

Chemoselective Coupling

Site-Differentiated Polyboron Arenes Prepared by Direct C–H Borylation and Their Highly Selective Suzuki–Miyaura Cross-Coupling Reactions**

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Abstract: Di- and polyboron (hetero)arenes, site-differentiated with MIDA boronyl (MIDA = *N*-methyliminodiacetic acid) and pinacolato boronyl (Bpin), were prepared by an iridium-catalyzed direct C–H borylation of readily available (hetero)aryl MIDA boronates. The excellent synthetic uses of these multisite nucleophiles were demonstrated by the high-yield production of a variety of multifunctionalized poly(hetero)arenes with the highly chemoselective Suzuki–Miyaura coupling (SMC) of the Bpin moiety being an essential step.

Modular assembly of small polyfunctionalized building blocks into complex molecules is an inherently efficient and flexible approach in organic synthesis, therefore, methods for the facile synthesis and chemoselective transformation of polyfunctionalized compounds are highly desirable. In this context, poly(pseudo)halogen-substituted arenes and heteroarenes have been well studied and used as multisite electrophiles in chemoselective cross-coupling reactions.^[1] Excellent examples of haloboronic acids derivatives have also been harnessed for iterative electrophilic/nucleophilic couplings.^[2,3] In contrast, polymetallic arenes, which may behave as multisite nucleophiles for this purpose, have been much less developed.

To date, a few reports have described the successful synthesis of compounds bearing the combination of boron/tin,^[4] boron/silicon,^[5] or silicon/silicon^[6] moieties and their applications in selective cross-coupling reactions. Because of the broad availability of boronic acid derivatives, and general efficiency and mildness of Suzuki–Miyaura coupling (SMC),^[7] differentiated polyboron compounds would in principle represent a class of valuable polyvalent nucleophiles in such reactions. Despite their potential utility, few examples of differentiated diboron compounds have been described until recently (Scheme 1a).^[8] Suginome and co-workers first reported the synthesis of pinacolato/naphthalene-1,8-diamino

bis(boronyl) (Bpin/Bdan) arenes by Miyaura borylation of Bdan-incorporated bromoarenes. Subsequent SMC reaction was achieved exclusively on the Bpin moiety while the Bdan group was inactive under usual coupling conditions.^[9] Molander and Sandrock found that terminal alkenes equipped with an aryl trifluoroborate group underwent hydroboration with 9-BBN to produce corresponding alkyl boranes which were useful in subsequent efficient and selective SMC reactions.^[10] Gillis and Burke developed olefinic compounds functionalized with a *N*-methyliminodiacetic acid (MIDA)^[11] boronyl and a Bpin group, and applied them successfully in the synthesis of complex polyene natural products.^[12] Very recently, Hall and co-workers,^[13] and Yun and co-workers^[14] reported the synthesis of *gem* diboronyl compounds by enantioselective borylation of borylalkenes, and demonstrated their uses in stereoselective alkyl SMC reactions.

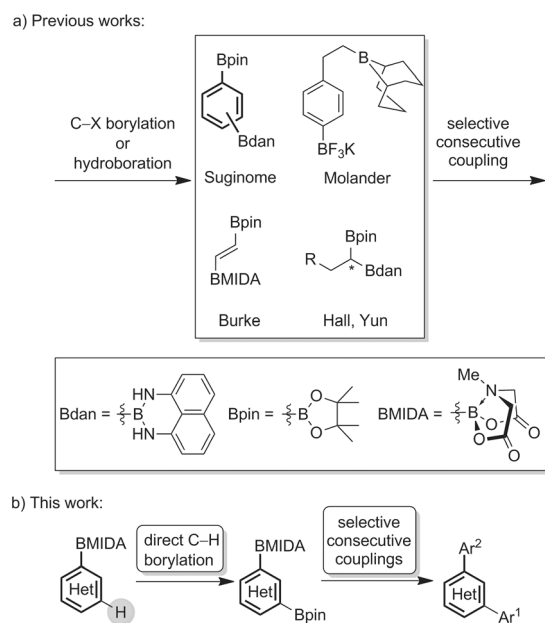
Despite the significant advancements highlighted above, current methods for the synthesis and selective transformation of differentiated di- or polyboron compounds suffer from numerous drawbacks. For example, current synthetic approaches start from monoboron molecules containing a (pseudo)halide or alkene group, which themselves require multistep preparations, and sometimes may be inaccessible. Furthermore, Suginome's modular synthesis of oligo- and

