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Calcium Carbonate as Heterogeneous Support for Recyclable Organocatalysts

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KEYWORDS

Solid-supported catalysis, calcium carbonate, surface functionalization, click chemistry, asymmetric catalysis, catalyst recycling, continuous flow processes.

ABSTRACT

The controlled synthesis of calcium carbonate particles surface-functionalized with azido groups and its subsequent copper-catalyzed alkyne-azide cycloaddition (CuAAC) reactions with organocatalysts bearing alkyne anchors allowed the preparation of novel catalytic materials. A calcium carbonate-supported □,□-diarylprolinol silyl ether prepared in this manner catalyzes Michael addition of aldehydes to *trans*-□-nitrostyrenes with very high diastereo- and enantioselectivity. The immobilized catalyst can be recovered by simple decantation and reused. In addition, this heterogeneous catalytic system can also be adapted to continuous-flow operation, affording a five-fold productivity increase in comparison with the batch process.

1. INTRODUCTION

Asymmetric catalysts have progressively gained a central role in the sustainable

production of chiral non-racemic substances [1-3]. Among them, organocatalysts are especially interesting due to their relatively low prices, moisture tolerance, readily availability, easy fine-tuning and easy handling. Organocatalysts, however, often possess similar polarity and solubility behaviors than the molecules they help to produce, and this translate into solvent, time and energy consuming chromatographic separations for product purification. To solve this problem, the heterogenization of homogeneous catalysts onto solid supports has evolved into a prevalent strategy. Noteworthy, this brings an additional advantage: immobilized not only facilitate catalyst/product separation, but also allow catalyst recycling and reuse by simple filtration or magnetic decantation [4-6]. As a further advantage, heterogeneous organocatalysts have been also proven effective in continuous-flow mode, thus allowing the integration of reaction and separation into a single operation with important process intensification [7-41].

The heterogenization of homogeneous organocatalysts has been performed onto supports of different nature, such as inorganic materials, organic polymers of different natures and magnetic nanoparticles. Primarily, materials where the degree of functionalization at the particle surface can be easily adjusted are highly attractive as solid supports, since a high density of active sites can be achieved. According to that, relatively low-cost organic and inorganic materials, such as polystyrene (PS) [8-10, 18, 23-30] and silica (SiO_2) [42-44], have been highlighted as excellent solid supports enabling reusability and operation in flow. Another option for supporting organocatalysts are magnetic nanomaterials [45]. Solid supports of this class, with sizes of approx. 5 nm have also received much attention as solid supports due to the high surface areas and the possibility of simple removal from the reaction mixture by magnetic decantation [46-52]. Other solid supports like graphene oxide, clays or potassium fluoride have also been investigated and reported [53-55]. Excellent reviews about the organocatalytic supported systems can be found in the literature [17, 56-58].

Herein we report the functionalization of calcium carbonate ($CaCO_3$), which is a highly tunable carrier, as new solid support for the covalent immobilization of

organocatalysts. This material is interesting in this context for several reasons. Firstly, the shape and size of $CaCO_3$ can be varied by adjusting the kinetics of crystallization, allowing a fine control of the support since its crystallization [59, 60]. Secondly, a high degree of particle surface functionalization can be potentially achieved by using ligands with functional groups like carboxylic acids, which perfectly fit at the crystal surface [61]. Furthermore, the low cost of this support, which has made this material highly attractive as carrier for gas phase catalyzed reactions [62] as well as for the encapsulation of hydrophobic drugs [63], represents an additional advantage. As representative examples, diphenylprolinol silyl ethers were chosen as organocatalyst for their broad applications in catalyzing organic transformations [23, 64], and the performance of these catalytic systems was tested in the asymmetric Michael reactions of *trans*-□-nitrostyrene with aldehydes, a reaction that was subsequently used for the implementation of a single-pass, continuous flow process.

2. EXPERIMENTS

All reagents were purchased from Aldrich and used as received. All reactions were carried out directly under open air unless otherwise noted.

2.1. Analytical techniques. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H, or at 100 MHz and 125 MHz for ^{13}C, respectively. TMS was used as internal standard for ^{1}H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. FT-IR measurements were carried out on a Bruker Optics FTIR Alpha spectrometer equipped with a DTGS detector. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. The experiments under microwave irradiation were carried out in a CEM Discover microwave reactor. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak columns and guard columns. Racemic standard products were prepared using racemic catalyst in order to establish HPLC conditions. TEM images were collected using a JEOL 1011 Transmission Electron Microscope operating at 100 kV and magnification values of 12–60k. The dried samples were placed onto carbon coated-

copper grids. The same equipment was applied to make Selected Area Electron Diffraction (SAED). SEM images were recorded using a JEOL JSM-6400 scanning microscope. The same equipment was applied to measure Energy-dispersive X-ray spectroscopy (EDX). The PXRD samples were prepared by placing the powders between two foils without background. PXRD data were acquired on a Bruker D8 Advance.

2.2. Synthesis of Supported Catalysts

2.2.1. Synthesis of Support-1. A solution of $CaCl_2 \cdot 2H_2O$ (1.46 g, 9.93 mmol) dissolved in deionized water (5 mL) was added into a solution of azido pentanoic acid (0.35 g, 2.41 mmol) in 10 g $PEG_{(200Mwt)}$ under vigorous stirring at 40 ºC [65]. Finally, a solution of Na_2CO_3 (1.052 g, 9.92 mmol) in deionized water (5 mL) was added dropwise and stirred for 30 minutes at 40 ºC. The resulting materials were isolated by centrifugation, washed three times with THF und finally dried under vacuum.

CHN analysis: 10.88 %C, 0.97 %H, 0.96 %N

2.2.2. Synthesis of Support 2. A solution of $CaCl_2 \cdot 2H_2O$ (1.46 g, 9.93 mmol) in deionized water (5 mL) was added into a solution of □-azido undecanoic acid (0.50 g, 2.20 mmol) in 10 g $PEG_{(200Mwt)}$ under vigorous stirring at 40 ºC [65]. Finally, a solution of Na_2CO_3 (1.05 g, 9.92 mmol) in deionized water (5 mL) was added dropwise and stirred for 30 minutes at 40 ºC. The resulting materials were isolated by centrifugation, washed three times with THF and finally dried under vacuum.

CHN analysis: 18.14 %C, 1.68 %H, 2.58 %N

2.2.3. Synthesis of Supports 3 and 4. A solution of $CaCl_2 \cdot 2H_2O$ (0.30 g, 2.03 mmol) in deionized water (5 mL) was added into a solution of □-azido undecanoic acid (0.50 g, 2.20 mmol) and co-ligand (2.20 mmol, octanoic acid or palmitic acid) in $THF/PEG_{(200Mwt)}$ (6/3) (9 mL) under vigorous stirring at 40 ºC [65]. Finally, a solution of Na_2CO_3 (0.21 g, 1.99 mmol) in deionized water (5 mL) was added dropwise and stirred for 30 minutes at 40 ºC. The resulting materials were isolated by centrifugation, washed three times with THF and finally dried under vacuum.

Support-3, CHN analysis: 26.05 %C, 3.20 %H, 2.72 %N

Support-4, CHN analysis: 56.04 %C, 8.66 %C, 1.45 %N

2.2.4. Synthesis of (2*S*,4*R*)-diphenyl(4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol. This compound was synthesized according to our reported procedure [66]. (2*S*,4*R*)-*tert*-butyl 2-(hydroxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine-1-carboxylate (2.8 g, 6.9 mmol) was dissolved in 4 M HCl solution of 1,4-dioxane (150 mL) and stirred at room temperature for 40 min. Then, the reaction mixture was cooled to 0 ºC and pH value was adjusted slowly to pH 8.0 using aqueous NaOH solution (20 wt.%). The mixture was extracted with ethyl acetate (3 x 100 mL) and the combined organic phase was washed with brine and dried ($MgSO_4$). Solvent removal under reduced pressure afforded 1.74 g of product (83% yield) that was directly used in the next step.

