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DBU Derived Ionic Liquids and Their Application in Organic Synthetic Reactions

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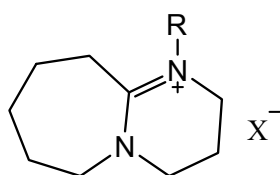
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1. Introduction

With the continuing depletion of natural resources and the growing environmental awareness, current and future chemists are being trained to develop synthetic routes in economically beneficial manner. One strategy to realize these green processes in organic synthesis is the replacement of toxic volatile organic solvents with environmentally more benign reaction mediums. Among the novel green solvents that have been reported, ionic liquids (ILs) have been one of the most active areas of green chemistry over the past decade, due to their excellent chemical and thermo properties such as good thermal stability, negligible vapor pressure, ease of handling, potential for recycling, good coordinating and dissolving capability. Thus, ILs were widely used in various organic transformations (Miao & Chan, 2006; Ying et al., 2008; Ying et al., 2008). However, most of the ILs studied by chemists are structurally based on imidazole which is inert for organic reactions. So the need for the developments of novel task-specific ionic liquids still exists.

On the other hand, 1,8-diazabicyclo[5.4.0]undec-7-ene(2,3,4,6,7,8,9,10- octahydroimidazo[1,2-a]azep-ine, DBU) was found to be superior to other tertiary amines as catalyst, base or promoter. For example, using DBU as catalyst for Balyis-Hillman reaction and aza-Michael addition was reported by Aggarwal and Kim respectively (Aggarwal & Mereu, 1999; Yeom et al., 2007). DBU-mediated CO₂-fixation reaction (Yoshida et al., 2008), DBU-promoted, S-N-type Smiles and Ireland-Claisen rearrangement reactions (Ma et al., 2007; Li et al., 2007), DBU-catalyzed addition reactions of sulfonylimidates (Matsubara & Kobayashi, 2008), DBU-promoted chemoselective cleavage of acetylenic TMS group (Yeom et al., 2008), and DBU-assisted unusual dehydrogenation (Kim et al., 2008) were all found to be very efficient. Considering the special role that DBU played in organic synthesis, ionic liquids with a DBU moiety (Scheme 1) were developed (Tolstikou & Shainyan, 2006). Because of its large size, low symmetry of cationic moiety and charge delocalization over the N-C=N triad render these type of ionic liquids low melting points.

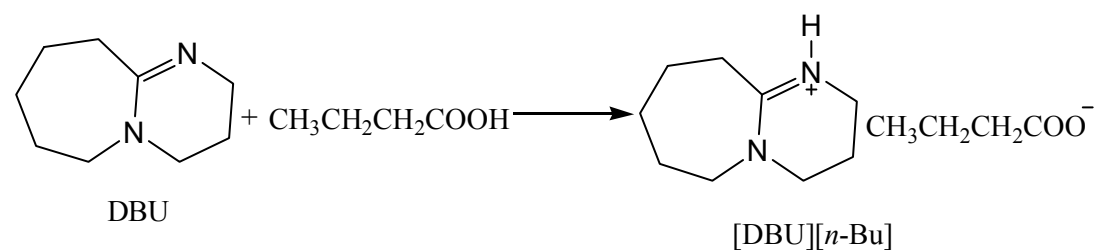
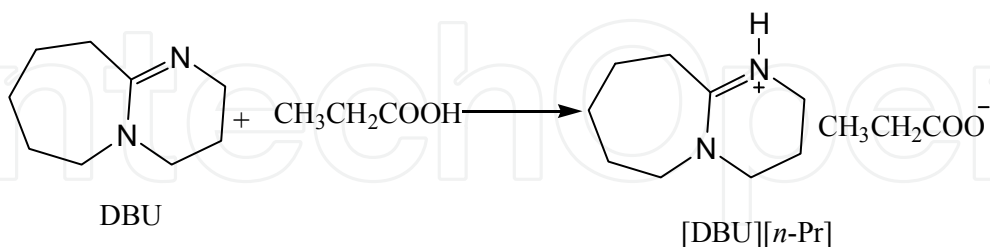
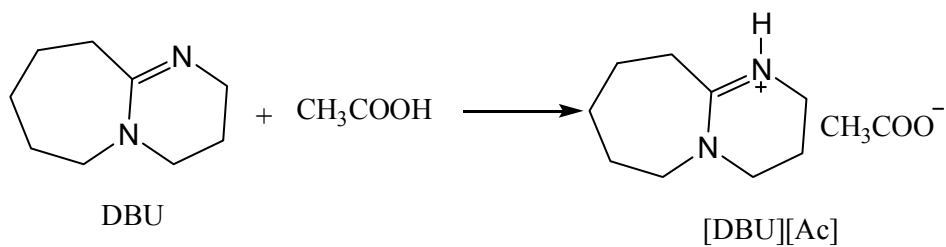
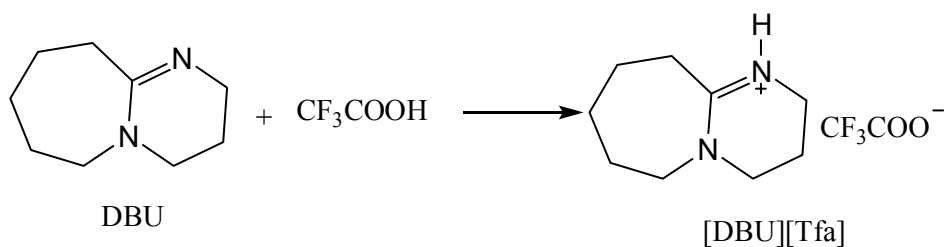
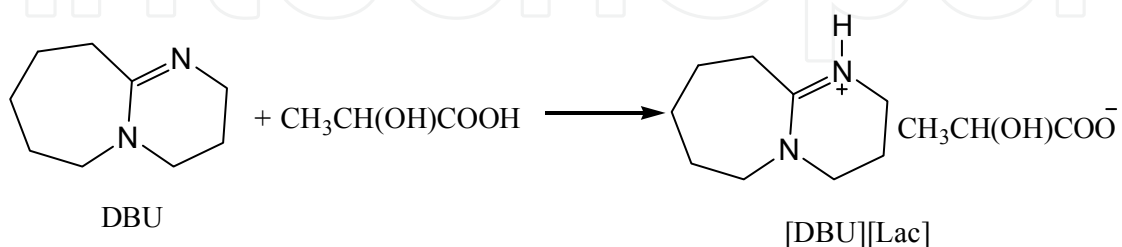
However, the salts in Scheme 1 are inert and can only be used as reaction solvents. Then, we attempted to develop a new class of task-specific DBU-derived ionic liquids which could not only serve as reaction medium but also as catalyst or promoter. The preparation of the five novel ILs can be simply realized by neutralization reaction of DBU and the corresponding carboxyl acids, including acetic acid, lactic acid, propionic acid and butyric acid (Scheme 2) (Ying et al., 2009; Ying et al., 2010; Ying, 2010). Among these ILs, [DBU][Tfa]



R=Me, Et, Bu, PhCH₂, H(CF)_nCH₂;

X=Cl, Br, OTs, OTf.

Scheme 1



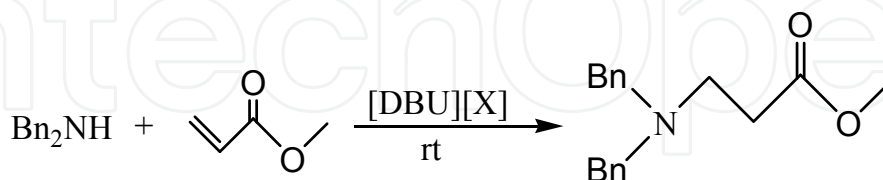
Scheme 2

is liquid with weak acidity at room temperature, while the other four ionic liquids, [DBU][Ac], [DBU][Lac], [DBU][n-Pr] and [DBU][n-Bu] show property of weak basicity^[11]. Next, we will investigate the applications of the novel DBU-based ionic liquids in Michael addition and Knoevenagel condensation. To improve the recycling capability, ionic liquids immobilized on Magnetic nanoparticles (MNP) will also be summarized in this chapter.

