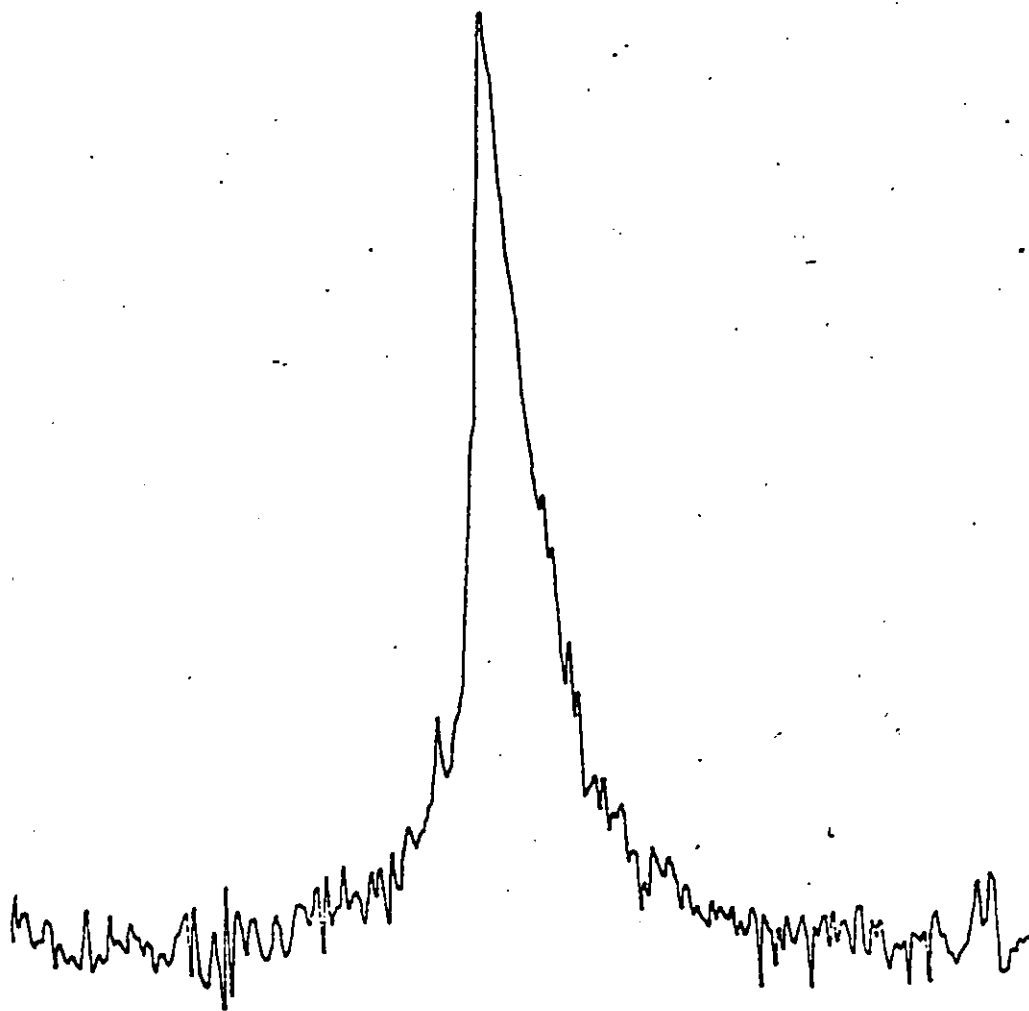


Figure (12) Expanded ^{13}C absorption of the $-\text{O}^{13}\text{CH}_3$ group of the polymer (68).

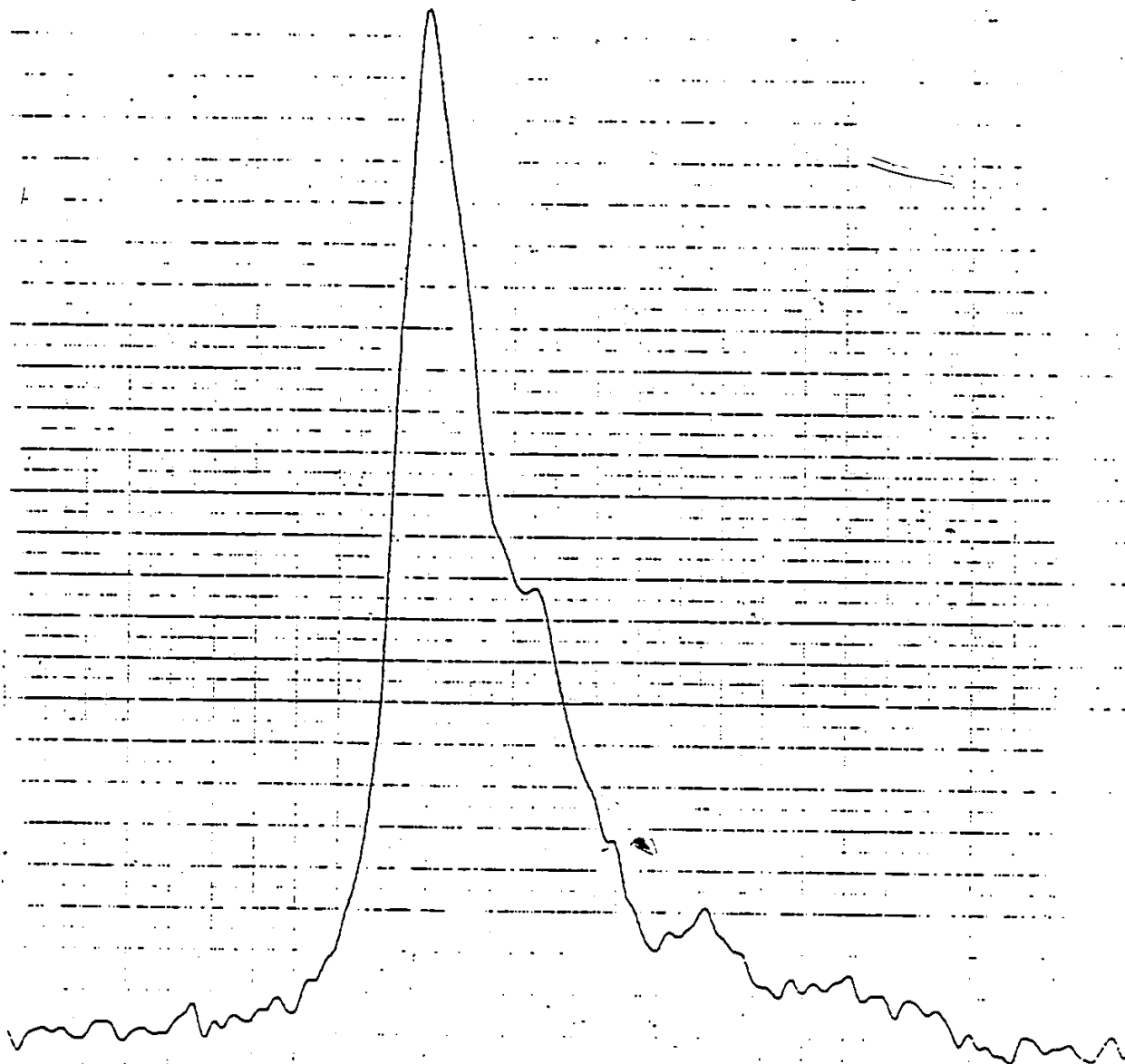


Figure (13) Expanded ^{13}C absorption of the $-\text{O}^{13}\text{CH}_3$ group of the polymer (69).

The hydrolysis of polymer (69) gave polymer (70) which had an IR spectrum showing a strong absorption at 1728 cm^{-1} and a ^{13}C NMR spectrum with a very small peak at 59.8 ppm indicating that almost all the oxazoline groups had been hydrolyzed.

Polymer (70) also had an optical rotation of $[\alpha]_D^{25} = +1.4^\circ$ in chloroform where its precursor polymers (68) and (69) had optical rotations $[\alpha]_D^{25} = -2.4^\circ$ and -2.0° respectively. The absence of any large amount of oxazoline groups in the final polymer (70) and also the positive optical rotation clearly indicate that the polymer is optically active and that its optical activity is not due to any chiral impurity but to the chiral centers which were formed on the polymer main chain by asymmetric induction. The optical rotations of the polymers (68), (69) and (70) are low and this is partly due to the fact that only a part of the nitrile groups in the starting polymer had been used up for the reaction.

The same reaction sequence was carried out on the nitrile polymer (47) using ^{13}C labelled amino alcohol (67). The polymeric oxazoline (49) (with a $-O-^{13}\text{CH}_3$ group) showed a strong absorption at 1669 cm^{-1} in its IR spectrum and an absorption due to $-\text{C}\equiv\text{N}$ was absent. The ^{13}C NMR of this polymer had a very strong and symmetrical peak at 59.2 ppm due to the $O-^{13}\text{CH}_3$ group. (Figure (14)). This polymer, after methylation to give (50), still showed the strong absorption at 1669 cm^{-1} in the IR spectrum, but the peak at 59.2 ppm in the ^{13}C NMR spectrum (Figure (15)) was broader than that of the polymer before methylation. This broadening could be due to the presence of two peaks close to each other, but these, if present, could not

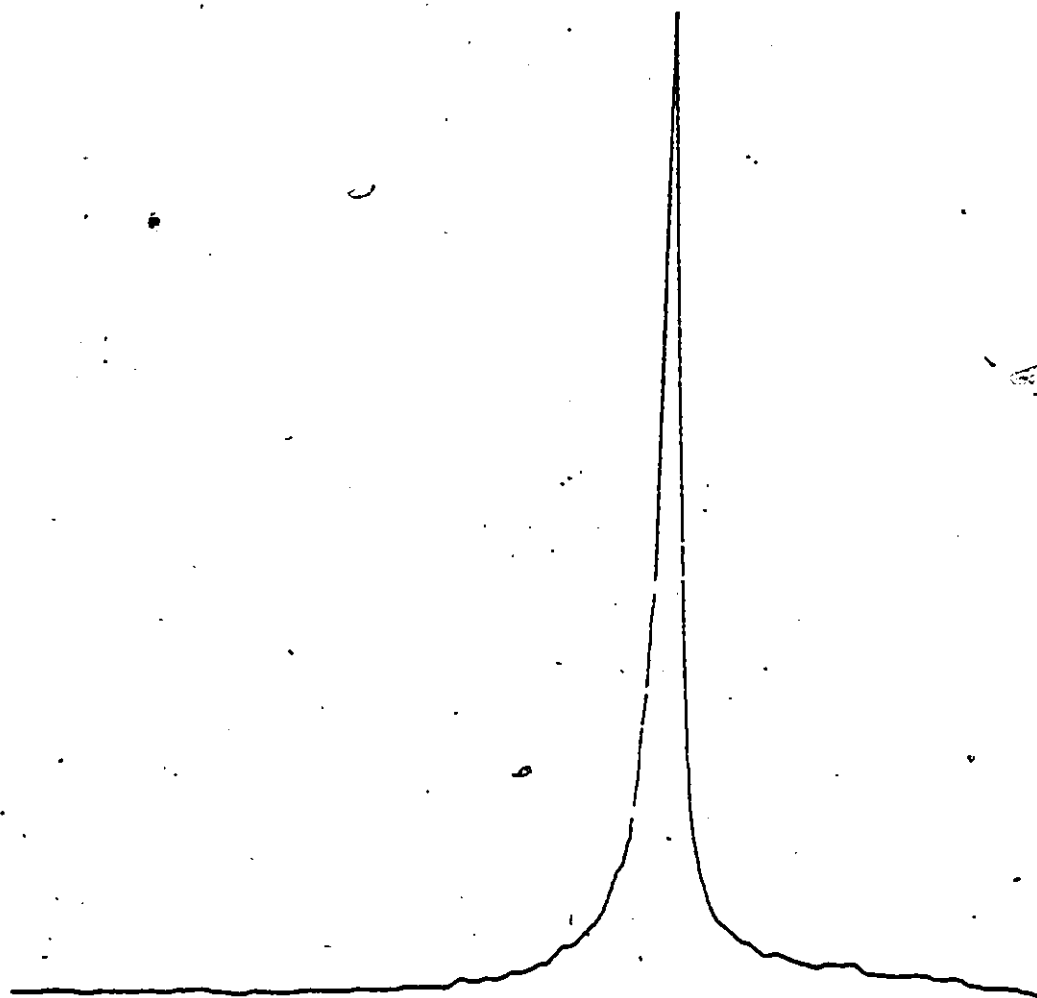


Figure (14) Expanded ^{13}C absorption of $-\text{O}^{13}\text{CH}_3$ group of the polymer (49) with a ^{13}C labelled $-\text{O}^{13}\text{CH}_3$ group.

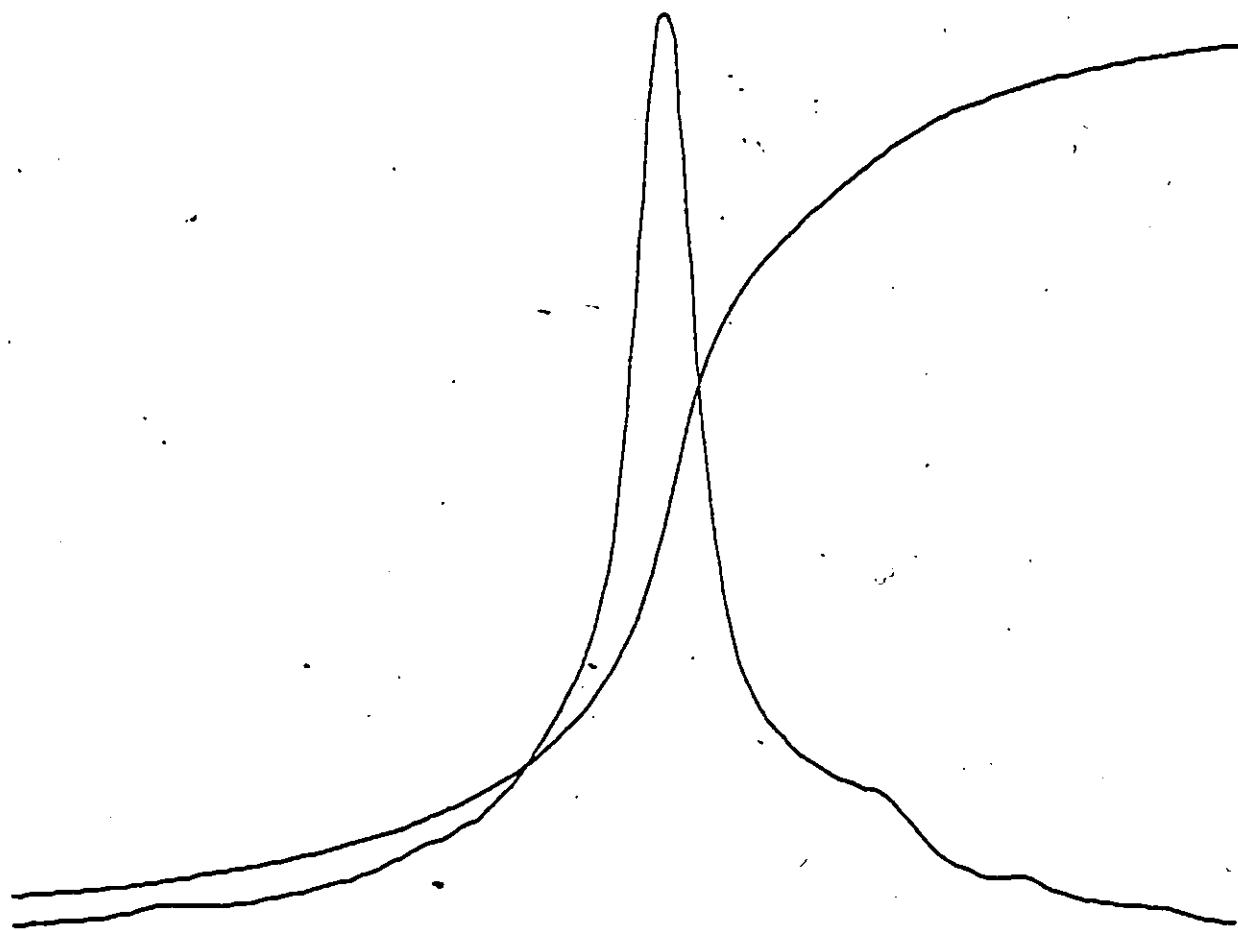


Figure (15) Expanded absorption of the $-O^{13}CH_3$ group of the polymer (50) with a ^{13}C labelled $-O^{13}CH_3$ group.

be resolved at 400 MHz. The optical rotations of the polymers before methylation and after methylation were $[\alpha]_D^{25} = -4.3^\circ$ and $[\alpha]_D^{25} = -3.1^\circ$ respectively. The methylated polymer when hydrolyzed showed a strong absorption at 1710 cm^{-1} in the IR spectrum but was insoluble in most of the organic solvents. The carboxylic acid groups of this polymer were converted to their methyl ester by reacting with diazomethane. All the carboxylic acid groups were converted to the ester in this reaction as the IR spectrum of the new polymer showed only one carboxyl absorption at 1730 cm^{-1} . The ^{13}C NMR spectrum of this polymer did not show a peak at 59.2 ppm indicating the absence of any unhydrolyzed ^{13}C labelled oxazoline groups or of its byproducts. It also had an optical rotation of $[\alpha]_D^{25} = +1.2^\circ$. These factors clearly indicate that the optical activity of the polymer is due to the presence of asymmetric carbon atoms in the side chains and not due to any chiral impurity.

