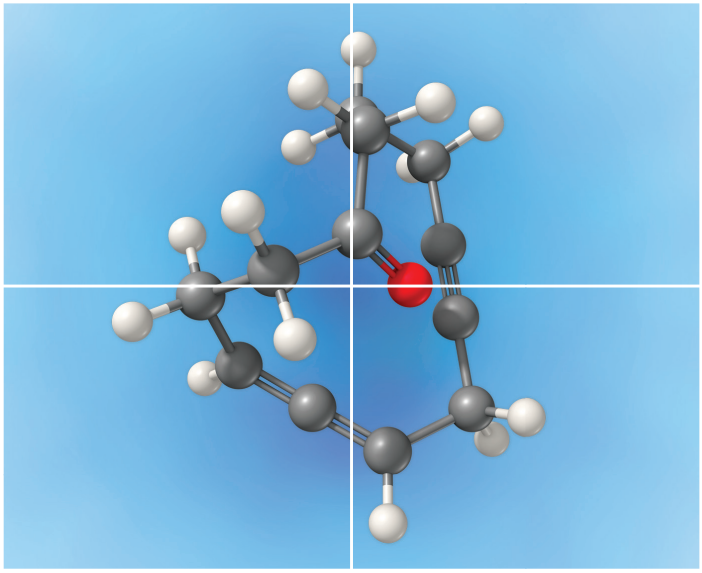
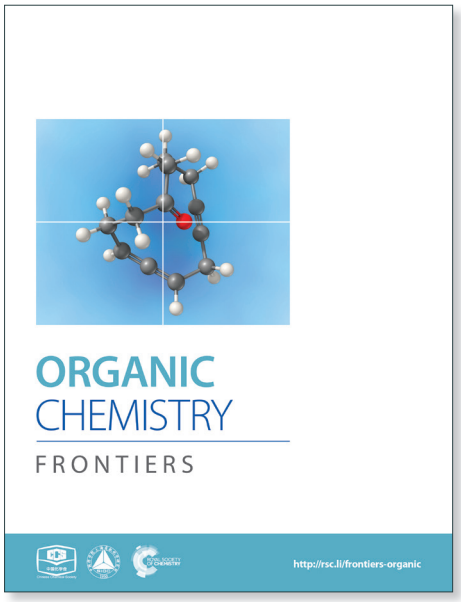
ORGANIC CHEMISTRY

FRONTIERS



Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Organic Chemistry Frontiers

RSCPublishing

COMMUNICATION

Efficient Synthesis of P-Chiral Biaryl Phosphonates by Stereoselective Intramolecular Cyclization

Cite this: DOI: 10.1039/x0xx00000x

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

Received 00th
Accepted 00th

DOI: /

www.rsc.org/

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 for the rapid development of asymmetric catalytic area.[2] Efficient construction of P-chiral phosphorus compounds have 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 (Figure 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.

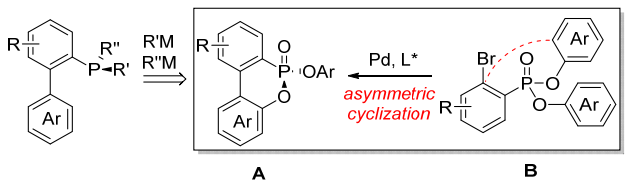


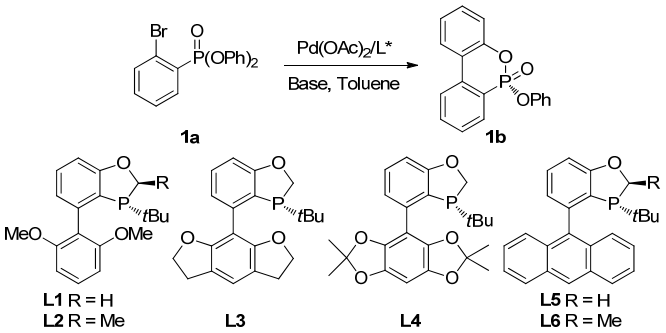
Figure 1. A new strategy for the synthesis of P-chiral biaryl monophosphorus ligands

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 monophosphorus ligand. Among 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 all achieved with acyclic or cyclic alkoxy moieties such as methoxy substituents, furans and dioxolanes (entries 1,3-4). In contrast, AntPhos (**L5**) proved to be ineffective (entry 5). Ligand **L2** with a methyl group at 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 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 relative 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 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-dichlorethane (DCE) did not enhance the enantioselectivity (entries 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 substrates scope of this asymmetric cyclization under the optimized conditions (Table 2). Thus, a series of substituted diphenyl *ortho*-bromo phenylphosphonates (1**b**,**e**,**h**,**c**) were successfully cyclized to provide the corresponding P-chrial phosphonates in high yields and good

enantioselectivites with **L3** as the ligand. Substituents such as methyl, methoxy, fluoro groups at *meta* or *para*-positions 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 1. Intramolecular asymmetric cyclization of diphenyl (2-bromophenyl)phosphonate (**1a**)

