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Asymmetric Ring Opening of *meso*-Epoxides with Aromatic Amines Catalyzed by a New Proline-Based *N,N′*-Dioxide-Indium Tris(triflate) Complex

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Abstract: The catalytic asymmetric ring opening of *meso*-epoxides with aromatic amines was achieved using a new proline-based *N,N′*-dioxide-indium tris(triflate) complex in high yields (up to 99%) with excellent enantioselectivities (up to 99% *ee*) under mild conditions. The coordination ability of *N,N′*-dioxide **1c** was investigated by X-ray and NMR analysis. A plausible seven-coordinate transition state model was proposed. The chiral *N,N′*-dioxides surveyed were synthesized from proline through only three conventional steps. The procedure could be run on a gram-scale without any loss of enantioselectivity. This protocol provides a highly practical and useful tool for the bulky preparation of optically pure β-amino alcohols.

Keywords: amino alcohols; aminolysis; asymmetric catalysis; *N,N′*-dioxide-indium tris(triflate) complex; *meso*-epoxides

Chiral β-amino alcohols are useful building blocks for biologically active compounds,[1] as well as important auxiliaries and ligands in asymmetric synthesis.[2] Several methods for the direct asymmetric synthesis of these units have been developed, such as functional group manipulation of a chiral synthon,[3] aminohydroxylation of olefins,[4] the addition of α-hydroxy ketones to imines,[5] aminolytic kinetic resolution of *trans*-aromatic epoxides[6a] and racemic terminal epoxides.[6b,c] Among them, the catalytic asymmetric ring opening of epoxides with amines is one of the most rational and straightforward strategies in combination with availability and atom economy. Indeed, some simple and multifunctional β-amino alcohols have been obtained using this strategy by the promotion of BINOL-based metal complexes[7a–g] or chiral bipyridine-metal complexes.[7h–j]

Compared with other asymmetric reactions, the catalysts developed for this reaction are still limited and some effective ligands[7f–j] are usually prepared under rigorous conditions. So, a new catalyst should be further developed in terms of effectivity and practicability. On the other hand, chiral *N*-oxide ligands are emerging for their distinctive impact in the field of asymmetric catalysis[8] and have been well developed in the reduction of ketones,[9] the allylation of aldehydes,[10] the epoxide opening,[11] and the aldol condensation.[12] Herein, we describe the first example of proline-based *N,N′*-dioxide-In(OTf)$_3$ complex-catalyzed asymmetric ring opening of *meso*-epoxides with aromatic amines.

As a part of our ongoing program, several proline-based *N,N′*-dioxide catalysts have been successfully applied to some nucleophilic additions, such as the cyanation of ketoimines[13a,b] and carbonyl compounds,[13c–e] the allylation of ketones.[13f] In these catalyses, all of the *N,N′*-dioxide ligands used were prepared *via* coupling of two amino acids units at the *N*-termini.[14] Since an amino acid has two reactive functional groups, it was logical to devise a new class of ligands (Figure 1) in which two prolines are connected at the *C*-termini by a diamine. Our efforts were encouraged by the fact that these *N,N′*-dioxides could be synthesized from proline through three conventional steps, namely, reductive amination, isobutyl chlorocarbonate-assisted coupling and directed amine oxidation.

Then, the aminolysis of *meso*-stilbene oxide with aniline was carried out using *N,N′*-dioxides **1a–h** as chiral ligands and In(OTf)$_3$ as metal reagent.[15] The results are summarized in Table 1. Initial ligand

