Catalysis Letters, Vol. 118, Nos. 3–4, October 2007 (© 2007)
DOI: 10.1007/s10562-007-9145-2

A novel type of chiral titanium phosphonates and hybrid titanium phosphonates for heterogeneous asymmetric catalysis

Yeling Ji, Xuebing Ma,* Xinjun Wu, Ning Wang, Qiang Wang, and Xilan Zhou
College of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P.R. China

Received 17 April 2007; accepted 18 May 2007

(1*R*, 2*S*)-(−)-2-amino-1, 2-diphenylethanol and (1*S*, 2*R*)-(+)-2-amino-1, 2-diphenylethanol had been immobilized on the layered titanium phosphonates **4a**–**d** and hybrid titanium phosphonates **5a**–**c** in spheroid form with interlayer space 20.845–19.407 Å which can be used as heterogeneous catalysts in the enantioseletive addition of diethylzinc to benzaldehyde to obtain optically active (*R*)-or (*S*)-1-phenylpropan-1-ol for the first time. It was shown that the titanium phosphonate **4a** led to active heterogeneous catalysis for asymmetric additions of diethylzinc to benzaldehydes in 88.5% yield and ee value of up to 40.8% which decreased at 16% ee lower than corresponding chiral ligand in homogeneous asymmetric catalysis. AFM showed that the distribution of 1,2-dipenyl-2-aminoethanol organic moieties on the surface of titanium phosphonates irregularly lined like flow mark.

KEY WORDS: hybrid; immobilized; titanium phosphonate; heterogeneous enantioseletive addition.

1. Introduction

Many pharmaceuticals, agrochemicals, flavours, fragrances and important intermediates are only desirable to one enantiomeric form. The increasing demand for enantiomerically pure compounds has fostered to develop the preparation methods affording pure enantiomers of chiral products [1]. Among the various methods, the enantioseletive catalysis is unique in a sense that a minute quantity of the chiral catalyst is sufficient to produce large amount of the desired chiral products. Specially, the heterogeneous catalysis over homogeneous catalysis have some advantages, such as facile separation of catalyst from reactants and products, stability, recovering and reuse [2], as well as being friendly to environment and economy. The methods of preparing heterogeneous chiral catalyst include modification of traditional heterogeneous catalyst with chiral molecules, immobilization of homogeneous chiral catalyst and polymer-supported chiral catalyst, and so on. Homogeneous chiral catalysts immobilized on polymer, alumina or silica gel to catalyze enantioselective addition of diethylzinc to aldehyde have been detailed by various research groups [3–6].

Tetravalent metal phosphates, phosphonates and hybrid phosphate-phosphonates are of interest because of their practical application in areas such as ion exchange, catalysis, intercalation chemistry and proton conduction. Being members of the layered metal phosphates family, the layered titanium (IV) phosphates have been of considerable interest recently [7]. The two main types, α- and γ-phase, of layered titanium (IV) phosphates, represented as $Ti(HPO_4)_2 \cdot H_2O$ (α-Tip) [8–12] and $Ti(H_2PO_4)(PO_4) \cdot 2H_2O$ (γ-Tip) [13–15], are well known for the present. These layered compounds were investigated extensively with respect to their ion-exchange properties and the synthetic methods of organically or inorganically pillared compounds [16–17]. But application for heterogeneous asymmetric catalysis had been reported until now. In this paper we reported a novel type of titanium phosphonates and hybrid titanium phosphonates (scheme 1) immobilized chiral (−) or (+)-2-amino-1, 2-diphenylethanol and their application for the enantioselective addition of diethylzinc to benzaldehyde for the first time.

2. Experimental

2.1. Materials, instruments and analytical procedures

(1*R*, 2*S*)-(−)-2-amino-1, 2-diphenylethanol, (1*S*, 2*R*)-(+)-2-amino-1, 2-diphenylethanol and diethylzinc were purchased from Astatech Pharmaceutical Co. Ltd and J&k Chemica respectively. Diethyl-2-bromo-ethylphosponate [$BrCH_2CH_2P(O)(OEt)_2$] was prepared by reaction of triethylphosphite with 1,2-dibromoethane according to literature [18–19]. All other materials used are of analytical grade.

^1H, ^{13}C and ^{31}P NMR were performed on an av-300 NMR instrument at ambient temperature at 300 MHz, 75 MHz and 121 MHz, respectively. IR spectra were

