SOLUBLE POLYMER-SUPPORTED CATALYSTS AND INITIATORS

A Dissertation Presented

by

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Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Organic Chemistry

May 2005

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DEDICATION

To Mom, Dad, Udo, Obi, Mekus, and Ngozi

ACKNOWLEDGEMENTS

First and foremost, I would like to thank God for blessing me with the strength, perseverance and tenacity that enabled me to complete this “scenic” Ph.D. program. I thank my advisor, Prof. Venkataraman (DV), for his indispensable guidance and support. His pristine passion for chemistry and science has not skipped a beat–from the day I walked into his office as a first-year graduate student–until this day. I thank the DV group and my colleagues who have offered their support and encouragement through the years: my dissertation committee (Prof. Coughlin, Prof. Lillya and Prof. Bianconi) for their guidance, Dr. Greg Dabkowski for the efficiency with which he carried out the microanalysis of my numerous molecules, and the world’s greatest graduate program manager, Kathy Tobiassen. I would also like to thank my friends, Chris (C-Mac) McDevitt, and the “Crampton Crew”. To my aunt Mercy and mama and Uncle (CY), Uncle Ebere (and family)–thanks for all the love and support. I want to specially thank my girl friend, and best friend, Uche. Thanks for being there for me.

Finally, to my greatest asset; Mom, Dad, Udo, Obi (“bob”), Emeka (“you know how we do”) and my baby sister Ngozi (“ōmumoskí batzup?”). I couldn’t have done it without you guys. Yes Oooh!

ABSTRACT

SOLUBLE POLYMER-SUPPORTED CATALYSTS AND INITIATORS

MAY 2005

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The development of polymer-supported chiral organic ligands for transition metal asymmetric catalysis is an area of research that is continuously receiving a lot of interest. This methodology addresses the major issue of recyclability and waste/product stream contamination in conventional homogeneous catalysis. The use of soluble polymers, as supports, couples the advantages of homogeneous and heterogeneous catalysis and offers a means of recycling often expensive chiral ligands. The goal is to recycle the catalysts over multiple runs without loss of its activity. A novel semi-continuous technique for recycling soluble polymer-supported catalysts–"Soxhlet-Dialysis"–has been developed whereby the catalyst's activity and enantioselectivity is maintained over multiple runs. It was also observed that the spacer that linked the polymer to the catalyst had an unprecedented effect on the activity and enantioselectivity of the catalyst. Electronic effects on enantioselectivity of chiral Zn-salen catalysts were studied, and logical interpretation of the results provided the basis for a postulated catalytic mechanism. "Living" Free Radical Polymerization using a soluble polymer supported initiator was employed for the design of well-defined cleavable PS-*b*-PEG diblock copolymers for the fabrication of nanoporous thin films.

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DCC	N,N-Dicyclohexylcarbidiimide
DHQ	Decahydroquinoline
DHQD	Dihydroxyquinidine
DIOP	(4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane)
DMAP	N,N-dimethylamino pyridine
DMF	N,N-dimethylformamide
DVB	Divinylbenzene
ee	enantiomeric excess
er	enantiomeric ratio
ERG	Electron Releasing Group
Et_2Zn	Diethylzinc
EWG	Electron Withdrawing Group
FT-IR	Fourier Transform Infra Red
GC	Gas Chromatography
GPC	Gel Permeation Chromatography
HRMS	High Resolution Mass Spectroscopy
LFER	Linear Free Energy Relationship
LFRP	Living Free Radical Polymerization
LPS	Liner Polystyrene
MsCl	Methanesulfonyl chloride
MW	Molecular Weight
MWCO	Molecular Weight Cut-Off
n-BuLi	*n*-Butyl Lithium
NMR	Nuclear Magnetic Resonance

PAA	Poly(acrylic acid)
PEG	Poly(ethylene glycol) monomethylether
PEG-OMs	Poly(ethylene glycol) monomethylether mesylate
PMMA	Poly(methyl methacrylate)
PNIPAM	Poly-N-*iso*-propyl acrylamide
TBHQ	*tert*-Butyl hydroquinone
TEMPO	2,2,6,6-tetramethyl piperidinyl -N-oxide
THF	Tertrahydrofuran
TIPSCl	Tri-*iso*-propylsilylchloride
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TMSCN	Trimethylsilyl cyanide
TS	Transition State
UV	Ultra Violet

CHAPTER 1

PROLOGUE

1.1 Introduction:

The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry, and also by other applications, including agricultural chemicals, flavors, fragrances, and materials. Asymmetric catalysis is one of the most important methods to prepare optically active organic molecules, and one that has seen tremendous research activity over the past two decades.[1,2] in an asymmetric reaction, a chiral catalyst are used to facilitate the selective transfer of chiral information to a substrate to furnish an enantiomerically enriched product. However, a major problem associated with these homogenous catalytic systems is the recovery and recycling of the chiral catalyst, which is often expensive. For example, chiral phosphines range from US$ 5000/kg to US$ 500,000/kg for industrial catalysts.[3] Recycling is also desirable from the downstream processing point of view and the removal of traces of metal from the product. A traditional solution to these problems has been to 'heterogenize' the homogeneous catalysts by anchoring them onto inert, insoluble cross-linked polymers.[3-6] the polymer-supported catalyst can be easily separated by simple filtration. It is also amenable for use in continuous flow reactor. Despite the advantage of facile catalyst separation of polymer-supported catalysts, the catalyst often suffers from lowered catalytic activity and enantioselectivity after it has been anchored onto a polymer.[7-11] this is often attributed to limited accessibility of the catalysts active sites due to the heterogeneous nature of the reaction. Also, the irregular achiral structure of the polymer-support, may create microenvironments at the catalytic sites that are very different from that of the homogeneous catalyst.

A way to circumvent this problem is to use low molecular weight soluble linear polymers as supports.[12-16] this is attractive since the soluble support ensures that the catalyst is in the same phase as the reactants and reagents. Thus, the reactivity and selectivity of the catalyst anchored on the soluble support can equal that of its unsupported homogenous analog. Recovery of the polymer supported catalyst can then be achieved by temperature-[17-21] or solvent-induced precipitation followed by filtration.[13,14] In 1996, Janda and co-workers reported the use of poly(ethylene glycol) monomethyl ether (PEG) bound hydroquinidine *Cinchona* alkaloid ligand, **1**, for the ligand-accelerated Sharpless asymmetric dihydroxylation of aliphatic monosubstituted olefins.[22] This was the first demonstration of the integration of a chiral ligand onto a soluble polymeric species where the selectivity of the supported catalyst was the same as that of its unsupported analog.. In 1997, Bolm and Gerlach also developed soluble pyrimidine and diphenylpyrazinopyridazine ligands, **2** and **3** respectively, using both DHQD and DHQ for the chiral ligand (Figure 1; only the DHQ derivative is shown).[23]

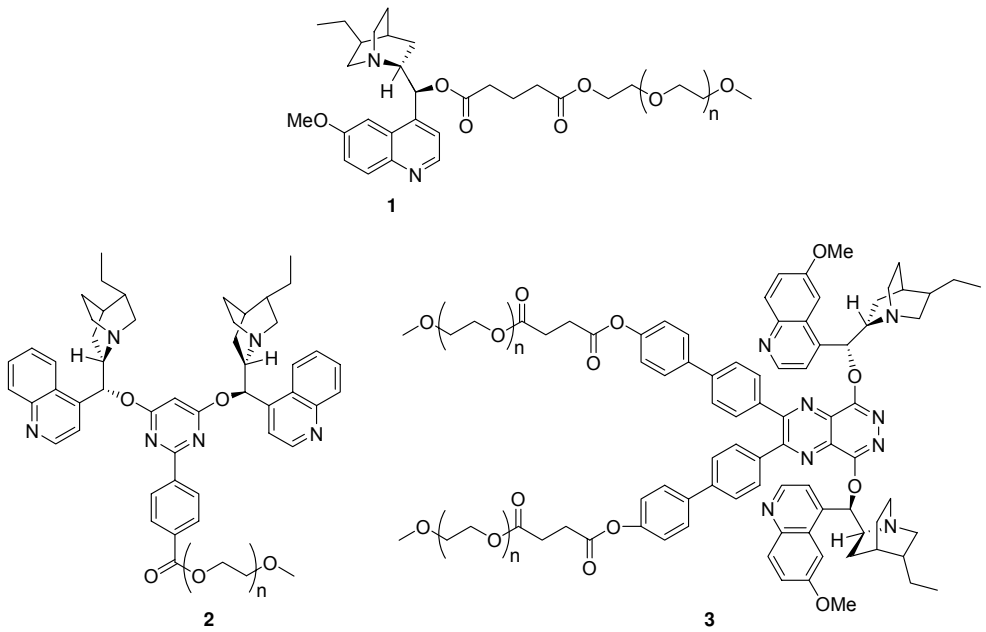


Figure 1.1: PEG-supported *Cinchona* ligands.

In 2000 Bengalia and co-workers reported a PEG-supported quaternary ammonium salt phase transfer catalyst.[24] It was the first example where a complete catalytic system had been supported on a soluble polymer. Its catalytic efficiency in a series of phase transfer reactions was examined and it was shown to be more reactive than the insoluble 2% cross-linked polystyrene supported analog. It was also observed that yields dropped with a shorter linker and that the PEG alone was not responsible for the extent of the phase transfer reaction. Shortly after, in a comparative study between soluble and insoluble matrices as supports for a chiral Mn salen catalyst, Janda reported the use of PEG as a soluble support.[25] The precipitated catalyst, in both cases, showed substantially reduced enantioselectivity and poor recyclability after two runs. This drop in selectivity appears to be the trend for most soluble polymer supported catalysts that have been reported in the literature.[10] There seems to be no general explanation for these observations, and in most cases the origin of the drop in catalyst selectivity is specific to the type of reaction as well as the reaction conditions.[25-28] As such, the challenge is to design a robust polymer supported chiral catalyst that mimics the activity and enantioselectivity of its unsupported analog and can be recovered and reused, over multiple runs.

In chapter 2, the development of soluble polymer supported chiral catalysts, as more effective alternatives to traditional heterogeneous catalysts, is discussed. We synthesized recyclable PEG-supported asymmetric catalysts based on a soluble mono-functional PEG support. A chiral salen ligand, attached at the terminus of the PEG polymer chain, is used to prepare a well-defined Zn-salen catalyst, for the asymmetric addition of Et_2Zn to aldehydes. A spacer is required to position the polymer chain away from the catalyst active site in order to achieve good enantioselectivities. The tethered polymer is inert to the reaction environment and does not influence the selectivity of the

chiral catalyst. While studying different modes of attachment of the polymer onto the catalyst, we observed an unprecedented effect of the spacers on the enantioselectivity of the catalyst. This could not be correlated to the electronic effects that have been reported to effect selectivity of unsupported metal-salen catalyst.

In chapter 3, we probe the effect that modification of the electronic structure of a chiral salen ligand has on the enantioselectivity of the Zn-salen complex catalyzed addition of Et_2Zn to benzaldehyde. This electronic modulation was exploited to achieve enhanced enantioselectivity. Hammett analysis of a series of Zn-salen complexes, with the 5,5' positions substituted with EWG's and ERG's, revealed a linear correlation between the electronic character of the catalyst and its enantioselectivity.

A novel method for recycling soluble polymer-supported catalysts–"Soxhlet-Dialysis"–is discussed in chapter 4. A semi-continuous process which couples dialysis and Soxhlet extraction is developed. Solvent resistant dialysis membranes of appropriate molecular weight cut-off are used in a simple and straightforward technique. Common problems associated with the physical isolation of polymer-supported catalysts from their reaction solutions, during recycling, are avoided. A model system; a PEG supported chiral Ti-salen catalyst for the asymmetric cyanosilylation of benzaldehyde; was used to assess the viability of this technique. The enantioselectivity of the catalyst was maintained, after recycling, over several runs, and essentially no leaching of the catalyst was observed.

We are also interested in the synthesis of soluble polymer supported initiators for the design of well-defined diblock copolymers. Using Living Free Radical Polymerization (LFRP), a PS-*b*-PEG diblock copolymer is synthesized from a PEG-supported initiator. The diblock copolymer, which contains a cleavable linker, can then used to fabricate nanoporous materials. A variety of applications in microelectronics, molecular recognition and catalysis can be envisaged. This is discussed in chapter 5.

1.2 References:

(1) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons Inc.: New York, 1994.

(2) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. 1-3.

(3) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, Germany, 2000.

(4) Leadbeater, N. E.; Marco, M. "Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis" *Chem. Rev.* **2002**, *102*, 3217-3274.

(5) Cole-Hamilton, D. J. "Homogeneous Catalysis - New Approaches to Catalyst Separation, Recovery, and Recycling" *Science* **2003**, *299*, 1702-1706.

(6) Fan, Q.-H.; Deng, G.-J.; Lin, C.-C.; Chan, A. S. C. "Preparation and Use of MeO-PEG-supported Chiral Diphosphine Ligands: Soluble Polymer-Supported Catalysts for Asymmetric Hydrogenation" *Tetrahedron: Asymmetry* **2001**, *12*, 1241-1247.

(7) Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217.

(8) Soai, K.; Wantanabe, M.; Yamamoto, A. "Enantioselective Addition of Dialkylzincs to Aldehydes Using Heterogeneous Chiral Catalysts Immobilized on Alumina and Silica Gel" *J. Org. Chem.* **1990**, *55*, 4832.

(9) Lasperas, M.; Bellocq, N.; Brunel, D.; Moreau, P. "Chiral Mesoporous Templated Silicas as Heterogeneous Inorganic Catalysts in the Enantioselective Alkylation of Benzaldehyde" *Tetrahedron: Asymmetry* **1998**, *9*, 3053.

(10) Kragl, U.; Dwars, T. "The Development of New Methods for Recycling Catalysts" Trends Biotechnol. **2001**, *19*, 442-449.

(11) Angelino, M. D.; Laibinis, P. E. "Synthesis and Characterization of a Polymer-Supported Salen Ligands for Enantioselective Epoxidation" *Macromolecules* **1998**, *31*, 7581.

(12) Zhao, X.; Janda, K. D. "Syntheses of alkylated malonates on a traceless linker derived soluble polymer support" *Tetrahedron Lett.* **1997**, *38*, 5437.

(13) Gravert, D. J.; Janda, K. D. "Organic Synthesis on Soluble Polymer Supports: Liquid-Phase Methodologies" *Chem. Rev.* **1997**, *97*, 489-509.

(14) Wentworth Jr., P.; Janda, K. D. "Liquid-Phase Chemisry: Recent Advances in Soluble Polymer-Supported Catalysts, Reagents and Synthesis" *Chem. Commun.* **1999**, 1917-1924.

(15) Dickerson, T. J.; Reed, N. N.; Janda, K. D. "Soluble Polymers as Scaffolds for Recoverable Catalysts and Reagents" *Chem. Rev.* **2002**, *102*, 3325-3344.

(16) Bergbreiter, D. E. "Using Soluble Polymers to Recover Catalysts and Ligands" *Chem. Rev.* **2002**, *102*, 3345-3384.

(17) Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C. M.; Osburn, P. L. "Phase-Selective Solubility of Poly(N-alkylacrylamide)s" *J. Am. Chem. Soc.* **2003**, *125*, 8244-8249.

(18) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. "Nonpolar Polymers for Metal Sequestration and Ligand and Catalyst Recovery in Thermomorphic Systems" *J. Am. Chem. Soc.* **2001**, *123*, 11105-11106.

(19) Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C. M.; Frels, J. D. "Using Soluble Polymers in Latent Biphasic Systems" *J. Am. Chem. Soc.* **2003**, *125*, 6254-6260.

(20) Bergbreiter, D. E.; Sung, S. D.; Li, J.; Oritz, D.; Hamilton, P. N. "Designing Polymers for Biphasic Liquid/Liquid Separations after Homogeneous Reactions" Org. Process Res. Dev. **2004**, *8*, 461-468.

(21) Mariagnanam, V. M.; Zhang, L.; Bergbreiter, D. E. "Polymer Ligands That Can Regulate Reaction Temperature in Smart Catalysts" *Adv. Mater.* **1995**, *7*, 69-71.

(22) Han, H.; Janda, K. D. "Soluble Polymer-Bound Ligand-Accelerated Catalysis: Asymmetric Dihydroxylation" *J. Am. Chem. Soc.* **1996**, *118*, 7632-7633.

(23) Bolm, C.; Gerlach, A. "Asymmetric dihydroxylation with MeO-polyethyleneglycol-bound ligands" *Angew. Chem., Int. Ed. Engl.* **1997**, *39*, 741.

(24) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. "A PEG-Supported Quartenary Ammonium Salt: An Efficient, Recoverable, and Recyclable Phase-Transfer Catalyst" *Org. Lett.* **2000**, *2*, 1737-1739.

(25) Reger, T. S.; Janda, K. D. "Polymer-Supported (Salen)Mn Catalyst for Asymmetric Epoxidation: A Comparison between Soluble and Insoluble Matrices" *J. Am. Chem. Soc.* **2000**, *122*, 6929-6934.

(26) Sasai, H.; Jayaprakash, D. "Synthesis and Catalytic Applications of a Soluble Polymer-Supported BINOL" *Tetrahedron: Asymmetry* **2001**, *12*, 2589-2595.

(27) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. "PEG-Supported Bisoxazolines as Ligands for Catalytic Enantioselective Synthesis" *J. Org. Chem* **2001**, *66*, 3160-3166.

(28) Cornejo, A.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martinez-Merino, V.; Mayoral, J. A. "The First Immobilization of Pyridine-Bis(oxazoline) Chiral Ligands" *Org. Lett.* **2002**, *4*, 3927-3930.

CHAPTER 2

DESIGN AND SYNTHESIS OF A PEG SUPPORTED CHIRAL SALEN CATALYST

2.1 Introduction:

The use of soluble polymers to recover catalysts and ligands has its origin in the synthetic approaches to peptide and oligonucleotide synthesis that were developed by Merrifield and Letsinger in the 1960s.[1,2] These discoveries revolutionalized the synthesis of biomolecules.[3] They provided impetus for research in industrial and academic laboratories that was directed toward developing immobilized or heterogenized homogeneous catalysts. In most cases, these studies focused on the same insoluble polymers Merrifield used–divinylbenzene (DVB)-cross-linked polystyrene.[4-7] The first example where a soluble polymer was used as an alternative to a cross-linked insoluble polymeric resin to support a chiral ligand, was reported in 1976 by Bayer and Schurig.[8] A DIOP (4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane) ligand was attached to a linear polystyrene. The resulting polystyrene-bound version of DIOP was allowed to react with $HRh(CO)\text{-}(PPh_3)_3$, and the resulting polymer-bound Rh complex was used to hydroformylate styrene. Hydroformylation products were obtained, but the *ee* was only 2%. The catalyst was isolated from the reaction products by membrane filtration. Over two decades later, the development of recyclable soluble polymer supported chiral catalysts for asymmetric transformations has now become the subject of extensive research.[9-20]

Soluble polymer-bound catalysts can be designed to have activity equivalent to that of their low molecular weight analogues. There are essentially three main modes of attachment of a ligand or catalysts onto a linear soluble polymer support; (a) a pendant-chain-bound motif, where the catalyst/ligand is attached along the polymer chain as side groups[21-24], (b) a main-chain bound motif, where the catalyst/ligand constitutes the polymer backbone[25,26], and (c) a terminus-bound motif, where the catalyst/ligand is

tethered at one chain end of the polymer[9,20,27]. The later motif, (c), has been established as the preferred mode of attachment of a chiral catalyst onto a linear soluble polymer.[12]

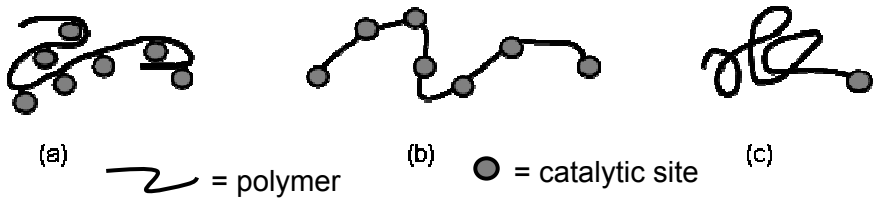


Figure 2.1: Modes of attachment for linear soluble polymer supported catalysts.

For main-chain and pendant-chain-bound polymer supported chiral catalysts, whereby, chiral ligands attached along the polymer chain are loaded with a metal catalyst, unequivocal determination of the loading of all ligand binging sites is an issue. As such, the possibility of vacant metal-free ligand binding sites exists. There is also an increased likelihood of local site-site interactions and microenvironmental effects which could be detrimental to the catalysts selectivity, especially when the sites are distributed unevenly along the polymer backbone.[28,29] Attaching a chiral catalyst to the terminus of a linear soluble polymer isolates the catalyst's active site, relative to the main chain.[27,30,31]

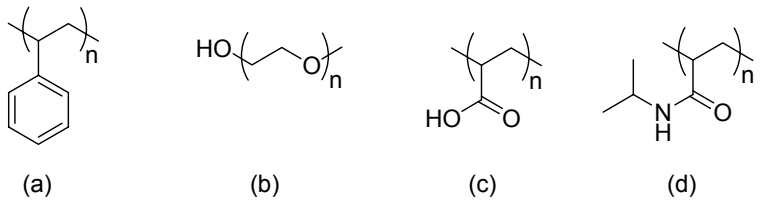


Figure 2.2: Soluble linear polymers that have been used as supports for catalysts: (a) LPS (b) PEG (c) PAA (d) PNIPAM

Various soluble polymers have been used in catalysis as well as other liquid phase methodologies. PEG and LPS are two of the most frequently used soluble

polymers for supporting homogenous catalysts.[12,32-34] PEG, poly(ethylene oxide) (PEO), poly(oxyethylene) (POE), and polyoxirane all refer to the linear polymer formed from the polymerization of ethylene oxide. By convention, PEG usually indicates the polyether of molecular weights less than 20,000; PEO signifies polymers of higher molecular weights, and POE and polyoxirane have been applied to polymers of a wide range of molecular weights.[35] PEGs of molecular weights ranging from 2000 to 20,000 are utilized as supports in organic synthesis and 5000 molecular weight PEG is typically used as supports for catalyst. These limits have been set by the physical properties of the polymer. Within this molecular weight range, PEG is both crystalline and has an acceptable loading capacity (1 − 0.1 mmol/g); lower molecular weight PEG exists as a liquid or wax at room temperature, and higher molecular weight PEG has a considerably lower loading capacity. Commercially available PEG does not exist as a singular molecular weight species, but as a distribution of molecular weights, although the polydispersity of commercial PEG is reasonably narrow.[35] Depending on polymerization conditions, PEG termini may consist of hydroxyl groups or may be selectively functionalized. Commercially available PEG is produced through anionic polymerization of ethylene oxide to yield a polyether structure possessing either hydroxyl groups at both ends or a methoxy group at one end and a hydroxyl group at the other (MeO-PEG). The polymer MeO-PEG is considered monofunctional because the methoxy group of MeO-PEG typically remains unchanged throughout chemical manipulations. PEG exhibits solubility in a wide range of solvents including DMF, DMSO, benzene, dichloromethane, toluene, acetonitrile, warm THF and water. PEG is insoluble in hexane, diethyl ether, *tert*-butyl ether, isopropyl alcohol,[36] and cold ethanol. These solvents have been used to induce PEG precipitation for isolation and purification of PEG supported molecules. Careful precipitation conditions or cooling of polymer solutions in alcoholic solvents

yields crystalline PEG due to the helical structure of the polymer that produces a strong propensity to crystallize.[35]

We chose to use PEG for several reasons: (1) it is available commercially and is relatively inexpensive; (2) it is available in a wide range of molecular weights as the monomethyl ether, MeO-PEG, and the diol form; (3) Characterization of PEG bound moieties is often straightforward as the polymer does not interfere with spectroscopic or chemical methods of analysis. The singlet signal (δ = 3.30 ppm) of the terminal monomethoxy group of MeO-PEG provides an internal standard for easy monitoring of reactions by ^{1}H NMR spectroscopy (Figure 2.3). A change in the chemical shift of the multiplet signal for the α-methylene protons (δ = 3.80 ppm) when MeO-PEG is functionalized at the free hydroxyl terminus is a convenient means of monitoring functionalization (Figure 2.4) and; (4) its solubility in a wide range of organic solvents, including water, gives it inherent phase-transfer catalytic properties. Although the characterization of soluble polymer supported catalysts is amenable to standard solution phase spectroscopic techniques, there can be some issues. Polymers that require elevated temperatures to achieve solubility in some solvents tend to pose a problem for bound catalysts that display dynamic behavior. For example, ligand exchange in a polyethylene oligomer bound Wilkinson's catalyst whose solubility in toluene-d^{8} was limited at 100 °C, resulted in an averaged solution-state ^{31}P NMR spectrum.[24]

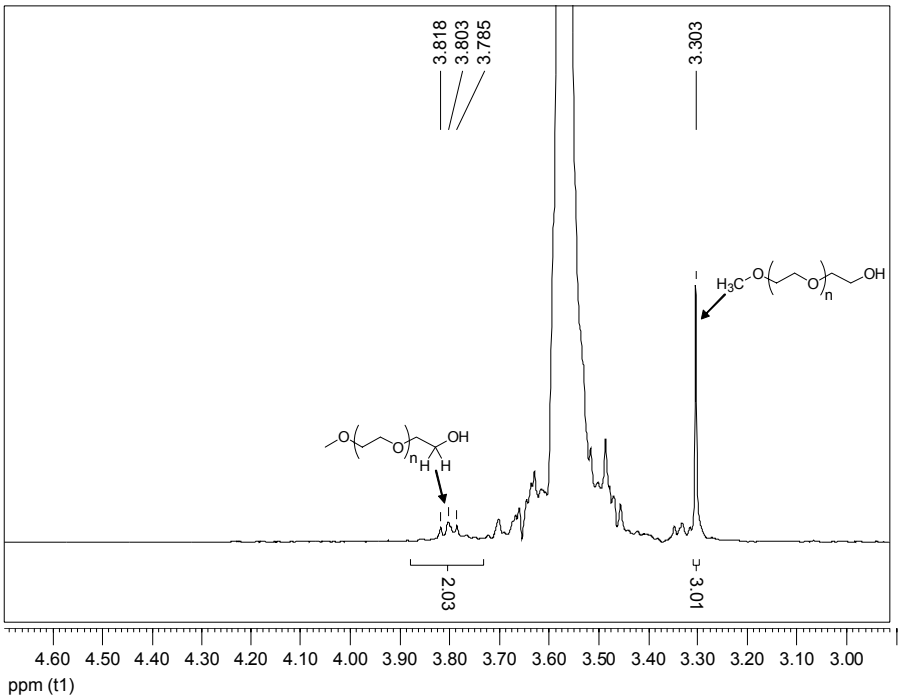


Figure 2.3: ^{1}H NMR spectra of MeO-PEG (MW = 2000)

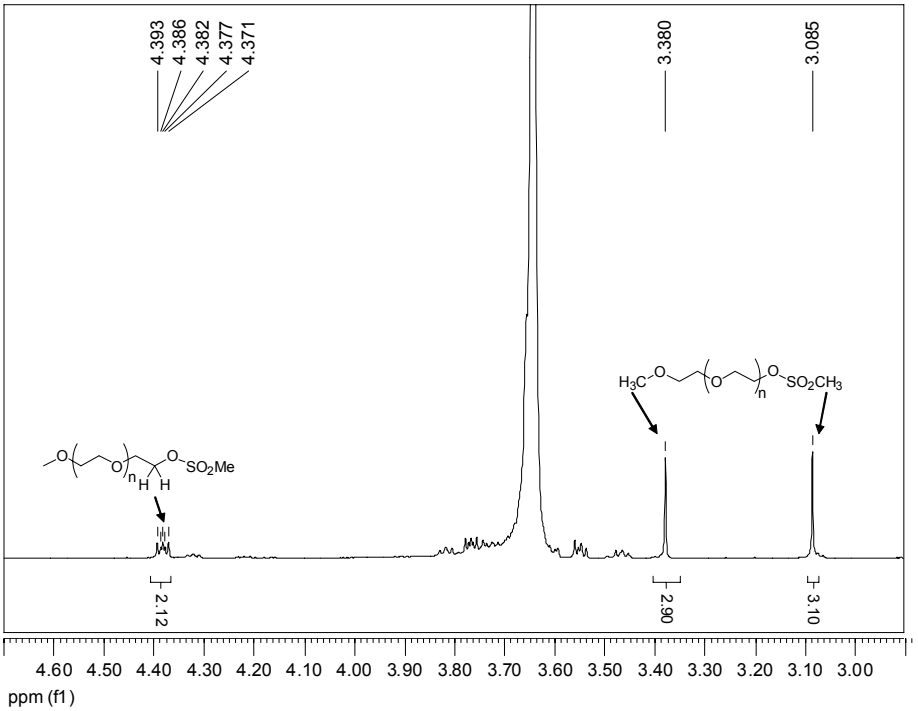


Figure 2.4: ^{1}H NMR of MeO-PEG-OMs; showing a change in chemical shift of the α-methylene protons after functionalization.

2.2 Chiral Metal Salen Complexes: Privileged Chiral Catalysts:

In 1864, Hugo Schiff described the condensation between an aldehyde and an amine leading to a Schiff base.[37] These Schiff bases are able to coordinate metals through imine nitrogen and another atom or group, usually linked to the aldehyde. When two equivalents of salicylaldehyde are condensed with a diamine, the so-called “Salen” chelating ligand is produced. Salen ligands form stable complexes with metal ions in various oxidation states via four coordinating sites, while leaving two axial sites open to auxiliary ligands and this makes them markedly attractive for catalytic applications.[37] This tetradentate binding motif is reminiscent of the porphyrin framework in heme-based oxidative enzymes, which inspired the original design of chiral metal salen complexes.

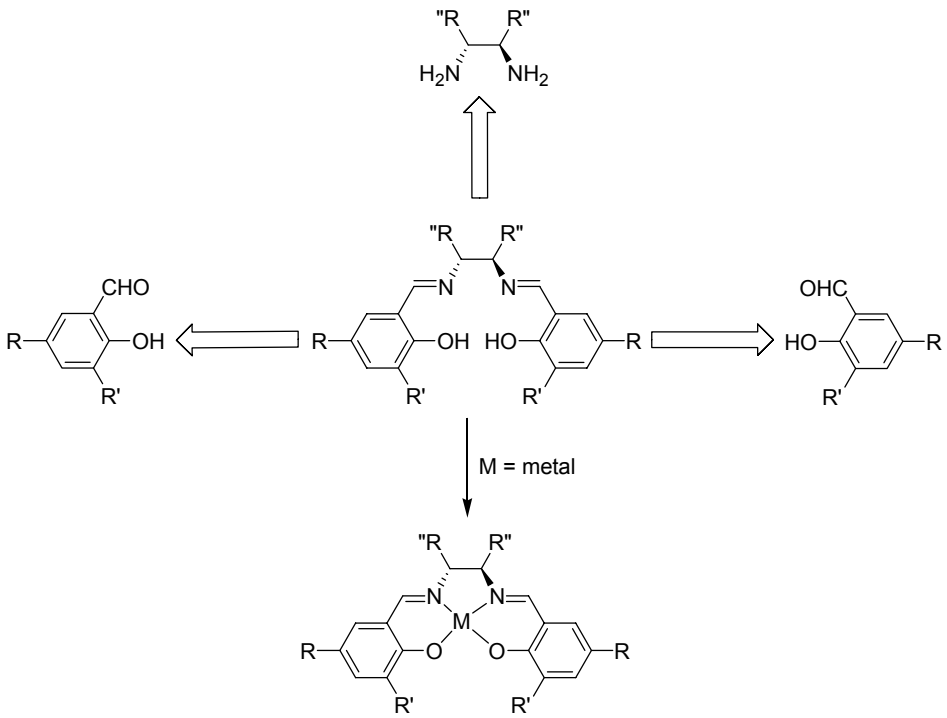
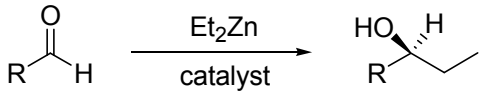


Figure 2.5: Typical salen ligand composed of two salicylaldehyde moieties and a chiral diamine; and a metal salen complex.

Following the success, in the early 1990's, of the Jacobsen-Katsuki asymmetric epoxidation of unfunctionalized olefins using chiral salen-type manganese (III) catalysts[38-40]; there has been a growing interest in the application of these ligands as scaffolds for asymmetric catalysts. Although stereogenic centers, typically located on the diamine moiety, are believed to be primarily responsible for asymmetric induction, subtle conformational changes in the ligand structure can affect the transfer of chiral information.[41] Bulky substituents on the aromatic aldehyde restrict prochiral substrates to preferential approach to the metal center, over the chiral diamine portion of the catalyst. This tends to maximize stereochemical communication in the transition state of the reaction. Typically best selectivities are obtained with ligands with *tert*-butyl groups at the 3,3' positions on the aromatic aldehydes. Metal complexes of chiral salen ligands are known to catalyze a broad range of asymmetric transformations of major synthetic importance to give reaction products with high enantiomeric excesses.[42] Coupled with the ability to systematically tune the steric environment and electronic structure (see Chapter 3) of the salen ligand in a synthetically straightforward manner;[43,44] they find themselves in a distinguished class of "privileged" chiral ligand structures.[42]

2.3 Asymmetric Addition of Et_2Zn to Aldehydes by a Chiral Zn-Salen Catalyst:



Scheme 2.1: The asymmetric addition of Et_2Zn to a prochiral aldehyde.

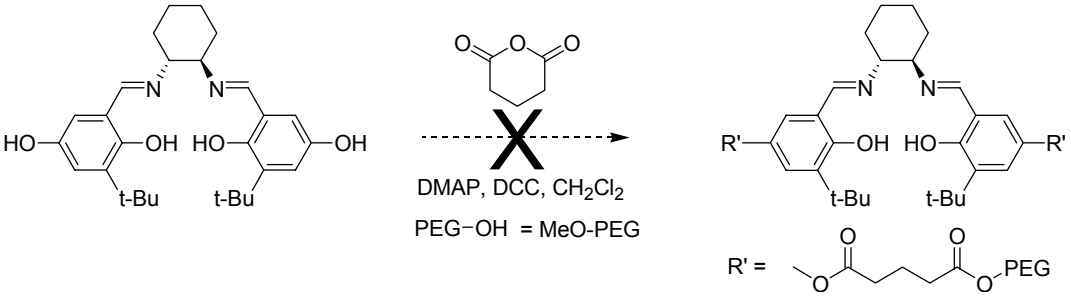
Nucleophilic addition of organometallic reagents to carbonyl substrates constitutes one of the most fundamental operations in organic synthesis.[45] The use of organozinc chemistry, in place of conventional organolithium or -magnesium chemistry,

has been developed into an ideal protocol for the catalytic enantioselective alkylation of aldehydes, leading to a diverse array of optically pure secondary alcohols.[46,47] The asymmetric addition of dialkyl zinc reagents to benzaldehyde has become an archetypical reaction for evaluating the activity of newly developed chiral catalysts. A plethora of chiral ligands (mainly β-amino alcohols and similar ligands) have been reported to be catalytically active towards this reaction, with selectivities ranging from mediocre to excellent.[48] In the absence of a catalyst or promoter, the reaction proceeds sluggishly with pure dialkyl zincs and often reduction of the aldehyde to the alcohol is observed. Cozzi and co-workers first reported the use of the Zn-salen complex for the asymmetric addition of Et_2Zn to benzaldehyde.[49] In 2001, Kozlowski reported a more reactive bifunctional salen catalyst analog with a 3,3' tethered tertiary amine Lewis base.[50] The amine was believed to activate the Et_2Zn nucleophile, thus increasing the reactivity of the catalyst.

2.4 A PEG Supported Chiral Zn-Salen Catalyst:

The only reported example of a PEG supported chiral salen complex was in a comparative study between soluble and insoluble matrices for the Mn(III)-salen catalyzed epoxidation of olefins by Janda and coworkers in 2000.[27] They reported the PEG bound Mn(III) salen catalyst to be inferior to the insoluble *JandaJel*™ bound analogue on the basis of poor recyclability due to depreciation in enantioselectivity upon reuse. The drop in selectivity was attributed to leaching of the Mn due to oxidative degradation of the salen ligand.[27] Our interests in the design and synthesis of PEG supported salen ligands began in 1999. Our initial attempt to synthesize the 5,5'- PEG bound salen ligand was unsuccessful due to synthetic issues associated with the characterization of the PEG salen dimer. We then turned to the synthesis of the

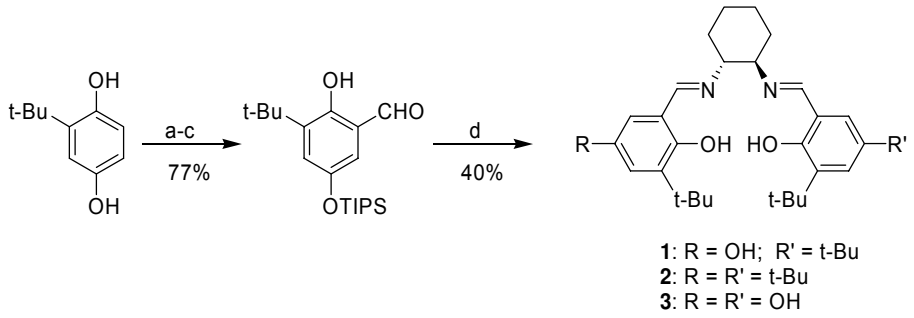
unsymmetrical C-5 PEG bound salen ligand; the catalyst thus being attached to the terminus of the PEG chain.



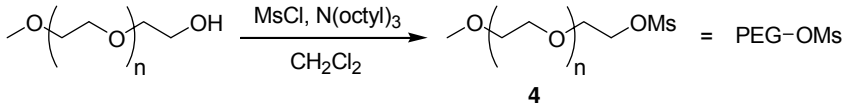
Scheme 2.2: Unsuccessful synthesis of 5,5'-supported PEG salen ligand.

2.5 Synthesis:

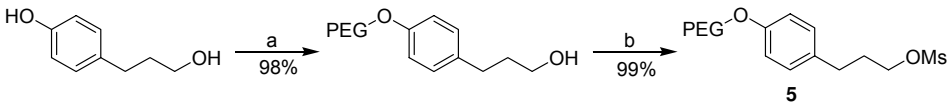
We synthesized the unsymmetrical salen ligand **1** starting from commercially available TBHQ, following a previously reported procedure.[51] This was isolated in 40% yield by column chromatography (gradient elution; ether/hexanes, 1:20 to 1:1) from side products, **2** (9 eq) and **3** (1 eq) (scheme 2.1). PEG-OMs was prepared quantitatively by treating PEG (MW = 5000) with and excess of MsCl in the presence of trioctylamine (scheme 2.2). Reacting **1** with PEG-OMs, **4**, in the presence of Cs_2CO_3 gave the PEG supported chiral salen ligand, **6**, in 96% yield (scheme 2.4). In order to explore the efficacy of the polymer-supported catalyst, 10 mol% of **6** (with respect to benzaldehyde) was treated with an equivalent amount of Et_2Zn in toluene to generate the Zn salen complex (Zn-**6**) *in situ*. Additional Et_2Zn (2.3 mol equivalents) was then added, followed by an equivalent of benzaldehyde (1 mol equivalent). After 18 h the product, 1-phenyl-1-propanol, was obtained in 90% yield and in 66:34 *er*. Under similar reaction conditions, when we used the catalyst derived from the unsupported chiral salen ligand, **2** (Zn-**2**), we obtained the product in 93% yield and in 91:9 *er*, after 18 h.



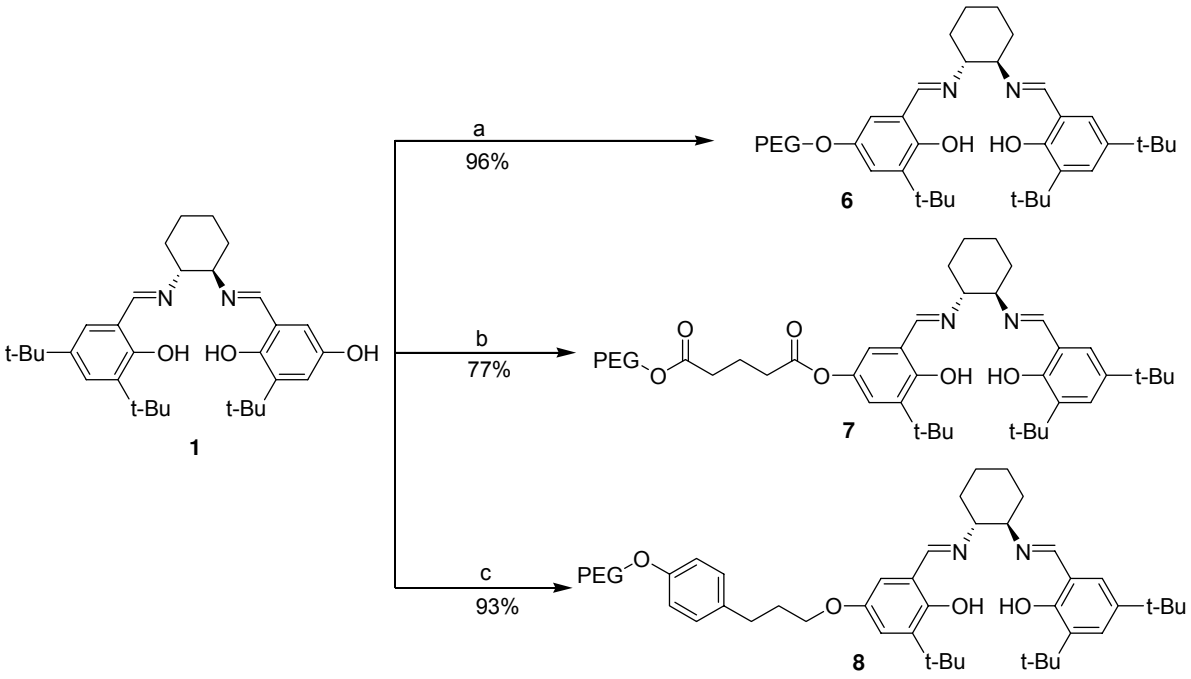
Scheme 2.3: Synthesis of unsymmetrical salen ligand **1**. Reaction conditions: (a) imidazole, DMAP, TIPSCl, CH_2Cl_2, 15 h. (b) (i) $SnCl_4$, 2,6-lutidine. (ii) $(CH_2O)_n$, toluene, reflux, 90 °C, 6 h.(c) TBAF, THF, 1 h. (d) 3,5-di-tert-butyl-salicylaldehyde (3 eq), (R,R)-1,2-diaminocyclohexane (2 eq), CH_2Cl_2, 12 h.



Scheme 2.4: Synthesis of PEG-OMs, **4**.



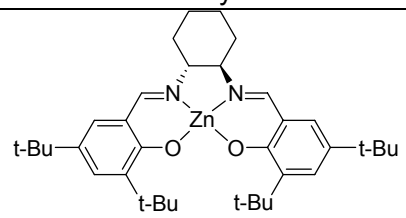
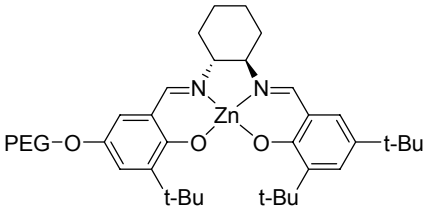
Scheme 2.5: Synthesis of PEG supported spacer, **5**. Reaction conditions: (a) Cs_2CO_3, **4**, DMF, 24 h. (b) MsCl, Et_3N, CH_2Cl_2, 24 h.



