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PAPER

Catalytic effect and recyclability of imidazolium-tagged bis(oxazoline) based catalysts in asymmetric Henry reactions†

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Functional imidazolium ionic liquids have been developed as a new class of versatile catalysts. C_2-symmetric imidazolium-tagged bis(oxazoline) ligands were prepared, and the anions of the ligands were altered. The catalysts based on the new ligands and $Cu(OAc)_2{\cdot}H_2O$ were applied in asymmetric Henry reactions between various aldehydes **3** and CH_3NO_2 **4**. The catalysts achieved a high level of enantioselectivity; product (*R*)-**5n** was attained at 94% *ee* in MeOH. Moreover, the catalyst could be recycled 6 times without an obvious loss of activity or enantioselectivity. In addition, a theoretical mechanistic study was conducted to explain the origin of the enantioselectivity.

Introduction

Chiral bis(oxazolines) have proven to be very effective ligands that afford high levels of activity and enantioselectivity in many reactions.[1–8] Because most catalysts are expensive and because the metal as well as the ligands are highly toxic to the environment and humans, the recycling of catalysts now assumes an even greater importance. However, the activity of the catalyst often dramatically decreases after several runs, and such decreases are usually caused by the catalysts leaching from the reaction system during product extraction or by the catalysts abating during the purification of the catalyst-containing phase before recycling.[9] A number of approaches to prevent the expensive chiral metal complex from running off during the recovery and/or recycling process have been investigated.[10] The limitations of a catalyst or ligand may be minimised by the presence of an ion tag on the frame of the ligand. The ionic nature could ideally render the catalyst or ligand insoluble in non-polar solvents such that the product could be extracted to leave a recyclable phase that contains the catalyst.[9,11] In addition, the properties of ionic liquids, such as low volatility, immiscibility with non-polar organic solvents and stability, make them excellent candidates for solvents in green processes.[12–15] The ion-tagging strategy has attracted more attention in recent years.

Chiral 2-nitro-1-arylalkanols, which are key intermediates and building blocks[16] for the synthesis of *β*-adrenergic drugs[17] and natural products, such as polyamino alcohols and polyhydroxylated amides,[18] are generally prepared *via* the Henry (nitroaldol) reaction.[19] Since the first asymmetric Henry reaction was reported by Shibasaki and co-workers using a series of heterobimetallic catalysts,[19–21] various effective catalytic systems have been developed. Many researchers, including Evans, have reported that bis(oxazoline) complexes derived from $Cu(OAc)_2{\cdot}H_2O$ were found to be promising catalysts for the Henry reaction at mild conditions.[22] To date, there are only a handful of reports about the immobilisation and recycling of a catalyst in asymmetric Henry reactions. Lee[16] immobilised a bis(oxazoline) ligand onto a magnetically separable hierarchically ordered mesocellular mesoporous silica (M-HMMS), and this new catalytic system was examined in the asymmetric Henry reaction between various aldehydes and nitromethane at ambient temperature. Up to 86.0% *ee* was observed when the free silanol groups of the mesoporous silica were capped by trimethylsilyl group. This catalyst was separated magnetically and reused 5 times with little loss of reactivity or enantioselectivity. Khan[23] reported the catalyst derived from C_2-symmetric chiral secondary bis-amines based on a 1, 2-diaminocyclohexane structure with copper acetate and its application in the asymmetric Henry reaction in the presence of different ionic liquids, with a focus on $[Emim]BF_4$. Up to 94% *ee* was achieved, and the catalyst could be reused 5 times with retention of enantioselectivity. However, to the best of our knowledge, none of the ionic-tagged box compounds have been used as ligands in the asymmetric Henry reaction nor has their recyclability been evaluated in this reaction.

Our group has designed and prepared imidazolium-tagged bis(oxazoline) compounds (Scheme 1). Their performance in the copper-catalysed asymmetric Diels–Alder reaction between

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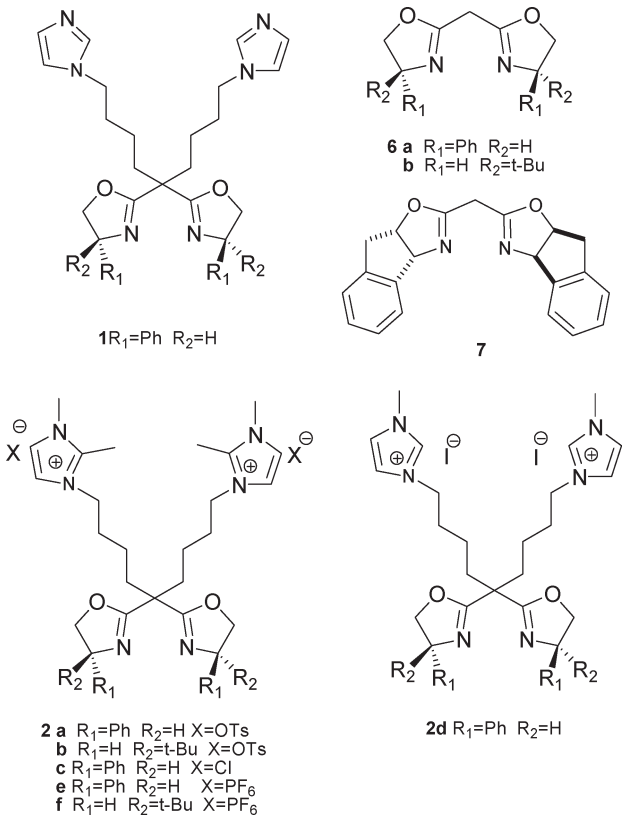


Scheme 1 Ligands applied in asymmetric Henry reaction.

