Efficient *in situ* three-component formation of chiral oxazoline-Schiff base copper(II) complexes: towards combinatorial library of chiral catalysts for asymmetric Henry reaction†

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Received 13th November 2009, Accepted 14th April 2010
First published as an Advance Article on the web 10th May 2010
DOI: 10.1039/b923835b

A combinatorial *in situ* three-component chiral oxazoline-Schiff base copper(II) complex catalyst formation method was developed. This simple combinatorial chiral catalyst approach provided a modular library of chiral oxazoline-Schiff base copper(II) complex catalysts. The catalytic activity of these *in situ* generated catalysts can be rapidly and conveniently evaluated in the asymmetric Henry reaction. Moderate to good yields and enantioselectivities (up to 92% ee) were obtained under the optimized condition. The combination of modular three-component catalyst formation and *in situ* asymmetric reaction provides a new technology in asymmetric catalysis.

Introduction

The development of efficient methodologies for providing enantiomerically pure products is of great value, due to the increasing demands for chiral compounds in the development of pharmaceuticals, agrochemicals, materials, and flavors.[1] Among the various approaches employed for obtaining chiral compounds, asymmetric catalysis using chiral metal complexes is one of the most efficient strategies. In order to achieve efficient and highly enantioselective organic transformations catalytically, the design and synthesis of chiral catalysts is very important. To the best of our knowledge, there is no general ligand or catalyst suitable for every reaction or every substrate. The successful development of an efficient chiral catalyst usually depends on the combination of rational design, experience, and a trial and error process. In this regard, the synthesis of a large number of chiral metal complexes for screening the highly efficient catalysts is a usual manner. However, the synthetic procedures toward most of the chiral ligands are always multi-step and tedious. The development of an efficient and flexible synthetic strategy of chiral ligands or catalysts is strongly desired. In recent years, using combinatorial approaches,[2] self-assembly,[3] or modular approaches[4] to generate a library of chiral metal complexes has emerged. Such a strategy takes advantage of its diversity and efficiency in discovering the highly efficient and enantioselective catalysts.

Schiff base ligands have been recognized as 'privileged ligands' because they can be easily prepared through the condensation between various aldehydes and primary amines.[5] Schiff base ligands are able to coordinate with various metals and stabilize them in various oxidation states, which enables the applications of Schiff base metal complexes in a large variety of useful catalytic transformations.[6] For example, as a representative type of chiral Schiff base, chiral Salen ligands have been successfully used in various asymmetric reactions with excellent results.[7,8]

Oxazoline is another type of 'privileged ligand' owing to its ready accessibility, modular nature, and successful applications in various catalytic asymmetric reactions.[5] The design and applications of chiral oxazoline ligands have gained much attention of chemists in recent years.[9] Our group has also paid much attention to the synthesis and applications of oxazoline ligands.[10] We envisioned that the combination of Schiff base and oxazoline would result in a new type of modular ligand possessing features of both two types of privileged ligands.[11] Using Schiff base formation as a diversity-generating step at late stage in modular ligand construction also has another significant advantage: its rapid formation under mild condition without addition of dehydration reagent or catalyst may provide us an opportunity to generate active catalyst *in situ* without isolation and make the screening more convenient.

Herein, we would like to document a remarkably effective strategy for modular catalyst development based upon *in situ* three-component chiral oxazoline-Schiff base copper(II) complex catalyst formation from readily available starting materials. The catalytic activity of these catalysts was tested in the asymmetric Henry (nitroaldol) reaction,[12,13] which can provide easy access to chiral β-nitroalcohols.