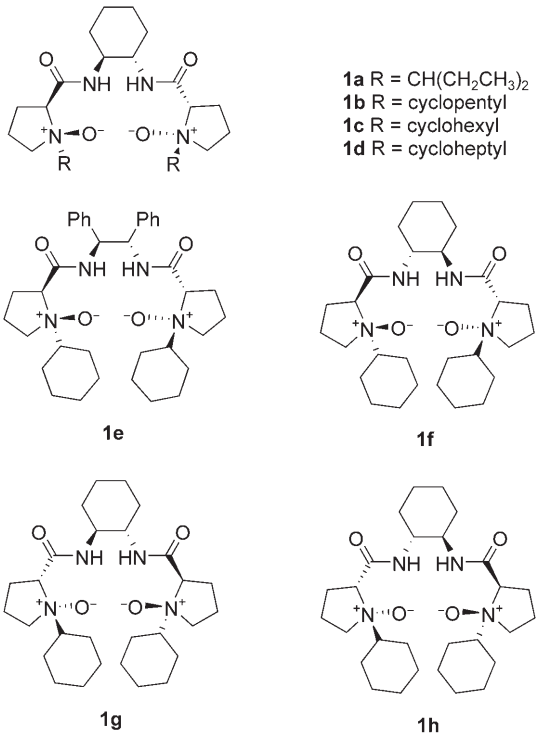


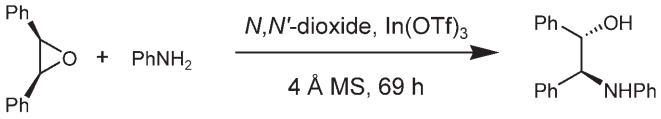
Figure 1. *N*,*N*′-dioxides **1a–h**.

screening of **1a–d** revealed that **1c** was effective to afford the product **3a** in 99% yield with 91% *ee*. When the substituent at *N*-termini was changed to 1-ethylpropyl **1a**, cyclopentyl **1b** and cycloheptyl **1d**, distinct enantioselectivity sacrifice (over 30% *ee*) was observed (entries 1, 2 and 4 *vs.* entry 3). Meanwhile, **1e** also showed a decreased enantioselectivity (entry 5). It suggested that there should be a strict conformation match between the annulation framework of the diamine and the cyclohexyl substituent.

Using **1c**-In(OTf)$_3$ complex as catalyst, the reaction conditions were further optimized. When 3 mol% catalyst were used, the reactivity and enantioselectivity were maintained (entry 6). Further reducing the catalyst loading to 1 mol% gave the same level of enantioselectivity, but a decreased reactivity (entry 7). A solvent survey revealed that THF and CH_2Cl_2 (entries 6 and 11) provided favorable results, while Et_2O, $PhOCH_3$ and toluene (entries 8–10) led to rather poor results. Excellent yields and enantiomeric excesses could be achieved smoothly at 0 °C and −20 °C (entries 6 and 13), but a decreased enantiomeric excess was obtained at 30 °C (entry 12).

To determine whether cooperative effects of configuration involving the cyclohexane-1,2-diamine and proline can give rise to a more effective catalyst, **1f–h** were investigated under the conditions of entry 6. As shown in Table 1, enantiomers **1f** and **1g** gave disappointing results with respect to reactivity and enantioselectivity (entries 14 and 15), while **1h** (the enantiomer of **1c**) displayed a good enantioselectivity with excellent yield (entry 16). Notably, the absolute configuration of the major product was predominated by the proline fragment (entries 6 and 14 *vs.* entries 15 and 16).

Table 1. Enantioselective ring opening of *meso*-stilbene oxide with aniline.[a]



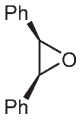
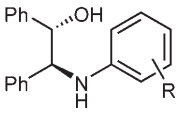
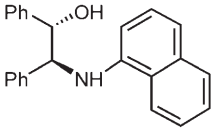
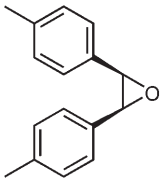
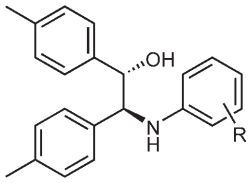
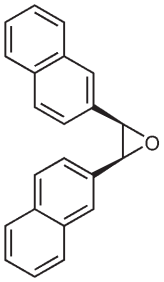
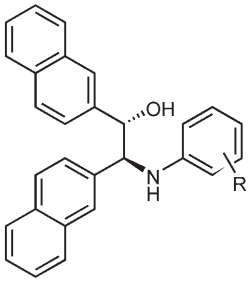
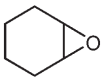
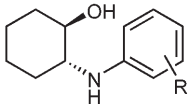
2a **3a**

