Articles

Universal Solid-Phase Approach for the Immobilization, Derivatization, and Resin-to-Resin Transfer Reactions of Boronic Acids

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Boronic acid-containing molecules are employed in a broad range of biological, medicinal, and synthetic applications. These compounds, however, tend to be difficult to handle by solution-phase methods. Herein, this problem is addressed with the development of the first general solid-phase approach for the derivatization of functionalized boronic acids. This approach is based on the use of a diethanolamine resin anchor that facilitates boronic acid immobilization by avoiding the need for exhaustive removal of water in the esterification process. The immobilization of a wide variety of boronic acids onto *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **1**) can be performed within minutes by simple stirring in anhydrous solvents at room temperature. Evidence for the formation of a bicyclic diethanolamine boronate with putative N−B coordination was shown by ^{1}H NMR analysis of DEAM-PS-supported *p*-tolylboronic acid. The hydrolytic cleavage of the same model boronic acid from the DEAM-PS resin was studied by UV spectroscopy. Hydrolysis and attachment were shown to occur under a rapidly attained equilibrium, and a large excess of water (>32 equiv) is required to effect a practically quantitative release of boronic acids from DEAM-PS. Despite their relative sensitivity to water and alcohols, DEAM-PS-bound arylboronic acids functionalized with a formyl, a bromomethyl, a carboxyl, or an amino group can be transformed in good to excellent yields into a wide variety of amines, amides, anilides, and ureas, respectively. Ugi multicomponent reactions on DEAM-PS-supported aminobenzeneboronic acids, derivatization of multifunctional arylboronic acids, and sequential reactions can also be carried out efficiently. These new DEAM-PS-supported arylboronic acids can be employed directly into resin-to-resin transfer reactions (RRTR). This type of multiresin process helps eliminate time-consuming cleavage and transfer operations, thereby considerably simplifying the outlook of combinatorial library synthesis by manual or automated means. This concept was illustrated by a set of optimized procedures for the Suzuki cross-coupling and the borono-Mannich reactions.

Introduction

Boronic acids have become an extremely important class of organic compounds. They are employed in a variety of biological and medicinal applications such as carbohydrate recognition,[1] protease enzyme inhibition,[2] neutron capture therapy for cancer,[3] and transmembrane transport.[4] In recent years, they have also gained tremendous popularity as substrates and building blocks in organic synthesis and combinatorial chemistry. The well-established Suzuki−Miyaura class of cross-coupling reactions[5,6] was recently complemented by a wide variety of novel, synthetically useful methodologies that employ boronic acids as substrates. Included among these new reactions are Miyaura's rhodium(I)-catalyzed addition to aldehydes;[7] variants of the latter for additions to activated[8] and unactivated alkenes;[9] copper diacetate-promoted cross-coupling reactions with various active hydrogen functionalities (nitrogen- or oxygen-contain-

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ing,[10] thiols[11]); palladium- or nickel-catalyzed coupling protocols involving sulfonium salts,[12] thioesters,[13] or thioalkynes;[14] nickel-catalyzed couplings with allylic compounds;[15] and mercury(II) acetate/lead tetraacetate-promoted couplings with active methylene compounds.[16] The three-component borono-Mannich reaction,[17] first reported by Petasis,[17a] allows the synthesis of various α-amino acid and *β*-amino alcohol derivatives. There are also a number of useful oxidative ipso-substitution methodologies for arylboronic acids.[18]

Many of the reactions described above are amenable to solid-phase and are thus particularly attractive for combinatorial library synthesis. These new types of synthetic transformations have created a demand for the commercial availability of a larger number of functionalized boronic acids. Yet, there are still relatively few boronic acids on the market.[19] The paucity of boronic acids can be explained by the nonexistence of natural ones and, in large part, by difficulties associated with the synthesis and derivatization of even the simplest functionalized ones by solution-phase methods. The isolation of compounds containing a boronic acid functionality can prove to be notoriously troublesome as a result of their amphiphilic character. They exist as water-soluble tetrahedral boronate anions at high pH and are thought to be hydrated at neutral pH[20] so that even those bearing a relatively hydrophobic group can be difficult to extract quantitatively into organic solvents under standard aqueous workup procedures. These problems are amplified when the desired boronic acid-containing compound comprises other sites with basic or acidic functionalities. Boronic acids are also typically slow-moving on silica gel and, consequently, must often be purified by recrystallization. In addition, although arylboronic acids are relatively stable and can be handled without special precautions, alkylboronic acids and, to some extent, alkenylboronic acids are sensitive to oxidation even under ambient air.[21] Some of these problems can be alleviated by protection of the boronic group as an ester.[22] However, these approaches require additional synthetic operations.

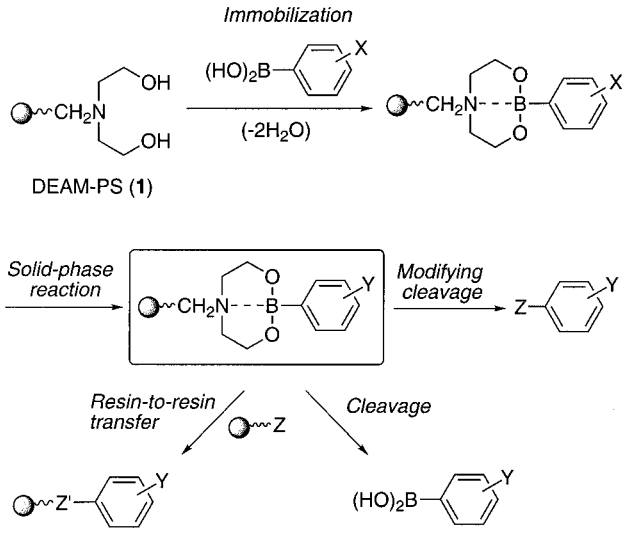

Figure 1. Immobilization and derivatization of functionalized boronic acids using *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **1**).

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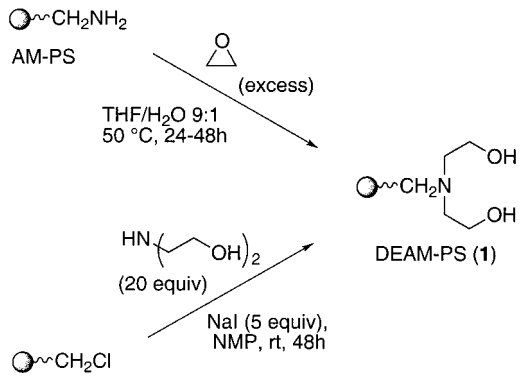
In view of all the above-mentioned impediments to handling boronic acids in solution phase, it is clear that a simple and general solid-phase approach for their immobilization and derivatization would be of tremendous usefulness. Indeed, solid-phase methods circumvent the need for aqueous workup and other time-consuming operations required to isolate the desired product from excess reagents and byproducts.

Herein, we describe a detailed account of the preparation, characterization, properties, and synthetic applications of *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **1**)[23,24] as support for the first general solid-phase approach to the immobilization and derivatization of boronic acids (Figure 1). Other types of supports based on diol anchors have been described recently.[25,26] However, unlike DEAM-PS, these supports do not allow the straightforward attachment and cleavage of boronic acids under mild conditions. The DEAM-PS resin can be used for the immobilization of several types of functionalized boronic acids that can undergo a wide variety of standard synthetic transformations as stable, supported diethanolamine esters (X → Y in Figure 1). Several options are available following the solid-phase derivatization of a DEAM-PS-supported boronic acid. The resulting product can be released either as a free boronic acid or through a modifying cleavage procedure such as oxidation to form a phenol derivative[25a] or as part of a reductive traceless strategy for arene synthesis.[25b] Alternatively, in cases where the new boronic acid is a substrate for a subsequent reaction, it is actually possible to streamline the supported substrate directly into a resin-to-resin transfer reaction (RRTR). By avoiding cleavage and transfer operations, this type of multiresin system is particularly attractive in combinatorial chemistry for use in automated library synthesis. In addition to these applications, diethanolamine-based resins such as DEAM-PS could also be useful as solid-supported scavengers[23,27] or as supports for affinity purification of boronic acids.

Results

Preparation and Characterization of *N*,*N*-Diethanolaminomethyl Polystyrene (1). We have first reported on the preparation of resin **1** from standard cross-linked aminomethylpolystyrene (AM-PS) by means of a double alkylation with ethylene oxide in a sealed tube (Scheme 1).[23] This transformation was carried out under temperature conditions known in solution phase to minimize quaternization of the desired tertiary amine.[28] A ninhydrin test on the final resin obtained after 48 h of reaction time hinted at the absence of any leftover

Scheme 1



primary and secondary amines. The carbon/nitrogen/oxygen ratio resulting from elemental analysis was satisfactory and in accordance with the loading of AM-PS stated by the supplier. In addition, coupling of (fluorenylmethoxy)carbonyl (Fmoc) glycine to the hydroxyl groups, followed by piperidine treatment and quantitative UV analysis of the fulvene adduct, confirmed the expected ratio of two hydroxyethyl arms per nitrogen. This preparative method, however, did not prove practical for making larger quantities of **1**; thus, we sought to develop a more convenient, pressure-free method. To this end, we have found that resin **1** can be made with ease from chloromethylated polystyrene (Merrifield) resin and diethanolamine in the presence of sodium iodide in *N*-methylpyrrolidinone (NMP) at room temperature.[29] While the latter method is more conveniently carried out, both methods afford DEAM-PS resin of similar characteristics with identical efficiency at immobilizing boronic acids.

