Phase-Switch Synthesis with Boronic Acids as Productive Tags

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Progress in chemical biology and medicinal chemistry relies extensively on the availability of large libraries of novel small molecules of high purity. In response to these demands, new techniques and strategies are needed to accelerate and facilitate the synthesis and purification of novel organic compounds. Phase-switching strategies are very attractive because they combine the respective advantages of solution and solid-phase synthesis techniques.[1] In phase-switch chemistry, reactions take place conveniently under homogeneous conditions, and product separation is facilitated by precipitation or a "catch-and-release" filtration operation. Phase trafficking is possible through functionalization of the substrate or reagents with a phase "tag". Several ingenious phase-switching strategies were developed and employ various tags such as perfluoroalkyl groups,[2] polyethylene glycol chains,[3] metal chelators,[4] hydrogen-bonding receptors,[5] polymerizable norbornene groups,[6] polyaromatics, and others.[7] While many of these strategies have been used only for tagging reagents or catalysts, a few were employed for tagging substrates and allow multistep syntheses to be performed. In all of these methods, however, the requirement for a phase-switch tag creates two chemically unproductive steps: attachment of the tag to the substrate and detagging of the product at the end. The latter operation often leaves an undesired remnant (or "trace") of the phase-switch tag. Although traceless fluorous syntheses have been reported,[2b] the required tags are complex and still need to be attached to the substrate. Herein, we describe a new phase-switching strategy involving the simple boronic acid functionality as a productively convertible tag. Rather than cleaving the extraneous tag at the end, as in other phase-switch systems, we can use the wide range of selective transformations known for this class of compound to productively derivatize the boronic acid tag. Because of the large number of commercially available boronic acids that can serve as potential substrates toward many synthetic applications, this phase-switch system can also circumvent the tag-attachment step.

The diethanolaminomethyl polystyrene (DEAM-PS) resin reported by our group can be used to immobilize a wide range of boronic acids, which can be cleaved mildly by simple exposure to aqueous THF.[9] Although a number of simple transformations were shown to be possible with the DEAM-PS-supported boronic acids,[10] heterogeneous conditions are not possible, and the boronate linker may lead to premature cleavage in the presence of strong nucleophiles. Given the facility with which boronic acids can be immobilized and released from the DEAM-PS resin, we envisioned that it could provide an efficient phase-switching strategy. Moreover, as boronic acids tend to be reactive only under a few very specific conditions (e.g., transition metal activation),[8] their use as inert tags should be compatible with a wide range of chemical transformations. As illustrated in Figure 1, excess reagents and side-products can be eliminated with ease upon immobilization (phase-switching), filtration, and washings of a boronic acid-tagged product. The pure DEAM-PS-supported product can then be phased-switched back into solution by simple treatment with aqueous THF, followed by solvent evaporation. This reaction cycle can be repeated as desired or terminated through a chemically productive conversion of the boronic acid tag as part of a diversity-oriented synthesis. Similar methods are known to effect protodeboronation of arylboronic acids, so that this system can also serve as a traceless phase-switching strategy for arenes.[11]

We first demonstrated the efficiency and usefulness of this phase-switching system in peptide synthesis, without a productive cleavage step. The purification of even the smallest peptides made in solution can be tedious and often troublesome because of the use of excess reagents and their remnants. Although solid-phase synthesis addresses the separation issue, it is not compatible with heterogeneous reaction conditions, and it is limited to small-scale preparations. Phase-switch chemistry addresses these issues in a significant way by making use of a high-loading scavenging resin (i.e., >2 mmol/g DEAM-PS) and is thus an attractive strategy for the preparation of peptide derivatives. As exemplified with the preparation of model tetrapeptide **1** (Scheme 1), a set of conditions was found that is completely compatible with a free boronic acid. This led to a simple reaction cycle initiated by the attachment of commercially available 4-borono-benzyl alcohol to a *t*-Boc-protected aminoacid (alanine in the case of **1**), followed by phase-switching with DEAM-PS. Removal of the *t*-Boc group and peptide elongation proceeded best with the use of HOBT/HBTU/NEt(*i*-Pr)$_2$ (the use of carbodiimides with HOBt and different bases provided much lower yields). These conditions do not affect the integrity of the boronic acid tag. Product recovery is technically straightforward and functions well in a wide range of non-hydroxylic solvents.[12] Each new coupling product was purified by the simple addition of a 2-fold excess of DEAM-PS to the reaction mixture, followed by filtration and thorough washings of the resin. Upon treatment with wet THF, the tagged product was released free of any traces of coupling reagents and byproducts. Using the cycle of Scheme 1, we isolated the final tri-, tetra-, and pentapeptides **1**−**5** in high homogeneity (as per NMR and HPLC analysis) without any extensive purification after

