CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000126

Highly Enantioselective Synthesis of 3-Amino-2-oxindole Derivatives: Catalytic Asymmetric α-Amination of 3-Substituted 2-Oxindoles with a Chiral Scandium Complex

Zhigang Yang, Zhen Wang, Sha Bai, Ke Shen, Donghui Chen, Xiaohua Liu, Lili Lin, and Xiaoming Feng*[a]

Abstract: A highly enantioselective α-amination of 3-substituted oxindoles with azodicarboxylates catalyzed by a chiral $Sc(OTf)_3$/*N*,*N*′-dioxide complex (Tf: triflate) has been developed and affords the corresponding 3-amino-2-oxindole derivatives in high yields (up to 98%) with excellent enantioselectivities (up to 99% *ee*). The procedure is capable of tolerating a relatively wide range of substrates, and excellent results (92–96% *ee*) can also be obtained, even in the presence of 0.5 mol% of catalyst loading under mild conditions. These results showed the potential value of the catalytic approach. Moreover, with high synthetic versatility, the product could be easily transformed into optically active 3-amino-3-methyloxindole bearing a chiral quaternary stereogenic center.

Keywords: amination · asymmetric catalysis · dioxides · oxindoles · scandium

Introduction

The asymmetric α-amination between carbonyl compounds and azodicarboxylates constitutes one of the most versatile synthetic methodologies for the construction of optically active α-amino carbonyl units, which are important building blocks for the conversion of many biologically active and therapeutic compounds.[1] Since the catalytic enantioselective electrophilic α-amination of carbonyl compounds with azodicarboxylates pioneered by Evans and Nelson,[2] a great effort has been devoted to the development of more selective and efficient catalytic systems for this kind of synthetically useful transformation,[3] such as chiral metal complexes,[4] chiral phase-transfer catalysts,[5] cinchona alkaloid derivatives,[6] chiral amine catalysts,[7] chiral thiourea catalysts,[8] and chiral guanidine catalysts.[9] Furthermore, the application of prochiral 3-substituted oxindoles as nucleophiles provides a very simple and straightforward approach for the synthesis of optically active 3-amino-2-oxindole derivatives with a chiral quaternary center, and studies in this field have received special attention because oxindoles bearing C3-quaternary structures are widely distributed in a number of natural products and pharmaceutical molecules.[10] Several catalytic asymmetric reactions of 3-substituted oxindoles, including the aldol reaction,[11] conjugate addition reaction,[12] Mannich reaction,[13] fluorination,[14] and other types of reaction,[15] have been successively reported. However, relatively fewer examples have been documented for catalytic asymmetric α-amination of oxindoles, which is very useful for the generation of quaternary 3-amino-2-oxindole alkaloid compounds. Only during the course of our study, Chen, Zhou, Barbas, and their respective co-workers independently described such a process with cinchona alkaloid analogues as promoters.[16] Moreover, Shibasaki, Matsunaga, and coworkers very recently developed a highly enantioselective version of this reaction by using Schiff base–nickel complexes as catalysts.[17] Despite these impressive contributions, the development of new and more efficient approaches for the enantioselective α-amination of 3-substituted oxindoles with azodicarboxylates is still challenging and in high demand.

As excellent chiral scaffolds, chiral *N*,*N*′-dioxide–metal complexes have exhibited excellent abilities for the activation of various substrates and have shown strong asymmetry-inducing capability for many reactions.[18,19] $Sc(OTf)_3$

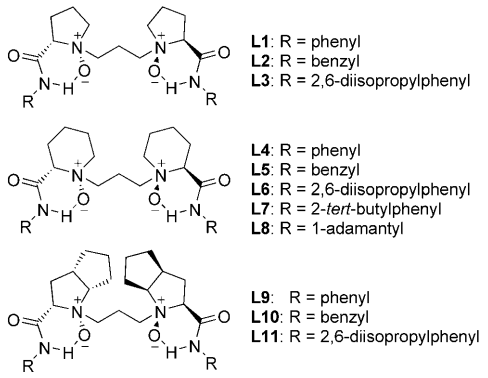
[a] Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, Dr. X. Liu, Dr. L. Lin, Prof. Dr. X. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064 (P.R. China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000126.

(Tf: triflate), which features advantages in stability, recovery, and reusability, has shown high catalytic activity in many transformations.[20] Herein, we would like to report our work on the efficient α-amination reaction of 3-substituted oxindoles and azodicarboxylates catalyzed by chiral *N,N′*-dioxide–scandium(III) complex systems. High yield and excellent enantioselectivity were obtained for a wide range of substrates in this reaction.

