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# Design and Synthesis of Polymeric Chiral Bicyclo[3.3.0] Diene as Reusable Ligand for Rhodium-Catalyzed Asymmetric 1,4-Addition[†]

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A series of A-B type sterically regular bicyclio[3.3.0] diene-based polymers were designed and synthesized as immobilized chiral diene ligands for asymmetric catalysis. With polymeric diene **6b**, good to excellent enantioselectivities can be achieved in Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to $\alpha,\beta$-unsaturated ketones.

**Keywords** asymmetric catalysis, chiral ligand, diene, rhodium, immobilization

## Introduction

In the past few years, chiral dienes have emerged as new exciting ligands for a variety of transition-metal-catalyzed asymmetric transformations since the pioneering studies of Hayashi and Carreira,[1] exhibiting high reactivity as well as excellent enantioselectivity.[2] However, despite their unique effectiveness in catalytic processes, many of them, prepared in enantiomerically pure from either chiral pool starting materials or the use of resolution techniques such as fractional crystallization or HPLC isolation by preparative chiral columns, are not easily accessible. From this point of view, the recovery and the reuse of expensive chiral diene ligands has become a particularly important subject. On the other hand, use of immobilized chiral catalysts for asymmetric reactions has been considered to be a promising solution to problems associated with the recovery and reuse of expensive chiral catalysts,[3] though the development of highly efficient strategies to immobilize the homogeneous chiral catalysts remains a challenging topic. Nevertheless, to the best of our knowledge, there have been no report of asymmetric catalysis using immobilized chiral diene ligand. In this context, we initiated an investigation into the possibility of incorporating chiral diene into a polymer chain to generate a self-supported polymeric olefin ligand that would enable recycling in asymmetric catalysis (Figure 1). Herein, we describe our effort on design and synthesis of polymeric chiral bicyclo[3.3.0] diene as reusable ligand for rhodium-catalyzed asymmetric 1,4-addition.

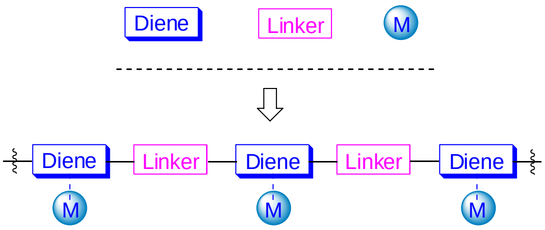

**Figure 1** Polymeric diene ligand proposal.

## Experimental

### Synthetic procedure for the preparation of polymeric diene ligand 6b

Under nitrogen, to a mixture of dibromide **2** (460 mg, 1 mmol), diborate **3** (358 mg, 1 mmol) and $PdCl_2(dppf)$ (37 mg, 5 mol%) in freshly distilled THF (20 mL) was added aqueous solution of $K_2CO_3$ (2 mol/L, 1.5 mL). The reaction was heated to reflux for 24 h. After cooling to room temperature, the reaction was quenched with saturated $NH_4Cl$. The mixture was extracted with $CH_2Cl_2$ (40 mL×3) and washed with brine (30 mL). The organic layer was dried and concentrated. The residue was dissolved in 5 mL of $CH_2Cl_2$ and the solution was added to 20 mL of petroleum ether. The resulting mixture was centrifuged to obtain the crude polymer, which was further washed with slurry in ether and acetone and filtrated to give the polymeric ligand as a grey solid. $[\alpha]_D^{20}$ +139 ($c$ 1.32, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$: 2.36 (d, $J$=17.4 Hz, 2H), 2.88 (d, $J$=17.1 Hz, 2H), 3.76 (s, 4H), 3.87 (s, 4H), 3.98 (br, 2H), 4.13 (s, 4H), 5.85 (s, 2H), 6.86 (d, $J$=8.7 Hz, 4H), 7.34 (d, $J$=8.7 Hz, 4H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$:

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38.64, 40.41, 65.01, 67.34, 69.77, 70.84, 114.43, 122.13, 127.30, 128.76, 144.47, 157.73. GPC (THF): $M_w$=4466, $M_p$=3028, $M_n$=3087 (PDI=1.45).

## Results and Discussion

Previously, we reported our discovery of a new family of $C_2$-symmetric chiral diene ligands bearing a simple bicyclic [3.3.0] backbone and their successful application in the rhodium-catalyzed enantioselective arylation of imines and electron-deficient alkenes with arylboronic acids.[4-6] During the studies, we noticed that substitution at the *para*-position of the benzene ring attached to double bond has generally less influence on the catalyst reactivity and enantioselectivity compared to the *ortho*- and *meta*-substitutions. It suggests that immobilization of $C_2$-symmetric bicyclic [3.3.0] diene ligand on these two *para*-sites might be achieved through appropriate strategy such as cross-linking polymerization.

