Journal of Organometallic Chemistry 723 (2013) 154–162

Contents lists available at SciVerse ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

Development and efficient 1-glycyl-3-methyl imidazolium chloride–copper(II) complex catalyzed highly enantioselective synthesis of 3, 4-dihydropyrimidin-2(1H)-ones

Parasuraman Karthikeyan, Sachin Arunrao Aswar, Prashant Narayan Muskawar, Pundlik Rambhau Bhagat*, S. Senthil Kumar

Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632 014, India

ARTICLE INFO

Article history:
Received 25 March 2012
Received in revised form
9 June 2012
Accepted 25 June 2012

Keywords:
3, 4-dihydropyrimidin-2(1H)-one
Ionic liquid
Copper complex
Amino acid

ABSTRACT

A novel, effective asymmetric 1-glycyl-3-methyl imidazolium chloride-copper(II) complex [[Gmim]Cl –Cu(II)] was synthesized and studied as organocatalyst for enantioselective Biginelli reaction under solvent free condition at 25°C. The hydrophobic group on amino acid favors reagent diffusion towards the chloroglycine moiety increasing the catalytic activity of supported palladium complex. Spectroscopic evidence of complex has been proved by Powder XRD, SEM, FT-IR and AFM. This method contains simplified product isolation and catalyst recycling, affording substituted aldehydes imparting high yield with excellent stereoselectivity. 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

Multicomponent reactions are very attractive tools to obtain the complex molecules from one-pot procedures. Moreover, Dihydropyrimidinones are vital synthons, pharmaceuticals or precursors. Furthermore, these compounds have emerged as the integral backbones of several calcium-channel blockers. However, some marine alkaloids containing the dihydropyrimidine core unit to interesting biological properties; batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors. Recently, dehydro pyrimidinones have been considered as a new lead for the development of new anticancer drugs [1–3].

In recent years, imidazolium functionalized 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 makes the metal complexes potentially attractive alternatives to environmentally unfavorable organic co-solvents, notably chlorinated hydrocarbons. They are particularly promising as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes [4,5].

Furthermore, asymmetric metal complex is an intensively developing area of modern organic chemistry. It was ascertained that the reaction could be performed at higher rate and selectivity under the action of some more elementary organic molecules [6]. These contain amino acid derivatives, other natural amino acid, and small peptide derivatives as well as some other small chiral molecules used as catalysts which 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 thinks in terms of large scale production or of green chemistry.

During the last two years, copper complex has been used for several organic transformations such as the epoxidation of styrene [7–10], oxidation of alcohol and alkane [11–16], asymmetric synthesis [17–19], amination [20,21] and also for the Suzuki cross-coupling [22–24] reactions. Recently, Chengjian Zhu and co-workers have reported the highly enantioselective Biginelli reaction using a new chiral ytterbium catalyst: asymmetric synthesis of dihydropyrimidines [25]. However, Liu-Zhu Gong et al., was described the highly enantioselective organocatalytic Biginelli reaction [26]. Zhiwei Miao [27] and Shi-Wei Luo et al. [28], organocatalyst modified by 3,3′-disubstituents of phosphoric acids or chiral bifunctional primary amine–thiourea catalysts: for enantioselective Biginelli reaction in the presence of organic co-solvent. Furthermore; Li-Wen Xu et al., was achieved the high enantioselective in presence of $NbCl_5$/primary amine [29].

* Corresponding author. Tel.: +91 9047289073; fax: +91 416 22404119.
E-mail address: drprbhagat111@gmail.com (P.R. Bhagat).

0022-328X/$ – see front matter © 2012 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jorganchem.2012.06.022

Over all the methods provide good yield, but some have drawbacks such as lengthy work-up procedure, harsh reaction conditions (organic co-solvents) and require absolutely dry and inert media. From these literature no report was found for enantioselective Biginelli reaction catalyzed by 1-glycyl-3-methyl imidazolium chloride-copper(II) complex (Fig. 1). Hence, we felt it would be keen interest to investigate the alternative method for the synthesis of high enantioselective Biginelli reaction. In this regard, we have developed an easy and selective synthetic route, expand an operationally simple, safe and widely usable 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 [30] by covalent linking of organocatalytic unit 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 [31–35]. This strategy was also applied to Biginelli reaction providing high yield and enantioselective and good recyclability of the organocatalyst.

The objectives of the present study are indeed: (i) prepare tetra-coordinated 1-glycyl-3-methyl imidazolium chloride-copper (II) complex and to explore its application as catalyst system, (ii) develop an efficient synthetic process for the facile conversion of enantioselective Biginelli reaction. The present method developed for the enantioselective Biginelli reaction offer many advantages including high 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–Cu(II) 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. AFM and SEM were recorded on (Nano Surf Easy Scan-2 Switzerland), (Carl Zeiss EVO MA 15(model)) respectively. 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 $\lambda = 589$ nm.

2.2. Preparation of [Gmim]Cl–Cu(II) complex

2.2.1. Protection of amino group using di. tert Butyl pyrocarbonate (Boc)

A solution of the glycine (10 mmol) in a mixture of dioxane (10 mL), water (5 mL) and 0.5 N NaOH (5 mL) was stirred and cooled in an ice-water bath. Boc (8 mmol) was added and agitation continued at 25°C for 30 to 45 min. The resulting solution was concentrated in vacuo, cooled in an ice-water bath, covered with a layer of ethyl acetate (15 mL). Then, the reaction mixture was acidified to pH 2–3 using $KHSO_4$. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The ethyl acetate layer washed with water, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was recrystallized using ethanol [36,37].

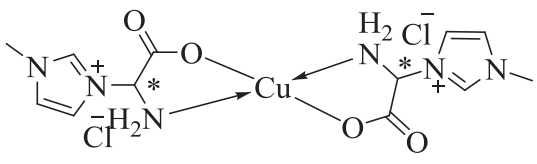


Fig. 1. 1-glycyl-3-methyl imidazolium chloride-Copper (II) complex [Gmim]Cl–Cu (II).

