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Preparation of Building Blocks for Iterative Suzuki-Miyaura Reactions via Direct Bromination of Aryl Boronic Acids: One-Pot Total Syntheses of Dictyoterphenyls A and B

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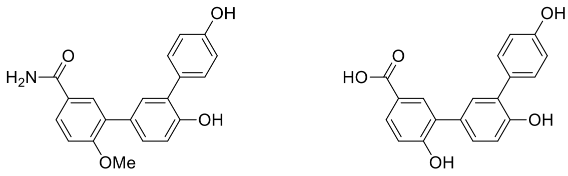
Abstract. A highly efficient method for the preparation of 4-alkoxy-3-bromophenyl boronic acid N-methyliminodiacetic acid (MIDA) esters as building blocks in iterative Suzuki-Miyaura reactions from the 4-alkoxyphenylboronic acids is described using a boronic acid moiety as a blocking group in bromination reactions. With these MIDA boronates, the total syntheses of dictyoterphenyls A and B were developed in only two separate one-pot operations. Furthermore, we have developed a more practical protocol for the preparation of meta-terphenyl natural products by simply adding the second aryl halide and water to the reaction mixture via the controlled release technique.

Keywords: Blocking Group; Dictyoterphenyls A and B; Iterative Suzuki-Miyaura reaction; MIDA Boronates; Pot-economy

Natural terphenyls, aromatic hydrocarbons consisting of a chain of three benzene rings, have attracted considerable attention from the synthetic and pharmaceutical communities, since some of them display interesting biological activities.[1] Although most naturally occurring terphenyls are *para*-terphenyl derivatives, some *meta*-terphenyl natural products have been isolated from plants. Since these *meta*-terphenyls also exhibit interesting biological activities, the total syntheses of these natural products have been considered an important field of research to obtain a sufficient amount of materials for further biological evaluation.

For example, dictyoterphenyls A and B (**1** and **2**, Fig. 1), recently isolated from the cellular slime mold *Dictyostelium polycephalum* by Kikuchi and co-workers, were found to display interesting biological activities including a cancer-cell selective antiproliferative activity.[2] Soon after their isolation, the first total syntheses of dictyoterphenyls A (**1**) and B (**2**) were completed by the same research group in 12 and 11 steps, respectively.[2] However, considering the size and complexity of these natural products, it seemed that the previous total synthesis of dictyoterphenyls A (**1**) and B (**2**) might require relatively lengthy synthetic sequences, presumably due to the lack of general methods available to access the *meta*-terphenyl structure.

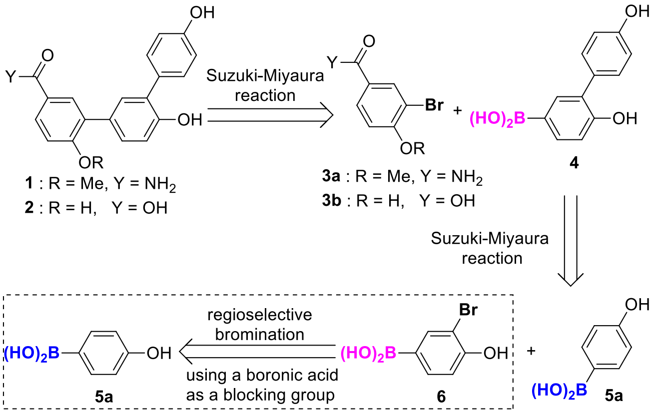


Dictyoterphenyl A (**1**) Dictyoterphenyl B (**2**)

Figure 1. Structures of Dictyoterphenyls A (**1**) and B (**2**).

Herein, we describe the development of a new approach to access *meta*-terphenyl natural products via iterative Suzuki-Miyaura reactions.[3-8] The direct bromination of 4-alkoxyaryl boronic acid N-methyliminodiacetic acid (MIDA) esters where a MIDA boronate moiety served as a blocking group provided *meta*-bromoaryl MIDA boronates as building blocks for iterative Suzuki-Miyaura reactions.[9] Using these building blocks, the total syntheses of dityoterphenyls A (**1**) and B (**2**), representatives of *meta*-terphenyl natural products, were completed through iterative Suzuki-Miyaura reactions in only two separate one-pot operations.

