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Recyclable copper catalysts based on ionic-tagged C_2-symmetric Indabox ligands and their application in asymmetric Henry reactions

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ABSTRACT

New imidazolium/pyrrolidinium-tagged Indabox ligands were designed and prepared. Catalysts based on these ligands with $Cu(OAc)_2 \cdot H_2O$ were applied to the asymmetric Henry reaction using various aldehydes and CH_3NO_2, the products were obtained in high enantioselectivity. Specifically, (*R*)-1-(2-methoxylphenyl)-2-nitroethanol was obtained in 94% *ee* in MeOH. Furthermore, the catalyst based on **7** could be recycled at least 12 times by simple wash without an obvious loss of activity or enantioselectivity. This catalytic procedure demonstrated the potential for catalyst recyclability in the asymmetric Henry reaction. Additionally, a theoretical mechanistic study was conducted to explain the origin of the enantioselectivity.

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1. Introduction

Enantioenriched 2-nitro-1-arylalkanols, which are key intermediates and building blocks for the synthesis of β-adrenergic drugs and natural products such as polyamino alcohols and polyhydroxylated amides, are generally prepared via the Henry (nitroaldol) reaction [1–6]. Since the first asymmetric Henry reaction was reported by Shibasaki and co-workers, who used a series of heterobimetallic catalysts [7], a large number of effective asymmetric metal-based catalytic systems have been developed [8–10], and they [11–14] have all demonstrated their ability to promote the asymmetric Henry reaction in high yields with high enantioselectivities. Among these protocols, copper-based asymmetric catalytic systems have been employed with various ligands [15–18]. Moreover, bis(oxazoline) complexes derived from $Cu(OAc)_2 \cdot H_2O$, like those employed by Evans et al., were found to be promising catalysts for the Henry reaction under mild reaction conditions [17].

Chiral bis(oxazoline) (box) ligands have proven to be very effective in generating high levels of activity and enantioselectivity in many reactions [19–29]. The recyclability of box ligands has now emerged as a priority. However, to date, there are only a handful of reports describing the immobilization and recycling of a catalyst in asymmetric Henry reactions [3,30–37]. Lee [3] immobilized a box 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 CH_3NO_2. This catalyst was separated magnetically and reused 5 times with little loss of reactivity or enantioselectivity. Khan [31] reported catalysts derived from C_2-symmetric chiral secondary bis-amines based on the 1,2-diaminocyclohexane structure. Partnered with copper acetate, its application was investigated in the asymmetric Henry reaction in the presence of different ionic liquids, with a focus on [Emim] BF_4. In this context, the catalyst could be reused 5 times with retention of the enantioselectivity. More recently, Didier [32] reported that an anthracenyl-modified chiral bis(oxazoline) copper complex was recovered through the formation of a charge transfer complex between the chiral ligand and trinitrofluorenone and its subsequent precipitation with pentane. In recent years, the use of ionic liquids as biphasic systems and the use of catalysts based on ionic-tagged ligands are promising recycling methods [33]. However, to the best of our knowledge, only a few of the ionic-tagged box compounds have been used as ligands in the asymmetric Henry reaction (Scheme 1).

Following our previous work on imidazolium-tagged box ligands and their good performance and recyclability in asymmetric reactions [37], we designed and prepared new ionic-tagged Indabox ligands and investigated their performance in asymmetric

