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Highly Enantioselective Henry (Nitroaldol) Reaction of Aldehydes and α-Ketoesters Catalyzed by *N*,*N*′-Dioxide-Copper(I) Complexes

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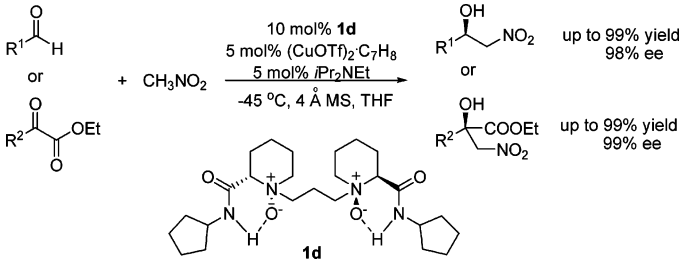
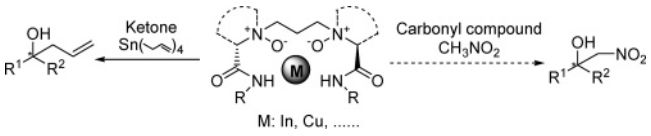


A new chiral *N*,*N*′-dioxide-Cu^{I} catalyst has been developed for the asymmetric Henry (nitroaldol) reaction. The approach benefited from the easy modification of the chiral space. As the highly effective *N*-oxide ligand, **1d** has been adopted for the Henry reaction with both aromatic and heteroaromatic aldehydes. The corresponding nitro-alcohol products were obtained in good yields with high enantiomeric excesses up to 98%. Moreover, α-ketoesters were also catalyzed by this catalyst to give attractive optically active α-hydroxy *β*-nitro esters containing chiral quaternary carbon centers (up to 99% ee). On the basis of a combination of several techniques including the ^{1}H NMR, ESI-HRMS, and MM2 calculations, the proposed mechanism was presented to explain the origin of reactivity and asymmetric inductivity.

Introduction

The discovery and development of novel chiral ligands are of significant importance in asymmetric catalysis.[1] *N*-oxides, known for their notable electron-donating property, have been applied in many reactions as organocatalysts.[2,3] In these reactions, the mechanism was mainly based on the activation of Si atom by *N*-oxide as Lewis base, which confined the application of *N*-oxide in asymmetric catalysis. On the other hand, there have been few attempts to employ *N*-oxides as chiral ligands to achieve high levels of efficiency in asymmetric reaction.[4] Therefore, it is still a *challenge* to develop the *N*-oxide as a ligand for the highly enantioselective reactions. In light of our recent success of enantioselective allylation and cyanation of carbonyl compound utilizing chiral *N*,*N*′-dioxides as ligands,[5] we investigated the asymmetric Henry (nitroaldol) reaction (Scheme 1).

SCHEME 1. Asymmetric Allylation and Henry Reaction Catalyzed by *N*,*N*′-Dioxide-Metal Complex



The Henry (nitroaldol) reaction has long been known as a powerful and efficient method for the construction of carbon−carbon bonds in organic chemistry.[6,7] It provided an efficient access to valuable functionalized structural motifs such as 1,2-amino alcohols and α-hydroxy carboxylic acid.[8] Since the first example was reported by Shibasaki and co-workers in 1992,[9] interests in the enantioselective Henry reactions had been triggered involving several chiral metal complexes[10] and chiral

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(1) For review of the chiral ligand design, see: (a) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561−3651. (b) Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674−7715. (c) Fonseca, M. H.; König, B. *Adv. Synth. Catal.* **2003**, *345*, 1173−1185.

(2) For review of chiral *N*-oxide, see: (a) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29−36. (b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373−1389.

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organocatalysts.[11,12] However, few examples have been made to employ an efficient catalytic system for both aldehydes and ketones in enantioselective Henry reactions.[13]

Herein, we wish to describe our efforts in the application of chiral *N*,*N*′-dioxide-copper(I) complex to the highly enantioselective Henry reaction with a broad range of substrates including aldehydes and α-ketoesters.

