Lanthanide-BINOL containing rotaxanes as catalysts for the enantioselective transformation of polybutadiene

Section A - Project Summary

In recent years, rotaxanes have been used in molecular machines to perform various functions as ‘molecular motors’, ‘molecular shuttles’ or ‘molecular muscles’. However, only one example of catalytically active rotaxanes has been reported as of now which consists of a manganese-porphyrin/glycoluril clip threaded onto a polybutadiene strand, moving along the polymer and catalyzing the epoxidation of the double bonds. Although the yield and regioselectivity reported are still modest, this system demonstrates the possibility of developing catalysts which can run along a polymer thread while catalyzing its transformation. In nature, enzymes like T4 DNA polymerase holoenzyme and λ-exonuclease can efficiently perform the replication, repair and recombination of DNA by enclosing the biopolymer while moving along its chain.

In this proposal the synthesis of chiral polymers from polybutadiene using lanthanide containing rotaxanes is proposed. Lanthanide binaphtholates were recently found to very efficiently catalyze both the asymmetric epoxidation of α,β-unsaturated amides and the regioselective epoxide ring opening in one pot by simply changing the reaction conditions. The glycoluril molecule used to support the manganese-porphyrin system mentioned above will be covalently bound to a carefully pre-selected lanthanide binaphtholate complex forming a new generation of catalysts topologically linked to a polymeric substrate. The choice of a catalyst system capable of promoting different reactions in one vessel leans toward the development of more environmentally benign synthetic processes which minimize waste generation.

With the increasing demand for novel materials with controlled stereochemistry, this method will provide a new path for the synthesis of chiral polymers from achiral monomers. Optically active polymers have found numerous applications because of their capacity for chiral recognition. For example, the stationary phase used in chiral HPLC separation is one of the most successful applications.
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Background

**Rotaxanes as molecular machines.**
During the last decade, there have been many reports of the construction of elegant molecular gadgets such as motors, switches, shuttles, lifts, muscles etc… Many of these molecular machines contain rotaxanes motifs which are defined as structures in the form of a rod ended by two bulky stopper groups, encircled by a macrocycle. For example, the molecular muscle reported by Sauvage et al. consists of a rotaxane dimer capable of stretching and contracting under the action of a chemical stimulus. Another recent example of rotaxane-based molecular device is the manganese-porphyrin/glycoluril clip threaded onto a polybutadiene strand developed by Nolte et al. In this case, a previously known catalyst for epoxidation reactions was covalently bound to a glycoluril receptor and topologically linked to the polymeric substrate to catalyze its transformation while moving along the chain.

Already two types of glycoluril receptors linked to a metal-porphyrin molecule have been prepared with different shapes and sizes of cavity, exhibiting interesting host-guest properties. These structures could be used as building blocks for a new generation of topologically linked catalysts promoting sequential polymer transformations. Lanthanide-binaphthyl systems are very good catalysts candidates which could be bound to these receptors. Not only were they proved many times to be very efficient catalysts in asymmetric synthesis but they were also successfully linked to various supports without loosing their catalytic properties. Moreover, their chemistry could be easily applied to the chiral transformation of polybutadiene (PD), PD being the polymeric substrate of choice for such studies since it is readily available and easily characterized.

**Binaphthyl systems.**
Because of their highly stable chiral conformation, 2,2’-substituted 1,1’-binaphthyl ligands (Scheme 1) have been extensively used to control many asymmetric processes and have demonstrated outstanding chiral discrimination properties. 1,1’-bi-2-naphthol (BINOL) often serves as the starting material for obtaining these chiral binaphthyl compounds. The 2,2’-hydroxyl groups can easily be converted into other functional groups and the 3,3’, 4,4’- and 6,6’- positions can be selectively functionalized, leading to a variety of binaphthyl derivatives. Various metal complexes of these systems have been used to catalyze diverse reactions with very high yield and selectivity. For example, rhodium and ruthenium complexes of phosphino-binaphthyl ligands are known catalysts for asymmetric hydrogenation reactions whereas titanium complexes of tridentate imino-binaphthyl ligands have been used in asymmetric aldol condensations.
The very rich chemistry performed by these systems led to an increasing interest in the synthesis of a variety of 1,1'-binaphthyl derivatives. As a result, many of the synthetic routes which would be required to build a BINOL containing rotaxane have been performed with at least one of these related systems if not with BINOL itself.

