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Polymer-Bound Chiral Auxiliaries in Asymmetric Hydride Reductions

by

Pierre Lecavalier

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of the requirements for the degree of

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UNIVERSITY OF OTTAWA

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1.]nonane
Bn	benzyl
b.p.	boiling point
c	concentration
C	Celsius
C.Y.	chemical yield
d	doublet
DF	degree of functionalization
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DVB	divinylbenzene
ee	enantiomeric excess
eqn	equation
g	gram
h	hour
HPLC	high pressure liquid chromatography
IR	infrared
LAH*	lithium aluminium hydride*
m	multiplet
meq	milliequivalent
min	minute
mmol	millimole
m.p.	melting point
MS	mass spectra
n-buLi	n-butyllithium
NMR	nuclear magnetic resonance

O.Y.	optical yield
Ph	phenyl
ppm	part per million
PS	polystyrene
PTSA	p-toluenesulfonic acid
q	quadruplet
RT	room temperature
s	singlet
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography

*In more recent publications a new, more systematic, nomenclature for hydrides has been adopted. For example

old	new
Lithium aluminium hydride	Lithium tetrahydroaluminate Lithium tetrahydridoaluminate
Lithium trialkoxyaluminium hydride	Lithium trialkoxyhydrido-aluminate

Because the majority of publications quoted here utilize the older terminology it is still used predominantly throughout the present thesis.

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ABSTRACT

The preparation of chiral amino alcohols which can be used in the asymmetric reduction of acetophenone is described. These amino alcohols were complexed with lithium aluminum hydride (LAH) and achiral agents in various ratios and once treated with acetophenone, afforded 1-phenylethanol in poor to moderate optical yields (20%-70%). These chiral molecules were grafted to 1% crosslinked polystyrene and the polymeric hydride complexes yielded 1-phenylethanol in lower optical yield than the model compounds. A detailed study of this behavior using l-ephedrine as the chiral auxiliary allowed us to conclude that site interactions as well as site accessibility were responsible for a decrease in the optical yield of the alcohol when the polymer-supported reagent was used in the reduction of the ketone. This polymer behavior is referred to as the "polymer effect". By making use of polymers with a low degree of functionalization, it was nonetheless possible to obtain optical yields comparable to that of the model molecules.

Some amino alcohols were also tested as complexes of diborane and similar optical yields to those of the aluminum hydride complexes were obtained. In order to study the limitation of polymer aluminum complexes vs the borane complexes, we attempted to prepare polymer-supported 83 and 84. Because of the lability of the benzyl ether bond, the desired polymers were not obtained in sufficiently high yield to allow their use in the reduction of acetophenone.

INTRODUCTION

1.1 HYDRIDES AS REDUCING AGENTS: GENERAL CONSIDERATIONS

The reduction of functional groups is probably one of the most useful transformations available to the synthetic chemist. As a consequence, organic chemists have developed a great variety of reducing agents which differ in strength and selectivity and which have been extensively studied with respect to both mechanism and kinetics.

Despite the fact that zinc, iron and hydrogen sulfide are among the oldest reducing agents and have been used for almost one hundred and fifty years , two major discoveries brought about the field as it is known today: catalytic hydrogenation (1897)[1] and reduction with metal hydrides (1947)[2]. This last group consists mainly of hydrides of the elements of the Main Groups I-IV and this study will focus on the use of derivatives of two specific ones; lithium aluminum hydride (LAH) and borane.

LAH is prepared by reacting lithium hydride with aluminum chloride in diethyl ether (eqn 1).

$$4LiH + AlCl_3 \longrightarrow LiAlH_4 + 3LiCl \qquad (1)$$

The precipitated lithium chloride is filtered off and solid LAH can be isolated after evaporation of the solvent.

Because of the hazards associated with handling powdered LAH, it is very often commercialized as a solution in various ethers. The most common solvents are diethyl ether and tetrahydrofuran (THF) in which the solubility of LAH at 25°C is respectively 35-40 and 13 g/100 mL of solvent.

The concentration of the hydride in these solvents is determined by gasometric analysis where water is added dropwise to a sample of the solution. The decomposition occurs as follows

$$LiAlH_4 + 4H_2O \longrightarrow LiOH + Al(OH)_3 + 4H_2 \qquad (2)$$

Thus 98.0 mL of hydrogen are evolved from the hydrolysis of 1.0 mL of a 1.0 M solution at 25°C and at normal pressure.

In spite of its great convenience LAH suffers from certain limitations. It is an exceedingly powerful hydride reagent, capable of reducing a very large number of organic functional groups. Consequently, it is quite difficult to apply this reagent to the selective reduction of a multifunctional molecule. It then becomes desirable to develop means of controlling the reducing power of LAH. One way to achieve this goal consists in decreasing the reactivity of LAH. This was done by replacing some of the hydrogens of LAH with alkoxy groups[3] (eqn 3).

$$LiAlH_4 + nROH \longrightarrow LiAlH_{4-n}(OR)_n + nH_2 \qquad (3)$$

Depending on the nature of R, these reagents were less reactive and more selective than LAH. For example, the reagent obtained from the reaction of three equivalents of methanol and LAH reduced acids to alcohols or nitriles to amines while these functional groups were inert towards lithium tri-tert-butoxyaluminium hydride[4].

Another way of controlling the reducing power of complex hydrides involved the development of other reagents such as diborane. Because of their Lewis acid properties these reagents exhibit entirely different relative reactivities towards functional groups.

Borane which is used in the form of a molar solution in THF was prepared from sodium borohydride and boron trifluoride etherate[5] (eqn 4).

$$3NaBH_4 + 4BF_3 + 4\ THF \longrightarrow 4\ THF\ BH_3 + 3NaBF_4 \quad (4)$$

The solution was stabilized with 5 mole % of sodium borohydride in order to minimize the loss of hydride due to cleavage of the solvent[6]. The concentration was also determined by gasometry according to eqn 5[7].

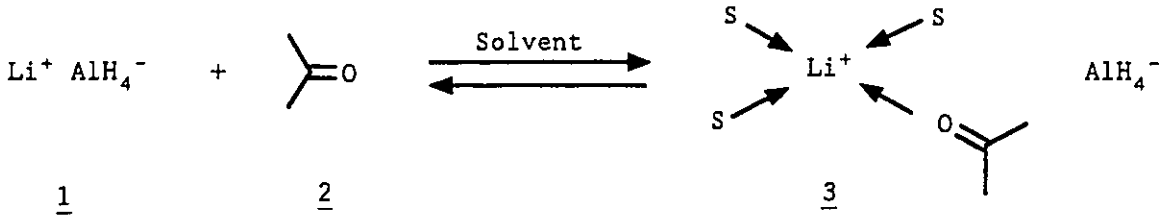
$$BH_3 + 3H_2O \longrightarrow H_3BO_3 + 3H_2 \quad (5)$$

In order to account for the stereochemical outcome of an asymmetric reduction it is first important to understand the mechanism of the reduction using simple metal hydrides. To explain this mechanism more information about the transition state of the reaction is needed.

The present study is limited to the reduction of ketones and no attempt is made to explain the behavior of the reagents towards other functional groups.

Ashby and Boone[8] have demonstrated that the first step in the reduction of ketones using LAH was the coordination of the carbonyl oxygen by the cation (scheme I). Involvement of the cation was supported by the observation that reductions with LAH were ten times faster than with $NaAlH_4$. This was explained by the stronger coordination of the carbonyl to the lithium cation as compared to sodium, which in turn, facilitated greatly the hydride transfer. As well, no reduction was observed in experiments where the cation was complexed with a crown ether[9] despite the fact that LAH is a powerful reducing agent. When $LiAlD_4$ was used instead of LAH the overall rate of the ketone disappearance was decreased by a factor of 1.27 indicating that the rate determining step was the hydride

Scheme I



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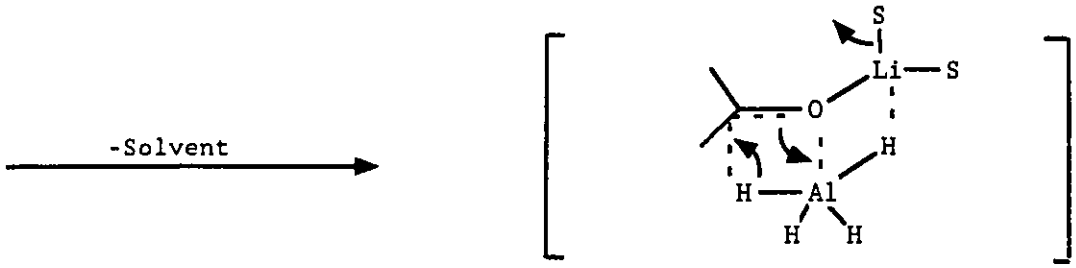

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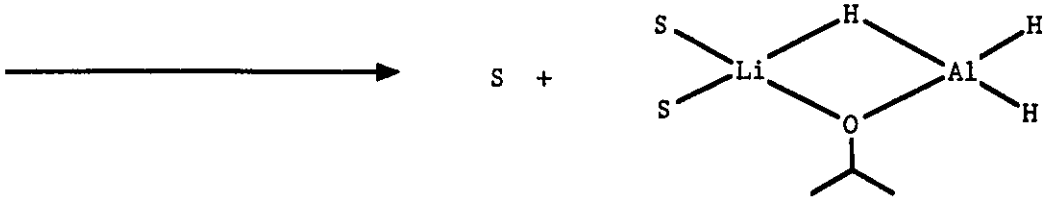

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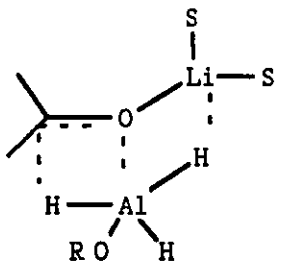

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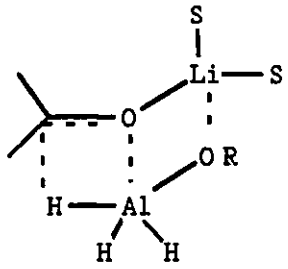

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transfer to the carbon atom of the carbonyl group. In addition, the entropy of activation for the reaction using LAH was smaller (more negative) than in the case of $NaAlH_4$. This required that the transition state for LAH reduction be more ordered than that of $NaAlH_4$. This is also in agreement with the weaker coordination capacity of sodium giving rise to a less rigid transition state.

The experimental findings allow the authors[8] to suggest that the cyclic structure 4 was the probable transition state in the obtention of alcohols. However, this model does not take into account the reaction of species 5 with a second and a third molecule of ketone which can yield dialkoxy- and trialkoxyaluminium hydride. This being the case, the hydride atom would compete with the oxygen of the alkoxide in complexing lithium (6 vs 7). This point was however not clarified by the authors.

It was proposed that alkoxyhydrides of secondary alcohols were not involved in the reduction of ketones, but as soon as they were formed they disproportionated to give LAH, which was the only effective reducing agent throughout the reaction[10]:

$$R_2CO + LiAlH_4 \longrightarrow LiAlH_3(OCHR_2) \qquad (6)$$

$$4LiAlH_3(OCHR_2) \longrightarrow LiAl(OCHR_2)_4 + 3LiAlH_4 \qquad (7)$$

Haubenstock and co-workers were the first researchers to propose this pathway on the basis of results they obtained from the reduction of substituted cyclohexanones. The reduction of cyclic ketones leading to the formation of a mixture of stereoisomers will be discussed later. Two groups, Brown in 1964[11] and Smith in 1977[12], offered experimental evidence to support the disproportionation mechanism. Through analytical means, Brown demonstrated that LAH reacted with isopropanol to give a precipitate

which contained no active hydride. On the other hand, the clear solution above the precipitate contained exclusively LAH. This study also showed that primary and tertiary alkoxyaluminium hydrides did not undergo disproportionation. Several other authors reported the stability of primary and tertiary alkoxides of aluminum[10,13,14].

Care should be taken when appling this mechanism to the simple reduction of ketones as LAH is known to react with some optically active secondary alcohols to give intermediates which were effective in inducing asymmetry in achiral ketones[15,16]. This last observation can only be explained on the basis of the existence of alkoxyhydrides of secondary alcohols even if it should be mentioned that these alcohols often contained a tertiary amine which stabilized the complexed hydride[16].

Having considered the nature of the transition state, one must also consider the stereochemistry of addition of hydride reagents to the carbonyl functionality.

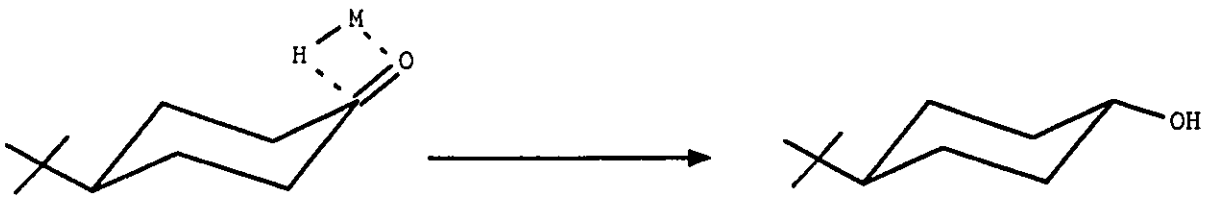
Two factors govern the nucleophilic attack by a complex hydride on a ketone group. The attack of a nucleophile can take place from the less crowded side of the molecule which is referred to as the steric approach or the steric strain control. Or the attack of the hydride can occur so as to give the thermodynamically most stable molecule, an effect called product development or product stability control. These two terms refer in a relative sense to the position of the transition state along the reaction coordinate, approach control inferring a reactant-like or early transition state such as in the case of hindered ketones and product development control a product-like or late transition state as for unhindered ketones.

However, application of the Hammond postulates[17] suggests that for a reaction of such high exothermicity and low activation energy, as the LAH reduction of ketones, the transition state should resemble the starting material rather than the product and therefore there would be no obvious reason why the relative stabilities of the two epimeric products should be reflected in the transition states leading to them. So it may be assumed that product control is more affected by the steric approach than by the stability of the product even if there has been some controversy about the contribution of the latter effect to the stereochemical outcome of the reduction[18].

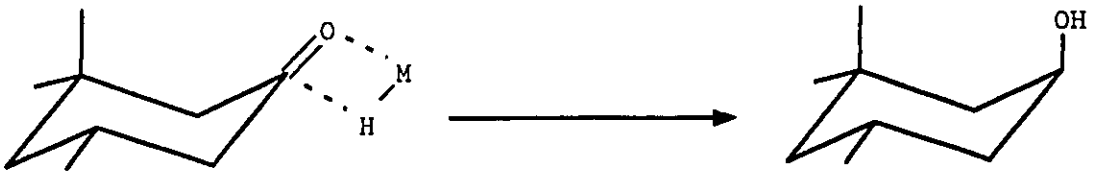
As was mentioned above, the stereoselectivity of the process and the stereochemistry of the products is of additional importance in the reduction of cyclic ketones. The outcome of the reduction strongly depends on both the structure of the ketone and of the reagent, and may be affected by the solvents. Experimental evidence for the contribution of these two factors was afforded by the observation that reductions of ketones by complex hydrides were influenced in the same way by asymmetry in the substrate and in the reagent. Thus, ketones with diastereotopic carbonyl groups could be reduced by achiral hydrides to diastereotopic alcohols[19], while enantiotopic carbonyl groups reacted with chiral hydrides to give optically active alcohols[15,16].

According to this concept, unhindered cyclohexanones react to give the most stable product. For example, reduction of 4-tert-butylcyclohexanone by LAH in ether gave 90% of the more stable trans product 9[18], while under the same reaction conditions 3,3,5-trimethylcyclohexanone yielded the less stable isomer, 3,3,5-trimethylcyclohexanol 11, in 58% yield[10] (scheme II).

Scheme II

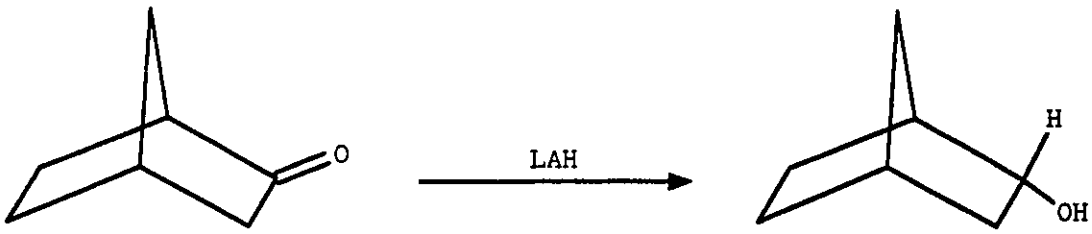


8 9 (8)

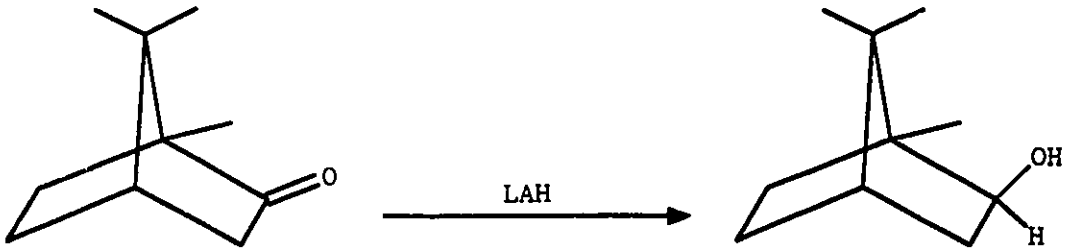


10 11 (9)

Scheme III



12 13 (10)



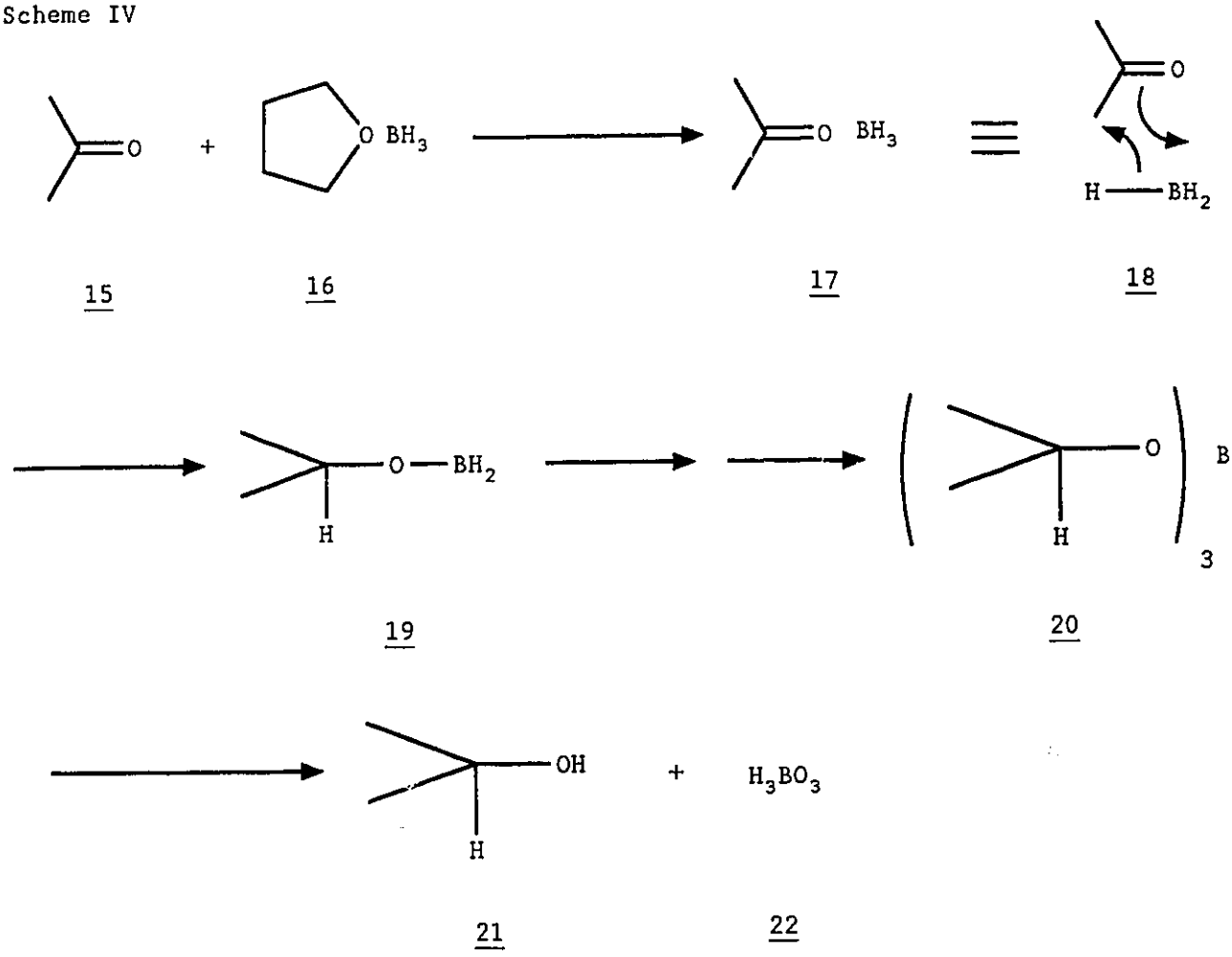
14 15 (11)

It should be noted that an increase in the steric bulk of the attacking complex hydride species destabilized the transition state 8, leading to the equatorial alcohol, but did not change the transition state 10, leading to the axial alcohol (scheme II). This explains why lithium trimethoxyaluminium hydride afforded the trans alcohol 9 in 59% yield while the same reagent reduced the ketone 10 to the less stable alcohol 11 in 98% yield.

The effect of the steric hindrance was also nicely demonstrated in the case of two bicyclic ketones, norcamphor and camphor[20]. Reduction of these with LAH in diethyl ether or THF afforded the less stable isomer in yields of more than 90% (scheme III).

The mechanism of reduction by boranes differs somewhat from that of complex hydrides. The main difference is in the entirely different chemical nature of the two reducing agents. Whereas complex hydride anions are strong nucleophiles which attack positions of lowest electron density, boranes are electrophiles and combine with parts of the organic molecules which have free electron pairs. Therefore, the first step in borane reduction was usually considered to involve attack by borane at the basic oxygen to form the complex 17 (scheme IV)[21, 22]. Originally the second step in the mechanism was thought to involve an intramolecular hydride transfer from boron to carbon, 18, to give an alkoxyborane 19[21]. This was based on the observation that dialkoxyboranes and trialkoxyboranes can be isolated as intermediates in the reduction of ketones[23]. However, later studies on the rate of reduction of substituted cyclohexanones in THF have shown that the reaction is first order in ketone and three-halves order in diborane specie in solution[22]. This finding excluded the intramolecular

Scheme IV



15 16 17 18

19 20

21 22

$$3\ BH_3\ THF \rightleftharpoons (THF)_2BH_2^+ + B_2H_7^- + THF \qquad (12)$$

$$BH_3\ THF + BH_4^- \longrightarrow B_2H_7^- \xrightarrow[\text{slow}]{\text{ketone}} \text{products} \qquad (13)$$

hydride transfer as the possible mechanism in the formation of alcohols since the rate expression would only be half order in diborane. In addition when the ketone was complexed with boron trifluoride prior to reaction with the hydride species, the order of the reaction with respect to diborane fell to one, indicating that the complexing agent served only to activate the carbonyl functionality and was not participating in the reduction. The attack of species 17 by diborane was also proposed as the rate determining step, taking into account the order of the reaction in boron, but it has been firmly established that diborane in THF exists as a borane-THF adduct[24]. The kinetics of the reaction can be explained by the existence of an equilibrium between 3 moles of borane-THF and the species BH_2^+ and $B_2H_7^-$ (eqn 12). The $B_2H_7^-$ ion has been shown to exist as the singly hydrogen bridged species, $H_3B\text{-}H\text{-}BH_3^-$ [25]. Support for this explanation was provided by the fact that the reduction in the presence of lithium borohydride was first order in ketone, borane and borohydride (eqn 13). The exact structure of the transition state formed in the reduction of the carbonyl group by $B_2H_7^-$ species is not known so that it is not possible to predict the stereochemistry of addition of borane to ketones. However, it should be noted from results regarding the reduction of cyclic ketones with diborane that the distribution of products follows a very similar trend to that of aluminum hydrides reduction.

Other explanations have been proposed to account for the outcome of the reduction leading to two different stereoisomers such as in the case of substituted cyclohexanones. These include orbital symmetry[14,26] and torsional strain[18,27] but their theoretical aspect will not be covered in the present work.

1.2 ASYMMETRIC REDUCTION OF KETONES USING NON-POLYMERIC CHIRAL HYDRIDE COMPLEXES

Among the wide variety of asymmetric reactions, the enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied chiral transformations[28]. This was first proposed by Bothner-By[29] who suggested that LAH partially decomposed by optically active molecules could potentially induce asymmetry in the reduction of ketones (eqn 14).

$$LiAlH_4 + nR^*OH \longrightarrow [LiAlH_{(4-n)}(OR^*)_n] + nH_2$$

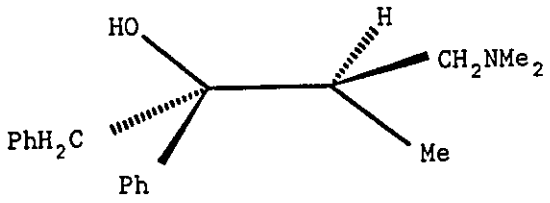
$$\xrightarrow{RCOR'} \underset{OH}{RCH^*R'} \qquad \underline{23} \qquad (14)$$

Despite the fact that he was not successful several researchers used the idea but it was not until 1964 that his predictions were verified[30]. Since then a number of reagents have been elaborated to give what is known today as a classical method for the preparation of optically active alcohols.

The principle of this reaction lies in the fact that the chiral environment of the hydride atom enables the reagent to differentiate between the re and si face of the carbonyl group, based on a combination of both electronic and steric factors as will be discussed later.

One group of molecules which has received much attention as chiral auxiliaries in the reduction of ketones is the amino alcohols. In order to be practical these compounds must possess high optical purity and be available at moderate cost which has prompted organic chemists to look at natural molecules and their derivatives. Because of the complexity of the reaction, numerous factors and experimental conditions have been studied in order to optimize the asymmetry of the hydride addition to the ketone

group. In a very complete study, Mosher[31] has shown that in addition to expected factors such as temperature and solvent, the "age" of the reagent was also important in determining the absolute configuration of the product. They reacted (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol, 24, with LAH in various ratios to give chiral reducing agents represented by the formula 23. When the reagent was used within few minutes of its formation, at which stage it was insoluble in the reaction medium, acetophenone was reduced quantitatively to the R-(+)-phenylmethylcarbinol. However, if this heterogeneous reagent was refluxed in ether or aged, to give a homogeneous solution, the (S)-enantiomer of the alcohol was obtained as the product. This reversal in stereoselectivity seems to be associated in part with a less soluble or more soluble form of the reagent 23. It was also observed that despite the presence of a 1-3 molar excess of hydride reagent, unreduced carbonyl compound could be recovered from the reaction mixture. This phenomenon has also been noted by Meyers[32], Noyori[33] and Mukaiyama[34]. For example, Noyori reduced propiophenone with the chiral complex 25, derived from (R)-(+)-binaphthol, and isolated the carbinol in 77% chemical yield as well as 27% of unreacted ketone and 21% of active hydrogen atom after quenching with methanol. When this reaction mixture, without methanol quenching, was further treated with 1 equivalent of acetophenone, the alcohol 27 (77%) and hydrogen (21%) were produced. Acetophenone and propiophenone were recovered in 100% and 23% yield respectively. It seems that the alcohol/ketone ratio reached a constant value, 77/23, and even though some aluminum hydride still survived, further reaction did not proceed. This has been attributed to the fact that the remaining hydride was presumably residing in a highly hindered environment and therefore incapable of being transferred to a carbonyl carbon[32-34].



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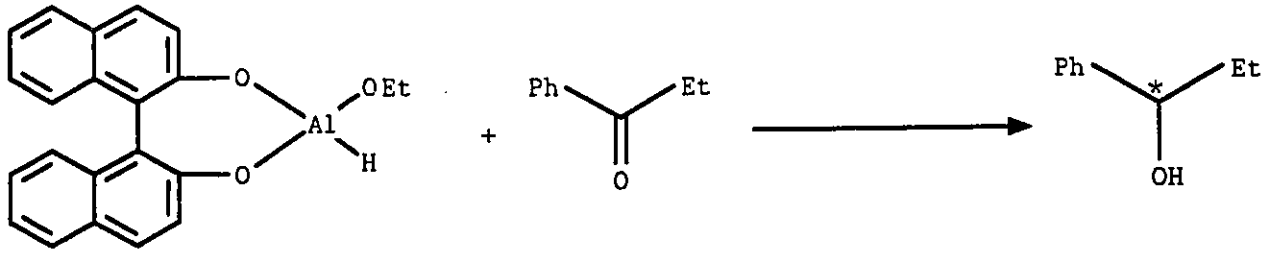


25 26 27

Table 1. Asymmetric reduction of acetophenone using various complexes of LAH and 24[31], (T= 0°C).

molar ratio LAH	R^*OH	ee(%)
1	0.77	31
1	1.00	52
1	1.54	65
1	2.00	40
1	2.30	68
1	3.00	26

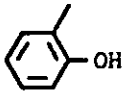
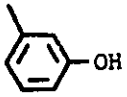
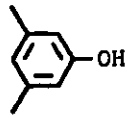
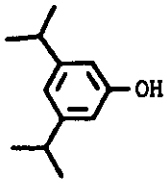
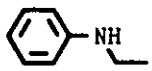
Another interesting aspect of asymmetric reductions of ketones is the relationship between the ratio of LAH to chiral compound and the optical yield of the reaction. It might be thought that larger values of n in the formula 23 would enable the remaining hydride(s) to improve the differentiation between the faces of the ketone functionality. However, some examples seem to indicate that this is not always the case[31,32,35-37]. For example, Mosher[31] has shown that the optical yield obtained by the use of the complex $LiAlH(OR)_3$, where OR is the alkoxide derived from 24, was 26%, much lower than the optimum value of 68% (table 1). It should be noted however, that N-methylephedrine, 28, is an exception to this observation and a slight increase in the enantiomeric excess (ee) was noticed when the value of n changes from 1 to 3[38]. For this reason, many of the chiral hydride complexes were decomposed with various achiral additives in order to improve their selectivity (eqn 15).

$$LiAlH_4 + nR^*OH \longrightarrow LiAlH_{(4-n)}(OR^*)_n \quad 23$$

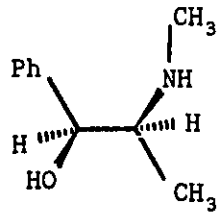
$$\xrightarrow{mR'OH} LiAlH_{4-(m+n)}(OR^*)_n(OR')_m \quad 30 \qquad (15)$$

Vigneron and Jacquet[38], among others[32,39-41], have shown that an achiral molecule will drastically change the extent of the asymmetric induction of the process (table 2). A slight variation in the structure of the achiral molecule had a great effect on the optical purity of the alcohol. For example, varying the achiral agent from the ortho to the meta isomer of methyl phenol changed the stereospecificity of the reagent from 9.5% to 58%. The best results were obtained with 3,5-dimethylphenol and N-ethylaniline. Despite the fact that Vigneron did not explain these observations we suggested an intermediate[44] which accounts for the stereochemical outcome of the reduction. This aspect will be covered in the discussion section of this thesis.

