Preparation of chitosan-supported urea materials and their application in some organocatalytic procedures

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Abstract

An efficient and mild procedure was developed for the preparation of three chitosan-supported ureas containing electron-withdrawing groups. These catalysts were characterized and employed as organocatalysts in different transformations, including the enantioselective cyanosilylation of α-ketoesters and aldehydes, the asymmetric addition of formaldehyde *tert*-butyl hydrazone to prochiral α-ketoesters and a Friedel-Crafts reaction. Several parameters that can affect the activity and selectivity of the reactions were analysed. The supported catalysts can be reused for more than 10 cycles with only a small loss in their properties. Finally, theoretical DFT calculations were carried out to interpret the results of the catalysed reactions.

Highlights

- Chitosan-based ureas are easily prepared by a mild and efficient procedure

- Chitosan-supported ureas catalyse valuable chemical reactions in a range of yields

- These heterogeneous catalysts are robust and can be employed for several catalytic cycles

Keywords

Chitosan-supported ureas; Organocatalysis; Cyanosilylation; Chiral tertiary alcohols; Heterogeneous catalysis; DFT calculations.

Chemical compounds

Acetophenone (PubChem CID: 7410); Ethyl benzoylformate (PubChem CID: 15349); Ethyl 2-oxo-4-phenybutyrate (PubChem CID: 562087); Benzaldehyde (PubChem CID: 240); 4-Chlorobenzaldehyde (PubChem CID: 7726); Trimethylsilyl cyanide (PubChem CID: 82115); Indole (PubChem CID: 798); *tert*-Butylhydrazine hydrochloride (PubChem CID: 81889); *trans*-β-Nitrostyrene (PubChem CID: 5284459); *p*-Nitrophenol (PubChem CID: 980).

Abbreviations

CS: Chitosan; DFT: Density functional theory; FTBH: Formaldehyde *tert*-butyl hydrazone; HOBt: 1-Hydroxybenzotriazole hydrate; TBME: *tert*-Butyl methyl ether; TMSCN: Trimethylsilyl cyanide.

1. Introduction

In asymmetric synthesis, chiral catalysts usually include small organic molecules and metal complexes. In particular, organocatalysis avoids the use of metal complexes, with chiral organic scaffolds being responsible for asymmetric induction. Since the beginning of the present century, this technique has experienced great development for the preparation of optically active molecules (Berkessel & Groger, 2005; Bertelsen & Jorgensen, 2009; List, 2009; Dalko, 2013; Rossi, Benaglia, Massolo, & Raimondi, 2014).

Catalysis through hydrogen-bond interactions falls within the category of non-covalent organocatalysis. The hydrogen bond represents a well-known interaction of high interest, as it is a strong force with a crucial role for maintaining the structure of a vast number of different molecules (Gilli, & Gilli, 2016; Sweetman et al., 2014). This bond has been employed as an assisting force in catalytic procedures in organic synthesis (Dekamin, Karimi, & Farahmand, 2012; Pihko, 2009). Among the different molecules that can perform hydrogen bond interactions, ureas, thioureas, and more recently squaramides (Alemán, Parra, Jiang, & Jorgensen, 2011), are the most employed, due to their ability to establish a double hydrogen-bond interaction with the substrates. Since the initial studies on ureas and thioureas as organocatalysts, both of them have been widely employed in several catalytic procedures for the preparation of valuable compounds (Kotke, & Schreiner, 2009). Recently, bifunctional hydrogen bond catalysts have been widely investigated to perform asymmetric processes via a dual activation of both the reaction's nucleophile and electrophile components (Sonsona, Marques-López, & Herrera, 2016).

Organocatalysts are, in general, robust, inexpensive, non-toxic and easily available, whereas organocatalyzed processes are conducted under mild reaction conditions and in the absence of metals (Hernández & Juaristi, 2012). The preparation of supported organocatalysts represents a valuable tool in asymmetric catalysis. In addition, supported organocatalysts facilitate product recovery and purification (Gruttaduria, Giacalone, & Noto, 2008; Munirathinam, Huskens, & Verboom, 2015).

Chitosan is a non-toxic, biocompatible, and biodegradable linear polysaccharide of randomly distributed β(1→4) linked D-glucosamine (>60%) and *N*-acetyl-D-glucosamine. It is obtained from the alkaline deacetylation of chitin and has emerged as a valuable polymer with several applications (Ravi Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004), such as solvent sensing (Jatunov et al., 2015), non-lineal optics (Franconetti, Contreras-Bernal, Prado-Gotor, & Cabrera-Escribano, 2015), chiral recognition of enantiomers (Jafari, Tashkhourian, & Absalan, 2018), including carbamates (Bai, et al., 2017) and ureidyl derivatives (Wang, Xi, Chen, Huang, & Bai, 2017), and catalysis (Dekamin, Azimoshan, & Ramezani, 2013; El Kadib, 2015; Mahé, Brière, & Dez, 2015). From a catalytic perspective, chitosan can be used following two strategies, that is, directly as a heterogeneous catalyst or as a platform supporting the corresponding organocatalyst. For the first strategy, native chitosan hydrogels have proved to be an effective catalyst for Knoevenagel reactions (Franconetti, Domínguez-

Rodríguez, Lara-García, Prado-Gotor, & Cabrera-Escribano, 2016), aldol reactions and Henry reactions, among others (Kühbeck, Saidulu, Reddy, & Díaz-Díaz, 2012). Chitosan derivatives have also served as a valuable support for several types of organocatalysts (Chtchigrovsky, et al. 2009). Thus, cycloadditions of carbon dioxide and epoxides to obtain cyclic carbonates (Zhao, et al., 2007), Michael additions for the preparation of different functionalized heterocycles (Khalil, & Al-Matar, 2013), and aldol reactions (Zhang et al., 2009), have been developed by employing different types of organocatalysts supported on chitosans. Very recently, chitosan-supported thioureas have been employed in the aza-Henry reaction between *N*-Boc-protected imines and nitroalkanes (Andrés, González, Maestro, Pedrosa, & Valle, 2017).

Due to the interest of supported organocatalytic systems, we hypothesized that chitosan could be a used as suitable support for hydrogen-boding catalysts in different interesting reactions without loss of its activity. These novel organocatalysts can be considered a greener alternative to that supported on synthetic resins. As chitosan is able to act itself as base catalyst, it should be crucial to demonstrate that these reactions selectively proceed through hydrogen-bonding activation.

In the present work, we report the simple preparation and perfect characterization of a set of chitosan-supported ureas. These materials were effectively employed as robust hydrogen-bonding organocatalysts in three different reactions: the cyanosilylation of α-ketoesters and aldehydes, the addition of formaldehyde *tert*-butyl hydrazone to α-ketoesters and a Friedel-Crafts process. In addition, the catalytic results are supported by DFT calculations, which were performed to explain the role of the substituent on the hydrogen bond donor capability of these catalysts.

2. Materials and Methods

2.1 Materials and methods

Low molecular weight chitosan (**CS 1**) [HPLC/SEC ($g \cdot mol^{-1}$) $M_n = 48675$; $M_w = 87875$] with a DD (Fernández-Megía, Novoa-Carballal, Quiñoá, & Riguera, 2005) of 84% and polydispersity index of 1.81, and *medium molecular weight* chitosan (**CS 2**) were purchased from Sigma-Aldrich. Acetophenone (**1a**), ethyl benzoylformate (**2a**), ethyl 4-cyanobenzoylformate (**3a**), benzaldehyde (**5a**), 4-chlorobenzaldehyde (**6a**), trimethylsilyl cyanide, acetone cyanohydrin, *tert*-butylhydrazine hydrochloride, *trans*-β-nitrostyrene, *p*-nitrophenol, and 1-hydroxybenzotriazole hydrate were also purchased from Sigma-Aldrich. Ethyl 2-oxo-4-phenylbutyrate (**4a**) was obtained from Alfa Aesar. Indole (**8**) was a product from TCI Europe.