![Scheme 1](image.png)

Scheme 1. Monomeric and bridged-binaphthyl ligands with selected substituents.

**BINOL/bridged-BINOL.**

BINOL is a well known chiral auxiliary used in host-guest chemistry for its high chiral recognition properties and in asymmetric synthesis. Monomeric compounds as well as singly or multiply linked compounds have been used as supporting ligands for a wide range of metals such as Ln, Ti, Zr, Al, Zn, etc. to catalyze various reactions such as carbon-carbon bond formations, epoxidation reactions, and epoxide ring-opening reactions. The catalytic active species is usually generated in situ by mixing the metal alkoxide with the BINOL derivative. Monometallic as well as bimetallic systems were prepared.

In many cases when monomeric BINOL is used, the active species is thought to contain several equivalents of ligand per metal center causing a severe stability problem due to irreversible ligand exchange at the metal center under the reaction conditions. Bridged-BINOLs were designed in order to form more stable complexes toward ligand exchange without adverse effects on the asymmetric environment. For example, bridged-BINOL systems (Scheme 1, R=CH₂OCH₂) developed by Shibasaki et al. were found to yield highly stable, storable and reusable homogeneous catalysts for asymmetric Michael reactions and epoxide ring opening reactions. Whereas only monomeric BINOL has been used in epoxidation reactions, both monomeric and bridged BINOLs are known to catalyze ring opening reactions. In general, these systems are interchangeable in term of type of reaction catalyzed but bridged-BINOLs are more stable and easier to handle than labile monomeric ones.

Moreover, examples of polymer supported BINOL and bridged BINOL have been reported where the ligand is attached at the 3,3'- and 6,6'-positions. These polymer supported catalysts were found to be substantially more enantioselective than their homogeneous analogues with comparable yields.

These results suggest that covalent binding of BINOL or bridged-BINOL systems to a receptor unit should not result in any loss of reactivity and may even enhance the selectivity of the reaction.
Based on these studies, we propose to synthesize Lanthanide-BINOL containing rotaxanes with glycoluril receptors as catalysts for the enantioselective transformation of polybutadiene. A three step approach will be used to execute this plan. Firstly, comparative runs using BINOL and linked-BINOL lanthanide systems will be performed with linear olefins and polymers. The desired binaphtholate clip will then be synthesized by covalently linking the best of these catalysts to a glycoluril receptor molecule. Finally, this clip will be threaded onto a polybutadiene strand to form the target rotaxane and its catalytic properties will be studied.

Experimental

Selection of catalyst systems.
Lanthanide binaphtholate complexes (Ln = La or Sm) are known to epoxidize double bonds of \(\alpha,\beta\)-unsaturated amides, ketones and other carboxyl compounds with very high yields and selectivity (Schemes 2 and 3).\(^6,20,25\) Although the speculated active species generated in situ by mixing the lanthanide alkoxide (Ln(O-\(i\)-Pr)\(_3\)), BINOL and triphenylphosphine or arsine oxide (Ph\(_3\)P=O or Ph\(_3\)As=O) is a 1:1:1 complex of these reagents, the major species in solution contains two BINOL units per metals.\(^25\) The proposed mechanism for asymmetric epoxidation involves the formation of a lanthanide peroxide and binding of the substrate to the metal center prior to oxidation.\(^6,25\)

Scheme 2. Catalytic Asymmetric Epoxidation of \(\alpha,\beta\)-Unsaturated Simple Amides Promoted by the Sm-(S)-BINOL-Ph\(_3\)As=O Complex 1 – ref\(^6\)

Scheme 3. Catalytic Asymmetric Epoxidation of \(cis\)-Enone 3 (a) and Dienone 5 (b) Using the La-(R)-BINOL-Ph\(_3\)As=O Complex – ref\(^25\)
Enantioselective *meso*-epoxide ring-opening can also be performed by lanthanide binaphtholate complexes (Table 1) \((\text{Ln} = \text{Sm or Pr})\)\(^{23,24}\) as well as gallium heterobimetallic bridged-binaphtholate complexes \((R = \text{CH}_2\text{OCH}_2)\).\(^{29}\) In this case, a wider range of substrates including simple *cis*-2,3-epoxybutane, or cycloalkene oxides were transformed to the corresponding amino alcohol or phenolic alcohol.

