SUPPORTING INFORMATION
FOR

A GENERAL APPROACH FOR PREPARATION OF POLYMER-SUPPORTED CHIRAL ORGANOCATALYSTS VIA ACRYLIC COPOLYMERIZATION

Part I

Tor E. Kristensen, Kristian Vestli, Martin G. Jakobsen, Finn K. Hansen and Tore Hansen

Department of Chemistry, University of Oslo,

P.O. Box 1033 Blindern, NO-0315 Oslo, Norway

TABLE OF CONTENTS

GENERAL

All commercially available reagents except benzoyl peroxide were used as received, and all solvents were obtained from commercial sources and used without further purification. Inert atmosphere (N_2) is utilized only where noted specifically, and magnetic stirring is used throughout. The heating mantles used in this work were of the all-metal type, either fluoropolymer coated or with anodized finish.

Thin layer chromatography (TLC) was performed on TLC-plates with a fluorescent silica coating, carried on either aluminium sheets or glass. They were visualized by UV-light, or by immersion in a solution of either $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ and $Ce(SO_4)_2{\cdot}4H_2O$ in aqueous H_2SO_4, a solution of *p*-anisaldehyde, conc. H_2SO_4 and glacial CH_3CO_2H in 96% EtOH or a solution of $KMnO_4$, K_2CO_3 and NaOH in water (followed by heating for all). Silica gel 60 (40-63 μm) was used for flash chromatography, either manually or with an automated system, using EtOAc/hexanes of technical quality.

^{1}H NMR and ^{13}C NMR spectra were recorded on a spectrometer operating at 300/200 MHz (^{1}H) or 75/50 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are, unless otherwise noted, reported relative to internal references of the solvent: 3.30/49.0 for CD_3OD, 2.49/39.7 for DMSO-d_6 and 7.26/77.0 for $CDCl_3$. Electrospray ionization mass spectra were recorded on an ESI-TOF mass spectrometer and infrared spectra were recorded on FTIR spectrometers. Melting points were determined on a standard melting point apparatus and optical rotation was recorded with a polarimeter at room temperature. Enantiomeric excess was determined by HPLC analysis using analytical columns (250 mm × 4.6 mm) packed with either cellulose tris(3,5-dimethylphenylcarbamate) coated on 10 μm silica gel, amylose tris[(*S*)-α-methylbenzylcarbamate] coated on 5 μm silica gel or amylose tris(3,5-dimethylphenylcarbamate) coated on 10 μm silica gel.

Important notes:

Several of the reactions in this work using methacrylates were undertaken without adding additional stabilizer/inhibitor than the one added originally by the manufacturer of the methacrylic starting material. As methacrylates from different suppliers may contain different amounts and types of inhibitor, a small quantity of an appropriate free radical inhibitor such as hydroquinone, hydroquinone monomethyl ether (MEHQ) or 2,6-di-*tert*-butyl-*p*-cresol (BHT) can be beneficial. **However, excessive use of inhibitors is completely detrimental in the preparation of these polymer beads unless steps are taken to remove them before polymerization.**

For noncrystalline compounds that could not be purified by recrystallization, residual solvents from chromatography were gently driven off by adding $CHCl_3$ and evaporating *in vacuo* after addition of a small amount of inhibitor. NMR spectra were then recorded immediately. Because of the reactive nature of noncrystalline methacrylates towards polymerization, all traces of solvents cannot always be removed before recording spectra (this is marked in the NMR spectra).

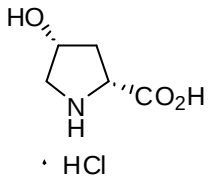
In the free radical polymerization of unsaturated monomers, azo initiators should be used whenever free amino groups (or amine salts) are present because they tend to quickly react with peroxides.

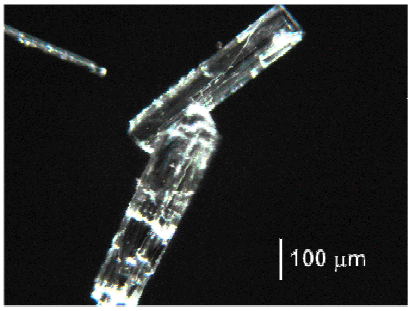
Experimental details contained in previous disclosures

The preparation of acrylic proline-derivatives **2**-**6**, as well as the preparation of polymer-supported prolines **9** and **11**-**14** has been reported by us earlier.[1,2] In addition, the experimental procedures connected to the results of Table 1 have also been detailed by us previously.[2] Polymer-supported proline **9** is prepared in complete analogy with **10** by simply using *trans*-4-hydroxy-L-proline instead of *cis*-4-hydroxy-D-proline hydrochloride.[2]

***cis*-4-Hydroxy-D-proline hydrochloride**

A 500 mL round bottom flask was charged with *trans*-4-hydroxy-L-proline (42.40 g, 323 mmol) and acetic anhydride (250 mL, 2645 mmol). The mixture was stirred for 16 h at 90 °C to give a clear, light brown solution. This was concentrated *in vacuo*, using a water bath kept at 60 °C, to give a viscous brown oil. This residual oil was dissolved in aqueous HCl (2 M, 250 mL) and refluxed for 3 h to give a dark, nearly black, solution. The solution was treated with activated charcoal (1.14 g) while hot (for 15 min under stirring) and then vacuum-filtered through a short pad of kieselguhr. The light yellow filtrate was evaporated *in vacuo*, using a water bath kept at 70 °C, to give an off-white, crystalline solid. The fibrous crystals were dissolved by addition of 96% EtOH (200 mL), under heating to the boiling point, to give a clear solution. The solution was poured into a beaker and stirred at the boiling point while, carefully, methyl *tert*-butyl ether (MTBE, 100 mL) was added, keeping the mixture at the boiling point. Towards the end of the addition, crystals started to form. Stirring and heating was immediately discontinued, and the solution left for crystallization at room temperature for 1 ½ h. The solution was then cooled in an ice/water bath for ~30 min, vacuum-filtered, the crystals washed with MTBE (100 mL) and dried at room temperature for 20 h to give *cis*-4-hydroxy-D-proline hydrochloride (38.16 g, 70%) as colorless crystals. The same crystals could, if needed, be recrystallized once more from EtOH/MTBE (4:1) to give material of analytical purity (84% recovery), or from pure 96% EtOH (74% recovery) to give the needle-shaped crystals depicted on the micrograph to the right. This is a well-known compound.[3] M.p. 118-121 °C, $[\alpha]_D^{20}$ = +11.4 (c = 1.07, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 2.28-2.41 (m, 1H, H-3), 2.51 (ddd, 1H, *J* = 14.1 Hz, 10.0 Hz and 4.2 Hz, H-3), 3.32-3.46 (m, 2H, H-5), 4.46-4.56 (m, 2H, H-2 and H-4) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 38.3, 54.8, 59.5, 70.1, 171.8 ppm. IR (KBr): 3423, 3272, 3023, 1710, 1584 cm^{-1}. HRMS (ESI) calcd for $C_5H_{10}NO_3^+$ [*M*–Cl^-]: 132.0660; found 132.0660.

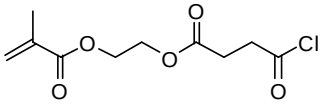




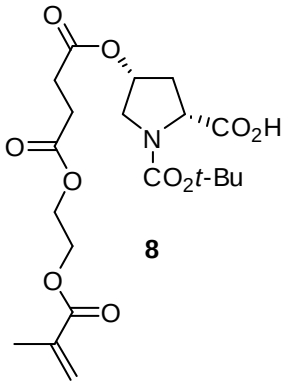
Note: The interesting mechanism of this transformation involves trapping of the hydroxyl (in position 4) to give the *cis*-product from a planar ring-closed acyl-intermediate.[3a]

Crosslinked methacrylic polymer beads by suspension copolymerization (10)

Commercial 2-methacryloyloxyethylsuccinic acid (25.0 mL, 129 mmol, containing 750 ppm MEHQ) was added to neat $SOCl_2$ (50.0 mL, 689 mmol) and stirred at room temperature for 30 min and at 50 °C for 1 h. The excess $SOCl_2$ was evaporated under reduced pressure to give 2-methacryloyloxyethylsuccinoyl chloride **1** as a slightly yellow oil. We have reported this transformation earlier.[2]

