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Asymmetric Suzuki–Miyaura cross-coupling of 1-bromo-2-naphthoates using the helically chiral polymer ligand PQXphos†

Yuto Akai,[a] Laure Konnert,‡[a] Takeshi Yamamoto[a] and Michinori Suginome*[ab]

A single-handed helical polymer ligand PQXphos afforded axially chiral biaryl esters with high enantioselectivities in asymmetric Suzuki–Miyaura cross-coupling. The use of naphthyl bromide bearing a 2,4-dimethyl-3-pentyl ester resulted in both high yields and high enantioselectivities. Either enantiomer could be synthesized selectively by using a single PQXphos through a solvent-dependent switch of the helical chirality.

Recently, much attention has been focused on the synthesis and functions of axially chiral biaryls, which are found in biologically active intermediates[1] and in chiral catalysts.[2] Highly enantioselective syntheses of axially chiral biaryls have been achieved by various asymmetric routes involving asymmetric C–C cross-coupling,[3,4] enantioselective oxidative coupling of phenols,[5] and enantioselective [2+2+2] cycloaddition of alkynes.[6] Among these approaches, the asymmetric Suzuki–Miyaura cross-coupling tends to be the most reliable and straightforward route to such axially chiral biaryl compounds.[4] Since the initial report on the asymmetric Suzuki–Miyaura reaction, a variety of chiral ligands have been employed, including axially chiral binaphthyl phosphines,[4a,f,j] planar chiral ferrocenylmonophosphanes,[4b,c] and chiral bishydrazones.[4d] Through these studies, it has been established that the enantioselectivities depend critically upon the substituents at the *ortho* position of the substrates. It is thus highly desirable to develop an asymmetric cross-coupling of substrates bearing easily convertible *ortho* substituents for the synthesis of a wide range of axially chiral biaryl derivatives. From this point of view, the carboxyl group would constitute an attractive functional group as the *ortho* substituent. Among the family of carboxyl derivatives, a number of amide derivatives were found to give high enantioselectivities by optimization of the structure of the amine component.[4f,i] On the other hand, more easily available and convertible ester derivatives have been much less often explored for use in asymmetric Suzuki–Miyaura reactions. Although methyl 1-bromo-2-naphthoate afforded high enantioselectivities of up to 88% ee,[4e] no further optimization has been made in terms of the alcohol component of the naphthoates. We have been particularly interested in the possibility of improving the enantioselectivity of asymmetric Suzuki–Miyaura coupling of 1-bromo-2-naphthoate derivatives by optimizing the alcohol component and catalyst structure.

We have recently developed helically chiral poly(quinoxaline-2,3-diyl)-based phosphine (PQXphos) as a monodentate chiral ligand for palladium-catalyzed asymmetric reactions (Fig. 1).[7,8] The single-handed helical structure of PQXphos was induced by a chiral terminal group[7a] or chiral side chains.[7b–f] Reactions performed with PQXphos as the ligand showed high enantioselectivities in the hydrosilylation of styrenes,[7a,b] silaborative C–C bond cleavage of *meso*-methylenecyclopropanes,[7d] and ring-opening arylation of 1,4-epoxy-1,4-dihydronaphthalenes.[7f] A key feature of PQXphos is a reversible switch of the helical chirality of the main chain, which is induced by the solvent.[9] For instance, (*R*)-PQXphos, bearing (*R*)-2-butoxymethyl side chains, adopts a right-handed helical structure in chloroform, whereas a left-handed helical structure is induced when 1,1,2-trichloroethane is used as the solvent.

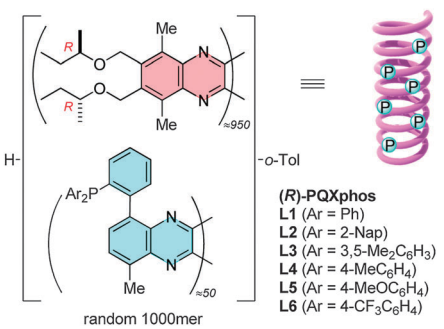

Fig. 1 Poly(quinoxaline-2,3-diyl)-based helically chiral phosphine ligand PQXphos.

[a] Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan. E-mail: suginome@sbchem.kyoto-u.ac.jp
[b] CREST, Japan Science and Technology Agency (JST), Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

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‡ On leaving from Institut des Biomolécules Max Mousseron, UMR 5247 CNRS-UM-ENSCM, Place Eugène Bataillon, cc 1703, 34095 Montpellier, France.

