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Synthesis and catalytic properties of diverse chiral polyamines

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ABSTRACT

Chiral polyamines can be utilized for a variety of potential applications, ranging from asymmetric catalysis to nonviral gene delivery systems for DNA and RNA. They can also be utilized to solubilize carbon nanotubes. Thus, methods for the straightforward synthesis of chiral polyamines are needed. We present herein two synthetic strategies for accessing chiral polyamines. The potential of these chiral amines to catalyze two organic reactions with a high degree of chiral induction was also explored.

1. Introduction

Chiral polyamines have been utilized for a variety of applications. First, polyamines are polycationic at neutral pH; as such, they interact strongly with both DNA and RNA.[1] They can therefore be utilized as effective nonviral gene delivery agents.[2] Second, chiral polyamines are efficient catalysts for various organic transformations.[3] Polyamines have also been used to solubilize carbon nanotubes.[4] Finally, chiral polyamines are excellent ligands for many transition metals.[5] Due to their numerous applications, high-yielding synthetic strategies for their preparation are in great demand. We present herein two synthetic strategies for accessing chiral polyamines, and the potential of these chiral amines to catalyze two organic reactions.

2. Synthetic strategy I—synthesis of chiral amines from the reduction of chiral amides

Chiral polyamines can be obtained via the reduction of polypeptides and proteins, which present a myriad of chiral centers with diverse substituents. Previous work in our group demonstrated that small peptides with up to three residues could be reduced to the corresponding chiral amines using borane complexed to THF.[6] Other researchers have also demonstrated that the synthesis of polyamines via the reduction of polypeptides is possible;[7] however, many of these methods require harsh conditions to break up the amine-borane complex.[8]

We synthesized five oligopeptides with up to eight amino acid residues via standard solution-phase peptide coupling. We reduced these oligopeptides to the corresponding polyamines in excellent yield by refluxing them with excess dimethylsulfide-borane in THF (>20 equiv of borane per carbonyl) (Fig. 1).

We synthesized two chiral amines from the coupling of cyclen with Boc-protected amino acids, followed by deprotection, and reduction with dimethylsulfide-borane (Fig. 2). These compounds could potentially serve as chiral ligands for lanthanide metals. The synthesis of compound **6a** proceeded to yield a potential 8-coordinate ligand. In our synthesis of compound **6b**, only three of the four acylations took place to yield a potential 7-coordinate chiral ligand.

Additionally, we synthesized C_2-symmetric chiral amines via borane-mediated amide reduction. We synthesized compound **7a** from the coupling of 1,2-diaminobenzene with Boc-protected phenylalanine, followed by deprotection, and reduction with dimethylsulfide-borane (Fig. 3). We synthesized compound **7b** via an analogous sequence.

Finally, we synthesized two other chiral amine catalysts (Fig. 4). We synthesized L-α-methylvaline **8** using methodology[9] developed by Seebach.[10] We synthesized chiral pyridine **9** from commercially available precursors in good yield.[11]

3. Synthetic strategy II—Synthesis of chiral polyamines via polymerization

Previously, Saegusa synthesized polymer **12** from the cationic polymerization of oxazoline **10**, followed by hydrolysis of the formyl groups (Eq. 1).[12] These polymers were effective catalysts in the asymmetric transamination of ketoacids to amino acids, yielding L-valine in up to 66% ee.[13] In an effort to fully explore the chemistry of these polymers, we synthesized a variety of polymeric analogues.

Synthesis of *S*-benzyl chiral polyamines:

We synthesized polymer **15** via the cationic polymerization of THF, which was terminated with a sub-stoichiometric amount of benzyloxazoline **10**. Further cationic polymerization of benzyloxazoline followed by hydrolysis yielded the poly-THF polyamine block co-polymer **15** (Eq. 2).[14]

Synthesis of poly-THF polyamine block co-polymers:

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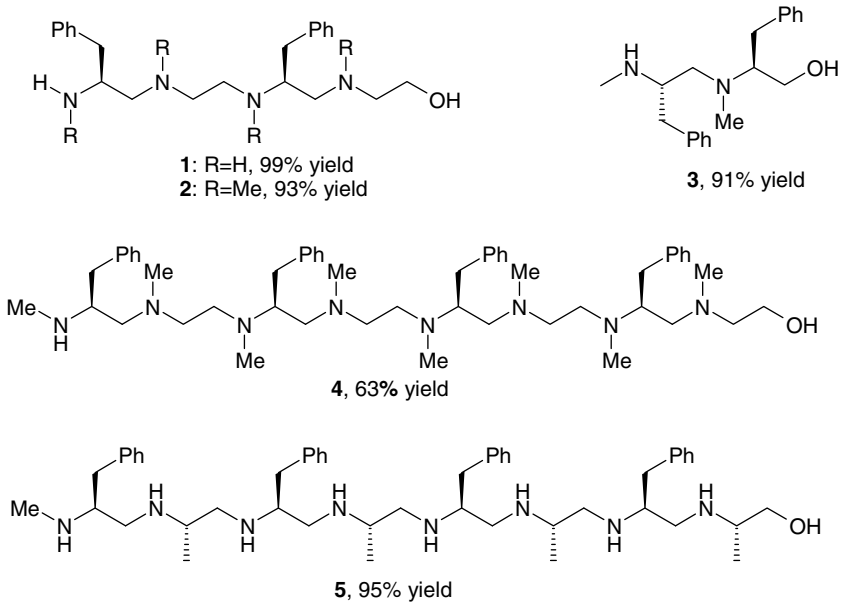


Figure 1. Chiral amines derived from reduced oligopeptides (% yield of the reduction).

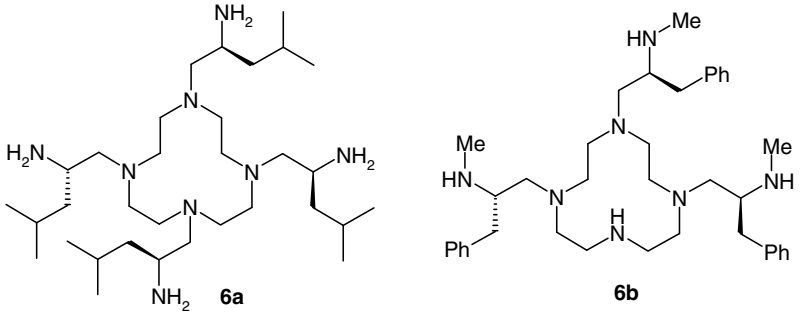


Figure 2. Cyclen-derived chiral amines.

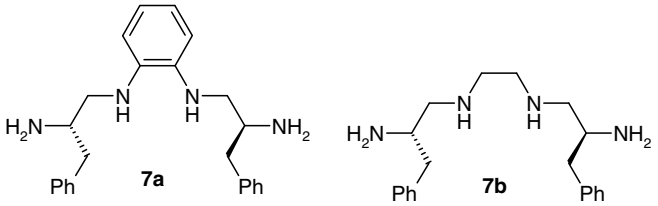


Figure 3. C_2-symmetric chiral amines.

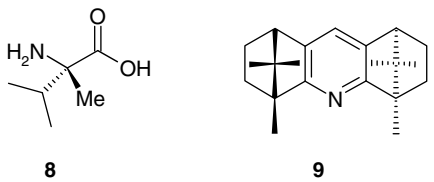
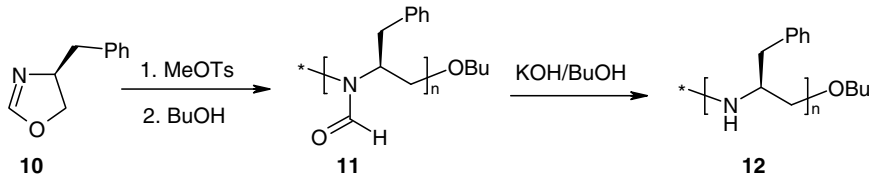
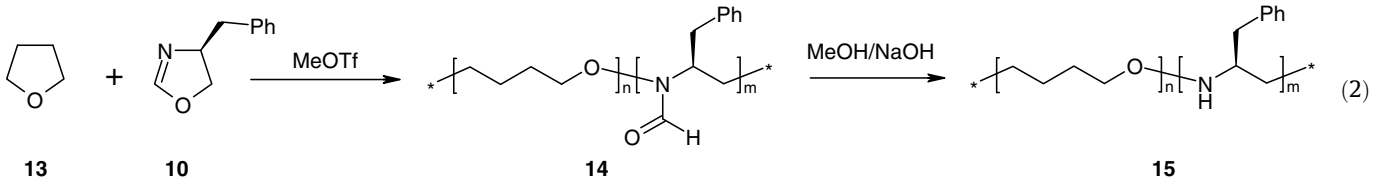


Figure 4. Other chiral amines.