N-acryloyloxazolidinones and 1,3-cyclohexandiene in the ionic liquid 1-butyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]-imide [Bmim]NTf_2 yielded up to 98% conversion with a 97% *ee*.[24] The catalyst could be recycled 20 times. Aiming at expanding the scope of application of the imidazolium-tagged bis(oxazoline), we evaluated their performance in the asymmetric Henry reaction. Up to 94% *ee* was obtained when using a catalyst based on **2a**. More importantly, the catalyst in the reaction system could be recycled 6 times without obvious loss of activity and enantioselectivity.

Results and Discussion

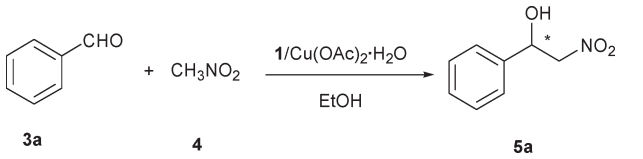
Preparation of C_2-symmetric imidazolium-tagged bis(oxazoline)

New ligands **1** and **2** were prepared from **6a** and **6b** according to methods in our previous report.[24] C_2-symmetric imidazolium-tagged bis(oxazoline) ligands were prepared successfully and efficiently. The anions of the ligands could be altered by ion exchange.

Asymmetric Henry reaction

For a preliminary study, the asymmetric Henry reaction was catalysed by the catalyst based on **1**. Benzaldehyde was taken as a representative aldehyde, and the effect of the ligand/metal ratio was tested at room temperature. The results are shown in Table 1. It was found that the activity and enantioselectivity of the asymmetric Henry reaction were the best when the ratio of ligand to metal was 1 : 1.25 (Table 1, entry 4), while increasing

Table 1 Screening of ligand/metal ratio for the asymmetric Henry reaction under catalysis of the complex based on **1**



3a 4 5a

Entry	Ligand:metal	Yield/%[a]	*ee*/%[b]
1	1 : 0.5	98	20 (*R*)
2	1 : 0.8	97	38 (*R*)
3	1 : 1	97	41 (*R*)
4	1 : 1.25	98	43 (*R*)
5	1 : 2	98	42 (*R*)

[a] Yields were calculated based on benzaldehyde. The ligand's loading was 15 mol%. [b] *ee* values were determined by HPLC analysis using a Chiralcel® OD-H column, hexane/iPrOH 85 : 15, 0.8 ml min^{-1}.

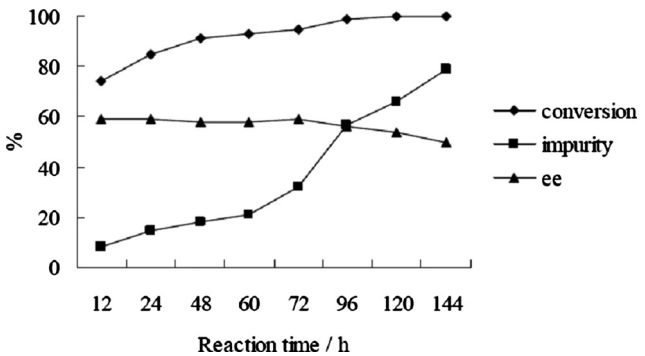
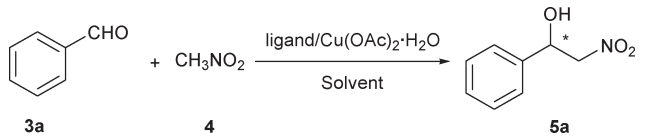


Fig. 1 Effects of reaction time and temperature on the asymmetric Henry reaction using the catalyst based on **1**.

or decreasing of the ratio led to lower activity or enantioselectivity (Table 1, entries 1–3, entry 5). The ligand/metal ratio of 1 : 1.25 was chosen as the optimised reaction condition. The effects of reaction time and temperature on the asymmetric Henry reaction using the catalyst based on **1** was investigated, and the results are shown in Fig. 1. The reaction was carried out at 0 °C for 72 h, after which the temperature increased at a rate of 10 °C 24 h^{-1}. It can be observed that the reaction was almost complete within 48 h at 0 °C. The *ee* value was not affected significantly by the reaction time, but the amount of the by-product (dehydration of the main product) increased as time passed. Once the temperature was increased, the by-product formation increased rapidly, and the *ee* value decreased from 59% to 50%.