With this idea in mind, we conceived to anchor $C_2$-symmetric chiral bicyclo[3.3.0] diene ligand **1** to an achiral well-defined linker by covalent bond to form a sterically regular chiral diene polymer (Scheme 1a). As illustrated, a series of A-B type sterically regular bicyclio[3.3.0] diene-based chiral polymer ligands were designed and synthesized using the Suzuki cross coupling protocol (Scheme 1b).[7] Successful examples of immobilizing highly effective monomeric catalysts (such as BINOL and BINAP) via such A-B polymerization method have been reported by Pu.[8] The advantages of this polymeric design over traditional approach include: the microenvironment of the catalytic sites in the polymers can be expected to be more similar to those in monomeric catalysts; a symmetric modification of the polymer structure can be easily achieved to possibly tune the physical and chemical properties.

Among the polymer ligands prepared, **5a** and **5b** were found to be poorly soluble in most organic solvents, while the others were all soluble in common organic solvents such as $CH_2Cl_2$, $CHCl_3$, and THF. In particular, **4c**, **6a** and **6b** with poly(ethylene glycol) subunit were found to have good solubility in dioxane, suggesting that they might be more applicable in asymmetric catalysis (Table 1). To evaluate whether these polymeric dienes can act as effective chiral ligands, the rhodium-catalyzed 1,4-addition of 2-cyclohexenone with phenylboronic acid in dioxane was carried out. Despite the high activity of monomer ligand **1**,[4b] only trace amount of product was observed when **4a** was used as ligand at room temperature (Entry 1). However, with the increasing of reaction temperature to 55 ℃, the reaction took place to give an improved yield of 43% with 62% *ee* (Entry 2). This result is encouraging, albeit with moderate yield and enantioselectivity; it suggests the potential of using a self-supported polymeric diene as ligand in asymmetric catalysis. Nevertheless, no better yield

**Scheme 1** Polymeric chiral diene ligands

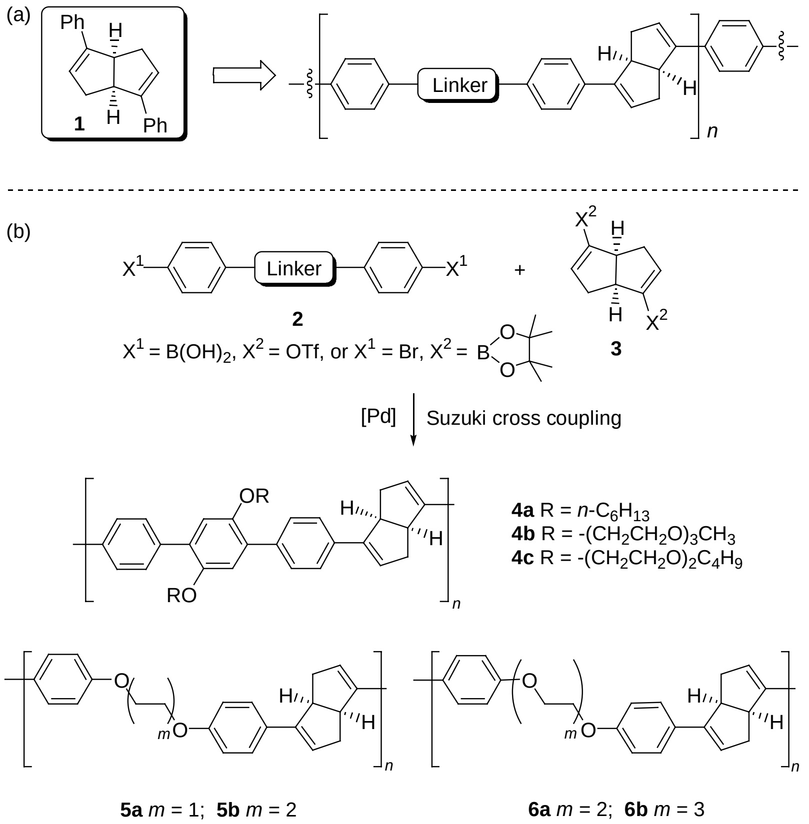
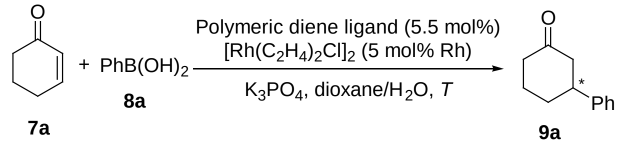