Results and discussion

The oxazoline moieties **1a–d** were obtained *via* a three-step process encompassing coupling of 2-nitrobenzoic acid with chiral amino alcohols, oxazoline ring formation, and reduction of the nitro group. Compared with other approaches,[14] the synthesis can be conveniently conducted on a large scale from cheap starting materials. The details can be found in the ESI.† In our early experiment, when the oxazoline moiety **1a** was mixed with salicylaldehyde **2a** in EtOH, a clear orange solution was formed immediately at room temperature without addition of a dehydration reagent and TsOH

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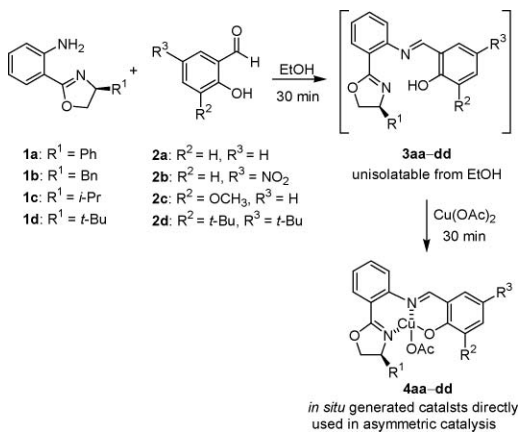
† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C NMR spectra of new compounds, and HPLC diagrams. See DOI: 10.1039/b923835b

catalyst, which indicated the generation of the desired Schiff base. However, the ligand can neither precipitate from EtOH, nor be isolated through column chromatography (decomposed to amine and salicylaldehyde), which made the NMR characterization of the ligand **3aa** impossible. After the addition of one equivalent of $Cu(OAc)_2$ to the solution, a dark green solution of the complex catalyst **4aa** was obtained and TLC showed the salicylaldehyde **2a** and oxazoline **1a** disappeared. After several unsuccessful attempts to isolate the catalyst **4aa**, 4-nitrobenzaldehyde **5a** and nitromethane **6** were added to the solution for asymmetric Henry reaction. To our delight, the *in situ* generated inseparable complex catalyst **4aa** showed significant catalytic activity in the model Henry reaction. Under unoptimized conditions, 91% yield and 39% ee were obtained.

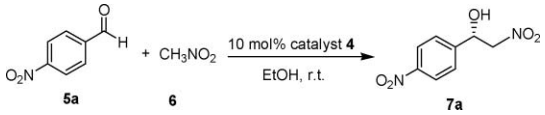
Inspired by the above observation, a library of novel chiral oxazoline-Schiff base metal complex catalysts may be easily obtained through this *in situ* three-component formation way. As a standard protocol (Scheme 1), the oxazoline moieties were mixed with equimolar amount of salicylaldehyde derivatives in EtOH for 30 min. After the addition of $Cu(OAc)_2$, the mixture was stirred for another 30 min. Thus, a 16-membered library of chiral oxazoline-Schiff base copper(II) complex catalysts was obtained through employing various commercially available salicylaldehyde derivatives, the oxazoline moieties, and $Cu(OAc)_2$. The asymmetric Henry reaction was chosen as the model reaction for the evaluation of the catalytic activity of the library members.



Scheme 1 Construction of chiral oxazoline-Schiff base copper(II) complex catalysts library.

The library of chiral oxazoline-Schiff base copper(II) metal complex catalysts was formed *in situ* and screened in an asymmetric Henry reaction of 4-nitrobenzaldehyde **5a** with nitromethane **6** at room temperature. The screening results were summarized in Table 1. Under the catalysis of 10 mol% catalysts **4aa–dd** for 8 h, up to 98% yield and 69% ee can be obtained, while the best result was achieved when catalyst **4db** composed by *t*-Bu substituted oxazoline **1d** and NO_2 substituted salicylaldehyde **2b** was used (entry 14). For clearness, a graphic presentation of these data was given (Fig. 1), which suggests the important role of the aldehyde component **2** for enantioselectivity. Ligands generated from aldehydes **2b** and **2d** gave high enantioselectivities similarly, while the substituents R^1 of the chiral oxazoline **1** seem to have little effect on selectivity.

