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Highly Diastereoselective Synthesis of Atropisomeric Bridged P,N-Ligands and Their Applications in Asymmetric Suzuki–Miyaura Coupling Reaction

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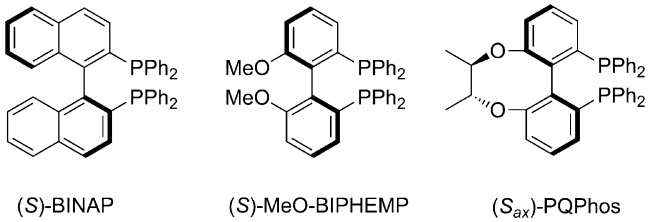
Abstract: Three novel atropisomeric bridged P,N-ligands were prepared using a highly efficient central-to-axial transfer strategy as the protocol. The new chiral ligands were successfully applied in the palladium-catalyzed asymmetric Suzuki–Miyaura coupling reaction, Up to 98% yield and 82% *ee* were obtained in the enantioselective synthesis of axially chiral biarylphosphonates.

Keywords: asymmetric catalysis; chirality transfer; diastereoselective synthesis; phosphine ligands; Suzuki–Miyaura reaction

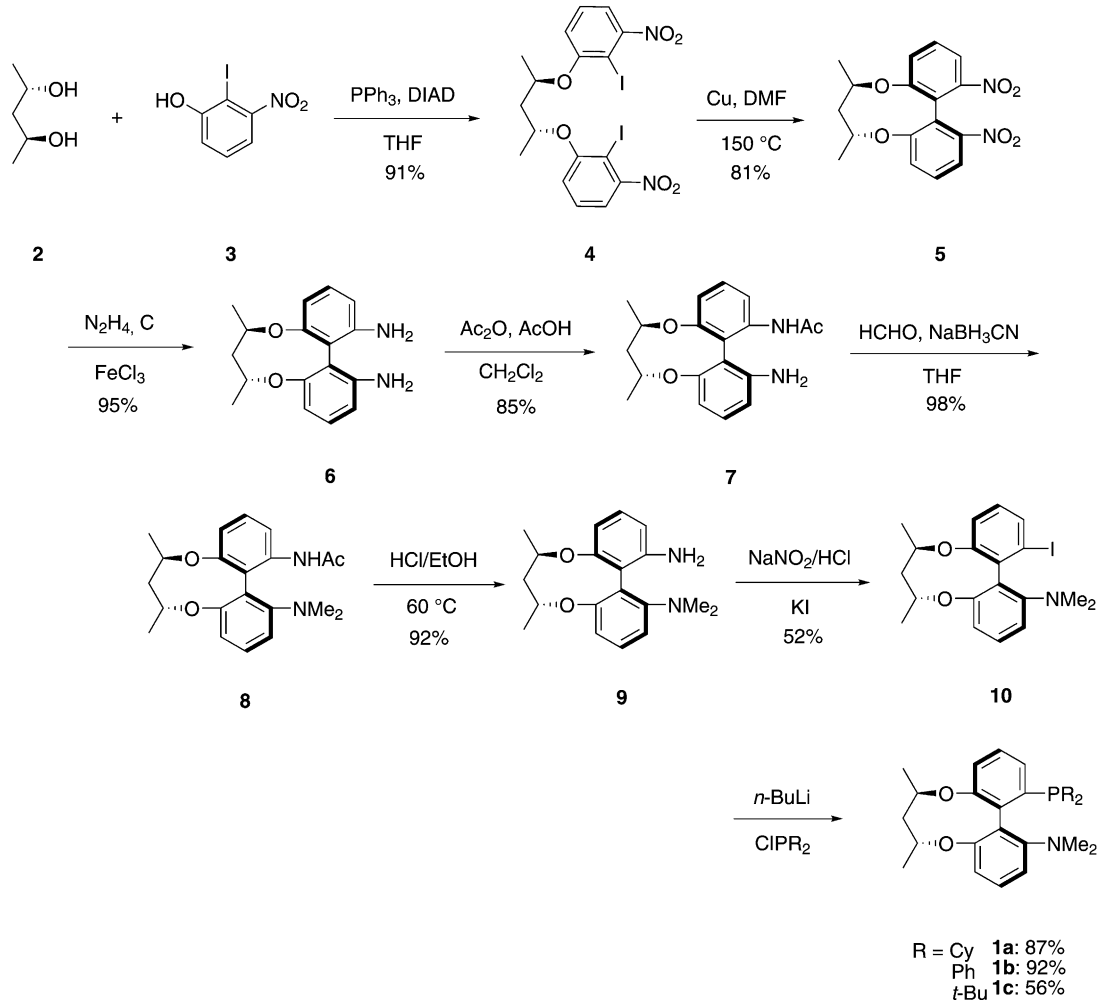
Atropo-molecules, in which the chirality originates from restricted rotation along a chiral axis rather than a stereogenic center, have received considerable attention since they are key structural motifs found in a number of natural products from various origins and have a wide range of biological properties.[1] Relevant atropisomers also prove to be efficient ligands and show remarkable enantioselectivies in a number of asymmetric catalysis processes.[2] Among them, the phosphine ligands of C_2-symmetrical atropisomeric biaryl backbones (1,1′-binaphthyl or biphenyl derivatives) such as BINAP, MeO-BIPHEP (Figure 1) and other biaryl skeletons, have become most notable.[3–5] However, they usually require a resolution step to obtain optically pure C_2-symmetrical chiral ligands from the racemate, which is very tedious and sometimes difficult for further optimization in industry.[6] To tackle these problems, a protocol of central-to-axial chirality transfer was introduced to the ligand development *via* a key step of extremely high diastereomeric aryl-aryl coupling reaction,[7,8] some kind of chiral ligands have been prepared and the tedious resolution procedure was avoided in the synthetic route (Figure 1). These newly developed ligands were found to be highly effective in some asymmetric catalytic reactions and the additional chiral centers on the ligand backbones exerted significant influence on the enantioselectivity and activity of the catalysts for their highly modular nature.[7] In contrast to widespread uses of monodentate and bidentate ligands derived from the binaphthalene scaffold, much less attention has been paid to atropisomeric P,N-ligands of the biphenyl moiety although its steric and electronic properties can be modified in a more flexible manner.[9]

