CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000284

Efficient Synthesis of β-Hydroxy-α-Amino Acid Derivatives via Direct Catalytic Asymmetric Aldol Reaction of α-Isothiocyanato Imide with Aldehydes

Xiaohong Chen, Yin Zhu, Zhen Qiao, Mingsheng Xie, Lili Lin, Xiaohua Liu, and Xiaoming Feng*[a]

Abstract: An easily available and efficient chiral *N,N′*-dioxide–nickel(II) complex catalyst has been developed for the direct catalytic asymmetric aldol reaction of α-isothiocyanato imide with aldehydes which produces the products in morderate to high yields (up to 98%) with excellent diastereo- (up to >99:1 d.r.) and enantioselectivities (up to >99% *ee*). A variety of aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes were found to be suitable substrates in the presence of 2.5 mol% L-proline-derived *N,N′*-dioxide **L5**–nickel(II) complex. This process was air-tolerant and easily manipulated with available reagents. Based on experimental investigations, a possible transition state has been proposed to explain the origin of reactivity and asymmetric inductivity.

Keywords: aldol reaction · amino acids · asymmetric catalysis · nickel · nitrogen oxides

Introduction

Chiral β-hydroxy-α-amino acids are important structural motifs for the preparation of many bioactive compounds. Many biologically active natural products, such as vancomycin ristocetin, and biphenomycin A, contain β-hydroxy-α-amino acids within their structural frameworks.[1–3] A number of highly efficient catalytic enantioselective variants for the construction of these molecules have been established, although the majority of methods require the use of preformed enolate equivalents.[4–7] The direct catalytic enantioselective aldol reaction between a glycine equivalent and carbonyl compounds, involving the creation of a C–C bond and two stereogenic centers in a single operation, is one of the most attractive and atom-efficient methods to obtain such chiral building blocks, and intense effort has been devoted to this area. Willis and co-workers described the first highly enantioselective aldol reaction of aldehydes with α-isothiocyanato imide by using a chiral Mg^{II}–Pybox complex.[8b] Subsequently, an effective metal-free catalyst has been developed by the Seidel group by employing chiral thiourea.[8c] Quite recently, Shibasaki and co-workers achieved a breakthrough with Mg^{II}–Schiff base complexes in the direct asymmetric aldol reaction of α-isothiocyanato esters with ketones.[8d,9] Despite these outstanding contributions, the development of new, easily accessed, and efficient asymmetric catalytic systems is still in high demand.

Dicarbonyl compounds are promising candidates as substrates because they can chelate a series of metals, such as Fe^{II}, Co^{II}, and Ni^{II} complexes, and engage in two-point binding to the central metal, which allows a chelate-ordered transition state to occur.[10] Meanwhile, because nickel is a nonprecious metal, nickel complex catalysts have been widely applied to catalytic organic synthesis. For instance, nickel-catalyzed [4+4], [4+2], and [2+2+2] cycloadditions have received considerable attention.[11,12] Over the past decade, nickel-catalyzed reductive cyclizations and couplings have evolved into a broadly useful strategy for assembling synthetically versatile substructures and complex molecules.[13] Moreover, chiral nickel complexes are becoming potential practical catalysts in enantioselective transformations.[14] Also, as excellent chiral scaffolds, *N,N′*-dioxide–metal complexes have exhibited great potential in many asymmetric reactions.[15,16] Moreover, *N,N′*-dioxide–nickel(II) complexes have successfully been applied in asymmetric

[a] X. Chen, Y. Zhu, Z. Qiao, M. Xie, Dr. L. Lin, Dr. X. Liu, Prof. Dr. X. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064 (China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000284.

carbonyl–ene reactions and oxa–Michael additions.[17] Herein, we present an efficient chiral catalyst system based on an easily available *N*,*N*′-dioxide–nickel-(II) complex for the direct asymmetric aldol reaction of α-isothiocyanato imide with aldehydes. Excellent diastereo- (up to >99:1 d.r.) and enantioselectivities (up to >99% *ee*) were obtained for a broad range of substrates with 2.5 mol% catalyst loading under mild conditions.

Results and Discussion

Initially, *N*,*N*′-dioxide **L1** (Figure 1) was coordinated with various metal salts and used to catalyze the direct aldol reaction of α-isothiocyanato imide **1** with benzaldehyde **2a**

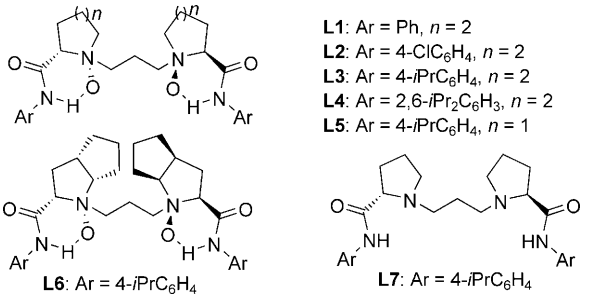
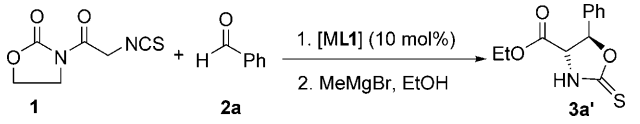


Figure 1. Ligands employed in this study.

