Journal of Catalysis 282 (2011) 112–119

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Supported L-proline on zirconium phosphates methyl and/or phenyl phosphonates as heterogeneous organocatalysts for direct asymmetric aldol addition

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ARTICLE INFO

Article history:
Received 15 March 2011
Revised 5 May 2011
Accepted 2 June 2011
Available online 7 July 2011

Keywords:
Chiral heterogeneous catalysts
Supported L-proline
Zirconium phosphates
Aldol addition
Aqueous medium

ABSTRACT

Zirconium phosphates methyl and/or phenyl phosphonates-supported L-proline have been prepared as amorphous solids by precipitation of (*4R*)-4-(phosphonooxy)-L-proline, methyl and/or phenyl phosphonic acid with $ZrOCl_2$. The supported L-proline catalysts were tested on the direct asymmetric aldol addition of cyclohexanone to *p*-nitrobenzaldehyde in DMF/H_2O (9:1) and in sole water. The hydrophobic groups on solid surface favor reagents' diffusion toward proline chiral moiety increasing the catalytic activity of supported L-proline. High diastereoselectivity (*anti/syn* up to 94:6) and high enantiomeric excess up to 97% have been obtained.

1. Introduction

In recent years, significant achievements in the area of solid-phase chemistry have resulted in an enormous progress on the interdisciplinary research devoted to stereoselective heterogeneous catalysis [1]. While homogeneous catalysts may boast a higher activity and selectivity, potential advantages of heterogeneous catalysis, such as easier product isolation, efficient catalyst recycling, minimization of metal traces in the product, and improved process control, are recognized to be very effective in reducing the cost of a chemical transformation. Benefits of both homogeneous and heterogeneous catalysis should be combined to reach the overall highest efficiency [2].

Although not fully understood, the support plays an important role in determining the accessibility to the active sites, and therefore, it crucially influences the course of an enantioselective transformation [3]. In this concern, several different approaches have been explored, including the use of organic polymers, porous inorganic oxides, dendrimers, membrane supports, aqueous biphasic systems, and ionic liquids [1–4]. Recently, a new class of hybrid organic–inorganic material prepared from organic linkers and metal nodes has received great attention since they are synthesized under mild conditions and in principle allow to incorporate and fine-tuning the desired chemical and physical properties by a judicious choice of the building blocks [5].

In addition, the application of inorganic materials as heterogeneous supports offers a numbers of advantages: their rigid structure does not allow the aggregation of active catalysts, they do not swell and are insoluble in organic solvents and water [6]. Inorganic supports possess better thermal and mechanical stability under catalysis conditions. Among these, the class of zirconium phosphate and/or phosphonates represents a valid choice thanks to their interesting physical–chemical properties and high versatility [7]. The layered inorganic backbone of this compounds may be considered as a hook onto which organic groups with different functionality may be attached (e.g. acidic, basic, polar, and hydrophobic), allowing to control both the reactivity and selectivity of the organic process [7,8]. These materials can be easily prepared by a self-assembly approach, and since they are insoluble in water and organic solvents they can be easily recovered and reused [7–9]. Only a few papers report the use of zirconium phosphonate, as a solid support for chiral ligands [3a,5a,8a,10,11]. Zirconium phosphate containing chiral functionalities such as BINOL or BINAP has been prepared, and the amorphous materials have been efficiently used as heterogeneous catalysts in the stereoselective addition of diethylzinc to benzaldehyde, aldol condensation, hydrogenation of aromatic ketones and of β-keto esters [10a–10c]. Cinconidine with different arm lengths was covalently immobilized onto the backbone of zirconium phosphate to afford mesoporous materials that were used in the stereoselective addition of diethylzinc to aldehydes [10d]. Zirconium phosphonates have been used for the preparation of supported oxidation catalysts by the immobilization of Mn(III) phorphyrins [10e] and chiral salen Mn(III) complex [10f]. Chiral borane of layered α-zirconium-N-(*m*-solfophenyl)-L-valine-phosphonate

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doi:10.1016/j.jcat.2011.06.004

methanphosphonate has been used in the asymmetric Mukaiyama aldol reaction [8a].

On the other hand, organic catalysts have attracted the interest of chemists since they are water and air tolerant and offer mild, practical and generally simple method. In this context, L-proline and its derivative have been widely used as organic catalysts for a wide range of enantioselective transformations [12], in particular asymmetric aldol [13], Michael [14], Mannich [15], α-amination [16], Diels–Alder [17], Baylis–Hillman [18] reactions.

Also, proline and its derivatives have been immobilized [19] onto various types of materials, and several examples are reported in the literature: poly-(ethylene glycol)-supported proline [20], polystyrene-supported proline [21], and L-proline supported on mesoporous materials [22]. Alternative strategies involve (i) simple physisorpion of L-proline on γ-Al_2O_3 [23], (ii) ion-exchange method: L-proline has been intercalated into layered materials such as double hydroxides (LDH) [24], hydrotalcite clays [25] or layered montmorillonites (MMT) [26], and (iii) the use of supported ionic liquid phase for L-proline recycling [27].

