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

Guangqing Xu, Minghong Li, Shouliang Wang and Wenjun Tang*

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.

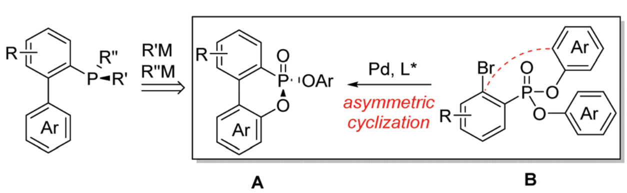

Fig. 1 A new strategy for the synthesis of *P*-chiral biaryl monophosphorus ligands.

State Key Laboratory of Bio-Organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, 345 Ling Ling Rd, Shanghai 200032, P. R. China. E-mail: tangwenjun@sioc.ac.cn

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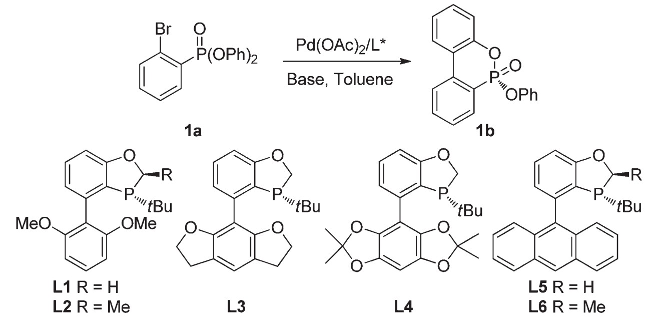
We chose diphenyl(2-bromophenyl)phosphonate (**1a**) as the substrate for study. As shown in Table 1, the palladium-catalyzed asymmetric cyclization of **1a** proceeded smoothly at 80 °C in toluene with KOAc as the base to afford the cyclization product **1b** in excellent yields in the presence of a *P*-chiral 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 $PhCH_2COOK$ as the base. Although the cyclization yield was comparable to that with KOAc, its enantioselectivity was slightly inferior (entry 9). With $Ph_2CHCOOK$ 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

Table 1 Intramolecular asymmetric cyclization of diphenyl(2-bromophenyl)phosphonate (**1a**)



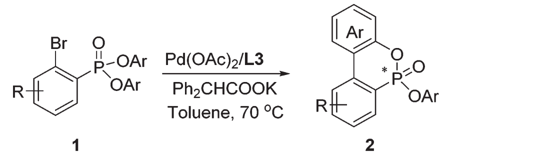
Entries[a]	L*	Base	Solvent	T (°C)	Yield[b] (%)	% ee[c]
1	**L1**	KOAc	Toluene	80	91	71
2	**L2**	KOAc	Toluene	80	91	16
3	**L3**	KOAc	Toluene	80	93	77
4	**L4**	KOAc	Toluene	80	93	66
5	**L5**	KOAc	Toluene	80	81	1
6	**L3**	KOPiv	Toluene	80	70	70
7	**L3**	1-AdCOOK	Toluene	80	76	77
8	**L3**	PhCOOK	Toluene	80	34	83
9	**L3**	$PhCH_2COOK$	Toluene	80	94	75
10	**L3**	$Ph_2CHCOOK$	Toluene	80	93	78
11	**L3**	$Ph_2CHCOOK$	Toluene	70	70	82
12	**L3**	$Ph_2CHCOOK$	CyHex	70	88	76
13	**L3**	$Ph_2CHCOOK$	Dioxane	70	26	37
14	**L3**	$Ph_2CHCOOK$	THF	70	19	74
15	**L3**	$Ph_2CHCOOK$	DCE	70	97	74
16[d]	**L3**	$Ph_2CHCOOK$	Toluene	70	83	88

