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# Catalytic Synthesis of Chiral Phosphole Oxides via Desymmetric C–H Arylation of *o*-Bromoaryl Phosphine Oxides

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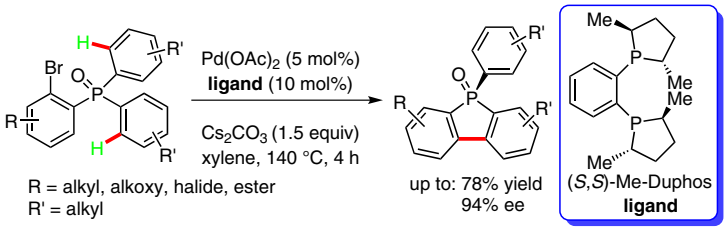


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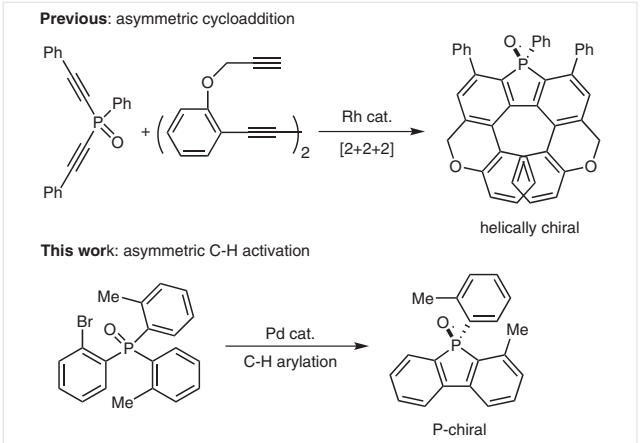
**Abstract** A palladium-catalyzed intramolecular direct arylation reaction of *o*-bromoaryl phosphine oxides was developed to afford a variety of P-stereogenic phosphole oxides in good yields. The enantioselectivities were closely associated with the specific structures of substrates, which ranged from 4–94%. As a result of ready availability of starting materials and simple operation to improve the enantioselectivities of the products with low ee values, the method provides a simple and straightforward procedure for the synthesis of P-stereogenic phosphole oxides.

**Key words** asymmetric catalysis, C–H activation, direct arylation, phosphole oxides, palladium

Chiral phosphorus compounds have found a plethora of applications in asymmetric synthesis, typically as useful ligands[1] in transition-metal catalysis and as versatile organocatalysts.[2] Owing to the remarkable chiral induction during the catalytic transformation by a stereogenic phosphorus atom stemming from its closer proximity to the catalytic center,[3] those with P-chiral centers are particularly attractive. In fact, P-chiral compounds have proven very efficient and stable as ligands and even some have been applied in the pharmaceuticals and agrochemicals. The conventional methods for the preparation of P-stereogenic compounds need stoichiometric amounts of chiral auxiliaries, including resolution of diastereomeric mixtures[4] and enantioselective deprotonation[5] of prochiral phosphines. Recently, metallo-, organo-, and biocatalytic synthetic methods have been reported, such as enantioselective cycloaddition of symmetric dialkynylphosphine oxides,[6] asymmetric ring-closing metathesis of symmetric dialkenylphosphine oxides,[7] and asymmetric alkylation[8] and arylation[9] of alkyl and aryl halide with secondary phosphines as well as their catalytic asymmetric addition to electron-deficient olefins[10] and to benzoquione.[11] Meanwhile, other more efficient and atom-economical routes to these compounds have been developed by several groups through asymmetric C–H activation in which the P-stereogenic compounds can be constructed in excellent enantioselectivities for both intra- and intermolecular desymmetrization reactions (Scheme 1).[12] Notably, the substrates have common structural units of phosphinamides that provided the nitrogen atoms to coordinate to metals to facilitate the C–H cleavage. However, the successful examples on asymmetric catalytic C–H functionalization of substrates without directing groups, unlike phosphinamides, have not appeared until now.