Scheme 2.6: Synthesis of monomethoxy PEG supported salen ligands, **6, 7** and **8.** Reaction conditions: (a) PEG-OMs, Cs_2CO_3, DMF, 24 h. (b) (i) glutaric anhydride, DMAP, CH_2Cl_2, 12 h. (ii) PEG, DCC, DMAP, CH_2Cl_2, 24 h. (c) Cs_2CO_3, **5**, DMF, 24 h.

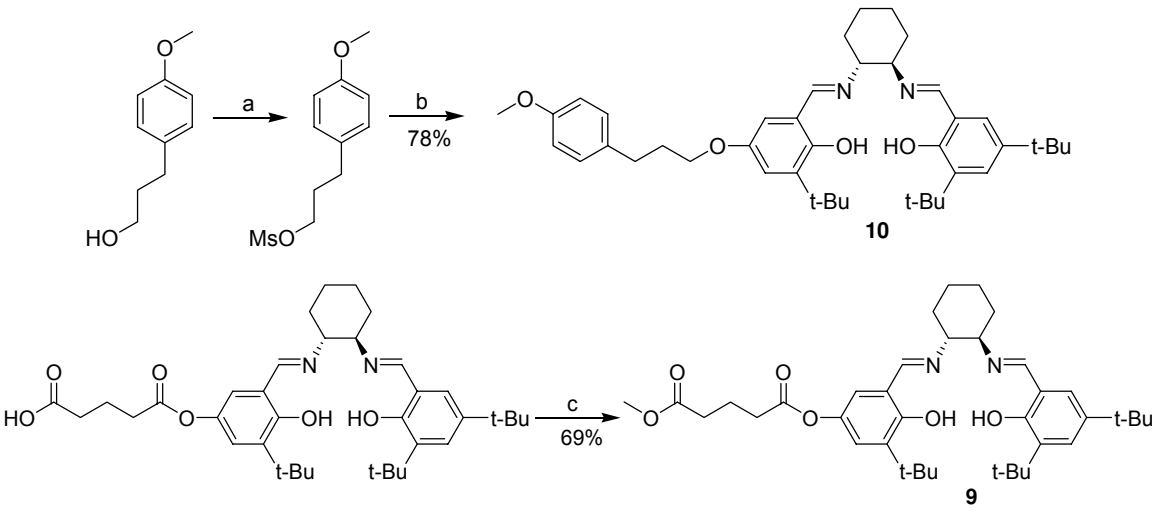
In order to explain the productivity and selectivity differences between Zn-**6** and Zn-**2**, we surmised that the PEG support might be sterically interfering with the active site of the catalyst. Hence, as a control experiment, we carried out the reaction of Et_2Zn with benzaldehyde under the same conditions and with Zn-**2**, in the presence of a catalytic amount (10 mol%) of PEG. The desired product was obtained in 88% yield and 91:9 *er*, after 18 h. This ruled out the initial suggestion that the PEG was responsible for the lowered enantioselectivity of Zn-**6** due to unfavorable steric interactions or interaction of Et_2Zn with the PEG ether backbone. Detrimental side reactions associated with the polymer main-chain, such as metal coordination and solvation, have been reported to reduce the activity of soluble polymer supported complexes relative to their unsupported analogs.[12,52]

Table 2.1: Comparison of the selectivity and productivity of Zn-**1** and Zn-**2**.

catalyst	time (h)	yield (%)	*er*
 **2**	18	93	91:9
 **1**	18	90	66:34

2.6 Effect of Spacers on the Enantioselectivity and Productivity of the Catalyst:

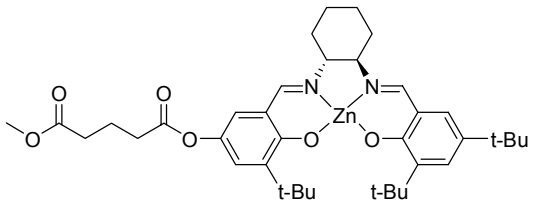
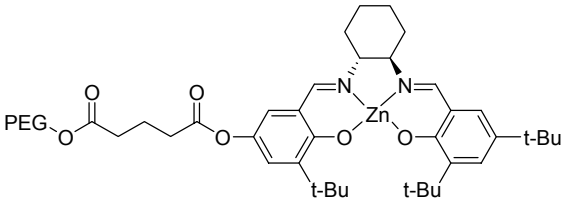
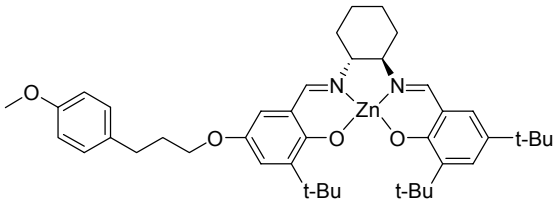
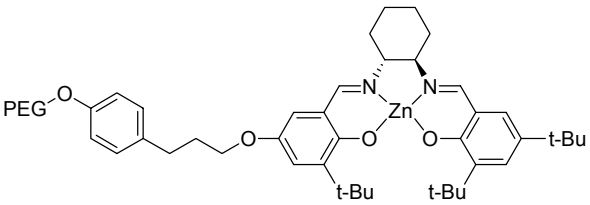
We then hypothesized that the PEG support might be affecting the microenvironment of the catalyst as a result of the covalent attachment of the polymer directly onto the salen ligand to test our hypothesis. We then synthesized the PEG supported ligand, **7**, with a glutarate spacer between the ligand and the polymer. This catalyst under the aforementioned reaction conditions, furnished the product, 1-phenyl-1-propanol, in 91:9 *er*, but required 32 h for a 90% yield. This result showed that while the spacer was effective in isolating the catalyst active site from the PEG, thus, improving the enantioselectivity of Zn-**7** over that of Zn-**6**, there was a decrease in its productivity. In catalyst Zn-**7**, the salen ligand was tethered on the PEG through a glutarate spacer with an electron-withdrawing ester functionality at the point of attachment on the salen ligand. We then sought to explore the effect of introducing a spacer with an electron donating ether bond at the point of attachment to the salen ligand.



Scheme 2.7: Synthesis of **9** and **10**. Reaction conditions: (a) MsCl, Et_3N, CH_2Cl_2, 24 h. (b) Cs_2CO_3, **1**, DMF, 24 h. (c) MeOH, EDCI, DMAP, CH_2Cl_2, 24 h.

We synthesized the PEG supported spacer, **5**, in near quantitative yield, from commercially available 4-hydroxybenzyl alcohol and mesylate, **4** (scheme 2.2). The salen ligand, **8**, was then synthesized in 93% yield, by treating **5** with **1** in the presence of Cs_2CO_3. The reaction of Et_2Zn and benzaldehyde, in the presence of Zn-**8**, gave the product in 91% yield in 18 h but the enantioselectivity dropped to 84:16 *er*. The results indicated that Zn-**8** was more productive than Zn-**7** but not as selective. In order to understand the role that the PEG may play in these observed changes in selectivity; we synthesized unsupported analogs of **7** and **8**–ligands **9** and **10** respectively. Zn-**9** gave the product in 91% yield and in 91:9 *er* after 18 h, whereas, Zn-**10** required 32 h to achieve a 94% yield and 81:19 *er*. Based on these results, we concluded that the productivities and selectivities of Zn-**7** and Zn-**8** were similar to those of Zn-**9** and Zn-**10** respectively. *Hence, these differences are clearly due to the presence of the spacer, and not as a result of the PEG support*.

Table 2.2: Comparison of the selectivities and productivities of PEG supported catalysts, Zn-**7** and Zn-**8** and their unsupported analogs, Zn-**9** and Zn-**10**

catalyst	time (h)	yield (%)	*er*
	32	91	91:9
	32	90	91:9
	18	94	81:19
	18	91	84:16

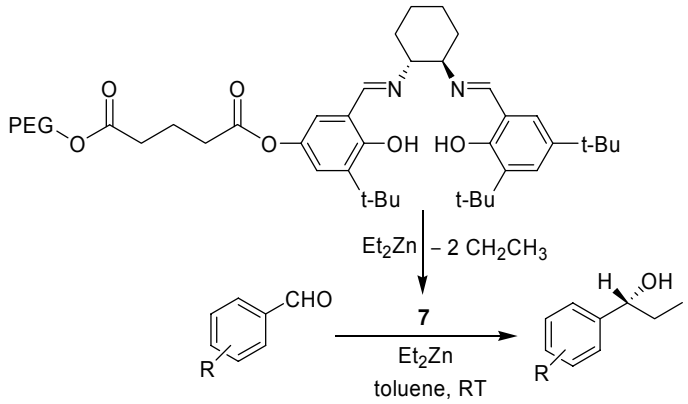
This raises the question; are the enantioselectivity changes due to the presence of the spacer moieties or, are they due to perturbations in the electronic structure of the catalyst as a result of the functionality of the linker at the 5,5' position on the salen ligand. Jacobsen had established that substitution at the 5,5' positions on the aromatic ring of the salen ligand affected the selectivity of the Mn(III) salen catalyzed epoxidation of olefins.[39] Catalysts with EWG's at the 5,5′ gave lower selectivities than those bearing ERG's at the same position. A Linear correlation was observed between the logarithms

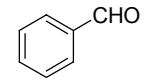
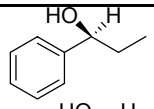
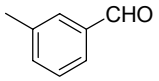
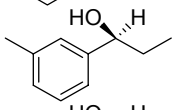
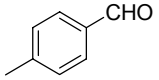
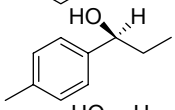
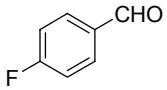
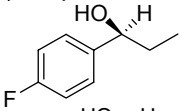
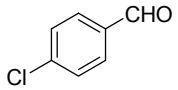
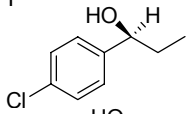
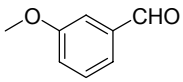
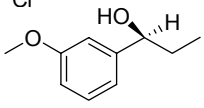
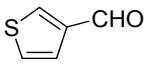
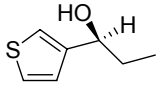
of the enantiomeric ratios and the Hammett substituent parameters,[53] σ_p, of a series of 5,5′-substituted catalysts suggested electronic control of stereoselectivity. However, Janda reported that a chiral PEG supported Mn(III) complex, of similar ligand structure to **7**, with an EWG glutarate spacer (σ_p = 0.3) was *as selective* as the unsupported salen complex with *tert*-butyl ERG's at the 5,5′ positions (σ_p = -0.20).[27] If the effect of the glutarate spacer was purely electronic, then based on Jacobsen's correlation, the enantioselectivity of the epoxidation should have been considerably lower. Therefore, we concluded the effect of the spacer on the selectivity of the catalyst could not be correlated to the electronic effects in the unsupported catalyst.

2.7 Conclusion:

Since **7** provided the highest selectivity, it was used in the addition of Et_2Zn to a series of aromatic aldehydes.[9] The respective chiral secondary alcohols were obtained in good isolated yields (75–90%) and enantiomeric ratios (76:24–91:9). In the absence of the catalyst, the addition of Et_2Zn to benzaldehyde gave marginal conversion to the product, 5%, even after 48 h. Quantitative recovery of the catalyst, at the end of the reaction, was facilitated by precipitation from diethyl ether. The catalyst was used in a second run to achieve a 91% yield and 91:9 *er*. The catalyst was recycled up to three times without any significant loss in selectivity.

Table 2.3: Synthesis of various aromatic aldehydes using PEG supported catalyst, Zn-**7**



aldehyde	product	yield (%)	*er*
		90	91:9
		82	84:16
		87	76:24
		88	87:13
		75	88:12
		90	94:6
		92	91:9

2.8 References:

(1) Merrifield, R. B. "Solid-Phase Synthesis (Nobel Lecture)" *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 799-810.

(2) Letsinger, I.; Wagner, T. E. "Regulation of Rate of Reaction of a Polyuridylic Acid Derivative by Use of Suppressor and Anti-Suppressor Molecules" *J. Am. Chem. Soc.* **1966**, *88*, 2062-&.

(3) Angeletti, R. H.; Bonewald, L. F.; Fields, G. B. *Six-Year Study of Peptide Synthesis*, 1997; Vol. 289, pp 780.

(4) Holy, N. L. "Versatile Polymer-Bound Hydrogenation Catalysts–Rhodium(I)-Catalyzed Hydrogenation," *J. Org. Chem.* **1979**, *44*, 239-243.

(5) Manecke, G.; Storck, W. "Polymeric Catalysts" *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 657-670.

(6) Holy, N. L.; Shalvoy, R. "Hydrogenation with Anthranilic Acid Anchored, Polymer-Bound Nickel-Catalysts" *J. Org. Chem.* **1980**, *45*, 1418-1420.

(7) Whitehurst, D. D. "Catalysis by Heterogenized Transition-Metal Complexes" *CHEMTECH* **1980**, *10*, 44-49.

(8) Bayer, E.; Schurig, V. "New Class of Catalysts" *CHEMTECH* **1976**, *6*, 212-214.

(9) Anyanwu, U. K.; Venkataraman, D. "Effect of Spacers on the Activity of Soluble Polymer Supported Catalysts for the Asymmetric Addition of Diethylzinc to Aldehydes" *Tetrahedron Lett.* **2003**, *44*, 6445-6448.

(10) Zhang, J.-L.; Che, C.-M. "Soluble Polymer-Supported Ruthenium Porphyrin Catalyst for Epoxidation, Cyclopropanation, and Aziridination of Alkenes" *Org. Lett.* **2002**, *4*, 1911-1914.

(11) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. "Recoverable Catalysts for Asymmetric Organic Synthesis" *Chem. Rev.* **2002**, *102*, 3385-3466.

(12) Dickerson, T. J.; Reed, N. N.; Janda, K. D. "Soluble Polymers as Scaffolds for Recoverable Catalysts and Reagents" *Chem. Rev.* **2002**, *102*, 3325-3344.

(13) Bolm, C.; Tanyeli, C.; Grenz, A.; Dinter, C. L. "ROMP-Polymers in Asymmetric Catalyst: The role of the Polymer Backbone" *Adv. Synth. Catal.* **2002**, *344*, 649-656.

(14) Bergbreiter, D. E. "Using Soluble Polymers to Recover Catalysts and Ligands" *Chem. Rev.* **2002**, *102*, 3345-3384.

(15) Guerreiro, P.; Ratovelomanana-vidal, V.; Genet, J.-P.; Dellis, P. "Recyclable Diguanidinium-BINAP and PEG-BINAP Supported Catalyst: Synthesis and Use in Rh(I) and Ru(II) Asymmetric Hydrogenation Reactions" *Tetrahedron Lett.* **2001**, *42*, 3423-3426.

(16) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. "PEG-Supported Bisoxazolines as Ligands for Catalytic Enantioselective Synthesis" *J. Org. Chem* **2001**, *66*, 3160-3166.

(17) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, Germany, 2000.

(18) Kobayashi, S.; Endo, M.; Nagayama, S. "Catalytic Asymmetric Dihydroxylation of Olefins Using a Recoverable and Reusable Polymer-Supported Osmium Catalyst" *J. Am. Chem. Soc.* **1999**, *121*, 11229-11230.

(19) Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. "Soluble Polymer Supported Catalyst for Asymmetric Ketone Reduction" *Tetrahedron: Asymmetry* **1998**, *9*, 1975.

(20) Han, H.; Janda, K. D. "Soluble Polymer-Bound Ligand-Accelerated Catalysis: Asymmetric Dihydroxylation" *J. Am. Chem. Soc.* **1996**, *118*, 7632-7633.

(21) Ohkubo, K.; Fujimori, K.; Yoshinaga, K. "Asymmetric Hydrogenation of Prochiral Unsaturated-Acids by Soluble and Insoluble Polymer-Supported Rhodium(I) Chiral Diphosphine Complexes" *Inorg. Nucl. Chem. Lett.* **1979**, *15*, 231-234.

(22) Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C. M.; Osburn, P. L. "Phase-Selective Solubility of Poly(N-alkylacrylamide)s" *J. Am. Chem. Soc.* **2003**, *125*, 8244-8249.

(23) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. "Nonpolar Polymers for Metal Sequestration and Ligand and Catalyst Recovery in Thermomorphic Systems" *J. Am. Chem. Soc.* **2001**, *123*, 11105-11106.

(24) Bergbreiter, D. E.; Chandran, R. "Polyethylene-Bound Rhodium(I) Hydrogenation Catalysts" *J. Am. Chem. Soc.* **1987**, *109*, 174-179.

(25) Fan, Q. H.; Ren, C. Y.; Yeung, C. H.; Hu, W. H.; Chan, A. S. C. "Highly Effective Soluble Polymer-Supported Catalysts for Asymmetric Hydrogenation" *J. Am. Chem. Soc.* **1999**, *121*, 7407-7408.

(26) Hu, Q.-S.; Huang, W.-S.; Pu, L. "A New Approach to Highly Enantioselective Polymeric Chiral Catalysts" *J. Org. Chem.* **1998**, *63*, 2798-2799.

(27) Reger, T. S.; Janda, K. D. "Polymer-Supported (salen)Mn Catalyst for Asymmetric Epoxidation: A Comparison between Soluble and Insoluble Matrices" *J. Am. Chem. Soc.* **2000**, *122*, 6929-6934.

(28) Altava, B.; Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Luis, S. V.; Mayoral, J. A.; Vicent, M. J. "How Important is the Inert Matrix of Supported Enantiomeric Catalysts? Reversal of Topicity with Two Polystyrene Backbones" *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1503.

(29) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Vicent, M. J.; Mayoral, J. A. "Supported Chiral Catalysts: The Role of the Polymeric Network" *React. Funct. Polym.* **2001**, *48*, 25-35.

(30) Benaglia, M.; Danelli, T.; Fabris, F.; Sperandio, D.; Pozzi, G. "Poly(ethylene glycol)-supported tetrahydroxyphenyl porphyrin: A convenient, recyclable catalyst for photooxidation reactions" *Org. Lett.* **2002**, *4*, 4229–4232.

(31) Benaglia, M.; Danelli, T.; Pozzi, G. "Synthesis of poly(ethylene glycol)-supported manganese porphyrins: efficient, recoverable and recyclable catalysts for epoxidation of alkenes" *Org. Biomol. Chem.* **2003**, *1*, 454–456.

(32) Toy, P. H.; Janda, K. D. "Soluble Polymer-Supported Organic Synthesis" *Acc. Chem. Res.* **2000**, *33*, 546-554.

(33) Gravert, D. J.; Janda, K. D. "Organic Synthesis on Soluble Polymer Supports: Liquid-Phase Methodologies" *Chem. Rev.* **1997**, *97*, 489-509.

(34) Wentworth Jr., P.; Janda, K. D. "Liquid-phase Chemisry: Recent Advances in Soluble Polymer-Supported Catalysts, Reagents and Synthesis" *Chem. Commun.* **1999**, 1917-1924.

(35) Harris, J. M.; Dust, J. M.; McGill, R. A.; Harris, P. A.; Edgell, M. J.; Sedaghatherati, R. M.; Karr, L. J.; Donnelly, D. L. "New Polyethylene Glycols for Biomedical Applications" *Acs Symposium Series* **1991**, *467*, 418-429.

(36) Zhao, X. Y.; Metz, W. A.; Sieber, F.; Janda, K. D. "Expanding on the Purification Methodology of Polyethylene glycol (PEG) Bound Molecules: The synthesis of 3,5-Pyrazolidinediones" *Tetrahedron Lett.* **1998**, *39*, 8433-8436.

(37) Cozzi, P. G. "Metal-Salen Schiff Base Complexes in Catalysis: Practical Aspects" *Chem. Rev.* **2004**, *33*, 410-421.

(38) Katsuki, T. "Catalytic Asymmetric Oxidations Using Optically-Active (Salen)Manganese (III) Complexes as Catalysts" *Coord. Chem. Rev.* **1995**, *140*, 189-214.

(39) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. "Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by (Salen)Manganese Complexes" *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

(40) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. "Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins" *Tetrahedron Lett.* **1990**, *31*, 7345-7348.

(41) Katsuki, T. "Some Recent Advances in Metallosalen Chemistry" *Synlett* **2003**, 281-297.

(42) Yoon, T. P.; Jacobsen, E. N. "Privileged Chiral Catalysts" *Science* **2003**, *299*, 1691-1693.

(43) Campbell, E. J.; Nguyen, S. T. "Unsymmetrical salen-type ligands: high yield synthesis of salen-type Schiff bases containing two different benzaldehyde moieties" *Tetrahedron Lett.* **2001**, *42*, 1221-1225.

(44) Jacobsen, E. N.; Zhang, W.; Guler, M. L. "Electronic Tuning of Asymmetric C atalysts" *J. Am. Chem. Soc.* **1991**, *113*, 6703-6704.

(45) Noyori, R.; Kitamura, M. "Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification" *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(46) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford Press: New York, 1999.

(47) Edrick, E. *Organozinc Reagents in Organic Synthesis Press*; CRC Press: New York, 1996.

(48) Pu, L.; Yu, H.-B. "Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds" *Chem. Rev.* **2001**, *101*, 757-824.

(49) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. "Enantioselective Addition of Diethylzinc to Aldehydes Promoted by a Chiral Schiff Base Metal Complex" *Tetrahedron Lett.* **1996**, *37*, 4613-4616.

(50) DiMauro, E. F.; Kozlowski, M. C. "Salen-derived catalysts containing secondary basic groups in the addition of diethylzinc to aldehydes" *Org. Lett.* **2001**, *3*, 3053-3056.

(51) Annis, D. A.; Jacobsen, E. N. "Polymer-Supported Chiral Co(Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides" *J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

(52) Jayaprakash, D.; Sasai, H. "Synthesis and catalyric applications of soluble polymer-supported BINOL" *Tetrahedron: Asymmetry* **2001**, *12*, 2589-2595.

(53) Hansch, C.; Leo, A.; Taft, R. W. "A Survey of Hammett Substituent Constants and Resonance and Field Parameters" *Chem. Rev.* **1991**, *91*, 165-195.

CHAPTER 3

STEREOELECTRONIC TUNING OF A CHIRAL CATALYST

3.1 Introduction:

It is well established in asymmetric catalysis that effective stereochemical communication between the substrate and the chiral environment of the catalyst ligand is crucial in obtaining high enantioselectivities.[1] Nature achieves this, rather elegantly, in biochemical reactions, through enzymatic processes. Enzymes are able to induce substrate precoordination at the vicinity of the active site prior to the reaction, thereby, effectively minimizing the degrees of freedom in the critical transition state of the reaction, thus, maximizing the selectivity-determining interactions between the catalyst's chiral environment and the substrate.[2] Several archetypal nonenzymatic asymmetric catalyst systems also operate on this substrate-directed principle.[3,4] In contrast to these systems, a number of practical and effective nonenzymatic asymmetric catalysts have been developed, which do not require a specific pre-coordinating group on the substrate in order to obtain high enantioselectivities.[5-9] In these catalyst systems, enhanced stereoselectivity is achieved by modifications in the reaction environment by either; (a) changes in the catalyst's ligand structure or (b) modifications of the reaction conditions; or a combination of both. Steric interactions are generally perceived to play the predominant role in determining the mechanism of asymmetric induction, however, changes in the electronic structure of catalyst's ligand have also been known to affect the stereochemical outcome of some asymmetric reactions.[10-17]

3.2 Stereoelectronic Tuning of a Chiral Metal-Salen Catalyst:

An attractive feature of chiral salen catalysts is the modular nature of the ligand; being comprised of two salicylaldehyde molecules and a chiral diamine moiety (Figure 3.2). As such, steric and electronic tuning of the catalyst in a synthetically straightforward

manner is readily achievable by altering the substitution on the aromatic ring of the salicylaldehyde and/or changing the chiral diamine components. The effects of such logical structural modifications may be exploited during ligand design for the optimization of catalyst performance; the ultimate goal being, the de novo design of highly effective and enantioselective chiral catalysts.

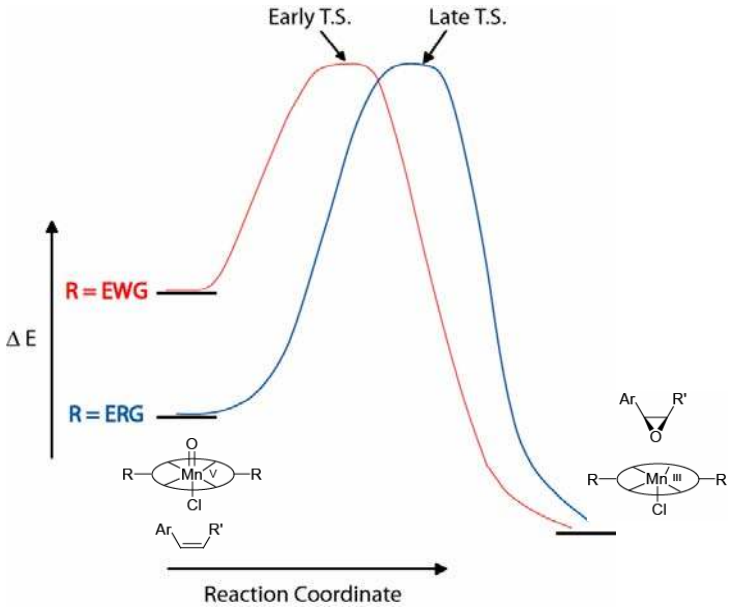


Figure 3.1: Schematic energy diagram illustrating the proposed effect of ligand substituents on the reaction coordinate of the Mn-salen catalyzed epoxidation reaction.

In 1991, Jacobsen and co-workers reported the observation of dramatic catalyst electronic effects on the enantioselectivity of Mn(III) salen catalyzed epoxidation of cis-disubstituted olefins.[13] The importance of electronic effects in asymmetric catalytic reactions has since been increasingly appreciated.[10-17] Jacobsen's study revealed that the electronic character of 5,5' substituents on C-2 symmetric chiral Mn(III) salen catalysts had a significant influence the *ee* of the product epoxides. ERG's, at these positions, were found to lead to higher *ee's* while EWG's gave decreased *ee's.* These

effects were initially interpreted according to a Hammond Postulate argument, wherein, the ligands substituents influence enantioselectivity by modulating the reactivity of the high-valent Mn-salen oxo intermediate.[13] EWG's furnished a more reactive Mn-salen oxo intermediate which would add to the olefin in a comparatively early transition state, thus, affording lower levels of enantioselectivity. Conversely, ERG's attenuated the reactivity of the oxo species; which would transfer oxygen to the olefin in a comparatively late transition state, thus, leading to a higher *ee's* (Figure 3.1). In a more detailed study into the mechanistic basis for the observed electronic effects, Jacobsen and co-workers uncovered further evidence to suggest that control of the position of the transition state along the reaction coordinate was responsible for the observed electronic effects on enantioselectivity.[26]

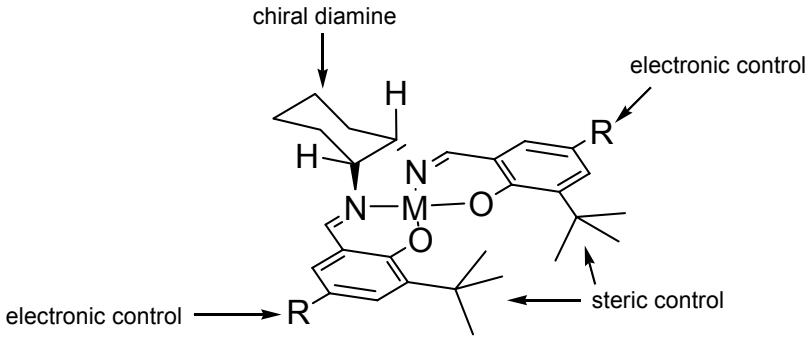


Figure 3.2: Modular metal salen complex: R = EWG, low *er*'s; R = ERG, high *er*'s.

Despite the broad range of asymmetric transformations achievable with chiral metal-salen complexes, the analysis of the effects on enantioselectivity as a result of changes in the catalysts electronic structure, have only been limited to oxidation reactions via metal oxo (salen) complexes. We have probed these effects and the results of our studies have helped us propose, for the first time, a logical mechanism for

the Zn-salen catalyzed addition of Et_2Zn to benzaldehyde, that account for our observations.

3.3 Addition of Dialkylzincs to Aldehydes: Catalytic Mechanism:

The mechanism of the addition of dialkyl zinc to aldehydes, using traditional β-amino alcohols as ligands, has been studied by Soai[27] and Noyori[28-31] and fully elucidated with a combination of kinetic and computational studies.[32,33] Monomeric zinc alkoxide, **1.1**, which is in equilibrium with the inactive dimeric alkoxide,**1**, reacts with an equivalent of Et_2Zn to form the monoalkoxide-Et_2Zn complex, **1.2**; or reacts with an equivalent of the aldehyde to form **1.3**. The intermediate adduct **1.4**, can either be generated from the addition of Et_2Zn to **1.3**, or the addition of the addition of the aldehyde to **1.2**. Attack of the aldehyde at the carbonyl by the coordinated Et_2Zn in intermediate **1.4**, yields the alkoxide **1.5**. This species is converted back to the complexes **1.2** and **1.3** upon addition of Et_2Zn or aldehyde respectively, with concomitant formation of the zinc alkoxide **1.6**; which affords the alcohol **1.7**, upon aqueous work up. In the selectivity determining step, first proposed by Itsuno and Fréchet,[34] and later supported and elaborated by Noyori and co-workers,[35] the reactants are gathered together by the bifunctional alkyl zinc ligand complex, yielding a *μ*-oxo transition structure of the type depicted in Figure 3.3.

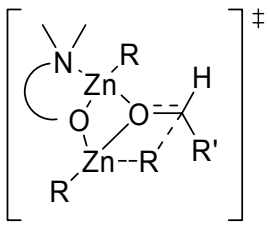


Figure 3.3: Proposed transition state for the addition of dialkyl zincs to aldehydes.

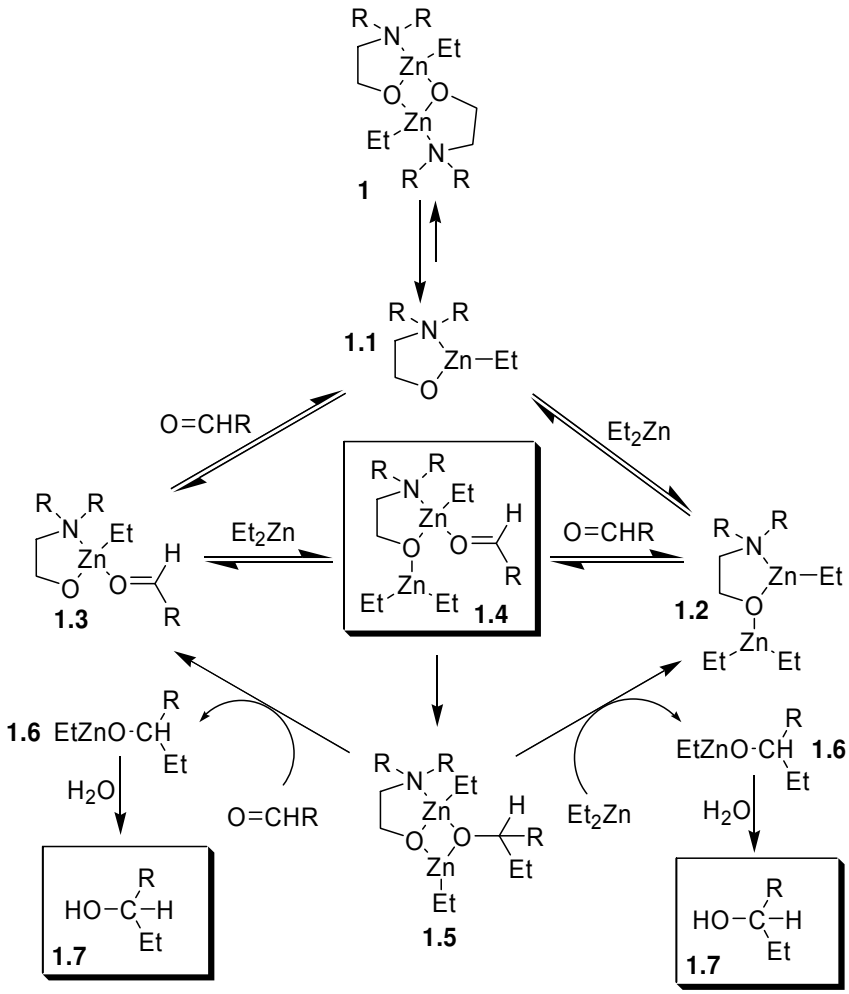


Figure 3.4: Mechanism for the addition of Et_2Zn to aldehydes catalyzed by β-amino alcohols.

Metal-salen complexes, as catalysts, have been known to act in a cooperative manner involving the activation of a nucleophile and electrophile; studies into the mechanism of the hydrolytic kinetic resolution of terminal epoxides using chiral Cr and Co-salen catalysts suggest a cooperative mechanism for epoxide ring opening.[36-40] The mechanism of metal-salen catalyzed addition of dialkyl zinc to aldehydes, however, still remains to be studied in detail. In attempts to rationalize the results obtained form the enantioselective addition of Et_2Zn to aldehydes catalyzed by a chiral salen complex, preliminary studies by Cozzi and coworkers suggest the formation of a bimetallic *μ*-oxo-

Zn-salen-Et_2Zn complex.[41] On addition of one equivalent of Et_2Zn to a solution of the salen ligand, disappearance of the ^1H NMR resonance signals due to the phenolic protons and no evidence of the ethyl proton signals (ethane is liberated), accompanied by a broadening of the proton signals of the ligand, indicated insitu formation of the square planar Zn-salen complex. On addition of Et_2Zn, and broadening of the ^1H NMR ethyl protons and a change in appearance of the signals due to ligand was attributed to the coordination of the added Et_2Zn to the ligating oxygen atoms of the Zn-salen complex. On the basis of these observations, a plausible transition state (TS) complex as depicted in Figure 3.5 can be proposed.

Correlation between the enantioselectivity of the asymmetric addition of Et_2Zn to benzaldehyde and the *ee* of the salen ligand reveals the absence of a nonlinear effect,[42] which is consistent with the proposed TS structure in Figure 3.5. When the reaction was carried out with salen ligands of varied enantiomeric purity (50% and100% *ee*); we observed a linear correlation between the *ee* of the salen ligand and that of the product (82% and 42% *ee*) (Figure 3.6). This strongly indicates that only one molecule of the salen catalyst is involved in the enantio-differentiating step of the reaction, thus, suggesting a one-point substrate-catalyst Lewis acid–Lewis base double activation takes place in the transition state (figure 3.5). *This is clearly in contrast to the positive non-linear effects observed for β-amino alcohol catalyzed addition of dialkylzincs to aldehydes.* A similar linear correlation has also been observed in the Zn-salen catalyzed enantioselective alkynylation of ketones.[43] The coordination of metals to the oxygen atoms of Schiff base-metal complexes[44-46] and bimetallic Schiff base complexes similar to the proposed Zn-salen complex (figure 3.5) have also been crystallographically characterized.[47] It is also pertinent to note that the *ee* of the reaction does not vary significantly with conversion, further indicating that the composition of the catalytic species is constant over the course of the reaction.

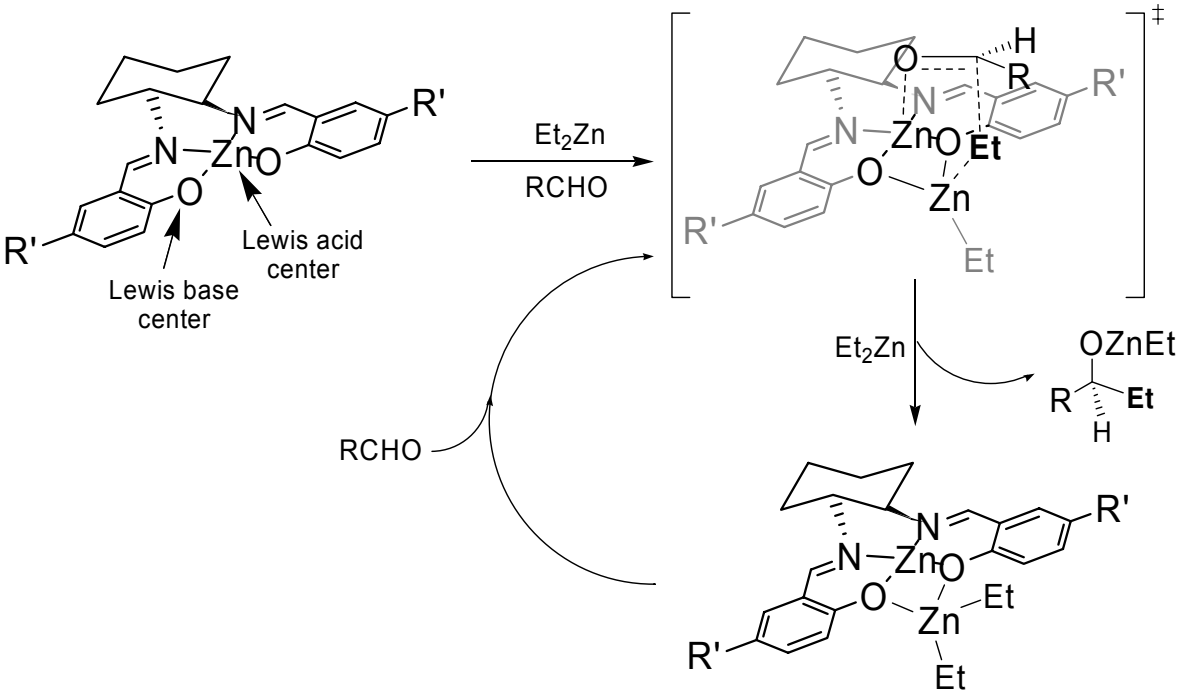


Figure 3.5: Bifunctional Zn-salen complex and a proposed bimetallic TS structure (the 3,3'-*tert*-butyl substituents on the salen ligand have been omitted for clarity purposes).

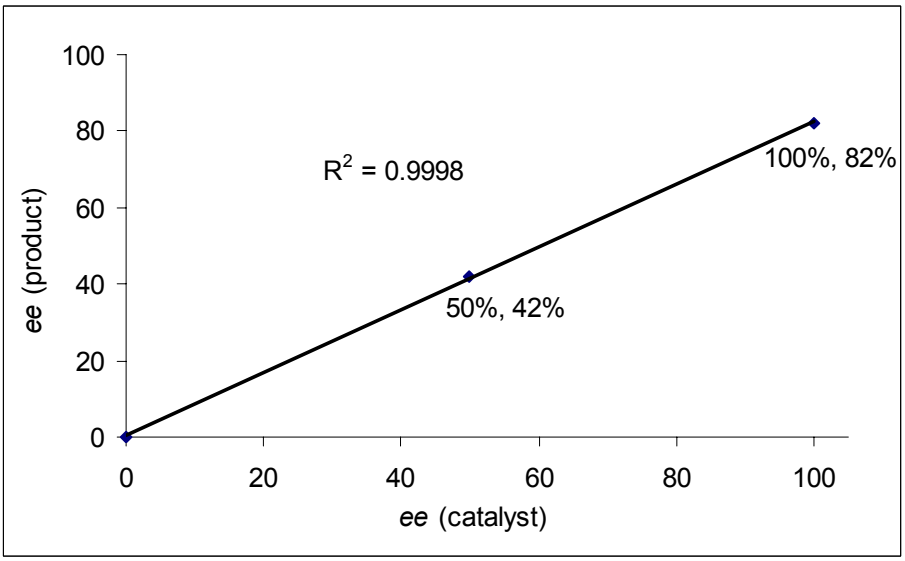
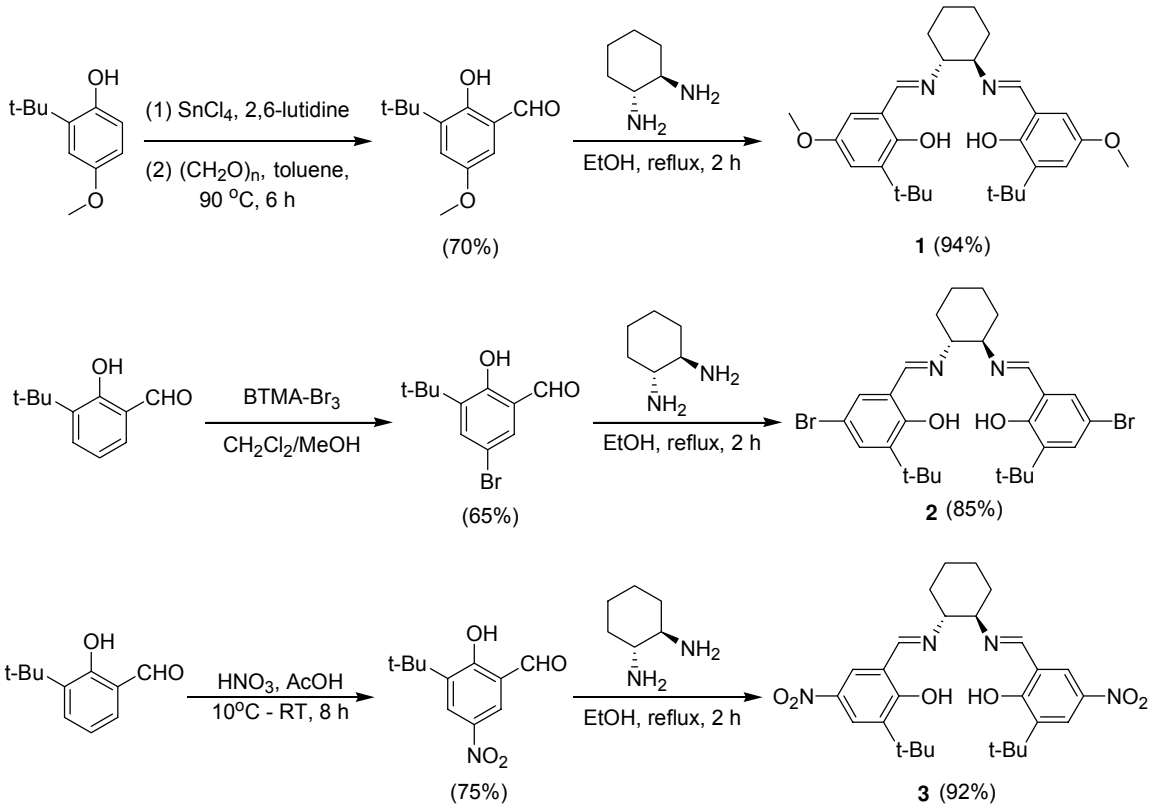


Figure 3.6: Absence of nonlinear effect in the Zn-salen catalyzed addition of Et_2Zn to benzaldehyde using salen ligand **6**.