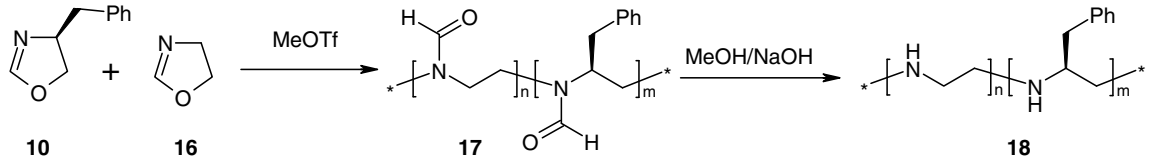
(1)



(2)

We synthesized polymer **18** via the cationic mixed polymerization of oxazolines **10** and **16**, followed by hydrolysis of the formyl groups to yield the mixed co-polymer (Eq. 3).

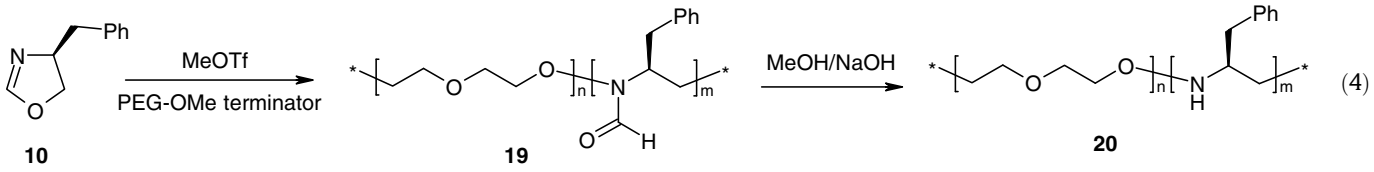
Synthesis of mixed co-polymer:



(3)

We synthesized polymers **20** via the cationic polymerization of compound **10**, which was terminated with commercially available polyethyleneglycol (PEG) methyl ether (Eq. 4). Subsequent hydrolysis then yielded the chiral block co-polymers **20**. We synthesized two co-polymers via this method: polymer **20a** contained 30 amine monomer units, terminated with PEG methyl ether with approximate M_n = 2000. Polymer **20b** contained 50 amine monomer units, terminated with PEG methyl ether with M_n = 2000.

Synthesis of PEG-polyamine block copolymers:



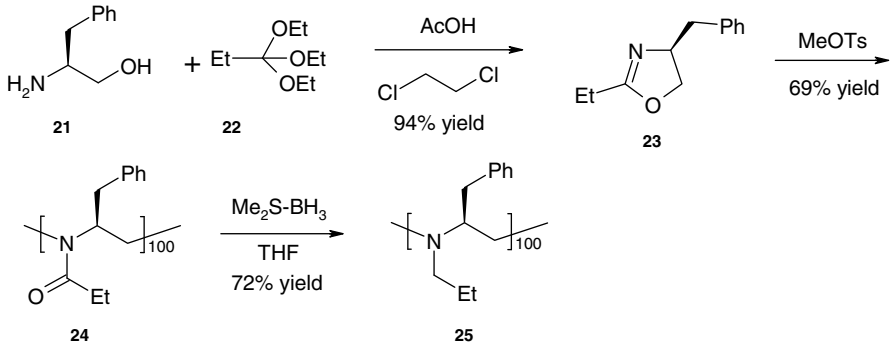
(4)

Finally, we synthesized polymer **25** via the cationic polymerization of oxazoline **23**, followed by reduction of the amides using dimethylsulfide-borane (Scheme 1).

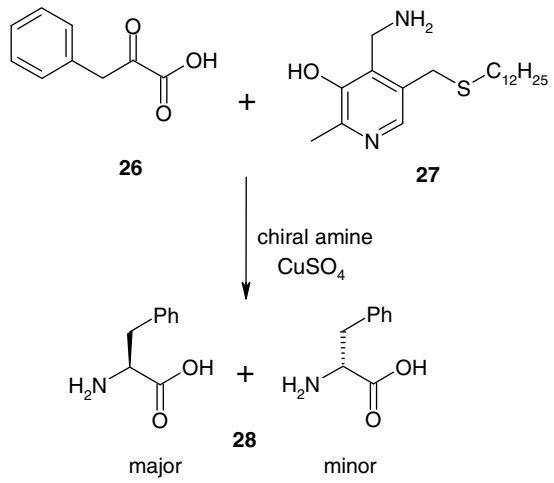
4. Catalytic properties of chiral amines—reaction I: the transamination of phenylpyruvic acid to phenylalanine

We explored the ability of the chiral amines to catalyze organic reactions. First, we investigated the transamination of phenylpyruvic acid to phenylalanine. Many other groups have studied the synthesis of chiral amino acids from ketoacids via transaminase mimics.[15] Our research group has also had some success in achieving the asymmetric synthesis of amino acids from ketoacids using chiral transaminase mimics.[6,16] We used the newly synthesized chiral amines in the transamination reaction of phenylpyruvic acid to phenylalanine (Scheme 2). We found that in the presence of copper(II) sulfate, moderate enantioselectivities were obtained in the product phenylalanine. In the absence of copper(II) sulfate, only very low enantioselectivies were observed.