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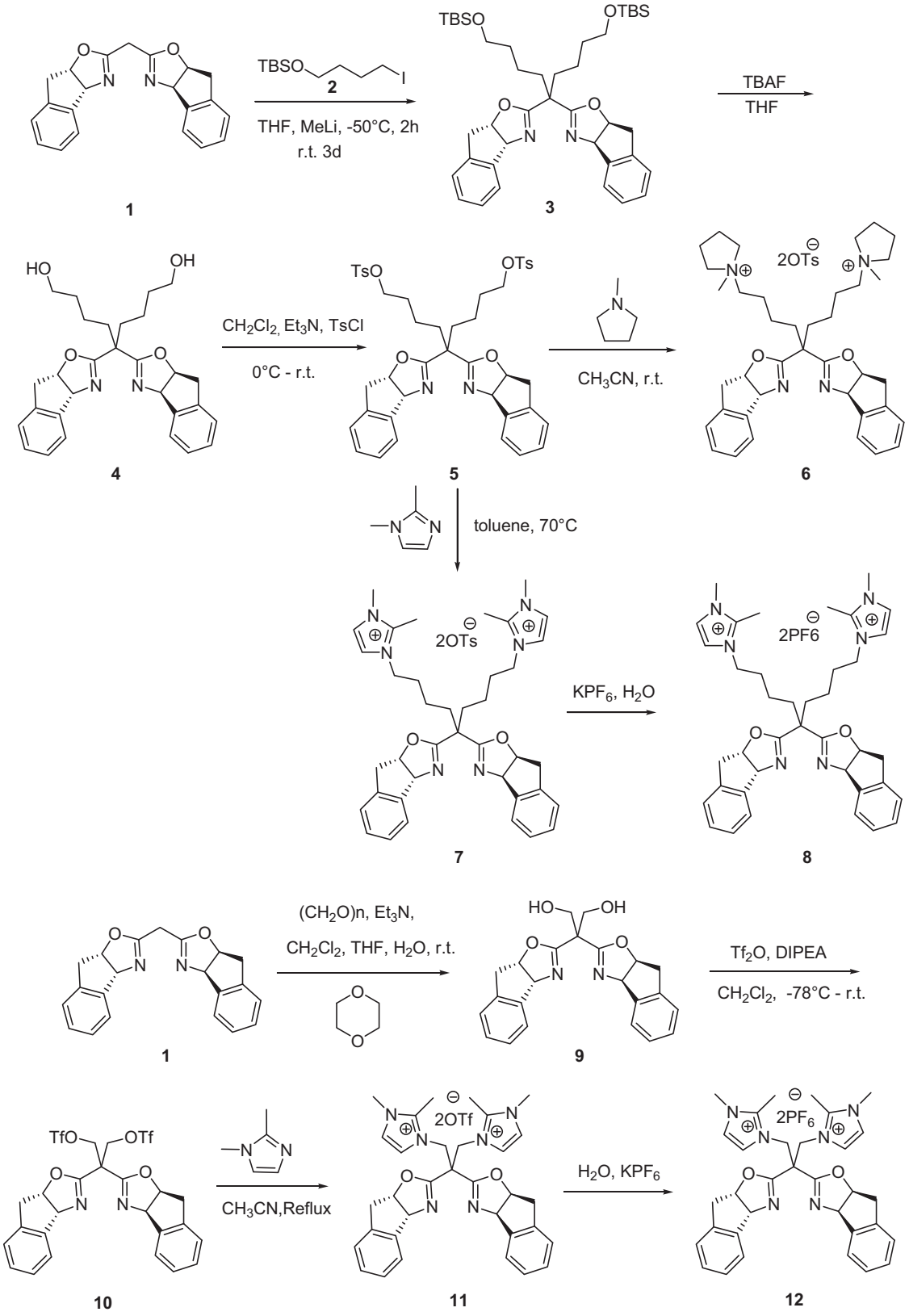


Scheme 1. Preparation of new ionic-tagged Indabox ligand.

Henry reactions as task-specified catalysts. Because ionic liquids can be made to have the ideal combination of cations and anions for a given reaction, the cation moiety of the new ligands were altered in our work. The imidazolium salt and the pyrrolidinium salt could both be prepared, and the anion of ligands could be changed. High enantioselectivities were obtained (up to 94% *ee*) in the asymmetric Henry reaction between 2-methoxybenzaldehyde and CH_3NO_2. Furthermore, the catalyst could be reused 12 times without any

obvious loss in activity or in enantioselectivity. As the catalyst was immobilized by ionic tag, it could be recycled in the absence of additional ionic liquids. The recycling procedure was simple and easy to operate.

2. Experimental

2.1. Synthesis of new ligands

2.1.1. Synthesis of (3aR,8aS)-2-(1,9-bis(tert-butyldimethylsilyloxy)-5-((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonan-5-yl)-8,8a-dihydro-3aH-indeno[1,2-d] oxazole **3**

A solution of **1** (1.975 g, 6.00 mmol) in 90 mL of dry THF was cooled to −50 °C under a N_2 atmosphere. A solution of MeLi (8.30 mL, 1.6 M in Et_2O, 13.0 mmol) was added to the solution drop wise, the resulting mixture was stirred at −50 °C for 1 h, and then **2** (4.710 g, 15.0 mmol) was added slowly to the mixture. After the addition was complete, the solution was left to warm to room temperature and stirred for an additional 3 days. The reaction mixture was quenched by the addition of water (60 mL) and extracted with EtOAc (3× 30 mL). The organic fractions were combined, washed with brine (1× 40 mL) and H_2O (1× 40 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to afford a thick, dark, oily residue, which was purified by column chromatography (SiO_2, PE/EtOAc, 10/1) to afford **3** as a pale yellow solid; yield: 3.360 g (80%). Mp 76–78 °C. $[\alpha]_D^{20} = 186.6$ (c = 0.12, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (m, 2H, Ph-*H*), 7.28–7.43 (m, 6H, Ph-*H*), 5.54 (d, J = 8.0 Hz, 2H, oxazoline-C*H*N), 5.22–5.20 (dd, J = 8.0 Hz and 7.0 Hz, 2H, oxazoline-C*H*O), 3.42–3.34 (m, 4H, CH_2CH_2O), 3.30–3.25 (dd, J = 7.0 Hz and 17.5 Hz, 2H, C*H*(CH)CH), 2.90–2.87 (d, J = 17.5 Hz, 2H, C*H*(CH)CH), 1.94–1.86 (m, 4H, CCH_2CH_2), 1.41–4.33 (m, 4H, $CH_2CH_2CH_2$), 1.05–0.82 (m, 4H, $CH_2CH_2CH_2$), 0.90(s, 18H, *tBu*) 0.01 (s, 12H, $OSi(CH_3)_2$). ^{13}C NMR (125 MHz, $CDCl_3$): 167.8, 141.9, 139.5, 128.3, 127.3, 125.6, 124.9, 82.8, 76.3, 62.9, 45.6, 39.5, 32.9, 31.5, 26.0, 19.7, 18.2, −5.2. MS (ESI): m:z = 703.4 M+1$^+$.