2.2.5. Synthesis of (2*S*,4*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine. This compound was synthesized according to our reported procedure [64]. To a solution of (2*S*,4*R*)-diphenyl(4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol (460 mg, 1.13 mmol) in DCM (25 mL) at □20 ºC was added triethylamine (0.31 mL, 2.15 mmol) and trimethylsilyl trifluoromethanesulfonate (0.39 mL, 2.15 mmol). The solution was then allowed to reach 0 ºC and was stirred for 3 h at this temperature. The reaction was quenched with water and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash chromatography on silica gel (cyclohexane:ethyl acetate 1:1) to afford the desired product as a pale yellow oil (288 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = □ 0.11 (s, 9H), 1.67-1.70 (m, 2H), 1.74 (br, NH), 2.36 (t, *J* = 2.4 Hz, 1H), 2.79 (dd, *J* = 11.8 and 4.85 Hz, 1H), 2.95 (dd, *J* = 11.8 and 2.4 Hz, 1H), 3.91-3.95 (m, 1H), 4.05 (dd, *J* = 2.3 and 1.2 Hz, 2H), 4.32 (t, *J* = 7.9 Hz, 1H), 7.18-7.47 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 2.3, 34.2, 52.8, 56.2, 63.7, 74.1, 79.4, 80.2, 83.0, 127.0-128.6 (CH, Ar), 145.5, 146.8.

2.2.6. Synthesis of (2*S*,4*R*)-2-(((*tert*-butyldimethylsilyl)oxy)diphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine. This compound was synthesized according to our

reported procedure [64]. (2*S*,4*R*)-diphenyl(4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol (0.92 g, 3 mmol) was dissolved in dry DCM (15 mL), and the solution was cooled to 0 ºC with an ice-water bath. Then, 2,6-lutidine (24 mmol) and TBSOTf (12 mmol) were added. The reaction mixture was maintained in the bath and allowed to warm to room temperature. After the reaction was completed (8 h), saturated aqueous NH_4Cl solution (20 mL) was added and the product was extracted with DCM (2 x 20 mL). The combined organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by fast flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate (4/1), to afford 0.86 g of pure product (68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): □ = □0.48 (s, 3H), □0.21 (s, 3H), 0.95 (s, 9H), 1.68-1.78 (m, 3H), 2.35 (t, *J* = 2.4 Hz, 1H), 2.65 (dd, *J* = 12.1 and 4.9 Hz, 1H), 2.90 (ddd, *J* = 12.1, 2.5 and 1.2 Hz, 1H), 3.88-3.78 (m, 1H), 4.03 (dd, *J* = 2.4 and 1.3 Hz, 3H), 4.30 (dd, *J* = 8.8 and 7.0 Hz, 1H), 7.21-7.29 (m, 6H), 7.30-7.36 (m, 2H), 7.51-7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): □ = 146.3, 145.0, 129.3, 128.5, 127.8, 127.3, 127.2, 127.1, 82.9, 80.2, 79.5, 77.4, 77.2, 76.9, 74.1, 63.9, 56.2, 52.8, 34.6, 26.5, 19.2, □2.5, □3.2.

2.2.7. Synthesis of (2*S*,4*R*)-2-(diphenyl((triisopropylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine. This compound was synthesized using the same procedure as synthesizing TBS protected monomer [64]. 61% yield was obtained from (2*S*,4*R*)-diphenyl(4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol and TIPSOTf. ^{1}H NMR (500 MHz, $CDCl_3$): □ = 0.82 (m, 3H), 0.93 (t, *J* = 7.5 Hz, 18H), 1.71-1.74 (m, 1H), 1.96 (dd, *J* = 14.1 and 7.3 Hz, 1H), 2.35 (t, *J* = 2.4 Hz, 1H), 2.39 (dd, *J* = 12.0 and 4.5 Hz, 1H), 2.84 (ddd, *J* = 12.0, 2.3 and 1.6 Hz, 1H), 3.73 (dq, *J* = 4.4 and 2.3 Hz, 1H), 4.03 (d, *J* = 2.4 Hz, 2H), 4.41 (t, *J* = 7.8 Hz, 1H), 7.20-7.30 (m, 6H), 7.35-7.42 (m, 2H), 7.48-7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): □ = 146.0, 144.6, 129.4, 129.3, 127.6, 127.5, 127.1, 83.5, 80.3, 79.7, 77.4, 77.2, 76.9, 74.0, 64.1, 56.2, 52.4, 34.6, 18.7, 18.6, 13.9.

2.2.8. Synthesis of catalysts CXS-1-6. Azide functionalized solid supports (1 equiv, 0.22-0.75 mmol) were functionalized with silyl protected organocatalysts (1.5

equiv, 0.33-1.125 mmol) using CuI (1.05 equiv), DIPEA (0.2 equiv) and a mixture of THF/DMF=1/1 (3.5 mL) in microwave conditions, 80 °C, for 2.5 hours. The supported catalyst was separated by centrifugation, washed several times with THF, and dried under vacuum.

CXS-1, CHN analysis: 13.75 %C, 0.68 %H, 1.17 %N

CXS-2, CHN analysis: 18.08 %C, 1.25 %H, 1.52 %N

CXS-3, CHN analysis: 27.78 %C, 3.13 %H, 1.93 %N

CXS-4, CHN analysis: 41.76 %C, 6.18 %H, 1.63 %N

CXS-5, CHN analysis: 18.03 %C, 1.59 %H, 1.44 %N

CXS-6, CHN analysis: 18.33 %C, 1.45 %H, 1.39 %N

2.3. Catalysts test.

Immobilized catalyst (10 mol%, 40 mg) and *trans*-□-nitrostyrene (1.0 equiv, 0.1 mmol) were mixed in a 1 mL vial with DCM (0.5 mL). Then, propanal (1.5 equiv or 5.0 equiv) was added and this mixture was shaken at room temperature. The reaction was stopped at a given time by removing the catalyst by centrifugation, and the solvent was removed under reduced pressure. The dr values and conversions were determined by ^{1}H NMR with crude product. The ee was determined by HPLC with chiral column.

2.4. Recycling experiments with catalyst CXS-5.

Immobilized catalyst CXS-5 (10 or 20 mol%, 40 or 80 mg) and *trans*-□-nitrostyrene (1.0 equiv, 0.1 mmol) were mixed in a 1 mL vial with DCM (0.5 mL). Then, propanal (1.5 equiv or 5.0 equiv) was added and this mixture was shaken (at room temperature or 0 ºC). The reaction was stopped at a given time by removing the catalyst by centrifugation, and the solvent was removed under reduced pressure. The dr values and conversions were determined by ^{1}H NMR with crude product. The ee was determined by HPLC with chiral column.

2.5. Continuous-flow process. The packed-bed reactor consisted of a vertical mounted and fritted low-pressure Omnifit glass chromatography column (10 mm diameter, 10 mm pore size and up to maximal 70 mm of adjustable bed height) loaded with the catalyst CXS-5 (500 mg, 0.1 mmol, f ≈ 0.2 mmol·g^{-1}, 8 mm bed height), 2

beds of CPG 75C porous SiO_2 (5 mm bed height each in order reduce the pressure inside the column) and a bed of Merrifield resin (4 mm bed height, at the end of the column in order to prevent the catalyst leaching through the column). At the start, DCM was pumped at a flow rate of 250 $\mu L \cdot min^{-1}$ using an Asia syringe pump by Syrris for an hour. After that, the solvent channel was switched to a solution of *trans*-□-nitrostyrene (6.3 mmol, 1.3 g) and propanal (3.1 mL, 43 mmol) in 44 mL of DCM was flushed a flow rate of 250 $\mu L \cdot min^{-1}$ through the system until the solution filled the column. Then, the flow rate was reduced to 25 $\mu L \cdot min^{-1}$ and the system was run for 21 h. The reactor outlet was connected to a receiving flask where the product was collected. Samples were collected from 2h (when the experiment was stabilized) to 7 h (showing both constant conversion and stereoselectivity) of periodically collected samples. The solvent from the collected samples were removed under reduced pressure to give a yellow oil which was submitted to flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate (5/1), to give pure Michael adduct (0.081 g, 0.39 mmol) as a yellow oil. Productivity: 0.65 mmol product·$(\text{mmol catalyst})^{-1} \cdot h^{-1}$; theoretical yield during 6 h = 1.8 mmol.