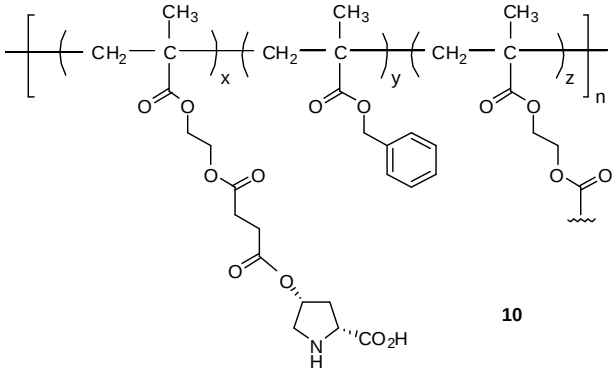


A 500 mL round bottom flask was charged with *cis*-4-hydroxy-D-proline hydrochloride (11.236 g, 67 mmol) and hydroquinone (11 mg), and dissolved by addition of CF_3CO_2H (40.0 mL) to give a clear and colorless solution. The crude methacrylic acid chloride was added, and the reaction mixture was stirred at room temperature for 2 h. The solution was cooled in an ice/water bath and Et_2O (250 mL) was added (slowly at first) under vigorous stirring. A syrupy precipitate forms, stirring was discontinued, and the precipitate was allowed to settle by gravity for 1 h. The reaction flask was removed from the ice/water bath, the supernatant was decanted and Et_2O (100 mL) was added, swirled and then decanted. The residual syrupy *O*-(2-methacryloyloxyethylsuccinoyl)-*cis*-4-hydroxy-D-proline hydrochloride **7** was dissolved by addition of CH_2Cl_2 (150 mL) together with some hydroquinone (20 mg, excessive amounts are detrimental for subsequent polymerization!). A solution of di-*tert*-butyl dicarbonate (14.615 g, 67 mmol) and Et_3N (25.0 mL, 179 mmol) in CH_2Cl_2 (100 mL) was added carefully under cooling from an ice/water bath. After the initial reaction had subsided, the solution was refluxed for 1 h and then cooled in an ice/water bath. A solution of $NaHSO_4$ (25.93 g, 188 mmol) in water (200 mL) was added. The mixture was stirred for 5 min, separated, and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine (50 mL) containing a few drops of 88% H_3PO_4, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give a pale yellow oil of crude *N*-*tert*-butyloxycarbonyl-*O*-(2-methacryloyloxyethylsuccinoyl)-*cis*-4-hydroxy-D-proline **8**, used immediately for the next step. An analytical sample was prepared by adding a small sample of crude material dissolved in CH_2Cl_2 onto a small column of silica, washing with a portion of *n*-pentane and then eluting the pure compound with Et_2O. Data are reported for the mixture of carbamate rotamers. Colorless oil, $[\alpha]_D^{20}$ = +22.1 (c = 0.579, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34/1.38 (s, 9H, *tert*-Bu), 1.85 (s, 3H, Me), 2.20-2.60 (m, 6H, 2×H-3 and $O_2CCH_2CH_2CO_2$), 3.37-3.67 (m, 2H, 2×H-5), 4.25 (s, 4H, OCH_2CH_2O), 4.27-4.44 (m, 1H, H-2), 5.18 (br. s, 1H, H-4), 5.51 (s, 1H, methacrylic H), 6.03 (s, 1H, methacrylic H), 9.36 (s, 1H, CO_2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 28.0 (2×C), 28.4, 28.8, 34.3/35.9, 51.6/52.2, 57.4 (2×C), 62.1, 62.2, 71.9/72.8, 80.4/81.2, 126.0, 135.6, 153.6/155.1, 167.0, 171.2/171.4, 171.8, 174.0/175.4 ppm. IR (film): 3464, 3247, 2980, 2934, 1739, 1733, 1638 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{29}NO_{10}Na^+$ [*M*+Na^+]: 466.1689; found 466.1699.



8

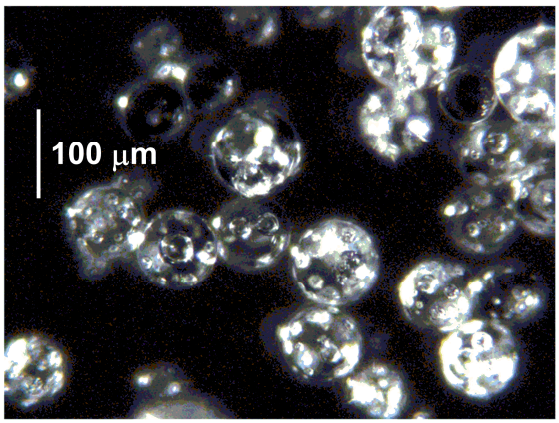
A three-necked 500 mL round bottom flask was charged with an egg-shaped stirring bar (1½ × $^5/_8$ in), potassium iodide (80 mg, inhibits polymerization in the aqueous phase), 0.5 wt% aqueous polyvinyl alcohol (M_w ~ 205 000 and 88% hydrolysis, 300 mL) and 88% H_3PO_4 (0.30 mL). All the oily *N*-*tert*-butyloxycarbonyl-*O*-(2-methacryloyloxyethyl-succinoyl)-*cis*-4-hydroxy-D-proline **8** (obtained in about 72% overall yield) was dissolved in benzyl methacrylate (43.27 g, 246 mmol) together with ethyleneglycol dimethacrylate (1.290 g, 6.51 mmol), toluene (30.0 ml) and benzoyl peroxide (442 mg, purified by recrystallization from $CHCl_3$/MeOH). This monomer mixture was added carefully to the aqueous solution under stirring and the system was flushed with N_2 for 5 min. The suspension



10

was polymerized under N_2 in a heating mantle at 80 °C for 15 h at a constant stirring rate of 700 rpm. The suspension was cooled to room temperature and poured into MeOH (500 mL). The beads were allowed to settle by gravity for 10 min, and the supernatant was decanted off. The process was repeated with more MeOH (500 mL). The beads were then vacuum-filtered and washed with MeOH (200 mL) and water (2000 mL), and dried for 71 h at room temperature to give nearly colorless polymer beads (58.91 g) as a free-flowing powder.

A portion of these beads (20.80 g) was purified by Soxhlet-extraction with CH_2Cl_2 (300 mL) for 22 h in a cellulose thimble (43×123 mm), transferred to a beaker, "collapsed" by addition of MeOH (250 mL), vacuum-filtered, washed with MeOH (100 mL) and dried at room temperature for 27 h to give colorless beads (20.18 g), useful for subsequent peptide couplings or other reactions. CHN-Analysis (%): N 0.82, C 67.79, H 7.01 (catalyst loading: 0.59 mmol/g).

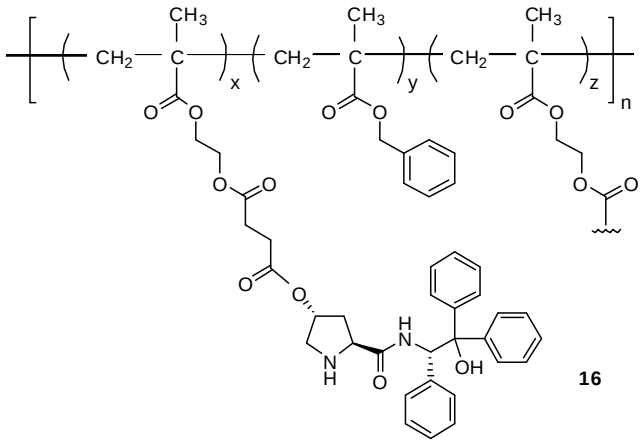


Another portion of the beads (21.37 g) was swollen in CH_2Cl_2 (200 mL) and CF_3CO_2H (50 mL) was added. The suspension was stirred gently at room temperature for 4 h. The beads were then vacuum-filtered and washed with CH_2Cl_2 (200 mL), Et_3N/MeOH (1:9, 200 mL), Et_3N/THF (1:9, 100 mL), THF (100 mL) and finally MeOH (200 mL). The beads were loaded into a cellulose thimble (43×123 mm), and Soxhlet-extracted with CH_2Cl_2 (300 mL) for 19 h. The swollen beads were transferred to a beaker, MeOH (250 mL) was added and the suspension was vacuum-filtered. The beads were washed with MeOH (100 mL), dried at room temperature for 46 h to give slightly colored beads **10** (19.16 g). CHN-Analysis (%): N 0.90, C 67.53, H 6.75 (catalyst loading: 0.64 mmol/g). IR (KBr): 3436, 3091, 3066, 3034, 2992, 2954, 1730, 1632 cm^{-1}.

Note: If necessary, beads that agglomerate to "lumpy" and unpractical material can give nice powders, either by gently using a porcelain pestle or by reslurrying the beads in MeOH, vacuum-filtering, washing with water and drying at room temperature.

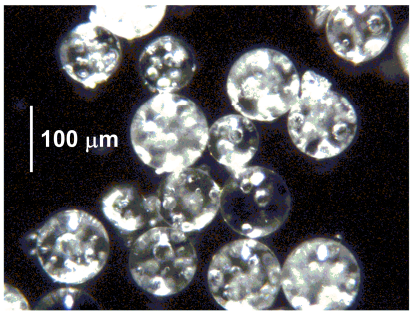
Prolineamide beads by peptide coupling (16)

A portion of Boc-protected acrylic beads (5.6735 g) prepared from *trans*-4-hydroxy-L-proline (see ref. 2) was swollen in CH_2Cl_2 (100 mL) and *i*Pr_2NEt (1.7269 g, 13.36 mmol) was added, followed by (*S*)-2-amino-1,1,2-triphenylethanol (*S*-**15**, 3.1983 g, 11.05 mmol)[4] and *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 3.9069 g, 12.17 mmol). The mixture was stirred at room temperature for 4 h.



16

The beads were vacuum-filtered, washed with small amounts of CH_2Cl_2 (a total of 200 mL), transferred to a 150 mL beaker and formic acid (98-100%, 50 mL) was added. The mixture was stirred for 19 h at room temperature and vacuum-filtered. The

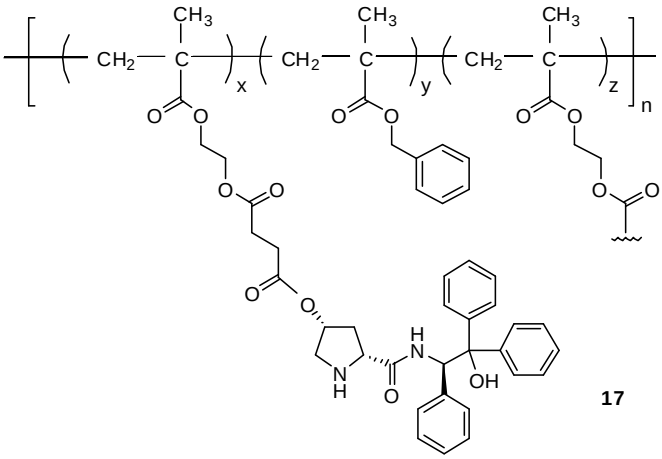


beads were washed with water (200 mL), saturated aqueous $NaHCO_3$ (200 mL), water (200 mL) and MeOH (100 mL). The beads were then loaded into a cellulose thimble (25×100 mm), Soxhlet-extracted with CH_2Cl_2 (200 mL) for 20 h and transferred to a 150 mL beaker. A portion of MeOH (120 mL) was added, and the suspension was vacuum-filtered. The product was dried at room temperature for 26 h to give colorless beads **16** (5.9327 g). CHN-analysis (%): N 1.41, C 69.57, H 6.49 (catalyst loading: 0.50 mmol/g). IR (KBr): 3503, 3433, 3090, 3064, 3033, 2991, 2953, 2891, 1733, 1681 cm^{-1}.