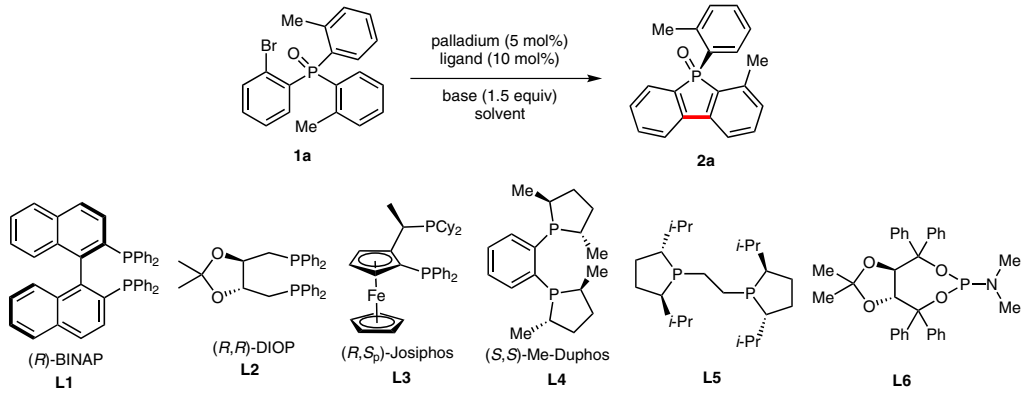

**Scheme 1** Transition-metal-catalyzed synthesis of chiral phosphole oxides

It was recognized that phospholes are valuable building blocks for tailoring organic π-conjugated materials, and their photophysics and redox properties can be efficiently tuned through the diverse and reversible phosphorus

chemistry.[13] In addition, chiral phosphole oxides have the vast potential in asymmetric catalysis as Lewis base catalysts or precursors of chiral ligands.[2,14] Despite the utilities of chiral phosphole oxides in organic synthesis, the effective approaches to them are extremely limited in number, especially for their catalytic synthesis. Previously, we reported a practical method for the synthesis of dibenzophosphole oxides via a palladium-catalyzed direct arylation strategy from the readily available *ortho*-haloarylphosphine oxides.[15] We envision that the P-stereogenic phospholes might be obtained in a catalytic C–H arylation via desymmetrization of prochiral *ortho*-haloarylphosphine oxides in the presence of chiral palladium catalyst.

The substrates were readily synthesized by the reactions of proper chlorophosphines with aryl Grignard reagents followed by oxidation with hydrogen peroxide.[16] Initially, **1a** was chosen as a model substrate to enact our proposed enantioselective C–H arylation strategy. To obtain the optimal reaction conditions, several reaction parameters related to this transformation including metal salt, ligand, base, solvent, and temperature were screened in detail (Table 1). Among the six commercially available chiral ligands tested in this reaction, bidentate ligands gave supe-

**Table 1** Optimization of Reaction Conditions[a]




| Entry | Ligand | Metal | Base | Solvent | Temp (°C) | Time (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **L1** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 70 | 33 |
| 2 | **L2** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 75 | 27 |
| 3 | **L3** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 62 | 24 |
| 4 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 68 | 70 |
| 5 | **L5** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 52 | 43 |
| 6 | **L6** | $Pd(OAc)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 73 | 5 |
| 7 | **L4** | $Pd(OAc)_2$ | $K_2CO_3$ | toluene | 100 | 16 | 80 | 22 |
| 8 | **L4** | $Pd(OAc)_2$ | $K_3PO_4$ | toluene | 100 | 16 | 58 | 2 |
| 9 | **L4** | $Pd(OAc)_2$ | KOAc | toluene | 100 | 16 | trace | n.d. |
| 10 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | DMAc | 100 | 16 | 95 | 0 |
| 11 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | hexane | 100 | 16 | 53 | 11 |
| 12 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | dioxane | 100 | 16 | 45 | 20 |
| 13 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | benzene | 100 | 16 | trace | n.d. |
| 14 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | xylene | 100 | 16 | 55 | 36 |
| 15 | **L4** | $Pd_2(dba)_3$ | $Cs_2CO_3$ | toluene | 100 | 16 | 20 | 35 |
| 16 | **L4** | $Pd(acac)_2$ | $Cs_2CO_3$ | toluene | 100 | 16 | 75 | 62 |
| 17 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | xylene | 120 | 4 | 68 | 60 |
| 18 | **L4** | $Pd(OAc)_2$ | $Cs_2CO_3$ | xylene | 140 | 4 | 74 | 75 |

