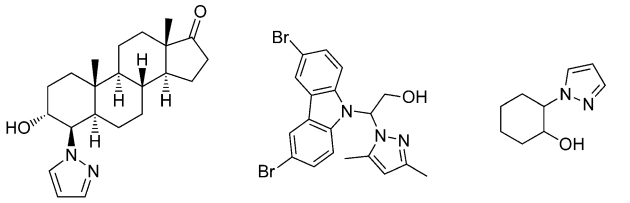
DOI: 10.1002/chem.201103792

Enantioselective Synthesis of β-Pyrazole-Substituted Alcohols through an Asymmetric Ring-Opening Reaction of *meso*-Epoxides

Xiaolei Hu, Bo Gao, Yangyang Chu, Wei Li, Xiaohua Liu, Lili Lin, and Xiaoming Feng*[a]

Pyrazole, a five-membered heterocycle containing two adjacent nitrogen atoms, is a motif found in a number of small molecules that possess diverse chemical, biological, and pharmaceutical activities.[1] Accordingly, β-pyrazole-substituted alcohols emerged as potential neuromuscular blocking agents, compounds possessing proneurogenic activity, and also a potential ligand for vanadium catalysts (Scheme 1).[2]



Scheme 1. Examples of β-pyrazole-substituted alcohols.

A facile way to construct β-pyrazole-substituted alcohols in an enantiomerically enriched form is the asymmetric ring-opening reaction. In recent years, the reactions have been accomplished with a wide range of nucleophiles.[3–12] Reactions with aza-nucleophiles, azide,[7] amine,[8] and indole[11b–d] have been well developed. However, the investigation of azole was challenging and important. To the best of our knowledge, only benzotriazole has been explored by the Kobayashi group.[11c] And pyrazole as a novel aza-nucleophile has seldom been reported before. On the other hand, reactions with cycloalkene oxides have been well conducted with striking results, but only a few examples of the aryl-substituted oxides were documented.[5b,6f,8j,9e,g,i,11] A possible reason for this is that the Lewis acid or base catalyst could trigger the rearrangement of the epoxide, through migration of the group to give carbonyl compounds.[3e,11b,14] Since our group has successfully applied *N,N′*-dioxide-metal complexes to promote various kinds of asymmetric transformations.[13] And chiral *N,N′*-dioxide-metal complexes exhibited cooperative effects[15] on nucleophiles and substrates such as aldehydes,[13d] ketones,[13e,f] imines,[13c] and α,β-unsaturated compounds[13b,g] and so forth. It is reasonable to assume that the desymmetrization of *meso*-epoxides by nucleophiles could be induced by the same method.[8l] Herein, we report a highly diastereoselective and enantioselective ring-opening reaction of *meso*-epoxide using a pyrazole derivative as the particular nucleophile.

Our initial investigation began with the screening of efficient Lewis acid catalysts for the ring-opening of *cis*-stilbene oxide **1a** with 3,5-dimethyl-4-nitro-1*H*-pyrazole **2a** in CH_2Cl_2 at 35 °C (Table 1). Several chiral Lewis acid catalysts

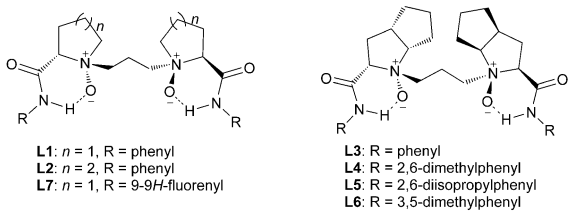
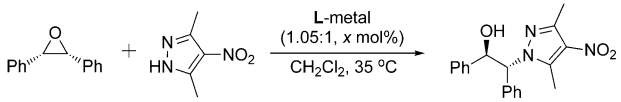


Table 1. Optimization of the reaction conditions.[a]