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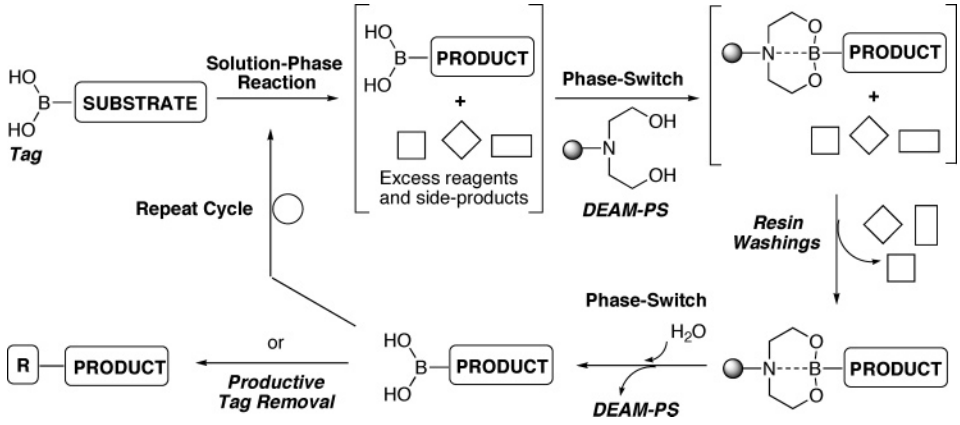
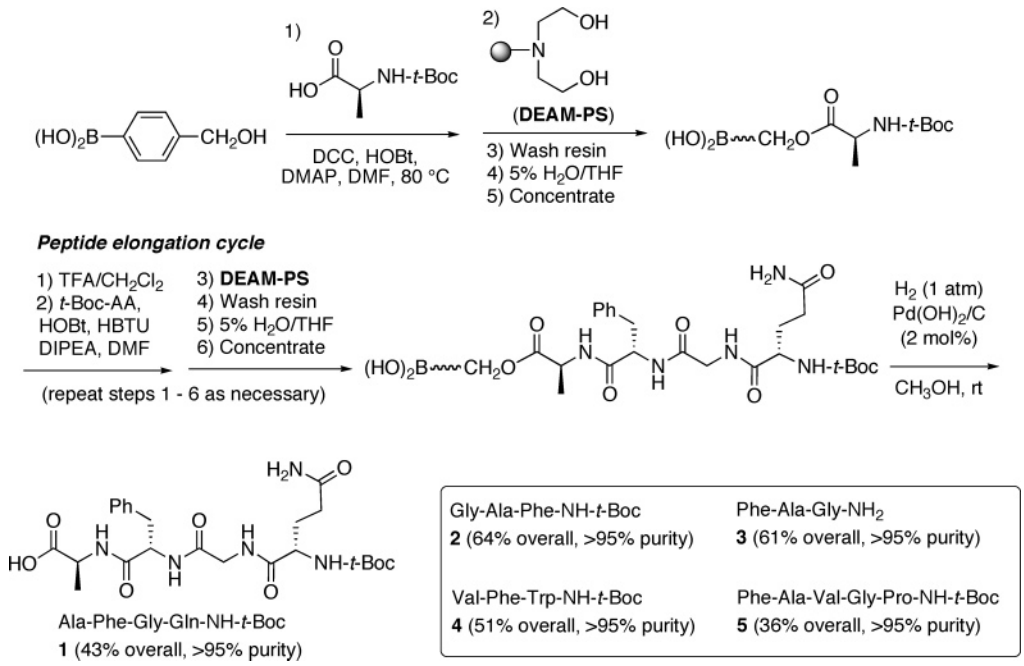


