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Ionic amino acids: Application as organocatalysts in the aza-Michael reaction

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ABSTRACT

The ethyl methyl imidazolium salts of amino acids, [emim][AA], have been used as catalysts in the aza-Michael reaction. Furthermore, when chiral amino acids were used, a stereoselective reaction was achieved. The mechanism of the transformation was verified by the detection of a key intermediate by electrospray ionization mass spectroscopy (ESI-MS).

1. Introduction

Research focused on the development of organic reactions using amino acid derivatives as organocatalysts [1] has progressed dramatically since the work of List et al., which described the proline-catalyzed aldol reaction of acetone with aromatic and aliphatic aldehydes [1a]. In many cases, however, the direct use of an amino acid as a catalyst has not promoted the reaction effectively because of the limited solubility of many amino acids in common organic solvents. Furthermore, the nucleophilicity of the amino group in the amino acid, which is an active site of the catalysis, is decreased by the neighboring carboxyl group. The direct use of amino acids as catalysts has therefore been limited to only a few applications [2]. Significant efforts have been focused on improving the effectiveness of amino acids as organocatalysts and proline-based systems in particular have attracted considerable attention, with multiple catalysts having been proposed involving modifications to the carboxyl [2a, 2b, 3] and pyrrolidine [2c, 4] moieties. Complex and skillful molecular design processes are invariably required to develop high-performance catalysts and the resulting catalytic systems are invariably quite far removed from their parent amino acid frameworks. Nevertheless, catalysts designed and synthesized through multistep transformations of the specific amino acids, such as proline, have been reported with greater frequency than those utilizing simple amino acids. For the current study, we have focused on readily available ionic amino acids possessing diverse functional groups and an asymmetric center with the goal of developing novel amino acid-derived organocatalysts for use in organic reactions.

2. Experimental

2.1. Materials and methods

All solvents used in the catalytic test were of analytical grade and were used as received from Ardrich, Wako Chemical, and TCI. Purification of reaction products was carried out by flash chromatography using 100–200 mesh silica gel, and a mixture of ethyl acetate and petroleum ether as the eluting agent. All the products were characterized by ^{1}H NMR spectroscopy. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded using a JEOL JNM-LA400, Varian 400-MR, and Varian Mercury300 spectrometers. Proton chemical shifts are relative to solvent peaks [chloroform: 7.27 (^{1}H), 77.00 (^{13}C); deuterium oxide: 4.79 (^{1}H)]. IR (ATR) spectra were measured with JASCO ATR PRO450-S with Ge. High-resolution mass spectra were measured by JEOL JMS-700. Ionic amino acids ([emim][AA]s) were prepared from corresponding amino acids and [emim][OH] by literature procedure [5a]. HPLC was carried out with LC-20AD, SPD-20A and CTO-20A. The ees of the Michael product were determined by chiral-phase HPLC analysis using a TCI Chiral BP-S column and Chiralcel OD column with the indicated eluent systems. LCMS was carried out with LCMS-2020 systems.

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2.2. General procedure for the synthesis of ionic amino acids

1-Ethyl-3-methylimidazolium hydroxide ([emim][OH]) aqueous solution was prepared from 1-ethyl-3-methylimidazolium bromide using anion exchange resin (AMBERLITE IRA 400 OH). An [emim][OH] aqueous solution was added dropwise to a slightly excess equimolar amino acid aqueous solution. The mixture was stirred under room temperature for 12 h. Then water was evaporated, and then 90 mL of acetonitrile and 10 mL of methanol. The mixture was then filtered to remove excess amino acid. Filtrate was evaporated to remove solvents. The product was dried in vacuo.

2.3. Typical procedure for aza-Michael reaction of chalcone and aniline

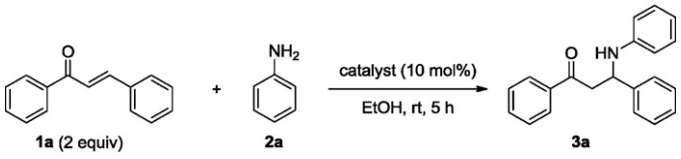
To a solution of ethanol was added catalyst (10 mol%) in the presence of chalcone (62.5 mg, 0.300 mmol) and aniline (13.7 μL, 0.150 mmol) at room temperature. After being stirred at the same temperature for 5 h, diluted with water (2 mL), the precipitated solid collected by filtration, and washed with water. The crude product was purified via recrystallization from ethanol to afford a 1,3-diphenyl-3-(phenylamino)propan-1-one (**3a**) as a white solid.

