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The first 4,4'-imidazolium-tagged C₂-symmetric bis(oxazolines): application in the asymmetric Henry reaction†

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Highly efficient and recyclable imidazolium-tagged bis(oxazolines), with an imidazolium tagged onto the 4,4'-position of the box, have been designed and prepared for the first time. They have been synthesized from dimethylmalonic acid and used as chiral ligands in the copper(II)-catalyzed classic asymmetric Henry reaction between aldehydes and nitromethane. A systematic analysis of the anions showed that the best ligand was one of a medium size; the catalyst achieved a high activity and enantioselectivity as well as good recyclability, *i.e.*, product (*R*)-**11k** was attained at 94% ee in MeOH. Moreover, the catalyst was successfully recycled six times, without an obvious loss in activity or enantioselectivity. Finally, a theoretical mechanistic study was conducted to explain the origin of the enantioselectivity and how the size of anions affects the reaction.

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Introduction

C₂-Symmetric bis(oxazolines) (boxes) have been proven to be an important class of chiral ligands and have been successfully used in plenty of metal-catalyzed asymmetric reactions in the past decade. These box ligands show excellent enantioselectivity in a variety of organic reactions.¹ Nowadays the recycling of catalysts is a rapidly growing area of modern organic chemistry. This not only reduces costs, but also reduces the environmental pollution in line with the needs of green chemistry. Speaking of this, the boxes present inherent disadvantages: hard to separate from the reaction mixture and to recycle. These issues have been addressed by immobilizing box ligands on supports.^{2,3}

The immobilization of chiral catalysts based on box ligands is conducive to the development of efficient chiral heterogeneous catalysts and homogeneous catalysts.³ The immobilization strategy has been used and discussed extensively during the past several decades. This strategy includes various methods, *e.g.*, immobilization by covalent or non-covalent bonding on organic or on inorganic supports.⁴ Although highly successful, heterogeneous catalysts, compared to homogeneous catalysts, suffer from a series of drawbacks,

including unequal distribution, limited mobility, and accessibility of the active sites.⁵

Ionic liquids, especially task-specific ionic liquids (TSILs), have recently received much more attention as recyclable catalysts. Besides some common tunable properties⁶ of ionic liquids, TSILs catalysts have several other remarkably attractive advantages: (1) the high polarity and insoluble in non-polar solvent, which make them easily separate from the reagents and reaction products after the reaction and recycled for further use; (2) easier synthesized from inexpensive starting compounds, more stable and lower loading capacity, which let them be the more economic candidates; (3) their properties can be altered easily by modifying the structure of the cations or anions, in order to meet the requirements in reactions, such as steric demand in asymmetric reactions. Those advantages mentioned allow them to become the attractive and ideal candidates for reusable homogeneous catalysts in reactions. During our ongoing studies on the development of recyclable box ligands, we have focused on this novel ionic-liquid-supported (ILS) strategy, which employs ionic liquids as recyclable supports for asymmetric homogeneous catalysis in organic synthesis. Recently, a very large number of catalysts designed by this methodology have been successfully applied to a wide range of reaction including cross-coupling,⁷ olefin metathesis,⁸ Heck reaction,⁹ oxidation,¹⁰ polymerization reaction,¹¹ Biginelli reaction¹² and asymmetric organocatalysis.¹³

Doherty and co-workers were interested in imidazolium ILS bis-(oxazolines). For the first time, they prepared and used the unsymmetric imidazolium ILS boxes 1–3 (Fig. 1) as chiral ligands in the copper(II)-catalyzed Diels–Alder reaction.¹⁴ They

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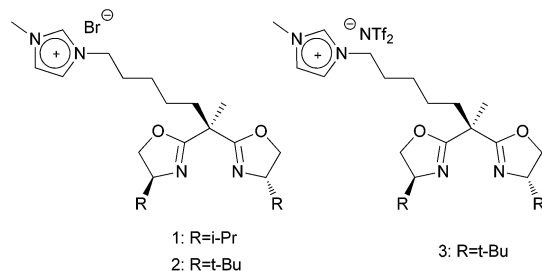


Fig. 1 C_2 -Unsymmetric imidazolium ILS boxes.

got excellent results that the reaction finished within 2 min in [EMIM] [NTf₂] with 100% conversion and 95% ee value. Furthermore, the ILS catalyst was successfully recycled at least ten times with no loss in activity or enantioselectivity. Immediately after, they utilized ILS ligand 3 for the copper(II)-catalyzed asymmetric Mukaiyama aldol reaction under homogeneous conditions.¹⁵ We have recently synthesized a series of novel C_2 -symmetric imidazolium-tagged bis(oxazoline) ligands with excellent results.¹⁶ For instance, in the copper-catalyzed asymmetric Diels–Alder reaction between *N*-acryloyloxazolidin-ones and 1,3-cyclohexadiene in the ionic liquid, the resulting product was isolated 98% yield and 97% ee. In addition, the best catalyst was recycled twenty times. These results confirmed that these C_2 -symmetric ligands perform significantly better than unsymmetric ones.