Figure 1. Phase-switch synthetic cycle using a boronic acid-tagged substrate and diethanolaminomethyl-polystyrene (DEAM-PS). At the end of the cycle, the boronic acid tag is removed concomitantly with its productive conversion into a final product.

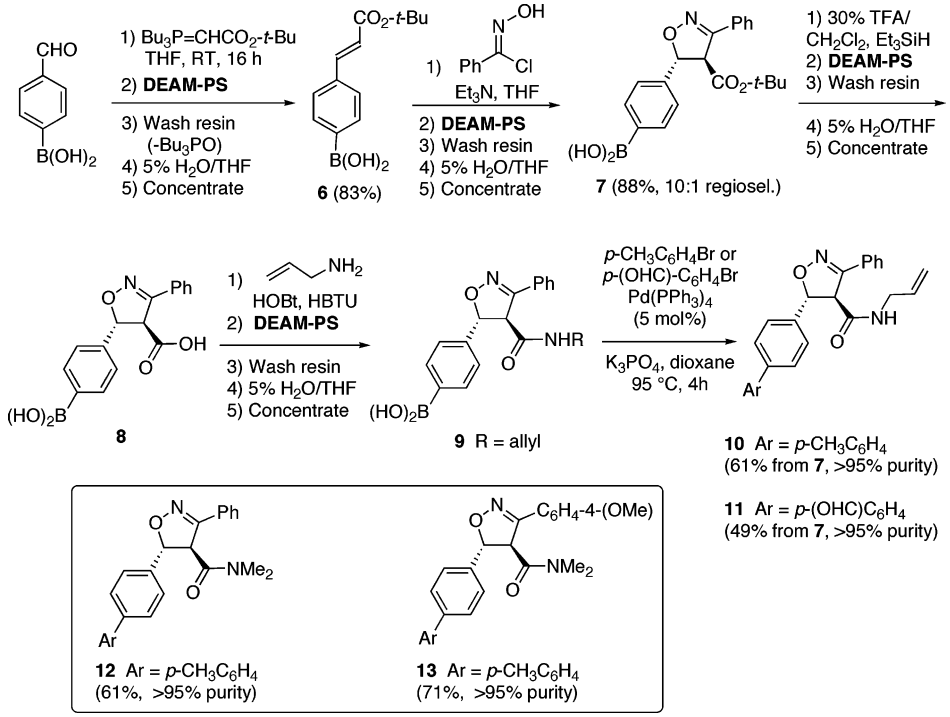
Scheme 1



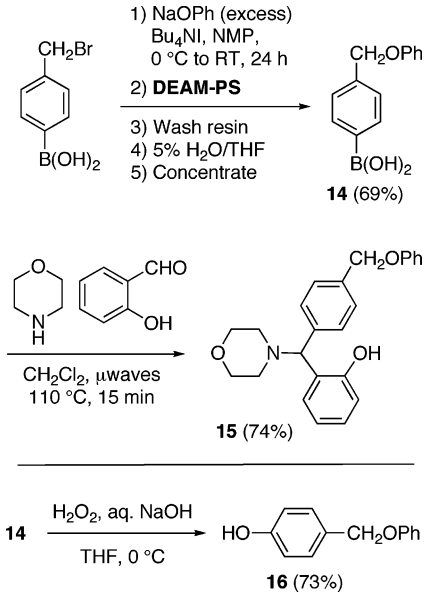
hydrogenolytic detagging. To this end, the use of $Pd(OH)_2$ as a heterogeneous catalyst was more efficient than Pd(C). The determination of the purity of final products was based on a combination of ^1H NMR analysis and HPLC chromatography (with combined UV and ESMS detection). Most final products did not show any impurities with peak integrations accounting for more than 5%. It is also noteworthy that the DEAM-PS resin used in the phase-switching operations can be recycled and reused several times without a noticeable loss of efficiency.