Formaldehyde *tert*-butyl hydrazone (FTBH) was prepared according to literature procedure (Lehn, Javed, & Hoffman, 2007). The physical and spectral properties of the synthesized compounds (*R*)-**5**,**6b**, (*R*)-**5**,**6c**, (*R*)-**5**,**6d** (Li, He, Qin, Feng, & Zhang, 2004), (*R*)-**7** (Crespo-Peña et al., 2012) and **9** (Herrera, Sgarzani, Bernardi, & Ricci, 2005) are in accord with those reported. The absolute configurations of chiral compounds (*R*)-**7,** (*R*)-**5d** and (*R*)-**6d** were established by comparing the HPLC chromatograms with the

patterns described in previous experiments for the known configurations (Li et al., 2004; Crespo-Peña et al., 2012). The spectra were recorded in $CDCl_3$ at [^{1}H NMR (300, 400 or 500 MHz); ^{13}C NMR (75, 100 or 125 MHz)] with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C, respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminium backed plates (1.5 × 5.0 cm) precoated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). The compounds were visualized by exposure to UV light or by dipping the plates in solutions of $KMnO_4$ or vanillin stains followed by heating. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. HPLC analyses for the determination of the optical purities were performed on a Waters 2695 Instrument equipped with a Waters 996 Photodiode Array Detector.

*2.2. Synthesis of chitosan-supported ureas **I-III***

To a homogenous solution of chitosan **CS** (100 mg) in an acetic acid aqueous mixture 1:1 MeOH:H_2O (50 mL) at a pH value around 6.0, an excess of the corresponding isocyanate was added. The reaction was allowed to stand at room temperature and its completion was noted by TLC (MeOH as eluent) absorption UV (254 nm) at the origin, corresponding to the polymer that incorporated the aromatic unit. After completion, the resulting heterogeneous mixture was precipitated by adding 4.0 M NaOH until pH 9.0 was reached. The obtained solid was filtered and then exhaustively washed with H_2O, MeOH, CH_2Cl_2 and acetone, affording the corresponding pure chitosan-supported urea.

N-(3-Trifluoromethylphenylcarbamoyl)chitosan **I**: Application of the general procedure to **CS 1** (200 mg) and 3-trifluoromethylphenyl isocyanate (250 µL, 1.8 mmol), after 120 h (pH 6.0), afforded compound **I** (177 mg) as a white solid (Franconetti, et al., 2016). DS: 0.14. IR: 3364, 2920, 1655, 1595, 1558, 1420, 1374, 1335, 1256, 1150, 1059, 1026 and 893 cm^{-1}. ^{1}H NMR (500 MHz, AcOD/D_2O): δ 7.75 (br s, H-2''), 7.57 (br s, H-4'' or H-6''), 7.50 (br s, H-6'' or H-4''), 7.38 (br d, J = 7.3 Hz, H-5''), 5.70 (br s, H-1'), 4.95 (br s, H-1), 4.11-3.53 (br m, H-3, H-4, H-5, H-6 and H-6'), 3.26 (br s, H-2) and 2.09 (br s, NHCOCH_3, overlapped with AcOD).

N-[3,5-Bis(trifluoromethyl)phenylcarbamoyl]chitosan, **II**: Application of the general procedure to **CS 1** (400 mg) and 3,5-bis(trifluoromethyl)phenyl isocyanate (951 µL, 5.5 mmol), after 96 h (pH 6.3), afforded compound **II** (358 mg) as a white solid. DS: 0.06. IR: 3368, 3299, 2871, 1663, 1560, 1417, 1371, 1313, 1246, 1149, 1062, 1026 and 896 cm^{-1}. ^{1}H NMR (500 MHz, AcOD/D_2O): δ 8.23 (br s, H-2'' or H-6''), 8.00 (br s, H-6'' or H-2''), 7.64 (br s, H-4''), 5.69 (br s, H-1'), 4.95 (br s, H-1), 4.18-3.53 (br m, H-3, H-4, H-5, H-6 and H-6'), 3.26 (br s, H-2) and 2.09 (br s, NHCOCH_3, overlapped with AcOD).

N-(3-Trifluoromethylphenylcarbamoyl)chitosan, **III**: Application of the general procedure to **CS 2** (200 mg) and 3-trifluoromethylphenyl isocyanate (250 µL, 1.8 mmol), after 120 h (pH 6.3), afforded compound **III** (173 mg) as a white solid. DS: 0.02. IR: 3288, 2879, 1638, 1543, 1394, 1314, 1155, 1060, 1028 and 897 cm^{-1}. ^{1}H NMR (500 MHz,

AcOD/D_2O): δ 7.75 (br s, H-2''), 7.57 (br s, H-4'' or H-6''), 7.50 (br s, H-6'' or H-4''), 7.39 (br d, J = 7.3 Hz, H-5''), 5.60 (br s, H-1'), 4.95 (br s, H-1), 4.20-3.50 (br m, H-3, H-4, H-5, H-6 and H-6'), 3.26 (br s, H-2) and 2.09 (br s, NHCOCH_3, overlapped with AcOD).

2.3. Characterization of chitosan-supported ureas

NMR spectra (500 MHz) were acquired on a Bruker Avance III spectrometer equipped with a 5 mm CryoProbe TCI using a 1:0.85 AcOD/D_2O solution. Degrees of *N*-substitution (DS) were calculated from the relative integral value of ^{1}H NMR spectra as follows:

$$DS = [(I_{Ar}/n)/(I_{H2\text{-}H6}/6)]$$

Where I_{Ar} is the relative area of the ureidyl moiety peaks (3 for compound **II** or 4 for compounds **I** and **III**) and $I_{H2\text{-}H6}$ corresponds to the integral for protons H-2 to H-6 of the pyranose ring.

To confirm effective substitution into the polymer backbone, diffusion-filtered ^{1}H NMR experiments were carried out applying a standard gradient pulse (Bruker pulse program *ledbpgps2*) (Wu, Chen, & Johnson, 1995).

Finally, infrared spectra were recorded on a Jasco FT/IR-4100 spectrophotometer applying 30 scans per sample at a resolution of 4 cm^{-1}.

*2.4 General procedure for the organocatalyzed cyanosilylation of α-ketoesters **1-6a** in the presence of trimethylsilyl cyanide.*

Trimethylsilyl cyanide (99 µL, 0.75 mmol) was added to a solution of ketones or aldehydes **1-6a** (0.5 mmol) and the corresponding chitosan-based urea **I-III** (15 mg) in the proper solvent (0.5 mL) at the specified temperature. The mixture was stirred for the time established (TLC monitoring). The catalyst was filtered and washed twice with the corresponding solvent. To the crude reaction, 1.0 mL of a saturated solution of NH_4Cl was added, and the mixture was extracted with EtOAc (2 × 5 mL). The organic phase was washed with 5.0 mL of a saturated solution of NaCl, dried with Na_2SO_4, and the solvents were removed under reduced pressure. The residue was purified by column chromatography using 8:2 *n*-hexane/EtOAc for compounds **2-4b** and 9:1 *n*-hexane/EtOAc for products **5**,**6b**, affording the corresponding *O*-protected cyanohydrins **2-4b** and (*R*)-**5**,**6b**.

Ethyl 2-cyano-2-phenyl-2-[(trimethylsilyl)oxy]acetate, **2b,** was synthesized from ethyl benzoylformate **2a** using catalyst **II** at -30 ºC in toluene. Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.43-7.41 (m, 3H), 4.31-4.18 (m, 2H), 1.26 (t, $^3J_{HH}$ = 8.1 Hz,), 0.21 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 167.2 (C=O), 134.2 (C_{Ar}), 129.2 (2 × CH_{Ar}), 128.1 (2 × CH_{Ar}), 124.8 (CH_{Ar}), 116.4 (C≡N), 72.1 (C), 64.2 (CH_2), 12.9 (CH_3), 0.0 (3 × Si-CH_3); HRMS: m/z calcd. for $C_{14}H_{19}NNaO_3Si$ (M^+ + Na): 300.1026; found: 300.1032.