From these labeled studies, it is possible to conclude that the starting achiral nitrile polymers undergo asymmetric induction during the synthesis and that the final carboxylic acid polymers are optically active. The most valuable information about the asymmetric induction was obtained from the ^{13}C NMR studies of the ^{13}C labelled polymeric oxazoline (69) which showed the formation of two diastereomers in the ratio 75:25, in agreement with the data in the literature for similar alkylations.

Although several optically active polymers whose optical activity is due to chiral main chains have been reported in the literature, as is mentioned in the introduction, the above synthesis is the first involving a chemical modification of an achiral polymer with asymmetric induction.

III

Experimental

The resins used for the preparation of polymer supported reagents were 1% crosslinked divinylbenzene-styrene copolymers (Bio-beads SX-1) purchased from Bio-Rad Laboratories. Dioxane and THF used for the reactions in anhydrous medium were purified by distillation over sodium and benzophenone. Ethanol was dried by distilling over magnesium. All other chemicals were reagent grade and used without further purification unless specified.

Proton NMR spectra were recorded on Varian T-60, Varian EM 360A or Varian HA-100 Spectrometers, the first two operating at 60 MHz and the third at 100 MHz. Infrared spectra were recorded on Pye-Unicam SP 1100 or Nicolet MX-1 Fourier transform spectrophotometers. ^{13}C NMR spectra were recorded using a Varian CFT 80 spectrometer operating at 20 MHz, a Varian XL 200 xP spectrometer operating at 200 MHz or a Bruker WH-400⁺ operating at 400 MHz. Elemental analyses were performed by Canadian Microanalytical Serv. , MHW Laboratories, Galbraith Laboratories or in our laboratory (halogen analyses). Mass spectra were recorded using AEI MS 902 or VG 7070 E mass spectrometers.

G.L.C. analyses were done using a Gow Mac Gas Chromatograph series 550 with thermal conductivity detector using carbowax 20M on chromosorb P or 4% Silicone SE 30 on chromosorb G columns.

The nitrile polymer (62) was received from Dr. Fréchet. Optical rotations were taken on Perkin Elmer 141 and 241 electronic spectropolarimeters with digital readout.

III.1. Washing of Crosslinked polystyrene resin

Commercially available polystyrene Bio-Beads SX-1 was washed as described below to remove any impurity before subjecting it to chemical modifications.

with 1N NaOH at 60°C for 30 min.

1N HCl at 60°C for 30 min.

1N NaOH at 60°C for 30 min.

1N HCl at 60°C for 30 min.

H₂O at 25°C for 30 min.

DMF at 40°C for 10 min.

1N HCl at 60°C for 30 min.

H₂O at 60°C for 30 min.

CH₂Cl₂/CH₃OH (2:3) at 25°C for 5 min.

THF at 60°C for 30 min.

Ether at 25°C for 30 min.

The polymer was dried in vacuo at 60°C for 16 hrs. and weighed.

Wt. of polymer before washing = 94.84 gms.

Wt. of polymer after washing = 93.61 gms.

III.2. Polymeric Reagents

III.2.1. Bis(Polystyryldiphenylphosphine) Copper (I)

Tetrahydroborate [P]-(Ph)₂, CuBH₄

III.2.1.1. Preparation of [P]-Br

50 g of prewashed polymer were suspended in 600 ml of CCl₄ and to this was added 0.85 g of FeCl₃. The whole system

was protected from light, then treated with 27.5 ml of Br₂ in 50 ml of CCl₄. Stirring was continued for 2 hrs. at room temperature and then at reflux temperature until no further HBr fumes were evolved from the reaction flask (3 1/2 hrs), indicating the completion of the reaction. The polymer was then filtered, washed with CCl₄, acetone (four times), THF, and THF/water. Subsequent washings were carried out in a Soxhlet extractor using dioxane for 24 hrs. and then dioxane/water (80:20) for a further 20 hrs. The polymer was filtered, washed with methanol, and dried in vacuo at 40°C for 16 hrs. 90.23 g of polymer were obtained having 5.1 mequiv Br/g. D.F. = 0.87.

III.2.1.2. Preparation of $\text{P}^{\oplus}\text{-P(Ph)}_2$ (3)

30 g of brominated polystyrene $\text{P}^{\oplus}\text{-Br}$ (5.1 mequiv/g) were dispersed in 600 ml of THF cooled to 0°C under nitrogen and to this was added 48 ml of chlorodiphenylphosphine via a syringe, followed by 4.3 g of Li (shots). The mixture was stirred at room temperature for 18 hrs. under nitrogen, then treated with 300 ml of methanol while stirring for a further 30 min. The polymer was filtered, washed with distilled water (four times), THF, acetone, CH₂Cl₂ and methanol and dried in vacuo at 40°C for 16 hrs. 36.17 g of polymer were recovered. The polymer contained 2.9 mequiv. P/g. D.F. = 0.70.

III.2.1.3. Preparation of $[\text{P}^{\oplus}\text{-P(Ph)}_2]\text{-CuCl}$ (5)

4.08 g of copper (I) chloride were reacted with 4.79 g of tetramethylethylenediamine in 400 ml of acetone. The

unreacted copper (I) chloride was removed by filtration and to the bluish-green filtrate were added 22 g of $\text{P}(\text{Ph})_2$ and the mixture was stirred at room temperature for 16 hrs. The polymer was filtered and washed with acetone (four times), methanol (two times), acetone/methanol (1:1), and then with methanol in a Soxhlet extractor for 20 hr. It was dried in vacuo at 40°C for 16 hrs. 23.88g of polymer were obtained.

III.2.1.4. Preparation of $[\text{P}(\text{Ph})_2]_2\text{CuBH}_4$ reagent. (6)

1.04 g of sodium borohydride was dissolved in 100 ml. of ethanol and to this solution were added 22 g of $[\text{P}(\text{Ph})_2]_2\text{CuCl}$. The mixture was stirred at room temperature for 16 hrs. The polymer was filtered and washed with ethanol, water (three times), water/methanol (1:1), THF, CHCl_3 and methanol (twice), then dried in vacuo at 40°C for 16 hrs. 21.34 g of polymeric reagent were obtained. The polymer contained 1.5 mequiv. B/g. D.F. = 0.89.

Preparation of heptanoyl chloride

To 15 g (115 mmol.) of heptanoic acid were added 20.4 g (173 mmol.) of thionyl chloride and the mixture was stirred at reflux temperature for 3 hrs. The crude product was then subjected to distillation and 11.03 g (65%) of heptanoyl chloride were isolated (boiling point 173°C).

Preparation of cyclohexane carboxylic acid chloride

To 20 g. (155 mmol.) of cyclohexane carboxylic acid were added 22.5 g (190 mmol.) of thionyl chloride and the mixture was stirred at reflux temperature for 4 hrs. The crude product was distilled under reduced pressure. 18.93 g (83%) of cyclohexane acid chloride were obtained. (Boiling point 70°C at 15 torr)

III.2.1.5. Reduction of carboxylic acid chlorides

with $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$

Reduction of cyclohexane carboxylic acid chloride with $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$

1 g of $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$ was dispersed in 5 ml of acetone and to this was added 268 μl . (2 mmol.) of cyclohexane carboxylic acid chloride slowly via a syringe. The reaction was monitored by Gas Chromotography. The G.C. yield of cyclohexane carboxaldehyde was 68%.

Reduction of heptanoyl chloride with $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$

1 g of $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$ was dispersed in 5 ml acetone and to this was added 310 μl . (2 mmol.) of heptanoyl chloride slowly via a syringe. The reaction was monitored by Gas Chromotography. The G.C. yield of heptanal was 73%.

III.2.1.6. Reduction of carboxylic acid chlorides with

excess $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$

Reduction of cyclohexane carboxylic acid chloride with excess

$[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$

0.262 g (1 mmol.) of triphenyl phosphine was dissolved in 5 ml of acetone and 1.5 g of $[(\text{P})-\text{P}(\text{Ph})_2]_2\text{CuBH}_4$ was

dispersed in it. To this was added 134 μ l. (1 mmol.) of cyclohexane carboxylic acid chloride slowly via a syringe and the reaction was monitored by Gas Chromotography. The G.C. yield of cyclohexane carboxaldehyde was 96%.

Reduction of Heptanoyl chloride with excess $[(P) - P(Ph)_2]_2CuBH_4$

0.262 g of triphenyl phosphine was dissolved in 5 ml of acetone and 1.5 g of $[(P) - P(Ph)_2]_2CuBH_4$ was dispersed in this solution. To this was added 155 μ l. (1 mmol.) of heptanoyl chloride slowly via a syringe. The reaction was monitored by Gas Chromotography. G.C. yield of heptanal was 96%.

Reduction of benzoyl chloride with excess $[(P) - P(Ph)_2]_2CuBH_4$

0.262 g of triphenyl phosphine was dissolved in 5 ml of acetone and 1.5 g of $[(P) - P(Ph)_2]_2CuBH_4$ was dispersed in it. To this was added 112 μ l. (1 mmol.) of benzoyl chloride slowly via a syringe and the reaction was monitored by Gas Chromotography. G.C. yield of benzaldehyde was 100%. 0.10 g of benzaldehyde (94%) was isolated by thin layer chromatography using hexane/ethyl acetate as the eluent.

III.2.1.7. Regeneration of the spent reagent $[(P) - P(Ph)_2]_2CuCl$

To a dispersion of 5.0 g of spent reagent $[(P) - P(Ph)_2]_2CuCl$ in 25 ml of ethanol was added 0.065 g of triphenylphosphine. To this was added 0.35 g of sodium borohydride and the mixture was stirred at room temperature for 16 hrs. The polymer was filtered washed with ethanol, water (three times), water/methanol (1:1), THF, $CHCl_3$ and methanol.

and dried in vacuo at 40°C for 16 hrs. 4.84 g of polymer were obtained.

III.2.1.8. Reduction of carboxylic acid chlorides with the regenerated reagent.

Reaction of Heptanoyl Chloride with the regenerated reagent.

0.262 g of triphenyl phosphine was dissolved in 5 ml of acetone and 1 g of regenerated polymeric reagent $[(\textcircled{\text{P}}-\text{P}(\text{Ph})_2)_2\text{CuBH}_4]$ was dispersed in it. To this was added 155 μl of heptanoyl chloride slowly via a syringe and the reaction was monitored by Gas Chromotography. G.C. yield of heptanal was 93%.

Reductions of cyclohexane carboxylic acid chloride and benzoyl chloride with the regenerated polymeric reagent $[(\textcircled{\text{P}}-\text{P}(\text{Ph})_2)_2\text{CuBH}_4]$ were similar to the one described for heptanoyl chloride.

Reductions of acid chlorides using the polymeric reagent $[(\textcircled{\text{P}}-\text{P}(\text{Ph})_2)_2\text{CuBH}_4]$ were tried out in different solvents like benzene, toluene, ether and an ether/toluene mixture. The reaction procedure was the same as that described above. Yields of aldehydes were less than 50%.

III.2.1.9. Other attempted preparations
of $[(\textcircled{\text{P}}-\text{P}(\text{Ph})_2)_2\text{CuBH}_4]$

To a solution of 0.34 g (2.16 mmol.) of CuSO_4 in 5 ml of methanol were added 2.0 g of $(\textcircled{\text{P}}-\text{P}(\text{Ph})_2)$ (2.16 mequiv/g). The

mixture was stirred for 20 hrs, and the resulting polymer was filtered, washed with water (four times), acetone (two times), THF and methanol and dried in vacuo at 40°C for 16 hrs. 2.04 g of polymer were obtained.

The above polymer was dispersed in 10 ml of ethanol and to this was added 0.25 g of NaBH₄ and the mixture was stirred at room temperature for 16 hrs. The polymer was filtered, washed with ethanol, water (three times), acetone, THF, CHCl₃ and methanol and dried in vacuo at 40°C for 16 hrs. 1.90 g of polymer were obtained.

Using pyridine as a solvent for CuCl

To a solution of 0.31 g (3.2 mmol.) of copper (I) chloride in 10 ml. of pyridine were added 2 g of $\textcircled{\text{P}}$ -P(Ph)₃ (2.16 mequiv/g) and the mixture was stirred at room temperature for 16 hrs. The polymer was filtered and washed with pyridine, water, acetone, THF and methanol. It was suspended in 10 ml of ethanol and to this was added 0.12 g (3 mmol.) of NaBH₄ and the mixture stirred at room temperature for 16 hrs. It was filtered, washed with ethanol, water, acetone, THF and methanol and dried in vacuo at 40°C for 16 hrs. 2.04 g of polymer were obtained.

III.2.1.10. Preparation of [(Ph)₃P]₂CuBH₄

To a stirred solution of 5.34 g of triphenylphosphine in 35 ml of CHCl₃ was added 1 g of finely powdered copper (I) chloride slowly and the mixture was stirred until all copper (I) chloride had dissolved. To this was then added a suspension of

0.38 g of NaBH_4 in 4 ml of ethanol and stirring was continued for 30 min. The reaction mixture was added to water, mixed and the CHCl_3 layer was separated, washed with water, dried with MgSO_4 and treated with ether. $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$ precipitated out. It was filtered, washed with ether and dried in vacuo at 30°C for 5 hrs. 3.23 g of $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$ were isolated.