Next, we examined the effect of various solvents, including ionic liquids, on the asymmetric Henry reaction of benzaldehyde with nitromethane using 3 ligands. The results are summarised in Table 2. As can be seen in Table 2, using traditional **1** as the ligand, the solvents affect the reaction activity and enantioselectivity. Protic solvents (alcohols) are superior to aprotic solvents. For alcohols, the activity and enantioselectivity increased in the following order: iPrOH < EtOH < MeOH (Table 2, entries 1–3). Reaction in CH_2Cl_2 was not observed at all (Table 2, entry 5). For the coordinating THF, the reaction reached completion; however, the enantioselectivity was only 27% (Table 2, entry 4). The imidazolium-tagged bis(oxazoline) compounds **2a** and **2e**

Table 2 Effects of solvent on the asymmetric Henry reaction



3a 4 5a

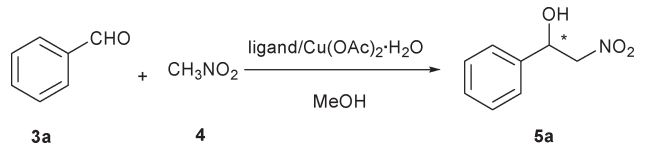
Entry[a]	Ligand	Solvent	Yield/%[b]	*ee*/%[b]
1	**1**	MeOH	96	61 (*R*)
2	**1**	EtOH	98	49 (*R*)
3	**1**	iPrOH	98	37 (*R*)
4	**1**	THF	100	27 (*R*)
5	**1**	CH_2Cl_2	—	—
6	**1**	[Bmim]PF_6	97	0
7	**1**	[Bmim]BF_4	98	0
8	**2e**	iPrOH	61	67 (*R*)
9	**2e**	EtOH	65	75 (*R*)
10	**2e**	MeOH	71	77 (*R*)
11	**2e**	[Bmim]PF_6	94	0
12	**2e**	[Bmim]BF_4	95	0
13	**2a**	iPrOH	67	68 (*R*)
14	**2a**	EtOH	72	76 (*R*)
15	**2a**	MeOH	77	78 (*R*)
16	**2a**	[Bmim]PF_6	97	0
17	**2a**	[Bmim]BF_4	98	0

[a] The ratio of benzaldehyde : CH_3NO_2 : ligand : $Cu(OAc)_2{\cdot}H_2O$ is 1.0 : 50.0 : 0.15 : 0.18, and the reactions were carried out at 0 °C for 24 h. [b] Yields were calculated based on benzaldehyde. % ee values were determined by HPLC analysis using a Chiralcel OD-H column, hexane/iPrOH 85 : 15, 0.8 ml min^{-1}.

yielded better results than ligand **1**, and the effect of the solvents was consistent with that of **1**. **2a** yielded the best result among the 3 ligands (Table 2, entries 13–15). Reactions in ionic liquids achieved yields of more than 94%; however, there was no enantioselectivity (Table 2, entries 6–7, entries 11–12, entries 16–17). MeOH was then chosen as the optimised solvent.

We further screened the ligands to evaluate their catalytic performance using the optimised conditions at 0 °C (Table 3). Phenyl-substituted bis(oxazoline) was the optimum ligand and yielded higher *ee*s than its *tert*-butyl-substituted counterpart in most cases (Table 3, entries 3–4, entries 8–9). The catalyst derived from **2a** yielded the product at 75% conversion and 78% *ee* in MeOH (Table 3, entry 3), whereas the catalyst derived from **2b** yielded 60% *ee* (Table 3, entry 8). The anions of the ligands affect the enantioselectivity and activity. The tosyl-anion ligand **2a** yielded better enantioselectivities and activities than hexafluorophosphoric, chloride or iodide salts (Table 3, entries 3–6). The opposite result was found for *tert*-butyl-substituted counterparts (Table 3, entries 8–9). On the other hand, the imidazolium-tagged bis(oxazoline) compounds **2a** and **2e** performed better than the traditional ligand **1** and **6a** (Table 3, entries 1–2, entries 3–4), which demonstrated that our ligands have potential for the asymmetric Henry reaction.

Table 3 Screening of ligands for the asymmetric Henry reaction of nitromethane and benzaldehyde



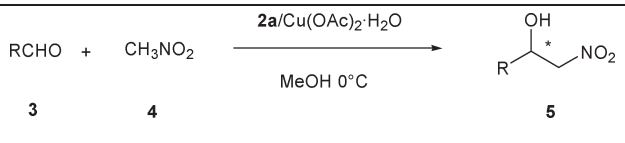
3a 4 5a

Entry	Ligand	Time/h	Yield/%[a]	*ee*/%[b]
1	**1**	24	96	61 (*R*)
2	**6b**	24	86	45 (*S*)
3	**2a**	24	75	78 (*R*)
4	**2e**	24	71	77 (*R*)
5	**2c**	24	70	49 (*R*)
6	**2d**	24	67	43 (*R*)
8	**2b**	24	38	60 (*S*)
9	**2f**	24	35	78 (*S*)

[a] Yields were calculated based on benzaldehyde. [b] *ee* values were determined by HPLC analysis using a Chiralcel OD-H column, hexane/iPrOH 85 : 15, 0.8 ml min^{-1}.

