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reactions using chiral bis(oxazoline)-copper complex in an ionic liquid

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ABSTRACT

An optimal hydrophobic ionic liquid was discovered as a solvent for highly enantioselective glyoxylateene reactions catalyzed by a chiral bis(oxazoline)–copper complex. The reactivity and stereoselectivity were highly dependent upon the property of the ionic liquids; reactions between olefins and ethyl glyoxylate in [Bmim]SbF₆ at ambient temperature provided remarkably enhanced reactivity and stereoselectivity, which greatly exceed those of the corresponding reactions in dichloromethane. Furthermore, the metal–ligand complex was readily recycled up to eight times while exhibiting no significant decrease in reaction efficiency.

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Tetrahedron

1. Introduction

Over the past decade, a great deal of interest has been focused on ionic liquids (IL) due to their unique properties, such as low vapor pressure, low melting points, and negligible flammability, which satisfy the requirements of modern green chemistry.¹ They have often been utilized as alternatives to conventional organic solvents in catalytic reactions due to efficient separation and recycling of expensive catalysts.² Moreover, ionic liquids sometimes offer additional advantages for asymmetric reactions such as rate acceleration, enantioselectivity enhancement, and easy immobilization of the catalytic species without additional structural modification.^{3,4} In this regard, many asymmetric catalysis reactions using various ligand–metal complexes have been tested in ionic liquids to achieve superior results to homogenous systems.

In connection with this, the chiral C_2 -symmetric bis(oxazoline) (BOX)–Cu complex has proven to be a highly promising candidate for the application of ionic liquids as reaction media.⁵ This versatile system has demonstrated a wide range of applicability in many asymmetric transformations. However, this Lewis acidic catalyst suffers from several drawbacks, such as the need for a relatively large amount of the complex (generally 8–10 mol %), high cost of the catalyst, and the requirement for careful reaction control often at very low temperatures, which restrict their use in practical applications.⁶ In order to overcome these problems, a number of heterogeneous systems incorporating the chiral BOX complex have been developed.⁷ Generally, the use of the heterogeneous system involves anchoring of the catalysts onto stationary supports, and we have also reported our investigation in this area employing

mesoporous mesocellular silica foam (MCF) and SBA-15.⁸ Nevertheless, extra modifications of the catalyst are required and the immobilized catalyst systems often exhibit inferior reactivity and stereoselectivity to those obtained from homogeneous systems.

Compared to other asymmetric transformations promoted by the BOX–Cu complex, only a handful of reports have appeared so far on carbonyl-ene reactions⁹ especially those under heterogenous conditions¹⁰ in spite of their importance in the construction of optically active homoallylic alcohols with an additional carbonyl functional group. The olefin moiety can be converted into a carbonyl functionality through oxidation, adding versatility to the reaction. As part of our ongoing research on the utilization of the BOX–Cu complex system,^{8,11} we investigated the enantioselective glyoxylate-ene reaction in ionic liquids,¹² and were pleased to find that the reactions proceeded with enhanced enantioselectivities at ambient temperatures and disclose the results herein.

2. Results and discussion

A representative asymmetric ene reaction of α -methylstyrene with ethyl glyoxylate was studied using the complex prepared from ligand **3** (11 mol % relative to α -methyl styrene), which was premixed with Cu(OTf)₂ in various ionic liquids for 1 h (Scheme 1). Ionic liquids can largely be classified into two groups according to their hydrophobicity.¹³ Initially, a series of ionic liquids containing the 1-butyl-4-methyl-imidazolium cation (Bmim) were screened, varying the anionic part as BF₄⁻, OTf, PF₆⁻, and SbF₆⁻, to examine the influence of the anion toward the reaction. The results are summarized in Table 1. Reactions in hydrophilic ionic liquids, such as [Bmim]BF₄ and [Bmim]OTf gave poor results: only a minute amount of racemic adducts was obtained after 30 min at room temperature (Table 1, entries 1 and 2). On the other hand, reactions



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Scheme 1. Catalytic enantioselective ene reaction of α -methyl styrene 1 and ethyl glyoxylate 2 with complex 4 in various ionic liquids.