III.2.1.11. Reduction of heptanoyl chloride with
 $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$

To a solution of 0.262 g of triphenylphosphine in 5 ml of acetone was added 0.63 g of $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$. To this suspension was added 155 μl . of heptanoyl chloride slowly via syringe. The reaction was followed by Gas Chromatography. The G.C. yield was 90%.

III.2.1.12. Preparation of $[(\text{Ph})_3\text{P}]_2\text{CuCl}$ using CuCl -TMEDA
complex

To a solution of 1 g of copper (I) chloride and 1.2g of TMEDA in 130 mL of acetone were added 5.24 g of triphenylphosphine. The mixture was stirred for 90 min. The precipitate formed was filtered, washed with acetone and ether, and dried in vacuo at 30°C for 6 hrs. 4.17 g of $[(\text{Ph})_3\text{P}]_2\text{CuCl}$ were isolated.

III.2.1.13. Preparation of $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$ using
 $[(\text{Ph})_3\text{P}]_2\text{CuCl}$

To a solution of 3.14 g (5.6 mmol.) of $[(\text{Ph})_3\text{P}]_2\text{CuCl}$ in 30 ml of CHCl_3 was added 0.29 g (7 mmol.) of NaBH_4 in 4 ml ethanol. The mixture was stirred for 90 min. and poured to water. The CHCl_3 layer was separated and washed with water. It was dried with MgSO_4 and treated with ether. The precipitate was filtered, washed with ether and dried in vacuo at 30°C for 5 hrs. 2.68 g of $[(\text{Ph})_3\text{P}]_2\text{CuBH}_4$ were isolated. (80% yield).

III.2.2. Formylation agents for Grignard reagents

III.2.2.1. Preparation of phenyl formate

To 69 g (1.5 mol) of formic acid were added 158 g (1.5 mol) of acetic anhydride while keeping the temperature below 45°C . The solution was stirred at 45°C for 1 hr. and to this were added 1.18 g (0.015 mol) of pyridine and 94.1 g (1 mol) of phenol while maintaining the temperature at 20°C . Stirring was continued at 20°C for 45 hrs. and the unreacted acids and anhydrides were removed under reduced pressure using the rotory evaporator. The crude product was distilled under reduced pressure two times. 97.6 g (80%) of phenyl formate were collected at $45\text{--}48^\circ\text{C}$ (4 torr).

$^1\text{H NMR}$ (CDCl_3) δ = 7.50 (m, 5H); 8.30 (s, 1H).

IR ν_{max} = 1741 cm^{-1} strong, 1762 cm^{-1} weak.

Preparation of N-(N-formyl)amino piperidine

To 15 g (0.15 mol) of N-amino piperidine were added 16.5 g (0.17 mol) of phenyl formate and the mixture was stirred at room temperature for 18 hrs. The excess phenyl formate was removed under reduced pressure and the crude product was subjected to distillation under reduced pressure. 9.45 g (65%) of N-(N-formyl)amino piperidine were obtained at 55-60°C (2 torr). 3.62 g of N-amino piperidine was also recovered. Pale yellow solid, M.P. 75-76°C.

^1H NMR (CDCl_3) δ =1.56 (m, 6H); 3.33 (m, 4H); 7.86 (s, 1H); 8.20 (b.s, 1H)

IR ν_{max} = 1695 cm^{-1} strong broad.

Preparation of N-(N-formyl, N-methyl)amino piperidine (10)

17.3 g (0.14 mol) of potassium tert. butoxide were dissolved in 200 ml of THF under nitrogen and to this were added 17.9 g (0.14 mol) of N-(N-formyl)amino piperidine. The reaction mixture was stirred for 15 min. at room temperature and then at reflux temperature for 30 min. It was cooled to room temperature and 21.8 g (0.15 mol) of CH_3I in 30 ml THF were added while stirring. Stirring was continued for 16 hrs. at reflux temperature. After the reaction mixture had cooled to room temperature it was filtered and the white solid was washed with THF (two times). The solvent was removed from the combined organic solution under reduced pressure and the crude product was subjected to distillation under reduced pressure. 16.65 g (83.6%) N-(N-formyl, N-methyl)amino piperidine were collected at 70°C (2 torr). (New compound). Mol. Wt. = 142.11 (From M.S.)

^1H NMR (CDCl_3) δ =1.50 (m, 6H); 2.66 (m, 7H); 8.33 (s, 1H)

IR ν_{max} = 1678 cm^{-1} strong sharp. M.S. = 142, 113, 83, 55

Preparation of 2-(N-formyl) amino pyrimidine

To 6.0 g (64 mmol.) of 2-amino pyrimidine were added 9.8 ml (98 mmol.) of phenyl formate and the mixture was stirred at 100 °C for 18 hrs. The reaction mixture, when cooled to room temperature, solidified. It was powdered and suspended in THF to remove any unreacted phenyl formate, N-amino pyrimidine and other side products. It was filtered and dried in vacuo at room temperature for 16 hrs. 7.5 g (95%) of 2-(N-formyl)amino pyrimidine were obtained. M.P. 212-213°C. (New compound)

^1H NMR (CDCl_3) δ =7.30 (t, 1H, J=4Hz); 8.70 (d, 2H, J=5Hz); 9.50 (b.s., 1H); 11.00 (b.s., 1H). M.S. = 123, 95, 79, 68

IR ν_{max} = 1690 cm^{-1} strong broad, 3205 cm^{-1} moderate sharp.

Preparation of 2-(N-formyl - N-methyl)amino pyrimidine (11)

This compound was prepared according to the procedure described for N(N-formyl - N-methyl)amino piperidine. 2-(N-formyl - N-methyl)amino piperidine was obtained in 61% yield. Yellow solid. M.P. 75-76°C. (New compound)

Elemental Analysis = C - 52.64% H - 5.33% N - 3.04%

^1H NMR (CDCl_3) δ =3.40 (s, 3H); 7.06 (t, 1H, J=4Hz); 8.66 (d, 2H, J=5Hz); 9.80 (s, 1H).

IR ν_{max} = 1672 cm^{-1} strong sharp.

Preparation of 2-(N-formyl)amino thiazole

To 10 g (0.1 mol) of 2-amino thiazole were added 15.4 g (0.13 mol) of phenyl formate and the mixture was stirred at 100°C for 16 hrs. The excess phenyl formate was removed under reduced pressure. The resulting brown solid was dissolved in THF and recrystallized by adding pet. ether (BP30-60°C) followed by cooling. The crystals were filtered and dried in vacuo at 30°C for 16 hrs. 9.7 g (76%) of 2-(N-formyl)amino thiazole were obtained. (New compound)

M.P. 160-162°C.

¹H NMR (DMSO) δ =3.40 (s, 1H); 7.26 (d, 1H, J=4Hz); 7.50 (d, 1H, J=4Hz); 8.5 (s, 1H)

IR $\nu_{\max}$ = 1694 cm⁻¹ strong broad

Preparation of 2-(N-formyl-N-methyl)amino thiazole (12)

This compound was prepared according to the procedure described for the preparation of N-(N-formyl, N-methyl)amino piperidine. 2-(N-formyl-N-methyl)amino thiazole (two isomers in 1:4 ratio) was obtained in 79% yield. Pale yellow solid. M.P. 57-59°C. (New compound). C - 42.42%, H - 4.31%, N - 19.53%
¹H NMR (CDCl₃) δ =3.3 (s, 1/4H); 3.55 (s, 3H); 6.90 (M, 5/4H); 7.35 (M, 5/4H); 8.50 (s, 1H); 9.10 (s, 1/4H)
 IR $\nu_{\max}$ = 1670 cm⁻¹ strong sharp, 1755 cm⁻¹ weak sharp.

Preparation of 2-(N-formyl)amino pyridine

This was prepared as described by Comins and Meyers¹⁵⁷. 2-(N-formyl)amino pyridine was obtained in 98% yield. White solid, M.P. 71-73°C. Literature M.P. 72-73°C¹⁵⁷

^1H NMR (CDCl_3) δ =6.96 (m, 2H); 7.66 (t, 1H J =8Hz);
8.33 (m, 3/2H); 9.26 (b.s, 1/2H); 9.93 (b.s, 1H)

IR ν_{max} = 1690 cm^{-1} strong broad.

Preparation of 2-(N-formyl-N-methyl)amino pyridine (10)

This was prepared as described by Comins and Meyers¹⁵⁷

2-(N-formyl-N-methyl)amino pyridine was obtained in 93% yield.

^1H NMR (CDCl_3) δ =3.35 (s, 3H); 7.12 (m, 2H); 7.74 (m, 1H); 8.38 (m, 1H); 9.30 (s, 1H).

IR ν_{max} = 1690 cm^{-1} strong sharp.

Preparation of 2-(N-benzyl-N-formyl)amino pyridine (13)

This was prepared according to the procedure described for the preparation of 2-(N-formyl-N-methyl)amino pyridine by Comins and Meyers¹⁵⁸. 2-(N-benzyl-N-formyl)amino pyridine was obtained in 79% yield. Light brown solid. M.P. 55-56°C.

^1H NMR (CDCl_3) δ =5.13 (s, 1H); 7.20 (m, 8H); 8.33 (m, 1H); 9.13 (s, 1H). Mol. Wt. = 212.091 (from M.S.)

IR ν_{max} = 1674 cm^{-1} strong sharp. M.S. = 212, 183, 121, 91.

Preparation of N-formyl piperidine (14)¹⁵⁸

To 10.6 g (0.12 mol) of piperidine were added 21.3 g (0.17 mol) of phenyl formate and the mixture was stirred at room temperature for 20 hrs. The crude product was subjected to distillation under reduced pressure. The fraction that distilled at 60-72°C (5 torr) was collected. This fraction was distilled again under reduced pressure to remove phenol which was found to be present with it. As this distillation was also

not successful, the phenol was extracted with 10% NaOH, the organic layer was dried with MgSO_4 and distilled under reduced pressure. 9.4 g (70%) of N-formyl piperidine were obtained at 45-47°C (2 torr). (New compound).

^1H NMR (CDCl_3) δ = 1.56 (m, 6H); 3.40 (m, 4H); 7.96 (s, 1H).

IR ν_{max} = 1660 cm^{-1} strong sharp.

N-formyl pyrrolidine (15) was purchased from Aldrich Chemical company and distilled under reduced pressure. Boiling point 92-94°C at 15 torr.

Preparation of 2-methoxy(N-formyl) aniline

This was prepared as described by Comins and Meyers¹⁵⁷. The crude product was distilled under reduced pressure. The fraction which distilled at 110-115°C was collected and washed with saturated NaHCO_3 to remove phenol. It was recrystallized from CH_2Cl_2 and pet. ether (B.P. 30-60°C). 2-Methoxy (N-formyl) aniline was obtained in 67% yield. M.P. 84-85°C. (New compound)

^1H NMR (CDCl_3) δ = 3.86 (s, 3H); 7.00 (m, 4H); 8.43 (s, 1H).

IR ν_{max} = 1660 cm^{-1} strong broad. M.S. = 151, 123, 108, 80.

Preparation of 2-methoxy(N-formyl-N-methyl) aniline (16)

This compound was prepared according to the procedure described for the preparation of N-(N-formyl-N-methyl)amino piperidine. 2-methoxy(N-formyl-N-methyl) aniline was obtained in 89% yield. Boiling point 120°C at 3 torr.

^1H NMR (CDCl_3) δ = 3.16 (s, 3H); 4.80 (s, 3H); 7.10 (m, 5H);

8.13 (s, 1H). M.S. = 165, 137, 122, 106

IR ν_{max} = 1674 cm^{-1} strong sharp. Mol. Wt. = 165.0789 (from M.S.)

Preparation of N-formyl piperazine

To 25.8 g (0.3 mol) of piperazine were added 18.7 g (0.15 mol) of phenyl formate. The mixture was stirred at 60-65°C for 48 hrs. The crude product was subjected to distillation under reduced pressure. 12.5 g (38%) of N-formyl piperazine were collected. B.P. 112-116°C (2 torr).

^1H NMR (CDCl_3) δ = 2.60 (m, 5H); 3.33 (m, 4H); 7.96 (s, 1H).

IR ν_{max} = 1694 cm^{-1} strong broad.

Preparation of N-benzyl-N-formyl piperazine (17)

To 5.0 g (44 mmol.) of N-formyl piperazine were added 3.4 g (44 mmol.) of pyridine and 6.1 g (48 mmol.) of benzyl chloride. The mixture was stirred at room temperature for 15 hrs. To this was added 25 ml of water and the solution was made basic (pH=9) with sodium hydroxide. It was then extracted with CH_2Cl_2 (four times) and the combined organic solution was dried with MgSO_4 and concentrated. This crude product was then subjected to distillation under reduced pressure. 4.81 g (54%) of N-benzyl-N-formyl piperazine were obtained. B.P. 140-143°C (1 torr). New compound.

^1H NMR (CDCl_3) δ = 2.40 (t, 4H, $J=5\text{Hz}$); 3.40 (m, 6H); 7.20 (s, 5H); 7.96 (s, 1H).

IR ν_{max} = 1671 cm^{-1} strong sharp.

M.S = 204, 203, 175, 113, 91.

III.2.2.3. Formylation of Grignard and alkyl lithium reagents with different formylation reagents

General procedure for the formylation of Grignard reagents.

To a cooled (ice-bath) solution of the formylating agent (10 mmol.) in THF (10 ml) was added dropwise a solution of the Grignard reagent (10 mmol.) in THF (10 ml). When the reaction was complete (monitored by TLC) it was stirred for a further 5 min. and concentrated. The crude mixture was subjected to column chromatography using hexane/ethyl acetate (5:1) as the eluant. Aldehyde and the secondary alcohol (if there is any) were isolated.

Reaction of Phenyl magnesium bromide with N-(N-formyl-N-methyl)amino piperidine (10)

The reaction was carried out according to the general procedure described earlier. Benzaldehyde was isolated in 85% yield. No benzhydrol was present in the reaction mixture. Benzaldehyde was identified from its proton NMR and infrared spectra.

Reaction of Phenyl magnesium bromide with 2-(N-formyl-N-methyl)amino pyrimidine (11)

The reaction was carried out according to the general procedure described earlier. Benzaldehyde was isolated in 84% yield. No benzhydrol was present in the reaction mixture.

Reaction of Phenyl magnesium bromide with 2(N-formyl-N-methyl)amino thiazole (12)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 66% yield. Benzhydrol was isolated in 11% yield and was identified from its proton NMR and infrared spectra.

Reaction of Phenyl magnesium bromide with 2(N-formyl-N-methyl)amino pyridine (9)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 79% yield. No benzhydrol was isolated.

Reaction of Phenyl magnesium bromide with 2(N-benzyl-N-formyl)amino pyridine (13)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 77% yield. No benzhydrol was isolated.

Reaction of Phenyl magnesium bromide with N-formyl piperidine (14)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 64% yield and benzhydrol was isolated in 14% yield.

Reaction of Phenyl magnesium bromide with N-formyl pyrrolidine (15)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 63% yield. Benzhydrol was isolated in 9% yield.

Reaction of Phenyl magnesium bromide with 2-methoxy
(N-formyl-N-methyl) aniline (16)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 60% yield and benzhydrol was isolated in 11% yield.

