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Development of highly enantioselective asymmetric aldol reaction catalyzed by 1-glycyl-3-methyl imidazolium chloride–iron(III) complex

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ABSTRACT

A novel, effective asymmetric 1-glycyl-3-methyl imidazolium chloride–iron(III) [[Gmim]Cl–Fe(III)] complex was synthesized and studied as organocatalyst in asymmetric aldol addition under solvent free condition at 25 °C. The hydrophobic group of amino acid favors reagent diffusion toward the chloroglycine moiety increasing the catalytic activity of supported iron complex. This method contains simplified product isolation and catalyst recycling, affording substituted aromatic aldehydes imparting high yield of aldol with excellent stereo-selectivity. This recyclable heterogeneous catalyst provides a simple strategy for the generation of a variety of new C—C bonds under environmentally benign condition.

1. Introduction

Asymmetric aldol addition is an important reaction due to its wide range of applications in both laboratory and industry. The significance of these aldol resides in the synthesis of carbohydrates, amino sugars, steroids, pharmaceutically active chiral compounds and various potential synthons [1]. As a rule, the major reaction products have anti-configuration, whereas syn-aldols are formed exclusively in native aldolase catalyzed aldol reaction [2].

In recent years, chiral ionic liquids have emerged as a set of green solvent with unique properties such as tunable polarity, high thermal stability and immiscibility with a number of organic solvents, negligible vapor pressure and recyclability. Their non-volatile character and thermal stability make the metal complexes potentially attractive alternatives to environmentally unfavorable organic co-solvents, notably chlorinated hydrocarbons. In particular, they show promising role as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes [3,4].

Furthermore, the asymmetric metal complex is an intensively developing area of modern organic chemistry. It was ascertained that the reaction could be performed at a higher rate and selectivity under the action of some more elementary organic molecules [5]. These contain amino acid derivatives, other natural amino acid, and small peptide derivatives as well as some other small chiral molecules used as catalysts allow the synthesis of complex poly functional compounds of high enantiomeric purity from simple achiral precursors. Although the natural amino acid functionalized metal complexes are cheap, recycling of organocatalysts can be an issue if one think in terms of large scale production or of green chemistry.

During the last two years, iron complex has been used for several organic transformations such as the epoxidation of styrene [6], oxidation of alcohol [7], asymmetric synthesis [8], amination [9] and also for the Michel addition [10] reactions. Recently, Wu et al. [11] have reported the simple and recyclable O-acylation serine derivatives catalyzed for the large-scale asymmetric direct aldol reaction in the presence of water. However, Calogero et al. [12] was described the L-proline supported zirconium phosphate catalyzed for direct asymmetric aldol addition. Siyutkin et al. [5] and Khan et al. [13] used the ionic liquid modified by hydroxy-α-amino acid or tagged organocatalysts moieties, for asymmetric aldol reaction in the presence of water. All the above mentioned methods provide a good yield whereas, some of these reactions are sluggish requiring at least 24 h for the reaction completion, harsh reaction conditions (organic co-solvents) and require absolutely dry and inert media. From these literatures no report was found in asymmetric aldol addition catalyzed by 1-glycyl-3-methyl imidazolium chloride–iron(III) complex (Fig. 1). Hence, we felt it would be interesting to investigate the alternative method for the synthesis of aldols. In this regard, we have developed an easy and a selective

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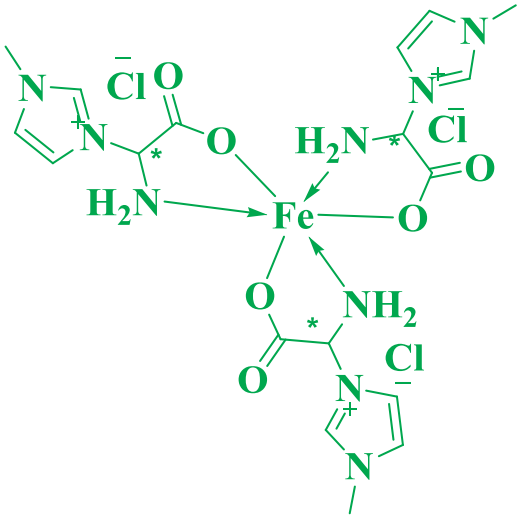


Fig. 1. 1-Glycyl-3-methyl imidazolium chloride–iron(III) complex ([Gmim]Cl–Fe(III)).

synthetic route, expand an operationally simple, safe and widely used eco-friendly method.

