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An active ferrocenyl triarylphosphine for palladium-catalyzed Suzuki–Miyaura cross-coupling of aryl halides†

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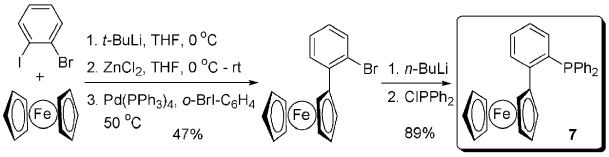
Pd-catalyzed Suzuki–Miyaura reaction of aryl chlorides was accomplished through the use of an active ferrocene-based triarylphosphine ligand. This air- and moisture-stable ligand was found to be effective for the cross-coupling of aryl halides at room temperature to 115 °C.

Recent advances in cross-coupling methodologies have made significant contribution to organic synthesis as well as pharmaceutical and agricultural chemistry.[1] Suzuki–Miyaura cross-coupling is one of the most attractive and practical protocols for carbon-carbon bond formation due to its tolerance of a wide range of functional groups and the simple separation of products.[2] Recently, improved catalyst systems for Suzuki–Miyaura couplings have been described, such as Pd-complexes of trialkylphosphines,[3] *ortho*-biaryl or ferrocenyl dialkylphosphines,[4,5] and other ligands,[6] that allow couplings to be carried out under mild conditions for the preparation of substituted biaryl compounds from relatively inexpensive aryl chlorides.[7] Despite the intensive attention this area has received, few examples are known where triarylphosphines were used in Suzuki–Miyaura couplings employing aryl chlorides.[8,9] Since triarylphosphines are usually prepared from relatively inexpensive chlorodiphenylphosphine with Grignard or organolithium reagents, it would add a further attractive feature if these modified triarylphosphines are active and similar to some results of Pd-trialkylphosphine or -dialkylarylphosphine catalyzed reactions. We report a simple and active ferrocenyl triarylphosphine for Suzuki–Miyaura cross-coupling of sterically hindered aryl bromides at room temperature and aryl chlorides at elevated temperatures.[10]

In view of the electronic and steric differences between a benzene ring and the cyclopentadienyl ring of ferrocene, we envisioned that the replacement of a benzene ring with ferrocene would generate a new class of potentially active ligand for cross-coupling reactions. To our delight, the active ligand **7** demonstrated that even Pd-triarylphosphine moiety could catalyze Suzuki–Miyaura coupling using aryl chloride as the substrates.

Triarylphosphine **7** was prepared from commercially available ferrocene in two steps (Scheme 1). Since ferrocene cannot be directly halogenated, the use of the Kagan lithiation protocol is necessary.[11] Ferrocene was lithiated with *t*-BuLi in THF to afford ferrocenyllithium and subsequent transmetallation with $ZnCl_2$ to obtain the Negishi coupling precursor (Scheme 1). Heating the mixtures in the presence of 3% $Pd(PPh_3)_4$ and *ortho*-bromoiodobenzene led to the formation of 2-bromophenylferrocene. Lithiation with *n*-BuLi and subsequent reaction with $ClPPh_2$ cleanly gave air-stable ligand **7** in good yield (Scheme 1).



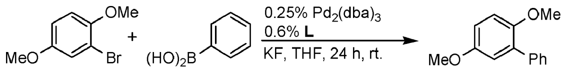
Scheme 1 Synthesis of ferrocenyl triarylphosphine ligand.

To test the effectiveness of this new ligand **7**, we used it in comparison with various commercially available triarylphosphine ligands in the Suzuki–Miyaura coupling of an *ortho*-substituted aryl bromide (eqn. (1) and Table 1). While *rac*-BINAP and tri-*o*-tolylphosphine gave moderate conversions, the new monodentate ferrocenyl triarylphosphine **7** showed superior results in Suzuki coupling of sterically hindered aryl bromide at room temperature. In addition, the triarylphosphine **7** has the highest activity over the other triarylphosphines in Suzuki coupling of aryl chloride (eqn. (2), Table 1).

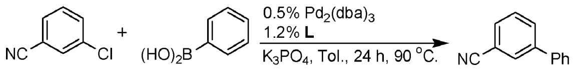
This interesting finding led us to the exploration of using **7** in the coupling of various substituted aryl bromides (Table 2). *ortho*-Phenyl substituted aryl bromide was coupled with phenyl boronic acid in excellent yield (Table 2, entry 2). Highly substituted aryl bromides, such as 2,6-diisopropyl or 2-*tert*-butyl-6-methoxy substituted bromobenzene required slightly higher temperature (30 °C) (Table 2, entries 4 and 5).

The combination of variety of solvents and bases were screened for coupling of aryl chlorides. Potassium phosphate monohydrate was found to be superior in toluene. Functional groups such as aldehyde, keto, nitrile and ester were found to be compatible under these reaction conditions (Table 3). Electron-deficient aryl chloride can be coupled with arylboronic acid at room temperature (Table 3, entry 4). The coupling of deactivated aryl chlorides with *ortho*-substituted arylboronic acids required slightly higher catalyst loading (Table 3, entry 6). Interestingly, about 2% of diarylmethanol was observed from GC-MS (Table 3, entry 2), possibly resulting from the addition of arylboronic acid to the carbonyl group.[12] Aryl-aryl exchange reactions between Pd-Ar and P-Ar are typical side reactions encountered when triarylphosphine ligands are employed in coupling reactions,[13] however, no such side products were formed from under these reaction conditions when ligand **7** was employed in Suzuki–Miyaura coupling.[14]

Table 1 Triarylphosphine ligands screening in Pd-catalyzed Suzuki–Miyaura cross-coupling of aryl bromide and chloride



