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Enhanced Catalyst Activity and Enantioselectivity with Chirality-Switchable Polymer Ligand PQXphos in Pd-Catalyzed Asymmetric Silaborative Cleavage of *meso*-Methylenecyclopropanes

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Supporting Information

ABSTRACT: The poly(quinoxaline-2,3-diyl)-based helically chiral phosphine ligands PQXphos exhibited high enantioselectivities up to 97% ee in palladium-catalyzed desymmetrization of *meso*-1,2-dialkylsubstituted-3-methylenecyclopropanes through silaborative cleavage of the C−C bond. The observed enantioselectivities were higher than those obtained with 2-diarylphosphino-1,1′-binaphthyl in our original report. Remarkable rate enhancement was also observed with a series of PQXphos in comparison with the corresponding low-molecular weight ligands.

Much attention has been focused on the development of polymer-based chiral ligands in organic synthesis from the viewpoint of practicality on the basis of their ease in recovery from the reaction mixture and reusability.[1] Efforts are now being devoted to the exploration of next-generation chiral polymer ligands, whose chiral reaction environment relies largely on the polymer backbone.[2] The establishment of new catalyst systems that feature higher enantioselectivities, higher catalytic activities, and reusability is eagerly desired on the basis of the polymer-based approach. Furthermore, it is also expected for the next-generation polymer catalysts that the polymer backbones play a positive effect on the enhancement of catalyst activities through their huge "long-range steric effect," which is proposed as the steric effect remote from the reaction center, around which enough space for the reaction is still left.[3] Such special steric effect is established only for the finely synthesized large molecules, including some bowl-shaped bulky phosphine ligands.[3]

We have recently reported a new class of polymer-based chiral ligand PQXphos (e.g., **L1**−**L3**), whose chirality relies on a single-handed helical structure of the backbone of poly(quinoxaline-2,3-diyl) (Figure 1).[4−7] The new polymer-based ligand showed remarkably high enantioselectivities in Pd-catalyzed hydrosilylation of styrenes[4a,b] and Suzuki−Miyaura coupling of phosphinyl-substituted 1-naphthylbromide with *o*-methylarylboronic acids.[4c] In the latter case, enantioselectivities higher than the original low-molecular weight system were attained, demonstrating the advantage of using a polymer-based chiral ligand system in obtaining higher enantioselectivities. Also noteworthy is that the polymer ligand underwent reversible, perfect switching of helical chirality by the solvent effect,[8] leading to production of either enantiomer from a single catalyst with high enantioselectivities. However, the polymer system has so far