However, recovery and leaching can occur in the extractive work up leading to a loss of the catalyst in the reaction mixture on the one hand and requests additional effort to purify the extracted product. To overcome such problems, novel complex was developed [14] by covalent linking of organic catalytic units with an ionic liquid moiety (often chloroglycine). This imparts a low solubility of catalyst in the solvents used for extraction of the product on the one hand and high solubility in the reaction medium on the other hand [15–19]. This strategy was also applied to aldol reaction providing high yield and stereoselectivities and good recyclability of the organocatalyst.

The objectives of the present study are: (i) preparation of hexacoordinated 1-glycyl-3-methyl imidazolium chloride–iron(III) complex and its application as a catalyst system, (ii) development of competent synthetic process for the facile conversion of asymmetric aldol addition. The present method developed for the asymmetric aldol addition offer many advantages including high stereoselectivity and conversion, short duration and the involvement of non-toxic reagents.

2. Experimental

2.1. Materials and methods

All solvents and chemicals were commercially available and used without further purification unless otherwise stated. The [Gmim]Cl–Fe(III) complex was characterized by powder X-ray diffraction (P-XRD) diffractometry with a Bruker D8 (advance model), Germany and lynx eye detector operating with nickel filtered Cu-K radiation. The ^{1}H-NMR spectra were recorded on a Bruker 500 MHz using $CDCl_3$/DMSO-d_6 as the solvent and mass spectra were recorded on JEOL GC MATE II HRMS (EI) spectrometer. FT-IR spectra were recorded on an AVATRA 330 spectrometer with DTGS detector. Column chromatography was performed on silica gel (200–300 mesh). Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel GF-254 plates. Analytical high performance liquid chromatography (HPLC) was carried out on Agilent 1200 instrument using Chiralpak OJ-H (4.6 mm × 250 mm), optical rotations were measured on a JASCO P-1010 Polarimeter at λ = 589 nm.

2.2. Preparation of [Gmim]Cl–Fe(III) complex

The chiral [Gmim]Cl–Fe(III) complex was synthesized according to literature [20,21] while the other ionic liquids were synthesized using the literature procedure reported elsewhere [22–25]. The optical rotations for [Gmim]Cl–Fe(III) is $[\alpha]_D^{25} = -28.2$ (c 1, MeOH).

2.3. Procedure for asymmetric aldol addition

A mixture of cyclohexanone (1.2 mmol), p-nitrobenzaldehyde (1 mmol) and chiral [Gmim]Cl–Fe(III) (0.01 mmol) was added and stirred at 25 °C for 6 h. The product and excess of cyclohexanone were extracted with ethyl acetate (2 × 3 mL). The organic phase was separated and dried over anhydrous Na_2SO_4 and evaporated. The resulting crude was purified by column chromatography to give the desired pure product with excellent enantioselectivities.

2.4. Recycling of the catalyst for the model reaction of p-nitrobenzaldehyde with cyclohexanone using [Gmim]Cl–Fe(III) under solvent free condition

p-Nitrobenzaldehyde (1 mmol) was reacted with cyclohexanone (1.2 mmol) in the presence of [Gmim]Cl–Fe(III) (0.01 mmol) at ambient temperature. After completion of the reaction (TLC), the product was extracted as stated in the preceding general method. The brownish yellow solid [Gmim]Cl–Fe(III) was isolated by centrifugation. The recovered complex was washed with diethyl ether and dried with nitrogen. The resulting catalyst was charged to another batch of the similar reaction. This was repeated for eight runs to complete the reaction in 6 h, to give the desired product with 90–98% enantioselectivities (Table 7).

3. Results and discussion

3.1. Characterization of iron complex

[Gmim]Cl–Fe(III) catalyst has been characterized by FT-IR and XRD.

3.2. FT-IR analysis

Compounds	C—N	C=O	Fe—O	Fe—N	O—H	N—H
[Gmim]Cl–Fe(III)	1394s	1723s	480m	407m	–	3342m
[Gmim]Cl	1382s	1626s	–	–	3429s	3372m
Chloroglycine	1392s	1625s	–	–	3378s	3335m