3. RESULTS AND DISCUSSION

Two strategies were devised in order to synthesize the target catalytic system. In both, precipitation of $CaCO_3$ was induced using Ca^{2+} and CO_3^{2-} sources, and the catalytic monomer was immobilized onto the solid support *via* a triazole linker, which was formed using a copper-catalyzed alkyne-azide cycloaddition (CuAAC) reaction as the click strategy [67, 68]. The main difference between the catalytic materials (CXS) lies in the synthetic pathway used for the formation of the solid support. On the one hand, the post-functionalization strategy (Figure 1, upper route) in which, $CaCO_3$ particles are first formed and then treated with azide-substituted long-chain carboxylic acids to deliver ready-to-click materials. The advantage of this method for the preparation of solid supports is that the size and the crystal structure of $CaCO_3$ can be easily adjusted by changing the crystallization kinetics before surface functionalization (see Figure S1). In each case, the amount of azide groups present in the resulting powder, was

determined by nitrogen elemental analysis (EA), since the only source of nitrogen in the samples is the azido group present in the organic ligand [69].

The surface functionalization achieved in the structures with more surface area, those with vaterite structure [70-75], was relatively low (up to 0,14 mmol/g) (see Table S1). On the other hand, the biomineralization strategy targeted the formation of $CaCO_3$ using azide containing long-chained carboxylic acids as crystal-mimicking ligands during the crystallization (Figure 1, bottom route).

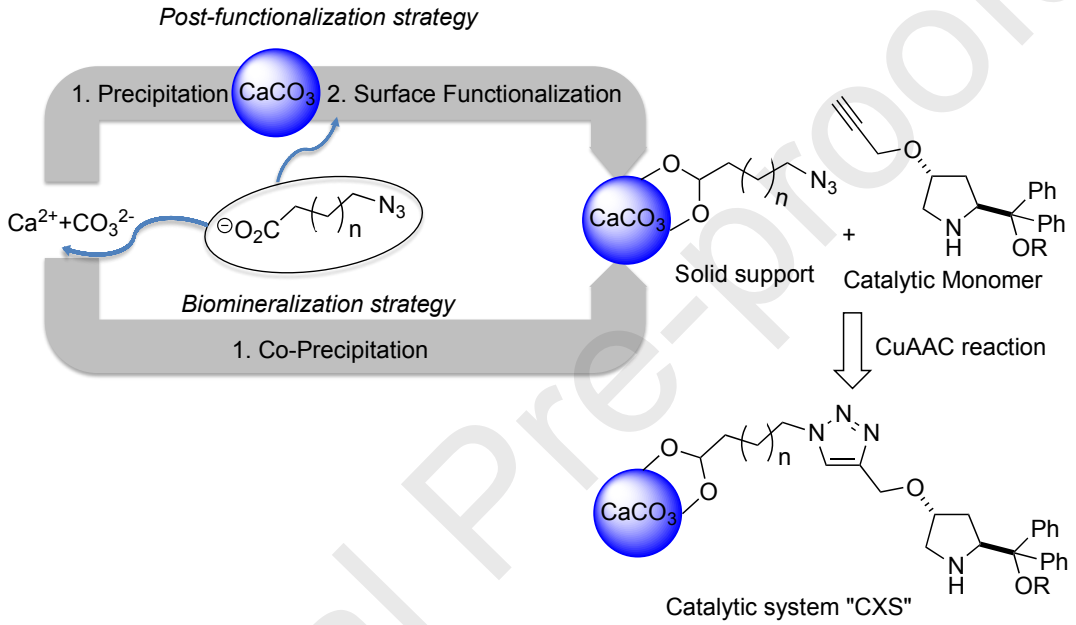


Figure 1. Synthesis of catalytic materials

Interestingly, the use of these ligands during the crystallization process directs crystal growth in specific directions because of the good fit between these carboxylate anions and certain crystal lattices of the emerging inorganic surfaces [63]. These approaches has been widely used during the past decades, and are still being used for the formation of new materials, particularly in the formation of anisotropic materials [76-80]. A nice illustration of this use can be found in the work by Mahapatra *et al*, who triggered the formation of $CaCO_3$ particles with lauric acid and successfully tested the resulting $CaCO_3$ materials depicting non-polar surfaces as oil absorbent materials [81].

Different supports have been synthesized using this approach. The characterization of Support-1 can be seen in Figure 2. Support-1 has been synthesized

using 5-azido-pentanoic acid as ligand in the co-precipitation route. The SEM image of Support-1 is shown in Figure 2a, here particles with both spherical and ill-defined shape can be seen.

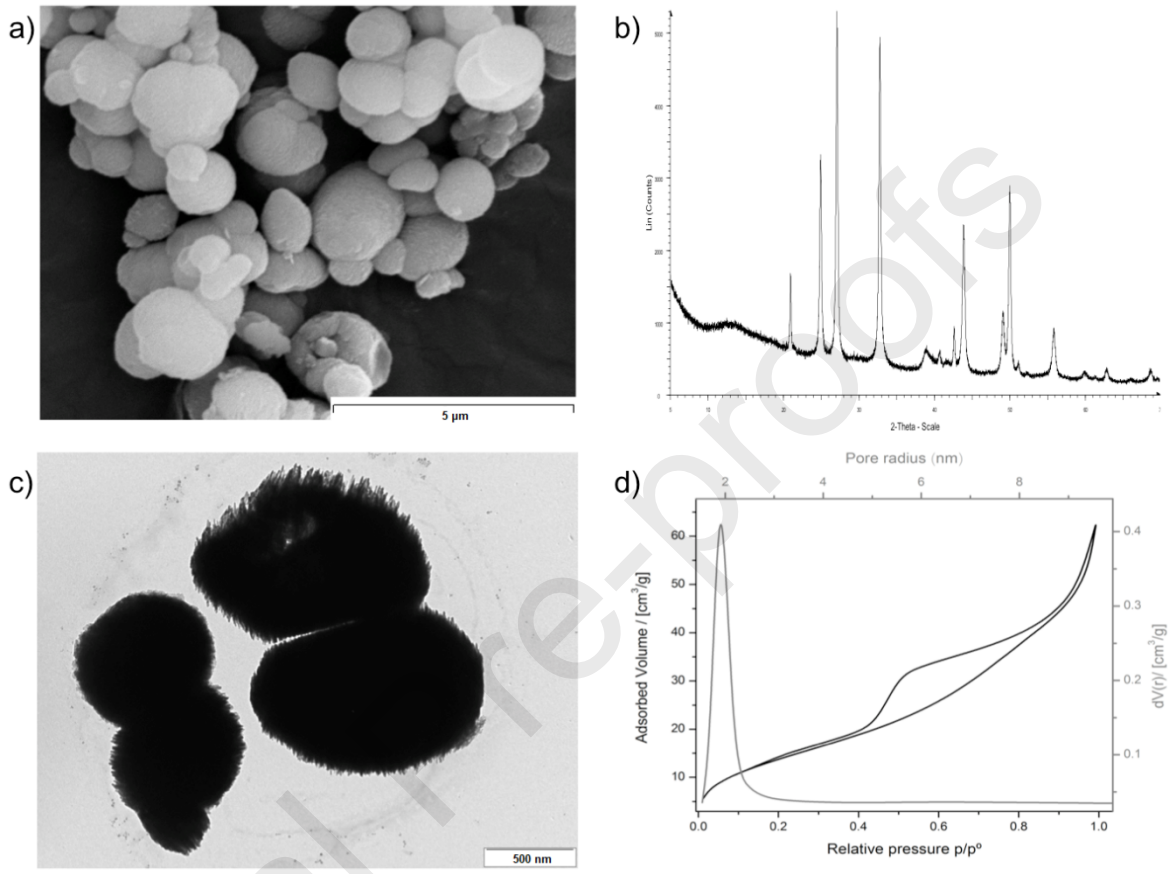


Figure 2. a) SEM image of Support-a, b) Powder X-ray diffraction (PXRD) of Support-a, c) TEM image of Support-a, d) N_2 adsorption/desorption isotherm of Support-a.

The PXRD showed in Figure 2b confirmed the formation of $CaCO_3$ with vaterite structure. As observed in Figure 2c, the spherical particles are composed by smaller nanocrystals and, therefore, they are polycrystalline. Moreover, the degree of functionalization of the resulting materials calculated from EA was found to be much higher in this case (Table 1) with values ranging from 0.23 to 0.65 mmol/g depending on the nature of the ligand and the co-ligand used in the formation of the particles. Finally, it is noticeable that N_2 adsorption desorption isotherm indicated a specific surface area of 52 m^2/g. From a practical perspective, the resulting materials can be well-dispersed in most of the organic solvents like tetrahydrofuran (THF),

dichloromethane (DCM), chloroform or toluene due to their non-polar surfaces, and this facilitates further chemical modification. To complete the preparation of the immobilized catalysts, the azide functionalized particles were reacted with the propargyloxy-modified Jørgensen-Hayashi catalyst (**1**) using a CuAAC reaction as a "click" method [67] to combine the two fragments (Figure 1).

