

COMMUNICATION

Synthesis of P-Chiral Phosphine Compounds by Palladium-Catalyzed C–P Coupling Reactions

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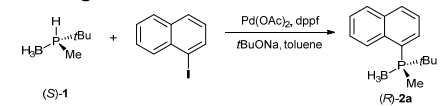
An efficient C–P coupling reactions of enantiopure *tert*-butylmethylphosphine-boranes with aryl and heteroaryl halides is developed by using Pd(OAc)₂/dppf as a catalyst, affording a series of (*S*) or (*R*)-P-chiral phosphines with moderate to high yields and ee values (up to 99% ee). Moreover, the reaction time could be reduced from 72 h to 6 h but with increased ee values under microwave conditions.

Chiral phosphines are widely used for diverse catalytic asymmetric synthesis, both acting as auxiliary ligand for transition metal complexes or as organocatalyst on its own right.¹ In literatures, many chiral phosphine ligands have been developed, but the great majority of which are *C*-stereogenic, axial-chiral and planar-chiral ones. Enantioenriched *P*-stereogenic phosphorus compounds are much less well-established due to the lack of efficient synthetic methods.² Traditional preparation of *P*-stereogenic phosphines require the use of stoichiometric amount of chiral reagents.^{3–5} Methods relying the direct metal-catalyzed coupling reactions of secondary phosphines with electrophiles have emerged as an efficient alternative and attracted much attention. As up to now, transition-metal-catalyzed alkylation,⁶ allylation,⁷ arylation,⁸ hydrophosphination of unsaturated bonds (such as alkene, alkyne, imine etc.)⁹ reactions have been developed to construct *P*-stereogenic phosphines. Despite these advances, the

development of efficient methods to construct *P*-chiral phosphines remains a challenge.

We propose to develop an efficient route to prepare chiral phosphine-boranes having *tert*-butylmethylphosphino group for the following reasons. First, phosphine-boranes do not readily oxidized on exposure to air. Second, bulky *tert*-butyl group of phosphine ligands is able to enhance the stability and enantioselectivity of metal catalysts.^{10,11} Third, *P*-chiral phosphines with *tert*-butylmethylphosphino group have been shown to display excellent enantioselectivity and high catalytic activity in metal-catalyzed asymmetric hydrogenation and borylation reactions.¹¹ However, this type of ligands are prepared by the reaction of enantiopure *tert*-butylmethylphosphine-boranes with *n*BuLi and aryl halides,¹¹ requiring harsh reaction conditions and substrates bearing hydroxyl, carbonyl and cyano groups are not suitable for this method. In this work, we have developed a simple and efficient method for the synthesis of *P*-chiral phosphines with *tert*-butylmethylphosphino group.

Table 1 Screening of the reaction conditions^a



Entry	T (°C)	Pd(OAc) ₂ (%)	dppf (%)	t (h)	Yield (%)	ee (%)
1	80	2	4	12	23	34
2	40	2	4	48	52	54
3	25	2	4	48	21	82
4	25	5	10	48	42	91
5	25	10	20	48	45	91
6	25	5	10	48	53	91 ^b
7	25	5	10	48	58	83 ^c
8	25	5	10	72	68	91 ^b

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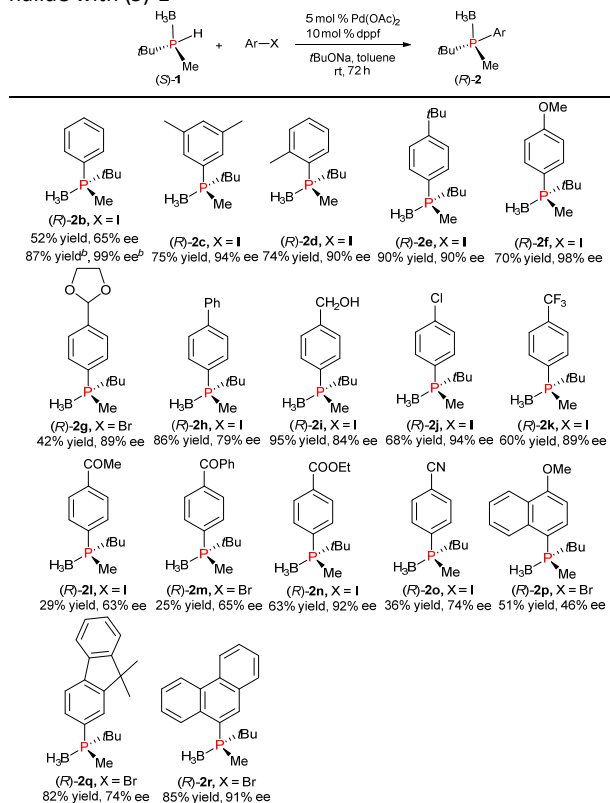
† Footnotes relating to the title and/or authors should appear here. ¹H, ¹³C, ¹⁹F and

