Tetrahedron 69 (2013) 3075–3081

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile synthesis of chiral 1,2-chlorohydrins via the ring-opening of *meso*-epoxides catalyzed by chiral phosphine oxides

Shunsuke Kotani [a,*], Haruka Furusho [b], Masaharu Sugiura [b], Makoto Nakajima [b,*]

[a] *Priority Organization for Innovation and Excellence, Kumamoto University, Kumamoto, Japan*
[b] *Graduate School of Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan*

ARTICLE INFO

Article history:
Received 14 December 2012
Received in revised form 17 January 2013
Accepted 21 January 2013
Available online 31 January 2013

Keywords:
Chlorohydrin
meso-Epoxide
Enantioselective
Halogenation
Lewis base

ABSTRACT

The facile synthesis of chiral 1,2-chlorohydrins via the enantioselective ring-opening of *meso*-epoxides with silicon tetrachloride in the presence of a chiral phosphine oxide was accomplished. The chiral 1,2-chlorohydrins were also obtained from the corresponding *cis*-alkenes in one-pot without significant loss in the selectivity, thereby permitting easy access to the 1,2-chlorohydrins from *cis*-alkenes with good yields and enantioselectivities.

1. Introduction

The asymmetric desymmetrization of *meso*-compounds is an effective strategy for directly accessing optically active chiral products.[1] This reaction is exemplified by the asymmetric desymmetrization of *meso*-cyclic compounds via selective ring-opening at one of the enantiotopic carbons. The *meso*-epoxides comprise a versatile class of substrates because they react with a variety of nucleophiles to afford several types of chiral alcohols with contiguous chiral centers. Such products provide useful intermediates and chiral building blocks.[2] For example, the desymmetrization of *meso*-epoxides using halide anions produces the chiral 1,2-halohydrins.[3] In 1988, Yamamoto developed the chiral organoaluminium-mediated asymmetric ring-opening of cyclohexene oxide to give the corresponding 1,2-halohydrin.[4] Brown reported the enantioselective synthesis of 1,2-halohydrins using chiral borane reagents.[5,6] In 1998, a striking achievement has been developed by Denmark, who applied chiral phosphoramides as a Lewis base catalyst to the ring-opening of *meso*-epoxides with silicon tetrachloride, producing chiral 1,2-chlorohydrins enantioselectively.[3,7,8] Thereafter, exciting advances have been achieved in this field.[9–16] Here, we report a full description of the enantioselective ring-opening of *meso*-epoxides catalyzed by a chiral phosphine oxide.[11] We have additionally developed a more convenient synthetic method for producing chiral 1,2-chlorohydrins from *cis*-alkenes in one-pot.

2. Result and discussion

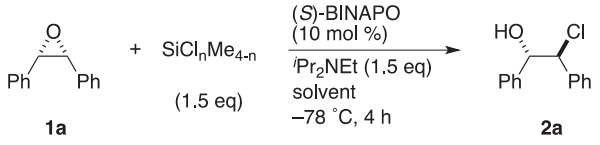
2.1. Enantioselective ring-opening of *meso*-epoxides catalyzed by phosphine oxide

We initially performed the ring-opening of *cis*-stilbene oxide (**1a**) using 1.5 equiv of silicon tetrachloride in the presence of 10 mol % (*S*)-BINAP dioxide (BINAPO) and 1.5 equiv of diisopropylethylamine (Table 1). The choice of solvent was crucial for the reaction. Dichloromethane gave the corresponding 1,2-chlorohydrin (**2a**) in 94% yield and 90% ee (entry 1). In toluene, the solubility of the phosphine oxide catalyst was quite low, thereby promoting a non-catalytic process and reducing the enantioselectivity (entry 2). Propionitrile slightly decreased both the isolated yield and the enantioselectivity (entry 3). THF gave the same level of the enantioselectivity as dichloromethane (90% ee), but the yield of chlorohydrin **2a** decreased due to the formation of the by-product **3**, which may have been produced by the reaction with THF (entry 4, Fig. 1). We next performed the ring-opening of *cis*-stilbene oxide (**1a**) using chloromethylsilanes in place of silicon tetrachloride. The use of chlorotrimethylsilane dramatically reduced both the yield and selectivity (entry 5). The use of trichloromethylsilane favored the product, but the selectivity was lower than the selectivity achieved using silicon tetrachloride (entry 6).

* Corresponding authors. Tel.: +81 963714394; e-mail address: skotani@gpo.kumamoto-u.ac.jp (S. Kotani).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.01.066

Table 1
Enantioselective ring-opening of *cis*-stilbene oxide (**1a**) under various reaction conditions[a]



Entry	Chlorosilane	Solvent	Yield, %[b]	Ee, %[c]
1	$SiCl_4$	CH_2Cl_2	94	90
2	$SiCl_4$	Toluene	70	25
3	$SiCl_4$	EtCN	83	74
4	$SiCl_4$	THF	56 (29)[d]	90
5	Me_3SiCl	CH_2Cl_2	13	1
6	$MeSiCl_3$	CH_2Cl_2	84	0

[a] The reaction was performed by adding a chlorosilane (1.5 equiv) to a solution containing **1a** (1.0 equiv), diisopropylethylamine (1.5 equiv), and (*S*)-BINAPO (10 mol %) at −78 °C under an argon atmosphere.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The yield of by-product **3** is given in parenthesis.