Table 1. Different prepared supports

Support	Ligand	Co-Ligand	Functionalization (mmol/g)
Support-1	5-azido-pentanoic acid	-	0.228
Support-2	□-azido-undecanoic acid	□	0.613
Support-3	□-azido-undecanoic acid	Octanoic Acid	0.647
Support-4	□-azido-undecanoic acid	Palmitic Acid	0.344

The progress of the CuAAC reaction leading to the preparation of the catalytic systems (CXS-1-4) was monitored by IR spectroscopy using the azide stretching band at *ca*. 2100 cm^{-1} as a diagnostic tool (Figure 3). It can be observed in Figure 3a that this signal had disappeared from all supports when the reactions were completed. In that moment, all nitrogen present in the samples is due to the generated 1,2,3-triazole moieties (see Figure 1, Catalytic Systems CXS), so that nitrogen elemental analysis continues to be the method of choice for the determination of the functionalization of the catalytic materials.

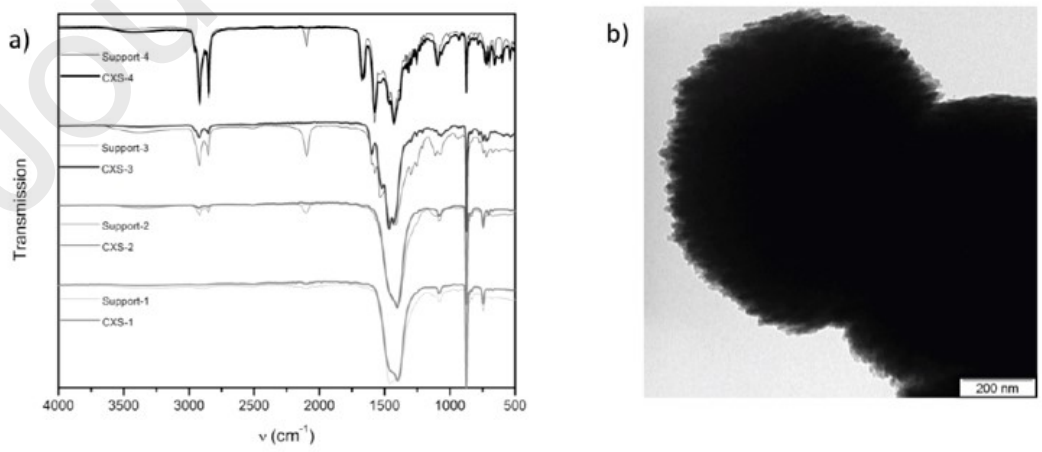


Figure 3. a) IR of the catalytic systems (CXS-1-4) and the support materials

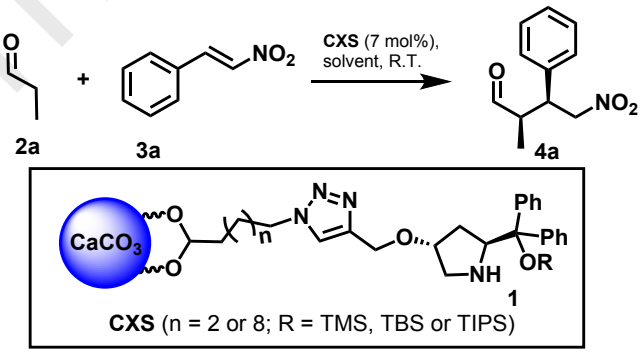
(Support-1-4) and b) TEM image of the catalytic material (CXS-1)

Table 2. Functionalization of the catalytic systems (CXS1-4)

Catalyst	CXS-1	CXS-2	CXS-3	CXS-4
Support	Support-1	Support-2	Support-3	Support-4
Functionalization (mmol/g)	0,208	0,278	0,343	0,291

Therefore, we assumed that the □□□-diphenyl prolinol trimethyl silyl ether catalytic units were successfully immobilized at the particle surfaces (with catalyst loading between 0.21 and 0.34 mmol/g, Table 2). The TEM image of **CXS-1** was taken as a confirmation that the supports remained stable after the CuAAC reaction (Figure 3b). With the first family of organocatalysts immobilized onto $CaCO_3$ in hand (**CXS-1-4**), their ability to catalyze enantioselective Michael additions was tested in the reaction of propanal (**Y**) with *trans*-□-nitrostyrene (**Z**), which is one of the most successful applications of the Jørgensen-Hayashi-type organocatalysts (Table 3) [23, 64]. As previously mentioned, the supported-organocatalyst allowed us to recover the catalyst from the reaction products for reuse by simple decantation of the supernatant and washing of the precipitate.

Table 3. Reaction condition optimization in Michael additions catalyzed by CXS immobilized catalysts



Entry	Support	Catalyst	R	Solvent	t (h)	conv. (%)[a]	dr (%)[a]	ee (%)[b]
1	Support-2	CXS-2	TMS	Toluene	24	42	91/9	64
2	Support-2	CXS-2	TMS	THF	24	4	n.d.	n.d.

3	Support -2	CXS-2	TMS	CHCl3	24	n.c.	-	-
4	Support -1	CXS-1	TMS	DCM	24	95	93/7	74
5	Support-2	CXS-2	TMS	DCM	24	89	89/11	75
6	Support-3	CXS-3	TMS	DCM	24	83	91/9	76
7	Support-4	CXS-4	TMS	DCM	120	n.c.	-	-
8	Support-2	CXS-2	TMS	DCM	24	89	93/7	75
9	Support-2	CXS-5	TBS	DCM	48	82	97/3	98
10	Support-2	CXS-6	TIPS	DCM	48	35	91/9	95

a) Determined by ^{1}H NMR spectroscopy of the crude mixture. b) Determined by HPLC using a chiral stationary phase. n.c. = no conversion, n.d. = not determined.

After the screening of different solvents, we observed that the best conversions, diastereo- and enantioselectivities were achieved in DCM. Interestingly, noticeable differences between the four catalytic systems were observed depending on the chemical composition of the surface of the supports [82]. We thus noticed that no reaction was taking place if the co-ligands (C16) involve longer chains than the ligands (C11) used for catalyst immobilization (Table 3, entry 7) [65], possibly due to the inaccessibility of the catalyst to the reactants. To our delight, excellent diastereoselectivities (93/7) and moderate enantioselevitivies (up to 76%) were observed with other $CaCO_3$ supported catalysts.

In order to improve the stereoselectivity of the process, the catalytic site was fine-tuned by modifying the nature of the silyl ether group nearby. In this respect, we have already reported that modification of this group involving increased bulkiness leads to increased robustness of the catalyst as well as to much better control of enantioselectivity [64].

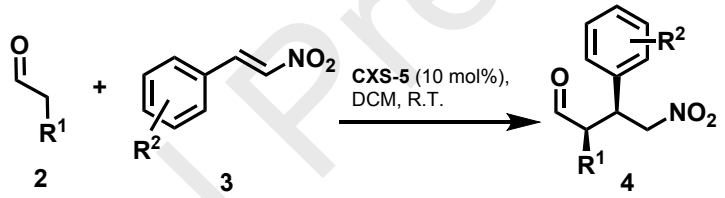
Accordingly, more sterically demanding silyl group could result in a better control of enantioselectivity of the reaction. In our case, when we changed the trimethyl silyl ether group (TMS) by tert-butyldimethylsilyl group (TBS) and triisopropylsilyl group (TIPS) in the catalytic sites, a remarkable increase in enantioselectivity was observed (Table 3， entries 8-10). Thus, **CXS-5** containing a TBS protecting group, led to

excellent diastereoselectivity (97/3) and enantioselectivity in the major product (98% ee), as it can be seen by comparison of the results in entries 1 and 2, while **CXS-6** containing the more stable, but more difficult to introduce TIPS group led to slightly less optimal results (entry 10).

It has to be mentioned that **CXS-5** and **CXS-6**, involving more sterically demanding silyl groups are affected by a slight decrease in catalytic activity with respect to those involving TMS groups. In any case, full conversion is recorded with catalyst **CXS-5** after 48 h reaction (vs. 24 h with **CXS-1** to **CXS-3**).