Ligand **2a** was selected as the best ligand, and the efficiency of **2a** was evaluated for various aldehydes under the optimised conditions. As summarised in Table 4, in general, benzaldehydes with electron-withdrawing nitro substituents gave better yields than substrates with weak electron-withdrawing or even electron-donating properties (Table 4, entries 1–8). However, benzaldehydes with electron-donating substituents gave better *ee* values than substrates with electron-withdrawing substituents, especially for 3, 4-dimethoxybenzaldehyde, which had *ee* values of 78% and 94% at 20 °C and 0 °C, respectively (Table 4, entry 14, entry 17). As can be seen in Table 4, temperature affects the activity and the enantioselectivity to a great extent. The *ee* value

Table 4 Enantioselective Henry reaction of nitromethane with various aldehydes catalysed by a complex based on **2a**

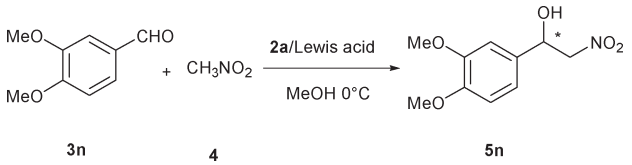


3 4 5

Entry	*R*	*T*/°C	Time/h	Yield/%[a]	*ee*/%[b]
1	Ph (**3a**)	20	24	84	64 (*R*)
2	2-$OMeC_6H_4$ (**3b**)	20	24	17	63 (*R*)
3	3-$OMeC_6H_4$ (**3c**)	20	24	30	73 (*R*)
4	4-$OMeC_6H_4$ (**3d**)	20	24	62	71 (*R*)
5	4-$NO_2C_6H_4$ (**3e**)	20	24	100	67 (*R*)
6	2-$NO_2C_6H_4$ (**3f**)	20	24	89	59 (*R*)
7	2-ClC_6H_4 (**3g**)	20	24	32	53 (*R*)
8	4-ClC_6H_4 (**3h**)	20	24	37	55 (*R*)
9	3-BrC_6H_4 (**3i**)	20	24	40	42 (*R*)
10	4-BrC_6H_4 (**3j**)	20	24	85	47 (*R*)
11	2-FC_6H_4 (**3k**)	20	24	35	61 (*R*)
12	4-FC_6H_4 (**3l**)	20	24	82	69 (*R*)
13	1-naphthyl (**3m**)	20	24	77	23 (*R*)
14	3,4-di$OMeC_6H_3$ (**3n**)	20	24	54	78 (*R*)
15	Ph (**3a**)	0	24	75	78 (*R*)
16	2,4-diClC_6H_3 (**3o**)	0	24	10	65 (*R*)
17	3,4-di$OMeC_6H_3$ (**3n**)	0	24	34	94 (*R*)
18	3,5-di$OMeC_6H_3$ (**3p**)	0	24	29	80 (*R*)
19	4-pyridyl (**3q**)	0	48	95	30 (*R*)
20	2-furyl (**3r**)	0	48	83	77 (*R*)
21	3,4,5-tri$OMeC_6H_2$ (**3s**)	0	48	20	82 (*R*)
22[c]	2-$OMeC_6H_4$ (**3b**)	0	48	42	73(*R*)
23[c]	3,4-di$OMeC_6H_3$ (**3n**)	0	48	23	92(*R*)
24[c]	3,5-di$OMeC_6H_3$ (**3p**)	0	48	37	75(*R*)
25[c]	3,4,5-tri$OMeC_6H_2$ (**3s**)	0	48	27	73(*R*)
26[c]	4-$NO_2C_6H_4$ (**3e**)	0	48	61	64(*R*)

[a] Yields were calculated based on aldehyde. [b] *ee* values were determined by HPLC analysis using Chiralcel OD-H, Chiralpak AD-H and Chiralcel OJ-H columns. [c] Catalyst based on **2e**.