According to the urgent needs for a more environmentally responsible chemistry, alternative reaction media are currently taking a leading role in the development of efficient and cleaner organic chemistry. Among the alternative reaction media, water is one of the most intriguing due to its peculiar properties. It is known that water used as substoichiometric additive or in large excess (as reaction medium) plays an important role in the development of new synthetic processes both by improving the chemical efficiency and reducing the environmental impact [28].

Recently, we have been involved in the development of novel solid catalysts to be used in benign reaction media for the definition of chemically and environmentally efficient organic processes [8b–8d,29,30]. We reported the preparation and characterization of new amorphous zirconium hydrogen phosphate alkyl and/or aryl phosphonates of general formula $Zr(PO_3OH)_{2-(x+y)}(PO_3R)_x(PO_3R^1)_y$ (with R = R^1 = Me, Ph, Pr or R = Me R^1 = Ph) [8d]. The presence of hydrophobic groups as Me, Ph, and Pr is associated with a high micro- and mesopore volume and an extraordinary specific surface area (200–380 m^2/g). They efficiently catalyze (conversion up 99%) the direct aza-Diels–Alder reaction of 2-cyclohexen-1-one with N-PMP-*p*Cl-benzaldimine in water without any additive [8d].

Based on this excellent result, we have decided to use, for the first time, zirconium phosphate as inorganic support for the immobilization of a covalently linked chiral organic catalyst based on L-proline moiety. The L-proline functionalized phosphate/phosphonates have been prepared as amorphous solids by using the self-assembly approach. The catalytic activity has been modulated by inserting different hydrophobic R group (R = Me, Ph) on solid surface in order to steer the reagents toward the proline catalytic site.

In this paper, we report the preparation of these novel L-proline-based solid catalysts and the results obtained by testing their catalytic activity in the aldol addition of cyclohexanone to *p*-nitro-benzaldehyde in DMF/H_2O 9:1 and in sole water as reaction media.

2. Experimental

2.1. General remarks

All chemicals were purchased and used without any further purification. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded at 400 MHz, 100.6, and 161.9 MHz, respectively. TG and DTA analysis were performed by STA 449 C Jupiter (thermal analyzer). P and Zr elementary analysis were performed by Inductively Coupled Plasma-Optical Emission Spectrometers (ICP-OES). C, H, N elementary analysis were performed by EA1108 CHN Fison Instruments. Nitrogen adsorption–desorption isotherms [31] were determined with a Micromeritics ASAP 2010 instrument at 77 K on samples outgassed overnight at 373 K. The specific surface area was calculated by B.E.T. method [32]. Micropore volume and external surface area were evaluated by *t*-plot [33] method using non-porous α-ZrP as reference material [34]. Mesopore characterization has been performed by Barrett, Joyner, Halenda method [35]. Centrifugation was performed at 12,000 rpm for 15 min. Thin-layered chromatography analysis was performed on silica gel on aluminum plates (Silica gel 60 F_{254}, Fluka). Column chromatographies to purify the aldol products were performed by using silica gel 230–400 mesh (Silica gel 60, Merk) eluting with petroleum ether/ethyl acetate 80:20.

The *anti*/*syn* ratio was determined by ^{1}H NMR of crude product in $CDCl_3$; C*H*OH δ: syn 5.48 ppm, *J* = 2.2 Hz; *anti*: 4.90 ppm, *J* = 8.4 Hz. The enantiomeric excess (*ee%*) was determined by chiral HPLC analysis with CHIRALPACK AD-H, eluting with *n*-hexane/isopropanol 75:25, flow rate 0.5 mL/min and UV detector (λ = 264 nm): T_R 20.9 min (*anti* minor), T_R 26.3 min (*anti* major). The major product had (2*S*,1′*R*) absolute stereochemistry in accord with L-proline catalyzed aldol addition [13,21b].

2.2. Synthesis of (4*R*)-4-phosphonooxy-L-proline

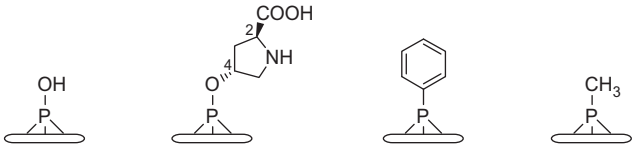
In a flask of 500 mL equipped with a traps for the HCl, under stirring and N_2 atmosphere, $POCl_3$ (23 mL, 0.25 mol) was added dropwise over a period of 1 h to 9 mL of water (0.5 mol). During the addition, the temperature was kept under 25 °C. After 30 min, the *trans*-4-hydroxy-L-proline (6.55 g, 0.05 mol) was added at 60 °C, under stirring, in 15 min and the mixture was stirred at 60 °C for 2 h. After cooling to r.t., water (3.6 mL) and HCl 1 N (15 mL) were added. The mixture was heated at 100 °C for 20 min under N_2, and then, in sequence, ethanol (60 mL) and diethyl ether (200 mL) were slowly added with the formation of a white suspension. The flask was allowed to stand overnight at 4 °C, and a viscous oil was separated at the bottom of the flask. The supernatant was removed, 20 mL of ethanol was added, and magnetic stirring was kept until a finely dispersed solid was obtained. The solid (4*R*)-4-phosphonooxy-L-proline was separated from ethanol by centrifugation, dried under reduced pressure and then purified by leaving it under magnetic stirring for 4 days in ethanol/water 60:2 solution. The solvent was removed by centrifugation, the solid (4*R*)-4-phosphonooxy-L-proline washed twice with ethanol to remove the traces of water and finally dried under reduced pressure (7.1 g, 68% yield).