Next, we focused on studying the scope of the reaction catalyzed by **CXS-5**. As it is shown in Table 4, *trans*-□-nitrostyrenes (**3a-e**) bearing electron-donating and electron-withdrawing groups in different positions of the ring were tested in Michael reactions with aldehydes **2a-b** as donors.

Table 4. Scope of the Michael addition catalyzed by the $CaCO_3$ immobilized organocatalyst CXS-5.[a]



Entry	2	3	**4** (yield, %) [b]	dr (%) [b]	ee (%) [c]
1	**2a** (R^1=Me)	**3a** (R^2=H)	99	92/8	98
2	**2a** (R^1=Me)	**3b** (R^2=2-F)	90	94/6	96
3	**2a** (R^1=Me)	**3c** (R^2=3-Cl)	80	92/8	95
4	**2a** (R^1=Me)	**3d** (R^2=4-Br)	84	91/9	92
5	**2a** (R^1=Me)	**3e** (R^2=4-Me)	91	92/8	96
6	**2b** (R^1=*n*-Pent)	**3a** (R^2=H)	45	82/18	93

a) The reaction was carried out for 24 h. b) Determined by ^{1}H NMR spectroscopy of the crude mixture. c) Determined by HPLC using a chiral stationary phase.

When propanal was used under the previously optimized conditions, the addition products were obtained in high yields (80-99%), with diastereo- and enantioselectivities (Table 4, entries 1–5). However, it must be noted that when structural changes in the Michael donor were introduced, the stereoselectivity remained constant (ee = 93%), but

decrease of yield (45%) and diastereoselectivity (dr = 82/18) was observed possibly due to the steric hindrance effect of the longer alkyl chain [66] and the catalyst architecture [83] respectively (Table 4, entry 6).

After demonstrating the behaviour of the catalytic systems and its recoverability, we focused our efforts on the recyclability for CXS-5 in the reaction between propanal and *trans*-□-nitrostyrene. Firstly, we attempted the recycling of CXS-5 by submitting the reaction mixture to centrifugation (2000 rpm, 10 min), then separating the solution, and repeating the whole process before the next use. However, using this workflow, we observed a decrease in conversion between cycles, although stereoselectivities remained constant (see Table 5).

Table 5. Recycling experiment of the $CaCO_3$ immobilized organocatalyst CXS-5. Particles centrifuged in DCM

Catalyst	Cycle	Conversion (%)[a]	*syn*/*anti* (%)[a]	ee (%)[b]
CXS-5	1	87	91/9	97
	2	41	85/15	97
	3	18	80/20	97

a) Determined by ^{1}H NMR spectroscopy of the crude mixture. b) Determined by HPLC using a chiral stationary phase.

The elemental analysis of a sample of catalyst CXS-5 used in three reaction cycles with this protocol showed a significant decrease in functionalization (a drop of 60% was observed), providing clear indication on the origin of catalyst deactivation (Table 6).

Table 6. Functionalization of the catalytic systems before and after recycling.

Catalyst – CXS-5	Functionalization (mmol/g)
Cycle 1	0,343
Cycle 3	0,136

At this moment, we reasoned that the very high dispersibility of the catalytic

materials in DCM could be the reason for the loss of catalytic sites between cycles. Taking into account that the primarily observed spherically-shaped $CaCO_3$ particles are in fact agglomerates of smaller particles, it is logical to expect that, after centrifugation, the smallest $CaCO_3$ particles, which are those with higher surface area and, therefore, those bearing higher functionalization, could remain in solution as colloids, and would be lost with the solution in the inter-cycle treatments. Under this assumption, we modified the recycling protocol in the following manner: Once the reaction was complete, DCM was evaporated and the semi-solid residue was treated with *n*-pentane, where the particles are not so well-dispersed, but the reaction product is very soluble.

Finally, we centrifuged and washed the particles with *n*-pentane to recover the catalyst before reuse. Table 7 shows the results of the catalytic performance of the recycled CXS-5. Using this approach (centrifugation in *n*-Pentane), we were able to run two cycles at different temperature (0 and 25 ºC) and loading of catalyst (10 and 20 mol%) obtaining constant conversions and excellent stereoselectivities. However, we observed that after every cycle, longer times of reaction were needed and that after the third cycle, the conversion started to drop, even under the best conditions (20 mol% catalyst at 25 ºC, Table 7).

Table 7. Recycling experiment of the $CaCO_3$ immobilized organocatalyst CXS-5. Particles centrifuged in DCM

Catalyst	Cycle	T (ºC)	Time (h)	%mol	Conversion (%)[a]	*syn*/*anti* (%)[a]	ee (%)[b]
CXS-5	1	0	47	10	62	96/4	94
	2	0	68	10	66	93/7	93
	3	0	68	10	17	96/4	93
CXS-5	1	25	24	20	>99	91/9	94
	2	25	36	20	>99	90/10	95
	3	25	72	20	72	92/8	93

a) Determined by ^{1}H NMR spectroscopy of the crude mixture. b) Determined by HPLC using a chiral stationary phase.

As the ultimate test for sustainable use, catalyst **CXS-5** was tested in continuous flow [66] for the Michel addition of propanal (**2a**) to *trans*-□-nitrostyrene (**3a**) process in order to have clear evidence that the reaction was occurring at the interface of the

particles. The system consisted of a low-pressure chromatography column with two adjustable endpieces, which was loaded with the catalyst **CXS-5** and connected to a single pump used to feed the reactor with the reagents. The reaction was conducted at room temperature, and preliminary experiments showed that a flow rate of 25 □L·min^{-1} was the best option to produce the product with very good stereoselectivity and moderate conversion. Thus, 0.1 mmol of catalyst **CXS-5** (500 mg, f ≈ 0.2 mmol·g^{-1}) was loaded onto the column and the reaction was performed using *trans*-□-nitrostyrene (6.3 mmol) and propanal (43 mmol) in DCM (44 mL), so that the concentrations of the reactants was 0.143 M.

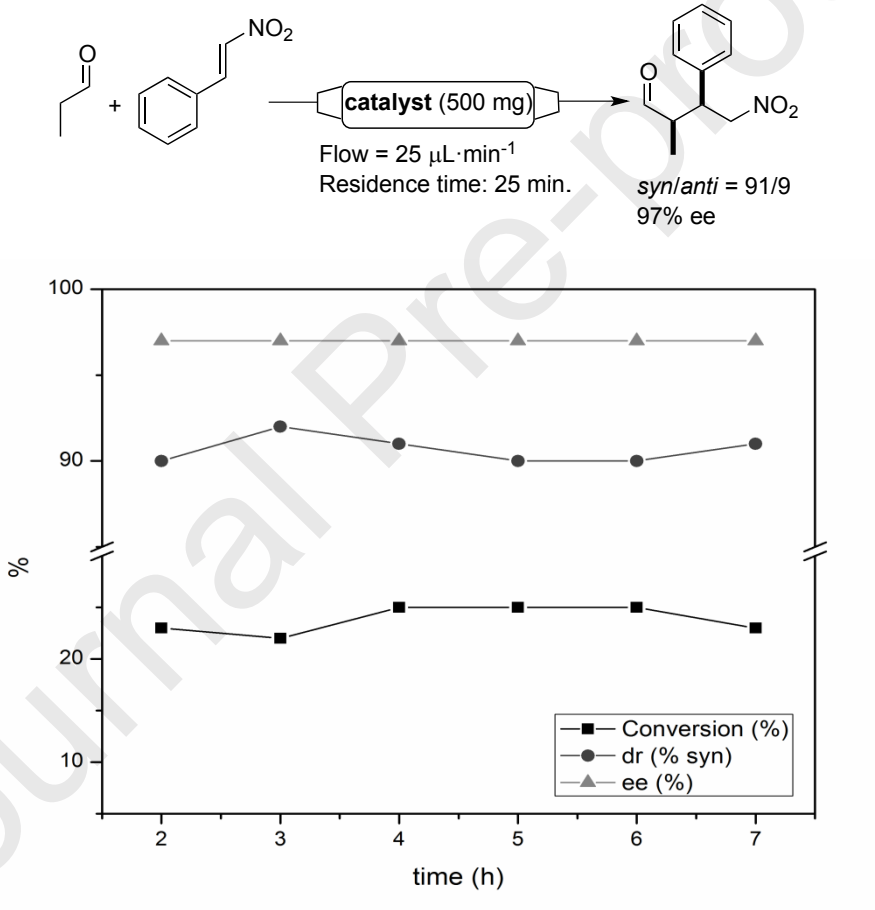


Figure 4. Synthesis of the Michael adduct 4a using catalyst CXS-5 in continuous flow

The flow experiment showed both constant conversion and stereoselectivity for a 7 h run (Figure 4). Notably, the process produced **4a** with high diasteremeric purity

(*syn*/*anti* = 91/9) and higher enantiopurity (97% ee) than the batch process (the average ee after three cycles in batch was 94%, see Table 7). In addition, the flow process was characterized by a productivity of 0.65 mmol **4a**·(mmol catalyst)$^{-1}$·h^{-1}, which represents a five-fold increase in productivity compared to the batch process (the accumulated productivity in batch after 3 reaction cycles was 0.13 mmol **4a**·(mmol catalyst)$^{-1}$·h^{-1}, see Table 7).