*To whom correspondence should be addressed.
E-mail: zcj123@swu.edu.cn

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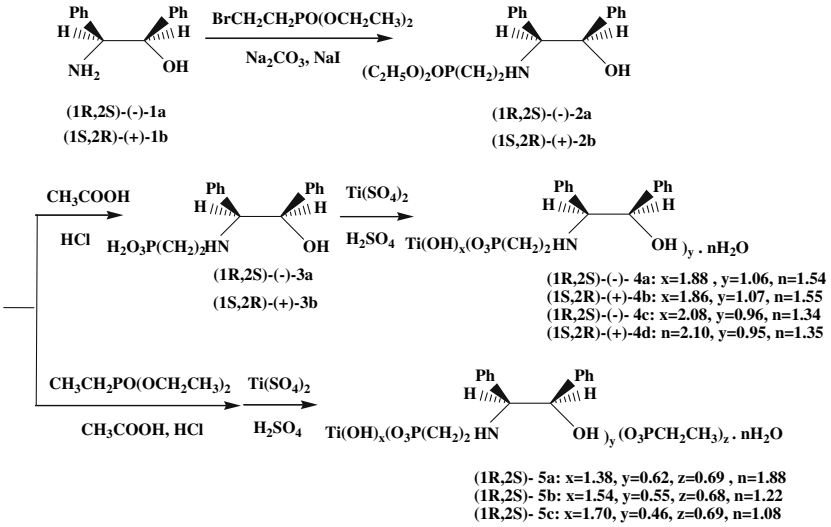

Scheme 1. The synthetic route to titanium phosphonates **4** and hybrid titanium phosphonates **5**.

obtained on a Spectrum GX Perkin Elmer using polystyrene as a standard (KBr pellet). The interlayer spacings were obtained on a Phillips (model 1710) semiautomatic X-ray power diffractometer using Cu Kα radiation (36 kV and 20 mA) with a scanning speed of $2^\circ \cdot min^{-1}$ in the range 2θ = 2–40°. TG analyses were carried out with a Q-Derivatograph thermal analyzer at a heating rate of 20 °C $\cdot$ min^{-1} under a nitrogen atmosphere. The morphology of the samples was observed through an atomic force microscopy on an Multimode SPM Veew instruments inc (USA) and a scanning electron microscope on a Hitachi S-3000N scanning electron mircroscope. C, H and N elemental analyses were obtained from an EA^{TM} 1112 Automatic Elemental Analyzer (USA) instrument. GC analyses were performed on a gas chromatograph (Agilent 6820, USA) using a 30 m Chiral Cyclodex-B capillary column: temperature program 70 °C, 5 min, 3 C $\cdot$ min^{-1}, 160 °C, 35 min. Optical rotations were determined on a Perkin-Elmer 341 polarimeter.

In order to determine titanium (IV), a weighed amount of titanium phosphonates **4** and **5** (0.500 g) were refluxed for 2 days in 50 mL of 1 mol $\cdot$ L^{-1} Na_2CO_3, respectively. The precipitate was separated from the solution and then refluxed up to complete solubilization in a solution containing 10 g of $(NH_4)_2SO_4$ in 25 mL of concentrated H_2SO_4. The resulting solution was diluted to 100 mL and its titanium content determined colorimetrically as described in Ref. [20].

^{31}P NMR of titanium phosphonates **4** was determined by dissolving a weighed amount of sample (30 mg) in 0.5 mL of CH_3OD. The molar ratio of diphenylethanol/ethyl organic moieties on the surface of titanium phosphonate **5** was determined by the intergration areas of liquid ^{31}P NMR on the solution obtained by dissolving a weighed amount of sample (30 mg) in 0.5 mL of D_2O with two drops of fluorhydric acid. The amount of phosphonate in titanium phosphonates **4** and **5** was quantitatively determined by comparing the intergration areas of phosphorus with that of accurately known phosphonate **2**. The shifts of the signals of (1*R*, 2*S*)-(−)-2-[*N*-(ethylphosphonic acid)]imino-1, 2-diphenylethanol and ethylphosphonic acid were 35.6 and 24.2 ppm, respectively. A suitable time delay (d_1 = 5 s) was set to ensure quantitative measurements. The shifts are relative to 85% H_3PO_4 in D_2O.

2.2. *Preparation of (1R, 2S)-(−)-2-[N-(diethyl ethylphosphonate)]imino-1, 2-diphenylethanol (2a) and (1S, 2R)-(+)-2-[N-(diethyl ethylphosphonate)]imino-1, 2-diphenylethanol (2b)*

To a solution of (4.26 g, 20 mmol) (1*R*, 2*S*)-(−)-2-amino-1, 2-diphenylethanol (**1a**) or (1*S*, 2*R*)-(+)-2-amino-1, 2-diphenylethanol (**1b**) in 100 mL ethanol, a catalytic amount of sodium iodide (0.1 g) and diethyl 2-bromoethylphosponate (9.00 g, 40 mmol) were added. The reaction mixture was stirred for 6–7 d at 50–60 °C with the tracking of TLC, and the solution of sodium carbonate (1 mol $\cdot$ L^{-1}) was used to maintain pH in the range of 7–8. Then the reaction mixture was extracted by $CHCl_3$ (30 mL × 3), the organic phase was combined and concentrated under reduced pressure. The crude product was purified by recrystalizing with ethyl acetate, filtered and dried in vacuum. White crystals 6.67 g of (1*R*, 2*S*)-(−)-**2a** and 6.91 g of (1*S*, 2*R*)-(+)-**2b** in 88.5% and 91.6% yield respectively were obtained. M.p. 126–127 °C, $[\alpha]_D^{25} = -23.6^\circ$ [0.1 mol $\cdot$ L^{-1} (1*R*, 2*S*)-(−)-**2a**, $CHCl_3$)], $[\alpha]_D^{25} = +25.6^\circ$ [0.1 mol $\cdot$ L^{-1} (1*S*, 2*R*)-(+)-**2b**, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$): δ 7.29–7.24 (6 H, m), 7.15–7.09 (4 H, m), 4.90 (OCH, 1 H, d, ^3J = 6.0 Hz), 4.04 (OCH_2, 4 H, m), 3.99 (NCH, 1 H, d, ^3J = 5.4 Hz),