Results and Discussion

Our initial studies of catalytic asymmetric Henry reaction focused on the addition of nitromethane to benzaldehyde in the presence of the complex of chiral *N*,*N*′-dioxide **1a** as a ligand (Figure 1). Unfortunately, the *N*,*N*′-dioxide **1a**-$InBr_3$ complex could not catalyze the Henry reaction, unlike its efficiency in the enantioselective allylation of ketones (Table 1, entry 1).[5a] While using the catalysts with $Zn(OTf)_2$, $Cu(OTf)_2$, and $Ti(OiPr)_4$ as central metals, the corresponding product **4a** could not be obtained (Table 1, entries 2−3 and 6). Fortunately, **1a**-$Ni(OAc)_2 \cdot 4H_2O$ and **1a**-$(CuOTf)_2 \cdot C_7H_8$ complexes could catalyze the Henry reaction, and moderate enantioseletivity (45% ee) was obtained with $(CuOTf)_2 \cdot C_7H_8$ (Table 1, entries 4 and 5). After screening the steric and electronic effect of *N*,*N*′-dioxides, we found that the reactivity and enantioselectivities were closely dependent on both the chiral backbone and the R substituents of the amide moiety. The results showed that L-piperidinamide derivative **1d** was superior to L-proline-derived **1f** in both the yield and ee value (Table 1, entry 9 vs 11). Poor results were obtained using the bulkier 2,6-diisopropylphenyl (Table 1, entry 7). When the amide R was *tert*-butyl or (*S*)-

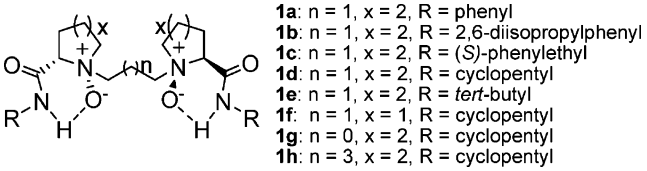
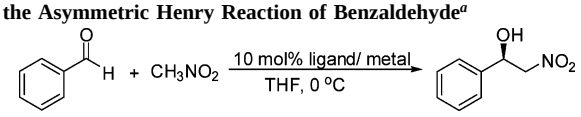


FIGURE 1. Chiral *N*,*N*′-dioxides as ligands for the asymmetric Henry reaction.

TABLE 1. Screening of Central Metals and *N*,*N*′-Dioxide Ligands in the Asymmetric Henry Reaction of Benzaldehyde[a]



2a **4a**

entry	ligand	metal	*t* (h)	yield (%)[b]	ee (%)[c]
1	**1a**	$InBr_3$	36	ND[d]	−
2	**1a**	$Zn(OTf)_2$	36	ND[d]	−
3	**1a**	$Cu(OTf)_2$	36	ND[d]	−
4[e]	**1a**	$(CuOTf)_2 \cdot C_7H_8$	12	77	45 (*R*)
5	**1a**	$Ni(OAc)_2 \cdot 4H_2O$	12	60	26 (*R*)
6	**1a**	$Ti(OiPr)_4$	36	ND[d]	−
7[e]	**1b**	$(CuOTf)_2 \cdot C_7H_8$	12	trace	0
8[e]	**1c**	$(CuOTf)_2 \cdot C_7H_8$	12	70	20 (*R*)
9[e]	**1d**	$(CuOTf)_2 \cdot C_7H_8$	12	97	80 (*R*)
10[e]	**1e**	$(CuOTf)_2 \cdot C_7H_8$	12	85	11 (*R*)
11[e]	**1f**	$(CuOTf)_2 \cdot C_7H_8$	12	88	7 (*S*)
12	**1g**	$(CuOTf)_2 \cdot C_7H_8$	12	77	20 (*S*)
13	**1h**	$(CuOTf)_2 \cdot C_7H_8$	12	46	16 (*S*)

[a] Reactions were carried out on a 0.1 mmol scale of benzaldehyde in the mixture of THF (0.5 mL) and nitromethane (20 equiv) at 0 °C. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC on a Chiral OD-H column. The absolute configurations were established by comparison of the sign of the optical rotation values with that in the literature.[10i] [d] Not detected. [e] Reactions were performed with $(CuOTf)_2 \cdot C_7H_8$ (5 mol %).

