

Chiral bis(oxazoline)–copper complex catalyzed Diels–Alder reaction in ionic liquids: remarkable reactivity and selectivity enhancement, and efficient recycling of the catalyst

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Abstract—Ionic liquid was found to be an excellent medium for asymmetric Diels–Alder reaction catalyzed by chiral bis(oxazoline)–copper complex. The reactivity and selectivity of reactions were highly dependent upon the property of the ionic liquids. Reactions of β -substituted acryloyl dienophiles in [Bmim]SbF₆ at ambient temperature provided remarkably enhanced reactivity and stereoselectivity compared to homogeneous reactions in non-ionic liquid solvent at -78 °C. Due to the increased reactivity, the amount of metal catalyst could be reduced down to 0.6 mol % without any significant selectivity compromise. Additionally, recycling of the ligand–metal complex was achieved efficiently up to 18 times.

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Chiral C_2 -symmetric bis(oxazoline) (BOX)–Cu complex has been one of the focal points of current interest in asymmetric synthesis due to its generous applicability to many selective asymmetric transformations.¹ A number of enantioselective C–C bond forming reactions have been developed employing this complex,¹ and evaluation of the BOX complexes in yet other asymmetric reactions is still in progress.² Nevertheless, asymmetric reactions using the complex leave a room for improvement; for example, the requirement of a relatively large amount (generally 8–10 mol %) and high cost of the catalyst, which restrict its usage in practical applications. Accordingly, many reports on the recycling of this ligand–metal complex have been recorded, however, most of them require extra modifications of the catalyst and the reactions often exhibit inferior reactivity and stereoselectivity to those of the homogeneous systems.³ Furthermore, many bis(oxazoline)-mediated asymmetric reactions have still been limited to carefully controlled reaction conditions such as very low temperatures, thus often accompanied with very low turnover frequencies. From our continuing effort in the development of efficient heterogeneous catalyst systems,⁴ we have also

investigated reactions employing BOX ligand immobilized onto solid matrices such as mesocellular silica foam (MCF) and SBA-15, and have observed some satisfactory results in catalyst recycling.^{4b,c}

Recently, ionic liquids (IL's) consisting of 1,3-dialkylimidazolium ions have received a considerable attention as powerful media for organic reactions due to their efficiency in product separation and catalyst recycling.^{5,6} Besides, some unexpected transformations have been unveiled in IL's, which would not be possible under ordinary reaction conditions.⁶

Asymmetric Diels–Alder (D–A) reaction^{7–9} is one of the representative reactions of the BOX–metal catalyzed reactions, and there had been a number of previous attempts in the immobilization of catalysts.¹⁰ Previously, Oh and a co-worker reported on the rate enhancement of D–A reaction in an ionic liquid over in methylene chloride.^{9a} We have also reported efficient organocatalyst-mediated asymmetric D–A reactions in IL-based upon the ionic nature of the intermediate.^{9b} During careful investigation on the asymmetric D–A reactions in IL's, we were curious if the ionic nature of the IL's would influence the reactivity and selectivity of the reaction using metal–BOX catalyst systems,¹¹ since the anions of the metal–BOX complex are known to play a critical role in the D–A reaction.^{7c} With the use of the ionic liquid, we had three goals in mind: (1)

Keywords: Asymmetric Diels–Alder; Bis(oxazoline)–copper complex; Ionic liquids; Recycling; Enantioselectivity.

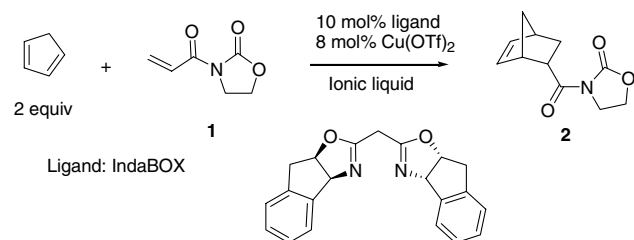
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significant reactivity enhancement, (2) stereoselectivity improvement, and (3) efficient recycling of the catalyst. To our delight, all of these goals were attained along with some additional benefits, and the results are disclosed herein.

