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A simple and highly efficient P,O-type ligand for Suzuki–Miyaura cross-coupling of aryl halides

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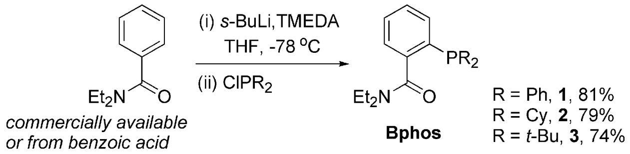
A simple and efficient hemilabile-type phosphine ligand, found to be highly effective in Suzuki–Miyaura cross-coupling of aryl chlorides with generally low Pd-catalyst loading (0.05%), was prepared in one step based on an economically attractive approach from commercially available benzamide starting material.

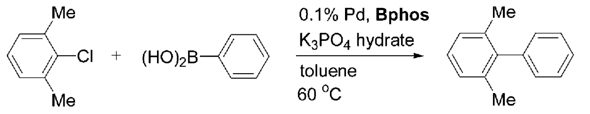
The Suzuki–Miyaura cross-coupling reaction is one of the most powerful protocols for construction of diversified biaryls,[1] which form an important class of compounds for pharmaceutical, material and agricultural chemistry.[2] Recently, electron-rich phosphine[3–7] and Buchwald's elegantly designed biphenyl-type phosphine ligands[8] have shown high reactivity in Suzuki–Miyaura reactions, with the application of readily available and inexpensive aryl chloride as the substrates.[9] Various observations and comments have been made in connection with high activity of biphenyl-based dialkylphosphines. These commentaries included the isolation of η^2-aryl palladium complex from a related phenanthrene based ligand.[10] Particularly noteworthy was that the mechanistic study, which was performed by the same group, revealed that the elimination of the *ortho* hydrogen on the bottom ring (that was not bound to the dialkylphosphino group) of the biphenyl-based ligand was important for catalyst activity and longevity.[11] Herein, we report a simple and efficient hemilabile P,O-type ligand for Suzuki–Miyaura coupling of aryl chlorides at low catalyst loading.[12]



Scheme 1 Direct synthesis of simple hemilabile P,O-type ligands.

We designed this new class of ligand based on several stand points: (1) starting material should be inexpensive (or readily available from single step synthesis); (2) to incorporate a hemilabile group[13] on the ligand that can perform 'on and off' dynamic interaction to stabilize the metal center whenever needed in order to give a higher TON; and (3) the ligand synthesis should be direct and simple (an elimination of metal/halogen exchange (from ArBr or ArI) would be even more advantageous). To fulfil the above criteria, we chose the commercially available and inexpensive benzamide as the precursor to synthesize the P,O type ligand in good yields by DMG (direct-metallation group) directed *ortho*-lithiation[14] and subsequent reaction with $ClPR_2$ (Scheme 1). Bphos (*B*enzamide derived *phos*phine) ligands **1–3** were found to be highly air and moisture stable.[15] To test the effectiveness of these new ligands, we used the sterically hindered 2-chloro-*m*-xylene as

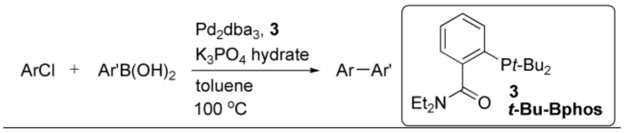
Table 1 Ligand effect in Suzuki–Miyaura coupling of hindered ArCl[a]

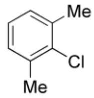
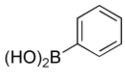
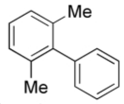
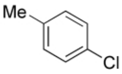
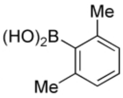
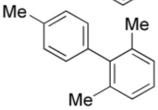
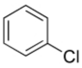
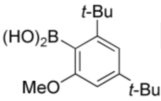
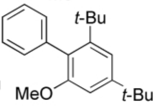
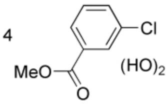
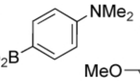
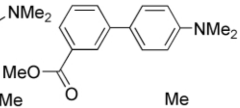
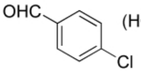
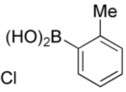
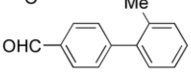
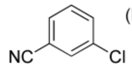
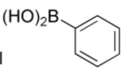
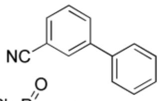
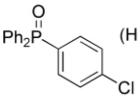
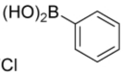
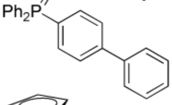
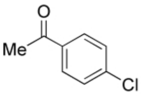
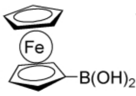
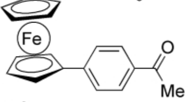
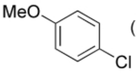
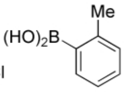
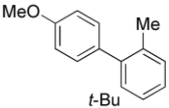
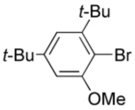
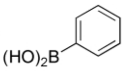
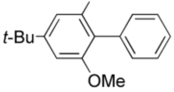


Entry	Ligand	Time/h	Conversion (%)	Yield (%)
1	Ph-Bphos, **1**	48	5	0
2	Cy-Bphos, **2**	24	94	92 (91)
3	*t*-Bu-Bphos, **3**	24	> 99	98 (95)
4	*o*-(*t*-Bu_2P)biphenyl	24	83	81

[a] GC conversions and yields were reported, isolated yield in parentheses.