Entry	Metal	L	x	Yield [%][b]	d.r.[c]	ee [%][d]
1	$In(OTf)_3$	**L1**	10	53	90:10	11
2	$Zn(OTf)_2$	**L1**	10	35	84:16	0
3	$La(OTf)_3$	**L1**	10	33	86:14	4
4	$Sc(OTf)_3$	**L1**	10	99	99:1	84
5	$Sc(OTf)_3$	**L2**	10	81	99:1	82
6	$Sc(OTf)_3$	**L3**	10	99	99:1	97
7	$Sc(OTf)_3$	**L4**	10	41	94:6	16
8	$Sc(OTf)_3$	**L5**	10	34	99:1	60
9	$Sc(OTf)_3$	**L6**	10	99	99:1	98
10	$Sc(OTf)_3$	**L6**	5	99	99:1	98
11	$Sc(OTf)_3$	**L6**	1	76	99:1	98
12[e]	$Sc(OTf)_3$	**L6**	1	99	99:1	98

[a] Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol) and 1.5 equiv of **2a** in CH_2Cl_2 (0.3 mL) at 35 °C for 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis and NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 3 Å MS (20 mg) was added and the reaction time was 18 h.

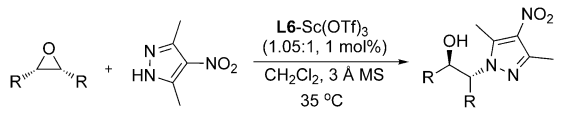
[a] X. L. Hu, Dr. B. Gao, Y. Y. Chu, W. Li, Dr. X. H. Liu, Dr. L. L. Lin, Prof. Dr. X. M. Feng
Key Laboratory of Green Chemistry & Technology
Ministry of Education, College of Chemistry
Sichuan University, Chengdu 610064(China)
Fax: (+86) 28-8541-8249
E-mail: xmfeng@scu.edu.cn

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103792.

generated in situ from metal salts and *N,N′*-dioxide **L1** were evaluated. Pleasingly, $Sc(OTf)_3$ produced **3aa** in 99% yield with 84% enantiomeric excess (*ee*) and 99:1 diastereomeric ratio (d.r.) (Table 1, entry 4 vs. entries 1–3). Based upon this result, various ligands of *N,N′*-dioxides were screened to be attached to $Sc(OTf)_3$. Modification of the chiral backbone and the amide of the ligand gave an interesting insight into the structural elements that were crucial for the enantioselectivity of the process. The L-ramipril derivative **L3** was superior to L-proline-derived **L1** and L-pipecolic acid derived **L2** in both stereoselectivity and reactivity (Table 1, entry 6 vs. entries 4 and 5). The steric hindrance of the amide subunits of L-ramipril-derived *N,N′*-dioxides had a crucial influence on both the yield and the stereoselectivity of the reaction. The use of ligand **L4** containing 2,6-dimethyl aniline gave the product in only 41% yield, 94:6 d.r., and 16% *ee*, whereas ligand **L6** containing 3,5-dimethyl aniline provided excellent enantioselectivity (98% *ee*) and diastereoselectivity (99:1 d.r.) as well as high reactivity (Table 1, entry 9 vs. entry 7). Thus, the combination of **L6** and $Sc(OTf)_3$ was adopted as the optimal catalyst system. Pleasingly, when the catalyst loading was reduced from 10 to 5 mol%, the enantioselectivity and yield of the desired product, **3aa**, was maintained. Carrying out the reaction with an even lower catalyst loading (1 mol%) in the presence of 3 Å molecular sieves maintained the striking results (Table 1, entry 12 vs. entry 11). Other conditions, such as the solvent and reaction temperature, were also investigated, but no superior results were obtained.

