An Enzyme-Labile Safety Catch Linker for Synthesis on a Soluble Polymeric Support

Uwe Grether[a, b] and Herbert Waldmann*[a]

Abstract: The development of new and broadly applicable linker groups which are stable under a variety of reaction conditions and allow release of the desired products from the solid support under very mild conditions is of great interest in organic synthesis and combinatorial chemistry. We describe an enzyme-labile safety-catch linker which releases alcohols and amines through i) enzymatic cleavage of an amino group and ii) subsequent lactam formation. The linker group was investigated on different polymeric supports: TentaGel, PEGA, CPG-beads and the soluble polymer POE-6000. From these linker–polymer conjugates 2-methoxy-5-nitrobenzyl alcohol was released by penicillin G acylase catalysed cleavage of a phenylacetamide and attack of the liberated benzylamine on the neighbouring ester group in *ortho* position. The model study revealed that only in the case of soluble POE-6000 conjugate high yields for the cleavage could be achieved. In the case of the other solid supports the enzyme does not have access to the interior of the polymer matrix. The application of the POE-6000 linker conjugate was investigated for various esters in Pd^0-catalysed Heck-, Suzuki- and Sonogashira reactions as well as in a Mitsunobu reaction and cycloadditions. These studies proved that the linker is stable under a broad variety of reaction conditions and that the enzymatic method allows for release of the desired product alcohols under extremely mild conditions at pH 7 and 37 °C. In addition, the enzymatic reaction proceeds with complete chemoselectivity, that is other esters or amides are not attacked by the biocatalyst. In addition to alcohols amines can also be cleaved by means of the enzyme-initiated two-step process. In these cases the higher stability of amides as compared to esters requires warming to 60 °C to induce cyclization and release of the desired product.

Keywords: combinatorial chemistry · enzyme catalysis · penicillin G acylase · safety-catch linker · solid-phase synthesis

Introduction

Combinatorial chemistry and parallel synthesis of compound libraries on polymeric supports are efficient methods for the generation of new substances with a predetermined profile of properties.[1] Paramount to the success of this approach is the availability of suitable polymers and widely applicable linker groups for the attachment of the desired compounds to the polymeric carrier. Recent research in this field has focussed on and achieved the successful transfer of a steadily growing number of reaction types to synthesis on solid supports, and the demands on the linker groups concerning their stability under different reaction conditions and selective cleavage have risen accordingly. Therefore, new and broadly applicable linkers which are stable under a variety of reaction conditions, but which at the same time allow release of the synthesized products under the mildest conditions possible are of great interest in organic synthesis and combinatorial chemistry.[2] Enzymatic methods may open up advantageous alternatives to classical chemical techniques since enzyme-catalysed transformations often proceed under very mild conditions (pH 5–8, 25–37 °C) and very high chemo-, regio- and stereoselectivity.[3] We now report on the development of a new enzyme-labile safety catch linker for combinatorial chemistry[4] on a soluble polymeric support, allowing for the release of the target compounds in high yields and under neutral conditions.

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Results and Discussion

In the design of the new linker group a biocatalysed transformation was combined with a subsequent intramolecular

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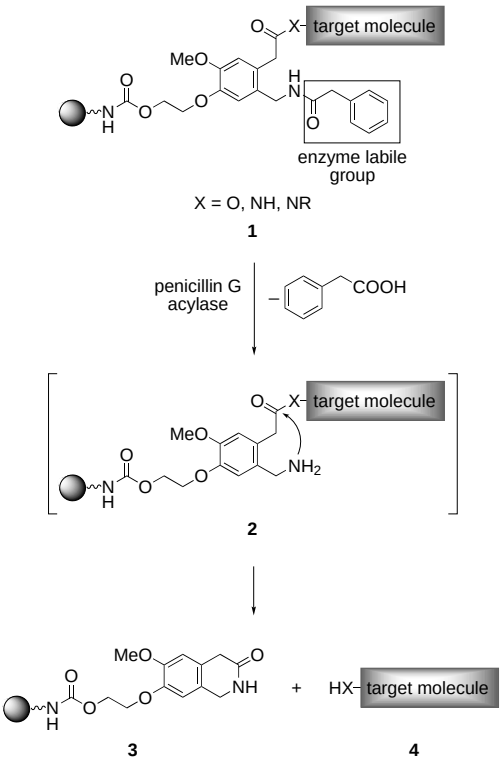
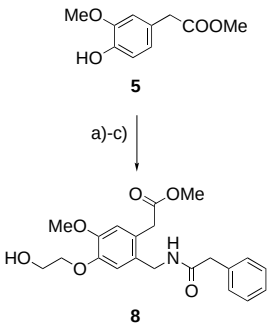
cyclization reaction according to the principle of "assisted removal"[5] of the desired target molecules. To this end the linker embodies a functional group which is recognized and attacked by the biocatalysts. The enzyme liberates an intermediate which cyclizes with release of the target compounds. Furthermore, the linker carries an additional functional group for attachment to the polymeric support. The realization of this principle is shown in Scheme 1. The linker



Scheme 1. Principle of the enzyme-labile safety catch linker.

group is attached as urethane to an amino-functionalized carrier (→**1**). It allows for the attachment of, for example, alkyl halides, alcohols or amines as carboxylic acid esters and amides and their subsequent conversion to product libraries. The enzyme-labile functional group, a phenylacetic acid amide, is remote from the structures to be generated by combinatorial synthesis. Thereby possible steric or electronic interactions of the biocatalyst with the synthesis products which might lead to a reduction of the substrate tolerance of the enzyme are minimized. The release of the target molecules proceeds according to the safety catch principle in an two-step process. In the first step the amidase penicillin G acylase hydrolyses the phenylacetamide with complete chemo- and regioselectivity and under exceptionally mild conditions (pH 7.0, room temperature or 37 °C).[6] Subsequently benzylamine **2** thereby generated as activated intermediate cyclizes to polymer-bound lactam **3** and releases the corresponding target molecule **4**.

The linker was synthesized from commercially available homovanilinic acid methyl ester **5** (Scheme 2). After alkylation of the phenolic hydroxyl group with THP-protected bromoethanol in high yield the resulting trisubstituted aromatic compound **6** was subjected to a completely regioselective electrophilic amidoalkylation with *N*-hydroxymethylphenylacetic acid amide.[7] Under the acidic reaction conditions the THP ether was simultaneously converted into the corresponding acetate **7** which was then saponified. By means of this three-step sequence linker **8** is accessible in an overall yield of 67 %.



Scheme 2. Synthesis of the linker group **8**. a) THP-OCH_2CH_2Br, K_2CO_3, DMF, 90 °C, 10 h, 94 % (→**6**); b) $PhCH_2C(O)NHCH_2OH$, $HOAc/H_2SO_4$ 20:1, 20 °C, 10 h, 83 % (→**7**); c) NaOMe, MeOH, 0 °C, 1 h, 87 %.

Paramount to the successful development of the enzyme-labile linker system is the choice of an appropriate solid support. It has to be compatible with the conditions required for the enzymatic transformation and ideally must give the enzyme access to all functionalized sites. From earlier work on the use of biocatalysts on solid supports[4b, 6d] we were aware of the fact that, in general, polar polymeric supports are preferable (see also [4d]) and that the polymer must swell well under the reaction conditions to allow entry of the biocatalyst into the polymer matrix. For these reasons TentaGel[8] and the PEGA[9] resin were chosen. In addition, controlled pore glass (CPG) beads were investigated because they had already proven to be compatible with the use of the enzyme penicillin acylase,[6d] that is allowing for quantitative removal of phenylacetamido protecting groups from oligonucleotides assembled on CPG beads. In order to quantify the efficiency of the enzymatic transformations an assay was established that is based on the enzyme-initiated release of 2-methoxy-5-nitrobenzyl alcohol from the corresponding polymer-bound esters and its determination by means of UV spectroscopy. This system was established in solution by employing a soluble non-polymer-bound ester analogue as substrate.

The 2-methoxy-5-nitrobenzyl group was coupled to the linker by nucleophilic esterification of carboxylic acid **9** with benzyl bromide **10** (Scheme 3). Subsequent conversion of the primary alcohol present in product **11** with chloroformic acid *p*-nitrophenyl ester **12** or phosgene yielded activated reagents **13** and **14**. Treatment of amino-functionalized PEGA-resin or CPG beads with carbonate **13** resulted in quantitative acylation of the solid support as judged by means of the ninhydrin test (see Experimental Section).

Alternatively, methyl ester **8** was first converted into the corresponding activated carbonate **18** which was used to acylate TentaGel quantitatively (Scheme 4). In this case successful loading of the resin was also confirmed by means of gel phase ^{13}C NMR spectroscopy. Saponification of the methyl ester **19** and subsequent nucleophilic esterification yielded polymer-bound nitrobenzyl ester **21**. By analogy soluble ester **23** was synthesized (Scheme 5). Safety catch protecting group **22** required for this purpose was synthesized by analogy to the synthesis of linker group **8** from homoveratric acid and *N*-hydroxymethyl phenylacetic acid.[10]

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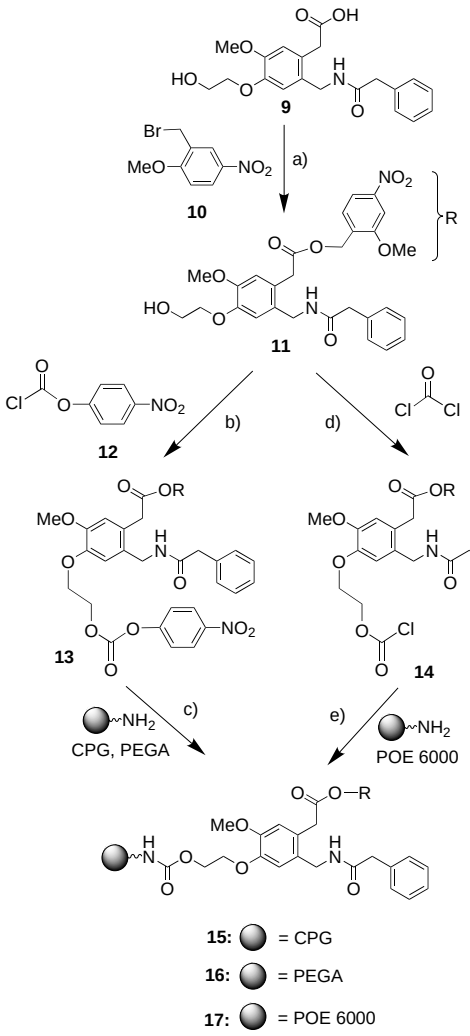
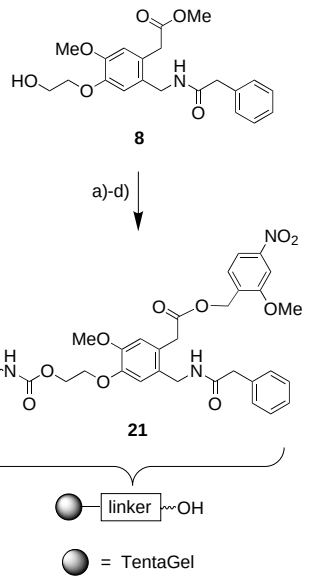
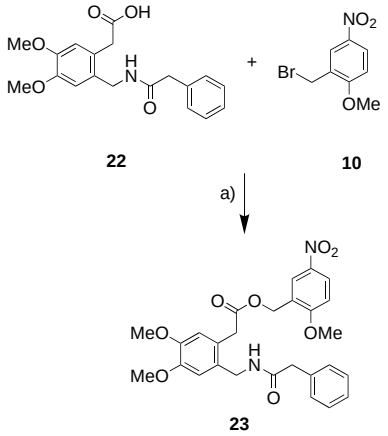


Scheme 3. Synthesis of polymer-bound linker 2-methoxy-5-nitrophenyl esters **15**–**17**. a) **10**, Cs_2CO_3, H_2O/EtOH then DMF, rt, 82%; b) **12**, DMAP, CH_2Cl_2, rt, 61%; c) CPG-NH_2 or PEGA-NH_2, HOBt, EtN(*i*Pr)$_2$, DMF, quant.; d) phosgene, CH_2Cl_2, rt, quant.; e) POE-NH_2, DMAP, HOBt, CH_2Cl_2, rt, 92%. HOBt = 1-hydroxybenzotriazole, DMAP = 4-dimethylaminopyridine.



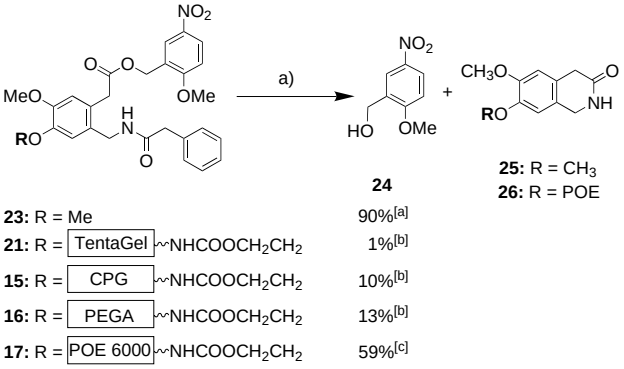
Scheme 4. Synthesis of TentaGel-bound 2-methoxy-5-nitrophenyl ester **21**. a) **12**, DMAP, CH_2Cl_2, 0 °C, 1 h then 20 °C, 24 h, 48% (→**18**); b) TentaGel-NH_2, HOBt, DMF, 20 °C, 10 h, quant. (→ **19**); c) 0.5 M LiOH/CH_3OH 1:1, 20 °C, 2 h, quant. (→ **20**); d) **10**, Cs_2CO_3, DMF, rt, 81%.



Scheme 5. Synthesis of model ester **23**. a) Cs_2CO_3, DMF, rt, 68%.

In order to determine whether penicillin G acylase accepts in principle substrates of type **23** this phenylacetamide was treated with the enzyme at pH 7 in the presence of 20 vol% acetone and dimethyl-β-cyclodextrin as solubilizing agents. After 48 h benzyl alcohol **24** and lactam **25** were obtained in 90% and 86% yield, respectively (Scheme 6). In the absence of the biocatalyst formation of the alcohol could not be detected, that is non-enzymatic hydrolysis does not occur under the reaction conditions employed.

Encouraged by this finding the release of alcohol **24** from resins **15**, **16** and **21** was investigated (Scheme 6). In a series of experiments the pH value (pH 6–8), the reaction temperature (20–37 °C), the reaction time and the cosolvent were varied. The amount of released product **24** was quantified by detecting its absorption at 307 nm (the enzyme does not absorb at this wavelength). For all polymeric supports the highest yields were obtained in the presence of 10 vol% of methanol at pH 7 and 37 °C. However, disappointingly only low yields in the cleavage from the different polymeric



Scheme 6. Enzyme-initiated cleavage of 2-methoxy-5-nitro benzyl alcohol (**24**) from different polymeric supports and in solution; a) penicillin G acylase, conditions; [a] immobilized penicillin G acylase, 20% acetone, dimethyl-β-cyclodextrin, 37 °C; [b] penicillin G acylase suspension, 10% methanol, 37 °C; [c] penicillin G acylase suspension, 10% methanol, 20 °C.