Table 2. Reduction of acetophenone using the complex LiAlH(N-methylephedrine)$(R)_2$.

R	ee(%)
	9.5
	58
	71 (84)[1]
	42
	84[2]

1. Obtained after optimization of the reaction conditions
2. Data taken from reference 42



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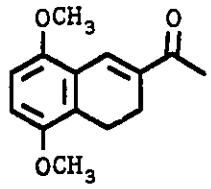

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Table 3. Reduction of 2-acetyl-5,8-dimethyl-1,4-dihydronaphthalene, 29, by LiAlH(N-methylephedrine)(N-ethylaniline)$_2$ at -78°C[43].

solvent	ee(%)
diethyl ether	92
THF	5
toluene	28

In general the optical yield of the reduction of the carbonyl group appeared to increase by lowering the reaction temperature[15,31,33]. Despite an exception to this rule[38], Noyori[33] calculated that the difference between the activation energy of the reactions leading to the S and R carbinols of acetophenone is 1.66 kcal/mol for an optical purity of 98% at $-78^{\circ}C$.

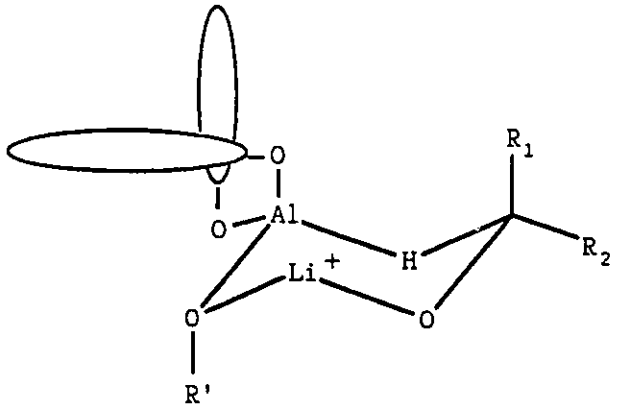
The solvent also influences the enantioselectivity of the reaction by disrupting the geometry of the chiral complex. In all cases reported in the literature where LAH derivatives were utilized, it was noted that THF led to the carbinol with the lowest optical purity when compared to diethyl ether or toluene (table 3). This was attributed to the complexing power of THF towards Li^+ which prevented the formation of an ordered transition state. Noyori[33] proposed the transition state 30 in the reduction of ketones (R_1COR_2). Note that the chiral reagent was obtained from the reaction of one equivalent of LAH, (R)-(+)-binaphthol and an achiral alcohol (R'OH). The ellipses in the structure 30 represent the binaphthol ring system which are perpendicular to each other. It can also be visualized as being the electron density created by this ring system. In addition, the structure 31 includes the electron density of the oxygen as well as the electron density arising from the aromatic ring of the ketone being reduced (Un). These are represented by the smaller ellipses. This model was also partially built from the mechanism proposed by Ashey and Boone for the simple case of LAH reduction of ketones[8]. It becomes evident that removal of Li^+ from this intermediate, by complexation with an external ligand, will totally destroy the geometry of this transition state and therefore reduces greatly the stereoselectivity of the reagent.

This model has also been used by the authors to account for the fact that chiral reagents derived from LAH (and most of those derived from diborane) rarely reduced aliphatic ketones with optical yields exceeding 45%[33,38,45-47].

This was explained by a n-π type electronic repulsion between the axially oriented binaphthoxyl oxygen and the unsaturated moiety (structure 31). Such an electronic repulsion is absent in 32 which makes this diastereotopic transition state thermodynamically favoured over 31 and explains the formation of the S alcohol. In the case of aliphatic ketones, which lack the n- type electronic repulsion, the enantiomeric excess will solely be determined by steric factors, that is the bulkiness of R_1 vs R_2 (30). A similar mechanistic approach has been successfully used with other types of nucleophilic additions to the carbonyl group[48]. In addition, the 1,3-diaxial type steric repulsion becomes significant by increasing the bulkiness of the R group but does not overcome the overwhelming electronic influence. It nonetheless contributed to an important decrease in the enantiomeric excess of the alcohol (table 4). This has also been observed by several authors with other reducing reagents[48,49].

Finally if the transition state 32 is responsible for the formation of the S enantiomer, an increase in the steric bulk of the achiral additive R'OH should lead to a decrease in the stereoselectivity of the reagent. This has indeed been observed with a variety of alcohols[33].

The predictable behavior and the efficiency of the binaphthoyl reagent has led to its commercialization and some research has focused on inexpensive ways of achieving its optical resolution[50]. In some cases, the



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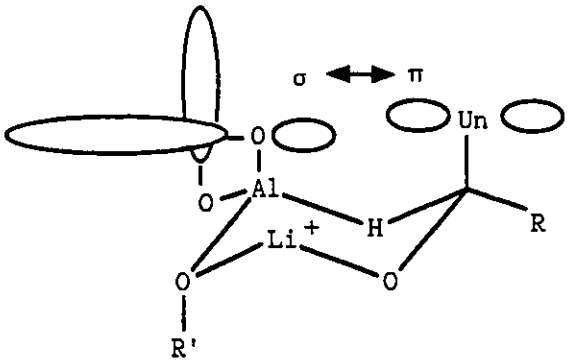

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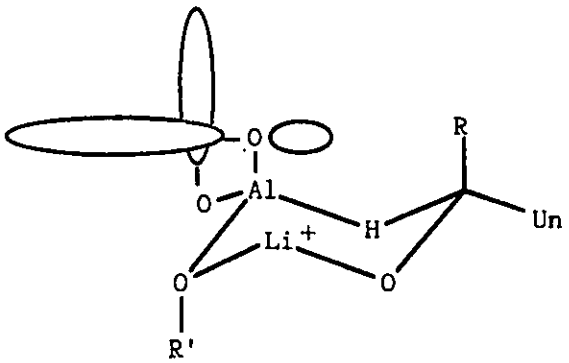


32

Table 4. Reduction of unsaturated ketones, PhCOR, by complex 25 at 30°C[33].

R	ee(%)
methyl	65
ethyl	72
isopropyl	56
t-butyl	20

reagent has proven more efficient than most of those found in the literature[51].

Diborane has also been widely utilized in conjunction with chiral amino alcohols in the reduction of ketones. Most of the work in this area has been initialized by Itsuno et al. both with respect to model molecules and polymeric reagents.

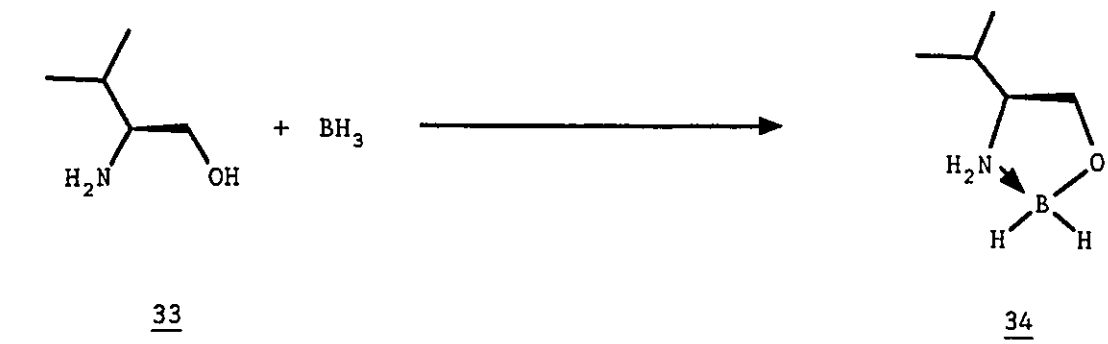
Because of their mechanism of action these reagents behave in a totally different way than those derived from LAH. This is first reflected by the absence of a counter cation. The complexing capacity of the solvent will be of little effect in this type of asymmetric reduction and in fact the best optical yields were obtained in THF[37] which is in contrast to observations made in the aluminum hydride reductions (table 5). As well, the polarity of the solvent did not seem to be a major factor when one compares THF and pentane, for example.

These reagents are never used in conjunction with an achiral molecule and as a consequence the chiral amino alcohol bears three labile hydrogens. But because of the lower reactivity of diborane with respect to LAH, not all of these labile protons are abstracted. Itsuno and co-workers[37] have shown that (S)-valinol, 33, reacted with half an equivalent of diborane to give a complex containing two active hydrides as analyzed by hydrolytic gasometry (scheme V). They concluded that the intermediate 34 was formed based on the fact that borane was known to react with alcohols to give alkoxyborane derivatives while it normally formed coordinated complexes with amine[52]. However, when an additional half equivalent of diborane was added, the resulting chiral hydride complex was shown to contain four

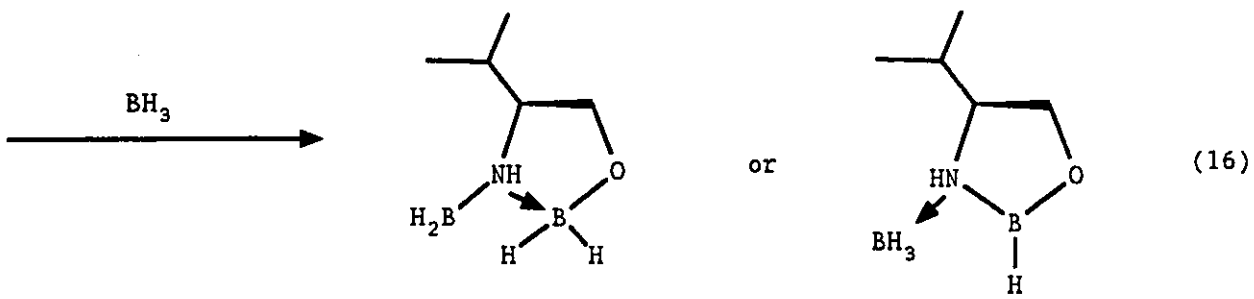
Table 5. Reduction of n-propyl phenyl ketone with a 2:1 borane and (S)-valinol reagent at 30°C[37].

Solvent	ee(%)
THF	69
benzene	54
pentane	60
CCl_4	55
t-butanol	28

Scheme V



33 34



(16)

35 36

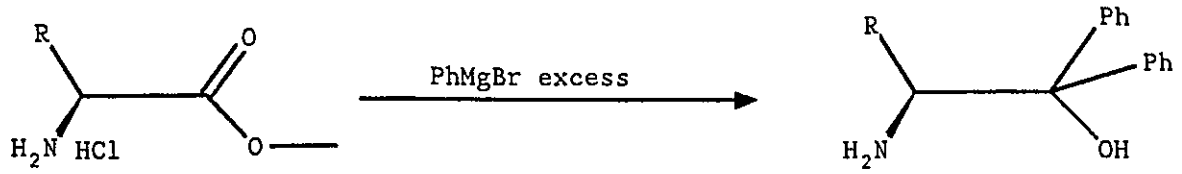
equivalents of hydride species resulting in the reaction of the amine with borane to give the complex 35 or 36. The exact structure of the complex has not been investigated by the authors.

Contrary to LAH complexes the ratio of diborane to chiral amino alcohol is not very crucial. That is, the optimum stereoselectivity was observed over a ratio varying from 1.0 to 1.5 and even when an excess of hydride was used (ratio diborane/(S)-valinol = 2), n-propyl phenyl ketone was reduced with 45% ee. Itsuno et al.[53] also looked at a wide variety of amino acid derivatives. These were prepared as shown in scheme VI and used in the reduction of aliphatic ketones at a temperature of 30°C (table 6). Optical yields up to 89% were obtained which is a net improvement over other types of reagents. They also noted that the effeciency of the reduction increased with the steric bulk of the chiral reagent. When the same amino derivatives were utilized to reduce aromatic ketones, enantioselectivities of up to 97% could be obtained[53].

Finally, they found that amino alcohol-borane complexes reduced ketones at a much faster rate than diborane itself[54,55] but did not account for these results. We can nonetheless explain this by a decrease in the electropositive character of boron when complexed by the lone pair of nitrogen which probably weakens the bond strength with hydrogen.

Following Itsuno's reports, several authors have investigated the use of other chiral complexes of borane in the reduction of ketones[49,56-57]. For example, Corey et al. prepared the oxazaborolidine 38 which complexes borane and could reduce aromatic as well as aliphatic ketones in excellent optical yields (>96%)[56].

Scheme VI



37a R = Me

37b R = $CH(CH_3)_2$

37c R = $CH_2CH(CH_3)_2$

37d R = $CH(CH_3)C_2H_5$

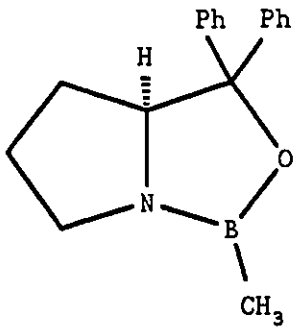
37e R = CH_2Ph

37f R = $CH_2CH_2SCH_3$

37g R = $CH_2C_6H_4OCH_2Ph$

Table 6. Reduction of 3,3-dimethylbutan-2-one with the chiral amino alcohols borane complex in THF at 30°C[53].

aminol alcohol	optical yield of alcohol
33	44
37a	72
37b	74
37c	55
37d	89
37e	83
37f	65



38

Much of the chemistry developed by Itsuno et al. has been applied to polymeric reagents as will be discussed in the next section.

1.3 POLYMER-SUPPORTED REAGENTS IN ORGANIC CHEMISTRY

1.3.1 General considerations

The introduction of polymeric reagents in organic chemistry can be attributed both to Merrifield[58] and to Letsinger and Kornet[59]. When a reagent is covalently bound to a polymer, it acquires the physical properties of the latter. As a consequence, if the polymer is insoluble in most organic solvents, for example due to its crosslinking, several advantages can be anticipated over non-polymeric reagents. First, the separation of the product from the reagent can be achieved by simple filtration. This renders the purification of the product much simpler and as a consequence the polymer can be regenerated and further used for the same chemical transformation. Therefore, expensive reagents can be recovered which makes certain processes economically feasible. Lastly, the bulkiness of the polymer backbone may give rise to additional steric effects which are normally absent in model compound chemistry. As a consequence, it is expected that polymeric reagents will behave differently than their low molecular weight counterparts. This could, for example, be reflected in the kinetics or the stereochemical outcome of a chemical process. This special behavior of polymer-supported reagents, which we will call "polymer effect", will be discussed in detail in section 1.3.3.

Polymer mediated reactions fall into three main categories[60]:

1. The first type includes reactions in which the polymer acts as a carrier for the substrate. The product remains attached to the support while the by-product, excess reagents and solvents all remain in solution and can be removed by filtration. This category includes most of the solid phase synthesis work performed by Merrifield[58].
2. The second type includes reactions in which a polymer incorporates a synthetic reagent. In this case the product remains in solution and is recovered by filtration of the polymer.
3. Finally, a third type includes reactions in which the polymeric reagent acts as a catalyst. This is basically the same as the second type except that catalytic reactions are present.

A wide range of polymers are available for polymer-mediated synthesis but most of the examples found in the literature are based on polystyrene-divinylbenzene (PS-DVB) backbones (figure 1). The DVB acts as the crosslinking agent which renders the polymer insoluble and gives it its special swelling properties. Swelling refers to the change of dimensions of the polymeric resin as a function of the solvent polarity. This will vary depending on the solvent, the nature of the polymer and the percentage of crosslinking. For example some crosslinked polystyrene derivatives are known to absorb a volume of solvent equal to ten times their dry volume[44].

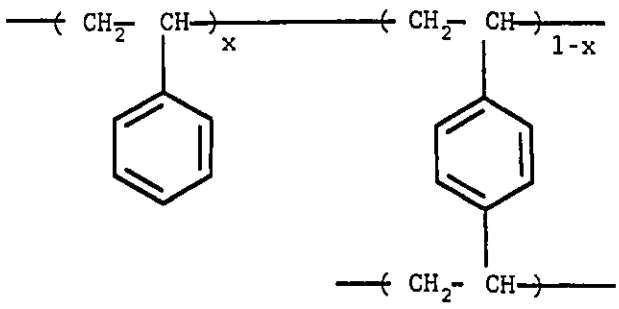
The following discussion will be limited to the polymers falling under the definition of the second type and based on the PS-DVB system. There are many reasons why PS-DVB has been extensively used in a variety of organic synthesis. It possesses several advantages over other resins: (1) Aromatic ring functionalization is achieved easily to give reactive, yet selective styrene-based reagents. (2) The type and degree of crosslinking

in the polymer influence its swelling nature and polymer beads of both a swelling and nonswelling type can be made. (3) Being hydrocarbon-like, these polymers are compatible with organic solvents so that functional groups are easily accessible to the reagents and solvents. (4) The polymers are not degraded by most chemical reagents under ordinary conditions and can withstand the chemical treatments and physical handling required in sequential synthesis as was nicely demonstrated by Merrifield[58].

One of the most useful transformations of crosslinked polystyrene is its chloromethylation[58]. This was carried out using a Lewis acid catalyst and chloromethyl methyl ether (fig 2). The Friedel-Crafts catalysts used for this reaction were $SnCl_4$[59], BF_3[61] and anhydrous $ZnCl_2$[62]. In addition to its direct use, chloromethyl groups were readily modified into other functional groups[63]. The more important functional groups that have been introduced via chloromethylation are shown in figure 4. If necessary most of these new functionalities can be derivatized further according to known organic transformations. Note that chloromethylated polystyrene is abbreviated as Ⓟ-CH_2Cl in the present work.

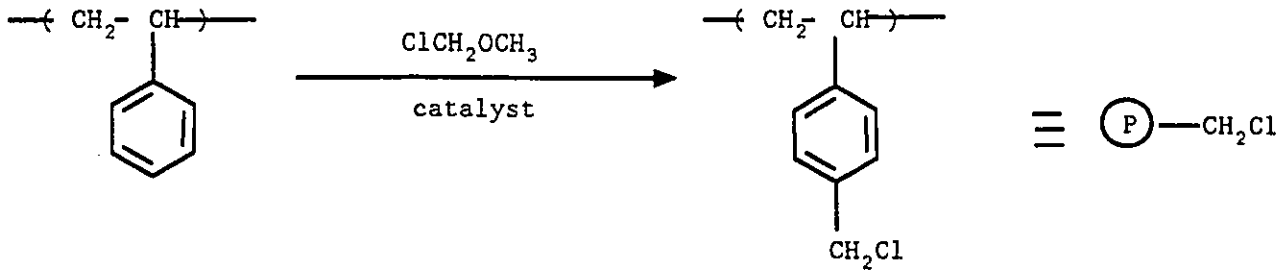
The second most versatile method for the functionalization of polystyrene includes its bromination followed by lithiation of the resulting polymer (fig 3). Polystyryllithium can then be reacted with a wide range of electrophiles as shown in figure 5. Several other methods exist which allow further derivatization of polystyrene but this extensively reviewed field of polymer chemistry[64-65] will not be discussed in the present thesis.

Figure 1. Crosslinked polystyrene.



39 PS-DVB

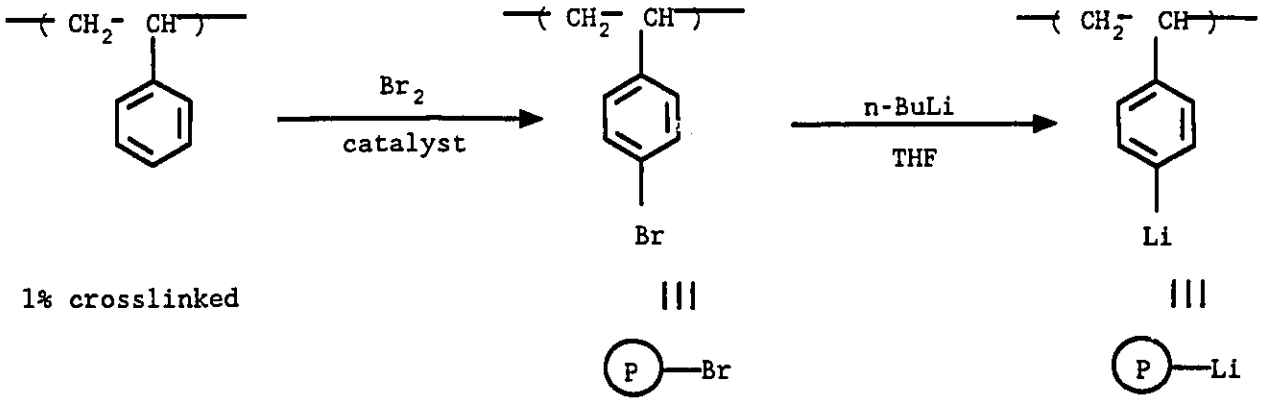
Figure 2. Chloromethylation of crosslinked polystyrene.



1% crosslinked

1% crosslinked

Figure 3. Bromination of crosslinked polystyrene followed by lithiation of the resulting polymer.



1% crosslinked

Figure 4. Transformation of chloromethylated polystyrene.

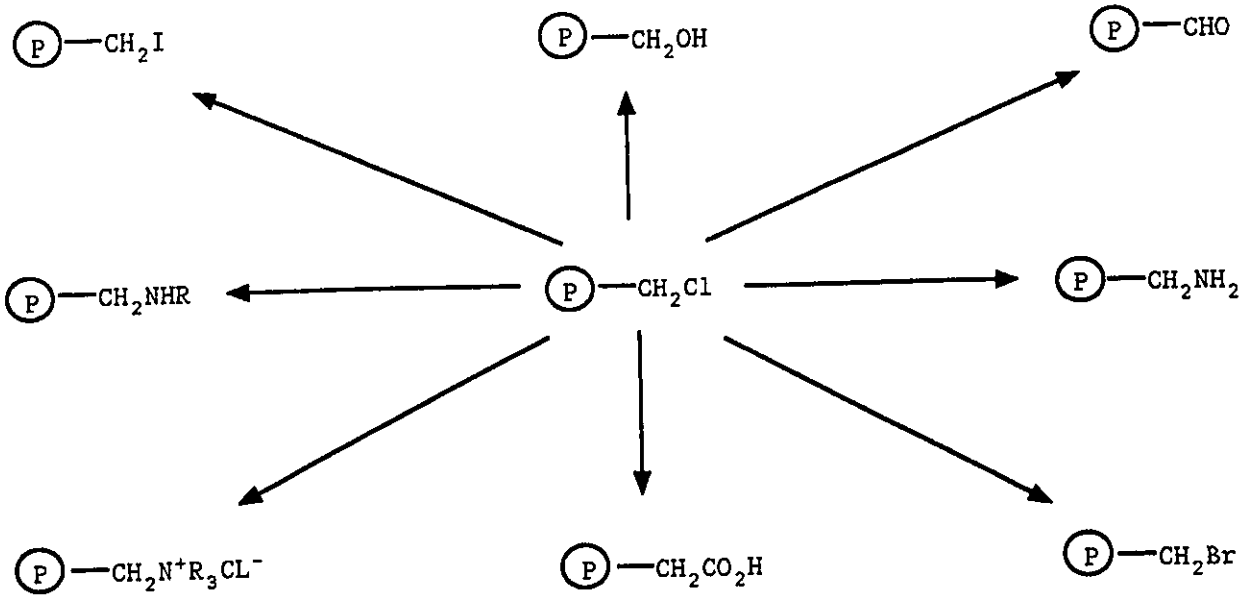
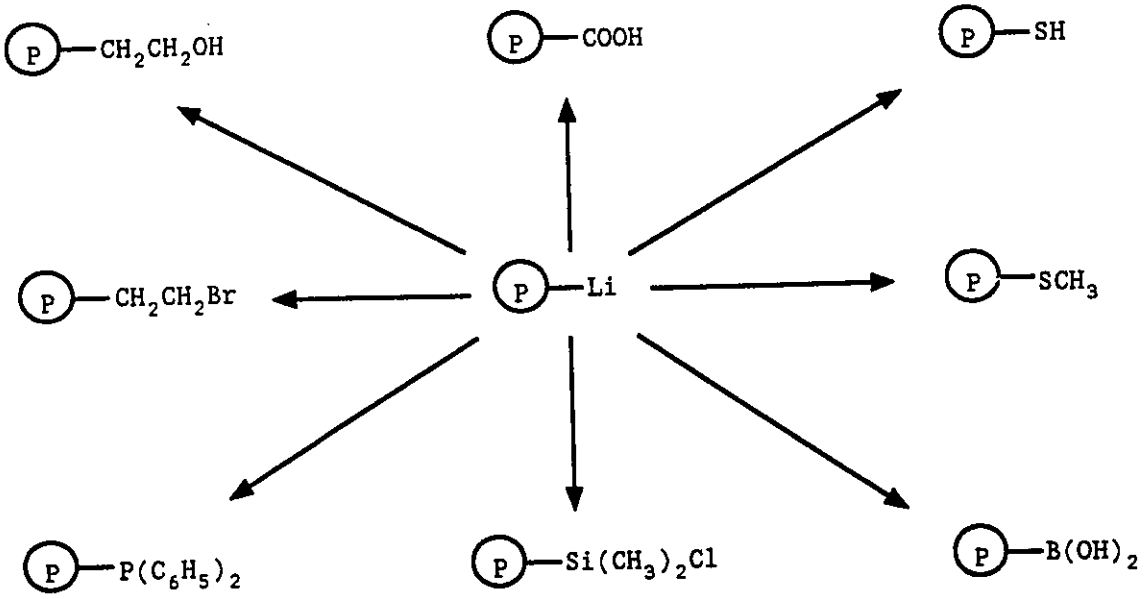


Figure 5. Transformation of brominated polystyrene via lithiation.



1.3.2 Polymer-supported chiral reagents in organic chemistry

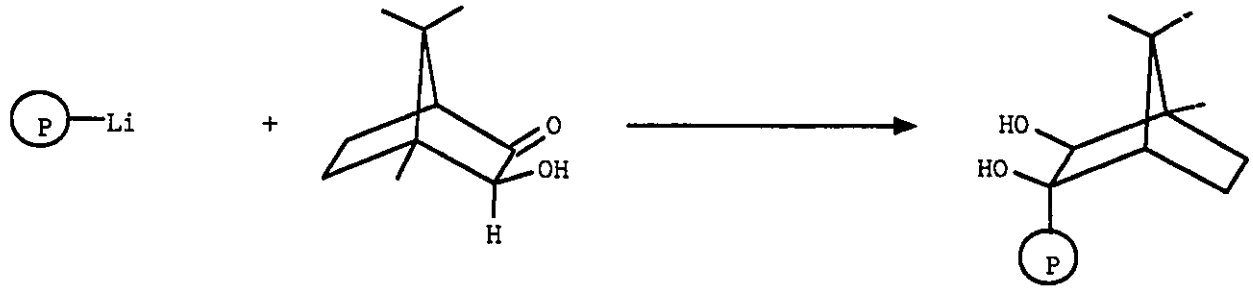
Polymer-supported chiral reagents have been used both for asymmetric synthesis and for the chemical resolution of racemates[66]. Early examples can be found where the asymmetric synthesis was performed on the polymeric support[67]. This approach however suffered from the fact that recovery of the chiral product necessitated the cleavage of the chemical bond linking the polymer to the derivatized substrate. An alternative approach involves reacting an achiral substrate with a polymeric chiral reagent or catalyst. As the chiral auxiliary is liberated unchanged during or at the end of the reaction, it appears to be particularly advantageous to use an insoluble polymer thereby facilitating its recovery, purification and re-use. These advantages has been the main asset of polymer-assisted reactions since the development of the general concept by Merrifield[58] in the early sixties.

One of the first examples of the use of a chiral polymer in organic synthesis was reported by Tsuboyama[68]. He prepared various chiral polymers containing amine functionalities. These polymers served as catalysts in the addition of hydrogen cyanide to benzaldehyde. This early attempt in a new field of polymer chemistry yielded products with an optical purity of 20%. Following this report chiral polymers have found numerous applications in areas as diversified as supports for the resolution on enantiomers[66], preparation of chiral metal complexes which found uses in asymmetric hydrogenation of organic molecules[69], chiral recognition by host complexes[70], chiral phase transfer catalysts[71], asymmetric synthesis[72,73] and finally asymmetric hydride reductions[44,74].

The use of polymer chiral reagents as aids in asymmetric hydride reduction has been overlooked compared to other asymmetric transformations using polymeric reagents. This is probably due to the late development of the asymmetric reduction with model compounds which took place in the seventies and early eighties as well as the complexity governing this reaction as discussed earlier.