Reaction of phenyl magnesium bromide with N-benzyl-N-formyl
piperazine (17)

The reaction was carried out according to the general procedure described before. Benzaldehyde was isolated in 65% yield and benzhydrol was isolated in 9% yield.

Reaction of phenyl magnesium bromide with DMF (18)

The reaction was carried out according to the general procedure described before. DMF was dried over phosphorus pentoxide and distilled again before use. Benzaldehyde and benzhydrol were isolated in 69% and 9% yield respectively.

Reaction of phenethyl magnesium bromide with N(N-formyl-N-
methyl)amino piperidine. (10)

The reaction was carried out according to the general procedure described before. 3-phenyl propionaldehyde was isolated in 86% yield. No secondary alcohol was isolated.

$^1\text{H-NMR}$ (CDCl_3) δ = 2.76 (m, 4H); 7.33 (s, 5H); 9.70 (s, 1H)

IR ν_{max} = 1720 cm^{-1} strong sharp, 2720 and 2820 cm^{-1} weak.

Reaction of phenethyl magnesium bromide with 2(N-formyl-
N-methyl)amino pyrimidine (11)

The reaction was carried out according to the general procedure described before. 3-phenyl propionaldehyde was isolated in 81% yield. No secondary alcohol was isolated.

Reaction of phenethyl magnesium bromide with N-formyl piperidine

The reaction was carried out according to general procedure described before. 3-phenyl propionaldehyde was isolated in 71% yield. 1,5-diphenylpentanol-3 was isolated in 9% yield.

^1H NMR δ = 1.96 (m, 4H); 2.70 (m, 4H); 3.60 (b.s, 1H); 4.76 (t, 1H, $J=5\text{Hz}$); 7.16 (s, 10H)

Reaction of phenethyl magnesium bromide with DMF (18)

The reaction was carried out according to general procedure described before. 3-phenyl propionaldehyde was isolated 67% yield. 1,5-diphenylpentanol-3 was isolated in 14% yield.

Reaction of phenyl acetylene magnesium iodide with N-(N-formyl-N-methyl)amino piperidine (10)

To a solution of 1.12 g (11 mmol.) of phenyl acetylene in 5 ml of THF were added 3.94 ml (11 mmol.) of methyl magnesium iodide (2.8 M solution in ether) dropwise at 0°C. The mixture was stirred at 0°C for 25 min. and was used in the formylation reaction. The rest of the procedure was similar to the general procedure for the formylation of Grignard reagents described before. The aldehyde, 3-phenyl-2-propynal was isolated in 73% yield. The secondary alcohol, 1,5-diphenyl-1,4-pentadiyne-3-ol was isolated in 1% yield. They were identified from their proton NMR, infrared and Mass spectra. When the reaction was done at -10°C, the aldehyde was isolated in 80% yield. No secondary alcohol was formed.

Aldehyde: ^1H NMR (CDCl_3) δ = 2.00 (m, 4H); 2.76 (m, 4H); 3.60 (b.s, 1H); 7.43 (m, 5H); 9.40 (s, 1H)

IR $\nu_{\max}$ = 1650 cm^{-1} strong sharp, 2225 cm^{-1} strong sharp, 2720 and 2825 cm^{-1} weak.

Alcohol: ^1H NMR (CDCl_3) δ = 2.66 (b.s, 1H); 5.56 (s, 1H); 7.33 (m, 10H); M.S. = 233, 215, 202, 129, 102

IR $\nu_{\max}$ = 2225 cm^{-1} strong sharp.

Reaction of phenyl acetylene magnesium iodide with N-formyl piperidine. (14)

This reaction was carried out according to the procedure described for the reaction of phenyl acetylene magnesium iodide with N(N-formyl, N-methyl) amino piperidine. The aldehyde, 3-phenyl-2-propynal was isolated in 60% yield. The secondary alcohol, 1,5-diphenyl-1,4-pentadiyne-3-ol was isolated in 12% yield.

When the reaction was carried out at -10°C the aldehyde was isolated in 68% yield and the secondary alcohol in 10% yield.

Reaction of phenyl acetylene magnesium iodide with DMF (18)

The reaction was carried out according to the procedure described for the reaction of phenyl acetylene magnesium iodide with N(N-formyl - N-methyl) amino piperidine. The aldehyde was isolated in 64% yield. The secondary alcohol was isolated in 10% yield.

Reaction of Phenyl acetylene lithium with N-(N-formyl-N-methyl) amino piperidine (10)

To a solution of 0.56g (5.5 mmol.) of phenyl acetylene in 2.5 ml THF were added 2.5 ml (5.5 mmol.) of n-butyllithium (2.2 M solution in hexane) dropwise at 0°C . The mixture was

(145)

stirred at 0°C for 25 min. and used in the formylation reaction. The rest of the reaction procedure is similar to the general procedure for the formylation of Grignard reagents described before. 3-phenyl-2 propynal was isolated in 92% yield. No secondary alcohol 1,5-diphenyl-1,4-pentadiyne-3-ol was isolated.

Reaction of phenyl acetylene lithium with N-formyl piperidine
(14)

The reaction was carried out according to the procedure for the reaction of phenyl acetylene lithium with N-(N-formyl-N-methyl)amino piperidine described above. The aldehyde 3-phenyl-2-propynal was isolated in 71% yield when the reaction was done at -10°C. The secondary alcohol 1,5-diphenyl-1,4-pentadiyne-3-ol was isolated in 6% yield.

Reaction of phenyllithium with N-(N-formyl-N methyl) amino
piperidine (10)

Phenyllithium was purchased from Aldrich Chemical Company and used as is. The reaction procedure was similar to the general procedure described for the formylation of Grignard reagents. Benzaldehyde was isolated in 79% yield and benzhydrol was isolated in 5% yield.

When the reaction was done at -10°C no benzhydrol was formed. Benzaldehyde was isolated in 81% yield.

Reaction of Phenyllithium with 2-(N-formyl-N-methyl)amino
pyrimidine (11)

The reaction procedure was similar to the general procedure described for the formylation of Grignard reagents.

Benzaldehyde was isolated in 81% yield. No benzhydrol was isolated.

Reaction of Phenyllithium with N-formyl piperidine (14)

The reaction procedure was similar to the general procedure described for the formylation of Grignard reagents. When the reaction was done at -10°C , 68% benzaldehyde and 18% benzhydrol were isolated.

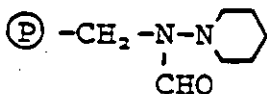
Reaction of Phenyllithium with DMF (18)

The reaction procedure was similar to the general procedure described for the formylation of Grignard reagents. When the reaction was done at -10°C 69% benzaldehyde and 9% benzhydrol were isolated.

III.2.2.4. Polymer supported formylation agents

III.2.2.5. Preparation of $\textcircled{\text{P}}-\text{CH}_2\text{I}$ from $\textcircled{\text{P}}-\text{CH}_2\text{Cl}$

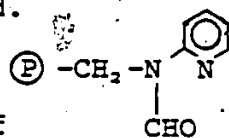
18 g (118 mmol.) of sodium iodide were dissolved in 50 ml of acetone and to this were added 10 g of $\textcircled{\text{P}}-\text{CH}_2\text{Cl}$ (4.0 mequiv g (D.F. 0.52)). The mixture was stirred at room temperature for 36 hrs. The polymer was filtered and washed with acetone (two times), water (four times), dioxane:water 2:1, methyl ethyl ketone (three times), and finally in a Soxhlet extractor with dioxane:water (80:20) for 24 hrs. The polymer was dried in vacuo at 40°C for 16 hrs. 13.52 g of polymer were obtained. D.F = 0.52.



III.2.2.6 Preparation of (24)

To a mixture of 2.11 g (17 mmol.) of potassium tert. butoxide in 20 ml of THF were added 1.96 g (15 mmol.) of N(N-formyl)amino piperidine under nitrogen. The reaction mixture was

stirred at room temperature for 15 min. and then at reflux temperature for 30 min. To this were added 3.50 g of $\text{P}-\text{CH}_2\text{I}$ (2.9 mequiv/g) and stirring was continued at reflux temperature for 48 hrs. The polymer was filtered, washed with THF, water (four times), THF:water (2:1) (three times), dioxane, CH_2Cl_2 and methanol. It was then dried in vacuo at 40°C for 16 hrs. 3.62 g of polymer were isolated. N analysis = 3.6 mequiv/g. D.F. = 0.25.



III.2.2.7. Preparation of $\text{P}-\text{CH}_2-\text{N} \begin{array}{c} \text{CHO} \\ \text{N} \end{array}$ (23)

The reaction procedure is similar to that described for the preparation of $\text{P}-\text{CH}_2-\text{N} \begin{array}{c} \text{CHO} \\ \text{N} \end{array}$ (24).

Using $\text{P}-\text{CH}_2\text{I}$ (2.9 mequiv/g), a polymeric reagent (23) with 3.01 mequiv.N/g was obtained after the reaction. D.F. = 0.19.

III.2.2.8. Preparation of $\text{P}-\text{CH}_2-\text{N} \begin{array}{c} \text{N-CHO} \end{array}$ (25)

To a dispersion of 6.0 g of $\text{P}-\text{CH}_2\text{Cl}$ (2.5 mequiv/g) (D.F. 0.30) in 30 ml of DMF was added 5.13 g (45 mmol.) of N-formyl piperazine. The reaction mixture was stirred at 90°C for 72 hrs. The polymer was filtered, washed with DMF, water (several times), dioxane, 0.5 N NaOH (30 ml of 0.5 NaOH with 10 ml dioxane and the polymer was left in the mixture for 60 min.), water (several times), dioxane/water (2:1), dioxane, CH_2Cl_2 and finally with methanol. The polymer was dried in vacuo for 16 hrs. at 40°C . 7.06 g of polymer were obtained. D.F. = 0.28. IR ν_{max} = 1670 cm^{-1} . N analysis = 4.0 mequiv/g.

III.2.2.9. General procedure for Formylation of Grignard reagents with polymeric formylation agents

12 mmol (60g) of polymeric reagent was dispersed in 40 ml of THF and to this were added dropwise 18 mmol (3.2g) of phenyl magnesium bromide in 20 ml of THF and the reaction was stirred at room temperature for 3-4 hrs. To this were added 25 ml of 5% HCl and stirred for a further 15 min. The polymer was filtered and washed with THF (two times). The combined filtrate was extracted with ether (four times). The combined organic solution was dried with MgSO_4 and the solvents were evaporated under reduced pressure. The crude product was then subjected to column chromatography using hexane:ethyl acetate (5:1) as the eluant. Benzaldehyde was isolated and the results are shown in Table (8). The same reaction was carried out at 60°C with the reagent (25) and the benzaldehyde was isolated in 60% yield. No benzhydrol was isolated.

III.2.2.10. Regeneration of spent polymeric formylation agent

The polymer obtained after the formylation reaction was washed with 0.5N NaOH (30 ml of 0.5 NaOH and 10 ml dioxane), water (several times), dioxane:water (2:1), dioxane, CH_2Cl_2 and methanol and dried in vacuo at 40°C for 16 hrs. To this polymer was added phenyl formate sufficient to make a suspension and the mixture was stirred at 55-60°C for 48 hrs. The polymer was filtered, washed with CH_2Cl_2 (four times), dioxane, ether (twice) and methanol and dried under vacuum at 40°C for 16 hrs.

III.2.2.11. Préparation of (P) -CHO from (P) -Li with different formylation agents.

General procedure

To 1 g of (P) -Br (2.99 mequiv/g) in 5 ml of benzene were added 2.5 ml of n-butyllithium (2.4 M in hexane) and the mixture was stirred under nitrogen at 55°C for 2 1/2 hrs. The polymer was filtered, washed with benzene (two times) and THF (two times). It was then dispersed in 5 ml of THF, cooled to room temperature and to this was added 9 mmol of formylation agent. The mixture was stirred at room temperature for 2 hrs. To this were added 5 ml of 5% HCl and stirring was continued for a further 15 min. The polymer was filtered, washed with THF, water (several times), acetone and then in a Soxhlet extractor with dioxane/water (80:20) for 16 hrs. The polymer was dried under vacuum at 40°C for 16 hrs.

Preparation of (P) -CHO from (P) - Li with excess DMF

The reaction was carried out according to general procedure described earlier. Instead of 9 mmol of DMF a large excess was used.

Preparation of (P) -C=N-OH from (P) -CHO

General Procedure

To 0.5 g of (P) -CHO, prepared as described earlier, in 5 ml of pyridine was added 0.315 g of hydroxylamine hydrochloride and the mixture was stirred at room temperature for 16 hrs. The polymer was filtered and washed with pyridine (two times), water (three times), water/dioxane (1:2), dioxane, THF and methanol. It was dried under vacuum at 40°C for 16 hrs.

The polymers were characterized by their IR spectra and nitrogen analysis. (Table(7)).

III.2.3. Chiral polymer-supported oxazolines for asymmetric synthesis

III.2.3.1. Preparation of imino ether (53)¹⁵⁹

To 50 g of freshly distilled acetonitrile were added 58.0 ml of anhydrous ethanol. Dry HCl gas was bubbled through this solution for 6 hrs. at room temperature. To this were then added 200 ml of dry ether and the mixture was cooled in a dry-ice/acetone bath. The solid formed was crushed, washed with dry ether and dried under vacuum at 40°C for 16 hrs. 99.5 g (80%) of imino ether (53) were obtained. M.P. 97-98°C.

¹H NMR (CDCl₃) δ = 1.30 (t, 3H, J=7Hz); 2.85 (q, 2H, J=7Hz); 4.70 (m, 2H).

IR ν_{max} = 1657 cm⁻¹ strong broad.

III.2.3.2. Preparation of oxazoline (35)¹⁵⁹

75 g (0.34 mol) of imino ether (53) were dispersed in 300 ml. of CH₂Cl₂, cooled to 0°C and to this were added 91.5 g. (0.55 mol) of (1S,2S)-(+)-2-phenyl-2-amino-1,3-propanediol. The mixture was stirred at 0°C for 8 hrs., poured onto 150 g of crushed ice and mixed thoroughly. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (three times). The combined organic solution was dried with MgSO₄ and solvent was evaporated under reduced pressure. The solid obtained was dissolved in 200 ml of ether and cooled in dry-ice acetone. The crystals obtained were filtered, washed with cold ether and dried under vacuum at room temperature for 16 hrs.

90.6 g (81%) of oxazoline (35) were obtained. M.P. 58-60°C.

^1H NMR (CDCl_3) δ = 1.16 (t, 3H, $J=8\text{Hz}$); 2.43 (q, 2H, $J=7\text{Hz}$); 3.83 (m, 4H); 5.33 (d, 1H, $J=8\text{Hz}$); 7.26 (s, 5H)

IR ν_{max} = 1670 cm^{-1} strong sharp.

III.2.3.3. Preparation of oxazoline (54) 159

To a stirred dispersion of 6.3 g (0.26 mol) of sodium hydride in 25 ml THF were added 45.0 g (0.22 mol) of oxazoline (38) in 125 ml of THF dropwise. The reaction mixture was then stirred at reflux temperature for 3 1/2 hrs. and allowed to cool to room temperature. To this were then added 40.5 g (0.28 mol) of methyl iodide in 25 ml of THF dropwise and stirring was continued at room temperature for 16 hrs. It was then poured onto 200 g of crushed ice and mixed thoroughly. The organic layer was separated and the aqueous layer was extracted with ether (four times). The combined organic solution was dried with MgSO_4 and the solvents were evaporated under reduced pressure. The crude product was subjected to distillation under reduced pressure. 43.9 g (91%) of oxazoline (54) were collected. Boiling point 120-125°C at 4 torr.