Ethyl 2-cyano-2-(4-cyanophenyl)-2-[(trimethylsilyl)oxy]acetate, **3b**: Prepared from ethyl 4-cyanobenzoylformate **3a**, using catalyst **II** in toluene at -30 ºC. Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.60 (m, 2H), 7.58-7.55 (m, 2H), 4.15-4.03 (m, 2H), 1.10 (t, $^{3}J_{HH}$ = 7.8 Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 165.5 (C=O), 140.7 (C_{Ar}), 131.8 (2 × CH_{Ar}), 125.7 (2 × CH_{Ar}), 117.2 (C≡N), 116.6 (C≡N), 113.1 (C_{Ar}), 73.6 (C), 63.3 (CH_2), 13.1 (CH_3), 0.0 (3 × Si-CH_3); HRMS: m/z calcd. for $C_{15}H_{18}N_2NaO_3Si$ (M^+ + Na): 325.0984; found: 325.0980.

Ethyl 2-cyano-4-phenyl-2-[(trimethylsilyl)oxy]butanoate, **4b**, was prepared starting from ethyl 2-oxo-4-phenylbutyrate **4a** in the presence of catalyst **II** in toluene at -30 ºC. Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.20 (m, 2H), 7.19-7.10 (m, 3H), 4.23-4.15 (m, 2H), 2.77-2.71 (m, 2H), 2.23-2.17 (m, 2H) 1.26 (t, $^{3}J_{HH}$ = 8.0 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 167.0 (C=O), 139.0 (C_{Ar}), 127.8 (2 × CH_{Ar}), 127.6 (2 × CH_{Ar}), 125.6 (CH_{Ar}), 117.3 (C≡N), 72.1 (C), 62.4 (CH_2), 41.4 (CH_2), 29.1 (CH_2), 13.3 (CH_3), 0.0 (3 × Si-CH_3). HRMS: m/z calcd. for $C_{16}H_{23}NNaO_3Si$ (M^+ + Na): 328.1339; found: 328.1342.

*2.5 General procedure for the hydrolysis of the O-protected cyanohydrins **2-6b**. Synthesis of **2-6c**.*

The corresponding cyanohydrin trimethylsilyl ether **2-6b** (0.2 mmol) was dissolved in THF (2.0 mL), and then 1.0 N HCl (2.0 mL) was added dropwise to the mixture. The reaction was stirred at room temperature for 4 h and the aqueous phase was then extracted with Et_2O (2 × 5mL). The combined organic layers were dried with Na_2SO_4 and the solvent was eliminated under reduced pressure to obtain the free cyanohydrins **2-6c**. Compounds **2-4c** were directly employed to measure the optical purities. In case of cyanohydrins **5,6c** a further acetylation step was required to determine the enantiomeric excesses. The optical purities of cyanohydrins **2-4c** were determined using a Chiralpak ADH-H column (25 cm × 0.46 cm) from Daicel (95:5 *n*-hexane/*i*-PrOH, 1.0 mL/min, 30 ºC).

(–)-Ethyl 2-cyano-2-hydroxy-2-phenylacetate, (–)-**2c**: Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H), 7.37-7.35 (m, 3H), 4.33-4.18 (m, 2H), 1.20 (t, $^{3}J_{HH}$ = 8.0 Hz, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 168.1 (C=O), 134.9 (C_{Ar}), 129.9 (2 × CH_{Ar}), 128.9 (2 × CH_{Ar}), 125.6 (CH_{Ar}), 117.1 (C≡N), 72.7 (C), 65.0 (CH_2), 13.7 (CH_3); HRMS: m/z calcd. for $C_{11}H_{11}NNaO_3$ (M^+ + Na): 228.0631; found: 228.0635. HPLC data: t_r (–) = 12.5 min., t_r (+) = 13.7 min. $[\alpha]_D^{25}$: - 15.6 (*c* 1.0, $CHCl_3$, 24% *ee)*.

(–)-Ethyl 2-cyano-2-hydroxy-2-(4-cyanophenyl)acetate, (–)-**3c**: Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.66 (m, 4H), 4.37 (br s, 1H, OH), 4.15-4.03 (m, 2H), 1.10 (t, $^{3}J_{HH}$ = 8.0 Hz, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 167.0 (C=O), 139.5 (C_{Ar}), 132.7 (2 × *C*H_{Ar}), 126.6 (2 × *C*H_{Ar}), 117.8 (C≡N), 116.3 (C≡N), 114.1 (C_{Ar}), 72.1 (C), 65.8 (CH_2), 13.7 (CH_3); HRMS: m/z calcd. for $C_{12}H_{10}N_2NaO_3$ (M^+ + Na): 253.0589; found: 253.0592. HPLC data: t_r (–) = 28.4 min., t_r (+) = 34.7 min. $[\alpha]_D^{25}$: - 17.2 (*c* 1.45, $CHCl_3$, 28% *ee)*.

(–)-Ethyl 2-cyano-2-hydroxy-4-phenylbutanoate, (–)-**4c**: Yellow pale oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 6.98-6.95 (m, 3H), 4.38-4.29 (m, 2H), 2.84-2.78 (m, 1H), 2.69-2.63 (m, 1H), 2.31-2.20 (m, 2H), 1.28 (t, $^{3}J_{HH}$ 8.1 Hz, 3H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 167.1 (C=O), 137.4 (C_{Ar}), 128.6 (2 × CH_{Ar}), 127.7 (2 × CH_{Ar}), 127.3 (CH_{Ar}), 116.4 (C≡N), 69.7 (C), 65.4 (CH_2), 40.1 (CH_2), 29.2 (CH_2), 13.7 (CH_3); HRMS: m/z calcd. for $C_{13}H_{15}NNaO_3$ (M^+ + Na): 256.0944; found: 256.0950. HPLC data: t_r (–) = 11.2 min., t_r (+) = 18.1 min. $[\alpha]_D^{25}$: - 5.9 (*c* 0.70, $CHCl_3$, 21% *ee)*.

*2.6 General procedure for the acetylation of free cyanohydrins **5c** and **6c**.*

Free cyanohydrins **5-6c** (0.1 mmol) were dissolved in CH_2Cl_2 (2 mL), and pyridine (16 μL, 0.2 mmol), 4-dimethylaminopyridine (catalytic) and acetic anhydride (19 μL, 0.2 mmol) were added dropwise. The reaction was stirred at room temperature for 1 h, and the crude mixture was washed with 1.0 N HCl (2 × 5 mL). The organic layer was dried with Na_2SO_4 and the solvents were evaporated to give the corresponding acetates **5-6d**, which were used without further purification for the determination of the enantiomeric excesses using a Chiracel OD (25 cm × 0.46 cm) column from Daicel (99:1 *n*-hexane/*i*-PrOH, 1.0 mL/min, 30 ºC). HPLC data: Cyanohydrin **5d**: t_r (*R*) = 12.4 min., t_r (*S*) = 13.6 min; Cyanohydrin **6d**: t_r (*R*) = 14.8 min., t_r (*S*) = 17.0 min.

*2.7. General procedure for the catalytic enantioselective reaction of formaldehyde tert-butyl hydrazone (**1**) with α-ketoester **2a**.*

Formaldehyde *tert*-butyl hydrazone (134 μL, 1.2 mmol) was added to a solution of ethyl benzoylformate (**2a**) (106 mg, 0.6 mmol) and the chitosan-based urea **I-III** (15 mg) in the proper solvent (0.6 mL) at the specified temperature. The mixture was stirred for the time established. After that, the catalyst was filtered and washed with the corresponding solvent (2 × 2 mL). The solvent was then removed under reduced pressure and the crude reaction mixture was purified by column chromatography using 6:1 toluene/EtOAc as eluent, in order to afford the corresponding azomethyl alcohol (*R*)-**7**. The enantiomeric excess of this compound was determined with a Chiralpak AD-H column (98:2 *n*-hexane/*i*-PrOH, 1.0 mL/min, 30 ºC), t_r (*R*) = 13.0 min., t_r (*S*) = 19.2 min.