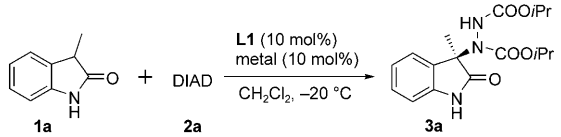
Results and Discussion

In the preliminary study, L-proline-based *N,N′*-dioxide **L1** (Scheme 1) was employed as an organocatalyst for the enantioselective α-amination of 3-methyloxindole (**1a**) and diisopropylazodicarboxylate (DIAD; **2a**) in CH_2Cl_2 at −20 °C. Unfortunately, the reaction gave the desired product **3a** in less than 5% yield with only 4% *ee* (Table 1, entry 1). **L1** was then complexed with various metal salts to catalyze the asymmetric α-amination. A significant effect of the central metal ion on the enantioselectivity was observed, as shown in Table 1. Products of low enantiomeric excess were obtained with $Y(OTf)_3$, $Yb(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, $La(OTf)_3$, or $In(OTf)_3$ as the Lewis acid (Table 1, entries 2–5, 7, and 8). Fortunately, the **L1**–$Sc(OTf)_3$ complex could catalyze the reaction to give adduct **3a** in 55% *ee* (Table 1, entry 6).



Scheme 1. Ligands employed for the α-amination reaction.

Table 1. Screening of central metal ions in the asymmetric α-amination of 3-methyloxindole (**1a**) and diisopropylazodicarboxylate (DIAD; **2a**).[a]



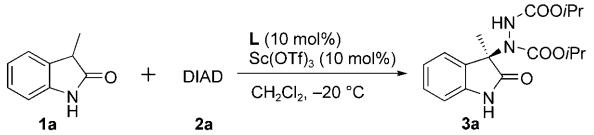
1a 2a 3a

Entry	Metal	Yield [%][b]	*ee* [%][c]
1	none	<5	4
2	$Y(OTf)_3$	5	9[d]
3	$Yb(OTf)_3$	<5	0
4	$Cu(OTf)_2$	trace	N.D.[e]
5	$Zn(OTf)_2$	6	6
6	$Sc(OTf)_3$	<5	55
7	$La(OTf)_3$	<5	16[d]
8	$In(OTf)_3$	trace	N.D.[e]

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (1.0 mL) with a catalyst loading of 10 mol% (metal/ligand = 1:1) under nitrogen at −20 °C for 3 d. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] An opposite configuration of product was obtained as determined by HPLC. [e] N.D.: not determined.

Further optimization of the reaction conditions was aimed at exploring the effectiveness of $Sc(OTf)_3$ with other *N,N′*-dioxide ligands (Table 2). After examining the steric and electronic effects of *N,N′*-dioxides, we found that the reactivity and enantioselectivities were closely dependent on the R substituents of the amide moiety and that bulkier groups provided better results (Table 2, entries 1–6 and 9–11). The results also showed that, with regard to the chiral backbone moiety, (*S*)-pipecolic acid derived *N,N′*-dioxides were found to give superior *ee* values to L-proline and L-ramipril acid derived ones (Table 2, entries 4 vs. 1 and 9, 5 vs. 2 and 10, and 6 vs. 3 and 11). With the bulkier 2,6-diisopropylphenyl-derived *N,N′*-dioxide **L6**, 90% *ee* and 43% yield could be afforded (Table 2, entry 6). However, no better result was obtained by using the 2-*tert*-butylphenylamine-based *N,N′*-dioxide **L7** (Table 2, entry 7). When the R group of the amide moiety was the bulkier 1-adamantyl group, the reaction had unexpectedly low enantioselectivity and reactivity (Table 2, entry 8). Accordingly, **L6** was chosen as the best ligand for the next investigation.

Table 2. Ligand screening in the asymmetric α-amination of 3-methyloxindole (**1a**) and DIAD (**2a**).[a]



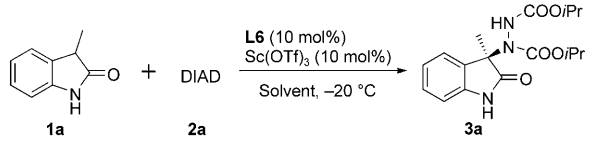
1a 2a 3a

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**L1**	<5	55
2	**L2**	<5	23
3	**L3**	21	61
4	**L4**	<5	56
5	**L5**	17	59
6	**L6**	43	90
7	**L7**	61	85
8	**L8**	<5	33
9	**L9**	<5	55
10	**L10**	<5	15
11	**L11**	46	75

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (1.0 mL) with a catalyst loading of 10 mol% (metal/ligand = 1:1) under nitrogen at −20 °C for 3 d. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

Subsequently, we examined the effect of solvents in the presence of 10 mol% **L6**–$Sc(OTf)_3$ (1:1) complex. As shown in Table 3, both the enantioselectivity and the yield were very dependent on the solvent. If the reaction was carried

Table 3. Effect of solvent in the α-amination of 3-methyloxindole (**1a**) and DIAD (**2a**).[a]



