

Tetrabutylphosphonium amino acid ionic liquids as efficient catalysts for solvent-free Knoevenagel condensation reactions

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Abstract—Five tetrabutylphosphonium amino acid ionic liquids ([P₄₄₄₄][AA]) were prepared, characterized, and used as catalysts for solvent-free Knoevenagel condensation reactions. The tetrabutylphosphonium proline ([P₄₄₄₄][Pro]) showed excellent catalytic activity and selectivity in Knoevenagel condensation reactions of active methylene compounds with various aromatic aldehydes, and all the yields of corresponding products were more than 85% under mild conditions. Furthermore, a plausible reaction mechanism for the excellent performance of [P₄₄₄₄][Pro] has been proposed, and [P₄₄₄₄][Pro] could be used repetitively at least six times without obvious decrease in activity and quantity.

Keywords: Ionic Liquid, Knoevenagel Condensation, Aromatic Aldehydes, Active Methylene Compounds, Amino Acid

INTRODUCTION

The Knoevenagel condensation [1] of aldehydes with active methylene compounds (Scheme 1) is one of the most important reactions in organic chemistry for carbon-carbon double bond formation [2]. The condensation products, α,β -unsaturated carbonyl compounds, are the key intermediates for the synthesis of natural products [3], therapeutic drugs [4], polymer [5], cosmetics and perfumes [6]. Generally, this reaction is performed easily in organic solvents using weak bases as catalysts, such as primary, secondary or tertiary amines and their salts [2]. However, most of those conditions are associated with the disadvantages of hazardous and carcinogenic solvents and unrecoverability of the catalysts, which limits their applications in industrial process. Thus, the development of heterogeneous base catalyst for Knoevenagel condensation has attracted much attention, due to the effortless removal, recyclability and reusability of catalyst [7].

Over the past few years, various solid catalysts have been employed in this reaction such as hydrotalcites, mesoporous materials, magnetic nanoparticles, polymer, and metal-organic frameworks [8-14]. Good to excellent yields for corresponding products have been obtained in solution or under solvent-free conditions. However, there are still many drawbacks for these heterogeneous catalysts. For example, Lewis acidic catalyst ZnCl₂ is found to be unstable and easily hydrolyzed in water, resulting in the metal con-

tamination of the product [15]. High temperature, long time or microwave irradiation must be required for the reaction to achieve excellent yields [16-18].

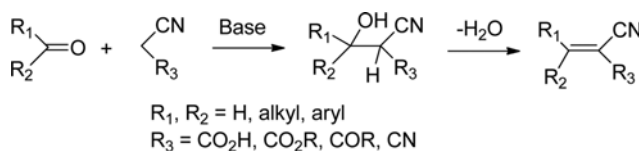
In recent years, ionic liquids (ILs) have attracted significant attention as environmental-friendly reaction media and green solvents for many chemical and biochemical transformations [19-26], due to their excellent thermal stability, negligible vapor pressure, tunable acidity, remarkable solubility and effortless reusability. Thus, much more functional ILs have been synthesized and utilized as catalysts for many organic reactions, such as Henry reaction [27], Friedel-Crafts reaction [28], Baylis-Hillman reaction [29], Fischer esterification [30], Diels-Alder reactions [31], Michael addition [32] and Knoevenagel condensation [33]. Numerous catalysis systems have been developed for these reactions with excellent results, but they often suffer from long reaction time, excessive catalyst amount, necessity of organic volatile solvents, and anhydrous environment. Therefore, from the viewpoint of green chemistry, it is still a great necessity to develop an efficient ILs catalytic system for solvent-free Knoevenagel condensation under mild conditions.

In this work, a series of tetrabutylphosphonium amino acid ionic liquids ([P₄₄₄₄][AA]) were synthesized via simple neutralization reactions, and then their catalytic behavior in Knoevenagel condensation reaction of active methylene compounds with various aromatic aldehydes was investigated under solvent-free conditions. The reaction parameters such as kind of ILs, temperature, catalyst loading, and initial molar ratio of reactants were explored in detail to obtain the optimum conditions. In addition, the reusability and the synergistic catalysis of [P₄₄₄₄][AA] catalyst were also studied to propose the possible reaction mechanism.

EXPERIMENTAL

1. Materials

Tetrabutylphosphonium bromide (purity $\geq 99\%$) and anion exchange resin 717(I) (purity $\geq 99\%$) were purchased from Aladdin (Shanghai, China). Other reagents such as aromatic aldehydes, ethyl cyanoacetate, malononitrile, amino acid, and ethanol were of ana-



Scheme 1. Base-catalyzed Knoevenagel condensation reactions.

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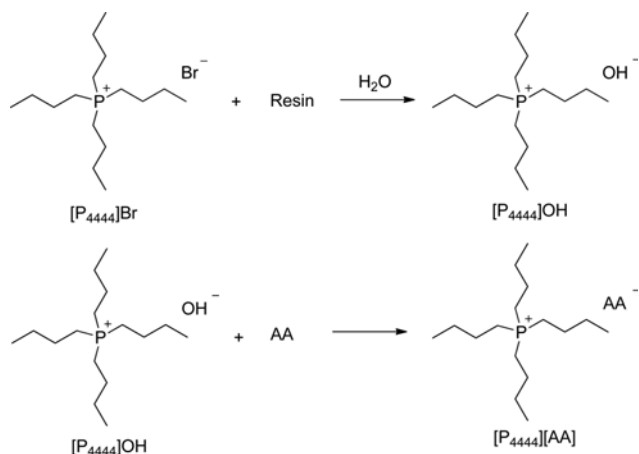


Fig. 1. General route for the synthesis of [P₄₄₄][AA] ILs.

lytical grade and used without any further purification.

