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Efficient synthesis of *P*-chiral biaryl phosphonates by stereoselective intramolecular cyclization†

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A series of *P*-chiral biaryl phosphonates were efficiently synthesized from diaryl 2-bromo arylphosphonates in high yields (up to 92%) and good enantioselectivities (up to 88% ee) through a palladium-catalyzed asymmetric cyclization with a novel *P*-chiral biaryl monophosphorus ligand. The *P*-chiral biaryl phosphonate can be rapidly transformed to both antipodes of a *P*-chiral dialkyl biaryl monophosphorus structure. The method provides a convenient access to various *P*-chiral biaryl monophosphines.

Since Knowles first introduced *P*-chiral phosphines CAMP and DIPAMP for rhodium-catalyzed asymmetric hydrogenation almost half a century ago,¹ *P*-chiral phosphorus ligands have played significant roles in the rapid development of the asymmetric catalysis area.² Efficient construction of *P*-chiral phosphorus compounds has become a hot subject of research.³ Various efficient methods were developed including chemical resolutions,⁴ asymmetric synthesis by using chiral auxiliaries or reagents,⁵ and recently catalytic asymmetric methods.⁶ Because of the increasing applications of *P*-chiral biaryl monophosphorus ligands in organic synthesis,⁷ we propose to develop a general and efficient synthetic method for *P*-chiral biaryl monophosphorus ligands from a *P*-chiral biaryl phosphonate **A** through two consecutive stereospecific substitutions at the phosphorus center (Fig. 1). The challenge is whether the *P*-chiral biaryl phosphonate **A** can be efficiently synthesized from the readily accessible *ortho*-bromo arylphosphonate **B** through an enantioselective palladium-catalyzed desymmetric

intramolecular cyclization.⁸ Herein we disclose our study on this asymmetric cyclization and its transformations toward *P*-chiral biaryl monophosphorus ligands.

We chose diphenyl(2-bromophenyl)phosphonate (**1a**) as the substrate for study. As shown in Table 1, the palladium-catalyzed asymmetric cyclization of **1a** proceeded smoothly at 80 °C in toluene with KOAc as the base to afford the cyclization product **1b** in excellent yields in the presence of a *P*-chiral biaryl monophosphorus ligand. Among the several *P*-chiral biaryl monophosphorus ligands employed (entries 1–5),⁹ the newly developed ligand **L3** with a tetrahydrobenzodifuran moiety provided an excellent yield (93%) and a good enantioselectivity (77% ee) with potassium acetate as the base. Apparently, the substituents on the low aryl ring of the *P*-chiral biaryl ligands exert significant influence on the enantioselectivity. Moderate ees were achieved with acyclic or cyclic alkoxy moieties such as methoxy substituents, furans and dioxolanes (entries 1, 3 and 4). In contrast, AntPhos (**L5**) proved to be ineffective (entry 5). Ligand **L2** with a methyl group at the 2 position of the oxophosphole ring also provided a diminished ee (entry 2). When **L3** was employed for further optimization, a dramatic base effect was observed. A more hindered base KOPiv afforded an inferior yield and ee value (entry 6). Meanwhile, 1-AdCOOK could provide comparable enantioselectivity to KOAc but with lower yield (entry 7). When PhCOOK was employed as a base, a higher ee value (88%) was achieved, albeit with a low yield (34%, entry 8). The low yield could be largely due to its relatively weak basicity. We thus employed PhCH₂COOK as the base. Although the cyclization yield was comparable to that with KOAc, its enantioselectivity was slightly inferior (entry 9). With Ph₂CHCOOK as the base, we obtained a similar yield to that with KOAc, but with a slightly better ee value (entry 10). When the reaction temperature was reduced to 70 °C, the ee value of **1b** was improved to 82% (entry 11). Change of the solvent to cyclohexane, 1,4-dioxane, THF, and 1,2-dichloroethane (DCE) did not enhance the enantioselectivity (entries



Fig. 1 A new strategy for the synthesis of *P*-chiral biaryl monophosphorus ligands.