1a 2a 3a

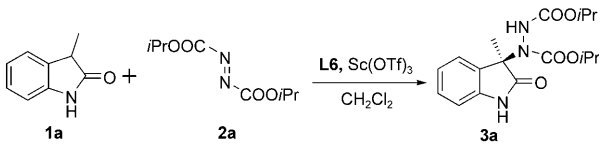
Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	43	90
2	tetrahydrofuran (THF)	5	47
3	toluene	16	57
4	EtOH	25	65[d]
5	*N*,*N*-dimethylformamide (DMF)	5	8
6	$CHCl_3$	24	73
7	$ClCH_2CH_2Cl$	68	87
8	EtOAc	21	9[d]

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2a** (0.1 mmol) in the indicated solvent (1.0 mL) with $Sc(OTf)_3$/**L6** (10 mol%; 1:1) under nitrogen at −20°C for 3 d. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] An opposite configuration of product was obtained as determined by HPLC.

out in THF, toluene, or EtOH, it only afforded the desired product **3a** with up to 65% *ee* (Table 3, entries 2–4). A significant drop in both the reactivity and enantioselectivity was found for many other solvents, such as DMF and EtOAc (Table 1, entries 5 and 8). As CH_2Cl_2 was a better solvent for this reaction, other chlorinated alkanes such as $CHCl_3$ and $ClCH_2CH_2Cl$ were investigated, but no superior result was obtained (Table 3, entry 1 vs. 6 and 7). Therefore, CH_2Cl_2 was chosen as the best solvent for this reaction (Table 3, entry 1).

Next, we turned our attention toward investigating the influence of the molar ratio of the central metal ion to the ligand on the α-amination of 3-methyloxindole (**1a**) and DIAD (**2a**; Table 4, entries 1–5). This ratio was found to be another important factor for the reactivity. The results indicated that an increase in the amount of ligand **L6** was favorable for the reactivity (Table 4, entries 1–3). When the ratio of ligand **L6** to $Sc(OTf)_3$ was changed from 1:1 to 1.2:1, a better yield was obtained and the enantioselectivity was maintained. (Table 4, entry 2 vs. 3). To our delight, when the molar ratio of ligand **L6** to $Sc(OTf)_3$ was increased to 1.5:1, the product was obtained in excellent yield (96%) and the enantioselectivity (92% *ee*) was not changed (Table 4, entry 1). In contrast, no products were obtained with the use of an excess amount of metal in the catalytic system (Table 4, entry 4). Furthermore, the reaction could not occur with only $Sc(OTf)_3$ as the catalyst (Table 4, entry 5).

Table 4. Screening of the ratio of ligand/metal and the catalyst loading in the α-amination of 3-methyloxindole (**1a**) and DIAD (**2a**).[a]



1a 2a 3a

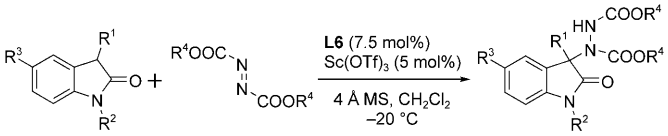
Entry	Catalyst loading [mol%]		*T* [°C]	*t* [d]	Yield [%][b]	*ee* [%][c]
	L6	$Sc(OTf)_3$				
1	15	10	−20	3	96	92
2	12	10	−20	3	79	91
3	10	10	−20	3	43	90
4	10	15	−20	3	trace	N.D.[d]
5	0	10	−20	3	trace	N.D.[d]
6	7.5	5	−20	4	95	91
7[e]	7.5	5	−20	2.5	93	92

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and **2a** (0.1 mmol) in CH_2Cl_2 (1.0 mL). [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] N.D.: not determined. [e] In the presence of 4 Å molecular sieves (MS; 5 mg).

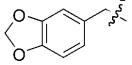
When the catalyst loading was only 5 mol% with a prolonged reaction time at −20°C, high yield and enantioselectivity were achieved (Table 4, entry 6). To improve the reactivity of the reaction, 4 Å molecular sieves (5 mg) were employed. In this instance, the reaction was completed within 2.5 d to give product **3a** with the enantioselectivity slightly increased from 91 to 92% *ee* (Table 4, entry 7). The role of the 4 Å molecular sieves (extraction of water) might be helpful for the promotion of an equilibrium for the formation of an enolate intermediate and to accelerate the reaction rate.[6d] Hence, we found that treatment of 3-methyloxindole (**1a**) and DIAD in the presence of *N*,*N*′-dioxide **L6** (7.5 mol%), $Sc(OTf)_3$ (5 mol%), and 4 Å molecular sieves (5 mg) gave the desired product **3a** in 93% yield with 92% *ee*.