In the perspective of ultimately running a one pot sequential olefin epoxidation and epoxide ring opening reaction, the monometallic monomeric BINOL system is a good candidate for our study since an overlap of epoxidation and epoxide ring opening reactions have been reported with these systems. However, for stability reasons, bridged BINOL complexes might be more suitable for sequential reactions. As mentioned earlier, bridged BINOL systems are known to have very similar properties than the corresponding monomeric BINOL.

Therefore, the family of complexes which will be tested are monomeric lanthanide binaphtholate systems (with \(\text{Ln} = \text{La, Sm and Pr}\)) (catalysts C-1 = monomeric BINOL systems) as well as Ln-bridged-BINOL systems \((R = \text{CH}_2\text{OCH}_2 - \text{catalysts C-2 = bridged-BINOL systems})\). Monomeric compounds will be prepared from \(\text{Ln(O-}_{\text{i-Pr}}{\text{3}}\)) and BINOL. Bridged compounds will be synthesized following published procedures\(^{22}\) or purchased when commercially available. The effect of triphenylphosphine or arsine oxide additives will be studied and the experimental conditions will be optimized for each reaction run independently then sequentially (see below).

### Table 1. Catalytic asymmetric ring opening reaction with *p*-anisidine. Applications to several *meso*-epoxides – ref.\(^{24}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>((R))-BINOL (x mol equiv. to Pr)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
<th>Configuration</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>1.5</td>
<td>13</td>
<td>71</td>
<td>31</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>2.0</td>
<td>14</td>
<td>87</td>
<td>35</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>1.5</td>
<td>15</td>
<td>72</td>
<td>50</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>2.0</td>
<td>16</td>
<td>75</td>
<td>53</td>
<td>(1R,2R)</td>
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<td>5</td>
<td>14</td>
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<td>17</td>
<td>82</td>
<td>50</td>
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<td>6</td>
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<td>2.0</td>
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<td>71</td>
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</tr>
<tr>
<td>7</td>
<td>16</td>
<td>1.5</td>
<td>19</td>
<td>62</td>
<td>36</td>
<td>(1R,2R)</td>
</tr>
<tr>
<td>8</td>
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<td>2.0</td>
<td>20</td>
<td>76</td>
<td>38</td>
<td>(1R,2R)</td>
</tr>
</tbody>
</table>

Epoxidation reactions.

Because we are interested in using these systems for polyolefin epoxidation followed by epoxide ring-opening reaction, a series of olefins (1-decene, trans-5-decene and cyclooctene) and polybutadiene (PD) itself will be used as substrates. Olefin epoxidation using lanthanide binaphtholate systems has not been described as of yet but it is reasonable to believe that these systems should promote olefin epoxidation since they promote double bond epoxidations in \(\alpha,\beta\)-unsaturated carbonyls. In absence of carbonyl groups which can bind to the metal center bringing the substrate next to the active site of the catalyst, yields are expected to be lower with regular olefins than for previously reported reactions but the selectivity should remain high. This problem of low yield will be solved later on in the project when the rotaxane is built since in that case, the...
polymeric substrate will be physically brought closer to the metal center and the presence of the carbonyl group should not be needed to achieve high conversions.

