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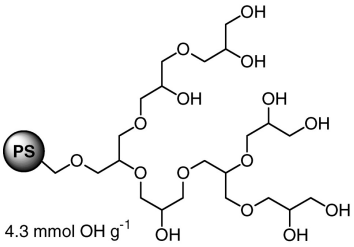

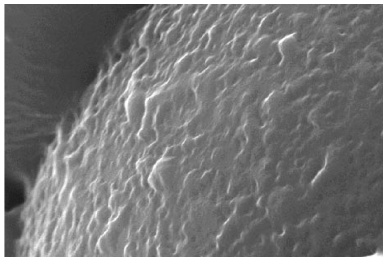

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Polystyrene-*graft*-Polyglycerol Resins: A New Type of High-Loading Hybrid Support for Organic Synthesis

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The preparation of a dendritic graft polymer by a very efficient synthesis of polyglycerol directly on a polystyrene resin is presented. This one-step process can be performed on a multigram scale to provide a chemically stable polymeric support. The resulting hybrid polymers were fully characterized by diverse analytical methods (NMR, IR, ESEM, UV detection of cleaved protecting groups, and mass-spectrometric methods). They combine a high loading capacity (up to 4.3 mmol g^{-1}) with good swelling properties in a wide range of solvents (including water), which is the major drawback for many existing solid phase supports. In comparison to the widely employed PEGylated resins, these hybrid materials offer a 10-fold higher loading capacity. Their suitability as supports for organic synthesis and for the immobilization of reagents has been demonstrated. These materials also swell in water, and consequently, it should be possible to use these new hybrid materials for synthesis in protic solvents.

Introduction

In recent years, the use of polymeric supports has become increasingly important, especially for automated synthesis and combinatorial chemistry. To a large extent, weakly cross-linked polystyrene (PS) beads were primarily used for this application. However, the low loading of functional groups (typically <1.5 mmol g^{-1}) and the limited swelling properties of this unpolar matrix in polar solvents are the major disadvantages of these solid-phase supports. Also, the ability to screen the final product directly on the resin is becoming more and more attractive. To obtain beads with better NMR characteristics and to achieve better swelling properties in a large variety of solvents, PS-based resins have been equipped with poly(ethylene glycol) (PEG) chains as spacers, solubilizing groups, or cross-linking units.[1,2] Perfect dendrons were grafted stepwise onto PS beads to overcome the poor loading capacities and to obtain high-loading supports (up to 2.2 mmol g^{-1}).[3,4] Two systems based on aryl ether dendrons have been reported and synthesized stepwise (6 steps for generation 3) on the PS support.[4] These PS−polyether hybrid materials combine high chemical stability and good swelling properties in polar solvents. The major drawbacks of these perfect dendrons attached to the PS backbone, however, are tedious synthesis and still limited swelling in protic solvents. Linear high-loading PS hybrid polymers, such as Rasta silanes,[5] ROMPSpheres,[6] and PS resins, containing linear polyglycidol groups[7] also require a multistep approach. Here, we report a simple and efficient one-step approach to dendritic polyetherpolyols grafted onto solid-phase PS beads and their application as supports for multistep organic synthesis and for boronic ester reagents in Suzuki couplings. Furthermore, these high-loading hybrid supports show interesting physicochemical properties, such as swelling in many solvents including protic solvents such as water and methanol.

Results and Discussion

For the heterogeneous (gel phase) synthesis of the dendritic polystyrene-*graft*-polyglycerol hybrid polymer beads (PS-*g*-PG) (Scheme 1), we have modified an efficient protocol for the homogeneous anionic ring-opening polymerization of glycidol, which was reported recently.[8,9] To achieve a reasonable swelling of the solid-phase support and a homogeneous graft polymerization throughout the bead, we used DMF/diglyme or dioxane as solvents. In addition, the complete metalation of the initiator (e.g., hydroxyethylated PS **1a**) became necessary to achieve high conversions. This is in contrast to soluble hyperbranched polyglycerol (PG), where only about 10% of the initiator is deprotonated.[8,10] A significant advantage of this heterogeneous process is the easy separation of autoinitiated monomer, which forms soluble PG, by simple filtration. Several dendritic PS-*g*-PG hybrid polymers **2a**−**d** with different degrees of polymerization (DPs) have been prepared starting from the monoalcohol **1a** with a loading capacity of 1.3 mmol g^{-1} (Table 1). The loading capacities of the new hybrid materials were determined by esterification with an Fmoc amino acid, followed by Fmoc cleavage and quantification by UV measurement.[11]