Under the optimal reaction conditions (Table 4, entry 7), a variety of oxindoles **1** and azodicarboxylates **2** were investigated. First, the ester-group effect of the azodicarboxylate was tested for the asymmetric α-amination of 3-methyloxindole. The ester groups apparently had little or no effect on the enantioselectivity of the reaction (Table 5, entries 1–3). Diethylazodicarboxylate (DEAD) turned out to be an outstanding electrophile and the reaction was accomplished in 2 d in 98% yield with 92% *ee* (Table 5, entry 2). With DEAD as the electrophilic substrate, various substituted oxindoles were then examined (Table 5, entries 4–23). In general, the reactions took place efficiently with good yields (70–95%) and excellent levels of enantioselectivity (83–99% *ee*). This catalyst system was efficient when the R^1 group was an aliphatic nonbranched alkyl group (Table 5, entries 4 and 6), a branched alkyl group (Table 5, entry 5), or a cyclohexylmethyl group (Table 5, entry 7), with the respective reactions leading to the corresponding adducts **3d–g** in good yields with 97–98% *ee* values. It is interesting that either the electronic nature or the position of the substituents on the aromatic ring of the R^1 group had a limited influence on the enantioselectivity of the α-amination (Table 5, entries 8–16). Remarkably, substrates bearing condensed-ring or heteroaromatic-ring in R^1 substituents were also suitable substrates for the reaction and afforded the corresponding products **3q–s** with excellent enantioselectivities (Table 5, entries 17–19). When 3-phenyloxindole, which bears a bulky phenyl group as the R^1 group, was used, 93% *ee* and 85% yield could be obtained (Table 5, entry 20). Fortunately, high enantioselectivity (91% *ee*) was also observed for the 5-bromo-3-methyloxindole substrate (Table 5,

Table 5. Catalytic asymmetric α-amination of 3-substituted oxindoles **1** with azodicarboxylates **2** under the optimal conditions.[a]



1 2 3

Entry	R^1	R^2	R^3	R^4	Yield [%][b]	*ee* [%][c]
1	Me	H	H	*i*Pr	93 (**3a**)	92 (*R*)[d]
2[e]	Me	H	H	Et	98 (**3b**)	92
3[f]	Me	H	H	Bn	92 (**3c**)	90 (*R*)
4	*n*-propyl	H	H	Et	78 (**3d**)	98
5	*i*-propyl	H	H	Et	70 (**3e**)	97
6	*n*-butyl	H	H	Et	77 (**3f**)	98
7	cyclohexylmethyl	H	H	Et	71 (**3g**)	98
8	Bn	H	H	Et	91 (**3h**)	98
9	2-MePhCH$_2$	H	H	Et	81 (**3i**)	98
10	3-MePhCH$_2$	H	H	Et	80 (**3j**)	98
11	4-MePhCH$_2$	H	H	Et	95 (**3k**)	98
12	4-MeOPhCH$_2$	H	H	Et	85 (**3l**)	98
13		H	H	Et	72 (**3m**)	98
14	2-ClPhCH$_2$	H	H	Et	86 (**3n**)	98
15	4-ClPhCH$_2$	H	H	Et	94 (**3o**)	97
16	2,4-Cl$_2$PhCH$_2$	H	H	Et	95 (**3p**)	99
17	1-naphthylmethyl	H	H	Et	80 (**3q**)	98
18	2-naphthylmethyl	H	H	Et	80 (**3r**)	98
19	2-thienylmethyl	H	H	Et	83 (**3s**)	98
20	Ph	H	H	Et	85 (**3t**)	93
21	Me	H	Br	Et	93 (**3u**)	91
22	Bn	Me	H	Et	85 (**3v**)	95
23	Bn	Bn	H	Et	80 (**3w**)	83

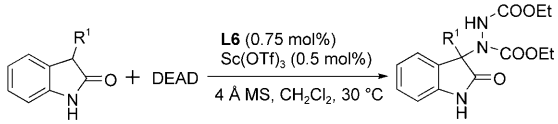
[a] Unless otherwise noted, the reactions were carried out with **1** (0.1 mmol) and **2** (0.1 mmol) in CH_2Cl_2 (1.0 mL) with 5 mol% scandium(III) triflate, 7.5 mol% **L6**, and 4 Å MS (5 mg) under nitrogen at −20°C for 2–3 d. Bn: benzyl. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by comparison with literature data.[16a] [e] Reaction time was 2 d. [f] The reaction was carried out at −30°C for 2.5 d, and dibenzylazodicarboxylate (0.2 mmol) was used.

entry 21). Notably, N-protected groups apparently had little effect on the results of the reaction (Table 5, entries 22 and 23).

Synthetic application with a low catalyst loading is clearly desirable for a catalytic asymmetric reaction. Although the asymmetric α-amination of carbonyl compounds with azodicarboxylates had been reported, most of these processes required 5 mol% or more of catalyst loading for sufficient formation of the product and maintenance of the enantioselectivity.[1–9,16] The reaction reported herein could be performed without notable loss of reactivity (85–95% yield) and enantioselectivity (92–96% *ee*) even with a catalyst loading of 0.5 mol%, although the reaction temperature was increased from −20°C to 30°C (Table 6, entries 1–7). Further attempts to decrease the catalyst loading (0.1 mol% and 0.01 mol%) led to a decrease in the yield and enantiomeric excess of the product, and the reaction time was prolonged (Table 6, entries 8 and 9).

