Novel Biodegradable Chitosan-derived Thioureas as Recoverable Supported Organocatalysts. Application to the Stereoselective Aza-Henry Reaction.

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Abstract.

Eight different biodegradable, grafted chitosan with bifunctional chiral thioureas have been prepared as a greener and more sustainable alternative to those supported on petrochemical-derived polymers. These organocatalysts are able to promote the enantioselective aza-Henry reaction with good yields and enantioselection. The activity and stereoselectivity of those materials are dependent on the accessibility of the reactants to the active site, and they increase with the length of the tether connecting the thiourea and the biopolymer. The best catalyst can be recovered and recycled for five times without loss of activity.

Key words: Aza-Henry reaction; Asymmetric catalysis; Catalyst recycling; Chitosan; Supported thioureas.

Introduction

The recovering and reusing of the catalysts constitute one of the main problems in organocatalyzed reactions. A valuable solution consists on the use of the active molecule supported on different solid materials, which allows for the easily recycling of the catalysts.[1] Inorganic compounds,[2] and different commercially available polystyrene resins[3] have been used as supports. In a different approach, some of these catalysts have been bottom-up synthesized by co-polymerization of the functionalized monomers.[4]

Recently, and related with the increasing concern about environment impact, efforts are being driven to the substitution of petrochemical-derived materials to natural polymers, increasing the greenness of the chemical processes.[5] In that way, chitosan which is a natural polysaccharide obtained by partial deacetylation of Chitin,[6] has attracted particular attention. Chitosan is a co-polymer constituted by β-2-amino-2-deoxy-D-glucopyranose and 2-acetamido-2-deoxy-D-glucopiranose units, and consequently, it is insoluble in organic solvents and has a lot of easily functionalizable amino groups, which allow for its chemical modification,[7] including the formation of some thioureas used as a source of chitosan isothiocyanates,[8] or macromolecular fluorophores for different applications.[9]

Chitosan itself has been used as recyclable catalyst for a series of organic transformations, including Knoevenagel, Henry, and aldol reactions,[10] and to enhance copper adsorption.[11] Grafted chitosan with ammonium halides catalyzed the cycloaddition of CO_2 with epoxides leading to cyclic carbonates,[12] whereas pyridine derivatives[13] or chitosan-grafted sulfonic acid[14] promote the synthesis of different heterocycles. Supported metal species on chitosan have also been used as catalysts in different transformations.[15]

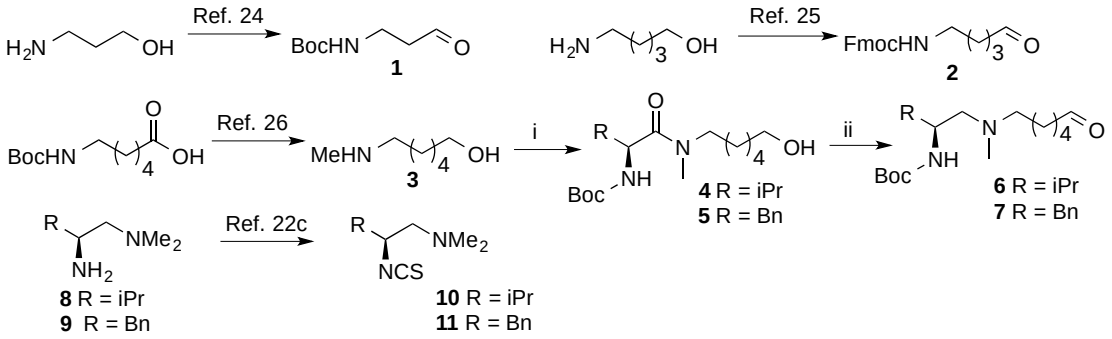
It has recently been demonstrated that aerogel and hydrogel chitosan is able to transfer its inherent chirality in stereoselective aldol reactions,[16] but the support of chiral molecules on chitosan and their study as catalysts in stereoselective transformations have attracted less attention.[17] In that way, anchored chiral dihydronicotinamide derivatives have used in enantioselective reduction of α-keto esters in low enantiomeric excesses.[18] Chitosan grafted with *L*-proline catalyzed enantioselective direct aldol,[19] and Henry[20] reactions, whereas asymmetric Michael additions have been promoted by chitosan decorated with quinine and cinchonine.[21]

The interest of chitosan as a biodegradable natural polymer led us to consider the synthesis of supported chiral bifunctional thioureas on this polysaccharide as a greener alternative to that previously described by us on synthetic resins.[22] Now we report on the synthesis of a series of chiral bifunctional thioureas anchored on chitosan, and their use as catalysts for the stereoselective aza-Henry reaction.[23]

Results and discussion

It is well known that the effectiveness of a supported catalyst is dependent not only on the activity of the catalytic structure but also on the accessibility of the reactants to the active site. For the present study, we have prepared eight supported catalysts (**16**-**23**), which differ in the length of the tether linking the biopolymer and the thiourea, the substituent at the stereogenic carbon of the thioureas unit, and the position of the stereocenter in the chain.

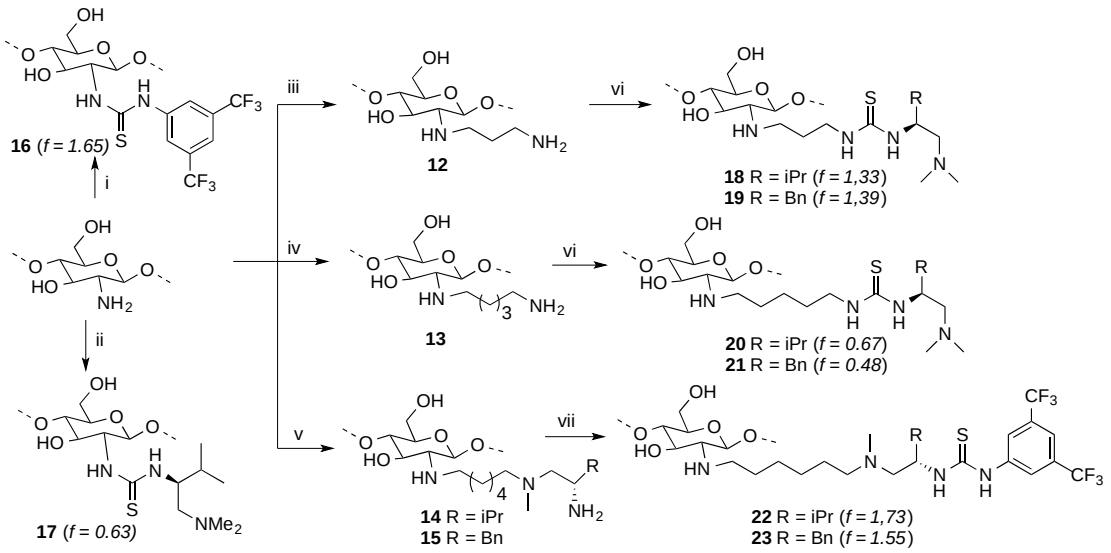
Because the enlargement of the chain was planed by reductive amination, protected amino aldehydes **1**, **2**, **6**, and **7** were prepared from cheap and commercially available amino alcohols as summarized in Scheme 1. N-Boc 3-aminopropanal[24] (**1**), and Fmoc 5-aminopentanal[25] (**2**) were obtained, in two steps, from 3-aminopropanol and 5-aminopentanol, respectively. 6-(N-methylamino) hexanol (**3**) was prepared by total LAH reduction[26] of Boc-6-amino hexanoic acid, and reacted with Boc-L-valine or Boc-L-phenylalanine to yield hydroxyamides **4** and **5**, respectively, in excellent yields. Chemoselective reduction of these compounds to the corresponding Boc-diamino alcohols, followed by Swern oxidation yielded chiral protected amino aldehydes **6** and **7**, maintaining the stereochemical integrity.[27]