2.2.2. Protection of acid group using methyl ester

Boc-glycine (10 mmol) was suspended in 2, 2-di methoxypropane (DMP) (50 mL) and concentrated HCl (5 mL) was added. The mixture was allowed to stand at 25°C over night. The volatile reactant was removed in vacuo at 60 °C, the residue dissolved in a minimum amount of dry methanol and the solution diluted with dry ether (50 mL). The crystalline methyl ester hydrochloride was collected on a filter, washed with ether and dried in vacuo over NaOH. Recrystallization from methanol–ether (9:1 mL) affords the analytically pure ester [38].

2.2.3. Chlorination of protected glycine

In 100 mL RB, Thionyl chloride (6 mmol) was added and cooled in an ice-water bath. The protected glycine (4 mmol) was dissolved in ethanol and added to RB drop wise at (0 °C) and stirred at 25°C for 48 h. The resulting solution was concentrated under vacuo, cooled in an ice-water bath to get the desired precipitate. Recrystallization of the product using ethanol–ether affords the analytically pure chloroglycine.

2.2.4. Removal of protecting group using hydrobromic acid in acetic acid

An about 33% (10 mL) solution of HBr in acetic acid is placed in a 100 mL RB flask and protected chloroglycine (4 mmol) was added with stirring. The flask was closed with a cotton filled drying tube and swirled to effect complete dissolution of the protected chloroglycine. The deprotection occurred with evolution of CO_2 and heat. When the gas evolution ceases, dry ether (50 mL) was added with swirling and the reaction mixture was stored in an ice-bath. The precipitated chloroglycine ester was collected on a filter, washed with ether and dried over NaOH in vacuo.

Furthermore, a solution chloroglycine ester (4 mmol) in methanol (10 mL) was surrounded by water bath at ambient temperature and NaOH (20 mL) was added with stirring. The mixture was stored at 25 °C for overnight. Dilute HCl (10 mL) was added and methanol removed in vacuo. The aqueous solution was cooled in ice-water for 2 h. Chloroglycine was collected on a filter, washed with ether and dried in air [39–42]. ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.28 (s, 2H), 5.49 (s, 2H), 10.83 (s, 1H). HR-MS (EI): $C_2H_4ClNO_2$ (found: 108.92), cal (108.99). Micro analytical data: Cal (C: 21.94; N: 12.79; H: 3.68), found: (C: 21.90; N: 12.76; H: 3.64). $[\alpha]_D^{25} = +152.77$ (*c* 1, MeOH).

2.2.5. Synthesis of 1-glycyl-3-methyl imidazolium chloride [Gmim]Cl

Initially, chloroglycine (0.01 mol) reacted with N-Methyl-imidazole (0.011 mol) in 50 mL acetonitrile at 70 °C for 24 h to generate chloroglycine ligand modified by imidazole salt (3-(amino(carboxy)methyl)-1-methyl-1H-imidazol-3-ium chloride) [Gmim]Cl. The solvent (acetonitrile) was removed under reduced pressure at 80 °C (water bath temperature). Then the residue was mixed with 50 mL water and extracted with ethyl acetate (3 × 5 mL). Further, the water phase was evaporated under reduced pressure at 80 °C until the mass of the residue did not change. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.2 (s, 1H), 3.3 (s, 3H), 5.0 (s, 2H), 6.92 (d, 1H), 7.0 (d, 1H), 7.6 (s, 1H), 9.1 (s, 1H). HR-MS (EI): $C_6H_{10}ClN_3O_2$ (found: 191.10), cal (191.05). FT-IR (KBr, cm^{-1}): 3429, 3372, 2933, 2855, 1628, 1526 and 1382. $[\alpha]_D^{25} = +47.12$ (*c* 1, MeOH).

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

Entry	Base	Time (h)	Yield[b] (%)	ee[c]
1	K_2CO_3	24	Trace	Trace
2	KOH	24	40	60
3	NaOH	24	37	70
4	Py	24	41	67
5	Imidazole	24	58	70
6	Et_3N	24	60	75
7	–	24	94	98
8	–	12	95	98
9	–	9	92	98
10	–	6	90	92
11	–	3	85	90
12	–	1	82	88

[a] Reaction condition: 4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

2.2.6. Synthesis of 1-glycyl-3-methyl imidazolium chloride-Copper(II) complex [Gmim]Cl–Cu(II)

In RB, [Gmim]Cl (0.02 mmol) was treated with $CuCl_2$ (0.01 mmol) in 100 mL methanol at 50 °C for 12 h to deliver the [Gmim]Cl modified by copper complex [Gmim]Cl–Cu(II). The solvent (methanol) was removed under reduced pressure at 80 °C (water bath temperature). Finally, pale blue solid [Gmim]Cl–Cu(II) complex was obtained in 96% [42] $[\alpha]_D^{25} = +45.44$ (c 1, MeOH).

3. General procedure for Biginelli reaction

A mixture of substituted aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu(II) complex (0.01 mmol%) was added to a 50 mL round-bottomed flask and stirred at 25 °C for the appropriate time (see Table 5) (The reaction was monitored by TLC, until the aldehyde was disappeared). The product was extracted with diethyl ether (3 × 5 mL) and dried over $MgSO_4$ and evaporated under reduced pressure. The resulting crude was purified by flash chromatography to give the desired pure product with excellent enantioselectivities.

3.1. Recycling of the catalyst for model reaction using [Gmim]Cl–Cu(II) under solvent free condition

4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu(II) complex (0.01 mmol%) stirring at 25°C. After completion of the reaction (TLC), the product was extracted as stated in the preceding general method. The pale blue solid [Gmim]Cl–Cu(II) was isolated by centrifugation. The recovered complex was washed with diethyl ether and dried in air. The resulting catalyst was charged to another batch of the similar reaction. This was repeated for seven runs to complete the reaction in 12 h, to give the desired product with 98–90% with enantioselectivities (Table 6).

Table 2
Optimization of solvent for the asymmetric Biginelli reaction[a].

Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c]
1	DCM	35	24	38	50
2	$CHCl_3$	50	24	43	54
3	THF	50	24	40	47
4	1,4-dioxane	85	24	50	60
5	Ethanol	65	24	53	63
6	CH_3CN	60	24	50	54
7	DMF	130	24	60	60
8	PhMe	90	24	63	57
9	Solvent free	25	12	95	98
10	Solvent free	20	12	95	97
11	Solvent free	35	12	93	98
12	Water (5 ml)	90	24	40	65

[a] Reaction condition: 4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

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

Entry	Catalyst	Time (h)	Yield[b]	ee[c]
1	L-glycine	24	Trace	Trace
2	Chloroglycine [Cl-gly]	24	35	40
3	[Cemim] Br	24	42	48
4	[Aemim] Br	24	44	50
5	$CuCl_2$/[Cemim] Br	24	60	52
6	$CuCl_2$/[Aemim] Br	24	71	65
7	$CuCl_2$/[Gmim]Cl	24	75	70
8	[Gmim]Cl–Cu (II)	12	96	98
9	[Gmim]Cl–Cu (II)[d]	13	97	98

[a] Reaction condition: 4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).
[d] Reaction time 13 h.

4. Results and discussion

4.1. Characterization copper complex

[Gmim]Cl–Cu(II) catalyst has been characterized by FT-IR, XRD, SEM and AFM.

4.1.1. FT-IR analysis

Compounds	C–N	C=O	Cu–O	Cu–N	O–H	N–H
[Gmim]Cl–Cu (II)	1394 s	1723 s	521 m	407 m	–	3342 m
[Gmim]Cl	1382 s	1626 s	–	–	3429 s	3372 m
Chloroglycine	1392 s	1625 s	–	–	3378 s	3335 m

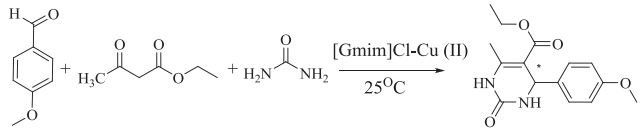
FT-IR spectra of [Gmim]Cl–Cu(II) at different dissociation degrees are shown in Fig. 2. For carboxylate ion, the absorption band at 1723 cm^{-1} corresponds to carbonyl symmetric stretching. The asymmetric stretching of carboxylate was shifted to 1626 cm^{-1} [Gmim]Cl in contrast with the shift to 1625 cm^{-1} in chloroglycine, which appeared when [Gmim]Cl was treated with $CuCl_2$ and thus the carbonyl stretching was decreased.

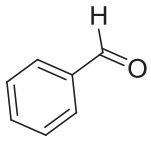
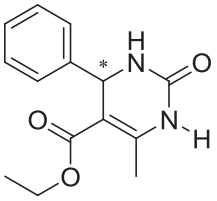
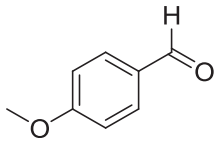
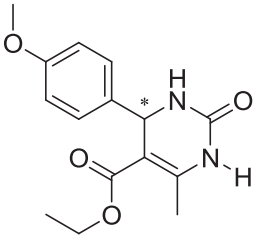
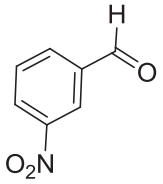
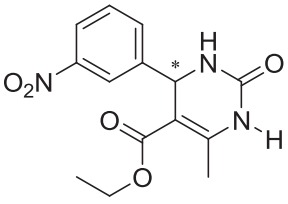
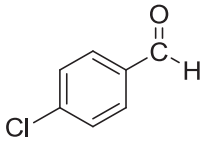
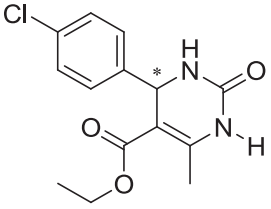
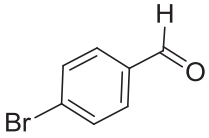
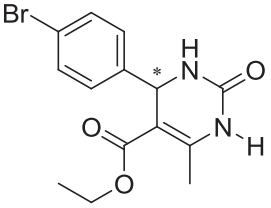
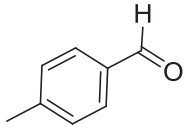
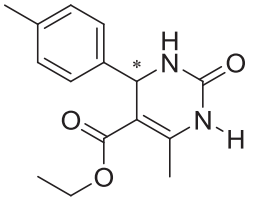
Table 4
Effect of the catalyst loading on asymmetric Biginelli reaction[a].

Entry	[Gmim]Cl–Cu (II) mmol%	Time (h)	Yield[b]	ee[c]
1	–	24	Trace	Trace
2	0.1	12	96	98
3	0.075	12	96	98
4	0.050	12	96	98
5	0.025	12	95	98
6	0.01	12	96	98
7	0.0075	12	90	96
8	0.005	12	84	90

[a] Reaction condition: 4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

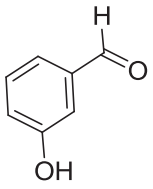
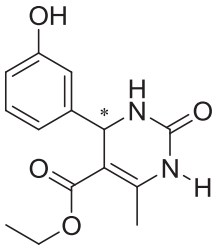
Table 5
Asymmetric Biginelli reaction of different aldehyde in the presence [Gmim]Cl–Cu (II) under solvent free condition[a].



S. No	Reactant	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1			12	94	97
2[a,d]			12	96	98
3			14	95	98
4			14	90	93
5			14	90	92
6			18	82	92

(*continued on next page*)

Table 5 (*continued*)

S. No	Reactant	Product	Time (h)	Yield[b] (%)	ee[c] (%)
7			20	80	90

[a] Reaction condition: Substituted aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H) and comparison of the retention times with literature data [25–29].
[d] Reaction condition: 4-metoxy benzaldehyde (10.0 mol), ethyl acetoacetate (10.0 mol), urea (12.0 mol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.

However, the plane of C–OH at 3378, 3429 cm^{-1} was present in chloroglycine, [Gmim]Cl respectively, but when the network were treated with $CuCl_2$ no signal was observed for the –OH group, indicates the formation of Cu–O (521 cm^{-1}) bond. Although, the NH_2 signal in chloroglycine, [Gmim]Cl was detected at 3335, 3372 cm^{-1} with doublet, but in the case of [Gmim]Cl–Cu(II), we also found the doublet at 3342 cm^{-1}, this also shows the formation of Cu-NH (407 cm^{-1}) bond in the catalyst [43]. 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 copper complex with ionisable groups had been synthesized.

