Repetitive Two-step Method for Oligoarene Synthesis through Rapid Cross-coupling of Hydroxyphenylboronic Acids and Anhydrides

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A two-step Suzuki–Miyaura coupling–triflation procedure, which features the use of hydroxyphenylboronic acids or anhydrides in the palladium-catalyzed cross-coupling step, has been developed for the synthesis of oligoarenes.

Oligo- and polyarenes, which are composed of aromatic rings such as benzene rings connected through a single bond, constitute an important class of compounds in various research areas.[1] Although several synthetic methods have been developed, the efficient construction of highly functionalized oligoarenes (Figure 1a), which have a great potential as functional molecules, remains a challenging task. This type of oligoarenes can be compared to biopolymers such as polypeptides with various amino acid residues. For polypeptides, repetition of coupling–deprotection steps, using *N*-protected amino acids for example, has allowed efficient synthetic methods including solid-phase synthesis[2] and automation. Similarly, a stepwise, repetitive two-step cross-coupling–activation procedure[3] may prove to be an efficient synthetic methodology of functionalized oligoarenes (Figure 1b). Such scheme will require: 1) mild reaction conditions that are compatible with the various functional groups, 2) avoidance of high or low (e.g., −78 °C) temperatures for experimental simplicity, and 3) steps that proceed rapidly and almost quantitatively.

Cross-coupling of arylboronic acids with aryl halides or sulfonates such as triflates (Suzuki–Miyaura coupling) is one of the best synthetic methods to afford biaryls with various functional groups.[4] Accordingly, we envisaged the cross-coupling of hydroxyphenylboronic acids and subsequent triflation of the hydroxy group as an effective strategy for oligoarene synthesis (Figure 1c).[5] Herein, we describe a novel repetitive two-step procedure for oligoarene synthesis under reaction conditions that satisfy the criteria mentioned above. Repetition of the sequence afforded unfunctionalized oligoarene backbones in excellent yields. This method will be applied to the synthesis of oligoarenes with various functional groups.

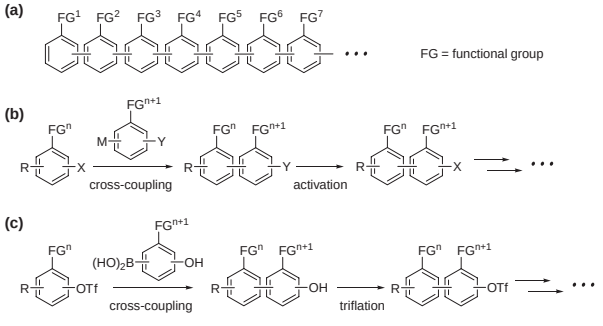
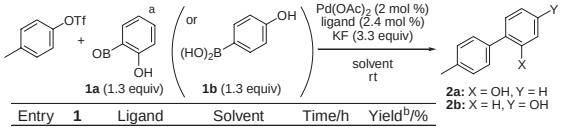


Figure 1. (a) Functionalized oligoarene. (b) Cross-coupling–activation procedure. (c) Use of hydroxyphenylboronic acid in the cross-coupling–triflation procedure.

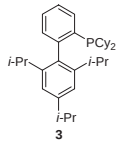
The three isomers of hydroxyphenylboronic acids (2-, 3-, and 4-hydroxyphenylboronic acids or anhydrides) are known in the literature.[6] Among them, pure 2- and 3-hydroxyphenylboronic acids can be obtained as their anhydride forms by recrystallization. Therefore, we first tested 2-hydroxyphenylboronic anhydride (**1a**) to determine the optimal conditions for the cross-coupling with *p*-tolyl triflate as the model substrate. The use of $Pd(OAc)_2$, PCy_3, and KF in THF[7] afforded **2a** in unsatisfactory yield (Table 1, Entry 1). However, significantly improved reaction rate and yield were obtained with the use of aqueous DMF (Entry 3), in which the optimal DMF/H_2O ratio was 4/1 (Entries 4–6).[8,9] In contrast, the use of aqueous THF was less effective (Entry 7).

In the next set of reactions, ligands **3**[10] and **4**,[11] developed by Buchwald et al., were employed as ligands. Interestingly, in terms of the reaction solvents, results for these ligands were opposite to those for PCy_3—aqueous THF was found to be significantly better than aqueous DMF (Entry 10 vs 11, and 16 vs 17). Under aqueous THF conditions, the reaction proceeded rapidly and was complete in 2 h, yielding **2a** quantitatively. As for amounts of **1a**, 1.1 equiv. was deemed sufficient (Entry 12). Although the reaction time was longer, 0.1 mol % $Pd(OAc)_2$ resulted in a high yield of **2a** (Entry 13). The use of $K_3PO_4 \cdot H_2O$ in dry THF[11] resulted in low yield (Entry 18). It is noted that the effect (albeit small) of added water was also observed for 4-hy-

Table 1. Cross-coupling of 2-hydroxyphenylboronic anhydride or 4-hydroxyphenylboronic acid