Palladium-catalyzed Suzuki–Miyaura cross-coupling has become one of the most versatile and powerful tools in organic synthesis for the formation of carbon-carbon bonds and construction of biaryl fragments.[10] Recently, some achiral bulky and electron-rich monodentate biarylphosphine ligands,[11] for instance X-Phos,[12] S-Phos[13] and CM-Phos[14] were applied to these kinds of reactions and achieved great success even for the coupling of sterically hindered substrates. In contrast, there was little progress for a long period in the synthesis of enantiomerically enriched biaryls



(*S*)-BINAP (*S*)-MeO-BIPHEMP (S_{ax})-PQPhos

Figure 1. Some chiral atropisomeric C_2-symmetric and chiral bridged biaryl ligands.



Scheme 1. Synthetic route to ligands **1a**, **1b** and **1c**.

by asymmetric catalysis. The main difficulty is the lack of appropriate chiral ligands for fulfilling this target. Due to wide applications of the axially chiral biaryl scaffold[15] and ubiquitous structural motifs in natural products,[1] it is no doubt very urgent to develop asymmetric Suzuki–Miyaura coupling catalysts of high efficacy. Although some advances occurred recently,[16–17] there still remains a huge challenge for chemists to broaden the scope of substrate tolerance and acquire acceptable catalytic activity in this area.

As part of our continuing efforts in designing new ligand scaffolds using diastereoselective synthesis techniques,[7] we herein disclose the synthesis of novel atropisomeric bridged P,N-ligands **1a**, **1b** and **1c** with their applications in the asymmetric Suzuki–Miyaura coupling reaction. To the best of our knowledge, these are the first axially chiral biphenyl P,N-ligands.

