THE SYNTHESIS OF AN UNSYMMETRICAL SALEN-TYPE LIGAND AND ITS COBALT COMPLEX AS AN EFFICIENT CATALYST FOR THE HYDROLYTIC KINETIC RESOLUTION OF EPICHLOROHYDRIN

Nam T. S. Phan[1], Christopher W. Jones[2]

[1]*Ho Chi Minh City University of Technology, Vietnam*

[2]*Georgia Institute of Technology, Atlanta, USA*

Received 3 August 2010

Abstract

An unsymmetrical salen-type ligand, (*R,R*)-*N*-(3,5-di-*tert*-butylsalicylidene)-*N*'-[3-*tert*-butyl-5-(4-vinylphenyl)salicylidene]cyclohexane-1,2-diamine, was readily synthesized using the condensation of (*R,R*)-cyclohexane-1,2-diamine with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde in an isolated yield of 80%. The ligand was characterized using ^{1}H and ^{13}C NMR, MS and HRMS, elemental analysis. The corresponding cobalt (II) complex was subsequently prepared and characterized using HRMS and elemental analysis. It was observed that the salen-type cobalt complex exhibited excellent activity and selectivity in the hydrolytic kinetic resolution of racemic mixture of epichlorohydrin, with more than 99% ee and 53% conversion being achieved within 2 h at the catalyst loading of 0.5 mol%.

1. INTRODUCTION

Chiral salen-type complexes, discovered by Jacobsen, represent a powerful family of catalysts for several important organic transformations [1]. They constitute a standard system in coordination chemistry, in which the ligand backbone and the coordinated metal ion can be easily varied, making these catalysts especially useful in catalytic studies [2]. Pioneering work mostly involved the synthesis *via* direct condensation of one equivalent of a diamine and two equivalents of the salicylaldehyde derivative, resulting in a symmetric salen ligand [3]. However, interests in the design, synthesis and characterization of unsymmetrical salen-type ligands have recently been increasing despite difficulties in synthesis. This trend comes from the realization that the unique structure of the unsymmetrical ligands allows tuning both the electronic properties from one side and the steric effects from the other side simultaneously and collectively to maximize the performance of the catalysts [4].

The preparation of enantioenriched epoxides has long stood as a most significant target for asymmetric synthesis, as the ring opening of epoxides allows straightforward elaboration of new useful functionality [5]. Furthermore, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis [6]. The Jacobsen hydrolytic kinetic resolution of commercially available racemic terminal epoxides, among available methods, has emerged as an useful and powerful strategy for the synthesis of valuable enantiopure epoxides and the corresponding diols in a single step [7]. In this paper, we wish to report the synthesis of a chiral unsymmetrical salen-type ligand based on (*R,R*)-cyclohexane-1,2-diamine, using a one-pot practical protocol. The ligand was readily complexed with cobalt (II) acetate, achieving an excellent catalyst of the hydrolytic kinetic resolution of racemic mixture of epichlorohydrin.

2. EXPERIMENTAL

2.1. Materials and instrumentation

Reagents were purchased from Aldrich, Acros, or Alfa, and used as received unless noted below. Dichloromethane, toluene and tetrahydrofuran were dried by passing through columns of activated copper and alumina successively. Chlorobenzene was distilled under an atmosphere of argon prior to use. (*R,R*)-cyclohexane-1,2-diamine monohydrochloride salt, 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde, and 5-bromo-3-*tert*-butyl-2-hydroxybenzaldehyde, were prepared according to published procedures [8-10]. ^{1}H and ^{13}C-NMR spectra were acquired with a Varian Mercury 400 MHz spectrometer. Mass spectra were

recorded with a VG 7070 EQ-HF hydrid tandem mass spectrometer. Enantiomeric excesses were determined by capillary gas-phase chromatography (GC) analysis on a Shimadzu GC 14 A instrument equipped with a FID detector and a Chiraldex G-TA column (30 m × 25 mm) with helium as a carrier gas. Elemental analyses were performed by Desert Analytics Lab (Tucson, AZ, USA) and Atlantic MicroLab (Norcross, GA, USA).