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.25 mmol), base (1.5 equiv), PivOH (0.4 equiv), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%) in solvent (1 mL) under $N_2$.
[b] Isolated yield.
[c] The ee values were determined by HPLC analysis.

rior level of chiral induction to that with monodentate ligand (Table 1, entries 1–6), which is in contrast to the results of the intramolecular arene C–H activation of phosphinamide substrate.[12d,e] (*S*,*S*)-Me-Duphos (**L4**) combined with $Pd(OAc)_2$ gave the satisfactory yield and better enantioselectivity (Table 1, entry 4). We then turned our attention to base and reaction medium that proved to have major influence on the reaction. Although replacement of $Cs_2CO_3$ by $K_2CO_3$ led to slightly improvement of product yield, the enantioselectivity decreased markedly from 70% to 22%. Other bases proved ineffective for this reaction, and the C–H activation did not happened at all with KOAc as a base (Table 1, entries 7–9). The similar trend was observed when surveying the other solvents instead of toluene. Although excellent yield (up to 95%) was obtained in DMAc, unfortunately, racemic compound was produced (Table 1, entry 10). Likewise, the change of $Pd(OAc)_2$ to other palladium precursors did not result in further improvement of reaction result (Table 1, entries 15 and 16). To our delight, higher yield and ee were achieved by conducting the intramolecular arylation reaction in xylene at higher temperature and shorter time (Table 1, entries 17 and 18).

With the optimized conditions in hand, the steric and electronic influence of substituents on the aromatic rings was investigated, and the results are summarized in Figure 1.[17] Compared with **2a**, a substrate with larger steric hindrance on phenyl group bearing C–H bonds to be cleaved caused lower yield and ee of the desired product **2b**. On the other hand, it was found that the reaction of **1c** with the methyl group at bromoarene moiety furnished the product **2c** in comparable yield but with much lower ee, which suggested that substitution at the arenes with cleavable C–H bonds is beneficial for construction of P-stereogenic molecules with a higher degree of enantiotopic differentiation. For example, the substrates with electron-withdrawing groups at *para* position to phosphorus atom gave the corresponding products **2d–f** in good yields and low ee values under the present catalytic system. The compound **2g** having a $CF_3$ group *para* to P atom was obtained in satisfactory yield but with poor enantioselectivity. The developed catalytic system tolerated the bulky tertiary butyl and phenyl groups well, thus affording the **2h** and **2j** in moderate enantioselectivities, respectively. It is worth noting that the reaction of **1i**, comprising a methyl substituent at *para* position to P atom, underwent smooth asymmetric arylation, giving **2i** in good yield with excellent enantioselectivity (94% ee). Strongly electron-donating group such as OMe at the bromoaryl moiety will be detrimental for this class of chiral induction in spite of its position. As demonstrated by the reactions of **1k** and **1l**, the desired products were obtained in comparable yields but with much lower ee values, especially for **2l** whose enantioselectivity decreased to only 4%.

