Synthesis of Tetra-*ortho*-Substituted Biaryls Using Aryltriolborates

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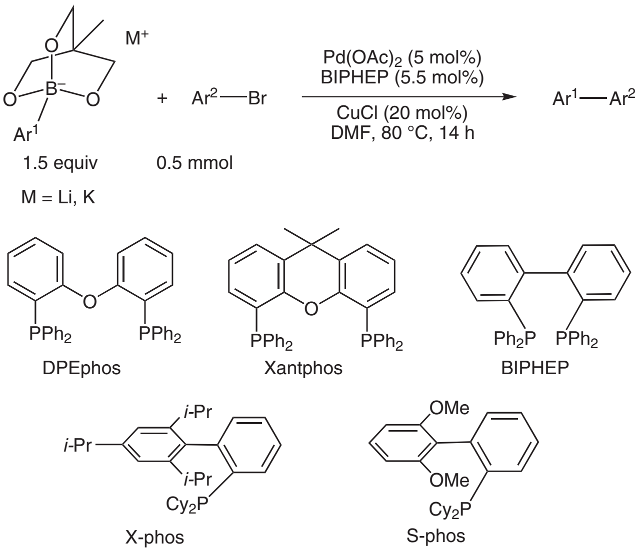
Abstract: Tetra-*ortho*-substituted biaryls were synthesized by cross-coupling between 2,6-disubstituted bromoarenes and aryltriolborates possessing substituents at *ortho* carbon. The use of a copper(I) halide such as CuCl (20 mol%) with a palladium catalyst was found to be highly effective to give such sterically hindered biaryls in good yields.

Key words: cross-coupling, palladium catalyst, aryltriolborates, tetra-*ortho*-substituted biaryls

Transition-metal-catalyzed cross-coupling reactions are effective synthetic methods for the formation of C–C bonds.[1] Cross-coupling reaction between aryl metal compounds and aryl electrophiles is a recent variant of traditional Ullman coupling for the synthesis of biaryls. Although this protocol has been extensively studied using a variety of organometallic reagents and electrophiles,[1] interest has recently been shown in the use of nonmetallic boron compounds because of their high stability in air and water and compatibility with a broad range of functional groups. Tetra-*ortho*-substituted biaryls are important fragments of organic functional materials[2] and many biologically active compounds such as michellamine and steganone.[3] A recent advance is the use of electron-rich and sterically demanding ligands, such as tri-*tert*-butylphosphine,[4] dialkylarylphosphines,[5–9] N-heterocyclic carbenes,[10–12] and other ligands,[13,14] for the synthesis of sterically hindered biaryl compounds. However, the use of large amounts of a base, especially a strong base, may be a major limitation for these applications. The development of an efficient, mild, and operationally simple catalyst system avoiding the use of large amounts of a base remains a challenge and has becomes an urgent issue.

We recently reported that aryltriolborates, which have air- and water-stability and high solubility in organic solvents, undergo very smooth transmetalation to various transition-metal complexes. The utility of these tetracoordinated arylboron compounds was demonstrated in palladium-catalyzed cross-coupling,[15] copper-catalyzed N-arylation of amines,[16] and rhodium-catalyzed 1,4-addition to enones.[17]

The reaction under aqueous conditions gives undesirable results due to competitive hydrolytic B–C bond cleavage. Such cleavage is accelerated by *ortho* substituents and significantly accelerated by adjacent heteroatoms in the boronic acid derivative.[18] 2-Pyridylboronic acid does not give coupling products because of its very raid protodeboronation.[19] High performance of 2-pyridine triolborates for metal-catalyzed bond-forming reactions was demonstrated in palladium- and copper-catalyzed cross-coupling reactions.[15b,c,16,17] Herein, we report a novel approach for the synthesis of tri- or tetra-*ortho*-substituted biaryls using *ortho*-substituted aryltriolborates (Scheme 1).