³¹P NMR spectra, crystallographic data for (*R*)-2h and (*S*)-2q. CCDC 2017887 and 2017943. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

^a (*S*)-**1** (0.30 mmol), 1-iodonaphthalene (0.50 mmol), Pd(OAc)₂, dpfp and *t*BuONa (0.36 mmol) in toluene (3 mL) under N₂. ^b *t*BuONa (0.60 mmol). ^c *t*BuONa (0.90 mmol).

Initially, the C–P coupling reaction of enantiopure *tert*-butylmethylphosphine-borane (*S*)-**1** with 1-iodonaphthalene in the presence of *t*BuONa was investigated by using Pd(OAc)₂/dpfp (dpfp = 1,1'-Ferrocenebis(diphenylphosphine)) as a catalyst for optimization of the reaction conditions (Table 1). The desired C–P coupling product (*R*)-**2a** was obtained in 23% yield, with only 34% ee at 80 °C (Table 1, entry 1). When the reaction temperature was reduced to 25 °C, the ee value of the product (*R*)-**2a** was improved to 82%, but the yield was only 21% (Table 1, entry 3). When the loading of Pd(OAc)₂ was increased from 2 mol% to 5 mol%, 42% product yield and 91% ee were obtained. With 10 mol% loading of Pd(OAc)₂, a similar product yield and ee value was observed (Table 1, entries 4 and 5). Moreover, the yield of (*R*)-**2a** was improved to 53% with 2 equivalent of *t*BuONa, and the ee value remained intact. However, the ee value decreased from 91% to 83% with 3 equivalent of *t*BuONa (Table 1, entries 6 and 7). Upon increasing the reaction time to 72 h, 68% product yield and 91% ee were obtained with 2 equivalent of *t*BuONa (Table 1, entry 8).

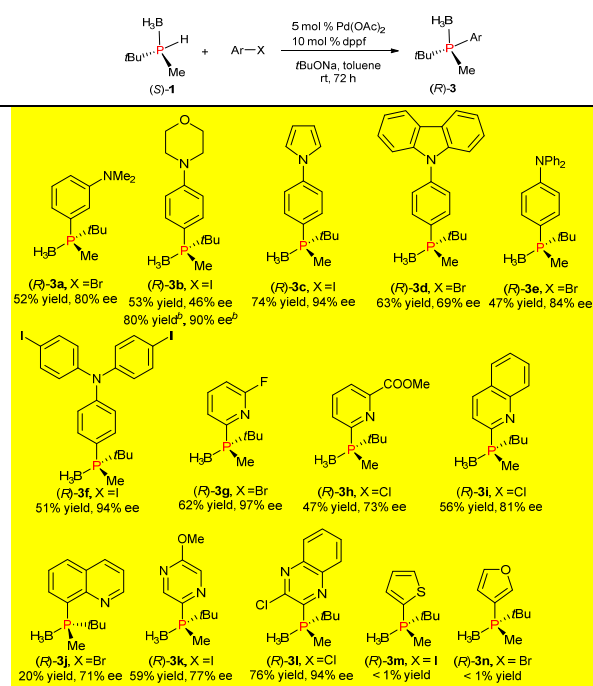
Table 2 Substrate scope for the C–P coupling reaction of aryl halide with (*S*)-**1**^a



^a (*S*)-**1** (0.30 mmol), aryl halide (0.50 mmol), Pd(OAc)₂ (0.015 mmol), dpfp (0.03 mmol) and *t*BuONa (0.60 mmol) in toluene (3 mL) at room temperature for 72 h under N₂. ^b 6 h, under microwave irradiation.