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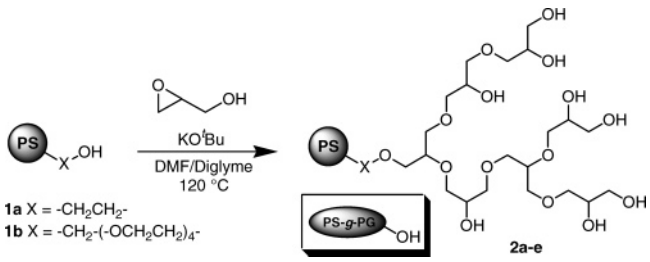
Scheme 1. Synthesis of Different PS-*g*-PG Hybrid Polymers **2a**−**e** (see also Table 1)



Because of the living character of this polymerization, different sizes of dendritic structures can be grafted onto the PS resin. Depending on the amount of added glycidol monomer (2−10 equiv) various DPs (2−6) could be achieved, which results in loading capacities in the range of 2−5 mmol of OH g^{-1} (Table 1). In addition, a tetra(ethylene glycol) (TEG) graft, **2e**, was prepared (initiator **1b**) and linked to the resin as a benzyl ether; the soluble TEG−PG was cleaved by trifluoroacetic acid (TFA) and trimethylsilylbromide (TMSBr) to determine its degree of polymerization by ESI-MS and its degree of branching (DB = 60%) by ^{13}C NMR.

For the investigation of the grafting process, we also studied the surface morphology of the polymer beads by environmental scanning electron microscopy (ESEM) (Figure 1). In contrast to the starting resin **1a** (smooth surface) and the PEGylated resins (crystalline surface),[1] the surface of these hybrid materials was covered by the honeylike structure of PG. This might be caused by the absence of a melting point and the low glass-transition temperature (T_g = −35 °C) for PG.

The resulting hybrid material, **2**, also shows good swelling properties in a wide range of solvents including water and methanol (Table 2).[12] These polymer characteristics are important for their performance in (bio)organic synthesis and are similar to those of PEGylated resins. However, it is noteworthy that these polystyrene-*graft*-polyglycerols (PS-*g*-PG) have loading capacities which are a factor of 10 higher than those of PEGylated[1] resins.

Further evidence for this new type of high-loading hybrid polymer (**2a**) was obtained from its ^{13}C NMR spectrum (Figure 2). In the ^{13}C NMR spectrum of polystyrene-*graft*-polyglycerol resin **2a**, intense signals of dendritic polyglycerol are present, similar to those of soluble polyglycerol: 63.6 ppm primary terminal alcohol, 69.6 ppm secondary alcohol in the chain, 71.1 ppm secondary terminal alcohol, and 73.1 ppm neighboring carbon to secondary alcohol in the chain.[8,10] The signals of the partially hydroxyethylated polymer backbone are also apparent, but they show significant line broadening.

To demonstrate the utility of these high-loading supports (**2d**) in organic synthesis, we performed a multistep synthesis of a drug analogue on these supports and used them for the immobilization of reagents or catalysis (i.e., boronic acids for Suzuki couplings).

The commercial drug gabapentin **4**, as an analogue of GABA (γ-aminobutyric acid) **3**, is useful in the therapy of certain cerebral disorders, such as some forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Recently, gabapentin-lactam **5**, was accidentally found to show novel neuroprotective properties.[13]

Our retrosynthetic approach traces these compounds back to a polymer-supported (diethylphosphono)acetic acid, **6**, and a carbonyl compound (i.e., cyclohexanone).[14] To test the potential of this newly developed high-loading polymeric support in multistep organic synthesis, we performed the four-step synthesis of gabapentin-lactam **5** on the hybrid polymer **2d** (Scheme 2).