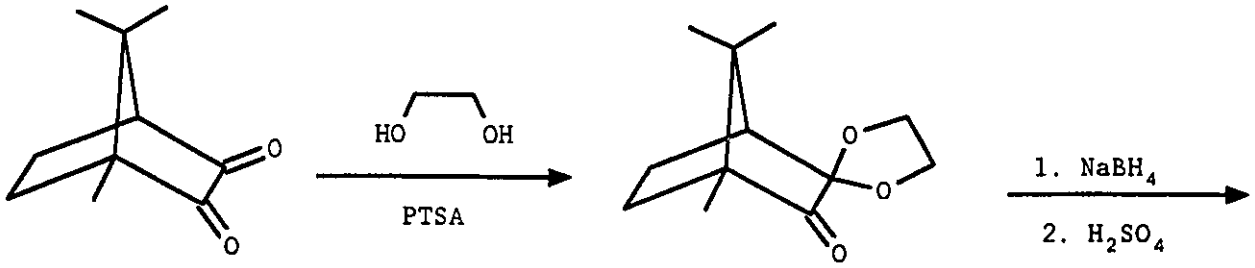
The first example of asymmetric reduction of ketones with the use of a chiral polymeric resin was published in 1983 by Kondo et al.[75]. They prepared the polymer 42 (scheme VII) by reaction of polystyryl lithium 40 and (-)-2-exo-hydroxy-3-bornanone 41. The yield of this reaction varied between 52% and 78%, the remaining substituted aromatic rings probably carrying a bromine or an hydroxyl functional group. Similarly, the model compound 45 was prepared as shown in scheme VIII. Note that the reduction of the ketone 44 occurred as discussed previously from the less crowded face of the molecule to give the less stable exo isomer. Similarly, the attack of the nucleophile on molecule 41 also proceeded according to this concept to give the cis diol. The chiral diols 42 and 45 were then complexed with LAH (scheme XIX) and reductions carried out using acetophenone at various temperatures. The results published by these authors are reproduced in table 7 and it should be noted that reported enantiomeric excesses are too high by a factor of approximately 20%. This error was due to the fact the authors reported optical yields comparing optical rotations measured in benzene with those reported in the literature for the neat product. However, optical rotations for 1-phenylethanol are 20% higher in benzene than for the neat compound. For example a commercial sample of 1-phenylethanol with a neat optical rotation of 38.6° will show a rotation in the range of 45.0° to 46.3° for concentrations varying

Scheme VII

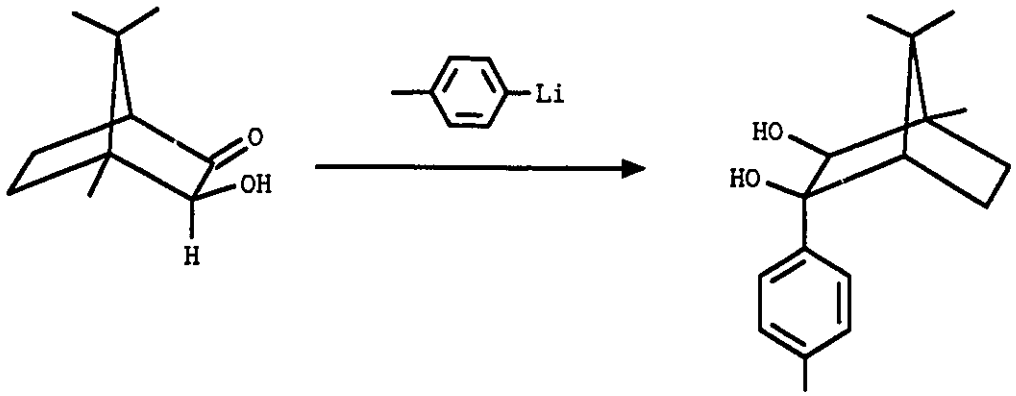


40 41 42

Scheme VIII



43 44



41 45

Scheme IX

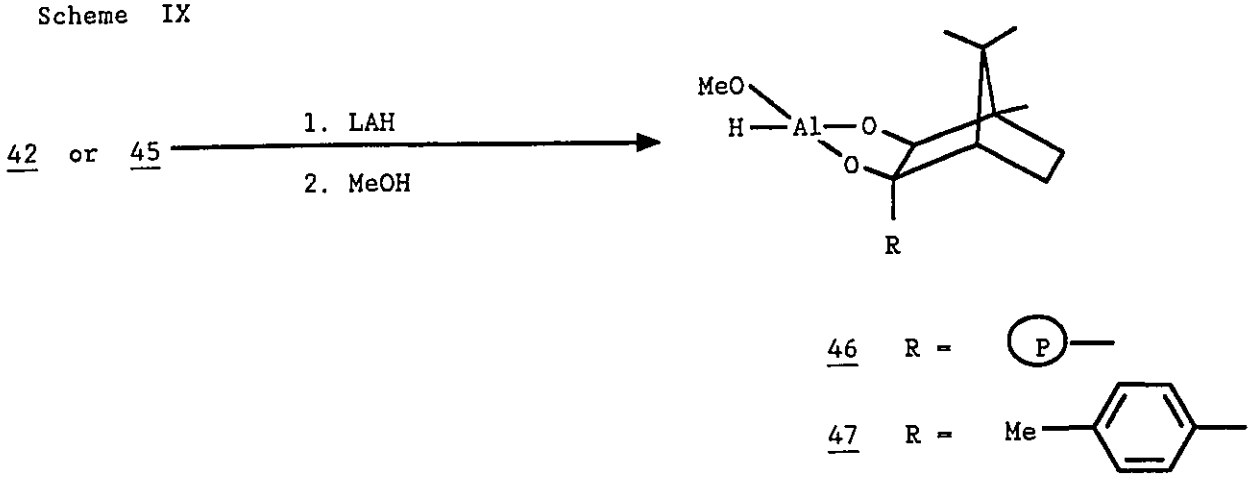


Figure 6. Enantioface differentiation of acetophenone by 1% crosslinked polystyrene containing chiral units 46 (○) and by the low molecular weight model compound 47 (●) at various temperatures.

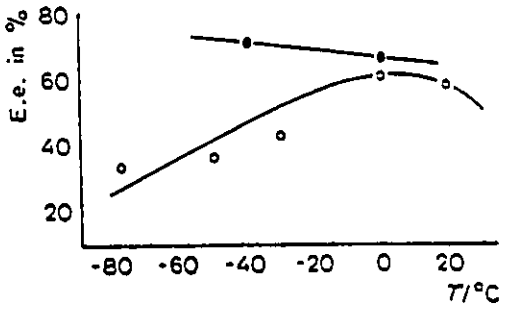


Table 7. Asymmetric reduction of acetophenone at -78°C for 26 h with the use of complex 46 where the achiral alcohol is methanol.

Temperature C	$[\alpha]^{30}$ (benzene, g/mL)	ee[a] %	corrected value[b] %
-78	+ 14.9 (0.07)	32.4	27.4
-50	+ 15.8 (0.12)	33.4	26.7
-30	+ 18.7 (0.13)	43.1	34.5
0	+ 26.6 (0.07)	61.2	49.0
20	+ 25.5 (0.12)	58.7	47.0

a) Based on $[\alpha]^{27.2}$ (max) = -43.5 (neat)

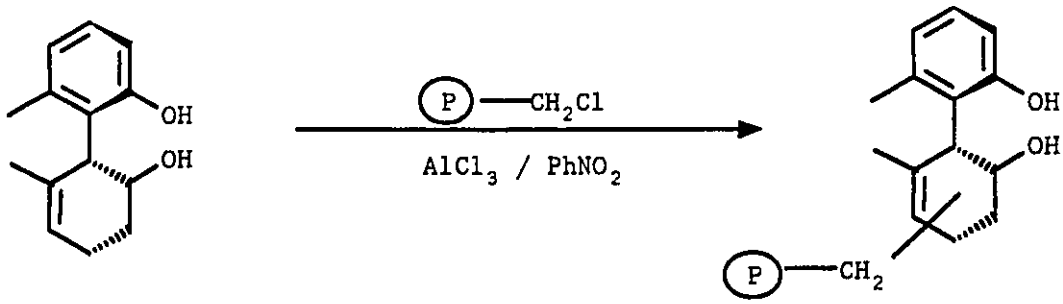
b) Based on measured rotations for various concentrations in benzene

between 4.144 g/100 mL and 10.064 g/100 mL of benzene. As well, it is known that the optical rotation of a substance depends on the temperature, solvent and concentration of that sample. This implies that the best optical yield they obtained was 49.0% as shown in the column "corrected value" in table 7. This correction should also be applied to the polymer data of the graph of figure 6. More recently other authors published their results on the use of chiral polymeric reagents in asymmetric reduction where the same error, regarding the effect of the solvent on the optical rotation, was repeated[76].

Following this report, polymers based on biphenyl chiral moieties appeared in the literature. Suda[77] prepared the polymer 49 (scheme X) by the Friedel-Crafts alkylation of 48 in unreported yield. The complex hydride reagents prepared from one equivalent of LAH, one equivalent of an achiral alcohol and one equivalent of polymer 49 reduced acetophenone in 18% optical yield in their best instance while 2,2'-dihydroxy-6,6'-dimethylbiphenyl typically reduced acetophenone under the same reaction conditions with 75% stereoselectivity. The results obtained by Suda[77] and Kondo[75] which they did not account for will be discussed later in view of our findings.

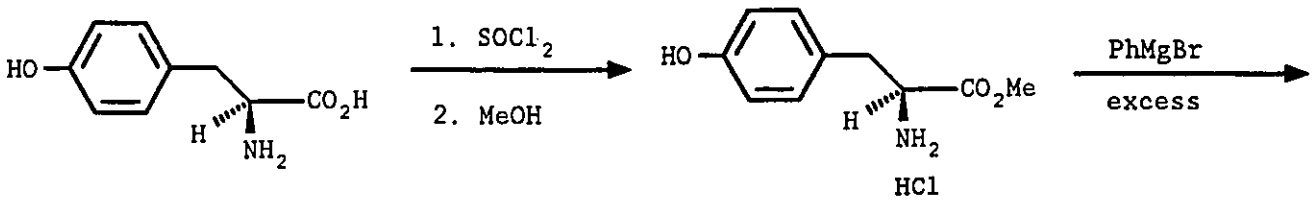
More recently polymeric reagents based on chiral amino alcohols and borane have been used more successfully than the examples previously discussed. Much of the advance in this area was the result of the work of Itsuno and co-workers. Following their results with amino acid derivatives[37,46,53-54] they undertook the study of similar polymeric reagents. Few amino acids bear functional groups which are not attached to the chiral center of the molecule and which would allow their fixation

Scheme X

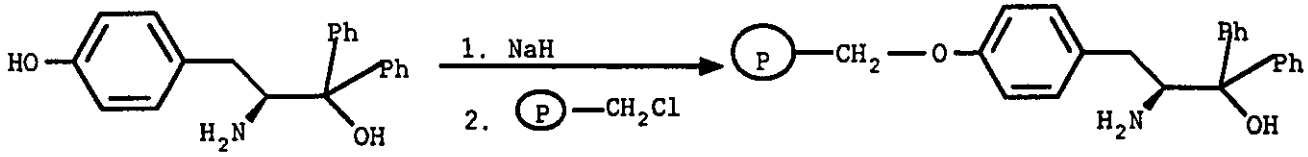


48 49

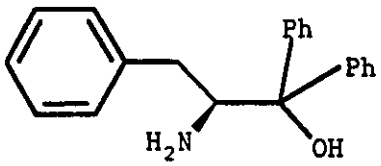
Scheme XI



50 51



52 53



model compound 54

to a resin. For this reason, Itsuno et al. have concentrated much of their efforts on derivatives of tyrosine and prolinol. (S)-Tyrosine, 50, was derivatized and the polymer or model compound prepared[55] as depicted in scheme XI.

The first observation from Itsuno's results regarding the reduction of butyl phenyl ketone with the diborane complex of 53 was that the reaction proceeded at a much faster rate than for diborane itself. This is shown in figure 7. The reaction was essentially completed within one minute with the polymer diborane complex while diborane alone required more than 10 minutes to yield 100% of alcohol. This behavior is however not related to the polymeric nature of the reagent as it is known that diborane complexes of amino alcohols are more reactive towards ketone than diborane itself[54-55]. Asymmetric reductions performed with this polymer complex gave much better results than those based on LAH[75,77]. Table 8 shows results for both the polymer and the model compound and good agreement between both systems was obtained with acetophenone and propiophenone while n-propyl and n-butyl phenyl ketone could be reduced more effectively by the borane complex of polymer 53. In addition, polymer 53 could be used again for the same reaction (table 9) with the optical yield being increased from 78% to 97% upon recycling. When Itsuno attempted to use the polymer 53 to reduce acetophenone oxime O-alkyl ether, enantiomeric excesses in the range of 18%-25% ee[55] were obtained. However, when the same chiral amino alcohol was anchored to a polymer via the polymerization of the corresponding monomer[78] and the loading was decreased to 10%, as compared to 50% for 53, acetophenone O-methyl oxime could be reduced to 1-phenylethylamine with an enantioselectivity of 99%. This large difference in enantiomeric excesses

Figure 7. Time-conversion curves for the reduction of n-butyl phenyl ketone with BH_3 (○) and with 53-BH_3 complex (●).

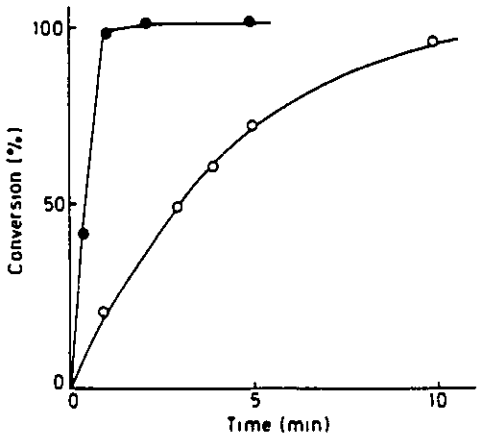


Table 8. Asymmetric reduction of prochiral ketones with 53-BH_3 complex in THF at 30°C. Yield of alcohol was 100% in each case. Values in parentheses were obtained with the use of the model compound 54.

ketone	alcohol produced	
	Optical Yield (%)	Absolute Configuration
MeCOPh	76 (87)	R (R)
EtCOPh	79 (79)	R (R)
n-PrCOPh	88 (82)	R (R)
n-BuCOPh	97 (93)	R (R)

Table 9. Recycle of 53-BH_3 complex in the reduction of n-butyl phenyl ketone in THF at 30°C. Yield of alcohol was 100% in each case.

Reuse	1-Phenylpentanol	
	Optical Yield (%)	Absolute Configuration
1	78	R
2	97	R
3	92	R
4	92	R

between the two processes was attributed to the swellability of the polymers which varies as a function of DF[78].

Polymer-supported chiral amino alcohols have also been used in other asymmetric transformations. For example, the polymer-supported amino isoborneol moiety was nicely utilized to demonstrate the mechanism of the catalytic addition of diethylzinc to aldehyde[79]. This reaction has recently been performed using other polymer-supported chiral aminoalcohols[72,80].

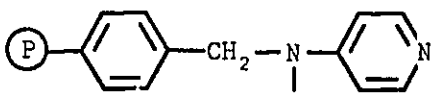
1.3.3 A special polymer behavior: the "polymer effect"

The fact that polymeric reagents find some use in organic reactions demonstrates that they may offer special advantages over the corresponding low molecular weight counterparts. As discussed earlier, these advantages are related to the ease of separation of the products as well as to the regeneration of the reagent. In addition, polymers may contribute to the overall chemical transformation by playing an additional role that cannot be reproduced in small molecule chemistry. That is, reactions where electronic and/or steric effects are important factors in determining the ratio of products or the rate of reaction will often behave very differently whether the catalyst is polymeric or not in nature. This difference can be accounted for by the presence of a polymer backbone which drastically increases the steric bulk of the reagent which is grafted to a polymer. As well, if the polymer contains π electrons, as in polystyrene

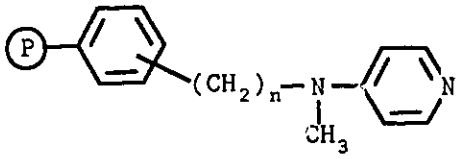
based reagents, additional electronic effects can be expected to arise from the use of such polymers. The term "polymer effect" refers to this difference in behavior between model compounds and the corresponding polymers arising from additional electronic and steric effects in the case of the latter. This effect can be beneficial or not as will be discussed.

Recently, Frechet[81] and Tomoi[82] have demonstrated the polymer effect in the case of polymer-supported N,N-dimethylaminopyridine (DMAP). For example, Tomoi prepared the polymers 55 to 59 (figure 8) and used them in the catalytic acetylation of linalool (scheme XII). DMAP as the model compound catalyzed the reaction of scheme XII with the largest rate constant. All the polymeric reagents 55-59 were not as efficient towards the acetylation of linalool. This can be attributed to the additional steric effect created by the presence of the polymer backbone which was responsible for a decrease in the rate of reaction between the intermediate 61 and linalool. Interestingly, when the spacer-chain length was increased, the rate of the reaction also increased. For example, the polymer 55 gave the lowest yield of acetate at a specific reaction time when compared to 57 which in turn reacted slower than polymers 58 and 59. Tomoi also studied the acetylation of linalool with polymers which differed in their catalyst content (DF). Here again it is reported that the polymers did not perform as well as the small molecule counterpart DMAP. For example, it was observed that the rate of reaction decreased with increasing catalyst content in the case of the polymer 55 which had 10%, 19% and 40% of its aromatic rings substituted by the catalyst. A similar behavior was noted for the polymer 57. This is explained, as pointed out by Frechet[81], by the formation of a microenvironment in which the

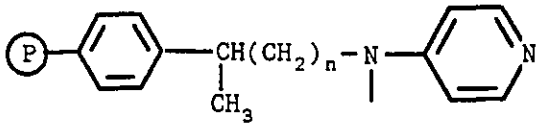
Figure 8. List of polymer-supported amino pyridines prepared by Tomoi[82].



55

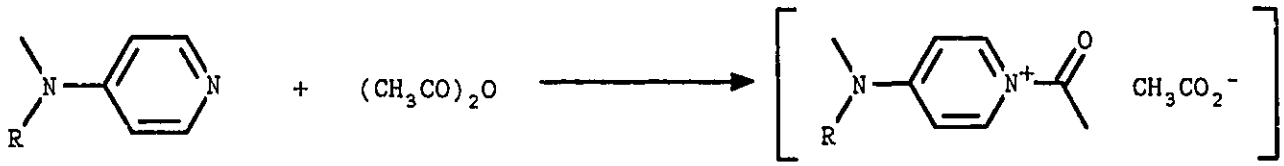


56 n = 4, 57 n = 7



58 n = 9, 59 n = 15

Scheme XII



60 61

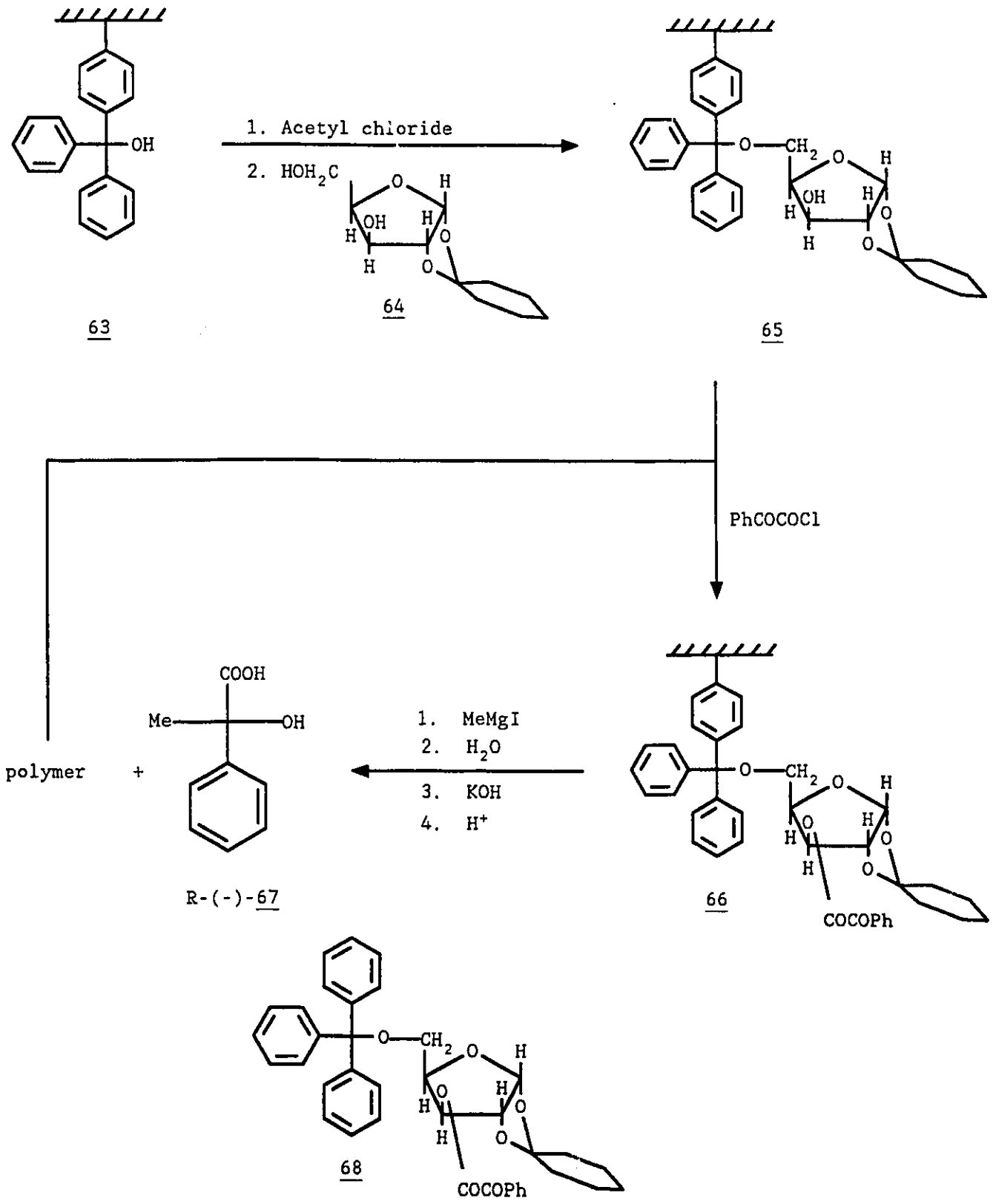
62

concentration of reactive sites is high. This has the effect of increasing the polarity of the reaction medium in the vicinity of the reaction sites. Indeed, it 's known that the acetylation of alcohol using DMAP as a catalyst proceeds faster in non polar solvents[83].

The polymer effect has been reported in numerous occasions[84] but it was rarely accounted for. Examples can be found where the use of a polymeric reagent contributed positively to the formation of the desired product. This contribution appeared as an increase in the chemical yield[85] or the ability to carry the reaction at room temperature rather than at low temperature[86]. In the case of polymer-supported asymmetric reactions, the polymer effect may act by a mechanism based on steric and electronic effects. Therefore, such an effect would be desirable if it could contribute to the enhancement of the stereoselectivity of the reaction.

The first example of polymer backbone enhancement of the stereoselectivity in an asymmetric reaction was published by Kawana and Emoto[67]. They prepared the polymer-supported sugar moiety 65 (scheme XIII) which was transformed into the keto ester 66 by reaction with phenyl glyoxyl chloride. Addition of methyl magnesium iodide to the polymer followed by hydrolysis of the ester afforded (-)-atrolactic acid 67 in 73% chemical yield and 58% optical yield. However, when the same reaction was carried out with the model compound 68, (-)-atrolactic acid was obtained with a chemical and optical yield of 68% and 53% respectively. This difference was explained by the authors as arising from the bulkiness of the substituent on C-4 of the furan ring which plays an important role in increasing the stereoselectivity of the Grignard reagent.

Scheme XIII


1. Acetyl chloride
2. HOH2C
63
64
65
PhCOCOCl
66
COCOPh
1. MeMgI
2. H2O
3. KOH
4. H+
polymer +
COOH
Me
OH
R-(-)-67
68
COCOPh

More drastic effects were latter reported by Kobayashi et al.[87] Copolymers of quinidine and quinine with acrylonitrile could catalyze the Michael addition of benzyl mercaptan to nitrostyrene with enantioselectivities which were up to nine times higher than those catalyzed by model compound reactions.

Following our report on polymer-bound ephedrine[44], other groups have used the same polymer as catalyst in the addition of diethylzinc to aldehydes[80]. Interestingly, the polymeric reagent yielded products of higher optical purities than those obtained from the use of the low molecular weight counterpart. More recently, polymer-bound alkaloids used for the dihydroxylation of alkenes demonstrated a similar behavior whereby the polymer was more efficient than the model compound[88].

As a last example, Kondo[75] and Suda[77] have used polymer-supported chiral moieties in hydride asymmetric reduction and their results discussed previously show that in such cases polymeric reagents do not seem to perform as well as their unbound counterparts. This was observed with respect to both the chemical and the optical yield and will be explained later in view of our findings.

RESULTS AND DISCUSSION

2.1 THE ASYMMETRIC REDUCTION OF ACETOPHENONE USING CHIRAL COMPLEXES OF LAH.

2.1.1 The study of low molecular weight amino alcohols.

At the beginning of our study on polymer-supported reagents, polymers had not been utilized as reagents in chemical transformations such as the asymmetric reduction of ketones. In addition, the reaction with low molecular weight reactants was not well understood and it was our belief that the use of a polymer could elucidate some of the mechanistic aspects of this reaction. Finally, in view of the discussion on the polymer effect we wanted to study whether or not a polymer-bound chiral moiety could give rise to enantioselectivities which could be superior to that obtained with the model compound. This last aspect was of particular interest as polymers could prove to be unique in their behavior and it would lead to new developments in the field of asymmetric synthesis.

In order to observe whether a polymer effect would be noticed in the asymmetric reduction of ketones, it was first necessary to choose a model compound giving rise to a degree of enantioselectivity ranging from fair to good. Metal hydride complexes which can reduce the carbonyl functionality with optical yields above 90% would render any improvement difficult to be observed once the complexing molecule is grafted to a polymer. For that reason, it was necessary to undertake a complete study of asymmetric

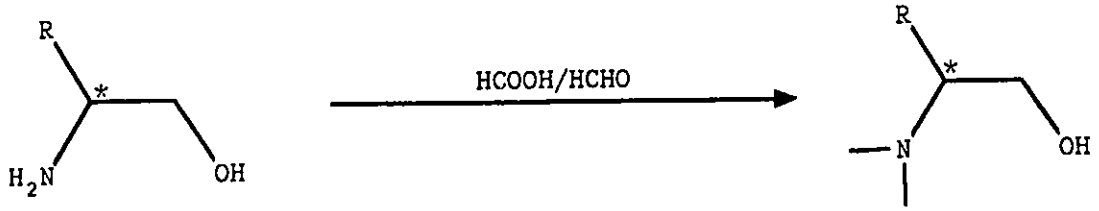
reductions of the ketone group using non-polymeric reagents. Once the desirable molecule was found, attachment to a polymer matrix could be done and the reduction performed under similar conditions to that of the model compounds. As exposed above, the understanding of the polymeric reagent was more important than the development of a new a reagent and for that reason our study concentrated on the reduction of acetophenone. No attempt was made to find out if other ketones could be reduced with the same efficiency as acetophenone by our reagents.

In view of the examples found in the literature it appeared that chiral amino alcohols were the best choice of model compounds. They possess several advantages over other types of chiral molecules. The desired products could easily be derived from natural molecules. As a consequence, they were relatively inexpensive materials with high optical purities and no resolution of the starting materials and/or the products was necessary. They also contained the desired functionalities to complex metal hydrides and most important, some of these functional groups allowed attachment to a polymer backbone. This last point was of great importance in the choice of our model compounds. It was indeed desirable to obtain the polymeric reagents from a single step synthesis involving a polymer and the chiral molecules. This step should also be the result of a mild reaction to avoid possible racemization of the chiral center the purity of which could not be verified once attached to the polymer. The chemical modification of polymers requiring several steps could lead to partial racemization of the chiral center depending on the reaction conditions but mostly they could give rise to unreacted specie or side reactions if the chemical reactions were not quantitative. That would render our results

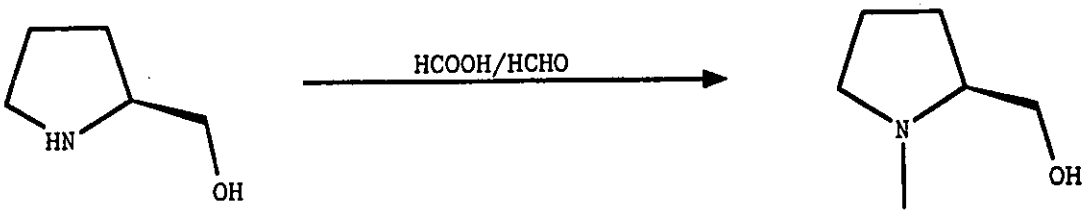
difficult to analyze as the exact chemical nature of the polymer would be unknown.

Our model study involved the synthesis of chiral tertiary amino alcohols. These were obtained from the Eschweiler-Clark methylation of primary and secondary amines[89]. This method consisted of the reaction of an amine with an excess of a formaldehyde/formic acid mixture. The intermediate formamide was reduced to the methyl group and CO_2 was evolved upon reflux for 4 hours. For example, when (S)-2-amino-1-propanol, 69a, was treated with a 5 fold excess of formic acid and 2.2 fold excess of formaldehyde, (S)-2-dimethylamino-1-propanol, 70, could be isolated in 39% yield after distillation. Similarly, (R)-2-amino-1-butanol, 69b, D-2-amino-2-phenylethanol, 69c, and L-pyrrolidin-2-yl-methanol, 73, were converted into the tertiary amines. This is outlined in scheme XIV which also reports the chemical yield of purified products. Note that the yields of the product were relatively low in all cases because of the low boiling points of these compounds under reduced pressure as well as their fairly large solubilities in water. Therefore, some product was lost in the aqueous phase during work-up as well as during the evaporation of the solvent under reduced pressure. Four other model compounds were also considered for this study, including N-methyl-L-ephedrine, 28, which we have already discussed, and N-benzyl-L-ephedrine 76. It was also interesting to look at the molecules 85 and 86 (scheme XV) which differ from the ephedrine derivatives by the presence of an extra ether group on carbon-3. These last two compounds were prepared by a route similar to that described by Meyers[90].