(Table 1). Unfortunately, $Mg(ClO_4)_2$, which had been proved to be effective for this kind of reaction, did not work well (Table 1, entry 1),[8b] and racemic products were obtained with $[Cu(acac)_2]$ and $[Fe(acac)_2]$ as Lewis acids (Table 1, entries 2–3). However, $[Co(acac)_2]$ and $[Ni(acac)_2]$ showed good inductive potential in this reaction (Table 1, entries 4–5). The cheap and air-stable $[Ni(acac)_2]$ was especially attractive because 72% yield, 75:25 d.r., and 57% *ee* could be achieved. Furthermore, the counterion also affected the reactivity, diastereo-, and enantioselectivity greatly; strong acidic anions resulted in a poor outcome (Table 1, entries 6–9).

Table 1. Survey of central metals in the aldol reaction of α-isothiocyanato imide **1** with benzaldehyde **2a**.[a]

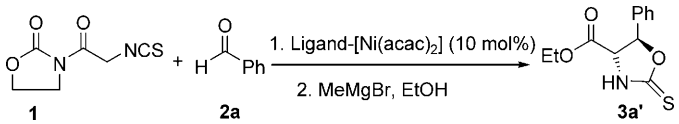


Entry	Metal	Yield[b] [%]	*trans*/*cis*[c]	*ee*[d] [%]
1	$Mg(ClO_4)_2$	n.r.[e]	–	–
2	$[Cu(acac)_2]$	56	45:55	0
3	$[Fe(acac)_2]$	78	60:40	0
4	$[Co(acac)_2]$	83	58:42	13
5	$[Ni(acac)_2]$	72	75:25	57
6	$[Ni(Tfacac)_2]\cdot 2H_2O$[f]	69	68:32	46
7	$Ni(ClO_4)_2\cdot 6H_2O$	trace	n.d.[g]	n.d.[g]
8	$NiBr_2$	48	48:52	0
9	$Ni(OTf)_2$	n.r.[e]	–	–

[a] Unless otherwise noted, all reactions were carried out by using **L1**/M (1:1; 10 mol%), **1** (0.1 mmol), **2a** (0.2 mmol), and 5 Å MS (40.0 mg) in THF (1.6 mL) at 0°C for 12 h. [b] Isolated yield of the combined diastereomers. [c] Determined by using chiral HPLC analysis. [d] *ee* of the *trans* isomer, measured by using chiral HPLC with a Chiracel IB column. [e] n.r. = no reaction. [f] Tfacac = 1,1,1-trifluoroacetylacetonate. [g] n.d. = not determined.

Subsequently, the effect of ligands **L2**–**L7** was examined (Figure 1). The studies on the effect of the amide moiety demonstrated that ligand **L3** with an electron-donating group at the *para* position of aniline could provide better results, with 82% yield, 82:18 d.r., and 77% *ee* (Table 2, entry 3 vs. entries 1 and 2). Ligand **L4** with a bulky isopropyl group led to a dramatic decrease in enantioselectivity (Table 2, entry 4). L-Proline derivative **L5** was superior to L-ramipril-derived **L6** and L-pipecolic-acid-derived **L3** in both reactivity, diastereoselectivity, and enantioselectivity (Table 2, entry 5 vs. entries 3 and 6). It is worth noting that when the amide **L7**, the precursor of *N*,*N*′-dioxide, was used as the ligand, a racemic product was obtained (Table 2, entry 7), which revealed that the *N*-oxide group was essential for the reaction. When the reaction was performed at −20°C, a slight increase in the enantioselectivity was observed, but the reactivity decreased. High temperatures were detrimental to asymmetric induction (Table 2, entries 8, 9). In addition, the configuration of product **3a′** was assigned by comparison of the optical rotation to the reported value of the corresponding enantiomer (4*S*,5*R*).[8b,18]

Table 2. Identification of the most efficient catalyst system and optimization of the reaction conditions.[a]

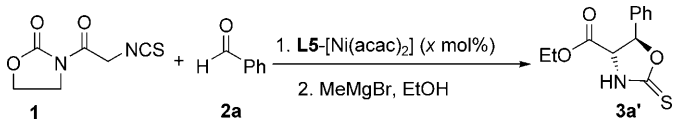


Entry	Ligand	*T* [°C]	Yield[b] [%]	*trans*/*cis*[c]	*ee*[d] [%]
1	**L1**	0	72	75:25	57
2	**L2**	0	67	68:32	45
3	**L3**	0	82	82:18	77
4	**L4**	0	36	58:42	8
5	**L5**	0	94	92:8	90
6	**L6**	0	90	88:12	35
7	**L7**	0	89	46:54	0
8[e]	**L5**	RT	94	80:20	75
9[f]	**L5**	−20	81	90:10	92

[a] Unless otherwise noted, all reactions were carried out by using **L**/[Ni(acac)$_2$] (10 mol%), **1** (0.1 mmol), **2a** (0.2 mmol) and 5 Å MS (40.0 mg) in THF (1.6 mL) at 0°C for 12 h. [b] Isolated yield of combined disastereomers. [c] Determined by chiral HPLC analysis. [d] The *ee* of the *trans* isomer was measured by using chiral HPLC with a Chiracel IB column. [e] The reaction time was 2 h. [f] The reaction time was 28 h.