For the immobilization, we found that *p*-tolylboronic acid can be coupled in high yields by esterification with **1** through simple mixing for less than 15 min in anhydrous solvents at room temperature (vide infra). As expected from the behavior of diethanolamine boronates in solution phase,[30] there was no need to drive the reaction forward by exhaustive trapping of the water released in this immobilization process. This constitutes a significant advantage over other types of diols, whether solid-supported or not, which usually require azeotropic removal of the water.[25,26] In fact, we have confirmed the much lower efficiency of commercially available glycerol resin.[31] Using standard immobilization conditions developed for **1**, PS-glycerol coupled to *p*-tolylboronic acid with only 50% yield. These results highlight the importance of the nitrogen atom from the aminodiol anchor of DEAM-PS. Evidence for the existence of N−B coordination in diethanolamine boronic esters has been reported with soluble adducts.[32] Because this seems to be a crucial factor in the efficiency and ease with which DEAM-PS resin immobilizes boronic acids, we were interested in examining the role of the diethanolamine nitrogen in the

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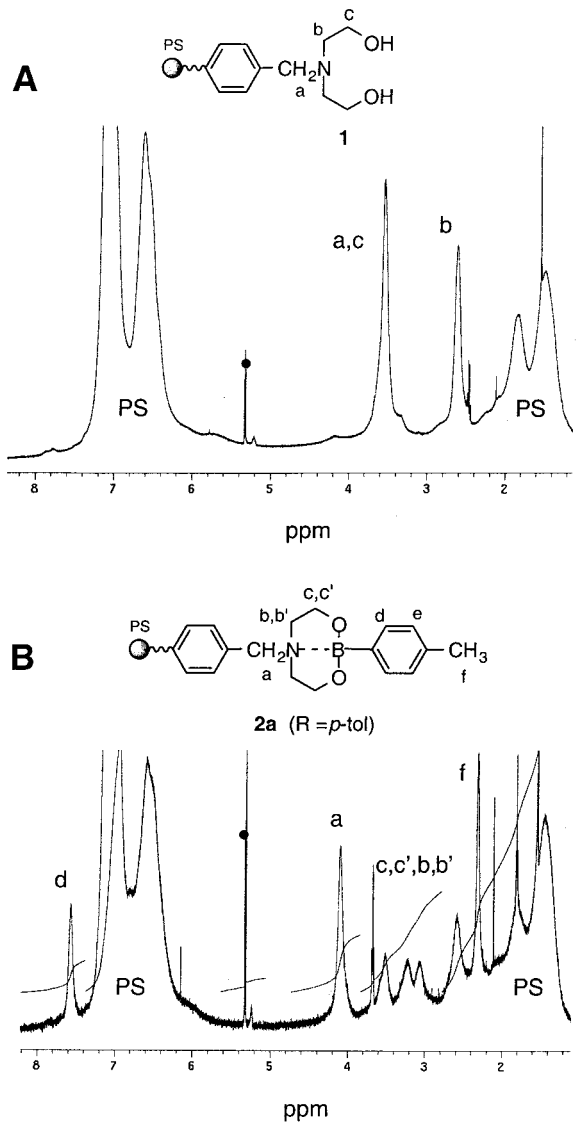


Figure 2. Gel-phase ^{1}H NMR spectra (500 MHz) of DEAM-PS (A) and DEAM-PS-supported *p*-tolylboronic acid (B) using a magic angle spinning nanoprobe. Solvent is CD_2Cl_2 (peak identified by a dot). Conditions are as follows: A; acquisition time (at) = 3, pulse width (pw) = 2.5, d1 = 0, spinning at 2119 Hz. B; at = 3, pw = 2.0, d1 = 0, spinning at 2300 Hz (Note that the signal at 3.7 ppm is residual THF). PS: polystyrene resonances.

polymer-supported case. To this end, we have compared gel-phase proton NMR spectra of the free form of DEAM-PS and the *p*-tolylboronic acid conjugated form (**2a**) using a magic angle spinning nanoprobe (Figure 2). Aside from resonances exhibited by the polystyrene matrix, two broad singlets show up at 2.6 and 3.5 ppm in the spectrum of free DEAM-PS (Figure 2A). Presumably, the largest, most unshielded peak contains resonances from both benzylamino and hydroxymethyl methylenes. In theory, upon formation of a cis fused bicyclic diethanolamine boronate adduct with two nonequivalent faces, the ring hydrogens become diastereotopic. As expected, the resulting spectrum of **2a** (Figure 2B) showed extensive degeneration of the methylenic protons in the hydroxyethyl arms. As many as four peaks were now seen between 2.2 and 3.6 ppm, thereby lending support to a tetrahedral, nitrogen-coordinated boronic ester.

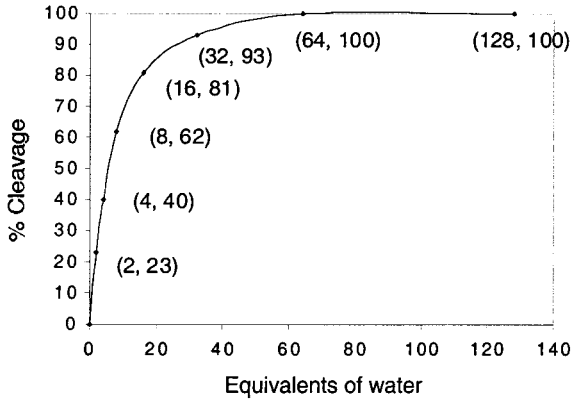


Figure 3. Percentage of hydrolytic cleavage of DEAM-PS-supported *p*-tolylboronic acid (**2a**) followed by UV spectroscopy (225 nm) as a function of water stoichiometry.

Immobilization and Cleavage of Boronic Acids. To effect release of DEAM-PS-supported boronic acids, we originally reported on the use of a wet THF solution containing acetic acid (THF/H_2O/AcOH 90:5:5).[23] We have since found that no acid is necessary and that a 5:95 H_2O/THF solution alone is sufficient to quickly liberate the boronic acids from the support. To avoid product contamination and boronic acid oxidation into the corresponding phenol, it is preferable to employ a cleavage solution prepared from air- and peroxide-free, freshly distilled THF.[33] To investigate the extent to which the diethanolamine−boronate linkage is sensitive to water, we have devised a UV spectroscopic assay whereby the hydrolysis of DEAM-PS-supported *p*-tolylboronic acid (**2a**) was monitored quantitatively both in a time-related fashion and with respect to the amount of water used. In principle, a minimum of 2 mol equiv of water is required to effect quantitative cleavage of DEAM-PS-supported boronic acid **2**. This type of boronate exchange process involving water and a competing diol like DEAM-PS (**1**), however, is usually under equilibrium:

$$\mathbf{2} + 2H_2O \rightleftarrows \mathbf{1} + RB(OH)_2$$

$$K_{eq} = \frac{[\mathbf{1}][RB(OH)_2]}{[\mathbf{2}][H_2O]^2}$$

A time profile of boronic acid release from **2a** with variable amounts of water (2, 10, and 30 equiv) showed that the extent of boronic acid cleavage rapidly reached a plateau within less than 1 min (data not shown). A comparison of the percentage of boronic acid release with different numbers of equivalents of water is shown in Figure 3. Overall, the resulting data confirmed that hydrolysis is under equilibrium and that a large excess of water (>32 equiv) is required to provide a practically quantitative hydrolysis. As a rule of thumb, such a quantity of water corresponds roughly to the use of 10 mL of cleavage solution (5% H_2O/THF) per gram of resin at a 0.8 mmol/g of resin loading. This deduction, however,

(33) The 2,6-di-*tert*-butyl-*p*-cresol used as stabilizer in nondistilled THF often was found to accumulate in the polymer matrix of DEAM-PS and contaminate the products upon cleavage. This can be prevented by the use of distilled THF for resin washing and for the cleavage solution. However, in the absence of the stabilizer, freshly distilled THF must be used in order to avoid a presumed buildup of peroxides, which cause oxidation of the boronic acids into the corresponding phenols.

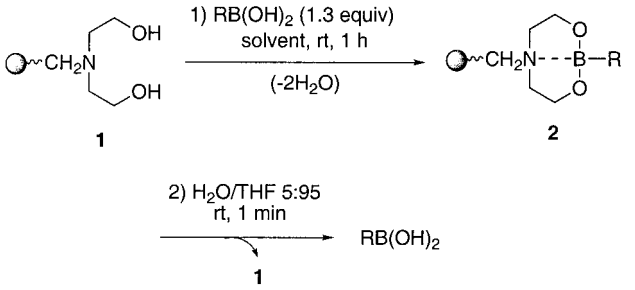
may not be generalized to all types of functionalized boronic acids. In particular, some ortho-substituted arylboronic acids may behave differently[34] and prove to be more difficult to liberate from DEAM-PS. In these cases, a larger proportion of water or the use of acidic conditions (THF/H_2O/AcOH 90:5:5) may be advisable. The above hydrolysis study also suggests that the reverse process, boronic acid immobilization from DEAM-PS, by releasing 2 mol equiv of water cannot be quantitative in THF, unless a large excess of boronic acid is employed to shift the equilibrium. Otherwise, according to Figure 3, the approximate maximum yield of immobilization for equimolar amounts of DEAM-PS and boronic acid is 80%. Thus, to optimize the yield of immobilization, the boronic acid must be largely monodehydrated before use.[35] Yet, one molecule of water is released even from the corresponding boroxines ($(RBO)_3$), so the esterification process is limited to about 90% efficiency in THF. The use of homogeneous dehydrating agents such as tetramethylorthoformate (TMOF) did not help to improve the immobilization efficiency.

A series of boronic acids presenting different steric and electronic characteristics was tested as a means to evaluate the generality of immobilization onto DEAM-PS (Table 1). These studies were carried out under conditions planned to optimize the yield of immobilization. Thus, a slight excess of the boronic acid (ca. 1.3 equiv), predried in vacuo as the monoanhydride form, was shaken with DEAM-PS at room temperature for 1 h. Percentages of recovery are based on the amount of boronic acid isolated after cleavage of **2** with H_2O/THF (5:95). A solvent profile study using *p*-tolylboronic acid revealed that a wide range of anhydrous solvents can be employed (entries 1−6, Table 1). Whereas THF was found to be a general solvent to solubilize and immobilize boronic acids efficiently, we have found that dichloromethane provides higher yields of immobilization (entry 5 vs entry 6, Table 1). Presumably, the limited solubility of water in dichloromethane minimizes the back-reaction (hydrolysis). When THF is used as solvent, a wide variety of functionalized arylboronic acids presenting different steric and electronic characteristics were found to immobilize efficiently onto DEAM-PS (entries 6−18, Table 1). With the exceptions of *o*-carboxyphenylboronic acid (entry 10, Table 1) and exceptionally hindered or electron-poor arylboronic acids (entries 15 and 16, Table 1), the coupling yields were very high. Immobilization of alkenylboronic acids is also possible (entry 18, Table 1). All of these boronic acids were recovered intact, and the leftover DEAM-PS resin can be recycled with no apparent loss of efficiency after neutralization with base (dilute triethylamine) followed by the usual rinses.

