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Boron-Masking Strategy for the Selective Synthesis of Oligoarenes via Iterative Suzuki−Miyaura Coupling

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The palladium-mediated coupling of organoboronic acid derivatives with organic halides, i.e., the Suzuki−Miyaura coupling (SMC), is one of the most reliable and convenient reactions for C−C bond formation.[1] The high efficiency of the reaction, high stability of the organoboron compounds toward air and moisture, and high functional group compatibility make SMC one of the most widely used of all the available cross-coupling systems. Recent advances have provided new catalyst systems which permit the highly efficient synthesis of a variety of organic compounds,[2] including oligo- and polyarene derivatives, which are of significant importance in materials science and technology.[3]

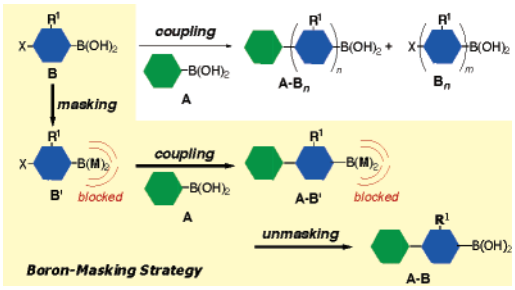
In this report, we describe a novel strategy for an iterative SMC,[4] which leads to the synthesis of a wide range of functionalized oligoarenes. The critical design element is the use of an efficient masking group for the boronyl group, which temporarily renders it inactive, allowing the use of bifunctional (nucleophile/electrophile) arenes in the coupling reaction. As far as we are aware, a masking/unmasking strategy has never been used to control reactivity of organoboronic acids in the coupling reaction.[5]

To illustrate the approach, the synthesis of biarylboronic acids **A**−**B** via SMC is shown in Scheme 1. The coupling of arylboronic acid **A** with haloboronic acid **B** would not provide the desired compound, leading instead to the formation of a mixture of oligoarenes **A**−**B**$_n$ and **B**$_n$ via oligomerization of **B**.[6] This difficulty would be overcome if the oligomerization of **B** could be suppressed through masking of the boronyl group of **B**. Coupling of the "masked" haloarylboronic acid **B′** with **A** would then provide the masked biarylboronic acid derivative **A**−**B′** selectively. After unmasking, the desired **A**−**B** is obtained. It is important to note that these steps (i.e., coupling and subsequent unmasking) can be applied a second time, leading to the formation of terarylboronic acid derivatives **A**−**B**−**C** by coupling with reagent **C′** (Scheme 2). This iterative SMC offers a new efficient route to oligoarene derivatives (e.g., **A**−**B**−**C**−**D**). Despite the potential merit of this strategy, no effective masking group for the boronyl group in SMC has been described thus far. However, the usefulness of iterative synthesis has been well documented,[7] and efficient iterative SMC using a different approach involving a "hydroxy-activating strategy" appeared recently.[4e]

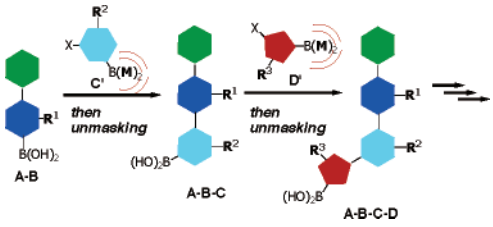
For the masking group to be truly practical, there are some requirements including (1) easy installation, (2) high stability during coupling and isolation processes, and (3) easy unmasking. Since it is commonly accepted that the Lewis acidity of the boron atom is the key factor governing the reactivity of the organoboronic acid in SMC,[1a] we decided to introduce a masking group that lowers the Lewis acidity of the boron atom. Amino groups seemed to be good candidates for the masking group since the nitrogen atoms donate their lone pair electrons to the vacant p-orbital of the boron atom, thus lowering the acidity significantly in comparison with that of the corresponding boronic acids and their esters.[8] To increase overall stability, diamines, which form cyclic diaminoboranes, were examined.