Though more and more C_2 -symmetric bis(oxazolines) have been synthesized, one of their main differences is the substituent at the 4,4'-position, which intermediates in important enantioselective catalytic processes. In the vast majority of cases, the structure of 4-substituted groups of the boxes, which are considered to be the best ligands in a large number of reactions, is three-dimensional rather than planar. In particular, *tert*-butyl-substituted bis(oxazolines) are the most widely reported ligands in literature.¹ Inspired by this, we designed and prepared imidazolium ILS boxes, with the imidazolium tagged onto the 4,4'-position of the box. Unlike previously reported systems, the imidazolium group, in addition to facilitating catalyst recovery and reuse, is also involved in the catalytic process. Most importantly, these boxes have a further advantage: their chemical and physical properties can be finely tuned for a range of applications by varying the cations or anions; at the same time, the size of the imidazolium fragment can be easily changed by ion exchange to meet the steric demand needed in asymmetric reactions. In this study, we describe the synthesis, characterization, and application of the new imidazolium-tagged recyclable boxes (Scheme 1). We then examine the applications of these boxes in asymmetric catalysis, the asymmetric Henry reaction being our initial focus. As one of the most important C–C bond-forming reactions, the Henry reaction affords products that are versatile building blocks and intermediates in organic synthesis.¹⁷

Results and discussion

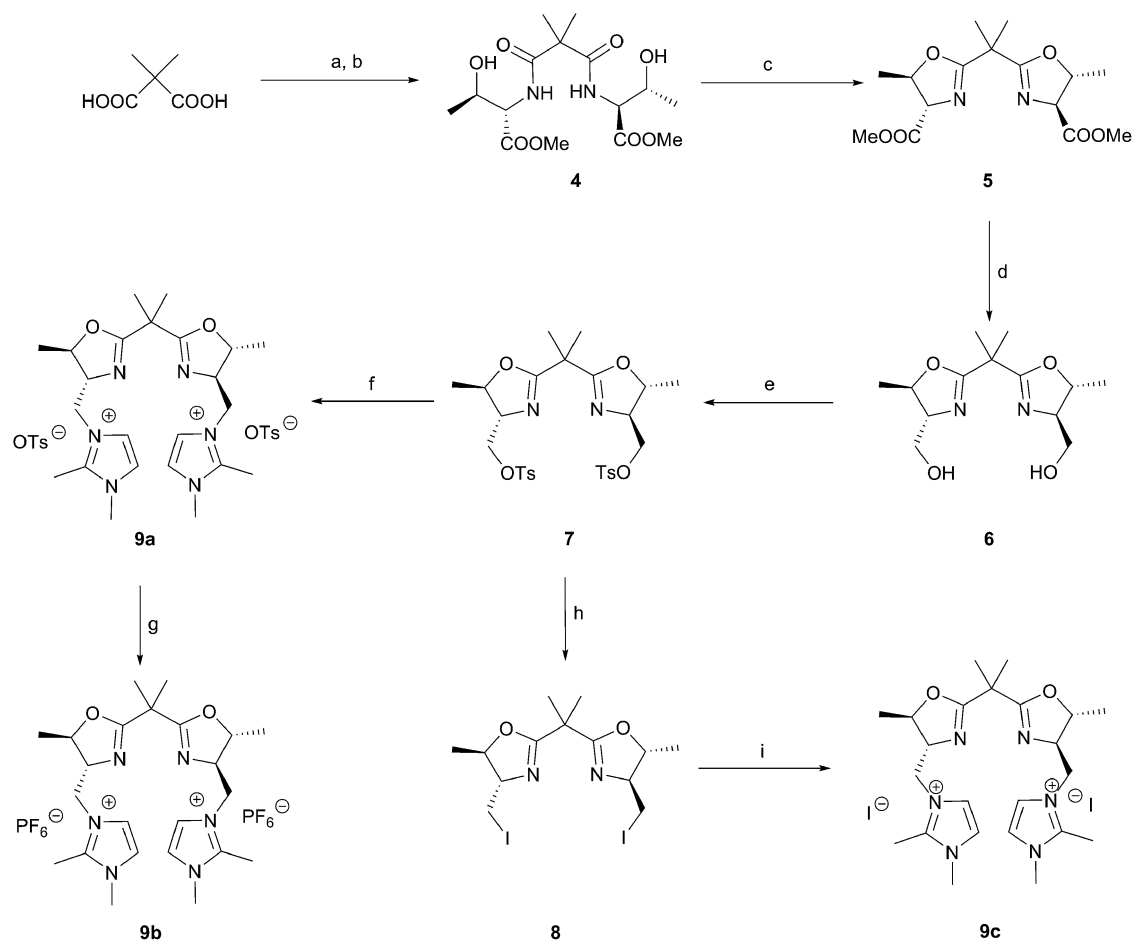
Preparation of C_2 -symmetric imidazolium-tagged bis(oxazoline)

Imidazolium-tagged bis(oxazolines) **9a**, **9b**, and **9c** were identified as potential TSILs because they are relatively straightforward to prepare from inexpensive and readily available starting materials. The synthesis of bis(oxazolines) **9a** and **9b** bearing a pendent imidazolium tag is shown in Scheme 1. Starting from the commercially available dimethylmalonic acid, compounds **4**, **5**, and **6** were prepared as previously reported.¹⁸ C_2 -Symmetric box **7** was obtained when **6** was reacted with TsCl in DCM, catalyzed by Et₃N. The imidazolium tag was introduced in the final step by reacting **7** with 1,2-dimethylimidazole in toluene at 90 °C to afford the tosyl salt **9a**; the anion exchange in water with KPF₆ afforded the desired hexafluorophosphate imidazolium salt **9b**. **7** was reacted with NaI in acetone to give **8**. Finally, **9c** was obtained using the same method employed for **9a** by the reaction of **8** with 1,2-dimethyl-1*H*-imidazole in toluene at 90 °C.