4. CONCLUSIONS

Calcium carbonate has been used for the first time as a competent support for the immobilization of organocalaysts. A Jørgensen-Hayashi catalyst immobilized onto this support has been used in the highly enantioselective Michael addition of aldehydes to *trans*-□-nitrostyrene derivatives. By adjusting the crystallization of $CaCO_3$ through the addition of long-chain carboxylic acids functionalized at the terminal position with azido groups yielded low-cost, azide-functionalized supports suitable for universal CuAAC reactions with terminal alkynes. Interestingly, the resulting supports were polycrystalline in nature, and the preparative approach used allowed a fine control of the particle surfaces. The azide-functionalized $CaCO_3$ supports were successfully loaded with different propargyloxy-functionalized □□□-diphenylprolinol silyl ether containing increasingly demanding silyl groups. The possibility of adjusting the chemical composition with respect to ligand/co-ligand at the particle surface has served to rationalize the effect of the relative chain length of these species on the catalytic performance of the system. The recoverability and recyclability of the optimal heterogenenized organocatalyst (**CXS-5**) has been tested under batch processes and then successfully transferred to a continuous-flow operation, which has allowed the preparation of a Michael product with significant improvements in terms of productivity referred to batch process. According to these findings, calcium carbonate can be considered as a suitable support for the further heterogenization of more organocatalysts working under non-acidic conditions. Finally, this contribution provides indication that control of the crystalline nature of inorganic supports during its formation can allow the fine-tuning of their catalytic activity. According to this,

research aiming at the controlled formation of supports using co-precipitation approaches offers important potential in view of the introduction of new supports, complementary to those already existing, for the immobilization of catalytic species.

ASSOCIATED CONTENT

Supporting Information. Experimental details are provided in the Supporting Information.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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References

1. Shibasaki M; Yoshikawa N, Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chemical Reviews* **2002**; *102* (6): 2187-210.
2. Pàmies O; Bäckvall J-E, Combination of Enzymes and Metal Catalysts. A Powerful Approach in Asymmetric Catalysis. *Chemical Reviews* **2003**; *103* (8): 3247-62.
3. Qin Y; Zhu L; Luo S, Organocatalysis in Inert C–H Bond Functionalization. *Chemical Reviews* **2017**; *117* (13): 9433-520.
4. Lu J; Toy PH, Organic Polymer Supports for Synthesis and for Reagent and Catalyst Immobilization. *Chemical Reviews* **2009**; *109* (2): 815-38.
5. Zhao G; Chai Z, *Recoverable and Recyclable Catalysts*. Wiley, Chichester: 2009.

6. Kristensen TE; Hansen T, Polymer-Supported Chiral Organocatalysts: Synthetic Strategies for the Road Towards Affordable Polymeric Immobilization. *European Journal of Organic Chemistry* **2010**; *2010* (17): 3179-204.

7. Puglisi A; Benaglia M; Chiroli V, Stereoselective organic reactions promoted by immobilized chiral catalysts in continuous flow systems. *Green Chemistry* **2013**; *15* (7): 1790-813.

8. Tsubogo T; Ishiwata T; Kobayashi S, Asymmetric Carbon–Carbon Bond Formation under Continuous-Flow Conditions with Chiral Heterogeneous Catalysts. *Angewandte Chemie International Edition* **2013**; *52* (26): 6590-604.

9. Zhao D; Ding K, Recent Advances in Asymmetric Catalysis in Flow. *ACS Catalysis* **2013**; *3* (5): 928-44.

10. Pastre JC; Browne DL; Ley SV, Flow chemistry syntheses of natural products. *Chemical Society Reviews* **2013**; *42* (23): 8849-69.

11. Wiles C; Watts P, Continuous process technology: a tool for sustainable production. *Green Chemistry* **2014**; *16* (1): 55-62.

12. Munirathinam R; Huskens J; Verboom W, Supported Catalysis in Continuous-Flow Microreactors. *Advanced Synthesis & Catalysis* **2015**; *357* (6): 1093-123.

13. Atodiresei I; Vila C; Rueping M, Asymmetric Organocatalysis in Continuous Flow: Opportunities for Impacting Industrial Catalysis. *ACS Catalysis* **2015**; *5* (3): 1972-85.

14. Ayats C; Henseler AH; Pericàs MA, A Solid-Supported Organocatalyst for Continuous-Flow Enantioselective Aldol Reactions. *ChemSusChem* **2012**; *5* (2): 320-5.

15. Bogdan A; McQuade DT, A biphasic oxidation of alcohols to aldehydes and ketones using a simplified packed-bed microreactor. *Beilstein Journal of Organic Chemistry* **2009**; *5*: 17.

16. Calogero S; Lanari D; Orrù M; Piermatti O; Pizzo F; Vaccaro L, Supported l-proline on zirconium phosphates methyl and/or phenyl phosphonates as heterogeneous organocatalysts for direct asymmetric aldol addition. *Journal of Catalysis* **2011**; *282* (1): 112-9.

17. Gruttadauria M; Giacalone F; Noto R, Supported proline and proline-derivatives as recyclable organocatalysts. *Chemical Society Reviews* **2008**; *37* (8): 1666-88.

18. Kristensen TE; Vestli K; Fredriksen KA; Hansen FK; Hansen T, Synthesis of Acrylic Polymer Beads for Solid-Supported Proline-Derived Organocatalysts. *Organic Letters* **2009**; *11* (14): 2968-71.

19. Kristensen TE; Vestli K; Jakobsen MG; Hansen FK; Hansen T, A General Approach for Preparation of Polymer-Supported Chiral Organocatalysts via Acrylic Copolymerization. *The Journal of Organic Chemistry* **2010**; *75* (5): 1620-9.

20. Lazar A; Sharma P; Singh AP, Chiral VIVO-Sal-Indanol complex over modified SBA-15: An efficient, reusable enantioselective catalyst for asymmetric sulfoxidation reaction. *Microporous and Mesoporous Materials* **2013**; *170*: 331-9.

21. Liu J; Li P; Zhang Y; Ren K; Wang L; Wang G, Recyclable Merrifield resin-supported organocatalysts containing pyrrolidine unit through A3-coupling reaction linkage for asymmetric Michael addition. *Chirality* **2010**; *22* (4): 432-41.

22. Miao T; Wang L, Polystyrene-immobilized pyrrolidine as a highly stereoselective and recyclable organocatalyst for asymmetric Michael addition of cyclohexanone to nitroolefins. *Tetrahedron Letters* **2008**; *49* (13): 2173-6.

23. Klier L; Tur F; Poulsen PH; Jørgensen KA, Asymmetric cycloaddition reactions catalysed by diarylprolinol silyl ethers. *Chemical Society Reviews* **2017**; *46* (4): 1080-102.

24. Shylesh S; Zhou Z; Meng Q; Wagener A; Seifert A; Ernst S; Thiel WR, Sustainable, green protocols for heterogenized organocatalysts: N-Phenylthiazolium salts heterogenized on organic–inorganic hybrid mesoporous supports. *Journal of Molecular Catalysis A: Chemical* **2010**; *332* (1): 65-9.

25. Yan J; Wang L, Merrifield Resin Supported Dipeptides: Efficient and Recyclable Organo-catalysts for Asymmetric Aldol Reactions under Neat Reaction Conditions. *Synthesis* **2008**; *2008* (13): 2065-72.