The concise synthetic route to atropisomeric bridged P,N-ligands **1a**, **1b** and **1c** is depicted in Scheme 1. The chiral bis(nitrophenol ether) containing a central stereogenic linkage **4** was prepared *via* Mitsunobu reaction with 2-iodo-3-nitrophenol[18] and (2*S*,4*S*)-pentanediol. The double Mitsunobu reaction proceeded smoothly and afforded a single diastereoisomer (2*R*,4*R*)-**4** in 91% yield without any sonication being needed.[8b] A copper-mediated intramolecular Ullmann reaction of chiral diiodide **4** was carried out in DMF and gave the corresponding atropisomeric dinitro compound **5** in 81% yield with extremely high diastereoselectivity (>99% *de*), that is, the diastereoselective differentiation was highly controlled by the chiral bridge for this key Ullmann-type coupling reaction.[19] Subsequent reduction of the nitro groups in the intermediate **5** provided chiral diamine **6** in 95% yield utilizing hydrazine hydrate along with catalytic amount of ferric chloride. Selective protection of one amino group of **6** by acetylation furnished **7** in 85% yield. The *N*-Methylated product **8** was acquired almost quantitatively through reaction of **7** with formaldehyde followed by reduction with cyanoborohydride. Removing the acetyl group *via* hydrolysis of **8** in a mixed solution of hydrochloric acid and alcohol gave chiral monoamino compound **9** in 92% yield. Diazotization of **9** and successive reaction with potassi-

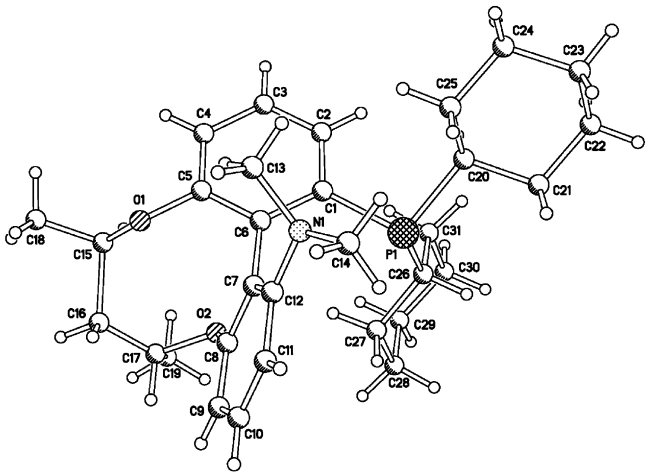


Figure 2. X-ray crystal structure of ligand **1a** (ORTEP drawing).

um iodide yielded **10** as a precursor.[20] Finally, the iodide **10** was readily transformed into the target optically pure P,N-ligands **1a**, **1b** and **1c** in moderate to high yields by treatment with *n*-butyllithium and trapping with the corresponding dialkylphosphine or diarylphosphine chlorides. The different solvent choices for this step reaction must be pointed out. THF was a satisfactory solvent in the synthesis of ligand **1a** and **1b**. However, diethyl ether was needed instead of THF in the synthesis of ligand **1c** for high yield. This is because *in situ* generated aryllithium reacted slowly with di-*tert*-butylchlorophosphine, and better stability of the aryllithium reagent was achieved in ether than in THF.[21]

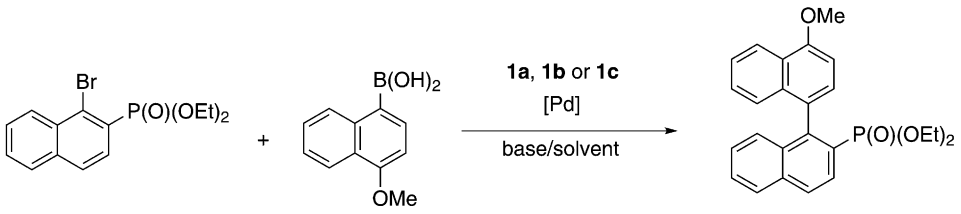
A single crystal X-ray diffraction study revealed ligand **1a** to have the S_{ax}-form axial chirality and (*R*,*R*)-form central chirality on the chiral bridge.[22] The same configurations were also deduced for the analogues **1b** and **1c** (Figure 2).

