DOI: 10.1002/ejoc.200500450

Asymmetric Michael Reactions on Polymeric Support: Auxiliary Immobilization and Stereoselective Construction of Quaternary Stereocenters

Burkard Kreidler,[a] Angelika Baro,[a] and Jens Christoffers*[a]

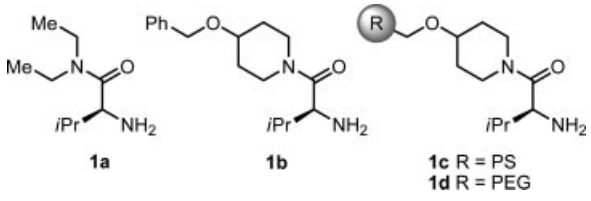
Keywords: Chiral auxiliary / Michael reaction / Solid support / Transesterification / Quaternary stereocenters

Several strategies for the immobilization of a L-valine-derived auxiliary on a Merrifield resin and on poly(ethylene glycol) are reported. The latter is shown to work excellently in asymmetric copper(II)-catalyzed Michael reactions of cyclic β-oxo esters **2** with methyl vinyl ketone (**4**), yielding the corresponding addition products **5** with quaternary stereocenter in selectivities of 97–99% *ee*. The PEG-supported auxiliary **1d** can be precipitated from diethyl ether solutions and reused. A sulfur-containing β-oxo ester **2c** was prepared in 92% yield by a DMAP-catalyzed transesterification method in order to detect enamine formation on solid support. The sulfur content can be used as an additional parameter in combustion analysis and therefore, may act as a diagnostic probe for enamine formation.

Introduction

The asymmetric Michael reaction belongs to the important tools for stereoselective C–C bond formation.[1] Some of the various chiral auxiliaries and catalysts published in the literature have proved their utility in the construction of quaternary stereocenters, however, a search for new, more effective ones is still a great challenge for synthetic organic chemistry.[2] There have been several reports on polymer-bound catalysts in this field,[3] but only very few of them give Michael adducts with high stereoselectivity. One of the most successful systems so far was the polystyrene-supported (Merrifield resin) cinchona alkaloid catalyst developed by d'Angelo and co-workers, allowing the generation of quaternary stereocenters with 87% *ee*.[4] A stereoselective Michael reaction based on a valine derivative **1a** as chiral auxiliary has been introduced by our group.[5] The chiral auxiliary and β-oxo esters or β-diketones initially form enamines which are converted in a copper(II)-catalyzed reaction with methyl vinyl ketone at ambient temperature to give the corresponding Michael products. After completion of the reaction, the auxiliary can be reisolated during the workup procedure. For this purpose L-valine diethylamide (**1a**) turned out to be the optimal auxiliary in homogeneous phase.

In order to facilitate auxiliary separation and recovery and furthermore, to operate the Michael reaction sequence continuously, we envisioned to develop a solid-phase variant of this successful concept. One essential issue for a well-suited auxiliary is sufficient electron density at the carbonyl oxygen of the amino acid derivative, which is realized by choosing the carboxamide function as the copper coordinating group. Moreover, *E*/*Z* isomerism at the amide N–C bond should be avoided by appropriate symmetry of the nitrogen substituents. Furthermore, the auxiliary should be bound to the solid support by an inert linkage, for example by ether formation. As known from polymer-bound catalysts, the polymer resin should be attached far away from the reactive center, thus, *N*-alkyl substituents appear to be the ideal groups for the linkage to the solid support. Taking these requirements into account the L-valine-derived auxiliaries **1c** and **1d** shown in Scheme 1 seem to be suitable candidates for our strategy. In this paper we report their synthesis, their immobilization and their application in the asymmetric Michael reaction.



1a **1b** **1c** R = PS **1d** R = PEG

Scheme 1. L-Valine diethylamide (**1a**) and derived new auxiliaries **1b**–**1d**; PS = polystyrene (Merrifield resin), PEG = poly(ethylene glycol).

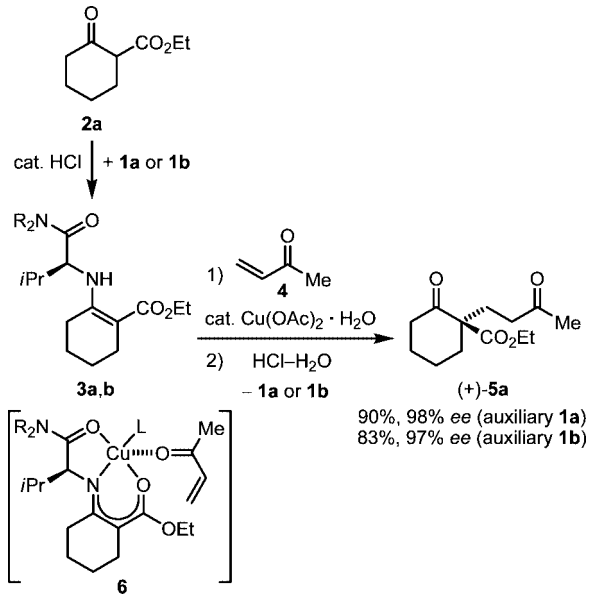
Results and Discussion

Enamine Formation and Michael Reactions

According to our concept we prepared the auxiliary **1b** as key intermediate (vide infra) bearing a symmetrically substituted amide nitrogen and a secondary alcohol func-

[a] Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: +49-711-6854269
E-mail: jchr@oc.uni-stuttgart.de

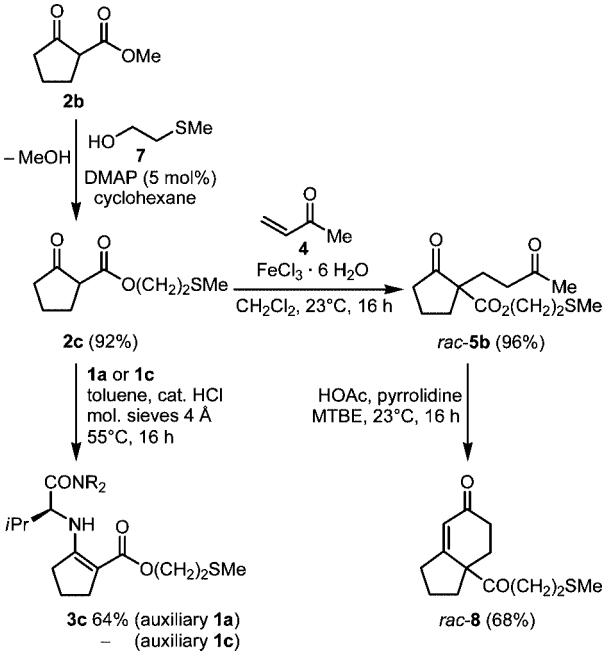
tion for further linkage to a polymer. Thus, derivative **1b** with benzyl ether functionalized piperidine ring was considered to be a monomeric model of polystyrene-bound valine derivative **1c**. In order to investigate whether yield and selectivity are influenced by replacing the diethylamino group in **1a** with the piperidine ring, model **1b** was initially compared with **1a**. After enamine formation with β-oxo ester **2a** in 61% yield, we followed our standard protocol of asymmetric copper(II)-catalyzed Michael reaction with methyl vinyl ketone (**4**). Aqueous workup with hydrochloric acid afforded product **5a** in 83% yield with 97% *ee* for the newly generated quaternary stereocenter (Scheme 2). Thus, auxiliary **1b** is nearly as efficient as L-valine diethylamide (**1a**), indicating that neither yield nor selectivity was influenced by the structural variation.



Scheme 2. Asymmetric copper-catalyzed Michael reaction by using the chiral auxiliaries L-valine diethylamide (**1a**) and polystyrene model **1b**, respectively.

According to our mechanistic model,[6] the reaction occurs via intermediate **6** which is formed by deprotonation of the enamine by acetate, followed by coordination of the resulting azadionato anion to the metal ion. Coordination to the amide oxygen leads to a second chelate. Ketone **4** coordinates and alkylates from the *Re* face, giving after acidic hydrolysis the (*R*)-configured product **5a**. This mechanistic view agrees with the absolute configuration of (+)-**5a**, which is known to be (*R*).[7]

Next, we prepared (vide infra) and investigated the application of polystyrene-bound auxiliary **1c** in the Michael reaction with β-oxo ester **2a**. In the presence of various Brønsted acids, however, no enamine derived from **1c** and **2a** could be detected by elemental analyses, mass balances and FTIR measurements. As we could not exclude that these measurements are incorrect or that traces of water in the solvents used for washing gave rise for hydrolysis of a previously formed enamine, we decided to introduce sulfur as an additional parameter in combustion analysis of the polymer. Since sulfur plays the role of a probe for successful enamine formation (by elemental analysis), we prepared methylthio-functionalized β-oxo ester **2c** (Scheme 3).



Scheme 3. Synthesis of β-oxo ester **2c** by azeotropic transesterification, racemic iron(III)-catalyzed Michael reaction and enamine formation in homogeneous and on solid phase.

In analogy to a recently published procedure,[8] β-oxo ester **2b** and 2-(methylthio)ethanol (**7**) were subjected to a DMAP-mediated azeotropic transesterification in cyclohexane to give the desired β-dicarbonyl compound **2c** in 92% yield under release of MeOH (Scheme 3). The key issue of this method is azeotrop formation of MeOH and cyclohexane in the vapour phase although immiscibility prevails in the condensed phase.

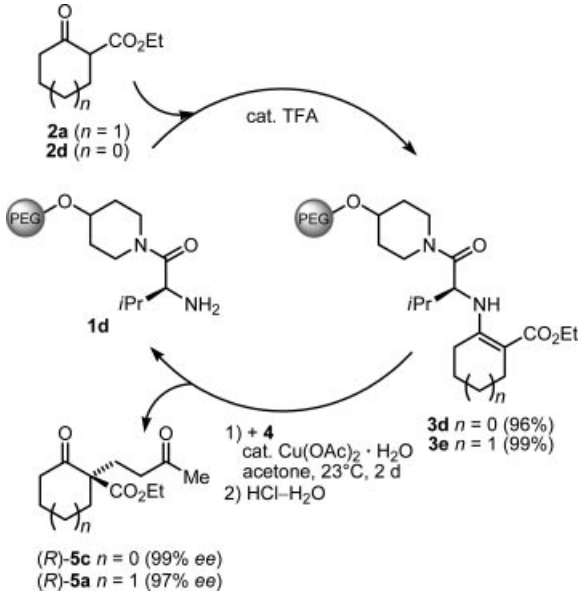
Because racemic material of the corresponding Michael product **5b** was necessary for establishment of a separation method via GLC on a chiral phase, the donor **2c** was converted with methyl vinyl ketone (**4**) in the presence of catalytic amounts of $FeCl_3 \cdot 6\ H_2O$[9] into diketone *rac*-**5b** almost quantitatively. No catalyst poisoning by the thioether was observed. However, the enantiomers of *rac*-**5b** could not be separated by GLC. Therefore, Michael product *rac*-**5b** was submitted to annulation by AcOH/pyrrolidine to yield the bicyclic compound *rac*-**8** (Scheme 3). The enantiomers of *rac*-**8** gave baseline resolution at gas chromatography on a chiral phase.

Sulfur-containing donor **2c** and L-valine diethylamide (**1a**) formed enamine **3c** in 64% yield in toluene at 55 °C in the presence of molecular sieves (4 Å) and catalytic amounts of HCl (Scheme 3). Applying these conditions and a number of variations to the reaction of polystyrene-supported auxiliary **1c** with **2c**, practically no sulfur was found in the elemental analyses, thus indicating that **3c** was not formed.