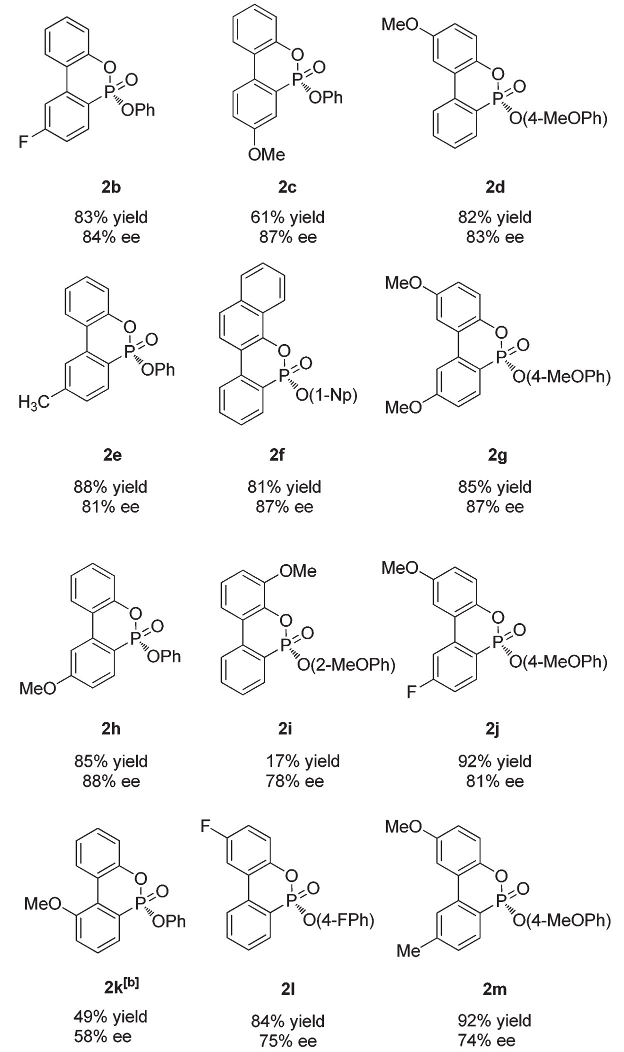
[a] Unless otherwise specified, the reactions were performed at the designated reaction temperature in organic solvent (1 mL) with aryl bromide (0.2 mmol) under nitrogen for 24 h in the presence of $Pd(OAc)_2$ (5 mol%), **L*** (6 mol%), and base (0.3 mmol), the absolute configuration of **1b** was assigned 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**, **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]

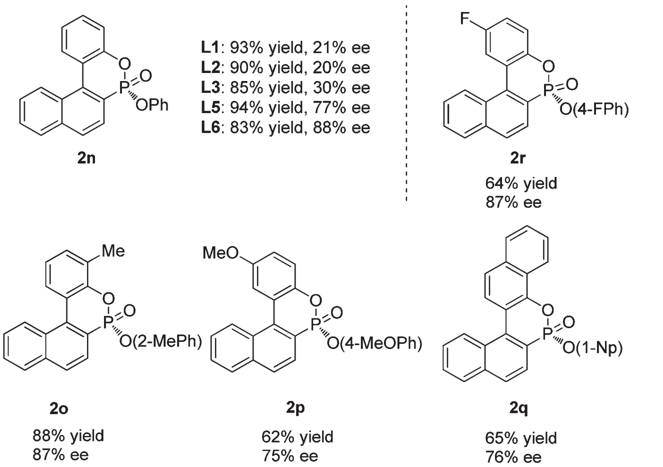
Table 2 Synthesis of *P*-chiral biaryl phosphonates by asymmetric cyclization I[a]



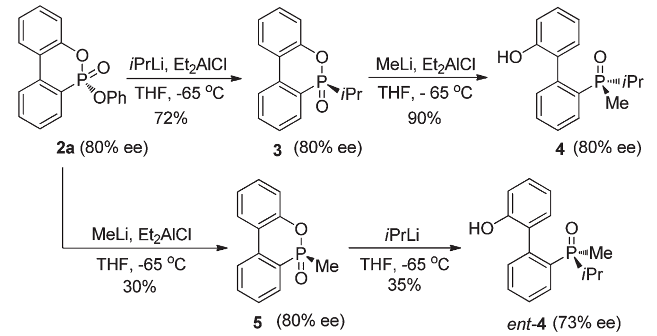


[a] Unless otherwise specified, the reactions were performed in toluene (1 mL) at 70 °C under nitrogen for 24 h with aryl bromide (0.2 mmol), $Pd(OAc)_2$ (4 mol%), **L3** (8 mol%), and $Ph_2CHCOOK$ (0.3 mmol); isolated yields; ee values were determined by chiral HPLC. The absolute configuration of **2f** was determined by X-ray crystallography, others were assigned by analogy. [b] **L6** as a ligand.

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



[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.



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

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_2AlCl to form isopropyl substituted product **3** without erosion of enantioselectivity. Subsequent treatment of **3** with methyllithium stereospecifically provided *P*-chiral dialkyl biarylphosphine oxide **4**.[12] Alternatively, treatment of **2a** (80% ee) with methyllithium 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[13] 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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