Table 1 Screening of *in situ* generated catalysts for the Henry reaction of 4-nitrobenzaldehyde with nitromethane[a]



Entry	*In situ* generated catalyst (component source)	Yield (%)[b]	ee (%)[c]
1	**4aa** (**1a** + **2a** + $Cu(OAc)_2$)	91	39
2	**4ab** (**1a** + **2b** + $Cu(OAc)_2$)	90	42
3	**4ac** (**1a** + **2c** + $Cu(OAc)_2$)	94	25
4	**4ad** (**1a** + **2d** + $Cu(OAc)_2$)	93	62
5	**4ba** (**1b** + **2a** + $Cu(OAc)_2$)	95	44
6	**4bb** (**1b** + **2b** + $Cu(OAc)_2$)	90	62
7	**4bc** (**1b** + **2c** + $Cu(OAc)_2$)	95	33
8	**4bd** (**1b** + **2d** + $Cu(OAc)_2$)	90	64
9	**4ca** (**1c** + **2a** + $Cu(OAc)_2$)	91	47
10	**4cb** (**1c** + **2b** + $Cu(OAc)_2$)	90	62
11	**4cc** (**1c** + **2c** + $Cu(OAc)_2$)	96	27
12	**4cd** (**1c** + **2d** + $Cu(OAc)_2$)	98	64
13	**4da** (**1d** + **2a** + $Cu(OAc)_2$)	93	49
14	**4db** (**1d** + **2b** + $Cu(OAc)_2$)	90	69
15	**4dc** (**1d** + **2c** + $Cu(OAc)_2$)	98	27
16	**4dd** (**1d** + **2d** + $Cu(OAc)_2$)	92	64

[a] Reactions were performed with 0.5 mmol of 4-nitrobenzaldehyde and 5.0 mmol of nitromethane in 2 mL of EtOH in the presence of 10 mol % catalyst **4** (*in situ* generated) at room temperature for 24 h. [b] Isolated yields after column chromatography purification. [c] Determined by HPLC using a Daicel Chiracel OD-H column (n-hexane–isopropanol 80 : 20 v/v, 1.0 mL min^{-1}, 254 nm).

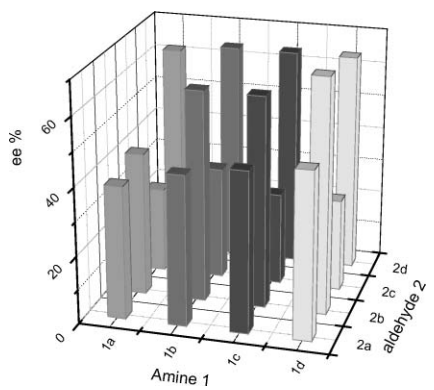


Fig. 1 Screening of *in situ* generated catalysts.

As indicated by the equation in Scheme 1, the *in situ* formation of catalyst **4** would generate one equivalent of water and one equivalent of acetic acid, which may affect the catalytic reaction. To validate the reproducibility, several additives were tested in the reaction. As shown in Table S1 (see ESI†), addition of Et_3N or NaOH to remove the acetic acid formed in the catalyst generation step led to a significant decrease of enantioselectivity. Considering that the acetate anion coordinated to Cu(II) works as a weak base when it was displaced by substrate in the catalytic cycle, the drop of enantioselectivity can be attributed to the formation of an excess amount of acetate anion which may catalyze the background Henry reaction. Addition of 4 Å molecular sieves and anhydrous Na_2SO_4 to remove water also did not improve the enantioselectivity further. When the reaction was conducted at lower temperature, the ee values increased to some extent, while

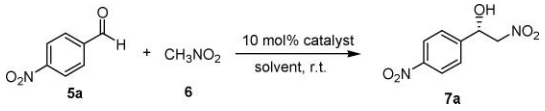
the time for full conversion had to be prolonged by several times. To our surprise, the catalytic system was not very sensitive to high temperature. The room temperature was chosen for the compromise between reactivity and enantioselectivity.