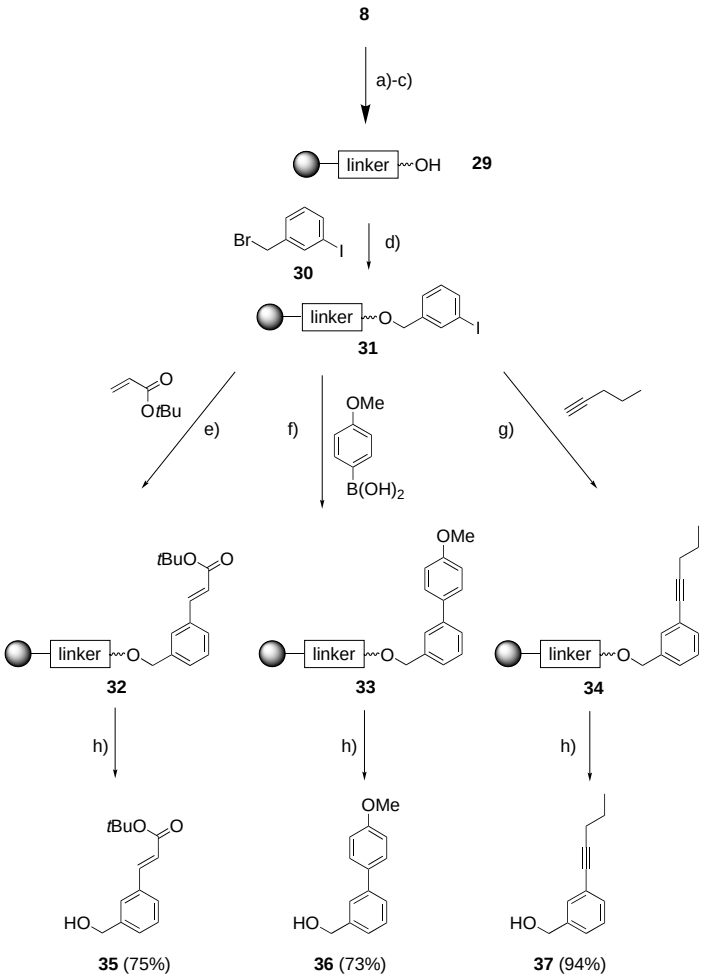
supports were obtained (Scheme 6). From TentaGel **21** only 1% of the calculated amount could be cleaved. Obviously, in this case only the outer surface of the bead is accessible to the biocatalyst. This is in line with observations made by us earlier in the development of a fragmenting enzyme-labile linker.[4b] In this case a small lipase that tolerated high amounts of cosolvent had to be used to obtain preparatively viable results. Penicillin acylase, however, has a molecular weight of about 80 kDa and appears to be too large to penetrate efficiently into the interior of the TentaGel beads. Similar results were obtained by Lebl et al. and Balasubramanian et al.[11] In the case of PEGA and CPG beads significantly higher yields were determined (10–13%), although the results obtained with these commercially available insoluble carriers were still not satisfying. A possible solution to this problem might be to use longer spacers for the functionalization of the CPG beads, or to employ PEGA6000[12] instead of PEGA-1500. This resin incorporates longer polyethyleneglycol building blocks and has larger cavities; however, it is not yet commercially available.

Since the major obstacle for the enzymatic reaction appeared to be the very limited access of the biocatalyst to the surface of the insoluble solid supports we envisaged that the use of a soluble polymer should serve to overcome this problem. Therefore, a soluble polyethyleneglycol functionalized at both termini with an amino group and with an average molecular mass of 6000 Da (POE 6000) was investigated.[13] POE 6000 is soluble in numerous organic solvents but can be precipitated, filtered off, and washed after addition of diethyl ether, thereby facilitating the separation of surplus reagents and the side products. It allows for NMR spectroscopic monitoring of the reactions[14] and, due to its pronounced solubility in water, for biocatalysed transformations it offers the advantage that the substrates are accessible to the biocatalyst in homogeneous phase.

The required functionalized POE 6000 was synthesized by treatment of chloroformic acid ester **14** with the amino-modified polymer as shown in Scheme 3. The resulting polymer–linker conjugate **17** was then subjected to the enzymatic reaction, and the desired benzyl alcohol **24** was obtained in 59% yield after 48 h incubation at pH 7 and 37 °C (Scheme 6). This result encouraged us to investigate the use of the enzyme-labile safety catch linker together with POE 6000 as soluble polymeric support for applications in combinatorial chemistry.

The applicability of the polymer–linker conjugate was investigated for a variety of transformations. First, a simplified and straightforward procedure for the synthesis of the conjugate was established. To this end, linker building block **8** was treated with phosgene to give the chloroformic acid ester **27** in quantitative yield. For the subsequent coupling to the polymer the solvent simply had to be removed, and the polymer was then acylated in quantitative yield. Finally, the methyl ester incorporated into the linker was saponified to give the desired polymer–linker conjugate **29** (Scheme 7).

In a first series of experiments the suitability of the polymer–linker conjugate in Pd^0-catalysed transformation that are widely used in organic synthesis and combinatorial chemistry was investigated. To this end, first the carboxyl group of the linker was esterified with *m*-iodobenzylbromide **30** and the polymer-bound aryl iodide **31** generated was then further transformed in a Heck[15] reaction to a cinnamic acid ester, a Suzuki[16] reaction to a biphenyl and a Sonogashira[17] reaction to give an alkine (Scheme 7). NMR spectroscopic



Scheme 7. Pd^0-catalysed reactions on polymer **31** and enzyme-catalysed release of the coupling products from the polymeric supports. a) phosgene, CH_2Cl_2, rt, quant. (→ **27**); b) POE-NH_2, DMAP, HOBt, CH_2Cl_2, rt, 93% (→ **28**); c) $LiOH \cdot H_2O$/THF 2:1, rt, 99%; d) **30**, Cs_2CO_3, DMF, 50 °C, 24 h, 95%; e) $[Pd(OAc)_2]$, Bu_4NBr, PPh_3 DMF/Et_3N/H_2O 9:1:1, 50 °C, 20 h, 91%; f) $[Pd(PPh_3)_4]$, K_3PO_4, DMF, 80 °C, 20 h, 93%; g) $[Pd(PPh_3)_2Cl_2]$, CuI, dioxane/Et_3N 2:1, 20 °C, 24 h, 97%; h) penicillin G acylase, pH 7.0, 10% MeOH, 37 °C.

analysis revealed that these transformations proceeded quantitatively. Compounds **32**–**34** were then incubated with penicillin G acylase at pH 7 and 37 °C. After 48 h, benzyl alcohols **35**–**37** were isolated in high yields and with a purity of >95% by simple extraction with diethyl ether.

For polymer-bound alkine **34** it was demonstrated that incubation with the enzyme for 24 h instead of 48 h already delivers the desired product in preparatively useful yield of 71%, that is if necessary, the time for the enzymatic reaction can be shortened considerably. In all three cases control experiments without enzyme were carried out which revealed that in the absence of the biocatalyst the linker group is completely stable. To verify that the linker group is cleaved by

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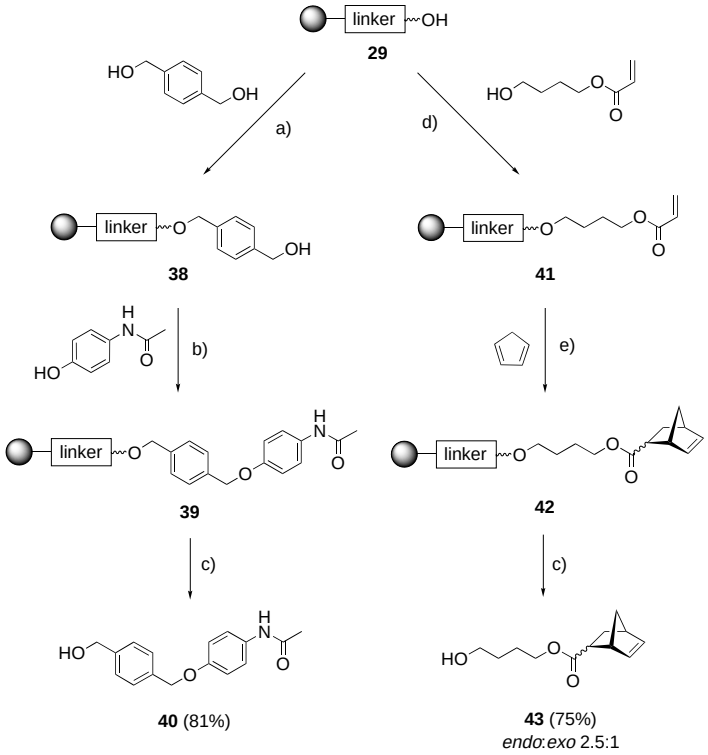
enzyme-initiated lactam formation, polymer-bound lactam **26** (Scheme 6) was isolated in 82% yield after the cleavage of alcohol **35** and characterized spectroscopically (see the Experimental Section).

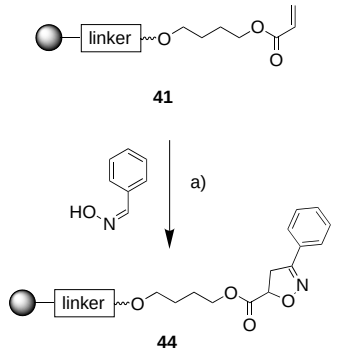
In another series of experiments Mitsunobu esterification and Diels–Alder reactions were investigated (Scheme 8). For the Mitsunobu reaction, the polymer was esterified quantitatively with 1,4-bis(hydroxymethyl)benzene. The obtained



Scheme 8. Mitsunobu- and Diels–Alder reaction on polymeric support and penicillin G acylase mediated cleavage of the target molecules. a) DIC, DMAP, HOBt, DMF, pyridine, 0 °C, 1 h, then 20 °C, 24 h, 92%; b) DEAD, PPh_3, THF/CH_2Cl_2 1:1, −5 °C, 2 h, then 20 °C, 20 h, 86%; c) penicillin G acylase, pH 7.0, 10% MeOH, 37 °C, 48 h; d) DIC, DMAP, HOBt, DMF, pyridine, 0 °C, 1 h, then 20 °C, 24 h, 97%; e) THF, 60 °C, 15 h, 93%.

polymer-bound benzyl alcohol **38** was then treated with 4-acetamidophenol in the presence of the Mitsunobu reagent to give phenyl ether **39** in quantitative yield. By subsequent treatment of polymeric substrate **39** with penicillin G acylase, aryl benzyl ether **40** could be obtained in 81% yield. For the Diels–Alder reaction, 4-hydroxybutyl acrylate was coupled to the linker and the polymer-bound acrylic acid ester **41** was treated with cyclopentadiene. This reaction was carried out at 60 °C at ambient pressure, and at 100 °C in a closed glass vial to investigate the pressure and temperature stability of the polymer-bound linker. According to NMR spectroscopic analysis cycloaddition product **42** was formed with an *endo*/*exo* ratio of 2.5:1[18] and with quantitative conversion. Subsequent enzymatic release delivered alcohol **43** in high yield and purity. The examples shown in Scheme 8 prove quite impressively the chemoselectivity of penicillin G acylase since the enzyme attacks only the phenylacetamide unit and not the ester and amide groups which are also present.

In a second type of cycloaddition polymer-bound acrylic acid ester **41** was subjected to a 1,3-dipolar cycloaddition with phenylnitrile oxide generated in situ from benzaldehyde oxime by treatment with sodium hypochlorite. Cycloadduct **44** was formed quantitatively,[19] which demonstrates that the linker group is stable under oxidative conditions (Scheme 9). After incubation of **44** with penicillin G acylase

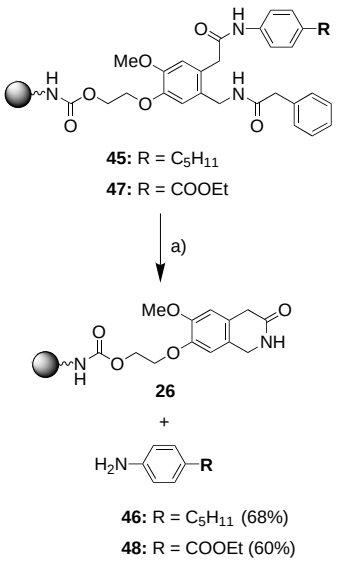


Scheme 9. 1,3-Dipolar cycloaddition to give the isoxazoline **44**. a) 0.7 M NaOCl, THF, 20 °C, 4 h, 94%.

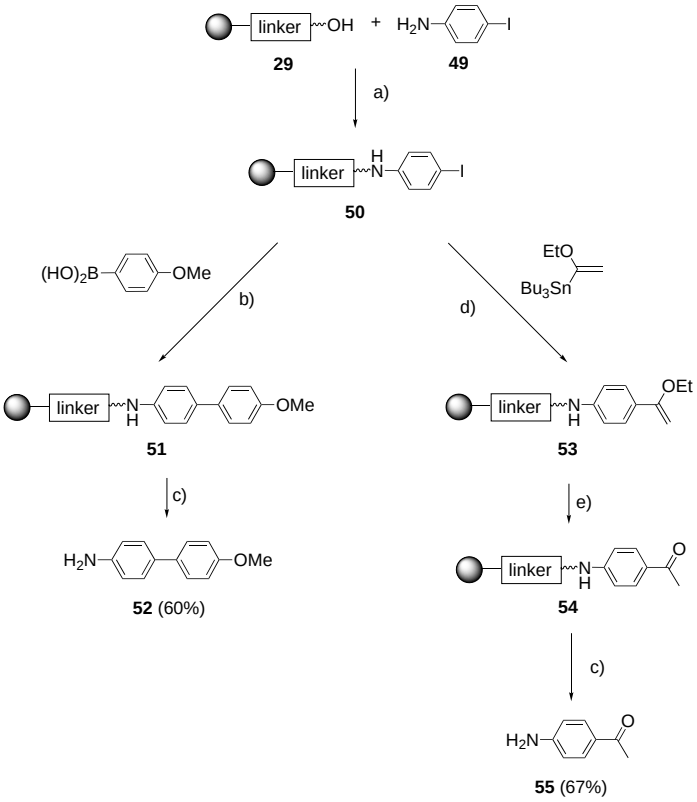
under the conditions detailed above POE-bound lactam **26** was formed quantitatively, however, only traces of the desired isoxazoline were isolated. Synthesis of reference compound in organic solution and subsequent exposure to aqueous methanol showed that the unsaturated heterocycle is not stable under these conditions. Thus, while the enzyme-labile linker group is stable to the conditions required for formation and transformation of nitrile oxides, the cycloadducts have to be converted into more stable compounds before enzyme-initiated release from the solid support is attempted.