4.1.2. Powder XRD analysis

The formation of the Cu(II) catalyst was also supported by the XRD patterns with those of chloroglycine, $CuCl_2$, Cu(II) complex. In comparison with chloroglycine, $CuCl_2$ and Cu(II) complex which showed major peaks respectively at 16.37, 31.42 and 45.82 (confirming copper peak with JCPDS data care no: 99-100-1542 for Cu(II), the [Gmim]Cl–Cu(II) pattern was in good agreement with peak at 31.42 (Fig. 3).

4.1.3. SEM analysis

The SEM image of the catalyst is shown in Fig. 4. From this image it is clear that [Gmim] Cl–Cu(II) has nano sphere like morphology with particles of dimensions ca. 250–300 nm and these are distributed uniformly throughout the material.

4.1.4. AFM analysis

The 3D AFM images of the 1-glycyl-3-methyl imidazolium chloride and [Gmim]Cl–Cu(II) complex is shown in Fig. 5. The 3D image for 1-glycyl-3-methyl imidazolium chloride was present 10.2 μm^2 size of the particles. It can be seen that the surface was very smooth crystalline ligand are notably different, the grain size and the shape vary significantly (Fig. 5(a)). After doping the $CuCl_2$ to the [Gmim]Cl, Fig. 5(b) 3D AFM image was obtained. From this image, the larger scan size also emphasizes the differences between the [Gmim]Cl and [Gmim]Cl–Cu(II). The surface of copper doped ionic liquid, showed in the rough topography that confirmed the formation of film with copper complex in the size of 3.92 μm^2.

Table 6
Recycling of the catalyst[a].

Entry	Run	Yield[b] (%)	ee[c]
1	0	96	98
2	1	95	96
3	2	94	95
4	3	94	95
5	4	93	95
6	5	93	92
7	6	92	92

[a] Reaction condition: 4-metoxy benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.2 mmol) and [Gmim]Cl–Cu (II) complex (0.01 mmol%) stirring at 25 °C for 12 h.
[b] Isolated yield by flash chromatography.
[c] Determined by chiral HPLC analysis (OJ-H).

The copper complex catalyzed Biginelli reaction was carried out using 4-metoxy benzaldehyde, ethyl acetoacetate and urea 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 copper center. Although, the effect of the base in the Biginelli reaction is still imperfectly understood and many recent works were concern on this subject. Recently, Ruyu Chen have studied the role of the base in the Biginelli reaction using chiral bifunctional primary amine-thiourea catalysts (enamine intermediate) and concluded that the oxidative addition step (when performed from substituted aldehyde) becomes slower and the carbanion step turn into faster in the absence of the base [27].

Furthermore, we have screened several solvents for the reaction between 4-metoxy benzaldehyde, ethyl acetoacetate and urea (Table 2). According to publications from Chengjian Zhu [25] and co-workers and Liu-Zhu Gong [26] polar, aprotic solvents tend to give the best results for the asymmetric Biginelli reaction, while Shi-Wei Luo [28] obtained high-activity catalysts in Toluene solvent. We employed several solvents in the 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 Cu(II) catalyst. It has also been reported that H_2O molecule is required in some cases to activate the Cu(II) 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

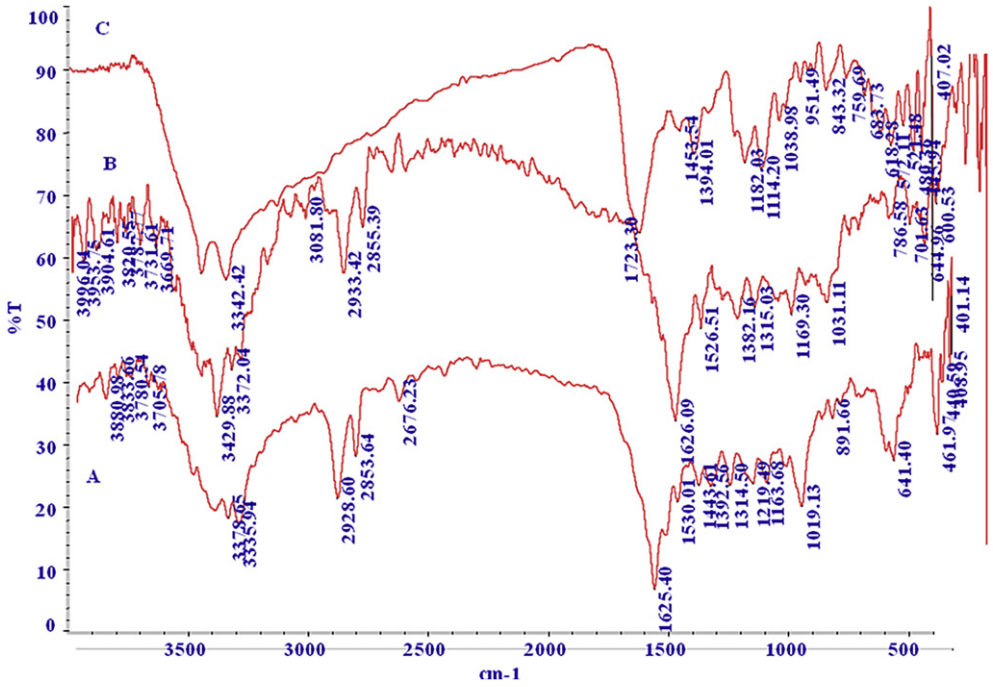


Fig. 2. FT-IR of (a) chloroglycine (b) 1-glycyl-3-methyl imidazolium chloride [Gmim]Cl (c) 1-glycyl-3-methyl imidazolium chloride-Copper (II) complex [Gmim]Cl–Cu (II).

different catalysts and the results are given in Table 3. When the reaction was carried out using various catalysts such as L-glycine, Chloroglycine, 1-carboxy ethyl-3-methyl imidazolium bromide [Cemim] Br, 1-aminoethyl-3-methyl imidazolium bromide [Aemim] Br, $CuCl_2$/[Cemim] Br, $CuCl_2$/[Aemim] Br and $CuCl_2$/[Gmim]Cl in absence of solvent, it gave trace to 70% of enantioselectivities product. However, when the same reaction was conducted with [Gmim]Cl–Cu(II) 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 copper complex. According to literature, Li-Wen Xu [29] and co-workers obtained good yield in the asymmetric Biginelli reaction using 10 mol% of air and water stable $Cu(OTf)_2$ in the presence of 1,4-dioxane. Among the previous report, increasing the quantity of the catalyst can improve the reaction yield and shorten reaction time (Table 4). First, Biginelli 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–Cu(II), 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 asymmetric Biginelli reaction was carried out at the molar ratio of 4-metoxy benzaldehyde, ethyl acetoacetate, urea and [Gmim]Cl–Cu(II) 1:1:1.2:0.01 mmol% under solvent free condition at 25°C.