With the optimized catalyst in hand, solvents were screened for further improvement. As summarized in Table S2 (see ESI†), alcohols other than EtOH gave comparable enantioselectivities but lower yields, while 2,2,2-trifuoroethanol with high acidity inhibited the reaction completely. Ether-type solvents such as Et_2O, THF, and TBME improved the enantioselectivity significantly. Dioxane retarded the reaction for its ability to coordinate with a copper cation as a chelation ligand. The enantioselectivity can also be improved in toluene, benzene, and dichloromethane, while much lower yields were obtained. When the catalyst loading was reduced to 5 mol% and 2.5 mol%, lower enantioselectivities and yields were obtained. On the basis of the data, the optimized condition was room temperature in Et_2O using 10 mol% catalyst.

In order to prove that the above catalytic system was the oxazoline-Schiff base copper complex catalyst, control experiments were carried out. When aminophenyl oxazoline moieties **1a–d** were used as ligands with $Cu(OAc)_2$ to catalyze the model Henry reaction of 4-nitrobenzaldehyde, moderate yields (67–72%) and low enantioselectivities (21–46% ee) for the same (*S*) enantiomer were achieved. The significantly inferior result indicates that effective ligands are not the aminophenyl oxazolines **1a–d**, but the oxazoline-Schiff bases. During our screening of solvents, we observed that the Schiff base ligands derived from NO_2 substituted salicylaldehyde and four oxazoline moieties can precipitate from isopropanol. This discovery provided us the opportunity to characterize the structures of the ligands **3ab–db** by NMR, ESI-MS, and IR. Other ligands can neither precipitate, nor be isolated through column chromatography owing to the decomposition to amine moieties and salicylaldehydes. Thus, the characterization of other ligands is impossible. This discovery also provided us evidence to verify that the possibility of the *in situ* oxazoline-Schiff base formation. The copper(II) complex catalysts formed using pure Schiff base ligands **3ab–3db** were also tested in the Henry reaction of 4-nitrobenzaldehyde with nitromethane in EtOH (Table 2), similar results to *in situ* generated catalysts were obtained (Table 2, entry 4 *vs.* Table S2, entry 1†). Meanwhile, the copper(II) complex catalysts formed using pure Schiff base ligands **3ab–3db** were also tested in the Henry reaction of 4-nitrobenzaldehyde with nitromethane in the optimized solvent Et_2O, also similar yields and enantioselectivities to *in situ* generated catalysts **4ab–4db** were obtained (Table 2, entries 9–11 *vs.* entries 5–8), which demonstrated that the *in situ* three-component generated catalysts were equivalent to the ones generated from pure oxazoline-Schiff base ligands and $Cu(OAc)_2$. Further evidence is ESI mass spectra of *in situ* generated catalyst **4db**, where there is a peak of $[M–OAc]^+$ at *m*/*z* 429.

The efficiency of our *in situ* catalytic system was evaluated for various aldehydes under the optimized condition. In general, moderate to good yields and enantioselectivities can be achieved in most cases (75–92% ee). As summarized in Table 3, benzaldehydes with strong electron-withdrawing nitro substitutions gave good results within 24 h, which indicates their high reactivity in Henry reaction (entries 1–3). On the contrary, substrates with weak electron-withdrawing or even electron-donating substitutions need prolonged reaction time to get acceptable conversion and enantioselectivities (entries 4–8). In the cases of other aromatic aldehydes such as 1-naphthaldehyde and 2-furanaldehyde, comparable enantioselectivities and moderate yields with the case of benzaldehyde were obtained (entries 9–10). We also tested α,β-unsaturated cinnamaldehyde and aliphatic aldehydes, and observed similar results to former cases (entries 11–15). The moderate catalytic activity of our catalyst may be attributed to the anionic and electron-rich nature of the oxazoline-Schiff base ligand. The absolute configurations of the products were elucidated though comparison of the optical rotation data with literature data.