2. Application in Michael addition

2.1 Michael addition (aliphatic amines as Michael donors)

Carbon-nitrogen bond forming reaction is one of the most important methodologies in synthetic organic chemistry for preparation of β -aminocarbonyl compounds, which not only constitute a component of biologically active natural products but also serve as a key intermediate for the synthesis of β -aminoalcohols, β -lactams and β -amino acids (Kleinmann, 1991; Georg, 1993; Corey, 1989). Mannich reaction between enolates and imines provide a classic route for the construction of β -amino carbonyl compounds (Arend et al., 1998; Kobayashi & Ishitani, 1999). However, this type of reaction often requires harsh reaction conditions and long reaction time. Compared with the Mannich reaction, the aza-Michael addition of amines to electron deficient alkenes has attracted considerable attention as an alternative protocol for C-N bond formation due to its atomic economy and operational simplicity. Most aza-Michael reactions are usually carried out with a strong acid or a base, which would lead to by-products or undesired harmful residues. Thus, milder Lewis acidic catalysts such as LiClO_4 (Azizi & Said, 2004), $\text{Yb}(\text{OTf})_3$ (Jenner, 1995; Matsubara et al., 1994), $\text{Bi}(\text{NO}_3)_3$ (Srivastava & Banik, 2003), $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ (Xu et al., 2004), $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Bartoli et al., 2001), InCl_3 (Loh & Wei, 1998), SmI_2 (Reboule et al., 2005), $\text{Cu}(\text{OTf})_2$ (Xu et al., 2005), and so on are employed in the Michael protocol. Recently, some novel reagents used as catalyst or promoter in conjugate addition have been reported, including β -cyclodextrin (Surendra et al., 2006), bromodimethylsulfonium bromide (Khan et al., 2007), boric acid in water (Chaudhuri et al., 2005), $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ on montmorillonite K10 (Hashemi et al., 2006), imidazolium-based polymer supported CuI (Alleti et al., 2008), $\text{KF}/\text{Al}_2\text{O}_3$ (Kantam et al., 2008), $[\text{HP}(\text{HNCH}_2\text{CH}_2)_3\text{N}]\text{NO}_3$ (Yang et al., 2005), etc. However, many of the above methods suffered from some drawbacks, such as the requirement for a large excess of reagents, substrate-selective for some catalysts, and often involvement of some toxic solvents such as 1,2-dichloroethane or acetonitrile.



Among the five ionic liquids, [DBU][Ac] showed slightly higher catalytic activity than the other ionic liquids (Table 1, entry 7 and entries 10-13). For the comparison with DBU as promoter for aza-Michael addition reported by Kim et al., 50 mol % of the ionic liquid [DBU][Ac] was employed for the model reaction between dibenzylamine and methyl acrylate in acetonitrile at room temperature (Yeom et al., 2007). The reaction catalyzed by [DBU][Ac] was slightly faster than that promoted by its parent base DBU (Table 1, entries 1-2), indicating the rationality of [DBU][Ac] as catalyst for the reaction. Other solvents such as methanol, toluene, and dichloromethane were also tested and they were all effective

Entry	Catalyst	Solvent	Catalyst amount (mmol)	Time (h)	Yield (%)
1b	DBU	Acetonitrile	0.5	6	95
2	[DBU][Ac]	Acetonitrile	0.5	5	94
3	[DBU][Ac]	Methanol	0.5	5	86
4	[DBU][Ac]	Toluene	0.5	5	89
5	[DBU][Ac]	Dichloromethane	0.5	5	90
6	[DBU][Ac]	Solvent-free	0.5	4.5	96
7	[DBU][Ac]	Solvent-free	0.3	4.5	95
8	[DBU][Ac]	Solvent-free	0.1	4.5	72
9	[DBU][Ac]	Solvent-free	0.01	4.5	43
10	[DBU][Tfa]	Solvent-free	0.3	4.5	83
11	[DBU][Lac]	Solvent-free	0.3	4.5	92
12	[DBU][<i>n</i> -Pr]	Solvent-free	0.3	4.5	89
13	[DBU][<i>n</i> -Bu]	Solvent-free	0.3	4.5	83

Table 1. Aza-Michael reaction of dibenzylamine (1 mmol) with methyl acrylate (1.3 mmol) under **various reaction conditions**

^a Isolated yields. ^b reference (Yeom et al., 2007): using DBU as catalyst.

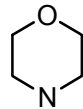
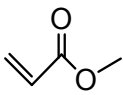
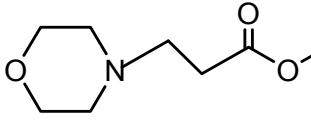
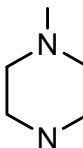
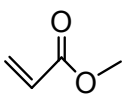
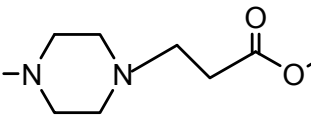
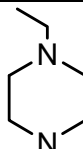
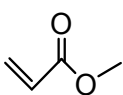
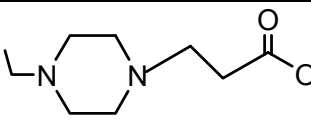

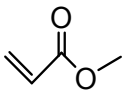
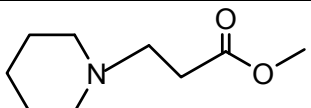

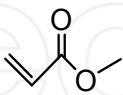
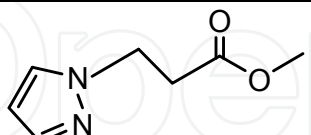
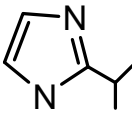
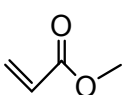
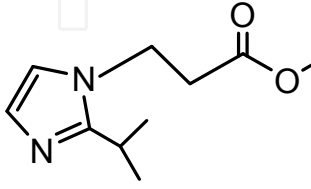

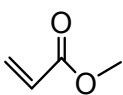
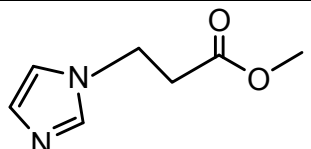
The main aim of the work is to examine if the non-solvent addition of aliphatic amines to electron deficient olefins can proceed smoothly with DBU based task-specific ionic liquids as catalysts.

Reaction medium for the model reaction (entries 3-5). However, because of the toxicity of organic solvents and our pursuit for the establishment of the environmentally benign process for organic transformations, we attempted to conduct the reaction of dibenzylamine and methyl acrylate under solvent-free condition and to our delight, good yield (96 %) was obtained within 4.5 h (Table 1, entry 6). So we chose solvent-free conditions for further study. Next, the amount of catalyst [DBU][Ac] was reduced to 0.3 equiv and almost no decrease of yield was observed (entry 7). However, the product yield decreased obviously when the amount was further reduced to 0.01 equiv (Table 1, entries 8-9). As a result, we adopted 0.3 equiv of [DBU][Ac] under solvent-free condition at room temperature for the following investigations.

With the optimal catalytic system in hand, we investigated the suitability of a wide range of nitrogen nucleophiles for the [DBU][Ac] catalyzed aza-Michael reactions using methyl acrylate as substrate, aliphatic secondary amines such as morpholine, piperidine, 1-methylpiperazine, 1-ethylpiperazine and pyrazole underwent conjugate reaction with methyl acrylate favourably and excellent yields of Michael adducts were obtained at ambient temperature under solvent-free conditions within short reaction time (Table 2, entries 1-4). Morpholine, piperidine and pyrazole reacted faster and afforded higher products yields in the presence of ionic liquid [DBU][Ac] than those promoted by DBU (entries 1, 4 and 5). It is worthy to note that when imidazole were treated as Michael donor with methyl acrylate, it disappeared in 2 hours and no Michael product was detected with the formation of acylation product. Judging from the disappearance of OCH₃ group of products from ¹H NMR spectrum, it may provides a possible method for acylation reaction of Michael acceptors. However, 2-isopropylimidazole could react with methyl acrylate and 93 % Michael adduct yield was obtained in 10 hours. From the above, steric bulkiness of

reagent can assist the formation of Michael adduct and is detrimental to acylation process. Primary amine, benzylamine, were also treated with methyl acrylate and 20 % yield of di-substituted product was formed which was the same with that catalyzed by DBU (Yeom et al., 2007) (Table 2, entry 8).

Having obtained favourable results with methyl acrylate, we studied the solventless reaction of morpholine with other electron-deficient olefins under the same conditions. Other various vinyl esters, acrylonitrile and acrylamide were effective substrates to give desired products in good to excellent yields (Table 2, entries 9-11 and 13-14). Among the acrylate esters, the increasing of carbon number acrylates would lead to decreased reactivity (entries 9 and 10), as reported by Lin et al. (2007) α -Methyl and β -benzene substituted ester, ethyl cinnamate were also tested as acceptors respectively and were found that the former gave the rational yield in short time and the latter exhibited relatively inert reaction activity due to steric hindrance of benzene at β position (entries 11 and 12).