The benzyloxycarbonyl (Cbz) groups of product **3c** can be easily removed so it is conveniently transformed into an optically active quarternary 3-amino-3-methyloxindole, which is a useful medicinal chemistry intermediate.[21] As shown in Scheme 2, catalytic asymmetric α-amination of 3-methyloxindole (**1a**) and dibenzylazodicarboxylate (**2c**) was accomplished with good results (80% yield, 85% *ee*) by using only

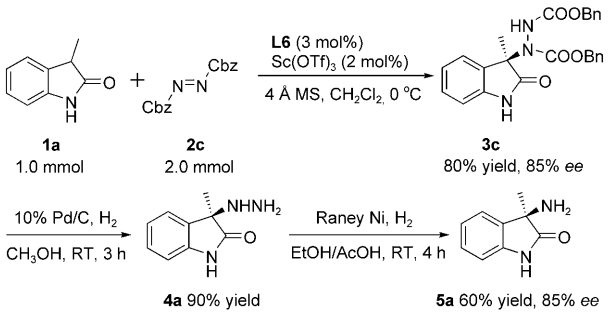
Table 6. Substrate scope of the asymmetric α-amination of 3-substituted oxindoles and diethylazodicarboxylate with 0.5 mol% catalyst loading.[a]



1 (1.0 mmol) 2b (1.0 mmol) 3

Entry	R^1	*t* [d]	Yield [%][b]	*ee* [%][c]
1	cyclohexylmethyl	2	95 (**3g**)	92
2	Bn	2.5	92 (**3h**)	94
3	2-MePhCH$_2$	2	88 (**3i**)	94
4	3-MePhCH$_2$	2	85 (**3j**)	96
5	4-MeOPhCH$_2$	2	92 (**3l**)	95
6	2-ClPhCH$_2$	2	90 (**3n**)	94
7	2,4-Cl$_2$PhCH$_2$	2	91 (**3p**)	94
8[d]	Bn	4	85 (**3h**)	80
9[e]	Bn	4	80 (**3h**)	74

[a] Unless otherwise noted, the reactions were carried out with **1** (1.0 mmol) and **2b** (1.0 mmol) in CH_2Cl_2 (3.0 mL) with 0.5 mol% scandium(III) triflate, 0.75 mol% **L6**, and 4 Å MS (20 mg) under nitrogen at 30°C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Catalyst loading was 0.1 mol%. [e] Catalyst loading was 0.01 mol%.



Scheme 2. Elaboration of adduct **3c** after the α-amination of 3-methyloxindole (**1a**) and dibenzylazodicarboxylate (**2b**).

2 mol% of **L6**–Sc(OTf)$_3$ at 0°C. Compound **3c** was treated with Pd/C hydrogenation to remove the Cbz group with 90% yield; this was followed by N–N bond cleavage with Raney nickel to afford 3-amino-3-methyloxindole (**5a**) in 60% yield, without loss of enantioselectivity (85% *ee*).

To gain a preliminary insight into the mechanism, a C_2-symmetric amide, compound **6** (Figure 1a), which is the precursor of chiral *N*,*N*′-dioxide **L6**, was synthesized and explored in the asymmetric α-amination of 3-methyloxindole (**1a**) and DIAD (**2a**). No product was obtained under the same reaction conditions. The results suggested that only the **L6**–Sc(III) complex could form the active catalyst due to

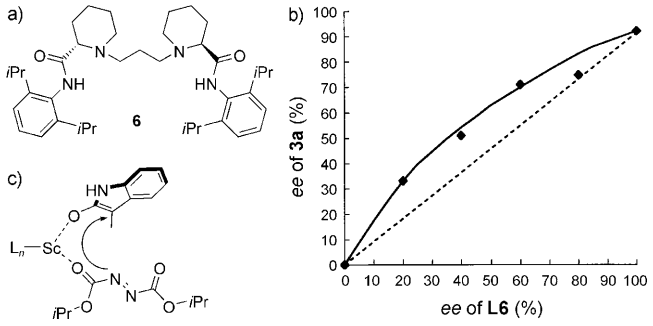


Figure 1. a) Precursor of the chiral *N*,*N*′-dioxide **L6**. b) Chiral amplification in the amination of **1a** with **2a** catalyzed by the **L6**–Sc(OTf)$_3$ complex. c) Proposed transition-state model.

the double *N*-oxide moieties. Next, the relationship between the *ee* values of ligand **L6** and product **3a** was investigated under the optimal conditions shown in Table 5. A positive nonlinear effect was observed (Figure 1b), which suggests that oligomeric aggregates of **L6**–Sc(OTf)$_3$ might exist in the reaction system. On the basis of the experimental results obtained and the X-ray structure of the *N*,*N*′-dioxide–Sc(OTf)$_3$ complex recently reported by us, as well as our previous reports of using *N*,*N*′-dioxide–Sc(OTf)$_3$ complexes as catalysts,[19m,t] we propose that the carbonyl group of the oxindole would coordinate to the active $\mathbf{L_n}$–Sc complex to form an enolate (Figure 1c). The azodicarboxylate also can coordinate to the central metal ion through an ester carbonyl group. Subsequently, diisopropylazodicarboxylate electrophilic attack on the enolate would afford the corresponding product **3a** with excellent enantioselectivity (Figure 1c).

