

一种新型线性手性聚(联萘酚-炔)的合成及其在 Et_2Zn 不对称醛加成反应中的应用*

伍凌林 郑立飞 黄小波 成义祥**

(南京大学化学化工学院 介观化学教育部重点实验室 南京 210093)

摘 要 (*S*)-5,5'-二溴-6,6'-二(4-三氟甲基苯基)-2,2'-联萘酚与(*S*)-5,5'-二乙炔基-6,6'-二丁基-2,2'-二丁氧基-1,1'-联萘酚通过 Pd 催化的 Sonogashira 反应合成了一种新的手性线性高分子聚合物,研究了这种高分子在 Et_2Zn 不对称醛加成反应中的应用.结果表明这种高分子在 $\text{Ti}(\text{O}^i\text{Pr})_4$ 的存在条件下展示了良好的反应活性.而且,这种高分子配体在循环利用 10 次后可仍然保持较好的活性.

关键词 (*S*)-联萘酚, Sonogashira 反应, 不对称加成

SYNTHESIS OF A NEW LINEAR CHIRAL POLYMER BASED ON POLYBINAPHTHOLS AND ITS APPLICATION IN ENANTIOSELECTIVE ADDITION OF Et_2Zn TO ALDEHYDES*

Ling-lin Wu, Li-fei Zheng, Xiao-bo Huang, Yi-xiang Cheng

(Key Laboratory of Mesoscopic Chemistry of MOE, School of Chemistry and Chemical Engineering,
Nanjing University, Nanjing 210093)

Abstract A new linear chiral polymer ligand was synthesized by the polymerization of (*S*)-5,5'-dibromo-6,6'-di(4-trifluoromethylphenyl)-2,2'-binaphthol (*S*-**M-1**) with (*S*)-5,5'-diethynyl-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl (*S*-**M-2**) via Pd-catalyzed Sonogashira reaction. The application of the chiral polymer ligand in the asymmetric addition of Et_2Zn to various aromatic aldehydes had been studied. The results showed that this kind of soluble chiral polybinaphthols ligand in combination with $\text{Ti}(\text{O}^i\text{Pr})_4$ could exhibit good reactivity and enantioselectivity for the asymmetric addition of Et_2Zn to aromatic aldehydes. Moreover, the chiral polymer ligand showed superior enantioselectivity over the model compound *S*-**1** and could keep similar reactivity as well as enantioselectivity after ten recycles.

Keywords (*S*)-1,1'-bi-2-naphthol, Sonogashira coupling, Asymmetric addition

1 INTRODUCTION

Enantioselective catalysis using chiral metal complexes as Lewis acid provides one of the most

general and flexible methods for asymmetric synthesis. These metal complexes are well known to possess a range of activities that can be influenced by the chiral ligand structure. The chiral ligand,

* Invited paper for the special topic of "Asymmetric Polymerization and Chiral Materials". Received January 25, 2013, Revised February 6, 2013; This work was supported by the National Natural Science Foundation of China (Nos. 21074054, 51173078 and 21172106) and National Basic Research Program of China (No. 2010CB923303).

** Corresponding authors: Yi-xiang Cheng (成义祥), E-mail: yxcheng@nju.edu.cn

doi:10.3724/SP.J.1105.2013.13052

optimized for a given transformation, must have suitable functionalities, appropriate elements of asymmetry, and substituents capable of differentiating the available space in the vicinity of the metal center^[1-4]. As one of the most effective chiral ligands, optically active 1,1'-bi-2-naphthol (BINOL) and its derivatives are the most important C_2 symmetric compounds. The 3,3'-, 5,5'- and 6,6'-positions of the skeletal structure of BINOL can be selectively functionalized at the well-defined molecular level and lead to a variety of BINOL-based derivatives which can exhibit remarkably stable chiral configuration as well as high chiral induction in molecular recognition and asymmetric processes^[1,3,5-9].

Asymmetric catalytic C—C bond formation reactions have been extensively studied in the past ten years owing to their diversified applications to the synthesis of bioactive compounds^[10-13]. In view of construction of C—C bonds, organozinc compounds are the most reliable reagents due to their mild reactivity and controllable characteristics for achieving excellent stereoselectivity. In cases of dialkylzinc additions to aldehydes, recoverable titanium catalysts of binaphthols (BINOLs) have attracted intensive attention^[14-18]. In the past decade, Pu and his coworkers have proposed and designed a series of new chiral polymer ligands based on polybinaphthols as the Lewis acid to carry out highly enantioselective organic reactions, such as the additions to aldehydes, hetero-Diels-Alder reactions, 1,3-dipolar cycloadditions, reductions of ketones, and others^[19-21]. Yashima *et al.* also reported the soluble chiral polymer-supported catalysts incorporating the chiral units in the helical polymer main-chain backbone, which showed high reactivity and stereoselectivity in asymmetric Henry reaction^[22] and stoichiometric oxidation of sulfides and amines^[23]. Soluble chiral polymer homogeneous ligands used as catalysts of asymmetric synthesis offer several advantages over small chiral molecule ligands, such as simple separation, recover and reuse of the catalysts, and the possibility of use under continuous flow conditions^[2,24-26]. In particular, high

