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Boronic ester as a linker system for solid phase synthesis

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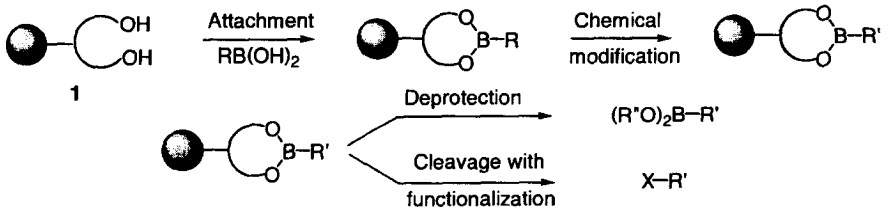
Abstract

A method for attaching boronic acids to a macroporous polymer-supported 1,3-diol was developed. Chemical modifications of some polymer-bound arylboronic acids were realised using various reaction conditions. Transesterification gave new boronates in high purity while oxidative cleavage directly led to phenols.

The generation of non-peptidic small organic molecules by solid phase methods has proven to be a successful strategy in both increasing the number and the diversity of new pharmacologically active substances.[1] Most of the linkers used for combinatorial chemistry are borrowed from previous research on the generation of peptide, oligonucleotide and oligosaccharide libraries. After cleavage from the support, they usually release one specific functional group e.g. alcohol, carboxylic acid or amine. Alternatively, the synthesis of new libraries may require additional groups and, therefore, new linkers and cleavage methods. Thus, several boron derivatives have been recently reported to play a significant role in a variety of biological processes.[2] Following our previous investigations concerning this topic,[3] we envisioned a boron-based linking technology which could give access to a wide range of boronic acids and esters. Furthermore, the versatility of the organoborane chemistry should give rise to an additional diversity in the final cleavage step.[4]



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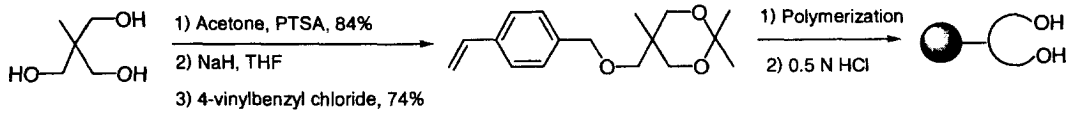
Critical to this approach is the choice of the polymeric support and the diol moiety. The post-functionalisation of styrene-based polymers is, by far, the most widely used route to access supports for catalysts, reagents and for solid phase synthesis. The commercially available resins used in this approach are almost exclusively polystyrene beads lightly crosslinked (1 to 2%) with divinylbenzene. These supports, called gel-type, need to be swollen in compatible solvents (toluene, THF) in order to allow a good diffusion of reagents. On the other hand, macroporous type supports, having a permanent porosity, can be used in almost any solvent, show a better mechanical strength under stirring and allow better site isolation. Following our previous works on polymer-supported catalysis,[5] we prepared our own macroporous support from a tailor-made styrene-based monomer **1**.[6] The diol moiety was chosen to ensure a good resistance to a wide variety of reaction conditions without preventing a selective cleavage from the support in the last step.[7]

The styrene derivative **1** was obtained from the sodium salt of 2-methyl-2-(hydroxymethyl)-1,3-propanediol acetonide and 4-vinylbenzyl chloride. Polymerisation was achieved through the dispersion of the monomer in an aqueous phase using AIBN as initiator, poly(diallyldimethyl ammonium chloride) as stabiliser and 2-ethyl-hexanol as solvent.[8,9] Hydrolysis (0.5N HCl, THF) enabled us to recover the free 1,3 diol.



Before examining the stability of the boronic linker in some classical experimental conditions, a search for the optimal attachment and cleavage conditions was first undertaken by varying the reaction parameters (i.e. solvent, temperature and time). For each step, the amount of boron bound to the support was determined by elemental analysis. The best results were obtained by heating the diol resin and $RB(OH)_2$ in refluxing THF. Cleavages were carried out using a Soxhlet apparatus.[10] The resin was placed in the thimble and the methyl boronic esters **2**, obtained by transesterification, were continuously extracted at reflux in a mixture of methanol, THF and CH_2Cl_2 (5/5/2). It is noteworthy that **2** are not only precursors of the corresponding boronic acids by simple treatment with water, but also of various esters by efficient transesterification reactions.[4] The cleavage method proved to be very reliable, although it required prolonged reaction times (2 days). Yields (two steps) were calculated on pinacol esters derivatives[11,12] (Table 1) assuming that the loading in 1,3 diol moieties of the support (estimated at about 1 mmol/g) was directly correlated with the molar fraction of **1** in the monomer feed and that all the monomers involved were inserted in the same proportion due to the high conversion level reached during the polymerisation.