Hydroxylic solvents such as methanol and ethanol allow a dynamic transesterification process to take place, leading to nonquantitative immobilization (Table 1, entry 1). We have measured the extent of transesterification of DEAM-PS-supported *p*-tolylboronic acid (**2a**, R = *p*-tolyl) in 7:1 THF/ethanol.[17p] Equilibrium was reached within 15 min of exposure of the supported *p*-tolylboronic acid to the 7:1 THF/ethanol solvent. Successive incubations of the resin under constant resin/solvent proportions, followed by rinses with dry THF, revealed that approximately 40% of the *p*-tolylboronic acid is released from the resin under these conditions. The reverse reaction (**1** + *p*-tolylboronic acid) gave a similar outcome under the same conditions, showing that the transesterification process is under equilibrium.

A diisobutanolaminomethyl-substituted resin (**3**) was made from isobutylene oxide (Scheme 2) to investigate whether increased steric bulk would improve tolerance of the support to water and hydroxylic solvents. Immobilization and cleavage of *p*-tolylboronic acid from resin **3**, however, did not show any improvement in this respect when carried out under similar conditions as those for resin **1**. The relative sensitivity of the dietha-

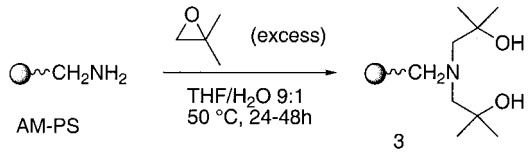
Table 1. Immobilization of Various Boronic Acids onto 1[a]



entry	R	solvent	yield (%)[b]	purity[c]
1	4-Me-C_6H_4	MeOH	72	>95
2	4-Me-C_6H_4	NMP	80	>95
3	4-Me-C_6H_4	Et_2O	90	>95
4	4-Me-C_6H_4	toluene	88	>95
5	4-Me-C_6H_4	CH_2Cl_2	98	>95
6	4-Me-C_6H_4	THF	89	>95
7	4-Br-C_6H_4	THF	97	>95
8	4-MeO-C_6H_4	THF	87	>95
9	4-HO_2C-C_6H_4	THF	90	>95
10	2-HO_2C-C_6H_4	THF	51	>95
11	3-H_2N-C_6H_4	THF	91	>95
12	2-CHO-C_6H_4	THF	98[d]	>95
13	4-PhO-C_6H_4	THF	93	>95
14	4-$BrCH_2$-C_6H_4	THF	85	>95
15	2,6-di-Me-C_6H_3	THF	46	>95
16	2,4-di-F-C_6H_3	THF	46	>95
17	2-naphthyl	THF	89[d]	>95
18	(*E*)-PhCH=CH	THF	81	>95

[a] Coupling reactions were conducted by shaking resin **1** (1 equiv, 120 mg, 1.15 mmol/g) with the boronic acid (1.3 equiv) in the indicated solvent (1.5 mL) at room temperature for 1 h in a polypropylene fritted vessel. [b] Yields of boronic acid recovered after cleavage from the resin with 5% H_2O/THF for 1 min at room temperature and washing with 5% H_2O/THF (3×). The resin was rinsed with the reaction solvent (3×) prior to cleavage. For entries 4 and 5, additional THF rinses were carried out (3×). The reported yields are an average of mass balance and internal standardization (see Supporting Information for details) based on the loading of resin **1** measured by elemental analysis. [c] Estimated by comparison of ^1H NMR spectra of starting and recovered boronic acids. [d] Calculated only from mass balance; the tendency of this boronic acid to form anhydrides made NMR quantitation difficult.

Scheme 2



(34) Cai, S. X.; Keana, J. F. W. *Bioconjugate Chem.* **1991**, *2*, 317−322.

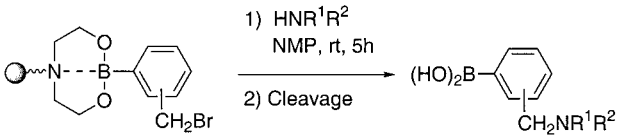
(35) Although commercial boronic acids tend to come as largely dehydrated anhydride forms, it is advisable to further dry them in vacuo prior to immobilization with DEAM-PS. For a pertinent review, see: Lappert, M. F. *Chem. Rev.* **1956**, *56*, 959.

nolamine boronic ester linkage to water and alcohols should be taken into account when using DEAM-PS for the derivatization of functionalized boronic acids. It appears that anhydrous and alcohol-free reaction conditions are preferable to avoid premature cleavage of products. On the other hand, there can be significant practical aspects to derivatizing functionalized boronic acids on DEAM-PS, as they could be directly released in an aqueous buffer required for biological screening.

Solid-Phase Derivatization of Functionalized Boronic Acids. We set out to develop a series of useful solid-phase reaction protocols to derivatize functionalized, DEAM-PS-supported boronic acids. To evaluate the scope of reaction conditions compatible with DEAM-PS-supported boronic acids, simple functional group interconversion methods were examined (Tables 2−6). All supported substrates were easily prepared in high yield from **1** as described in the previous section. Most boronic acid products obtained after cleavage with 5% H_2O/THF were not further purified and were characterized by mass spectrometry, IR, and ^1H and ^{13}C NMR spectroscopy. The reported yields of products are inclusive of the boronic acid immobilization step, which as discussed in the previous section, may not be quantitative.[32] Percentage yields were calculated as an average value of mass balance and internal standardization with ethyl acetate as compared with the theoretical loading of free DEAM-PS resin. These two methods were almost always found to be within a 5% range using optimized analytical methods (see Supporting Information). The indicated purity values for the products are a conservative estimate based on inspection of NMR spectra and quantitation of peaks from the expected product relative to signals from possible byproducts and starting material. In general, all compounds were obtained with a minimum of 90% purity, and in a majority of cases, there were no detectable byproducts by NMR analysis.

Table 2 summarizes the results for the substitution of bromomethyl-derivatized benzeneboronic acids with representative primary and secondary amines. In this case involving amphoteric aminomethyl-substituted products, the advantages of a solid-phase approach for product isolation are optimal vis-à-vis solution-phase methods. The optimal conditions found from alkylations of meta and para substrates **5** and **6** involve simple stirring of DEAM-PS-supported bromomethylbenzeneboronic acid with the amine in NMP for approximately 5 h at room temperature. As much as 10 equiv of secondary amines was employed to ensure reaction completion under these conditions. To suppress cross-linking of the substrate by double alkylation with primary amines, it was found to be preferable to use a low-loading DEAM-PS resin (<0.60 mmol/g) with a larger excess of the amine (50 equiv). Because of the large excess of primary amine reactant used, the yields of the secondary amine products may suffer from premature cleavage of the supported boronic acid. Nonetheless, these protocols provided good to excellent yields of isolated secondary and tertiary amine products **8** and **9**. Unfortunately, these and several other conditions failed to provide any expected product in the case of ortho-substituted substrate **4**. For yet unexplained reasons, facile premature cleavage was observed. These ortho-aminomethyl-substituted products, however, can be obtained from reductive amination chemistry (vide infra). Sodium phenoxide has been used as an example of an oxygen-based nucleophile (Scheme 3). Treatment of **6** with PhONa in the presence of iodide ion in NMP for 24 h provided ether derivative **10** only in moderate yield after cleavage from the resin followed by rapid filtration through silica gel. We suspect that the phenoxide ion causes substantial premature cleavage from the resin.

Table 2. Substitution Reactions on 5 and 6

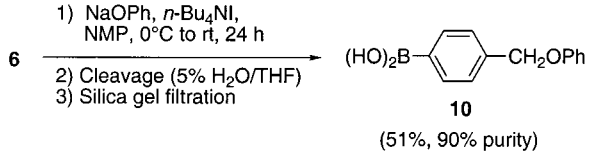


4 *o*-, **5** *m*-, **6** *p*- **7** *o*-, **8** *m*-, **9** *p*-

entry	substrate	conditions[a]	product {R^1, R^2}	yield[b] (%)	purity[c] (%)
1	**5**	A	**8a** {H, CH_2Ph}	69	95
2	**5**	A	**8b** {H, $CH_2CH(CH_3)_2$}	50	>90
3	**5**	B	**8c** {$(CH_2)_2O(CH_2)_2$}	85	95
4	**5**	B	**8d** {Me, CH_2Ph}	75	>95
5	**6**	A	**9a** {H, CH_2Ph}	69	>90
6	**6**	A	**9b** {H, $CH_2CH(CH_3)_2$}	53	95
7	**6**	B	**9c** {$(CH_2)_2O(CH_2)_2$}	98	>90
8	**6**	B	**9d** {Me, CH_2Ph}	94	95

[a] Reactions were carried out by shaking the supported benzyl bromide with the amine in NMP at room temperature for approximately 5 h (typical scale, 0.12 mmol of **5** or **6**). Conditions were as follows: (A) 50 equiv of primary amine, use of low-loading DEAM-PS resin (0.60 mmol/g); (B) 10 equiv of secondary amine, use of either low-loading (0.60 mmol/g) or high-loading (1.14 mmol/g) DEAM-PS resin. [b] Nonoptimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for greater than 12 h. The reported values are an average of mass balance and internal standardization (see Supporting Information for details). [c] Estimated from ^1H and ^{13}C NMR data.

