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Polystyrylboronic acid as a reusable polymeric support for oligosaccharide synthesis

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Abstract

Polystyrylboronic acid is an attractive polymeric support for oligosaccharide synthesis that can easily be prepared in high loading capacity and re-used after a synthetic sequence. Saccharides were loaded by heating in pyridine and released by treatment with a mixture of acetone and water. NIS/TMSOTf mediated glycosidations of thioglycosides gave a quantitative formation of disaccharides. © 2000 Published by Elsevier Science Ltd.

Solid-supported synthesis provides a powerful method for the preparation of oligopeptides, oligonucleotides and many small molecules.[1] The development of methods for polymer supported oligosaccharide synthesis has been slow.[2] Although the first attempts were reported in the 1970s, their success was limited and only simple disaccharides could be obtained. These disappointing results were primarily a consequence of the absence of efficient methods for glycosidic bond formation. During the last 15 years, many powerful glycosylation approaches have been developed.[3–6] These methods have given a new impetus to polymer-supported synthesis of oligosaccharides.

A critical step in polymer-supported synthesis is the immobilization of a glycosyl acceptor or donor through a cleavable linker. Several attractive linkers for polymer-supported oligosaccharide synthesis have been reported.[7] Most of these linkers require several chemical steps for either attachment to a polymeric support or saccharide, offsetting potential advantages of polymer supported oligosaccharide synthesis.

Here, we report that polystyrylboronic acid[8] is an attractive resin for polymer-supported oligosaccharide synthesis. The functionalized cross-linked polystyrene resin can easily be prepared in high loading capacity. Heating a mixture of saccharide and resin in pyridine results in attachment and a product can easily be released by treatment with a mixture of acetone/water. Thus, only solvents are required for loading and cleavage. The latter feature is very attractive for library synthesis by a mix and split approach where cleavage conditions should not leave any reagents or impurities. After cleavage, the original polymer is obtained which can be re-used for future polymer-supported oligosaccharide synthesis.

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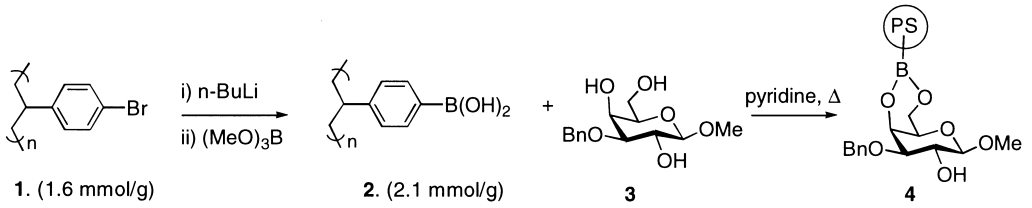
Polystyrylboronic acid (**2**) could easily be obtained by treatment of commercially available bromopolystyrene (**1**, 1% cross-linked with divinylbenzene, 1.6 mmol/g) with BuLi, followed by quenching of the lithiated intermediate with an excess of trimethyl borate (Scheme 1).[8] This procedure leads to a material with a loading capacity of 2.1 mmol boronic acid functionalities per gram resin. Immobilization could easily be accomplished by heating a mixture of saccharide and polymer (**2**) in pyridine with azeotropic removal of water that is formed during the ester formation. This method was applied to methyl 3-*O*-benzyl-β-galactoside **3**[9] to give immobilized saccharide **4**.[10] The best results were obtained when a small excess of saccharide was used. Any unbound saccharide could easily be removed by filtration followed by washing of the resin with DMF and CH_2Cl_2.



Scheme 1.

Immobilized **3** was glycosylated with glycosyl donors **5**,[4] **6**[11] and **7** and after washing the resin with DMF and CH_2Cl_2, the resulting products were cleaved from the solid support by refluxing in an acetone/water mixture. The yields presented in Scheme 2 are based on the loading capacity of polymer **2**. The use of the trichloroacetimidate **5** gave a relatively low yield of disaccharide **8** and a significant quantity of methyl 3-*O*-benzyl-β-galactoside was recovered. Analysis of the liquid phase of the reaction revealed that most of the donor had rearranged to the analogous anomeric amide. The application of fluoride **6** in combination with the mild activator Cp_2ZrCl_2/AgOTf,[12] also gave a modest conversion of the acceptor and in this case most of the donor had decomposed into an intractable mixture of products. Fortunately, NIS/TMSOTf mediated glycosylation[13,14] of thioglycoside **7** with immobilized **4** gave, after cleavage from the solid support, disaccharide **8** in a yield of 86%. In this case, no starting material was recovered and furthermore, the glycosylation required only 3 equivalents of donor.

