



Mesoporous aluminosilicate nanocage-catalyzed three-component coupling reaction: an expedient synthesis of α -aminophosphonates

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ABSTRACT

Here we demonstrate for the first time the synthesis of α -aminophosphonates through the three-component coupling reaction of aldehydes, amines, and diethyl phosphite by using highly acidic 3D mesoporous aluminosilicate nanocage catalyst, which gave excellent yield with a high selectivity in a short reaction time due to its high acidity, 3D pores, and a huge space in the nanocages.

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1. Introduction

The synthesis of α -aminophosphonates, structural analogs of the corresponding α -amino acids and heterocyclic phosphonates, has been receiving much attention in synthetic and modern pharmaceutical chemistry owing to their application as peptide mimics, antibiotics, herbicides, anti-cancer, antifungal and antibacterial activities, and enzyme inhibitors.^{1–4} Consequently, various synthetic methods have been reported for the synthesis of α -aminophosphonates. Of these methods, three-component reaction of aldehyde, amines, and diethyl phosphite catalyzed by acid catalysts such as lanthanide triflate, InCl_3 , $\text{TaCl}_5\text{-SiO}_2$, $\text{Bi}(\text{NO}_3)_3\cdot 5\text{H}_2\text{O}$, sulfamic acid, oxalic acid, lithium perchlorate, and heteropoly acids is reported to be the best approach for the synthesis of α -aminophosphonates.⁵ Although the reaction was efficiently promoted by the above catalysts, they suffer from one or more disadvantages such as high cost, use of a huge amount of catalyst, moisture sensitive, and trigger environment related problems as they are highly corrosive and can not be regenerated for further use. Thus it is highly imperative to find out stable, cheap, and recyclable heterogeneous catalysts for the synthesis of α -aminophosphonates. Heterogeneous catalysts such as ionic liquids, $\text{SbCl}_3/\text{Al}_2\text{O}_3$, Amber-

lite-IR 120 resin, and $[\text{Cu}(3,4\text{-tmtppa})](\text{MeSO}_4)_4$ have also been used for the synthesis of α -aminophosphonates.⁶ Unfortunately, these catalysts possess poor textural characteristics such as a low surface area and pore volume which limit the efficiency of the catalysts. Zeolites and mesoporous materials have been widely used as heterogeneous catalysts in several organic transformations owing to their excellent textural characteristics such as high surface area, uniform pores, large pore volume, and high thermal stability.^{7,8} Unfortunately, the diameter of the pore channels of zeolites is too small to carry out the three-component coupling reactions. On the other hand, the usage of the mesoporous material for the synthesis of α -aminophosphonates is quite limited because of its low acidity. Because of these limitations, to the best of our knowledge, there has been no report available on the synthesis of α -aminophosphonates using mesoporous catalysts. Very recently, Vinu and co-workers reported the preparation of 3D mesoporous metallosilicate catalyst (AIKIT-5) with large cage-type pores and a high acidity, which showed superior performance in the acetylation of aromatics over zeolites and other mesoporous catalysts.⁹

Here we report on the use of the highly acidic AIKIT-5 catalysts for the synthesis of α -aminophosphonates through a three-component coupling reaction of aldehydes, amines, and diethyl phosphite. The catalyst was found to be highly active and selective, affording excellent yield with a high selectivity in a short reaction time.

AIKIT-5 was prepared by using pluronic F127, and tetraethyl orthosilicate and aluminum isopropoxide as a structure directing

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Table 1
One-pot synthesis of α -aminophosphonates using different catalysts and solvents

Entry	Catalyst	Solvent	Yield (%)
1	AIKIT-5(10)	Acetonitrile	86
2	AISBA-15(45)	Acetonitrile	70
3	AIMCM-41(23)	Acetonitrile	56
4	AIKIT-5(10)	Ethanol	70
5	AIKIT-5(10)	1,4-Dioxane	65
6	AIKIT-5(10)	1,2-Dichloroethane	68
7	AIKIT-5(10)	Toluene	45
8	AIKIT-5(10)	Tetrahydrofuran	52

agent, and the sources of silica and aluminium, respectively. The detailed synthesis and the textural characterization of the materials can be found in our previous reports.⁹ AIKIT-5(10) where the number in the parenthesis denotes the Si/Al ratio was used for the synthesis of α -aminophosphonates. AIKIT-5(10) possesses well-ordered 3D pore structure with a face-centered-cubic *Fm3m* symmetry and large cage-type pores. The specific surface area, pore volume, pore diameter, cage diameter, and the acidity of the AIKIT-5(10) is found to be 989 m²/g, 0.68 cm³/g, 6 nm, 12 nm, and 0.51 mmol of NH₃/g, respectively.