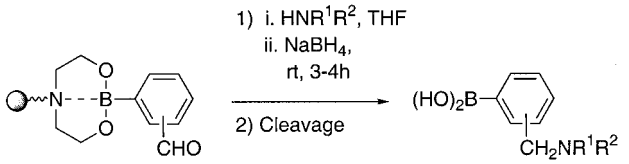
Scheme 3



The results for the reductive amination of supported formyl-substituted benzeneboronic acids with various primary and secondary amines are compiled in Table 3. The single set of conditions found to avoid premature cleavage of the boronic acid involves preformation of the imine in THF and then addition of sodium borohydride as the hydride source. Other hydride reagents tested (e.g., $NaBH(OAc)_3$, $NaBH_3CN$) led to premature cleavage of the supported boronic acid. Interestingly, only the ortho substrate **11** gave satisfactory yields of product **7** with good purity. This chemistry thus complements the bromomethyl substitution method described above. The less hindered meta and para substrates **12** and **13** gave the respective amine products **8** and **9** in a significantly lower purity. Although there was no evidence for double alkylation in the case of primary amines, the desired products were accompanied by unidentified impurities. In a similar way, the inverse process, reductive alkylation of supported aniline substrates (i.e., substrates **20**−**22**), was also unsuccessful both for aromatic and aliphatic aldehydes.

The formation of amide derivatives from DEAM-PS-supported carboxy-functionalized arylboronic acids proved to be very general with respect to reaction conditions (Table 4). A substrate limitation, however, was observed

Table 3. Reductive Amination on Aldehyde 11[a]

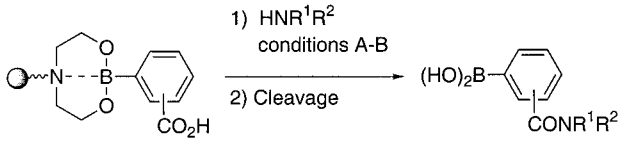


11 *o*-, **12** *m*-, **13** *p*- **7** *o*-, **8** *m*-, **9** *p*-

entry	substrate	product {R^1, R^2}	yield[b] (%)	purity[c] (%)
1	**11**	**7a** {H, CH_2Ph}	66	>90
2	**11**	**7b** {H, $CH_2CH(CH_3)_2$}	55	>90
3	**11**	**7c** {H, $(CH_2)_3Ph$}	62	95
4	**11**	**7d** {H, $(CH_2)_3CH_3$}	73	>95

[a] Typical scale was 0.1 mmol. Reactions were carried out by preforming the imine from supported aldehyde and the amine (2 equiv) in THF at room temperature for approximately 2.5 h. Sodium borohydride was added, and the suspension was shaken for approximately 4 h. [b] Nonoptimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for greater than 12 h. The reported values are an average of mass balance and internal standardization (see Supporting Information for details). [c] Estimated from ^1H and ^{13}C NMR data.

Table 4. Amide Synthesis from 15 and 16



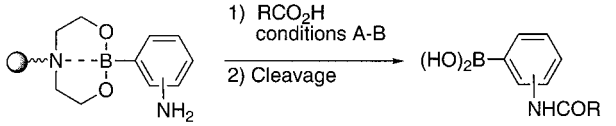
14 *o*-, **15** *m*-, **16** *p*- **17** *o*-, **18** *m*-, **19** *p*-

entry	substr	condns[a]	product {R^1, R^2}	yield[b] (%)	purity[c] (%)
1	**15**	A	**18a** {H, $(CH_2)_3Ph$ }	57	95
2	**15**	A	**18b** {H, $CH(CH_3)_2$}	60	>90
3	**15**	A	**18c** {H, $(CH_2)_3CH_3$}	56	>90
4	**15**	B	**18d** {H, Ph}	82	>95
5	**15**	A	**18e** {Et, Et}	77	90
6	**15**	A	**18f** {Bu, Bu}	79	90
7	**15**	A	**18g** {CH_2Ph, CH_2Ph}	60	>90
8	**16**	B	**19a** {H, $(CH_2)_3Ph$ }	65	>95
9	**16**	B	**19b** {H, $CH(CH_3)_2$}	81	>95
10	**16**	A	**19c** {H, $(CH_2)_3CH_3$}	64	95
11	**16**	A	**19d** {H, Ph}	67	>95
12	**16**	A	**19e** {Et, Et}	59	>90
13	**16**	A	**19f** {Bu, Bu}	53	90
14	**16**	B	**19g** {CH_2Ph, CH_2Ph}	70	95
15	**16**	A	**19h** {H, $CH_2CH_2NEt_2$}	70	>95

[a] Typical scale was 0.1 mmol. Conditions were as follows: (A) reactions were carried out by shaking the supported carboxylic acid with the amine (4 equiv), diisopropylcarbodiimide (DIC) (4 equiv), and HOBT/H_2O (4 equiv) in NMP or DMF at room temperature for 18 h; (B) reactions were carried out by shaking the supported carboxylic acid with the amine (2 equiv), diisopropylethylamine (DIPEA) (4 equiv), and PyBOP (2 equiv) in DMF at room temperature for 20 h. [b] Nonoptimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for greater than 12 h. The reported values are an average of mass balance and internal standardization (see Supporting Information for details). [c] Estimated from ^1H and ^{13}C NMR data.

as the ortho-substituted substrate **14** failed to provide the expected coupling products. As shown in Table 1, the yield of immobilization of *o*-carboxyphenylboronic acid to DEAM-PS is low (entry 10, Table 1), and it was cleaved prematurely during reactions. The meta- and para-carboxy-substituted substrates **15** and **16** provided good yields of amide products. In most cases, the use of

Table 5. Anilide Synthesis from Anilines 20−22[a]



20 *o*-, **21** *m*-, **22** *p*- **23** *o*-, **24** *m*-, **25** *p*-

entry	substr	condns[a]	product {R}	yield[b] (%)	purity[c] (%)
1	**20**	B	**23a** {CH_2CH_3}	61	>95
2	**20**	B	**23b** {Ph}	60	>90
3	**21**	A	**24a** {CH_2CH_3}	42	>90
4	**21**	A	**24b** {Ph}	52	>95
5	**21**	B	**24a** {CH_2CH_3}	72	95
6	**21**	B	**24b** {Ph}	82	95
7	**21**	B	**24c** {$CH_2CH_2CH{=}CH_2$}	70	>95
8	**21**	B	**24d** {CCPh}	75	>95
9	**21**	B	**24e** {(*S*)CH(Me)NHFmoc}	51	95
10	**22**	B	**25a** {CH_2CH_3}	61	>95
11	**22**	B	**25b** {Ph}	46	95

[a] Typical scale was 0.1 mmol. Conditions were as follows: (A) reactions were carried out by shaking the supported aniline with the carboxylic acid (2 equiv), DIC (2 equiv), and HOBT/H_2O (2 equiv) in DMF at room temperature for 20 h; (B) reactions were carried out by shaking the supported aniline with the carboxylic acid (2 equiv), PyBOP (2 equiv), and DIPEA (4 equiv) in NMP at room temperature for 20 h. [b] Nonoptimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for greater than 12 h. The reported values are usually an average of mass balance and internal standardization (see Supporting Information for details). [c] Estimated from ^1H and ^{13}C NMR data.

carbodiimide/1-hydroxybenzotriazole (HOBT) protocols was satisfactory for the coupling of both primary and secondary amines and even aromatic amines (entries 4 and 11, Table 4). In the most unfavorable cases, however, it was found to be preferable to employ coupling reagents such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) or 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU). This is exemplified for the case of isopropylamine (entry 9, Table 4). Moreover, we have found that conditions using these coupling reagents generally induce less premature cleavage as compared to those using carbodiimide reagents.

A noticeable example of amide formation with supported boronic acids is that of entry 15 (Table 4) involving **16** and *N*,*N*-diethylethylenediamine. The resulting amphoteric *p*-boronobenzamide product **19h**, a known melanoma-seeking agent with potential use in boron neutron capture therapy,[36] was obtained pure in a 70% yield after cleavage from the resin. Previously reported syntheses of **19h** involve protection of the boronic acid and extensive manipulations such as successive recrystallizations.[36]

We have previously shown that borono-anilide derivatives can be obtained from the reaction of DEAM-PS-supported aminobenzeneboronic acids with acid chlorides.[37] Herein, we report that compounds of this sort can also be isolated in a variable range of yields (ca. 50%−80%) by reaction of carboxylic acids with supported anilines **20**−**22** (Table 5). All three substitution patterns are possible for this type of chemistry. The optimal

(36) Parry, D.; Papon, J.; Moins, N.; Moreau, M.-F.; Morin, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 361−364.
(37) Gravel, M.; Bérubé, C.; Hall, D. G. *J. Comb. Chem.* **2000**, *2*, 228−231.

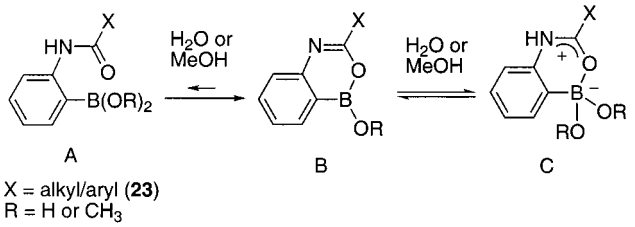


Figure 4. Possible forms of *o*-acylaminobenzeneboronic acids (**23**) in hydroxylic solvents (e.g., water or methanol). Structure B is the naphthalene-like form originating from dehydrative cyclization of A. Structure C is the putative ate form arising from 1,4-addition of water or methanol.