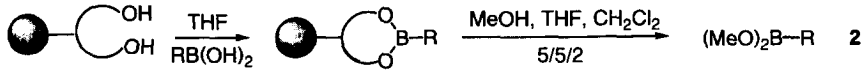
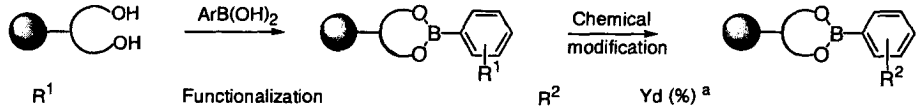


Table 1
Sequential attachment and cleavage of boronic acids

	R	Yield	Purity [a]		R	Yield	Purity [a]		R	Yield	Purity [a]
2a	3-NH_2-C_6H_4	75%	96%	**2d**	3-NO_2-C_6H_4	68%	98%	**2g**	4-Me-C_6H_4	64%	99%
2b	4-CO_2H-C_6H_4	52%	98%	**2e**	4-MeO-C_6H_4	63%	99%	**2h**	1-decyl	80%	99%
2c	4-Br-C_6H_4	56%	97%	**2f**	2-MeO-C_6H_4	55%	90%	**2i**	1-decen-1-yl	50%	95%

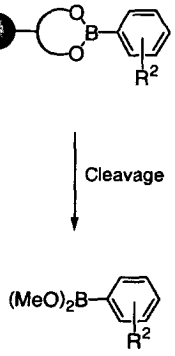
[a] The purity of the products was established by ^1H NMR and GC.

Aryl boronic acids and esters have been used in boroneutrotherapy,[13] as inhibitors of angionesis,[14] as synthetic carriers of carbohydrates and ribonucleosides for selective membrane transport, chemosensors and receptors of mono- and disaccharides.[15] We therefore chose to carry out the preliminary studies of the functionalisation of polymer-bound boronates with this class of organoboranes and showed that some simple successful transformations can be realised using various reagents such as acid chloride, sulfonyl chloride, isocyanate, thionyl chloride and allylboronate.[16] Cleavage was done as previously described and gave substituted aryl boronates in good yields.



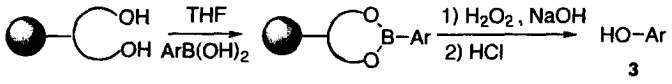
R^1	Functionalization	R^2	Yd (%) [a]
3-NH_2	Propionyl chloride, Pyridine, CH_2Cl_2	3-NHCOEt	63
3-NH_2	4-Toluenesulfonyl chloride, $EtN(iPr)_2$, CH_2Cl_2	3-$NHSO_2$Tol	54
3-NH_2	Phenylisocyanate, CH_2Cl_2	3-NHCONHPh	59
4-CO_2H	i, $SOCl_2$ ii, BuOH, Pyridine, toluene	4-CO_2Bu	65
4-CH_2OH	Propionyl chloride, $EtN(iPr)_2$, CH_2Cl_2	4-CH_2OCOEt	54
4-CHO	Pinacol allyl boronate, CH_2Cl_2 [16]	4-CH(OH)-Allyl	67

[a] Overall yields based on resin loading



A wide range of other boronic acids are commercially available or easily prepared by well-known procedures.[4] Most of them contain one or several additional functional groups and can therefore constitute interesting sources to produce large numbers of new compounds via solid-support synthesis. In addition to the advantages of this route compared with the chemistry in solution (use of excess of reagents, easy separation of supported species and products, high purity of the final compounds), this approach was not limited to the preparation of organoboron compounds.