(*R*)-Ethyl-3-[2-(*tert*-butyl)hydrazono]-2-hydroxy-2-phenylpropanoate, (*R*)-**7**: Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, $^{3}J_{HH}$ = 7.2 Hz, 2H), 7.36 (t, $^{3}J_{HH}$ = 7.2 Hz, 3H), 7.30 (d, $^{3}J_{HH}$ = 7.2 Hz, 1H), 4.71-4.63 (m, 1H), 4.27-4.20 (m, 2H), 4.04 (s, 1H), 4.03-3.95 (m, 1H), 1.26 (t, $^{3}J_{HH}$ = 7.5 Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 172.1 (C=O), 139.8 (C_{Ar}), 128.3 (2 × CH_{Ar}), 128.0 (2 × CH_{Ar}), 125.9 (CH_{Ar}), 77.8 (C), 75.1 (C), 68.3 (CH_2), 62.0 (CH_2), 26.5 (CH_3), 14.1 (CH_3); HRMS calcd. for $C_{15}H_{23}N_2O_3$ (M^+): 278.1630; found: 278.1624.

2.8. General procedure for the Friedel-Crafts reaction between indole and trans-β-nitrostyrene.

To a solution of *trans*-β-nitrostyrene (30 mg, 0.2 mmol) and the corresponding chitosan-supported urea **I-III** (15 mg) in the selected solvent (0.6 mL), indole **8** (35 mg, 0.3 mmol)

was added in one portion. The test tube was stirred at the chosen temperature for the times established. After the reaction finished (monitoring by TLC), the catalyst was filtered and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography (8:2 *n*-hexane-EtOAc). The enantiomeric excess of product **9** was measured using a Chiralpack AD-H column (9:1 *n*-hexane/*i*-PrOH, 1.0 mL/min, 30 ºC), t_r = 24.7 min., and 27.2 min.

(±)-3-(2-nitro-1-phenylethyl)-1*H*-indole, (±)-**9**: Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (br s, 1H), 7.43-7.03 (m, 10H), 5.21 (t, $^3J_{HH}$ = 8.0 Hz, 1H), 5.00 (m, 1H), 4.93 (m, 1H); ^{13}C NMR (74.5 MHz, $CDCl_3$): δ 139.2 (C_{Ar}), 137.9 (C_{Ar}), 128.9 (C_{Ar}), 127.8 (2 x CH_{Ar}), 127.6 (2 × CH_{Ar}), 124.7 (CH_{Ar}), 122.7 (CH_{Ar}), 121.6 (CH_{Ar}), 120.0 (CH_{Ar}), 118.9 (CH_{Ar}), 114.5 (C_{Ar}), 111.4 (CH_{Ar}), 79.5 (CH_2), 41.6 (CH); HRMS: calcd. for $C_{16}H_{14}N_2O_2$ (M^+): 266.1055; found: 266.1049.

2.9. Computational details

Theoretical calculations were computed employing the program Gaussian 09 (Frisch et al, 2009). All DFT optimizations were performed without symmetry restrictions using the hybrid Minnesota functional M06-2X (Zhao et al, 2006a, b, 2008) at 6-31++G(d,p) level of theory. Analyses of frequencies were carried out revealing that all optimized structures were minima (no imaginary frequencies). Monomers of methyl 2-deoxy-2-(3-trifluoromethylphenylureide)-4-*O*-methyl-β-D-glucopyranoside and methyl 2-deoxy-2-[3,5-di-(trifluoromethyl)phenylureide]-4-*O*-methyl-β-D-glucopyranoside were used as models for chitosan-based catalysts **I** and **II** in which hydroxyl functions at C-1 and C-4 positions were methylated to simulate the β(1→4) glycosidic linkage.
Binding energies (kcal mol^{-1}) for non-covalent interactions were calculated at the same level of theory as follows:

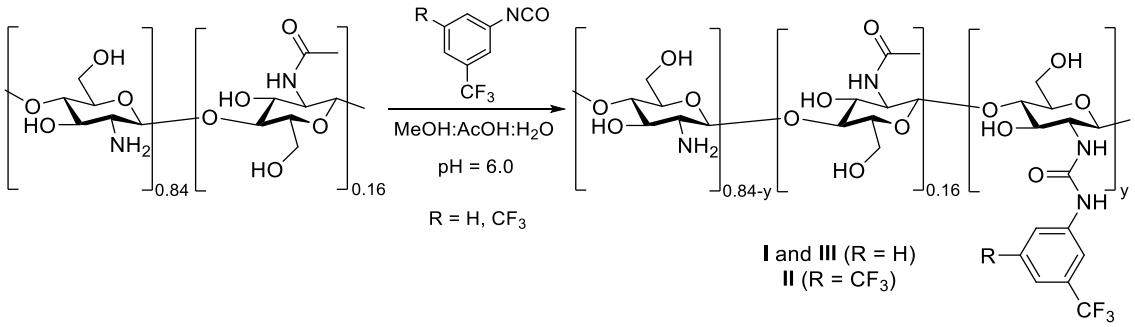
$$\Delta E_{bind} = E_{system} - E_{carbohydr} - E_{Ar}$$

Where E_{system} corresponds to the interaction between the catalyst model and the corresponding aromatic ring, whereas $E_{carbohydr}$ and E_{Ar} are the energy for single optimized structures for the catalyst and the aromatic acceptor, respectively.

3. Results and Discussion

The synthesis of chitosan-based ureas **I-III** (Scheme 1) was carried out under homogeneous conditions as was previously described in the experimental section, starting from native chitosans and the corresponding 3-mono- or 3,5-bistrifluoromethylphenyl isocyanate. In this context, the electron-deficient isocyanates can even react with the polar reaction solvents (H_2O and MeOH) and, therefore, an excess of these reactants was needed. Chitosans with different molecular weights and degrees of deacetylation were used for the preparation of ureidyl derivatives **I-III**. Thus, catalysts **I** (R = H) and **II** (R = CF_3) were obtained from the *low molecular weight* chitosan (DD = 84 %), whereas material **III** was prepared from *medium molecular weight* chitosan (DD = 81 %).

Applying the conditions described above, a DS average between 0.02 and 0.14 for these derivatives was calculated using ^{1}H NMR spectra. DS values for each compound were easily controlled by modification of the pH value of the reaction medium. For instance, it was observed in compound **I** that a higher pH value induced a higher DS (with a maximum of 0.14) due to an increase of the nucleophilic properties of the unprotonated amino groups.



Scheme 1. Synthesis of chitosan supported-ureas **I-III**. Different repeating units of these materials are shown as molar fractions (*y* values are obtained from the corresponding DS parameters)

It is necessary to note that ^{1}H NMR spectra for catalysts **I** and **III** showed signals at 7.75, 7.57, 7.50 and 7.38 ppm, corresponding to the C-H protons of the ureidyl moiety, whereas only three signals at 8.23, 8.00 and 7.65 ppm were observed for the bis-3,5-trifluoromethyl moiety in catalyst **II**. From a NMR point of view, the effective attachment into the polymer backbone arises from two key points: (a) a broadening of signals takes place after the incorporation, and (b) ureidyl ^{1}H NMR peaks continue to be observed upon application of a diffusion gradient. Indeed, diffusion-filtered NMR experiments (Figure 1) provided a routine tool to corroborate any substitution on chitosan. In addition, FTIR spectra brought to light exclusively the *N*-substitution pattern on the basis of the absorbance peak ratios A_{1025}/A_{1061} that remained unchanged.