Note: Deprotection with formic acid is beneficial here, since deprotection with CF_3CO_2H/CH_2Cl_2, followed by Et_3N/MeOH in the standard manner have been found earlier by us to be detrimental to the enantioselectivity of the catalyst in the aldol reaction of *p*-nitrobenzaldehyde and acetone.[2]

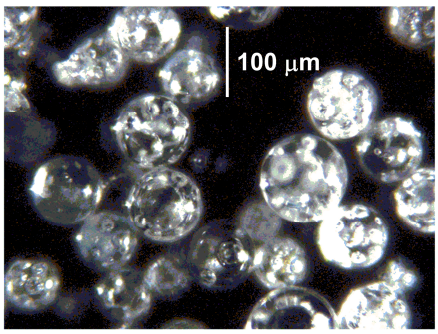
Prolineamide beads by peptide coupling (17)

A portion of Boc-protected acrylic beads (5.6229 g) prepared from *cis*-4-hydroxy-D-proline (see above) was swollen in CH_2Cl_2 (100 mL) and iPr_2NEt (1.7422 g, 13.48 mmol) was added, followed by (*R*)-2-amino-1,1,2-triphenylethanol (*R*-**15**, 3.3321 g, 11.52 mmol)[4] and *O*-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU, 3.9721 g, 12.37 mmol). The mixture was stirred at room temperature for 4 h.



17

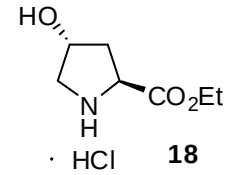
The beads were vacuum-filtered, washed with small amounts of CH_2Cl_2 (a total of 200 mL), transferred to a 150 mL beaker and formic acid (98-100%, 50 mL) was added. The mixture was stirred for 19 h at room temperature and vacuum-filtered. The beads were washed with water (200 mL), saturated aqueous $NaHCO_3$ (200 mL), water (200 mL) and MeOH (100 mL). The beads were then loaded into a cellulose thimble (25×100 mm), Soxhlet-extracted with CH_2Cl_2 (200 mL) for 21 h and transferred to a 150 mL beaker. A portion of MeOH (120 mL) was added, and the suspension was vacuum-filtered. The product was dried at room temperature for 49 h to give colorless beads **17** (6.2086 g). CHN-analysis (%): N 1.55, C 70.55, H 6.55 (catalyst loading: 0.55 mmol/g). IR (KBr): 3512, 3370, 3090, 3064, 3033, 2991, 2952, 2890, 1729, 1672 cm^{-1}.



Note: Both enantiomers of 2-amino-1,1,2-triphenylethanol (**15**) are commercially available. However, both are very easily prepared on large scale by treating the methyl ester hydrochloride of L- or D-phenylglycine with PhMgBr in Et_2O.[4]

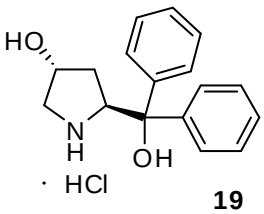
***trans*-4-Hydroxy-*α*,*α*-diphenyl-L-prolinol hydrochloride (19)**

To a stirred suspension of *trans*-4-hydroxy-L-proline (55.38 g, 422 mmol) in EtOH (96%, 500 mL), cooled in an ice/water bath, was added $SOCl_2$ (46.0 mL, 634 mmol) via an addition funnel over a period of 15 min. The suspension was then heated to reflux and kept there for 3 h. The resultant clear and colorless solution was cooled in an ice/water bath, and the product crystallized. A portion of Et_2O (500 mL) was added, and the suspension was stirred vigorously, vacuum-filtered and washed with Et_2O (100 mL). The product was dried at room temperature for 23 h to give *trans*-4-hydroxy-L-proline ethyl ester hydrochloride **18** (73.12 g, 88%) as white fibrous crystals.



18

A three-necked 2000 mL round bottom flask equipped with a long reflux condenser, addition funnel and glass stopper was charged with an oval stirring bar (50×20 mm) and Mg-turnings (40.24 g, 1655 mmol). Dry Et_2O (80 mL) was added to the Mg-turnings, followed by a small portion of a solution of bromobenzene (175 mL, 1665 mmol) in dry Et_2O (500 mL) to initiate the reaction. The rest of the PhBr-solution was then added over a period of 1 h 40 min, keeping the addition rate so as to maintain gentle reflux. After addition, stirring was continued for 1 h to dissolve most Mg and the mixture was diluted with dry Et_2O (420 mL) and cooled in an ice/water bath. *trans*-4-Hydroxy-L-proline ethyl ester hydrochloride **18** (46.46 g, 237 mmol) was added under stirring, the reaction flask was transferred to a heating mantle and refluxed for 5 h under stirring, giving a quite clear solution and a heavy precipitate. The reaction flask was then cooled in an ice/water bath, and its contents were carefully poured into crushed ice (1250 mL) contained in a 3000 mL beaker. Concentrated aqueous HCl (37%, 140 mL) and water (600 mL) was added under stirring by a glass rod. As much as possible of the colored top organic layer was decanted, Et_2O (200 mL) was added and then decanted off again after some stirring. Concentrated aqueous NH_3 (25%, 25 mL) was added to adjust pH of the slurry to approximately 9, and the slurry was vacuum-filtered. The filter cake was washed with water (1000 mL) and MTBE (200 mL) and transferred to a 600 mL beaker. The crude product was suspended in MeOH (250 mL) and CF_3CO_2H (19 mL, 247 mmol) was added to dissolve the material to give a dark-colored, but clear, solution which was vacuum-filtered to remove residual Mg. An ice-cold methanolic HCl solution (prepared by dropping 25 mL of acetyl chloride into 100 mL of MeOH under cooling from an ice/water bath) was added, followed by Et_2O (700 mL). A precipitate quickly formed, the suspension was stirred vigorously for 10 min, then vacuum-filtered, and the product washed with Et_2O (350 mL). A second portion of material precipitated from the mother liqueur on standing and was isolated (after cooling in an ice/water bath) in the same manner. The material was dried for 24 h at room temperature to give *trans*-4-hydroxy-α,α-diphenyl-L-



19

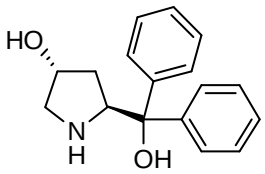
prolinol hydrochloride **19** (32.10 g, 44% in total) as near colorless and fibrous material of good purity, used as is for the next step. An analytical sample was prepared by recrystallization of this material from 96% EtOH. M.p. 266-268 °C (dec.), $[\alpha]_D^{20}$ = +8.6 (c = 0.232, MeOH). ^{1}H NMR (200 MHz, CD_3OD, calibrated by residual EtOH at δ = 1.17): δ = 1.95 (dd, 1H, *J* = 13.7 Hz and 6.8 Hz, H-3), 2.19 (ddd, 1H, *J* = 13.7 Hz, 10.7 Hz and 4.1 Hz, H-3), 3.22 (d, 1H, *J* = 12.2 Hz, H-5), 3.34 (dd, 1H, *J* = 12.2 Hz and 3.4 Hz, H-5), 4.53 (br. s, 1H, H-4), 5.07 (dd, 1H, *J* = 10.7 Hz and 6.8 Hz, H-2), 7.18-7.45 (m, 6H, Ph-H), 7.47-7.54 (m, 2H, Ph-H), 7.62-7.70 (m, 2H, Ph-H) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 36.4, 55.4, 66.6, 70.7, 78.2, 126.7, 126.8, 128.6, 128.8, 129.5, 129.9, 145.3, 145.4 ppm. IR (KBr): 3400, 3306, 3027, 1450, 991 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{20}NO_2^+$ [*M*-Cl$^-$]: 270.1494; found 270.1491.

Note: Kapfhammer and Matthes reported already in 1933 a procedure very analogous to the one above for preparation of the same compound as its free amine.[5] That procedure was found useful for preparation of material on the 1-5 g scale. However, we found their procedure unworkable at larger scales. The product (as free amino alcohol) is a poorly soluble material that requires disproportionate amounts of solvents for both extraction and subsequent recrystallization. In our procedure above, the crude material is brought into solution as its more soluble trifluoroacetate salt and precipitated as its less soluble hydrochloride with good purity.

