Synthesis of Tetra-*ortho*-substituted Biaryls using Aryltriolborates

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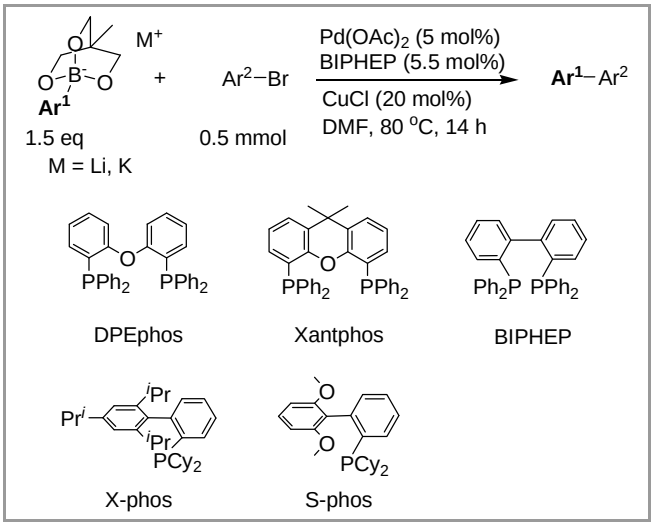
Abstract: Tetra-*ortho*-substituted biaryls were synthesized by cross-coupling between 2,6-disubstituted bromoarenes and aryltriolborates possessing substituents at *ortho*-carbon. The use of a copper(I) halide such as CuCl (20 mol%) with a palladium catalyst was found to be highly effective to give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

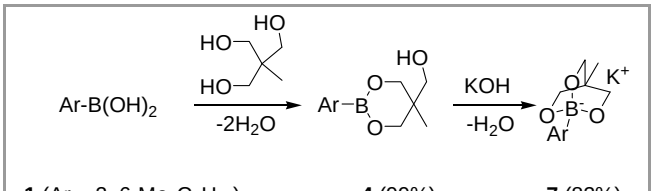
We recently reported that aryltriolborates, which have air- and water-stability and high solubility in organic solvents, undergo very smooth transmetalation to various transition metal complexes. The utility of these tetra-coordinated arylboron compounds was demonstrated in palladium-catalyzed cross-coupling,[15] 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 synthesis of tri- or tetra-*ortho*-substituted biaryls using *ortho*-substituted aryltriolborates.



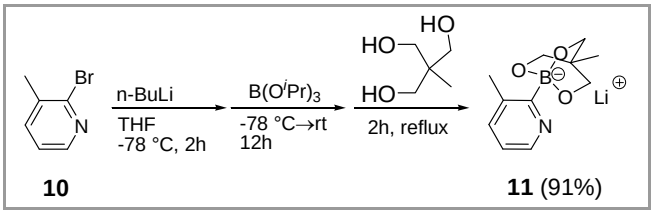
Scheme 1 Synthesis of Tetra-*ortho*-substituted Biaryls using Aryltriolborates

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**, **8** and **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-pyridyltriolborate (**11)** was synthesized by arylation of $B(O^iPr)_3$ 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.



1 (Ar = 2, 6-$Me_2C_6H_3$-)	**4** (99%)	**7** (82%)
2 (Ar = 2, 4, 6-$Me_3C_6H_2$-)	**5** (97%)	**8** (73%)
3 (Ar = 2-methl-1-naphthalenyl-)	**6** (99%)	**9** (87%)

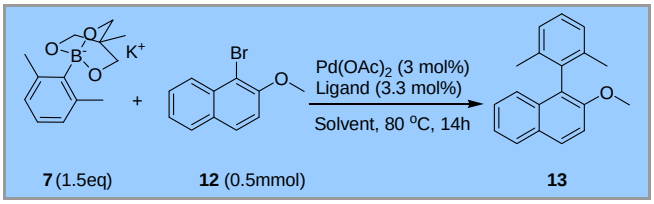
Scheme 2 Synthesis of *ortho*-substituted aryltriolborates



