Asymmetric Synthesis

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Highly Enantioselective Synthesis of Axially Chiral Biarylphosphonates: Asymmetric Suzuki–Miyaura Coupling Using High-Molecular-Weight, Helically Chiral Polyquinoxaline-Based Phosphines**

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Dedicated to Christian Bruneau on the occasion of his 60th birthday.

Asymmetric synthesis has developed rapidly with the exploration of chiral molecular scaffolds for use as chiral ligands, reagents, and auxiliaries.[1] Some molecular frameworks such as 1,1′-binaphthyl are widely recognized as privileged scaffolds for chiral sciences and technologies, including not only asymmetric synthesis, but also chiral recognition and separation.[2] In addition to those small-molecule-based chiral scaffolds for asymmetric synthesis, recent efforts have also been devoted to the development of macromolecular chiral scaffolds for asymmetric synthesis. The discovery of polymer-based privileged scaffolds for asymmetric synthesis takes advantage of the unique properties of macromolecules.[3,4] However, those reported macromolecular chiral ligands generally suffer from insufficient enantioselectivity. Only a DNA system in which the catalyst moieties are introduced noncovalently has been used to achieve excellent enantioselectivity, eventhough the use of naturally occurring scaffolds made accessibility to the enantiomeric catalyst difficult.[5]

We have recently established poly(quinoxaline-2,3-diyl)-based phosphine (PQXphos) as a new macromolecular chiral ligand for asymmetric hydrosilylation of styrenes.[6–8] In addition to its high enantioselectivities [up to 97% enantiomeric excess (*ee*)] and reusability, the catalyst system exhibited a highly characteristic switch of enantioselection because of solvent-dependent inversion of the helical chirality.[6,9] It appears that application of PQXphos to other catalytic reactions such as asymmetric C–C bond-formation reactions is highly attractive. We herein report the asymmetric Suzuki–Miyaura cross-coupling to form axially chiral biaryls by using the high-molecular-weight PQXphos bearing various diorganophosphorus groups on the helical polymer backbones.

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Despite the practicality and usefulness of Suzuki–Miyaura couplings (SMCs) in aryl–aryl bond-forming reactions, only a few systems for catalytic asymmetric biaryl synthesis through SMCs have been established.[10–14] In one of the first systems, reported by Buchwald and co-workers in 2000, 2-dicyclohexylphosphino-2′-dimethylamino-1,1′-binaphthyl (KenPhos) was used in the coupling of dialkoxyphosphinyl ($P(O)(OR)_2$)-substituted naphthyl bromides with *ortho*-substituted arylboronic acids to give up to 92% *ee*. The group of Uozumi recently reported a highly enantioselective coupling of the same naphthyl bromide with 2-methoxy-1-naphthylboronic acid, wherein the enantioselectivity of the reaction was not clearly shown, but was determined only after crystallization (99% *ee*).[14] We decided to examine the coupling of 1-bromo-2-naphthylphosphinates using our polymer-based chiral ligands because the product biarylphosphinates serve as direct precursors for the synthesis of chiral phosphine ligands, as demonstrated by Buchwald and co-workers.[10]

The 20 mer-based block copolymers (*S*,*S*)-(*R*)-**L1a–d** were prepared by living block copolymerization of a chiral spacer monomer bearing (*R*)-2-butoxymethyl side chains and a phosphorus-containing monomer in the presence of a chiral initiator, whose chiral group remained at the termini of the polymer (Figure 1a).[6a,8] In addition, the 1000 mer-based

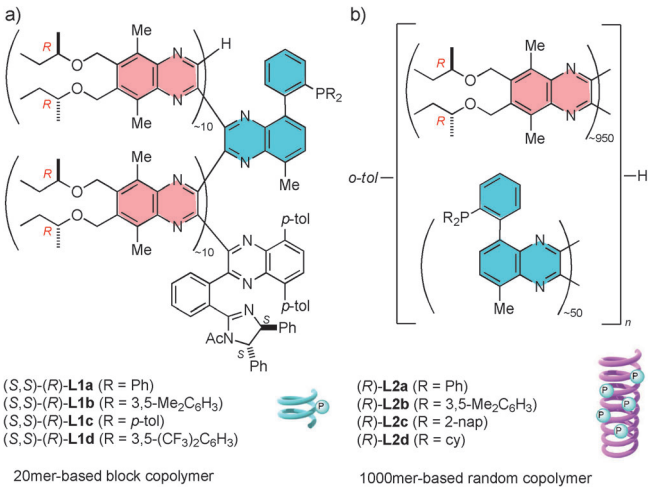
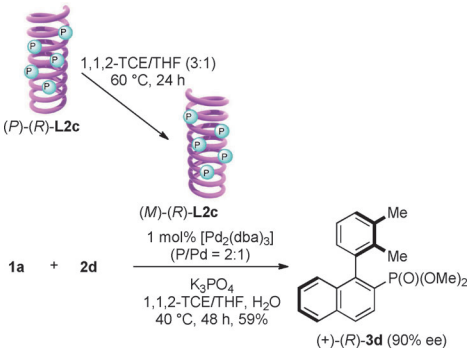


