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A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki−Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks

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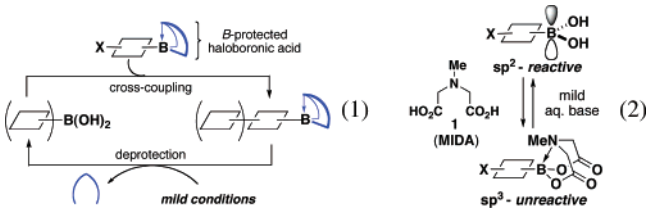
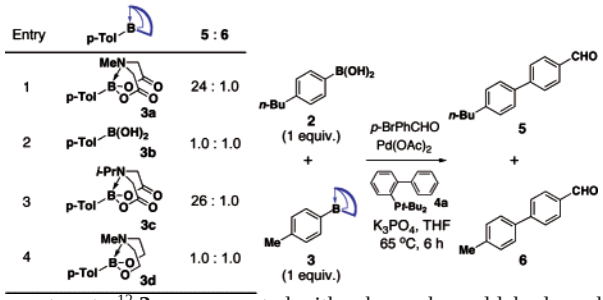
Most of the functional molecules found in living systems, including most "small molecules", are biosynthesized via iterative coupling of bifunctional building blocks. Polypeptides,[1] oligonucleotides,[2] and to a growing extent oligosaccharides[3] can be similarly prepared in the laboratory via simple oligomerization of suitably protected versions of their constituent monomers. Analogous approaches involving iterative cross-coupling of bifunctional arenes have greatly facilitated the preparation of oligoarene-type polymers.[4] These types of processes are now routinely automated. In stark contrast, the laboratory synthesis of small molecules remains a relatively inefficient and nonsystematized process. The Suzuki-Miyaura (SM) reaction[5] between an organohalide and a boronic acid represents a powerful, functional group tolerant, and increasingly general method for C−C bond formation in complex molecule synthesis.[6] We herein report a simple and highly modular strategy for making small molecules via iterative SM coupling of bifunctional *haloboronic acid* building blocks (eq 1).[7]



Realizing the proposed iterative cycle of C−C bond formation in the context of small molecule synthesis required the discovery of a ligand for boronic acids that can attenuate transmetalation under various SM conditions and then be cleaved using mild reagents. Current data suggest that transmetalation between boronic acids and Pd(II) requires formation of an electronically activated *anionic* boron "ate" complex and/or a hydroxo μ_2-bridged organoboronate−Pd(II) intermediate.[8] Both mechanisms necessitate a vacant and Lewis acidic boron p-orbital. Bidentate ligands that contain strongly electron-donating heteroatoms are known to inhibit the cross-coupling of organoboron compounds, presumably by reducing the Lewis acidity of the sp^2-hybridized boron center.[8a] Harnessing this effect, others have reported a few selective cross-couplings with B-protected organoboranes that contain halogens.[9] These types of heteroatom−boron bonds tend to be very strong,[10] however, and the relatively harsh conditions required for cleaving these ligands are generally incompatible with complex molecule synthesis. We envisioned an alternative approach for reactivity attenuation involving rehybridization of the boron center from sp^2 to sp^3 via complexation with a trivalent ligand. We further anticipated that such a ligand might be cleavable using relatively mild reagents because heteroatom−boron bonds in tetrahedral adducts are predicted to be weaker than those in their tricoordinate counterparts.[10,11] We herein report the realization of these expectations using the commercially available trivalent ligand, *N*-methyliminodiacetic acid (MIDA, **1**; eq 2).

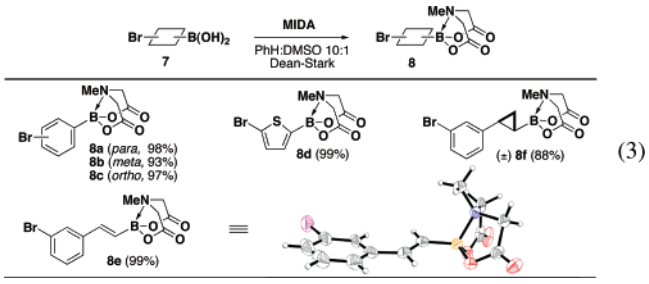
To test the hypothesis that boron pyramidalization will inhibit cross-coupling, stoichiometric quantities of boronic acid **2** and