Scheme 1. Synthesis of starting aminoaldehydes and isothiocyanates. *Reagents and conditions*: (i) Boc-L-Val or Boc-L-Phe, DCC, CH_2Cl_2, 0 ºC to rt. (ii) 1. $LiAlH_4$ (3 equiv), THF, 0 ºC, 3h. 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C.

Chiral isothiocyanates **10** and **11**[22c] were used to obtain thioureas (**18**-**21**), which differ in the position of the stereogenic center in the chain with respect to **22** and **23**. These isothiocyanates were obtained by reaction of diamines **8** and **9**[28] with carbon disulfide in triethylamine, followed by treatment with ditertbutyl dicarbonate, and catalytic DMAP in ethanol.[29]

The anchorage of thioureas on the biopolymer was done taking into account the reactivity of the amino group in the pyranose unit in a raw commercially available chitosan,[30] with a deacetylation degree of 94.5%.[31] The simplest supported thiourea **16** was directly prepared by reacting excess of 3,5-bis(trifluoromethyl) phenyl isothiocyanate with a solution of chitosan in a mixture (1/4, v/v) of 5 % aqueous AcOH and methanol at 36 °C for 24 h, and thiourea **17**, with an additional stereocenter, was obtained by treatment for 73 h of chitosan with isothiocyanate **10**, derived from L-valine, in the same reaction conditions (Scheme 2).



Scheme 2. *Reagents and conditions*: (i) 3,5-$(CF_3)_2C_6H_3NCS$ (3 equiv), 5% AcOH/MeOH (1/4, v/v). (ii) **10** (3 equiv), 5 % AcOH/MeOH (1/4, v/v). (iii) 1. **1** (1.5 equiv), 0.33% HOAc-MeOH, 1h; then $NaCNBH_3$ (5 equiv), 24h. 2. TFA, CH_2Cl_2, rt, 24h. (iv) 1. **2** (1.5 equiv), 0.33% AcOH-MeOH, 1h; then $NaCNBH_3$ (5 equiv), 24h. 2. 20% NH_3, rt, 24h. (v) 1. **6** or **7**, AcOH-MeOH, 1h, then $NaCNBH_3$, 24h. 2. TFA, CH_2Cl_2, rt, 24h. (vi) Isothiocyanate **10** or **11** (2 equiv), MeCN, MW (65 ºC, 6 x 3 min, 150W). (vii) 3,5-$(CF_3)_2C_6H_3NCS$, MeCN, MW (65 ºC, 4 x 3min, 150W).

Thioureas **18**-**23** were prepared from chitosan as summarized in Scheme 2. First, the installation of the chain into the chitosan structure was carried out by reaction of amino aldehydes **1**, **2**, **6**, and **7** (1.5 equivalents) with a solution of chitosan in

AcOH/MeOH for 1 h at rt, followed by addition of $NaCNBH_3$ and stirring for 24 h. The intermediates were isolated from the reaction mixture by precipitation with EtOH, and thoroughly washed with DCM. The hydrolysis of the Boc derivatives with TFA in DCM lead to supported amines **12**, **14**, and **15**, whereas **13** was obtained after deprotection of the Fmoc intermediate with an aqueous solution of NH_3. Thioureas **18** and **19**, were obtained from **12** by heating under MW irradiation with excess of chiral isothiocyanates **10** and **11**, respectively, whereas **20** and **21** were prepared in the same way starting from amine **13**. Thioureas **22** and **23** were synthesized by reaction of amines **14** and **15** with bis-3,5-(trifluromethyl) phenyl isothiocyanate.

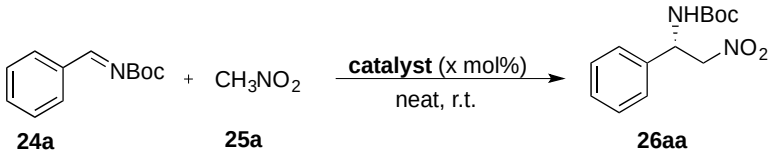
The characterization of the final thioureas was established on the basis of their IR absorption bands, and the effective functionalization (*f*) was calculated from the analytical data of the sulfur atom in the final products.

The activity of all the catalysts was tested taking as a model the aza-Henry reaction of N-Boc benzaldimine (**24a**) with nitromethane (**25a**). The reactions were run in heterogeneous conditions (without solvent), in 6 fold excess of nitromethane at room temperature, with 10 mol% of catalyst. In the described experimental conditions, the reactants were recovered unchanged after stirring for 40 h. in the presence of chitosan, indicating that the biopolymer is inactive as catalyst in that transformation.

Interestingly, thioureas **16** and **17** were also unable to promote the aza-Henry reaction in the same reaction conditions, probably because the difficulties of the reactants to approach the encumbered backbone of the grafted catalysts. In both cases, only benzaldehyde, resulting from the hydrolysis of the imine, was isolated from the reaction mixture in 60-80% after 20 h. of reaction. Fortunately, the distance of the thiourea to the backbone of the biopolymer facilitates the accessibility of the reagents to the active site increasing the activity of the catalyst.

