Synthesis of α-Aminophosphonates in the Presence of a Magnetic Recyclable Fe₃O₄@SiO₂-2mimSO₃H Nanocatalyst

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A highly efficient magnetic Brønsted acid catalyst was synthesized based on immobilization of 2-methylimidazole functionalized by chlorosulfonic acid on the surface of silica-coated magnetic nanoparticles (Fe₃O₄@SiO₂-2mimSO₃H). The catalyst has an excellent activity and recyclable for at least 6 reaction runs and is proven to be highly effective in the synthesis of α-aminophosphonate compounds in a green way. The facile recovery of the catalyst is carried out by applying an external magnet device. It is both “green” and efficient. The catalyst was fully characterized by techniques of TEM, SEM, FT-IR, TGA, and elemental analysis (CHNS).

Acid-catalyzed processes are among the most important industrial transformations, including large-scale alklylation, isomerization and esterification processes.¹ The use of conventional Brønsted acidic catalysts (HF, sulfuric or phosphoric acids, and zeolites) bears various drawbacks, such as high volatility, toxicity, waste generation, and limited solubility/phase contact with the starting materials.² Brønsted acidic ionic liquids (ILs functionalized by acidic groups) may be promising greener alternatives to conventional Brønsted acids for catalysis, helping to overcome some of these drawbacks.

Brønsted acidic ionic liquids have been of interest because they are able to carry an acidic group such as –SO₃H. These acidic ILs have been used as efficient Brønsted acid catalyst and solvent for various reactions and generated higher yields and selectivity against traditional acid catalysts.³,⁴ Although the ability of acid-functionalized ILs has been demonstrated successfully in many reactions, their widespread use in process chemistry is still hampered by drawbacks such as catalyst homogeneity which makes it difficult for product isolation and catalyst recovery and also the use of relatively large amounts of ILs in biphasic systems which is costly and may cause toxicological concerns.⁵

To overcome these drawbacks, these homogeneous catalysts have been immobilized on the surface of solid-supported materials such as inorganic silica, especially porous inorganic materials with high surface areas⁶,⁷ and organic polymers.⁸,⁹ However, in heterogeneous reactions, a substantial decrease in activity of the immobilized catalyst is commonly observed; moreover, catalysts were recovered by tedious procedures such as centrifugation and filtration and this leads to loss of solid catalyst in the separation process. These issues can be addressed by magnetic separation.¹⁰,¹¹ Magnetic nanoparticles (MNPs) were more interesting for immobilization of homogeneous catalysts because their magnetic response causes simple separation of catalyst by using an external magnet. However, magnetic nanoparticles with core–shell structure may enable the development of a new type of catalyst. The shell consists of the catalytically active species, and the magnetic core can act as anchor to separate and recycle the catalyst.¹²,¹³

There are some reports on the use of magnetic heterogeneous Brønsted acid catalysts for the synthesis of organic compounds.¹⁴–²⁴ α-Aminophosphonates are an important class of biologically active compounds,²⁵,²⁶ and their synthesis has received considerable interest because of their structural analogy to α-amino acids. Also, α-aminophosphonates act as peptide mimics,²⁷ antibiotics, and pharmacological agents.²⁸ The synthesis of α-aminophosphonate involves a three-component reaction between an aldehyde, amine, and dialkyl or trialkyl phosphate promoted by Lewis or Brønsted acids.²⁹,³⁰ However these methods suffer from drawbacks such as long reaction time, use of hazardous and expensive catalysts, low yield of products, use of solvents, and harsh reaction conditions hence do not comply with green chemistry protocols. Along with this, most Lewis acids cannot be used in this one-pot reaction because of the presence of free amines and water produced in the imine formation. Therefore, the development of an effective, convenient, and green protocol for synthesis of α-aminophosphonates is still a challenge.

In continuation of our research on the development of synthetic methods³¹,³² and also introduce new catalysts for organic reactions,³³–³⁵ herein, we have developed an efficient method for the synthesis of α-aminophosphonate compounds in the presence of Fe₃O₄@SiO₂-2mimSO₃H catalyst as a recyclable catalysts in mild reaction conditions and excellent yields (Scheme 1).