Asymmetric Henry reactions

Our initial studies focused on the catalytic activities of various metal salts and catalyst loading for the asymmetric Henry reaction, catalyzed by the catalyst based on **9a** and 4-nitrobenzaldehyde as a representative aldehyde in MeOH at 25 °C for 24 h (Table 1). The reaction was performed with Zn(OAc)₂·2H₂O, Zn(OTf)₂, Cu(OTf)₂, CuCl₂·2H₂O, CuI, and Co(OAc)₂·4H₂O, however, it turned out that the product was obtained in moderate to good yield, but with low ee values (Table 1, entries 2–8). As reported,¹⁹ the air-stable Cu(OAc)₂·H₂O used as a Lewis acid (Table 1, entry 1), providing the best result with 89% yield and 56% ee. We then carried out the reaction under different amount of the catalyst to investigate the effect of this factor (Table 1). A lower catalyst loading resulted in lower activities and enantioselectivities (Table 1, entries 11). However, an increase in the catalyst loading did not bring us a significant improvement in the activity or enantioselectivity either (Table 1, entries 13 and 14). As can be seen in Table 1, the optimal ratio of Cu(OAc)₂·H₂O to ligand **9a** proved to be 1 : 1 (Table 1, entry 1). Increasing or decreasing this ratio led to lower activities or enantioselectivities (Table 1, entries 9 and 10).

Solvents always play an important role in asymmetric reactions. The influence of various solvents, including ionic liquids and water, were tested in the asymmetric Henry reaction between 4-nitro benzaldehyde with nitromethane in combination with Cu(OAc)₂·H₂O and **9a**; results are summarized in Table 2. Unfortunately, the ionic-tagged ligand showed almost no reactivity in ionic liquids (Table 2, entries 5 and 6), which is consistent with previous studies.¹⁶ Data in Table 2 showed that solvents do affect the reaction activity and enantioselectivity. In particular, protic solvents (alcohols) are superior to aprotic solvents. In the case of alcohols, the activity and enantioselectivity increased in certain order: iPrOH < EtOH < MeOH (Table 2, entries 8–10); no reaction was observed in H₂O



Scheme 1 Synthesis of imidazolium-tagged bis(oxazolines) **9a**, **9b**, **9c**. (a) $(\text{COCl})_2$, DMF, DCM, rt, 85%; (b) L-threonine methyl ester hydrochloride, Et_3N , DCM, 65%; (c) $(\text{NH}_4)_2\text{MoO}_4$ (2 mol%), toluene, azeotropic reflux, 69%; (d) NaBH_4 , EtOH, rt, 75%; (e) TsCl , Et_3N , DCM, 65%; (f) 1,2-dimethyl-1H-imidazole, toluene, 90 °C, 56%; (g) KPF_6 , H_2O , rt, 85%; (h) NaI , acetone, reflux, 73%; (i) 1,2-dimethyl-1H-imidazole, toluene, 90 °C, 51%.

(Table 2, entry 7). We then tried $\text{MeOH-H}_2\text{O}$ solvents, though we did not get the best results, it's much better than pure water (Table 2, entries 15–18). When other solvents were used, the reaction progressed with good yields, but the enantioselectivity decreased (Table 2, entry 1–4). We also tested the base to find if there has an enhancement effect on the enantioselectivity (Table 2, entries 11 and 12). The results showed that the addition of base significantly decreased the enantioselectivity of the catalyst.

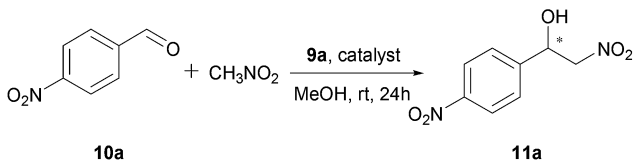
The reaction temperature has a significant effect on the chemical yield and ee values of the nitroaldol product, so the optimization of the temperature was examined (Table 2, entries 13 and 14). Decreasing the reaction temperature from room temperature to 0 °C caused the ee value to increase considerably and increased the reaction time (Table 2, entry 13). However, at –5 °C, the selectivity was slightly decreased (Table 2, entry 14).

We then screened the ligands to evaluate their catalytic performance on the asymmetric Henry reaction (Table 3). The imidazolium-tagged bis(oxazoline) **9b** was found to be the optimum ligand and yielded the highest ee of all studied ligands (Table 3, entry 3). The ligand **9b** with

hexafluorophosphoric anion yielded higher enantioselectivities and activities than with other anions (Table 3, entry 2–4). Thus, our experimental results showed that the steric demand of these reactions was met, and the best results were obtained by a simple change in the size of the imidazolium fragment.

The asymmetric Henry reaction was performed with different aromatic aldehydes with electron-withdrawing and electron-donating substituents under the optimized conditions, *i.e.*, 10 mol% $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in MeOH for ligands **9a** and **9b**. The results summarized in Table 4 show that aromatic aldehydes react in very good yields with nitromethane, producing β -nitro alcohols in modest to good enantioselectivities. Benzaldehydes with electron-withdrawing substituents gave better yields than substrates with weakly electron-withdrawing or electron-donating ones (Table 4, entries 1–14). In contrast, benzaldehydes with electron-donating substituents gave better enantiomeric excess.