Encouraged by the initial results in the asymmetric aldol reaction, various solvents were screened, and the results are listed in Table 3. Although CH_2Cl_2 gave a comparable reactivity for the reaction, it led to a dramatic loss of enantioselectivity (Table 3, entry 2 vs. 1). Toluene provided enantioselectivity equal to THF, but the diasteroselectivity was lower

Table 3. Screening of solvents in the aldol reaction of benzaldehyde.[a]



1 2a 3a'

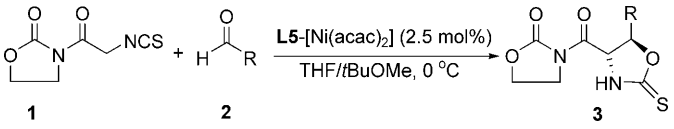
Entry	Solvent	x [mol%]	Yield[b] [%]	*trans*/*cis*[c]	*ee*[d] [%]
1	THF	10	94	92:8	90
2	CH_2Cl_2	10	97	88:12	80
3	$PhCH_3$	10	63	65:35	90
4	Et_2O	10	54	68:32	66
5	PhOMe	10	84	78:22	87
6	*t*BuOMe	10	80	96:4	95
7[e]	THF/*t*BuOMe	10	95	97:3	97
8[e]	THF/*t*BuOMe	5	95	97:3	96
9[e,f]	THF/*t*BuOMe	2.5	95	97:3	96
10[e,g]	THF/*t*BuOMe	1	95	97:3	96

[a] Unless otherwise noted, all reactions were carried out by using **L5**/[Ni(acac)$_2$] (10 mol%), **1** (0.1 mmol), **2a** (0.2 mmol) and 5 Å MS (40.0 mg) in solvent (1.6 mL) at 0°C for 12 h. [b] Isolated yield of combined diastereomers. [c] Determined by chiral HPLC analysis. [d] The *ee* value of the major diastereomer was measured by using chiral HPLC with a Chiracel IB column. [e] THF/*t*BuOMe = 1:1. [f] The reaction time was 24 h. [g] The reaction time was 40 h.

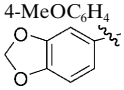
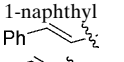
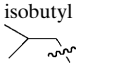
(Table 3, entry 3 vs. 1). Further solvent studies focusing on ethers revealed that *t*BuOMe provided the product with favorable diastereo- and enantioselectivity, but led to moderate reactivity (Table 3, entries 4–6). Fortunately, by using THF as a cosolvent, adduct **3a′** could be obtained with the best results (95% yield, 97:3 d.r., and 97% *ee*; Table 3, entry 7). Moreover, on decreasing the catalyst loading from 10 to 2.5 mol%, the results were maintained (Table 3, entries 8–9). The catalyst loading was further reduced to 1 mol%, which led to similar results with longer reaction time (Table 3, entry 10). Further screening of the reaction conditions identified that the best conditions were 2.5 mol% **L5**–[Ni(acac)$_2$] complex, 5 Å molecular sieves (MS; 40.0 mg), 0.1 mmol α-isothiocyanato imide **1**, and 0.2 mmol benzaldehyde **2a** in 1.6 mL THF/*t*BuOMe (1:1) at 0°C. Note that the process is air and moisture tolerant.

A wide range of aldehydes were examined under these optimal reaction conditions, and the corresponding products were obtained in high diastero- and enantioselectivities (Table 4). Benzaldehydes with different substituents on the aromatic ring were found to be suitable, affording the desired products in good to excellent results (Table 4, entries 1–21). Also, substrates with either electron-donating or -withdrawing substituents reacted smoothly with α-isothiocyanato imide to give moderate to high yields and excellent diastereo- and enantioselectivities. Moreover, α,β-unsaturated, heteroaromatic, and aliphatic aldehydes could also be converted to the corresponding adducts with good to excellent results (Table 4, entries 22–30). Other substrates, such as ketones, also were explored, but no adduct was detected.[19] In addition, when the reaction with **2d** was scaled up fivefold with 2.5 mol% nickel complex, excellent results with 98% yield, 97:3 d.r. and 95% *ee* were still obtained (Table 4, entry 31). The transformation of **3d** into amino acid **6d** was performed (Scheme 1). After oxidation of **4d** into **5d**, the oxazolidinethione moiety was converted into a protected oxazolidinone by using a reported procedure without any loss of enantioselectivity.[20] Significantly, **5d** can be easily transformed into chiral β-hydroxy-α-amino acid **6d**.