^1H NMR (CDCl_3) δ = 1.33 (t, 3H, $J=8\text{Hz}$); 2.46 (q, 2H, $J=8\text{Hz}$); 3.56 (m, 5H); 4.20 (m, 1H); 5.35 (d, 1H, $J=7\text{Hz}$); 7.36 (s, 5H).

IR ν_{max} = 1670 cm^{-1} strong sharp.

III.2.3.4. Preparation of amino alcohol (29) 159

To 43 g of oxazoline (54) were added 230 ml of 3N HCl and the mixture was stirred at reflux temperature for 5 hrs., then allowed to cool to room temperature. This solution was made basic (pH9) by adding NaOH. It was then extracted with ether (four times). The combined organic solution was dried

with MgSO_4 and solvent was evaporated. The crude product was then dissolved in 25 ml of ether and cooled in an ice bath for crystallization. Crystals were filtered, washed with cold ether, and dried under vacuum at room temperature for 16 hrs.

25.5 g (71%) of amino alcohol (29) were obtained. M.P. 48-50°C.

^1H NMR (CDCl_3) δ = 2.46 (b.s, 3H); 3.06 (q, 1H, J 7Hz), 3.86 (m, 1H), 5.35 (d, 1H, J=7Hz); 7.36 (s, 5H).

$[\alpha]_D^{25} = +24.3^\circ$ (c=2, CHCl_3)

III.2.3.5. Attempted preparation of oxazoline (38).

5.0 g (10 mmol) of oxazoline (35) were dissolved in 60 ml of pyridine cooled in an ice bath and to this solution were added 10 g (15 mmol) of freshly crystallized p-toluenesulfonyl chloride. This was stirred until all the p-toluenesulfonyl chloride was dissolved and then left in the freezer for 24 hrs. It was then poured into 400 g of ice-water and stirred for 15 min. The crude organic layer was separated and the aqueous layer was extracted with ether (three times). The combined organic solution was dried with MgSO_4 and the solvents were evaporated. Crystallization was attempted with ether/pet. ether (B.P. 30-60°C) (2:1). 2.0 g of white solid was isolated. The proton NMR of this compound was complex and did not agree with that expected for oxazoline (38).

III.2.3.6. Preparation of oxazoline (39)

2.05 g (10 mmol) of oxazoline (35) were dissolved in 10 ml of dry CCl_4 and to this solution were added 3.4 g (13 mmol) of triphenylphosphine. The mixture was stirred at reflux

temperature for 1 hr. The reaction was stopped and to this was added 5 ml of pet. ether (B.P.30-60°C). The precipitate was filtered, the solvents were evaporated from the filtrate, and the crude was subjected to column chromatography using benzene/methanol (50:1) as the eluant. 1.83 g (77%) of oxazoline (39) was obtained. Pale yellow oil. (New compound)

$^1\text{H NMR}$ (CDCl₃) δ = 1.23 (t, 3H, J=8Hz); 2.40 (q, 2H, J=8Hz); 3.63 (m, 2H); 4.23 (m, 1H); 5.33 (d, 1H, J=6Hz); 7.33 (s, 5H).

IR ν_{max} = 1670 cm⁻¹ strong sharp.

M.S. = 223, 130, 117, 82.

III.2.3.7. Preparation of oxazoline (40)

2.05 g (10 mmol) of oxazoline (35) were dissolved in 10 ml. of acetonitrile under nitrogen and to this were added 3 g (20 mmol) of NaI and 1.21 g (12 mmol) of triethylamine. To this stirred solution was added 1.08 g (10 mmol) of chlorotrimethylsilane. The stirring was continued at room temperature for 3 hrs. and then the reaction was poured onto 50 g of ice-water mixture. The organic layer was separated and the aqueous layer was extracted with ether (three times). The combined organic solution was washed once again with water, 5% Na₂S₂O₃, brine, dried with MgSO₄ and the solvents were evaporated. 2.64 g (80%) of oxazoline (40) were obtained. (New compound).

$^1\text{H NMR}$ (CDCl₃) δ = 1.13 (t, 3H, J=8Hz); 2.26 (q, 2H, J=7Hz); 3.66 (m, 3H); 5.20 (d, 1H, J=7Hz); 7.10 (s, 5H)

IR ν_{max} = 1670 cm⁻¹.

III.2.3.8. Preparation of Oxazoline (37)a) Under phase transfer conditions.

To a solution of 0.20g (1mmol.) of oxazoline (39) in 2 ml. of 1,2-dichloroethane were added 0.19 (3mmol.) of phenol, 2 ml of 5N NaOH and 20 mg of tert. butyl ammonium hydroxide and the reaction mixture was stirred at room temperature for 5 hrs. It was extracted with methylene chloride (three times) and the solvents were evaporated under reduced pressure. The crude product was subjected to column chromatography using ether - pet.ether (B.P. 30-60 °C). 0.15g of hydroxy-methyl oxazoline (35) was isolated as the only product.

b) Under homogeneous conditions.

To a solution of 0.20g (1mmol.) of oxazoline (39) in 3 ml. of DMSO was added 0.33g (3mmol.) of freshly prepared potassium phenolate and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC and the starting material remained unchanged even after 15 hrs.

III.3. Synthesis of optically active polymers

III.3.1. Preparation of polymers with chiral substituents in the side chain

III.3.1.1. Preparation of p-acetyl,(2-chloroethyl)benzene (39)

48 g (0.61 mol) of acetyl chloride were dissolved in 80 ml of 1,2-dichloroethane and to this were added 45 g (0.34 mol) of aluminum chloride while cooling. This solution was then added to 40.5 g (0.29 mol) of (2-chloroethyl)benzene in 100 ml of 1,2-dichloroethane over a period of 10 min. with stirring. The stirring was continued for 75 min. and the reaction mixture was poured slowly onto a mixture of 500 g of crushed ice and 100 ml of concentrated HCl. They were mixed thoroughly, the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (two times). The combined organic solution was washed with 10% HCl, 10% NaOH and finally with water. It was then dried with MgSO₄ and the solvents were evaporated. The crude product was then subjected to distillation under reduced pressure. The fraction boiling at 109-113°C (2 torr) was collected and weighed. 45.1 g (90.4%) of p-acetyl(2-chloroethyl)benzene (43) were isolated. Pale yellow oil.

¹H NMR (CDCl₃) δ = 2.60 (s, 3H); 3.13 (t, 2H, J=7Hz); 3.76 (t, 2H, J=7Hz); 7.33 (d, 2H, J=8Hz); 7.90 (d, 2H, J=8Hz)

IR ν_{max} = 1685 cm⁻¹ strong sharp, 2240 cm⁻¹ weak.

III.3.1.2. Preparation of p-acetyl(2-cyanoethyl)benzene (44)

To 5.92 g (0.12 mol) of sodium cyanide in 30 ml of dimethyl sulfoxide were added 20 g (0.11 mol) of p-acetyl(2-chloroethyl)benzene. The mixture was then stirred at 130°C for 4 hrs. It was allowed to cool to room temperature and to this were added 100 ml of water. This solution was then extracted with ether (five time). The combined organic solution was washed with water (three times), dried with MgSO_4 and solvents were evaporated. The crude was subjected to distillation under reduced pressure. 14.02 g (79%) of p-acetyl(2-cyanoethyl)-benzene (44) were obtained. Boiling point 152-154°C at 2 torr. Colourless oil. (New compound).

^1H NMR (CDCl_3) δ = 2.83 (m, 7H); 7.26 (d, 2H, J = 8Hz); 7.83 (d, 2H, J =8Hz).

IR ν_{max} = 1685 cm^{-1} strong sharp, 2240 cm^{-1} weak

M.S. = 173, 158, 130, 118, 103.

III.3.1.3. Preparation of p-1-hydroxyethyl(2-cyanoethyl)benzene (45)

To a stirred solution of 14 g (80 mmol) of p-acetyl(2-cyanoethyl)benzene in 30 ml of ethanol was added 1.65 g (45 mmol) of sodium borohydride. The stirring was continued at room temperature for 2 hrs. To this were added 75 ml of 1% NaOH and mixed thoroughly. It was then extracted with ether (three times), the combined organic solution was dried with MgSO_4 , and the solvents were evaporated. 13.21 g (94%) of

p-1-hydroxyethyl(2-cyanoethyl)benzene (45) were obtained.

Colourless oil. (New compound).

^1H NMR (CDCl_3) δ = 1.50 (d, 3H, $J=6\text{Hz}$); 2.7 (m, 5H); 4.86 (q, 1H, $j=9\text{Hz}$); 7.20 (m, 4H).

IR ν_{max} = 2240 cm^{-1} weak, 3500 cm^{-1} strong broad.

III.3.1.4. Preparation of p-(2-cyanoethyl)styrene. (46)

0.38 g of 4-tert. butyl catechol was dissolved in 30.5g of p-1-hydroxyethyl(2-cyanoethyl)benzene and to this was added 0.38g of potassium bisulphate. The mixture was stirred at 190°C for 60 min. The water formed in the reaction was removed under reduced pressure from time to time during this period. The crude product was then subjected to high pressure liquid chromatography using hexane:ethyl acetate (3:1) as the eluant. 8.8g (32%) of p-(2-cyanoethyl)styrene (46) were obtained. Pale yellow oil. (New compound).

^1H NMR (CDCl_3) δ = 2.90 (m, 4H); 5.36 (d, 1H, $J(\text{cis})=8\text{Hz}$); 5.83 (d, 1H, $J(\text{trans})=16\text{Hz}$); 6.83 (q, 1H, $J(\text{cis})=8\text{Hz}$); 7.26 (d, 2H, $j=8\text{Hz}$); 7.50 (d, 2H, $J=8\text{Hz}$)

IR ν_{max} = 2240 cm^{-1} weak sharp

M.S. = 157, 128, 117, 102, 91, 77.

III.3.1.5. Preparation of styrene-p-(2-cyanoethyl)styrene co-polymer (47)

To 0.15 g of benzoyl peroxide in a special polymerization tube were added 6.0g (57 mmol) of styrene and 3.0g (19 mmol) of p-(2-cyanoethyl)styrene. They were mixed

well and the benzoyl peroxide was allowed to dissolve. The tube was then immersed in a liquid nitrogen bath and was evacuated. The tube was sealed and placed in an oven at 60°C for the polymerization to occur. The tube was taken out after 48 hrs., broken and the hard solid polymer was dissolved in CH₂Cl₂. The polymer was precipitated in methanol and dried under vacuum at 40°C for 16 hrs. 7.95 g (88%) of styrene-p-(2-cyanoethyl)styrene copolymer (47) were obtained.

¹H NMR (CDCl₃) δ = 1.00-3.10 (20 aliphatic hydrogens); 6.00-7.40 (19 aromatic-hydrogens)

IR $\nu_{\max}$ = 2245 cm⁻¹ weak sharp.

III.3.1.6. Preparation of polymeric imidate (48)

7.0 g of styrene-p-(2-cyanoethyl)styrene co-polymer were dissolved in 150 ml of dry dioxane and to this were added 100 ml of dry ethanol. Dry HCl gas was bubbled through this stirred solution for 8 hrs. The solvents were removed under reduced pressure until the total volume of the solution was about 4 ml. The polymer was precipitated in dry ether and dried under vacuum at 40°C for 16 hrs. 8.05 g of polymeric imidate (48) were obtained.

IR $\nu_{\max}$ = 1658 cm⁻¹ strong, 2800-3200 cm⁻¹ strong broad.

III.3.1.7. Preparation of polymeric oxazoline (49)

6.5 g of the polymeric imidate (48) were dispersed in 100 ml of CH₂Cl₂ and cooled in an ice bath. To this were added 3.2 g of amino alcohol (29) and stirring was continued at 0°C

for 8 hrs. The solvent was evaporated under reduced pressure and the polymer was dissolved in 3 ml of THF, then precipitated in water. It was filtered and dried under vacuum at 30°C for 16 hrs. 6.82 g of polymeric oxazoline (49) were obtained.

^1H NMR (CDCl_3) δ = 1.00-3.00 (16 aliphatic hydrogens); 3.00-3.70 (5 hydrogens); 3.90-4.20 (1 hydrogen); 5.20-5.40 (1 hydrogen); 6.10-7.40 (24 hydrogens)

IR ν_{max} = 1645 cm^{-1} strong sharp.

III.3.1.8. Preparation of polymeric oxazoline (50)

4.0 g of polymeric oxazoline (49) were dissolved in 75 ml of THF under nitrogen and to this was added at -78°C , 6.3 mmol of lithium diisopropylamide, prepared from 2.97 ml of *n*-butyllithium and 0.88 ml (6.3 mmol) of diisopropylamine. The reaction mixture was stirred at -78°C for 2 hrs. The temperature was decreased to -98°C using a liquid nitrogen-methanol bath and allowed to equilibrate for 30 min. To this was added 0.56 ml (6.3 mmol) of dimethyl sulfate in 15 ml of THF over a period of 30 min. Stirring was continued at -98°C for 5 hrs. and then at -78°C for 16 hrs., after which it was allowed to warm to room temperature. To this were added 4-5 drops of water and the solvents were removed under reduced pressure until the volume became about 4 ml. The polymer was precipitated in water, filtered and dried under vacuum at 30°C for 16 hrs. It was again dissolved in 3 ml of CH_2Cl_2 and reprecipitated in methanol. The polymer was filtered and dried under vacuum at 30°C for 16 hrs. 3.94 g of polymeric oxazoline (50) were obtained.

^1H NMR (CDCl_3) δ = 1.00-3.00 (19 aliphatic hydrogens); 3.00-3.70 (5 hydrogens); 3.90-4.20 (1 hydrogen); 5.20-5.40 (1 hydrogen); 6.10-7.40 (24 hydrogens)

IR ν_{max} = 1645 cm^{-1} strong sharp.

III.3.1.9. Preparation of polymeric carboxylic acid (51)

2 g of polymeric oxazoline (50) were dissolved in 25 ml of THF and to this were added 25 ml of 6N HCl. The mixture was then stirred at reflux temperature for 24 hrs. Solvents were evaporated under reduced pressure, and the polymer was dissolved again in 4 ml of THF, then precipitated in water. It was dried under vacuo at 40°C for 16 hrs. The polymer was dissolved again in 4 ml. of CH_2Cl_2 and reprecipitated in methanol and dried under vacuo at 40°C for 16 hrs. 1.78 g of polymeric carboxylic acid (51) were obtained.

IR ν_{max} = 1710 cm^{-1} strong sharp, 2500-3300 cm^{-1} broad.

$[\alpha]_D^{25}$ is given in Table (9).

III.3.1.10. Esterification of polymeric carboxylic acid (51) with diazomethane

0.5 g of polymeric carboxylic acid (51) was dissolved in 10 ml of THF and cooled in an ice bath. To this stirred solution were added 20 ml. of diazomethane solution (approximately 1.4 M in ether) slowly. The reaction mixture was stirred at 0°C for 1 hr. and the solvents were evaporated. The resulting polymer was dissolved in 2 ml of THF, precipitated in methanol, and dried under vacuum at 40°C for 16 hrs. 0.49 g of polymeric ester (52) was obtained.