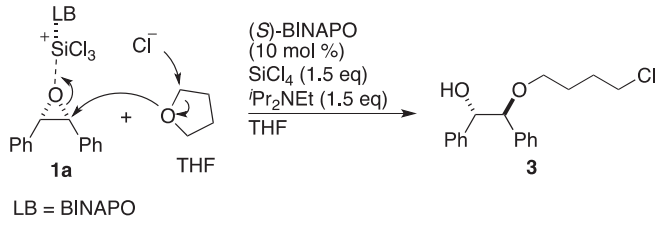


Fig. 1. Ring-opening of THF.

Additives were screened in dichloromethane (Table 2). Without additives, the chlorohydrin **2a** was obtained quantitatively; however, the observed selectivity was lower than the selectivity achieved using diisopropylethylamine (entry 2). The low selectivity results from the presence of a small amount of hydrogen chloride, which was adventitiously generated from silicon tetrachloride and promoted the non-selective reaction course.[17] Triethylamine gave the product with a lower enantioselectivity than was achieved using diisopropylethylamine (entry 3), whereas pyridine dramatically reduced the selectivity (entry 4). Pyridine may coordinate to silicon tetrachloride in the reaction media to form an achiral hypervalent silicon species, yielding the racemic product **2a**. Interestingly, the addition of 2-methyl-2-butene also improved the enantioselectivity (entry 5). These results support the notion that acid scavenging is essential for achieving a high enantioselectivity. Excess or low equivalents of diisopropylethylamine to silicon tetrachloride gave almost the same results, but the selectivities decreased slightly in both cases (entries 6 and 7).

Table 2
Effect of additives on the ring-opening of **1a**[a]

Entry	Additive (equiv)	Yield, %[b]	Ee, %[c]
1	^{i}Pr$_2$NEt (1.5)	94	90
2	None (1.5)	99	59
3	Et_3N (1.5)	98	82
4	Pyridine (1.5)	83	11
5	2-Methyl-2-butene (1.5)	93	85
6	^{i}Pr$_2$NEt (0.75)	97	86
7	^{i}Pr$_2$NEt (3.0)	90	88

[a] The reaction was performed by adding silicon tetrachloride (1.5 equiv) to a solution containing **1a** (1.0 equiv), an additive, and (*S*)-BINAPO (10 mol %) in dichloromethane at −78 °C under an argon atmosphere.
[b] Isolated yield.
[c] Determined by HPLC analysis.

We next screened the chiral phosphine oxides in an effort to increase the selectivity under the optimized conditions (Fig. 2). Both tol-BINAPO and xyl-BINAPO significantly reduced the enantioselectivities relative to BINAPO. Substituents on the phenyl ring had a large effect on the enantioselectivities of **1a**. H_8-BINAPO and SEGPHOSO, bearing different types of biaryl skeletons, afforded enantioselectivities similar to that of BINAPO. DIOPO was ineffective in the enantioinduction of the ring-opening reactions of *meso*-epoxides.[18] These results indicated that both the biaryl skeleton and the phenyl groups were important for obtaining a high selectivity.

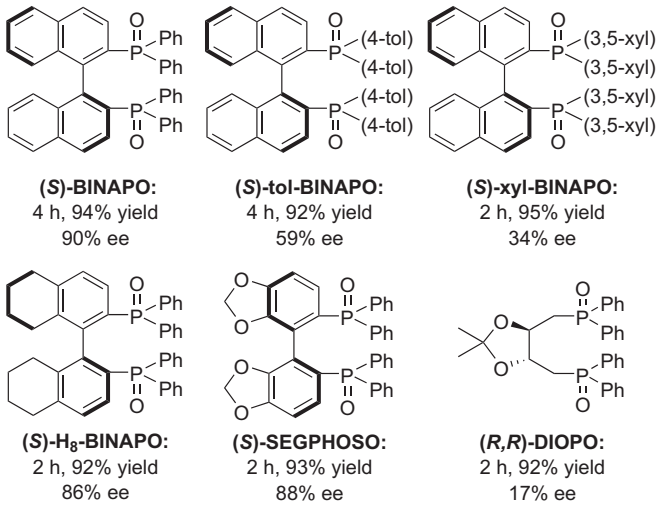
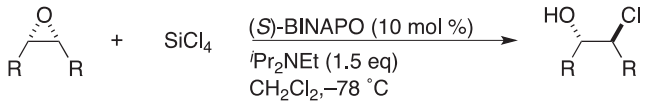


Fig. 2. Screening of the chiral phosphine oxides.

The ring-opening of various *meso*-epoxides **1** was achieved using BINAPO as the catalyst (Table 3). Variations in the substituents on the aromatic ring did not influence the reaction efficiency, and high enantioselectivities were obtained in all cases (entries 2–4). Conversion of the *meso*-epoxide **1e** derived from a linear olefin to the corresponding chlorohydrin **2e** was good, although the selectivity was low, presumably due to the conformational flexibility of **1e** (entry 5). Cyclohexene oxide (**1f**) gave a good selectivity (entry

Table 3
Substrate scope of the ring-opening for various *meso*-epoxides **1**[a]



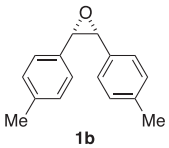
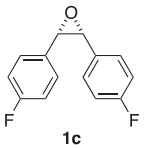
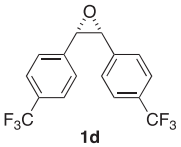
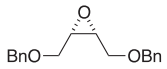
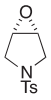
Entry	Substrate **1**	Time, h	Product **2** or **4**	Yield, %[b]	Ee, %[c] (config)
1	 **1a**	4	**2a**	94	90 (1*S*,2*S*)
2	 **1b**	2	**2b**	93	84 (1*S*,2*S*)
3	 **1c**	0.25	**2c**	96	86 (1*S*,2*S*)