Entry	Ligand	Catalyst Loading [mol%][b]	Solvent	*T* [°C]	Yield [%][c]	*ee* [%][d]
1	**1a**	5	THF	0	99	59
2	**1b**	5	THF	0	72	26
3	**1c**	5	THF	0	99	91
4	**1d**	5	THF	0	99	51
5	**1e**	5	THF	0	75	77
6	**1c**	3	THF	0	99	91
7	**1c**	1	THF	0	48	91
8	**1c**	3	Et_2O	0	7	24
9	**1c**	3	$PhOCH_3$	0	6	30
10	**1c**	3	toluene	0	3	16
11	**1c**	3	CH_2Cl_2	0	98	90
12	**1c**	3	THF	30	99	86
13	**1c**	3	THF	−20	95	91
14	**1f**	3	THF	0	27	52
15	**1g**	3	THF	0	26	40[e]
16	**1h**	3	THF	0	95	83[e]

[a] All reactions were performed with *meso*-stilbene oxide (0.2 mmol), aniline (0.3 mmol) and 4 Å MS (20 mg) in solvent (0.1 mL) for 69 h.
[b] 1.1:1 molar ratio of ligand to In(OTf)$_3$.
[c] Isolated yield.
[d] Determined by HPLC on Chiralcel OD-H column.
[e] The absolute configuration of major product was (1*R*,2*R*).

Encouraged by the above results, a variety of other substrates were then examined (Table 2). Substrates with both electron-donating and electron-withdrawing groups at *ortho* or *para* positions of the anilines gave rise to excellent asymmetric induction (entries 2–8, 10 and 12). 3-Chloroaniline (entry 9) and 3-bromoaniline (entry 11), however, exhibited somewhat lower enantioselectivities (86% *ee*). Condensed ring amine also showed high reactivity and enantioselectivity (entry 13). Aliphatic amines did not yield the desired products, presumably because stronger nucleophilicity made them coordinate irreversibly to the indium(III) complex. Other aromatic epoxides **2b** and **2c** reacted with aniline and 2-methoxyaniline in high yields and enantioselectivities as well (entries 14–17). Cyclohexene oxide (**2d**) delivered the products **3q** and **3r** in

Table 2. Enantioselective ring opening of *meso*-epoxides with amines promoted by **1c**-In(OTf)$_3$ complex.[a]

Entry		Epoxide	Amine	Product	Yield [%][d]	*ee* [%][e]
1	**2a**		$PhNH_2$	 **3a**[b] R = H	99	91
2	**2a**		2-CH_3O-$C_6H_4NH_2$	**3b**[b] R = 2-CH_3O	99	98
3[f]	**2a**		2-CH_3O-$C_6H_4NH_2$	**3b**[b] R = 2-CH_3O	81	99
4	**2a**		4-CH_3O-$C_6H_4NH_2$	**3c**[b] R = 4-CH_3O	99	94
5	**2a**		2-CH_3-$C_6H_4NH_2$	**3d** R = 2-CH_3	90	91
6	**2a**		4-CH_3-$C_6H_4NH_2$	**3e**[b] R = 4-CH_3	99	96
7	**2a**		4-*i*-Pr-$C_6H_4NH_2$	**3f** R = 4-*i*-Pr	90	91
8	**2a**		4-CF_3O-$C_6H_4NH_2$	**3g** R = 4-CF_3O	99	92
9	**2a**		3-Cl-$C_6H_4NH_2$	**3h** R = 3-Cl	95	86
10	**2a**		4-Cl-$C_6H_4NH_2$	**3i**[b] R = 4-Cl	99	94
11	**2a**		3-Br-$C_6H_4NH_2$	**3j** R = 3-Br	94	86
12	**2a**		4-Br-$C_6H_4NH_2$	**3k**[b] R = 4-Br	96	93
13	**2a**		napthalene-1-amine	 **3l**[b]	92	88
14	**2b**		$PhNH_2$	 **3m**[b] R = H	82	89
15	**2b**		2-CH_3O-$C_6H_4NH_2$	**3n** R = 2-CH_3O	90	97
16	**2c**		$PhNH_2$	 **3o**[b] R = H	86	93
17	**2c**		2-CH_3O-$C_6H_4NH_2$	**3p** R = 2-CH_3O	89	98
18	**2d**		$PhNH_2$	 **3q**[c] R = H	93	22
19	**2d**		2-CH_3O-$C_6H_4NH_2$	**3r**[c] R = 2-CH_3O	88	24
20[g]	**2d**		$PhNH_2$	**3q**[c] R = H	90	76
21[g]	**2d**		2-CH_3O-$C_6H_4NH_2$	**3r**[c] R = 2-CH_3O	82	57