Unlike most of the linkers which were traditionally designed to release one specific functional group, our boron-based linker is well suited for multidirectional cleavage procedures. As a first example of cleavage with functionalisation, we converted some attached boronic esters to the corresponding phenols **3** by oxidation with hydrogen peroxide in the presence of sodium hydroxide.[17]



Ar	Yd	Purity [a]
3-NO_2-C_6H_4	63%	99%
4-Br-C_6H_4	65%	88%
4-NHCOEt-C_6H_4	74%	95%

[a] Estimated by ^1H NMR and GC

These standard oxidation conditions have been proved to be compatible with many functional groups.[18] Other more chemioselective methods, which have been reported recently,[4] could be also considered and tested on supported boronates if necessary.

In summary, we have reported a simple and efficient procedure for the attachment, the chemical modification and the cleavage of boronic esters on solid support. Furthermore, the presence of the versatile boronic ester functionality allows the diversification of a library in the cleavage step. Other transformations of boron derivatives on solid support are currently underway.

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7. We chose to prepare cyclic esters on solid support because of their greater stability compared with the corresponding alkyl alcohol or ethylene glycol derivatives. For the synthesis of boronic esters in solution from the boronic acids, see Ref. 4.
8. In a typical experiment, an organic phase (41 ml) of **1** (16 mmol), styrene (71 mmol), divinylbenzene (80% commercial mixture, 26 mmol), 2-ethylhexanol (16 ml) as the porogen and AIBN (200 mg) as the free radical source, were suspended in 400 ml of aqueous phase containing poly(diallyldimethyl ammonium chloride) (1.75% w/v) as the stabiliser and gelatin (0.37% w/v) as the dispersant agent. The stirring speed was adjusted (between 500 and 600 rpm) in order to obtain, visually, droplets of satisfactory size. The reactor was then placed in a thermostated bath and the polymerisation was run out at 80°C for 12 hours. After cooling, the reaction mixture was filtered and the polymer beads were washed with water and ethanol then continuously extracted with THF in a Soxhlet apparatus for 24 hours. After a last washing with ether, the beads were dried under vacuum at 60°C for 24 hours. Yield of usable recovered beads 27 g (84%); sizing: (diameter range(μm)/weight%) >800/38; 500–800/23; 315–500/17; 200–315/12; <200/10. Specific surface area (BET)=68 m^2/g, pore volume (BJH)=0.3 cm^3/g, average pore radius (BJH)=7 nm. The N_2 adsorption–desorption isotherm is of Class IV with an important hysteresis loop indicating a macroporous structure (Webb, P. A.; Orr, C. Surface area and pore structure by gas adsorption. In *Analytical Methods in Fine particle technology*; Micrometrics Instruments: Norcross, GA, USA, 1997; Chapter 3, p. 53.
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10. Attachment of boronic acids: To a suspension of 500 mg of the resin (1 mmol/g) in 5 ml of THF was added 3 equiv. of boronic acid. The suspension was stirred for 16 h under reflux. The resin was filtered, washed successively with THF (3×5ml), CH_2Cl_2 (3×5ml), Et_2O (3×5ml) and dried under vacuum at 60°C for 3 h. Cleavage: The resin was placed in the thimble of a Soxhlet apparatus which is fitted to a flask containing a mixture of methanol, THF, dichloromethane (v/v: 5/5/2). The methyl boronic ester obtained by transesterification was continuously extracted for 48 h. The methyl boronic ester was isolated from the solution by distillation of the solvents and directly treated with 1.2 equivalent of pinacol in Et_2O. The mixture was stirred for 6 h at room temperature, then washed with water to eliminate excess of pinacol. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired pinacol boronate.
11. Methyl boronates are air-sensitive. They were converted to the corresponding stable pinacol esters to allow a more accurate determination of the yield.
12. As the products prepared in this study are known compounds, their identity were confirmed by reference to published melting point and/or comparison of their ^1H NMR spectra with those of authentic materials.
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17. General procedure: To a suspension of 500 mg of the resin (1 mmol/g) in 5 ml of THF was added at 0°C 1.5 equivalent of 35% hydrogen peroxide and 1 equivalent of 3 M sodium hydroxide. Stirring was continued for 1 h at 0°C and at room temperature for 2 h. The mixture was treated with 1N aqueous HCl until pH 4. The resin was filtered, washed successively with THF (3×5ml), CH_2Cl_2 (3×5ml), Et_2O (3×5ml). The filtrate was partially evaporated and the product was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated to give the phenol derivative.
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