To overcome this problem we decided to replace the crosslinked polystyrene by poly(ethylene glycol) (PEG), a

polymer soluble in most organic solvents. In the past years soluble polymers have gained attraction due to practically homogeneous reaction conditions,[10] and a number of reviews have appeared on the use of soluble polymer-supported catalysts and reagents.[11] Also the application of soluble polymer catalysts for a continuously operated asymmetric reaction was reported.[12]

After preparation of the PEG-immobilized chiral linker **1d** (vide infra), enamine formation with cyclopentanone and cyclohexanone carboxylate **2d** and **2a** was carried out in the presence of catalytic amounts of TFA without removal of water (Scheme 4). The corresponding PEG-bound enamines **3d** and **3e**, which are formed almost quantitatively, were converted with methyl vinyl ketone (**4**) in asymmetric Michael reactions catalyzed by copper(II) acetate. After acidic workup, Michael products **5a** and **5c** were obtained with excellent enantioselectivities of 97% (**5a**) and 99% (**5c**) for the quaternary stereocenter (Scheme 4).

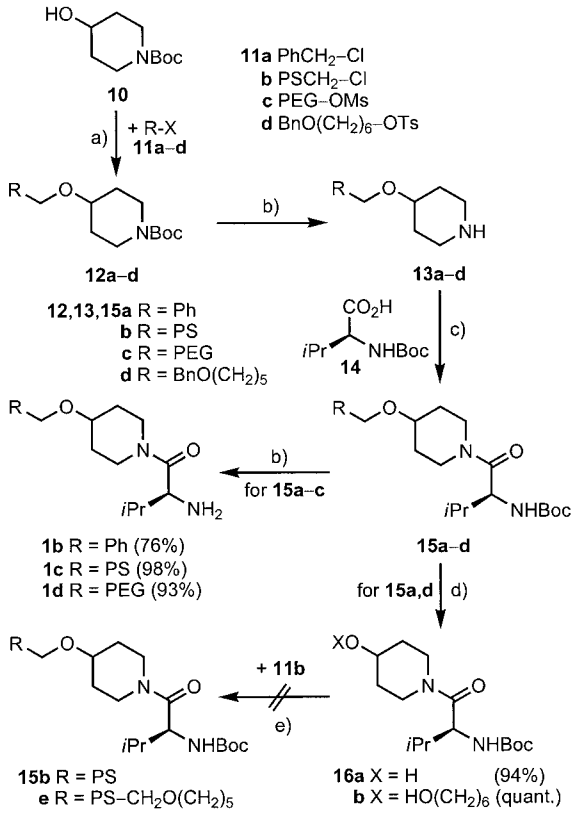


Scheme 4. Envisioned concept of an enamine formation/Michael reaction cycle with PEG-supported auxiliary **1d**; only one of the two polyglycol chain termini is shown.

To the best of our knowledge, these are so far the highest *ee* values of quaternary stereocenters obtained by polymer-supported auxiliaries. After hydrolysis, the PEG-immobilized auxiliary **1d** was reisolated by precipitation from diethyl ether and applied in second cycle of enamine formation with β-oxo ester **2a** and following Michael reaction with methyl vinyl ketone (**4**) to yield **5a** still with excellent selectivity of 90% *ee* for the quaternary stereocenter.

Synthesis of the L-Valine-Derived Auxiliaries

The synthetic routes to the auxiliaries and their precursors involve etherification reactions, deprotections, amide formations, debenzylations, and linkages to a resin and are summarized in Scheme 5 and Table 1. First of all, model derivative **1b** was synthesized by reacting our starting material, *N*-Boc-protected 4-hydroxypiperidine (**10**),[13] with benzyl chloride (**11a**) to give the *O*-benzylated compound **12a** in 94% yield. After removal of the Boc protective group with TFA, the free amine **13a**[14] was isolated in 87% yield. Reaction of **13a** with *N*-Boc-L-valine (**14**) in a DCC-mediated coupling yielded amide **15a** with 90% yield (Table 1). Deprotection of the amino function again with TFA finally accomplished the synthesis of model auxiliary **1b**, which was isolated in 76% yield (Scheme 5).



Scheme 5. Synthesis of L-valine-derived auxiliaries. Reagents and conditions: a) alkylating agents **11**, NaH, TBAI, 23 °C; b) TFA, CH_2Cl_2, 23 °C, 16 h; c) DCC, CH_2Cl_2, 23 °C, 16 h; d) Pd/C, H_2, EtOH, EtOAc, 23 °C; e) NaH, DMF, TBAI, 23 °C, 14 d.

Table 1. Preparation of L-valine-derived auxiliary precursors **15** starting from *N*-Boc-protected 4-hydroxypiperidine **10** by etherification, deprotection, and amide formation.

Starting materials		Products					
11	RX	**12**	Yield (%)	**13**	Yield (%)	**15**	Yield (%)
a	$PhCH_2Cl$	**a**	94	**a**	87	**a**	90
b	$PSCH_2Cl$	**b**	87[a]	**b**	–	**b**	52[a,b]
c	PEGOMs	**c**	99[c]	**c**	94[c]	**c**	91[c]
d	$BnO(CH_2)_6OTs$	**d**	64	**d**	quant.	**d**	93

[a] Yields were calculated from the nitrogen content in elemental analysis. [b] Over two steps. [c] Yields are referred to the mass of reisolated polymer.

Next, we anticipated the attachment to a Merrifield-type resin **11b** in an analogous manner starting from *O*-benzylated derivative **15a** (Scheme 5). Hydrogenolytic debenzylation of **15a** afforded amide **16a** with a secondary alcohol function in 94% yield, which should undergo Wil-

liamson etherification under Finkelstein conditions (iodide-mediated)[15] with chloromethylated polystyrene **11b**. However, even after 14 days of shaking, significant amounts of immobilized auxiliary **15b** could not be detected in the reaction, which was monitored by mass balances and the nitrogen and chlorine contents in elemental analyses.

Neither variation of the base nor elevation of the temperature or stirring instead of shaking turned out to be helpful. The secondary alkoxide in proximity to an isopropyl and a *tert*-butyl group evidently seems to be too bulky for the diffusion into the soaked polymer. We therefore considered to introduce a flexible hexamethylene linker into the auxiliary in order to reduce the local constraints at the reacting center analogously to our previous synthetic route (Scheme 5). First, alkylating agent **11d** was prepared from 1,6-hexanediol by monobenzylation[16] and subsequent esterification with tosyl chloride.[17] Derivative **11d** was etherified with *N*-Boc-protected hydroxypiperidine **10** to provide derivative **12d** (64%). After removal of the nitrogen protective group, resulting amine **13d** was coupled with **14** to give amide **15d** in 93% yield (Table 1). Hydrogenolytic debenzylation of **15d** afforded quantitatively compound **16b** with hexyl side chain. But again, the linkage to the Merrifield resin **11b** failed.

Because the bulkiness of the auxiliary is assumed to be responsible for low conversion rates, we changed our synthetic strategy. Instead of linking a fully assembled auxiliary to the Merrifield resin **11b**, we decided to start with **11b** and build up the auxiliary stepwise on the solid support. Thus, in the initial reaction step protected hydroxypiperidine **10** was attached to chloromethylated polystyrene **11b**, yielding the corresponding derivative **12b** after 14 days reaction time (practically quantitative substitution of chlorine was observed). The further manipulation followed our previous route, however, reactions now were performed with a resin. After *N*-Boc deprotection with TFA, resin-bound piperidine **13b** was coupled with *N*-Boc-L-valine **14** to give amide **15b**, which furnished the auxiliary **1c** after deprotection with TFA (Scheme 5).

In analogy to polystyrene derivatives, the PEG-immobilized auxiliary **1d** was prepared starting from the corresponding PEG mesylate **11c** (Scheme 5). The reaction of **10** with **11c** yielded ether **12c** almost quantitatively (Table 1). The latter was deprotected to give the free amine **13c** (94%). Coupling of **13c** with L-valine derivative **14** afforded auxiliary precursor **15c**, which gave finally the PEG-immobilized auxiliary **1d** after *N*-deprotection with TFA (Scheme 5). The final polymer load was 74%, calculated from elemental analyses and ^{1}H NMR spectra.[18] These calculations usually resemble in a range of 5%.

Conclusions

Novel L-valine-derived auxiliaries *N*-benzyloxypiperidide **1b** and polymer-supported compounds **1c** and **1d** are conveniently accessible starting from *N*-Boc-protected hydroxypiperidine **10** in a four-step reaction sequence of etherification, deprotection, amide formation with *N*-Boc-L-valine **14** and deprotection. Model auxiliary **1b** is as effective as L-valine diethylamide (**1a**) in the Cu^{II}-catalyzed Michael reaction of β-oxo ester **2a** with methyl vinyl ketone (**4**). From the two polymer-immobilized auxiliaries only **1d**, bound to poly(ethylene glycol), is suitable for this reaction giving Michael products **5a**,**c** with excellent enantioselectivities up to 99% *ee*. After recovery by precipitation from Et_2O, auxiliary **1d** worked in a second reaction cycle with donor **2a** to provide product **5a** with 90% *ee*.

Experimental Section

General: Melting points were measured on a Büchi 510 and are uncorrected. Column chromatography was carried out using Merck SiO_2 60 or Merck basic Alumina (act. I) with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EtOAc) as eluents. ^{1}H NMR spectra were recorded on a Bruker ARX 500 (500 MHz) or a Bruker ARX 300 (300 MHz). ^{13}C NMR spectra were recorded on a Bruker ARX 500 (126 MHz), a Bruker ARX 300 (75 MHz) or a Bruker AC 250 (63 MHz). Multiplicities were determined with DEPT experiments. Chloromethylated polystyrene 1% cross-linked with divinylbenzene (100–200 mesh, 3 mmol Cl g^{-1}) (compound **11b**) was purchased from Acros, poly(ethylene glycol) 2000 dimesylate (average M_n 2000) (compound **11c**) from Fluka.

2-(Methylthio)ethyl 2-Oxocyclopentane-1-carboxylate (2c): A solution of **2b** (10.0 g, 70.3 mmol), 2-methylthioethanol **7** (6.48 g, 7.03 mmol) and DMAP (433 mg, 3.52 mmol) in cyclohexane (50 mL) was refluxed for 18 h in a Dean–Stark trap. After removal of all volatile materials, the residue was purified by chromatography on SiO_2 (PE/EtOAc, 3:1, R_f = 0.29) to give **2c** (13.1 g, 64.8 mmol, 92%) as a pale pink oil. No enol tautomer is detectable in NMR spectra. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.83–1.95 (m, 1 H), 2.11–2.21 (m, 1 H), 2.17 (s, 3 H, CH_3), 2.28–2.36 (m, 4 H), 2.75 (t, ^3J = 7.0 Hz, 2 H; SCH_2), 3.18 (t, ^3J = 9.0 Hz, 1 H; 2-H), 3.11 [A-part of an ABX_2 system, ^2J = (–)15.6, ^3J = 6.9 Hz, 1 H; OCH_2], 3.11 [B-part of an ABX_2 system, ^2J = (–)15.6, ^3J = 6.8 Hz, 1 H; OCH_2] ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 15.8 (CH_3), 21.0 (CH_2), 27.4 (CH_2), 32.4 (CH_2), 38.1 (CH_2), 54.7 (CH; C-2), 63.8 (CH_2; OCH_2), 169.2 (C; COO), 212.1 (C; C-1) ppm. IR (ATR): $\tilde{\nu}$ = 1752 (s), 1720 (vs), 1337 (m), 1296 (m), 1252 (m), 1181 (m), 1109 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 202 (3) [M^+], 111 (13) [$M^+ - C_3H_8OS$], 92 (2) [$C_3H_8OS^+$], 74 (100) [$C_3H_6S^+$], 61 (9) [$C_2H_5S^+$], 55 (9). $C_{19}H_{14}O_3S$ (202.27): calcd. C 53.44, H 6.98, S 15.85; found C 53.20, H 6.75, S 15.73.