Two characteristics are noted in this synthetic strategy. First, the chiral linking bridge of the 2,4-pentanediol ether is very simple and just flexible enough for the chirality transfer from central-to-axial chirality in the Ullmann coupling reaction with complete diastereodifferentiation. This avoids a tedious and time-consuming routine resolution step. Besides, no unwanted intermolecular coupling happened. Second, the enantiomerically pure iodide **10** of defined axial chirality allows for easy introduction of different aryl or alkyl substituents of the PR_2 moieties, which opens up a convenient pathway to afford various P,N-ligands.

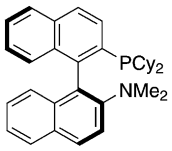
The palladium-catalyzed asymmetric Suzuki–Miyaura coupling between diethyl 1-bromo-2-naphthylphosphonate **11a** and 4-methoxyl-1-naphthaleneboronic acid **12a** was selected as the model reaction to examine the stereo-communication efficiency for our ligands. Preliminary experiments for optimized conditions such as Pd source, base, solvent and temperature were performed and the results are shown in Table 1. The coupling reactions were carried out at 40 °C with ligands **1a**, **1b** and **1c**. Ligand **1a** with an electron-rich cyclohexyl substituent gave higher activity than ligand **1b** as the phenyl counterpart, the reaction system with the latter needed prolongation of the reaction time to 48 h for complete conversion. On the contrary, the enantioselectivities acquired from **1b** were significantly increased under the same reaction conditions in spite of getting different yields (Table 1, entries 1, 2, 4, 5). However, ligand **1c** with a more steric *t*-Bu moiety provided quite lower activities and enantioselectivities in comparison to the two other ligands (Table 1, entries 3, 6). Among the three ligands, **1b** was the best for the enantiodifferentiation. A survey of reaction variables indicated that K_3PO_4 as the base was better than CsF or $Ba(OH)_2$ (Table 1, entries 7–9). THF was superior to toluene, dioxane or DME as the solvent, and use of the former gave a high *ee* value (Table 1, entries 2, 5, 10, 11). $Pd_2(dba)_3$ was preferred to $Pd(OAc)_2$ (Table 1, entries 12–15), a slightly lower yield and *ee* value were obtained when employing the latter instead. It is worth noting that the coupling reaction proceeded smoothly even at room temperature and a full conversion was obtained using **1a** or **1b** as the ligand (Table 1, entries 12–14). Accordingly, a better enantioselection was acquired at lower temperature. In contrast, higher temperature and longer reaction time were needed and lower enantioselectivity was given when KenPhos was used for this reaction (Table 1, entry 16).[16a] This means that ligand **1b** is better than KenPhos in this reaction for achieving much higher catalytic activity and enantioselectivity (82% *vs.* 71% *ee*, Table 1, entries 15 and 16). The chiral ligand was also found to be essentially necessary in the reaction. Otherwise, no target coupling product was formed (Table 1, entry 17). Furthermore, the ligand-less system (the molar ratio of ligand *vs.* metal <1) provided lower yield, but no variation in the enantioselectivity was observed.

After establishing the optimized reaction conditions, we next explored the substrate scope. Some 1-naphthylboronic acids or arylboronic acids of an *ortho*-substituent and substituted 1-bromo-2-naphthylphosphonates were examined in this reaction (Table 2). The results showed the reaction of 1-naphthylboronic acids **12a**–**12c** with **11a** provided better results employing ligand **1b** instead of ligand **1a**, an excellent yield and moderate *ee* were observed from the latter (82% *vs.* 66% *ee*, 68% *vs.* 48% *ee*, 69% *vs.* 50% *ee*, Table 2, entries 1–6). Interestingly, alkyl-substituted phenylboronic acids including those with methyl, ethyl or isopropyl groups (**12d**–**12f**) performed well with ligand **1a**, affording the corresponding coupling products **13d**–**13j** in excellent yields and good *ee* values at room temperature (up to 82% *ee*, entries 8–

Table 1. Optimization experiments with ligands **1a**–**1c**.[a]