Scheme 1 Synthesis of tetra-*ortho*-substituted biaryls using aryltriolborates

The synthesis of cyclic triolborates has been reported in our previous work.[15] By using the same procedure, we successfully synthesized *ortho*-substituted triolborates **7**–**9** by treatment of hindered arylboronic acids with 1,1,1-tris(hydroxymethyl)ethane, producing ester intermediates that were further easily converted into aryltriolborates at the work of potassium hydroxide (Scheme 2). 3-Methyl-2-pyridyl triolborate **11** was synthesized by arylation of $B(Oi\text{-}Pr)_3$ with aryllithiums followed by ester exchange with triol (Scheme 3). This protocol afforded high yields for 2-pyridylboronates sensitive to B–C bond cleavage with water.

We chose 2,6-dimethylphenyltriolborates **7** and 1-bromo-2-methoxynapthalene to undergo coupling to optimize the reaction conditions (Table 1). Water proved to disfavor the sterically demanding coupling (Table 1, entries1–4). To our delight, the $Pd(OAc)_2/CuOAc$ condition using Ph_3P as a ligand gave 31% yield of the product (Table 1, entry 5). Encouraged by this promising result, we further

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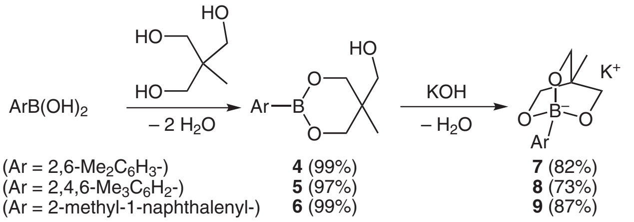
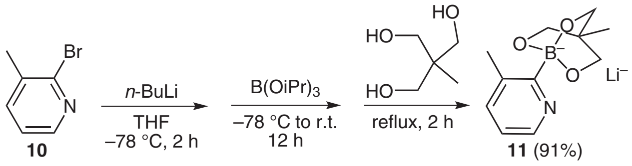
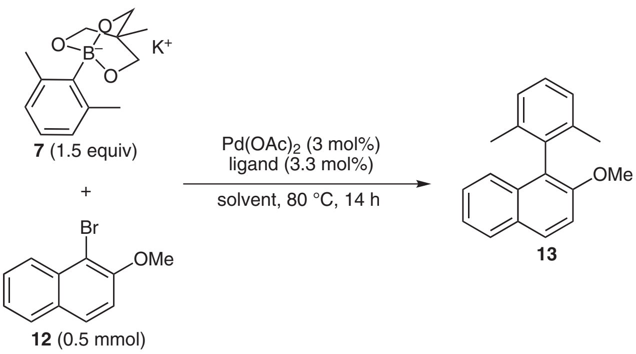


Scheme 2 Synthesis of *ortho*-substituted aryltriolborates



Scheme 3 Synthesis of 3-methyl-2-pyridyltriolborate

Table 1 Optimization of Tetra-*ortho*-Substituted Biaryls



Entry	Ligand	Additive (equiv)	Solvent	Yield (%)
1	Ph_3P	none	DMF–H_2O (5:1)	0
2	Ph_3P	none	DMF–H_2O (5:1)	0
3	Ph_3P	K_3PO_4 (1)	DMF–H_2O (5:1)	trace
4	Ph_3P	$Cu(OAc)_2$ (0.3)	DMF–H_2O (5:1)	0
5	Ph_3P	CuOAc (0.3)	DMF	31
6	Ph_3P	CuI (0.3)	DMF	50
7	Ph_3P	CuCl (0.3)	DMF	64
8[a]	Ph_3P	CuCl (0.3)	DMF	34
9	Ph_3P	CuCl (0.3)	1,4-dioxane	trace
10	X-phos	CuCl (0.3)	DMF	trace
11	S-phos	CuCl (0.3)	DMF	76
12	Xantphos	CuCl (0.3)	DMF	72
13	DPEphos	CuCl (0.3)	DMF	75
14	BIPHEP	CuCl (0.3)	DMF	84
15[b]	BIPHEP	CuCl (0.3)	DMF	91
16[b]	BIPHEP	CuCl (0.2)	DMF	95
17[b]	BIPHEP	CuCl (0.4)	DMF	87
18[c]	BIPHEP	CuCl (0.3)	DMF	94
19	BIPHEP	none	DMF	0