Initially, to find out an optimal medium for the reaction, we screened a set of IL's composed of 1-butyl-4-methylimidazolium cation (Bmim), varying the anionic counterpart: BF_4^- , OTf^- , PF_6^- , and SbF_6^- . The former two are known to provide hydrophilic environment, and the latter two hydrophobic.¹² For our study, IndaBOX was chosen as a chiral ligand.^{7b} A copper salt and slightly excess ligand were mixed in ionic liquid to form a ligand–metal complex. The mixture was stirred vigorously at 20 °C to dissolve both the ligand and the metal through complexation. Then, cyclopentadiene (2 equiv) was added along with a dienophile. The results of the D–A reaction between cyclopentadiene and 3-(acryloyl)oxazolidin-2-one in various IL's are summarized in Table 1. From this study, it was apparent that the reactivity and stereoselectivity are strongly affected by the nature of IL's. When the reactions were carried out for an hour in hydrophilic IL's such as [Bmim] BF_4 and [Bmim] OTf at 20 °C, the D–A adducts were

obtained in moderate yields as 89:11 *endo/exo* mixtures (entries 1 and 2), however, no asymmetric induction was observed at all. On the other hand, reactions in hydrophobic IL's such as [Bmim] PF_6 and [Bmim] SbF_6 were complete when the reaction was checked in 10 min and in the case of entry 6, even in 10 s. The reactions proceeded with good diastereo- and enantioselectivities (entries 3–5),¹³ though the enantioselectivities of the reactions in [Bmim] PF_6 at either 20 or 3 °C (entries 3 and 4, respectively) were still inferior to that of the homogeneous reaction at –78 °C.^{7b} When $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ instead of $\text{Cu}(\text{OTf})_2$ was introduced, the enantioselectivity of the reaction dropped significantly (69% ee, entry 7), which bodes well with the reactivity difference according to the hydrophobicity of the ionic liquid. Consequently, hydrophobic IL and $\text{Cu}(\text{OTf})_2$ were adopted as an optimal combination. Through extensive optimization, the best result was achieved using [Bmim] SbF_6 at 3 °C, and a 97:3 *endo/exo* mixture of the adduct was obtained in 90% yield with the *endo* isomer exhibiting 94% ee (entry 6), which is quite comparable to the enantioselectivity obtained in the homogeneous reaction at –78 °C (entry 10).^{7b} Strikingly, the rate of the D–A reactions was extremely accelerated in the cases where hydrophobic IL's were used; the reactions were complete within 10 s. When the reaction was run at 3 °C in CH_2Cl_2 , the D–A adduct of 94:6 *endo/exo* selectivity was obtained in 93% yield after 10 min with the *endo* product in 68% ee (Table 1, entry 9) indicating pronounced selectivity enhancement in the IL.

Table 1. Results of asymmetric Diels–Alder reaction between cyclopentadiene and **1** using IndaBOX–Cu complex in various ionic liquids for 10 min



Entry	Ionic liquid	Temp. (°C)	Yield ^a (%)	<i>endo:exo</i> ^b	<i>endo</i> ee ^c (%)
1 ^d	[Bmim] BF_4	20	76 ⁱ	89:11	0
2 ^d	[Bmim] OTf	20	72 ⁱ	89:11	0
3	[Bmim] PF_6	20	86	96:4	83
4	[Bmim] PF_6	3(±1)	86	97:3	85
5	[Bmim] SbF_6	20	89	96:4	87
6 ^e	[Bmim] SbF_6	3(±1)	90	97:3	94
7 ^f	[Bmim] SbF_6	3(±1)	88	94:6	69
8 ^g	[Bmim] SbF_6	20	27 ⁱ	91:9	0
9	CH_2Cl_2	3(±1)	93	94:6	68
10 ^h	CH_2Cl_2	–78	98	99:1	94

^a Yields of the isolated cycloadducts unless otherwise noted.

^b *endo/exo* ratios were determined through ¹H NMR (300 MHz) and HPLC analyses using Chiralcel OD column.

^c Ee's were determined through HPLC analyses using Chiralcel OD column.

^d Reactions were carried out for 1 h.

^e The reaction was complete upon the addition of cyclopentadiene (within 10 s).

^f $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ was used instead of $\text{Cu}(\text{OTf})_2$.

^g This reaction was performed without a catalyst for 1 h.

^h The result of homogeneous reaction for 6 h previously reported by Ghosh et al.^{7b}

ⁱ Yield determined from ¹H NMR analysis.