With the optimized conditions, we first investigated the scope of aryl halides (Table 2). The desired (*R*)-**2b–2h** products bearing electron-donating groups (alkyl and ether) as well as phenyl on their aryl rings were obtained from moderate to high yields (42–95%) with 65–98% ee. It is noted that (4-iodophenyl)methanol was also a suitable substrate to give (*R*)-**2i** in 95% yield and 84% ee. 1-Chloro-4-iodobenzene was also effective to afford product (*R*)-**2j** in 68% yield and 94% ee. Electron-withdrawing groups, such as -CF₃, -COMe, -COOEt, and -CN were also tolerated and the corresponding products (*R*)-**2k–2o** were obtained in moderate yields (25–63%) with 63–92% ee. Additionally, 1-bromo-4-methoxynaphthalene, 2-bromo-9,9-dimethyl-9*H*-fluorene and 9-bromophenanthrene also reacted smoothly with (*S*)-**1** to give products ((*R*)-**2p–2r**) in good yields (51–85%) with 46–91% ee, respectively.

Table 3 Substrate scope for the C–P coupling reaction of aryl / heteroaryl halide with (*S*)-**1**^a

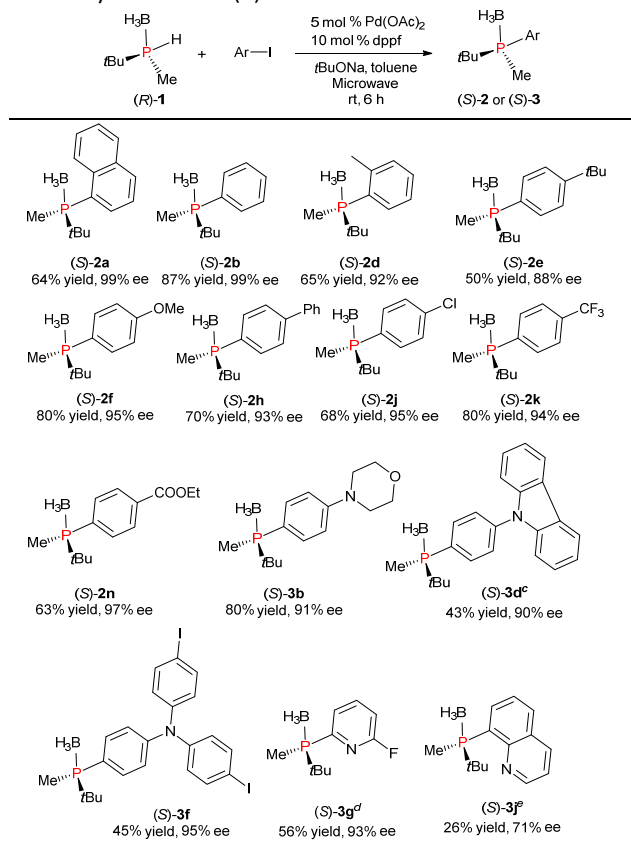


^a (*S*)-**1** (0.30 mmol), aryl or heteroaryl halides (0.50 mmol), Pd(OAc)₂ (0.015 mmol), dpfp (0.03 mmol) and *t*BuONa (0.60 mmol) in toluene (3 mL) at room temperature for 72 h under N₂. ^b 6 h, under microwave irradiation.

Due to the effect of coordination of heteroatom to transition-metal catalysts that would result in suppression of the catalytic process, efficient C–P coupling reaction of heteroaryl halides remains a challenge.⁸ To further extend the reaction scope, we extended the substrate scope to the ones containing nitrogen atom. As shown in Table 3, substrates bearing amine and pyrrolyl groups reacted with (*S*)-**1** affording the products (*R*)-**3a–3f** in moderate yields (47–74%) with 46–94% ee. The reaction was applicable to other heteroaryl halides containing pyridine,

quinoline, pyrazine and quinoxaline groups, producing (*R*)-**3g-3l** in moderate yields (20-76%) with 71-97% ee. However, 2-iodothiophene and 3-bromofuran did not give the corresponding products.