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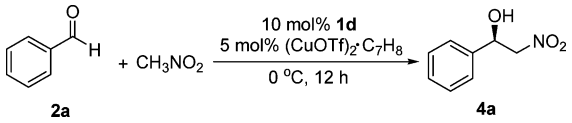
TABLE 2. Screening of the Solvents in the Asymmetric Henry Reaction of Benzaldehyde[a]



entry	solvent	yield (%)[b]	ee (%)[c]
1	THF	97	80
2	Et_2O	72	76
3	*t*-BuOMe	45	77
4	CH_2Cl_2	ND[d]	–
5	$ClCH_2CH_2Cl$	ND[d]	–
6	CH_3CN	58	71
7	toluene	67	72
8	DMF	ND[d]	–
9	methanol	ND[d]	–

[a] Reactions were carried out on a 0.1 mmol scale of benzaldehyde in the presence of $(CuOTf)_2 \cdot C_7H_8$ (5 mol %) and ligand **1d** (10 mol %) using nitromethane (20 equiv) in solvent (0.5 mL) at 0 °C for 12 h. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC on a Chiral OD-H column. The absolute configuration (*R*) was established by comparison of the sign of the optical rotation values with that in the literature.[10i] [d] Not detected.

TABLE 3. Screening of the Ratio of Ligand/Metal and Temperature in the Asymmetric Henry Reacion of Benzaldehyde[a]

entry	ligand **1d** (mol %)	Cu^I (mol %)	*T* (°C)	*t* (h)	yield (%)[b]	ee (%)[c]
1	20	10	−20	24	60	85
2	10	10	−20	24	80	90
3	10	20	−20	24	ND[d]	–
4	10	10	0	12	97	80
5	10	10	−45	36	ND[d]	–

[a] Reactions were carried out on a 0.1 mmol scale of benzaldehyde with nitromethane (20 equiv) in THF (0.5 mL). [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC on a Chiral OD-H column. The absolute configuration (*R*) was established by comparison of the sign of the optical rotation values with that in the literature.[10i] [d] Not detected.

phenylethyl moiety, the reaction gave the unexpectedly low enantioselectivities (Table 1, entries 8 and 10). The enantioselectivity could dramatically increase when the cyclopentyl moiety instead of phenyl moiety was used (Table 1, entry 9 vs 4). The linker length of three carbons was also essential for good enantioselectivity (Table 1, entry 9 vs 12 and 13).

Encouraged by the initial results in the asymmetric Henry reaction, various solvents were screened in the presence of 10 mol % catalyst (Table 2). While no products were obtained in halogenated solvents or polar solvents, such as CH_2Cl_2, $ClCH_2CH_2Cl$, DMF, or methanol (Table 2, entries 4−5, 8−9), CH_3CN and toluene gave moderate yields and ee values (Table 2, entries 6 and 7). Ethers were found to be superior to other solvents in terms of the enantioselectivity (Table 2, entries 1−3). THF exhibited the best performance (Table 2, entry 1).

When the ratio of ligand **1d** to copper(I) was 1:1, the results were superior to that of the ratio of 2:1 in better yield and enantioselectivity (Table 3, entry 2 vs 1). With the 1:2 ratio of ligand **1d** to copper(I), the reaction did not occur (Table 3, entry 3), which suggested that one molecule of *N,N′*-dioxide might combine with two molecules of copper(I) and the catalyst structure was changed, forming an inactive species. Then further optimization revealed that excellent enantioselectivity was obtained when the reaction temperature decreased from 0 °C to −20 °C, whereas the reaction hardly proceeded at −45 °C (Table 3, entries 4 and 5).

When the catalyst loading was only 5 mol % at −20 °C, the reactivity was decreased sharply (Table 4, entry 2). To increase the reactivity, some additives were screened in this reaction. As expected, the yields of nitroaldol products were improved dramatically when using the 3 Å or 4 Å molecular sieve (Table 4, entries 3 and 4), whereas the 5 Å molecular sieve had no effect on the reaction (Table 4, entry 5). However, some acidic additives, such as phenol and TsOH, were extremely harmful for the reaction (Table 4, entries 6 and 7). Furthermore, when decreasing the reaction temperature (−45 °C), the reaction could not be performed smoothly, even though the catalyst loading was increased to 10 mol % (Table 4, entries 8 and 9). Enlightened by the concept of dual acid/base catalysis,[14] we added some amines into the reaction system. Using 5 mol % iPr_2NEt, the enhanced reactivity was observed with maintaining the high enantioselectivity (Table 4, entry 10). When *N*-methylmorpholine as a weak base was added, the enantioselectivity was decreased with the low reactivity (Table 4, entry 11). In addition, Et_3N also increased the reaction rate (Table 4, entry 12). The results showed that the strong organic base could improve the reactivity.

