Free and Polymer-Supported Chiral Lithium Amides:

Synthesis and Applications

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By

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In the loving memory of my parents Danuta and Władysław

and

to my husband Michael with infinite gratitude

This is for you.

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Abstract

This dissertation deals primarily with applications of chiral lithium amides (free and polymer-supported) as bases in the synthesis of α-functionalized carbonyl compounds.

Two cyclic ketones, tropinone and 1,4-cyclohexanedione monoethylene ketal were deprotonated with several chiral bases in solution. Tropinone was deprotonated enantioselectively in up to 96-99% ee in the presence of LiCl as the additive. This successful outcome was the result of extensive methodological studies. Nine chiral lithium amides and ten different additives were tested. The enolate was trapped with 2,2,2-trichloroethyl chloroformate. The complexation effect of a chiral amine to the lithium enolate of the cyclic ketone was studied. 1,4-Cyclohexanedione monoethylene ketal was deprotonated with two chiral lithium amides, and the corresponding lithium enolate was trapped with benzaldehyde to give the optically active aldol product.

Three methods for the synthesis of insoluble and soluble polymer-supported chiral amines were developed. The chiral lithium amides were successfully generated and they were applied as bases in the deprotonation of different carbonyl compounds, a ketone, and a □-ketoester. The corresponding α-functionalized compounds were obtained in good yield and enantioselectively (where applicable). Two soluble polymer-supported chiral amino-alcohols were synthesized and used as a proton donor in diastereoselective, and enantioselective protonation of the lithium enolates derived from cyclic ketones.

This is the first reported generation and application of novel, polymer-supported chiral lithium amides. Hopefully, the work presented in this thesis will lay the foundation of a new way of performing organic synthesis.

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List of Abbreviations

AD	asymmetric dihydroxylation
AcOH	acetic acid
AcOEt	ethyl acetate
AIBN	azobisisobutyronitrile
n-BuLi	n-butyl lithium
bp	boiling point
(Boc)$_2$O	di-*tert*-butyl dicarbonate
d	day
DCC	dicyclohexylcarbodiimide
DIPEA	diisopropylethanolamine
DMF	dimethyl formamide
DVB	p-divinylbenzene
ee	enantiomeric excess
EPC	enantiomerically pure compounds
functionaliy of polymer	mmols of reacting groups per gram of polymer
h	hour
HMPA	hexamethylphosphoramide
HPLC	hight pressure liquid chromatography
homopolymer	polymer composed of only one type of monomer
insoluble polymer	a polymer which does not dissolve in organic solvents and water
IPA	isopropyl alcohol
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
linker	carbon chain separating the reactive group from the polymer matrix

liquid-phase synthesis	organic synthesis where soluble, polymer-supported reagents are used
loading	value describing the number of mmols of reacting groups per 1 gram of the resin
LP	liquid-phase
LPS	liquid-phase synthesis
IR	infra red
mp	melting point
min	minutes
MS	mass spectroscopy
NMR	nuclear magnetic resonance
o/n	over night
PEG	polyethyleneglycol
PS	polystyrene
rt	room temperature
solid-phase synthesis	organic synthesis where insoluble, polymer-supported reagents are used
soluble polymer	polymer which dissolves in organic solvents and water
SP	solid-phase
SPS	solid-phase synthesis
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMSCl	trimethylchlorosilane
TrocCl	2,2,2-trichloroethyl chloroformate
UV	ultra violet

CHAPTER I: INTRODUCTION

Selected topics in chemistry of polymer-supported amines

The work presented in this thesis deals primarily with the synthesis and applications of chiral amines in organic synthesis. Chiral amines in solution are described in Part A of the Results and Discussion section. Their lithium amides were used as bases in deprotonation of two cyclic ketones: tropinone and 1,4-cyclohexanedione monoethylene ketal. Deprotonation of cyclic ketones with chiral lithium amides derived from the corresponding chiral amines has been the subject of many literature reviews. Therefore it will not be discussed in this chapter.[1 – 13] The main purpose of this chapter is to review the literature dealing with the synthesis and applications of polymer-supported chiral amines and their derivatives.

Organic synthesis utilizing polymer-supported reagents experienced very rapid growth in the past ten years. Solid-phase synthesis was invented by Merrifield in 1963.[14] This technique revolutionized the synthesis of peptides. Known methods of the coupling of amino acids were used but peptide purification after every step of the synthesis was reduced to filtration of the polymer-supported compound followed by washing to remove the excess of reagents. After the desired peptide was synthesized it was cleaved from the polymer support and could be purified by conventional methods (e.g: reverse-phase column chromatography). The solid-phase method for synthesizing complicated peptides became so popular that automatic peptide synthesizers were developed. It was thought that solid phase methods could be used for the synthesis of small organic compounds. The first publications dealing with this area of research were reported in the early 1970's by Leznoff[15] and other researchers[16 – 18] but this new approach towards the synthesis of small compounds did not become popular until the publication of seminal papers by Ellman,[19] the Chiron group,[20] and the group at Parke-Davis.[21] There are already reviews compiling reactions that can be performed on solid supports.[22] Synthesizers for small molecules were built similar to the peptide synthesizers.[21, 23]

The growth in the area of solid-phase synthesis can be illustrated by the number of publications on the topic, which have appeared in the chemical literature (Figure 1).[24]
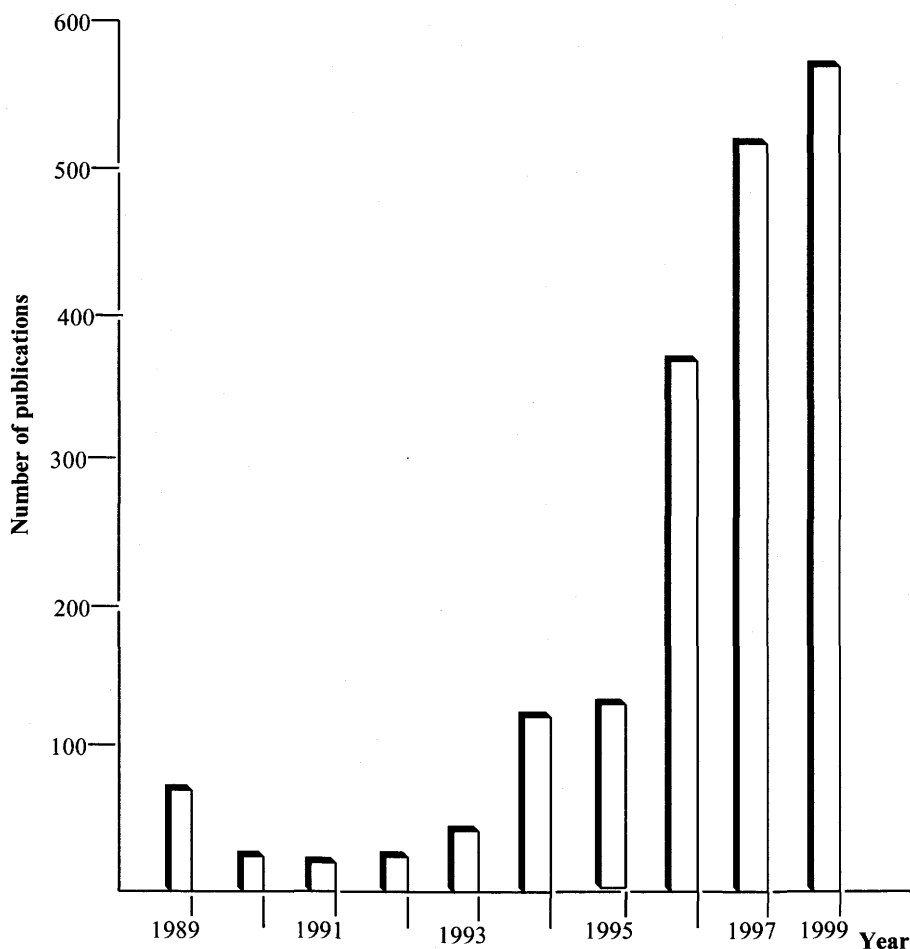
Figure 1. Number of articles dedicated to solid-phase organic synthesis (ref. 24).

Chiral amines are one of the most commonly used compounds in organic synthesis. They can be used as chiral auxiliaries, ligands, reagents, catalysts, and resolving agents.[25] Chiral amines can also be used as precursors for the generation of chiral lithium amides[1-13] that can serve as bases in the enolization of ketones, esters and amides.

Before my work was started there were essentially no literature precedents describing synthesis of polymer-supported chiral secondary amines, but the syntheses of polymer-supported primary and tertiary amines, and amino-alcohols were documented to some extent, and selected publications are cited in this section. Different applications of

these compounds are discussed. General concepts in SPS (solid-phase synthesis) and LPS (liquid-phase synthesis) involving reagents on polymer-support are going to be presented as well.

1.1 Synthesis of small organic molecules involving compounds supported on insoluble polymers.

There are three general approaches in the polymer-supported synthesis (SPS) of small organic molecules involving polymer-bound reagents (Scheme 1), polymer-bound catalysts (Scheme 2), or polymer-bound protecting groups (Scheme 3).

Scheme 1
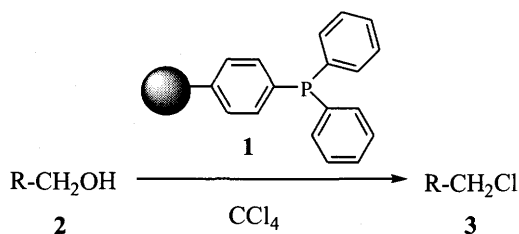
Polymer-supported triphenylphosphine 1 was used as the reagent in the conversion of n-alkyl alcohols 2 into the corresponding n-alkyl halides 3.[26] The synthesis of small organic molecules employing polymer-bound reagents is less popular than the methods using polymer-bound catalysts or polymer-bound protective groups.[26] In order to broaden the chemistry of polymer-bound reagents we have developed the synthesis of several polymer-supported chiral secondary amines and chiral amino-alcohols, which were used in the deprotonation of ketones and protonation of lithium enolates. This work will be discussed in part B of Results and Discussion.

An example of a polymer-bound catalyst is presented in Scheme 2

Scheme 2
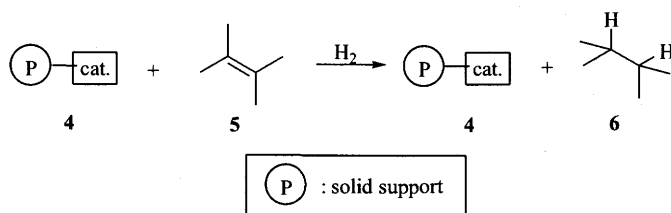
This is a schematic representation of a reduction of an alkene in the presence of a polymer-supported catalyst. After the reaction is completed, the catalyst remains bound to the polymer-support and the product stays in solution. A number of polymer-bound catalysts are now commercially available, but many researchers still have not recognized the advantages associated with polymer-supported catalysts and solid phase synthesis.[27]

In the last approach to SPS of small organic molecules, polymeric protecting groups are used. One of the functional groups of the substrate **7** is protected with polymer **8** while another is derivatized. The chemical transformations employing this approach require two additional steps: anchoring of the substrate to the resin and cleaving the final product after completion of the reaction. A general description of this approach is offered in Scheme 3.

Scheme 3
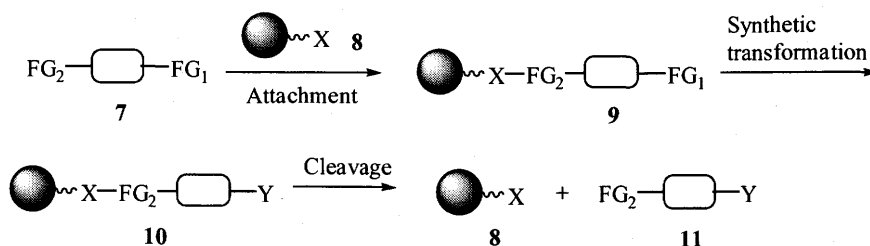
Supports and linkers in solid phase synthesis (SPS).

In order to attach a molecule to the resin a covalent linking group, called the linker (or spacer) is often required. The linker is usually a carbon chain of different length and complexity, which separates reactive groups from the polymer matrix. It has to be stable to all the reagents used in the SPS but must allow cleavage of the small molecule from the polymer at the end of the synthesis. It should be pointed out that the requirement for the linker adds two additional steps to a solid phase reaction sequence compared to the solution route. The correct choice of the most appropriate linker for a particular class of a target molecule is the key factor in designing the SPS.[28] Available linkers can be divided according to their properties and the desired cleavage strategy: (i) cyclative cleavage; (ii) linkers which release specific functional groups; (iii) traceless linkers which form C-H bonds after cleavage;[29] (iv) active-able linkers (safety catch);[30] (v) cleavable and functional group interconversion; (vi) linkers developed for stability/ selectivity and (vii) recyclable linkers.[28]

Figure caption content:

$\widehat{P}$: solid support

⬮ : reagent or starting material
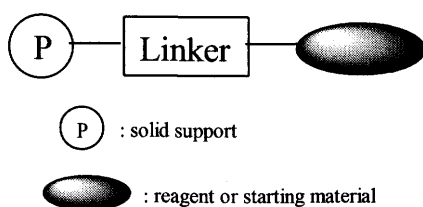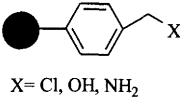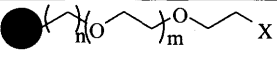
Figure 2: General structure of a polymer-supported reactant.

The solid support must also be carefully chosen when solid-phase synthesis is concerned. The general structure of a polymer-supported reagent (substrate) is shown in Figure 2. The most popular insoluble resins that were used as supports in a majority of the published articles dealing with SPS are *p*-chloromethylstyrene-styrene-*p*-divinylbenzene copolymers (PS/DVB), and polyethylene glycol (PEG) grafted on a PS/DVB copolymer.[28] General structures of polystyrene and PEG type polymers and their properties are presented in Table 1.

Table 1. Properties of polystyrene (PS) and polyethyleneglycol (PEG) type copolymers.

Solid support	Functional groups that could be attached	Particle size	Loading (mmol/g)	Chemical compatibility
Polystyrene type	X= Cl, OH, NH₂ X= Cl (Merrifield resin)	100 – 200 mesh 200 – 400 mesh	0.5 – 4.0	Swells in: DMF, DCM, THF, toluene; thermally stable
PEG type (TentaGel)	X= Br, OH, NH₂, SH, CO₂H	variable	0.2 – 0.5	Swells in: polar solvents, DCM

It can be clearly seen that the two most important variables that guarantee the success of a planned solid phase synthesis are the correct choice of the support and the linker.

Analysis and monitoring of solid-phase (SP) reactions.

After selection of the suitable support and the linker a method for the analysis and monitoring of the progress of the SP reaction has to be found. It should be pointed out that every step in SPS yields a polymer-bound intermediate, the characterization of which can pose a serious problem. Quantifying the loading (which corresponds to yield) and determining the structure of the polymer-supported product(s) and possible by-products is rather difficult, and special techniques are needed. In addition to the standard procedures like derivatization, cleavage, purification and analysis, several analytical methods such as:[27] (i) FT-IR and FT-Raman spectroscopy; (ii) solid state and gel-phase NMR spectroscopy and ^{1}H-^{13}C correlation spectroscopy; (iii) ^{1}H Magic Angle Spinning (MAS); (iv) matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF); (v) elemental analysis; (vi) titration of reactive groups (e.g: NH₂, CO₂H,

ArOH, SH)[28]; (vii) gravimetric analysis and (viii) photometry e.g: NH_2 group monitored by photometric Fmoc determination are available for characterizing a polymer-supported compound.

The conventional IR and NMR spectra of polymer-supported compounds are difficult to interpret due to the interference of the polymer matrix. Measurements by FT-IR under defined conditions can give qualitative data. Developments in the area of solid-state and gel-state NMR in the last decade have led to the elaboration of suitable methods for monitoring SPS reactions.[27] Gel state NMR is a mixture of standard solution NMR and solid state NMR spectroscopy eg.: a sample of a PS/DVB supported compound is transferred to the ordinary NMR tube and allowed to swell in an appropriate solvent. After degassing, the NMR spectrum can be taken under typical conditions used for dissolved samples.[27] It should be pointed out that the ^{1}H and ^{13}C NMR spectra are dominated by the signals given by the polymer matrix, making signals from the attached compound difficult to observe. Due to the strong baseline broadening, simple NMR spectra are difficult to interpret. The problem can be solved by applying a combination of MAS (Magic Angle Spinning) and gel-phase NMR. Another analytical method that can be used to obtain structural information about polymer-supported compounds is MALDI-TOF MS.[31] This technique is used to determine the mass of polymer-supported compounds after they are cleaved from the resin.

Application of SP reactions.

Until recently, new compounds were synthesized individually and then tested for their potential biological or catalytic activity. After solid phase synthesis became more popular, the procedures of searching for new lead structures became more efficient than ever before. Progress in biotechnology, molecular biology, robotics and automation led to the development of new screening assays. As a consequence, the number of compounds waiting to be tested rapidly become depleted, and standard methods for synthesizing new compounds are not efficient enough to satisfy the demand.[27] Two new methods for the efficient synthesis of a variety of organic compounds were developed: parallel synthesis

and "split-pool" synthesis. These two methods employ SP reactions, and belong to a relatively new area of organic chemistry called combinatorial synthesis.

Parallel synthesis is used to synthesize relatively larger quantities of libraries containing a small number of compounds (Scheme 4).

Scheme 4
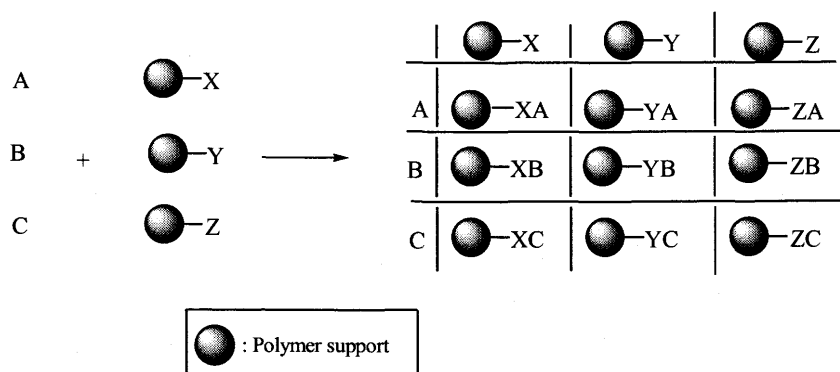
In this method only one compound is prepared per reaction vessel. This technique is especially suitable for the rapid optimization of previously identified lead structures.[27]

The "split-pool" synthesis is used to prepare smaller quantities of libraries containing a large number of compounds (Scheme 5).

Scheme 5
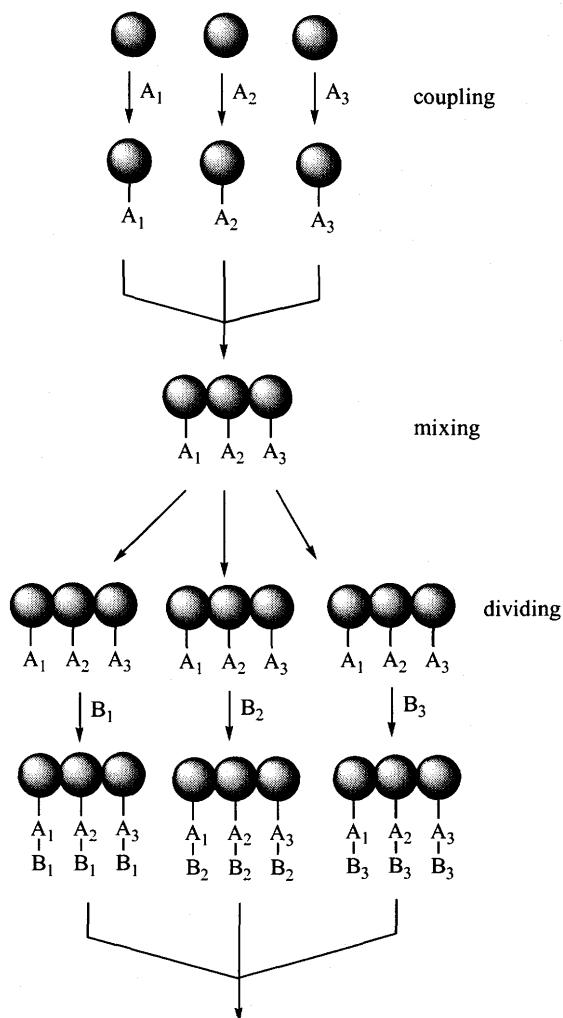
Many different compounds having a common backbone can be synthesized simultaneously in each reaction vessel.[27] First, the portions of the resin are allowed to react with several building blocks $A_1 - A_3$. After the reaction is completed, the resin beads are mixed and then divided into portions of the same size followed by a reaction with another set of building blocks ($B_1 - B_3$). Thus, it is possible to obtain a mixture ("library") of nine different compounds after only two steps.

Advantages of SPS compared to classical methods.

More than thirty years ago, when the polymer-supported synthesis of peptides became popular, several advantages over classical methods in solution were noticed. The same advantages can be attributed to solid phase synthesis of small organic molecules, and they are as follows: (i) Time consuming purification and isolation of the product is eliminated. The substrate and the product are covalently bound to a support and the excess of reagents can be removed by filtration. (ii) The polymer support can be regenerated and reused if appropriate cleavage conditions to release the product are developed. (iii) It is possible to use "the principle of high dilution" for a reaction with polymer-supported reagents if loading values of reactive groups are less than 0.8 mmol/g. This prevents undesired reactions like cross-linking or multiple couplings to occur.[27, 28]

There are also drawbacks to polymer-supported synthesis. The main disadvantages of SP chemistry include the need to develop a new synthetic route, the limited availability of supports and linkers, and the limited number of analytical methods that could be used to monitor the progress of a reaction. Solid phase synthesis also requires two additional steps in the reaction sequence: the attachment of a starting material to a resin and the cleavage of a final product.

The influence of the polymer support on the reaction.

It is important to realize that polymer-supported reactions are often completely different from reactions conducted in solution. The presence of a resin can influence the result of the SP reaction and the reaction can exhibit different substrate selectivity, different rate, or give different stereoisomers.[32, 33] This is due to effects that can take place inside a polymer bead which can be grouped into three categories: (i) the need for dissolved reactants to gain access to the supported reactants; (ii) microenviromental effects and (iii) site-site interactions.

Access: Amongst the most popular polymer supports used in SPS are microporous polystyrene type polymers that are cross-linked with 1% or 2% divinylbenzene. To allow

the reagents in solution access to polymer-supported substrates the polymer has to be swollen by a solvent. The extent of swelling decreases with the increase of cross-linking, thus the 1% cross-linked polymer swells more than the 2% cross-linked one. It should be stressed here that the functional groups attached to the polymer can change the swelling properties, and this change can also take place during a reaction when one functionality is changed into another.[32] The choice of solvent for a reaction with polymer-supported reagents is therefore crucial and the optimal solvent may be different than the solvent commonly used for an equivalent reaction conducted in solution. One should realize that most of the reacting sites in a polymer-supported reagent are situated inside a bead. When a polymer is swollen these reactive sites are more exposed and they are more accessible for reagents in solution.

Microenviromental effects: It was established that the microenvironment inside a polymer bead might be different than outside due to a difference in polarity or different steric crowding. The difference can encourage or discourage reagents in solution from diffusing into the bead.[32] According to Hodge, if the diffusion barriers are not too high, equilibrium may be set up between the soluble reactant inside and outside the bead.[32] The presence of such microenviromental effects can also influence selectivity of a reaction e.g.: chlorination of a polystyrene containing methyl groups in the *para* position takes place on the side chain rather than on the polymer backbone.[34] This is due to the fact that the microenvironment in the vicinity of the polymer backbone is sterically crowded.[32] Steric effects are more pronounced when reactive groups are directly attached to the polymer matrix. If the reactive group is separated from the polymer matrix by a spacer, the steric effects might disappear making the group more accessible to reagents in solution.[35]

Site-site interactions: When the synthesis of polymer-supported peptides became popular in the early 1970s, it was thought that the reactive sites within the resin were isolated and thus could not react with the polymer matrix or with each other.[32] Ford, however, demonstrated that this was not the case.[36] It is possible for the polymer-supported starting material to react with the support rather than with reagents in solution,

especially if the polarities of the microenvironment inside the bead are different from outside. It is also possible for the polymer-supported reactive groups to interact with each other. One has to remember that in most SP reactions the concentration of reactive sites in a resin bead is quite high eg.: if a polymer-supported reactant has a loading of 1.0 mmol/g, and the polymer swells in the reaction solvent by a factor of 3, the concentration of reactive groups is 3.0 mmol/g.[32] If the concentration of reactive groups is high and they can react with each other, it is possible that new cross-linking would take place and the polymer beads would have reduced swelling ability.

In summary there are numerous factors that have to be taken into consideration when polymer-supported synthesis is concerned: solid support, linker, solvent, availability of analytical methods to monitor the progress of the reaction, and influence of the polymer matrix on the reaction result. In order to obtain the desired result, solid phase synthesis has to be very carefully planned.

1.2 Applications of insoluble polymer-supported chiral amines.

A common goal in solid-phase synthesis is to adapt a reaction which is well known in solution and find conditions under which it works well on a resin. Chiral amines are one of the most commonly used classes of compounds in asymmetric synthesis conducted in solution. They are used as reagents, catalysts, ligands or resolving agents. The chemistry of polymer-supported primary and tertiary chiral amines and their derivatives has been investigated for some time and relevant papers are discussed below.

SP chiral amines as auxiliaries.

The first applications of SP chiral amines in asymmetric synthesis were reported by Leznoff[37], Takemoto[38] and Frechet.[39] These authors were able to support different

chiral primary amines on an insoluble polymer and use them as auxiliaries in the alkylation of cyclic ketones. The synthesis of a SP chiral amine described by Leznoff is presented in Scheme 6.

Scheme 6
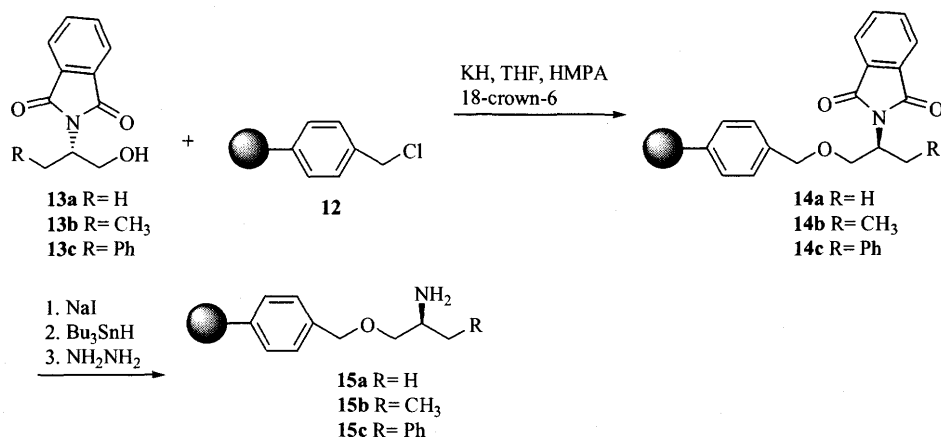
The N-protected (S)-amino-alcohols **13a – c** were attached to the insoluble Merrifield resin **(12)** by O-alkylation to give polymers **14a – c**. The loading of unreacted chloromethyl groups in the polymers (**14a – c**) was determined by reaction with pyridine followed by analysis of the solution phase for chloride.[37] The unreacted chloromethyl groups were removed in two steps: the chlorine atoms were converted to iodine atoms using the Finkelstein reaction, which was followed by free radical dehalogenation with tributyl tin hydride. The resulting polymers were treated with hydrazine to afford amines **15a – c**. Final loading of the polymeric amines (**15a – c**) was 0.5 mmol of NH_2/g.

The synthesis of other polymer-supported chiral amines is shown in Scheme 7.[38]

Scheme 7
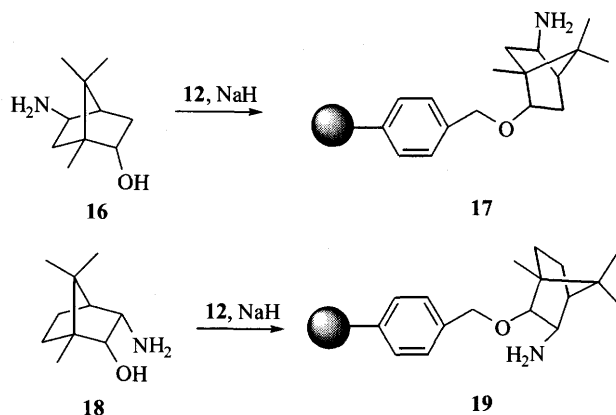
Compounds **16** and **18** were prepared according to an earlier described method.[40] They were coupled with cross-linked chloromethyl polystyrene **12** in the presence of an excess of NaH. Different conditions were examined in order to find the most effective method for the attachment of amino-alcohols **16** and **18** to the polymer. It was found that the mole fraction of substituted benzyl groups in the polymer **12** was affected by the amount of compounds **16** and **18**, the reaction time and the temperature. In the end, the reaction required two equivalents of NaH and refluxing in dry THF for 14 days, which illustrates how a reaction involving a polymer can differ from the solution system. Fixation of compound **16** onto the resin **12** was found to be easier than compound **18**, which exhibits steric hindrance of the amino group.

Another method for the preparation a polymer-supported chiral amine, later used as the auxiliary in the alkylation of cyclic ketones, involved polymerization of monomers containing the chiral amine moiety (Scheme 8).[39]

Scheme 8
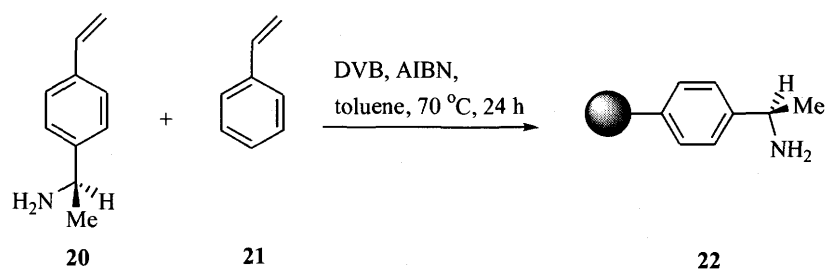
Amine **22** was synthesized by free radical copolymerization of (R)-1-(4-vinylphenyl)ethylamine (**20**) with styrene (**21**) in the presence of DVB. Elemental analysis of the polymer **22** indicated that the resin contained 1.65% of N, which corresponded to loading value of 1.18 mmol of NH_2/g.

The use of insoluble polymers containing chiral reactive groups has received increasing attention in the last decade.[41, 48] The resins were used as auxiliaries in chemical transformations of prochiral substrates. The method appeared to have a promising future due to several advantages: (i) the polymer-supported chiral auxiliaries were easily recovered and could be reused, (ii) the supported lithiated species should have increased reactivity in comparison to their equivalents in solution, and (iii) it should be possible to obtain high yields and enantioselectivities in reactions of polymer-supported substrates due to their reduced mobility. Taking these three reasons into consideration, polymer-supported amines **15a – c, 17, 19** and **22** were used in the alkylation of cyclohexanone (**25**). The general reaction is shown in Scheme 9 and the results are presented in Table 2.

Scheme 9

15a Linker= 23a
15b Linker= 23b
15c Linker= 23c
17 Linker= 23d
19 Linker= 23e
22 Linker= 24

25

25a Linker= 23a
25b Linker= 23b
25c Linker= 23c
25d Linker= 23d
25e Linker= 23e
25f Linker= 24

recycle

1. LDA
2. RX

15a - c, 17, 19, 22

27

26a - f

- - -Linker-NH₂*

23a R= H
23b R= Me
23c R= Ph

23d

23e

24
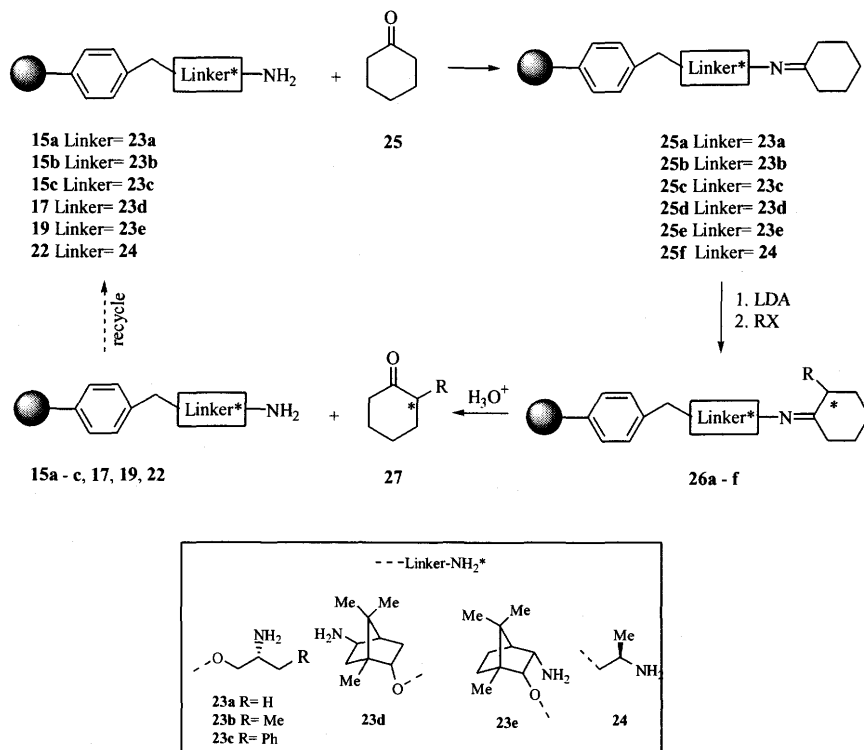
Cyclohexanone (**25**) was attached to the resin (**15a – c, 17, 19** or **24**) by formation of the corresponding imine.[37 - 39] The resulting chiral imines (**25a – f**) were lithiated with LDA and alkylated with alkyl halides to give compounds **26a – f**. The polymer-supported auxiliaries were removed by hydrolysis and α-alkylated cyclohexanone **27** was obtained.[37 - 39]

Table 2. Alkylation reactions of polymer-supported imines **25a – f**.

Entry	Method	Polymer	RX	temp. (°C)	yield (%)	ee (%)
1	Leznoff[37]	**15c**	MeI	20	87	94
2	Leznoff[37]	**15a**	MeI	0	50	94
3	Leznoff[37]	**15c**	MeI	-78	72	98
4	Takemoto[38]	**17**	MeI	20	-	8
5	Takemoto[38]	**19**	MeI	20	-	65
6	Takemoto[38]	**19**	PrI	20	-	54
7	Frechet[39]	**22**	MeI	0	-	58
8	Frechet[39]	**22**	MeI	-78	-	61

The best results in terms of the yields and enantioselectivities, were obtained by the Leznoff group.[37] This might have been due to the fact that the chiral amine moiety in polymers **15a – c** was separated from the polymer backbone by a linker, which made the amine group more accessible for the formation of the imine **25a – c**.

Besides alkylation reactions of cyclic ketones, there are other very interesting examples of applying SP chiral amines derivatives as auxiliaries in asymmetric synthesis. An SP chiral amide was employed as the chiral auxiliary in enantioselective alkylation of the lithium enolate derived from an ester.[41] The synthesis of polyacrylic resins **43a – c** with pendent chirality is presented in Scheme 10.

Scheme 10
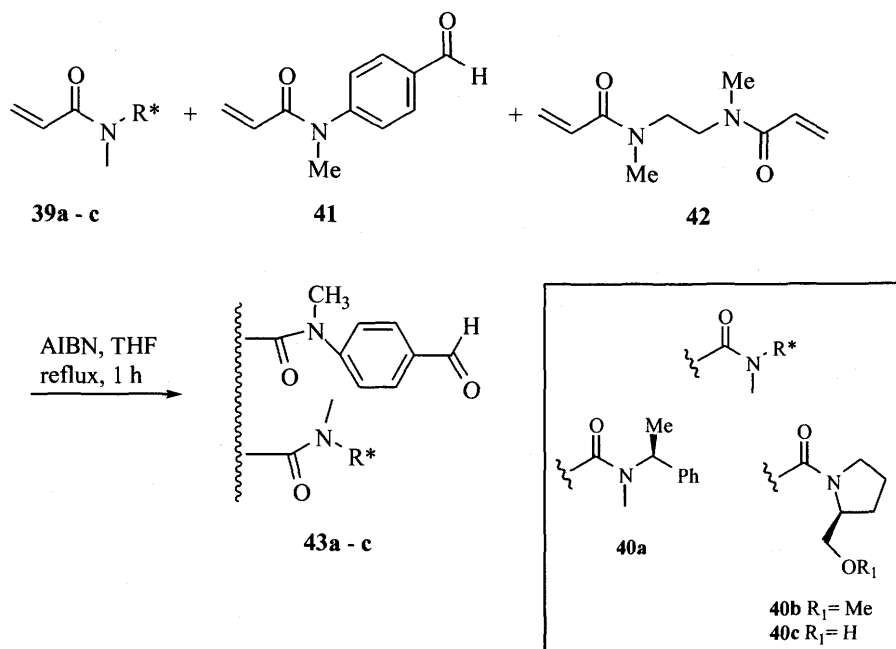
Polyacrylic resins **43a – c** were synthesized by free radical copolymerization of three monomers: 65% (by weight) of the N-acryloyl derivative of (S)-N-methyl-α-phenylethyl amine **39a**, or (S)-prolinol methyl ether **39b** or (S)-prolinol **39c** as the chiral element; 10% of N,N'-dimethylethylenebisacrylamide (**42**) as the cross-linking agent, and 25% of N-acryloyl N-methyl p-aminobenzaldehyde (**41**) as the functionalizing agent. The loading of the polymers **43a – c** was 1.00 mmol of aldehyde/g, which meant that one aldehyde group was surrounded by three to four chiral pendants. Resins **43a – c** were used as the auxiliaries in the alkylation reaction of t-butyl glycinate (**44**).[41]
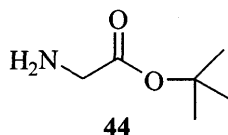
The glycinate was attached to the resin **43a – c** by acid catalyzed condensation to give the corresponding Schiff base (**45a – c**), followed by deprotonation with LDA and alkylation with an alkyl halide (Scheme 11).

Scheme 11
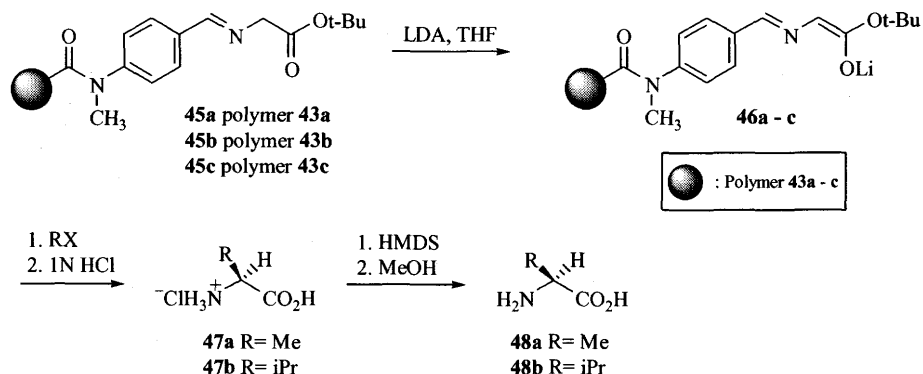
Deprotonation of the polymer-supported esters (**45a** – **c**) with LDA gave the corresponding lithium enolates (**46a** – **c**). Subsequent reaction with an alkyl halide, followed by hydrolysis with HCl afforded the amino acid chloride **47a** or **47b**. Reaction with HMDS, and then treatment with an excess of MeOH gave the pure, α-alkylated amino acid **48a** or **48b**. The results of the alkylation reaction of t-butyl glycinate (**44**) are presented in Table 3.

Table 3. Alkylation reactions of the lithiated compounds **46a** – **c**.

Entry	Resin	RX	temp. (°C)	yield (%)	ee (%)[b]
1	**43a**	MeI	-78	68	21
2	**43b**	MeI	-78	58	61
3	**43b**	MeI	20	87	55
4	**43b**	iPrI	-78	62	63
5	**43b**	iPrI	20	83	56
6[a]	**43c**	MeI	-78	75	88
7[a]	**43c**	MeI	20	85	82
8a	**43c**	iPrI	-78	77	89
9[a]	**43c**	iPrI	20	84	84

[a] 2 eq. of LDA were used. [b] *(S)* enantiomer was the major product in all cases.

As shown in Table 3, the enantiomeric excess in the alkylation reaction of the esters **45a** – **c** depended on the nature of the polymer support used as the auxiliary (Table 3 entries 1 – 3 vs. entries 6 – 9).[41] The lowest yield and ee were obtained with polymer **43a** as the auxiliary (Table 3, entry 1). This was explained by its limited interaction with the supported lithium enolate of **44**. Better results were obtained with polymer **43b** as the auxiliary (Table 3, entries 2 – 5). The best results were obtained when polymer **43c** was used as the auxiliary. The α-alkylated derivatives of ester **44** were obtained in up to 85% yield and 89% ee. The addition of Ti(O-^{i}Pr)$_4$ did not improve enantioselectivity and the replacement of LDA with t-BuOK, followed by alkylation with MeI gave a large amount of a dialkylated derivative of **44**.

In summary, the syntheses of several chiral amines and their derivatives supported on polymer have been described in the literature. The resins were successfully employed as the auxiliaries in the alkylation reaction of cyclohexanone (**25**) and t-butyl glycinate (**44**). The corresponding α-functionalized products were obtained in very good yields and enantioselectivities. Surprisingly, the polymer-supported chiral auxiliaries did not become popular in the synthesis of organic compounds considering the aforementioned advantages.

Protonation of polymer-supported compounds.

Protonation of lithium enolates is a method complementary to alkylation in the synthesis of enantiomerically enriched α-functionalized carbonyl compounds. There are two literature reports of the protonation of lithium enolates of carbonyl compound where a polymer-supported chiral amine or amide was used as an auxiliary.[37c, 41] The synthesis of the polymer-supported auxiliaries used in asymmetric protonation is presented in Schemes 6[37c] and 9.[41] Resins **15a** – **c** were used in protonation reaction of the lithiated imine derived from 2-methylcyclohexanone (**49**) and a chiral amine (Scheme 12).

Scheme 12

15a R= H
15c R= Ph

49 (racemic)

50a R= H
50c R= Ph

1. LDA, -78 °C
2. HA, -78 °C
3. AcOH, NaOAc, H$_2$O

49 (optically active)
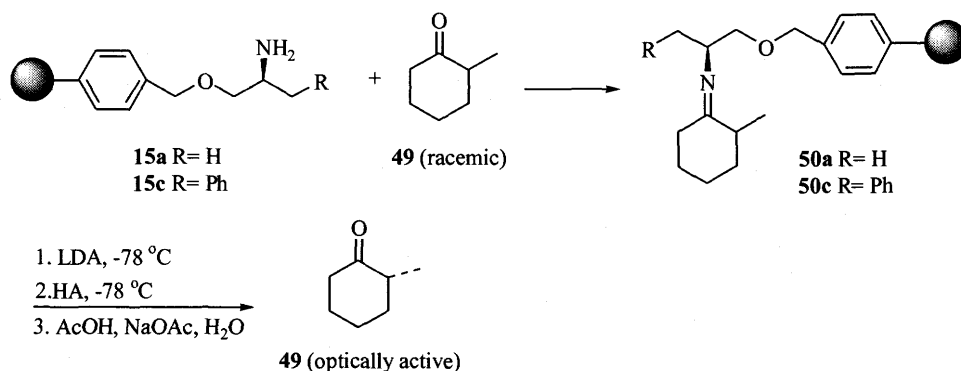
The racemic ketone **49** was attached to the polymers **15a** or **15c** by formation of a Schiff base with the amine moiety giving imines **50a** or **50c**. The imines were lithiated with LDA, and than protonated with various proton sources. The subsequent hydrolysis gave enantiomerically enriched 2-methylcyclohexanone (**49**). The results are presented in Table 4.

Table 4. The influence of the polymeric auxiliary **15a** and **15c** on the protonation of the lithiated derivatives of **50a** and **50c**.

Entry	Polymer	HA	ee (%)[a]
1	**15a**	Et$_3$N · HCl in THF	36 (R)
2	**15a**	EtOH	22 (R)
3	**15c**	EtOH	90 (S)
4	**15c**	EtOH, Et$_3$N · HCl in THF	82 (S)

[a] Based on known optical rotation of pure *(R)*-2-methylcyclohehanone (ref. 42).

Selectivity was dependent on the nature of auxiliary and the proton source. The highest enantioselectivity was obtained when the polymer **15c** was used as the auxiliary and EtOH was used as the proton source (Table 4, entry 3). When the proton source was changed to t-BuOH the racemic product **49** was obtained. When a similar reaction was

tried in solution using *(S)*-2-aminopropyl benzyl ether as the auxiliary, the product did not exhibit optical activity.[37c]

The protonation of polymer-supported lithium species is not restricted to ketones. A study of the protonation of polymer-supported lithium enolates of esters was described.[41] The resins **43b – c** were used as the auxiliaries (Scheme 13).

Scheme 13

51a polymer 43b, R= Me
51b polymer 43b, R= Bn
51c polymer 43c, R= Me
51d polymer 43c, R= Bn

52a - d

: Polymer 43b or 43c

47a R= Me
53a R= Bn

48a R= Me
54a R= Bn
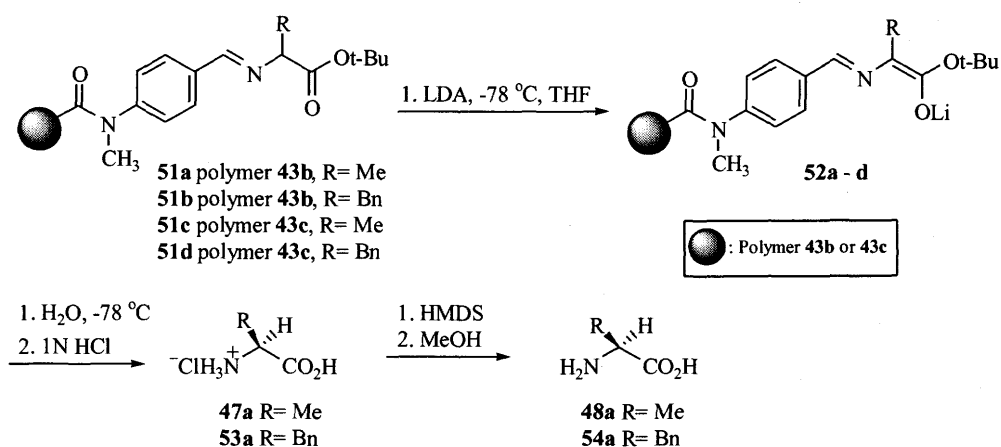
Racemic alanine or phenylalanine was attached to the polymers **43b** and **43c** by formation of Schiff bases to give esters **51a – d**. The resulting compounds were lithiated with LDA, followed by the addition of water and cleavage from the polymer by hydrolysis to give amino acid hydrochlorides **47a** and **53a**. Pure amino acids **48a** and **54a** were obtained after treatment of these salts with HMDS and an excess of MeOH. The results of protonation of compounds **51a – d** are summarized in Table 5.

Table 5. Protonation of polymer-supported lithium enolates **52a – d**.

Entry	resin	Polymer-supported ester	Amino acid	yield (%)	ee (%)[a]
1	43b	51a	48a	90	55
2	43b	51b	54a	90	49
3[b]	43c	51c	48a	95	61
4[b]	43c	51d	54a	95	54

[a] R enantiomer of alanine (**48a**) and phenylalanine (**54a**) was the major product. [b] Two equivalents of LDA were used.

As shown in Table 5, the yield of protonation of polymer-supported lithium enolates **52a – d** was excellent in all cases but the enantioselectivity was moderate (Table 5, entries 1 – 4).

In summary, polymer-supported chiral amines **15b – c**, and polymer-supported derivatives of chiral amines **43b** and **43c** were used as auxiliaries in the deracemization of cyclic ketone **49** and two amino acids: alanine (**48a**) and phenylalanine (**54a**). Optically active compounds **49** (Table 4), **48a** and **54a** (Table 5) were obtained in very good yields and promising enantioselectivity. However, the application of polymer-supported chiral amines and their derivatives as auxiliaries in the protonation of the lithiated carbonyl compounds, unfortunately, did not become very popular despite its advantages associated with the polymer supported synthesis. More work is needed in order to gain further insight into the chemistry of such reagents.

SP chiral amines as ligands.

The strategy of attaching chiral ligands to a polymer support offers several advantages in catalytic asymmetric synthesis over the use of the same ligand in solution. These advantages were mentioned before (page 10).

Diethylzinc addition to aldehydes in the presence of chiral polymer supported ligands.

Enantioselective addition of diethylzinc to aldehydes employing polymer-supported amino-alcohols as ligands has been studied extensively during the last decade.[43] – [47] When the reaction was performed in solution, the yields and enantioselectivities were usually up to 95%.[45] The enantioselectivity of the addition depends on the structure of the chiral ligand. The syntheses of various polymer-supported chiral ligands were reported, and can be divided into two groups: synthesis of ligands directly attached to a resin, and synthesis of ligands separated from a resin by a linker.[43] – [47]

Polymer-supported ephedrine derivatives could be easily synthesized from commercially available starting materials. The synthesis of polymer-supported ephedrines **56a – d** and compound **57** directly attached to the resin is shown in Scheme 14.[43]

Scheme 14

55a (1R, 2S) R= Me
55b (1S, 2R) R= Et
55c (1S, 2R) R= n-Pr
55d (1S, 2R) R= Bu

12, K$_2$CO$_3$, toluene
reflux, 30 h

56a - d

57

58
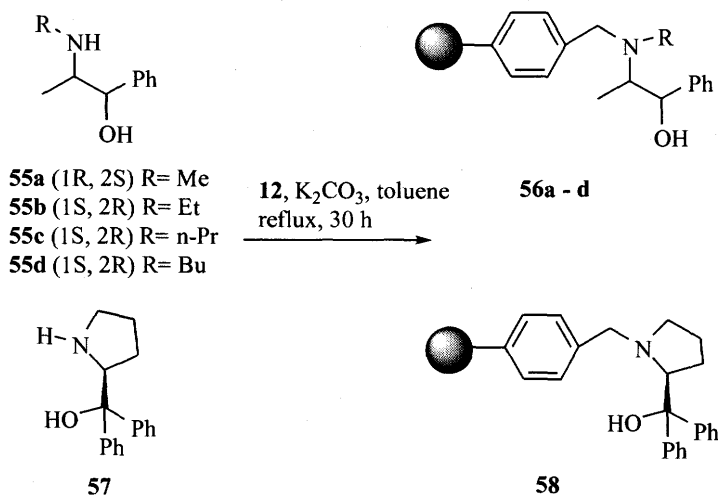
N-Alkylated derivatives of norephedrine **55a – d** and compound **57** were attached to the commercially available 1% cross-linked p-chloromethyl polystyrene **12** (0.8 mmol of Cl/ g) in a one step reaction to give the corresponding ligands **56a – d** and **58** in 84% – 93% yield.[43]

The syntheses of other catalysts separated from a polymer matrix by a linker are presented in Schemes 15[44], 16[45], 17[47] and 18[46].

Scheme 15
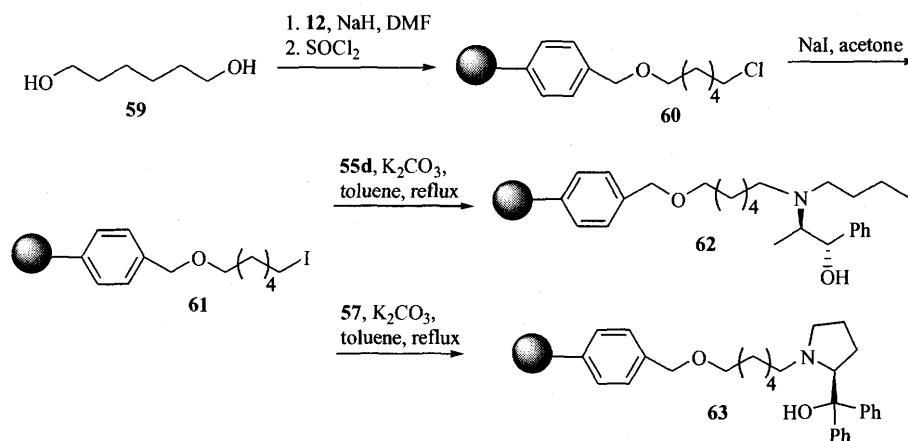
The synthesis of the ligands **62** and **63** started from attachment of a 1,6-hexanediol (**59**) to the 1% cross-linked p-chloromethyl polystyrene **12** (0.8 mmol of Cl/g) by O-alkylation of the alkoxide, followed by conversion of the hydroxyl group to chloride. The chlorine atom was replaced by iodine in the next step, and resin **61** was obtained. The last step was the attachment of compounds **55d** and **57**, resulting in polymer-supported amino-alcohols **62** and **63**.

When the synthesis of the polymer-supported compound is a concern there are two variables that can be changed: a resin and a linker. A synthesis of the polymer-supported analogue of ligand **63** is shown in Scheme 16.[45]

Scheme 16
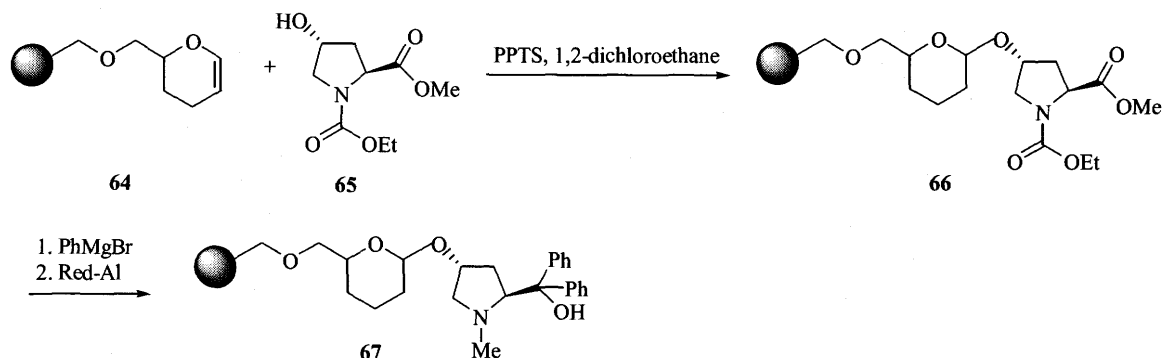
Compound **65** was coupled to the resin **64** using PPTS in 1,2-dichloroethane and the polymer **66** was obtained. The coupling efficiency was determined by mass balance after cleavage of the material from the support. Next, a large excess of phenylmagesium bromide was added to resin **66**, followed by reduction with Red-Al to give polymer **67**.

The synthesis of ligands **71a – c** and **73a – c** is presented in Scheme 17. The reactive groups were separated from a polymer matrix by a linker. Mesoporous silica with pore sizes between 2 – 10 nm was used as the solid supports and a carbon chain was used as the linker. Silica MCM-41 and SBA-15 were synthesized using self-assemblies of surfactants and block copolymers as templates.[47]

Scheme 17

68a Amorphous silica
68b MCM-41
68c SBA-15

69a – c

71a – c

69a – c

72a – c
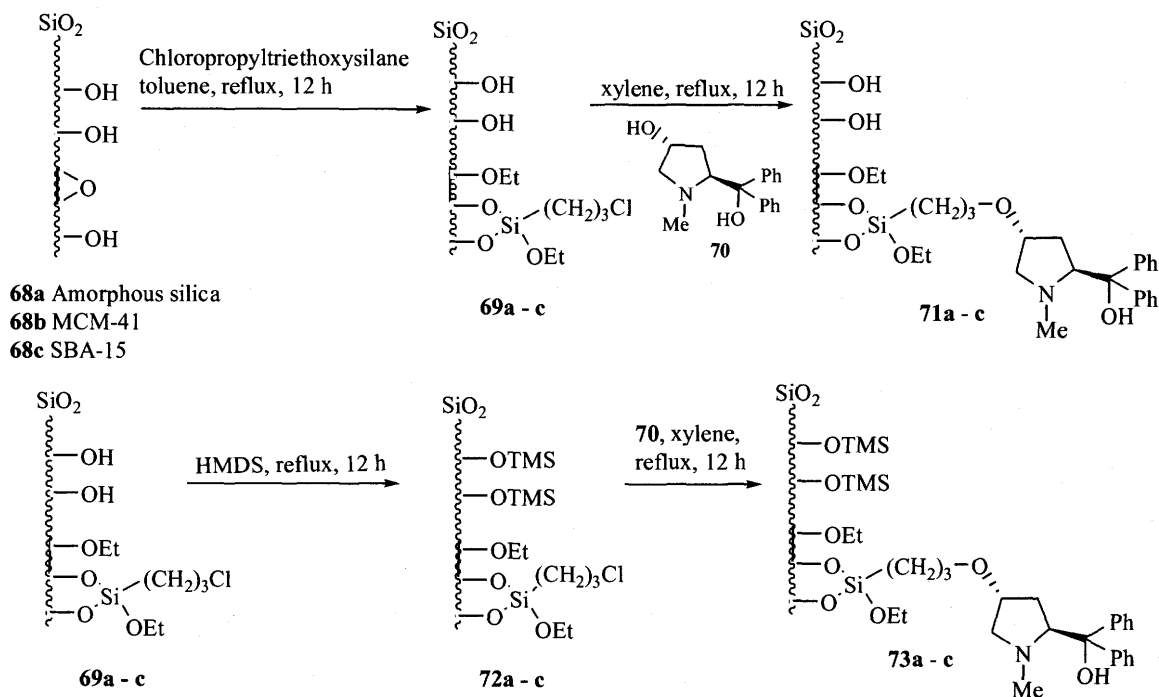
73a – c

The first step in the synthesis of compounds **71a – c** and **73a – c** was the attachment of the linker. A chloropropyl linker was grafted on the polymer (**68a – c**) by treating the resin with chloropropyltriethoxysilane in toluene. Reaction of the resulting resin (**69a – c**) with compound **70** yielded the polymer-supported ligands **71a – c**. The surface area of the resin **71b** was 655 m^2/g, the mean pore diameter was 2.4 nm, and the loading was 0.4 mmol of N/g. The surface area of the resin **71c** was 320 m^2/g, the mean pore diameter was 8.4 nm, and the loading 0.36 mmol of N/g. It was thought that free SiOH moieties on the silica surface could interfere during a diethylzinc addition to aldehydes, so it was decided to cap these functional groups with TMS.[47] The transformation was achieved by treating the polymer (**69a – c**) with HMDS. The final polymer-supported ligands (**73a – c**) were obtained by O-alkylation of compound **70** with the polymer-supported *n*-propyl chlorides (**72a – c**). The resins **71a – c** and **73a – c** were employed as ligands in diethylzinc addition to benzaldehyde (Scheme 19).

The synthesis of a very efficient ligand **76** for diethylzinc addition to various aromatic aldehydes is shown in Scheme 18. Barlos resin (**74**) was used as the solid support since Merrified resin **12** proved to be ineffective.[46]

Scheme 18
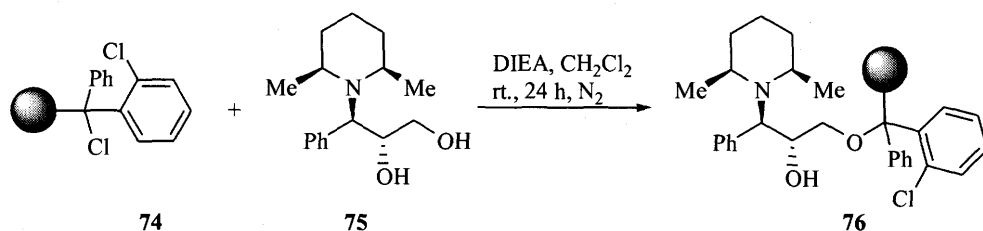
The polymer-supported ligand **76** was prepared by the reaction of Barlos resin (**74**) with compound **75**. It was characterized by gel phase ^{13}C NMR, and the loading, established by elemental analysis was found to be 1.2 mmol of N/g.

