

Polyglycerol as a High-Loading Support for Boronic Acids with Application in Solution-Phase Suzuki Cross-Couplings

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Abstract: In this paper, we describe the usage of a soluble high-loading polyglycerol support for functionalized boronic acids without further linker design. The quantitatively formed polyglycerol boron esters were subsequently employed in homogeneous Suzuki cross-coupling reactions to give high yields (84–91%) of functional biaryls with minimal amounts of the Pd catalyst (0.2 mol %). In situ precipitation and ultrafiltration were used as simple and effective purification protocols. Furthermore, the reaction conditions were optimized by the choice of the solvent and the catalyst.

Boronic acids have grown into an important class of organic compounds over the last few years due to their broad application potential in organic synthesis. Especially in the palladium-catalyzed Suzuki cross-coupling reaction¹ boronic acids and esters are popular substrates in the synthesis of organic building blocks as well as druglike molecules. This C–C coupling reaction can be achieved efficiently with arylic bromides and chlorides (in some cases) and does not require expensive aryl iodides. In addition, a broad tolerance toward functional groups is observed. In recent years, Suzuki couplings have also become very popular in combinatorial chemistry. Efforts were made to support one or two components to simplify the workup protocol.² Typically a solid support, like the Wang or Merrifield resin, is chosen to support the aryl halide,³ the boronic acid,⁴ or the catalyst.⁵ However, these resins show some characteristic disadvantages: they usually possess low loading capacities (typically <1.5 mmol g⁻¹), and the resulting heterogeneous reaction conditions require large amounts of

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catalyst.⁶ Alternatively, soluble linear and perfect dendrimers were used to support aryl halides and thereby avoid these problems.⁷ Another class of high-loading supports for organic synthesis are dendritic polymers, such as polyglycerol (PG) **1**.⁸ This soluble polymer is easily accessible via anionic ring-opening polymerization of glycidol in kilogram quantities⁹ and recently became commercially available.⁹ A major advantage of PG is its high loading capacity of about 4.1 mmol g⁻¹ of terminal 1,2-diol groups, which can be directly used as linkers for various substrates, reagents, and ligands.^{2a,8}

We here report on the synthesis of high-loading polyglycerol boronic esters which are subsequently used for solution-phase Suzuki cross-coupling reactions and describe a simple workup protocol. The formation of the boron esters 2a-2d occurs at room temperature within 4-18 h in dimethylformamide (DMF) by reacting a boronic acid with the dendritic PG support (Scheme 1, Table 1). This procedure is performed on the unfunctionalized polymer and does not require an additional linker design. Small amounts of molecular sieves were added to drive the reactions to completion. Quantitative conversions (>95%) were obtained for all substrates (Table 1), and no further purification procedure was required as demonstrated by ¹H NMR analysis.

It appears that under the above-described conditions the size of the polymeric support plays an important role. For example, for the formation of 2d with a large PG support (average molecular weight of 21000) only a poor loading of 33% could be obtained. By far better loadings were achieved by choosing a smaller PG support with an average molecular weight (M_n) of 8000 (83%). In the case of thiophene boronic acid **2d** an additional slightly increased temperature (50 °C) is necessary to obtain a quantitative loading (>95%). The reason for the poor loadings when using a high molecular weight PG can be due to a back-folding of the polymer chains with a resulting hindrance in the diffusion of the substrate. Consequently, polyglycerol with an average molecular weight of 8000 was used. As depicted in Table 1 all products 2a-2d show excellent conversions and high loadings of boronic acid $(2.5-3.0 \text{ mmol g}^{-1})$. The soluble

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SCHEME 1. Immobilization of Various Boronic Acids onto Dendritic Polyglycerol 1 without Further Linker Design^a

^{*a*} Cf. Table 1. The depicted polymer structures **1** and **2** show only one possible isomer and a small fragment of the polyglycerol ($M_n = 8000$) scaffold.