11a **12a** (–)-**13a**

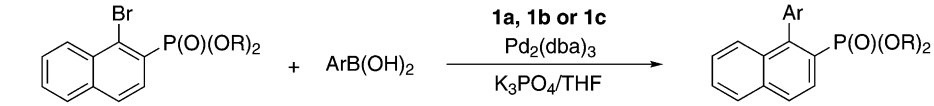
Entry	Ligand	[Pd]	Base	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	$Pd_2(dba)_3$	K_3PO_4	toluene	40	24	98	57
2	**1b**	$Pd_2(dba)_3$	K_3PO_4	toluene	40	24	96	77
3	**1c**	$Pd_2(dba)_3$	K_3PO_4	toluene	40	24	18[d]	23
4	**1a**	$Pd_2(dba)_3$	K_3PO_4	THF	40	24	97	62
5	**1b**	$Pd_2(dba)_3$	K_3PO_4	THF	40	24	96	80
6	**1c**	$Pd_2(dba)_3$	K_3PO_4	THF	40	24	16[d]	n. d.[e]
7	**1b**	$Pd_2(dba)_3$	CsF	toluene	40	24	88	45
8	**1b**	$Pd_2(dba)_3$	CsF	THF	40	24	76	42
9	**1b**	$Pd_2(dba)_3$	$Ba(OH)_2$	toluene	40	24	23	n. d.
10	**1b**	$Pd_2(dba)_3$	K_3PO_4	dioxane	40	24	91	55
11	**1b**	$Pd_2(dba)_3$	K_3PO_4	DME	40	24	89	50
12	**1b**	$Pd(OAc)_2$	K_3PO_4	toluene	r.t.[f]	48	97	79
13	**1b**	$Pd(OAc)_2$	K_3PO_4	THF	r.t.	48	95	81
14	**1a**	$Pd_2(dba)_3$	K_3PO_4	THF	r.t.	48	98	66
15	**1b**	$Pd_2(dba)_3$	K_3PO_4	THF	rt	48	96	82
16[g]		$Pd_2(dba)_3$	K_3PO_4	toluene	40	92	97	71
17		$Pd_2(dba)_3$	K_3PO_4	THF	40	48		n.d.[h]

(*S*)-KenPhos

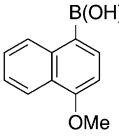
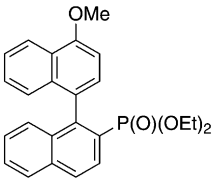
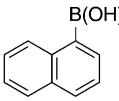
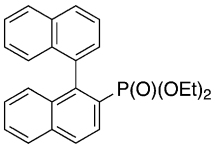
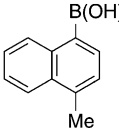
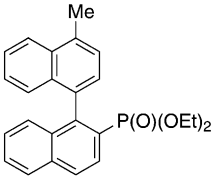
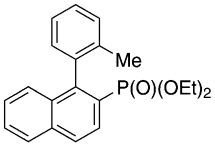
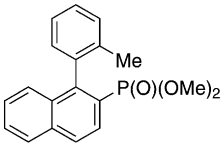
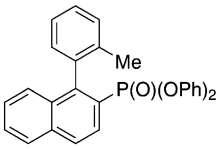
[a] *Reaction conditions:* 1.0 equiv. of **11a**, 2.0 equiv. of **12a**, 2 mol% Pd and 2.4 mol% of **1a**, 4 mol% Pd and 4.8 mol% of **1b** or **1c**, 3.0 equiv. of base.
[b] Yield of isolated product.
[c] The *ee* values were determined by HPLC with a Chialcel AD-H column.
[d] Major dehalogenated product with small amount of unreacted bromide.
[e] Not determined.
[f] Room temperature.
[g] 4 mol% Pd and 4.8 mol% of ligand, for details see ref.[16a]
[h] Major dehalogenated product and no desired coupling product was detected.