This observation is especially true for 3,4-dimethoxybenzaldehyde, which provides ee values of 94% with good yield (Table 4, entry 11). The most relevant difference between our new ligands and the ligands that we reported previously is

Table 1 Screening metal salts and catalyst loading in the asymmetric Henry reaction^a


Entry	Metal salt	Catalyst (mol%)	Yield ^b (%)	ee ^c (%)
1	Cu(OAc) ₂ ·H ₂ O	10	89	56
2	Cu(OTf) ₂	10	73	9
3	CuSO ₄ ·5H ₂ O	10	0	—
4	CuI	10	71	0
5	Zn(OTf) ₂	10	63	9
6	Zn(OAc) ₂ ·2H ₂ O	10	84	1
7	Co(OAc) ₂ ·4H ₂ O	10	75	8
8	CuCl ₂ ·2H ₂ O	10	65	47
9 ^d	Cu(OAc) ₂ ·H ₂ O	10	65	50
10 ^e	Cu(OAc) ₂ ·H ₂ O	10	67	54
11	Cu(OAc) ₂ ·H ₂ O	5	70	39
12	Cu(OAc) ₂ ·H ₂ O	10	89	56
13	Cu(OAc) ₂ ·H ₂ O	15	72	52
14	Cu(OAc) ₂ ·H ₂ O	20	67	52

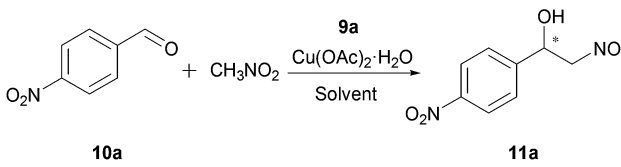
^a All reactions were conducted on a 1 mmol scale with ligand **9a** (10 mol%), copper salt (10 mol%), and nitromethane (20 equiv.) in MeOH (1 mL) at rt for 24 h. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column (hexane/i-PrOH: 85 : 15, 0.8 mL min⁻¹). ^d The rate of metal/ligand is 1/1.25. ^e The rate of metal/ligand is 1/0.8.

that, with [PF₆]⁻, the ligand performs better in terms of activity and enantioselectivity than with [OTf]⁻. The results showed that ligand **9b** is the best ligand for the Henry reaction.

This asymmetric reaction was then applied to the synthesis of the enantiomerically enriched compound **14**; which is the key intermediate of propanolol,²⁰ the synthetic route being shown in Scheme 2. Nitroalcohol **14** was obtained with 86% ee catalyzed by our ligand **9b**.

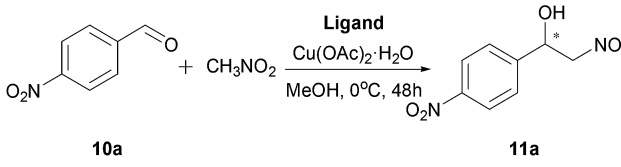
Recyclability of the catalysts

The recyclability of the catalyst based on the C₂-symmetric imidazolium-tagged box **9b** was studied, results summarised in Fig. 2. We performed the asymmetric Henry reaction between 3,4-dimethoxybenzaldehyde and CH₃NO₂. The reaction was carried out in a homogeneous system, and then the catalyst was separated through the formation of a heterogeneous system. MeOH was removed under reduced pressure after the completion of the reaction, and owing to the insolubility of the catalyst in diethyl ether, the residue was extracted with diethyl ether transferring the product and remaining material into diethyl ether. The residual catalyst was subjected to vacuum to remove traces of diethyl ether; it was then flushed with an inert gas and charged with additional portions of MeOH, aldehyde, and CH₃NO₂. The activity and the enantioselectivity were

Table 2 Effects of the solvents and reaction temperature on the asymmetric Henry reaction^a


Entry	Solvent	Temp. (°C)	Yield ^b (%)	ee ^c (%)
1	CH ₂ Cl ₂	rt	48	35
2	THF	rt	78	37
3	Toluene	rt	53	33
4	DMF	rt	72	48
5	[Bmim]PF ₆	rt	Trace	—
6	[Bmim]BF ₄	rt	Trace	—
7	H ₂ O	rt	Trace	—
8	EtOH	rt	86	46
9	i-PrOH	rt	84	42
10	MeOH	rt	89	56
11 ^d	MeOH	rt	95	23
12 ^e	MeOH	rt	98	1
13 ^f	MeOH	0	78	65
14 ^g	MeOH	-5	65	57
15	MeOH/H ₂ O, 8 : 1	rt	83	43
16	MeOH/H ₂ O, 2 : 1	rt	73	20
17	MeOH/H ₂ O, 1 : 2	rt	54	14
18	MeOH/H ₂ O, 8 : 1	0	71	49

^a All reactions were conducted on a 1 mmol scale with ligand **9a** (10 mol%), Cu(OAc)₂·H₂O (10 mol%), and nitromethane (20 equiv.) in 1 mL of solvent at rt for 24 h. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column (hexane/i-PrOH: 85 : 15, 0.8 mL min⁻¹). ^d 10 mol% of Et₃N used as a base. ^e 10 mol% K₂CO₃ used as a base. ^f Reaction time of 48 h. ^g Reaction time of 62 h.