Table 4. Substrate scope for the catalytic asymmetric aldol reaction of aldehydes.[a]

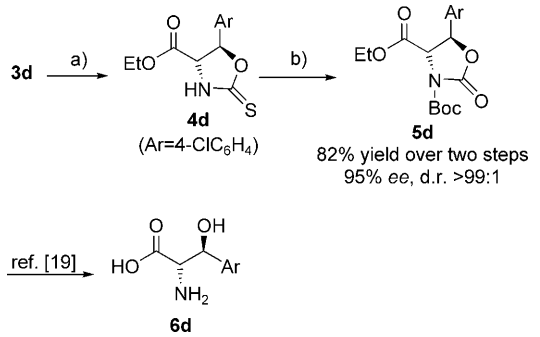


1 2 3

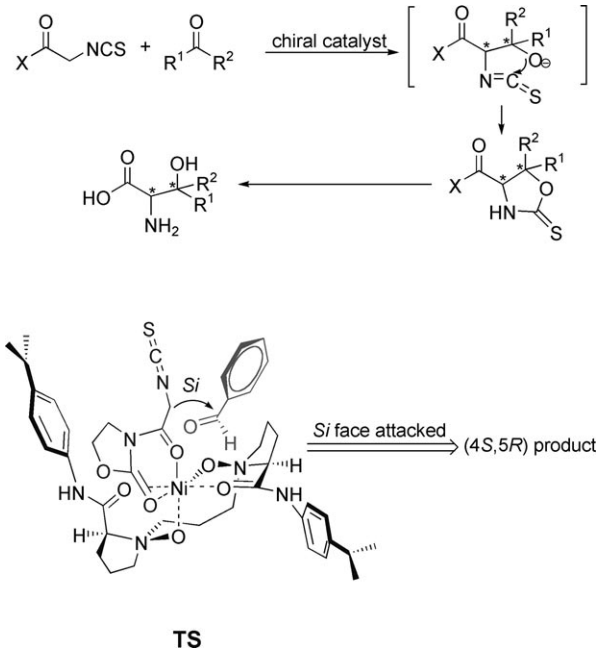
Entry	R	3	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	Ph	**3a**	92	97:3	96[e]
2	4-FC_6H_4	**3b**	95	97:3	96
3	4-BrC_6H_4	**3c**	98	97:3	95
4	4-ClC_6H_4	**3d**	98	96:4	93
5	4-MeC_6H_4	**3e**	90	97:3	97
6	4-PhC_6H_4	**3f**	96	>99:1	93
7	4-$CF_3C_6H_4$	**3g**	90	95:5	91
8	2-MeC_6H_4	**3h**	90	91:9	91
9	3,4-$Cl_2C_6H_3$	**3i**	92	92:8	90
10	3-BrC_6H_4	**3j**	97	93:7	>99
11	3-$CF_3C_6H_4$	**3k**	90	91:9	90
12	3-ClC_6H_4	**3l**	96	93:7	>99
13	3-MeC_6H_4	**3m**	90	>95:5	91
14	3-$MeOC_6H_4$	**3n**	87	>95:5	92
15	2-FC_6H_4	**3o**	84	85:15	90
16	2-$MeOC_6H_4$	**3p**	80	85:15	92
17	3-$PhOC_6H_4$	**3q**	95	>95:5	93[e]
18	4-$MeOC_6H_4$	**3r**	88	91:9	96[e]
19		**3s**	83	>95:5	97[e]
20	2-naphthyl	**3t**	90	94:6	95[e]
21	1-naphthyl	**3u**	86	93:7	93
22		**3v**	82	85:15	90
23		**3w**	80	85:15	92
24	3-furyl	**3x**	86	92:8	93
25	2-thienyl	**3y**	90	90:10	93
26	3-thienyl	**3z**	89	95:5	95
27	*n*-hexyl	**3aa**	77	92:8	82 (>99)[f]
28	cyclohexyl	**3bb**	68	85:15	81
29	isobutyl	**3cc**	72	90:10	80
30		**3dd**	70	90:10	83
31[g]	4-ClC_6H_4	**3d**	98	97:3	95

[a] Unless otherwise noted, all reactions were carried out with **L5**/[Ni(acac)$_2$] (2.5 mol%), **1** (0.2 mmol), **2** (0.4 mmol) and 5 Å MS (80.0 mg) in THF/*t*BuOMe (1/1) (3.2 mL) at 0°C for 16–48 h. [b] Isolated yield of combined diastereomers. [c] Entries 1–9: determined by chiral HPLC analysis; entries 10–30: determined by ^{1}H NMR spectroscopy. [d] The *ee* value of the major diastereomer. [e] The *ee* value of the major diastereomer was measured for the ethyl ester derivative. [f] Recrystallized from CH_2Cl_2/petroleum ether 56% yield. [g] The reaction was carried out on a 1.0 mmol scale.

To understand the reaction process, a possible pathway was assumed based on the literature (Scheme 2).[8d] We presumed that the reaction passed through the intermediate in which the inherent instability of the aldol adducts formed by using aldehyde **2a** was trapped by the isothiocyanato imide reagent. Also, some control experiments were performed to provide insight into the mechanism. As shown in Table 5, no



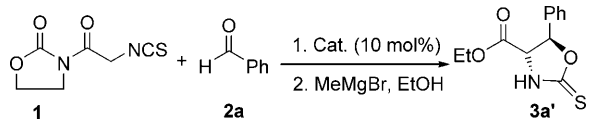
Scheme 1. Transformation of product **3d**. Reagents and conditions: a) MeMgBr, EtOH, 0 °C, 3 min; b) Boc_2O, cat. 4-dimethylaminopyridine, CH_2Cl_2, 0 °C, 30 min then H_2O_2, HCOOH, 0 °C, 30 min (Boc = *tert*-butyloxycarbonyl).



