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, tetraortho-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-tertbutylphosphine,4 dialkylarylphosphines5-9 N-heterocyclic carbenes10-12 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- 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.

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 Bi(OiPr)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 1](image-url)

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

![Scheme 2](image-url)

**Scheme 2** Synthesis of ortho-substituted aryltriolborates
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 Pd(OAc)2/CuOAc condition using PPh3 as a ligand gave 31% yield of the product (entry 5). Encouraged by this promising result, we further examined the efficiency of CuCl20,21 and CuCl21 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 CH3CN, which may be caused by poor solubility for aryltriolborates 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, tetrabromo-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.21a-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 aryltriolborates (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 –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.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 biaryl in high yields (entries 23 and 24).

In summary, we have described a novel and efficient catalyst system for the synthesis of tetrabromo-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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**References**

Table 2  Hindered coupling between aryltriolborates and aryl bromides

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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 ºC for 14 h. b Isolated yields by chromatography. c 1.2 eq aryltriolborate was used. d 2.0 eq aryltriolborate was used.


(11) Song, C.; Ma, Y.; Cui, Q.; Ma, C.; Tran, W.; Adrus, M. B. Tetrahedron 2005, 61, 7438-7446.


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:

![Graphical abstract image]

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