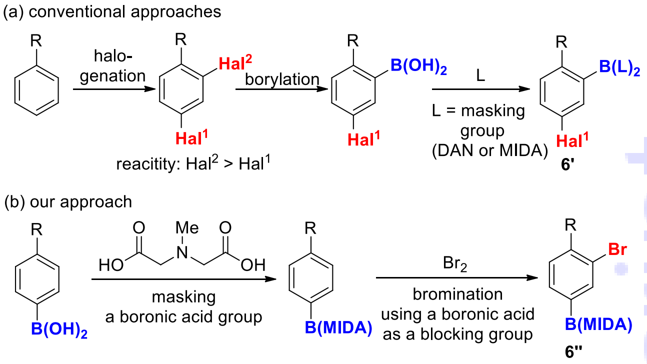
Since there have been no general methods to access the meta-terphenyl scaffold, we planned to develop a general synthetic route that could be applicable to the synthesis of various meta-terphenyl natural products. To showcase our approach, dictyoterphenyls A (**1**) and B (**2**) were chosen as the representative target molecules for meta-terphenyl natural products. The retrosynthetic analysis for dictyoterphenyls A (**1**) and B (**2**) is depicted in Scheme 1. Dictyoterphenyls A (**1**) and B (**2**) could be readily prepared via Suzuki-Miyaura coupling reactions between biphenyl boronic acid **4** and an aryl bromide (**3a** or **3b**). Biphenyl boronic acid **4** could also be prepared via the Suzuki-Miyaura coupling reaction between 4-hydroxyphenyl boronic acid **5a** and aryl bromide **6** carrying an additional boronic acid functionality at the *meta*-position.



Scheme 1. Retrosynthetic Analysis of Dictyoterphenyls A (**1**) and B (**2**).

The key to the success of this approach would be the selective formation of biphenyl boronic acid **4** from 4-hydroxyphenyl boronic acid **5a** and aryl bromide **6** via Suzuki-Miyaura coupling reaction without the formation of the homo-coupled product of **6**.[10] In order to accomplish the desired hetero-coupled Suzuki-Miyaura reaction between **5a** and **6**, the reactivity of the boronic acid present in **6** must be modulated as an off-state during the Suzuki-Miyaura reaction between **5a** and **6**.[3] Furthermore, the masked reactivity of the boronic acid in the resulting cross-coupled biphenyl **4** must then be restored as an on-state to undergo the next Suzuki-Miyaura reaction with compound **3** to generate the *meta*-terphenyl scaffold. Since several known methods have been developed to control the reactivity of the boronic acid functional group in iterative Suzuki-Miyaura coupling reactions by decreasing the Lewis acidity of the boron atom via complexation with a strong π-donor ligand[7] or conversion of the sp^2 hybridization of the boron atom to sp^3 with a tridentate ligand,[4-6] there was little concern over the feasibility of preparing the *meta*-terphenyl scaffold via iterative Suzuki-Miyaura reactions.

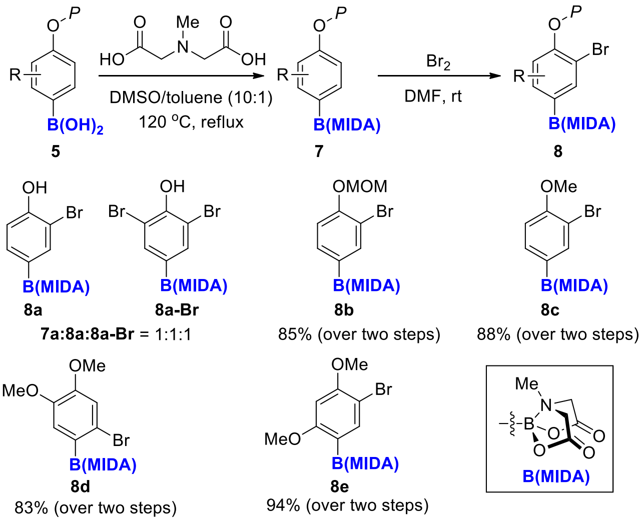
The more serious challenge in our approach was the preparation of aryl bromide **6** carrying a boronic acid moiety at the *meta*-position to the bromide substituent. Although *meta*-halogenated aryl boronic acids **6'** with a controlled reactivity have been previously prepared as building blocks for iterative Suzuki-Miyaura reactions, these building blocks possess a boronic acid moiety ortho to the other substituent (R) and the halide functionality is incorporated at the para-position (Scheme 2a). In addition, most of the substrates were prepared through introduction of two different halogen functional groups at the proper positions followed by the installation of a boronic acid moiety at the more reactive halogen group.[5],[7] Subsequent protection of the boronic acid moiety with a proper ligand led to building blocks suitable for iterative Suzuki-Miyaura reactions, which generally requires relatively lengthy syntheses and suffers from moderate yields of the resulting boronic acids.