Table 1



boronate ester[12] **3a** were reacted with *p*-bromobenzaldehyde under Buchwald's anhydrous SM conditions[6a] (Table 1). Gratifyingly, a 24:1 ratio of biaryls **5** and **6** was observed, consistent with strong preferential reactivity with the sp^2-hybridized boronic acid **2** (entry 1). The control experiment with *p*-tolylboronic acid **3b** yielded a 1:1 mixture of products (entry 2). Sterically bulky *N*-alkyl substitution was tolerated but not significantly advantageous (entry 3). *N*-Methyl diethanolamine adducts such as **3d**, which are known to be significantly less conformationally rigid than their iminodiacetic acid counterparts,[12c] demonstrated no selectivity (entry 4). To the best of our knowledge, this type of reactivity attenuation with neutral, sp^3-hybridized boronate esters is unprecedented, and further studies into the nature and potentially broad utility of this effect are ongoing.[13] Strikingly, although these boronate esters are protected from anhydrous SM coupling even at 80 °C for 28 h, *deprotection can be achieved at 23 °C using extremely mild aqueous basic conditions, such as* 1 M aq NaOH/THF, 10 min, or even aq $NaHCO_3$/MeOH, 6 h (see below).

A variety of haloboronic acids were complexed with MIDA to yield a series of B-protected bifunctional building blocks (eq 3).



All three positional isomers of bromophenyl boronic acid as well as the heteroaromatic 5-bromothiopheneboronic acid reacted cleanly to generate **8a**−**d** in excellent yields. The same complexation conditions yielded vinyl and alkyl boronate esters **8e** and **8f**. The pyramidalized nature of the (*N*→B)-vinyl-[*N*-methyliminodiacetate-*O*,*O*′,*N*]borane **8e** was confirmed via single-crystal X-ray diffraction analysis.[12] Remarkably, these pyramidalized boronate esters are stable to and readily purified by silica gel chromatography (all yields in eq 3 represent materials isolated as analytically pure, colorless crystalline solids after a single chromatographic step). Moreover, in stark contrast to the corresponding boronic acids,[10] *all of these boronate esters are indefinitely bench stable under air*.

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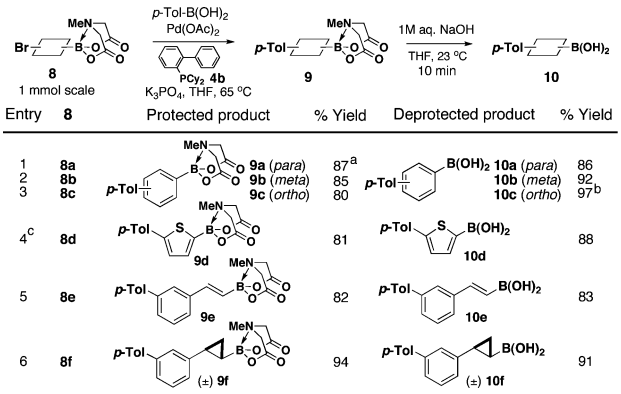
Table 2



Entry	8	Protected product	% Yield	Deprotected product	% Yield
1	8a	9a (*para*)	87[a]	10a (*para*)	86
2	8b	9b (*meta*)	85	10b (*meta*)	92
3	8c	9c (*ortho*)	80	10c (*ortho*)	97[b]
4[c]	8d	9d	81	10d	88
5	8e	9e	82	10e	83
6	8f	(±) 9f	94	(±) 10f	91