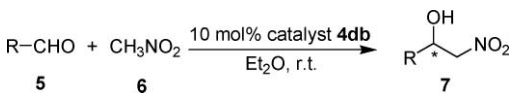
Table 2 Comparison of enantioselective Henry reactions using *in situ* generated catalysts with pure oxazoline-Schiff base ligands and $Cu(OAc)_2$



Entry	Catalyst	Solvent	Yield (%)[b]	ee (%)[c]
1	**3ab** + $Cu(OAc)_2$	EtOH	95	56
2	**3bb** + $Cu(OAc)_2$	EtOH	94	62
3	**3cb** + $Cu(OAc)_2$	EtOH	93	57
4	**3db** + $Cu(OAc)_2$	EtOH	95	70
5	**4ab**	Et_2O	92	69
6	**4bb**	Et_2O	93	72
7	**4cb**	Et_2O	94	70
8	**4db**	Et_2O	97	80
9	**3ab** + $Cu(OAc)_2$	Et_2O	94	69
10	**3bb** + $Cu(OAc)_2$	Et_2O	95	72
11	**3cb** + $Cu(OAc)_2$	Et_2O	95	72
12	**3db** + $Cu(OAc)_2$	Et_2O	96	82

[a] Reactions were performed with 0.5 mmol of 4-nitrobenzaldehyde and 5.0 mmol of nitromethane in 2 mL of solvent in the presence of 10 mol % catalyst at room temperature for 24 h. [b] Isolated yields after column chromatography purification. [c] Determined by HPLC using a Chiracel OD-H column (n-hexane–isopropanol 80 : 20 v/v, 1.0 mL min^{-1}, 254 nm).

Table 3 Enantioselective Henry reactions of various aldehydes with nitromethane catalyzed by *in situ* three-component generated catalyst[a]



Entry	R in product	Time/h	Yield (%)[b]	ee (%)[c]
1	4-$NO_2C_6H_4$ (**7a**)	24	96	82 (*S*)[d]
2	3-$NO_2C_6H_4$ (**7b**)	24	97	76 (*S*)
3	2-$NO_2C_6H_4$ (**7c**)	24	95	84 (*S*)
4	4-ClC_6H_4 (**7d**)	72	86	87 (*S*)
5	4-BrC_6H_4 (**7e**)	72	81	79 (*S*)
6	C_6H_5 (**7f**)	72	85	83 (*S*)
7	4-$MeOC_6H_4$ (**7g**)	96	43	75 (*S*)
8	4-MeC_6H_4 (**7h**)	96	71	80 (*S*)
9	1-Naphthyl (**7i**)	72	65	80 (*S*)
10	2-Furanyl (**7j**)	72	56	88 (*R*)
11	PhCH=CH (**7k**)	72	79	75 (*S*)
12	$PhCH_2CH_2$ (**7l**)	72	71	86 (*S*)
13	*c*-C_6H_{11} (**7m**)	48	92	82 (*S*)
14	*i*-C_3H_7(**7n**)	48	82	87 (*S*)
15	*t*-C_4H_9 (**7o**)	48	81	92 (*S*)

[a] Reactions were performed with 0.5 mmol of aldehyde and 5.0 mmol of nitromethane in 2 mL of Et_2O in the presence of 10 mol % catalyst **4db** at room temperature. [b] Isolated yields after the column chromatography purification. [c] Determined by HPLC on Daicel Chiracel OD-H, OF, and Chiralpak IA column. [d] By comparison with the literature data.[13]

Conclusions

In summary, we reported an efficient and practical strategy for modular catalyst construction based upon *in situ* three-component chiral oxazoline-Schiff base copper complexes formation. The simple combinatorial chiral catalyst approach provided a library of novel modular chiral oxazoline-Schiff base copper complex catalysts. The catalytic activity of these catalysts was tested in the model asymmetric Henry reaction, and the chiral nitro alcohols were obtained in moderate to good yields and enantioselectivities (up to 92% ee). The method of *in situ* generation of catalysts for rapid screening in asymmetric reactions matches the increasing demands for environmentally benign and economic synthetic processes. Further investigations on the applications of these catalysts in other asymmetric reactions are underway in our laboratory.