2.80 (NCH_2, 2 H, m), 2.01 (NH, H, m), 1.93 (CH_2P, 2 H, m), 1.27 (CH_3, 6 H, t, ^3J = 5.4 Hz). ^{31}P NMR ($CDCl_3$): δ 31.7. ^{13}C NMR ($CDCl_3$): 140.3, 138.7, 128.3, 127.8, 127.6, 126.9 (–Ph), 76.5 (OCH), 68.4 (OCH_2), 61.7 (NCH), 40.9 (d, $^2J_{c-p} = 4.5$ Hz, NCH_2), 26.4 (d, CH_2P, $^1J_{c-p} = 140.4$ Hz), 16.5 (d, CH_3, $^3J_{c-p} = 5.3$ Hz). IR (KBr, ν, cm^{-1}): 3335 (m), 3064 (s), 3026 (s), 2983 (s), 2925 (m), 2872 (m), 1599 (m), 1548 (m), 1494 (m), 1452 (m), 1390 (s), 1291 (s), 1026 (s), 704 (s), 676 (w).

2.3. Preparation of semi-crystalline titanium phosphonates 4a and 4b

A mixture of (1*R*, 2*S*)-(−)-**2a** or (1*S*, 2*R*)-(+)-**2b** (0.377 g, 1 mmol), 20 mL of acetic acid and 10 mL of concentrated hydrochloric acid was stirred for 12 h at 80 °C [21]. The reaction mixture was cooled to room temperature, 10 mL of distilled water was added, and a solution of titanium sulphate (0.12 g, 0.5 mmol) in 5 mL of diluted sulfuric acid (0.4 $mol \cdot L^{-1}$) was added dropwise with stirring. After stirring for another 12 h at ambient temperature, white precipitation solid was filtered, washed with sodium bicarbonate solution (1 $mol \cdot L^{-1}$) and water to pH at about 6.0. White solids of 0.313 g (1*R*, 2*S*)-(−)-**4a** and 0.321 g (1*S*, 2*R*)-(+)-**4b** were obtained in 91.3% and 93.5% yield, respectively. The anal. calc. for (1*R*, 2*S*)-(−)-**4a** ($C_{16.96}H_{24.04}N_{1.06}O_{7.66}P_{1.06}Ti$): C, 45.7; H, 5.39; N, 3.33. Found: C, 45.0; H, 5.20; N, 3.40. The anal. calc. for (1*S*, 2*R*)-(+)-**4b** ($C_{17.12}H_{24.22}N_{1.07}O_{7.69}P_{1.07}Ti$): C, 45.7; H, 5.39; N, 3.33. Found: C, 45.2; H, 5.21; N, 3.37.

2.4. Preparation of crystalline titanium phosphonates 4c and 4d

To a mixture of (1*R*, 2*S*)-(−)-**2a** or (1*S*, 2*R*)-(+)-**2b** (0.377 g, 1 mmol), 20 mL of acetic acid and 10 mL of concentrated hydrochloric acid was added a solution of titanium sulphate (0.240 g, 1 mmol) in 5 mL of diluted sulfuric acid (0.4 $mol \cdot L^{-1}$) and 20 mL of distilled water. The mixture was stirred at room temperature for 1 h, followed by transferring to a 100 mL Teflon-lined stainless-steel autoclave and heating under autogenous pressure at 150 °C for 10 days. The colourless and spicular crystals were recovered by filtration, washed by sodium bicarbonate solution (1 $mol \cdot L^{-1}$) and distilled water to pH 6.0 and dried overnight in vacuo at 60 °C. 0.259 g of (1*R*, 2*S*)-(−)-4c and 0.263 g of (1*S*, 2*R*)-(+)-4d were obtained in 75.5% and 76.7% yield, respectively. The anal. calc. for (1*R*, 2*S*)-(−)-**4c** ($C_{15.36}H_{22.04}N_{0.96}O_{7.26}P_{0.96}Ti$): C, 44.57; H, 5.38; N, 3.25. Found: C, 44.80; H, 5.10; N, 3.45. The anal. calc. for (1*S*, 2*R*)-(+)-**4d** ($C_{15.36}H_{22.04}N_{0.96}O_{7.26}P_{0.96}Ti$): C, 44.57; H, 5.38; N, 3.25. Found: C, 44.72; H, 5.08; N, 3.38.