With the optimized conditions in hand, various *cis*-stilbene oxide derivatives were examined. As summarized in Table 2, *meso*-epoxides with electron-withdrawing or electron-donating substituents at the *meta*- or *para*-position of the aryl group allowed the maintenance of the high enantioselectivity (up to 99% *ee*) and complete *syn*-diastereoselectivity (99:1 d.r.), although the yields of the products were dependent on the electronic effect of the substituents (Table 2, entries 2–12). Generally, 3,3′-dihalostilbene oxides reacted more slowly than 4,4′-dihalostilbene oxides, and longer reaction times were needed to achieve satisfactory yields (Table 2, entries 2 and 3 vs. entries 7 and 8). Comparatively, epoxides **1i** and **1j** with electron-donating substituents at the *meta*-position showed higher reactivity than epoxides **1g** and **1h** with electron-withdrawing groups (Table 2, entries 9 and 10 vs. entries 7 and 8).

Table 2. Scope of epoxides for the reaction[a]



1 2a 3

Entry	1	R	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**1a**	Ph	12	99	99:1	98
2	**1b**	4-FC_6H_4	12	81	99:1	99
3[e]	**1c**	4-ClC_6H_4	12	85	99:1	96
4	**1d**	4-BrC_6H_4	18	99	99:1	95
5[e]	**1e**	4-$CF_3C_6H_4$	96	47	99:1	97
6	**1f**	4-PhC_6H_4	27	89	99:1	99
7	**1g**	3-FC_6H_4	72	90	99:1	93
8[e]	**1h**	3-ClC_6H_4	48	99	99:1	97
9	**1i**	3-MeC_6H_4	14	82	99:1	98
10	**1j**	3-$MeOC_6H_4$	14	89	99:1	98
11	**1k**	3-$PhOC_6H_4$	27	69	99:1	97
12	**1l**	2-naphthyl	18	99	99:1	98
13[f]	**1m**	-$(CH_2)_4$-	24	57	99:1	45

[a] Unless otherwise noted, reactions were carried out with **1** (0.1 mmol), 1.5 equiv of **2a** and 3 Å MS (20 mg) in CH_2Cl_2 (0.3 mL) at 35 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis and NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 5 mol% of catalyst was used. [f] 10 mol% of **L7**–$Sc(OTf)_3$ catalyst was used.

For 4,4′-ditrifluoromethylstilbene oxide **1e**, a moderate yield with 97% *ee* was obtained in the presence of 5 mol% of **L6**–$Sc(OTf)_3$ catalyst with a longer reaction time (Table 2, entry 5). However, the current catalyst system was not efficient for reactions with cycloalkene oxides. After a slight modification of the ligand structure, ligand **L7** coordinated with $Sc(OTf)_3$ gave a moderate *ee* value for cyclohexene oxide **1m** (Table 2, entry 13).

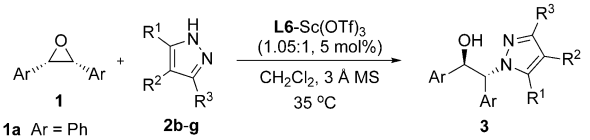
Given the remarkable performance of the present catalyst system, its further applicability was also examined with more pyrazole derivatives (Table 3). To our delight, the corresponding *syn*-β-pyrazole-substituted alcohols were obtained in good to excellent yields and high diastereo- and enantioselectivities at 5 mol% catalyst loading (Table 3, entries 1–10). Dimethyl-substituted 1*H*-pyrazole **2c** provided the corresponding products with higher enantioselectivity than 1*H*-pyrazole **2b** (Table 3, entries 2, 7, and 9 vs. entry 1). A 4-nitro substituent on 1*H*-pyrazole had a slight influence on the stereoselectivity but reduced the reactivity sharply (Table 3, entries 1 and 3). 4-Bromo-3,5-dimethyl-1*H*-pyrazole **2f** gave comparable stereoselectivities with either 4,4′-difluorostilbene oxide **1b** or 3,3′-dimethoxylstilbene oxide **1j** (Table 3, entries 5, 8, and 10). Remarkably, 1*H*-indazole gave the desired 2-indazolyl-1,2-diphenylethanol with up to 99% *ee* (Table 3, entry 6). Additionally, almost complete conversions of epoxides **1b** and **1j** could be achieved with pyrazole **2c** in 92% and 97% *ee*, respectively (Table 3, entries 7 and 9).