Polymer-supported amino-alcohols **56a – d, 58, 62, 63, 67, 71a - c, 73a – c** and **76** were used as chiral ligands in diethylzinc addition to aliphatic and aromatic aldehydes (Scheme 19). Structures of these ligands are presented in Figure 3.
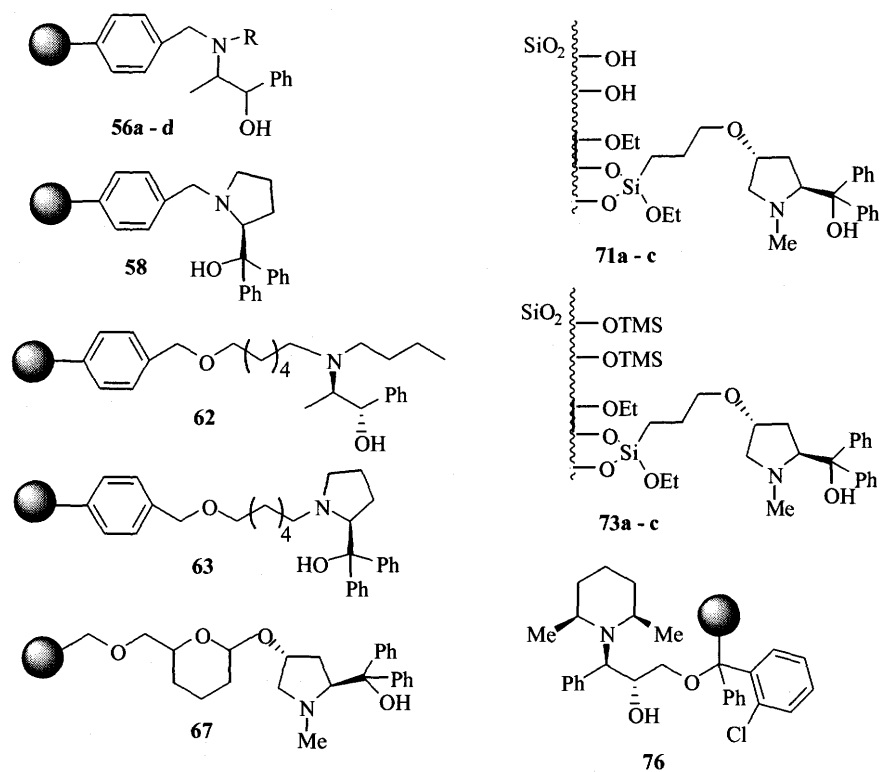
Figure 3. Structure of chiral ligands used in addition of diethylzinc to aldehydes.

Scheme 19

77a R= Ph
77b R= Me(CH$_2$)$_2$
77c R= i-Bu

78a R= Ph
78b R= Me(CH$_2$)$_2$
78c R= i-Bu
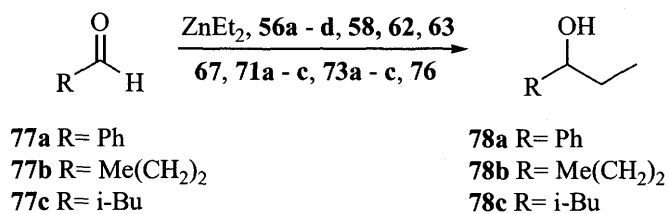
Diethylzinc was added to aldehydes **77a – c**. The detailed experimental procedures are described in the literature.[43–48] The selected results are presented in Table 6.

Table 6. Diethylzinc addition to aldehydes catalyzed by polymer-supported chiral ligands.

Entry	R	Polymer-supported ligand	yield (%)	ee (%)
1	Ph	**56a**	83	89[a, b]
2	Me(CH$_2$)$_2$	**56b**	88	80[a]
3	i-Bu	**56c**	49	57[a]
4	Ph	**58**	68	24[a]
5	Ph	**62**	91	82[a]
6	Ph	**63**	91	61[a]
7	Ph	**67**	100	89[a]
8	Ph	**71a**	69	41[c]
9	Ph	**71b**	84	26[c]
10	Ph	**71c**	97	52[c]
11	Ph	**73a**	74	43[c]
12	Ph	**73b**	96	64[c]
13	Ph	**73c**	98	75[c]
14	Ph	**76**	99	94[d]

[a] Enantioselectivity based on the known values of $[\alpha]_D$ (ref. 43 and 45). [b] (R) Enantiomer was the major product. [c] Enantioselectivity was measured by HPLC using Chiralcel OD column (ref. 47). [d] Enantioselectivity was measured by GC using β-Dex 120 column (ref. 46).

Aliphatic and aromatic aldehydes were used as the starting materials, and the corresponding alcohols were obtained in high yields and moderate to high enantioselectivity (Table 6). The aldehyde that was studied in the most detail was benzaldehyde (**77a**). It was possible to obtain the corresponding alcohol **78a** in high yield and enantioselectivity (Table 6, entry 14). This result was very comparable to the results obtained in solution.[45]

SP chiral amines as ligands in asymmetric dihydroxylation of olefins.

Sharpless catalytic asymmetric dihydroxylation (AD) of alkenes using catalytic amounts of OsO_4 in the presence of cinchona alkaloid derivatives, leading to a variety of enantiomerically pure vicinal diols, is one of the most useful and reliable organic reactions.[49] To explore the possibility of recycling both the expensive OsO_4 and the chiral ligand, a variety of the polymer-supported ligands were employed.[48] Most of those polymer-supported ligands required complicated synthesis, and their efficiency was not satisfactory for practical purposes.

It was established that substituted pyrimidine bis-cinchona alkaloid ligands gave improved enantioselectivity in the AD reaction of monosubstituted terminal olefins.[50] The synthesis of the polymer-supported ligand **82** is shown in Scheme 20. The general AD reaction is shown in Scheme 22 and the results are presented in Table 7.

Scheme 20
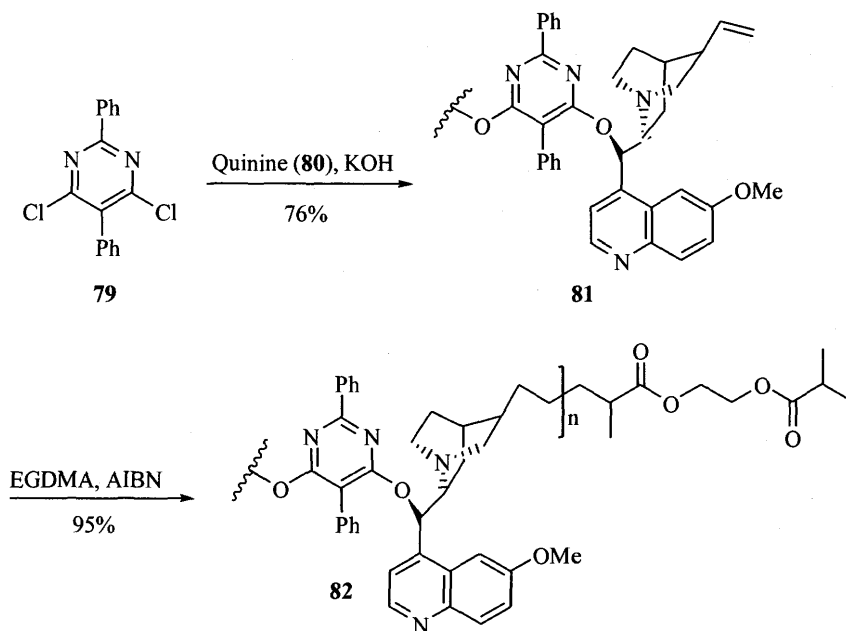
The chiral precursor **81** was prepared by nucleophilic substitution of compound **79** and quinine (**80**) according to a known method.[48] The polymer-supported ligand **82** was obtained by free radical copolymerization of monomer **81** and ethylene glycol dimethylacrylate (EGDMA). Loading of the resin **82** as determined by elemental analysis was 0.1 mol/g.

As mentioned before, one of the variables that could be changed during the synthesis of a polymer-supported ligand is the solid support. Synthesis of a novel polymer-supported cinchona alkaloid has been reported by Crudden.[51] The authors were studying a new class of silicates that are called mesoporous molecular sieves and have well defined pores of nanometer size and a very narrow pore size distribution. The exact size of the pores and their shape could be tailored depending on how they were prepared. Hexagonal mesoporous molecular sieves of SBA-15 type were employed as supports for the synthesis of polymer-supported ligands (Scheme 21).

Scheme 21
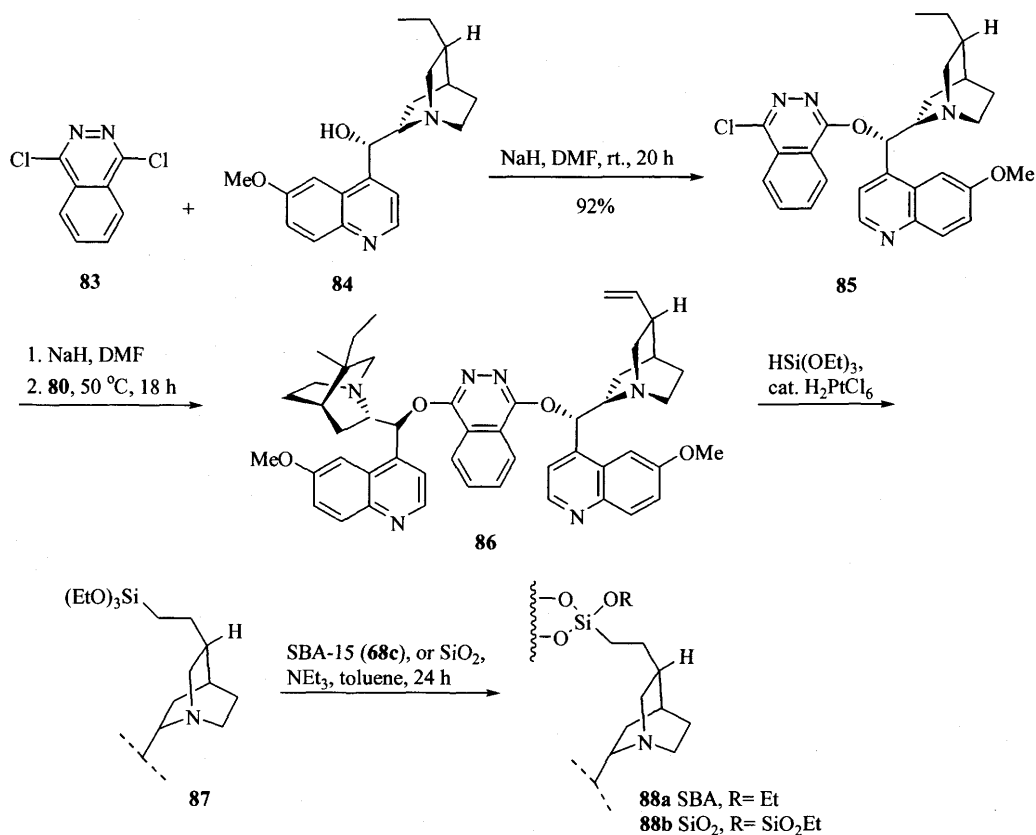
The first step in the synthesis was the reaction of dichlorophthalazine (**83**) with dihydroquinidine (**84**) to give compound **85**, followed by reaction with quinine (**80**) to yield compound **86**. Hydrosilylation with $HSi(OEt)_3$ in the presence of H_2PtCl_6 gave **87**, which was grafted on two silicas: SBA-15 (**68c**) and amorphous silica gel (**68a**) providing ligands **88a** and **88b**. The loading of these two resins was determined by elemental analysis and found to be 0.13 mmol/g for **88a**, and 0.09 mmol/g for **88b**, respectively.

The Polymer-supported chiral ligands **82**, **88a** and **88b** were used in the asymmetric hydroxylation of olefins (Scheme 22).

Scheme 22

89a R=R$_1$= Ph
89b R= Ph, R$_1$= H
89c R= t-Bu, R$_1$= H
89d R= Ph, R$_1$= Me
89e R= CO$_2$Me, R$_1$= Ph
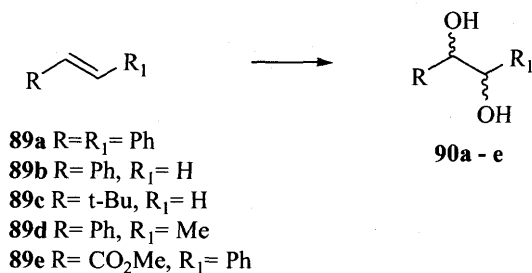
90a - e

The AD reaction is a very versatile transformation.[49] Both terminal and internal olefins were used. All transformations gave the corresponding diols (**90a – e**) in high yield and enantioselectivity, and the results are summarized in Table 7.[48, 51]

Table 7. AD reaction catalyzed by polymer-supported quinidine ligands (ref. 48, 51).

Entry	R	R_1	Ligand	yield (%)	ee (%)
1	Ph	Ph	**82**[a]	92	84[c]
2	Ph	H	**82**[a]	92	67[c]
3	t-Bu	H	**82**[a]	80	76[c]
4	Ph	Ph	**88a**[b]	97	>99[d]
5	Ph	Me	**88a**[b]	98	98[d]
6	CO_2Me	Ph	**88b**[b]	72	94[d]
7	Ph	H	**88b**[b]	85	87[d]

[a] Molar ratio of olefin: OsO_4: ligand **82** 1: 0.0025: 0.005 (ref. 48). [b] Percentage of OsO_4 1%, percentage of ligands **88a** and **88b** 2% (ref. 51). [c] Enantioselectivity was determined by comparison of $[\alpha]_D^{20}$ with literature values (ref. 48). [d] Enantioselectivity was determined by preparation of bis Mosher's esters and confirmed by optical rotation of unreacted diols (ref. 51).

The ligand **82** proved to be less effective than ligands **88a** and **88b** (Table 7, entries 1 – 3 vs. 4 – 7). The results obtained with resins **88a** and **88b** are almost identical to the results obtained in solution (dihydroxylation of **89a** with $DHQD_2PHAL$ gave the corresponding diol **90a** in 99% yield and >99% ee).[49, 51]

In summary, syntheses of various polymer-supported chiral ligands were reported. These ligands were employed in diethylzinc addition and AD reaction of olefins. The corresponding products were obtained in high yields and very good enantioselectivities (Table 6 and Table 7) and the results were comparable to those obtained with chiral ligands in solution.

SP chiral amines as catalysts.

Reduction of ketones and oximes

The enantioselective reduction of prochiral ketones using chiral catalysts or chiral reagents has received a lot of attention in the past 20 years.[53, 54] A variety of catalysts and reagents have been developed for this purpose. However, the recovery and purification of these reagents has proven to be problematic. Immobilization on solid support offers a solution to the problem. The immobilized reagents can be recovered by filtration at the end of the reaction without the loss of activity. Several polymer-supported chiral ligands derived from amino-alcohols have been developed, but only a few of them have displayed high enantioselectivity.[52, 55] The synthesis of polymer-supported catalysts **94a –** **c** is shown in Scheme 23.

Scheme 23
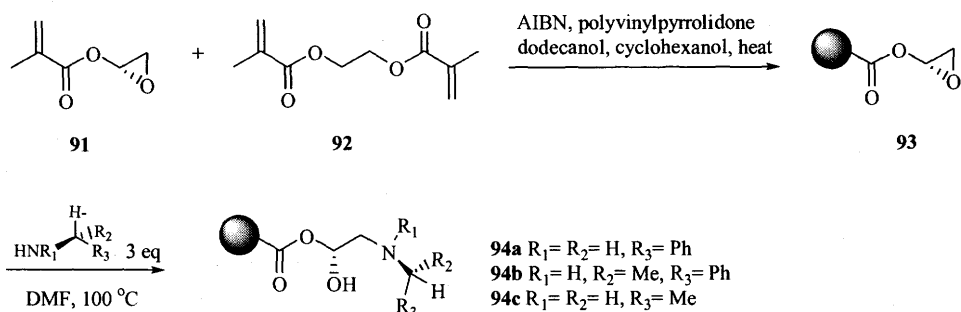
Free radical copolymerization of compound **91** with **92** afforded cross-linked copolymer **93** in high yield.[52] Optically active polymers containing amino alcohol functionalities **94a** **– c** were then formed from **93** through epoxide ring opening with a number of chiral amines. The loading of the polymer-supported catalysts was determined by elemental analysis, and was 1.20 mmol of N/g, 1.21 mmol of N/g, and 0.76 mmol of N/g for **94a –** **c**, respectively. It was shown that ruthenium complexes based on these compounds were effective catalysts for the enantioselective reduction of acetophenone (Scheme 25).[52]

The synthesis of the Noyori's catalyst analogues supported on polymers is presented in Scheme 24. In solution, *(S,S)*- or *(R,R)*-N-(p-tolylsulfonyl)-1,2-diphenylethylenediamine are excellent chiral ligands for the ruthenium catalyzed hydrogenation of aryl ketones, alkynyl ketones and imines giving products with up to 90% ee.[55]

Scheme 24
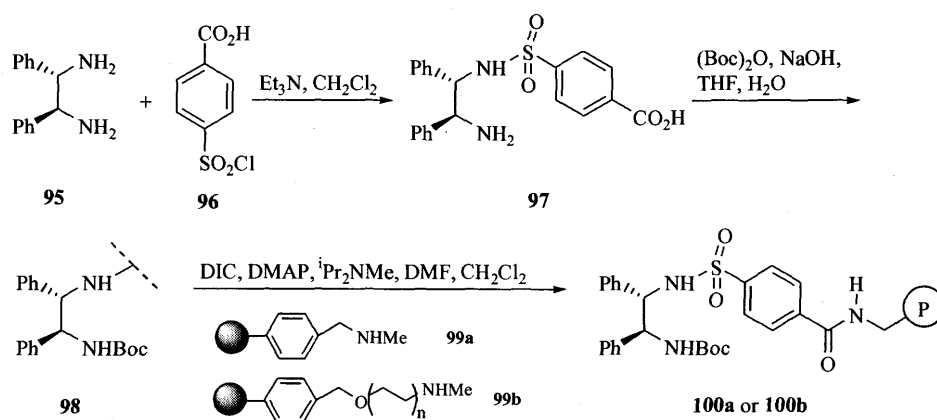
In the first step chiral diamine **95** was sulfonylated with reagent **96** to give compound **97**. Protection of the amino group in compound **97** with (Boc)$_2$O yielded compound **98**, which was coupled to two different resins **99a** and **99b**, to yield the corresponding polymer-supported ligands **100a** and **100b**. Loading of the polymers **100a** and **100b** determined by mass increase was 0.70 mmol/g and 0.22 mmol/g, respectively. The active hydrogen catalyst was formed by mixing the resins **100a** and **100b** with an equimolar amount of [RuCl$_2$(p-cymene)]$_2$.[55]

The effectiveness of resins **94a – c**, **100a** and **100b** was assessed by using the reduction of acetophenone as the model (Scheme 25). The results are summarized in Table 8.

Scheme 25
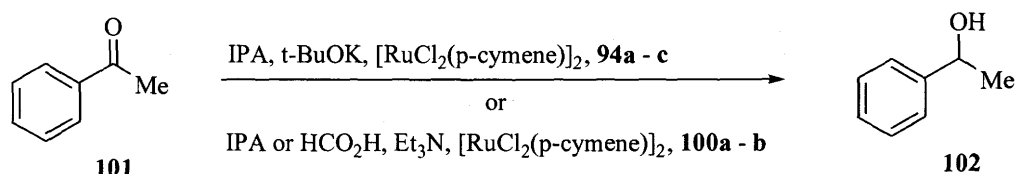
Table 8. Reduction of acetophenone catalyzed by resins **94a – c**, **100a** and **100b**.

Entry	Resin	Hydrogen source	yield (%)	ee (%)
1	**94a**	IPA	94	70[b]
2	**94b**	IPA	94	45[b]
3	**94c**	IPA	95	65[b]
4	**100a**[a]	IPA	88	90[c]
5	**100a**	HCO$_2$H: Et$_3$N	71	>99[c]
6	**100b**	HCO$_2$H: Et$_3$N	100	92[c]

[a] Reaction was run in CH$_2$Cl$_2$. [b] (R)-Enantiomer was the major product; method for determining the enantioselectivity was not reported (ref. 52). [c] (S)-Enantiomer was the major product; enantioselectivity was determined by HPLC with Diacel Chiracel OD column (ref. 55).

As can be seen from Table **8**, the optically active alcohol **102** was obtained in each case. The absolute stereochemistry depended on which resin was used (Table 8, entries 1 – 3 vs. entries 4 – 6), and better results were obtained with resin **100a** or **100b** (Table 8, entries 4 – 6). Recycling of the resin (Table 8, entry 1) resulted in a marked decrease in yield (27% comparing to 94%) and enantioselectivity (54% comparing to 70%).[52] It was thought that the addition of co-solvents might improve the yield and enantioselectivity for polymers **100a** and **100b**. The reaction had to be conducted in CH$_2$Cl$_2$ for the resin **100a** otherwise the alcohol **102** was obtained in 21% yield and 91% ee. The addition of CH$_2$Cl$_2$ and DMF to the reaction when polymer **100b** was used resulted in low yield of the product **102** (42% for CH$_2$Cl$_2$ and 46% for DMF).[55]

Enantioselective reduction of the C=N double bond is an important synthetic strategy for the preparation of optically active amines.[57] Polymer-supported catalysts are receiving considerable attention as useful tools for automated reactions with unique microenvironments which can be used for stereoselective reactions.[56] The synthesis of novel, polymer- supported oxazaborolidine catalysts **105a – d** is shown in Scheme 26. The chiral monomer **103** was not commercially available, and was synthesized according to known methods.[56]

Scheme 26
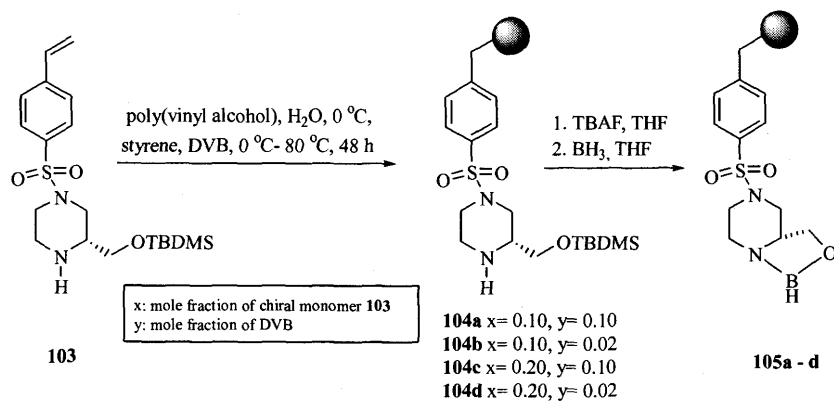
The first step in the synthesis was radical copolymerization of chiral monomer **103** with styrene and DVB in water in the presence of poly(vinyl alcohol) to give resins **104a - d**. The resins were converted to the corresponding polymer-supported oxazaborolidines (**105a – d**) by the reaction with tetrabutylammonium fluoride (TBAF), followed by treatment with BH$_3$ in THF. The loading of the resins **105a – d** was determined by elemental analysis and was 0.71 mmol/g.

Polymer-supported catalysts (**105a – d**) were used in the borane reduction of O-methyloximes (**106a – c**) to give the corresponding chiral primary amines (**107a – c**) (Scheme 27). Selected results are shown in Table 9.

Scheme 27

106a R$_1$= Ph, R$_2$= Me   107a R$_1$= Ph, R$_2$= Me
106b R$_1$= p-MeOPh, R$_2$= Me   107b R$_1$= p-MeOPh, R$_2$= Me
106c R$_1$= Ph, R$_2$= Et   107c R$_1$= Ph, R$_2$= Et
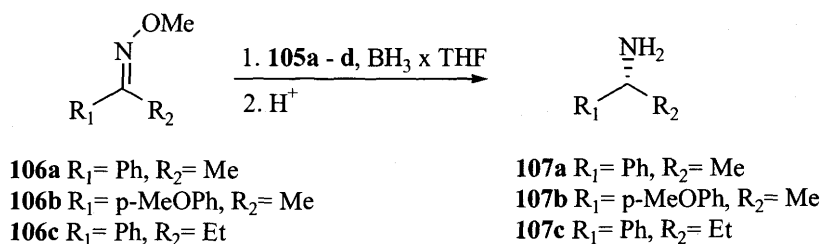
Table 9. Enantioselective reduction of oxime ethers (**106a** – **c**) with BH$_3$ · THF catalyzed by polymer-supported catalysts (**105a** – **d**) (ref. 56)

Entry	Oxime	Polymer-supported catalyst	Yield (%)	Ee (%)[a]
1	106a	105a	56	72
2	106a	105c	60	82
3	106a	105d	65	96
4	106a	105d	70	99
5	106b	105d	75	86
6	106c	105d	81	93

[a] Enantioselectivity was determined by GC with a chiral stationary column.

The absolute configuration of the major product of the borane reduction of oximes **106a** – **c** was *R* in all cases. As can be seen from the above Table, the polymer-supported catalyst **105d** gave better results than catalysts **105a** and **105c** (Table 9, entries 3 – 6 vs. entries 1 and 2). Moderate yields of amines **107a** – **c** (Table 9, entries 1 – 4) were caused by the difficulties in the removal of byproducts including methoxyamine. When oxime **106a** was reduced with catalyst **105d**, the corresponding amine **107a** was obtained in 96 – 99% ee. The polymer-supported catalyst **105d** proved to be even more effective than the catalyst in solution. When oxime **106a** was reduced with *(S)*-4-(p-toluenesulfonyl)-2-piperazinemethanol, the corresponding amine **107a** was obtained in 84% ee.[57] The reduction of oximes **106a** – **c** with polymer-supported catalysts **105a** – **d** is an example of

how the presence of the polymer matrix can influence the reactivity and selectivity of a catalyst.

Polymer-supported chiral catalysts in Michael addition.[58]

Sundararajan described another interesting application of a polymer-supported catalyst in Michael addition.[58] The problems associated with these reactions performed in solution lie in the separation of the product from the catalyst. The catalytic activity and selectivity in solution could be lowered in some cases by formation of oligomers by the catalyst.[58] Supporting a catalyst on a polymer could restrict such aggregation. A synthesis of the catalyst is presented in Scheme 28.

Scheme 28
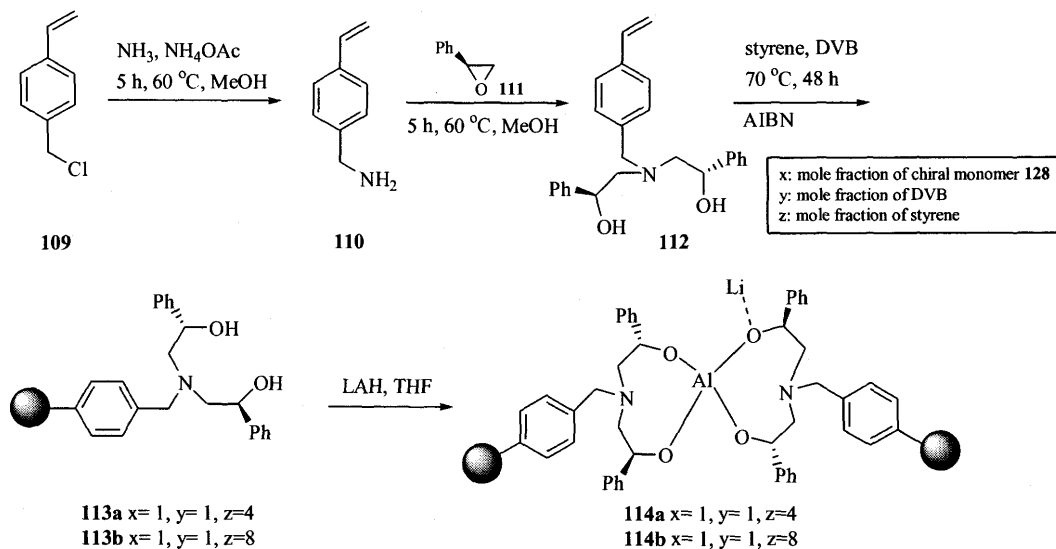
First, the amine **110** was synthesized by reaction of p-chloromethyl styrene with ammonia. In the next step, compound **110** reacted with *(R)*-(+)-styrene epoxide (**111**) to give chiral monomer **112**, which was copolymerized with different amounts of styrene and DVB as cross-linking agent to give resins **113a** – **b**. The corresponding chiral catalysts **114a** – **b** were obtained in the reaction of compounds **113a** – **b** with LiAlH$_4$ in

THF. The effectiveness of catalyst (**114a**) was evaluated in three different Michael reactions (Scheme 29).[58]

Scheme 29
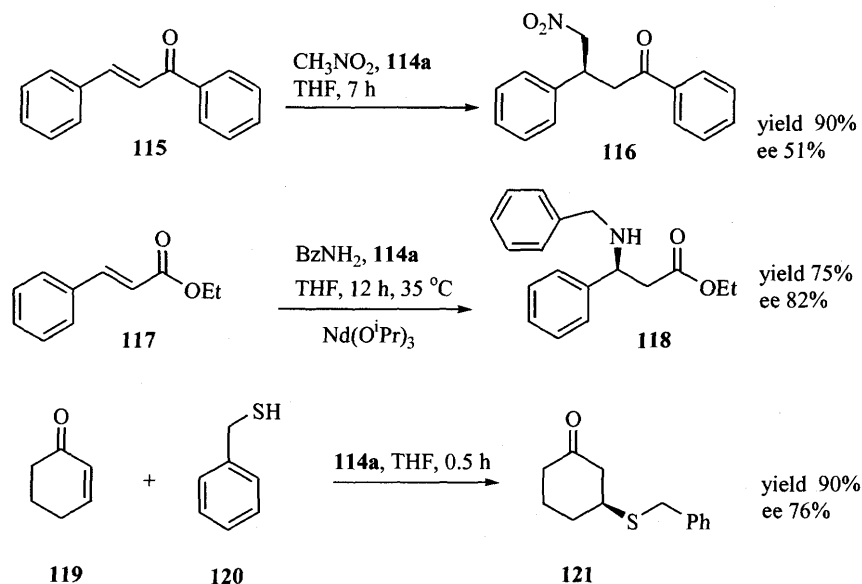
Michael addition catalyzed by resin **114a** proved to be a very general reaction. The products **116**, **118** and **121** were obtained in excellent yield and good enantioselectivity in each case. The chiral catalyst could be recycled by washing the polymer **114a** with 1 N HCl then reused.[58]

Polymer-supported catalyst for the kinetic resolution of racemic secondary alcohols.

Traditionally, kinetic resolution reactions are performed using enzyme catalysts that react selectively with only one enantiomer of the racemic starting material.[53] More recently, nonenzymatic kinetic resolution of alcohols was achieved.[61, 62] The preparation of the polymer-supported proline based diamine catalyst **127** for the kinetic resolution of the racemic mixtures of secondary alcohols is shown in Scheme 30.

Scheme 30
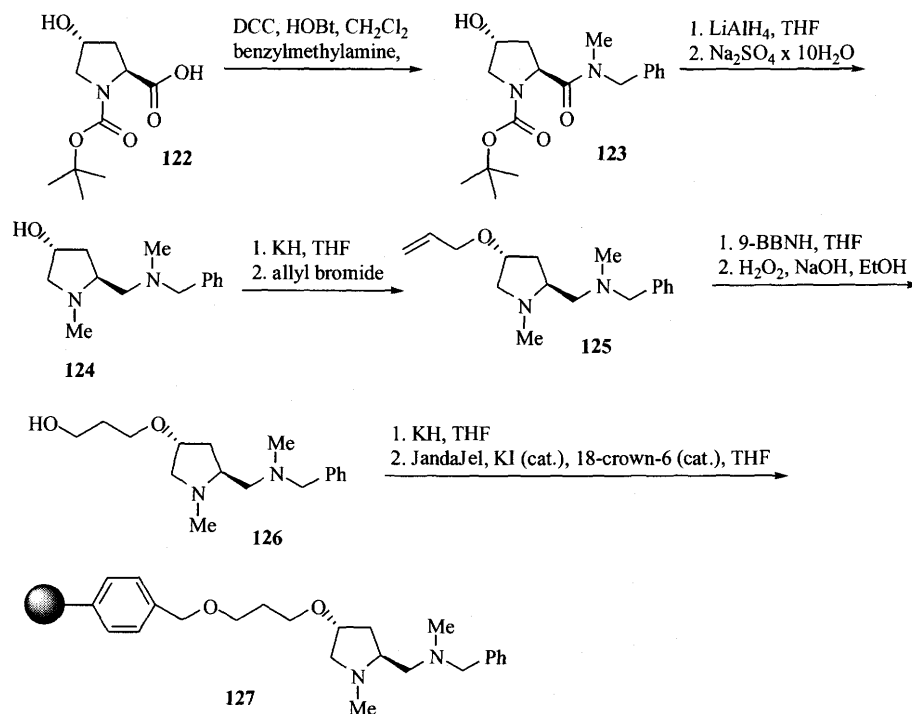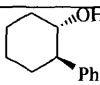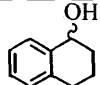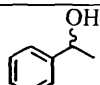
Hydroxyproline **122**, protected as a BOC-derivative, reacted with benzylmethylamine, and the corresponding amide **123** was obtained in 98% yield. Next, the diamine **(124)** was prepared by reduction of the carbamate **(123)** with LiAlH$_4$. Subsequently, it was treated with an excess of KH and the corresponding alkoxide was O-allylated with allyl bromide to provide diamine **125**. Compound **125** was treated with 9-BBN to give the hydroxypropyl ether **126** after oxidation. Compound **126** was successfully coupled to chloromethyl JandaJel *via* Williamson ether formation to yield polymer-supported resolving agent **127**.[61, 62] The loading of resin **127** was calculated by mass increase and was 0.59 mmol/g.

After the synthesis of polymer **127** was completed the stage was set for testing its effectiveness in the resolution of racemic mixtures of different alcohols (Scheme 31). The selected results of the process are presented in Table 10.

Scheme 31
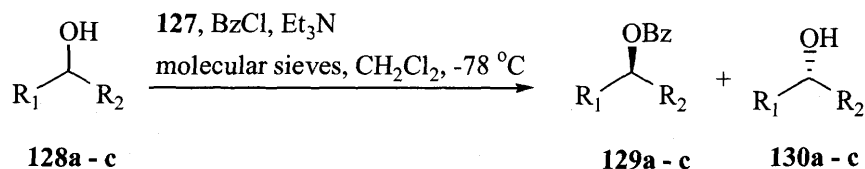
Table 10. Kinetic resolution of the racemic alcohols (**128a – c**) using catalyst **127**.

Entry	Alcohol	yield of ester (%)	ee of ester (%)	yield of alcohol (%)	ee of alcohol (%)
1	⌬ᴼᴴ Ph **128a**	44	96 (1S, 2R)	45	85
2	OH **128b**	44	58 (R)	47	50
3	OH **128c**	46	16 (S)	49	16

The optimal conditions that were used in all experiments (Table 10) were as follows: 2.0 equivalents of the polymer-supported catalyst (**127**), 0.75 equivalent of BzCl, 0.5 equivalent of Et₃N and molecular sieves. The reactions were conducted at –78 °C in CH₂Cl₂ for 11 h. Optical purity of the products **129a – c** and **130a – c** was determined by HPLC with a chiral column. The corresponding esters (**129a – c**) and unreacted chiral alcohols (**130a – c**) were obtained in excellent yields. The results of the resolution catalyzed by resin **127** were almost the same as those obtained in solution.[59] For the resolution of alcohol **128a** conducted in solution with diamine **131**, the corresponding ester **129a** was obtained in 48% yield and 97% ee, and the alcohol **130a** was obtained in 49% yield and 97% ee.

131
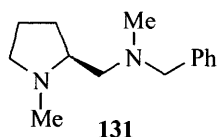
When the resolution of **128a** was performed with recycled catalyst **127** there was no significant decrease in enantioselectivity and yield of product **129a** (36% yield and 96% ee). It was shown that the polymer-supported catalyst **127** was as effective as its solution equivalent **131**. The reaction was fully automatable, did not require an aqueous workup, and gave the selectivity factors comparable to those obtained in the solution phase.[59]

In summary, syntheses of several polymer-supported chiral amines and their derivatives have been reported by several groups. The compounds were successfully applied as: (i) chiral auxiliaries (alkylation of cyclohexanone or amino acid derivative, and protonation of lithium enolates derived from 2-methylcyclohexanone and an ester), (ii) chiral ligands for the addition of diethylzinc to aldehydes and dihydroxylation of olefins, and (iii) chiral catalysts for the reduction of ketones and oximes, Michael addition, and kinetic resolution of racemic alcohols. The corresponding products of these reactions were obtained in good yields, and the enatioselectivities were comparable to the values obtained in solution. The polymeric amines and their derivatives possessed several typical advantages for SP compounds: they could be separated by filtration, and they could be regenerated and reused. It should be emphasized here that there has been no publication in the literature describing polymer-supported chiral amines as reagents. I decided to synthesize several different polymer-supported chiral amines and investigate their properties as reagents. The work is described in detail in part B of the Results and Discussion.

1.3 Soluble resins - the potential for combining the advantages of solution phase chemistry with macromolecular properties of reagents.

Reagents and catalysts attached to insoluble polymers such as Merrifield resin proved to be very practical since the separation of the products from the reaction mixtures involved only filtration. Although solid-phase synthesis is often highly successful, it still exhibits several shortcomings due to the heterogeneous reaction conditions.[63] Unequal distribution of reactive groups, access to reaction sites, solvation, and other synthetic problems associated with the solid-phase led researchers to look for different methodologies that could restore the homogeneous conditions of a reaction.[63] By replacing insoluble resins with soluble polymer supports the familiar reaction conditions of classical organic chemistry could be restored and purification of a product would still be facilitated through macromolecular properties of the reagent.[63 – 65] This methodology is called "liquid-phase-synthesis" (LPS).[63]

1.3.1 Requirements for soluble resins.

Polymers employed as soluble supports for LPS must fulfill the following requirements: (i) they have to be commercially available or amenable to rapid and convenient preparation; (ii) they must have good mechanical and chemical stability and (iii) they have to provide appropriate functional groups for easy attachment of chemical moieties. Additionally, one should realize that soluble polymers (bought or prepared in the laboratory) consist of macromolecules of variable sizes. As polymer properties vary with chain length, the molecular weight range should be narrow. The resins should have a molecular weight high enough to be a solid at room temperature.[63, 64]

A soluble resin must be stable towards a variety of reaction conditions, and must possess reactive groups allowing for anchoring organic molecules. If the conditions of polymerization and choice of a monomer allow for suitable polymer functionalization,

then anchoring of the initial structure can be made directly to a support for LPS.[63] In order to improve the accessibility of a polymer reactive group towards reagents in solution, the former should be separated from the polymer matrix by a linker.

Polymers chosen as supports for "liquid-phase synthesis" should provide a reasonable compromise between loading (functionality) and solubility. High loadings are desired in order to make the synthesis more manageable on a large scale, but it is known that the solubility of the resin can decrease as the loading capacity increases.[63] When soluble polymers with high loadings are used as supports, the influence of neighboring anchoring sites on the reaction course has to be taken into consideration.[63] Multiple attachment of compounds may result in unequal reactivity of bound species, which can be unevenly distributed along the polymer.[63]

In order to ensure the success of liquid phase synthesis two variables have to be chosen very carefully: the soluble support and the linker. If the support is not commercially available, a polymerization procedure has to be elaborated in such fashion that the resulting polymer has a narrow molecular weight range. Next, the correct conditions for the anchoring of the linker must be designed. After the linker is attached to the chosen resin, the stage is set for performing the "liquid-phase synthesis".

1.3.2 Methods of separating soluble polymers from reaction mixtures.

The filtration method, which is used as the technique to separate insoluble polymers from the reaction mixture, cannot be used in the case of soluble polymers. Most of the time the reaction mixture containing the soluble resin is diluted with a solvent inducing polymer precipitation. Next, the precipitated resin is separated by filtration and the excess reagents can be washed away. The precipitation of polymers often requires careful choice of solvent and temperature. Although precipitation is the most popular technique for separating soluble polymers from the reaction mixture there are other methods that can be used as well. They include: dialysis using semipermeable

membranes,[66] membrane filtration,[63] centrifugation methods,[63] gel permeation chromatography,[67] and adsorption chromatography.[67] One should realize that these methods isolate the polymer-supported products from soluble impurities, but do not purify the products from polymer-supported impurities. Consequently, the total purification of intermediates cannot be achieved. Instead all reactions have to be optimized and driven to completion in order to avoid a complicated mixture of products at the end of a synthesis.

1.3.3   Analytical methods used in LPS.

Compounds attached to a soluble polymer can be characterized by conventional methods like ¹H NMR, ¹³C NMR, IR and UV-visible spectroscopy. Moreover, samples taken for analysis by these non-destructive methods can be returned to a reaction flask after recovery.[63] Sometimes, TLC can be used to monitor the reaction without preliminary cleavage from the resin.[68] Chemical methods such as titration and derivatization can be routinely performed, and allow subsequent characterization of compounds in the presence of a solid support.

1.3.4   Commercially available soluble polymers.

Soluble polymers that are used in LPS are listed in Table 11 and their structures are presented in Figure 4.[63, 64]
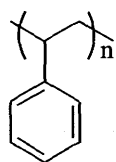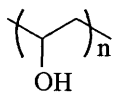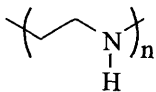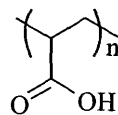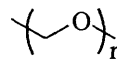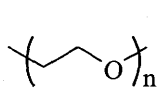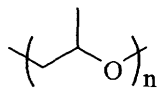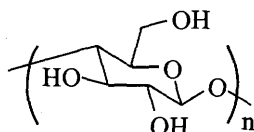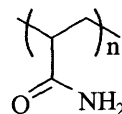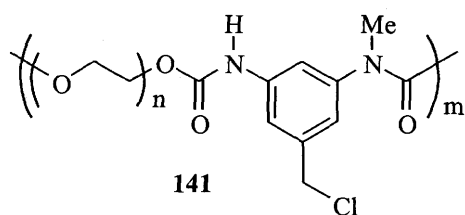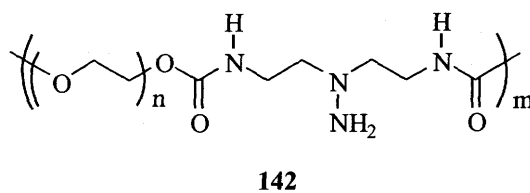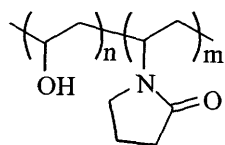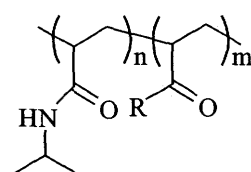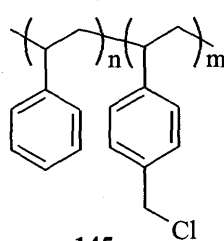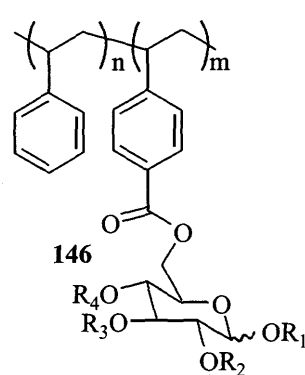
Figure 4. Structures of soluble polymers used in LPS (ref. 63).

Table 11. Soluble polymers utilized in "liquid-phase-synthesis" (ref. 63).

Polymer	Application			
Homopolymers:	a	b	c	d
1. polystyrene (non-cross-linked) (**132**)	+	+	+	-
2. polyvinyl alcohol (**133**)	+	+	+	+
3. polyethylene imine (**134**)	+	-	-	-
4. polyacrylic acid (**135**)	+	-	-	-
5. polymethylene oxide (**136**)	+	-	-	-
6. polyethylene glycol (PEG) (**137**)	+	+	+	+
7. polypropylene oxide (**138**)	+	-	-	-
8. cellulose (**139**)	+	+	-	-
9. polyacrylamide (**140**)	+	-	+	-
Copolymers				
10. PEG with 3,5-diisocyanatobenzyl chloride (**141**)	+	-	-	-
11. PEG with 3-nitro-3-azapentane -1,5-diisocyanate (**142**)	+	-	-	-
12. polyvinyl alcohol-poly-(1-vinyl-2-pyrrolinone) (**143**)	+	+	-	-
13. poly(N-isopropylacrylamide)-poly (acrylic acid derivatives) (**144**)	-	-	+	-
14. polystyrene-poly(p-chloromethyl styrene (**145**)	+	-	-	+
15. polystyrene-poly(vinyl-substituted mono saccharides) (**146**)	-	-	-	+

[a] Peptide synthesis. [b] Oligonucleotide synthesis. [c] Oligosaccharides synthesis. [d] Synthesis of small molecules.

Polyethylene glycol (PEG) (**137**) is the most popular soluble resin for LPS and thus a brief discussion of its properties is justified. Depending on the polymerization conditions of ethylene glycol, PEG termini may consist of hydroxyl groups or may be substituted. Commercially available PEG can possess hydroxyl groups, methoxy groups or both at the ends of its chains.[65] The polymer has a molecular weight between 2000 and 20000 with a loading capacity of 0.1 – 1.0 mmol/g. It has good mechanical properties and it is crystalline at room temperature.[63] The polydispersity of commercially available PEG resins is narrow, which corresponds to the narrow distribution of the molecular weight of macromolecules.[68c] The polymer is soluble in a wide range of organic solvents and in water but it is not soluble in hexane, Et_2O and *tert*-butyl methyl ether. Careful precipitation using these solvents or cooling of the polymer solutions in EtOH or MeOH yields crystalline PEG, which can be separated from the reagents in solution by simple filtration. One of the main advantages of this resin is that the supported organic compounds can be analyzed by conventional ^1H NMR and ^{13}C NMR spectroscopy since PEG-MeO contains a single methoxy group and ethylene protons of the polymer backbone, which can be used as the internal standards.

1.3.5 Applications of LP reactions.

Insoluble polymers are used intensively in the synthesis of compound libraries, since product purification can be achieved by simple filtration and rinsing. As discussed before, solid-phase synthesis has several shortcomings, which are caused by the heterogeneous conditions of a reaction. In order to overcome these limitations, liquid-phase combinatorial synthesis was developed as the alternative method for the construction of libraries of small molecules.[63] The application of soluble resins combines the advantages of SPS and the benefits of classical chemistry.[68b] Liquid phase synthesis can be applied in combinatorial chemistry, in fact both the "split-pool" and the parallel methods, which were described above for insoluble polymers can be used. The validity of the LP method was demonstrated by the synthesis and screening of a peptide-based

library that led to the identification of several compounds showing strong binding to an anti β-endorphin monoclonal antibody.[68b]

1.4 Chemistry of soluble polymer-supported chiral amines.

Immobilization of chiral ligands and catalysts on polymer supports is the current subject of intense research activity.[70] The efforts are aimed at improving the efficiency of asymmetric catalysis by allowing for recycling of the chiral ligand or catalyst. While the use of insoluble resins has been investigated to some extent, immobilization on soluble resins has received much less attention. This is surprising, since soluble polymers allow for the reaction to be carried out under homogeneous conditions, and to secure higher enantioselectivities and more catalytic cycles than insoluble supports, as recently demonstrated by several researchers.[70]

Chiral amines as chiral ligands.

The ligand-accelerated catalytic (LAC) asymmetric dihydroxylation of olefins based on the cinchona alkaloid ligands was described by Sharpless in 1988[49a] and since then, the reaction has been further developed. From the standpoint of cost, ligand and/or metal recovery and recycling are of prime interest because cinchona alkaloids and osmium tetroxide are the most expensive components of the procedure. In this regard several groups have reported AD reaction using insoluble, polymer-supported alkaloids.[48, 51] The solid-phase methodology was less satisfactory than reactions in solution[49] because of the increased reaction times and highly variable yields. In order to overcome these problems a synthesis of soluble polymer-supported ligands was designed and is presented in Scheme 32.[69]

Scheme 32

147   148   149

150
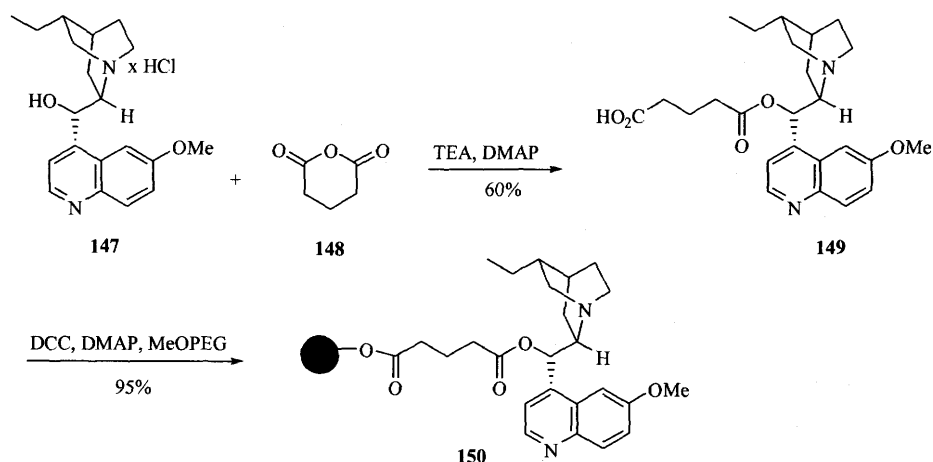
The commercially available hydrochloride salt of hydroquinidine **147** was acylated using glutaric anhydride (**148**) to provide carboxylate monoester **149**. This simple reaction provided the linking unit for attachment to the homopolymer MeOPEG, which was achieved in the next step. The resulting resin **150** was soluble in an acetone/water mixture (v/v= 10:1). The conditions of the asymmetric dihydroxylation reaction of olefins catalyzed by **150** were homogeneous, and the transformation was completed within the same amount of time as a reaction conducted in solution with no decrease in yield and selectivity.[69] The general AD reaction of olefins is shown in Scheme 34, and results are presented in Table 12.

Ligand **150** was not the most effective one in the AD reaction.[69] Therefore, an attempt to improve yields and enantioselectivities was made and the synthesis of ligand **152** was designed (Scheme 33).[70]

Scheme 33
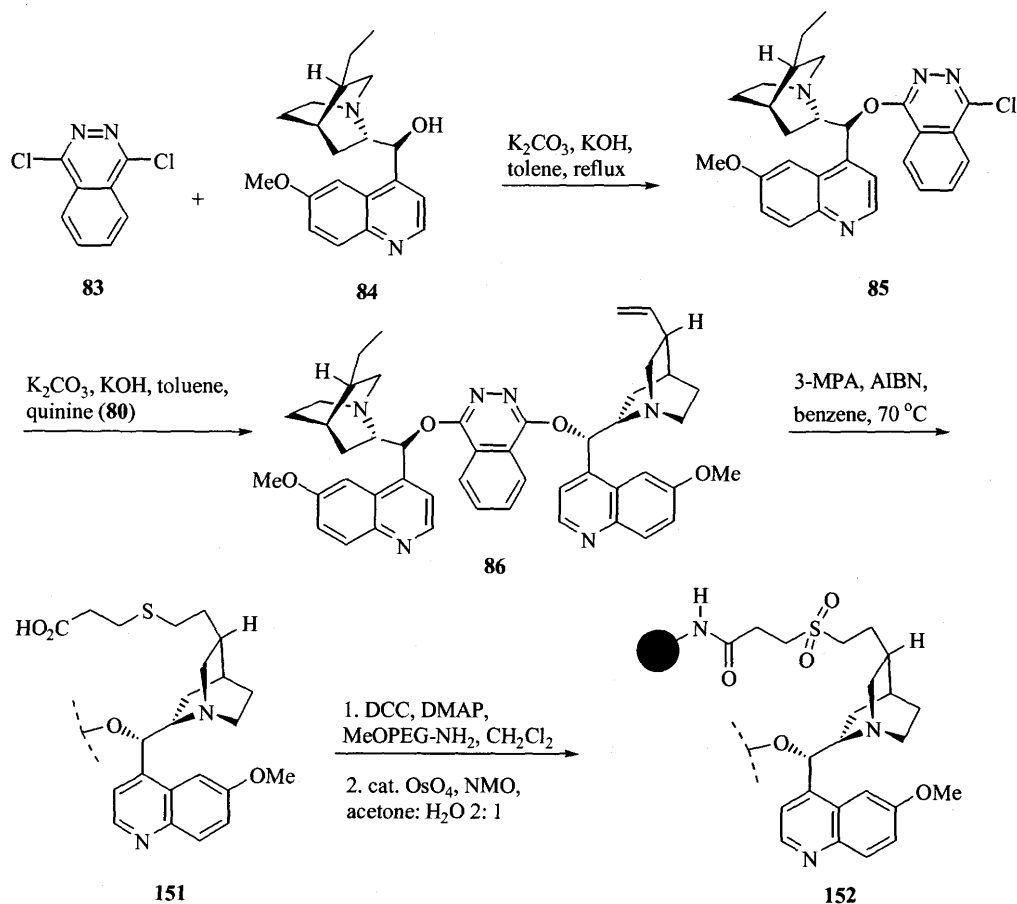
In the first step of the synthesis, dihydroquinidine (**84**), 1,4-dichlorophthalazine (**83**), KOH and K$_2$CO$_3$ were refluxed in dry toluene to give the mono-substituted chlorophthalazine **85**. Next, quinine (**80**) was attached and compound **86** was obtained. Heating of **86** with 3-mercaptopropionic acid (3-MPA) and AIBN gave the intermediate **151**. The acid **151** was coupled with MeOPEG-NH$_2$ in the presence of DCC and DMAP, followed by oxidation with OsO$_4$/ NMO to give the desired sulfone **152**. Ligand **152** was employed in the AD reaction of olefins (Scheme 34). Selected results are presented in Table 12.

Scheme 34

89a $R_1 = R_2 = Ph$ **90a** $R_1 = R_2 = Ph$
89b $R_1 = Ph, R_2 = H$ **90b** $R_1 = Ph, R_2 = H$
89d $R_1 = Ph, R_2 = Me$ **90d** $R_1 = Ph, R_2 = Me$
153 $R_1 = R_2 = n\text{-}Bu$ **154** $R_1 = R_2 = n\text{-}Bu$
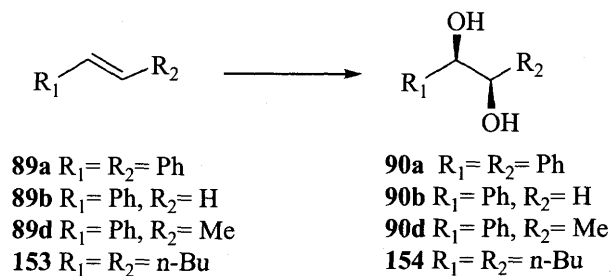
Table 12. Selected results for AD reactions catalyzed by LP ligands.

Entry	Olefin	Ligand	Oxidant	Yield (%)	ee (%)
1	89a	150	NMO	89	88
2	89b	150	NMO	80	60
3	89d	150	NMO	80	84
4	153	150	NMO	62	42
5	89a	152	K_3FeCN_6	95[a]	99
6	89b	152	K_3FeCN_6	88[a]	98
7	89d	152	K_3FeCN_6	83[a]	99
8	153	152	K_3FeCN_6	80[a]	97

[a] Higher yields but lower enantioselectivities were obtained with NMO as the oxidant (ref. 70).

As seen from Table 12, better results were obtained with ligand **152** (Table 12, entries 5 – 8) than with ligand **150** (Table 12, entries 1 – 4) considering the yield and enantioselectivities. The reaction conditions were homogeneous, and the polymers **150** and **152** could be recycled and reused, which reduced the cost of an AD transformation.

In summary, the synthesis of two soluble polymer-supported ligands for asymmetric dihydroxylation of olefins was reported.[69, 70] The ligands were as effective as their equivalents in solution.[49, 50] This methodology is a good example of the successful

combination of macromolecular properties of a polymer-supported compound and solution conditions of the reaction.

LP chiral amines as ligands in reduction of prochiral ketones.

Perhaps the most successful method for the reduction of prochiral ketones involves 1,3,2-oxazaborolidines as catalysts. The method was developed by Itsuno[72], and improved by Corey and co-workers (CBS reducing agent).[74] Some of the oxazaborolidines were extensively studied, however the development of cost effective catalysts that exhibit high reactivity and enantioselectivity is still a challenging task.[71] One approach to reduce the cost of a product specific catalyst is to recover a catalyst and reuse after completion of a reaction. Towards this end, a soluble, polymer-bound catalyst **159** was invented (Scheme 35).[71]

Scheme 35
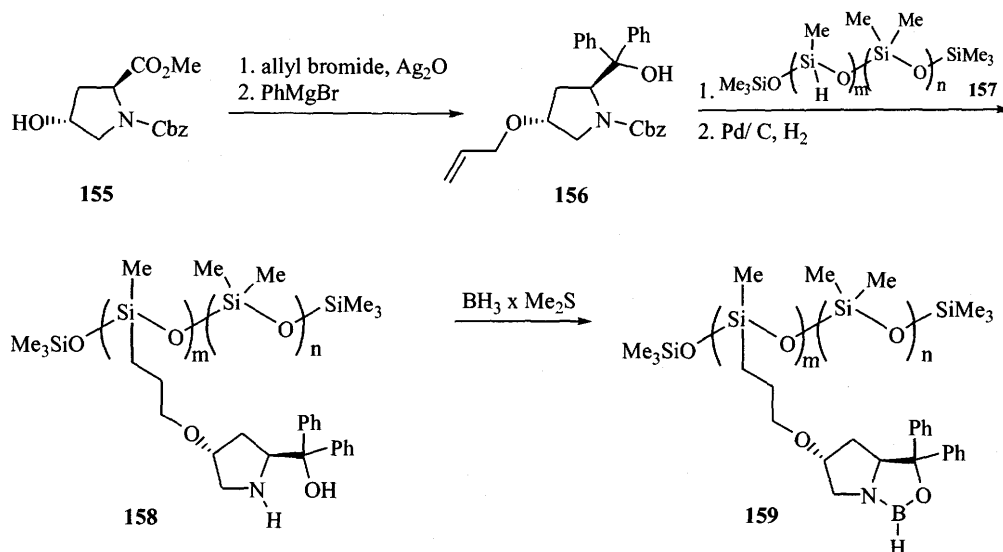
The first step in the synthesis of this catalyst was O-allylation of the precursor **155**, followed by a Grignard addition of phenylmagnesium bromide to the ester group to give

the chiral monomer (**156**). This monomer was then subjected to platinum catalyzed hydrosilylation with polymer **157** to give, after deprotection, resin **158**. The chiral, polymer-supported oxazaborolidine **159** was obtained in the reaction of the corresponding amino-alcohol **158** with $BH_3 \cdot Me_2S$ complex, according to the procedure described before.[71] The activity of the polymer **159** was tested in the reduction of prochiral ketones (Scheme 36, Table 13).

Scheme 36

101 R= Me	102 R= Me
160a R= Et	161a R= Et
160b R= CH_2Cl	161b R= CH_2Cl
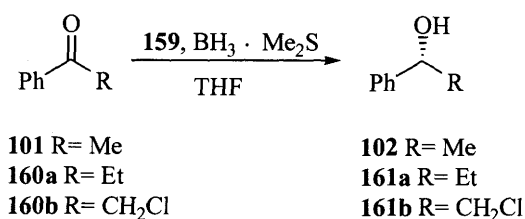
Table 13. Enantioselective reduction of prochiral ketones with reagent **159**.

Entry	ketone	yield (%)[a]	ee (%)[b]	Config.[c]
1	**101**	86	97	R
2	**160a**	88	89	R
3	**160b**	83	94	S

[a] Yield was determined after purification. [b] Enantioselectivity was determined by HPLC (ref. 71). [c] Determination of the absolute configuration was based on the sign of the known $[\alpha]_D$ for the pure enantiomers of the product (ref. 71).