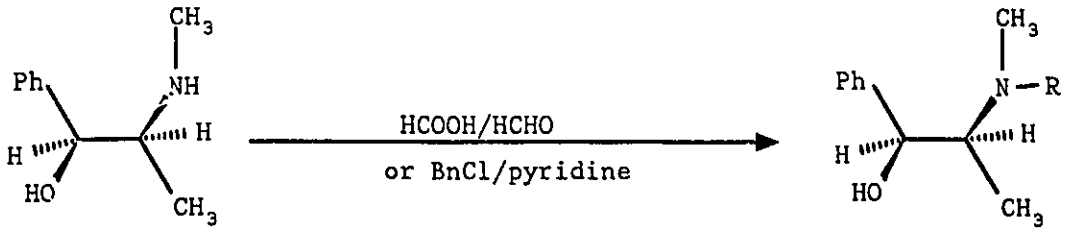
Scheme XIV



69a	R = Me	70	R = Me 39%
69b	R = Et	71	R = Et 64%
69c	R = Ph	72	R = Ph 63%



73 74 71%

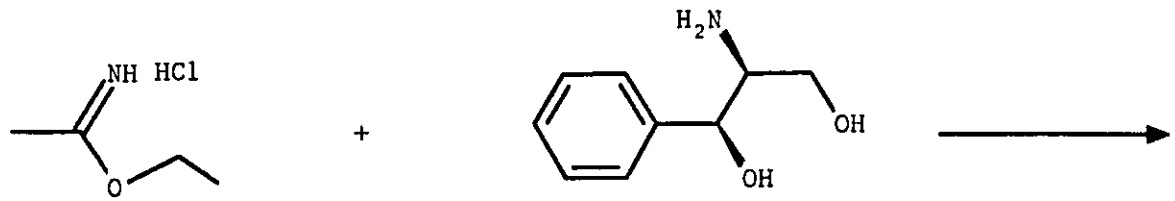


75

28 R = Me

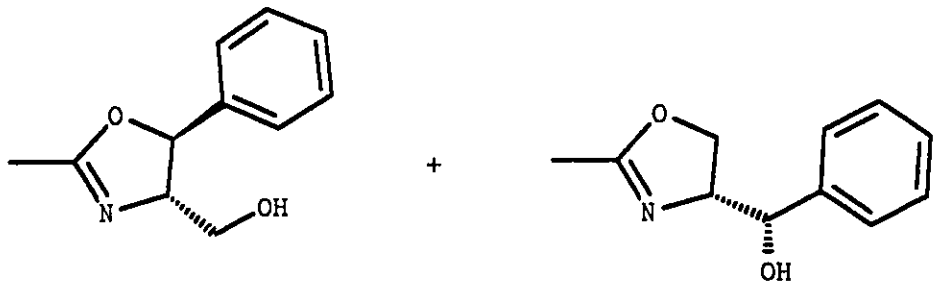
76 R = Bn

Scheme XV



77

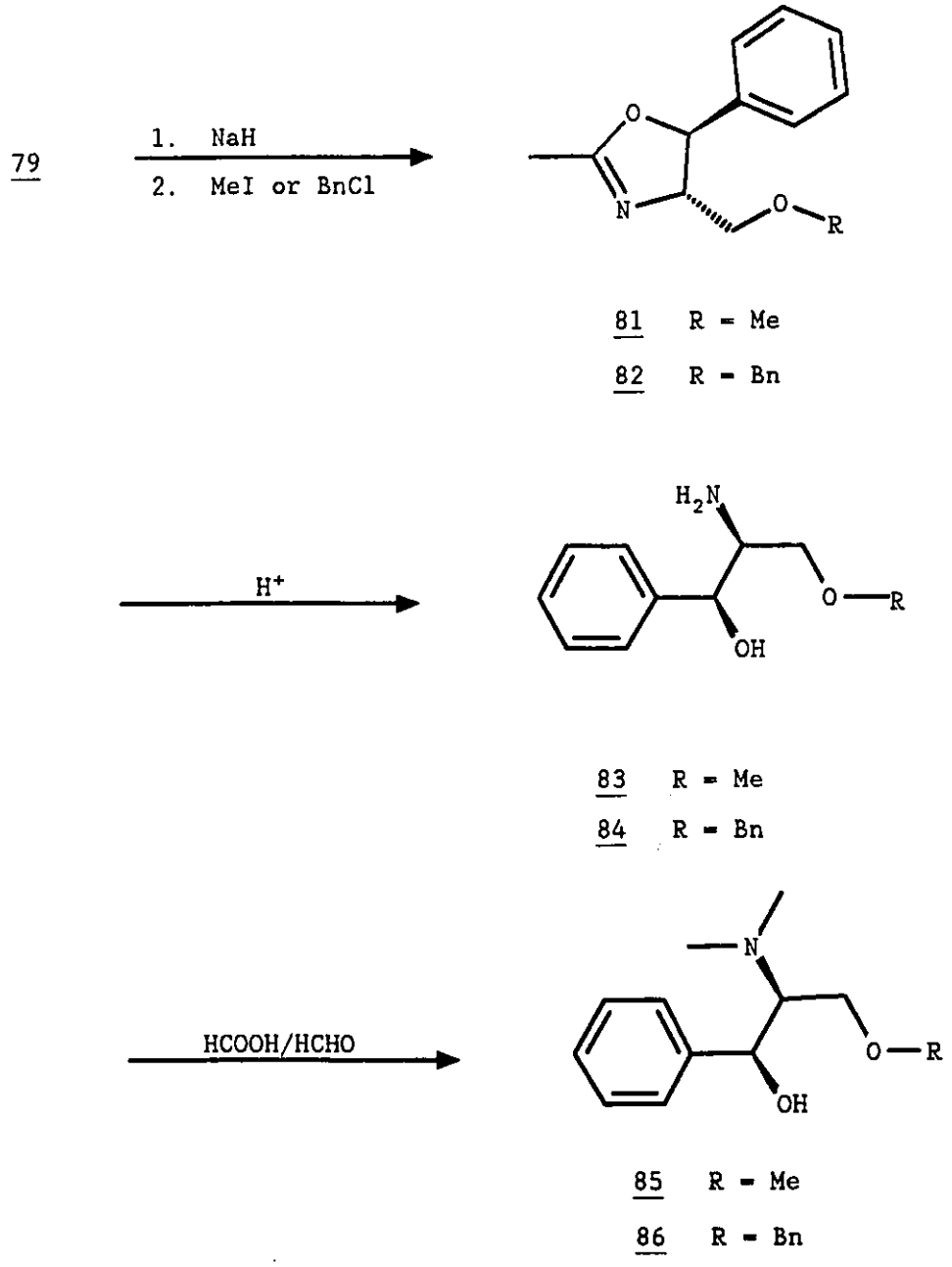
78



79

80

Scheme XV continued

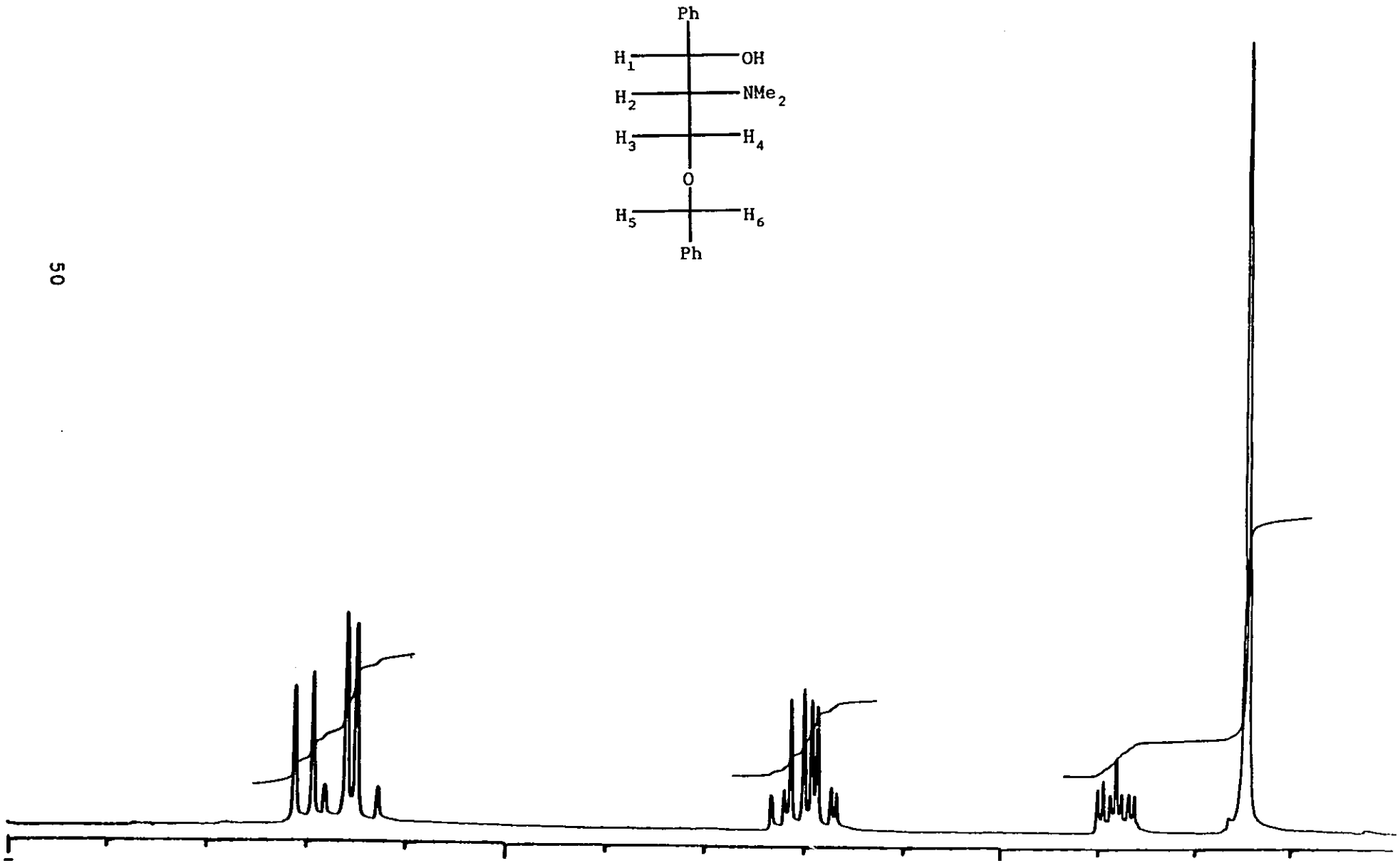


HCl was bubbled through an equimolar solution of acetonitrile and ethanol for a total of 5 hours. After addition of diethyl ether and cooling, the iminoether 77 could be isolated as a white solid. A suspension of this solid in dichloromethane could be condensed with commercially available 78 to give a mixture of the oxazolines 79 and 80. The isomer 79 could be purified by recrystallization and isolated in 78% yield. The purity of 79 was ascertained by its proton NMR spectrum, which was quite distinct from that of its stereoisomer 80. The alkoxide derived from 79 was treated with iodomethane or benzyl chloride to give 81 or 82 in 76% and 40% yields respectively. Acid hydrolysis of the oxazoline gave the amino alcohols 83 and 84 which after methylation afforded the desired model compounds 85 and 86.

The hydrolysis of the oxazoline was almost quantitative for the methyl ether derivative 81 but 84 was obtained in lower yield because of a side reaction in which the benzyl ether was cleaved. The acid sensitivity of the benzyl ether linkage was also noticed in the methylation step where 86 was prepared in 65% yield from 84 as compared to 87% for its methylated counterpart 85.

Characterization of the chiral molecules included standard techniques such as NMR, IR, mass spectra and optical rotations. In view of the asymmetric center of the model molecules it is interesting to look at the NMR spectra of these compounds. For example, the 300 MHz NMR spectrum of the amino alcohol 86 is shown in figure 9. It is interesting to note the splitting patterns of the different protons of this molecule. For this purpose the protons of the structure 86 have been numbered and are also shown in figure 9. We first observe the large singlet for the aminomethyl

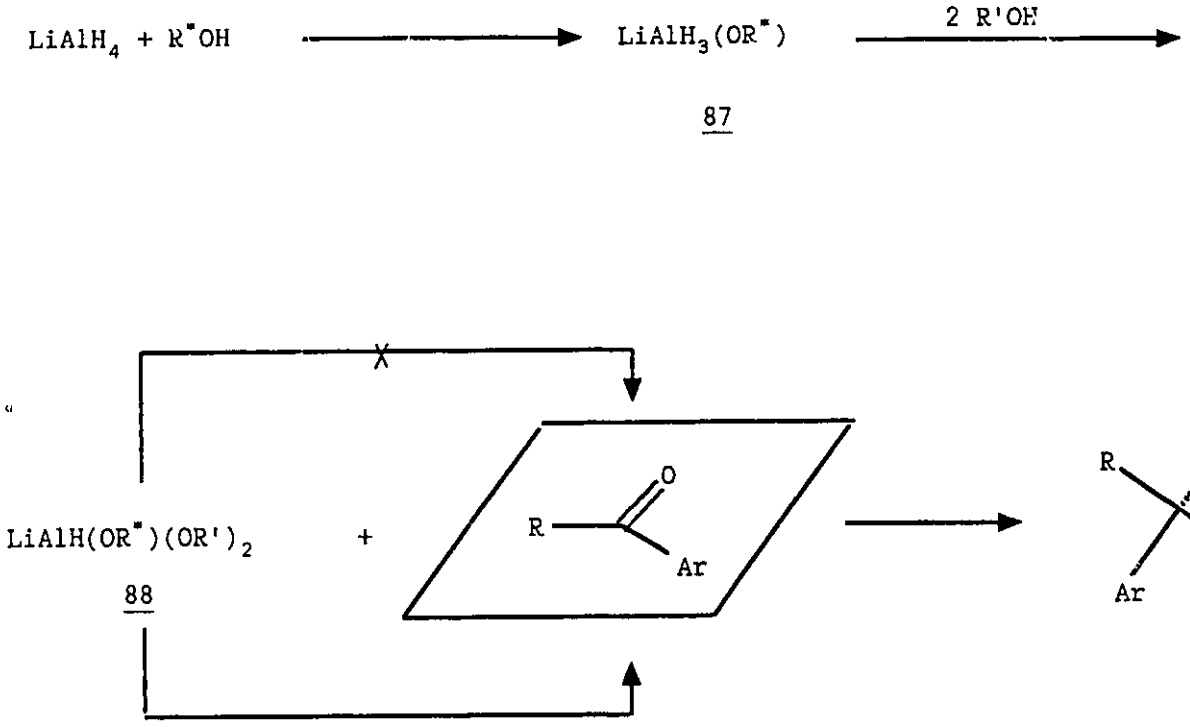
Figure 9. 300 MHz NMR spectrum of the amino alcohol 86.



groups at 2.50 ppm. The next pattern that could be easily recognized was that of H_1 which couples with H_2 and give the doublet at the extreme left of the figure (4.4 ppm). The coupling constant for this doublet is 10 Hz. Because of the nature of this molecule the benzylic protons H_5 and H_6 are diastereotopic and will possess different chemical shifts. In addition, they will couple to each other. The two sets of expected doublets appear at 4.20 and 4.26 ppm (next to H_1). The value of the geminal coupling constant is 11 Hz. The splitting pattern of H_3 and H_4 is more complicated. These protons are also diastereotopic but in addition to being magnetically different they will interact with the alpha proton H_2 and two quartets are expected. These can be seen between 3.2 and 3.4 ppm. Note that the value of the coupling constant arising from the interaction of H_3 and H_2 is not equal to the one arising from H_4 and H_2. Finally, H_2 appears at 2.70 ppm on the NMR spectra. It couples to H_1 with a constant of 10 Hz, to H_3 and H_4 with a constant of 4 Hz and 8 Hz. It was not possible to assign to which of H_3 or H_4 is H_2 interacting to give a coupling constant of 8 Hz. The aromatic protons appear between 7.15 and 7.25 ppm and are of no particular interest which is why that they were not included in figure 9. The other chiral molecules also had very interesting NMR spectra and details of these can be found in the experimental section.

The chiral molecules containing a tertiary amine group were used to complex LAH in a 1:1 stoichiometry (figure 10, 87) and upon addition of 2 equivalents of an achiral additive such as 3,5-dimethylphenol (3,5-DMP) or N-ethylaniline (NEA) a metal hydride complex 88 was obtained. These complexes possess the ability to differentiate between the faces of a carbonyl group since the remaining hydride atom resides in a chiral

Figure 10.



R*OH = 70-72, 74, 28, 76, 85 and 86

R'OH = 3,5-DMP or NEA

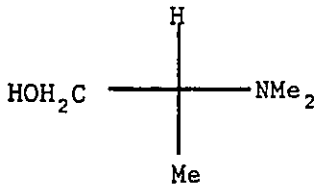
environment. For example, in figure 10 the chiral hydride reagents are shown as preferentially attacking the carbonyl functionality from its si face leading to a predominance of the R-alcohol. Results regarding the use of compounds 70-72, 74, 85 and 86 towards acetophenone are shown in table 10. We first observed that for the amino alcohols with a single center of chirality, 70-72, increasing the steric requirements near the chiral and the reactive center contributed to raising the optical yield of the reaction (runs 1, 4, 5). The extent of asymmetric induction in this series was expected to be low as the reactive hydroxyl group was not directly attached to the chiral carbon. It was quite interesting to note that there was no relation between the absolute configuration of the carbinols obtained from the reduction and that of the amino alcohols. The Fischer projections of the amino alcohols 70-72 are shown in figure 11. Based on the opposite configuration of the amino alcohols, it would be expected that the hydride complex formed from the use of 70 would lead to the carbinol with an absolute configuration opposite to the one resulting from the use of 72. Similarly, it could be expected that the complex derived from the amino alcohol 72 would reduce acetophenone with the same absolute configuration as the complex obtained from 71. These predictions are totally erroneous as seen from the table 10. For example, the molecule 70 with an S absolute configuration formed a complex with LAH and 3,5-DMP which reduced acetophenone to (R)-1-phenylethanol (run 5). By analogy, (S)-1-phenylethanol was obtained when the reaction was carried out with the complex derived from 71 which is the R enantiomer (run 4). However, the amino alcohol 72 whose absolute configuration is R (the same as 71) formed a complex which yielded (R)-1-phenylethanol (runs 1-3). It thus seems that in the case of the chiral molecule bearing the phenyl group the electronic effect predominated over the bulkiness created by the aromatic ring. Based

Table 10. Asymmetric reduction of acetophenone with LAH complexes of the model compounds and achiral additives.

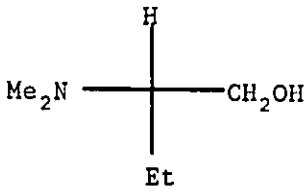
Run	Chiral molecules	Achiral additives[1]	Molar ratio of LAH/chiral/achiral	T (^{o} C)	Optical yield (%)[2]	Configuration
1	72	3,5-DMP	1:1:2	-15	26	R
2	72	3,5-DMP	1:1:2	-78	38	R
3	72	NEA	1:1:2	-78	13	R
4	71	3,5-DMP	1:1:2	-15	19[3]	S
5	70	3,5-DMP	1:1:2	-15	12	R
6	74	3,5-DMP	1:1:2	-15	24	S
7	74	3,5-DMP	1:1:2	-78	44	S
8	74	NEA	1:1:2	-78	25	S
9	85	3,5-DMP	1:1:2	-15	52	S
10	85	3,5-DMP	1:1:1	-15	51	S
11	85	none	1:1:0	-15	2	S
12	85	3,5-DMP	1:1:1	0	50	S
13	85	NEA	1:1:2	-78	66	R
14	85	NEA	1:1:1	-78	17	R
15	86	3,5-DMP	1:1:2	-15	42	S
16	86	NEA	1:1:2	-15	59	R

1. 3,5-DMP = 3,5-dimethylphenol and NEA = N-ethylaniline
2. The alcohol was purified by TLC
3. Corrected for the optical purity of 71

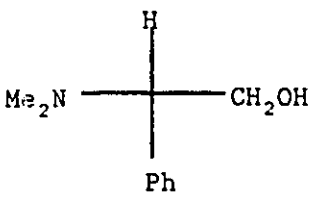
figure 11.



70

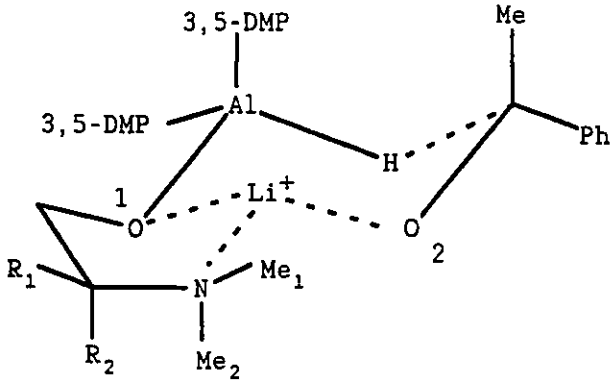


71

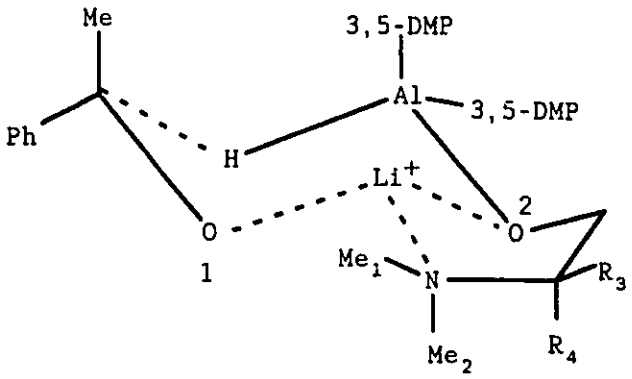


72

figure 12.



89



90

on the observations of Ashby and Boone[8] as well as those of Noyori[33] it was possible to construct a model which accounted for the results observed in the present work. The plausible intermediates leading to both enantiomers of 1-phenylethanol are shown in figure 12. Note that in both cases the phenyl group of acetophenone adopts the equatorial position to reduce steric effects with 3,5-DMP, but most important it eliminates the electronic interaction between the electrons of that aromatic ring and those of the 3,5-DMP oxygens. The last factor is the most important one which governs the stereochemistry of the hydride addition as discussed previously with the examples of Noyori[33]. The intermediate 89 leads to (S)-1-phenylethanol while 90 gave the enantiomeric carbinol. Based on steric factors we have to compare in the case of the amino alcohol 71 the following intermediates; 89 (R_1=H, R_2=Et) vs 90 (R_3=Et, R_4=H). It is possible with the help of models to show that the intermediate 90 is thermodynamically less stable than 89. With the conformation that seems to minimize steric interactions between the various groups of this intermediate, the interaction between R_3 and the N-Me_1 can only be avoided at the expense of eclipsing the N-Me_2 and the Li-O_1 bond. This last interaction can be avoided by additional distortion of the five membered-ring but that causes other type of interactions to appear, for example, that of R_4 and the lone pair of electrons on the oxygen atom-2. With the intermediate 89 all the bonds can be in a gauche conformation without any of the interactions encountered in 90. This accounts for the predominant formation of the S alcohol when the model compound 71 was used to complex LAH. The amino alcohol 70 whose absolute configuration is opposite to that of 71 yielded the R alcohol, based on the same arguments. But since the methyl group is less bulky than the ethyl group, the difference in the thermodynamic stability of both intermediates 89 (R_1 = Me, R_2 = H) and 90

(R_3 = H, R_4 = Me) is inferior to that of the ethyl case described above and a less stereoselective process took place.

The case of the phenyl group was much simpler to resolve and is represented by 89 (R_1=H, R_2=Ph) vs 90 (R_3=Ph, R_4=H). With the help of models, it was easy to note that 89 leads to very strong interactions between the π electrons of the phenyl ring (R_2) and the lone pair of the oxygen atom (O_1). This can avoided only at the cost of conformational instability. The transition state 90 lacks all these factors and gives rise to a much more stable transition state than 89 explaining the predominant formation of (R)-1-phenylethanol. This series of amino alcohols also confirmed that electronic factors were more important than steric factors in determining the most stable transiton state. If the steric effect was a more important factor than the electronic effect, then the reductions performed with the hydride complex obtained from the amino alcohol 72 would have given rise to a carbinol with the same absolute configuration as the one arising from the reduction with the complex derived from 71. With the prolinol derivative 74 results similar to those of 72 were obtained with a maximum optical yield of 44% at -78°C.

Some interesting observations could be made when compounds 85 and 86 were used as chiral auxiliaries in the reduction reaction. First, and as expected from published studies with similar compounds[38,42,91], the reactions generally led to moderate optical yields, typically in the 40-70% range depending on reaction conditions. Next, a strong dependence of the stereochemical outcome of the reaction on the nature of the chiral complex was observed. Most significant perhaps was the effect of both the nature and the amount of achiral additive. As can be seen in table 10, runs 9-11,

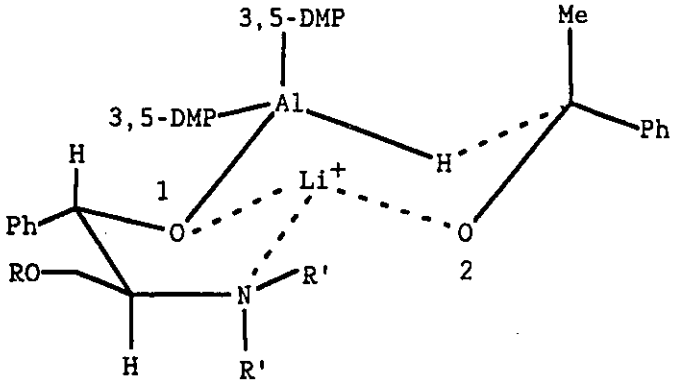
changing the molar ratio of the 3,5-DMP additive from 2 to 1 mole in a reaction with 1 equivalent of LAH and chiral auxiliary, has no significant effect as (S)-1-phenylethanol was obtained in approximately 50% e.e. in both cases; in contrast, total removal of the 3,5-DMP completely destroyed the stereoselectivity of the reaction. This finding was at variance with the observations of Vigneron et al.[38] in similar reactions with N-methylephedrine; in these reactions lowering the amount of 3,5-DMP from 2 to 1 with respect to LAH resulted in a significant decrease in the stereoselectivity of the reduction. Our observation with 85 suggested that the additional oxygen ligand which is present in the compound may play an important role through a contribution to the stabilization of the intermediate species involved in the key step of the reaction.

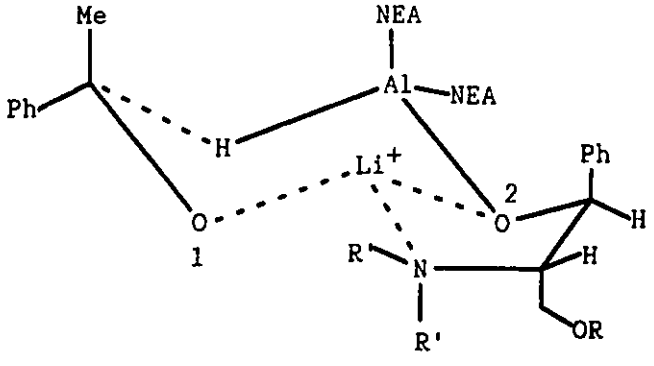
When NEA was used as achiral additive instead of 3,5-DMP in reactions involving 85 and 86, the amount of NEA used in the reaction appeared to be extremely important as very low optical yields resulted from a decrease in NEA/LAH ratio from 2:1 to 1:1 (run 13 and 14). In addition, the stereochemical outcome of the reaction was reversed as (R)-1-phenylethanol was obtained as the major component of the asymmetric reduction. Based on our previous discussion it was possible to construct models of the two intermediates leading to both enantiomers of 1-phenylethanol. They are shown in figure 13. The complex 91 is the one where two of the hydride atoms have been consumed by reacting LAH with 3,5-DMP. This is the intermediate leading to the S enantiomer. The use of the achiral additive NEA gives the complex 92 leading to the R enantiomer. Construction of the models shows that the interaction between the electrons of the phenyl group of the amino alcohol and O_1 is a predominant one which can only be avoided by a change in the conformation of the intermediate which in turn creates

Table 11. Relationship between the enantiomeric excess and standard free-energy difference at -15.0°C and at 25°C (based on F = -RTlnK where R = -1.987 cal deg^{-1} mol^{-1}).

ee %	$F_{-15}{}^{\circ}C$ cal/mol	$F_{25}{}^{\circ}C$ cal/mol
10	101	119
20	208	240
30	318	367
40	434	502
50	563	651
60	710	821
70	889	1028
80	1126	1302
90	1509	1745
96	1995	2306
98	2356	2723
99.8	3540	4092
99.98	4721	5457

figure 13.





91 R = Me or Ph
R'= Me

92 R = Me or Ph
R'= Me

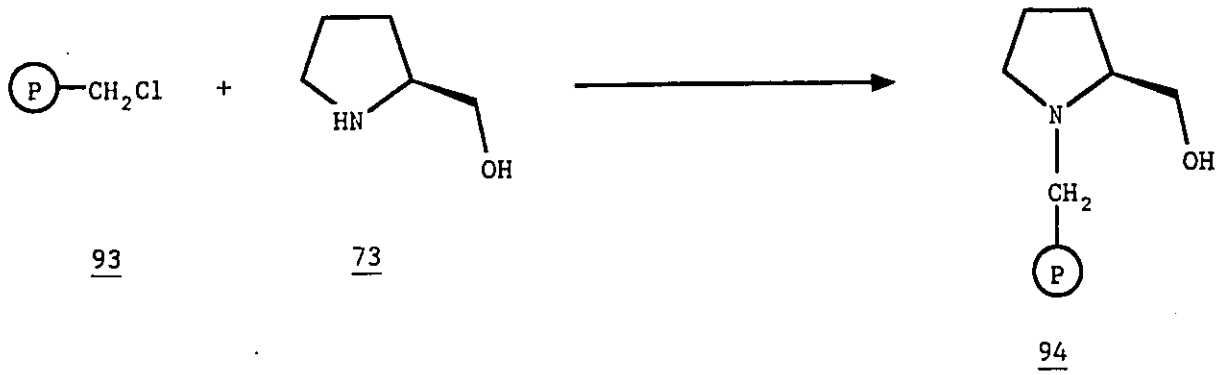
additional interactions between the same phenyl group and the substituent on the aluminum atom. This intermediate will therefore be more stable with 3,5-DMP as the achiral additive since it is less bulky than NEA and this will minimize 1,3-steric interactions. On the same basis, no such interactions exist in the intermediate 92 since the phenyl group is anti with respect to the lone pair on the oxygen atom. As a consequence, this complex can adopt a conformation which will minimize 1,3-interactions between the phenyl group and the aluminum substituents. In this case, the use of more bulky substituents such as NEA causes less destabilization of the intermediate and the R enantiomer predominates in the product of this type of reduction. It was also interesting to note that only the intermediate 91 gives rise to an extra complexation between the ether oxygen and the Li^+ atom. This probably increases the rigidity of the intermediate 91 which explains why a decrease in the 3,5-DMP/LAH ratio has less effect on the optical yield than in the case of the intermediate 92 which lacks that extra rigidity.

It should be noted that the proposed models are the ones which use conformations which appear to minimize steric and electronic effects. Table 11 shows the difference in energy between complexes giving rise to a known enantiomeric excess. From the best result reported in table 10 (run 13) we gather that the activation energies of the path leading to the R and S enantiomers differ by less than 1 kcal/mol. Therefore, care should be taken since the models cannot be an absolute tool even though they can explain the observed results.