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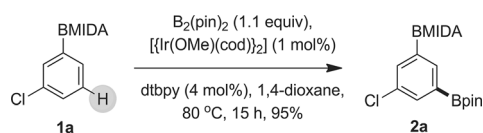


Scheme 1. a) Previous diboron compounds in selective Suzuki–Miyaura coupling. b) The outline of this work.

polyarenes, a very useful class of organic molecules, remains the sole demonstration of the use of site-differentiated diboron arenes.^[9a] In the Suginome method, the Bdan group must be hydrolyzed to the boronic acid prior to the second coupling, thus an additional step involving relatively harsh reaction conditions (e.g. 5 M hydrochloric acid) is required. Finally, to the best of our knowledge, site-differentiated polyboron arenes have never been documented.

To overcome these limitations, we herein report an alternative and straightforward approach to the preparation of polyboron arenes and their subsequent application in SMC reactions (Scheme 1b). Starting from simple and readily available aryl MIDA boronates, we proposed that differentiated di- or polyborylated arenes might be obtained by direct C–H borylation. This idea was inspired by two important research areas. Recent work by Gillis and Burke^[15] and Yudin and co-workers^[16] showed that the MIDA boronyl group could be carried through an array of transformations, thus rendering these substrates an appropriate starting point for our studies. Additionally, iridium-catalyzed C–H borylation, pioneered by Smith et al.^[17] and Hartwig et al.,^[18] has proven to be an effective means for rapid functionalization of a variety of (hetero)arenes.^[19] Consequently, we envisioned developing a direct C–H borylation of aryl MIDA boronates^[20] and utilizing the resulting products as polyvalent reagents for modular construction of complex aromatic molecules by consecutive chemoselective SMC.

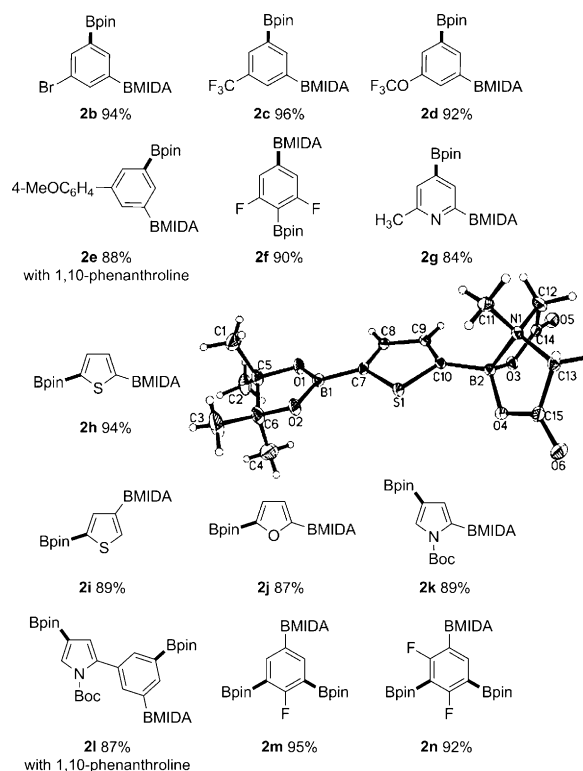
The 3-chlorophenyl MIDA boronate **1a** was used as a model substrate and subjected to various reaction conditions for iridium-catalyzed C–H borylation (for details see Table S1 in the Supporting Information; Scheme 2). To our



Scheme 2. The model reaction of the C–H borylation. cod = cyclo-1,5-octadiene.

delight, the *meta*-borylation product **2a** could be isolated in 95% yield under our optimized reaction conditions: 1 mol% $[\text{Ir}(\text{OMe})(\text{cod})_2]$, 4 mol% 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy), and 1.1 equivalents of bis(pinacolato)diboron ($\text{B}_2(\text{pin})_2$) as the borylating reagent in 1,4-dioxane at 80 °C for 15 hours. The result indicated that the MIDA boronyl group was well tolerated under the reaction conditions. As previously demonstrated by Smith and co-workers and Hartwig et al., the borylation occurred at the least sterically hindered position.^[17–19,21]

With the optimized reaction conditions in hand, we explored the substrate scope for this direct C–H borylation of aryl MIDA boronates as shown in Scheme 3. Various substituents at the 3-position (**2b–e**) on the phenyl ring were well tolerated, thus affording the corresponding borylated products in high to excellent yields. Borylation also occurred efficiently at the *ortho*-position of fluorine-substituted arenes



Scheme 3. Substrate scope of the C–H borylation. Thermal ellipsoids shown at 50% probability.^[31] Boc = *tert*-butoxycarbonyl.