$^1\text{H NMR}$ (CDCl_3) δ = 1.00-3.00 (18 aliphatic hydrogens); 3.50-3.80 (3 aliphatic hydrogens); 6.00-7.3 (19 aromatic hydrogens)

$\text{IR } \nu_{\text{max}}$ = 1738 cm^{-1} strong sharp.

$[\alpha]_{\text{D}}^{25}$ is given in Table (9).

III.3.2. Model studies

III.3.2.1. Preparation of (2-cyanoethyl)benzene (56)

6.9 g (0.12 mol) of sodium cyanide were dispersed in 90 ml of dimethyl sulfoxide and to this were added 15.0 g (0.08 mol) of (2-bromoethyl)benzene and the mixture was stirred at 130°C for 16 hrs. It was then allowed to cool to room temperature and to this were added 150 ml of water. This solution was extracted with ether (four times), and the combined organic solution was washed with water (three times), dried with MgSO_4 , and the solvents were evaporated. The crude was then subjected to distillation under reduced pressure. 8.96 g (84%) of (2-cyanoethyl)benzene (56) were obtained. Pale yellow oil.

$^1\text{H NMR}$ (CDCl_3) δ = 2.66 (m, 2H); 2.96 (m, 2H); 7.23 (s, 5H).

$\text{IR } \nu_{\text{max}}$ = 2245 cm^{-1} weak sharp.

III.3.2.2. Preparation of imino ether (57)

To 7.0 g (0.5 mol) of (2-cyanoethyl)benzene were added 3 ml (0.06 mol) of anhydrous ethanol, and dry HCl gas was bubbled through the stirred solution for 4 hrs. The reaction mixture was then left in the freezer overnight. The white-yellow solid was crushed, washed with dry ether and dried under vacuum at 30°C for 16 hrs. 10.01 g (88%) of imino ether (57) were isolated. White solid. (New compound).

$\text{IR } \nu_{\text{max}}$ = 1657 cm^{-1} strong broad.

Preparation of Oxazoline (58)

15.0 g (0.07 mol) of imino ether (57) were dispersed in 200 ml of dry CH_2Cl_2 , cooled in an ice bath and to this was added 13.9 g (0.077 mol) of amino alcohol (29). This was stirred at 0°C for 5 hrs. and then mixed with 150 g of crushed ice. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (two times). The combined organic solution was dried with MgSO_4 and the solvents were evaporated under reduced pressure. The crude product was then subjected to column chromatography using hexane/ethyl acetate (4:1) as the eluant. 13.58 g (66%) of oxazoline (58) were obtained. Pale yellow oil. (New coumped).

^1H NMR (CDCl_3) δ = 3.00 (m, 4H); 3.60 (m, 5H); 4.10 (m, 1H); 5.30 (d, 1H, $J=7\text{Hz}$); 7.26 (s, 10H).

IR ν_{max} = 1665 cm^{-1} strong sharp

M.S. = 295, 250, 222, 149, 105, 91.

Preparation of oxazoline (59)

7.37 g (25 mmol) of oxazoline (58) were dissolved in 100 ml of THF cooled to -78°C under nitrogen and to this was added 25 m.mol of lithium diisopropylamide prepared at -78°C by reacting 10.37 ml (25 mmol) of n-butyl lithium with 3.5 ml (25 mmol) diisopropylamine in 20 ml of THF. The reaction mixture was stirred at -78°C for 60 min. The temperature was decreased to -98°C and the reaction mixture was allowed to equilibrate for 30 min. To this were added 2.2 ml (25 mmol) of dimethyl sulfate in 25 ml of THF over a period of 25 min. Stirring was continued at -98°C for 5 hrs. and at -78°C for 16

hrs. The reaction mixture was allowed to warm up to room temperature and added to 100 g of crushed ice. The organic layer was separated and the aqueous layer was extracted with ether (three times). The combined organic layer was dried with MgSO_4 and the solvents were evaporated under reduced pressure. The crude product was purified by passing through a silica gel column using hexane/ethyl acetate (6:1) as the eluant. 5.56 g (72%) of oxazoline (59) were isolated. Pale yellow oil.

^1H NMR (CDCl_3) δ = 1.26 (m, 3H); 2.93 (m, 3H); 3.50 (m, 5H); 4.10 (m, 1H); 5.30 (d, 1H, $J=7\text{Hz}$); 7.26 (s, 10H).

IR ν_{max} = 1665 cm^{-1} strong sharp.

Preparation of chiral 3-phenyl-2-methyl propanoic acid (55)

To 4 g of oxazoline (59) were added 100 ml of 6N HCl and the mixture was stirred at reflux temperature for 26 hrs. The reaction mixture was allowed to cool and extracted with ether (three times). The combined organic solution was dried with MgSO_4 and concentrated. The crude product was subjected to column chromatography (silica gel) using benzene/methanol (10:1) as the eluant. 1.7 g (80%) of 3-phenyl-2-methyl propanoic acid (55) was isolated. Pale yellow oil.

^1H NMR (CDCl_3) δ = 1.16 (d, 3H, $J=6\text{Hz}$); 2.83 (m, 3H); 7.15 (s, 5H); 10.15 (s, 1H).

IR ν_{max} = 1710 cm^{-1} strong sharp, $2500\text{--}3300\text{ cm}^{-1}$ strong.

$[\alpha]_{\text{D}}^{25}$ = -19.4° [$C=2, \text{CHCl}_3$].

III.3.3. Preparation of polymers with main chain chirality

III.3.3.1. Preparation of polymeric imidate (63)

5.0 g of styrene-acrylonitrile copolymer (4.42 mmol N/g) were dissolved in 185 ml of anhydrous dioxane and to this were added 125 ml of anhydrous ethanol. Dry HCl gas was bubbled through this solution for 24 hrs. The solvents were removed under reduced pressure until the total volume was about 5 ml. The polymer was precipitated in anhydrous ether and dried under vacuum at 40°C for 16 hrs. 5.61 g of polymeric imidate (63) were obtained.

IR $\nu_{\max}$ = 1658 cm^{-1} strong sharp, 2500-3200 cm^{-1} strong.

III.3.3.2. Preparation of polymeric Oxazoline (64)

3.5 g of polymeric imidate (63) were dispersed in 75 ml of CH_2Cl_2 and cooled to 0°C. To this were added 3.04 g of amino alcohol(29) and the reaction mixture was stirred at 0°C for 16 hrs. The solvent was removed under reduced pressure, and the resulting polymer was dissolved in 5 ml of THF and precipitated in water. It was filtered and dried under vacuum at 40°C for 16 hrs. 3.85 g of polymeric oxazoline (64) were obtained.

^1H NMR (CDCl_3) δ = 0.80-2.50 (main chain aliphatic hydrogens); 3.00-3.40 (methoxy methyl hydrogens); 3.40-4.20 (methylene hydrogens and the hydrogen on the tert. carbon next to the nitrogen of the oxazoline ring); 5.80-6.20 (hydrogen on the tert. carbon next to the oxygen of the oxazoline ring); 6.50-7.50 (aromatic hydrogens).

IR $\nu_{\max}$ = 1645 cm^{-1} strong sharp. 2235 cm^{-1} weak sharp.

III.3.3.3. Preparation of polymeric oxazoline (65)

2.0 g of polymeric oxazoline (64) were dissolved in 100 ml of THF under nitrogen and the solution was cooled to -78°C . To this was added 5.1 mmol of lithium diisopropylamide prepared at -78°C by reacting 2.15 ml (5.1 mmol) of n-butyllithium and 0.45 g (5.1 mmol) of diisopropylamine in 15 ml of THF. The stirring was continued at -78°C for 2 hrs. The reaction temperature was decreased to -98°C and allowed to equilibrate for 30 min. To this was added 0.45 ml (5.1 mmol) of dimethyl sulfate in 10 ml of THF slowly over a period of 30 min. Stirring was continued at -98°C for 5 hrs. and then at -78°C for 16 hrs. It was allowed to warm up to room temperature, and 4-5 drops of water were added, mixed thoroughly, and the solution concentrated until total volume became about 4 ml. The polymer was precipitated in water, filtered and dried under vacuum at 40°C for 16 hrs. It was dissolved again in 4 ml of CH_2Cl_2 and reprecipitated in methanol and dried under vacuum at 40°C for 16 hrs. 1.99 g of polymeric oxazoline (65) were obtained.

^1H NMR in CDCl_3 was similar to that of (64) except for the three additional aliphatic hydrogens at $\delta = 0.80-2.40$.

IR $\nu_{\text{max}} = 1645$ strong sharp. 2235 cm^{-1} weak sharp.

III.3.3.4. Preparation of polymeric carboxylic acid (66)

1.5 g of polymeric oxazoline (65) were dissolved in 30 ml of THF and to this were added 25 ml of 6N HCl. The mixture was stirred at reflux temperature for 24 hrs. The solvent and

water were removed under reduced pressure, and the polymer was dissolved in 4 ml of THF and precipitated in water. It was filtered and dried under vacuum at 40°C for 16 hrs. The polymer was dissolved again in 4 ml of CH₂Cl₂, reprecipitated in methanol, filtered, and dried under vacuum at 30°C for 16 hrs.

1.25 g of polymeric carboxylic acid (66) were obtained.

¹H NMR (CDCl₃) δ = 0.80-2.50 (aliphatic hydrogens); 6.20-7.50 (aromatic hydrogens)

IR $\nu_{\max}$ = 1728 cm⁻¹ strong sharp, 2235 cm⁻¹ weak sharp.

III.3 ¹³C label studies

III.3.4.1. Preparation of ¹³C labelled oxazoline (68)

To a dispersion of 0.90 g of sodium hydride in 10 ml of THF was added a solution of 3.33 g of oxazoline (35) in 10 ml of THF under nitrogen. Stirring was continued at reflux temperature for 2 hrs. After the reaction mixture had cooled to room temperature, 3.0 g of ¹³C labelled methyl iodide (90% ¹³C enriched) in 5 ml of THF were added dropwise. Stirring was continued at room temperature for 5 hrs. The mixture was poured into 50 g of crushed ice and mixed thoroughly. The organic layer was separated and the aqueous layer was extracted with ether (three times). The combined organic solution was dried with MgSO₄ and the solvents were evaporated. The crude was then subjected to distillation (bulb to bulb) under reduced pressure. 3.40 g of ¹³C labelled oxazoline (68) were obtained. Pale yellow oil.

^1H NMR (CDCl_3) δ = 1.25 (t, 3H, $J=7\text{Hz}$); 2.33 (q, 2H, $J=7\text{Hz}$); 3.30 (d, 1H, $J=140\text{Hz}$); 3.50 (m, 2H); 4.03 (m, 1H); 5.22 (d, 1H, $J=7\text{Hz}$); 7.16 (s, 5H).

IR ν_{max} = 1665 cm^{-1} strong sharp.

III.3.4.2. Preparation of ^{13}C labelled amino alcohol (67)

To 3.30 g of ^{13}C labelled oxazoline (68) was added 15 ml of 3N HCl and the mixture was stirred at reflux temperature for 5 hrs. It was allowed to cool to room temperature and was made basic (pH9) by adding NaOH. This was then extracted with ether (four times). The combined organic solution was dried with MgSO_4 and concentrated. The crude was dissolved in 3 ml of ether and cooled in an ice bath. Crystals were filtered, washed with cold ether, and dried under vacuum at 30°C for 16 hrs.

1.88 g (69%) of ^{13}C labelled amino alcohol (67) were obtained.

White solid. M.P. $48-50^\circ\text{C}$.

^1H NMR (CDCl_3) δ = 2.30 (b.s, 3H, exchanged with D_2O); 3.00 (d, 3H, $J=140\text{Hz}$); 3.16 (m, 3H); 4.53 (d, 1H, $J=7\text{Hz}$); 7.30 (s, 5H).

$[\alpha]_D^{25} = +24.2^\circ$ ($c=2$, CHCl_3).

Preparation of ^{13}C labelled polymeric oxazoline (69)

The reaction was carried out according to the procedure described for the preparation of polymeric oxazoline (64) using ^{13}C labelled amino alcohol (67).

^1H NMR (CDCl_3) δ = 0.80-2.50 (main chain aliphatic hydrogens and half of the methoxy hydrogens); 3.40-4.40 (methylene hydrogens, the hydrogen on the tert. carbon

next to the nitrogen of the oxazoline ring and part of the methoxy methyl hydrogens); 5.80-6.20 (hydrogen on the tert. carbon next to the oxygen of the oxazoline ring); 6.50-7.50 (aromatic hydrogens).

IR $\nu_{\max}$ = 1645 cm^{-1} strong sharp.

^{13}C NMR (CDCl_3) δ = 59.8 ppm strong.

Preparation of ^{13}C labelled polymeric oxazoline (70)

The reaction was carried out according to the procedure described for the preparation of polymeric oxazoline (65) using ^{13}C labelled polymeric oxazoline (69).

^1H NMR in CDCl_3 was similar to that of polymer (69) except for the three additional hydrogens at δ = 0.80-2.40.

IR $\nu_{\max}$ = 1645 cm^{-1} strong sharp.

^{13}C NMR CDCl_3 = 59.8 strong.

Preparation of chiral polymeric carboxylic acid (71)

The reaction was carried out according to the procedure described for the preparation of polymeric carboxylic acid (66). ^{13}C labelled polymeric oxazoline (70) was used for this preparation.

^1H NMR (CDCl_3) δ = 0.80-2.50 (aliphatic hydrogens); 6.20-7.50 (aromatic hydrogens).

IR $\nu_{\max}$ = 1728 cm^{-1} strong sharp

^{13}C NMR (CDCl_3) very small band at δ = 59.8.

Preparation of ^{13}C labelled polymeric oxazoline (72)

The reaction was carried out according to the procedure described for the preparation of polymeric oxazoline (49) using ^{13}C labelled amino alcohol (67) and polymeric imidate (48).

^1H NMR (CDCl_3) δ = 0.80-3.00 (main chain aliphatic

hydrogens and half of the methoxy hydrogens); 3.00-4.40 (methylene hydrogens, the hydrogen on tert. carbon next to the nitrogen of the oxazoline ring and part of the methoxy methyl hydrogens); 5.0-0 (hydrogen on the tert. carbon next to the oxygen of the oxazoline ring); 6.50-7.50 (aromatic hydrogens).

IR $\nu_{\max}$ = 1667 cm^{-1} strong sharp

^{13}C NMR (CDCl_3) = 59.2 very strong.

Preparation of ^{13}C labelled polymeric oxazoline (73)

The reaction was carried out according to the procedure described for the preparation of polymeric oxazoline (50) using ^{13}C labelled polymeric oxazoline (72).

^1H NMR in CDCl_3 was similar to that of the polymer (72) except for the three additional hydrogens at δ = 0.80-3.00.

IR $\nu_{\max}$ = 1667 cm^{-1} strong sharp.

^{13}C NMR (CDCl_3) δ = 59.2 very strong.

Preparation of chiral polymeric carboxylic acid (74)

This reaction was carried out according to the procedure described for the preparation of polymeric carboxylic acid (51) using ^{13}C labelled polymeric oxazoline (73).

IR $\nu_{\max}$ = 1710 cm^{-1} strong sharp, 2500-3300 cm^{-1} strong.