Table 3 (*continued*)

Entry	Substrate	Time, h	Product		
	1		**2** or **4**	Yield, %[b]	Ee, %[c] (config)
4	 **1d**	0.5	**2d**	97	86 (1*S*,2*S*)
5	 **1e**	12	**2e**	92	35 (1*S*,2*S*)
6	 **1f**	1	**2f**[d]	81	71 (1*S*,2*S*)
7	 **1g**	72	**2g**[d]	81	50 (1*S*,2*S*)
8	 **1h**	1	**2h**	95	34
9	 **1i**	1	**2i**[d]	73	39
10	 **1j**	48	**4j**[d]	60	66

[a] The reaction was performed by adding silicon tetrachloride (1.5 equiv) to the solution containing the *meso*-epoxide **1** (1.0 equiv), diisopropylethylamine (1.5 equiv), and (*S*)-BINAPO (10 mol %) in dichloromethane at −78 °C under an argon atmosphere.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Isolated as 4-nitrobenzoate.

6), whereas in the reaction of cyclooctene oxide (**1g**), the selectivity of chlorohydrin **2g** was modest (entry 7). The heterocyclic epoxides **1h** and **1i** were smoothly converted into the corresponding products **2h** and **2i** with modest selectivities (entries 8 and 9). The reaction of norbornene oxide (**1j**) yielded the major product in moderate yield and selectivity (entry 10); however, the product could not be definitively assigned as 1,2- or 1,4-chlorohydrin by NMR analysis because the spectra for these chrolohydrins are quite similar.[15,16,19] X-ray crystal structure analysis of the crystalline 4-nitrobenzoate of the major product revealed that the obtained product was 1,4-chlorohydrin **4j** (Fig. 3). The 1,4-chlorhydrin **4j** may be obtained through the reaction mechanism shown in Fig. 4.[16] Norbornene oxide (**1j**) may be activated by chiral silicon species, leading to an enantiotopic Wagner–Meerwein rearrangement. The intramolecular addition of a chloride anion from hypervalent silicate to the cationic species, produced the 1,4-chlorohydrin **4j**.

2.2. One-pot synthesis of 1,2-chlorohydrins from the *cis*-alkenes

The combination of stepwise transformations in a one-pot reaction offers a powerful organic synthesis method by reducing the number of synthetic process and the amounts of chemical reagents

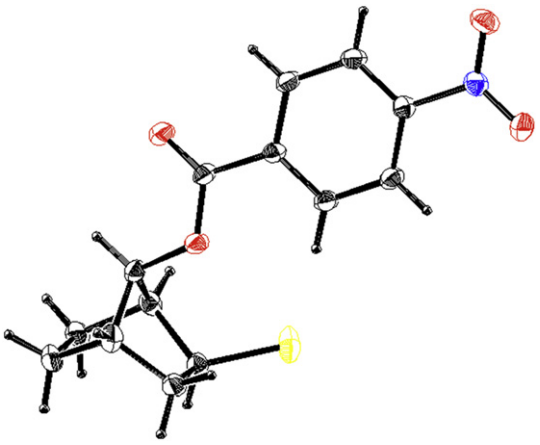


Fig. 3. X-ray structure of **4j**-NB.

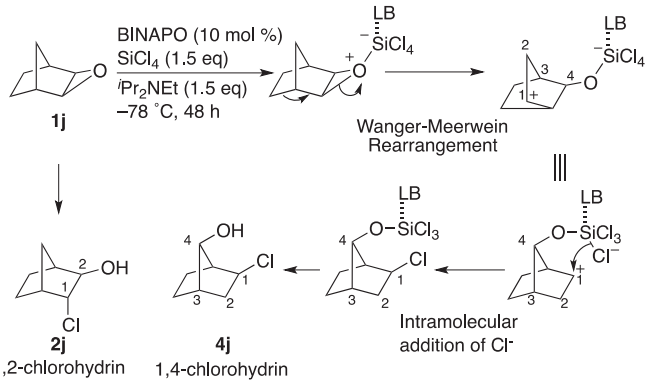


Fig. 4. Plausible reaction mechanism for the preparation of 1,4-chlorohydrine **4j**.

needed to obtain a desired product.[20] One-pot synthetic approaches are ideally highly efficient and permit ready access to an optically active product. The *meso*-epoxides used in the ring-opening were generally synthesized from the corresponding *cis*-alkenes using an oxidant. We therefore sought to combine these processes in one-pot and to establish a chlorohydrin syntheses from the *cis*-alkenes.[21]

1,2-chlorohydrin **2a** was synthesized from *cis*-stillbene (**5a**) (Fig. 5). The reaction was performed via oxidation to the epoxide **1a** in the presence of 1.2 equiv of *m*-chloroperbenzoic acid (*m*-CPBA)[22] and 10 mol % of BINAPO, followed by ring-opening under the above reaction condition. Oxidation was completed within 5 h at room temperature. The resulting solution was cooled to −78 °C, and diisopropylethylamine and silicon tetrachloride were added successively. Fortunately, the desired 1,2-chlorohydrin **2a** was obtained in good yield, but the observed enantioselectivity was lower than was achieved in the ring-opening of isolated *meso*-epoxide **1a**.