Table 1
Results of asymmetric ene reactions between ethyl glyoxylate and 1 using a BOX-Cu
complex in various ionic liquids or dichloromethane for 30 min ^a

Entry	Ionic liquid	Temperature (°C)	Yield ^b (%)	ee ^c (%)
1	[Bmim]BF ₄	20	3	0
2	[Bmim]OTf	20	1	0
3	[Bmim]PF ₆	20	92	84
4	[Bmim]SbF ₆	20	93 ^f	94 ^f
5	CH_2Cl_2	20	45	79
6	CH_2Cl_2	0	17	83
7 ^d	CH_2Cl_2	0	43	83
8 ^e	CH_2Cl_2	-78	44	86

 a All reactions were performed on a 0.5 mmol scale of $\alpha\text{-methyl}$ styrene 1 at a 0.5 M concentration for 30 min.

^b Yields of isolated products after chromatographic purification.

^c ee's were determined from HPLC analyses using Chiralcel OJ-H column.

^d Reaction was carried out for 3 h.

^e Reaction was carried out for 12 h.

^f Best yield and enantioselectivity.

in hydrophobic ionic liquids such as [Bmim]PF₆ and [Bmim]SbF₆ afforded the desired products in excellent vields and enantioselectivities under otherwise identical reaction conditions (Table 1, entries 3 and 4). When a control reaction was performed in dichloromethane at room temperature using the same catalyst complex 4, the product was obtained in 45% yield and with low enantioselectivity (79% ee) (Table 1, entry 5). These results indicate a significant enhancement of the reactivity and selectivity in IL compared to the reaction in dichloromethane. When the reaction temperature was lowered from 0 °C to -78 °C for the reaction in methylene chloride, the enantioselectivity of the product was improved to some extent (86% ee). Nonetheless, the reactivity dropped significantly in spite of extended reaction time (Table 1, entries 6-8). This rate acceleration in hydrophobic ionic liquids may come from a favorable interaction between [Bmim]⁺ and ethyl glyoxylate allowing the relative stabilization of a transition state, which was previously suggested by Jorgensen and Evanseck using a computational model.¹⁴ However, the precise reasons for the enantioselectivity improvement in hydrophobic IL are not clear at this time and further studies should be carried out.

In order to examine whether we could reduce the catalyst loading without hampering the reactivity or stereoselectivity, a series of reactions involving ethyl glyoxylate and α -methylstyrene were carried out by varying the amount of the catalyst (Table 2). First, a control reaction was performed to examine the existence of a non-selective pathway catalyzed possibly by the ionic liquid itself. With only IL, a trace amount of racemic adduct was formed at a given reaction time, which implied that the influence of the nonselective transformation is minimal. As the amount of the catalytic complex was gradually decreased from 10 to 3 mol %, the reaction rates were concomitantly reduced. However, the enantiodifferenti-

Table 2

Influence of metal-ligand loading contents on the reaction yield and enantioselectivity in $[Bmim]SbF_6^a$

Entry	Ligand 3 /metal (mol %)	Temperature (°C)	Yield ^b (%)	ee ^c (%)
1	None/none	20	Trace	0
2	None/10	20	28	0
3	11/10	20	93	94
4	8/7	20	91	93
5	6/5	20	75	93
6	4/3	20	49	93
7 ^d	4/3	20	93 ^e	93 ^e
8 ^d	1.5/1	20	4	90

 $^a\,$ All reactions were carried out at 20 $^{\rm o}{\rm C}$ for 30 min unless otherwise noted. $^b\,$ Values are isolated yields after chromatographic purification.

ee was determined by HPLC analysis using a Chiralcel OJ-H column.

^d These reactions were carried out for 2 h.

^e Best yield and enantioselectivity.

ating power was sustained judging from the nearly constant ee's (93%) of the product. Even with 3 mol % of the catalytic species, the same level of reactivity (93% yield) and enantioselectivity (93% ee) was obtained at a prolonged reaction time (2 h) (entry 7). Below this critical level of ligand-metal complex, a reasonable yield of the product was hardly obtained despite extended reaction times, and with 1 mol % catalyst there was a slight drop in enanti-oselectivity, which may imply the intervention of a non-selective pathway (entry 8).

To test the scope of the substrates for this reaction, olefins, such as methylenecyclohexane and methylenecyclopentane were employed for the glyoxylate-ene reaction. Both cases afforded successful outcomes under the same reaction conditions as shown in Table 3.