White solid, mp 160–165 °C, $[\alpha]_D$ – 26.1 (*c* = 1.2, H_2O); ^{1}H NMR (400 MHz, D_2O) δ: 2.06 (ddd, 1H, C_3HH, *J* = 14.4, 10.6, 4.2 Hz), 2.45 (ddd, 1H, C_3HH, *J* = 14.4, 7.9, 1.2 Hz), 3.33 (ABX system, 2H, H_5), 4.36 (dd, 1H, H_2, *J* = 10.6, 7.9), 4.73 (m, 1H, H_4); ^{13}C NMR (100.6 MHz, D_2O) δ: 36.1 (d, C_3, *J* = 4.1), 52.5 (d, C_5, *J* = 5.2), 58.4 (s, C_2), 74.0 (d, C_4, *J* = 4.8), 171.8 (s, COOH); ^{31}P NMR (200 MHz, D_2O) δ: – 1.2 ppm.

2.3. General procedure for preparation of L-proline functionalized zirconium phosphate/phosphonates

A $ZrOCl_2$ aqueous solution (2 mmol in 4 mL of water) was slowly added, under stirring, at r.t. to an aqueous solution of (4*R*)-4-phosphonooxy-L-proline and methyl and/or phenylphosphonic acids (6 mmol in 18 mL of water). The molar ratio between phosphoric acid and phosphonic acid used during the preparation is reported in Table 2. The preparation conditions were as follows: molar ratio P/Zr^{IV} = 3, precipitation temperature 25 °C, precipitation time 15 h. The obtained L-proline functionalized zirconium phosphate/phosphonates were separated from aqueous medium

Table 1
The ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectral data of solids **CAT1**, **CAT2**, and **CAT3**.[a]



	^{1}H NMR				^{13}C NMR				^{31}P NMR
	H	Molt.	δ (ppm)	J (Hz)	C	Molt.	δ (ppm)	J (Hz)	δ (ppm)
P-OH	–	–	–	–	–	–	–	–	0.0
P-Prol	$C_{(3)}HH$	ddd	2.02	14.5, 10.5, 4.1	C_3	d	35.5	3.8	−1.3
	$C_{(3)}HH$	dd	2.38	14.5, 7.9	C_5	d	52.2	5.4	
	$C_{(5)}H_2$	ABX	3.26	–	C_2	s	57.7	–	
	H_2	dd	4.33	10.5, 7.9	C_4	s	74.7	–	
	H_4	m	4.69	–	COOH	s	170.5	–	
P-C_6H_5	H_3, H_5	m	7.19	–	C_3, C_5	d	128.3	15.0	17.4
	H_4	t	7.27	7.4	C_2, C_6	d	130.1	10.6	
	H_2, H_6	dd	7.43	13.6, 8.0	C_4	d	132.1	2.9	
					C_1	d	129.8	183.8	
P-Me	CH_3	d	1.15	17.4	CH_3	d	11.2	134.4	30.8

[a] Recorded in D_2O/HF solution.

by centrifugation, washed with water (4 × 100 mL), and finally dried at 80 °C for 24 h.

Table 1 reports the ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectral data of L-proline-based solid catalysts.

2.4. General procedure for aldol addition with catalyst *CAT3*

In a 2-mL vial, DMF/H_2O (9:1) solution (200 μL) or water (150 μL) was added to 4-nitrobenzaldehyde (18.9 mg, 0.125 mmol) and catalyst **CAT3** (27.5 mg, 0.062 mmol of solid catalyst, 0.0375 mmol of P-Prol groups (30 mol%)). The mixture was stirred for 10 min at r.t., and then, cyclohexanone (64.5 μL, 0.625 mmol, 5 equiv.) was added. The mixture was left under stirring for 4 days at 30 °C and then diluted with water. The products were extracted with ethyl acetate (3 × 1 mL). The organic phase was separated by centrifugation, and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude products were purified by column chromatography eluting with petroleum ether/ethyl acetate 80:20.