FT-IR spectra of [Gmim]Cl–Fe(III) at different dissociation degrees are shown in Fig. 2. For carboxylate ion, the absorption band at 1723 cm^{-1} corresponds to carbonyl symmetric stretching. The asymmetric stretching of carboxylate was shifted to 1626 cm^{-1} [Gmim]Cl in contrast with the shift to 1625 cm^{-1} in chloroglycine, which appeared when [Gmim] Cl was treated with $FeCl_3$ and thus the carbonyl stretching was decreased. However, the plane of C—OH at 3378, 3429 cm^{-1} was present in chloroglycine, [Gmim]Cl, respectively, but when the network was treated with $FeCl_3$ no signal was observed for the —OH group, indicates the formation of Fe—O (480 cm^{-1}) bond. Although, the NH_2 signal in chloroglycine, [Gmim]Cl was detected in 3335, 3372 cm^{-1} with doublet, but in the case of [Gmim]Cl–Fe(III), we also found the doublet at 3342 cm^{-1}, this also shows the formation of Fe—NH (407 cm^{-1}) bond in the catalyst [27]. In all spectra, stretching of C—N was observed at 1394, 1382 and 1392 cm^{-1}, respectively. Notably, the FT-IR spectra revealed that a series of new iron complex with ionizable groups had been synthesized.

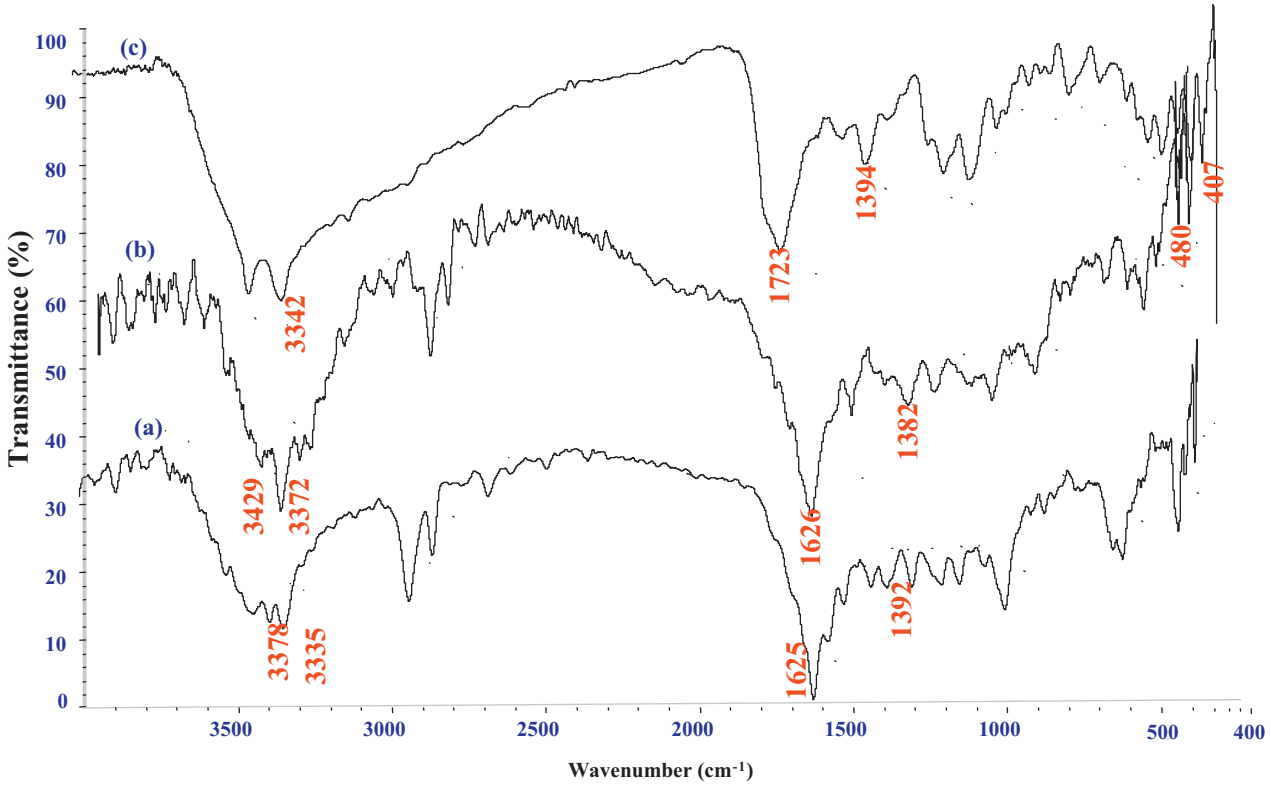


Fig. 2. FT-IR of (a) chloroglycine, (b) 1-glycyl-3-methyl imidazolium chloride ([Gmim]Cl) and (c) 1-glycyl-3-methyl imidazolium chloride–iron(III) complex ([Gmim]Cl–Fe(III)).