Entry	Nitrogen nucleophile	Michael acceptor	Reaction time/Ref. 19 (h)	Product	Yieldb/Ref. 19 (%)
1			1.5/4		93/90
2			1.5		90
3			1.5		87
4			1.5/4		92/88
5			5/14		93/95
6			10		93
7			2/14		0/95

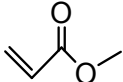
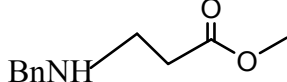

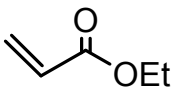
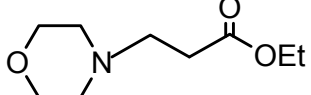

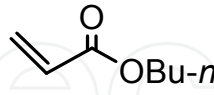
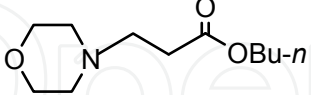

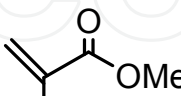
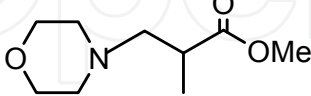

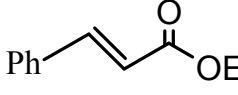
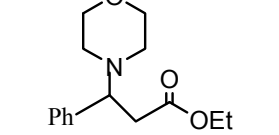

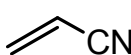
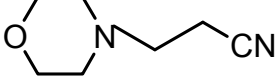

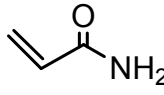
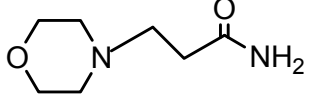
8	BnNH ₂		3/3		80/75
9			3		90
10			5		93
11			4		90
12			15		65
13			3		88
14			3		93

Table 2. Results of aza-Michael addition of various aliphatic amines to electron-deficit alkenes using [DBU][Ac] as catalyst under solvent-free conditions^a

^a Reactions were carried out on 1.0 mmol scale of substrate with 1.3 equiv of α,β -unsaturated compounds in the presence of 0.3 equiv ionic liquid at room temperature;

^b Yields of isolated products.

In order to demonstrate the industrial applicability of this methodology, the solvent-free aza-Michael condensation of piperidine and methyl acrylate was carried out on a larger scale (100 mmol). The reaction was completed in 2 hours, excellent yield of 94% for the conjugate product was obtained. On the same scale, the recyclability of catalytic system was investigated using the same reaction as model reaction. Upon the completion of the reaction, the product was isolated through vacuum distillation while the residue ionic liquid was dried to remove water at 60 °C under vacuum. The recovered ionic liquid was reused in subsequent reactions. As shown in Figure 1, the ionic liquid [DBU][Ac] can be recycled for six times without considerable decrease of activity and the used ionic liquid remained intact (¹H NMR).

Although [DBU][Ac] has weaker basicity than DBU, its catalytic property for aza-Michael reaction is better than that of DBU. The reason, we speculated, is that amines exhibited higher nucleophilicity in the presence of ionic liquids than in organic solvents (Xu et al., 2007; Kim et al., 2002; Crowhurst et al., 2006; Meciarova et al., 2006).

In conclusion, we have developed a mild, simple and efficient methodology using a new basic ionic liquid [DBU][Ac] as catalyst for the conjugate reaction of various aliphatic and aromatic amines with a variety of structurally diverse olefins. The reactions are conducted at

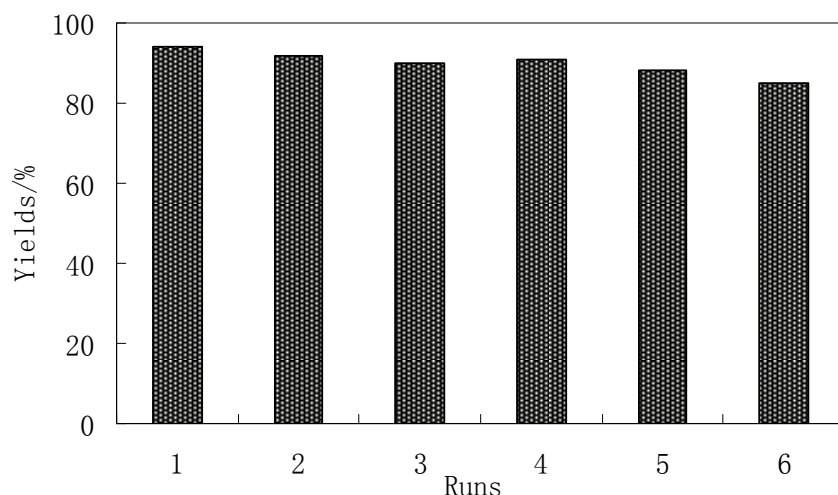


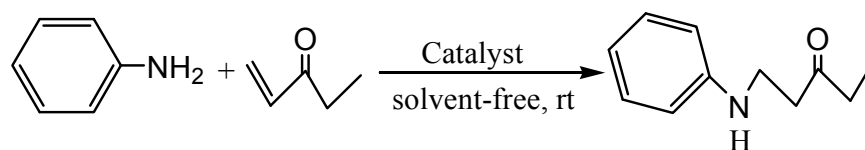
Fig. 1. Reuse of ionic liquid for aza-Michael reaction between piperidine (100 mmol) and methyl acrylate under solvent-free conditions

room temperature under solvent-free conditions and in most cases, from high to excellent yields of the desired 1,4-adducts were obtained. Also, the protocol could be scaled up to 100 mmol and proceeded smoothly, showing the potential for industrial applicability. Upon completion of the reaction, the catalyst [DBU][Ac] could be recovered by drying under vacuum at 60 °C and reused for six times without significant loss of activity. The applicability of the task-specified ionic liquid [DBU][Ac] in other fields of organic transformation are underway in our laboratory.

2.2 Michael addition (aromatic amines as Michael donors)

Because of the inertness of arylamines compared with aliphatic amines, most of the available methods suitable for Michael addition of aliphatic amines are not successful with aromatic amines. Duan and his co-workers used CAN (ceric ammonium nitrate) as effective promoter for aza-Michael addition of aromatic and aliphatic amines to α,β -unsaturated electrophiles in absence of solvent under ultrasound irradiation (Duan et al., 2006). Very recently, Bhanage et al. reported $Y(NO_3)_3 \cdot 6H_2O$ catalyzed aza-conjugate reaction between weakly nucleophilic aromatic amines and various Michael acceptors such as esters, nitriles and amides under solvent-free conditions (Bhanushali et al., 2008). However, both of the two procedures utilized transition metal catalysts, which limited their application from economic and environmental viewpoints, and more importantly, they have not been involved in the aza-Michael reaction with α,β -unsaturated ketones as Michael acceptors. Basic ionic liquid [bmim]OH (1-butyl-3-methylimidazolium hydroxide) was first introduced as catalyst for the conjugate reaction of aromatic amines and to our disappointment, however, relatively long reaction times were required (Yang et al., 2006). Thus, the development of the efficient and green protocol for aza-Michael addition of aromatic amines to electron-deficient ketones still remains a challenging task and is highly desirable. Herein we wish to use our recently developed task-specific ionic liquids rather than the reported inert ionic liquids (Tolstikova & Shainyan, 2006) derived from DBU for aza-Michael addition of aromatic amines to α,β -unsaturated ketones at room temperature under solvent-free conditions.

The reaction of aniline and ethyl vinyl ketone (EVK) was selected as model to optimize the reaction conditions. Firstly, using [bmim]OH which is highly efficient in Michael reaction of carbon nucleophiles and aliphatic amines as catalyst (Yang et al., 2007), 8 h was required for consumption of the starting material (Table 3, entry 6) (Yang et al., 2007). Inert ionic liquid [bmim]BF₄ (1-butyl-3-methylimidazolium tetrafluoroborate) was also tested as promoter of the reaction and only 55 % yield of the desired product was obtained in 40 min (Table 3, entry 7). For comparison, some Lewis bases such as DMAP, PPh₃, and DBU were subjected to the model reaction and bis-adduct was formed thereby decreasing the product yield (Table 3, entries 8-10). Especially, with DBU, the bis-addition product was produced as much as 32 % yield while using its corresponding ionic liquids [DBU][Ac], [DBU][Lac], [DBU][n-Pr], [DBU][n-Bu] and [DBU][Tfa] no bis-addition reaction was observed and 89-99 % yields were afforded within the same period, demonstrating good chemo- and regio-selectivity of these ionic liquids in the reaction of aniline and ethyl vinyl ketone (Table 3, entries 1-5). Among the three ionic liquids, [DBU][Lac] performed better than the other ionic liquids, [DBU][Ac], [DBU][n-Pr], [DBU][n-Bu] and [DBU][Tfa] (entries 1-5). So we chose [DBU][Lac] as catalyst for further investigations. A blank experiment was also carried out to demonstrate the catalytic activity of the DBU-based task-specific ionic liquids (Table 3, entry 11). To optimize the details of the reaction conditions, solvent effect was studied in the same model reaction between aniline and EVK (Table 3, entry 1). Toluene, CH₂Cl₂, CH₃OH, and CH₃CN were all found to be effective media for the reaction and relatively lower reactant concentration in organic solvent than that under solvent-free conditions decreased the reaction rate. We then selected the solvent-free conditions rather than using organic solvents on consideration of the environmental effect and reaction rate.