2.1.2 The study of polymer-supported chiral complexes of LAH.

Since the model compounds gave rise to moderate optical yields we were interested in the preparation of the polymer bearing the same optically active molecules to study whether or not such reagents would give rise to an improvement in the enantioselectivity of the reduction when compared to the model compound. We decided to work with 1% crosslinked chloromethyl polystyrene as a starting material since its insolubility in all organic media renders this polymer and derivatives easy to isolate and recycle. As well, it can be prepared from crosslinked polystyrene with the use of chloromethyl alkyl ether and $SnCl_4$ as a catalyst[59] to give polymers with various degrees of functionalization. Finally, quantitative displacement of chlorine by numerous nucleophiles is easily achieved[64]. We first looked at the preparation of polymer-supported L-prolinol, 94, according to scheme XVI. Typically, the reaction was carried out with a three fold excess of L-prolinol used as the nucleophile as well as the acid acceptor. The yield for this reaction was almost quantitative as shown by elemental analysis, and a polymer in which 10% of the styrene aromatic rings were substituted with a chiral molecule could be obtained. As was done previously with the model compounds, testing of the polymer-bound chiral auxiliaries was accomplished using the reduction of acetophenone with partially deactivated LAH complexes (Table 12). All the reactions were carried out at $-15^{o}C$ in ether using a 1:1 ratio of LAH/chiral polymer and achiral additives such as 3,5-DMP and NEA. As can be seen in Table 12, both the nature of the achiral additive and the molar ratio LAH/chiral auxiliary/achiral additive have an influence on the outcome of the reaction. With the polymer-bound prolinol 94, almost no enantioselectivity was observed in the absence of

Scheme XVI



93 73 94

Table 12. Asymmetric reduction of acetophenone with $LiAlH_4$ complexes of the polymer 94.

run	Achiral Additive	Molar ratio[1]	%yield[2]	%ee	configuration
1	3,5-DMP	1:1:2	34	4	S
2	3,5-DMP	1:1:1	65	5	R
3	none	1:1:0	61	4	R
4	NEA	1:1:2	67	20	S
5	NEA	1:1:1	71	13	S

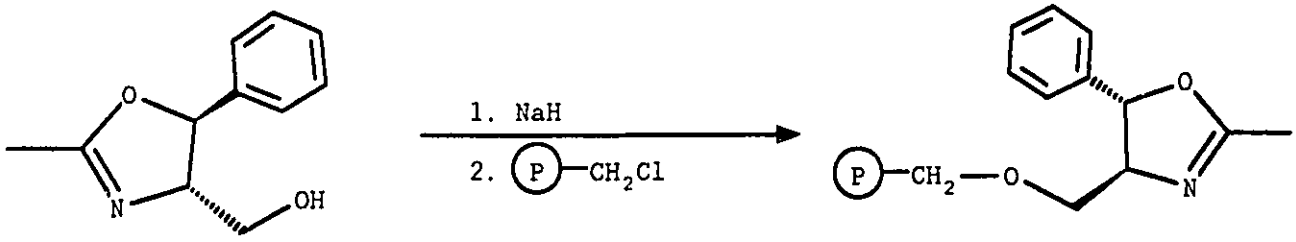
1. Molar ratio LAH:polymer:achiral additive
2. % Yield refers to isolated yield of pure 1-phenylethanol after chromatography

achiral additive or in the presence of 3,5-DMP (runs 1-3). Interestingly, varying the amount of 3,5-DMP caused a reversal of the absolute configuration of the carbinol (run 1 and 2). This is in sharp contrast with the results of the model reactions using 74 and the polymer-assisted reactions involving NEA as an achiral additive. The latter reaction with added NEA (run 4) afforded essentially the same results with the polymer-bound as with the low molecular weight chiral auxiliary.

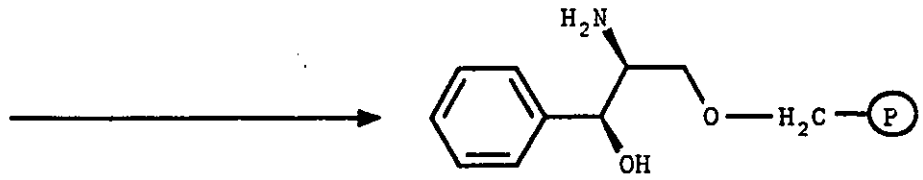
We were also interested in the preparation of the polymer equivalent of the amino alcohol 86. For that purpose the oxazoline 79 could be reacted with chloromethylated polystyrene (DF = 0.09) to give the polymer-supported chiral oxazoline 95 in quantitative yield as determined from the nitrogen analysis and the infrared spectrum (scheme XVII). The characteristic band of the C=N functional group can be observed at 1674 cm^{-1} in the infrared spectrum. Acid hydrolysis of the protecting group was achieved in refluxing HCl. The nitrogen analysis also revealed that the reaction was quantitative and complete disappearance of the oxazoline band at 1674 cm^{-1} could be noticed. The methylation of 96 was carried out in a similar fashion to that of the model compound using an excess of formic acid/formaldehyde mixture. Disappearance of the amine band in the infrared spectrum combined with a slight decrease in the nitrogen content of the polymer, indicated that the desired polymer 97 was obtained. No carbonyl could be detected in the infrared spectrum. A carbonyl band would have indicated the presence of the formamide group which is an intermediate in this reaction.

Similarly, chloromethyl polystyrene was reacted with a 2.5 fold excess of the amino alcohol 83 to yield the polymer 99 in nearly quantitative

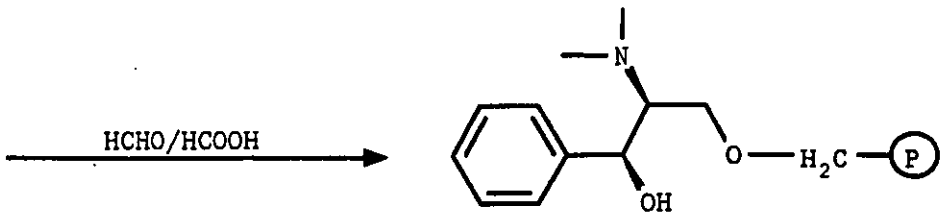
Scheme XVII



79 95



96



97

yield as determined from elemental analysis (scheme XVIII). An excess of amino alcohol was utilized to avoid quaternization of the amine and after washing and drying of the polymer the infrared spectrum showed both the alcohol and amine functionalities. This polymer was methylated as described for 96.

The polymers 97, 98 and 99 contained approximately 8% of derivatized styrene rings. The aluminum hydride complex of these polymers used in conjunction with an achiral additive could be utilized in the reduction of acetophenone. The results are shown in table 13. As with the model compounds, changing the nature of the achiral additives gave rise to a reversal of the absolute configuration of the product 1-phenylethanol (runs 1,2 and runs 5,6). In addition, increasing the steric environment of the remaining hydride in the reagent by decomposing LAH with a polymer containing two reactive functional groups such as 98 did not give rise to a improvement in the optical yield (run 3 and 4). On the contrary, the enantioselectivity of such processes was almost nil. This in in agreement with low molecular weight counterparts where substituting achiral additives by chiral molecules does not improve enantiomeric excesses[31,32,35-37]. The best result with the polymer chiral auxiliaries was obtained with 97 (run 1) but in all the cases the polymers afforded lower optical yields than their low molecular weight analogs.

As previously mentioned, only two other examples can be found in the literature where chiral polymers complexing LAH were used in the asymmetric reduction of ketones[75,77]. It was interesting to note that in both of these cases the polymeric reagents did not perform as well as the model compounds. This was in agreement with our findings but unfortunately no

Scheme XVIII

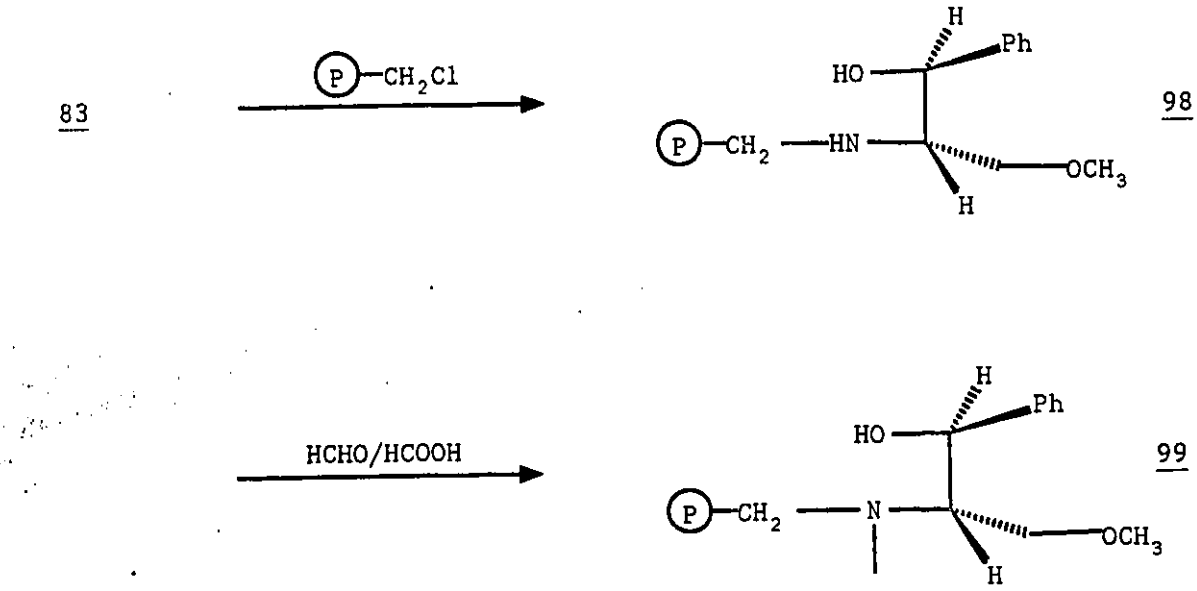


Table 13. Asymmetric reduction of acetophenone at −15°C with LAH complexes of the polymers 97, 98 and 99.

run	Chiral polymer	Achiral additive	Molar ratio[1]	%yield[2]	%ee	configuration
1	97	3,5-DMP	1:1:2	77	37	S
2	97	NEA	1:1:2	72	17	R
3	98	NEA	1:1:1	63	2	R
4	98	3,5-DMP	1:1:1	58	2	R
5	99	3,5-DMP	1:1:2	81	25	S
6	99	NEA	1:1:2	79	15	R

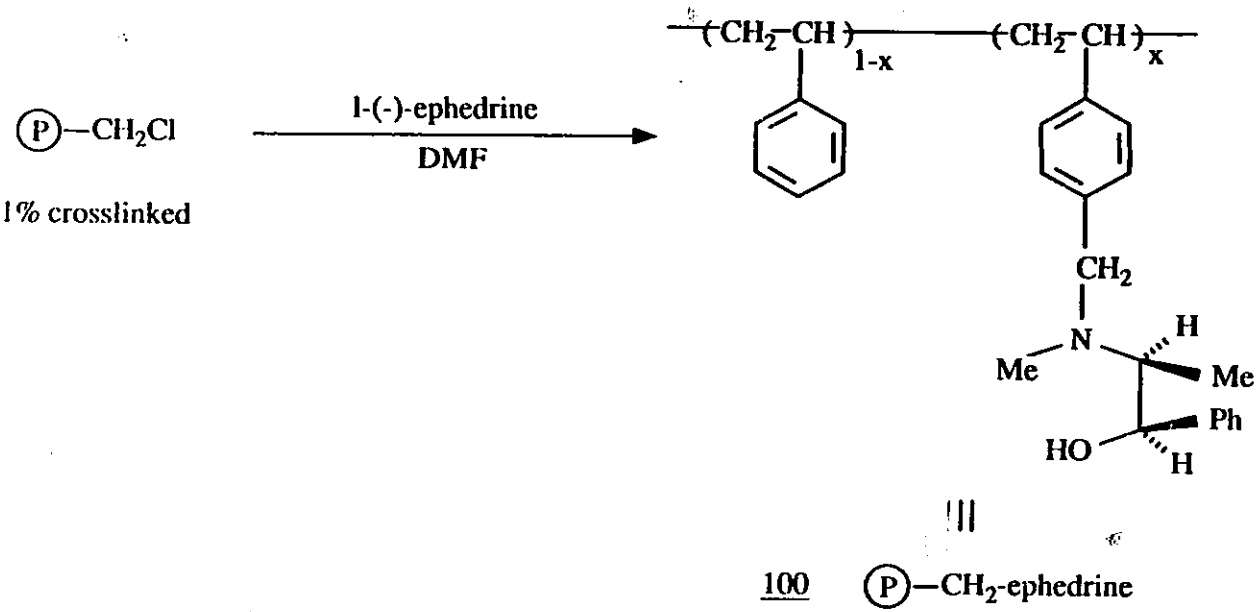
1. Molar ratio LAH:chiral polymer:achiral additive.
2. %yield refers to isolated yield of pure 1-phenylethanol after chromatography.

explanation was given by these authors to account for the peculiar behavior of the polymers. This prompted us to look in more detail at this particular polymeric reaction as polymer-supported reagents do not usually behave in that manner. Indeed, numerous examples can be found where the polymer-supported reagents can duplicate the chemical transformation of the model compound with the same efficiency[53,54]. In order to undertake a complete study of this particular aspect of polymers we decided to prepare the model compound N-benzyl-l-(-)-ephedrine and the corresponding polymer.

This work was performed in conjunction with Dr. Edwald Bald. Some results obtained by Dr. Bald are listed in the appendices A-C and will be referred to throughout the discussion.

The ephedrine derivatives were chosen for their ready availability, their low cost and the fact that reduction using their hydride complexes only proceeded in moderate optical yields in the case of the unbound moiety, thereby allowing for the observation of any eventual polymer effect on the enantioselectivity. In addition, the preparation of the polymer was a single step reaction therefore avoiding multistep synthesis on solid support such as the protection-deprotection sequence encountered in the preparation of 97. N-benzyl-l-ephedrine, 76, was simply prepared by the reaction of l-(-)-ephedrine with benzyl chloride in dry pyridine. 60 % of the pure material could be obtained after chromatography. The insoluble polymer-bound N-methylstyryl analogue 100 was prepared most conveniently by chemical modification of crosslinked chloromethylated polystyrene (scheme XIX). Although several procedures were effective the best results leading to quantitative displacement of chloride from the polymer were obtained by using a 3-fold excess of l-(-)-ephedrine in DMF in 85°C. In contrast,

Scheme XIX



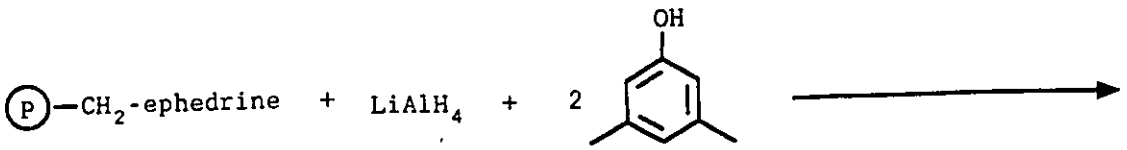
100 (P)—CH_2-ephedrine

reactions carried out in DMSO led to some oxidation of the polymer as observed by the presence of an aldehyde band in the IR spectrum. The use of other solvents or of smaller amounts of l-(-)-ephedrine in the presence of acid acceptors generally led to incomplete replacement of chloride. The final degree of functionalization (DF) of polymer 100 was determined solely by the initial degree of functionalization of the chloromethylated resin and, in our preliminary experiments, we chose to work with polymers in which 28-35% of the aromatic rings of the styrene repeating units carried the ephedrine moiety. This relatively high DF was thought to be desirable to reduce the amount of polymer and solvent used in each experiment.

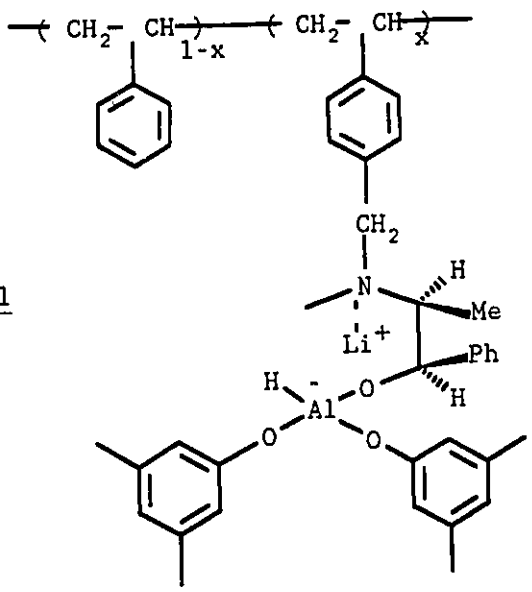
In a typical experiment, the chiral reducing agent 101 was prepared as shown in scheme XX by successive treatment of a solution of LAH with 2 molar equivalents of 3,5-DMP and, after a period of equilibration, 1 molar equivalent of the solid polymer. This approach is analogous to that used by Vigneron et al.[38] and others in work with N-methylephedrine-LAH or other similar complexes; ideally it would afford after equilibration a chiral reducing complex such as 101, with a single hydride functionality remaining in a chiral environment. Based on the models previously proposed, the reduction of a prochiral ketone such as acetophenone would be expected to proceed through the preferential formation of an intermediate such as 102 in which Ⓟ represents the partially parasubstituted polystyrene backbone, thereby resulting in an enantioselective reduction. Indeed, all the reductions carried out with the ephedrine derivatives gave (R)-1-phenylethanol which is in agreement with the model 102.

Unfortunately, the results obtained in this reaction were extremely disappointing at first, as shown in table 14. The complex prepared from

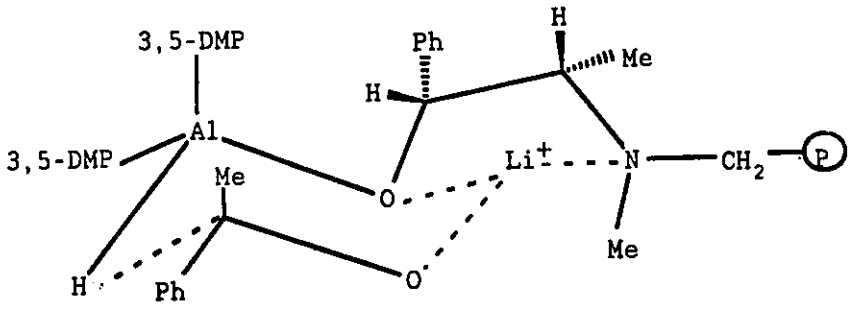
Scheme XX



100



101



102

the model compound N-benzyl-l-(-)-ephedrine reduced acetophenone with 85% enantioselectivity which was slightly better than the results obtained with N-methyl-l-(-)-ephedrine under similar conditions[38] (run 1). However, the polymer 100 seemed incapable of affording high enantioselectivities. Under similar conditions to that of the model compound, the polymer complex afforded R-(l)-phenylethanol in only 7.2% optical yield (run 2). Similar results were also found by Dr. Bald when he used a highly loaded polymer-bound ephedrine (Appendix A). Contrary to what would have been expected from model studies, the enantioselectivity of the reaction with polymer 100 was not inversely related to temperature as is often the case, better results being obtained at $-15^{o}C$ rather than $-78^{o}C$ (runs 2 and 3). Changing the solvent to THF had little effect on the outcome of the reaction despite the fact that THF should be a better medium than ether for this reaction due to its ability to better swell the polymer (run 1 and 4, run 2 and 5). 1% cross-linked polystyrene will swell to up to 10 times its original value when immersed in THF.

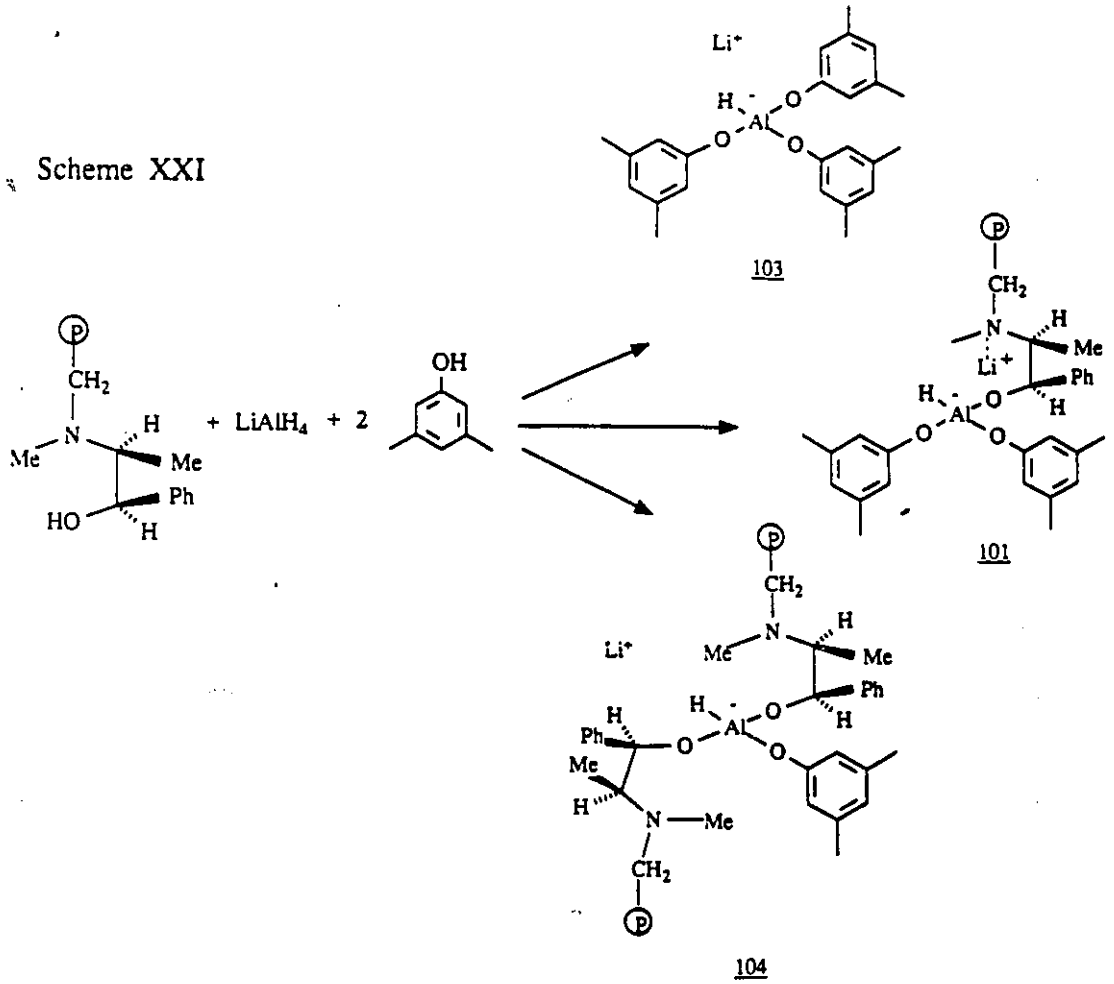
So here again it was noticed that LAH complexes of polymeric reagents could not duplicate model compound behavior, which was similar to our previous results. These observations and comparison with miniature analogues suggest that it was an inherent property of the polymer itself, rather than of the bound ligand, that was responsible for the loss in enantioselectivity. There were two possible explanations which could account for these observations. The first one was related to the accessibility of the reactive sites. The presence of chiral complexes inside the polymer beads implied that the LAH reagent diffused inside the beads to form the complexed sites prior to reaction with acetophenone. This not being the case, we would be left with achiral hydride reagent in

Table 14. Reduction[1] of acetophenone with a highly loaded polymer-bound ephedrine[2].

Run	Solvent	Temperature (°C)	Chemical Yield (%)	Optical Yield (%)
1[3]	ether	-15	86	85
2	ether	-15	39	7.2

1. Molar ratio LAH/polymer/3,5-DMP was 1:1:2 in all the cases.
2. Reactions with 1.25:1 ratio of LAH/acetophenone using 1% cross-linked gel type polymer-bound ephedrine with a capacity of 2.35 mmol/g of polymer (DF = 0.39).
3. Reduction carried out with the model compound N-benzyl-1-ephedrine.

Scheme XXI



solution which would reduce acetophenone in an achiral manner. The second explanation has to do with neighboring groups effect. Due to the proximity of the ephedrine units in the polymer it was possible for aluminum hydride to link two of them by covalent bonds (scheme XXI). The consequence of that disproportionation was that we did not know the exact nature of the reagent responsible for the reduction of acetophenone and the desired complex 101 was not the only species formed in the reaction of LAH with 3,5-DMP and polymer 100. Scheme XXI shows two of the other three trialkoxyaluminum hydride complexes, 103 and 104, which could be formed in addition to 101. Similarly a great variety of mono or dialkoxyaluminum hydride complexes not shown in scheme XXI could be formed and all, as well as uncomplexed LAH, could participate in the reaction.

These hypotheses are the result of the changes brought about by the solvent of the reaction medium. With small molecules it is known that THF is a solvent leading to lower optical yields than diethyl ether[15,33,38]. However, in the case of the polymer-bound ephedrine the opposite effect was observed (Appendice A, runs 3 and 6). This was due to the fact that THF swelled polymer beads and therefore increased the site accessibility. Since we increased the number of chiral complexes formed by such an effect, a better optical yield was observed. This suggested that when ether was used as a solvent not all the chiral sites were available for reaction. To verify this hypothesis, a series of experiments was carried out using a different procedure (B in Appendix B) whereby the polymer was filtered and washed, after formation of the chiral polymer-bound complex and equilibration, to remove any reducing agent which might not have become bound to the polymer. As can be seen in this table, run 4, the use of this procedure resulted in a sharp increase in the stereoselectivity of the

reaction with a concurrent lowering of the chemical yield indicating that the initial ether solution in which the polymer was suspended contained some hydride reagent which could only be achiral in nature since it was not bound to the polymer. By this filtration procedure we increased the participation of the polymer chiral complexes and an increase in the enantioselectivity of the process was observed (run 1 vs run 4). As a last evidence to show that only the surface of the polymer beads participated in the reduction we thought we would completely destroy the hydride reagent by reaction with two equivalents of ephedrine units and two equivalents of 3,5-DMP. So with a ratio LAH/polymer/3,5-DMP of 1:2:2 there should not be any hydride left on the aluminum atom. However, as seen in Appendix B, run 7 and 8, it was possible to reduce 84% of the initial amount of acetophenone under these conditions. Using the same ratio and filtering the sample prior to the addition of acetophenone to remove unbound LAH showed that some LAH diffused inside the beads to form chiral complexes and was not destroyed by the achiral agent as some reduction took place (run 8).

However, when a macroporous resin with capacity of 1.81 mmol/g of polymer was used, in which case we did not expect any problem with the site accessibility, much lower enantioselectivity were obtained (Appendix B, run 3 and 5). Similarly, after filtration of the polymeric reagent to remove unbound hydrides it was still not possible to reproduce the model compound behavior. This suggested to us that with such highly loaded polymers (DF = 0.27) site-site interactions were taking place and may in fact be responsible for the lack of accessibility of the chiral units. To verify this hypothesis several polymer samples with varying capacity were prepared and tested in asymmetric reductions of acetophenone. The results regarding

Table 15. Influence of polymer capacity on the enantioselectivity[1]

run	capacity (mmol/g)	DF	yield (%)	ee (%)
1	2.35	0.39	39	7.2
2	0.90	0.14	73	53
3	0.70	0.09	97	78.8

1. All reactions using 0.8 molar equivalent of acetophenone with 1% cross-linked polymer in ether at $-15^{o}C$ with a molar ration LAH/polymer/3,5-DMP of 1:1:2 and using once recycled polymer in procedure A.

their use are shown in table 15. As the DF of the polymer was reduced from 0.39 to 0.09 the optical yield increased from 7% to 78% (run 1 and 3). This follows a similar trend to what has been reported by Dr. Bald (Appendix C, table 1). Such a large increase, which brought the enantioselectivity of the reaction to a level equivalent to that obtained by Vigneron et al.[38] with similar N-methylephedrine complexes, suggested that with the lightly loaded polymers, equilibration of the final complex responsible for the reduction of acetophenone was more uniform and produced species which likely resemble 101 and 102 in the key steps of the overall process. In addition, the results given in table 15 confirm that all the groups in polymer 100 with DF = 0.09 were fully accessible and point toward the formation of complexes having structure 101 and an intermediate such as 102 when the proper stochiometry was maintained in a medium which can be fully penetrated by all reagents. Thus, while both high chemical yields and high enantioselectivities were obtained with 1:1:2 molar ratio LAH/chiral polymer/achiral phenol, the use of a 1:2:2 ratio (Appendix C, table 2) led to the complete neutralization of LAH and no reduction was observed. Indeed this result confirmed the accessibility of all the sites of 100 to the hydride reagent and is in sharp contrast to the results

reported in Appendix B, run 7 and 8 , where high reduction yields were obtained despite the presence of excess ligands which would have been expected to deactivate fully LAH had all the reactive sites of the polymer been available. Similarly, Appendix C, table 2 shows that an increase in the amount of chiral ligand with respect to LAH, which forces the interactions of several sites of the polymer, caused a decrease in both chemical and optical yields (run 6 and 7). Finally, if the molar ratio of the chiral and achiral alcoholic components were adjusted (run 8) to form complexes with an average of one remaining hydride but with some units incorporating more than one ligand, the chemical yield was high while the optical yield was depressed with respect to the standard reaction (run 2).

We have also confirmed the ability of the polymer-bound ephedrine 101 to be recycled and reused through dozens of separate experiments; typical results are shown in the first entries of table 2 (Appendix C). It was generally observed that the first reaction cycle afforded a slightly lower enantioselectivity than subsequent cycles. As analytical monitoring of the polymer showed no remaining chloromethyl groups in 100 prior to the first reaction and no apparent change in either nitrogen content or infrared spectrum after one or more uses, it could only be assumed that this enhancement of the polymer was due to very minor changes in composition or structural arrangement within the polymer beads. Indeed, a freshly prepared polymer subjected to rapid treatment with LAH then washed with acid and base afforded results comparable to those of a recycled polymer. Although THF is a far better swelling agent than ether, its use with lightly loaded polymer 100 free from site interactions resulted in a lowering of the optical yield when compared to the same reaction in ether; this is also the case with all the model compounds[15,33,38]. As mentioned

previously, this is likely due to the better solvating properties of THF itself which competes effectively with the polymer's nitrogen ligand in the complexation of the lithium cation and therefore disrupts the selective formation of the intermediate 102.