Scheme 2. Comparison of Conventional Approaches with Our Work in Preparation of Building Blocks for Iterative Suzuki-Miyaura Reactions.

Recently, we have developed a new method for the synthesis of ortho-functionalized electron-rich arenes from the corresponding *para*-substituted aryl boronic acids using a boronic acid moiety as a blocking group in electrophilic aromatic substitution (EAS) reactions followed by the removal of the boronic acid moiety through metal-free thermal protodeboronation of the boronic acid.[9] In these studies, we found that a decrease in the Lewis acidity of the boron atom in the boronic acid moiety significantly decreased the reactivity towards *ipso*-substitution via halodeboronation,[11] causing the boronic acid moiety to behave as a blocking group in EAS reactions. Since a decrease in the Lewis acidity of the boron atom in a boronic acid was found to be beneficial both for a masking strategy in iterative Suzuki-Miyaura reactions[3] and for a blocking strategy in the EAS reactions,[9] we envisioned that substrates for iterative Suzuki-Miyaura reactions could be prepared from the corresponding boronic acids with a suitable protecting group using a boronic acid moiety as a blocking group via EAS reactions. Particularly, since MIDA boronates of aryl boronic acids have been utilized as masking groups in iterative Suzuki-Miyaura coupling reactions,[4-6] we hypothesized that if a MIDA boronate moiety in MIDA boronates derived from para-substituted phenyl boronic acid derivatives acted as a blocking group in bromination reactions, the bromination reactions would take place at the ortho-position to the substituent (R) leading to MIDA boronates of 3-bromo-4-substituted phenyl boronic acids **6''** as new building blocks for the iterative Suzuki-Miyaura coupling reactions (Scheme 2b).

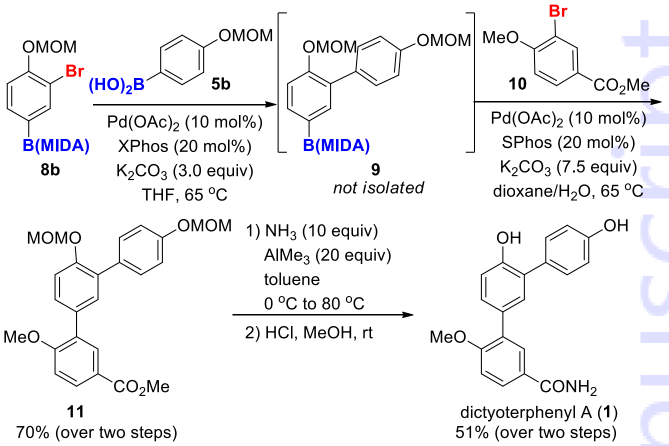
Based on this idea, we began our research with the preparation of MIDA boronates of *meta*-bromoaryl boronic acids using a boronic acid moiety as a blocking group in EAS reactions (Scheme 3).



Scheme 3. Preparation of Building Blocks in the Iterative Suzuki-Miyaura Reaction Using a MIDA Boronate Moiety as a Blocking Group in Bromination Reactions.

Particularly, since most *meta*-terphenyl natural products including dictyoterphenyls A and B possess a hydroxy group in the middle phenyl ring, we first attempted to prepare substrates from MIDA boronates of 4-hydroxyphenyl boronic acid derivatives. MIDA boronate **7a** was readily prepared by the condensation reaction of 4-hydroxyphenyl boronic acid **5a** with MIDA using azeotropic distillation.[12] Interestingly, the resulting MIDA boronate **7a** could be obtained in a quantitative yield via recrystallization in common organic solvent.[13] Next, **7a** was subjected to bromination with a stoichiometric amount of bromine. Although the MIDA boronate moiety perfectly worked as a blocking group in an electrophilic bromination reaction, the desired 2-brominated product **8a** was obtained along with the 2,6-dibrominated product **8a•Br** and starting material **7a** remained unreacted in the reaction mixture. This result suggested that the hydroxy substituent in **7a** was too reactive to selectively control the mono-bromination reaction. Thus, we decided to protect the phenolic hydroxy group in boronic acid **5a** to decrease the reactivity toward bromination reaction.[14] Similar to boronic acid **5a**, the corresponding MIDA boronates **7** derived from *para*-alkoxyphenylboronic acids were easily prepared in quantitative yields via simple recrystallization.[13] When these MIDA boronates **7** were subjected to bromination with Br_2, the MIDA boronate moiety perfectly acted as a blocking group and the bromination successfully took place at the ortho-position to the protected hydroxy group to provide the *meta*-brominated MIDA boronates **8** in high yields. Under these conditions, we investigated further the bromination reactions of MIDA boronates of 4-alkoxyphenyl boronic acid derivatives bearing an additional alkoxy group and, in every case, obtained the desired brominated MIDA boronates **8** in high yields. It should be noted that bromoaryl MIDA boronates **8**, key building blocks for iterative Suzuki-Miyaura reactions, could be prepared from commercially available aryl boronic acids in high yields with very simple operations.