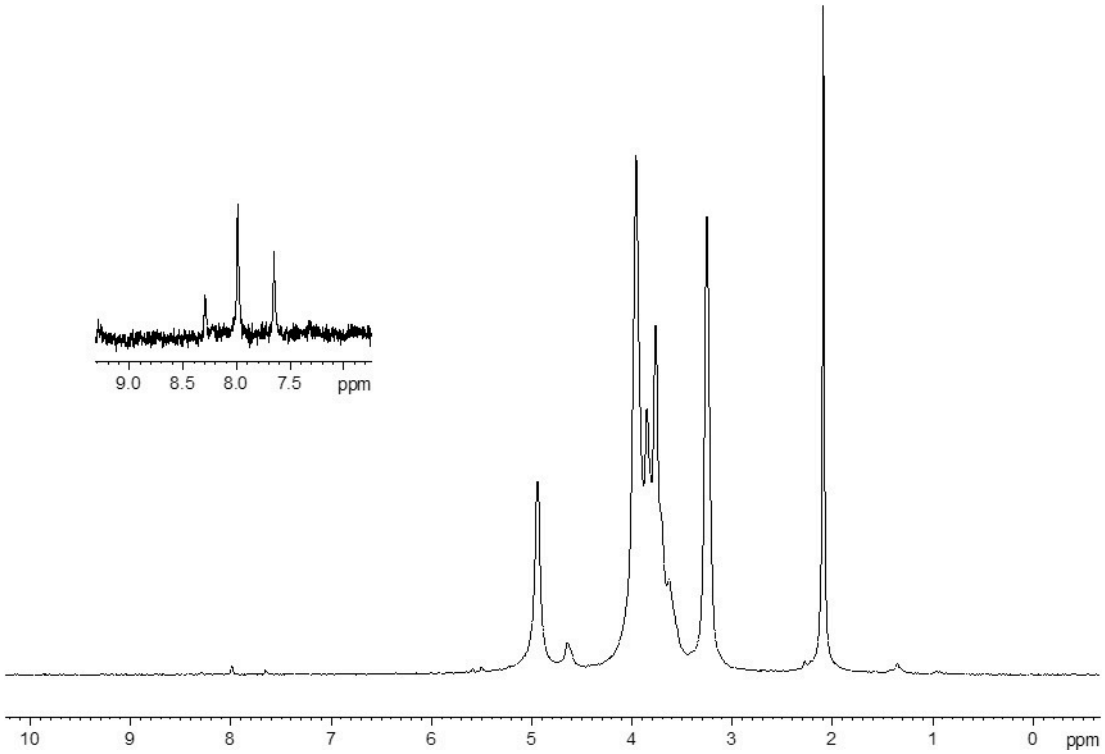


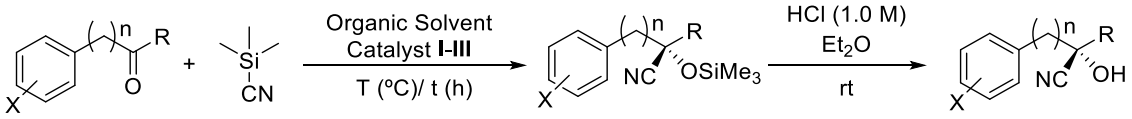
Figure 1. ^{1}H NMR diffusion-filtered experiment for chitosan-supported urea **II** in AcOD/D_2O at 500 MHz.

On the other hand, from a microscopic perspective, it is known that unmodified chitosan usually has a very low surface area (Kühbeck, et al., 2012). Measurements of N_2 absorption isotherms for catalysts **I-III** show that the introduction of ureidyl moieties did not modify the porous surface area (see Table S1, Supplementary data), as it was similar to that of native chitosan. In addition, these materials were also morphologically characterized by Field Emission Scanning Electron Microscopy (FESEM). The obtained FESEM images (see Fig. S1, Supplementary data) reveal an amorphous structure with a heterogeneous distribution of pore sizes in agreement with those calculated by absorption isotherms.

3.1. Chitosan-supported ureas for the organocatalyzed cyanosilylation of carbonyl compounds

The asymmetric cyanosilylation of aldehydes and ketones is a process of great interest in organic synthesis (Kurono, & Ohkuma, 2016), as optically active cyanohydrins are versatile building blocks which can be converted into several valuable compounds (Gregory, 1999). Several methodologies have been developed for the preparation of chiral cyanohydrins, including the use of hydrogen bond catalysts. Different ureas and thioureas have been employed, achieving the best results generally in the presence of Jacobsen type (thio)ureas (Zuend, & Jacobsen, 2007) or cinchona-based catalysts (Kong, Fan, Wu, & Miao, 2012). Both families of compounds are bifunctional organocatalysts, presenting in addition to the (thio)urea moiety an amine group that is able to activate the cyanide nucleophile. The use of silyl cyanides as cyanation reagents has gained great interest in

the last few years, as these compounds present good reactivity and they do not show volatility and toxicity issues due to hydrogen cyanide (Dekamin, & Mokhtari, 2012). In addition, the obtained *O*-silylated cyanohydrins can be easily hydrolysed by treatment with a diluted aqueous solution of HCl in organic solvents.



1a, X: H; n: 0; R: CH_3
2a, X: H; n: 0; R: CO_2Et
3a, X: *p*-CN; n: 0; R: CO_2Et
4a, X: H, n: 2; R: CO_2Et
5a, X: H, n: 0; R: H
6a, X: *p*-Cl, n: 0; R: H

Scheme 2. Organocatalyzed cyanosilylation of carbonyl compounds **1-6a** by chitosan supported ureas **I-III**.

Firstly, the cyanosilylation of acetophenone (**1a**) with TMSCN was carried out in the presence of the three chitosan-supported urea catalysts **I-III**, although no reaction was observed after long reaction times (72 h) at room temperature. Thereby, it was decided to test activated ketones, such as α-ketoesters, in which the presence of an electron-withdrawing group makes the carbonyl group more reactive. The addition of 1.5 equivalents of TMSCN to ethyl benzoylformate **2a** was performed at room temperature in the presence of catalyst **II**. Under these conditions, a very high yield of the racemic *O*-silylated cyanohydrin **2b** was obtained after 22 h (Table 1, entry 1), whereas no reaction was observed in the absence of catalyst.

The cyanosilylation of **2a** catalysed by both chitosans **I** and **II** was also performed at 4 ºC. The results for cyanosilylation reactions highlight that catalyst **II** is more active than catalyst **I**. Despite this fact, the *O*-silylated cyanohydrin **2b** was obtained with very low optical purity (entries 2 and 3), regardless of the catalyst employed. Thereby, the reaction temperature was further decreased to -10 ºC (results shown in entries 4 and 5). At this temperature, longer reaction times were required to obtain high conversions, whereas the enantiomeric excesses of **2b** were close to 15% with both catalysts. The *O*-protected cyanohydrin **4b** was obtained from the aliphatic ketoester **4a** (as the reactive centre was linked to an aliphatic carbon atom) with a similar result (86% yield and 12% *ee*, entry 6) using chitosan-based urea **II**. In order to improve the selectivity of the process, reactions were conducted at -30 ºC. After 30 h, catalyst **I** yielded 87% of **2b** with a slightly higher optical purity (*ee*=20%), while catalyst **II** afforded the *O*-silylated cyanohydrin with 84% yield and 24% *ee* after 24 h (entry 8). Medium molecular weight chitosan **III** showed much lower activity and selectivity (entry 9). We have also conducted a cyanosilylation employing unmodified low molecular weight chitosan **CS 1**, in order to verify whether this chitosan was able to catalyse the process. After 24 h, only 5% yield was observed (entry 10), indicating that most of the cyanohydrin formed was due to the urea-driven

hydrogen-bond catalysis. A further decrease in the reaction temperature to -45 ºC led to obtain **2b**, with 61% yield after 40 h and a minimal effect on the final product optical purity (entry 11).