At this point, it was interesting to compare our results to those reported by other for similar reductions, using polymer-bound LAH complexes. The data reported by Liu, Kondo and Takemoto[75], after downward correction of all reported optical yields (table 7, page 32), can be interpreted and explained using the conceptual model we have developed with polymer 100. In their work[75], a polymer-supported bornadiol, 42, was used as a chiral auxiliary, in the asymmetric reduction of acetophenone with LAH partly neutralized by addition of an equivalent of methanol. Because of the cis arrangement of the diol, the polymeric reagent could easily form a bidentate complex with LAH, minimizing the number of reactive hydride species that could be present in the mixture, yet this did not preclude the formation of fully deactivated aluminum complexes if two neighboring chiral sites combine to a single LAH molecule. Thus, Liu et al. generally reported ee's which were significantly lower for a crosslinked polymer with DF 0.31 than for the soluble miniature model compound, and they also noticed a further decrease in optical yield as the percent crosslinking was increased and therefore the accessibility of the reactive sites was decreased. In addition, with a highly loaded polymer and in the absence of added achiral components, no enantioselectivity was obtained while reduction still took place[75]. This was probably due to site interactions where there was formation of fully deactivated 2:1 complexes of the

polymer-supported bornanediol with LAH and a lack of accessibility of reactive sites within the beads.

Similarly, the extremely low enantioselectivities reported by Suda et al.[77] for their polymer-based chiral dihydroxybiphenyl-LAH complexes (49, page 34) was probably due to extensive site interactions in the high-capacity polymer they chose to use. Again, the formation of a bidentate complex with LAH, though decreasing the number of active complexes which could possibly be formed, did not prevent interaction of sites which, in this case again, resulted in significant amounts of soluble achiral reducing agent being present in the reaction mixture, thus lowering the enantioselectivity of the reaction. Also interesting was the fact that when Suda et al. used their model compound for the reduction of acetophenone in the absence of achiral additive the optical yield dropped from 79% to 2%, indicating that even in solution formation of the bidentate predominated over the monodentate chiral hydride reagent.

2.2 THE REDUCTION OF ACETOPHENONE USING CHIRAL COMPLEXES OF BORANE

2.2.1 The study of model compounds

Because of our interest in the use of polymer-supported reagents in the asymmetric reduction of ketones we also wanted to look at chiral borane complexes since it has been shown by Itsuno et al.[46] that such polymeric

reagents do not suffer from the same limitations as the aluminum hydride polymer complexes.

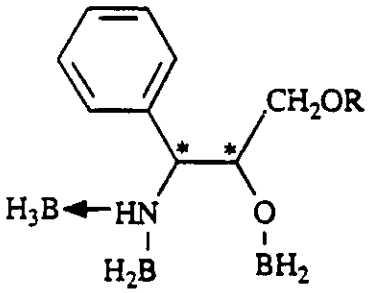
Borane complexes do not usually require that the amine functionality be tertiary and in fact better results were obtained with primary amines[46]. For that reason, previously prepared 83 and 84 could be utilized directly without further transformation. Before the chiral borane complexes of these molecules were used to reduce acetophenone, we wanted to understand the chemical nature of these complexes. We were interested in the effect that the extra oxygen could induce since it could act as a extra ligand towards boron. For that purpose the amino alcohol 83 was reacted with various amounts of borane and after equilibration the volume of hydrogen evolved was measured upon acid hydrolysis. The results are shown in table 16.

We first note that upon addition of one equivalent of borane and after 15 hours of reaction only 0.5 equivalent of borane was consumed (run 1). This was repeated several times since this result was unexpected. In all cases, the ratio of hydrogen evolved to the amount of chiral molecule were in good agreement with each other. Upon addition of a second equivalent of borane it could be seen that four active hydride atoms remain in solution (run 2). This has been reported previously[21] and can be associated with the formation of the intermediate 35 or 36 (page 21) but after evacuation of the solution to remove any uncomplexed borane it was found that this ratio decreased by half (run 3). For that reason, we looked at the IR spectra of two amino alcohol-borane complexes. The complex formed from molecule 83 and borane in a ratio of 2.5 and the complex of molecule 84 and borane in a ratio 3.5 were utilized for this study. The complexes were

Table 16. Mole of hydrogen evolved upon hydrolysis of the chiral complex of 83 and various amount of borane.

run	ratio BH_3/83	equivalent H_2/83
1	1	2.5[1]
2	2	4
3	2	2[2]

1. Repeated five times with 0.3 difference between the extreme values.
2. Same as run 2 except that vacuum was applied to remove any free BH_3 prior to hydrolysis.



105

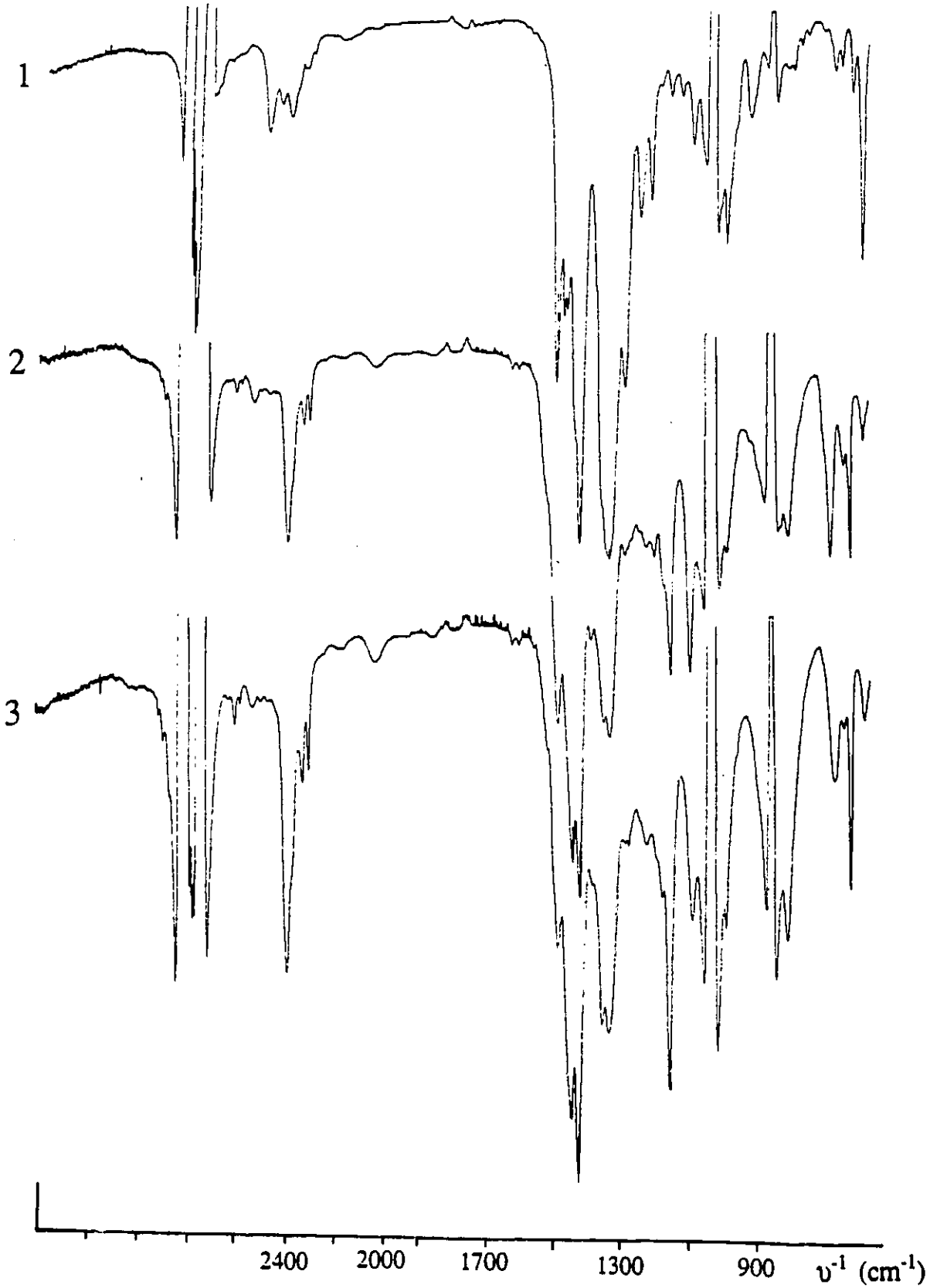


Figure 14. IR spectra of 1) 1.0 M BH_3 in THF 2)complex of BH_3 and 83, ratio 2.5/1 3) complex of BH_3 and 84, ratio 3.5/1.

prepared in a similar way to that of the complexes for which hydrogenolysis was performed but the spectra were taken prior to hydrolysis. The spectra are shown in figure 14 for the range 1000-2600 cm^{-1}. We first note the two regions of interest from the 1.0 M borane in THF (spectrum 1). The B-H stretching frequencies appeared at 2400-2525 cm^{-1} and the large band at 1336 cm^{-1} was associated with the boron-oxygen complexation. Upon reaction with molecule 83 the band at 2524 and 2461 cm^{-1} disappeared to give a predominant band at 2409 cm^{-1}. Most important was the disappearance of the band at 1336 cm^{-1}. A strong band in this region has been associated with resonance forms of these complexes giving a partial double bond character to the B-O bond[92]. The occurrence of these resonance forms is supported by dipole-moment studies[93]. Upon complexation with pyridine, for example, this band became weaker and was shifted to lower frequencies because of the increasing single bond character of the B-O bond[94]. It can be seen that the spectrum 2 shows a band of medium intensity in that area which could be accounted for by the presence of a boron-nitrogen complex which disrupted the nature of the B-O bond. The presence of an undisturbed B-N bond could also be eliminated since such a bond would possess double bond character and would show a strong absorption at 1340 cm^{-1}. What was in fact observed was a band at 1178 cm^{-1} associated with an amine-borane complex. The spectrum 3 for which the amount of borane was increased shows the same band pattern as spectrum 2 except that the relative intensity of the bands varies. The B-H band at 2409 cm^{-1} and the B-N band 1178 cm^{-1} are proportionally larger than in spectrum 2. As well, the band at 1336 cm^{-1} gets slightly larger. Spectrum 3 suggested that upon addition of a large amount of borane more B-N nitrogen complexation took place and the double bond character of the B-O increased. This could be explained by a complex of the type 105 (page 80) where the B-O bond was partially freed from the

interaction of nitrogen. The fact that the 1336 cm^{-1} band did not become the predominant band in the spectrum, as predicted by structure 105, shows that the nature of the reducing chiral complex is much more complicated than suggested in figure 2. Nonetheless these observations favour the intermediate 35 in the case where the ratio of borane to chiral molecule was 2 and it is conceivable that further addition of borane leads to a complex of the type depicted by the structure 105.

We then looked at the effect of the ratio of borane to chiral molecule on the optical yield of the reduction. These results are shown in table 17 and 18 respectively for the amino alcohols 83 and 84. We first observed that this process was not critically dependent on a specific ratio of amino alcohols to borane. This was in contrast with LAH reductions where optimum enantioselectivities were obtained over a narrow range of ratio[24]. It can be seen that there is essentially no difference between the maximum optical yields found for both molecules (table 17, run 3; table 18, run 4). This indicated that the bulkiness of the ether group was of little importance and it allowed us to suggest that the ether oxygen was probably not participating in the complexation of the boron atom. Even when four equivalents of borane were utilized both 83 and 84 were capable of giving rise to good optical yields. Under such conditions there is free borane in solution. It appears that the uncomplexed borane was not participating in the reduction of acetophenone. This can be explained by a kinetic effect. It has been shown that amino alcohol complexes of borane are capable of reducing ketones at a rate approximately ten times faster than borane itself[16,17]. Therefore once the optimum ratio of borane/chiral molecule was obtained, any further addition of borane had little effect on the process as the complex responsible for the asymmetric induction was much

Table 17. Reduction of acetophenone by complexes of 83 and various amounts of borane.

Run	Ratio BH_3/83	Chemical Yield (%)	Optical Yield (%)
1	1.5	45	22
2	2.0	92	65
3	2.5	82	65
4	3.0	>41	65
5	3.5	88	62
6	4.0	93	64

Table 18. Reduction of acetophenone by complexes of 84 and various amounts of borane.

Run	Ratio BH_3/84	Chemical Yield (%)	Optical Yield (%)
1	2.0	89	65
2	2.5	90	68
3	3.0	84	67
4	3.5	78	70
5	4.0	>69	67

more reactive than borane itself. This optimum ratio appeared to be when a one fold excess of borane was used with respect to the chiral compound, that is the smallest ratio of BH_3/amino alcohol (table 17, 18) giving rise to the optimum enantioselectivity.

2.2.2 Attempts to prepare other chiral borane complexes.

We were then interested in the study of the corresponding polymeric reagent. These polymers were envisaged as being prepared according to scheme XVII. Because of the poor results obtained from the use of that polymer when aluminum hydride complexes were formed, a much more detailed synthesis was studied. As in the previous cases, the polymer was a 1% crosslinked polystyrene resin which was chloromethylated according to a known procedure[59] as to give various amounts of functionalized aromatic rings. Attachment of the oxazoline to the polymer was performed in DMF using NaH as a base. Quantitative displacement of the chloride ion resulted from this heterogeneous reaction as shown in table 19. This reaction was easily reproducible and, after washing the resin to remove inorganic salts as well as the excess oxazoline, excellent agreement was found between the expected nitrogen content and the results from the analysis. Two types of resin were prepared; one with a low content of chiral group (DF = 0.14) and one with a high content of substituted aromatic ring (DF = 0.60). Cleavage of the polymeric oxazoline proved to be a very difficult task. If we recall that the yield of 84 was low because of the acid hydrolysis of the benzyl ether it was expected that a similar problem would arise with the polymer. This has been reported[95] to

Table 19. Preparation of the polymer 95

#	Expected elemental analysis		Found		meq/g	DF
	N	Cl	N	Cl		
C771	1.55	0	1.56	traces	1.11	0.15
C778	3.60	0	3.73	traces	2.66	0.60
C794	1.42	0	1.50	traces	1.07	0.14
C816	1.42	0	1.45	traces	1.01	0.136
C831	3.63	0	3.65	traces	2.60	0.58

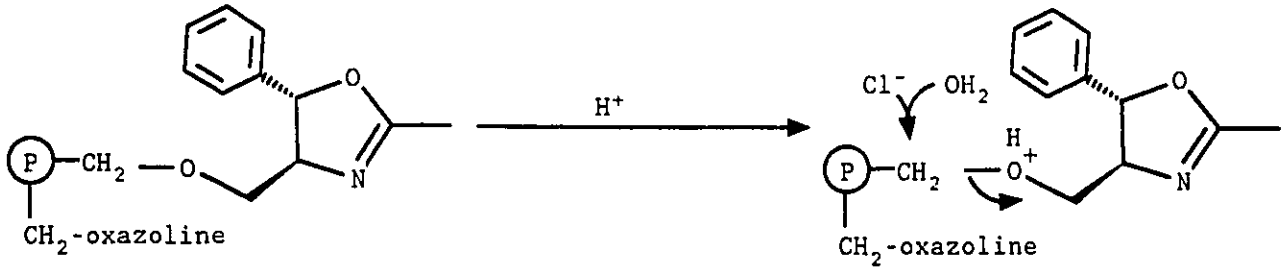
be the case but it was thought that the use of a non-nucleophilic acid would give rise to quantitative ring opening without any side reaction. The results of the second step of the polymer-supported synthesis are shown in table 20. It can be seen that the chloride ion was too nucleophilic and the protonated intermediate 106 underwent some ether cleavage (run 1 and 2) according to the reaction of scheme XXII. From elemental analysis we calculated that 71% of the functional group was lost via this reaction. For that reason, an ethanolic solution of sulfuric acid was utilized as the non-nucleophilic character of the sulfate ion should eliminate this side reaction. When the reaction was carried out for 5 days the amount of nitrogen remaining on the polymer was lower than expected (run 3). Actually, the washings from the same reaction done on a small scale showed some optical activity indicating that some oxazoline was being cleaved (run 4). By decreasing the reaction time it was possible to eliminate this problem and it can be seen that reaction time of 24 h and 7 h gave no loss in the nitrogen content of the polymer (run 5 and 6). The reaction of run 6 was repeated on a large scale with two different polymers and complete analysis of the products indicated that the sample C830 (run 7) contains 4.03% of oxygen arising from ether cleavage while the sample C834 contains 2.60% of oxygen from such a source. From this, it was possible to

Table 20. Preparation of the polymer-supported amino alcohol 96

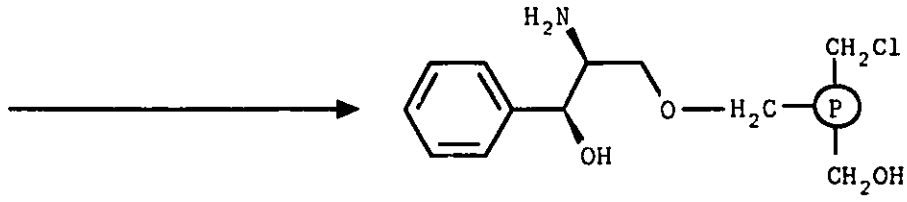
run	#	DF of polymeric oxazoline	DF of amino alcohol	Analysis Expected N	Expected Cl	found N	found Cl	reagent
1	C774	0.15	0.043	1.60	0	0.40	2.50	HCl 3N
2	C780	0.60	0.366	3.7	0	1.72	2.79	HCL 3N
3	C793	0.60		3.30	0	1.17	0	H_2SO_4 6N in ethanol, 5 days
4	C802[1,2]	0.14		1.42	--	1.29	--	H_2SO_4 6N in ethanol, 6 days
5	C821[2]	0.14		1.45	--	1.48	--	H_2SO_4 6N in ethanol, 24 h
6	C822[2]	0.14		1.45	--	1.44	--	H_2SO_4 6N in ethanol, 7 h
7	C830	0.14	0.037	1.45	--	1.35	--	H_2SO_4 6N in ethanol, 8 h
8	C834	0.58	0.32	3.88	--	2.79	--	H_2SO_4 6N in ethanol, 8 h

1. Washings from this reaction showed some optical activity
2. Small scale reaction for which only the nitrogen analysis was done so no data available to estimate DF of the amino alcohol

Scheme XXII

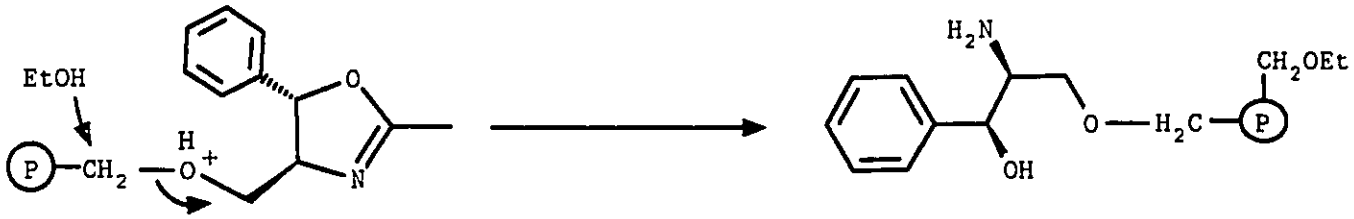


95 106



107

Scheme XXIII



108 109

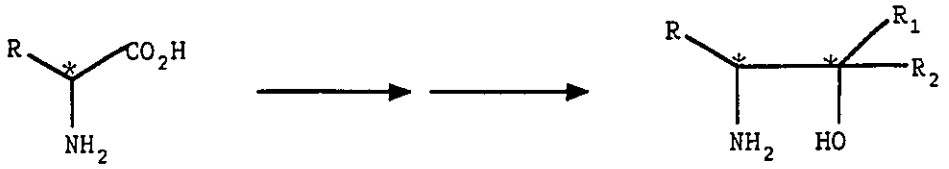
calculate the DF of amino alcohol assuming that the side reaction is as shown in scheme XXIII. It is seen that the highly loaded resin (run 8) lost 45% of its chiral functionality while the undesired side reaction, probably leading to 109, occurred to an extent of 73% with the lightly loaded polymer (run 7). It was concluded that the desired polymer 96 could not be prepared quantitatively as was also observed by McManus[95] despite the fact that milder hydrolysis conditions such as diluted sulfuric acid and shorter reaction times indicated that it could be done on a small scale. These observations probably explain why the LAH complex of polymer 97 could not duplicate the model compound behavior despite the low content of chiral supported units of that polymer.

Multistep synthesis on polymer-supported reagents which gives rise to undesirable side reactions renders the results obtained from the use of such polymers very difficult to analyze. We nonetheless looked at the reduction of acetophenone with the use of the polymers described above. The polymers were reacted with two equivalents of borane (as calculated from the DF of the amino alcohol) for 24 h, followed by acetophenone for 5 days. In all the cases 1-phenylethanol was isolated in yields ranging from 50-60%. The polymer C780 (table 20) containing the chiral amino alcohol as well as the chloromethyl group gave rise to very low asymmetric induction (10%). This probably arose from the consumption of some borane by the chloromethyl and benzyl alcohol groups. This changed the stochiometry and low optical and chemical yields were observed for this reaction. However, when the sample C780 (structure 96) was refluxed in a THF-LAH mixture for 36 h and the reduction performed with the chlorine free polymer, the optical yield was improved by a factor of 3 (36%). This was a net improvement even if it did not duplicate the model compound behavior.

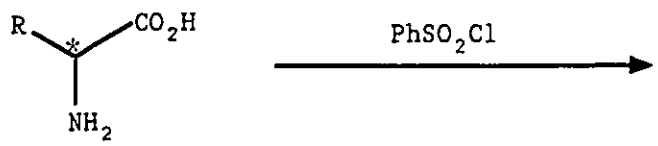
Similar results were obtained with the sample C830 (structure 96) which yielded the alcohol in 32% enantiomeric excess.

In the course of our study on the reduction of acetophenone by chiral borane reagents we noticed that the polymers prepared by Itsuno were derived from tyrosine in spite of the fact that model compound studies have shown that valine is more efficient in terms of the asymmetry which is induced at the chiral center of the alcohol[53,55]. For this reason, we attempted to transform L-valine and (S)-(+)-2-phenylglycine into useful derivatives according to the general scheme XXIV. Hopefully R_1 or R_2 would allow attachment to a polymer matrix. The most useful approach consisted in the transformation of the carboxylic acid into a ketone group according to a procedure similar to that reported by Rapoport[96,97]. The amine was first protected with the N-phenylsulfonyl group by reaction with benzene sulfonyl chloride (scheme XXV). The yield for this reaction was approximately 65% after recrystallization. In order to create additional steric effect during the course of the asymmetric reduction, it was desirable for R_2 to be a long or bulky aliphatic group. For that reason, molecule 112 was reacted with allyl magnesium bromide and the product 114 was isolated in 64% yield after chromatography. Similarly, 115 was prepared in a lower yield. This reaction required at least 3 equivalents of organometallic reagent as two protons were very acidic under the reaction conditions. In fact, generation of an anion at the nitrogen center prevented racemization of the chiral center as the acidity of that proton was reduced drastically by the nitrogen anion[96,97]. Other derivatives were also prepared but in very poor yield. For example, reaction of 112 with n-butyllithium gave 116 in 10% yield. Iso-propyl and ethyl magnesium bromide or sec-butyllithium did not give the corresponding

Scheme XXIV



Scheme XXV

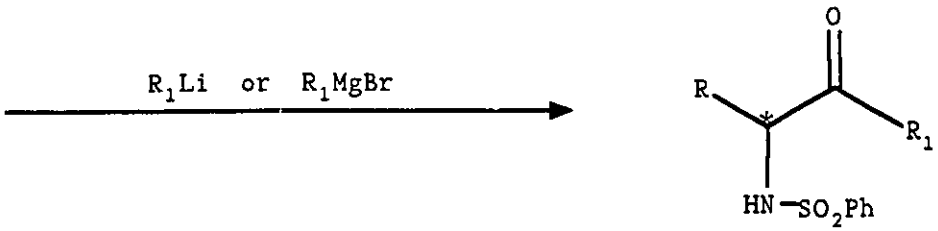


110 R = iso-propyl

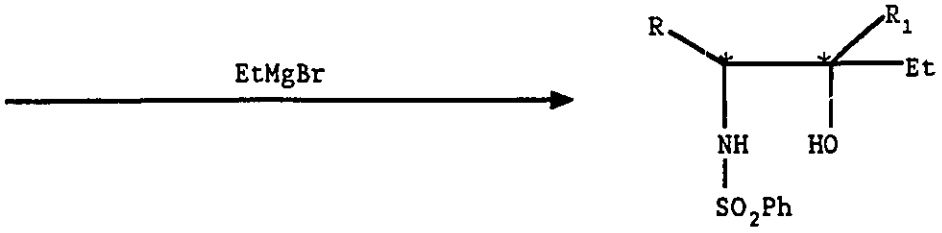
111 R = phenyl

112 R = iso-propyl 67%

113 R = phenyl 63%



114	R = iso-propyl	$R_1 = CH_2CH{=}CH_2$	64%
115	R = Ph	$R_1 = CH_2CH{=}CH_2$	46%
116	R = iso-propyl	R_1 = n-Bu	10%
117	R = Ph	R_1 = n-Bu	8%
118	R = iso-propyl	R_1 = Ph	37%

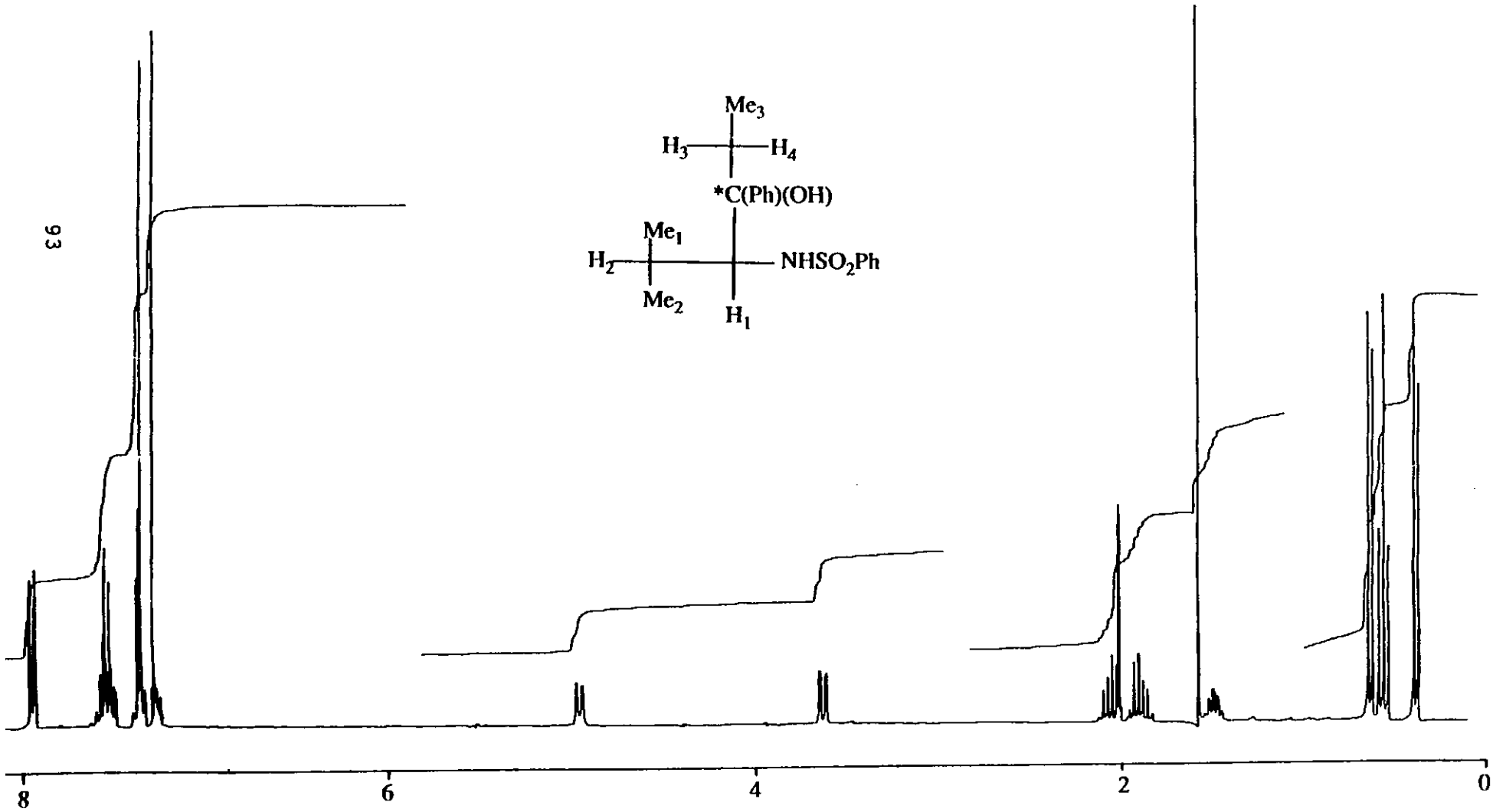


119 R = iso-propyl R_1 = Ph

ketone in sufficiently high yield to allow its isolation and characterization.

Reaction of the ketones 114 and 115 with Grignard reagents was not successful because of the preferential hydrogen abstraction at the allylic position. But the derivative 118 which could also be obtained in a reasonable yield reacted with 2 equivalents of ethyl magnesium bromide to give the amino alcohol 119 as a 9:1 mixture of diastereomers. The major component was isolated and its NMR is shown in figure 15. The purity of this diastereomer is easily ascertained from this spectrum. For example, the amine proton is observed as a doublet at 4.96 ppm while H_1 to which it couples, appears at 3.64 ppm. Both diastereotopic isopropyl methyls Me_1 and Me_2 show up as doublets at 0.4 ppm and 0.64 ppm while Me_3 appears as a triplet at 0.5 ppm. H_3 and H_4 being diastereotopic protons will couple to each other and will also be split by Me_3. The expected octets are seen at 1.90 ppm and 2.06 ppm with the hydroxy singlet in between. Finally, H_2 appears as a complex multiplet at 1.52 ppm. Also interesting is the mass spectrum of this compound. The major peak of the chemical ionization spectrum had a mass of 330, 18 units lower than expected. This arose from the loss of water that this molecule easily underwent. This tertiary alcohol will eliminate a molecule of water to give the conjugated molecule 121 (scheme XXVI). The consequence of the instability of alcohol 119 is that despite all attempts to deprotect the amino group it was not possible to isolate the desired product 120. The cleavage of a sulfonamide group is well documented[98] and several procedures were attempted but the sensitivity of the alcohol functional group did not lead to the desired product 120. This project was not pursued as it was thought that these tertiary amino

Figure 15. 300 MHz NMR spectrum of compound 119.



alcohols would suffer from the same chemical instability once grafted to a polymer.