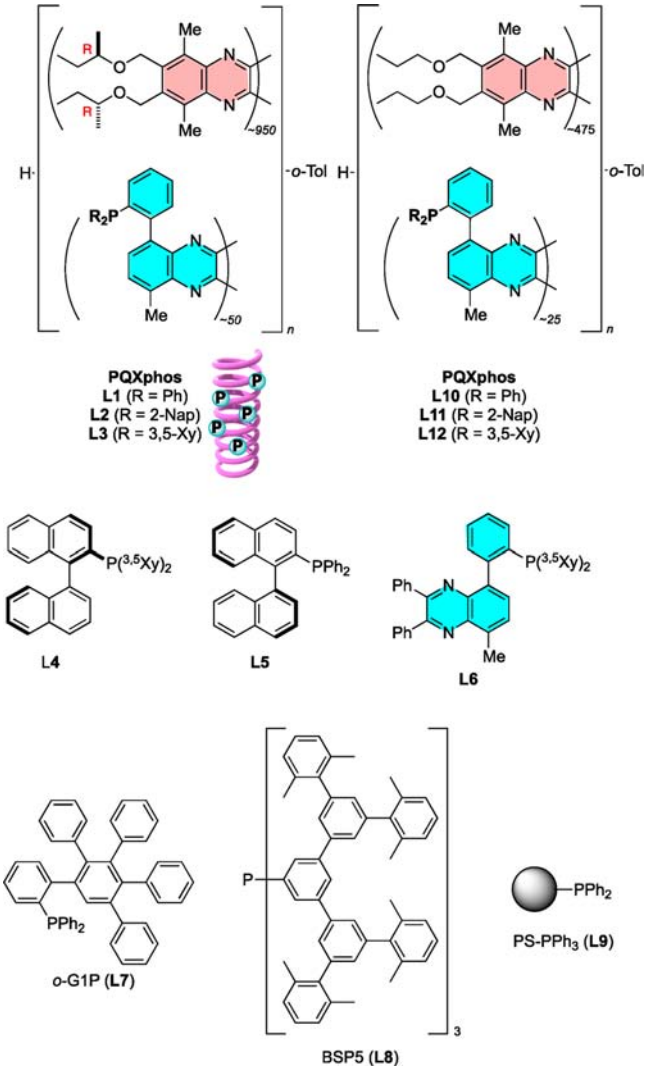

Figure 1.

shown almost the same or rather low catalytic activities in comparison with the corresponding low-molecular weight ligand systems.[9] We wondered if our polyquinoxaline backbone could

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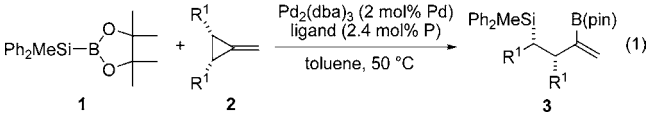
show significant rate enhancement in asymmetric catalysis on the basis of the long-range steric effect. In this paper, we demonstrate that, using PQXphos as a ligand, Pd-catalyzed reaction of *meso*-methylenecyclopropanes with silylborane proceeds with much higher enantioselectivities along with a much higher reaction rate than the original silaboration system using 2-diarylphosphino-1,1′-binaphthyl (MOP) as ligands. In addition, remarkably sharp dependence of the enantioselectivity upon the substituents on the phosphorus atoms of PQXphos has been established.

In 2007, we reported asymmetric silaboration of *meso*-methylenecyclopropanes (*meso*-MCPs) using a palladium catalyst bearing a MOP-type, monodentate chiral phosphine ligand **L4** (eq 1 and Figure 1).[10] Although up to 91% ee was



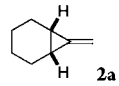
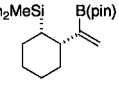
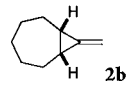
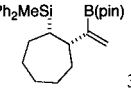
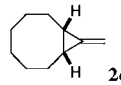
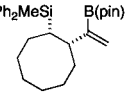
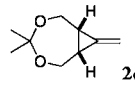
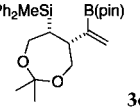
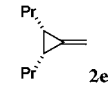
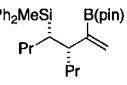
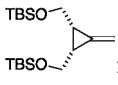
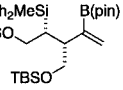
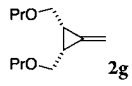
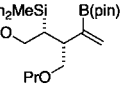
attained for bicyclic MCPs whose three-membered ring is fused to five- to eight-membered ring cycloalkanes, monocyclic MCPs gave much lower enantioselectivity up to 81% ee. Furthermore, MCPs having oxygen functionalities showed much lower reactivities than the unfunctionalized, hydrocarbon derivatives. We chose this reaction system for the test of our polymer-based ligand as a more active and enantioselective chiral ligand.