Other parameters were studied in the urea **II**-catalysed cyanosilylation of **2a** at -30 ºC. Reactions carried out in TBME, CH_2Cl_2 or MeCN led to slightly higher yields than in toluene (more than 90% for both solvents). When using TBME, **2b** was recovered with 22% *ee*, while both CH_2Cl_2 and CH_3CN afforded the cyanohydrin with lower optical purities. When the reaction was performed in EtOAc, a low yield was achieved, whereas the enantiomeric excess of **2b** was similar to that of toluene. Since it has been described that the presence of small amounts of alcohols or phenols helps to generate cyanide as the active nucleophile (Kong et al., 2012), the use of different additives was also tested. Thus, addition of TMSCN to **2a** was carried out in toluene with 10 mol% of *p*-nitrophenol; however, as shown in entry 16, no improvements in neither activity nor selectivity were observed. 1-Hydroxybenzotriazole hydrate (HOBt) was also employed as additive in this reaction, leading to a loss in activity, with the final product being obtained almost as a racemic mixture, as shown in entry 17. This additive is commonly used for the activation of carbonyl groups (Franconetti, Jatunov, Borrachero, Gómez-Guillén, & Cabrera-Escribano, 2013). Nevertheless, HOBt proved to be capable of forming chitosan-based water-soluble salts (Fangkangwanwong, Akshi, Kida, & Chirachanchai, 2006), which is, for the purpose of this study, an undesired process that could explain the loss in activity.

The reactions catalysed by chitosan **II** at -30 ºC in toluene were extended to other α-ketoesters. The 4-cyanophenyl derivative **3b** was obtained with a higher yield compared to its phenyl analogue (entry 18) and 28% *ee* after 24 h, whereas the reaction using aliphatic substrate **4a** led to both lower activity and selectivity (entry 19) in the formation of the chiral *O*-silylated cyanohydrin **4b**.

Table 1. Asymmetric cyanosilylation of α-ketoesters **2-4a** catalysed by chitosan-supported ureas.

Entry	Chitosan Catalyst	Substrate	Solvent	T (ºC)	time (h)	Yield (%)[a]	*ee* (%)[b]
1	**II**	**2a**	Toluene	25	22	95	≤3
2	**I**	**2a**	Toluene	4	22	85	6
3	**II**	**2a**	Toluene	4	22	94	11
4	**I**	**2a**	Toluene	-10	24	78	13
5	**II**	**2a**	Toluene	-10	24	91	15
6	**II**	**4a**	Toluene	-10	24	86	12
7	**I**	**2a**	Toluene	-30	30	87	20
8	**II**	**2a**	Toluene	-30	24	84	24
9	**III**	**2a**	Toluene	-30	30	67	6
10	**CS 1**	**2a**	Toluene	-30	24	5	≤3
11	**II**	**2a**	Toluene	-45	40	61	27
12[c]	**II**	**2a**	TBME	-30	24	92	22

13[d]	**II**	**2a**	CH_2Cl_2	-30	24	92	15
14	**II**	**2a**	CH_3CN	-30	24	90	12
15	**II**	**2a**	EtOAc	-30	24	70	18
16[d]	**II**	**2a**	Toluene	-30	24	88	22
17[e]	**II**	**2a**	Toluene	-30	24	72	21
18[c]	**II**	**3a**	Toluene	-30	24	95	28
19[c]	**II**	**4a**	Toluene	-30	24	68	21

[a] Isolated yield
[b] Determined by HPLC.
[c] Optimal reaction conditions explored for this substrate (also see Table S2).
[d] Reaction carried out in the presence of 10 mol% of *p*-nitrophenol as additive.
[e] Reaction performed with 10 mol% of HOBt hydrate as additive.

The feasibility of the heterogeneous chitosan-supported urea **II** system was studied in the catalysed cyanosilylation of substrate **2a** in toluene at 4 ºC. After 24 h, the reaction was completed and the urea was filtered off and washed several times with toluene. The recovered catalyst was then employed for a further reaction. The results are summarized in Figure 2. During the first five cycles, catalyst **II** maintained high activity, which made it possible to obtain **2b** with almost quantitative yield. From the sixth cycle, although a slight loss in urea activity was observed, even after 13 reactions this catalyst showed high robustness, affording 73% conversion of the *O*-silylated cyanohydrin. Regarding the catalyst selectivity, it was maintained throughout each of the cycles performed.

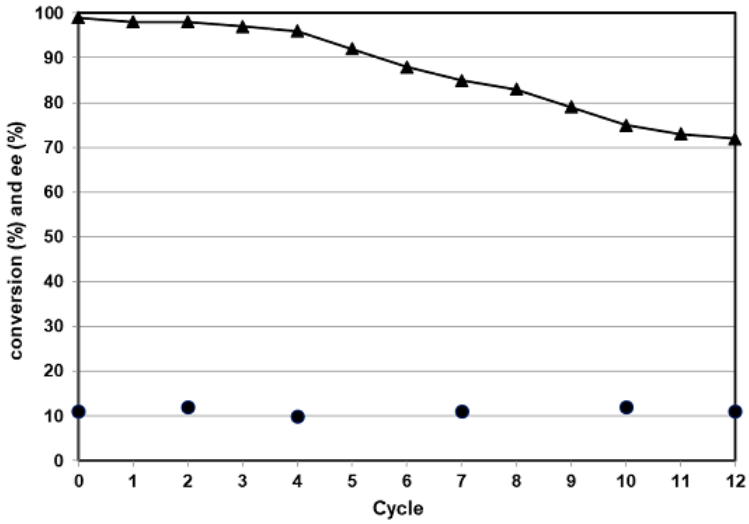
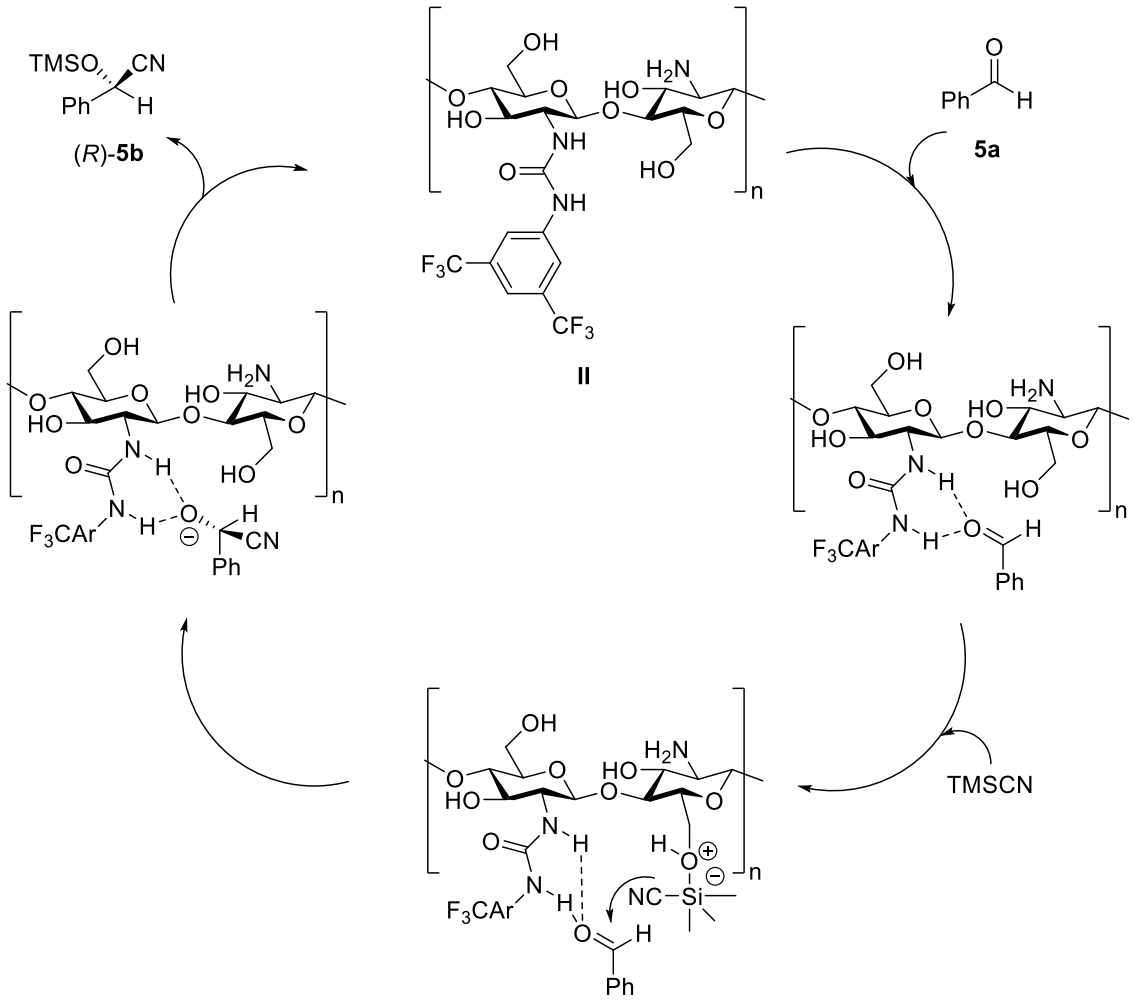


