

Facile separation of diastereo-chiral N,N'-diamine ligand via fractional crystallization and demetalation of corresponding Zn(II) complex



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ABSTRACT

Enantiopure N,N'-diamine has been obtained in an economical manner via demetalation of its corresponding dichloro Zn(II) complex, which is separated by fractional crystallization of two diastereomeric Zn(II) complexes. Polymerization of rac-lactide (rac-LA) initiated by diisopropoxide derivative proceeds rapidly at room temperature in a living fashion to yield heterotactic polylactide (PLA) with $P_r = 0.90$.

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Chiral vicinal diamines are important structures in asymmetric catalysis because of their utility and enantioselectivity for a variety of reactions [1–3]. The diamines, especially those with C_2 -symmetry, have considerable importance, since they are used in a wide range of organometallic catalysts and organocatalysts to provide asymmetry for reactions such as hydrogenations, oxidations, ring-openings, and carbon–carbon bond-formations [4]. Furthermore, diamine functionality appears in various compounds showing a broad spectrum of biological activities, including antibacterial, anticancer, and antihypertensive [5]. Undeniably, numerous enantiopure diamines that require elaborate synthesis and/or are expensive have been reported [6]. One method for the synthesis of enantiopure N,N'-diamines is the grafting of alkyl moieties at imine carbons, which results in various diastereomers [7]. The ratios of these diastereomeric components may vary depending on the reaction conditions. The separation of these diastereomers to obtain enantiopure ligands in appreciable amounts for various asymmetric reactions is a crucial step [8]. To date this area of separation is dominated by traditional column chromatography with impractical amounts of enantiopure ligands. To the best of our knowledge, no report has explored enantiopure ligand generation by demetalation of enantiopure metal complexes, which have been obtained in a very economic manner by fractional crystallization from a mixture of two diastereomeric complexes. Herein, the preliminary results of a facile separation technique

based on the fractional crystallization of two diastereomeric complexes and subsequent demetalation of the major enantiopure Zn(II) complex to obtain enantiopure ligand in facile yield and high purity, are reported. In addition the catalytic application in ROP of rac-LA has been performed keeping in view the growing interest in the development of stereospecific catalysts to obtain PLA [9–13] owing to PLA's biodegradability, biocompatibility and the possibility of deriving monomer from renewable resources [14,15].

Alkylation of **1** [16] with MeLi resulted in two diastereomers of the secondary diamine **2** [8], which could not be separated by column chromatography even after several trials. Analysis of **2** by ^1H NMR spectroscopy clearly showed two quartets for methine protons at δ 3.78 and 3.69 for two diastereomers. The grafting of alkyl groups at the ethylene backbone showed distereoselectivity for RR- compared to SS- and RS- diastereomers at a ratio of 1:0.4:0. Lacking a readily available separation process, crude ligand **2** was subjected to the next reaction without separation. Ligation of **2a** and **2b** with ZnCl_2 resulted in a mixture of two diastereomeric Zn(II) complexes in a 1:0.3 ratio as confirmed by ^1H NMR (Fig. 1b). The enantiopure Zn(II) complexes, **3a** and **3b** were separated by fractional crystallization in EtOH. The ^1H NMR (Fig. 1c) spectrum clearly showed a sextet at δ 4.15 for the methine proton of pendent chiral amine moieties. Demetalation of **3a** resulted in enantiopure ligand **2a** (Fig. 1d) in quantitative yields (Scheme 1). Structural characterizations of enantiopure ligand **2a** and the Zn(II) complexes **3a** and **3b**, were investigated by IR and elemental analyses, coupled with ^1H and ^{13}C NMR spectroscopy. As RR(R,R) and SS(R,R) are diastereomers and have different physical properties and complex **3b** was more soluble in EtOH, practical amount of solid **3b** was not obtained compared to **3a**.

