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Asymmetric Henry Reaction Catalyzed by C_2-Symmetric Tridentate Bis(oxazoline) and Bis(thiazoline) Complexes: Metal-Controlled Reversal of Enantioselectivity

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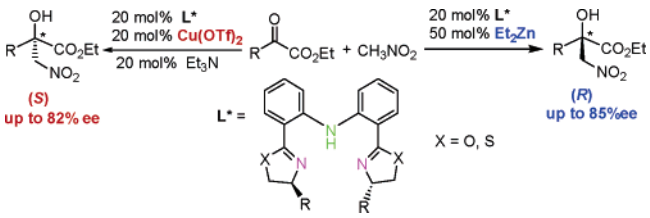

C_2-symmetric tridentate bis(oxazoline) and bis(thiazoline) ligands with a diphenylamine backbone have been investigated in the catalytic asymmetric Henry reaction of α-keto esters with different Lewis acids. Their $Cu(OTf)_2$ complexes furnished *S* enantiomers, while Et_2Zn complexes afforded *R* enantiomers, both of them with higher enantioselectivities (up to 85% ee). Reversal of enantioselectivity in asymmetric Henry reactions was achieved with the same chiral ligand by changing the Lewis acid center from Cu(II) to Zn(II). The results show that the NH group in C_2-symmetric tridentate chiral ligands plays a very important role in controlling both the yields and enantiofacial selectivity of the Henry products.

The Henry or nitroaldol reaction, a coupling reaction between a nitroalkane and a carbonyl compound, forms a new carbon−carbon bond and generates a β-nitro alcohol, which can further be converted to various valuable structural motifs.[1] Catalytic asymmetric Henry reactions have gained particular attention and made much progress in recent years.[2−8] Shibasaki and co-workers have reported[2] that rare-earth−lithium−BINOL complexes could be applied as catalysts for the enantioselective reaction of aldehydes with nitroalkanes. Jørgensen and co-workers reported[3] the catalytic asymmetric Henry reaction of α-keto esters with nitromethane in the presence of readily available chiral bis(oxazoline) catalysts. Trost et al. have recently disclosed a catalytic enantioselective Henry reaction employing a bimetallic zinc complex.[4] Recently, Reiser et al.[5a] and Lin[5b] have demonstrated that the Henry reaction could be promoted by diethylzinc in the presence of either diamines or amino alcohols. Evans' group has successfully developed the asymmetric Henry reaction of aldehydes using bis(oxazoline)−copper acetate complexes.[6]

Although some privileged chiral catalysts have been synthesized, the structural features accounting for their superior performance have not been elucidated.[9] Because of their ready accessibility, modular nature and proven success in various catalytic asymmetric reactions, C_2-symmetric chiral bis(oxazoline) ligands have gained much attention of chemists to their designing and applications in recent years.[10] Our group has paid continuing attention to the synthesis and application of the bis(oxazoline) and bis(thiazoline) ligands.[11] During the development of asymmetric synthetic methodology, the challenge of preparing both enantiomers must be met. Reversal of

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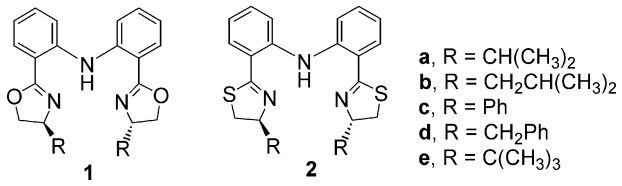
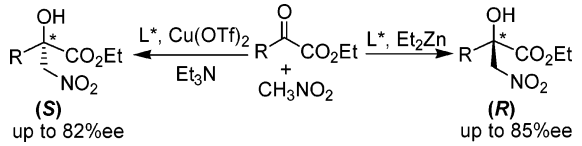


FIGURE 1.

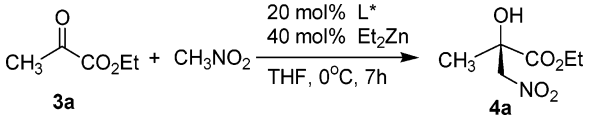
SCHEME 1



enantioselectivity is most obviously achieved through the use of enantiomeric ligands. However, the chiral ligand is not always readily or economically available in both antipodes. For example, sparteine is a ligand available in only one enantiomer. In such cases there is motivation to devise means of reversing stereochemical outcomes with the single enantiomeric ligand available.[12] One appealing way to reverse enantioselectivity would involve use of different Lewis acids.[13,14] Herein, we further investigate C_2-symmetric tridentate chiral bis(oxazoline) ligands **1** and corresponding bis(thiazoline) ligands **2** (Figure 1) in the enantioselective catalytic Henry reaction.[11a,15] Reversal of enantioselectivity with the same chiral ligand was achieved by changing the Lewis acid center from Cu(II) to Zn(II) (Scheme 1).