2.2. Synthesis of salen ligand

Salen ligand (*R*,*R*)-*N*-(3,5-di-*tert*-butylsalicylidene)-*N*'-[3-*tert*-butyl-5-(4-vinylphenyl)salicylidene]cyclohexane-1,2-diamine was synthesized as previously reported [11]. A 250 mL flask was charged with (R,R)-cyclohexane-1,2-diamine monohydrochloride salt (0.49 g, 3.26 mmol), activated 3 Å molecular sieves (1.5 g), anhydrous methanol (15 mL), and anhydrous ethanol (15 mL). 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (0.76 g, 3.26 mmol) was added in one portion and the reaction mixture was stirred at room temperature for 6 hours. After complete consumption of the aldehyde as monitored by TLC, a solution of 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde (0.91 g, 2.36 mmol) in dichloromethane (25 mL) was added to the reaction system, followed by the slow addition of triethylamine (0.91 mL, 6.52 mmol). The reaction mixture was stirred at room temperature overnight, followed by the removal of the solvents. The residue was dissolved in dichloromethane (100 mL), washed with aqueous hydrochloric acid (1 M, 50 mL) and water (2 × 50 mL), and dried with anhydrous magnesium sulfate. Flash chromatography of the crude product with ether/hexanes (1/50) afforded the target salen ligand as a yellow solid. Further purification was achieved by re-crystallization in hexanes. Yield 1.55 g (80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.22 (s, 9 H; CMe_3), 1.42 (s, 9 H; CMe_3), 1.44 - 1.51 (m, 2 H; C*H*$_2$), 1.46 (s, 9 H; CMe_3), 1.70 - 1.84 (m, 2 H; C*H*$_2$), 1.88 - 1.91 (m, 2 H; C*H*$_2$), 1.97 - 2.02 (m, 2 H; C*H*$_2$), 3.30 - 3.78 (m, 2 H; 2 NC*H*CH$_2$), 5.25 (d, *J* = 11.0 Hz, 1 H; CH=C*H*$_2$), 5.77 (d, *J* = 17.6 Hz, 1 H; CH=C*H*$_2$), 6.74 (dd, *J* = 11.0, 17.6 Hz, 1 H; C*H*=CH$_2$), 6.97 (d, *J* = 2.5 Hz, 1 H; Ar*H*), 7.21 (d, *J* = 2.5 Hz, 1 H; Ar*H*), 7.31 (d, *J* = 2.5 Hz, 1 H; Ar*H*), 7.40 - 7.45 (m, 4 H; Ar*H*), 7.49 (d, *J* = 2.5 Hz, 1 H; Ar*H*), 8.30 (s, 1 H; N=C*H*), 8.35 (s, 1 H; N=C*H*), 13.69 (br s, 1 H; O*H*), 14.01 ppm (br s, 1 H; OH); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 24.53 (*C*H$_2$), 24.54 (*C*H$_2$), 29.59 (*C*H$_2$), 29.62 (*C*H$_2$), 31.60 (3 *C*H$_3$), 33.32 (3 *C*H$_3$), 33.37 (3 *C*H$_3$), 34.23 (*C*Me$_3$), 35.15 (*C*Me$_3$), 35.17 (*C*Me$_3$), 72.58 (2 overlapping lines, 2 *C*H-N=), 113.64 (CH=*C*H$_2$), 117.98 (Ar*C*-CN), 118.94 (Ar*C*-CN), 126.22 (Ar*C*), 126.74 (Ar*C*), 126.88 (Ar*C*), 127.11 (Ar*C*), 128.23 (Ar*C*), 128.33 (Ar*C*), 130.51(Ar*C*), 135.99 (Ar*C*), 136.59 (Ar*C*), 136.68 (Ar*C*), 137.76 (Ar*C*), 140.21 (Ar*C*), 140.70 (Ar*C*), 158.15 (Ar*C*-OH), 160.26 (Ar*C*-OH), 165.81 (*C*=N), 166.24 (*C*=N) ppm; MS (EI): *m*/*z* (%) 592 (100) [M^+]; HRMS (EI) *m*/*z*: 592.4004 (M), $C_{40}H_{52}N_2O_2$ requires 592.4028; elemental analysis calcd (%) for $C_{40}H_{52}N_2O_2$: C 81.04, H 8.84, N 4.73; found: C 81.15, H 8.87, N 4.81.