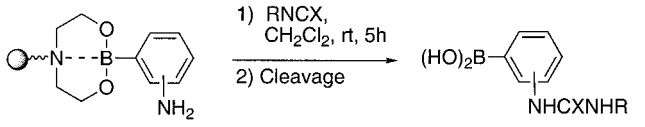
reagents and conditions found are the use of PyBOP as a coupling agent in NMP or DMF for 20 h at room temperature. As shown from entries 3−6 (Table 5), a comparison of carbodiimide methods with the use of PyBOP revealed the superiority of the latter method. A wide variety of carboxylic acids was tested, including Fmoc-protected alanine (entry 9, Table 5), which provided a 51% yield of the expected amide product **24e**. All meta- and para-substituted substrates provided the expected anilide products. According to ES-MS analysis, it appears that the ortho-substituted anilides **23** rather exist in a cyclic monodehydrated form (Form B in Figure 4).[38] This is probably true even in aqueous or alcoholic solutions as a consequence of the partial aromatic character of these boron-containing heterocycles. In fact, it has even been proposed that these and similar compounds such as ureas can add one molecule of water or alcohol by 1,4-addition and thus exist in equilibrium with form C (Figure 4).[39] These ortho-acylamino-substituted benzeneboronic acids (**23**) were found to have limited solubility in all solvents; thus, they were also characterized as their pinacol ester (form A, Figure 4) in order to unambiguously demonstrate their identity by ^{1}H and ^{13}C NMR.

Ureas of type **27** and **28** were isolated from the reaction of the respective meta- and para-substituted anilines **21** and **22** with various isocyanates of different electronic characteristics in dichloromethane for 5−6 h at room temperature (Table 6). An example of thiourea was also obtained with ease (**27e**, entry 5, Table 6). Yields of products are excellent for all reported examples regardless of the electronic characteristics of the isocyanate reagent. Unfortunately, the ortho-substituted substrate **20** provided products **26** accompanied with varying amounts of double addition products. This was found to be unavoidable even when using a minimal quantity of isocyanate.

In addition to the functional group transformations described above, we examined whether more elaborate types of transformations could be tolerated by the diethanolamine−boronate resin linkage. For instance, a prototypical Ugi multicomponent reaction[40] was carried out with success on DEAM-PS-supported aniline **21** and provided dipeptide derivative **30** in high purity after cleavage of its resin-bound form **29** (Scheme 4). Derivatization of multifunctional arylboronic acids and sequential transformations were also examined (Scheme 5). As

(38) Soloway, A. H. *J. Am. Chem. Soc.* **1960**, *82*, 2442−2444.
(39) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597−7605.
(40) (a) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 115−122. (b) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168−3210.

Table 6. Synthesis of Ureas from Anilines 21 and 22



20 *o*-, **21** *m*-, **22** *p*-

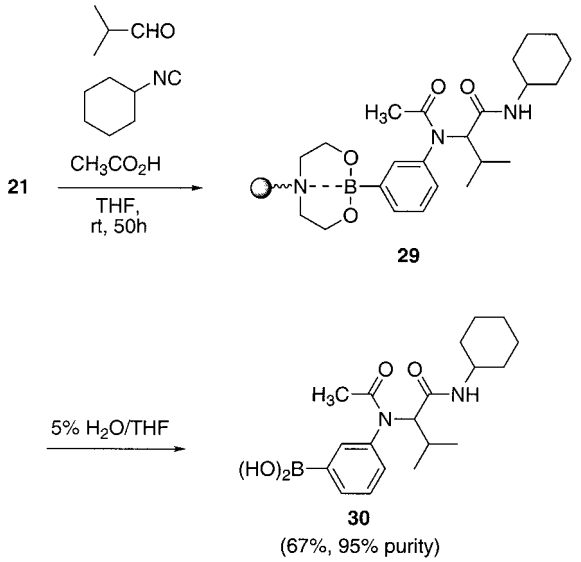
X = O
26 *o*-, **27a-d** *m*-, **28** *p*-

X = S: **27e**

entry	substrate	conditions[a]	product {R}	yield[b] (%)	purity[c] (%)
1	**21**	B	**27a** {$CH(CH_3)_2$}	66	95
2	**21**	A	**27b** {Ph}	79	>95
3	**21**	A	**27c** {4-MeO-C_6H_4}	82	>95
4	**21**	A	**27d** {4-NO_2-C_6H_4}	80	>95
5	**21**	A	**27e** {Ph}	85	95
6	**22**	B	**28a** {$CH(CH_3)_2$}	65	>95
7	**22**	A	**28b** {Ph}	85	>95
8	**22**	A	**28c** {4-MeO-C_6H_4}	88	>95
9	**22**	A	**28d** {4-NO_2-C_6H_4}	92	95

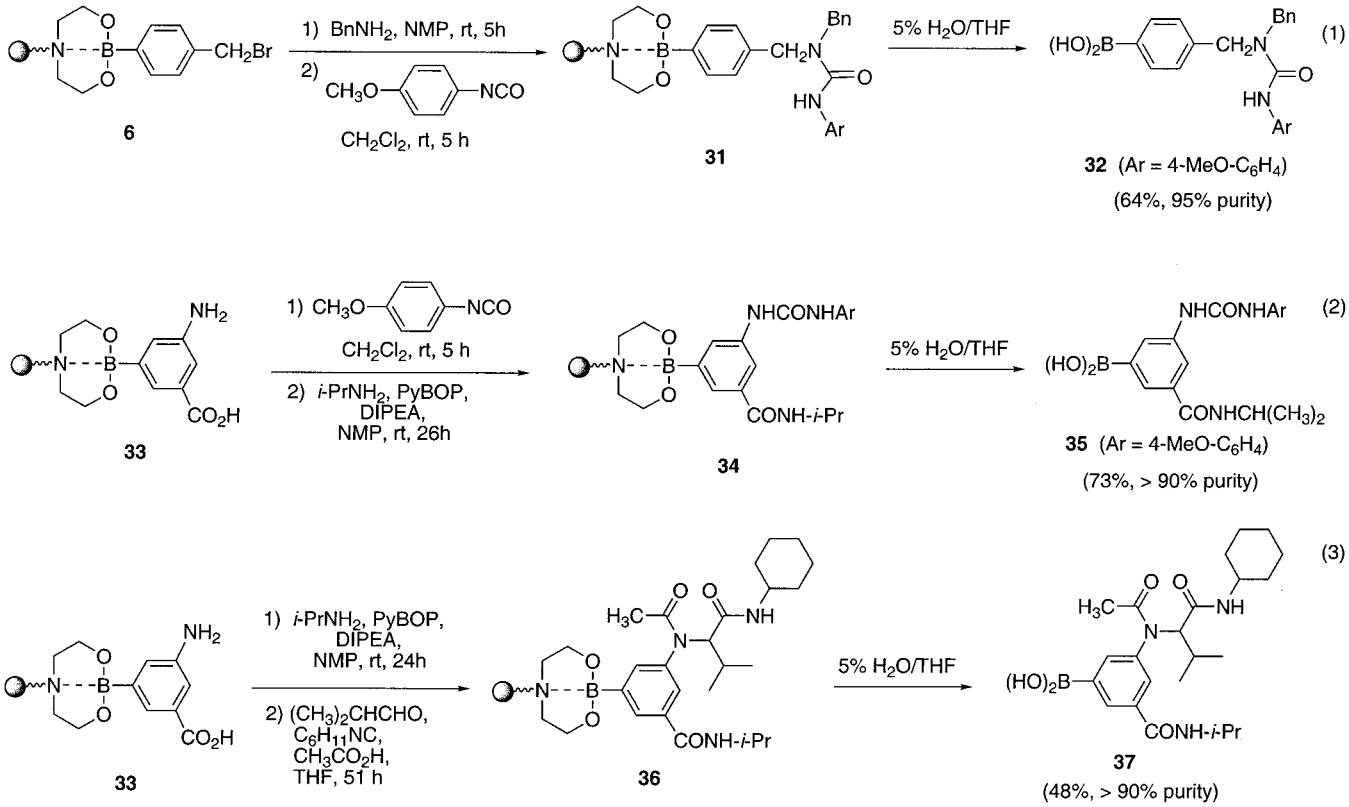
[a] Typical scale was 0.1 mmol. Conditions were as follows: (A) reactions were carried out by shaking the supported aniline with the isocyanate (2 equiv) in CH_2Cl_2 at room temperature for 5−6 h; (B) reactions were performed as described in A but with a longer reaction time (20−45 h). [b] Nonoptimized yields of crude products after cleavage from the resin with 5% H_2O/THF and drying in vacuo for greater than 12 h. The reported values are usually an average of mass balance and internal standardization (see Supporting Information for details). [c] Estimated from ^{1}H and ^{13}C NMR data.

Scheme 4



shown in eq 1 of Scheme 5, the para-bromomethyl-substituted substrate **6** was first treated with benzylamine as described above (Table 2). Following resin washes, the resulting substitution product was reacted with *p*-methoxyphenylisocyanate to give **31**. The expected boronic acid product **32** was obtained in 64% yield and high purity after cleavage from the support. In a similar fashion, supported 3-amino-5-carboxyphenylboronic acid (**33**) was treated with *p*-methoxyphenyl isocyanate (eq 2, Scheme 5). The carboxyl functionality was then coupled with isopropylamine to give, after treatment of resin **34** with wet THF, the final product **35** in 73% yield. Amide formation can also be effected as the first step on the same substrate, which can then undergo a Ugi reaction involving the aniline functionality, ultimately providing boronic acid **37** (eq 3, Scheme 5). In principle, the use of

Scheme 5



DEAM-PS is not limited to the procedures described herein, and many other types of transformations could be envisaged. These examples clearly demonstrate that multistep transformations can be carried out with high efficiency provided that anhydrous reaction conditions are employed to minimize premature release of the DEAM-PS-supported boronic acid. Synthetic schemes such as these ones could be employed to rapidly assemble two-dimensional combinatorial libraries of new boronic acids for biological screening or as building blocks for subsequent reactions. All of these reactions could be performed easily on a gram scale, especially with the use of high-loading DEAM-PS. The use of DEAM-PS resin for solid-phase derivatization of functionalized boronic acids is also potentially advantageous for handling and storage purposes. Indeed, boronic acids can be protected against slow air oxidation through immobilization as diethanolamine adducts.