***trans*-4-Hydroxy-α,α-diphenyl-L-prolinol**

This material can be prepared as reported (see discussion above).[5] For convenience, the properties and copies of NMR spectra of this compound is included here for a very pure sample prepared by recrystallization of the free amino alcohol in a MeOH/PhMe/THF-mixture as the literature values in our finding tends to be a little inconsistent:

M.p. 190-192 °C, $[\alpha]_D^{20}$ = –115.3 (c = 0.215, DMSO). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.17-1.31 (m, 1H, H-3), 1.50-1.67 (m, 1H, H-3), 2.37 (s, 1H, *sec*-OH), 2.72 (dd, 1H, *J* = 10.9 Hz and 1.4 Hz, H-5), 2.94 (dd, 1H, *J* = 10.9 Hz and 4.4 Hz, H-5), 4.08 (s, 1H, OH or NH), 4.44-4.56 (m, 2H, H-2 and H-4), 5.05 (s, 1H, OH or NH), 7.06-7.31 (m, 6H, Ph), 7.40-7.47 (m, 2H, Ph), 7.54-7.62 (m, 2H, Ph) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 36.7, 55.6, 63.0, 71.2, 77.5, 125.5, 126.1, 126.2, 126.7, 127.9, 146.8, 148.3 ppm. IR (KBr): 3301, 3281, 3087, 3059, 2977, 1495, 1446 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{20}NO_2^+$ [*M*+H$^+$]: 270.1494; found 270.1488.



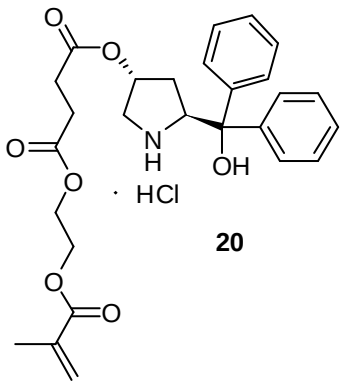
***O*-(2-Methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride (20)**

A 250 mL round bottom flask was charged with commercial 2-methacryloyloxyethylsuccinic acid (48.54 g, 211 mmol, containing 750 ppm MEHQ) and $SOCl_2$ (75.0 mL, 1034 mmol) was added. The reaction mixture was stirred at room temperature for 30 min, MEHQ (25 mg) was added, and stirring was continued at 50 °C for 30 min. Excess $SOCl_2$ was removed *in vacuo* to give the 2-methacryloyloxyethylsuccinoyl chloride **1** as a light yellow oil.

A 500 mL round bottom flask was charged with *trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride **19** (32.00 g, 105 mmol), which was then dissolved by addition of CF_3CO_2H (100 mL). The solution was cooled in an ice/water bath, and the crude methacrylic acid chloride was added. The light brown reaction mixture was removed from the ice/water bath and was stirred at room temperature for 2 h. It was then cooled down again in an ice/water bath and carefully diluted with Et_2O (500 mL). The resulting dispersion was stirred vigorously for

20 min, then removed from the ice/water bath and vacuum-filtered. The solid was washed with Et_2O (300 mL) and dried at room temperature overnight.

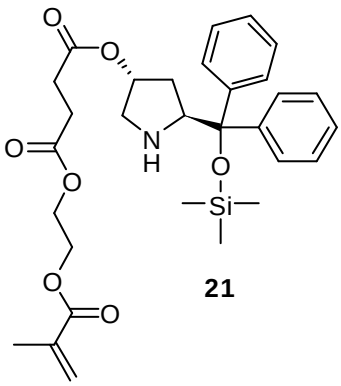
The crude product was transferred to a 500 mL beaker together with hydroquinone (120 mg) and dissolved in EtOH (96 vol%, 300 mL) under stirring by heating to the boiling point. Boiling MTBE (200 mL) was added slowly to the colored solution. Crystallization initiated, stirring was discontinued, and the solution left for crystallization at room temperature for 5 h. The crystals were vacuum-filtered, washed with MTBE (300 mL) and dried at room temperature for 65 h to give *O*-(2-methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride **20** as a white and fluffy solid (37.78 g, 70%). M.p. 187-190 °C (dec.), $[\alpha]_D^{20}$ = –87.7 (c = 0.195, $CHCl_3$). ^{1}H NMR (200 MHz, DMSO-d_6): δ = 1.60-1.75 (m, 1H, H-3), 1.85 (s, 3H, Me), 2.21-2.40 (m, 1H, H-3), 2.63 (s, 4H, $O_2CCH_2CH_2CO_2$), 3.23-3.56 (m, 2H, 2×H-5), 4.28 (s, 4H, OCH_2CH_2O), 5.01 (br. s, 1H, H-2), 5.24 (s, 1H, H-4), 5.66 (s, 1H, methacrylic H), 6.02 (s, 1H, methacrylic H), 6.69 (s, 1H, OH), 7.12-7.42 (m, 6H, Ph-H), 7.43-7.54 (m, 2H, Ph-H), 7.65-7.78 (m, 2H, Ph-H), 8.99 (br. s, 1H, NH), 10.51 (br. s, 1H, NH) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ = 18.1, 28.7, 29.1, 32.6, 51.2, 62.2, 62.6, 64.0, 73.1, 77.1, 125.4, 126.3 (2×), 127.2, 127.5, 128.4, 128.6, 135.8, 144.4, 144.6, 166.6, 171.6, 172.1 ppm. IR (KBr): 3235, 2960, 1733, 1636, 1169, 1149 cm^{-1}. HRMS (ESI) calcd for $C_{27}H_{32}NO_7^+$ [*M*-Cl^-]: 482.2178; found 482.2163.



20

_O_-(2-Methacryloyloxyethylsuccinoyl)–_trans_–4-hydroxy-α,α-diphenyl-L-prolinol trimethylsilyl ether (21)

O-(2-Methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride **20** (5.2975 g, 10.2 mmol) was suspended in CH_2Cl_2 (40 mL) and aqueous K_2CO_3 (10%, 40 mL) was added. The mixture was stirred vigorously for 5 min and separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ and filtered into a round bottom flask. The $MgSO_4$ was washed with extra CH_2Cl_2 (20 mL) and filtered into the same flask. Iodine (0.0410 g, 0.16 mmol) and HMDS (3.20 mL, 15.3 mmol) were added to the clear solution, and the reaction mixture was stirred at room temperature for 4 h and quenched by addition of MeOH (3 mL). After stirring for 10 min, the volatiles were evaporated *in vacuo* and the residual oil was dissolved in CH_2Cl_2 (40 mL) and treated with a solution of $Na_2S_2O_3 \cdot 5H_2O$ (4.52 g, 18.2 mmol) in water (40 mL) under stirring for 5 min. The mixture was separated, and the organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to to give *O*-(2-methacryloyloxyethylsuccinoyl)–*trans*–4-hydroxy-α,α-diphenyl-L-prolinol trimethylsilyl ether **21** as a clear and only slightly colored oil of good purity, and used as is for the polymerization. An analytical sample was prepared by adding a small sample of crude material dissolved in CH_2Cl_2 onto a small column of silica, washing with a portion of *n*-pentane and then eluting the pure compound with Et_2O. Colorless oil, $[\alpha]_D^{20}$ = –8.5 (c = 0.106,



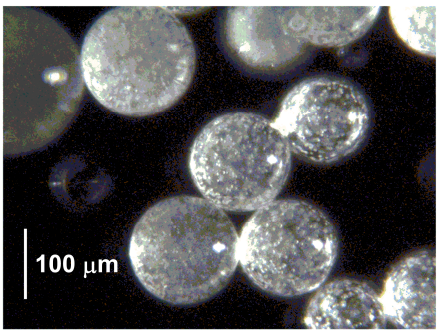
21

$CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = –0.10 (s, 9H, TMSO), 1.65 (dd, 1H, *J* = 14.2 Hz and 7.0 Hz, H-3), 1.81-1.96 (m, 5H, H-3, Me and NH), 2.58-2.66 (m, 4H, $O_2CCH_2CH_2CO_2$), 2.92-2.97 (m, 2H, H-5), 4.27-4.36 (m, 5H, H-2 and OCH_2CH_2O), 4.95-5.04 (m, 1H, H-4), 5.59 (quint, 1H, *J* = 1.5 Hz, methacrylic H), 6.12 (br. s, 1H, methacrylic H), 7.20-7.50 (m, 10H, 2×Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 2.0, 18.1, 28.8, 29.1, 34.5, 53.0, 62.1, 62.2, 63.8, 75.6, 82.6, 125.9, 126.8, 127.0, 127.3, 127.4, 127.6, 128.3, 135.7, 144.9, 146.2, 166.9, 171.7, 171.9 ppm. IR (film): 3087, 3059, 3025, 2957, 2896, 1738, 1732 cm^{-1}. HRMS (ESI) calcd for $C_{30}H_{40}NO_7Si^+$ [*M*+H$^+$]: 554.2574; found 554.2563.

Crosslinked methacrylic polymer beads by suspension copolymerization (22)

A three-necked 250 mL round bottom flask was charged with an egg-shaped magnetic stirring bar (1 ½ × $^5/_8$ in), potassium iodide (60 mg, inhibits polymerization in the aqueous phase), K_2CO_3 (185 mg) and 0.5 wt% aqueous polyvinyl alcohol (M_w ~ 205 000 and 88% hydrolysis, 130 mL). A mixture of all the *O*-(2-methacryloyloxyethylsuccinoyl)–*trans*–4-hydroxy-α,α-diphenyl-L-prolinol trimethylsilyl ether **21** prepared as described above was dissolved in methyl methacrylate (16.55 g, 165 mmol) together with ethyleneglycol dimethacrylate (0.712 g, 3.59 mmol), toluene (20 ml) and 2,2'-azobis(2-methylbutyronitrile) (222 mg). This monomer mixture was added carefully to the aqueous solution under stirring, and the system was flushed with N_2 for 5 min. The suspension was polymerized under N_2 in a heating mantle at 70 °C for 16 h at a constant stirring rate of 550 rpm.