(*R*)-PQXphos gave either enantiomer with high enantioselectivity in palladium-catalyzed asymmetric reactions through solvent-dependent helix inversion. In 2011, we reported on the asymmetric Suzuki–Miyaura cross-coupling of naphthyl bromide bearing a phosphonate, with *ortho*-substituted arylboronic acids.[7b] In the report, we demonstrated that PQXphos showed higher enantioselectivities (up to 98% ee) than the original system in which 1-bromo-2-naphthyl phosphonates were used as substrates along with KenPhos[4a,f] (2-dicyclohexylphosphino-2′-dimethylamino-1,1′-binaphthyl), as a chiral ligand. Herein, we demonstrate the application of our polymer system to asymmetric Suzuki–Miyaura cross-coupling of 1-bromo-2-naphthoate derivatives, the ester function of which is expected to serve as a convenient handle for further transformation into axially chiral biaryls.

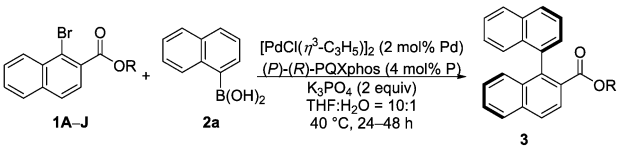
Palladium-catalyzed asymmetric Suzuki–Miyaura cross-coupling of aryl bromide **1A**, bearing a methoxy carbonyl group, with 1-naphthaleneboronic acid (**2a**) was carried out in THF at 40 °C in the presence of chiral polymer ligands **L1–L6**. (*P*)-(*R*)-PQXphos **L1**, which has a right-handed helical structure (indicated by the suffix (*P*)-), gave binaphthyl **3Aa** in 91% yield with 59% ee (Table 1, entry 1). Ligands **L2–L6** all showed comparable selectivities (entries 2–6). PQXphos **L6**, bearing 4-$CF_3C_6H_4$ groups, showed the highest selectivity (70% ee) among the ligands tested (entry 6).

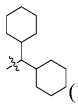
We examined the effect of the ester group of **1** on enantioselectivity. Substrates **1B–1G**, with secondary alkyl esters, afforded products with higher enantioselectivities than those obtained with the methyl ester (entries 7–12). It was found that ester **1D**, obtained from 2,4-dimethyl-3-pentanol, showed the highest enantioselectivity (87% ee; entry 9).[12] *t*-Butyl ester **1H** and phenyl ester **1I** showed lower selectivities (entries 13 and 14). It should be noted that 2,6-dimethylphenyl ester **1J** showed enantioselectivity comparable to that obtained with **1D** (85% ee; entry 15).

We also optimized the chiral ligand for cross-coupling of **1D** with 2-methylphenylboronic acid (**2b**) (Table 2).[12] PQXphos **L3**, bearing 2-naphthyl groups, showed the highest enantioselectivity (88% ee; entry 3). In contrast, PQXphos **L6**, which showed the best results in the cross-coupling of 1-naphthaleneboronic acid (**2a**), showed only 76% ee (entry 6).

A wide range of arylboronic acids were cross-coupled with **1D** in the presence of polymer ligands **L3** or **L6** (Table 3). Using **L6** as a chiral ligand, 4-substituted 1-naphthaleneboronic acids **2c–2e** gave the corresponding products **3** with high enantioselectivities (entries 1–3). Cross-coupling of 1-pyreneboronic acid (**2f**) afforded the corresponding product **3Df** in 96% yield with 95% ee (entry 4). By using **L3** as a chiral ligand, cross-coupling of 2,3- and 2,5-dimethylphenylboronic acids **2g** and **2h** afforded the corresponding products with high enantioselectivities (entries 5–7). A gram-scale synthesis of axially chiral biaryl ester was demonstrated with a P/Pd ratio of 1.2/1, giving 1.31 g of (*S*)-**3Dg** (87% yield) with 96% ee (entry 6). The use of 2-methylphenylboronic acids bearing methoxy or fluoro groups resulted in good yields and high enantioselectivities of the coupling products (entries 8–10). Although 4-fluoro-2-methylphenylboronic acid showed slightly lower enantioselectivity (87% ee), a single recrystallization gave **3Dj** with 96% ee (entry 9).

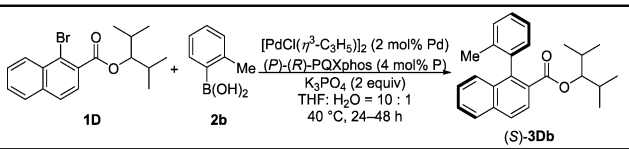
Table 1 Ligand and substrate screening[a]