Catalysts **18**-**21** worked well in the addition of **25a** to **24a**, leading to **26aa** in good yields although moderate enantioselectivities (entries 1-4 in Table 1), but the best results were obtained with catalysts **22** and **23**. These catalysts with the longer spacer and the higher activation, provided by the 3,5-bis(trifluoromethyl) phenyl substituent at the thiourea, yielded the addition product in higher yields and much better enantioselection (entries 5, 6). Additionally, catalyst loading of **23** can be reduced to 5 mol% maintaining the yield and enantioselection without decreasing the reaction rate significantly (entry 7 in Table 1). These results are very similar to those previously obtained for the reaction catalyzed by polystyrene-supported thioureas. [4o, 22a]

Table 1. Screening of different catalysts for the aza-Henry reaction of **24a** and **25a**.



24a **25a** **26aa**

Entry[a]	Catalyst	mol%	Time (h)	Yield (%)[b]	Er[c]
1	**18**	10	22	65	86:14
2	**19**	10	20	62	88:12
3	**20**	10	22	72	82:18
4	**21**	10	30	65	82:18
5	**22**	10	30	70	92:8
6	**23**	10	10	72	93:7
7	**23**	5	14	70	93:7

[a] Reactions were conducted at 0.3 mmol scale in 0.1 mL of nitromethane (6 equiv). [b] Isolated yield. [c] Enantiomeric ratio determined by HPLC analysis using a chiral column, and absolute configuration was determined by comparison of the HPLC retention time with that of literature data.

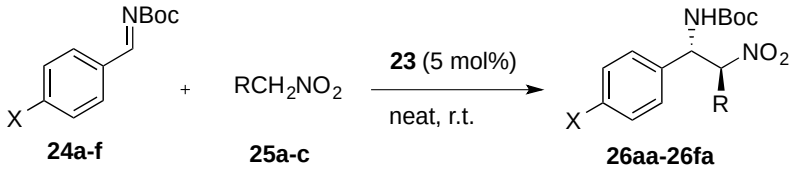
Catalyst **23** (5 mol%) was selected to test the stereoselection in the reaction of different substituted aryl aldimines **24b-f** with nitroalkanes **25a-c** in the described reaction conditions (Table 2). All reactions occurred easily, leading to the addition products in good yields. Substrates with electron-withdrawing groups reacted faster than those bearing electron-donor substituents (compare entries 2-4 *versus* 5, 6 in Table 2), maintaining good level of enantioselection except for p-nitro and p-methoxy-substituted aldimines, which lead to **26da** and **26fa** in only moderate enantioselectivity.

The level of stereoselection was only moderate for the reaction of the parent benzaldimine (**24a**) with nitroethane (**25b**), leading to **26ab** in 89:11 er and 78:22 dr. Much better results were obtained when nitropropane (**25c**) was used as nucleophile, yielding **26ac** in very good enantioselectivity and good diastereoselectivity (entry 8 in Table 2). That fact has been previously observed for aza-Henry reactions promoted by supported thioureas.[22a]

The recovery and recyclability of the catalyst were studied for **23** in the model addition of nitromethane (**25a**) to N-Boc benzaldimine (**24a**). The reaction was carried out without solvent, at room temperature, 5 mol% of catalyst, and a fixed time of reaction of 14 h. After each cycle, the catalyst was recovered by filtration, washed with DCM, dried under vacuum, and reused in the next cycle. The results collected in Table 3 shown that the enantioselection was maintained, and the yield decreased only

slightly along five cycles, demonstrating that the catalyst is very stable, and it does not suffer significant deterioration during the set of cycles studied.

Table 2. Aza-Henry reaction of different aldimines and nitroalkanes catalyzed by **23**.



Entry[a]	X/R	Time (h)	Product (Yield)[b]	Er[c]	Dr[c]
1	H/H	14	**26aa** (70)	93:7	-
2	CF_3/H	6	**26ba** (72)	94:6	-
3	Cl/H	9	**26ca** (74)	92:8	-
4	NO_2/H	7	**26da** (68)	87:13	-
5	CH_3/H	20	**26ea** (66)	92:8	-
6	MeO/H	36	**26fa** (76)	81:19	-
7	H/Me	14	**26ab** (71)	89:11[d]	78:22
8	H/Et	18	**26ac** (82)	95:5[d]	84:16

[a] The reactions were carried out with imines **24a-f** (0.3 mmol) and nitroalkane **25a-c** (6 equiv) at room temperature in the presence of the catalyst (0.05 equiv). [b] Isolated yield after chromatography. [c] Enantiomeric and diastereomeric ratio determined by HPLC analysis using a chiral column and absolute configuration was determined by comparison of the HPLC retention time with that of literature data. [d] Values refer to the major *anti* diastereoisomers.

Table 3. Recyclability of thiourea **23** in the addition of **25a** to **24a**.

Entry	Catalyst (mol%)	Cycle	t (h)	Yield[a]	Er[b]
1	**23** (5)	1	14	74	92:8
2	**23** (5)	2	14	68	93:7
3	**23** (5)	3	14	70	93:7
4	**23** (5)	4	14	66	92:8
5	**23** (5)	5	14	64	92:8

[a] Isolated yield after column chromatography.[b] Determined by chiral HPLC.

Conclusions

We have demonstrated that biodegradable biopolymer chitosan can be used as a greener alternative to petrochemical-derived polymers for supporting chiral bifunctional thioureas. The activity of the grafted material is dependent on the length of the spacer joining the polymer to the active thiourea. In that way, both chitosan and thioureas directly attached to the polymer are inactive as organocatalysts in

enantioselective aza-Henry reaction, and the activity increases with the length of the tether. The best catalyst (**23**) corresponds to a bis-3,5-(trifluromethyl) phenyl isothiocyanate-derived thiourea with a chain of six carbon atoms connecting the active site with the polymer. That catalyst can be reused for five cycles without apparent loss of activity.

Experimental part

General

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded in $CDCl_3$ as solvent. For protons, chemical shifts are reported in ppm from TMS with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration. Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT–IR spectrometer and are reported in frequency of absorption. Specific rotations were measured on a Perkin–Elmer 341 digital polarimeter using a cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated compounds.

TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F254 indicator, and visualized by either staining with phosphomolybdic acid solution or under UV irradiation. Chiral HPLC analysis was performed on a JASCO HPLC system (JASCO PU-2089 pump and UV-2075 UV/Vis detector), using a Daicel Chiralpak AD-H or Chiralcel OJ analytical columns (250 x 4.6 mm). UV detection was monitored at 210, 220 or 254 nm.

Elemental analysis were carried out at the Elemental Analysis Center of the Complutense University of Madrid, using a Perkin Elmer 2400 CHN. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system.