In order to test the substrate generality of [Gmim]Cl–Cu(II) complex catalyzed asymmetric Biginelli reaction, the condensation of various aldehyde with ethyl acetoacetate and urea were studied under the optimized conditions. The results are summarized in Table 5. It can be noticed that a wide range of aldehyde can efficiently contribute in the Biginelli reaction. However, the

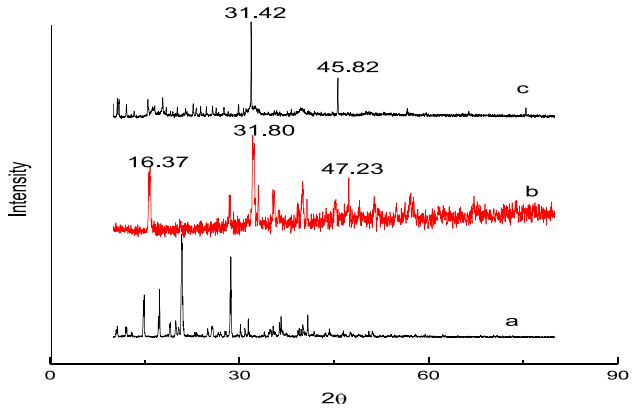


Fig. 3. Powder X-ray diffraction patterns of (a) chloroglycine (b) $CuCl_2$ (c) 1-glycyl-3-methyl imidazolium chloride-copper (II) complex [Gmim] Cl–Cu (II).

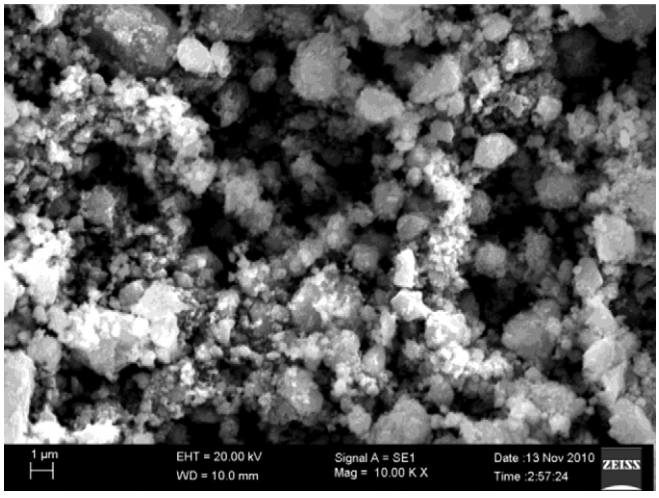


Fig. 4. SEM image of [Gmim]Cl–Cu (II).

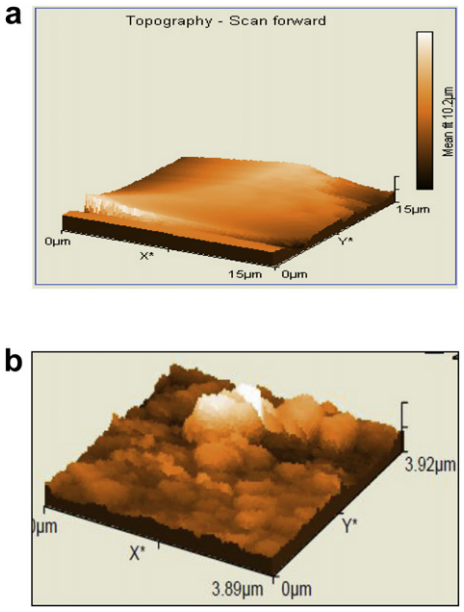


Fig. 5. (a) AFM image of 1-glycyl-3-methyl imidazolium chloride (b) AFM image of 3-(amino (carboxy) methyl)-1-methyl-1H-imidazol-3-ium chloride supported copper complex.

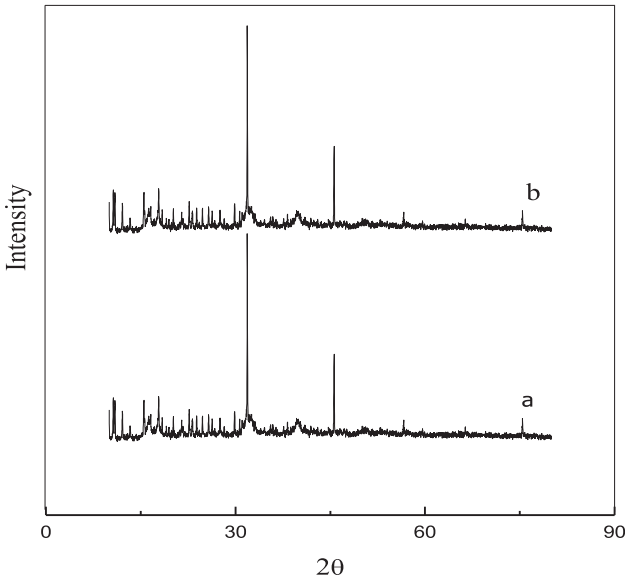


Fig. 6. Powder X-ray diffraction patterns of the [Gmim]Cl–Cu (II)complex a) before reaction b) After reaction (7th run).

benzaldehyde bearing electron-withdrawing substituents furnished Biginelli reaction with excellent yields (90–96%) and enantioselectivities (92–98% ee) within 12–14 h. On the other hand, longer reaction times (18–20 h) were required for aldehyde containing an electron-donating group to give comparatively inferior yields (90–92%), without lacking of enantioselectivities. This can be explained that electron-withdrawing groups improve the electrophilicity of carbonyl carbons aldehyde, which facilitates the reaction, while electron-donating groups reduce the electrophilicity. Moreover, the asymmetric Biginelli reaction of neutral aldehyde catalyzed by the copper complex also afforded the Biginelli product with high enantioselectivities and diastereoselectivities. All the condensation reactions of substituted aldehyde, ethyl acetoacetate, urea and [Gmim]Cl–Cu(II) afford the subsequent products with excellent yield (80–96%) and enantioselectivities (90–98% ee).