A procedure similar to that described for the epoxidation of $\alpha,\beta$-unsaturated amino carboxy compounds using Sm-(S)-BINOL-Ph$_3$As=O catalyst will be used (Scheme 1). All reactions will be carried out in dry solvents under argon atmosphere. In a typical experiment the BINOL or bridged BINOL ligands will be premixed with the additive triphenylphosphine or arsine oxide in presence of molecular sieve (MS 4A) in tetrahydrofuran (THF). This mixture will be added to the lanthanide alkoxide solution generating the desired lanthanide complex. Alternatively, the BINOL ligand can be premixed with the lanthanide alkoxide in THF followed by addition of the triphenylphosphine or arsine oxide additive. At this stage, the lanthanide-BINOL complex will be isolated or not as a solid and redissolved in the desired solvent if necessary (for example dichloromethane or toluene). Slight excess (1.2 to 3 equivalents versus Ln) of tert-butyl hydroperoxide (TBHP) in decane will then be added followed by the substrate (small olefin or polymer). The relative concentration of catalyst versus double bond will be varied from 5 to 10% mol. Initial trials will be run at room temperature. Aliquots will be taken from the reaction mixture with a syringe at recorded times and immediately poured into a 5% aqueous citric acid and ethylacetate (EtOAc).

After solvent evaporation, the products will be analyzed by $^1$H NMR. The regioselectivity will be determined by looking at the chemical shifts for both small molecules and polymeric substrates.$^{2,30,31}$

**Epoxide ring opening reactions.**

Epoxide ring opening reactions with aromatic amines like aniline, $o$-anisidine, $p$-anisidine as the nucleophile will be investigated using commercially available cis and trans-2,3-epoxybutane as well as epoxy/hydroxy functionalized polybutadiene (PE). Catalysts which showed some reactivity in epoxidation of olefins will be tried for ring opening reactions.

A procedure similar to that described for the asymmetric ring opening reaction with $p$-anisidine using Pr(O-$i$-Pr)$_3$, (R)-BINOL and Ph$_3$P=O will be used (Table 1).$^{24}$ The preparation of the catalyst will be done the same way as for the epoxidation reaction. The solution of the complex will then be added to the epoxide solution. Finally, the solution of the aromatic amine will be added slowly by syringe pump for several hours (10 to 24h). Initial trials will be run at room temperature but optimal yields will be checked at temperatures ranging from -40 °C to 50 °C. The reaction will be quenched by addition of aqueous citric acid (or HCl) then neutralized and extracted with dichloromethane (or diethyl ether). For small molecules, after evaporation of the solvent, the crude product will be purified by thin layer chromatography on silica gel (heptane/ethyl acetate 80/20) prior to analysis. Polymers will be analyzed without purification.

Optimal conditions for sequential epoxidation and epoxide ring opening reactions will then be determined using catalysts that showed best reactivity in both reactions. Olefins used in epoxidation reactions will be used as substrates. Changes in the catalyst load, study of the effect of additives, temperature and solvent will be performed.

At the end of this study, the best catalyst system (C-1 or C-2) will be selected and the corresponding clip will be build as described in later sections.
Absolute configuration determination.
For small molecules, the enantioselectivity of the ring opened products will be determined by chiral HPLC, using a chiralcel OD-H column and $^1$H NMR.$^{6,23,24}$ Polymers will be analyzed by $^1$H NMR and circular dichroism (CD).$^{32,33}$ CD is one of the most informative tools for the evaluation of enantioselectivity in polymer synthesis.$^{32}$ $^1$H NMR can be used to determine the regioselectivity but usually not the absolute configuration of the asymmetric carbons in polymers due to extensive spectral overlaps. In our case, the aromatic rings of the incoming amines will be used as chromophores and should be easily detected in the UV region (230-350 nm) typically used for CD analysis. The CD spectra of the polymeric products will need to be compared to that of related small molecules in order to assign the absolute configuration of the asymmetric carbons and evaluate the potential contribution of a secondary structure which might interfere with CD analysis.$^{34}$

Synthesis of the BINOL/Diphenylglycoluril clips.
Clip molecules will be synthesized which have the pre-selected metal-BINOL catalyst situated above the receptor cavity. The choice of receptor size and rigidity will depend on the bulkiness of the catalyst’s platform (i.e. monomeric BINOL ligand or bridged-BINOL ligand). Preliminary molecular modeling calculations indicate that previously synthesized porphyrin supports R-1 (Scheme 5) and R-2 (Scheme 8)$^8$ can be used as starting material to build the desired lanthanide catalyst clips, respectively bearing catalyst C-1 or C-2. Space filling models generated using Chem Draw 3D shown in Figure 1 revealed that in both cases, the size of the cavity is large enough to accommodate a guest, like a linear olefin or polybutadiene strand.