Commercially available compounds were used without further purification. Solvents were dried and stored over microwave–activated 4 Å molecular sieves. Chitosan (molecular weight: 600,000-800,000) was purchased from ACROS Organics. Protected amino aldehydes **1**[24] and **2**[25], amino alcohol **3**[26], isothiocyanates **10**[22c]

and **11**[22c] and Boc-imines **24a–f** [22a] were prepared according to literature procedures. Racemic reference samples were prepared by using DABCO (5 mol %) following the same procedure as described below.

***tert*-Butyl (S)-(1-((6-Hydroxyhexyl)(methyl)amino)-3-methyl-1-oxobutan-2-yl) carbamate (4).** Boc-*L*-valine (2.69 g, 12.4 mmol, 1.25 equiv) and *N,N'*-dicyclohexylcarbodiimide (DCC) (2.5 g, 12.4 mmol, 1.25 equiv) were dissolved in dichloromethane (30 mL) and cooled down to 0 ºC. After the solution was stirred for 30 min, a solution of 6-(methylamino) hexan-1-ol (**3**) (1.3 g, 9.9 mmol, 1 equiv) in anhydrous DCM (5 mL) was added. After the addition was complete, the mixture was warmed to room temperature and stirred for another 10 h. After filtration and removal of solvent at reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent, hexane/ethyl acetate: 4/1) to yield 4.0 g of amide **4** (9.7 mmol, 98%) as colorless oil. $[\alpha]_D^{20}$ = +15.4 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (d, J = 9.7 Hz, 1H, NH); 4.39 (m, 1H, CHN); 3.57 (m, 2H, CH_2OH); 3.43 (m, 1H, CHHN); 3.22 (m, 1H, CHHN); 3.03 (s, 1.7H, CH_3N); 2.89 (s, 1.3H, CH_3N); 1.90 (m, 1H, $CH(CH_3)_2$); 1.51 (m, 4H, CH_2); 1.38 (s, 9H, $(CH_3)_3C$); 1.44-1.20 (m, 2H, CH_2); 0.93-0.85 (m, 6H,CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1 and 172.0 (CON); 155.9 and 155.7 (CO_2tBu); 79.4 and 79.3 ($C(CH_3)_3$); 62.5 and 62.4 (CH_2OH); 55.0 and 54.8 (CHN); 49.6 and 47.6 (CH_2N); 35.3 (CH_3N); 32.5 (CH_2CH_2OH); 32.0 and 31.3 ($CH(CH_3)_2$); 28.3 ($CH_3)_3C$); 26.8 (CH_2); 26.1 (CH_2); 25.1 (CH_2); 19.6 and 19.5 (CH_3); 17.3 and 17.2 (CH_3). IR (ATR) 3435, 3321, 2967, 2931, 2861, 1703, 1633, 1491, 1369, 1243, 1170, 1084, 1043, 1015, 881, 637 cm^{-1}. HRMS calcd. for $C_{17}H_{34}N_2O_4$ +H: 331.2591; found: 331.2596.

***tert*-Butyl (*S*)-(1-((6-Hydroxyhexyl)(methyl)amino)-1-oxo-3-phenylpropan-2-yl) carbamate (5)**. Obtained by reaction of **3** (1.50 g, 11.5 mmol) with Boc-*L*-phenylalanine (3.80 g, 14.3 mmol) in the presence of DCC by the procedure described for the preparation of **4** and purified by flash column chromatography on silica gel (hexane/EtOAc: 2/1). Yield: 4.1 g (10.9 mmol, 95%). Colorless oil. $[\alpha]_D^{20}$ = +22.9 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.16 (m, 5H, Har); 5.40 (br s, 1H, NH); 4.75 (m, 1H, CHN); 3.59 (t, *J* = 6.4 Hz, 2H, CH_2OH); 3.23 (m, 2H, CH_2Ph); 2.92 (m, 2H, CH_2N); 2.81 (s, 1.2H, CH_3N); 2.60 (s, 1.8H, CH_3N); 2.33 (brs, 1H, OH); 1.50 (m, 2H, CH_2); 1.38 and 1.37 (s, 9H, CH_3); 1.43-1.29 (m, 4H, CH_2); 1.20 (m, 2H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4 (CON); 155.1 and 154.9 (CO_2tBu); 136.4

(Car); 129.4, 128.3, 126.8, 126.8 (CHar); 79.6 and 79.5 ($C(CH_3)_3$); 62.5 and 62.4 (CH_2OH); 51.5 and 51.1 (CHN); 49.2 and 47.8 (CH_2N); 40.6 and 40.1 (CH_2Ph); 34.9 (CH_3N); 32.4 (CH_2); 28.3 (CH_3); 26.7 (CH_2); 26.2 (CH_2); 25.2 (CH_2). IR (ATR) 3429, 3319, 2973, 2932, 2854, 1701, 1632, 1493, 1452, 1363, 1249, 1163, 1053, 1020, 731, 698 cm^{-1}. HRMS calcd. for $C_{21}H_{34}N_2O_4$ +H: 379.2592; found: 379.2591.

***tert*-Butyl (*S*)-(3-Methyl-1-(methyl(6-oxohexyl)amino)butan-2-yl) carbamate (6).** A solution of amide **4** (2.3 g, 6.96 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.79 g, 20.9 mmol, 3 equiv) in anhydrous THF (30 mL) at 0 ºC and the mixture was stirred under nitrogen atmosphere for 1 h. Then, the suspension was sequentially treated at 0 °C with water (0.8 mL), *aq*. 15% NaOH solution (0.8 mL) and water (3 x 0.8 mL) and stirred for 2h. The white solids were removed by filtration and washed with Et_2O. The filtrate was evaporated on the rotavapor and the residue was purified by flash column chromatography on silica gel (EtOAc/MeOH: 5/1) to yield the corresponding Boc-diamino alcohol as colorless oil (1.45 g, 4.6 mmol, 66%). $[\alpha]_D^{20}$ = +4.4 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (br s, 1H); 3.60 (m, 2H, CH_2OH); 3.55 (m, 1H, CHN); 2.35 (m, CHHN); 2.27 (m, 3H, CHHN and CH_2N); 2.18 (s, 3H, CH_3N); 1.89 (m, 1H, $CH(CH_3)_2$); 1.54 (m, 2H, CH_2); 1.42 (s, 9H, $(CH_3)_3C$); 1.39-1.20 (m, 6H, CH_2); 0.88 (d, *J* = 6.8 Hz, 3H, CH_3); 0.83 (d, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.2 (CO_2tBu); 78.9 ($C(CH_3)_3$); 62.7 (CH_2OH); 58.7 (CHN); 57.5 (CH_2N); 52.9 (CH_2N); 42.4 (CH_3N); 32.6 (CH_2); 29.9 ($CH(CH_3)_2$; 28.4 $(CH_3)_3C$); 26.9 (2 CH_2); 25.6 (CH_2); 18.9 (CH_3); 17.1 (CH_3). IR (ATR) 3325, 2930, 2857, 2800, 1690, 1527, 1503, 1463, 1389, 1365, 1247, 1170, 1052, 865, 735 cm^{-1}. HRMS calcd. for $C_{17}H_{36}N_2O_3$ +H: 317.2799; found: 317.2804.