26. Zhang L; Cui L; Luo S; Cheng J-P, *Green Techniques for Organic Synthesis and Medicinal Chemistry*. John Wiley & Sons Ltd.: 2012.

27. Kasaplar P; Riente P; Hartmann C; Pericàs MA, A Polystyrene-Supported, Highly Recyclable Squaramide Organocatalyst for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitrostyrenes. *Advanced Synthesis & Catalysis* **2012**; *354* (16): 2905-10.

28. Osorio-Planes L; Rodríguez-Escrich C; Pericàs MA, Polystyrene-Supported (2S)-(−)-3-exo-Piperazinoisoborneol: An Efficient Catalyst for the Batch and Continuous Flow Production of Enantiopure Alcohols. *Organic Letters* **2012**; *14* (7): 1816-9.

29. Martín-Rapún R; Sayalero S; Pericàs MA, Asymmetric anti-Mannich reactions in continuous flow. *Green Chemistry* **2013**; *15* (12): 3295-301.

30. Kasaplar P; Rodríguez-Escrich C; Pericàs MA, Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide. *Organic Letters* **2013**; *15* (14): 3498-501.

31. Fan X; Rodríguez-Escrich C; Sayalero S; Pericàs MA, Paraldehyde as an Acetaldehyde Precursor in Asymmetric Michael Reactions Promoted by Site-Isolated Incompatible Catalysts. *Chemistry – A European Journal* **2013**; *19* (33): 10814-7.

32. Osorio-Planes L; Rodríguez-Escrich C; Pericàs MA, Enantioselective Continuous-Flow Production of 3-Indolylmethanamines Mediated by an Immobilized Phosphoric Acid Catalyst. *Chemistry – A European Journal* **2014**; *20* (8): 2367-72.

33. Sagamanova I; Rodríguez-Escrich C; Molnár IG; Sayalero S; Gilmour R; Pericàs MA, Translating the Enantioselective Michael Reaction to a Continuous Flow Paradigm with an Immobilized, Fluorinated Organocatalyst. *ACS Catalysis* **2015**; *5* (11): 6241-8.

34. Kasaplar P; Ozkal E; Rodríguez-Escrich C; Pericàs MA, Enantioselective α-amination of 1,3-dicarbonyl compounds in batch and flow with immobilized thiourea organocatalysts. *Green Chemistry* **2015**; *17* (5): 3122-9.

35. Izquierdo J; Ayats C; Henseler AH; Pericàs MA, A polystyrene-supported 9-amino(9-deoxy)epi quinine derivative for continuous flow asymmetric Michael reactions. *Organic & Biomolecular Chemistry* **2015**; *13* (14): 4204-9.

36. Izquierdo J; Pericàs MA, A Recyclable, Immobilized Analogue of Benzotetramisole for Catalytic Enantioselective Domino Michael Addition/Cyclization Reactions in Batch and Flow. *ACS Catalysis* **2016**; *6* (1): 348-56.

37. Osorio-Planes L; Rodríguez-Escrich C; Pericàs MA, Removing the superfluous: a supported squaramide catalyst with a minimalistic linker applied to the enantioselective flow synthesis of pyranonaphthoquinones. *Catalysis Science & Technology* **2016**; *6* (13): 4686-9.

38. Llanes P; Sayalero S; Rodríguez-Escrich C; Pericàs MA, Asymmetric cross- and self-aldol reactions of aldehydes in water with a polystyrene-supported triazolylproline organocatalyst. *Green Chemistry* **2016**; *18* (12): 3507-12.

39. Clot-Almenara L; Rodríguez-Escrich C; Osorio-Planes L; Pericàs MA, Polystyrene-Supported TRIP: A Highly Recyclable Catalyst for Batch and Flow Enantioselective Allylation of Aldehydes. *ACS Catalysis* **2016**; *6* (11): 7647-51.

40. Cañellas S; Ayats C; Henseler AH; Pericàs MA, A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow. *ACS Catalysis* **2017**; *7* (2): 1383-91.

41. Rodríguez-Escrich C; Pericàs MA, Catalytic Enantioselective Flow Processes with Solid-Supported Chiral Catalysts. *The Chemical Record* **2019**; *19* (9): 1872-90.

42. Parvin MN; Jin H; Ansari MB; Oh S-M; Park S-E, Imidazolium chloride immobilized SBA-15 as a heterogenized organocatalyst for solvent free Knoevenagel condensation using microwave. *Applied Catalysis A: General* **2012**; *413-414*: 205-12.

43. Shanmuganathan S; Greiner L; Domínguez de María P, Silica-immobilized piperazine: A sustainable organocatalyst for aldol and Knoevenagel reactions. *Tetrahedron Letters* **2010**; *51* (50): 6670-2.

44. Somanathan R; Flores-López LZ; Chávez D; Parra-Hake M; Aguirre G, Immobilized organocatalysts and their application in asymmetric aldol reaction. *Current Topics in Catalysis* **2012**; *10*: 1-16.

45. Zhang H; Zou Y; Wang Y-M; Shen Y; Zheng X, Asymmetric Epoxidation of cis/trans-β-Methylstyrene Catalysed by Immobilised Mn(Salen) with Different Linkages: Heterogenisation of Homogeneous Asymmetric Catalysis. *Chemistry – A European Journal* **2014**; *20* (25): 7830-41.

46. Gleeson O; Davies G-L; Peschiulli A; Tekoriute R; Gun'ko YK; Connon SJ, The immobilisation of chiral organocatalysts on magnetic nanoparticles: the support particle cannot always be considered inert. *Organic & Biomolecular Chemistry* **2011**; *9* (22): 7929-40.

47. Polshettiwar V; Baruwati B; Varma RS, Magnetic nanoparticle-supported glutathione: a conceptually sustainable organocatalyst. *Chemical Communications* **2009**; (14): 1837-9.

48. Pourjavadi A; Hosseini SH; Hosseini ST; Aghayeemeibody SA, Magnetic nanoparticles coated by acidic functionalized poly(amidoamine) dendrimer: Effective acidic organocatalyst. *Catalysis Communications* **2012**; *28*: 86-9.

49. Riente P; Mendoza C; Pericás MA, Functionalization of Fe3O4 magnetic nanoparticles for organocatalytic Michael reactions. *Journal of Materials Chemistry* **2011**; *21* (20): 7350-5.

50. Riente P; Yadav J; Pericàs MA, A Click Strategy for the Immobilization of MacMillan Organocatalysts onto Polymers and Magnetic Nanoparticles. *Organic Letters* **2012**; *14* (14): 3668-71.

51. Schätz A; Grass RN; Stark WJ; Reiser O, TEMPO Supported on Magnetic C/Co-Nanoparticles: A Highly Active and Recyclable Organocatalyst. *Chemistry – A European Journal* **2008**; *14* (27): 8262-6.

52. Yacob Z; Nan A; Liebscher J, Proline-Functionalized Magnetic Core-Shell Nanoparticles as Efficient and Recyclable Organocatalysts for Aldol Reactions. *Advanced Synthesis & Catalysis* **2012**; *354* (17): 3259-64.

53. Tan R; Li C; Luo J; Kong Y; Zheng W; Yin D, An effective heterogeneous l-proline catalyst for the direct asymmetric aldol reaction using graphene oxide as support. *Journal of Catalysis* **2013**; *298*: 138-47.

54. Srivastava V; Gaubert K; Pucheault M; Vaultier M, Organic–Inorganic Hybrid Materials for Enantioselective Organocatalysis. *ChemCatChem* **2009**; *1* (1): 94-8.

55. Miranda PO; Lizandara-Pueyo C; Pericàs MA, Potassium fluoride: A convenient, non-covalent support for the immobilization of organocatalysts through strong hydrogen bonds. *Journal of Catalysis* **2013**; *305*: 169-78.

56. Zhang L; Luo S; Cheng J-P, Non-covalent immobilization of asymmetric organocatalysts. *Catalysis Science & Technology* **2011**; *1* (4): 507-16.

57. Szőllősi G, Asymmetric one-pot reactions using heterogeneous chemical catalysis: recent steps towards sustainable processes. *Catalysis Science & Technology* **2018**; *8* (2): 389-422.

58. Molnár Á; Papp A, Catalyst recycling—A survey of recent progress and current status. *Coordination Chemistry Reviews* **2017**; *349*: 1-65.