Experimental
Preparation of Fe₃O₄ Magnetic Nanoparticles (MNPs). An iron salt solution was vigorously stirred (700 rpm) by mixing 0.005 mol of iron(III) (FeCl₃·6H₂O) and 0.0025 mol
of iron(II) (FeCl$_2$·4H$_2$O) in 50 mL of deoxygenated distilled water under N$_2$ atmosphere, such that Fe$^{3+}$/Fe$^{2+} = 2$ in molar. Twenty milliliters of 1.5 M NaOH was rapidly poured into the iron(III) salt solution under magnetic stirring at room temperature (RT). A black precipitate was instantly formed. After continuously stirring for 10 min, the precipitate was separated by centrifugation and washed with deoxygenated distilled water four times, followed with the deoxygenated anhydrous ethanol once, then vacuum-dried at 50 °C overnight, and thus the naked Fe$_3$O$_4$ nanoparticles were obtained.

**Fe$_3$O$_4$ Magnetic Nanoparticles Coated by Silica (Fe$_3$O$_4$@SiO$_2$).** Three grams of Fe$_3$O$_4$ magnetic nanoparticles was ultrasonically dispersed in a solution containing 240 mL of ethanol and 60 mL of water, and then loaded into a three-necked bottle. The pH value was adjusted to 9 with an ammonium solution and 4 mL of TEOS was added dropwise under vigorous stirring. After 10 h, the solution was heated at 50°C to further hydrolyze for another 12 h. The particles were again separated by centrifugation and washed with the deoxygenated distilled water and anhydrous ethanol, then vacuum-dried at 50 °C overnight.

**Synthesis of Fe$_3$O$_4$@SiO$_2$-2min.** Three grams of silica-coated Fe$_3$O$_4$ nanoparticles (Fe$_3$O$_4$@SiO$_2$) was ultrasonically dispersed in a solution containing 100 mL of toluene. Then, 6 mL of (3-chloropropyl)trimethoxysilane was added under reflux for 24 h. After cooling to room temperature, magnetic nanoparticles were separated by an external magnet and washed three times with dry methanol, and dried under vacuum for 24 h. After this step, 2 g of chloride-functionalized magnetic nanoparticle was suspended in 50 mL of dry methanol by sonication for 20 min. Then, an excess amount of sodium 2-methylimidazole (2 g, 20 mmol) was added under reflux condition for 48 h. Sodium 2-methylimidazole was produced by addition of 2-methylimidazole (1.64 g, 20 mmol) to sodium methoxide solution which was obtained from solving sodium methoxide (1.08 g, 20 mmol in methanol). After cooling to room temperature, functionalized magnetic nanoparticles were separated by an external magnet and washed three times with dry methanol, and dried under vacuum for 24 h.

**Synthesis of Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H.** The resulting Fe$_3$O$_4$@SiO$_2$-2min (1 g) was suspended again in 50 mL of CH$_3$Cl$_2$ and then an excess of CISO$_3$H (chlorosulfonic acid, 1 mL) was added dropwise for 2 h. Then, the mixture was vigorously stirred at room temperature for 12 h. The resulting Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H was magnetically separated and washed three times with methanol, and dried under vacuum for 24 h.

**pH Analysis of Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H.** To an aqueous solution of NaCl (1 M, 25 mL) with an initial pH 6.32, the Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H (0.1 g) was added and the resulting mixture stirred for 2 h after which the pH of solution decreased to 2.69. This was equal to a loading 0.51 mmol g$^{-1}$ of H$^+$. This result was confirmed by back-titration analysis of the Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H catalyst. To this analysis, first, 10 mL of a standard 0.1 M sodium hydroxide solution was added to 100 mg of the synthesized catalyst in a 50-mL Erlenmeyer flask. Excess base was neutralized by addition of a standard 0.1 M HCl solution to the equivalence point of titration. The required volume of HCl to this point was 9.49 mL. This was equal to a loading 0.51 mmol SO$_3$H g$^{-1}$.

**Elemental Analysis of Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H Catalyst.** For confirmation of catalyst loading obtained from TGA analysis, pH analysis, back-titration, and elemental analysis was carried out using a Vario EL-III CHNS elemental analyzer. Characterization of Fe$_3$O$_4$@SiO$_2$-2minSO$_3$H magnetic catalyst showed 1.69% S (≈ 0.53 mmol SO$_3$H g$^{-1}$). This result confirmed the catalyst loading obtained from pH analysis and back-titration.