22). In contrast, the reaction became less effective when ligand **1b** was applied instead of **1a**. Thus the reaction temperature had to be elevated to 40 °C for an acceptable conversion and this resulted in a decreased yield and a slightly lower *ee* compared to using **1a**. Like the same phenomenon that occurred in the reaction of 1-naphthylboronic acid **12a** with **11a**, the catalyst system with ligand **1c** still showed poor activity using phenylboronic acid **12d** as the substrate (Table 2, entries 3, 10). Major dehalogenated product along with a small amount of unreacted bromide **11a** was recovered. This may be explained as follows: ligand **1c** with a bulky *t*-Bu moiety was sterically too demanding. However, the chiral linking bridge of the 2,4-pentanediol ether limited the rotation range of the chiral axis and this caused the difficulty in forming the active $L_1Pd(0)$ species for the catalysis.[23] The influence of steric hindrance for different substituted substrates **12** on the reaction was preliminarily explored. For *o*-ethylarylboronic acid **12e**, the reaction provided the product in 96% yield and the highest enantioselectivity (82% *ee*, Table 2, entry 15). While a negative effect was presented for **12d** and **12f**. For **12f** with a more hindered *o*-isopropyl group, only 88% yield and 71% *ee* were obtained (Table 2, entry 21). The relationship between the size of the *ortho*-alkyl substituent and the *ee* of the process remains unclear at present. Reaction of diethylphos-

Table 2. Asymmetric Suzuki–Miyaura coupling with ligands **1a**, **1b** or **1c**.[a,b]



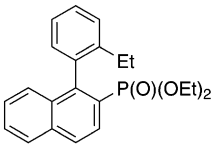
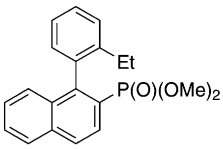
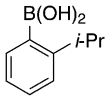
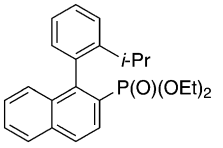
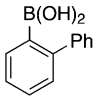
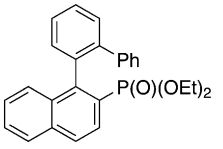
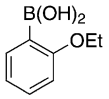
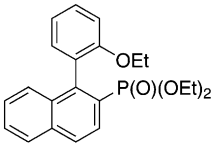
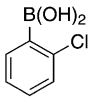
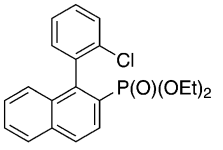
R = Et (**11a**), Me (**11b**), Ph (**11c**) **12** **13**

Entry	Halide	$ArB(OH)_2$	Product	Ligand	Yield [%][c]	*ee* [%][d]
1				**1a**	97	66
2[e]				**1b**	96	82
3				**1c**	16	n.d.[f]
	11a	 **12a**	 (–)-**13a**			
4				**1a**	92[g]	48
5				**1b**	81[g]	68
	11a	 **12b**	 (–)-**13b**			
6				**1a**	88	50
7				**1b**	84	69
	11a	 **12c**	 (–)-**13c**			
8				**1a**	95	80
9				**1b**	76	73
10	**11a**		 (+)-(*R*)-**13d**	**1c**	18[h]	28
11				**1a**	94	78
12				**1b**	73	74
	11b	 **12d**	 (+)-(*R*)-**13e**			
13				**1a**	92	81
14				**1b**	72	72
	11c		 (–)-**13f**			

phoryl or diphenylphosphoryl derivatives **11a** or **11c** with *o*-methyl- or ethylphenylboronic acids gave the corresponding products with 71–82% *ee*s in the presence of ligand **1a** or **1b**. Comparatively, slightly lower yields and *ee*s were obtained employing dimethylphosphoryl-substituted **11b** instead of **11a** or **11c** as the substrate (Table 2, entries 8–20). This suggests that the difference in the phosphoryl substituent has only a small impact on the catalytic activity and stereoselectivity in this reaction.

To gain insight into the broad functional group tolerance of this system, various *ortho*-substituted arylboronic acids with different electronic effects were tested as well. Electron-rich boronic acid **12h** bearing an electron-donating OEt group reacted with **11a** rapidly at room temperature and yielded product **13l** almost quantitatively for both ligands **1a** and **1b**. However, the enantioselectivities decreased to 61% and 55% *ee*s (Table 2, entries 25 and 26). On the contrary, 2-chlorophenylboronic acid **12i**, an electron-de-

Table 2. (Continued)