(**2f**, **2m** and **2n**), thus providing multifunctionalized fluoroarenes in a step-economic fashion. Heterocyclic boronic acid derivatives are important building blocks in medicinal and materials chemistry, but their preparations are challenging because of their instability.^[22] We found that C–H borylation of readily available monoborylated pyridine, thiophene, furan, and pyrrole derivatives directly provided differentially diborylated heteroarenes (**2g–l**) in high yields.^[23] Polyboron compounds are interesting building blocks for construction of multifunctionalized structures. When excess (3.3 equivalents) bis(pinacolato)diboron was used, double borylation occurred to afford high yields of **2l–n**. These compounds represent the first examples of (hetero)arenes which are substituted by differently masked polyboronyl groups. For the cases of **2e** and **2l**, 1,10-phenanthroline was found to be superior to dtbpy as the ligand. Notably, all of these di- or polyborylated (hetero)arenes were crystalline solids, and in most cases, could be isolated in good purity by a simple workup procedure including solvent removal, precipitation, and washing with diethyl ether, although we still purified them by flash chromatography for general considerations.

The utility of the site-differentiated polyboron arenes in chemoselective SMC reactions was subsequently assessed. The 2,5-diborylated thiophene **2h** and 3-bromoanisole were chosen as the model substrates (Table 1). After extensive variation of reaction parameters, we found that a system using $[\text{Pd}_2(\text{dba})_3]$ as the catalyst and SPhos^[24] as the ligand in anhydrous acetonitrile as the solvent worked best in terms of reactivity and selectivity. Thus, under the optimal reaction

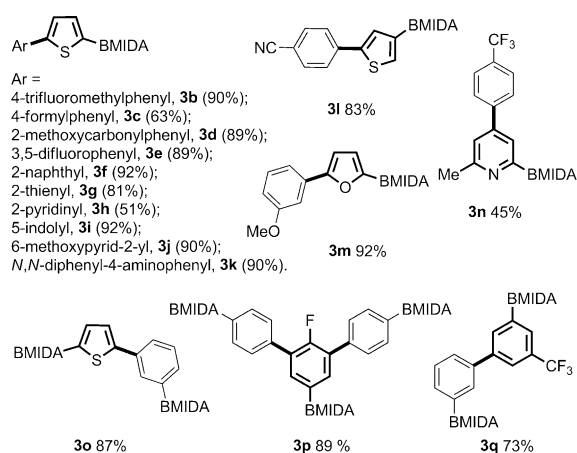
Table 1: Reaction conditions for the selective mono SMC.

Entry	Solvent	Yield [%] ^[b] 3 a	Yield [%] ^[a] 3 aa
1	MeCN	96	< 5
2	1,4-dioxane	29	< 5
3	toluene	63	< 5
4	THF	26	< 5
5	DMF	80	< 5
6	MeCN ^[b]	46	28
7	MeCN	94 ^[c]	< 5

[a] Yields of analytically pure isolated compounds. [b] 5.0 equiv of water added. [c] 2.1 equiv of aryl bromide used. DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran.

conditions (50 °C, 10 h), the Bpin group could be selectively transformed into the aryl group while the BMIDA group remained intact.^[12a,b] After workup and purification, the desired product **3a** was isolated in 96% yield (entry 1). Solvent choice was critical for the success of this reaction. For example, solvents such as 1,4-dioxane, toluene, or THF led to much lower conversions (entry 2–4), while DMF gave full conversion but diminished yield (entry 5). Addition of water to the reaction mixture was detrimental to the selectivity, presumably because both pinacol and MIDA boronates were hydrolyzed to boronic acids (entry 6).^[2b] It is worthy to mention that the chemoselectivity was remarkably high even in the presence of excess aryl bromide (entry 7). These results suggest that the BMIDA group was nearly inert in anhydrous acetonitrile but could be activated by hydrolysis under aqueous conditions.