Conclusion

We have developed a highly enantioselective α-amination of 3-substituted oxindoles with azodicarboxylates by using a chiral *N*,*N*′-dioxide–Sc^{III} complex as the catalyst. This simple experimental protocol affords various optically active 3-amino-2-oxindole derivatives in high yields (up to 98%) with excellent enantioselectivities (up to 99% *ee*). Moreover, a relatively wide range of substrates can be tolerated and excellent results can still be obtained with 0.5 mol% catalyst loading; these results show the potential value of this catalyst system. The product with enantiomeric excess can be conveniently transformed into an optically active quarternary 3-amino-3-methyloxindole in two steps. Further efforts will be devoted to the investigation of the α-amination reaction with other kinds of carbonyl compounds and to the application of this reaction to the synthesis of biologically interesting molecules.

Experimental Section

General: ^{1}H NMR spectra were recorded at 400 or 600 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance used as the internal standard. ^{13}C NMR data were collected at 100 or 150 MHz with complete proton decoupling. Enantiomeric excess (*ee*) values were determined by chiral HPLC analysis on Daicel Chiralcel AD-H, IA, and IB columns by comparison with the authentic racemates. ESI-HRMS spectra were recorded on a commercial apparatus, and methanol or acetonitrile was used to dissolve the sample. All reactions were performed in sealed oven-dried glass tubes under an atmosphere of nitrogen unless otherwise noted. THF and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled over CaH_2. Unless noted, commercial reagents were used without further purification. 3-Methyloxindole is commercially available and was used without further purification. The other oxindoles were prepared according to the literature and references therein.[11–16] The *N*,*N*′-dioxide ligands were prepared according to the literature.[19]

General procedure for the enantioselective α-amination of 3-substituted oxindoles with azodicarboxylates: *N*,*N*′-dioxide **L6** (4.9 mg, 0.0075 mmol), scandium triflate (2.5 mg, 0.005 mmol), 3-methyloxindole (**1a**; 14.7 mg, 0.10 mmol), and 4 Å molecular sieves (5 mg) were stirred in a dry reaction tube in CH_2Cl_2 (1.0 mL) under nitrogen at 30 °C for 0.5 h and then cooled to −20 °C, at which point diisopropylazodicarboxylate (**2a**; 20 μL, 0.1 mmol) was added. The reaction mixture was stirred at −20 °C for 2.5 d. Purification by silica gel column chromatography (eluent: petroleum ether/ethyl acetate, 2:1) afforded the desired product **3a** in 93% yield with 92% *ee*: $[a]_D^{20} = -7.0$ ($c = 0.65$ in $CHCl_3$) (ref. [16a]: $[a]_D^{20} = +6.0$ ($c = 0.5$ in $CHCl_3$, 78% *ee*)); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (s, 1H), 7.77 (d, $J = 7.6$ Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 1H), 7.05 (t, $J = 7.2$ Hz, 1H), 6.94 (d, $J = 4.4$ Hz, 1H), 6.84 (d, $J = 7.6$ Hz, 1H), 5.05 (dt, $J = 12.8$, 6.4 Hz, 1H), 4.73 (dt, $J = 12.4$, 6.0 Hz, 1H), 1.54 (s, 3H), 1.33 (dd, $J = 6.4$, 2.0 Hz, 6H), 1.08 (d, $J = 6.4$ Hz, 3H), 0.93 ppm (br s, 3H); HPLC (chiral AD-H column; *i*PrOH/hexane (10:90), 1.0 mL min^{-1}, 254 nm): t_R (major) = 12.8 min, t_R (minor) = 16.7 min, 92% *ee*.

Acknowledgements

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

[1] For selected examples, see: a) H. Heimgartner, *Angew. Chem.* **1991**, *103*, 271; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 238; b) M. Arend, *Angew. Chem.* **1999**, *111*, 3047; *Angew. Chem. Int. Ed.* **1999**, *38*, 2873; c) S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561; d) T. Ooi, M. Takahashi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2002**, *124*, 7640; e) J. T. Suri, D. D. Steiner, C. F. Barbas III, *Org. Lett.* **2005**, *7*, 3885; f) T. B. Poulsen, C. Alemparte, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 11614; g) G. Li, L. Dai, S. You, *Chem. Commun.* **2007**, 852.

[2] D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452.

