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The synthesis of chiral amino diol tridentate ligands and their enantioselective induction during the addition of diethylzinc to aldehydes

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ABSTRACT

A series of C_2-symmetric chiral amino diol tridentate ligands **3a–g** were prepared from achiral bulky organolithiums, achiral bulky primary amines, and optically active epichlorohydrin (ECH). The prepared C_2-symmetric chiral amino diol tridentate ligands were capable of inducing enantioselectivity in the model reaction of aromatic and aliphatic aldehydes with diethylzinc with an ee of up to 96%. The enantioselectivity can be modulated by adjusting the steric hindrance of the achiral reagents employed in the synthesis of the chiral ligand. The configuration of the addition product depended on the configuration of the amino diol ligands, which can be simply controlled as desired by using the ECH with the desired configuration during the preparation of the ligand.

1. Introduction

Chiral amino alcohols possess the ability to induce enantioselective reactions and have been used as chiral ligands in many asymmetric reactions, such as asymmetric additions of diethylzinc to aldehydes,[1–6] asymmetric Michael addition reactions,[7–9] asymmetric Diels–Alder reactions,[10,11] and asymmetric hydrogenations of aromatic ketones.[12–15] There are two common methods for preparing a chiral amino alcohol: one is to reduce a natural amino acid,[16–19] while the other is to resolve a racemic amino alcohol.[20–22] With the method that reduces a natural amino acid, the structure of the obtained amino alcohol is restricted by the structure of the amino acid used. With the method that resolves a racemic amino alcohol, an expensive chiral reagent must be employed. In order to diversify the structure of chiral amino alcohols, the reaction of an amine with an optically active epoxide has been used in recent years. Manickam and Sundararajan applied the reaction of optically active styrene oxide with benzylamine to obtain a chiral, C_2-symmetric amino diol tridentate ligand[23] and found that the obtained amino diol possessed the ability to enantioselectively induce Michael addition reactions[24] and Diels–Alder reactions.[25] Grassi et al. prepared (+)-(*S*,*S*,*S*)-triisopropanolamine with 94% ee via the reaction of (*S*)-(+)-1-amino-2-propanol with ammonia[26] while Nugent employed (+)-(*S*,*S*,*S*)-triispropanolamine as a ligand to prepare a chiral Lewis acid to catalyze enantioselective additions of azides to meso epoxides.[27] The problem for preparing chiral amino diol when applying the reaction of an amine with optically active epoxide is the source of the chiral epoxide. There are two methods for preparing optically active epoxides: one is by kinetic resolution of a racemic epoxide[28] while the other is by asymmetric epoxidation of an olefin.[29–33] There is no universal kinetic resolving method and no universal resolving conditions for the resolution of epoxides with various structures. Therefore, the availability of optically active epoxides is limited.

Recently, a method for the kinetic resolution of racemic epichlorohydrin (ECH) has been established. Due to the ease of recovering and recycling the hydrolyzing product, ECH is not lost during the kinetic resolution process. So far, the kinetic resolution of ECH has been industrialized and both (*R*)-ECH and (*S*)-ECH have become very inexpensive (ca. US$ 9 per kilogram).[34] Based on the inexpensive optically active ECH, C_2-symmetric chiral amino diol tridentate ligands were synthesized using optically active ECH as the chiral source and their enantioselective inductivity in the addition of diethylzinc to aldehydes was assessed.

2. Results and discussion

2.1. The design strategy for the synthesis of chiral amino diol tridentate ligands

The reaction of an organometallic reagent R–M with optically active ECH should create an optically active, substituted propylene epoxide **2** (Scheme 1). The reaction of **2** with a primary amine should create chiral amino diol tridentate ligand **3**. The designed synthetic route to the amino diols is shown in Scheme 1.

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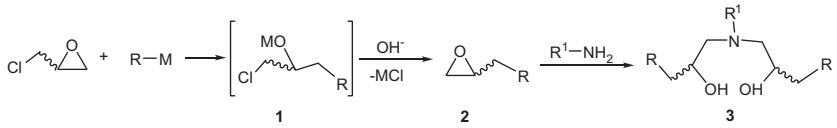


Scheme 1. Route for synthesizing chiral amino diol tridentate ligands.

By selecting various R and R^1 groups, the steric hindrance of the chiral amino diol ligand **3** could be adjusted and the enantioselective influence of **3** improved. We assumed that an increase in the bulk of R would be favorable not only to the enhancement of the enantioselectivity of the ligand, but also to the reinforcement of the attack at the CH_2 group of the epoxide ring and to the suppression of attack at the CH of the epoxide ring. Therefore, the bulky organolithium reagents 9-ethyl-9-lithiumfluorene **A**, triphenylmethyl-lithium **B**, and 5-pentyl-5-lithiumdibenzo[*a*,*e*] suberane (**C**) (Fig. 1) were selected as nucleophilic reagents to react with by *n*-BuLi to afford solutions of organolithium **A** and organolithium **B**, respectively.