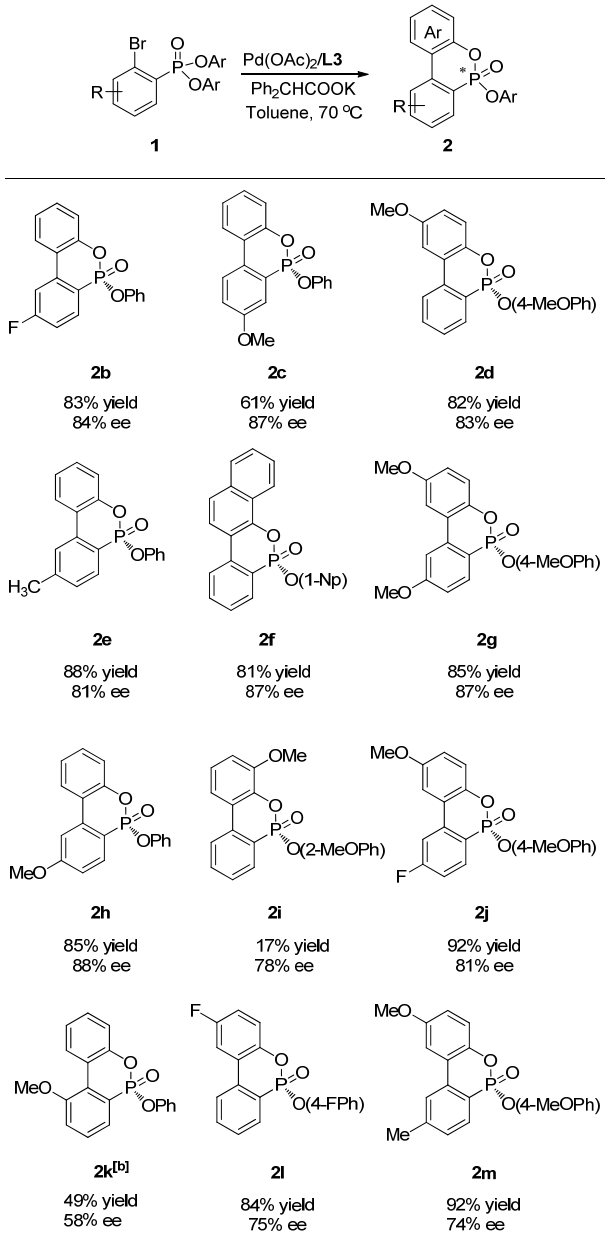


Entries[a]	L*	Base	Solvent	T (°C)	Yield (%)[b]	Ee%[c]
1	**L1**	KOAc	Toluene	80	91	71
2	**L2**	KOAc	Toluene	80	91	16
3	**L3**	KOAc	Toluene	80	93	77
4	**L4**	KOAc	Toluene	80	93	66
5	**L5**	KOAc	Toluene	80	81	1
6	**L3**	KOPiv	Toluene	80	70	70
7	**L3**	1-AdCOOK	Toluene	80	76	77
8	**L3**	PhCOOK	Toluene	80	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 %).

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 substitutent on 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(substitutedaryl) 1-bromo-2-naphthyl)phosphonate (**1o-r)** were also subjected for 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-naphathyl) phosphonate substrate **1q** afforded the corresponding products **2p** and **2q** in slightly lower ee values, respectively.

Table 2. Synthesis of P-Chiral biaryl phosphonates by asymmetric cyclization I[a]

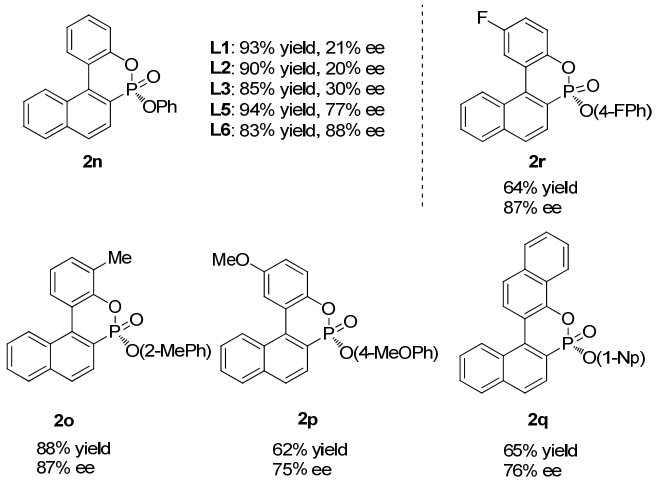


[a] Unless otherwise specified, the reactions were performed in toluene (1 mL) at 70 °C under nitrogen for 24 h with aryl bromide (0.2 mmol), $Pd(OAc)_2$ (4 mol %), **L3** (8 mol %), and $Ph_2CHCOOK$ (0.3 mmol); isolated yields; ee values were determined by chiral HPLC. The