2.5. Preparation of hybrid titanium phosphonates 5a–c

An identical synthetic procedure was followed for all of the hybrid stoichiometry compounds (y = 0.62, 0.55, and 0.46). The following procedure is given for the y = 0.62 case, while for the other compounds the stoichiometric ratios of the two phosphonic acids were varied as necessary.

A mixture of (1*R*, 2*S*)-(−)-**2a** (0.377 g, 1 mmol), diethyl ethylphosphonate (0.249 g, 1.5 mmol), 20 mL of acetic acid and 10 mL of hydrochloric acid was stirred for 12 h at 80 °C [22]. The mixture was cooled to room temperature, 10 mL of distilled water was added, and 10 mL of titanium sulphate (0.600 g, 2.5 mmol) in diluted sulfuric acid (0.4 $mol \cdot L^{-1}$) was added dropwise with stirring. After stirring for another 12 h at ambient temperature, white precipitation was filtered, washed with sodium dicarbonate solution (1 $mol \cdot L^{-1}$) and distilled water thoroughly to pH 6.0. White solids of 0.306 g (1*R*, 2*S*)-(−)-**5a** was obtained in 60.2% yield. The anal. calc. for (1*R*, 2*S*)-(−)-**5a** ($C_{11.3}H_{19.75}N_{0.62}O_{7.81}P_{1.31}Ti$): C, 39.47; H, 5.79; N, 2.53. Found: C, 39.21; H, 4.12; N, 2.46. The anal. calc. for (1*R*, 2*S*)-(−)-**5b** ($C_{10.16}H_{17.28}N_{0.56}O_{7.0}P_{1.23}Ti$): C, 35.34; H, 5.05; N, 2.23. Found: C, 34.82; H, 4.20; N, 2.50. The anal. Calc. for (1*R*, 2*S*)-(−)-**5c**($C_{8.74}H_{15.59}N_{0.46}O_{6.69}P_{1.15}Ti$): C, 33.05; H, 4.95; N, 2.03. Found: C, 34.82; H, 4.55; N, 2.51. ^{31}P NMR (HF) of **5a**: 35.4, 24.0; **5b**: 37.6, 25.6; **5c**: 35.6, 24.2.

2.6. Typical procedure of the enantioselective additon of diethylzinc to benzaldehyde [23, 24]

The catalyst (7.5 mol%) in anhydrous toluene (5 mL) was activated by stirring for 18 h at 10 °C, and 1 mL of diethylzinc (2 $mol \cdot L^{-1}$ in hexane solution) was added dropwise under an argon atmosphere at 0 °C. After the resulting mixture was stirred for 3 h, benzaldehyde (53 mg, 0.5 mmol, 50 μL) was added. The reaction mixture was stirred for 48 h at 10 °C, quenched by a saturated aqueous NH_4Cl solution and extracted with ethyl acetate (5 mL × 3). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column using acetic ether/petroleum ether [1:5 (v/v)] to give optically active 1-phenylpropanol which was analyzed by GC to give the yields and ee values.

2.7. The reusability of catalyst

About 0.296 g of used catalyst (1*R*, 2*S*)-**4a** was washed with diluted hydrochloric acid (1 mol/L, 10 mL) to removed zinc oxide formed in the catalytic reaction and then washed with sodium bicarbonate (1 $mol \cdot L^{-1}$) and water to pH 6–7, dried in vacuo at 60 °C for 12 h to get 0.190 g (1*R*, 2*S*)-**4a** which can be reused for the enantioselective addition of diethylzinc to benzaldehyde.