Commercially available haloarylboronic acids were treated with 1,8-diaminonaphthalene in refluxing toluene with azeotropic removal of water, affording the corresponding naphthalene-1,8-diamido derivatives **1** in high yields (eq 1).[9] We prepared haloarenes

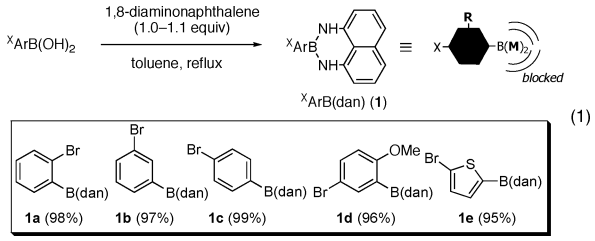
Scheme 1. Boron-Masking Strategy in the Synthesis of Biarylboronic Acid via Suzuki−Miyaura Coupling



Scheme 2. Iterative Suzuki−Miyaura Coupling Using Masked Haloarylboronic Acids for Selective Synthesis of Oligoarenes



1a−**e** bearing this masked boronyl group, which were isolated either by recrystallization or even by column chromatography on silica gel in high yields. Although other diamines and amine derivatives such as 4,5-dimethyl-*o*-phenylenediamine, *N*,*N*′-dimethylethylenediamine, 1,2-diaminocyclohexane, *o*-aminobenzyl alcohol, and anthranilic acid were examined for the masking group, they were all unstable toward aqueous workup or silica gel column chromatography.



(1)

The masked haloarylboronamides **1a**−**e**, having a 1,8-diaminonaphthalene group, were subjected to SMC with arylboronic acids in the presence of a Pd[P(*t*Bu)$_3$]$_2$ catalyst with 2 equiv of CsF (Table 1).[2a] Reactions of *p*-tolylboronic acid (**2a**) with *o*-, *m*-, and *p*-bromophenylboronamide **1a**−**c** afforded the corresponding biaryls **3a**−**c** in high yields, in which the masked boronyl groups were left intact (entries 1−3). It is noteworthy that the coupling took place so selectively that no oligomers were formed as byproducts. In addition, methoxy-substituted **1d** afforded the corresponding coupling product selectively in high yield (entry 4). With **1d**, arylboronic acids **2b**−**d** also afforded the corresponding coupling products **3e**−**g** in high yields (entries 5−7). Thiophene derivative

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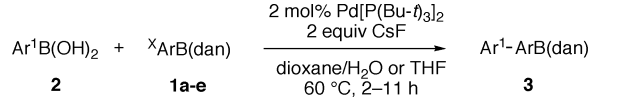
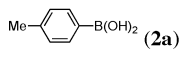
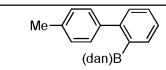
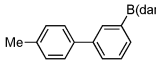
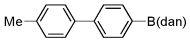
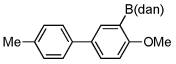
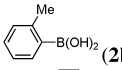
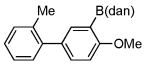
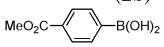
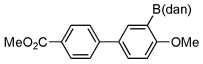
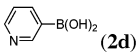
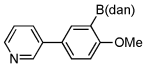
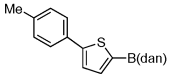
Table 1. Pd-Catalyzed Coupling of Arylboronic Acids with Bromoarylboronic Acid 1,8-Diaminonaphthalene Amides[a]



entry	2	1	product	yield /%[b]
1	 (**2a**)	**1a**		95 (**3a**)
2	**2a**	**1b**		99 (**3b**)
3	**2a**	**1c**		97 (**3c**)
4	**2a**	**1d**		99 (**3d**)
5	 (**2b**)	**1d**		99 (**3e**)
6	 (**2c**)	**1d**		89 (**3f**)
7	 (**2d**)	**1d**		99 (**3g**)
8	**2a**	**1e**		95 (**3h**)

[a] **2** (0.43 mmol), **1** (0.43 mmol), Pd[P(^{t}Bu$_3$)]$_2$ (8.5 μmol), and CsF (0.85 mmol). [b] Isolated yield.

1e also afforded the corresponding 2-tolylthiophene derivative **3h** in the coupling with **2a** (entry 8).