2. Preparation and Characterization of [P₄₄₄][AA]

Five [P₄₄₄][AA] ILs, [P₄₄₄][Ser], [P₄₄₄][Pro], [P₄₄₄][Val], [P₄₄₄][Gly] and [P₄₄₄][Ala] were synthesized by the procedure as follows (Fig. 1). In the first step, [P₄₄₄]OH aqueous solution was obtained from the metathesis of [P₄₄₄]Br with anion exchange resin 717(I) following the method in the previous literature [34,35]. In the second step, [P₄₄₄]OH aqueous solution was then neutralized with a slight excess of amino acid by stirring at room temperature for 6 h. After being dried at 323 K under vacuum, ethanol was added to the residue and the solution was agitated completely so that the excess amino acids were deposited. After filtration, the ethanol was removed by evaporation. Then [P₄₄₄][AA] was in a vacuum oven containing P₂O₅ at 353 K for 48 h to remove the residual ethanol prior to use. Five [P₄₄₄][AA] ILs were thus obtained with the yields of more than 80% (on the base of [P₄₄₄]Br). After that, the structures of [P₄₄₄][AA] ILs were confirmed by ¹H NMR, FT-IR spectra, and thermal analysis (available as Supplementary Information).

3. Typical Procedures for the Knoevenagel Condensation

[P₄₄₄][AA] ILs catalyst was added into a round-bottom flask (25 mL) with a magnetic stirrer and condenser. Then, the reactor was heated to the designated temperature in an oil bath with stirring. The temperature of the reaction mixture was controlled with a temperature controller with an accuracy of ±0.01 K. After the reaction was completed, the reaction mixture was cooled and dissolved by dichloromethane. Then the mixture was extracted with deionized water (10 mL×3) to form a liquid-liquid biphas. The aqueous phase containing [P₄₄₄][AA] ILs can be isolated simply by decantation, and [P₄₄₄][AA] ILs thus was recovered and reused in the next run after heat treatment to remove water under vacuum at 353 K for 12 h. The organic phase composed of mainly products was then combined and analyzed by HP 6890 GC analyzer (Agilent) equipped with a hydrogen flame ionization detector (FID). A capillary column HP-1 (30 m×0.32 mm×1 μm) was used to determine the composition of the samples using *n*-dodecane as an internal standard in the presence of nitrogen as the carrier gas at a flow rate of about 3 mL/min. The temperature of the column, the inlet and the detector was kept at 523, 543, and 573 K, respectively. In addition, the reaction product analysis was further confirmed by GC-MS using a Hewlett-Packard GC-MS 5972 with an RTX-5MS column (30 m×

0.25 m×0.5 μm). The temperature program for GC-MS analysis heated samples from 333 to 553 at 10 K/min and held them at 553 K for 2 min. Inlet temperature was set constant at 553 K. MS spectra were compared with the spectra gathered in the NIST library, showing that no by-product was detected. Some ¹H NMR spectra of typical isolated products are listed in Supplementary Information.

4. Definition of Product Yield

The yield of Knoevenagel condensation product is defined as the ratio of the number of moles of Knoevenagel condensation product in the reaction to the total number of moles of aromatic aldehydes initially added.

$$\text{Yield} = \frac{\text{mol (Knoevenagel condensation product)}}{\text{moles of active methylene compounds initially added}}$$

RESULTS AND DISCUSSION

1. Catalyst Selection

The Knoevenagel condensation reaction of benzaldehyde with ethyl cyanoacetate in the presence of [P₄₄₄][AA] ILs as catalysts was conducted to assess their catalytic activity under solvent-free conditions. The results are summarized in Table 1. No product was detected in the blank reaction, showing that this Knoevenagel condensation is very difficult without catalyst (Entry 1). Moreover, it was obviously indicated that these five [P₄₄₄][AA] catalysts had different catalytic performance, and the sequence was [P₄₄₄][Pro]>[P₄₄₄][Val]>[P₄₄₄][Ala]=[P₄₄₄][Gly]>[P₄₄₄][Ser] (Entries 2-6). Among

Table 1. Results of Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate in the presence of [P₄₄₄][AA] ILs as catalysts^a

Entry	Catalyst	Yield of ethyl 2-cyano-3-phenylacrylate [%] ^b
1	Blank	-
2	[P ₄₄₄][Pro]	93
3	[P ₄₄₄][Val]	87
4	[P ₄₄₄][Ala]	85
5	[P ₄₄₄][Gly]	85
6	[P ₄₄₄][Ser]	81

^aReaction conditions: benzaldehyde (4.5 mmol), ethyl cyanoacetate (3 mmol), catalyst loading (1 wt% based on benzaldehyde), reaction temperature (313 K), reaction time (20 min)