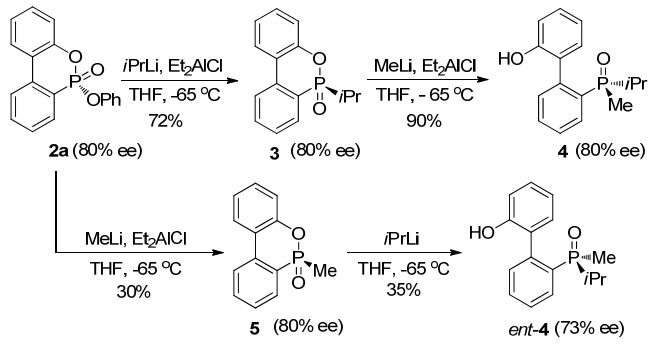
absolute configuration of **2f** was determined by X-ray crystallography, others were assigned by analogy. [b] **L6** as ligand.

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 2), 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 啊 light erosion of 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.

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

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 a 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.

Notes and references

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

† Electronic Supplementary Information (ESI) available: [detailed procedures of cross-coupling reactions, characterization data, and spectra]. See DOI: 10.1039/c000000x/

1. (a) W. S. Knowles and M. J. Sabacky, *Chem. Commun.* 1968, 1445. (b) W. S. Knowles, M. J. Sabacky, B. D. Vineyard and D. J. Weinkauff, *J. Am. Chem. Soc.* 1975, **97**, 2567.
2. (a) P. C. J. Kamer and P. W. N. M. Van Leeuween, Ed. *Phosphorus (III) Ligands in homogeneous Catalysis: Design and Synthesis.* Wiley & Sons: West Sussex, 2012. (b) W. Tang and X. Zhang, *Chem. Rev.* 2003, **103**, 3029. (c) A. Grabulosa, Ed. *P-Stereogenic Ligands in Enantioselective Catalysis.* Cambridge: RSC, 2011.
3. For reviews on the synthesis of P-chiral phosphines, see: (a) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.* 1994, **94**, 1375; (b) A. Grabulosa, J. Granell and G. Muller, *Coord. Chem. Rev.* 2007, **251**, 25; (c) J. S. Harvey and V. Gouverneur. *Chem. Commun.* 2010, **46,** 7477. (d) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* 2012, **23**, 1.
4. For selective examples, see: (a) K. Tani, L. D. Brown, J. Ahmed, J. A. Ibers, M. Yokota, A. Nakamura and S. Otsuka, *J. Am. Chem. Soc.* 1977, **99**, 7876; (b) N. K. Roberta and S. B. Wild, *J. Am. Chem. Soc.* 1979, **101**, 6254; (c) T. Imamoto, K. V. L. Crépy and K. Katagiri, *Tetrahedron: Asymmetry* 2004, **15**, 2213; (d) D. Liu and X. Zhang, *Eur. J. Org. Chem.* 2005, 646.
5. For selective examples, see: (a) O. Korpiun and K. Mislow, *J. Am. Chem. Soc.* 1967, **89**, 4784; (b) D. Gatineau, L. Giordano and G. Buono, *J. Am. Chem. Soc.* 2011, **133**, 10728; (c) O. Berger and J-L. Montchamp, *Angew. Chem., Int. Ed.* 2013, **52**, 11377; (d) S. Jugé, M. Stephan, J. A. Laffitte and J. P. Genet, *Tetrahedron Lett.* 1990, **31**, 6357; (e) Z. S. Han, N. Goyal, M. A. Herbage, J. D. Sieber, B. Qu, Y. Xu, Z. Li, J. T. Reeves, J-N. Desrosiers, S. Ma, N. Grinberg, H. Lee, H. P. R. Mangunuru, Y. Zhang, D. Krishnamurthy, B. Z. Lu, J. J. Song, G. Wang and C. H. Senanayake, *J. Am. Chem. Soc.* 2013, **135**, 2474
6. For selective examples, see: (a) J. R. Moncarz, N. F. Laritcheva and D. S. Glueck, *J. Am. Chem. Soc.* 2002, **124**, 13356; (b) V. S. Chan, I. C. Stewart, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.* 2006, **128**, 2786; (c) C. Scriban and D. S. Glueck, *J. Am. Chem. Soc.* 2006, **128**, 2788; (d) N. F. Blank, J. R. Moncarz, T. J. Brunker, C. Scriban, B. J. Anderson, O. Amir, D. S. Glueck, L. N. Zakharov, J. A. Golen, C. D. Incarvito and A. L. Rheingold, *J. Am. Chem. Soc.* 2007, **129**, 6847; (e) V. S. Chan, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc.* 2007, **129**, 15122; (f) C. Scriban, D. S. Glueck, J. A. Golen and A. L. Rheingold, *Organometallics* 2007, **26**, 1788; (g) B. J. Anderson, M. A. Guino-o, D.