***N*-(2-Ethoxycarbonyl-1-cyclohexenyl)-L-valine 4-(Benzyloxy)piperidide (3b):** A suspension of **1b** (250 mg, 0.86 mmol), β-oxo ester **2a** (220 mg, 1.30 mmol), 1 drop of conc. hydrochloric acid and molecular sieves (4 Å, 1.42 g) in absolute toluene (1 mL) was heated for 16 h at 60 °C. After cooling to room temperature, the mixture was purified by chromatography on Al_2O_3 (PE/EtOAc = 3:1, R_f = 0.17) to give **3b** (232 mg, 0.52 mmol, 61%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.99 (d, ^3J = 6.8 Hz, 3 H; CH_3), 1.03 (d, ^3J = 6.8 Hz, 3 H; CH_3), 1.26 (t, ^3J = 8.9 Hz, 3 H; CH_2CH_3), 1.51–1.68 (m, 7 H), 1.83–1.89 (m, 2 H, 3-H), 2.01–2.12 (m, 2 H, CH_2), 2.18–2.32 (m, 2 H, CH_2), 3.26–3.42 (m, 2 H, 3-H_{eq}), 3.66 (tt, ^3J = 7.4, ^3J = 3.7 Hz, 1 H; OCH), 3.70–3.84 (m, 1 H, 2-H_{eq}), 3.88–4.03 (m, 1 H, 2-H_{eq}), 4.12 (d, ^3J = 7.1 Hz, 1 H; C*H*NH), 4.13 (q, ^3J = 6.9 Hz, 2 H; OCH_2), 4.55 [A-part of an AB system, d, ^2J = (–)25.7 Hz, 1 H; Ph-CH_2], 4.57 [B-part of an AB system, d, ^2J = (–)25.7 Hz, 1 H; Ph-CH_2], 7.28–7.36 (m, 5 H, Ar-H), 9.31 (br. d,

^3J = 8.8 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 18.5 (CH_3), 19.9 (CH_2CH_3), 22.4 (CH_2), 22.6 (CH_2), 23.9 (CH_2), 26.8 (CH_2), 30.7 (CH_2; C-3), 32.0 (CH_2; C-3), 39.4 (CH_2; C-2), 42.7 (CH_2; C-2), 58.5 (CHNH), 58.8 (OCH_2), 70.1 (Ph-CH_2), 73.2 (CH; C-4), 91.5 (C), 127.5 (CH; *o*-CH), 127.7 (CH; *p*-CH), 128.5 (CH; *m*-CH), 138.4 (C; *i*-C), 157.5 (C, br. signal; CNH), 170.5 (C), 170.7 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3267 (w), 2930 (m), 2866 (w), 1723 (w), 1640 (s), 1588 (s), 1496 (s), 1361 (m), 1227 (vs), 1164 (s), 1085 (s), 1059 (s), 776 (m), 736 (m), 698 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 442 (5) [M^+], 397 (2) [$M^+ - C_2H_5O$], 354 (1), 314 (5), 275 (2) [$M^+ - C_9H_{13}NO_2$], 224 (100) [$C_{13}H_{22}NO_2^+$], 186 (6), 178 (46), 124 (9), 106 (23), 91 (57) [$C_7H_7O^+$], 72 (53) [$C_4H_{10}N^+$]. HRMS (EI, 70 eV) calcd. for $C_{26}H_{38}N_2O_4$ 442.2832, found 442.2833. $C_{26}H_{38}N_2O_4$ (442.59): calcd. C 70.56, H 8.65, N 6.33; found C 70.24, H 8.73, N 6.10. $[\alpha]_D^{20}$ = +154 (*c* = 6.5 in $CHCl_3$).

***N*-[2-(2-Methylthioethyloxycarbonyl)-1-cyclopentenyl]-L-valine Diethylamide (3c):** According to the procedure for **3b**, β-oxo ester **2c** (200 mg, 0.99 mmol) and **1a** (272 mg, 0.99 mmol) were converted in toluene (3 mL) in the presence of one drop of conc. hydrochloric acid and molecular sieves (4 Å, 1.00 g) to give **3c** (226 mg, 0.63 mmol, 64%) after chromatography on Al_2O_3 [PE/EtOAc, 3:1, $R_f(SiO_2)$ = 0.27] as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.98 (d, ^3J = 6.9 Hz, 3 H; $CHCH_3$), 0.98 (d, ^3J = 6.9 Hz, 3 H; $CHCH_3$), 1.12 (t, ^3J = 7.1 Hz, 3 H; NCH_2CH_3), 1.20 (t, ^3J = 7.1 Hz, 3 H; NCH_2CH_3), 1.82 (quint, ^3J = 7.3 Hz, 2 H; 4′-H), 2.03 (oct, ^3J = 6.6 Hz, 1 H; $CHCH_3$), 2.17 (s, 3 H, SCH_3), 2.38–2.59 (m, 4 H, 3′-H and 5′-H), 2.76 (t, ^3J = 6.9 Hz, 2 H; SCH_2), 3.14 [dq, ^2J = (–)13.4, ^3J = 6.9 Hz, 1 H; NCH_2], 3.26 [dq, ^2J = (–)14.9, ^3J = 7.2 Hz, 1 H; NCH_2], 3.42 [dq, ^2J = (–)14.9, ^3J = 7.2 Hz, 1 H; NCH_2], 3.64 [dq, ^2J = (–)13.4, ^3J = 6.9 Hz, 1 H; NCH_2], 3.92 (dd, ^3J = 9.9, ^3J = 6.1 Hz, 1 H; $CHNH$), 4.28 [A-part of an ABX_2 system, ^2J = (–)19.5, ^3J = 6.9 Hz, 1 H; OCH_2], 4.31 [B-part of an ABX_2 system, ^2J = (–)19.5, ^3J = 6.9 Hz, 1 H; OCH_2], 7.80 (br. d, ^3J = 9.9 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 75 MHz): δ = 12.9 (CH_3; CH_2CH_3), 14.7 (CH_3; CH_2CH_3), 17.5 (CH_3; SCH_3), 19.8 (CH_3; $CHCH_3$), 20.94 (CH_3; $CHCH_3$), 20.95 (CH_2; C-4′), 29.2 (CH_2), 32.7 (CH; $CHCH_3$), 32.8 (CH_2), 32.9 (CH_2), 40.2 (CH_2; NCH_2), 41.6 (CH_2; NCH_2), 59.8 (CH; CHNH), 61.8 (CH_2; OCH_2), 93.6 (C; C-2′), 162.8 (C), 167.4 (C), 170.5 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3315 (w), 2965 (s), 2876 (m), 1655 (s), 1597 (vs), 1463 (m), 1373 (m), 1263 (s), 1113 (m), 895 (m), 674 (w), 637 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 356 (8) [M^+], 256 (35) [$M^+ - CONEt_2$], 164 (15), 100 (3) [$CONEt_2^+$], 75 (100) [$C_3H_7S^+$]. HRMS calcd. for $C_{18}H_{32}N_2O_3S$ 356.2133; found 356.2132.

Purification of Poly(ethylene glycol). General Procedure A: After removal of all volatile materials, the residue was dissolved in H_2O (20 mL per 1 g of polymer). The mixture was washed with Et_2O (3 × 20 mL) and the organic layers were re-extracted with H_2O (20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers washed with H_2O and dried ($MgSO_4$). After concentration to 2 mL, the mixture was precipitated from Et_2O (50 mL).

PEG-Supported *N*-(2-Ethoxycarbonyl-1-cyclopentenyl)-L-valine 4-Hydroxypiperidide (3d): Polymer **1d** (0.50 g), β-oxo ester **2d** (1.00 g, 6.40 mmol) and one drop of TFA were allowed to react in toluene (5 mL) for 16 h at 55 °C. After cooling to 23 °C, the polymer was precipitated twice from Et_2O (30 mL) according to General Procedure A to give a pale yellow polymer **3d** (0.48 g, 96%). Load according to ^1H NMR: 42%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.98 (d, ^3J = 6.0 Hz, 3 H; $CHCH_3$), 1.28 (t, ^3J = 6.0 Hz, 3 H; CH_2CH_3), 1.51–1.68 (m, 2 H), 1.75–1.85 (m, 5 H), 2.26–2.45 (m, 2 H), 2.52 (t, ^3J = 7.5 Hz, 4 H), 3.17–3.38 (m, 2 H), 3.54–3.76 (m, 213 H, PEG–H), 3.88 (dd, ^3J = 6.0, ^3J = 3.0 Hz, 1 H; $CHNH$), 4.16 (q, ^3J = 6.0 Hz, 1 H; CH_2Me), 4.17 (q, ^3J = 6.0 Hz, 1 H; CH_2Me), 7.75 (br. d, ^3J = 9.0 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 19.8 (CH_3), 20.8 (CH_2), 22.1 (CH_3), 27.4 (CH_2), 29.3 (CH_2), 30.6 (CH_2), 32.1 (CH; $CHCH_3$), 32.6 (CH_2), 39.3 (CH_2; C-2′), 42.7 (CH_2; C-2′), 58.5 (OCH_2), 59.8 (CHNH), 67.4–74.1 (m, CH_2; PEG–CH_2), 161.9 (C, br. signal; CNH), 167.9 (C; CON), 170.0 (C; COO) ppm. IR (ATR): $\tilde{\nu}$ = 3502 (w, br), 2882 (s), 2741 (w), 1963 (w), 1734 (w), 1637 (m), 1466 (m), 1359 (m), 1341 (s), 1279 (m), 1240 (m), 1146 (s), 1102 (vs), 947 (s), 841 (s) cm^{-1}. Found C 55.70, H 9.06, N 1.05.

PEG-Supported *N*-(2-Ethoxycarbonyl-1-cyclohexenyl)-L-valine 4-Hydroxypiperidide (3e): According to the procedure for **3d**, β-oxo ester **2a** (3.00 g, 17.6 mmol), polymer **1d** (2.50 g, 1.54 mmol) and one drop of TFA were allowed to react in toluene (8 mL) to give a pale yellow polymer **3e** (2.58 g, 99%) after twofold precipitation from Et_2O (80 mL) according to General Procedure A. Load according to ^1H NMR: 65%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.00 (d, ^3J = 6.9 Hz, 3 H; CH_3), 1.03 (d, ^3J = 6.9 Hz, 3 H; CH_3), 1.26 (t, ^3J = 7.1 Hz, 3 H; CH_2CH_3), 1.47–1.68 (m, 6 H), 1.77–1.92 (m, 2 H), 1.95–2.14 (m, 2 H), 2.21–2.32 (m, 3 H), 3.23–3.36 (m, 2 H), 3.50–3.74 (m, 140 H, PEG–H), 3.91–4.01 (m, 1 H), 4.13 (q, ^3J = 7.2 Hz, 2 H; OCH_2), 9.31 (br. d, ^3J = 8.8 Hz, 1 H; NH) ppm. Missing signals are overlapped by resonances of the polymer backbone. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 14.7 (CH_3), 18.4 (CH_3), 19.9 (CH_2CH_3), 22.4 (CH_2), 22.6 (CH_2), 23.9 (CH_2), 26.8 (CH_2), 30.7 (CH_2, br. signal; C-3′), 31.8 (CH_2, br. signal; C-3′), 32.0 (CH; $CHCH_3$), 39.5 (CH_2, br. signal; C-2′), 42.7 (CH_2, br. signal; C-2′), 58.4 (CH; CHNH), 58.7 (CH_2; OCH_2), 74.4 (CH; OCH), 91.5 (C; C-2′′), 157.5 (C, br. signal; CNH), 170.5 (C; CON); 170.6 (C; COO) ppm. IR (ATR): $\tilde{\nu}$ = 3483 (w, br), 2882 (s), 1741 (w), 1957 (w), 1645 (m), 1592 (m), 1466 (m), 1359 (m), 1341 (s), 1279 (m), 1233 (s), 1146 (m), 1103 (vs), 1063 (vs), 948 (s), 841 (s), 776 (m) cm^{-1}. Found C 56.42, H 9.18, N 1.57.