^bGC-MS analysis, no by-product was detected

Table 2. pH values of different IL aqueous solutions^a

ILs	pH value
[P ₄₄₄][Pro]	9.67
[P ₄₄₄][Val]	9.57
[P ₄₄₄][Ala]	9.55
[P ₄₄₄][Gly]	9.15
[P ₄₄₄][Ser]	8.56

^aMeasured at 25 °C, concentration was 0.1 mol·L⁻¹

Table 3. The catalytic activities of various catalysts in Knoevenagel condensation

Catalyst	Reaction condition	Yield [%]	Ref.
Polyguanidine	15 min, 298 K, 20 mol% catalyst 3 mL H ₂ O solvent	92	[11]
AAPTM@K10	12 h, 298 K, 0.05 g catalyst solvent free	88	[16]
[DEMA][Ac]	30 min, 298 K, 20 mol% catalyst solvent free	99	[36]
CN-Mic	4 h, 363 K, 4.6 wt% catalyst 5 mL <i>n</i> -butanol solvent	51	[37]
NN-MCM-41	30 min, 393 K, 1 wt% catalyst solvent free	99	[38]
Ti-PCS	12 h, 323 K, 5 mol% catalyst ethyl acetate solvent	95	[39]
Recovered Pb (C catalyst)	18 h, 298 K, 1 mol% catalyst ethanol solvent	98	[40]
HMTA-AcOH	20 min, 303 K, 100 mol% catalyst 60 mL H ₂ O solvent	46	[41]
UMCM-1-NH2	130 min, 313 K 5 mL DMF solvent	72	[42]
IRMOF-3		62	
MIXMOF		63	
[P ₄₄₄₄][Pro]	20 min, 313 K, 1 wt% catalyst solvent free	93	This work

the ILs catalysts, [P₄₄₄₄][Pro] catalyzed the reaction to have the highest ethyl 2-cyano-3-phenylacrylate yield of 93% at 20 min. Therefore, these results in Table 1, together with pH values from Table 2, demonstrate that the catalytic activities of [P₄₄₄₄][AA] ILs are closely relevant to their basicities. The IL possessing strong basicity can induce relatively high yield in Knoevenagel condensation. Compared with the other four ILs, [P₄₄₄₄][Pro] shows more alkalinity and thus catalyzes the reaction to have the best yield.

Furthermore, we compared the catalytic performance of [P₄₄₄₄][Pro] with the results of other base catalysts published in 2013 [11, 16,36-42]. These catalysts included ionic liquids, microporous material, polymer, metal-organic frameworks and so on. The data listed in Table 3 show that most of these catalysts also exhibit considerable catalytic performance in the reaction, but always suffer from many harsh reaction conditions such as high temperature, long reaction time, large catalyst dosage, and the use of organic solvent. Therefore, [P₄₄₄₄][Pro] is considered to be a promising catalyst with high activity and selectivity for Knoevenagel condensation under mild reaction conditions (solvent free, short reaction time, low reaction

temperature, low catalyst dosage). [P₄₄₄₄][Pro] was thus chosen as the catalyst for further studies.

2. Optimization of Reaction Conditions

The investigation of the effect of temperature is very important because this information is essential for Knoevenagel condensation. Thus, the reaction of benzaldehyde with ethyl cyanoacetate was performed using [P₄₄₄₄][Pro] as the catalyst at temperatures ranging from 293 to 333 K. As seen from Fig. 2, the yield of ethyl 2-cyano-3-phenylacrylate increased rapidly with the increase of reaction temperature. For example, the yield increased obviously from 64% to 93% with the rise of temperature from 293 K to 313 K. However, while the temperature was further increased to 323 K and 333 K, the yield was only improved to a limited extent (from 93% to 96%). Therefore, an optimized reaction temperature would be chosen at 313 K.

As is well known, catalyst loading and molar ratio are very important factors in performing a reaction study. The effect of catalyst loading on Knoevenagel reaction was evaluated, and the results are shown in Fig. 3. Catalyst loading has an obvious influence on the

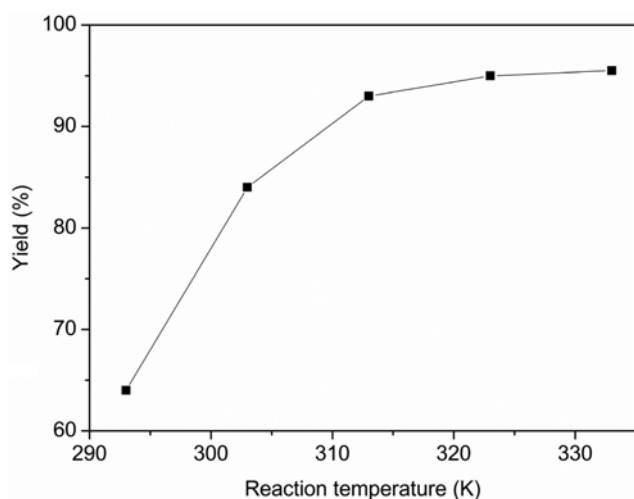


Fig. 2. Effect of reaction temperature on Knoevenagel condensation. Reaction conditions: benzaldehyde (4.5 mmol), ethyl cyanoacetate (3 mmol), catalyst loading (1 wt%), reaction time (20 min).