**Results and Discussion**

**Preparation and Characterization of the Catalyst.** Supported ionic liquid catalysts were prepared either by...
simple physical adsorption or by covalent attachment of ILs onto the surface of a solid support. We chose the covalent attachment to immobilize the IL since this provided better stability in the catalytic reaction and less leaching during the work up. The catalyst (Fe₃O₄@SiO₂-2mimSO₃H) was synthesized in four steps. Briefly: the first step magnetic nanoparticles (MNPs) (Fe₃O₄) were synthesized by chemical coprecipitation in the basic condition. The resulting MNPs were mixed with TEOS at pH 9 and hydrolyzed to produce silica-coated Fe₃O₄ nanoparticles (Fe₃O₄@SiO₂). It is interesting to note that silica coating is one of the most ideal methods for protection of MNPs, due to its high chemical and thermal stabilities, large surface areas and good compatibilities. Then, (3-chloropropyl)triethoxysilane was treated with Fe₃O₄@SiO₂, where the binding between the groups occurred through covalent bonds giving 3-chloropropyl-silica-coated Fe₃O₄ nanoparticles. After this, nucleophilic addition of the sodium 2-methylimidazole to 3-chloropropyl-silica-coated Fe₃O₄ nanoparticles was done under reflux. Finally, addition of chlorosulfonic acid produced Fe₃O₄@SiO₂-2mimSO₃H catalyst (Scheme 2).¹¹,¹³,³⁶,³⁷

**Scheme 2.** Preparation of Fe₃O₄@SiO₂-2mimSO₃H as a Bronsted acid catalyst.

**Catalyst Characterization.** Figure 1 shows the FT-IR spectra of (a) Fe₃O₄@SiO₂, (b) Fe₃O₄@SiO₂ treated with (3-chloropropyl)triethoxysilane, (c) Fe₃O₄@SiO₂-2mim, and (d) Fe₃O₄@SiO₂-2mimSO₃H. As shown in Figure 1, peaks at 564 and 1097 cm⁻¹ are related to stretching vibration of Fe-O and Si-O, respectively. The bands at 807 and 467 cm⁻¹ in all spectra are due to the deformation of Si–O bond.³⁸ Absorption peaks at 2856 and 2926 cm⁻¹ are attributed to the stretching vibration of C–H groups. Absorption peak at 1462 cm⁻¹ is also associated with the stretching vibration of C=N bond. Additionally, the peak at about 1179 cm⁻¹ is attributed to the typical symmetric stretching vibration of S=O bond in SO₃H which can be seen as a shoulder near the Si–O peak.³⁹–⁴¹ Finally, the broad peak at 3447 cm⁻¹ and the band around 1670 cm⁻¹ are due to the O–H vibration and the bending vibration of water molecules adsorbed on the surface, respectively.

Thermogravimetric analysis (TGA) of Fe₃O₄@SiO₂-2mimSO₃H catalyst was performed to prove its thermal stability (Figure 2). The first weight loss curve around 100°C is attributed to the residual physisorbed water and organic solvents, which were applied during the catalyst preparation. The largest
showed that the encapsulation of nanoparticles was successful and the surface functionalizations were achieved using 3-chloropropyltriethoxysilane as a linker.

Transmittance (a) and SEM (b) images of Fe₃O₄@SiO₂-2mimSO₃H catalyst (Figure 3).

weight loss occurred after 100 °C which is a characteristic of the surface functionalities and the ionic liquid decomposition. From the weight loss in Fe₃O₄@SiO₂-2mimSO₃H, it was found that the loading of sulfonic acid grafted to the silica surface was 0.42 mmol g⁻¹. It is worth mentioning that this value of loading for Fe₃O₄@SiO₂-2mimSO₃H catalyst may not be so accurate because the dehydroxylation of residual silanol groups on the silica surface may occur despite decomposition on the surface after 100 °C. Therefore, pH analysis, back-titration, and elemental analysis (CHNS) are a better way to determine the loading of sulfonic acid grafted to the silica surface.

Both the scanning electron microscopy (SEM) and TEM showed that the encapsulated nanoparticles were present as uniform particles (Figure 3).