22



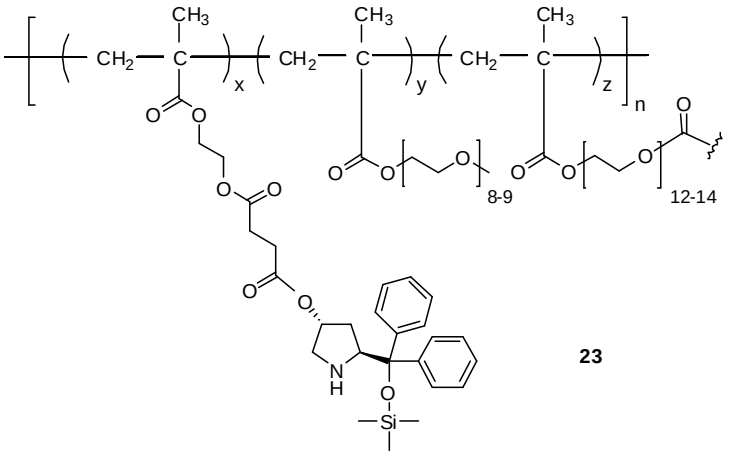
The suspension was allowed to cool and then poured into a beaker containing MeOH (300 mL). The beads were allowed to settle by gravity, and the supernatant was decanted off. The process was repeated once more after addition of MeOH (300 mL), the beads were then slurried in water, vacuum-filtered and washed with water (1500 mL). Drying at room temperature gave a quantitative recovery of polymer beads **22** containing immobilized Jørgensen/Hayashi diarylprolinol *O*-TMS-ether.

CHN-Analysis (%): N 0.48, C 60.74, H 7.61 (catalyst loading: 0.34 mmol/g). IR (KBr): 3437, 2998, 2954, 2846, 1734, 1630 cm^{-1}.

PEG-methacrylate polymer beads by suspension copolymerization (23)

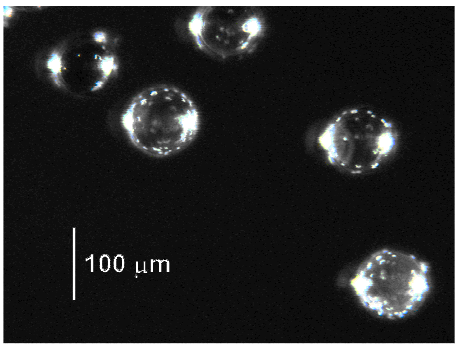
A portion of *O*-(2-methacryloyloxyethylsuccinoyl)–*trans*–4-hydroxy-α,α-diphenyl-L-prolinol trimethylsilyl ether **21** was prepared in completely quantitative yield from *O*-(2-methacryloyloxyethylsuccinoyl)-*trans*-4-hydroxy-α,α-diphenyl-L-prolinol hydrochloride **20** (5.451 g, 10.5 mmol), HMDS (3.30 mL, 15.8 mmol) and I_2 (32 mg, 0.13 mmol) in CH_2Cl_2 (a total of 100 mL) for 4 h in a completely analogous manner as to that described above for the same compound.

A three-necked 250 mL round bottom flask was charged with an egg-shaped magnetic stirring bar (1 ½ × $^5/_8$ in), potassium iodide (36 mg, inhibits polymerization in the aqueous phase), K_2CO_3 (46 mg), 0.5 wt% aqueous polyvinyl alcohol (M_w ~ 205 000 and 88% hydrolysis, 150 mL). A mixture of all the *O*-(2-methacryloyloxyethylsuccinoyl)–*trans*–4-hydroxy-α,α-diphenyl-L-prolinol trimethylsilyl ether **21** prepared as described above was dissolved in PEG 600 dimethacrylate (M_n ~750, 7.71 g) together with PEG 400 methyl ether methacrylate (M_n ~475, 7.82 g), toluene (20 ml) and 2,2'-azobis(2-methylbutyronitrile) (216 mg). This monomer mixture was added carefully to the aqueous solution under stirring, and the system was flushed with N_2 for 5 min. The suspension was polymerized under N_2 in a heating mantle at 70 °C for 16 h at a constant stirring rate of 600 rpm.



23

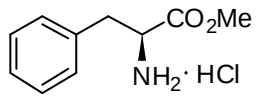
The suspension was allowed to cool to room temperature under stirring and became milky-white (at lower temperatures, the PEG chains become hydrated and the porogen = toluene is forced out of the beads). The mixture was poured into a 600 mL beaker, followed by water (350 mL). The beads were allowed to settle by gravity for 30 min, and the milky supernatant was decanted off. More water (300 mL) was added, and the mixture was vacuum-filtered and washed thoroughly with water (2000 mL) and MeOH (500 mL). This washing was done by adding the solvent in small portions on the Büchner-funnel, allowing most of it to drain by gravity, and applying vacuum to drain away the rest of it before the next portion of solvent was added. The beads were dried at room temperature for 45 h to give slightly colored polymer beads **23** (19.22 g). CHN-Analysis (%): N 0.69, C 57.08, H 8.25 (catalyst loading: 0.49 mmol/g). IR (KBr): 3446, 2874, 1733, 1636 cm^{-1}.



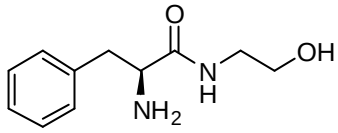
Note: Unlike the more conventional microporous beads, these beads are of a swellable macroporous type and are easier to purify. They do generally not require Soxhlet-extraction prior to use.

(5*S*)-5-Benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride (25)

L-Phenylalanine (45.75 g, 277 mmol) was suspended in MeOH (350 mL), and the suspension was cooled in an ice/water bath. Thionyl chloride (24.2 mL, 332 mmol) was added over a period of 15 min, the reaction flask was removed from the ice/water bath and the clear solution was stirred at room temperature for 28 h. Volatiles were removed *in vacuo* and the residual solid was slurried in Et_2O (200 mL), filtered by vacuum, washed with Et_2O (100 mL) and dried at room temperature for 15 h to give L-phenylalanine methyl ester hydrochloride as a white solid (58.46 g, 98%).

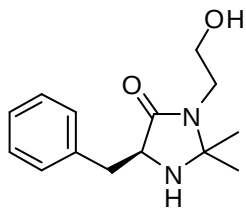


A portion of L-phenylalanine methyl ester hydrochloride (58.27 g, 270 mmol) was dissolved in ethanolamine (100 mL, 1662 mmol), and the viscous solution was stirred at room temperature for 26 h. The reaction mixture was transferred to a 1000 mL separatory funnel and was diluted with CH_2Cl_2 (400 mL) and then with aqueous K_2CO_3 (20% by weight, 300 mL). The mixture was thoroughly swirled and separated. The aqueous phase was extracted with CH_2Cl_2 (3×200 mL), and the combined organic phase was dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* in a 1000 mL round bottom flask to give essentially pure L-phenylalanylaminoethanol (53.82 g, 96%) as a white solid. If necessary, a small amount of Et_2O can be used to initiate crystallization.



All the L-phenylalanylaminoethanol in the 1000 mL round bottom flask was dissolved together with *p*-TsOH·H_2O (1.497 g, 7.9 mmol) in a mixture of acetone (250 mL) and *i*-PrOH (350 mL). The round bottom flask was fitted with a Dean-Stark trap, placed in a heating mantle and heated to 85 °C over 20 min and stirred at this temperature for 5 h, the liquid collected in the Dean-Stark trap (a total of 93 mL over 5 h) was discarded. The reaction mixture was concentrated *in vacuo* to give a light brown oil. The oil was diluted with MeOH (50 mL) and an ice-cold methanolic HCl-solution (prepared from 30 mL of acetyl chloride added carefully under vigorous stirring to 100 mL MeOH under cooling from an ice/water bath) was added over a couple of minutes. The warm solution was diluted with Et_2O (500 mL) slowly under vigorous stirring (1 ½ × ⅝ inch egg-shaped stirring bar) to give a suspension of white product crystals in a light brown solution. The suspension was stirred for 40 min, filtered by vacuum, washed with Et_2O (150 mL) and dried at room temperature for 40 h to give (5*S*)-5-benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride **25** (62.77 g, 85%) as a practically white powder. This was essentially pure product, but was slightly colored and subsequently recrystallized as follows:

All of the product was dissolved in MeOH (200 mL) in a 1000 mL beaker by heating to the boiling point. The beaker was removed from the heating source and under vigorous stirring (50×12 mm triangular stirring bar), Et_2O (500 mL) was added. Crystals formed, and the mixture was stirred at room temperature for 40 min, vacuum-filtered, and the



25 · HCl

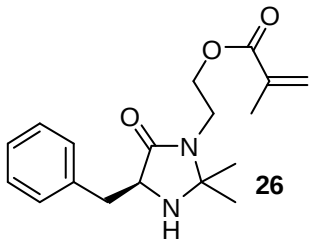
crystals were washed with Et_2O (150 mL). The crystals were dried at room temperature for 27 h to give pure (5*S*)-5-benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride **25** (58.74 g, 94% recovery). M.p. 144-146 °C (dec.), $[\alpha]_D^{20}$ = –84.1 (c = 1.03, MeOH). ^{1}H NMR (200 MHz, CD_3OD): δ = 1.64 (s, 3H, Me), 1.80 (s, 3H, Me), 3.16 (dd, 1H, *J* = 15.1 Hz and 10.6 Hz, benzylic H), 3.35-3.58 (m, 3H, benzylic H and -CH_2N), 3.63-3.82 (m, 2H, -CH_2O-), 4.67 (dd, 1H, *J* = 10.6 Hz and 3.7 Hz, H-5), 7.25-7.50 (m, 5H, Ph) ppm. ^{13}C NMR (50 MHz, CD_3OD): δ = 23.7, 25.0, 34.9, 44.1, 59.3, 60.1, 79.3, 128.7, 130.1, 130.3, 136.6, 168.7 ppm. IR (KBr): 3146, 3088, 2939, 2692, 2540, 1721 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{21}N_2O_2^+$ [*M*-Cl$^-$]: 249.1603; found 249.1595.