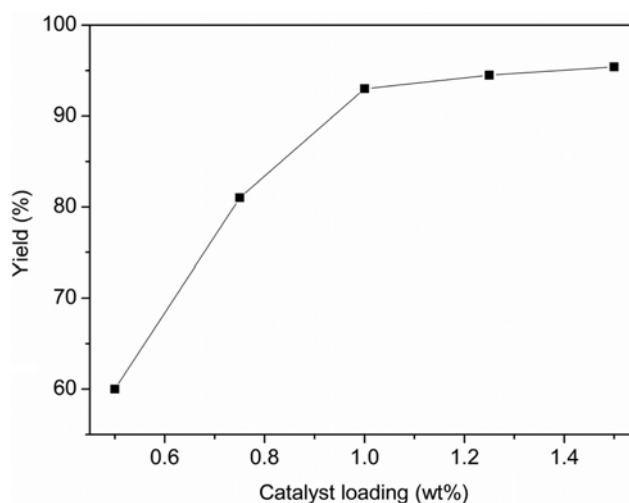


Fig. 3. Effect of catalyst loading on Knoevenagel condensation. Reaction conditions: benzaldehyde (4.5 mmol), ethyl cyanoacetate (3 mmol), reaction time (20 min), reaction temperature (313 K).

reaction. The yield of product increases rapidly by increasing the amount of catalyst. The yields increased from 60% to 93% with the rise of catalyst loadings from 0.5 wt% to 1 wt%. However, while the catalyst loading further increased to 1.25 and 1.5 wt%, the yield was only improved to a limited extent (from 93% to 96%). This means that too large catalyst loading is not favorable for this reaction. Thus, considering the reaction rate and the cost of ILs, 1 wt% is taken as the optimum catalyst loading and used in most of the Knoevenagel experiments, and this optimized catalyst loading is much lower than that in the case of other base catalysts [11,36,41]. In addition, Fig. 4 shows the effect of reaction time on Knoevenagel condensation. With the increase in reaction time, the product yield was enhanced. For example, when the reaction time was increased from 0 to 20 min, the yield significantly increased from 0% to 93%. However, only a slight increase in the yield was observed

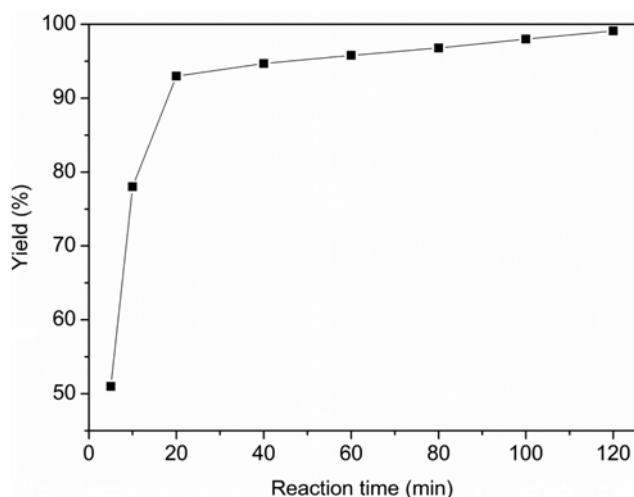


Fig. 4. Effect of reaction time on Knoevenagel condensation. Reaction conditions: benzaldehyde (4.5 mmol), ethyl cyanoacetate (3 mmol), catalyst loading (1 wt%), reaction temperature (313 K).

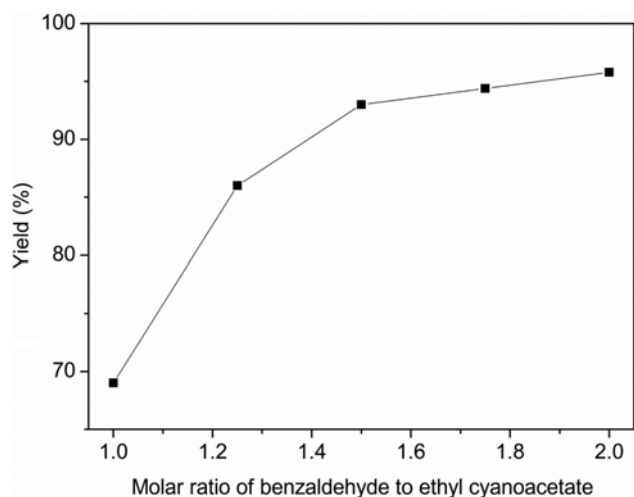


Fig. 5. Effect of initial molar ratio of benzaldehyde to ethyl cyanoacetate on Knoevenagel condensation. Reaction conditions: ethyl cyanoacetate (3 mmol), catalyst loading (1 wt%), reaction temperature (313 K), reaction time (20 min).

at the reaction time of 120 min. Beyond a certain reaction time, further increase in the reaction time is not very necessary, and an appropriate reaction time to choose would be 20 min for Knoevenagel condensation.