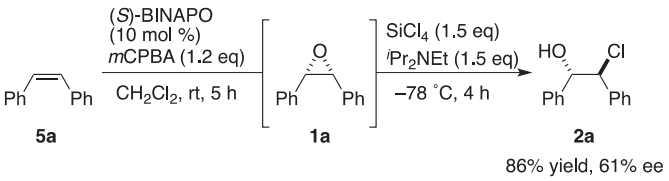
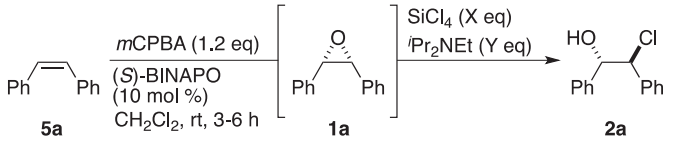


Fig. 5. One-pot 1,2-chlorohydrin synthesis from *cis*-stilbene (**5a**).

The stepwise and one-pot synthetic approaches differed in the use of *m*-CPBA as the oxidant and the production of *m*-chlorobenzoic acid. These reagents may interfere with the stereoselective ring-opening of *meso*-epoxide **1a**, thereby reducing the selectivity.

Thus, we reexamined the reaction conditions in an effort to mitigate the effects of these reagents on the selectivity (Table 4). Lowering the equivalents of diisopropylethylamine dramatically decreased the enantioselectivity (entry 2). By contrast, a small excess of the amine improved the selectivity (entries 3 and 4); 1.6 equiv of diisopropylethylamine gave a level of selectivity similar to the selectivity achieved for the ring-opening of the isolated *meso*-epoxide **1a** (entry 3); however, excess amounts of amine tended to reduce the selectivity of **2a** (entries 4 and 5). Increasing or decreasing both the silicon tetrachloride and the diisopropylethylamine reduced the selectivity (entries 6 and 7).

Table 4
Optimization study of the reaction conditions for the one-pot chlorohydrin synthesis[a]

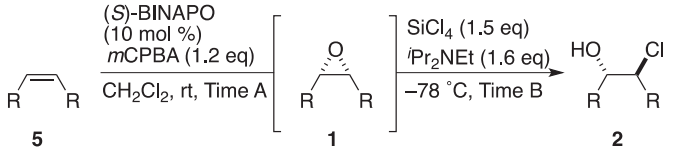


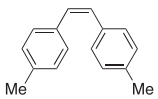
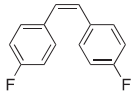
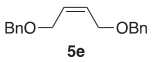
Entry	X	Y	Time, h	Yield, %[b]	Ee, %[c]
1	1.5	1.5	4	86	61
2	1.5	1.0	4	84	29
3	1.5	1.6	2	83	88
4	1.5	2.0	3	82	80
5	1.5	2.5	18	87	43
6	1.2	1.3	1	87	72
7	2.0	2.1	2	81	84

[a] The reaction was performed by adding *m*-CPBA (1.2 equiv) to a solution containing **5a** (1.0 equiv) and (*S*)-BINAPO (10 mol %) in dichloromethane at room temperature under an argon atmosphere, followed by the addition of diisopropylethylamine and silicon tetrachloride at −78 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.

With the optimal conditions in hand, we performed the reaction using various *cis*-alkenes **5** (Table 5). The *cis*-stilbene derivatives **5b** and **5c** gave high enantioselectivities similar to those achieved for ring-opening of the isolated *meso*-epoxides (entries 2 and 3). 1,4-Bis(benzyloxy)-2-butene (**5e**) also afforded the corresponding chlorohydrin **2e** (entry 4). Cyclohexene (**5f**) was smoothly oxidized

Table 5
One-pot chlorohydrin synthesis of various *cis*-alkenes[a]



Entry	Substrate 5	Time A, h	Time B, h	Product 2, 4	Yield, %[b]	Ee, %[c] (config)
1	 5a	6	2	**2a**	83	88 1*S*,2*S*)
2	 5b	7	1	**2b**	81	85 (1*S*,2*S*)
3	 5c	8	1	**2c**	83	85 (1*S*,2*S*)
4	 5e	0.5	0.5	**2e**	62	40 (1*S*,2*S*)
5	 5f	3	1	**2f**[d]	88	64 (1*S*,2*S*)
6	 5g	18	24	**2g**[d]	94	47 (1*S*,2*S*)
7[e]	 5h	72	6	**2h**	81	35
8[e]	 5i	12	6	**2i**[d]	61	37
9	 5j	5	48	**4j**[d]	60	67

[a] The reaction was performed by adding *m*-CPBA (1.2 equiv) to a solution containing the *cis*-alkene **5** (0.5 mmol) and (*S*)-BINAPO (10 mol %) in dichloromethane at room temperature under an argon atmosphere, followed by addition of diisopropylethylamine (1.6 equiv) and silicon tetrachloride (1.5 equiv) at −78 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Isolated as 4-nitrobenzoate.
[e] 5.0 equiv of silicon tetrachloride were used.

to the epoxide **1f**, which then reacted with silicon tetrachloride to give the chlorohydrin **2f** in good yield with good selectivity (entry 5). By contrast, cyclooctene (**5g**) was less reactive with respect to both epoxidation and the ring-opening, giving a modest selectivity (entry 6). The five-membered cyclic alkenes **5h** and **5i** bearing heteroatoms required 5 equiv of silicon tetrachloride to promote the ring-opening presumably due to the chelating effects of heteroatoms toward silicon tetrachloride. These reactions afforded the corresponding chlorohydrins **2h** and **2i**[23] (entries 7 and 8). The reaction of norbornene (**5j**) produced 1,4-chlorohydrin **4j** in good yield with good selectivity (entry 9).