As can be seen from Table 13, the corresponding alcohols **102**, **161a** and **161b** were obtained in high yield and enantioselectivity, and the results can be successfully compared to the results obtained with solution phase reagents (compound **102** was obtained in 96% ee).[72] The enantioselectivity and the yield of the reduction of acetophenone (**101**) (Table 13, entry 1) can be compared to the results obtained with insoluble ligands **94a** – **c** and **100a** – **c** (Scheme 25, Table 8). The soluble ligand **159**

could be recycled and reused in the reduction of ketones (**101, 160a** and **160b**) without significant decrease of selectivity.

Cozzi and co-workers described another interesting application of derivatives of LP chiral amines as ligands in enantioselective synthesis.[74] These researchers synthesized two soluble polymer-supported bisoxazolines **168a – b** that were used as the chiral inductors in two different reactions (Scheme 38). The synthesis of resins **168a – b** is presented in Scheme 37.

Scheme 37
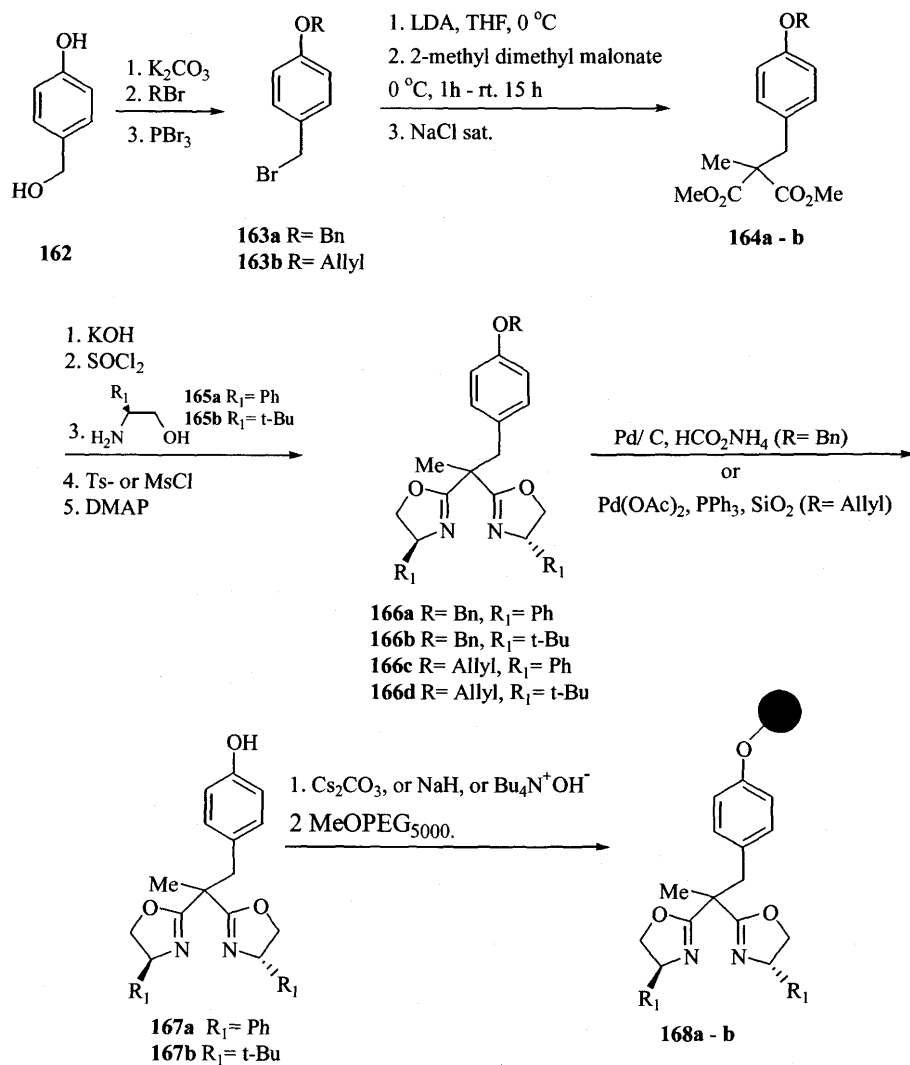
O-Benzylated and allyl protected 4-alkoxybenzyl bromides **163a** and **163b** were easily obtained from compound **162** by phenoxide ion alkylation and reaction with PBr₃. Those bromides were used to alkylate the lithium enolate of dimethyl methylmalonate to afford the corresponding esters (**164a** – **b**). Conversion of compounds **164a** – **b** to the oxazolines **166a** – **d** was achieved in the reaction with commercially available (S)-amino-alcohols **165a** – **b**, followed by alcohol activation as tosylates or mesylates, and ring closure promoted by DMAP. After deprotection of the hydroxyl moiety, the oxazolines (**167a** – **b**) were coupled to the soluble polymer (MeOPEG) and resins **168a** and **168b** were obtained. These supported ligands were tested in the cycloadditions that are shown in Scheme 38. The results are summarized in Table 14.

Scheme 38
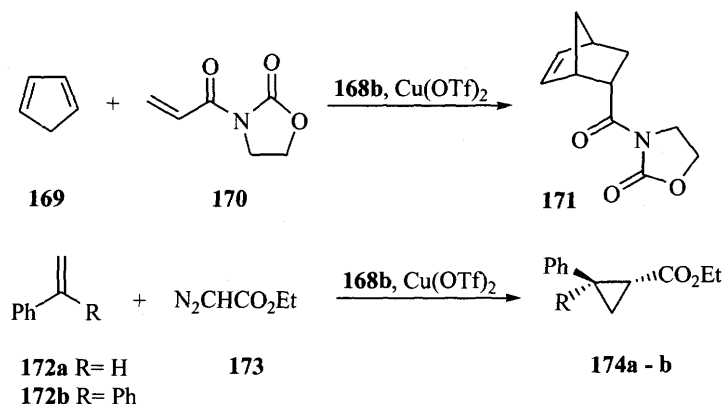
Table 14. Selected results for enantioselective Diels-Alder reactions catalyzed by **168b** (ref. 74).

Entry	Catalyst	Product	yield (%)	de (%)	ee (%)[b]
1	**168b**	**171**	83	>98: 2[a]	45
2	**168b**	**174a**	63	77: 23[a]	91
3	**168b**	**174b**	45	-	93

[a] Diastereoselective ratio for product **171** was endo: exo, for product **174a** the ratio was trans: cis. [b] Enantioselectivity was determined by ^{1}H NMR with chiral shift reagent for product **171**, by optical comparison of the known $[\alpha]_D$ value for pure enantiomers with $[\alpha]_D$ for products **174a – b**

It can be seen from Table 14 that the products were optically active but the enantioselectivity for compound **171** was low (Table 14, entry 1). Cozzi postulated that it could be caused by three factors: the supported ligand **168b** did not possess the C2 symmetry (which is the necessary requirement for a ligand to be selective),[75] the presence of the PEG, and the contamination of resin **168b**. Unfortunately it was not possible to confirm these hypotheses.[74] Other products (**174a – b**) were obtained with very good enantioslectivity (Table 14, entries 2 and 3). The polymer-supported ligands **168a – b** were recovered and reused. Overall, the resin **168b** proved to be effective as the ligand and it could be used preferentially to the solution phase analogues in giving products in high yield and ee. The cost of the reaction would be lowered due to the possibility of the recovery of chiral ligands.

In summary, the syntheses of a few chiral ligands supported on soluble polymers were reported by several groups.[69, 70, 71, 74] Those chiral ligands were successfully applied as chiral promoters in enantioselective reactions, such as Sharpless asymmetric dihydroxylation, reduction of prochiral ketones and cycloaddition reactions. All resins were completely soluble in the organic solvents used in these reactions, which restored the homogeneous conditions. It should be noted that there were fewer publications

describing soluble polymer-supported chiral amines and their derivatives than papers dealing with insoluble resins. Obviously, more work is needed in order to adapt the catalysts and reagents that work well in solution to reactions on a soluble support.

CHAPTER II: RESULTS AND DISCUSSION

Part A of this chapter deals with the deprotonation of cyclic ketones. This reaction of has been studied since 1986.[13, 76] The formation of enolates is the first step in many C-C bond-forming reactions (e.g., aldol, alkylation, Michael, Robinson annulation and acylation). The base commonly employed in the formation of an enolate is the lithium amide, derived from the chiral secondary amine. If the lithium amide is chiral, a chiral enolate can be obtained. This is due to the fact that a chiral base can differentiate between two enantiotopic axial hydrogens present in a cyclic ketone. The enolization of a ketone, followed by the reaction of the corresponding enolate with an electrophile can be influenced by the addition of different substances such as inorganic salts and organic compounds. An increase of enantioselectivity was observed in many cases.[13] A study of the effect of such substances on deprotonation of cyclic ketones, and on the reaction of the lithium enolate with an electrophile was performed, and the results will be discussed.

Part B of this chapter deals with the synthesis and application of novel, polymer-supported reagents. The concept of solid-phase synthesis was introduced by Merrifield thirty years ago.[14] Since then, many support-bound reagents were developed for conducting a variety of reactions on solid support. These reagents simplify the performance of a reaction (especially the workup), the support can be regenerated (very important from the economical point of view), and a reaction can be automated. As mentioned before, chiral lithium amides are used as the bases in the formation of enolates. The reactions of enolates with electrophiles are amongst the most employed reactions for the construction of a carbon framework in solution. The synthesis of polymer-supported chiral lithium amides was developed and their application will be described.

Part A: Deprotonation of cyclic ketones

2.A.1 Introduction

Deprotonation of ketones with chiral lithium amides has been studied since 1986.[1] [-13, 76] The deprotonation process (with both achiral and chiral lithium amides) is much more complicated than was thought. One has to consider numerous effects: aggregation of lithium amides, aggregation of lithium enolates, complexation of chiral lithium amides to the carbonyl group before the deprotonation step, and complexation of chiral amines to an enolate *via* lithium after the deprotonation step.[13] The deprotonation reaction of a cyclic ketone followed by a reaction of the corresponding enolate with an electrophile is shown in Scheme 39.

Scheme 39
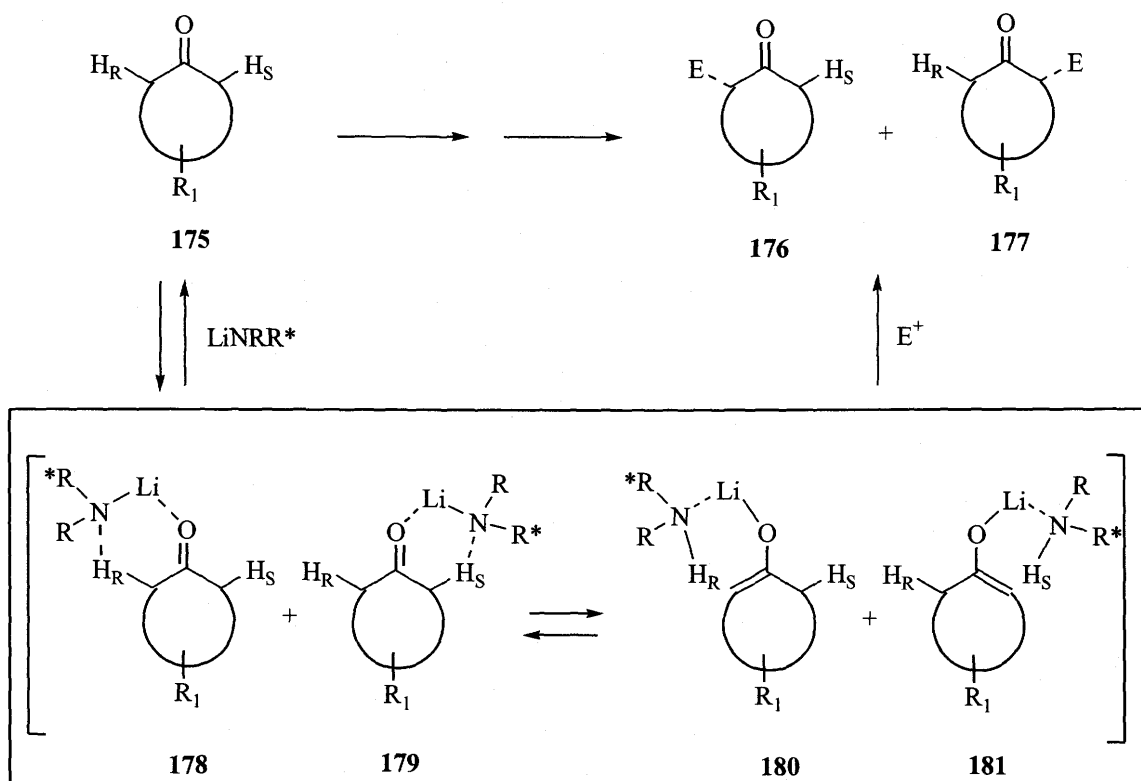
Most advanced organic chemistry textbooks ignore the complexity of the deprotonation reaction of ketones.[77] One must realize that all of the structures shown in the box in Scheme 39 are oligomers, which makes the study of a deprotonation reaction of a ketone, followed by the reaction of the corresponding enolate with an electrophile, quite complex. Another factor that complicates the study of these two reactions is the equilibration between complexes **178** or **179** and **180** or **181**.

The formation of an enolate of a cyclic ketone, followed by the reaction with an electrophile can be an enantiotopic group selective or enantiotopic face selective process.
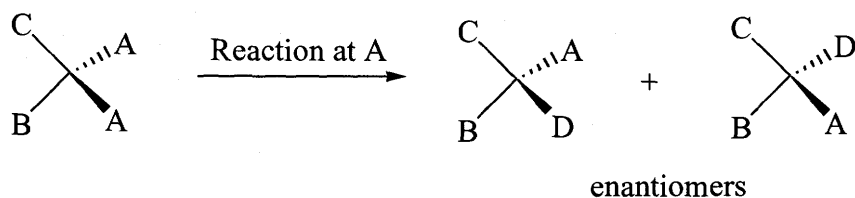
Figure 5. Enantiotopic group selective reaction.

An enantiotopic group selective process involves a preferential reaction at one of the two-enantiotopic groups A (Figure 5).[78] If one considers that an achiral substrate has an internal plane of symmetry, then one can say that the two groups A have an enantiotopic relationship. If one replaces either one of the groups A with a group D, a mixture of enantiomers is obtained. For the reaction to be enantioselective (i.e., to give one of the enantiomers in excess), the substrate requires a chiral environment: reagent, catalyst or solvent. Deprotonation of ketones can be an enantiotopic group selective reaction if a ketone belongs to a C_S symmetry point group (Scheme 39, R_1= alkyl, allyl or aryl). It is known that one of the axial hydrogens can be abstracted preferentially by a base in the deprotonation step.[13] If a lithium amide used for a deprotonation is chiral, then it can differentiate between two enantiotopic axial hydrogens, and the enolates **180** and **181** are not going to be obtained in a 1: 1 ratio. The ratio of the enolates should be reflected in the ratio of the products **176** and **177** if the yield of the reaction is 100%.
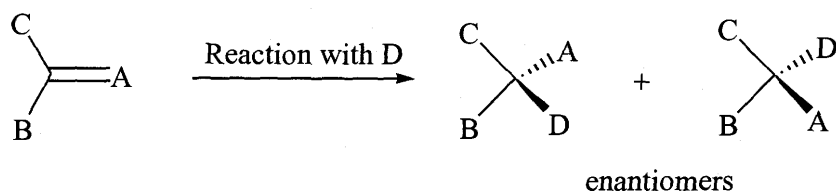
Figure 6. Enantiotopic face selective reaction.

An enantiotopic face selective reaction involves preferential addition to one of the two enantiotopic faces of a trigonal atom e.g., addition to C=C or C=O (Figure 6). The substrate molecule is achiral, since it has a plane of symmetry. For the process to result in a non-racemic mixture, the reaction requires a chiral element (i.e., reagent, catalyst or solvent), which causes discrimination between the two enantiotopic faces.[78] It is possible to obtain an enantiomerically enriched ketone, which is functionalized at the α position. The stereochemistry of this process can be controlled by face selectivity of the formed enolate. If a ketone belongs to the C_{2v} symmetry point group (Scheme 39, R_1= H) only one enolate is formed. The faces of the complex **180 = 181** became diastereotopic and they react with different rates with an electrophile. The products **176** and **177** will not be formed in a 1: 1 ratio.

Effect of achiral additives on the deprotonation of cyclic ketones.

Deaggregation of the oligomeric enolates

It is known that in solution and in the crystalline stages Li-enolates exist as oligomers. The crystalline enolates were analyzed by X-ray structural analysis and were found to exist as dimers, tetramers or hexamers.[79a, 79b] The structures of lithium enolates were further validated by NMR studies, which indicated that lithium enolate aggregates are directly involved in reactions with electrophiles.[80] The reactivity, and the regio- as well as stereoselectivity of reactions of these aggregates could be modified by the addition of different substances.

The effect of the addition of a lithium salt on a reaction of a lithium enolate with an electrophile is shown in Scheme 40.[80] One must remember that enolates can exist as more complexed oligomers. In Scheme 40 only a dimeric form of enolate **182** is shown to simplify the discussion. If a lithium salt was not added to the solution of dimeric lithium enolate **182** than the only obtained product would be product P_1. After addition of a lithium salt, the dimer **182** could be converted to mixed aggregate **184**, and the only product obtained would be P_2. In the presence of an equilibration between dimer **182** and mixed aggregate **184**, the mixture of products P_1 and P_2 would be formed in the same ratio as the ratio of **182** to **184**.

Scheme 40
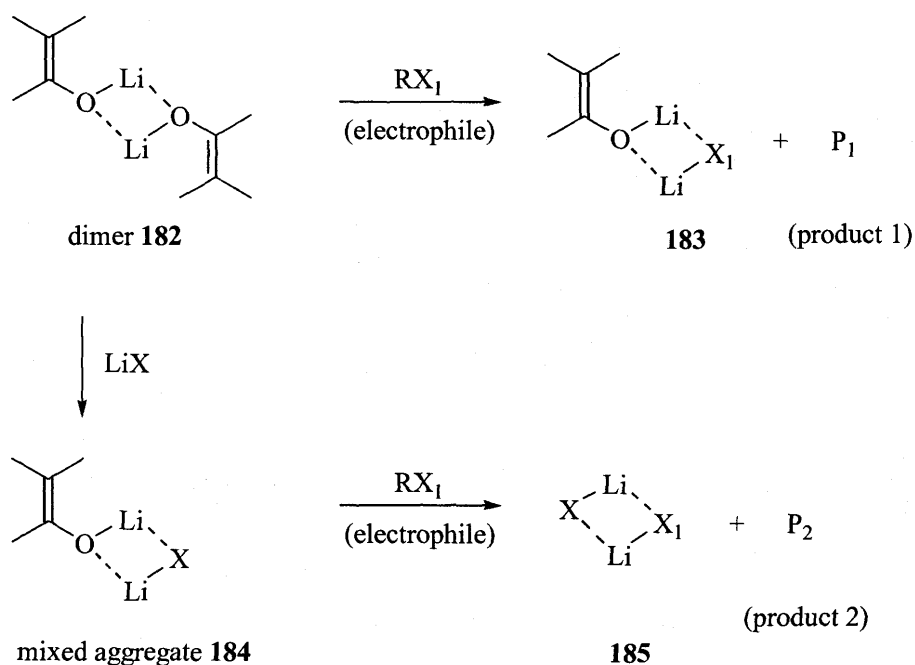
The structures of typical reactive mixed aggregates of lithium enolates and lithium salts are presented in Figure 7.

186

$[(LiEn)_3 \cdot LiX \cdot S_4]$

187

$[(LiEn)_2 \cdot (LiX)_2 \cdot S_4]$

188

$[LiEn \cdot (LiX)_3 \cdot S_4]$

189

$[LiEn \cdot LiX \cdot S_4]$
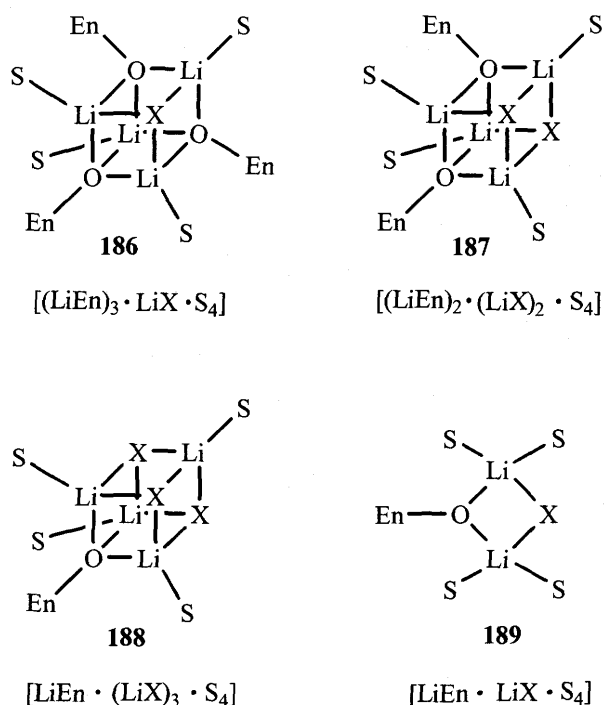
Figure 7. The structures of the reactive mixed aggregates of a lithium enolate (ref. 80).

Deaggregation of oligomeric chiral lithium amides

It has been observed that the selectivity of deprotonation with lithium amides can be influenced by the addition of lithium salts.[81, 82] It has also been reported that LDA forms mixed aggregates with lithium chloride.[79b] It was postulated that similar to LDA mixed aggregates should be formed from a chiral lithium amide and lithium chloride. In the NMR study of the solution of chiral lithium amide **190b** Koga found that in the absence of lithium halides, a chiral lithium amide existed predominantly as a dimer (a small amount of a monomer was also found).[83]

(R)-**190a** X= H
(R)-**190b** X= Li
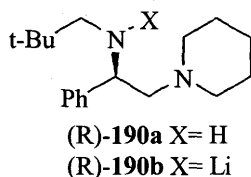
In the presence of lithium halides the chiral lithium amide **190** existed as two aggregates having different stoichiometry, 1 : 1 lithium amide: lithium halide **193** (major) and 2 : 1 lithium amide: lithium halide **194** (minor). Similar aggregates were also observed by other scientists.[79b, 85] The general structures of all aggregates are presented in Figure 8.
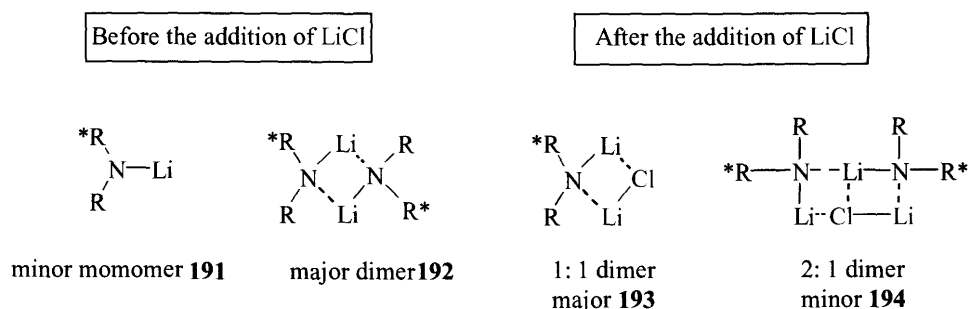
Figure 8. Structures of lithium amides aggregates.

The hypothesis of a mixed dimmer of lithium amide: lithium chloride acting as the deprotonating agent was validated by Williard in crystallographic and computational studies.[84, 85] The transition structure proposed by Williard is shown in Figure 9.
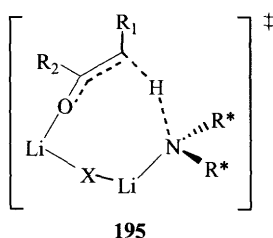
Figure 9. Mixed dimer based transition state structure for deprotonation of ketones. (ref. 84, 85).

The structure consists of a cyclic eight-member complex **195** that involves the mixed lithium amide – lithium halide dimer and the ketone molecule. The proton is transferred in a nearly linear fashion.[86]

2.A.2. Effects of lithium salts and other additives on deprotonation of cyclic ketones described in the literature.

Lithium salts are known to accelerate the rate and selectivity of various reactions e.g., LiBr affected the diastereoselectivity of the aldol reaction of cyclohexanone (25) with benzaldehyde.[85] The reaction is shown in Scheme 41 and the selected results are presented in Table 15.

Scheme 41
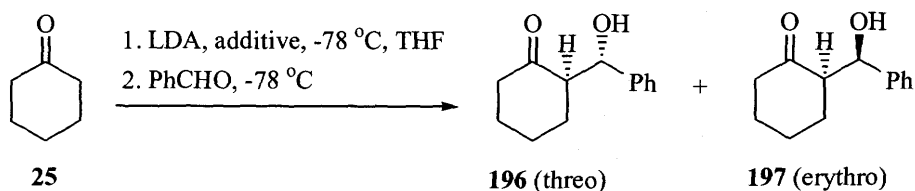
Table 15. The effect of LiBr on the aldol reaction of cyclohexanone.

Entry	LiBr (eq.)	Ratio 196 : 197
1	-	84 : 16
2	1	62 : 38
3	2	52 : 48

As can be seen, the addition of one or more equivalents of LiBr diminished substantially the diastereoselectivity of the aldol addition of benzaldehyde to cyclohexanone (25).

Addition of LiBr also had an effect on the deprotonation reaction of 3,5-dimethylcyclohexanone (198) by a chiral lithium amide (Scheme 42).[82] The results are presented in Table 16.

Scheme 42
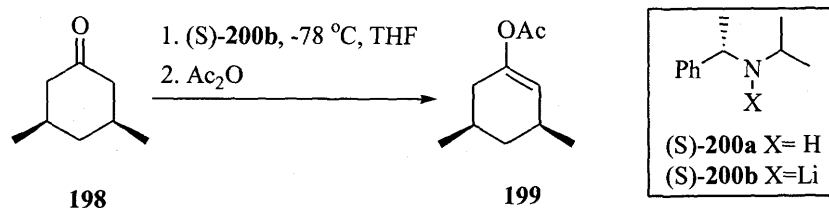
Table 16. The effect of the LiBr on the deprotonation of ketone **198**.

Entry	LiBr (eq.)	ee (%)
1	-	30
2	1	64

It is usually difficult to predict the effect of lithium salts on an outcome of a deprotonation reaction of a ketone, but it can be easily determined experimentally, e.g., deprotonation of tropinone (**201**) (Scheme 43).[2] The results are presented in Table 17 and in Figure 10.

Scheme 43
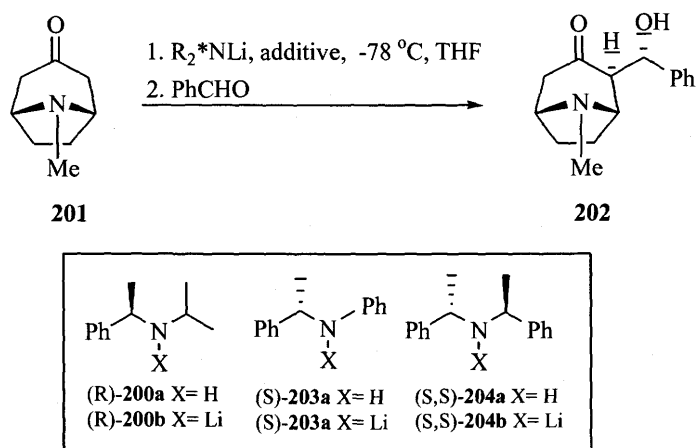
Table 17. The effect of LiCl on the enantioselectivity of the deprotonation of tropinone (**201**), followed by the aldol reaction of the corresponding enolate.

Entry	Lithium amide	LiCl (eq.)	ee (%)[a]
1	(R)-200b	-	23
2	(R)-200b	1	71
3	(S)-203b	-	23
4	(S)-203b	1	45
5	(S,S)-204b	-	36
6	(S,S)-204b	1	90

[a] The enantiomeric excess of product **202** was measured by ^{1}H NMR in the presence of the chiral solvating agent (S)-(+)-TFAE.

As can be seen from Table 17 and Figure 10, the three monodenate chiral lithium amides (R)-**200b**, (S)-**203b** and (S,S)-**204b** showed significant LiCl effects. The highest effect was achieved by the C$_2$ symmetric lithium amide (S,S)-**204b**. The increase of the enantioselectivity was observed after addition of about half an equivalent of LiCl. The enantioselectivity did not increase significantly after the addition of one or more equivalents of lithium salt. Those results suggest that the species that are involved in the deprotonation of tropinone (**201**) are mixed aggregates comparable with the general structures shown in Figure 8.
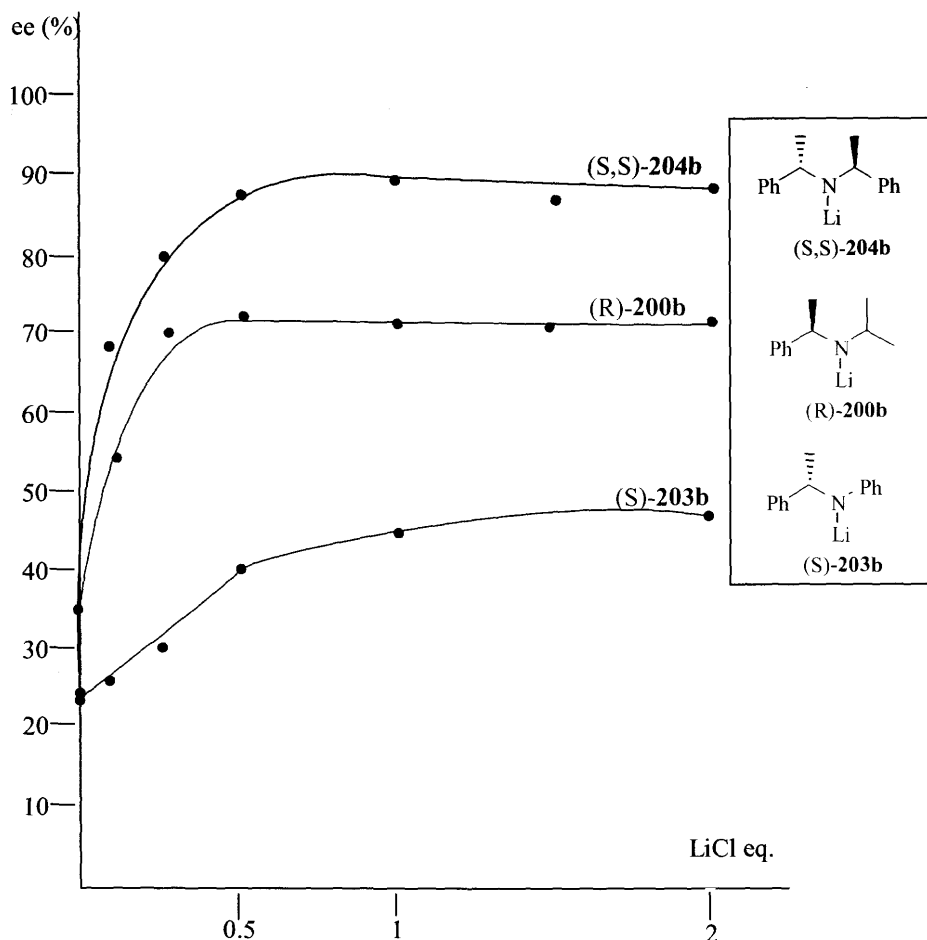
Figure 10. The effect of added equivalents of LiCl on the deprotonation of tropinone (**201**), followed by the aldol reaction of the corresponding enolate (ref. 2).

When tropinone (**201**) was deprotonated with bidenate lithium amide (R)-**190b** in the presence of varying equivalents of LiCl, and the corresponding enolate was reacted with PhCHO, it was noticed that the enantioselectivity of the aldol reaction was independent of the amount of LiCl used, but dependent on the solvent in which the reaction was performed.

(R)-**190a** X= H
(R)-**190b** X= Li
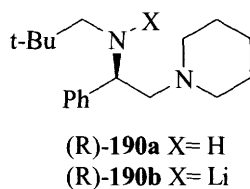
The enantioselectivity was in the range of 94 - 97% in THF but only 45 - 57% in Et$_2$O.[2] The cause of the different ee values in these two solvents is due to the fact that lithium amide (R)-**190b** is a monomer in THF and a dimer in Et$_2$O.[83] The structures of the monomer and the dimer of lithium amide (R)-**190b** are shown in Figure 11.

(R)-**190b**
monomer
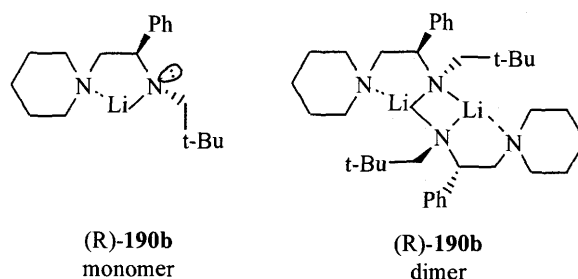
(R)-**190b**
dimer

Figure 11. The structures of the monomer and the dimer of (R)-**190b**.

The results showed in Figure 10 demonstrated that the enhancement of enantioselectivity was always observed when LiCl was added. The magnitude of this effect was dependant on the nature of the chiral lithium amide, starting ketone, and solvent in which the reaction was performed. To gain more insight into the nature of the LiCl effect other ketones were studied by our group: dioxanone **205** and ketone **207** (Scheme 44).[13] The most remarkable results were observed in the case of the aldol reaction of dioxanone **205** with (R)-**200b**. In the absence of LiCl, the reaction gave the dextrorotatory enantiomer **206** as the major product. The addition of 1 equivalent of LiCl caused the levorotatory enantiomer of product **206** to be obtained.[12] These results are presented in Table 18.

Scheme 44
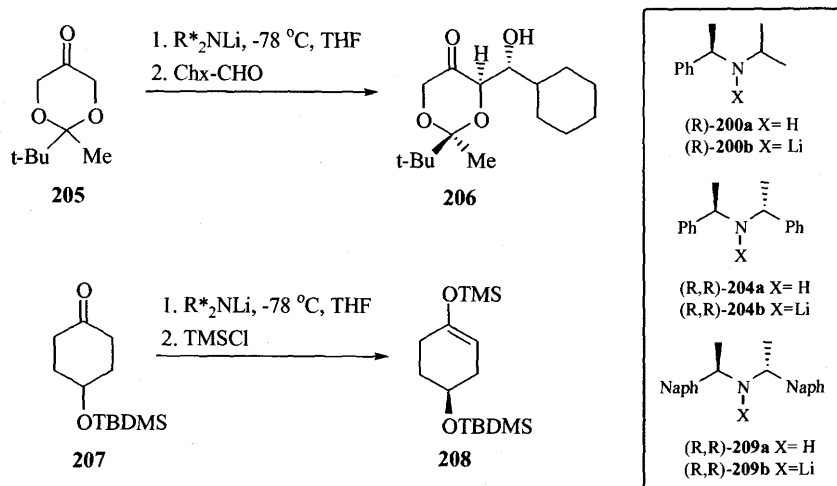
Table 18. The effect of LiCl on the deprotonation of ketones **205** and **207**.

Entry	Lithium amide	Product	LiCl (eq.)	ee (%)
1	(R)-**200b**	**206**	–	15
2	(R)-**200b**	**206**	1	54[a]
3	(R,R)-**204b**	**206**	–	18
4	(R,R)-**204b**	**206**	0.5	60
5	(R)-**200b**	**208**	–	36
6	(R)-**200b**	**208**	1	70
7	(R,R)-**209b**	**208**	–	74
8	(R,R)-**209b**	**208**	1	77

[a] Levorotatory enantiomer of **206** was the major one.

At the same time as our group was investigating the deprotonation of different cyclic ketones[88] other research groups were conducting similar studies.[80, 81, 83, 89 – 94] During the work on the deprotonation of 4-*tert*butylcyclohexanone (**210**), Koga made an interesting observation.[83] The enantioselectivity of the silyl enol ether (**211**), formed when the

"internal quench" technique was employed with (R,R)-**204b**, was strongly dependent on the kind of silylating reagent used. The enantioselectivity varied from 90% for TMSCl to 31% for TMSI. When the enolate **210a** was trapped with the TMSCl (the "external quench" technique), the effect was smaller but it was still dependent on what kind of halide was used as the additive. The selectivity was 88% for LiCl and only 44% for LiI (Scheme 45).[83]

Scheme 45

"Internal quench"

X= Cl, ee= 90%
X= Br, ee= 65%
X= I, ee= 31%

210   **211**

"External quench"

no LiX, ee= 44%
X= Cl, ee= 88%
X= Br, ee= 63%
X= I, ee= 44%

210   **210a**   **211**
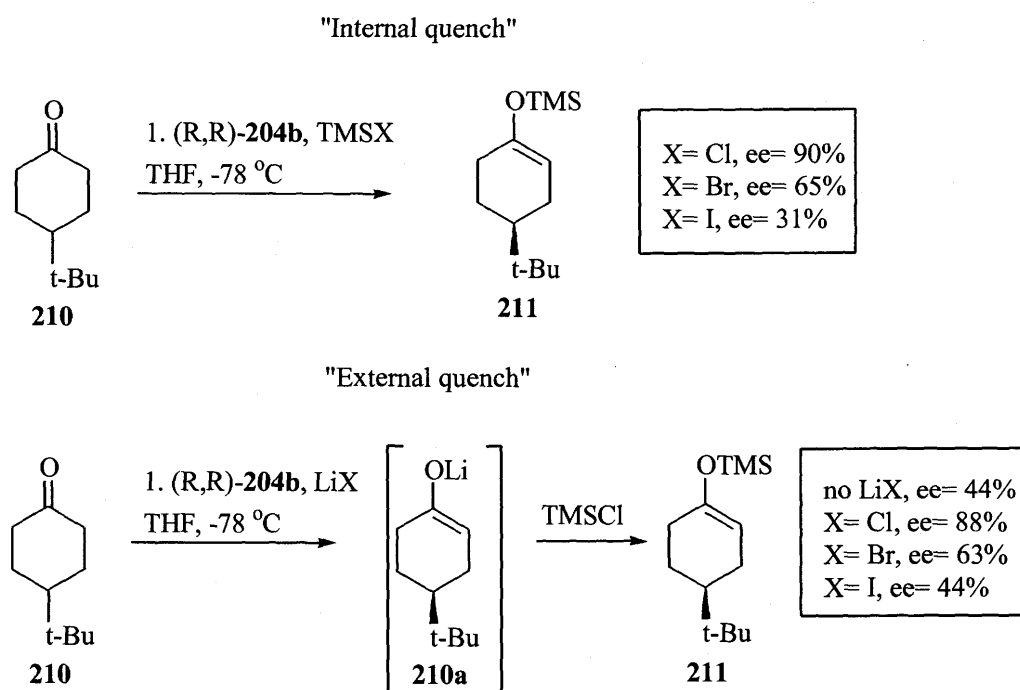
Based on the similarity of the results from both experiments, Koga concluded that trimethyl silyl halides acted as the *in situ* source of lithium salts, and that the chiral lithium amide (R,R)-**204b** existed as the dimer in the absence of lithium salts.[83] In the presence of lithium salts the chiral lithium amide (R,R)-**204b** existed as the monomer. The general structures of oligomers formed by chiral lithium amides were shown in Figure 8. The difference in the results of the deprotonation reaction of ketone **210** was attributed to the difference in the position of the equilibrium between the dimer and the mixed dimer. In the case of LiCl, the equilibrium was shifted heavily towards the mixed

dimer whereas LiI did not form an appreciable amount of mixed dimer. Besides LiCl, other lithium salts and other inorganic and organic compounds (e.g., ZnCl$_2$, HMPA, TMEDA, DMPU) could be used as the additives to increase the yield and/or the selectivity of the deprotonation reaction of various cyclic ketones.[80, 89] One of the most common polar co-solvents used as an additive is HMPA. It was used to improve the enantioselectivity of the deprotonation reaction of 4-*tert*-butylcyclohexanone (**210**) with (R)-**190b** (Scheme 46, Table 19, Figure 12).[90]

<div align="center">Scheme 46</div>
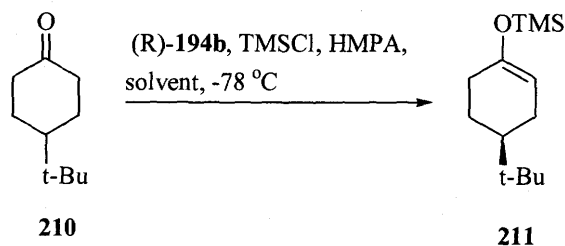
Table 19. Solvents effects on the formation of silyl enol ether **211** from 4-*tert*-butylcyclohexanone (**210**) with (R)-**190b**.

Entry	Solvent	HMPA (eq.)	ee (%)
1	THF	-	84
2	THF	2	82
3	Et$_2$O	-	64
4	Et$_2$O	2	82
5	DME	-	70
6	DME	2	81
7	PhMe	-	58
8	PhMe	2	82
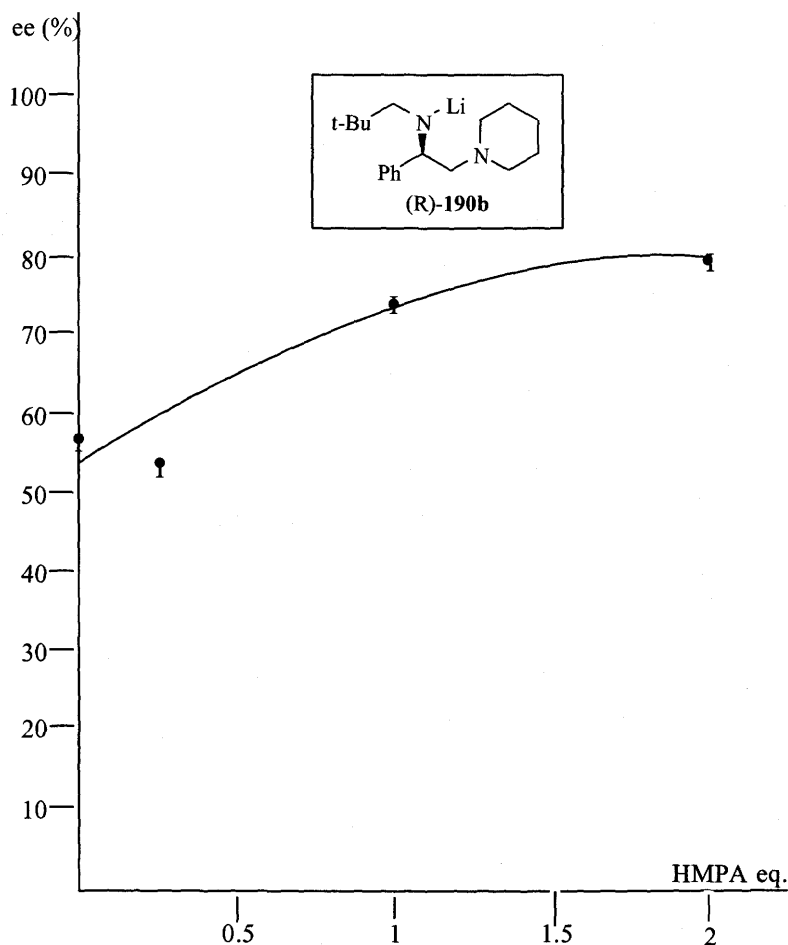
Figure 12. The effect of the addition of HMPA on the enantioselectivity of the formation of silyl enol ether **211** in toluene (ref. 90).

As can be seen from Table 19, HMPA did not have any effect on the enantioselectivity of the reaction when the reaction was conducted in THF because bidenate lithium amide (R)-**190b** exists as a reactive monomer. In other solvents: Et_2O and toluene, bidenate amine (R)-**190b** exists as a dimer. The dimer can be deaggregated by the addition of HMPA. HMPA caused the dimer to break to more reactive monomers, which are also more selective deprotonating agents (Figure 12).[90 – 93] In the case of lithium amides derived from the corresponding, monodenate chiral amines a different trend was observed. The enantioselectivity of a deprotonation reaction is often decreased or remains the same if the reaction is carried in THF. HMPA complexes easily to the lithium atom, but does not necessarily break up the unreactive dimer.

Simpkins discovered that zinc chloride had a remarkable effect on the enantioselectivity of the enolization of sulfur and oxygen bridged, bicyclic ketones (Scheme 47, Figure 13).[94]

Scheme 47
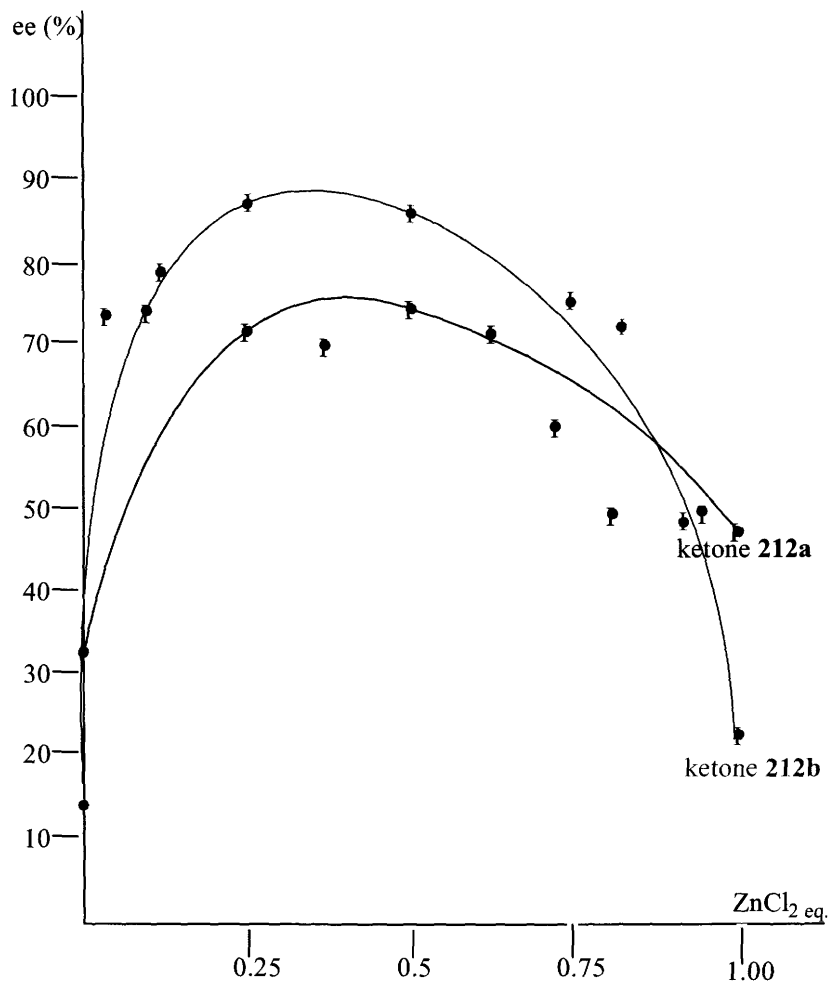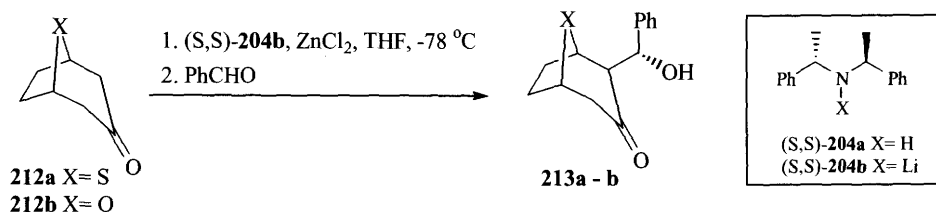
Figure 13. The effect ZnCl$_2$ on the enantioselectivity of the deprotonation of ketones 212a – b (ref. 94).

As can be seen from Figure 13, the maximum enantiomeric excess was observed in both reactions when 0.5 equivalents of $ZnCl_2$ were added. When more equivalents of $ZnCl_2$ were added, the ee decreased. This phenomenon could be explained as occurring because zinc chloride reacted with lithium amide (S,S)-**204b** to produce lithium chloride. However, the difference in profiles of the LiCl vs. $ZnCl_2$ graphs (Figure 13) suggests that the explanation of the $ZnCl_2$ effect is actually far more complicated.[94]

2.A.3. Effects of chiral additives on the enantioselectivity of α-functionalization of cyclic ketones.

The chiral additives that could influence the outcome of the deprotonation reaction of cyclic ketones are chiral lithium amides (Scheme 48) and chiral amines (Scheme 49).[80]

Scheme 48

dimer **214**

chiral mixed aggregate **215**

optically active product **216**
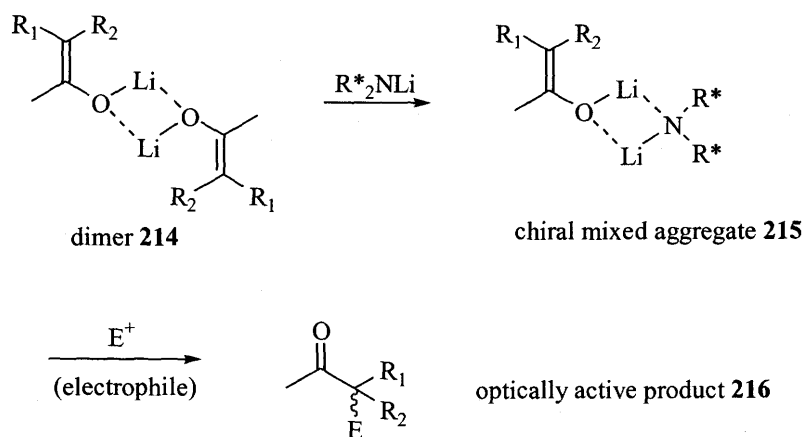
Addition of a chiral lithium derivative e.g., chiral lithium amide to an achiral dimer **214**, can yield a chiral mixed aggregate **215**. A lithium amide breaks the dimer **214** by complexation to the oxygen atom *via* the lithium atom. The faces of complex **215** are diastereotopic and they react at different rates with an electrophile. In principle, it should

be possible to obtain an enantiomerically enriched product **216** from a reaction between two achiral reagents.[80]

Scheme 49

achiral enolate **217**   chiral complex **218**

racemic **216**   optically active **216**
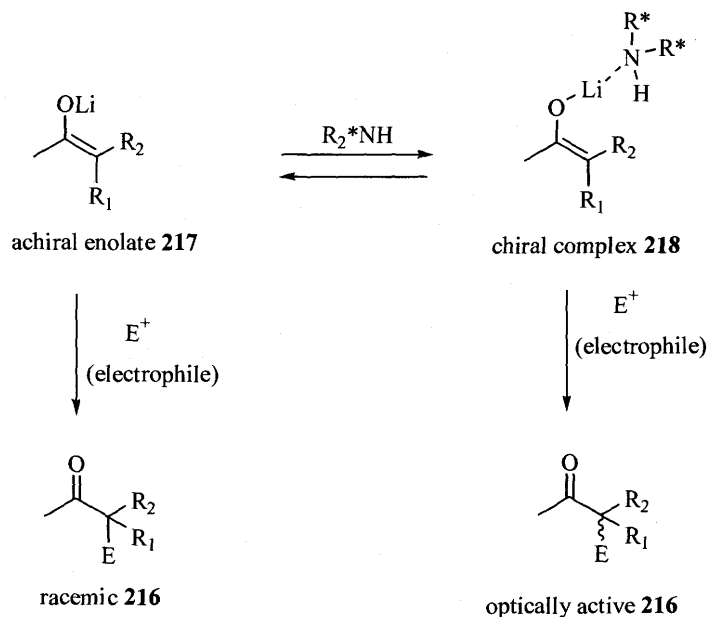
Addition of a chiral secondary amine can also have an effect on a reaction of an achiral enolate **217** with an electrophile. Faces of the enolate **217** are enantiotopic before addition of a chiral amine, and if a chiral environment is not present (solvent or ligand), they would react at the same rate with an electrophile giving racemic **216**. A chiral amine, after addition to the achiral enolate **217**, becomes complexed to the enolate *via* the lithium atom to give complex **218**. The faces of the complex **218** are diastereotopic and they react at different rates with an electrophile so that the optically active product **216** is obtained.[80] In many cases the α-functionalization conditions are chosen in such a fashion that both a chiral lithium amide and a chiral amine are present together with the achiral enolate in the reaction mixture.[80]

The use of chiral additives (chiral amines, lithium amides and alkoxides) in aldol and Michael reactions has been investigated by Seebach's group since the early 1980s.[80] Cyclohexanone (**25**) was used as the model ketone. The enantioselectivity was low with a few exceptions (Scheme 50, Table 20).

Scheme 50
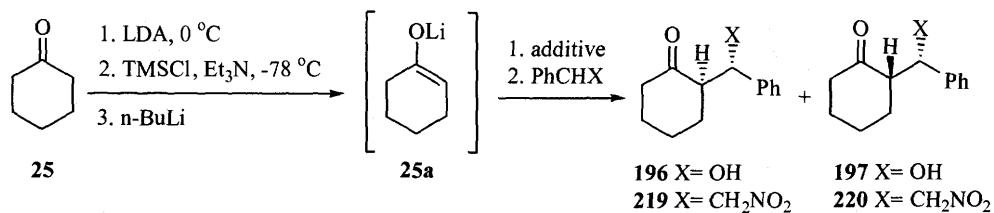
Table 20. The results of Seebach's study (ref. 80).

Entry	PhCHX	Chiral additive	Yield (%)	ee (%)
1	PhCHO		80	34
2	Ph(CH$_2$)$_2$NO$_2$		18	70

Another example of a face selective reaction of cyclic ketones was reported by Koga in 1990.[95] 1-Tetralone (**221**) and cyclohexanone (**25**) were chosen as the model systems. For the purpose of this discussion only the results for 1-tetralone (**221**) are shown (Scheme 51).

Scheme 51
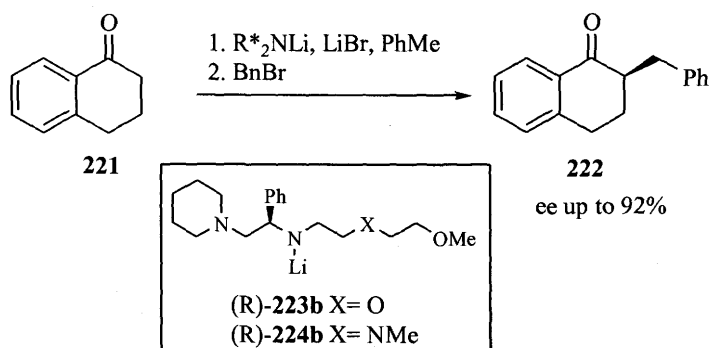
Face selective reactions are not only limited to cyclic ketones. Shioiri[96] and Landais[97] investigated, independently, the aldol reaction of 2,2-dimethyl-3-pentanone (**225**) (Scheme 52). The results of the aldol reaction of **225** with lithium amide **227b** are presented in Table 21, and with lithium amides **228b** and **229b** in Table 22.

Scheme 52
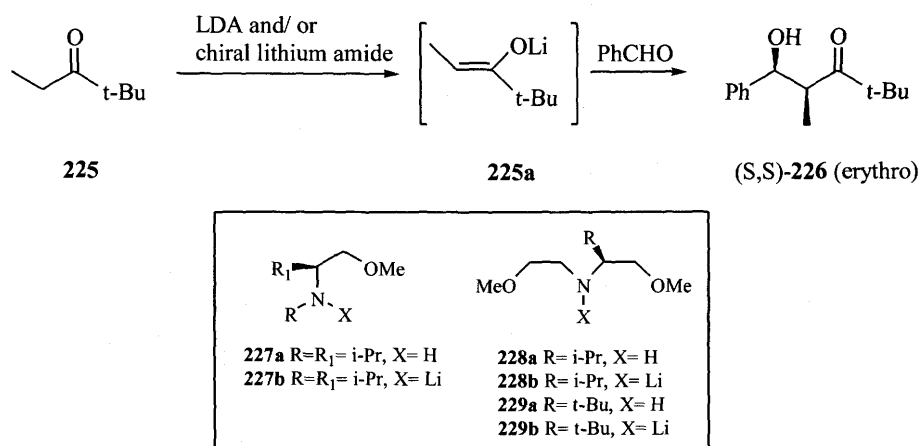
Enolization of ketone **225** with LDA, followed by the reaction with an aldehyde (benzaldehyde in this example) is known to give erythro aldol diastereoselectively.[98]

Table 21. Results of the aldol reaction of ketone **225** with base **227b**.

entry	yield (%)	ee (%)[c]
1[a]	90	18
2	93	68
3[b]	92	47

[a] No LDA was added. [b] n-BuLi was added to **225a** solution before addition of PhCHO. [c] Determined by HPLC with a chiral column and by ^{1}H NMR of (R)-MTPA ester (ref. 96).

When chiral lithium amide **227b** was used without LDA, the aldol **226** was obtained in 90% yield but only 18% ee (Table 21, entry 1). The addition of LDA caused the

enantioselectivity to increase to 68% (entry 2). It was postulate, that LDA acted as the strong base and that the chiral ligand **227b** was more effective than the corresponding amine **227a**.[96]

Table 22. Results of the aldol reactions of ketone **225** with bases **228b** and **229b**.

entry	Lithium amide	TMEDA (eq.)	Yield (%)	ee (%)[c]
1	**228b**	2.4	61	78
2[a]	**228b**	-	58	48
3[a]	**228b**	1.2	60	62
4	**228b**	3.6	58	36
5[b]	**228b**	2.4	59	5
6	**229b**	2.4	57	12

[a] No LDA was added. [b] No n-BuLi was added after formation of **229a**. [c] Determined by HPLC with a chiral column and by ^{1}H NMR of (R)-MTPA ester (ref. 97).

During his work Landais made several interesting observations.[97] The secondary amine **228a** or **229a** or i-Pr$_2$NH formed during the formation of enolate **225a** had to be redeprotonated (Table 22, entry 1 vs. entry 5). Koga and Shioiri observed the same phenomenon in their earlier work.[94, 99] They suggested that a free amine was a poor ligand, when it was not tightly bound to an enolate. Addition of TMEDA (2 eq. for every eq. of a chiral base) before the addition of benzaldehyde increased the ee of the reaction (Table 22, entry 1). When the ratio of TMEDA to a chiral base was different, e.g., more than 2: 1, the enantioselectivity of the aldol reaction of **225** decreased (Table 22, entry 1 vs. entry 4). This trend was explained by the change in the stoichiometry of the mixed aggregate (chiral lithium amide **228b**-lithium enolate **225a**). In the case of the lithium amide **229b** (Table 22, entry 6), the decreased enantioselectivity was explained in terms of formation of the mixed aggregate (chiral lithium amide **228b**-lithium enolate **225a**) that was affected by the steric interaction.

Conclusions:

The deprotonation reaction of cyclic ketones has been studied for more than twenty years.[13] It is a first step to many organic reactions, e.g., hydroxylation, alkylation, Michael, Mannich or Robinson annulation. Very often, these simple reactions are used for the synthesis of complex natural products. It is possible to conduct deprotonation in an enantioselective fashion and obtain up to 95% ee, if a chiral lithium amide is employed. It was established that addition of even small amounts of lithium salts could improve enantioselectivity of deprotonation. These reactions are classified as enantiotopic group selective reactions. It was also shown that it was possible to obtain enantiomerically enriched, α-functionalized ketones, if chiral ligands combined with LDA were used. Those reactions are classified as enantiotopic face selective reactions. Study of both types of reactions was complicated by the fact that lithium enolates and chiral lithium amides form oligomers of different order, e.g., dimers, mixed dimers, tetramers and hexamers. In order to better understand what is going on during enolization of a ketone, followed by a reaction of a corresponding enolate with an electrophile, more research in this area of organic chemistry is needed.

2.A.4. Objectives of the deprotonation project.

In order to better understand the limitations of methods for enolization of a ketone and a reaction of the corresponding lithium enolate with an electrophile, it was decided to study α-functionalization of two cyclic ketones in more detail.

1. To find reagents and conditions for high enantioselectivity and yield of tropinone in order to broaden the scope of the method.