Fig. 5 shows the effect of benzaldehyde to ethyl cyanoacetate molar ratio on Knoevenagel condensation. Increasing the amount of benzaldehyde is beneficial to the yield of ethyl 2-cyano-3-phenylacrylate. For example, the yield was obviously increased from 68% to 93% in 20 min, while the initial molar ratio of benzaldehyde to ethyl cyanoacetate increased from 1 : 1 to 1.5 : 1. Nevertheless, the reaction rates in the initial molar ratio of 1.75 : 1 and 2 : 1 were just comparable to the case of 1.5 : 1, indicating that a further increase in the amount of benzaldehyde cannot continue to improve the yield. So an initial excess of benzaldehyde is not necessary for Knoevenagel condensation. In summary, the optimal molar ratio of benzaldehyde to ethyl cyanoacetate is suggested to be 1.5 : 1.

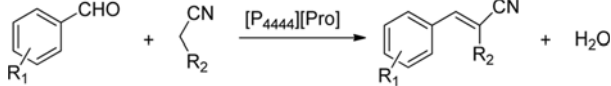
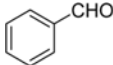
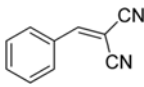
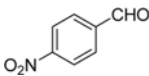
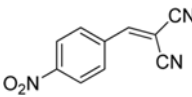
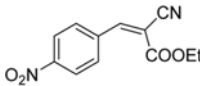
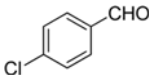
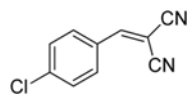
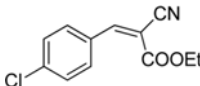
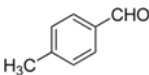
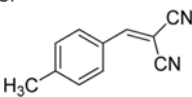
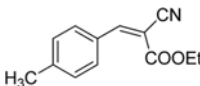
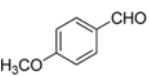
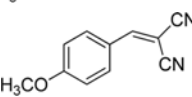
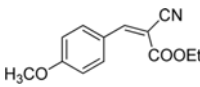
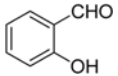
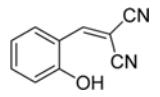
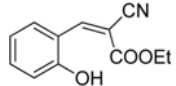
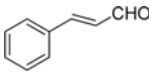
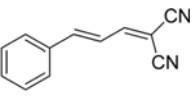
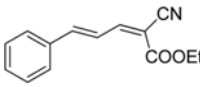
3. Knoevenagel Condensation of Active Methylene Compounds with Aromatic Aldehydes

With the aim of examining the wide application of $[P_{444}][AA]$ ILs, we further tested the activity of $[P_{444}][Pro]$ in a series of Knoevenagel condensations between various aromatic aldehydes and activated methylene compounds under the above-mentioned optimized conditions, and the corresponding results are listed in Table 4. It is obvious that all the substrates were received with good yields of Knoevenagel product within short reaction time, indicating that $[P_{444}][Pro]$ can be an efficient catalyst for Knoevenagel condensation. Compared to the Knoevenagel reactions of malononitrile with aromatic aldehydes, the reactions of ethyl cyanoacetate with the same aromatic aldehydes needed more time. Because the electron-withdrawing ability of the CN group is stronger than that of the carbonyl or carboxylic group, the methylene group of malononitrile is more activated than ethyl cyanoacetate, and readily reacts with aromatic aldehydes [36]. Furthermore, the electron donor/withdrawing capability of substituent in the benzene ring of benzaldehyde derivatives has a significant effect on the relevant Knoevenagel condensation. Higher yields were obtained in the cases of benzaldehyde derivatives with electron withdrawing substituent such as 4-nitrobenzaldehyde and 4-chlorobenzaldehyde due to the role of -I effect (electron withdrawing inductive effect) (Entries 2, 3). The electron donating group such as $-CH_3$, $-OCH_3$, and $-OH$ on the aromatic ring decreases the yields due to existence of -I effect (electron donating inductive effect) (Entries 4-6). These results agree well with the mechanism of imine intermediate involved in the amine-catalyzed Knoevenagel condensation [16].

4. Recycling of Catalyst

The recovery and reuse of catalysts is highly preferable for a greener chemical process. Thus, the catalyst $[P_{444}][Pro]$ was recycled for six times to test its activity as well as stability. The data obtained in six consecutive runs are shown in Fig. 6. The experimental results indicated that no obvious drop in product yield was observed during these six successive recycles, which shows that the IL catalyst is stable enough and the presence of water produced in the Knoevenagel condensation reaction has less impact on the catalytic activity of $[P_{444}][Pro]$. The slight decrease in the activity may be ascribed to the slight loss of $[P_{444}][Pro]$ due to the transferring of samples during the regeneration. In addition, compared with the fresh $[P_{444}][Pro]$ catalyst, these above characteristic bands also appeared in the

Table 4. Results of Knoevenagel reaction between various aromatic aldehydes and activated methylene compounds over [P₄₄₄₄][Pro]^a

					
Entry	Aromatic aldehyde	R2	Product	Reaction time [min]	Yield [%] ^b
1		CN		1	89
2		CN		1	97
		COOEt		15	95
3		CN		1	92
		COOEt		15	91
4		CN		2	87
		COOEt		20	88
5		CN		2	92
		COOEt		20	91
6		CN		3	99
		COOEt		20	90
7		CN		3	94
		COOEt		20	85

^aReaction conditions: aromatic aldehydes (4.5 mmol), active methylene compounds (3 mmol), catalyst loading (1 wt%), reaction temperature (313 K)

^bGC-MS analysis, no by-product was detected

reused [P₄₄₄₄][Pro] catalyst (Fig. S3 in Supplementary Information). This further indicated that [P₄₄₄₄][Pro] catalyst could be very stable in Knoevenagel condensation reactions for several runs.