In the reaction of bicyclic MCP **2a** in the presence of PQXphos **L1**–**L3**, enantioselectivities varied significantly, depending on the aryl groups on the phosphorus atoms (Table 1, entries 1–3).[11] Although the diphenylphosphino derivative **L1** showed 67% ee, 2-naphthyl derivative **L2** resulted in 7% ee. In contrast, 3,5-xylyl derivative **L3** showed remarkably high enantioselectivity (96% ee), exceeding the enantioselectivity of 91% ee obtained with MOP-type ligand **L4** modified with 3,5-xylyl groups on the phosphorus atom.[10a,12] It should be noted that **L2** and **L3** showed similarly high enantioselectivities in asymmetric Suzuki–Miyaura coupling in our previous report, while such varied selectivities are obtained in the present reaction system. The enantioselectivities were generally higher than those with **L4** for some additional MCPs, including fused and nonfused MCPs. In particular, the selectivity (95% ee) for the nonfused MCP **2e** with **L3** was significantly higher than that with **L4** (81% ee) (entry 7).[10a] MCPs **2f** and **2g** bearing oxygen functionalities, which were hardly reactive with **L4** in the previous system, successfully underwent the silaboration with high enantioselectivities (entries 8 and 9).

The right-handed helical PQXphos **L3** was dissolved in a 3/1 mixture of 1,1,2-trichloroethane (1,1,2-TCE) and toluene at 60 °C for 24 h, leading to the complete switch of the main chain helical chirality to *M* (left-handed) (Scheme 1). Upon use of a palladium complex of the inverted PQXphos (*M*)-(*R*,*R*)-**L3** under the same reaction conditions as those for (*P*)-(*R*,*R*)-**L3**, the reaction of **2a** was found to be significantly slower. Although we observed a reasonable reaction rate and the formation of an enantiomeric product under the solvent-free reaction conditions, enantioselectivity was moderate (75% ee), probably because of *M*-to-*P* helix reinversion during the reaction at 50 °C. We could improve the enantioselectivity to 91% ee by using a small amount of 1,1,2-TCE as an additive, which is likely to maintain the left-handed helical structure during the reaction.

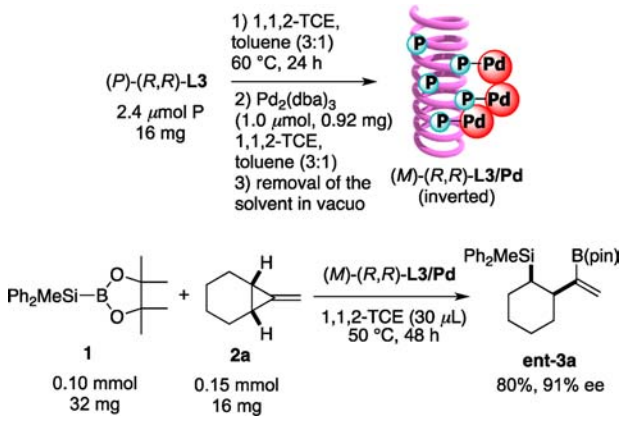
We observed interesting rate acceleration with the polymer-based PQXphos ligands. The MCP **2f** hardly underwent the silaborative C–C cleavage in the presence of $Pd_2(dba)_3$/PPh_3

Table 1. Asymmetric Silaborative C–C Cleavage of *meso*-MCPs Using PQXphos (*P*)-L1–3 as Chiral Ligands[a]

entry	MCP	ligand	product	% yield[b]	% ee[c]
1	 **2a**	**L1**	 **3a**	81	67
2		**L2**		67	7
3		**L3**		84	96
4	 **2b**	**L3**	 **3b**	85	94
5	 **2c**	**L3**	 **3c**	97	96
6	 **2d**	**L3**	 **3d**	68	96
7	 **2e**	**L3**	 **3e**	86	95
8	 **2f**	**L3**	 **3f**	62	95
9	 **2g**	**L3**	 **3g**	55	95

[a]MCP **2** (0.30 mmol), $Ph_2MeSiB(pin)$ (0.20 mmol), $Pd_2(dba)_3$ (2.0 μmol), and ligand (4.8 μmol) were heated with toluene (0.40 mL) at 50 °C. Reaction time: 168 h (entry 1); 240 h (entry 2); 48 h (entries 3–5 and 7–9); 72 h (entry 6). [b]Isolated yield. [c]Determined after oxidation to the corresponding β-silyl ketones.