2. To evaluate the effectiveness of several chiral lithium amides as bases in the deprotonation reaction of tropinone followed by the reaction of the corresponding lithium enolate with 2,2,2-trichloroethyl chloroformate.

3. To study the combined effect of different chiral lithium amides and additives in order to find the most effective combination of both reagents.

4. To gain some insight into the effect of a chiral ligand, e.g., a chiral amine or a chiral lithium amide. The enantioselectivity of this reaction is controlled by face selectivity of the enolate-chiral ligand complex. 1,4-Cyclohexanedione monoethylene ketal was chosen as the model system, and two chiral ligands were selected.

2.A.5. The ring-opening of tropinone.

Although many aspects of enolate chemistry can be examined, the two most important variables are: the structure of the chiral lithium amide and the structure of the substrate. Even after several years of enantioselective deprotonation research, it is not possible to reliably choose a chiral base for a C_S symmetric substrate that will give a high ee without much experimentation. Usually, a trial and error study that involves different chiral lithium amides and different additives is required to elaborate conditions for high enantioselectivities and yields.[100] A reaction that was chosen to be the model in my studies of enantioselective deprotonation of a ketone belonging to the C_S symmetry point group was the ring-opening reaction of tropinone (201) (Scheme 53).

Scheme 53
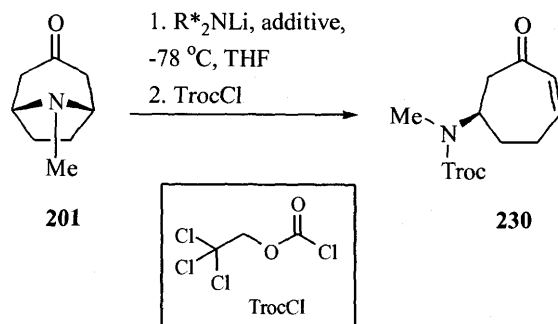
This reaction was developed in our group during attempts to α-functionalize tropinone (**201**) with 2,2,2-trichloroethyl chloroformate (TrocCl). The enone **230** was obtained instead of the expected α-substituted derivative of tropinone. [101] The mechanism of this reaction is interesting but still not fully understood. The preliminary experiments done in our group resulted in the low enantioselectivities.[101] It was decided to optimize conditions for this reaction, so that it could be used for the enantioselective synthesis of tropane alkaloids e.g., 6β– and 7β-acetoxytropanes (**231** and **232**) and physoperuvine (**233**).

231 R= Ac
232 R= Tg

233
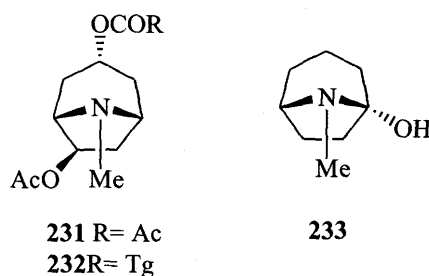
Several chiral lithium amides were used as the bases in the study of the enantioselective deprotonation of tropinone (**201**), structures of which are shown in Figure 14. The lithium amides are shown in the order that they were studied.
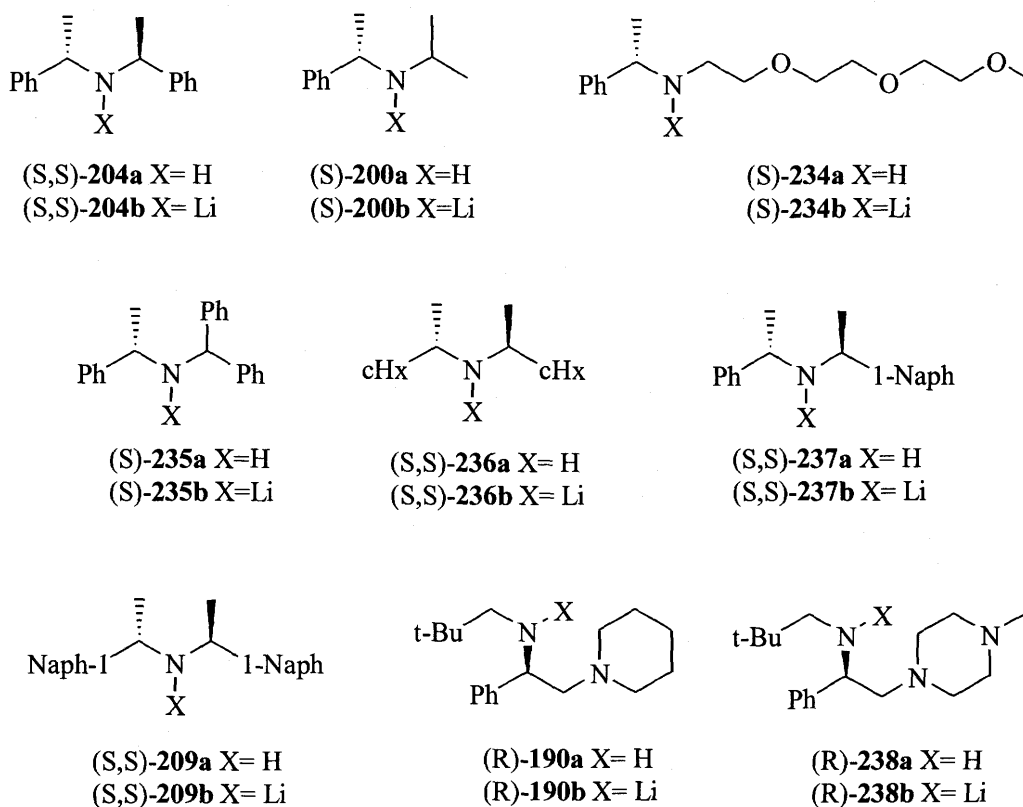
Figure 14. The structures of chiral lithium amides used in the study of the effect of different additives on the selectivity of the deprotonation of tropinone (**201**).

The major product of the reaction was the dextrorotatory enantiomer in all cases. The absolute stereochemistry was established by correlation with anhydroecgonine.[88d]

The starting point of this project was to investigate the effect of lithium chloride on the enantioselectivity of the ring-opening reaction of tropinone (**201**) (Scheme 53). The results are presented in Table 23 and in Figure 15. All the data are presented in Appendix 1. Selected parts of the results are discussed below.

Table 23. The effect of LiCl on the enantioselectivity of the ring-opening reaction of tropinone (**201**).

Entry	Lithium amide	LiCl (eq.)	Yield (%)[a]	ee (%)[b]
1	(S,S)-**204b**	0	70	44
2	(S,S)-**204b**	1[c]	74	93
3	(S,S)-**204b**	1	92	96
4	(S)-**200b**	0	52	29
5	(S)-**234b**	0	98	14
6	(S)-**235b**	0	86	78
7	(S)-**235b**	1	86	87
8	(S,S)-**236b**	0	22	17
9	(S,S)-**236b**	1	60	72
10	(S,S)-**237b**	0	50	48
11	(S,S)-**237b**	1[c]	89	88
12	(S,S)-**209b**	1[c]	71	77
13	(R)-**190b**	0	82	83
14	(R)-**190b**	1	85	95
15	(R)-**238b**	0	80	87
16	(R)-**238b**	1	97	96

[a] Yield after purification of the crude product by flash chromatography. [b] Enantioselectivity was measured on the crude product by HPLC with a Chiralpack AD column and 15% IPA in hexane as the solvent system. [c] Amine hydrochloride salt was used to generate *in situ* the 1:1 Li-amide-LiCl complex.
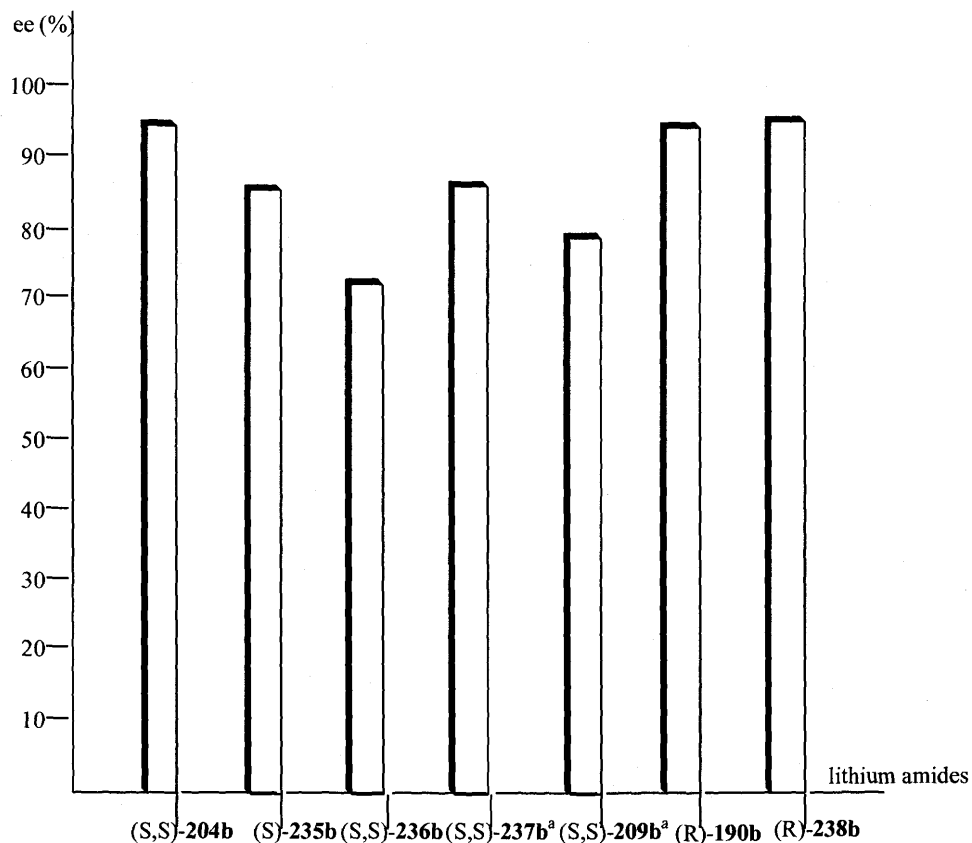
^{a} Amine hydrochloric salt was used to generate the 1: 1 Li-amide-LiCl complex

Figure 15. The effect of 1 eq. of LiCl on the ring-opening of tropinone (**201**) with different lithium amides.

Most of the tested lithium amides gave low enantioselectivity without LiCl (Table 23, entries 1, 4, 5, 8 and 10). The two exceptions were bidenate lithium amides (R)-**190b** and (R)-**238b**, previously developed by Koga[102], which gave the product **230** in 83% ee and 87% ee, respectively. The addition of one equivalent of LiCl prior to enolization resulted in the enhancement of the enantioselectivity when monodenated lithium amides were used, especially lithium amide (S,S)-**204b** (Table 23, entry 3). Lithium chloride had a much smaller effect on the already efficient bidenate lithium amides (R)-**190b** and (R)-**238b**, but it still caused improvement in the enantioselectivity of the ring-opening reaction (Scheme 53). The lithium amide (S,S)-**204b** became the base of choice because the two latter bases were much more difficult to prepare. It was decided to investigate the effect of different amounts of LiCl on enantioselectivity, as well as the effect of other

lithium salts (e.g., LiBr, LiF), and polar co-solvents (e.g., TMEDA, HMPA, DMPU) (Table 24, Figure 16).

Table 24. The results of different additives on the enantioselectivity of the ring-opening reaction of tropinone (**201**) with (S,S)-**204b**.

Entry	Additive (eq.)	Yield (%)[a]	ee (%)[b]
1	-	70	44
2	LiCl (0.1)	84	49
3	LiCl (0.25)	92	85
4	LiCl (0.5)	90	95
5	LiCl (1.0)	92	96
6	LiCl (2.0)	94	95
7	LiBr (0.1)	90	35
8	LiBr (0.25)	82	54
9	LiBr (0.5)	88	63
10	LiBr (1.0)	93	73
11	LiBr (2.0)	85	88
12	CeCl$_3$ (0.1)	94	36
13	CeCl$_3$ (0.25)	82	44
14	CeCl$_3$ (0.5)	24	38
15	CeCl$_3$ (1.0)	71	80
16	ZnCl$_2$ (0.1)	72	80
17	ZnCl$_2$ (0.25)	45	62
18	ZnCl$_2$ (0.5)	40	86
19	ZnCl$_2$ (1.0)	40	90
20	ZnCl$_2$ (2.0)	42	88

[a] Yield after purification of a crude product by flash chromatography. [b] Enantioselectivity was measured on the crude product by HPLC with a Chiralpack AD column.
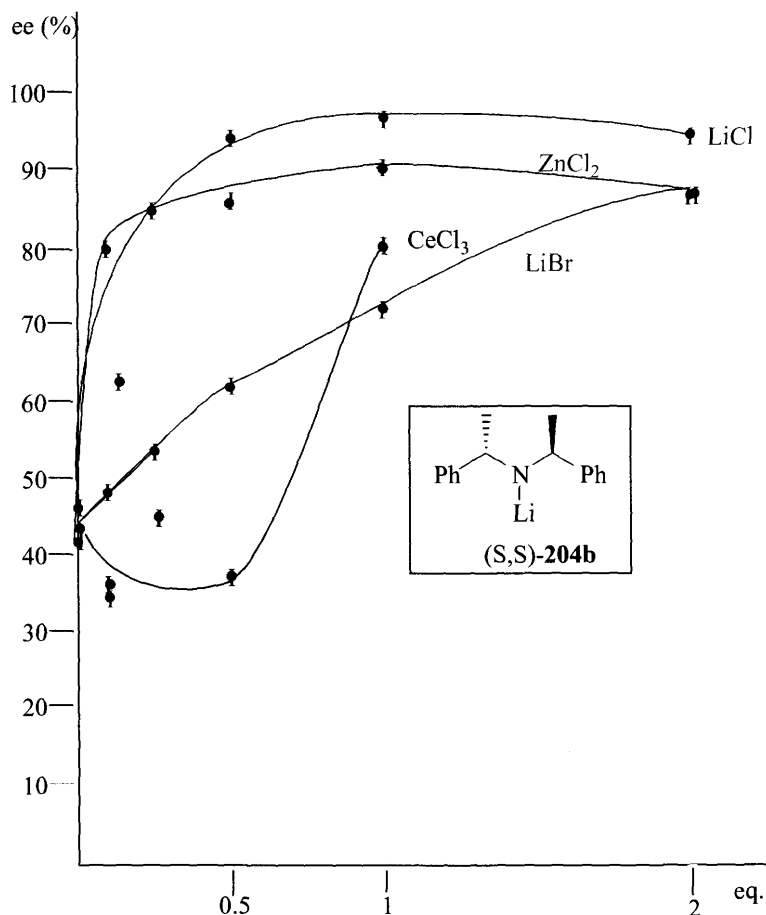
Figure 16. The change of enantioselectivity of the ring-opening of tropinone (**201**) as a function of the addition of increasing equivalents of different additives.

As can be seen from Figure 16 and Table 24 (entries 2 – 11) addition of even a small amount of LiCl or LiBr resulted in a significant increase of the enantioselectivity. The salt effect "wore off" after addition of one (for LiCl) equivalent of the halide. Zinc dichloride showed a salt effect similar to LiCl or LiBr, but it should be noted that all of the experiments with $ZnCl_2$ resulted in a relatively low yield (Table 24, entries 16 - 20).

The comparison between the effects of one equivalent of different additives on the enantioselectivity of the ring-opening reaction of tropinone (**201**) with the C2 symmetric base (S,S)-**204b** is presented in Figure 17.
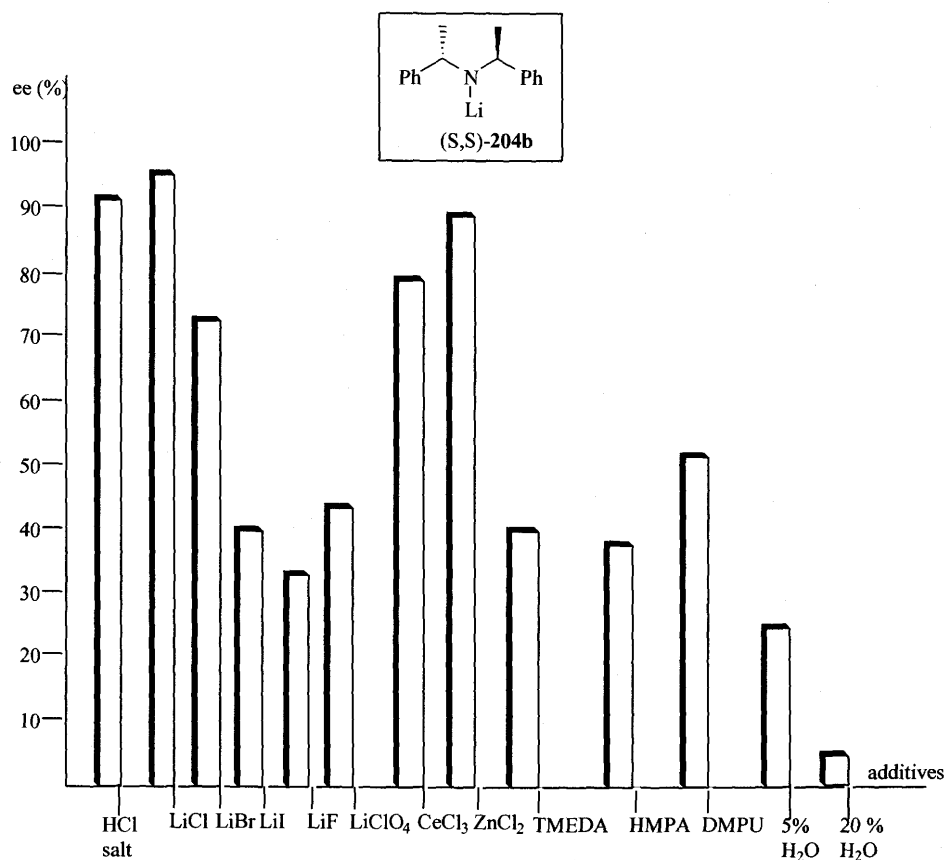
Figure 17. The effects of the addition of one equivalent of different compounds on the enantioselectivity of the ring-opening reaction of tropinone (**201**).

It is known that lithium amides form aggregates.[83 – 86, 102] General structures of such aggregates of lithium amides were shown in Figure 8. After the addition of a lithium salt the chiral lithium amides are believed to exist as mixed dimers.[83 – 86] The increase of the enantioselectivity of the deprotonation (Scheme 53) after the addition of LiCl and LiBr could be explained by assuming that the major mixed aggregate was acting as a more selective deprotonating agent. The differences in the results of the deprotonation with different lithium halides (e.g., LiCl, LiBr and LiI) were attributed to the difference in the position of the equilibrium between the dimer and the mixed dimer formed by a chiral lithium amide. In the case of LiCl the equilibrium was shifted heavily towards the mixed major dimer, LiI on the other hand did not form an appreciable amount of mixed dimer. Other lithium salts LiF, LiClO$_4$, and the polar co-solvents TMEDA, HMPA and DMPU had no effect on the enantioselectivity. It should be noted that the deliberate addition of

water (0.05 mmol or 0.2 mmol), followed by the addition of excess of *n*-BuLi (0.05 mmol or 0.2 mmol), practically destroyed the enantioselectivity and the yield of the reaction.[88d] The water and the excess of *n*-BuLi were added in order to stimulate the presence of LiOH. This could not be explained by the simple fact that some molar amount of the generated enolate was quenched by the addition of water. If 5% or 20% of the enolate were quenched by the addition of 5% or 20% of water than the remaining 95% or 80% of enolate would still react with 2,2,2-trichloroethyl chloroformate and yield the product. This surprising result could be explained by considering that the oligomer composed of the lithium enolate of tropinone-additive became more complexed and less reactive towards the electrophile. The practical observation from these results is that it is not enough to titrate the *n*-BuLi solution prior to use. If the reagent contains large quantities of LiOH, the reaction will not work, despite use of the excess of *n*-BuLi.

A very short study was performed on the lithium amide (R)-**190b**. The results are shown in Table 25.

(R)-**190b**
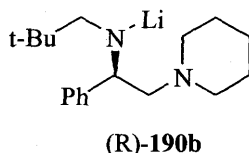
The addition of even 0.1 equivalent of LiCl resulted in an increase of enantioselectivity (Table 25, entry 2) with the maximum value of 99% at 0.25 equivalent of LiCl (entry 3). The addition of HMPA had no effect on the enantioselectivity (Table 25, entries 7 – 11), and the addition of water resulted in the loss of both the yield and the enantioselectivity (entries 12 and 13).

Table 25. The results of the ring-opening of tropinone (**201**) (Scheme 53) with (R)-**190b**.

Entry	Additive (eq.)	Yield (%)[a]	ee (%)[b]
1	-	82	83
2	LiCl (0.1)	67	94
3	LiCl (0.25)	82	99
4	LiCl (0.5)	86	94
5	LiCl (1.0)	85	95
6	LiCl (2.0)	79	94
7	HMPA (0.1)	91	81
8	HMPA (0.25)	57	80
9	HMPA (0.5)	74	86
10	HMPA (1.0)	56	86
11	HMPA (2.0)	49	85
12	H_2O (0.2)	8	6
13	H_2O (0.2), LiCl (1.0)	8	10

[a] Yield after purification of the crude product by flash chromatography. [b] Enantioselectivity was measured on the crude product by HPLC with a Chiralpack AD column.

Conclusions:

It was shown that tropinone (**201**) could be deprotonated with a chiral lithium amide to give the corresponding lithium enolate in moderate (for monodenate chiral lithium bases) to good (for bidenate chiral lithium amides) enantioselectivity. Different additives were studied including lithium salts (LiF, LiCl, LiBr, LiI and $LiClO_4$), $ZnCl_2$, $CeCl_3$, and organic co-solvents (HMPA, DMPU and TMEDA), but LiCl gave the best results. Addition of even a small amount of LiCl increased the enantioselectivity of the deprotonation reaction with all chiral bases. The best combination of base and additive

proved to be the C2 symmetric chiral lithium amide (S,S)-**204b** with one equivalent of LiCl. The enolate of tropinone was generated with this set of reagents, and trapped with 2,2,2-trichloroethyl chloroformate. The product **230** was obtained in 92% yield and 96% ee. The ring-opening reaction of tropinone could now be used in the enantioselective synthesis of tropane alkaloids e.g., 6β- and 7β-acetoxytropanes (**231** and **232**) and physoperuvine (**233**).

2.A.6. Studies of deprotonation of 1,4-cyclohexanedione monoethylene ketal.

It should be noted that the enantioselectivity in the deprotonation reaction of the cyclic ketones with C_S symmetry is a sum of two effects:

1. Differentiation between the two axial α-hydrogens that are enantiotopic by a chiral lithium amide (Scheme 39, R_1= alkyl, allyl or aryl). Two complexes **180** and **181** are not formed in a 1: 1 ratio. An enantiomerically enriched product is formed after a reaction of these complexes with an electrophile.

2. After the deprotonation step is completed the chiral amine remains complexed to the enolate *via* the lithium atom (Scheme 39, R_1= alkyl, allyl or aryl). The faces of the complexes **180** or **181** became diastereotopic, and they react at different rates with an electrophile giving one of the enantiomers **176** or **177** in excess.

In most cases, it seems that when a researcher deprotonates a ketone and obtains the α-functionalized product in high yield and enantioselectivity, often not wondering what was the cause of the result (the first effect or the second one, or the sum of both). When I started this project, there were only a couple of precedents in the literature showing that the complexation of a chiral amine to the enolate was enough to introduce enantioselectivity into the final product. I decided to investigate this hypothesis in more

detail. The compound of choice for this study was 1,4-cyclohexanedione monoethylene ketal (239), with "average symmetry" of C_{2v}.[78, 103] Deprotonation of ketone 239, followed by a reaction with an electrophile is presented in Scheme 54.

Scheme 54

239   242

240   241
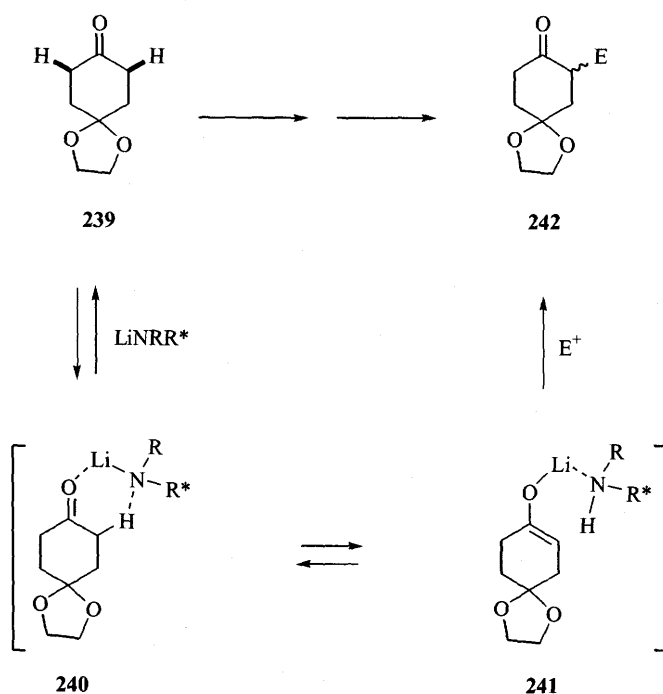
The axial α-hydrogens in ketone 239 are homotopic, so the chiral lithium amide will not differentiate between them. The base can abstract either of them giving only complex 241 as the result. The faces of the complex 241 are diastereotopic. They would react at different rates with an electrophile, and the optically active product 242 could be obtained.

The ketone 239 was deprotonated with the two chiral lithium amides (S,S)-204b and (S)-200b. The corresponding enolate was "trapped" with benzaldehyde (Scheme 55, Table 26).

Scheme 55
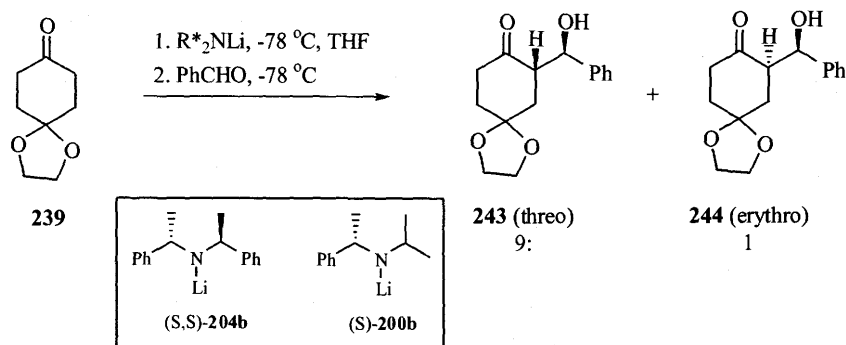
The geometry of the enolate formed in this reaction is E. The major product of the aldol reaction of **239** is threo-aldol **243**. It can be rationalized from the Zimmerman-Traxler model.[104] The enantioselectivity was measured by ^{1}H NMR with shift reagent Eu(tfc)$_3$. The results are presented in Table 26. The relative stereochemistry of product **243** was determined by the literature method.[105] The absolute stereochemistry is not known.

Table 26. The results of the deprotonation reaction of **239**.

Entry	Lithium amide	Yield (%)	ee (%)
1	(S,S)-**204b**	85	14
2	(S,S)-**204b**	85	14
3[a]	(S,S)-**204b**	80	13
4[a]	(S, S)-**204b**	79	13
5	(S)-**200b**	50	6
6	(S)-**200b**	53	8
7[a]	(S)-**200b**	40	6
8[a]	(S)-**200b**	45	7

[a] An additional equivalent of n-BuLi was added to the reaction mixture before the addition of PhCHO.[93]

The addition of a second equivalent of n-BuLi prevents the "internal proton return" phenomenon.[107] This phenomenon is depicted in Scheme 56.

Scheme 56
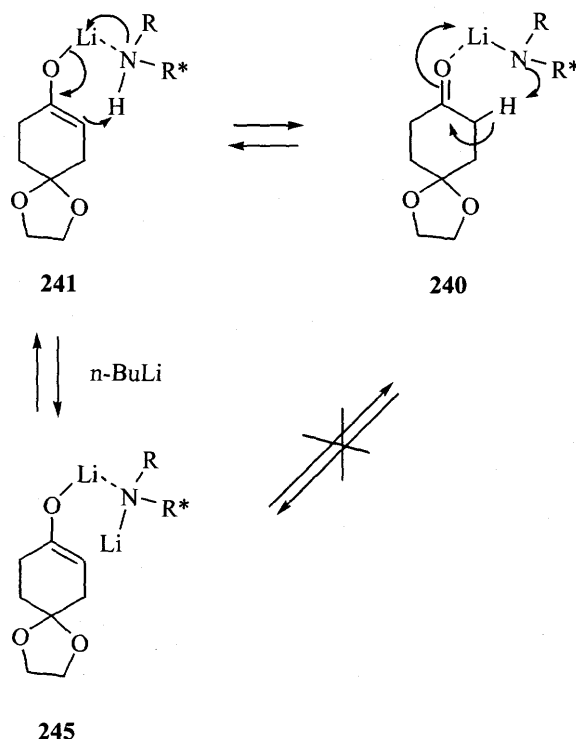
241   **240**

n-BuLi

245

After the deprotonation step is completed, the chiral amine remains complexed to the enolate. The chiral amine can act as the proton donor, and intramolecular proton transfer can take place, in which case the equilibrium between complex **241** and complex **240** is established. If the proton transfer is rapid, it can diminish the yield and the selectivity of the reaction of the enolate with an electrophile. After addition of a second equivalent of n-BuLi, the chiral amine is transformed into the lithium amide, which can still remain complexed to the enolate (complex **245**), but the proton transfer is not possible anymore, and the yield and the selectivity should be improved.

To avoid a "proton transfer" between the enolate and the complexed chiral amine, the enolate can be generated from the corresponding silyl enol ether. The synthesis of silyl enol ether **246** is shown in Scheme 57.

Scheme 57

239 → **246**

1. LDA, -78 °C, THF
2. TMSCl, Et₃N, -78 °C
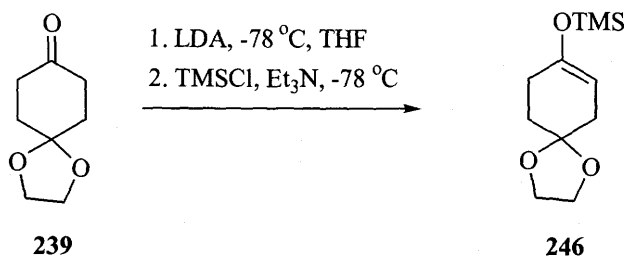
The enolate formed in this reaction was trapped with TMSCl. The silyl enol ether **246** was separated from the reaction mixture and purified before the conversion to the "amine-free enolate". The phrase "amine-free enolate" means that the chiral amine is no longer coordinated to the lithium enolate. As mentioned before, a chiral amine and a chiral lithium amide can also be used as the chiral additives. The aldol reaction of the silyl enol ether **246** is shown in Scheme 58.

Scheme 58

246

1. n-BuLi, THF, -78 °C
2. chiral additive
3. PhCHO

243 (threo)   +   **244** (erytrho)

Chiral additives:

(S,S)-**204a** X= H
(S,S)-**204b** X= Li

(S)-**200a** X= H
(S)-**200b** X= Li
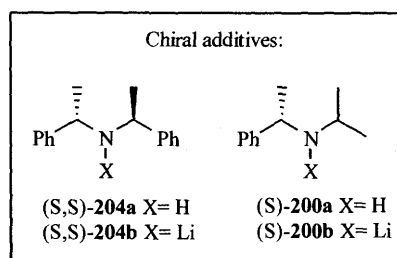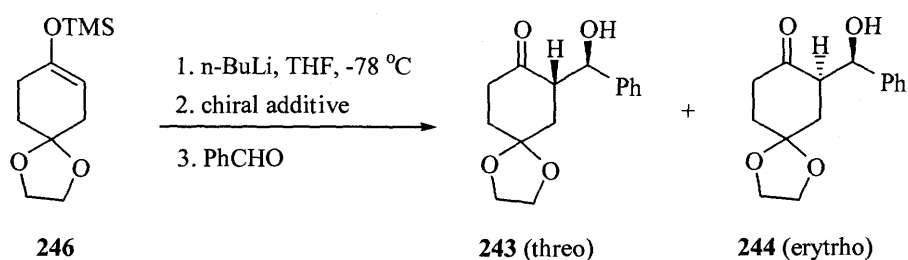
The "amine-free enolate" can also be generated with n-BuLi instead of MeLi.[106] The major product of this reaction is aldol **243**. The enantiomer ratio of **243** was calculated by ¹H NMR with chiral shift reagent Eu(tfc)₃. The diastereoselectivity, which was not the

main subject of my study showed an interesting trend (Table 27). The enantioselectivity of the aldol reaction of **246** (Scheme 58) is presented in Table 28.

Table 27. The diastereoselectivity of aldol reaction of the compound **246**.

entry	Additive	Ratio **243: 244**
1	-	99: 1
2	(S,S)-**204a** or (S)-**200a**	94: 6
3	(S,S)-**204a** or (S)-**200a** and 1 eq. of n-BuLi	84: 16
4	(S,S)-**204b** or (S)-**200b**	84: 16

Table 28. The results of the aldol reaction of silyl enol ether **246**.

Entry	Chiral additive	Yield (%)	ee (%)
1[a]	(S,S)-**204a**	60	15
2	(S,S)-**204b**	69	14
3	(S,S)-**204a**	77	14
4	(S,S)-**204a**	81	13
5[a]	(S)-**200a**	55	6
6[a]	(S)-**200a**	50	5
7	(S)-**200b**	65	6
8	(S)-**200b**	60	7
9	(S)-**200a**	75	4
10	(S)-**200a**	76	4

[a] An additional equivalent of n-BuLi was added before the addition of benzaldehyde.[93]

The results presented in Table 28 show that for the amine (S,S)-**200a** enantioselectivity of the aldol reaction of the silyl enol ether **246** was between 4% and 7% (entries 5 – 10), and

the enantioselectivity for amine (S)-**204a** (entries 1 – 4) was slightly better. The same trend was observed when ketone **239** was used as the starting material in the aldol reaction (Scheme 55; Table 26, entries 1 – 4 vs. 5 – 8).

2.A.7 Conclusions

The lithium enolate of 1,4-cyclohexanedione monoethylene ketal (**239**) was obtained using two different methods: from **239** by deprotonation (LDA and two chiral lithium amides) and from silyl enol ether **246**. Chiral ligands (S)-**200a**, (S)-**200b**, (S,S)-**204a** and (S,S)-**204b** were added to the solution of the lithium enolate before the addition of benzaldehyde, and enantiomerically enriched aldol **243** was obtained as a result. The enantioselectivity of this reaction was low (between 15% and 4%). It was shown that the effect of complexation of a chiral ligand to an achiral enolate was small, and can be neglected when considering enantioselective α-functionalization of cyclic ketones.

Part B: Polymer-supported chiral lithium amides

2.B.1. Introduction

A continuing challenge in developing chemistry that involves reactants on solid support (Solid Phase Synthesis (SPS) for insoluble polymers, and Liquid Phase Synthesis (LPS) for soluble resins) is to elaborate solution phase reactions to work well on the resin.[26, 27, 33, 63 – 65, 107 – 114] As confidence in the generality of solid phase chemistry grows, more challenging aspects of synthetic chemistry such as asymmetric synthesis are being developed in the SPS and LPS context.[47, 58, 59, 115 – 122, 163] One aspect of asymmetric synthesis, which had not been investigated before my project was started, involves the use of polymer-supported bases to generate lithium enolates. Chiral amines are among the most commonly used species in the synthesis of enantiomerically pure compounds (EPC synthesis).[13, 27c, 123] They are used in many chemical reactions as the resolving agents, chiral ligands, catalysts, reagents and auxiliaries. Chiral lithium amides derived from the corresponding amines are widely used in the deprotonation reaction of carbonyl compounds and in ring-opening of epoxides. Deprotonation of ketones is the first step in many organic reactions, e.g.: aldol, Michael, Robinson and alkylation. These processes are among the most popular reactions for the formation of carbon skeletons during the syntheses of complex natural products.[13]

Our group has been interested in the development of chiral lithium amide bases for several years.[13] Elaborating the synthesis of chiral lithium amides supported on a resin seemed like an attractive idea due to a potential connection to SPS and LPS. It should be noted that applications of substrates and reagents on a solid support are not limited to combinatorial chemistry (c.f., the literature review section). There are a number of potential benefits, which could arise from using such reagents including easy recovery of expensive chemicals, easier control of environmental contamination, new chemical reactor design, etc.[27, 33, 63, 108, 109, 111]

2.B.2.Objectives of the polymer project:

When the project was initiated it was decided:

1. To synthesize a number of chiral amines on a polymer support.
2. To transform these chiral amines into the corresponding chiral lithium amides and to test them as deprotonating reagents on a model system.

It was not clear if solid-phase and liquid-phase chemistry would be compatible with highly reactive reagents like n-butyllithium or carbanions. Fortunately, no major problems on this score were encountered. The synthesis of all chiral amines on solid support will be described first, although in reality synthesis of each amine was followed by brief testing, which led to suggestion of another amine, etc.

2.B.3. Synthesis of chiral amines on an insoluble polymer support.

As mentioned before, at the time that this project was started, there was no information in the literature on the synthesis of chiral secondary amines supported on an insoluble resin. Reactions involving polymers, such as connection of new fragments containing functional groups to the polymer backbone are significantly different from the reactions in solution. As the result, even if the reaction in solution is well described and easy to perform, development of an analogous reaction involving polymeric reagents might be difficult. Two general methods for the synthesis of chiral amines were developed: (i) direct attachment of a chiral amine to a solid support, and (ii) attachment of a chiral amine to a solid support *via* a linker.

Chloromethyl polystyrene **12** (200-400 mesh) was chosen as the solid support for the initial studies. The general method elaborated for the direct attachment of a chiral amine to the resin is shown in Scheme 59.

Scheme 59
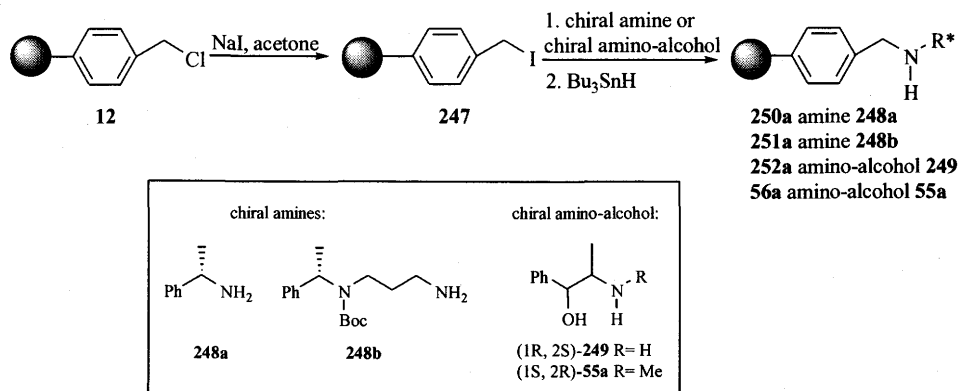
It is known from classical chemistry that benzyl iodide is more reactive than benzyl chloride in substitution reactions (I^- is a better leaving group than Cl^-).[76] The replacement of chlorine in **12** with iodine was done using the Finkelstein reaction. The loading (i.e. mmol of iodine per 1g of the resin) for polymer **247** was not determined at this step. Next, N-alkylation of chiral primary amines (**248a** and **248b**) and amino-alcohols (**249** and **55a**) was performed. The primary amine was used in excess in order to avoid overalkylation of **247** and formation of tertiary amines or quaternary ammonium salts. One has to remember that in a synthesis conducted on a solid support it is not possible to separate the attached product from the impurities and, because of that, the reaction conditions have to be carefully chosen. After the reaction was completed, the resins (**250a – 252a** and **56a**) were separated by filtration, washed with the following solvents: THF, MeOH, MeOH: H_2O (1: 1), H_2O, NaOH, H_2O, MeOH, Et_2O, and dried under high vacuum to constant weight. The polymers swelled in THF and Et_2O, but did not in polar protic solvents like MeOH or H_2O. First, the resins **250a – 252a** and **56a** were washed with the swelling solvents, so some of the impurities that had been absorbed could be removed. The wash with THF was followed by a wash with a solvent, which did not have good swelling properties (MeOH and/or H_2O). The structures of the amines are shown in Figure 18.

250a X= H
250b X= Li

251a X= H
251b X= Li

(1R, 2S)-**252a** X=R= H
(1R, 2S)-**252b** X= Li, R= Li
(1S, 2R)-**56a** X= Me, R= H
(1S, 2R)-**56b** X= Me, R= Li
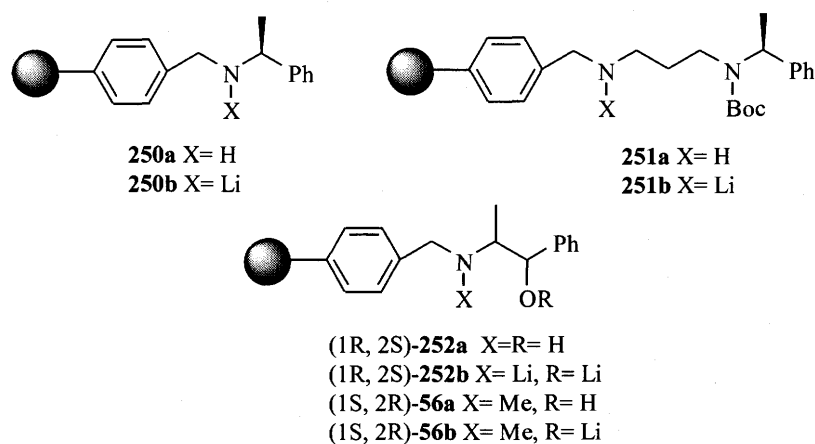
Figure 18. Structures of polymer-supported, chiral secondary amines attached to Merrifield resin (the shaded ball represents the insoluble polymer).

Next, a method for the determination of the amount of nitrogen in the polymer-supported reagents had to be elaborated. This was necessary in order to use the correct amount of n-BuLi during generation of the corresponding, polymer-supported chiral lithium amides. It was decided to try the Volhard titration method first.[124] This method is normally used for titration of Ag^+ ions. To determine the concentration of Cl^-, back titration was necessary. First, a known amount of standard HCl was added to the polymer-supported amine sample, which gave the corresponding salt. The Cl^- ions not trapped by the amine moieties, were precipitated by addition of a known excess of a standard solution of $AgNO_3$. The AgCl precipitate was isolated, and the excess of Ag^+ ions was titrated with a standard solution of KSCN in the presence of Fe^{3+} as the indicator. The end point was indicated by the formation of a deep red complex of $FeSCN^{2+}$. After several trials, it was found that HCl was being incorporated into the polymer matrix (the measured loading of the resin **250a** was much higher than the Cl loading of the original Merrifield resin **12**). This absorption of HCl on the polymer was confirmed by several "blind titration" experiments, i.e., the commercially available Merrifield resin **12** was treated with a known amount of the standard HCl, the resin was separated by filtration, and the filtrate was titrated using the Volhard method. Overall, the Volhard method, which necessitated treatment of the polymer with HCl, was not effective.

Another method was then tried, the Fajans titration method, which relied on the analysis of SO_4^{2-} ions.[124] A known excess of a standardized solution of H_2SO_4 was added to a sample of the polymer-supported chiral amine. The amine groups reacted with the SO_4^{2-} ions to form the salt, and then the unreacted sulfate anions were titrated with $Ba(OH)_2$ in the presence of alizaryn red S as the indicator. This method allowed for a reasonably accurate determination of the amine loading.[124]

The third method used for the determination of the nitrogen content in polymeric amines was elemental analysis. The loading values of all insoluble, polymer-supported amines are presented in Table 29.

Table 29. Nitrogen loading of chiral amines on insoluble polymer.

Entry	Amine	Loading (mmol of NH/g)	Yield (%)[a]
1	**250a**	0.604	60
2	**251a**	0.485	45
3	**252a**	1.257	63
4	**56a**	1.064	97
5	**260a**	0.636	59
6	**261a**	0.707	42
7	**264a**	0.414	38
8	**265a**	0.536	49

[a] Yields correspond to the molar ratio of nitrogen in the final resin to chlorine in the commercially available resin (Merrifield resin **12**), which was used for the synthesis of the specific polymeric amine. The value of the initial loading of the Merrifield resin **12** is given in the Experimental Section.

After the loading determination, it became clear that the N-alkylation reaction did not go to completion. Since halide groups on the polymer could interfere with the next step of the reactions (generation of polymer-supported chiral lithium amides), a dehalogenation procedure was performed according to the method described by Leznoff.[37b] During the work on methylation of the polymer-supported imines **25a** – **c** derived from

cyclohexanone (**25**) and the polymer-supported primary amines **15a – c** (Scheme 9), Leznoff noticed that the presence of unreacted chloride was interfering with the course of the reaction, and lowering the enantioselectivities. However the nature of this interference was not explained.[37a, b] In our case, the remaining alkyl halide moieties could react with *n*-BuLi that was added to the suspension of a polymeric amine in THF in order to generate the lithium amide causing the amine-amide conversion to be incomplete. It is known that Bu_3SnH acts as a hydrogen donor in the radical dehalogenation of alkyl halides,[125] so an excess of Bu_3SnH solution was added to the suspension of polymer **250a** in THF in order to remove the unreacted alkyl halide groups.

One question that should be addressed here is how one could monitor a SP reaction. Normal techniques like TLC cannot be used, the interpretation of IR spectra is troublesome because of the adsorption bands from the polymer backbone, and also NMR spectroscopy usually does not give clear answers. The signals prevailing in the ^1H NMR, and ^{13}C NMR spectra result from the polymer backbone. A literature search revealed that the presence of amino groups attached to a polymer could be detected by a reaction of the resin with a solution of bromophenol blue.[109] This method was developed by Lam and co-workers in order to monitor a coupling reaction of aminoacids. A library of insoluble, polymer-supported tetrapeptides with free terminal amino groups was treated with a solution of bromophenol blue, which made the beads uniformly colored. A sample of the library (ca. 20,000 beads) was placed on a Petri dish under the microscope, and a solution of Fmoc-Val-OH, HOBt and DIC was added. Progress of the reaction was observed by monitoring the color change of individual beads.[109]

In the present study, the commercially available Merrifield resin **12** and the polymer-supported amine **250a** were treated with bromophenol blue solution in EtOH. The beads were mixed with the dye for several hours, separated by filtration, washed with the usual cocktail of solvents (i.e., THF, EtOH, H_2O, EtOH, MeOH), and dried to constant weight under high vacuum. Next, the samples were put under a microscope and pictures were taken (Figure 19).
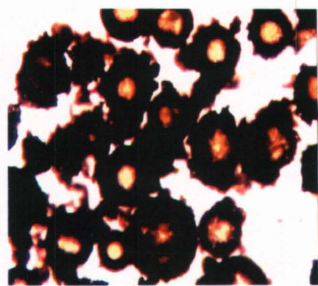
(a)   (b)

Figure 19. (a) Merrifield resin after mixing with a solution of bromophenol blue (beads remained yellow). (b) Resin **250a** after mixing with a dye solution. The presence of amino groups is indicated by a color change from yellow to blue.

The amine **248b** needed for the synthesis of resin **251a** is not commercially available and had to be synthesized in solution (Scheme 60). The resin **251a** is the precursor for the chiral lithium amide **251b** that could have chelating properties.

251b
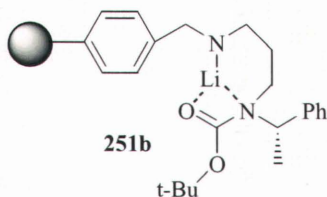
Scheme 60
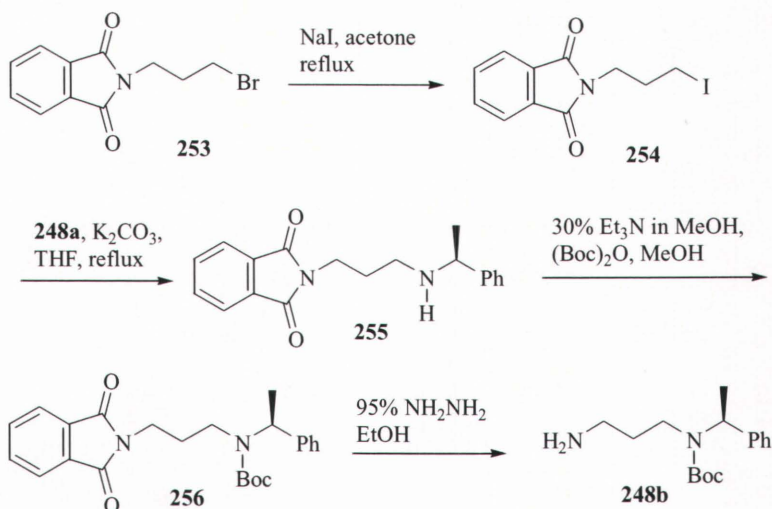
The bromine in the alkyl halide moiety present in compound **253** was replaced by iodide using a Finkelstein reaction, which was followed by reaction with (*S*)-(α)-methylbenzyl amine (**248a**). The NH group in the resulting amine **255** was protected with (Boc)$_2$O, and the phthalimide protective group was cleaved with hydrazine giving the amine **248b** in 30 % yield.

After development of the method for the synthesis of secondary amines directly attached to the polymer (the phrase "directly attached" is used throughout this thesis to describe a situation where no linker was used; for cases involving linkers *vide infra*), it was decided to explore this chemistry further in order to generate some structurally different chiral amines. It had been shown in our laboratory that the structure of chiral bases had a dramatic effect on the selectivity of deprotonation of cyclic ketones.[2, 12, 13] These studies had been performed in solution and are referred to as the "solution phase chemistry". The difference between "solid-phase", "liquid-phase" and "solution-phase" chemistry was discussed by Janda in his seminal paper in 1997.[63]

When polymer-supported reagents are used most of the reacting groups are situated inside a polymer bead. These reacting sites are not easily accessible to reagents in solution, but the situation can be improved by distancing the reactive groups from the rigid polymer matrix by a linker. The work with linkers initiated in this study can be divided in two groups: (i) a linker is first attached to the polymer, followed by the reaction of a resulting modified resin with a chiral amine, and (ii) the chiral amine containing a linker is first synthesized in solution, followed by its attachment to the resin.

Selection of the proper linker can be critical to the success of SP chemistry.[27, 63, 108 – 111, 167] Initially, two simple linkers derived from 1,3-propanediol (**257**) and 1,6-hexanediol (**59**) were used. They were attached to the polymer-supported benzyl chloride **12** by a modified literature method (Scheme 61).[44b]

Scheme 61
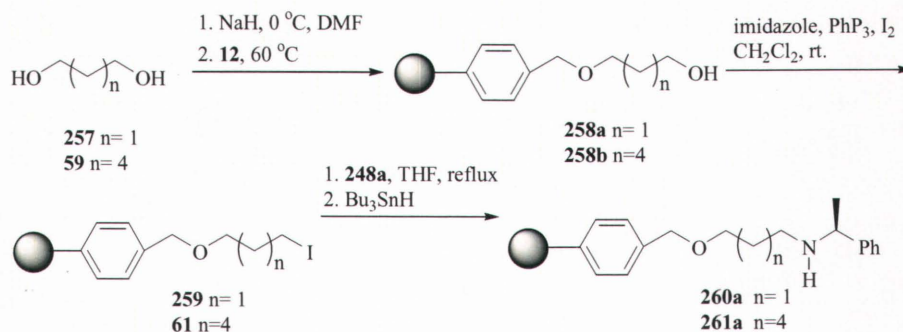
The linkers were attached to the polymer-supported benzyl chloride **12** by O-alkylation, followed by functional group manipulation using methods well known in the context of the reactions in solution.[126] Polymer-supported amines **260a** and **261a** were obtained by simple N-alkylation of (S)-(α)-methylbenzyl amine (**248a**) with the iodides **259** and **61**, respectively. The loading of the resulting resins (**260a** and **261a**) was determined by elemental analysis and is shown in Table 29 (entry 5 and entry 6).

The presence of the amino group in compound **261a** was detected by the reaction of **261a** with bromophenol blue (Figure 20).

(a)   (b)
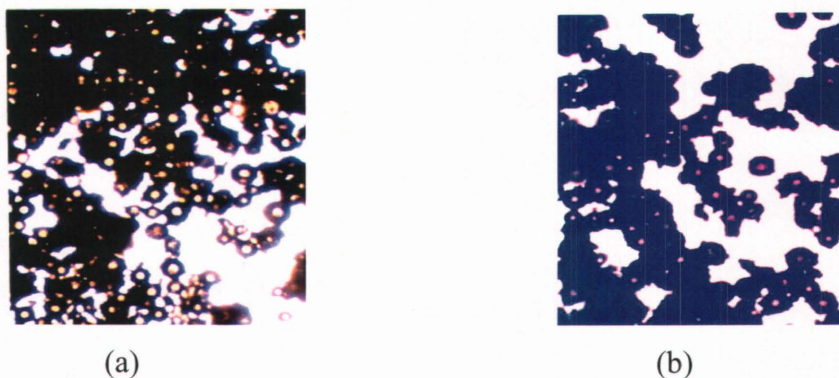
Figure 20. (a) Merrifield resin after mixing with a solution of bromophenol blue (yellow). (b) Resin **261a** after mixing with a dye solution. The presence of the amino groups is indicated by a color change from yellow to blue.

The last method that was invented for the synthesis of chiral secondary amines attached to the resin is shown in Scheme 62. In this method chiral amino-alcohols were

used as the starting materials. Ideally, the amino-alcohols should be commercially available or easy to synthesize in high yield. There were some precedents in the literature of chiral amino-alcohols attached to an insoluble polymer and used as catalysts for addition of diethyl zinc to aldehydes.[43 - 47,118] The compounds described in the literature were attached either by N-alkylation[43, 44] or, in the case of a tertiary amino group, by O-alkylation.[47, 118]

Scheme 62
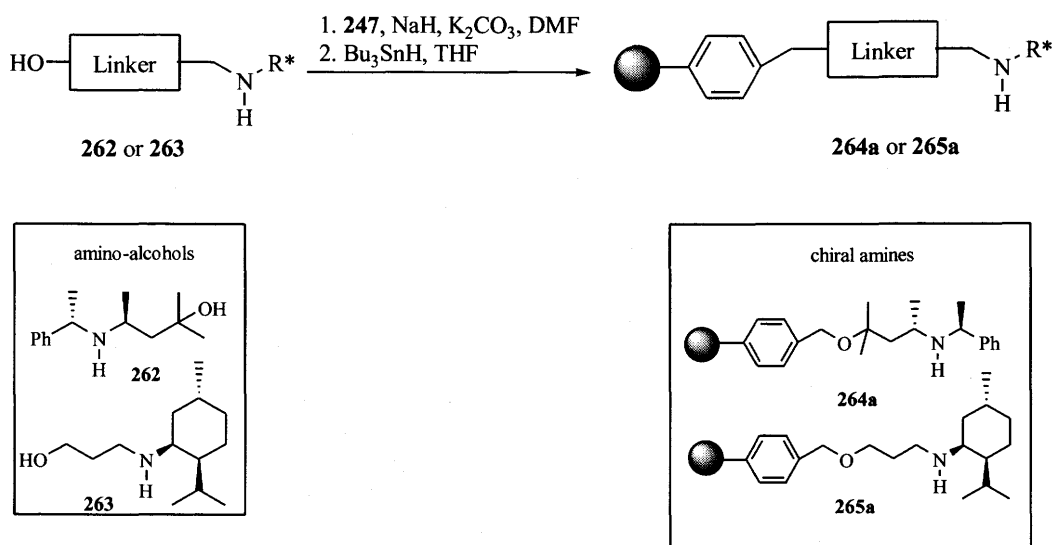
Amino-alcohols **262** or **263** were attached to the insoluble polymer by O-alkylation of the corresponding alkoxides with the polymer-supported benzyl iodide **247**. The loading of polymers **264a** and **265a** was determined by elemental analysis and is shown in Table 29 (entries 7 and 8).

Compounds **262** and **263** used in these studies were synthesized by the reductive amination method (Scheme 63).

Scheme 63
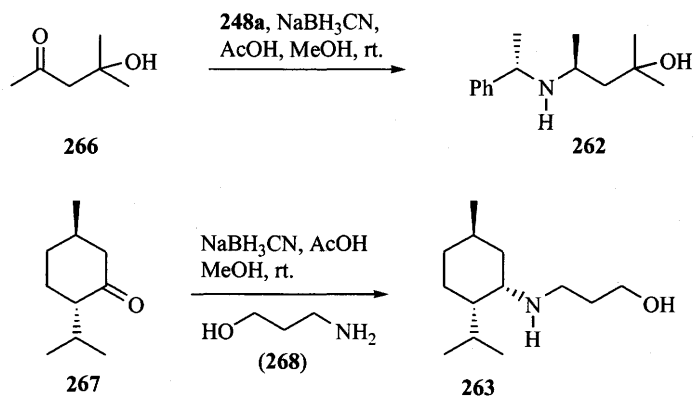
In summary, three general methods for the synthesis of chiral secondary amines supported on Merrifield resin were developed, and a variety of polymer-supported reagents **250a** – **252a**, **56a**, **260a**, **261a**, **264a** and **265a**, were synthesized. A method for the determination of the nitrogen content in a polymer-supported amine (loading) was elaborated.
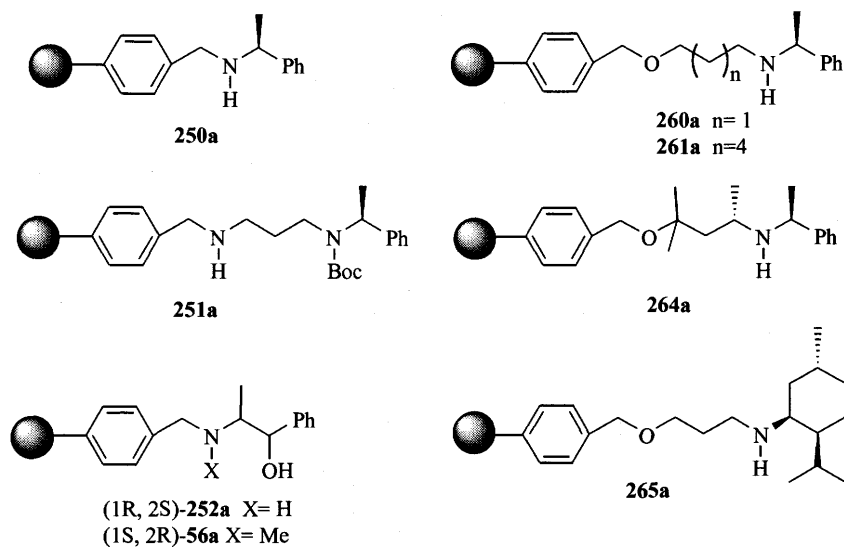
2.B.4. Synthesis of chiral amines supported on a soluble polymer.

The first problem that had to be addressed was the choice of the soluble polymer that would suit the conditions of generating the chiral lithium amides from the polymer-supported chiral amines. The most popular soluble polymer is polyethylene glycol (PEG).[63] It is soluble in a wide range of organic solvents and in water, but it is not soluble in hexane, Et$_2$O, t-butyl methyl ether and THF at low temperatures, typical of solvents used for the generation of lithium amides. The solubility of PEG in H$_2$O eliminates the aqueous workup of a reaction, which is a desirable feature in this project. One of the byproducts formed in the α–functionalization of cyclic ketones, when chiral lithium amides are used in a deprotonation step, are lithium salts. They are removed in the aqueous extraction of a reaction mixture with water and an organic solvent. The soluble polymer of choice was the non-cross-linked co-polymer of styrene and chloromethyl styrene **145** (Scheme 64).[113] The chlorine moiety in this polymer was easily exchanged to iodine by the Finkelstein reaction yielding the compound **270** (Scheme 64).