[a] All reactions were performed under the conditions of entry 6 (Table 1), unless otherwise noted.
[b] Absolute configuration of the major product was assigned as (1*S*,2*S*) by comparison of the rotation values in the literature.
[c] Absolute configuration of the major product was assigned as (1*R*,2*R*) by comparison of the rotation values in the literature.
[d] Isolated yield.
[e] Determined by HPLC (see Supporting Information).
[f] The reaction was performed with *meso*-stilbene oxide (1.177 g, 6 mmol) and 2-methoxylaniline (1.02 mL, 9 mmol) in THF (3 mL) with 4 Å MS (600 mg) for 70 h at 0 °C using **1c** (99.9 mg, 0.198 mmol) and In(OTf)$_3$ (102.2 mg, 0.180 mmol).
[g] Ligand **1e** was used.

high yields and good enantioselectivities using **1e** (entries 20 and 21) instead of **1c** (entries 18 and 19) under identical reaction conditions. In addition, the ring opening of *meso*-stilbene oxide with 2-methoxyaniline was tested on a gram scale and afforded the product in 99% *ee* and good yield (entry 3), which could provide a highly practical and useful tool for the preparation of optically pure β-amino alcohols.

To gain some information about the coordination abilities of *N,N′*-dioxide **1c**, suitable crystals for X-ray analysis were grown from THF/hexane.[16] In the unit cell ($C_{28}H_{50}N_4O_5$), which involved only one diastereoisomer (Figure 2), each *N*-oxide is *syn* to the amide at

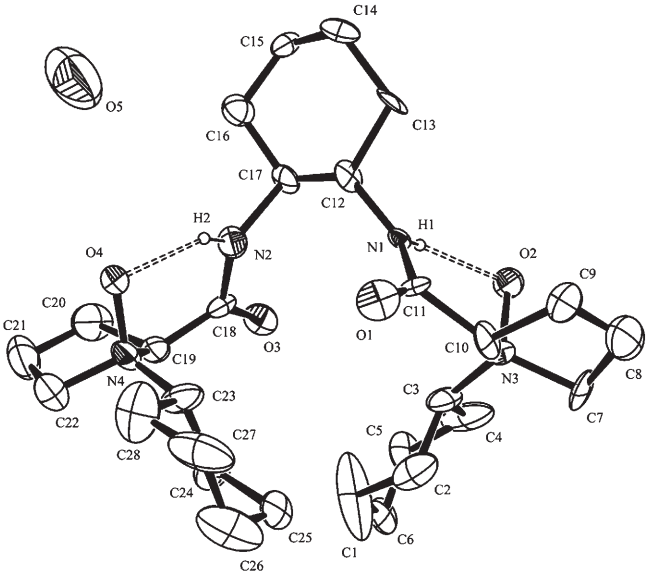


Figure 2. X-ray crystal structure of *N,N′*-dioxide **1c**·H_2O.