Experimental

General methods

Melting points were measured on an XT-4 melting point apparatus without correction. The ^{1}H NMR spectra were recorded on Mercury 200 and 300 MHz spectrometers, while ^{13}C NMR spectra were recorded at 50 and 75 MHz, respectively. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrometer. The ESI-MS spectra were obtained on Thermo Finnigan LCQ Deca XP Plus mass spectrometer. Optical rotations were measured on Perkin-Elmer 341 LC or WZZ–3 spectrometer. The enantiomeric excesses of the products were determined by chiral HPLC using Agilent 1200 LC instrument on Daicel Chiralcel OD-H, OF and Chiralpak IA columns. Elemental analysis was carried out on Elementar Vario EL instrument. Commercially available compounds were used without further purification. Column chromatography was carried out using silica gel (200–300 mesh).

Preparation of oxazoline-Schiff base ligands 3ab–db

A solution of 2-(2-aminophenyl)oxazoline **1a–d** (0.5 mmol), 5-nitrosalicylaldehyde **2b** (84 mg, 0.5 mmol) and *i*-PrOH (5 mL) was stirred for 3 h at room temperature, and lots of orange precipitate was formed. The reaction mixture was cooled to 0 °C, filtered and washed with cold *i*-PrOH (3 × 1 mL) to afford oxazoline-Schiff base ligands **3ab–db**.

2-((1*E*)-(2-((*S*)-4-Phenyl-4,5-dihydrooxazol-2-yl)phenylimino)-methyl)-4-nitrophenol 3ab. Orange solid, yield 93%; m.p. 153–154 °C. $[\alpha]_D^{25} = +127.4$ ($c = 1.38$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 13.98$ (br s, 1H), 8.60 (s, 1H), 8.31 (s, 1H), 8.16 (d, $J = 9.0$ Hz, 1H), 8.02 (d, $J = 7.5$ Hz, 1H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.39–7.24 (m, 6H), 6.96 (d, $J = 9.0$ Hz, 1H), 5.44 (t, $J = 9.0$ Hz, 1H), 4.79 (t, $J = 9.0$ Hz, 1H), 4.29 (t, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.3$, 163.3, 160.18, 160.16, 146.5, 141.9, 139.6, 132.3, 131.0, 128.6, 128.4, 128.3, 127.5, 127.4, 126.6, 118.5, 118.4, 118.3, 74.2, 70.1; IR (KBr): ν 3467, 1622, 1492, 1339, 1292, 1096, 947, 835, 750, 700 cm^{-1}; HR-ESIMS: m/z calcd for $C_{22}H_{18}N_3O_4$ (M+H): 388.12526. Found: 388.12918.

2-((1*E*)-(2-((*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl)phenylimino)-methyl)-4-nitrophenol 3bb. Orange solid, yield 96%; m.p. 145–146 °C. $[\alpha]_D^{25} = +24.6$ ($c = 1.17$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 14.06$ (br s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.25 (d, $J = 9.0$ Hz, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.40–7.19 (m, 6H), 7.06 (d, $J = 9.0$ Hz, 1H), 4.66 (dd, $J = 5.4$ Hz, $J = 6.9$ Hz, 1H), 4.35 (t, $J = 9.0$ Hz, 1H), 4.14 (t, $J = 7.8$ Hz, 1H), 3.29 (dd, $J = 4.5$ Hz, $J = 13.8$ Hz, 1H), 2.77 (dd, $J = 9.0$ Hz, $J = 13.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.4$, 162.4, 159.88, 159.86, 146.4, 139.7, 137.8, 132.2, 130.8, 129.2, 128.5, 127.4, 126.5, 122.4, 118.7, 118.63, 118.60, 118.1, 71.3, 68.1, 41.5; IR (KBr): ν 3462, 1631, 1490, 1339, 1292, 1094, 834, 751, 700 cm^{-1}; HR-ESIMS: m/z calcd for $C_{23}H_{20}N_3O_4$ (M+H): 402.14091. Found: 402.14483.