Scheme 64
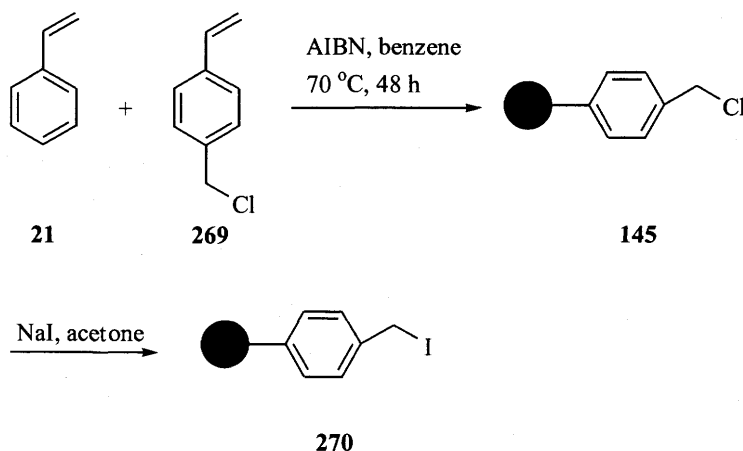
Compound **145** was chosen as the soluble support because of the following factors: it can be prepared from the commercially available starting materials in an inexpensive way, it is soluble in commonly used organic solvents such as: THF, CH$_2$Cl$_2$, CHCl$_3$, AcOEt, and benzene, even at low temperatures, and it is insoluble in MeOH and H$_2$O. The reaction

products can be purified using aqueous extraction and polymer precipitation. Attached compounds can be characterized by conventional methods (^{1}H-NMR and ^{13}C-NMR spectroscopy can be performed in solution because the resin is soluble in most organic solvents), and the loading can be controlled by a designing the synthesis.[127] Polymer **273** was used as the support in a direct attachment of chiral amines, when the reaction of a chiral amine with polymer **145** resulted in a low loading.

Chiral amines were attached to polymer **145** or **270** according to two general methods described before: (i) direct attachment of a chiral amine to polymer **145** or **270**, (ii) a linker was attached to polymer **145** or **270** first, followed by the reaction of the modified resin with a chiral amine.

A general method for the direct attachment of chiral amines to polymer **145** or **270** is shown in Scheme 65.

Scheme 65

145 Hal= Cl or **270** Hal= I

271a amino-alcohol **55a**, Hal= Cl
272a amino-alcohol **275**, Hal= Cl
273a amine **248a**, Hal= I
274a amine **276**, Hal= I

chiral amino-alcohols:

(1R, 2S)-**55a**   (1S, 2S)-**275**

chiral amines:

248a   **276**
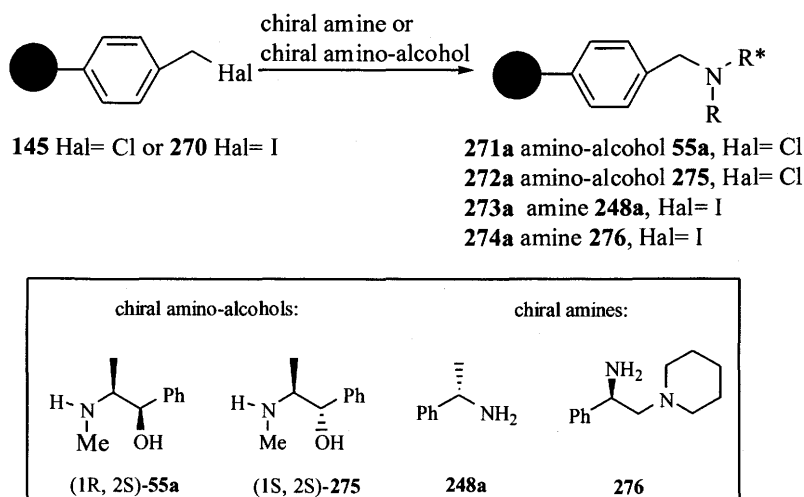
Chiral amino-alcohols *(1R,2S)*-**55a** or *(1S,2S)*-**275**, and chiral amines **248a** and **276** were attached to the soluble polymer-supported benzyl chloride **145** (for **55a** and **275**) or benzyl iodide **270** (for amines **248a** and **276**) by N-alkylation. The compounds **55a**, **275**,

248a, and **276** were added to the polymers **145** and **270** in an excess in order to avoid overalkylation leading to tertiary amines or quaternary ammonium salts. All reactions were easy to carry out, and the resins **(271a – 274a)** were isolated by precipitation from cold (-45 °C) MeOH, separated by filtration, washed with H₂O and MeOH, and dried to constant weight under high vacuum. The structures of soluble, polymer-supported amines **271a – 274a** are presented in Figure 21.

271a X= H
271b X= Li

272a X= H
272b X= Li

273a X= H
273b X= Li

274a X= H
274b X= Li
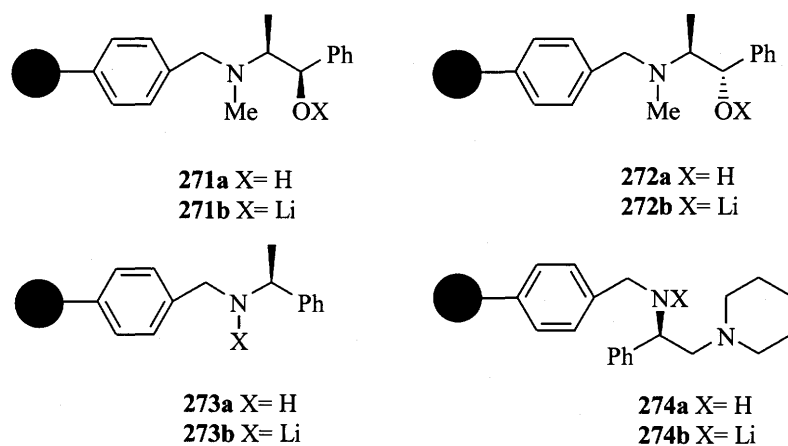
Figure 21. Structures of chiral amines and the corresponding lithium amides directly attached to a soluble resin (the black ball represents the soluble polymer support).

The loading of all soluble polymer-supported amines **271a – 274a, 286a, 287a** and **292a** was determined by elemental analysis and is summarized in Table 30.

Table 30. Nitrogen loading of chiral amines on soluble polymer.

Entry	Amine	Loading (mmol of NH/g)	Yield (%)[a]
1	**271a**	1.000	100
2	**272a**	1.000	100
3	**273a**	0.690	69
4	**274a**	0.850	85
5	**286a**	0.905	90
6	**287a**	0.742	74
7	**292a**	0.644	64

[a] Yields correspond to the mole ratio of nitrogen in the final resin to chlorine in the starting polymer, which was 1.00 mmol of Cl/g.

The loading values (Table 30, entries 3 – 7) indicated that N-alkylation did not proceed to completion. The radical dehalogenation method for the removal of unreacted alkyl halide groups was not useful here, due to the partial solubility of these polymers in hexane. Hexane is conventionally used in the workup of the dehalogenation reaction because of the solubility of the tin byproducts in this solvent, which makes them easy to remove from a reaction mixture.

Chiral amine **276** used for the synthesis of compound **274a** was not commercially available but it could be easily synthesized. Syntheses of similar amines have been performed in our group, and the synthesis of amine **276** relied on the previously described procedures (Scheme 66).[1, 2, 12,]

Scheme 66

277 **278** **279**

280 **276**
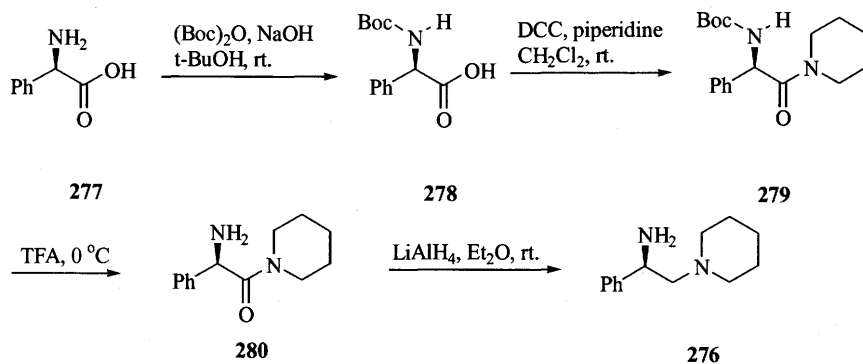
The second general method elaborated for the attachment of chiral amines to the soluble polymers (**145** or **270**) is shown in Scheme 67.

Scheme 67

145 X= Cl **281** **282**

283
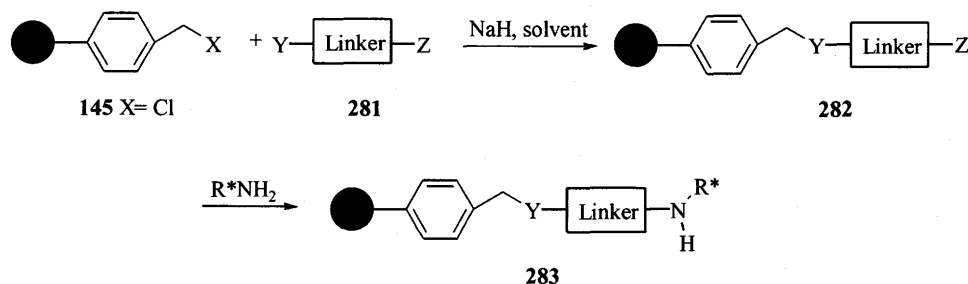
The linker was attached first to the soluble polymer **145**, followed by the mamipulation of functional group and the attachment of a chiral amine. It was thought that the attachment of the linker would allow for the amino group to be located further away from the rigid polymer matrix, and that it would make it more accessible to *n*-BuLi during generation of chiral lithium amides. Two specific examples are shown in Schemes 68 and 69.

Scheme 68

257 n= 1
59 n= 4

284a n= 1
284b n= 4

285a n= 1
285b n= 4

286a n= 1
287a n= 4
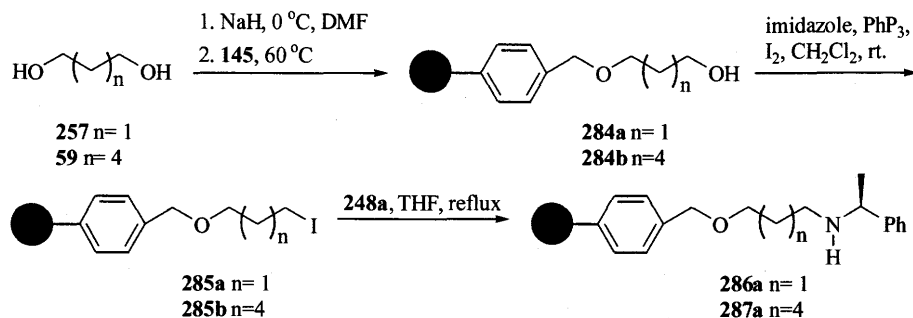
Polymers **286a** and **287a** were synthesized according to the modified procedure described for amines **260a** and **261a**. The resins were precipitated by cold MeOH (-45 °C), separated by filtration, washed with H_2O and MeOH, and dried to constant weight under high vacuum. Both compounds **286a** and **287a** were characterized by ^{1}H and ^{13}C NMR. The loading of the amines (**286a** and **287a**) was determined by elemental analysis and is presented in Table 30 (entry 5 and entry 6).

A somewhat different synthesis is shown in Scheme 69.

Scheme 69

288

289

290

291

292a
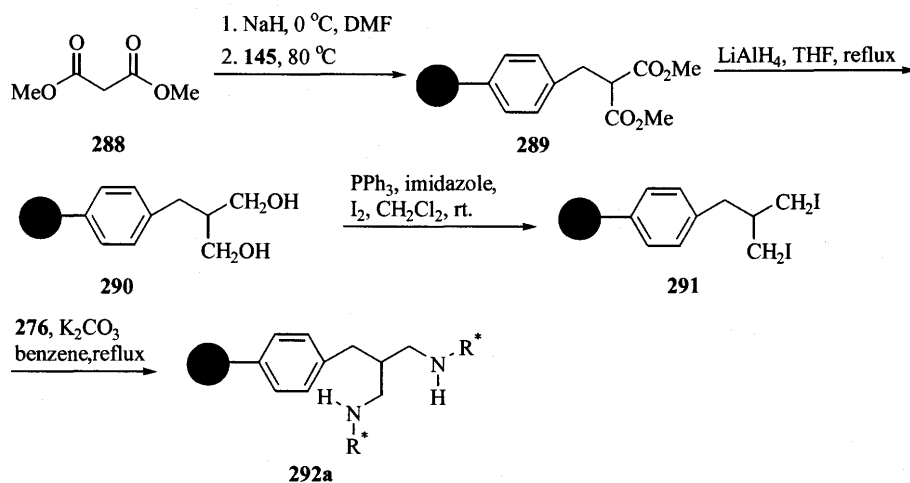
In this example, dimethyl malonate (**288**) was chosen as the linker and was attached to the polymeric benzyl chloride **145** using the C-alkylation method. The bulk of DMF was removed by distillation, and the polymer **289** was precipitated from cold MeOH (-45 °C). The resin **289** was separated by filtration, washed with H_2O and MeOH, and dried to constant weight under high vacuum. In the next step, the ester functional groups were reduced with $LiAlH_4$, which was followed by the conversion of the hydroxyl moiety to the iodide by the method described before.[126] The amine **276** was attached by the N-alkylation method to give polymer **292a**. The polymeric amine **292a** was precipitated by addition of MeOH at –45 °C, separated by filtration from the excess of reagents, and washed with H_2O and MeOH. The reagent was extracted with MeOH overnight in a Soxhlet apparatus, and dried to constant weight under vacuum. The loading of polymer **292a** was determined by elemental analysis and is shown in Table 30 (entry 7).

In summary, the syntheses of seven soluble, polymer-supported chiral amines: **271a, 272a, 273a, 274a, 286a, 287a** and **292a** was designed and successfully elaborated. The amines were obtained in good to excellent yields. All intermediates in the synthesis of these resins were characterized by ${}^1H$ and ${}^{13}C$ NMR spectroscopy. Methods for determining the loading characteristics of the resins were developed.

2.B.5. Reactions of polymer-supported amines.

2.B.5.1 Generation of lithium amides

After the synthesis of the insoluble (**250a – 254a, 56a, 260a, 261a, 264a** and **265a**), and soluble, polymer-supported reagents (**271a - 274a, 286a, 287a** and **292a**) was completed, the stage was set for trying to generate the corresponding chiral lithium amides. This is a very simple reaction in solution. There are numerous procedures described in the literature, and it is difficult to cite all of them. The reader's attention is directed to only a few references.[1, 2, 12, 101, 123, 128, 129] Chiral lithium amides are usually

generated by addition of *n*-BuLi (1 equivalent) to the solution of a chiral amine in an appropriate solvent: Et$_2$O, THF or toluene. Sometimes additives like lithium salts (e.g. LiCl, LiBr) or polar co-solvents (e.g. HMPA or TMEDA) are used.[13]

A procedure for generation of polymer-supported lithium amides was designed by analogy with solution chemistry. The general method is shown in Scheme 70, and the structures of polymer-supported lithium amides are summarized in Figure 22.

Scheme 70
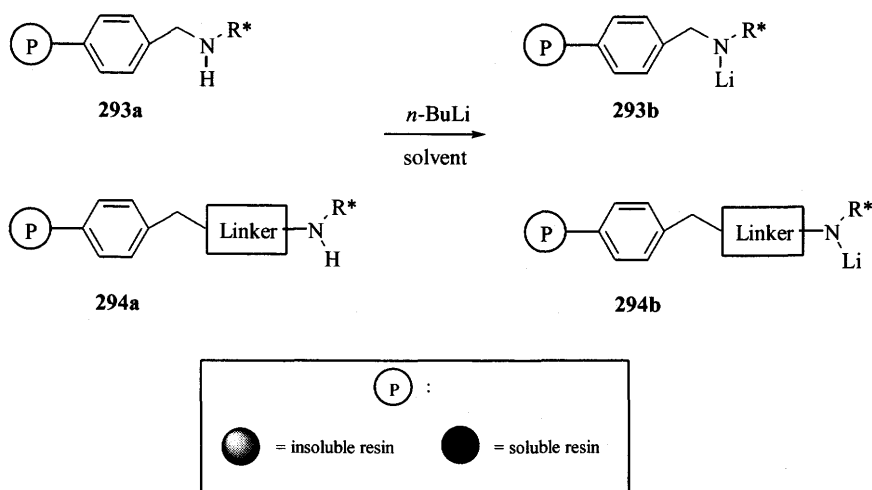
Polymer-supported chiral lithium amides were generated at 0 °C in THF. In the case of insoluble polymer-supported chiral lithium amides (**250b – 252b, 56b, 260b, 261b, 264b** and **265b**) THF is a solvent that greatly swells the polymer matrix. One has to remember that if an insoluble, polymer-supported reagent is used in a reaction, the reaction conditions are heterogeneous, and the reaction takes place inside a polymer bead. In order to obtain the highest yield and selectivity (if more than one product is possible), the conditions of a reaction should be homogeneous. This means the solvent that swells a particular polymer well, should be used. The "swelling of a polymer" term describes the polymer ability to dissolve. The reactive sites are exposed to the reagents present in solution, and the reaction takes place. If soluble, polymer-supported lithium amides (**273b, 274b, 286b, 287b** and **292b**) were used, the heterogeneity of a reaction was not an

issue because those reagents simply dissolved in THF, and homogeneous conditions of a reaction were restored.

During generation of the insoluble and soluble, polymer-supported lithium amides from the corresponding chiral amines a color change was observed (the suspension changed color from yellow to light reddish-brown in the case of insoluble reagents; the solution changed color from yellow to red or purple in the case of soluble ones). This could be attributed to the formation of unidentified by-products. It was determined qualitatively, that if the color change did not occur, the reaction did not proceed or if the color was very dark (dark brown), the yield of the reaction was usually low.
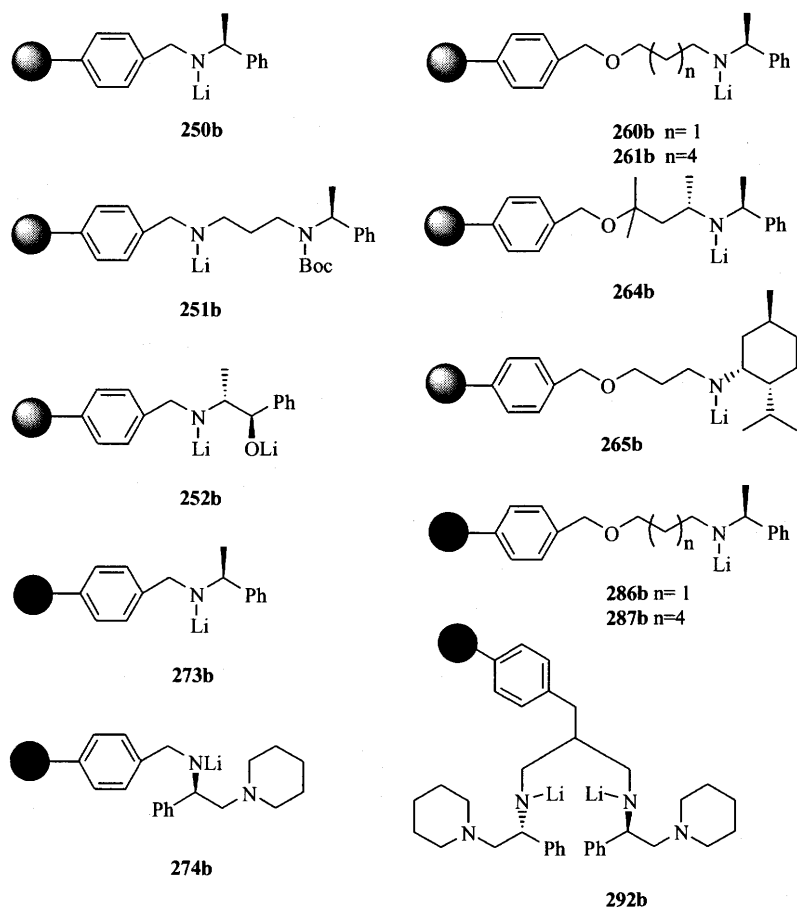
Figure 22. Structures of polymer-supported chiral lithium amides. Shaded balls represents insoluble support, black balls represents soluble support.

After the conditions for the generation of polymer-supported chiral lithium amides were elaborated, a question arose as whether these reagents could be applied as bases in organic reactions. The use of polymer-supported reagents could have several advantages over chiral lithium amides generated in solution. Some of those advantages could be: simplifying reaction procedures, the possibility of easily regenerating the polymer bound reagent, and the suppression of undesired side reactions such as cross-linking by using more solvent (the principle of high dilution).[27] Polymer-bound reagents are usually more stable, and a possibility for the automation of reactions exists when dealing with polymer-supported chiral lithium amides.

The reaction that was chosen to be the model was the aldol reaction of cyclohexanone (25). In solution, this reaction was studied numerous times before, and the conditions for deprotonation of ketone 25 with LDA were well established.[79, 86, 133] The enolization of cyclohexanone (25) with lithium amide 250b, followed by addition of the benzaldehyde is shown in Scheme 71.

Scheme 71
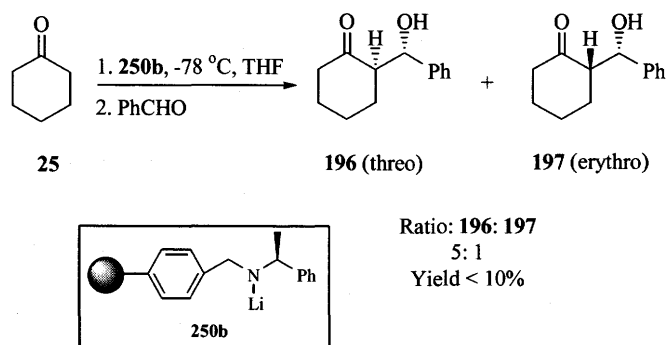
It was established experimentally that the results (yield and diastereoselectivity) of the aldol reaction of the lithium enolate of cyclohexanone (25) depended on the nature of the additives, and on the workup conditions.[86, 130 – 132] If the reaction was allowed to warm up to room temperature before extracting of the aqueous layer then the retro-aldolization was possible, and the diastereoselectivity was lowered. In order to avoid retro-aldolization, the reaction had to be extracted with appropriate solvent immediately after quenching

with aqueous solution of a weak acid. These workup conditions were not possible to apply with SP reagent **250b**. After quenching, the polymer-supported amine **250a** had to be separated by filtration before the extraction could take place. During this process, the reaction mixture was warmed up to room temperature. Despite the low yield and selectivity, the results were promising; the polymer-supported chiral lithium amide (**250b**) that enolized a ketone (**25**) was generated.

After it was determined that polymer-supported lithium amides could be used for generation of the lithium enolates, the stage was set for investigation of the properties of these reagents in more detail. Two groups of reactions were subsequently studied: deprotonation reaction of ketones and β-ketoesters and protonation of cyclic lithium enolates.

2.B.5.2 Deprotonation of carbonyl compounds.

The choice of the model compound(s) is critical when the versatility of a reaction is studied or a new reaction is developed. Tropinone (**201**) was chosen as the first model compound for this project. The reasons for selecting this ketone involved its structural simplicity, and the fact that tropinone was previously enantioselectively deprotonated in solution, yielding the chiral enolate with high selectivity.[2, 13, 88d, 101] The first reaction under study was the aldol addition reaction. The experimental procedure for the reaction conducted in solution is well known, and the enantioselectivity of the aldol product can by analyzed by ^{1}H NMR with the chiral solvating agent (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[2] The reaction is shown in Scheme 72, and the results are presented in Tables 31 (SP reagents) and 32 (LP reagents).

Scheme 72
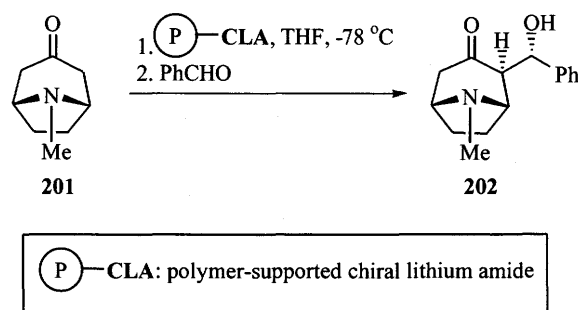
Table 31. The results of deprotonation of tropinone (201) with SP lithium amides, followed by the aldol reaction of the corresponding enolate.

Entry	Lithium amide	Addition of ketone (min.)	Additive (eq.)	Yield (%)[a]	ee (%)[a]
1	**250b**	2-3	-	38	14
2	**250b**	45	-	40	20
3	**250b**	2-3	LiCl (1 eq.)	45	24
4	**261b**	2-3	-	30	10
5	**261b**	2-3	LiCl (1 eq.)	35	20

[a] Yields and enantioselectivity refer to compound **202**.

The optimization of conditions for a reaction conducted in solution can be a difficult task. In some cases, numerous experiments are required before the precise variables are elaborated (the correct order for the addition of reagents, solvent, time and temperature) in order to achieve high yield and selectivity. When polymer-supported reagents are used, the quest for the optimal conditions of a reaction is even more complicated because more variables have to be taken into consideration; e.g., the polymer matrix, the nature of the linker, etc. The polymer matrix can either react with the reagents in solution in an undesirable fashion giving raise to by-products and/or microenvironmental effects of an unknown nature are present.[32] The reagents that are supported on a polymer have restricted mobility due to the rigidity of the polymer matrix. Usually, longer times are

required for reactions in which such reagents are employed. The first problem that had to be addressed was how much time would be required for the complete conversion of the chiral amine to the corresponding lithium amide. When the aldol reaction of tropinone (**201**) was conducted in solution, generation of the lithium amide was completed after 1 – 2.5 h (for details cf. Experimental Section). For the SP reaction 8 h were required for successful generation of the lithium amide. This was established experimentally for the resin **250b**. Deprotonation of tropinone (**201**) by SP lithium amide took 15 h (compared with 2.5 h for the reaction in solution- Experimental Section), followed by 6 h for the subsequent addition reaction (detailed procedures are described in the Experimental Section).

Every procedure for performing an organic reaction has several parts, "the actual reaction" and "the workup" being the most important, and these stages have to be carefully designed. Even if one succeeded in obtaining the desired product in "the actual reaction", the product could decompose if inappropriate workup conditions were applied. The second task was to design the workup of a reaction with polymer-supported reagents. When an aldol reaction is conducted in solution, it is usually quenched with an aqueous solution of a weak acid, followed by a simple extraction. The organic products stay in the organic layer, and inorganic by-products (lithium salts) are in the aqueous layer.[1, 2, 12, 101,128, 129, 133] The situation is different when reagents supported on solid support are involved. After an aldol reaction was quenched, the reaction mixture could not be extracted before the removal of SP reagent. After much trial and error the following procedure proved to be effective: the reaction was quenched by addition of an aqueous solution of NH$_4$Cl, the polymers **250a** and **261a** were separated by filtration and washed with THF. The aqueous layer of the filtrate was extracted with Et$_2$O, dried, concentrated *in vacuo* and the crude product **202** was obtained. The enantioselectivity of the aldol reaction of tropinone (**201**) was measured on the crude aldol **202** by ^{1}H NMR with the chiral solvating agent (S)-(+)-TFAE. The SP reagents **250a** and **261a** were recycled, and washed with THF, H$_2$O, MeOH and Et$_2$O. Next, they were mixed with a 1M solution of H$_2$SO$_4$, separated by filtration, washed with H$_2$O, followed by mixing with a 2M solution of NaOH. The polymeric amines **250a** and **261a** were separated by filtration, washed with H$_2$O until the filtrate pH was 7, MeOH and THF, followed by an overnight

extraction with THF. The polymers were then dried to constant weight under high vacuum.

Both, the yield and the enantioselectivity of the aldol reaction of tropinone (**201**) were modest. Perhaps the heterogeneous conditions were lowering the efficiency and selectivity of the reaction. In order to maintain the homogenicity of a reaction and still have some of the advantages of SPS, chiral lithium amides were attached to the soluble polymer. Compounds **274b**, **286b**, and **287b** were subsequently employed as the bases in the aldol reaction of tropinone (**201**) (Table 32). In this case, the extraction was applied before the precipitation of the polymer, which made the workup much easier. After quenching the reaction, the mixture was simply diluted with AcOEt, and the aqueous layer was further extracted with AcOEt. The detailed procedure is given in the Experimental Section.

Table 32. The results of the aldol reaction of tropinone (**201**) with LP reagents.

Entry	Lithium amide	Addition of ketone (min.)	Additive (eq.)	Yield (%)	ee (%)
1[a]	**274b**	2 - 3	-	20	5
2	**274b**	2 - 3	LiCl (1 eq.)	51	70
3	**286b**	2 - 3	-	10	11
4	**286b**	2 - 3	LiCl (1 eq.)	35	26
5[a]	**286b**	2 - 3	LiCl (1 eq.)	25	14
6[a]	**287b**	2 - 3	LiCl (1 eq.)	40	35

[a] Reaction was performed in 50 mL of THF instead of 30 mL in order in to investigate "the concentration effect".

A few trends were observed during the work on elaborating the conditions for the aldol reaction of tropinone (**201**) with LP reagents **274b**, **286b**, and **287b**: [135]

1.   Lithium chloride is a necessary additive in the deprotonation step. The lithium amide could not be generated without the additive, possibly due to formation of a gel, which made the reaction mixture heterogeneous. It was suggested that formation of a gel

126

could be caused by a non-covalent cross-linking of polymer-chains because of possible aggregation of the polymer-supported lithium amide. After the addition of a LiCl solution, the gel disappeared due to the formation of mixed aggregates: R*$_2$NLi-LiCl (Figure 23).

2.   There seems to be a concentration effect in the aldol reactions involving soluble polymer-supported lithium amides **273b**, **274b**, **286b** and **287b**, e.g.: the concentration of amide **273b** cannot be too high; the ee of the aldol **204** was 75% at 0.026 M of **273b**, but only 30% when the concentration of **273b** was raised to 0.075 M.[135] The opposite effect was observed for other lithium amides (Table 32).
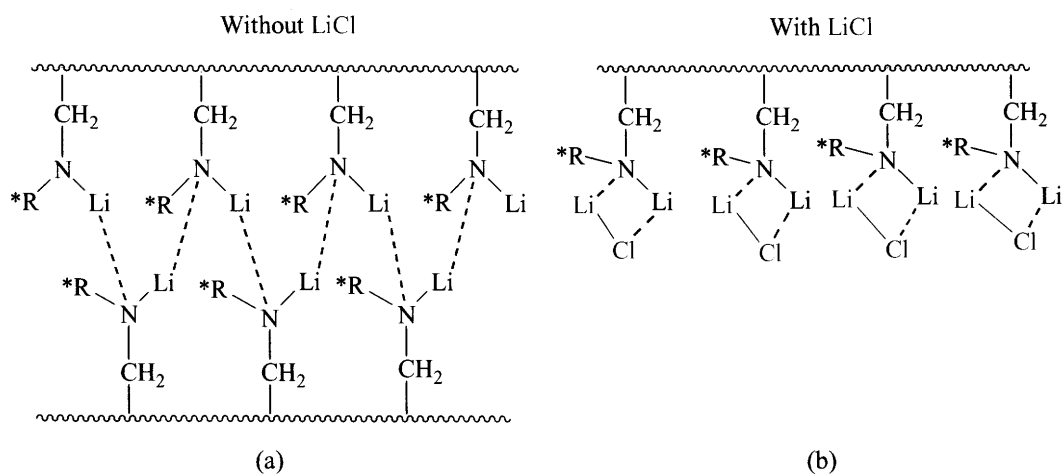
Figure 23: The hypothetical structures of (a) a dimer involving chiral lithium amide supported on soluble polymer and (b) mixed aggregates involving lithium amide and LiCl connected to the polymer.

Another reaction of tropinone (**201**) that was studied in solution in great detail by our group was ring-opening (Scheme 73).[2, 88d, 101] The reaction is easy to carry out in solution, and the method for measuring the enantiomeric excess of the product **230** is known. Those qualities made this transformation a good model for expanding the methodology study of polymer-supported lithium amides (Scheme 73). The results are presented in Tables 33 (SP reagents) and 34 (LP reagents).

Scheme 73
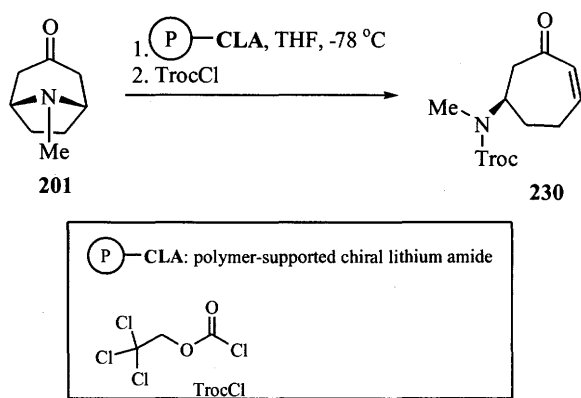
Table 33. The results of the deprotonation of tropinone (**201**) with SP reagents, followed by the ring-opening of the corresponding enolate.

Entry	Lithium amide	Addition of ketone (min.)	Additive (eq.)	Yield (%)	ee (%)[c]
1	**250b**	2 - 3	-	13	2
2	**250b**	45	-	28	10
3	**250b**	2 - 3	LiCl (1 eq.)	37	59
4[a]	**251b**	2 - 3	-	10	-13
5	**251b**	2 - 3	LiCl (1 eq.)	15	36
6[a, b]	**252b**	2 - 3	-	5	-1.5
7[a]	**252b**	2 - 3	-	7	-6.5
8[a]	**252b**	2 - 3	LiCl (1 eq.)	10	-13
9	**260b**	2 - 3	-	42	3
10	**260b**	2 - 3	LiCl (1 eq.)	48	6
11	**261b**	2 - 3	-	22	2
12	**261b**	2 - 3	LiCl (1 eq.)	25	22
13[a]	**264b**	2 - 3	-	5	-11
14	**264b**	2 - 3	LiCl (1 eq.)	11	9
15	**265b**	2 - 3	-	5	3

[a] Levorotatory enantiomer of **230** was the major product. [b] The reaction was performed in 2,5-tetramethyltetrahydrofuran. [c] Enantioselectivity was measured with HPLC using Chiralpack AD column and 15% isopropanol in hexane as the solvent system.

The highest ee in this series of experiments was obtained with lithium amide **250b** and 1 equivalent of LiCl (Table 33, entry 3). Interesting results were obtained with lithium amides **251b** (Table 33, entries 4 and 5) and **264b** (Table 33, entries 13 and 14). In both cases, the major product was a dextrorotatory enantiomer of **234** when deprotonation was performed in the absence of LiCl; however, after the addition of 1 equivalent of LiCl the levorotatory enantiomer was the major product. The mechanism of deprotonation of ketones with SP chiral lithium amides is not well understood. It could be suggested, by analogy with a reaction conducted in solution that the origin of the LiCl effect lies in

different lithium amide species acting as the deprotonating agents. It is known that in ethere solution chiral lithium amides exist as oligomers, with the major component is the dimer and the minor component is the monomer.[83, 85, 86] Recent investigations, however suggested that the monomer is the more reactive species in deprotonation.[85, 136] After addition of LiCl, mixed aggregates that have different reactivity can form. Structures of the possible aggregates are shown in Figure 8. On the other hand, formation of a dimer by an insoluble, polymer-supported lithium amide seemed to be quite unlikely, because of the rigid nature of the polymer matrix. The reactive lithium amide groups should be separated from each other, and formation of dimers is then difficult. The explanation why the dextrorotatory enantiomer of product **230** is formed without LiCl, and the levorotatory enantiomer **230** is formed in the presence of LiCl has to await a detailed mechanistic study.

The yields and enantioselectivities varied from mediocre to low with only a few exceptions (Table 33, entries 3, 5 and 10). It has to be remembered that the reaction conditions were heterogeneous. The addition of the linker in order to separate the chiral lithium amide (compounds **260b**, **261b**, **264b** and **265b**) from the polymer rigid backbone did not seem to make a difference. Obviously, the steric hindrance that reagent **250b** exhibits is necessary for the reaction to proceed with a useful degree of enantioselectivity.[135]

In order to avoid microenvironmental effects that could be present in the SP reactions, e.g., side interaction of an insoluble polymer chain, and to restore homogeneous reaction conditions soluble, lithium amides **273b**, **274b**, **286b** and **287b** were employed (Table 34).

Table 34. The results of the deprotonation of tropinone (**201**) with LP reagents, followed by the ring-opening of the corresponding enolate.

Entry	Lithium amide	Additive (eq.)	Yield (%)
1[a]	**273b**	-	3
2[a]	**273b**	LiCl, (1 eq.)	6
3	**273b**	LiCl, n-BuLi, (1 eq.)	47
4[a]	**274b**	-	8
5[a]	**274b**	LiCl (1 eq.)	10
6	**274b**	n-BuLi (1 eq.)	42
7[b]	**274b**	LiCl (1 eq.) and n-BuLi (1 eq.)	57
8[a]	**286b**	-	3
9[a]	**286b**	LiCl (1 eq.)	5
10[a]	**287b**	-	3
11	**287b**	LiCl (1 eq.)	10

[a] The same reaction conditions as for the aldol reaction were applied. [b] The enantioselectivity of the reaction was 30%.

A plausible explanation of the low yield of the ring-opening reaction of tropinone (**201**) (entries 1, 2, 8 – 11) is offered in Scheme 74.

Scheme 74
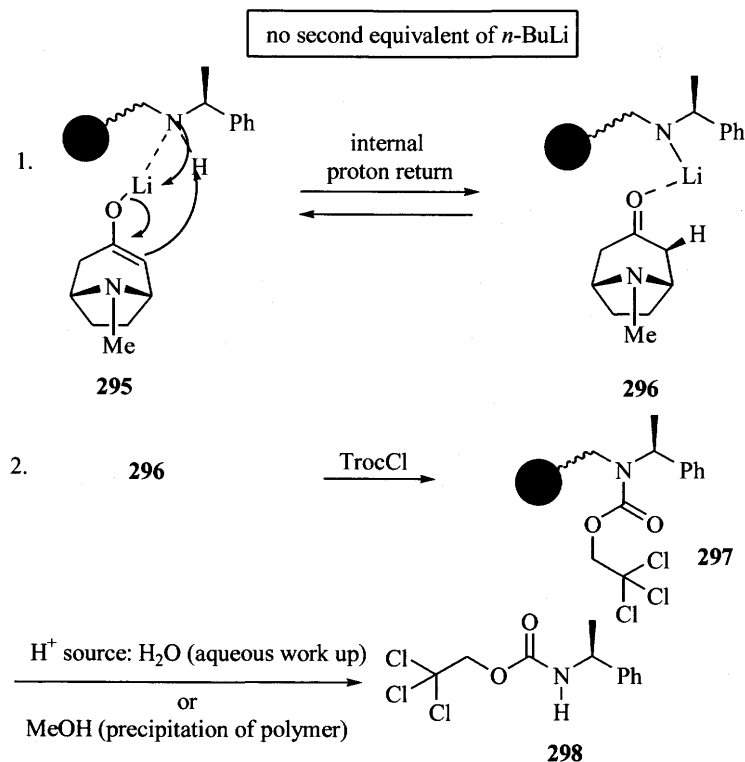
It is known from studies of enolates in solution that after the deprotonation step the chiral amine stays coordinated to the enolate *via* the lithium atom.[79] One could assume that polymer-supported amines behave in a similar fashion. A complexed amine could act as the proton source, and an "internal proton return" could take place (Scheme 74, step 1). The "internal proton return" phenomenon in reactions conducted in solution has been described by other researchers.[80, 131, 132] The reattachment of the hydrogen connected to the amine portion of the complex to the enolate component takes place at a faster rate than the reaction of the latter with electrophiles. In the next step 2,2,2-trichloroethyl chloroformate could react with an LP lithium amide giving the corresponding carbamate, which could be cleaved from the resin during the aqueous workup or the precipitation of the polymeric reagent from methanol. The byproduct **298** was observed, and unreacted tropinone (**201**) was recovered. The situation was different when the second equivalent of *n*-BuLi was added before the addition of an electrophile (Scheme 75).

Scheme 75
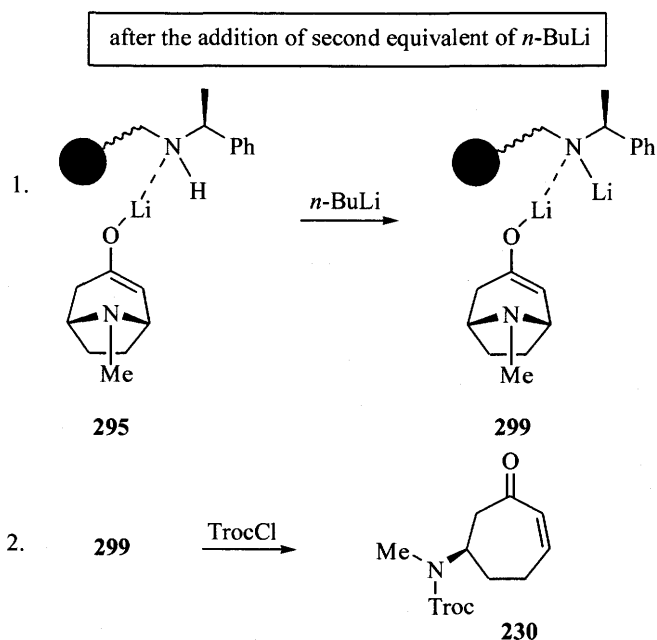
After the addition of another equivalent of *n*-BuLi to the reaction mixture the internal proton return does not occur because the complexed amine is converted to the lithium amide (step 1) and the electrophile reacts with the lithium enolate to yield the final product **230** (step 2).

I would like to point out that for, simplicity, all structures in Schemes 74 and 75 are shown as monomers. However, one has to remember that chiral lithium amides and enolates have the tendency to form oligomers in solution. The structures of those oligomers were presented in Figures 7 and 8.

Other reactions were studied in order to explore the potential of soluble polymer-supported lithium amides in more detail and to gain more understanding of how they work. One of these reactions was the α-alkylation of a β-ketoester. Alkylation of β-ketoesters is well known.[137 – 143] Generally, such alkylations are not difficult to perform and the alkylated derivatives can be obtained in high yields. This reaction can be also viewed as an alternative method of synthesis of α-alkylated ketones. Alkylation of ketones is often troublesome.[144 – 149] General α-alkylation of a β-ketoester is shown

in Scheme 76; the reaction is usually followed by decarboxylation to obtain the α-alkylated ketone.

Scheme 76
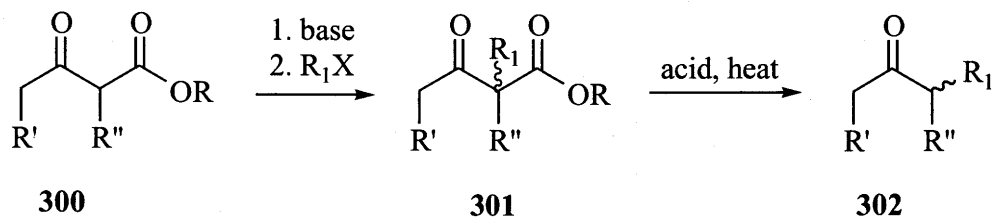
In the first step, the β-ketoester is deprotonated with a base (NaH, LiNH₂ or RO⁻) generating the enolate, followed by alkylation with an alkyl halide. Interestingly, there seemed to be no literature precedent of using LDA to generate the monoanion from a β-ketoester. According to Weiler, the use of 2 equivalents of LDA to generate the dienolate, followed by the reaction with an alkylating agent gave the γ-alkylated β-ketoester in low yield.[150] A literature procedure for generation of monoenolates of a β-ketoester with LiNH₂ was found.[139] It seemed interesting to try deprotonation of ethyl 2-oxo-cyclopentanecarboxylate (303) with LDA. If this was successful, a reaction with a chiral lithium amide e.g., 305b would be tried (both reactions were conducted in solution). As mentioned before, optimization of the conditions of a new reaction in solution can be difficult, but this task becomes even more complicated when LP reactions are concerned. The course of these reactions is often completely different from their equivalents in solution. After the procedure for deprotonation of 303 in solution was established, the soluble, polymer-supported lithium amides 274b and 292b were to be tried as bases. The benzylation reaction of 303 is shown in Scheme 77, and the results for the reaction in solution are presented in Table 35.

Scheme 77

303 → **304**

305b

274b   **292b**
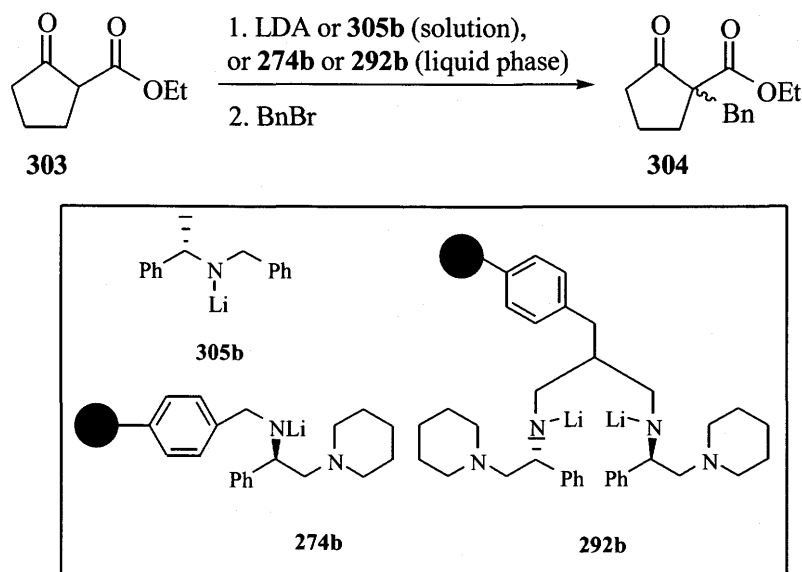
Table 35. The influence of the reaction conditions (temperature and time) on the results of the benzylation of β-ketoester **303** in solution.

Entry	Lithium amide	Conditions of deprotonation	Conditions of alkylation	Conv. (%)[b]	Yield (%)
1[a]	LDA	-78 °C, 45 min	2.5 h, rt.	0	-
2	LDA	-20 °C, 45 min	2.5 h, rt.	7	-
3	LDA	-20 °C, 4 h	12 h, -78 °C	14	-
4	LDA	As above	12 h, -40 °C	18.5	-
5	LDA	-20 °C, 4 h then 0 °C, 2 h	12 h, 0 °C then rt., 24 h	100	62
6	**305b**	As above	As above	80	47

[a] MeI was used as an alkylating agent. [b] The percentage (%) of the starting material that was converted into the product(s).

As seen from Table 35 the conditions for the alkylation reaction of β-ketoester **303** with LDA were established (entry 5). First, the enolate was generated at –20 °C, followed by raising the temperature to 0 °C. The lithium enolate of the β-ketoester was alkylated with BnBr, and compound **304** was obtained in 62% yield. This was a very promising result when compared to the results of benzylation under "typical" conditions.[137 - 139, 141] The benzylated derivative **304** was obtained in 55% yield when KH was used as the base to generate the corresponding potassium enolate from compound **303** at 0 °C.[138] The solution of the enolate was warmed to room temperature, and after stirring for 3 hours, benzyl bromide was added followed by heating of the reaction mixture for 3 hours to 50 °C. Compernolle and co-workers were able to obtain the benzylated derivative **304** in 89% yield when the K$_2$CO$_3$ was applied as the base, and the benzylation reaction took place at room temperature for 24 hours.[141] The chiral lithium base **305b** proved to be less effective than LDA (Table 35, entry 6), and unfortunately the reaction was not enantioselective. It was thought that a polymer-supported chiral lithium amide could be used as the base for generation of the enolate of the β-ketoester. The base would be more bulky than LDA and the lithium amide **305b**, because of the presence of the polymer-support, might be beneficial in the deprotonation step. The benzylation reaction of compound **303** was performed with the two soluble polymer-supported lithium amides **274b** and **292b** (Table 36).

Table 36. The influence of conditions (temperature and time) on the results of the deprotonation reaction of **303** with LP bases, followed by the alkylation of the corresponding monoanion.

Entry	LP base	Deprotonation (temp. and time)	Alkylation (temp. and time)	Proton source	Conv (%)^c	Yield (%)
1	**274b**	-20 °C, 4 h; 0 °C, 2 h	0 °C, 12 h; rt. 24 h	H_2O	80	47
2	**274b**	As above	0 °C, 24 h; rt. 12 h	H_2O	81	40
3	**274b**	Procedure from entry 1	Procedure from entry 1	citric acid^a	72	46
4	**274b**	Procedure from entry 1; LiCl (1 eq.), 0 °C, 12 h	Procedure from entry 2	citric acid^a	91	47
5	**274b**	As above	As above	AcOH^b	41	71
6	**292b**	As above	As above	AcOH^b	0	–
7	**292b**	As above	As above	phthalimide^b	100	70
8	**292b**	As above	As above	MeOH^b	100	76

^{a} 10% solution was used as the proton source. ^{b} A non-aqueous workup of the reaction was applied. ^{c} The percentage (%) of the starting material that was converted into the product/(s).

The phrase "non-aqueous workup" means that the reaction mixture was poured directly onto cold MeOH (–45 °C) and the polymeric amines (**274a** and **292a**) precipitated. They were separated by filtration, and washed with MeOH. The filtrate was evaporated, and the crude product **304** was obtained. It was possible to apply LS reagents **274b** and **292b** as the bases in the deprotonation of β-ketoester **303**. The best result was obtained with **292b** (Table 36, entries 7 and 8). The enolate was generated at –20 °C, and the temperature of the reaction was raised to 0 °C. One equivalent of LiCl was added to the

mixture in order to prevent formation of a gel. The gelation of LP reagents was observed during work on deprotonation of tropinone (**201**), and an explanation of the effect was given before. The enolate was alkylated with benzyl bromide, and racemic product **304** was obtained.

In summary, it was demonstrated that insoluble and soluble polymer-supported lithium amides could be used as bases in deprotonation reactions of ketones and β-ketoesters. The products of these reactions were obtained in reasonable yields. It was possible to obtain the optically active α-functionalized ketone.

2.B.5.3 Protonation of cyclic lithium enolates.

Optically active carbonyl compounds bearing a stereogenic center α to the carbonyl group are important intermediates or buildings blocks in the synthesis of optically active natural compounds. Enantioselective and diastereoselective protonation of enolates are important methods for the preparation of optically active α-substituted ketones or esters. These methods are complementary to asymmetric alkylation. The protonation reaction can be performed directly on an achiral lithium enolate (Scheme 78) or auxiliaries can be used (Scheme 79).

Scheme 78

R$_2$= H, enantioselective protonation
R$_2$= alkyl, diastereoselective protonation
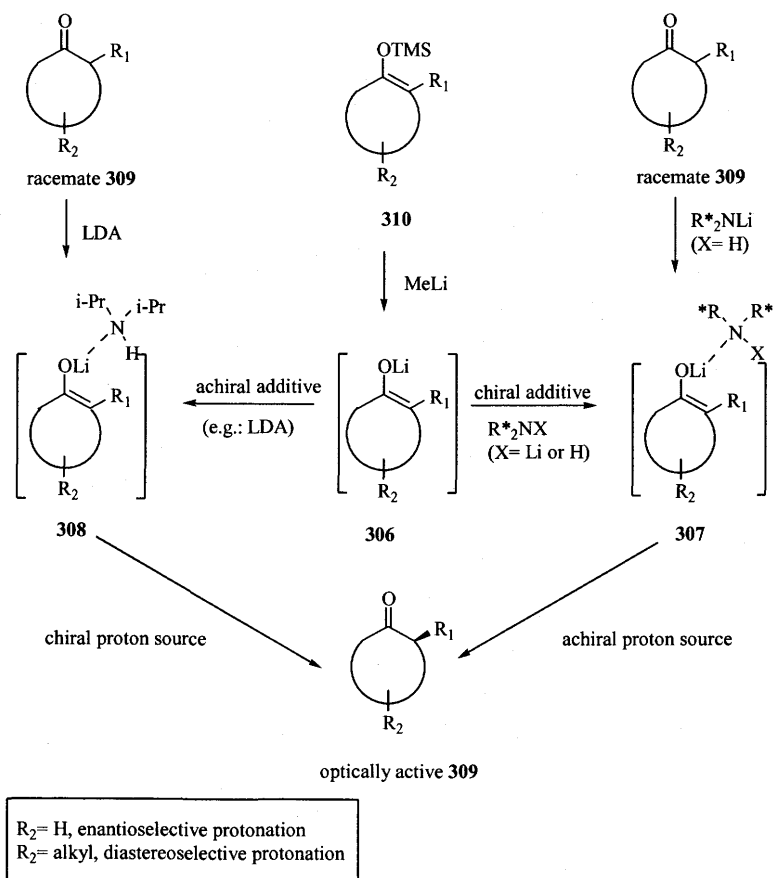
The lithium enolate of a cyclic ketone can be generated in three ways: by deprotonation of the racemic ketone **309** with a chiral lithium amide, with an achiral lithium amide (e.g., LDA) or from the corresponding silyl enol ether **310**. In the first case, the chiral amine is complexed to an enolate *via* the lithium atom after the deprotonation step. The faces of the complex **307** (R$_2$= H, alkyl, aryl) are diastereotopic, thus they react at different rates with an achiral proton source giving the enantiomerically enriched ketone **309** as the result. In the second approach, the racemic ketone **309** (R$_2$= H or alkyl) reacts with an achiral base (LDA in this example) to give the corresponding achiral enolate (R$_2$= H). Faces of the complex **308** are enantiotopic (R$_2$= H), and they react at different rates with chiral proton sources yielding the enantiomerically enriched product **309**. If R$_2$= alkyl or aryl the faces of the complex **308** are diastereotopic. The enolate **306** (R$_2$= H or alkyl) can also be generated from the corresponding silyl enol ether **310**. Additives (chiral

or achiral) can be added to the solution of the enolate **306**, and the complexes **307** and
308 are obtained as the result. Protonation of these complexes was described above.

Scheme 79
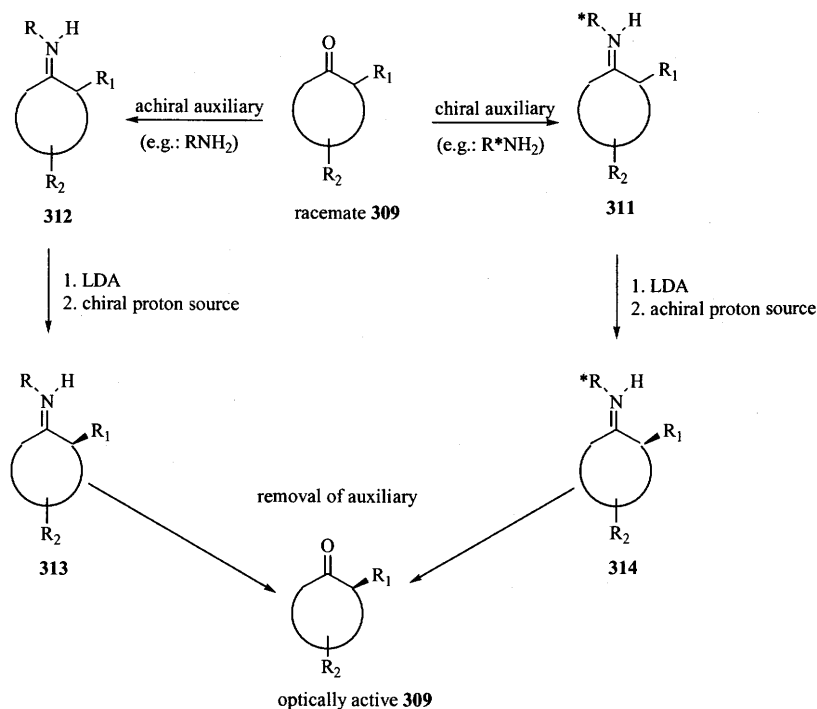
R$_2$= H, enantioselective protonation
R$_2$= alkyl, diastereoselective protonation

A primary amine (achiral or chiral) can be used as the auxiliary in the enantioselective
(R$_2$= H) or diastereoselective (R$_2$= alkyl) protonation of lithiated derivatives **311**or **312**.
The pioneering work in the area was done by Duhamel,[151] and continued later by
others.[152 – 161] Most of the reagents employed as chiral proton sources are weakly acidic
compounds. These include organic acids[151d], alcohols, amides, hydrochlorides of
amines, combinations of chiral secondary amines and chiral or achiral weak acids,[158, 161]
chiral anilines[154] and chiral imides.[153, 154, 157, 159]

Three examples of protonation where polymer-supported reagents were used are reported (Scheme 80).[37c, 115a, 115b]

Scheme 80

Leznoff,. 1982[37c]

1. LDA, -78 °C, THF
2. EtOH, -78 °C
3. AcOH/ AcONa/ H₂O

yield 98%
ee 90%

50c   **49**

Verducci, 1994[115a]

1. -40 °C, THF
2. H⁺/ H₂O

yield 95%
ee 94%

315   **316**   **317**

Krause, 1998[115b]

-80 °C, AcOEt

318   **319**   **320**   **321**

              97:            3
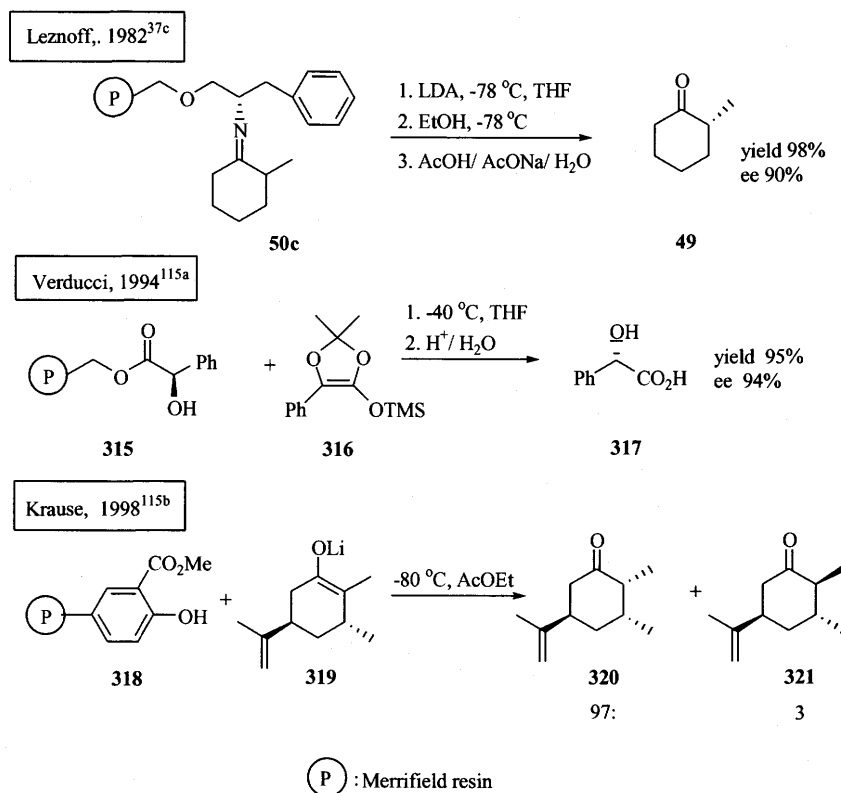
(P) : Merrifield resin

The first example of such protonation was reported by Leznoff in 1982.[37c] Racemic 2-methylcyclohexanone was attached to a chiral primary amine supported on Merrifield resin *via* imine formation. The lithiated derivative of the imine (**50c**) was protonated with an achiral proton source and the optically active 2-methylcyclohexanone **49** was obtained in 90% ee. Two other examples described the use of polymer-supported proton donors. (D)-Mandelic acid was attached to the Merrifield resin affording the polymer-supported chiral proton donor **315**, which was used in enantioselective protonation of the silyl enol ether **316**, giving the optically active product **317**.[115a] In 1998 Krause and co-workers reported a diastereoselective protonation reaction of the chiral enolate **319** with the achiral, polymer-supported proton donor **318**.[115b] The insoluble polymer **318** containing methyl salicylate units was synthesized, and used in diastereoselective

protonation of the lithium enolate **319** derived from (R)-carvone. The products **320** and **321** were obtained in 94% de, but the yield was not reported.