3. Results and discussion

3.1. Investigations on catalysts and reaction conditions

Although amino acids are poorly soluble in organic solvents because of the polarized carboxyl and amino groups, they can be effectively solubilized in organic solvents when the carboxyl group is neutralized with an imidazolium cation [5]. In the current study, ethyl methyl imidazolium [emim] has been as a counter cation for the carboxyl group, and the resulting ethyl methyl imidazolium salts of amino acid ([emim][AA]) were evaluated as organocatalysts in a variety of different organic reaction. As a result [emim][Gly] was established as an effective catalyst in the aza-Michael reaction of chalcone (**1a**) with aniline (**2a**) to give amino ketone **3a** (Table 1, entry 1) [6]. The glycine moiety was found to be important to the catalytic activity, and the reaction did not proceed effectively when [Gly] was replaced with [Br] or [OH] (Table 1, entries 2 and 3). In addition, the [emim] moiety was also found to be necessary, in that glycine itself did not promote the reaction (Table 1, entry 4).

Table 1
Investigation of catalysts in aza-Michael reaction.[a]



Entry	Catalyst	Yield (%)[b]
1	[emim][Gly]	97 (90)[c]
2	[emim][Br]	0
3	[emim][OH]	0
4	Glycine	0
5[d]	[emim][Gly]	66
6[e]	[emim][Gly]	58
7[f]	[emim][Gly]	8

[a] Reactions performed using **1a** (0.3 mmol), **2a** (0.15 mmol), catalyst (0.015 mmol), and EtOH (0.3 mL).
[b] Yield determined by NMR using $CHCl_2CHCl_2$ as an internal standard.
[c] Reactions performed using **1a** (3.0 mmol), **2a** (1.5 mmol), catalyst (0.15 mmol), and EtOH (3 mL). Isolated yield after recrystallization.
[d] Reaction performed for 3 h.
[e] Reaction performed at 50 °C.
[f] Reaction performed at 0 °C.

A reaction time of 5 h was found to be optimal, and when the reaction was stopped after 3 h, the yield of 3a was reduced to 66% (Table 1, entry 5). Furthermore, ambient temperature was found to be the optimal reaction temperature. When the reaction was conducted at 50 and 0 °C, the yields of **3a** were reduced to 58% and 8%, respectively (Table 1, entries 6 and 7). Alcohols were found to be suitable solvents for the transformation (MeOH: 69%, *n*-PrOH: 66%, *i*-PrOH: 68%, *t*-BuOH: 71%), whereas aprotic solvents (THF, DMF and DMSO) and water inhibited the reaction.

3.2. Scope of the reaction

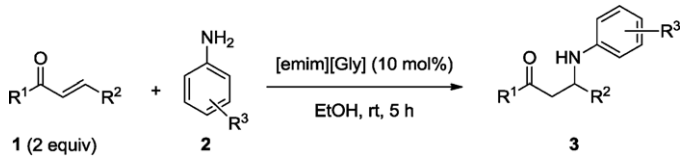
With the optimum reaction conditions in hand, we next examined the substrate scope for the [emim][Gly]-catalyzed aza-Michael reaction. The enone component of the reaction was fixed as chalcone (**1a**) and the scope for introducing functional groups on the benzene ring of the aniline **2** was investigated. When anilines bearing electron donating methyl or methoxy groups at the *para*-position (**2b** and **2c**) were used, the corresponding products (**3b** and **3c**) were obtained in good yields (Table 2, entries 1–3). Halogenated anilines (**2d** and **2e**) also underwent the aza-Michael reaction (Table 2, entries 4 and 5), whereas *p*-trifluoromethylaniline (**2f**) gave only a low yield of the corresponding product **3f**, even following a longer reaction time (Table 2, entries 6 and 7). Similarly, *p*-nitroaniline performed poorly in this catalytic system (not listed in Table 2). These results indicate that electron withdrawing substituents on the phenyl ring of the aniline component were not well tolerated in the transformation. The substituents on enone **1** also affected the product yield. For example, the presence of electron donating methyl or 4-methoxyphenyl groups at the α position of a carbonyl moiety suppressed the reaction (Table 2, entries 8–10). In contrast, the presence of a methyl group at the terminal alkene position did not inhibit the reaction (Table 2, entry 11). The corresponding cyclic enone systems were not well tolerated under the reaction conditions, with cyclohexen-1-one (**1e**) providing product **3j** in only 35% yield (Table 2, entry 12). When a substrate containing a nucleophilic OH group at the *ortho*-position was used (**1f**), we found that an intramolecular conjugate addition occurred as opposed to the desired aza-Michael reaction to give 3-phenylchroman-4-one (**3k**) as the only product (Table 2, entry 13) [7]. In addition, the reaction did not progress at all when alkylamine, which is more nucleophilic than aniline, was used as a substrate [8].