Note: A different portion of crude product crystals (54.75 g) was recrystallized in a 1000 mL round bottom flask by dissolution in EtOH (96%, 300 mL) by heating to the boiling point. Under vigorous stirring (1 ½ × ⅝ inch egg-shaped stirring bar), MTBE (500 mL) was added slowly, keeping the mixture at the boiling point. Crystals started to appear at the end of the addition and the reaction flask was removed from the heating source and stirred at room temperature for 1 ½ h and then under cooling from an ice/water bath for 30 min. The crystals were filtered by vacuum and dried at room temperature for 45 h to give pure (5*S*)-5-benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride **25** (47.23 g, 86% recovery).

Recrystallization in pure MeOH, EtOH or mixtures of those with *i*-PrOH was also possible, but gave much poorer recovery of product.

(5*S*)-5-Benzyl-2,2-dimethyl-3-(2-methacryloyloxyethyl)-imidazolidin-4-one (26)

A 100 mL round bottom flask was charged with anhydrous $MeSO_3H$ (40.0 mL) and cooled in an ice/water bath. Over a period of 20 min, a portion of (5*S*)-5-benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride **25** (10.14 g, 35.6 mmol) was added in small portions. The salt dissolved under HCl-evolution. Methacryloyl chloride (6.90 mL, 71.3 mmol) was added and the reaction mixture was stirred at 0-5 °C for 3 h 30 min (giving off HCl) to give a clear solution. The clear solution was carefully diluted with Et_2O (50 mL) while still under cooling, and the solution was transferred to a 1000 mL separatory funnel. More Et_2O (550 mL) was added to give phase separation, the mixture was swirled and allowed to separate. The bottom yellow layer of the product methanesulfonate was allowed to drip directly into a stirred mixture of CH_2Cl_2 (200 mL) and a solution of K_2CO_3 (42.80 g, 310 mmol) in water (250 mL). The mixture was stirred for 5 min after completed addition and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (2×100 mL), and the combined organic phases were dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to give a nearly completely colorless oil of (5*S*)-5-benzyl-2,2-dimethyl-3-(2-methacryloyloxyethyl)-imidazolidin-4-one **26** (8.69 g, 77%) of very good purity and used immediately in the next step. An analytical sample was prepared by adding a small sample of crude material dissolved in CH_2Cl_2 onto a small column of silica, washing with a portion of *n*-pentane and then eluting the pure compound with Et_2O. Colorless oil, $[\alpha]_D^{20}$ = –45.3 (c = 0.232, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.17 (s, 3H, Me), 1.28 (s, 3H, Me), 1.86-1.95 (m, 4H, Me and NH), 3.10 (d, 2H, *J* = 5.4 Hz,



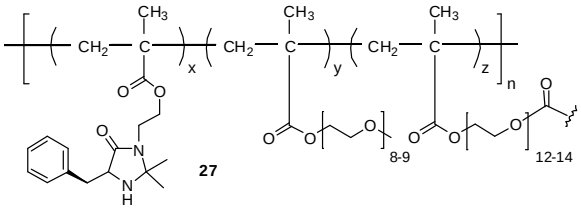
26

benzylic H), 3.25 (dt, 1H, *J* = 14.3 Hz and 6.6 Hz, 1×H in -CH_2N), 3.61 (dt, 1H, *J* = 14.3 Hz and 5.7 Hz, 1×H in -CH_2N), 3.80 (t, 1H, *J* = 5.4 Hz, H-5), 4.19-4.32 (m, 2H, -CH_2O-), 5.58 (quint, 1H, *J* = 1.6 Hz, methacrylic H), 6.09 (t, 1H, *J* = 1.2 Hz, methacrylic H), 7.17-7.35 (m, 5H, Ph) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 26.3, 27.7, 36.7, 39.0, 58.5, 61.7, 75.8, 125.8, 126.7, 128.3, 129.3, 135.7, 136.5, 166.9, 174.3 ppm. IR (film): 3433, 3029, 2978, 2929, 1718, 1687, 1637 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{25}N_2O_3^+$ [*M*+H^+]: 317.1865; found 317.1870.

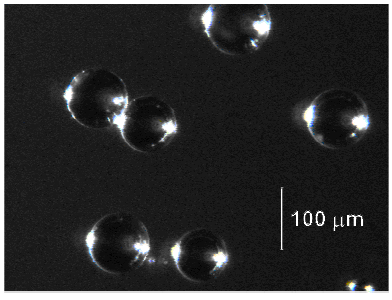
Note: The yield of the final product should be taken as indicative as it contains traces of CH_2Cl_2. As a control experiment for the structural integrity of the imidazolidinone skeleton under these acidic conditions, a sample of (5*S*)-5-benzyl-2,2-dimethyl-3-(2-hydroxyethyl)-imidazolidin-4-one hydrochloride **25** in $MeSO_3H$ (since $MeSO_3H$ has a higher affinity for these amines than does HCl, the latter is evolved when HCl is present or developed during a reaction) was left in a polarimeter for several hours to observe any change in optical activity. This experiment verified that this imidazolidinone is completely stable under the reaction conditions. However, at elevated temperatures, there will be a slow decomposition over time.

PEG-methacrylate polymer beads by suspension copolymerization (27)

A three-necked 500 mL round bottom flask was charged with an egg-shaped magnetic stirring bar (1 ½ × $^5/_8$ in), potassium iodide (84 mg, inhibits polymerization in the aqueous phase), K_2CO_3 (88 mg), 0.5 wt% aqueous polyvinyl alcohol (M_w ~ 205 000 and 88% hydrolysis, 300 mL). A mixture of all the (5*S*)-5-benzyl-2,2-dimethyl-3-(2-methacryloyloxyethyl)-imidazolidin-4-one **26** prepared as described above was dissolved in PEG 600 dimethacrylate (M_n ~750, 15.86 g) together with PEG methyl ether methacrylate (M_n ~475, 15.40 g), toluene (30 ml) and 2,2'-azobis(2-methylbutyronitrile) (343 mg). This monomer mixture was added carefully to the aqueous solution under stirring, and the system was flushed with N_2 for 5 min. The suspension was polymerized under N_2 in a heating mantle at 70 °C for 15 h at a constant stirring rate of 800 rpm.



27



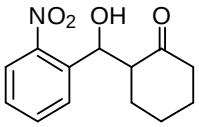
The suspension was allowed to cool to room temperature under stirring and became milky-white (at lower temperatures, the PEG chains become hydrated and the porogen = toluene is forced out of the beads). The mixture was poured into a 1000 mL beaker, followed by water (500 mL). The beads were allowed to settle by gravity for 1 h, and the milky supernatant was decanted off. More water (500 mL) was added, and the mixture was vacuum-filtered and washed thoroughly with water (2000 mL) and MeOH (500 mL). This washing was done by adding the solvent in small portions on the Büchner-funnel, allowing most of it to drain by gravity, and applying vacuum to drain away the rest of it before the next portion of solvent was added. The beads were dried at room temperature for 68 h to give completely colorless polymer beads **27** (35.21 g). CHN-Analysis (%): N 1.80, C 56.70, H 8.37 (catalyst loading: 0.64 mmol/g). IR (KBr): 3436, 2874, 1734, 1697 cm^{-1}.

General procedure for the asymmetric aldol reaction of benzaldehydes with cyclohexanone

Benzaldehyde derivative (0.40 mmol) was dissolved in cyclohexanone (2.0 mmol), contained in a small vial (by gentle heating on a water bath if necessary). Water (0.14 mL) was added, followed by the polymer beads (**9** or **10**, 10 mol%). For noncrystalline benzaldehydes, the vial is charged with polymer beads first, followed by the benzaldehyde derivative and solvents/additives.

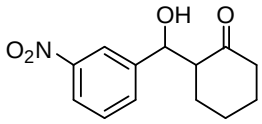
The reaction was mixed gently with a closed capillary tube and then left without stirring for 24 h. The reaction mixture was diluted with EtOAc and transferred to a small folded paper filter. The polymer beads were washed with additional small quantities of EtOAc (20 mL in total for dilution and washing), and the filtrate was evaporated *in vacuo* to yield the crude product. Purification by flash column chromatography on silica gel with EtOAc/hexanes yielded the pure aldol product. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product, and the enantiomeric excess was determined by HPLC analysis of the purified product. All the aldol products are well-known compounds with spectroscopic data in accordance with literature.[6]

2-(Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one



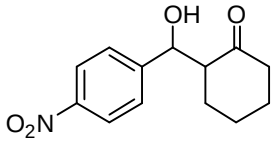
Purified by flash column chromatography on silica gel with EtOAc/hexanes (10-20% EtOAc). Yellow oil.[6a,b] HPLC (Daicel Chiralpak OD-H, 10% *i*-PrOH in isohexane, 0.5 mL/min, λ = 254 nm): t_R = 15.1 and 16.6 min (syn), t_R = 20.8 and 24.1 min (anti).