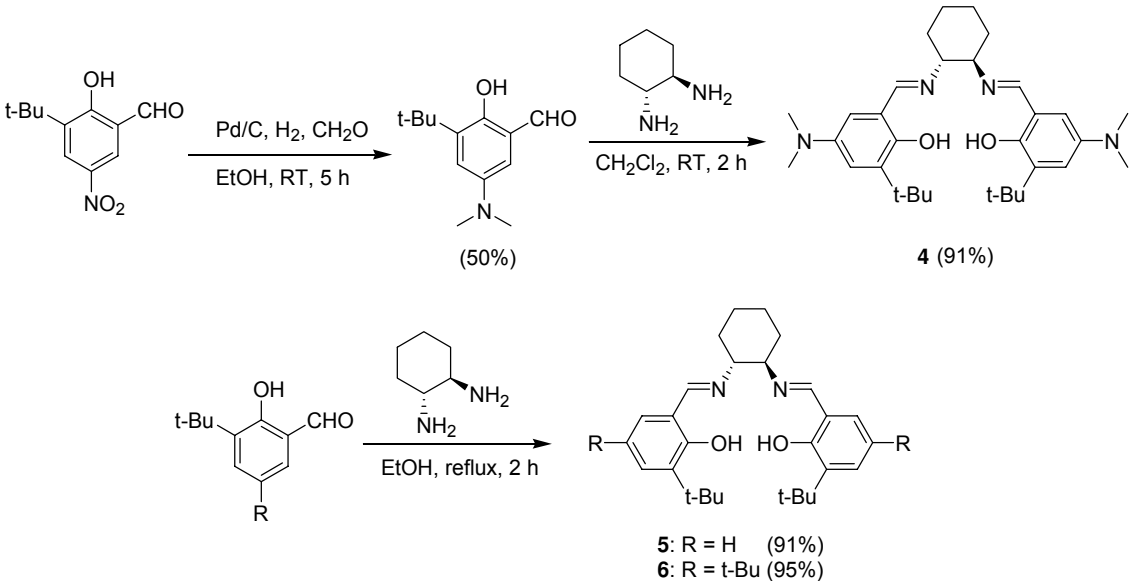
In our attempts to gain more insight into the mechanism of this reaction and a better understanding of the factors necessary for the design of highly active and enantioselective catalyst, we studied the effects that the electronic modification of the salen ligand structure would have on the enantioselectivity and reactivity of a model reaction; asymmetric addition of Et_2Zn to benzaldehyde.

3.4 Synthesis:

We synthesized a series of salen ligands, **1- 6** (bearing EWG and ERG at their 5,5′ position) in good yields (95%–85%), from their respective 5-substituted *tert*-butyl salicylaldehydes by condensation with (*R,R*)-1,2-diaminocyclohexane.



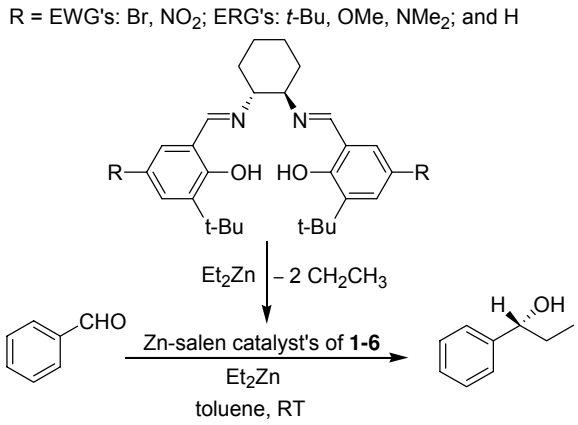
Scheme 3.1: Synthesis of 5,5'-substituted salen ligands. “Continued, next page”



Scheme 3.1 Continued: Synthesis of 5,5'-substituted salen ligands.

The Zn-salen catalyst was generated *insitu* by treating a solution of the salen ligand in toluene with an equivalent amount of Et_2Zn and allowing the reaction mixture to stir at room temperature for 1 h. Following the addition of benzaldehyde and Et_2Zn, the reaction was allowed to proceed until deemed complete by GC. The results are summarized in Table 3.1. Catalysts with EWG's at the 5,5′ positions gave lower selectivities than those with ERG's at the same positions following the trend of decreasing enantioselectivity: $N(CH_3)_2$ > OCH_3 > *t*-Bu > H > Br > NO_2. This is in agreement with the aforementioned hypothesis, wherein, catalysts with 5,5'-substituted EWG's were expected to be more enantioselective that those with ERG's. All catalysts furnished the product 1-phenyl-1-propanol in good yields. The catalysts with EWG substituents appeared to be more active than those bearing ERG; **3** gave quantitative conversion of benzaldehyde to the product in 9 h, whereas, **1** and **4** required 24 h and 36 h to a achieve 90% and 95% conversions respectively. The significance of these observations will be discussed in the section 3.6. Jacobsen reported that the difference

in diastereomeric transition state energies for nitro- and methoxy- 5,5'-substituted Mn(III)-salen catalyzed epoxidation of cis-disubstituted olefins was 2.0 kcal/mol.[26] It was interesting to note that for our system, the enantioselectivity differences between Zn-salen catalysts of **3** and **4**, 43:57 *er* and 98:2 *er* respectively, also corresponded to a remarkable difference in the diastereomeric transition state energies, $\Delta\Delta G^{\ddagger}$, greater than 2.0 kcal/mol. The enantioselectivity of **4**, 98:2 *er*, is the highest enantioselectivity reported, to date, for a metal-salen catalyzed addition of Et_2Zn to benzaldehyde.



Scheme 3.2: Addition of Et_2Zn to benzaldehyde using Zn-salen catalysts of **1-6**.

Table 3.1: Stereoelectronic effects of 5,5'-substituted Zn-salen catalysts. [a] Enantiomeric ratios; determined by chiral GC (Cyclosil-B® column). [b] Determined by GC.

catalyst	R	*er*[a]	time (h)	conv. (%)[b]
4	NMe_2	98:2	36	95
1	OMe	93:7	24	90
6	*t*-Bu	91:9	18	95
5	H	85:15	18	97
2	Br	74:26	12	100
3	NO_2	43:57	9	100

3.5 Linear Free Energy Relationship:

Of the many techniques for studying reaction mechanisms, analysis of linear free energy relationships (LFER) is the most readily applicable and general. LFER's are empirical observations which are derived upon the general assumption that the shapes of the potential energy surfaces of a reaction are not substantially altered by varying the substituents on the reactant(s). The kinetic and thermodynamic components of LFER's can be described as follows:

Rate constants (*kinetic*) are related to free energy changes through the Eyring equation:

$$\log k = \log\left(\frac{k_B T}{h}\right) - \frac{1}{2.303RT}\Delta G^{\#}$$

$$\text{linear relationship: } \log k \approx -\Delta G^{\#}$$

Equilibrium constants are related to the free energy changes through the thermodynamic equation:

$$\log K = -\frac{1}{2.303RT}\Delta G^{o}$$

$$\text{linear relationship: } \log K \approx -\Delta G^{o}$$

Comparing the effect of two substituents, A and B on the same reaction at the same temperature; the rate constants are:

$$\log k_A = \log\left(\frac{k_B T}{h}\right) - \frac{1}{2.303RT}\Delta G^{\#}_A$$

$$\log k_B = \log\left(\frac{k_B T}{h}\right) - \frac{1}{2.303RT}\Delta G^{\#}_B$$

Taking the difference of two equations results in

$$\log k_A - \log k_B = -\frac{1}{2.303RT}\left(\Delta G^{\#}_A - \Delta G^{\#}_B\right)$$

$$\log\left(\frac{k_A}{k_B}\right) = \frac{1}{2.303RT}\Delta\Delta G^{\#}_{BA}$$

If the reaction involving substituent B is the reference reaction (substituents = H) and that involving substituent A is the substituted reaction, then the free energy of activation for each reaction is related to the product of ρ (parameter characteristic of the type of reaction), and σ, (the Hammett substituent parameter); then

$$\text{if } \Delta G^{\#} = \rho\sigma \text{ ; then } \quad \log\left(\frac{k_A}{k_H}\right) = \rho(\sigma_A - \sigma_H)$$

If, σ_H = 0, the Hammett equation is obtained

$$\log\left(\frac{k_A}{k_H}\right) = \rho\sigma_A$$

For the equilibrium constant, similar analysis results in the expression

$$\log\left(\frac{K_A}{K_H}\right) = \rho\sigma_A$$

3.6 Hammett Analysis:

The Hammett equation[48,49] and its extended forms have been extensively exploited by chemists in the study of the fundamental mechanisms of organic reactions. It has also been applied to the derivation and study of structure-activity relationships for rational drug design[50] as well as a host of interactions involving organic compounds and biological systems.[51,52] Hammett summarized the effects of *meta*- or *para*-substituents on the rate constants or equilibrium constants of reactions of benzene derivatives. The Hammett equation is given by:

$$\log (k / k_o) = \rho\, \sigma_p \qquad (1)$$

where k and k_o are rate (or equilibrium) constants for the reactions of the substituted and unsubstituted compounds, σ_p is the Hammett constant (a measure of the electronic effect of replacing a H substituents with a given substituent in the *meta* or *para* position, and it is, in principle, independent of the nature of the reaction), and ρ is a reaction constant (a parameter characteristic of the type of reaction; including conditions such as solvent and temperature). The slopes of linear free energy correlations of electronic (or polar) substituent-effects are directly related to the changes in the electron density

(*effective charge*) at the reaction center.[53] Since charge differences are a function of changes in bonding, electronic substituents effects are related to bonding in the transition structure[54], relative to that in the reactant.[55]

A linear correlation between the enantioselectivities of the series of 5,5'-substituted Zn-salen catalysts and the Hammett substituent constants, σ_p, was observed (Figure 3.7). Based on our hypothetical model for the dual activation of benzaldehyde and Et_2Zn by the Zn-salen complex, and our proposed "selectivity determining" transition structure (figure 3.4); this linear correlation can be rationalized. Lewis acid activation of the aldehyde, via complexation to the Zn center of the Zn-salen complex, is a prerequisite for product formation (in the absence of a catalyst or promoter, no product formation is observed with pure dialkyl zinc, even after 72 h) EWG's at the 5,5' positions of the Zn-salen complex decrease the electron density (Lewis basicity) at the ligating O atoms of the salen complex; diminishing contributions of the Zn-salen-Et_2Zn transition state to enantioselectivity. Et_2Zn can now add to the aldehyde without enantio-face selectivity (derived from substrate precoordination) to give racemic products. This effectively leads to lowered enantiomeric purity of the product. Conversely, ERG's at the 5,5' positions of the Zn-salen complex increase the electron density at the ligating O atoms of the salen complex thus increasing their Lewis basicity. This effectively increases the contribution of the "selectivity-determining" Zn-salen-Et_2Zn transition structure to the over all enantioselectivity of the reaction; resulting in increased enantiomeric purity of the product.

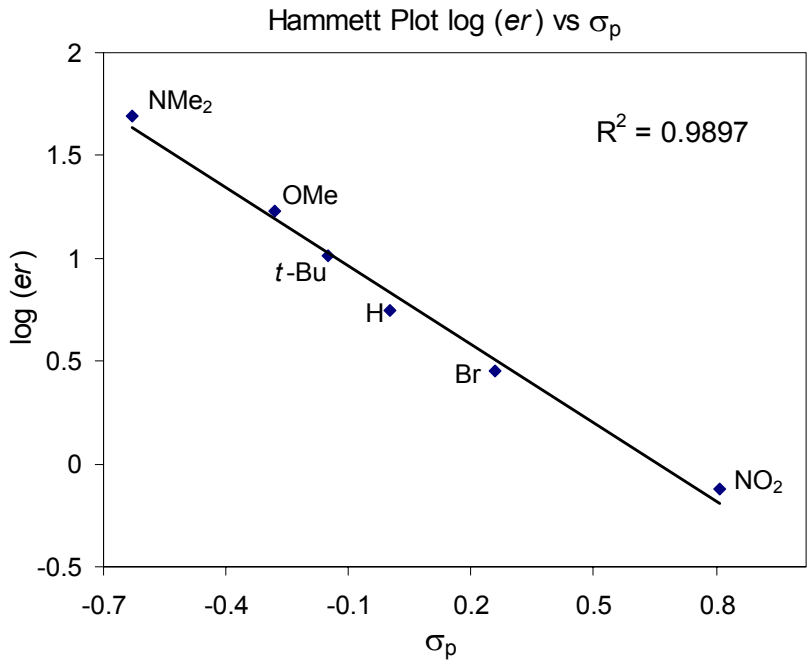


Figure 3.7: Linear correlation between *er* and σ_p of Zn-salen catalysts.

The observed trend in reactivity of catalysts **1-6** (calibrated as time required to achieve optimum conversion to product; see table 3.1), suggest that EWG's at the 5,5' positions decrease electron density at the Zn center thereby increasing its Lewis acidity, and the activity of the catalyst. ERG's attenuate the Lewis acidity of the catalyst by increasing electron density at the Zn center, hence, decreasing its activity. It has been established that steric perturbations in the ligand structure, imposed by 5,5′ substituents have insignificant effects on enantioselectivity of metal-salen catalysts. Therefore, the linearity of the Hammett plot is strong evidence that the electronic properties of the catalysts are responsible for the observed changes in enantioselectivity.

3.7 References:

(1) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. "Substrate-Directable Chemical-Reactions" *Chem. Rev.* **1993**, *93*, 1307-1370.

(2) Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman: New York, 1979.

(3) Halpern, J. "Mechanism and Stereoselectivity of Asymmetric Hydrogenation" *Science* **1982**, *217*, 401-407.

(4) Johnson, R. A.; Sharpless, K. B. *In Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993, pp Chapter 4.1.

(5) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. "Catalytic Asymmetric Dihydroxylation" *Chem. Rev.* **1994**, *94*, 2483-2547.

(6) Jacobsen, E. N. *In Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(7) Li, Z.; Conser, K. R.; Jacobsen, E. N. "Asymmetric Alkene Aziridination with Readily Available Chiral Diimine-Based Catalysts" *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.

(8) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. "Bis(Oxazoline) Copper-Complexes as Chiral Catalysts for the Enantioselective Aziridination of Olefins" *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.

(9) Doyle, M. P. *In Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(10) Casey, M.; Smyth, M. P. "Ligand Electronic Effects in Enantioselective Diethylzinc Additions" *Synlett* **2003**, 102-106.

(11) Bonaccorsi, C.; Bachmann, S.; Mezzetti, A. "Electronic Tuning of the PNNP Ligand for the Asymmetric Cyclopropanation of Olefins Catalysed by RuCl(PNNP)" *Tetrahedron: Asymmetry* **2003**, *14*, 845-854.

(12) Cavallo, L.; Jacobsen, H. "Electronic Effects in (Salen)Mn-Based Epoxidation Catalysts" *J. Org. Chem.* **2003**, *68*, 6202-6207.

(13) Jacobsen, E. N.; Zhang, W.; Guler, M. L. "Electronic Tuning of Asymmetric Catalysts" *J. Am. Chem. Soc.* **1991**, *113*, 6703-6704.

(14) McGarrigle, E. M.; Murphy, D. M.; Gilheany, D. G. "Ligand Tuning in the Chromium-Salen-Mediated Asymmetric Epoxidation of Alkenes" *Tetrahedron: Asymmetry* **2004**, *15*, 1343-1354.

(15) Park, H.; RajanBabu, T. V. "Tunable Ligands for Asymmetric Catalysis: Readily Available Carbohydrate-Derived Diarylphosphinites Induce High Selectivity in the Hydrovinylation of Styrene Derivatives" *J. Am. Chem. Soc.* **2002**, *124*, 734-735.

(16) Rajanbabu, T. V. "Controlling Asymmetric Catalyzed Reactions through Ligand Effects," *Chimica Oggi-Chemistry Today* **2000**, *18*, 26-31.

(17) Rajanbabu, T. V.; Ayers, T. A. "Electronic Effects in Asymmetric Catalysis - Hydroformylation of Olefins" *Tetrahedron Lett.* **1994**, *35*, 4295-4298.

(18) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. "Carbohydrate Phosphinites as Practical Ligands in Asymmetric Catalysis: Electronic Effects and Dependence of Backbone Chirality in Rh-catalyzed Asymmetric Hydrogenations. Synthesis of R- or S-amino Acids Using Natural Sugars as Ligand Precursors" *J. Org. Chem.* **1997**, *62*, 6012-6028.

(19) Rajanbabu, T. V.; Casalnuovo, A. L. "Electronic Effects in Asymmetric Catalysis - Enantioselective Carbon-Carbon Bond-Forming Processes" Pure Appl. Chem. **1994**, *66*, 1535-1542.

(20) RajanBabu, T. V.; Casalnuovo, A. L. "Role of Electronic Asymmetry in the Design of new Ligands: The Asymmetric Hydrocyanation Reaction" *J. Am. Chem. Soc.* **1996**, *118*, 6325-6326.

(21) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A.; Nomura, N.; Jin, J.; Park, H.; Nandi, M. "Ligand Tuning as a Tool for the Discovery of New Catalytic Asymmetric Processes" Curr. Org. Chem. **2003**, *7*, 301-316.

(22) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. "Electronic Effects in Asymmetric Catalysis: Structural Studies of Precatalysts and Intermediates in Rh-Catalyzed Hydrogenation of Dimethyl Itaconate and Acetamidocinnamic Acid Derivatives Using C-2-Symmetric Diarylphosphinite Ligands" *J. Org. Chem.* **1999**, *64*, 3429-3447.

(23) Sannicolo, F.; Benincori, T.; Rizzo, S.; Gladiali, S.; Pulacchini, S.; Zotti, G. "Electronic Tuning in C-1-Symmetric Chelating Diphosphane Ligands Supported on Stereogenic Aryl-Heteroaryl Templates" *Synthesis-Stuttgart* **2001**, 2327-2336.

(24) Yan, Y. Y.; RajanBabu, T. V. "Ligand Substituent Effects on Asymmetric Induction. Effect of Structural Variations of the DIOP Ligand on the Rh-Catalyzed Asymmetric Hydrogenation of Enamides" *Org. Lett.* **2000**, *2*, 4137-4140.

(25) Yan, Y. Y.; RajanBabu, T. V. "Ligand Tuning in Asymmetric Catalysis: Mono- and Bis-Phospholanes for a Prototypical Pd-Catalyzed Asymmetric Allylation Reaction" *Org. Lett.* **2000**, *2*, 569-569.

(26) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M.; Ishida, T.; Jacobsen, E. N. "The Mechanistic Basis for the Electronic Effects on Enantioselectivity in the (Salen)Mn(III)-Catalyzed Epoxidation Reaction" *J. Am. Chem. Soc.* **1998**, *120*, 948-954.

(27) Soai, K.; Yokoyame, S.; Hayasaka, T. "Chiral N, N-dialkylnorephedrines as Catalysts to the Highly Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes. The Asymmetric Synthesis of Secondary Aliphatic and Aromatic Alcohols of High Optical Purity" *J. Org. Chem.* **1991**, *56*, 4264.

(28) Kitamura, S.; Suga, S.; Kawai, K.; Noyori, R. "Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes" *J. Am. Chem. Soc.* **1986**, *108*, 6071.

(29) Kitamura, S.; Oka, H.; Noyori, R. "Asymmetric addition of dialkylzincs to benzaldehyde derivatives catalyzed by chiral beta-amino alcohols. Evidence for the monomeric alkylzinc aminoalkoxide as catalyst" *Tetrahedron* **1999**, *55*, 3605.

(30) Kitamura, S.; Suga, S.; Oka, H.; Noyori, R. "Quantitative analysis of the chiral amplification in the amino alcohol-promoted asymmetric alkylation of aldehydes with dialkylzincs" *J. Am. Chem. Soc.* **1998**, *120*, 9800.

(31) Noyori, R.; Kitamura, M. "Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification" *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(32) Kozlowski, M. C.; Dixon, S. L.; Panda, M.; Lauri, G. "Quantum Mechanical Models Correlating Structure with Selectivity: Predicting the Enantioselectivity of α-Amino Alcohol Catalysts in Aldehyde Alkylation" *J. Am. Chem. Soc.* **2003**, *125*, 6614-6615.

(33) Rasmussen, T.; Norrby, P.-O. "Characterization of New Six Membered Transition States of the Amino-Alcohol Promoted Addition of Dialkyl Zinc to Aldehydes" *J. Am. Chem. Soc.* **2001**, *123*, 2464-2465.

(34) Itsuno, S.; Fre´chet, J. M. J. "Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Polymer-Supported Chiral Amino Alcohols. Evidence for a Two Zinc Species Mechanism" *J. Org. Chem.* **1987**, *52*, 4142-4143.

(35) Yamakawa, M.; Noyori, R. "Asymmetric Addition of Dimethylzinc to Benzaldehyde Catalyzed by (2S)-3-exo(Dimethylamino)isobornenol. A Theoretical Study on the Origin of Enantioselection" *Organometallics* **1999**, *18*, 128-133.

(36) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. "The Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (Salen) Titanium Complexes" *J. Am. Chem. Soc.* **1999**, *121*, 3968-3973.

(37) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. "On the Mechanism of Asymmetric Nucleophilic Ring-Opening of Epoxides Catalyzed by (Salen)Cr-III Complexes" *J. Am. Chem. Soc.* **1996**, *118*, 10924-10925.

(38) Konsler, R. G.; Karl, J.; Jacobsen, E. N. "Cooperative Asymmetric Catalysis with Dimeric Salen complexes" *J. Am. Chem. Soc.* **1998**, *120*, 10780-10781.

(39) Annis, D. A.; Jacobsen, E. N. "Polymer-Supported Chiral Co(Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides" *J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

(40) Ready, J. M.; Jacobsen, E. N. "Highly active Oligomeric (Salen)Co Catalysts for Asymmetric Epoxide Ring-Opening Reactions" *J. Am. Chem. Soc.* **2001**, *123*, 2687-2688.

(41) Cozzi, P. G.; Papa, A.; UmaniRonchi, A. "Enantioselective Addition of Diethylzinc to Aldehydes Promoted by a Chiral Schiff Base Metal Complex" *Tetrahedron Lett.* **1996**, *37*, 4613-4616.

(42) Kagan, H. B. "Practical Consequences of Non-linear Effects in Asymmetric Synthesis" Adv. Synth. Catal. **2001**, *343*, 227-233.

(43) Cozzi, P. G. "Enantioselective Alkynylation of Ketones Catalyzed by Zn(Salen) Complexes," *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2895-2898.

(44) Cashin, B.; Cunningham, D.; Daly, P.; McArdle, P.; Munroe, M.; Ni Chonchubhair, N. "Donor Properties of the Vanadyl ion: Reactions of Vanadyl Salicylaldimine Beta-Ketimine and Acetylacetonato Complexes with Groups 14 and 15 Lewis Acids" *Inorg. Chem.* **2002**, *41*, 773-782.

(45) Cunningham, D.; McArdle, P.; Mitchell, M.; Ni Chonchubhair, N.; O'Gara, M.; Franceschi, F.; Floriani, C. "Adduct Formation Between Alkali Metal Ions and Divalent Metal Salicylaldimine Complexes Having Methoxy Substituents. A Structural Investigation" *Inorg. Chem.* **2000**, *39*, 1639-1649.

(46) Gallo, E.; Solari, E.; Floriani, C.; ChiesiVilla, A.; Rizzoli, C. "Use of Manganese(II) Schiff Base Complexes for Carrying Polar Organometallics and Inorganic Ion Pairs" *Inorg. Chem.* **1997**, *36*, 2178-2186.

(47) Boyce, M.; Clarke, B.; Cunningham, D.; Gallagher, J. F.; Higgins, T.; McArdle, P.; Cholcuin, M. N.; O'Gara, M. "Transition-Metal Schiff-Base Complexes as Ligands in Tin Chemistry" *Organomet. Chem.* **1995**, *498*, 241.

(48) Hammett, L. P. "The Effect of Structure on the Reactivity of Organic Compounds" *J. Am. Chem. Soc.* **1937**, *59*.

(49) Bronsted, J. N. "Acid Base Catalysis" *Chem. Rev.* **1928**, *5*.

(50) Martin, Y. C. *Quantitative Drug Design*; Dekker: New York, 1978.

(51) Hansch, C.; Klein, T. E. "Molecular Graphics and QSAR In The Study of Enzyme Ligand Interactions- on the Definition of Bioreceptors" *Acc. Chem. Res.* **1986**, *7*, 2858.

(52) Hansch, C.; Bjorkroth, J. P.; Leo, A. "Hydrophobicity and Central Nervous System Agents - on the Principle of Minimal Hydrophobicity in Drug Design" *J. Pharm. Sci.* **1987**, *76*, 663.

(53) Williams, A. "Effective Charge and Transition State Structure in Solution" *Adv. Phys. Org. Chem.* **1991**, *27*, 1.

(54) Maskill, H. *Mechanisms of Organic reactions*; Oxford Science Publications: Oxford, 1996.

(55) Muller, P. "Glossary of Terms used in Physical Organic Chemistry" *Adv. Phys. Org. Chem.* **1994**, *66*, 1077.

CHAPTER 4

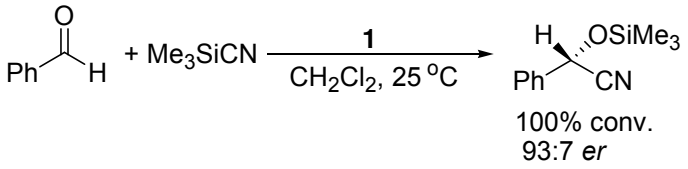
RECYCLING A SOLUBLE POLYMER-SUPPORTED CATALYSTS

4.1 Introduction:

There is a widespread interest in developing methods to recover homogeneous catalysts, particularly chiral catalysts, from a reaction mixture.[1-7] The impetus to recover and reuse homogenous catalysts stems not only from an economic standpoint (especially for chiral catalysts), but also from the need to eliminate contamination of the transition metal catalyst in the product and in the waste streams.[8] The challenge is to recover the catalyst for reuse, over multiple runs, without any significant loss in their reactivity and selectivity.[7] Among the strategies to recycle catalysts, the use of soluble supports to anchor chiral transition-metal complexes has received considerable attention in recent years.[1,5] The soluble support ensures that the catalyst is in the same phase as the reactants and reagents. Therefore, the reactivity and selectivity of the catalyst bound to the soluble support can be equal to that of its unsupported analogs. This is a significant advantage over catalysts anchored on insoluble supports.[4,9] Initial methods to recover catalyst for recycling were focused on precipitation and filtration of the supported catalyst by reducing the solubility of the support using an appropriate solvent[10] or by changing the temperature.[11] However, the precipitated catalyst often shows substantially reduced activity, enantioselectivity, and poor recyclability.[7] More recent methods have focused on retaining the catalyst in solution and separating it from the reactants and products. This offers a nondestructive method of catalyst recovery and circumvents common problems associated with solvent precipitation, such as co-precipitation of unwanted reaction by-products.[12] Methods that have aimed at achieving this include the use of liquid-liquid biphasic solvent systems[13-15] and pressurized-filtration using membranes with nanometer-sized pores.[16-21] We have been interested in using dialysis as a method recovering homogeneous polymer-supported catalysts for recycling.[22]

4.2 Soxhlet Dialysis:

Dialysis relies on a concentration gradient across a semi-permeable membrane and the rate of diffusion declines exponentially as the system approaches equilibrium. In order to re-establish the diffusion gradient, the bulk needs to be periodically replaced with fresh solvent.[23] Our initial attempts at using dialysis to recover the PEG-supported salen catalyst from the reaction products were tedious and required large amounts of solvent. A dialysis bag containing a solution of the substrates and polymer-supported catalyst in CH_2Cl_2 was placed in a beaker containing stirring CH_2Cl_2. Repeated replacement of the outer bulk solutions was required to maintain a concentration driven diffusion gradient. To address this issue, we developed a simple semi-continuous-flow dialysis set up using a soxhlet extractor, where the thimble was replaced with the dialysis bag (Fig. 4.1a). The dialyzed solution outside the membrane was continuously replaced with fresh solvent from the reflux, thereby maintaining the diffusion gradient. Of particular concern was the stability of dialysis membranes to organic solvents.[16,24] However, we found that commercially available Spectra/Por® regenerated cellulose membranes are stable to most organic solvents over extended periods of time.



Scheme 4.1: Asymmetric silylcyanation of benzaldehyde catalyzed by **1**.

(a)

(b)

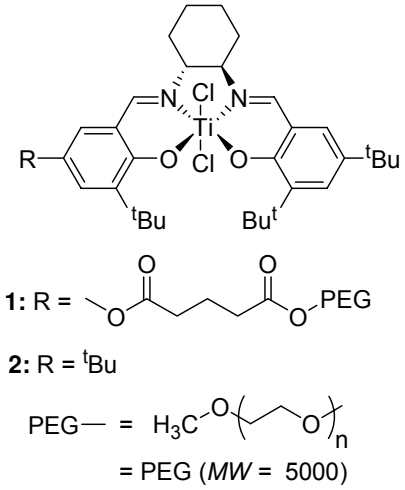


Figure 4.1: (a) "Soxhlet-Dialysis" apparatus. (b) PEG- and unsupported Ti-salen complex.

We chose asymmetric silylcyanation of benzaldehyde using a chiral titanium-salen complex as a model reaction (Scheme 4.1).[25] A solution of the PEG-supported salen ligand, in CH_2Cl_2, was treated with an equivalent amount of $TiCl_4$ and allowed to stir at room temperature for an hour to form the PEG-supported Ti-salen complex, **1**, insitu. This solution was treated with equimolar amounts of benzaldehyde and TMSCN (Figure 4.1b). The reaction proceeded with quantitative conversion of the aldehyde. The product, cyanohydrin trimethylsilyl ether, was obtained in 93:7 *er* after 24 h. This was similar to the enantioselectivity achieved with the unsupported catalyst, **2**.[13] The reaction was concentrated and placed into a dialysis tubing (MWCO = 3.5 kDa) with one end tied shut. A magnetic stir bar was then placed into the dialysis bag to prevent it from floating, and the open end of the tubing was tied shut with a string. The bag was then placed into the soxhlet chamber and CH_2Cl_2 was used as the recovery solvent. Dodecane was added to the solvent in the recovery flask as an internal standard in order to allow for

quantitative GC analysis of the product in the dialysate. The recovery flask was then placed in an oil bath and was heated to 60 ºC. The soxhlet chamber refilled every 20 minutes with fresh solvent from the reflux. After 38 h, 98% of the cyanohydrin trimethylsilyl ether was recovered. (Table 4.1).

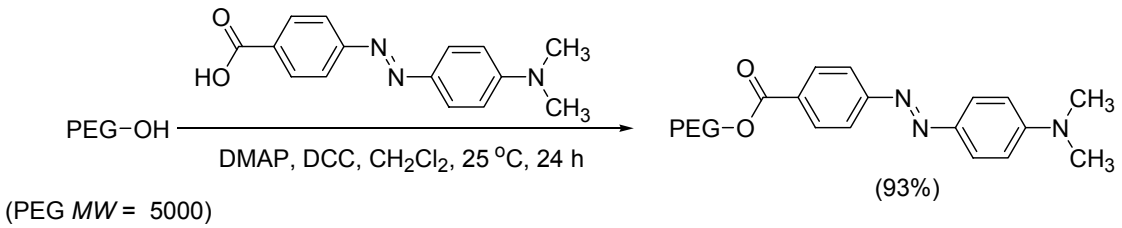
Table 4.1: Recovery of **1** and retention of *er* over 5 runs.

runs	*er*[a] (%)	conv.[b] (%)	recovery[c] (%)
1	93:7	>95	98
2	93:7	>95	99
3	93:7	>95	99
4	93:7	>95	98
5	93:7	>95	-

Soxhlet-Dialysis was carried out in CH_2Cl_2 at 60 ºC using a 3.5 kDa MWCO membrane. [a] Determined by chiral GC using a Cyclosil-B® column. [b] Determined by GC. [c] Determined by GC against a dodecane internal standard

After each cycle, the contents of the dialysis bag were poured into a round-bottomed flask and treated with fresh benzaldehyde and TMSCN under similar initial reaction conditions; *no fresh catalyst was added.* Complete conversion to the product was achieved in 24 h. The reaction solution was concentrated and subsequently subjected to another soxhlet-dialysis recovery cycle. The catalyst was recovered and reused for at least five runs without any loss in selectivity or reactivity (93:7 *er*, >99% conv.) (Table 4.1). It is noteworthy that attempts to recycle this catalyst by solvent precipitation were unsuccessful and a sticky residue, which was inactive towards subsequent reactions, was recovered. Even though the catalyst maintained its activity over multiple runs, it was still necessary to assess extent of its retention in the dialysis

bag. Therefore, we synthesized PEG attached to *p*-methyl-red (Scheme 4.2) as an analog of **1** that could be quantitatively analyzed.



Scheme 4.2: Synthesis of PEG-dye

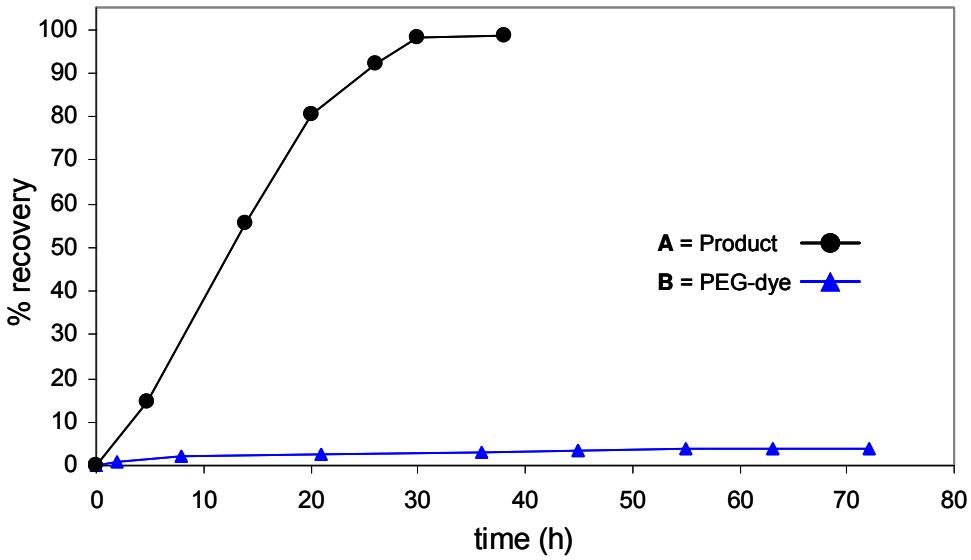


Figure 4.2: Retention of PEG-supported catalyst in dialysis bag; (A) Recovery of the product cyanohydrin TMS ether (B) Recovery of PEG-dye.

A solution of the PEG-dye in dichloromethane was subjected to a soxhlet-dialysis cycle under the same conditions used in the recovery of **1**. Samples of the dialysate were taken over a period of 38 h and analyzed by UV spectrometry. The PEG-dye

present in the dialysate was determined to be 3%, reflecting 97% retention in the dialysis bag. Even after 72 h, the amount of PEG-dye retained in the dialysis bag remained constant (Figure 4.2). We attributed the initial loss of PEG-dye to low molecular weight fractions of PEG present in the commercially available PEG. Once the low molecular weight species are lost, no further loss of the PEG-dye is observed. Based on the differences in the rates of diffusion between the small molecule product and the polymer-supported catalyst, we believe that the retention of the catalyst is much higher than 97%. This is further supported by the fact that no additional catalyst was required for subsequent runs.

4.3 Conclusion:

We have developed Soxhlet-Dialysis as a simple and straightforward method for the recovery of soluble polymer-supported catalysts *without any loss in its activity*. This method employs commercially available dialysis membranes and common laboratory apparatus. We believe that this methodology can be generally applied to recycling of soluble polymer-supported catalysts, without further modification of the original reaction conditions, as well as the purification of soluble polymers from low molecular weight impurities.

4.4 References:

(1) Bergbreiter, D. E. "Using Soluble Polymers to Recover Catalysts and Ligands" *Chem. Rev.* **2002**, *102*, 3345-3384.

(2) Bergbreiter, D. E.; Sung, S. D.; Li, J.; Oritz, D.; Hamilton, P. N. "Designing Polymers for Biphasic Liquid/Liquid Separations after Homogeneous Reactions" Org. Process Res. Dev. **2004**, *8*, 461-468.

(3) Cole-Hamilton, D. J. "Homogeneous Catalysis - New Approaches to Catalyst Separation, Recovery, and Recycling" *Science* **2003**, *299*, 1702-1706.

(4) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, Germany, 2000.

(5) Dickerson, T. J.; Reed, N. N.; Janda, K. D. "Soluble Polymers as Scaffolds for Recoverable Catalysts and Reagents" *Chem. Rev.* **2002**, *102*, 3325-3344.

(6) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. "Recoverable Catalysts for Asymmetric Organic Synthesis" *Chem. Rev.* **2002**, *102*, 3385-3466.

(7) Kragl, U.; Dwars, T. "The Development of New Methods for Recycling Catalysts," *Trends Biotechnol.* **2001**, *19*, 442-449.

(8) Chen, C.-Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. "Practical Asymmetric Synthesis of a Potent Cathepsin K Inhibitor. Efficient Palladium Removal Following Suzuki Coupling" *J. Org. Chem.* **2003**, *68*, 2633.

(9) Leadbeater, N. E.; Marco, M. "Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis" *Chem. Rev.* **2002**, *102*, 3217-3274.

(10) Wentworth Jr., P.; Janda, K. D. "Liquid-phase Chemisry: Recent Advances in Soluble Polymer-Supported Catalysts, Reagents and Synthesis" *Chem. Commun.* **1999**, 1917-1924.

(11) Mariagnanam, V. M.; Zhang, L.; Bergbreiter, D. E. "Polymer Ligands That Can Regulate Reaction Temperature in Smart Catalysts" *Adv. Mater.* **1995**, *7*, 69-71.

(12) Jayaprakash, D.; Sasai, H. "Synthesis and Catalytic Applications of Soluble Polymer-Supported BINOL" *Tetrahedron*: *Asymmetry.* **2001**, *12*, 2589-2595.

(13) Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C. M.; Frels, J. D. "Using Soluble Polymers in Latent Biphasic Systems" *J. Am. Chem. Soc.* **2003**, *125*, 6254-6260.

(14) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. "Nonpolar Polymers for Metal Sequestration and Ligand and Catalyst Recovery in Thermomorphic Systems" *J. Am. Chem. Soc.* **2001**, *123*, 11105-11106.

(15) Bergbreiter, D. E.; Li, C. M. "Poly(4-tert-butylstyrene) as a Soluble Polymer Support in Homogeneous Catalysis" *Org. Lett.* **2003**, *5*, 2445-2447.

(16) Dijkstra, H. P.; Kruithof, C. A.; Ronde, N.; van de Coevering, R.; Ramon, D. J.; Vogt, D.; van Klink, G. P. M.; van Koten, G. "Shape-persistent nanosize organometallic complexes: Synthesis and application in a nanofiltration membrane reactor" *J. Org. Chem.* **2003**, *68*, 675-685.

(17) Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. "The Use of Ultra- and Nanofiltration Techniques in Homogeneous Catalyst Recycling" *Acc. Chem. Res.* **2002**, *35*, 798-810.

(18) Datta, A.; Ebert, K.; Plenio, H. "Nanofiltration for Homogeneous Catalysis Separation: Soluble Polymer-Supported Palladium Catalyst for Heck, Sonogashira and Suzuki Coupling of Aryl Halides" *Organometallics* **2003**, *22*, 4685-4691.

(19) Nair, D.; Luthra, S. S.; Scarpello, J. T.; White, L. S.; dos Santos, L. M. F.; Livingston, A. G. "Homogenous Catalyst Separation and Re-Use Through Nanofiltration of Organic Solvents" *Desalination* **2002**, *147*, 301-306.

(20) Moskvin, L. N.; Nikitiana, T. G. "Membrane Methods of Substance Separation in Analytical Chemistry" *J. Anal. Chem.* **2004**, *59*, 2-16.

(21) Vankelecom, I. F. J.; Tas, D.; Parton, R. F.; Van de Vyyer, V.; Jacobs, P. A. "Chiral Catalytic Membranes" *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 1346.

(22) Anyanwu, U. K.; Venkataraman, D. "Effect of Spacers on the Activity of Soluble Polymer-Supported Catalysts for the Asymmetric Addition of Diethylzinc to Aldehydes" *Tetrahedron Lett.* **2003**, *44*, 6445-6448.

(23) Hess, P.; Wells, D. E. "Evaluation of Dialysis as a Technique for the Removal of Lipids Prior to the GC Determination of *Ortho*- and Non-*ortho*-Chlorobiphenyls, using C-14-Labelled Congeners" *Analyst* **2001**, *126*, 829-834.

(24) Wolfson, A.; Janssen, K. B.; Vankelecom, I. F. J.; Geresh, S.; Gottlieb, S.; Herskowitz, M. "Aqueous Enantioselective Hydrogenation of Methyl-2-acetamidoacrylate with Rh–MeDuPHOS Occluded in PDMS" *Chem. Commun.* **2002**, *4*, 388.

(25) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. "The Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (salen) Titanium Complexes" *J. Am. Chem. Soc.* **1999**, *121*, 3968-3973.

CHAPTER 5

NANOPOROUS THIN FILMS FROM A CLEAVABLE DIBLOCK CO-POLYMER

5.1 Introduction:

The preparation of material composed of well-defined nanoscale structures has been the focus of extensive research in recent years.[1] These materials show promise in a broad range of applications such as high-density data storage, thermoelectric cooling devices, nano-reactors and molecular separation membranes. As such, several techniques have emerged, which attempt to generate these nanoscopic arrays with well-defined size and periodicity.[1] Self-organization is a powerful route to the "bottom-up" approach to the fabrication of nanostructures.[2-5] It has been established that strongly immiscible amphilic diblock copolymers, upon annealing, will phase separate and self-assemble into periodic nanoscale domain structures. The morphology of these structures depends on the molecular weight, segment size (chain length) and strength of interaction of the polymer blocks, represented by the Flory-Huggins interaction parameter, χ.[2,5] The morphology also depends on the composition of the diblock copolymer, given by the volume fraction of one of the constituent blocks. As confirmed by theory[6] and experiment[5], the following domain structures have been shown to be stable: lamellar, hexagonal-packed cylinder, body-centered cubic, close-packed spherical and bicontinuous cubic gyroid structures.