Applications of DEAM-PS-Supported Boronic Acids in Resin-to-Resin Transfer Reactions (RRTR). In comparison with the traditional approach to solid-phase synthesis in which a single resin-bound substrate is employed, the simultaneous use of two or more heterogeneous substrates, reagents, or catalysts has seldom found real synthetic utility.[41] RRTR constitute one type of multiresin system that further simplifies the practice of solid-phase organic synthesis (SPOS).[42] In RRTR systems, one resin-bound substrate is transferred to solution phase by the action of a phase-transfer agent, or chaperone, and then coupled in situ to another resin-bound substrate. This concept allows for the convergent solid-phase synthesis and eventual coupling of fragments for which a linear SPOS strategy would involve incompatible reaction conditions.

In combinatorial chemistry, the concept of RRTR could find applications for the construction of new product libraries in which each resin-bound substrate is a member of a respective library assembled by solid-phase synthesis. As shown in the previous section, the DEAM-PS resin facilitates the synthesis of functionalized arylboronic acids that can otherwise be difficult to isolate and handle in solution. Their direct use with another resin-bound substrate in RRTR processes could eliminate time-consuming cleavage and transfer operations, thereby considerably simplifying the outlook of library synthesis by manual or automated means. The use of DEAM-PS-supported boronic acids facilitates the transfer of small quantities of boronic acid and also circumvents their tendency to dehydrate by forming anhydrides that are difficult to weigh out accurately.

Phase transfer in RRTR processes involving DEAM-PS−boronate adducts could be promoted from exposure to water or alcohols under conditions that must be compatible with the desired reaction. Both the added phase-transfer agent and the released DEAM-PS resin must be inert to all reagents used in these processes. With this in mind, we have developed a strategy for resin-to-resin Suzuki coupling reactions via phase transfer of DEAM-PS-supported arylboronic acids under both aqueous and anhydrous conditions.[37] The potential of these methods was demonstrated with the convergent solid-phase synthesis of compounds with unsymmetrically functionalized biphenyl units such as those represented in several biologically active molecules.[43]

(41) For selected examples, see: (a) Rebek, J. *Tetrahedron* **1979**, *35*, 723−731. (b) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620−7629. (c) Parlow, J. *Tetrahedron Lett.* **1995**, *36*, 1395−1396.

(42) For a recent example involving amide bond formation, see: Hamuro, Y.; Scialdone, M. A.; DeGrado, W. F. *J. Am. Chem. Soc.* **1999**, *121*, 1636−1644.

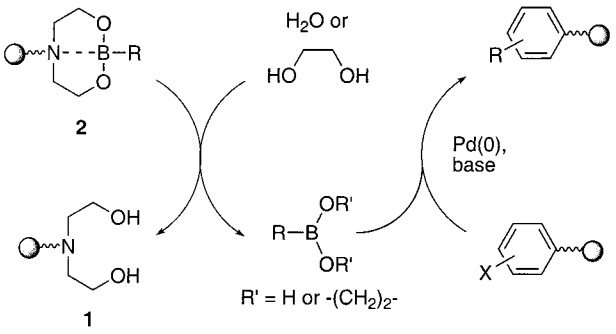
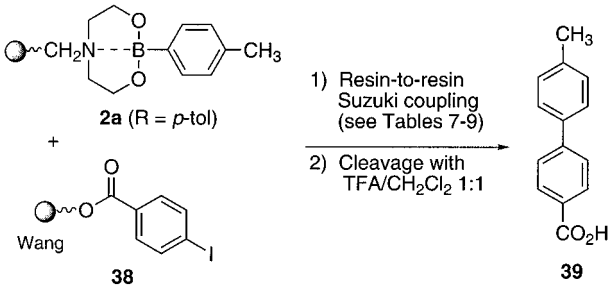


Figure 5. Resin-to-resin transfer between DEAM-PS-supported boronic acids (**2**) and haloarene resins by a Suzuki cross-coupling reaction.

Scheme 6



Herein, we describe the full optimization of the anhydrous Suzuki RRTR system. As shown conceptually in Figure 5, transesterification on the DEAM-PS−boronate linkage is expected to liberate the boronic acid in solution (as an ester) so that it can be transferred in situ to a haloarene resin under palladium(0) catalysis and added base.[44]

As a working model, the transfer of DEAM-PS resin-bound *p*-tolylboronic acid (**2a**) to Wang resin-bound *p*-iodobenzoic acid (**38**)[45] was attempted with different stoichiometries under various solvent, base, and temperature conditions (Scheme 6). The resulting resin mixture was then treated with 1:1 trifluoroacetic acid/dichloromethane to liberate the biphenyl product **39** and, if any, unreacted *p*-iodobenzoic acid. Any boronic acid still attached to the DEAM-PS support can be rinsed off prior to cleavage by carrying out aqueous washes. The leftover DEAM-PS resin does not liberate any byproducts upon treatment with TFA. The conversion results for optimization of the transfer agent are summarized in Table 7. These assays were carried out with 4 equiv of DEAM-PS-supported *p*-tolylboronic acid and 10−20% Pd(0) catalyst loading in various solvents and at various temperatures.

Knowing the propensity of diethanolamine and triethanolamine to transesterify boronic esters,[30] we examined their use as phase-transfer agents that could also function as the required base. However, as shown from entries 1−3 (Table 7), they were surprisingly ineffective.[46] The use of triethylamine as base in DMF, in conjunction with added diol, was then explored. Whereas pinacol led to low conversions (data not shown), the use of ethylene glycol as transfer agent was found to be satisfactory (entries 4−7, Table 7). When triethylamine and ethylene glycol (1:1) were used in large excess, full conversion was achieved at 85 °C for 20 h (entry 6, Table 7). Eventually, it was also found that substitution of $Pd(PPh_3)_4$ for a phosphine-free catalyst, $Pd_2(dba)_3$, led to crude reaction products of higher purity.[47]

Next, we explored the effect of the nature of the base on conversion using 50 mol % $Pd_2(dba)_3$ at 60 °C (Table 8). To this end, we found that only fluoride and triethylamine were satisfactory and even provided some biphenyl product at room temperature (entries 7 and 10, Table 8). We then sought general optimal conditions that are mild enough to minimize alcoholysis of the Wang ester linker while still providing complete coupling within 20 h at 105 °C with only 1.5 equiv of DEAM-PS-supported boronic acid and with a lower catalyst loading (Table 9). Triethylamine, essentially as a cosolvent (entries 7−8, Table 9),

Table 7. Anhydrous Suzuki RRTR of 2a and 38: Effect of Transfer Agent on Conversion[a]

entry	solvent	base	transfer agent	temp (°C)	time (h)	convn (%)[d]
1	DMF	$N(CH_2CH_2OH)_3$[b]		105	20	40
2	PhMe	$N(CH_2CH_2OH)_3$[b]		105	20	45
3	dioxane	$NH(CH_2CH_2OH)_2$[b]		85	20	45
4	DMF	Et_3N[b]	$(HOCH_2)_2$[b]	105	20	100
5	DMF	Et_3N[c]	$(HOCH_2)_2$[c]	105	20	100
6	DMF	Et_3N[b]	$(HOCH_2)_2$[b]	85	20	100
7	DMF	Et_3N[c]	$(HOCH_2)_2$[c]	85	20	85

[a] Typical trials were carried out with **38** (40 mg, 0.55 mmol/g) and **2** (4 equiv, 107 mg, 0.82 mmol/g) in 2 mL of degassed solvent with ca. 10−20 mol % of $Pd(PPh_3)_4$ as catalyst. [b] A large excess was used, ca. 10% v/v. [c] 20 equiv was used. [d] Measured by ^{1}H NMR integration of representative signals on crude reaction products.

Table 8. Anhydrous Suzuki RRTR of 2a and 38: Effect of Base and Temperature under $Pd_2(dba)_3$ Catalysis (50 mol %)[a]

entry	base	temp (°C)	conversion (%)[b]	yield (%)[c]
1	NaOH	60	*d*	0[d]
2	$Ba(OH)_2$	60	*d*	0[d]
3	K_2CO_3	60	*d*	0[d]
4	Cs_2CO_3	60	*d*	0[d]
5	K_3PO_4	60	*d*	0[d]
6	KF	60	>98	>98
7	KF	25	78	74
8	CsF	60	>98	>98
9	Et_3N	60	>98	>98
10	Et_3N	25	72	71

[a] Typical trials were carried out with **38** (20 mg, 0.55 mmol/g) and **2a** (3.2 equiv, 45 mg, 0.79 mmol/g) with the indicated base (10 equiv) and 50 mol % $Pd_2(dba)_3$ as catalyst in DMF/ethylene glycol 10:1 (2.5 mL) for 18 h. [b] Measured by ^{1}H NMR integration of representative signals on crude reaction products. [c] Nonoptimized yields of crude products after cleavage from the resin and drying in vacuo for greater than 12 h. The reported values are usually an average of mass balance and internal standardization (see Supporting Information for details). [d] Premature cleavage.

(43) Duncia, J. V.; Carini, J. D.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P. C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

(44) For a recent review discussing Suzuki cross-coupling reactions using a single supported substrate, see: Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(45) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169−5171.

(46) Control experiments have shown that these are competent transesterification agents; they release *p*-tolylboronic acid from DEAM-PS almost entirely after 0.5 h in a 9:1 mixture of DMF/triethylamine at 105 °C. Thus, to explain their lower efficiency, we suspect that transmetalation of the corresponding diethanolamine and pinacol boronic esters with the PS−Ar−Pd−I intermediate is significantly slower as compared to that of the ethylene glycol esters.

(47) Most final compounds were obtained as brown powders, suggesting the presence of residual palladium species (palladium black) that remained strongly absorbed to the polymer matrix prior to cleavage from the resin. Crude products can be further purified by chromatography to eliminate these impurities.

