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Highly Efficient Synthesis of a Class of Novel Chiral-Bridged Atropisomeric Monophosphine Ligands via Simple Desymmetrization and Their Applications in Asymmetric Suzuki–Miyaura Coupling Reaction

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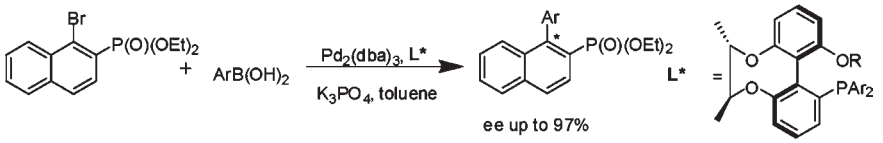
ABSTRACT



A series of novel chiral-bridged atropisomeric monophosphine ligands were synthesized via convenient and simple pathways. The prepared ligands, especially for ligand 7d, were found to be highly effective in the Pd-catalyzed Suzuki–Miyaura coupling reaction. The steric hindrance and electronic effect of substrates on the reactivity and enantioselectivity were explored preliminarily.

Atropo-molecules, in which the chirality originates from restricted rotation along a chiral axis rather than a stereogenic center, have received considerable attention since they are key structural motifs found in a number of natural products from various origins and have a wide range of biological properties.[1] Relevant atropisomers also prove to be efficient ligands and show remarkable enantioselectivies in a number of asymmetric catalyses.[2] In 1991, Hayashi and co-workers developed the first monophosphine ligand that is a well-known MOP (2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl) with oxygen as another coordinating atom (O,P-ligand), and it was successfully used in an asymmetric palladium-catalyzed hydrosilylation reaction.[3] Since then, MOP and its analogues[4] have been successfully employed in many types of catalytic asymmetric reactions and exhibited excellent enantioselective induction capability.[5] Substrates used for asymmetric

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catalysis are highly diverse, and this results in great demands for different chiral ligands and corresponding catalysts. However, good monophosphine ligands are still scarce in comparison with the biaryl diphosphine ligand family.[6] Thus, one of the most exciting and challenging subjects in the research of catalytic asymmetric synthesis is the development of highly effective chiral phosphine ligands suitable for different substrates and reaction types. In 2000, Harada reported a method for asymmetric synthesis of axially chiral 2,2′-biphenyldiols via desymmetrization of prochiral tetrahydroxybiphenyl.[7] However, applications of these chiral biaryldiols are not widespread to date.[8] As part of our continuing effort in designing chiral ligand scaffolds using a diastereoselective synthesis technique,[9] we herein demonstrate two simple and practical strategies for the preparation of a series of novel chiral-bridged atropisomeric monophosphine ligands **7a**−**7g** (Figure 1) via an asymmetric desymmetrization and annulation reaction. The synthesized ligands are highly effective in the asymmetric Suzuki−Miyaura coupling reaction.

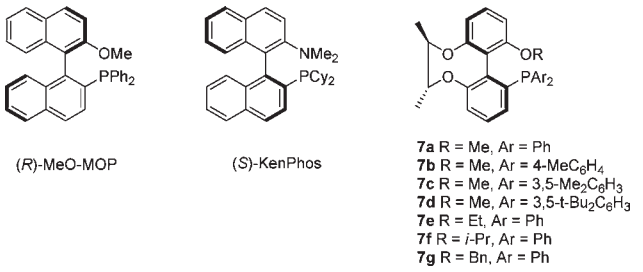
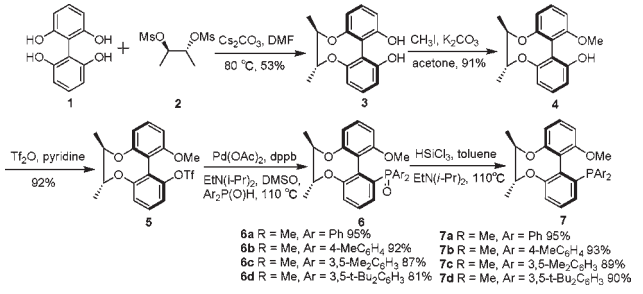


Figure 1. MeO-MOP, KenPhos, and our ligands.