Isolation of the heterogeneous catalyst was easily performed by separation or centrifugation. The isolated catalyst was washed with ether and dried in air. The regenerated catalyst was used for the reaction of 4-metoxy benzaldehyde with ethyl acetoacetate and urea for seven runs to afford ethyl (R)-ethyl 4-(4-methoxy phenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetra hydropyrimidine-5-carboxylate with 98-90% enantioselectivities (Table 6).

The [Gmim]Cl–Cu(II) 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. 6 The analysis specifies that the [Gmim]Cl–Cu(II) do not undergo any chemical and structural changes, thus proving its surface catalytic activity towards the condensation reaction of 4-metoxy benzaldehyde with ethyl acetoacetate and urea. On the other hand, presence of peaks due to metallic copper is noted in the powder XRD pattern of the complex in the case of 'Cu(II)' (Fig. 6(a–b)). Moreover, surface & size of that reused catalyst was captured by AFM. The surface of recycled copper complex showed in the rough topography evidence and reduced size of the particle 2.15 μm^2 (Fig. 7).

Furthermore; Cu leaching was also studied by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis, indicating that the product mixture contained zero ppm of copper accounting for 0.01 mmol% of the initially added amount of Cu. From those three experimental results, we believe that the no Cu leaching observed in asymmetric Biginelli reaction, it's due to immobilized copper in amino acid functionalized ionic liquid binding site located on the surface, which acts as a ligand through metal–ligand interaction. The anchoring of Cu species by amino acid sites supported on ionic liquid minimizes catalyst deterioration and no metal leaching and therefore allows efficient catalyst recycling. The copper(II) 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. The possible mechanism for the reaction is shown in Fig. 8(a) (pathway-1). In the transition state I (TS I), the amino acid moiety of [Gmim]Cl–Cu catalyst interacts through hydrogen bonding with the acyl group of benzylidene urea while the neighboring primary amine activates ethyl acetoacetate involving an enamine intermediate. The obtained absolute configuration of DHPMs was explained by the transition state I, in which the imine was predominantly approached by the enamine intermediate generated from ethyl acetoacetate and the primary amine group of the [Gmim]Cl–Cu

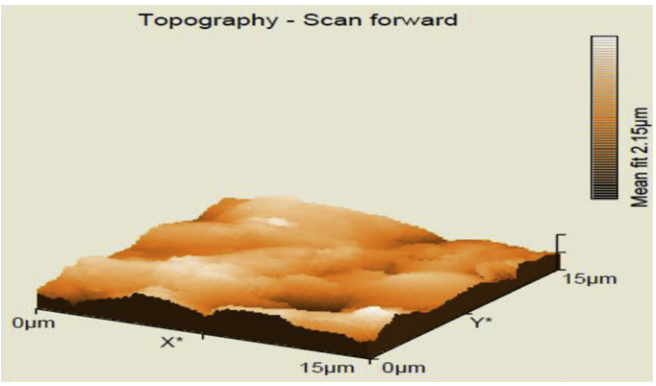


Fig. 7. AFM image of 3-(amino (carboxy) methyl)-1-methyl-1H-imidazol-3-ium chloride supported copper complex after 7th run.

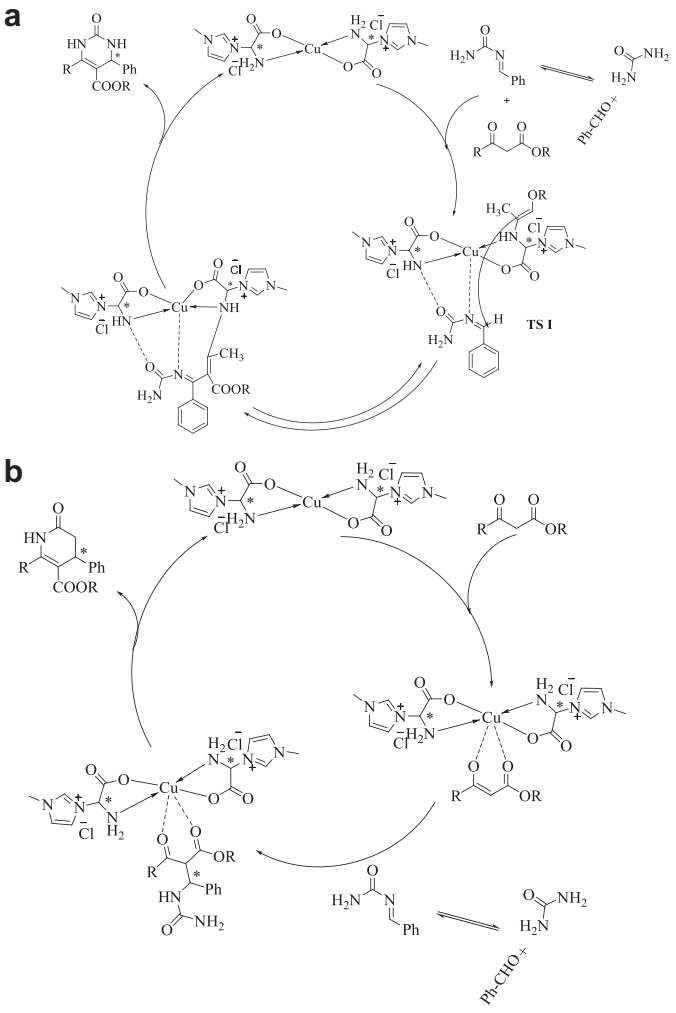


Fig. 8. (a) Plausible reaction mechanism (pathway-1) (b) Plausible reaction mechanism (pathway-2).

catalyst. The attack of the enamine to the benzylidene urea was restricted by the complex scaffold of the catalyst. The mechanism indicates that the amino acid moiety and copper scaffold of the copper catalyst play a significant role in controlling the regio and diastereoselectivity of the Biginelli reaction. The precise mechanism of the catalytic reaction needs to be elucidated, but it is noticeable that the mechanism is strongly modified depending of the copper catalyst employed, obtaining enantioselective 3, 4-dihydropyrimidin-2(1H)-ones as the main product Fig. 8(b) (pathway-2).