TABLE 1. Immobilization of Various Boronic Acids onto a Dendritic Polyglycerol Support

entry	boronic acid	product	temp. [°C]	conv. [%] ^a	loading [mmol g ⁻¹]
1	B(OH)2	2a	25	>95	3.01
2	CF ₃ B(OH) ₂	2b	25	>95	2.50
3	O ₂ N B(OH) ₂	2c	25	>95	2.65
4	B(OH)2	2d	50	>95	2.95

^{*a*} Determined by integration of the terminal C-atoms at 63 ppm and their corresponding chemical shift at 67–68 ppm in the ¹³C NMR, relaxation agent $Cr(acac)_3$.¹⁰

polymeric support allows for the easy determination of the loading by integration of the terminal methylene signal at 63 ppm in the ¹³C NMR spectrum (inverse gated). In the case of a quantitative boron ester formation the signal shifts completely to 67-68 ppm (see the Supporting Information). By adding Cr(acac)₃ as a relaxation agent, integration of these signals is possible to determine the exact loading (±5%).¹⁰ Subsequently, the polyglycerol boronic esters **2a**-**2d** were tested in solutionphase Suzuki couplings (Scheme 2). An excess of **2a**-**2d** (2 equiv) was treated with the particular aryl bromide (1.0 equiv), 0.2 mol % of the respective catalyst (see below), and potassium carbonate (2.5 equiv) in DMF at 120 °C for 18 h. Apart from DMF several other solvents, such as THF, toluene, or dioxane, have been described

for this reaction.^{4,11} On account of their favorable properties (less toxic, lower boiling point), these solvents could be preferential as compared to DMF. Therefore, the synthesis of 4-methoxybiphenyl was performed in these solvents to find the best for these homogeneous polymersupported Suzuki couplings using identical reaction conditions (Figure 1). However, the usage of these alternative solvents, THF, dioxane, chloroform, and toluene, resulted in comparatively low conversions. One possible explanation for this observation might be the solution process of the polyglycerol boron ester in the respective solvent. In all cases except DMF, a white clouding of the solution was observed. This process is known as the Tyndall effect and describes the formation of large polymer aggregates. The poor conversions can be due to the limited accessibility of either the boronic acid or the catalyst in these aggregates. Therefore, for all optimized reactions (Tables 2 and 3) we used DMF as solvent. It is noteworthy that in contrast to solid-phase

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FIGURE 1. Solvent screening: influence of different solvents on the conversion.

SCHEME 2. Polyglycerol Boronic Esters as Soluble Reagents for Suzuki Cross-Coupling Reactions^a



^a Cf. Tables 2 and 3.

 TABLE 2.
 Catalyst Screening: Effect of the Catalyst on the Conversion for Two Different Biphenyls

entry	catalyst	convn. [%] ^a	biphenyl		
1	Pd(dba) ₂	19			
2	Pd(PPh ₃) ₂ Cl ₂	79	2a+3a		
3	Pd(PPh ₃) ₄	98			
4	Pd(dba) ₂	96			
5	Pd(PPh ₃) ₂ Cl ₂	8			
6	Pd(PPh ₃) ₄	45	2b + 3b		
btained from the 14 NMP spectrum					

^a Obtained from the ¹H NMR spectrum.

Suzuki cross-couplings^{3,4} very low amounts of a Pd catalyst (0.2 mol %) are necessary to drive the reactions to completion (Scheme 2). That corresponds to a factor of 10-100 less as compared to solid-phase protocols and can be explained by the homogeneous reaction conditions.³

To find the best catalyst for two complementary examples, we chose two different systems consisting of two electron-donating components (Table 2, entries 1-3) and two electron-withdrawing components (Table 2,

entries 4-6). Three catalysts, Pd(dba)₂, Pd(PPh₃)₂Cl₂, and Pd(PPh₃)₄, were screened for the maximum conversion (Table 2). In the case of 4-methoxybiphenyl (entries 1-3), the highest conversion was obtained with Pd(PPh₃)₄ (>95%). In comparison, with Pd(dba)₂ only poor results (19%) were possible. For the complementary system, 1-(2'-trifluoromethylbiphenyl)-4-ethanone (entries 4–6), the best conversion was possible with Pd(dba)₂ while both other catalysts gave poor results. Thus, for the reactions summarized in Table 3, the optimal catalyst for each coupling system was chosen individually. This results in high conversions (>95%) for most examples, which was determined from the ¹H NMR spectra by integration of the methyl signal in each product vs the methyl signal in the starting material. As described previously, easy purification of all products can be achieved via ultrafiltration (UF)^{2,8} to give relatively pure products (>90%) as determined by GC-MS and ¹H NMR analysis. No polymer-supported boronic acid could be detected in any product.

