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Catechol pendant polystyrene for solid-phase synthesis

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Abstract—A catechol pendant polystyrene polymer was prepared from the Merrifield resin via a convenient procedure with high-density loading. Due to the high affinity binding between catechol and boronic acid, the polymer resin readily captures boronic acid compounds. The feasibility of using immobilized catechol to capture boronic acid products for purification and solid-phase transformation was demonstrated. Moreover, the immobilized catechol was also used for the preparation of resin-bound catecholborane, which can be used as a solid-phase amidation reagent. © 2002 Published by Elsevier Science Ltd.

Combinatorial chemistry and related parallel synthesis techniques have emerged as important tools for the discovery and development of new drugs, catalysts and materials.[1–3] In particular, synthetic techniques based on solid-phase chemistry have attracted much attention because of the ease of purification and automated manipulation. Along this line, polymer resins that selectively capture a functional group commonly seen in organic synthesis and drug development are very useful for the development of solid-phase synthesis. Boronic acids are important intermediates in organic synthesis and are useful for the development of biologically active agents. For example, boronic acids have been widely used in Suzuki cross-coupling reactions,[4] protection of diols,[5] Diels–Alder reactions,[6] selective reduction of aldehydes,[7] asymmetric synthesis of amino acids,[8] and as amidation catalysts.[9,10] In addition, this class of compounds has been used for the development of sensors for carbohydrates and amino acids;[11,12] antibody mimics that target on cell surface carbohydrates,[13] selective transporters of nucleosides, saccharides and nucleotides;[14] inhibitors of proteases and other enzymes;[15,16] and therapeutic agents in boron neutron capture therapy (BNCT) of certain brain tumors.[17] Our group has been engaged in the development of fluorescent sensors for saccharides using various boronic acid compounds.[18–20] In our experiments, we found that the boronic acid product was difficult to isolate and purify by conventional methods. We believe that solid-phase synthesis may provide a solution to the isolation and purification problem.

Four groups have reported the preparation of three kinds of diol resins that just be used as a liker system to immobilize boronic acids recently.[21–24] The macroporous polymer-supported 1,3-diol resin can sequester boronic acids in modest to good yield,[23] but the use of excess boronic acids and the requirement of high temperature limit their use. The *N*,*N*-diethanolaminomethyl polystyrene resin[21] is more efficient than the 1,3-diol one that can immobilize boronic acids in high yield under mild conditions. More recently, a fluorous version of the boronates was achieved by a 1,2-diol pendant fluorous tag.[25] In our recent systematic examination of the binding between boronic acid and various diol-containing compounds, it was found that catechol type of compounds have the highest affinity with boronic acid.[26] Therefore, we reasoned that immobilized catechol should allow for the high efficiency capture of boronic acids for purification and transformation applications under mild conditions. Moreover, catecholborane is a well-known reagent that has been used in reduction,[27] amidation,[28] hydroboration[29] and even borylation[30] of aryl halides reactions. Immobilization of catechol on a solid-phase material also allows us to prepare immobilized catecholborane for the aforementioned applications in solid-phase. Such unique applications cannot be achieved with either the other diol resins or the fluorous tag, which are developed solely for boronic acid immobilization.

The preparation of the catechol pendant polystyrene (**1**) started with commercially available 3,4-dihydroxybenzaldehyde **2** (Scheme 1). Treatment of compound **2** with methoxymethyl chloride and diisopropylethylamine gave the dihydroxy-protected aldehyde **3**, which was

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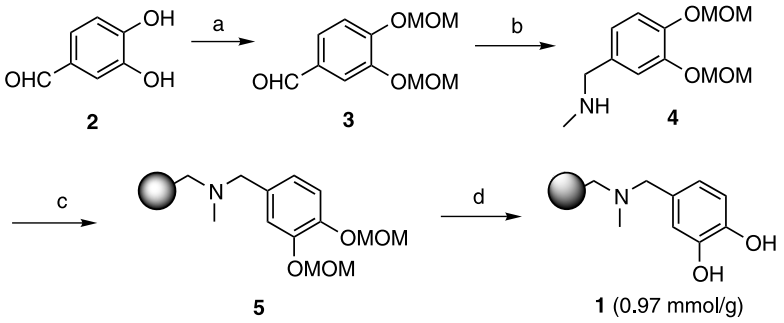


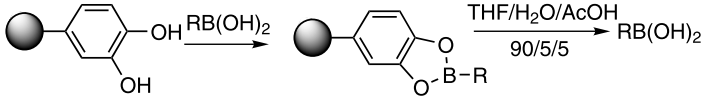
Scheme 1. *Reagents and conditions*: (a) *i*-Pr_2NEt, MOMCl; (b) (i) 40% $MeNH_2$, THF, MeOH, (ii) $NaBH_4$, 95% (three steps); (c) Merrifield resin (1.26 mmol/g), K_2CO_3, CH_3CN, 50°C; (d) TMSBr, DCM, −78°C to rt.