In a third series of experiments we investigated whether the enzymatic method also gives access to target molecules that are coupled to the linker as amides. For orientation studies 4-pentylaniline was coupled to the POE-derived carboxylic acid **29** and the resulting polymer **45** was incubated with penicillin G acylase at pH 7 and room temperature. As expected the phenylacetamide group of the linker was hydrolyzed rapidly. However, since amides are considerable more stable than esters the desired cyclization did not occur at room temperature. Upon warming to 60 °C lactam formation proceeded well and 4-pentylaniline **46** was isolated in 68% yield (Scheme 10). Similar results were recorded for an aniline carrying an ester group in the 4-position (see Scheme 10).

With these results in hands 4-iodoaniline **49** was coupled quantitatively to linker **29** and the polymer fixed aryliodide **50** obtained thereby was subjected to a Suzuki reaction[16] with 4-methoxyphenylboronic acid leading to biphenyl derivative **51** or a Stille reaction[20] to give enol ether **53** (Scheme 11). Upon treatment with 0.5 M hydrochloric acid, enol ether **53** yielded acetophenone **54**, thereby proving the acid stability of the linker. In order to release the coupling products, polymers **51** and **54** were incubated with penicillin G acylase at pH 7.0 and room temperature. As expected under these conditions the phenylacetamide was hydrolyzed. Upon warming of the reaction mixture to 60 °C, the expected lactam was formed and amines **52** and **55** were released from the polymer.



Scheme 10. Enzyme-catalysed release of model anilines from POE 6000. a) Penicillin G acylase, pH 7.0, 10% MeOH, 20 °C, 48 h, then 60 °C, 4 h.



Scheme 11. Pd^0-catalysed synthesis and enzyme-initiated cleavage of the anilines **52** and **55** from POE 6000. a) EDC, HOBt, DMF, ca. 20 °C, 12 h, 97%; b) $[Pd(PPh_3)_4]$, K_3PO_4, DMF/H_2O 10:1, 80 °C, 20 h, 95%; c) penicillin G acylase, pH 7.0, 10% MeOH, 20 °C, 48 h, then 60 °C, 4 h; d) $[Pd_2dba_3]$, $AsPh_3$, dioxane 60 °C, 24 h, 81%; e) 0.5 M HCl/THF 1:1, 20 °C, 4 h, 92%.

Conclusion

We have developed a new enzyme-labile safety catch linker that allows for the synthesis of different classes of compounds and the application of various reaction types. The release of the products proceeds under particularly mild conditions with pronounced selectivity and delivers the desired products in high yield and purity. The linker is stable under different conditions, even at elevated temperature. Beyond the devolopment of a new linker system for combinatorial chemistry our results prove that enzymes, in general, are valuable reagents for transformations on soluble polymeric supports.

Experimental Section

General: Melting points were determined in open capillaries using a Büchi 535 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AC 250, AM 400 or DRX 500 spectrometers at room temperature. The ^1H and ^{13}C NMR signals of the POE 6000 linker conjugate **29** always appeared around the same chemical shift (±0.2 ppm). Therefore, these signals were not mentioned in further transformations of the POE 6000 linker conjugate **29**. IR spectra were recorded on a Bruker IFS 88 spectrometer, UV/Vis spectra on a Perkin–Elmer Lambda 2 UV/Vis spectrometer. Mass spectra and high-resolution mass spectra (HRMS) were measured on a Finnigan MAT MS70 spectrometer. Elemental analyses were performed on a Heraeus CHN-Rapid apparatus.

Materials: Solvents were dried by standard methods and stored over molecular sieves. For column chromatography silica gel (40–60 μm, Baker) was used. Size-exclusion chromatography was done on Sephadex LH 20 (Pharmacia LKB Biotechnology). Commercially available reagents were used without further purification. All reactions except for those carried out with water were performed under argon. Penicillin G acylase (EC 3.5.1.11) was used as a suspension in phosphate buffer (Fluka) and immobilized on Eupergit C (Boehringer Mannheim). Amino-functionalized TentaGel and polyoxyethylene POE 6000 were obtained from Rapp Polymere, Tübingen, Germany, PEGA (crosslinked 2-acrylamidoprop-1-yl[2-aminopropy-1-yl]-polyethylene glycol) was acquired from Novabiochem and CPG with an average pore diameter of 500 Å from Fluka. Bisamino-functionalized POE 6000 has an average molecular weight of 6000 g mol^{-1}. Average molecular masses from compounds bound to this support are calculated on the basis of the average molecular weight of POE 6000.

Methyl {3-methoxy-4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethoxy]phenyl}-acetate (6): THP-protected bromoethanol[21] 14.8 g, 71 mol) was added to a suspension of homovanillic acid methyl ester (**5**, 10.8 g, 55 mol) and potassium carbonate (9.8 g, 71 mol) in DMF (120 mL). After stirring for 16 h at 90 °C the solvent was evaporated in vacuo. The residue was redissolved in ethyl acetate (150 mL) and washed with water (2 × 80 mL). The organic layer was dried over $MgSO_4$, the solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:10 to 1:1 *v*/*v*) to yield a colourless oil (16.6 g, 51 mol, 94%). $R_f = 0.67$ (ethyl acetate/hexane 1:1 *v*/*v*); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 6.89$ (d, $^3J(H,H) = 8.1$ Hz, 1H; arom. CH-5), 6.82–6.78 (m, 2H; arom. CH-2/6), 4.70 (t, $^3J(H,H) = 3.6$ Hz, 1H; CH), 4.20 (t, $^3J(H,H) = 4.9$ Hz, 2H; $COCH_2$), 4.07–4.03 (m, 1H; $CHOCH_{2ax}$), 3.90–3.82 (m, 2H; $COCH_2CH_2$), 3.85 (s, 3H; OCH_3), 3.69 (s, 3H; $COOCH_3$), 3.55 (s, 2H; $CH_2C(O)O$), 3.53–3.49 (m, 1H; $CHOCH_{2eq}$), 1.87–1.50 (m, 6H; $CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 172.22$ (C=O), 149.64 ($COCH_3$), 147.61 ($COCH_2$), 127.03 (CCH_2), 121.45 (arom. CH-6), 114.09 (arom. CH-5), 113.11 (arom. CH-2), 98.95 (CH), 68.64 ($COCH_2$), 65.74 ($COCH_2CH_2$), 62.09 ($CHOCH_2$), 55.97 (OCH_3), 52.01 ($COOCH_3$), 40.73 (CCH_2), 30.49 ($CHCH_2$), 25.44 ($CHCH_2CH_2$), 19.34 ($CHCH_2CH_2CH_2$); IR (KBr, drift): $\tilde{\nu} = 1739$ (C=O, ester), 1143 (C–O), 1036 cm^{-1} (C–O); MS (EI, 70 eV, 50 °C): *m*/*z* (%): 324 (65) $[M]^+$, 196 (41), 129 (100); HRMS (70 eV): calcd for $C_{17}H_{24}O_6$: 324.1573, found: 324.1584.]

Methyl (4-[2-(acetyloxy)ethoxy]-5-methoxy-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (7): A precooled solution (0 °C) of acetic acid (100 mL) and concentrated sulfuric acid (5 mL) was added to a mixture of *N*-hydroxymethyl-2-phenylacetamide[22] (8.1 g, 49 mol) and homovanillic acid derivative **6** (16.6 g, 51 mol). The solution was stirred for 2 h at 0 °C and for 12 h at room temperature. Then the reaction mixture was poured into ice water (200 mL), neutralized with 1 M aqueous NaOH at 0 °C and extracted with ethyl acetate (5 × 250 mL). The combined organic layers were dried over $MgSO_4$ and after evaporation of the solvent in vacuo the product was

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purified by chromatography on silica gel (ethyl acetate/hexane 2:1 *v*/*v*) to yield a white solid (17.5 g, 41 mol, 83 %). $R_f = 0.51$ (ethyl acetate+1 % acetic acid); m.p. 118–119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.34–7.24$ (m, 5H; arom. CH), 6.81 (s, 1H; arom CH-6), 6.69 (s, 1H; arom. CH-3), 6.24 (br s, 1H; NH), 4.40 (t, $^3J(H,H) = 4.8$ Hz, 2H; $COCH_2$), 4.34 (d, $^3J(H,H) = 5.6$ Hz, 2H; CH_2NH), 4.14 (t, $^3J(H,H) = 4.8$ Hz, 2H; $COCH_2CH_2$), 3.83 (s, 3H; OCH_3), 3.64 (s, 3H; $COOCH_3$), 3.59 (s, 2H; $PhCH_2$), 3.55 (s, 2H; $CH_2C(O)O$), 2.09 (s, 3H; $CH_3C(O)$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 172.55$ (C=O), 170.97 (C=O), 170.58 (C=O), 149.03 ($COCH_2$), 147.27 ($COCH_3$), 134.99 ($CCH_2C(O)NH$), 129.31 (2C; arom. CH), 128.83 (2C; arom. CH), 127.13 (2C; arom. CH, $CCH_2C(O)O$), 125.65 (CCH_2NH), 115.61 (arom. CH-3), 114.25 (arom. CH-6), 67.15 ($COCH_2$), 62.69 ($COCH_2CH_2$), 56.03 (OCH_3), 52.28 ($COOCH_3$), 43.81 ($PhCH_2$), 41.14 ($CH_2C(O)O$), 37.89 (CH_2NH), 20.91 ($CH_3C(O)$); MS (EI, 70 eV, 145 °C): *m*/*z* (%): 429 (15) $[M]^+$, 208 (10), 87 (100); HRMS (70 eV): calcd for $C_{23}H_{27}NO_7$: 429.1787, found: 429.1775; elemental analysis calcd (%) for: C 64.31, H 6.35, N 3.26; found: C 64.34, H 6.49, N 3.24.

Methyl (4-(2-hydroxyethoxy)-5-methoxy-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (8): A 30 % sodium methanolate solution in methanol (10.7 mL, 58.5 mol) was added at 0 °C dropwise to a solution of acetate **7** (2.5 g, 5.9 mol) in methanol (110 mL). After stirring for 1 h at 0 °C, the pH of the solution was adjusted to pH 6 with hydrochloric acid. Methanol was removed under reduced pressure and the remaining solution was extracted with ethyl acetate (5 × 100 mL). The combined organic layers were dried over $MgSO_4$. Evaporation of the solvent in vacuo yielded a white solid, which was used without further purification (1.97 g, 5.1 mol, 87 %). $R_f =$ 0.21 (ethyl acetate+0.5 % acetic acid); m.p. 107 °C; ^{1}H NMR (CD_3OD, 400 MHz): $\delta = 7.29–7.19$ (m, 5H; arom. CH), 6.81 (s, 1H; arom. CH-6), 6.76 (s, 1H; arom. CH-3), 4.29 (s, 2H; CH_2NH), 3.85–3.79 (m, 4H; CH_2CH_2OH), 3.78 (s, 3H; OCH_3), 3.64 (s, 2H; $PhCH_2$), 3.63 (s, 3H; $COOCH_3$), 3.49 (s, 2H; $CH_2C(O)O$); ^{13}C NMR (CD_3OD, 100.6 MHz): $\delta =$ 173.93 (C=O), 173.60 (C=O), 149.68 ($COCH_2$), 148.75 ($COCH_3$), 136.96 ($CCH_2C(O)NH$), 130.77 ($CCH_2C(O)O$), 130.07 (2C; arom. CH), 129.59 (2C; arom. CH), 127.90 (arom. CH), 126.57 (CCH_2NH), 115.75 (arom. CH-3), 115.15 (arom. CH-6), 71.64 ($COCH_2$), 61.59 (CH_2OH), 56.56 (OCH_3), 52.54 ($COOCH_3$), 43.93 ($PhCH_2$), 41.57 ($CH_2C(O)O$), 38.29 (CH_2NH); IR (KBr, drift): $\tilde{\nu} = 3524$ (O–H), 3291 (N–H), 1731 (C=O, ester), 1640 (C=O, amide I), 1522 (C=O, amide II), 1101 cm^{-1} (C–O); MS (EI, 70 eV, 160 °C): *m*/*z* (%): 387 (0.2) $[M]^+$, 237 (22), 163 (100); HRMS (70 eV): calcd for $C_{21}H_{25}NO_6$: 387.1682, found: 387.1700.

Synthesis of CPG- and PEGA-bound 2-methoxy-5-nitrobenzyl esters 15 and 16

2-Methoxy-5-nitrobenzyl (4-(2-hydroxyethoxy)-5-methoxy-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (11): A solution of cesium carbonate (83 mg, 0.26 mol) in water (10 mL) was added to a solution of acid **9** (191 mg, 0.51 mol) in ethanol (30 mL) and water (5 mL). After evaporation of the solvent under reduced pressure the residue was dried in vacuo. Then 2-methoxy-5-nitrobenzyl bromide (**10**, 138 mg, 0.56 mol) was added and the mixture was dissolved in precooled DMF (0 °C, 25 mL). The solution was stirred 1 h at 0 °C and for another 12 h at room temperature. After evaporation of the solvent the residue was dissolved in ethyl acetate (30 mL) and the solution was extracted with water (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Chromatography on silica gel (ethyl acetate/hexane 1:10 to ethyl acetate *v*/*v*) yielded a white solid (226 mg, 0.42 mol, 82 %). $R_f = 0.27$ (ethyl acetate+0.5 % acetic acid); m.p. 108–109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.19$ (dd, $^3J(H,H) = 9.0$ Hz, $^4J(H,H) = 2.7$ Hz, 1H; arom. CH), 8.08 (d, $^4J(H,H) = 2.5$ Hz, 1H; arom. CH), 7.30–7.20 (m, 5H; arom. CH), 6.93 (d, $^3J(H,H) = 9.1$ Hz, 1H; arom. CH), 6.81 (s, 1H; arom. CH-6), 6.72 (s, 1H; arom. CH-3), 6.43 (t, $^3J(H,H) = 4.9$ Hz, 1H; NH), 5.13 (s, 2H; $CH_2OC(O)$), 4.36 (d, $^3J(H,H) = 5.6$ Hz, 2H; CH_2NH), 4.00 (t, $^3J(H,H) =$ 4.5 Hz, 2H; $COCH_2$), 3.91 (s, 3H; OCH_3), 3.88 (t, $^3J(H,H) = 4.5$ Hz, 2H; CH_2OH), 3.78 (s, 3H; OCH_3), 3.70 (s, 2H; $PhCH_2$), 3.52 (s, 2H; $CH_2C(O)O$), 3.20 (br s, 1H; OH); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta =$ 171.62 (C=O), 170.78 (C=O), 161.80 (CNO_2), 148.95 ($COCH_2$), 147.51 ($COCH_3$), 141.14 ($COCH_3$), 135.03 ($CCH_2C(O)NH$), 129.39 (CCH_2O), 129.26 (2C; arom. CH), 128.77 (2C; arom. CH), 127.07 (arom. CH), 125.71 (arom. CH), 125.27 ($CCH_2C(O)O$), 125.17 (CCH_2NH), 124.10 (arom. CH), 115.59 (arom. CH), 113.92 (arom. CH-3), 110.09 (arom. CH-6), 70.98 ($COCH_2$), 61.17 (CCH_2O), 61.05 (CH_2OH), 56.28 (OCH_3), 55.90 (OCH_3), 43.67 ($CH_2C(O)O$), 41.02 ($PhCH_2$), 38.04 (CH_2NH); IR (KBr, drift): $\tilde{\nu} =$ 3594 (O–H), 1737 (C=O, ester), 1645 (C=O, amide I), 1522 (C=O, amide II; N=O), 1344 (N=O), 1028 cm^{-1} (C–O); MS (EI, 70 eV, 205 °C): *m*/*z* (%): 538 (0.02) $[M]^+$, 355 (51), 237 (79), 183 (100); HRMS (70 eV): calcd for $C_{28}H_{30}N_2O_9$: 538.1951, found: 538.1933; elemental analysis calcd (%) for: C 62.45, H 5.61, N 5.20; found: C 62.36, H 5.69, N 4.98.