3.3. Powder XRD analysis

The formation of the Fe(III) catalyst was also supported by the XRD patterns with those of glycine, chloroglycine, Fe(III) complex. In comparison with glycine, chloroglycine, Fe(III) complex which showed major peaks, respectively, in 20.55, 28.98, 25.12, 31.80 and 45.82 (confirming iron peak with JCPDS Data Care No.: 99-101-1980 for Fe(III)), the [Gmim]Cl–Fe(III) pattern was in good agreement with peak at 31.80 and 45.82 (Fig. 3).

The iron complex catalyzed aldol reaction was carried out using cyclohexanone and p-nitrobenzaldehyde as a model reaction to investigate different parameters, such as effect of solvent, diverse bases, catalysts and concentration of the catalyst. Initially, the influence of different bases to the model reaction was studied; these results are summarized in Table 1. It was observed that, base free condition found to be the most effective and thus chosen as the preferred for the reaction, although organic and inorganic bases can be used. This may be due to the blocking of free coordination sites on the iron center. Although, the effect of the base in the aldol reaction is still imperfectly understood and many recent works were concerned on this subject. Recently, Wu et al. [11] have studied the role of the base in the aldol reaction using O-acylation serine as catalytic precursors and concluded that the oxidative addition step (when performed from aromatic aldehyde) becomes slower and the carbanion step turn into faster in the absence of the base.

Furthermore, we have screened several solvents for the reaction between cyclohexanone and p-nitrobenzaldehyde (Table 2). According to publications from Siyutkin et al. [5] and Calogero et al.

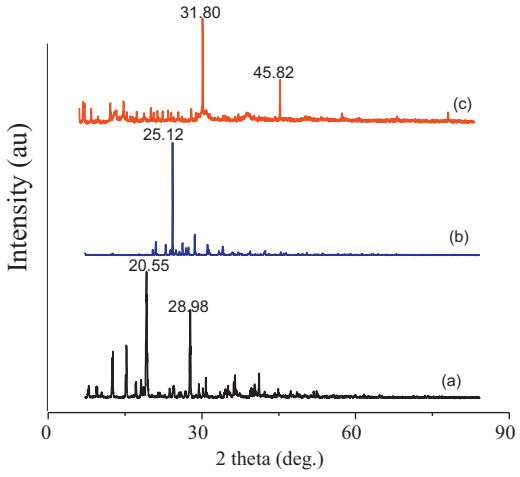


Fig. 3. Powder X-ray diffraction patterns of (a) glycine, (b) chloroglycine and (c) 1-glycyl-3-methyl imidazolium chloride–iron(III) complex ([Gmim]Cl–Fe(III)).

Table 1
Effect of the base on asymmetric aldol addition reaction.[a]

Entry	Base	Time (h)	Yield[b] (%)	Anti/syn[c]	ee of anti[c]
1	K_2CO_3	24	Trace	Trace	Trace
2	KOH	24	50	65/35	60
3	NaOH	24	47	73/27	70
4	Py	24	51	60/40	67
5	Imidazole	24	68	75/25	70
6	Et_3N	24	70	73/27	75
7	–	24	94	93/7	98
8	–	18	95	93/7	98
9	–	12	95	94/6	98
10	–	6	95	94/6	98
11	–	3	90	90/10	94
12	–	1	88	90/10	92

[a] *Reaction condition*: p-Nitrobenzaldehyde (1 mmol), cyclohexanone (1.2 mmol), different base (0.1 mmol) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

Table 2
Effect of the solvent on asymmetric aldol addition reaction.[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	Anti/syn[c]	ee of anti[c]
1	DCM	35	24	38	52/48	50
2	$CHCl_3$	50	24	43	60/40	54
3	THF	50	24	40	56/44	47
4	Methanol	50	24	50	65/35	60
5	Ethanol	65	24	53	60/40	63
6	CH_3CN	60	24	50	58/42	54
7	DMF	130	24	60	64/36	60
8	PhMe	90	24	63	67/33	57
9	Solvent free	25	6	95	94/6	98
10	Solvent free	20	6	95	92/8	97
11	Solvent free	35	6	93	95/5	98
12	Water (5 mL)	90	24	40	60/40	65

[a] *Reaction condition*: p-Nitrobenzaldehyde (1 mmol), cyclohexanone (1.2 mmol), different solvent (5 mL) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

[12] polar, aprotic solvents tend to give the best results for the aldol reaction, while Fu et al. [11] obtained high-activity catalysts in water solvent. We employed several solvents in the aldol model reaction. Among the previous reports, reaction under solvent free condition was the most productive, as compared with the polar and non-polar solvents. The catalyst was easily coordinating with organic co-solvents. It has also been reported that H_2O molecule sometimes is required to activate the Fe(III) catalyst. In our case, carrying out the reaction in H_2O (5 mL) 90 °C gave a negative effect on the product yield in comparison with solvent free condition and this lower yield could be due to the delocalization of the complex under aqueous condition.

