Synthetic method for multifunctionalized oligoarenes using pinacol esters of hydroxyphenylboronic acids†

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A synthetic method for multifunctionalized oligoarenes using rapid Suzuki–Miyaura coupling of pinacol esters of hydroxyphenylboronic acids and subsequent triflation of the hydroxy group was developed.

Functionalized oligoarenes are widely used in various research areas that involve self-assembling molecules,[1] biologically active compounds,[2] enzyme mimics,[3] and molecular electronics.[4] The rigid aromatic rings of the oligoarene framework allow for the precise positioning of various functional groups. In the course of our investigations on catalyst development, we envisaged multifunctionalized oligoarenes (Fig. 1a) as attractive candidates for catalytic macromolecules. Unfortunately, synthetic procedures of such multifunctionalized oligoarenes have yet to be established, thus requiring the development of an efficient synthetic methodology. We have previously reported on the synthesis of *un*functionalized oligoarenes,[5] which feature the use of hydroxyphenylboronic acids (HPBAs) or anhydrides in repetitive two-step (Suzuki–Miyaura coupling[6] and triflation) procedures (Fig. 1b, X_2B = $(HO)_2B$).[7] Although oligoarene backbones can be readily constructed using this method, the purification and characterization of the starting HPBAs proved to be problematic because of the complexity associated, not only with boroxine formation, but also with boronic ester formation of the OH group. Because the purification and characterization of various functionalized HPBAs are expected to be similarly troublesome, we proposed the use of pinacol esters of HPBAs (Fig. 1b, X_2B = pinB), which can be readily prepared, purified, and characterized.[8] However, in contrast to that of boronic acids, Suzuki–Miyaura coupling of pinacol esters has not been extensively developed. Heating of reaction mixtures to high temperatures is required in most cases.[9] Herein, we report a novel repetitive two-step method for the construction of multifunctionalized oligoarenes using pinacol esters of HPBAs under mild reaction conditions, in which the key cross-coupling steps can be carried out at room temperature.

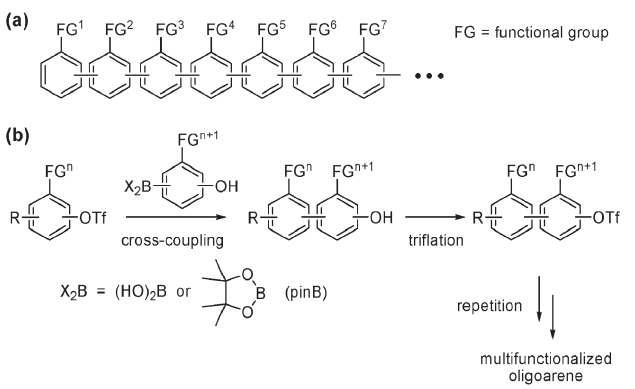
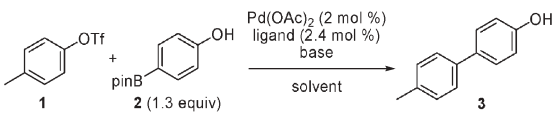


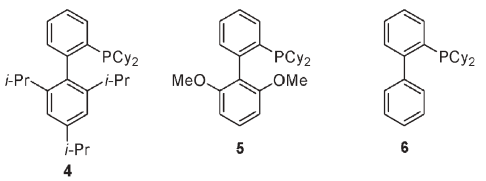
Fig. 1 (a) Functionalized oligoarene. (b) Repetitive synthetic method using hydroxyphenylboronic acid derivatives.

To optimize the mild reaction conditions for the key cross-coupling step, a model reaction was carried out using triflate **1** with the pinacol ester (**2**) of 4-hydroxyphenylboronic acid in the presence of a palladium catalyst at room temperature (Table 1). The reported conditions for the reactions of HPBAs,[5] which involve ligand **4**[10] and KF in THF–H_2O, were found to be ineffective (entry 1). Subsequently, the slightly improved yield using K_3PO_4 (entry 2) prompted us to explore stronger bases. Although such bases may cause hydrolysis of the triflate, our studies reveal that the nature of the countercation has a significant

Table 1 Optimization of cross-coupling conditions



Entry	Ligand	Base[a]	Solvent (v/v)	Time/h	Yield (%)[b]
1	**4**	KF	THF–H_2O (4:1)	5	4
2	**4**	K_3PO_4	THF–H_2O (4:1)	5	15
3	**4**	$CsOH·H_2O$	THF–H_2O (4:1)	5	0
4	**4**	$Ba(OH)_2·8H_2O$	THF–H_2O (4:1)	5	48
5	**4**	KOH	THF–H_2O (4:1)	5	89
6	**4**	$LiOH·H_2O$	THF–H_2O (4:1)	5	74
7	PCy_3	$LiOH·H_2O$	THF–H_2O (4:1)	5	1
8	PPh_3	$LiOH·H_2O$	THF–H_2O (4:1)	5	28
9	**5**	$LiOH·H_2O$	THF–H_2O (4:1)	5	31
10	**6**	$LiOH·H_2O$	THF–H_2O (4:1)	2	100 (100)[c]
11	**6**	$LiOH·H_2O$	THF	2	74
12	**6**	$LiOH·H_2O$	THF–H_2O (1:1)	2	100
13[d]	**6**	$LiOH·H_2O$	THF–H_2O (4:1)	2	(86)[c]



[a] 3.3 equiv. for entries 1–4, 2.4 equiv. for entries 5–13. [b] NMR yield. [c] Isolated yield. [d] The corresponding boronic acid was used instead of **2**.