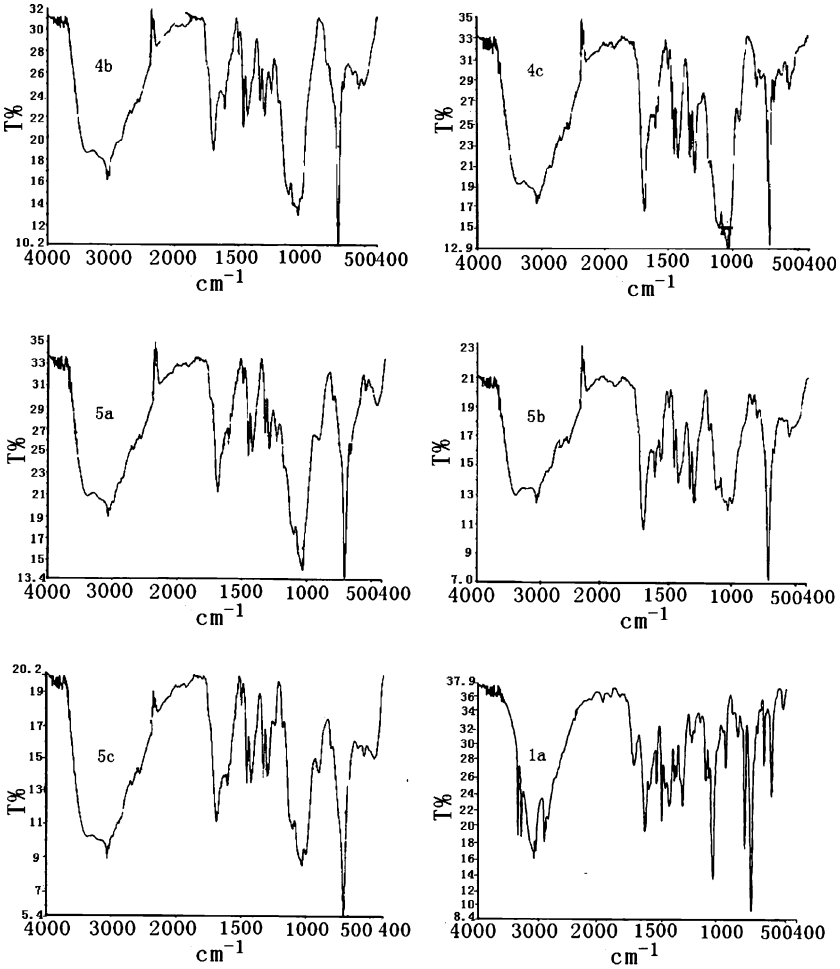

Figure 1. The infrared spectra of titanium phosphonates and hybrid titanium phosphonates.

3. Results and discussion

3.1. Infrared spectroscopy

The similar infrared spectra (figure 1) of titanium phosphonates **4a**–**d** and hybrid titanium phosphonates **5a**–**c** showed that strong and broad adsorption peak in the range of 2500–3500 cm^{-1} gave the evidence of the hydrogen bonding between imino (–NH–) group and hydroxy group (–OH) each other. The interval between 1100 and 900 cm^{-1} is of diagnostic value of phosphonate (–PO_3) structure in titanium phosphonates [25, 26]. The sharp adsorption peak at 1600–1450 cm^{-1} and 740 cm^{-1} are attributed to the stretch vibration of aromatic ring and flexural vibration of one-substituted aromatic ring, respectively.

3.2. XRD analysis

The X-ray powder pattern of titanium phosphonates **4a** and **4c**, hybrid titanium phosphonates **5a**–**c**, and titanium ethylphosphonate with a layered structure [27] whose interlayer spacings are 20.028, 19.407, 19.538, 19.530, 20.028 and 10.765 Å respectively presents one similar, single and broad peak with strong intensity (figure 2). For hybrid titanium phosphonates, there are two different structural possibilities for distribution of the organic groups: (i) a random dispersion within the interlayer and all layers identical; (ii) an ordered segregation or staging of the organic groups into layers of

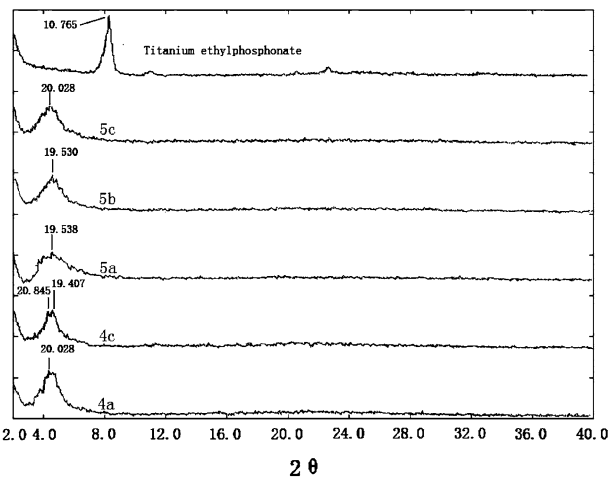

Figure 2. The X-ray diffraction of titanium phosphonates and hybrid titanium phosphonates.

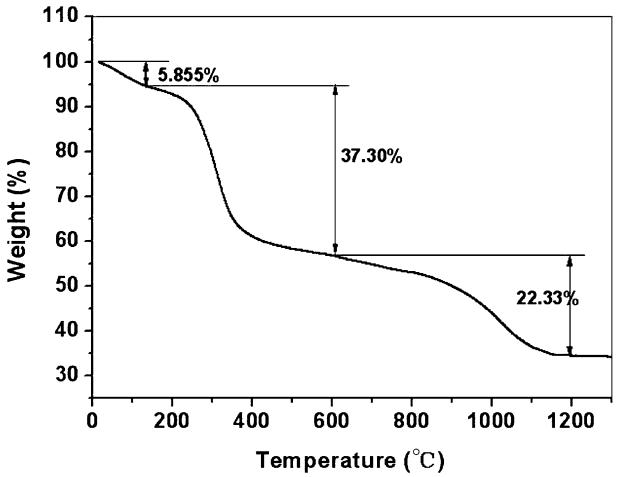

Figure 3. TG curve of titanium phosphonate **4c**.

distinct compositions [28]. Each of these arrangements will give rise to characteristic features in the X-ray diffraction pattern. The randomly distributed structure will show a single 001 XRD peak whose *d* spacing is between the values observed for the two parent titanium phosphonates. Although the molar ratio of ethylphosphonate moieties to phosphonate **3** on the interlayer surface of hybrid titanium phosphonates **5a**–**c** increased from 0, 1.11, 1.24 and 1.51, the interlayer space remain in the range of 20.845–19.407 Å with little change, which demonstrated the distribution of the two type of organic moieties is a random dispersion on the surface of titanium phosphonates frames.