Scheme 2. Proposed reaction pathway and transition state for the catalytic asymmetric aldol reaction.

corresponding adduct **3a′** was obtained by using only [Ni(acac)$_2$] (Table 5, entry 1), which suggested that the *N*,*N*′-dioxide ligand was necessary for this reaction (Table 5, entry 4 vs. 1). [Ni(acac)$_2$] coordinated with the amide **L7** as the catalyst could catalyze the aldol reaction of aldehyde with 89% yield, but low diastereoselectivity and no enantiomeric excess were observed (Table 5, entry 3). This important piece of evidence demonstrates that *N*-oxide plays a key role in the asymmetric inductivity. Moreover, ligand **L4**, with a bulky isopropyl group at the *ortho*-position, led to a dramatic decrease in enantioselectivity (Table 2, entry 4). This showed that a large hindrance is deleterious for high catalytic efficiency. In addition, the structure of the **L4**–Ni(BF$_4$)$_2$·6H$_2$O complex was determined by using X-ray crystallography.[21] As shown by the crystallography data, both the carbonyl oxygen atoms and the *N*-oxide oxygen atoms

Table 5. Control experiments.[a]



Entry	Ligand [mol%]	[Ni(acac)$_2$] [mol%]	Yield[b] [%]	*trans*/*cis*[c]	*ee*[d] [%]
1	–	10	n.r.[e]	–	–
2	**L5**(10)	–	35	49:51	6
3	**L7**(10)	10	89	46:54	0
4[f]	–	10	92	55:45	0

[a] Unless otherwise noted, all reactions were carried out by using catalyst (10 mol%), **1** (0.1 mmol), **2a** (0.2 mmol) and 5 Å MS (40.0 mg) in THF/*t*BuOMe (1.6 mL) at 0 °C for 12 h. [b] Isolated yield of the combined diastereomers. [c] Determined by using chiral HPLC analysis. [d] The *ee* value of the major diastereomer, measured by using chiral HPLC with a Chiracel IB column. [e] n.r. = no reaction. [f] 10 mol% Et_3N was added.

are coordinated with nickel in the complex. On the basis of the experimental results and the crystallographic data for the catalyst, a possible transition state is proposed in Scheme 2. We speculate that *N*,*N*′-dioxide **L5** and α-isothiocyanato imide **1a** coordinate with [Ni(acac)$_2$] to form a complex, which would increase the acidity of α-hydrogen of the isothiocyanato acetyl imide and facilitate deprotonation. In transition state **TS**, the α-isothiocyanato imide is much more accessible to attack the *Si* face of the carbonyl of the aldehyde; in comparison, the *Re*-face attack is unfavorable due to the steric repulsion between the phenyl groups of aldehyde **2a** and the amide moiety of the ligand. The attack on the *Si* face leads to the formation of the major (4*S*,5*R*) product, which is in accordance with the experimental results.

Conclusion

We have developed an easily accessible and efficient direct catalytic asymmetric aldol reaction of α-isothiocyanato imide with aldehydes by using a chiral *N*,*N*′-dioxide–nickel(II) complex. This process provides a promising approach for the synthesis of chiral β-hydroxy-α-amino acid derivatives with broad substrate scope. In the presence of 2.5 mol% *N*,*N*′-dioxide–nickel(II) complex, excellent yields and good to excellent diastereo- (up to >99:1) and enantioselectivities (up to >99% *ee*) were achieved for most substrates under mild conditions. This pathway was air-tolerant and easily manipulated, and the reagents are readily available. On the basis of the experimental results, a possible favorable transition state has been proposed. Furthermore, the method has been successfully applied to the synthesis of a protected oxazolidinone derivative, which can be easily transformed into a chiral β-hydroxy-α-amino acid. Further investigations of the mechanism of this catalytic system are still in progress.

Experimental Section

General Materials and Methods: ^{1}H and ^{13}C NMR spectra were recorded on commercial instruments (^{1}H: 400 or 600 MHz; ^{13}C: 100 or 150 MHz). Chemical shifts are reported in ppm relative to tetramethylsilane with solvent peaks being used as an internal standard (^{1}H: $CDCl_3$, $\delta=7.26$ and [D$_6$]-DMSO, $\delta=3.37$; ^{13}C: $CDCl_3$, $\delta=77.0$ and [D$_6$]-DMSO, $\delta=40.45$). ^{13}C NMR spectra were recorded with complete proton decoupling. HRMS was recorded on commercial apparatus (ESI Source). Enantiomeric excesses and diastereoselectivities were determined by HPLC by using the corresponding commercial chiral columns stated in the experimental procedures. Unless otherwise indicated, all materials were obtained from commercial sources and used as purchased, except for the aldehydes, which were distilled before use. Solvents were dried and distilled prior to use according to the standard methods. α-Isothiocyanato imide **1**, a white solid, was prepared according to the reported procedure.[8b] Molecular sieves (5 Å) were purchased from Acros as a powder (<50 μm), activated at 200 °C for 2 h, and stored under nitrogen. Racemic samples of **3** were prepared with 20% 1,4-diazabicyclo[2.2.2]octane (DABCO) as the catalyst and THF as the solvent.