Scheme 3 Synthesis of 3-methyl-2-pyridyltriolborate

We chose 2, 6-dimethylphenyl triolborates (**7**) and 1-bromo-2-methoxynapthalene to undergo coupling to optimize the reaction conditions (**Table 1**). Water proved to disfavor the sterically demanding coupling (entries1-4). To our delight, the $Pd(OAc)_2$/CuOAc condition using PPh_3 as a ligand gave 31% yield of the product (entry 5). Encouraged by this promising result, we further examined the efficiency of CuI[15b,c, 20] and CuCl[21] in this hindered coupling reaction and CuCl gave the best yield, improving the yield to 64% (entry 7). When $Pd(dba)_2$ was used in the same reaction, a decreased yield was observed (entry 8). Next we screened the solvent effects and no desired coupling product was observed in 1, 4-dioxane and CH_3CN, which may be caused by poor solubility for aryltriolborate in these solvents (entry 9). By examination of phosphine-based ligands, BIPHEP gave the best result, 84% yield (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 h (entry 16). No reaction was observed in the absence of CuCl (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]

Table 1 Optimization of tetra-*ortho*-substituted biaryls



entry	ligand	additive (eq)	solvent	yield/%
1	PPh_3	none	DMF/H_2O (5/1)	0
2	PPh_3	none	DMF/H_2O (5/1)	0
3	PPh_3	K_3PO_4 (1)	DMF/H_2O (5/1)	trace
4	PPh_3	$Cu(OAc)_2$ (0.3)	DMF/H_2O (5/1)	0
5	PPh_3	CuOAc (0.3)	DMF	31
6	PPh_3	CuI (0.3)	DMF	50
7	PPh_3	CuCl (0.3)	DMF	64
8[a]	PPh_3	CuCl (0.3)	DMF	34
9	PPh_3	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.

Under the optimized reaction conditions, hindered couplings occurred between aryltriolborates **7**, **8**, **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 (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 (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 (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-1H-pyrazole gave corresponding biaryls in high yields (entries 23 and 24).

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.de/ejournals/toc/synlett.

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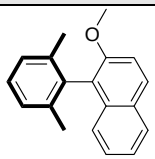
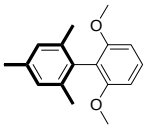
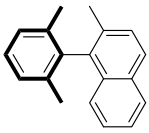
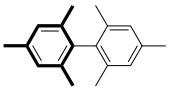
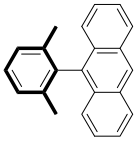
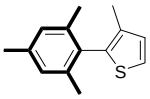
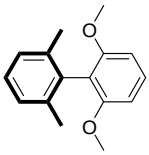
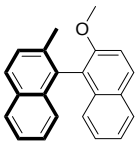
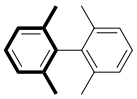
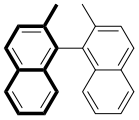
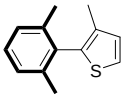
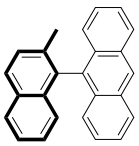
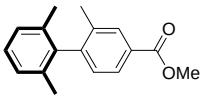
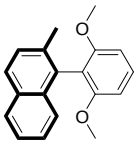
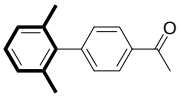
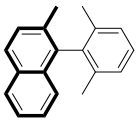
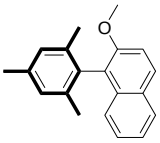
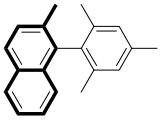
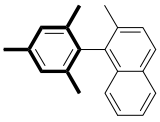
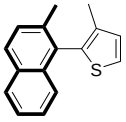
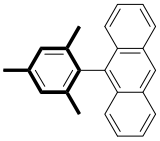
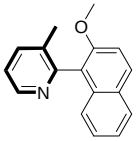
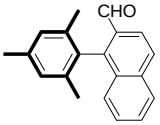
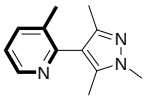
Table 2 Hindered coupling between aryltriolborates and aryl bromides[a]

entry	Ar^1-Ar^2		yield/%[b]	entry	Ar^1-Ar^2		yield/%[b]
1		(**13**)	95	13		(**25**)	84
2		(**14**)	88	14		(**26**)	99
3		(**15**)	83	15[c]		(**27**)	83
4		(**16**)	81	16		(**28**)	86
5		(**17**)	99	17		(**29**)	97
6[c]		(**18**)	90	18		(**30**)	82
7[c]		(**19**)	97	19		(**31**)	78
8[c]		(**20**)	99	20		(**14**)	84
9		(**21**)	92	21		(**22**)	91
10		(**22**)	90	22[c]		(**32**)	80
11		(**23**)	87	23[d]		(**33**)	88
12[d]		(**24**)	82	24[d]		(**34**)	90