Figure 1. PQXphos (*S*,*S*)-(*R*)-**L1** and (*R*)-**L2**. cy = cyclohexyl, nap = napthyl.

high-molecular-weight polymer ligands (*R*)-**L2** were prepared by living random copolymerization of the chiral and the phosphorus-containing monomers in a 950:50 ratio using an achiral organonickel initiator (Figure 1b).[6b,15,16] The 20 mer-based polymer ligands **L1** were finally obtained from their $CHCl_3$ solution by evaporation, and the 1000 mer-based ligands **L2** were obtained from their toluene solution by precipitation with MeOH. All polymer ligands possessed pure right-handed (*P*) helical structures, as judged by their circular dichroism (CD) spectra.

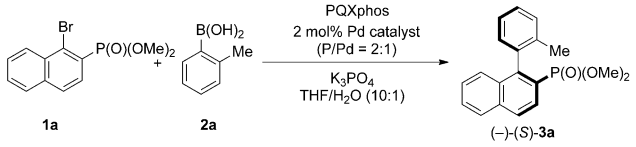
The polymer ligands were used in the SMC of dimethoxyphosphinyl-substituted 1-naphthyl bromide (**1a**) with *o*-tolylboronic acid (**2a**), a reaction that has been accomplished by Buchwald et al. with 86% *ee* using KenPhos at 60°C (Table 1). The coupling proceeded in the presence of (*S*,*S*)-(*R*)-**L1a** with a palladium catalyst at 40°C, thus affording higher *ee* values than at 60°C or 80°C (entries 1–3). Additional lowering of the reaction temperature made the reaction too sluggish. Among the 20 mer-based chiral ligands, (*S*,*S*)-(*R*)-**L1b**, which has 3,5-xylyl groups on the phosphorus atom, showed the highest enantioselectivity (entry 4), whereas the 3,5-bis(trifluoromethyl) derivative showed only a low *ee* value (entry 6). We then found that the corresponding 1000 mer-based PQXphos exhibited higher enantioselectivity: the Ph_2P derivative (*P*)-(*R*)-**L2a** showed higher selectivity than did the 20 mer-based ligand (*S*,*S*)-(*R*)-**L1a** (entry 7). Furthermore, the corresponding 3,5-xylyl and 2-naphthyl derivatives afforded the coupling product with remarkable enantioselectivities (entries 8 and 9), which clearly exceed the selectivity obtained in the original system. It is interesting to note, however, that the Cy_2P derivative showed only low enantioselectivity, in contrast to the original binaphthyl system using KenPhos.

Several biaryls were synthesized by asymmetric SMC in the presence of the high-molecular-weight (*R*)-**L2a–d**, which have right-handed helical structures (Table 2). Under the same reaction conditions as used for **1a**, diethoxyphosphinyl derivative **1b** afforded **3a′** with 94% *ee* in the presence of polymer ligand (*R*)-**L2c** (entry 3). The coupling of **1a** with 1-naphthylboronic acid (**2b**) was examined with the four polymer ligands (*R*)-**L2a–d**: ligand (*R*)-**L2a** bearing the PPh_2 group showed the highest enantioselectivity among the four (entries 4–7). Notably, the enantioselectivities thus far shown for both biaryls **3a** and **3a′** are higher than those obtained in the original system using KenPhos as a chiral ligand. We also examined the asymmetric SMC of **1** with selected *ortho*-methyl-substituted phenylboronic acids. The methoxy-substituted **2c** afforded the corresponding coupling product with high enantioselectivities (entries 8–10). In the coupling of the dimethyl-substituted **2d** and **2e**, the 2-