[a] $Pd(dba)_2$ (3 mol%) was used.
[b] $Pd(OAc)_2$ (5 mol%)/BIPHEP (5.5 mol%) were used.
[c] $Pd(OAc)_2$ (10 mol%)/BIPHEP (11 mol%) were used.

examined the efficiency of CuI[15b,c,20] and CuCl[21] in this hindered coupling reaction. CuCl gave the best yield, improving the yield to 64% (Table 1, entry 7). When $Pd(dba)_2$ was used in the same reaction, a decreased yield was observed (Table 1, entry 8). Next we screened the solvent effects, and no desired coupling product was observed in 1,4-dioxane and MeCN, which may be caused by poor solubility for aryltriolborate in these solvents (Table 1, entry 9). By examination of phosphine-based ligands, BIPHEP gave the best result (84% yield, Table 1, entry 14). By further investigations of the amounts of $Pd(OAc)_2$, CuCl, and BIPHEP, tetra-*ortho*-substituted biaryl was obtained finally in 95% yield using 5 mol% $Pd(OAc)_2$/5.5 mol% BIPHEP in the presence of 20% CuCl using DMF as a solvent at 80 °C for 14 hours (Table 1, entry 16).

No reaction was observed in the absence of CuCl (Table 1, entry 19). There has not yet been a mechanistic study; however, such an effect of copper salts has been successfully utilized in analogous coupling reactions of 2-heteroaryl boron compounds.[15b,c,20,21]The role of copper salts seem to be facilitate the transmetalation of aryltriolborates to the arylpalladium bromides by the generation of arylcopper species.[21]

Under the optimized reaction conditions, hindered couplings occurred between aryltriolborates **7**–**9** and **11** and a number of hindered aryl bromides (Table 2).[22] All of the *ortho*-substituted biaryls were obtained in excellent yields. 2-Bromo-3-methylthiophene was also evaluated in this hindered coupling. *ortho*-Substituted heterobiaryls were successfully formed in excellent yields using 1.2 equivalents of aryltriolborate (Table 2, entries 6 and 15). 2,6-Disubsituted aryltriolborate and hindered electron-deficient 1-bromo-2-naphthaldehyde gave the desired biaryl in good yield using 2 equivalents of aryltriolborate (Table 2, entry 12). To further demonstrate the efficiency of this protocol, some arenes with a base-sensitive functional group such as COOR or COR were also investigated and they smoothly yielded biaryls (Table 2, entries 7 and 8). Heteroaromatic boronic acids often fail to give biaryls due to the high sensitivity of the B–C bond of electron-deficient heteroaryl rings to hydrolytic B–C bond cleavage with water.[15,23] 3-Methyl-2-pyridylboronic acid is a typical example that undergoes very rapid cleavage with water. Cross-coupling reaction of 3-methyl-2-pyridyltriolborate (**11**) with 1-bromo-2-methoxynaphthalene or 4-bromo-1,3,5-trimethyl-1*H*-pyrazole gave corresponding biaryls in high yields (Table 2, entries 23 and 24).

Table 2 Hindered Coupling between Aryltriolborates and Aryl Bromides[a]

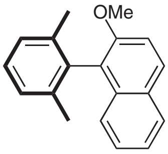
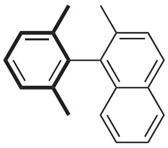
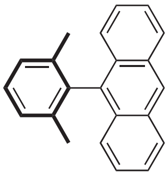
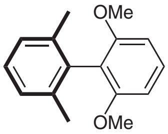
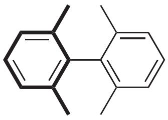
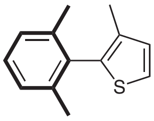
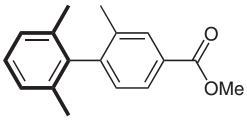
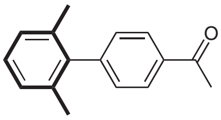
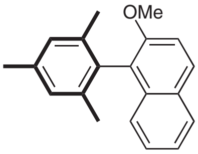
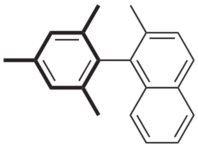
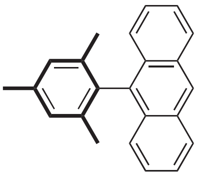
Entry	Ar^1–Ar^2		Yield (%)[b]
1		**13**	95
2		**14**	88
3		**15**	83
4		**16**	81
5		**17**	99
6[c]		**18**	90
7[c]		**19**	97
8[c]		**20**	99
9		**21**	92
10		**22**	90
11		**23**	87