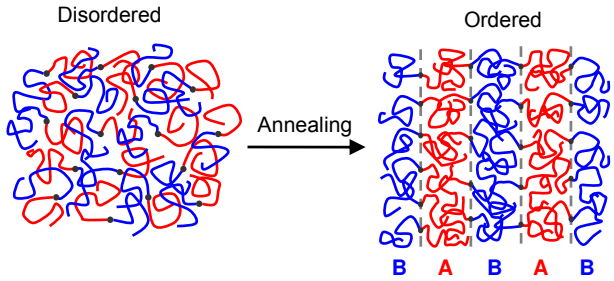


Figure 5.1: Microphase ordering (lamellae) a of symmetrical diblock copolymer

In thin films, in addition to composition and molecular weight, the domain structure is also a function of the surface energy of the blocks and geometrical constraints introduced by confinement into a thin film. Symmetric block copolymers form lamellae structure that can orient either parallel or perpendicular to the substrate. A number of possible arrangements of the lamellae are possible, depending on the surface energies of the blocks and that of the substrate, and whether the film is confined at one or both surfaces. In the case that a different block segregates to the substrate and to the polymer–air interface, wetting is asymmetric and a uniform film has a thickness (n + 1/2)d, where d is the domain spacing. If the initial film thickness is not equal to (n + 1/2)d, then islands or holes (quantized steps of height d) form to conserve the volume. In the case of symmetric wetting, a uniform film has thickness nd. Asymmetric block copolymers adopt hexagonal or cubic-packed spherical morphologies in the bulk; they form parallel cylinders (stripes) or arrays of dots (spheres or perpendicular cylinders) in two dimensions. More complex exotic morphologies such as gyroid structures and helices around cylinders have also been observed.[7,8]

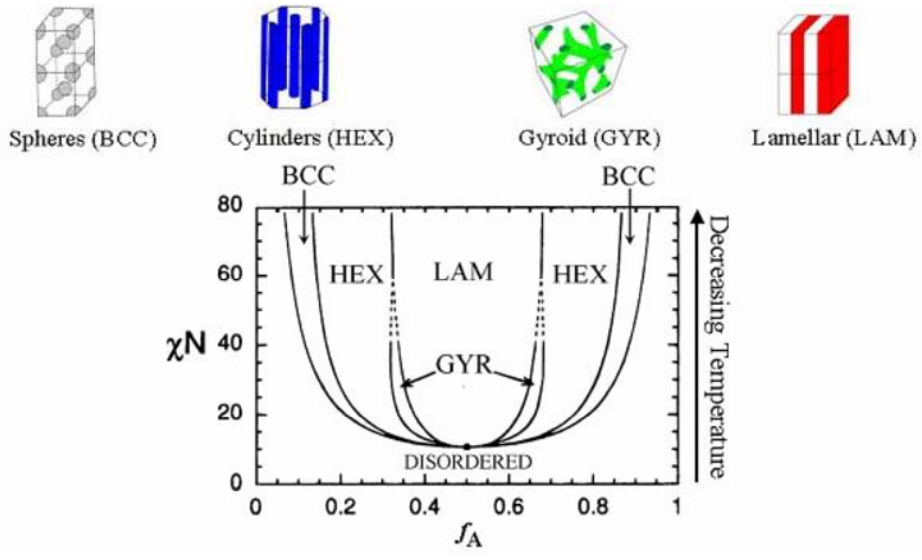


Figure 5.2: Phase diagram for microphase separated diblock copolymers (Source: www.princeton.edu/ ~polymer/phasedia.JPG.html)

Block co-polymer films are typically prepared by the spin coating technique, where drops of a solution of the polymer in a volatile organic solvent are deposited on a spinning solid substrate (usually silicon wafers, due to their uniform flatness). The polymer film spreads by centrifugal forces as the volatile solvent is rapidly driven off. With care, the method can give films with a low surface roughness over areas of square millimeters. The film thickness can be controlled through the spin speed, the concentration of the block copolymer solution or the volatility of the solvent, which also influences the surface roughness.[9] Dip-coating is another reliable method for fabricating uniform thin films.[10] Whatever the deposition technique, if the surface energy of the block copolymer is much greater than that of the substrate, then dewetting will occur. The mechanism of this process has been investigated.[11] However, by appropriate choice of substrate the problem of dewetting can usually be circumvented.

For many applications where regular periodic arrays are required, it will be necessary to generate alignment of nanostructures, normal to the substrate surface, in block copolymer films. This can be done in several ways; through the control of solvent evaporation, using electric fields or chemical or mechanical patterning. It has recently been suggested that a necessary condition to produce perpendicular cylinders through solvent evaporation is that a good solvent for both blocks be used, and that only one block is below its glass transition temperature at room temperature. It was noted that as the solvent evaporates, a concentration gradient front propagates through the film and the system passes through a disorder–order transition.[12] The structure formed can be trapped if one block goes through its glass transition. Perpendicular alignment of lamellae or cylinders has been achieved using a substrate that is coated with a random copolymer containing an appropriate composition of the corresponding diblocks. The substrate has a surface energy that is neutral with respect to each component. Russell and coworkers developed this approach using end-grafted PS/PMMA random block

copolymer layers.[13,14] Cylindrical domains of PS–*b*–PMMA formed the basis of an array of long and aligned conducting domains with typical size in the range of 100 nm.[15-17]

The re-orientation of block copolymer nanostructures using an electric field is possible if the field is high enough for a given difference in dielectric constant between blocks. Morkved *et al* first showed that PMMA cylinders in a PS matrix could be oriented parallel to the substrate using an in-plane field, applied in the molten state.[18] Using arrays of electrodes it is possible to obtain alignment over large areas— up to 2 cm^2.[19] Orientation of cylinders perpendicular to the substrate has also been achieved, by applying a field across electrodes sandwiching a block copolymer film.[20] A technique which uses applied electric fields to a polymer film confined by one smooth and one topographically patterned electrode has also been explored. The field creates instability in the polymer film which replicates the pattern on the electrode.[5]

5.2 Nanoporous Material From Diblock Co-polymers:

Because they can self-assemble into periodic structures in one, two and three dimensions, diblock copolymers are interesting templates for the design of photonic material.[21] The inherently low dielectric contrast between the polymeric domains can be overcome by selective doping and/or removal of one of the component. Another prime constraint is the requirement for telecommunications applications of a domain size of about 250 nm (to control near-IR radiation with a wavelength of 1.55 μm).[22] For successful applications, both long- and short-range order of the materials must be achieved.[23] It has been demonstrated that structured nanoporous arrays can be easily fabricated from thin-film templates made from PS–*b*–PMMA copolymers Russell and co-workers have shown that using the appropriate volume fraction (PS/PMMA ratio of about 70:30), the copolymer self-assembles into a morphology consisting of PMMA cylinders hexagonally packed in a PS matrix.[1] Orientation of the cylinders normal to the surface in

thin films can be realized by application of an external electric field[24] or control of the interfacial interactions.[14,25,26] The removal of PMMA, by deep UV light degradation, afford nanoporous cylindrical channels which serve as templates for the design of nanowires.[1] However, it was observed that these nanoscopic arrays segregated into domains which possessed short-range order and lacked long-range order (there domains within which the distances between pores were regular, but between which they were irregular)

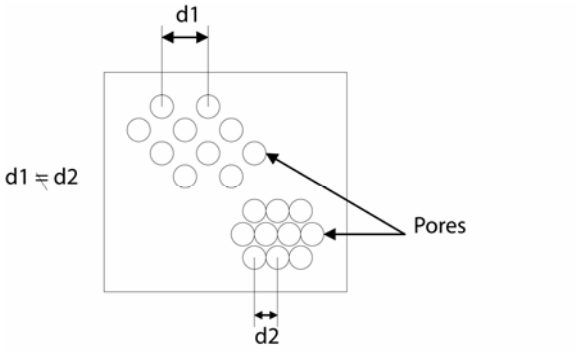


Figure 5.3: Lack of long range order in nanoporous PS matrix.

It was learned that similar material prepared from PS–*b*–PEG diblock copolymers showed both long- and short-range order.[24] However, a major problem is that PEG is not photo-degradable under UV light, and unlike PMMA, the PEG cylinders can not be selectively removed to afford the nanoporous PS matrix. Hence, it is highly desirable to develop a method to remove the PEG so that nanoporous structures with good long range order can be achieved. To solve this problem, we sought the approach of incorporating a cleavable linker into the PS–*b*–PEG backbone. This would facilitate the requisite cleavage of the PEG block after microphase separation to give the nanoporous PS matrix. Incorporating a cleavable linker which had a vinyl functional group, onto the terminus of the PEG chain, followed by subsequent polymerization of styrene off the

PEG chain would give the cleavable PS–*b*–PEG diblock copolymer. Since PEG is water soluble, the PEG block could be extracted with water and removed.

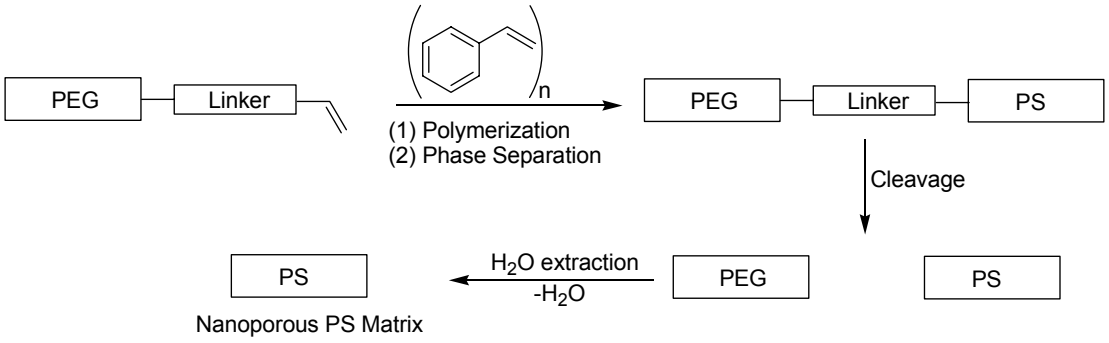
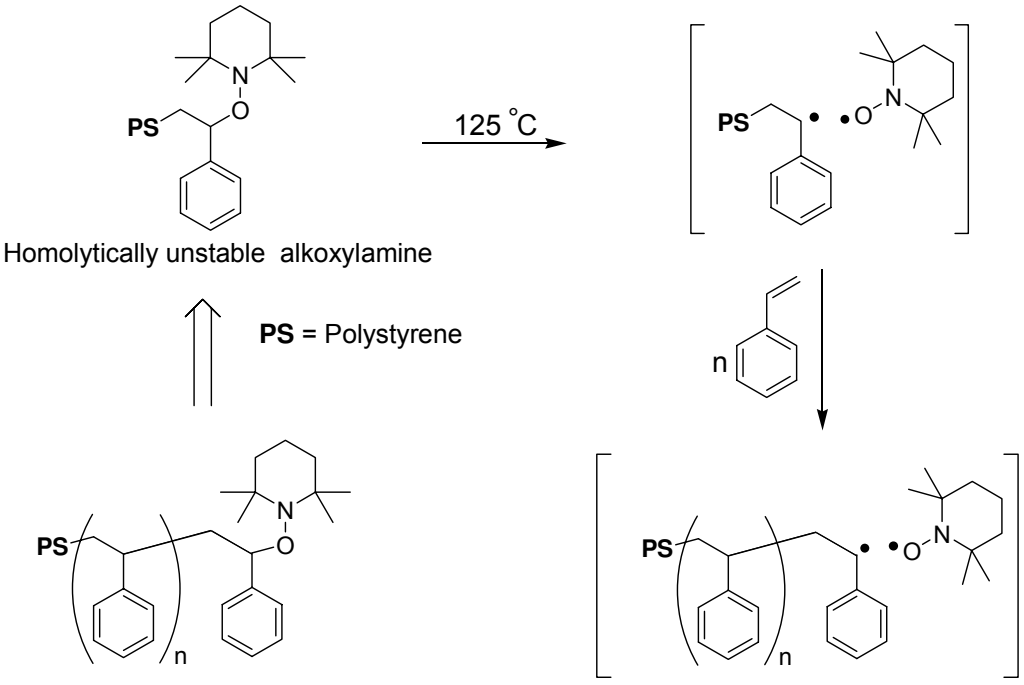


Figure 5.4: Approach to synthesize nanoporous polymer thin films from PS-*b*-PEG.

5.3 "Living" Free Radical Polymerization:

Strategies for controlling polymeric structure and macromolecular architecture are becoming an increasingly important aspect of polymer and materials science due to the continuing desire to prepare materials with new and/or enhanced physical properties.[27,28] Accurately controlled molecular weight; defined chain ends and low polydispersity are some of the prerequisites of a well-defined polymeric structure. One way of achieving this for linear vinyl polymers is through controlled "living" polymerization employing anionic or cationic polymerization.[29-31] Unfortunately, these techniques are synthetically demanding; they are extremely sensitive to water and oxygen, and require ultra-pure reagents and solvents. Moreover, the incompatibility of the carbanion or carbocation growing chain ends with many functional groups becomes an issue. To over-come these difficulties, we decided to explore the synthesis of well-defined PS-*b*-PEG diblock copolymers using nitroxide mediated "Living" Free Radical Polymerization (LFRP).[32-34]

The concept of using stable free radicals, such as nitroxides,[35] to reversibly react with the growing polymer radical chain end can be traced back to the pioneering work of Rizzardo and Moad.[36] They demonstrated that at low temperature (40°C–60°C) typically associated with standard free radical polymerizations, nitroxides such as TEMPO[37,38] reacted at near diffusion controlled rates with carbon–centered free radicals generated from the addition of initiating radicals to vinyl monomers. Georges further refined this technique to provide a basic model for all subsequent work in the area of LFRP.[39]



Scheme 5.1: TEMPO mediated "Living" Free Radical Polymerization.

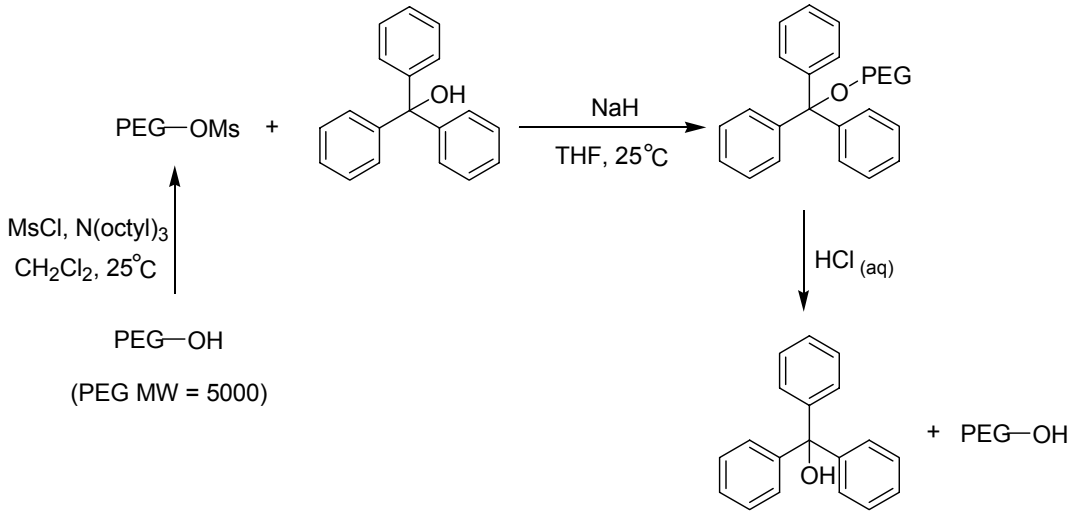
The key feature of nitroxide-mediated LFRP is that the carbon–oxygen bond of the dormant or inactive alkoxyamine is homolytically unstable and undergoes thermal cleavage to give a stable nitroxide and the polymeric radical. The nitroxide free radical does not initiate the growth of any extra polymer chains, but it does react at near-

diffusion-controlled rates with carbon-centered free radicals. In the absence of other reactions leading to initiation of new polymer chains, the concentration of the reactive chain ends is extremely low, minimizing irreversible termination reactions, such as combination or disproportionation. The polymeric radical can then undergo chain extension with monomer to yield a similar polymeric radical in which the degree of polymerization has increased. Recombination of the polymeric radical with the nitroxide then gives the dormant, unreactive alkoxylamine, and the cycle of homolysis–monomer addition–recombination can be repeated (Scheme 5.1). Typically LFRP's are carried out under non-demanding reaction conditions, and a mixture of the unstable alkoxylamine and styrene are added to a reaction flask and heated at 125 °C under a nitrogen atmosphere. The reaction set-up is very simple and rigorous purification of reagents is unnecessary. By varying the molar ratio of monomer to initiator in the reaction, a near linear relationship is observed between obtained experimental molecular weights and calculated theoretical molecular weights.[32] Compared to traditional free radical polymerization processes where the theoretically limiting polydispersity is 1.5 and normal experimental values are ca. 2.0, LFRP processes can approach polydispersity values of 1.03–1.05, which are typically obtained for well-behaved living anionic systems.

5.4 Synthesis of a PEG–Supported Initiator for LFRP of Styrene:

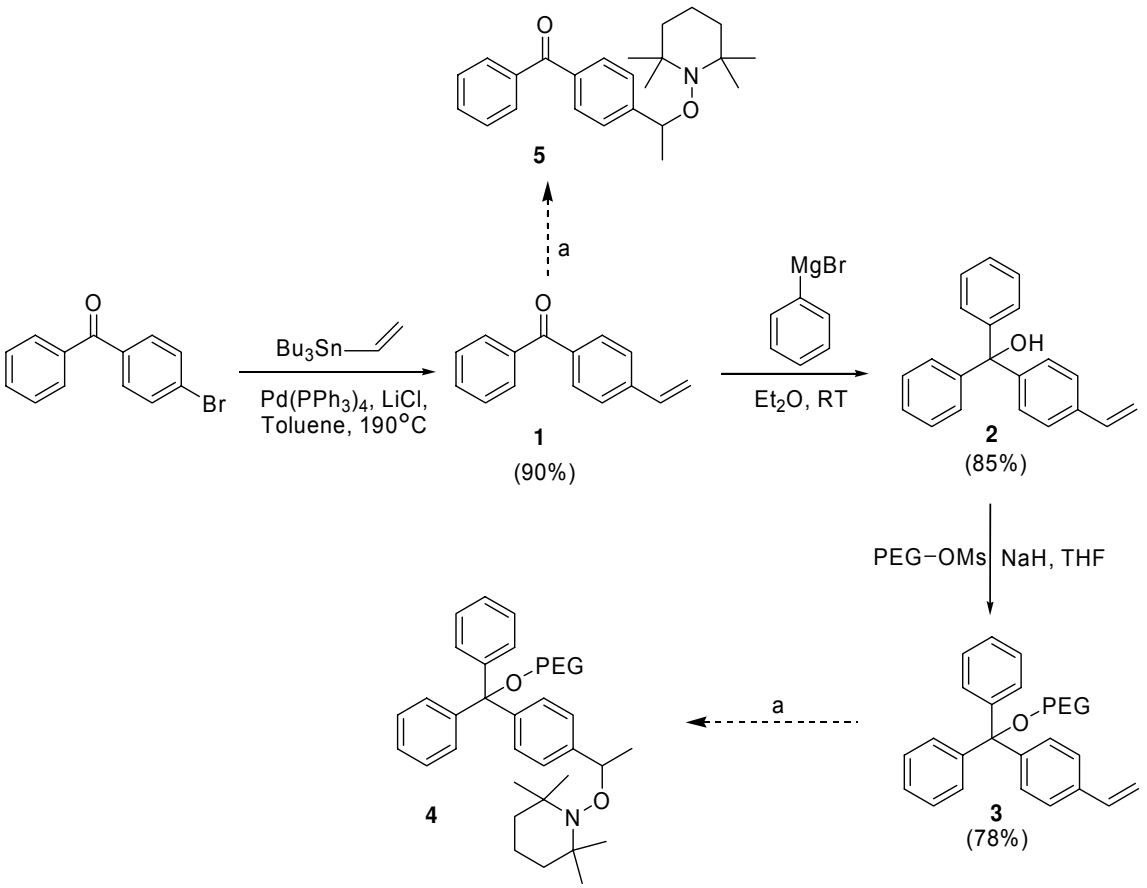
In the design of the PS–*b*–PEG diblock copolymer, the requirements for the cleavable linker were as follows: (1) The linker had to be stable towards the polymerization reaction conditions, (2) It should also survive the annealing conditions necessary to induce microphase separation, and (3) It should be cleaved quantitatively and easily. Following a search through the literature, we decided that a triphenylmethyl (trityl) group was the appropriate linker. The trityl ether bond could be easily cleaved under mild acidic conditions, with either dilute aqueous HCl or HCl vapor. This was

confirmed by a preliminary experiment where an aqueous solution of PEG–trityl ether was cleaved in the presence of 2 N HCl, after 15 minutes.



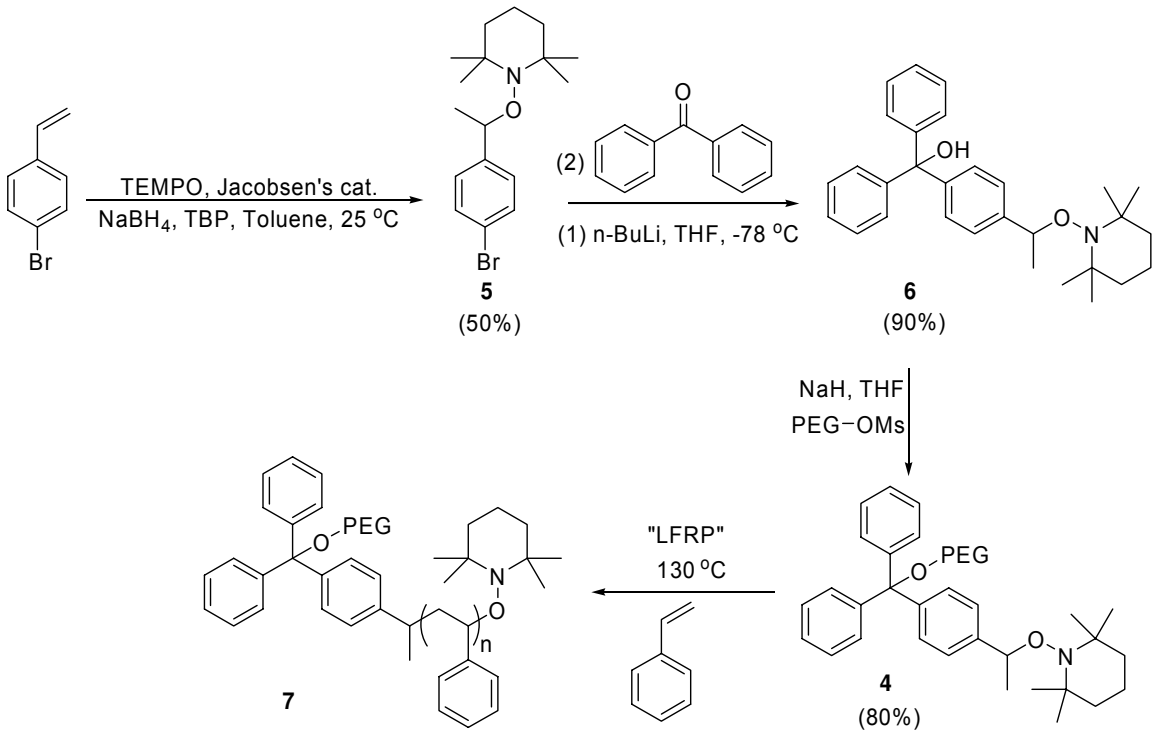
Scheme 5.2: The acid cleavage of PEG–trityl ether bond.

Our initial approach to the synthesis of the 4-vinyltrityl-PEG (PEG *MW* = 2000) ether involved the vinylation of 4-bromobenzophenone with a tributylvinyl tin reagent, the employing the Stille protocol.[40] Grignard addition of phenyl magnesium bromide to the product 4-vinyl benzophenone, **1**, gave the vinyl trityl alcohol, **2**, in an 85% yield. Subsequent etherification of **2** with PEG mesylate afforded the PEG trityl ether, **3**, in 78% yield. The synthesis of the trityl TEMPO alkoxylamine, **4**, using a protocol developed by Dao,[41] was unsuccessful. Attempts to synthesize the TEMPO adduct, **5**, from **1** was also unsuccessful. Possible single electron transfer processes would lead to the generation of a ketyl radical which is likely to be trapped by the TEMPO radical, thus impeding the reaction.



Scheme 5.3: Attempted synthesis of the PEG trityl TEMPO alkoxylamine, 4; (a) TEMPO, Jacobsen's catalyst, TBP, $NaBH_4$, toluene, 25 °C, 24 h.

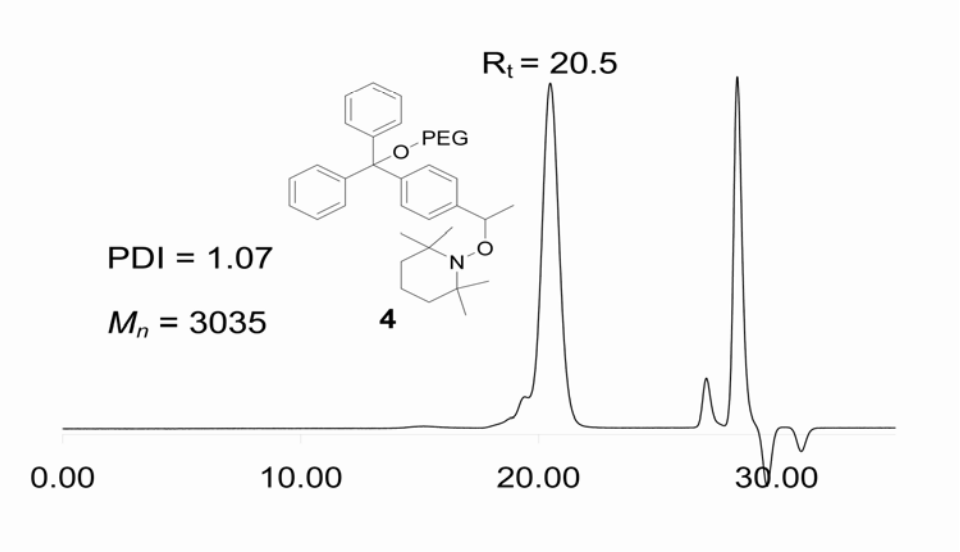
Faced with this problem, we devised an alternative synthetic route to the PEG-supported trityl TEMPO initiator, **4**. The TEMPO adduct, **5** (1-[1-(4-Bromo-phenyl)-ethoxy]-2,2,6,6-tetramethyl-piperidine), was synthesized form commercially available 4-bromo styrene in 50% yield. Lithium–halogen exchange of **5** in the presence on *n*-BuLi, followed by addition of benzophenone, afforded the triphenyl methanol TEMPO adduct, **6**, in 90% yield. Etherification of **6** with PEG, in refluxing THF at 70 °C, gave **4** in 80% yield. The fact that the etherification reaction could be carried out in refluxing THF is indicative of the stability of the TEMPO alkoxylamine adduct under 125 °C.



Scheme 5.4: Synthesis of PS–*b*–PEG diblock copolymer by LFRP.

The synthesis of well defined PS–*b*–PEG diblock copolymers could now be achieved through LFRP of **4**. In a preliminary polymerization reaction, a solution of **4** (Mn = 3035; PDI = 1.07) (Figure 5.5 a) and styrene (50 molar equivalents) in degassed toluene was heated to 130 °C under a nitrogen atmosphere. After 24 h, precipitation of the polymeric solution from methanol gave a white solid which was characterized by GPC (Mn = 8433; PDI = 1.08) (Figure 5.5 b). These narrow MW distributions were indicative of a “living” polymerization process.

(a)



(b)

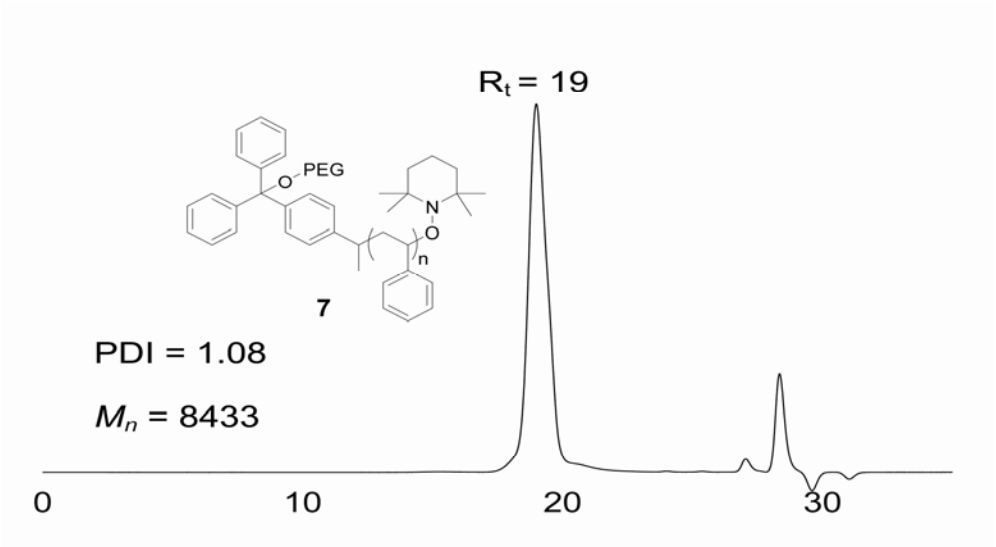


Figure 5.5: GPC data: (a) PEG-supported trityl TEMPO initiator, and (b) PS-*b*-PEG.

Preliminary results also indicate that the cleavage of **7** could be achieved by simply placing it in an open vial which was then placed in a chamber containing HCl vapors. After 1 h, the sample of **7** was removed and GPC data revealed cleavage of the PS-*b*-PEG (PS Mn = 6389; PEG Mn = 2464) (Figure 5.6).

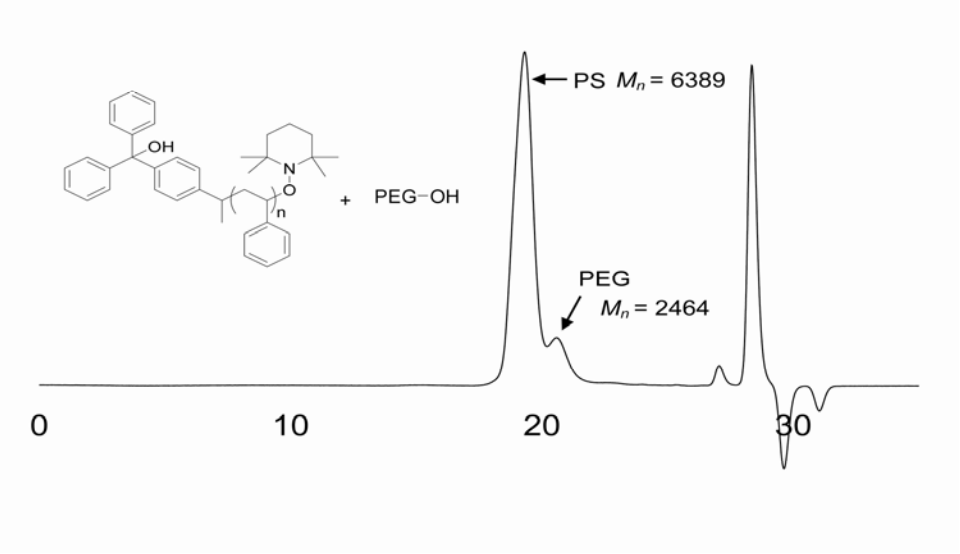


Figure 5.6: GPC data after the cleavage of **7** with HCl.

5.5 Conclusion:

We have designed and synthesized a PS-*b*-PEG diblock copolymer bearing a cleavable linker. Nitroxide mediated LRFP was used for the controlled polymerization of styrene from a PEG-supported trityl TEMPO initiator, and a narrow molecular weight distribution (PDI = 1.12) was indicative of a LFRP process. It was demonstrated that acid cleavage of the diblock was facile and this was confirmed by GPC analysis. Spin coating of thin films on an appropriate substrate, followed by annealing, should give microphase separated domain structure which will be used for the fabrication of nanoporous thin films.

5.6 References:

(1) Shin, K.; Leach, K. A.; Goldbach, J. T.; Kim, D. H.; Jho, J. Y.; Tuominen, M.; Hawker, C. J.; Russell, T. P. "A simple route to metal nanodots and nanoporous metal films" *Nano Lett.* **2002**, *2*, 933-936.

(2) Bates, F. S.; Fredrickson, G. H. "Block Copolymer Thermodynamics - Theory and Experiment" *Annu. Rev. Phys. Chem.* **1990**, *41*, 525-557.

(3) Hadjichristidis, N.; Pispas, S.; Floudas, G. *Block Copolymers. Synthetic Strategies, Physical Properties and Applications* New York, 2003.

(4) Hamley, I. W. *Developments in Block Copolymer Science and Technology*; Wiley: Chichester, 2003.

(5) Hamley, I. W. *The Physics of Block Copolymers*; Oxford Press: Oxford, 1998.

(6) Thompson, R. B.; Ginzburg, V. V.; Matsen, M. W.; Balazs, A. C. "Predicting the mesophases of copolymer-nanoparticle composites" *Science* **2001**, *292*, 2469-2472.

(7) Elbs, H.; Drummer, C.; Abetz, V.; Krausch, G. "Thin film morphologies of ABC triblock copolymers prepared from solution" *Macromolecules* **2002**, *35*, 5570-5577.

(8) Krausch, G.; Magerle, R. "Nanostructured thin films via self-assembly of block copolymers" *Adv. Mater.* **2002**, *14*, 1579.

(9) Strawhecker, K. E.; Kumar, S. K.; Douglas, J. F.; Karim, A. "The critical role of solvent evaporation on the roughness of spin-cast polymer films" *Macromolecules* **2001**, *34*, 4669-4672.

(10) Boker, A.; Muller, A. H. E.; Krausch, G. "Nanoscopic surface patterns from functional ABC triblock copolymers" *Macromolecules* **2001**, *34*, 7477-7488.

(11) Hamley, I. W.; Hiscutt, E. L.; Yang, Y. W.; Booth, C. "Dewetting of thin block copolymer films" *J. Colloid Interface Sci.* **1999**, *209*, 255-260.

(12) Jeong, U. Y.; Kim, H. C.; Rodriguez, R. L.; Tsai, I. Y.; Stafford, C. M.; Kim, J. K.; Hawker, C. J.; Russell, T. P. "Asymmetric block copolymers homopolymers: Routes to multiple length scale nanostructures" *Adv. Mater.* **2002**, *14*, 274.

(13) Kellogg, G. J.; Walton, D. G.; Mayes, A. M.; Lambooy, P.; Russell, T. P.; Gallagher, P. D.; Satija, S. K. "Observed surface energy effects in confined diblock copolymers" *Phys. Rev. Lett.* **1996**, *76*, 2503-2506.

(14) Mansky, P.; Liu, Y.; Huang, E.; Russell, T. P.; Hawker, C. "Controlling polymer-surface interactions with random copolymer brushes" *Science* **1997**, *275*, 1458-1460.

(15) Xu, T.; Kim, H. C.; DeRouchey, J.; Seney, C.; Levesque, C.; Martin, P.; Stafford, C. M.; Russell, T. P. "The influence of molecular weight on nanoporous polymer films" *Polymer* **2001**, *42*, 9091-9095.

(16) Zehner, R. W.; Sita, L. R. "Electroless deposition of nanoscale copper patterns via microphase-separated diblock copolymer templated self-assembly" *Langmuir* **1999**, *15*, 6139-6141.

(17) Guarini, K. W.; Black, C. T.; Milkove, K. R.; Sandstrom, R. L. "Nanoscale patterning using self-assembled polymers for semiconductor applications" *J. Vac. Sci. Technol. B* **2001**, *19*, 2784-2788.

(18) Morkved, T. L.; Lu, M.; Urbas, A. M.; Ehrichs, E. E.; Jaeger, H. M.; Mansky, P.; Russell, T. P. "Local control of microdomain orientation in diblock copolymer thin films with electric fields" *Science* **1996**, *273*, 931-933.

(19) Mansky, P.; DeRouchey, J.; Russell, T. P.; Mays, J.; Pitsikalis, M.; Morkved, T.; Jaeger, H. "Large-area domain alignment in block copolymer thin films using electric fields" *Macromolecules* **1998**, *31*, 4399-4401.

(20) Thurn-Albrecht, T.; Schotter, J.; Kastle, C. A.; Emley, N.; Shibauchi, T.; Krusin-Elbaum, L.; Guarini, K.; Black, C. T.; Tuominen, M. T.; Russell, T. P. "Ultrahigh-density nanowire arrays grown in self-assembled diblock copolymer templates" *Science* **2000**, *290*, 2126-2129.

(21) Hamley, I. W. "Nanostructure fabrication using block copolymers" *Nanotechnology* **2003**, *14*, R39-R54.

(22) Edrington, A. C.; Urbas, A. M.; DeRege, P.; Chen, C. X.; Swager, T. M.; Hadjichristidis, N.; Xenidou, M.; Fetters, L. J.; Joannopoulos, J. D.; Fink, Y.; Thomas, E. L. "Polymer-based photonic crystals" *Adv. Mater.* **2001**, *13*, 421-425.

(23) Fink, Y.; Urbas, A. M.; Bawendi, M. G.; Joannopoulos, J. D.; Thomas, E. L. "Block copolymers as photonic bandgap materials" *J. Lightwave Technol.* **1999**, *17*, 1963-1969.

(24) Lin, Z. Q.; Kim, D. H.; Wu, X. D.; Boosahda, L.; Stone, D.; LaRose, L.; Russell, T. P. "A rapid route to arrays of nanostructures in thin films" *Adv. Mater.* **2002**, *14*, 1373-1376.

(25) Mansky, P.; Russell, T. P.; Hawker, C. J.; Pitsikalis, M.; Mays, J. "Ordered diblock copolymer films on random copolymer brushes," *Macromolecules* **1997**, *30*, 6810-6813.

(26) Huang, E.; Pruzinsky, S.; Russell, T. P.; Mays, J.; Hawker, C. J. "Neutrality conditions for block copolymer systems on random copolymer brush surfaces" *Macromolecules* **1999**, *32*, 5299-5303.

(27) Webster, O. W. "Living Polymerization Methods" *Science* **1991**, *251*, 887-893.

(28) Frechet, J. M. J. "Functional Polymers and Dendrimers - Reactivity, Molecular Architecture, and Interfacial Energy" *Science* **1994**, *263*, 1710-1715.

(29) Fukui, H.; Sawamoto, M.; Higashimura, T. "Multifunctional Coupling Agents for Living Cationic Polymerization .2. Bifunctional Silyl Enol Ethers for Living Poly(Vinyl Ethers)" *Macromolecules* **1993**, *26*, 7315-7321.

(30) Sogah, D. Y.; Hertler, W. R.; Webster, O. W.; Cohen, G. M. "Group Transfer Polymerization - Polymerization of Acrylic-Monomers" *Macromolecules* **1987**, *20*, 1473-1488.

(31) Quirk, R. P.; Lynch, T. "Anionic Synthesis of Primary Amine-Functionalized Polystyrenes Using 1- 4- N,N-Bis(Trimethylsilyl)Amino Phenyl -1-Phenylethylene" *Macromolecules* **1993**, *26*, 1206-1212.

(32) Hawker, C. J. ""Living" free radical polymerization: A unique technique for the preparation of controlled macromolecular architectures" *Acc. Chem. Res.* **1997**, *30*, 373-382.

(33) Hawker, C. J.; Mecerreyes, D.; Elce, E.; Dao, J. L.; Hedrick, J. L.; Barakat, I.; Dubois, P.; Jerome, R.; Volksen, W. ""Living" free radical polymerization of macromonomers: Preparation of well defined graft copolymers" *Macromol. Chem. Phys.* **1997**, *198*, 155-166.

(34) Malmstrom, E. E.; Hawker, C. J. "Macromolecular engineering via 'living' free radical polymerizations" *Macromol. Chem. Phys.* **1998**, *199*, 923-935.

(35) Hawker, C. J.; Bosman, A. W.; Harth, E. "New polymer synthesis by nitroxide mediated living radical polymerizations" *Chem. Rev.* **2001**, *101*, 3661-3688.

(36) Moad, G.; Rizzardo, E.; Solomon, D. H. "Selectivity of the Reaction of Free-Radicals with Styrene" *Macromolecules* **1982**, *15*, 909-914.

(37) Yamamoto, K.; Nakazono, M.; Miwa, Y.; Hara, S.; Sakaguchi, M.; Shimada, S. ""Living" radical graft polymerization of styrene to polyethylene with 2,2,6,6-tetramethylpiperidine-1-oxyl" *Polymer Journal* **2001**, *33*, 862-867.

(38) Miwa, Y.; Yamamoto, K.; Sakaguchi, M.; Shimada, S. "Well-defined polystyrene grafted to polypropylene backbone by "living" radical polymerization with TEMPO" *Macromolecules* **2001**, *34*, 2089-2094.

(39) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. "Narrow Molecular-Weight Resins by a Free-Radical Polymerization Process" *Macromolecules* **1993**, *26*, 2987-2988.

(40) Sheffy, F. K.; Stille, J. K. "Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotins" *J. Am. Chem. Soc.* **1983**, *105*, 7173-7175.

(41) Dao, J.; Benoit, D.; Hawker, C. J. "A versatile and efficient synthesis of alkoxyamine LFR initiators via manganese based asymmetric epoxidation catalysts" *J. Polym. Sci. Part A: Polym. Chem.* **1998**, *36*, 2161-2167.

CHAPTER 6

EXPERIMENTAL

6.1 Synthesis of PEG-Supported Chiral Zn-Salen Catalyst for the Asymmetric Addition of Et_2Zn to Aldehydes:

Unless otherwise noted, all of the reactions reported herein were conducted under an inert atmosphere of N_2 in oven-dried glassware. All reagents were purchased from Acros and Aldrich and used without further purification. Et_2Zn was purchased from Aldrich as a 1M solution is hexanes. Toluene and THF were distilled from Na/benzophenone ketyl and CH_2Cl_2 was dried over 3 Å molecular sieves, distilled and stored under inert atmosphere. Extra dry DMF (dried with molecular sieves; water < 50 ppm) was purchased from Acros Organics. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. Reported yields refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^1H NMR, ^{13}C NMR. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were reported in ppm downfield from TMS as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; br, broad; q, quintet and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). IR spectra of a KBr pellet were carried out on MIDAC M-2000 FT-IR using GRAMS/32 software. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski.

Enantiomeric ratios (*er*) were determined by GC using a Hewlett-Packard 6850 gas chromatograph on a Cyclosil-B^{TM} capillary column purchased from J&W Scientific, Folsom, CA. Correction factors were determined using racemic acetate esters which were prepared by treating the corresponding alcohols with molar equivalents of DMAP/acetylchloride. In all cases, baseline separation of enantiomers was observed. All

gas chromatography (GC) operating conditions were set as follows: Carrier gas: H_2. Detector: temperature, 300 ºC; flow, 40 mL/min. Inlet: temperature, 300 ºC, 10.31 psi; 44.6 mL/min. Retention times for the acetate ester derivatives of the alcohol products are listed below:

1-phenyl-1-propyl acetate: t_R = 8.61 min, t_S = 8.67 min.

1-*m*-tolyl-propyl acetate.: t_R = 9.29 min, t_S = 9.33 min.

1-*p*-chlorophenyl-propyl acetate: t_R = 10.41 min, t_S = 10.45 min.

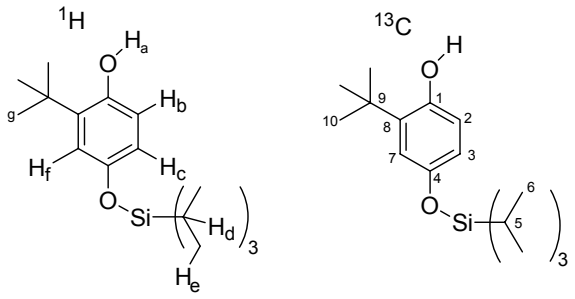
1-*p*-fluorophenyl-1-propyl acetate: t_R = 8.75 min, t_S = 8.83 min.

1-*p*-tolyl-1-propyl acetate: t_R = 9.52 min, t_S = 9.55 min.

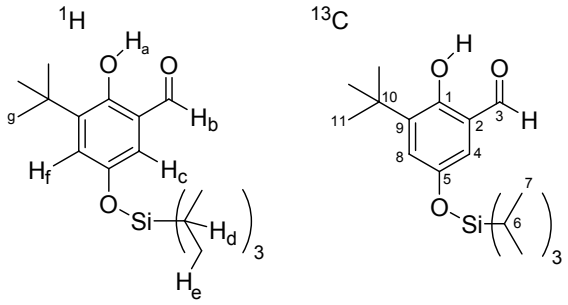
1-*p*-methoxyphenyl-1-propyl acetate: t_R = 8.74 min, t_S = 8.84 min.

1-(2-thiophenyl)-1-propyl acetate: t_R = 6.40 min, t_S = 6.62 min.