In all of the transamination reactions, the chiral amines were dissolved in methanol at the highest concentrations at which the amines were soluble. The resulting stock solution was utilized in the transamination reaction. The smaller amines **1–5** were soluble in methanol at higher concentrations than the polyamines **15–25**. Polyamine **20b**, with approximately 50 amine monomer units and a long PEG chain, gave the highest ee in the phenylalanine product (52.5 ± 0.3% L ee). This chiral induction was substantially higher than the induction achieved with the smaller chiral amines (**1–5**), and occurred despite the lower concentration of the chiral amine in the reaction mixture. Interestingly, the second-best results were obtained with chiral amine **1** (24.9 ± 5.8% L ee), which



Scheme 1. Synthesis of chiral polyamine **25**.



Scheme 2. Transamination of phenylpyruvic acid to phenylalanine.

is structurally similar to polyamine **20b** (chiral benzyl groups, all secondary nitrogens).

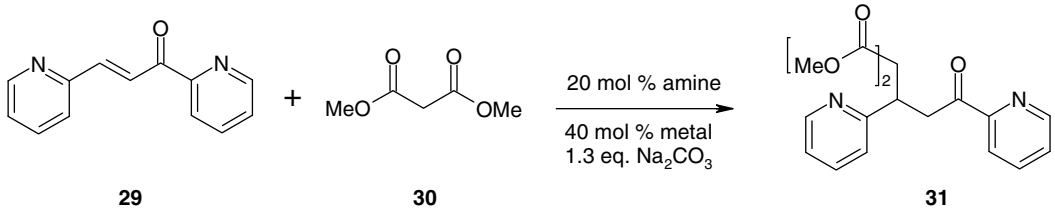
5. Reaction II: the Michael addition

We explored the use of the chiral amines in the Michael addition of dimethylmalonate **30** to azachalcone **29** (Eq. 5). These efforts complement the work of various other research groups in the use of chiral organocatalysts in the Michael reaction.[17] However, most of the effective organocatalysts are small molecules, not organic polymers. The use of a chiral organic polymer could create a macromolecular chiral and hydrophobic environment for asymmetric organic reactions.

The choice of this reaction was guided by three primary considerations:

1. The mechanism of the Michael reaction involves several steps that can be catalyzed by a general acid or general base. As polyamines titrate over a wide pH range, they are expected to serve as effective acid–base catalysts.[18]
2. The chiral polyamines that contain hydrophobic side chains could create a hydrophobic environment for the hydrophobic azachalcone **29**.
3. Chiral polyamines contain a large number of amino groups that can bind to a metal center. A variety of metals were tested for their ability to catalyze the Michael reaction in conjunction with chiral amines. Nickel sulfate and zinc acetate were found to give the best results, both in terms of yield and enantioselectivities.

Michael addition reaction:



29 30 31 (5)

The enantioselectivities obtained using chiral amines to catalyze the Michael reaction varied from 0% to 45% ee. In general, the N-methylated analogues gave better enantioselectivity than the free NH analogues, especially in the presence of zinc acetate. The most effective catalyst is compound **3**, which gave the desired product in 83–94% yield and up to 45.9% ee. This compound was more effective than monoamines like L-α-methylvaline **8** (92% yield, 2.9 ± 0.5% ee in the presence of $Zn(OAc)_2$), as well as large polyamine **25** (59% yield, 4.6 ± 1.7% ee in the presence of $NiSO_4$) and the polyamine-PEG block copolymers **20** (polymer **20a**: 96% yield, 3.1 ± 0.4% ee in the presence of $Zn(OAc)_2$). Compound **3** is readily accessible from the reduction of the corresponding dipeptide. Furthermore, other dipeptide analogues are accessible via peptide coupling of two amino acids, followed by reduction of the carbonyls and N-methylation. Future work can be directed toward the synthesis of other reduced dipeptides and their use as chiral catalysts.

In summary, the synthesis of a diverse suite of chiral amines has been described. These chiral amines range in size from an α-methyl amino acid to polymers with 100 chiral amine residues. The use of these chiral amines in catalyzing two different organic reactions has been explored, and the products were synthesized in moderate to good enantioselectivities. Further applications of these chiral amines are under investigation, including enamine catalysis, and will be reported in due course.

Supplementary data

Synthesis and spectroscopic characterization of all new compounds, HPLC parameters, reaction conditions, and full results for the transamination reaction and the Michael reaction are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.108.

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