Table 2 Hindered Coupling between Aryltriolborates and Aryl Bromides[a] (continued)

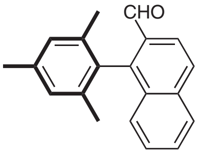
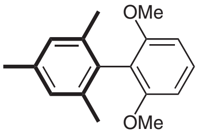
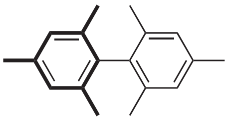
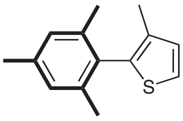
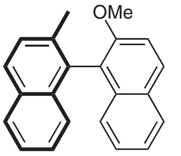
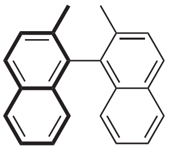
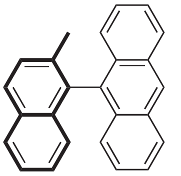
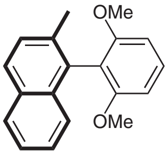
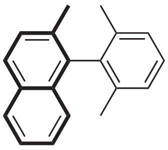
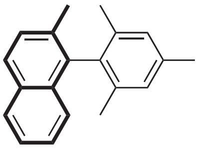
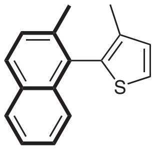
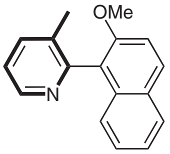
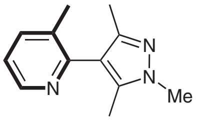
Entry	Ar^1–Ar^2		Yield (%)[b]
12[d]		**24**	82
13		**25**	84
14		**26**	99
15[c]		**27**	83
16		**28**	86
17		**29**	97
18		**30**	82
19		**31**	78
20		**14**	84
21		**22**	91

Table 2 Hindered Coupling between Aryltriolborates and Aryl Bromides[a] (continued)

Entry	Ar^1–Ar^2		Yield (%)[b]
22[c]		**32**	80
23[d]		**33**	88
24[d]		**34**	90

[a] A mixture of Ar^{1}B(OCH$_2$)$_3$CMe (0.75 mmol), Ar^{2}Br (0. 5 mmol), Pd(OAc)$_2$ (5 mol%), BIPHEP (Pd/P = 1:1.1) and CuCl (0.1 mmol) in anhyd DMF was stirred at 80 °C for 14 h.

[b] Isolated yields by chromatography.

[c] 1.2 equiv aryltriolborate were used.

[d] 2.0 equiv aryltriolborate were used.

In summary, we have described a novel and efficient catalyst system for the synthesis of tetra-*ortho*-substituted biaryls using aryltriolborates. Since the use of a base is avoided, a variety of functional groups may be accommodated in this reaction system.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(22) **General Procedure for the Synthesis of *ortho*-Substituted Biaryls**
The aryl bromide (0.5 mmol), aryl triolborate (0.75 mmol), $Pd(OAc)_2$ (5 mol%), BIPHEP (5.5 mol%), and CuCl (0.1 mmol) were placed in a flash under nitrogen atmosphere. Anhyd DMF (5 mL) was added. The mixture was stirred at 80 °C for 14 h. After cooling to r.t., the crude mixture was filtered through a plug of Celite and washed with Et_2O. The filtrate was then concentrated in vacuo to afford the crude product, which was further purified by chromatography on silica gel with hexanes–EtOAc (99:1 to 10:1).

(23) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469.