Next, in order to optimize the reaction conditions for a particular catalyst the condensation reaction was executed using different catalysts and the results are given in Table 3. When the reaction was carried out using various catalysts such as glycine, chloroglycine, 1-carboxyethyl-3-methylimidazoliumbromide ([Cemim]Br) [26], 1-aminoethyl-3-methylimidazoliumbromide ([Aemim]Br) [26], $FeCl_3$/[Cemim]Br, $FeCl_3$/[Aemim]Br and $FeCl_3$/[Gmim]Cl in absence of solvent, it gave trace to 80% of enantioselectivities product. However, when the same reaction was conducted with [Gmim]Cl–Fe(III) as a catalyst it gave remarkable yield of product in short duration. Almost similar yield was obtained when increasing the duration.

The catalytic reaction which can be carried out with a small amount of expensive complexes is the most useful feature of synthetic reaction involving iron complex. According to literature, Jankowska et al. [28] obtained good yield in the Mukaiyama-aldol reaction of benzaldehyde with Z-enol silyl ether using 20 mol% of air and water stable $FeCl_2{\cdot}4H_2O$ in the presence of $EtOH/H_2O$. Using $Fe(CO)_3$ in the range between 1 mol% and 5 mol%, Gree et al. [29]

Table 3
Effect of the various catalysts on asymmetric aldol addition reaction.[a]

Entry	Catalyst	Time (h)	Yield[b]	Anti/syn[c]	ee of anti[c]
1	Glycine	24	Trace	Trace	Trace
2	Chloroglycine [Cl-gly]	24	50	–	–
3	[Cemim]Br	24	42	–	
4	[Aemim]Br	24	44	–	–
5	$FeCl_3$/[Cemim]Br	24	60	60/40	52
6	$FeCl_3$/[Aemim]Br	24	71	70/30	75
7	$FeCl_3$/[Gmim]Cl	24	75	75/25	80
8	[Gmim]Cl–Fe(III)	6	96	94/6	98
9	[Gmim]Cl–Fe(III)	7	97	93/7	98

[a] *Reaction condition*: p-Nitrobenzaldehyde (1 mmol), cyclohexanone (1.2 mmol) and different catalyst (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

Table 4
Effect of the catalyst loading on asymmetric aldol addition reaction.[a]

Entry	[Gmim]Cl–Fe(III) (mmol)	Time (h)	Yield[b]	Anti/syn[c]	ee of anti[c]
1	–	24	Trace	Trace	Trace
2	0.1	6	96	94/6	98
3	0.075	6	96	94/6	98
4	0.050	6	96	94/6	98
5	0.025	6	96	94/6	98
6	0.01	6	96	94/6	98
7	0.0075	6	94	90/10	96
8	0.005	6	93	86/14	90

[a] *Reaction condition*: p-Nitrobenzaldehyde (1 mmol), cyclohexanone (1.2 mmol) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

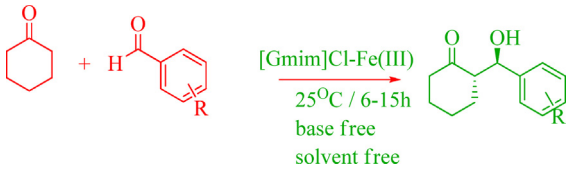
observed acceptable rate in the aldol reaction of alcohols. Among the previous reports, increasing the quantity of the catalyst can improve the reaction yield and shorten reaction time (Table 4). First, aldol reaction was carried out in absence of catalyst at ambient temperature; it was found that no product formed even after 24 h. Even though amount of the catalyst decreased from 0.1 to 0.025 mmol, no change in the yields, whereas using 0.01 mmol [Gmim]Cl–Fe(III), in model reaction generated 96% product. Almost dissimilar yield was obtained when decreasing the catalyst amount from 0.01 to 0.005 mmol. Therefore, the aldol addition reaction was carried out at the molar ratio of p-nitrobenzaldehyde, cyclohexanone and [Gmim]Cl–Fe(III) 1:1.2:0.01 mmol under solvent free condition at ambient temperature.