The reusability of the [emim][Gly] catalyst was also examined. Following the reaction of chalcone (**1a**) with *p*-anisidine (**2c**) in the presence of catalytic [emim][Gly], CH_2Cl_2 and water were added, and the unreacted materials and product **3c** were extracted with CH_2Cl_2. The aqueous phase was then collected and evaporated to dryness to give a residue that was dried in a vacuum at ambient temperature for 6 h. This technique provided at least 98% recovery of the catalyst and allowed the catalyst to be used for the next reaction. The catalyst could be reused at least 3 times without decrease of the product yield (see Supplementary Data).

3.3. Application for stereoselective reaction

It was envisaged that the use of a chiral amino acid would provide a catalytic asymmetric aza-Michael reaction [9,10]. We prepared a series of [emim][AA] catalysts from 20 natural amino acids and evaluated them as catalysts in the aza-Michael reaction (Fig. 1). The [emim][L-Pro] catalyst gave the desired product in the highest yield, whereas [emim][L-Phe] provided the highest enantiomeric excess of (*S*)-**3a** [11]. An schematic explanation for the stereospecific formation of the (*S*)-isomer of **3a** has been shown in

Table 2
Scope of substrates.[a]



1 (2 equiv) 2 3

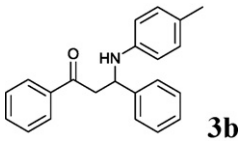
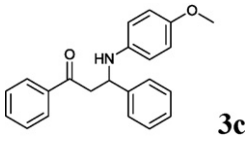
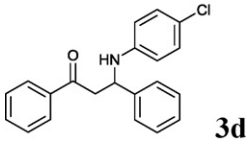
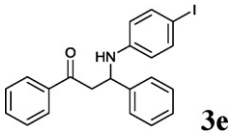
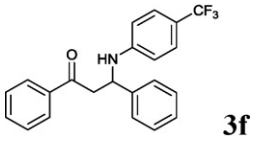
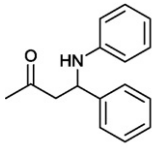
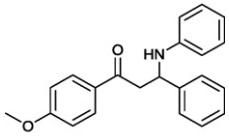
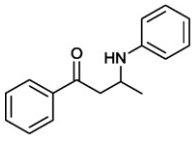
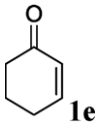
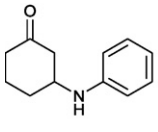
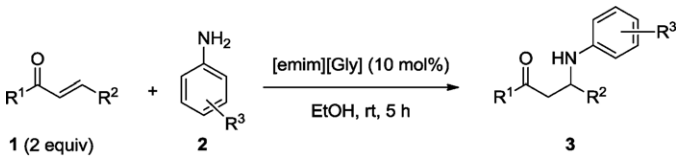
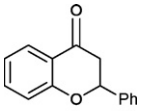
Entry	1	R^1	R^2	2	R^3	3	Yield (%)[b]
1	**1a**	Ph	Ph	**2b**	4-CH_3	 **3b**	92
2[c]	**1a**	Ph	Ph	**2b**	4-CH_3	**3b**	63
3	**1a**	Ph	Ph	**2c**	4-OCH_3	 **3c**	91
4	**1a**	Ph	Ph	**2d**	4-Cl	 **3d**	52
5	**1a**	Ph	Ph	**2e**	4-I	 **3e**	77
6	**1a**	Ph	Ph	**2f**	4-CF_3	 **3f**	Trace
7[d]	**1a**	Ph	Ph	**2f**	4-CF_3	**3f**	15
8[d]	**1b**	CH_3	Ph	**2a**	H	 **3g**	0
9	**1c**	(4-OCH_3)C_6H_4	Ph	**2a**	H	 **3h**	Trace
10[e]	**1c**	(4-OCH_3)C_6H_4	Ph	**2a**	H	**3h**	21
11	**1d**	Ph	CH_3	**2a**	H	 **3i**	91
12	 **1e**			**2a**	H	 **3j**	35