Finally we have studied other types of chiral reducing agents based on complexes of 9-borabicyclo[3.3.1.]nonane (9-BBN) and pinene derivatives. This type of asymmetric reduction has not been applied to polymeric reagent despite its extensive use by Brown et al.[99] and Midland et al.[100]. Because of our interest in polymer chemistry, suitable derivatives must be chosen which will allow their attachment to a polymer matrix. Nopol, 122 (scheme XXVII), allows such a transformation by reaction of the alkoxide with chloromethylated polystyrene. The model compound nopol benzyl ether, 123, was prepared by a modification of the procedure of Midland et al.[100b] in 92% yield after distillation. The polymer-supported reagents, 124, with DF = 0.089 and 0.28 were prepared by a similar approach to that of the model compound and up to 98% of the chlorine atoms could be substituted by the nopol unit as determined by the oxygen content of the resin.

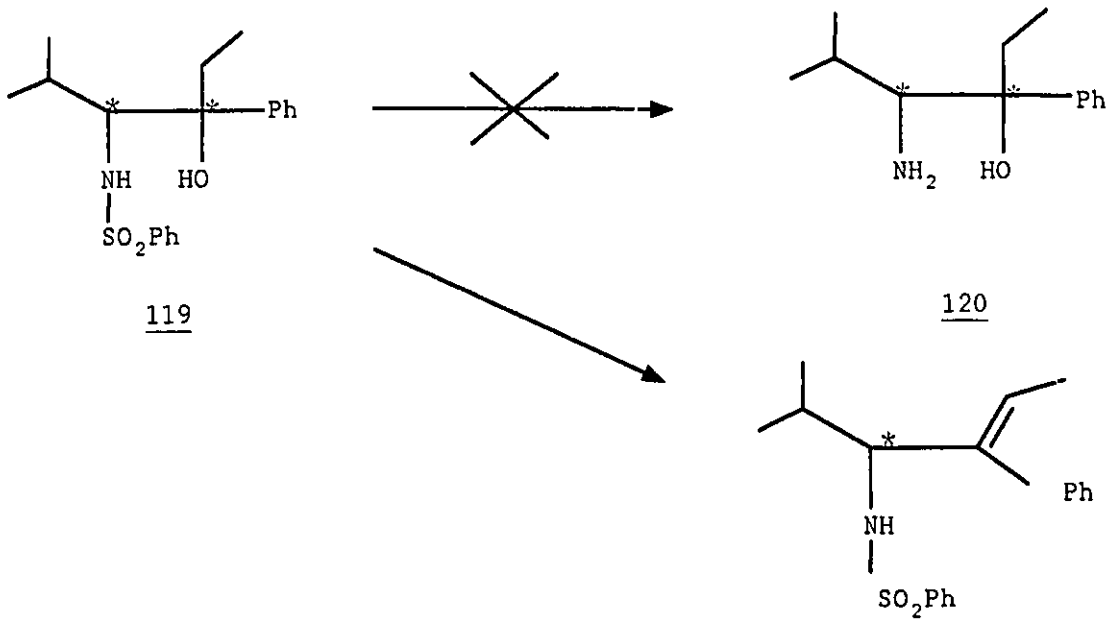
In a first attempt, both the polymer and the model compound were reacted with 9-BBN and after refluxing in THF, the complex 125 was formed (scheme XXVIII). This complex was not isolated but further reacted with 1-octyn-3-one. The corresponding alcohol which was not sensitive to UV radiation and iodine vapor was isolated by chromatography whereby all the fractions were evaporated and their NMR spectrum recorded. Thus, this first attempt yielded a pure fraction of the alcohol with 57% optical purity could be isolated in the case where the model compound was used as the chiral reagent. This was lower than the reported value for the same

experiment (95% ee)[100]. The polymer with a high content of nopol units yielded the same alcohol in 23% ee.

However, we believed that the polymers with nopol pendant units could not be regenerated to their original state because of the lability of the benzyl bond. That would lead to the introduction of alcohol groups in the polymer matrix destroying their ability to complex 9-BBN in a manner leading to asymmetric induction.

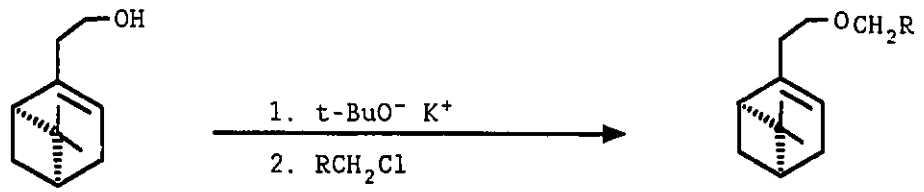
These last two projects that were briefly explored demonstrated that quantitative chemical transformations are necessary in order to exploit the recycling capability of polymer-supported reagents.

Scheme XXVI



119 120 121

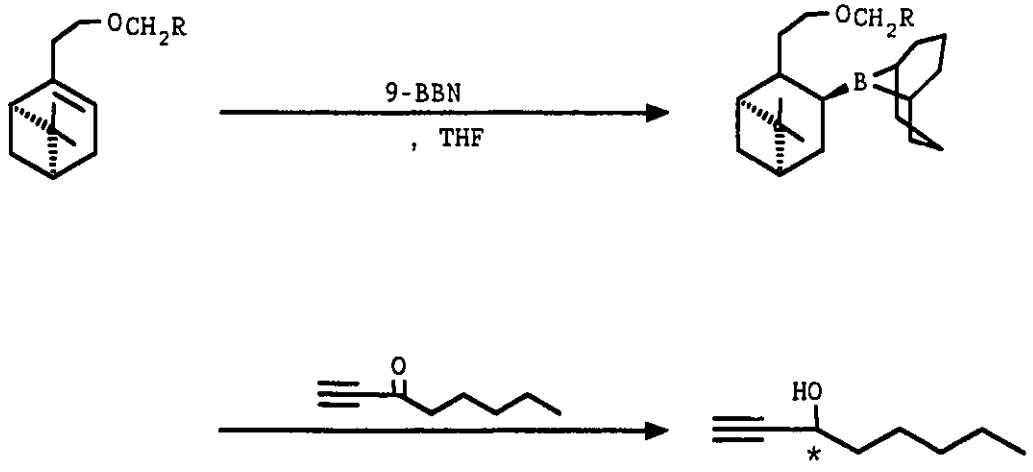
Scheme XXVII



122 123 R = Ph

124 R = Ⓟ

Scheme XXVIII



EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer Model 241 digital polarimeter using the D line of the sodium lamp. NMR spectra were measured on Varian EM-360, CFT 80 or XL-300 spectrometers in $CDCl_3$ solutions (unless otherwise noted) with tetramethylsilane as a standard. Infrared spectra were recorded on Nicolet MX-1 and 10-DX Fourier transform spectrometers, using KBr pellets for solid samples or neat films between NaCl disks for liquids. Mass spectra were taken using a VG-7070E double-focusing mass spectrometer with diethyl ether as the chemical ionization agent. Preparative HPLC separations were carried out on a Waters 500 LC fitted with a 500 g silica gel column.

The crosslinked polystyrene resins used are commercially available from Bio-Rad Laboratories, in most cases the 1% crosslinked SX-1 resin was used. The capacities of the functional polymers were estimated both from gravimetric and analytical data and are expressed in milliequivalents of functional group per gram (meq/g), as degrees of functionalization (DF), or both. The DF of a polystyrene-based functional polymer is a measure of the proportion of aromatic polystyrene rings which carry the desired functionality; for example, DF= 0.11 indicates that 11% of the styrene repeating units are functionalized.

(1S,2S)-2-Amino-1-phenyl-1,3-propanediol, L-pyrrolidin-2-yl-methanol, D-2-amino-2-phenylethanol, (S)-2-amino-1-propanol, L-proline, (S)-(+)-2-phenylglycine, (1S)-(-)-nopol and L-valine purchased from Aldrich, had reported optical purities of 98%. (R)-2-amino-1-butanol (Aldrich) had a reported optical purity of 70%. (1R,2S)-(-)-ephedrine was obtained from

Sigma Chemical Co.. All the optically active compounds were used without further purification. All asymmetric reductions were carried out under argon using ethereal solutions of $LiAlH_4$ (Aldrich) or THF solutions of diborane unless otherwise indicated. The solvents used for the reductions were purified as follows; THF was distilled over benzophenone-sodium while commercial anhydrous ether was used directly. Chromatography was performed with the high purity grade of chloroform while hexanes and ethyl acetate were distilled. All yields are reported for isolated materials. Optical yields were calculated from optical rotations measured in cyclopentane (c = 7.2) with $[\alpha]_D = +43.1^{\circ}$ for pure (R)-1-phenylethanol[31].

Details of the spectral data

NMR: When reporting this data, the number before the parenthesis refers to the chemical shift as measured in ppm from tetramethylsilane. The multiplicity of a peak is indicated by the first term in the parenthesis, the integration is given by the second term, then follows the coupling constant when appropriate.

IR: The number before the parenthesis refers to the infrared frequency of a given band expressed in reciprocal centimeters. The term inside the parenthesis assigns the structural unit responsible for the band.

MS: The number before the parenthesis indicates the value of m/e for a given peak. The term in the parenthesis gives the chemical formula of the fragment responsible for that peak followed by the intensity of the peak relative to the largest peak.

(S)-2-Dimethylamino-1-propanol (70)[91]

The N-methylation procedure used in all experiments was adapted from that of Clarke et al.[89]. L-Alaninol, 2.00 g (26.6 mmol), having 98% optical purity was added to 6.81 g (133.0 mmol) of ice cooled 90% formic acid and the mixture was stirred for 5 min prior to the addition of 4.53 g (55.8 mmol) of 37% formaldehyde solution. After 15 min the ice bath was removed and stirring was continued for a further 24 h followed by a 3 h reflux period. After cooling, slightly more than one equivalent of HCl was added, and the excess formaldehyde and formic acid were evaporated. After the medium was rendered alkaline by the addition of solid NaOH, the product was extracted with ether and the crude product was distilled (50°C at 19 Torr) to afford 1.07 g of pure material (39% yield) with $[\alpha]_D$= +43.6° (c= 3.9, $CHCl_3$). (c=2.5, $CHCl_3$).

NMR: 0.87 (d, 3H), 2.26 (s, 6H), 2.80 (s, broad, 1H), 3.30 (t, 1H, alcohol), 3.44 (m, 2H).

IR: 3395 (OH), 1050 (C-O stretch), band at 1600 disappears upon methylation, band at 3300 changed from a doublet to broad singlet.

MS: 72 ($C_4H_{10}N^+$, 100%), 44 ($C_2H_6N^+$, 49%), 42 ($C_2H_4N^+$, 42%), 58 ($C_3H_8N^+$, 40%).

(R)-2-Dimethylamino-1-butanol (71)

This compound was prepared in 64% yield from a sample of (R)-2-amino-1-butanol with 70% optical purity using the N-methylation procedure described above for 70. The product had a b.p. of 69°C at 20 Torr and $[\alpha]_D$= -25.2° (c= 2.3, $CHCl_3$).

Analysis: (calculated for $C_6H_{15}NO$) C= 61.49, H= 12.90, N= 11.95;

(found) C= 61.41, H= 12.97, N= 11.72

NMR: 0.90 (t, 3H), 1.10 (m, 1H), 1.62 (m, 1H), 2.30 (s, 6H), 2.50 (m, 1H), 3.24 (t, 1H, alcohol), 3.58 (AB, q, 2H).

IR: 3410 (OH), 1050 (C-O stretch); band at 1600 disappears upon methylation, doublet at 3300 becomes a broad singlet.

MS: 118 (M+1; chemical ionization), 86 ($C_5H_{12}N^+$, 100%), 71 ($C_4H_9N^+$, 46%), 44 ($C_2H_6N^+$, 35%), 42 ($C_2H_4N^+$, 28%).

D-2-Dimethylamino-2-phenylethanol (72)

This compound[91] was prepared in 63% yield using 98% optically pure D-2-amino-2-phenylethanol with the N-methylation procedure described above for 70 . The product had a b.p. of 77°C at 0.5 Torr, $[\alpha]_D$= -27.3° (c= 1.6, $CHCl_3$).

NMR: 2.20 (s, 6H), 2.80 (s, broad, 1H), 3.80 (ABX, 3H, J_{AX}= 10Hz, J_{BX}= 9Hz, J_{AB}= 5Hz), 7.32 (s, 5H).

IR: 3401 (OH band), 1040 (C-O stretch).

MS: 134 ($C_9H_{12}N^+$, 100%), 91 ($C_7H_7^+$, 8%), 42 ($C_2H_4N^+$, 9%).

L-1-Methyl-pyrrolidin-2-yl-methanol (74)

A sample of L-pyrrolidin-2-yl-methanol, 2.00 g (19.8 mmol), having 98% optical purity was added to 2.60 g (50.8 mmol) of ice cooled 90% formic acid and the mixture was stirred for 5 min prior to the addition of 1.60 g (19.7 mmol) of 37% formaldehyde solution. After 15 min the ice bath was removed and stirring was continued for a further 24 h followed by a 3 h reflux period. After cooling, slightly more than one equivalent of HCl was added, and the excess formaldehyde and formic acid were evaporated. After the medium was rendered alkaline by the addition of solid NaOH, the product was extracted with ether and the crude product was distilled (20.5 Torr, 77°C) to afford 1.62 g of pure 74 (71.1% yield) with $[\alpha]_D$= -5.3° (c=2.5,

$CHCl_3$). The data for the product was similar to that reported by Hayashi et al.[91].

NMR: 1.64-1.96 (m, 4H), 2.12-2.40 (m 2H), 2.36 (s, 3H), 3.04-3.20 (m, broad, 2H), 3.54 (m, 2H,).

IR: 3356 (OH band), 1045 (C-O stretch).

MS: 115 (M^+, 3%), 84 ($C_5H_{10}N^+$, 100%), 42 ($C_2H_4N^+$, 99%), 82($C_5H_8N^+$, 36%).

(1R, 2S)-N-Methyl-l-ephedrine (28)

This compound was prepared from commercially available l-(-)-ephedrine using the procedure described above for the N-methylation of 70. The compound was obtained in 90% yield and the spectral data were in complete agreement with those reported by Vigneron and Jacquet[38]. $[\alpha]_D$= -29.35° (c= 4.535, $CHCl_3$), m.p.= 88.5°-89.5°C (reported m.p. = 86-87°C).

NMR: 0.80 (d, 3H), 2.30 (s,6H), 2,40 (m, 1H), 3.55 (s, broad, 1H), 4.90 (d, 1H), 7.25 (s, 5H).

MS: 180 (M+1, chemical ionization), 72 ($C_4H_{10}N^+$, 100%).

(1R, 2S)-N-Benzyl-l-ephedrine (76)

To a solution of 12.06 g (73.0 mmol) of l-ephedrine in 20.0 mL of dry pyridine was added 9.24 g (80.3 mmol) of freshly distilled benzyl chloride. After the mixture was stirred for 72 h at room temperature, 20.0 mL of water was added and the mixture was extracted 3 times with ethyl acetate, dried over $MgSO_4$ and evaporated to afford 11.84 g of crude product. After chromatography (9:1 hexane-ethyl acetate), 9.87 g of the desired compound was obtained (yield= 60%). The product had a m.p. of 48°-49°C and $[\alpha]_D$= +9.44° (c= 1.97, $CHCl_3$).

Analysis: (calculated for $C_{17}H_{21}NO$) C= 79.96, H= 8.29, N= 5.48;
(found) C= 79.84, H= 8.46, N= 5.59

NMR: 0.97 (d, 3H), 2.17 (s, 3H), 2.90 (m, 1H), 3.23 (s, broad, 1H), 3.53 (s, 2H), 4.80 (d, 1H), 7.23 (d, 10H).

^{13}C NMR: 9.732 (q), 38.653 (q), 59.158 (t), 63.479 (d), 73.465 (d), 126.136-142.295 (aromatic).

IR: 3112 (OH), 1025 (C-O).

MS: 256 (M+1, chemical ionization), 148 ($C_{10}H_{14}N^+$, 100%), 91 ($C_7H_7^+$, 95%).

Ethyl iminoacetate hydrochloride (77)[90]

Dry hydrogen chloride was passed through a solution of dry acetonitrile (52.2 mL, 1.00 mole) and absolute ethanol (64.6 mL, 1.1 mole) in a 500 mL three-necked flask. A white precipitate appeared after 40 min of reaction time. The flask was ice cooled and HCl was bubbled through the solution for another 5 h. The flask was well stoppered and stored in the refrigerator for 12 h after which 200 mL of anhydrous ether was added and the mixture was cooled in an acetone-dry ice bath. A thick white solid was formed which was filtered and dry under vacuum for 15 h. The product was obtained in 94.3% yield (116.6 g).

NMR: 1.50 (t, 3H), 2.50 (s, 3H), 4.60 (q, 2H)

IR: 3100 (broad,), 1712 (C=N), 1140 (C-O)

(4S, 5S)-2-Methyl-4-hydroxymethyl-5-phenyl-2-oxazoline (79)

This compound was prepared according to a procedure reported by Meyers et al.[90]. To an ice cooled suspension of 44.86 g (0.363 mole) of ethyl iminoacetate hydrochloride, 77, in 300 mL of dichloromethane, was added 61.00 g (0.365 mol) of (1S, 2S)-1-phenyl-2-amino-1,3-propanediol and the mixture was stirred for a total of 6 h. The flask was stoppered and stored in the refrigerator for 15 h. It was then stirred at room temperature for 1 h and it was poured onto 150 g of ice. The product was extracted 4 times

with 25 mL of dichloromethane. The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The solid was recrystallized twice from ethyl acetate-hexane to give 54.5 g of the desired product, yield= 78.5%, m.p.= 61°-63°C (reported m.p. = 64-65°C) and $[\alpha]_D$= -163.9° (c= 10.553, $CHCl_3$).

NMR: 2.10 (s, 3H), 3.85 (m, 3H), 4.80 (s, broad, 1H), 5.35 (d, 1H, J= 7 Hz), 7.35 (s, 5H).

IR: 3200 (OH), 1675 (C=N), 1059 (C-O)

MS: 85 ($C_4H_7NO^+$, 100%), 43 ($C_2H_3O^+$, 77%), 68 ($C_4H_6N^+$, 57%), 91 ($C_7H_7^+$, 52%), 160 (M^+-CH_2OH, 49%).

(4S, 5S)-2-Methyl-4-methoxymethyl-5-phenyl-2-oxazoline (81)[90]

To a suspension of 3.82 g (0.159 mole) of sodium hydride in 25 mL of dry THF was added 25.36 g (0.133 mole) of oxazoline 79 dissolved in 125 mL of THF was added over a period of 45 min. A thick slurry was obtained which was stirred for an additional hour. A solution of 23.6 g (0.166 mole) of methyl iodide in 25 mL of THF was added over a period of 30 min. The reaction mixture was stirred for 15 h and poured over 100 g of ice, extracted 4 times with dichloromethane, dried over $MgSO_4$ and evaporated to give an oil. The yellow liquid was vacuum distilled (b.p.= 90.0°C at 1 Torr) to yield 20.7 g of product, yield= 76%, $[\alpha]_D$= -103.6° (c= 1.944, $CHCl_3$) (reported b.p. = 85-87°C at 0.20 Torr).

NMR: 2.05 (s, 3H), 3,35 (s, 3H), 3.50 (m, 2H), 4.00 (m, 1H), 5.20 (d, 1H, J= 7 Hz), 7.25 (s, 5H).

IR: 1677 (C=N), 1217 (C-O), 1129 (C-O).

MS: 68 ($C_4H_6N^+$, 100%), 91 ($C_7H_7^+$, 64%), 43 ($C_2H_3O^+$, 57%), 119 ($C_8H_7O^+$, 53%), 160 ($M^+-CH_2OCH_3$, 49%).

(1S, 2S)-(+)-1-Phenyl-2-amino-3-methoxy-1-propanol (83)[90]

A solution of 20.2 g (0.098 mole) of oxazoline 81 in 200 mL of HCl 3N was refluxed for 5 h. The reaction vessel was brought to RT, solid KOH was added until the pH was approximately 10 and the product was extracted 4 times with ether, dried over $MgSO_4$ and the solvent was evaporated to give an oil. Ether, 5 mL, was added to the flask which was stored in the refregirator. White crystals with m.p.= 44.5°-46.5°C and $[\alpha]_D$= +24.5° (c= 1.557, $CHCl_3$) were isolated in 96.8% yield (17.2 g) (reported m.p. = 48.5-50°C).

Analysis: (calculated for $C_{10}H_{15}NO_2$) C= 66.27, H= 8.34, N= 7.73;
(found) C= 66.42, H= 8.51, N= 7.80

NMR: 1.56 (s, broad, 3H), 2.98 (m, 1H), 3.24 (s, 3H), 3.26 and 3.36 (q, 1H, J_{AB}= 4 Hz, J_{AX}= 10 Hz), 4.52 (d, 1H, J= 6 Hz), 7.20 (s, 5H).

IR: 3326, 3277 (NH_2), 1605 (C-N), 1083 (C-O).

MS: 182 (M+1; chemical ionization), 74 ($C_3H_8NO^+$, 100%), 44 ($C_2H_2O^+$, 21%).

(1S, 2S)-1-Phenyl-2-dimethylamino-3-methoxy-1-propanol (85)

This compound was prepared in 87% yield from the amino alcohol 83 using the N-methylation procedure described above for 70. The product had a b.p. of 87°C at 0.5 Torr and $[\alpha]_D$= +15.9° (c= 3.9, $CHCl_3$).

Analysis: (calculated for $C_{12}H_{19}NO_2$) C= 68.87, H= 9.15, N= 6.69;
(found) C= 69.01, H= 9.28, N= 6.56

NMR: 2.48 (m, 7H), 2.70 (m, 1H), 3.20 (s,3H), 3.30 (m, 2H), 4.38 (d, 1H, J= 10 Hz), 7.38 (s, 5H).

IR: 3337 (OH), 1130 (C-O), 1050 (C-O).

MS: 210 (M+1, chemical ionization), 102 ($C_5H_{12}NO^+$, 100%), 71 ($C_4H_9N^+$, 10%), 58 ($C_3H_8N^+$, 14%).

(4S, 5S)-2-Methyl-4-benzyloxymethyl-5-phenyl-2-oxazoline (82)

Sodium hydride, 0.301 g (12.55 mmol), was suspended in 50 mL of DMF and 2.00 g (10.46 mmol) of oxazoline 79 dissolved in 15 mL of DMF was added over 30 min. A freshly distilled sample of benzyl chloride, 1.39 g (11.0 mmol), diluted in 15 mL of DMF was added to the slurry over a period of 10 min. The mixture was stirred for 15 h, poured on ice and extracted 4 times with dichloromethane. The organic phase was washed twice with large volumes of water to remove DMF, dried over $MgSO_4$, evaporated to give 1.18g (yield= 40%) of pure compound. $[\alpha]_D$= -50.7° (c= 2.06, $CHCl_3$).

Analysis: (calculated for $C_{18}H_{19}NO_2$) C= 76.84, H= 6.81, N= 4.98;
(found) C= 76.61, H= 7.00, N= 4.91

NMR: 2.10 (s, 3H), 3.56 (q, 1H) and 3.68 (q, 1H); (ABX, J_{AB}= 8.5 Hz, J_{AX}= 7 Hz), 4.10 (m, 1H), 4.57 (s, 2H), 5.30 (d, 2H, J= 8 Hz), 7.30 (s, 10H).

IR: 1675 (C=N), 1122 (C-O), 1220 (C-O).

MS: 282 (M+1, chemical ionization), 91 ($C_7H_7^+$,100%), 84 ($C_4H_6NO^+$, 84%), 119 ($C_8H_7O^+$, 57%).

(1S, 2S)-1-Phenyl-2-amino-3-benzyloxy-1-propanol (84)

A solution of 12.3 g (43.7 mmol) of the oxazoline 82 in 100 mL of 6N H_2SO_4 was refluxed for 6 h. It was rendered alkaline by the addition of solid KOH and the product was extracted 4 times with diethyl ether, backwashed with water, dried over $MgSO_4$, and the solvent was evaporated. The oil crystallized on standing and it was further purified by recrystallizing it twice from diethyl ether. The desired compound was obtained in 52% yield (5.85 g) with m.p.= 74.0°-75.0°C and $[\alpha]_D$= -1.71° (c=2.801, $CHCl_3$).

Analysis: (calculated for $C_{16}H_{19}NO_2$) C= 74.68, H= 7.44, N= 5.44;
(found) C= 74.58, H= 7.50, N= 5.51

NMR: 3.10 (s, broad, 3H), 3.16 (q, 1H), 3.36 (q, 1H) and 3.44 (q, 1H); (ABX, J_{AB}= 4 Hz, J_{AX}= 10 Hz), 4.42 (q, 2H), 4.64 (d, 1H, J= 6 Hz), 7.28 (s, 10H).

IR: 3337, 3290 (NH_2), 1612 (C-N), 1049 (C-O).

MS: 258 (M+1, chemical ionization), 91 ($C_7H_7^+$, 100%), 150 ($C_9H_{12}NO^+$, 53%).

(1S, 2S)-1-Phenyl-2-dimethylamino-3-benzyloxy-1-propanol (86)

This compound was prepared from the amino alcohol 84 according to the procedure described above for the N-methylation of 70. The yield of the reaction was 69%. The product had a b.p. of 156°C at 1 Torr and $[\alpha]_D$= -11.07° (c= 2.069, $CHCl_3$).

Analysis: (calculated for $C_{18}H_{23}NO_2$) C= 75.76, H= 8.12, N= 4.91;
(found) C= 75.62, H= 8.09, N= 4.90

NMR: 2.50 (s, 6H), 2.70 (m, 1H), 3.28 (q, 1H, J_{gem}= 12 Hz, J_{vic}= 4 Hz), 3,36 (q, 1H, J_{gem}= 12 Hz, J_{vic}= 8 Hz), 4,20 and 4.26 (d, 1H, J= 11 Hz), 4.36 (d, 1H, J= 10 Hz), 7.15 (s, 5H), 7.25 (s, 5H), the hydroxy proton was not observed.

IR: 3330 (OH), 1043 (C-O), 1115 (C-O).

MS: 286 (M+1, chemical ionization), 91 ($C_7H_7^+$, 100%), 178 ($M^+-C_7H_7O^+$, 54%).

Chloromethyl ethyl ether[101]

To 142.9 g (4.76 moles) of paraformaldehyde in a 1 L three-necked flask was added 300 mL of 99% ethanol (5.06 moles). The mixture was cooled to 0°C and gaseous HCl was bubbled through the solution for 4 h. After this period no HCl was absorbed by the solution and 2 phases were observed. The top layer was stored over $CaCl_2$ overnight. The clear liquid was distilled at normal pressure (b.p.= 81°C). The first 25 mL was discarded

and 232.18 g of chloromethyl ethyl ether was collected (yield= 51%).

NMR: 1.25 (t, 3H), 3.70 (q, 2H), 5.40 (s, 2H).

Preparation of Chloromethylated Polystyrene (93)

1% Cross-linked polystyrene (Bio-Beads SX-1, Bio-Rad Laboratories) was chloromethylated as described previously[58,102] to yield the chloromethylated polymer with loading which varies with reaction conditions. Typical procedures are given below.

Polystyrene (105.8 g) in a 2 L three-necked flask was swelled in 1.1 L of $CHCl_3$. The mixture was mechanically stirred and 100 mL of chloromethyl ethyl ether was added. The solution was stirred for 40 min and 14 mL of $SnCl_4$ was added dropwise over 40 min. An extra 33 mL of chloromethyl ethyl ether was added to the pale brown reaction mixture and stirring was continued for 1.5 h. The polymer was filtered and washed as follows; 2 times with $CHCl_3$, CH_3OH, THF:H_2O:HCl (conc) (4:2:1), 3 times H_2O, THF, acetone, CH_2Cl_2, 2 times CH_3OH and it was dry under vacuo for 15 h to give 117.8 g of polymer. Elemental analysis revealed that the chlorine content was 8.37% or 2.36 meq/g, (DF= 0.22).

Polystyrene (30.0 g) was swelled in 300 mL of $CHCl_3$ and 30 mL of chloromethyl ethyl ether was added. The mixture was mechanically stirred for 3 h and 2.10 mL of $SnCl_4$ in 10.2 mL of chloromethyl ethyl ether was added over 15 min. The reaction was continued for another 40 min, the polymer was filtered and washed as described above. Elemental analysis revealed that the chlorine content was 1.80% or 0.51 meq/g, (DF = 0.054).

Polystyrylmethyl-N-L-prolinol (94)

A suspension of 10.0 g of chloromethylated polystyrene (1.0 meq Cl/g or DF= 0.11) in 75 mL of DMF containing 3.22 g of L-prolinol was heated and

stirred for 3 days at 60°-70°C. After cooling the polymer was collected on a filter and washed thoroughly with a variety of solvents to remove all impurities: dioxane:water (3:1) until no chloride could be detected in the filtrate (as tested with a $AgNO_3$ solution), dioxane, methyl ethyl ketone, acetone, methanol, ethanol, ether and dried under vacuo for 15 h at 40°C. A sample of 10.61 g of a polymer with a nitrogen content of 1.24% (0.89 meq/g) was obtained indicating DF = 0.10 for a functional yield of 93%, a result in good agreement with the gravimetric data.

IR: 3460 (OH), 1070 (C-O).

Polymer-bound oxazoline (95)

A suspension of 2.30 g (95.8 mmol) NaH in 150 mL DMF was treated with a solution of 16.00 g (83.75 mmol) oxazoline 79 in 75 mL of DMF over a period of 30 min. The mixture was stirred mechanically for 2 h at 60°C and 25.00 g of chloromethylated polystyrene (1.34 meq/g, 33.5 meq) was added in one portion. Stirring was continued for 7 days. After filtration and thorough washing with DMF, methanol, water, dioxane-water (3:1) (until no Cl^- could be detected in the filtrate), dioxane, acetone, methanol and ether, the polymer was dried overnight to yield 27.93 g (maximum 30.18 g) of sample. The polymer contained 1.56% of nitrogen (theory 1.55%, DF= 0.15).

IR: 1674 (C=N), 1068 and 1027 (C-O).

Other polymers with DF= 0.59 were also prepared by a similar procedure using the quantitative displacement of chloride from appropriately functionalized chloromethylated resins. The results are summarized in table 19 (page 86).