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Table 1 Intramolecular asymmetric cyclization of diphenyl(*ortho*-bromophenyl)phosphonate (**1a**)

Entries ^a	L*	Base	Solvent	T (°C)	Yield ^b (%)	% ee ^c
1	L1	KOAc	Toluene	80	91	71
2	L2	KOAc	Toluene	80	91	16
3	L3	KOAc	Toluene	80	93	77
4	L4	KOAc	Toluene	80	93	66
5	L5	KOAc	Toluene	80	81	1
6	L3	KOPiv	Toluene	80	70	70
7	L3	1-AdCOOK	Toluene	80	76	77
8	L3	PhCOOK	Toluene	80	34	83
9	L3	PhCH ₂ COOK	Toluene	80	94	75
10	L3	Ph ₂ CHCOOK	Toluene	80	93	78
11	L3	Ph ₂ CHCOOK	Toluene	70	70	82
12	L3	Ph ₂ CHCOOK	CyHex	70	88	76
13	L3	Ph ₂ CHCOOK	Dioxane	70	26	37
14	L3	Ph ₂ CHCOOK	THF	70	19	74
15	L3	Ph ₂ CHCOOK	DCE	70	97	74
16 ^d	L3	Ph ₂ CHCOOK	Toluene	70	83	88

^a Unless otherwise specified, the reactions were performed at the designated reaction temperature in organic solvent (1 mL) with aryl bromide (0.2 mmol) under nitrogen for 24 h in the presence of Pd(OAc)₂ (5 mol%), L* (6 mol%), and base (0.3 mmol), the absolute configuration of **1b** was assigned by analogy according to the X-ray crystal structure of **2f**. ^b Isolated yield. ^c ee values were determined by chiral HPLC on a chiralcel AD-H column. ^d Pd(OAc)₂ (4 mol%), L3 (8 mol%).

12–15). When the mole ratio of Pd/L3 increased from 1/1.2 to 1/2 (4 mol% Pd), a better ee value (88%) was achieved along with an acceptable yield (entry 16). Other bases were also tested, but no further improvement of the ee value was achieved.¹⁰

We then investigated the substrate scope of this asymmetric cyclization under optimized conditions (Table 2). Thus, a series of substituted diphenyl *ortho*-bromo phenylphosphonates (**1b**, **e**, **h**, **c**) were successfully cyclized to provide the corresponding *P*-chiral phosphonates in high yields and good enantioselectivities with L3 as the ligand. Substituents such as methyl, methoxy, and fluoro groups at the *meta*- or *para*-position were well tolerated. A substrate with a methoxy substituent adjacent to the bromine atom **1k** provided the corresponding cyclization product **2k** in only 27% ee and 52% yield. However, an improved ee (58%) value was achieved when L6 was employed as the ligand. In addition, various di(substituted aryl)*ortho*-bromo phenylphosphonates were also applicable to provide the corresponding cyclization products (**2d**, **2f–g**, **2j**,

Table 2 Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization I^a

2b	2c	2d
83% yield 84% ee	61% yield 87% ee	82% yield 83% ee
2e	2f	2g
88% yield 81% ee	81% yield 87% ee	85% yield 87% ee
2h	2i	2j
85% yield 88% ee	17% yield 78% ee	92% yield 81% ee
2k^b	2l	2m
49% yield 58% ee	84% yield 75% ee	92% yield 74% ee

^a Unless otherwise specified, the reactions were performed in toluene (1 mL) at 70 °C under nitrogen for 24 h with aryl bromide (0.2 mmol), Pd(OAc)₂ (4 mol%), L3 (8 mol%), and Ph₂CHCOOK (0.3 mmol); isolated yields; ee values were determined by chiral HPLC. The absolute configuration of **2f** was determined by X-ray crystallography, others were assigned by analogy. ^b L6 as a ligand.