General procedure for direct catalytic enantioselective aldol reaction: A mixture of [Ni(acac)$_2$] (1.3 mg, 0.005 mmol), **L5** (2.7 mg, 0.005 mmol), α-isothiocyanato imide (372.4 mg, 0.2 mmol), and 5 Å MS (80 mg) in THF/*t*BuOMe (1:1, 3.2 mL) was stirred in an open vessel at ambient temperature for 30 min. The temperature was then reduced to 0 °C and stirred for 15 min. Benzaldehyde (40 μL, 0.4 mmol) was then added and the mixture was stirred for a further 24 h at 0 °C. The *trans* and *cis* mixture of products were isolated by using column chromatography on silica gel (CH_2Cl_2/EtOAc, 9:1). The residue was dissolved in dry THF (4.4 mL), and cooled to 0 °C. A solution of MeMgBr (3 M in Et_2O, 180 μL, 0.52 mmol) in EtOH (2.0 mL) at 0 °C was added. After 3 min, the reaction was quenched by the addition of aq phosphate buffer solution (3.0 mL, pH 7). The mixture was concentrated under reduced pressure, and the residue was dissolved in aq HCl (1 M, 1.5 mL) and CH_2Cl_2 (8 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The organic portions were combined, dried (Na_2SO_4), and concentrated. The residue was purified by using flash chromatography (SiO_2, CH_2Cl_2/EtOAc, 50:1) to give **3a′** as colorless crystals (92% isolated yield).

Typical procedure for the preparation of *N*,*N*′-dioxide ligands: 4-Methylmorpholine (0.48 mL, 4.4 mmol) and isobutyl carbonochloridate (520 μL, 4.0 mmol) were added to a solution of L-Boc-proline (861.0 mg, 4 mmol) in THF (20 mL) at 0 °C with stirring. After 5 min, 4-isopropylaniline (0.50 mL, 4 mmol) was added. The reaction was allowed to warm to RT and was monitored by TLC. After 3 h, the mixture was washed with aq $KHSO_4$ (1 M), sat. aq $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatograph (EtOAc/petroleum ether, 1:5) to afford a white solid. Trifluoroacetic acid (TFA; 4 mL) was added to a solution of the amide in CH_2Cl_2 (4 mL), and stirred until the reaction was finished (2 h). The solvent was evaporated and H_2O (10 mL) was added. The pH of the mixture was brought into the range of 10–12 by the addition of aq NaOH (1 M). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with brine, dried over anhyd Na_2SO_4, and evaporated in vacuo to give a residue that was directly used in the next step. K_2CO_3 (608 mg, 4.4 mmol) and 1,3-dibromopropane (204 μL, 2 mmol) were added to a solution of L-*N*-isopropylphenyl-2-carboxamide in CH_3CN (4 mL) with stirring, then heated at reflux and monitored by TLC. The K_2CO_3 was removed by filtration and washed by CH_2Cl_2. The filtrate was concentrated and purified by silica gel column chromatography (EtOAc/petroleum ether, 1:1) to give the desired product (1.522 g, 76% isolated yield). *N*,*N*′-dioxide **L5** was prepared by oxidation with *m*-chloroperoxybenzoic acid in CH_2Cl_2 (20 mL) at −20 °C for 30 min and purified by using chromatograph (EtOAc/MeOH). Finally, **L5** was obtained as a white foamy solid (1.236 g, 58% isolated yield). The synthesis and ^{1}H and ^{13}C NMR spectra for the other ligands can be found in the references.[16,17]

L-Proline-based *N*,*N*′-dioxide L5: White solid; m.p. = 112–114 °C; $[\alpha]_D^{15}=-94.0$ ($c=1.0$, in EtOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=13.16$ (s, 2H), 7.48–7.45 (t, 4H), 7.25–7.13 (t, 4H), 3.69–3.60 (m, 4H), 3.59–3.44(m, 4H), 3.43–3.25 (m, 2H), 2.83 (dd, $J=6.8$ Hz, 2H), 2.55–2.48 (m, 2H), 2.43–2.03 (m, 6H), 1.21–1.16 ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.01$, 144.98, 135.38, 126.85, 120.20, 120.09, 68.12, 64.69, 33.63, 27.59, 24.05, 20.03, 19.86 ppm; ESI-HRMS: *m*/*z* calcd for $C_{31}H_{44}N_4O_4$: 537.3435 $[M+H]^+$; found: 537.3455.

Acknowledgements

We thank the National Natural Science Foundation of China (nos. 20732003 and 20872097), PCSIRT (no. IRT0846) and National Basic Research Program of China (973 Program; no. 2010CB833300) for financial support. We also thank Sichuan University Analytical and Testing Center for NMR spectroscopic analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

[1] *Glycopeptide Antibiotics* (Ed.: R. Nagarajan), Marcel Dekker, New York, **1994**.

[2] a) K. Isono, K. Asahi, S. Suzuki, *J. Am. Chem. Soc.* **1969**, *91*, 7490; b) G. J. Sharman, D. H. Williams, D. F. Ewing, C. Ratledge, *Biochem. J.* **1995**, *305*, 187.

[3] a) R. Barclay, C. Ratledge, *J. Bacteriol.* **1983**, *153*, 1138; b) C. M. Harris, H. Kopecka, T. M. Harris, *J. Am. Chem. Soc.* **1983**, *105*, 6915; c) M. K. Renner, Y. C. Shen, X.-C. Cheng, P. R. Jensen, W. Frankmoelle, C. A. Kauffman, W. Fenical, E. Lobkovsky, J. Clardy, *J. Am. Chem. Soc.* **1999**, *121*, 11273.