catalytic activities and enantioselectivities can be achieved in such a way that the amplified effects of multiple chiral units in chiral polymer homogeneous ligands backbone. To our knowledge, there have been few reports on polymerization at the 5,5'-positions of the binaphthyl unit except that we reported a facile method for the direct bromination of BINOL at 5,5'-positions under mild conditions and afterward prepared a chiral polymer ligand incorporating the alternative (*S*)-2,2'-binaphthol at 5,5'-positions and (*S*)-1,1'-binaphthyl at 6,6'-positions^[6,27]. The polymeric ligand exhibited excellent enantioselectivity for phenylethynylzinc addition to both aromatic and aliphatic aldehydes. But there have been no reports about linear chiral polymer incorporating 1,1'-binaphthyl and 2,2'-binaphthol at 5,5'-positions. In this paper, we prepared a new linear chiral polymer incorporating the alternative (*S*)-2,2'-binaphthol and (*S*)-1,1'-binaphthyl at 5,5'-positions, and studied its application in the asymmetric addition of diethylzinc to various aromatic aldehydes. The results showed that this kind of soluble chiral polybinaphthols ligand in combination with $\text{Ti}(\text{O}^i\text{Pr})_4$ could exhibit good enantioselectivity for asymmetric diethylzinc additions to aromatic aldehydes. The recovered polymer ligand could keep similar catalytic activity and enantioselectivity as the original polymer after three cycles.

2 EXPERIMENTAL

2.1 General

^1H - and ^{13}C -NMR spectra measurements were recorded on a 300-Bruker spectrometer with TMS as internal standard. FTIR spectra were taken on a Nexus 870 FTIR spectrometer. Specific rotation was determined with a Ruololph Research Analytical Autopol III. The ee value determination was carried out using chiral P-E Series200 HPLC with a Chiralcel OD-H column on a Waters chromatograph with a P-E Series200 UV/Vis-detector. All solvents and reagents were commercially available A. R. grade. (*S*)-1,1'-bi-2-naphthol (BINOL) was purchased from Aldrich and directly used without

purification. THF and toluene were purified by distillation from sodium in the presence of benzophenone. CH_2Cl_2 was distilled from P_2O_5 .

2.2 Synthesis of (S)-5, 5'-Dibromo-6, 6'-Dibutyl-2,2'-Dibutoxy-1,1'-Binaphthyl

A mixture of (S)-5, 5'-dibromo-6, 6'-dibutyl-2, 2'-binaphthol (5.0 g, 9.0 mmol), K_2CO_3 (8.3 g, 60 mmol) and 1-bromobutane (4.1 g, 30.0 mmol) in 70 mL CH_3CN was refluxed overnight. Upon being evaporated to dryness, the residue was poured to 5% aqueous NaOH (50 mL), and the solution was extracted by petroleum ether (3×50 mL). The combined organic layers were washed with saturated brine and then dried over anhydrous Na_2SO_4 . After the solvent was removed under the reduced pressure, the residue was purified by chromatography on silica gel with petroleum ether as eluent. (S)-5, 5'-dibromo-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl was obtained as a viscous product in a 91% yield (5.5 g). $[\alpha]_{\text{D}}^{20} = -66.2$ (c 0.29, CH_2Cl_2). $^1\text{H-NMR}$ (300 MHz, CDCl_3 , δ): 8.44 (d, $J = 9.2$ Hz, 2H), 7.47 (d, $J = 9.3$ Hz, 2H), 7.03 (dd, $J_1 = 8.6$ Hz, $J_2 = 8.9$, 4H), 3.97 (m, 4H), 2.93 (m, 4H), 1.65 (m, 4H), 1.41 (m, 8H), 1.06 (m, 4H), 0.96 (t, $J = 7.4$ Hz, 6H), 0.68 (t, $J = 7.4$ Hz, 6H).

2.3 Synthesis of (S)-5, 5'-Diiodo-6, 6'-Dibutyl-2, 2'-Dibutoxy-1, 1'-Binaphthyl

To a solution of (S)-5, 5'-dibromo-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl (2.8 g, 4.1 mmol) in THF (30 mL) was added a hexane solution of *n*-BuLi (2.5 mol/L; 10 mL, 25 mmol) at -78°C under argon. The reaction mixture was stirred for 30 min, and then a solution of iodine (8.0 g) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature over 24 h and quenched with water. The resulting mixture was treated with aqueous saturated Na_2SO_3 to destroy excess iodine. After being stirred for 30 min and removed the organic layer, the remains was extracted by ethyl acetate (3×30 mL). The combined organic layers were washed with saturated brine and then dried over anhydrous Na_2SO_4 . After evaporation of the solvents, the residue was purified by silica gel

column chromatography with petroleum ether as eluent. (S)-5, 5'-diiodo-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl was obtained as a viscous product in a 62% yield (1.9 g). $[\alpha]_{\text{D}}^{20} = -63.1$ (c 0.27, CH_2Cl_2). $^1\text{H-NMR}$ (300 MHz, CDCl_3 , δ): 8.44 (d, $J = 9.6$ Hz, 2H), 7.48 (d, $J = 9.5$ Hz, 2H), 7.07 (s, 4H), 4.00 (m, 4H), 2.99 (m, 4H), 1.68 (m, 4H), 1.47 (m, 8H), 1.08 (m, 4H), 1.01 (t, $J = 7.2$ Hz, 6H), 0.72 (t, $J = 7.4$ Hz, 6H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ): 154.0, 137.8, 132.7, 129.5, 128.4, 127.7, 126.1, 125.5, 121.1, 116.2, 70.0, 35.6, 33.5, 31.8, 29.5, 25.7, 22.7, 14.2.