In our previous paper,[11a] we reported that $Cu(OTf)_2$−**1** and $Cu(OTf)_2$−**2** complexes can catalyze the Henry reaction of α-keto esters with nitromethane. We found that the configuration of the major enantiomer of the Henry product is *S* when $Cu(OTf)_2$−**1** was used as a catalyst (up to 82%ee), while it changed to *R* configuration with $Zn(OTf)_2$−**1**.[11a] However, the enantioselectivity of $Zn(OTf)_2$−bis(oxazoline)-catalyzed Henry product is only 16% ee, which is not enough for us to draw a decisive conclusion that *different Lewis acids cause reversal of enantioselectivity with the same chiral ligand*.

TABLE 1. Asymmetric Henry Reaction Catalyzed by Complexes of Et_2Zn−1 and Et_2Zn−2[a]



entry	ligand	yield[b] (%)	ee[c] (%)	config[d]
1	**1a**	80	77	*R*
2	**1b**	49	73	*R*
3	**1c**	73	47	*R*
4	**1d**	76	79	*R*
5	**1e**	62	57	*R*
6	**2a**	56	38	*R*
7	**2b**	38	56	*R*
8	**2c**	25	6	*R*
9	**2d**	44	68	*R*
10	**2e**	68	2	*R*

[a] Reaction conditions: ethyl pyruvate **3a** (0.25 mmol) with nitromethane (10 mmol) in 2 mL of THF. [b] Isolated yield by column chromatography. [c] Determined by HPLC on an OB column (hexane/2-propanol 90:10, 1.0 mL/min). [d] The absolute configuration of the products was assigned by comparison with the literature values.[3b]

TABLE 2. Effect of Ligand 1d and Et_2Zn Loading on the Asymmetric Henry Reaction[a]

entry	**1d** (%)	Et_2Zn (%)	yield[b] (%)	ee[c] (%)
1	20	20	81	73
2	20	30	78	72
3	20	40	76	79
4	20	50	79	83
5	20	60	76	82
6	10	25	64	74
7	5	13	27	56

[a] The reaction was performed with ethyl pyruvate (0.25 mmol) **3a** and nitromethane (10 mmol) in 2 mL of THF. [b] Isolated yield by column chromatography. [c] Determined by HPLC on an OB column (hexane/2-propane 90:10, 1.0 mL/min.).

To further explore this phenomenon, we used Et_2Zn−**1** and Et_2Zn−**2** complexes to catalyze the Henry reaction (Table 1). To our delight, enhancements of both the yields and enantioselectivities were observed (Table 1, entries 1 and 4). At the same time, the absolute configuration of the major enantiomer is *R* (Table 1, entries 1−10). This result demonstrates that reversal of enantioselectivity can be achieved with the same chiral ligand by changing the metal from Cu(II) to Zn(II). C_2-symmetric bis(thiazoline) ligands **2** combined with Et_2Zn also give the same sense and degree of enantioselectivitiy.[11a]

Since Et_2Zn−**1d** gave the highest enantioselectivity, we chose it as the catalyst to further optimize the reaction conditions. First, the effect of ratio of Et_2Zn to ligand **1d** was investigated. The reaction of **3a** with nitromethane in the presence of 20 mol % of **1d** and 20 mol % of Et_2Zn as the catalyst in THF gave 81% yield with 73% ee. With the increase of the ratio of Et_2Zn to ligand **1d**, the yield of Henry product is relatively constant (Table 2, entries 1−5), while the enantioselectivity reaches the highest at a ratio of 2.5 (Table 2, entry 4) and the enantioselectivity is maintained at higher ratios (Table 2, entry 5). We supposed that some Et_2Zn was consumed in the operation conditions and the ratio of Et_2Zn to ligand **1d** should be kept at 2.5 to guarantee the best enantioselectivity. We also tried to reduce the catalyst loading. However,