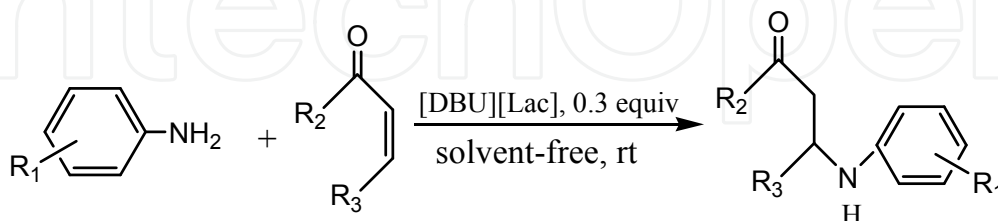
Entry	Catalyst	Time (min)	Yield ^b (%)
1	[DBU][Lac]	30	99 (82 ^c , 75 ^d , 76 ^e , 70 ^f)
2	[DBU][Ac]	40	96
3	[DBU][n-Pr]	40	90
4	[DBU][n-Bu]		89
5	[DBU][Tfa]	40	96
6 ^g	[bmim]OH	480	98 ^g
7	[bmim]BF ₄	40	55
8	DMAP	40	64
9	PPh ₃	40	59
10	DBU	40	43
11	-	40	37

Table 3. Aza-Michael Reaction of Aniline with Ethyl Vinyl Ketone under Various Reaction Conditions^a

^a Reactions conditions: aniline (1 mmol), ethyl vinyl ketone (1.5 mmol), catalyst (30 mol %), solvent-free conditions, rt. ^b GC yield. ^c Toluene. ^d CH₂Cl₂. ^e CH₃OH. ^f CH₃CN.

^g Reference: Yang et al., 2007.

With the efficient catalytic system in hand, EVK was treated with other aromatic amines. The results are summarized in Table 4 (entries 1-5). Aromatic amines with electron-donating group at benzene ring were effective nucleophiles to react smoothly with EVK and excellent yields were afforded in very short reaction time (Table 4, entries 1-2), while 2-Methyl substituted amine, due to its steric hindrance, reacted relatively slowly (entry 3). p-NO₂ substituted amine could not react all (entry 5). Arylamine with weakly electron-drawing substitution Cl was also tested with EVK under the above reaction conditions and 95 % GC yield was obtained in 1 h (entry 4).



Entry	R1	R2	R3	Time (h)	GC yield (%)	Isolated yield (%)
1	4-MeO	Et	H	0.5	98	95
2	4-Me	Et	H	0.1/8c	97/98c	90
3	2-Me	Et	H	0.8	92	85
4	4-Cl	Et	H	1/8c	95/97c	90
5	2-NO ₂	Et	H	2	NR	NR
6	4-H	-(CH ₂) ₃ -		5	89	82
7	4-Cl	-(CH ₂) ₃ -		6	90	79
8b	3-Cl	-(CH ₂) ₃ -		5	75	68
9	2-Me	-(CH ₂) ₃ -		8	85	77
10	4-Me	-(CH ₂) ₃ -		5/24c	95/71c	92
11 ^b	2-Cl	-(CH ₂) ₂ -		8	70	65
12 ^b	2-Br	-(CH ₂) ₂ -		8	75	69
13 ^b	2-Me	-(CH ₂) ₂ -		8	86	78
14 ^d	4-H	Ph	Ph	5	92	85
15 ^d	4-Cl	Ph	Ph	12	75	72
16 ^d	4-MeO	Ph	Ph	8	88	83
17 ^d	4-Me	Ph	Ph	8	91	87

Table 4. [DBU][Lac] catalyzed aza-Michael reactions of various aromatic amines with α,β -unsaturated ketones at room temperature^a

^a Reaction conditions: aromatic amines (1 mmol), α,β -unsaturated ketones (1.5 mmol), [DBU][Lac] (30 mol %), solvent-free conditions, rt. ^b Reaction conducted at 60 °C.

^c Results obtained from reference: Yang et al., 2007, reaction conditions: [bmim]OH (0.3 equiv.), aromatic amines (1.0 mmol), acceptors (1.5 mmol), rt, solvent-free. ^d 1.0 Equiv of [DBU][Lac] required for dissolving chalcone and aromatic amines.

In order to evaluate the generality of the ionic liquid [DBU][Lac] as catalyst for aza-Michael reaction of aromatic amines, 2-cyclohexen-1-one, 2-cyclopenten-1-one and chalcone were tested under the same conditions (Table 4, entries 6-17). To our delight, 2-cyclohexen-1-one and chalcone were effective Michael acceptors to react with various arylamines, giving good to excellent isolated yields (entries, 6-10, 14-17). However, 2-cyclopenten-1-one showed relatively lower reactivity. Accordingly, higher temperature (60 °C) was required (entries, 11-13). For further comparison with [bmim]OH, [DBU][Lac] was used as promoter for the additions of *p*-methyl aniline to EVK and *p*-methyl aniline to 2-cyclohexen-1-one respectively (entries, 2 and 10). With comparable or higher products yields obtained, the two reactions catalyzed by [DBU][Lac] proceeded much faster than those promoted by [bmim]OH. Moreover, chalcone reacted smoothly with various aromatic amines using [DBU][Lac] as catalyst (entries, 14-17) while no reaction occurred in the presence of the ionic liquid [bmim]OH (Yang et al., 2007). All cases summarized in Table 4 obviously demonstrate that the novel ionic liquid [DBU][Lac] has excellent catalytic activity for aza-Michael reaction of aromatic amines and α,β -unsaturated ketones.

The recyclability of the ionic liquid [DBU][Lac] was then studied using the reaction of aniline and 2-cyclohexen-1-one as model. The results are shown in Table 5. Upon the completion of the reaction, the reaction solution was extracted with ethyl acetate and purified by flash chromatography. The addition product was identified by ¹H NMR, ¹³C NMR and MS. The residual ionic liquid was washed with ethyl ether, dried under vacuum at 60 °C for 2 h and reused for subsequent reactions. As shown in Table 5, the recovered ionic liquid could be used for 8 times without obvious loss of catalytic activity. It is worthwhile to note that the ionic liquid [DBU][Lac] used for 8 runs remained intact, judging from its ¹H NMR spectrum.

Cycle	t (h)	GC yield ^b (%)
1	5	89
2	5	90
3	5	88
4	5	89
5	5	83
6	5	83
7	6	90
8	6	90

Table 5. Recycling and Reusability of the catalyst [DBU][Lac] in the Reaction between aniline and 2-cyclohexen-1-one^a

^a Reaction conditions: 1 mmol of aniline, 1.5 mmol of 2-cyclohexen-1-one, 0.3 mmol of [DBU][Lac] without solvents at rt. ^b GC yields.

As for the role of DBU-based ionic liquids for the activation in the aza-Michael addition of aromatic amines to α,β -unsaturated ketones, [DBU][Lac], [DBU][Ac], [DBU][*n*-Pr] and [DBU][*n*-Bu] were regarded as Brønsted bases to promote the addition and [DBU][Tfa] played the role as Brønsted acid for the this type of aza-Michael reaction. The reason for

relatively lower catalytic activity of [DBU][*n*-Pr] and [DBU][*n*-Bu] might be their much higher hindrance of anions. The reason for slightly higher catalytic activity of [DBU][Lac] than those of the other four ionic liquids may be the activation of carbonyl group of Michael acceptors by the hydroxyl group at the α -position of the carboxyl in lactate anion.

In conclusion, we have developed five task-specific ionic liquids, [DBU][Lac], [DBU][Ac], [DBU][*n*-Pr], [DBU][*n*-Bu] and [DBU][Tfa]. The ionic liquids were then used as catalysts for aza-Michael addition of aniline to EVK. Among the five ionic liquids, [DBU][Lac] exhibited the best catalytic activity. Using [DBU][Lac] as catalyst, various aromatic amines were subjected to 2-cyclohexen-1-one, 2-cyclopenten-1-one and chalcone, from good to excellent yields were obtained. This protocol also has some advantages, such as readily work-up of the reactions, excellent reaction selectivity and good recyclability of the ionic liquid (reused for 8 times without significant loss of activity).

3. Application in the Knoevenagel condensation

3.1 Condensation under solvent-free conditions

Knoevenagel condensation is one of the most important methodologies for carbon-carbon double bond formation in synthetic chemistry (Freeman, 1980; Tietze, 1996). The condensation products are the key intermediates for synthesis of natural and therapeutic drugs, polymer, cosmetics and perfumes (Tietze, 2004; Yu et al., 2000). Generally, Knoevenagel reactions are carried out by condensation of active methylene compounds with aldehydes using some organic bases with their salts as catalysts, including dimethylamino pyridine, piperidine, guanidine, ethylenediamine (Narsaiah et al., 2004; Han et al., 2008), and so on. Also, alternative protocols for Knoevenagel condensations catalyzed by Lewis acids such as ZnCl₂ (Shanthan Rao & Venkataratnam, 1991), CuCl₂ (Attanasi et al., 1983), TiCl₄ (Green et al., 1985), LaCl₃ (Narsaiah & Nagaiah, 2003), Mg(ClO₄)₂ (Bartoli et al., 2008) and various heterogeneous solid bases, including Zeolites (Saravanamurugan et al., 2006; Martins et al., 2008), sulfate-ion promoted Zirconia (Reddy et al., 2006), clay (Bigi et al., 1999), and layered double hydroxides (LDHs) (Kantam et al., 2006) have been reported in literatures. However, many of those procedures required the use of large amount of organic solvents as reaction medium, long reaction time, harsh reaction conditions and had difficulties in the reuse of catalysts, which prompt chemical researchers for further development of more environmentally benign, efficient and operationally simple Knoevenagel protocols.