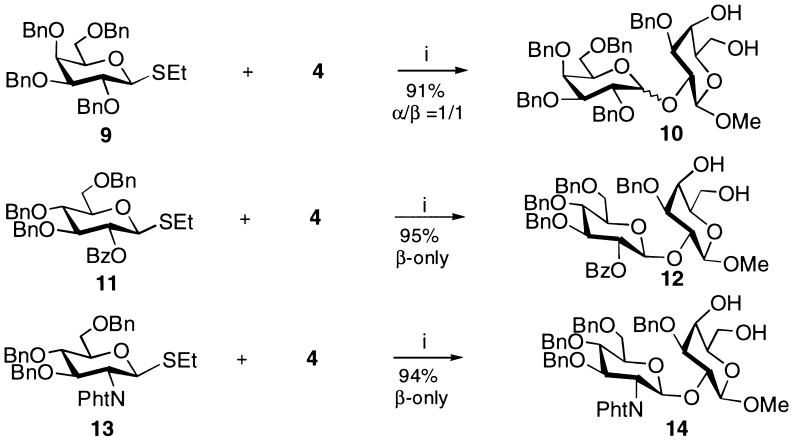
Leaving Group	Glycosylation conditions	Yields, α/β ratios
5. X = O, CCl_3, NH	TMSOTf/CH_2Cl_2	56%, α/β =1/1
6. X = F	Cp_2ZrCl_2/AgOTf, CH_2Cl_2	42%, α/β =1/1
7. X = SEt	NIS/TMSOTf, CH_2Cl_2	86%, α/β =1/1
7. X = SEt	NIS/TMSOTf, Dioxane/Tol.	83%, α/β =3/1

Scheme 2. Glycosylations followed by cleavage from the solid support

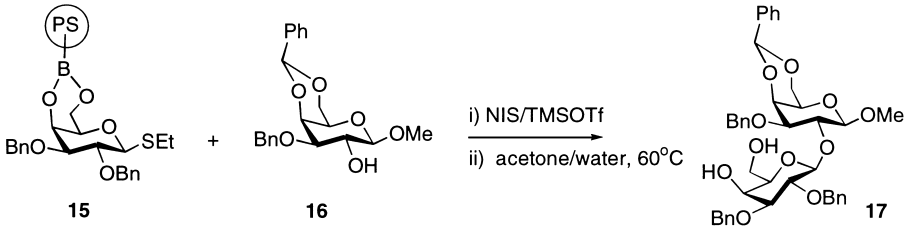
A mixture of anomers was obtained when the glycosylation was performed in CH_2Cl_2; however, mainly α-linked product was formed when toluene/dioxane was used as the reaction solvent.[15] It is important to note that high yields of disaccharide were only obtained when the polymer was fully loaded with saccharide. In the case of partial loading, a significant amount of starting material was isolated. We speculate that in this case, the 2-hydroxyl of the immobilized acceptor **3** reacts with the excess of boronic acids present on the polymer making it unavailable for glycosylation.

To demonstrate the generality of the approach, the glycosyl donors **9**, **11**[16] and **13**[17] were coupled with the immobilized acceptor **4** using NIS/TMSOTf as the promoter (Scheme 3). After cleavage from the solid support, the products **10**, **12** and **14** were isolated in almost quantitative yields and TLC, NMR and MALDI-TOF MS analysis of the crude products indicated the absence of acceptor. In the case of the fully benzylated thiogalactoside **9**, the product **10** was isolated as a mixture of anomers. The disaccharides **12** and **14** were obtained as β-anomers due to a neighboring group participation of the C-2 benzoyl or phthalimido functionality, respectively.

Encouraged by these results, we turned to the immobilized thioglycosyl donor **15**.[18] This derivative could easily be obtained by heating a mixture of resin **2** and ethyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside in pyridine. Coupling of **15** with acceptor **16** in the presence of NIS/TMSOTf, followed by cleavage from the solid support by heating in acetone/water, gave disaccharide **17**[19] in an overall yield of 68% (Scheme 4).



Scheme 3. (i) NIS/TMSOTf, CH_2Cl_2 then acetone/water, 60°C, 30 min



Scheme 4.

Cleavage of a product from the polymeric support affords the original polymer **2** which, in principle, can be reused for polymer-supported oligosaccharide synthesis. Indeed, washing the used polymer with dioxane/HCl followed by careful washing and drying gave a resin, which could be reused for synthesis and performed equally well as freshly prepared polymer.

In conclusion, it is demonstrated that polystyrylboronic acid is an attractive polymeric support for oligosaccharide synthesis. Saccharides can be loaded by heating in pyridine and released by treatment with a mixture of acetone and water. NIS/TMSOTf mediated glycosidations of thioglycosides gave a quantitative formation of disaccharides. The linker can be used for immobilized glycosyl donors and acceptors opening the way for an efficient combinatorial synthesis of oligosaccharides by a two-directional glycosylation strategy.[20]

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