[a] A mixture of **Ar**[1]$B(OCH_2)_3CCH_3$ (0.75 mmol), Ar^2Br (0. 5 mmol), $Pd(OAc)_2$ (5 mol%), BIPHEP (Pd : P = 1 : 1.1) and CuCl (0.1 mmol) in anhydrous DMF was stirred at 80 °C for 14 h. [b] Isolated yields by chromatography. [c] 1.2 eq aryltriolborate was used. [d] 2.0 eq aryltriolborate was used.

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(22) General procedure for synthesis of ortho-substituted biaryls
The aryl bromide (0.5 mmol), aryl triolborate (0.75 mmol), palladium acetate (5 mol %), BIPHEP (5.5 mol %), CuCl (0.1 mmol) were placed in a flash under nitrogen atmosphere. dry DMF (5 mL) was added. The mixture was stirred at 80 ^{o}C for 14 h. After cooling to room temperature, the crude mixture was filtered through a plug of Celite and washed with ether. The filtrate was then concentrated in vacuo to afford the crude product, which was further purified by chromatography on silica gel with hexanes/EtOAc (99:1-10:1).

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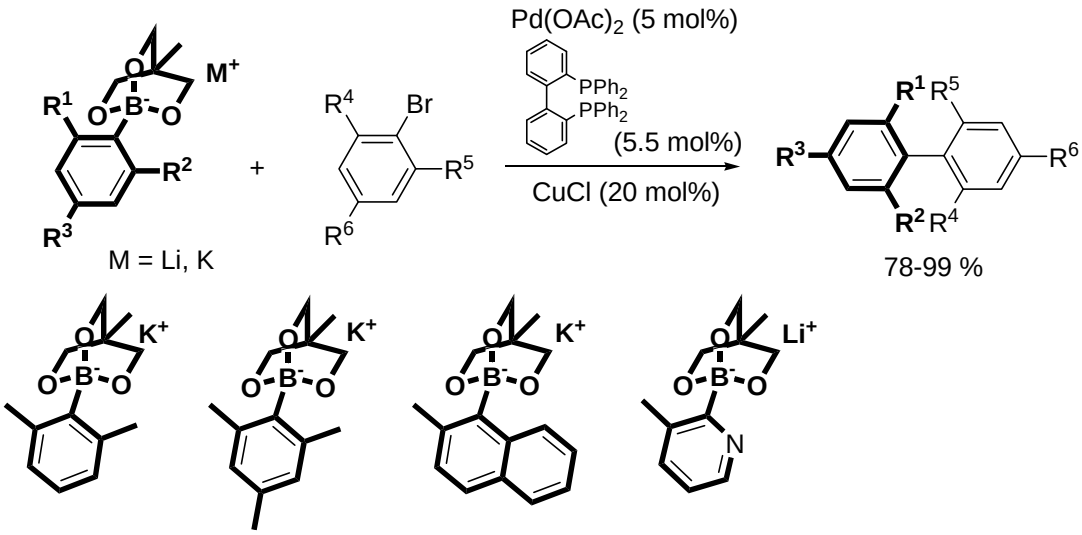
Synthesis of Tetra-*ortho*-substituted Biaryls using Aryl Triolborates

We have demonstrated the efficiency of aryl triolborates possessing substituents at *ortho*-carbon for synthesis of tetra-*ortho*-substituted biaryls by cross-coupling with 2,6-disubstituted bromoarenes. The use of CuCl (20 mol%) with a palladium catalyst was found to be highly effective to give such sterically hindered biaryls in good yields. Since the use of a base is avoided, a variety of functional groups may be accommodated in this reaction system.

Short title: synthesis of *ortho*-substituted biaryls

Graphical abstract:



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