It is worth pointing out that *trans*-stilbene oxide reacted sluggishly in current reaction conditions (Table 4, entry 1). When *cis*- and *trans*-stilbene oxides were mixed in a ratio of 1:1 or 3:1 as the starting materials, the *syn*-β-pyrazole substituted alcohol was observed in high diastereo- and enantioselectivity. These results indicated that the catalytic system is capable of distinguishing between *cis*- and *trans*-stilbene oxides. It provided an efficient way to get the *syn*-product even if a mixture of *cis*- and *trans*-stilbene oxides was used.

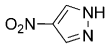
The absolute configuration of the β-pyrazole-substituted alcohol **3aa** was unambiguously determined to be (1*R*,2*R*) by single-crystal X-ray diffraction analysis of the corresponding methanesulfonyl-protected derivative **4** (Scheme 2).[16]

A mechanism to explain the large difference in the reactivity of the ring-opening reaction in the case of *cis*- and

Table 3. Asymmetric ring-opening of *meso*-epoxides with pyrazole derivatives.[a]

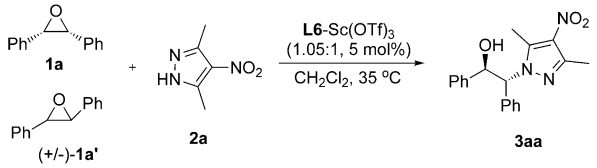


1a Ar = Ph
1b Ar = 4-FC_6H_4
1j Ar = 3-$MeOC_6H_4$

Entry	1	2	t [h]	Yield [%][b]	d.r.[c]	ee [%][d]
1	**1a**	 **2b**	24	99	99:1	87
2	**1a**	 **2c**	24	96	99:1	95
3	**1a**	 **2d**	24	88	99:1	89
4	**1a**	 **2e**	24	54	99:1	87
5	**1a**	 **2f**	24	95	99:1	95
6	**1a**	 **2g**	24	87	99:1	99
7	**1b**	**2c**	48	99	99:1	92
8	**1b**	**2f**	48	99	99:1	95
9	**1j**	**2c**	48	99	99:1	97
10	**1j**	**2f**	48	99	99:1	96

[a] Unless otherwise noted, reactions were carried out with **1** (0.1 mmol), 1.5 equiv of **2** and 3 Å MS (20 mg) in CH_2Cl_2 (0.3 mL) at 35 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis and NMR spectroscopy. [d] Determined by chiral HPLC analysis.

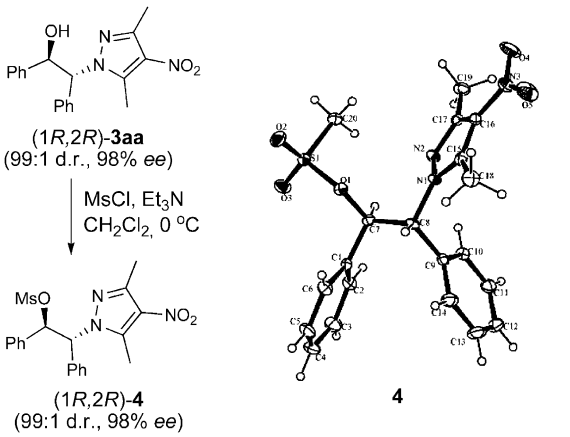
Table 4. The control experiments.[a]