Polymer-bound amino-alcohol (96)

A sample of the polymer-bound oxazoline 95 (DF= 0.60), 15.02 g, was refluxed in 300 mL of HCl 3N for 5 days. The polymer was filtered and washed with water several times, 5 times with 3 N NaOH-dioxane (1:5), dioxane-water until the pH was neutral and no Cl^- could be detected, methanol, $CHCl_3$, acetone, methanol and dried overnight under vacuum. 10.34 g of polymer were obtained.

Analysis: (calculated) N= 3.70, Cl= traces;

(found) N= 1.72, Cl= 2.79 (DF_N= 0.17, DF_{Cl}= 0.11)

Attempts to hydrolyze the oxazoline group with a non-nucleophilic acid such as an ethanolic solution of sulfuric acid resulted in partial cleavage of the benzylic ether bond. For example when a polymer-bound oxazoline with DF= 0.58 was refluxed in 100 mL of 6 N ethanolic H_2SO_4 for 8 h, the nitrogen content of the resulting polymer was 2.79 % instead of the calculated value of 3.88 % indicating a DF= 0.32. The results are summarized in table 20 (page 87).

Analysis: (calculated) N= 3.88;

(found) C= 80.49, H= 7.71, N= 2.79

IR: 3282 (OH and NH_2), disappearance of the band at 1674

Preparation of 97 by N-methylation of 96

A 9.03 g sample of the polymer-bound amino alcohol 96 (N= 0.99% or DF= 0.084) was added slowly and with stirring to cooled 90% formic acid (30 g). Once the addition was completed, the mixture was stirred 5 min, then 37% formaldehyde solution in water (20.7 g) was added and the mixture was heated to reflux for 5 days. The polymer was then collected on filter and washed thoroughly with a variety of solvents as for 74 and dried in vacuo.

Analysis: (found) N= 0.93% (DF= 0.080)

IR: Disappearance of the band at 3282 (N-H)

Reaction of polymer 96 with LAH or n-BuLi

A 3.00 g sample of the polymer supported amino alcohol 96 (DF_{Cl}= 0.235, DF= 0.366) was suspended in 30.0 mL of dry THF and 1.00 g (26.3 mmol) of LAH was added in one portion. The mixture was refluxed for 36 h, the polymer was filtered and washed with THF:HCl 1 N (1:1) until the gray color disappeared (approximately 24 h), THF/H_2O (1:1) 4 times, THF/NH_3 1 N (1:1) 4 times, THF/H_2O (3:1), dioxane, $CHCl_3$, acetone, methanol and dried overnight under vacuum to yield 2.88 g of polymer.

Analysis: (found) Cl= 0.81% (0.23 meq Cl/g polymer)

IR: 3200 (OH and NH_2), 1016 (C-O).

Similarly, the polymer 96 was reacted with an excess of n-butyllithium in THF at -78°C and washed as above.

Analysis: (found) Cl= 0.91% (0.26 meq Cl/g polymer)

IR: 3200 (OH and NH_2), 1017 (C-O).

Preparation of polymer 98

A suspension of 10.0 g of chloromethylated polystyrene (1.0 meq Cl/g) in 75 mL DMF containing 4.54 g (25 mmol) of (1S, 2S)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol 83 was stirred at 60-70°C for 4 days. After filtration and thorough washing with a variety of solvents as for 94 and drying in vacuo overnight 11.08 g of polymer was obtained.

Analysis: (found) N= 1.12% (DF= 0.098)

IR: 3475 (OH and NH), 1581 (C-N), 1050 (C-O).

Preparation of polymer 99 from the N-methylation of 98

The methylation of 98 was carried out exactly as described above for 97.

Analysis: (found) N= 0.092% (DF= 0.080)

IR 3330 (OH), 1027 (C-O).

Polymer-bound ephedrine (100)

A mixture of 10.00 g of chloromethylated polystyrene (2.36 mmol of Cl/g) and 11.7 g (70.8 mmol) of 1-(-)-ephedrine in 80 mL of DMF was stirred at 85°C for 4 days. The polymer was filtered and washed repeatedly with ethanol, water, THF:water (1:1) until no chloride ion was found in the wash liquid, THF and ethanol. After drying in vacuo at 40°C for 15 h, 13.01 g of polymer were obtained. Nitrogen analysis indicated a loading of ephedrine corresponding to 1.81 mmol/g while no chlorine remained on the polymer.

IR: 3369 (OH), 1600 (C-N), 1025 (C-O).

Other polymers with varying loadings were also prepared by a similar procedure using the quantitative displacement of chloride from appropriately functionalized chloromethylated resins.

(L)-N-(phenylsulfonyl)valine (112)

To a solution of 10.00 g (85.0 mmol) of (L)-valine in 100 mL of water containing 25.17 g (237 mmol) of Na_2CO_3 was added 17.2 g (98 mmol) of benzenesulfonyl chloride. The solution was stirred for 4 h and the pH was brought below 5 with the addition of concentrated HCl, the mixture was cooled to RT and the solid was filtered, washed with water several times and dried to yield 15.20 g of crude compound. It was recrystallized from methanol-water to give 14.67 g (yield= 67%) of the desired compound, [α]=

+15.1° (c= 2.852, $CHCl_3$) and m.p.= 152.0-152.5°C (reported m.p. = 149-150°C).

Analysis: (calculated for $C_{11}H_{15}NO_4S$) C= 51.35, H= 5.88, N= 5.44, S= 12.46;
(found) C= 51.45, H= 5.90, N= 5.51, S= 12.51

NMR: 0.85 (d, 3H), 1.00 (d, 3H), 2.15 (m, 1H), 3.70 (q, 1H, J_{AX}= 9 Hz, J_{AB}= 5 Hz, became a doublet, J= 9 Hz, upon D_2O exchange), 6.15 (d, 1H, J= 8 Hz, disappeared upon D_2O exchange), 7.55 (m, 3H), 7.90 (m, 2H), 9.65 (broad, 1H).

IR: 1702 (C=O), 3300 (sharp), 1166 and 1330 (sulfonyl).

MS: 258 (M+1, chemical ionization), 77 ($C_6H_5^+$, 100%), 212 (M^+-CO_2H, 78%), 141 ($C_6H_5SO_2^+$, 54%).

(2S)-N-(Phenylsulfonyl)-2-phenylglycine (113)

This compound was prepared according to the procedure described above for 112 in 63% yield using (S)-(+)-2-phenylglycine as the starting chiral amino alcohol. [α]= +129.5° (c= 3.802, DMSO) and m.p.= 186.5-187.3°C.

Analysis: (calculated for $C_{14}H_{13}NO_4S$) C= 57.72, H= 4.50, N= 4.81, S= 11.01;
(found) C= 57.81, H= 4.62, N= 4.80, S= 10.86

NMR: 5.10 (d, 1H, J= 7 Hz), 5.90 (d, 1H, J= 7 Hz), 7.16-7.76 (m, 10H).

IR: 3314, 1734 (C=O), 1130 and 1325 (sulfonyl).

MS: 292 (M+1, chemical ionization), 28 (CO_2, 100%), 77 ($C_6H_5^+$, 97%), 246 (M^+-CO_2H, 67%), 141 ($C_6H_5SO_2^+$, 33%).

(3S)-3-[Phenylsulfonyl)amino]-2-methyl-6-hepten-4-one (114)

A solution of 20.0 g (77.7 mmol) of 112 in 150 mL of dry THF was cooled to -78°C and 31.0 mL of 2.5 M n-BuLi was added dropwise followed by 210 mL of 1.0 M allyl magnesium bromide. The reaction mixture was slowly brought to RT by stopping the addition of Dry Ice and it was stirred

overnight. It was poured over 200 mL of 1 N HCl, extracted 3 times with $CHCl_3$, backwashed 2 times with saturated $NaCO_3$, brine, dried over $MgSO_4$ and evaporated to give 22.2 g of crude compound. A fraction of the mixture, 13.11 g, was separated on HPLC using $CHCl_3$:hexane:ethyl acetate (50:40:10) to afford 7.31 g of pure product (calculated yield= 64%). m.p.= 65.0-67.0°C and $[\alpha]$= +139.4° (c= 2.18, $CHCl_3$) (reported m.p. = 67-69°C).

Analysis: (calculated for $C_{14}H_{19}NO_3S$) C= 59.76, H= 6.81, N= 4.98, S= 11.39; (found) C= 59.80, H= 6.67, N= 5.02, S= 11.16

NMR: 0.685 (d, 3H, J=7 Hz), 1.04 (d, 3H, J=7 Hz), 2.02 (m, 1H), 2.74 (q, J_{vic}= 6 Hz, J_{gem}= 18 Hz), 3.02 (q, 1H, J_{vic}= 6 Hz, J_{gem}= 18 Hz), 3.82 (q, 1H), 4.86 (q, 1H, J= 15 Hz), 5.04 (q, 1H, J=9 Hz), 5.36 (d, NH), 5.48 (m, 1H), 7.46 (m, 3H), 7.76 (m, 2H).

IR: 1720 (C=O), 3257 (NH), 1169 and 1325 (sulfonyl).

MS: 282 (M+1, chemical ionization), 212 ($M^+-C_4H_5O$, 100%), 77 ($C_6H_5^+$, 71%), 141 ($C_6H_5SO_2^+$, 40%).

(1S)-1-[(Phenylsulfonyl)amino]-1-phenyl-4-penten-2-one (115)

This was prepared according to the procedure described above for 114 starting from 113. The desired compound was obtained in 46% yield. m.p.= 80.0-82.1°C and $[\alpha]$= 123.3° (c= 1.18, $CHCl_3$).

Analysis: (calculated for $C_{17}H_{17}NO_3S$) C= 64.74, H= 5.43, N= 4.44, S= 10.17; (found) C= 64.74, H= 5.53, N= 4.32, S= 10.03

NMR: 1.88 (d, 2H), 5.00 (d, 1H), 5.86 (d,1H), 6.16 (m,2 H), 7.00 (m, 1H), 7.06-7.38 (m, 8H).

IR: 3280 (NH), 1689 (C=O), 1168 and 1348 (sulfonyl).

MS: 316 (M+1, chemical ionization), 77 ($C_6H_5^+$, 100%), 246 ($M^+-C_4H_5O$, 80%), 141 ($C_6H_5SO_2^+$, 49%).

(3S)-3-[(Phenylsulfonyl)amino]-2-methyl-4-octanone (116)

To 1.03 g (4.00 mmol) of N-(phenylsulfonyl)-L-valine 112 dissolved in 50 ml of anhydrous ether at -78°C was added 7.50 mL (12.0 mmol) of 1.6 M n-BuLi dropwise. A precipitate appeared and the reaction mixture was stirred for 30 min at -78°C. It was brought to RT, stirred for another 30 min and poured over 100 mL of cold 40% H_3PO_4 in water, extracted 3 times with ether, backwashed 2 times with cold 5% NaOH, brine, dried over $MgSO_4$ and evaporated to yield 0.27 g of crude product. Separation by chromatography using ethyl acetate and hexane in 10:90 ratio afforded 0.12 g of pure product (yield= 10%) with m.p.= 49.5-52.0°C and $[\alpha]$= +128.5° (c= 2.469, $CHCl_3$).

Analysis: (calculated for $C_{15}H_{23}NO_3S$) C= 60.58, H= 7.79, N= 4.71, S= 10.78;
(found) C= 60.49, H= 7.76, N= 4.63, S= 10.66

NMR: 0.68 (d, 3H), 0.76 (d, 3H), 1.04 (m, 5H), 1.22 (m, 2H), 2.08 (m, 2H), 2.30 (m, 1H), 3.76 (q, 1H), 5.44 (d, 1H), 7.50 (m, 3H), 7.78 (m, 2H).

IR: 3281 (NH), 1711 (C=O), 1163 and 1331 (sulfonyl).

MS: 298 (M+1, chemical ionization), 212 (M^+-n-BuCO, 100%), 57 ($C_4H_9^+$, 87%), 77 ($C_6H_5^+$, 50%), 141 ($C_6H_5SO_2^+$, 31%).

(1S)-1-[(Phenylsulfonyl)amino]-1-phenyl-2-hexanone (117)

This compound was prepared in a manner similar to that described above for 116 starting from 113. The yield of the reaction was 8%. This compound had a m.p.= 84.5-85.8°C and $[\alpha]$= +236.1°C (c= 3.448, $CHCl_3$).

Analysis: (calculated for $C_{18}H_{21}NO_3S$) C= 65.52, H= 6.39, N= 4.23, S= 9.67;
(found) C= 65.59, H= 6.54, N= 4.09, S= 9.47

NMR: 0.72 (t, 3H), 1.06 (m, 2H), 1.34 (m, 2H), 2.22 (t, 2H), 5.02 (d, 1H, J= 6 Hz), 6.10 (d, 1H, J= 6 Hz), 7.00-7.60 (m, 10H).

IR: 3235 (NH), 1708 (C=O), 1168 and 1347 (sulfonyl).

MS: 332 (M+1, chemical ionization), 246 (M^+-n-BuCO, 100%), 77 ($C_6H_5^+$, 70%), 141 ($C_6H_5SO_2^+$, 28%).

(1S)-1-[(Phenylsulfonyl)amino]-2-methyl phenyl ketone (118)

This compound was prepared according to a procedure similar to that of 117, starting from 112, except that phenyl lithium 2.0 M was used instead of n-BuLi. Yield= 37%, m.p.= 101.5-102.5°C and [α]= +144.1° (c= 1.141, $CHCl_3$).

Analysis: (calculated for $C_{17}H_{19}NO_3S$) C= 64.33, H= 6.03, N= 4.41, S= 10.10;
(found) C= 64.49, H= 6.04, N= 4.49, S= 10.17

NMR: 0.74 (d, 3H), 1.16 (d, 3H), 2.08 (m, 1H), 4.74 (q, 1H), 5.66 (d, 1H), 7.24-7.82 (m, 10H).

IR: 3268 (NH), 1679 (C=O), 1169 and 1320 (sulfonyl).

MS: 318 (M+1, chemical ionization), 43 ($C_3H_7^+$, 100%), 103 (47%), 71 ($C_4H_9N^+$, 37%).

(1S)-2-[(Phenylsulfonyl)amino]-1-ethyl-1-phenyl-3-methyl-1-butanol (119)

To a solution of 1.12 g (3.53 mmol) of 118 in 50 mL of THF was added 2.50 mL of 2.85 M ethyl magnesium bromide (7.12 mmol). The mixture was stirred at RT for 2 h and 15 mL of 2 N HCl was added. The aqueous phase was extracted 3 times with $CHCl_3$, backwashed with brine, dried over $MgSO_4$ and evaporated to yield 1.59 g of crude product. Purification by chromatography gave 0.98 g (yield= 80 %) of the pure product. m.p.= 149.5-151.0°C and [α]= -31.5° (c= 1.387 , $CHCl_3$)

Analysis: (calculated for $C_{19}H_{25}NO_3S$) C= 65.68, H= 7.25, N= 4.03, S= 9.23;
(found) C= 65.72, H= 7.22, N= 4.13, S= 9.16

NMR: 0.40 (d, 3H, J= 8 Hz), 0.58 (t, 3H), 0.66 (d, 3H), 1.90 (m, 1H), 2.08 (m, 2H), 3.62 (d, 1H), 4.96 (d, 1H), 7.26-8.00 (m, 10H).

IR: 3512, 3295, 1165 and 1325 (sulfonyl).

MS: 330 ($M+1-H_2O$, chemical ionization], 135 ($C_9H_{11}O^+$, 100%), 212 ($C_{10}H_{14}NO_2S^+$, 62%), 77 ($C_6H_5^+$, 55%).

(1S)-(-)-Nopol benzyl ether (123)[100]

A sample of potassium tert-butoxide, 15.5 g (0.138 mol), was added to a solution of 20.0 g (0.120 mol) (1S)-(-)-nopol (6,6-dimethylbicyclo-[3.1.1]hepte-2-ene-2-ethanol) and 0.08601 g (0.32 mmol) of 18-crown-6 in 80 mL of toluene. The mixture was stirred for 30 min at RT and 30.38 g (0.24 mol) of benzyl chloride was added in 15 mL of toluene. After 24 h TLC showed no unreacted nopol. The organic phase was washed 3 times with water, dried over $MgSO_4$ and evaporated. The mixture was distilled (120°C at 1 Torr) to give benzyl chloride and 28.6 g (yield= 92%) of the desired product. $[\alpha]= -26.8^{\circ}$ (neat)

NMR: 0.85 (s, 3H), 1.30 (s, 3H), 1.30 (m, 1H), 2.25 (m, 7H), 3.45 (t, 2H), 4.45 (s, 2H), 5.20 (broad, 1H), 7.25 (s, 5H).

^{13}C NMR: 21.16 (q), 26.33 (q), 31.33 (t), 31.64 (t), 37.18 (t), 37.96 (s), 40.79 (d), 45.87 (d), 68.83 (t), 72.82 (t), 117.84 (d), 127.41-128.28 (aromatic C), 138.59 (s), 145.14 (s).

MS: 91 ($C_7H_7^+$, 100%), 107 ($C_7H_7O^+$, 26%), 105 (27%), 92 (33%).

Preparation of polymer-bound Nopol 124

To a suspension of 20.0 g (16.8 meq) of chloromethylated polystyrene (0.84 meq/g polymer) in 200 mL of dry toluene was added 0.140 g of 18-crown-6 (0.53 mmol). A neat sample of 3.27 g (19.7 mmol) of (1S)-(-)-nopol was added and the mixture was stirred for 20 min. Potassium tert-butoxide,

2.64 g (23.5 mmol), was added in one portion and the reaction was continued at 60° for 4 days. The polymer was filtered and washed with methanol, water, dioxane/H_2O 3:1 until no chloride ion could be detected, then with dioxane, $CHCl_3$, methyl ethyl ketone, acetone, methanol, ethanol, ether and dried overnight under vacuum. A mass of 22.2 g of the polymer was obtained (theory 22.18 g).

Analysis: (found) C= 90.37, H= 8.10 Cl= traces (0.74 meq nopol unit/g polymer, DF= 0.89 for a functional yield of 98%).

IR: 1601 (C=C), 1094 (C-O)

Reduction of acetophenone using LAH and amino alcohols

To 2.51 mL of LAH 1.0 M in ether diluted with 5.0 mL of anhydrous ether under argon was added 0.6423 g (2.51 mmol) of N-benzylephedrine dissolved in 4.0 mL of ether over a period 1 h. The mixture was stirred for 30 min and 0.6129 g (5.02 mmol) of 3,5-dimethylphenol dissolved in 4.0 mL of ether was added over a period of 30 min. The homogeneous mixture was stirred at RT for 2 h after which the temperature was lowered to -15° and 0.2513 g (2.09 mmol) of acetophenone in 1.5 mL of ether was added slowly over a period of 2 h. The reaction was continued at -15° for an additional hour, then 6N HCl was added to hydrolyze and dissolve the Al salts (acidic pH). The alcohol was extracted 3 times with ether and the combined organic phases were backwashed once with water, dried over $MgSO_4$, and evaporated. The crude product was separated on TLC plates by using a 4:1 mixture of hexane and ethyl acetate to yield 0.2190 g (86%) of isolated alcohol, $[\alpha]$= +36.8° (c= 7.260, cyclopentane) (max $[\alpha]$= -43.1° (c= 7.19, cyclopentane)).

Similarly, other amino alcohols were used for the reduction of

acetophenone. Various temperatures and amount of achiral agents were utilized as reported in tables 10 and 14 (run 1).

Asymmetric reduction of acetophenone with the use of insoluble polymeric reagent

To a stirred solution of LAH (1.25 mmol) and anhydrous ether (5 mL) was added dropwise an ethereal (5 mL) solution of 3,5-dimethylphenol (2.50 mmol) over a period of 30 min under an argon atmosphere. After the mixture was stirred 1 h at RT, the mixture was cooled to 0°C and stirred while the solid polymer-bound ephedrine (once used sample, 1.710 g or 1.25 mmol) was added slowly with a screw-type powder addition funnel over a period of 1 h. Stirring was continued for 2 h at 0°C to afford the desired ethereal suspension which was then cooled to -15°C and a solution of acetophenone (1.00 mmol) in ether (2 mL) was added dropwise over a 2 h period after which the heterogeneous mixture was stirred for an additional hour at -15°C. Workup was effected by addition of 0.1 N NaOH (5 mL) to the cooled reaction mixture which, after 15 min of stirring, was allowed to reach RT while the mixture was neutralized with 1 N HCl. The polymer was then washed several times with water and ether; the ethereal extracts were dried over $MgSO_4$ and concentrated to afford a product which was purified by preparative TLC (ethyl acetate:hexane, 1:3) to afford the pure 1-phenylethanol (0.1164 g, 97%) with $[\alpha]= +34^{\circ}$ (c= 7, cyclopentane) for ee of 78.8%.

Similarly other insoluble polymer-bound amino alcohols were used in the reduction of acetophenone.

Results from this procedures are shown in tables 14 and 15.

Reduction of acetophenone using a soluble polymer-bound ephedrine

To 1.75 mL of LAH 1.0 M in ether diluted with 5.0 mL of anhydrous ether under argon was added 0.4274 g (3.50 mmol) of 3,5-dimethylphenol in 4.0 mL of ether over 30 min. A solution of 0.6682 g (1.75 meq) of the soluble polymer-bound ephedrine in 15.0 mL of ether was added to the mixture over a period of 1 h. Upon addition of the polymer solution a precipitate was immediately formed. The heterogeneous solution was stirred at RT for 2 h after which the temperature was lowered to -15°C and 0.1512 g (1.26 mmol) of acetophenone in 1.5 mL of ether was added slowly over 2 h. After it was stirred for another hour at -15°C, the mixture was hydrolyzed with 6 N HCl. The polymer was filtered and rinsed with water and then ether, and the alcohol was isolated as described above to yield 0.1099 g of alcohol (71%) with optical rotation $[\alpha]= 13.9^{\circ}$ (c= 7.144, cyclopentane), ee= 32%.

Reduction of 1-octyn-3-one by Nopol benzyl ether and 9-BBN

A solution of 1.4102 g (5.50 mmol) of (1S)-(-)-Nopol benzyl ether 123 in 10 mL of 0.5 M 9-BBN in THF was refluxed under argon overnight. The THF was evaporated and 0.3107 g (2.50 mmol) of 1-octyn-3-one was added. The solution was stirred for 48 h and 1.7 mL of 3 M NaOH was added followed by 1.2 mL of 30% H_2O_2 and heating at 40°C for 2 h. The solution was saturated with anhydrous K_2CO_3, the organic phase separated and extracted 3 times with ether, dried over $MgSO_4$ and evaporated. The alcohol was purified by chromatography using ethyl acetate:hexane as a solvent mixture (20:80). Because the product did not absorb UV radiation or iodine several fractions were collected, evaporated and the NMR spectrum of each was taken. One of these fraction (96.4 mg, 30%) had an optical activity of $[\alpha]= -10.8^{\circ}$ (c= 2.12, ether) for a ee of 53%, (max $[\alpha]= +20.5^{\circ}$ (c= 2, ether))[42].

Reduction of 1-octyn-3-one with the use of polymer-bound Nopol

A sample of 2.3258 g (5.49 meq) of the polymer-bound Nopol (2.36 meq/g polymer) was evacuated and purged with argon several times. Dry THF, 10.0 mL, was added followed by 10.0 mL of 0.5 M 9-BBN in THF. The mixture was refluxed for 48 h. It was cooled at RT and 0.3135 g (2.52 mmol) of 1-octyn-3-one was added. The mixture was stirred for 72 h and 0.46 mL of freshly distilled propionaldehyde was added and the mixture stirred for another 24 h. A 3 N solution of NaOH, 1.7 mL, was added followed by 1.2 mL of 30% H_2O_2 and heating at 40°C for 2 h. The polymer was filtered, rinsed with ether and the alcohol isolated as described above. A total of 0.2285 g of crude mixture was obtained of which 112.8 mg was separated to yield a pure fraction of 25 mg alcohol (17%). $[\alpha]= -4.77^{\circ}$ (c= 2.16, ether), ee= 23%.

Reduction of acetophenone using the amino alcohols and diborane

A solution of borane (10.0 mL, 1.0 M in THF, 10 mmol) was added to 0.9064 g (5.00 mmol) of (1S, 2S)-(+)-1-phenyl-2-amino-3-methoxy-1-propanol 83 in 5.0 mL of THF at -78°C over 20 min. The temperature was gradually brought to RT and it was stirred for 18 h. Acetophenone (0.4802 g, 4.0 mmol) in 5.0 mL of THF was added over 5 min. It was stirred for an additional 1 h, hydrolyzed with 2 N HCl, extracted 3 times with ethyl acetate, backwashed twice with saturated NaCl, dried over $MgSO_4$ and evaporated. The alcohol was purified by chromatography and obtained in 88% yield (0.42951 g) with $[\alpha]= 27.5^{\circ}$C (c= 7.225, cyclopentane), ee= 64%.

The reduction was carried out in a similar manner with different ratios of amino alcohol to borane. As well, the compound 84 was tested for this reduction. Results for both series of trials are shown in table 17 and 18 (page 84).

Determination of the amount of hydride in the chiral complexes

A solution of 90.2 mg (0.5 mmol) of 63 in 5.0 mL of THF was cooled to -60°C and 0.5 mL of 1.0 M BH_3 was added dropwise. The solution was stirred at RT overnight and hydrolyzed with 3.0 mL of 2 N HCl. Stirring was continued for another 15 min and the volume of hydrogen evolved was 31.0 mL at 293°K and 761.4 mm Hg. Using the relation PV = nRT the volume of H_2 was calculated as corresponding to 1.3 mmol. Results of the hydrolysis for the complexes formed from various amount of borane and the amino alcohol 83 are shown in table 16 (page 80).

CONCLUSION

The reduction of acetophenone by chiral complexes of lithium aluminum hydride could be performed with selected amino alcohols to yield 1-phenylethanol in moderate optical yields. These amino alcohols were perfect candidates to anchor to a polymer backbone and study the "polymer effect". It was found that in the case of aluminum hydride complexes of polymers, high degree of functionalization led to site interactions which in turn was responsible for the poor accessibility of the supported reagents. As a consequence, the reduction of acetophenone took place in a less stereoselective manner than that observed with the model compounds. However, by lowering the content of the optically active molecules grafted to the polystyrene it was possible to reproduce the behavior of low molecular weight counterparts. These polymers offered the advantage that the purification of the optically active alcohol was performed by simple filtration. As well, these polymers could be recycled and re-used for the same process. However, due to the low capacity of the chiral moiety of this particular polymer a considerable mass of reagent was necessary to reduce limited amounts of the ketone.

Borane complexes of selected model compounds were utilized to reduce acetophenone but we were not successful in extending the study to the polymeric reagents in that particular case.

FUTURE WORK

It seems that for practical reasons, polymer-bound borane complexes are desirable since they do not suffer from the same limitation as aluminum hydride complexes.

Amino acids are a non-expensive source of chiral groups and their derivatives have proven to be useful in organic synthesis. Unfortunately, existing methods only allow those amino acids bearing functional groups other than the amino or carboxylic acid groups to be anchored on a solid support. It would therefore be of interest to devise a general synthesis allowing the attachment of these molecules to a polymer.

Finally, it would be possible to solve the problem encountered with the lability of the benzylic ether linkage by starting the synthesis of the polymers with chloroethyl polystyrene rather than the chloromethyl derivatives. The additional methylene group would drastically reduce the acid sensitivity of the ether bond. However, these polymers are not commercially available and their preparation involves a several-step synthesis.

APPENDIX A

Table 1. Reduction[1] of acetophenone with a highly loaded polymer-bound ephedrine[2].

Run	Solvent	Temperature (°C)	Chemical Yield (%)	Optical Yield (%)
1	ether	0	78	10.8
2	ether	-15	90.5	19.1
3	ether	-78	85	6.6
4	THF	0	87.5	6.7
5	THF	-15	84.5	20.1
6	THF	-78	50	18.3

1. Molar ratio LAH/polymer/3,5-DMP was 1:1:2 in all the cases.
2. Reactions with 1.25:1 ratio of LAH/acetophenone using 1% cross-linked gel type polymer-bound ephedrine with a capacity of 1.81 mmol/g of polymer (DF = 0.27).

APPENDIX B

Table 1. Reduction of acetophenone with highly loaded polymer-bound hydride reagent.

run	molar ratio LAH/polymer/3,5-DMP	solvent	T (^{o}C)	procedure[2]	chemical yield (%)	optical yield (%)
1	1:1:2	ether	-15	A	90.5	19.1
2	1:1:2	THF	-15	A	84.5	20.1
3	1:1:2[3]	THF	-15	A	60	5
4	1:1:2	ether	-15	B	47.5	36.5
5	1:1:2[3]	ether	-15	B	37	16.5
6	1:1:2[3]	ether	0	B	43	10
7	1:2:2	ether	-15	A	84	32.6
8	1:2:2	ether	-15	B	31	40

1. Reactions with 1.25:1 ratio of LAH/acetophenone using 1% cross-linked gel-type polymer-bound ephedrine with a capacity of 1.81 mmol/g.
2. Procedure A, normal addition; procedure B, filtration of soluble phase and washing of polymer prior to addition of acetophenone (see experimental section).
3. Macroporous Amberlite XE-305 resin.

APPENDIX C

Table 1. Influence of polymer capacity on the enantioselectivity[1]

run	capacity (mmol/g)	DF	yield (%)	ee (%)
1	2.1	0.35	86	5.5
2	1.9	0.30	89	14.1
3	1.8	0.27	90	19.5
4	0.7	0.09	97	78.8

1. All reactions using 0.8 molar equivalent of acetophenone with 1% cross-linked polymer in ether at -15°C with a molar ration LAH/polymer/3,5-DMP of 1:1:2 and using once recycled polymer in procedure A.

Table 2. Reduction of acetophenone with lightly loaded polymer-bound hydride reagent[1].

run	molar ratio LAH/polymer/3,5-DMP	solvent	T (°C)	reaction cycle	yield %	ee %
1	1:1:2	ether	-15	1	93	75.5
2	1:1:2	ether	-15	2	97	78.8
3	1:1:2	ether	-15	5	94	78.5
4	1:1:2	ether	0	1	98	71.4
5	1:1:2	THF	-15	1	70	29.1
6	1:1.1:2	ether	-15	2	70	29.1
7	1:1.15:2	ether	-15	2	65	59.8
8	1:1.15:1.85	ether	-15	2	88	60.8
9	1:2:2	ether	-15	2	0	0

1. Reduction of acetophenone with 1% cross-linked polymer having DF = 0.09

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