2.4 Synthesis of (S)-5, 5'-Diethynyl-6, 6'-Dibutyl-2, 2'-Dibutoxy-1, 1'-Binaphthyl

The mixture of (S)-5, 5'-diiodo-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl (1.7 g, 2.2 mmol), trimethylsilylacetylene (3.9 g, 40.0 mmol), Pd(PPh_3) $_2\text{Cl}_2$ (160 mg, 0.22 mmol), CuI (85 mg, 0.45 mmol), triethylamine (20 mL) and THF (26 mL) was heated at 50°C for 36 h under Ar. The mixture was cooled to room temperature and filtered through a short column of silica gel with ethyl acetate as eluent. After the removal of the solvent, the reactant was dissolved in methanol (25 mL) and THF (25 mL) containing 10 mL of KOH solution ($1\text{ mol}\cdot\text{L}^{-1}$). After being stirred for 3 h, the resulting mixture was concentrated to dryness and the residue was dissolved in ethyl acetate (50 mL). After washed with saturated brine twice and dried over anhydrous Na_2SO_4 , the solvent was then evaporated to afford the crude product which was purified on silica column with petroleum ether as eluent yielded 0.63 g (51%) of (S)-5, 5'-diethynyl-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl as a yellow viscous solid. $[\alpha]_{\text{D}}^{20} = -129.4$ (c 0.22, CH_2Cl_2). $^1\text{H-NMR}$ (300 MHz, CDCl_3 , δ): 8.50 (d, $J = 9.2$ Hz, 2H), 7.49 (d, $J = 9.2$ Hz, 2H), 7.10 (s, 4H), 3.97 (m, 4H), 3.71 (s, 2H), 2.98 (m, 4H), 1.69 (m, 4H), 1.42 (m, 8H), 1.04 (m, 4H), 0.97 (t, $J = 7.4$ Hz, 6H), 0.68 (t, $J = 7.4$ Hz, 6H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ): 154.4, 142.6, 132.3, 129.5, 127.5, 127.2, 126.4, 120.7, 117.5, 116.3, 85.4, 81.0, 69.2, 34.6, 33.1, 31.4, 22.6, 18.7, 14.0, 13.6. MS (m/z): 534 (100), 558 (M^+ , 72). Anal.

calcd. for $\text{C}_{40}\text{H}_{46}\text{O}_2$: C 85.98, H 8.30. Found: C 83.21, H 9.83.

2.5 Synthesis of the Chiral Polymer Ligand

A mixture of *S*-**M-1** (328 mg, 0.45 mmol), *S*-**M-2** (251 mg, 0.45 mmol), $\text{Pd}(\text{PPh}_3)_4$ (52 mg, 0.045 mmol, 10 mol %) and CuI (17 mg, 0.090 mmol) was dissolved in toluene (17 mL) and triethylamine (12 mL) and kept stirring at 90 °C under Ar for 36 h. After the reaction mixture was cooled to room temperature, it was filtered through a short column of silica gel with THF as eluent. After the removal of the solvent, the residue was dissolved in 3 mL of CH_2Cl_2 and 60 mL of methanol was added to precipitate the polymer. A pale yellow solid was filtered off and washed with methanol several times. Further purification could be conducted by dissolving the polymer in THF to precipitate in methanol again, the polymer was dried under vacuum at room temperature for 12 h. The final yield was 51% (259 mg). $[\alpha]_{\text{D}}^{20} = -335.1$ (c 0.11, CH_2Cl_2). $M_w = 20400$, $M_n = 7500$, PDI = 2.72. $^1\text{H-NMR}$ (300 MHz, CDCl_3 , δ): 8.60 (d, 4H), 7.82 (br, 2H), 7.57 (d, 6H), 7.17 (br, 12H), 5.14 (s, 2H), 4.02 (br, 4H), 3.07 (br, 4H), 1.77 (br, 4H), 1.58 ~ 1.44 (m, 8H), 1.28 (br, 4H), 1.08 ~ 1.03 (t, 6H), 0.74 ~ 0.69 (t, 6H). v_{max} (KBr): 3425.0, 2956.3, 2926.8, 2869.5, 2362.4, 1610.3, 1463.7, 1261.2, 1072.2, 813.8 cm^{-1} . Anal. Calcd. for $\text{C}_{74}\text{H}_{62}\text{F}_6\text{O}_4$: C 78.56, H 5.70. Found: C 78.61, H 7.93.