3. Conclusion

We developed a facile method to synthesize 1,2-chlorohydrins from *meso*-epoxides using a chiral phosphine oxide catalyst and silicon tetrachloride. We extended the utility of this transformation to a convenient one-pot approach from the corresponding *cis*-alkenes, thereby allowing ready access to the chiral 1,2-chlorohydrins in good yields without the isolation of the *meso*-epoxide intermediates.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with JEOL JNM-ECX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Tetramethylsilane (TMS) (δ=0 ppm) and $CDCl_3$ (δ=77.0 ppm) were served as internal standards for ^{1}H and ^{13}C NMR, respectively. Infrared spectra were recorded on JEOL JIR 6500-W. Mass spectra were measured with JEOL JMS-DX303HF mass spectrometer. Optical rotations were recorded on JASCO P- 1010 polarimeter. High-pressure liquid chromatography (HPLC) was performed on JASCO P-980 and UV-1575. Thin-layer chromatography (TLC) analysis was carried out using Merck silica gel plates. Visualization was accomplished with UV

light, phosphomolybdic acid, and/or anisaldehyde. Column chromatography was performed by using Kanto Chemical Silica Gel 60N (spherical, neutral, 63–210 mm). Dry dichloromethane (dehydrated) was purchased from Kanto Chemical. Propionitrile was purchased from Wako Pure Chemical Industries, and stored over 4 Å MS prior to use. All other solvents were purified based on standard procedures. Silicon tetrachloride was purchased from Tokyo Kasei Kogyo (TCI) and used without further purification. Chiral phosphine oxides were prepared by oxidation of the corresponding phosphines with hydrogen peroxide in acetone.[22] *m*-Chloroperoxybenzoic acid (*m*-CPBA, ca.70%) was purified by washing with satd $NaHCO_3$ and brine, and drying over $MgSO_4$. All other chemicals were purified based on standard procedures.

4.2. Typical procedure for ring-opening reaction of *meso*-epoxides

Under an argon atmosphere, silicon tetrachloride (0.044 mL, 0.38 mmol, 1.5 equiv) was added to a solution of *cis*-stilbene oxide **1a** (50 mg, 0.25 mmol, 1.0 equiv), diisopropylethylamine (0.65 mL, 0.38 mmol, 1.5 equiv), and (*S*)-BINAPO (16.6 mg, 0.025 mmol, 10 mol %) in CH_2Cl_2 (1 mL) at −78 °C. After being stirred for 4 h, the reaction was quenched with satd $NaHCO_3$ (1 mL) and satd KF/KH_2PO_4 (2 mL), and then the slurry was stirred for 0.5 h. The two-layers mixture was filtered through a cotton pad and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hex/EtOAc=10:1, SiO_2: 10 g) to give the corresponding chlorohydrin **2a** (55.4 mg, 94% yield).

*4.2.1. (1S,2S)-2-Chloro-1,2-diphenylethanol (**2a**).*[15] A colorless oil; $[\alpha]_D^{25}$ +19.7 (*c* 1.0, EtOH) for 90% ee [lit. [15]; $[\alpha]_D$ +21.2 (*c* 1.0, EtOH) for (1*S*,2*S*)-isomer of 94% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.04 (−O*H*, d, *J*=2.3 Hz, 1H), 4.95 (OH−C*H*, dd, *J*=2.3, 8.2 Hz, 1H), 4.99 (Cl−C*H*, d, *J*=8.2 Hz, 1H), 7.08–7.24 (Ar−*H*, m, 10H); The enantiomeric excess was determined to be 90% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent: hex/IPA=29:1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 23.3 min (1*R*,2*R*), 25.5 min (1*S*,2*S*)].

*4.2.2. (1S,2S)-2-Chloro-1,2-di(4-tolyl) ethanol (**2b**).*[15] A colorless oil; $[\alpha]_D^{29}$ −41.7 (*c* 0.98, $CHCl_3$) for 84% ee [lit. [15]; $[\alpha]_D$ −37.0 (*c* 0.8, $CHCl_3$) for (1*S*,2*S*)-isomer of 89% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (C*H*$_3$−Ar, s, 3H), 2.29 (C*H*$_3$−Ar, s, 3H), 2.97 (−O*H*, d, *J*=2.8 Hz, 1H), 4.93 (HO−C*H*, dd, *J*=2.8, 8.2 Hz, 1H), 4.98 (Cl−C*H*, d, *J*=8.2 Hz, 1H), 7.00–7.02 (Ar−*H*, m, 4H), 7.02 (Ar−*H*, d, *J*=8.2 Hz, 2H), 7.08 (Ar−*H*, d, *J*=8.2 Hz, 2H); The enantiomeric excess was determined to be 84% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent: hex/IPA=9:1; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 19.6 min (1*R*,2*R*), 21.9 min (1*S*,2*S*)].

*4.2.3. (1S,2S)-2-Chloro-1,2-bis(4-fluorophenyl) ethanol (**2c**).*[15] A colorless oil; $[\alpha]_D^{28}$ −3.1 (*c* 0.91, $CHCl_3$) for 86% ee [lit. [15]; $[\alpha]_D$ −4.0 (*c* 0.85, $CHCl_3$) for (1*S*,2*S*)-isomer of 93% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (−O*H*, d, *J*=2.3 Hz, 1H), 4.89 (HO−C*H*, dd, *J*=2.3, 8.7 Hz, 1H), 4.92 (Cl−C*H*, d, *J*=8.7 Hz, 1H), 6.86–6.95 (Ar−*H*, m, 4H), 7.02–7.07 (Ar−*H*, m, 2H), 7.09–7.14 (Ar−*H*, m, 2H). The enantiomeric excess was determined to be 86% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent: hex/IPA=97:3; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 23.0 min (1*R*,2*R*), 25.0 min (1*S*,2*S*)].