2-((1*E*)-(2-((*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)phenylimino)methyl)-4-nitrophenol 3cb. Orange solid, yield 82%; m.p. 123–124 °C. $[\alpha]_D^{25} = +31.3$ ($c = 1.29$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 14.00$ (br s, 1H), 8.64 (s, 1H), 8.37 (d, $J = 2.1$ Hz, 1H), 8.23 (dd, $J = 2.1$ Hz, $J = 9.0$ Hz, 1H), 7.95 (d, $J = 7.8$ Hz, 1H), 7.54 (t, $J = 7.8$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 1H), 7.26 (d, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 9.0$ Hz, 1H), 4.46–4.37 (m, 1H), 4.21–4.11 (m, 1H), 1.94–1.87 (m, 1H), 1.01 (d, $J = 6.6$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.5$, 161.9, 160.1, 146.3, 139.6, 132.0, 130.8, 129.5, 128.5, 128.3, 127.3, 122.6, 118.5, 118.2, 73.0, 69.6, 32.6, 18.9, 17.9; IR (KBr): ν 3466, 2960, 1637, 1511, 1339, 1292, 1092, 1056, 835, 751 cm^{-1}; HR-ESIMS: m/z calcd for $C_{19}H_{20}N_3O_4$ (M+H): 354.14091. Found: 354.14483.

2-((1*E*)-(2-((*S*)-4-*tert*-Butyl-4,5-dihydrooxazol-2-yl)phenylimino)methyl)-4-nitrophenol 3db. Orange solid, yield 80%; m.p. 142–143 °C. $[\alpha]_D^{25} = +36.2$ ($c = 2.82$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 14.05$ (br s, 1H), 8.62 (s, 1H), 8.36 (s, 1H), 8.23 (d, $J = 9.0$ Hz, 1H), 7.95 (d, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 1H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 9.3$ Hz, 1H), 4.35 (t, $J = 9.0$ Hz, 1H), 4.22 (t, $J = 8.4$ Hz, 1H), 4.09 (t, $J = 9.0$ Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.6$, 161.9, 160.3, 146.3, 139.6, 131.9, 130.8, 130.4, 128.5, 128.3, 127.3, 122.7, 118.5, 118.4, 68.3, 33.8, 25.82, 25.78; IR (KBr): ν 3462, 2951, 1622, 1577, 1520, 1475, 1340, 1292, 1096, 1051, 823, 751 cm^{-1}; HR-ESIMS: m/z calcd for $C_{20}H_{22}N_3O_4$ (M+H): 368.15656. Found: 368.16048.

General procedure for asymmetric Henry reaction using pure oxazoline-Schiff base ligand 3 and Cu(OAc)$_2$

The mixture of oxazoline-Schiff base pure ligand **3** (0.05 mmol) and anhydrous $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) were stirred for 30 min in EtOH or Et_2O. 4-Nitrobenzaldehyde **5a** (76 mg, 0.5 mmol) and nitromethane **6** (5.0 mmol, 0.26 mL) were added and the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated and purified by silica gel column chromatography using petroleum ether–ethyl acetate 5 : 1 as eluent.

General procedure for asymmetric Henry reaction catalyzed by *in situ* three-component generated complex catalyst

A solution of 2-(2-aminophenyl)oxazoline **1d** (10.9 mg, 0.05 mmol), 5-nitrosalicylaldehyde **2b** (8.4 mg, 0.05 mmol), and diethyl ether (2 mL) was stirred for 30 min at room temperature. Anhydrous $Cu(OAc)_2$ (9.1 mg, 0.05 mmol) was added and stirred for another 30 min, and the reaction mixture turned dark green. Aldehyde **5** (0.5 mmol) and nitromethane **6** (5.0 mmol, 0.26 mL)

were added and stirred for 24–96 h at room temperature. The reaction mixture was concentrated and purified by silica gel column chromatography using petroleum ether–ethyl acetate 5 : 1 as eluent.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (Grant No.20772006), the Development Program for Distinguished Young and Middle-aged Teachers of Beijing Institute of Technology and the Program for New Century Excellent Talents in University (NCET-07-0011) for financial support.

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