Entry	Halide	$ArB(OH)_2$	Product	Ligand	Yield [%][c]	*ee* [%][d]
15				**1a**	96	82
16				**1b**	71	78
	11a		(+)-**13g**			
17				**1a**	98	80
18				**1b**	72	75
	11b	**12e**	(+)-**13h**			
19				**1a**	95	82
20				**1b**	70	77
	11c		(–)-**13i**			
21				**1a**	88	71
22				**1b**	66	68
	11a	**12f**	(+)-**13j**			
23				**1a**	81	63
24[i]				**1b**	62	81
	11a	**12g**	(+)-**13k**			
25				**1a**	98	61
26[e]				**1b**	92	55
	11a	**12h**	(+)-**13l**			
27[i]				**1a**	76	60
28[g,i]				**1b**	55	50
	11a	**12i**	(+)-**13m**			

[a] *Reaction conditions:* 1.0 equiv. of **11**, 2.0 equiv. of **12**, 1 mol% of $Pd_2(dba)_3$ and 2.4 mol% of **1a**, 2 mol% of $Pd_2(dba)_3$ and 4.8 mol% of **1b** or **1c**, 3.0 equiv. of K_3PO_4, THF (6 mL mmol^{-1} bromide), room temperature for **1a**, 40 °C for **1b** and **1c**.
[b] The absolute configuration was determined by comparison to literature data.[17e]
[c] Yield of isolated product.
[d] The *ee* values were determined by HPLC with a Chiralcel OD-H or AD-H column.
[e] Carried out at room temperature.
[f] Not determined.
[g] A small amount of inseparable dehalogenated product was observed.
[h] Major dehalogenated product with small amount of unreacted bromide.
[i] 4 mol% catalyst was added in 2 portions; see Supporting Information for details.

ficient counterpart, displayed reduced reactivity and the corresponding reaction gave the product in 76% or 55% yield and 60% or 50% *ee* (Table 2, entries 27 and 28). This suggests that the yield of this kind of reaction is sensitive to electronic effects of the substrate. Arylboronic acids with an electron-withdraw-

ing group were found to have low activity during the course of reaction, which resulted in a certain amount of dehalogenated product formation, so decreasing the yield of the coupling product. Whereas arylboronic acids with an electron-donating group are more stable and it is beneficial to the increase of the reactivity and yield. An interesting phenomenon was observed when arylboronic acid **12g** with an *o*-phenyl substituent was used as the substrate. The reaction afforded a higher *ee* using ligand **1b** instead of **1a** (63% *vs.* 81% *ee*, Table 2, entries 23 and 24). A similar situation also existed in the reaction of naphthaleneboronic acids **12a–12c** with **11a** (Table 2, entries 1–6). The reason for higher enantioselectivty resulting from **1b** is ambiguous. As a hypothesis it was assumed that the conjugated groups were stabilized by one or two cooperative, π-stacking interactions with diphenylphoshinyl group of ligand **1a**.

In summary, a highly efficient strategy was successfully established for the preparation of new kind of atropisomeric bridged P,N-ligands *via* the complete diastereoselective coupling reaction. These newly developed ligands were found to be effective in the palladium-catalyzed asymmetric Suzuki–Miyaura coupling reaction. Up to 82% *ee* was achieved for the enantioselective synthesis of axially chiral biarylphosphonates. Further optimization of this fine-tunable ligand structure and their applications in asymmetric catalysis are currently being undertaken in our laboratory.

Experimental Section

General Procedure for the Asymmetric Suzuki–Miyaura Coupling

An oven-dried flask was charged with $Pd_2(dba)_3$ (1 mol% for **1a**, 2 mol% for **1b** or **1c**, L:Pd = 1.2:1), aryl bromide (0.5 mmol, 1.0 equiv.), arylboronic acid (1.0 mmol, 2.0 equiv.), and K_3PO_4 (3 equiv.). The flask was capped with a rubber septum and twice evacuated and backfilled with N_2. THF (6 mL per mmol aryl bromide) was injected into the flask and the mixture was stirred at the indicated temperature (room temperature or 40 °C) for 24–48 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and water, extracted and the combined organic layer was dried over Na_2SO_4 then concentrated. The obtained crude product was purified finally by flash chromatography on silica gel for analysis. For experimental procedures, characterization of the prepared new compounds, copies of the NMR spectra, chiral HPLC spectra of the asymmetric Suzuki–Miyaura coupling products, see the Supporting Information.

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