directly subjected to reductive amination to afford amine **4** in 95% overall yield. Attachment of the secondary amine to the Merrifield resin was achieved by heating the resin and amine **4** in the presence of potassium carbonate in acetonitrile. The resulting resin **5** gave a positive outcome with the bromophenol blue assay due to the presence of tertiary amines,[31] which indicated the success of the attachment of amine **4** to the resin. Deprotection of the MOM group in resin **5** using trimethylsilyl bromide gave the desired catechol pendant polystyrene **1**. The solid-phase reactions were also followed with IR. Upon deprotection of the MOM group in resin **5**, the peaks[32] at 1153 and 993 cm^{-1} disappeared, indicating the completion of the reaction. The generation of the free hydroxyl group in resin **1** was also reflected in the IR with the appearance of a broad intense peak at around 3450 cm^{-1}. The loading degree was determined to be about 0.97 mmol/g by nitrogen combustion analysis of the resin. Further determination of the loading level was pursued by immobilizing phenylboronic acid with 1/3 equiv. of resin **1** in toluene at 80°C, the calculated loading degree according to the recovered phenylboronic acid was in agreement with the elemental analysis result (Table 1, entry 4).

Resin **1** was found to be very efficient in immobilizing boronic acids in THF at room temperature (Table 1, entries 2, 6–8). A solvent profile study using phenylboronic acid as the model boronic acid and a slight excess of resin **1** (1.25 equiv.) showed that methylene chloride and toluene are also suitable for capture applications (Table 1, entries 1–3). Higher temperature and a large excess of boronic acid drove the attachment to completion (Table 1, entry 4). Cleavage of the boronic acids from the resin was achieved with a THF/water/acetic acid (90/5/5) mixture at room temperature to give the pure products as judged by their ^1H NMR. The resin (**1**) can be recycled with no apparent loss of efficiency after neutralization with base washings (for example, 5% sodium bicarbonate) and drying under vacuum at 60°C.

The applications of the resin (**1**) in solid-phase synthesis were further investigated. First we examined the feasibility of using immobilized boronic acid for further solid-phase transformations (Scheme 2). As an example, benzylamine was coupled to resin-bound *p*-carboxyphenylboronic acid **6**, under standard carbodiimide conditions, to afford the corresponding amide **7** in 53% yield after cleavage (Scheme 2a). The additional

Table 1. The immobilization and release of boronic acids[a]

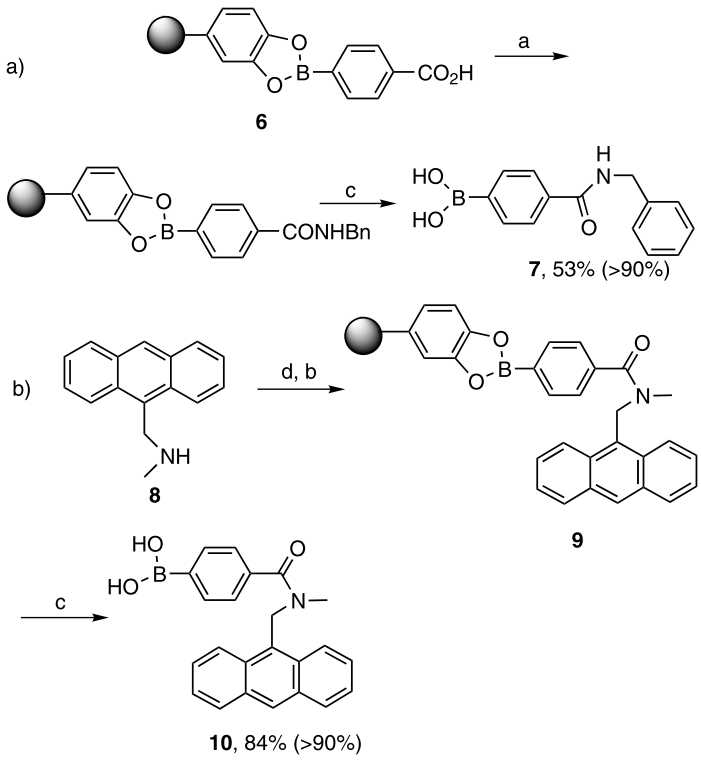


Entry	R (equiv.)	Solvent	Temperature	Yield (%)	Purity (%)[b]
1	C_6H_4 (0.8)	DCM	rt	86	>95
2	C_6H_4 (0.8)	THF	rt	67	>95
3	C_6H_4 (0.8)	Toluene	rt	90	>95
4[c]	C_6H_4 (3.0)	Toluene	80°C	100	>95
5	2-Me-C_6H_4 (0.8)	Toluene	rt	80	>95
6	4-CO_2H-C_6H_4 (0.8)	THF	rt	65	>95
7	4-CHO-C_6H_4 (0.8)	THF	rt	75	>90
8	2-CO_2H-C_6H_4 (0.8)	THF	rt	61	>90

[a] Loading was conducted by shaking a slight excess of resin **1** (300 mg, 0.97 mmol/g substitution) with the boronic acid (0.8 equiv.) in the indicated solvent (4.0 mL) at room temperature for 12 h in a solid-phase synthesis vessel. The release was carried out by shaking the resin-bound boronic acid for 2 h in a THF/H_2O/AcOH mixture (90/5/5).