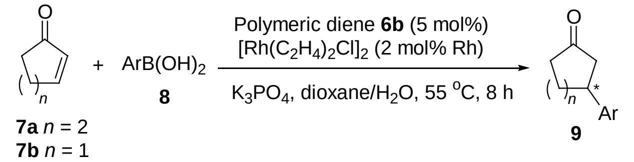
**Table 1** Polymeric diene ligand evaluation in 1,4-addition[a]



| Entry | Polymeric ligand | $T$/℃ | $t$/h | Yield[b]/% | *ee*[c]/% |
|---|---|---|---|---|---|
| 1 | **4a** | r.t. | 24 | Trace | ND[d] |
| 2 | **4a** | 55 | 12 | 43 | 62 |
| 3 | **4b** | 55 | 24 | 33 | ND |
| 4 | **4c** | 55 | 40 | 42 | ND |
| 5 | **5a** | 55 | 12 | Trace | ND |
| 6 | **5b** | 55 | 12 | Trace | ND |
| 7 | **6a** | 55 | 14 | 94 | 60 |
| 8 | **6b** | r.t. | 12 | $<$20 | ND |
| 9 | **6b** | 55 | 12 | 95 | 75 |
| 10[e] | **6b** | 55 | 8 | 94 | 78[f] |

[a] The reaction was conducted on 0.3 mmol of 2-cyclohexen-1-one (**7a**), 2 equiv. of phenylboronic acid in 1 mL dioxane with 100 μL of 1.5 mol/L aq $K_3PO_4$. [b] Isolated yield. [c] The *ee* values were determined by HPLC on a chiral column. [d] Not determined. [e] 0.5 mol% of $[Rh(C_2H_4)_2Cl]_2$ was used. [f] For comparison, 91% *ee* was observed with monomeric chiral diene ligand **1**.

**Table 2** Asymmetric 1,4-addition of arylboronic acids catalyzed by Rh/immobilized diene ligand **6b**[a]



| Entry | 7 | Ar | Yield[b]/% | *ee*[c]/% |
|---|---|---|---|---|
| 1 | **7a** | Ph | 94 | 78 |
| 2 | **7a** | 1-Naphthyl | 91 | 84 |
| 3 | **7b** | Ph | 98 | 85 |
| 4 | **7b** | 4-OMe-$C_6H_4$ | 94 | 89 |
| 5 | **7b** | 4-Me-$C_6H_4$ | 92 | 80 |
| 6 | **7b** | 4-F-$C_6H_4$ | 92 | 82 |
| 7 | **7b** | 4-Br-$C_6H_4$ | 96 | 72 |
| 8 | **7b** | 4-Cl-$C_6H_4$ | 92 | 76 |
| 9 | **7b** | 2-OMe-$C_6H_4$ | 96 | 78 |
| 10 | **7b** | 1-Naphthyl | 94 | 94 |

[a] The reaction was conducted on a 0.3 mmol scale, using 2 equiv. of phenylboronic acid in 1 mL of dioxane and 100 μL of aq $K_3PO_4$ (1.5 mol/L) at 55 ℃. [b] Isolated yield. [c] The *ee* values were determined by HPLC on a chiral column.

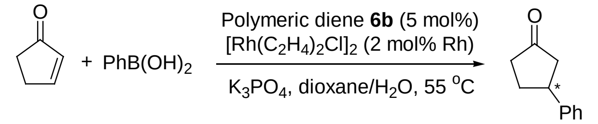
was obtained when **4b** and **4c** with better solubility in dioxane was employed (Entries 3 and 4). Not surprisingly, polymer **5a** and **5b** are not good ligand for catalysis due to their poor solubility (Entries 5 and 6). To our delight, **6a** and **6b** with diethylene glycol and triethylene glycol linker were found to exhibit very high catalytic activity. When they were used, the same reaction at 55 ℃ gave adduct **9a** in very high yield (94% and 95%) (Entries 7 and 9). In the case of **6b**, a best enantioselectivity of 75% was achieved. Interestingly, when the loading of $[Rh(C_2H_4)_2Cl]_2$ was reduced to 0.5 mol%, a same level of yield and enantioselectivity could be obtained (Entry 10). Compared to the corresponding monomeric ligand **1**, the immobilized diene ligand generally shows a decrease of enantioselectivity although the reactivity can be possibly maintained, suggesting the difficulty of controlling the chiral microenvironment of the catalytic sites in the polymers.