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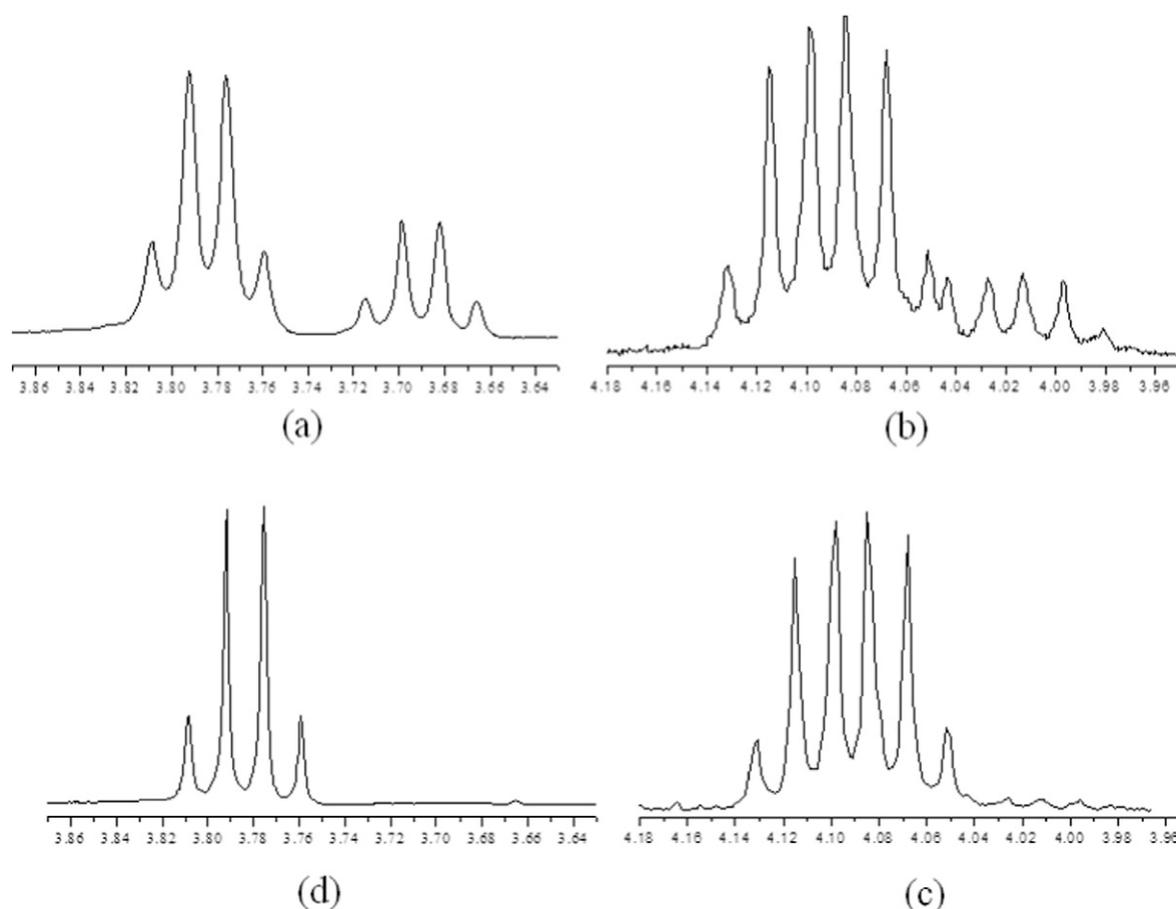


Fig. 1. Comparative view of ^1H NMR clearly demonstrating the methine protons of the ligand architecture in (a) **2**, (b) **3a** and **3b** and (c) **3a** and (d) **2a**.

Complex **3a** crystallized out as a single nuclear complex with a distorted tetrahedral geometry. The plane angle between Cl–Zn–Cl and N–Zn–N was found to be $83.76(5)^\circ$. The bond lengths and angles did not vary much from known values (ESI Table S2) [17–19]. Enantiomeric 1,2-diamine with chiral backbone blocked nitrogen atoms of secondary amines in a five membered ring in a homochiral fashion. The hydrogen atoms of the chiral carbons and nitrogens were in a head-to-tail conformation (Fig. 2). Furthermore the resultant five membered chelate ring Zn–N–C–C–N was solely in a Δ conformation.

Ring opening polymerization studies of rac-LA were carried out using diisopropoxide derivatives, generated in situ, of **3a**, which polymerizes rac-LA at room temperature with very high activity. The monomer was completely converted to PLA within 3 min; 94% conversion was observed after 2 min, as confirmed by ^1H NMR analyses. The polymerization was well processed with the diisopropoxide derivative of **3a**, yielding PLA which was highly enriched-heterotactic ($P_r = 0.90$). The $M_n = 7010$ determined by GPC agreed well with half of the predicted values, which meant that the catalyst possessed a dual active site. The narrow PDI (1.33) and linear correlation between M_n and percent conversion (by ^1H NMR) are indicative of a living polymerization. The polymer chain was end-capped with an isopropoxide $[-\text{C}(=\text{O})\text{CH}(\text{CH}_3)_2]$ group at one end and a hydroxyl group $[-\text{CHMe}-(\text{OH})]$ at the other, as determined from the ^1H NMR spectrum of the resultant PLA, $M_n = 7500$ which is a similar value by GPC. The observed results suggest that polymerization mediated by alkoxide Zn(II) complex may be initiated by a coordination insertion mechanism [20–23]. Reference experiments using LiOCHMe_2 in ROP of rac-LA under the same experimental conditions resulted in PLA in a quantifiable yield but at a slow rate and

low stereoselectivity ($P_r = 0.55$). Heterotactic-enriched PLA using in situ generated diisopropoxide derivative of enantiopure **3a** might have resulted from a chain end control mechanism with unclear assistance of the stereogenic centers, which is consistent with previously observed results [24,25]. Furthermore, the amount of **3b** was not optimum to carry out the polymerization with the mentioned complex. Thus, the observed stereoselectivity arises from the homochiral ligand architecture, which provided better control over the polymerization process and significantly influenced the stereoselectivity of the resulting PLA.

In conclusion, we developed a facile methodology to obtain an enantiopure ligand in appreciable amounts via demetalation of its dichloro Zn(II) complex, which was separated by fractional crystallization from mixture of diastereomeric complexes. Highly heterotactic PLA was obtained at room temperature from rac-LA using an in situ catalytic species of **3a** within 3 min. The polymerization proceeded in a living manner to yield PLA with high molecular weight and a narrow molecular weight distribution. Efforts to elucidate the mechanistic information in detail are underway. This enantiopure ligand, apart from its economical and facile separation, can be further utilized as a chiral auxiliary in various metal catalyzed transformations.

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