After immobilization of (diethylphosphono)acetic acid on the PS-*g*-PG-resin **2d** and condensation with cyclohexanone by a Horner−Wadsworth−Emmons reaction, compound **7** reacts in a Michael addition with nitromethane to an immobilized γ-nitroester **8**. One of the decisive disadvantages of solid-phase chemistry is the difficult reaction monitoring and product analysis. However, in this case, we could utilize IR spectroscopy, since we were able to directly compare the spectra to the analogous products on the soluble PG support, which have been characterized unambiguously via additional ^{1}H and ^{13}C NMR.[14] For example, the success of the immobilization step could be estimated by the appearance of a carbonyl band in the product IR. Furthermore, the Michael addition step could be monitored, since an alkene band decreased and a nitro band concomitantly increased (1647 and 1547 cm^{-1}, respectively, on both the insoluble and the soluble support). In the final step, in situ reduction of the nitro group to form the aminoester **9** and cyclative cleavage yielded gabapentin-lactam **5**. However, under the conditions employed (Zn/HCl/reflux), the release was not fully selective, and a mixture was obtained which required additional purification through column chromatography (52 mg of **5**, 39% over four steps from only 200 mg of resin). Nevertheless, we have demonstrated that our new dendritic hybrid materials can be used as solid supports for the multistep synthesis of biologically relevant molecules.

To demonstrate the applicability of these hybrid polymers as supports for reagents in catalysis, we immobilized phenylboronic acid on high-loading PS-*g*-PG **2d** and used the resulting boronic esters, **10**, as polymeric reagents in Suzuki coupling reactions (Scheme 3).

The IR spectra of the boronic ester **10** agreed well with those obtained from the soluble analogue.[15] In the Pd-catalyzed Suzuki coupling of *p*-bromoacetophenone with 2 equiv of phenylboronic ester **10**, quantitative conversion into 4-acetylbiphenyl **11** was achieved. The excess of the supported boronic ester could efficiently be removed by simple filtration.

Summary and Conclusions

In summary, we have demonstrated that these new high-loading polystyrene-*g*-polyglycerol hybrid polymers, **2**, have interesting physicochemical properties, which classify them as ideal polymeric supports for the multistep synthesis of druglike molecules and for the immobilization of reagents in catalysis. They combine high-loading capacity with good swelling properties in a wide range of solvents, which is lacking for many existing solid-phase supports. In comparison to the widely employed PEGylated resins, these hybrid

Table 1. Parameters and Loading Capacities of the Different PS-*g*-PG Hybrid Polymers **2a**−**e**

PS initiator	support	equiv glycidol	solvent	DP[a]	loading capacity (mmol g^{-1})	method
1a	**2a**	10	Dioxane	2	2.7	Fmoc
1a	**2b**	20	DMF/Diglyme	2−3	3.1	Fmoc
1a	**2c**	30	DMF/Diglyme	4−5	4.0	Fmoc
1a	**2d**	30	Dioxane	5−6	4.3	Fmoc
1b	**2e**	20	Dioxane	3−4	3.5	ESI-MS

[a] The DP was calculated based on Fmoc end-group analysis or absolute masses in the case of resin **2e**.

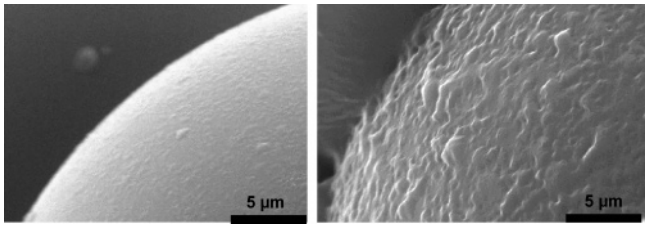


Figure 1. ESEM pictures of the hydroxyethylated PS beads **1a** (left) and the resulting hybrid polymer PS-*g*-PG beads **2d** (right).

Table 2. Swelling Properties of the PS-*g*-PG Hybrid Polymers in Various Solvents (mL g^{-1})

resin	CH_2Cl_2	dioxane	DMF	MeOH	H_2O
2a	7.5	6.6	5.7	2.8	2.1
2b	6,1	5,7	3.6	2.8	2.3
2c	5.5	6.0	4.8	2.9	2.5
2d	5.0	5.4	5.2	3.0	2.6
2e	7.0	7.0	5.9	2.6	2.0
Merrifield (PS)	8.3	7.8	5.6	1.6	0

materials offer a 10-fold higher loading capacity. Their suitability as supports for organic synthesis was demonstrated by the four-step synthesis of gabapentin-lactam **5**. All organic reactions carried out on the new PS-*g*-PG support, **2d**, were more straightforward because of the general applicability of a simple filtration step, compared to the membrane separation techniques used for the soluble polyglycerol supports. Because of their ability to swell in water, these new hybrid materials also may be suitable for synthesis in protic solvents.