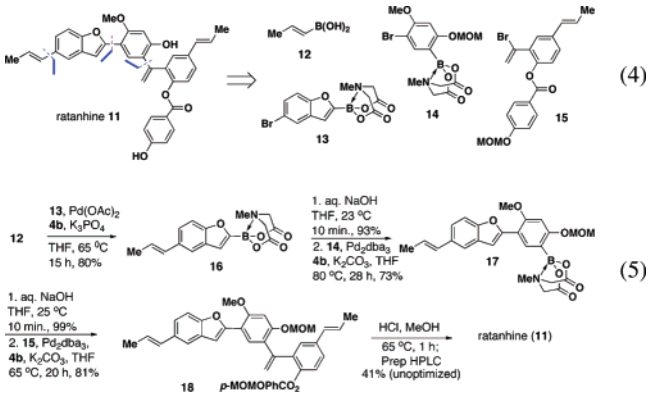
[a] The same yield was observed whether this reaction was set up in the glovebox or in the air. [b] B-Deprotection was also achieved with aq $NaHCO_3$/MeOH, 23 °C, 6 h, 85%. [c] 2-(Dicyclohexylphosphino)-2′,4′,6′-triisopropyl-1,1′-biphenyl was used instead of **4b**.

The potential of the MIDA ligand to enable selective cross-couplings was probed by reacting each of these B-protected bifunctional building blocks with *p*-tolylboronic acid (Table 2). Although the reactivity of aryl, heteroaryl, vinyl, and alkyl boronic acids can vary dramatically,[6] *the same protective group was effective with all four classes of nucleophiles* yielding selective cross-coupling products **9a**−**f**. All four classes of nucleophiles were also efficiently deprotected using a standard set of mild aqueous basic conditions (1 M aq NaOH/THF, 23 °C, 10 min). Aqueous $NaHCO_3$ is also effective (entry 3).

The strategy described herein is distinguished from related lynchpin-based approaches by its theoretically limitless potential for iteration. To begin exploration of this potential and the compatibility of this mild protective group methodology with small molecule substrates, we targeted the first total synthesis of the natural product ratanhine (**11**) (eq 4), the most complex member of a large family of neolignans isolated from the medicinal plant *Ratanhiae radix*.[14]

Retrosynthetic fragmentation of **11** into four simpler building blocks **12**−**15** was achieved via recursive application of three SM transforms (eq 4). There were several challenges associated with this plan that were anticipated to provide rigorous tests for the new methodology. For example, cross-coupling of aryl boronic acids tends to be more facile than that of their vinyl counterparts,[6a] making the selective cross-coupling between vinyl boronic acid **12** and bromoaryl boronate **13** unsecured. In addition, heteroaromatic boronic acids, such as the deprotected version of **13**, can be very sensitive to decomposition.[15] Moreover, cross-coupling with the highly electron-rich and sterically encumbered aryl bromide **14** was expected to require elevated temperatures and/or long reaction times that would test the limits of stability for the MIDA ligand.

With building blocks **12**−**15** in hand (see eq 5 and SI), the synthesis commenced with a successful selective cross-coupling between **12** and **13** to yield intermediate **16**. Strikingly, benzofuranyl boronates **13** and **16** were *bench stable under air for at least 1 month*. In contrast, the 2-benzofuranyl boronic acid that resulted from deprotection of **16** rapidly decomposed over the course of a few days. This challenge was overcome simply by deprotecting **16** just prior to cross-coupling with **14**. As expected, this electron-rich and sterically bulky aryl bromide **14** required both an elevated temperature (80 °C, sealed tube) and extended reaction time (28 h). Remarkably, the MIDA protective group was found to be completely stable to these forcing conditions, yielding advanced intermediate **17**. A final sequence of B-deprotection, cross-coupling with **15**, and cleavage of the two MOM ethers completed the first total synthesis of ratanhine.[16]



As demonstrated herein, this iterative cross-coupling strategy can dramatically simplify the process of small molecule synthesis. This natural product was prepared using a single mild reaction iteratively to bring together a collection of easily synthesized, readily purified, and highly robust building blocks. The synthesis is short[16] and highly modular, and thus a variety of derivatives should be readily accessible simply by substituting modified building blocks into the same pathway. Further studies will pursue the inherent adaptability of these methods to solid-phase and/or automated techniques. Although certain small molecules are at present more amenable to this approach than others, the rapidly expanding scope of the SM reaction, which increasingly includes sp^3-sp^3 couplings,[17] suggests significant potential for broad generality.

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Supporting Information Available: Procedures, spectral data, spectra, and X-ray crystallographic data (cif); full citations for refs 4a, 4b, 6a, 6b, 6c, 6d, 12b, 12c, 14 and 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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