Table 2 (*Continued*)



Entry	1	R^1	R^2	2	R^3	3	Yield (%)[b]
13	**1f**	(2-OH)C_6H_4	Ph	**2a**	H	 **3k**	0[f]

[a] Reactions performed using **1a** (0.3 mmol), **2a** (0.15 mmol), catalyst (0.015 mmol), and EtOH (0.3 mL).
[b] Isolated yield after recrystallization.
[c] Reaction performed for 3 h.
[d] Reaction performed for 24 h.
[e] Reaction performed for 48 h.
[f] Intramolecular cyclization of 1 h gave 3-phenylchroman-4-one (**3k**) as a sole product in 52% yield.

Fig. 2. The attack of the aniline (**2a**) on the *Si* face of chalcone (**1a**) was inhibited by the benzyl group of L-phenylalanine.

The stereochemistry of the product could be effectively controlled by carefully selecting the appropriate L- or D-amino acid. Thus, the opposite enantiomers were formed when [emim][L-Phe] and [emim][D-Phe] were used (HPLC spectra were shown in Supplementary Data) [12].

3.4. Mechanistic investigations

We attempted to confirm the presence of the reaction intermediate by electrospray ionization mass spectroscopy (ESI-MS) and therefore validate the proposed reaction mechanism because it was suggested that the reaction mechanism in this case was different from that previously reported for general examples of

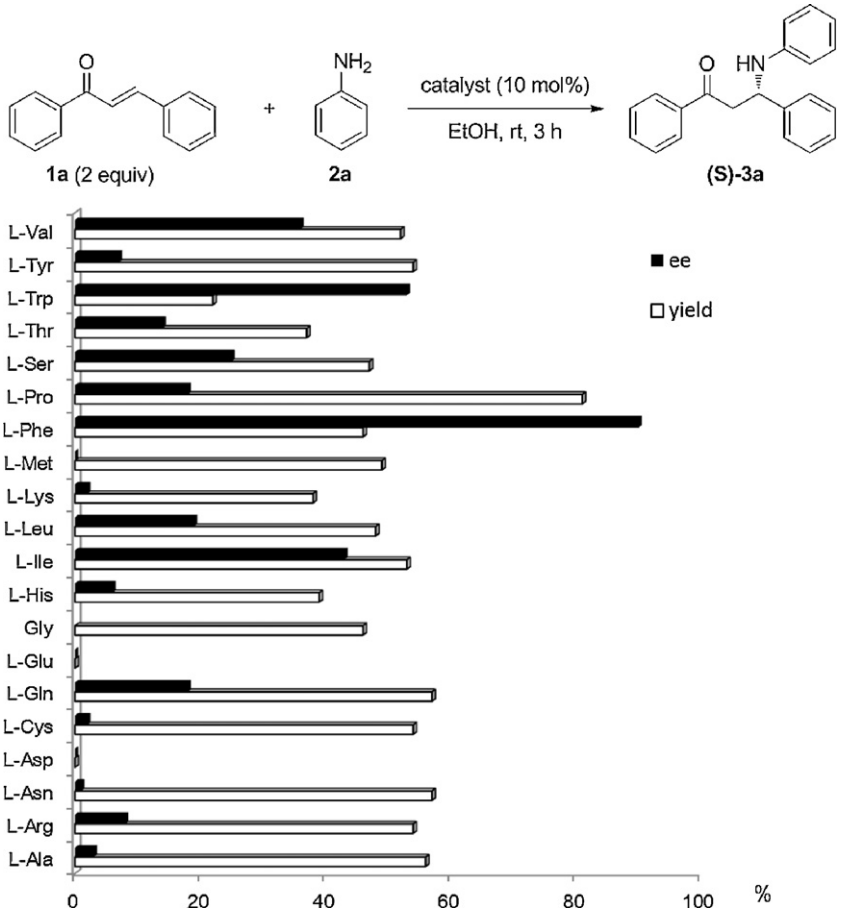


Fig. 1. Evaluation of [emim][L-AA] catalysts in the enantioselective aza-Michael reaction.