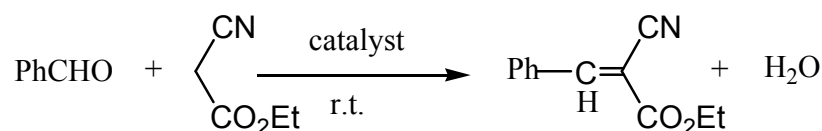
Ionic liquids, due to their unique properties such as good solvating ability, negligible vapor pressure, variable polarity, nonflammability and recyclability have been widely used as catalyst as well as reaction medium in Knoevenagel condensations with more or less success (Paun et al., 2007; Hu et al., 2005; Gao et al., 2007; Yue et al., 2008; Santamarta et al., 2008; Cai et al., 2006; Yeom et al., 2007). However, the costs of those methods increased because large excess amount of ionic liquids were required, which would greatly limit their industrial applications. From both environmental and economical points of view, Knoevenagel reaction promoted by catalytic amount of ionic liquid without solvent may be an attractive catalytic reaction system with many advantages such as lower cost, reduced pollution and simple operation.

Very recently, Kakade et al. investigated the use of DBU as catalyst for Knoevenagel reaction of 2-chloroquinoline-3-carbaldehyde and ethyl cyanoacetate under ultrasonic irradiation (Kakade et al., 2008). Encouraged by this, we tested the reaction of benzaldehyde with ethyl cyanocetate catalyzed by 20 mol % amount of DBU without solvent (Table 6,

entry 10) and were pleased to find that 91 % yield of condensation product was obtained within 20 min. However, using DBU as catalyst has some problems that it could not be reused and has unpleasant flavour during the operational process which also exists in other reaction with organic bases as promoters for synthetic transformation. In order to overcome these problems and prompted by our wish for invention of new task-specified ionic liquid used for organic transformations, we would like to report a novel, basic, task specific ionic liquids, [DBU][X](X=Tfa, Lac, Ac, *n*-Pr, *n*-Bu) and their use as catalysts for Knoevenagel reactions between aromatic aldehydes and active methylene ingredients.

Then we examined novel DBU derived ionic liquids used as catalyst for the reaction of benzaldehyde with ethyl cyanoacetate under solvent-free conditions at room temperature. The results shows that [DBU][Lac] demonstrates the most excellent catalytic activity (Table 6, entry 3 and entries 6-9). A remarkable yield of desired product was obtained (Table 6, entry 3). Some literatures reported that water could promote the Knoevenagel coupling (Shaabani et al., 2007; El-Rahman et al., 2007; Deb & Bhuyan, 2005). Thus, we carried out the reaction in water for the purpose of comparison with that under solvent-free conditions and found that solvent-free condensation is much faster than aqueous reaction (Table 6, entries 3, 4).

A blank experiment to demonstrate the catalytic ability of [DBU][Lac] was carried out. Only 37 % of the desired product was obtained in absence of [DBU][Lac] even with long reaction time (Table 6, entry 11). This result clearly indicated the effective catalytic role of the new ionic liquid in Knoevenagel condensation. To find a optimal amount of catalyst used for the model reaction of benzaldehyde and ethyl cyanoacetate, the amount of [DBU][Lac] was reduced from 0.5 equiv to 0.01 equiv. The results are collected in Table 5. The reactivity for lower loading of [DBU][Lac] (0.01 equiv) decreased obviously. Increasing the amount of [DBU][Lac] from 20 mol % to 50 mol %, expected improvement in yield of electrophilic alkene has not been observed (Table 6, entries 1-4). Thus, 0.2 equiv was the optimal amount of catalyst for further experiments.



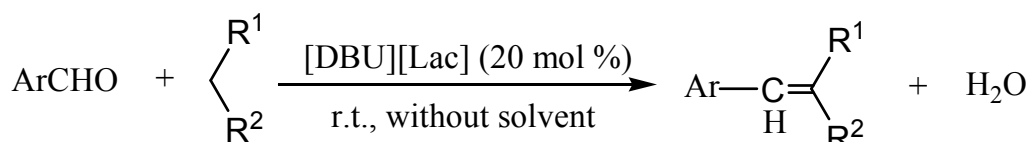
Entry	Catalysts (mol %)	Time (min)	Yields ^a (%)
1	[DBU][Lac] (0.1)	30	59
2	[DBU][Lac] (1)	30	73
3	[DBU][Lac] (20)	20	93
4b	[DBU][Lac] (20)	120	95
5	[DBU][Lac] (50)	20	94
6	[DBU][Ac] (20)	20	90
7	[DBU][<i>n</i> -Pr] (20)	20	85
8	[DBU][<i>n</i> -Bu] (20)	20	83
9	[DBU][Tfa] (20)	20	78
10	DBU (20)	20	91
11	-	10	37

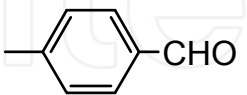
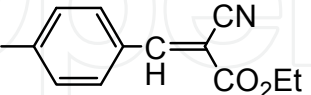
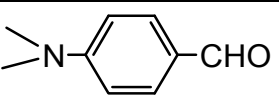
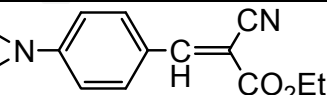
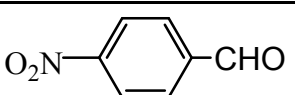
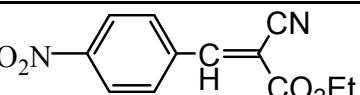
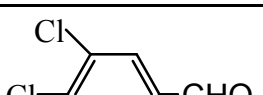
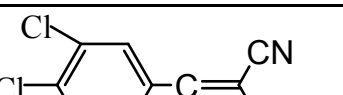
Table 6. Results of varying the amounts of [DBU][Lac] in the solvent-free Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate at room temperature

^a Isolated yields of products ^b Reaction in water.

With the best catalytic system in hand, we investigated the Knoevenagel reaction of various aromatic aldehydes with ethyl cyanoacetate and malononitrile. The results are shown in Table 7. A variety of structurally diverse aromatic aldehydes reacted favorably with active nucleophilic reagents to give the desired products in good to excellent yields. The products could be isolated by simple filtration. Some crude products need recrystallization in ethanol. All products were verified by their melting point, ^1H NMR and ^{13}C NMR spectroscopy which were in good agreement with literatures.

Aromatic aldehydes bearing withdrawing groups reacted with ethyl cyanoacetate, affording lower yields of desired products, while the reaction time is shorter than those with electron-donating substituents (Table 7, entries 1-6). Such results are mainly attributed to the strong activities of electro-deficient aromatic aldehydes, which led to some side reactions and thus resulted in lower yield. When malononitrile was treated with aromatic aldehydes carrying electron donating or withdrawing groups, the reactions proceeded within short time to achieve very high isolated yields (Table 7, entries 1-5). It is notable that electron-donating or electron-withdrawing substituents on aromatic rings have less effect on Knoevenagel reaction presumably due to the strong activity of acidic malononitrile. It can also be observed from Table 7 that more sluggish methylene compounds, acetylacetone can not converse completely and moderate yield afforded (Table 7, entry 17). The order of reaction rate as well as efficiency of Knoevenagel reaction is as follows: malononitrile > ethyl cyanoacetate > acetylacetone, which is accordance with the acidic activity of three nucleophiles. In addition, Knoevenagel condensation of hetero aromatic aldehydes such as 2-furaldehyde and 3-pyridinecarboxaldehyde with active methylene compounds also underwent smoothly at room temperature (Table 7, entries 7, 8, 14, 15). It is worthy to note that all products obtained are E-geometry exclusively and no subsequent Michael adduct is detected. Unfortunately, almost no desired condensation product was found when aliphatic aldehydes and ketones were used as the substrates under the above reaction conditions due to the inertness of these two types of compounds.