2.3. Metallation of the salen ligand

A 100 ml flask was charged with the salen ligand (266 mg, 0.45 mmol), anhydrous dichloromethane (10 ml) in a nitrogen glove box. A solution of anhydrous cobalt (II) acetate (80 mg, 0.45 mmol) in anhydrous methanol (10 ml) was then added. A brick-red precipitate was observed immediately in the reaction mixture. The reaction mixture was then heated at reflux for 24 h under an argon atmosphere. The suspension was then cooled to room temperature, and the flask was then transferred into a freezer in nitrogen glove box. The resulting solid was then recovered by filtration, re-crystallized in methanol, and dried under high vacuum at room temperature overnight. Yield 254 mg (87%) HRMS (EI) *m*/*z*: 649.3258 (M), $C_{40}H_{50}N_2O_2Co$ requires 649.3204; elemental analysis calcd (%) for $C_{40}H_{50}N_2O_2Co$: C 73.94, H 7.76, N 4.31; Found: C 74.26, H 7.97, N 4.66.

2.4. Procedure for the hydrolytic kinetic resolution of (*rac*)-epichlorohydrin

The Co (II) pre-catalyst (0.025 mmol on the basis of cobalt) was suspended in dichloromethane (1 ml) in a 5 mL pear-shaped flask with a half-round magnetic stirring bar. Glacial acetic acid (0.10 ml) was added, and the mixture was stirred in the open air at room temperature for 30 min. The solvent and the excess acetic acid were roughly removed by a rotovap. The brown-black residue was dried under high vacuum at room temperature for 30 min to give the Co (III) catalyst. Racemic epichlorohydrin (391 μL, 5.0 mmol) and chlorobenzene (50 μL, internal reference) were added to suspend the activated catalyst and the flask was immersed into a water bath at room temperature. Deionized water (0.7 equiv, 63 μL, 3.5 mmol) was injected into the system to start the reaction. Samples (1 μL) were taken from the reaction mixture with a micro-syringe at each designed time, diluted with anhydrous diethyl ether (2 mL), and passed through a plug of

silica gel in a Pasteur pipette to remove the cobalt catalyst and water. The conversions (with reference to chlorobenzene) and enantiomeric excesses of epichlorohydrin were measured by GC with a Chiraldex G-TA column (30 m × 25 mm). The retention times of products were also compared to those of authentic materials.

3. RESULTS AND DISCUSSION

The obvious difficulty in the synthesis of unsymmetrical salen ligands is that the straightforward condensation method universally applied for symmetrical salen ligands is no longer suitable. Unsymmetrical salen ligands must be prepared in two steps, involving the initial preparation of a so-called half-unit, followed by condensation of the half-unit with a salicylaldehyde derivative through its unreacted primary amine group [12, 13]. Accordingly, reports of the unsymmetrical salen ligands have been scarce up to now. Although the stepwise synthesis of the ligands containing two different donor units *via* mono-imines has recently been investigated and improvements have been made, the method is generally unreliable and the mono-imines prepared from salicylaldehydes and 1,2-diamines are always contaminated with various amounts of the symmetric *bis*-imines even after attempted purification [14]. As a result, condensations two different salicylaldehydes afford inevitably a mixture of three salens, one of which is the targeted unsymmetrical product while the two other products are symmetrical.