(1)



(2)

Entry	Ligand **L**	GC yield (%), eqn. (1)	GC yield (%), eqn. (2)
1	No ligand	8	0
2	*rac*-BINAP	32	5
3	DPPF	7	4
4	Xantphos	7	5
5	$(o\text{-tolyl})_3P$	55	15
6	Ph_3P	18	9
7	Ligand **7**	98	92

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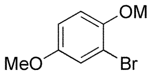
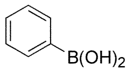
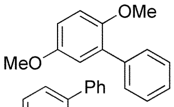
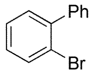
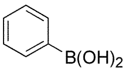
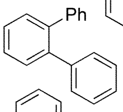
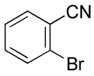
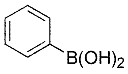
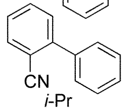
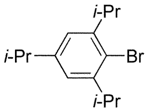
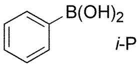
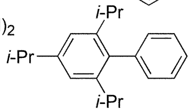
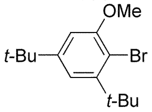
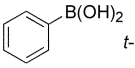
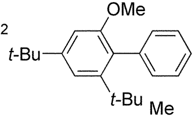
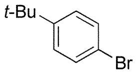
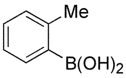
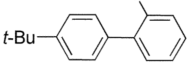
† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b4/b407661c/

DOI: 10.1039/b407661c

Table 2 Suzuki–Miyaura coupling of sterically hindered ArBr at RT[a]

Entry	ArBr	Ar′B(OH)$_2$	Product	% Yield[b]
1				98
2				96
3				95
4[c]				93
5[c]				87
6				90

[a] Reaction conditions: ArBr (1.0 mmol), Ar′B(OH)$_2$ (1.5 mmol), Pd$_2$(dba)$_3$ (0.5 mol%), ligand **7** (1.2 mol%), KF (3.0 mmol) and THF (2.0 mL) were charged in a Schlenk flask under N$_2$ and stirred at RT. [b] Isolated yields. [c] Reactions were conducted at 30 °C for 72 h.

Table 3 Pd-catalyzed Suzuki coupling of ArCl with Fc-ligand **7**[a]

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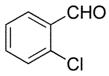
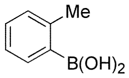
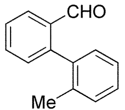
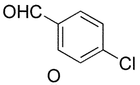
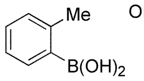
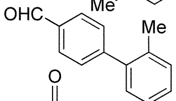
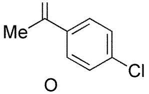
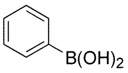
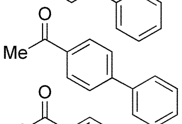
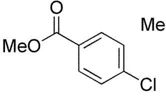
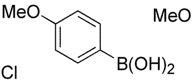
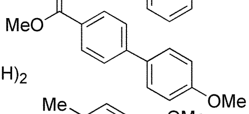
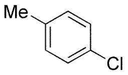
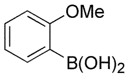
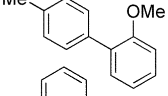
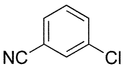
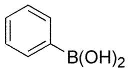
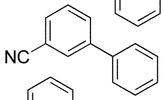
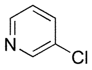
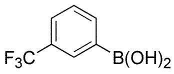
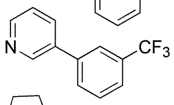
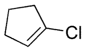
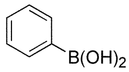
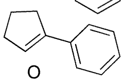
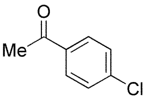
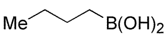
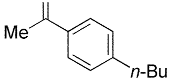
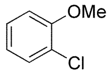
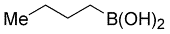
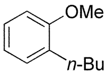
1				90
2				91
3 4[d]				94 91
5				92
6[c]				83
7				96
8				91
9				88
10[e]				95
11[e]				88

[a] Reaction conditions: ArCl (1.0 mmol), Ar′B(OH)$_2$ (1.5 mmol), Pd$_2$(dba)$_3$ (0.5 mol%), ligand **7** (1.2 mol%), K$_3$PO$_4$ • H$_2$O (3.0 mmol) and toluene (2.0 mL) were stirred at 110 °C under N$_2$ for 24 h; entry 3, 70 °C; entry 7, 90 °C. [b] Isolated yields. [c] Reactions were conducted with Pd$_2$(dba)$_3$ (2 mol%), ligand **7** (8 mol%), 115 °C, 28 h. [d] Pd$_2$dba$_3$ (2 mol%), ligand **7** (4 mol%), rt, 48 h. [e] K$_3$PO$_4$ (3.0 mmol) was used.

Heteroaryl and alkenyl chlorides were effective substrates. (Table 3, entries 8–9). Additionally, the cross-coupling of aryl chlorides with alkylboronic acids are rare.[15] Gratifyingly, a preliminary study of the couplings of alkylboronic acids with both electron-poor and rich aryl chlorides was found to be successful (Table 3, entries 10–11).

In summary, we have developed a new, air-stable and active ferrocenyl triarylphosphine and have established its effectiveness in the palladium-catalyzed Suzuki–Miyaura coupling of aryl halides. The capability of this system to achieve cross-coupling of activated aryl chloride at room temperature is noteworthy. In light of the fact that **7** is a triarylphosphine, the high reactivity of Pd-**7** is unexpected. In view of the ease with which the structure of **7** can be modified, we anticipate that further enhancements in reactivity as well as the design of versatile ligands for asymmetric catalysis will be a fruitful pursuit.

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Notes and references

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