Ethyl (*R*)-2-Oxo-1-(3-oxobutyl)cyclohexanecarboxylate (5a): A solution of enamine **3b** (50 mg, 0.11 mmol) and $Cu(OAc)_2 \cdot H_2O$ (1.1 mg, 0.060 mmol) in acetone (0.5 mL) was stirred for 1 h. Then **4** (16 mg, 0.22 mmol) was added and the mixture was stirred for a further 14 h at 23 °C. After evaporation of the solvent, hydrochloric acid (1 mL, *c* = 0.1 mol·dm^{-3}) was added and the mixture was stirred for 3 h at 0 °C. Extraction with CH_2Cl_2 (3 × 10 mL), drying ($MgSO_4$), evaporation and chromatography on SiO_2 (PE/EtOAc, 2:1, R_f = 0.32) yielded **5a** (22 mg, 0.09 mmol, 83%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (t, ^3J = 7.3 Hz, 3 H; OCH_2CH_3), 1.42–1.54 (m, 1 H), 1.59–1.92 (m, 4 H), 1.96–2.11 (m, 2 H), 2.13 (s, 3 H, CH_3), 2.30–2.64 (m, 5 H), 4.20 [A-part of an ABX_3 system, ^2J = (–)13.3, ^3J = 7.0 Hz, 1 H; OCH_2], 4.21 [B-part of an ABX_3 system, ^2J = (–)12.5, ^3J = 7.1 Hz, 1 H; OCH_2] ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 14.1 (CH_3; CH_2CH_3), 22.5 (CH_2), 27.5 (CH_2), 28.4 (CH_2), 29.9 (CH_3; $COCH_3$), 36.6 (CH_2), 38.8 (CH_2), 41.0 (CH_2), 41.1 (CH_2), 60.0 (C; C-2), 61.4 (CH_2; OCH_2), 172.0 (C; COO), 207.7 (C), 208.0 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2939 (w), 2867 (w), 1973 (w), 1706 (vs), 1146 (m), 1366 (m), 1213 (m), 1188 (s), 1168 (m), 1096 (m), 1021 (w), 860 (w) cm^{-1}. GC/MS (CI, CH_4), *m*/*z* (%): 241 (38) [MH^+], 223 (100), 212 (3) [$M^+ - C_2H_4$], 194 (5), 171 (18), 151 (33), 142 (4), 123 (5), 111 (3), 99 (8), 85 (8), 71 (2), 55 (5). $C_{13}H_{20}O_4$ (240.30): calcd. C 64.98, H 8.39; found C 65.02, H 8.39. GC: Bondex unβ, 80 °C isotherm (3 min), then gradient 2.5 °C min^{-1}, $t_R(R)$ = 30.01 min; $t_R(S)$ = 30.29 min, 97% *ee* [cf. racemate:[19] $t_R(R)$ = 30.02 min; $t_R(S)$ = 30.21 min].

Ethyl (*R*)-2-Oxo-1-(3-oxobutyl)cyclopentanecarboxylate (5c) from PEG-Supported (*R*)-*N*-[2-Ethoxycarbonyl-2-(3-oxobutyl)-1-cyclo-

pentylidene]-L-valine 4-Hydroxypiperidide: a) Polymer **3d** (0.40 g) and $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol) were dissolved in acetone (2 mL). After stirring at 23 °C for 1 h, **4** (1.00 g, 14.3 mmol) was added and the mixture was stirred for 2 d at 23 °C. Precipitation from Et_2O (50 mL) according to General Procedure A afforded a brown polymer (0.39 mg). Load according to ^1H NMR: 39%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.82 (d, ^3J = 6.1 Hz, 3 H; $CHCH_3$), 0.97 (d, ^3J = 6.3 Hz, 3 H; $CHCH_3$), 1.22 (t, ^3J = 7.1 Hz, 3 H; CH_2CH_3), 1.40–1.66 (m, 4 H), 1.67–1.89 (m, 7 H), 2.13 (s, 3 H, CH_3), 2.13–2.19 (m, 2 H), 2.20–2.37 (m, 4 H), 2.37–2.48 (m, 2 H), 2.62–2.76 (m, 1 H), 2.86–3.09 (m, 1 H), 3.32 (ddd, ^3J = 12.3, ^3J = 8.6, ^3J = 2.1 Hz, 1 H), 3.35–3.69 (m, 233 H, PEG–H), 4.11 (q, ^3J = 7.2 Hz, 3 H; OCH_2) ppm. IR (ATR): $\tilde{\nu}$ = 2882 (s), 2741 (w), 1721 (w), 1638 (m), 1466 (m), 1359 (m), 1341 (s), 1279 (s), 1240 (m), 1146 (s), 1102 (vs), 947 (s), 841 (s) cm^{-1}. Found C 55.84, H 8.91, N 1.05.

b) The PEG-bound imine (1.00 g, 0.34 mmol) was dissolved in hydrochloric acid (8 mL, c = 1 mol·dm^{-3}) and the mixture was stirred for 40 h at 23 °C. Immobilized auxiliary **1d** (732 mg) was recovered after purification according to General Procedure A. The corresponding ethereal layers were dried ($MgSO_4$) and evaporated to give **5c** (44 mg, 0.19 mmol, 56%) as a pale yellow oil. GC for determination of *ee* value (Bondex unγ): 60 °C isotherm, then gradient 0.5 °C min^{-1}, $t_R(S)$ = not detectable; $t_R(R)$ = 129.59 min, >99% *ee* [cf. racemate: $t_R(S)$ = 125.76 min; $t_R(R)$ = 129.53 min].

Ethyl (*R*)-2-Oxo-1-(3-oxobutyl)cyclohexanecarboxylate (5a) from PEG-Supported (*R*)-*N*-[2-Ethoxycarbonyl-2-(3-oxobutyl)-1-cyclohexylidene]-L-valine 4-Hydroxypiperidide: a) Polymer **3e** (0.40 g) and $Cu(OAc)_2 \cdot H_2O$ (4.0 mg, 0.02 mmol) were dissolved in acetone (2 mL). After stirring at 23 °C for 1 h, **4** (1.00 g, 14.3 mmol) was added and the mixture was stirred for 2 d. Precipitation from Et_2O (50 mL) according to General Procedure A afforded a brown polymer (0.39 g, 99%). ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (d, ^3J = 6.2 Hz, 3 H; $CHCH_3$), 0.92–1.02 (m, 3 H, $CHCH_3$), 1.25 (t, ^3J = 7.1 Hz, 3 H; CH_2CH_3), 1.41–1.90 (m, 8 H), 2.09–2.16 (m, 7 H), 2.22 (s, 3 H, $COCH_3$), 2.31–2.70 (m, 2 H), 2.51 (t, ^3J = 6.2 Hz, 2 H), 2.72–3.38 (m, 2 H), 3.44–3.81 (m, 131 H, PEG–H), 3.98–4.23 (m, 2 H), 4.11–4.21 (m, 2 H, OCH_2) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 18.9 (CH_3), 25.2 (CH_2), 28.4 (CH_2), 30.0 (CH_2), 32.6 (CH_2), 38.9 (CH_2; NCH_2), 42.9 (CH_2; NCH_2), 60.8 (CH; CHN), 67.6 (CH; OCH), 141.8 (C; CN), 173.9 (C; COO), 208.5 (C; CO) ppm. Missing signals cannot be identified from background noise.

b) The PEG-bound imine (1.00 g, 0.52 mmol) was stirred in hydrochloric acid (2 mL, c = 1 mol·dm^{-3}) at 0 °C for 3 h. H_2O (20 mL) was added, and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with H_2O (50 mL), dried ($MgSO_4$), and evaporated to give **5a** (108 mg, 0.45 mmol, 87%) as a colorless oil with 97% purity (determined by ^1H NMR spectroscopy). GC for determination of *ee* value: Bondex unβ [20 m × 0.3 mm with hydrogen carrier gas (0.4 bar)], 120 °C isotherm; $t_R(R)$ = 29.75 min; $t_R(S)$ = 30.88 min, 97% *ee*.

Extraction of the aqueous layers with CH_2Cl_2 (3 × 50 mL), subsequent washing of the combined CH_2Cl_2 layers with H_2O (50 mL), drying ($MgSO_4$), and removal of all volatile materials under high vacuum gave the reisolated polymer **1d** (867 mg).

2-(Methylthio)ethyl 2-Oxo-1-(3-oxobutyl)cyclopentane-1-carboxylate (*rac*-5b): Ketone **4** (519 mg, 7.42 mmol) was added to a mixture of **2c** (500 mg, 2.47 mmol) and $FeCl_3 \cdot 6H_2O$ (67 mg, 0.25 mmol). After stirring for 16 h at 23 °C, all volatile materials were removed and the residue was purified by chromatography on SiO_2 (PE/EtOAc, 1:1, R_f = 0.53) to give *rac*-**5b** (645 mg, 2.37 mmol, 96%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.84–2.17 (m, 5 H), 2.13 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 2.26–2.53 (m, 4 H), 2.67–2.78 (m, 1 H), 2.71 (t, ^3J = 6.8 Hz, 2 H; SCH_2), 4.27 [A-part of an ABX_2 system, ^2J = (–)14.5, ^3J = 6.9 Hz, 1 H; OCH_2], 4.28 [B-part of an ABX_2 system, ^2J = (–)14.5, ^3J = 6.9 Hz, 1 H; OCH_2] ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 15.6 (CH_3; SCH_3), 19.6 (CH_2), 27.0 (CH_2), 30.0 (CH_2), 32.5 (CH_2), 34.3 (CH_2), 38.0 (CH_2), 38.4 (CH_2), 59.0 (C; C-2), 63.4 (CH_2; OCH_2), 171.2 (C; COO), 207.7 (C; COMe), 214.6 (C; C-1) ppm. IR (ATR): $\tilde{\nu}$ = 2963 (w), 2920 (w), 1747 (s), 1711 (vs), 1427 (w), 1370 (w), 1318 (w), 1258 (m), 1227 (m), 1161 (s), 1116 (m), 1065 (w), 1013 (w) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 272 (3) [M^+], 137 (2), 111 (2), 74 (100) [$C_3H_6S^+$], 61 (2), 47 (4) [SMe^+], 43 (17) [$COMe^+$]. $C_{13}H_{20}O_4S$ (272.36): calcd. C 57.33, H 7.40, S 11.77; found C 57.35, H 7.40, S 11.44.