With these compounds **8** in hand, we first attempted to demonstrate the advantages of our protocol in the total synthesis of dictyoterphenyl A (**1**) (Scheme 4).

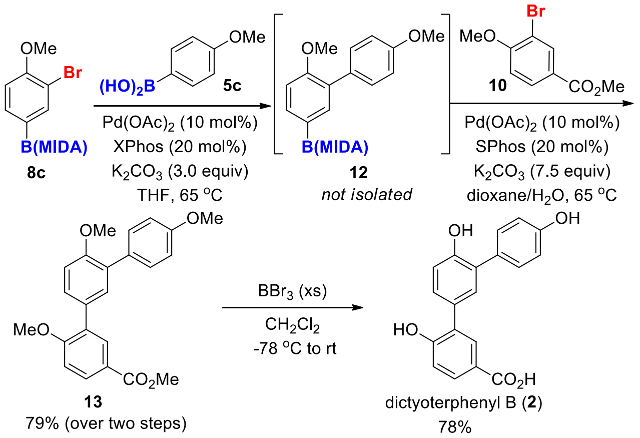


Scheme 4. Total Synthesis of Dictyoterphenyl A (**1**).

Suzuki-Miyaura coupling reaction of *meta*-bromoaryl MIDA boronate **8b** with boronic acid **5b** in the presence of a palladium catalyst under anhydrous conditions provided biphenyl MIDA boronate **9**. After concentrating the reaction mixture of the first reaction, biphenyl product **9** was subjected to the second Suzuki-Miyaura reaction with aryl bromide **10** in a mixture of dioxane and H_2O via a controlled release technique[5],[15] to provide terphenyl compound **11** in 70% yield from **8b** after one column separation operation. Conversion of the ester group into an amide followed by deprotection of the MOM groups with HCl provided dictyoterphenyl A (**1**) in 51% yield over two steps. Overall, we completed the total synthesis of dictyoterphenyl A (**1**) in 36 % yield by only two separate one-pot operations.[16]

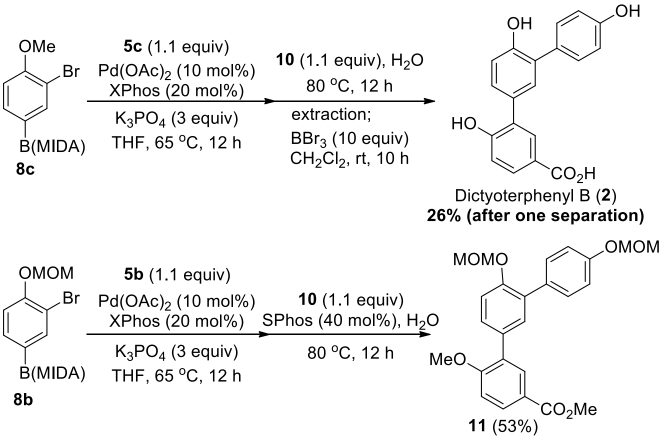
With a successful result on the total synthesis of dictyoterphenyl A (**1**), the total synthesis of dictyoterphenyl B (**2**) was attempted via the same protocol (Scheme 5). In this case, the same protocol was followed using of methoxy protected MIDA boronate **8c** in place of MOM protected analogue **8b**. Suzuki-Miyaura coupling reaction of MIDA boronate **8c** with boronic acid **5c** provided biphenyl MIDA boronate product **12**. Without complete isolation of **12**, the crude product of **12** was further subjected to the second Suzuki-Miyaura reaction with aryl bromide **10** in a mixture of dioxane and H_2O to provide the desired terphenyl compound **13** in 79% yield from **8c** after one-column separation. Removal of all the methoxy groups with an excess amount of

BBr_3 provided dictyoterphenyl B (**2**) in 78% yield. Overall, the total synthesis of dictyoterphenyl B (**2**) was accomplished in 62 % yield.