[3] For representative reviews on asymmetric α-amination reactions, see: a) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975; b) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem.* **2004**, 1377; c) E. Erdik, *Tetrahedron* **2004**, *60*, 8747; d) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292; e) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584; f) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807.

[4] For selected examples, see: a) D. A. Evans, D. S. Johnson, *Org. Lett.* **1999**, *1*, 595; b) K. Juhl, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 2420; c) M. Marigo, K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1367; d) S. Ma, N. Jiao, Z. Zheng, Z. Ma, Z. Lu, L. Ye, Y. Deng, G. Chen, *Org. Lett.* **2004**, *6*, 2193; e) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Commun.* **2005**, 5115; f) L. Bernardi, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.*

2005, *127*, 5772; g) D. P. Huber, K. Stanek, A. Togni, *Tetrahedron: Asymmetry* **2006**, *17*, 658; h) Y. K. Kang, D. Y. Kim, *Tetrahedron Lett.* **2006**, *47*, 4565; i) J. Comelles, À. Pericas, M. Moreno-Mañas, A. Vallribera, G. Drudis-Solé, A. Lledos, T. Parella, A. Roglans, S. García-Granda, L. Roces-Fernández, *J. Org. Chem.* **2007**, *72*, 2077; j) T. Mashiko, K. Hara, D. Tanaka, Y. Fujiwara, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2007**, *129*, 11342; k) Y. Hasegawa, M. Watanabe, I. D. Gridnev, T. Ikariya, *J. Am. Chem. Soc.* **2008**, *130*, 2158; l) T. Mashiko, N. Kumagai, M. Shibasaki, *Org. Lett.* **2008**, *10*, 2725; m) T. Mashiko, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 14990.

[5] For selected examples, see: a) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466; b) Q. Lan, X. Wang, R. He, C. Ding, K. Maruoka, *Tetrahedron Lett.* **2009**, *50*, 3280.

[6] For selected examples, see: a) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120; b) P. M. Pihko, A. Pohjakallio, *Synlett* **2004**, 2115; c) X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, *7*, 167; d) T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671; e) X. Liu, B. Sun, L. Deng, *Synlett* **2009**, 1685.

[7] For selected examples, see: a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254; c) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; d) H. Vogt, S. Vanderheiden, S. Bräse, *Chem. Commun.* **2003**, 2448; e) H. Iwamura, S. P. Mathew, D. G. Blackmond, *J. Am. Chem. Soc.* **2004**, *126*, 11770; f) Y. Liu, R. Melgar-Fernández, E. Juaristi, *J. Org. Chem.* **2007**, *72*, 1522.

[8] For selected examples, see: a) X. Xu, T. Yabuta, P. Yuan, Y. Takemoto, *Synlett* **2006**, 137; b) S. H. Jung, D. Y. Kim, *Tetrahedron Lett.* **2008**, *49*, 5527.

[9] M. Terada, M. Nakano, H. Ube, *J. Am. Chem. Soc.* **2006**, *128*, 16044.

[10] For selected examples, see: a) X. Zhang, C. D. Smith, *Mol. Pharmacol.* **1996**, *49*, 228; b) H. C. Malinakova, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 4083; c) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi, R. Nagata, *J. Med. Chem.* **2001**, *44*, 4641; d) T. D. Bagul, G. Lakshmaiah, T. Kawabata, K. Fuji, *Org. Lett.* **2002**, *4*, 249; e) K. C. Nicolaou, P. B. Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y.-K. Chen, S. A. Snyder, *Angew. Chem.* **2003**, *115*, 1795; *Angew. Chem. Int. Ed.* **2003**, *42*, 1753; f) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130; g) A. H. Abadi, S. M. Abou-Seri, D. E. Abdel-Rahman, C. Klein, O. Lozach, L. Meijer, *Eur. J. Med. Chem.* **2006**, *41*, 296; h) S. E. Reisman, J. M. Ready, M. M. Weiss, A. Hasuoka, M. Hirata, K. Tamaki, T. V. Ovaska, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2008**, *130*, 2087.

[11] S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2007**, *119*, 8820; *Angew. Chem. Int. Ed.* **2007**, *46*, 8666.

[12] a) R. He, C. Ding, K. Maruoka, *Angew. Chem.* **2009**, *121*, 4629; *Angew. Chem. Int. Ed.* **2009**, *48*, 4559; b) P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2009**, *15*, 7846; c) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 9168; d) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; e) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620.

[13] a) X. Tian, K. Jiang, J. Peng, W. Du, Y.-C. Chen, *Org. Lett.* **2008**, *10*, 3583; b) L. Cheng, L. Liu, H. Jia, D. Wang, Y.-J. Chen, *J. Org. Chem.* **2009**, *74*, 4650.

[14] a) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001; b) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164; c) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 4276; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; d) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 4225; *Angew. Chem. Int. Ed.* **2008**, *47*, 4157.