Experimental Section

General. NMR-spectra were obtained on a Bruker DRX 500 (solvent or external standards; sample amount for ^{1}H NMR 10−20 mg, for ^{13}C NMR 60−100 mg). IR spectra were obtained on a Bruker IFS66 FT-IR spectrometer in the range of 4000−500 cm^{-1}. If not otherwise stated, the commercially available chemicals are used without further purification. For water-free procedures, the solvents were dried conventionally. The glassware was dried overnight at 105 °C, heated under high vacuum at 400 °C, and flushed with Ar three times just before the reaction. The addition of chemicals was carried out under argon.

Polystyrene-*g*-polyglycerol 2c. In a 250 mL three-necked flask, hydroxyethylated PS beads (5.0 g, 1.3 mmol of OH groups/g polymer) were suspended in absolute diglyme (25 mL). After swelling, they were deprotonated using KO^{t}Bu (6.55 mL of a 1 M solution in absolute THF) at 40 °C over 12 h. THF and ^{t}BuOH were distilled off, and the residue was mixed with absolute DMF (50 mL). While the mixture was gently stirred with a mechanical stirrer, a solution of freshly distilled glycidol (13.1 mL, 14.6 g, 197 mmol) in absolute DMF (20 mL) was added to the reaction mixture at 120 °C over a period of 5 h using a dosing pump. The reaction was terminated with 1 N HCl (7 mL), and the mixture was filtered. The polymer was washed with MeOH/THF (100 mL) (gradient) and diethyl ether (20 mL) and finally dried in vacuo to yield 6.2 g of **2c** as pale yellow beads. IR (KBr): ν 3425 [OH], 3080, 3060, 3020 [Ar−H], 2920 [CH], 1630, 1510, 1450 [C═C], 1025 cm^{-1} [C−O−C].

(Diethylphosphono)ethanoic Acid PS-*g*-PG Ester 6. This reaction was performed under an inert gas atmosphere with exclusion of water. PS-*g*-PG **2d** (1 g, 4.34 mmol of OH g^{-1}) was treated with absolute CH_2Cl_2 (30 mL). (Diethylphosphono)acetic acid (1.4 mL, 1.7 g, 8.7 mmol, 2 equiv) and DMAP (0.095 g, 0.78 mmol, 0.18 equiv) were added. The flask was installed on a shaker, and while the mixture was shaken, a solution of DCC (1.79 g, 8.68 mmol, 2 equiv) in absolute CH_2Cl_2 (30 mL) was added via syringe drop by drop over a period of 1.5 h. In doing so, a white precipitate formed. The mixture was shaken for 12 h at room temperature and then filtered. The residue was washed intensively with a gradient from pure CH_2Cl_2 to pure THF and was then dried at high vacuum and analyzed via IR. IR (KBr): ν 3327, 2928, 2851, 1736, 1626, 1575, 1537, 1437, 1312, 1271, 1244, 1088, 1047, 968, 893, 642 cm^{-1}. The filtrate was concentrated in vacuo and analyzed by means of ^{1}H and ^{13}C NMR spectroscopy. It mainly contained the excess (diethylphosphono)acetic acid, DCC, and *N*,*N*′-dicyclohexylurea.

Cyclohexylidene-ethanoic Acid PS-*g*-PG Ester 7. This reaction was performed under an inert gas atmosphere with exclusion of water. A slurry of (diethylphosphono)acetic acid PS-*g*-PG ester **6** (max 4.34 mmol (diethylphosphono)acetic acid groups, 1 equiv) in absolute THF (30 mL) was mixed with cyclohexanone (0.68 mL, 0.64 g, 6.5 mmol, 1.5 equiv). The flask was installed on a shaker, and upon shaking, LDA (2.39 mL of a 2 M solution in *n*-heptane, 4.77 mmol, 1.1 equiv) was added dropwise via syringe over a period of 1.5 h. The mixture was shaken for 12 h at room temperature and then filtered. The residue was washed intensively with a gradient from pure THF to pure MeOH and back to pure THF and was then dried at high vacuum and analyzed via IR. IR (KBr): ν 3431, 2929, 3261, 2339, 1717, 1653, 1558, 1540, 1456, 1385, 1272, 1207, 1126, 850, 758, 699, 668 cm^{-1}.