3. Results and discussion

3.1. Catalysts preparation and characterization

The preparation of zirconium phosphate and phosphonates is closely related to the methods employed for the preparation of α-$Zr(HPO_4)_2{\cdot}H_2O$ (α-ZrP), i.e. refluxing the amorphous precipitates in phosphoric or phosphonic acid solutions, or by precipitation of an aqueous solution containing the suitable phosphoric or phosphonic acids with $ZrOCl_2$ in presence of hydrofluoridric acid. These organic–inorganic materials have a layered structure similarly to α-ZrP; amorphous materials can be obtained by direct precipitation in the absence of hydrofluoridric acid. It is possible to vary the acid properties of the phosphates from neutral (e.g. P-CH_3) or weak acid (e.g. P-CH_2COOH) to strong acid (e.g. P-$C_6H_4SO_3H$) or even to basic (e.g. P-$C_2H_4NH_2$), or to anchor chiral ligands [8a,10,11]. The only limitation to the synthesis is the use of organic groups with a cross section equal to or less than 24 Å^2. This is the free area around each phosphorous atom on the surface of the layers. However, more voluminous groups may be attached to the α-layers if their dimensions are compensated by introducing a small group R′ (R′ being H, OH, CH_3) to obtain bifunctional compounds of formula $Zr(PO_3R)_{2-x}(PO_3R')_x$ [7b,36].

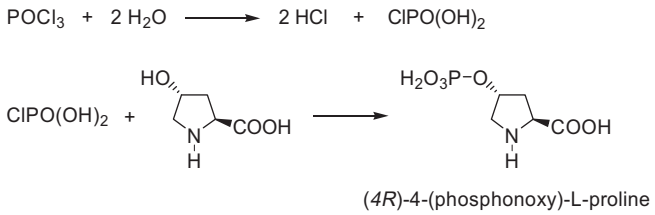
With the aim to obtain new and efficient chiral heterogeneous catalyst and to understand the role of support on the stereoselectivity of the aldol addition reaction, in this work, we have prepared new zirconium phosphate/phosphonates-supported L-proline by direct amorphous precipitation of suitable phosphoric and/or phosphonic acid with $ZrClO_2$ (P/Zr^{IV} = 3).

(4*R*)-4-(Phosphonooxy)-L-proline is the alkyl phosphoric acid chosen for the preparation of zirconium phosphate/phosphonates-supported L-proline. It has been synthesized by treatment of *trans*-4-hydroxy-L-proline with chloro-phosphonic acid, prepared *in situ* from PO_3Cl_3 and water according to a procedure described for the preparation of phosphoserine [37] (Scheme 1). The ^{31}P NMR spectra of the product showed only one detectable signal at –1.2 ppm, typical for a phosphate monoester group [38], highlighting that the phosphorylation was highly O-selective.

Three different functionalized zirconium phosphates methyl and/or phenylphosphonates have been prepared from: (i) (4*R*)-4-(phosphonooxy)-L-proline and methylphosphonic acid (1:1); (ii) (4*R*)-4-(phosphonooxy)-L-proline and phenylphosphonic acid (1:1); (iii) (4*R*)-4-(phosphonooxy)-L-proline, methylphosphonic and phenylphosphonic acids (1:1:1).

Table 2
Chemical and surface properties of prepared solids **CAT1–3**.

Solid	R	P-Prol/P-R solution molar ratio	P-Prol/P-R solid molar ratio	Molecular formula	P/Zr molar ratio	MW (u)	B.E.T. surface area (m^2/g)
CAT1	Me	1/1	1/1.2	$Zr(PO_3\text{-}OC_5H_8O_2N)_{0.93}(PO_3Me)_{1.15}{\cdot}1.5H_2O$	2.08	420.7	2.4
CAT2	Ph	1/1	1/1.2	$Zr(PO_3\text{-}OC_5H_8O_2N)_{1.02}(PO_3Ph)_{1.23}{\cdot}1.6H_2O$	2.25	525.1	5.2
CAT3	Ph, Me	1/1/1	1/1.5/1.1	$Zr(PO_3\text{-}OC_5H_8O_2N)_{0.60}(PO_3Ph)_{0.92}(PO_3Me)_{0.66}{\cdot}0.9H_2O$	2.19	439.3	4.1



Scheme 1. Synthesis of (4*R*)-4-(phosphonooxy)-L-proline.

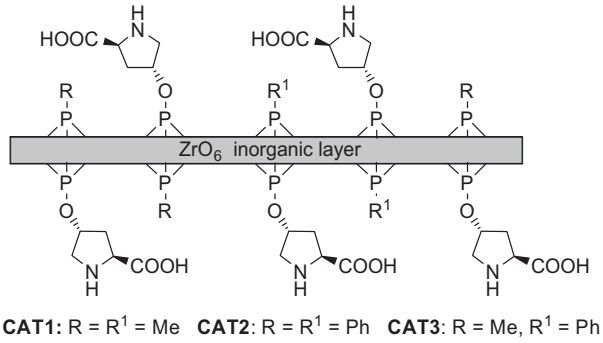


Fig. 1. Schematic arrangement of phosphate and phosphonate groups on the layer of L-proline functionalized zirconium phosphate methyl and/or phenyl phosphonates.

