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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 materials² 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 become 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 amines¹⁶ 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 rapid 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^{*i*}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.

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-methoxynaphthalene to undergo coupling to optimize the reaction conditions (**Table 1**). Water proved to disfavor the sterically demanding coupling (entries 1-4). To our delight, the $\text{Pd}(\text{OAc})_2/\text{CuOAc}$ 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 $\text{CuI}^{15\text{b,c}}$, CuCl^{21} in this hindered coupling reaction and CuCl gave the best yield, improving the yield to 64% (entry 7). When $\text{Pd}(\text{dba})_2$ 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 $\text{Pd}(\text{OAc})_2$, CuCl and BIPHEP, tetra-*ortho*-substituted biaryl was obtained finally in 95% yield using 5 mol% $\text{Pd}(\text{OAc})_2/5.5$

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

entry	ligand	additive (eq)	solvent	yield/%
1	PPh_3	none	$\text{DMF}/\text{H}_2\text{O}$ (5/1)	0
2	PPh_3	none	$\text{DMF}/\text{H}_2\text{O}$ (5/1)	0
3	PPh_3	K_3PO_4 (1)	$\text{DMF}/\text{H}_2\text{O}$ (5/1)	trace
4	PPh_3	$\text{Cu}(\text{OAc})_2$ (0.3)	$\text{DMF}/\text{H}_2\text{O}$ (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 $\text{Pd}(\text{dba})_2$ (3 mol%) was used.

^b $\text{Pd}(\text{OAc})_2$ (5 mol%)/BIPHEP (5.5 mol%) were used.

^c $\text{Pd}(\text{OAc})_2$ (10 mol%)/BIPHEP (11 mol%) were used.

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

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-Disubstituted 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 $-\text{COOR}$ or $-\text{COR}$ 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 Ar¹B(OCH₂)₃CCH₃ (0.75 mmol), Ar²Br (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 °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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