Entry	Ar	R1	R2	Time (min)	Products	Yields a (%)
1		CN	CO ₂ Et	30		95
2		CN	CO ₂ Et	60		95,
3		CN	CO ₂ Et	3		80
4		CN	CO ₂ Et	3		83

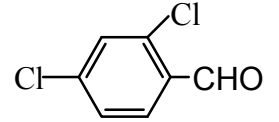
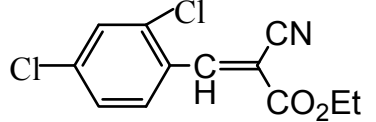
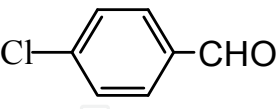
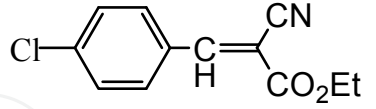
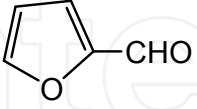
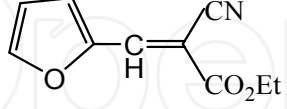
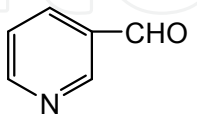
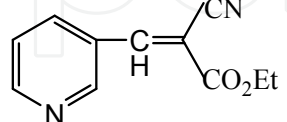
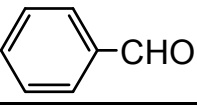
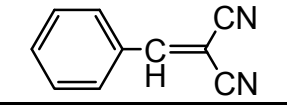
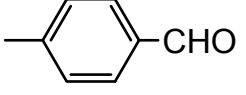
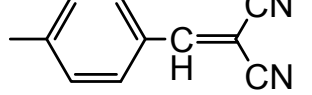
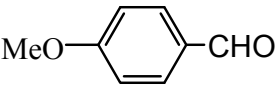
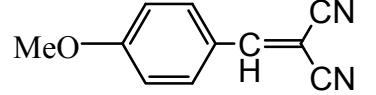
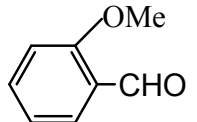
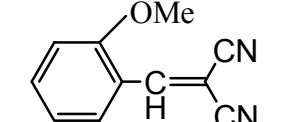
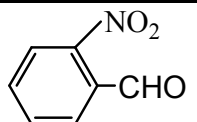
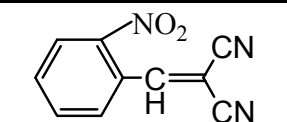
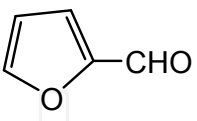
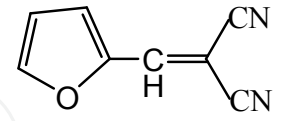
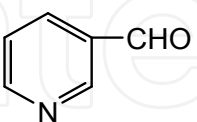
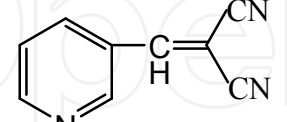
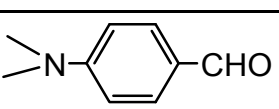
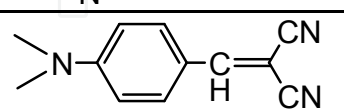
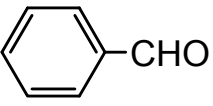
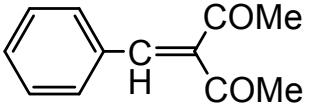
5		CN	CO ₂ Et	10		86
6		CN	CO ₂ Et	5		93
7		CN	CO ₂ Et	1		90
8		CN	CO ₂ Et	20		75
9		CN	CN	2		93
10		CN	CN	1		92
11		CN	CN	2		90
12		CN	CN	5		95
13		CN	CN	2		86
14		CN	CN	5		90
15		CN	CN	10		85
16		CN	CN	3		93
17c		COM _e	COMe	300		65

Table 7. Results of Knoevenagel condensation between various aromatic aldehydes and methylene active compounds at room temperature under solvent-free conditions^b

^a Isolated yields of desired products; ^b Reaction conditions: aromatic aldehydes (1 mmol),

active methylene compounds (1mmol) stirred with 20 mol % [DBU][Lac] as catalyst without solvent at room temperature; ^c Reactions at 60°C;

For the purpose of comparison with other methodologies on the catalytic efficiency, we carried out the reaction of sluggish substrate 4-(dimethylamino) benzaldehyde with ethyl cyanoacetate. As shown in Table 8, only reaction in guanidinium lactate provided the comparable yield (97.2 %) while it required 2.5 equiv amount of ionic liquid, which would limit its scale-up (Table 8, entry 4-5). There was a problem about recyclability of catalytic system in the condensation reaction promoted by phase-transfer catalyst TEBA (Table 8, entry 3). Other methods suffered from the longer reaction times as well as lower yields of products (Table 8, entries 1-2). All the results show that the present catalytic system (Table 8, entry 5) is very efficient and economic for Knoevenagel condensation.

Entry	Reaction conditions	Yields (%)	Ref.
1	Perfluoroalkylated pyridine catalyzed in n-octane, at 80°C for 10 h.	78	Yi & Cai, 2008
2	PEG as solvent, catalyzed by L-proline, reaction time: 210 min	81.2	Liu et al., 2008
3	Catalyst: TEBA, reaction time: 15 min	86	Rong et al., 2006
4	2.5 equiv amount of cyclic guanidinium lactate as solvent, reaction time: 3 min	97.2	Liang et al., 2008
5	60 min for reaction, 0.2 equiv [DBU][Lac] as catalyst	95	-

Table 8. Comparison of the present catalytic system with other reported protocols in the model reaction between 4-(dimethylamino) benzaldehyde with ethyl cyanoacetate.

Finally, in order to demonstrate the industrial applicability of this methodology, the solvent-free Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate was carried out on a larger scale (100 mmol). The reaction completed in 20 min., excellent yield of 94 % for the condensation product was achieved. On the same scale, the recyclability of catalytic system was investigated using the same reaction as model reaction. Upon the completion of the reaction, the product was isolated via readily filtration, washed with water and dried under vacuum without further separation, while the filtrate containing [DBU][Lac] was dried to remove water at 60 °C under vacuum. The recycled ionic liquid was reused in subsequent reactions. As shown in Figure 2, the ionic liquid [DBU][Lac] can be recycled for six times without considerable decrease of activity and the used ionic liquid remained intact (¹H NMR). As for the role of [DBU][Lac] in Knoevenagel condensation, we speculate that the basicity of the ionic liquid can attract the proton of the nucleophile to form carbon anion firstly, and secondly, catalytic amount of ionic liquid can improve the nucleophilicity of carbon anion to facilitate the condensation reaction, as same as the behavior observed in larger amount of ionic liquid (Kim et al., 2002; Kim et al., 2003; Liang et al., 2008). However, more work need to be done to clarify the exact mechanism of the [DBU][Lac] mediated Knoevenagel reaction.

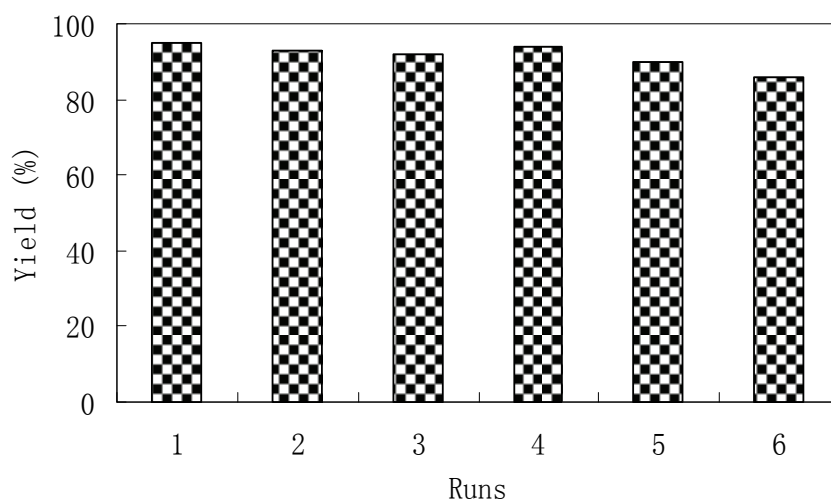


Fig. 2. Reuse of catalyst for Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate (100 mmol) under solvent-free conditions

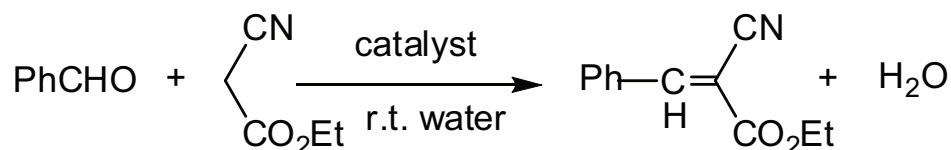
In conclusion, we have established a simple, mild and efficient methodology for solvent-free Knoevenagel condensation between aromatic aldehydes and methylene compounds at ambient temperature with ionic liquid [DBU][Lac] as catalyst. This protocol has notable advantages, such as high product yields, reuse of ionic liquid on large scale.

3.2 Condensation reaction in water

In the last decades, there has been incredible growth in research involving the use of water as a green, environmentally benign replacement for a wide range of processes that currently rely on conventional organic solvents from both environmental and economical points of view (Breslow, 1991; Li, 1993; Ribe & Wipf, 2001). More recently, Song and co-workers employed water as reaction solvent for Knoevenagel condensation between aromatic aldehydes and malononitrile (Cai et al., 2006). Compared with organic solvents media, the advantage of water is very obvious from points of reaction efficiency or environmental "greenness".

Then we examined DBU based ionic liquids as catalysts for the reaction of benzaldehyde with ethyl cyanoacetate in water at room temperature. Among the five ionic liquids, [DBU][Ac] has the best efficient catalytic activity (Table 9, entries 3 and 5-8). An excellent yield of desired product was obtained (Table 9, entry 3). The result is comparable with that catalyzed by parent catalyst DBU. Bhuyan et al. published a method for Knoevenagel reaction in aqueous medium without any catalyst (Deb & Bhuyan, 2005). However, the method was substrate-selective and the aqueous reaction of benzaldehyde with ethyl cyanoacetate in absence of [DBU][Ac] is very slow with low yield obtained (Table 9, entry 9). The result indicated that the ionic liquid [DBU][Ac] played an important role as catalyst during the reaction process.