Figure 1. Space filling model showing the target BINOL/glycoluril clips.

The conformation of the BINOL or bridged-BINOL ligand is maintained after binding which should result in retention of the catalytic activity and selectivity. The length of the linker between R- and C- can be varied from 1 to 2 atoms without major distortion. However, longer linkers would result in a much less stable system with a tendency of the platform to move to one side or the other of the clip similar to what was observed when a ‘small’ porphyrin was attached to the larger receptor R-2.$^8$ The clips proposed here are designed with atom linkers CH$_2$ and CH$_2$-O.
Diphenylglycoluril receptors.
The receptor component of the clip (R-1 or R-2) will be based on the U shaped
diphenylglycoluril unit 1 which has been extensively used as a building block for
receptors that bind dihydroxybenzene\textsuperscript{35,36} and viologen derivatives.\textsuperscript{37} 1 or 2 oxyethylene
spacers ended with a phenol or benzyl group will be used to attach the BINOL ligand to
this unit. The syntheses of compounds R-1 and R-2 have been previously described in the
literature.\textsuperscript{8} In both cases, a multi step synthesis is required starting from
diphenylglycoluril derivative 2 prepared from 1 and paraformaldehyde (Scheme 4).\textsuperscript{38}

![Scheme 4.](image)

Synthesis of the linked R-1/C-1 clip.
The synthesis of R-1\textsuperscript{8,37} will start with the treatment of diol 5 with p-toluenesulfonyl
chloride in pyridine, yielding the ditosyl compound 6 (Scheme 5). This compound will
then be attached to tetra (chloromethyl)-diphenylglycoluril 4, itself prepared from 2 in
two steps,\textsuperscript{39} by Friedel-Craft alkylation using SnCl\textsubscript{4} as a catalyst. After recrystallization
from toluene, pure compound 7 will be obtained and reacted with the desired ortho-
substituted phenol in acetonitrile using K\textsubscript{2}CO\textsubscript{3} as a base to give the tetra-phenyl
derivative R-1 or 8-X (X = OH, CHO) which will be purified at this step by column
chromatography.

![Scheme 5.](image)

The choice of the nature of group X is based on the retrosynthetic analysis of the full clip
[0-H] shown in Scheme 6. The simplest way of binding R-1 and C-1 with two atom
linker is to use a substitution reaction using tetrabrominated-BINOL derivative 18 (see
below for preparation) and the tetra phenol 8-OH in presence of K\textsubscript{2}CO\textsubscript{3}, in acetone/THF
under refluxing conditions.\textsuperscript{12} After deprotection of the alcohol groups of BINOL (see
Table 2 for most common procedures) and purification by column chromatography, the
desired clip with an O-CH\textsubscript{2}- linker will be obtained. One possible problem which could
be encountered with this procedure would be during the formation of 8-OH. A side reaction might occur where only two catechols would react with 7 to give a 1:2 product (instead of 1:4 for 8-OH). The use of an excess of catechol during this reaction should give higher yields of the desired product.

An alternative to this procedure would be to perform a Grignard reaction using already known tetra aldehyde 8-CHO prepared following published procedures (Scheme 5). The Grignard reagent 15 (Scheme 7) will be prepared in situ from 14 (see below for preparation) and solid magnesium in anhydrous diethylether/THF under reflux conditions and added to a solution of 8-CHO. After hydrolysis under mild acidic conditions using aqueous ammonium chloride, the desired linked compound bearing four secondary alcohols 15-OH will be obtained. Because these functions might interfere with binding of the lanthanide metal ion later on, these alcohols will be hydrogenated as follow. After conversion of 15-OH to the corresponding sulfonate ester using methanesulfonic acid chloride in presence of triethylamine at 0 °C, the mixture will be diluted with diethyl ether and washed with water and aqueous sodium bicarbonate. After drying over sodium sulfate and removal of the solvent under reduced pressure, the residue obtained will be dissolved in THF and reducing agent LiAlH₄ will be added at 0 °C. The reaction will be stopped by quenching with water and the desired organic product will be extracted by ethyl acetate and dried over sodium sulfate. After deprotection of the alcohol groups of BINOL and purification by column chromatography, the desired clip with an -CH₂-linker will be obtained.