Initially, we have attempted the coupling of benzaldehyde (1), aniline (2), and diethyl phosphite (3) in the presence of AIKIT-5(10) in acetonitrile. A mixture of benzaldehyde (1 mmol, 0.106 g), aniline (1 mmol, 0.093 g), diethyl phosphite (1 mmol, 0.138 g), and AIKIT-5 (20 mg) in acetonitrile (2 mL) was stirred at 80 °C for the specified amount of time (Table 1). The catalyst was found to be highly active and the reaction was completed in 4 h at 80 °C, affording almost 86% yield for the desired product **4a** (Scheme 1). The activity of the catalyst was also compared with other mesoporous catalysts such as AISBA-15 and AIMCM-41. Of the catalysts studied, AIKIT-5(10) was found to be the best, showing high yield and the selectivity to α -aminophosphonates. These results indicate the combination of well-ordered 3D cage-type porous structure, large pore volume, robust wall structure, and a high acidity is indispensable for the efficient synthesis of α -aminophosphonates.

The three-component reaction was also carried out over AIKIT-5(10) in various solvents such as acetonitrile, ethanol, 1,4-dioxane, 1,2-dichloroethane, toluene, and tetrahydrofuran at 80 °C, and the results are presented in Table 1. Among the solvents studied, acetonitrile seemed to give a high conversion. Thus, acetonitrile was used as the solvent for the further studies.

Although the reaction proceeds smoothly at room temperature, it requires a long reaction time to achieve complete conversion of the reactants. This result provided the incentive to extend the process for various substrates. Interestingly, a large number of aromatic aldehydes participated effectively in the three-component coupling reaction and gave the corresponding α -aminophosphonates in high yields (Table 2). The products were fully characterized by ¹H NMR, IR, and mass spectral analysis and also by comparison with authentic samples.² It has been also found that this method is equally effective for both electron-rich as well as electron-deficient aldehydes.

The reaction was also successful with heteroaromatic substrates such as pyridine-2-carboxaldehyde and thiophene-2-carboxaldehyde (entries n and o, Table 2). Both aromatic and aliphatic amines worked well in this reaction to give the corresponding α -aminophosphonates. Reasonable yields were also obtained when less-reactive aliphatic aldehydes were used in the synthesis (Table 2, entries p–r).

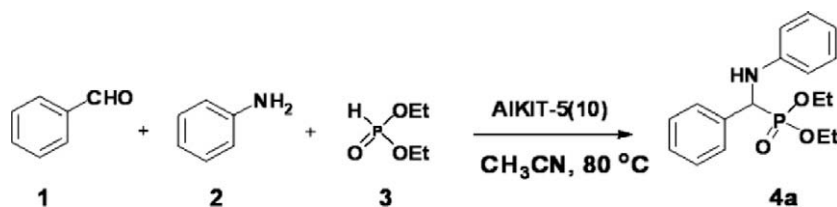
In general, the reactions were clean and the yields were high ranging from 65–94%. As can be seen in Table 2, the catalyst requires a less reaction time (3–6 h) to achieve a high yield of the α -aminophosphonates. The high activity of the AIKIT-5 is mainly due to its 3D cage-type pore structure where the reactant molecules can easily diffuse inside the channels and the large cages would allow the formation of the bulky intermediate during the course of the reaction. In addition, the acidity of the catalyst is very high and the large pore entrance of the cages in AIKIT-5 offers the easy access to the reactant molecules to adsorb on the active sites, affording a high yield to α -aminophosphonates.