Scheme 5. Total Synthesis of Dictyoterphenyl B (**2**).

Although we completed the total syntheses of dictyoterphenyls A (**1**) and B (**2**) in only two separate one-pot operations, there were still some rooms for improvement of our protocol. Particularly, we had to change the reaction media from THF into a mixture of dioxane and H_2O for the second Suzuki-Miyaura reaction, and use a different phosphine ligand for the second coupling reaction. Thus, we further investigated the possibility to carry out the second Suzuki-Miyaura reaction in the same pot by simply adding the reagents (i.e., aryl bromide **10** and H_2O) to the reaction mixture without any other extra operations (Scheme 6).



Scheme 6. One-Pot Total Syntheses of Dictyoterphenyls A (**1**) and B (**2**).

Suzuki-Miyaura reaction of MIDA boronate **8c** with boronic acid **5c** under anhydrous conditions (in THF solution) provided biphenyl MIDA boronate **12**, which was subjected to the second Suzuki-Miyaura reaction by simply adding aryl bromide **10** and H_2O to the reaction mixture via the controlled release technique to afford the desired terphenyl compound **13**.[17] After extracting the reaction mixture, direct treatment of the resulting crude product of **13** with BBr_3 afforded dictyoterphenyl B (**2**) in 26% yield after only one-column separation. In addition, we further attempted to apply the one-pot protocol to the synthesis of dictyoterphenyl A (**1**). Suzuki-Miyaura reaction of MIDA boronate **8b** with boronic acid **5b** under anhydrous conditions provided biphenyl MIDA boronate **9**. Unlike the synthesis of dictyoterphenyl B (**2**), the second Suzuki-Miyaura reaction of biphenyl MIDA boronate **9** with **10** did not occur by simply adding compound **10** and H_2O to the reaction mixture. However, simply addition of SPhos ligand to the above reaction mixture afforded *meta*-terphenyl compound **11** in 53 % yield after one-column separation.

In conclusion, we have developed a highly efficient method for the preparation of building blocks for iterative Suzuki-Miyaura reactions from the MIDA boronates of commercially available *para*-alkoxy substituted aryl boronic acids through electrophilic aromatic bromination reactions using a MIDA boronate moiety as a blocking group in bromination reactions. Various types of 4-alkoxyphenyl boronic acids were applicable to this protocol and the desired 4-alkoxy-3-bromophenyl MIDA boronates were obtained in excellent yields. With these building blocks in hand, the total syntheses of dictyoterphenyls A (**1**) and B (**2**) were completed in 36% and 62% yields, respectively, with only two separate one-pot operations. Furthermore, we have developed a more practical protocol for the preparation of *meta*-terphenyl natural products by simply adding the second aryl halide and H_2O to the reaction mixture via the controlled release technique. Further application of these building blocks to the synthesis of other natural products via the iterative Suzuki-Miyaura coupling reaction is currently underway in our laboratory and will be reported in due course.

Experimental Section

General procedure for the preparation of building blocks for the iterative Suzuki-Miyaura reaction (Scheme 3): To a solution of aryl boronic acid **5** (1.0 mmol) in a mixture of DMSO and toluene (1:10, 30 mL) were added MIDA (0.44 g, 3.0 mmol) and molecular sieves (4 Å, 0.50 g). The reaction mixture was refluxed with azeotropic removal of water using Dean−Stark condenser under an ambient atmosphere. After 16 h, the reaction mixture was cooled to room temperature and filtered to remove molecular sieves. Water was added to the filtrate and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was dissolved in acetone and reprecipitated in hexanes to provide the corresponding MIDA boronate **7**.

To a solution of the resulting MIDA boronate **7** (1.0 mmol) in anhydrous DMF (20 mL) was added Br_2 (0.16 g, 1.0 mmol) dropwisely under N_2 atmosphere. After complete consumption of compound **7**, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with ethyl acetate. The organic layer was separated, and then the aqueous layer was extracted with ethyl acetate a couple of times. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in acetone and reprecipitated from hexanes to give the brominated MIDA boronate **8**.

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UPDATE

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