Enantioselective protonation

It was decided to investigate protonation of the lithium enolate of a cyclic ketone with soluble polymer-supported chiral proton sources related to the previously described amines. Accordingly, two new reagents were synthesized.

271a X= H
271b X= Li

272a X= H
272b X= Li
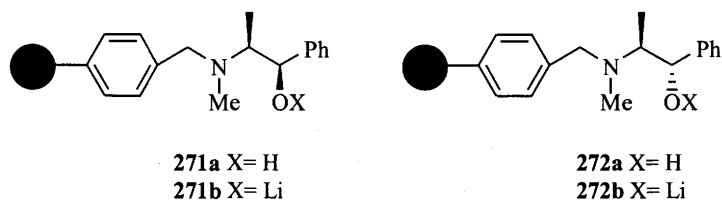
Enantioselective protonation of the enolate **322a** derived from racemic 2-methyl-1-tetralone (**323**) is a reaction documented well in the literature.[161, 162] The starting ketone is commercially available, and methods for measuring the optical purity of the α-alkyltetralones are known. These reasons made this reaction a logical choice to be considered for the study of enantioselective protonation (Scheme 81). The amine **292a** was investigated first. The results are summarized in Table 37.

Scheme 81
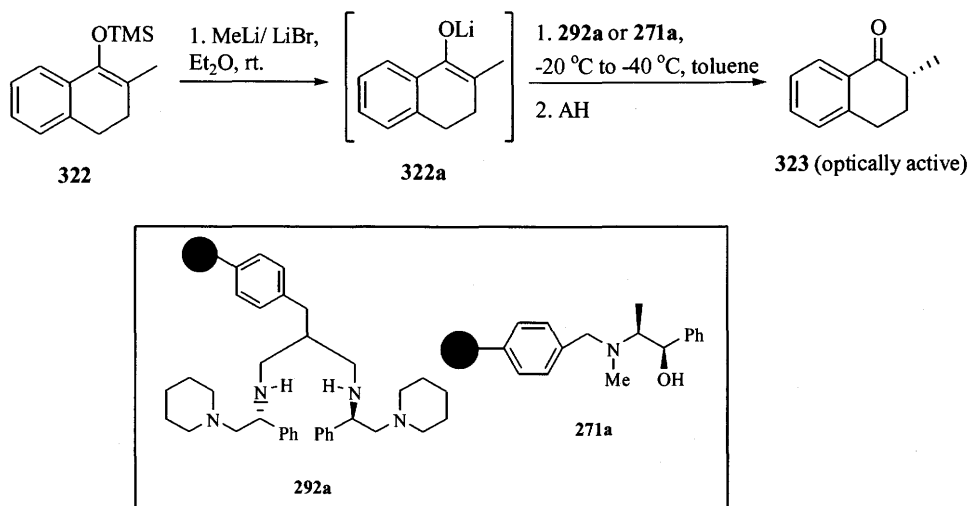
The chiral amine **292a** was chosen because Koga had successfully used its solution analogue **324a** as the chiral additive in stoichiometric and catalytic protonation of α-methyltetralone lithium enolate.[161]
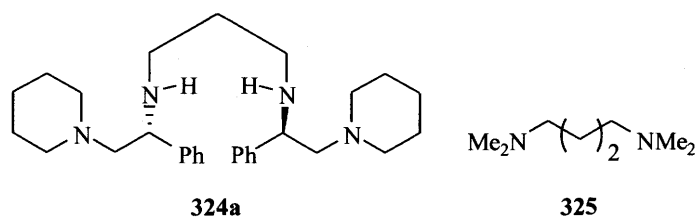
Stoichiometric conditions for protonation of lithium enolate **322a** (i.e., 1 equivalent of amine **324a** was used with achiral additive **325** and an achiral proton source) resulted in formation of the S enantiomer of α-methyltetralone (**323**) in 85-91% yield and 91-93% ee. In the case of catalytic conditions (ie., 0.10 equivalent of the chiral amine and 2.0 equivalents of the achiral amine **325**, and 10% citric acid as the proton source), the (S)-ketone **323** was obtained in 93% ee.

Table 37. The influence of the reaction conditions on the protonation of the lithium enolate of 2-methyl-1-tetralone (**322a**) with LP reagent **292a**.

Entry	Conditions of protonation (temperature and time)	AH	Yield (%)
1	−45 °C, 6h	10% citric acid[a]	62
2	−40 °C, 12 h	10% citric acid[a]	75
3	−40 °C, 12 h then −78 °C, 12 h	AcOH[b]	75
4	−78 °C, 12 h	AcOH[b]	55

[a] Fast extraction was applied: the reaction mixture was poured into the 10 mL of 10% citric acid and 75 mL of AcOEt, and extracted without warming to room temperature.
[b] The non-aqueous workup was applied.

The data in Table 37 show some interesting features of this reaction. The 2-methyl-1-tetralone (**323**) was obtained in a good yield but as the racemate (entries 1 – 4). When a polymer-supported reagent is used in a reaction it is very important to develop a workup that allows for the efficient recovery of the reagent. When an aqueous proton source was used (Table 37, entries 1 and 2) the recovery of polymer **292a** was only 60%. That was due to the fact that part of the resin **292a** precipitated from water as the gel, which did not dissolve in AcOEt. This problem was avoided when a non-aqueous workup was employed (Table 37, entries 3 and 4). The lack of the enantioselectivity in this reaction can be explained by the inability of the amine **292a** to complex to the enolate **322a** that was generated from the silyl enol ether **322**.

As mentioned before, chiral alcohols were used as proton sources in enantioselective protonation of cyclic enolates.[154, 156] It was also established that the acidity of the proton source played a crucial role in achieving high enantiomeric excess.[152 – 161, 165, 166] Proton exchange reactions are usually very fast, so it can be difficult to discriminate between the two diastereotopic transition states, therefore the

chiral proton source should be a weak acid (pK$_a$ of a simple alcohol is about 15).[77] The chiral proton source should be added in excess, be efficient, and it should also have electron-rich groups capable of undergoing chelation.[156] The use of an ephedrine analog **326** as the effective proton source for the protonation of lithium enolates in solution was reported by Fehr (Scheme 82).[156]

Scheme 82
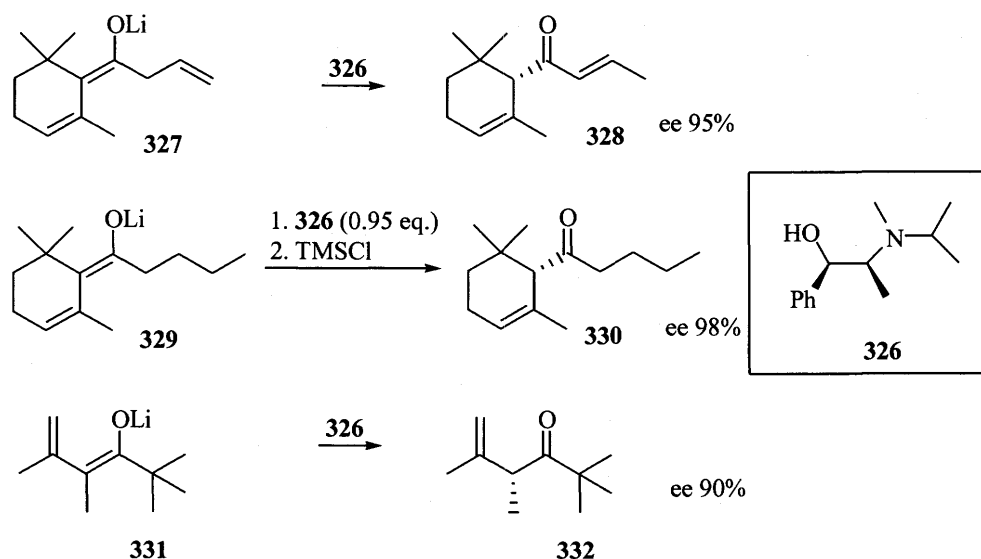
Keeping this fact in mind, it was decided to use polymer-supported ephedrine **271a** as the proton donor in the protonation reaction of the enolate **322a**. The rationalization of the idea is presented in Scheme 83.

Scheme 83
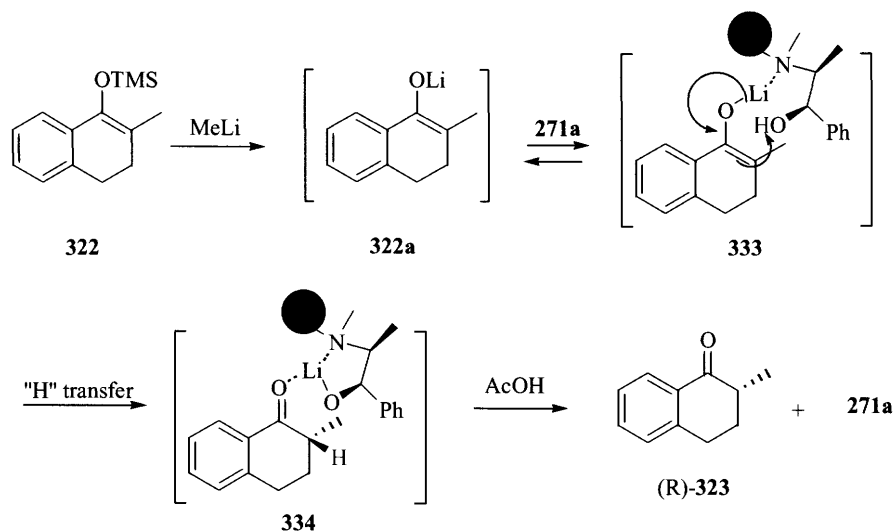
In the first step, the "amine-free" enolate **322a** is obtained. The phrase "amine-free" means that there is no amine complexed to the enolate *via* the lithium atom. After addition of LP ephedrine **271a**, the complex **333** can be formed, followed by the proton transfer, which leads to complex **334**. The enantiomerically enriched product (R)-**323** is produced, and the polymer-supported reagent **271a** is released after the addition of an achiral proton source (e.g. AcOH).

The results of the protonation reaction of lithium enolate **322a** are presented in Table 38.

Table 38. The influence of the reaction conditions on the protonation reaction of lithium enolate of 2-methyl-1-tetralone (**322a**) with LP reagent **271a**.

Entry	Solvent	Conditions of protonation (temp. and time)	AH	yield (%)	ee (%)[a]
1	THF	–20 °C, 2 h; –40 °C, 4 h	citric acid 10%	71	(-) 5
2	THF	–20 °C, 2 h; –40 °C, 12 h	citric acid 10%	57	0
3	THF	–20 °C, 2 h; –78 °C, 12 h	citric acid 10%	69	0
4	toluene	–20 °C, 1 h; –40 °C, 2 h	citric acid 10%	-	-
5	toluene	–20 °C, 2 h; –40 °C, 4 h	AcOH	75	(+) 13
6	toluene	–20 °C, 2 h; –40 °C, 12 h	AcOH	75	(+) 15
7	toluene	–20 °C, 2 h; at –78 °C, 12 h	AcOH	80	(+) 10

[a] The enantioselectivity of the protonation reaction was calculated by measuring the $[\alpha]$ value of the product and dividing by the known $[\alpha]$ value of the pure enantiomers of 2-methyl-1-tetralone (ref. 163).

The reaction was strongly solvent dependent. In THF, the product **323** was obtained in a good yield but as the racemate (Table 38, entries 1 – 3). When the solvent was changed to toluene, and non-aqueous workup conditions were applied, the yield was slightly improved, and (R)-**323** was obtained, (Table 38, entries 5 – 7). The "non-aqueous workup" means that the reaction was quenched with glacial AcOH, followed by precipitation of the polymer-supported ephedrine **271a** from cold MeOH (-45 °C). The LP reagent was separated by filtration, and the crude product **323** was left in the filtrate. The enantioselectivity of the protonation was measured on the pure product **323**, and the $[\alpha]_D$ value of the product was compared to the known $[\alpha]_D$ values for pure (R)- and (S)-enantiomers of 2-methyl-1-tetralone (**323**) reported by Meyers.[163] In order to improve the yield and enantioselectivity of the protonation of **322a**, a second equivalent on MeLi

was added before the addition of the proton source. The yield of the protonation was improved to 98%, but the enantioselectivity dropped to 3%. A plausible explanation of the results of protonation of lithium enolate **322a** with LP reagent **271a** is offered in Figure 24.
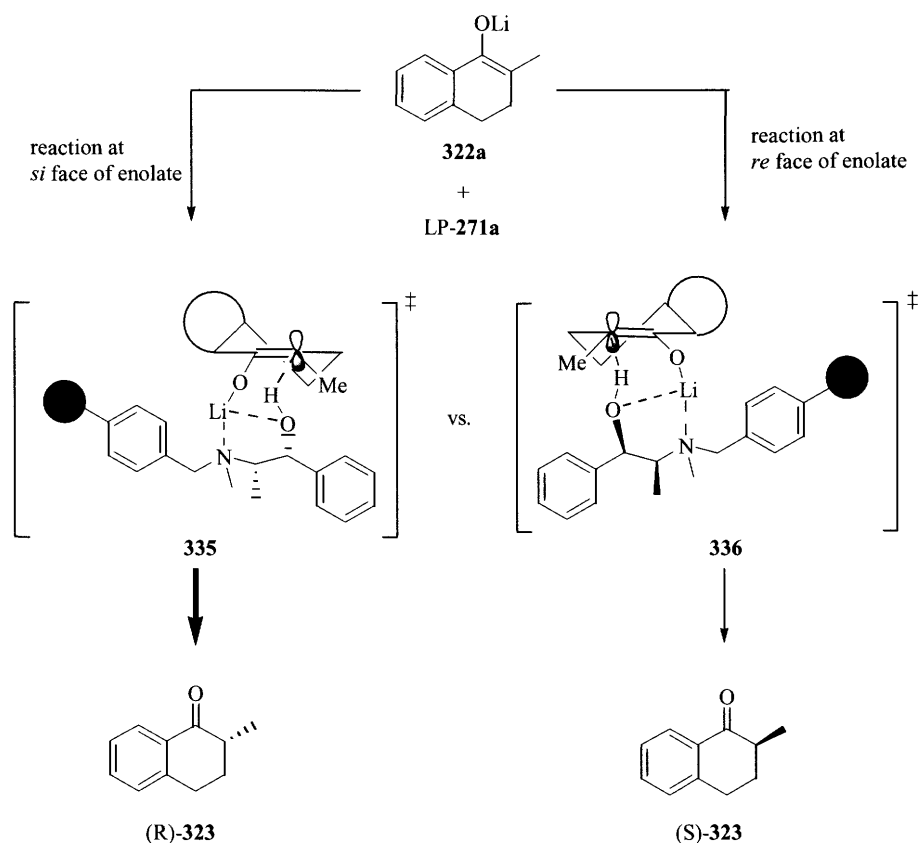
Figure 24. Proposed transition state structures of the enantioselective protonation of lithium enolate **322a** with LP proton source **271a**.

The faces of the lithium enolate **322a** are enantiotopic, and they react at different rates with the chiral proton source. The structures of the two corresponding transition states are shown in Figure 24. The complex **336** is likely less stable than the complex **335**, due to steric interactions between the methyl group in **322a** and the methyl group in the protonating reagent **271a**, and that is why the major product of protonation was (R)-2-methyl-1-tetralone (**323**). The enantioselectivity of this reaction was only 15%, which

could be explained by the small difference in the stability of the transition states **335** and **336**.

Diastereoselective protonation of cyclic enolates.

Protonation of chiral enolates is a fascinating subject with respect to diastereoselectivities, since double stereodifferentiation can be expected when a chiral proton source is used.[78, 159, 160] A new stereocenter generated in such a process is formed under the influence of both reagents: the chiral enolate, and the chiral proton source. It had been shown before that the chiral ephedrine derivative **326** was successfully applied as the proton donor in enantioselective protonation (Scheme 82).[156] Keeping that in mind, I wondered if I could apply chiral alcohols as proton sources in diastereoselective protonation of the lithium enolate of a cyclic ketone. The lithium enolate **337a** derived from the silyl enol ether of (-)-menthone was chosen as the model compound. The enolate was first protonated in solution with amino-alcohols **340a** and **341a**. Commercially available ephedrine (**55a**), and pseudoephedrine (**275**) were N-alkylated with benzyl bromide to give reagents **340a** and **341a**, respectively.

340a X= H
340b X= Li

341a X= H
341b X= Li
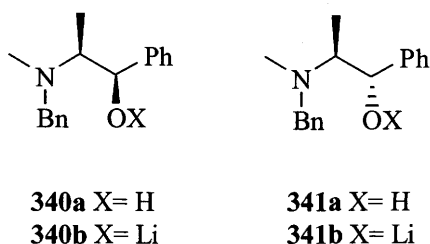
Protonation of enolate **337a** was performed in solution and in liquid-phase (Scheme 84). The results are summarized in Tables 39 (solution reagents) and 40 (LP reagents).

Scheme 84

337

337a

338 (major)   **339** (minor)
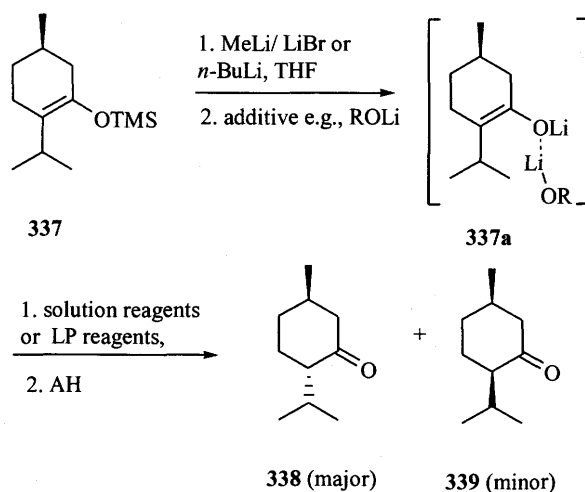
Table 39. The results of the study of diastereoselective protonation of **337a** conducted in solution.

Entry	Reagent	Additive	Yield[b] (%)	Ratio[c] 338: 339
1	**341a**	-	26	87: 13
2[a]	**341b**	**341a**	54	87: 13
3	**341a**	**341b**	74	97: 3

[a] Lithium enolate **337a** was generated first then aminoalcohol **341a** was added, followed by addition of the lithiated derivative **341b**. [b] The combined yield of both products. [c] The ratio was measured by ^{1}H NMR.

All reactions were performed in THF. The unreacted lithium enolate **337a** was trapped with TMSCl. The best result was obtained with N-benzylpseudoephedrine **341a** and its lithiated derivative **341b** (Table 39 entry 3). The products were obtained in a 97: 3 ratio (**338: 339**), and in 74% combined yield. This result is comparable with the result obtained by Yamamoto and co-workers (98% combined yield, ratio: 97: 3) during the studies on a protonation reaction of **337a** conducted in solution.[157] Chiral imide **342** was used as the proton source.

(S)-**342**
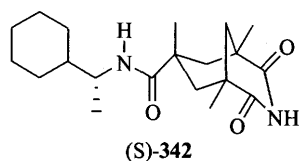
The conditions for the reaction in solution were elaborated, so the stage was set for the development of the protonation reaction of **337a** conducted in the "liquid phase" (Table 40).

Table 40. The influence of the conditions on the diastereoselectivity of protonation of lithium enolate **337a** with LP reagents.

Entry	Reagent	Additive	AH	Yield (%)	Ratio 338: 339
1	**271a**	-	BTH	44	67: 33
2[a]	**271a**	-	NH$_4$Cl aq.	-	-
3	**271a**	-	BTH (1 hour)	40	91: 9
4	**271b**	-	BTH (1 hour)	59	89.5: 11.5
5[b]	**341a**	**272b**	MeOH	98	91: 9
6[b]	**341a**	**272a**	MeOH	63	90: 10
7[b]	**341a**	t-BuOLi	MeOH	84	85: 15

[a] Starting material was recovered. [b] Non-aqueous workup was applied.

It can be seen from the above data that the best results of diastereoselective protonation of enolate **337a** were obtained, when the lithium enolate was generated in the presence of alkoxide (Table 40, entries 5 and 7) or when the additive was added (Table 40, entry 6). It is known that lithium halides, lithium alkoxides, and lithium amides can cause deaggregation of enolates. Lithium enolates form monomeric mixed aggregates with these species, as shown below.[156]

343   344   345

X*: chiral ligand
X: achiral ligand
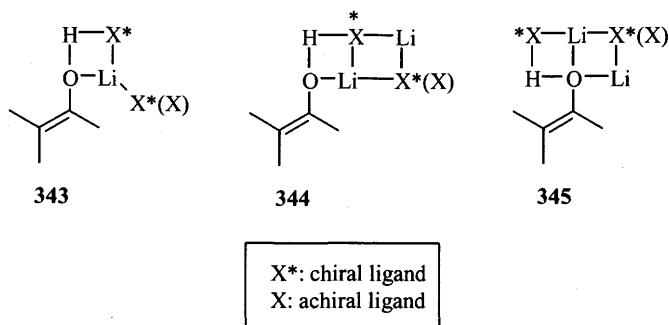
The formation of mixed aggregates **343 – 345** in solution is followed by C-protonation. When the polymer-supported alkoxide **272b** was added to the solution of **337a** it presumably caused deaggregation of the enolate **337a**, and formation of mixed aggregates of structures similar to **343 – 345**. The mixed aggregates were then protonated by **341a** and the products (**338** and **339**) were obtained in 91: 9 ratio (Table 40, entry 5). This result is comparable to the result obtained in solution by Yamamoto and coworkers.[157, 159] These authors generated the amine-free lithium enolate from (-)-menthone silyl enol ether **337**, and protonated this enolate with reagent **341**. A mixture of two diastereomers: **338** and **339** was obtained in 98% yield and in a 97: 3 ratio.[157] When LP alcohol **272a** was added to the solution of the enolate **337a**, the enolate was deaggregated as well, but the product was obtained in a lower yield (63%). This could be explained by the possibility of proton transfer between enolate **337a** and reagent **272a**. Another effect that likely had influence on the resultant protonation of **337a** was double stereodifferentiation.[78] When two chiral reagents undergo a reaction, the stereoselectivity can be higher than expected (matched pair) or lower (mismatched pair). The diastereoselectivity of the protonation of **337a** was increased after the addition of a chiral additive (Table 40, entries 5 and 6) compared to the achiral additive (Table 40, entry 7).

In summary, it was demonstrated that soluble, polymer-supported aminoalcohols and their lithiated derivatives could be successfully employed in the selective protonation of cyclic lithium enolates. The products were obtained in good to excellent yield and in good enantio- and diastereoselectivity.

2.B.6 Conclusions

1. The syntheses of two new classes of organic reagents were developed: insoluble and soluble polymer-supported chiral lithium amines and alcohols. They can be divided into two categories:

    (i)   reactive groups directly attached to the polymer matrix.

    (ii)   separated from the polymer matrix by a linker.

2. Methods for the determination of the nitrogen content in the polymer-supported reagents were developed.

3. It was shown that the presence of an amino group in the polymer could be confirmed by a bromophenol blue test (a change of color from yellow to blue was observed.)

4. General methods for the generation of the corresponding polymer-supported chiral lithium amides and alkoxides were elaborated.

5. SP and LP chiral lithium amides were successfully employed as bases in deprotonation reactions of tropinone and a β-ketoester.

6. LP reagents could be used in the stereoselective protonation of lithium enolates derived from cyclic ketones.

7. It was shown that the reactions, which work well in solution can be successfully adapted to solid and liquid phase synthesis involving polymer-supported reagents, thus providing a new methods of performing synthetically useful reactions.

CHAPTER III: SUMMARY AND FUTURE WORK

3.1 Summary

Deprotonation of ketones is a very complicated process. Chiral lithium amides used as bases to generate corresponding lithium enolates from cyclic ketones can form aggregates (dimers of different stoichiometry), which are less reactive species than monomers. The aggregation of lithium amides can be broken by addition of different substances.

Deprotonation of tropinone with nine chiral lithium amides was studied. The corresponding enolate was obtained, and captured with 2,2,2-trichloroethyl chloroformate. The influence of additives such as lithium salts (LiCl, LiBr, LiI, LiF, $LiClO_4$), polar co-solvents (HMPA, DMPU, TMEDA), and other compounds ($CeCl_3$, $ZnCl_2$) on the course on the reaction was investigated. The most efficient combination of the reagents was found to be the simple C2 chiral lithium amide and 1 equivalent of LiCl (the enone was obtained in 92% yield and 96% ee).

It is known that after the generation of lithium enolate, the chiral amine derived from the corresponding chiral lithium amide stays complexed to the enolate *via* the lithium atom, which can affect the enantioselectivity or diastereoselectivity of the reaction of the latter with an electrophile. Thus, the final enantioselectivity of deprotonation of ketones belonging to the C_S symmetry group is a result of two effects: preferential abstraction of one of the α axial hydrogens and complexation of the chiral amine to the enolate *via* the lithium atom. To study the complexation effect, 1,4-cyclohexanedione was deprotonated with two chiral bases. The ketone has the average symmetry C_{2V} so the chiral lithium amide will not differentiate between two α axial hydrogens. The corresponding enolate was captured with benzaldehyde, and the aldol product was obtained in 85% yield. The enantioselectivity of this reaction was only 14%, which indicates that the complexation effect of the chiral amine to the enolate *via* the lithium atom can be neglected when enantioselective deprotonation of cyclic ketones is considered.

The other part of the work presented in this thesis deals with synthesis, and application of polymer-supported lithium amides. At the beginning of this work little was known about the synthesis of these reagents and their properties, therefore it was decided to explore their chemistry.

Three general methods for the synthesis of the insoluble and soluble, polymer-supported chiral amines were elaborated. The synthetic procedures are general and easy to perform. A method for the loading determination (i.e., the number of mmol of NH groups in 1 g of resin) was elaborated. Polymer-supported chiral lithium amides were generated according to the procedure adapted from "the solution phase". The reagents were used as the bases in deprotonation of a cyclic ketone (tropinone) and a β-ketoester (ethyl 2-oxocyclopentanecarboxylate). The corresponding α-functionalized carbonyl compounds were obtained in good yield. It was possible to deprotonate tropinone enantioselectively. The aldol product was obtained in up to 70% ee with the soluble polymer-supported lithium amide; and the ring-opening product of tropinone was obtained in up to 59% ee with the insoluble polymer-supported lithium amide. It was not possible to obtain the enone enantioselectively with soluble polymer-supported lithium amides due to the leaching of amines from the resin. The benzylated β-ketoester was obtained in 76% yield, but not enantioselectively.

A preliminary study of protonation of the lithium enolate with polymer-supported chiral proton sources was performed. The lithium enolate of 2-methyl-1-tetralone was protonated enantioselectively with soluble polymer-supported ephedrine and the corresponding product was obtained in 80% yield and 15% ee. The lithium enolate derived from (-)-menthone was protonated diastereoselectively, and the corresponding ketone was obtained in 74% yield and 94% de.

3.2 Future work

The task of synthesizing the polymer-supported lithium amides proved to be very challenging. It was demonstrated in this preliminary study that these reagents could be used as bases in the deprotonation of carbonyl compounds. To fully understand the potential of this new class of bases a more detailed methodology study is needed.

The first task could be a more detailed study of the concentration effect, which was observed during the deprotonation of tropinone with soluble polymer-supported lithium amides. This work could be used in further optimization of the conditions of ring-opening reaction of tropinone and benzylation of ethyl 2-oxocyclopentanecarboxylate.

Other reactions catalyzed by chiral lithium bases should be tried. One of them is the catalytic deprotonation of cyclic ketones e.g., α-tetralone and 2-methyl-1-tetralone, which was studied by Koga in "the solution phase".[158] The chiral amine **324a** was used in a catalytic amount (0.3 equivalent), with 2-3 equivalents of the achiral amine **325**. The achiral amine (**346a** or **346b**) could be attached to the polymer by methods described previously.

346a (insoluble resin)
346b (soluble resin)

324
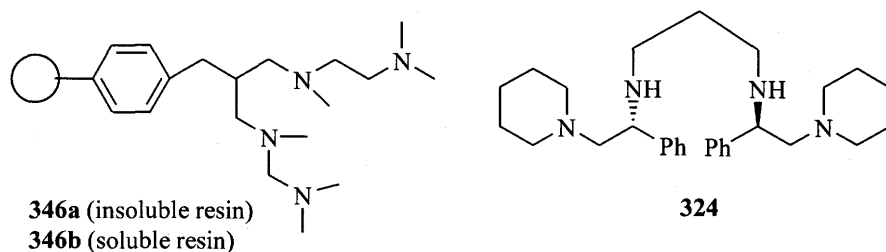
The achiral amine (**346a** and/or **346b**) could be recycled and reused after completion of reaction, which would minimize the cost of this transformation (the achiral amines used for the "solution phase" catalytic deprotonation are expensive).[125]

The ring-opening of epoxides could be another model reactions to be study with polymer-supported chiral lithium amides. The general reaction is shown in Scheme 85.

Scheme 85

347   **348**

RR*NLi

349a X= H
349b X= Li

350a R= X= H
350b R= X= Li
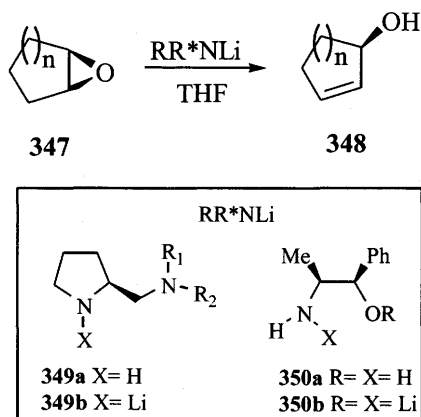
The reaction has been extensively studied in solution, and numerous procedures are available.[184] The chiral lithium amide (**349b** and/ or **350b**) could be attached to the resin to give polymer-supported chiral lithium amides **352b** – **355b** by methods described in this thesis, and than applied in the ring-opening of a simple epoxide.

352b (insoluble resin)
353b (soluble resin)

354b (insoluble resin)
355b (soluble resin)
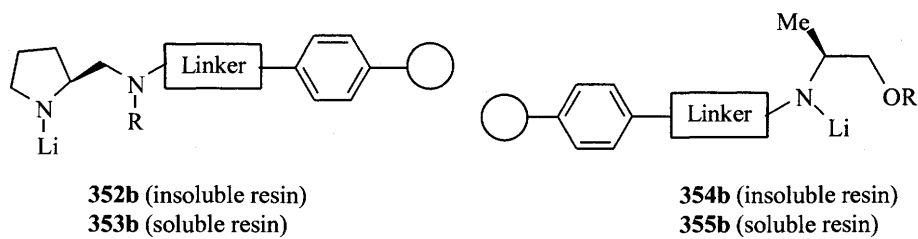
CHAPTER IV: EXPERIMENTAL

4.1 General methods

All air sensitive reactions were carried out under nitrogen. Tetrahydrofuran was distilled under nitrogen from sodium and benzophenone. Diisopropylamine, triethylamine and other amines used as precursors for lithium amides were distilled from calcium hydride. Chiral amines were prepared according to the procedures described in the literature.[168] Lithium chloride was dried at $130 - 150$ °C under high vacuum for 12 hours, dissolved in THF, and stored under nitrogen. Tetramethylethylenediamine (TMEDA), hexamethylphosphoric triamide (HMPA), and 1,3-dimethyl-3,4,5,6,-tetrahydro-2($1H$)-pyrimidinone (DMPU) were distilled from calcium hydride and stored under nitrogen. *tert*-Butyl alcohol was distilled from calcium hydride. The polymer-supported amines were recycled by mixing with a solution of sodium hydroxide, followed by filtration, washing of the polymers with water, methanol, and dried to the constant weight under high vacuum. The insoluble polymer-supported amines were pre-swollen in appropriate solvent for 1 hour before a reaction was started. *n*-BuLi was periodically titrated with 2,5-dimethoxybenzyl alcohol as the standard indicator.

Flash column chromatography (FCC) was carried out using Merc silica gel 60 (230-400 mesh). Dry-column flash chromatography was carried out using Sigma silica gel Type H (10 – 40 μm), and TLC was performed on precoated glass plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), or with a developing solution by charring on a hot plate. The developing solution was prepared by dissolving concentrated sulfuric acid (50 g), cerium (IV) sulfate (10 g), and phosphomolybdic acid hydrate (40 g) in water (1 L).

The known compounds described in this section were characterized by the melting/ boiling point temperature, R_f values, proton magnetic resonance and carbon magnetic resonance spectra. The literature references to the original publications are located after the compound name.

Melting points and boiling points are uncorrected. Melting points were measured on a Gallencamp melting point apparatus. The optical rotation of compounds described in this section, were recorded on a DigiPol 781 Automatic Polarimeter Rudolph Instrument (1 dm, 1 mL cell), all the concentrations are given in g/ 100 mL.

Proton magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer in CD_3Cl. Chemical shifts are reported in ppm of δscale with TMS as the internal standard. Coupling constants are reported to the nearest 0.5 Hz. In order to obtain a high signal to noise ratio, ^{1}H NMR spectra for analysis of the ee of the aldol of tropinone were recorded using 20 - 25 mg samples in 0.4 mL of chloroform-d in the presence of 20 mg of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (S-(+)-TFAE). ^{1}H NMR spectra for analysis of the ee of the anti aldol of 1,4-cyclohexanedione monoethylene ketal were recorded using 20 - 25 mg samples in 0.4 mL of chloroform-d in the presence of Eu(tfc)$_3$.

Gas chromatography was performed using a Hewlett Packard 5890A instrument fitted with a methyl silicone gum column (HP-1, 5 m x 0.53 mm). Chromatographic analyses of the enantiomeric purity of the ring-opening of tropinone were done on a computer controlled Gilson HPLC system with the ChiralPack AD column (Diacel) and a UV detector (at 254 nm). The solvent system was 85: 15 (vol/ vol) hexane: isopropanol at 0.8 ml/ min flow rate.

Infrared (IR) spectra were recorded on a Biorad FTS-40 Fourier Transform interferometer by means of the diffuse reflectance cell method. Only diagnostic peak frequencies are reported.

Mass spectra were recorded on a VG Analytical retrofit of a single sectored, magnetic scanning MS-12 (low resolution) or a double sectored MS VG 70-250-VSE (high resolution) and are reported as m/z ratio (relative intensity). Electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV.

The CHN elemental analyses were carried out using Perkin Elmer 2400 CHN Elemental Analyzer.

4.2. NMR spectroscopy of polymers.

One of the techniques giving the most information about the structure of polymers is ^1H and ^{13}C NMR spectroscopy. The abundance of the ^{13}C isotope of carbon is only 1.1 %, but the sensitivity of the NMR spectroscopy is high enough to allow signals given by ^{13}C atoms to be easily detected. The chemical shifts in ^{13}C NMR are considerably larger in comparison to ^1H NMR, and the spectral features can be observed with higher resolution. There are special techniques that are applied to sharpen up the otherwise very broad signals: "magic angle spinning" (MAS), "cross polarization" (CP), and "proton decoupling" (PD) but they all require special probes.

When this project was started, the department did not have a special NMR probe that could be used for performing ^1H and ^{13}C NMR experiments on polymers. The ^1H and ^{13}C spectra for insoluble polymers were recorded in a gel phase (a polymer swollen in chloroform-d forming a gel) or in a very viscous solution of soluble resins. The peaks in ^1H and ^{13}C spectra were very broad, many of them were overlapping therefore it was not possible to obtain detailed information about the structure of a resin. The number of hydrogens assigned to each signal in ^1H spectra for the insoluble and soluble polymers was calibrated from the signal given by the hydrogen nuclei of the CH_2Cl or CH_2I groups. The numbers of aromatic hydrogen included mostly hydrogens from the polymer backbone, and hydrogens from the attached compound. The number of aliphatic hydrogens represents the number of the aliphatic hydrogens present in the polymer matrix (mostly), and aliphatic hydrogens of the attached compound.

X= Cl or I

A= O or N

Linker= -(CH$_2$)- chain

FG= functional group: OH, I, CO$_2$R or ArNH
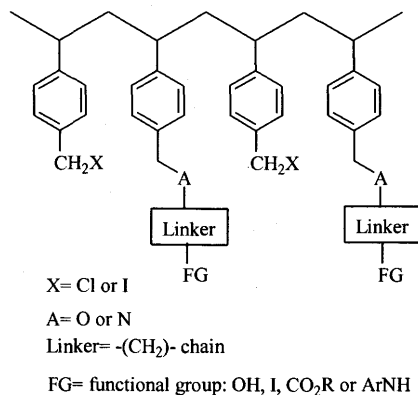
It is known, that the chemical shifts in ^{13}C NMR are considerably larger than in ^{1}H NMR, so the spectral features can be observed with better resolution.[169] Unfortunately this was not the case, when it came to polymer-supported reagents synthesized during this project. The signals in ^{13}C NMR were broad, but the diagnostic peaks were observed, and are reported. The signals given by aromatic carbon consisted of carbons from the polymer matrix, and carbons of the attached compound. It was not possible to differentiate between specific carbons. The MAS technique was not feasible due to the lack of appropriate probe for the 300 MHz NMR instrument present at the Department during my work on the synthesis of polymer-supported chiral amines.

4.3. Methodology study performed in solution

Procedure A: Generation of racemic lithium tropinone enolate (**201a**) using LDA.[2]
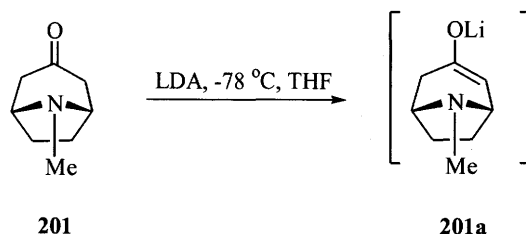
A solution of n-BuLi (2.25 M, 0.49 mL, 1.1 mmol) was added to the solution of diisopropylamine (0.150 mL, 0.112 g, 1.10 mmol) in THF (6 mL) at 0 °C under N_2 and the resulting solution was stirred for 25 minutes. After cooling to −78 °C, a solution of tropinone (**201**) (0.139 g, 1.00 mmol) in THF (2 mL) was added over a period of 3 minutes and the resulting mixture was stirred for 45 minutes.

Procedure B: Generation of non-racemic tropinone lithium enolate (**201a**) using a chiral lithium amide prepared from corresponding chiral amine (and an additive).[2]
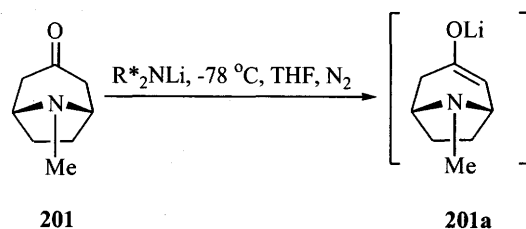
A solution of n-BuLi (2.25 M, 0.20 mL, 0.44 mmol) was added to the solution of a chiral amine (0.44 mmol) in THF (3 mL) at 0 °C under N_2 and the resulting solution was stirred for 2 – 2.5 hours. (A solution of an additive was added; the number of equivalents, and the type of additive are specified in Appendix 1). After cooling to −78 °C, a solution of

tropinone **(201)** (0.056 g, 0.400 mmol) in THF (0.80 mL) was added over a period of 3 minutes and the resulting mixture was stirred for 1 hour.

Procedure C: Generation of non-racemic lithium enolate of tropinone **(201a)** with a chiral lithium amide prepared from a corresponding chiral amine hydrochloride.

201 → **201a**
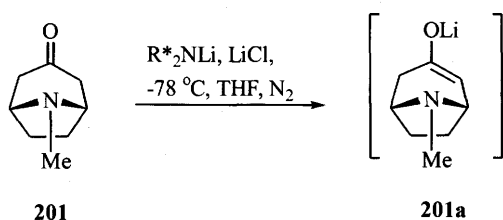
A solution of n-BuLi (2.25 M, 0.40 mL, 0.88 mmol) was added to the solution of a chiral amine hydrochloride salt (0.440 mmol) in THF (3 mL) at 0 °C under N_2 and the resulting solution was stirred for 2.5- 3 hours. After cooling to −78 °C, a solution of tropinone **(201)** (0.056 g, 0.400 mmol) in THF (0.80 mL) was added over a period of 3 minutes and the resulting mixture was stirred for 1 hour at this temperature.

Procedure D: Generation of the lithium enolate of 1,4-cyclohexanedione monoethylene ketal **(239)**.[1]

239 → **239a**
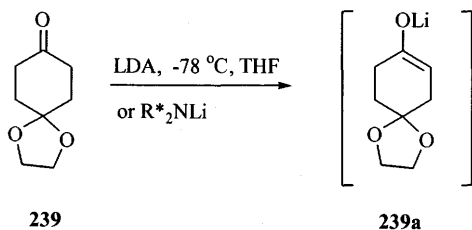
A solution of n-BuLi (1.45 M, 0.76 mL, 1.1 mmol) was added to the solution of diisopropylamine (0.14 mL, 0.11 g, 1.1 mmol) in THF (5 mL) at 0 °C under N_2 and the resulting solution was stirred for 0.5 hour. After cooling to −78 °C, a solution of ketone

239 (0.156 g, 1.00 mmol) in THF (1 mL) was added over a period of 3 minutes, and the resulting mixture was stirred for 0.5 hour.

Alternatively:

A solution of n-BuLi (1.45 M, 0.76 mL, 1.1 mmol) was added to the solution of a chiral amine (1.10 mmol) in THF (5 mL) at 0 °C under N_2 and the resulting solution was stirred for 1.5 hour. After cooling to –78 °C, a solution of ketone **239** (0.156 g, 1.00 mmol) in THF (1 mL) was added over a period of 3 minutes, and the resulting mixture was stirred for 2.5 hour.

Procedure E: Generation of the lithium enolate of 1,4-cyclohexanedione monoethylene ketal (**239**) with second equivalent of n-BuLi.
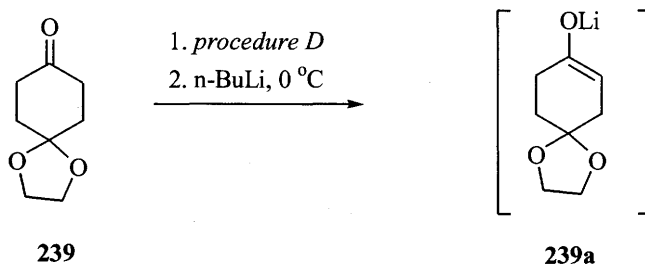
A solution of n-BuLi (1.45 M, 0.76 mL, 1.10 mmol) was added to the solution of the lithium enolate **239a** prepared by *procedure D* (1.00 mmol). The reaction mixture was warmed to 0 °C and stirred for 0.5 hour followed by cooling down to – 78 °C before addition of benzaldehyde.

Procedure F: Generation of the lithium enolate **239a** from 8-trimethylsilyloxy-1,4-dioxaspiro[4.5]dec-7-ene (**246**) without any additive.
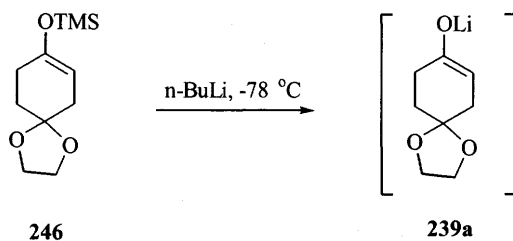
A solution of n-BuLi (1.45 M, 0.24 mL, 0.35 mmol) was added to the solution of silyl enol ether **246** (0.08 g, 0.35 mmol) in THF (3 mL) at -78 °C under N_2, and the resulting solution was stirred for 2.5 hour.

Procedure G: Generation of the lithium enolate **239a** from the corresponding silyl enol ether **246** with the additives.
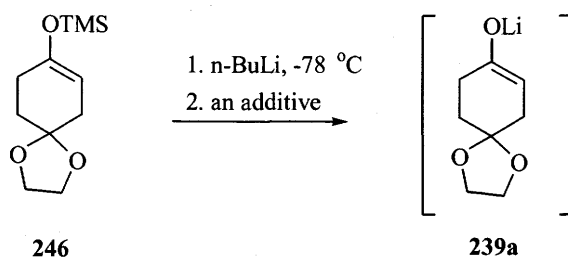
A solution of chiral amine (0.48 mmol) in THF (1 mL) was added to the solution of lithium enolate **239a** generated by *procedure E*, and the stirring was continued for an additional 2.5 hour.

Alternatively:

A solution of chiral amine (0.48 mmol) in THF (1 mL) was added to the solution of lithium enolate **239a** generated by *procedure E*, and the stirring was continued for an additional 2.5 hour. The reaction mixture was warmed to 0 °C and a solution of n-BuLi in

hexane (1.45 M, 0.34 mL, 0.48 mmol) was added. The mixture was stirred at 0 $^{\circ}$C for 0.5 hour, before it was cooled to −78 $^{\circ}$C.

6-[N-(2,2,2-Trichoroethoxy)carbonyl-N-methyl]amino-2-cyclohepten-1-one (230)[2]

201a   **230**
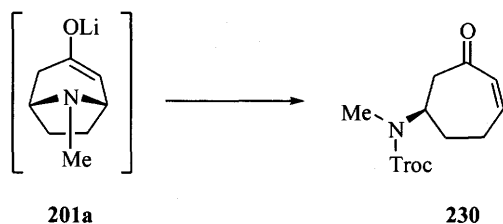
2,2,2-Trichloroethyl formate (0.16 mL, 0.246 g, 1.16 mmol) was added to the tropinone lithium enolate **201a** generated by *procedure A* (1.0 mmol), and the reaction mixture was stirred for 0.5 hour.

Alternatively:

2,2,2-Trichloroethyl formate (0.080 mL, 0.123 g, 0.580 mmol) was added to the tropinone lithium enolate **201a** generated by *procedure B or C* (0.400 mmol) and the reaction mixture was stirred for 0.5 hour.

After quenching with 40% K_2CO_3 (5 mL) and warming to room temperature, the reaction mixture was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with a solution of citric acid (3 x 30 mL), followed by brine, and were dried with $MgSO_4$. The solvents were removed *in vacuo* giving the crude product. The crude product was purified by crystallization from hexane or by FCC (hexane: AcOEt 4:1 – 1: 1). The yield of the racemic product is 76 % and the yields of the optically active products are shown in Appendix 1.

R_f= 0.55 (1: 1 hexane: AcOEt)

mp: (racemic) 58 - 60 °C (lit. 59 - 61 °C)[2]

The pure product **230** was characterized by ^{1}H NMR, and the spectrum was in agreement with previous results.[2, 86, 101]

^{1}H NMR δ: 6.64 (ddd, J= 12 Hz, J= 6 Hz, J= 5 Hz, 1H), 6.05 (d, J= 12 Hz, 1H), 4.75 (s, 2H), 4.55 (br, 1 H), 2.90 (s, 3H), 2.92 – 2.82 (m, 2H), 2.68 – 2.45 (m, 2H), 2.20 – 1.90 (m, 2H).

**1,4-Dioxaspiro[4.5]dec-8-trimethylsilyloxy-7-ene (246)**[1]
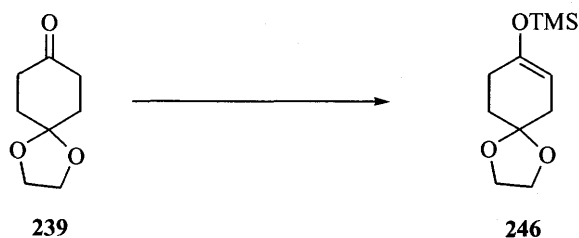
A solution of n-BuLi (1.45 M, 1.59 mL, 2.20 mmol) was added to the solution of diisopropylamine (0.28 mL, 0.22 g, 2.2 mmol) in THF (10 mL) at 0 °C under N_2, and the resulting mixture was stirred for 0.5 hour. After cooling to –78 °C, freshly distilled Et_3N (0.700 mL, 0. 510 g, 5.03 mmol) was added, followed by the addition of TMSCl (0.53 mL, 0.45 g, 4.2 mmol). The mixture was stirred for 5 minutes, and the solution of ketone **239** (0.312 g, 2.00 mmol) in THF (2 mL) was added over a period of 3 minutes. The resulting mixture was stirred for 1 hour. After quenching with saturated solution of NH_4Cl (20 mL), the reaction mixture was extracted quickly with Et_2O (3 x 75 mL). The combined organic layers were washed with brine, and dried with $MgSO_4$. The solvents were removed *in vacuo* to give crude product **246** (0. 420 g). The crude product was purified by DFC (hexane, hexan: AcOEt 9:1) yielding the pure **246** (0.365 g, yield 80%).

R_f= 0.49 (hexane: AcOEt 8: 1)

The ^{1}H NMR spectrum was in agreement with previous results:[1]

^{1}H NMR δ: 4.67 – 4.65 (m, 1H), 3.92 (s, 4H), 2.22 – 2.21 (br. s, 2H), 2.21 – 2.13 (m, 2H), 1.78 – 1.74 (t, J= 6.6 Hz, 2H), 0.14 (s, 9H).

1,4-Dioxaspiro[4.5]decan-7-(hydroxyphenylmethyl)-8-one (243)[1]
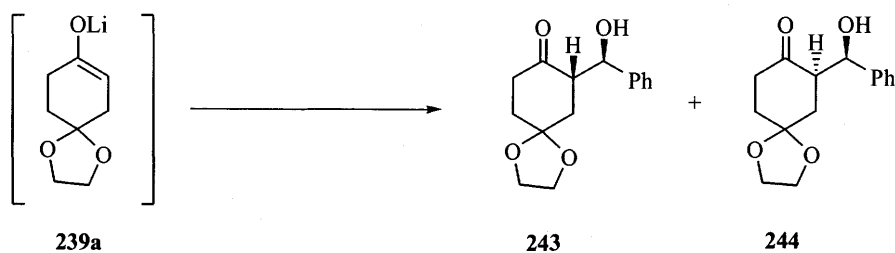
Benzaldehyde (0.11 mL, 0.120 g, 1.10 mmol) was added to the solution lithium enolate **239a** (1.00 mmol) generated by *method D or E* at – 78 °C, and the reaction mixture was stirred for 0.5 hour.

Alternatively:

Benzaldehyde (0.05 mL, 0.052 g, 0.490 mmol) was added to the solution of lithium enolate **239a** (0.35 mmol) generated by *method G or F* at – 78 °C, and the reaction mixture was stirred for 0.5 hour.

After quenching with phosphorane buffer (10 mL) the reaction mixture was extracted quickly with Et$_2$O (3 x 50 mL). The combined organic layers were washed with brine, and dried with MgSO$_4$. The solvents were removed *in vacuo* to give the two diasteromeric products: **243** and **244**. The crude products were purified by DFC (hexane: CH$_2$Cl$_2$ 9: 1, hexane: AcOEt 5:1) to yield the pure threo isomer **243**.

Diastereoselectivity of this reaction is shown in Table 2 in Appendix 1.

mp= 140-141 °C (lit. 141-142 °C)[1]

^{1}H NMR δ : 7.35 - 7.27 (m, 5H), 4.79 (d, J= 8.6 Hz, 2H), 3.96 - 3.80 (m, 5H), 2.98 (m, 1H), 2.67 (m, 1H), 2.43 (m, 1H), 2.04 - 1.94 (m, 2H), 1.67 - 1.48 (m, 2H).

4.4 Methods for determination of polymer loading:

1. Determination of N content in a polymer sample

    (i) the original Volhard titration method[124]:

The Vohlard titration method is a procedure for the titration of Ag^+. To determine Cl^- a back titration is necessary. First, the Cl^- is precipitated by a known, excess quantity of standard $AgNO_3$:

$$Ag^+ + Cl^- \longrightarrow AgCl\,(s)$$
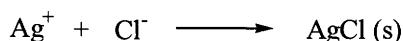
The AgCl is isolated and the excess of Ag^+ is titrated with standard KSCN in the presence of Fe^{3+}:

$$Ag^+ + SCN^- \longrightarrow AgSCN\,(s)$$
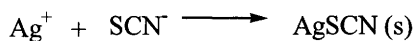
When Ag^+ is consumed, than SCN^- reacts with Fe^{3+} to form a red complex:

$$Fe^{3+} + SCN^- \longrightarrow FeSCN^{2+}$$

The appearance of red color indicats the end point. The amount of SCN^- required for back titration was known, so the amount of Ag^+ left over from the reaction with Cl^- was known as well. To calculate the amount of Cl^-, the leftover amount of Ag^+ has to be subtracted from the total, known amount of Ag^+.

General procedure:

An excess of standard HCl (V_{HCl}, C_{HCl}) was added to the sample of a polymeric amine (m_{amine}= mg), and the mixture was stirred for 3 hours. The polymer was separaed by filtration and washed with distilled water. The Vohlard titration was performed on the filtrate. An excess of $AgNO_3$ solution was added to the filtrate (V_1, C_1). The white

precipitate was formed (AgCl), which was covered with nitrobenzene. 3 Drops of Fe^{3+} solution were added, and the remaining Ag^+ ions were titrated with standard KSCN solution (V_2, C_2). The red color indicated the end point. The loading of a sample was calculated from the following equation:

Loading of a polymer (mmol of N/g of polymer)

$$\frac{\{V_{HCl} \cdot C_{HCl} - [(V_1 \cdot C_1) - (V_2 \cdot C_2)]\} \cdot 1000}{m_{amine}}$$

V_{HCl}: used volume of standard HCl mL

C_{HCl}: molar concentration of standard HCl, mol/L

V_1: used volume of standard $AgNO_3$, mL

C_1: molar concentration of standard $AgNO_3$, mol/L

V_2: used volume of standart KSCN solution, mL

C_2: molar concentration of standard KSCN solution, mol/L

m_{amine}: weight of a polymer sample, mg

It was found, experimentally, that this procedure was giving higher loading values than were possible. This was due to the fact that HCl was absorbed on the Merrifield resin. This observation was confirmed by "blind" titration of the Merrifield resin. The nitrogen content of a polymer-supported amine was calculated by Fajans titration method or by elemental analysis.

(ii) Fajans titration method[124]:

The Fajans titration method is based on the formation of an insoluble salt on which surface an indicator is being absorbed. In this particular example SO_4^{2-} ions were titrated with a standardized $Ba(OH)_2$ in 50% aqueous MeOH.

$$Ba^{2+} + SO_4^{2-} \longrightarrow BaSO_4 \ (s)$$
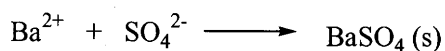
Alizarin red S was used as an indicator. The end point was visualized by color change of precipitate ($BaSO_4$) from white to light pink.

General procedure:

An excess of standard H_2SO_4 solution (V_1, C_1) was added to a sample of a polymer-supported amine, and the suspension was stirred for 3 hours. The polymer was separated by filtration and washed with aqueous MeOH (1: 1 MeOH: H_2O). The Fajans titration was performed on the filtrate. Alizarin red S solution (5 drops) was added to the filtrate, and the remaining SO_4^{2-} ions were titrated with standard Ba^{2+} solution. The end point was indicated by the color change of the precipitate ($BaSO_4$) from white to light pink due of the absorbtion of the dye on its surface.

Loading value of the sample was calculated from the following equation (mmol of N/g):

$$\frac{[(V_1 \cdot C_1) - (V_2 \cdot C_2)] \cdot 1000}{2 \cdot m_{amine}}$$

V_1: used volume of standard H_2SO_4, mL

C_1: molar concentration of standard H_2SO_4, mol/L

V_2: used volume of standard Ba^{2+} solution, mL

C_2: molar concentration of standard Ba^{2+} solution, mol/L

m_{amine}: weight of a polymer sample, mg

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(iii) determination of nitrogen content by elemental analysis

Loading of a polymer (mmol of N/g of a polymer) was calculated from the following equation:

$$\frac{N\% \cdot 1000}{100\% \cdot M_N}$$

N%: percentage of nitrogen present in a sample used for an elemental analysis
M_N: atomic mass of nitrogen

2. Determination of OH content in a polymer sample.

A method for determining the concentration of an organolithium reagent was described for the first time in 1980 by Ronald and co-workers.[170] 2,5-Dimethoxybenzyl alcohol was used as the primary standard. In the first step an OH functionalized resin is reacted with an excess of *n*-BuLi:
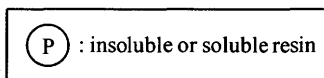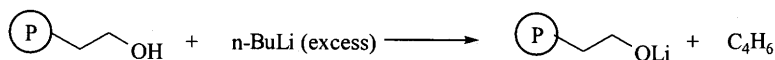
Then, the remaining excess of *n*-BuLi is back titrated with a standard solution of the indicator:
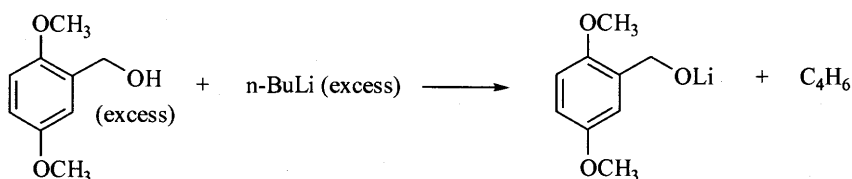
Finally, the excess of 2,5-dimethoxybenzyl alcohol is titrated with *n*-BuLi:
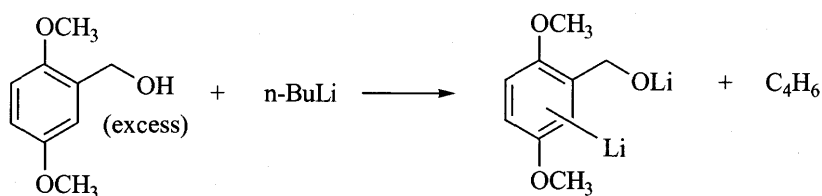
General procedure:

A polymer sample (200 ~ 300 mg) was pre-swollen by the appropriate solvent (3.00 mL, THF or benzene) for 30 minutes at room temperature under N_2. The sample was cooled down to 0 °C (for THF) or –15 °C (for benzene), and n-BuLi was added (2 ~ 3 equivalents, based on an estimated loading of a precursor resin (V_1, mL; C_{n-BuLi}, M). The reaction mixture was stirred at the appropriate temperature for an additional hour. Subsequently, 2,5-dimethoxybenzyl alcohol was added (1.00 mmol, $V_{indicator}$, mL; $C_{indicator}$, M), and the reaction mixture was warmed to room temperature. After stirring for 30 minutes, the yellowish suspension was titrated with n-BuLi (V_2, mL; C_{n-BuLi}, M). The endpoint is characterized by a green, brown or greenish brown color. The loading of a resin (mmol of OH/g) was calculated from the following equation:

$$\frac{[(V_1 + V_2) \cdot C_{n-BuLi} - V_{indicator} \cdot C_{indicator}] \cdot 1000}{m_{amine}}$$

$V_1 + V_2$: used volume of n-BuLi

C_{n-BuLi}: molar concentration of n-BuLi, mol/L

$V_{indicator}$: used volume of 2,5-dimethoxybenzyl alcohol, mL

$C_{indicator}$: molar concentration of 2,5-dimethoxybenzyl alcohol, mol/L

m_{amine}: weight of a polymeric sample, mg

The gravimetric analysis:

The gravimetric determination of polymer loading is explained in the following example:
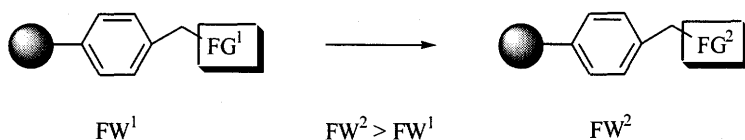
loading: 2.00 mmol of FG^1/ g

Polymer-FG^1 (eg., 1.00 g, 2.00 mmol of FG^1/g) was transformed into polymer-FG^2. The yield of the reaction was 100%. The theoretical weight of the polymer-FG^2, and the theoretical loading of polymer-FG^2 can be calculated from the following equations:

$$\text{theoretical weight of polymer-}FG^2: \quad \frac{(FW^1 - FW^2) \cdot 2 + 1}{1000}$$

FW^1: molar weight of functional group 1 (FG^1)

FW^2: molar weight of functional group 2 (FG^2)

2.: initial loading values of polymer-FG^1 (2.00 FG^1/g)

1: mass of polymer-FG^1 (1.00 g)

$$\text{theoretical loading of polymer-}FG^2: \quad \frac{2}{\text{theoretical weight of polymer-}FG^2}$$

4.5 Synthesis of insoluble polymer-supported chiral amines.

Cross-linked (CL) polystyrene-supported methyl iodide (247)

12   247

Sodium iodide (5.00 g, 33.4 mmol) was added to the pre-swollen Merrifield resin (12) (4.00 g, 4.00 mmol, original loading: 1.00 mmol of Cl/g) in acetone (50 mL), and the resulting suspension was refluxed for 48 hours. After the reaction was completed, the polymer 247 was separated by filtration, and washed with 100 mL of each of the following solvents: acetone, THF, ethanol, methanol, 1: 1 methanol - water, NaOH, water, methanol, and ethanol. The polymer 247 was dried to constant weight under high vacuum, and 3.862 g of 251 was obtained. The loading of polymer 247 was not determined.