![Figure 1. FT-IR spectra of (a) Fe₃O₄@SiO₂, (b) Fe₃O₄@SiO₂ treated by (3-chloropropyl)triethoxysilane, (c) Fe₃O₄@SiO₂-2mim, and (d) Fe₃O₄@SiO₂-2mimSO₃H.](image)

![Figure 2. Thermal gravimetric analysis (TGA) of Fe₃O₄@SiO₂-2mimSO₃H catalyst.](image)

![Figure 3. TEM (a) and SEM (b) images of Fe₃O₄@SiO₂-2mimSO₃H catalyst.](image)

**Table 1.** Synthesis of α-Aminophosphonates Catalyzed by Fe₃O₄@SiO₂-2mimSO₃H*(a)

<table>
<thead>
<tr>
<th>Product</th>
<th>R¹CHO</th>
<th>R²NH₂</th>
<th>Time/min</th>
<th>Yield/%</th>
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<tr>
<td>4a</td>
<td>C₆H₅–</td>
<td>C₆H₅–</td>
<td>20</td>
<td>94</td>
</tr>
<tr>
<td>4b</td>
<td>4-Cl-C₆H₄–</td>
<td>C₆H₅–</td>
<td>25</td>
<td>92</td>
</tr>
<tr>
<td>4c</td>
<td>4-Me-C₆H₄–</td>
<td>C₆H₅–</td>
<td>55</td>
<td>87</td>
</tr>
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<td>4-Cl-C₆H₄–</td>
<td>50</td>
<td>85</td>
</tr>
<tr>
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<td>3-NO₂-C₆H₄–</td>
<td>C₆H₅–</td>
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<td>96</td>
</tr>
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<td>Furfuryl–</td>
<td>C₆H₅–</td>
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<td>92</td>
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<td>83</td>
</tr>
<tr>
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<td>C₆H₅–</td>
<td>4-Br-C₆H₄–</td>
<td>25</td>
<td>87</td>
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<td>2,6-Me-C₆H₄–</td>
<td>55</td>
<td>82</td>
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<td>4-Br-C₆H₄–</td>
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<td>4k</td>
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<td>82</td>
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<td>90</td>
<td>81</td>
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<td>n-Propyl–</td>
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<td>83</td>
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<td>4q</td>
<td>tert-Butyl–</td>
<td>C₆H₅–</td>
<td>70</td>
<td>80</td>
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</table>

*(a) Reaction conditions: aldehyde (1 mmol), aniline (1 mmol), triethyl phosphate (1.2 mmol), and Fe₃O₄@SiO₂-2mimSO₃H (5 mg), room temperature, solvent-free conditions. b) Isolated yield.

To check the activity of synthesis catalyst, we investigated the synthesis of α-aminophosphonates in a one-pot three-component procedure. In a typical reaction, the reaction of an aldehyde 1 (1.0 mmol), an amine 2 (1.0 mmol), and triethyl phosphate 3 (1.2 mmol) in the presence of Fe₃O₄@SiO₂-2mimSO₃H (5 mg, 0.21 mol %) Brønsted acid catalyst was done in a round bottom flask at room temperature for appropriate time in solvent-free conditions (Scheme 1). The proposed mechanism for the synthesis of α-aminophosphonates is also shown in Scheme 1. As seen from Scheme 1, the sulfonic active sites of the IL anchored in the silica surface can catalyze the reaction. After completion of the reaction indicated by TLC, CH₃Cl₂ was added and the catalyst was magnetically separated and washed with methanol, then dried in vacuum for the next runs. The organic phase was washed with water two times, dried over Na₂SO₄ and concentrated under vacuum. The crude mixture was purified by recrystallization in ethanol. In a similar manner, a wide range of aldehydes including aromatic and heteroaromatic and also amines reacted efficiently with triethyl phosphate under the same reaction conditions to give the corresponding substituted α-aminophosphonate products (Table 1).