With immobilized chiral diene ligand **6b** in hand, we proceeded to investigate the reaction generality. As summarized in Table 2, a series of arylboronic acids **8** with different substituents on benzene ring were reacted with 2-cyclohexenone (**7a**) or 2-cyclopentenone (**7b**) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (1 mol%) in aqueous $K_3PO_4$ (1.5 mol/L)/dioxane at 55 ℃. In all cases, the reaction went to completion smoothly in 8 h with moderate to good enantioselectivities. When 2-cyclopentenone (**7b**) was subjected to the reaction, higher levels of enantioselectivities were afforded (Entries 1, 2 vs. 3, 10). The electronic nature of the phenyl ring of boronic acid substrates has apparent influence on the reaction enantioselectivity (Entries 3—8), which is quite different from the catalytic system using **1** as ligand. A decrease in enantioselectivity was observed with electron-drawing groups on the benzene ring. On the other hand, with the sterically more hindered 1-naphthyl-boronic acid, slightly better enantiomeric excesses of the adducts were achieved (Entries 2 and 10) and up to 94% *ee* was obtained in the case of 1,4-addition of 2-cyclopentenone (**7b**).

As the polymeric ligand **6b** was found to be insoluble in ether, it could be easily recovered by simple precipitation (ether and water), centrifugation, washing (acetone), and drying after the catalytic reaction. To further test the efficiency of the recovered ligand, we reused it in the asymmetric 1,4-addition of 2-cyclopentenone (**7b**) with phenyl boronic acid **8a** under the above same reaction conditions. As can be seen from the results summarized in Table 3, the recovered polymer ligand **6b** can be recycled at least three times without significant loss of enantioselectivity. Unfortunately, a dramatic drop of both yield and enantioselectivity was observed in the fourth run. It should be mentioned that the reaction time was extended in turn since a drop in catalytic activity for each successive run was noticed. This decrease in reactivity may be attributed to a number of reasons, such as contamination of the polymer ligand by organic and inorganic chemicals during the recycling process, but it should be mainly inherent in the catalyst immobilization.

We have also examined the polymeric ligand **6b** in rhodium-catalyzed arylation of *N*-tosylarylimine with arylboronic acid (Scheme 2). However, unlike in the monomer ligand system, only 29% yield and 69% *ee* was obtained after 18 h at 55 ℃ in $KHF_2$/toluene.

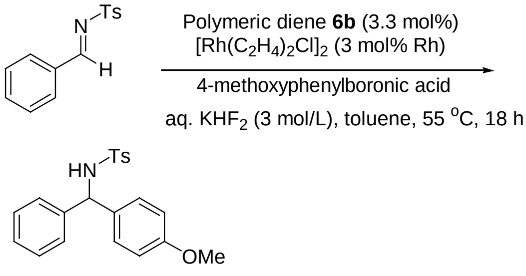
**Table 3** Recovery and reuse of the polymeric chiral diene ligand **6b** in enantioselective 1,4-addition of 2-cyclopentenone (**7b**)[a]



| Entry | Time/h | Yield$^b$/% | *ee*$^c$/ |
|---|---|---|---|
| 1 | 8 | 98 | 83 |
| 2 | 10 | 91 | 81 |
| 3 | 12 | 85 | 78 |
| 4 | 16 | 39 | 63 |

[a] The reaction was conducted on a 0.3 mmol scale, using 2 equiv. of phenylboronic acid in 1 mL of dioxane and 100 μL of aq $K_3PO_4$ (1.5 mol/L) at 55 ℃ following the general procedure, [Rh($C_2H_4$)$_2$Cl]$_2$ was added at every time of the reuse. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral OB-H column [detected at 214 nm; eluent: *n*-hexane/*iso*-propanol=99/1 (*V*/*V*), flow rate=1.0 mL/min].

**Scheme 2** Rh-catalyzed arylation using polymeric diene ligand **6b**



29% yield, 69% *ee*

## Conclusions

For the first time the sterically regular A-B type polymeric chiral diene ligands bearing a nonbridged bicyclic [3.3.0] backbone were designed and synthesized for transition-metal-catalyzed asymmetric reactions. The resulting immobilized diene ligand **6b** well behaved in Rh-catalyzed 1,4-addition of arylboronic acid to *α*,*β*-unsaturated carbonyl compounds under reaction conditions, showing relatively good activity and good to excellent enantioselectivity (up to 94% *ee*). The immobilized chiral diene ligand can be easily recycled and reused for three times without significant loss of enantioselectivity, while the drop in reactivity can be overcome by prolonging the reaction time. This work should provide useful information for future design and development of other polymeric chiral ligands for asymmetric catalysis.

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