2.6 General Procedure for the Addition of Et_2Zn to Aldehydes

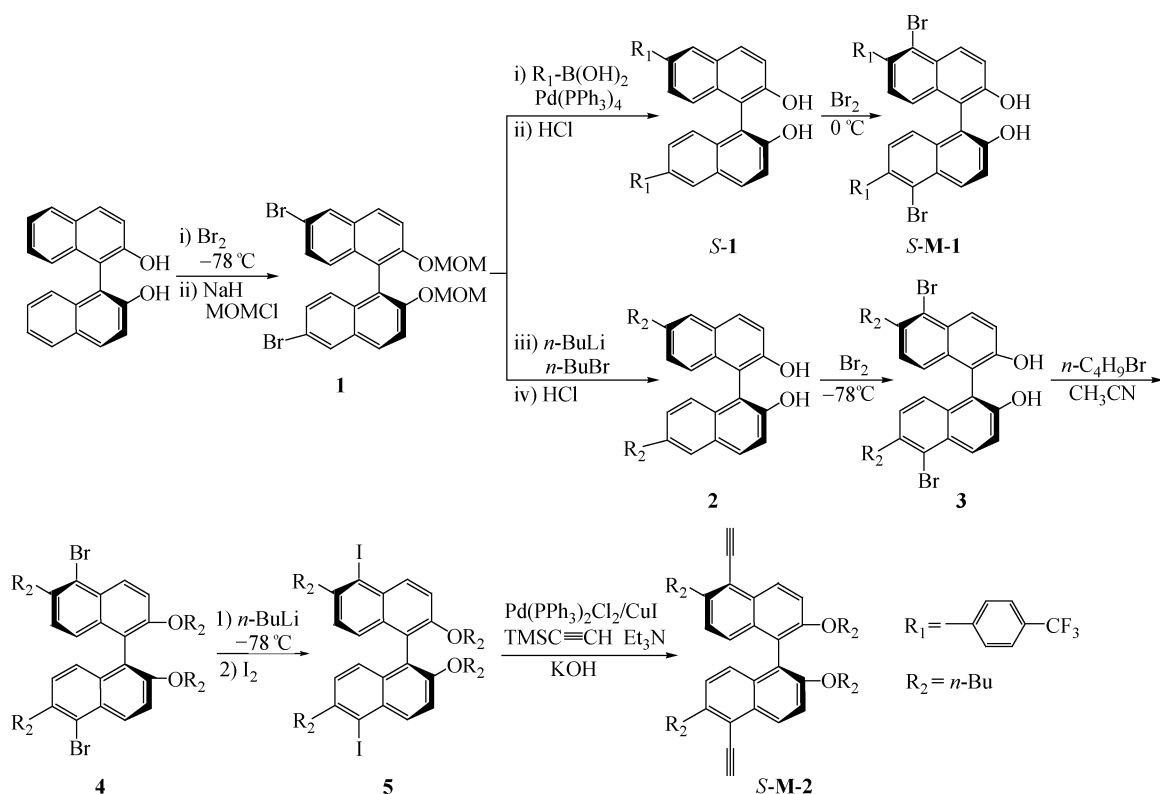
A dry Schlenk tube with a magnetic stirring bar under an Ar atmosphere was charged with 30 μL titanium tetrakisopropoxide (0.0875 mmol), 7.0 mg polymer (0.00625 mmol), and 1.0 mL dry toluene and the mixture was stirred at room temperature for 30 min. Into this solution was added 0.1 mL of 2.5 $\text{mol}\cdot\text{L}^{-1}$ solution of Et_2Zn in toluene (0.25 mmol) and the mixture was stirred for another 30 min. Then aromatic benzaldehyde (0.0625 mmol) was added to the solution and the final mixture was allowed to stirred at rt for 12 h. The reaction was stopped by the addition of 1.0 mL of 1.0 $\text{mol}\cdot\text{L}^{-1}$ hydrochloric acid

and the product was extracted with ethyl acetate (3 $\times$ 5 mL). The combined organic layers were washed with water and brine, and then dried over anhydrous Na_2SO_4 . The solution was concentrated in vacuo and treated with MeOH, and then the polymer was filtrated and washed with water. The chiral polymer was washed with 1 $\text{mol}\cdot\text{L}^{-1}$ HCl several times to recover the chiral ligand for the next cycle of reaction. The MeOH solution was concentrated under reduced pressure, and the crude product can be purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) (5:1, V/V) to afford a pure product. The enantiomeric purity of the product was determined by HPLC on Chiralcel OD-H column. The absolute configurations of the products were assigned by comparison to literature values.

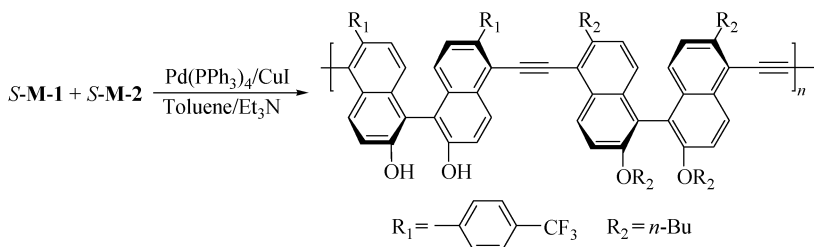
3 RESULTS AND DISCUSSION

3.1 Synthesis and Feature of the Chiral Monomers and the Chiral Polymer Ligand

The chiral model compound (*S*)-6, 6'-di (4-trifluoromethylphenyl)-2, 2'-binaphthol (*S*-**1**), the chiral monomers (*S*)-5, 5'-dibromo-6, 6'-di (4-trifluoromethylphenyl)-2, 2'-binaphthol (*S*-**M-1**) and (*S*)-5, 5'-diethynyl-6, 6'-dibutyl-2, 2'-dibutoxy-1, 1'-binaphthyl (*S*-**M-2**) were synthesized from (*S*)-BINOL. The whole synthesis procedures are shown in Scheme 1. *S*-**1** and *S*-**M-1** could be prepared according to our previously reported literature^[6]. (*S*)-1, 1'-bi-2-naphthol was directly and quantitatively brominated at 6, 6'-positions, and then the hydroxyl groups of (*S*)-6, 6'-dibromo-2, 2'-binaphthol were protected by methoxymethyl chloride (MOMCl) to afford the MOM-protected intermediate (*S*)-6, 6'-dibromo-2, 2'-bis (methoxymethoxy)-1, 1'-binaphthyl (**1**). The compound **1** was first lithiated by *n*-BuLi at -78 °C, and then followed by the gradual addition of *n*-butyl bromide to afford a MOM-protected intermediate in a high yield. The product (*S*)-6, 6'-dibutyl-2, 2'-binaphthol (**2**) could be obtained by the removal of the protecting MOM groups in HCl solution. **3** could directly be obtained by electrophilic aromatic bromination of **2** at 5, 5'-positions in CH_2Cl_2 at -78 °C with 1.05