<table>
<thead>
<tr>
<th>OH protection</th>
<th>Solvent</th>
<th>Reagent</th>
<th>Deprotection</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-</td>
<td>acetone</td>
<td>CH₃I, K₂CO₃</td>
<td>BBr₃</td>
<td>12</td>
</tr>
<tr>
<td>Et-</td>
<td>acetone</td>
<td>BrEt</td>
<td>BBr₃</td>
<td>28</td>
</tr>
<tr>
<td>MOM- = CH₂OCH₂-</td>
<td>THF/DMF</td>
<td>NaH, MOMCl</td>
<td>1PrOH, HCl</td>
<td>29, 21, 27</td>
</tr>
</tbody>
</table>

Table 2. Most common protecting groups used during modification of BINOL.
Modified BINOL.
BINOL derivatives 18 and 15 (Scheme 7) needed to complete the synthesis of the R-1/C-1 clip will be prepared from commercially available BINOL 11. After bromination at the 3,3’,40 and 6,6’-17 positions, the tetrabrominated-BINOL compound 14 will be isolated and purified by column chromatography. This compound can then be used to prepare the Grignard reagent 15 by reaction with magnesium in anhydrous diethyl ether/THF under reflux conditions, which can be used directly for the preparation of the clip or to react with formaldehyde yielding the tetrahydroxymethylated-BINOL 16 after hydrolysis under mild acidic conditions. Tetrabrominated-BINOL derivative 18 can be easily prepared by bromination of 16 using PBr3. An alternative path for the preparation of 18 would be to methylate 14 using lithiumdimethylcuprate prepared in situ from methyliodide, lithium and CuI in anhydrous diethyl ether. Once again, tetrabrominated-BINOL derivative 18 can be easily prepared by bromination of 17 using N-bromosuccinimide (NBS) in chloroform.

Scheme 7.

Synthesis of the linked R-2/C-2 clip.
The synthesis of R-2 will start with the treatment of the diphenylglycoluril derivative 2 with the benzene derivative 9a in a mixture of acetic anhydride and trifluoroacetic acid yielding the tetrapodant compound 9 which can be isolated by precipitating out after addition of methanol (Scheme 8).39 This compound will then be reacted with the desired meta-substituted phenol in acetonitrile in presence of Na2CO3 and NaI to give the tetraphenyl derivative R-2 or 10-Y (X = OH, CHO) which will be purified at this step by column chromatography. The linking of R-2 to C-2 will be done using the same strategy and experimental procedures than described for the R-1/C-1 system above.
Modified bridged-BINOL.

The synthesis of 6,6’-brominated bridged-BINOL 19 (Scheme 9) will be achieved using the same procedure than that used for non brominated bridged-BINOL.\textsuperscript{21,26} The synthesis will start with the ortho-lithiation with \textit{t}-BuLi of the MOM-protected 6,6’-brominated-BINOL 20. After addition of DMF, the 3-formyl-BINOL 21 will be isolated then reduced to the corresponding 3-hydroxymethyl-BINOL 22 using sodium borohydride in methanol/THF at 0 oC. After mesylation in presence of triethylamine, in toluene, filtration and treatment with LiBr in DMF, compound 23 will be isolated. Reductive coupling of 22 and 23 in THF will yield the desired 6,6’-brominated bridged-BINOL 19. The corresponding Grignard reagent and bromomethyl derivative can be prepared following the same procedures than that described for monomeric brominated-BINOL.

Scheme 9.

Metal complex synthesis.

After purification and full characterization of the organic clip, the corresponding lanthanide complex will be synthesized by mixing the clip with triphenylphosphine or arsine oxide in anhydrous THF and adding this mixture to the lanthanide alkoxide solution. The same procedure without triphenylphosphine or arsine oxide will also be
tried. Optimal conditions for the generation of the desired complex will be found. The complex will be fully characterized by UV-vis, MALDI-TOF, elemental analysis and possibly x-ray diffraction if suitable crystals are grown. This procedure will be used later on to prepare the target metal rotaxane. Moreover, this compound will be used as a control in catalysis studies.