To illustrate the virtues of the boronic acid functionality as a productive tag, we optimized a reaction cycle for a diversity-oriented synthesis of polysubstituted biaryl-containing isoxazolines (Scheme 2). In the planning of a synthetic cycle to a desired compound class, the initial boronic acid substrate is selected from a broad choice of commercial ones, and the boronic acid functionality is simply preserved until the last step of productive tag removal. Here, the cycle was initiated by a Wittig reaction on commercially available *p*-boronobenzaldehyde, the use of which as substrate circumvents the need for a tag-attachment step. The removal of the phosphine oxide byproduct was greatly facilitated by the phase-switching operation with DEAM-PS, giving, after hydrolytic release and evaporation, the pure acrylate product **6**. The latter underwent a [3 + 2] cycloaddition with a nitrile oxide[13] to give, in very good regioselectivity,[14] the trans trisubstituted isoxazoline intermediate **7** after a series of simple phase-switching operations. The removal of the *t*-Boc group and coupling of the resulting carboxylic acid **8** with a primary amine, allylamine, proceeded to give amide intermediate **9**. Here again, no formal purifications were needed as a result of the efficient phase-switching with the DEAM-PS resin.[12] The boronic acid tag was derivatized by a Suzuki cross-coupling with *p*-bromotoluene or p-bromobenzaldehyde to provide, in a synthetically productive detagging operation, biaryl-containing isoxazoline products **10** and **11** to end the cycle. Because both the tag-attachment and -removal steps are avoided, the final element of diversity of this multistep synthesis comes at no extra cost.[15,16] Isoxazolines **12** and **13**, synthesized in the same manner,

Scheme 2



Scheme 3



demonstrate that secondary amides and other nitrile oxides are suitable components. Although the final isoxazoline products **10**−**13** required a routine chromatographic purification to display the indicated level of >95% homogeneity, no purification was necessary for any of the intermediates in the multistep synthesis. These examples clearly highlight the value of this phase-switching strategy in facilitating the synthesis of highly functionalized biaryl products, which are very important components of pharmaceutical drugs and natural products. Because boronic acids can be transformed into a plethora of other products,[8] this productive phase-switching concept is not limited to biaryl compounds. For example, branched benzhydryl amine **15** was produced through a Petasis borono-Mannich reaction/detagging on **14** (Scheme 3).[17,18] The latter originates from substitution of commercially available *p*-bromomethylphenylboronic acid with excess sodium phenoxide. The compatibility of the boronic acid tag with such highly basic conditions, combined with the simple and efficient phase-switching, further demonstrates the potential of this system. Furthermore, the preparation of phenol **16** emphasizes the possibility of using the tag as a masked hydroxyl group.

In summary, we have described a novel phase-switch chemistry system involving a productive tag for use in multistep organic synthesis. This system, based on the DEAM-PS resin, exploits the boronic acid functionality as a phase tag because of its simplicity, ease of handling, and compatibility with several reaction conditions. Because of the large number of commercially available boronic acids that can serve as potential substrates, this phase-switch system can circumvent the tag-attachment step. Most importantly, boronic acids can be converted selectively into a wide variety of useful products to terminate the synthetic cycle concomitantly with the detagging operation. The examples of peptides and polysubstituted biaryl isoxazolines highlighted herein represent only a small subset of the possibilities that can be envisioned with this novel phase-switching strategy.

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Supporting Information Available. Full experimental details and characterization data for all new compounds with copies of the ^{1}H and ^{13}C NMR spectra and selected HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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