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Enantioselective arylation of aldehydes catalyzed by a soluble optically active polybinaphthols ligand

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ABSTRACT

A soluble chiral polymer ligand was synthesized by the polymerization of (*R*)-6,6′-dibutyl-3,3′-diformyl-2,2′-binaphthol (***R*-M-1**) with 2,5-diaminopyridine (**M-2**) via a nucleophilic addition–elimination reaction. While arylboronic acids were used as the source of the transferable aryl group, the chiral polybinaphthols ligand in combination with Et_2Zn without $Ti(O^iPr)_4$ exhibited higher enantioselectivity in asymmetric addition to aromatic aldehydes than alphatic aldehydes. When aromatic aldehydes with electron-withdrawing groups were chosen as substrates, the resulting diarylmethanols were produced in higher ee values than those with electron-donating groups as substrates. 2-Naphthaldehyde used as a substrate afforded product in 95% ee, which could be ascribed to the steric effect influence on this asymmetric arylation reaction. Moreover, the chiral polymer was easily recovered and reused, but exhibited a decrease of enantioselectivity in the third recycle.

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Optically active 1,1′-bi-2-naphthol (BINOL) is one of the most important C_2 symmetric compounds. The chirality of BINOL and its derivatives is derived from the restricted rotation of the two naphthalene rings.[1] The versatile skeletal structure of BINOL at 3,3′-, 5,5′- and 6,6′-positions can be systematically modified by strategic placement of substituents at the well-defined molecular level. These novel BINOL-based derivatives exhibit efficient and stable chiral configuration as well as high chiral induction in molecular recognition and asymmetric processes.[2] In the past decade, there have been a few reports on the design and synthesis of a series of the polymer ligands incorporating optically active binaphthol moiety in the polymer main chain backbone. These chiral polybinaphthols are often used to coordinate with metal ions such as Al(III), Ti(IV), Zn(II) and Ln(III) to generate highly enantioselective Lewis acid catalysts for many asymmetric organic transformations.[3]

The enantioselective arylation of aldehydes has received increased attention because it gives access to chiral diarylmethanols, which play an important role in synthesis of some pharmacological and biologically active compounds in recent years.[4] Since Fu and co-workers first reported the enantioselective addition of diphenylzinc to aldehydes by using a catalyst based on a planar-chiral azoferrocene ligand,[5] there have been some reports on the enantioselective arylation of aldehydes catalyzed by different chiral ligands.[6] Bolm and co-workers described a notable method to synthesize various chiral diarylmethanols using commercially available aryl boronic acids as the source of the transferable aryl groups.[7] This improved methodology broadened the scope of this asymmetric addition reaction as it avoided the tedious and difficult preparation of diarylzinc reagents. But so far this asymmetric arylation of aldehydes by using boronic acids as the aryl source has not been extensively studied. Development of an efficient chiral ligand for this kind of asymmetric aryl transfer reaction still remains to be an attractive topic.[8]

To our knowledge, there has not been any report on the BINOL-based polymer ligand for the enantioselective arylation of aldehydes using boronic acids as the aryl source. In this Letter, we describe the synthesis of a soluble chiral polymer ligand and its application in the asymmetric catalytic arylation of aldehydes. The chiral ligand incorporating (*R*)-2,2′-binaphthol and pyridine-based imine moieties can be alternatively organized in a regular polymer chain. This kind of bifunctional Lewis-acid base ligand has attracted much attention in asymmetric catalytic reactions, such as the addition of dialkylzinc to aldehydes.[2a] In order to improve solubility of the polymer ligand in the common organic solvents, *n*-butyl group is introduced into the 6,6′-positions of BINOL as the side chain. The use of soluble chiral polymer catalyst for asymmetric synthesis has practical advantages.[9] First, the chiral polymer catalyst can show excellent catalytic activity and enantioselectivity due to the homogeneous reaction system. Second, when the reaction is completed, the polymer catalyst can be easily separated from the reaction mixture by precipitation and simple filtration upon the addition of MeOH solvent.

The synthesis of monomer ***R*-M-1** and the polymer ligand is shown in Scheme 1. ***R*-M-1** was obtained from a 7-step reaction