The preparation of organolithium reagent **C** is described in Scheme 3. 5-Methene dibenzosuberane was reacted with *n*-butyllithium in tetrahydrofuran (THF) to afford a solution of **C**.

A solution of optically active ECH was added dropwise to a solution of the organolithium reagent at −70 °C with stirring. After the addition, the reaction mixture was stirred at −70 °C for 1 h and then stirred at room temperature for 2 h to create the optically active propene oxide **2**. The yield obtained for **2a**, **2b**, and **2c** was

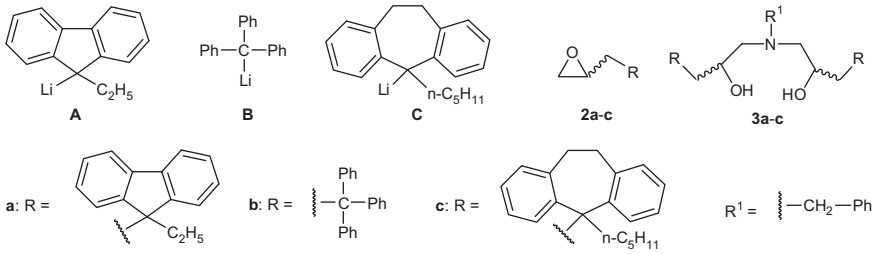


Figure 1. The structures of the organolithium reagent, substituted propylene epoxides **2a**–**c**, and chiral amino diol tridentate ligands **3a**–**c**.

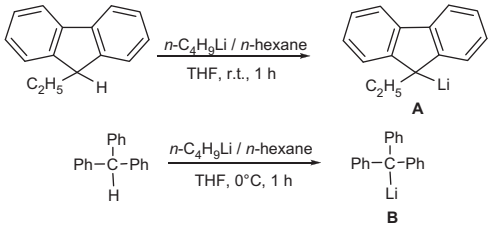
optically active ECH to create optically active, substituted propylene epoxides **2a**–**c**, respectively (Fig. 1). The bulk of the R^1 group should also have an impact on the enantioselectivity of **3**.

With benzylamine in hand, amino diols **3a**–**c** (Fig. 1) were synthesized. The impact of the R group on the enantioselectivity of the amino diol chiral ligand was examined in order to determine which R group gave the amino diol ligand with the best enantioselectivity. Then with the R group established, other amino diols were synthesized and the impact of the R^1 group on the enantioselectivity of the chiral amino diol ligand was examined.

2.2. The synthesis of chiral amino diol ligands 3

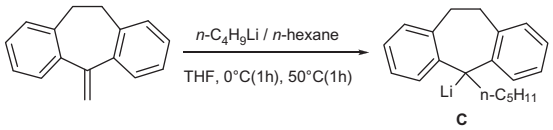
2.2.1. The synthesis of substituted propene oxides 2

The preparation of organolithium reagent **A** and organolithium reagent **B** is described in Scheme 2. 9-Ethylfluorene and triphenyl-



Scheme 2. The preparation of organolithium **A** and **B**.

methane were used, respectively as starting materials. The active hydrogen atom of the starting material molecule was removed



Scheme 3. The preparation of organolithium **C**.

70.3%, 64.8%, and 46.7% respectively. The mechanism of the reaction is shown in Scheme 4.

The nucleophilic reagent R^- attacks the epoxide ring at the less hindered CH_2 to create the ring-opening intermediate **4**. After the temperature is increased to room temperature, the elimination of LiCl from the intermediate **4** takes place to create epoxide **2**. The configuration of the stereogenic carbon atom is retained because it is not involved in the reaction process.

In order to confirm the mechanism, the reaction of organolithium **A** with ECH was quenched with water after the addition of ECH and intermediate **5a** (R = 9-ethylfluoren-9-yl) was obtained in 81.3% yield. When **5a** was stirred in aqueous NaOH at room temperature for two hours, epoxide **2a** was formed.

The ECH addition temperature was chosen to be −70 °C in order to ensure that nucleophilic attack took place entirely at the methene CH_2– of the epoxide ring, rather than at the sterically hindered methine CH–. The yield of **2** was high (>67%) when the ECH addition temperature was below −20 °C. When the addition temperature rose to 0 °C, the yield of **2** decreased dramatically (22%). The structures of **2a**–**c** were determined by ^1H NMR, ^{13}C NMR, and elemental analysis. Analysis by chiral high performance liquid chromatography (HPLC) confirmed that the enantiomeric excess of **2a**–**c** was the same as that of the starting material ECH (98.8% ee). The configuration of **2** was (*S*) when (*S*)-ECH was used as