the same proline fragment and is respectively stabilized by intramolecular hydrogen bond of H1−O2 (1.876 Å) and H2−O4 (1.855 Å), and each cyclohexane annulation adopts a chair conformation. The observed differences of bond lengths and angles between the two proline fragments reveal a pseudo-C_2-symmetric geometry of **1c**. The unit cells are aggregated to a hexagonal system by two intermolecular hydrogen bonds between one H_2O and two *N*-oxides in adjacent cells. When the coordination abilities of **1c** are considered, the X-ray structure suggests that the amide nitrogens are unlikely to take part in coordination to the hard In^{3+} because their lone pairs are delocalized in amide carbonyl π-bonds. This is indicated by the short bond length of N(amide)-C(amide) compared to that of N(amide)-C(cyclohexyl) (N1−C11 1.276 Å *vs.* N1−C12 1.430 Å, and N2−C18 1.405 Å *vs.* N2−C17 1.501 Å).[17]

The coordiantion abilities of **1c** were further determined by NMR analysis. When one equivalent of **1c** and $In(OTf)_3$ was treated with 4 Å MS in THF and dried under vacuum at room temperature, the ^{1}H NMR spectra showed an obvious up-field shift for the amide proton from 11.88 ppm to 8.34 ppm.[18] This indicated that, in the *N,N′*-dioxide-In(III) complex, the intramolecular hydrogen bonds (Figure 2) should be dissociated and the two *N*-oxides might be stabilized *via* coordination with In^{3+}. The ^{13}C NMR spectra also showed an obvious up-field shift for the amide carbon from 168.1 ppm to 166.4 ppm.[18] This strongly suggested that there should be a coordination between amide and In^{3+}.

Based on the above findings, a plausible seven-coordinate transition state model[19] was proposed (Figure 3), in which the *N*-oxides and amide oxygens

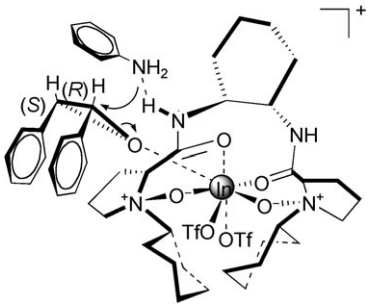


Figure 3. Proposed transition state model.

of **1c** coordinated to In^{3+} in a tetradentate manner to form two six-membered chelate rings, the triflyl groups maintained on In^{3+} were blocked by two cyclohexyl substituents, respectively, and the incoming *meso*-stilbene oxide was attached to In^{3+} from the favorable backward side, meanwhile, the aniline was fixed by the hydrogen bond with the amide proton and preferred to attack the adjacent (*R*)-carbon of the epoxide.

In summary, we have developed a novel proline-based *N,N′*-dioxide-$In(OTf)_3$ complex-catalyzed asymmetric ring opening of *meso*-epoxides with aromatic amines, in which chiral β-amino alcohols were obtained in high yields (up to 99%) and excellent enantioselectivities (up to 99% *ee*). This protocol provides a highly practical and useful tool for the bulk preparation of optically pure β-amino alcohols. Further efforts are being devoted to elucidating the detailed mechanism and investigating the scope of the applied catalyst.

Experimental Section

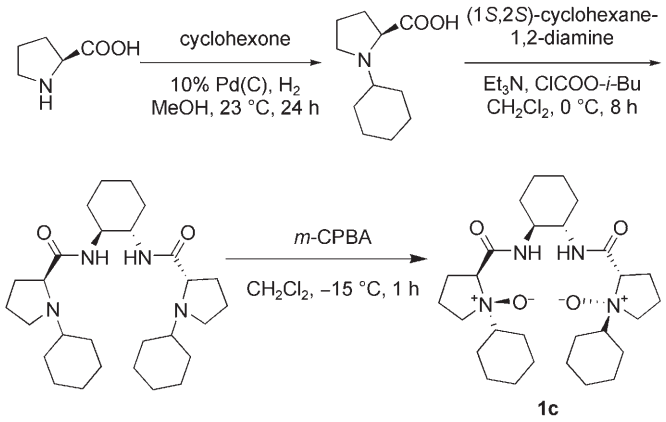
General Remarks

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk or glove-box techniques. ^{1}H

and ^{13}C NMR spectra were recorded at 400 MHz or 600 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CDCl_3$ ($\delta = 7.27$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. HR-MS was recorded on Bruker-APEX-2 (SIMS). Optical rotation data were obtained using a commerical polarimeter and reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). Melting points were measured on an electrothermal digital melting point apparatus and uncorrected. Enantiomeric excesses (*ee*) were determined by HPLC using corresponding commercial chiral columns as stated in the data of products with UV detection at 254 nm and the retention times were compared to those of the corresponding racemic samples.