5. Reaction Mechanism

Fig. 7 depicts a plausible mechanism for [P₄₄₄₄][Pro] catalyzed Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate. First, the C=O bond of aromatic aldehydes can be activated by the formation of hydrogen bond (N-H...O) with the secondary amine group of [P₄₄₄₄][Pro]. The next step involves abstraction of

acidic proton from the active methylene group of ethyl cyanoacetate by the carboxyl group of [P₄₄₄₄][Pro]. The conjugate base carboanion is stable due to conjugation with the cyano groups. Then, this carboanion makes nucleophilic attack on the carbonyl-carbon atom of aromatic aldehydes to form oxyanions. The oxyanions abstract H⁺ from the protonated carboxyl group of [P₄₄₄₄][Pro] and then the catalyst [P₄₄₄₄][Pro] is regenerated [43]. After that, the formed hydroxyl molecule eliminates water molecules, leading to the formation of Knoevenagel product. Therefore, it is obviously demon-

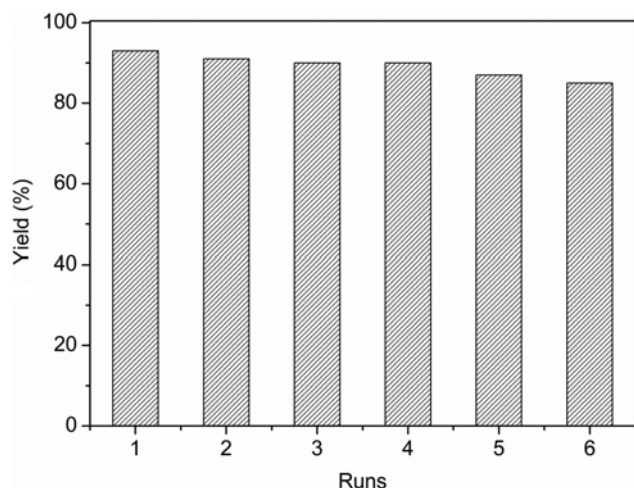


Fig. 6. The recycle test of $[P_{444}][Pro]$ catalyst. Reaction conditions: benzaldehyde (4.5 mmol), ethyl cyanoacetate (3 mmol), catalyst loading (1 wt%), reaction time (20 min), reaction temperature (313 K).

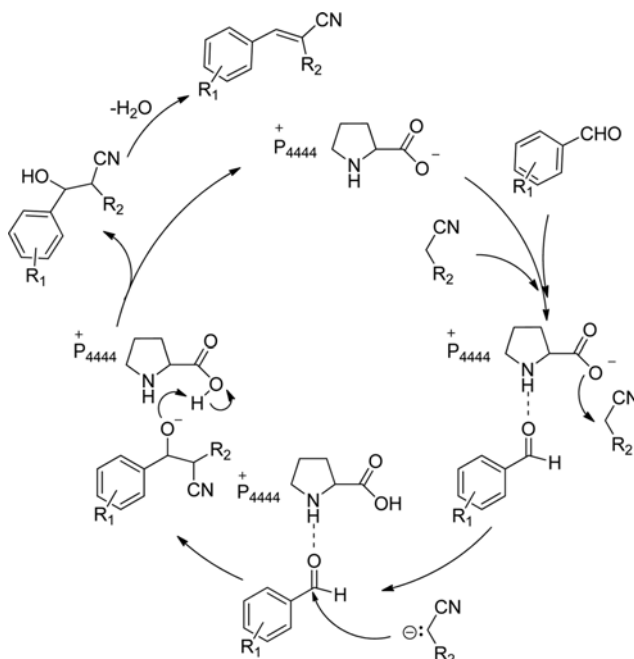


Fig. 7. Plausible reaction mechanism for Knoevenagel condensation over $[P_{444}][Pro]$.

strated that the synergistic dual activation catalysis of $[P_{444}][Pro]$ is highly favorable for Knoevenagel condensation and thus catalyzes this reaction to have good yields of Knoevenagel product.

CONCLUSIONS

Five $[P_{444}][AA]$ ILs were prepared successfully and applied in the Knoevenagel condensations of aromatic aldehydes with active methylene compounds. Among five ILs, $[P_{444}][Pro]$ was investigated as an efficient catalyst for solvent-free Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate with the highest yields

of 93%. $[P_{444}][Pro]$ also showed excellent catalytic activities in other Knoevenagel reactions of benzaldehyde derivatives with various electro-donating and electro-withdrawing substituents. The catalyst can be readily recovered and reused up to six runs without loss of catalytic activity. All of these features make $[P_{444}][Pro]$ a remarkable candidate for solvent-free Knoevenagel condensation. The use of the $[P_{444}][AA]$ ILs in other base-catalyzed reactions is in progress.