Scheme 1 Synthesis procedures of S-1, S-M-1 and S-M-2



Scheme 2 Synthesis procedure of the linear chiral polymer ligand

equiv of bromine without any further purification. (*S*)-5,5'-dibromo-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl (**4**) could be obtained by the etherization of hydroxyl groups of **3** with *n*-butyl bromide in the presence of K_2CO_3 in refluxing CH_3CN solution. We failed in the direct synthesis of (*S*)-5,5'-diethynyl-6,6'-dibutyl-2,2'-binaphthol through the reaction of **4** with trimethylsilylacetylene *via* Pd-catalyzed Sonogashira reaction. Sonogashira coupling reaction is one of the most important C—C coupling reactions in organic chemistry synthesis. Normally the reactivity order of organic halides for Sonogashira coupling reaction is vinyl iodine $\sim$ vinyl triflate $>$ vinyl bromide $>$ vinyl chloride $>$ aryl iodide $>$ aryl bromide $>$ aryl chloride, and is $\text{Pd(PPh}_3)_4 >$

$\text{Pd(PPh}_3)_2\text{Cl}_2 >$ Pd(AcO)_2 for Pd-catalyst. We chose $\text{Pd(PPh}_3)_4$ as the catalyst and CuI as a cocatalyst. However, (*S*)-5,5'-diethynyl-6,6'-dibutyl-2,2'-binaphthol could only obtained in very low yield even we enhanced the reaction temperature, extended reaction time or increased the amount of **4**. This may be attributed to the enhancement of electron density at 5,5'-positions which lead to inactivity of bromine atoms. Therefore, we replaced the bromine with iodine to improve the activity of the halogen. (*S*)-5,5'-diiodo-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl (**5**) could be easily obtained in a satisfactory yield by the treatment of (*S*)-5,5'-dibromo-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl (**4**) with *n*-BuLi and I_2 at

$-78\text{ }^\circ\text{C}$. **5** could go through Pd-catalyzed Sonogashira reaction smoothly under mild condition to afford the chiral monomer (*S*)-5,5'-diethynyl-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl (**S-M-2**) in a 51% yield.

A typical Sonogashira reaction condition was applied to the synthesis of the chiral polymeric ligand (Scheme 2)^[28-31]. The C—C cross coupling process was easily carried out in toluene and Et_3N solution in the presence of a catalytic amount (10 mol%) of $\text{Pd}(\text{PPh}_3)_4$ and 20 mol % of cocatalyst CuI at $90\text{ }^\circ\text{C}$ under Ar atmosphere to give the resulting polymer in a 51% yield. The molecular weight was determined by gel permeation chromatography (GPC): $M_w = 20400$, $M_n = 7500$, $\text{PDI} = 2.72$. The GPC result indicates that the chiral polymeric ligand afford a high molecular weight. This kind of linear chiral polymeric ligand was composed of two alternative chiral moieties (*S*)-6,6'-di(4-trifluoromethylphenyl)-2,2'-binaphthol and (*S*)-6,6'-dibutyl-2,2'-dibutoxy-1,1'-binaphthyl *via* ethynyl bridge. This kind of ethynyl bridge can reduce steric hindrance between backbone rings and groups, and also have a beneficial effect on the stability of corresponding polymer. The chiral moieties can distribute regularly along the main-chain backbone of the linear chiral polymer. This kind of linear polybinaphthols ligand incorporating 2,2'-binaphthol at 5,5'-positions has not been reported so far. The polymer is an air stable solid with pale yellow color and shows good solubility in some common solvents, such as THF, CH_2Cl_2 , CHCl_3 , toluene and DMF, which can be attributed to the flexible *n*-butyl and *n*-butoxy substituent groups as the side chain of the polymer. Therefore, this kind of soluble polymer ligand used as the catalyst for asymmetric addition of diethylzinc to aromatic aldehydes can undergo homogeneous reactions. Generally, the soluble polymer ligands can afford higher catalytic activity and enantioselectivity than the insoluble ones. Moreover, the polymeric catalysts can be easily separated from the reaction mixture by simple filtration or precipitation upon the addition of methanol. This polymer shows no glass transition

temperature (T_g). Thermogravimetric analysis (TGA) of the polymer ligand was carried out under a N_2 atmosphere at a heating rate of 20 K/min . According to Fig. 1, the polymer exhibits two-step degradation process. There is about 16% loss of weight at the first step degradation ranging from 220 to $425\text{ }^\circ\text{C}$. The second step degradation appears at temperature ranging from 425 to $600\text{ }^\circ\text{C}$. The polymer tends to completely decompose at $700\text{ }^\circ\text{C}$ and a total loss of about 49% was observed when the polymer was heated to $800\text{ }^\circ\text{C}$.