Scheme 7

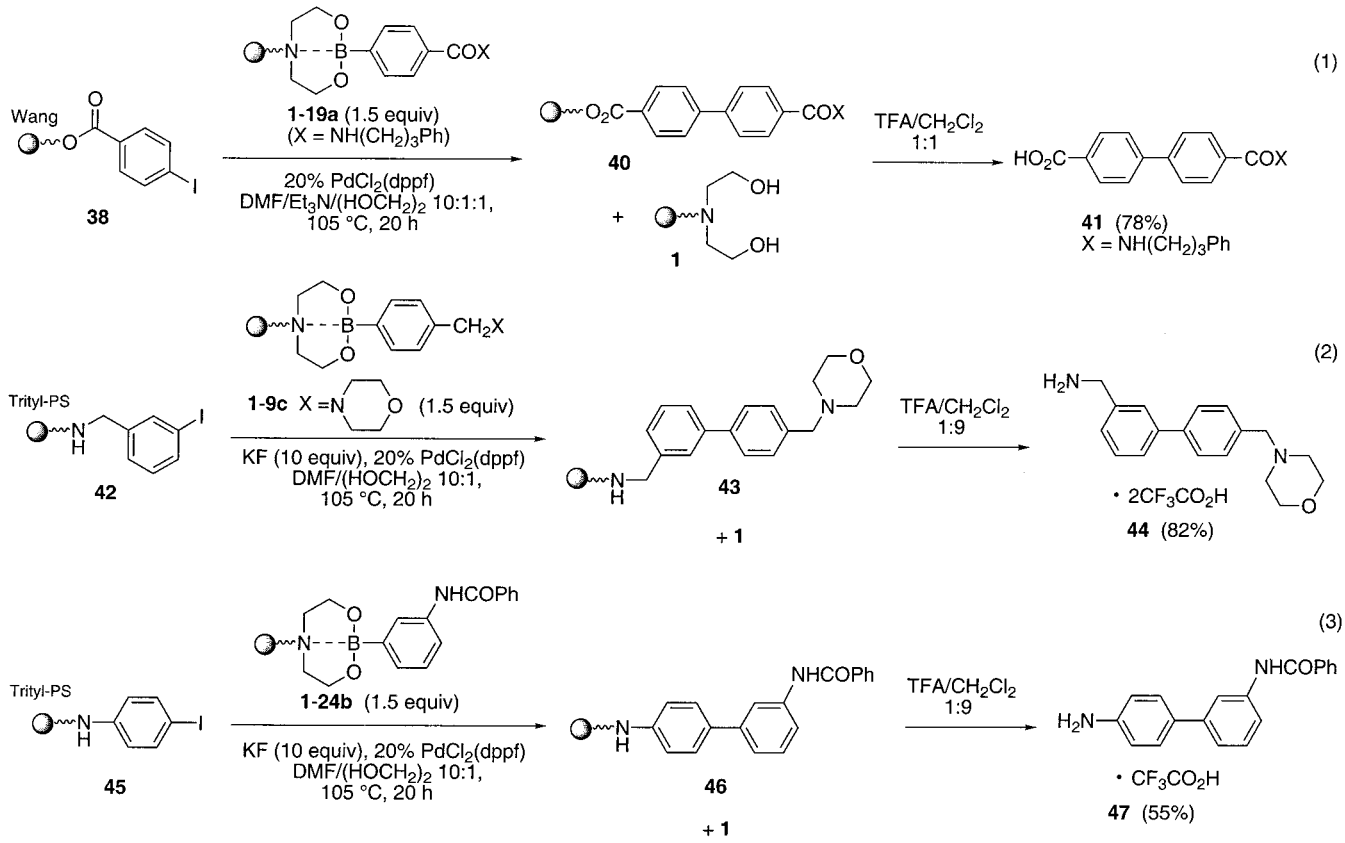


Table 9. Anhydrous Suzuki RRTR of 2a and 38: Effect of Base and Catalyst at High Temperature (105 °C)[a]

entry	base	catalyst	conversion (%)[b]	yield (%)[c]
1	NaF	$Pd_2(dba)_3$	29	33
2	TBAF	$Pd_2(dba)_3$	>98	<2
3	CsF	$Pd_2(dba)_3$	>98	3
4	KF	$Pd_2(dba)_3$	93	65
5	KF	$PdCl_2(dppf)$	>98	48
6	Et_3N[d]	$Pd_2(dba)_3$	42	58
7	Et_3N[d]	$PdCl_2(dppf)$	81	63
8	Et_3N[d]	$PdCl_2(dppf)$[e]	>98	64

[a] Typical trials were carried out with **38** (40 mg, 0.98 mmol/g) and **2** (1.5 equiv, 58 mg, 1.07 mmol/g) with the indicated base (10 equiv) and catalyst (10 mol % $Pd_2(dba)_3$ or 20 mol % $PdCl_2(dppf)$) in DMF/ethylene glycol 10:1 (2.5 mL) at 105 °C for 20 h. [b] Measured by ^1H NMR integration of representative signals on crude reaction products. [c] Nonoptimized yields of crude products after cleavage from the resin and drying in vacuo for greater than 12 h. The reported values are based on internal standardization (see Supporting Information for details). [d] A large excess was used (0.25 mL). [e] The catalyst was added in two portions, one at the start and one after 8 h.

was found to be the most effective base in combination with 20% $PdCl_2(dppf)$ as catalyst. The latter was preferably added in two to three portions at a few hours interval in order to minimize the effects of catalyst inactivation.[47] Interestingly, although the use of cesium fluoride and TBAF as bases led to full conversion (entries 2−3, Table 9), unlike potassium fluoride, they induced complete premature cleavage of the product at 105 °C. This most likely occurs by alcoholysis of the Wang ester linker with ethylene glycol. Efforts to lower the effective temperature of reaction by using Buchwald's[48] or Fu's[49] newly discovered ligand systems failed.

Control experiments were devised to confirm the role and the efficiency of ethylene glycol as the phase-transfer agent. Resin-to-resin cross-coupling of model substrates **2a** and **38** in the absence of ethylene glycol gave largely incomplete transfer as shown by a lower than 50% conversion to product **39**. Treatment of DEAM-PS-supported *p*-tolylboronic acid alone in hot anhydrous DMF/Et_3N (9:1, 105 °C, 24 h) led to less than 25% leaching of the boronic acid. These experiments confirmed the expected advantage of using the phase-transfer agent. In fact, ethylene glycol transesterifies the resin-bound boronic acid within a time scale that minimizes any rate lowering of the cross-coupling. When resin **2a** was treated for 0.5 h in an 8:1:1 mixture of DMF/triethylamine/ethylene glycol at 105 °C, less than 10% of the boronic acid remained bound to the DEAM-PS support after 0.5 h.

The usefulness of DEAM-PS to synthesize new arylboronic acids and the potential of the resin-to-resin Suzuki coupling strategy were clearly demonstrated by the convergent syntheses of unsymmetrically functionalized biphenyl compounds (Scheme 7, eqs 1−3). The DEAM-PS-supported amide derivative **1·19a** was made as described in Table 4. Following washing and drying operations, it was reacted with **38** using the optimal conditions of Table 9, affording 4,4′-biphenyl dicarboxylic acid monoamide **41** after cleavage from the resin mixture (**40** + **1**) (eq 1, Scheme 7). This example makes a very significant case for using a convergent RRTR strategy in solid-phase synthesis. Indeed, as *p*-carboxybenzeneboronic acid is inept as a substrate in Suzuki reactions,[50] a linear solid-phase strategy involving its coupling to **38** followed by amide formation would not be possible.

(48) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.
(49) Littke, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388.

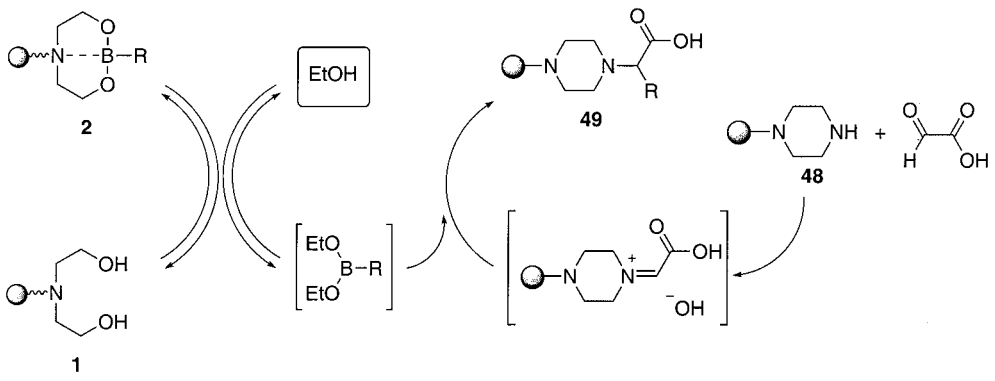


Figure 6. Resin-to-resin transfer by a borono-Mannich reaction between DEAM-PS-supported boronic acids (**2**) and resin-bound iminium intermediates formed from dialkylamino resins (e.g., **48**) and glyoxylic acid.