Inspired by the extremely high reactivity and selectivity of this system, we envisioned that the catalyst–substrate ratio could be reduced significantly without loss of the reactivity or stereoselectivity. Hence, D–A reactions between cyclopentadiene and 3-(acryloyl)oxazolidin-2-one in [Bmim] SbF_6 were carried out varying the amounts of the ligand and the metal species. The ligand loading was decreased gradually from 10 to 0.2 mol %, and that of $\text{Cu}(\text{OTf})_2$ was also decreased accordingly and the results are summarized in Table 2. To our delight, upon lowering the amount of the metal and the ligand, a consistently high levels of *endo/exo* ratios and enantioselectivities were observed, and even 0.6 mol % of $\text{Cu}(\text{OTf})_2$ was enough to catalyze the

Table 2. Influence of ligand-to-substrate ratio on the reactivity and stereoselectivity in asymmetric D–A reactions between cyclopentadiene and **1** in [Bmim] SbF_6 at 3(±1) °C

Entry	Ligand (mol %)	$\text{Cu}(\text{OTf})_2$ (mol %)	Time (min)	Yield ^a (%)	<i>endo:exo</i>	<i>endo</i> % ee
1	10	8	10	90	97:3	94
2	5	4	10	91	97:3	94
3	2	1.5	30	92	97:3	94
4	0.85	0.6	40	93	97:3	94
5	0.4	0.3	60	73	90:10	0
6	0.2	0.1	60	69	90:10	0
7	None	None	60	15 ^b	91:9	0
8	None	8	10	90 ^b	91:9	0

^a Yield of isolated cycloadducts unless otherwise noted.

^b Yield was determined from ¹H NMR analysis of the crude reaction mixture.

reaction with the same enantioselectivity of 94% ee, though prolonged reaction time (40 min) was required for the completion of the reaction (entry 4). When the amount of $\text{Cu}(\text{OTf})_2$ was reduced to 0.3 mol %, a considerable deterioration of stereoselectivities was observed (entries 5 and 6), presumably due to nonselective catalysis through IL or uncomplexed copper species. To confirm this, two control experiments were performed; a reaction without the ligand in the absence or presence of $\text{Cu}(\text{OTf})_2$. With IL only, the reaction proceeded to some extent yielding a 91:9 *endo/exo* mixture of the racemic adduct in 15% yield (entry 7), and in the presence of 8 mol % $\text{Cu}(\text{OTf})_2$, reaction was complete (90% yield) within 10 min, also providing racemic products in a similar diastereoselectivity (*endo/exo* = 91:9, entry 8). From these results, we concluded that the D–A reaction could be catalyzed by the IL and the copper reagent itself and below a critical amount of the ligand–metal complex (0.85 mol % ligand and 0.6 mol % $\text{Cu}(\text{OTf})_2$) the nonselective reaction would prevail.

To investigate the scope of this system, we screened D–A reactions of various substrates and the results are summarized in Table 3. At first, various dienophiles such as β -methyl, ethyl, and phenyl-substituted acryloyl derivatives were examined with cyclopentadiene. As shown in Table 3, all D–A reactions of β -substituted dienophiles with cyclopentadiene exhibited uniformly impressive results; significant acceleration of the reaction rates and enhanced stereoselectivity were observed compared to those of reactions in CH_2Cl_2 . Among them, the most striking outcome was observed in the reaction with dienophile **5**, which afforded the corresponding D–A cycloadduct in 93% yield with 93/7 *endo*-selectivity and the *endo* isomer with 96% ee (entry 4). This result compares exceedingly favorably against

the homogeneous results (80/20 *endo/exo* ratio and 35% ee at -78°C).^{7b} Another diene, 1,3-cyclohexadiene was also examined in the reaction with 3-acryloyl-2-oxazolidinone and the result showed excellent diastereoselectivity, 98/2 *endo/exo* ratio in 86% yield, however, the *endo* isomer showed slightly lower enantiomeric enrichment, 86% ee.

To test the recycling capability of this system, reactions between cyclopentadiene and 3-(acryloyl)oxazolidin-2-one in $[\text{Bmim}]\text{SbF}_6$ were examined repetitively (Table 4). After each cycle, product was extracted thoroughly

Table 4. Results of asymmetric Diels–Alder reaction between cyclopentadiene and **1** with recycled $[\text{Bmim}]\text{SbF}_6$ containing IndaBOX–Cu complex^{a,b,c}

Run	<i>endo:exo</i>	<i>endo</i> ee
1 ^d	97:3	94
2	97:3	94
3	97:3	93
4	97:3	92
6	96:4	88
8	96:4	88
10	95:5	86
15	93:7	84
17	93:7	84
18 ^e	94:6	86

^a All reactions were carried out on 0.5 mmol scale with 2 equiv of cyclopentadiene at $3(\pm 1)^\circ\text{C}$.

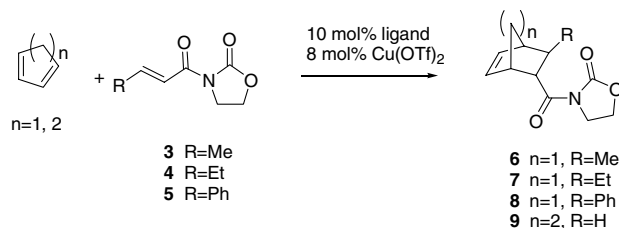
^b Reactions were carried out for 10 min for the consistency of experiment and operational convenience.