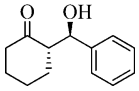
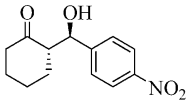
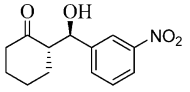
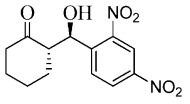
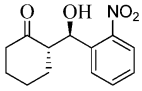
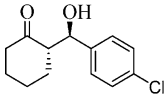
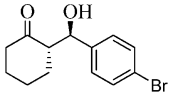
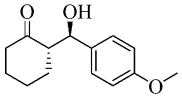
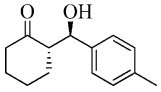
In order to test the substrate generality of [Gmim]Cl–Fe(III) complex catalyzed direct aldol reaction, the condensation of various aromatic aldehydes with cyclohexanone were studied under the optimized conditions. The results are summarized in Table 5. It can be noticed that a wide range of aromatic aldehydes can efficiently contribute in the aldol reactions. However, the reaction between cyclohexanone and aromatic aldehydes bearing electron-withdrawing substituents furnished β-hydroxy carbonyl aldol products with excellent yields (80–98%) and enantioselectivities (93–98% ee for anti-isomer) within 6–12 h, particularly the p-nitrobenzaldehyde and o-nitrobenzaldehyde. On the other hand, longer reaction times (15 h) were required for aromatic aldehydes containing an electron-donating group to give comparatively inferior yields (70–75%), without lacking of enantioselectivities, in particular the p-toulaldehyde. This can be explained that electron-withdrawing groups improve the electrophilicity of carbonyl carbons in aldehydes, which facilitates the reaction, while electron-donating groups reduce the electrophilicity. Moreover, the direct aldol reaction of neutral aldehydes catalyzed by the iron complex also afforded the aldol products with high enantioselectivities and diastereoselectivities. All the condensation reactions of cyclohexanone with aromatic aldehydes afford the subsequent products with excellent yield (70–98%) and enantioselectivities (93–98% ee of anti-isomers).

Finally, condensation of cyclopentanone with different aromatic aldehydes was investigated. In these reactions, variety of aldehyde were treated with cyclopentanone in the presence of [Gmim]Cl–Fe(III) at room temperature in absence of solvent. The reaction proceeded smoothly with the formation of aldols with 87–93% enantioselectivities. In addition, it was found that substituted group of aromatic aldehydes have an effect on aldol; aromatic aldehydes with withdrawing group was observed to be more reactive than that of electron donating group (Table 6).

Isolation of the heterogeneous catalyst was easily performed by separation or centrifugation. The isolated catalyst was washed with ethyl acetate and dried in air. The regenerated catalyst was used for the reaction of p-nitrobenzaldehyde with

Table 5
Asymmetric aldol addition reaction of different aromatic aldehydes with cyclohexanone in the presence [Gmim]Cl–Fe(III) under solvent free condition.[a]



Entry	Product	Time (h)	Yield[b] (%)	Anti/syn[c]	ee of anti[c]
1		8	80	90/10	93
2		6	96	94/6	98
3		6	97	95/5	98
4		6	97	97/3	98
5		6	98	97/3	98
6		12	85	92/8	94
7		12	85	92/8	95
8		15	75	91/9	93
9		15	70	90/10	95

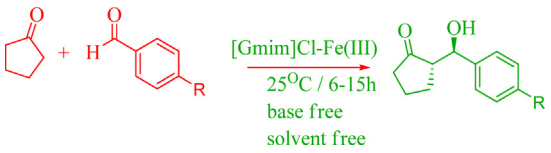
[a] *Reaction condition*: Aldehydes (1 mmol), ketone (1.2 mmol) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H) and comparison of the retention times with literature data [11].

cyclohexanone for eight runs to afford (S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexanone with 98–90% enantioselectivities (Table 7).

For practical application in the asymmetric aldol reaction, the life time of the heterogeneous catalysts and their reusability are very important factors. For the comparative study, asymmetric aldol reaction was carried out with model reaction at the optimized conditions in presence of Fe/C catalyst. However, a significant difference in Fe leaching was observed. Without exclusion of air about 26% of the total iron amount were lost from the Fe/C and found in solution (AAS) compared to [Gmim]Cl–Fe(III) where no leaching detected.