2-(Methylthio)ethyl 3-Oxobicyclo[4.3.0]-1-nonene-6-carboxylate (*rac*-8): Pyrrolidine (83 mg, 1.2 mmol) and conc. HOAc (70 mg, 1.2 mmol) were added to a solution of *rac*-**5b** (732 mg, 1.37 mmol) in MTBE (5 mL) and the reaction mixture was stirred for 3 d at 23 °C. After removal of all volatile materials, the residue was dissolved in satd. $NaHCO_3$ solution (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and the solvents evaporated. The residue was purified by chromatography on SiO_2 (PE/EtOAc, 3:1, R_f = 0.24) to yield *rac*-**8** (237 mg, 0.93 mmol, 68%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.62–1.66 (m, 1 H), 1.79–1.91 (m, 3 H), 2.13 (s, 3 H, CH_3), 2.39–2.44 (m, 3 H), 2.49–2.67 (m, 2 H), 2.72 (t, ^3J = 6.6 Hz, 2 H; SCH_2), 2.76–2.88 (m, 1 H), 4.29 [A-part of an ABX_2 system, ^2J = (–)19.5, ^3J = 6.5 Hz, 1 H; OCH_2], 4.32 [B-part of an ABX_2 system, ^2J = (–)19.5, ^3J = 6.7 Hz, 1 H; OCH_2], 5.95 (t, ^3J = 1.9 Hz, 1 H; 5-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 15.6 (CH_3), 22.1 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 33.3 (CH_2), 34.8 (CH_2), 38.4 (CH_2), 54.4 (C; C-1), 63.3 (CH_2; OCH_2), 123.6 (CH; C-5), 170.1 (C), 173.3 (C), 198.8 (C; C-4) ppm. IR (ATR): $\tilde{\nu}$ = 2970 (m), 2867 (m), 1727 (vs), 1671 (s), 1455 (m), 1366 (m), 1227 (s), 1217 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 254 (25) [M^+], 179 (2), 135 (12) [$M^+ - C_4H_7O_2S$], 107 (5), 91 (5), 75 (100) [$C_3H_7S^+$], 60 (5) [$C_2H_4S^+$]. $C_{13}H_{18}O_3S$ (254.35): calcd. C 61.39, H 7.13, S 12.60; found C 61.17, H 7.11, S 12.75. GC: Bondex unα/β, isothermic elution at 140 °C. t_1 = 68.33 min; t_2 = 69.75 min.

***tert*-Butyl 4-Hydroxypiperidine-1-carboxylate (10):** To a solution of 4-hydroxypiperidine (5.06 g, 50.0 mmol) in H_2O/THF (100 mL, 50:50, v/v) at 0 °C was added a solution of Boc_2O (10.9 g, 50.0 mmol) in THF (50 mL). After warming up to 23 °C, the reaction mixture was stirred for a further 16 h. Then H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and evaporated to yield **10** (9.90 g, 49.2 mmol, 98%) as a colorless solid, m.p. 68 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.39–1.54 (m, 2 H, 3-H_{ax}), 1.46 (s, 9 H, 1-H), 1.67 (br. s, 1 H, OH), 1.83–1.88 (m, 2 H, 2-H_{eq}), 3.03 [dtd, ^2J = (–)23.3, ^3J = 9.8, ^3J = 3.4 Hz, 2 H; 3-H_{eq}], 3.80–3.88 (m, 3 H, 2-H_{eq} and 4-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 28.4 (CH_3), 34.1 (CH_2; C-3), 41.0 (CH_2; C-2), 41.5 (CH_2; C-2), 67.5 (CH), 79.6 (C), 154.9 (C; C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3455 (s), 2952 (m), 2929 (w), 2860 (w), 1655 (vs), 1422 (vs), 1367 (s), 1298 (s), 1167 (s), 1120 (s), 1091 (m), 1020 (s), 1009 (m), 972 (m), 941 (m), 862 (m), 770 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 201 (10) [M^+], 145 (17) [$M^+ - C_4H_8$], 128 (16) [$M^+ - C_4H_9O$], 127 (16) [$M^+ - C_4H_9OH$], 100 (8) [$C_4H_{10}NO^+$], 83 (8) ($C_5H_9N^+$), 57 (100) [$C_4H_9^+$]. $C_{10}H_{19}NO_3$ (201.26): calcd. C 59.68, H 9.52, N 6.96; found C 59.47, H 9.53, N 6.98.

6-Benzyloxy-1-hexyl 4-Toluenesulfonate (11d): Pyridine (20.0 g, 131 mmol) was added dropwise to a solution of 6-(benzyloxy)-1-

hexanol (18.2 g, 87.1 mmol) and tosyl chloride (25.0 g, 131 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After warming up to 23 °C, the reaction mixture was stirred for a further 16 h. Then a mixture of ice (100 g) and conc. hydrochloric acid (30 mL) was added and the resulting mixture stirred for 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and the solvents evaporated. Chromatography on SiO_2 (PE/EtOAc, 3:1, R_f = 0.41) afforded **11d** (24.4 g, 67.2 mmol, 77%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.29–1.32 (m, 4 H), 1.56 (quint, ^3J = 6.7 Hz, 2 H), 1.62 (quint, ^3J = 6.8 Hz, 2 H), 2.42 (s, 3 H, CH_3), 3.42 (t, ^3J = 6.5 Hz, 2 H; OCH_2), 4.00 (t, ^3J = 6.5 Hz, 2 H; OCH_2), 4.47 (s, 2 H, Ph-CH_2), 7.30–7.33 (m, 7 H, Ar-H), 7.76–7.78 (m, 2 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 21.6 (CH_3), 25.2 (CH_2), 25.5 (CH_2), 28.7 (CH_2), 29.5 (CH_2), 70.1 (CH_2; OCH_2), 70.6 (CH_2; OCH_2), 72.8 (CH_2; Ph-CH_2), 127.5 (CH; *p*-CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.8 (CH), 133.1 (C), 138.6 (C), 144.7 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3013 (w), 3031 (w), 2936 (s), 2860 (s), 1598 (w), 1495 (w), 1454 (w), 1360 (s), 1307 (w), 1189 (m), 1176 (vs), 1097 (m), 961 (w), 926 (w) cm^{-1}. MS (CI, CH_4), *m*/*z* (%): 363 (79) [MH^+], 344 (5), 271 (4) [$M^+ - C_7H_7$], 191 (10), 181 (9), 173 (27) [H_2OTs^+], 155 (3), 119 (3), 107 (25) [$C_7H_7O^+$], 99 (30), 91 (100) [$C_7H_7^+$], 83 (6), 65 (3). $C_{20}H_{26}O_4S$ (362.48): calcd. C 66.27, H 7.23, S 8.84; found C 66.23, H 7.22, S 8.94.

Purification of Polystyrene Resins. General Procedure B: If necessary, the reaction mixture was hydrolyzed with water. The mixture was washed in a fritted funnel five to ten times each with the given solvents. Then the resin was soaked and shrunk five times with CH_2Cl_2 and PE prior to evaporation under high vacuum for at least 12 h.

Preparation of *tert*-Butyl Piperidinecarboxylates 12. General Procedure C: NaH (55–60% in mineral oil) was washed with absolute PE (3 × 10 mL) in a fritted funnel and dried under vacuum. After suspension of the residue in DMF, a solution of alcohol **10** in DMF was added dropwise at 0 °C followed by addition of the respective **11** and TBAI. The mixture was stirred for 60 h at 23 °C. Then H_2O was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL) or EtOAc (for **12d**). The combined organic layers were washed with H_2O, dried ($MgSO_4$) and the solvents evaporated. The residue was purified by chromatography on SiO_2 with PE/EtOAc (5:1) to afford product **12**.

***tert*-Butyl 4-(Benzyloxy)piperidine-1-carboxylate (12a):** NaH (9.77 g, 224 mmol) in DMF (75 mL), **10** (15.0 g, 74.5 mmol) in DMF (75 mL), **11a** (14.2 g, 112 mmol) and TBAI (2.75 g, 7.50 mmol) were allowed to react according to General Procedure C. Chromatography (R_f = 0.32) gave **12a** (20.5 g, 70.4 mmol, 94%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.46 (s, 9 H, CH_3), 1.53–1.64 (m, 2 H, 3-H_{ax}), 1.83–1.88 (m, 2 H, 2-H_{ax}), 3.76–3.80 (m, 2 H, 3-H_{eq}), 3.56 (tt, ^3J = 8.2, ^3J = 3.7 Hz, 1 H; OCH), 3.78 [dt, ^2J = (–)13.0, ^3J = 5.1 Hz, 2 H; 2-H_{eq}], 4.56 (s, 2 H, Ph-CH_2), 7.26–7.29 (m, 1 H, *p*-H), 7.33–7.35 (m, 4 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 28.4 (CH_3), 40.9 (CH_2; C-2), 41.7 (CH_2; C-2), 69.8 (CH_2; C-3), 73.9 (CH; C-4), 79.4 (C), 127.4 (CH; *o*-CH), 127.5 (CH; *p*-CH), 128.2 (CH; *m*-CH), 138.7 (C; *i*-C), 154.8 (C; C=O) ppm. IR (ATR): $\tilde{\nu}$ = 2927 (w), 2930 (m), 2865 (w), 1693 (vs), 1423 (m), 1366 (m), 1274 (s), 1238 (m), 1170 (s), 1027 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 291 (4) [M^+], 235 (49) [$M^+ - C_4H_8$], 185 (11), 144 (12), 129 (47) [$C_6H_{11}NO_2^+$], 91 (82) [$C_7H_7^+$], 57 (100) [$C_4H_9^+$]. $C_{17}H_{25}NO_3$ (291.39): calcd. C 70.07, H 8.65, N 4.81; found C 70.03, H 8.77, N 4.83. HRMS (EI, 70 eV): calcd. for $C_{17}H_{25}NO_3$ 291.1834; found 291.1834 (M^+).

PS-Supported *tert*-Butyl Piperidine-1-carboxylate (12b): NaH (260 mg, 10.8 mmol) and **10** (2.17 g, 10.8 mmol) in ice-cold THF (10–20 mL) were allowed to react according to General Procedure C. The solvent was removed, **11b** (100–200 mesh, 1.00 g, ca. 3.00 mmol Cl g^{-1}) and TBAI (100 mg, 0.269 mmol) in DMF (20 mL) were added. After shaking at 500–1000 rpm for 14 d at 23 °C and purification with H_2O, DMF, MeOH, and CH_2Cl_2 (General Procedure B), **12b** (1.27 g, 87%) was obtained. IR (ATR): $\tilde{\nu}$ = 3057 (w), 3024 (w), 2920 (s), 2852 (m), 2562 (w), 2196 (w), 1961 (w), 1694 (s), 1601 (s), 1492 (vs), 1451 (vs), 1419 (s), 1364 (m), 1236 (m), 1169 (m), 1074 (m), 1028 (m) cm^{-1}. Found: C 80.70, H 8.23, N 2.90.

PEG-Supported *tert*-Butyl Piperidine-1-carboxylate (12c): NaH (2.73 g, 62.5 mmol) in absolute THF (50 mL), **10** (8.60 g, 50.0 mmol) and **11c** (5.00 g, 5 mmol) were allowed to react according to General Procedure C. After refluxing for 16 h and purification (General Procedure A), **12c** (5.02 g, 99%) was obtained. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.43–1.54 (m, 2 H, 3-H_{ax}), 1.46 (s, 9 H, 1-H), 1.81–1.89 (m, 2 H, 2-H_{eq}), 3.03 (ddd, ^3J = 13.4, ^3J = 9.5, ^3J = 3.4 Hz, 2 H; 3-H_{eq}), 3.58–3.66 (m, 115 H, PEG–H), 3.78–3.90 (m, 3 H, 2-H_{eq} and 4-H) ppm. Load according to ^1H NMR: 77%. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 28.8 (CH_3), 34.6 (CH_2; C-3), 41.6 (CH_2; C-2), 67.7 (CH), 70.9–71.2 (m, CH_2; PEG-CH_2), 79.9 (C), 155.2 (C; C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3511 (w, br), 2882 (s), 2741 (w), 1963 (w), 1691 (w), 1466 (w), 1359 (w), 1341 (s), 1279 (m), 1240 (m), 1200 (w), 1146 (m), 1102 (vs), 947 (s), 841 (s), 799 (w), 719 (w) cm^{-1}.