Scheme 1. Use of Inverted PQXphos (*M*)-(*R*,*R*)-L3 as a Ligand for Asymmetric Silaboration of *meso*-MCP 2a



(Pd/P = 1:1.2) (Table 2, entry 1). Under the same reaction conditions, even the MOP ligand **L4**, which showed the best enantioselectivity in the original report, just exhibited low catalytic activity (entry 2). The quinoxaline-based triarylphosphine ligand **L6**, which was prepared as a model of PQXphos, also failed to give reasonable conversion (entry 3). When we used racemic PQXphos **L10**–**L12** bearing achiral side chains, significant enhancement of the reaction rate was observed

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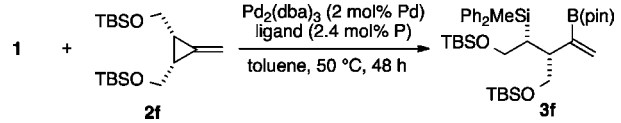
Table 2. Silaboration of *meso*-MCP 2f in the Presence of Various Phosphine Ligands[a]



entry	ligand	% yield[b]	% ee[c]
1	PPh_3	0	–
2	**L4**	3	–
3	**L6**	5	–
4	**L10**	23	–
5	**L11**	22	–
6	**L12**	61	–
7	(*P*)-**L1**	30	75
8	(*P*)-**L2**	51	49
9	(*P*)-**L3**	98	95

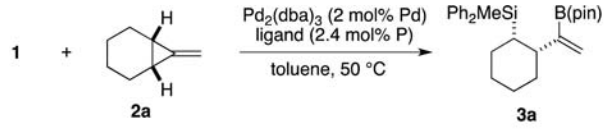
[a]MCP (0.15 mmol), $Ph_2MeSiB(pin)$ (0.10 mmol), $Pd_2(dba)_3$ (1.0 μmol), and ligand (2.4 μmol) were heated with toluene (0.20 mL) at 50 °C for 48 h. [b]NMR yield. [c]Determined after oxidation to the corresponding β-silyl ketones.

(entries 4–6). Among racemic PQXphos **L10**–**L12** bearing phenyl (**L10**), 2-naphthyl (**L11**), and 3,5-xylyl (**L12**) groups on the phosphorus atom of PQXphos, **L12** showed remarkably higher reactivity than the other PQXphos-based ligands (**L10** and **L11**) and low-molecular weight ligands **L4** and **L6**. The remarkable effect of the 3,5-xylyl group on the phosphorus ligand held for single-handed PQXphos (*P*)-**L1**–**L3** bearing chiral side chains (entries 7–9). Only **L3** bearing the di(3,5-xylyl)phosphino group showed acceptable catalytic activity at 50 °C, giving the silaboration product **3** in good yield and high enantioselectivity, as shown above (Table 1, entry 8; Table 2, entry 9).

A higher catalyst efficiency was also observed in silaboration of the rather reactive MCP **2a**. Use of triphenylphosphine and low-molecular weight ligands **L4**–**L6** showed significantly slow reaction rates (Table 3, entries 1–4). This sluggishness had been overcome by applying higher concentration (0.4 mmol silylborane with 0.2 mL toluene) in our previous report using **L4** as a chiral ligand. It is interesting to note that, during our screening of bulky ligands, 2,3,4,5-tetraphenylphenyl-substituted triarylphosphine **L7**[13] showed similar rate enhancement (entry 5). On the other hand, a bulky bowl-shaped triarylphosphine (BSP5) **L8**,[3] which showed a similar rate acceleration effect to **L7** in Pd-catalyzed cross-coupling of aryl chlorides, gave no remarkable rate enhancement in the present reaction (entry 6). To look at the effect of the polymer backbone on the catalytic activity, diphenylphosphino-polystyrene **L9**[14] was tested, resulting in almost no catalytic activity (entry 7). In contrast, PQXphos **L10**–**L12** and **L1**–**L3** showed apparently higher reaction rates (entries 8–13). Comparing the catalytic activities of a PPh_2 series (PPh_3, **L1**, **L5**, **L7**, **L9**, and **L10**), we observed high catalytic activity of **L1** on the basis of the unique steric characteristics of the polyquinoxaline backbone. The effect does not arise from a local electronic effect or a simple polymer effect. The apparent rate enhancement with the bulky *o*-G1P (**L7**) ligand supports this hypothesis. It should be noted that use of highly active **L3** allowed us to apply a lower catalyst loading (0.2 mol % Pd at 50 °C) and room temperature reaction conditions (Scheme 2). The latter reaction condition afforded us the highest enantioselectivity of 97% ee by virtue of the lower reaction temperature.