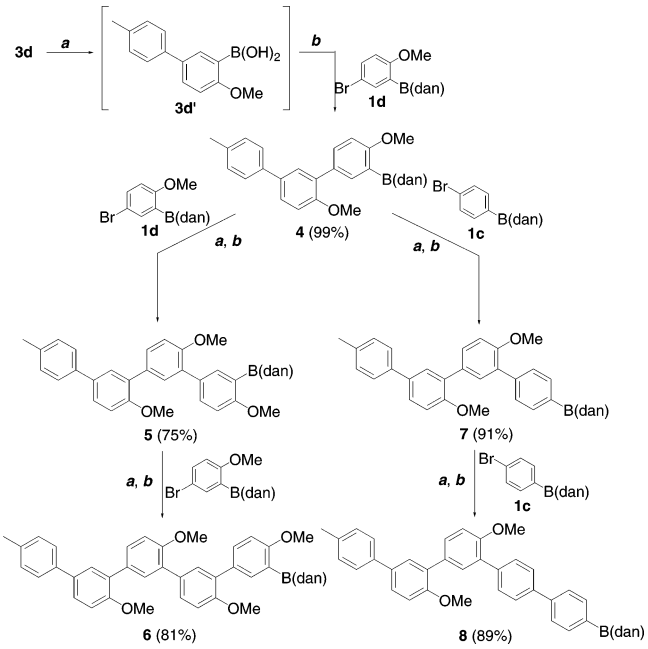
The protocol was extended to the selective synthesis of higher oligoarenes. To unmask the 1,8-diaminonaphthalene group, the biarylboronamide **3** was treated with diluted sulfuric acid or hydrochloric acid at room temperature. We observed clean deprotection of the 1,8-diaminonaphthalene group, which could be removed from the reaction mixture just by washing with acid. The unmasked boronic acids were then subjected to the cross-coupling with **1**. The second coupling also proceeded efficiently, giving terarylboronamide **4** in high yield (Scheme 3). Repetition of the unmasking−coupling sequence using **4** provided quateraryl and quinquearyl derivatives **5** and **6** selectively. Furthermore, starting with the same terarylboronamide **4**, quateraryl- and quinquearylboronic acid derivatives **7** and **8** were isolated in high yields via iterative cross-coupling using **1c**.

Finally, functionalization of the oligomer was facilitated by virtue of the reactivity of the boryl group at the terminus of the quinquearyl **8**. After the unmasking step, hydrogen peroxide oxidation,[10] cross-coupling with alkenyl halide,[1,2] and Rh-catalyzed conjugate addition to methyl vinyl ketone[11] were applied to the quinquearylboronic acid **8**, affording the corresponding products **9**−**11** (Scheme 4).

In summary, we have established new strategy for the iterative SMC by using 1,8-diaminonaphthalene as an efficient masking group for the boronyl group. The masking group is robust enough to avoid undesirable coupling and is easily unmasked by simple treatment with aqueous acid. The applicability of this strategy to the automated synthesis of oligoarene derivatives is of great interest.[7] Furthermore, the concept of boron masking or protection may be extended to a variety of reactions, where the native boronyl group is not tolerated.

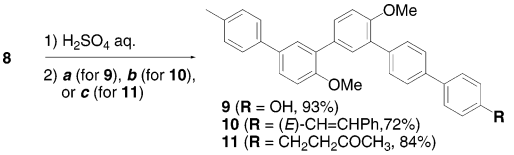
Supporting Information Available: Experimental procedures and spectral data for the new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

Scheme 3. Synthesis of Teraryl, Quarteraryls, and Quinquearyls via Iterative Cross-Coupling[a]



[a] Reaction conditions: (**a**) H_2SO_4 aq. or HCl aq., THF, rt; (**b**) Pd[P(^{t}Bu$_3$)]$_2$ (2 mol %), CsF (2 equiv), THF, 60 °C.

Scheme 4. Functionalization of the Terminus of Quinquearyl Derivative **8**



Reaction conditions: (**a**) H_2O_2, NaOH aq.; (**b**) (*E*)-BrCH=CHPh, Pd[P(^{t}Bu$_3$)]$_2$, NaOH aq.; (**c**) CH_2=$CHCOCH_3$, Rh(acac)(C_2H_4), BINAP.

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