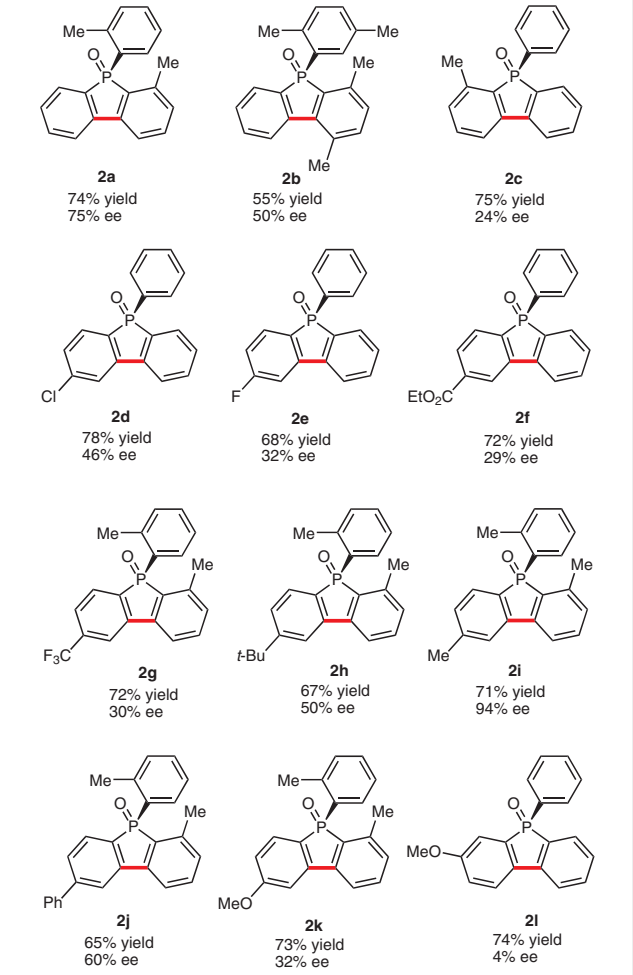
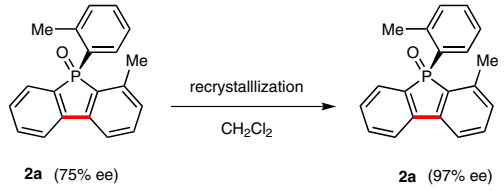



**Figure 1** Substrate scope. *Reagents and conditions*: phosphine oxide **1b–l** (1 mmol), $Cs_2CO_3$ (1.5 mmol), PivOH (0.4 mmol), $Pd(OAc)_2$ (5 mol%), **L4** (10 mol%) in xylene (4 mL) at 140 °C for 4 h under $N_2$.

It needs to be emphasized that the resulting coupling products have good ability to crystallize, which provided a simple and effective method to obtain optically pure P-stereogenic phospholes. As illustrated in Scheme 2, the ee value of **2a** can be improved from 75–97% in high yield after once recrystallization in $CH_2Cl_2$. Furthermore, a single crystal suitable for X-ray diffraction analysis was collected, and the absolute configuration of **2a** was determined to be (*S*) by X-ray crystallographic analysis with Cu Kα radiation (Figure 2).[18]

In summary, we have developed a novel method for the synthesis of P-stereogenic phosphole oxides through enantioselective C–H bond functionalization of *o*-bromoaryl phosphine oxides in the presence of in situ formed chiral palladium catalyst. The resulting active catalytic system showed high reactivity for most substrates, and up to 78% yield and 94% ee can be achieved under optimal conditions.




**Scheme 2** Further improvement of ee value of the product **2a**

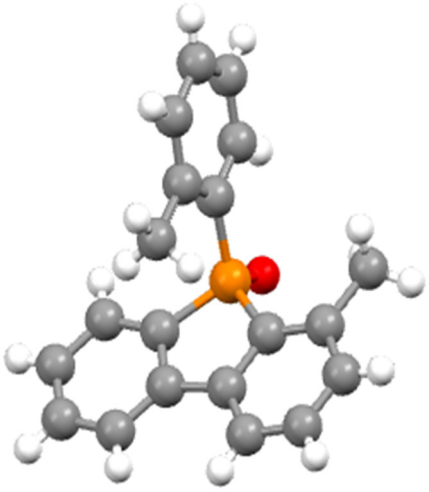


**Figure 2** X-ray crystal structure of **2a**[18]

In addition, the enantioselectivities for the products with low ee values can be improved to some extent after simple crystallization, thus providing an alternative and convenient route to chiral phosphole oxides.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588983.

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(16) (a) **General Procedure for the Synthesis of *o*-Bromoarylphosphine Oxide**

To a stirred solution of *o*-bromoiodobenzene (1.3 mL, 10 mmol) in THF (10 mL) was added dropwise a solution of isopropylmagnesium chloride (2.0 M in THF, 5 mL, 10 mmol) at –40 °C. After 1 h, $PCl_3$ (0.9 mL, 10 mmol) was added and stirred for 40 min at the same temperature. The mixture was then allowed to stand at r.t. for 12 h and cooled at –40 °C again. A solution of proper arylmagnesium bromide (1.0 M in THF, 22 mL, 22 mmol) was added dropwise. After 1 h, the resulting mixture was then stirred at r.t. overnight. A sat. aq solution of $NH_4Cl$ was added, and the reaction mixture was extracted three times with $Et_2O$. The combined organic layer was washed with water and brine and dried over $MgSO_4$. The solvent was then evaporated in vacuo, and the residue was purified by silica gel column chromatography with hexane as eluent to afford the corresponding phosphines. After oxidation by $H_2O_2$ in acetone, the crude products were purified by using flash chromatography with EtOAc as eluent, giving the pure products.