The obtained solids **CAT1, CAT2, CAT3** have been characterized by ^{1}H NMR, ^{13}C NMR and ^{31}P NMR, TG DTA, ICP-OES and by nitrogen adsorption–desorption isotherms at 77 K analysis.

Table 2 reports the molar ratio between phosphoric and phosphonic acid used during the preparation, the molar ratio between phosphonate groups (P-R, R = Me and/or Ph) and L-proline phosphate group (P-Prol) in the solid with the molecular formula and molecular weight, the Zr/P molar ratio and the calculated B.E.T. surface area. Fig. 1 shows the schematic arrangement of phosphate and phosphonate groups on the layer of L-proline functionalized zirconium phosphate methyl and/or phenylphosphonates.

The molecular formulas were obtained by thermogravimetric (TG) and differential thermal analysis (DTA) curves and P-Prol/P-R molar ratio determined by ^{31}P NMR analysis. As a representative example, the TG–DTA curves of catalyst **CAT3** are reported in Fig. 2. Thermal decomposition occurs in two steps: the first, between 50 and 180 °C, corresponds to the loss of 3.6% of the initial weight and is due to the water of crystallization, the second, between 180 and 1000 °C, corresponds to the loss of 36% of the initial weight and is due to the oxidation of the organic groups. At 1000 °C, the formation of cubic ZrP_2O_7 is considered, as shown by the XRPD spectrum of a sample heated at 1000 °C (data not shown). These data together with the P-Prol/P-Ph/P-Me molar ratio (1:1.5:1.1) allow to obtain the molecular formula of solid **CAT3** (Table 2).

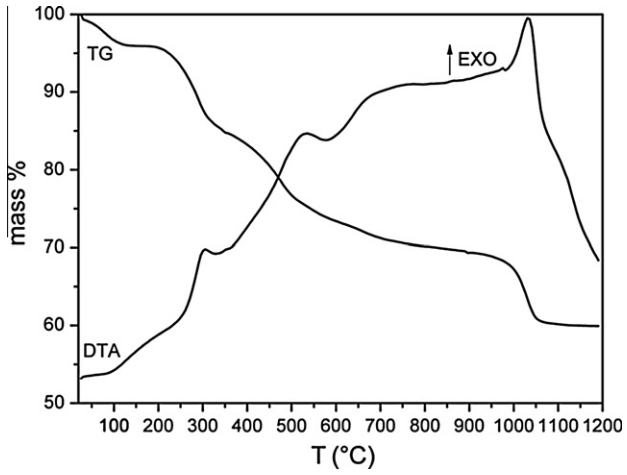


Fig. 2. Thermogravimetric (TG) and differential thermal analysis (DTA) curves of catalyst **CAT3** obtained at a heating rate of 10 °C/min under air atmosphere.

Table 3
Elemental analysis of **CAT1**, **CAT2,** and **CAT3.**

		% Zr	% P	% C	% H	% N
CAT1	Calcd.	21.68	15.32	16.54	3.30	3.09
	Found	21.26	15.68	15.90	3.38	2.95
CAT2	Calcd.	17.37	13.28	28.52	3.33	2.72
	Found	17.69	13.28	27.95	3.45	2.49
CAT3	Calcd.	20.76	15.45	25.10	3.00	1.91
	Found	20.74	15.77	24.56	3.17	1.89

The chemical compositions of solid are in good agreement with those obtained by P, Zr, performed by ICP, and C, H, N elemental analysis (Table 3).

The prepared solids show low specific surface area (2.4–5.2 m^2/g) and are not micro and mesoporous (V_{micro} and V_{meso} < 0.01 cm^3/g) (data not shown).

3.2. Catalytic activity

Among the L-proline-mediated organic reactions, aldol addition has been deeply investigated since it is one of the most important tools in organic synthesis for the C–C bond formation [39]. L-Proline-mediated aldol addition is typically performed in organic solvent, such as DMSO, DMF, or chloroform, and although addition of a small amount of water often accelerates reactions and/or improves enantioselectivities, addition of a large amount of water as reaction solvent has typically resulted in low yield with low or no enantioselectivity [40]. Recently, several papers have described the role of water in proline-mediated aldol reactions [28j,28l,41].

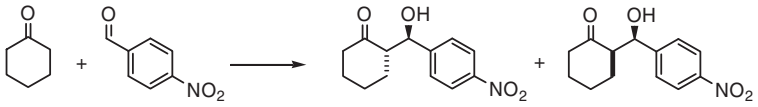
The aldol addition of *p*-nitrobenzaldehyde to cyclohexanone to give *anti* and *syn* diasteromers of 2-[hydroxy(*p*-nitrophenyl) methyl]cyclohexanone was chosen as test reaction for evaluating the catalytic activity of L-proline functionalized zirconium phosphate methyl and/or phenylphosphonates.

We started the study with the solid **CAT1** that presents the methyl group as spacer for the voluminous L-proline groups (Table 4).