2-Methoxy-5-nitrobenzyl (5-methoxy-4-(2-{[(4-nitrophenoxy)carbonyl]oxy}ethoxy)-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (13): Precooled CH_2Cl_2 (0 °C, 20 mL) was added to a mixture of acetate **11** (518 mg, 0.96 mol), DMAP (123 mg, 1 mol), chloroformic acid-4-nitrophenyl ester **12** (203 mg, 1 mol) and 4 Å molecular sieves. The reaction mixture was stirred for 2 h at 0 °C and at room temperature overnight. Then the molecular sieves were filtered off, the solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:1 to 2:1 *v*/*v*) to yield a colourless oil (414 mg, 0.59 mol, 61 %). $R_f =$ 0.50 (ethyl acetate/hexane 2:1 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 8.28$ (d, $^3J(H,H) = 9.0$ Hz, 2H; arom. CH), 8.23 (dd, $^3J(H,H) = 8.9$ Hz, $^4J(H,H) = 2.8$ Hz, 1H; arom. CH), 8.08 (d, $^4J(H,H) = 2.8$ Hz, 1H; arom. CH), 7.51 (d, $^3J(H,H) = 9.0$ Hz, 2H; arom. CH), 7.32–7.21 (m, 5H; arom. CH), 6.95 (d, $^3J(H,H) = 8.9$ Hz, 1H; arom. CH), 6.87 (s, 1H; arom. CH-6), 6.76 (s, 1H; arom. CH-3), 6.22 (br s, 1H; NH), 5.14 (s, 2H; CCH_2O), 4.63 (t, $^3J(H,H) = 4.7$ Hz, 2H; $COCH_2$), 4.40 (d, $^3J(H,H) = 5.6$ Hz, 2H; CH_2NH), 4.24 (t, $^3J(H,H) = 4.7$ Hz, 2H; $COCH_2CH_2$), 3.92 (s, 3H; OCH_3), 3.83 (s, 3H; OCH_3), 3.72 (s, 2H; $PhCH_2$), 3.54 (s, 2H; $CH_2C(O)O$).

General procedure for the synthesis of polymer-bound 2-methoxy-5-nitrobenzyl esters: Amino-functionalized polymer (47 μmol) was washed with DMF (5 × 8 mL) to remove water. Then acetate (**13**, 100 mg, 0.14 mol), HOBt (38 mg, 0.28 mol) and 4 Å molecular sieves were added and the mixture was suspended in ice-cold DMF (10 mL). After 30 min *N*,*N*-diisopropylethylamine (12 μL, 70 μmol) was added and the reaction mixture was shaken 1 h at 0 °C and 48 h at room temperature afterwards. The polymer was filtered off and washed with DMF, methanol, ethyl acetate and CH_2Cl_2 (3 × 8 mL each).

General method to determine the loading of the polymer with 2-methoxy-5-nitrobenzyl alcohol (24): A defined amount of polymer-bound 2-methoxy-5-nitrobenzyl ester was suspended in 0.5 % NaOH/THF 1:1 (5 mL) and shaken for 24 h at room temperature. The polymer was filtered off and washed with water and THF (3 × each). The filtrate was adjusted to pH 7 with diluted hydrochloric acid and the solvent evaporated in vacuo. The residue was redissolved in methanol (10 mL) and the cleaved amount of 2-methoxy-5-nitrobenzyl alcohol (**24**) was determined through UV spectroscopy with a calibration curve (detection at 307 nm).

General procedure to determine the loading of the polymer by qualitative ninhydrin test:[23] The polymer (20 mg) was suspended in 1 % aqueous ninhydrin solution and heated for 5 min to 100 °C. If the colour of the polymer turns blue, the loading was not quantitative. If the polymer keeps its colour the reaction was quantitative.

CPG-bound 2-methoxy-5-nitrobenzyl ester 15: According to the general procedure for the synthesis of polymer-bound 2-methoxy-5-nitrobenzyl esters amino-functionalized CPG (677 mg, 47 μmol, loading 70 μmol per g), acetate **13** (100 mg, 0.14 mol), HOBt (38 mg, 0.28 0.28 mol) and *N*,*N*-diisopropylethylamine (12 μL, 70 μmol) were stirred in DMF (10 mL). After washing the polymer was dried in vacuo. Ninhydrin test: quantitative reaction.

PEGA-bound 2-methoxy-5-nitrobenzyl ester 16: According to the general procedure for the synthesis of polymer-bound 2-methoxy-5-nitrobenzyl esters amino-functionalized PEGA (878 mg, 47 μmol, loading 0.4 mol per g), acetate **13** (100 mg, 0.14 mol), HOBt (38 mg, 0.28 mol) and *N*,*N*-diisopropylethylamine (12 μL, 70 μmol) were stirred in DMF (10 mL). After washing the polymer was dried in vacuo. Ninhydrintest: quantitative reaction; IR (PEGA, KBr, drift): $\tilde{\nu} = 1719$ (C=O, ester, urethane), 1645 (C=O, amide I), 1521 cm^{-1} (C=O, amide II).

Methyl (5-methoxy-4-(2-{[(4-nitrophenoxy)carbonyl]oxy}ethoxy)-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (18): Precooled CH_2Cl_2 (0 °C, 15 mL) was added to a mixture of alcohol **8** (400 mg, 1.0 mol), DMAP (126 mg, 1.0 mol), chloroformic acid-4-nitrophenyl ester (**12**, 208 mg, 1.0 mol) and 4 Å molecular sieves. The reaction mixture was stirred for 2 h at 0 °C and then at room temperature overnight. The molecular sieves were filtered off, the solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:1 *v*/*v*, $R_f = 0.14$) to yield a colourless oil (276 mg, 0.5 mol, 48 %).

^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.28$ (d, ^3J(H,H) = 9.2 Hz, 2H; arom. CH), 7.41 (d, ^3J(H,H) = 9.2 Hz, 2H; arom. CH), 7.34–7.25 (m, 5H; arom. CH), 6.85 (s, 1H; arom. CH-6), 6.71 (s, 1H; arom. CH-3), 6.27 (br s, 1H; NH), 4.62 (t, ^3J(H,H) = 4.5 Hz, 2H; $COCH_2$), 4.35 (d, ^3J(H,H) = 5.6 Hz, 2H; CH_2NH), 4.24 (t, ^3J(H,H) = 4.7 Hz, 2H; $COCH_2CH_2$), 3.85 (s, 3H; OCH_3), 3.65 (s, 3H; $COOCH_3$), 3.60 (s, 2H; $PhCH_2$), 3.55 (s, 2H; $CH_2C(O)O$); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 172.57$ (C=O), 170.73 (C=O), 155.47 (*C*OC(O)), 152.43 (C=O carbonate), 149.09 (*C*OCH_2), 147.03 (*C*OCH_3), 145.42 (CNO_2), 134.92 (*C*$CH_2C(O)NH$), 129.43 (*C*$CH_2C(O)O$), 129.33 (2C; arom. CH), 128.85 (2C; arom. CH), 127.16 (arom. CH), 126.00 (*C*CH_2NH), 125.31 (2C; arom. CH), 121.80 (2C; arom. CH), 115.87 (arom. CH-6), 114.33 (arom. CH-3), 67.25 (CO*C*H_2), 66.74 ($COCH_2$*C*H_2), 56.05 (OCH_3), 52.34 (COO*C*H_3), 43.82 ($PhCH_2$), 41.10 (*C*$H_2C(O)O$), 37.95 (CH_2NH); IR (KBr, drift): $\tilde{\nu} = 3291$ (N–H), 1764 (C=O, carbonate), 1733 (C=O, ester), 1641 (C=O, amide I), 1521 (C=O, amide II; N=O), 1348 cm^{-1} (N=O); MS (EI, 70 eV, 190 °C): *m*/*z* (%): 552 (0.4) $[M]^+$, 210 (40), 139 (63), 91 (100); HRMS (70 eV): calcd for $C_{28}H_{28}N_2O_{10}$: 552.1744; found: 552.1758.

TentaGel-bound methyl ester 19: Amino-functionalized TentaGel (500 mg, 0.15 mol, loading 0.29 mmol per g) was washed with CH_2Cl_2 (3 × 30 mL) to remove water. Then the polymer was swollen in CH_2Cl_2 (20 mL). After 20 min HOBt (118 mg, 0.15 mol), *N*,*N*-diisopropylethylamine (49 μL, 0.29 mol) and carbonate **18** (160 mg, 0.29 mol) were added and the suspension was shaken for 24 h at room temperature. The polymer was filtered off and washed with CH_2Cl_2, ethyl acetate, methanol, DMF, methanol, ethyl acetate and CH_2Cl_2 (3 × 15 mL each) and dried in vacuo. Ninhydrin test: quantitative reaction. Gel-phase ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 172.49$ (C=O), 170.79 (C=O), 156.46 (C=O urethane), 148.85 (*C*OCH_2), 147.40 (*C*OCH_3), 135.31 (*C*$CH_2C(O)NH$), 129.54 (*C*$CH_2C(O)O$), 129.37 (2C; arom. CH), 128.80 (2C; arom. CH), 127.08 (arom. CH), 125.43 (*C*CH_2NH), 115.55 (arom. CH-3), 114.21 (arom. CH-6), 70.6–70.0 (CH_2 polymer), 67.81 ($COCH_2$*C*H_2), 63.32 (CO*C*H_2), 56.07 (OCH_3), 52.27 (COO*C*H_3), 43.71 ($PhCH_2$), 40.99 (*C*$H_2C(O)O$), 40.87 ($NHCH_2$ polymer), 37.90 (CH_2NH); IR (KBr, drift): $\tilde{\nu} = 1719$ (C=O, ester, urethane), 1669 (C=O, amide I), 1521 cm^{-1} (C=O, amide II).

TentaGel-bound carboxylic acid 20: Polymer-bound methyl ester **19** (100 mg, ca. 30 μmol) was suspended in 0.25 M LiOH/ethanol 1:1 (4 mL) and shaken at room temperature for 4 h. The resin was filtered off and washed with water/acetic acid 5:1, methanol, ethyl acetate and CH_2Cl_2 (3 × 5 mL each) and dried in vacuo. IR (KBr, drift): $\tilde{\nu} = 1717$ (C=O, carboxylic acid, urethane), 1669 (C=O, amide I), 1521 cm^{-1} (C=O, amide II).

TentaGel-bound 2-methoxy-5-nitrobenzyl ester 21: A mixture of TentaGel-bound acid **20** (100 mg, 29 μmol), 2-methoxy-5-nitrobenzyl bromide (**10**, 71 mg, 290 μmol), cesium carbonate (47 mg, 145 μmol) and 4 Å molecular sieves were suspended in DMF (8 mL). The suspension was shaken 1 h at 0 °C and another 44 h at room temperature. Then the polymer was filtered off and washed with DMF, water, methanol, ethyl acetate and CH_2Cl_2 (3 × 8 mL each) and dried in vacuo. Loading: 81 % (see general description to determine the loading of the polymer with 2-methoxy-5-nitrobenzyl alcohol); IR (KBr, drift): $\tilde{\nu} = 1720$ (C=O, ester, urethane), 1668 (C=O, amide I), 1519 cm^{-1} (C=O, amide II).

2-Methoxy-5-nitrobenzyl (4,5-dimethoxy-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (23): Cesium carbonate (237 mg, 0.73 mol) was added to a solution of acetic acid **22** (500 mg, 1.5 mol) in ethanol (60 mL) and water (20 mL). After evaporation of the solvent under reduced pressure the residue was dried in vacuo. Then 2-methoxy-5-nitrobenzyl bromide (**10**, 394 mg, 1.6 mol) and 4 Å molecular sieves were added and the mixture was dissolved in precooled DMF (0 °C, 50 mL). The solution was stirred 2 h at 0 °C and for another 12 h at room temperature. After evaporation of the solvent the residue was dissolved in ethyl acetate (100 mL) and washed with water (50 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Chromatography on silica gel (ethyl acetate/hexane 1:1 *v*/*v*) yielded a colourless oil (504 mg, 1.0 mmol, 68 %). $R_f = 0.27$ (ethyl acetate/hexane 2:1 *v*/*v*+0.5 % acetic acid); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 8.23$ (dd, ^3J(H,H) = 9.0 Hz, ^4J(H,H) = 2.8 Hz, 1H; arom. CH), 8.12 (d, ^4J(H,H) = 2.8 Hz, 1H; arom. CH), 7.32–7.22 (m, 5H; arom. CH), 6.94 (d, ^3J(H,H) = 9.1 Hz, 1H; arom. CH), 6.78 (s, 1H; arom. CH-6), 6.71 (s, 1H; arom. CH-3), 6.18 (br s, 1H; NH), 5.14 (s, 2H; OCH_2), 4.40 (d, ^3J(H,H) = 5.6 Hz, 2H; CH_2NH), 3.92 (s, 3H; OCH_3), 3.83 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 3.70 (s, 2H; $PhCH_2$), 3.54 (s, 2H; $CH_2C(O)O$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.76$ (C=O), 170.60 (C=O), 161.78 (*C*OCH_3), 148.50 (*C*OCH_3), 148.42 (*C*OCH_3), 141.23 (CNO_2), 134.98 (*C*$CH_2C(O)NH$), 129.32 (2C; arom. CH), 129.19 (*C*CH_2O), 128.84 (2C; arom. CH), 127.14 (2C; arom. CH, *C*CH_2NH), 125.75 (arom. CH), 125.29 (*C*$CH_2C(O)O$), 124.25 (arom. CH), 113.46 (arom. CH), 112.82 (arom. CH-3), 110.04 (arom. CH-6), 61.24 (OCH_2), 56.25 (OCH_3), 55.96 (OCH_3), 55.93 (OCH_3), 43.85 (*C*$H_2C(O)O$), 41.25 ($PhCH_2$), 38.10 (CH_2NH); IR (KBr, drift): $\tilde{\nu} = 1721$ (C=O, ester), 1645 (C=O, amide I), 1522 (C=O, amide II; N=O), 1346 (N=O), 1100 cm^{-1} (C–O); UV/Vis (MeOH): λ_{max} (ε) = 193 (68400), 204 (64300), 287 (10000), 306 nm (9600 mol^{-1} dm^3 cm^{-1}); MS (EI, 70 eV, 175 °C): *m*/*z* (%): 508 (6) $[M]^+$, 399 (36), 224 (31), 207 (100); HRMS (70 eV): calcd for $C_{27}H_{28}N_2O_8$: 508.1846, found: 508.1828; elemental analysis calcd (%) for: C 63.76, H 5.55, N 5.51; found: C 63.77, H 5.35, N 5.79.