Entry	1	Ligand	Solvent	Time/h	Yield[b]/%
1	**1a**	PCy_3	THF	25	61
2	**1a**	PCy_3	DMF	25	87
3	**1a**	PCy_3	DMF/H_2O (4/1)	5	100
4	**1a**	PCy_3	DMF/H_2O (4/1)	2	84
5	**1a**	PCy_3	DMF/H_2O (1/1)	2	62
6	**1a**	PCy_3	DMF/H_2O (10/1)	2	59
7	**1a**	PCy_3	THF/H_2O (4/1)	2	45
8	**1a**	**3**	DMF	25	31
9	**1a**	**3**	THF	25	85
10	**1a**	**3**	DMF/H_2O (4/1)	2	8
11	**1a**	**3**	THF/H_2O (4/1)	2	100
12[c]	**1a**	**3**	THF/H_2O (4/1)	2	96
13[d]	**1a**	**3**	THF/H_2O (4/1)	70	93
14	**1a**	**4**	DMF	25	19
15	**1a**	**4**	THF	25	73
16	**1a**	**4**	DMF/H_2O (4/1)	2	10
17	**1a**	**4**	THF/H_2O (4/1)	2	99
18[e]	**1a**	**4**	THF	2	27
19	**1b**	**4**	THF	2	83
20	**1b**	**4**	THF/H_2O (4/1)	2	95



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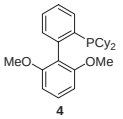

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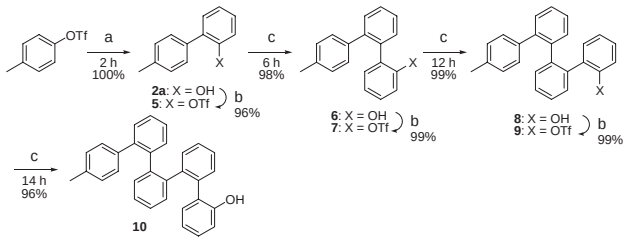
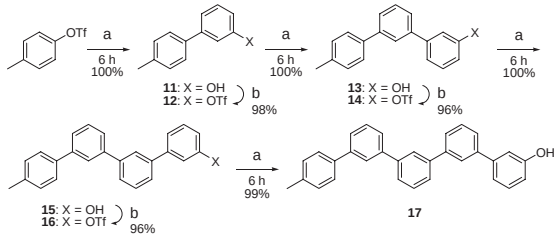
[a]The anhydride form of 2-hydroxyphenylboronic acid. [b]Isolated yield. [c]**1a** (1.1 equiv.). [d]$Pd(OAc)_2$ (0.1 mol %), ligand (0.12 mol %). [e]$K_3PO_4 \cdot H_2O$ was used in place of KF.



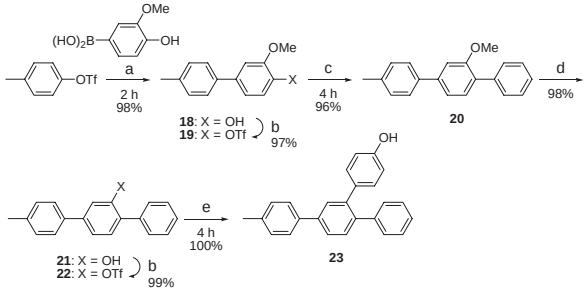
Scheme 1. Synthesis of an oligoarene with *ortho*-connection. Conditions: (a) **1a** (1.3 equiv.), $Pd(OAc)_2$ (2 mol %), **3** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt. (b) Tf_2O (1.2 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 0 °C, 20 min. (c) **1a** (1.6 equiv.), $Pd(OAc)_2$ (2 mol %), **4** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt.



Scheme 2. Synthesis of an oligoarene with *meta*-connection. Conditions: (a) 3-hydroxyphenylboronic anhydride (1.3 equiv.), $Pd(OAc)_2$ (2 mol %), **3** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt. (b) Tf_2O (1.2 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 0 °C, 20 min.

droxyphenylboronic acid (**1b**) (Entry 19 vs 20). To summarize, whereas PCy_3 in aqueous DMF may be economically preferable, ligand **3** or **4** in aqueous THF is the ligand of choice in the cross-coupling of hydroxyphenylboronic acids or anhydrides.

As shown in Scheme 1, the cross-coupling conditions were applied to the synthesis of oligoarene backbones, in which a pentamer **10**, with benzene rings connected at *ortho*-position, was readily synthesized through the rapid cross-coupling–triflation procedure. Note that, despite the presence of a bulky oligoarene chain at the *ortho*-position, the yield of each cross-coupling step was nearly quantitative, while longer reaction times and larger amounts of **1a** were required as the oligoarene chain increased. An oligoarene **17** that was connected through the *meta*-position



Scheme 3. Synthesis of a branched oligoarene. Conditions: (a) 4-hydroxy-3-methoxyphenylboronic acid (1.3 equiv.), $Pd(OAc)_2$ (2 mol %), **4** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt. (b) Tf_2O (1.2 equiv.), pyridine (1.5 equiv.), CH_2Cl_2, 0 °C, 20 min. (c) Phenylboronic acid (1.3 equiv.), $Pd(OAc)_2$ (2 mol %), **3** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt. (d) BBr_3 (2.0 equiv.), CH_2Cl_2, 0 °C to rt, 2 h. (e) **1b** (1.3 equiv.), $Pd(OAc)_2$ (2 mol %), **4** (2.4 mol %), KF (3.3 equiv.), THF/H_2O (4/1), rt.

was also synthesized in excellent yield (Scheme 2). In this case, the use of ligand **3** rather than **4** gave better results in the cross-coupling step.

As shown in Scheme 3, the "branching" of an oligoarene chain was realized using a mono-protected dihydroxyphenylboronic acid. First, 4-hydroxy-3-methoxyphenylboronic acid was employed in the cross-coupling step to generate a "branch" point (step a). Next, the main chain was elongated (steps b and c). The methyl ether was then cleaved to give the OH group (step d) that can be elongated (steps b and e). Using this methodology, the "branch" and main chains can be independently extended.

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