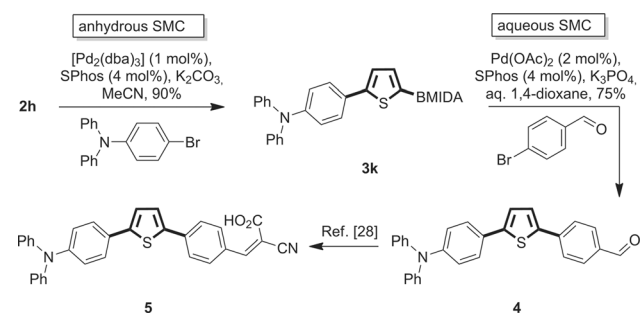
The generality of this selective SMC was subsequently examined using various combinations of (hetero)aryl bromides and (hetero)arenes site-differentiated with Bpin and BMIDA groups. Collected in Scheme 4 are the products, all



Scheme 4. Substrate scope of the selective mono SMC.

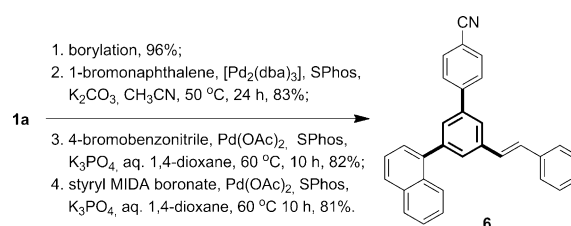
obtained in good to excellent yields. The only exception is the compound **3n**, which was obtained in acceptable yield when the less stable diboronyl pyridine **2g** was used. It is worth noting that when aryl bromide functionalized with BMIDA reacted with a differentiated di- or triboron compound, the same chemoselectivity in SMC was achieved with the production of polyaryls equipped with two or three MIDA boronyl groups. These compounds represent a new type of multisite nucleophile (**3o–q**) which are expected to be useful for further chemical elaborations.

Taking the advantage that reactivity of the MIDA boronyl group could be switched by simply adding water, we envisioned a two-step consecutive sequence for convergent and flexible SMC reactions. In comparison with Suginome's Bdan-based method,^[2a,9a,b] this sequence eliminated the extra step for activation with strongly acidic conditions. We took **2h** as an example, since thiophene is among the most important subunits in organic dyes,^[25] semiconducting^[26] and electro-optical molecules, and polymers.^[27] Thus, the advanced intermediate **4** was synthesized in two high-yielding steps involving sequential anhydrous and aqueous SMC reactions of **2h** (Scheme 5). The compound **4** could be elaborated into the high-performance donor–acceptor dye **5** as previously reported in the literature.^[28] Therefore, doubly nucleophilic heterocycles such as **2h** may serve as versatile building blocks in relevant areas.^[4a,b]



Scheme 5. Sequential anhydrous and aqueous SMC reactions of **2h**. dba = dibenzylideneacetone.

The flexibility and efficiency of this successive and selective coupling scheme was further demonstrated with the high-yield synthesis of the multisubstituted arene **6** (Scheme 6). Multiply arylated or vinylated arenes are important motifs in materials^[29] and medicinal research.^[30] Follow-



Scheme 6. Successive and selective SMC reactions for the synthesis of the multisubstituted arene **6**.

ing our standard protocol, the commercially available **1a** was borylated on a 2 mmol scale to quantitatively produce **2a**, which then underwent three sequentially chemoselective SMC reactions with 1-bromonaphthalene, 4-bromobenzonitrile, and styryl MIDA boronate to afford **6**.

In conclusion, an efficient regioselective iridium-catalyzed C–H borylation has been developed for the synthesis of differentiated di- and polyboron-substituted (hetero)arenes from readily available aryl and heteroaryl MIDA boronates. Further investigations culminated in a highly chemoselective Suzuki–Miyaura cross-coupling of these products. Thus they may serve as polyvalent nucleophiles for modular construction of multifunctionalized poly(hetero)arenes by consecutive cross-coupling reactions. The mode of selective transformations of these reagents is complementary to that of poly-(pseudo)halogen and haloboronic acid derivatives.^[1,2] Together, these methods enable rapid, efficient, and flexible synthesis of complex molecules from simple building blocks. We anticipate that the protocol described herein will find wide use in organic synthesis, materials science, and medicinal chemistry.

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