2.1.2. Synthesis of 5,5-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonane-1,9-diol **4**

A solution of **3** (0.50 g, 0.70 mmol) in 4 mL of dry THF was cooled to 0 °C under N_2 atmosphere. TBAF (0.371 g) in 3 mL of THF was added to the solution drop wise, and the resulting mixture was warmed to room temperature and stirred for 8 h. The reaction mixture was subsequently quenched by the addition of water (10 mL), washed with EtOAc (10 mL) and then with brine (10 mL), extracted with EtOAc (2× 5 mL). The organic fractions were dried over Na_2SO_4, and the solvent was removed under vacuum to afford the crude product, which was purified by column chromatography (SiO_2, EtOAc to EtOAc/EtOH, 1:1) to afford **4** as a yellow solid; yield: 0.236 g (71%). Mp: 120–121 °C. $[\alpha]_D^{20} = 261.9$ (c = 0.40, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.48 (m, 2H, Ph-*H*), 7.27 (m, 6H, Ph-*H*), 5.56–5.54 (d, J = 7.5 Hz, 2H, oxazoline-C*H*N), 5.29–5.26 (dd, J = 7.5 Hz and 7.0 Hz, 2H, oxazoline-C*H*O), 3.48 (m, 4H, CH_2CH_2O), 3.305–3.31 (dd, J = 7.5 Hz and 18.0 Hz, 2H, C*H*(CH)CH), 2.90–2.87 (d, J = 18.0 Hz, 2H, C*H*(CH)CH), 1.89–1.83 (m, 4H, CCH_2CH_2), 1.46–1.27 (m, 4H, $CH_2CH_2CH_2$), 1.15–0.95 (m, 4H, $CH_2CH_2CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$): 168.1, 141.7, 139.4, 128.4, 127.5, 125.6, 125.0, 83.1, 75.8, 61.5, 45.7, 39.4, 31.9, 19.5. MS (ESI): m:z = 475.2 M+1$^+$.

2.1.3. Synthesis of 5,5-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonane-1,9-ditosylate **5**

To a solution of **4** (0.474 g, 1.0 mmol) in 5 mL of DCM, TsCl (0.760 g, 4.0 mmol) and Et_3N (0.404 g, 4.0 mmol) were added under N_2 atmosphere, the mixture was stirred for 8 h. The reaction mixture was subsequently quenched by the addition of brine (10 mL). The organic layer was washed with water (3× 10 mL) and dried over Na_2SO_4, the solvent was removed under vacuum to afford the crude product, which was purified by column chromatography (SiO_2, EtOAc/PE 1/1 to EtOAc) to afford **5**; yield: 0.430 g (55%). Mp: 42–45 °C. $[\alpha]_D^{20} = 131.8$ (c = 0.28, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.71 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*), 7.50–7.48 (m, 2H, Ph-*H*), 7.37 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*), 7.26–7.24 (m, 6H, Ph-*H*), 5.53–5.52 (d, J = 8.0 Hz, 2H, oxazoline-C*H*N), 5.24–5.22 (dd, J = 7.0 Hz and 6.5 Hz, 2H, oxazoline-C*H*O), 3.75–3.71 (m, 4H, CH_2CH_2OTs), 3.32–3.24 (dd, J = 7.0 Hz and 18.0 Hz, 2H, C*H*(CH)CH), 2.90 (d, J = 18.0 Hz, 2H, C*H*(CH)CH), 2.49 (s, 6H, OTs-CH_3), 1.82–1.74 (m, 4H, CCH_2CH_2), 1.44–1.27 (m, 4H, $CH_2CH_2CH_2$), 0.88 (m, 4H, $CH_2CH_2CH_2$). MS (ESI): m:z = 783.2 M+1$^+$.

2.1.4. Synthesis of 1,1′-{5,5-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonane-1,9} bis-(1-methyl-pyrrolidinium) diOTs **6**

5 (0.206 g, 0.263 mmol) and 1-methylpyrrolidine (0.09 g, 1.05 mmol) were dissolved in 1 mL of CH_3CN, and the solution was stirred for 24 h under N_2 atmosphere. CH_3CN was removed under high vacuum. The residue was washed with Et_2O (3× 10 mL) until it changed to a white solid; yield: 0.075 g (30%). Mp: 181–184 °C. $[\alpha]_D^{20} = 111.3$ (c = 0.18, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.69 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*) 7.46 (m, 2H, Ph-*H*), 7.25–7.21 (m, 6H, Ph-*H*), 7.12 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*), 5.50–5.49 (d, J = 7.5 Hz, 2H, oxazoline-C*H*N), 5.22–5.20 (dd, J = 7.5 Hz and 7.0 Hz, 2H, oxazoline-C*H*O), 3.42 (m, 4H, CH_2CH_2N), 3.34–3.32 (dd, J = 7.0 Hz and 18.0 Hz, 2H, C*H*(CH)CH), 2.92–2.90 (br, 8H, pyrrolidine-*H*), 2.87–2.83 (d, J = 18.0 Hz, 2H, C*H*(CH)CH), 2.45 (s, 6H, OTs-C*H*3), 2.31 (s, 6H, pyrrolidine-CH_3) 2.02 (br, 8H, pyrrolidine-*H*), 1.91–1.85 (m, 4H, CCH_2CH_2), 1.61–1.52 (m, 4H, $CH_2CH_2CH_2$), 1.04–1.01 (m, 4H, $CH_2CH_2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): 167.2, 143.9, 141.8, 139.5, 139.2, 128.6, 128.2, 127.3, 125.8, 125.0, 83.0, 75.9, 64.0, 48.1, 45.1, 39.3, 30.9, 23.7, 21.4, 20.2. HRMS (ESI): calc. for $C_{39}H_{54}N_4O_2^{2+}$: 305.2117; found: 305.2111.