Enzyme-initiated release of 2-methoxy-5-nitrobenzyl alcohol (24) in the solution phase: 2-Methoxy-5-nitrobenzyl ester (**23**, 50 mg, 0.1 mol) and 2,6-di-*O*-methyl-β-cyclodextrin (1.96 g, 1.47 mol) were dissolved in acetone (20 mL). Then sodium phosphate buffer (0.05 M, pH 7.0, 80 mL) was added under ultrasonication and the suspension was incubated with immobilized penicillin G acylase (100 U) at 37 °C. After 12 h and 24 h the same amount of penicillin G acylase was added again and after 48 h the biocatalyst was filtered off and washed with buffer solution (pH 7.0, 5 × 5 mL) and acetone (5 × 10 mL). Then the solvent was evaporated in vacuo and benzyltriethylammonium chloride (448 mg, 1.97 mol) was added. The mixture was redissolved in water (70 mL) and extracted with ethyl acetate (5 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:4 to ethyl acetate *v*/*v*). **24**: White solid (16 mg, 90 μmol, 90 %); $R_f = 0.45$ (ethyl acetate/hexane 1:2 *v*/*v*); m.p. 123 °C, ref.[24]:123–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.26$ (d, ^4J(H,H) = 2.8 Hz, 1H; arom. CH-6), 8.19 (dd, ^3J(H,H) = 9.0 Hz, ^4J(H,H) = 2.8 Hz, 1H; arom. CH-4), 6.93 (d, ^3J(H,H) = 9.0 Hz, 1H; arom. CH-3), 4.73 (d, ^3J(OH,CH_2) = 4.1 Hz, 2H; CH_2), 3.97 (s, 3H; OCH_3), 2.31 (br s, 1H; OH); UV/Vis (MeOH): λ_{max} (ε) = 193 (16100), 228 (9900), 307 nm (10200 mol^{-1} dm^3 cm^{-1}); HRMS (70 eV): calcd for $C_8H_9NO_4$: 183.0531, found: 183.0518; the spectroscopic data are in agreement with the literature.[24]

6,7-Dimethoxy-1,4-dihydro-2*H*-isoquinoline-3-one (25):[10] Colourless oil (18 mg, 84 μmol, 86 %); $R_f = 0.09$ (ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.60$ (br s, 1H; NH), 6.64 (s, 1H; arom. CH), 6.63 (s, 1H; arom. CH), 4.46 (d, ^3J(H,H) = 1.6 Hz, 2H; *C*H_2NH), 3.88 (s, 3H; OCH_3), 3.87 (s, 3H; OCH_3), 3.52 (s, 2H; $CH_2C(O)$); HRMS (70 eV): calcd for $C_{11}H_{13}NO_3$: 207.0895, found: 207.0883; the spectroscopic data are in agreement with the literature.[10]

General procedure for the enzyme-initiated cleavage of 2-methoxy-5-nitrobenzyl alcohol (24) from the solid phase: A defined amount of polymer-bound 2-methoxy-5-nitrobenzyl ester was suspended in aqueous sodium phosphate buffer (0.05 M, pH 7.0) and cosolvent. After 30 min a suspension of penicillin G acylase (70 mg mL^{-1}, 560 U mL^{-1}) in aqueous potassium phosphate buffer (0.1 M, pH 7.5) was added and the reaction mixture was shaken at room temperature or 37 °C respectively. After an incubation period ranging from 24 to 168 h the polymer was filtered off and washed repeatedly with methanol (3 ×), water (4 ×) and methanol (4 ×). The combined filtrates were evaporated under reduced pressure. Then the residue was redissolved in methanol (10 mL) and the detached amount of 2-methoxy-5-nitrobenzyl alcohol (**24**) was determined by UV spectroscopy (detection at 307 nm). The polymer was subsequently washed with ethyl acetate (3 ×) and CH_2Cl_2 (3 ×), dried in vacuo and investigated by IR spectroscopy. For detailed reaction conditions and the results of the enzymatic cleavage of 2-methoxy-5-nitrobenzyl alcohol see Scheme 6.

Synthesis of POE 6000-bound 2-methoxy-5-nitrobenzyl ester 17

2-Methoxy-5-nitrobenzyl (4-{2-[(chlorocarbonyl)oxy]ethoxy}-5-methoxy-2-{[(phenylacetyl)amino]methyl}phenyl)acetate (14): A 1.93 M solution of phosgene in toluene (1.05 mL, 2 mol) was added at −5 °C to a solution of acetate **11** (177 mg, 0.33 mol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent in vacuo yielded a white solid, which was used without further purification (198 mg, 0.33 mol, quant.). $R_f = 0.66$ (ethyl acetate); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 8.23$ (dd, ^3J(H,H) = 8.8 Hz, ^4J(H,H) = 2.7 Hz, 1H; arom. CH), 8.08 (d, ^4J(H,H) = 2.7 Hz, 1H; arom. CH), 7.33–7.22 (m, 5H; arom. CH), 6.94 (d, ^3J(H,H) = 8.9 Hz, 1H; arom. CH), 6.84 (s, 1H; arom. CH-6), 6.73 (s, 1H;

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arom. CH-3), 6.17 (brs, 1H; NH), 5.13 (s, 2H; CCH_2O), 4.48 (d, $^3J(H,H) = 6.9$ Hz, 2H; CH_2NH), 4.04 (t, $^3J(H,H) = 5.5$ Hz, 2H; $COCH_2CH_2$), 3.92 (s, 3H; OCH_3), 3.90 (t, $^3J(H,H) = 5.5$ Hz, 2H; $COCH_2CH_2$), 3.82 (s, 3H; OCH_3), 3.71 (s, 2H; $PhCH_2$), 3.54 (s, 2H; $CH_2C(O)O$); $C_{29}H_{29}ClN_2O_{10}$ (601.0).

POE-bound 2-methoxy-5-nitrobenzyl ester 17: A mixture of acetate (**14**, 98 mg, 0.16 mol), diamino-functionalized polyoxyethylene POE 6000 (164 mg, 27 μmol), DMAP (37 mg, 0.3 mol) and HOBt (11 mg, 82 μmol) was dried for 8 h over P_2O_5 in vacuo. The mixture was dissolved in CH_2Cl_2 (20 mL), stirred overnight at room temperature and washed with diluted hydrochloric acid (pH 4, 2 × 15 mL). The organic layer was dried over $MgSO_4$. Evaporation of the solvent yielded a white solid, which was redissolved in CH_2Cl_2 (2 mL). The polymer was precipitated through slow addition of ice-cold diethyl ether, filtered off and washed with ice-cold diethyl ether and ice-cold ethanol (0 °C). The precipitate was dissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 177 mg, 25 μmol, 92 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum; Ninhydrin test: also quantitative: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 8.22$ (dd, $^3J(H,H) = 9.0$ Hz, $^4J(H,H) = 2.7$ Hz, 1H; arom. CH), 8.10 (d, $^4J(H,H) = 2.7$ Hz, 1H; arom. CH), 7.33–7.20 (m, 5H; arom. CH), 6.95 (d, $^3J(H,H) = 9.1$ Hz, 1H; arom. CH), 6.87 (s, 1H; arom. CH-6), 6.71 (s, 1H; arom. CH-3), 6.36 (brs, 1H; NH amide), 5.67 (brs, 1H; NH urethane), 5.12 (s, 2H; CCH_2O), 4.38 (d, $^3J(H,H) = 5.6$ Hz, 2H; CH_2NH), 4.15 (t, $^3J(H,H) = 4.5$ Hz, 2H; $COCH_2CH_2$), 3.91 (s, 3H; OCH_3), 3.90 (t, $^3J(H,H) = 4.5$ Hz, 2H; $COCH_2CH_2$), 3.82 (s, 3H; OCH_3), 3.78–3.48 (m, $CH_2C(O)O$, $PhCH_2$, CH_2 polymer), 3.38 (t, $^3J(H,H) = 4.5$ Hz, 2H; $NHCH_2CH_2OCH_2$ polymer); average molecular weight: 7129 g mol^{-1}.

Enzyme-catalysed cleavage of 2-methoxy-5-nitrobenzyl alcohol (24) from POE 6000: A suspension of penicillin G acylase (1 μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5) was added to a solution of POE-bound 2-methoxy-5-nitrobenzyl ester **17** (10 mg, 2.8 μmol) in methanol (0.5 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 4.5 mL). The reaction mixture was shaken at room temperature. After 12, 24 and 36 h the same amount of enzyme was added again and after 48 h the solvent was removed in vacuo. The residue was dissolved in ethyl acetate (2 mL), filtered over silica gel, then the solvent was removed in vacuo. The amount of detached 2-methoxy-5-nitrobenzyl alcohol **24** was determined according to the general procedure for the enzyme-initiated cleavage of 2-methoxy-5-nitrobenzyl alcohol from the solid phase. Yield: 59 %.

Synthesis of the POE-bound carboxylic acid 29

Methyl (4-{2-[(chlorocarbonyl)oxy]ethoxy}-5-methoxy-2-{[(phenylacetyl)-amino]methyl}phenyl)acetate (27): A 1.93 M solution of phosgene in toluene (4 mL, 7.74 mol) was added at −5 °C to a solution of alcohol **8** (500 mg, 1.29 mol) in CH_2Cl_2 (30 mL). The reaction mixture was stirred overnight at room temperature. Evaporation of the solvent in vacuo yielded a white solid, which was used without further purification (580 mg, 1.29 mol, quant.). $R_f = 0.92$ (ethyl acetate); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.34–7.24$ (m, 5H; arom. CH), 6.79 (s, 1H; arom. CH-6), 6.63 (s, 1H; arom. CH-3), 6.24 (brs, 1H; NH), 4.60 (t, $^3J(H,H) = 4.5$ Hz, 2H; $COCH_2CH_2$), 4.35 (d, $^3J(H,H) = 4.3$ Hz, 2H; CH_2NH), 4.20 (t, $^3J(H,H) = 4.6$ Hz, 2H; $COCH_2$), 3.83 (s, 3H; OCH_3), 3.64 (s, 3H; $COOCH_3$), 3.63 (s, 2H; $PhCH_2$), 3.58 (s, 2H; $CH_2C(O)O$); HRMS (70 eV): calcd for $C_{22}H_{24}ClNO_7$: 449.1225, found: 449.1241.

POE-bound methyl ester 28: A mixture of acetate (**27**, 1.36 g, 3.0 mol), diamino-functionalized polyoxyethylene POE 6000 (3.0 g, 0.5 mol), DMAP (674 mg, 5.5 mol) and HOBt (203 mg, 1.5 mol) was dried for 8 h over P_2O_5 in vacuo. The mixture was dissolved in CH_2Cl_2 (50 mL), stirred overnight at room temperature and washed with diluted hydrochloric acid (pH 4, 2 × 30 mL). The organic layer was dried over $MgSO_4$. Evaporation of the solvent yielded a white solid, which was redissolved in CH_2Cl_2 (4 mL). The polymer was precipitated through slow addition of precooled diethyl ether (0 °C), filtered off and washed with diethyl ether (0 °C) and ethanol (0 °C). The precipitate was dissolved in CH_2Cl_2 (4 mL) and the procedure repeated to yield a white solid. Isolated amount of polymer: 3.19 g, 0.47 mol, 93 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum; Ninhydrin test: also quantitative. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.34–7.25$ (m, 5H; arom. CH), 6.88 (s, 1H; arom. CH-6), 6.68 (s, 1H; arom. CH-3), 6.44 (brs, 1H; NH amide), 5.68 (brs, 1H; NH urethane), 4.40 (brs, 2H; $COCH_2$), 4.35 (d, $^3J(H,H) = 5.7$ Hz, 2H; CH_2NH), 4.15 (brs, 2H; $COCH_2CH_2$), 3.83 (s, 3H; OCH_3), 3.79–3.51 (m, $CH_2C(O)O$, $PhCH_2$, CH_2 polymer), 3.39 (brs, 2H; $NHCH_2CH_2OCH_2$ polymer), 2.05 (s, 3H; $COOCH_3$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta =$ 172.52 (C=O), 170.79 (C=O), 156.41 (C=O urethane), 148.85 ($COCH_2$), 147.41 ($COCH_3$), 135.02 ($CCH_2C(O)NH$), 129.30 (2C; arom. CH), 128.78 (2C; arom. CH), 128.54 ($CCH_2C(O)O$), 127.09 (arom. CH), 125.33 (CCH_2NH), 115.60 (arom. CH-3), 114.07 (arom. CH-6), 70.77–70.30 ($COCH_2CH_2$, CH_2 polymer), 67.79 ($COCH_2$), 55.99 (OCH_3), 52.24 ($COOCH_3$), 43.71 ($NHCH_2$ polymer), 42.31 ($PhCH_2$), 41.05 ($CH_2C(O)O$), 37.90 (CH_2NH); IR (KBr, drift): $\tilde{\nu} = 1724$ (C=O, ester, urethane), 1652 (C=O, amide I), 1522 (C=O, amide II), 1114 cm^{-1} (C–O); average molecular weight: 6827 g mol^{-1}.

POE-bound carboxylic acid 29: A solution of the POE-bound methyl ester **28** (430 mg, 63 μmol) in 0.25 M LiOH/THF (2:1, 30 mL) was stirred at room temperature. After 4 h diluted hydrochloric acid was added to adjust to pH 4. The solution was extracted with $CHCl_3$ (6 × 30 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated in vacuo to yield a colourless solid, which was used without further purification. Isolated amount of polymer: 424 mg, 62 μmol, 99 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.32–7.21$ (m, 5H; arom. CH), 6.84 (s, 1H; arom. CH-6), 6.74 (s, 1H; arom. CH-3), 6.51 (brs, 1H; NH amide), 5.72 (brs, 1H; NH urethane), 4.37 (t, $^3J(H,H) = 4.4$ Hz, 2H; $COCH_2$), 4.34 (d, $^3J(H,H) = 5.7$ Hz, 2H; CH_2NH), 4.21 (t, $^3J(H,H) = 4.5$ Hz, 2H; $COCH_2CH_2$), 3.81 (s, 3H; OCH_3), 3.78 (t, $^3J(H,H) = 4.6$ Hz, 2H; $NHCH_2CH_2$ polymer), 3.73–3.49 (m, $CH_2C(O)O$, $PhCH_2$, CH_2 polymer), 3.37 (t, $^3J(H,H) = 4.8$ Hz, 2H; $NHCH_2CH_2OCH_2$ polymer); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 173.57$ (C=O carboxylic acid), 171.35 (C=O amide), 156.41 (C=O urethane), 148.80 ($COCH_2$), 147.27 ($COCH_3$), 135.03 ($CCH_2C(O)NH$), 129.24 (2C; arom. CH), 128.71 (2C; arom. CH), 128.47 (arom. CH), 127.04 (CCH_2COOH), 125.74 (CCH_2NH), 115.43 (arom. CH-3), 114.14 (arom. CH-6), 72.57 ($NHCH_2CH_2$ polymer), 72.42–69.92 ($COCH_2CH_2$, CH_2 polymer), 55.97 (OCH_3), 43.29 ($PhCH_2$), 41.14 ($NHCH_2$ polymer), 40.76 (CH_2COOH), 37.95 (CH_2NH); average molecular weight: 6799 g mol^{-1}.