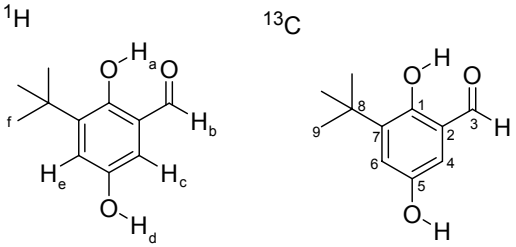
• **2-*tert*-Butyl-4-triisopropylsiloxyphenol**: To a solution of TBHQ (2.50 g, 15.1 mmol) in dichloromethane (100 mL) was added imidazole (1.33 g, 19.6 mmol) and DMAP (0.93 g, 7.6 mmol). To this solution was added TIPSCl (3.48 g, 18.1 mmol) in 8 mL of dichloromethane in a dropwise manner and the mixture was then stirred for 15 h at 25 °C. The mixture was then filtered and the solution was concentrated under vacuum. The resultant residue was purified by flash column chromatography on silica gel (1:4 EtOAc/hexanes) to yield the product as a clear liquid (4.39 g, 91% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 2.8 Hz, 1 H; H_c), 6.59 (d, *J* = 2.8 Hz, 1H; H_f), 6.52 (d, *J* = 8.29 Hz, 1H; H_b), 4.50 (s, 1 H; H_a), 1.38 (s, 9 H; H_g), 1.28-1.25 (m, 3 H; H_d), 1.10-1.08 (d, 18 H; H_e); ^{13}C NMR (300 MHz, $CDCl_3$) δ 149.5 (C_4), 148.1 (C_1), 137 (C_8), 118.8 (C_3), 117.2 (C_7), 116.8 (C_2), 34.5 (C_{10}), 29.5 (C_9), 17.9 (C_6), 12.6 (C_5). Anal. Calcd. for $C_{19}H_{34}O_2Si$: C, 70.81; H, 10.56; Found C, 70.22; H, 10.78.



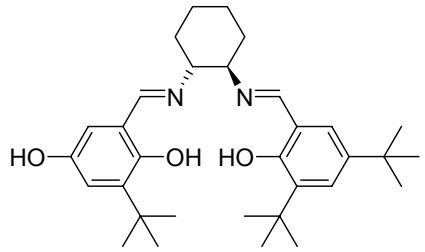
• **3-*tert*-Butyl-2-hydroxy-5-triisopropylbenzaldehyde**: A three-necked round-bottom flask equipped with an addition funnel, reflux condenser and a magnetic stir-bar was connected to a nitrogen inlet and was charged with 2,6-lutidine (3.12 mL, 26.8 mmol), 4-*tert*-butylphenol (7.19 g, 22.3 mmol), $SnCl_4$ (0.79 mL, 6.70 mmol) and toluene (200 mL). The resulting yellow heterogeneous mixture was stirred at 25 °C under nitrogen for 10 min. followed by the addition of paraformaldehyde (2.68 g, 89.3 mmol). The mixture was heated under reflux at 90 °C for 6 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to 25 °C and water (200 mL) and diethyl ether (200 mL) was added. The resulting emulsion was filtered through a pad of Celite and the layers were separated. The organic layer was washed with water (x1), brine (x1), and dried over anhydrous Na_2SO_4, and then concentrated. The crude product was purified by flash column chromatography on silica gel (1:9 ethylacetate/hexanes) to afford the title compound as a pale yellow oil (5.04 g, 65% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.40 (s, 1 H; H_b), 9.70 (s, 1 H; H_a), 7.14 (d, *J* = 3.0 Hz, 1 H; H_c), 6.85 (d, *J* = 3.0 Hz, 1 H; H_f), 1.39 (s, 9 H; H_g), 1.28-1.24 (m, 3 H; H_d), 1.11 (d, *J* = 6.8 Hz, 18 H; H_e); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 197.1 (C_3), 156.2 (C_5), 148.4 (C_1), 139.9 (C_9), 127.9 (C_2), 120.6 (C_4), 120.3 (C_8), 35.3 (C_{11}), 29.5 (C_{10}), 18.3 (C_7), 12.9 (C_6). Anal. Calcd. for $C_{20}H_{34}O_3Si$: C, 68.57; H, 9.71; Found: C, 68.51; H, 9.99.



• **3-*tert*-Butyl- 2,5-dihydroxybenzaldehyde**: TBAF (a 1.0 M solution in THF, 7.03 mL, 7.03 mmol) was added dropwise to a solution of 3-*tert*-Butyl-2-hydroxy-5-triisopropylbenzaldehyde (2.05 g, 5.86 mmol) in 15 mL of THF at 25 °C and the mixture was allowed to stir for 3 h. The reaction mixture was then poured into 50 mL of water and extracted (50 mL x 2), dried over anhydrous magnesium sulfate and concentrated in vacuuo. The crude product was purified by flash column chromatography on silica gel (1:4, diethyl ether/hexanes) to give 0.9 g (80% yield) of the product as a yellow crystalline solid: Mp. 181-183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.39 (s, 1 H; H_b), 9.79 (s, 1 H; H_a), 7.10 (d, *J* = 3.0 Hz, 1 H; H_c), 6.83 (d, *J* = 3.0 Hz, 1 H; H_e), 4.60 (s, 1 H; H_d), 1.40 (s, 9 H; H_f); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 196.5 (C_3), 153.1 (C_5), 149.6 (C_7), 138.4 (C_1), 122.9 (C_2), 115.4 (C_4), 101.8 (C_6), 34.4 (C_8), 28.8 (C_9). Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27; Found: C, 67.90; H, 7.22.

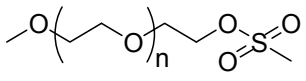


• **Unsymmetrical salen ligand 3:** To a solution of 3, 5-di-*tert*-butylsalicylaldehyde (1.72 g, 7.53 mmol), and 3-*tert*-butyl- 2,5-dihydroxybenzaldehyde (0.48 g, 2.45 mmol) in CH_2Cl_2 (15 mL) was added R-1,2-diaminocyclohexane (0.56 g, 4.89 mmol). The reaction mixture was allowed to stir at 25 °C for 15 h, after which it was concentrated in vacuuo to give a yellow foaming solid. This crude product (mixture of salen ligands) was purified by column chromatography on silica gel (gradient elution: 1:20 to 1:1, diethyl ether/hexanes) to give **2** (0.68 g, 55% yield) as a yellow foam. IR (KBr pellet): 3316 (br), 2954, 2864, 1630, 1598, 1465, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.28 (s, 1 H, -N=C-*H*), 8.18 (s, 1 H, -N=C-*H*), 7.31 (d, *J* = 2.4 Hz, 1 H, H_{Ar}), 6.96 (d, *J* = 2.4 Hz, 1 H, H_{Ar}), 6.80 (d, *J* = 3.2 Hz, 1 H, H_{Ar}), 6.45 (d, *J* = 3.2 Hz, 1 H, H_{Ar}), 3.33-3.29 (m, 2 H), 2.0-1.45 (m, 8 H, $H_{cyclohexyl}$), 1.41 (s, 9 H), 1.38 (s, 9 H), 1.23 (s, 9 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 165.4, 164.5, 157.6, 154.0, 146.2, 139.5, 138.1, 135.9, 126.4, 117.8, 117.4, 117.3, 114.1, 71.9, 34.5, 34.4, 33.6, 32.7, 31.2, 30.9, 28.9, 28.7, 23.8. Anal. Calcd for $C_{32}H_{46}N_2O_3$: C, 75.89; H, 9.71; N, 5.53 Found: C, 75.70; H, 9.25; N, 5.34; HRMS (EI) Calcd., *m/z* 506.3508 ($C_{32}H_{46}N_2O_3$), Found, 506.3517.

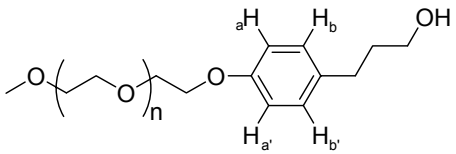


• **PEG mesylate 4**: To a solution of PEG monomethylether (MW = 5000) (5.00 g, 1 mmol) in CH_2Cl_2 (50 mL) is added an excess of tri-*n*-octylamine (6.37 g, 18 mmol) and the reaction mixture was allowed to stir for 30 min. Next, MsCl (0.69 g, 0.47 mL, 6 mmol) was added drop-wise to the stirring solution and the reaction mixture was left to stir at 25

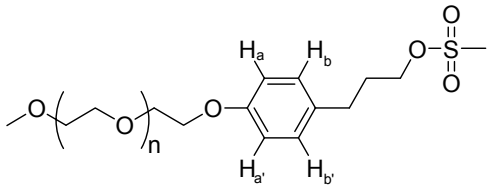
°C for 24 h. The solvent was then removed in vacuo and the resultant oily residue added drop-wise to stirring diethyl ether. The precipitate was filtered and the solid collected and dissolved in a minimal amount of CH_2Cl_2 and triturated with diethyl ether at 0 ºC and vacuum filtered. The PEG mesylate was isolated as a white solid (4.57 g, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.38-4.36 (t, 2 H; -C*H*$_2$-SO_2-), 3.63 (m, 180 H; -C*H*$_2$-C*H*$_2$-PEG backbone), 3.37 (s, 3H; C*H*$_3$-O-PEG-), 3.07 (s, 3 H; C*H*$_3$-SO_2-).



• **3-(4-MeO-PEG phenyl)-1-propanol**: Into a 100 mL round bottomed flask was placed a magnetic stir bar, 3-(4-hydroxyphenyl)-1-propanol (0.50 g, 3.29 mmol), Cs_2CO_3 (1.18 g, 3.62 mmol) and dry DMF (20 mL) and the solution was allowed to stir at 25 °C for 10 minutes. Next, PEG mesylate, **4**, (5.56 g, 1.09 mmol) was added to the stirring solution and the reaction mixture was allowed to stir at 25 °C for 24 h. Upon completion of the reaction, the reaction mixture was filtered, concentrated, in vacuuo, to 5 mL and added drop-wise to stirring ether at 0 ºC. The solid precipitate was collected by vacuum filtration and dried in vacuo to yield the polymeric alcohol as an off-white solid. (5.49 g, 98 % yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.10-7.07 (d, *J* = 8.5 Hz, 2H; $H_{a,a'}$), 6.84-6.81 (d, *J* = 7.5 Hz, 2H; $H_{b,b'}$), 4.11-4.08 (t, *J* = 5.1 Hz, 2 H; PEG-O-CH_2-*CH*$_2$-O-Ar), 3.87 (t, *J* = 5.1 Hz, 2H; PEG-*CH*$_2$-CH_2-O-Ar), 3.36 (s, 3 H; *CH*$_3$-O-PEG-CH_2-CH_2-O-Ar), 2.77 (t, *J* = 6.5 Hz, 2H; Ar-*CH*$_2$-), 2.06 (m, *J* = 6.5 Hz, 2H; Ar-CH_2-*CH*$_2$- CH_2-).

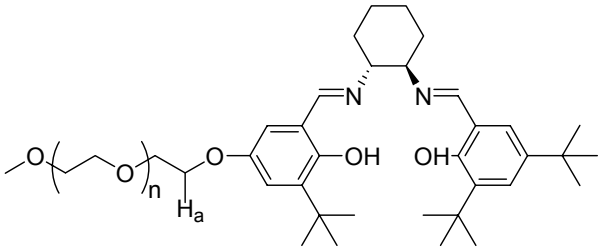


• **3-(4-PEG phenyl)-1-propylmesylate 5**: To a solution 3-(4-MeO-PEG phenyl)-1-propanol (1.88 g, 0.37 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (0.67 g, 6.59 mmol) and the resultant orange solution is allowed to stir for 10 minutes at RT. Next, the solution was cooled to 0 ºC and MsCl (0.25 g, 2.20 mmol) is added drop-wise and the reaction mixture was left to slowly warm to 25 °C and stir for 24 h. The reaction mixture was then concentrated in vacuuo to 5 mL and added drop-wise to stirring ether (200 mL) at 0 ºC and the precipitate is vacuum filtered and washed with *iso*-propanol (100 mL). The solid was dried in vacuo and the polymeric mesylate is obtained as a white solid (1.83 g, 95% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.08-7.06 (d, *J* = 8.7 Hz, 2H; $H_{a,a'}$), 6.85-6.82 (d, *J* = 8.6 Hz, 2H; $H_{b,b'}$), 4.22-4.18 (t, *J* = 6.5 Hz, 2 H; Ar-CH_2-CH_2-*CH_2*-O-SO_2), 4.11-4.08 (t, *J* = 5.1 Hz, 2 H; PEG-O-CH_2-*CH_2*-O-Ar), 3.87 (t, *J* = 5.1 Hz, 2H; PEG-*CH_2*-CH_2-O-Ar) 3.37 (s, 3 H; *CH_3*-O-PEG-), 2.98 (s, 3 H; -O-SO_2-*CH_3*), 2.73 (t, *J* = 6.5 Hz, 2H; Ar-*CH_2*-), 2.06 (m, *J* = 6.5 Hz, 2H; Ar-CH_2-*CH_2*- CH_2-).



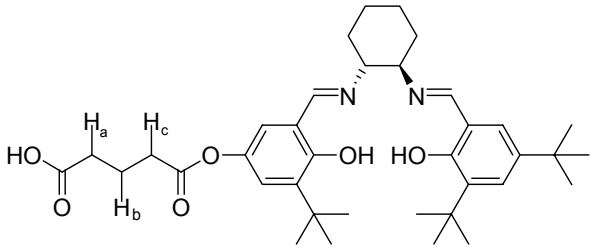
• **PEG-supported salen ligand 6**: PEG mesylate (2.0 g, 0.39 mmol) was added to a solution of the unsymmetrical salen **3** (0.51 g, 1.0 mmol) and Cs_2CO_3 in dry DMF (20 mL), in a 100 mL round bottomed flask fitted with a magnetic stir bar. After stirring at 25 °C for 24 h, the reddish-brown solution was filtered and then concentrated under vacuum to about half its original volume. This solution was then slowly added drop-wise to cold stirring ether (200 mL) to precipitate the polymeric catalyst. The solid was further

washed in ether (50 mL) followed by *iso*-propanol (50 mL) and dried in vacuo to yield the polymeric ligand **6** (2.05 g, 96 % yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 (s(br), 1 H, -N=C-*H*), 8.20 (s (br), 1 H, -N=C-*H*), 6.75 (d, 1 H, H_{Ar}), 6.63 (s(br), 1 H, H_{Ar}), 6.21 (d, 1 H, H_{Ar}), 6.19 (s (br), 1 H, H_{Ar}), 4.09 (t, 2 H, H_a), 3.36 (s, 3 H; C*H*$_3$-O-PEG-salen), 2.10-1.50 (m, 8 H, $H_{cyclohexyl}$), 1.33 (s, 9 H, $H_{t\text{-}Bu}$), 1.30 (s, 9 H, $H_{t\text{-}Bu}$), 1.19 (s, 9 H, $H_{t\text{-}Bu}$).

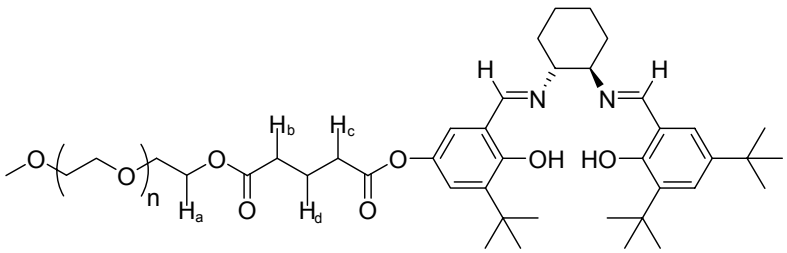


• **Salen glutarate (mono-ester)** : Into a 50 mL two-necked round-bottom flask, fitted with a nitrogen inlet, was placed a stir bar, glutaric anhydride (164 mg, 1.44 mmol), the unsymmetrical salen **3** (607 mg, 1.20 mmol), DMAP (176 mg, 1.44 mmol) and anhydrous CH_2Cl_2 (6 mL). The mixture was left to stir, under a nitrogen atmosphere, for 15 h at 25 °C after which it was concentrated in vacuuo. The crude yellow oil was purified by flash column chromatography on silica gel (1:19, methanol/CH_2Cl_2). The title compound was obtained as a foaming yellow solid (446 mg, 60% yield). IR (KBr pellet) 2940 (b), 1758, 1712, 1630, 1439 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (s, 1 H), 8.23 (s, 1 H), 7.31 (d, *J* = 2.5 Hz, 1 H), 6.98 (d, *J* = 2.5 Hz, 1 H), 6.92 (d, *J* = 2.8 Hz, 1 H), 6.77 (d, *J* = 2.8 Hz, 1 H), 3.34 (m, 2 H), 2.60 (t, *J* = 7.4 Hz, 2 H, H_c), 2.50 (t, *J* = 7.2 Hz, 2 H_a), 2.05 (q, *J* = 7.4 Hz, 2 H, H_b), 1.98-1.5 (m, 8 H, $H_{cyclohexyl}$), 1.42 (s, 9 H, $H_{t\text{-}Bu}$), 1.38 (s, 9 H, $H_{t\text{-}Bu}$), 1.25 (s, 9 H, $H_{t\text{-}Bu}$); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 178.7, 171.8, 165.8, 158.2, 157.9, 141.3, 139.9, 138.8, 136.3, 126.9, 125.9, 122.7, 121.3, 118.2, 117.7, 72.4, 72.2, 53.4, 34.9, 33.9, 33.2, 32.9, 31.6, 31.4, 29.4, 29.1, 24.2, 22.7, 22.6,

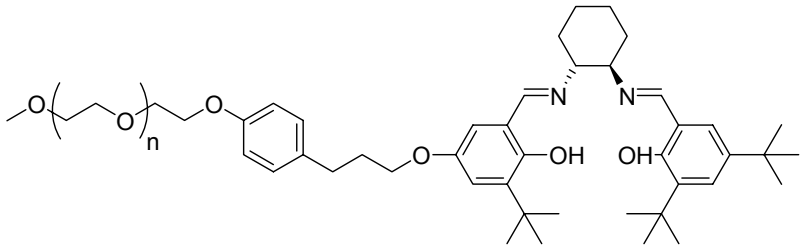
19.7, 14.1. Anal. Calcd for $C_{37}H_{52}N_2O_6$: C, 71.61; H, 8.39; N, 4.52. Found: C, 70.51; H, 8.42; N, 4.43; HRMS (EI) calcd *m/z* 620.3825 ($C_{37}H_{52}N_2O_6$), found 620.3799.



• **PEG-supported salen ligand 7:** To a solution of PEG_{5000} (2.60 g, 0.52 mmol), the unsymmetrical salen **3** (0.65 g, 1.04 mmol), and DMAP (0.03 g, 0.26 mmol) in CH_2Cl_2 (20 mL), was added DCC (0.23 g, 1.10 mmol). The reaction mixture was stirred at 25 °C for 24 h and the urea by-product was removed by filtering through a pad of Celite. The filtrate was then concentrated to 5 mL and then added drop-wise into 200 mL of cold stirring diethyl ether. The yellow solid precipitate was filtered off, and dried under vacuum (2.25 g, 77% yield): IR (KBr pellet) 3330, 2890 (b), 1756, 1737, 1630, 1461, 1349 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.27 (s (br), 1 H, -N=C-*H*), 8.20 (s (br), 1 H, -N=C-*H*), 7.31 (d, 1 H, H_{Ar}), 6.95 (s (br), 1 H, H_{Ar}), 6.88 (d, 1 H, H_{Ar}), 6.73 (s (br), 1 H, H_{Ar}), 4.20 (t, 2H, H_a), 3.34 (s, 3 H, C*H*$_3$-O-PEG-), 2.54 (t, *J* = 7.3 Hz, 2H, H_c), 2.42 (t, *J* = 7.3 Hz, 2H_b), 2.10-1.50 (m, 10 H, H_d, $H_{cyclohexyl}$), 1.36 (s, 9 H, $H_{t\text{-}Bu}$), 1.34 (s, 9 H, $H_{t\text{-}Bu}$), 1.19 (s, 9 H, $H_{t\text{-}Bu}$).



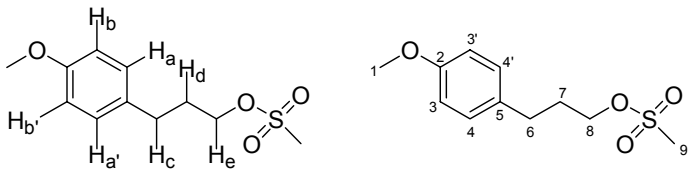
• **PEG-supported salen ligand 8**: The unsymmetrical salen ligand **3** (0.44 g, 0.87 mmol), Cs_2CO_3 (0.28 g, 0.87 mmol), a magnetic stir bar and DMF (10 mL) were placed into a 100 mL round-bottomed flask and the solution was allowed to stir at 25 °C for 10 minutes. Next, the PEG-supported phenyl-1-propylmesylate (1.51 g, 0.29 mmol) was added to the stirring solution and the reaction mixture was left to stir at 25 °C for 24 h. The solution was then concentrated in vacuo to remove the solvent and the residue was taken up in CH_2Cl_2 (5 mL) and added drop-wise to stirring ether (250 mL) at 0 ºC. The precipitated solid was vacuum filtered and then dissolved in chloroform (5 mL) and precipitated from cold ether again. The precipitate was filtered and dried in vacuo to give the PEG-supported salen as a yellow solid (1.53 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.25 (s, 1 H, N=C-*H*), 8.24 (s, 1 H, N=C-*H*), 7.33 (d, 1 H, *J* = 8.3 Hz, H_{Ar}), 7.16 (d, 2 H, *J* = 8.3 Hz, H_{Ar}), 6.94 (d, 1 H, *J* = 2.3 Hz, H_{Ar}), 6.90 (d, 1 H, *J* = 3.0 Hz, H_{Ar}), 6.81 (d, 2 H, *J* = 2.3 Hz, H_{Ar}), 6.43 (d, 1 H, *J* = 2.8 Hz, H_{Ar}), 4.11-4.07 (t, *J* = 5.1 Hz, 2 H; PEG-O-CH_2-*CH_2*-O-Ar), 3.88 (t, *J* = 5.1 Hz, 2H; PEG-*CH_2*-CH_2-O-Ar), 2.72 (t, 2 H, *J* = 7.9 Hz, *CH_2*-O-salen), 2.02-1.53 (m, 12 H, Ar-*CH_2*-*CH_2*- and $H_{cyclohexyl}$), 1.42 (s, 9 H, $H_{t\text{-}Bu}$), 1.41 (s, 9 H, $H_{t\text{-}Bu}$), 1.25 (s, 9 H, $H_{t\text{-}Bu}$)



• **3-(4-methoxyphenyl)-1-propylmesylate**: To a solution of 3-(4-methoxyphenyl)-1-propanol (2.50 g, 15.06 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (15.24 g, 0.15 mmol) and the mixture was allowed to stir at 25 °C for 10 minutes. Next, MsCl (8.63 g, 75.30 mmol) was added drop-wise to the solution at 0 ºC after which the reaction

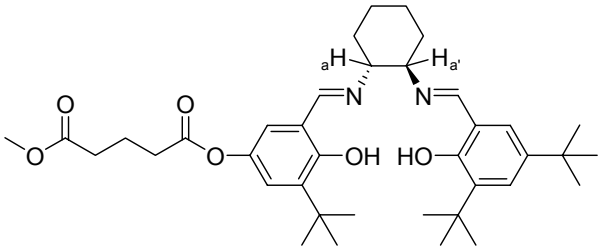
mixture is left to warm to 25 °C and stir for 24 h. The reaction mixture was then concentrated in vacuo and the crude oil obtained is purified by flash column chromatography over a plug of silica gel (hexanes/ethylacetate, 4:1). The product mesylate was obtained as an orange oil (3.56 g, 97 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.11-7.08 (d, *J* = 8.7 Hz, 2H; $H_{a,a'}$), 6.85-6.82 (d, *J* = 8.6 Hz, 2H; $H_{b,b'}$), 4.19 (t, *J* = 6.4 Hz, 2H; -CH_2-*CH_2*-O-SO_2), 3.77 (s, 3H; *CH_3*-O-Ar), 2.97 (s, 3H; -O-SO_2-*CH_3*), 2.68 (t, J = 7.9 Hz, 2H; Ar-*CH_2*-), 2.07-1.98 (m, 2H; Ar-CH_2-*CH_2*-CH_2-); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 157.9 (C_2), 132.1 (C_5), 129.2 ($C_{4,4'}$), 113.8 ($C_{3,3'}$), 69.1 (C_8), 55 (C_1), 36.9 (C_9), 30.6 (C_6), 30.3 (C_7). Anal. Calcd for $C_{37}H_{52}N_2O_6$: C, 54.08; H, 6.60; S, 13.12. Found: C, 53.41; H, 6.64; S, 13.61.

^{1}H ^{13}C



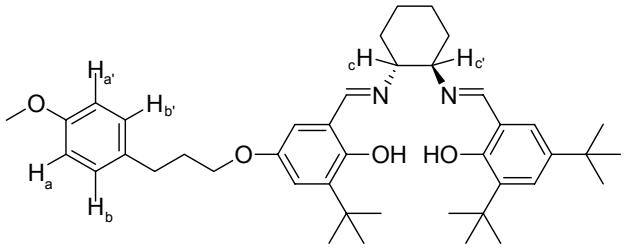
• **Salen glutarate methyl ester 9**: To a solution of **7** (0.16 g, 0.25 mmol), DMAP (0.032 g, 0.29 mmol) and methanol (0.01 g, 0.29 mmol) in CH_2Cl_2 (5 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (0.10 g, 0.53 mmol), and the solution was left to stir at 25 °C for 16 h. Next, the solution was concentrated in vacuuo and the residue purified by flash column chromatography on silica gel (1:4 EtOAc/hexanes). The product was obtained as a yellow foaming solid (0.11 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.30 (s, 1 H, -N=C-*H*), 8.23 (s, 1 H, -N=C-*H*), 7.31 (d, 1 H, *J* = 2.5 Hz, H_{Ar}), 6.98 (d, 1 H, *J* = 2.5 Hz, H_{Ar}), 6.92 (d, 1 H, *J* = 2.5 Hz, H_{Ar}), 6.76 (d, 1 H, *J* = 2.5 Hz, H_{Ar}), 3.69 (s, 3 H, H_a), 3.34 (m, 2 H, $H_{a,a'}$), 2.58 (t, 2 H, *J* = 7.3 Hz, -*CH_2*-CO_2-salen), 2.45 (t, 2 H, *J* = 7.5 Hz, CH_3O_2C-*CH_2*-), 2.06-1.67 (m, 10 H, -

CH$_2$-CH_2-CO_2-salen and $H_{cyclohexyl}$), 1.40 (s, 9 H, $H_{t\text{-}Bu}$)**,** 1.38 (s, 9 H, $H_{t\text{-}Bu}$), 1.23 (s, 9 H, $H_{t\text{-}Bu}$)**;** ^{13}C NMR (300 MHz, $CDCl_3$) δ = 171.9, 165.6, 164.7, 158.2, 157.9, 141.4, 140.1, 138.6, 136.5, 126.9, 126.0, 122.8, 121.5, 118.2, 117.7, 72.4, 72.2, 51.6, 34.9, 34.8, 34.0, 33.2, 33.1, 33.0, 32.9, 31.4, 29.2, 29.1, 24.4, 20.0. Anal. Calcd for $C_{38}H_{54}N_2O_6$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.74; H, 8.54; N, 4.37.



• **3-(4-methoxyphenyl)-1-propyl-salen ligand 10**: The unsymmetrical salen ligand **3** (0.16 g, 0.32 mmol), Cs_2CO_3 (0.31 g, 0.96 mmol), a magnetic stir bar and DMF (10 mL) were placed into a 100 mL round-bottomed flask and the solution was allowed to stir at RT for 10 minutes. Next, 3-(4-methoxyphenyl)-1-propylmesylate (0.08 g, 0.32 mmol) was added to the stirring solution and the reaction mixture was left to stir at 25 °C for 24 h. The solution was then concentrated in vacuuo to remove the solvent and the residue purified by flash column chromatography on silica gel (1:4 ethylacetate/hexanes) to obtain the title compound as a yellow solid (0.16 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (s, 1 H, N=C-*H*), 8.21 (s, 1 H, N=C-*H*), 7.31 (d, 1 H, *J* = 2.3 Hz, H_{Ar}), 7.14 (d, 2 H, *J* = 8.5 Hz, $H_{b,b'}$), 6.97 (d, 1 H, *J* = 2.5 Hz, H_{Ar}), 6.90 (d, 1 H, *J* = 3.0 Hz, H_{Ar}), 6.84 (d, 2 H, *J* = 8.7 Hz, $H_{a,a'}$), 6.44 (d, 1 H, *J* = 2.8 Hz, H_{Ar}), 3.79 (s, 3 H, *CH*$_3$-O-Ar), 3.33 (m, 2 H, $H_{c,c'}$), 2.72 (t, 2 H, *J* = 7.9 Hz, *CH*$_2$-O-salen), 2.10-1.50 (m, 12 H, Ar-*CH*$_2$-*CH*$_2$- and $H_{cyclohexyl}$), 1.42 (s, 9 H, $H_{t\text{-}Bu}$), 1.41 (s, 9 H, $H_{t\text{-}Bu}$), 1.24 (s, 9 H, $H_{t\text{-}Bu}$); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 165.9, 165.3, 157.9, 157.8, 154.8, 150.5, 139.9, 138.6, 136.3, 129.4, 126.8,

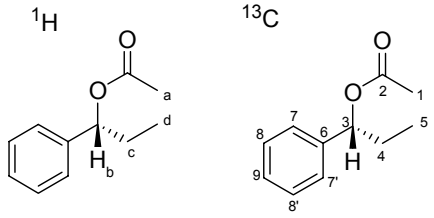
125.9, 118.7, 117.9, 117.8, 113.8, 112.4, 72.5, 72.3, 67.5, 55.2, 34.9, 34.8, 34.0, 33.2, 31.4, 31.2, 29.7, 29.4, 29.3, 24.3, 22.7, 14.1. Anal. Calcd for $C_{42}H_{58}N_2O_4$: C, 77.02 H, 8.93; N, 4.28. Found: C, 76.23; H, 9.04; N, 3.91.



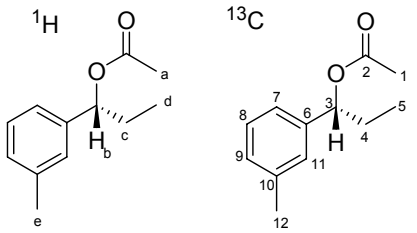
• **General Procedure for the Addition of Diethylzinc to Aldehydes**. The polymer-supported salen (0.1 mmol) was placed into a dry glass reaction tube, fitted with a magnetic stir-bar and a rubber septum. The reaction tube was successively evacuated and then purged with nitrogen. The salen was then dissolved in dry toluene (3 mL) and Et_2Zn (0.1 mL, 1 M solution in hexanes, 0.1 mmol) was added dropwise. The yellow homogenous mixture was allowed to stir at 25 °C for 1 h to form the Zn-salen complex *in situ*. Next, Et_2Zn (2.3 mL, 1 M solution in hexanes, 2.3 mmol) was added to the reaction mixture and after 5 minutes, the aldehyde (1 mmol) was added to the reaction mixture at 0 ºC and then left to warm to 25 °C. To monitor the reaction progress, 0.1 mL aliquots were taken from the reaction mixture, added to ether (0.5 mL), to precipitate the polymeric catalyst, quenched with 1 N HCl and the ether layer subjected to GC analysis. Upon completion of the reaction, the mixture was then slowly triturated into cold stirring ether and the precipitate was collected by vacuum filtration, washed in iso-propanol and dried in under vacuum. The filtrate was concentrated and treated with acetic anhydride (6 equiv) and allowed to stand for 6 h after which it was washed in water (x1), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash

column chromatography on silica gel (1:4, ethylacetate/hexanes) to yield the product as an acetate ester in the form of a clear liquid.

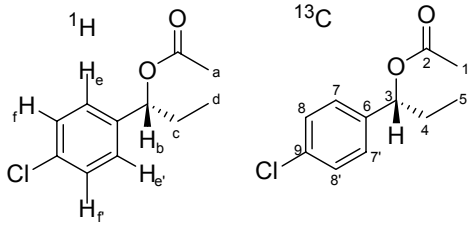
• **(*R*)-(+)-1-Phenyl-1-propyl acetate**: This compound was prepared from benzaldehyde (0.31 g, 2.90 mmol) following the general procedure reported above. The product was isolated as a colorless liquid (0.51 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28-7.18 (m, 5 H; Ar), 5.63-5.58 (t, *J* = 7.0 Hz, 1 H; H_b), 2.00 (s, 3 H; H_a), 1.89-1.72 (m, 2 H; H_c), 0.84-0.79 (t, *J* = 7.5 Hz, 3 H; H_d); ^{13}C NMR (300 MHz, $CDCl_3$)) δ = 169.8 (C_2), 136.9 (C_6), 128.6 ($C_{7,\ 7'}$), 126.3 ($C_{8,8\ '}$), 125.9 (C_9), 75.9 (C_3), 28.5 (C_4), 20.6 (C_1), 9.8 (C_5). Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; Found: C, 73.93; H, 8.02.



• **(*R*)-(+)-1-*m*-tolyl-propyl acetate**: This compound was prepared from *m*-tolylaldehyde (0.45 g, 3.75 mmol) following the general procedure. The product was isolated as a colorless liquid (0.69 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$)) δ = 7.23 (m, 4 H; Ar), 5.63 (t, *J* = 6.9, 1H; H_b), 2.35 (s, 3 H; H_a), 2.08 (s, 2 H; H_e), 1.96 (m, 2 H; H_c), 0.88 (t, *J* = 7.4 Hz, 3H; H_d); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 170.5 (C_2), 140.3 (C_{10}), 137.8 (C_6), 128.5, 127.2, 123.5 (C_{Ar}), 77.3 (C_3), 29.2 (C_4), 21.3 (C_1), 21.1 (C_{12}), 9.9 (C_5). Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; Found: C, 74.73; H, 8.16

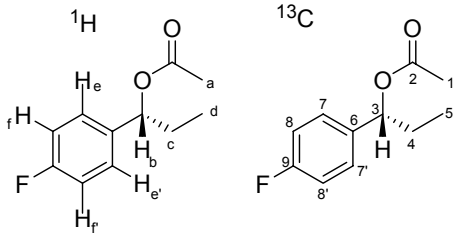


• **(*R*)-(+)-1-*p*-chloro-propyl acetate**: This compound was prepared from *p*-chlorobenzaldehyde (0.49 g, 3.50 mmol) following the general procedure reported above. The product was isolated as a colorless liquid (0.72 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) □ = 7.24 (dd, *J* = 8.7 Hz, 2H; $H_{f,f'}$), 7.19 (dd, *J* = 8.5, 2H; $H_{e,e'}$), 5.53 (t, *J* = 6.9 Hz, 1H; H_b), 1.98 (s, 3 H; H_a), 1.87 (m, 2 H; H_c), 0.79 (t, *J* = 7.3 Hz, 3H; H_d); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 170.3 (C_2), 139 (C_6), 133.5 (C_9), 128.5 ($C_{7,7'}$), 127.8 ($C_{8,8'}$), 76.6 (C_3), 29.1 (C_4), 21.1 (C_1), 9.8 (C_5). Anal. Calcd. for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.16; Cl, 16.67; Found: C, 62.37; H, 6.03; Cl, 16.47

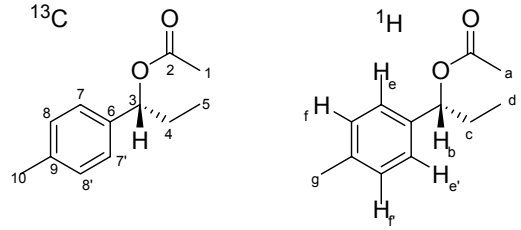


• **(*R*)-(+)-1-*p*-fluoro-propyl acetate**: This compound was prepared from *p*-fluorobenzaldehyde (0.43 g, 3.50 mmol) following the general procedure reported above. The product was isolated as a colorless liquid (0.67 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.24-7.21 (m, 2H; $H_{e,\,e'}$), 6.97-6.91 (m, 2H; $H_{f,\,f'}$), 5.55 (t, *J* = 7.4 Hz, 1H; H_b), 1.99 (s, 3H; H_a), 1.86-1.65 (m, 2H; H_c), 0.79 (t, *J* = 7.5 Hz, 3H; H_d); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 170 (C_2), 136.7 (C_6), 128.7 (C_9), 115.7 (C_7), 77.0 (C_8), 30.1 (C_3), 29.6 (C_4), 21.6 (C_1),

10.2 (C_5). Anal. Calcd. for $C_{11}H_{13}FO_2$: C, 67.33; H, 6.68; F, 9.68; Found: C, 67.48; H, 6.75; F, 9.6.



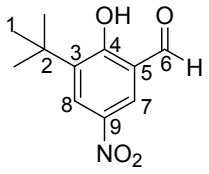
• **(*R*)-(+)-1-*p*-tolyl-propyl acetate**: This compound was prepared from *p*-tolylaldehyde (0.42 g, 3.50 mmol) following the general procedure. The product was isolated as a colorless liquid (0.65 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ =^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29-7.27 (d, *J* = 8.7 Hz , 2H; $H_{e, e'}$), 7.21-7.18 (d, *J* = 8.7 Hz , 2H; $H_{f, f'}$), 5.68 (t, *J* = 7.4 Hz, 1H; H_b), 2.38 (s, 3H; H_a), 2.11 (s, 3H; H_g), 2.02-1.79 (m, 2H; H_c), 0.92 (t, *J* = 7.5 Hz, 3H; H_d) ^{13}C NMR (300 MHz, $CDCl_3$) δ = 170.1 (C_2), 137.2 (C_9), 134.3 (C_6), 128.8 ($C8_{,8'}$), 126.3 ($C_{7,7'}$), 76.3 (C_3), 28.8 (C_1), 20.9 (C_4), 9.6 (C_5). Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; Found: C, 75.04; H,.8.44.



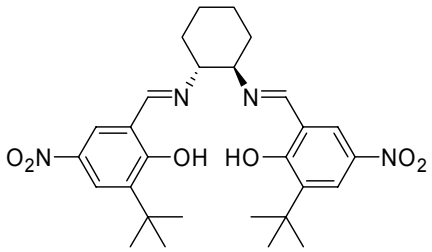
6.2 Synthesis of 5,5'-Substituted Salen Ligands:

• **3-*tert*-butyl-5-nitro-2-hydroxybenzaldehyde**: To a solution of 3-*tert*-butyl-2-hydroxybenzaldehyde (3.71 g, 20.82 mmol) in glacial acetic acid (30 mL) at 10 ºC was slowly added nitric acid (1.32 mL, 20.82 mmol). The cold bath was removed and the reaction mixture was allowed to stir at 25 °C for 8 h after which it was poured into crushed ice and water was added to a total volume of 100 mL. The aqueous mixture was

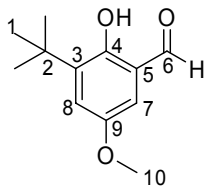
extracted with ether (2 x 30 mL) and the organic phase washed with water (4 x 15 mL) and then once with brine (10 mL) and then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified by flash column chromatography on silica gel (17:3 hexanes/ ethylacetate) to afford a pale yellow crystalline solid (3.49 g, 75% yield). Mp. 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.44 (s, 1 H; -C<u>H</u>O), 9.97 (s, 1 H; -O<u>H</u>), 8.41 (m, 2 H; H_{Ar}), 1.45 (s, 9 H; -C(C<u>H</u>$_3$)$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = . Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.72; Found: C, 59.97; H, 6.25; N, 5.98.



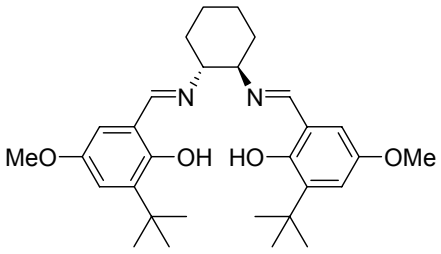
• **3,3'-di-*tert*-butyl-5,5'-nitro-salen**: To a solution of (R,R)-1,2-diaminocyclohexane (0.51 g, 4.46 mmol) in ethanol (50 mL) was added 3-*tert*-butyl-5-nitro-2-hydroxybenzaldehyde (1.99 g, 8.91 mmol) and the reaction mixture was allowed to heat at reflux for 8 h after which it was cooled to 25 °C. The solvent was then removed under vacuum to give a yellow foaming solid (4.30 g, 92% yield). Mp. 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 15.03 (s, 2 H; -O<u>H</u>), 8.35 (s, 2 H; -C<u>H</u>=N-), 8.15-8.14 (d, *J* = 2.8 Hz, 2 H; H_{Ar}), 7.99-7.98 (d, *J* = 2.8 Hz, 2 H; H_{Ar}), 3.49-3.46 (m, 2 H; -C=N-C<u>H</u>-), 2.11-1.74 (m, 8 H; (-C<u>H</u>$_2$-)$_4$, 1.39 (s, 18 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 163.7, 160.6, 140.7, 135.3, 125, 124.3, 122.4, 58.8, 31.8, 28.2, 23.6, 22.5. Anal. Calcd. for $C_{28}H_{36}N_4O_6$: C, 64.10; H, 6.92; N, 10.68; Found: C, 62.89; H, 6.92; N, 10.54.