For those conformation, [Gmim]Cl–Fe(III) catalyst was collected after the completion of the reaction and analyzed by powder X-ray diffraction method and the diffraction patterns are given in Fig. 4. The analysis specifies that the [Gmim]Cl–Fe(III) do not undergo any

Table 6
Asymmetric aldol addition reaction of different aromatic aldehydes with cyclopentanone in the presence [Gmim]Cl–Fe(III) under solvent free condition.[a]



Entry	Product (R)	Time (h)	Yield[b] (%)	Anti/syn[c]	ee of anti[c]
1	H	8	75	85/15	87
2	NO_2	6	94	90/10	95
3	Cl	12	85	83/17	93
4	Br	12	85	85/15	93
5	OCH_3	12	70	90/10	90
6	CH_3	15	68	80/20	90

[a] *Reaction condition*: Aldehydes (1 mmol), ketone (1.2 mmol) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H) and comparison of the retention times with literature data [11].

Table 7
Recycling of the catalyst for the reaction of p-nitrobenzaldehyde with cyclohexanone.[a]

Entry	Run	Yield[b] (%)	Anti/syn[c]	ee of anti[c]
1	0	96	94/6	98
2	1	96	93/7	98
3	2	96	93/7	95
4	3	94	93/7	95
5	4	93	92/8	95
6	5	93	92/8	92
7	6	92	90/10	92
8	7	90	90/10	90

[a] *Reaction condition*: p-Nitrobenzaldehyde (1 mmol), cyclohexanone (1.2 mmol) and [Gmim]Cl–Fe(III) (0.01 mmol) stirring at 25 °C for 6 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

chemical and structural changes, thus proving its surface catalytic activity toward the condensation reaction of p-nitrobenzaldehyde with cyclohexanone. On the other hand, presence of peaks due to metallic iron is noted in the powder XRD pattern of the complex in the case of 'Fe(III)' (Fig. 4a and b). Furthermore, Fe leaching was also studied by inductively coupled plasma atomic emission spectroscopy (ICP-OES) analysis, indicating that the product mixture contained 0 ppm of iron accounting for 0.1 mmol of the initially added amount of Fe. From those experimental results,

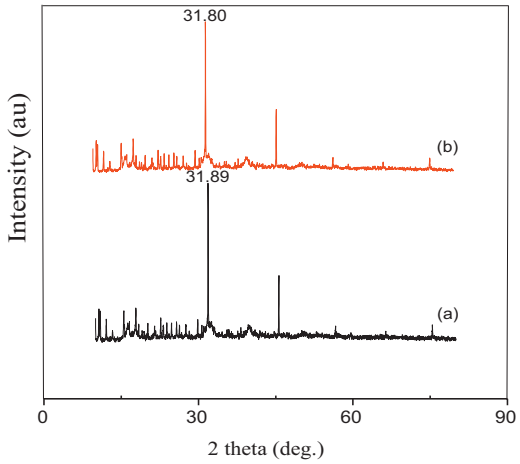
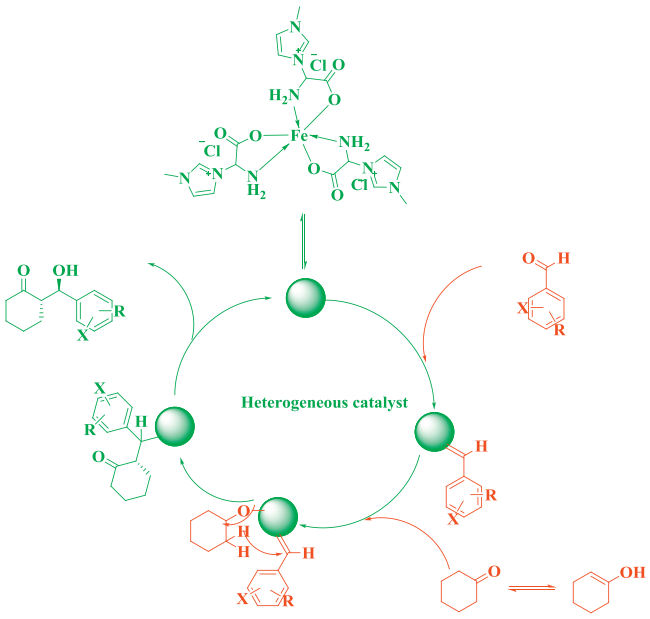


Fig. 4. Powder X-ray diffraction patterns of the [Gmim]Cl–Fe(III)complex: (a) before reaction and (b) after reaction (8th run).