**Threading of the clip onto polybutadiene.**

Once synthesized, the selected linked BINOL/diphenylglycoluril clip [0-H] will need to be threaded onto a polybutadiene strand to form the target polymer-clip rotaxane (Scheme 10). Two approaches can be taken to achieve this goal: 1) the polymeric substrate could be first synthesized from commercially available PD followed by the formation of the rotaxane which can then be ‘locked on’ by modification of the end groups\(^2,3\) or 2) a rotaxane precursor could be formed bearing the desired end groups and an alkene in the middle of the ‘rod’ which can then be used to grow the polybutadiene polymer by olefin metathesis reaction.\(^3,41\) In both cases, the formation the rotaxane complex will be templated by the strong host-guest properties of the glycoluril unit for viologen residues.\(^8,37\)

![Scheme 10](image_url)

Although the first route may appear simpler since the BINOL/clip itself is only involved in the last step of the synthesis and commercially available carboxy ended PD can be used as a starting material, the second route will be chosen here since different sizes of
polymer can be easily obtained by changing the load of 1,5-cyclooctadiene (COD). This will be useful for the characterization of the products of the second step of the reaction as discussed below. Moreover, commercially available carboxy ended PD is not stereochemically pure and contains all three isomers $cis$, $trans$ and vinyl bonds in various amounts.

Viologen derivative 24 will be prepared from 4, 4$'$-bipyridine$^{8,42}$ and mixed with linked BINOL/diphenylglycoluril clip. The resulting solution of pseudo rotaxane [1-H] will be treated with 16% mol of ruthenium carbene Ru-1$^{41}$ in dichloroethane (DCE) at 55 °C to form the rotaxane [2-H]. After purification by column chromatography, the structure of [2-H] will be determined by $^1H$ NMR and MALDI-TOF. Finally compound [2-H] will be used as a chain transfer agent in the polymerization of COD catalyzed by the ruthenium carbene Ru-2$^{43}$ to form target rotaxane [3-H] with different chain sizes. The corresponding lanthanide rotaxane will then be prepared using the same procedure than that used to prepare the ‘free’ metal complex.

**Polymer transformation.**

The catalytic transformation of the PD strand of rotaxane [3-Ln] will be performed by sequential epoxidation and epoxide ring opening reactions (Scheme 11).

![Scheme 11](image)

Scheme 11.

Different chain sizes will be used and the reaction will be run under the optimal conditions found during the initial part of the project. Rotaxane [3-Ln] will first be transformed into [4-Ln] by action of TBHP. Then, addition of the aromatic amine will produce the chiral rotaxane [5-Ln] with a polymeric structure bearing alcoholic and amino groups.

The regioselectivity of each reaction will be analyzed by $^1H$ NMR. MALDI-TOF will be performed on all products to show the incorporation of the incoming oxygen or amino group respectively. The enantioselectivity of the second reaction will be determined by $^1H$ NMR and CD on small oligomers. The major isomers of larger polymers will be deduced from CD analysis and by extrapolation of the selectivity obtained with shorter oligomers originally bearing just one or two double bonds.
Timeline

The first year of the project will be mainly devoted to the selection of the best catalyst system and optimization of the reaction conditions. The set up of catalysis experiments should take up six months during which both the reagents and products of reaction will be thoroughly characterized and the series of lanthanide BINOL and linked-BINOL catalysts will be ordered or prepared. Small molecules will be characterized by $^1$H NMR and chiral HPLC. Polymeric reagents and products will be characterized by $^1$H NMR and circular dichroism. Chiral HPLC and circular dichroism techniques will need to be adjusted for each series of compound in order to find optimal conditions for best detection. Key instrumentation like a chiral HPLC column, a circular dichroism spectrophotometer and a stainless steel glove box will need to be ordered. Catalysis experiments will be run and optimal conditions will be found for a one pot sequential olefin epoxidation and epoxide ring opening reaction. The best catalyst will be revealed from these studies which will determine the type of clip and BINOL system that need to be synthesized. The synthesis of the glycoluril receptor will also start during that year.