Table 2 Suzuki–Miyaura coupling of various aryl chlorides[a]



entry	ArCl	Ar'B(OH)$_2$	product	mol% Pd	%yield[b]
1				0.05% 16 h	95
2				0.05% 18 h	92
3				0.1% 24 h	90
4				0.05% 16 h	93
5				0.02% 18 h	91
6				0.01% 14 h	94
7				0.5% 14 h	90
8				0.02% 16 h	89
9				0.05% 16 h	91
10				0.05% 60 °C, 16 h	92

[a] Reaction conditions: ArCl (1.0 mmol), Ar′B(OH)$_2$ (1.5 mmol), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), stock solution of Pd-catalyst (Pd : L = 1 : 2), toluene (3.0 mL) were stirred at 100 °C under nitrogen. [b] Isolated yield.

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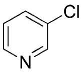
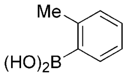
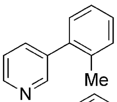
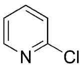
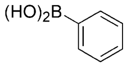
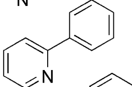
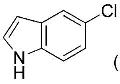
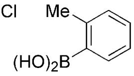
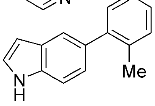
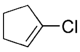
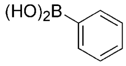
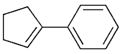
Table 3 Suzuki–Miyaura coupling of heteroaryl and alkenyl chlorides[a]

entry	Het-ArCl	Ar'B(OH)$_2$	product	mol% Pd	%yield[b]
1				0.05% 19 h	95
2				0.01% 18 h	96
3				0.5% 18 h	92
4				0.05% 19 h	88

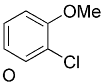
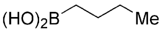
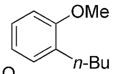
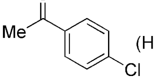
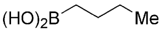
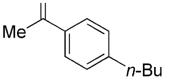
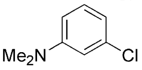
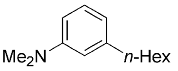
[a] Reaction conditions: see Table 2. [b] Isolated yield.

the prototypical substrate for the Suzuki–Miyaura reaction (Table 1). Ph-Bphos **1** gave nearly no conversion of aryl chloride, while electron rich Cy-Bphos **2** and *t*-Bu-Bphos **3** furnished the biaryl product in excellent yield in the presence of 0.1% Pd catalyst at 60 °C (Table 1, entries 2–3). This interesting finding led us to the exploration of using ligand **3** in the coupling of various aryl chlorides with low catalyst loading (Table 2). Highly substituted 2,4-di-*tert*-butyl-6-methoxyphenylboronic acid and 2-*m*-xylylboronic acid were coupled with aryl chlorides in good yields (Table 2, entries 2–3). Functional groups such as ester, aldehyde, nitrile and keto were found to be compatible under these reaction conditions (Table 2, entries 4–8). Recently, the construction of aryl-ferrocenyl bond from aryl iodides was found to be an excellent method for the synthesis of new chiral ferrocenyl ligands.[16] Our findings of the coupling of aryl chloride with ferrocenylboronic acid in good yield offer a beneficial opportunity for the pursuit of practical and useful synthetic methodologies (Table 2, entry 8).

Apart from functionalised aryl chlorides, heteroaryl and alkenyl chlorides were effective substrates for Suzuki–Miyaura coupling using 0.01–0.5% Pd as the catalyst (Table 3). Unprotected chloroindole was coupled with tolylboronic acid in good yield (Table 3, entry 3). In addition, preliminary studies of the couplings of alkylboronic acid with both electron-poor and electron-rich aryl chlorides were successful (Table 4).[17]

In summary, we have developed a new class of simple and highly active P,O-type ligand for Suzuki–Miyaura cross coupling of aryl chlorides in low Pd-catalyst loading (with 0.05% in general). The high stability of the hemilabile ligand gave relatively high turnover numbers in the Suzuki–Miyaura reaction. The inexpensiveness of benzamide starting material, as well as the simplicity of the ligand synthesis made this type of hemilabile ligand highly attractive. In view of the easy modification of the Bphos **1–3** structure including the use of a polymer-support scaffold through the amide group, we anticipate that further enhancements in reactivity, as well as in the versatility of the ligands will be attainable.

Table 4 Suzuki–Miyaura coupling of ArCl with alkyl boronic acid[a]

entry	ArCl	alkyl-B(OH)$_2$	product	mol% Pd	%yield[b]
1				0.05% 18 h	90
2				0.05% 12 h	96
3		*n*-Hex-B(OH)$_2$		0.05% 18 h	92

[a] Reaction conditions: see Table 2. [b] Isolated yield.

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Notes and references

1 (*a*) N. Miyaura, *Top. Curr. Chem.*, 2002, **219**, 11; (*b*) A. Suzuki, *J. Organomet. Chem.*, 2002, **653**, 83; (*c*) N. Miyaura, *J. Organomet. Chem.*, 2002, **653**, 54; (*d*) A. Suzuki, *J. Organomet. Chem.*, 1999, **576**, 147; (*e*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633.

2 (*a*) B. H. Kaae, P. Krogsgaard-Larsen and T. N. Johansen, *J. Org. Chem.*, 2004, **69**, 1401; (*b*) M. Hocek, A. Holý, I. Votruba and H. Dvořáková, *J. Med. Chem.*, 2000, **43**, 1817; (*c*) N. Zou, J.-F. Liu and B. Jiang, *J. Comb. Chem.*, 2003, **5**, 754.

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