Table 2 shows a comparison between catalytic efficiency of Fe₃O₄@SiO₂-2mimSO₃H and other catalysts found in the literature. As seen in Table 2, the reaction did not proceed without any catalyst at room temperature. Amberlite-IR 120, H₂SO₄, and NH₂SO₃H as catalyst at room temperature have given 31, 63, and 87% yield at different times. Using Fe₃O₄@SiO₂ as catalyst has given only 15% yield in 100 min. Entries 6 and 7 show a comparison between the activity of catalysts Fe₃O₄@SiO₂-2mimSO₃H (in our work) and MNP(CH₂)₃NH₂SO₃H in literature which have the same core-shell nanoparticles. Fe₃O₄@SiO₂-2mimSO₃H catalyst shows
Table 2. A Comparison between Catalytic Efficiency of Fe₃O₄@SiO₂-2mimSO₃H and Other Catalysts Found in Literature for the One-Pot Three-Component Coupling Reaction of Benzaldehyde, Aniline, and Triethyl Phosphite

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Amount of catalyst/mg</th>
<th>Time/min</th>
<th>Yield/% [Ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>120</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>Amberlite-IR 120</td>
<td>100</td>
<td>45</td>
<td>31 [11]</td>
</tr>
<tr>
<td>3</td>
<td>H₂SO₄</td>
<td>10</td>
<td>45</td>
<td>63 [11]</td>
</tr>
<tr>
<td>4</td>
<td>NH₄SO₃H</td>
<td>10</td>
<td>120</td>
<td>87 [11]</td>
</tr>
<tr>
<td>5</td>
<td>Fe₃O₄@SiO₂</td>
<td>20</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>MNP@((CH₂)₃NHSO₃H</td>
<td>30</td>
<td>60</td>
<td>78 [24]</td>
</tr>
<tr>
<td>7</td>
<td>Fe₃O₄@SiO₂-2mimSO₃H</td>
<td>5</td>
<td>20</td>
<td>94</td>
</tr>
</tbody>
</table>

a) Reaction conditions: solvent-free and room temperature.

Figure 4. Catalyst reusability. Reaction conditions: benzaldehyde (1.0 mmol), aniline (1 mmol), and triethyl phosphite (1.2 mmol), Fe₃O₄@SiO₂-2mimSO₃H (5 mg, 0.21 mol %) Brønsted acid catalyst quenched after 20 min, solvent-free, and room temperature.

more activity in the synthesis of α-aminophosphonates. Greater activity of Fe₃O₄@SiO₂-2mimSO₃H catalyst may be due to direct connection of sulfonic groups to the positive nitrogen atom of imidazolium aromatic ring which increases the activity of Fe₃O₄@SiO₂-2mimSO₃H catalyst with respect to MNP@((CH₂)₃NHSO₃H catalyst.

The structures of compounds 4a–4k were deduced from their IR and ¹H NMR spectroscopic data (See Supporting Information). For example, the ¹H NMR spectrum of 4a exhibited two triplets at 1.15, 1.31 (2CH₃) and two multiplets at 3.75, 3.96 (OCH₂CH₃), a broad singlet at 4.78 (NH), a doublet at 4.82 (J = 5.9 Hz, N-CH-P) and two multiplets at 6.45–6.75 (3CH arom), 7.13–7.51 (7CH arom).

It is interesting to note that magnetically driven separations made the recovery of catalysts in a liquid-phase reaction much easier than by cross-flow filtration and centrifugation, especially when the catalysts were in the sub-micrometer size range. The recyclability of the Fe₃O₄@SiO₂-2mimSO₃H catalyst was investigated in the synthesis of α-aminophosphonates by choosing a reaction between benzaldehyde, aniline and triethyl phosphate as modeling reaction at room temperature and solvent-free condition. After completion of the reaction, monitored by TLC, the immobilized catalyst was magnetically separated (Figure 4) and reused in another reaction vessel under the same conditions. As seen in Figure 4, even after six cycles, products were obtained in high yield.

Conclusion

We have developed a green and efficient magnetic catalyst for the synthesis of α-aminophosphonates in solvent-free conditions at room temperature. The catalyst was recycled and reused six times. The main advantages of the present synthetic protocol are mild, solvent-free conditions, green catalysis, and easy magnetic separation of the catalyst. It is expected that the present methodology will find application in organic synthesis.

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Supporting Information

Materials, General procedure for one-pot synthesis of α-aminophosphonates, and ¹H NMR of selected products. This material is available free of charge on J-STAGE.

References

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