We used a commercially available solvent-resistant stirred pressure cell (6 bar, 47 mm) in combination with solvent-resistant membranes. Typical separation times were 2-3 h (including conditioning of the membrane) per product. In some cases (e.g., Table 3, entries 5 and 6), however, we observed that most of the polymer-supported boronic compound precipitated during the reaction, and therefore no further purification (UF) was required.

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TABLE 3.	Solution-Phase Suzuki	Couplings	Using 2a-2d u	under Optimized (Conditions
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entry	PG-boron ester	aryl halide	product	catalyst	convn. [%] ^a	yield [%] ^b		
1	2a	р- Д-Br		Pd(PPh ₃) ₄	98	88		
2	2a	°→−−Br	$\bigcirc - \bigcirc + \checkmark$	Pd(PPh ₃) ₄	99	84		
3	2b	Ø-√_Br	CF3	Pd(PPh ₃) ₄	97	89		
4	2b	°→−−Br		Pd(dba) ₂	87	91°		
5	2c	,o-√_−Br	°2N	Pd(PPh ₃) ₄	96	86		
6	2c	°→−Sr−Br	°2N	Pd(dba) ₂	99	91		
7	2d	р- — Вr	$ () \rightarrow ()$	Pd(PPh ₃) ₄	87	90		
8	2d	° Br		Pd(dba) ₂	94	88		

^a Obtained from the ¹H NMR spectrum. ^b Isolated yields after ultrafiltration. ^c This sample contains 13% of an unspecified side product.

Nonetheless, with both methods a quantitative removal of catalyst traces was not yet possible. This will be subject to further investigations.

In summary, we have demonstrated that dendritic polyglycerol 1 is well suited as a soluble polymeric support for boronic acids. High loading values (2.5-3.0 mmol g^{-1}) are possible without further linker design. These polyglycerol boronic esters can be used in excess (2.0 equiv) for solution-phase Suzuki cross-coupling reactions and allow for the simple purification of the biaryl products. Compared with normal homogeneous methods, a much easier and faster purification protocol results, which becomes significant when several reactions (typically 5-20) are performed simultaneously. In contrast to common solid-phase techniques, the separation of the soluble polymeric support is more time consuming (1-3)h), which makes this approach less suitable for high throughput. However, the separation strategies used here (precipitation and ultrafiltration) allow the efficient workup on a preparative scale (1-5 mmol), which is not easily achieved with solid-phase resins. Despite the unique PG architecture ("built-in" diol groups), no further linker design is necessary for the loading with boronic acids. Furthermore, only very small amounts of a Pd catalyst (0.2 mol %) were necessary to obtain high conversions (87-99%).

Experimental Section

General Procedures. All reactions were performed under a nitrogen atmosphere with magnetic stirring. The employed reagents and solvents were commercial grade. NMR spectra were recorded in CDCl₃ at 300 MHz for ¹H and at 75 MHz for $^{13}\mathrm{C}$ with the solvent as the internal standard. For ultrafiltration a commercially available solvent-resistant stirred pressure cell (6 bar, 47 mm) in combination with solvent-resistant membranes were used.

General Experimental Procedure for the Polyglycerol Boron Ester Formation. To a solution of 1.0 g of polyglycerol and 4.0 mmol of boronic acid in 10 mL of DMF was added 0.2 g of 4 Å molecular sieves, and the resulting solution was stirred for 4–18 h at 25–50 °C (cf. Table 1). After filtration, the solvent was removed and the product dried in high vacuum. Despite thorough drying of the products, they still contained some DMF. For application in Suzuki coupling reactions the filtered DMF solution can be used directly without further concentration.

General Experimental Procedure for the PG-Supported Suzuki couplings. To a suspension of 1.25 mmol of potassium carbonate in 7.5 mL of DMF were added 1.0 mmol of polyglycerol boronic ester **2a**-**d**, 0.5 mmol of aryl halide **3a,b**, and 0.001 mmol of palladium catalyst (cf. Table 3), and the resulting solution was stirred for 18 h at 120 °C. When the reaction was completed, the solvent was substituted by toluene for ultrafiltration (cf. ref 8). In some cases (Table 3, entries 5 and 6), the precipitation of the polymeric boron compound was quantitative and no ultrafiltration was required.

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Supporting Information Available: Analytical data and NMR spectra of boronic esters **2a–2d** and all biaryls. This material is available free of charge via the Internet at http://pubs.acs.org.

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