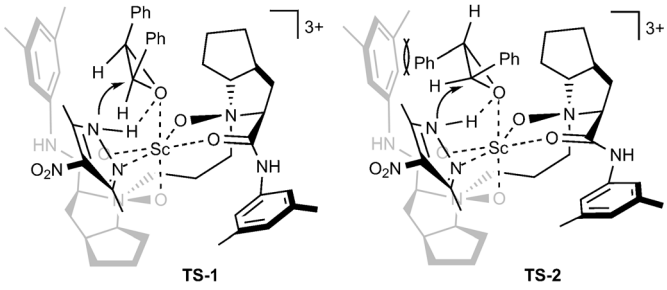
1a (+/-)-**1a'** **2a** **3aa**

Entry	1a [mmol]	1a′ [mmol]	2a [mmol]	Yield [%][b]	d.r.[c]	ee [%][d]
1	0	0.1	0.1	trace	50:50	0
2	0.05	0.05	0.075	54	97:3	96
3	0.05	0.05	0.1	54	93:7	96
4	0.05	0.05	0.15	56	91:9	95
5	0.075	0.025	0.15	78	96:4	97

[a] Unless otherwise noted, reactions were carried out with 3 Å MS (20 mg) in CH_2Cl_2 (0.3 mL) at 35 °C within 18 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Determined by chiral HPLC analysis.



Scheme 2. Determination of the configuration of the product by single-crystal X-ray analysis. Ellipsoids set at 30% probability.

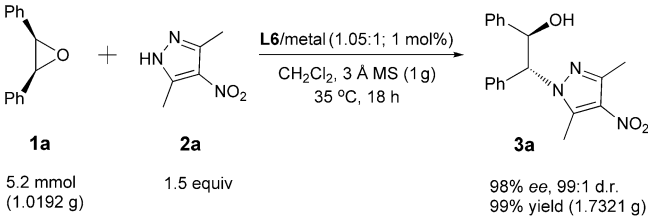


Scheme 3. Proposed catalytic model of the ring-opening reaction.

trans-stilbene oxides is shown in Scheme 3. In light of the steric arrangement of the product and the catalyst, we proposed that pyrazole, firstly, coordinated to the central metal at the horizontal position.[17] Subsequently, the *cis*-stilbene oxide was activated by coordination to Sc^{III} at the vertical site to form a hexadentate intermediate. The nitrogen of the pyrazole preferentially attacks the neighboring carbon atom from the rear side of the epoxide. At the same time, the strained three-membered ring was cleaved and the proton was transferred from the nitrogen atom to the oxide atom predominantly to give the (1*R*,2*R*)-configured product (Scheme 3, TS-1). When *trans*-stilbene oxide was used as the substrate, as shown in TS-2, the steric hindrance between the aryl group of the epoxide and the amide subunit of the ligand lowered the activation efficiency of the epoxide, which resulted in the low yield.

To show the synthetic application of the current system, a large-scale synthesis of **3aa** was tested. In the presence of 1 mol% of **L6**-Sc(OTf)$_3$, 5.2 mol of *cis*-stilbene oxide **1a** (1.0192 g) reacted with 1.5 equivalents of pyrazole **2a** to provide the desired product **3aa** in 99% yield without any loss in the enantioselectivity and diastereoselectivity (Scheme 4).

In summary, we have developed an efficient way to synthesize β-pyrazole-substituted alcohols through an asymmetric ring-opening reaction of *meso*-epoxides by using the novel nucleophilic pyrazole derivatives. In the presence of 1 mol% of the *N,N'*-dioxide–Sc(OTf)$_3$ complex catalyst, ex-



Scheme 4. Scaled-up version of the ring-opening reaction of *cis*-stilbene oxide **1a** with pyrazole **2a**.

cellent diastereoselectivities (99:1), enantioselectivities (up to 99% *ee*), and high yields were obtained under mild reaction conditions. The *syn*-product could easily be obtained from the mixture of *cis*- and *trans*-substrates. Meanwhile, a proposed transition-state model was put forward to explain the origin of the asymmetric induction. Additional investigations into the mechanism of the asymmetric induction and the extension of the methodology to other types of asymmetric ring-opening reactions are ongoing.