59. Hench LL; West JK, The sol-gel process. *Chemical Reviews* **1990**; *90* (1): 33-72.

60. Navrotsky A, Energetic clues to pathways to biomineralization: Precursors, clusters, and nanoparticles. *Proceedings of the National Academy of Sciences of the United States of America* **2004**; *101* (33): 12096.

61. Mann S; Heywood BR; Rajam S; Birchall JD, Controlled crystallization of CaCO3 under stearic acid monolayers. *Nature* **1988**; *334* (6184): 692-5.

62. Lu J; Bravo-Suárez JJ; Haruta M; Oyama ST, Direct propylene epoxidation over modified Ag/CaCO3 catalysts. *Applied Catalysis A: General* **2006**; *302* (2): 283-95.

63. Kurapati R; Raichur AM, Composite cyclodextrin–calcium carbonate porous microparticles and modified multilayer capsules: novel carriers for encapsulation of hydrophobic drugs. *Journal of Materials Chemistry B* **2013**; *1* (25): 3175-84.

64. Fan X; Sayalero S; Pericàs MA, Asymmetric α-Amination of Aldehydes Catalyzed by PS-Diphenylprolinol Silyl Ethers: Remediation of Catalyst Deactivation for Continuous Flow Operation. *Advanced Synthesis & Catalysis* **2012**; *354* (16): 2971-6.

65. Belser T; Stöhr M; Pfaltz A, Immobilization of Rhodium Complexes at Thiolate Monolayers on Gold Surfaces: Catalytic and Structural Studies. *Journal of the American Chemical Society* **2005**; *127* (24): 8720-31.

66. Alza E; Pericàs MA, A Highly Selective, Polymer-Supported Organocatalyst for Michael Additions with Enzyme-Like Behavior. *Advanced Synthesis & Catalysis* **2009**; *351* (18): 3051-6.

67. Kolb HC; Finn MG; Sharpless KB, Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angewandte Chemie International Edition* **2001**; *40* (11): 2004-21.

68. Meldal M; Tornøe CW, Cu-Catalyzed Azide−Alkyne Cycloaddition. *Chemical Reviews* **2008**; *108* (8): 2952-3015.

69. Vidal-Ferran A; Bampos N; Moyano A; Pericàs MA; Riera A; Sanders JKM, High Catalytic Activity of Chiral Amino Alcohol Ligands Anchored to Polystyrene Resins. *The Journal of Organic Chemistry* **1998**; *63* (18): 6309-18.

70. Ahmed J; Menaka; Ganguli AK, Controlled growth of nanocrystalline rods, hexagonal plates and spherical particles of the vaterite form of calcium carbonate. *CrystEngComm* **2009**; *11* (5): 927-32.

71. Beuvier T; Calvignac B; Delcroix GJ-R; Tran MK; Kodjikian S; Delorme N; Bardeau J-F; Gibaud A; Boury F, Synthesis of hollow vaterite CaCO3 microspheres in supercritical carbon dioxide medium. *Journal of Materials Chemistry* **2011**; *21* (26): 9757-61.

72. Fricke M; Volkmer D; Krill CE; Kellermann M; Hirsch A, Vaterite Polymorph Switching Controlled by Surface Charge Density of an Amphiphilic Dendron-calix[4]arene. *Crystal Growth & Design* **2006**; *6* (5): 1120-3.

73. He L; Xue R; Song R, Formation of calcium carbonate films on chitosan substrates in the presence of polyacrylic acid. *Journal of Solid State Chemistry* **2009**; *182* (5): 1082-7.

74. Qi L; Li J; Ma J, Biomimetic Morphogenesis of Calcium Carbonate in Mixed Solutions of Surfactants and Double-Hydrophilic Block Copolymers. *Advanced Materials* **2002**; *14* (4): 300-3.

75. Xiao J; Wang Z; Tang Y; Yang S, Biomimetic Mineralization of CaCO3 on a Phospholipid Monolayer: From an Amorphous Calcium Carbonate Precursor to Calcite via Vaterite. *Langmuir* **2010**; *26* (7): 4977-83.

76. Imai H; Tochimoto N; Nishino Y; Takezawa Y; Oaki Y, Oriented Nanocrystal Mosaic in Monodispersed CaCO3 Microspheres with Functional Organic Molecules. *Crystal Growth & Design* **2012**; *12* (2): 876-82.

77. Wang X; Wu C; Tao K; Zhao K; Wang J; Xu H; Xia D; Shan H; Lu JR, Influence of Ovalbumin on CaCO3 Precipitation during in Vitro Biomineralization. *The Journal of Physical Chemistry B* **2010**; *114* (16): 5301-8.

78. Xiao J; Yang S, Polymorphic and morphological selection of CaCO3 by magnesium-assisted mineralization in gelatin: magnesium-rich spheres consisting of centrally aligned calcite nanorods and their good mechanical properties. *CrystEngComm* **2011**; *13* (7): 2472-8.

79. Yan X; Li J; Möhwald H, Templating Assembly of Multifunctional Hybrid Colloidal Spheres. *Advanced Materials* **2012**; *24* (20): 2663-7.

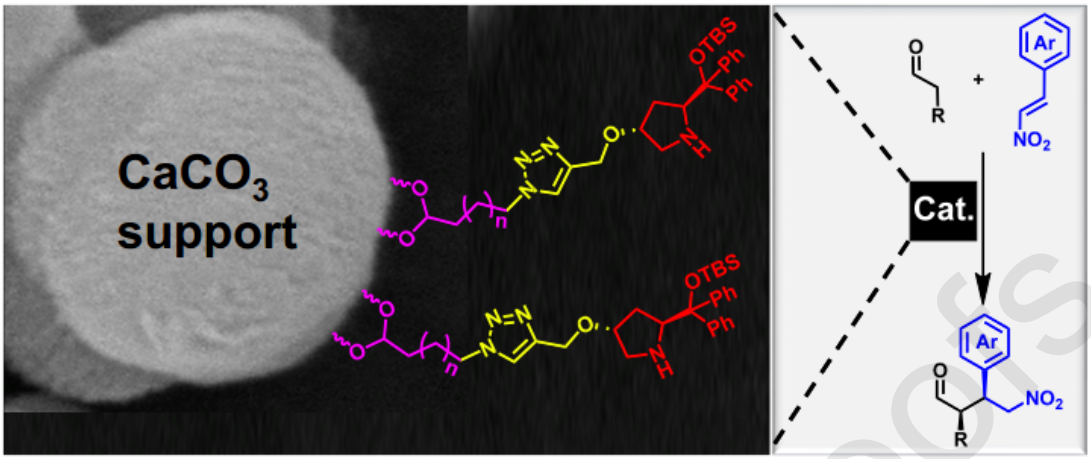
80. Yashchenok A; Parakhonskiy B; Donatan S; Kohler D; Skirtach A; Möhwald H, Polyelectrolyte multilayer microcapsules templated on spherical, elliptical and square calcium carbonate particles. *Journal of Materials Chemistry B* **2013**; *1* (9): 1223-8.

81. Sarkar A; Ghosh AK; Mahapatra S, Lauric acid triggered in situ surface modification and phase selectivity of calcium carbonate: its application as an oil sorbent. *Journal of Materials Chemistry* **2012**; *22* (22): 11113-20.

82. Zhao Y; Zhou H; Chen W; Tong Y; Zhao C; Lin Y; Jiang Z; Zhang Q; Xue Z; Cheong W-C; Jin B; Zhou F; Wang W; Chen M; Hong X; Dong J; Wei S; Li Y; Wu Y, Two-Step Carbothermal Welding To Access Atomically Dispersed Pd1 on Three-Dimensional Zirconia Nanonet for Direct Indole Synthesis. *Journal of the American Chemical Society* **2019**; *141* (27): 10590-4.

83. Laura C; Biagia M; Leonardo D; Giuseppe R; Renzo L, Microreactor-Mediated Organocatalysis: Towards the Development of Sustainable Domino Reactions. *Journal of Flow Chemistry* **2013**; *3* (2): 29-33.

Graphical abstract



Highlights:

--The $CaCO_3$ particles are evaluated in the heterogenization of homogeneous asymmetric catalysts for the first time.

--The $CaCO_3$-supported Jørgensen-Hayashi catalysts are developed for asymmetric Michael additions.

--Recycling of $CaCO_3$ heterogeneous catalysts are achieved by condition optimization.

--$CaCO_3$ heterogeneous catalysts are adapted in catalytic continuous flow processes.