

## RESEARCH ARTICLE

View Article Online  
View Journal | View IssueCite this: *Org. Chem. Front.*, 2015, 2, 1342Received 30th April 2015,  
Accepted 1st August 2015

DOI: 10.1039/c5qo00142k

rsc.li/frontiers-organic

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,<sup>1</sup> *P*-chiral phosphorus ligands have played significant roles in the rapid development of the asymmetric catalysis area.<sup>2</sup> Efficient construction of *P*-chiral phosphorus compounds has become a hot subject of research.<sup>3</sup> Various efficient methods were developed including chemical resolutions,<sup>4</sup> asymmetric synthesis by using chiral auxiliaries or reagents,<sup>5</sup> and recently catalytic asymmetric methods.<sup>6</sup> Because of the increasing applications of *P*-chiral biaryl monophosphorus ligands in organic synthesis,<sup>7</sup> 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.<sup>8</sup> 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),<sup>9</sup> 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 PhCH<sub>2</sub>COOK as the base. Although the cyclization yield was comparable to that with KOAc, its enantioselectivity was slightly inferior (entry 9). With Ph<sub>2</sub>CHCOOK 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

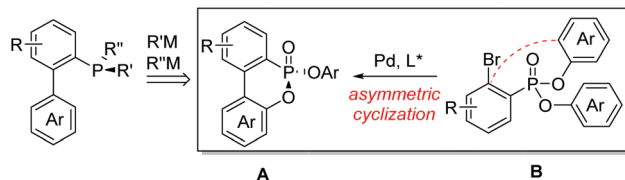
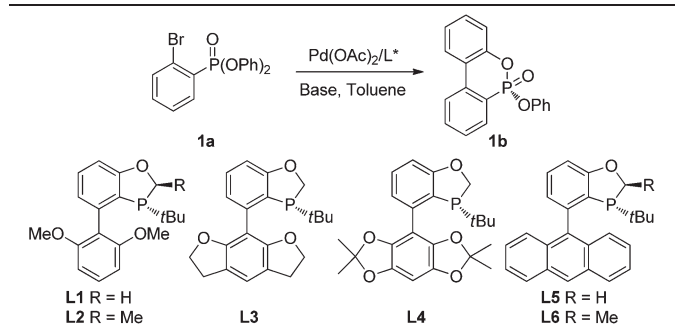


Fig. 1 A new strategy for the synthesis of *P*-chiral biaryl monophosphorus ligands.

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† Electronic supplementary information (ESI) available: Detailed procedures of cross-coupling reactions, characterization data, and spectra. CCDC 1062715. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00142k

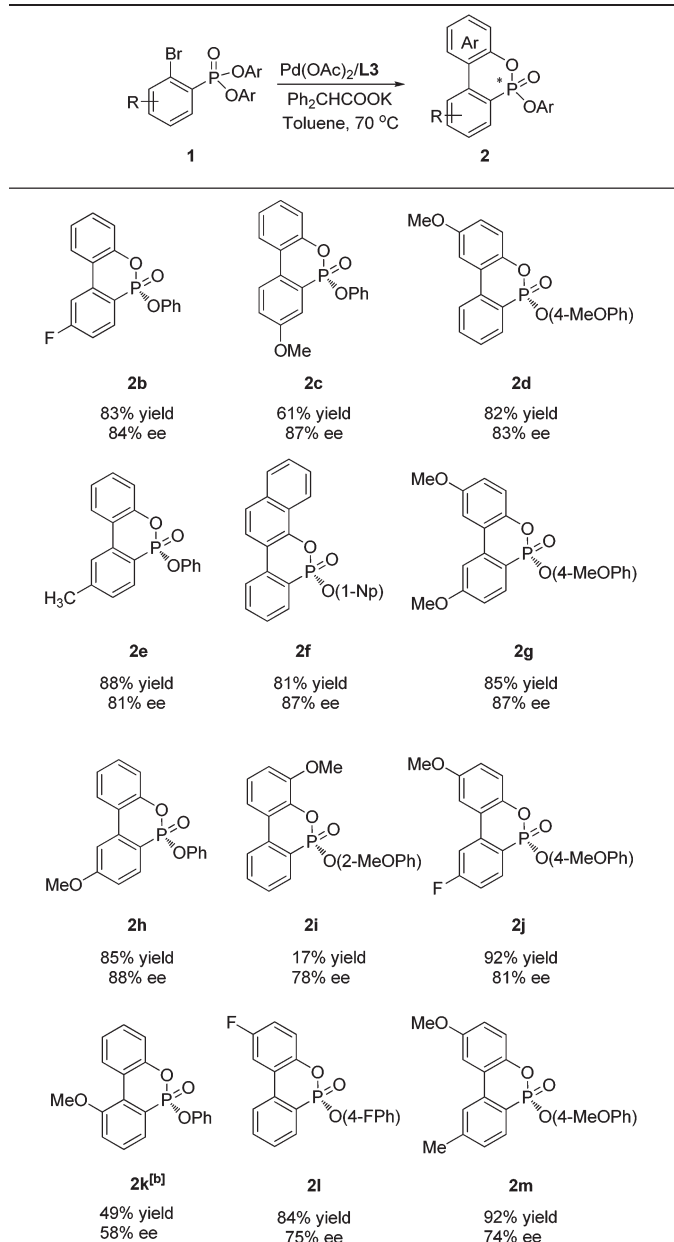
**Table 1** Intramolecular asymmetric cyclization of diphenyl(*ortho*-bromophenyl)phosphonate (**1a**)