The Suzuki RRTR strategy is also useful to afford monoalkylated biphenyl dibenzylamines (Scheme 7, eq 2). For example, DEAM-PS-bound *p*-(*N*-morpholinomethyl)benzeneboronic acid (**9c**) (Table 2) was treated with trityl-PS-bound *m*-iodobenzylamine (**42**) under a slightly modified RRTR method (KF as base) and, after cleavage of the resin mixture, afforded crude diamine **44** in 82% yield and high purity (>90% by ^{1}H NMR).[51] As shown through the isolation of **47**, monoacylated biphenyl dianilines can also be synthesized efficiently (Scheme 7, eq 3). In the above examples, cleavage and handling of the boronic acid prior to the Suzuki coupling was obviously eliminated, and there was no need for transferring the resin to a new reaction vessel after washing and drying operations. These advantages have been demonstrated in the synthesis of a small model library of biphenyl compounds using a commercial, semiautomated, parallel synthesizer.[37,52]

The boronic acid Mannich reaction is compatible with a wide range of solvents, including hydroxylic ones.[17] Thus, an alcohol cosolvent could act as the neutral phase-transfer agent required to cleave the DEAM-PS-supported boronic acids under mild conditions appropriate to a RRTR system. The boronic acid liberated in situ as an ester could then add to the iminium intermediate formed between a dialkylamino-functionalized resin and an activated aldehyde such as glyoxylic acid (Figure 6).[17c,17p] The resulting arylglycine products obtained after cleavage of the resin mixture are compounds of particular interest for their biological activity.[53] We have first optimized conditions using DEAM-PS-supported *p*-tolylboronic acid (**2a**, R = 4-Me-C_6H_4-), piperazinetrityl resin (**48**), and glyoxylic acid in a semiautomated synthesizer.[52] The reaction was found to be rather slow and strongly dependent on the nature of the solvent system, THF/EtOH (7:1) being identified as the best mixture (Table 10). Optimal experimental conditions first involve incubating the dialkylamino resin with glyoxylic acid monohydrate (1.1 equiv) for 2 h in dry THF at room temperature. Then, 4 equiv of DEAM-PS-bound boronic acid (**2**) is added along with the appropriate volume of 8:3 THF/EtOH. The suspension is shaken at 65 °C for up to 48 h. In this way, conversion levels superior to 75% were observed in the case of *p*-tolylboronic acid, as seen after cleavage of the final resin mixture **1** and **49a** with 5% trifluroacetic acid/dichloromethane to give the corresponding amino acid product **50a** as a bis(triflurooroacetate) salt (Table 11, entry 1). The rest of the unreacted starting resin **48** is cleaved into the bis(trifluoroacetate) salt of piperazine (**51**), which can be eventually removed by precipitation (Scheme 8). There are no other byproducts observed, as the leftover DEAM-PS resin (**1**) does not give any artifacts upon treatment with trifluoroacetic acid in the product release step. As indicated above, the transesterification of resin **2** with ethanol, a process

Table 10. Optimization of the Solvent System, at 65 °C for 24 H, for the Borono-Mannich RRTR of 48 and 2a To Give 50a[a]

entry	solvent	conversion (%)[b]
1	7:1 DMF/EtOH	65
2	7:1 DMF/*n*-BuOH	54
3	7:1 dioxane/*n*-BuOH	23
4	7:1 THF/$(HOCH_2)_2$	37
5	7:1 THF/EtOH	79

[a] Preparation of resin substrates, RRTR trials, and subsequent cleavage of the resin mixture were carried out as indicated in the Supporting Information. [b] Based on the relative amounts of product and bis(trifluoroacetate) salt **51** calculated by integration of relevant signals by ^{1}H NMR after 24 h of reaction time.

Table 11. Preparation of Arylglycine Derivatives by a Borono-Mannich RRTR[a]

entry	amino resin	DEAM-PS−boronate **2**	product	conversion (%)[b]	yield (%)[c]
1	**48**	R = 4-Me-C_6H_4	**50a**	79	85
2	**48**	R = 2-Me-C_6H_4	**50b**	81	73
3	**48**	R = 4-MeO-C_6H_4	**50c**	90	>95
4	**48**	R = 4-Br-C_6H_4	**50d**	21	10
5	**48**	R = 1-Naph	**50e**	85	90
6	**48**	R = *E*-HC=CH(Bu)	**50f**	89	>95
7	**52**	R = 4-MeO-C_6H_4	**54c**	95	91
8	**56**	R = 4-MeO-C_6H_4	**57c**	76	82

[a] Preparation of resin substrates, RRTR trials, and subsequent cleavage of the resin mixture were carried out as indicated in the Supporting Information. [b] Based on the relative amounts of product and respective bis(trifluoroacetate) salt **51**, **55**, or **58** calculated by integration of relevant signals by ^{1}H NMR after 24−48 h of reaction time. [c] Yields of crude product based on ^{1}H NMR analysis with an internal standard.

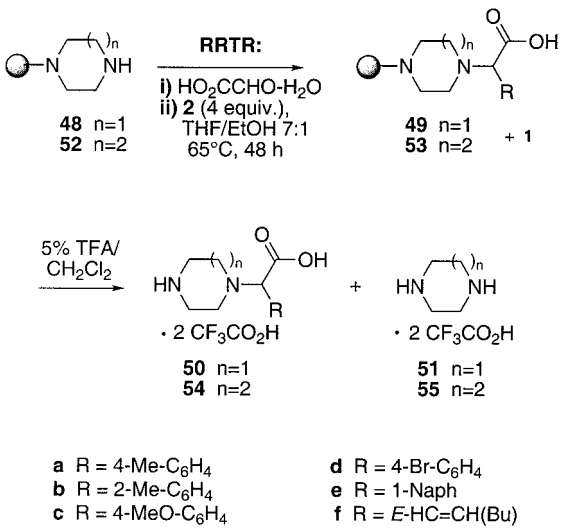
(50) As reported in: Wendeborn, S.; Berteina, S.; Brill, W. K.-D.; De Mesmaeker, A. D. *Synlett* **1998**, 671−575. Our own attempts at coupling *p*-carboxybenzene boronic acid also failed.

(51) A linear synthesis based on the cross-coupling of **42** with *p*-(bromomethyl)benzeneboronic acid would be hampered by incompatible reaction conditions. The basic conditions required in the Suzuki coupling could promote nucleophilic displacement on the benzylic bromide which, in addition, can react slowly with palladium(0) by oxidative addition.

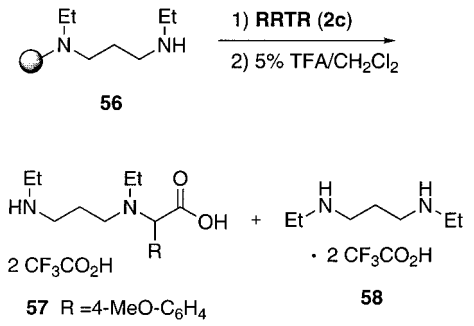
(52) A Quest 210 instrument with solvent wash unit was employed (Argonaut Technologies). Cleavage was effected in line, and crude products were obtained after evaporation of solvents.

(53) For example, see: Bedingfield, J. S.; Kemp, M. C.; Jane, D. E.; Tse, H. W.; Roberts, P. J.; Watkins, J. *J. Pharmacol.* **1995**, *116*, 3323−3330.

Scheme 8



Scheme 9



required for phase transfer of the boronic acid, appears to be a dynamic equilibrium. The latter process is driven forward by the large excess of ethanol and through consumption of the boronic acid which adds to the putative iminium intermediate to form the supported product **49** (Figure 6). In fact, because of the transesterification equilibrium, there is some leftover DEAM-PS-supported boronic acid (**2**) at the end. Consequently, it is necessary to include water/THF washes in order to rinse off all excess boronic acid from the resin mixture prior to the acidolytic cleavage of products **50**.

Next, we have studied substrate generality for this new RRTR system (Scheme 8). As shown in Table 11, conversion values and product yields were generally good, except for the RRTR of electron-poor arylboronic acids. Thus, conversion values were highest for DEAM-PS-supported *p*-methoxybenzeneboronic acid (entries 3, 7, 8, Table 11) and lowest for *p*-bromobenzeneboronic acid (entry 4, Table 11). According to entry 6 in Table 11, DEAM-PS-supported alkenylboronic acids are also appropriate substrates. An example using an acyclic amine (**56**) was equally successful (entry 8, Table 11), showing that in principle a variety of secondary amines such as terminal *N*-alkylamino acids could be employed (Scheme 9).[17m] Although only electron-rich arylboronic acids currently provide satisfactory conversions to crude material of high purity, analytically pure samples of most reported compounds can be obtained following precipitation with a methanol/ether system and filtration of the unreacted dialkylamine as a bis(trifluoroacetate) diammonium salt. We have also confirmed that the examples performed in a RRTR format provide yields comparable to reactions using nonsupported boronic acids.

The concept of RTRR involving DEAM-PS-supported boronic acids, successfully demonstrated in this article for the Suzuki cross-coupling and the borono-Mannich reactions, could potentially be expanded to other types of processes employing boronic acids as substrates.

Conclusions

This article describes the first general solid-phase approach to the immobilization and derivatization of functionalized boronic acids. This approach is based on the use of *N,N*-diethanolaminomethyl polystyrene (DEAM-PS), a support containing a diethanolamine resin anchor that facilitates the immobilization of a wide variety of boronic acids in anhydrous solvents at room temperature. Evidence for the formation of a bicyclic diethanolamine boronate with putative N−B coordination was shown by ^{1}H NMR analysis of DEAM-PS-supported *p*-tolylboronic acid. From UV spectroscopic studies using the same boronic acid as a model, hydrolysis and attachment were shown to occur under a rapidly attained equilibrium. DEAM-PS-supported arylboronic acids functionalized with a formyl, a bromomethyl, a carboxyl, or an amino group can be transformed in good to excellent yields into a wide variety of amines, amides, anilides, and ureas, respectively. Moreover, Ugi multicomponent reactions, derivatization of multifunctional arylboronic acids, and sequential reactions can also be carried out efficiently. These novel boronic acid derivatives can be released mildly from the DEAM-PS support by simple stirring in a wet THF solution (5% H_2O/THF). Alternatively, the DEAM-PS-supported arylboronic acids can be employed directly into resin-to-resin transfer reactions. This type of multiresin process helps eliminate time-consuming cleavage and transfer operations, thereby considerably simplifying the outlook of combinatorial library synthesis by manual or automated means. Herein, this concept was illustrated with a set of optimized procedures for the Suzuki cross-coupling and the borono-Mannich reactions.

Overall, the use of DEAM-PS resin greatly facilitates access to functionalized arylboronic acid derivatives that can be otherwise difficult to synthesize and isolate by solution-phase methods. Thus, this general solid-phase approach has significant practical value for all organic and combinatorial chemists performing research involving the use of boronic acids.

Experimental Section

Full experimental details and characterization of new compounds are provided in the Supporting Information.

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Supporting Information Available: Full experimental details, characterization of new compounds, and reproductions of proton and carbon NMR spectra for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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