• **3-*tert*-butyl-5-methoxy-2-hydroxybenzaldehyde**: Into a 3-necked round-bottomed flask fitted with a reflux condenser and purged with nitrogen was placed a Teflon stir bar, 2-*tert*-butyl-4-methoxyphenol (5 g, 27.7 mmol), toluene (100 mL), $TiCl_4$, dropwise (0.72 g, 2.77 mmol), and 2,6-lutidine (1.19 g, 11.08 mmol) and the reaction mixture was allowed to stir for 20 min at 25 °C. Next, paraformaldehyde (2 g, 66.5 mmol) was added and the reaction mixture was refluxed at 90 ºC for 8 h. After the reaction was complete, as determined by TLC, the mixture is cooled to 25 °C and poured into water (2 L), acidified with 2 N HCl to a pH of 2 and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3x100 mL), the organic phases combined, washed with brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The crude oil was purified by flash column chromatography on silica gel (5:2 hexanes/ ethylacetate) to afford a pale yellow oil (4.03 g, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.54 (s, 1 H; -C<u>H</u>O), 9.82 (s, 1 H; -C<u>H</u>O), 7.12-7.19 (d, *J* = 3.1 Hz, 1 H; H_{Ar}), 6.83-6.82 (d, *J* = 3.1 Hz, 1 H; H_{Ar}), 3.82 (s, 3 H; -OC<u>H</u>$_3$), 1.43 (s, 9 H; C(C<u>H</u>$_3$)$_3$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 188.0 (C6), 154.7 (C9), 145.5 (C4), 135.8 (C3), 124.4 (C5), 118.3 (C8), 112.2 (C7), 31 (C1), 25.7 (C2). Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74; Found: 69.32; H, 7.71

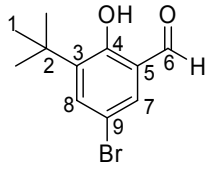


• **3,3'-di-*tert*-butyl-5,5'-methoxy-salen**: To a solution of (R)-1,2-diaminocyclohexane (0.32 g, 5.43 mmol) in ethanol (50 mL) was added 3-*tert*-butyl-5-methoxy-2-hydroxybenzaldehyde (1.33 g, 5.43 mmol) and the reaction mixture was allowed to stir while heating at reflux for 8 h after which it was cooled to 25 °C. The solvent was removed in vacuo to afford the product as a yellow foaming solid (2.52 g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ =13.42 (s, 2 H, -OH), 8.24 (s, 2 H, -CH=N-), 6.91-6.85 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 6.48-6.47 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 3.69 (s, 1 H; -OCH_3), 3.33-3.29 (m, 2 H; -C=N-CH-), 2.01-1.61 (m, 8 H; (-CH_2-)$_4$), 1.40 (s, 18 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 164.3, 154.3, 146.3, 135.8, 114.5, 112.3, 57.9, 56, 32.5, 28.9, 24.2, 20.9. Anal. Calcd. for $C_{30}H_{42}N_4O_4$: C, 72.84; H, 8.56; N, 5.66; Found: C,73.98; H, 8.66

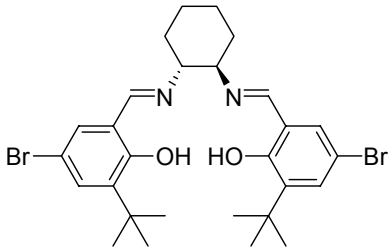


• **3-*tert*-butyl-5-bromo-2-hydroxybenzaldehyde**: To a solution of benzyl-*tri*-methylammonium-*tri*-bromide ($BTMABr_3$) in 20 mL of CH_2Cl_2/MeOH (6:4) was added, dropwise, a solution of 3-*tert*-butyl-2-hydroxybenzaldehyde (2.6 g, 14.5 mmol) in 100 mL of CH_2Cl_2/MeOH (6:4). The reaction mixture was left to stir at 25 °C and monitored by TLC until complete consumption of the starting material was observed. The solution was then concentrated in vacuo and the resultant crude solid was recrystallized from MeOH to afford a white crystalline solid (1.55 g, 65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.72 (s, 1 H; -CHO), 9.81 (s, 1 H, -OH), 7.58-7.57 (d, *J* = 2.4 Hz, 1 H; H_{Ar}), 7.52-7.51 (d, *J* = 2.4 Hz, 1 H; H_{Ar}), 2.33 (s, 1 H; -CH_3), 1.41 (s, 9 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$)

δ = 193.5 (C6), 154.7 (C4), 138.4 (C8), 135.7 (C3), 131.1 (C7), 127.5 (C5), 114.5 (C9), 32.8 (C1), 23.9 (C2). Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10; Br, 31.08; Found: C, 51.36; H, 5.24; Br, 31.41

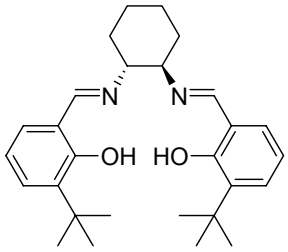


• **3,3'-di-*tert*-butyl-5,5'-bromo-salen**: To a solution of (R)-1,2-diaminocyclohexane (0.13 g, 1.12 mmol) in ethanol (50 mL) was added 3-*tert*-butyl-5-bromo-2-hydroxybenzaldehyde (0.58 g, 2.24 mmol) and the reaction mixture was allowed to stir while heating at reflux for 8 h. The reaction mixture was then cooled to 25 °C and the solvent was removed in vacuuo to afford the product as a yellow foaming solid (1.13 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 13.11 (s, 2, -OH), 8.48 (s, H, -CH=N-), 7.42-7.44 (d, *J* = 2.4 Hz, 1 H; H_{Ar}), 3.43-3.39 (m, 2 H; -C=N-CH-), 1.78-1.41 (m, 8 H; $(-CH_2-)_4$), 1.34 (s, 18 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 163.8, 154.3, 136.6, 132.9, 130.6, 126.4, 114.5, 57.9, 32.9, 28.8, 23.4, 22.2. Anal. Calcd. for $C_{11}H_{13}BrO_2$: C, 51.38; H, 5.10; Br, 31.08; Found: C, 51.55; H, 5.57; Br, 30.98



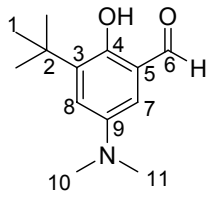
• **3,3'-di-*tert*-butyl-5,5'-hydro-salen**: To a solution of (R)-1,2-diaminocyclohexane (0.5 g, 4.39 mmol) in ethanol (20 mL) was added 3-*tert*-butyl-5-bromo-2-hydroxybenzaldehyde (1.56 g, 8.78 mmol) and the reaction mixture was allowed to stir

while heating at reflux for 2 h. The reaction mixture was then cooled to 25 °C and the solvent was removed in vacuo to afford the product as a yellow crystalline solid (3.47 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ =13.95 (s, 2 H, -OH), 8.32 (s, 2 H, -CH=N-), 7.32-7.29-6.85 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 7.01-7.03 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 6.79-6.73 (t, *J* = 3.0 Hz, 2 H; H_{Ar}), 3.37-3.34 (m, 2 H; -C=N-CH-), 2.02-1.76 (m, 8 H; $(-CH_2-)_4$), 1.47 (s, 18 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 165.4, 160.3, 136.9, 129.8, 129.1, 118.5, 117.7, 72.2, 34.7, 33.1, 29.3, 24.2. Anal. Calcd. for $C_{28}H_{38}N_2O_2$: C, 77.38; H, 8.81; N, 6.45; Found: C, 77.33; H, 9.02; N, 6.21.

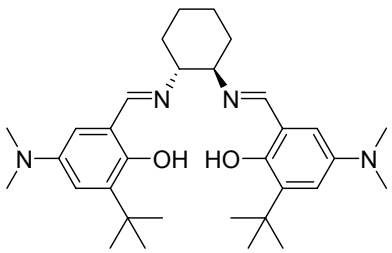


• **3-*tert*-butyl-5-N,N-dimethylamino-2-hydroxybenzaldehyde**: In a Parr hydrogenator bottle, a solution of 3-*tert*-butyl-5-nitro-2-hydroxybenzaldehyde (2.14 g, 9.59 mmol) in 95% ethanol (50 mL) was combined with 10% Pd/C (480 mg) and 37% aqueous formaldehyde solution (7 mL). This was shaken under H_2 pressure (42 psi) for 5 h. The reaction mixture was filtered to remove the catalyst, and the solid was washed with hot ethanol. The combined filtrates were treated with HCl to pH 2. Removal of solvent gave an oily residue, which was triturated with H_2O (100 mL), filtered, treated with charcoal, filtered again, and neutralized with NaOH. The product was extracted into diethyl ether, and the organic layer was subsequently washed with H_2O and aqueous NaCl. Drying over $MgSO_4$, filtration, and removal of solvent gave a crude solid, which was recrystallized from methanol to give 1.06 g (50% yield) of the title compound as orange crystalline needles. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.19 (s, 1 H; -CHO), 6.77-6.76 (d, *J* =

2.1 Hz, 1 H; H_{Ar}), 6.71-6.70 (d, *J* = 2.1 Hz, 1 H; H_{Ar}), 5.10 (s, 1 H, -OH), 2.85 (s, 6 H; N(CH_3)$_2$), 1.41 (s, 9 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 189.9 (C6), 144.7 (C4), 136.4 (C3), 1324.8 (C9), 124.3 (C5), 115.1 (C7), 111.0 (C8), 42.5 (C10,11), 31.5 (C1), 19.7 (C2). Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33; Found: C, 70.98; H, 68.85; N, 6.21.



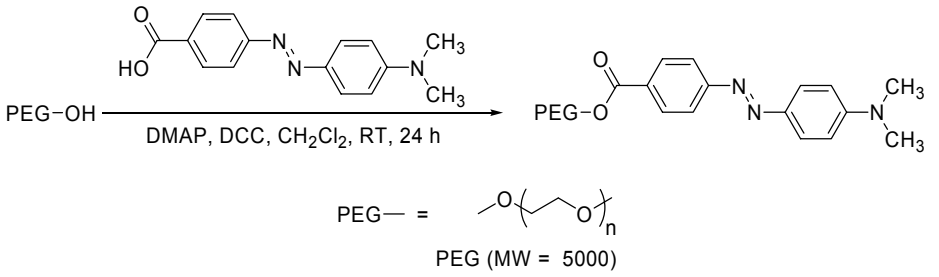
• **3,3'-di-*tert*-butyl-5,5'-N,N-dimethylamino-salen**: To a solution of (R)-1,2-diaminocyclohexane (0.12 g, 1.02 mmol) in ethanol (10 mL) was added 3-tert-butyl-5-N,N-dimethylamino-2-hydroxybenzaldehyde (0.45 g, 2.03 mmol) and the reaction mixture was allowed to stir while heating at reflux for 2 h. The reaction mixture was then cooled to 25 °C and the solvent was removed in vacuuo. The crude residual oil was purified by flash column chromatography on silica gel (5:2 hexanes/ ethylacetate) to afford the product as a yellow foaming solid (0.48 g, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.12 (s, 2 H, -OH), 8.17 (s, 2 H, -CH=N-), 6.62-6.58 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 6.52-6.47 (d, *J* = 3.0 Hz, 2 H; H_{Ar}), 3.33-3.29 (m, 2 H; -C=N-CH-), 2.85 (s, 12 H; -N(CH_3)$_2$), 2.21-1.61 (m, 8 H; (-CH_2-)$_4$), 1.34 (s, 18 H; $H_{t\text{-}Bu}$); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 165.8, 144.3, 136.8, 134.5, 124.4, 110.6, 55.9, 41.3, 33.1, 28.9, 24, 22.5. Anal. Calcd. for $C_{32}H_{48}N_4O_2$: C, 73.81; H, 9.29; N, 10.76; Found: C, 73.66; H, 9.02; N, 10.21.



6.3 Recycling a Soluble Polymer-Supported Catalyst: Soxhlet-Dialysis:

Regenerated cellulose Spectra/Por ® Biotech dialysis membranes (MWCO: 3.5 kDa) were purchased from Spectrum Laboratories. UV spectroscopic analysis was carried out on a Shimadzu® UV-240 1PC spectrophotometer using UV-Probe software. Enantiomeric ratios were determined by GC using a Hewlett-Packard 6850 gas chromatograph on a Cyclosil-B^{TM} capillary column purchased from J&W Scientific, Folsom, CA. In all cases, baseline separation of enantiomers was observed. All GC operating conditions were set as follows: Carrier gas: H_2. Detector: temperature, 300 ºC; flow, 40 mL/min. Inlet: temperature, 300 ºC, 10.31 psi; 44.6 mL/min. The column was calibrated with a racemic mixture of the product cyanohydrin trimethylsilyl ether.

• **PEG-supported *p*-methyl-red**: To a solution of *p*-methyl-red (0.79 g, 2.97 mmol) in CH_2Cl_2 (50 mL), was added DCC (0.64 g, 3.11 mmol), DMAP (0.09 g, 0.74 mmol) and PEG (MW = 5000) (7.42 g, 1.48 mmol), and the solution was allowed to stir at 25 °C. After 24 h, the reaction mixture was concentrated to 5 mL and added dropwise into 250 mL stirring diethyl ether at 0 °C. The precipitate was collected by vacuum filtration and dried under vacuum to give the PEG-dye (7.14 g, 1.36 mmol) : IR (KBr pellet) 2890 (b), 1685, 1602, 1520, 1467, 1360, 1242 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.36-7.49 (m, 8 H, H_{Ar}), 4.32 (t, 2H), 3.34 (s, 3 H, CH_3-O-PEG-), 3.14 (s, 6 H, -N-$(CH_3)_2$).



• **General Procedure for the Asymmetric Addition of TMSCN to Benzaldehyde**

The polymer supported salen ligand (0.1 g, 0.018 mmol), dichloromethane (10 mL) and a magnetic stir bar, are placed into a 25 mL round-bottomed flask. $TiCl_4$ (3.4 mg, 0.018 mmol) was then added and the solution was allowed to stir at 25 °C for 1 h. Next, benzaldehyde (1.9g, 18 mmol) and TMSCN (1.8 g, 18 mmol) were added to the reaction mixture which was left to stir at 25 °C for 24 h. The product trimethylsilyl cyanide ether was obtained from complete conversion of the starting materials (3.7 g, >99% yield), and in 93:7 *er* by chiral GC. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50-7.31 (m, 5 H, H_{Ar}), 5.43 (s, 1 H, -O<u>H</u>), 0.15 (s, 9 H, -O-Si-(CH_3)$_3$).

• **Catalysts Recovery by Soxhlet-Dialysis**: On completion of the reaction, the solution was concentrated in vacuuo to 5 mL. A 4 cm length of the dialysis tubing (flat width, 16/22 mm; diameter, 10 mm; vol./length, 1.5 mL/cm) was washed with distilled water, and one end tied shut. The reaction solution and a magnetic stir bar were transferred into the dialysis tubing and the open end of the tubing was tied with a string. The Soxhlet-Dialysis apparatus was set up as depicted in the picture below. The dialysis bag was washed with CH_2Cl_2 and placed in the soxhlet chamber. Next, CH_2Cl_2 was poured into the soxhlet chamber (25 mL) and the three-necked recovery flask (100 mL) (dodecane was added to the solvent in the recovery flask as an internal standard for GC analysis) and it was placed in an oil bath and heated to 60 ºC. The soxhlet chamber was periodically replaced with fresh CH_2Cl_2 from the reflux every 20 min. The solution in the recovery flask was sampled over 38 h, and a recovery of 97% was achieved.

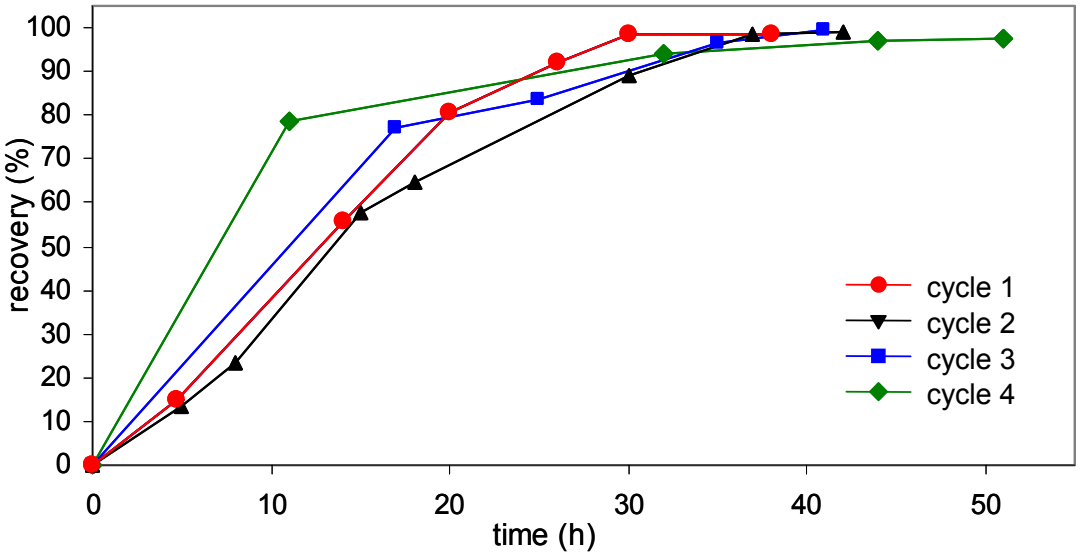
After each cycle, the contents of the dialysis bag was poured into a 25 mL round bottomed-flask and fresh substrates (benzaldehyde and TMSCN) were added. The reaction was then carried out with stirring at RT for 24 h until complete conversion of benzaldehyde was observed by GC. This reaction solution was then subjected to another Soxhlet-Dialysis cycle. The PEG-supported chiral Ti-salen catalysts could thus be recycled up to five times (average recovery = 98%) with no loss in selectivity and reactivity.

- **Soxhlet-Dialysis of PEG-dye: UV Experiments**.

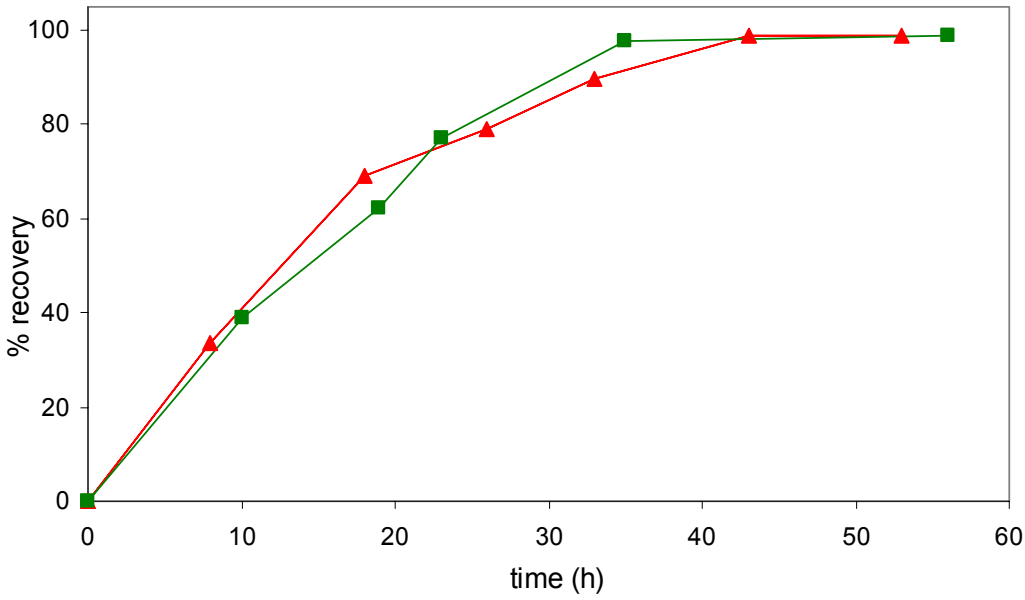
A solution of the PEG-dye in CH_2Cl_2 (10 mL of a 10 mM solution , 0.1 mmol) and a magnetic stir bar, were placed in a 3.5 kDa dialysis bag. To the soxhlet chamber and three-necked recovery flask was placed 25 mL and 50 mL of CH_2Cl_2 respectively. Soxhlet-Dialysis was carried out under similar conditions as mentioned previously. Samples of the dialysate were taken periodically from the recovery flask immediately after reflux from the solvent in the soxhlet back into the recovery flask. The samples were analyzed by UV spectroscopy and their absorbances at λ_{max} were recorded. The molar concentration of the PEG-dye in the samples was thus calculated using the Beer-Lambert's Law. $A = (\varepsilon)(c)(l)$; where A = absorbance, ε = molar absorptivity, c = molar concentration and l = path length (1 cm). The A at λ_{max} of a standard solution of the PEG-dye was recorded and this was used to determine ε (1.23×10^4) and ultimately c of each sample. The results are reported in the table below:

time (h)	**A (at λ_{max})**	**c (mM)**	**% dialyzed[a]**
0	0	0	0
2	0.133	0.011	0.8
8	0.323	0.026	1.9
19	0.401	0.033	2.5
25	0.503	0.041	3.1
33	0.588	0.048	3.6
48	0.618	0.05	3.7
62	0.628	0.051	3.8
72	0.63	0.051	3.8

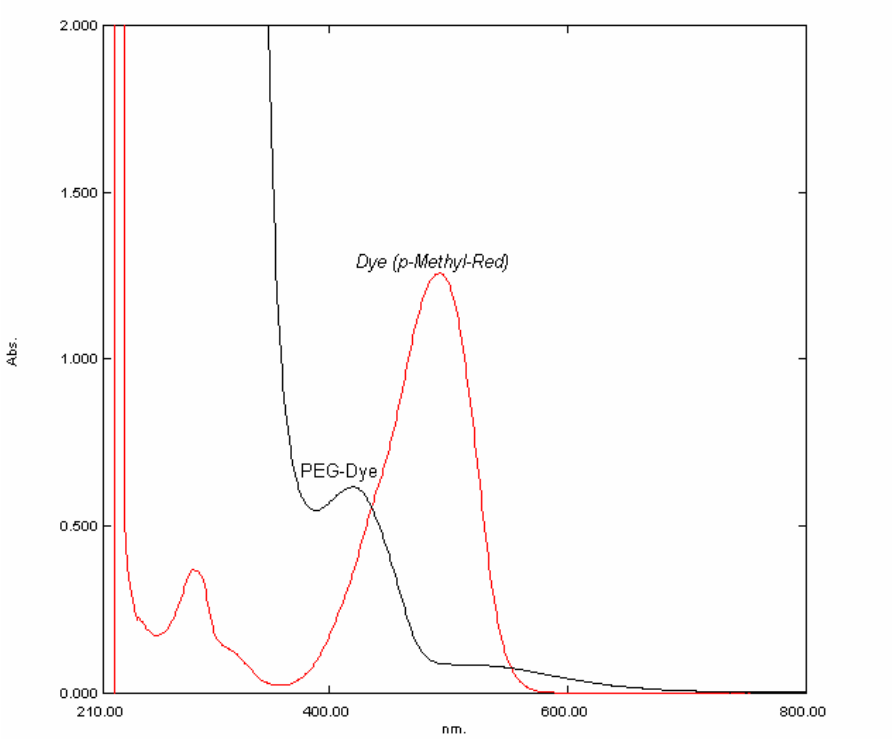
[a]The theoretical maximum concentration of the PEG-dye possible in the recovery flask is 1.33 mM (0.1 mmol of PEG-dye in 75 mL of CH_2Cl_2); the % dialyzed out can be computed as; [(**c**) / (1.33 mM) × 100]



Soxhlet-Dialysis for the recovery of **1**: average recovery = 98%



Change in the rate of Soxhlet Dialysis by changing the capacity of the soxhlet chamber: ▲ = 50 mL soxhlet chamber; ■ = 100 mL soxhlet chamber.



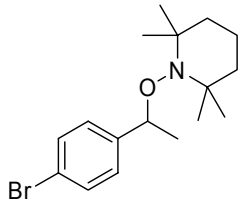
UV absorption spectra of PEG-dye and *p*-Methyl-Red dye.

6.4 Nanoporous Thin Films from a Cleavable Diblock Co-polymer:

All of the reactions reported herein, unless otherwise noted, were conducted under an inert atmosphere of N_2 in oven-dried glassware. PEG (purchased from Aldrich, MW = 5000) was used without further purification. Styrene and bromostyrene were freshly distilled over calcium hydride prior to use. All solvents (THF, toluene and diethyl ether) were distilled from a Na/benzophenone ketyl and stored under inert atmosphere. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. Reported yields refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR, ^{13}C NMR. NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer. Chemical shifts were reported in ppm downfield from TMS as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; br, broad; and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The PS-*b*-PEG diblock co-polymer was characterized by GPC

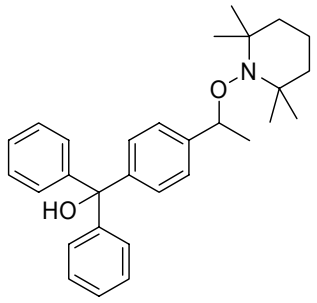
• **1-[1-(4-Bromo-phenyl)-ethoxy]-2,2,6,6-tetramethyl-piperidine 4**: To a solution of *p*-bromo styrene (5 g, 27.3 mmol) and TEMPO (4.27 g, 27.3 mmol) in 1:1 toluene/ethanol (500 mL) was added [N, N' –bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato] manganese (III) chloride (Jacobsen's catalyst) (2.6 g, 4.10 mmol) followed by di-*tert*-butyl peroxide (3.99 g, 27.3 mmol) and sodium borohydride (2.07 g, 54.6 mmol). The reaction mixture was then stirred (opened to the atmosphere) at 25 °C for 24 h, evaporated to dryness and partitioned between CH_2Cl_2 (100 mL) and water (200 mL), and the aqueous layer was further extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with anhydrous sodium sulfate, evaporated to dryness, and the crude product purified by flash column chromatography eluting with 1:7 CH_2Cl_2/hexanes. The *p*-bromo alkoxyamine, **4**, was recrystallized from acetonitrile to afford a white

crystalline solid (4.65 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.64, 1.00, 1.14, 1.27 (each s, 12 H, -C*H*$_3$), 1.25-1.60 (m, 6 H, -C*H*$_2$-), 1.43-1.44 (d, *J* = 6.7 Hz, 3H, -C*H*$_3$), 4.70-4.75 (q, *J* = 6.7 Hz, 1H, -C*H*), 7.17-7.19 (d, *J* = 8.4 Hz, 2 H, H_{Ar}), 7.41-7.43 (d, *J* = 8.4Hz, 2 H, H_{Ar}); Anal. Calcd. for $C_{17}H_{26}BrNO$: C, 60.00; H, 7.70; Br, 23.48; N, 4.12; Found: C, 60.07; H, 7.80; N, 4.16.



• **Diphenyl-{4-[1-(2,2,6,6-tetramethyl-piperidin-1-yloxy)-ethyl]-phenyl}-methanol 6**: To a stirring solution of **4** (0.5 g, 1.47 mmol) in THF (10 mL) at -78 °C, was added *n*-butyl lithium (1.1 mL. 1.76 mmol), dropwise via a syringe and needle. The resultant pale-orange solution was allowed to stir for 30 minutes after which it was transferred, via a syringe and needle, to a stirring solution of benzophenone (0.27 g, 1.47 mmol) in THF (5 mL) at -78 °C. The reaction mixture turned bluish-green and then back to pale-orange. On completion of the reaction, as determined by TLC analysis (4:1 hexanes/ethylacetate), the reaction mixture was concentrated in vacuo and the oily residue taken up in water, acidified (2 N HCl), extracted with CH_2Cl_2 (3 x 50 mL) and washed with brine (1 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, evaporated to dryness, and the resultant white solid was recrystallized from hexanes to afford white crystals of **6** (0.52 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.19, 1.26, 1.45, 1.90 (each s, 12 H, -C*H*$_3$), 1.45-1.74 (m, 6 H, -C*H*$_2$-), 1.74-1.76 (d, *J* = 4 Hz, 3H -C*H*$_3$), 6.23-6.28 (q, *J* = 4 Hz, 1H, -C*H*), 7.24-7.50 (m, 14 H, H_{Ar}), 13.52 (s (br), 1 H, -O*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 15.8, 21, 23.7, 28.6, 36.8, 81.9, 84.9, 126.4, 127.4,

127.8, 128, 128.3, 140, 146.6, 147.0; Anal. Calcd. for $C_{30}H_{37}NO_2$: C, 81.22; H, 8.41; N, 3.16; Found:



• **PEG-supported trityl-TEMPO initiator 4:** Into a 100 mL Schlenk flask was placed a magnetic stir-bar, **6** (0.25 g, 0.56 mmol), sodium hydride (95 wt% suspension in mineral oil) (0.04 g, 1.68 mmol) and THF (20 mL). The suspension was heated to 70 °C for 48 h after which it changed into an orange solution. Next, a solution of PEG mesylate (PEG MW = 5000) (1.43 g, 0.28 mmol) in THF (10 mL) was added to the reaction mixture and it was allowed to stir at 70 °C. After 24 h, the reaction mixture was left to cool to room temperature, filtered through a pad of celite and concentrated in vacuo. The oily residue was added drop-wise to stirring diethyl ether at 0 °C and the precipitate taken up in a minimal amount of CH_2Cl_2, and precipitated from diethyl ether (x 2). The white solid obtained (1.36 g, 90%) was dried under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.59, 0.99, 1.12, 1.24 (each s (br), 12 H, -C*H*$_3$), 1.25-1.42 (m (br) 6 H, -C*H*$_2$-), 1.43-1.47 (d, *J* = 4 Hz, 3H -C*H*$_3$), 3.36 (s, 3 H, C*H*$_3$-O-PEG-), 4.71-4.76 (q, 2 H, -CH$_2$-C*H*$_2$-O-trityl-), 6.44-6.50 (q, *J* = 4 Hz, 1H, -C*H*), 7.18-7.44 (m, 14 H, H_{Ar}).

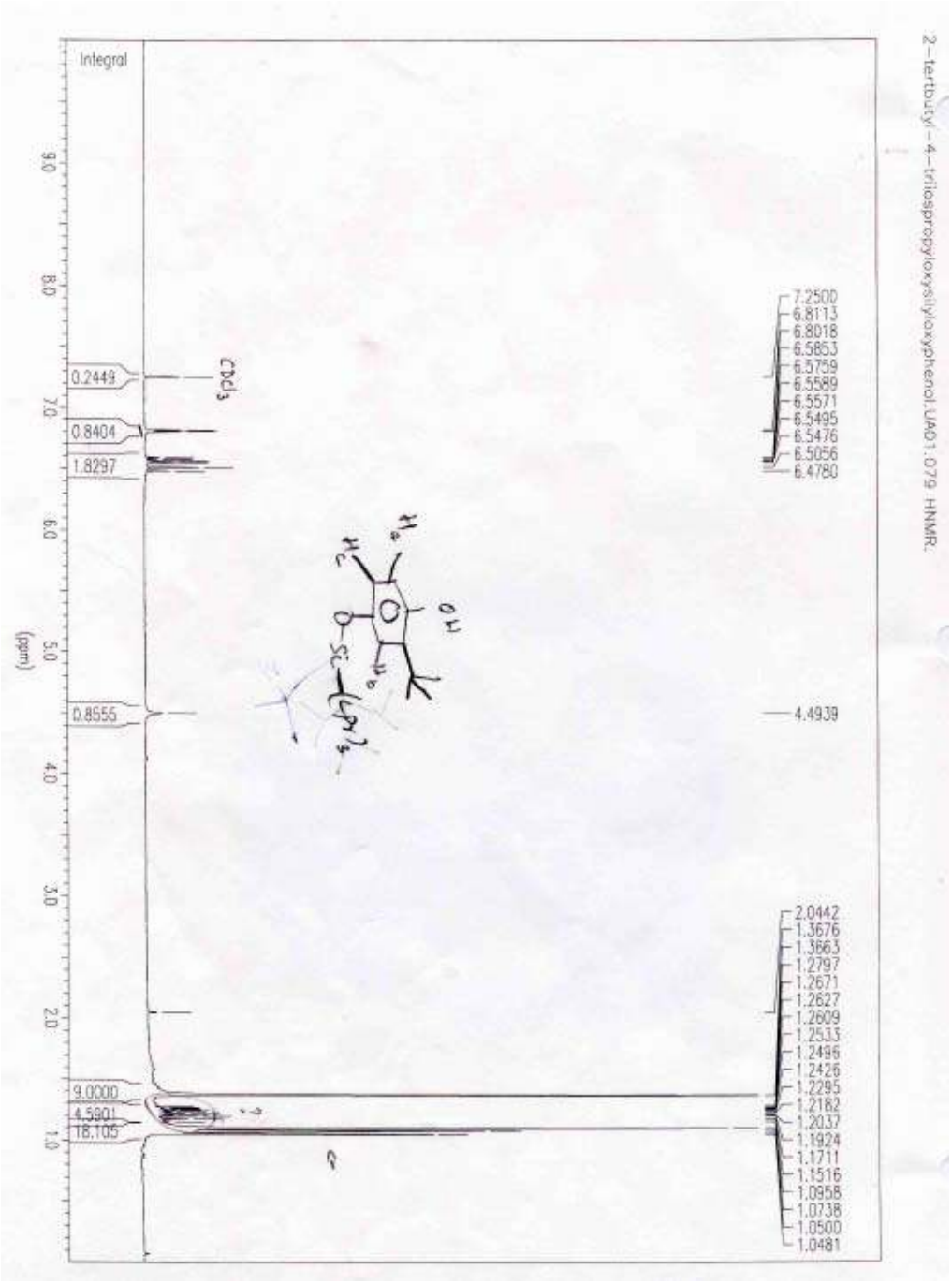
- **“Living” Free radical Polymerization**:

The typical procedure for LFRP of the PEG-supported initiator, **4**, was as follows: To a solution of **4** (0.05 g, 0.021 mmol) in degassed toluene (1.0 mL), is added styrene (100 molar equiv., 0.22 g, 2.06 mmol). The reaction mixture is heated to 130 °C for 24 h. The reaction mixture was cooled to room temperature and added drop-wise to stirring methanol to precipitate the PS-*b*-PEG diblock co-polymer, **7**, as a white solid. This was characterized by GPC.

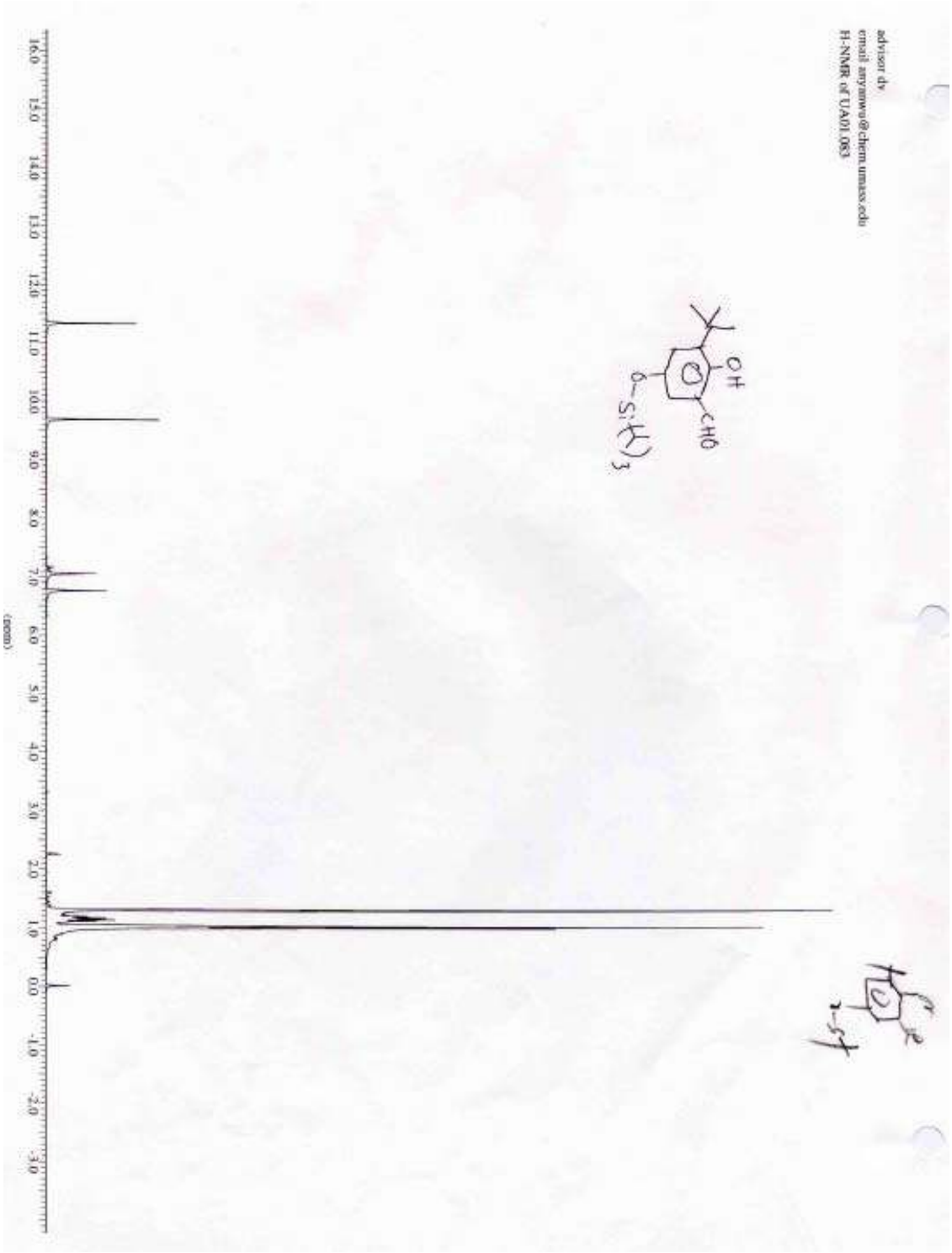
APPENDIX

SPECTRAL DATA

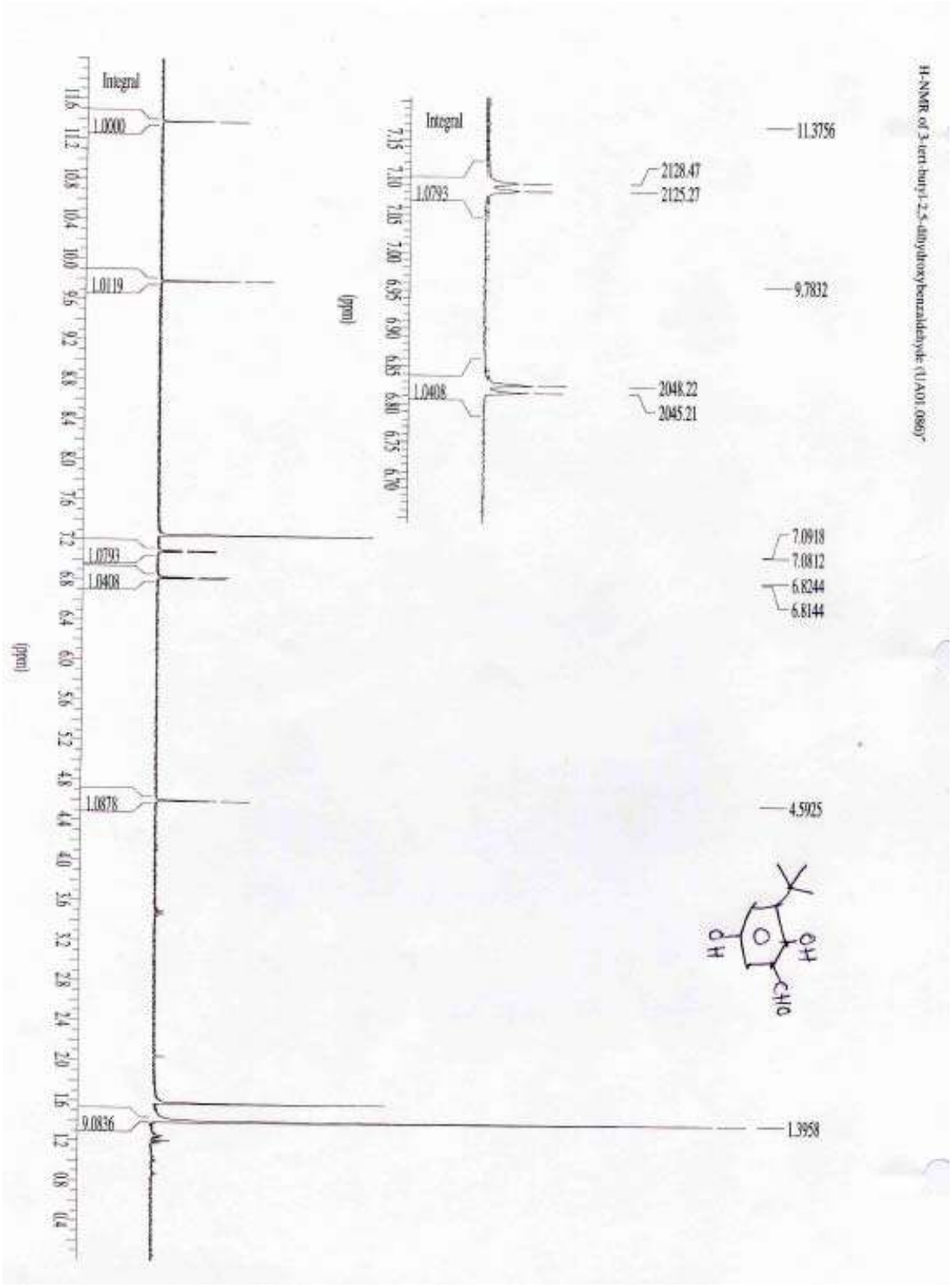
^{1}H NMR spectrum of 2-*tert*-butyl-4-tri-*iso*-propyloxysilyloxyphenol



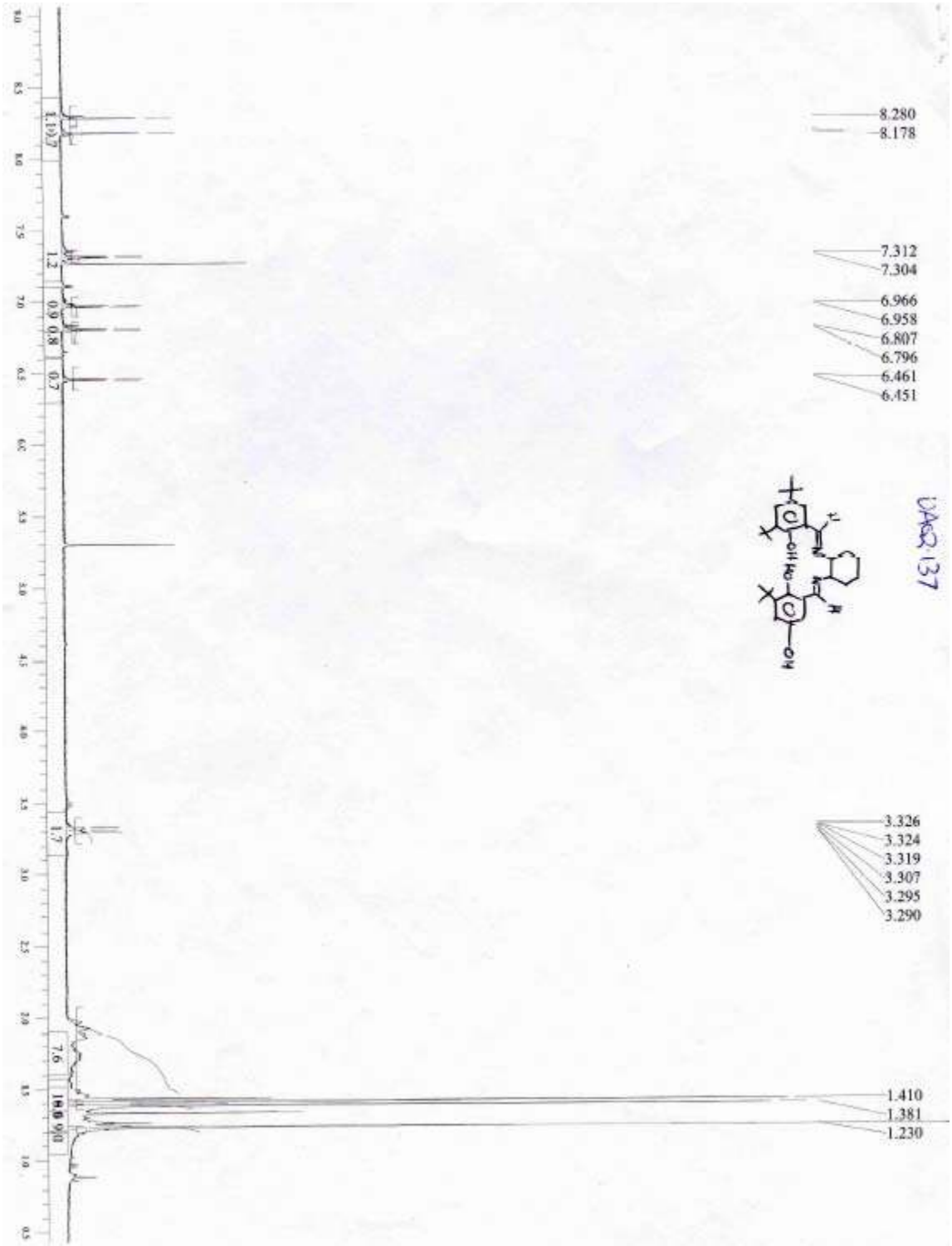
^{1}H NMR spectrum of 2-hydroxy-3-*tert*-butyl-5-tri-*iso*-propyloxysilyloxybenzaldehyde