[4] For reviews, see: a) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger, *Angew. Chem.* **1999**, *111*, 2230; *Angew. Chem. Int. Ed.* **1999**, *38*, 2096; b) C. Najera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584; c) *Modern Aldol Reactions* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**.

[5] For selected examples, see: a) D. L. Boger, M. A. Patane, J.-C. Zhou, *J. Am. Chem. Soc.* **1994**, *116*, 8544 for epoxide opening; b) I. H. Kim, K. L. Kirk, *Tetrahedron Lett.* **2001**, *42*, 8401 for aminohydroxylation; c) L. Dong, M. J. Miller, *J. Org. Chem.* **2002**, *67*, 4759 for dihydroxylation; d) C. Loncaric, W. D. Wulff, *Org. Lett.* **2001**, *3*, 3675 for azirdine opening; e) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Angew. Chem.* **2004**, *116*, 900; *Angew. Chem. Int. Ed.* **2004**, *43*, 882 for dynamic kinetic resolution; f) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 4724; *Angew. Chem. Int. Ed.* **2002**, *41*, 4542; and g) N. Yoshikawa, M. Shibasaki, *Tetrahedron* **2002**, *58*, 8289 for phase-transfer catalysis.

[6] For approaches that involve oxazoline intermediates, see: a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405; b) H. Suga, K. Ikai, T. Ibata, *J. Org. Chem.* **1999**, *64*, 7040; c) D. A. Evans, J. M. Janey, N. Magomedov, J. S. Tedrow, *Angew. Chem.* **2001**, *113*, 1936; *Angew. Chem. Int. Ed.* **2001**, *40*, 1884.

[7] For selected examples that involve an enolate or an enolate surrogate, see: a) H. Sugiyama, T. Shioiri, F. Yokokawa, *Tetrahedron Lett.* **2002**, *43*, 3489; b) J. B. MacMillan, T. F. Molinski, *Org. Lett.* **2002**, *4*, 1883; c) S. Caddick, N. J. Parr, M. C. Pritchard, *Tetrahedron* **2001**, *57*, 6615; d) M. Horikawa, J. Busch-Peterson, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843; e) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431; f) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 9192; g) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233; h) K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 5644; i) S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, *70*, 5235; j) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164.

[8] a) M. C. Willis, V. J.-D. Piccio, *Synlett* **2002**, 1625; b) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem.* **2005**, *117*, 1567; *Angew. Chem. Int. Ed.* **2005**, *44*, 1543; c) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248; d) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082.

[9] For the use of α-isothiocyanato imides in direct catalytic asymmetric Mannich-type reactions with aldimines, see: a) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632; b) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648; c) Z. G. Shi, P. Y. Yu, P. J. Chua, G. F. Zhong, *Adv. Synth. Catal.* **2009**, *351*, 2797.

[10] For selected examples of dicarbonyl compounds as chelating candidates, see: a) A. Mekonnen, R. Carlson, *Eur. J. Org. Chem.* **2006**, 2005; b) G. H. Spikes, E. Bill, T. Weyhermüller, K. Wieghardt, *Angew. Chem.* **2008**, *120*, 3015; *Angew. Chem. Int. Ed.* **2008**, *47*, 2973.

[11] a) G. Wilke, *Angew. Chem.* **1988**, *100*, 189; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 185; b) P. W. Jolly, *Comprehensive Organometallic Chemistry, Vol. 8* (Ed.: G. Wilkinson), Pergamon, Oxford, **1982**, p. 615; c) J. Montgomery in *Science of Synthesis (Houben–Weyl Methods of Molecular Transformations), Vol. 1* (Eds.: B. M. Trost, M. Lautens), Thieme, Stuttgart, **2001**, p. 11; d) R. Benn, B. Büssemeier, S. Holle, P. W. Jolly, R. Mynott, I. Tkatchenko, G. Wilke, *J. Organomet. Chem.* **1985**, *279*, 63; e) W. Keim, *Angew. Chem.* **1990**, *102*, 251; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 235; f) P. A. Wender, N. C. Ihle, *Tetrahedron Lett.* **1987**, *28*, 2451; g) P. A. Wender, M. L. Snapper, *Tetrahedron Lett.* **1987**, *28*, 2221; h) P. A. Wender, N. C. Ihle, C. R. D. Correia, *J. Am. Chem. Soc.* **1988**, *110*, 5904; i) P. A. Wender, M. J. Tebbe, *Synthesis* **1991**, 1089; j) P. A. Wender, J. M. Nuss, D. B. Smith, A. Suárez-Sobrino, J. Vågberg, D. Decosta, J. Bordner, *J. Org. Chem.* **1997**, *62*, 4908; k) P. A. Wender, N. C. Ihle, *J. Am. Chem. Soc.* **1986**, *108*, 4678.