Recycling experiments were conducted to find out the stability of the catalyst after the reaction. The catalyst was easily separated by centrifuge and reused after activation at 500 °C for 3–4 h. For example, the reaction of benzaldehyde, aniline, and diethyl phosphite gave the corresponding α -aminophosphonate in 86%, 83%, and 81% yields over three cycles. The reactions of several aldehydes, amines, and diethyl phosphite were examined in the presence of AIKIT-5(10) and the results were also summarized in Table 2. These results indicate that the AIKIT-5 catalyst is highly efficient for the synthesis of α -aminophosphonates and could avoid the necessity of anhydrous conditions, highly expensive and toxic reagents, and moisture sensitive Lewis acids. In addition, we have also carried out scale up experiments with 1 gm of benzaldehyde (entry a) using AIKIT-5. The catalyst gave the product yield of ca. 85% which is almost similar to the reported yield in Table 2 (entry a), revealing that the catalyst could easily be commercialized.

In conclusion, mesoporous 3D aluminosilicate nanocage catalyst with large cage type pores, high surface area, large pore volume, and a high acidity was found to be an excellent catalyst for the synthesis of α -aminophosphonates through a three-component coupling reaction of aldehydes, amines and diethyl phosphite. The catalyst afforded a high yield of the α -aminophosphonates in a short reaction time and can be recycled for several times without any loss in its activity. The heterogeneous nature, large cage type porous structure and a high acidity of the catalyst make the preparation of α -aminophosphonates simple, convenient and practical, and could solve the problems of corrosion, toxicity, waste production, and a high cost that are being currently encountered by the conventional homogeneous catalysts.

2. Experimental section

All chemicals and solvents were obtained from Aldrich and used without further purification. Column chromatographic separations were carried out on silica gel 100–200 mesh size. The ¹H NMR spectra of samples were recorded on a JEOL 300-MHz NMR spec-



Scheme 1. Synthesis of α -aminophosphonates using AIKIT-5(10).

Table 2
One-pot synthesis of α -aminophosphonates with different substrates using AIKIT-5(10)

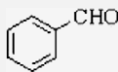
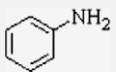
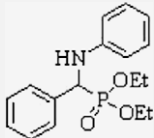
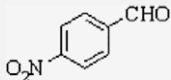
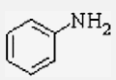
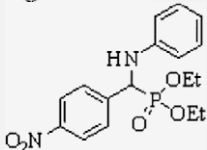
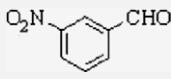
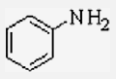
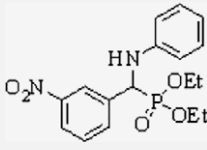
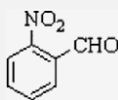
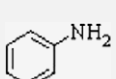
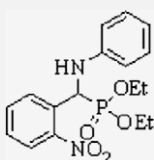
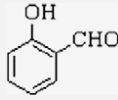
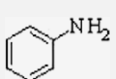
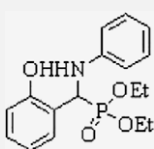
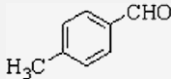
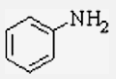
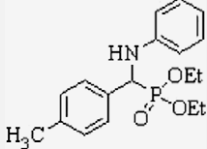
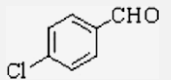
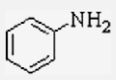
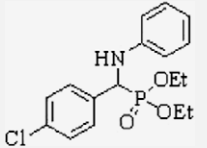
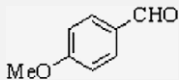
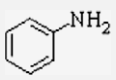
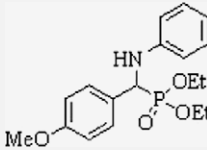
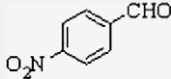
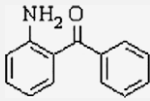
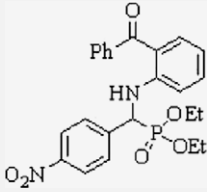
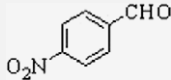
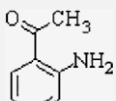
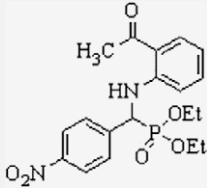
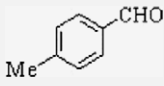