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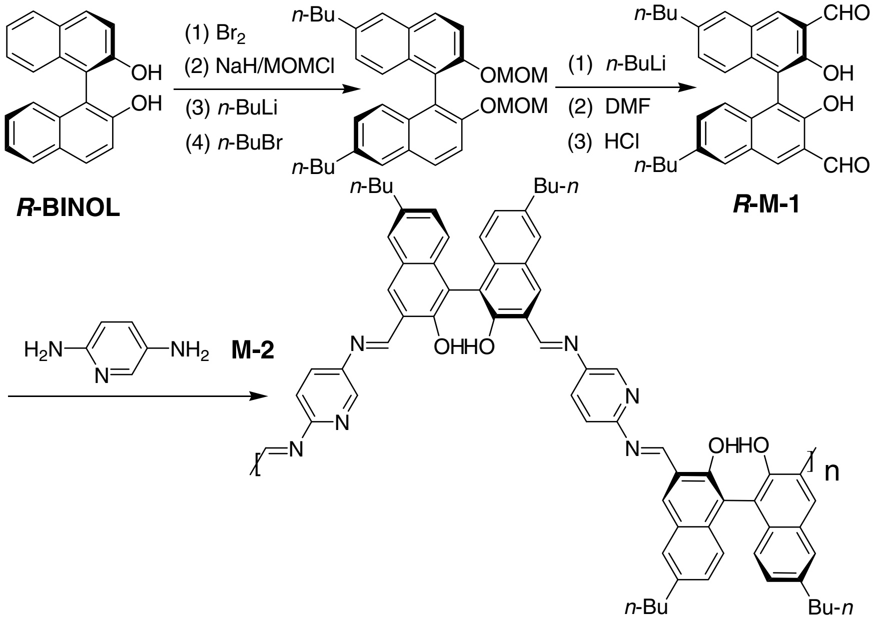


Scheme 1. Synthesis procedures for the chiral polymer ligand.

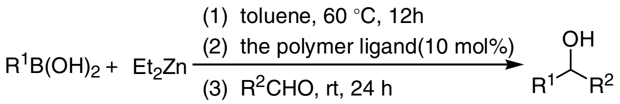
procedure from (*R*)-BINOL. (*R*)-6,6′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl and (*R*)-6,6′-dibutyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl were synthesized according to reported literature.[10] (*R*)-6,6′-Dibutyl-2,2′-bis(methoxymethoxy)-1,1′-binaphthyl was first lithiated with *n*-BuLi, and then followed by carbonylation to afford the MOM-protected intermediate. The crude product ***R*-M-1** was obtained by the removal of the protecting groups in HCl solution. The purification of ***R*-M-1** was carried out by column chromatography on silica gel to afford a solid product in 38.4% yield.[11] The chiral polymer was prepared in 75.9% yield by the reaction of ***R*-M-1** with monomer 2,5-diaminopyridine (**M-2**).[12] The specific rotation value ($[\alpha]_D^{25}$) of the monomer ***R*-M-1** is +216.0 (*c* 0.5, CH_2Cl_2), while the chiral polymer ligand is −298.0 (*c* 0.1, CH_2Cl_2) with the reversed signal. The catalytical centre of optically active 2,2′-binaphthol can orient in a well-defined spatial arrangement. Unlike the traditional chiral polymeric catalysts, which are prepared by anchoring a chiral ligand to a flexible and sterically irregular achiral polymer backbone, these stereoregular chiral BINOL-based polymer ligands can generate regularly oriented catalytic sites along the polybinaphthols chain backbone and produce a well-defined microenvironment around the catalytically chiral centres. Therefore, it is possible to systematically adjust the microenvironment of the catalytic sites in the chiral polymer ligand to achieve the desired catalytic activity and enantioselectivity.[13]

The GPC result of the chiral polymer shows the moderate molecular weight. The chiral polymer ligand is an air stable solid with deep yellow colour and shows good solubility in some common solvents, such as THF, CH_2Cl_2, $CHCl_3$, toluene, and DMF, which could be attributed to the twisted polymer chain backbone and the flexible *n*-butyl as the side chain of the polymer. Moreover, this soluble polymer ligand used as the catalyst for asymmetric addition of arylboronic acid to aldehydes can undergo homogeneous reaction. The results demonstrate that the chiral polymer ligand is a good enantioselective catalyst and can produce as high as 95% ee while 2-naphthaldehyde is used as a substrate (Table 1, entry 12).

Based on the previous reports, some reactions of diethylzinc or diarylzinc addition to aldehydes require an additive, such as dimethoxy poly(ethyleneglycol) (DiMPEG), or co-catalyst like $Ti(O^i\text{-}Pr)_4$ to ensure high enantioselectivity.[2b,7,8b,12] In our study, we found that the ee value (83%, entry 1) of the diarylmethanol obtained by asymmetric addition in the presence of $Ti(O^iPr)_4$ was lower than that without $Ti(O^iPr)_4$ (91%, entry 2). Therefore in this Letter, chiral polybinaphthols ligand in combination with Et_2Zn without $Ti(O^iPr)_4$ was used to catalyze the asymmetric addition reactions. In order to evaluate the enantioselectivity of the chiral ligand for asymmetric addition, both aromatic and alphatic aldehydes were chosen as substrates, and different solvents, such as toluene, THF and CH_2Cl_2, were screened too. The enantioselective data are summarized in Table 1. The results showed that toluene gave the best yield and enantioselectivity (entries 2, 3 and 4). So, asymmetric addition reactions were conducted using arylboronic acids, Et_2Zn, chiral polymer ligand (based on BINOL unit) and aldehyde with a molar ratio of 2.4:7.2:0.1:1 in toluene. The resulting catalyst can be obtained by the reaction of chiral polymer in combination with Et_2Zn and the boronic acids at 60 °C for 10 h. The absolute configuration and ee of the corresponding alcohol product can be assigned to *R* or *S* by comparing its HPLC data with those previously reported in the literature.[6h,j,7,8g,h,14]