Table 3 Optimization of the reaction ligands^a


Entry	Ligand	Temp. (°C)	Yield ^b (%)	ee ^c (%)
1	7	0	73	57
2	9a	0	79	65
3	9b	0	84	75
4	9c	0	82	25

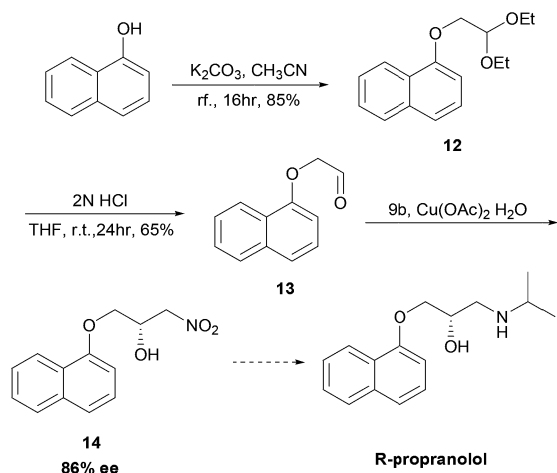
^a All reactions were conducted on a 1 mmol scale with 10 mol% ligand, Cu(OAc)₂·H₂O (10 mol%), and nitromethane (20 equiv.) in 1 mL of MeOH at 0 °C for 48 h. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column (hexane/i-PrOH: 85 : 15, 0.8 mL min⁻¹).

maintained even after the catalyst was reused six times. The asymmetric Henry reaction with the catalyst based on **9b** and 3,4-dimethoxybenzaldehyde as the substrate provided 61%

Table 4 Substrate scope

$\text{R}-\text{CHO} + \text{CH}_3\text{NO}_2 \xrightarrow[\text{MeOH, 0}^\circ\text{C}]{\text{Ligand (10mol\%)}, \text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}} \text{R}-\text{CH}(\text{OH})-\text{CH}_2\text{NO}_2$						
			Ligand 9a		Ligand 9b	
Entry	R	Product	Yield ^a (%)	ee ^b (%)	Yield ^a (%)	ee ^b (%)
1	Ph(a)	11a	67	85	70	89
2	4-NO ₂ C ₆ H ₄ (b)	11b	81	65	84	75
3	2-NO ₂ C ₆ H ₄ (c)	11c	78	70	81	74
4	2,4-(Cl) ₂ C ₆ H ₃ (d)	11d	80	61	88	79
5	4-ClC ₆ H ₄ (e)	11e	77	81	80	83
6	4-FC ₆ H ₄ (f)	11f	70	81	73	85
7	2-MeC ₆ H ₄ (g)	11g	71	85	73	91
8	4-MeC ₆ H ₄ (h)	11h	68	79	74	90
9	2-OMeC ₆ H ₄ (i)	11i	58	83	68	91
10	3-OMeC ₆ H ₄ (j)	11j	56	85	66	92
11	3,4-(OMe) ₂ C ₆ H ₃ (k)	11k	59	88	71	94
12	3,5-(OMe) ₂ C ₆ H ₃ (l)	11l	57	83	67	92
13	3,4,5-(OMe) ₃ C ₆ H ₂ (m)	11m	52	79	70	93
14	1-Naphthyl(n)	11n	54	77	63	89

^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.



Scheme 2 Synthesis of (R)-14.

yield and 90% ee on the 6th cycle. It can be said that the ionic tagged catalyst has a good recyclability.

Theoretical mechanistic study

A theoretical mechanistic study was conducted to explore the origin of the enantioselectivity at a molecular level. A similar work was carried out in our preliminary study; however, only a complex consisting of a ligand and copper salt was considered, without coordination of nitromethane. According to the model proposed by Evans,¹⁹ a weakly Lewis acidic metal complex

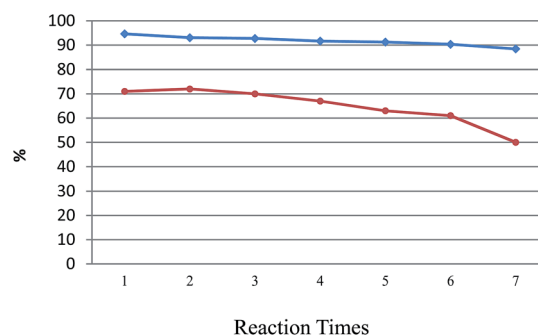


Fig. 2 Variation in percentage conversion (red) and percentage ee (blue) on recycling the Henry reactions between **11k** and CH₃NO₂ in MeOH using catalysts generated from **9b** and Cu(OAc)₂·H₂O.

bearing moderately basic charged ligands may facilitate the deprotonation of nitroalkanes as a first step to the aldol addition. Based on this, the deprotonated nitromethane was included into the new model. Calculations of the geometry of the complex Cu(OAc)₂-ligands with the deprotonated nitromethane were performed with the B3LYP/6-31G(d) level of theory using the Gaussian03 software package. For the sake of comparison, models with large and small size anions, *i.e.*, 4-methylbenzenesulfonate and hexafluorophosphate, were employed. The optimal configurations as well as selected bond lengths and angles of the two complex models are displayed in Fig. 3. The optimized geometries of the two complexes resemble the shape of an airplane, with the protonated methane sitting