POE-bound aryl iodide 31: A suspension of polymer-bound carboxylic acid **29** (234 mg, 34 μmol), cesium carbonate (58 mg, 178 μmol), 2-iodo benzyl bromide (**30**, 104 mg, 349 μmol) and 4 Å molecular sieves in DMF (10 mL) was stirred at 50 °C. After 24 h the molecular sieves were filtered off and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (15 mL) and washed with saturated ammonium chloride solution (10 mL). Then the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried over $MgSO_4$. After evaporation of the solvent the residue was dissolved in CH_2Cl_2 (2 mL). The polymer was precipitated through slow addition of ice-cold diethyl ether, filtered off and washed with diethyl ether (0 °C) and ethanol (0 °C). The precipitate was dissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 234 mg, 32 μmol, 95 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.66$ (d, $^3J(H,H) = 7.9$ Hz, 1H; arom. CH), 7.62 (s, 1H; arom. CH), 7.32–7.24 (m, 1H; arom. CH), 7.09 (t, $^3J(H,H) = 7.8$ Hz, 1H; arom. CH), 4.99 (s, 2H; CH_2O); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.75$ (C=O ester), 137.84 (CCH_2O), 137.38 (arom. CH), 136.87 (arom. CH), 128.84 (arom. CH), 125.12 (arom. CH), 94.35 (CI), 65.85 (CH_2O); IR (KBr, drift): $\tilde{\nu} = 1719$ (C=O, ester, urethane), 1653 (C=O, amide I), 1106 cm^{-1} (C–O); average molecular weight: 7231 g mol^{-1}.

POE-bound cinnamic acid *tert*-butyl ester 32: A solution of polymer-bound aryl iodide (**31**, 110 mg, 30 μmol), tetrabutylammonium bromide (10 mg, 30 μmol) and triphenylphosphine (8 mg, 30 μmol) in DMF/H_2O/Et_3N 9:1:1 (5.5 mL) was degassed for 20 min under ultrasonication. Then acrylic acid *tert*-butyl ester (22 μL, 153 μmol) and $Pd(OAc)_2$ (3 mg, 15 μmol) was added and the solution was stirred at 50 °C. After 24 h the solvent was evaporated under reduced pressure, the residue was redissolved in CH_2Cl_2 (10 mL) and the insoluble components were filtered off. The volume of the solution was reduced in vacuo, then the polymer was precipitated through slow addition of precooled diethyl ether (0 °C), filtered off and washed with ice-cold diethyl ether and ice-cold ethanol. The precipitate was dissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 99 mg, 27 μmol, 91 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz):

$\delta = 7.56$ (d, $^3J_{trans} = 16.0$ Hz, 1H; CC*H*=CH), 7.46 (m, 2H; arom. CH), 7.36 (t, $^3J(H,H) = 7.6$ Hz, 1H; arom. CH), 7.32–7.24 (m, 1H; arom. CH), 6.38 (d,$^3J_{trans} = 16.0$ Hz, 1H; CCH=C*H*), 5.07 (s, 2H; CH_2O), 1.54 (s, 9H; $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.85$ (C=O ester), 166.03 (CH*C*(O)O), 142.79 (C*C*H=CH), 136.27 (*C*CH_2O), 135.10 (*C*CH), 129.65 (arom. CH), 127.90 (arom. CH), 127.65 (arom. CH), 127.10 (arom. CH), 120.92 (CCH=CH), 80.64 (*C*$(CH_3)_3$), 66.45 (CH_2O), 28.19 (3C; C(*C*$H_3)_3$); IR (KBr, drift): $\tilde{\nu} = 1718$ (C=O, ester, urethane), 1669 (C=O, amide I), 1638 (C=C, α,β-unsaturated carbonyl group), 1114 cm^{-1} (C–O); average molecular weight: 7233 g mol^{-1}.

POE-bound (4′-methoxy[1,1′-biphenyl]-3-yl)methanol 33: A solution of polymer-bound aryl iodide **31** (200 mg, 56 μmol), 4-methoxyphenylboronic acid (42 mg, 276 mol) and $K_3PO_4 \cdot 3H_2O$ (30 mg, 110 mol) in DMF/H_2O 6:1 (14 mL) was degassed for 20 min under ultrasonication. Then $[Pd(PPh_3)_4]$ (1 mg, 1 μmol) was added and the reaction mixture was stirred at 80 °C. After 4 h the solvent was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (20 mL) and washed with water (15 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was redissolved in CH_2Cl_2 (2 mL), then the polymer was precipitated through slow addition of precooled diethyl ether (0 °C), filtered off and washed with ice-cold diethyl ether and ice-cold ethanol. The precipitate was dissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 187 mg, 52 μmol, 93%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.50$ (d, $^3J(H,H) = 7.8$ Hz, 1H; arom. CH), 7.45 (d, $^3J(H,H) = 8.7$ Hz, 2H; arom. CH), 7.44 (s, 1H; arom. CH), 7.39 (t, $^3J(H,H) = 7.6$ Hz, 1H; arom. CH), 7.23–7.21 (m, 1H; arom. CH), 6.97 (d, $^3J(H,H) = 8.7$ Hz, 2H; arom. CH), 5.13 (s, 2H; CH_2O), 3.85 (s, 3H; OCH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.84$ (C=O ester), 156.36 (*C*OCH_3), 141.22 (*C*CH_2O), 136.04 (CH_2CCH*CC*), 132.96 (CH_2CCH*C*C), 129.01 (arom. CH), 128.06 (2C; arom. CH), 127.01 (arom. CH), 126.66 (arom. CH), 126.34 (arom. CH), 114.26 (2C; arom. CH), 63.21 (CH_2O), 55.31 (OCH_3); average molecular weight: 7191 g mol^{-1}.

POE-bound [3-(1-pentynyl)phenyl]methanol 34: 1-Pentine (41 μL, 423 μmol) was added to a solution of polymer-bound aryl iodide **31** (153 mg, 42 μmol) in dioxane/Et_3N 2:1 (12 mL) and the solution was degassed for 15 min under ultrasonication. Then cuprous iodide (2 mg, 11 μmol) and $[Pd(PPh_3)_2Cl_2]$ (3 mg, 4 μmol) were added and the reaction mixture was stirred at room temperature. After 24 h, $CHCl_3$ (15 mL) was added and the solution was washed with saturated aqueous ammonium chloride (10 mL). Then the aqueous phase was washed with $CHCl_3$ (2 × 15 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (2 mL) followed by precipitation of the polymer by slow addition of ice-cold diethyl ether. The solid was filtered off, washed with diethyl ether (0 °C) and ethanol (0 °C), then the precipitate was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 147 mg, 41 μmol, 97%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.35$ (t, $^4J(H,H) = 1.7$ Hz, 1H; arom. CH), 7.32–7.24 (m, 2H; arom. CH), 7.18 (d, $^3J(H,H) = 7.6$ Hz, 1H; arom. CH), 5.02 (s, 2H; CH_2O), 2.38 (t, $^3J(H,H) = 7.0$ Hz, 2H; C$H_2$$CH_2CH_3$), 1.63 (sext, $^3J(H,H) = 7.2$ Hz, 2H; CH_2CH_3), 1.05 (t, $^3J(H,H) = 7.4$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.87$ (C=O ester), 135.61 (*C*CH_2O), 131.53 (arom. CH), 131.28 (arom. CH), 128.52 (arom. CH), 127.09 (arom. CH), 124.57 (*C*$CCCH_2$), 90.95 (*C*CH_2CH_2), 80.21 (*C*CCH_2), 63.27 (CH_2O), 22.15 (C*C*H_2CH_2), 21.37 (*C*H_2CH_3), 13.58 (CH_3); average molecular weight: 7111 g mol^{-1}.

General procedure for the enzyme-initiated cleavage of alcohols from POE 6000: A defined amount of polymer-bound substrate was dissolved in methanol and 0.2 M aqueous sodium phosphate buffer (pH 7.0). Then a suspension of penicillin G acylase (70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5) was added and the reaction mixture was shaken at 37 °C. The same amount of enzyme was added after 12, 24 and 36 h. After 48 h the reaction mixture was extracted with diethyl ether (6 × 20 mL). The combined organic layers were dried over $MgSO_4$, then the solvent was removed in vacuo to yield the cleaved alcohol. After that the aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The polymer obtained thereby was dried in vacuo.

Enzyme-catalysed release of *tert*-butyl(2*E*)-3-[3-(hydroxymethyl)phenyl]-2-propenoate (35): According to the general procedure for the enzyme-initiated cleavage of alcohols from POE 6000 cinnamic acid *tert*-butyl ester **32** (43 mg, 12 μmol) was dissolved in methanol (2 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 18 mL) and incubated with a suspension of penicillin G acylase (4 μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **35**: Colourless oil (2.1 mg, 9 μmol, 75%); $R_f = 0.2$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.55$ (d, $^3J_{trans} = 16.0$ Hz, 1H; CC*H*=CH), 7.49 (s, 1H; arom. CH), 7.41–7.39 (m, 1H; arom. CH), 7.37–7.33 (m, 2H; arom. CH), 6.36 (d, $^3J_{trans} = 16.0$ Hz, 1H; CCH=C*H*), 4.69 (s, 2H; CH_2), 2.33 (br s, 1H; OH), 1.53 (s, 9H; $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 166.40$ (C=O), 143.39 (C*C*H=CH), 141.61 (*C*CH_2O), 134.87 (*C*CH), 128.99 (arom. CH), 128.47 (arom. CH), 127.18 (arom. CH), 126.29 (arom. CH), 120.36 (CCH=CH), 80.63 (*C*$(CH_3)_3$), 64.80 (CH_2), 28.19 (3C; C(*C*$H_3)_3$); IR (KBr, drift): $\tilde{\nu} =$ 3434 (O–H), 1707 (C=O, ester), 1637 (C=C, α,β-unsaturated carbonyl), 1153 cm^{-1} (C–O); MS (EI, 70 eV, 45 °C): *m*/*z* (%): 234 (82) $[M]^+$, 178 (100), 160 (89), 131 (66); HRMS (70 eV): calcd for $C_{14}H_{18}O_3$: 234.1256, found: 234.1241.

Polymer-bound lactam 26: Isolated amount of polymer: 32 mg, 10 μmol, 82%; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 8.84$ (br s, 1H; NH lactam), 6.73 (s, 1H; arom. CH), 6.67 (s, 1H; arom. CH), 5.53 (br s, 1H; NH urethane), 4.55 (br s, 2H; CH_2NH), 4.43 (br s, 2H; $COCH_2$), 4.20 (br s, 2H; $COCH_2$CH_2), 3.86 (s, 3H; OCH_3), 3.78 (t, $^3J(H,H) = 4.6$ Hz, 2H; NHCH_2 polymer), 3.74–3.55 (m, CH_2C(O)NH, CH_2 polymer), 3.50 (t, $^3J(H,H) = 5.1$ Hz, 2H; NHCH$_2$CH_2O polymer), 3.37 (t, $^3J(H,H) = 4.7$ Hz, 2H; NHCH_2CH_2OCH_2 polymer); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 173.8$ (C=O lactam), 157.7 (C=O urethane), 149.5 (*C*OCH_2), 147.5 (*C*OCH_3), 127.6 (*C*CH_2C(O)NH), 126.0 (*C*CH_2NH), 112.1 (arom. CH), 111.5 (arom. CH), 73.2 (NHCH_2CH_2 polymer), 72.8–69.8 (CH_2 polymer), 68.2 (NHCH_2CH_2OCH_2 polymer), 66.5 ($COCH_2$CH_2), 63.2 (CO*C*H_2), 56.4 (OCH_3), 45.05 (NHCH_2 polymer), 41.8 (CH_2NH), 34.1 (CH_2C(O)NH); IR (KBr, drift): $\tilde{\nu} = 1720$ (C=O, urethane), 1665 (C=O, lactam), 1116 cm^{-1} (C–O); average molecular weight: 6529 g mol^{-1}.

Enzyme-catalysed cleavage of (4′-methoxy[1,1′-biphenyl]-3-yl)methanol (36): According to the general procedure for the enzyme-initiated cleavage of alcohols from POE 6000, POE-bound biphenyl **33** (27 mg, 7.6 μmol) was dissolved in methanol (1 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 9 mL) and incubated with a suspension of penicillin G acylase (3 μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **36**:[25] white solid (1.2 mg, 5.5 μmol, 73%); $R_f = 0.47$ (ethyl acetate/hexane 1:2 *v*/*v*); m.p. 94 °C, lit.[25]: 95 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.53$ (s, 1H; arom. CH), 7.51 (td, $^3J(H,H) = 8.7$ Hz, $^4J(H,H) = 3.0$ Hz, 2H; arom. CH), 7.46 (d, $^3J(H,H) = 7.8$ Hz, 1H; arom. CH), 7.38 (t, $^3J(H,H) = 7.6$ Hz, 1H; arom. CH), 7.27 (d, $^3J(H,H) = 6.5$ Hz, 1H; arom. CH), 6.95 (td, $^3J(H,H) = 8.7$ Hz, $^4J(H,H) = 3.0$ Hz, 2H; arom. CH), 4.71 (s, 2H; CH_2), 3.83 (s, 3H; OCH_3), 2.03 (br s, 1H; OH); MS (EI, 70 eV, 60 °C): *m*/*z* (%): 215 (12) $[M+H]^+$, 214 (100) $[M]^+$, 199 (12); HRMS (70 eV): calcd for $C_{14}H_{14}O_2$: 214.0994, found: 214.0985. The spectroscopic data are in agreement with the literature.[25]

Enzyme-catalysed cleavage of [3-(1-pentynyl)phenyl]methanol (37): According to the general procedure for the enzyme-initiated cleavage of alcohols from POE 6000, POE-bound alkine **34** (19 mg, 5.3 μmol) was dissolved in methanol (1 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 9 mL) and incubated with a suspension of penicillin G acylase (2μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **37**: Colourless oil (0.9 mg, 5.0 μmol, 94%); $R_f = 0.2$ (ethyl acetate/hexane 1:6 *v*/*v*); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.38$ (s, 1H; arom. CH), 7.33–7.22 (m, 3H; arom. CH), 4.59 (s, 2H; CH_2OH), 2.38 (t, $^3J(H,H) = 7.0$ Hz, 2H; CC$H_2$$CH_2$), 2.29 (s, 1H; OH), 1.62 (sext, $^3J(H,H) =$ 7.4 Hz, 2H; CH_2CH_3), 1.05 (t, $^3J(H,H) = 7.3$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 140.81$ (*C*CH_2OH), 130.75 (arom. CH), 130.05 (arom. CH), 128.45 (arom. CH), 126.10 (arom. CH), 124.28 (*C*$CCCH_2$), 90.51 (*C*CH_2CH_2), 80.56 (*C*$CCCH_2$), 64.88 (CH_2OH), 22.21 (C*C*H_2CH_2), 21.39 (*C*H_2CH_3), 13.60 (CH_3); IR (KBr, drift): $\tilde{\nu} = 3310$ (O–H), 2228 (alkine), 1019 cm^{-1} (C–O); MS (EI, 70 eV, 60 °C): *m*/*z* (%): 174 (24) $[M]^+$, 114 (29); HRMS (70 eV): calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1030.