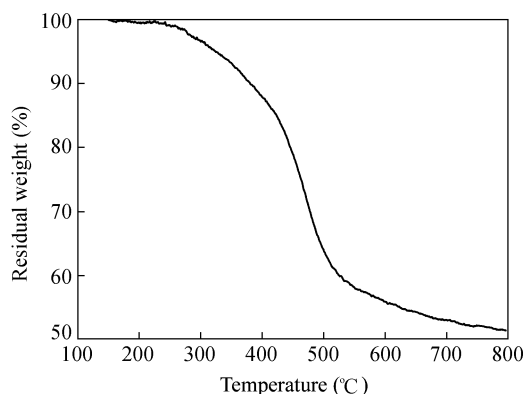


Fig. 1 TGA curve of the chiral polymer ligand

3.2 Enantioselective Addition of Et_2Zn to Aldehydes

As far as we know, there has been no reports on the linear polybinaphthol based on 5,5'-positions of BINOL. In this paper, we chose the asymmetric addition of Et_2Zn to aldehydes as a model reaction to evaluate the efficiency of this chiral polymer ligand. The asymmetric addition reactions were catalyzed by the chiral polymer ligand and the chiral model compound **S-1** in the presence of excessive $\text{Ti}(\text{O}^i\text{-Pr})_4$ in different solvents. According to Pu's report, chiral polymer ligand showed very poor reactivity and enantioselectivity in asymmetric addition of Et_2Zn to aldehydes without $\text{Ti}(\text{O}^i\text{-Pr})_4$ ^[32]. We also proved this conclusion and found that $\text{Ti}(\text{O}^i\text{-Pr})_4$ is indispensable to this asymmetric addition reaction. Since benzaldehyde has been most extensively studied previously, we first chose benzaldehyde as a substrate in our initial study. In order to optimize the reaction, several common factors, such as the solvent, reaction temperature and catalyst loading

which are known to affect the enantioselectivity and reactivity of the catalyst system were carefully examined. As is evident from Table 1, we found that the chosen solvent exhibited great influence on Et₂Zn addition to benzaldehyde. If other conditions kept unchanged, toluene would give the best yield and enantioselectivity (entry 1, 63% yield and 90% ee). In contrast, THF or CH₂Cl₂ used as the solvent showed a little decrease of the reactivity and remarkable decrease of enantioselectivity (entries 1 and 2). So in this paper, we chose toluene as the preferred solvent for the asymmetric addition of Et₂Zn to aldehydes.

The catalyst loading was also screened. Based on entries 3 ~ 5 of Table 1, we found that 10 mol% of the chiral polymer ligand could give the most scientific result (entry 3), and 5 mol% of the molar ratio of the polymer ligand showed an obvious decrease of the yield and ee (entry 4). But increasing the catalyst loading (20 mol%) could not greatly improve its

result (entry 5). In addition, the temperature effect was detectable but not significant. As expected, at lower temperature, the rate of this asymmetric reaction of Et₂Zn with benzaldehyde was found to decrease and the enantioselectivity exhibited a little increase (entries 3, 6, 7). So in this paper the catalytic reaction was conducted at room temperature. We also found that both yield and enantioselectivity of the asymmetric addition reaction appeared obvious decrease while we shortened the reaction time from 12 to 3 h (entry 8). The added order of Et₂Zn and Ti(O^{*i*}Pr)₄ was found to be very important for the addition reaction. If Et₂Zn was added first and Ti(O^{*i*}Pr)₄ subsequently, the result showed no enantioselectivity even though the higher yield could be observed, which demonstrates that the chiral polybinaphthols ligand can coordinate with Ti(IV) to generate highly enantioselective Lewis acid catalyst for the asymmetric addition of Et₂Zn to aldehydes.

Table 1 Optimization of the enantioselective addition of Et₂Zn to benzaldehyde^a

Entry	Solvent	Temperature(℃)	Ligand ^b (%)	Yield ^c (%)	ee ^d (%)
1	THF	r. t.	10	56	82
2	CH ₂ Cl ₂	r. t.	10	59	67
3	Toluene	r. t.	10	73	90
4	Toluene	r. t.	5	30	80
5	Toluene	r. t.	20	65	88
6	Toluene	0	10	52	90
7	Toluene	- 15	10	50	92
8 ^e	Toluene	r. t.	10	41	84
9 ^f	Toluene	r. t.	10	80	0

^a Benzaldehyde; Et₂Zn: Ti(O^{*i*}Pr)₄ = 1 : 4 : 14 (molar ratio) ; ^b Based on the repeating unit ; ^c Isolated yields ; ^d Determined by HPLC on chiralcel OD-H column ; ^e The reaction time is 3 h ; ^f Et₂Zn was added before Ti(O^{*i*}Pr)₄ .

Based on the above optimized reaction conditions, the asymmetric addition reactions of Et₂Zn to different aldehydes were conducted at 20 ℃ using aldehyde, chiral ligands, Ti(O^{*i*}Pr)₄ and Et₂Zn with a molar ratio of 1 : 0.1 : 14 : 4. All the enantioselective datas are summarized in Table 2. The results show that the electronic effect of the substrate was less effective than the steric hindrance effect. The resulting addition products could exhibit similar enantioselectivity as benzaldehyde when *p*-or

m-aromatic aldehydes were substituted by electron-withdrawing and electron-donating groups (entries 3 ~ 6, 11). On the contrary, the *o*-substituted aldehydes and 2-naphthyldehyde afforded significantly lower ee (entries 12 ~ 15). Particularly, 9-anthyldehyde only gave as low as 15% ee value. According to Chan's report, this kind of detrimental effect on enantioselectivity of *o*-substituted aromatic aldehydes weakened the coordination of the aldehyde and catalyst and consequently lowered the

Table 2 Reaction of Et_2Zn with different aromatic aldehydes in the presence of chiral ligand^a

$$\text{R}-\text{CHO} + \text{Et}_2\text{Zn} \xrightarrow[\text{Ti}(\text{O}^i\text{Pr})_4]{\text{Chiral ligand}} \text{R}-\text{CH}(\text{OH})-\text{CH}_3$$