(Table 5, entry 1): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 7.46$ min (minor) and 9.55 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (t, $J = 7.2$ Hz, 3H), 2.28 (s, 3H), 3.40 (dd, $J = 6.8$ Hz, 7.2 Hz, 2H), 5.14 (d, $J = 3.2$ Hz, 1H), 7.34–7.23 (m, 5H), 7.72 (s, 1H), 9.17 (s, 1H). Micro analytical data: Cal (C: 64.85; N: 10.80; H: 5.83), found: (C: 64.81; N: 10.75; H: 5.80). FT-IR (KBr, cm^{-1}): ν 3186, 2981, 2926, 1663, 1710, 1474, 830.

(Table 5, entry 2): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 13.12$ min (minor) and 9.45 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (t, $J = 7.2$ Hz, 3H), 2.53 (s, 3H), 3.72 (s, 3H), 3.99 (q, $J = 6.8$ Hz, 2H), 5.9 (d, $J = 3.2$ Hz, 1H), 6.86 (d, $J = 8.8$ Hz, 3H), 7.15 (d, $J = 8.8$ Hz, 2H), 9.15 (s, 1H). Micro analytical data: Cal (C: 62.27; N: 9.68; H: 5.92), found: (C: 62.25; N: 9.64; H: 5.87). FT-IR (KBr, cm^{-1}): ν 3157, 2996, 1707, 1648, 1593, 1486, 1324, 1274, 1189, 1093, 755, 694.

(Table 5, entry 4): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 9.12$ min (minor) and 7.53 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.10 (t, $J = 7.2$ Hz, 3H), 2.26 (s, 3H), 3.40 (dd, $J = 7.2$, 6.8 Hz, 2H), 5.15 (d, $J = 3.2$ Hz, 1H), 7.26 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.75 (s, 1H), 9.22 (s, 1H). Micro analytical data: Cal (C: 57.25; N: 9.54; H: 4.80), found: (C: 57.21; N: 9.50; H: 4.77). FT-IR (KBr, cm^{-1}): ν 3422, 3215, 2980, 2928, 1707, 1652, 1570, 1465, 1194, 1179, 1099, 748.

(Table 5, entry 5): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 9.60$ min (minor) and 7.72 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.08 (t, $J = 7.2$ Hz, 3H), 2.25 (s, 3H), 3.99 (q, $J = 7.2$ Hz, 2H), 5.13 (d, $J = 3.2$ Hz, 1H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 9.25 (s, 1H). Micro analytical data: Cal (C: 49.72; N: 8.28; H: 4.17), found: (C: 49.68; N: 8.24; H: 4.13). FT-IR (KBr, cm^{-1}): ν 3304, 3186, 2981, 2926, 1663, 1576, 1460, 1193, 1115, 770, 666.

(Table 5, entry 6): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 8.82$ min (minor) and 7.50 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.11 (t, $J = 7.2$ Hz, 3H), 2.25 (d, $J = 7.6$ Hz, 6H), 3.98 (q, $J = 6.8$ Hz, 2H), 5.3 (d, $J = 3.2$ Hz, 1H), 7.10 (s, 4H), 9.13 (s, 1H). Micro analytical data: Cal (C: 65.92; N: 10.25; H: 6.27), found: (C: 65.88; N: 10.10; H: 6.23). FT-IR (KBr, cm^{-1}): ν 3354, 2987, 1652, 1486, 1570, 1274, 1093, 800, 750.

(Table 5, entry 7): Enantiomeric excess was determined by HPLC with a Chiralpak (OJ-H) (4.6 mm × 250 mm) column (n-hexane/*i*-PrOH 9/1, 1.0 mL/min, $\lambda = 254$ nm, 25 °C): $t_R = 13.43$ min (minor) and 10.82 min (major). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14–1.10(t, $J = 7.1$ Hz, 3H), 2.04 (s, 3H), 4.14–4.10 (q, $J = 7.1$ Hz, 2H), 5.20 (s, 1H), 6.50 (s, 1H), 6.72–6.65 (m, 2H), 6.78 (m, 1H), 7.04–6.99 (m, 1H). Micro analytical data: Cal (C: 60.86; N: 10.14; H: 5.84), found: (C: 60.91; N: 10.11; H: 5.83). FT-IR (KBr, cm^{-1}): ν 3310, 3228, 1710, 1550, 1532, 1382, 1170, 650.

5. Conclusions

In conclusion, the results from the investigation demonstrate that the 1-glycyl-3-methyl imidazolium chloride-copper (II) complex was efficient catalyst for highly enantioselective asymmetric Biginelli 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-copper (II) complex; (2) its catalytic activity was tested in asymmetric Biginelli reaction; (3) 0.01 mmol% of catalyst was sufficient to furnish the Biginelli products with excellent yields (up to 96%) and enantioselectivities (up to 98%); (4) The catalyst can be readily recovered and reused without significant loss of its activity and stereoselectivity; Notably, (5) this organo catalyzed asymmetric Biginelli 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.