3.3. TG analysis and chemical analysis

On heating the samples **4a**, **4c** and hybrid titanium phosphonates **5a**–**c**, similar behaviors of their thermostability over a broad temperature range of 40–1200 °C were observed (figure 3). The samples **4a**, **4c** and hybrid titanium phosphonates **5a**–**c** lost the 6.854%, 5.855%, 9.261%, 6.240% and 6.512% exact weight calculated for n = 1.54, 1.34, 1.88, 1.22 and 1.08 waters of hydration in the temperature range of 40–150 °C individually. The similar fragmentation of the appended organic groups on either of titanium phosphonates **4a**, **4c** or hybrid titanium phosphonates **5a**–**c** took place in two steps in the temperature range of 150–600 °C and 600–1200 °C respectively, and the total 60.85%, 59.63%, 48.37%, 45.33% and 34.78% weight losses which are attributed to the fragmentation of appended organic moieties are accord with the theoretical content of their pendant organic component.

Unfortunately, the two types of pendant organic moieties do not pyrolize discretely but instead volatilize together over a somewhat broadened range. So it is difficult to detect the content of the different pendant phosphonate organic moieties by TG analysis using the change in percent weight loss for hybrid titanium phosphonates **5a**–**c**. The molar ratio of pendant ethylphosphonate to phosphonate **3** organic moieties in hybrid **5a**–**c** is 1.11, 1.24 and 1.51, respectively, which conformed by the values of intergration areas on the basis of liquid ^{31}P NMR.

Analytical determinations and liquid ^{31}P NMR for titanium phosphonate **4c** gave $[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]/Ti = 0.96$. Taking into account chemical analysis and water weight loss 5.855% in the temperature range of 40–150 °C by TG curve, the titanium phosphonate **4c** can be represented by the formula $Ti(OH)_{2.08}[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]_{0.96} \cdot 1.34\ H_2O$, Which was accord with elemental analysis and TG analysis. In the same procedure the formulae of **4a, 5a**–**c** were represented as $Ti(OH)_{1.88}[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]_{1.06} \cdot 1.54\ H_2O$, $Ti(OH)_{1.38}[O_3PCH_2CH_3]_{0.69}[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]_{0.62} \cdot 1.88\ H_2O$, $Ti(OH)_{1.54}[O_3PCH_2CH_3]_{0.68}[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]_{0.55} \cdot 1.22\ H_2O$ and $Ti(OH)_{1.70}[O_3PCH_2CH_3]_{0.69}[O_3P(CH_2)_2NHCH(Ph)CH(Ph)OH]_{0.46} \cdot 1.08\ H_2O$ respectively.

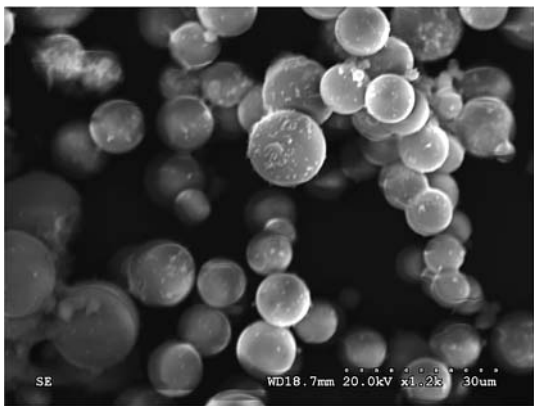

Figure 4. SEM image of chiral titanium phosphonate **4a**.

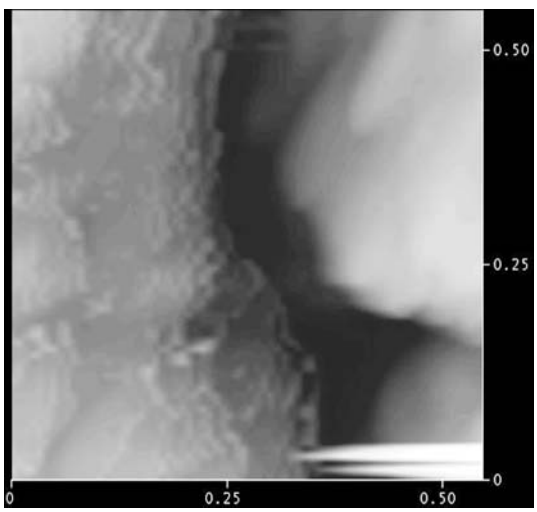

Figure 5. AFM image of chiral titanium phosphonate **4a**.

