Most of the functional molecules found in living systems, including most “small molecules”, are biosynthesized via iterative coupling of bifunctional building blocks. Polypeptides, oligonucleotides, and to a growing extent oligosaccharides 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. 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 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. 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).

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. As the heteroaromatic 5-bromothiopheneboronic acid reacted cleanly as the heteroaromatic 5-bromothiopheneboronic acid reacted cleanly with Buchwald’s anhydrous SM conditions (Table 1). Gratifyingly, a 24:1 ratio of biaryls 5 and 6 was observed, consistent with strong preferential reactivity with the sp3-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, demonstrated no selectivity (entry 4). To the best of our knowledge, this type of reactivity attenuation with neutral, sp3-hybridized boronate esters is unprecedented, and further studies into the nature and potentially broad utility of this effect are ongoing. 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 NaHCO3/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-methylimidodiacetate-O,O′]-borane 8e was confirmed via single-crystal X-ray diffraction analysis. 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, all of these boronate esters are indefinitely bench stable under air.
of neolignans isolated from the medicinal plant Ratanhiae radix acids can vary dramatically,6 although the reactivity of aryl, heteroaryl, vinyl, and alkyl boronic bifunctional building blocks with couplings was probed by reacting each of these B-protected substrates, we targeted the first total synthesis of the natural product. For example, cross-coupling of aryl boronic acids tends to be more facile than that of their vinyl counterparts,6a making this plan that were anticipated to provide rigorous tests for the new methodology. For example, cross-coupling of aryl boronic acids, such as the deprotected version of 13-bromoaryl boronate can be very unsecured. In addition, heteroaromatic boronic acids, such as the deprotected version of 13, was achieved via recursive application of three SM coupling was also recently reported (ref 9d).

As demonstrated herein, this iterative cross-coupling strategy was given orally by M.D.B. at the NIH Mentoring Conference, Greenbelt, MD, May 12, 2006. (b) A related strategy for oligoarene synthesis via iterative SM coupling was also recently reported (ref 9d).

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 short16 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 sp3−sp2 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.

References

(7) a) A preliminary presentation of this iterative cross-coupling strategy was given orally by M.D.B. at the NIH Mentoring Conference, Greenbelt, MD, May 12, 2006. (b) Related strategy for oligoarene synthesis via iterative SM coupling was also recently reported (ref 9d).
(15) Tyrrell, E.; Brookes, P. Synthesis 2003, 4, 469.
(16) Seven steps in the shortest linear sequence.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Protected product</th>
<th>Deprotected product</th>
<th>% Yield</th>
<th>% Yield</th>
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<td>1</td>
<td>8b</td>
<td>9b (pTol)</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>8c</td>
<td>9c (pTol)</td>
<td>85</td>
<td>95</td>
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<tr>
<td>3</td>
<td>8d</td>
<td>9d (pTol)</td>
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<td>91</td>
</tr>
<tr>
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<tr>
<td>5</td>
<td>8f</td>
<td>9f (pTol)</td>
<td>94</td>
<td>91</td>
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