Figure 2. Chitosan-supported urea **II** recycling study on the cyanosilylation of prochiral α-ketoester **2a** with 1.5 equivalents of TMSCN in toluene at 4 ºC.

The organocatalyzed cyanosilylation of aromatic aldehydes was also tested with a set of benzaldehydes. These compounds have been selectively cyanosilylated in presence on different homogeneous hydrogen bond catalysts, being possible to obtain the *O*-silylated cyanohydrins with excellent optical purities (Kurono, & Ohkuma, 2016), but no heterogenous version of this procedure as been reported. Reactions using benzaldehyde as model substrate (**5a**, Table 2) were initially conducted at 4 ºC in toluene using chitosans **I** and **II**. After 7 h, 95% of racemic cyanohydrin (±)-**5b** was isolated with both catalysts.

In view of these results, reactions were carried out at -30 ºC. The use of catalyst **I** afforded 53% yield of cyanohydrin (*R*)-**5b** after 22 h (entry 3), whereas only 8 h were required to achieve 92% yield in the presence of chitosan **II**, as shown in entry 4. For both catalysts, the optical purities of the final product were around 15-20% *ee*. A possible mechanism for the *R*-selective cyanosilylation of **5a** to yield (*R*)-**5b** in the presence of catalyst **II** is proposed in Scheme 3.



Scheme 3. Proposed mechanism for the TMSCN addition to benzaldehyde (**5a**) catalysed by catalyst **II**.

The cyanosilylation of benzaldehyde (**5a**) followed a mechanism similar to those previously described (Kong, Fan, Wu, & Miao, 2012; Dekamin, Azimoshan, & Ramezani, 2013). Benzaldehyde is coordinated to the urea moiety through a hydrogen bonding interaction. The nucleophilic attack of cyanide (CN^-), which is also coordinated to the chitosan through the O-Si interaction in the TMSCN, from the *Re* face of the aldehyde, leads to the formation of the *R*-configured enantiomer as the major product. Cyanide attack to the Si face is partially restricted by the polysaccharide chain, which also serves as chiral auxiliary. After this, cyanohydrin (*R*)-**5b** is released and a new catalytic cycle will start again.

In this study, 4-chlorobenzaldehyde (**6a**) was also tested as substrate in the cyanosilylation catalysed by **I** and **II** at -30 ºC. Catalyst **II** showed higher activity than **I**, with 90% yield after 6 h (entry 6), although the processes took place with low selectivity (*ee* = 15%). The reaction of **6a** with TMSCN catalysed by unmodified chitosan **CS 1** led to 28% yield of racemate **6b** after 36 h (entry 7), indicating again that the urea-driven hydrogen-bond catalysis was the main force in these processes. On the other hand, the effect of a non-silylated cyanide source was studied. Thus, hydrocyanation of **6a** catalysed by **II** was conducted with 1.5 equivalents of acetone cyanohydrin in toluene at -30 ºC. The advantage of using this reagent was that the final free cyanohydrin (*R*)-**6c** was directly obtained, which made the hydrolysis step unnecessary. This reaction occurred with very low yield (13% after 9 h) and 10% *ee*, as shown in entry 8.

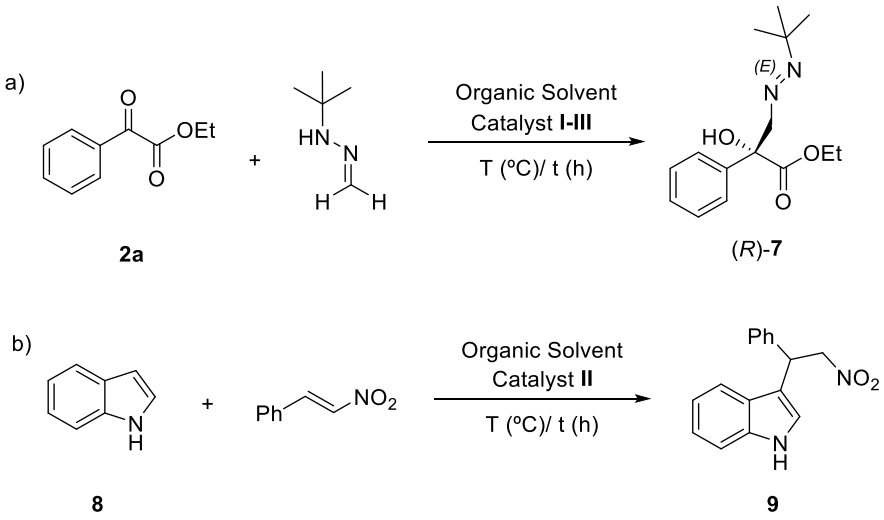
Table 2. Chitosan-based ureas catalysed preparation of (*R*)-cyanohydrins **5c** and **6c** starting from aromatic aldehydes **5a** and **6a**.

Entry	Chitosan Catalyst	Aldehyde	Solvent	T (ºC)	time (h)	Yield (%)[a]	*ee* (%)[b]
1	**I**	**5a**	Toluene	4	7	95	≤3
2	**II**	**5a**	Toluene	4	7	95	≤3
3	**I**	**5a**	Toluene	-30	22	53	19
4[c]	**II**	**5a**	Toluene	-30	8	92	14
5	**I**	**6a**	Toluene	-30	22	70	9
6[c]	**II**	**6a**	Toluene	-30	6	90	15
7	**CS 1**	**6a**	Toluene	-30	36	28	≤3
8[e]	**II**	**6a**	Toluene	-30	9	13	10

[a] Isolated yield
[b] Determined by HPLC on the *O*-acetylated derivatives **5-6d**.
[c] Optimal reaction conditions explored for this substrate (also see Table S2).
[e] Reaction performed employing 1.5 equivalents of acetone cyanohydrin as cyanide source.

3.2. Chitosan-supported ureas catalysed addition of formaldehyde tert-butyl hydrazone to α-ketoesters.

Formaldehyde *tert*-butyl hydrazone has been widely employed as a versatile carbon nucleophile in organocatalyzed additions to electrophilic compounds (Crespo-Peña et al., 2012; Monge et al., 2013; Retamosa, Matador, Monge, Lassaletta, & Fernández, 2016; Carmona et al., 2017), in order to obtain the corresponding optically active azomethyl alcohols (Scheme 4a, azo compounds, R–N=N–R′). These compounds constitute an important family of molecules with a wide variety of applications in organic chemistry (Patai, 1997).



Scheme 4. Reactions catalysed by chitosan-based ureas: a) Synthesis of (*R*)-azo compound (*R*)-**7** by addition of formaldehyde *tert*-butyl hydrazone to ethyl benzoylformate **2a**, and b) Organocatalyzed Friedel-Crafts alkylation between indole **8** and *trans*-β-nitrostyrene.