Table 1
The effect of the solvents and temperature on the asymmetric addition of diethylzinc to benzaldehye using **4a**

Entry	Catalyst (mol %)	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)	Ee[a] (%)	Conf.[b]
1	**4a** (10)	Toluene	10	48	96.8	33.0	*R*
2	**4a** (10)	Hexane	10	48	68.6	32.5	*R*
3	**4a** (10)	T:H (1:1)[c]	10	48	85.0	24.1	*R*
4	**4a** (7.5)	Toluene	−20	48	21.7	5.0	*R*
5	**4a** (7.5)	Toluene	0	48	61.5	38.8	*R*
6	**4a** (7.5)	Toluene	10	48	88.5	40.8	*R*
7	**4a** (7.5)	Toluene	20	48	90.0	31.8	*R*

[a] Decided by GC (Chiral Cyclodex-B column, Agilent).
[b] Determined from the specific rotation of (*S*)-1-phenylpropanol: $[\alpha]_D^{25}$: −47.6($CHCl_3$).
[c] T is toluene, H is hexane.

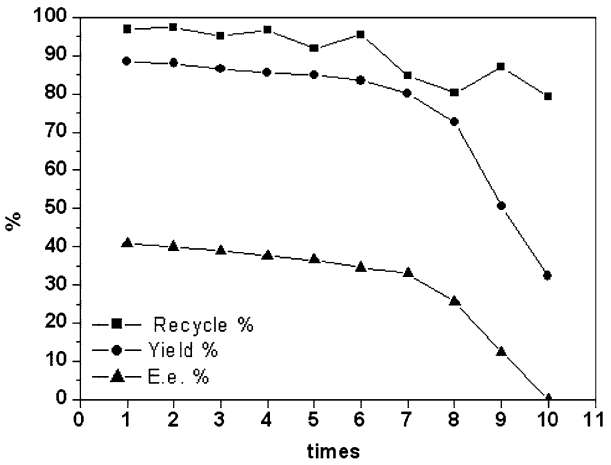

Figure 6. The percent of recycle, catalytic yield and ee of the titanium phosphonate **4a**.

3.4. Analysis of surface morphology

Scanning electron microscope (SEM) and atomic force microscopy (AFM) were used as the tools to understand the diameter (figure 4) and the distribution of the appended organic moieties (figure 5) on the surface of titanium phosphonate **4a**. SEM results showed that these materials were in spheroid form and submicron in size, and AFM showed that 1,2-dipenyl-2-iminoethanol organic moieties on the surface of titanium phosphonate irregularly lined like flow mark.

3.5. Enantioselective addition of diethylzinc to benzaldehye

Enantioselective addition of benzaldehyde to diethylzinc was catalyzed by using 2-[*N*-(diethyl ethyl- phosphonate)]imino-1, 2-diphenylethanol **2** and their supported titanium phosphonates analogues as chiral auxiliaries to yield optically active (*R*)-or (*S*)-1-phenylpropan-1-ol via their alcoholates. The effect of solvent, temperature, the molar ratio of catalyst and reactants and swelling time on the yields and the enantioselectivities was investigated.

3.5.1. Effect of the solvent and temperature

Solvent and temperature play an important role in the asymmetric catalytic reactions. From table 1 it was concluded that the solvent of toluene and 10 °C are advisable. The solvent of toluene and higher temperature are benefit for improving yield, but proper temperature is effective for the high asymmetric addition of diethylzinc to benzaldehye.

3.5.2. Effect of the amount of catalyst and diethylzinc

As shown in table 2, the different amount of catalyst or diethylzinc was evaluated to check the asymmetric addition of diethylzinc to benzaldehye. The appropriate ratio of benzaldehyde, catalyst and diethylzinc is 1.0/0.075/4.0.

3.5.3. Effect of density of organic ligands on the surface

From table 2, it was shown that titanium phosphonate **4a** with chiral 2-aminoalcohol auxiliary led to active heterogeneous catalysis for asymmetric addition of diethylzinc to benzaldehyde with 88.5% yield and ee value of up to 40.8% which decreased at 16% ee lower

Table 2
The effect of the amount of benzaldehyde, catalyst and diethylzinc using **4a** and **5a–c**