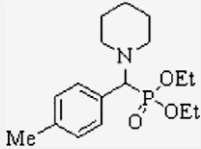
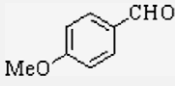

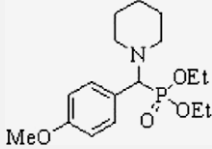
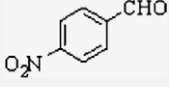
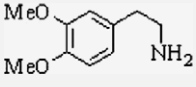
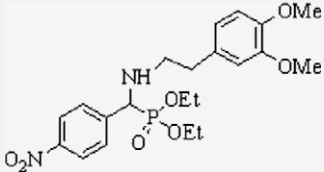
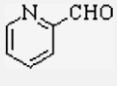
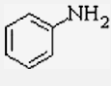
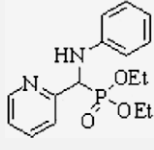
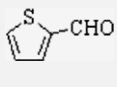
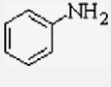
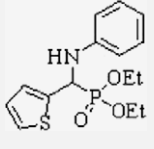
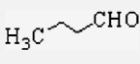
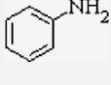
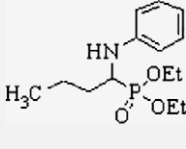

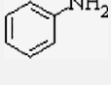
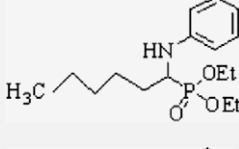

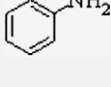
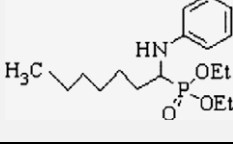
Entry	Aldehyde	Amine	Time (h)	Product	Yield (%)
a			4.0		86
b			3.0		94
c			3.0		85
d			3.0		79
e			4.0		83
f			3.5		90
g			3.5		92
h			4.0		90
i			5.0		85
j			5.0		65

Table 2 (continued)

Entry	Aldehyde	Amine	Time (h)	Product	Yield (%)
k			4.0		85
l			4.0		83
m			6.0		75
n			5.0		82
o			5.0		89
p			6.0		72
q			6.0		68
r			6.0		66

trometer using TMS as an internal standard in CDCl_3 . Mass spectra were recorded on a MALDI-MS.

The AIKIT-5 materials with different $n_{\text{Si}}/n_{\text{Al}}$ ratios were synthesized using polymeric Pluronic F127 as a template, and tetraethyl orthosilicate (TEOS) and aluminium isopropoxide as the sources of silicon and aluminium, respectively. In a typical synthesis, pluronic F127 (5 g) was dissolved in concd HCl (3 g, 35 wt %) and distilled water (240 g). To this mixture, TEOS (24 g) and the required amount of the aluminium source were added, and the resulting mixture was stirred for 24 h at 45 °C. Subsequently, the reaction mixture was heated for 24 h at 100 °C under static condition for hydrothermal treatment. After hydrothermal treatment, the final solid product was filtered off and then dried at 100 °C without washing. The white colored product was calcined at 540 °C for

10 h. The samples are denoted as AIKIT-5(x) where x denotes the $n_{\text{Si}}/n_{\text{Al}}$ ratio in the final product. The molar gel composition of the reaction mixture was 1.0:0.041–0.071:0.0035:0.25:116.6 $\text{SiO}_2/\text{Al}_2\text{O}_3/\text{F127}/\text{HCl}/\text{H}_2\text{O}$.

The powder X-ray diffraction (XRD) patterns of the AIKIT-5 catalysts with different Al contents were collected on a Rigaku diffractometer using $\text{CuK}\alpha$ ($\lambda = 0.154$ nm) radiation. The diffractograms were recorded in the 2θ range of 0.8–10° with a 2θ step size of 0.01° and a step time of 10 s. Nitrogen adsorption and desorption isotherms were measured at –196 °C on a Quantachrome Autosorb 1C sorption analyzer. All samples were outgassed at 250 °C for 24 h. The specific surface area was calculated using the Brunauer–Emmett–Teller (BET) method. The pore size distributions were obtained from the adsorption branch of the nitrogen