In the absence of any solvent at 30 °C, both the reactivity and the selectivity were low (Table 4, Entry 1). In the presence of traces of water (1.1 μL), the reactivity increased slightly, but the selectivity remained unchanged (Table 4, Entry 2). Similar results were obtained in DMF or DMF/H_2O 1:1 (Table 4, Entries 3 and 4). The best selectivity was obtained at 30 °C in DMF/H_2O (9:1) with a 86/14 *anti/syn* ratio and an enantiomeric excess of the major *anti* product of 91%, but the conversion was still too low (16%) (Table 4, Entry 5). Increasing the reaction temperature to 50 °C, we observed a slight increase of the reactivity with a significant decrease of enantioselectivity (Table 4, Entry 6).

In our previous work, we developed new zirconium hydrogen phosphate alkyl and/or aryl phosphonates as heterogeneous Brønsted acid catalysts for the direct aza-Diels–Alder reaction of 2-cyclohexen-1-one with N-PMP-*p*Cl-benzaldimine in sole water, and we observe that the presence of hydrophobic groups, such as Me, Ph, and Pr, on the solid surface catalyst favors reagents' diffusion toward the acidic sites, aiding proton transfer to the reagents,

Table 4
Aldol addition reaction of *p*-nitrobenzaldehyde to cyclohexanone catalyzed by L-proline functionalized zirconium phosphates **CAT1**, **CAT2,** and **CAT3**.



Entry[a]	Solid (mol%)	Medium	*T* (°C)	Conv.[b,c] (%)	*anti*/*syn*[c]	*ee*[d] (%)
1	**CAT1**	SolFC	30	17	63/37	68
2	**CAT1**	SolFC[e]	30	32	66/34	70
3	**CAT1**	DMF	30	14	65/35	64
4	**CAT1**	DMF/H_2O (1:1)	30	18	88/12	84
5	**CAT1**	DMF/H_2O (9:1)	30	16	86/14	91
6	**CAT1**	DMF/H_2O (9:1)	50	27	79/21	75
7	**CAT2**	DMF/H_2O (9:1)	30	30	80/20	84
8	**CAT3**	DMF/H_2O (9:1)	30	54 (50)	94/6	96
9	**CAT3**	DMF/H_2O (9:1)[f]	30	75	91/9	93
10	**CAT3**	DMF/H_2O (9:1)[g]	30	35	86/14	78
11	**CAT3**	DMF/H_2O (9:1)	25	34	94/6	97
12	**CAT3**	DMF/H_2O (9:1)[f]	25	70 (64)	93/7	96

[a] Reaction conditions: *p*-nitrobenzaldehyde 0.125 mmol, cyclohexanone 5 equiv., medium 200 μL, catalyst 30 mol% in P-Prol groups, reaction time 4 days.
[b] The complement to 100% is unreacted *p*-nitrobenzaldehyde.
[c] Determined by ^{1}H NMR of crude product. The yield of isolated products is given in parentheses.
[d] Determined by chiral HPLC analysis for *anti* product.
[e] In the presence of 1.1 μL of water.
[f] Medium 100 μL.
[g] Medium 400 μL.

increasing the catalytic activity of the prepared solids compared with α-zirconium hydrogen phosphate (α-ZrP) [8d].

Based on these results, we supposed that the insertion of more hydrophobic groups on the surface of L-proline functionalized zirconium phosphate should lead to an increase of catalytic activity.

For this purpose, the catalysts **CAT2** (P-Prol/P-Ph = 1:1.2) and **CAT3** (P-Prol/P-Ph/P-Me = 1:1.5:1.1) were tested under the best condition used for **CAT1** (Table 4, Entries 7 and 8 vs. Entry 5).

The presence of phenyl group in **CAT2** (Table 4, Entry 6) increases the hydrophobicity of solid catalyst surface but makes the system very rigid. In fact, we observed an increase of reactivity but the selectivity decreased in comparison to **CAT1** (84% vs. 91%). When both P-Me and P-Ph group are present together with the L-proline group (**CAT3**), we obtained the best results with a conversion of 54%, an *anti/syn* ratio of 94:6 and *ee* of *anti* product of 96% (Table 4, Entry 8). The presence of P-Me group is crucial to separate the bulky group P-Ph and P-Prol, while the P-Ph group is necessary to increase the hydrophobicity of solid surface.

In order to increase the catalytic activity of solid **CAT3**, we evaluate the effect of temperature and concentration of reagents on the reactivity and selectivity (Table 4, Entries 9–12). In particular, reducing by half the volume of reaction medium (from 200 μL to 100 μL per 0.125 mmol of *p*-nitrobenzaldehyde; Table 4, Entry 9 vs. 8), we observed a significantly higher conversion (75%) with a slight decrease of selectivity (*anti/syn* = 91:9, *ee* 93%), while doubling the volume of reaction medium (from 200 μL to 400 μL per 0.125 mmol of *p*-nitrobenzaldehyde; Table 4, Entry 10 vs. 8), we observed poorer reactivity and selectivity. Lowering the reaction temperature to 25 °C (Table 4, Entry 11 vs. 8) the reactivity decreased but the selectivity was higher (*ee* 97%). The best result was obtained at 25 °C with 100 μL of DMF/H_2O 9:1 per 0.125 mmol of *p*-nitrobenzaldehyde (Table 4, Entry 12) where a good conversion was still observed (70%) and a high stereoselectivity was achieved (*anti/syn* 93:7; *ee* 96%).