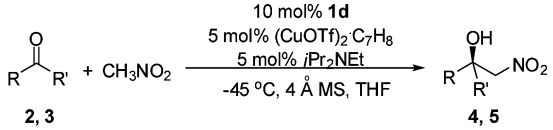
As shown in Table 5, the scope of the catalytic enantioselective Henry reaction was demonstrated by treatment of various aromatic aldehydes with nitromethane in the presence of 10 mol % *N,N′*-dioxide **1d**-CuOTf complex, 5 mol % iPr_2Net, and 200 mg/mmol 4 Å MS in THF. In all cases, the reactions were clean and proceeded in good yields with good to excellent enanti-

TABLE 4. Screening of Additive and Base in the Asymmetric Henry Reacion of Benzaldehyde[a]

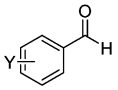
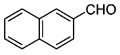
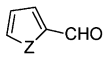
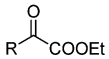
entry	additive	loading of additive	base	loading of base (mol %)	catalyst loading (mol %)	*T* (°C)	yield (%)[b]	ee (%)[c]
1	none	–	none	–	10	−20	97	90
2	none	–	none	–	5	−20	34	84
3	3 Å MS	20 mg	none	–	5	−20	97	90
4	4 Å MS	20 mg	none	–	5	−20	98	90
5	5 Å MS	20 mg	none	–	5	−20	43	89
6	phenol	10 mol %	none	–	5	−20	ND[d]	–
7	TsOH	10 mol %	none	–	5	−20	ND[d]	–
8	4 Å MS	20 mg	none	–	5	−45	ND[d]	–
9	4 Å MS	20 mg	none	–	10	−45	50	95
10	4 Å MS	20 mg	iPr_2NEt	5	10	−45	95	95
11	4 Å MS	20 mg	*N*-methylmorpholine	5	10	−45	trace	37
12	4 Å MS	20 mg	Et_3N	5	10	−45	95	93

[a] Reactions were carried out on a 0.1 mmol scale of benzaldehyde with nitromethane (20 equiv) in THF (0.5 mL). [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC on a Chiral OD-H column. The absolute configuration (*R*) was established by comparison of the sign of the optical rotation values with that in the literature.[10i] [d] Not detected.

TABLE 5. Substrate Scope of Catalytic Asymmetric Henry Reaction of Aldehydes and α-Ketoesters[a]



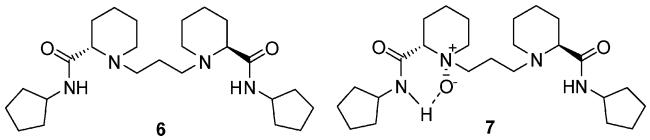
2, 3 4, 5

Entry	Substrate		*t* (h)	Yield[b] (%)	ee[c] (%)
1		**2a** Y = H	36	95	95 (*R*)
2		**2b** Y = 2-Me	36	60[d]	88 (*R*)
3		**2c** Y = 3-Me	36	87	93
4		**2d** Y = 4-Me	36	44[d]	91
5		**2e** Y = 3-MeO	36	99	95
6		**2f** Y = 3-PhO	36	99	93
7	**2a-k**	**2g** Y = 4-Ph	36	99	93 (*R*)
8		**2h** Y = 2-NO_2	24	81	73 (*R*)
9		**2i** Y = 3-NO_2	24	99	85
10		**2j** Y = 4-NO_2	12	99	85 (*R*)
11		**2k** Y = 4-Cl	36	99	86 (*R*)
12		**2l**	36	77[d]	93 (*R*)
13		**2m**	36	88	95
14		**2n** Z = O	24	99	98
15	**2n, 2o**	**2o** Z = S	36	80	95
16		**3a** R = Me	24	99	98
17	**3a, 3b**	**3b** R = *n*-Pr	24	79[d]	99

[a] Reactions were carried out on a 0.1 mmol scale of aldehyde with $(CuOTf)_2 \cdot C_7H_8$ (5 mol %), ligand **1d** (10 mol %), 20 mg 4 Å MS, and iPr_2NEt (5 mol %) with nitromethane (20 equiv) in THF (0.5 mL) at −45 °C. [b] Isolated yield. [c] Enantiomeric excesses were determined by HPLC. The absolute configurations of nitroaldol adducts were assigned by comparison with literature compounds.[10d,10h,10i,10p] [d] Relatively lower reactive rate than other entries while no side reaction was observed.