Entry	Aldehyde ^a	Yield ^b (%)	ee ^c (%)	Configuration ^d
1	PhCHO	73	90	s
2	<i>p</i> -BrC ₆ H ₄ CHO	85	76	s
3	<i>p</i> -ClC ₆ H ₄ CHO	73	86	s
4	<i>p</i> -FC ₆ H ₄ CHO	78	80	s
5	<i>p</i> -CH ₃ OC ₆ H ₄ CHO	72	86	s
6	<i>p</i> -NO ₂ C ₆ H ₄ CHO	90	96	s
7 ^e	<i>p</i> -NO ₂ C ₆ H ₄ CHO	92	98	s
8 ^f	<i>p</i> -NO ₂ C ₆ H ₄ CHO	92	95	s
9 ^g	<i>p</i> -NO ₂ C ₆ H ₄ CHO	87	91	s
10 ^h	<i>p</i> -NO ₂ C ₆ H ₄ CHO	83	87	s
11	<i>m</i> -NO ₂ C ₆ H ₄ CHO	80	85	s
12	<i>o</i> -BrC ₆ H ₄ CHO	63	60	s
13	<i>o</i> -ClC ₆ H ₄ CHO	66	74	s
14	<i>o</i> -CH ₃ C ₆ H ₄ CHO	58	65	s
15	2-NaphthylCHO	63	76	s
16	9-AnthrylCHO	61	15	s
17	PhCH=CHCHO	92	83	s

^a Aldehyde: polymer (based on the repeating unit) : Et_2Zn : $\text{Ti}(\text{O}^i\text{Pr})_4$ = 1 : 0.1 : 4 : 14 (molar ratio) ; ^b Isolated yields ; ^c Determined by HPLC on chiralcel OD-H column ; ^d All the absolute configurations were determined as (S) by the comparison of the known elution order from a chiral OD column ; ^e First recycled and reused ; ^f Second recycled and reused ; ^g Third recycled and reused ; ^h **S-1** was used as the ligand.

enantioselectivity of the asymmetric addition reaction^[33]. Since *p*-nitrobenzaldehyde as the substrate could afford 90% yield and as high as 96% ee, we chose it to evaluate the recovery and reuse efficiency of the chiral polymer ligand (entry **6**). In this paper, the chiral polymer ligand was recovered conveniently without loss by precipitation with methanol. We found that 98%, 95% and 91% e. e. could be still obtained while the chiral polymer ligand was reused three times for the asymmetric addition reaction of Et_2Zn to *p*-nitrobenzaldehyde (entries **7 ~ 9**). It is important to remark that, we managed to run up to ten cycles without any decrease in either enantioselectivity or conversion and ee% maintained 90 %. The results showed that the recovered and recycled polymer catalyst could keep similar catalytic activity and enantioselectivity as the original polymer.

Traditionally, polymeric chiral catalysts are prepared by anchoring a chiral ligand to a flexible

and sterically irregular achiral polymer backbone^[34,35]. It is generally observed that the polymer-supported chiral catalysts are usually less efficient than their monomeric version, which indicates that the microenvironment of the catalytic sites in the polymers is very important for their effectiveness in steric control. The flexible and sterically irregular polymer backbone of the traditional polymeric chiral catalysts generates randomly oriented catalytic sites which can not be systematically modified to achieve the desired catalytic active center and stereoselectivity^[15,36 ~ 38]. Unlike the traditional chiral polymer catalysts, BINOL-based polymer ligands can generate regularly oriented catalytic sites along the polybinaphthols chain backbone and produce a well-defined microenviroment around the catalytically chiral centers. Therefore it is possible to systematically adjust the microenvironment of the catalytic sites in these chiral polymer ligands to achieve the desired catalytic activity and stereoselectivity^[27,39]. Based on our study, the results indicated that this kind of soluble chiral polybinaphthols ligand in combination with $\text{Ti}(\text{O}^i\text{Pr})_4$ could show higher enantioselectivity than the corresponding model compound (*S*)-6,6'-di (4-trifluoromethylphenyl)-2, 2'-binaphthol **S-1** (entries **6** and **10**). The absolute configuration of the corresponding chiral alcohol products is assigned to *S* by comparing its HPLC data to literatures^[40 ~ 45].

4 CONCLUSION

Pd-catalyzed Sonogashira reaction offered a simple access to the optically active polybinaphthols ligand. The chiral polymer ligand showed good solubility in some common solvents due to the flexible *n*-butoxy and *n*-butyl groups as side chain of the chiral polymer ligand, so the asymmetric addition reactions can be carried out in homogeneous solution. The results showed that this soluble chiral polybinaphthols ligand in combination with $\text{Ti}(\text{O}^i\text{Pr})_4$ could exhibit good reactivity and enantioselectivity for the asymmetric addition of Et_2Zn to aromatic aldehydes. Moreover, the chiral polymer ligand showed superior enantioselectivity over the

model compound **S-1**. The chiral polymer ligand reactivity decrease.
could be easily recovered and reused without