General procedure for the esterification of the POE-bound carboxylic acid 29: DIC (34 μL, 220 μmol), pyridine (18 μL, 220 μmol) and the respective alcohol were added at 0 °C to a solution of polymer-bound carboxylic acid **29** (100 mg, 29 μmol), DMAP (1 mg, 8 μmol) and HOBt (1 mg, 7 μmol) in

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DMF (3 mL). After 1 h the ice bath was removed and the reaction mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo, the residue redissolved in CH_2Cl_2 (15 mL) and washed with 0.05 M hydrochloric acid (15 mL). Then the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) followed by precipitation of the polymer by slow addition of ice-cold diethyl ether. The solid was filtered off, washed with diethyl ether (0 °C) and ethanol (0 °C), then the precipitate was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated. The polymer was dried in vacuo.

POE-bound benzyl alcohol 38: According to the general procedure polymer-bound carboxylic acid **29** (100 mg, 29 μmol), DMAP (1 mg, 8 μmol), HOBt (1 mg, 7 μmol), DIC (34 μL, 220 μmol), pyridine (18 μL, 220 μmol) and 4-(hydroxymethyl)-benzyl alcohol (81 mg, 588 μmol) were allowed to react in DMF (3 mL). White solid; isolated amount of polymer: 94 mg, 27 μmol, 92 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.34-7.29$ (m, 2H; arom. CH), 7.25–7.23 (m, 2H; arom. CH), 5.06 (s, 2H; OCH_2), 4.66 (s, 2H; CH_2OH); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.71$ (C=O ester), 141.56 (*C*CH_2OH), 134.57 (*C*CH_2O), 128.28 (2C; arom. CH), 126.97 (2C; arom. CH), 63.84 (OCH_2), 63.12 (CH_2OH); IR (KBr, drift): $\tilde{\nu} = 3325$ (O–H), 1722 (C=O, ester, urethane), 1666 (C=O, amide I), 1519 (C=O, amide II), 1115 cm^{-1} (C–O); average molecular weight: 7039 g mol^{-1}.

POE-bound benzyl ether 39: A solution of polymer-bound benzyl alcohol **38** (28 mg, 8 μmol), 4-acetamidophenol (12 mg, 79 μmol) and triphenylphosphine (10 mg, 39 μmol) in THF/CH_2Cl_2 1:1 (600 μL) was stirred at −5 °C for 15 min in the presence of 4 Å molecular sieves. Then diethyl azodicarboxylate (6 μL, 39 μmol) was slowly added and the reaction mixture was stirred 1 h at 0 °C and 12 h at room temperature. The molecular sieves were filtered off, the solvent was evaporated in vacuo and the residue was purified by size-exclusion chromatography (chloroform/methanol 1:1 *v*/*v*) on Sephadex LH 20 to yield a colourless solid. Isolated amount of polymer: 25 mg, 7 μmol, 86 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 7.62 (brs, 1H; NH), 7.42 (d, ^3J(H,H) = 9.0 Hz, 2H; arom. CH), 7.39 (d, ^3J(H,H) = 8.0 Hz, 2H; arom. CH), 7.31–7.23 (m, 2H; arom. CH), 6.88 (d, ^3J(H,H) = 9.0 Hz, 2H; arom. CH), 5.07 (s, 2H; $CH_2OC(O)$), 5.03 (s, 2H; CH_2O), 2.14 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.83$ (C=O ester), 168.35 (C=O anilide), 155.15 (*C*OCH_2C), 135.25 (*C*CH_2OC), 135.06 (*C*$CH_2OC(O)$), 131.73 (CNH), 128.49 (2C; arom. CH), 127.61 (2C; arom. CH), 121.59 (2C; arom. CH), 115.13 (2C; arom. CH), 70.05 (CO*C*H_2), 57.31 (*C*$H_2OC(O)$), 24.28 (CH_3); IR (KBr, drift): $\tilde{\nu} = 1722$ (C=O, ester, urethane), 1673 (C=O, amide I, anilide), 1511 (C=O, amide II), 1115 cm^{-1} (C–O); average molecular weight: 7307 g mol^{-1}.

Enzyme-catalysed cleavage of *N*-(4-{[4-hydroxymethyl)benzyl]oxy}phenyl)-acetamide (40): According to the general procedure for the enzyme-initiated cleavage of alcohols from POE 6000, POE-bound benzyl phenyl ether **39** (20 mg, 6 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (3 μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). The crude product was purified by chromatography on silica gel (ethyl acetate/hexane 1:1 to 2:1 *v*/*v*) to yield a colourless oil (1.2 mg, 4.4 μmol, 81 %). $R_f = 0.15$ (ethyl acetate/hexane 2:1 *v*/*v*); ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.43-7.37$ (m, 6H; arom. CH), 7.03 (brs, 1H; NH), 6.92 (d, ^3J(H,H) = 8.8 Hz, 2H; arom. CH), 5.05 (s, 2H; OCH_2), 4.71 (s, 2H; CH_2OH), 2.15 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 168.07$ (C=O), 155.60 (*C*OCH_2), 140.68 (*C*CH_2OH), 136.45 (*C*CH_2OC), 131.20 (CNH), 127.73 (2C; arom. CH), 127.25 (2C; arom. CH), 121.84 (2C; arom. CH), 115.27 (2C; arom. CH), 70.06 (OCH_2), 65.14 (CH_2OH), 24.43 (CH_3); IR (KBr, drift): $\tilde{\nu} = 3286$ (O–H), 1735 (C=O, ester), 1659 (C=O, anilide), 1533 (C=O, amide II), 1049 cm^{-1} (C–O); MS (EI, 70 eV): *m*/*z* (%): 272 (4) $[M+H]^+$, 271 (36) $[M]^+$, 121 (100); HRMS (70 eV): calcd for $C_{16}H_{17}NO_3$: 271.1208, found: 271.1203.

POE-bound acrylic acid derivative 41

According to the general procedure polymer-bound carboxylic acid **29** (100 mg, 29 μmol), DMAP (1 mg, 8 μmol), HOBt (1 mg, 7 μmol), DIC (34 μL, 220 μmol), pyridine (18 μL, 220 μmol) and 4-hydroxybutylacrylate (30 μL, 220 μmol) were allowed to react in DMF (3 mL) to yield a white solid. Isolated amount of polymer: 101 mg, 29 μmol, 97 %. The reaction was quantitative as determined ^{1}H NMR spectrum; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 6.39$ (d, $^3J_{trans} = 17.3$ Hz, 1H; CH=CH_{2a}), 6.10 (dd, $^3J_{trans} =$ 17.3 Hz, $^3J_{cis} = 10.4$ Hz, 1H; C*H*=CH_2), 5.82 (d, $^3J_{cis} = 10.4$ Hz, 1H; CH=CH_{2b}), 4.19–4.12 (m, 2H; CHC(O)O*C*H_2), 4.08 (t, ^3J(H,H) = 6.8 Hz, 2H; $CH_2C(O)OCH_2$), 1.72–1.64 (m, 4H; $OCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 172.6$ (C=O ester), 164.2 (O*C*(O)CH), 131.3 (CH=CH_2), 126.9 (*C*H=CH_2), 64.1 ($CH_2C(O)OCH_2$), 63.1 (CHC(O)O*C*H_2), 25.0 ($CH_2C(O)OCH_2CH_2$), 25.05 (CHC(O)OCH_2*C*H_2); IR (KBr, drift): $\tilde{\nu} =$ 1721 (C=O, ester, urethane), 1666 (C=O, amide I), 1519 (C=O, amide II), 1116 cm^{-1} (C–O); average molecular weight: 7051 g mol^{-1}.

POE-bound Diels–Alder adduct 42

Method A: A solution of polymer-bound acrylic acid ester **41** (44 mg, 13 μmol) in freshly distilled cyclopentadiene/THF 1:1 (2 mL) was heated to 60 °C. After 24 h the solvent was evaporated in vacuo, the residue was dissolved in CH_2Cl_2 (2 mL) followed by precipitation of the polymer by slow addition of ice-cold diethyl ether. The solid was filtered off, washed with diethyl ether (0 °C) and ethanol (0 °C) and dissolved in CH_2Cl_2 (2 mL). The procedure was repeated to yield a white solid. Isolated amount of polymer: 42 mg, 12 μmol, 93 %, *endo*/*exo* 2.5:1. The reaction was quantitative as determined by the ^{1}H NMR spectrum.

Method B: Polymer-bound acrylic acid ester **41** (29 mg, 8 μmol) and a trace of hydroquinone were dissolved in freshly distilled cyclopentadiene/toluene 3:2 (2.5 mL) in a glass vial. The vial was evacuated, sealed and heated for 24 h in a bomb tube. After cooling the vial was opened, CH_2Cl_2 (1 mL) was added and the polymer was precipitated by slow addition of precooled diethyl ether (0 °C). The solid was filtered off, washed with ice-cold diethyl ether and ice-cold ethanol. The residue was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 20 mg, 6 μmol, 70 %, *endo*/*exo* 2.5:1. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 6.21-6.09$ (m, 3H; CHCHC*H*=CH *endo*, CHCHC*H*=CH *exo*, CHCHCH=C*H* *endo*), 5.92–5.88 (m, 1H; CHCHCH=C*H* *exo*), 4.14 (brs, 2H; CHC(O)O*C*H_2), 3.74–3.50 (m, 2H; $CH_2C(O)OCH_2$), 3.18 (brs, 1H; C(O)CHC*H* *endo*), 3.01 (brs, 1H; C(O)CHC*H* *exo*), 2.95–2.86 (m, 2H; C(O)CHCH_2C*H* *endo*, C(O)CHCH_2C*H* *exo*), 2.25–2.23 (m, 1H; C(O)CH), 1.96–1.86 (m, 1H; C(O)CHCH_{2a}), 1.73–1.64 (m, 4H; C(O)OCH_2CH_2CH_2), 1.61–1.52 (m, 1H; C(O)CHCH_{2b}), 1.46–1.21 (m, 2H; C(O)CHCHCH_2); average molecular weight: 7183 g mol^{-1}.

Enzyme-catalysed cleavage of 4-hydroxybutyl-bicyclo[2.2.1]hept-5-ene-carboxylate (43): According to the general procedure for the enzyme-initiated cleavage of alcohols from POE 6000, POE-bound adduct **42** (41 mg, 11 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (5 μL, 70 mg mL^{-1}, 560 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). The crude product was purified by chromatography on silica gel (ethyl acetate/hexane 1:3 *v*/*v*) to yield a colourless oil (1.8 mg, 9 mol, 75 %, *endo*:*exo* 2.5:1). $R_f = 0.17$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 6.22-6.15$ (m, 1H; CHCHCH=C*H* *endo*), 6.15–6.08 (m, 2H; CHCHC*H*=CH *exo*, CHCHCH=C*H* *exo*), 5.95–5.90 (m, 1H; CHCHC*H*=CH *endo*), 4.13 (t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2 *exo*), 4.05 (t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2 *endo*), 3.69 (brs, 2H; CH_2OH), 3.20 (brs, 1H; C(O)CHC*H* *endo*), 3.03 (brs, 1H; C(O)CHC*H* *exo*), 2.96–2.88 (m, 1H; C(O)CHCH_2C*H*), 2.24–2.21 (m, 1H; C(O)CH), 1.97–1.85 (m, 1H; C(O)CHCH_{2a}), 1.79–1.59 (m, 4H; CH_2CH_2CH$_2$OH), 1.55–1.32 (m, 4H; OH, C(O)CHCH_{2b}, C(O)CHCHCH_2); IR (KBr, film): $\tilde{\nu} = 3434$ (O–H), 1729 (C=O, ester), 1570 (C=C), 1176 (C–O), 1046 cm^{-1} (C–O); MS (EI, 70 eV, 40 °C): *m*/*z* (%): 210 (0.5) $[M]^+$, 138 (11), 66 (100); HRMS (70 eV): calcd for $C_{12}H_{18}O_3$: 210.1256, found: 210.1248.

POE-bound isoxazoline 44: *syn*-Benzaldehyde oxime (8 μL, 71 μmol) was added to a solution of polymer-bound acrylic acid ester **41** (50 mg, 14 μmol) in THF (500 μL). Then a 0.7 M aqueous solution of sodium hypochlorite (100 μL, 140 μmol) was added to the reaction mixture. After 4 h at room temperature the solvent was evaporated in vacuo, the residue was redissolved in CH_2Cl_2 (10 mL) and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL) and the polymer was precipitated by slow addition of precooled diethyl ether (0 °C). The solid was filtered off, washed with ice-cold diethyl ether and ice-

cold ethanol, then the precipitate was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 48 mg, 13 μmol, 94%. The reaction was quantitative as determined ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.68$ (dd, $^3J(H,H) = 7.9$ Hz, $^4J(H,H) = 1.3$ Hz, 2H; arom. CH), 7.44–7.40 (m, 3H; arom. CH), 5.16 (dd, $^3J(OCH,CH_{2a}C{=}N) = 10.1$, $^3J(OCH,CH_{2b}C{=}N) = 7.1$ Hz, 1H; OCH), 4.20 (t, $^3J(H,H) = 2.4$ Hz, 2H; $CHC(O)OCH_2$), 4.12 (t, $^3J(H,H) = 4.5$ Hz, 2H; $CH_2C(O)OCH_2$), 3.73–3.54 (m, 2H; $CH_2C{=}N$), 1.75–1.69 (m, 4H; $OCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 172.04$ (C=O ester), 170.14 (O*C*(O)CH), 156.37 (C=N), 130.56 (arom. CH), 129.41 (*C*C=N), 128.79 (2C; arom. CH), 126.92 (2C; arom. CH), 78.06 (OCH), 61.70 ($CH_2C(O)OCH_2$), 57.30 ($CHC(O)OCH_2$), 38.76 ($CH_2C{=}N$), 25.15 ($CH_2C(O)OCH_2CH_2$), 25.06 ($CHC(O)OCH_2CH_2$); IR (KBr, drift): $\tilde{\nu} =$ 1726 (C=O, ester, urethane), 1666 (C=O, amide I), 1519 (C=O, amide II), 1116 cm^{-1} (C–O); average molecular weight: 7289 $g\,mol^{-1}$.