2.1.5. Synthesis of 1,1′-{5,5-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonane-1,9} bis-(1,2-dimethyl-1H-imidazole) diOTs **7**

5 (0.252 g, 0.32 mmol) and 1,2-dimethyl-1*H*-imidazole (0.193 g, 2.0 mmol) were dissolved in 2 mL of toluene, and the solution was heated to 70 °C for 24 h under N_2 atmosphere. Toluene was removed under high vacuum. The residue was washed with Et_2O (3× 10 mL) until it changed to a light-yellow solid; yield: 0.156 g (51%). Mp: 77–79 °C. $[\alpha]_D^{20} = 38.5$ (c = 0.26, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.65 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*), 7.46 (m, 2H, Ph-*H*), 7.38 (s, 2H, imidazole-C*H*), 7.28 (s, 2H, imidazole-C*H*), 7.21 (d, J = 8.0 Hz, 4H, OTs-ph-C*H*), 7.09 (m, 6H, Ph-*H*), 5.51–5.50 (d, J = 8.0 Hz, 2H, oxazoline-C*H*N), 5.24–5.21 (dd, J = 7.0 Hz and 7.0 Hz, 2H, oxazoline-C*H*O), 3.82–3.70 (m, 10H, CH_2CH_2mim + imidazole-CH_3), 3.31–3.26 (dd, J = 7.0 Hz and 18.5 Hz, 2H, C*H*(CH)CH), 2.92 (d, J = 18.5 Hz, 2H, C*H*(CH)CH), 2.59 (s, 6H, imidazole-CH_3), 2.49 (s, 6H, OTs-CH_3), 1.85–1.79 (m, 4H, CCH_2CH_2), 1.52–1.22 (m, 4H, $CH_2CH_2CH_2$), 0.90–0.75 (m, 4H, $CH_2CH_2CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$): 167.3, 143.7, 141.9, 139.3,139.1, 128.6, 128.4, 125.4, 125.1, 122.7, 120.4, 119.0, 83.2, 76.0, 48.1, 45.1, 39.4, 35.5, 34.1, 32.1, 29.4, 21.2, 20.3, 10.7, 9.8. HRMS (ESI): calc. for $C_{39}H_{48}N_6O_2^{2+}$: 316.1914; found: 316.1918.

2.1.6. Synthesis of 1,1′-{5,5-bis((3aR,8aS)-8,8a-dihydro-3aH-indeno[1,2-d] oxazol-2-yl)nonane-1,9} bis-(1,2-dimethyl-1H-imidazole) diPF$_6$ **8**

7 (0.125 g, 0.13 mmol) was dissolved in 2 mL of H_2O, KPF_6 (0.048 g, 0.26 mmol) was added to the solution and stirred for 6 h at room temperature. The resultant white solid was filtered

and dried under vacuum to afford the product; yield: 0.100 g (83%). Mp: 162–165 °C. $[\alpha]_D^{20} = 88.2$ (c = 0.06, $CHCl_3$). ^{1}H NMR (500 MHz, DMSO): δ = 7.59 (s, 2H, imidazole-C*H*), 7.51 (s, 2H, imidazole-C*H*), 7.38 (m, 2H, Ph-*H*), 7.30–7.27 (m, 6H, Ph-*H*), 5.46–5.44 (d, J = 7.5 Hz, 2H, oxazoline-C*H*N), 5.23–5.20 (dd, J = 7.5 Hz and 7.0 Hz, 2H, oxazoline-C*H*O), 3.87–3.85 (m, 4H, CH_2CH_2mim), 3.72 (s, 6H, imidazole-CH_3), 3.29–3.28 (dd, J = 7.0 Hz and 18.0 Hz, 2H, C*H*(CH)CH), 2.78–2.75 (d, J = 18.0 Hz, 2H, C*H*(CH)CH), 2.51 (s, 6H, imidazole-CH_3), 1.77 (m, 4H, CCH_2CH_2), 1.55–1.54 (m, 4H, $CH_2CH_2CH_2$), 0.95–0.94 (m, 4H, $CH_2CH_2CH_2$). ^{13}C NMR (125 MHz, DMSO): 166.6, 144.5, 142.4, 140.2, 128.7, 127.6, 125.7, 122.7, 121.2, 82.7, 76.1, 47.6, 45.3, 39.3, 35.1, 32.0, 29.8, 29.4, 20.4, 9.5. HRMS (ESI): calc. for $C_{39}H_{48}N_6O_2^{2+}$: 316.1914; found: 316.1918; calc. for PF_6^-: 144.9807, found: 144.9809.