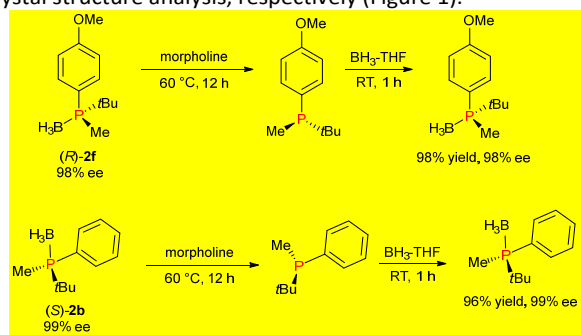
Table 4 Substrate scope for the C–P coupling reaction of aryl / heteroaryl halide with (*R*)-**1** under microwave irradiation^a



^a (*R*)-**1** (0.30 mmol), aryl or heteroaryl iodides (0.50 mmol), Pd(OAc)₂ (0.015 mmol), dppf (0.03 mmol) and tBuONa (0.60 mmol) in toluene (3 mL) at room temperature for 6 h under N₂ and microwave irradiation. ^b 2-bromo-1*H*-indene is used as a substrate. ^c 9-(4-bromophenyl)-9*H*-carbazole is used as a substrate. ^d 2-chloro-6-fluoropyridine is used as a substrate. ^e 8-bromoquinoline is used as a substrate.

Generally, long reaction time (20-72 h) was required for transition-metal catalyzed asymmetric C–P cross-coupling reaction. In this work, we found that the reaction of iodobenzene and 4-(4-iodophenyl)morpholine under microwave irradiation just required 6 h for completion, affording the corresponding products with increased yields and ee values ((*R*)-**2b**: 87% yield, 99% ee and (*R*)-**3b**: 80% yield, 90% ee). The reaction with enantiopure *tert*-butylmethylphosphine-borane (*R*)-**1** was then examined under microwave irradiation for 6 h, and the results are shown in Table 4. The reaction with 1-iodonaphthalene gave the product (*S*)-**2a** in 64% yield with 99% ee. A series of aryl halides bearing electron-donating or electron-withdrawing groups on the aryl rings were all well tolerated, furnishing desired products in

moderate to high yields (43-87%) with high ee values (88-99% ee). Additionally, the reactions with 2-chloro-6-fluoropyridine and 8-bromoquinoline afforded the respective products (*S*)-**3g** (56% yield, 93% ee) and (*S*)-**3l** (26% yield, 71% ee). These P-stereogenic phosphines are stereochemically stable after decomplexation. For example, the ee values of (*R*)-**2f** and (*S*)-**2b** are maintained after decomplexation with morpholine and addition with BH₃ (Scheme 1). Among these P-chiral compounds, the absolute configuration of products (*R*)-**2h** and (*S*)-**2q** were unambiguously determined to be *S* and *R* by X-ray crystal structure analysis, respectively (Figure 1).



Scheme 1 The ee values of P-stereogenic phosphines are maintained after decomplexation and addition.

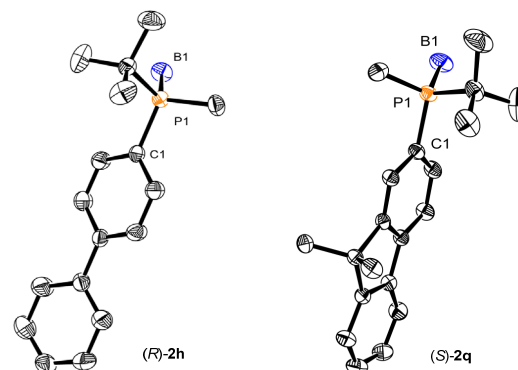


Figure 1 View of (*R*)-**2h** and (*S*)-**2q**. The thermal ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

In summary, we have developed a facile method of Pd(OAc)₂/dppf-catalyzed C–P cross-coupling for the efficient construction of (*S*) or (*R*)-P-chiral phosphine compounds containing *tert*-butylmethylphosphino groups in moderate to high ee values. The reaction is applicable to a series of aryl halides bearing electron-donating or electron-withdrawing groups, and heteroaryl halides are also well tolerated. Additionally, the reaction time could be significantly reduced but with increased ee values under microwave conditions. Efforts to discover new asymmetric reactions using these P-chiral compounds as a supporting ligand, are currently ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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