To a stirred solution of oxalyl chloride (0.25 mL, 3.0 mmol, 1.35 equiv) in anhydrous CH_2Cl_2 (6 mL) cooled to -78 ºC under nitrogen atmosphere was added DMSO (0.44 mL, 6.2 mmol, 2.8 equiv). After stirring the mixture for 15 min, a solution of the above Boc-protected derivative (0.71 g, 2.2 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (6 mL) was added portion wise, and the mixture was stirred for 1 h at -78 ºC before addition of triethylamine (0.9 mL, 6.3 mmol, 3.0 equiv). Then the reaction was allowed to warm to rt under stirring for 1 h and the mixture was quenched with water (6 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine. The

organic phase was dried ($MgSO_4$) and concentrated to give compound **6** as colorless oil (0.68 g, 2.16 mmol, 98%). $[\alpha]_D^{20}$ = +4.2 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (t, J = 1.9 Hz, 1H, C<u>H</u>O); 4.55 (br s, 1H, NH); 3.56 (m, 1H, C<u>H</u>N); 2.41 (m, 2H, C<u>H</u>$_2$CHO); 2.35 (m, 1H, C<u>H</u>HN); 2.29 (m, 3H, CH<u>H</u>N and C<u>H</u>$_2$); 2.19 (s, 3H, C<u>H</u>$_3$N); 1.90 (m, 1H, C<u>H</u>(CH$_3$)$_2$); 1.62 (quintuplet, J = 7.5 Hz, 2H, C<u>H</u>$_2$); 1.44 (m, 2H, C<u>H</u>$_2$); 1.42 (s, 9H, (C<u>H</u>$_3$)$_3$C); 1.31 (m, 2H, C<u>H</u>$_2$); 0.89 (d, J = 6.9 Hz, 3H, C<u>H</u>$_3$); 0.83 (d, J = 6.9 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (<u>C</u>HO); 156.1 (<u>C</u>O$_2$tBu); 78.9 (<u>C</u>(CH$_3$)$_3$); 58.8 (<u>C</u>HN); 57.5 (<u>C</u>H$_2$N); 52.9 (<u>C</u>H$_2$N); 43.8 (<u>C</u>H$_2$CO); 42.4 (<u>C</u>H$_3$N); 29.9 (CH(CH$_3$)$_2$); 28.4 (<u>C</u>H$_3$)$_3$C); 26.9 (<u>C</u>H$_2$); 26.8 (<u>C</u>H$_2$); 21.9 (<u>C</u>H$_2$); 18.9 (CH$_3$); 17.1 (CH$_3$). IR (ATR) 3325, 2930, 2849, 2796, 1698, 1519, 1459, 1389, 1365, 1243, 1170, 1088, 1043, 865, 779, 735, 641 cm^{-1}. HRMS calcd. for $C_{17}H_{34}N_2O_3$ +H: 315.2645; found: 315.2642.

***tert*-Butyl (*S*)-(1-(Methyl(6-oxohexyl)amino)-3-phenylpropan-2-yl) carbamate (7).** Boc–amide **5** (1.94 g, 5.15 mmol) was reacted with LAH (0.59 g, 15.45 mmol) in THF at 0 ºC for 1h as described for **4** and the residue was purified by flash chromatography (EtOAc/MeOH: 7/1) to afford Boc-protected diamino alcohol (1.2 g, 3.3 mmol, 64%) as a colorless oil. $[\alpha]_D^{20}$ = +8.7 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H, <u>H</u>ar); 4.73 (br s, 1H, N<u>H</u>); 3.85 (m, 1H, C<u>H</u>N); 3.62 (t, J = 6.5 Hz, 2H, C<u>H</u>$_2$OH); 2.89 (m, 1H, C<u>H</u>HPh); 2.83 (m, 1H, CH<u>H</u>Ph); 2.40-2.22 (m, 4H, C<u>H</u>$_2$N); 2.19 (s, 3H, C<u>H</u>$_3$N); 1.55 (m, 2H, C<u>H</u>$_2$); 1.41 (s, 9H, (<u>C</u>H$_3$)$_3$C); 1.34 (m, 4H, C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.8 (<u>C</u>O$_2$tBu); 138.1 (<u>C</u>ar); 129.6, 128.2, 126.2 (CHar); 79.2 (<u>C</u>(CH$_3$)$_3$); 62.7 (<u>C</u>H$_2$OH); 60.2 (<u>C</u>HN); 57.5 (2 <u>C</u>H$_2$N); 42.2 (<u>C</u>H$_3$N); 39.2 (<u>C</u>H$_2$Ph); 32.6 (<u>C</u>H$_2$); 28.4 (<u>C</u>H$_3$)$_3$C); 27.0 (<u>C</u>H$_2$); 26.9 (<u>C</u>H$_2$); 25.5 (<u>C</u>H$_2$). IR (ATR) 3356, 2973, 2932, 2855, 2798, 1689, 1498, 1453, 1363, 1249, 1167, 1049, 743, 699 cm^{-1}. HRMS calcd. for $C_{21}H_{36}N_2O_3$ +H: 365.2799; found: 365.2795.

The Boc-protected diamino alcohol (0.5 g, 1.37 mmol) was submitted to Swern oxidation as described for **6** to yield **7** (0.47 g, 1.3 mmol, 95%). Colorless oil. $[\alpha]_D^{20}$ = +4.3 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, J = 1.8 Hz, 1H, C<u>H</u>O); 7.31-7.25 (m, 2H, <u>H</u>ar); 7.22-7.15 (m, 3H, <u>H</u>ar); 4.66 (br s, 1H, N<u>H</u>); 3.84 (m, 1H, C<u>H</u>N)); 2.90 (m, 1H, C<u>H</u>HPh); 2.82 (dd, *J* = 13.5, 6.4 Hz, 1H, CHHPh); 2.42 (td, J = 7.5, 2.0 Hz, 2H, C<u>H</u>$_2$CHO); 2.36-2.21 (m, 4H, C<u>H</u>$_2$N); 2.18 (s, 3H, C<u>H</u>$_3$N); 1.63 (quintuplet, *J* = 7.5 Hz, 2H, C<u>H</u>$_2$); 1.48-1.38 (m, 2H, C<u>H</u>$_2$); 1.42 (s, 9H, (C<u>H</u>$_3$)$_3$C); 1.33 (m, 2H, C<u>H</u>$_2$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.6 (<u>C</u>HO); 155.7 (<u>C</u>O$_2$tBu);