Entry	R (bromide)	Ligand	Product	Yield[b] (%)	ee[c] (%)
1	Me (**1A**)	**L1**	(*S*)-**3Aa**	91	59
2	Me (**1A**)	**L2**	(*S*)-**3Aa**	83	56
3	Me (**1A**)	**L3**	(*S*)-**3Aa**	95	42
4	Me (**1A**)	**L4**	(*S*)-**3Aa**	80	66
5	Me (**1A**)	**L5**	(*S*)-**3Aa**	49	54
6	Me (**1A**)	**L6**	(*S*)-**3Aa**	87	70
7	i-Pr (**1B**)	**L6**	(*S*)-**3Ba**	84	79
8	 (**1C**)	**L6**	(*S*)-**3Ca**	68	82
9	 (**1D**)	**L6**	(*S*)-**3Da**	64	87
10	 (**1E**)	**L6**	(*S*)-**3Ea**	79	82
11	Cyclohexyl (**1F**)	**L6**	(*S*)-**3Fa**	90	80
12	Cyclooctyl (**1G**)	**L6**	(*S*)-**3Ga**	70	80
13	*t*-Bu (**1H**)	**L6**	(*S*)-**3Ha**	67	68
14	Ph (**1I**)	**L6**	(*S*)-**3Ia**	45	78
15	 (**1J**)	**L6**	(*S*)-**3Ja**	67	85

[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.15 mmol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (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). [b] Isolated yield. [c] Determined by HPLC or SFC analysis with chiral stationary phase. The absolute configuration of **3Aa** was determined by comparing its optical rotation with reported data.[10] The absolute configuration of **3Da** was determined by converting its corresponding carboxylic acid.[3a,11] The absolute configurations of other biaryl compounds were assigned by analogy.

Table 2 Ligand screening in asymmetric cross-coupling of 2-methylphenylboronic acid[a]

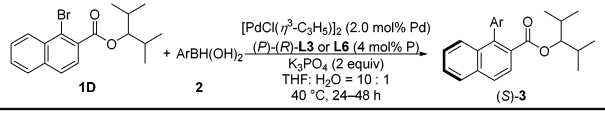


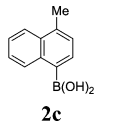
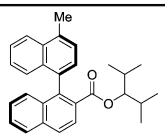
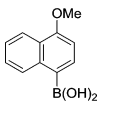
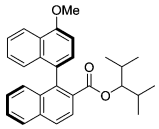
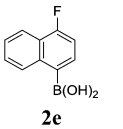
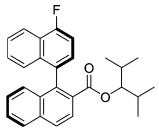
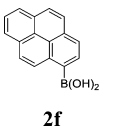
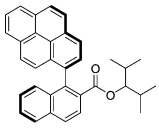
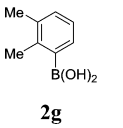
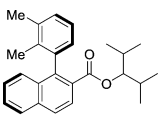
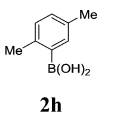
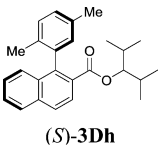
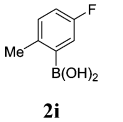
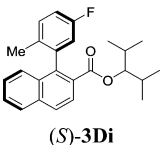
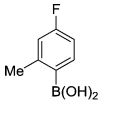
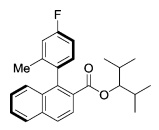
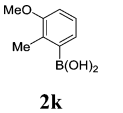
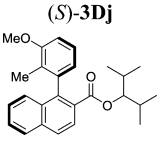
Entry	Ligand	Yield[b] (%)	ee[c] (%)
1	**L1**	57	85
2	**L2**	59	82
3	**L3**	**52**	**88**
4	**L4**	53	82
5	**L5**	47	79
6	**L6**	66	76

[a] Reaction conditions: see footnote *a* in Table 1. [b] Isolated yield. [c] Determined by HPLC or SFC analysis with chiral stationary phase. The absolute configuration of **3Db** was determined by converting its corresponding alcohol.[13] See ESI.

It is noteworthy that the reaction of 1-chloro-2-naphthoate **1D′** with **2g** gave (*S*)-**3Dg** in 89% yield with 97% ee (eqn (1)).

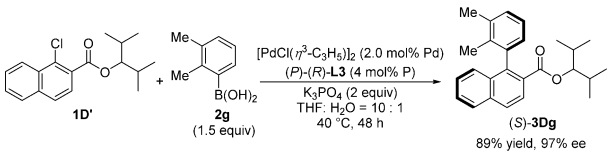
Table 3 Asymmetric Suzuki–Miyaura coupling of arylboronic acids with **1D** using PQXphos[a]



Entry	$ArB(OH)_2$	Product	Ligand	Yield[b] (%)	ee[c] (%)
1	 **2c**	 (*S*)-**3Dc**	**L6**	66	92
2	 **2d**	 (*S*)-**3Dd**	**L6**	89	88
3	 **2e**	 (*S*)-**3De**	**L6**	94	90
4	 **2f**	 (*S*)-**3Df**	**L6**	96	95
5			**L3**	88	96
6[d]	 **2g**	 (*S*)-**3Dg**	**L3**	87	96
7	 **2h**	 (*S*)-**3Dh**	**L3**	61	91
8	 **2i**	 (*S*)-**3Di**	**L3**	93	93
9	 **2j**	 (*S*)-**3Dj**	**L3**	98 (59)[e]	87 (96)[e]
10	 **2k**	 (*S*)-**3Dk**	**L3**	91	90