***tert*-Butyl 4-[6-(Benzyloxy)hexyloxy]piperidine-1-carboxylate (12d):** NaH (4.34 g, 99.4 mmol) in ice-cold DMF (20 mL) and **10** in DMF (40 mL) were allowed to react according to General Procedure C. After warming up to 23 °C, the mixture was stirred for a further 15 min, **11d** (18.0 g, 49.7 mmol) was added and the reaction mixture was heated to 70 °C for 16 h. Ice (100 g) was added and the mixture extracted with EtOAc (3 × 50 mL). Chromatography (R_f = 0.23) gave **12d** (12.6 g, 32.1 mmol, 64%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.36–1.39 (m, 4 H), 1.45 (s, 9 H, CH_3), 1.48–1.64 (m, 6 H), 1.75–1.84 (m, 2 H), 3.02–3.11 (m, 2 H), 3.39–3.48 (m, 5 H), 3.69–3.81 (m, 2 H), 4.49 (s, 2 H, Ph-CH_2), 7.27–7.33 (m, 5 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 26.0 (CH_2), 26.1 (CH_2), 28.4 (CH_3), 29.7 (CH_2), 30.0 (CH_2), 31.1 (CH_2), 41.2 (br. s, NCH_2), 67.9 (CH_2; OCH_2), 60.3 (CH_2; OCH_2), 72.8 (CH_2; OCH_2), 74.4 (CH; C-4), 79.3 (C; *C*CH_3), 127.4 (CH; *p*-CH), 127.6 (CH; *o*-CH), 128.3 (CH; *m*-CH), 138.7 (C; *i*-C), 154.8 (C; NCOO) ppm. IR (ATR): $\tilde{\nu}$ = 3300 (w), 2933 (s), 2859 (s), 1694 (vs), 1453 (w), 1423 (m), 1366 (m), 1314 (w), 1275 (m), 1238 (m), 1171 (m), 1099 (s), 1029 (w), 867 (w) cm^{-1}. MS (CI, CH_4), *m*/*z* (%): 392 (37) [MH^+], 382 (4), 334 (43) [$M^+ - C_4H_9$], 318 (11) [$M^+ - C_4H_9O$], 290 (100) [$M^+ - C_5H_9O_2$], 228 (8), 200 (6), 185 (4), 145 (3), 127 (15), 101 (8) [$C_5H_9O_2^+$], 91 (28) [$C_7H_7^+$], 82 (33), 57 (18) [$C_4H_9^+$]. $C_{23}H_{37}NO_3$ (391.56): calcd. C 70.55, H 9.53, N 3.58; found C 70.44, H 9.58, N 3.52.

Cleavage of the *N*-Boc Protective Group. General Procedure D: TFA was added slowly to a cooled solution of **12** or **15** in CH_2Cl_2 at 0 °C. After stirring at 23 °C for 3 d (**13a**) or 16 h, 20% KOH–H_2O was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O, dried ($MgSO_4$), evaporated and purified to give product **13** and **1**, respectively.

4-(Benzyloxy)piperidine (13a): TFA (14.9 g, 131 mmol), **12a** (6.68 g, 22.9 mmol) in CH_2Cl_2 (10 mL) and KOH–H_2O (80 mL) were allowed to react according to General Procedure D; kugelrohr distillation (170 °C/12 mbar) gave **13a** (3.80 g, 19.9 mmol, 87%) as a colorless solid, m.p. 64–65 °C. ^1H NMR ($CDCl_3$, 250 MHz): δ = 1.42–1.57 (m, 2 H, 3-H_{ax}), 1.61 (s, 1 H, NH), 1.97 [dtd, ^2J = (–)12.8, ^3J

= 5.6, ^3J = 3.9 Hz, 2 H; 2-H_{ax}], 2.60 [dtd, ^2J = (–)23.1, ^3J = 10.3, ^3J = 2.9 Hz, 2 H; 3-H_{eq}], 3.11 [dt, ^2J = (–)12.9, ^3J = 4.3 Hz, 2 H; 2-H_{eq}], 3.47 (tt, ^3J = 12.9, ^3J = 4.0 Hz, 1 H; OCH), 4.57 (s, 2 H, Ph-CH_2), 7.25–7.38 (m, 5 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 33.3 (CH_2; C-3), 44.8 (CH_2; C-2), 69.9 (CH_2; Ph-CH_2), 75.3 (CH; C-4), 127.8 (CH; *p*-CH), 127.9 (CH; *o*-CH), 128.6 (CH; *m*-CH), 139.3 (C; *i*-C) ppm. IR (ATR): $\tilde{\nu}$ = 3397 (w), 3029 (w), 2943 (w), 2853 (m), 1621 (w), 1475 (s), 1417 (vs), 1318 (s), 1276 (s), 1092 (s), 1071 (s), 1028 (m), 959 (s) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 191 (2) [M^+], 100 (25) [$M^+ - C_7H_7$], 91 (62) [$C_7H_7^+$], 85 (100) [$C_5H_{11}^+$]. HRMS (EI, 70 eV): calcd. for $C_{12}H_{17}NO$ 191.1310; found 191.1309 (M^+).

PS-Supported Piperidine 13b: Resin **12b** (300 mg) was suspended in a mixture of CH_2Cl_2 and TFA (5 mL each) and shaken for 16 h at 23 °C. After evaporation under high vacuum, the resin was purified (General Procedure B) with 20% KOH–H_2O, H_2O, MeOH, 10% DBU in CH_2Cl_2, and CH_2Cl_2. After drying, **13b** (286 mg) was obtained. IR (ATR): $\tilde{\nu}$ = 3330 (w), 3024 (w), 2920 (s), 2851 (w), 2563 (w), 2192 (w), 1969 (w), 1601 (m), 1492 (s), 1451 (vs), 1420 (m), 1069 (m), 1028 (m) cm^{-1}. Found: C 79.34, H 7.58, N 2.30.

PEG-Supported Piperidine 13c: TFA (20 mL) and **12c** (4.80 g, 4.8 mmol) in CH_2Cl_2 (20 mL) were allowed to react according to the General Procedure D. All volatile materials were removed and the residue dissolved in KOH–H_2O (30 mL). The solution was extracted with CH_2Cl_2 and the polymer purified (General Procedure A) to give **13c** (4.52 g, 94%) as a colorless waxy solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.40–1.50 (m, 2 H, 3-H_{ax}), 1.63–1.74 (m, 2 H, 2-H_{ax}), 1.93 (dd, ^3J = 12.5, ^3J = 3.6 Hz, 1 H; NH), 2.61 (ddd, ^3J = 13.0, ^3J = 10.3, ^3J = 2.9 Hz, 2 H; 3-H_{eq}), 3.09 (dt, ^3J = 12.9, ^3J = 4.1 Hz, 2 H; 2-H_{eq}), 3.35–3.37 (m, 1 H, 4-H), 3.58–3.77 (m, 137 H, PEG–H) ppm. Load according to ^1H NMR: 64%. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 32.9 (CH_2; C-3), 44.5 (CH_2; C-2), 67.0–70.9 (m, CH_2; PEG-CH_2), 76.0 (CH; C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3458 (w), 3146 (w), 2882 (s), 2740 (w), 1669 (w), 1629 (w), 1603 (w), 1558 (w), 1530 (w), 1466 (m), 1359 (m), 1341 (s), 1279 (s), 1240 (m), 1209 (w), 1146 (m), 1098 (vs), 1060 (s), 1032 (s), 958 (s), 876 (m), 841 (s) cm^{-1}. Found C 53.91, H 9.11, N 0.94.

4-[6-(Benzyloxy)hexyloxy]piperidine (13d): TFA (35 mL), **12d** (11.5 g, 29.4 mmol) and KOH–H_2O (80 mL) were allowed to react according to the General Procedure D; the solvent was distilled off under high vacuum to give **13d** (8.57 g, 29.4 mmol, quant.) as a light yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.34–1.57 (m, 7 H), 1.54–1.68 (m, 4 H), 1.88–1.94 (m, 2 H), 2.55–2.64 (m, 2 H), 3.05–3.11 (m, 2 H), 3.27–3.36 (m, 1 H, OCH), 3.42–3.49 (m, 4 H), 4.50 (s, 2 H, Ph-CH_2), 7.24–7.37 (m, 5 H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 75 MHz): δ = 25.6 (CH_2), 25.8 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 42.0 (NCH_2), 69.1 (CH_2), 70.1 (CH_2), 70.5 (CH_2), 73.0 (CH), 128.7 (CH), 128.9 (CH), 135.7 (C; *i*-C) ppm. IR (ATR): $\tilde{\nu}$ = 3294 (m, br), 2933 (vs), 2854 (s), 1453 (w), 1363 (w), 1316 (w), 1269 (w), 1103 (m), 894 (w) cm^{-1}. MS (CI, CH_4), *m*/*z* (%): 292 (100) [MH^+], 200 (25) [$M^+ - C_7H_7$], 185 (14), 100 (31), 91 (35) [$C_7H_7^+$], 85 (67), 68 (10). HRMS (EI, 70 eV): calcd. for $C_{18}H_{29}NO_2$ 291.2198; found 291.2193 (M^+).

L-Valine 4-(Benzyloxy)piperidide (1b): TFA (3 mL), **15a** (846 mg, 2.17 mmol) in CH_2Cl_2 (2 mL) and KOH–H_2O (10 mL) were allowed to react according to the General Procedure D; extraction with CH_2Cl_2 (3 × 10 mL) and chromatography on SiO_2 (EtOAc/MeOH, 20:1, R_f = 0.04) gave **1b** (477 mg, 1.64 mmol, 76%) as a pale brown oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.90 (d, ^3J = 7.0 Hz, 3 H; CH_3), 0.98 (d, ^3J = 6.5 Hz, 3 H; CH_3), 1.61–1.72 (m, 2 H, 3-H_{ax}), 1.73–1.93 (m, 3 H, 2-H_{ax} and CH_3–C*H*), 3.23–3.32 (m, 1 H, 3-H_{eq}), 3.35–3.43 (m, 1 H, 3-H_{eq}), 3.53 (t, ^3J = 5.0 Hz, 1 H; C*H*NH_2), 3.65–3.73 (m, 2 H, 2-H_{eq}), 3.94–3.99 (m, 1 H, OCH), 4.56 [A-part of an AB system, d, ^2J = (–)21.0 Hz, 1 H; Ph-CH_2], 4.58 [B-part of an AB system, d, ^2J = (–)21.0 Hz, 1 H; Ph-CH_2], 7.27–7.31 (m, 1 H, Ar-H), 7.33–7.37 (m, 4 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 16.5 (CH_3), 20.1 (CH_3), 30.7 (CH_2; C-3), 31.70 (CH_2; C-3), 31.73 (CH; CH_3*C*H), 39.2 (CH_2; C-2), 42.5 (CH_2; C-2), 56.0 (CH; $CHNH_2$), 70.0 (CH_2; Ph-CH_2), 73.3 (CH; C-4), 127.4 (CH; *o*-CH), 127.5 (CH; *p*-CH), 128.4 (CH; *m*-CH), 138.5 (C; *i*-C), 173.5 (C; CON) ppm. IR (ATR): $\tilde{\nu}$ = 3369 (w, br), 2956 (s), 2869 (m), 1712 (w), 1636 (vs), 1452 (s), 1360 (w), 1219 (w), 1097 (m), 740 (w), 700 (w) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 290 (1) [M^+], 273 (5) [$M^+ - NH_3$], 247 (2) [$M^+ - C_3H_7$], 190 (2) [$M^+ - C_5H_{10}NO$], 91 (27) [$C_7H_7O^+$], 72 (100) [$C_4H_{10}N^+$]. $C_{17}H_{26}N_2O_2$ (290.42): calcd. C 70.31, H 9.02, N 9.65; found C 70.57, H 8.89, N 9.07. HRMS (EI, 70 eV): calcd. for $C_{17}H_{26}N_2O_2$ 290.1994, found 290.1994 (M^+). $[\alpha]_D^{20}$ = +12.9 (*c* = 11.5 in $CHCl_3$).