138.1 (Car); 129.6, 128.2, 126.2 (CHar); 79.0 ($C(CH_3)_3$); 60.3 (CHN); 57.4 (CH_2N); 53.4 (CH_2N); 43.8 (CH_2); 42.2 (CH_3N); 28.4 ($(CH_3)_3C$); 26.9 (CH_2); 26.8 (CH_2); 22.0 (CH_2). IR (ATR) 2977, 2932, 2854, 2801, 1705, 1498, 1452, 1363, 1249, 1167, 1049, 1024, 735, 702 cm^{-1}. HRMS calcd. for $C_{21}H_{34}N_2O_3$ +H: 363.2642; found: 363.2643.

Compound Boc-12. A solution of chitosan (209 mg, 1.30 mmol) in aqueous AcOH (0.33% v/v, 24 mL), was diluted with MeOH (24 mL) and Boc-amino aldehyde **1** (366 mg, 1.82 mmol, 1.4 equiv) in MeOH (4 mL) was added. After stirring at room temperature for 1h, $NaCNBH_3$ (408 mg, 6.5 mmol, 5 equiv) was added and the mixture stirred for 24 h. The reaction was stopped by precipitation with EtOH and stirred for another hour. Then the product was isolated by filtration, thoroughly washed with ethanol and DCM and dried under vacuum to give Boc-**12** (393 mg, 95%). Yellow solid. IR (ATR) 3344, 2973, 2932, 2875, 2321, 1685, 1518, 1453, 1391, 1363, 1253, 1277, 1163, 1061, 1025, 862, 780, 564 cm^{-1}.

Compound 12. Boc-**12** (120 mg, 0.38 mmol) was suspended in a 4:1 mixture of DCM/TFA (2.0 mL) and stirred at rt for 24 h. After this period, the solid was filtered and washed with EtOH/Et_3N 80:20 (10 mL) and DCM (10 mL). Then, the solid was dried under vacuum to give **12** (58 mg, 70%). Yellow solid. IR (ATR) 3270, 2924, 2863, 1673, 1469, 1432, 1375, 1184, 1127, 1061, 1029, 837, 796, 719 cm^{-1}.

Compound Fmoc-**13.** Chitosan (107 mg, 0.66 mmol) was dissolved in aq. 0.33% (v/v) HOAc solution (13 mL), the resulting solution was diluted with MeOH (13 mL) and Fmoc-protected amino aldehyde **2** (320 mg, 1.0 mmol, 1.5 equiv) in MeOH (4 mL) was added. After stirring at room temperature for 1h, $NaCNBH_3$ (210 mg, 3.3 mmol, 5 equiv) was added to the mixture and stirred for 24 h. The reaction was stopped by precipitation with EtOH and stirred for another hour. Then the product was isolated by filtration, thoroughly washed with water, and methanol, and dried under vacuum to give Fmoc-**13** (272 mg, 88%). Colorless solid. IR (ATR) 3414, 3333, 2935, 2866, 1698, 1524, 1450, 1247, 1137, 1101, 1068, 1032, 759, 739, 666, 621 cm^{-1}.

Compound 13. Fmoc-**13** (0.270 g, 0.58 mmol) was stirred in aq. 35% NH_3 solution (4 mL) for 24h. Then, EtOH (3 mL) was added and the precipitate was filtered and washed repeatedly with water and acetone. The orange solid was dried under vacuum

until constant weight (113 mg, 79%). IR (ATR) 3362, 2927, 2861, 1658, 1572, 1467, 1369, 1316, 1145, 1060, 1027, 901, 666 cm^{-1}.

Compound Boc-14. This compound was prepared as described for **Boc-12** but starting from chitosan (183 mg, 1.14 mmol) and aldehyde **6** (500 mg, 1.59 mmol, 1.4 equiv) to give **Boc-14** (471 mg, 90%) as a light yellow solid. IR (ATR): 3337, 2972, 2936, 2866, 2324, 1698, 1581, 1518, 1459, 1367, 1102, 862, 774, 733, 637, 612 cm^{-1}.

Compound 14. This compound was prepared as described for **12**, but starting from Boc-**14** (700 mg, 1.52 mmol) to give **14** (520 mg, 95% yield). Yellow solid. IR (ATR): 3392, 2936, 2866, 1673, 1559, 1470, 1422, 1393, 1198, 1105, 829, 799, 719, 638, 612 cm^{-1}.

Compound Boc-15. This compound was obtained from chitosan (100 mg, 0.62 mmol) by reaction with aldehyde **7** (315 mg, 0.87 mmol, 1.4 equiv) as described for Boc-**14** to give Boc-**15** (220 mg, 70%). Yellow solid. IR (ATR): 3336, 2936, 2863, 2325, 2166, 1693, 1452, 1367, 1249, 1159, 1118, 1049, 1025, 752, 699 cm^{-1}.

Compound 15. Boc-**15** (160 mg, 0.32 mmol) was treated with a 4:1 mixture of CH_2Cl_2/TFA (3 mL) as described for Boc-**14** to give **15** (110 mg, 84% yield). Yellow solid. IR (ATR): 3299, 2932, 2855, 1677, 1563, 1453, 1375, 1318, 1200, 1131, 1098, 1065, 1028, 902, 833, 800, 748, 699 cm^{-1}.

Thiourea 16. Chitosan (100 mg, 0.62 mmol) was dissolved in aq. 5% (v/v) HOAc solution (2.5 mL), the resulting solution was diluted with MeOH (10 mL) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.34 mL, 1.86 mmol, 3 equiv) was added. After stirring at 36 ºC for 24h, the product was isolated by filtration, thoroughly washed methanol and dried under vacuum to give thiourea **16** (147 mg, 75%). IR (ATR): 3302, 2941, 2876, 1541, 1468, 1379, 1278, 1123, 1062, 1026, 953, 888, 681 cm^{-1}. The effective functionalization, f = 1.65 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 38.70, H: 3.98, N: 6.30, S: 5.28).