As shown in Table 1, the resulting configuration of products was *R* when aromatic aldehydes were used as substrates (entries 1–12), but *S* when the substrates were aliphatic aldehydes (entries 13–15). Based on Pu's reports, the catalytic diarylzinc (prepared in situ) occurred at the *re* face of the aldehydes, and the arylboronic acids addition to aldehydes may be mechanistically similar to the diethylzinc or diphenylzinc addition to aldehydes.[6j,15] It was also noticed that aryl aldehydes undergo aryl addition in high yield and ee (82%, entry 9 and 92%, entry 5). However, aliphatic aldehydes afford alcohol products in lower yields and ee values (entries 13–15). We also explored the asymmetric addition of non-aromatic boronic acid to benzaldehyde, and the result indicated the use of *n*-butylboronic acid afforded the corresponding product in 50% yield with 83% ee (entry 16). In the case of aromatic aldehydes, electronic effect of the substituents on aromatic aldehydes plays an important role in asymmetric addition. Diarylmethanols were obtained in higher ee values when aromatic aldehydes with electron-withdrawing groups were used as substrates (entries 6 and 7). While benzaldehydes substituted with electron-donating groups afforded the addition products in lower ee values (entries

Table 1
Asymmetric arylation of aldehydes with aryl boronic acids[a]



Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)	Configuration[e]
1[f]	4-Methylphenyl	Phenyl	68	83	*R*
2	4-Methylphenyl	Phenyl	75	91	*R*
3[g]	4-Methylphenyl	Phenyl	63	35	*R*
4[h]	4-Methylphenyl	Phenyl	68	53	*R*
5	4-Trifluoromethylphenyl	Phenyl	73	92[d]	*R*
6	Phenyl	4-Trifluoromethylphenyl	80	84[d]	*R*
7	Phenyl	4-Fluorophenyl	78	91[d]	*R*
8	Phenyl	4-Methylphenyl	81	71	*R*
9	Phenyl	4-Methoxyphenyl	82	75	*R*
10	Phenyl	2-Chlorophenyl	77	81	*R*
11	Phenyl	2-Bromophenyl	75	85	*R*
12	Phenyl	2-Naphthyl	65	95	*R*
13	Phenyl	*n*-Hexyl	58	60	*S*
14	Phenyl	*n*-Heptyl	60	53	*S*
15	Phenyl	2-Phenylethenyl	40	40	*S*
16	*n*-Butyl	Phenyl	50	83	*S*
17[i]	4-Methylphenyl	Phenyl	70	91	*R*
18[j]	4-Methylphenyl	Phenyl	68	89	*R*
19[k]	4-Methylphenyl	Phenyl	67	74	*R*

[a] Arylboronic acid:Et$_2$Zn:ligand:aldehyde = 2.4:7.2:0.1:1.
[b] Isolated yields.
[c] Determined by HPLC on Chiralcel OD-H column.
[d] Determined by HPLC on Chiralcel OB-H column.
[e] Determined by comparison with literature data.
[f] 0.1 equiv of Ti(O^{i}Pr)$_4$ was added.
[g] Using THF as solvent.
[h] Using CH$_2$Cl$_2$ as solvent.
[i] First recycled and reused.
[j] Second recycled and reused.
[k] Third recycled and reused.

8 and 9). With regard to the positions of the substituent in the benzaldehyde, we also noted that ortho-substituted benzaldehydes afforded good enantioselectivity (entries 10 and 11). Especially, 2-naphthaldehyde afforded excellent result with 95% ee (entry 12), which may be ascribed to the steric effect on this asymmetric arylation of aldehydes. In this Letter, the chiral polymer ligand was recovered conveniently without loss by precipitation with methanol. The polymer was recycled and reused three times for the asymmetric addition reaction of 4-methylphenylboronic acid to benzaldehyde, the diarylmethanol could be obtained in 91%, 89% and 74% ee, respectively (entries 17–19). The results show that the recycled polymer catalyst can keep similar catalytic activity and enantioselectivity as the original polymer in the first and second recycles, but exhibits a decrease of ee in the third recycle.

In summary, a soluble chiral polybinaphthols ligand in combination with Et$_2$Zn without Ti(O^{i}Pr)$_4$ had been developed as an efficient catalyst for asymmetric arylation of aldehydes while arylboronic acids are used as the source of the transferable aryl group. The results show that benzaldehydes with electron-withdrawing groups and bigger steric groups as substrates can afford diarylmethanols in high ee values. The chiral polymer could be easily recovered and reused, but exhibits a decrease of ee in the third recycle.

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