To find an optimal loading amount of catalyst for the model reaction of benzaldehyde and ethyl cyanoacetate, the amount of [DBU][Ac] was reduced from 0.5 equiv to 0.01 equiv. The results are collected in Table 9. Considering both catalytic activity and the cost of catalyst, we chose 0.2 equiv as optimal amount of catalyst for further examinations.



Entry	Catalysts (mol %)	Time (h)	Yields ^a (%)
1	[DBU][Ac] (1)	3	59
2	[DBU][Ac] (5)	3	73
3	[DBU][Ac] (20)	2	95
4	[DBU][Ac] (50)	2	94
5	[DBU][Lac] (20)	2	92
6	[DBU][n-Pr] (20)	2	90
7	[DBU][n-Bu] (20)	2	85
8	[DBU][Tfa] (20)	2	85
9	-	10	36
10	DBU (20)	2	93

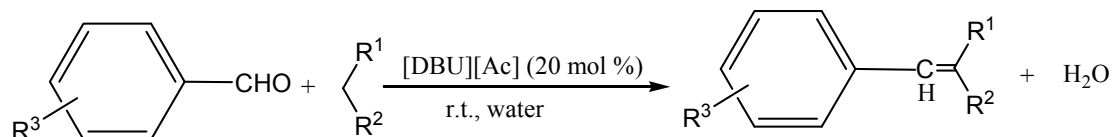
Table 9. Results of DBU and varying the amounts of [DBU][Ac] in the aqueous Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate at room temperature

^a Isolated yields of products

With the rational catalytic system in hand, we studied the Knoevenagel reaction of various aromatic aldehydes with malononitrile and ethyl cyanoacetate. The results are shown in Table 10. A variety of structurally diverse aromatic aldehydes reacted favorably with active nucleophilic reagents, giving desired products in good to excellent yields. The products could be isolated by simple filtration without further tedious purification process. All products were verified by their melting point, ¹H NMR and ¹³C NMR spectroscopy which were in good agreement with the data in other published literatures.

In order to demonstrate the industrial applicability of this methodology, the Knoevenagel condensation of benzaldehyde and ethyl cyanoacetate was carried out on a larger scale (100 mmol) in water (100 mL). The reaction completed in 2 h, excellent yield of 97% for the condensational product was achieved. On the same scale, the recyclability of catalytic system was investigated using the same reaction as model. Upon the completion of the reaction, the high pure product was afforded by readily filtration without further separation, while the remaining aqueous medium containing [DBU][Ac] was reused directly without additional recovery. As shown in Figure 3, the catalytic system of [DBU][Ac] in water can be reused for ten times without noticeable loss of activity.

In summary, we have established a simple, mild and efficient methodology for Knoevenagel condensation between aromatic aldehydes and methylene compounds at ambient temperature in water with ionic liquid [DBU][Ac] as catalyst. This protocol has notable advantages, such as high product yields, aqueous reaction medium, ease of work-up, reuse of ionic liquid on large scale, which make it more efficient and cleaner with industrial potential.



Entry	R3	R1	R2	Time (h)	Yields ^a (%)
1	H	CN	CN	0.3	93
2	4-Me	CN	CN	0.3	94
3	4-MeO	CN	CN	0.3	94
4	2-MeO	CN	CN	0.3	90
5	2-NO ₂	CN	CN	0.2	88
6d	4-Dimethyl	CN	CO ₂ Et	6	96
7	4-Me	CN	CO ₂ Et	4	95
8	4-NO ₂	CN	CO ₂ Et	1	90
9	3,4-Dichloro	CN	CO ₂ Et	3	82
10	2,4-Dichloro	CN	CO ₂ Et	2	75
11	4-Cl	CN	CO ₂ Et	1.5	95
12d	H	COMe	COMe	10	63 ^b
13	2-Furaldehyde	CN	CN	1	86
14	3-Pyridinecarboxaldehyde	CN	CN	1	96
15	2-Furaldehyde	CN	CO ₂ Et	3	92
16	3-Pyridinecarboxaldehyde	CN	CO ₂ Et	3	94

Table 10. Results of Knoevenagel condensation between various aromatic aldehydes and methylene active compounds at room temperature in aqueous media^c

^a Isolated yields of desired products ^b Starting materials detected

^c Reaction conditions: aromatic aldehydes (1 mmol), active methylene compounds (1mmol) stirred in water (1mL) with 20 mol % [DBU][Ac] as catalyst at room temperature

^d Reactions at 60°C

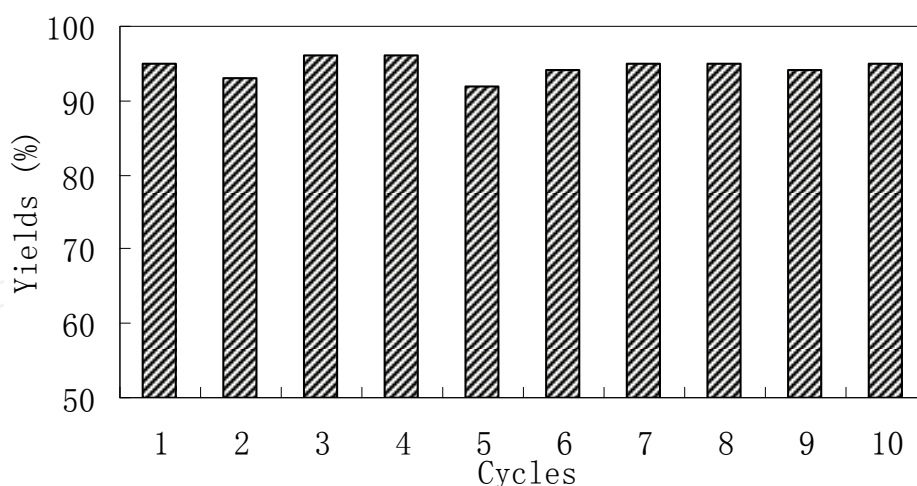


Fig. 3. Reuse of catalyst for Knoevenagel condensation between benzaldehyde and ethyl cyanoacetate (100 mmol) in 100 mL water

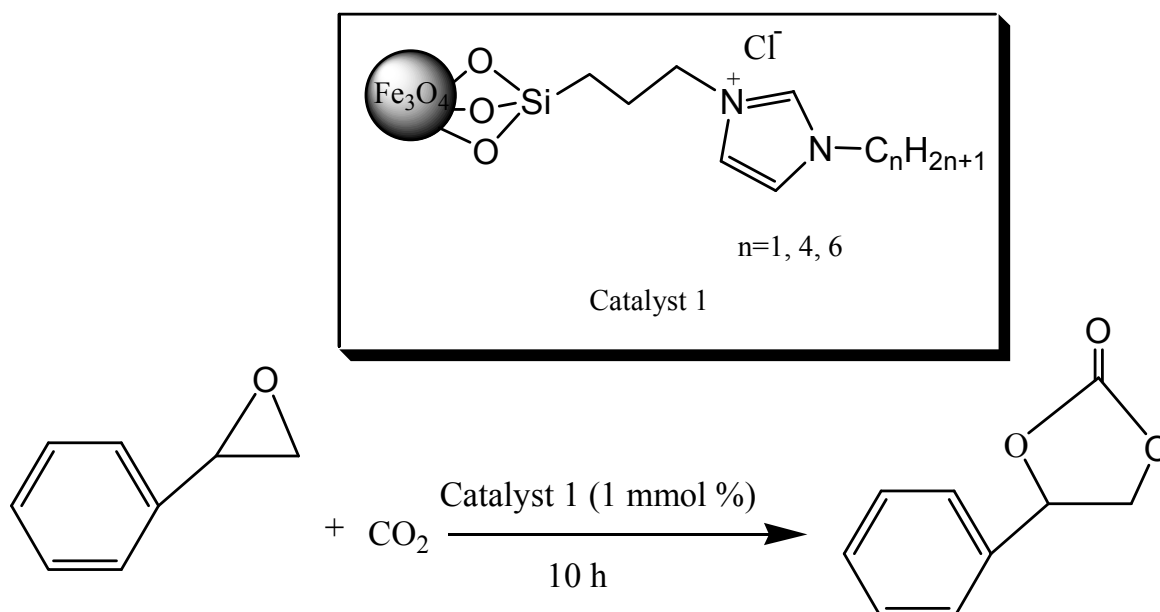
4. Ionic liquids immobilized on MNP and their applications in organic synthesis

In order to improve the recycling and reuse property of ionic liquids, immobilization of ionic liquids on polymers is frequently employed (Welton, 2004). However, the reduced

activities of these type of ionic liquids catalysts are often observed because of poor dispersion of supported ionic liquids in the reaction system. Thus, novel supports that ensure both good recyclability and catalytic activity are still desirable.