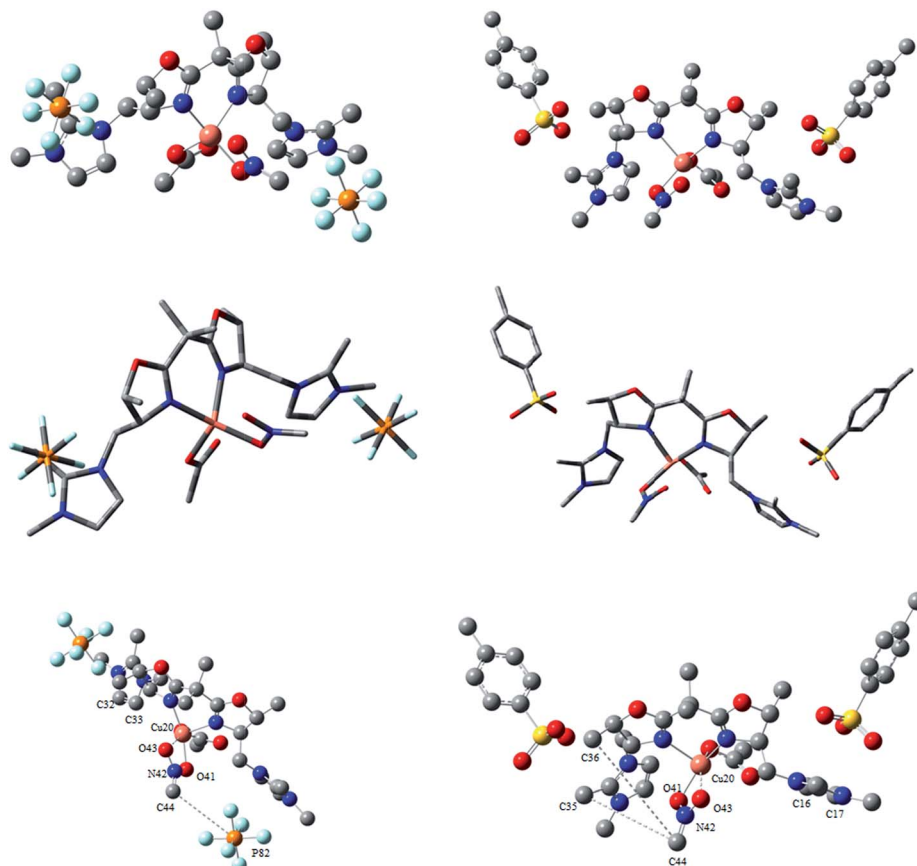


Fig. 3 B3LYP/6-31G(d) optimized geometries of CuOAc-**9a**-CH₂NO₂ and CuOAc-**9b**-CH₂NO₂ complex models (H omitted for clarity) and possible transition structure for the asymmetric Henry reaction. Features are: **9b**: Cu(20)-O(41) 1.96 Å, Cu(20)⋯O(43) 2.05 Å, C(44)⋯P(82) 4.24 Å, N(42)-Cu(20)-C(32)-C(33) 167.8°; **9a**: Cu(20)-O(41) 2.01 Å, Cu(20)⋯O(43) 2.05 Å, C(44)⋯C(36) 6.21 Å, C(44)⋯C(35) 5.19, N(42)-Cu(20)-C(16)-C(17) 67.1°.

on the belly of the airplane, and the anions being over (for OTs⁻) or beneath (for PF₆⁻) the wings. For the complex with sulfonate, the perpendicular position at the reactive C=N double bond Re-face was blocked by the 5-methyl group on the oxazoline ring; for the complex with phosphate, the anion and the imidazole sterically hindered the Re-face of the reactive C=N bond. A further comparison suggested that the difference between the open dihedral angles of the Si-face of reactive C=N bond may play a critical role in the activity and enantioselectivity. A larger dihedral angle would obviously provide a larger space for the Si-attack by the approaching aldehydes, leading to higher enantioselectivities. In fact, the complex module for PF₆⁻ showed a larger dihedral angle, therefore providing higher enantioselectivities than that of the complex with sulfonate; this is demonstrated by our experimental results shown in Table 4. Therefore, we concluded that, although the ligand with I⁻ has a significantly larger dihedral angle, it can exert only a small steric hindrance, which shields the Si-face by the ion fragment. This explains the reasons why a high yield and low ee value was obtained in the reaction catalyzed by **9c**.

Conclusions

Novel C₂-symmetric 4,4'-imidazolium-tagged bis(oxazoline) ligands were successfully and conveniently prepared by two relatively straightforward steps from readily available starting materials; the anions of the ligands were simply altered by ion exchange. The catalysts based on the new ligands and Cu(OAc)₂·H₂O were applied to the asymmetric Henry reaction between various aldehydes and CH₃NO₂. Our experiments proved that the ion fragments play a key role in the steric hindrance. A theoretical mechanistic study revealed that the anions should possess a suitable size to assemble a favorable configuration. This is the reason why PF₆⁻ ensured a better selectivity than bulkier OTs⁻ or smaller I⁻. The catalyst derived from **9b** yielded the adduct (*R*)-**11k** with 94% ee in MeOH. In the reaction of 3,4-dimethoxybenzaldehyde with CH₃NO₂, the ligand **9b** was recycled at least 6 times without an obvious loss in activity or enantioselectivity. Furthermore, the synthetic utility of the catalytic enantioselective Henry reaction was demonstrated by the application of a short-step synthesis of nitroalcohol **14**, which, in two steps, led to the formation of propranolol which as a β-adrenergic receptor blocking agent.