2.2. General procedure for the enantioselective Henry reaction

To an oven-dried 10 mL two-necked round-bottomed flask were added a solution of ligand (0.05 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (9.80 mg, 0.05 mmol) in MeOH (1 mL) and the mixture was stirred for 2 h at 25 °C. Next, the aldehyde (0.34 mmol) and CH_3NO_2 (6.8 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.

2.3. General procedure for recycling the catalyst

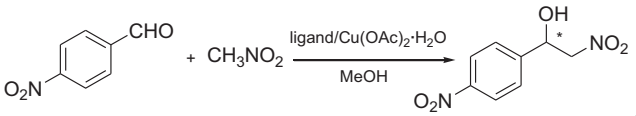
After the completion of the reaction, the MeOH was removed under reduced pressure and the residue was extracted with diethyl ether (until there was no product in diethyl ether could be determined by TLC), and transferred to another flask. Owing to the insoluble nature of the catalyst in diethyl ether, the catalyst could be separated through the formation of a heterogeneous system. The residual catalyst was subjected to vacuum for 1 h, flushed with an inert gas and charged with additional portions of MeOH (1 mL), aldehyde (0.34 mmol) and CH_3NO_2 (6.8 mmol).

3. Results and discussion

3.1. Optimization of asymmetric Henry reaction

For a preliminary study, the asymmetric Henry reaction was catalyzed by the catalyst based on **7**, 4-nitrobenzaldehyde was used as a representative aldehyde. As reported previously [19], the activity and the enantioselectivity of the asymmetric Henry reaction were found to be optimal when the Lewis acid was the air-stable $Cu(OAc)_2{\cdot}H_2O$ (Table 1, entry 1), providing a yield of 97% and an *ee* value of 77%. Next, we screened the ligands to evaluate their catalytic performance on the asymmetric Henry reaction (Table 1). The imidazolium-tagged bis(oxazoline) **7** was found to be the optimum ligand and yielded a higher *ee* than the other ligands in most cases (Table 1, entry 1). The anions of the ligands were found to affect the enantioselectivity and the activity. The tosyl-anion ligand **7** yielded better enantioselectivities and activities than the hexafluorophosphoric salts (Table 1, entries 1–2). Meanwhile, the cation also affected the enantioselectivity and activity. Specifically, the catalyst derived from **6** provided the product in 75% *ee*. This enantioselectivity was comparable to that of ligand **7**; however, a lower yield was achieved (Table 1, entry 3). Ligands with shorter alkyl-chains on the carbon bridge yielded comparable enantioselectivities and lower conversions than ligands with longer alkyl-chains (Table 1, entries 4–5). Examining of solvents indicated that MeOH was the optimized solvent in our system. Consistent with the literature [38], the moderate catalytic activity of our catalyst may be attributed to the electron-rich nature of the imidazolium-tagged box ligand.

Table 1
Screening of ligands for the asymmetric Henry reaction of CH_3NO_2 and 4-nitrobenzaldehyde.



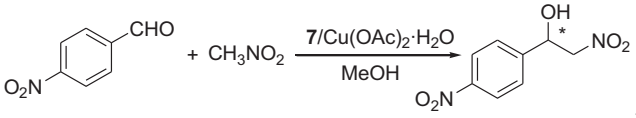
Entry[a]	Ligand	Yield/%[b]	*ee*/%[b]
1	7	97	77
2	8	61	64
3	6	75	75
4	11	72	76
5	12	82	60

[a] The ratio of aldehyde/CH_3NO_2/ligand/$Cu(OAc)_2{\cdot}H_2O$ is 1.0/50.0/0.15/0.18. The reaction was carried out at 25 °C for 24 h.
[b] Yields were calculated based on 4-nitrobenzaldehyde. % *ee* values were determined by HPLC analysis using a chiralcel OD-H column, hexane/*i*-PrOH: 85/15, 0.8 mL/min.

To investigate the effect of the quantity of the catalyst on the activity and the enantioselectivity, we carried out the reaction by varying the amount of the catalyst (Table 2). The reaction was found to proceed with a low catalyst loading (5 mol%, Table 2, entry 1). It seems that the catalyst loading did not cause much difference in the activity or in the enantioselectivity (Table 2, entries 1–4), and since Reiser had reported ligand/metal ratio affect the results of other asymmetric reactions [39,40], the effect of the ligand/metal ratio was tested at rt and these results are outlined in Table 2. We observed that the activity and the enantioselectivity of the asymmetric Henry reaction were the best when the ratio of the ligand to the metal was 1:1 (Table 2, entry 6). Increasing or decreasing this ratio led to lower activities or enantioselectivities (Table 2, entries 3 and 5).

The ratio of ligand to metal of 1:1 was chosen and the efficiency of **7** was evaluated for various aldehydes using 15 mol% of the catalyst (Table 3). Aiming to improve the enantioselectivity in MeOH, the reaction temperature was decreased to 0 °C. The temperature affects the activity and the enantioselectivity to a great extent. Once the reaction temperature was decreased, the yield dropped sharply and a longer reaction time was required. Benzaldehydes with electron-withdrawing nitro substituents provided better yields than substrates with weakly electron-withdrawing or electron-donating properties (Table 3, entries 1–14). However, benzaldehydes with electron-donating substituents gave better *ee* values than substrates with electron-withdrawing substituents.