The synthetic route to ligands **7a**−**7d** was shown in Scheme 1.

Scheme 1. Synthesis of Ligands **7a**−**7d**



Our approach started with achiral 2,2′,6,6′-tetrahydroxybiphenyl through two anchored hydroxy groups of the biphenyl by (*R*,*R*)-2,3-butanediol bis(mesylate) through a Williamson synthesis.[7] A dsymmetrization reaction was completed, and annulation product **3** was afforded in 53% yield. The (*R*,*R*)-configuration from the central chirality of **2** was changed into the (*S*,*S*)-form via an S_N2 substitution reaction. At the same time, perfect chirality transfer from central to axial chirality and complete diastereoselectivity were attained. This overcomes the limitation of the maximum 50% yield for the desired atropisomer via the traditional resolution step. Monomethylation of **3** using methyl iodide provided **4** in 91% yield. Then trifluoromethanesulfonic anhydride was added to a solution of **4** in pyridine at 0 °C, and the reaction system was stirred at room temperature for 12 h and gave product **5**. An aryl phosphine oxide moiety was introduced by reacting **5** with $Ar_2P(O)H$ in DMSO at 110 °C for 16 h in a palladium acetate, 1,4-bis(diphenylphosphino) butane, and *i*-Pr_2NEt catalyst system, and monophosphine oxides **6a**−**6d** were yielded. Ligands **7a**−**7d** were finally prepared via subsequent reductions of **6a**−**6d** with trichlorosilane and *i*-Pr_2NEt. The molecular structure of **7a** was confirmed by single-crystal X-ray diffraction. It is noteworthy that only five steps are needed in this synthetic process, which is less than the case for the synthesis of MeO-MOP.[3a]

Another pathway was adopted for the synthesis of ligands **7e**−**7g**. Detailed information is given in the Supporting Information. It diverged from compound **3**, and the subsequent synthetic steps were similar to those in the preparation of MOP.[3b] In the above-mentioned two synthetic protocols, no resolution step is necessary. The chiral bridge not only performs the function of chiral induction but also becomes a part of the ligand skeleton.

Suzuki−Miyaura coupling has gained popularity as a versatile and powerful synthetic tool for carbon−carbon bond formation;[10] some achiral monophosphine ligands were developed and displayed good efficiency in this kind of reaction.[11] However, successful asymmetric versions of the reaction merely emerged in recent years. Limited results were disclosed,[12] and deep explorations are warmly

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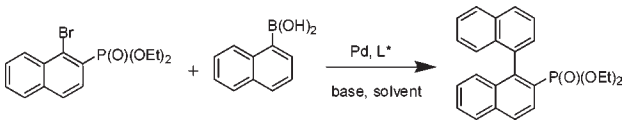
expected. Buchwald and co-workers found that the reaction of aryl halides bearing an *ortho* phosphonate group and boronic acid possessing an *o*-alkyl substituent could proceed with high enantioselectivities.[12b,c] Coupling of the same naphthyl bromide with 2-methoxy-1-naphthylboronic acid was carried out by Uozumi et al. using a chiral imidazoindole phosphine supported on an amphiphilic PS-PEG resin as the ligand, and 99% ee was obtained for the product only after crystallization.[12d] During the preparation of this paper, Suginome reported a class of helically chiral PQXphos ligands for the coupling reaction to form axially chiral biarylphosphinic esters with excellent enantioselection.[13] Importantly, the phosphonate moiety in these compounds is suitable for further functionalization to prepare various atropisomeric monophosphine ligands. Thus, the asymmetric Suzuki–Miyaura coupling between diethyl 1-bromo-2-naphthylphosphonate and naphthyl boronic acid was selected as the model reaction to examine the chiral catalytic efficiency for our ligands. Various solvents, Pd sources, bases, and ligands were screened at first, and the results are outlined in Table 1.