Representative Synthetic Procedure and Analytical Data for *N*,*N*′-Dioxide 1c

Step 1:[10d] Palladium on carbon (10% by wt, dry, 0.12 g) was suspended in methanol (10 mL) in a dry 50-mL flask and flushed with N_2. To this suspension was charged L-proline



(1.15 g, 10 mmol) and cyclohexone (1.2 mL, 11 mmol). The flask was charged with H_2 and was kept under a balloon of H_2 for 24 h. At this time the reaction was purged with N_2 and filtered through celite. Removal of the methanol under reduced pressure led to the unpurified acid (1.93 g, 98% unpurified yield).

Step 2: The unpurified acid (1.90 g, 9.6 mmol) was dissolved in CH_2Cl_2 (20 mL) at 0 °C. Then Et_3N (1.4 mL, 9.6 mmol) and isobutyl chlorocarbonate (1.4 mL, 9.6 mmol) were added. After 20 min, (1*S*,2*S*)-cyclohexane-1,2-diamine (0.50 g, 4.4 mmol) was added and the reaction was monitored by TLC. After the conversion was completed, saturated aqueous $NaHCO_3$ solution (10 mL) was added. The organic layer was washed by brine, dried over anhydrous Na_2SO_4 and concentrated to give a crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to give the pure amide; yield: 1.06 g (51%).

Step 3: The purified amide (1.00 g) was then dissolved in CH_2Cl_2 (10 mL) at −15 °C, and *m*-CPBA (0.94 g of 85% purifity, 4.6 mmol) was added, then the reaction was allowed to stir at −15 °C for 1 h. At this time, the reaction mixture was warmed to room temperature and purified by silica gel chromatography (ethyl acetate:methanol = 1:1) to give the pure **1c** as a white solid; yield: 1.01 g (95%); mp 154–156 °C; $[\alpha]_D^{25}$: −16.4° (*c* 0.390, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.12$–1.15 (m, 2H), 1.34–1.51 (m, 9H), 1.67–1.69 (m, 2H), 1.81–1.94 (m, 8H), 2.01–2.04 (m, 2H), 2.18 (m, 4H), 2.35–2.45 (m, 7H), 2.54–2.56 (m, 2H), 3.24–3.33 (m, 2H), 3.35–3.42 (m, 4H), 3.69 (m, 2H), 3.90 (m, 2H), 11.42 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.9$, 22.4, 25.2 (25.19), 25.2 (25.25), 25.3, 27.8 (27.75), 27.8 (27.82), 28.4, 28.8, 30.9, 49.5, 64.5, 71.8, 74.8, 77.2, 167.6; ESI-HR-MS: $m/z = 505.3754$, calcd. for $C_{28}H_{48}N_4O_4 + H^+$: 505.3754.

Typical Aminolysis Procedure

To a stirred mixture of ligand **1c** (0.0066 mmol), $In(OTf)_3$ (0.006 mmol) and 4 Å MS (20 mg) in THF (0.1 mL) were added the epoxide (0.2 mmol) and amine (0.3 mmol) at 0 °C. Then the reaction was performed at 0 °C for 69 h. After completion, the reaction mixture was purified by silica gel chromatography with mixtures of petroleum ether-ethyl acetate as eluent to give the pure amino alcohol. All known compounds were compared with data reported in the literature; all new compounds were fully characterized.

Acknowledgements

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[17] CCDC 658823 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.
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