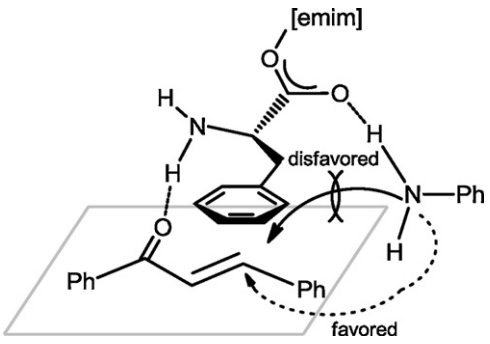


Fig. 2. Rationale for the observed stereoselectivity. Aniline attacks from the *Si* face of the chalcone (as indicated by the dashed arrow).

organocatalysts [13]. Amine-type organocatalysts can typically control the reactivity and stereoselectivity of the reaction by generating the corresponding iminium ion or enamine [14]. When we mixed chalcone (**1a**) and the general amino acid organocatalyst L-proline, a peak with an *m*/*z* value of 306 was detected by ESI(+)-MS that corresponded to the iminium ion formed between L-proline and chalcone (Fig. 3(a)). An equivalent mass pattern for the iminium ion was not detected, however, when **1a** was mixed with [emim][L-Pro] or [emim][L-Phe], suggesting that the [emim][AA]-catalyzed reaction would not proceed through an iminium ion intermediate (Fig. 3(b-1)). In contrast, when [emim][L-Phe] and aniline (**2a**) were mixed, a peak with an *m*/*z* value of 351 was detected by ESI(−)-MS that corresponded to an intermediate consisting of [L-Phe]$^-$ and two molecule of **2a** (Fig. 3(c)) [15]. Furthermore, the subsequent addition of chalcone (**1a**) led the detection of a peak by ESI(−)-MS

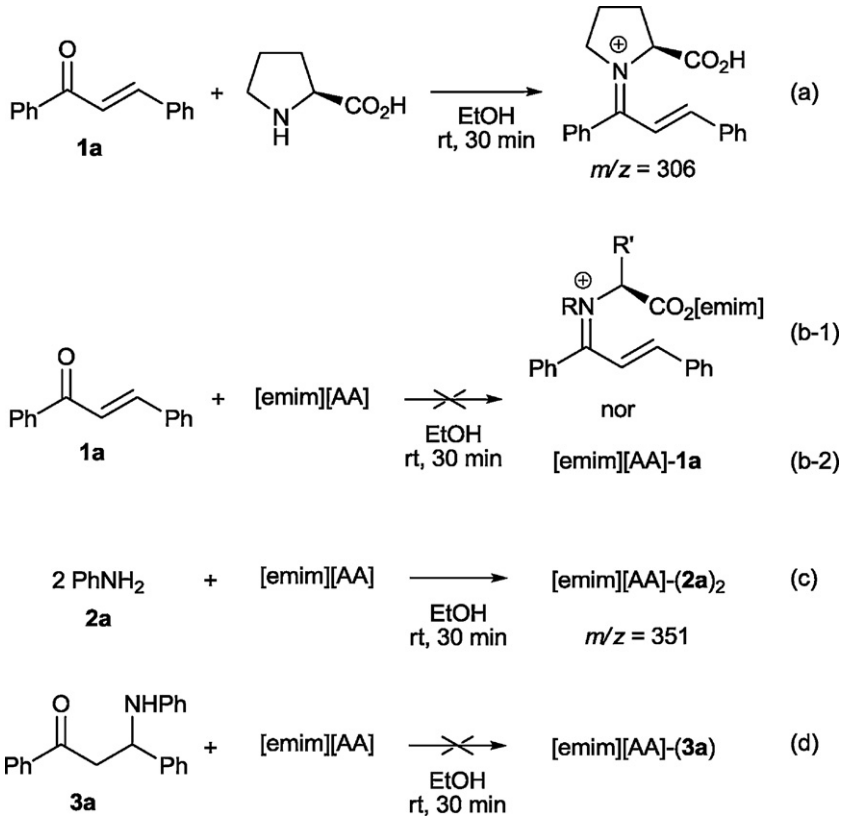


Fig. 3. (a) Formation of iminium ion by the reaction of **1a** with proline. (b) No interaction between **1a** with [emim][AA]. (c) Complex formation of [emim][AA] with **2a**. (d) No interaction between **3a** with [emim][AA].