2-(Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one



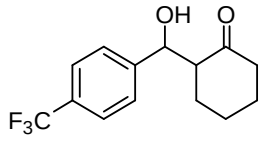
Purified by flash column chromatography on silica gel with EtOAc/hexanes (10-20% EtOAc). Colorless solid.[6a,b] HPLC (Daicel Chiralpak AD-H, 10% *i*-PrOH in isohexane, 0.5 mL/min, λ = 218 nm): t_R = 33.9 and 35.5 min (syn), t_R = 39.5 and 49.5 min (anti).

2-(Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one



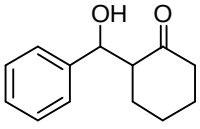
Purified by flash column chromatography on silica gel with EtOAc/hexanes (10-20% EtOAc). Yellow solid.[2,6a] HPLC (Daicel Chiralpak AD-H, 10% *i*-PrOH in isohexane, 1.0 mL/min, λ = 254 nm): t_R = 18.1 and 20.8 min (syn), t_R = 23.2 and 31.4 min (anti).

2-(Hydroxy(4-trifluoromethylphenyl)methyl)cyclohexan-1-one



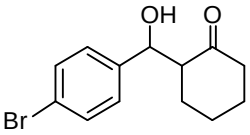
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-10% EtOAc). Colorless solid.[6b] HPLC (Daicel Chiralpak OD-H, 5% *i*-PrOH in isohexane, 0.5 mL/min, λ = 217 nm): t_R = 16.5 and 18.3 min (syn), t_R = 22.6 and 28.4 min (anti).

2-(Hydroxy(phenyl)methyl)cyclohexan-1-one



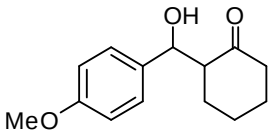
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Colorless oil.[6a,b] HPLC (Daicel Chiralpak AS-H, 5% *i*-PrOH in isohexane, 0.5 mL/min, λ = 210 nm): t_R = 32.4 and 36.3 min (syn), t_R = 41.3 and 44.4 min (anti).

2-(Hydroxy(4-bromophenyl)methyl)cyclohexan-1-one



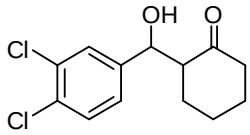
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Colorless solid.[6a,b] HPLC (Daicel Chiralpak AS-H, 10% *i*-PrOH in isohexane, 0.5 mL/min, λ = 217 nm): t_R = 23.2 and 26.4 min (syn), t_R = 30.6 and 32.8 min (anti).

2-(Hydroxy(4-methoxyphenyl)methyl)cyclohexan-1-one



Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Colorless oil.[6b] HPLC (Daicel Chiralpak AD-H, 5% *i*-PrOH in isohexane, 0.5 mL/min, λ = 220 nm): t_R = 64.6 and 68.5 min (syn), t_R = 78.8 and 80.9 min (anti).

2-(Hydroxy(3,4-dichlorophenyl)methyl)cyclohexan-1-one



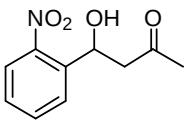
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Colorless solid.[6c] HPLC (Daicel Chiralpak AD-H, 10% *i*-PrOH in isohexane, 0.3 mL/min, λ = 215 nm): t_R = 32.8 and 36.6 min (syn), t_R = 45.1 and 49.0 min (anti).

General procedure for the asymmetric aldol reaction of benzaldehydes with acetone

Benzaldehyde derivative (0.40 mmol) was dissolved in acetone (8.0 mmol), contained in a small vial. Water (0.14 mL) was added, followed by the polymer beads (**16** or **17**, 10 mol%). For noncrystalline benzaldehydes, the vial is charged with polymer beads first, followed by the benzaldehyde derivative and solvents/additives.

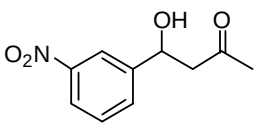
The reaction was mixed gently with a closed capillary tube and then left without stirring for 24 h. The reaction mixture was diluted with EtOAc and transferred to a small folded paper filter. The polymer beads were washed with additional small quantities of EtOAc (20 mL in total for dilution and washing), and the filtrate was evaporated *in vacuo* to yield the crude product. Purification by flash column chromatography on silica gel with EtOAc/hexanes yielded the pure aldol product. The enantiomeric excess was determined by HPLC analysis of the purified product. All the aldol products are well-known compounds with spectroscopic data in accordance with literature.[7]

4-Hydroxy-4-(2-nitrophenyl)butan-2-one



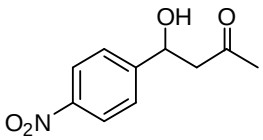
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-30% EtOAc). Light yellow oil.[7a,c,d] HPLC (Daicel Chiralpak AD-H, 3% *i*-PrOH in isohexane, 0.5 mL/min, λ = 254 nm): t_R = 47.4 and 49.8 min.

4-Hydroxy-4-(3-nitrophenyl)butan-2-one



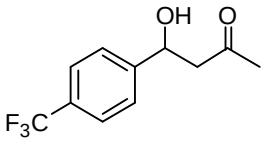
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-30% EtOAc). Colorless oil.[7a,c,e] HPLC (Daicel Chiralpak AS-H, 20% *i*-PrOH in isohexane, 1.0 mL/min, λ = 254 nm): t_R = 12.9 and 16.8 min.

4-Hydroxy-4-(4-nitrophenyl)butan-2-one



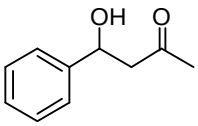
Purified by flash column chromatography on silica gel with EtOAc/hexanes (20% EtOAc). Light yellow solid.[7a,d] HPLC (Daicel Chiralpak AS-H, 20% *i*-PrOH in isohexane, 1.0 mL/min, λ = 254 nm): t_R = 16.2 and 20.4 min.

4-Hydroxy-4-(4-trifluoromethylphenyl)butan-2-one



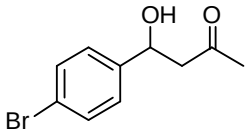
Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-30% EtOAc). Light yellow oil.[7b,d] HPLC (Daicel Chiralpak AS-H, 5% *i*-PrOH in isohexane, 1.0 mL/min, λ = 230 nm): t_R = 14.1 and 17.7 min.

4-Hydroxy-4-phenylbutan-2-one



Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Colorless oil.[7b] HPLC (Daicel Chiralpak AS-H, 5% *i*-PrOH in isohexane, 1.0 mL/min, λ = 210 nm): t_R = 20.9 and 23.3 min.

4-Hydroxy-4-(4-bromophenyl)butan-2-one



Purified by flash column chromatography on silica gel with EtOAc/hexanes (0-20% EtOAc). Light yellow oil.[7a,c] HPLC (Daicel Chiralpak AS-H, 15% *i*-PrOH in isohexane, 1.0 mL/min, λ = 230 nm): t_R = 10.4 and 12.2 min.

Recycling experiments on the aldol reaction of acetone and 4-nitrobenzaldehyde

A vial was charged with prolineamide polymer beads (**16**, 10 mol%), 4-nitrobenzaldehyde (4.0 mmol), acetone (80.0 mmol) and water (1.40 mL). The reaction was stirred gently at room temperature for 24 h. The polymer beads were filtered, and the vial and beads were washed with EtOAc (50 mL). The combined organic phase was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (20% EtOAc in hexanes) to give pure aldol product as a yellow solid. Enantiomeric excess was determined by HPLC analysis of the purified product as described above.

The polymer beads were left to dry in the filter paper and reused without further purification. A small correction was undertaken for any mechanical loss of polymer beads.

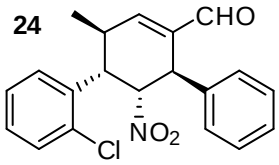
Cycle	Isolated yield	%*ee*
1	76%	84
2	85%	99
3	79%	98
4	82%	91
5[a]	81%	90

[a] Before the fifth cycle, the beads were treated with HCO_2H for 4 h, washed with $NaHCO_3$ (aq) and MeOH and dried at room temperature before use. Although this treatment removed residues, it left the catalyst performance virtually unaffected.