REFERENCES

- 1 Chen Y, Yekta S, Yudin A K. *Chem Rev*, 2003, 103: 3155 ~ 3212
- 2 Osorio-Plane L, Rodriguez-Esrich C, Pericas M A. *Org Lett*, 2012, 14: 1816 ~ 1819
- 3 Turlington M, Du Y, Ostrum S G, Santosh V, Wren K, Lin T, Sabat M, Pu L. *J Am Chem Soc*, 2011, 133: 11780 ~ 11794
- 4 Trost B M, Ngai M Y, Dong G. *Org Lett*, 2011, 13: 1900 ~ 1903
- 5 Brunel J M. *Chem Rev*, 2005, 105: 857 ~ 898
- 6 Zhang S W, Liu Y, Huang H, Zheng L F, Wu L L, Cheng Y X. *Synlett*, 2008, 853 ~ 856
- 7 Pu L. *Chem Rev*, 2004, 104: 1687 ~ 1716
- 8 Liang X F, James T D, Zhao J Z. *Tetrahedron*, 2008, 64: 1309 ~ 1315
- 9 Wang Q, Chen X, Tao, L, Wang L, Xiao D, Yu X Q, Pu L. *J Org Chem*, 2007, 72: 97 ~ 101
- 10 Ramón D J, Yus M. *Chem Rev*, 2006, 106: 2126 ~ 2208
- 11 Xi Z, Zhu L, Luo S, Cheng J P. *J Org Chem*, 2013, 78: 606 ~ 613
- 12 Paderes M C, Keister J B, Chemler S R. *J Org Chem*, 2013, 78: 506 ~ 515
- 13 Shibasaki M, Kanai M. *Chem Rev*, 2008, 108: 2853 ~ 2873
- 14 Da C S, Wang J R, Yin X G, Fan X Y, Liu Y, Yu S L. *Org Lett*, 2009, 11: 5578 ~ 5581
- 15 Liu Y, Da C S, Y S L, Yin X G, Wang J R, Fan X Y, Li W P, Wang R. *J Org Chem*, 2010, 75: 6869 ~ 6878
- 16 DeBerardinis A M, Turlington M, Ko J, Sole L, Pu L. *J Org Chem*, 2010, 75: 2836 ~ 2850
- 17 Yue Y, Turlington M, Yu X-Q, Pu L. *J Org Chem*, 2009, 74: 8681 ~ 8689
- 18 Zou X W, Zhang S W, Cheng Y X, Liu Y, Huang H, Wang C Y. *J Appl Polym Sci*, 2007, 106: 821 ~ 827
- 19 Qin Y C, Liu L, Pu L. *Org Lett*, 2005, 7: 2381 ~ 2383
- 20 Xu M H, Lin J, Hu Q S, Pu L. *J Am Chem Soc*, 2002, 124: 14239 ~ 14246
- 21 Yu H B, Hu Q S, Pu L. *J Am Chem Soc*, 2000, 122: 6500 ~ 6501
- 22 Tang Z, Irda H, Hu H Y, Yashima E. *ACS Mro Lett*, 2012, 1: 261 ~ 265
- 23 Iida H, Iwahana S, Mizoguchi T, Yashima E. *J Am Chem Soc*, 2012, 134: 15103 ~ 15113
- 24 Pericas M A, Herreras C I, Sola L. *Adv Synth Catal*, 2008, 350: 927 ~ 932
- 25 Rolland J, Cambeiro X C, Rodriguez-Esrich C, Pericas M A. *Beilstein J Org Chem*, 2009, 5: 56
- 26 Hu Q S, Huang W S, Pu L. *J Am Chem Soc*, 1997, 119: 12454 ~ 12464
- 27 Wu L L, Zheng L F, Zong L L, Xu J Q, Cheng Y X. *Tetrahedron*, 2008, 64: 2651 ~ 2657
- 28 Sonogashira K, Tohda Y, Hagihara N. *Tetrahedron Lett*, 1975, 16: 4467 ~ 4470
- 29 Wang W L, Xu J W, Lai Y H, Wang F K. *Macromolecules*, 2004, 37: 3546 ~ 3553
- 30 Sonogashira K. *J Org Chem*, 2002, 67: 46 ~ 55
- 31 Chinchilla R, Nájera C. *Chem Rev*, 2007, 107: 874 ~ 922
- 32 Yu H B, Zheng X F, Hu Q S, Pu L. *Polym Prepr*, 1999, 40: 546 ~ 548
- 33 Zhang F Y, Yip C W, Cao R, Chan A S C. *Tetrahedron: Asymmetry*, 1997, 8: 585 ~ 589
- 34 Leadbeater N E, Marco M. *Chem Rev*, 2002, 102: 3217 ~ 3274
- 35 Gruttadauria M, Giacalone F, Noto R. *Chem Soc Rev*, 2008, 37: 1666 ~ 1688
- 36 Nogami H, Matsunaga S, Kanai M, Shibasaki M. *Tetrahedron Lett*, 2001, 42: 279 ~ 283
- 37 Arai T, Sekiguti T, Otsuki K, Takizawa S, Sasai H. *Angew Chem Int Ed*, 2003, 42: 2144 ~ 2147
- 38 Halm C, Kurth M J. *Angew Chem Int Ed*, 1998, 37: 510 ~ 512
- 39 Pu L. *Tetrahedron: Asymmetry*, 1998, 9: 1457 ~ 1477
- 40 Sugiyama S, Aoki Y, Ishii K. *Tetrahedron: Asymmetry*, 2006, 17: 2847 ~ 2856
- 41 Zhang F Y, Chan A S C. *Tetrahedron: Asymmetry*, 1997, 8: 3651 ~ 3655
- 42 Lin R X, Chen C P. *J Mol Catal A: Chem*, 2006, 243: 89 ~ 98
- 43 Superchi S, Mecca T, Giorgio E, Rosini C. *Tetrahedron: Asymmetry*, 2001, 12: 1235 ~ 1239
- 44 Xu J X, Wei T Z, Zhang Q H. *J Org Chem*, 2004, 69: 6860 ~ 6866
- 45 Hui A L, Zhang J T, Fan J M, Wang Z Y. *Tetrahedron: Asymmetry*, 2006, 17: 2101 ~ 2107