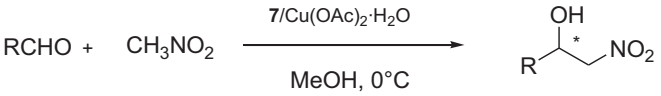
Table 2
Effect of the quantity of the chiral catalyst based on ligand **7** and the ligand/metal ratio in the preparation of **15**.



Entry[a]	Ligand:metal	Cat. loading	Yield/%[b]	*ee*/%[b]
1	1:1.25	5 mol%	87	71
2	1:1.25	10 mol%	91	72
3	1:1.25	15 mol%	97	77
4	1:1.25	20 mol%	98	76
5	1:0.8	15 mol%	83	78
6	1:1.0	15 mol%	95	82

[a] The reaction was carried out at 25 °C for 24 h.
[b] Yields were calculated based on 4-nitrobenzaldehyde. % *ee* values were determined by HPLC analysis using a chiralcel OD-H column, hexane/i-PrOH: 85/15, 0.8 mL/min.

Table 3
The enantioselective Henry reaction of CH_3NO_2 with various aldehydes catalyzed by a complex based on **7**.



Entry[a]	R	Yield/%[b]	*ee*/%[b]
1	Ph (**a**)	67	90
2	4-$NO_2C_6H_4$ (**b**)	71	78
3	2-$NO_2C_6H_4$ (**c**)	62	64
4	2-ClC_6H_4 (**d**)	56	76
5	2,4-diClC_6H_3 (**e**)	51	65
6	4-ClC_6H_4 (**f**)	57	77
7	4-BrC_6H_4 (**g**)	55	81
8	4-FC_6H_4 (**h**)	49	88
9	2-MeC_6H_4(**i**)	53	86
10[c]	4-MeC_6H_4(**j**)	40	93
11	2-$OMeC_6H_4$ (**k**)	55	91
12	3,4-di$OMeC_6H_3$ (**l**)	41	89
13	3,5-di$OMeC_6H_3$ (**m**)	50	89
14	3,4,5-tri$OMeC_6H_2$ (**n**)	51	87
15	4-pyridyl (**o**)	53	37
16	1-naphthyl (**p**)	53	80
17	3-phenylpropanal (**q**)	37	59
18[d]	Ph (**r**)	25 (*Anti*/*Syn* = 72:28)	55
19[d]	4-$NO_2C_6H_4$ (**s**)	29 (*Anti*/*Syn* = 99:1)	66

[a] The ratio of aldehyde/CH_3NO_2/ligand/$Cu(OAc)_2{\cdot}H_2O$ is 1.0/50.0/0.15/0.15. The reaction was carried out at 0 °C for 48 h.
[b] Yields were calculated based on aldehyde. % *ee* values were determined by HPLC analysis using chiralcel OD-H and chiralpak AD-H columns, hexane/i-PrOH.
[c] The amount of CH_3NO_2 is 20.0 equiv.
[d] CH_3NO_2 was replaced with $C_2H_5NO_2$.

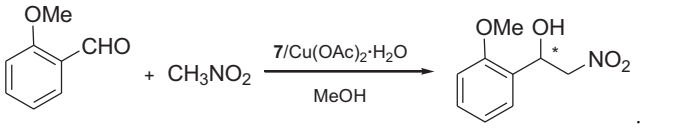
This observation is especially true for 2-methoxybenzaldehyde, which provided *ee* values of 91% at 0 °C (Table 3, entry 11). Moderate to good enantioselectivities could be achieved in most cases when the reaction was carried out at 0 °C (Table 3, entries 1–14). In the cases of other aromatic aldehydes, such as 1-naphthaldehyde, isonicotinaldehyde and 3-phenylpropanal, lower or comparable enantioselectivities and yields relative to benzaldehyde were obtained (Table 3, entries 15–17). The optimized catalyst system was also applied to the asymmetric Henry reaction with nitroethane as nucleophile. The reaction of nitroethane provided the adduct with good *Anti*-selectivity (Table 3, entries 18–19). Though the enantioselectivity was moderate, the catalyst had its potential in diasteroselective Henry reaction.

The addition of base decreased the enantioselectivity of the reaction [8], for when 1.0 equiv. of base (Et_3N, pyridine, DMAP, 1,2-dimethyl-1*H*-imidazole) was added, the yield of the asymmetric Henry reaction increased, but the *ee* value decreased (Table 4, entries 1–4), and we observed that the stronger bases more negatively affected the resulting enantioselectivity provided by the catalyst. In addition, the amount of CH_3NO_2 added was decreased and the results are shown in Table 4. Decreasing the amount of CH_3NO_2 to 20.0 equiv. led to an increase in the *ee* to 94%; however, the yield decreased to 49% (Table 4, entry 5). Decreasing the amount of CH_3NO_2 further led to even lower yields; however, the *ee* values remained constant at 94% (Table 4, entries 6–7).