General procedure for the synthesis of POE-bound anilides: A mixture of POE-bound carboxylic acid **29**, the respective aniline, EDC and HOBt was dissolved in DMF. The reaction mixture was stirred 3 h at 0 °C and 9 h at room temperature. Then the solvent was evaporated in vacuo, the residue was dissolved in $CHCl_3$ (30 mL) and washed with 0.05 N hydrochloric acid (2 × 20 mL). The combined aqueous layers were extracted with $CHCl_3$ (3 × 30 mL) and the combined organic layers were dried over $MgSO_4$. Then the solvent was removed under reduced pressure, the residue was redissolved in CH_2Cl_2 (2 mL) and the polymer was precipitated by slow addition of pre-cooled diethyl ether (0 °C). The solid was filtered off and washed with ice-cold diethyl ether and ice-cold ethanol. The precipitate was dissolved in CH_2Cl_2 (2 mL) and the procedure was repeated. The polymer was dried in vacuo.

POE-bound 4-pentylaniline 45: According to the general procedure for the synthesis of POE-bound anilides, POE-bound carboxylic acid **29** (100 mg, 29 μmol), EDC (22 mg, 116 μmol), HOBt (20 mg, 145 μmol) and 4-pentylaniline (**46**, 42 μL, 240 μmol) were allowed to react in DMF (5 mL). White solid; Isolated amount of polymer: 91 mg, 26 μmol, 89%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 8.80$ (br s, 1H; NH), 7.47 (d, $^3J(H,H) = 8.4$ Hz, 2H; arom. CH), 7.06 (d, $^3J(H,H) = 8.4$ Hz, 2H; arom. CH), 2.54 (t, $^3J(H,H) = 7.5$ Hz, 2H; CCH_2), 1.59–1.53 (m, 2H; CCH_2CH_2), 1.32–1.25 (m, 4H; $CH_2CH_2CH_3$), 0.87 (t, $^3J(H,H) = 3.2$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.24$ (C=O anilide), 136.17 (CNH), 135.00 (*C*CH_2), 128.56 (2C; arom. CH), 119.54 (2C; arom. CH), 35.27 (C*C*H_2), 31.35 ($CH_2CH_2CH_3$), 29.63 (CCH_2CH_2), 22.47 (CH_2CH_3), 14.02 (CH_3); IR (KBr, drift): $\tilde{\nu} = 1720$ (C=O, urethane), 1673 (C=O, amide I, anilide), 1517 (C=O, amide II), 1115 cm^{-1} (C–O); average molecular weight: 7089 $g\,mol^{-1}$.

POE-bound 4-aminobenzoic acid ethyl ester 47: According to the general procedure for the synthesis of POE-bound anilides POE-bound carboxylic acid **29** (126 mg, 37 μmol), DIC (17 μL, 111 μmol), HOBt (19 mg, 139 μmol) and 4-aminobenzoic acid ethyl ester (**48**, 37 mg, 222 μmol) were allowed to react in DMF (4 mL). White solid; Isolated amount of polymer: 118 mg, 33 μmol, 90%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.93$ (d, $^3J(H,H) = 9.0$ Hz, 2H; arom. CH), 7.67 (d, $^3J(H,H) = 9.0$ Hz, 2H; arom. CH), 7.48 (br s, 1H; NH), 4.41–4.29 (m, 2H; CH_2), 1.40 (t, $^3J(H,H) = 7.5$ Hz, 3H; CH_3); IR (KBr, drift): $\tilde{\nu} = 1751$ (C=O, ester), 1718 (C=O, urethane), 1670 (C=O, amide I, anilide), 1521 (C=O, amide II), 1118 cm^{-1} (C–O); average molecular weight: 7093 $g\,mol^{-1}$.

General procedure for the enzyme-initiated cleavage of anilines from POE 6000: A definite amount of polymer-bound anilide was dissolved in methanol and 0.05 M aqueous sodium phosphate buffer (pH 7.0). Then a suspension of penicillin G acylase (72 $mg\,mL^{-1}$, 1368 $U\,mL^{-1}$) in 0.1 M aqueous potassium phosphate buffer (pH 7.5) was added and the reaction mixture was shaken at 37 °C. After 12, 24 and 36 h the same amount of enzyme was added again and after 48 h the solution was heated to 60 °C for 4 h. The reaction mixture was filtered over celite and the filtrate was extracted with diethyl ether (4 × 30 mL). The combined organic layers were dried over $MgSO_4$, then the solvent was evaporated in vacuo to yield the detached aniline. After that the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The polymer was dried in vacuo.

Enzyme-catalysed release of 4-pentylaniline (46): According to the general prescription for the enzyme-initiated cleavage of anilines from POE 6000, POE-bound 4-pentylaniline **45** (44 mg, 13 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (4 μL, 72 $mg\,mL^{-1}$, 1368 $U\,mL^{-1}$) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **46**:[26] Colourless oil (1.5 mg, 9 μmol, 68%); $R_f = 0.38$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 6.97$ (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 6.61 (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 3.47 (br s, 2H; NH_2), 2.50 (t, $^3J(H,H) = 7.5$ Hz, 2H; CCH_2), 1.58 (q, $^3J(H,H) = 7.5$ Hz, 2H; CCH_2CH_2), 1.38–1.22 (m, 4H; $CH_2CH_2CH_3$), 0.90 (t, $^3J(H,H) = 7.5$ Hz, 3H; CH_3). The spectroscopic data are in agreement with the literature.[26]

Polymer-bound lactam 26: Colourless solid; isolated amount of polymer: 36 mg, 11 μmol, 85%. The reaction was quantitative as determined by the ^{1}H NMR spectrum.

Enzyme-catalysed release of 4-aminobenzoic acid ethyl ester (48): According to the general procedure for the enzyme-initiated cleavage of anilines from POE 6000, POE-bound 4-aminobenzoic acid ethyl ester **47** (40 mg, 11 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (4 μL, 72 $mg\,mL^{-1}$, 1368 $U\,mL^{-1}$) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **48**:[27] Colourless oil (1.1 mg, 7 μmol, 60%); $R_f = 0.37$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.81$ (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 6.60 (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 4.28 (q, $^3J(H,H) = 6.4$ Hz, 2H; CH_2), 4.01 (br s, 2H; NH_2), 1.32 (t, $^3J(H,H) = 6.4$ Hz, 3H; CH_3); $C_9H_{11}NO_2$ (165.2); The spectroscopic data are in agreement with the literature.[27]

POE-bound 4-iodoaniline 50: According to the general procedure for the synthesis of POE-bound anilides, POE-bound carboxylic acid **29** (250 mg, 74 μmol), EDC (56 mg, 292 μmol), HOBt (50 mg, 368 μmol) and 4-iodoaniline (**49**, 129 mg, 589 μmol) were allowed to react in DMF (5 mL). White solid; Isolated amount of polymer: 258 mg, 72 μmol, 97%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.25$ (br s, 1H; NH), 7.54 (d, $^3J(H,H) = 8.6$ Hz, 2H; arom. CH), 7.40 (d, $^3J(H,H) = 8.6$ Hz, 2H; arom. CH); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.98$ (C=O anilide), 137.55 (2C; arom. CH), 134.56 (CNH), 121.56 (2C; arom. CH), 86.78 (CI); IR (KBr, drift): $\tilde{\nu} = 1719$ (C=O, urethane), 1675 (C=O, amide I, anilide), 1521 (C=O, amide II), 1114 cm^{-1} (C–O); average molecular weight: 7201 $g\,mol^{-1}$.

POE-bound biphenyl aniline 51: A solution of polymer-bound 4-iodoaniline **50** (200 mg, 55 μmol), 4-methoxyphenylboronic acid (42 mg, 277 μmol) and $K_3PO_4 \cdot 3H_2O$ (29 mg, 110 μmol) in DMF/H_2O 10:1 (5.5 mL) was degassed for 20 min under ultrasonication. Then $[Pd(PPh_3)_4]$ (1.3 mg, 1 μmol) was added and the reaction mixture was stirred at 80 °C. After 20 h the solvent was evaporated in vacuo, the residue was redissolved in CH_2Cl_2 (20 mL) and washed with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (2 mL), the polymer precipitated through slow addition of ice-cold diethyl ether, filtered off and washed with diethyl ether (0 °C) and ethanol (0 °C). The precipitate was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 186 mg, 52 μmol, 95%. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 8.99$ (br s, 1H; NH), 7.65 (d, $^3J(H,H) = 8.5$ Hz, 2H; arom. CH), 7.48 (d, $^3J(H,H) = 8.6$ Hz, 2H; arom. CH), 7.45 (d, $^3J(H,H) = 8.5$ Hz, 2H; arom. CH), 6.95 (d, $^3J(H,H) = 8.8$ Hz, 2H; arom. CH), 3.85 (s, 3H; OCH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.47$ (C=O anilide), 137.43 (*C*OCH_3), 136.25 (NHCCHCH*C*C), 133.24 (NHCCHCHC*C*), 133.24 (CNH), 127.75 (2C; arom. CH), 126.87 (2C; arom. CH), 119.92 (2C; arom. CH), 114.16 (2C; arom. CH), 55.31 (OCH_3); IR (KBr, drift): $\tilde{\nu} = 1718$ (C=O, urethane), 1670 (C=O, amide I, anilide), 1521 (C=O, amide II), 1109 cm^{-1} (C–O); average molecular weight: 7161 $g\,mol^{-1}$.

Enzyme-catalysed release of 4′-methoxy[1,1′-biphenyl]-4-amine (52): According to the general procedure for the enzyme-initiated cleavage of anilines from POE 6000, POE-bound biphenyl aniline **51** (38 mg, 10 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (3 μL, 72 $mg\,mL^{-1}$, 1368 $U\,mL^{-1}$) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). **52**:[28] Colourless oil (1.2 mg, 6 μmol, 57%); $R_f = 0.25$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta =$ 7.42 (d, $^3J(H,H) = 8.2$ Hz, 2H; arom. CH), 7.35 (d, $^3J(H,H) = 8.2$ Hz, 2H; arom. CH), 6.91 (d, $^3J(H,H) = 9.3$ Hz, 2H; arom. CH), 6.72 (d, $^3J(H,H) =$

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9.3 Hz, 2H; arom. CH), 3.73 (s, 3H; OCH_3); MS (EI, 70 eV, 50 °C): *m*/*z* (%): 199 (100) $[M]^+$, 184 (59); HRMS (70 eV): calcd for $C_{13}H_{13}NO$: 199.0997, found: 199.0972. The spectroscopic data are in agreement with the literature.[28]

POE-bound enol ether 53: A solution of polymer-bound 4-iodoaniline **50** (200 mg, 55 μmol) and triphenylarsine (3 mg, 10 μmol) in dioxane (4 mL) was degassed for 20 min under ultrasonication. Then tributyl(1-ethoxyvinyl)stannane (52 μL, 156 μmol) and $[Pd_2(dba)_3]\cdot CHCl_3$ (2.6 mg, 2.6 μmol) were added and the reaction mixture was stirred 24 h at 60 °C. Then the solution was decanted to remove a precipitate which formed during the reaction. The polymer was precipitated through slow addition of ice-cold diethyl ether, filtered off and washed with diethyl ether (0 °C) and ethanol (0 °C). The precipitate was redissolved in CH_2Cl_2 (2 mL) and the procedure was repeated to yield a white solid. Isolated amount of polymer: 74 mg, 21 μmol, 81 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 9.00$ (br s, 1H; NH), 7.56 (d, $^3J(H,H) = 8.8$ Hz, 1H; arom. CH), 7.52 (d, $^3J(H,H) = 8.7$ Hz, 1H; arom. CH), 7.31–7.23 (m, 2H; arom. CH), 4.56 (d, $^2J(H,H) = 2.3$ Hz, 1H; C=CH_{2a}), 4.14–4.13 (m, 1H; C=CH_{2b}), 3.90 (q, $^3J(H,H) = 7.0$ Hz, 2H; OCH_2), 1.41 (t, $^3J(H,H) = 6.9$ Hz, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 171.34$ (C=O anilide), 159.49 (*C*=CH_2), 135.00 (CNH), 125.76 (2C; arom. CH), 119.58 (*C*C=CH_2), 119.00 (2C; arom. CH), 81.31 (C=CH_2), 63.16 (OCH_2), 14.53 (CH_3); IR (KBr, drift): $\tilde{\nu} = 1721$ (C=O, urethane), 1667 (C=O, amide I, anilide), 1515 (C=O, amide II), 1116 cm^{-1} (C–O); average molecular weight: 7089 g mol^{-1}.

POE-bound acetophenone 54: A solution of polymer-bound enol ether **53** (74 mg, 21 μmol) in 0.5 M hydrochloric acid/THF 1:1 (10 mL) was stirred for 4 h at room temperature. Then the pH of the reaction mixture was adjusted to pH 7 with $NaHCO_3$ solution and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated in vacuo to yield a colourless solid. Isolated amount of polymer: 68 mg, 19 μmol, 92 %. The reaction was quantitative as determined by the ^{1}H NMR spectrum. ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 9.57 (br s, 1H; NH), 7.86 (d, $^3J(H,H) = 8.7$ Hz, 2H; arom. CH), 7.70 (d, $^3J(H,H) = 8.7$ Hz, 2H; arom. CH), 2.56 (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 196.87$ (C=O ketone), 171.62 (C=O anilide), 143.20 (CNH), 132.24 (*C*C(O)), 127.70 (2C; arom. CH), 118.77 (2C; arom. CH), 26.30 (CH_3); IR (KBr, drift): $\tilde{\nu} = 1712$ (C=O, urethane, ketone), 1670 (C=O, amide I, anilide), 1519 (C=O, amide II), 1116 cm^{-1} (C–O); average molecular weight: 7033 g mol^{-1}.

Enzyme-catalysed release of 4-aminoacetophenone (55): According to the general procedure for the enzyme-initiated cleavage of anilines from POE 6000, POE-bound acetophenone **52** (29 mg, 8 μmol) was dissolved in methanol (3 mL) and 0.2 M aqueous sodium phosphate buffer (pH 7.0, 26 mL) and incubated with a suspension of penicillin G acylase (3 μL, 72 mg mL^{-1}, 1368 U mL^{-1}) in 0.1 M aqueous potassium phosphate buffer (pH 7.5). The crude product was purified by chromatography on silica gel (ethyl acetate/hexane 1:4 *v*/*v*) to yield a colourless oil (0.7 mg, 5 μmol, 67 %). **55**:[29] $R_f = 0.28$ (ethyl acetate/hexane 1:4 *v*/*v*); ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta =$ 7.81 (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 6.68 (d, $^3J(H,H) = 9.1$ Hz, 2H; arom. CH), 4.13 (br s, 2H; NH_2), 2.51 (s, 3H; CH_3); C_8H_9NO (135.2); The spectroscopic data are in agreement with the literature.[29]

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