(1′-Nitromethyl-cyclohex-1′-yl)ethanoic Acid PS-*g*-PG Ester 8. Cyclohexylidene-ethanoic acid PS-*g*-PG ester **7** (max 4.34 mmol α,β-unsaturated ester groups, 1 equiv) was washed with a gradient of pure THF to pure DMF and mixed with nitromethane (0.94 mL, 1.06 g, 4 equiv) and TBAF (8.68 mL of a 1 M solution in THF, 8.68 mmol, 2 equiv).

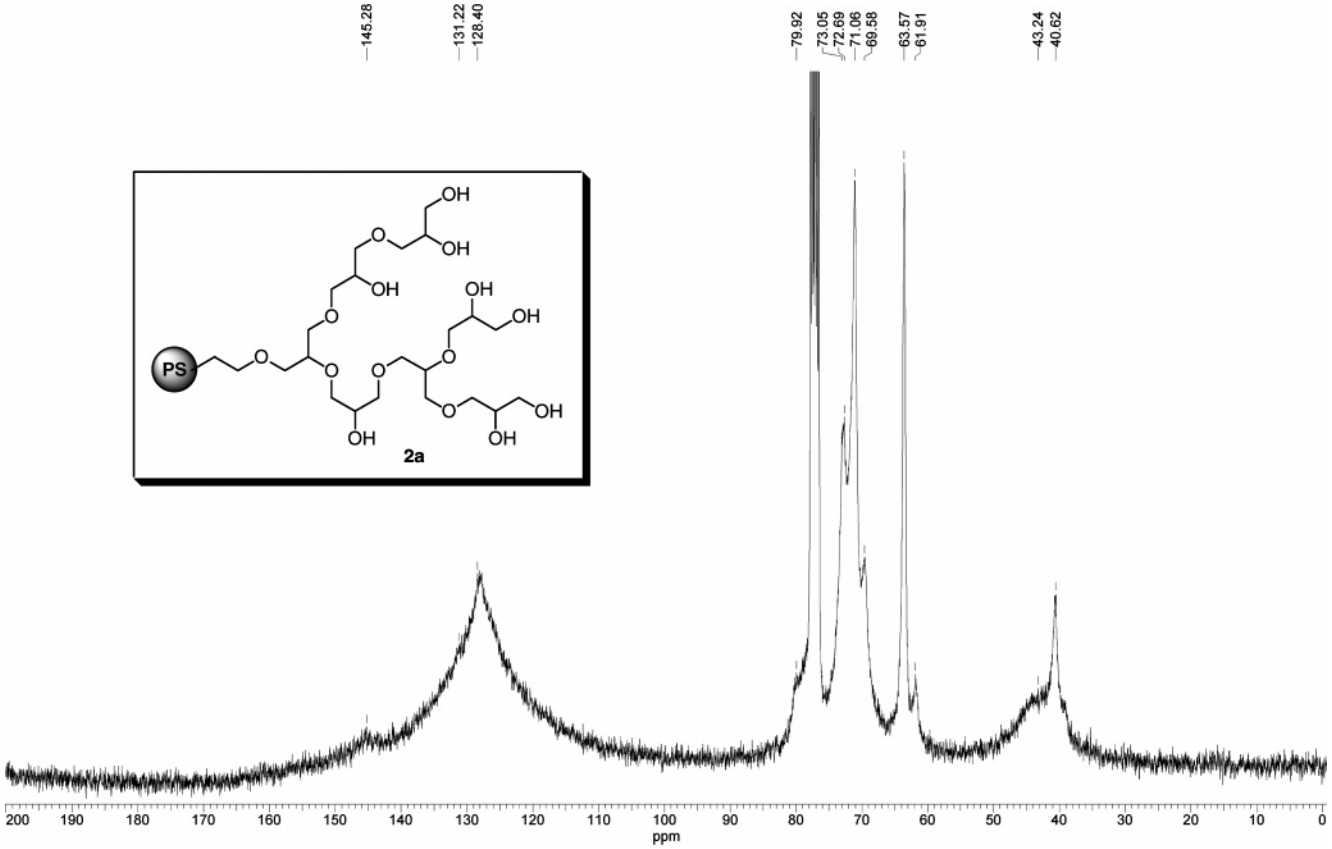
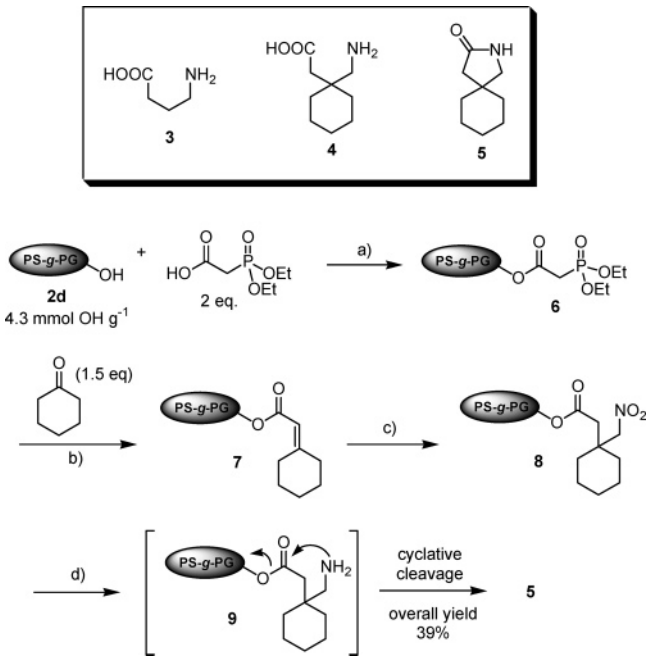