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Supporting Information

Tetrabutylphosphonium amino acid ionic liquids as efficient catalysts for solvent-free Knoevenagel condensation reactions

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Five $[P_{4444}][AA]$ ILs had been synthesized via simple acid-base neutralization reactions, and all the yields of such ILs were more than 80%. 1H NMR (Bruker DPX-300), FT-IR spectra (Thermo Nicolet 870) and thermogravimetry (PerkinElmer Diamond TG/DTA) characterization for each $[P_{4444}][AA]$ ILs synthesized.

$[P_{4444}][Gly]$. 1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 12H, $(CH_3CH_2CH_2CH_2)_4P$), 1.53 (s, 16H, $(CH_3CH_2CH_2CH_2)_4P$), 1.69 (s, 1H, CH_2NH_2), 2.42 (s, 8H, $(CH_3CH_2CH_2CH_2)_4P$), 3.16 ppm (s, 1H, CH_2NH_2). FT-IR $\bar{\nu}$ =2958, 2931, 2872, 1589, 1593, 1465, 1377, 1090, 907, 863 cm^{-1} . (Yield 87% based on the amount of $[P_{4444}][Br]$).

$[P_{4444}][Ala]$. 1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 12H, $(CH_3CH_2CH_2CH_2)_4P$), 1.30 (s, 3H, CH_3CH), 1.53 (s, 16H, $(CH_3CH_2CH_2CH_2)_4P$), 2.43 (s, 8H, $(CH_3CH_2CH_2CH_2)_4P$), 3.28 ppm (s, 1H, $CHNH_2$). FT-IR $\bar{\nu}$ =2958, 2931, 2872, 1465, 1377, 1161, 1097, 907, 863 cm^{-1} . (Yield 89% based on the amount of $[P_{4444}][Br]$).

$[P_{4444}][Ser]$. 1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 12H, $(CH_3CH_2CH_2CH_2)_4P$), 1.53 (s, 16H, $(CH_3CH_2CH_2CH_2)_4P$), 2.36 (s, 8H, $(CH_3CH_2CH_2CH_2)_4P$), 3.26 (s, 1H, $CHNH_2$), 3.47-3.52 (m, 1H, CH_2CH), 3.69 ppm (m, 1H, CH_2CH). FT-IR $\bar{\nu}$ =2958, 2931, 2872, 1594, 1465, 1381, 1098, 1043, 907, 817 cm^{-1} . (Yield 85% based on the amount of $[P_{4444}][Br]$).

$[P_{4444}][Pro]$. 1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 12H, $(CH_3CH_2CH_2CH_2)_4P$), 1.53 (s, 16H, $(CH_3CH_2CH_2CH_2)_4P$), 1.68 (m, 2H, CH_2CH_2CH), 1.96-2.10 (m, 2H, CH_2CH_2CH), 2.40 (s, 8H, $(CH_3CH_2CH_2CH_2)_4P$), 2.89 (m, 1H, CH_2NH), 3.14 (m, 1H, CH_2NH), 3.63 ppm (m, 1H, $CHNH$). FT-IR $\bar{\nu}$ =2958, 2931, 2872, 1584, 1465,

1367, 1098, 907, 816 cm^{-1} . (Yield 88% based on the amount of $[P_{4444}][Br]$).

$[P_{4444}][Val]$. 1H NMR (300 MHz, $CDCl_3$) δ 0.86-0.97 (m, 18H, $(CH_3CH_2CH_2CH_2)_4P+(CH_3)_2CH$), 1.52 (s, 16H, $(CH_3CH_2CH_2CH_2)_4P$), 2.16 (s, 1H, $(CH_3)_2CH$), 2.46 (s, 8H, $(CH_3CH_2CH_2CH_2)_4P$), 3.05 ppm (s, 1H, $CHNH_2$). FT-IR $\bar{\nu}$ =2958, 2931, 2872, 1584, 1465, 1381, 1098, 907, 817 cm^{-1} . (Yield 87% based on the amount of $[P_{4444}][Br]$).

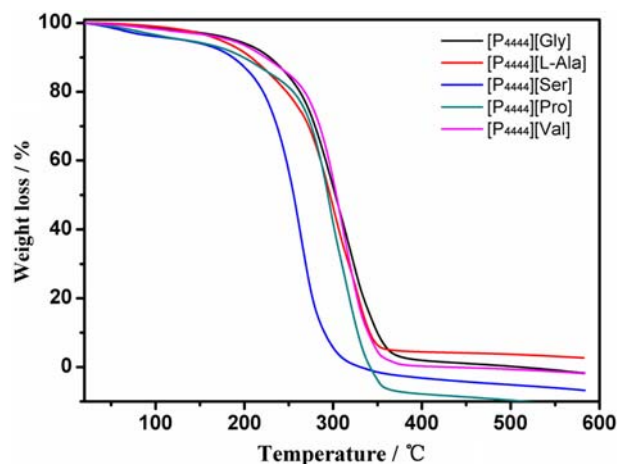


Fig. S2. TGA curves for five $[P_{4444}][AA]$ ILs.