In summary, we have established the third reaction system in which PQXphos serves as highly efficient chiral ligand/catalysts

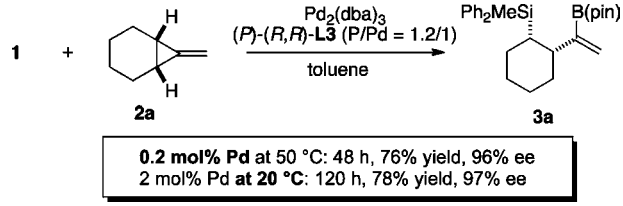
Table 3. Dependence of Time Course of Silaboration of *meso*-MCP 2a on Phosphine Ligands[a]



entry	ligand	% conversion[b] 6 h	24 h	48 h	120 h	% yield[c]	% ee[d]
1	PPh_3	<5	<5	<5	**<5**	<5	–
2	**L4**	7	19	24	**25**	17	–90
3	**L5**	<5	7	9	**12**	9[e]	72
4	**L6**	5	15	20	**32**	25	–
5	**L7**	7	27	49	**72**	62	–
6	**L8**	7	14	19	**19**	8[e]	–
7	**L9**	<5	<5	<5	**<5**	<5	–
8	**L10**	15	23	36	**62**	47	–
9	**L11**	5	20	34	**47**	37	–
10	**L12**	38	80	**>95**		81	–
11	(*P*)-**L1**	16	43	62	**82**	77	68
12	(*P*)-**L2**	15	37	56	**64**	55	6
13	(*P*)-**L3**	**>95**				80	96

[a]MCP (0.15 mmol), $Ph_2MeSiB(pin)$ (0.10 mmol), $Pd_2(dba)_3$ (1.0 μmol), ligand (2.4 μmol), and n-tetradecane (internal standard, 30 μL) were heated with toluene (0.2 mL) at 50 °C. [b]Determined by GC. [c]Isolated yield unless otherwise noted. [d]Determined after oxidation to the corresponding β-silyl ketones. [e]GC yield.

Scheme 2. Asymmetric Silaboration with Lower Catalyst Loading or at Room Temperature



with high enantioselectivities comparable with or better than the known asymmetric catalyst systems. It is particularly interesting that a clear rate enhancement was observed with the polymer-based ligands, while it is widely accepted that the polymer backbone should have an adverse effect in terms of catalytic activity as well as on enantioselectivity. We assume that the rate enhancement is due to a type of "long-range steric effect" reported previously, which would make catalytically active monomeric palladium species more favorable and more stable.[3] It should be pointed out that this result clearly shows that fine polymer synthesis can greatly contribute to the development of highly stereoselective and catalytically active chiral catalysts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) M_n and M_w/M_n values (GPC, polystyrene standard) of the polymer ligands are as follows. **L1**, $M_n = 2.7 \times 10^5$, $M_w/M_n = 1.20$; **L2**, $M_n = 2.1 \times 10^5$, $M_w/M_n = 1.31$; **L3**, $M_n = 1.8 \times 10^5$, $M_w/M_n = 1.52$. See the Supporting Information for details.

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(14) PS-PPh_3 was purchased from Biotage. Resin type, 1% cross-linked poly(styrene-co-divinylbenzene); loading, 2.09 mmol/g (based on uptake of benzylbromide); mean bead size, 123 μm, 100−200 mesh (95% within).