Table 5 Effects of Lewis acid on the asymmetric Henry reaction of 3, 4-dimethoxybenzaldehyde under the catalysis of complex based on **2a**



Entry	Metal	Solvent	Time/h	Yield/%[a]	*ee*/%[b]
1	$Cu(OTf)_2$	MeOH	24	0	—
2	$Cu(OAc)_2·H_2O$	MeOH	24	34	94 (*R*)
3	$Pd(OAc)_2·H_2O$	MeOH	48	0	—
4	$TiCl_4$	MeOH	48	0	—
5	$Co(OAc)_2·4H_2O$	MeOH	48	3	47 (*R*)
6	$AlCl_3$	MeOH	48	0	—
7	$Ti(iPrO)_4$	MeOH	48	0	—

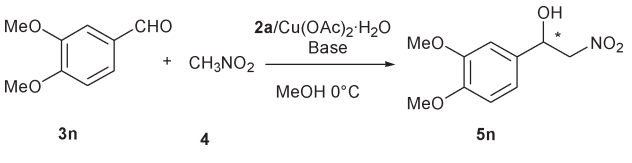
[a] Yields were calculated based on 3, 4-dimethoxybenzaldehyde. [b] *ee* values were determined by HPLC analysis using a Chiralcel OD-H, hexane/iPrOH 85 : 15, 0.8 ml min^{-1}.

increased up to 18% when the temperature decreased from 20 °C to 0 °C (Table 4, entry 1, entries 14–15, entry 17). Moderate to good enantioselectivities could be achieved in most cases when the reaction was carried out at 0 °C (Table 4, entry 1, entries 15–21). Once the reaction temperature was decreased, the yield dropped sharply, and a longer time was required to complete the reaction. In the cases of other aromatic aldehydes, such as 1-naphthaldehyde, isonicotinaldehyde and 2-furanaldehyde, lower or comparable enantioselectivities and good yields relative to benzaldehyde were obtained. Next, the catalyst based on **2e** was applied to asymmetric Henry reaction with several substrates (Table 4, entries 22–26), it can be seen from the results that the tosyl-anion ligand **2a** yielded better enantioselectivities than hexafluorophosphoric ligand **2e** in most cases. Consistent with literature,[25] the moderate catalytic activity of our catalyst may be attributed to the anionic and electron-rich nature of the imidazolium-tagged bis(oxazoline) ligand, and their better performance in MeOH may also result from this nature.

To examine the role of Lewis acids on the asymmetric Henry reaction, several metal salts were investigated in the presence of ligand **2a** (Table 5). As reported previously, air stable $Cu(OAc)_2·H_2O$ could act as a suitable Lewis acid for the asymmetric Henry reaction (Table 5, entry 2). Additionally, $Co(OAc)_2·4H_2O$ facilitated the reaction and afforded the product in poor yield with moderate *ee* value (Table 5, entry 5). Other Lewis acids investigated, such as $Cu(OTf)_2$, $Pd(OAc)_2·H_2O$, $TiCl_4$, $AlCl_3$ and $Ti(iPrO)_4$, made no contribution to the reaction (Table 5, entry 1, entries 3–4, entries 6–7).

We also attempted to improve the efficacy of these transformations in MeOH using 5 mol% of an organic or inorganic base, such as Et_3N, DMF, KOAc, CsOAc or CH_3NO_2, as the additive (Table 6). It can be observed that the addition of base decreased the enantioselectivity of the catalyst. When 5 mol% of Et_3N was added, the yield of the asymmetric Henry reaction increased while the *ee* value decreased from 94% to 92% (Table 6, entries 1–3). Once the amount of Et_3N increased from 5 mol% to 15 mol%, the *ee* value decreased to 90% (Table 6, entry 4). The *ee* value also decreased using 5 mol% of DMF as additive.

Table 6 Effects of base on the asymmetric Henry reaction of 3, 4-dimethoxybenzaldehyde under the catalysis of complex based on **2a**



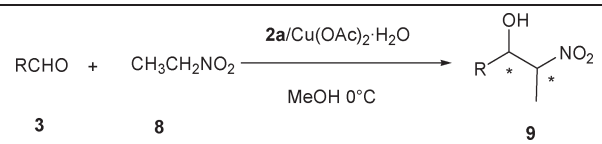
Entry	Base	Solvent	Time/h	Yield/%[a]	*ee*/%[b]
1	Et_3N(5 mol%)	MeOH	24	42	92 (*R*)
2	Et_3N(5 mol%)	MeOH	48	50	93 (*R*)
3	Et_3N(5 mol%)	MeOH	60	57	92 (*R*)
4	Et_3N(15 mol%)	MeOH	24	55	90 (*R*)
5	KOAc(5 mol%)	MeOH	24	35	73 (*R*)
6	DMF (5 mol%)	MeOH	24	37	91 (*R*)
7	CsOAc(5 mol %)	MeOH	24	41	88 (*R*)
8[c]	—	MeOH	24	54	93 (*R*)
9	—	MeOH/DMF (1 : 1)	24	8	88 (*R*)
10	—	$MeNO_2$/MeOH (7 : 1)	24	0	—

[a] Yields were calculated based on 3, 4-dimethoxybenzaldehyde. [b] *ee* values were determined by HPLC analysis using a Chiralcel OD-H, hexane/iPrOH 85 : 15, 0.8 ml min^{-1}. [c] 50 mol% of ligand used.