*4.2.4. (1S,2S)-2-Chloro-1,2-bis(4-trifluoromethylphenyl)ethanol (**2d**).*[15] A colorless oil; $[\alpha]_D^{30}$ −11.6 (*c* 0.82, $CHCl_3$) for 86% ee [lit. [15]; $[\alpha]_D$ −11.9 (*c* 0.65, $CHCl_3$) for (1*S*,2*S*)-isomer of 87% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (−O*H*, br s, 1H), 5.02 (HO−C*H*, s, 1H), 5.04 (Cl−C*H*, s, 1H), 7.24 (Ar−*H*, d, *J*=8.2 Hz, 2H), 7.31 (Ar−*H*, d, *J*=8.2 Hz, 2H), 7.49 (Ar−*H*, d, *J*=8.2 Hz, 2H), 7.52 (Ar−*H*, d, *J*=8.2 Hz, 2H); The enantiomeric excess was determined to be 86% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent; hex/IPA=9:1; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 11.8 min (1*R*,2*R*), 15.2 min (1*S*,2*S*)].

*4.2.5. (2S,3S)-1,4-Bis(benzyloxy)-3-chlorobutan-2-ol (**2e**).*[8] A colorless oil; $[\alpha]_D^{25}$ +1.0 (*c* 1.0, $CHCl_3$) for 35% ee [lit. [8]; $[\alpha]_D^{25}$ +2.8 (*c* 1.0, EtOH) for (2*S*,3*S*)-isomer of 71% ee]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.52 (−O*H*, d, *J*=6.0 Hz, 1H), 3.50–3.62 (BnO−C*H*$_2$, m, 2H), 3.72–3.77 (BnO−C*H*$_2$, m, 1H), 3.79–3.85 (BnO−C*H*$_2$, m, 1H), 4.15–4.17 (C*H*−OH, m, 1H), 4.23–4.26 (C*H*−Cl, m, 1H), 4.54–4.61 (C*H*$_2$−Ph, m, 4H), 7.29–7.37 (Ar−*H*, m, 10H); The enantiomeric excess was determined to be 35% ee by HPLC analysis with Daicel Chiralcel OD-H column [eluent; hex/EtOH=24:1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 15.2 min (2*S*,3*S*), 19.0 min (2*R*,3*R*)].

*4.2.6. 4-Chloro-1-tosyl-3-pyrrolidinol (**2h**).*[11] Colorless needles; mp: 115.5–116.0 °C; $[\alpha]_D^{26}$ +1.2 (*c* 1.0, $CHCl_3$) for 34% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (−O*H*, br s, 1H), 2.43 (C*H*$_3$, s, 3H), 3.39 (C*H*$_2$, d, *J*=11.4 Hz, 1H), 3.53 (C*H*$_2$, dd, *J*=2.3, 11.4 Hz, 1H), 3.63 (C*H*$_2$, dd, *J*=4.6, 11.4 Hz, 1H), 3.86 (C*H*$_2$, dd, *J*=4.6, 11.4 Hz, 1H), 4.06 (OH−C*H*, t, *J*=2.3 Hz, 1H), 4.28 (Cl−C*H*, br s, 1H), 7.32 (Ar−*H*, d, *J*=8.3 Hz, 2H), 7.73 (Ar−*H*, d, *J*=8.3 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 21.6, 53.0, 53.4, 54.1, 60.0, 127.5, 129.7, 133.5, 143.9; IR (KBr): 1324, 1596, 3467 cm^{-1}; LR-FABMS: *m*/*z* 276 $[M+H]^+$; HR-FABMS: Calcd for $C_{11}H_{14}ClNO_3S$ 276.0461, found 276.0435; The enantiomeric excess was determined to be 34% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent; hex/IPA=9:1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 25.4 min (minor), 27.0 min (major)].

4.3. Typical procedure for ring-opening reaction of *meso*-epoxides and 4-nitrobenzoylation

Under an argon atmosphere, silicon tetrachloride (0.087 mL, 0.76 mmol, 1.5 equiv) was added to a solution of cyclohexene oxide (**1f**) (0.51 mmol, 1.0 equiv), diisopropylethylamine (0.130 mL, 0.76 mmol, 1.5 equiv), and (*S*)-BINAPO (33.3 mg, 0.050 mmol, 10 mol %) in CH_2Cl_2 (2 mL) at −78 °C. After being stirred for 1 h, the reaction was quenched with satd $NaHCO_3$ (1 mL) and satd KF/KH_2PO_4 (2 mL), and then the slurry was stirred for 0.5 h. The two-layers mixture was filtered through a cotton pad and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was dissolved in CH_2Cl_2 (10 mL), and then *p*-nitrobenzoyl chloride (470 mg, 2.5 mmol, 5.0 equiv) and triethylamine (0.70 mL, 5.0 mmol, 10 equiv) were added to the resulting solution at room temperature. After being stirred for 12 h, the reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with 10% HCl (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hex/EtOAc=12:1, SiO_2: 10 g) to give the corresponding product **2f**-NB (116 mg, 81% yield).