General procedure for asymmetric cascade reaction

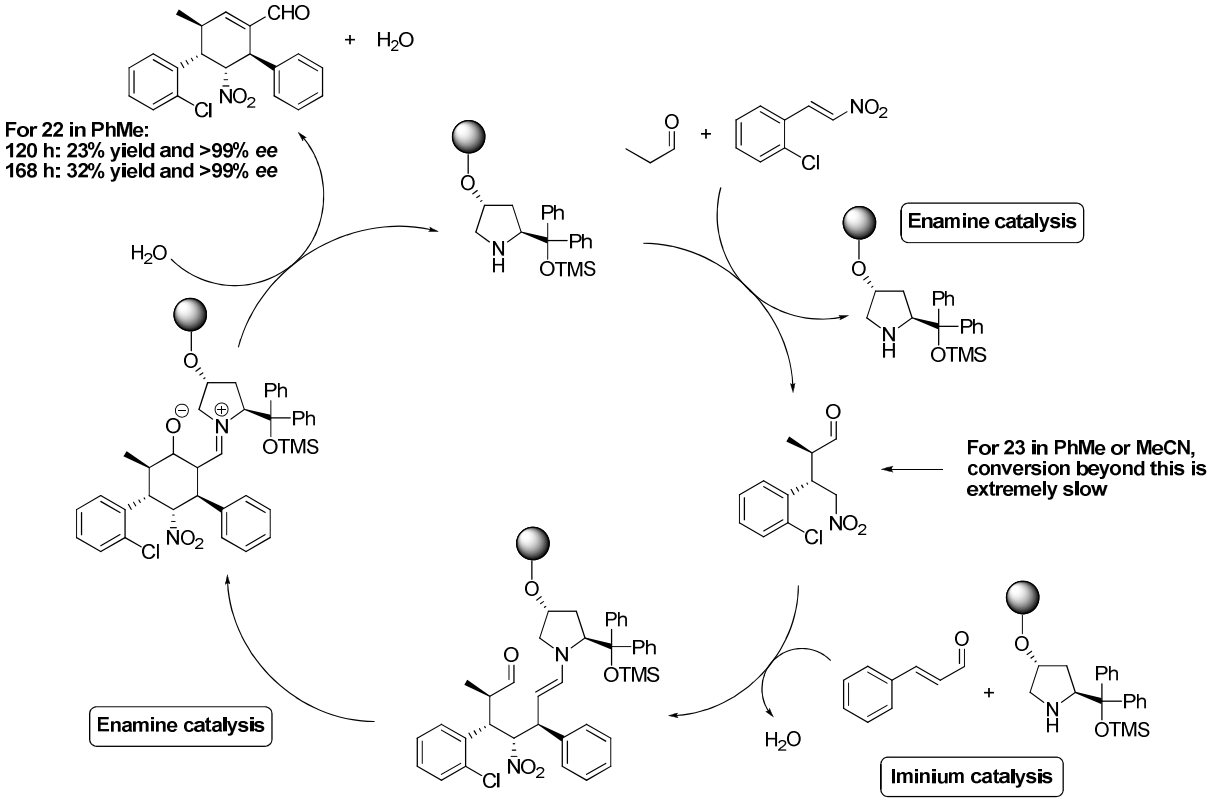
A vial was charged with polymer beads (**22**, 20 mol%) and 2-chloro-β-nitrostyrene (1.00 mmol). Toluene (4.0 mL) was added together with a stirring bar, cinnamaldehyde (1.05 mmol) and propanal (1.20 mmol). The reaction mixture was stirred for approximately 2 hours, in which time the polymer beads had swollen considerably, and further stirring was discontinued. The reaction mixture was then left at room temperature for the indicated time. The reaction mixture was transferred to a filter paper with a small amount of EtOAc. The vial and the polymer beads were washed several times with small amounts of EtOAc (50 mL in all for transfer and washing). The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (0 - 20% EtOAc in hexanes) to give the product as a white solid. Spectroscopic properties in accordance with literature.[8] HPLC (Daicel Chiralpak OD-H, 10% *i*-PrOH in isohexane, 1.0 mL/min, λ = 240 nm): t_R = 12.7 (major) and 19.7 min (minor, only detectable for the racemic sample).

24



For reactions with PEG-support **23**, the procedure is completely analogous except that the toluene was substituted with MeCN (2.0 mL) in one of the experiments.

Using ref. 8, and adopting the specific substrates and catalysts, the following catalytic cycle can be suggested:



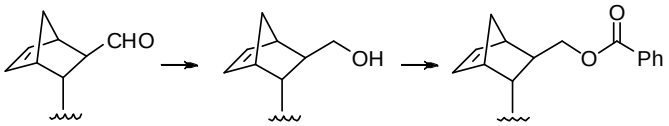
For the corresponding standard monomeric catalyst, (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, the reported yield in the original work of Enders *et. al*. is 51% after 16-24 h reaction time.[8] It seems like only a well-expanded microporous network as that of **22** can accommodate the necessary conditions for the second step and subsequent ring-closure to take place.

Asymmetric Diels-Alder reactions of 4-nitrocinnamaldehyde and cyclopentadiene

A vial was charged with PEG-methacrylic polymer beads (**27**, 15 mol%) and 4-nitrocinnamaldehyde (1.5 mmol). A solvent mixture of MeCN and water (95:5, 1.50 mL) was added, followed shortly by CF_3CO_2H (~0.23 mmol) and freshly cracked cyclopentadiene (4.5 mmol, prepared by cracking dicyclopentadiene in a heating mantle at 190 °C as shown to the right). The mixture was stirred gently at room temperature for 24 h and then diluted with EtOAc and filtered. The polymer beads were washed with EtOAc (totally 25 mL for dilution and washing) in small portions. The organic phase was washed with brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give the crude product as a brown oil. The crude product was purified by loading onto a column of silica gel and eluting with *n*-pentane followed by 40% Et_2O in *n*-pentane.

The *exo*/*endo* relationship was determined by ^{1}H-NMR analysis. The enantiomeric excess was determined by HPLC-analysis after reduction of the product to the corresponding alcohol with $NaBH_4$ and subsequent conversion to the benzoyl ester.[9] A typical procedure is given below for the racemic sample:

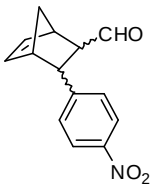
A sample of racemic and purified Diels-Alder adduct (0.1103 g, 0.45 mmol), prepared from 4-nitrocinnamaldehyde, cyclopentadiene and (±)-2,2,3-trimethyl-5-benzyl-4-imidazolidinone hydrochloride **28**, was dissolved in MeOH (2.0 mL) and $NaBH_4$ (0.0213 g, 0.56 mmol) was added. The mixture was stirred at room temperature overnight (15 h) in a vial. Water (10 mL) and conc. HCl (1.0 mL) were added. The mixture was stirred for 5 min, extracted with Et_2O (25 mL), and the organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a near colorless oil. The oil was dissolved in CH_2Cl_2 (7.0 mL) and Et_3N (0.20 mL, 1.43 mmol) and benzoyl chloride (0.10 mL, 0.86 mmol) were added under cooling from an ice/water bath. The mixture was stirred for 4 h, in which time the water bath was allowed to expire, and then diluted with Et_2O (25 mL) and aqueous HCl (0.5 M, 25 mL). The mixture was swirled thoroughly, separated, and the organic phase was washed with aqueous HCl (0.5 M, 25 mL), saturated aqueous $NaHCO_3$ (25 mL) and finally brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a slightly yellow oil of good purity and suited for direct HPLC analysis.



For the experiment conducted on gram-scale with the catalyst in its HCl-form, the procedure is completely analogous except that 4-nitrocinnamaldehyde (7.5 mmol) and cyclopentadiene (22.5 mmol) was used with polymer beads **27** (15 mol%) and MeCN/H_2O (95:5, 7.50 mL) containing one equivalent of HCl (relative to the catalyst). Work-up scaled accordingly (125 mL EtOAc and 100 mL brine).

For recycling experiments, the polymer beads were left to dry in the filter paper and reused without further purification. A small correction was undertaken for any mechanical loss of polymer beads.

***exo*- And *endo*-3-(4-nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde**



Light yellow oil.[10] Enantiomeric excess was determined after conversion to a benzoyl ester as described above.[9] HPLC (Daicel Chiralpak AD-H, 2% *i*-PrOH in isohexane, 1.0 mL/min, 300 nm): t_R = 21.0 (*exo*, major), 22.5 (*endo*, major), 28.7 (*exo*, minor) and 40.4 (*endo*, minor) min.

REFERENCES

1) Kristensen, T. E.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem*. **2009**, 387-395.
2) Kristensen, T. E.; Vestli, K.; Fredriksen, K. A.; Hansen, F. K.; Hansen, T. *Org. Lett*. **2009**, *11*, 2968-2971.
3) a) Dalla Croce, P.; La Rosa, C. *Tetrahedron: Asymm.* **2002**, *13*, 197-201. b) Lowe, G: Vilaivan, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 539-546. c) Baker, G. L.; Fritschel, S. J.; Stille, J. R.; Stille, J. K. *J. Org. Chem.* **1981**, *46*, 2954-2960. d) Peng, J.; Clive, D. L. J. *J. Org. Chem.* **2009**, *74*, 513-519. e) Heindl, C.; Hübner, H.; Gmeiner, P. *Tetrahedron: Asymm.* **2003**, *14*, 3141-3152.
4) Kristensen, T. E.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem*. **2009**, 5185-5191.
5) Kapfhammer, J.; Matthes, A. *Hoppe-Seylers Z. Physiol. Chem*. **1933**, *223*, 43-52.
6) a) Chen, J. –R.; Lu, H. –H.; Li, X. –Y.; Cheng, L.; Wan, J.; Xiao, W. –J. *Org. Lett.* **2005**, *7*, 4543-4545. b) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417-4420. c) Chimni, S. S.; Singh, S.; Mahajan, D. *Tetrahedron: Asymm*. **2008**, *19*, 2276-2284.
7) a) Da, C. –S.; Che, L. –P.; Guo, Q. –P.; Wu, F. –C.; Ma, X.; Jia, Y. –N. *J. Org. Chem.* **2009**, *74*, 2541-2546. b) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411-9416. c) Tong, S. –T.; Harris, P. W. R.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2008**, 164-170. d) Wu, F. –C.; Da, C. –S.; Du, Z. –X.; Guo, Q. –P.; Li, W. –P.; Yi, L.; Jia, Y. –N.; Ma, X. *J. Org. Chem.* **2009**, *74*, 4812-4818. e) Choudary, B. M.; Chakrapani, L.; Ramani, T.; Kumar, K. V.; Kantam, M. L. *Tetrahedron* **2006**, *62*, 9571-9576.
8) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861-863.
9) He, H.; Pei, B. –J.; Chou, H. –H.; Tian, T.; Chan, W. –H.; Lee, A. W. M. *Org. Lett.* **2008**, *10*, 2421-2424.
10) Lemay, M.; Ogilvie, W. W. *Org. Lett*. **2005**, *7*, 4141-4144.