PS-Supported L-Valine 4-Hydroxypiperidide (1c): Polymer **15b** (2.49 g) was suspended in a mixture of CH_2Cl_2 and TFA (10 mL each) and shaken for 16 h at 23 °C. After evaporation under high vacuum, the resin was purified (General Procedure B) with DBU/CH_2Cl_2 (1:1), H_2O, MeOH and shaken for 16 h in CH_2Cl_2. Filtration and drying of the residue under high vacuum gave **1c** (2.24 g, 98%). IR (ATR): $\tilde{\nu}$ = 3343 (w, br), 3024 (w), 2920 (s), 2852 (m), 2571 (w), 2188 (w), 1962 (m), 1684 (m), 1632 (s), 1602 (s), 1492 (s), 1451 (vs), 1363 (m), 1200 (m), 1176 (m), 1078 (m), 1017 (m) cm^{-1}. Found C 81.82, H 8.02, N 3.89.

PEG-Supported L-Valine 4-Hydroxypiperidide (1d): TFA (20 mL), **15c** (3.30 g) in CH_2Cl_2 (15 mL) and KOH–H_2O (20 mL) were allowed to react according to the General Procedure D. Extraction with CH_2Cl_2 (3 × 50 mL) and purification of the combined organic layers (General Procedure A) gave **1d** (3.08 g, 93%). Load according to ^1H NMR: 74%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (d, ^3J = 6.6 Hz, 3 H; CH_3), 0.98 (d, ^3J = 6.9 Hz, 3 H; CH_3), 1.52–1.67 (m, 2 H, 3′-H_{ax}), 1.75–1.95 (m, 3 H, 2′-H_{ax} and CH_3–C*H*), 2.27 (br. s, 2 H, NH), 3.20–3.36 (m, 1 H, 3′-H_{eq}), 3.35–3.43 (m, 1 H, 3′-H_{eq}), 3.57–3.72 (m, 123 H, PEG–H and C*H*NH), 3.91–4.01 (m, 1 H, OCH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 16.6 (CH_3), 20.1 (CH_3), 30.7 (CH_2; C-3), 31.7 (CH_3–*C*H), 31.74 (CH_2; C-3′), 39.3 (CH_2; C-2′), 42.6 (CH_2; C-2′), 55.9 ($CHNH_2$), 70.3–70.8 (m, CH_2; PEG-CH_2), 74.3 (CH; C-4′), 173.0 (C; CON) ppm. IR (ATR): $\tilde{\nu}$ = 3512 (w, br), 2882 (s), 2740 (w), 2165 (w), 1996 (w), 1634 (m), 1466 (m), 1359 (m), 1340 (s), 1279 (m), 1240 (m), 1146 (m), 1101 (vs), 1060 (vs), 958 (s), 842 (s) cm^{-1}. Found C 55.05, H 9.21, N 1.67.

Preparation of Amides 15 by Coupling Amines 13 with *N*-Boc-L-Valine 14. General Procedure E: DCC was added portionwise to a cooled solution of **14** in CH_2Cl_2 at 0 °C, and the mixture was stirred for a further 30 min. The respective **13** was added and the reaction mixture was stirred for 16 h at 23 °C. After filtration through a short pad of SiO_2, the filtrate was concentrated and the residue purified by chromatography on SiO_2 with PE/EtOAc (3:1) to give product **15**.

***N*-*tert*-Butyloxycarbonyl-L-valine 4-(Benzyloxy)piperidide (15a):** DCC (648 mg, 3.14 mmol), **14** (682 mg, 3.14 mmol) in CH_2Cl_2 (2.5 mL) and **13a** (500 mg, 2.62 mmol) were allowed to react according to General Procedure E. Chromatography (R_f = 0.28) gave **15a** (925 mg, 2.37 mmol, 90%) as a colorless, viscous oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.89 (d, ^3J = 6.7 Hz, 3 H; CH_3), 0.96 (d, ^2J = 6.8 Hz, 3 H; CH_3), 1.43 (s, 9 H, Boc-CH_3), 1.69 [dtd, ^2J = (–)16.6, ^3J = 9.7, ^3J = 3.8 Hz, 2 H; 3-H_{ax}], 1.65–1.74 (m, 3 H, 2-H_{ax} and CH_3–C*H*), 3.35–3.44 (m, 2 H, 3-H_{eq}), 3.66–3.80 (m, 2 H, 2-H_{eq}), 3.82–3.98 (m, 1 H, OCH), 4.49 (dd, ^3J = 8.9, ^3J = 5.4 Hz,

1 H; C*H*NH), 4.54 [A-part of an AB system, ^2J = (–)14.5 Hz, 1 H; Ph-CH_2], 4.57 [B-part of an AB system, ^2J = (–)14.5 Hz, 1 H; Ph-CH_2], 5.35 (br. d, ^3J = 8.9 Hz, 1 H; NH), 7.28–7.38 (m, 5 H, Ar-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 14.2 (CH_3), 17.0 (CH_3), 28.4 (CH_3; Boc), 30.6 (CH_2; C-3), 31.6 (CH_2; C-3), 31.63 (CH_3–*C*H), 39.1 (CH_2; C-2), 42.9 (CH_2; C-2), 54.7 (CHNH), 70.1 (CH_2; Ph-CH_2), 73.1 (CH; C-4), 79.4 (C; Boc), 127.5 (CH; *o*-CH), 127.6 (CH; *p*-CH), 128.5 (CH; *m*-CH), 138.4 (C; *i*-C), 155.9 (C; OCON), 170.4 (C; CON) ppm. IR (ATR): $\tilde{\nu}$ = 3302 (w), 2964 (m), 2930 (m), 2871 (w), 1707 (s), 1636 (vs), 1797 (m), 1452 (s), 1366 (m), 1171 (s), 1090 (m), 734 (m) cm^{-1}. MS (FAB; matrix: 4-nitrobenzyl alcohol), *m*/*z* (%): 391 (100) [MH^+], 335 (31) [$MH^+ - C_4H_8$], 317 (7) [$MH^+ - C_4H_8$], 291 (48) [$MH^+ - C_4H_8 - CO_2$], 190 (18) [$C_{12}H_{16}NO^+$], 116 (16) [$C_5H_{10}NO_2^+$], 91 (49) [$C_7H_7^+$], 72 (23) [$C_4H_8O^+$], 57 (27) [$C_4H_9^+$]. $C_{22}H_{34}N_2O_4$ (390.52): calcd. C 67.66, H 8.78, N 7.17; found C 67.60, H 8.75, N 7.04. HRMS (FAB): calcd. for $C_{22}H_{34}N_2O_4$ 391.2597; found 391.2591 (M^+). $[\alpha]_D^{20}$ = +25 (*c* = 7.3 in $CHCl_3$).

PS-Supported *N*-*tert*-Butyloxycarbonyl-L-valine 4-Hydroxypiperidide (15b): DCC (2.37 g, 11.5 mmol), **14** (2.50 g, 11.5 mmol) in CH_2Cl_2 (15 mL) and **13b** (1.00 g) were allowed to react according to General Procedure E. Shaking at 500 rpm for 16 h, purification with MeOH and CH_2Cl_2 (General Procedure B) and drying gave **15b** (1.06 g, 52% over two steps). IR (ATR): $\tilde{\nu}$ = 3316 (w, br), 3024 (w), 2922 (w), 2188 (w), 1962 (m), 1684 (s), 1643 (s), 1493 (s), 1450 (vs), 1365 (s), 1250 (m), 1219 (m), 1160 (s), 1088 (s), 1019 (m) cm^{-1}. Found C 80.13, H 8.02, N 3.59.

PEG-Supported *N*-*tert*-Butyloxycarbonyl-L-valine 4-Hydroxypiperidide (15c): DCC (8.67 g, 42.0 mmol), **14** (9.12 g, 42.0 mmol) in CH_2Cl_2 (30 mL) and **13c** (4.20 g) were allowed to react according to General Procedure E. The mixture was filtered off and the filtrate was purified (General Procedure A) to give a colorless polymer **15c** (3.81 g, 91%). Load according to ^1H NMR: 72%. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, ^3J = 6.5 Hz, 3 H; CH_3), 0.96 (d, ^3J = 6.9 Hz, 3 H; CH_3), 1.43 (s, 9 H, Boc-CH_3), 1.55–1.68 (m, 2 H, 3′-H_{ax}), 1.78–1.94 (m, 3 H, 2′-H_{ax} and CH_3–C*H*), 3.26–3.38 (m, 2 H, 3′-H_{eq}), 3.58–3.71 (m, 123 H, PEG–H and 4′-H), 4.48 (dd, ^3J = 8.8, ^3J = 5.3 Hz, 1 H; C*H*NH), 5.35 (br. d, ^3J = 9.2 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 16.7 (CH_3), 19.7 (CH_3), 28.4 (CH_3; C*C*H_3), 30.7 (CH_2; C-3′), 31.56 (CH_2; C-3′), 31.6 (CH_3–*C*H), 39.2 (CH_2; C-2′), 42.9 (CH_2; C-2′), 54.5 (CHNH), 70.0–71.3 (m, CH_2; PEG-CH_2), 74.1 (CH; C-4′), 79.3 (C; *C*CH_3), 155.9 (C; OCON), 170.4 (C; CON) ppm. Found C 55.43, H 9.39, N 1.93.

***N*-*tert*-Butyloxycarbonyl-L-valine 4-[(6-Benzyloxy)hexyloxy]piperidide (15d):** DCC (8.00 g, 38.8 mmol), **14** (7.00 g, 32.3 mmol) and **13d** (9.40 g, 32.3 mmol) were allowed to react according to General Procedure E. Chromatography (R_f = 0.16) gave **15d** (14.81 g, 30.2 mmol, 93%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, ^3J = 6.7 Hz, 3 H; CH_3), 0.96 (d, ^3J = 6.8 Hz, 3 H; CH_3), 1.37–1.39 (m, 4 H), 1.43 (s, 9 H, Boc-CH_3), 1.55–1.65 (m, 6 H), 1.72–1.96 (m, 3 H, 2-H_{ax} and CH_3–C*H*), 3.23–3.52 (m, 5 H), 3.47 (t, ^3J = 6.5 Hz, 2 H), 3.17–3.29 (m, 1 H), 3.32– 3.42 (m, 1 H), 4.46–4.50 (m, 1 H), 4.50 (s, 2 H, Ph-CH_2), 5.36 (br. d, ^3J = 8.9 Hz, 1 H; NH), 7.27–7.34 (m, 5 H, Ar-H) ppm. $^{13}C\{^1H\}$NMR ($CDCl_3$, 75 MHz): δ = 14.2 (CH_3), 17.0 (CH_3), 26.07 (CH_2), 26.1 (CH_2), 28.4 (CH_3; Boc), 29.7 (CH_2), 30.0 (CH_2), 30.6 (CH_2; C-3), 31.6 (CH_3–*C*H), 31.7 (CH_2; C-3), 39.3 (CH_2; C-2), 42.9 (CH_2; C-2), 54.7 (CHNH), 68.2 (CH_2), 70.4 (CH_2; Ph-CH_2), 73.0 (CH_2), 73.6 (CH; C-4), 79.3 (C; Boc), 127.5 (CH; *o*-CH), 127.6 (CH; *p*-CH), 128.3 (CH; *m*-CH), 138.7 (C; *i*-C), 155.9 (C; OCON), 170.3 (C; CON) ppm. A shoulder at δ = 31.7 ppm indicates the missing CH signal. IR (ATR): $\tilde{\nu}$ = 3302 (w), 2931 (m), 2861 (m), 1705 (vs), 1634 (vs), 1497 (m), 1451 (s), 1390 (w), 1366 (m), 1251 (m), 1169 (s), 1092 (m), 1017 (w) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 490 (15) [M^+], 434 (3) [$M^+ - C_4H_8$], 417 (5), 389 (3), 373 (3) [$M^+ - NH_3 - CO_2 - C_4H_8$], 347 (2), 320 (3), 290 (4) [$M^+ - C_{10}H_{18}NO_3^+$], 172 (33) [$C_9H_{18}NO_2^+$], 128 (3), 116 (100) [$NHBoc^+$], 91 (49) [$C_7H_7^+$], 84 (11), 72 (86), 57 (33) [$C_4H_9^+$]. $C_{28}H_{46}N_2O_5$ (490.68): calcd. C 68.54, H 9.45, N 5.71; found C 68.47, H 9.45, N 5.66. $[\alpha]_D^{20}$ = +21 (*c* = 5.2 in $CHCl_3$).

