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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.

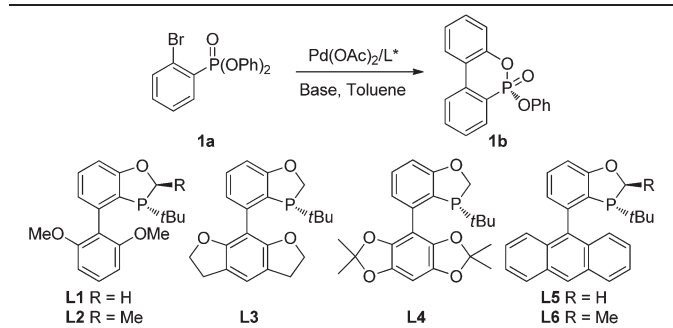
We chose diphenyl(2-bromophenyl)phosphonate (**1a**) as the substrate for study. As shown in Table 1, the palladium-catalyzed asymmetric cyclization of **1a** proceeded smoothly at 80 °C in toluene with KOAc as the base to afford the cyclization product **1b** in excellent yields in the presence of a *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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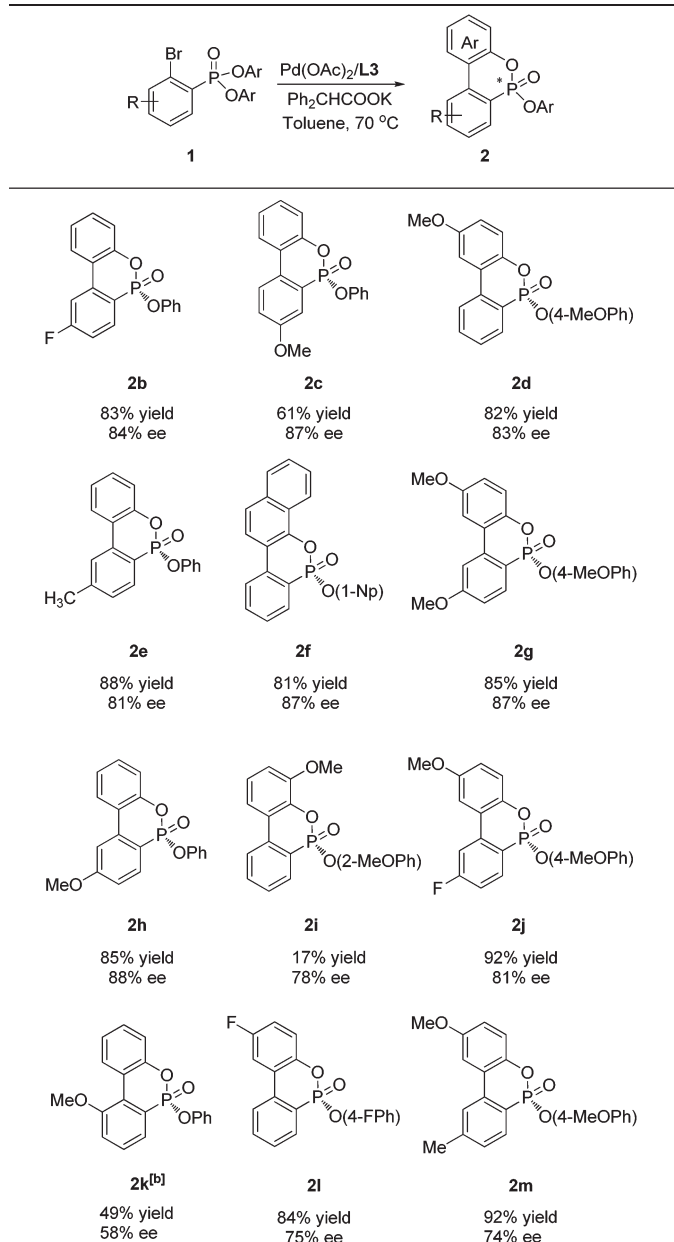
Table 1 Intramolecular asymmetric cyclization of diphenyl(*ortho*-bromophenyl)phosphonate (**1a**)

| 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

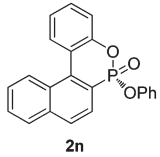
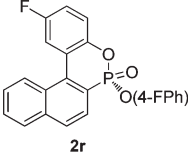
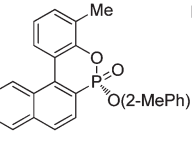
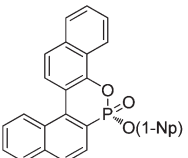
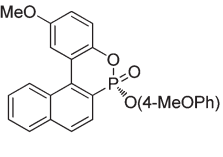
We then investigated the substrate scope of this asymmetric cyclization under optimized conditions (Table 2). Thus, a series of substituted diphenyl *ortho*-bromo phenylphosphonates (**1b**, **e**, **h**, **c**) were successfully cyclized to provide the corresponding *P*-chiral phosphonates in high yields 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^{1a}

^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 |
|  | | |
| 62% yield 75% 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.

Acknowledgements

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