Scheme 1. Proposed catalytic mechanism.

we believe that the no Fe leaching observed in asymmetric aldol reaction, it's due to immobilized iron in amino acid functionalized ionic liquid binding site located on the surface, which acts as a ligand through metal–ligand interaction. The anchoring of Fe species by amino acid sites supported on ionic liquid minimizes catalyst deterioration and no metal leaching and therefore allows efficient catalyst recycling. The precise mechanism of the catalytic reaction needs to be elucidated, but it is noticeable that the mechanism is strongly modified depending of the substituted aromatic aldehydes employed, obtaining highly enantioselective asymmetric aldols (anti) as the main product (Scheme 1).

The [Gmim]Cl–Fe(III) complex stumble on superiority over most of the reported catalysts with many advantages: facile synthesis, thermal stability and structural versatility, easy handling, catalytic performance in air at 25 °C, without any additives, no inert atmosphere required without leaching of catalyst.

(S)-2-((R)-hydroxy(phenyl)methyl)cyclohexanone (Table 5, entry 1): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.39 (d, J = 2.3 Hz, 1H, syn, minor), 4.79 (d, J = 8.8 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 22.5 min (minor) and 20.8 min (major).

(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclohexanone (Table 5, entry 2): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.48 (d, J = 1.8 Hz, 1H, syn, minor), 4.89 (d, J = 8.8 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 26.3 min (minor) and 34.9 min (major). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.12–1.31 (m, 6H), 2.49–2.32 (m, 2H), 2.63–2.57 (m, 1H), 4.07 (s, 1H), 4.89 (d, J = 8.4 Hz, 1H), 7.50 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 8.6 Hz, 2H). ^{13}C-NMR: δ 24.7, 27.7, 30.8, 42.7, 57.2, 74.0, 123.5, 127.9, 147.6, 148.4, 214.8.

(S)-2-((R)-hydroxy(3-nitrophenyl)methyl)cyclohexanone (Table 5, entry 3): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.50 (m, 1H, syn, minor), 4.92 (d, J = 8.4 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 47.0 min (minor) and 35.5 min (major).

(S)-2-((R)-(4-bromophenyl)(hydroxy)methyl)cyclohexanone (Table 5, entry 7): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.30 (d, J = 2.6 Hz, 1H, syn, minor), 4.75 (d, J = 8.5 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 14.1 min (minor) and 16.4 min (major).

(S)-2-((R)-hydroxy(4-methoxyphenyl)methyl)cyclohexanone (Table 5, entry 8): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.32 (m, 1H, syn, minor), 4.74 (d, J = 8.8 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 43.2 min (minor) and 34.4 min (major).

(S)-2-((R)-hydroxy(phenyl)methyl)cyclopentanone (Table 6, entry 1): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.31 (m, 1H, syn, minor), 4.71 (d, J = 8.7 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 20.8 min (minor) and 16.5 min (major).

(S)-2-((R)-hydroxy(4-nitrophenyl)methyl)cyclopentanone (Table 6, entry 2): The diastereomeric anti/syn ratio was determined by ^{1}H-NMR analysis of the crude product: δ 5.42 (m, 1H, syn, minor), 4.85 (d, J = 8.9 Hz, 1H, anti, major). Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 4/1, 1.0 mL/min, λ = 254 nm, 25 °C): t_R = 77.4 min (minor) and 81.6 min (major).

4. Conclusions

In conclusion, the results from the investigation demonstrate that the 1-glycyl-3-methyl imidazolium chloride–iron(III) complex was efficient catalyst for highly enantioselective aldol addition reaction. The procedure is easy and does not require special precautions. All the reaction was conducted in the air without the use of an organic co-solvent. Noteworthy features of this catalysis system are: (1) synthesized a novel green 1-glycyl-3-methyl imidazolium chloride–iron(III) complex; (2) its catalytic activity was tested in direct aldol reaction; (3) 0.01 mmol of catalyst was sufficient to furnish the aldol products with excellent yields (up to 98%) and enantioselectivities (up to 98%); (4) the catalyst can be readily recovered and reused without significant loss of its activity and stereo selectivity; notably, (5) this organo catalyzed direct asymmetric aldol reaction can be performed on a large-scale with the enantio selectivity being maintained at the same level, which offers a great possibility for applications in industry.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata.2013.08.029.

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