2l–2m) in good yields and enantioselectivity. Di(*ortho*-methoxyphenyl)*ortho*-bromo phenylphosphonate (**1i**) also provided a decent ee value (78%) albeit with a low yield of **2i**. The absolute configuration of **2f** was determined as R by X-ray crystallographic analysis.¹¹

Table 3 Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization II^a

	L1: 93% yield, 21% ee L2: 90% yield, 20% ee L3: 85% yield, 30% ee L5: 94% yield, 77% ee L6: 83% yield, 88% ee	
	88% yield 87% ee	
	65% yield 76% ee	

^a Unless otherwise specified, the reactions were performed for 24 h under nitrogen at 70 °C in toluene (1 mL) with naphthyl bromide (0.2 mmol), Pd(OAc)₂ (5 mol%), L6 (6 mol%), and KOAc (0.3 mmol); isolated yields; ee values were determined by chiral HPLC; the absolute configurations were assigned by analogy.

Interestingly, when diphenyl (1-bromo-2-naphthyl)phosphonate (**1n**) was employed for cyclization under similar reaction conditions, the cyclization product **2n** was formed in only 30% ee and in 85% yield. In order to obtain a better enantioselectivity, we further screened the *P*-chiral biaryl monophosphorus ligands in our laboratory. As can be seen in Table 3, ligands L1–3 all provided very poor enantioselectivities. To our surprise, AntPhos (L5) formed the cyclization product in 77% ee. L6 with a methyl substituent on the oxophosphole ring deriving from L5 afforded the cyclization product in 88% ee and 83% yield. It was thus chosen as the ligand for this series of substrates. By using these conditions, various di(substituted-aryl) (1-bromo-2-naphthyl)phosphonates (**1o–r**) were also subjected to the cyclization and the corresponding cyclization products (**2o–r**) were formed in good yields and high enantioselectivities. The di(*para*-methoxy)phosphonate substrate **1p** and di(1-naphthyl)phosphonate substrate **1q** afforded the corresponding products **2p** and **2q** in slightly lower ee values, respectively.

The *P*-chiral phosphonates **2a–q** can be envisioned as useful precursors for a variety of *P*-chiral biaryl phosphorus ligands. Because both aryloxy substituents of the phosphonate can be displaced stereospecifically by different alkyl lithium or Grignard reagents sequentially, both antipodes of a *P*-chiral biaryl structure could be prepared from a single *P*-chiral phosphonate product. In order to demonstrate this utility (Scheme 1), the *P*-chiral biaryl phosphonate **2a** was treated first with isopropyllithium in the presence of Et₂AlCl in the presence of Et₂AlCl to form isopropyl substituted product **3** without erosion of enantioselectivity. Subsequent treatment of **3** with methyllithium stereospecifically provided *P*-chiral dialkyl biarylphosphine

**Scheme 1** Stereospecific transformation of *P*-chiral phosphonate **2a** to *P*-chiral biaryl phosphine oxides **4** and *ent*-**4**.

oxide **4**.¹² Alternatively, treatment of **2a** (80% ee) with methyl-lithium and isopropyllithium sequentially provided *ent*-**4** in an unoptimized yield with light erosion of the ee value (73% ee). Stereospecific reduction of **4** and *ent*-**4** with a reported procedure¹³ could provide both antipodes of a *P*-chiral dialkyl biaryl phosphine, respectively.

In summary, we have developed an efficient Pd-catalyzed desymmetric intramolecular cyclization of diaryl *ortho*-bromo aryl phosphonates that have led to a series of *P*-chiral biaryl phosphonates in high yields (up to 92%) and good enantioselectivities (up to 88% ee) under very mild conditions. The *P*-chiral biaryl phosphonates have been demonstrated as excellent precursors to both antipodes of *P*-chiral dialkyl biaryl monophosphines. This method has provided convenient access to various *P*-chiral biaryl monophosphine ligands, which should have increasing applications in the area of asymmetric catalysis.

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