Thiourea 17. Chitosan (50 mg, 0.31 mmol) was dissolved in aq. 5% (v/v) HOAc solution (1.25 mL), the resulting solution was diluted with MeOH (5 mL) and isothiocyanate **10** (0.16 mL, 0.93 mmol, 3 equiv) was added. After stirring at 36 ºC for 72h, the product was isolated by filtration, thoroughly washed methanol, and dried under vacuum to give thiourea **17** (73 mg, 71%). IR (ATR): 3361, 3286, 2872, 2324, 1657, 1554, 1377, 1061, 1029, 734, 667 cm^{-1}. The effective functionalization, f = 0.63

mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 36.39, H: 6.19, N: 7.35, S: 2.00).

Thiourea 18. To a suspension of **12** (120 mg, 0.55 mmol) in MeCN (2 mL) was added isothiocyanate **10** (197 mg, 1.1 mmol, 2 equiv) and the mixture was heated in MW (65 ºC, 8 x 3 min, 150W). Then the solid was collected by filtration, washed, and dried under vacuum to give **18** as a pale orange solid (142 mg, 66%). IR (ATR) 3280, 3081, 2930, 2874, 1710, 1674, 1548, 1467, 1373, 1304, 1182, 1149, 1064, 1023, 893, 799, 722 cm^{-1}. The effective functionalization, f = 1.33 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 41.35, H: 6.49, N: 9.06, S: 4.24).

Thiourea 19. The same procedure for thiourea **18** was followed, starting from **12** (72 mg, 0.33 mmol) and isothiocyanate **11** (145 mg, 0.66 mmol, 2 equiv) as reactants. Yield: 82 mg (57%). Yellow solid. IR (ATR) 3287, 3067, 3026, 2928, 2863, 1673, 1542, 1497, 1457, 1355, 1200, 1175, 1127, 1029, 833, 800, 719, 699 cm^{-1}. The effective functionalization, f = 1.39 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 42.43, H: 5.70, N: 8.58, S: 4.44).

Thiourea 20. To a suspension of **13** (50 mg, 0.2 mmol) in MeCN (2 mL) was added isothiocyanate **10** (71 mg, 0.4 mmol, 2 equiv) and the mixture was heated in MW (65 ºC, 8 x 3 min, 150W). Then the solid was collected by filtration, washed, and dried under vacuum to give **20** as an orange solid (43 mg, 51%). IR (ATR) 3280, 2927, 2853, 1544, 1463, 1369, 1145, 1060, 1027, 901, 816, 792, 674 cm^{-1}. The effective functionalization, f = 0.67 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 40.47, H: 6.72, N: 8.53, S: 2.14).

Thiourea-21. The same procedure for thiourea **20** was followed, using **13** (200 mg, 0.81 mmol) and isothiocyanate **11** (357 mg, 1.6 mmol, 2 equiv) as reactants. Yield: 250 mg (74%). Orange solid. IR (ATR) 3311, 2925, 2862, 1540, 1452, 1371, 1304, 1150, 1061, 1025, 748, 726, 700, 564 cm^{-1}. The effective functionalization, f = 0.48 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 55.98, H: 6.96, N: 6.66, S: 1.55).

Thiourea 22. To a suspension of **14** (359 mg, 1.0 mmol) in MeCN (2 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.55 mL, 3.0 mmol, 3 equiv) and the mixture was heated in a MW (65 ºC, 4 x 3min, 150W). Then the solid was collected by filtration, washed, and dried under vacuum to give **22** as a yellow solid (385 mg,

61%). IR (ATR): 3297, 2939, 2877, 1713, 1676, 1544, 1474, 1378, 1278, 1105, 885, 848, 799, 723, 700, 682, 634, 616 cm^{-1}. The effective functionalization, f = 1.73 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 40.31, H: 4.13, N: 3.14, S: 5.55).

Thiourea 23. The same procedure for thiourea **22** was followed, starting from **15** (116 mg, 0.28 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.16 mL, 0.85 mmol, 3 equiv) as reactants. Yield: 176 mg (91%). Yellow solid. IR (ATR) 3287, 2940, 2867, 1714, 1530, 1473, 1375, 1273, 1167, 1123, 1065, 1029, 882, 845, 735, 699, 678 cm^{-1}. The effective functionalization, f = 1.55 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis (C: 41.29, H: 3.90, N: 6.06, S: 4.95).

General procedure to enantioselective Aza-Henry reaction using chitosan supported thioureas as catalysts. To a mixture of Boc-imine **24a-f** (0.3 mmol) and catalyst (0.015-0.03 mmol, 0.05-0.1 equiv), nitroalkane (1.8 mmol, 6 equiv) was added and the reaction mixture was stirred at rt in a wheaton vial until consumption of the starting material (TLC). The catalyst was filtered off and washed. After removal of the solvent under reduced pressure, the crude mixture was purified by flash column chromatography to afford the corresponding product. The enantiomeric ratio was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

Recyclability of the supported thiourea catalysts in aza-Henry reaction.

At the end of the aza-Henry reaction between Boc-imine and nitromethane, the catalysts were filtered and washed. After being dried under vacuum, the supported catalysts could be reused directly without further purification.

***tert*-Butyl (*S*)-(1-Phenyl) 2-nitroethyl carbamate (26aa).**[32] Obtained according to general procedure, using Boc-imine **24a** (62 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26aa** (56 mg, 0.21 mmol, 70%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, C$\underline{H}_3$), 4.71 (m, 1H, C$\underline{H}$HN), 4.85 (m, 1H, CH$\underline{H}$N), 5.29 (m, 1H, C$\underline{H}$N), 5.35 (br. s, 1H, N$\underline{H}$); 7.31-7.39 (m, 5H, $\underline{H}$ar). HPLC (Chiralpak AD-H, hexano/isopropanol 95:5, 1mL/min, λ= 210 nm) t_R = 27.9 min (mayor, *S*), 29.7 min (minor, *R*). (er 93:7).

***tert*-Butyl (*S*)-1-(4-Trifluoromethylphenyl)-2-nitroethyl carbamate (26ba).**[33] Obtained according to general procedure, using Boc-imine **24b** (82 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26ba** (72 mg, 0.22 mmol, 72%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, C$\underline{H}_3$), 4.74 (d, J= 11.8Hz, 1H, C$\underline{H}$HN), 4.86 (m, 1H, CH$\underline{H}$N), 5.43 (m, 1H, C$\underline{H}$N), 5.43 (br s, 1H, N$\underline{H}$), 7.46 (d, J = 8.0 Hz, 2H, $\underline{H}$ar), 7.66 (d, J = 8.0 Hz, 2H, $\underline{H}$ar). HPLC (Chiralpak AD-H, hexane/*iso*-propanol = 90:10, 210 nm, 1.0 mL/min): t_R =11.2 min (major, *S*), 17.2 min (minor, *R*) (er 94:6).