^c At every run, the conversion of dienophile was $>97\%$ as determined by ^1H NMR and HPLC analysis, and yield of isolated cycloadducts was within a range of 88–92%.

^d Initial dienophile/IndaBOX/ $\text{Cu}(\text{OTf})_2$ molar ratio was 1/0.1/0.08.

^e Additional IndaBOX (0.05 equiv) and $\text{Cu}(\text{OTf})_2$ (0.04 equiv) were added at this run.

Table 3. Results of asymmetric Diels–Alder reaction between cyclopentadiene (cPt) or cyclohexadiene (cHx) and various β -substituted dienophiles in $[\text{Bmim}]\text{SbF}_6$ ^a



Entry	Diene	Dienophile	Product	Time (min)	Yield ^b (%)	<i>endo/exo</i> ^c	<i>endo</i> ee ^d (%)
1	cPt	3	6	40	97	95:5	96
2 ^e	cPt	3	6	48 h	77	90:10	84
3	cPt	4	7	1.5 h	92	95:5	97
4	cPt	5	8	3 h	93	93:7	96 ^f
5 ^e	cPt	5	8	72 h	78	80:20	35
6	cHx	1	9	3 h	86	98:2	86 ^g

^a All reactions were carried out on a 0.5 mmol scale with 3 equiv of diene at rt (20°C).

^b Yield of the isolated cycloadducts.

^c *endo/exo* ratios were determined through ^1H NMR (300 MHz) analysis and confirmed again from HPLC analysis.

^d Ee's were determined through HPLC analysis using Chiralcel OD column.

^e The results of homogeneous reaction using (1R,2S)-BOX ligand at -78°C reported by Ghosh et al.^{7b}

^f Ee was determined after derivatization to the corresponding α -benzyl methyl amide.^{7a}

^g Ee's were determined through HPLC analysis using Chiralpak AD-H column.

with ethyl ether, and purified through silica gel filtration. Remaining IL containing the catalytic complex was dried under reduced pressure and reused without further treatment. Upon repeated use, almost consistent quantitative conversions of the dienophile (>97%) were observed, however, the *endo/exo* ratio (from 97:3 to 93:7) and ee's of the *endo*-isomer gradually decreased over repeated recycling (from 94% to 84% ee's, runs 1–17). This indicates that there may be a slight, gradual deterioration of the catalytic complex upon recycling. Nonetheless, stereoselectivities were maintained to a good level even upon 17th cycle, exhibiting 93:7 *endo*-selectivity and 84% ee for the *endo*-isomer. At 18th cycle, additional ligand and metal species were introduced, and the diastereomeric ratio and enantioselectivity of the reaction rebounded slightly, but not to the initial level.

In summary, we have developed an efficient strategy to immobilize the chiral BOX–Cu complex in hydrophobic IL.¹⁴ This system exhibited superior reactivity and enantioselectivity to the homogeneous system and previous D–A results from the immobilization and recycling of BOX–Cu complexes. We anticipate that this IL-based strategy can be applied to other related reactions such as hetero-Diels–Alder reaction considering the versatility of the BOX ligand and this avenue will be the subject of further investigation.

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- A representative procedure for the asymmetric Diels–Alder reaction using IndaBOX–Cu complex immobilized in ionic liquid. IndaBOX (16.5 mg, 0.05 mmol) and copper(II) trifluoromethanesulfonate (14.8 mg, 0.04 mmol) were placed in a screw-capped, flat-bottom vial (10 mL capacity), and 1 mL of 1-butyl-4-methylimidazolium hexafluoroantimonate was added. 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). The mixture was stirred vigorously at rt to dissolve both the ligand and the metal species. This catalyst aging turned out to be a critical process for the overall efficiency of the reaction. In our case, reliable and reproducible results

were obtained when the solution color turned green, indicating the full complexation. After 1 h, the reaction temperature was lowered to 3 °C, and 3-(acryloyl)oxazolidin-2-one (71 mg, 0.5 mmol) was added portionwise. As soon as the dienophile was dissolved into the reaction mixture, freshly cracked cyclopentadiene (81 μ L, 1 mmol) was introduced. The reaction was complete immediately

(within 10 s), and organic materials were extracted with ethyl 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 from filtration through silica gel to afford a diastereomeric mixture of the adduct (93 mg, 90% yield). Recovered ionic liquid was dried under vacuum, and reused for the next reaction.