^{1}H NMR δ: 7.60 - 5.74 (m, 25H, Ar), 4.65 - 4.03 (m, 2H, CH$_2$X), 2.47 - 1.05 (m, 17H, CH$_2$, and CH, polymer matrix).

^{13}C NMR d: 145.3 (C-Ar), 128.2 (C-Ar), 125.9 (C-Ar), 44.1 (CH$_2$, polymer matrix), 40.6 (CH, polymer matrix), 6.6 (CH$_2$I).

CL polystyrene-supported *(S)*-N-methyl-1-phenylethylamine (250a)
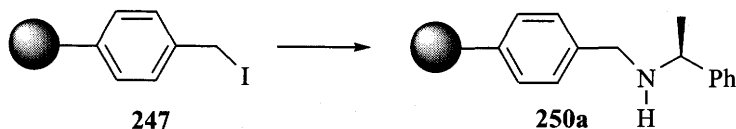
S-(-)-α–Methylbenzylamine (**248a**) (3.645g, 3.880 mL, 30.12 mmol) was added to the pre-swollen polymer **247** (6.026 g) in THF (100 mL). The mixture was refluxed under N_2 for 48 h. After the reaction was completed, the polymer **250a** was separated by filtration and washed with 150 mL of each of the following solvents: THF, acetone, methanol, 1: 1 methanol: water, water, NaOH, water, methanol, ethanol and Et_2O. The polymer was dried under high vacuum to constant weight, and 6.000 g of resin **250a** was obtained. The loading of the polymeric amine **250a** was determined by Fajans titration method or by elemetal analysis, and was 0.604 mmol of NH/g.

Dehalogenation procedure:[37b]

A solution of tributyl tin hydride (3.645 g, 3.300 mL, 12.54 mmol) was added to the suspension of polymer **250a** (6.122 g, 4.180 mmol, loading of 0.604 mmol of N/ g) in THF (125 mL), and the reaction mixture was refluxed under N_2 for 48 hours. After the reaction was completed, the polymer **250a** was separated by filtration and washed with the following solvents (150 mL): hexane, THF, methanol, 1: 1 methanol: water, water, NaOH, water, methanol, ethanol, hexane and Et_2O. The polymer was dried under reduced pressure to constant weight, and 5.387 g of the polymer-supported amine **250a** was obtained. The loading of the polymer was determined by elemental analysis, and was 0.604 mmol of NH/g.

^{1}H NMR δ: 8.05 - 5.75 (m, 28H, Ar), 3.87 - 3.11 (m, 3H, PhCH$_2$-N, and CH-N), 2.14 - 0.44 (m, 12H, CH$_2$, CH, polymer matrix, and CH$_3$, amine moiety).

^{13}C NMR δ: 145.8 (C-Ar), 128.1 (C-Ar), 126.9 (C-Ar), 125.9 (C-Ar), 58.1 (CH-N), 52.3 (PhCH$_2$-N), 40.6 (CH, polymer matrix), 24.7 (CH$_3$).

Anal. (Found): C, 81.43; H, 6.55; N, 1.83, which was used to determine the loading of amine **250a**.

CL polystyrene-supported 3-methoxy-1-propanol (258a)
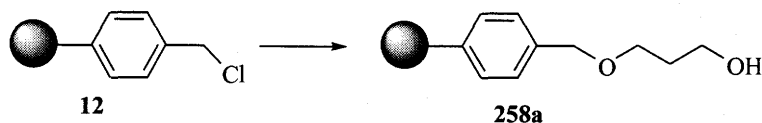
1,3-Propanediol (**257**) (10.94 g, 10.40 mL, 144.0 mmol) was added to the suspension of pre-washed sodium hydride* (1.728 g, 75.13 mmol) in DMF (100 mL) and the reaction mixture was stirred at 0 °C under N_2 for 2 hours. Chloromethyl polystyrene **12** (8.00 g, 8.80 mol, 1.10 mmol of Cl/ g) was added, and the reaction mixture was refluxed under N_2 for 48 hours. The reaction was quenched by addition of water (100 mL) at 0 °C, and polymer **258a** was separated by filtration. The resin **258a** was washed with 150 mL of each of the following solvents: water, methanol, ethanol, and Et_2O, followed by extraction with 1:1 mixture of THF and ethanol (150 mL) for 4 hours, and dried to constant weight under high vacuum. The amount of polymer **258a** obtained was 8.125 g. The loading was determined by gravimetric analysis, and was 0.825 mmol of OH/g.

^{1}H NMR δ: 8.57 - 6.30 (m, 24H, Ar), 4.28 - 3.37 (m, 8H, CH_2Cl, polymer matrix, and $PhCH_2O$-, -OCH_2 and -CH_2OH, alcohol moiety), 2.18 - 1.09 (m, 8H, CH_2, CH polymer matrix, and CH_2, alcohol moiety).

^{13}C NMR δ: 128.4 (C-Ar), 68.1 ($PhCH_2O$-), 62.5 (OCH_2-), 40.5 (CH, polymer matrix), 25.8 (CH_2).

*NaH was purified according to the following procedure:

Dry pentane (50 mL) was added *via* syringe to NaH (1.900 g, 80% dispersion in oil) at room temperature under N_2 and the suspension was stirred for 0.5 hour. The solvent was removed *via* syringe and fresh portion of pentane was added. This was repeated three times. The purified NaH was dried under N_2 to constant weight before being used.

CL polystyrene-supported 6-methoxy-1-hexanol (258b)
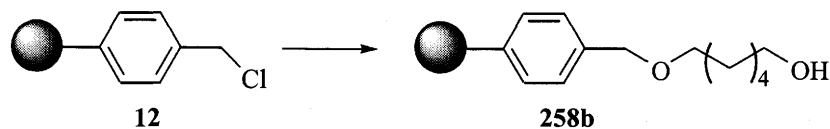
1,6-Hexanediol (**59**) (8.069 g, 68.38 mmol) was added to the suspension of washed sodium hydride (0.821 g, 35.7 mmol) in DMF (100 mL) and the reaction mixture was stirred at 0 °C under N_2 for 2 hours. Chloromethyl polystyrene **12** (3.800 g, 4.180 mol, 1.100 mmol of Cl/ g) was added, and the reaction mixture was refluxed under N_2 for 48 hours. The reaction was quenched by addition of water (100 mL) at 0 °C, and the polymer **258b** was separated by filtration. The polymer **258b** was washed with the 100 mL of each of the following solvents: water, methanol, ethanol, and Et_2O, followed by extraction with 1:1 mixture of THF and ethanol (100 mL) for 4 hours, and drying to constant weight under high vacuum. The amount of obtained resin **258b** was 3.946 g. The loading was determined by OH titration, and was 0.800 mmol of OH/g.

^{1}H NMR δ: 8.20 - 6.02 (m, 46H, Ar), 4.75 - 4.24 (m, 2H, CH_2Cl), 4.00 - 3.23 (m, 7H, $PhO-CH_2$, $-OCH_2-$, CH_2OH, and OH), 2.15 - 0.70 (m, 26H, CH_2, CH, polymer matrix and CH_2, alcohol moiety).

^{13}C NMR δ: 128.1 (C-Ar), 66.0 ($PhCH_2O-$), 63.0 ($-OCH_2$), 40.6 (CH, polymer matrix), 32.9 (CH_2), 30.0 (CH_2), 25.8 (CH_2).

CL polystyrene-supported 1-methoxy-3-iodopropane (259)

258a → 259
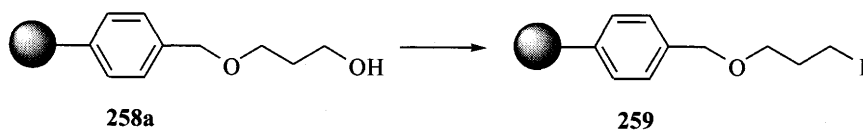
Imidazole (1.138 g, 16.74 mmol) was added to the solution of triphenylphosphine (4.386 g, 16.74 mmol) in dry CH_2Cl_2 (150 mL). Next, the iodine (4.252 g, 16.74 mmol) was added, followed by the addition of polymer **258a** (6.973 g, 5.753 mmol, 0.825 mmol of OH/ g). The reaction mixture was protected from light, and was stirred under N_2 for 96 hours. After the reaction was completed, the polymer **259** was separated by filtration and washed with 200 mL of each of the following solvents: diethyl ether, benzene, water, methanol, and diethyl ether. Polymer **259** was dried to constant weight under high vacuum, and 7.210 g of the resin was obtained. The loading of the polymer **259** was estimated from gravimetric analysis and was 0.750 mmol of I/g.

^{1}H NMR δ: 8.50 - 5.90 (m, 148H, Ar), 4.93 - 4.13 (m, 4H, CH_2Cl, polymer matrix, and $PhCH_2O$-), 3.82 - 2.85 (m, 12H, -OCH_2, and CH_2I), 2.35 - 0.80 (m, 52H, CH_2, CH, polymer matrix, and CH_2, iodide moiety)

^{13}C NMR δ: 128.8 (C-Ar), 68.1 ($PhCH_2$-O), 41.0 (CH, polymer matrix), 33.8 (CH_2), 3.7 (CH_2I)

CL polystyrene-supported 1-methoxy-6-iodohexane (61)
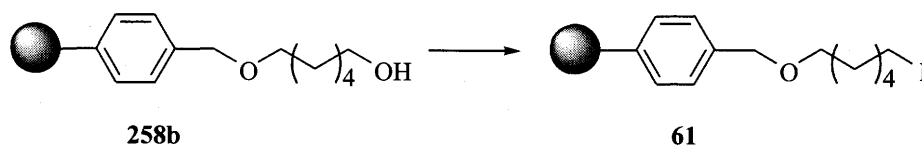
Imidazole (0.5750 g, 8.047 mmol) was added to the solution of triphenylphosphine (2.108 g, 16.74 mmol) in dry CH_2Cl_2 (100 mL). Next, the iodine (2.044 g, 8.047 mmol) was added, followed by the addition of polymer **258b** (3.353 g, 2.682 mmol, 0.800 mmol of OH/ g). The reaction mixture was protected from light, and was stirred under N_2 for 96 hours. After the reaction was completed, the polymer **61** was separated by filtration and washed with 100 mL of each of the following solvents: diethyl ether, benzene, water, methanol, and diethyl ether. The polymer was dried to constant weight under high vacuum, and 3.515 g of the resin **61** was obtained. The loading of the polymer **61** was estimated from gravimetric analysis, and was 0.790 mmol of I/g.

^{1}H NMR δ: 8.50 - 5.90 (m, 148H, Ar), 4.93 - 4.13 (m, 4H, CH_2Cl, polymer matrix, and $PhCH_2O$-), 3.82 - 2.85 (m, 12H, -OCH_2, and CH_2I), 2.35 - 0.80 (m, 52H, CH_2, CH, polymer matrix, and CH_2, attached iodide).

^{13}C NMR δ: 128.1 (C-Ar), 70.05 ($PhCH_2O$-), 66.0 (OCH_2-), 40.6 (CH, polymer matrix), 33.6 (CH_2), 30.5 (CH_2), 29.8 (CH_2), 25.4 (CH_2), 7.3 (CH_2I)

CL polystyrene-supported *(S)*-N-(3-methoxypropyl)-1-phenylethylamine (260a)
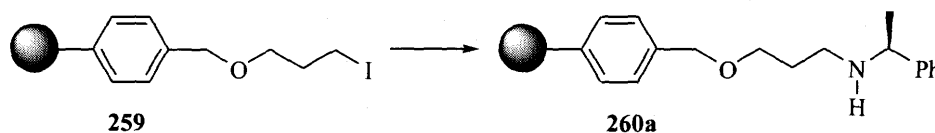
(S)-(-)-α-Methylbenzyl amine (**248a**) (3.225 g, 3.430 mL, 26.65 mmol) was added to the pre-swollen polymer **259** (5.33 g, 3.99 mmol, 0.750 mmol of I/ g) in THF (150 mL). The reaction mixture was refluxed under N_2 for 72 hours. After the reaction was completed the polymeric amine **260a** was separated by filtration, and washed with 150 mL of each of the following solvents: THF, acetone, methanol, 1: 1 methanol: water, water, NaOH, water, methanol, ethanol and ether. The polymer **260a** was dried under high vacuum to constant weight, and 5.00 g of the resin was obtained. The loading of the polymer **260a** was determined from elemental analysis, and was 0.636 mmol of NH/g.

Dehalogenation procedure:[37b]
The dehalogenation was conducted according for the procedure described for the amine **250a**. The polymeric amine **260a** was dried to constant weight under high vacuum, and 4.850 g of the resin was obtained. The loading was the same as before the dehalogention procedure.

^{1}H NMR δ: 8.35 - 6.50 (m, 25H, Ar), 4.04 - 3.15 (m, 5H, $PhCH_2O$, $O-CH_2$, CH-N), 2.10 - 0.70 (m, 10H, CH_3, CH_2, CH, polymer matrix, and CH_3, CH_2, amine moiety)

^{13}C NMR δ: 128.5 (C-Ar), 126.7 (C-Ar), 68.8 ($PhCH_2O-$), 66.2 (OCH_2), 58.6 (CH-N), 45.5 (CH_2N), 40.6 (CH, polymer matrix), 31.0 (CH_2), 24.7 (CH_3)

Anal. Found: C, 87.68; H, 7.57; N, 0.92, which was used for the loading determination of amine **260a**.

CL polystyrene-supported *(S)*-N-(6-methoxyhexyl)-1-phenylethylamine (261a)
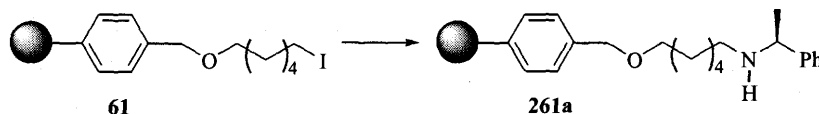
(S)-(-)-α-Methylbenzyl amine **(248a)** (6.450 g, 6.860 mL, 53.30 mmol) was added to the pre-swollen polymer **61** (7.331 g, 5.776 mmol, 0.790 mmol of I/ g) in THF (250 mL). The reaction mixture was refluxed under N_2 for 72 hours. After the reaction was completed, the polymeric amine **261a** was separated by filtration, and washed with 200 mL of each of the following solvents: THF, acetone, methanol, 1: 1 methanol: water, water, NaOH, water, methanol, ethanol and ether. The polymer **261a** was dried under high vacuum to constant weight and 7.000 g of the resin was obtained. The loading of the polymer **261a** was determined from elemental analysis, and was 0.707 mmol of NH/g.

Dehalogenation procedure:[37b]

The dehalogenation was conducted according for the procedure described for amine **250a**. The polymeric amine **261a** was dried to constant weight under high vacuum, and 6.950 g of the resin was obtained. The loading was the same as before the dehalogention procedure.

^{1}H NMR δ: 7.60 - 6.13 (m, 32H, Ar, polymer matrix and amine moiety), 4.50 - 4.27 (br s, 2H, PhCH$_2$O-), 3.95 - 3.70 (br s, 1H, N-CH), 3.58 - 3.15 (br s, O-CH$_2$), 2.70 - 0.70 (m, 25H, CH$_3$, CH$_2$, CH, polymer matrix, and CH$_3$, CH$_2$, amine moiety).

^{13}C NMR δ: 145.4 (C-Ar), 128.2 (C-Ar), 127.9 (C-Ar), 125.9 (C-Ar), 73.0 (PhCH$_2$O-), 58.6 (CH-N), 45.4 (CH$_2$N), 44.0 (CH$_2$), 42.0 (CH$_2$, polymer matrix), 40.7 (CH, polymer matrix), 29.9 (CH$_2$), 26.4 (CH$_2$).

Anal. Found: C, 86.25; H, 7.80; N, 0.903, which was used to determine the loading of amine **261a**.

CL polystyrene-supported *(1R, 2S)*-2-methylamino-1-phenyl-1-propanol (256a)
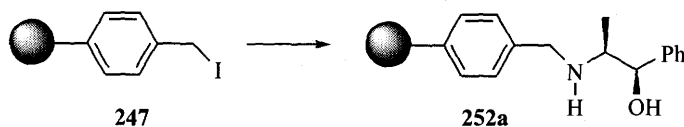
A solution of *(1R,2S)*-(-)-norephedrine **(249)** (2.052 g, 13.60 mmol) in benzene (10 ml) was added to the pre-swollen mixture of polymeric benzyl iodide **247** (5.00 g) in benzene (100 mL), followed by the addition of sodium carbonate (2.00 g, 18.9 mmol). The reaction mixture was refluxed for 48 hours. The reaction was cooled down to room temperature, and the polymer **252a** was separated by filtration. The polymer was washed with 200 mL of each of the following solvents: water, MeOH, THF, MeOH. It was dried under the high vacuum to constant weight, and 5.50 g of the polymer-supported ephedrine **252a** was obtained. The loading of the polymer was determined by elemental analysis, and was 1.257 mmol of NH/g.

Dehalogenation procedure:[37b]

The dehalogention step was performed according to the procedure described for the polymer **250a**. The loading of the polymer was the same as before dehalogentaion.

^{1}H NMR δ: 8.60 - 5.65 (m, 50H, Ar), 5.00 - 4.35 (m, 3H, CH$_2$Cl, polymer matrix, and CH-OH), 3.98 - 2.65 (m, 5H, PhCH$_2$-N, N-CH$_2$, NH and OH), 2.35 - 0.00 (m, 25H, CH$_2$, CH, polymer matrix, and CH$_3$, amino-alcohol moiety)

^{13}C NMR δ: 128.9 (C-Ar), 68.1 (PhCH$_2$-N), 66.0 (N-CH), 40.5 (CH, polymer matrix), 15.5 (CH$_3$)

Anal. Found: C, 86.09; H, 7.50; N, 1.76, which was used to determine the loading of amino-alcohol **252a**.

CL polystyrene-supported *(1S, 2R)*-2-dimethylamino-1-phenyl-1-propanol (56a)
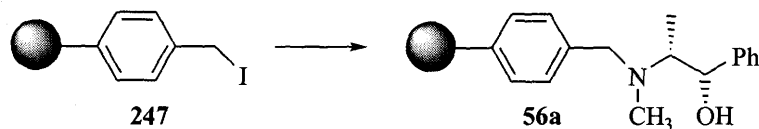
A solution of *(1S,2R)* ephedrine (**55a**) (2.052 g, 12.44 mmol) in benzene (10 ml) was added to the pre-swollen mixture of polymeric benzyl iodide **247** (5.000 g) in benzene (100 mL), followed by the addition of sodium carbonate (1.00 g, 9.45 mmol). The reaction mixture was refluxed for 48 hours. The reaction was cooled down to room temperature, and **56a** was separated by filtration. The polymer **56a** was washed with 150 mL of each of the following solvents: water, MeOH, THF, MeOH. It was dried under high vacuum to constant weight, and 5.310 g of the polymer-supported ephedrine **56a** was obtained. The loading of the polymer was determined by elemental analysis, and was 1.064 mmol of NH/g.

Dehalogenation procedure:[37b]

The dehalogention step was performed according to the procedure described for the polymer **250a**. The loading of the polymer was the same as before dehalogenation.

^{1}H NMR δ: 8.63 - 6.10 (m, 16H, Ar), 5.20 - 4.67 (m, 1H, CH-OH), 4.60-4.15 (m, 1H, OH), 4.09 - 3.14 (m, 3H, PhCH$_2$-N and N-CH), 2.40 - 0.45 (m, 9H, CH$_3$, CH$_2$, CH, polymer matrix, and N-CH$_3$, CH$_3$, amino-alcohol moiety)

^{13}C NMR δ: 143.8 (C-Ar), 128.4 (C-Ar), 73.9 (CH-OH), 66.1 (N-CH), 63.8 (PhCH$_2$-N), 40.8 (CH, polymer matrix), 25.7 (N-CH$_3$), 15.5 (CH$_3$)

Anal. Found: C, 85.0; H, 7.96; N, 1.49, which was used to determine the loading of amino-alcohol **56a**.

N-(3-iodopropyl)-phthalimide (254)[171]
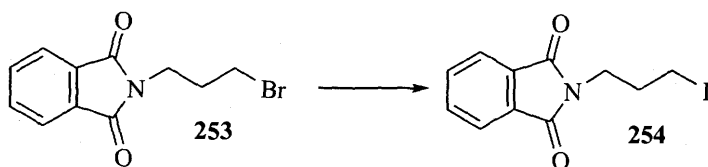
A solution of N-(3-bromopropyl)-phthalimide (**253**) (0.50 g, 1.86 mmol) in acetone (2 mL) was added to the suspension of sodium iodide (1.395 g, 9.300 mmol) in acetone (15 mL), and the reaction mixture was refluxed for 2.5 hour. Acetone was evaporated, the residue was diluted with Et_2O (35 mL), and saturated solution of $Na_2S_2O_3$ (30 mL) was added. The aqueous layer was extracted with Et_2O (3 x 35 mL). The organic layers were combined, dried with $MgSO_4$, and the solvent was removed *in vacuo* giving the crude product **254** (0.6g). The crude product was purified by DFC (hexane, hexane: AcOEt 4:1) yielding the pure **258** (0.53 g, 90% yield).

^{1}H NMR δ: 7.85 - 7.57 (m, 4H), 3.71 (t, J= 6.8 Hz, 2H), 3.11 (t, J= 7.2 Hz, 2H), 2.19 (quint, J= 7.0 Hz)

^{13}C NMR δ: 168.3, 134.1, 132.0, 123.4, 38.7, 32.6, 1.4

R_f= 0.37 (hexane: AcOEt 4:1)

mp= 84-86 °C (lit. 86-88 °C)[171]

(S)-(-)-(3-phthalimidopropyl)-1-phenylethylamine (255)
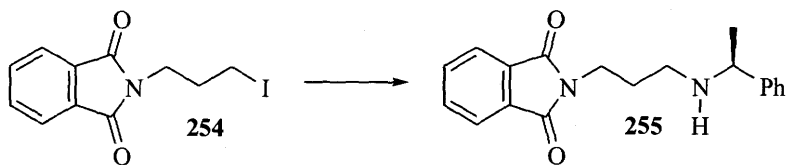
A solution of *(S)*-α-methylbenzylamine (**252a**) (0.363 g, 3.00 mmol) in THF (5 mL) was added to the solution of iodide **254** (0.473g, 1.50 mmol) in THF (15 mL). The reaction mixture was refluxed for 1.5 hour, and potassium carbonate (0.207 g, 1.50 mmol) was added. The reflux was continued overnight. The reaction mixture was cooled to room temperature, a saturated solution of sodium bicarbonate (20 mL) was added, and the mixture was extracted with Et$_2$O (3 x 30 mL). The organic layers were combined, washed with brine, and dried with MgSO4. The solvent was removed *in vacuo* yielding the crude product **255** (0.65 g). The crude product was purified by DFC (hexane, hexane: AcOEt 1:1) and the pure compound **255** was obtained (0.265 g, 57% yield).

^{1}H NMR δ: 7.80 - 7.70 (m, 2H), 7.65 - 7.57 (m, 2H), 7.27 - 7.08 (m, 5H), 3.80 - 3.52 (m, 3H), 2.70 - 2.31 (m, 2H), 1.77 (quint. *J*= 6.7 Hz, *J*= 13.4 Hz, 2H), 1.48 (br. s, 1H, NH), 1.27 (d, *J*= 6.6 Hz, 3H).

^{13}C NMR δ: 168.3, 145.7, 133.8, 132.1, 128.3, 126.7, 126.5, 123.0, 58.2, 44.6, 35.9, 28.8, 24.3.

IR: 2958, 1708, 1395 cm^{-1}.

MS: (EI) 293 (M-1, 97), 231 (6), 188 (32), 160 (42), 134 (16), 105 (100), 79 (11).

Anal. Calculated for C$_{19}$H$_{20}$N$_2$O$_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.98; H, 6.49; N, 8.94.

mp= 82 - 85 $^{\circ}$C

$[\alpha]_D{}^{25}$ –34.23 (c 1.15, CH$_2$Cl$_2$)

R$_f$= 0.27 (hexane: AcOEt 1 : 1)

(S)-(-)-[N-tert-Butoxycarbonyl-(3-phthalimidopropyl)]-1-phenylethylamine (260)
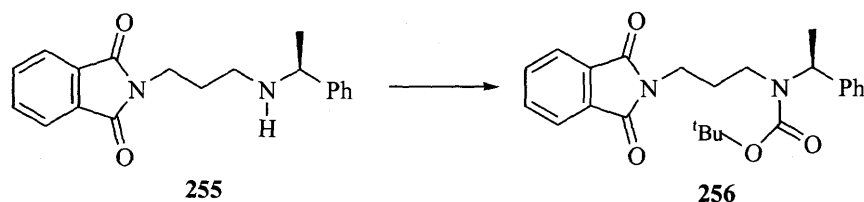
This compound was prepared according to a general procedure for protection of amines. For the convenience of the reader, the specific procedure is given below.

A solution of 30% Et$_3$N in MeOH (2.5 mL) was added to the solution of amine **255** (0.500 g, 1.62 mmol) in MeOH (20 mL), followed by the addition of (Boc)$_2$O (1.769 g, 8.110 mmol) in MeOH (10 mL) during which the reaction was stirred vigorously. The reaction mixture was refluxed overnight. The mixture was cooled to room temperature, and the solvent was removed *in vacuo* giving the crude product (0.454 g), which was purified by DFC (hexane, hexane: AcOEt 1:1), giving the pure compound **256** (0.433 g, 70% yield).

^{1}H NMR δ: 7.80 - 7.60 (m, 4H), 7.25 - 7.00 (m, 5H), 5.65 - 5.14 (br s, 1H), 3.53 - 3.36 (m, 2H), 3.03 - 2.85 (br s, 2H), 1.89 - 1.68 (m, 2H), 1.50 - 1.41 (d, J= 7.1 Hz, 3H), 1.41 - 1.30 (s, 9H)

^{13}C NMR δ: 167.6, 155.2, 141.2, 133.5, 131.8, 127.9, 126.8, 122.7, 79.2, 59.8, 35.4, 28.0, 20.6, 16.9, 13.9

IR: 2974, 1710, 1687, 1394, 1365 cm^{-1}.

Anal. Calculated for C$_{24}$H$_{28}$N$_2$O$_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.30; H, 7.08; N, 6.75.

MS: (CI-NH$_3$) 409 (M + 1, 82), 370 (17), 353 (26), 309 (100), 266 (10), 203 (8), 120 (15).

$[\alpha]^{25}_{D}$ –56.31 (c 1.38, CH$_2$CL$_2$)

R$_f$= 0.66 (hexane: AcOEt, 1: 1)

bp= 150 - 152 ^{o}C/ 0.05 mm Hg

(S)-(-)-3-[tert-Butoxycarbonylamino-(1-phenylethyl)]-1-propylamine (248b)
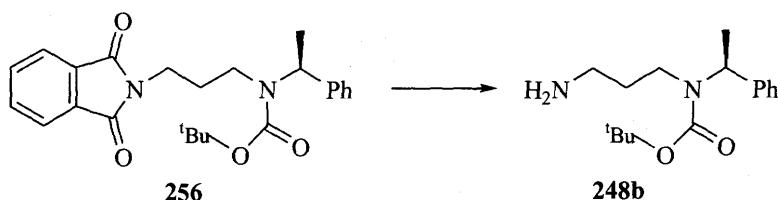
A solution of 95 % hydrazine (1 mL) was added to the solution of amide **256** (0.20 g, 0.49 mmol) in EtOH (10 mL), and the reaction was stirred at room temperature overnight. A white solid (phthalazine-1,4-dione) was filtered off, and washed with EtOH (10 mL). The filtrate was concentrated *in vacuo*. The residue was diluted with Et$_2$O (10 mL), and a saturated solution of sodium bicarbonate was added (10 mL). The aqueous layer was extracted with Et$_2$O (2 x 10 mL). The organic layers were combined, washed with brine (30 mL), and dried with MgSO$_4$. The solvent was removed *in vacuo*, and the crude product **248b** was obtained (0.15 g). The crude product was purified by DFC (hexane, hexane: AcOEt 1: 1), giving the pure amine **248b** (0.11g, 81% yield).

^{1}H NMR δ: 7.45 - 7.09 (m, 5H), 5.59 - 4.98 (br s, 1H), 3.23 - 2.70 (m, 2H), 2.65 - 2.35 (m, 2H), 1.55 - 1.47 (d, J= 7.0 Hz, 3H), 1.47 - 1.23 (m, 11H).

^{13}C NMR δ: 155.9, 141.9, 128.3, 127.0, 79.6, 53.7, 49.7, 41.4, 39.7, 33.7, 28.5, 17.5.

IR: 2973, 2931, 1685, 1406, 1365, 699 cm^{-1}.

Anal. Calculated for C$_{16}$H$_{26}$N$_2$O$_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.07; H, 9.16; N, 9.99.

MS (CI-NH$_3$) 279 (M + 1, 100), 223 (23), 179 (24), 120 (5)

R_f= 0.40 (CH$_2$Cl$_2$: MeOH, 85: 15)

$[\alpha]^{25}_D$ –77.29 (c 1.11, CH$_2$Cl$_2$)

bp= 235 ^{o}C/ 15 mm Hg

CL polystyrene-supported (S)-(N-tert-butoxycarbonyl-3-methylpropylamino)-1-phenylethylamine (251a)
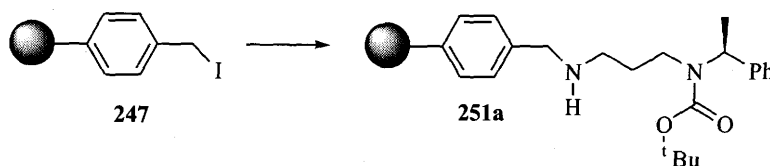
A solution of amine **248b** (1.26 g, 4.50 mmol) in THF (10 mL) was added to the pre-swollen polymeric benzyl iodide **247** (2.25g) in THF (75 mL), and the resulting suspension was refluxed under N_2 for 4 hours. Potassium carbonate (1.24 g, 9.00 mmol) was added, and the reflux was continued for an additional 68 hours. The amine **255a** was separated by filtration, and washed with 100 mL of each of the following solvents: THF, MeOH, H_2O, MeOH, Et_2O, THF. The polymer **251a** was dried under high vacuum to constant weight (2.40 g). The loading of the resin was calculated by subtractions the recovered molar amount of amine **251b** from the total molar amount of **251b** used for attachment to the polymer **247**. The loading of **251a** was 0.485 mmol of NH/g and was confirmed by elemental analysis.

^{1}H NMR δ: 8.55 - 4.80 (m, 105H, Ar, and CH-N), 3.70 - 3.10 (m, 4H, PhCH$_2$-N, and N-CH$_2$), 2.64 - 0.00 (m, 110H, CH$_3$, CH$_2$, CH, polymer matrix, and CH$_3$, CH$_2$, amine moiety)

^{13}C NMR δ: 128.2 (C-Ar), 65.3 (C-O), 40.5 (CH, polymer matrix), 28.5 (CH$_3$-C), 17.3 (CH$_3$)

Anal. Found: C, 84.12; H, 8.07; N, 2.72, which was used to determine the loading of resin **251a**.

(S,S)-(+)-4-(1-phenylethylamino)-2-methyl-1-pentanol (262)
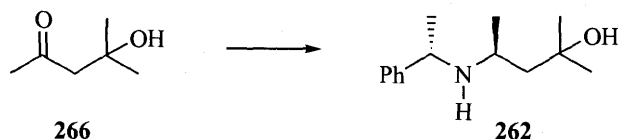
266   262

This compound was prepared according to a general procedure for reductive amination of ketones.[172] For the convenience of the reader, the specific procedure is given below.

A solution of 4-hydroxy-4-methyl-2-pentanone (**266**) (1.00 g, 1.07 mL, 8.62 mmol) in MeOH (5 mL) was added to the solution of *(S)*-α-methylbenzylamine (**248a**) (0.949 g, 1.00 mL, 7.84 mmol) in MeOH (25 mL), followed by the addition of NaBH$_3$CN (0.518 g, 8.23 mmol). The reaction was stirred at room temperature overnight. The solvent was removed *in vacuo*, 10% solution of hydrochloric acid (50 mL) was added to the residue, and the aqueous layer was extracted with Et$_2$O (30 mL). The acidic aqueous layer was cooled to 0 °C, and it was made basic by the slow addition of NaOH (ca. 4 g). The basic solution was extracted with Et$_2$O (3 x 50 mL). The organic layers were combined, washed with brine (75 mL), and dried with MgSO$_4$. The solvent was removed *in vacuo* giving the mixture of two products in a 5:1 ratio (GC). The products were separated by DFC (hexane, hexane: AcOEt 1:1) and the major isomer **262** was obtained (0.866 g, 50% yield). Only the major isomer was fully characterized.

^{1}H NMR δ: 7.28-7.05 (m, 5H), 3.82 (quart, *J*= 6.5 Hz, 1H), 3.20-3.04 (m, 1H), 1.41-1.33 (m, 2H), 1.28 (d, *J*= 6.5 Hz, 3H), 1.23 (s, 3H), 1.11 (s, 3H), 1.19 (d, *J*= 6.2 Hz, 3H)

^{13}C NMR δ: 145.6, 128.5, 127.2, 126.3, 70.2, 54.7, 48.3, 31.8, 28.5, 22.1, 21.3

IR: 3310, 2943, 2913, 2865, 1454, 1071 cm^{-1}.

MS: (NH$_3$) 222 (M + 1, 100), 148 (9), 105 (5)

Anal. Calculated for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33; Found: C, 75.87; H, 10.51; N, 6.60.

$[\alpha]^{26}_D$ +67.74 (c 3.06, CH_2Cl_2)

R_f= 0.31 (CH_2Cl_2: MeOH, 97: 3)

bp= 135 - 139 ^oC/ 6 mmHg

CL polystyrene-supported (S, S)-N-[2-(4-methoxy-4-methyl)pentyl]-1-phenylethylamine (264a)
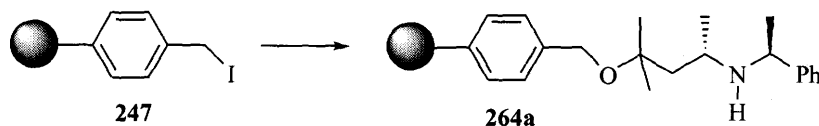
A solution of amine **262** (2.00 g, 9.05 mmol) in dry DMF (5 mL) was added to the washed suspension of NaH (0.350 g, 14.6 mmol) in DMF (80 mL) at 0 °C under N_2. The reaction mixture was stirred for 1 hour at 0 °C, and the polymer-supported benzyl iodide **247** (6.50 g) was added, followed by the addition of dry K_2CO_3 (2.498 g, 18.10 mmol). The reaction mixture was heated at 80 °C for 72 hours. The mixture was cooled to room temperature, and polymer **264a** was separated by filtration, washed with H_2O (500 mL), followed by washing with 150 mL of each of the following solvents: MeOH, EtOH, THF, MeOH, Et_2O. The polymer **264a** was dried to constant weight under high vacuum (7.00 g). The loading of the resin **264a** was determined by elemental analysis and was 0.414 mmol of NH/g.

^{1}H NMR δ: 9.00 - 6.00 (m, 33H, Ar), 3.90 - 2.60 (m, 6H, CH_2Cl, polymer matrix, and $PhCH_2O$-, Ph-CH-N, CH-N), 2.10 - 0.10 (m, 12H, CH_2, CH, polymer matrix, and CH_3, CH_2, amine moiety)

^{13}C NMR δ: 128.1 (C-Ar), 66.0 (O-C), 45.5 (CH), 40.7 (CH, polymer matrix), 15.5 (C-CH_3).

Anal. Found: C, 89.23; H, 7.64; N, 0.58, which was used to determine the loading of resin **264a**.

3-[*(1R, 2R, 5S)*-2-isopropyl-5-methylcyclohexylamino]-1-propanol (263)
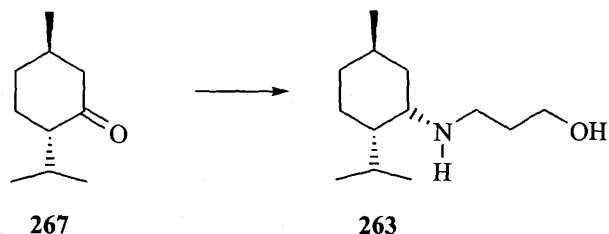
This compound was prepared according to a general procedure for reductive amination of ketones.[172] For the convenience of the reader, the specific procedure is given below.

A solution of 3-aminopropanol (**268**) (2.212 g, 2.250 mL, 29.50 mmol) in dry MeOH (10 mL) was added to the solution of (-)-menthone (**267**) (5.00 g, 5.60 mL, 32.5 mmol) in dry MeOH (50 ml), followed by the addition of $NaBH_3CN$ (2.047 g, 32.50 mmol). The pH of the reaction was adjusted to 6 by addition of glacial acetic acid, and the reaction mixture was stirred overnight at room temperature. The mixture was diluted with water (30 mL), and Et_2O (75 mL) was added. The organic layer was extracted with 10% solution of HCl (3 x 50 mL). The acidic aqueous layers were made basic by slow addition of solid NaOH. The basic solution was extracted with Et_2O (3 x 50 mL). The organic layers were combined, dried with $MgSO_4$ and the solvent was removed *in vacuo* giving the crude product as two diastereomers in 1: 6 ratio (GC) (7.00 g). The crude product was purified by DFC (hexane, hexane: AcOEt 1:1) giving the pure compound **263** (3.50 g, 55% yield).

^{1}H NMR δ: 3.63 (dd, *J*= 5.2 Hz, *J*= 5.2 Hz, 2H), 2.86 (dt, *J*= 5.4 Hz, *J*= 11.2 Hz, 1H), 2.73 (d, *J*= 2.9 Hz, 1H), 2.47 (dt, *J*= 5.7 Hz, *J*= 11.5 Hz, 1H), 1.81 (dd, *J*= 2.4 Hz, *J*= 13.8 Hz, 1H), 1.61 - 1.48 (m, 4H), 1.48 - 1.35 (m, 1H), 1.30 (ddd, *J*= 6.6 Hz, *J*= 3.2 Hz, *J*= 13.2 Hz, 1H), 1.04 - 0.87 (m, 1H), 0.75 (d, *J*= 2.6 Hz, 3H), 0.74 - 0.69 (m, 9 H).

^{13}C NMR δ: 64.4, 54.3, 48.1, 47.9, 37.5, 35.2, 31.5, 28.9, 25.6, 24.8, 22.5, 21.4, 20.5

IR: 3250, 2969, 1600, 1374, 700 cm^{-1}.

MS: (CI-NH$_3$) 214 (M + 1, 100), 128 (22)

$[\alpha]^{29}_D$ +22.39 (c 1.14, CH$_2$Cl$_2$)

bp= 145 - 147 ^{o}C/ 7 mmHg

R$_f$= 0.52 (CH$_2$Cl$_2$: MeOH, 85:15)

Anal. Calculated for C$_{13}$H$_{27}$NO: C, 73.18; H, 12.75; N, 6.56; Found: C, 73.13; H, 12.91; N, 6.87.

CL polystyrene-supported *(1R, 2R, 5S)*-[N-(1-metoxypropyl)]-2-isopropyl-5-methylcyclohexylamine (265a)

247   265a
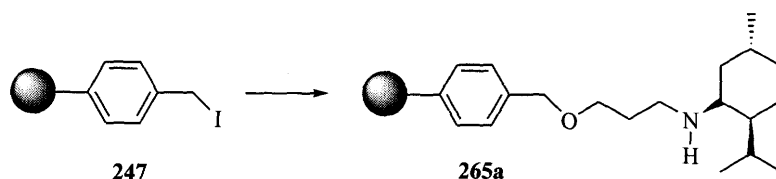
A solution of amino-alcohol **263** (3.443 g, 16.20 mmol) in DMF (10 mL) was added to the suspension of washed NaH (0.450 g, 18.7 mmol) in DMF (100 mL) at 0 °C, and the reaction mixture was stirred under N_2 for 2 hours. The mixture was warmed to room temperature, and resin **247** was added (6.50 g), followed by the addition of dry K_2CO_3 (2.235 g, 16.20 mmol). The reaction mixture was heated at 80 °C for 72 hours. The reaction mixture was cooled to room temperature, and the polymeric amine **269a** was separated by filtration. The polymer **265a** was washed with water (500 mL), followed by washing with 200 mL of each of the following solvents: water: MeOH (1:1), MeOH, EtOH, THF, MeOH, Et_2O, and THF. The resin **265a** was dried under high vacuum to constant weight (7.00 g). The loading of the polymer **265a** was determined by the elemental analysis and was 0.536 mmol of NH/g.

^{1}H NMR δ: 8.40 - 5.60 (m, 44H, Ar), 3.90 - 3.70 (m, 4H, CH_2Cl, polymer matrix, and PhCH$_2$O-), 3.70 - 3.40 (m, 8H, OCH$_2$, and CH$_2$N), 2.70 - 1.42 (m, 4H, CH, polymer matrix, CH$_2$ in the ring), 1.42 - 0.60 (m, 10H, CH$_2$, polymer matrix, and CH$_3$, CH$_2$, CH, amine moiety).

^{13}C NMR δ: 128.1 (C-Ar), 66.0 (PhCH$_2$O-), 54.5 (CH-i-Pr), 48.8 (CH-N), 45.5 (CH$_2$N), 40.7 (CH, polymer matrix), 25.8 (CH$_3$), 15.5 (CH$_3$).

Anal. Found: C, 88.70; H, 8.42; N, 0.75, which was used to determine the loading of resin **265a**.

4.6 Synthesis of soluble polymer-supported chiral amines.

Non-cross-linked (NCL) polystyrene-supported methyl chloride (145)[69]
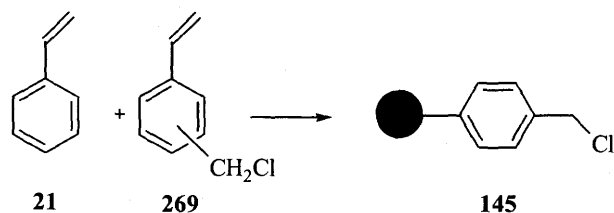
The resin **145** was prepared according to the procedure described in the literature.[69] For the convenience of the reader the specific procedure is presented below.

A solution of chloromethyl polystyrene **269** (2.42 g, 2.19 mL, 15.0 mmol) in benzene (20 mL) was added to a solution of styrene **21** (17.04 g, 14.72 mL, 155.0 mmol) in benzene (100 mL). The oxygen was purged from the reaction vessel* and AIBN (0.128 g, 0.780 mmol) was added. The reaction mixture was heated to 80 °C under N_2 for 48 h. After the reaction was completed, the bulk of benzene was removed under vacuum, and the soluble polymer **145** was precipitated by addition of MeOH (ca. 500 mL) at –40 °C. The polymer **145** was separated by filtration, and washed with 250 mL of each of the following solvents: MeOH, water: MeOH (1: 1), water and MeOH. The polymer **145** was dried to constant weight under high vacuum (20.00 g). The loading of the resin **145** was 1.00 mmol of Cl/g.

^{1}H NMR δ: 7.35 - 6.93 (m, 30 H, Ar), 6.93 - 6.37 (m, 20H, Ar), 4.69 - 4.46 (br s, 2H, CH_2Cl), 2.23 - 1.79 (br s, 7H, CH; polymer matrix), 1.78 - 1.30 (br s, 18 H, CH_2; polymer matrix).

^{13}C NMR δ: 145.5 (C-Ar), 137.0 (C-Ar), 128.7 (C-Ar), 128.5 (C-Ar), 128.2 (C-Ar), 128.0 (C-Ar), 126.4 (C-Ar), 125.8 (C-Ar), 46.5 (CH$_2$Cl), 40.6 (CH$_2$, polymer matrix).

*Oxygen was purged from the reaction vessel by applying vacuum, and flushing with N$_2$. This was repeated three times.

NCL polystyrene-supported methyl iodide (270)
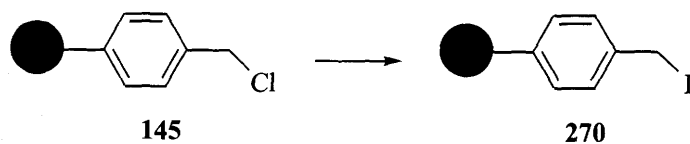
Sodium iodide (31.2 g, 208 mmol) was added to the solution of soluble polymer **145** (34.69 g, 34.69 mol, 1.00 mmol of Cl/ g) in acetone (500 mL), and the reaction mixture was refluxed for 24 hours. After the reaction was completed, the bulk of acetone was distilled off. The residue was cooled to –40 °C and MeOH (ca. 600 mL) was added. The polymer **270** was separated by filtration, and washed with the 500 mL of each of the following solvents: water and MeOH. The polymer **270** was dried to constant weight under high vacuum (36.50 g). Loading of the polymer was not determined after this reaction.

^{1}H NMR δ: 7.31 - 6.85 (m, 25 H, Ar), 6.82 - 6.33 (m, 15H, Ar), 4.55 - 4.33 (br s, 2H, CH_2X), 2.18 - 1.72 (m, 5H, CH, polymer matrix), 1.72 - 1.35 (m, 18 H, CH_2 and CH_3 polymer matrix)

^{13}C NMR δ: 145.4 (C-Ar), 136.5 (C-Ar), 128.2 (C-Ar), 127.8 (C-Ar), 126.4 (C-Ar), 125.8 (C-Ar), 44.0 (CH2, polymer matrix), 42.8 (CH, polymer matrix), 6.5 (CH_2I)

NCL polystyrene-supported _(S)_-N-(methyl)-1-phenylethylamine (273a)

270   273a
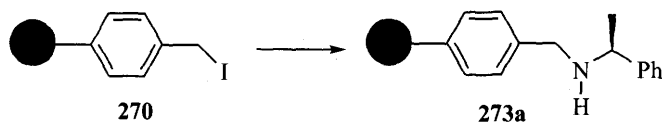
A solution of _(S)_-(-)-α-methylbenzyl amine (**248a**) (10.00 g, 10.64 mL, 82.64 mmol) in benzene (20 mL) was added to the solution of polymer **270** (20.00 g, 20.00 mmol, 1.000 mmol of halide/ g) in benzene (100 mL), and the reaction mixture was refluxed for 48 hours. The mixture was cooled to room temperature, and the solvent was removed _in vacuo_. The residue was cooled to –45 °C, and MeOH was added (300 mL). The amine **273a** precipitated and, was separated by filtration, washed with water (100 mL) and MeOH (500 mL). The amine was dried to constant weight under high vacuum (20.50 g). The loading of the polymer **273a** was determined by elemental analysis and was 0.69 mmol of N/g.

^{1}H NMR δ: 7.41 - 6.98 (m, 102 H, Ar), 6.98 - 6.45 (m, 66H, Ar), 4.74 - 4.54 (br s, 2H, CH2X,) 4.29 (q, _J_= 6.4 Hz, 2H, CH-N), 4.01 - 3.55 (m, 9 H, CH$_2$ and NH), 2.20 - 1.86 (m, 30H, CH, polymer matrix), 1.78 - 1.40 (m, 72H, CH$_3$, amine moiety and CH$_2$, CH$_3$, polymer matrix)

^{13}C NMR δ: 145.2 (C-Ar), 128.8 (C-Ar), 128.6 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 127.0 (C-Ar), 126.1 (C-Ar), 125.8 (C-Ar), 57.6 (-CH-N), 51.1 (CH$_2$N), 46.4 (CH$_2$Cl), 43.9 (CH$_2$, polymer matrix), 40.5 (CH, polymer matrix), 24.4 (CH$_3$, amine moiety)

$[α]^{25}_D$ –8.2 (c 5.20, CH$_2$Cl$_2$, polymer)

Anal. Found: C, 89.16; H, 7.74; N, 1.47, which was used to determine the loading of resin **273a**.

NCL polystyrene-supported 3-methoxy-1-propanol (284a)
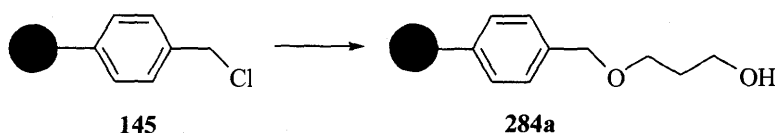
A solution of 1,3-propanediol (**257**) (6.84 g, 6.58 mL, 90.0 mmol) in THF (20 mL) was added to the suspension of washed NaH (1.20 g, 50.0 mmol) in THF (100 mL) at 0 °C under N_2. After stirring for 2 hours, the solution of soluble polymer **145** (15.00 g, 15.00 mmol, 1.00 mmol of Cl/ g) in THF (75 mL) was added dropwise, and the reaction mixture was refluxed for 48 hours. The mixture was cooled to 0 °C, and water (50 mL) was added. The layers were separated, and the aqueous layer was extracted with AcOEt (3 x 300 mL). The organic layers were combined, dried with $MgSO_4$, and the bulk of the solvents were removed *in vacuo*. The residue was added to cold (-45 °C) MeOH (300 mL), and the polymer **284a** precipitated. The polymer **28a** was separated by filtration, washed with water (500 mL) and MeOH (750 mL). The polymer was dried under high vacuum to constant weight (15.50 g). The loading of resin **284a** was calculated by gravimetric analysis and was 0.90 mmol of OH/g.

^{1}H NMR δ: 7.40 - 6.86 (m, 79 H, Ar), 6.86 - 6.30 (m, 50H, Ar), 4.55 - 4.35 (m, 2H, CH_2Cl), 3.89 - 3.73 (m, 2H, CH_2OH), 3.73 - 3.55 (m, 2H, CH_2O), 3.45 - 3.25 (m, 1H, OH), 2.35 - 2.10 (m, 10 H, CH_2), 2.05 - 1.73 (m, 25 H, CH, polymer matrix), 1.70 - 1.24 (m, 47 H, CH_2, CH_3, polymer matrix)

^{13}C NMR δ: 145.4 (C-Ar), 131.2 (C-Ar), 128.9 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 73.3 (CH_2-OAr), 69.3 (-OCH_2), 62.1 (CH_2OH), 45.5 (CH_2Cl), 44.0 (CH_2, polymer matrix), 40.6 (CH, polymer matrix), 32.4 (CH_2, alcohol moiety).

NCL polystyrene-supported 6-methoxy-1-hexanol (284b)
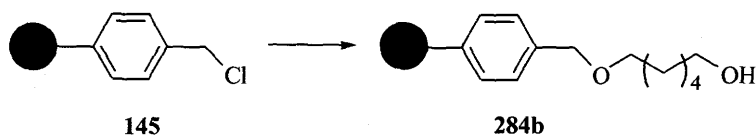
A solution of 1,6-hexanediol (**59**) (9.912 g, 84.00 mmol) in dry DMF (30 mL) was added to the cold (0 °C) suspension of washed NaH (1.200 g, 50.00 mmol) in DMF (150 mL) and the reaction was stirred under N_2 for 2 hours. Soluble polymer **145** (12.00 g, 12.00 mmol, 1.000 mmol of Cl/ g) was added. The reaction mixture was heated to 80 °C for 48 hours. The bulk of DMF was removed by distillation under reduced pressure. The residue was cooled to –45 °C, and MeOH (500 mL) was added. The polymer **284b** precipitated, and was separated by filtration. The compound **284b** was washed with water (250 mL), MeOH (500 mL), and dried under high vacuum to constant weight (12.50 g). The loading of the polymer **284b** was determined by OH titration method, and was 0.98 mmol of OH/g.

^{1}H NMR δ: 7.45 - 6.35 (m, 55H, Ar), 4.55 - 4.34 (m, 2H, CH2Cl), 3.75 – 3.60 (m, 2H, O-CH$_2$Ph, 3.55 - 3.30 (m, 4H, OCH$_2$, CH$_2$OH), 2.35 - 1.25 (m, 41H, CH$_2$, CH, CH$_3$, polymer matrix), 1.1 - 0.85 (m, 8H, CH$_2$).

^{13}C NMR δ: 145.4 (C-Ar), 138.0 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 73.5 (CH$_2$-OAr), 64.3 (OCH$_2$), 63.0 (CH$_2$OH), 45.5 (CH$_2$Cl), 44.4 (CH$_2$, polymer matrix), 40.6 (CH, polymer matrix), 32.9 (CH$_2$), 29.9 (CH$_2$), 26.3 (CH$_2$), 25.8 (CH$_2$).

NCL polystyrene-supported 1-methoxy-3-iodopropane (285a)
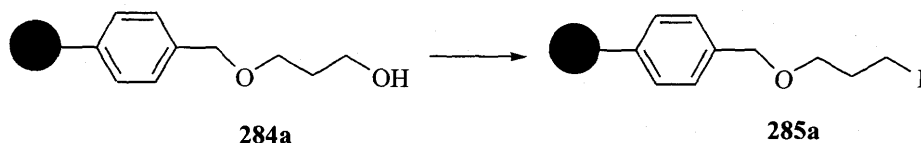
284a   285a

Imidazole (2.652 g, 39.00 mmol) was added to the solution of triphenylphosphine (10.22 g, 39.00 mmol) in dry CH_2Cl_2 (200 mL), followed by addition of iodine (9.906 g, 39.00 mmol), and polymeric alcohol **284a** (10.0 g, 9.00 mmol, 0.90 mmol of OH/ g). The reaction mixture was protected from light, and stirred under N_2 at room temperature for 48 hours. The mixture was then extracted with a saturated solution of $Na_2S_2O_3$ (3 x 50 mL). The organic layers were dried with $MgSO_4$, and the bulk of CH_2Cl_2 was removed *in vacuo*. The residue was cooled to –45 °C, and MeOH (500 mL) was added. The polymer **285a** precipitated, was separated by filtration, washed with H_2O (200 mL) and MeOH (500 mL). The resin **285a** was dried under high vacuum to constant weight (10.5 g). The loading of the polymer **285a** was not determined at this stage.

^{1}H NMR δ: 7.27 - 6.27 (m, 84 H, Ar), 4.55 - 4.33 (m, 2H, CH_2Cl), 4.25 - 3.92 (m, 2H, CH_2-OAr), 3.60 - 3.41 (m, 2H, OCH_2), 3.39 - 3.20 (m, 2H, CH_2I), 3.89 - 3.50 (m, 2H, CH_2), 2.15 - 1.18 (m, 44 H, CH, CH_2, CH_3, polymer matrix).

^{13}C NMR δ: 145.3 (C-Ar), 132.1 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 73.2 (CH_2-OAr), 69.5 (O-CH_2), 44.3 (CH_2Cl), 42.0 (CH_2, polymer matrix), 40.6 (CH, polymer matrix), 33.7 (CH_2), 3.7 (CH_2I).

NCL polystyrene-supported 1-methoxy-6-iodohexane (285b)
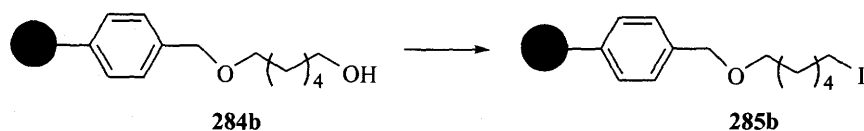
Imidazole (2.652 g, 39.00 mmol) was added to the solution of triphenylphosphine (10.22 g, 39.00 mmol) in dry CH_2Cl_2 (200 mL), followed by addition of iodine (9.906 g, 39.00 mmol), and polymeric alcohol **284b** (10.0 g, 9.80 mmol, 0.98 mmol of OH/ g). The reaction mixture was protected from light, and stirred under N_2 at room temperature for 48 hours. The mixture was then extracted with a saturated solution of $Na_2S_2O_3$ (3 x 50 mL). The organic layers were dried with $MgSO_4$, and the bulk of CH_2Cl_2 was removed *in vacuo*. The residue was cooled to –45 °C and MeOH (500 mL) was added. The polymer precipitated, was separated by filtration and washed with H_2O (200 mL) followed by MeOH (500 mL). The polymer **285b** was dried under high vacuum to constant weight (10.68 g). The loading of the resin was not determined at this stage.

^{1}H NMR δ: 7.40 - 6.25 (m, 120H, Ar), 4.57 - 4.32 (m, 2H, CH_2Cl), 4.3 - 3.92 (m, 2H, O-CH_2Ar), 3.62 - 3.35 (m, 2H, OCH_2), 3.30 - 3.11 (m, 2H, CH_2I), 2.98 - 2.54 (m, 4H, CH_2, alcohol moiety), 2.38 - 1.05 (m, 80H, CH_2, CH, polymer matrix, and CH_2 alcohol moiety).

^{13}C NMR δ: 145.4 (C-Ar), 132.2 (C-Ar), 128.6 (C-Ar), 128.0 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 73.0 (CH_2-OAr), 70.3 (OCH_2), 40.5 (CH, polymer matrix), 33.6 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 25.5 (CH_2), 7.5 (CH_2I).

NCL polystyrene-supported *(S)*-N-(3-methoxypropyl)-1-phenylethylamine (286a)
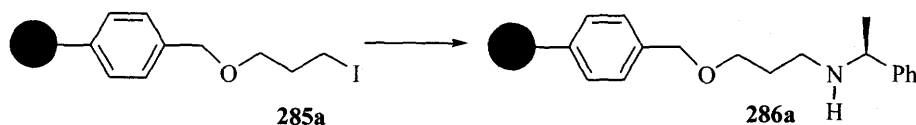
A solution of *(S)*-(-)-α-methylbenzylamine (**248a**) (4.588 g, 4.880 mL, 37.90 mmol) in benzene (10 mL) was added to a solution of polymer **286a** (6.32 g) in benzene (150 mL), and the reaction mixture was refluxed under N_2 for 48 hours. The mixture was cooled to room temperature, and the bulk of benzene was removed *in vacuo* followed by further cooling to –45 °C and slow addition of MeOH (300 mL). The polymeric amine **286a** precipitated, was separated by filtration, washed with water (250 mL) and MeOH (300 mL). The polymer **286a** was dried to constant weight under high vacuum (6.00 g). The loading of amine **286a** was determined by elemental analysis and was (0.905 mmol/g)

^{1}H NMR δ: 7.50 - 6.40 (m, 142H, Ar), 4.59 - 4.33 (m, 2H, CH_2Cl), 4.28 - 4.16 (m, 1H, CH-OAr), 3.98 - 3.80 (m, 1H, CH-OAr), 3.70 - 3.35 (m, 3H, OCH_2, CH-N), 2.85 - 2.57 (m, 2H, N-CH_2), 2.53 - 1.13 (m, 80H, CH_2, CH, CH_3, polymer matrix and CH_2, CH_3, amine moiety).

^{13}C NMR δ:145.3 (C-Ar), 135.0 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 126.8 (C-Ar), 125.8 (C-Ar), 72.9 (CH_2-OAr), 68.9 (OCH_2), 64.4 (CH-N), 58.7 (CH_2-N), 45.4 (CH_2Cl), 44.1 (CH_2, polymer matrix), 40.5 (CH, polymer matrix), 30.0 (CH_2), 24.5 (CH_3).

$[\alpha]^{26}_D$ –4.02 (c 1.12, AcOEt, polymer).

Anal. Found: C, 87.50; H, 8.03; N, 1.17, which was used to determine the loading of resin **286a**.