[a] Reaction conditions: see footnote *a* in Table 1. [b] Isolated yield. [c] Determined by HPLC or SFC analysis with chiral stationary phase. The absolute configurations were assigned by analogy. [d] Reaction conditions: **1D** (4.0 mmol), **2g** (6.0 mmol), $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (40 μmol), **L3** (96 μmol P), K_3PO_4 (8.0 mmol) were heated in THF (16 mL) and H_2O (1.6 mL) at 40 °C for 72 h. [e] After a single recrystallization.

This result indicates that our polymer catalyst system is applicable to less reactive chloro-derivatives without decreasing the yield and enantioselectivity.

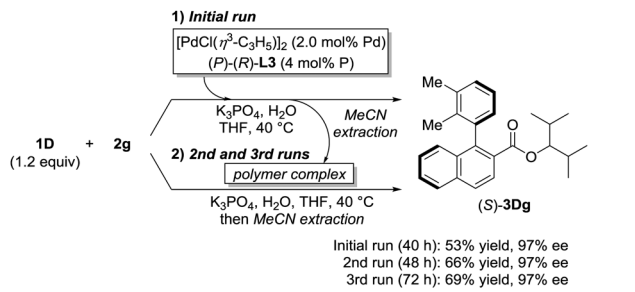


(1)

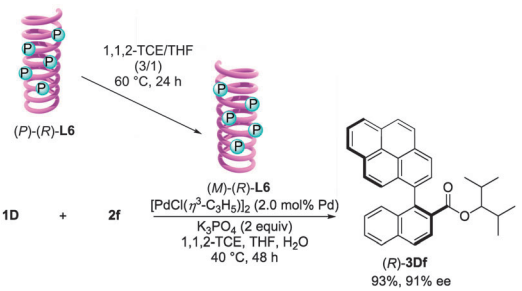
Taking advantage of macromolecular scaffold, we examined the reuse of the polymer catalyst. To avoid deactivation of the catalyst, the reaction was carried out with 1.2 equiv. of **1D** over **2g** (Scheme 1). After the initial run, acetonitrile was added to the mixture to precipitate the polymer complex. The insoluble materials were washed by acetonitrile to extract the product (53% yield, 97% ee). The polymer complex remaining in the reaction vessel was dried under vacuum, and then used for the next run. Although the catalyst activity decreased slightly, the whole catalyst could be reused two times without any drop of enantioselectivity.

The other enantiomer was synthesized through solvent-dependent helix inversion of PQXphos (Scheme 2).[7,9] The left-handed helical polymer ligand (*M*)-(*R*)-**L6** was prepared by heating a solution of (*P*)-(*R*)-**L6** in a 3:1 mixture of 1,1,2-trichloroethane and THF at 60 °C for 24 h. By using thus prepared (*M*)-(*R*)-**L6** as a chiral ligand, cross-coupling of **1D** with **2f** afforded (*R*)-**3Df** with 91% ee.

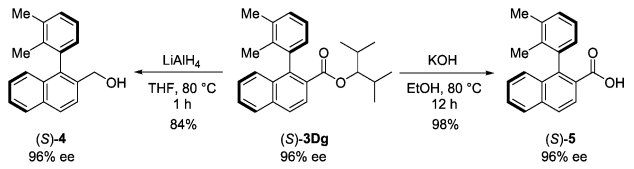
Product **3Dg**, bearing a 2,4-dimethyl-3-pentyl ester group, could be readily converted into alcohol (*S*)-**4** through reduction with $LiAlH_4$ at 80 °C or into carboxylic acid (*S*)-**5** through hydrolysis using KOH at 80 °C (Scheme 3). Both reactions proceeded without racemization.



Scheme 1 Reuse of the polymer complex.



Scheme 2 Suzuki–Miyaura coupling with helically inverted PQXphos.



Scheme 3 Reduction and hydrolysis of **3Dg**.

In summary, we have reported the asymmetric Suzuki–Miyaura cross-coupling of 1-bromo-2-naphthoates with PQXphos as chiral ligands. The steric effect of the ester groups determined the enantioselectivity of this reaction. From the range of ester groups tested, 2,4-dimethyl-3-pentyl ester showed high enantioselectivities for cross-coupling with 1-naphthaleneboronic acids and 2-methylphenylboronic acids. This ester can be readily converted into other functional groups. Further exploration of the asymmetric Suzuki–Miyaura cross-coupling using PQXphos is underway in our laboratory.

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