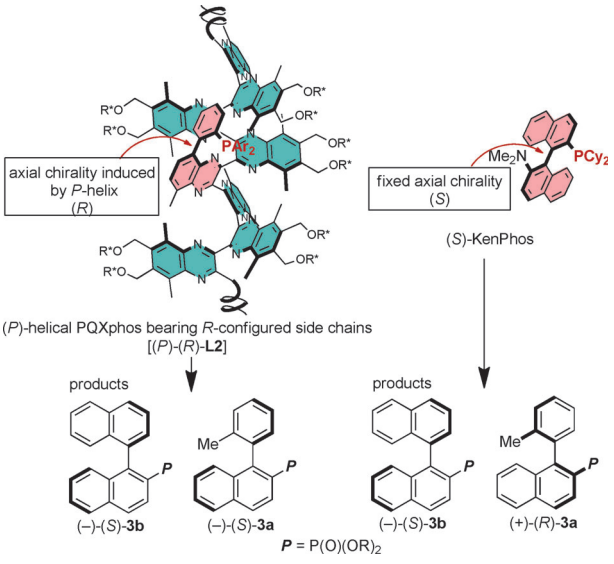
Scheme 1. The Suzuki–Miyaura coupling using helically inversed PQXphos. 1,1,2-TCE = 1,1,2-trichloroethane.

Table 1: Asymmetric Suzuki–Miyaura coupling with PQXphos (*S*,*S*)-(*R*)-**L1a–d** and (*R*)-**L2a–d**.[a]



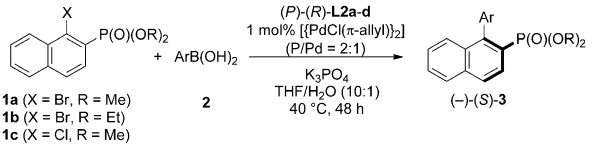
Entry	PQXphos	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*S*,*S*)-(*R*)-**L1a**	80	22	57	71
2	(*S*,*S*)-(*R*)-**L1a**	60	24	70	74
3	(*S*,*S*)-(*R*)-**L1a**	40	180	62	78
4	(*S*,*S*)-(*R*)-**L1b**	40	96	81	86
5	(*S*,*S*)-(*R*)-**L1c**	40	96	74	84
6	(*S*,*S*)-(*R*)-**L1d**	40	108	41	35
7	(*P*)-(*R*)-**L2a**	40	48	78	83
8	(*P*)-(*R*)-**L2b**	40	48	69	92
9	(*P*)-(*R*)-**L2c**	40	48	80	94
10	(*P*)-(*R*)-**L2d**	40	48	72	40

[a] Reaction conditions for entries 1–6: **1a** (0.10 mmol), **2a** (0.15 mmol), $[Pd_2(dba)_3]$ (1.0 μmol), the polymer ligand (4.8 μmol P), and K_3PO_4 (0.30 mmol) were heated in THF (0.25 mL) and H_2O (0.025 mL); for entries 7–10: **1a** (0.10 mmol), **2a** (0.15 mmol), $[\{PdCl(\pi\text{-allyl})\}_2]$ (1.0 μmol), ligand (4.0 μmol P), and K_3PO_4 (0.20 mmol) were heated in THF (0.40 mL) and H_2O (0.040 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis (chiral stationary phase). dba = dibenzylideneacetone, THF = tetrahydrofuran.



Scheme 2. Possible structures of chiral catalysts and the products that they generate.

Table 2: Asymmetric Suzuki–Miyaura of arylboronic acids with aryl halides with the high-molecular-weight PQXphos (*P*)-(*R*)-**L2a–d**.[a]



Entry	Halide	$ArB(OH)_2$	Product	Ligand	Yield [%][b]	*ee* [%][c]
1	**1b**			**L2a**	75	86
2	**1b**			**L2b**	67	93
3	**1b**	**2a**	(−)-(*S*)-**3a′**	**L2c**	70	94
4[d]	**1a**			**L2a**	42	94
5[d]	**1a**			**L2b**	24	92
6[d]	**1a**	**2b**	(−)-(*S*)-**3b**	**L2c**	56	90
7[d]	**1a**			**L2d**	68	78
8	**1a**			**L2a**	86	91
9	**1a**			**L2b**	84	95
10	**1a**	**2c**	(−)-(*S*)-**3c**	**L2c**	78	94
11	**1a**			**L2a**	74	92
12	**1a**			**L2b**	58	96
13	**1a**	**2d**	(−)-(*S*)-**3d**	**L2c**	78	98
14	**1a**			**L2a**	88	84
15	**1a**			**L2b**	69	89
16	**1a**	**2e**	(−)-(*S*)-**3e**	**L2c**	93	94
17	**1c**			**L2c**	78	95
18[d]	**1a**	**2f**	(−)-(*S*)-**3f**	**L2c**	60	94