Entry	Catalyst (mol %)	Benzaldehyde (mmol)	Et_2Zn (2mol·L^{-1})	Time (h)	Yield (%)	Ee (%)	Conf.
1	**4a** (5.0)	0.5	1.0 mL	48	48.0	31.2	R
2	**4a** (7.5)	0.5	1.0 mL	48	88.5	40.8	R
3	**4a** (10.0)	0.5	1.0 mL	48	96.8	33.0	R
4	**4a** (7.5)	0.5	0.5 mL	48	19.3	23.3	R
5	**4a** (7.5)	0.5	1.0 mL	48	88.5	40.8	R
6	**4a** (7.5)	0.5	1.5 mL	48	43.7	26.8	R
7	**2a** (7.5)	0.5	1.0 mL	48	95.0	57.0	R
8	**4c** (7.5)	0.5	1.0 mL	48	82.4	32.8	R
9	**5a** (7.5)	0.5	1.0 mL	48	75.6	10.8	R
10	**5b** (7.5)	0.5	1.0 mL	48	78.2	5.2	R
11	**5c** (7.5)	0.5	1.0 mL	48	76.2	0	∼

Reactions were performed in toluene at 10 °C

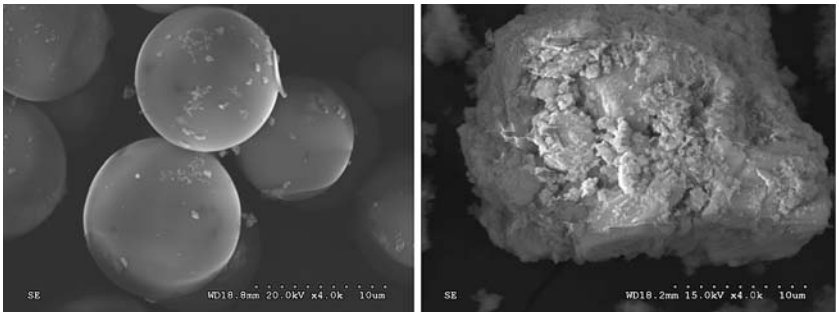

Figure 7. The comparation SEM images of titanium phosphonate **4a** with one used seven times.

than corresponding chiral ligand in homogeneous asymmetric catalysis. With regard to the difficulty for the reactants to approach the surface of catalytic sites in heterogeneous reactions, we speculated that the enantioselectivity might be optimized by enlarging internal areas of the solid catalysts by introducing small molecules to dilute the concentration of chiral ligand. So a series of hybrid titanium phosphonates **5a–c** had been prepared in order to make the reactants easy to approach catalytic sites. But the results were not satisfactory and the enantioselectivity decreased with the amount of the appended phosphonate **2** , which may be due to the exposure of the P–O in small ethylphosphonate molecules and surface hydroxyl on the layered titanium plane which can catalyze the the alkylation of benzaldehyde without enantioselectivity.

3.5.4. Effect of time of swelling

Although titanium phosphonates **4** and hybrid titanium phosphonates **5a–c** possess 20.845–19.407 Å interlayer space, one of vital disadvantages of solid catalysts is found that the reactants are difficult to access internal catalytic sites. The catalyst (7.5 mol%) in anhydrous toluene (5 mL) was not activated and diethylzinc (0.5 $mol \cdot L^{-1}$ in hexane solution) was added immediately, no (*R*)-1-phenylpropan-1-ol was obtained. From the yield and ee value catalyzed by the titanium phosphonate **4a** in different swelling time, the optimum time of swelling in toluene is 18 h in the exiperimental conditions shown in table 2, entry 2.

3.5.5. The reusability of catalyst

From figure 6, it was concluded that the titanium phosphonate **4a** can be reused seven times, and then strongly decrease from 33.0% to 25.5% ee, which may be due to several factors such as the dilution of zinc oxide formed in the addition of Et_2Zn to benzaldehyde, the loss of the catalyst and the decomposition of titanium frame. The comparative SEM images of recovered titanium phosphonate **4a** was found that the spheroid form of titanium phosphonates collapsed and irregular morphology formed (figure 7), which may be the reason the titanium phosphonate **4a** lose the catalytic activities and enantioselectivities.

4. Conclusions

A novel type of titanium phosphonates and hybrid titanium phosphonates immobilized chiral (−) or (+)-2-amino-1, 2-diphenylethanol had been prepared and their application for the enantioselective addition of diethylzinc to benzaldehyde had been investigated for the first time. Titanium phosphonates **4a–d** and hybrid titanium phosphonates **5a–c** are layered and spheroidal materials with interlayer space 20.845–19.407 Å. The titanium phosphonate **4a** led to active heterogeneous catalysis for asymmetric addition of diethylzinc to benzaldehyde in 88.5% yield and ee values of up to 40.8% which decreased at 16% ee lower than corresponding chiral ligand **2** in homogeneous asymmetric catalysis. The effect of solvent, temperature, the molar ratio of catalyst, reactants and swelling time on the yield and the catalytic enantioselectivities was investigated. The optimum heterogeneous asymmetric catalytic reaction conditions are swelling for 18 h, and then stirring for 48 h at 10 °C with the 1.0/0.075/4.0 ratio of benzaldehyde, catalyst and diethylzinc. The catalyst can be reused seven times.

Acknowledgments

The authors acknowledge the support by the Science Foundation of Southwest University.

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