Acknowledgments

We gratefully acknowledge the management of VIT University for providing required facilities and SAIF (IITM) for providing the spectral data

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.jorganchem.2012.06.022. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] P. Biginelli, Gazz. Chim. Ital 23 (1893) 360–416.
[2] A. Dondoni, A. Massi, Acc. Chem. Res. 39 (2006) 451–463.
[3] Z.D. Aron, L.E. Overman, Chem. Commun. (2004) 253–265.
[4] T. Welton, Chem. Rev. 99 (1999) 2071–2084.
[5] R. Rajgopal, D.V. Jarikote, R.J. Lahoti, D. Thomas, K.V. Srinivasan, Tetrahedron Lett. 44 (2003) 1815–1817.
[6] D.E. Siyutkin, A.S. Kucherenko, S.G. Zlotin, Tetrahedron 65 (2009) 1366–1372.
[7] Y. Yang, Y. Zhang, S. Hao, Q. Kan, Chem. Eng. J. 171 (2011) 1356–1366.
[8] Y. Yang, J. Guan, P. Qiu, Q. Kan, Appl. Surface. Sci. 256 (2010) 3346–3351.
[9] S. Jana, S. Bhunia, B. Dutta, S. Koner, Appl. Catal. A: Gen. 392 (2011) 225–232.
[10] A. Shaabani, A. Bazgir, F. Teimouri, Tetrahedron Lett. 44 (2003) 857–859.
[11] M.V. Kirillova, A.M. Kirillov, D. Mandelli, W.A. Carvalho, A.J.L. Pombeiro, G.B. Shulpin, J. Catal. 272 (2010) 9–17.
[12] R.R. Fernandes, J. Lasri, M.F.C. Guedes da Silva, J.A.L. da Silva, J.J.R. Frausto da Silva, A.J.L. Pombeiro, Appl. Catal. A: Gen. 402 (2011) 110–120.
[13] S.M. Islam, A.S. Roy, P. Mondal, M. Mubarak, S. Mondal, D. Hossain, S. Banerjee, S.C. Santra, J. Mol. Catal. A: Chem. 336 (2011) 106–114.
[14] M.V. Kirillova, Y.N. Kozlov, L.S. Shulpina, O.Y. Lyakin, A.M. Kirillov, E.P. Talsi, A.J.L. Pombeiro, G.B. Shulpin, J. Catal. 268 (2009) 26–38.
[15] A.M. Kirillov, M.V. Kirillova, L.S. Shulpina, P.J. Figiel, K.R. Gruenwald, M.F.C. Guedes da Silva, M. Haukkad, A.J.L. Pombeiro, G.B. Shulpine, J. Mol. Catal. A: Chem. 350 (2011) 26–34.
[16] M.V. Kirillov, A.M. Kirillov, A.J.L. Pombeiro, Appl. Catal. A: Gen. 401 (2011) 106–113.
[17] W.S. Lee, C.T. Yeung, K.C. Sham, W.T. Wong, H.L. Kwong, Polyhedron 30 (2011) 178–186.
[18] H.B. Zhu, Z.Y. Dai, W. Huang, K. Cui, S.H. Gou, C.J. Zhu, Polyhedron 23 (2004) 1131–1137.
[19] M. Sedlak, P. Drabina, R. Keder, J. Hanusek, I. Cısarova, A. Ruzick, J. Organomet. Chem. 691 (2006) 2623–2630.
[20] S.S. Chavan, S.K. Sawant, V.A. Sawant, G.K. Lahiri, Inorg. Chem. Commun. 14 (2011) 1373–1376.
[21] S.K. Sawant, G.A. Gaikwad, V.A. Sawant, B.A. Yamgar, S.S. Chavan, Inorg. Chem. Comm. 12 (2009) 632–635.
[22] M. Konig, L.M. Reith, U. Monkowius, G. Knor, K. Bretterbauer, W. Schoefberger, Tetrahedron 67 (2011) 4243–4252.
[23] B.S. Zhang, C. Wang, J.F. Gong, M.P. Song, J. Organomet. Chem. 694 (2009) 2555–2561.
[24] S.M. Islam, P. Mondal, A. Singh Roy, S. Mondal, D. Hossain, Tetrahedron Lett. 51 (2010) 2067–2070.
[25] Y. Huang, F. Yang, C. Zhu, J. Am. Chem. Soc. 127 (2005) 16386–16387.
[26] X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, J. Am. Chem. Soc. 128 (2006) 14802–14803.
[27] Y. Wang, H. Yang, J. Yu, Z. Miao, R. Chena, Adv. Synth. Catal. 351 (2009) 3057–3062.
[28] N. Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, J. Am. Chem. Soc. 131 (2009) 15301–15310.
[29] Y.-F. Cai, H.-M. Yang, L. Li, K.-Z. Jiang, G.-Q. Lai, J.-X. Jiang, L.-W. Xu, J. Org. Chem. (2010) 4986–4990.
[30] R. Sebest, I. Kmentov, S. Tom, Green. Chem. 10 (2008) 484–496.
[31] W.S. Miao, T.H. Chan, Adv. Synth. Catal. 348 (2006) 1711–1718.
[32] M. Lombardo, F. Pasi, S. Easwar, C. Trombini, Adv. Synth. Catal. 349 (2007) 2061–2065.
[33] P. Karthikeyan, P.N. Muskawar, S.A. Aswar, P.R. Bhagat, S.K. Sythana, J. Mol. Catal. A: Chem. 358 (2012) 112–120.
[34] M. Lombardo, F. Pasi, S. Easwar, C. Trombini, Synlett (2008) 2471–2474.
[35] M. Lombardo, S. Easwar, A. DeMarco, F. Pasi, C. Trombini, Org. Biomol. Chem. 6 (2008) 4224–4229.
[36] D.S. Tarbell, Y. Yamamoto, B.M. Pope, Proc. Acad. Sci. U S A 69 (1972) 730–732.
[37] L. Moroder, S. Hallett, E. Wunsch, O. Keller, G. Wersin, Z. Hoppe Seyler's, Physiol. Chem. 357 (1976) 1651.
[38] J.R. Rachele, J. Org. Chem. 28 (1963) 2898.
[39] D. Ben-ishai, A. Berger, J. Org. Chem. 17 (1952) 1564–1570.
[40] D. Ben-ishai, J. Org. Chem. 19 (1954) 62–66.
[41] M. Bodanszky, V. du Vigneaud, J. Am. Chem. Soc. 81 (1959) 5688–5691.
[42] X. Hu, J. Mao, Y. Sun, H. Chen, H. Li, Catal. Commun. 10 (2009) 1908–1912.
[43] A.A. El-Sherif, Inorg. Chim. Acta 362 (2009) 4991–5000.