[a] Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), [{PdCl(π-allyl)}$_2$] (1.0 μmol), polymer ligand (4.0 μmol P), K_3PO_4 (0.20 mmol) were heated in THF (0.40 mL) and H_2O (0.040 mL) at 40 °C for 48 h, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC analysis (chiral stationary phase). [d] Used 0.20 mmol **2**.

naphthyl-substituted ligand (*R*)-**L2c** again exhibited the highest enantioselectivities of up to 98% *ee* (entries 11–16). The optimized reaction conditions could be applied to the coupling of the naphthyl chloride **1c**, which afforded highly enantioenriched coupling product **3e** (entry 17). The chlorine-substituted arylboronic acid **2f** could also be utilized in the SMC with **1a**, thereby giving the corresponding product carrying a chlorine group for additional functionalization (entry 18).

The helical sense of the high-molecular-weight PQXphos (*R*)-**L2b–d** was found to be switchable, as observed for (*R*)-**L2a** in our previous report.[6b] We obtained the left-handed helical polymer ligand (*M*)-(*R*)-**L2c** by heating a 1,1,2-trichloroethane/THF solution of (*P*)-(*R*)-**L2c** (Scheme 1). Inversion of the helical sense was complete after 24 hours. The resultant left-handed helical polymer (*M*)-(*R*)-**L2c** was used as a ligand in the SMC of **1a** with **2d** at 40 °C. Although the reaction yield was still moderate, the (+)-(*R*) enantiomer of biaryl **3d** was obtained with 90% *ee*.

Finally, it seems important to note that the stereochemical course of our system is significantly different from that observed in the Buchwald system using KenPhos as a chiral ligand. The structure of (*P*)-(*R*)-**L2**, which is predicted from the semi-empirical AM1 calculation of the model compound,[17] and that of (*S*)-KenPhos, both of which produce *S*-binaphthyl products,[10a] for example., (−)-(*S*)-**3b**, in the coupling of naphthylboronic acid with **1**, are shown in Scheme 2. In the PQXphos, the axial chirality at the phenyl quinoxaline ring is induced by the right-handed helical structure of the poly(quinoxaline) backbone, whose helical chirality is in turn induced by the chiral side chains. Interestingly, in the coupling of *ortho*-tolylboronic acids, our (*P*)-(*R*)-**L2** ligand afforded (−)-(*S*)-**3a** (94% *ee*), whereas (*S*)-KenPhos gave its enantiomer (+)-(*R*)-**3a** (86% *ee*), whose absolute configuration (*R*) was determined by a single-crystal X-ray analysis of a related derivative.[10b] We separately confirmed the absolute configuration by its vibrational circular dichroism (VCD) spectrum.[18] The measured VCD spectrum of (−)-**3d** was in good agreement with the calculated VCD spectrum for (*S*)-**3d**, as judged from most of the major VCD signals.[17] These results indicate that the type of stereochemical control with PQXphos is significantly different from that with KenPhos, probably because of the absence of the dimethylamino group. In our system, the methyl groups in **2a** and the C5–C8 ring of the naphthyl group of **2b** may serve equally as having steric effects in the stereo-determining step.

In summary, we have shown that helically chiral PQXphos serves as a highly enantioselective ligand in the asymmetric Suzuki–Miyaura coupling reaction to form axially chiral biarylphosphinic esters. The organic groups on the phosphorus atom in the side chains of PQXphos have a considerable effect on the enantioselectivities of the reactions. The high-molecular-weight PQXphos bearing bulky P(2-nap)$_2$ groups successfully underwent solvent-dependent helical inversion, thus leading to the highly enantioselective production of the enantiomeric product. Although we have not shown it in this

paper, the enantiomeric products can also be obtained using the enantiomeric polymer catalyst bearing *S*-configured side chains. Further optimization of the ligand structure, attempts at expanding the substrate scope, and utilization of the polymer-based chiral ligand to other catalytic reactions are currently being undertaken in this laboratory.

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