Experimental Section

General procedure: The prepared catalyst solution (1–5 mol%, 0.05 M in THF, see the Supporting Information) was introduced into a dry reaction tube. After removing the THF under reduced pressure, pyrazole derivative (1.5 equiv) and 3 Å molecular sieves (20.0 mg) were added. Then the mixture was stirred in CH_2Cl_2 (0.3 mL) for 5 min at 35 °C under a nitrogen atmosphere. Subsequently, the epoxide (0.1 mmol) was added at 35 °C, and the reaction mixture was stirred until the epoxide was no longer consumed (as determined by TLC). The residue was purified by flash chromatography on silica gel to afford the desired product.

Acknowledgements

We appreciate financial support from the National Natural Science Foundation of China (Nos. 21021001 and 21172151), and National Basic Research Program of China (973 Program: No. 2011CB808600). We also thank Sichuan University Analytical & Testing Center for NMR spectroscopic analysis.

Keywords: alcohols · asymmetric synthesis · epoxides · ring-opening reactions · scandium

[1] For a review, see: S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev.* **2011**, *111*, 6984–7034.

[2] a) X. B. Ke, H. Hu, K. D. Zhang, W. J. Xu, Q. F. Zhu, L. M. Wu, X. M. Hu, *Chem. Commun.* **2009**, 1037–1039; b) A. A. Pieper, S. H. Xie, E. Capota, S. J. Estill, J. Zhong, J. M. Long, G. L. Becker, P. Huntington, S. E. Goldman, C. H. Shen, M. Capota, J. K. Britt, T. Kotti, K. Ure, D. J. Brat, N. S. Williams, K. S. MacMillan, J. Naidoo, L. Melito, J. Hsieh, J. D. Brabander, J. M. Ready, S. L. McKnight, *Cell* **2010**, *142*, 39–51; c) H. Glas, K. Köhler, E. Herdtweck, P. Maas, M. Spiegler, W. R. Thiel, *Eur. J. Inorg. Chem.* **2001**, *4*, 2075–2080.

[3] For reviews, see: a) C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9–17; b) M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765–1784; c) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; d) R. W. Hoffmann, *Angew. Chem.* **2003**, *115*, 1128–1142; *Angew. Chem. Int. Ed.* **2003**, *42*, 1096–1109; e) A. K. Yudin, *Aziridines and Epoxides in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; f) A. Padwa, S. S. Murphree, *ARKIVOC*, **2006**, *3*, 6–33; g) M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979–4988; h) A. Gansäuer, C. A. Fan, F. Keller, P. Karbaum, *Chem. Eur. J.* **2007**, *13*, 8084–8090; i) C. Ogawa, M. Kokubo, S. Kobayashi, *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 718–728.

[4] Selected examples of ring-opening reactions of epoxides with a cyanide nucleophile: a) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671; b) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707; c) S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001–1004; d) C. J. Zhu, F. Yuan, W. J. Gu, Y. Pan, *Chem. Commun.* **2003**, 692–693; e) Y. N. Belokon, D. Chusov, D. A. Borkin, L. V. Yashkina, A. V. Dmitriev, D. Katayev, M. North, *Tetrahedron: Asymmetry* **2006**, *17*, 2328–2333; f) B. Saha, M. H. Lin, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 8648–8655; g) Y. N. Belokon, D. Chusov, A. S. Peregudov, L. V. Yashkina, G. I. Timofeeva, V. I. Maleev, M. North, H. B. Kagan, *Adv. Synth. Catal.* **2009**, *351*, 3157–3167.

[5] Selected examples of ring-opening reactions of epoxides with alcohols: a) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260; b) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem.* **2004**, *116*, 5809–5812; *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694.

[6] Selected examples of ring-opening reactions of epoxides with thiols: a) H. Yamashita, T. Mukaiyama, *Chem. Lett.* **1985**, *14*, 1643–1646; b) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; c) M. H. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 5252–5254; d) J. Wu, X. L. Hou, L. X. Dai, L. J. Xia, M. H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 3431–3436; e) Y. J. Chen, C. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 1313- 1319; f) M. V. Nandakumar, A. Tschöp, H. Krautscheid, C. Schneider, *Chem. Commun.* **2007**, 2756–2758.