3.2. Recyclability of the catalyst based on ligand 7

To evaluate the recyclability of the catalysts generated from ligand **7** (Fig. 1), the MeOH was removed under reduced pressure after the completion of the reaction, and the residue was extracted with diethyl ether until there was no product in diethyl ether could be determined by TLC, and transferred to another flask. Owing to the insoluble nature of the catalyst in diethyl ether, the

Table 4
Effects of the base on the asymmetric Henry reaction of 2-methoxybenzaldehyde under the catalysis of complex based on **7**.



Entry[a]	Base/equiv	Yield/%[b]	*ee*/%[b]
1	Et_3N/1.0	79	81
2	Pyridine/1.0	53	90
3	DMAP/1.0	67	81
4	1,2-dimethyl-1*H*-imidazole/2.0	75	87
5	CH_3NO_2/20.0	49	94
6	CH_3NO_2/10.0	39	94
7	CH_3NO_2/5.0	33	94

[a] The reaction was carried out at 0 °C for 48 h.
[b] Yields were calculated based on the aldehyde. % *ee* values were determined by HPLC analysis using a chiralcel OD-H column, hexane/i-PrOH: 85/15, 0.8 mL/min.

reaction was carried out in a homogeneous system, and the catalyst could be separated through the formation of a heterogeneous system. The product and the remaining material were transferred in diethyl ether. The residual catalyst was subjected to vacuum to remove traces of diethyl ether and was flushed with an inert gas and charged with additional portions of MeOH, aldehyde and CH_3NO_2. The activity and the enantioselectivity were maintained even after the catalyst was reused 12 times, and as far as we known, none of other procedures reported has achieved so many recycle times in this reaction. The asymmetric Henry reaction using the catalyst

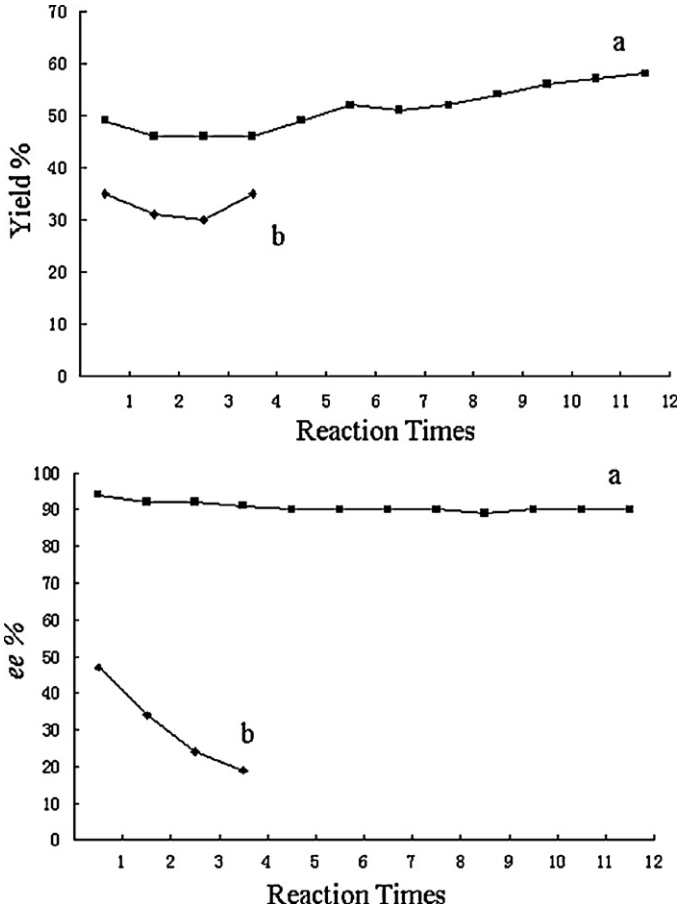


Fig. 1. Variations in percentage yield (1) and percentage *ee* (2) upon recycling of the catalyst. (a) ligand is **7**, substrate is 2-methoxybenzaldehyde and (b) ligand is **1**, substrate is 2-methoxybenzaldehyde.