Moreover, using 1 : 1 of MeOH/DMF as solvent, the *ee* value decreased to 88% with a trace yield (Table 6, entry 6, entry 9). Inorganic bases, such as KOAc and CsOAc, affect the reaction more than organic base. The presence of these two bases in the reaction system resulted in *ee* values lower than 90% (Table 6, entry 5, entry 7). The use of 7 : 1 of CH_3NO_2/MeOH as solvent provided no product (Table 6, entry 10). Presumably the presence of a strong base could perturb the catalyst structure.[16]

The optimized catalyst system was also applied to the asymmetric Henry reaction with nitroethane as the nucleophile. The reaction could form two chiral centers and provide diasteroisomers, the corresponding results were summarized in Table 7. The reaction of nitroethane provided the adduct with good *anti*-selectivity (entries 1–2), and needed more time to give the products than nitromethane. Though the enantioselectivity was moderate, the catalyst has potential in the diasteroselective Henry reaction.

Table 7 Diasteroselective Henry reaction of nitroethane with aldehydes catalysed by a complex based on **2a**



Entry	*R*	Yield/%[a]	*Anti*/*syn*[b]	*ee* of *anti*
1	Ph (**3a**)	27	72 : 28	63%
2	4-$NO_2C_6H_4$ (**3e**)	91	81 : 19	68%

[a] Reactions were carried out at 0 °C for 60 h. Yields were calculated based on aldehyde. [b] *Anti*/*syn* and *ee* values were determined by HPLC analysis using Chiralcel OD-H and Chiralpak AD-H columns, hexane/iPrOH.

Recyclability of the catalysts

To evaluate the recyclability of the catalysts generated from our new ligands **2a** and **2e**, we performed the asymmetric Henry reaction in MeOH. After completion of the reaction, MeOH was removed under reduced pressure, and the residue was extracted with diethyl ether and transferred. The residual catalyst was subjected to vacuum to remove traces of diethyl ether, flushed with inert gas and charged with further portions of MeOH, aldehyde and CH_3NO_2. The activity and enantioselectivity were maintained even after the catalyst was reused 6 times. The asymmetric Henry reaction using the catalyst based on **2a** and 3,4-dimethoxybenzaldehyde as substrate provided conversion of 41% and an *ee* value of 91% on the 6th cycle; a conversion of 80% and *ee* value of 78% were obtained using same catalyst and benzaldehyde as substrate. The asymmetric Henry reaction using the catalyst based on **2e** and 2-methoxybenzaldehyde as substrate provided a conversion of 59% and an *ee* value of 74% on the 6th cycle; a conversion of 70% and an *ee* value of 75% were obtained using the same catalyst and benzaldehyde as substrate. It was found that the conversion and enantioselectivity were better in the second cycle in most cases. Presumably, in the second cycle, the ligand and metal reached a better coordination, which resulted in better conversion and enantioselectivity (Fig. 2). In contrast, a conversion of 35% and *ee* value of 47% were obtained using catalyst based on **7** with 2-methoxybenzaldehyde as substrate, the catalyst was reused only 4 times, provided a low yield of 35% and an poor *ee* value of 19% on the 4th cycle. It can be seen that, in our case, it is the ionic tag of the catalyst which assured the good recyclability.

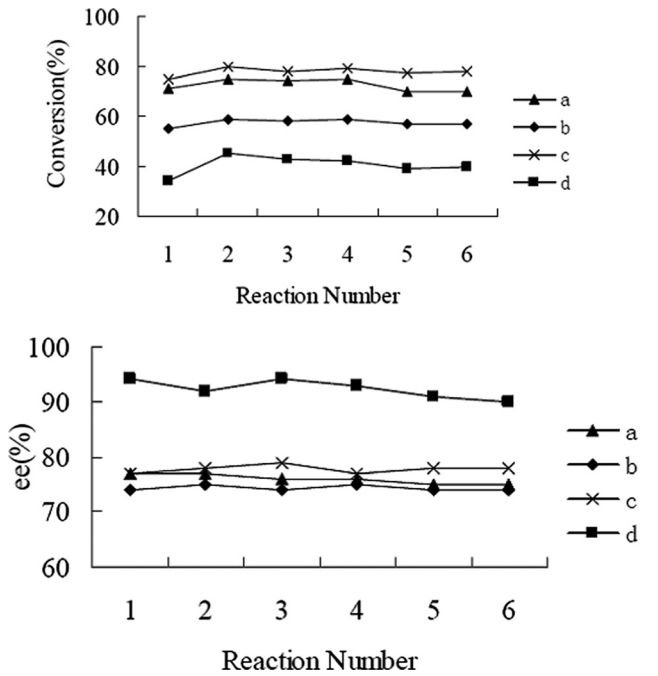


Fig. 2 Variations in percentage conversion (1) and percentage *ee* (2) upon recycling of the catalyst. a: Ligand is **2e**, substrate is benzaldehyde; b: ligand is **2e**, substrate is 2-methoxybenzaldehyde; c: ligand is **2a**, substrate is benzaldehyde; d: ligand is **2a**, substrate is 3, 4-dimethoxybenzaldehyde.