Figure 2. ^{13}C NMR spectrum of polystyrene-*graft*-polyglycerol resin **2a** (swollen in $CDCl_3$).

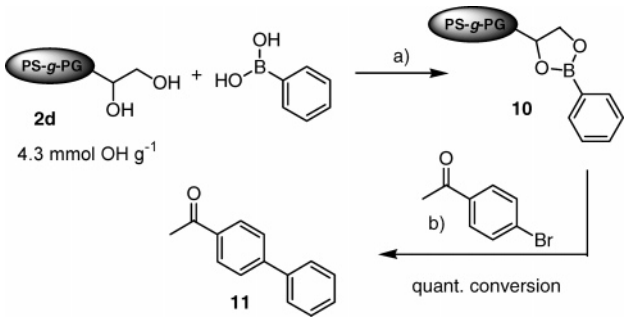
Scheme 2. Structures of the Neurotransmitters GABA **3**, Gabapentin **4**, Gabapentin-lactam **5**, and Synthetic Route to **5** on PS-*g*-PG Hybrid Supports



(a) DCC (2 equiv), cat. DMAP, abs. CH_2Cl_2, RT, 12 h; (b) LDA (1.1 equiv), abs. THF, RT, 12 h; (c) $MeNO_2$ (4 equiv), TBAF (2 equiv), DMF, 40 °C, 48 h; (d) Zn/HCl, EtOH/THF (1:1), reflux, 4 h.

The flask was installed on a shaker, and the mixture was shaken for 24 h at room temperature and then stirred for 24 h at 40 °C. After filtration and washing with DMF, the residue was dried at high vacuum and analyzed via IR. IR

Scheme 3. Immobilization of Phenylboronic Acid on the PS-*g*-PG-support **2d** and Application in Suzuki Cross-Coupling Reactions



(a) $CHCl_3$ reflux; (b) 4 mol % $Pd(PPh_3)_4$, K_2CO_3, DMF, 120 °C, 72 h.

(KBr): 3409, 2928, 1736, 1647, 1547, 1453, 1384, 1271, 1126, 759, 700, 540 cm^{-1}.