Conditional experiments showed that toluene, $Pd_2(dba)_3$, and K_3PO_4 were the best combination for this reaction (Table 1, entries 1–11). This exactly matches the result with KenPhos as the ligand. Under the optimal reaction conditions, much better enantioselectivities were achieved using our ligands **7a**–**7g** instead of KenPhos and MeO-MOP although a small decrease in conversions occurred (Table 1, entries 1 and 14–19 vs entries 12 and 13). Ligand **7d** with a bulky 3,5-di-*tert*-butylphenyl group attached to the phosphine atom afforded the best ee. The corresponding ligands **7b**–**7c** possessing less bulky aryl groups such as 4-methylphenyl and 3,5-dimethylphenyl obtained similar results as ligand **7a** (Table 1, entries 14 and 15). The influence of the alkyl group linked to the oxygen atom of the ligands on the enantioselectivity of the model reaction was also investigated. The best conversion and enantioselectivity were obtained when the alkyl group was methyl. In contrast, a negative effect was observed using other counterparts (Et-, iPr-, Bn-) instead of the small CH_3 (Table 1, entry 1 vs entries 17–19). Different mole ratios of metal vs ligand (2:1, 5:4, 1:1, 4:5, 1:2) were tested; no variation on the ee value was observed. However, the activity of the catalyst dropped when the ratio was less than 1. This indicates that the central metal palladium complexed with the ligand at a ratio of 1:1. In Suginome's report, PQXphos was employed as the ligands to the coupling between dimethyl 1-bromo-2-naphthylphosphonate and naphthyl boronic acid and it afforded the product with 94% ee, whereas the yield decreased sharply to 42%.[13] Encouraged by these results, we expanded the reaction to a broader substrate scope employing **7d** as the ligand. In Buchwald's and Suginome's research, *o*-alkyl substituted boronic acids were mainly focused.[12b,c,13] But the alkyl groups are difficult for further functionalization. Widely used ligands such as MOP's analogues can only been synthesized by *o*-alkyloxy boronic acids. Introduction of some functionalized substituents at the *ortho* position is no doubt significant for the development of useful ligand precursors. On the other hand, different kinds of aryl boronic acids can also be used to test substrate tolerance for the catalyst system. The results are summarized in Table 2.

Table 1. Optimization Experiments



entry[a]	L*	Pd	solvent	base	conversion[b] (%)	ee[c] (%)
1	**7a**	$Pd_2(dba)_3$	toluene	K_3PO_4	90	85
2	**7a**	$Pd_2(dba)_3$	DMF	K_3PO_4	20	72
3	**7a**	$Pd_2(dba)_3$	DMSO	K_3PO_4	23	16
4	**7a**	$Pd_2(dba)_3$	DME	K_3PO_4	90	81
5	**7a**	$Pd_2(dba)_3$	THF	K_3PO_4	88	81
6	**7a**	$Pd_2(dba)_3$	DME+ H_2O[e]	K_3PO_4	84	81
7	**7a**	$Pd(OAc)_2$	toluene	K_3PO_4	92	83
8	**7a**	$PdCl_2$	toluene	K_3PO_4	90	82
9	**7a**	$Pd_2(dba)_3$	toluene	CsF	70	82
10	**7a**	$Pd_2(dba)_3$	toluene	$CsCO_3$	46	83
11	**7a**	$Pd_2(dba)_3$	toluene	$Ba(OH)_2$	50	83
12	MeO-MOP	$Pd_2(dba)_3$	toluene	K_3PO_4	75	46
13	Ken Phos	$Pd_2(dba)_3$	toluene	K_3PO_4	97	57[d]
14	**7b**	$Pd_2(dba)_3$	toluene	K_3PO_4	88	84
15	**7c**	$Pd_2(dba)_3$	toluene	K_3PO_4	90	84
16	**7d**	$Pd_2(dba)_3$	toluene	K_3PO_4	62	88
17	**7e**	$Pd_2(dba)_3$	toluene	K_3PO_4	88	77
18	**7f**	$Pd_2(dba)_3$	toluene	K_3PO_4	87	71
19	**7g**	$Pd_2(dba)_3$	toluene	K_3PO_4	65	77

[a] Conditions: 1 equiv of aryl bromide, 2 equiv of naphthyl boronic acid, 4% Pd, 4.8% of ligand, 3 equiv of base, solvent, 40 °C, 40 h. [b] Determined by GC, NMR analysis. [c] Determined by HPLC with a Chiralcel OD-H column. [d] Cited in the literature.[12b] [e] The ratio of DME and H_2O was 10:1.