In this work, an enantiopure unsymmetrical salen-type ligand was synthesized according to a straightforward one-pot protocol using a 1:1:1 molar ratio of a hydrogen chloride-protected chiral diamine and two different salicylaldehydes (figure 1). The ligand possesses a styrene moiety as a functional group, which is ready for the immobilization of the salen onto solid supports, or for the polymerization / co-polymerization to synthesize functional polymers. The results of these topics will be published later in due course. Starting with 3-*tert*-butyl-2-hydroxybenzaldehyde, a bromination reaction was carried out at room temperature in glacial acetic acid, yielding 5-bromo-3-*tert*-butyl-2-hydroxybenzaldehyde in an isolated yield of 90% [9]. A Suzuki cross-coupling reaction of the brominated aldehyde with 4-vinylphenylboronic acid in the presence of a palladium catalyst and K_2CO_3 as a base was then subsequently performed [10] (reaction sequence 1, figure 1). The crude product of the reaction was purified by flash chromatography with ether/hexanes (1/50). It was observed that the desired product, 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde, was formed in an isolated yield of 72%.

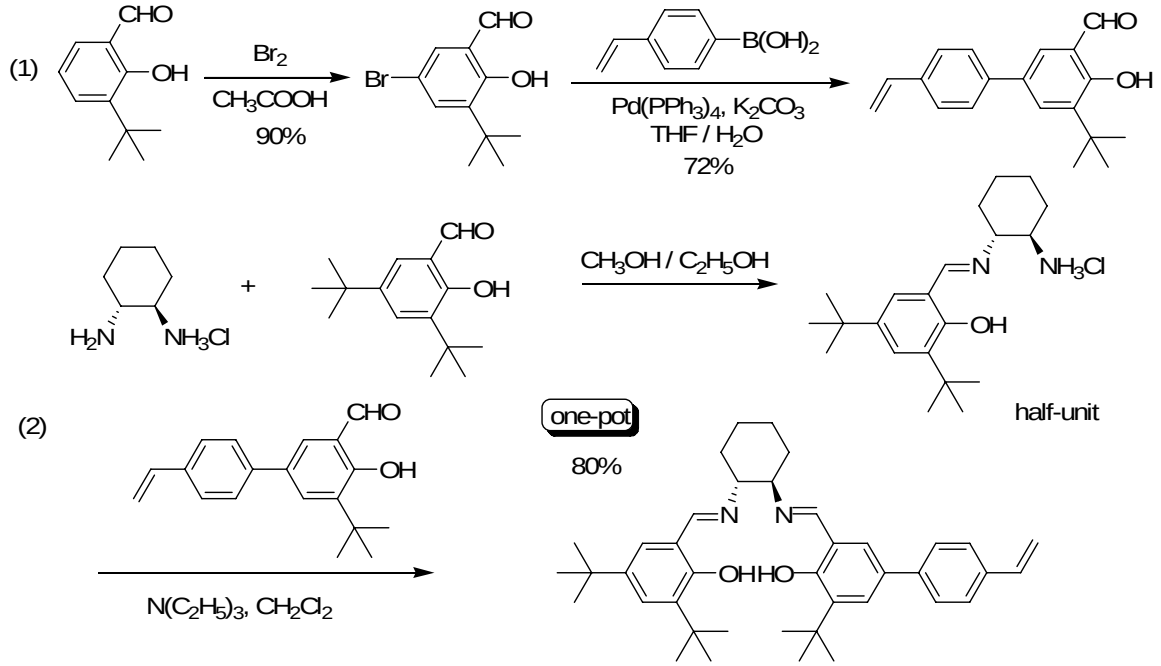

Figure 1: The synthesis of unsymmetrical salen-type ligand

In the next step, anhydrous hydrochloric acid was used to selectively protect one amino group of the (*R*,*R*)-cyclohexane-1,2-diamine [8]. The resulting ammonium salt (*i.e.* (*R*,*R*)-cyclohexane-1,2-diamine monohydrochloride salt) was added to 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde providing