Recycling experiments were carried out in order to examine the capability of the catalytic complex in an ionic liquid for repeated use (Table 4). We started with only 3 mol % of the BOX-Cu complex in [Bmim]SbF₆ for the first run since it was the minimum amount of the catalyst required for the completion of the reaction within 2 h (Table 2, entry 7). Products were collected after each run via biphasic extraction using ethyl ether, and the IL layer containing the catalyst was reused directly after simple drying under reduced pressure. Both the reactivity and enantioselectivity remained almost the same level up to the 4th recycle and then gradually decreased afterward, which may indicate that leaching out or deterioration of the catalyst below the critical concentration might have occurred during the recycling process. At the 9th recycle, an additional portion of the ligand and metal reagent was added; however, the yield and enantioselectivity rebounded only slightly (89% yield and 88% ee, respectively).

We next examined the storage capability of the catalyst in ionic liquid to see if the catalytic activity could be preserved for a long Table 3

Enantioselective glyoxylate-ene reactions between ethyl glyoxylate and other olefins^{a,b}



^a All reactions were performed on a 0.5 mmol scale at a 0.5 M concentration with 2 equiv of ethyl glyoxylate at 20 °C for 30 min.

^b Initial enophile/ligand/Cu(OTf)₂ molar ratio was 1/0.11/0.1.

^c Yield of isolated product after chromatographic purification.

^d Enantiomeric excess was determined from GC analysis using a Cyclodex-β column or HPLC using an OJ-H column.

Table 4

Results of the recycling catalytic enantioselective ene reactions between α -methyl styrene and 2.^a



 $^{\rm a}$ All reactions were carried out on a 0.5 mmol scale at 0.5 M concentration with 2 equiv of ethyl glyoxylate at 20°C for 2 h.

^b Yields of isolated products.

^c Enantiomeric excess was determined by HPLC analysis.

^d Additional Cu(OTf)₂ (0.04 equiv) and ligand **3** (0.05 equiv) were added at this run.

^e Additional Cu(OTf)₂ (0.04 equiv) and ligand **3** (0.05 equiv) were added at this run.

period of time. Thus, the [Bmim]SbF₆ containing BOX–Cu complex was recovered after a run, and kept at -20 °C for a month. When it was reused after a month for the same transformation, it still exhibited the same level of reactivity and stereoselectivity (Scheme 2).

3. Conclusion

In conclusion, we have demonstrated that a hydrophobic ionic liquid, $[Bmim]SbF_6$ can be utilized as a powerful medium for

bis(oxazoline)-copper catalyzed asymmetric ene reactions. This system exhibited far better reactivity and enantioselectivity to those of the reaction in dichloromethane, and to those using immobilized BOX-Cu complexes. The amount of catalyst was reduced to 3 mol % without any negative effect on the yield or enantioselectivity; this 3 mol % catalyst complex in an ionic liquid could be easily recycled through simple operations. Reactions using even one month-old catalyst in an ionic liquid proceeded with the same level of reactivity and enantioselectivity. We anticipate that this IL-based technique will facilitate the practical use of



First run: 93% yield, 93% ee Second run after one month of storage : 92% yield, 93% ee

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Scheme 2. Results of the catalytic enantioselective ene reaction with a freshly prepared and a month-old [Bmim]SbF₆ containing BOX-Cu complex.

asymmetric ene reactions, and so further work is currently in progress for the extension of its scope to other useful catalytic asymmetric processes.

4. Experimental

4.1. General

Ionic liquids were purchased from C-TRI Co., Ltd (www.c-tri.com) as a solvent grade (>98% purity, water content: 1000– 10,000 ppm, halogen content: 100–1000 ppm) or Fluka (>98.5% purity) and used without further purification. HPLC analysis was carried out with HP using a Chiral cel OJ-H column. GC analysis was carried out with HP 6880 gas chromatograph using a Cyclodex- β column.

4.2. A representative procedure for the asymmetric glyoxylateene reaction

Chiral bis(oxazoline) ligand **3** (5.9 mg, 0.020 mmol) and copper(II) triflate (5.4 mg, 0.015 mmol) were placed in a 10 mL screw-capped, flat-bottom vial, and 1.0 mL of 1-butyl-4-methyl-imidazolium hexafluoroantimonate was added. The mixture was stirred vigorously at rt to dissolve both the ligand and the metal species. After 1 h, α -methylstyrene (65 μ L, 0.50 mmol) was added portionwise. As soon as the olefin was dissolved into the reaction mixture, freshly distilled ethyl glyoxylate (100 μ L, 1.0 mmol) was introduced. After 2 h, the organic materials were extracted with diethyl ether (6–8 times) until TLC indicated no product in the IL layer. The combined ether layer was concentrated, and the resulting residue was purified by filtration through silica gel to afford the desired product (100 mg, 93% yield). The recovered ionic liquid was dried under vacuum, and reused for the next run.

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