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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

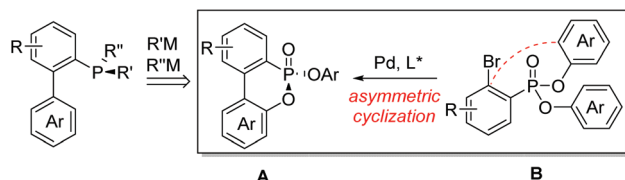


Fig. 1 A new strategy for the synthesis of *P*-chiral biaryl monophosphorus ligands.

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

Reaction scheme for Table 1: Intramolecular asymmetric cyclization of diphenyl(*ortho*-bromophenyl)phosphonate (**1a**) to form product **1b**. Reagents: Pd(OAc)₂/L*, Base, Toluene.

Chemical structures of ligands L1-L6 are shown below the reaction scheme:

- L1: R = H, L2: R = Me
- L3: R = H
- L4: R = Me
- L5: R = H
- L6: R = Me

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

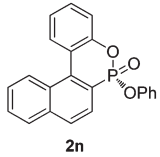
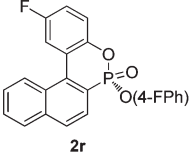
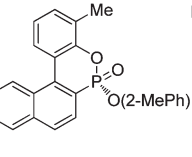
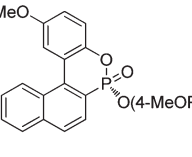
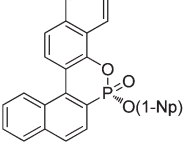
Reaction scheme for Table 2: Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization I. Reagents: Pd(OAc)₂/L3, Ph₂CHCOOK, Toluene, 70 °C.

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

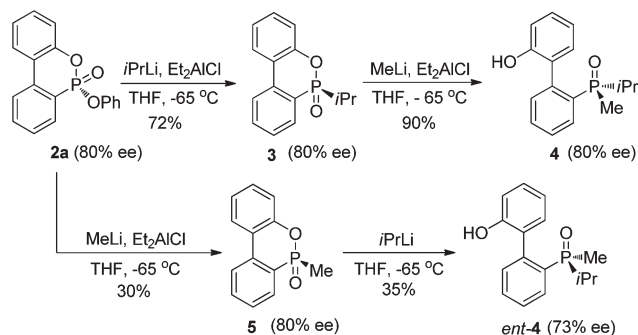
Table 3 Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization II^a

 2n	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	 2r
 2o		 2p
88% yield 87% ee		62% yield 75% ee
		 2q
		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 isopropylolithium 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 isopropylolithium 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.

Acknowledgements

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