While no studies about the use of 4,4'-imidazolium tagged box-based catalysts in asymmetric catalysis have been reported, this work has clearly shown the potential advantages of the strategy employed here, which include high enantioselectivities, efficient recovery and reuse of the catalyst, and great potential as an environmentally friendly process in the chemical industry. Further research on C_2 -symmetric ionic-tagged box ligands and their performance in asymmetric reactions are underway 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. THF, Et₂O and toluene were distilled from Na. DCM was distilled from calcium hydride. MeOH and EtOH were distilled from Mg. All the chemicals used were purchased from commercial suppliers and used as received without further purification. IR spectra were recorded on a Bruker Alpha-p. ¹H and ¹³C NMR spectra were recorded on a Varian mercury-plus 400 instrument. High resolution mass spectra (HRMS) were recorded at Analytical Instrumentation Center, Peking University. Enantiomeric ratios were determined by chiral HPLC analysis using Daicel Chiralpak AD-H and OD-H columns.

General procedure for the enantioselective Henry reaction

To an oven-dried 10 mL two necked round-bottomed flask, a solution of ligand (0.013 mmol) and Cu(OAc)₂·H₂O (2.64 mg, 0.013 mmol) in MeOH (1 mL) was stirred for 1 h at 25 °C. Then the aldehyde (0.13 mmol) and nitromethane (2.6 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, 1 : 3) to afford the pure 2-nitroalcohol.

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, aldehyde and CH₃NO₂.

Synthesis of ((4*R*,4'*R*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl))bis(methylene)bis(4-methylbenzenesulfonate) **7**

To a solution of **6** (1 g, 3.7 mmol) in dry DCM (30 mL), Et₃N (1.5 g, 14.8 mmol) and TsCl (2.1 g, 11.1 mmol) were added at 0 °C under Ar atmosphere, the mixture was stirred overnight at r.t. The reaction mixture was subsequently quenched by the

addition of brine (50 mL). The organic layer was washed with water (3 × 40 mL) and dried over Na₂SO₄, the solvent was removed under vacuum to afford the crude product, which was purified by column chromatography (SiO₂, EtOAc/PE, 1/10 to 2/1) to afford **7** as white crystal; yield: 1.5 g (65%). Mp: 104–106 °C. $[\alpha]_D^{20} = 128.4$ ($c = 0.50$, CH₂Cl₂). $R_f = 0.15$ (PE–EtOAc 1 : 2); IR (film) 2981, 2931, 1642, 1353, 1177, 965, 811, 790 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.78–7.75 (m, 4H, Ar-*H*), 7.35–7.33 (m, 4H, Ar-*H*), 4.51–4.48 (m, 2H, oxazoline-CHN), 4.11 (dd, $J = 3.2$ Hz, 2H, oxazoline-CHO), 3.887–3.78 (m, 4H, CH₂-OTs), 2.44 (s, 6H, Ar-CH₃), 1.38 (s, 6H, CCH₃), 1.25 (d, $J = 6$ Hz, 6H, CHCH₃). ¹³C NMR (400 MHz, CDCl₃) δ = 170.7, 145.2, 132.8, 130.0, 128.1, 79.3, 70.9, 70.3, 38.8, 23.9, 21.8, 20.8. MS (ESI): $m/z = 579.2$ [$M + 1$]⁺.

Synthesis of 3,3'-(((4*R*,4'*R*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl))bis(methylene))bis(1,2-dimethyl-1*H*-imidazol-3-ium) diOTs **9a**

7 (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 90 °C for 24 h under Ar atmosphere. Toluene was removed under high vacuum. The residue was washed with Et₂O (3 × 10 mL) until it changed to a light-yellow solid; yield: 0.156 g (56%). Mp: 77–79 °C. $[\alpha]_D^{20} = 96.2$ ($c = 0.60$, MeOH). IR (film) 2980, 2930, 1734, 1649, 1356, 1174, 1118, 1031, 1010, 816 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 8.31 (s, 2H, imidazole-*H*), 7.99 (s, 2H, imidazole-*H*), 7.79–7.77 (d, 4H, Ar-*H*), 7.17–7.15 (d, 4H, Ar-*H*), 5.08 (s, 2H, CH₂-OTs), 4.71 (d, $J = 16$, 2H, oxazoline-CHN), 4.24 (dd, $J = 4$ Hz, 2H, oxazoline-CHO), 3.92 (s, 6H, imidazole-NCH₃), 2.55 (s, 6H, Ar-CH₃), 2.34 (s, 6H, imidazole-CCH₃), 1.89 (s, 2H, CH₂-OTs), 1.35 (d, $J = 4$ Hz, 6H, CHCH₃), 1.28 (s, 6H, CCH₃). ¹³C NMR (400 MHz, CDCl₃) δ = 170.9, 145.2, 132.8, 130.1, 128.2, 122.3, 121.6, 79.3, 71.0, 50.3, 38.8, 24.0, 21.8, 20.8, 9.7. MS (ESI): m/z (TsO⁻) = 171.0. HRMS (ESI): calc. for C₂₃H₃₆N₆O₂²⁺: 428.28888, found: 214.14451; calc. for C₃₀H₄₃N₆O₅S⁺ [$M - OTs$]⁺: 599.30102, found: 599.30069.