| Entries <sup>a</sup> | L* | Base                   | Solvent | T (°C) | Yield <sup>b</sup> (%) | % ee <sup>c</sup> |
|----------------------|----|------------------------|---------|--------|------------------------|-------------------|
| 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 <sub>2</sub> COOK | Toluene | 80     | 94                     | 75                |
| 10                   | L3 | Ph <sub>2</sub> CHCOOK | Toluene | 80     | 93                     | 78                |
| 11                   | L3 | Ph <sub>2</sub> CHCOOK | Toluene | 70     | 70                     | 82                |
| 12                   | L3 | Ph <sub>2</sub> CHCOOK | CyHex   | 70     | 88                     | 76                |
| 13                   | L3 | Ph <sub>2</sub> CHCOOK | Dioxane | 70     | 26                     | 37                |
| 14                   | L3 | Ph <sub>2</sub> CHCOOK | THF     | 70     | 19                     | 74                |
| 15                   | L3 | Ph <sub>2</sub> CHCOOK | DCE     | 70     | 97                     | 74                |
| 16 <sup>d</sup>      | L3 | Ph <sub>2</sub> CHCOOK | Toluene | 70     | 83                     | 88                |

<sup>a</sup> 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)<sub>2</sub> (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**. <sup>b</sup> Isolated yield. <sup>c</sup> ee values were determined by chiral HPLC on a chiralcel AD-H column. <sup>d</sup> Pd(OAc)<sub>2</sub> (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.<sup>10</sup>

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<sup>11</sup>

<sup>a</sup> 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)<sub>2</sub> (4 mol%), L3 (8 mol%), and Ph<sub>2</sub>CHCOOK (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. <sup>b</sup> 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.<sup>11</sup>

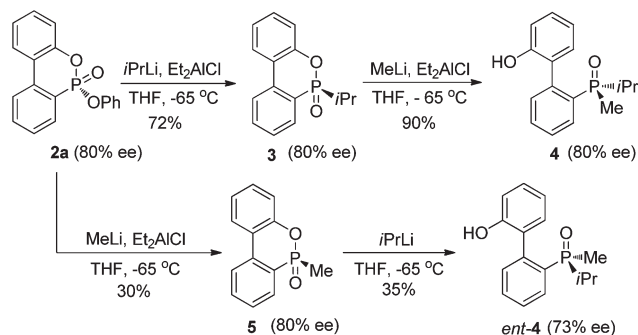
**Table 3** Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization II<sup>a</sup>

|                     |                                                                                                                           |                     |
|---------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------|
|                     | L1: 93% yield, 21% ee<br>L2: 90% yield, 20% ee<br>L3: 85% yield, 30% ee<br>L5: 94% yield, 77% ee<br>L6: 83% yield, 88% ee |                     |
|                     |                                                                                                                           |                     |
|                     | 64% yield<br>87% ee                                                                                                       |                     |
| 88% yield<br>87% ee | 62% yield<br>75% ee                                                                                                       | 65% yield<br>76% ee |

<sup>a</sup> 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)<sub>2</sub> (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 Et<sub>2</sub>AlCl 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**.<sup>12</sup> 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 procedure<sup>13</sup> 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

We are grateful to the NSFC (21432007, 21272254), STCSM (13J1410900), the “Thousand Plan” Youth program.

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