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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 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 triolborate compounds 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(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.

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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 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$_3$CN, 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 boronic acids$^{15,23}$.

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 arynes 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 heteroaroyl 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.

Acknowledgment

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References

(1) For reviews, see: (a) Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457-2483. (b) Suzuki, A. in Metal-Catalyzed Cross-Coupling Reactions ed. by Diederich, F.; and Stang, P. J. Wiley-VCH, Weinheim, 1998; p. 49-98. (c) Miyaura, N. in Advances in Metal-Organic
### Table 2: Hindered coupling between aryltrioleborates and aryl bromides

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*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. Isolated yields by chromatography. 1.2 eq aryltrioleborate was used. 2.0 eq aryltrioleborate was used.
Acknowledgments


References


(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/エトオハ (99:1-10:1).

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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