Thus, it was also decided to evaluate the chitosan-supported ureas as heterogeneous catalysts for the addition of this hydrazone to ethyl benzoylformate **2a** as model substrate. The homogenous counterpart of this reaction has been performed using a (*R*)-BINAM-derived bis-urea, achieving (*R*)-**7** with a 90% *ee* after 42 hours at -30 ºC (Crespo-Peña et al., 2012). The first experiment was conducted with catalyst **II** in toluene at 4 ºC. As shown in Table 3, after 22 h, a 58% yield of the racemic azomethyl alcohol **7** was obtained (entry 1). At this temperature, the reaction in the absence of catalyst led to 28% of the azo compound, which can partially explain the absence of selectivity. Thereby, the reactions were carried out at -30 ºC in toluene. Under these conditions, no background reaction was observed after 24 h. Ureas **I** and **III** led to (*R*)-**7** with yields around 20% (entries 3 and 5, respectively), whereas catalyst **II** afforded the azo compound with 33% yield and 16% *ee*. The use of TBME as solvent allowed increasing the yield up to 42% (entry 6), although the optical purity of **7** remained very similar. The use of acetonitrile as solvent (entry 7) afforded (*R*)-**7** with higher yield and only 10% *ee*, whereas the process performed in EtOAc showed low activity (entry 8). The reactions catalysed by chitosan **II** in toluene and TBME were also conducted at -45 ºC (entries 9 and 10). The reaction catalysed by TBME led to 41% of (*R*)-**7** with 24% *ee* after 48 h, whereas toluene showed lower performance (32% yield, 20% *ee*).

Table 3. Chitosan-based ureas catalysed addition of FTBH to ethyl benzoylformate **2a**.

Entry	Chitosan Catalyst	Solvent	T (ºC)	time (h)	Yield (%)[a]	*ee* (%)[b]
1	**II**	Toluene	4	22	58	≤3
2	None	Toluene	4	22	28	≤3
3[c]	**I**	Toluene	-30	24	23	15

4	**II**	Toluene	-30	24	33	16
5	**III**	Toluene	-30	24	20	7
6	**II**	TBME	-30	24	42	19
7	**II**	CH_3CN	-30	24	47	10
8	**II**	EtOAc	-30	24	23	15
9	**II**	Toluene	-45	48	32	20
10[d]	**II**	TBME	-45	48	41	24

[a] Isolated yield.
[b] Determined by HPLC.
[c] No reaction in the absence of catalyst was observed after 24 h.
[d] Optimal reaction conditions explored for this substrate (also see Table S2).

3.3. Catalytic Friedel-Crafts alkylation of indole catalysed by chitosan-based ureas.

The addition of aromatic compounds to electron-deficient alkenes is a kind of Friedel-Crafts alkylation (Scheme 3b), a synthetic process of great interest in organic chemistry. The catalytic version of this reaction has been reported using metal catalysts (Bandini, Melloni, & Umani-Ronchi, 2004) and organocatalysts (Herrera, Sgarzani, Bernardi, & Ricci, 2005), being obtained the final adduct **9** with 82% *ee* and good conversion when employing an homogeneous thiourea derived from 1-indanol as catalyst at -24 ºC.

In order to evaluate the performance of the chitosan-based catalyst **II** for Friedel-Craft reactions, we have investigated the model reaction between indole (**8**) and *trans*-β-nitrostyrene (Table 4). Since no product was observed at 0 ºC after 72 h, the reactions were performed at 25 ºC in different organic solvents. Adduct **9** was obtained with 47% yield after 48 h in TBME, whereas the use of CH_2Cl_2, CH_3CN or toluene led to slightly lower yields (from 45% to 37%), and the reaction in EtOAc afforded the final product with only 25% yield (entry 6). At this temperature, the reaction in the absence of catalyst yielded 17% of **9** after 65 h, which can explain to a certain extent the lack of selectivity.

Table 4. Catalyzed Friedel-Crafts alkylation of indole by *trans*-β-nitrostyrene in the presence of chitosan-supported urea **II**.

Entry	**Chitosan Catalyst**	**Solvent**	**T (ºC)**	**time (h)**	**Yield (%)[a]**	***ee* (%)[b]**
1	**II**	Toluene	0	72	≤3	--
2	**II**	Toluene	25	48	37	≤3
3[c]	**II**	TBME	25	48	47	≤3
4	**II**	CH_2Cl_2	25	48	43	≤3
5	**II**	CH_3CN	25	48	45	≤3
6	**II**	EtOAc	25	48	25	≤3
7	None	Toluene	25	65	17	≤3

[a] Isolated yield.
[b] Determined by HPLC.
[c] Optimal reaction conditions explored for this substrate (also see Table S2).

3.4 Theoretical calculations for mechanistic considerations

In order to understand the mechanism of the cyanosilylation reaction of benzaldehyde **5a** catalysed by chitosan-based ureas, theoretical calculations were performed. The optimization process of models for chitosan-supported ureas **I** and **II** based on methyl 2-deoxy-2-(3-trifluoromethylphenylureide)-4-*O*-methyl-β-D-glucopyranoside and methyl 2-deoxy-2-[3,5-di-(trifluoromethyl)phenylureide]-4-*O*-methyl-β-D-glucopyranoside provided minima (no imaginary frequencies) in which the *gauche-trans* rotamer was the most stabilized one. Initial screening applying the B3LYP functional revealed a non-covalent interaction between aromatic rings. Therefore, this study was carried out applying the M06-2X functional at 6-31++G(d,p) level of theory.

The outcomes (Figure S2) brought to light a π-π interaction for the interplay between models (for **I** and **II**) and benzaldehyde **5a**, as well as the corresponding hydrogen bonding between both moieties. Binding energies are indicative of higher stabilization for model **II** with respect to compound **I** (ΔE = 0.9 kcal mol^{-1}), with only one electron-withdrawing trifluoromethyl group. Despite being a similar structure from a geometrical point of view, a deep analysis showed slight but significant equilibrium distances (ΔR = 0.06 Å, Table S3) between centroids.

In fact, we suggest that the improved catalytic behaviour of chitosan-supported urea **II** is due to the fact that these π-π interactions govern the stabilization of the corresponding aldehyde, slightly modulated by dual hydrogen bonding between the carbonyl group and -NH- hydrogen bond donors.

4. Conclusions

Making use of the unique properties of chitosan as a valuable support, a set of chitosan-supported ureas containing electron-withdrawing groups in their structure was easily synthesised and characterized. These organocatalysts were tested in three different reactions involving asymmetric C-C bond formation: cyanosilylation of α-ketoesters and aldehydes, addition of formaldehyde *tert*-butyl hydrazone to an activated carbonyl compound and a Friedel-Crafts reaction. The optimal reaction conditions for each reaction are summarized in Table S2. All three chitosan-supported ureas **I-III** catalyzed these processes with moderate to good activities, with the highest activities being achieved for catalyst **II**, which presented a 3,5-bistrifluoromethylphenyl group in its structure. Different parameters were analysed to obtain the highest yields and optical purities, although a further optimization procedure should be performed in terms of the catalysts selectivity, as the enantiomeric excesses of the compounds synthesized are still much lower when compared with non-supported organocatalysts. It has to be considered that the heterogeneous chitosan-based ureas employed in this paper present a different structure to the optimized homogeneous organocatalysts for each one of the catalytic processes described.

As a proof of concept, catalyst **II** was employed in the cyanosilylation of ethyl benzoylformate for 13 cycles without changes in selectivity and only a slight loss in its activity. This chitosan-supported urea seems to be an affordable and robust hydrogen-

bonding catalyst that can improve the product isolation of the organocatalyzed reactions, as only a simple filtration is required to separate the catalyst from the final product. This work represents one of the first examples in which chitosans support hydrogen bond catalysts.

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