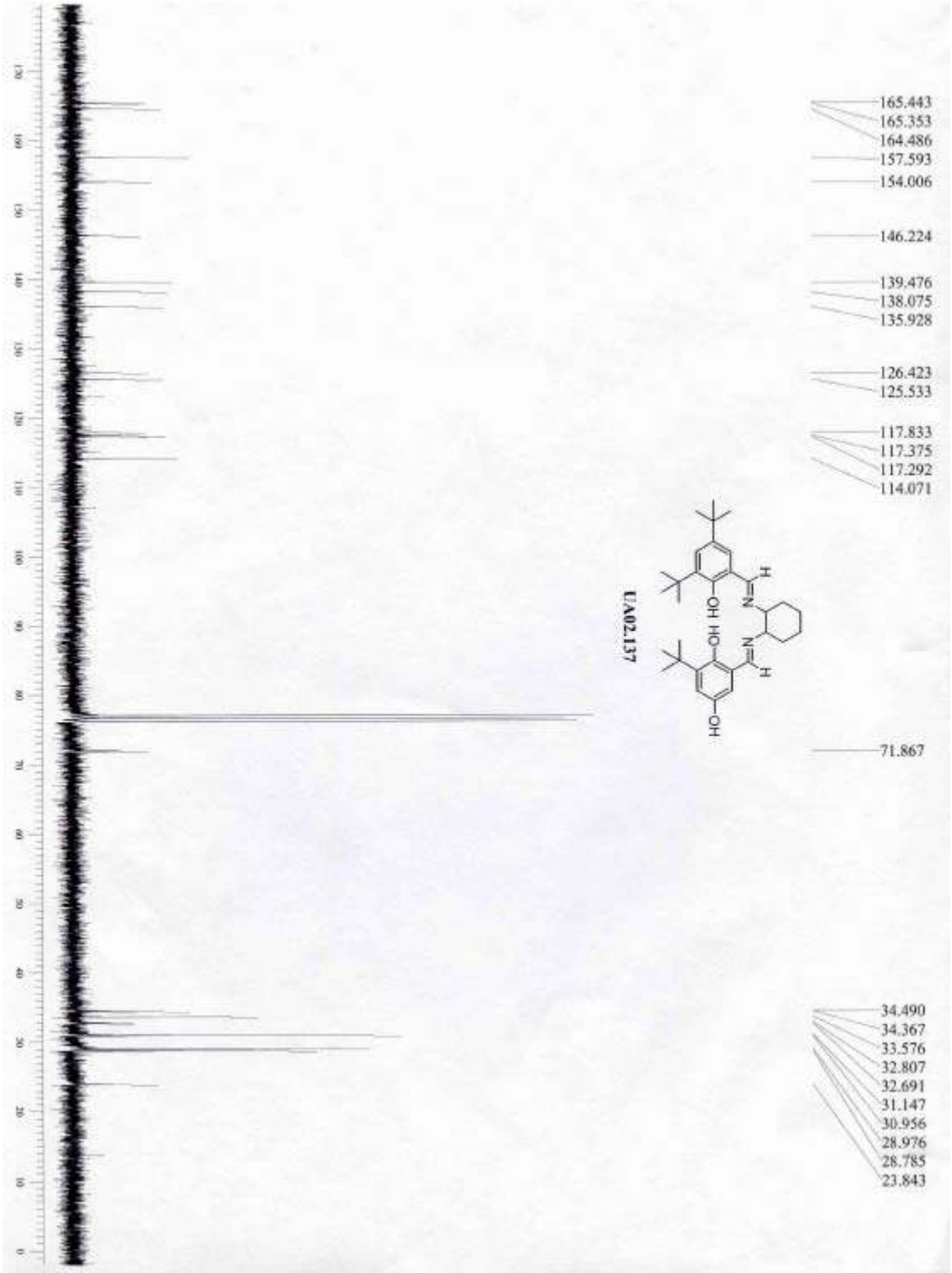
^{1}H NMR spectrum of 3-*tert*-butyl-2,5-dihydroxybenzaldehyde



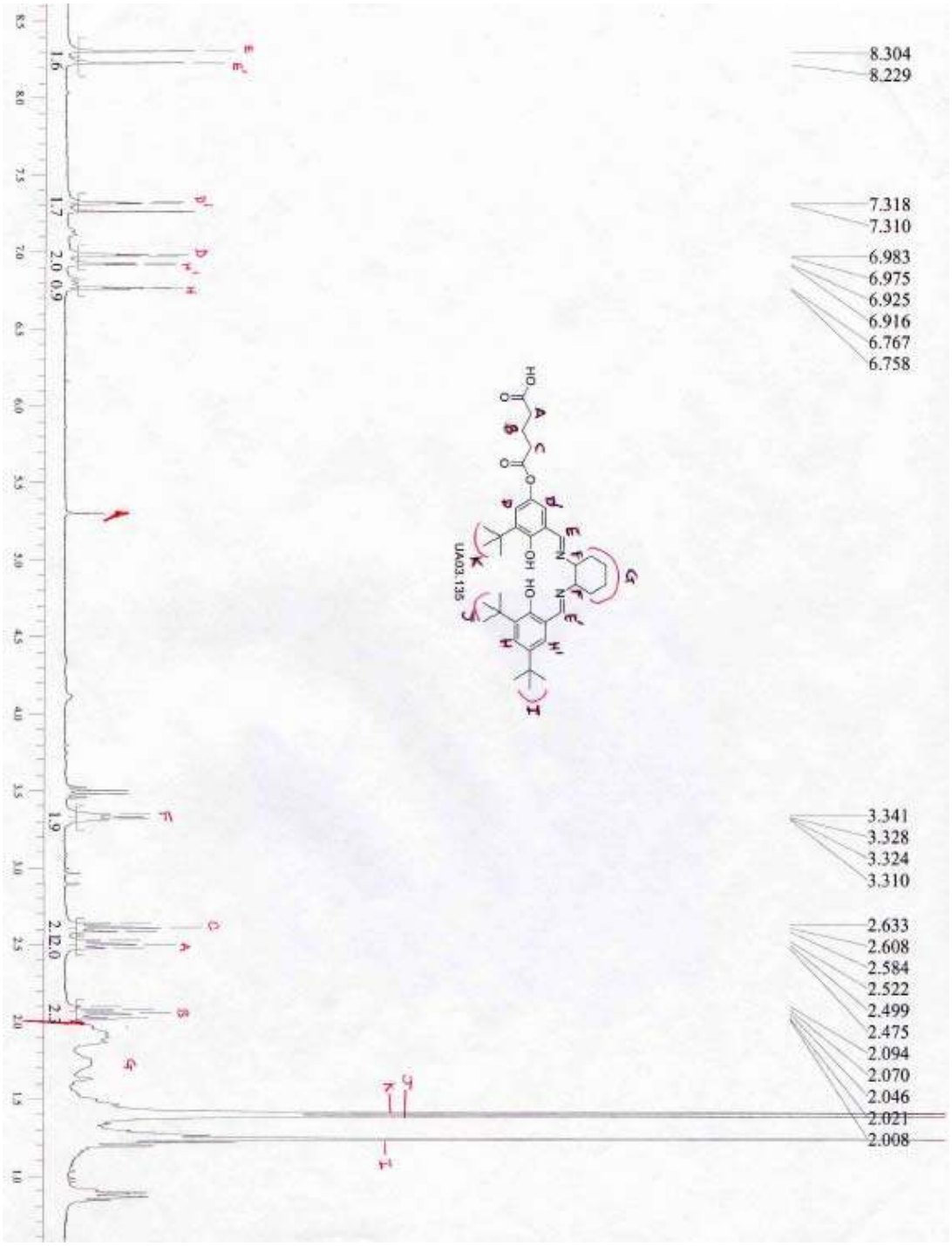
^{1}H NMR spectrum of unsymmetrical salen ligand **1**



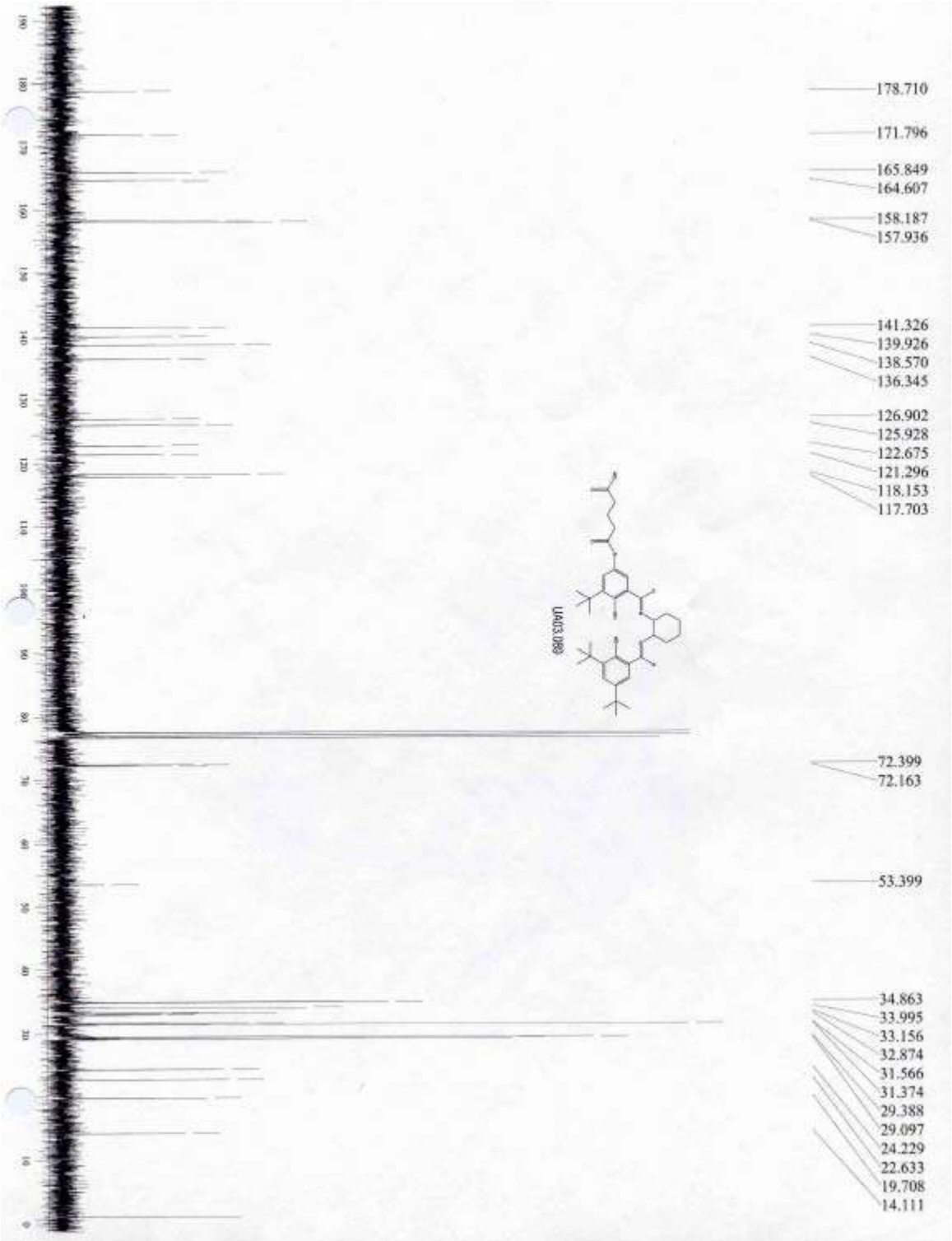
^{13}C NMR spectrum of unsymmetrical salen ligand **1**



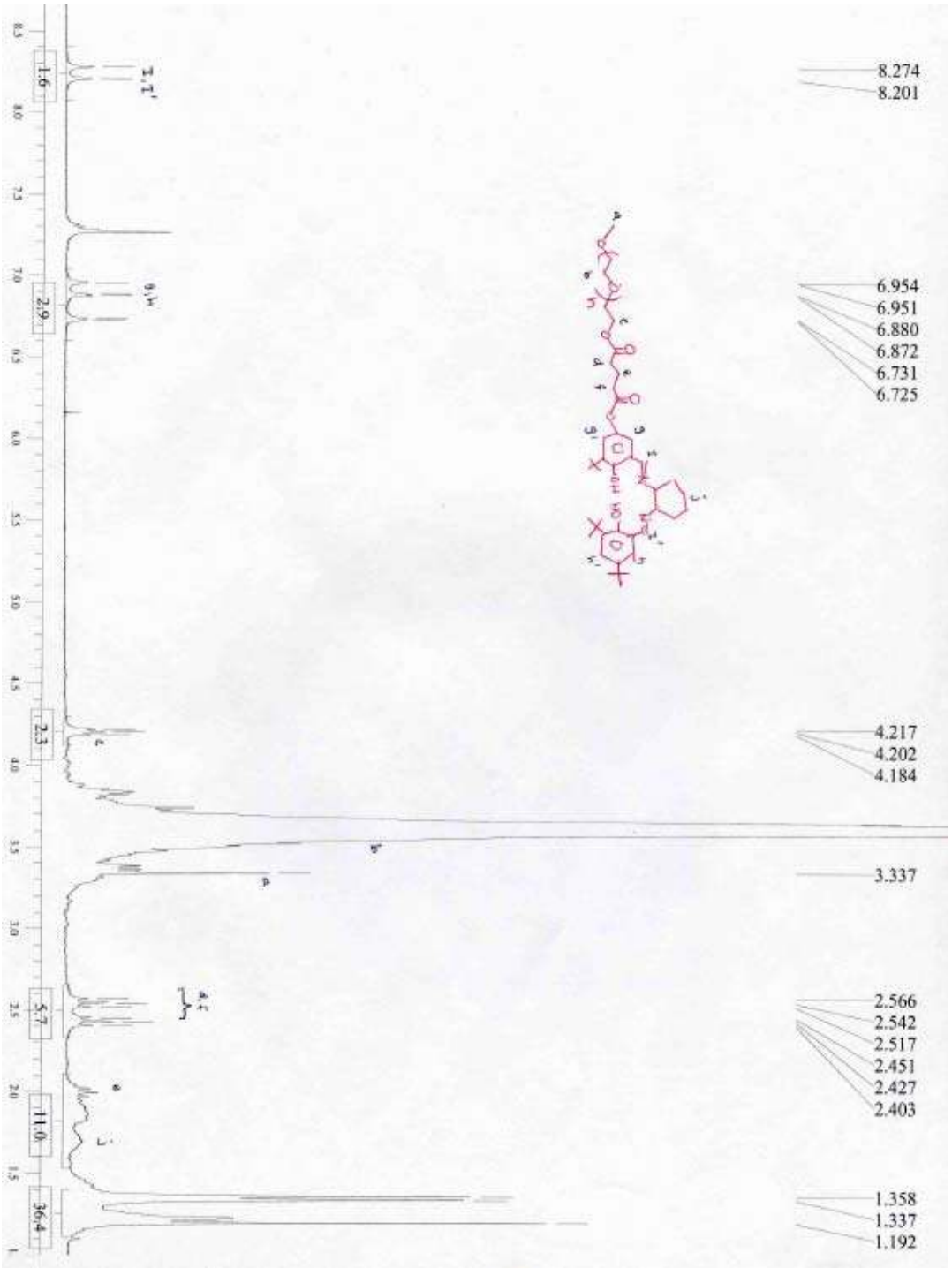
^{1}H NMR spectrum of salen glutarate ester



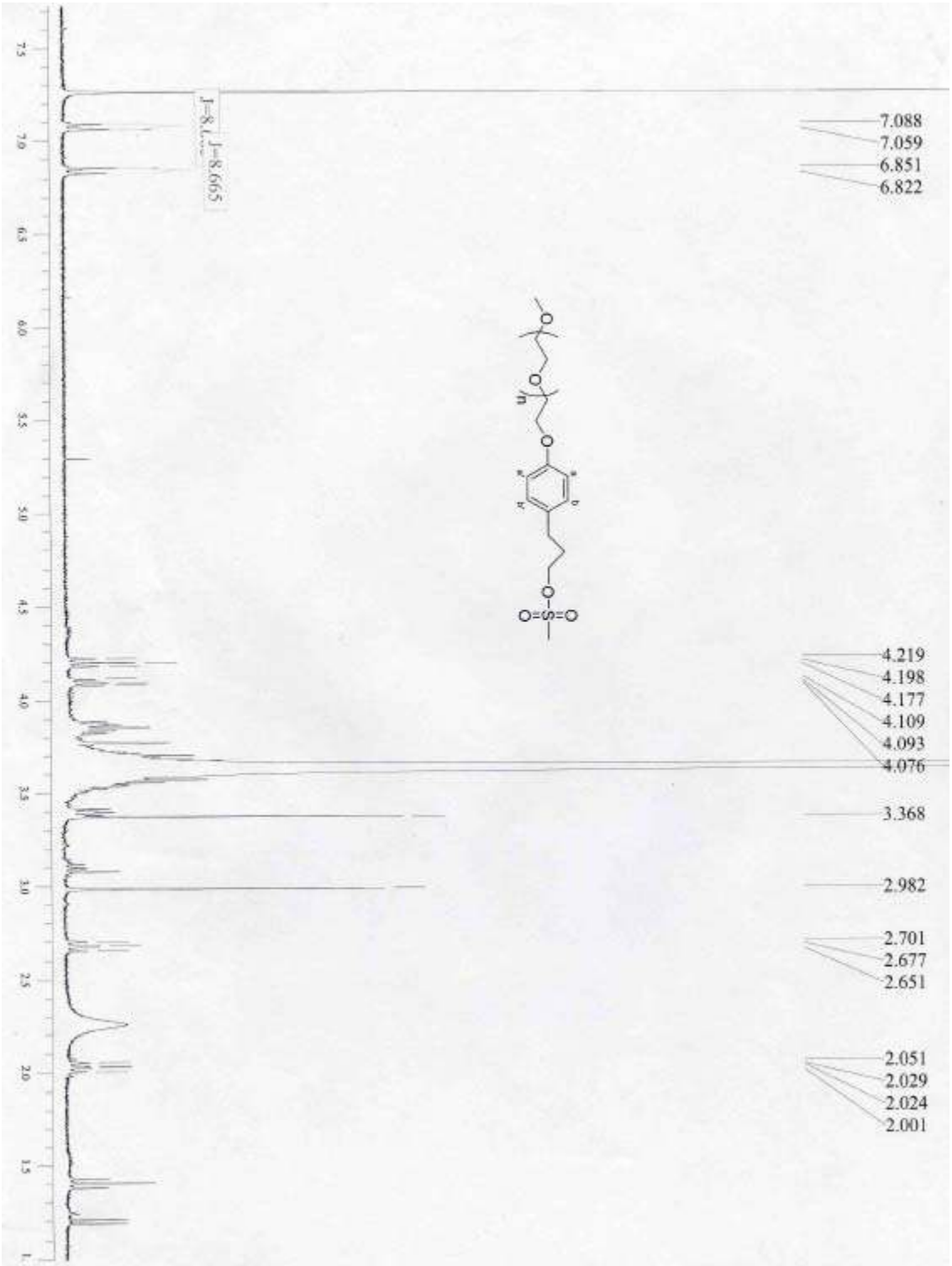
^{13}C NMR spectrum of salen glutarate ester



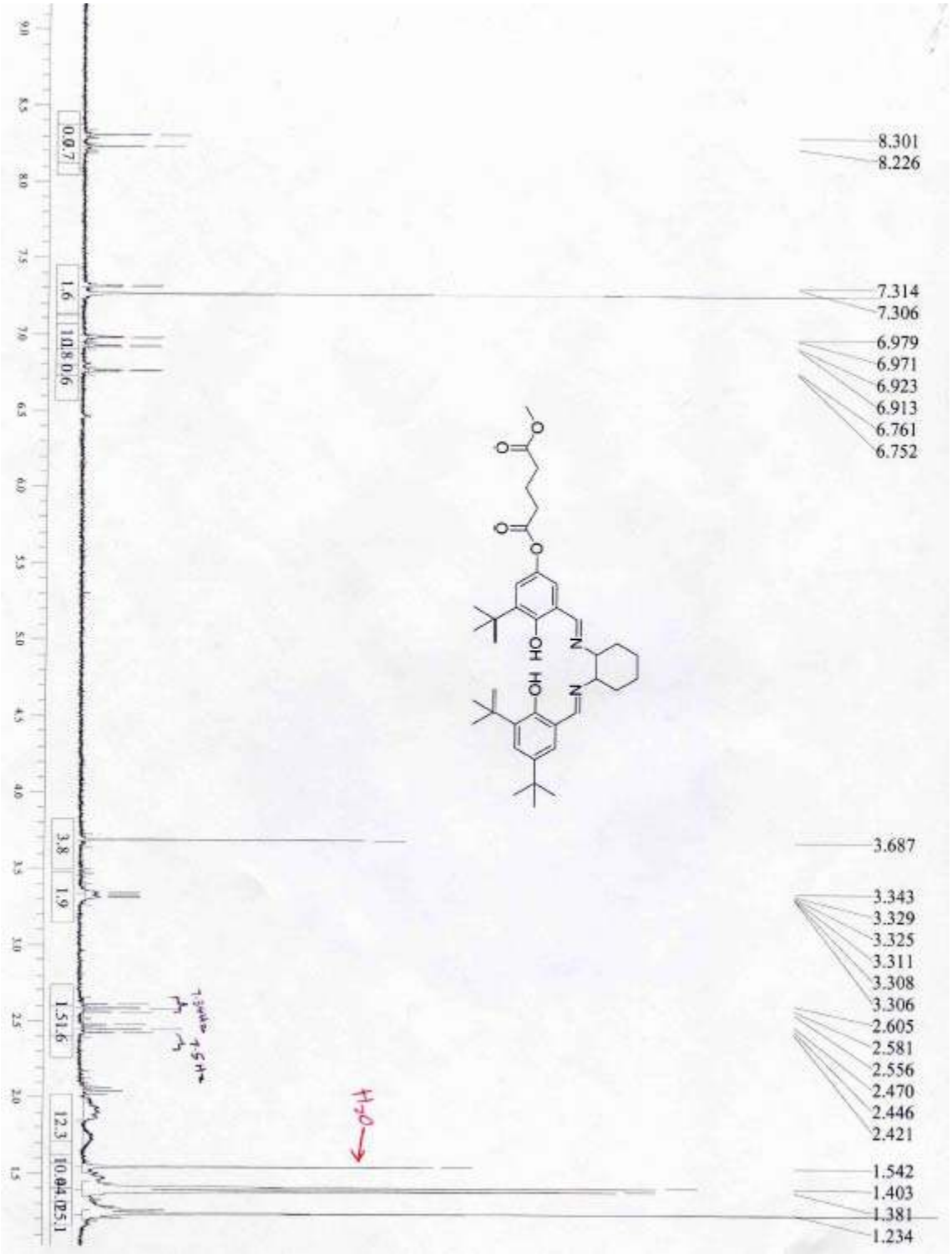
^{1}H NMR spectrum of PEG-supported salen ligand **7**



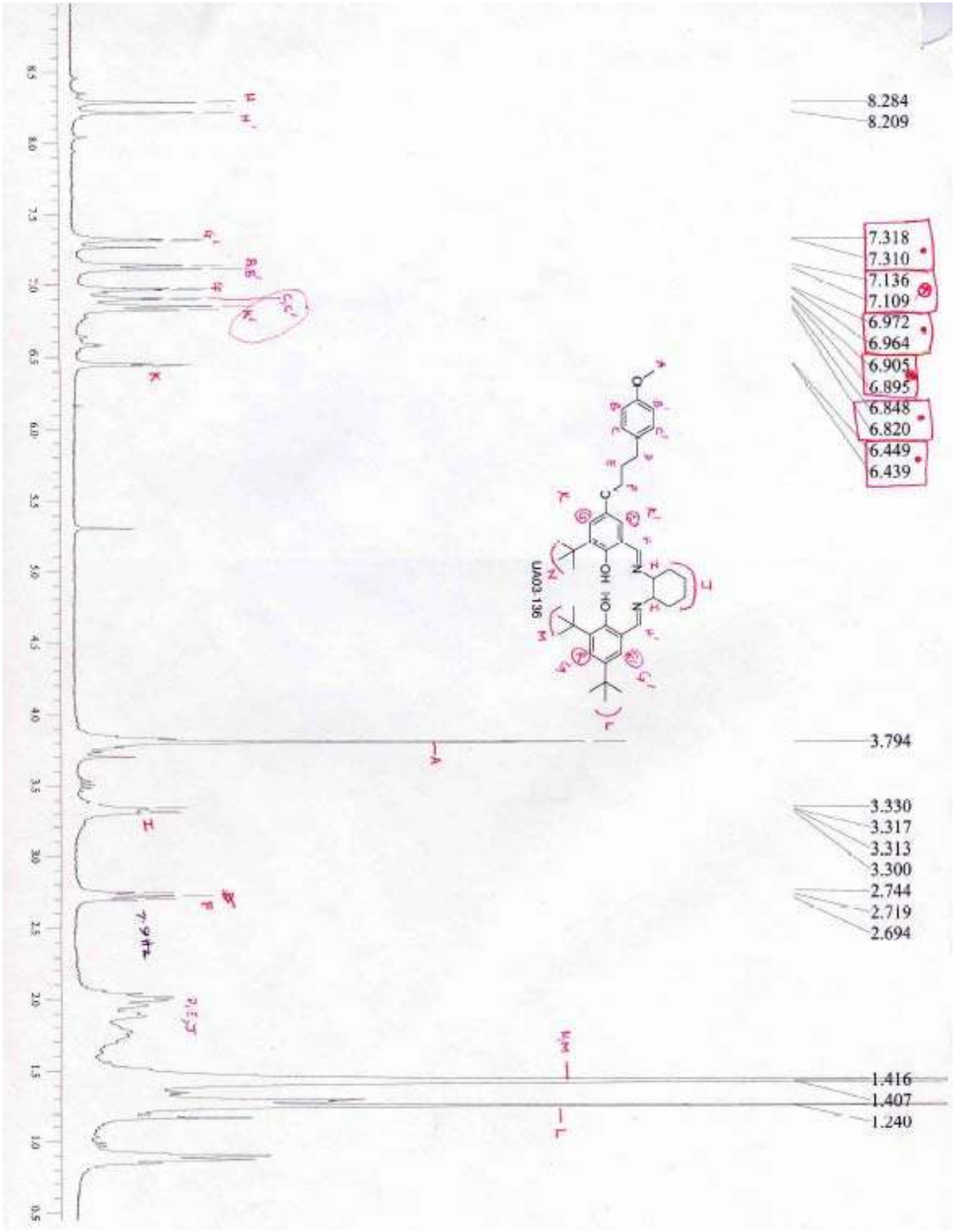
^{1}H NMR spectrum of PEG-supported linker **5**



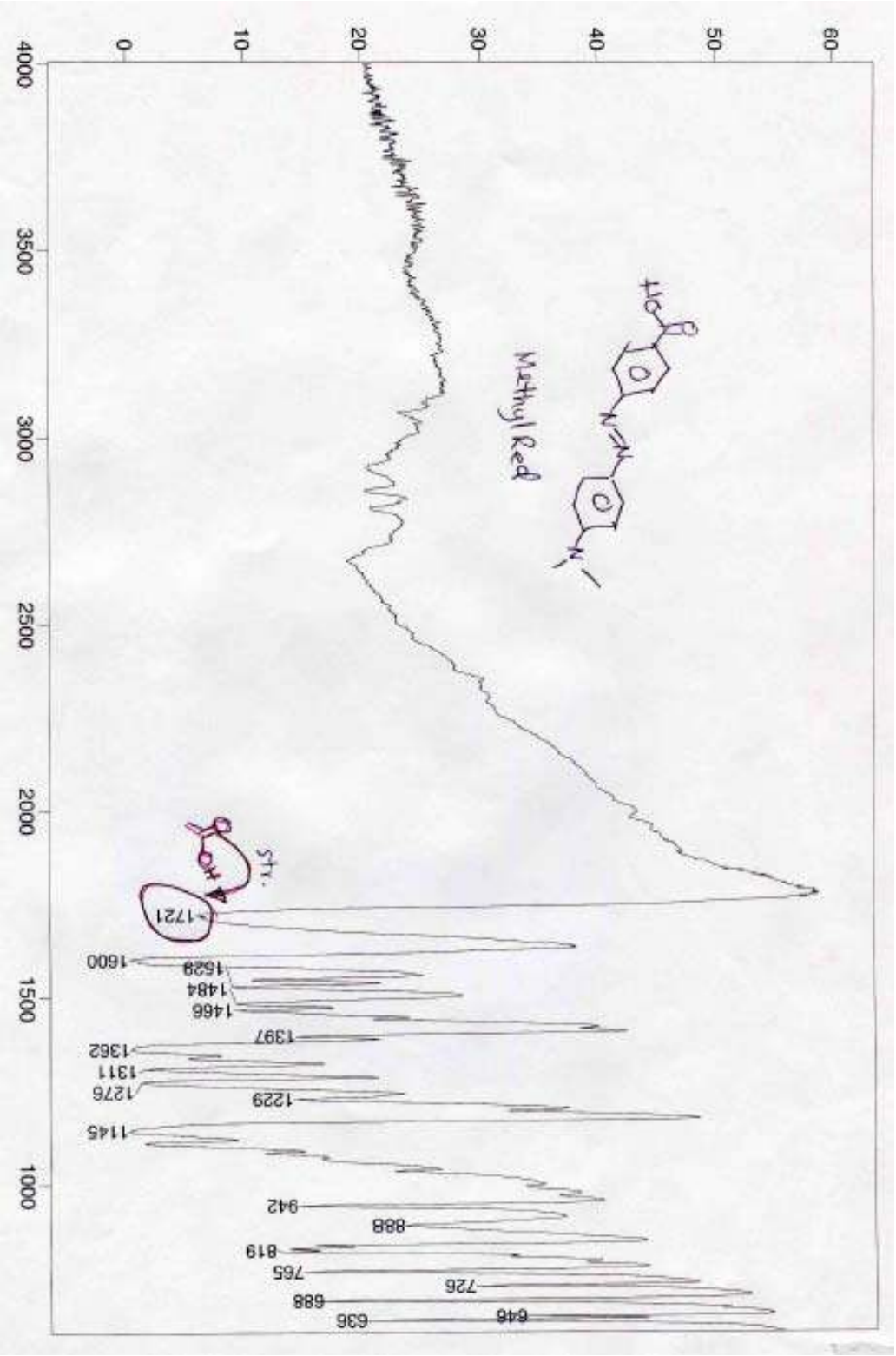
^{1}H NMR spectrum of PEG-supported salen ligand **9**



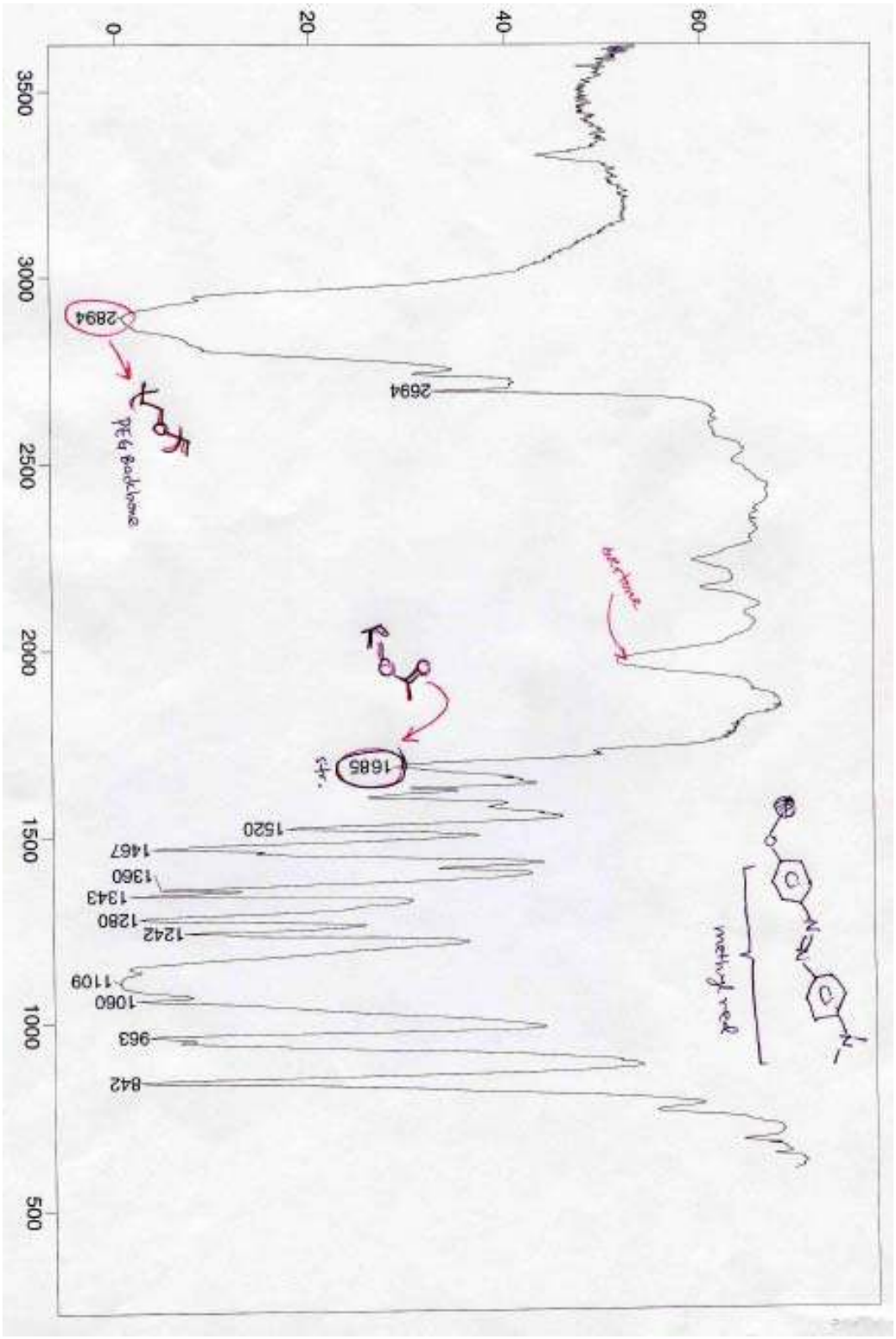
^{1}H NMR spectrum of PEG-supported salen ligand **10**



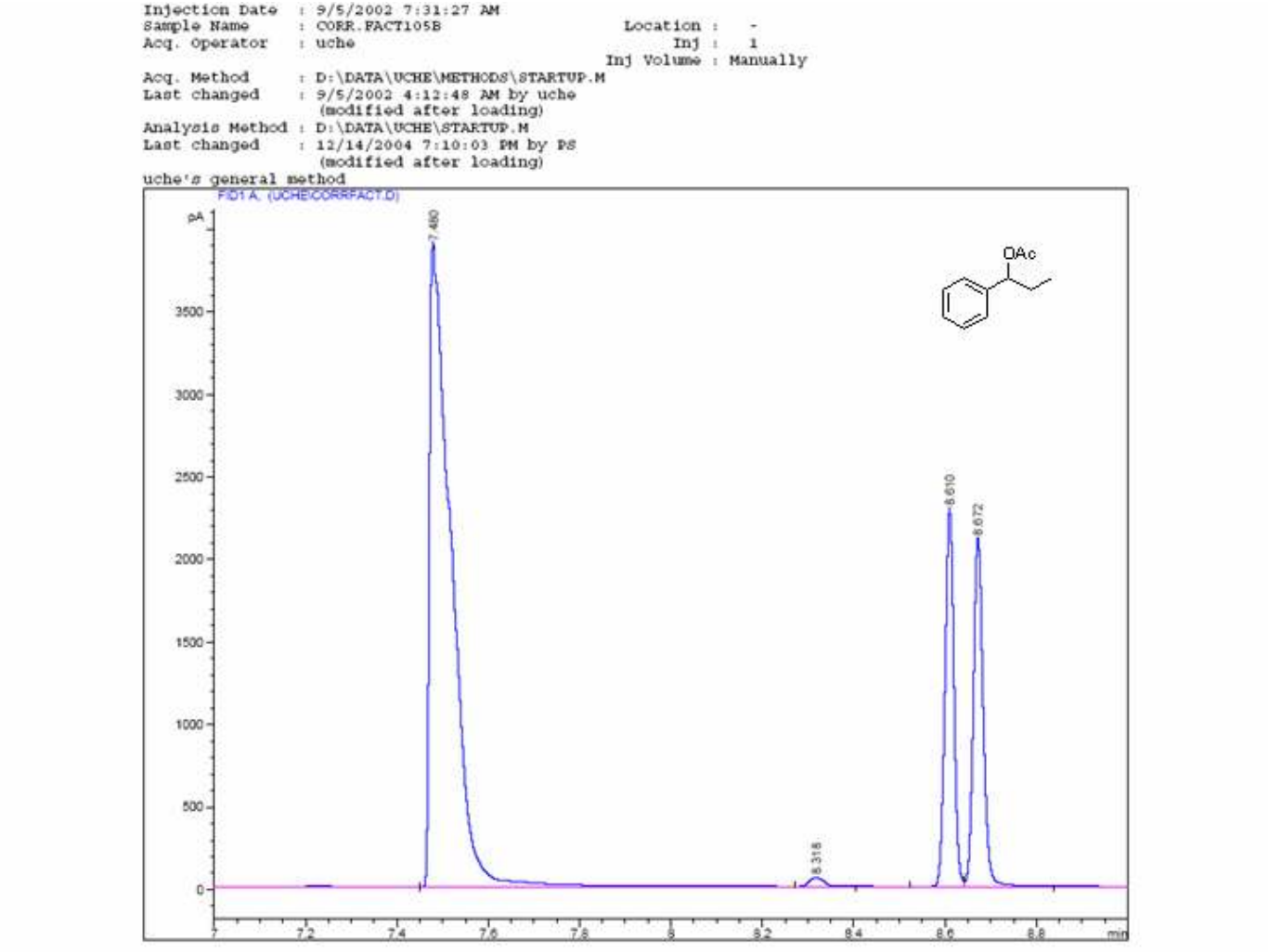
FT-IR spectrum of *p*-methyl red (dye)



FT-IR spectrum of PEG-dye



Chiral GC spectrum of rac-1-phenyl-1-propyl acetate



Dodecane internal standard was used to calibrate the GC column sensitivity for enantiomers. Enantiomeric ratio (*er*) was calculated as:

$$\frac{\text{(Peak area of S enantiomer)}}{\text{(Peak area of S enantiomer) + (Peak area of R enantiomer)}}$$