Theoretical mechanistic study

A theoretical mechanistic study was conducted to explain the origin of the enantioselectivity at the molecular level. Computational calculations of the geometry of the complex $Cu(OAc)_2$ **2a** were performed with the B3LYP/6-31G(d) scheme in the Gaussian03 software package. The optimal geometry is presented in Fig. 3. Because of the imidazolium salt tagged to the long alkyl chains on the carbon bridge between the two oxazolines, the steric environment was enhanced. The most probable transition structure for the asymmetric Henry reaction was also illustrated in Fig. 3. According to the model proposed by Evans,[20,22] the most reactive transition structure was in a mode such that the CH_3NO_2, as a nucleophile, is perpendicular to the ligand plane and the aldehyde, as electrophile, is in the ligand

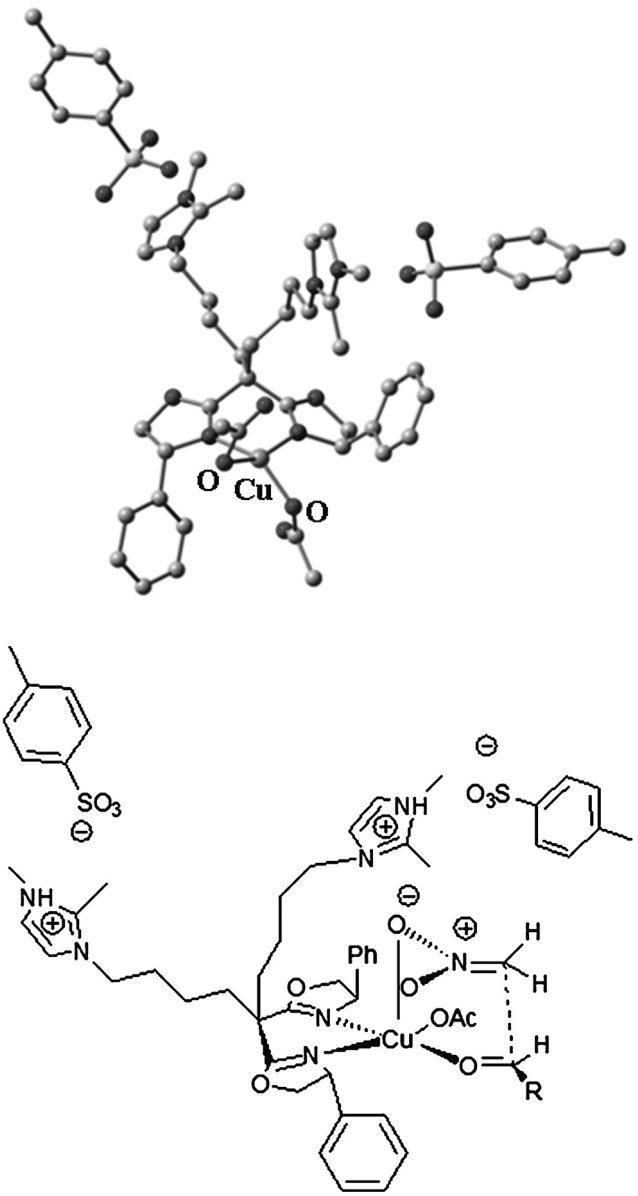


Fig. 3 Computational geometry of complex $Cu(OAc)_2$-2a (H was omitted for clarity) and possible transition structure for the asymmetric Henry reaction.

plane. This transition structure was favorable on the basis of both steric and electronic considerations. Because one of the long alkyl chains on the carbon bridge was more curved than the other, and with the imidazolium salt tagged to it, the bulky $[OTs]^-$ anion was closely coordinated to the Cu(II); this increased the steric bulk, made it more difficult for the nitronate to attack from the *si*-face thereby increasing the enantioselectivity. $Cu(OAc)_2$-**2a** afforded adducts with an (*R*)-configuration, indicating that the nitronate attacks the *re*-face of the aldehyde.

Conclusions

In conclusion, catalysts based on the new imidazolium-tagged bis(oxazoline) ligands and $Cu(OAc)_2 \cdot H_2O$ were applied to the asymmetric Henry reaction between various aldehydes **3** and CH_3NO_2 **4**. The catalyst derived from **2a** yielded adduct (*R*)-**5n** at 94% *ee* in MeOH. Furthermore, the catalyst based on **2a** could be recycled at least 6 times without an obvious loss of activity or enantioselectivity. At the same time, a theoretical mechanistic study was conducted to explain the origin of the enantioselectivity. The synthetic utility of the catalytic enantioselective Henry reaction could be demonstrated by the application of a short-step synthesis of a telmisartan analogue, a type of angiotensin II receptor antagonists. Our process, which was simple and easy to operate, possesses potential as an environmentally friendly process in the chemical industry. Further research on C_2-symmetric imidazolium-tagged bis(oxazoline) ligands and their performance in asymmetric reactions is ongoing in our laboratory.