2-Aza-spiro[4.5]decan-3-one (Gabapentin-lactam) 5. The PS-*g*-PG-supported γ-nitroacid **8** (max 0.87 mmol nitrogroups, 1 equiv) was slurried in EtOH/THF (1:1). Zinc powder (1.0 g, 15 mmol, 18 equiv) and concentrated aqueous HCl (1.0 mL, 35 mmol, 40 equiv) were added, and the mixture was refluxed for 4 h. Reaction control was performed via TLC (TBME/MeOH 95:5, detection UV/$KMnO_4$, R_f = 0.26). The reaction mixture was filtered over Celite, and the filtrate was neutralized with saturated aqueous $NaHCO_3$ and concentrated in vacuo. Diethyl ether and H_2O were added until all solids were dissolved. After phase separation, the aqueous layer was extracted three times with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated. The release reaction was not fully selective, and the crude product contained considerable amounts of

nonidentified byproducts. Purification by means of column chromatography (eluent TBME/MeOH 95:5) gave 52 mg (39%) of **5**. The analytical data (^{1}H, ^{13}C NMR) agreed well with the published data.[14]

Phenylboronic Acid PS-*g*-PG Ester (2-Phenyl-4-PS-*g*-PG-[1,3,2]-dioxaborolan) 10. In a 100 mL flask with a magnetic stirrer, PS-*g*-PG **2d** (1.00 g, 1.45 mmol terminal 1,2-diol groups) was preswollen in p.a. $CHCl_3$ for 1 d. Phenylboronic acid (1.77 g, 14.5 mmol, 10 equiv) was added, and the mixture was refluxed under Dean−Stark conditions for 30 h with gentle stirring. After it was cooled, the mixture was filtered, and the residue was washed intensively with $CHCl_3$ and dried at high vacuum to give the immobilized boronic acid **10** in quantitative yield. IR (KBr): ν 3429, 3056, 3025, 2920, 2361, 1603, 1498, 1441, 1399, 1368, 1322, 1218, 1097, 1027, 993, 800, 761, 699, 644 cm^{-1}.

4-Acetylbiphenyl 11. In a 100 mL two-necked flask, phenylboronic acid PS-*g*-PG ester **10** (113 mg, approximately 0.15 mmol boronic acid groups, 2 equiv) was suspended in water-free DMF (5 mL) under an argon atmosphere. Potassium carbonate (26 mg, 0.19 mmol, 2.4 equiv), *p*-bromoacetophenone (15 mg, 0.08 mmol), and tetrakis(triphenyl)-phosphine palladium(0) (4 mg, 0.003 mmol, 0.04 equiv) were added, and the mixture was heated with gentle stirring to 120 °C for 72 h. For determination of the conversion, the crude product was filtered, and the solvent was evaporated in vacuo. Detailed analysis (^{1}H, ^{13}C NMR, TLC) revealed the quantitative conversion of *p*-bromoacetophenone to 4-acetylbiphenyl **11** (crude sample contains traces of catalyst). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.64 (s, 3H, Me), 7.40−7.47 (m, 3H, 3′-H, 4′-H), 7.62−7.68 (m, 4H, 2-H, 2′-H), 8.03 ppm (m, 2H, 3-H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 26.8 (Me), 127.4, 127.4 (2-C, 2′-C), 128.4 (4′-C), 129.1, 129.1 (3-C, 3′-C), 136.0 (4-C), 140.0 (1′-C), 145.9 (1-C), 198.0 ppm (C═O).

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Abbreviations

DCC: *N*,*N*′-dicyclohexylcarbodiimide
DMAP: *N*,*N*-(dimethylamino)pyridine
DMF: *N*,*N*-dimethylformamide
DB: degree of branching
DP: degree of polymerization
ESEM: environmental scanning electron microscopy
ESI: electron spray ionization
Fmoc: fluorenylmethoxycarbonyl
GABA: γ-aminobutyric acid
MS: mass spectrometry
NMR: nuclear magnetic resonance
PEG: poly(ethylene glycol)
PG: polyglycerol
PS: polystyrene
ROMP: ring-opening metathesis polymerization
TBAF: tetrabutylammoniumfluoride
TBME: *tert*-butyl methyl ether
TEG: tetra(ethylene glycol)
TFA: trifluoroacetic acid
T_g: glass transition temperature
TMS: trimethylsilyl

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