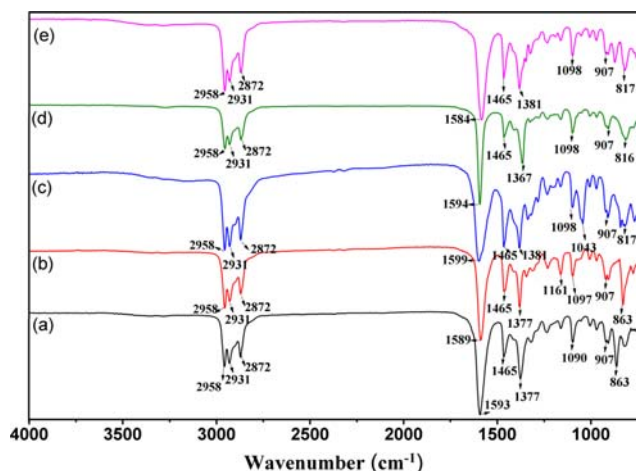


Fig. S1. FT-IR spectra of (a) $[P_{4444}][Gly]$, (b) $[P_{4444}][Ala]$, (c) $[P_{4444}][Ser]$, (d) $[P_{4444}][Pro]$, (e) $[P_{4444}][Val]$.

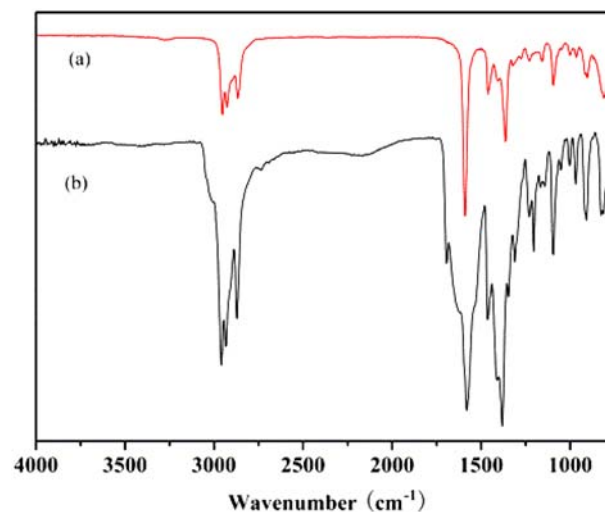
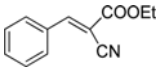
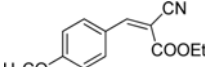
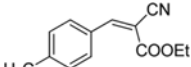


Fig. S3. FT-IR spectra of fresh $[P_{4444}][Pro]$ catalyst (a), and used $[P_{4444}][Pro]$ catalyst after 6 times run (b).

¹H NMR spectra for several typical isolated Knoevenagel condensation products.

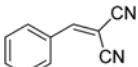
 ¹H NMR (300 MHz, CDCl₃) δ 1.40 (t, J =7.1 Hz, 3H, CH₃) 4.39 (q, J =7.1 Hz, 2H, CH₂) 7.48-7.59 (m, 3H, ArH) 8.00 (d, J =7.2 Hz, 2H, ArH) 8.25 ppm (s, 1H, CH=).

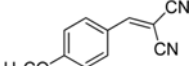
 ¹H NMR (300 MHz, CDCl₃) δ 1.40 (t, J =7.1 Hz, 3H, CH₃) 3.91 (s, 3H, CH₃O) 4.38 (q, 2H, CH₂) 7.01 (d, J =8.9 Hz, 2H, ArH) 8.02 (d, J =8.9 Hz, 2H, ArH) 8.19 ppm (s, 1H, CH=).

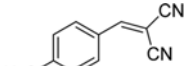
 ¹H NMR (300 MHz, CDCl₃) δ 1.41 (t, J =7.2 Hz, 3H, CH₃) 2.44 (s, 3H, Ar-CH₃) 4.37 (q, J =7.2 Hz, 2H, CH₂) 7.31 (d, J =8.1 Hz, 2H, ArH) 7.94 (d, J =8.1 Hz, 2H, ArH) 8.23 ppm (s, 1H, CH=).

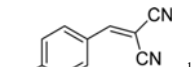
 ¹H NMR (300 MHz, CDCl₃) δ 1.42 (t, J =7.1

Hz, 3H, CH₃) 4.43 (q, J =7.1 Hz, 2H, CH₂) 7.68 (d, J =8.6 Hz, 2H, ArH) 7.88 (d, J =8.6 Hz, 2H, ArH) 8.21 ppm (s, 1H, CH=).

 ¹H NMR (300 MHz, CDCl₃) δ 7.55 (t, J =8.1 Hz, 2H, ArH) 7.64 (t, J =7.6 Hz, 1H, ArH) 7.78 (s, 1H, CH=) 7.91 ppm (d, J =7.6 Hz, 2H, ArH).

 ¹H NMR (300 MHz, CDCl₃) δ 3.92 (s, 3H, CH₃O) 7.01 (t, J =8.8 Hz, 2H, ArH) 7.66 (s, 1H, CH=) 7.90 ppm (d, J =8.8 Hz, 2H, ArH).

 ¹H NMR (300 MHz, CDCl₃) δ 2.46 (s, 3H, CH₃) 7.34 (t, J =8.1 Hz, 2H, ArH) 7.72 (s, 1H, CH=) 7.81 ppm (d, J =8.1 Hz, 2H, ArH).

 ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, J =8.7 Hz, 2H, ArH) 7.74 (s, 1H, CH=) 7.78 ppm (d, J =8.7 Hz, 2H, ArH).