MNP have recently appeared as a new type of catalyst support because of their easy preparation and functionalization, large surface area ratio, facile separation via magnetic force as well as low toxicity and price (Yoon et al., 2003; Stevens et al., 2005; Lee et al., 2006; Abu-Reziq et al., 2006; Luo et al., 2008). These features have made MNP a promising alternate of porous/mesoporous catalyst supports.

Combined advantages of ionic liquids with those of MNP, MNP-supported ionic liquid catalysts (MNP-ILs) were developed by some famous research groups. Luo and his co-workers (Zheng et al., 2009) developed a series of novel MNP-ILs and successfully utilized these catalyst in CO₂ cycloaddition reactions (Scheme 3). The activity of the supported catalyst is comparable with that of the free ILs catalysts for this reaction. The catalysts could be easily recycled using a magnetic force and reused for up to 11 times with essentially no loss of activity.

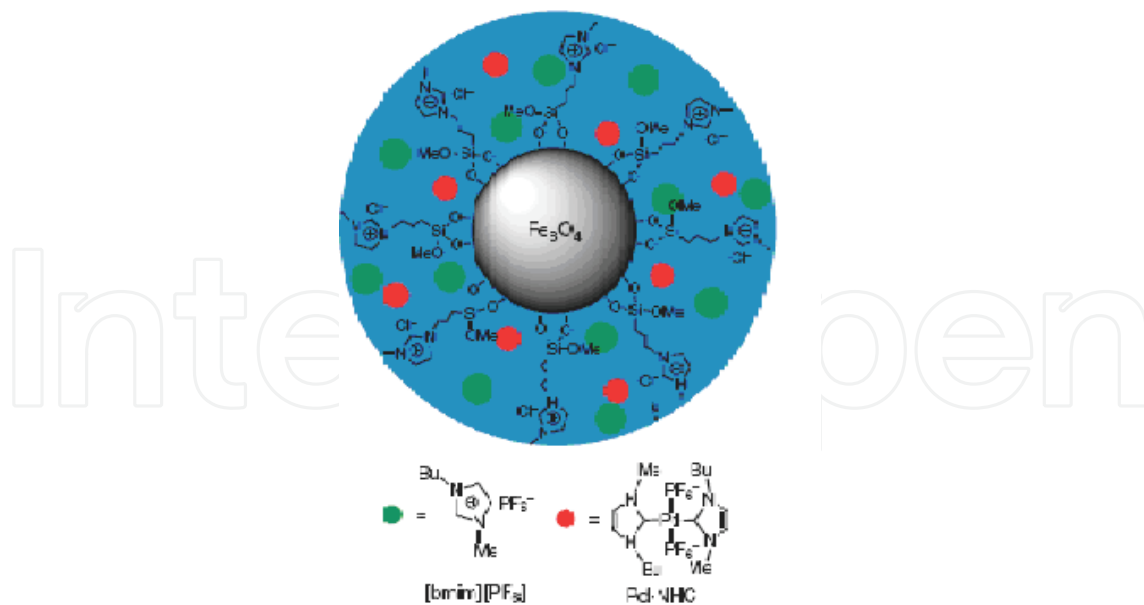


Scheme 3

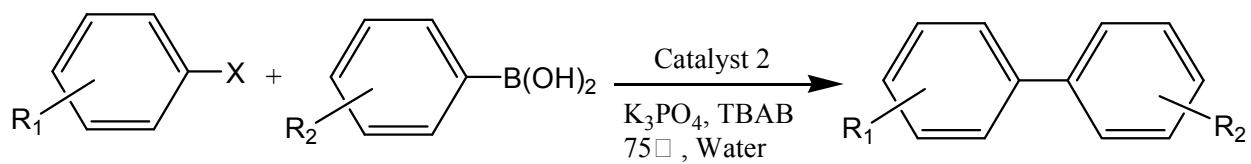
Pd-NHC-ionic liquid matrix was immobilized into ionic liquid layers coated on the surface of Fe₃O₄ (Taher et al., 2009). The catalyst 2 has shown excellent catalytic activity and high stability for the Suzuki coupling reaction in water (Scheme 4). This heterogeneous catalyst can be recycled for five times without significant loss of the catalytic activity. Furthermore, recovery of the catalyst by an external permanent magnet is facile and efficient.

Shan and his co-workers (Wang et al., 2010) prepared a novel magnetic nano-solid acid catalyst, which includes grafting ionic liquid onto Fe₃O₄ nanoparticles, followed by the sulfonation of phenyls groups in the ionic liquid. The catalyst 3 shows an excellent performance in the acetalization of the carbonyl under mild reaction conditions (Scheme 5), and it can be recycled without obvious loss of catalytic activity.

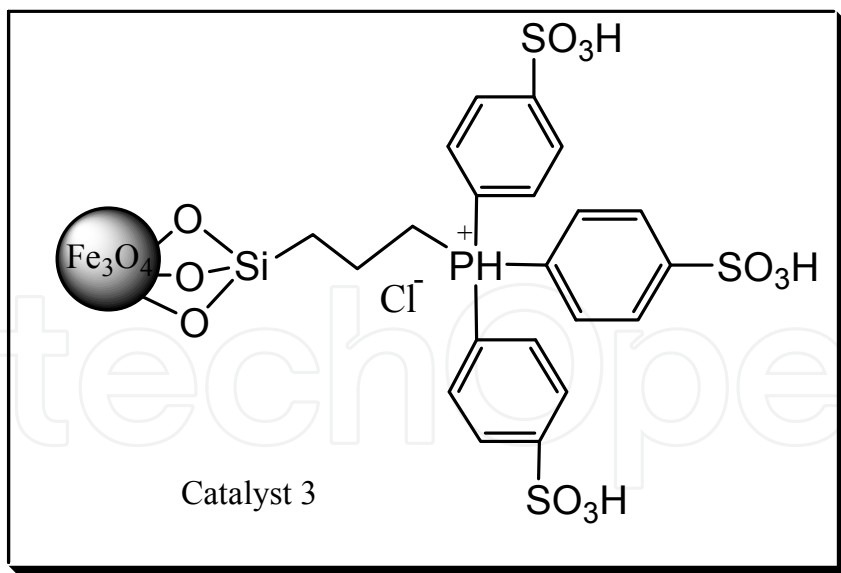
In summary, MNP-supported ionic liquid catalysts (MNP-ILs) have been developed, which overcome the disadvantages of both magnetic nano-particles and ionic liquids. The three examples have showed the excellent catalytic activities and facile work-up of the MNP-ILs.



Catalyst 2



Scheme 4



Scheme 5

5. Conclusion

This chapter has mainly described our recently prepared task-specific ionic liquids derived from DBU, [DBU][Tfa], [DBU][Lac], [DBU][Ac], [DBU][*n*-Pr], and [DBU][*n*-Bu], and their applications in aza-Michael addition and Knoevenagel condensation. Compared with some conventional catalysts, the novel DBU based ionic liquid catalysts demonstrate relatively higher catalytic activities, much better chemo- and stereo-selectivity, readily recovery property and excellent recyclability. However, the application of DBU based ionic liquids in other organic transformations including asymmetric organic synthesis need to be further developed.

Magnetic nanoparticles (MNP) are of great interest in researchers because of their good stability, easy preparation and functionalization, large surface ratio and facile separation. Considering the features of ionic liquids, MNP-supported ionic liquid catalysts (MNP-ILs) have been developed by chemists. Very recently, MNP-ILs used as catalysts have been successfully utilized in cycloaddition reactions, Suzuki coupling reaction and acetalization reaction. The results show that MNP-ILs can smoothly catalyze reaction, be readily recovery from reaction solution *via* magnetic force, as well as good recyclability and stability. It is hoped that this review will help stimulate the relevant research of MNP-ILs to move forward.

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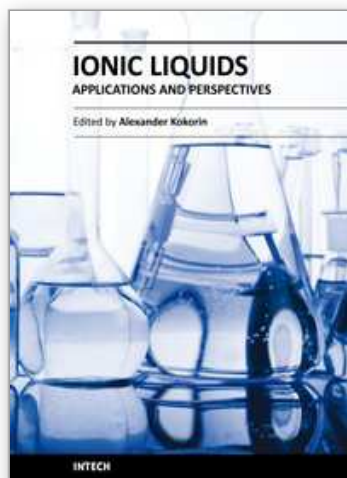
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This book is the second in the series of publications in this field by this publisher, and contains a number of latest research developments on ionic liquids (ILs). This promising new area has received a lot of attention during the last 20 years. Readers will find 30 chapters collected in 6 sections on recent applications of ILs in polymer sciences, material chemistry, catalysis, nanotechnology, biotechnology and electrochemical applications. The authors of each chapter are scientists and technologists from different countries with strong expertise in their respective fields. You will be able to perceive a trend analysis and examine recent developments in different areas of ILs chemistry and technologies. The book should help in systematization of knowledges in ILs science, creation of new approaches in this field and further promotion of ILs technologies for the future.

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