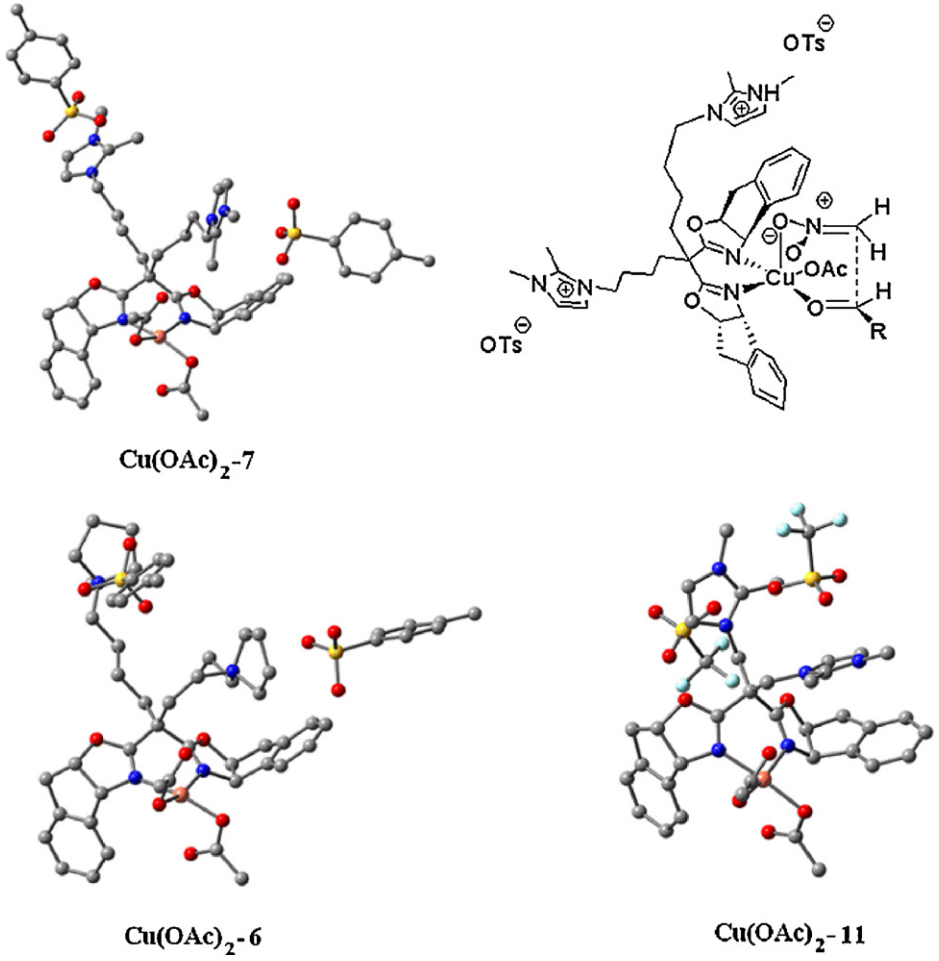


Fig. 2. Computational geometry of complex $Cu(OAc)_2$-**7**, $Cu(OAc)_2$-**6** and $Cu(OAc)_2$-**11** (H was omitted for clarity) and possible transition structure for the asymmetric Henry reaction.

based on **7** and 2-methoxybenzaldehyde as the substrate provided a yield of 58% and an *ee* value of 90% on the 12th cycle. We assume that the increase in yield was caused by the residual CH_3NO_2, which remained with the catalyst after the diethyl ether wash. In contrast, a conversion of 35% and an *ee* value of 47% were obtained using the catalyst based on **1** with 2-methoxybenzaldehyde as the substrate. In this experiment, the catalyst was only able to be reused 4 times, providing a lowered yield of 35% and a poor *ee* value of 19% on the 4th cycle. We discerned that the ionic tag of the catalyst assured the good recyclability.

As the catalyst was immobilized by ionic tag, it could be recycled in the absence of additional ionic liquids. Furthermore, procedure for catalyst recycling is operationally easy and simple [32]. Although the catalyst loading is not very low, our procedure possesses the potential to be used as an environmentally friendly process in the chemical industry considering the good recyclability of the catalyst.

3.3. Mechanistic study

A theoretical mechanistic study was conducted to explain the origin of the enantioselectivity at the molecular level. Computational calculations of the geometries of the complexes $Cu(OAc)_2$-**6**, $Cu(OAc)_2$-**7** and $Cu(OAc)_2$-**11** were performed with the B3LYP/6-31G(d) scheme in the Gaussian03 software package. The optimal geometries are presented in Fig. 2. For complex $Cu(OAc)_2$-**7,** because of the imidazolium salt tagged to the long alkyl chains on the carbon bridge between the two oxazolines, the steric environment was enhanced. 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, making it more difficult for the nitronate to attack from the *Si* face, thereby increasing the enantioselectivity.

According to the model proposed by Evans [7,19], the most reactive transition structure was in a mode such that the CH_3NO_2 is perpendicular to the ligand plane and the aldehyde is in the ligand plane. $Cu(OAc)_2$-**7** afforded adducts with an (*R*)-configuration, indicating that the nitronate attacks the *Re*-face of the aldehyde. Conversely, we found that the geometry of complex $Cu(OAc)_2$-**6** was similar to that of complex $Cu(OAc)_2$-**7**, especially with respect to the steric environment at the catalytic centre. This might be the reason for their comparable *ee* values obtained when used as catalysts. For complex $Cu(OAc)_2$-**11**, which contains a fewer number of alkyl-chain carbon atoms on the carbon bridge, the steric environment at the reaction site is similar, and thus, its enantioselectivity is predicted to parallel that of complex $Cu(OAc)_2$-**7**.

4. Conclusions

In conclusion, new imidazolium/pyrrolidinium-tagged Indabox ligands were designed and prepared conveniently from readily available starting materials. The cation or anion moieties of these new ligands could be readily altered. Preliminary studies revealed that the task-specific catalysts performed well in the asymmetric Henry reaction. The catalyst derived from **7** yielded adduct (*R*)-**15k**

in 94% *ee* in MeOH. Furthermore, the catalyst could be recycled at least 12 times without an obvious loss of activity or enantioselectivity, which makes it a green chemical process. Additionally, the catalyst recycling procedure is simple and easy to operate.

At the same time, the origin of the enantioselectivity was explained by a theoretical mechanistic study. Further research on C_2-symmetric ionic-tagged box ligands and their performance in asymmetric reactions is ongoing in our laboratory.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.apcata.2012.02.044.

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