***N*-*tert*-Butyloxycarbonyl-L-valine 4-Hydroxypiperidide (16a):** Benzyl ether **15a** (7.88 g, 20.2 mmol) and Pd/C (5%, 2.50 g) were dissolved in a mixture of ethanol (18 mL) and EtOAc (2 mL) in a Schlenk flask. After removal of air (freeze, pump, thaw), hydrogen was added from a balloon. The mixture was stirred for 18 h at 23 °C, then two drops of conc. hydrochloric acid were added. After stirring for a further 2 d, the mixture was filtered through a short pad of SiO_2 and the residue washed with MeOH. Evaporation of the combined filtrates afforded **16a** (5.69 g, 18.9 mmol, 94%) as a colorless solid, m.p. 111–112 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, ^3J = 6.7 Hz, 3 H; CH_3), 0.96 (d, ^3J = 6.7 Hz, 3 H; CH_3), 1.43 (s, 9 H, Boc-CH_3), 1.46–1.64 (m, 2 H, 3-H_{ax}), 1.86–1.95 (m, 3 H, 2-H_{ax} and CH_3–C*H*), 2.22 (s, br. signal; OH), 3.18–3.37 (m, 2 H, 3-H_{eq}), 3.82 (tt, ^3J = 12.1, ^3J = 4.7 Hz, 1 H; OCH), 3.88–4.11 (m, 2 H, 2-H_{eq}), 4.48 (dd, ^3J = 9.1, ^3J = 5.6 Hz, 1 H; C*H*NH), 5.39 (br. d, ^3J = 9.0 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 126 MHz): δ = 17.5 (CH_3), 20.0 (CH_3), 28.7 (CH_3; Boc), 31.9 (CH; OCH), 34.1 (CH_2; C-3), 35.0 (CH_2; C-3), 39.6 (CH_2; C-2), 43.2 (CH_2; C-2), 55.1 (CHNH), 66.8 (OCH), 79.8 (C; Boc), 156.3 (C; OCON), 170.9 (C; CON) ppm. IR (ATR): $\tilde{\nu}$ = 3345 (w), 3264 (m), 2963 (m), 2926 (m), 2874 (m), 2204 (w), 1976 (m), 1680 (s), 1632 (vs), 1536 (s), 1440 (s), 1364 (s), 1269 (s), 1252 (s), 1217 (s), 1159 (vs), 1115 (m), 1012 (vs), 940 (s), 869 (m) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 300 (11) [M^+], 227 (9), 172 (27), 128 (12), 116 (73), 72 (100) [NEt_2^+], 57 (60). $C_{15}H_{28}N_2O_4$ (300.41): calcd. C 59.97, H 9.40, N 9.33; found C 59.91, H 9.35, N 9.11. $[\alpha]_D^{20}$ = +29.9 (*c* = 10.2 in $CHCl_3$).

***N*-*tert*-Butyloxycarbonyl-L-valine 4-(6-Hydroxyhexyloxy)piperidide (16b):** According to the procedure for **16a**, benzyl ether **15d** (13.9 g, 28.3 mmol) and Pd/C (5%, 1.5 g) were converted in a mixture of ethanol (18 mL) and EtOAc (2.5 mL) to give **16b** (11.3 g, 28.3 mmol, quant.) as a colorless solid. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, ^3J = 6.7 Hz, 3 H; CHC*H*$_3$), 0.96 (d, ^3J = 6.7 Hz, 3 H; CHC*H*$_3$), 1.26 (s, 1 H, OH), 1.24–1.41 (m, 3 H), 1.43 (s, 9 H, CH_3), 1.50–1.65 (m, 7 H), 1.74–1.96 (m, 3 H), 3.24–3.57 (m, 5 H), 3.64 (t, ^3J = 6.5 Hz, 2 H), 3.69–3.81 (m, 1 H), 3.83–3.94 (m, 1 H), 4.48 (dd, ^3J = 8.6, ^3J = 5.3 Hz, 1 H; C*H*NH), 5.37 (br. d, ^3J = 8.9 Hz, 1 H; NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 17.0 (CH_3), 19.7 (CH_3), 25.6 (CH_2), 26.1 (CH_2), 28.4 (CH_3; Boc-CH_3), 30.0 (CH_2), 30.8 (CH_2), 31.64 (CH_2), 31.6 (CH; *C*HCH$_3$), 32.7 (CH_2), 39.3 (CH_2), 43.0 (CH_2), 54.7 (CH; CHNH), 62.9 (CH_2), 68.0 (CH; OCH), 73.6 (CH_2), 79.4 (C; *C*CH_3), 155.9 (C; OCON), 170.4 (CON) ppm. IR (ATR): $\tilde{\nu}$ = 3409 (w), 3299 (w), 2930 (s), 2860 (m), 1703 (s), 1633 (vs), 1522 (m), 1500 (m), 1451 (s), 1390 (w), 1365 (m), 1328 (w), 1251 (w), 1221 (w), 1171 (s), 1107 (m), 1089 (m), 1043 (m), 1017 (w), 969 (w) cm^{-1}. MS (EI, 70 eV), *m*/*z* (%): 400 (9) [M^+], 327 (6), 283 (5), 200 (5) [$C_{10}H_{18}NO_3^+$], 172 (32) [$C_9H_{18}NO_2^+$], 128 (7), 116 (99) [$C_5H_{10}NO_2^+$], 101 (10) [$C_5H_9O_2^+$], 84 (17), 72 (100) [$C_4H_8O^+$], 57 (51) [$C_4H_9^+$], 43 (54) [$C_3H_7^+$]. $C_{21}H_{40}N_2O_5$ (400.55): calcd. C 62.97, H 10.07, N 7.00; found C 62.77, H 9.98, N 6.79. $[\alpha]_D^{20}$ = +26 (*c* = 9.2 in $CDCl_3$).

Attempts of Enamine Formation Using Polystyrene-Supported 1c: To a suspension of **1c** (100 mg) and molecular sieves (4 Å, 1.00 g)

in absolute chloroform, benzene, or toluene was added β-oxo ester **2a** (5 g) and 2 drops and 10 mg, respectively, of HCl, HCO_2H, HOAc, TFA, HOTf, HOTs, or PPTS and the reaction mixture was shaken for 16 h at 55 °C. The residue was filtered and purified with absolute CH_2Cl_2 and PE under nitrogen according to the General Procedure B. IR measurements, elemental analyses and mass balances did not show any conversion.

Acknowledgments

We acknowledge generous support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for this work. B.K. thanks the Landesgraduiertenförderung Baden-Württemberg for a fellowship.

[1] Reviews: a) J. Christoffers, in: *Encyclopedia of Catalysis*, vol. 5 (Ed.: I. Horvath), John Wiley & Sons, New York, **2003**, pp. 99–118; b) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; c) P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Tetrahedron Organic Chemistry Series vol. 9; Pergamon: Oxford, **1992**; d) D. A. Oare, C. H. Heathcock, in: *Topics in Stereochemistry*, vol. 19 (Eds.: E. L. Eliel, S. H. Wilen), Wiley Interscience, New York, **1989**, pp. 227–407; e) E. D. Bergmann, D. Ginsburg, R. Pappo, *Org. React.* **1959**, *10*, 179–563; f) B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771–806.

[2] Reviews: a) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11943–11948; b) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; c) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; d) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401.

[3] a) K. Hermann, H. Wynberg, *Helv. Chim. Acta* **1977**, *60*, 2208–2212; b) N. Kobayashi, K. Iwai, *J. Am. Chem. Soc.* **1978**, *100*, 7071–7072; c) N. Kobayashi, K. Iwai, *J. Polym. Sci., Polym. Chem. Ed.* **1980**, *18*, 923–932; d) M. Inagaki, J. Hiratake, Y. Yamamoto, J. Oda, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4121–4126; e) P. Hodge, E. Khoshdel, J. Waterhouse, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2205–2209.

[4] R. Alvarez, M.-A. Hourdin, C. Cavé, J. d'Angelo, P. Chaminade, *Tetrahedron Lett.* **1999**, *40*, 7091–7094.

[5] a) J. Christoffers, A. Mann, *Angew. Chem.* **2000**, *112*, 2871–2874; *Angew. Chem. Int. Ed.* **2000**, *39*, 2752–2754; b) J. Christoffers, A. Mann, *Chem. Eur. J.* **2001**, *7*, 1014–1027; c) J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505–1508; d) J. Christoffers, B. Kreidler, H. Oertling, S. Unger, W. Frey, *Synlett* **2003**, 493–496; e) J. Christoffers, B. Kreidler, S. Unger, W. Frey, *Eur. J. Org. Chem.* **2003**, 2845–2853; f) J. Christoffers, K. Schuster, *Chirality* **2003**, *15*, 777–782; g) B. Kreidler, A. Baro, W. Frey, J. Christoffers, *Chem. Eur. J.* **2005**, *11*, 2660–2667; h) B. Kreidler, A. Baro, J. Christoffers, *Synlett* **2005**, 465–468; review: i) J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862–4867.

[6] J. Christoffers, W. Frey, H. Scharl, A. Baro, *Z. Naturforsch., Teil B* **2004**, *59*, 375–379.

[7] a) J. Christoffers, U. Rößler, T. Werner, *Eur. J. Org. Chem.* **2000**, 701–705; b) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.

[8] J. Christoffers, N. Önal, *Eur. J. Org. Chem.* **2000**, 1633–1635.

[9] Review: J. Christoffers, *Synlett* **2001**, 723–732.

[10] a) M. Mutter, H. Hagenmaier, E. Bayer, *Angew. Chem.* **1971**, *83*, 883–884; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 811–812; b) E. Bayer, M. Mutter, *Nature* **1972**, *237*, 512–513; c) P. Wentworth, Jr., K. D. Janda, *Chem. Commun.* **1999**, 1917–1924.

[11] a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; b) see also the thematic issue 10, 2002: J. A. Gladysz, *Chem. Rev.* **2002**, *102*, 3215–3216.

[12] S. B. Tsogoeva, J. Wöltinger, C. Jost, D. Reichert, A. Kühnle, H.-P. Krimmer, K. Drauz, *Synlett* **2002**, 707–710.

[13] R. Kucznierz, F. Grams, H. Leinert, K. Marzenell, R. A. Engh, W. von der Saal, *J. Med. Chem.* **1998**, *41*, 4983–4994.

[14] H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981–13996.

[15] S. C. Schürer, S. Gessler, N. Buschmann, S. Blechert, *Angew. Chem.* **2000**, *112*, 4062–4065; *Angew. Chem. Int. Ed.* **2000**, *39*, 3898–3901.

[16] S. Quici, A. Manfredi, L. Raimondi, A. Sironi, *J. Org. Chem.* **1995**, *60*, 6379–6388.

[17] K. Matsumoto, M. Shimojo, M. Hatanaka, *Chem. Lett.* **1997**, 1151–1152.

[18] Load values were calculated from ^{1}H NMR integrals based on the polymer signal at δ = 3.45–3.80 ppm. In the case of **3d** the signal at δ = 4.13 ppm (2 H) and for the corresponding imine the signal at δ = 2.22 ppm (3 H) were used for integration.

[19] J. Christoffers, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141–3149.

Received: June 21, 2005
Published Online: October 20, 2005