[7] Selected examples of ring-opening reactions of epoxides with azides: a) H. Yamashita, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213–1220; b) M. Hayashi, K. Kohmura, N. Oguni, *Synlett* **1991**, 774–776; c) W. A. Nugent, *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769; d) L. E. Martínez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898; e) H. Adolfsson, C. Moberg, *Tetrahedron: Asymmetry* **1995**, *6*, 2023–2031; f) J. L. Leighton, E. N. Jacobsen, *J. Org. Chem.* **1996**, *61*, 389–390; g) J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421; h) K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925; i) B. W. McCleland, W. A. Nugent, M. G. Finn, *J. Org. Chem.* **1998**, *63*, 6656–6666; j) R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780–10781; k) D. Y. Ma, H. Norouzi-Arasi, E. Sheibani, K. Wärnmark, *ChemCatChem* **2010**, *2*, 629–632.

[8] Selected examples of ring-opening reactions of epoxides with amines: a) X. L. Hou, J. Wu, L. X. Dai, L. J. Xia, M. H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 1747–1752; b) S. Sagawa, H. Abe, Y. Hase, T. Inaba, *J. Org. Chem.* **1999**, *64*, 4962–4965; c) A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron* **2002**, *58*, 75–82; d) F. Carrée, R. Gil, J. Collin, *Tetrahedron Lett.* **2004**, *45*, 7749–7751; e) F. Carrée, R. Gil, J. Collin, *Org. Lett.* **2005**, *7*, 1023–1026; f) S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.* **2005**, *7*, 4593–4595; g) C. Ogawa, S. Azoulay, S. Kobayashi, *Heterocycles* **2005**, *66*, 201–206; h) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, E. Suresh, R. V. Jasra, *Eur. J. Org. Chem.* **2006**, 1303–1309; i) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, S. Agrawal, V. J. Mayani, R. V. Jasra, *Tetrahedron Lett.* **2006**, *47*, 5277–5279; j) K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 973–975; *Angew. Chem. Int. Ed.* **2007**, *46*, 955–957; k) H. Bao, J. Zhou, Z. Wang, Y.

Guo, T. You, K. Ding, *J. Am. Chem. Soc.* **2008**, *130*, 10116–10127; l) B. Gao, Y. H. Wen, Z. G Yang, X. Huang, X. H. Liu, X. M. Feng, *Adv. Synth. Catal.* **2008**, *350*, 385–390; m) M. Kokubo, T. Naito, S. Kobayashi, *Tetrahedron* **2010**, *66*, 1111–1118.

[9] Selected examples of ring-opening reactions of epoxides by a halide: a) C. E. Garrett, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 4534–4535; b) W. A. Nugent, *J. Am. Chem. Soc.* **1998**, *120*, 7139–7140; c) S. E. Denmark, P. A. Barsanti, K. T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428–2429; d) S. Bruns, G. Haufe, *J. Fluorine Chem.* **2000**, *104*, 247–254; e) B. Tao, M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354; f) M. Nakajama, M. Saito, M. Uemura, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 8827–8829; g) G. Haufe, S. Bruns, *Adv. Synth. Catal.* **2002**, *344*, 165–171; h) E. Tokuoka, S. Kotani, H. Matsunaga, T. Ishizuka, S. Hashimoto, M. Nakajama, *Tetrahedron: Asymmetry* **2005**, *16*, 2391–2392; i) S. E. Denmark, P. A. Barsanti, G. L. Beutner, T. W. Wilson, *Adv. Synth. Catal.* **2007**, *349*, 567–582; j) N. Takenaka, R. S. Sarangthem, B. Captain, *Angew. Chem.* **2008**, *120*, 9854–9856; *Angew. Chem. Int. Ed.* **2008**, *47*, 9708–9710; k) A. V. Malkov, M. R. Gordon, S. Stončius, J. Hussain, P. Kočovský, *Org. Lett.* **2009**, *11*, 5390–5393; l) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268–3269.