Compound **1a**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.67 (dddd, *J* = 12.9, 5.8, 4.8, 3.4 Hz, 2 H), 7.48–7.37 (m, 4 H), 7.31 (dd, *J* = 7.5, 4.3 Hz, 2 H), 7.26–7.14 (m, 4 H), 2.50 (s, 6 H). $^{31}$P NMR (202 MHz, $CDCl_3$): δ = 35.37 (s). $^{13}$C NMR (101 MHz, CDCl3): δ = 143.45 (d, *J* = 7.9 Hz), 135.82 (d, *J* = 9.8 Hz), 134.89 (d, *J* = 7.4 Hz), 133.63 (t, *J* = 9.5 Hz), 133.14 (d, *J* = 2.2 Hz), 132.70 (s), 132.19–131.79 (m), 130.00 (s), 128.95 (s), 127.24 (d, *J* = 10.8 Hz), 126.88 (d, *J* = 4.4 Hz), 125.40 (d, *J* = 13.2 Hz), 21.92 (d, *J* = 4.1 Hz).

(17) (a) **General Procedure for the Synthesis of P-Stereogenic Phosphole Oxide**

To a mixture of *ortho*-bromoarylphosphine oxides **1a–l** (1.0 mmol), $Cs_2CO_3$ (489 mg, 1.5 mmol), $Pd(OAc)_2$ (11.2 mg, 5 mol%), and **L4** (30.6 mg, 10 mol%) under nitrogen atmosphere was added 4 mL of xylene in a 25 mL Schlenk tube equipped with a magnetic stir bar. The Schlenk tube was stirred at r.t. for 20 min and then at 140 °C for 4 h. The reaction mixture was cooled to r.t. and quenched with water and then extracted with $CH_2Cl_2$. The extraction was washed with brine and dried over $Na_2SO_4$. The solvent was then evaporated in vacuo, and the residue was purified by using $SiO_2$ column with EtOAc as eluent to afford the final products.

Compound **2a**: $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 13.7, 7.6 Hz, 1 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 7.57 (t, *J* = 8.6 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.43–7.32 (m, 2 H), 7.29 (t, *J* = 7.5 Hz, 2 H), 7.04 (dd, *J* = 12.1, 6.0 Hz, 2 H), 2.25 (s, 3 H), 1.79 (s, 3 H). $^{31}$P NMR (202 MHz, $CDCl_3$): δ = 31.93 (s). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 142.53 (s), 142.26 (d, *J* = 10.5 Hz), 142.11 – 141.87 (m), 141.02 (d, *J* = 11.0 Hz), 134.31 (d, *J* = 9.5 Hz), 133.55 (d, *J* = 7.9 Hz), 133.14 (d, *J* = 2.0 Hz), 132.54 (s), 132.23 (d, *J* = 2.7 Hz), 131.40 (t, *J* = 11.3 Hz), 130.83 (d, *J* = 9.8 Hz), 130.24 (s), 129.33 (t, *J* = 11.0 Hz), 128.72 (s), 127.74 (s), 126.01 (d, *J* = 11.9 Hz), 121.31 (d, *J* = 10.0 Hz), 118.75 (d, *J* = 10.1 Hz), 20.10 (d, *J* = 4.4 Hz), 19.42 (d, *J* = 4.6 Hz). Enantiomeric excess was determined by HPLC with a Chiralpak OD column (hexanes–2-PrOH = 70:30, 0.5 mL/min, 254 nm); major enantiomer $t_R$ = 12.3 min, minor enantiomer $t_R$ = 25.9 min. ESI-HRMS: *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}OP$: 305.1090; found: 305.1094. $[\alpha]_D^{20}$ –36.2 (*c* 1.21, $CHCl_3$).

(18) CCDC 1524935 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.