[12] a) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432; b) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1995**, *60*, 2962; c) P. A. Wender, T. E. Jenkins, S. Suzuki, *J. Am. Chem. Soc.* **1995**, *117*, 1843; d) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1996**, *61*, 824; e) P. A. Wender, T. E. Smith, *Tetrahedron* **1998**, *54*, 1255; f) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; g) P. Bhatarah, E. H. Smith, *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163; h) Y. Sato, T. Nishimata, M. Mori, *J. Org. Chem.* **1994**, *59*, 6133; i) S. I. Ikeda, H. Watanabe, Y. Sato, *J. Org. Chem.* **1998**, *63*, 7026; j) M. Shanmugasundaram, M. S. Wu, M. Jeganmohan, C.-W. Huang, C.-H. Cheng, *J. Org. Chem.* **2002**, *67*, 7724; k) J. Louie, J. E. Gibby, M. V. Farnworth, T. N. Tekavec, *J. Am. Chem. Soc.* **2002**, *124*, 15188.

[13] For selected examples of catalysis by nickel complexes, see: a) J. Montgomery, *Angew. Chem.* **2004**, *116*, 3980; *Angew. Chem. Int. Ed.* **2004**, *43*, 3890; b) M. Chen, Y. Weng, M. Guo, H. Zhang, A. Lei, *Angew. Chem.* **2008**, *120*, 2311; *Angew. Chem. Int. Ed.* **2008**, *47*, 2279; c) R. D. Baxter, J. Montgomery, *J. Am. Chem. Soc.* **2008**, *130*, 9662.

[14] For selected examples, see: a) K. Itoh, S. Kanemasa, *J. Am. Chem. Soc.* **2002**, *124*, 13394; b) K. Itoh, M. Hasegawa, J. Tanaka, S. Kanemasa, *Org. Lett.* **2005**, *7*, 979; c) D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005**, *127*, 9958; d) D. A. Evans, R. J. Thomson, F. Franco, *J. Am. Chem. Soc.* **2005**, *127*, 10816; e) D. A. Evans, S. Mito, D. Seidel, *J. Am. Chem. Soc.* **2007**, *129*, 11583; f) H. Suga, A. Funyu, A. Kakehi, *Org. Lett.* **2007**, *9*, 97; g) J. Esquivias, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2007**, *129*, 1480; h) J. Shi, M. Zhao, Z. Lei, M. Shi, *J. Org. Chem.* **2008**, *73*, 305; i) C. Fischer, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 4594; j) Z. Chen, H. Morimoto, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 2170; k) K. Soai, T. Hayasaka, S. Ugajin, *J. Chem. Soc., Chem. Commun.* **1989**, 516; l) S. Kanemasa, Y. Oderaotoshi, E. Wada, *J. Am. Chem. Soc.* **1999**, *121*, 8675; m) Y. S. Kwak, E. J. Corey, *Org. Lett.* **2004**, *6*, 3385; n) A. D. Sadow, A. Togni, *J. Am. Chem. Soc.* **2005**, *127*, 17012; o) J. D. Sieber, J. P. Morken, *J. Am. Chem. Soc.* **2008**, *130*, 4978.

[15] For reviews on chiral *N*-oxides in asymmetric catalysis, see: a) G. Chelucci, G. Murineddu, G. A. Pinna, *Tetrahedron: Asymmetry* **2004**, *15*, 1373; b) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29; c) I. A. O'Neil, N. D. Miller, J. V. Barkley, C. M. Low, S. B. Kalindjian, *Synlett* **1995**, 617, and references therein.

[16] For examples of asymmetric catalytic reactions based on *N*,*N*′-dioxide, see: a) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem.* **2008**, *120*, 1328; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; b) D. J. Shang, J. G. Xin, Y. L. Liu, X. Zhou, X. H. Liu, X. M. Feng, *J. Org. Chem.* **2008**, *73*, 630; c) C. Tan, X. H. Liu, L. W. Wang, J. Wang, X. M. Feng, *Org. Lett.* **2008**, *10*, 5305; d) X. Yang, X. Zhou, L. L. Lin, L. Chang, X. H. Liu, X. M. Feng, *Angew. Chem.* **2008**, *120*, 7187; *Angew. Chem. Int. Ed.* **2008**, *47*, 7079; e) Y. L. Liu, D. J. Shang, X. Zhou, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 2055; f) S. K. Chen, Z. R. Hou, Y. Zhu, J. Wang, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 5884; g) D. H. Chen, Z. L. Chen, X. Xiao, Z. G. Yang, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2009**, *15*, 6807; h) M. Kokubo, C. Ogawa, S. Kobayashi, *Angew. Chem.* **2008**, *120*, 7015; *Angew. Chem. Int. Ed.* **2008**, *47*, 6909.

[17] a) K. Zheng, J. Shi, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2008**, *130*, 15770; b) L. J. Wang, X. H. Liu, Z. H. Dong, X. Fu, X. M. Feng, *Angew. Chem.* **2008**, *120*, 8798; *Angew. Chem. Int. Ed.* **2008**, *47*, 8670.

[18] Product **3a′**: (4*S*,5*R*)-ethyl 5-phenyl-2-thioxooxazolidine-4-carboxylate.

[19] No product was obtained when acetophenone was tested as a substrate by using this catalyst system.

[20] D. A. Evans, A. E. Weber, *J. Am. Chem. Soc.* **1987**, *109*, 7151. See also reference [8c].

[21] CCDC-739905 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: February 2, 2010
Revised: April 12, 2010
Published online: July 19, 2010