In order to realize more eco-friendly processes, the catalytic activity of solid **CAT3** was also investigated in aqueous medium (Table 5). Under solvent-free conditions, at 30 °C, we observed a low reactivity and selectivity (Table 5, Entry 1), while in sole water, we obtained good results (Table 5, Entries 2–4) comparable with that obtained in DMF/H_2O 9:1 at 30 °C (Table 5, Entry 4 vs. Table 4, Entry 8). We also studied in aqueous medium the pH effect on the reactivity and selectivity. Starting from the initial pH value of 1.9 obtained by simply mixing the reactants, a moderate increasing to pH 3.5 (achieved by adding NaOH 0.2 M) leads to an increase of reactivity (conv. 71%) with still a good selectivity (*ee* 91%, Table 5, Entry 5), while at pH 6.0, a good stereoselectivity was observed but the reactivity decreased (Table 5, Entry 6).

Table 5
Catalytic activity of solid **CAT3** in aqueous medium.

Entry[a]	Medium	pH	Conv.[b,c] (%)	*anti*/*syn*[c]	*ee*[d] (%)
1	SolFC	–	60	70/30	73
2	H_2O (1.1 μL)	–	46	61/39	43
3	H_2O (50 μL)	–	57	76/24	81
4	H_2O (150 μL)	1.9	51	89/11	93
6	H_2O (100 μL) + NaOH 0.2 M (50 μL)	3.5	71	85/15	91
7	NaOH 0.2 M (150 μL)	6.0	49	84/16	92

[a] Reaction conditions: *p*-nitrobenzaldehyde 0.125 mmol, cyclohexanone 5 equiv., catalyst **CAT3** (30 mol% in P-Prol groups), at 30 °C for 4 days.
[b] The complement to 100% is unreacted *p*-nitrobenzaldehyde.
[c] Determined by ^{1}H NMR of crude product. The yield of isolated products is given in parentheses.
[d] Determined by chiral HPLC analysis for *anti* product.

In all cases, the major product of aldol addition had (2*S*,1′*R*) absolute stereochemistry [13e,21b]. Therefore, the enamine intermediate of L-proline supported zirconium phosphate/phosphonates favored a *re*-facial attack on the arylaldehyde in agreement with the homogeneous L-proline-catalyzed aldol reactions [13b,13e].

Ultimately, we have compared the reactivity and selectivity of heterogeneous catalyst **CAT3** with that of the corresponding homogeneous catalysts (Table 6). We obtained surprising and interesting results. In DMF/H_2O 9:1, the heterogeneous catalyst **CAT3** gave similar results to that of homogeneous (4*R*)-4-(phosphonooxy)-L-proline (Table 6, Entry 4 vs. Entry 3) while the homogeneous L-proline and *trans*-4-hydroxy-L-proline gave higher reactivity but lower selectivity (Table 6, Entries 1 and 2). In water, the homogeneous catalyst (4*R*)-4-(phosphonooxy)-L-proline gave only traces of products (Table 6, Entry 7) while the heterogeneous catalyst

Table 6
The reactivity and selectivity of homogeneous catalysts and heterogeneous catalyst **CAT3**.

Entry[a]	Catalyst	Medium	Conv.[b,c] (%)	*anti*/*syn*[c]	*ee*[d] (%)
1	L-Proline	DMF/H_2O (9:1)	99	66/34	79
2	*trans*-4-Hydroxy-L-Proline	DMF/H_2O (9:1)	98	91/9	85
3	(4*R*)-4-(Phosphonooxy)-L-proline	DMF/H_2O (9:1)	62	93/7	96
4	**CAT3**	DMF/H_2O (9:1)	54	94/6	96
5	L-Proline	H_2O	24	91/9	94
6	*trans*-4-Hydroxy-L-proline	H_2O	12	75/25	84
7	(4*R*)-4-(Phosphonooxy)-L-proline	H_2O	<2	–	–
8	**CAT3**	H_2O	51	89/11	93

[a] Reaction conditions: *p*-nitrobenzaldehyde 0.125 mmol, cyclohexanone 5 equiv., medium: DMF/H_2O (9:1) 200 μL or H_2O 150 μL, catalyst 30 mol% in P-Prol groups, at 30 °C for 4 days.
[b] The complement to 100% is unreacted *p*-nitrobenzaldehyde.
[c] Determined by ^{1}H NMR of crude product.
[d] Determined by chiral HPLC analysis for *anti* product.

Table 7
Recycling of solid catalyst **CAT3** in DMF/H_2O 9:1 and in aqueous medium.