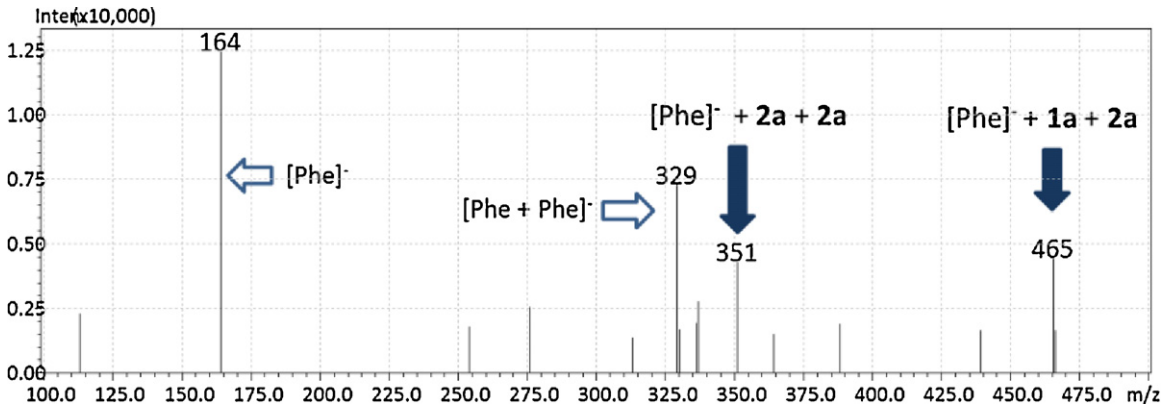
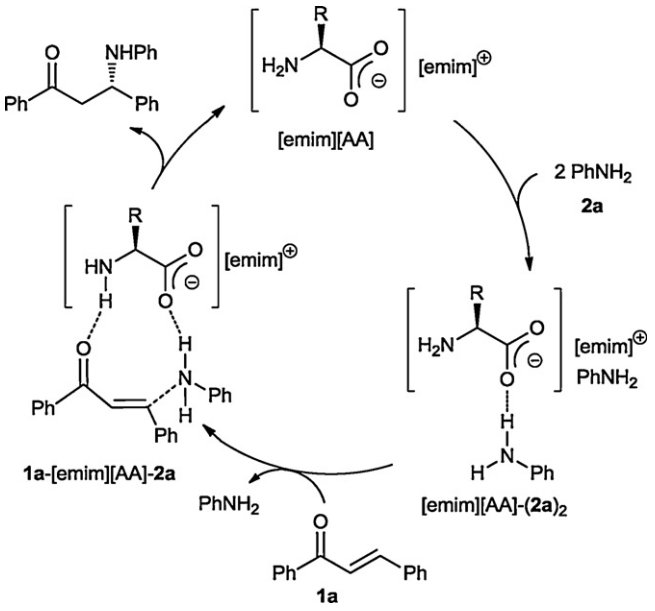


Fig. 4. ESI(−)-MS analysis of the reaction of aniline (**2a**), [emim][L-Phe], and chalcone (**1a**).



Scheme 1. Reaction mechanism.

with an m/z value of 465 that corresponded to a complex comprised of **1a**, **2a**, and [L-Phe]$^-$ (Fig. 4). In contrast, a complex of [L-Phe]$^-$ and **1a** (m/z = 372) was not detected (Fig. 3(b-2)). These results would suggest that [emim][AA] and aniline (**2a**) initially reacted to give [emim][AA]-**2a**, and that the subsequent reaction of this two component intermediate with chalcone (**1a**) led to the formation of a three component intermediate **1a**-[emim][AA]-**2a**, which existed like a supramolecular system (Scheme 1). We were not able to observe the composite (m/z = 465) when a mixture of [emim][L-Phe] and isolated **3a** were analysed by ESI(−)-MS (Fig. 3(d)).

4. Conclusions

In conclusion, we have successfully demonstrated that ionic amino acids can catalyze the aza-Michael reaction of α,β-unsaturated ketones and aromatic amines. Weak interactions, such as hydrogen bonding interactions, triggered the expression of the catalytic activity and enantioselectivity, and these factors could be effectively controlled using different types of amino acids. The precise design and selection of the cation (e.g., imidazole) and anion moieties (e.g., amino acid) could lead to the development of additional organocatalysts with enhanced levels of activity and selectivity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2012.11.012.

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