Chiral GC spectrum of (*R*)-(+)-1-phenyl-1-propyl acetate

```
Injection Date  : 9/5/2002 6:58:06 PM
Sample Name     : UA03.105b                    Location :   -
Acq. Operator   : uche                            Inj :   1
                                              Inj Volume : Manually

Acq. Method     : D:\DATA\UCHE\METHODS\STARTUP.M
Last changed    : 7/10/2002 1:50:00 PM by uche
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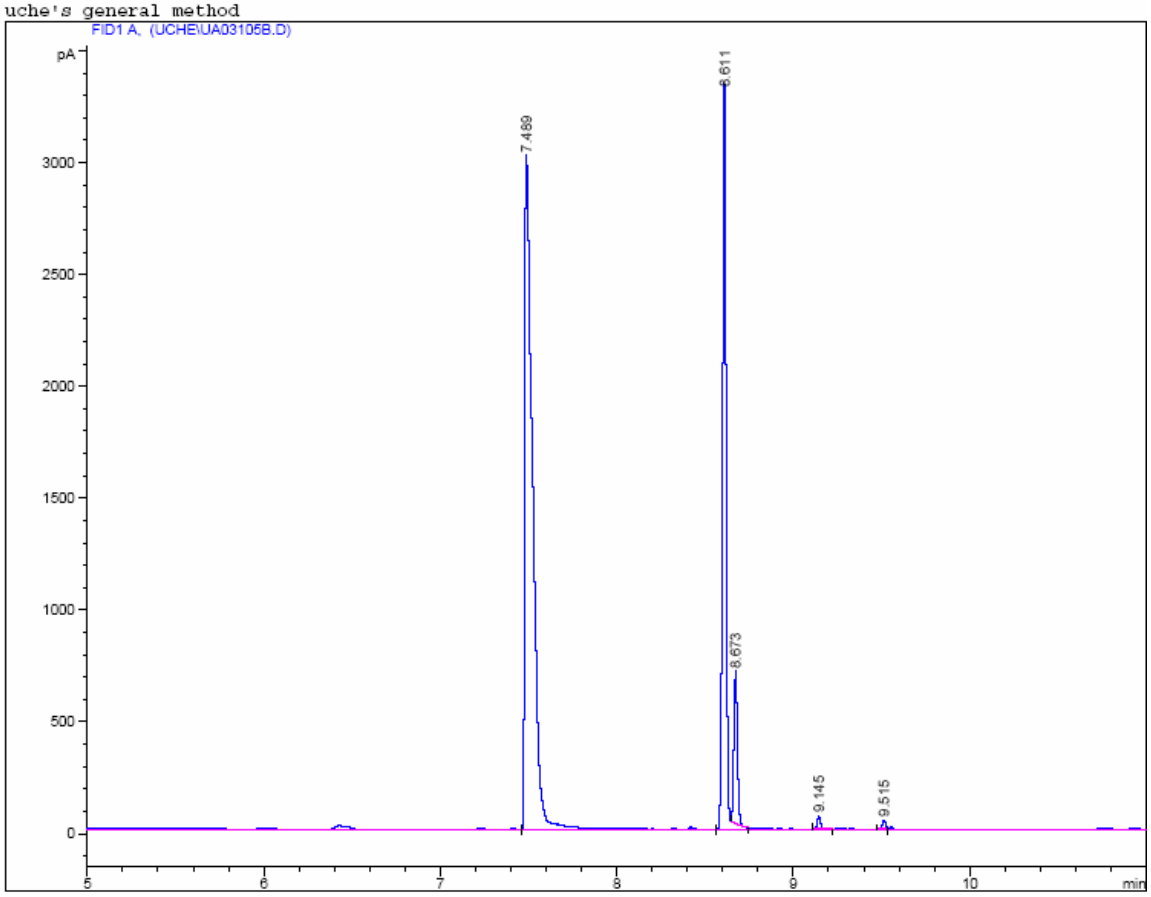

BIBLIOGRAPHY

(1) Aerts, S.; Weyton, H.; Buekenhoudt, A.; Gevers, L. E. M.; Vankelecom, I. F. J.; Jacobs, P. A. "Recycling of the homogenous Co-Jacobsen catalyst through solvent-resistant nanofiltration (SRNF)" *Chem. Commun.* **2004**, *6*, 710-711.

(2) Albrecht, M.; Hovestad, N. J.; Boersma, J.; van Koten, G. "Multiple use of soluble metallodendritic materials as catalysts and dyes" *Chem. Eur. J.* **2001**, *7*, 1289-1294.

(3) Altava, B.; Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Luis, S. V.; Mayoral, J. A.; Vicent, M. J. "How important is the inert matrix of supported enantiomeric catalysts? Reversal of topicity with two polystyrene backbones" *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1503.

(4) Altava, B.; Burguete, M. I.; Garcia-Verdugo, E.; Luis, S. V.; Vicent, M. J.; Mayoral, J. A. "Supported chiral catalysts: the role of the polymeric network" *React. Funct. Polym.* **2001**, *48*, 25-35.

(5) Angeletti, R. H.; Bonewald, L. F.; Fields, G. B. *Six-year study of peptide synthesis*, 1997; Vol. 289, pp 780.

(6) Angelino, M. D.; Laibinis, P. E. "Synthesis and Characterization of a Polymer-Supported Salen Ligands for Enantioselective Epoxidation" *Macromolecules* **1998**, *31*, 7581.

(7) Annis, D. A.; Jacobsen, E. N. "Polymer-Supported Chiral Co(Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides" *J. Am. Chem. Soc.* **1999**, *121*, 4147-4154.

(8) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. "PEG-Supported Bisoxazolines as Ligands for Catalytic Enantioselective Synthesis" *J. Org. Chem* **2001**, *66*, 3160-3166.

(9) Anyanwu, U. K.; Venkataraman, D. "Effect of spacers on the activity of soluble polymer supported catalysts for the asymmetric addition of diethylzinc to aldehydes" *Tetrahedron Lett.* **2003**, *44*, 6445-6448.

(10) Bates, F. S.; Fredrickson, G. H. "Block Copolymer Thermodynamics - Theory and Experiment" Annu. Rev. Phys. Chem. **1990**, *41*, 525-557.

(11) Bayer, E.; Schurig, V. "New Class of Catalysts" *Chemtech* **1976**, *6*, 212-214.

(12) Bednarski, M. D.; Chenault, H. K.; Simon, E. S.; Whitesides, G. M. "Membrane-Enclosed Enzymatic Catalysis (Meec) - a Useful, Practical New Method for the Manipulation of Enzymes in Organic-Synthesis" *J. Am. Chem. Soc.* **1987**, *109*, 1283-1285.

(13) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. "The Asymmetric addition of trimethylsilyl cyanide to aldehydes catalyzed by chiral (salen) titanium complexes" *J. Am. Chem. Soc.* **1999**, *121*, 3968-3973.

(14) Bergbreiter, D. E. "Using Soluble Polymers to Recover Catalysts and Ligands" *Chem. Rev.* **2002**, *102*, 3345-3384.

(15) Bergbreiter, D. E.; Chandran, R. "Polyethylene-Bound Rhodium(I) Hydrogenation Catalysts" *J. Am. Chem. Soc.* **1987**, *109*, 174-179.

(16) Bergbreiter, D. E.; Hughes, R.; Besinaiz, J.; Li, C. M.; Osburn, P. L. "Phase-Selective Solubility of Poly(N-alkylacrylamide)s" *J. Am. Chem. Soc.* **2003**, *125*, 8244-8249.

(17) Bergbreiter, D. E.; Li, C. M. "Poly(4-tert-butylstyrene) as a Soluble Polymer Support in Homogeneous Catalysis" *Org. Lett.* **2003**, *5*, 2445-2447.

(18) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. "Nonpolar Polymers for Metal Sequestration and Ligand and Catalyst Recovery in Thermomorphic Systems" *J. Am. Chem. Soc.* **2001**, *123*, 11105-11106.

(19) Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C. M.; Frels, J. D. "Using Soluble Polymers in Latent Biphasic Systems" *J. Am. Chem. Soc.* **2003**, *125*, 6254-6260.

(20) Bergbreiter, D. E.; Sung, S. D.; Li, J.; Oritz, D.; Hamilton, P. N. "Designing Polymers for Biphasic Liquid/Liquid Separations after Homogeneous Reactions," *Org. Process Res. Dev.* **2004**, *8*, 461-468.

(21) Bernard, G.; Chauvin, Y.; Commereuc, D. "Comparison between Homogeneous Catalysis and Supported Homogeneous Catalysis in Hydrogenation by Rhodium-Phosphine Complexes 2. Non Soluble Supported Catalyst" *Bulletin De La Societe Chimique De France Partie Ii-Chimie Moleculaire Organique Et Biologique* **1976**, 1168-1172.

(22) Boker, A.; Muller, A. H. E.; Krausch, G. "Nanoscopic surface patterns from functional ABC triblock copolymers" *Macromolecules* **2001**, *34*, 7477-7488.

(23) Bolm, C.; Tanyeli, C.; Grenz, A.; Dinter, C. L. "ROMP-polymers in asymmetric catalyst: The role of the polymer backbone" *Adv. Synth. Catal.* **2002**, *344*, 649-656.

(24) Bonaccorsi, C.; Bachmann, S.; Mezzetti, A. "Electronic tuning of the PNNP ligand for the asymmetric cyclopropanation of olefins catalysed by RuCl(PNNP)" *Tetrahedron: Asymmetry* **2003**, *14*, 845-854.

(25) Boyce, M.; Clarke, B.; Cunningham, D.; Gallagher, J. F.; Higgins, T.; McArdle, P.; Cholcuin, M. N.; O'Gara, M. "Transition-Metal Schiff-Base Complexes as Ligands in Tin Chemistry" *Organomet. Chem.* **1995**, *498*, 241.

(26) Bronsted, J. N. "Acid Base Catalysis" *Chem. Rev.* **1928**, *5*.

(27) Campbell, E. J.; Nguyen, S. T. "Unsymmetrical salen-type ligands: high yield synthesis of salen-type Schiff bases containing two different benzaldehyde moieties" *Tetrahedron Lett.* **2001**, *42*, 1221-1225.

(28) Casalnuovo, A. L.; Rajanbabu, T. V.; Ayers, T. A.; Warren, T. H. "Ligand Electronic Effects in Asymmetric Catalysis - Enhanced Enantioselectivity in the Asymmetric Hydrocyanation of Vinylarenes" *J. Am. Chem. Soc.* **1994**, *116*, 9869-9882.

(29) Casey, M.; Smyth, M. P. "Ligand electronic effects in enantioselective diethylzinc additions" *Synlett* **2003**, 102-106.

(30) Cashin, B.; Cunningham, D.; Daly, P.; McArdle, P.; Munroe, M.; Ni Chonchubhair, N. "Donor properties of the vanadyl ion: Reactions of vanadyl salicylaldimine beta-ketimine and acetylacetonato complexes with groups 14 and 15 Lewis acids" *Inorg. Chem.* **2002**, *41*, 773-782.

(31) Cavallo, L.; Jacobsen, H. "Electronic effects in (salen)Mn-based epoxidation catalysts" *J. Org. Chem.* **2003**, *68*, 6202-6207.

(32) Chen, C.-Y.; Dagneau, P.; Grabowski, E. J. J.; Oballa, R.; O'Shea, P.; Prasit, P.; Robichaud, J.; Tillyer, R.; Wang, X. "Practical Asymmetric Synthesis of a Potent Cathepsin K Inhibitor. Efficient Palladium Removal Following Suzuki Coupling" *J. Org. Chem.* **2003**, *68*, 2633.

(33) Cole-Hamilton, D. J. "Homogeneous Catalysis - New Approaches to Catalyst Separation, Recovery, and Recycling" *Science* **2003**, *299*, 1702-1706.

(34) Cozzi, P. G. "Enantioselective alkynylation of ketones catalyzed by Zn(salen) complexes" *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 2895-2898.

(35) Cozzi, P. G. "Metal-Salen Schiff base complexes in catalysis: practical aspects" *Chem. Rev.* **2004**, *33*, 410-421.

(36) Cozzi, P. G.; Papa, A.; UmaniRonchi, A. "Enantioselective addition of Et_2Zn to aldehydes promoted by a chiral Schiff base metal complex" *Tetrahedron Lett.* **1996**, *37*, 4613-4616.

(37) Cunningham, D.; McArdle, P.; Mitchell, M.; Ni Chonchubhair, N.; O'Gara, M.; Franceschi, F.; Floriani, C. "Adduct formation between alkali metal ions and divalent metal salicylaldimine complexes having methoxy substituents. A structural investigation" *Inorg. Chem.* **2000**, *39*, 1639-1649.

(38) Dao, J.; Benoit, D.; Hawker, C. J. "A versatile and efficient synthesis of alkoxyamine LFR initiators via manganese based asymmetric epoxidation catalysts" J. Polym. Sci., Part A: Polym. Chem. **1998**, *36*, 2161- 2167.

(39) Datta, A.; Ebert, K.; Plenio, H. "Nanofiltration for homogeneous catalysis separation: soluble polymer-supported palladium catalyst for Heck, Sonogashira and Suzuki coupling of aryl halides" *Organometallics* **2003**, *22*, 4685-4691.

(40) Datta, A.; Plenio, H. "Nonpolar biphasic catalysis: Sonogashira and Suzuki coupling of aryl bromides and chlorides" *Chem. Commun.* **2003**, 1504-1505.

(41) De Smet, K.; Pleysier, A.; Vankelecom, I. F. J.; Jacobs, P. A. "Recycling of homogeneous hydrogenation catalysts by dialysis coupled catalysis" *Chem. Eur. J.* **2003**, *9*, 334-338.

(42) De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinheim, Germany, 2000.

(43) Dickerson, T. J.; Reed, N. N.; Janda, K. D. "Soluble Polymers as Scaffolds for Recoverable Catalysts and Reagents" *Chem. Rev.* **2002**, *102*, 3325-3344.

(44) Dijkstra, H. P.; Kruithof, C. A.; Ronde, N.; van de Coevering, R.; Ramon, D. J.; Vogt, D.; van Klink, G. P. M.; van Koten, G. "Shape-persistent nanosize organometallic complexes: Synthesis and application in a nanofiltration membrane reactor" *J. Org. Chem.* **2003**, *68*, 675-685.

(45) Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. "The Use of Ultra- and Nanofiltration Techniques in Homogeneous Catalyst Recycling" *Acc. Chem. Res.* **2002**, *35*, 798-810.

(46) DiMauro, E. F.; Kozlowski, M. C. "Salen-derived catalysts containing secondary basic groups in the addition of diethylzinc to aldehydes" *Org. Lett.* **2001**, *3*, 3053-3056.

(47) DiMauro, E. F.; Kozlowski, M. C. "Development of bifunctional salen catalysts: Rapid, chemoselective alkylations of alpha-ketoesters," *J. Am. Chem. Soc.* **2002**, *124*, 12668-12669.

(48) Doyle, M. P. *In Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(49) Dreisbach, C.; Wischnewski, G.; Kragl, U.; Wandrey, C. "Changes in Enantioselectivity with the Substrate Ratio for the Addition of Diethylzinc to Aldehydes using a Catalyst Coupled to a Soluble Polymer" *J. Chem. Soc. Perkin 1* **1995**, 875-878.

(50) Edrick, E. *Organozinc Reagents in Organic Synthesis Press*; CRC Press: New York, 1996.

(51) Edrington, A. C.; Urbas, A. M.; DeRege, P.; Chen, C. X.; Swager, T. M.; Hadjichristidis, N.; Xenidou, M.; Fetters, L. J.; Joannopoulos, J. D.; Fink, Y.; Thomas, E. L. "Polymer-based photonic crystals" *Adv. Mater.* **2001**, *13*, 421-425.

(52) Effenberger, F. "Synthesis and reactions of optically active cyanohydrins" *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555.

(53) Elbs, H.; Drummer, C.; Abetz, V.; Krausch, G. "Thin film morphologies of ABC triblock copolymers prepared from solution" *Macromolecules* **2002**, *35*, 5570-5577.

(54) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. "Bis(Oxazoline) Copper-Complexes as Chiral Catalysts for the Enantioselective Aziridination of Olefins" *J. Am. Chem. Soc.* **1993**, *115*, 5328-5329.

(55) Fan, Q. H.; Ren, C. Y.; Yeung, C. H.; Hu, W. H.; Chan, A. S. C. "Highly effective soluble polymer-supported catalysts for asymmetric hydrogenation" *J. Am. Chem. Soc.***1999**, *121*, 7407-7408.

(56) Fan, Q.-H.; Deng, G.-J.; Lin, C.-C.; Chan, A. S. C. "preparation and use of MeO-PEG-supported chiral diphosphine ligands: soluble polymer-supported catalysts for asymmetric hydrogenation" *Tetrahedron: Asymmetry* **2001**, *12*, 1241-1247.

(57) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. "Recoverable catalysts for asymmetric organic synthesis" *Chem. Rev.* **2002**, *102*, 3385-3466.

(58) Fink, Y.; Urbas, A. M.; Bawendi, M. G.; Joannopoulos, J. D.; Thomas, E. L. "Block copolymers as photonic bandgap materials" *J. Lightwave Technol.* **1999**, *17*, 1963-1969.

(59) Frechet, J. M. J. "Functional Polymers and Dendrimers - Reactivity, Molecular Architecture, and Interfacial Energy" *Science* **1994**, *263*, 1710-1715.

(60) Fukui, H.; Sawamoto, M.; Higashimura, T. "Multifunctional Coupling Agents for Living Cationic Polymerization .2. Bifunctional Silyl Enol Ethers for Living Poly(Vinyl Ethers)" *Macromolecules* **1993**, *26*, 7315-7321.

(61) Gallo, E.; Solari, E.; Floriani, C.; ChiesiVilla, A.; Rizzoli, C. "Use of manganese(II) Schiff base complexes for carrying polar organometallics and inorganic ion pairs," *Inorg. Chem.* **1997**, *36*, 2178-2186.

(62) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. "Narrow Molecular-Weight Resins by a Free-Radical Polymerization Process" *Macromolecules* **1993**, *26*, 2987-2988.

(63) Giffels, G.; Beliczey, J.; Felder, M.; Kragl, U. "soluble polymer supported catalyst for asymmetric ketone reduction" *Tetrahedron: Asymmetry* **1998**, *9*, 1975.

(64) Gladysz, J. A.; Boone, B. J. "Chiral recognition in pi complexes of alkenes, aldehydes, and ketones with transition metal Lewis acids; Development of a general model for enantioface binding selectivities" *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 551-583.

(65) Gravert, D. J.; Janda, K. D. "Organic Synthesis on Soluble Polymer Supports: Liquid-Phase Methodologies" *Chem. Rev.* **1997**, *97*, 489-509.

(66) Gregory, R. J. H. "Cyanohydrins in Nature and the Laboratory: Biology, Preparations, and Synthetic Applications" *Chem. Rev.* **1999**, *99*, 3649-3682.

(67) Griengl, H.; Hickel, A.; Johnson, D.; Kratky, C.; Schmidt, M.; Schwab, H. "Enzymatic cleavage and formation of cyanohydrins: a reaction of biological and synthetic relevance" *Chem. Commun.* **1997**, 1933.

(68) Guarini, K. W.; Black, C. T.; Milkove, K. R.; Sandstrom, R. L. "Nanoscale patterning using self-assembled polymers for semiconductor applications" J. Vac. Sci. Technol., B: Microelectron. Nanometer Struct.-Process., Meas., Phenom. **2001**, *19*, 2784-2788.

(69) Guerreiro, P.; Ratovelomanana-vidal, V.; Genet, J.-P.; Dellis, P. "recyclable diguanidinium-BINAP and PEG-BINAP supported catalyst: synthesis and use in Rh(I) and Ru(II) asymmetric hydrogenation reactions" *Tetrahedron Lett.* **2001**, *42*, 3423-3426.

(70) Haag, R.; Sunder, A.; Hebel, A.; Roller, S. "Dendritic aliphatic polyethers as high-loading soluble supports for carbonyl compounds and parallel membrane separation techniques" *J. Am. Chem. Soc.* **2002**, *4*, 112-119.

(71) Hadjichristidis, N.; Pispas, S.; Floudas, G. *Block Copolymers. Synthetic Strategies, Physical Properties and Applications* New York, 2003.

(72) Halpern, J. "Mechanism and Stereoselectivity of Asymmetric Hydrogenation" *Science* **1982**, *217*, 401-407.

(73) Hamley, I. W. *The Physics of Block Copolymers*; Oxford Press: Oxford, 1998.

(74) Hamley, I. W. "Amphiphilic diblock copolymer gels: the relationship between structure and theology" Philos. Trans. R. Soc. London, A **2001**, *359*, 1017-1044.

(75) Hamley, I. W. *Developments in Block Copolymer Science and Technology*; Wiley: Chichester, 2003.

(76) Hamley, I. W. "Nanostructure fabrication using block copolymers" *Nanotechnology* **2003**, *14*, R39-R54.

(77) Hamley, I. W.; Hiscutt, E. L.; Yang, Y. W.; Booth, C. "Dewetting of thin block copolymer films" J. Colloid Interface Sci.**1999**, *209*, 255-260.

(78) Hammett, L. P. "The Effect of Structure Upon the Reactivity of Organic Compounds" *J. Am. Chem. Soc.* **1937**, *59*.

(79) Han, H.; Janda, K. D. "Soluble Polymer-Bound Ligand-Accelerated Catalysis: Asymmetric Dihydroxylation" *J. Am. Chem. Soc.* **1996**, *118*, 7632-7633.

(80) Hansch, C.; Bjorkroth, J. P.; Leo, A. "Hydrophobicity and central Nervous System Agents - on the Principle of Minimal Hydrophobicity in Drug Design" *J. Pharm. Sci.* **1987**, *76*, 663.

(81) Hansch, C.; Klein, T. E. "Molecular Graphics and QSAR In The Study of Enzyme Ligand Interactions- on the Definition of Bioreceptors" *Acc. Chem. res.* **1986**, *7*, 2858.

(82) Hansch, C.; Leo, A.; Taft, R. W. "A Survey of Hammett Substituent Constants and Resonance and Field Parameters" *Chem. Rev.* **1991**, *91*, 165-195.

(83) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. "On the mechanism of asymmetric nucleophilic ring-opening of epoxides catalyzed by (salen)Cr-III complexes" *J. Am. Chem. Soc.* **1996**, *118*, 10924-10925.

(84) Harris, J. M.; Dust, J. M.; McGill, R. A.; Harris, P. A.; Edgell, M. J.; Sedaghatherati, R. M.; Karr, L. J.; Donnelly, D. L. "New Polyethylene Glycols for Biomedical Applications" ACS Symp. Ser.**1991**, *467*, 418-429.

(85) Hawker, C. J. ""Living" free radical polymerization: A unique technique for the preparation of controlled macromolecular architectures," *Acc. Chem. Res.* **1997**, *30*, 373-382.

(86) Hawker, C. J.; Bosman, A. W.; Harth, E. "New polymer synthesis by nitroxide mediated living radical polymerizations" *Chem. Rev.* **2001**, *101*, 3661- 3688.

(87) Hawker, C. J.; Mecerreyes, D.; Elce, E.; Dao, J. L.; Hedrick, J. L.; Barakat, I.; Dubois, P.; Jerome, R.; Volksen, W. ""Living" free radical polymerization of macromonomers: Preparation of well defined graft copolymers" *Macromol. Chem. Phys.* **1997**, *198*, 155-166.

(88) Hess, P.; Wells, D. E. "Evaluation of dialysis as a technique for the removal of lipids prior to the GC determination of ortho- and non-ortho-chlorobiphenyls, using C-14-labelled congeners" *Analyst* **2001**, *126*, 829-834.

(89) Holy, N. L. "Versatile Polymer-Bound Hydrogenation Catalysts - Rhodium(I)-Catalyzed Hydrogenation" *J. Org. Chem.* **1979**, *44*, 239-243.

(90) Holy, N. L.; Shalvoy, R. "Hydrogenation with Anthranilic Acid Anchored, Polymer-Bound Nickel-Catalysts," *J. Org. Chem.* **1980**, *45*, 1418-1420.

(91) Horvath, I. T. "Fluorous Biphase Chemistry" *Acc. Chem. Res.* **1998**, *35*, 738-745.

(92) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. "Substrate-Directable Chemical-Reactions" *Chem. Rev.* **1993**, *93*, 1307-1370.

(93) Hu, Q.-S.; Huang, W.-S.; Pu, L. "A New Approach to Highly Enantioselective Polymeric Chiral Catalysts" *J. Org. Chem.* **1998**, *63*, 2798-2799.

(94) Huang, E.; Pruzinsky, S.; Russell, T. P.; Mays, J.; Hawker, C. J. "Neutrality conditions for block copolymer systems on random copolymer brush surfaces" *Macromolecules* **1999**, *32*, 5299-5303.

(95) Huckins, J. N.; Tubergen, M. W.; Lebo, J. A.; Gale, R. W.; Schwartz, T. R. "Polymeric Film Dialysis In Organic-Solvent media for Clean-up of Organic Contaminatns " *J. Assoc. Off. Anal. Chem.* **1990**, *73*, 290.

(96) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. "Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins" *Tetrahedron Lett.* **1990**, *31*, 7345-7348.

(97) Itsuno, S.; Fre´chet, J. M. J. "Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Polymer-Supported Chiral Amino Alcohols. Evidence for a Two Zinc Species Mechanism" *J. Org. Chem.* **1987**, *52*, 4142-4143.

(98) Jacobsen, E. N. *In Catalytic Asymmetric Synthesis*; VCH: New York, 1993.

(99) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. 1-3.

(100) Jacobsen, E. N.; Zhang, W.; Guler, M. L. "Electronic Tuning of Asymmetric Catalysts" *J. Am. Chem. Soc.* **1991**, *113*, 6703-6704.

(101) Janssen, K. B.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. "A dimeric form of Jacobsen's catalyst for improved retention in a polydimethylsiloxane membrane" *Tetrahedron: Asymmetry* **1997**, *8*, 3481.

(102) Jayaprakash, D.; Sasai, H. "Synthesis and catalyric applications of soluble polymer-supported BINOL" *Tetrahedron: Asymmetry.* **2001**, *12*, 2589-2595.

(103) Jeong, U. Y.; Kim, H. C.; Rodriguez, R. L.; Tsai, I. Y.; Stafford, C. M.; Kim, J. K.; Hawker, C. J.; Russell, T. P. "Asymmetric block copolymers homopolymers: Routes to multiple length scale nanostructures" *Adv. Mater.* **2002**, *14*, 274.

(104) Johnson, R. A.; Sharpless, K. B. *In Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993, pp Chapter 4.1.

(105) Kagan, H. B. "Practical consequences of non-linear effects in asymmetric synthesis," Adv. Synth. Catal. **2001**, *343*, 227-233.

(106) Katsuki, T. "Some recent advances in metallosalen chemistry" *Synlett* **2003**, 281-297.

(107) Kellogg, G. J.; Walton, D. G.; Mayes, A. M.; Lambooy, P.; Russell, T. P.; Gallagher, P. D.; Satija, S. K. "Observed surface energy effects in confined diblock copolymers," *Phys. Rev. Lett.* **1996**, *76*, 2503-2506.

(108) Kitamura, S.; Suga, S.; Kawai, K.; Noyori, R. "Catalytic Asymmetric induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes" *J. Am. Chem. Soc.* **1986**, *108*, 6071.

(109) Kleij, A. W.; Gossage, R. A.; Klein Gebbink, R. J. M.; Brinkmann, N.; Reijerse, E. J.; Kragl, U.; Lutz, M.; Spek, A. L.; van Koten, G. "A "Dendritic Effect" in Homogeneous Catalysis with Carbosilane-Supported Arylnickel(II) Catalysts: Observation of Active-Site Proximity Effects in Atom-Transfer Radical Addition" *J. Am. Chem. Soc.* **2000**, *122*, 12112.

(110) Knochel, P.; Jones, P. *Organozinc Reagents: A Practical Approach*; Oxford Press: New York, 1999.

(111) Kobayashi, S.; Endo, M.; Nagayama, S. "Catalytic Asymmetric Dihydroxylation of Olefins Using a Recoverable and Reusable Polymer-Supported Osmium Catalyst" *J. Am. Chem. Soc.* **1999**, *121*, 11229-11230.

(112) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. "Catalytic Asymmetric Dihydroxylation" *Chem. Rev.* **1994**, *94*, 2483-2547.

(113) Konsler, R. G.; Karl, J.; Jacobsen, E. N. "Cooperative asymmetric catalysis with dimeric salen complexes" *J. Am. Chem. Soc.* **1998**, *120*, 10780-10781.

(114) Kozlowski, M. C.; Dixon, S. L.; Panda, M.; Lauri, G. "Quantum Mechanical Models Correlating Structure with Selectivity: Predicting the Enantioselectivity of α-Amino Alcohol Catalysts in Aldehyde Alkylation" *J. Am. Chem. Soc.* **2003**, *125*, 6614-6615.

(115) Kragl, U.; Dreisbach, C. "Continuous Asymmetric Synthesis in a MembraneReactor" *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 642.

(116) Kragl, U.; Dwars, T. "The development of new methods for recycling catalysts," *Trends Biotechnol.* **2001**, *19*, 442-449.

(117) Krausch, G.; Magerle, R. "Nanostructured thin films via self-assembly of block copolymers" *Adv. Mater.* **2002**, *14*, 1579.

(118) Lasperas, M.; Bellocq, N.; Brunel, D.; Moreau, P. "Chiral mesoporous templated silicas as heterogeneous inorganic catalysts in the enantioselective alkylation of benzaldehyde" *Tetrahedron: Asymmetry* **1998**, *9*, 3053.

(119) Leadbeater, N. E.; Marco, M. "Preparation of Polymer-Supported Ligands and Metal Complexes for Use in Catalysis" *Chem. Rev.* **2002**, *102*, 3217-3274.

(120) Leffler, J. E.; Grunwald, E. *Equillibria of Organic reactions*; John Wiley: New York, 1963.

(121) Letsinger, I.; Wagner, T. E. "Regulation of Rate of Reaction of a Polyuridylic Acid Derivative by Use of Suppressor and Antisuppressor Molecules," *J. Am. Chem. Soc.* **1966**, *88*, 2062-&.

(122) Li, Z.; Conser, K. R.; Jacobsen, E. N. "Asymmetric Alkene Aziridination with Readily Available Chiral Diimine-Based Catalysts," *J. Am. Chem. Soc.* **1993**, *115*, 5326-5327.

(123) Lin, Z. Q.; Kim, D. H.; Wu, X. D.; Boosahda, L.; Stone, D.; LaRose, L.; Russell, T. P. "A rapid route to arrays of nanostructures in thin films," *Adv. Mater.* **2002**, *14*, 1373-1376.

(124) Liu, G.; Ellman, J. A. "A General Solid-Phase Synthesis Strategy for the Preparation of 2-Pyrrolidinemethanol Ligands," *J. Org. Chem.* **1995**, *60*, 7712-7713.

(125) Lu, Z.; Lindner, E.; Mayer, H. A. "Applications of Sol-Gel-Processed Interphase Catalysts" *Chem. Rev.* **2002**, *22*, 3543-3578.

(126) Lundgren, S.; Lutsenko, C. J.; Moberg, C. "Polymer-Supported Pyridine-Bis(oxazoline). Application to Ytterbium-Catalyzed Silylcyanation of Benzaldehyde" *Org. Lett.* **2003**, *5*, 3663-3665.

(127) Malmstrom, E. E.; Hawker, C. J. "Macromolecular engineering via 'living' free radical polymerizations," *Macromol. Chem. Phys.* **1998**, *199*, 923- 935.

(128) Manecke, G.; Storck, W. "Polymeric Catalysts," *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 657-670.

(129) Mansky, P.; DeRouchey, J.; Russell, T. P.; Mays, J.; Pitsikalis, M.; Morkved, T.; Jaeger, H. "Large-area domain alignment in block copolymer thin films using electric fields" *Macromolecules* **1998**, *31*, 4399-4401.

(130) Mansky, P.; Liu, Y.; Huang, E.; Russell, T. P.; Hawker, C. "Controlling polymer-surface interactions with random copolymer brushes" *Science* **1997**, *275*, 1458-1460.

(131) Mariagnanam, V. M.; Zhang, L.; Bergbreiter, D. E. "Polymer Ligands That Can Regulate Reaction Temperature in Smart Catalysts" *Adv. Mater.* **1995**, *7*, 69-71.

(132) Martin, Y. C. *Quantitative Drug Design*; Dekker: New York, 1978.

(133) Maskill, H. *Mechanisms of Organic reactions*; Oxford Science Publications: Oxford, 1996.

(134) McGarrigle, E. M.; Murphy, D. M.; Gilheany, D. G. "Ligand tuning in the chromium-salen-mediated asymmetric epoxidation of alkenes" *Tetrahedron: Asymmetry* **2004**, *15*, 1343-1354.

(135) McNamara, C. A.; Dixon, M. J.; Bradely, M. "Recoverable Catalysts and Reagents Using Recyclable Polystyrene-Based Supports" *Chem. Rev.* **2002**, *102*, 3275-3300.

(136) Merrifield, R. B. "Solid-Phase Synthesis (Nobel Lecture)" *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 799-810.

(137) Miwa, Y.; Yamamoto, K.; Sakaguchi, M.; Shimada, S. "Well-defined polystyrene grafted to polypropylene backbone by "living" radical polymerization with TEMPO" *Macromolecules* **2001**, *34*, 2089-2094.

(138) Moad, G.; Rizzardo, E.; Solomon, D. H. "Selectivity of the Reaction of Free-Radicals with Styrene" *Macromolecules* **1982**, *15*, 909-914.

(139) Morkved, T. L.; Lu, M.; Urbas, A. M.; Ehrichs, E. E.; Jaeger, H. M.; Mansky, P.; Russell, T. P. "Local control of microdomain orientation in diblock copolymer thin films with electric fields" *Science* **1996**, *273*, 931-933.

(140) Moskvin, L. N.; Nikitiana, T. G. "Membrane methods of substance separation in analytical chemistry" *J. Anal. Chem.* **2004**, *59*, 2-16.

(141) Muller, P. "Glossary of Terms used in Physical Organic Chemistry" *Adv. Phys. Org. Chem.* **1994**, *66*, 1077.

(142) Nair, D.; Luthra, S. S.; Scarpello, J. T.; White, L. S.; dos Santos, L. M. F.; Livingston, A. G. "Homogenous catalyst separation and re-use through nanofiltration of organic solvents" *Desalination* **2002**, *147*, 301-306.

(143) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. "Electronic Substituent Effect of Nitrogen Ligands in Catalytic Asymmetric Hydrosilylation of Ketones - Chiral 4-Substituted Bis(Oxazolinyl)Pyridines" *J. Org. Chem.* **1992**, *57*, 4306-4309.

(144) North, M. "Catalytic asymmetric cyanohydrin synthesis" *Synlett.* **1993**, 807.

(145) North, M. "Synthesis and applications of non-racemic cyanohydrins" *Tetrahedron: Asymmetry* **2003**, *14*, 147-176.

(146) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

(147) Noyori, R.; Kitamura, M. "Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification," *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.

(148) Ohkubo, K.; Fujimori, K.; Yoshinaga, K. "Asymmetric Hydrogenation of Prochiral Unsaturated-Acids by Soluble and Insoluble Polymer-Supported Rhodium(I) Chiral Diphosphine Complexes," *Inorg. Nucl. Chem. Lett.* **1979**, *15*, 231- 234.

(149) Ojima, I. *Catalytic Asymmetric Synthesis*; John Wiley & Sons: New York, 2000.

(150) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M.; Ishida, T.; Jacobsen, E. N. "The Mechanistic Basis for the Electronic Effects on Enantioselectivity in the (salen)Mn(III)-Catalyzed Epoxidation Reaction" *J. Am. Chem. Soc.* **1998**, *120*, 948-954.

(151) Park, S. B.; Murata, K.; Matsumoto, H.; Nishiyama, H. "Remote Electronic Control in Asymmetric Cyclopropanation with Chiral Ru-Pybox Catalysts" *Tetrahedron: Asymmetry* **1995**, *6*, 2487-2494.

(152) Pu, L.; Yu, H.-B. "Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds" *Chem. Rev.* **2001**, *101*, 757-824.

(153) Quirk, R. P.; Lynch, T. "Anionic Synthesis of Primary Amine-Functionalized Polystyrenes Using 1- 4- N,N-Bis(Trimethylsilyl)Amino Phenyl -1-Phenylethylene" *Macromolecules* **1993**, *26*, 1206-1212.

(154) Rajanbabu, T. V. "Controlling asymmetric catalyzed reactions through ligand effects" *Chimica Oggi-Chemistry Today* **2000**, *18*, 26-31.

(155) Rajanbabu, T. V.; Ayers, T. A. "Electronic Effects in Asymmetric Catalysis - Hydroformylation of Olefins," *Tetrahedron Lett.* **1994**, *35*, 4295-4298.

(156) Rajanbabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. "Electronic Amplification of Selectivity in Rh-Catalyzed Hydrogenations - D-Glucose-Derived Ligands for the Synthesis of D-Amino-Acids or L-Amino-Acids" *J. Am. Chem. Soc.***1994**, *116*, 4101-4102.

(157) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. "Carbohydrate phosphinites as practical ligands in asymmetric catalysis: Electronic effects and dependence of backbone chirality in Rh-catalyzed asymmetric hydrogenations. Synthesis of R- or S-amino acids using natural sugars as ligand precursors" *J. Org. Chem.* **1997**, *62*, 6012-6028.

(158) Rajanbabu, T. V.; Casalnuovo, A. L. "Electronic Effects in Asymmetric Catalysis - Enantioselective Carbon-Carbon Bond-Forming Processes" Pure Appl. Chem.**1994**, *66*, 1535-1542.

(159) RajanBabu, T. V.; Casalnuovo, A. L. "Role of electronic asymmetry in the design of new ligands: The asymmetric hydrocyanation reaction" *J. Am. Chem. Soc.* **1996**, *118*, 6325-6326.

(160) RajanBabu, T. V.; Casalnuovo, A. L.; Ayers, T. A.; Nomura, N.; Jin, J.; Park, H.; Nandi, M. "Ligand tuning as a tool for the discovery of new catalytic asymmetric processes" *Curr. Org. Chem.* **2003**, *7*, 301-316.

(161) RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. "Electronic effects in asymmetric catalysis: Structural studies of precatalysts and intermediates in Rh-catalyzed hydrogenation of dimethyl itaconate and acetamidocinnamic acid derivatives using C-2-symmetric diarylphosphinite ligands" *J. Org. Chem.* **1999**, *64*, 3429-3447.

(162) Rasmussen, T.; Norrby, P.-O. "Characterization of New Six Membered Transition States of the Amino-Alcohol Promoted Addition of Dialkyl Zinc to Aldehydes" *J. Am. Chem. Soc.* **2001**, *123*, 2464-2465.

(163) Ready, J. M.; Jacobsen, E. N. "Highly active oligomeric (salen)Co catalysts for asymmetric epoxide ring-opening reactions," *J. Am. Chem. Soc.* **2001**, *123*, 2687-2688.

(164) Reetz, M. T.; Waldvogel, S. R.; Goddard, R. "Substituent effects in the rhodium-catalyzed hydroformylation of olefins using bis(diarylphosphino)methylamino ligands," *Tetrahedron Lett.* **1997**, *38*, 5967-5970.

(165) Reger, T. S.; Janda, K. D. "Polymer-Supported (salen)Mn Catalyst for Asymmetric Epoxidation: A Comparison between Soluble and Insoluble Matrices" *J. Am. Chem. Soc.* **2000**, *122*, 6929-6934.

(166) Rissom, S.; Beliczey, J.; Giffels, G.; Kragl, U.; Wandrey, C. "Asymmetric Reduction of Acetophenone in Membrane Reactors" *Tetrahedron: Asymmetry.* **1999**, *10*, 923-928.

(167) Ryan, D.; Johnson, R. "Dialysis and ultrafiltration of molasses for fermentation enhancement," *Separation and Purification Technology* **2001**, *22*, 239-245.

(168) Seden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995.

(169) Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. "Immobilization of BINOL by cross-linking copolymerization of styryl derivatives with styrene, and applications in enantioselective Ti and Al Lewis acid mediated additions of Et2Zn and Me3SiCN to aldehydes and of diphenyl nitrone to enol ethers" *Chem. Eur. J.* **2000**, *6*, 3692-3705.

(170) Sellner, H.; Seebach, D. "Dendritically Cross-Linked Chiral Ligands: High Stability of a PS-Bound Ti-TADDOLate Catalyst with Diffusion Control," *Angew. Chem., Int. Ed. Eng.* **1999**, *38*, 1918-1920.

(171) Sheffy, F. K.; Stille, J. K. "Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotins" *J. Am. Chem. Soc.* **1983**, *105*, 7173- 7175.

(172) Shibasaki, M.; Kanai, M.; Funabashi, K. "Recent progress in asymmetric two-center catalysis" *Chem. Commun.* **2002**, 1989-1999.

(173) Shin, K.; Leach, K. A.; Goldbach, J. T.; Kim, D. H.; Jho, J. Y.; Tuominen, M.; Hawker, C. J.; Russell, T. P. "A simple route to metal nanodots and nanoporous metal films" *Nano. Letters* **2002**, *2*, 933-936.

(174) Soai, K.; Wantanabe, M.; Yamamoto, A. "Enantioselective addition of dialkylzincs to aldehydes using heterogeneous chiral catalysts immobilized on alumina and silica gel" *J. Org. Chem.* **1990**, *55*, 4832.

(175) Soai, K.; Yokoyame, S.; Hayasaka, T. "Chiral N, N-dialkylnorephedrines as Catalysts to the Highly Enantioselective Addition of Dialkylzincs to Aliphatic and Aromatic Aldehydes. The Asymmetric Synthesis of Secondary Aliphatic and Aromatic Alcohols of High Optical Purity" *J. Org. Chem.* **1991**, *56*, 4264.

(176) Sogah, D. Y.; Hertler, W. R.; Webster, O. W.; Cohen, G. M. "Group Transfer Polymerization - Polymerization of Acrylic-Monomers" *Macromolecules* **1987**, *20*, 1473-1488.

(177) Strawhecker, K. E.; Kumar, S. K.; Douglas, J. F.; Karim, A. "The critical role of solvent evaporation on the roughness of spin-cast polymer films" *Macromolecules* **2001**, *34*, 4669-4672.

(178) Thompson, R. B.; Ginzburg, V. V.; Matsen, M. W.; Balazs, A. C. "Predicting the mesophases of copolymer-nanoparticle composites" *Science* **2001**, *292*, 2469-2472.

(179) Thurn-Albrecht, T.; Schotter, J.; Kastle, C. A.; Emley, N.; Shibauchi, T.; Krusin-Elbaum, L.; Guarini, K.; Black, C. T.; Tuominen, M. T.; Russell, T. P. "Ultrahigh-density nanowire arrays grown in self-assembled diblock copolymer templates" *Science* **2000**, *290*, 2126-2129.

(180) Toy, P. H.; Janda, K. D. "Soluble Polymer-Supported Organic Synthesis" *Acc. Chem. Res.* **2000**, *33*, 546-554.

(181) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. "Dendrimers as Supports for Recoverable Catalysts and Reagents" *Chem. Rev.* **2002**, *102*, 3717-3756.

(182) Vankelecom, I. F. J. "Polymeric Membranes in Catalytic Reactors" *Chem. Rev.* **2002**, *102*, 3779-3810.

(183) Venkataraman, D.; Anyanwu, U. K. "Catalysis through dialysis" *Abstr. Pap. Am. Chem. Soc.* **2001**, *222*, U91-U91.

(184) Venkataramanan, N. S.; Premsingh, S.; Rajagopal, S.; Pitchumani, K. "Electronic and steric effects on the oxygenation of organic sulfides and sulfoxides with oxo(salen)chromium(V) complexes" *J. Org. Chem.* **2003**, *68*, 7460-7470.

(185) VidalFerran, A.; Moyano, A.; Pericas, M. A.; Riera, A. "Synthesis of a family of fine-tunable new chiral ligands for catalytic asymmetric synthesis. Ligand optimization through the enantioselective addition of diethylzinc to aldehydes" *J. Org. Chem.* **1997**, *62*, 4970-4982.

(186) Walsh, C. *Enzymatic Reaction Mechanisms*; W. H. Freeman: New York, 1979.

(187) Webster, O. W. "Living Polymerization Methods" *Science* **1991**, *251*, 887-893.

(188) Wentworth Jr., P.; Janda, K. D. "Liquid-phase Chemisry: Recent Advances in Soluble Polymer-Supported Catalysts, Reagents and Synthesis" *Chem. Commun.* **1999**, 1917-1924.

(189) Whitehurst, D. D. "Catalysis by Heterogenized Transition-Metal Complexes" *CHEMTECH* **1980**, *10*, 44-49.

(190) Williams, A. "Effective Charge and Transition State Structure in Solution" *Adv. Phys. Org. Chem.* **1991**, *27*, 1.

(191) Wolfson, A.; Janssen, K. B.; Vankelecom, I. F. J.; Geresh, S.; Gottlieb, S.; Herskowitz, M. "Aqueous enantioselective hydrogenation of methyl 2-acetamidoacrylate with Rh–MeDuPHOS occluded in PDMS" *Chem. Commun.* **2002**, *4*, 388.

(192) Xu, T.; Kim, H. C.; DeRouchey, J.; Seney, C.; Levesque, C.; Martin, P.; Stafford, C. M.; Russell, T. P. "The influence of molecular weight on nanoporous polymer films" *Polymer* **2001**, *42*, 9091-9095.

(193) Yamakawa, M.; Noyori, R. "Asymmetric Addition of Dimethylzinc to Benzaldehyde Catalyzed by (2S)-3-exo(Dimethylamino)isobornenol. A Theoretical Study on the Origin of Enantioselection" *Organometallics* **1999**, *18*, 128-133.

(194) Yamamoto, K.; Nakazono, M.; Miwa, Y.; Hara, S.; Sakaguchi, M.; Shimada, S. "Living" radical graft polymerization of styrene to polyethylene with 2,2,6,6-tetramethylpiperidine-1-oxyl" Polym. J. (Tokyo) **2001**, *33*, 862-867.

(195) Yan, Y. Y.; RajanBabu, T. V. "Ligand tuning in asymmetric catalysis: Mono- and bis-phospholanes for a prototypical Pd-catalyzed asymmetric allylation reaction (vol 2, pg 199, 2000)" *Org. Lett.* **2000**, *2*, 569-569.

(196) Yan, Y. Y.; RajanBabu, T. V. "Ligand substituent effects on asymmetric induction. Effect of structural variations of the DIOP ligand on the Rh-catalyzed asymmetric hydrogenation of enamides" *Org. Lett.* **2000**, *2*, 4137-4140.

(197) Yao, Q. "A Soluble Polymer-Bound Ruthenium Carbene Complex: A Robust and Reusable Catalyst for Ring-Closing Olefin Metathesis" *Angew. Chem., Int. Ed. Eng.* **2000**, *39*, 3896.

(198) Yoon, T. P.; Jacobsen, E. N. "Privileged chiral catalysts" *Science* **2003**, *299*, 1691-1693.

(199) Zehner, R. W.; Sita, L. R. "Electroless deposition of nanoscale copper patterns via microphase-separated diblock copolymer templated self-assembly" *Langmuir* **1999**, *15*, 6139-6141.

(200) Zhang, J.-L.; Che, C.-M. "Soluble Polymer-Supported Ruthenium Porphyrin Catalyst for Epoxidation, Cyclopropanation, and Aziridination of Alkenes" *Org. Lett.* **2002**, *4*, 1911-1914.

(201) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. "Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by (Salen)Manganese Complexes" *J. Am. Chem. Soc.* **1990**, *112*, 2801-2803.

(202) Zhao, X. Y.; Metz, W. A.; Sieber, F.; Janda, K. D. "Expanding on the purification methodology of polyethylene glycol (PEG) bound molecules: The synthesis of 3,5-pyrazolidinediones" *Tetrahedron Lett.* **1998**, *39*, 8433-8436.