The second year will focus more on the organic synthesis of the glycoluril receptor, the modified BINOL ligand and ultimately their linkage to form the desired clip. The overall time expected to achieve the synthesis is one year and a half but will mostly be performed during the second year of the project. The synthesis and purification of the glycoluril receptor is a 3 to 6 step synthesis which should be completed in about six months. The tetrabromo-BINOL precursor (3-4 step synthesis) will also be synthesized and purified in about six months. The linkage of these two units and insertion of the metal with purification and full characterization of the organic clip and its metal complex will take up another six months. Schlenk techniques will need to be used extensively so the appropriate glassware will need to be ordered as well as all other classic organic chemistry apparatus.

In the third year of this project, the synthesis of the glycoluril clip will end and the target rotaxane will be synthesized by threading the previously synthesized clip onto a polybutadiene strand using the olefin metathesis route. The synthesis of the rotaxane itself with and without metal should be achievable in six months. Rotaxanes with different length of polymer strands will be prepared and characterized. The catalytic properties of these systems in epoxidation and epoxide ring opening reactions will also be studied. Characterization of the chiral polymeric products and determination of the exact configuration of the ring opened epoxides is expected to take up the rest of the time. Optimal reaction conditions and analytical techniques developed during the first year of the project will be used as starting points for these later studies.
Impact

The aim of this research is to design novel, synthetically useful, chiral catalysts able to achieve sequential reactions without isolating the intermediate. This type of catalyst would minimize waste as compared to stepwise reactions and avoid the handling of fairly reactive intermediates like epoxides. Moreover, the threading of these active catalysts onto polymeric strands as rotaxanes, promoting similar reactions onto polymeric substrates, will open up a new generation of enantioselective polymer transformations. This novel route for chiral polymer synthesis starting from non chiral monomers will lead the way towards the preparation of a variety of new and highly valuable specialty polymer products.

In the course of this work, one graduate student (three years), one undergraduate student (six months - initial small molecule characterization) and one postdoctoral fellow (half-time for two years - synthetic organic chemistry) will be trained in enantioselective catalysis, organometallic chemistry and synthetic organic chemistry. Exposure to the state of the art analytical techniques for analysis of chiral compounds will be very valuable. Handling of air sensitive compounds with the use of glove boxes and Schlenk techniques will help students learn very precise laboratory skills. This project will also teach how to plan catalysis experiments, synthesize and characterize a wide variety of organic, inorganic and polymeric compounds.

Future directions

Understanding the mechanism of action of these catalytically active rotaxanes will be the next goal of this research. Like in the previously reported porphyrin/glycoluril rotaxane, it is not clear how to determine whether these synthetic topologically linked catalysts proceed sequentially or randomly. Detailed kinetic studies and product characterization will need to be performed in order to answer these questions.

Another interesting direction for this project would be to extend the range of nucleophiles to be used in epoxide ring opening reactions and synthesize a wider variety of chiral polymers. Other types of reactions like Michael reactions which are already known to be catalyzed by Ln-BINOL systems could also be investigated in view of transforming other types of polymers.
Section D – References


### Section E – Budget

<table>
<thead>
<tr>
<th>Cost per year ($)</th>
<th>Duration (months)</th>
<th>Total cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salary and wages:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Principal investigator / Sonia Taktak</td>
<td>56k</td>
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<tr>
<td>Post doctoral associate</td>
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<td>Graduate student / Research assistant</td>
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<td><strong>Total cost of the project and amount requested</strong></td>
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</table>

**Budget justification.**

Summer funding is requested for the principal investigator based on three ninth of an average academic year starting salary. Funding for two years, half-time of one post doctoral researcher with experience in multi step synthetic organic chemistry is also requested as well as funding for one graduate student for three years.

Several pieces of instrumentation are vital for this research like a chiral HPLC column, to be used on the departmental instrument, a circular dichroism spectrophotometer, a glove box and a rotary evaporator. Smaller pieces of equipment are budgeted in material and supplies.

Funds for traveling to national as well as international conferences are requested. The principal investigator or other investigator will present ongoing research studies at at least one conference per year.