Synthesis of 3,3'-(((4*R*,4'*R*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl))bis(methylene))bis(1,2-dimethyl-1*H*-imidazol-3-ium) dihexafluorophosphate **9b**

9a (0.125 g, 0.16 mmol) was dissolved in 2 mL of H₂O, KPF₆ (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 (85%). Mp: 163–165 °C. $[\alpha]_D^{20} = 93.7$ ($c = 0.60$, MeOH). IR (film) 2983, 2940, 1731, 1650, 1375, 1241, 1175, 1041, 829 cm⁻¹. ¹H NMR (400 MHz, DMSO) δ = 7.64–7.62 (m, 4H, imidazole-*H*), 4.53–4.50 (m, 2H, oxazoline-CHN), 4.37 (dd, $J = 4$ Hz, 2H, oxazoline-CHO), 4.14–4.09 (m, 2H, CH₂-OTs), 3.96–3.93 (m, 2H, CH₂-OTs), 3.77 (s, 6H, imidazole-NCH₃), 2.59 (s, 6H, imidazole-CCH₃), 1.27 (s, 6H, CCH₃), 1.22 (d, $J = 8$ Hz, 6H, CHCH₃). ¹³C NMR (400 MHz, DMSO) δ = 168.8, 145.2, 122.3, 121.6, 78.4, 71.2, 50.3, 34.8, 23.5, 20.3, 9.7. HRMS (ESI): calc. for C₂₃H₃₆N₆O₂²⁺: 428.28888; found: 214.14439, calc. for C₂₃H₃₆F₆N₆O₂P⁺ [$M - PF_6$]⁺: 573.25361, found: 573.25326.

Synthesis of (4*S*,4'*S*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl)bis(4-(iodomethyl)-5-methyl-4,5-dihydrooxazole) 8

A solution of **7** (440 mg, 0.76 mmol) in acetone (15 mL) was treated with sodium iodide (1.14 g, 7.6 mmol) and the reaction mixture was stirred under reflux. After 12 h, the reaction mixture was treated with saturated Na₂S₂O₃ solution (15 mL). The resulting solution was extracted with Et₂O (3 × 20 mL) and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the product as white solid; yield: 320 mg (73%). Mp: 114–116 °C. $[\alpha]_D^{20} = 67.2$ ($c = 0.25$, CH₂Cl₂). $R_f = 0.2$ (PE–EtOAc 1 : 2); IR (film) 2969, 2924, 1638, 1376, 1259, 1143, 1032, 988, 871, 795 cm^{−1}. ¹H NMR (400 MHz, CDCl₃) $\delta = 4.41$ – 4.38 (m, 2H, oxazoline-CHN), 3.80–3.76 (m, 2H, CH₂-OTs), 3.35 (dd, $J = 3.6$, 2H, oxazoline-CHO), 3.1–3.06 (m, 2H, CH₂-OTs), 1.52 (s, 6H, CCH₃), 1.3 (d, $J = 6.4$ Hz, 6H, CHCH₃). ¹³C NMR (400 MHz, CDCl₃) $\delta = 170.0$, 82.1, 72.9, 39.1, 24.3, 21.3, 10.6. MS (ESI): $m/z = 591.0$ [$M + 1$]⁺.

Synthesis of 3,3'-(((4*R*,4'*R*,5*R*,5'*R*)-2,2'-(propane-2,2-diyl)bis(5-methyl-4,5-dihydrooxazole-4,2-diyl))bis(methylene))bis(1,2-dimethyl-1*H*-imidazol-3-ium) diI **9c**

8 (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 90 °C for 24 h under Ar atmosphere. Toluene was removed under high vacuum. The residue was washed with Et₂O (3 × 10 mL) until it changed to a light-yellow solid; yield: 0.156 g (51%). Mp: 77–79 °C. $[\alpha]_D^{20} = 96.2$ ($c = 0.60$, MeOH). IR (film) 3091, 2978, 2928, 1728, 1648, 1518, 1454, 1281, 1240, 1121 cm^{−1}. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.64$ – 7.62 (m, 4H, imidazole-*H*), 4.53–4.50 (m, 2H, oxazoline-CHN), 4.37 (dd, $J = 4$ Hz, 2H, oxazoline-CHO), 4.14–4.09 (m, 2H, CH₂-OTs), 3.96–3.93 (m, 2H, CH₂-OTs), 3.77 (s, 6H, imidazole-NCH₃), 2.59 (s, 6H, imidazole-CCH₃), 1.27 (s, 6H, CCH₃), 1.22 (d, $J = 8$ Hz, 6H, CHCH₃). ¹³C NMR (400 MHz, DMSO) $\delta = 168.8$, 145.2, 122.3, 121.6, 78.4, 71.2, 50.3, 34.8, 23.5, 20.3, 9.7. MS (ESI): m/z (I^-) = 126.9. HRMS (ESI): calc. for C₂₃H₃₆N₆O₂²⁺: 428.28888; found: 214.14439, calc. for C₂₃H₃₆IN₆O₂⁺ [$M - I$]⁺: 555.19389, found: 555.19326.

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