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TABLE 3. Effects of Solvents on the Asymmetric Henry Reaction[a]

entry	solvent	T (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	CH_3CN	0	7	21	33
2	Et_2O	0	7	52	61
3	THF	0	7	64	74
4	CH_3NO_2	0	7	60	67
5	CH_2Cl_2	0	7	63	67
6	$ClCH_2Cl_2Cl$	0	7	65	66
7	toluene	0	7	26	41
8	hexane	0	7	83	77
9	hexane	30	7	81	61
10	hexane	-20	7	59	65
11	hexane[d]	0	24	97	84

[a] The reaction was performed with ethyl pyruvate **3a** (0.25 mmol), nitromethane (10 mmol), 10 mol % of **1d**, and 25 mol % of Et_2Zn in 2 mL of solvent. [b] Isolated yield by column chromatography. [c] Determined by HPLC on an OB column (hexane/2-propane 90:10, 1.0 mL/min.). [d] Using 20 mol % of **1d** and 50 mol % of Et_2Zn.

poorer yield and enantioselectivity were obtained, especially when the loading was below 10 mol % (entries 6 and 7).

Subsequently, we found that solvent played a significant effect on both the yields and enantioselectivity of the Henry products (Table 3). Under 10 mol % catalyst loading, various solvents were examined. The results clearly demonstrate the superiority of hexane as a solvent in terms of yield and enantioselectivity (Table 3, entry 8). The enantioselectivity decreased above or below the optimized temperature (0 °C) (Table 3, entries 9 and 10). An increase of the catalyst loading from 10 to 20 mol % in hexane gave a significant increase in conversion and enantioselectivity (Table 3, entry 11). We have also tried different sequences of the addition of reactants and additives (such as β-amino alcohols and naphthols), but no better result was obtained.

With the optimized reaction conditions in hand (20 mol % ligand **1d**; 50 mol % Et_2Zn; in hexane, 0 °C, 24 h), we then examined the Henry reaction of other α-keto esters (Table 4). It was found that the strong electron-withdrawing group CF_3 reduces the yield and enantioselectivity significantly (Table 4, entry 2). When the phenyl group is adjacent to the carbonyl group of the α-keto ester, high yield but low ee were observed (Table 4, entry 3). The results showed that unbranched alkyl groups afforded high yields and good enantioselectivities (Table 4, entries 1 and 4−8) at the same time. Both the electronic and steric effects play important roles in the yield and enantioselectivity in the reaction.

To determine if the ligand had any role in improving the efficiency of catalysis, we performed the reaction in the absence of **1d**. The yield of the reaction of **3a** with nitromethane declined to 58% in the absence of ligand **1d**. This result suggests that the ligand may improve catalyst stability or turnover frequency. The coordination of N atoms in the oxazoline rings to zinc(II) may increase the polarity of the alkyl−Zn bond to great extent, and the result is the enhancement of the donor property of the alkyl group and the acceptor character of the Zinc atom.[17]

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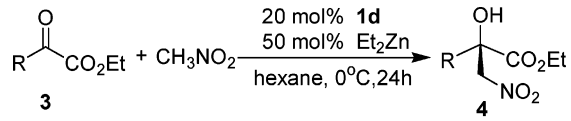
TABLE 4. Enantioselective Henry Reaction of α-Keto Esters 3a−h with Nitromethane Catalyzed by Et_2Zn−1d[a]

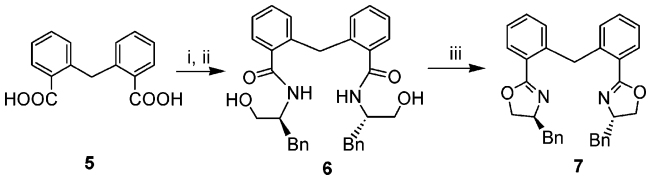


a: R = Me **e**: R = Et
b: R = CF_3 **f**: R = Bu
c: R = Ph **g**: R = *i*-Bu
d: R = $(CH_2)_2Ph$ **h**: R = Octyl

entry	R (α-keto ester)	product	yield[b] (%)	ee[c] (%)
1	Me (**3a**)	**4a**	97	84
2	CF_3 (**3b**)	**4b**	36	13
3	Ph (**3c**)	**4c**	96	16
4	$Ph(CH_2)_2$ (**3d**)	**4d**	95	71
5	Et (**3e**)	**4e**	70	85
6	Bu (**3f**)	**4f**	92	82
7	*i*-Bu (**3g**)	**4g**	88	65
8	Octyl (**3h**)	**4h**	85	80

[a] Reaction was performed with α-keto esters **3** (0.25 mmol) and nitromethane (10 mmol) in 2 mL of hexane. [b] Isolated yield by column chromatography. [c] Determined by HPLC.[16]

SCHEME 2[a]



[a] Reagents and conditions: (i) $SOCl_2$, DMF, reflux 4 h; (ii) L-phenylalaninol, DCM, Et_3N, rt, 12 h; (iii) TsCl, Et_3N, DMAP, DCM, reflux 12 h.