***tert*-Butyl (*S*)-1-(4-Chlorophenyl)-2-nitroethyl carbamate (26ca).**[32] Obtained according to general procedure, using Boc-imine **24c** (72 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26ca** (67 mg, 0.22 mmol, 74%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, C$\underline{H}_3$), 4.66 (dd, *J* = 5.0Hz, 12.6 Hz, 1H, C$\underline{H}$HN), 4.79 (m, 1H, CH$\underline{H}$N), 5.30 (m, 1H, C$\underline{H}$N), 5.38 (br s, 1H, N$\underline{H}$), 7.25 (d, J= 8.5Hz, 2H, $\underline{H}$ar), 7.36 (d, J= 8.5Hz, 2H, $\underline{H}$ar). HPLC (Chiralpak AD-H column, hexane/*iso*-propanol = 95:5, 220nm, 1.0 mL/min): t_R = 27.2 min (major, *S*), 35.7 min (minor, *R*). (92:8).

***tert*-Butyl (*S*)-1-(4-Nitrophenyl)-2-nitroethyl carbamate (26da).**[32] Obtained according to general procedure, using Boc-imine **24d** (75 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26da** (64 mg, 0.20 mmol, 68%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.43 (s, 9H), 4.79 (m, 1H, C$\underline{H}$HN), 4.89 (m, 1H, CH$\underline{H}$N), 5.50 (m, 1H, C$\underline{H}$N), 5.70 (br. s, 1H, N$\underline{H}$), 7.53 (d, *J* = 8.7 Hz, 2H, $\underline{H}$ar), 8.22 (d, *J* = 8.7 Hz, 2H, $\underline{H}$ar). HPLC (Chiralpak AD-H, hexane/*iso*-propanol = 90:10, 254 nm, 1.0 mL/min): t_R = 26.6 min (major, *S*), 55.4 min (minor, *R*). (er 87:13).

***tert*-Butyl (*S*)-1-(*p*-Tolyl)-2-nitroethyl carbamate (26ea).**[34] Obtained according to the general procedure, using Boc-imine **24e** (62 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26ea** (56 mg, 0.20 mmol, 66%). Colorless solid. 1H-NMR (500 MHz, CDCl3): δ 1.45 (s, 9H, CH3), 2.35 (s, 3H, CH3), 4.70 (m, 1H, CHHN), 4.84 (m, 1H,

CHHN), 5.23 (m, 1H, CHN), 5.34 (br s, 1H, NH), 7.19 (s, 4H, Har). HPLC (Chiralcel OJ, hexane/iso-propanol = 90:10, 220 nm, 1.0 mL/min): t_R = 21.3 min (major, *S*), 23.5 min (minor, *R*). (er 92:8).

***tert*-Butyl (*S*)-1-(4-Methoxyphenyl)-2-nitroethyl carbamate (26fa).**[32] Obtained according to the general procedure, using Boc-imine **24f** (70 mg, 0.3 mmol), nitromethane (0.1 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 8:1) to yield compound **26fa** (68 mg, 0.23 mmol, 76%). Colorless solid. 1H-NMR (500 MHz, CHCl3) δ 1.45 (s, 9H, CH_3), 3.81 (s, 3H, CH3), 4.68 (dd, J = 12.5 Hz, 5.5 Hz, 1H, CHHN), 4.85 (m, 1H, CHHN), 5.19 (m, 1H, CHN), 5.32 (br s, 1H, NH), 6.90 (m, 2H, Har), 7.23 (m, 2H, Har). HPLC (Chiralcel AD-H, hexane/iso-propanol = 90:10, 220 nm, 1 mL/min): t_R = 37.5 min (minor, *R*), 44.5 min (major, *S*). (er 81:19).

***tert*-Butyl [(1*R*, 2*S*)-2-Nitro-1-phenylpropyl] carbamate (26ab).**[34] Obtained according to general procedure, using Boc-imine **24a** (62 mg, 0.3 mmol), nitroethane (0.13 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 15:1) to yield compound **26ab** as a mixture 78:22 of *anti/syn* diastereomers (60 mg, 0.21 mmol, 71%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, C$\underline{H}_3$), 1.54 (d, *J* = 7.0 Hz, 3H, C$\underline{H}_3$), 4.92 (br s, 1H, N$\underline{H}$), 5.11 (m, 0.2H, CH$\underline{H}$N), 5.19 (t, *J* = 7.5 Hz, 0.8H, CH$\underline{H}$N), 5.34 (br s, 0.8H, C$\underline{H}$HN), 5.58 (m, 0.2H, C$\underline{H}$HN), 7.22-7.27 (m, 2H, $\underline{H}$ar), 7.32-7.37 (m, 3H, $\underline{H}$ar). HPLC (Chiralpak AD-H, hexane/*iso*-propanol = 95:5, 220 nm, 0.8 mL/min): *major (anti)*: t_R (major) = 25.3 min, t_R (minor) = 27.5 min, (er 89:11); t_R *minor (syn)*: t_R (major) = 40.1 min, t_r (minor) = 31.3 min. (er 78:22).

***tert*-Butyl [(1*R*, 2*S*)-2-Nitro-1-phenylbutyl] carbamate (26ac).**[34] Obtained according to general procedure, using Boc-imine **24a** (62 mg, 0.3 mmol), 1-nitropropane (0.16 mL, 1.8 mmol) and thiourea **23** (10 mg, 0.015 mmol). The crude reaction mixture was purified by flash column chromatography (hexane/ethyl acetate: 15:1) to yield compound **26ac** as a mixture 84:16 of *anti/syn* diastereomers (72 mg, 0.25 mmol, 82%). Colorless solid. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.0 Hz, 3H, C$\underline{H}_3$), 1.42 (s, 9H, C$\underline{H}_3$), 1.85-1.90 (m, 1H, C$\underline{H}$H), 2.04 (m, 1H, CH$\underline{H}$), 4.73 (br s, 1H, N$\underline{H}$), 5.13 (m, 2H, C$\underline{H}\underline{H}$N), 7.22 (m, 2H, $\underline{H}$Ar), 7.34 (m, 3H, $\underline{H}$Ar). HPLC (Chiralpak AD-H, hexane/iso-propanol = 95:5, 220 nm, 0.5 mL/min): *major (anti*): t_R

(major) = 17.2 min, t_R (minor), 19.0 min. (er 95:5); *minor (syn*): t_R (major) = 14.8 min, t_R (minor) = 21.8 min (er 79:21).

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Electronic Supporting Information available: Copies of ^{1}H-NMR, and ^{13}CNMR spectra for all new compounds, IR traces for novel chitosan supported derivatives, and HPLC chromatograms for the reaction mixtures.

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