Preparation of chiral polymeric carboxylic acid methyl ester (75)

This reaction was carried out according to the procedure described for the preparation of polymeric carboxylic acid ester (52) using polymeric carboxylic acid (74).

^1H NMR (CDCl_3) δ = 1.00-2.90 (aliphatic hydrogens);
3.40-3.60 (methyl ester group hydrogens); 6.00-7.20
(aromatic hydrogens).

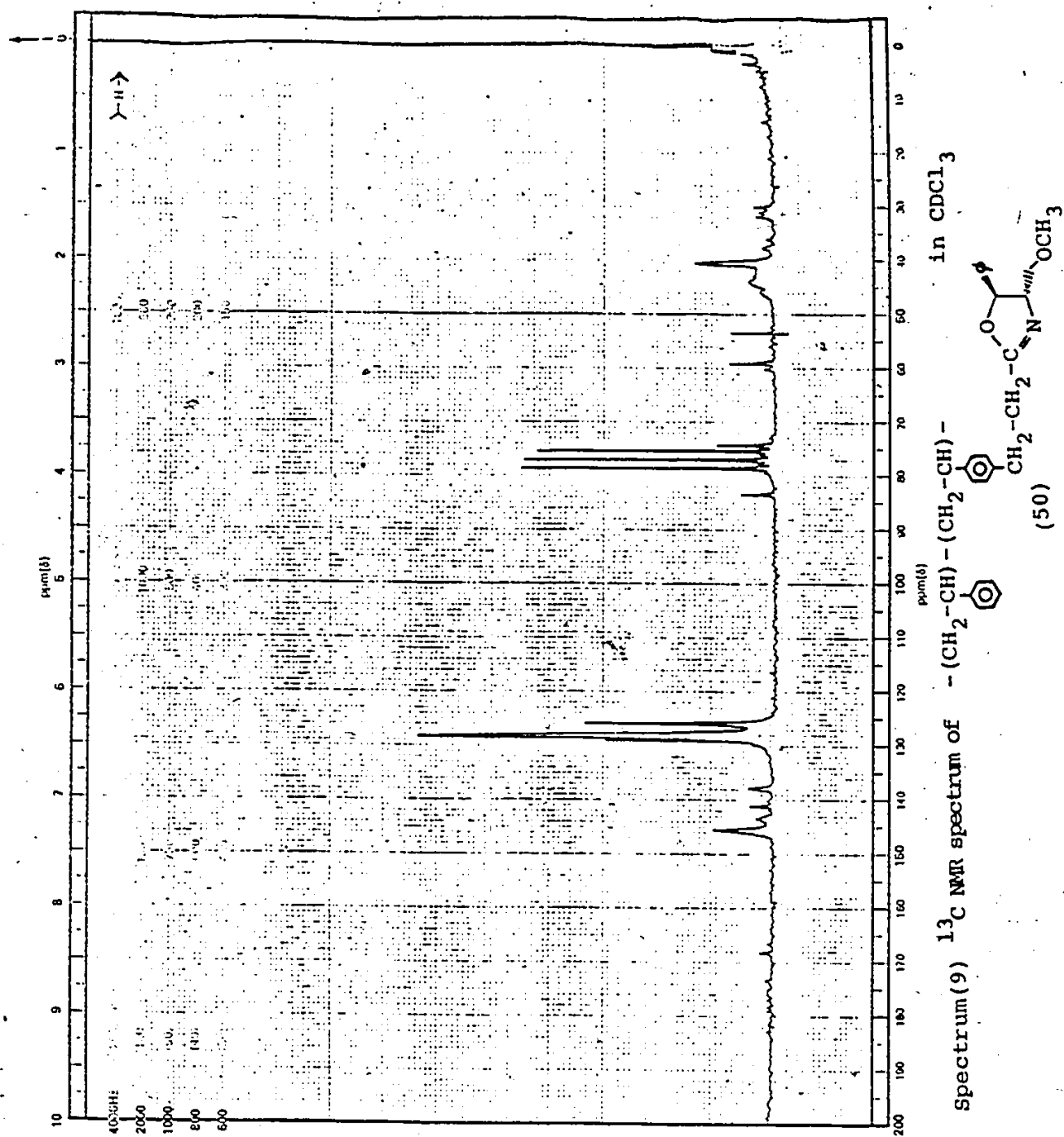
IR ν_{max} = 1738 cm^{-1} strong sharp

^{13}C NMR (CDCl_3) δ = 59.2 very weak, 173.9 weak broad.

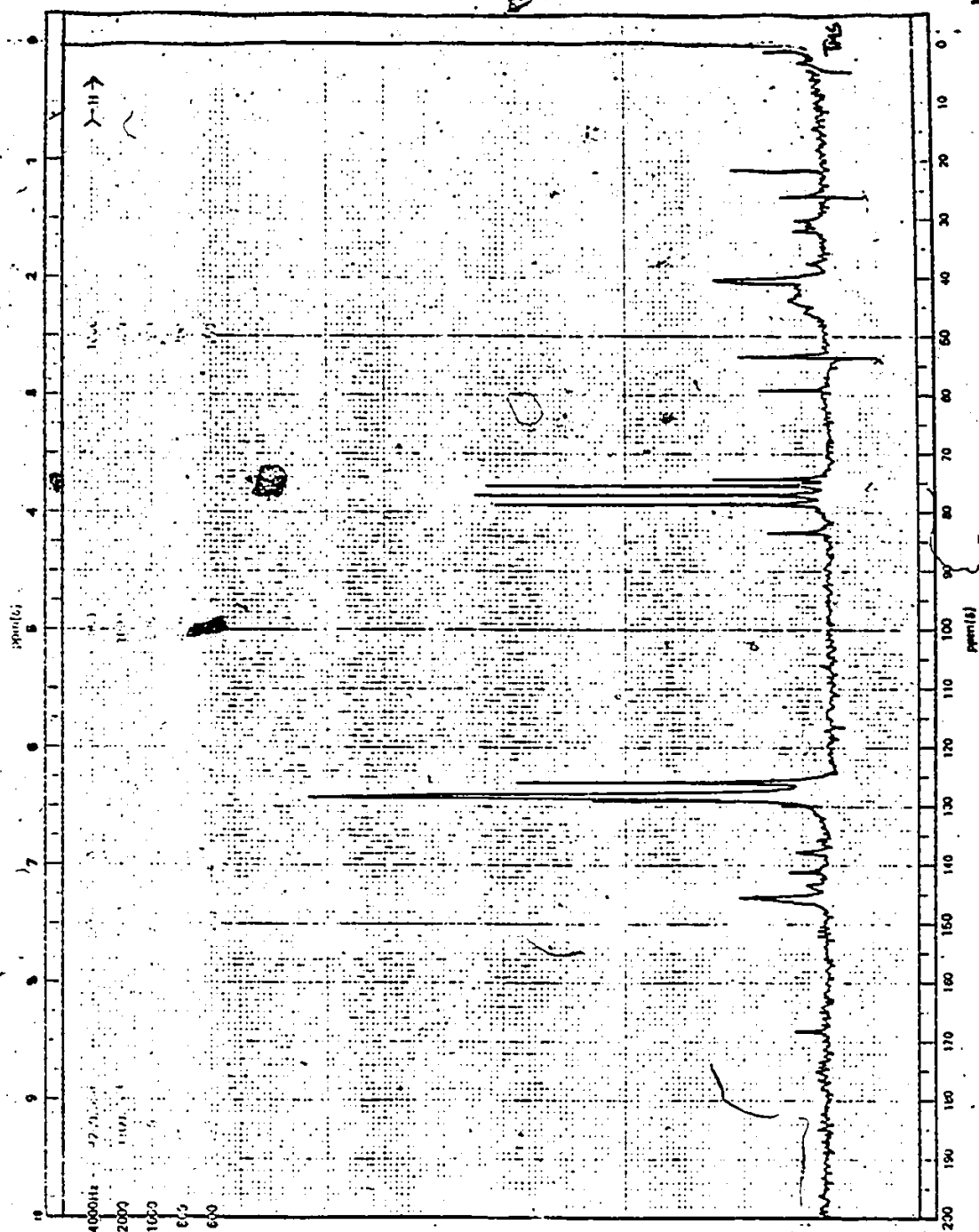
Claims to original research

1. Development of a a high capacity, fully recyclable polymer supported reagent agent for the reduction of carboxylic acid chlorides to aldehydes.
 2. Demonstration of the importance of the second nitrogen ligand in formylation reagents due to the formation of five and six-membered ring chelate intermediates in the formylation reactions of Grignard and alkyllithium compounds, which lead to the formation of aldehydes in very high yields.
 3. Development of polymer-supported formylation agents for Grignard and alkyllithium compounds, which were shown to be recyclable without any appreciable loss of activity.
 4. Synthesis of a chiral polymer with chiral side chains by a chemical modification of an achiral polymer with asymmetric induction.
 5. Synthesis of a chiral polymer with main chain chirality by a chemical modification of an achiral polymer with asymmetric induction.
- 

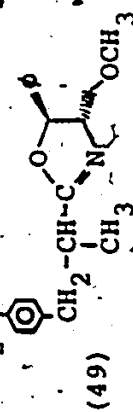
APPENDIX

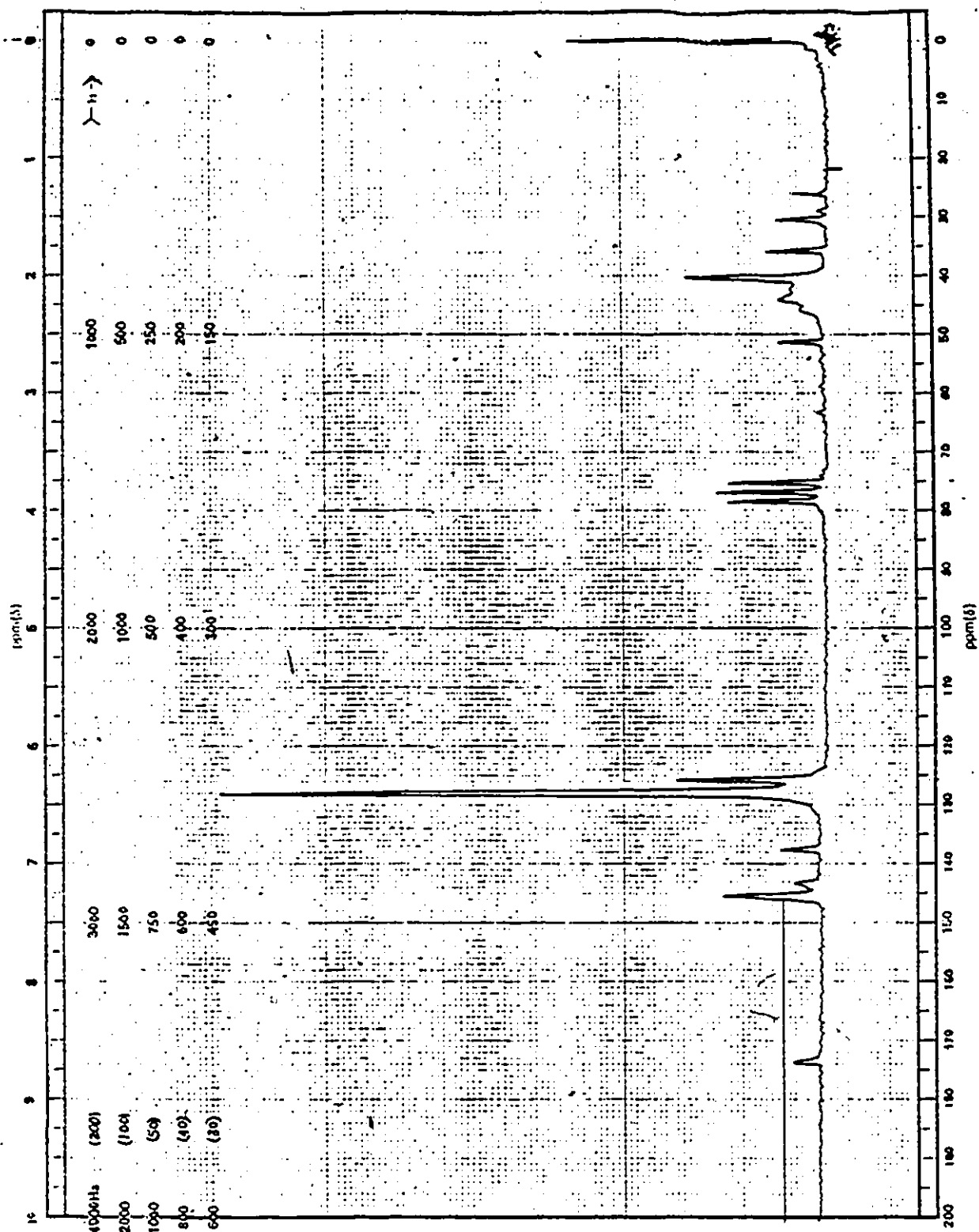


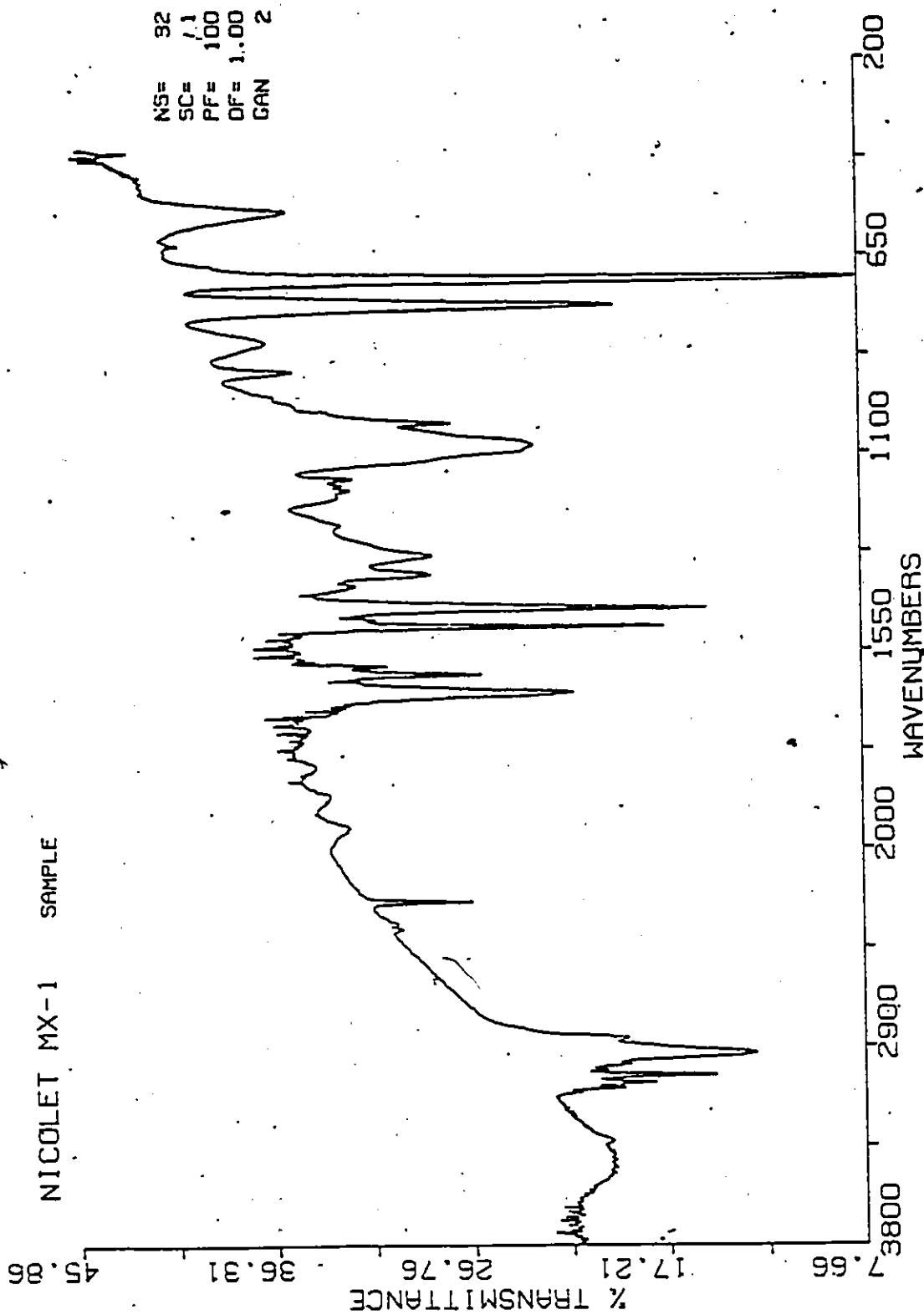
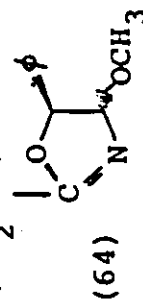
(173)