Experimental section

General methods

All manipulations involving air-sensitive materials were performed using standard Schlenk-line techniques under an atmosphere of nitrogen or argon in oven-dried glassware. DCM was distilled from calcium hydride, and methanol was distilled from Mg. $Cu(OAc)_2 \cdot H_2O$ and the ionic liquid were purchased from commercial suppliers and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 300 instrument. Analytical high-performance liquid chromatography (HPLC) was performed on a Knauer Smartline series HPLC equipped with a variable wavelength detector and Daicel Chiralpak AD-H and Chiralcel OD-H columns. Enantiomeric excess was calculated from the HPLC profile.

General procedure for the enantioselective Henry reaction

To an oven-dried 10 mL two necked round-bottomed flask, a solution of ligand (0.05 mmol) and $Cu(OAc)_2 \cdot H_2O$ (12.4 mg, 0.063 mmol) in MeOH (1 mL) was stirred for 2 h at 25 °C. Then the aldehyde (0.34 mmol) and nitromethane (17 mmol) were added, and the resulting mixture was stirred at 0 °C for the appropriate time. After completion, as monitored by TLC, the solvent was removed, and the resulting residue was purified by column chromatography on silica gel (Merck, 60–120 mesh, (ethyl acetate/hexane, 3 : 7) to afford the pure 2-nitroalcohol.

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Notes and references

1 D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726–728.
2 R. Rasappan, D. Laventine and O. Reiser, *Coord. Chem. Rev.*, 2008, **252**, 702–714.
3 E. J. Corey, N. Imai and H. Y. Zhang, *J. Am. Chem. Soc.*, 1991, **113**, 728–729.
4 J. Bayardon, O. Holczknecht, G. Pozzi and D. Sinou, *Tetrahedron: Asymmetry*, 2006, **17**, 1568–1572.
5 S. Doherty, P. Goodrich, C. Hardacre, V. Pârvulescu and C. Paun, *Adv. Synth. Catal.*, 2008, **350**, 295–302.
6 C. T. Qian and L. C. Wang, *Tetrahedron: Asymmetry*, 2000, **11**, 2347–2357.
7 P. O'Leary, N. P. Krosveld, K. P. De Jong, G. V. Koten and R. J. M. K. Gebbink, *Tetrahedron Lett.*, 2004, **45**, 3177–3180.
8 D. Frain, F. Kirby, P. McArdle and P. O'Leary, *Tetrahedron Lett.*, 2010, **51**, 4103–4106.
9 R. Šebesta, I. Kmentová and Š. Toma, *Green Chem.*, 2008, **10**, 484–496.
10 (*a*) D. Rechavi and M. Lemaire, *Chem. Rev.*, 2002, **102**, 3467–3493; (*b*) C. Jonsson, K. Hallman, H. Anderson, G. Stemme, M. Malkoch, E. Malmstrom, A. Hult and C. Moberg, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1857–1861.
11 M. Lombardo, M. Chiarucci and C. Trombini, *Chem.–Eur. J.*, 2008, **14**, 11288–11291.
12 J. Dupont, R. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667–3692.
13 V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615–2665.
14 S. F. Liu and J. L. Xiao, *J. Mol. Catal. A: Chem.*, 2007, **270**, 1–43.
15 P. Wasserscheid and P. S. Schulz, in: *Ionic Liquids in Synthesis*, ed. P. Wasserscheid, T. Welton, 2nd edn, Wiley-VCH, Weinheim, 2007, 369–463.
16 J. Lee, J. Y. Kim, Y. J. Shin, C. E. Yeom, J. E. Lee, T. Hyeon and B. M. Kim, *Tetrahedron: Asymmetry*, 2010, **21**, 285–291.
17 (*a*) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915–945; (*b*) G. Rosini and R. Ballini, *Synthesis*, 1988, **11**, 833–847; (*c*) G. Rosini, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, 321.
18 N Ananthi, U Balakrishnan and S Velmathi, *ARKIVOC*, 2010, **11**, 370–379.
19 B. Reddy, S. M. Reddy, S. Manisha and C. Madan, *Tetrahedron: Asymmetry*, 2011, **22**, 530–535.
20 Z. L. Guo, S. Zhong, Y. B. Li and G. Lu, *Tetrahedron: Asymmetry*, 2011, **22**, 238–245.
21 H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418–4420.
22 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692–12693.
23 N. H. Khan, E. A. Prasetyanto, Y. K. Kim, M. B. Ansari and S. E. Park, *Catal. Lett.*, 2010, **140**, 189–196.
24 Z. Zhou, Z. Li, X. Hao, X. Dong, X. Li, L. Dai, Y. Liu, J. Zhang, H. Huang, X. Li and J. Wang, *Green Chem.*, 2011, **13**, 2963.
25 W. Yang, H. Liu and D. Du, *Org. Biomol. Chem.*, 2010, **8**, 2956–2960.