To determine the function of the NH group in the ligands **1** and **2**, a new C_2-symmetric bis(oxazoline) ligand **7**, in which the NH group was replaced by methylene group, was designed and synthesized from the corresponding dicarboxylic acid **5** via intermediate **6** (Scheme 2).[16] When ligand **7** was used instead of ligand **1d** to carry out the asymmetric Henry reaction of **3a** under the optimized conditions in Table 4, **4a** was obtained in 83% yield with only 4% ee. However, when ligand **7** was used to perform $Cu(OTf)_2$-catalyzed asymmetric Henry reaction of **3a** as in Scheme 1, the corresponding reaction gave the product in 39% yield with 35% ee, while the configuration of the major enantiomer is R consistent with the known facts of bidentate C_2-symmetic bi(oxazoline)−$Cu(OTf)_2$-catalyzed Henry reaction reported by Jørgensen.[3b]

Jørgensen et al. have proposed a mechanism to elucidate the enantioselectivity in which both the α-keto ester and nitronate coordinate to the copper to form an intermediate **A** (Figure 2). For our case, in this paper, we assumed an intermediate **B** for the Cu(II)−ligand complex catalyzed Henry reaction. The NH group between two phenyl groups cannot be deprotonated by Et_3N. Thus, the NH is available to act as a hydrogen bond donor to orient the nitronate. The other two nitrogen atoms from oxazoline rings can coordinate to Cu(II), and the α-keto ester also chelates Cu(II) as suggested by Jørgensen et al. in their intermediate **A**.[3b] In this case, the α-keto ester is activated by Lewis acid and nitronate

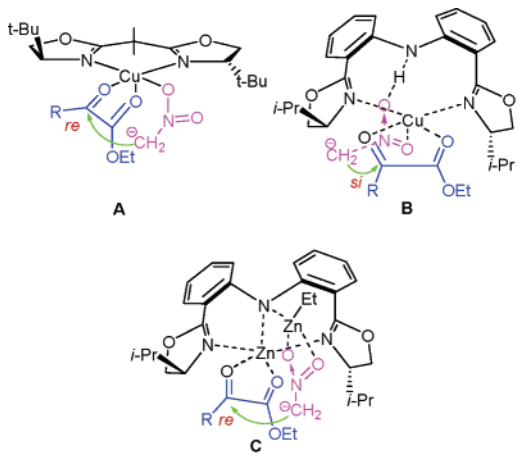


FIGURE 2.

is oriented by hydrogen bond. The *S* enantiomer is preferred by a nucleophilic attack of nitronate on the α-keto ester from the *si*-face under the chiral environment formed by C_2-symmetric tridentate chiral ligand and the copper atom.

In our previous work, the $Zn(OTf)_2$−ligand complex had been observed to give the major enantiomer opposite to that obtained by the Cu(II)−ligand complex.[11a] However, in that case the ee value was too poor to merit explanation. However in this work, for Et_2Zn−ligand complex catalyzed asymmetric Henry reaction, good ee values were achieved. With the same (*S*,*S*)-bis(oxazoline) or (*S*,*S*)-bis(thiazoline) ligands, the absolute configuration of the Henry adduct is *R* which means that the chiral carbon atom forms in the way that nitromethane attacks from the *re*-face of the α-keto functionality of the α-keto ester. We presumed an intermediate **C** in our Et_2Zn catalytic system. Diethylzinc causes the deprotonation of NH between two phenyl groups and leaves two electron pairs on the nitrogen atom. ^{1}H NMR of ligand **1d** with Et_2Zn (1:2) in $CDCl_3$ shows the disappearance of the signal of NH proton. The two imine nitrogen atoms of the oxazoline rings coordinate the same zinc atom with the diphenylamine anion nitrogen coordinating both zinc atoms simultaneously, utilizing both available electron pairs. Thus, a dinuclear Zn catalyst forms. One zinc atom is fixed by three nitrogen atoms and chelated by α-keto ester. Another zinc atom, which is coordinated by the nitrogen atom between phenyl groups and nitronate, has to be located above the *re*-face of the α-keto functionality. Then, α-keto ester is activated and nitronate is oriented by two zinc atoms, respectively. The Henry reaction proceeds by the nucleophilic attack of nitronate on the α-keto ester from the *re*-face under the chiral environment formed by C_2-symmetric tridentate chiral ligand and two zinc atoms.