*4.3.1. (1S,2S)-2-Chlorocyclohexyl 4-nitrobenzoate (**2f**-NB).* Yellow needles; mp: 58.0–59.0 °C; $[\alpha]_D^{25}$ +67.3 (*c* 1.0, $CHCl_3$) for 71% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38–1.57 (C*H*$_2$, m, 3H), 1.73–1.84 (C*H*$_2$, m, 3H), 2.25–2.35 (C*H*$_2$, m, 2H), 4.01–4.06 (O−C*H*, m, 1H), 5.05–5.11 (Cl−C*H*, m, 1H), 8.23 (Ar−*H*, d, *J*=9.2 Hz, 2H), 8.33 (Ar−*H*, d, *J*=9.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 23.3, 24.6, 30.8, 34.9, 60.5, 76.6, 123.5, 130.8, 135.6, 150.6, 163.8; IR (KBr): 1278, 1529,

1726 cm^{-1}; LR-FABMS: *m*/*z* 166, 283 $[M]^+$; HR-FABMS: Calcd for $C_{13}H_{14}ClNO_4$ 283.0611, found 283.0627; The enantiomeric excess was determined to be 71% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent: hex/IPA=99:1; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 53.0 min (major), 56.4 min (minor)]. The absolute configuration was determined to be 1*S*,2*S* after the conversion to **2f** by the comparison of the sign of the optical rotation ($[\alpha]_D^{20}$ +29.9 (*c* 1.0, $CHCl_3$) for 71% ee) [lit. [24]; $[\alpha]_D$ +32.9 (*c* 2.18, EtOH) for (1*S*,2*S*)-isomer of 79% ee].

*4.3.2. 2-Chlorocyclooctyl 4-nitrobenzoate (**2g**-NB).*[25] Yellow needles; mp: 86.0–87.0 °C; $[\alpha]_D^{26}$ +42.9 (*c* 1.0, $CHCl_3$) for 50% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45–1.63 (CH_2, m, 3H), 1.77–1.80 (CH_2, m, 4H), 1.88–1.94 (CH_2, m, 3H), 2.05–2.12 (CH_2, m, 1H), 2.27–2.34 (CH_2, m, 1H), 4.35–4.40 (O–C*H*, m, 1H), 5.35–5.41 (Cl–C*H*, m, 1H), 8.22 (Ar–*H*, d, *J*=7.5 Hz, 2H), 8.29 (Ar–*H*, d, *J*=7.5 Hz, 2H); The enantiomeric excess was determined to be 50% ee by HPLC analysis with Daicel Chiralcel OJ column [eluent: hex/IPA=49:1; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 29.3 min (1*S*,2*S*), 37.4 min (1*R*,2*R*)]. The absolute configuration was determined to be 1*S*,2*S* after the conversion to **2g** by the comparison of the sign of the optical rotation ($[\alpha]_D^{20}$ +18.6 (*c* 1.15, $CHCl_3$) for 50% ee) [lit. [16]; $[\alpha]_D$ −26.4 (*c* 1.0, $CHCl_3$) for (1*R*,2*R*)-isomer of 90% ee].

*4.3.3. 3-Chloro-2-tetrahydrofuranyl 4-nitrobenzoate (**2i**-NB).* A colorless oil; $[\alpha]_D^{28}$ +43.3 (*c* 1.34, $CHCl_3$) for 39% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 4.03–4.08 (CH_2, m, 2H), 4.33–4.41 (CH_2, m, 2H), 4.47–4.47 (O–C*H*, t, *J*=2.3 Hz, 1H), 5.55 (Cl–C*H*, d, *J*=4.1 Hz, 1H), 8.21 (Ar–*H*, d, *J*=9.2 Hz, 2H), 8.31 (Ar–*H*, d, *J*=9.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 58.9, 71.3, 74.4, 81.5, 123.6, 130.9, 134.4, 150.9, 163.6; IR (neat): 1268, 1527, 1727 cm^{-1}; LR-FABMS: *m*/*z* 271 $[M]^+$; HR-FABMS; Calcd for $C_{11}H_{10}ClNO_5$ 271.0248, found 271.0274; The enantiomeric excess was determined to be 39% ee by HPLC analysis with Daicel Chiralpak AD-H column [eluent hex/IPA=19:1; flow rate: 0.5 mL/min; detection: 254 nm; t_R: 49.2 min (major), 55.1 min (minor)].

*4.3.4. 1-Chlorobicyclo[2.2.1]heptyl 7-(4-nitrobenzoate) (**4j**-NB).* Yellow needles; mp: 94.5–95.5 °C; $[\alpha]_D^{29}$ −12.1 (*c* 1.06, $CHCl_3$) for 67% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24–1.36 (CH_2, m, 2H), 1.73–1.78 (CH_2, m, 1H), 1.82–1.86 (CH_2, m, 1H), 2.28 (CH_2, dd, *J*=7.8, 14.2 Hz, 1H), 2.36 (CH_2, dd, *J*=4.1, 14.2 Hz, 1H), 2.52 (CH_2, d, *J*=4.1 Hz, 1H), 2.70 (CH_2, d, *J*=4.1 Hz, 1H), 4.07 (Cl–C*H*, dd, *J*=4.1 Hz, 7.8 Hz, 1H), 5.07 (O–C*H*, s, 1H), 8.27-8.31 (Ar–*H*, m, 4H); ^{13}C NMR (400 MHz, $CDCl_3$) : δ 24.2, 24.8, 39.5, 41.7, 46.9, 59.6, 81.5, 123.5, 131.0, 135.6, 150.5, 164.6; IR (KBr): 1278, 1525, 1720 cm^{-1}; LR-FABMS: *m*/*z* 295 $[M]^+$; HR-FABMS: Calcd for $C_{14}H_{14}ClNO_4$ 295.0611, found 295.0639; The enantiomeric excess was determined to be 67% ee by HPLC analysis with Daicel Chiralpak AS-H column [eluent: hex/IPA=99:1; flow rate: 1.0 mL/min; detection: 254 nm; t_R: 19.4 min (minor), 24.4 min (major)]. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 915590.