Entry[a]	Medium	Run	Conv.[b] (%)	*anti*/*syn*[c]	*ee*[d] (%)	% of hydrolyzed P-Prol group[e]
1	DMF/H_2O (9:1)	Cycle 1	75	91/9	93	7
2	DMF/H_2O (9:1)	Cycle 2	64	61/39	72	19
3	DMF/H_2O (9:1)	Cycle 3	51	46/54	49	30
4	H_2O (pH = 3.5)	Cycle 1	71	85/15	91	5
5	H_2O (pH = 3.5)	Cycle 2	77	55/45	62	25

[a] Reaction conditions: *p*-nitrobenzaldehyde 0.5 mmol, cyclohexanone 5 equiv., medium: DMF/H_2O (9:1) 400 μL or H_2O (pH = 3.5) 600 μL, catalyst **CAT3** (30 mol% in P-Prol groups), at 30 °C, 4 days.
[b] The complement to 100% is unreacted *p*-nitrobenzaldehyde.
[c] Determined by ^{1}H NMR of crude product.
[d] Determined by chiral HPLC analysis for *anti* product.
[e] Determined by ^{31}P NMR analysis of recovered solid catalyst.

CAT3 induced higher reactivity than that of L-proline (51% vs. 24%) with comparable stereoselectivity (Table 6, Entry 8 vs. Entry 5).

When a solid catalyst is used, its reusability is an important issue [21g]. The recycling of catalyst **CAT3**, used in the reaction in DMF/H_2O 9:1 and in aqueous medium at pH 3.5, has been investigated (Table 7). At the end of reaction, the solid catalyst **CAT3** was recovered after removing of the reaction products by extraction with ethyl acetate followed by centrifugation. The solid was washed with water and dried at 80 °C for 15 h and reused. After the first cycle in DMF/H_2O 9:1 (Table 7, Entry 1), the ^{31}P NMR analysis of recovered catalyst evidenced the presence of the P-OH group on the catalyst surface of solid (7%), which was obtained by hydrolysis of P-Prol group. The decrease of stereoselectivity in the second cycle was therefore expected (*ee* 72% vs. 92%) (Table 7, Entry 2) because the P-OH group catalyzes the reaction *via* the formation of an achiral enol. At the end of second cycle, the percentage of hydrolyzed P-Prol group increases to 17% and in the third cycle, the selectivity decreases further (Table 7, Entry 3, *ee* 49%). The result of the catalyst recovery and reuse was also unsatisfactory in the case of the reaction performed in water (Table 7, Entries 4 and 5). To confirm our hypothesis, we performed the aldol addition in the presence of 30 mol% in P-OH groups of $Zr(PO_3OH)_{0.37}(PO_3Me)_{0.65}(PO_3Ph)_{0.98}$ prepared by us in a previous work [8d]. The solid acid catalyzed the non-stereoselective aldol addition both in DMF/H_2O 9:1, where we observe a 32% of conversion with a 43:57 *anti/syn* ratio, and in sole water with a conversion of 60% and a 39:64 *anti/syn* ratio.

The L-proline group is linked to inorganic layer by a phosphate ester bond; it is acid sensitive and easily hydrolyzable under the reaction conditions and this not permit the recycling of solid catalyst. The substitution of phosphate L-proline group with a more stable phosphonate L-proline group should lead to a recoverable and recyclable catalysts.

4. Conclusion

The results presented in this paper are encouraging and pave the way toward the development of new supports for chiral heterogeneous catalysts. Several L-proline functionalized zirconium phosphates/phosphonates have been prepared, and their catalytic activity was tested in the asymmetric aldol addition of *p*-nitrobenzaldehyde to cyclohexanone.

The catalyst **CAT3** where both P-Me and P-Ph group are present together with the L-proline group was the best catalyst. The presence of P-Me group is crucial to separate the bulky group P-Ph and P-Prol, while the P-Ph group is necessary to increase the hydrophobicity of solid surface.

This system was thought to mime the behavior of enzymes, which catalyze reactions in soft conditions, especially in water, using hydrophobic tasks. In fact, we obtained good results in both DMF/H_2O 9:1 (conv. 70%, *ee* 96%) and water (conv. 71%, *ee* 91%). Also, it was found that in water, the heterogeneous catalyst **CAT3** was a better catalytic system than the analogous homogeneous one.

However, the recover and the recycling of **CAT3** were unsatisfactory because of the hydrolysis of phosphate ester bond that links the L-proline group to the inorganic layer. Further efforts are currently directed to improve this aspect, and efficient and recyclable catalyst will be prepared in order to have L-proline phosphonates more stable than phosphates.

Acknowledgments

We gratefully acknowledge the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) within the financing programs PRIN 2008 and "Firb-Futuro in Ricerca" and the Università

degli Studi di Perugia for financial support. Dr. Fabio Marmottini and Dr. Morena Nocchetti are thanked for TG DTA, ICP-OES and B.E.T. surface area analysis.

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