It is delightful that ligand **7d** exhibited much higher enantioselection than Buchwald's KenPhos for the coupling using 2-biphenylboronic acid (85% ee vs 74% ee,[12b] Table 2, entry 2). The increase of the enantioselectivity was more significant for (4-methoxy-1-naphthalenyl)-boronic acid (97% ee vs 71% ee,[12b] Table 2, entry 3). The reaction activities are also comparable to those with KenPhos as the ligand. Further, some aryl boronic acids were first selected as the substrates to construct new biaryls containing a phosphonate moiety (Table 2, entries 4–10). In general, all the reactions for the aryl boronic acids with an electron-donating group achieved satisfactory yields. However, the ee values changed from 78% to 97% (Table 2, entries 4–9). This may be caused by a steric hindrance effect at both the *ortho* and *meta* positions. A small group such as OMe at the *ortho* position of phenylboronic acid gave only 78% ee

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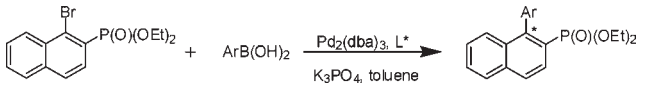
Table 2. Asymmetric Suzuki–Miyaura Coupling



entry[a]	$ArB(OH)_2$	L*	temp (℃)	time (h)	yield[b] (%)	ee[c] (%) (config.)
1		**7d**	40	48	62	88 (*R*)[d]
2		**7d**	60	48	75	85 (-)
3		**7d**	20	120	96	97 (+)
4		**7d**	20	120	93	97 (+)
5		**7d**	20	120	98	78 (-)
6		**7d**	20	120	98	92 (-)
7		**7d**	20	120	93	92(-)
8		**7d**	20	120	92	93(-)
9		**7d**	20	120	95	78 (-)
10		**7d**	50	72	65	90 (-)

[a] Conditions: 1.0 equiv of aryl bromide, 2 equiv of boronic acid, 2% $Pd_2(dba)_3$ (4% Pd), 4.8% of ligand **7d**, 3 equiv of K_3PO_4, toluene. [b] Yield of isolated product. [c] Determined by HPLC with a Chiralcel OD-H or AD-H column. [d] Cited in the literature.[12b]

(Table 2, entries 5 and 9). In contrast, phenylboronic acids with large groups at the *ortho* position provided higher enantioselectivities (92% ee for EtO- and *n*PrO-, and 93% ee for *i*PrO-, Table 2, entries 11–16). The bulky naphthyl boronic acids obtained much higher enantioselectivities (88%–97% ee, Table 2, entries 1, 3, and 4). It is noted that our catalyst system is quite active so that the reactions could proceed at room temperature. This supplies a new route for direct enantioselective synthesis of MOP's analogues. When 2-chlorophenylboronic acid was employed as the substrate, the reactivity slightly decreased. By raising the reaction temperature to 50 °C, excellent enantioselectivity (90% ee) was obtained despite a moderate yield for the product (Table 2, entry 10). This product may be a very important intermediate because it can be used for the synthesis of more complicated biaryls via general coupling reactions. These results suggest that the yields of this kind of reaction are sensitive to the electronic effect of the substrate. Generally, aryl boronic acids with an electron-withdrawing group are quickly deboronated during the reaction, whereas aryl boronic acids with an electron-donating group are more stable which is beneficial to the increase of the reactivity and yield.[14]

In summary, a series of new chiral-bridged atropisomeric monophosphine ligands were successfully synthesized via an asymmetric desymmetrization of 2,2′,6,6′-tetrahydroxybiphenyl through central-to-axial chirality transfer to obtain a versatile chiral biaryldiol with exclusive diastereoselectivity. Particularly noteworthy is that the traditional resolution step was not necessary in the ligand synthetic processes. This strategy of high atom economy provided a convenient and simple pathway for the design and development of atropisomeric monophosphine ligands. The newly developed ligands, especially for **7d**, were found to be highly effective in the palladium-catalyzed Suzuki–Miyaura coupling reaction. Further exploration of their applications in asymmetric catalysis are underway in our group.

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Supporting Information Available. Experimental details, spectroscopic data, and analytical data for ligands **7a-7g** and some intermediates and model reaction and crystallographic data for compound **7a** (CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.