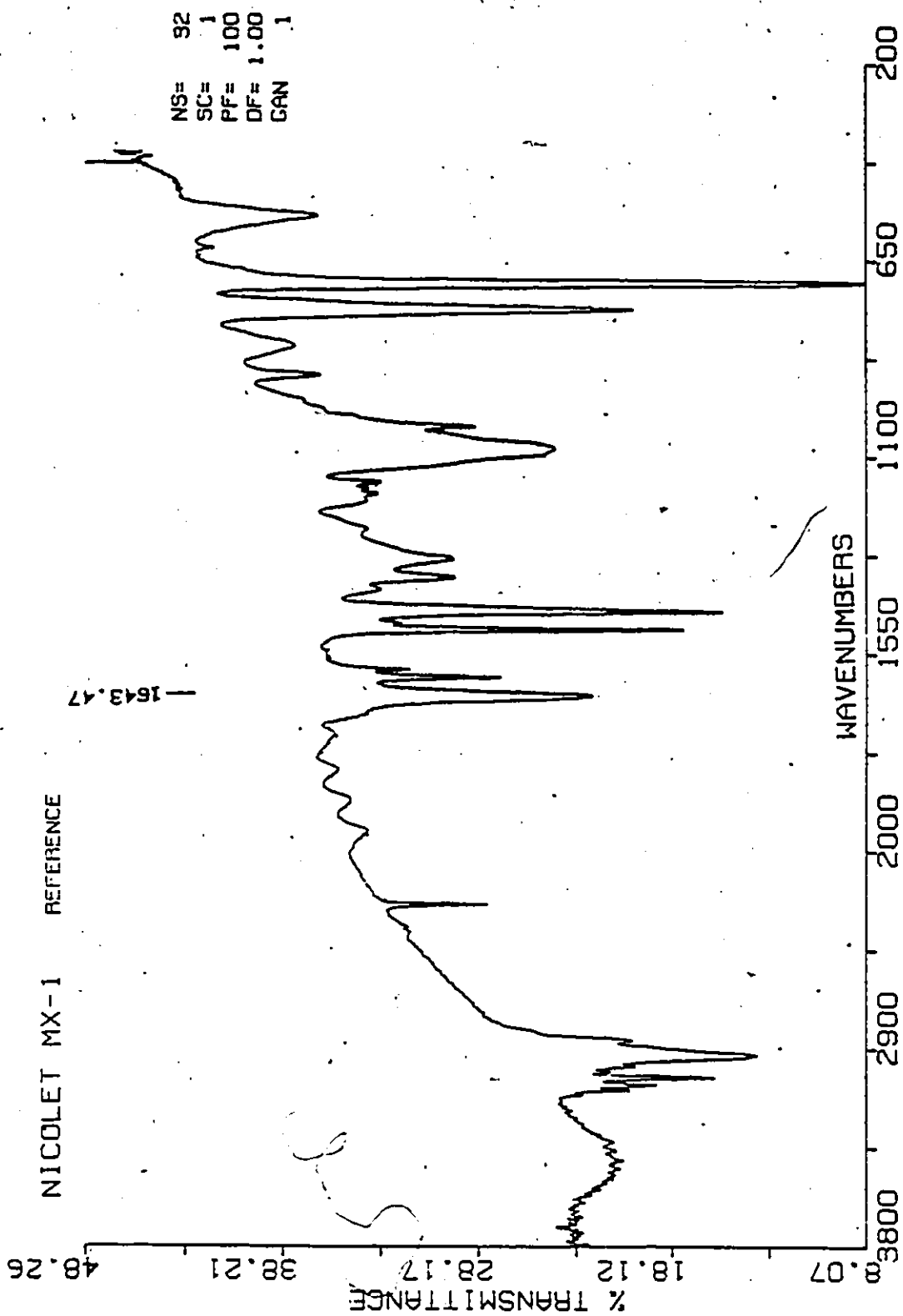


Spectrum (10) ^{13}C NMR spectrum of $-(\text{CH}_2-\text{CH})-(\text{CH}_2-\text{CH})-$ in CDCl_3

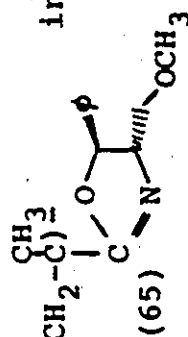




Spectrum (12) IR spectrum of $-(\text{CH}_2-\text{CH})-\text{C}_6\text{H}_5-(\text{CH}_2-\text{CH})-$ in KBr.

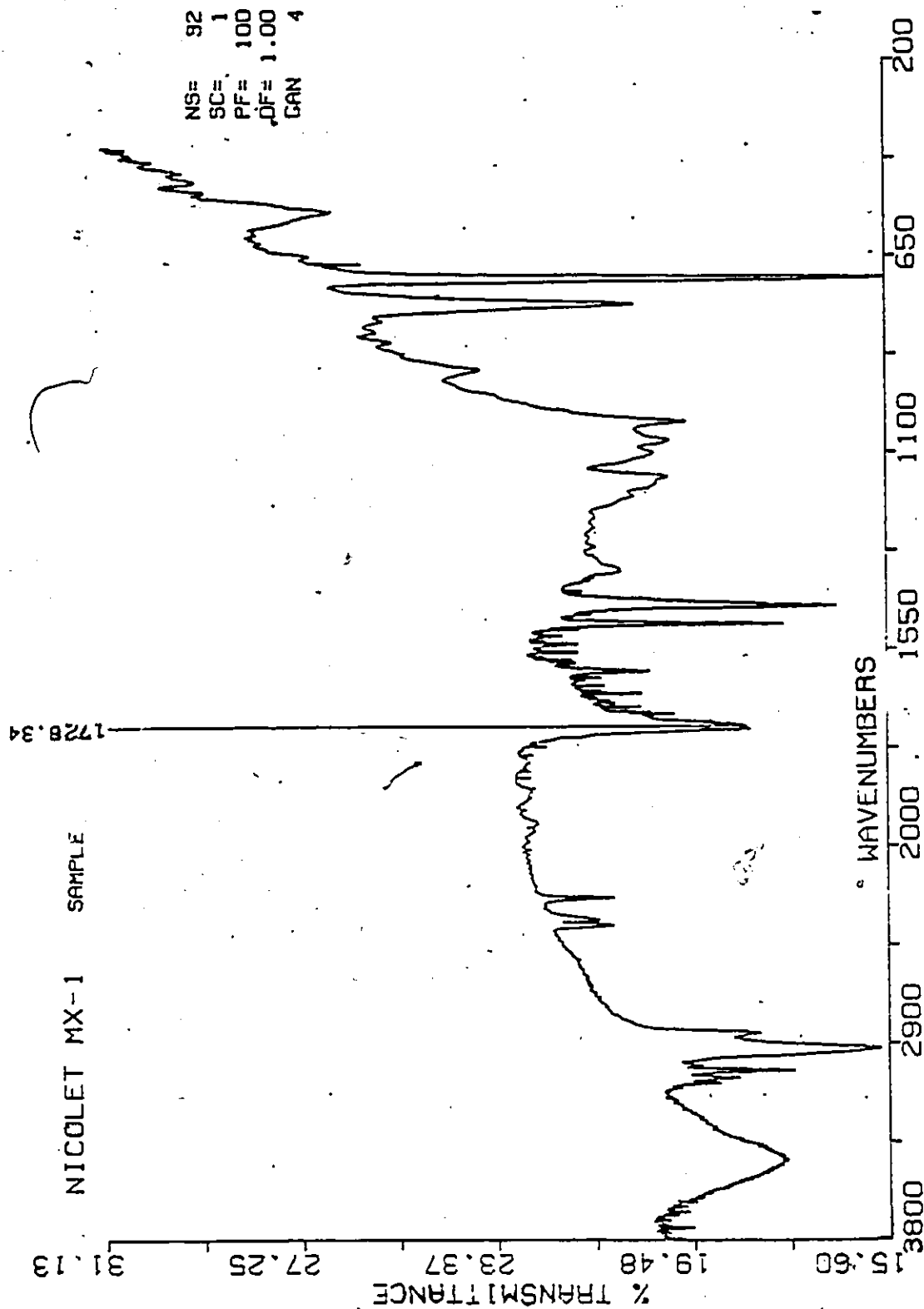


in KBr.

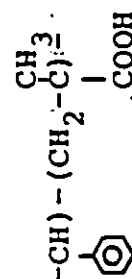


Spectrum(13) IR spectrum of

(177)

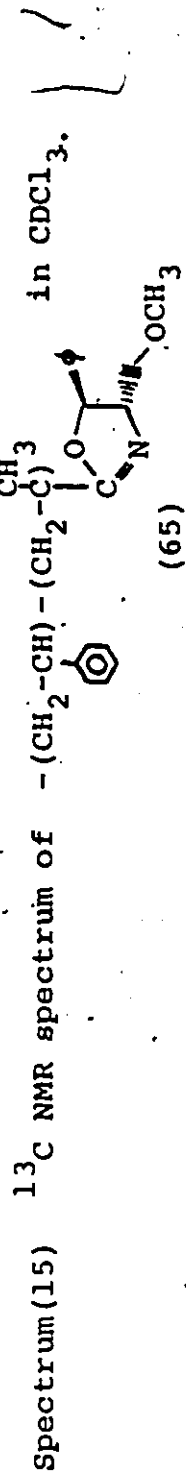


in KBr.

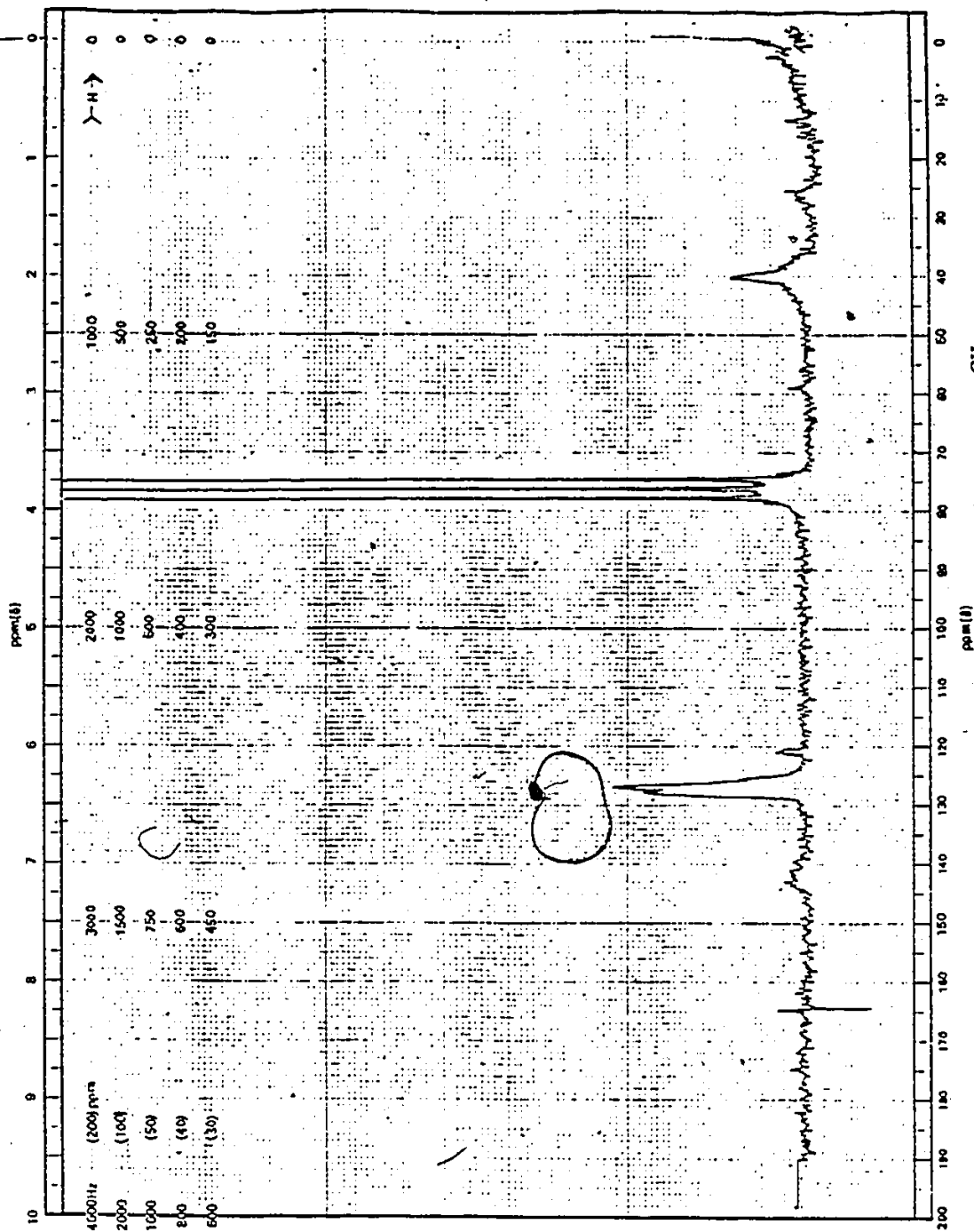


(66)

Spectrum(14) IR spectrum of



^{13}C NMR spectrum of $-(\text{CH}_2-\text{CH}(\text{CH}_3)-\text{C}(\text{CH}_3)_2)_n-$ in CDCl_3 .



Spectrum (16) ^{13}C NMR spectrum of $-(\text{CH}_2-\text{CH})_n-$ in CDCl_3 .
 CH_3
 COOH
 (66)

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1. W. Amaratunga and J.M.J. Fréchet. Polymeric Reagents. VII, Polystyryldiphenylphosphine Tetrahydroborate Copper (I), a new recyclable reducing agent. Polym. Prep., 22, 151 (1981).
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