access to a mono-imine product, known as the half-unit. This compound was then allowed to react with an equivalent of 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde in the presence of triethylamine to afford the unsymmetrical salen-type ligand [11] (reaction sequence 2, figure 1). The reaction sequence was carried out using one-pot protocol without separating and purifying the half-unit product. Triethylamine was used to convert the ammonium salt to a free primary amine group, allowing the condensation of the half-unit with the second aldehyde to occur. The unsymmetrical salen-type ligand, (*R*,*R*)-*N*-(3,5-di-*tert*-butylsalicylidene)-*N*'-[3-*tert*-butyl-5-(4-vinylphenyl)salicylidene]cyclohexane-1,2-diamine, was purified by flash chromatography with ether/hexanes (1/50), and dried under high vacuum to afford an isolated yield of 80%. The ligand was characterized by ^{1}H and ^{13}C NMR, MS and HRMS, and elemental analysis, indicating that it was not contaminated with the symmetrical salen ligand (see experimental section).

The salen-type ligand can be used to synthesize transitional metal complexes or it can be used as monomer to produce functional polymers/co-polymers. Initially, we synthesize a salen-type cobalt (II) complex, and then investigated its catalytic activity in the hydrolytic kinetic resolution of racemic mixture of epichlorohydrin. The salen-type ligand was converted to the corresponding cobalt (II) complex by refluxing it in the presence of anhydrous cobalt (II) acetate [3] (figure 2). The color of the reaction mixture changed from yellow to deep red, a characteristic of cobalt (II) salen species [6]. The crude product was purified by re-crystallization in methanol, and characterized by HRMS and elemental analysis, indicating a pure cobalt (II) salen-type complex (see experimental section). As the cobalt (II) species are paramagnetic, NMR data would not provide useful information for the structure elucidation of the salen-type complex. It should be noted that cobalt (II) salen complexes are prone to oxidation to the corresponding cobalt (III) salen species [6]. Therefore, the metallation of salen ligands should always be carried out under an inert atmosphere.