NCL polystyrene-supported *(S)*-N-(6-methoxyhexyl) -1-phenylethylamine (287a)
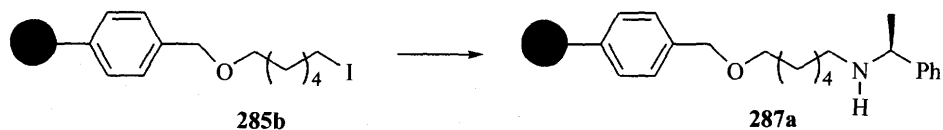
285b   287a

A solution of *(S)*-(-)-α-methylbenzylamine (**248a**) (4.588 g, 4.880 mL, 37.90 mmol) in benzene (10 mL) was added to a solution of polymer **285b** (9.25 g) in benzene (150 mL), and the reaction mixture was refluxed under N_2 for 48 hours. The mixture was cooled to room temperature, and the bulk of benzene was removed *in vacuo*. The residue was further cooled down to –45 °C, and MeOH (300 mL) was slowly added. The polymeric amine **287a** precipitated, was separated by filtration, washed with water (250 mL) and MeOH (300 mL). The polymer **287a** was dried to constant weight under high vacuum (9.50 g). The loading of amine **287a** was determined by elemental analysis, and was 0.742 mmol/g.

^{1}H NMR d: 7.25 - 6.25 (m, 179H, Ar), 4.60 - 4.35 (m, 2H, CH_2Cl), 4.25 - 4.13 (m, 1H, $ArO-CH_2$), 3.95 - 3.70 (m, 1H, $ArO-CH_2$), 3.55 - 3.30 (m, 4H, OCH_2, CH-N, NH), 2.65 - 0.90 (m, 115H, CH_2, CH polymer matrix, and CH_2N, CH_2, CH_3, amine moiety).

^{13}C NMR δ: 145.4 (C-Ar), 134.0 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 125.8 (C-Ar), 73.2 (CH_2-OAr), 70.5 (OCH_2), 64.3 (CH-N), 58.5 (CH_2N), 45.4 (CH_2, polymer matrix), 40.6 (CH, polymer matrix), 29.5 (CH_2), 27.3 (CH_2), 26.2 (CH_3).

$[\alpha]^{28}_D$ –2.9 (c 5.22, CH_2Cl_2, polymer).

Anal. (Found): C, 87.62; H, 7.69; N, 1.05, which was used to determine the loading of amine **287a**.

(R)-N-tert-Butoxycarbonylphenylglycine (278)[173]

277   278
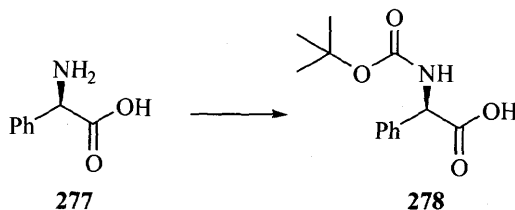
This compound was prepared according to the general procedure for protection of amino group.[173] For a convenience of the reader the specific procedure is given below.

(R)-Phenylglycine **(277)** (13.59 g, 90.00 mmol) was added to a stirred solution of NaOH (3.96 g, 0.10 mmol) in water (100 mL) and t-BuOH (54 ml). Di-*tert*-butyldicarbonate (20.07 g, 92.00 mmol) was added to the mixture in portions over a 1.5 hour period (a white precipitate was formed). The resulting suspension was stirred at room temperature, overnight. The cloudy mixture was diluted with water (100 mL), and extracted with CH$_2$Cl$_2$ (150 mL). The organic extract was washed with diluted aqueous NaOH (100 mL). The NaOH wash was combined with the basic water layer from the first extraction, cooled (ice bath) and slowly acidified with diluted H$_2$SO$_4$ (ca. 200 mL). The white product precipitated, and was extracted with CH$_2$Cl$_2$ (3 x 150 mL). The combined organic layers were washed with water (3 x 250 mL), dried with MgSO$_4$, and concentrated on the vacuum at a temperature not exceeding 30 °C. To remove the remaining t-BuOH, the crude product was dissolved in CH$_2$Cl$_2$ (250 mL), and the solvent was removed *in vacuo*. This was repeated 3 times. The product was dried under vacuum to give white crystalline solid of **278** (17.824 g, yield 79%).

mp= 87 - 90 °C (lit. mp= 88 - 91 °C)[174]

^{1}H NMR δ: 12.0 (s, 1H), 7.45-7.25 (m, 5H), 5.14 (d, *J*= 5.2 Hz, 1H), 1.02 (s, 9 H).

(R)-1-[2-(N-*tert*-Butoxycarbonylamino)-2-phenylacetyl]piperidine (279)[96]
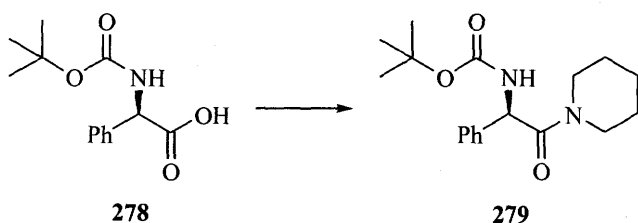
A solution of DCC (13.13 g, 64.00 mmol) in dry CH_2Cl_2 (50 mL) was cooled to 0 °C and t-Boc-phenylglycine (**278**) (16.00 g, 64.00 mmol) in dry CH_2Cl_2 (45 mL) was added , dropwise. After 15 minutes of stirring at 0 °C, piperidine (7.286 g, 9.000 mL, 86.00 mmol) was slowly added over a period of 3 hours using a syringe pump. The resulting mixture was stirred at room temperature, overnight. The solvent was removed under vacuum, AcOEt (250 mL) was added, and the resulting suspension was stirred over a period of 30 minutes. The white precipitate (dicyclourea) was filtered and washed with AcOEt (250 mL). The solvent was removed *in vacuo*, and the crude product was obtained (20.00 g, 98% yield). The crude product was subjected to deprotection without purification. The analytical sample **279** was crystallized from hexane.

mp= 94-95 °C (lit. 95.5-98 °C)[96]

¹H NMR: 7.40 - 7.26 (m, 5H), 6.13 (d, J = 10 Hz, 1H), 5.55 (d, J = 10 Hz, 1H), 3.80 - 3.70 (m, 1H), 3.50 - 3.38 (m, 1H), 3.35 - 3.20 (m, 2H), 1.68 - 1.33 (m, 5H), 1.38 (s, 9H), 1.00 - 0.85 (m, 1H).

R_f= 0.23 (hexane: AcOEt 4:1)

(R)-1-(2-Aminophenyl)ethyl-1-piperidine (276)[175]
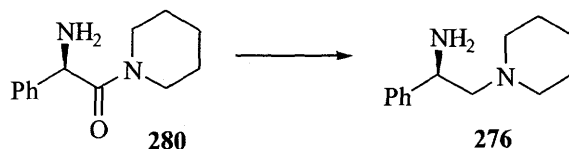
Crude amide **280** (17.00 g, 78.00 mmol) was dissolved in Et$_2$O (100 mL) and was added to the suspension of LiAlH$_4$ (8.00 g, 205 mmol) in Et$_2$O (200 mL). The resulting mixture was stirred at room temperature, overnight. Concentrated aqueous ammonia solution (ca.5 mL), and 40% K$_2$CO$_3$ solution (ca. 5mL) were added to the reaction mixture. Stirring was continued until all of LiAlH$_4$ decomposed (white precipitate was formed). Celite (ca. 6.0 g) was added, and the solid was filtered. The filtrate was extracted with Et$_2$O (3 x 150 mL). The filter cake (aluminum salts and celite) was washed with Et$_2$O (100 mL). The solid was filtered, and the filtrate was added to the organic layer from the first extraction. The ether layer was dried with MgSO$_4$, and the solvent was removed *in vacuo* yielding the crude product **276** (16.00 g). This was purified by DFC (hexane: AcOEt 9: 1, CH$_2$Cl$_2$: MeOH 9:1) giving the pure amine **276** (10.56 g, 71% yield).

^{1}H NMR δ: 7.41 - 7.28 (m, 5H), 4.10 (dd, *J*= 3.8 Hz, *J*= 10.2 Hz, 1H), 2.62 - 2.52 (m, 2H), 2.43-2.25 (m, 2H), 1.86 (s, 2H), 2.19 (s, 2H), 1.68 - 1.38 (m, 6H).

^{13}C NMR δ: 144.7, 128.3, 127.0, 126.7, 67.8, 55.0, 52.7, 26.3, 24.6.

bp= 200-204 °C/ 4 mm Hg (lit. 155 °C/ 0.1 mm Hg)[175]

NCL polystyrene-supported (R)-1-[(2-methylamino-2-phenyl)ethyl]piperidine (274a)
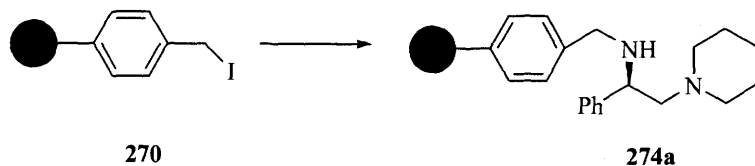
A solution of amine **276** (3.023 g, 15.00 mmol) in benzene (25 mL) was added to the solution of soluble polymer-supported benzyl iodide **270** (15.00 g) in benzene (150 mL), followed by the addition of K$_2$CO$_3$ (8.28 g, 60.0 mmol). The reaction mixture was refluxed under N$_2$ for 48 hours. The solvent was removed *in vacuo*, and the residue was cooled to –45 °C. Methanol (300 mL) was added, and the amine **274a** precipitated. The polymer **274a** was separated by filtration, washed with MeOH (200 mL), water (500 mL) and MeOH (750 mL). The resin was then dried to constant weight under high vacuum (16.10 g). The loading of amine **274a** was calculated by subtracting the molar amount of unreacted amine **276** from the total molar amount of **276** used for the attachment to the polymer and was 0.850 mmol of NH/g. Loading of the resin **274a** was confirmed by elemental analysis.

^{1}H NMR δ: 7.25 - 6.25 (m, 70H, Ar), 3.90 - 3.65 (m, 2H, CH$_2$-N), 3.53 - 3.18 (m, 3H, CH$_2$-N, CH-N), 2.83 - 2.58 (m, 2H, CH$_2$), 2.58 - 2.28 (m, 4H, CH$_2$), 2.20 - 1.10 (m, 40H, CH$_2$, CH, polymer matrix and CH$_2$ amine moiety)

^{13}C NMR δ: 145.5 (C-Ar), 143.3 (C-Ar), 128.5 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 127.3 (C-Ar), 125.8 (C-Ar), 66.7 (CH$_2$N), 55.1 (CH-N), 54.7 (CH$_2$-N), 40.6 (CH, polymer matrix), 26.4 (CH$_2$), 24.7 (CH$_2$)

$[\alpha]^{28}_D$ –21 (c 0.52, AcOEt, polymer)

Anal. Found: C, 87.81; H, 7.42; N, 1.91, which was used to calculate the loading of resin **274a**.

NCL polystyrene-supported methyl 2-methyloxycarbonylpropanoate (289)
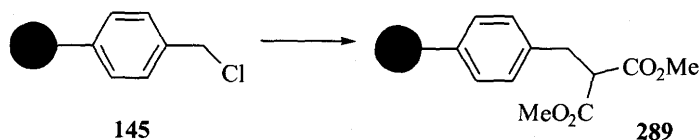
Dimethyl malonate (**288**) (9.24 g, 8.00 mL, 70.0 mmol) was added to the suspension of washed NaH (1.00 g, 38.2 mmol) in THF (250 mL) at 0 °C. The reaction mixture was stirred at this temperature for 2 hours, and the polymer **145** (30.00 g, 30.00 mmol, 1.00 mmol of Cl/g) was added. The reaction mixture was refluxed under N_2 for 48 hours. After the reaction was completed, the bulk of THF was evaporated and the polymer **289** was precipitated at –45 °C by addition of MeOH (ca. 600 mL). The polymer **289** was separated by filtration, and washed with the following solvents: water (300 mL) and MeOH (500 mL). The resin **289** was dried to constant weight under high vacuum (29.00 g). The loading of the polymer **289** was estimated by the subtraction of the recovered molar amount of dimethyl malonate (**288**) (2.627 g, 20 mmol) from the total molar amount that was used in the beginning (9.24 g, 70.0 mmol). The loading of the polymer **289** was 1.67 mmol of ester functionality/g.

^{1}H NMR δ: 7.46 - 6.25 (m, 37H, Ar), 4.33 - 4.10 (m, 4H, OCH_2), 3.77 - 3.55 (m, 1H, CH), 3.35 - 3.09 (m, 2H, CH_2Ph), 2.25 - 1.01 (m, 29H, CH_2, CH, polymer matrix and CH_3, ester moiety).

^{13}C NMR δ: 169.1 (C=O), 145.5 (C-Ar), 135.2 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 61.5 (CH_2-O), 54.0 (CH), 40.5 (CH, polymer matrix), 34.4 (CH_2Ph), 14.2 (CH_3).

NCL polystyrene-supported 2-methylhydroxy-1-propanol (290)
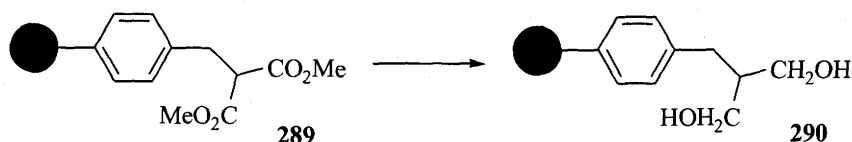
A solution of polymer **289** (30.0 g, 50.1 mmol, 1.67 mmol of CO_2Me/g) in THF (200 mL) was added dropwise to a suspension of $LiAlH_4$ (5.693 g, 150.0 mmol) in THF (200 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature, overnight. When the reaction was completed, the mixture was cooled to 0 °C, and the excess of $LiAlH_4$ was decomposed by slow addition of aqueous ammonia (5 mL) and AcOEt (50 mL). Another portion of AcOEt was added (200 mL), and the crude mixture was stirred at room temperature for 1 hour. Next, celite (ca. 5.00 g) was added, and the solid was filtered. The water layer was separated from the organic layer. The organic layer was washed with water (3 x 75 mL). The water layer was washed with AcOEt (3 x 150 mL). The organic layers were combined, dried with $MgSO_4$, and the solvent was evaporated. The cake (celite and aluminum salts) was refluxed with AcOEt (500 mL) overnight. The solid was filtered and the filtrate was dried with $MgSO_4$, and added to the crude polymer **290**. The solvent was removed *in vacuo*, and the resin **290** was precipitated at – 45 °C by addition of MeOH (500 mL). The polymer was separated by filtration, and washed with the following solvents: water (100 mL) and MeOH (500 mL). The resin was dried to constant weight under high vacuum (16.624 g). The loading of **290** was determined by titration of OH and was 1.6 mmol of OH/g.

^{1}H NMR δ: 7.35 - 6.08 (m, 132H, Ar), 3.90 - 3.35 (m, 8H, CH_2OH), 3.25 - 3.08 (m, 1H, OH), 2.70 - 2.35 (m, 2H, CH_2Ph), 2.32 - 0.90 (m, 73H, CH_2, CH, polymer and CH, linker).

^{13}C NMR δ: 145.4 (C-Ar), 128.1 (C-Ar), 125.8 (C-Ar), 65.5 (CH_2OH), 44.0 (CH, linker), 40.6 (CH, polymer matrix), 33.5 (CH_2Ph).

NCL polystyrene-supported 2-methyliodo-1-propyl iodide (291)
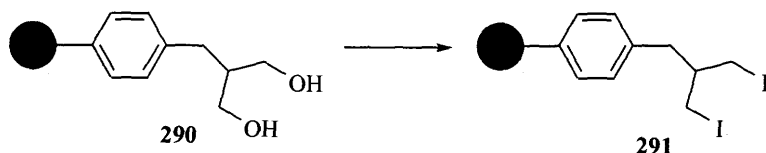
Imidazole (5.44 g, 80.0 mmol) was added to a solution of triphenylphosphine (20.1 g, 80.0 mmol) in dry CH_2Cl_2 (300 mL) followed by the addition of iodine (20.32g, 80.0 mmol). Next, polymer **290** was added (16.00 g, 25.60 mmol, 1.60 mmol of OH/g). The reaction mixture was protected from light, and stirred under N_2 at room temperature for 48 hours. After the reaction was completed the bulk of CH_2Cl_2 was evaporated and the polymer **291** was precipitated at –45 °C by addition of MeOH (300 mL), and separated by filtration. The polymer **291** was washed with water (150 mL), and MeOH (500 mL). It was dried to constant weight under high vacuum (16.413 g). The loading of **291** was not determined at this stage.

^{1}H NMR δ: 7.35 - 6.20 (m, 69H, Ar), 3.45 - 3.30 (m, 1H, CH_2I), 3.21 - 3.03 (m, 1H, CH_2I), 2.71 - 2.51 (m, 1H, CH, linker), 2.43 - 2.20 (m, 2H, CH_2Ph), 2.17 - 1.73 (m, 12H, CH, polymer matrix), 1.73 - 1.28 (m, 28H, CH_2, polymer matrix).

^{13}C NMR δ: 145.5 (C-Ar), 134.1 (C-Ar), 132.3 (C-Ar), 130.3 (C-Ar), 128.8 (C-Ar), 128.1 (C-Ar), 127.8 (C-Ar), 125.8 (C-Ar), 46.6 (CH, linker), 46.2 (CH_2Ph), 44.0 (CH_2, polymer matrix), 40.6 (CH, polymer matrix), 14.1 (CH_2I).

NCL polystyrene-supported (R,R)-N,N'-di-[1-phenyl-2-(1-piperidinyl)ethyl]-2-methyl-1,3-propanediamine (292)
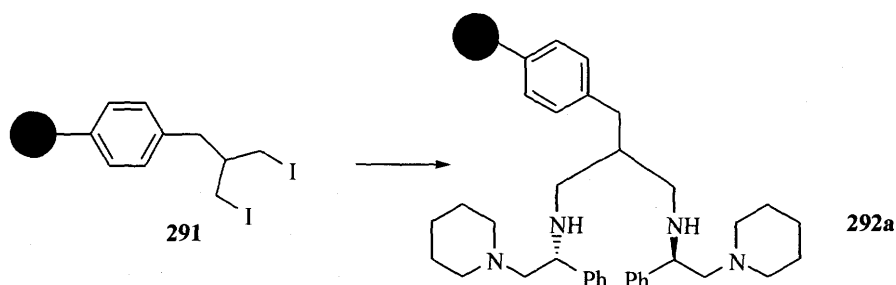
A solution of amine **272** (4.634 g, 22.70 mmol) in DMF (30 mL) was added to a solution of polymer **291** (8.40 g), followed by the addition of dry K_2CO_3 (5.00 g, 36.2 mmol). The reaction mixture was heated at 80 °C under N_2 for 48 hours. The solvent was removed by distillation under reduced pressure, and the residue was cooled to –45 °C, followed by the addition of MeOH (250 mL). The amine **292a** precipitated, and was separated by filtration. The polymer **292a** was washed with MeOH (250 mL), H_2O (250 mL), MeOH (500 mL), and dried to constant weight under vacuum (9.0 g). The loading of **292a** was calculated by Fajans titration and was 0.715 mmol of NH/g. The loading of the polymer **292a** was also estimated by subtracting the molar amount of the recovered amine **276** from the total molar amount of **276** used for the attachment to the polymer **291**. It was determined to be 0.704 mmol of NH/g. The loading determined by elemental analysis was 0.644 NH/g.

^{1}H NMR δ: 7.54 - 6.20 (m, 74H, Ar), 5.03 - 4.55 (m, 1H, CHN), 4.17 - 3.20 (m, 3H, CH_2N and NH), 2.73 - 0.70 (m, 47H, CH_2, CH polymer matrix, and CH_2Ph, CH, linker and CH_2N, CH_2, amine moiety).

^{13}C NMR δ: 145.6 (C-Ar), 137.1 (C-Ar), 128.2 (C-Ar), 127.9 (C-Ar), 125.9 (C-Ar), 55.1 (CH_2N), 46.2 (CHN), 44.1 (CH_2N), 42.8 (CH, linker), 40.6 (CH, polymer matrix), 30.0 (CH_2, linker), 26.4 (CH_2), 21.2 (CH_2).

$[\alpha]^{27}_D$ –4.40 (c 4.64, CH$_2$Cl$_2$, polymer)

Anal. (Found): C, 81.82; H, 7.09; N, 1.07, which was used to determine the loading of the resin **292a**.

NCL polystyrene-supported *(1R, 2S)*-2-dimethylamino-1-phenyl-1-propanol (271a)
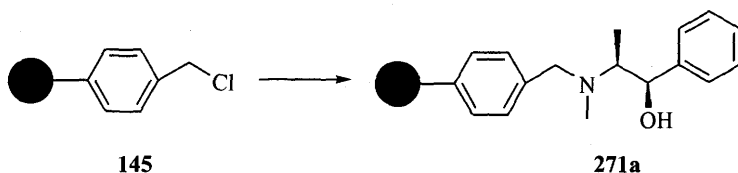
A solution of *(1R,2S)*-ephedrine **55a** (3.50 g, 21.3 mmol) in DMF (10 mL) was added to a solution of freshly prepared soluble polymer **145** (16.5 g, 15.0 mmol, 1.00 mmol of Cl/g) in DMF (100 mL). Sodium carbonate (2.258 g, 21.30 mmol) was added, and the reaction mixture was heated at 80 °C for 24 hours. DMF was removed by distillation, and the residue was cooled to − 45 °C, followed by addition of MeOH (250 mL). The polymer **271a** precipitated and was separated by filtration. It was washed with water (500 mL), MeOH (500 mL), and was dried to constant weight under high vacuum (17.0 g). The loading of polymer **271a** was determined by elemental analysis and was 1.00 mmol of NH/g.

^{1}H NMR δ: 7.66 - 6.80 (m, 38H, C-Ar, polymer matrix), 6.80 - 6.23 (m, 18H, ephedrine), 5.20 - 4.90 (m, 1H, CH-OH), 3.90 - 3.47 (m, 3H, CH$_2$Ph, CH), 3.16 - 2.85 (m, 1H, OH), 2.27 - 1.70 (m, 10H, CH, polymer matrix, and CH$_3$-N), 1.70 - 1.19 (m, 16H, CH$_2$, polymer matrix), 1.10 - 0.90 (m, 3H, CH$_3$)

^{13}C NMR δ: 145.4 (C-Ar), 142.6 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.2 (C-Ar), 127.8 (C-Ar), 127.2 (C-Ar), 126.4 (C-Ar), 126.2 (C-Ar), 125.8 (C-Ar), 72.5 (CH-OH), 60.9 (CH-N), 59.0 (CH$_2$Ph), 40.6 (CH, polymer matrix), 38.8 (CH$_3$-N), 12.6 (CH$_3$)

$[\alpha]^{26}_D$ +2.81 (c 1.82, AcOEt, polymer)

Anal. Found: C, 85.73; H, 7.25; N, 1.51, which was used to determine the loading of resin **271a**.

NCL polystyrene-supported *(1S, 2S)*-2-dimethylamino-1-phenyl-1-propanol (272a)
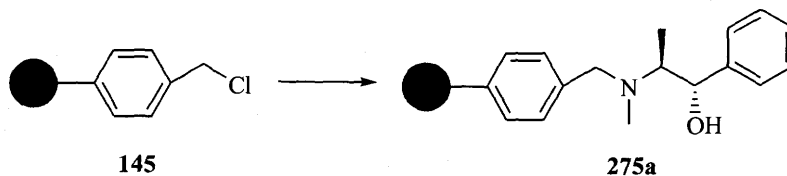
A solution of *(1S,2S)*-pseudoephedrine **275** (3.50 g, 21.3 mmol) in DMF (10 mL) was added to the solution of freshly prepared soluble polymer **145** (16.5 g, 15.0 mmol, 1.00 mmol of Cl/ g,) in DMF (100 mL). Sodium carbonate (2.258 g, 21.30 mmol) was added and the reaction mixture was heated at 80 °C for 24 hours. DMF was removed by distillation. The residue was cooled to – 45 °C, followed by addition of MeOH (250 mL). The polymer **272a** precipitated, and was separated by filtration. The resin **272a** was washed with water (500 mL), MeOH (500 mL), and dried to constant weight under high vacuum (17.279 g). The loading of **272a** was determined by elemental analysis and was 1.00 mmol of N/g.

^{1}H NMR δ: 7.55 - 6.89 (m, 34H, Ar, polymer matrix), 6.89 - 6.30 (m, 20H, Ar, pseudoephedrine), 4.45 - 4.30 (m, 1H, CH-OH), 3.85 - 3.58 (m, 1H, CH-N), 3.58 - 3.35 (m, CH$_2$-N), 2.94 - 2.68 (br s, 1H, OH), 2.30 - 2.10 (m, 3H, N-CH$_3$), 2.10 - 1.77 (m, 7H, CH, polymer matrix), 1.77 - 1.22 (m, 19H, CH$_2$, CH$_3$, polymer matrix), 0.92 - 0.75 (m, 3H, CH$_3$-N)

^{13}C NMR δ: 145.5 (C-Ar), 142.2 (C-Ar), 136 (C-Ar), 128.4 (C-Ar), 128.1 (C-Ar), 127.9 (C-Ar), 127.6 (Ar-C), 125.8 (C-Ar), 125.7 (C-Ar), 75.0 (CH$_2$OH), 65.3 (CH-N), 58.1 (CH$_2$-N), 44.0 (CH$_2$, polymer matrix), 40.5 (CH, polymer matrix), 30.5 (CH$_3$N), 7.7 (CH$_3$)

$[\alpha]^{25}_D$ +27.55 (c 2.72, AcOEt, polymer)

Anal. Found: C, 85.26; H, 7.16; N, 1.60, which was used to determine the loading of resin **272a**.

(1R,2S)-2-(benzylmethylamino)-1-phenyl-1-propanol (340a)[176-178]

55a   **340a**
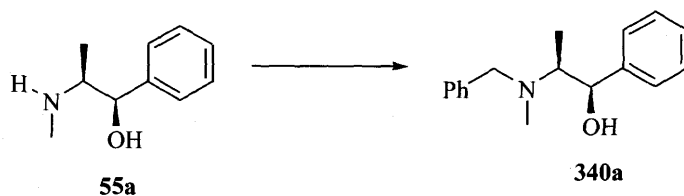
Benzyl bromide (5.00 g, 3.37 mL, 42.4 mmol) was added to a solution of *(1R,2S)*-ephedrine **(55a)** (7.00 g, 18.2 mmol) in dry DMF (125 mL), followed by the addition of K_2CO_3 (6.805 g, 42.40 mmol), and the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was cooled to room temperature, and the bulk of DMF was removed by distillation. Water was added (125 mL), and the residue was extracted with Et_2O (3 x 125 mL). The organic layers were combined and washed with aqueous NaOH (3 x 100 mL), dried with $MgSO_4$ and the solvent was removed *in vacuo* giving the crude product **340a**. The crude product was purified by distillation, followed by crystallization from hexane to give pure **340a** (10.0 g, 92% yield).

^{1}H NMR δ: 7.45-7.20 (m, 10H), 4.9 (d, *J*= 4.8 Hz, 1H), 3.70-3.55 (m, 2H), 2.95 (ddd, *J*= 6.7 Hz, *J*= 11.8 Hz, *J*= 6.7 Hz, 1H), 2.23 (s, 3H), 1.02 (d, *J*= 6.8 Hz, 3H).

mp= 46-47 °C (lit. 49-51 °C)[176]

R_f= 0.30 (hexane: AcOEt 4:1)

(1S,2S)-2-(benzylmethylamino)-1-phenyl-1-propanol (341a)[178]

278 → 344a
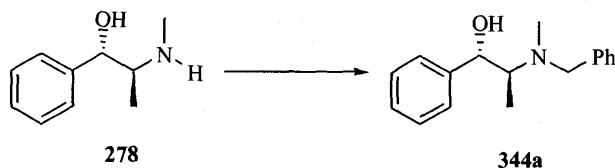
Benzyl bromide (5.00 g, 3.37 mL, 42.4 mmol) was added to a solution of *(1S,2S)*-pseudoephedrine **275** (7.00 g, 18.2 mmol) in dry DMF (125 mL), followed by the addition of K_2CO_3 (6.805 g, 42.40 mmol), and the reaction mixture was stirred at 80 °C for 24 hours. The mixture was cooled to room temperature, and the bulk of DMF was removed by distillation. Water was added (125 mL), and the residue was extracted with Et_2O (3 x 125 mL). The organic layers were combined, washed with aqueous NaOH (3 x 100 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo* giving the crude product **341a**. The crude product was purified by distillation, followed by crystallization from hexane and pure **341a** was obtained (9.68 g, 89% yield).

^{1}H NMR δ: 7.45 - 7.20 (m, 10 H), 5.10 (br s, 1H), 4.35 (d, *J*= 9.7 Hz, 1H), 3.79 (d, *J*= 12.9 Hz, 1H), 3.53 (d, *J*= 12.9 Hz, 1H), 2.85 - 2.73 (m, 1H), 2.27 (s, 3H), 0.85 (d, *J*= 6.5 Hz, 3H).

mp= 44-45 °C (lit. 43-46 °C)[178]

$[\alpha]_D^{25}$ +125 (c 1.0, $CHCl_3$) (lit. +126 (c 1.0, $CHCl_3$))[179]

R_f= 0.45 (hexane: AcOEt 4:1)

4.7. Methodology study of α-functionalization of carbonyl compounds using SP and LP reagents.

Procedure H: Generation of lithium tropinone enolate (**201a**) using insoluble, polymer-supported chiral lithium amide.
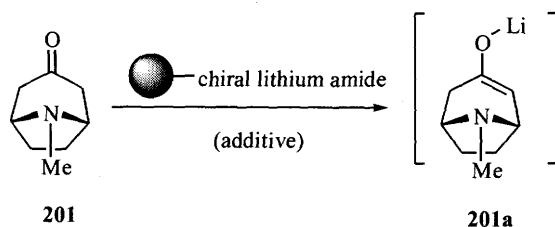
A solution of n-BuLi in hexane (1.45 M, 1.4 mL, 2.049 mmol) was added to a slurry of an insoluble polymer-supported chiral amine (2.049 mmol) in THF (20-25 mL) at 0 °C under N_2, and the resulting suspension was stirred for 8 hours. After cooling to –78 °C, tropinone (**201**) solution (0.258g, 1.86 mmol) in THF (2 mL) was added dropwise for over 3 or 45 minutes, and the resulting mixture was stirred at –78 °C, overnight.

Alternatively:

A solution of n-BuLi in hexane (1.45 M, 1.4 mL, 2.049 mmol) was added to a slurry of an insoluble, polymer-supported chiral amine (2.049 mmol) in THF (15 mL) at 0 °C under N_2, and the resulting suspension was stirred for 6 hours. A solution of lithium chloride in THF (0.63 M, 2.95 mL, 1.86 mmol) was added, and the stirring was continued for an additional 2 hours. After cooling to –78 °C, a solution of tropinone (**201**) (0.258 g, 1.86 mmol) in THF (2 mL) was added dropwise for over a period of 3 minutes, and the resulting mixture was stirred overnight.

Procedure J: Generation of the tropinone lithium enolate (**201a**) using a soluble polymer-supported chiral lithium amide
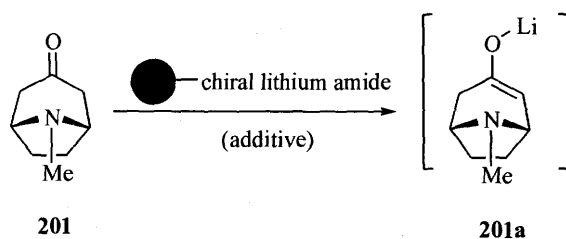
A solution of n-BuLi in hexane (1.9 M, 0.58 mL, 1.1 mmol) was added to a solution of a soluble polymer-supported chiral amine (1.1 mmol) in THF (25 mL) at 0 °C under N_2, and the resulting solution was stirred for 2.5 hours. After cooling to −78 °C, a solution of tropinone (**201**) (0.139g, 1.00 mmol) in THF (2 mL) was added dropwise for over a period of 3 minutes, and the resulting mixture was stirred for 3 hours.

Alternatively:

A solution of n-BuLi in hexane (1.9 M, 0.58 mL, 1.1 mmol) was added to a solution of a soluble polymer-supported chiral amine (1.1 mmol) in THF (25 mL) at 0 °C under N_2, and the resulting solution was stirred under N_2 for 1.5 hours. Lithium chloride in THF (1.0 mmol) was added, and the stirring was continued for an additional hour. After cooling to −78 °C, a solution of tropinone (**201**) (0.139 g, 1.00 mmol) in THF (2 mL) was added dropwise for over a period of 3 minutes, and the resulting mixture was stirred for 3 hours. (If necessary, a second equivalent of n-BuLi (1.9 M, 0.58 mL, 1.1 mmol) was added, and the reaction mixture was warmed p to 0 °C. The stirring was continued for 30 minutes, followed by cooling of the reaction mixture to −78 °C before the addition of an electrophile.)

(1S, 2R, 1'S)-2-(1'-Hydroxybenzyl)-8-methyl-8-azabicyclo[3.2.1]-octane-3-one (206)

2, 101

201a   202
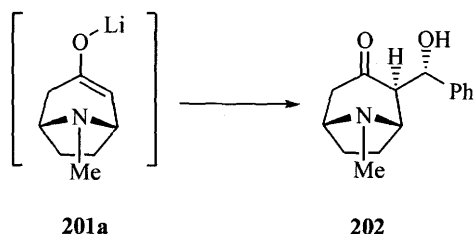
With SP chiral lithium amides:

Benzaldehyde (0.217 g, 0.208 mL, 2.049 mmol) was added to a solution of tropinone lithium enolate (**201a**) (1.86 mmol) generated by *procedure H*, and the reaction mixture was stirred for 4 hours. The mixture was quenchd with a saturated solution of NH₄Cl (10 mL). The polymeric amine was separated by filtration, washed with NH₄Cl solution and Et₂O. The water layer was separated and extracted with Et₂O (3 x 50.00 mL). The organic extracts were combined, dried with MgSO₄. The solvents were removed *in vacuo*, and the crude product was obtained. The crude product **202** was purified by DFC (hexane: AcOH 4: 1, CH₂Cl₂: MeOH 85: 15). The yield and enantioselectivity of the reaction are presented in Table 31 of Results and Discussion.

With LP chiral lithium amides:

Benzaldehyde (117 mg, 0.11 mL, 1.10 mmol) was added to a solution of tropinone enolate (**201a**) (1.0 mmol) generated by *procedure J*, and the reaction mixture was stirred for 1 hour. The mixture was quenched with a saturated solution of NH₄Cl (10 mL), and quickly extracted with AcOEt (3 x 100 mL). The organic extracts were combined, dried with MgSO₄, and the solvents were removed *in vacuo*. The residue was cooled to –40 °C, and MeOH (100 mL) was added. A soluble polymer-supported amine precipitated, and was separated by filtration. The filtrate was concentrated *in vacuo*, and the crude product

was obtained. It was purified by DFC (hexane: AcOH 4: 1, CH$_2$Cl$_2$: MeOH 85: 15) and the yield and enantioselectivity of the reaction is presented in Table 33.

The pure product **202** was characterized by ^{1}H NMR, and the spectrum was identical as that previously recorded.[2, 101]

^{1}H NMR δ: 7.42 - 7.20 (m, 5H), 5.23 (d, J= 3.0 Hz, 1H), 3.60 (d, J= 6.5 Hz, 1H), 3.60 - 3.45 (m, 1H), 2.86 (ddd, J_1= 15.5 Hz, J_2= 5.0 Hz, J_3= 1.5 Hz, 1H), 2.47 (s, 3H), 2.45 - 2.41 (m, 1H), 2.32 (ddd, J_1= 15.5 Hz, J_2= 4 Hz, J_3= 1.5 Hz, 1H), 2.35 - 2.10 (m, 2H), 1.70 - 1.50 (m, 2H).

6-[N-(2,2,2-Trichloroethoxycarbonyl)-N-methyl]-amino-2-cyclohepten-1-one (230)[2, 88d, 101]

201a   230
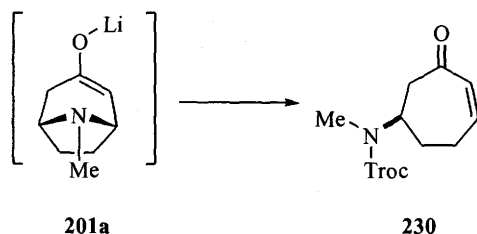
With PS chiral lithium amides:

2,2,2-Trichloroethyl chloroformate (0.434g, 0.28 mL, 2.05 mmol) was added to a solution of tropinone lithium enolate (**201a**) (1.86 mmol) generated by *procedure H*, and the reaction mixture was stirred for 8 hours. The reaction was quenched with a saturated solution of K_2CO_3 (10 mL), and a polymeric amine was separated by filtration, washed with saturated solution of K_2CO_3 (100 mL) and Et_2O (100 mL). The water layer was separated, and extracted with Et_2O (3 x 50.00 mL). The organic extracts were combined, and dried with $MgSO_4$. The solvents were removed *in vacuo*, and the crude product was obtained. The crude product was purified by DFC (hexane, hexane: AcOEt 1: 1) giving the pure **230**. The yields and the enantioselectivities of the reaction are presented in Table 33 of Results and Discusion.

With LP chiral lithium amides:

2,2,2-trichloroethyl chloroformate (277 mg, 0.18 mL, 1.30 mmol) was added to a solution of tropinone lithium enolate (**201a**) (1.0 mmol) generated by *procedure J* (with a second equivalent of n-BuLi), and the reaction mixture was stirred for 2 hours. The mixture was quenched with saturated solution of K_2CO_3 (10 mL), and was allowed to warm to room temperature followed by extraction with AcOEt (3 x 100 mL). The organic extracts were combined, dried with $MgSO_4$, and the solvents were evaporated. The residue was cooled to –40 °C, and MeOH (100 mL) was added. A soluble polymer-supported amine precipitated, and was separated by filtration. The filtrate was concentrated *in vacuo*, and

the crude product **230** was obtained. It was purified by DFC (hexane, hexane: AcOEt 1:1) to give the pure compound **230**. The yields are shown in Table 34 of Results and Discussion.

The pure product **230** was characterized by ^{1}H NMR, and the spectrum was identical as that recorded previously.[2, 88d, 101]

^{1}H NMR δ: 6.64 (ddd, J_1= 12.0 Hz, J_2= 6.0 Hz, J_3= 5.0 Hz, 1H), 6.05 (d, J= 12.0 Hz, 1H), 4.75 (s, 2H), 4.55 (s, 1H), 2.90 (s, 3H), 2.92 - 2.82 (m, 2H), 2.68 - 2.45 (m, 2H), 2.20 - 1.90 (m, 2H).

Ethyl 1-benzyl-2-oxocyclopentanecarboxylate (304)[141]
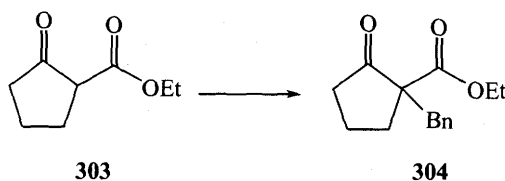
Experiment performed in solution:

A solution of n-BuLi in hexane (2.05 M, 1.08 mL, 2.20 mmol) was added to a solution of diisopropylamine (0.222 g, 0.30 mL, 2.20 mmol) in toluene (5 mL) at 0 °C under N_2, and the reaction mixture was stirred for 30 minutes. A solution of β-ketoester **303** (0.312 g, 0.290 mL, 2.00 mmol) in toluene (2 mL) was added, and the stirring was continued for an additional 6 hours. Benzyl bromide (0.855 g, 0.6 mL, 5.00 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 18 hours. A solution of NaOH (50 mL) was added, and the mixture was extracted with Et_2O (3 x 50 mL). The organic layers were combined, dried with $MgSO_4$. Solvents were removed *in vacuo*, and the crude product was obtained (300 mg), which was purified by DFC (hexane, hexane: AcOEt 1:1) to give pure **304** (0.246 g, 50% yield).

Experiment performed in "liquid phase":

A solution of n-BuLi in hexane (2.13 M, 0.590 mL, 1.25 mmol) was added to the solution of amine **292a** (1.925 g, 1.240 mmol, 0.644 mmol of N/ g) in toluene (50 mL) at 0 °C under N_2, and the reaction mixture was stirred for 2.5 hour. The reaction mixture was cooled to –20 °C, and β-ketoester **303** was added (0.100 g, 0.640 mmol) in toluene (0.5 mL). The stirring was continued at –20 °C for another 4 hours, followed by warming the mixture to 0 °C, and stirring for 2 additional hours at this temperature. Benzyl bromide (0.719 g, 0.50 mL, 4.20 mmol) was added, and the reaction mixture was stirred overnight. The reaction mixture was warmed to room temperature, and the stirring was

continued for an additional 24 hours. Next, phthalimide (0.735 g, 5.00 mmol) was added in THF: toluene mixture (1:1, 5 mL). The reaction mixture was poured to cold (-45 °C) MeOH (100 mL), and most of the polymeric amine **292a** precipitated as a very fine powder. The solvents were evaporated *in vacuo*, the residue was cooled to –45 °C, and MeOH was added (100 mL). The remaining polymeric amine **292a** precipitated, was separated by filtration, and washed with MeOH (3 x 50 mL). The methanol filtrate was combined with the one from the first filtration, and concentrated *in vacuo* giving the crude product **304** (0.120 g). It was purified by DFC (hexane, hexane: AcOEt 1:1) to give pure compound **304** (0.108 g, 67% yield).

Pure compound **304** was characterized by ^{1}H and ^{13}C NMR, and the spectra are in agreement with spectra reported in the literature.[180]

^{1}H NMR δ: 7.26 - 7.09 (m, 5 H), 4.15 (q, *J*= 7.1 Hz, *J*=14.3 Hz, 2H), 3.18 (d, *J*= 13.7 Hz, 1H), 3.09 (d, *J*= 13.7 Hz, 1H), 2.43 - 2.27 (m, 2H), 2.06 - 1.80 (m, 3H), 1.63 - 1.49 (m, 1H), 1.22 (t, *J*= 7.1 Hz, 3 H).

^{13}C NMR δ: 214.9, 171.0, 136.7, 130.3, 128.4, 126.9, 61.6, 61.5, 39.0, 38.4, 31.8, 19.5, 14.1.

2-Methyl-1-trimethylsilyloxy-tetralin-1-ene (322)[181]
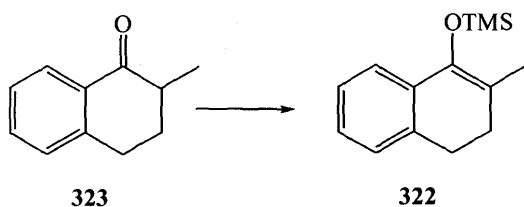
A solution of n-BuLi in hexane (2.5 M, 3.76 mL, 9.4 mmol) was added to the solution of diisopropylamine (0.949 g, 1.32 mL, 9.40 mmol) in THF (30 mL) at 0 °C, and the reaction mixture was stirred for 0.5 hour. The solution of LDA was cooled to −78 °C, and freshly distilled Et$_3$N (4.23 mL, 3.071 g, 30.08 mmol), followed by TMSCl (3.31 mL, 2.837 g, 30.08 mmol) was added. The reaction mixture was stirred for 5 minutes, racemic 2-methyl-1-tetralone (323) (1.50 g, 1.42 mL, 9.40 mmol) was added, and the stirring was continued for an additional 2.5 hour. The reaction mixture was quenched with a saturated solution of NH$_4$Cl (30 mL), and quickly extracted with Et$_2$O (3 x 100 mL). The organic extracts were washed with brine (150 mL), dried with MgSO$_4$ and the solvents were removed *in vacuo* The crude product 322 was obtained (2.175 g) and was purified by DFC (hexane, hexane: AcOEt 95: 5) to give silyl enol ether 322 (1.74 g, 80% yield).

The ^{1}H NMR spectrum was in agreement with the spectrum reported in the literature.[181]

^{1}H NMR δ: 7.34 (d, *J*= 7.5 Hz, 1H), 7.26 - 7.15 (m, 1H), 7.12 - 7.07 (m, 2H), 2.50 (t, *J*= 7.8 Hz, 2H), 2.28 (t, *J*= 8.0 Hz, 2H), 1.84 (s, 3H), 0.23 (s, 9 H).

(R)-2-Methyl-1-tetralone (323)[161]

322   (R)-323
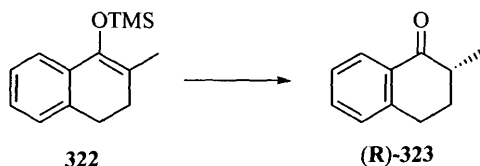
A solution of MeLi/ LiBr in Et$_2$O (1.5 M, 0.74 mL, 1.1 mmol) was added to the solution of silyl enol ether **322** (0.232 g, 1.00 mmol) in Et$_2$O (3 mL) at room temperature, and the reaction mixture was stirred under N$_2$ for 1.5 hour. The solution was cooled to –20 °C and toluene was added (10 mL). The solution was added *via* cannula to the solution of soluble polymer-supported chiral amino-alcohol **271a** (1.1 mmol) in toluene (30 - 50 mL). The reaction mixture was stirred at this temperature for 2 hours, then cooled down to –45 °C and the stirring was continued for additional 20 hours. The reaction mixture was cooled to –78 °C, and glacial acetic acid (0.36 g, 0.34 mL, 6.0 mmol) in toluene (2 mL) was added. The stirring was continued for 3 hours, and the reaction mixture was poured into cold MeOH (100 mL, –45 °C). The solvents were removed in *vacuo*, and the crude product **323**, along with **271a** was obtained. The residue was cooled to –45 °C again, and MeOH (100 mL) was added again. The resin **271a** precipitated, was separated by filtration, and washed with MeOH (3 x 75 mL). The methanol wash was combined with the filtrate, and the solvent was evaporated in *vacuo* giving the crude product **323**. It was purified by DFC (hexane, hexane: AcOEt 95: 5). Yields and enantioselectvities of the reaction are presented in Table 38 of Results and Discussion.

The pure compound **323** was characterized by ^{1}H NMR, and the spectrum was in agreement with a recorded spectrum of commercially available 2-methyl-1-tetralone.

^{1}H NMR δ: 8.30 (d, *J*= 7.8 Hz, 1H), 7.44 (t, *J*= 7.4 Hz, 1H), 7.34 - 7.16 (m, 2H), 3.11 - 2.88 (m, 2H), 2.57 (ddd, *J*= 6.8 Hz, *J*= 11.9 Hz, *J*= 18.6 Hz, 1H), 2.25 - 2.11 (m, 1H), 1.86 (dddd, *J*= 5.1 Hz, *J*= 11.7 Hz, *J*=11.7 Hz, *J*= 23.6 Hz, 1H), 1.26 (d, *J*= 6.8 Hz, 3H).

(R)-2-isopropyl-5-methyl-1-trimethylsilyloxy-1-cyclohexene (337)[182]

267   337
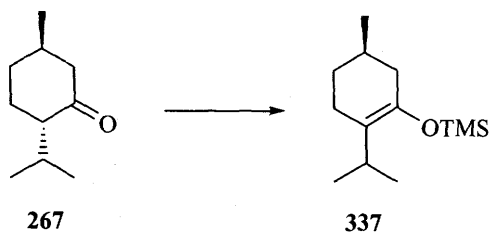
Triethylamine (1.640 g, 2.26 mL, 16.25 mmol) was added to a solution of (-)-menthone (**267**) (2.000 g, 2.24 mL, 13.00 mmol) in dry acetonitrile (30 mL), followed by the addition of TMSCl (1.762 g, 2.05 mL, 16.25 mmol) and sodium iodide (2.437 g, 16.25 mmol). The reaction mixture was stirred at room temperature for 2 hours. A saturated solution of NH_4Cl (30 mL) was added, and the mixture was extracted with hexane (3 x 75 mL). The organic layer was dried with $MgSO_4$, and the solvents were removed *in vacuo* giving the crude product **337** (2.6 g). It was purified by DFC (hexane, hexane: AcOEt 95:5) to give pure silyl enol ether **337** (2.428 g, 83 % yield).

The pure silyl enol **337** ether was characterized by ^1H and ^{13}C NMR. The spectra were in agreement with spectra reported in the literature.[182a]

^1H NMR δ: 3.01 (hept, *J*= 6.9 Hz, *J*= 18.9 Hz, 1 H), 2.11 - 1.89 (m, 2H), 1.76 - 1.58 (m, 3H), 1.34 - 1.28 (m, 1H), 1.08 - 1.13 (m, 1H), 0.94 (d, *J*= 6.0 Hz, 3H), 0.90 (d, *J*= 7.0 Hz, 6 H), 0.15 (s, 9H).

^{13}C NMR δ: 140.9, 120.5, 39.2, 31.4, 29.8, 26.3, 21.7, 20.7, 20.5, 0.9.

2-Isopropyl-5-methyl cyclohexanone (338 + 339)[157]
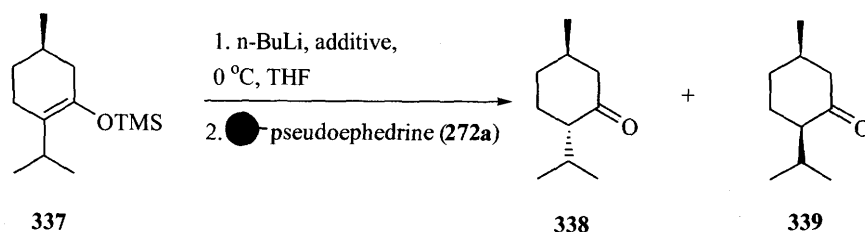
A solution of n-BuLi in hexane (0.94 mL, 2.21 M, 2.07 mmol) was added to the mixture of silyl enol ether **337** (232 mg, 1.02 mmol) and t-BuOH or N-benzylpseudoephedrine **(341a)** (1.05 mmol) in THF (10 mL) was added. The mixture was stirred at 0 °C under N_2 for 2 hours. The solution was cooled to −78 °C, and was added *via* cannula to the solution of soluble polymer-supported pseudoephedrine **(272a)** (1.00 g, 1.00 mmol/g, 1.00 mmol) in THF (20 mL). The reaction mixture was stirred at the temperature for 4 hours. The reaction mixture was poured down to the cold (-45 °C) MeOH (150 mL), polymer **272a** precipitated, and was separated by filtration. The filtrate was concentrated *in vacuo* giving the crude product as the mixture of **338** and **339**. The crude product was purified by DFC (hexane, hexane: AcOEt 95:5). The yields and diastereoselectivities of the reaction are presented in Table 40 of Results and Discussion.

The pure product **338** was characterized by ^{1}H NMR. The spectrum was in agreement with recorded spectrum of commercially available (-)-menthone and was also in agreement with the spectrum of (-)-menthone reported in the literature.[183]

^{1}H NMR δ: 2.19 (ddd, *J*= 1.6 Hz, *J*= 3.6, *J*= 12.7 Hz, 1H), 2.10 - 1.60 (m, 6H), 1.30 - 1.15 (m, 2H), 0.86 (dd, *J*= 1.8 Hz, *J*= 6.1 Hz, 3H), 0.76 (dd, *J*= 1.9 Hz, *J*= 6.6 Hz, 3H), 0.71 (dd, *J*= 1.9 Hz, *J*= 6.6 Hz, 3H).

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Table 1. The results of different additives on the enantioselectivity of the ring-opening of tropinone (**24**).

Entry	Chiral amine	Additive (eq.)	Yield (%)[a]	Ee (%)[b]
1	(S,S)-**204a**	-	70	44
2	(S,S)-**204a**	HCl salt	74	93
3	(S,S)-**204a**	LiCl (0.10)	84	49
4	(S,S)-**204a**	LiCl (0.25)	92	85
5	(S,S)-**204a**	LiCl (0.50)	90	95
6	(S,S)-**204a**	LiCl (1.0)	92	96
7	(S,S)-**204a**	LiCl (2.0)	94	95
8	(S,S)-**204a**	LiBr (0.10)	90	35
9	(S,S)-**204a**	LiBr (0.25)	82	54
10	(S,S)-**204a**	LiBr (0.50)	88	63
11	(S,S)-**204a**	LiBr (1.0)	93	73
12	(S,S)-**204a**	LiBr (2.0)	85	88
13	(S,S)-**204a**	LiI (0.10)	94	41
14	(S,S)-**204a**	LiI (0.25)	84	42
15	(S,S)-**204a**	LiI (0.50)	96	37
16	(S,S)-**204a**	LiI (1.0)	67	40
17	(S,S)-**204a**	LiI (2.0)	78	41
18	(S,S)-**204a**	$LiClO_4$ (0.10)	91	48
19	(S,S)-**204a**	$LiClO_4$ (0.25)	83	44
20	(S,S)-**204a**	$LiClO_4$ (0.50)	80	50
21	(S,S)-**204a**	$LiClO_4$ (1.0)	85	45
22	(S,S)-**204a**	$LiClO_4$ (2.0)	90	56
23	(S,S)-**204a**	$CeCl_3$ (0.10)	94	63
24	(S,S)-**204a**	$CeCl_3$ (0.25)	82	44
26	(S,S)-**204a**	$CeCl_3$ (0.50)	24	38
27	(S,S)-**204a**	$CeCl_3$ (1.0)	71	80

(R)-1-(2-Amino-2-phenylacetyl)piperidine (280)[96, 168]

279   **280**
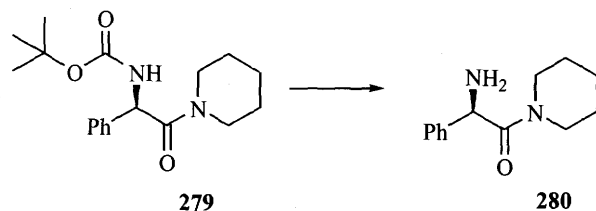
Trifluoroacetic acid (150 mL) was added to t-Boc-phenylglycine piperidine (**279**) (18.0 g, 57.0 mmol) at 0 °C, and stirred for 1 hour. Benzene (250 mL) was added to the resulting mixture, and the trifluoroacetic acid was removed with benzene under vacuum. This was repeated 3 times. The residue was made basic by treating with an excess of NaOH, and was extracted with Et$_2$O (3 x 150 mL), dried with MgSO$_4$ and concentrated under vacuum to give the crude product **280** (11.00 g, 89%). The crude product was subjected to reduction without further purification. The analytical sample of **280** was purified by DFC (10 % AcOEt in hexane: 10 % MeOH in CH$_2$Cl$_2$).

The analytical sample **280** was characterized by ^{1}H NMR, which was in agreement with the literature.[168]

^{1}H NMR δ: 7.40 - 7.23 (m, 5H), 4.75 (s, 1H), 3.80 - 3.68 (m, 1H), 3.50-3.40 (m, 1H), 3.30 - 3.15 (m, 2H), 2.19 (s, 2H), 1.63 - 1.25 (m, 5H), 1.05 - 0.85 (m, 1H).

28	(S,S)-**204a**	ZnCl$_2$ (0.10)	72	80
29	(S,S)-**204a**	ZnCl$_2$ (0.25)	45	62
30	(S,S)-**204a**	ZnCl$_2$ (0.50)	40	86
31	(S,S)-**204a**	ZnCl$_2$ (1.0)	40	90
32	(S,S)-**204a**	ZnCl$_2$ (2.0)	42	88
33	(S,S)-**204a**	HMPA (0.10)	66	43
34	(S,S)-**204a**	HMPA (0.25)	86	43
35	(S,S)-**204a**	HMPA (0.50)	77	45
36	(S,S)-**204a**	HMPA (1.0)	71	39
37	(S,S)-**204a**	HMPA (2.0)	85	35
38	(S,S)-**204a**	HMPA (3.0)	93	39
39	(S,S)-**204a**	TMEDA (0.10)	63	34
40	(S,S)-**204a**	TMEDA (0.25)	98	45
41	(S,S)-**204a**	TMEDA (0.50)	92	36
42	(S,S)-**204a**	TMEDA (1.0)	45	40
43	(S,S)-**204a**	TMEDA (2.0)	46	45
44	(S,S)-**204a**	LiF (0.10)	60	33
45	(S,S)-**204a**	LiF (0.25)	41	25
46	(S,S)-**204a**	LiF (0.50)	55	38
47	(S,S)-**204a**	LiF (1.0)	70	38
48	(S,S)-**204a**	LiF (2.0)	76	37
49	(S,S)-**204a**	DMPU (0.10)	99	43
50	(S,S)-**204a**	DMPU (0.25)	89	39
51	(S,S)-**204a**	DMPU (0.50)	98	54
52	(S,S)-**204a**	DMPU (1.0)	65	52
53	(S,S)-**204a**	DMPU (2.0)	57	38
54	(S,S)-**204a**	H$_2$O (0.005)	48	38
55	(S,S)-**204a**	H$_2$O, excess of n-BuLi (0.005)	41	24
56	(S,S)-**204a**	H$_2$O (0.005), LiCl (1.0)	48	81

57	(S,S)-204a	H$_2$O, excess of n-BuLi (0.005), LiCl (1.0)	48	36
58	(S,S)-204a	H$_2$O (0.02)	10	-
59	(S,S)-204a	H$_2$O, excess of n-BuLi (0.02)	13	5
60	(S,S)-204a	H$_2$O (0.02), LiCl (1.0)	6	3
61	(S)-200a	-	52	29
62	(S)-200a	TMEDA (1.0)	23	38
63	(S)-200a	TMEDA (2.0)	15	33
64	(S)-200a	HMPA (0.25)	88	22
65	(S)-200a	HMPA (0.50)	66	15
66	(S)-200a	HMPA (1.0)	87	19
67	(S)-200a	HMPA (2.0)	64	20
68	(S)-200a	HMPA (3.0)	44	19
69	(S)-200a	CeCl$_3$ (1.0)	11	34
70	(S)-200a	ZnCl$_2$ (0.05)	42	46
71	(S)-200a	ZnCl$_2$ (0.10)	87	57
72	(S)-200a	(0.50) ZnCl$_2$	39	31
73	(S)-200a	ZnCl$_2$ (1.0)	10	22
74	(S)-234a	-	98	14
75	(S)-235a	-	86	78
76	(S)-235a	LiCl (1.0)	86	87
77	(S,S)-236a	-	22	17
78	(S,S)-236a	LiCl (1.0)	60	72
79	(S,S)-237a	-	50	48
80	(S,S)-237a	HCl salt	89	88
81	(S,S)-209a	HCl salt	71	77
82	(R)-190a	-	82	83
83	(R)-190a	LiCl (0.10)	67	94
84	(R)-190a	LiCl (0.25)	82	99

85	(R)-**190a**	LiCl (0.50)	86	94
86	(R)-**190a**	LiCl (1.0)	85	95
87	(R)-**190a**	LiCl (2.0)	79	94
88	(R)-**190a**	LiCl (3.0)	62	98
89	(R)-**190a**	HMPA (0.10)	91	81
90	(R)-**190a**	HMPA (0.25)	57	80
91	(R)-**190a**	HMPA (0.50)	74	86
92	(R)-**190a**	HMPA (1.0)	56	68
93	(R)-**190a**	HMPA (2.0)	49	85
94	(R)-**190a**	HMPA (3.0)	54	84
95	(R)-**190a**	H_2O (0.02)	8	6
96	(R)-**190a**	H_2O (0.02), LiCl (1.0)	8	10
97	(R)-**238a**	-	80	87
98	(R)-**238a**	LiCl (1.0)	97	96

[a]: yield after purification of the crude product using flash chromatography; [b]: enantioselectivity measured on the crude product by HPLC with Chiralpack AD column with 85: 15 hexane: IPA

Table 2. Diastereoselectivity of the aldol reaction of the lithium enolate generated from 1,4-cyclohexanedione monoethylene ketal (**239**) followed by the aldol reaction.

Entry	Conditions for generation of the enolate (*procedure*)	Ratio **243: 244**
1	*D* (1 eq. of LDA)	9: 1
2	*D* (2 eq. of LDA)	2: 1
3	*E* (1 eq. of LDA, 1 eq. of n-BuLi)	3: 1
4	D (1 eq. of a chiral amine)	9: 1