oselectivities. Aromatic aldehydes bearing the electron-donating groups required longer reaction times, but the reaction obtained higher enantioselectivities (91−95% ee, Table 5, entries 3−7). Aldehydes bearing the electron-withdrawing nitro groups typically furnished the nitroaldol products in 1 day or less (Table 5, entries 8−10). 4-Chlorobenzaldehyde could also react smoothly with good enantioselectivity (86% ee, Table 5, entry 11). On the other hand, **2b** and **2h** with the ortho substituent gave lower ee (88% ee and 73% ee, Table 5, entries 2 and 8), which was caused by larger sterehindrance of the ortho substituent in the catalyst. Even with the bulker aldehydes such as 1-naphthaldehyde and 2-naphthaldehyde, the reactivity and enantioselectivity were still maintained (93% ee and 95% ee, Table 5, entries 12 and 13). Noteworthily, the heteroaromatic aldehydes also reacted with nitromethane in the presence of 10 mol % **1d**-CuOTf complex to give the optically active nitroaldol adducts **4n** and **4o** in good yields with excellent enantioselectivities (98% ee and 95% ee, Table 5, entries 14 and 15).

To date, only a few catalyst systems had been identified to afford synthetically meaningful enantioselectivity for the addition of nitromethane to α-ketoesters.[13,15] On the other hand, such a reaction, in combination with the synthetic versatility of the ester and the nitro groups, will provide enantioselective access



6 7

FIGURE 2. Diamide **6** and single-side *N*-oxide **7**.

to a broad range of optically active tertiary carbinols. Encouraged by the results achieved with a variety of aldehydes under *N*,*N*′-dioxide-Cu[I] catalysis, some α-ketoesters were subjected to the asymmetric Henry reaction. Ethyl pyruvate **3a** and **3b** reacted respectively with nitromethane to give **5a** in 99% yield with 98% ee and **5b** in 79% yield with 99% ee (Table 5, entries 16 and 17). It should be noted that the product **5a** had been

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(15) (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222−2223. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875−4881. (c) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732−733. (e) Mandal, T.; Samanta, S.; Zhao, C. G. *Org. Lett.* **2007**, *9*, 943−945.

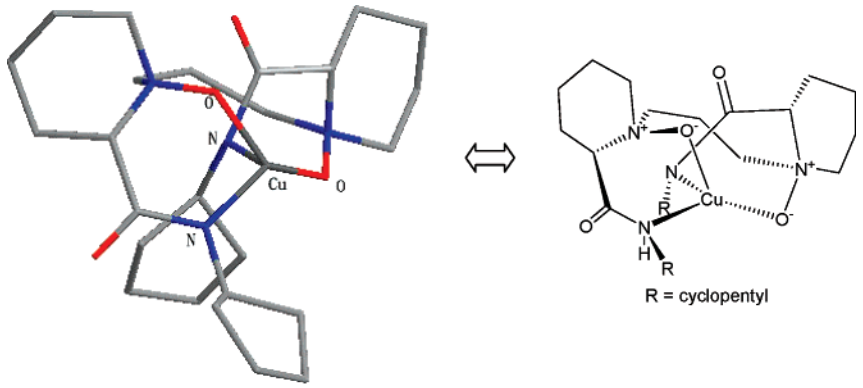

FIGURE 3. MM2 optimized geometry for *N,N′*-dioxide **1d**-Cu^{I} complex.

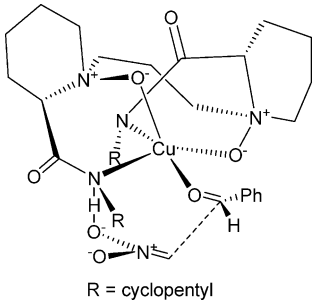

FIGURE 4. Proposed working model for the Henry reaction of aldehyde with nitromethane.

transformed to methylcusteine by Deng, which was the key intermediate in the total syntheses of mirabazoles and thiangazole.[15c]

To elucidate the mechanism of the *N,N′*-dioxide-Cu^{I}-catalyzed asymmetric Henry reaction, a combination of several techniques including the ESI-HRMS, ^{1}H NMR, and MM2 calculations was explored. The complex of *N,N′*-dioxide-Cu^{I} was directed by ESI-HRMS [calcd for $C_{25}H_{43}CuN_4O_4^+$: 526.2580; found: 526.2580], and poly-complex was not found. It was assumed that a monomeric Cu/**1d** = 1:1 complex without OTf moiety could be the active species for the Henry reaction.