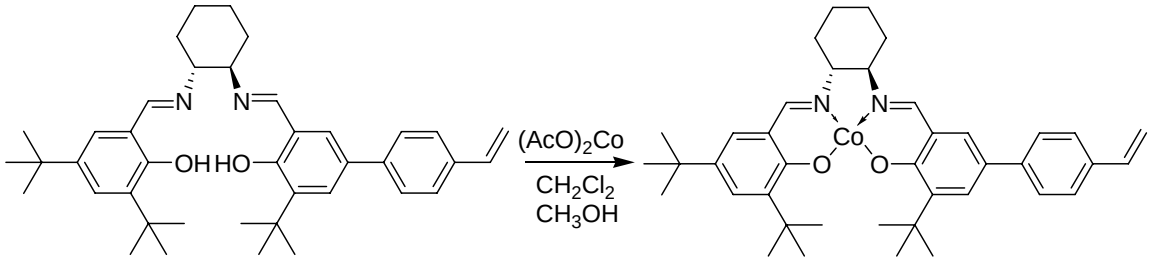

Figure 2: The preparation of the cobalt (II) salen-type complex

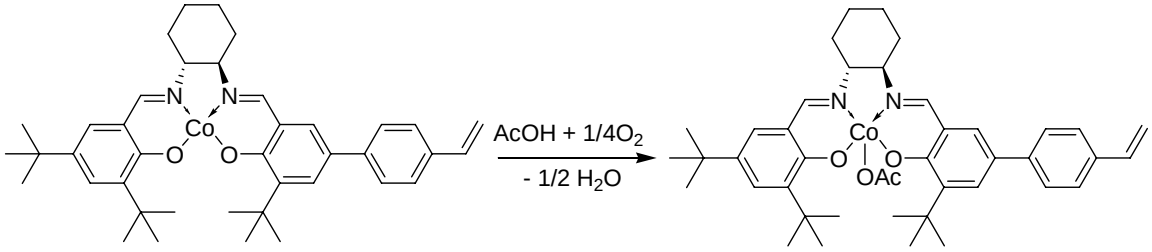

Figure 3: The generation of the active cobalt (III) salen-type catalyst

The cobalt (II) salen-type complex was examined for its catalytic activity in the hydrolytic kinetic resolution of racemic mixture of epichlorohydrin. Prior the catalytic reaction, cobalt (II) salen-type pre-catalyst was oxidized to the corresponding cobalt (III) active catalyst in open air with the help of excessive acetic acid (figure 3). Cobalt (II) salen complexes are catalytically inactive, and they must always be subjected to one-electron oxidation to produce catalytically active cobalt (III) salen complexes [6, 11]. Two methods for generation of cobalt (III) salen species were previously developed. The first method involved the isolation of the catalyst. The second method involved the generation of the catalyst just prior to the hydrolytic kinetic resolution reaction. It was previously reported that cobalt (III) salen species generated just prior to reaction exhibited better catalytic activity [11].

In this study, it was therefore decided to oxidize the cobalt (II) salen-type complex just prior to the hydrolytic kinetic resolution reaction. The oxidation process was evidenced by a dramatic color change from deep red to dark brown, which is well documented in the literature [6, 7]. The hydrolytic kinetic resolution of racemic mixture of epichlorohydrin was carried out at ambient temperature in the presence of 0.5 mol% catalyst, calculated on the basis of cobalt (figure 4). The reaction conversions (with reference to chlorobenzene as internal standard) and enantiomeric excesses (ee) of epichlorohydrin were determined by GC with a chiral column. It was observed that the catalyst was highly active and enantioselective for the resolution reaction with more than 99% ee of the (*S*)-epichlorohydrin and 53% conversion of the racemic mixture of epichlorohydrin being achieved within 2 h. The activity and selectivity of the salen-type catalyst observed in this study is almost identical to that of the best salen catalysts previously published [1]. It should be noted that resolution reactions should have an optimum conversion of 50% based on racemic starting material [5]. Furthermore, the catalyst possesses a styrene moiety as a functional group, which is ready for the immobilization of the salen onto solid supports, or for the polymerization/co-polymerization to synthesize functional polymers; and the results will be published later.

Figure 4: The hydrolytic kinetic resolution of racemic mixture of epichlorohydrin

4. CONCLUSIONS

In summary, we have synthesized an unsymmetrical salen-type ligand, (*R,R*)-*N*-(3,5-di-*tert*-butylsalicylidene)-*N'*-[3-*tert*-butyl-5-(4-vinylphenyl)salicylidene]cyclohexane-1,2-diamine using the condensation of (*R,R*)-cyclohexane-1,2-diamine with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde and 3-*tert*-butyl-2-hydroxy-5-(4-vinylphenyl)benzaldehyde in an isolated yield of 80%. Analytical data show that it was not contaminated with the corresponding symmetrical salen ligands. The ligand was readily complexed with cobalt (II) acetate, and the subsequent cobalt salen-type catalyst exhibited excellent activity in the hydrolytic kinetic resolution of racemic mixture of epichlorohydrin with more than 99% ee and 53% conversion being achieved within 2 h at the catalyst loading of 0.5 mol%. Furthermore, the styrene moiety on the ligand is able to act as a functional group for several transformations, and a full investigation will be a topic of an upcoming, separate paper. The catalyst its self, and its related structure materials offer potential advantages for asymmetric syntheses, and would be interested to the chemical industry.

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Corresponding author: **Phan Thanh Son Nam**
Ho Chi Minh City University of Technology, Vietnam
268 Ly Thuong Kiet, 10 district, Ho Chi Minh City, Vietnam
Email: ptsnam@hcmut.edu.vn or ptsnam@yahoo.com