[10] a) C. A. G. M. Weijers, *Tetrahedron: Asymmetry* **1997**, *8*, 639–647; b) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688; c) L. S. Zhao, B. Han, Z. L. Huang, M. Miller, H. J. Huang, D. S. Malashock, Z. L. Zhu, A. Milan, D. E. Robertson, D. P. Weiner, M. J. Burk, *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157; d) M. H. Yang, C. J. Zhu, F. Yuan, Y. J. Huang, Y. Pan, *Org. Lett.* **2005**, *7*, 1927–1930.

[11] a) A. Solladié-Cavallo, P. Lupattelli, C. Marsol, T. Isarno, C. Bonini, L. Caruso, A. Maiorella, *Eur. J. Org. Chem.* **2002**, 1439–1444; b) M. Bandini, P. G. Cozzi, P. Melchiorre, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 86–89; *Angew. Chem. Int. Ed.* **2004**, *43*, 84–87; c) M. Boudou, C. Ogawa, S. Kobayashi, *Adv. Synth. Catal.* **2006**, *348*, 2585–2589; d) M. Westermaier, H. Mayr, *Chem. Eur. J.* **2008**, *14*, 1638–1647; e) X. T. Pu, X. B. Qi, J. M. Ready, *J. Am. Chem. Soc.* **2009**, *131*, 10364–10365.

[12] M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1998**, *277*, 937–938.

[13] a) X. H. Liu, L. L. Lin, X. M. Feng, *Acc. Chem. Res.* **2011**, *44*, 574–587; b) Y. F. Cai, X. H. Liu, Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, L. L. Lin, X. M. Feng, *Angew. Chem.* **2010**, *122*, 6296–6300; *Angew. Chem. Int. Ed.* **2010**, *49*, 6160–6164; c) M. S. Xie, X. H. Chen, Y. Zhu, B. Gao, L. L. Lin, X. H. Liu, X. M. Feng, *Angew. Chem.* **2010**, *122*, 3887–3890; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799–3802; d) W. Li, J. Wang, X. L. Hu, K. Shen, W. T. Wang, Y. Y. Chu, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 8532–8533; e) K. Shen, X. H. Liu, G. Wang, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 4780–4784; *Angew. Chem. Int. Ed.* **2011**, *50*, 4684–4688; f) W. Li, X. H. Liu, X. Y. Hao, X. L. Hu, Y. Y. Chu, W. D. Cao, S. Qin, C. W. Hu, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2011**, *133*, 15268–15271; g) Z. Wang, Z. G. Yang, D. H Chen, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 5030–5034; *Angew. Chem. Int. Ed.* **2011**, *50*, 4928–4932.

[14] a) H. O. House, *J. Am. Chem. Soc.* **1955**, *77*, 3070–5083; b) A. C. Cope, P. A. Trumbull, E. R. Trumbull, *J. Am. Chem. Soc.* **1958**, *80*, 2844–2849; c) K. A. Bhatia, K. J. Eash, N. M. Leonard, M. C. Oswald, R. S. Mohan, *Tetrahedron Lett.* **2001**, *42*, 8129–8132; d) Y. M. Shen, B. Wang, Y. A. Shi, *Angew. Chem.* **2006**, *118*, 1457–1460; *Angew. Chem. Int. Ed.* **2006**, *45*, 1429–1432.

[15] a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2210; b) S. Y. Tosaki, R. Tsuji, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 2147–2155; c) T. Mashiko, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 14990–14999.

[16] CCDC-852929 (**4**) 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.

[17] 1*H*-Imidazole was employed in the ring-opening reaction of *meso*-epoxide. However, the desired product could not be detected. It proved that the two adjacent nitrogen atoms were crucial for the asymmetric catalysis.

Received: December 2, 2011
Published online: February 23, 2012