S. Glueck, J. A. Golen, A. G. DiPasquale, L. M. Liable-Sands and A. L. Rheingold, *Org. Lett*. 2008, **10**, 4425; (h) V. S. Chan, M. Chiu, R. G. Bergman and F. D. Toste, *J. Am. Chem. Soc*. 2009, **131**, 6021; (i) T. W. Chapp, D. S. Glueck, J. A. Golen, C. E. Moore and A. L. Rheingold, *Organometallics* 2010, **29**, 378; (j) C. Li, W.-X. Li, S. Xu and W.-L. Duan, *Chin. J. Org. Chem.* 2013, **33**, 799. (k) Y. Huang, Y. Li, P.-H. Leung and T. Hayashi, *J. Am. Chem. Soc*. 2014, **136**, 4865; (l) C. Li, B.-L. Bian, Li, S. Xu and W.-L. Duan, *Org. Chem. Front.* 2014, **1**, 541. (m) Z.-J. Du, J. Guan, G.-J. Wu, P. Xu, L.-X. Gao and F.-S. Han, *J. Am. Chem. Soc.* 2015, **137**, 632.

7. (a) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc*. 2000, **122**, 12051. (b) X. Shen, G. O. Jones, D. A. Watson, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.* 2010, **132**, 11278. (c) W. Tang, N. D. Patel, G. Xu, X. Xu, J. Savoie, S. Ma, M.-H. Hao, S. Keshipeddy, A. G. Capacci, X. Wei, Y. Zhang, J. J. Gao, W. Li, S. Rodriguez, B. Z. Lu, N. K. Yee and C. H. Senanayake, *Org. Lett.* 2012, **14**, 2258; (d) K. Li, N. Hu, R. Luo, W. Yuan and W. Tang, *J. Org. Chem.* 2013, **78**, 6350; (e) G. Xu, W. Fu, G. Liu, C. H. Senanayake and W. Tang, *J. Am. Chem. Soc.* 2014, **136**, 570; (f) K. Du, P. Guo, Y. Chen, Z. Cao, Z. Wang and Tang, W. *Angew. Chem., Int. Ed.* 2015, **54**, 3033.
8. During preparation of the manuscript, two examples of palladium-catalyzed enantioselective C-H arylation for the synthesis of P-stereogenic phosphinic amides were reported: (a) Z.-Q. Lin, W.-Z. Wang, S.-B. Yan and W.-L. Duan, *Angew. Chem., Int. Ed.* 2015, **54**, 6265; (b) L. Liu, A.-A, Zhang, Y. Wang, F. Zhang, Z. Zuo, W.-X. Zhao, C.-L. Feng and W. Ma, *Org. lett*. 2015, **17**, 2046.
9. For other applications of ligands **L1**-**2** and **L5**-**6** in catalysis, see ref. 7c-f and: (a) W. Tang, A. G. Capacci, X. Wei, W. Li, A. White, N. D. Patel, J. Savoie, J. J. Gao, S. Rodriguez, B. Qu, N. Haddad, B. Z. Lu, D. Krishnamurthy, N. K. Yee and C. H. Senanayake *Angew. Chem. Int. Ed.* 2010, **49**, 5879; (b) W. Tang, S. Keshipeddy, Y. Zhang, X. Wei, J. Savoie, N. D. Patel, N. K. Yee and C. H. Senanayake *Org. Lett.* 2011, **13**,1366. (c) Q. Zhao, C. Li, C. H. Senanayake and W. Tang *Chem. Eur. J.* 2013, **19**, 2261. (d) C. Li, G. Xiao, Q. Zhao, H. Liu, T. Wang and W. Tang *Org. Chem. Front.* 2014, **1**, 225. (e) G. Xu, Q. Zhao and W. Tang *Chin. J. Org. Chem.* 2014, **34**, 1919.
10. Ph_3CCOOK, $Ph_2CHCOOCs$, potassium 2-(naphthalen-1-yl)acetate were also tested as bases and the highest ee value was 85%.
11. CCDC 1062715 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
12. ^{1}H NMR and ^{31}P NMR spectra showed two atropisomers in a ratio of 2.2/1 at 25 °C.
13. For examples of reduction of chiral phosphine oxides, see ref 5c-f and the following literatures: (a) T. Imamoto, S.-i. Kikuchi, T. Miura and Y. Wada, *Org. Lett.* 2001, **3**, 87; (b) K. V. Rajendran and D. G. Gilheany, *Chem. Commun*. 2012, **48**, 817.