^{1}H NMR spectroscopy of *N,N′*-dioxide **1d** was studied to get a preliminary insight into the function of NH moiety. The NH proton showed a strong deshielding effect at 10.91 ppm, which was assigned to strong intramolecular hydrogen bonding between *N*-oxide and the NH proton. However, when an equal equivalent of CuOTf was mixed with the ligand **1d**, the signal of NH proton disappeared. It showed that the hydrogen bond was broken entirely, which was caused by the coordination of *N,N′*-dioxide ligand **1d** with Cu^{I}.

To investigate the function of the *N,N′*-dioxide moiety, the diamide **6** and single-side *N*-oxide **7** were synthesized and explored in the Henry reaction (Figure 2). While using **6** or **7** as ligands, no product was observed under the same reaction conditions. The results suggested that only the **1d**-Cu^{I} complex could form the active catalyst due to the double *N*-oxide moieties.

On the basis of the studies of ESI-HRMS, ^{1}H NMR, and previous works,[16] we speculated that the *N,N′*-dioxide **1d** coordinated to the copper via the amide nitrogens and *N*-oxide oxygens. The catalyst model was investigated by the ChemBats3D program package. The geometries of the catalyst were optimized at the MM2 level (Figure 3). The MM2 calculation illustrated that the *N,N′*-dioxide **1d** coordinates as a tetrahedral N_2O_2 donor via the amide nitrogens and the *N*-oxide oxygens. A *N*-oxide oxygen, the amide nitrogens, and the copper are in a distorted plane (the N_2O plane), while another *N*-oxide oxygen is almost perpendicular to the N_2O plane.

According to our investigations and the previous reports,[10i,10j,10o,15b] a proposed working model for this Henry reaction was depicted in Figure 4. A complex that binded the reaction partners was presented. The benzaldehyde, the electrophile, for maximal activation, should be positioned in one of the Lewis acidic equatorial sites in the N_2O plane which accords with steric and electronic considerations,[10i] while the nitronate was positioned by the hydrogen bonding. In this transition state, the nitronate would attack the benazldehyde from the Si face, thus the corresponding nitro-alcohol was obtained with *R* configuration.

Conclusion

In summary, we have developed a new class of C_2-symmetric *N,N′*-dioxide-Cu^{I} catalyst for the asymmetric Henry reaction of both aldehydes and α-ketoesters in good yield with good to excellent enantioselectivities (up to 99% ee). The catalytic system could be tolerant of air and moisture. Further investigations into other versions of asymmetric catalysis are in progress.

Experimental Section

Typical Experimental Procedure. The mixture of ligand **1d** (4.7 mg, 0.01 mmol), $(CuOTf)_2{\cdot}C_7H_8$ (2.6 mg, 0.005 mmol), and 4 Å molecular sieves (20 mg) was stirred in THF (0.3 mL) at room temperature under air atmosphere for 10 min to form the catalyst, then nitromethane (240 μL) and *i*Pr$_2$NEt (25 uL, c = 0.2 mol/L in THF, 5 mol %) were added to the mixture. After the addition, the resulting mixture was cooled to −45 °C, benzaldehyde (10 μL, 0.1 mmol) in THF (0.2 mL) was added, and stirring continued for 36 h. The reaction mixture was directly purified by column chromatography on silica gel and eluted (ether:petroleum ether, 1:3)

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to afford the nitroaldol product **4a** (15.9 mg, 95% yield) as a colorless oil, Chiralcel OD-H hexane/*i*PrOH 85:15, 0.8 mL/min, *R*: t_R(major) = 11.55 min, *S*: t_R(minor) = 13.96 min; $[\alpha]_D^{25}$ = −43.5 (*c* = 0.40 in CH_2Cl_2, 95% ee); ^{1}H NMR (300 MHz, $CDCl_3$) 8.33−8.20 (m, 2H), 7.79−7.59 (m, 2H), 5.63−5.60 (m, 1H), 4.67−4.57 (m, 2H), 3.26 (d, *J* = 3.5 Hz, 1H) ppm. The absolute configurations of nitroaldol adducts (*R*) were assigned by comparison with literature compounds.[10d]

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Supporting Information Available: Experimental procedures and characterization of products for catalysts and racemates, ^{1}H NMR and ^{13}C NMR spectra, HRMS and HPLC conditions, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

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