[15] For selected examples, see: a) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368; b) I. D. Hills, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4051; *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; c) A. Huang, J. J. Kodanko, L. E. Overman, *J. Am. Chem. Soc.* **2004**, *126*, 14043; d) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, *128*, 925; e) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *J. Am. Chem. Soc.* **2006**, *128*, 16488; f) B. M. Trost, Y. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 14548; g) D. Sano, K. Nagata, T. Itoh, *Org. Lett.* **2008**, *10*, 1593; h) D. Tomita, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 6946; i) K. Jiang, J. Peng, H.-L. Cui, Y.-C. Chen, *Chem. Commun.* **2009**, 3955; j) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900; k) B. M. Trost, Y. Zhang, *Chem. Eur. J.* **2010**, *16*, 296.

[16] a) L. Cheng, L. Liu, D. Wang, Y.-J. Chen, *Org. Lett.* **2009**, *11*, 3874; b) T. Bui, M. Borregan, C. F. Barbas III, *J. Org. Chem.* **2009**, *74*, 8935; c) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao, J. Zhou, *Chem. Commun.* **2009**, 6753.

[17] S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 1255.

[18] For reviews on chiral *N*-oxides in asymmetric catalysis, see: a) A. V. Malkov, P. Kočovský, *Eur. J. Org. Chem.* **2007**, 29; b) A. V. Malkov, P. Kočovský, *Curr. Org. Chem.* **2003**, *7*, 1737; c) G. Chelucci, G. Murineddu, G. A. Pinna, *Tetrahedron: Asymmetry* **2004**, *15*, 1373, and references therein.

[19] For our own work in this field, see: a) H. Zhou, D. Peng, B. Qin, Z. Hou, X. Liu, X. Feng, *J. Org. Chem.* **2007**, *72*, 10302; b) X. Zhang, D. Chen, X. Liu, X. Feng, *J. Org. Chem.* **2007**, *72*, 5227; c) K. Zheng, B. Qin, X. Liu, X. Feng, *J. Org. Chem.* **2007**, *72*, 8478; d) J. Huang, J. Wang, X. Chen, Y. Wen, X. Liu, X. Feng, *Adv. Synth. Catal.* **2008**, *350*, 287; e) B. Gao, Y. Wen, Z. Yang, X. Huang, X. Liu, X. Feng, *Adv. Synth. Catal.* **2008**, *350*, 385; f) Z. Yu, X. Liu, Z. Dong, M. Xie, X. Feng, *Angew. Chem.* **2008**, *120*, 1328; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; g) D. Shang, J. Xin, Y. Liu, X. Zhou, X. Liu, X. Feng, *J. Org. Chem.* **2008**, *73*, 630; h) X. Yang, X. Zhou, L. Lin, L. Chang, X. Liu, X. Feng, *Angew. Chem.* **2008**, *120*, 7187; *Angew. Chem. Int. Ed.* **2008**, *47*, 7079; i) L. Wang, X. Liu, Z. Dong, X. Fu, X. Feng, *Angew. Chem.* **2008**, *120*, 8798; *Angew. Chem. Int. Ed.* **2008**, *47*, 8670; j) C. Tan, X. Liu, L. Wang, J. Wang, X. Feng, *Org. Lett.* **2008**, *10*, 5305; k) K. Zheng, J. Shi, X. Liu, X. Feng, *J. Am. Chem. Soc.* **2008**, *130*, 15770; l) D. Shang, Y. Liu, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 3678; m) Y. Liu, D. Shang, X. Zhou, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 2055; n) S. Chen, Z. Hou, Y. Zhu, J. Wang, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 5884; o) D. Chen, Z. Chen, X. Xiao, Z. Yang, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2009**, *15*, 6807; p) Y. Hui, Q. Zhang, J. Jiang, L. Lin, X. Liu, X. Feng, *J. Org. Chem.* **2009**, *74*, 6878; q) X. Zhou, D. Shang, Q. Zhang, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2009**, *11*, 1401; r) F. Wang, X. Liu, Y. Zhang, L. Lin, X. Feng, *Chem. Commun.* **2009**, 7297; s) Y. Liu, D. Shang, X. Zhou, Y. Zhu, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, *12*, 180; t) W. Wang, X. Liu, W. Cao, J. Wang, L. Lin, X. Feng, *Chem. Eur. J.* **2010**, *16*, 1664.

[20] a) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227; b) K. Mikami, M. Terada, H. Matsuzawa, *Angew. Chem.* **2002**, *114*, 3704; *Angew. Chem. Int. Ed.* **2002**, *41*, 3554.

[21] a) A. S. Endler, E. I. Becker, *J. Am. Chem. Soc.* **1955**, *77*, 6608; b) M. J. Kornet, P. A. Thio, N. Malone, W. C. Lubawy, *J. Pharm. Sci.* **1975**, *64*, 639; c) S. J. O'Connor, Z. Liu, *Synlett* **2003**, 2135.

Received: January 18, 2010
Published online: April 20, 2010