In addition, the result of the asymmetric Henry reaction with ligand **7** also provides evidence for our hypothesis. Replacement of the NH group by a CH_2 group results in observation of the same phenomenon as that observed by Jørgensen. Ligand **7** with $Cu(OTf)_2$ preferentially affords the *R* enantiomer while ligand **7** with Et_2Zn affords poor enantioselectivity. The reversal of enantioselectivity proves that the potential ability of tridendate coordination and hydrogen donation of NH group in ligands **1** and **2** plays a crucial role in the enantioselective catalytic Henry reaction. The similar " NH effect" has been observed in the catalytic asymmetric transfer hydrogenation.[18]

In summary, we have expanded the application of C_2-symmetric tridentate bis(oxazoline) and bis(thiazoline) ligands containing a diphenylamine unit in the Lewis acid catalyzed asymmetric Henry reaction of α-keto esters with nitromethane. The Et_2Zn complex catalyzed Henry reaction proceeds in high yields and can give the optically active products in higher enantioselectivity (up to 85% ee) when unbranched alkyl groups are adjacent to the carbonyl group. The most important result is that with the same (*S*,*S*)-bis(oxazoline) or (*S*,*S*)-bis(thiazoline) ligands $Cu(OTf)_2$ complexes preferentially furnish the *S* enantiomer, while Et_2Zn complexes produce the *R* enantiomer. The reversal of enantioselectivity in the asymmetric Henry reaction can be achieved with the same chiral ligand by changing the Lewis acid center from Cu(II) to Zn(II), thus *killing two (enantiomeric) birds with one stone*. Furthermore, we have demonstrated that the NH group in C_2-symmetric tridentate chiral ligands **1** and **2** is crucial for the reversal enantioselectivity with different Lewis acids.

Experimental Section

General Procedure for the Catalytic Enantioselective Henry Reaction. To a mixture of ligand **1d** (24.4 mg, 0.05 mmol) and hexane (2 mL) at 0 °C was added Et_2Zn (125 μL, 0.125 mmol, 1.0 M in hexane) under nitrogen. The mixture was allowed to stir for 0.5 h, and α-keto ester **3** (0.25 mmol) was added followed by nitromethane (0.54 mL, 10 mmol). After being stirred for 24 h at 0 °C, the mixture was quenched by diluted HCl (2 mL, 1 mol/L) and then extracted with ether (5 mL × 2). Purification by column chromatography afforded the desired Henry product **4**. The ee was determined by HPLC on OB, OJ, or AS column.

2-Hydroxy-2-methyl-3-nitropropionic Acid Ethyl Ester (4a). Compound **4a** was prepared according to the general procedure using 29.1 mg (0.25 mmol) of α-keto ester **3a** and purified by column chromatography (25% AcOEt in petroleum ether) to yield 43.0 mg (97%) of **4a** as a pale yellow oil. The ee was determined by chiral HPLC on an OB column (hexane/2-propanol 90:10, 1.0 mL/min, t_{minor} = 12.0 min, t_{major} = 13.6 min). $[\alpha]^{20}_D$ = +15.5 (*c* = 0.26, CH_2Cl_2, 84% ee) [lit.[3b] $[\alpha]^{23}_D$ = +10.2 (*c* 1.19, CH_2Cl_2, 92% ee)]. ^{1}H NMR ($CDCl_3$): δ = 4.86 (d, *J* = 13.8 Hz, 1H), 4.58 (d, *J* = 13.8 Hz, 1H), 4.34 (m, 2H), 3.85 (s, 1H), 1.46 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ =173.4, 80.9, 72.4, 63.0, 23.8, 13.9.

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Supporting Information Available: Experimental procedures, copies of ^{1}H NMR and ^{13}C NMR spectra of **7**, and the HPLC spectra data for determining the enantiomeric purity of the Henry products. This material is available free of charge via the Internet at http://pubs.acs.org.

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