[b] Estimated through comparison of the ^1H NMR spectra of the recovered boronic acids and the starting material.

[c] This loading was conducted in a round-bottom flask fitted with a stir bar and a reflux condenser.



Scheme 2. NMR purities are given in brackets. *Reagents and conditions*: (a) $BnNH_2$ (2.5 equiv.), DIC (2.5 equiv.), HOBt (2.5 equiv.), DMF; (b) resin **1** (1.5 equiv.); (c) $THF/H_2O/AcOH$ 90/5/5; (d) *p*-carboxyphenylboronic acid (1.0 equiv.), EDC (2.0 equiv.), HOBt (1.2 equiv.), DCM.

use of resin **1** was borne out of the recently developed resin capture strategy.[33] In this regard, resin **1** could be used for capturing the organoboron products from complex reaction mixtures either for purification or to perform solid-phase transformations. As a significant demonstration of such an application, resin **1** was employed in the purification of crude fluorescent boronic acid compound **10**. Treatment of 9-(methylaminomethyl)anthracene **8** with *p*-carboxyphenylboronic acid under standard carbodiimide conditions furnished compound **10** in a reaction mixture. To the resulting solution was added resin **1** directly, and the resulting mixture was shaken overnight at room temperature in a solid-phase synthesis vessel to afford resin **9**. After cleavage, the fluorescent boronic acid compound **10** was obtained in 84% yield (Scheme 2b).

As mentioned earlier, catecholborane is a well-known reagent in synthetic chemistry and has many known applications. Resin **1** also allows for the preparation of solid-phase catecholborane (**11**). Therefore, resin **1** was treated with BH_3·THF to afford the immobilized catecholborane **11** (Table 2). To examine the feasibility of using this solid-phase reagent for chemical transformations, we chose to study catecholborane-mediated amidation reactions.[28] Again, in solution-phase catecholborane is known to mediate amidation by activating a carboxylic acid through anhydride formation.[34] The formation of the same type of intermediates is also the reason that boronic acid can catalyze amidation reactions.[9,10] In performing the amidation reaction, resin-bound catecholborane **11** was shaken with a carboxylic acid to give the activated anhydride. An amine was then added in. After shaking at room temperature overnight, the amide product was obtained in modest yield. However, these yields were comparable to what was obtained in solution-phase synthesis, in which the amide product was obtained with a yield in the range of 60–90%. Such results indicate that resin-bound catecholborane **11** behaves much the same way as free catecholborane in mediating amidation reactions.

In conclusion, we have developed a new versatile diol resin by immobilizing catechol to a polystyrene solid support, although other solid support materials can also be used. The immobilized catechol not only can be used as a linker system to capture boronic acids for purification and solid-phase transformations, but also for the preparation of a solid-supported reagent, immobilized catecholborane. Further work on expanding the use of the resin is under way.

Acknowledgements

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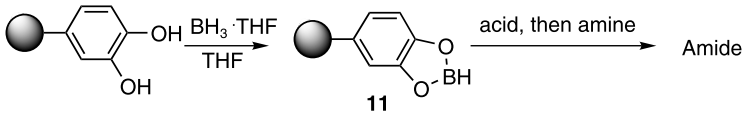
Table 2. Amidation reaction mediated by polymer-supported catecholborane **11**[a]



11

Entry	Acid	Amine	Product[b]	Yield (%)	Purity (%)[c]
1	Octanoic acid	Phenethylamine	*N*-Phenethyloctanoic amide	51	>90
2[d]	Octanoic acid	Phenethylamine	*N*-Phenethyloctanoic amide	52	>90
3[e]	Octanoic acid	Phenethylamine	*N*-Phenethyloctanoic amide	35	>90
4	Octanoic acid	Benzylamine	*N*-Benzyloctanoic amide	54	>95
5	Isovaleric acid	Phenethylamine	3-Methyl-*N*-phenethylbutyramide	47	>90
6	Isovaleric acid	Benzylamine	3-Methyl-*N*-benzylbutyramide	42	>95

[a] The reaction was conducted by shaking resin **1** (1.25 equiv.) with BH_3·THF (2.5 equiv.) in a solid-phase synthesis vessel. After washing with dry THF several times, the resulting resin **10** was treated with acid (0.8 equiv.) and amine (1.6 equiv.) in turn to afford amide after standard aqueous work-up.

[b] Product identity was established by comparison the ^{1}H NMR spectra with those of authentic samples.

[c] Estimated from ^{1}H NMR data.

[d] 2.5 equiv. of resin **1** was used.

[e] Mixed solvent (THF:DCM = 1:1) was used.

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