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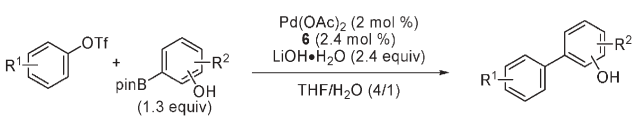
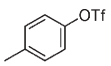
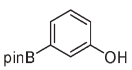
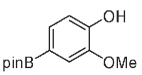
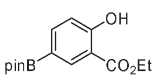
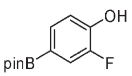
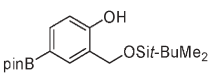
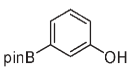
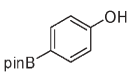
impact on the reaction. The use of CsOH resulted in complete hydrolysis of **1**, affording *p*-cresol (entry 3). In the cases of $Ba(OH)_2$ and KOH, the yields were significantly improved (entries 4 and 5), in spite of the presence of some *p*-cresol (2% or 8%, respectively). Remarkably, complete suppression of the hydrolysis of **1** and good yields of **3** (entry 6) were afforded by using LiOH, which was consequently chosen as the base for the reaction.

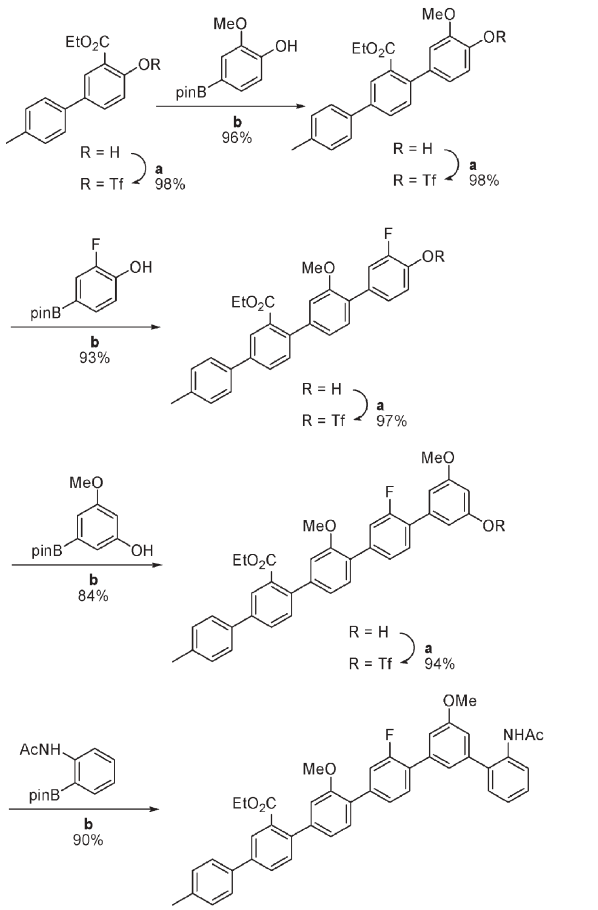
Studies to screen various phosphine ligands revealed that methoxy-substituted ligand **5**[9a] was less effective than **4** (entry 9). To our surprise, simpler ligand **6**[11] afforded **3** almost quantitatively in 2 h (entry 10). Although the use of an aqueous solvent was beneficial (entry 10 *vs.* 11), increasing the amount of water did not significantly affect the result (entry 12). Under these optimized conditions, however, the corresponding boronic acid resulted in a lower yield (entry 13).

Table 2 Cross-coupling of various substrates



Entry	ArOTf	pinBAr	Time/h	Yield (%)[a]
1			2	97
2			4	96
3			4	98
4			6	93
5			2	98
6			8	84
7			2	90
8			2	99
9			2	97

[a] Isolated yield.



Scheme 1 Synthesis of multifunctionalized oligoarene. Conditions: (a) Tf_2O, pyridine, CH_2Cl_2. (b) $Pd(OAc)_2$ (2 mol%), **6** (2.4 mol%), $LiOH{\cdot}H_2O$ (2.4 equiv.), THF–H_2O (4:1).

Next, using the optimized conditions (Table 1, entry 10), the reaction was carried out using various combinations of aryl triflates and HPBA esters (Table 2). In addition to *p*-hydroxy, the *o*- and *m*-hydroxy compounds also reacted smoothly to give the desired products in high yields (entries 1 and 2). Furthermore, HPBA esters with functional groups were successfully utilized (entries 3–6). It is noteworthy that a bulky 2,6-disubstituted phenyl triflate also gave the products in high yields (entries 7–9).

As shown in Scheme 1, oligoarene synthesis was carried out using pinacol esters of functionalized HPBAs. The simple combination of the cross-coupling and the subsequent triflation of the OH group readily produced the multifunctionalized oligoarene, in high yielding steps. Note that base-sensitive functional groups, such as an ester, survived during the multistep synthesis.

In summary, a method for the synthesis of multifunctionalized oligoarenes was developed. A key feature of the methodology is the use of pinacol esters of HPBAs. We found the Suzuki–Miyaura coupling conditions under which the pinacol esters can be used at room temperature. Using this method, together with a combinatorial approach, diverse sets of multifunctionalized oligoarenes can readily be prepared in the quest for novel functional molecules.

Further studies to develop functional molecules based on this strategy are currently underway.

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