isotherms by Barrett–Joyner–Halenda method. Elemental composition of the materials was determined by inductively coupled plasma atomic emission spectrometry (ICP-AES). The temperature-programmed desorption (NH₃-TPD) was carried out on a Micromeritics Autochem 2910 instrument. Approximately 0.2 g of a fresh sample was placed in a U-shaped, flow-through, quartz microreactor for each experiment. The catalyst was activated at 500 °C for 6 h under He flow (20 mL/min) and then cooled to 100 °C before being exposed to ammonia. The sample was flushed again in He for 2 h to remove any physisorbed ammonia, and desorption profile was then recorded by increasing the sample temperature from 100 to 550 °C at a ramp rate of 5 °C/min.

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References and notes

1. Allen, J. G.; Atherton, F. R.; Hall, J. M.; Hassall, C. H.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 684; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 677; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 696.
2. Hassall, C. H.; Hahn, E. F. In *Antibiotics*; Springer: Berlin, 1983; Vol. IV. pp 1–11.
3. Yadav, J. S.; Reddy, B. V. S.; Raj, K. S.; Reddy, B.; Prasad, A. R. *Synthesis* **2001**, 2277.
4. Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29; Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845; Allen, C. M.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652; Maier, L.; Diel, P. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *1*, 57; Allen, J. G.; Atherton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbet, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56; Pratt, R. F. *Science* **1989**, *246*, 917.
5. Manabe, K.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **2000**, 669; Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141; Chandrasekhar, S.; Prakash, S. J.; Jagadeeshwar, V.; Narsihmulu, Ch. *Tetrahedron Lett.* **2001**, *42*, 5561; Bhattacharya, A. K.; Kaur, T. *Synlett* **2007**, 745; Mitragotri, S. D.; Pore, D. M.; Desai, U. V.; Wadgaonkar, P. P. *Catal. Commun.* **2008**, *9*, 1822; Vahdat, S. M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S. M.; Khaksar, S. *Tetrahedron Lett.* **2008**, *49*, 6501; Heydari, A.; Karimian, A.; Ipaktschi, J. *Tetrahedron Lett.* **1998**, *39*, 6729; Heydari, A.; Hamadi, H.; Pourayoubi, M. *Catal. Commun.* **2007**, *8*, 1224.
6. Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P. *Adv. Synth. Catal.* **2003**, *345*, 564; Ambica, K. S.; Taneja, S. C.; Hundal, M. S.; Kapoor, K. K. *Tetrahedron Lett.* **2008**, *49*, 2208; Bhattacharya, A. K.; Rana, K. C. *Tetrahedron Lett.* **2008**, *49*, 2598; Sobhani, S.; Safaei, E.; Asadi, M.; Jalili, F. *J. Organomet. Chem.* **2008**, *693*, 3313.
7. Dyer, A. In *Zeolite Molecular Sieves*; Wiley-VCH: Weinheim, 1988; Vol. X1. p 149.
8. Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710; Zhao, D.; Huo, Q.; Feng, J.; Chmelka, B. F.; Stucky, G. D. *J. Am. Chem. Soc.* **1998**, *120*, 6024; Zhao, D.; Feng, J.; Huo, Q.; Melosh, N.; Fredrikson, G.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*; Vinu, A.; Murugesan, V.; Hartmann, M. *Chem. Mater.* **2003**, *15*, 1385; Vinu, A.; Krithiga, T.; Murugesan, V.; Hartmann, M. *Adv. Mater.* **2004**, *16*, 1817; Vinu, A.; Murugesan, V.; Bohlmann, W.; Hartmann, M. *J. Phys. Chem. B* **2004**, *108*, 11496; Vinu, A.; Srinivasu, P.; Miyahara, M.; Ariga, K. *J. Phys. Chem. B* **2006**, *110*, 801; Vinu, A.; Hossain, K. Z.; Satish Kumar, G.; Ariga, K. *Carbon* **2006**, *44*, 530.
9. Srinivasu, P.; Alam, S.; Balasubramanian, V. V.; Velmathi, S.; Sawant, D. P.; Bohlmann, W.; Mirajkar, S. P.; Ariga, K.; Halligudi, S. B.; Vinu, A. *Adv. Funct. Mater.* **2008**, *18*, 640.