4.4. Typical procedure for one-pot chlorohydrin synthesis from *cis*-alkenes

Under an argon atmosphere, a solution of purified *m*-chloroperoxybenzoic acid (103.6 mg, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) was added to a solution of a *cis*-stilbene (98.0 mg, 0.5 mmol, 1.0 equiv) and (*S*)-BINAPO (32.7 mg, 0.05 mmol, 10 mol %) in CH_2Cl_2 (1 mL) at room temperature, and the reaction mixture was stirred for 6 h. Diisopropylethylamine (0.14 mL, 0.8 mmol, 1.6 equiv) and silicon tetrachloride (0.086 mL, 0.75 mmol, 1.5 equiv) were added to the mixture at −78 °C successively. After being stirred for 2 h, the reaction was quenched with satd $NaHCO_3$ (3 mL), and 10% $Na_2S_2O_3$ (1 mL), and then the slurry was stirred for 0.5 h. The two-layer mixture was filtered through a cotton pad and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with 10% HCl (10 mL), satd $NaHCO_3$ (10 mL) and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hex/EtOAc=12:1, SiO_2: 10 g) to give the product **2a** (95.8 mg, 83% yield).

4.5. Typical procedure for one-pot chlorohydrin synthesis from *cis*-alkenes and 4-nitrobenzoylation

Under an argon atmosphere, a solution of purified *m*-chloroperoxybenzoic acid (103.6 mg, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) was added to a solution of cyclohexene (**5f**) (0.05 mL, 0.5 mmol, 1.0 equiv) and (*S*)-BINAPO (32.7 mg, 0.05 mmol, 10 mol %) in CH_2Cl_2 (1 mL) at room temperature, and the reaction mixture was stirred for 3 h. Diisopropylethylamine (0.14 mL, 0.8 mmol, 1.6 equiv) and silicon tetrachloride (0.086 mL, 0.75 mmol, 1.5 equiv) were added to the mixture at −78 °C successively. After being stirred for 1 h, the reaction was quenched with satd $NaHCO_3$ (3 mL) and 10% $Na_2S_2O_3$ (1 mL), and then the slurry was stirred for 0.5 h. The two-layers mixture was filtered through a cotton pad and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with 10% HCl (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration, the crude product was dissolved in CH_2Cl_2 (5 mL) and then *p*-nitrobenzoyl chloride (188.0 mg, 1.0 mmol, 2.0 equiv), triethylamine (0.21 mL, 1.5 mmol, 3.0 equiv), and DMAP (2 mol %) were added to the solution at room temperature. After being stirred for 16 h, the reaction was quenched with H_2O (5 mL). The two-layers mixture was separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with 10% HCl (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was purified by column chromatography (hex/EtOAc=12:1, SiO_2. 10 g) to give the product **2f**-NB (123.8 mg, 88% yield).

4.6. Procedure for one-pot chlorohydrin synthesis from 2,5-dihydrofuran (5i) and 4-nitrobenzoylation

Under an argon atmosphere, a solution of purified *m*-chloroperoxybenzoic acid (103.6 mg, 0.6 mmol, 1.2 equiv) in CH_2Cl_2 (1 mL) was added to a solution of 2,5-dihydrofuran (**5i**) (0.038 mL, 0.5 mmol, 1.0 equiv) and (*S*)-BINAPO (32.7 mg, 0.05 mmol, 10 mol %) in CH_2Cl_2 (1 mL) at room temperature, and the reaction mixture was stirred for 12 h. Diisopropylethylamine (0.14 mL, 0.8 mmol, 1.6 equiv) and silicon tetrachloride (0.286 mL, 2.5 mmol, 5.0 equiv) were added to the mixture at −78 °C successively. After being stirred for 6 h, the reaction was quenched with KF/KH_2PO_4 (5 mL), and then the slurry was stirred for 0.5 h. The two-layers mixture was filtered through a cotton pad and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. After filtration and concentration, the crude product was dissolved in CH_2Cl_2 (5 mL) and then *p*-nitrobenzoyl chloride (188.0 mg, 1.0 mmol, 2.0 equiv), triethylamine (0.21 mL, 1.5 mmol, 3.0 equiv), and DMAP (2 mol %) were added to the obtained crude product at room temperature. After being stirred for 16 h, the reaction was quenched with H_2O (5 mL). The two-layers mixture was separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with 10% HCl (10 mL), satd $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. After filtration and concentration, the obtained crude product was

purified by column chromatography (hex/EtOAc=12:1, SiO_2: 10 g) to give the product **2i**-NB (82.5 mg, 61% yield).

Acknowledgements

This work was partially supported by JSPS KAKENHI Grant Number 22790014 and by a Grant-in-Aid for Scientific Research on Innovative Areas 'Advanced Molecular Transformations by Organocatalysts' from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and notes

1. For reviews of desymmetrizations, see: (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361; (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*, Jacobsen, E. J., Pfaltz, A., Yamamoto, H., Eds.; Springer, 1999; Vol. 3, p 1309.
2. For reviews of the enantioselective ring-opening of *meso*-epoxides, see. (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421; (b) Schneider, C. *Synthesis* **2006**, 3919.
3. For reviews of the synthesis of 1,2-halohydrins using ring-opening of *meso*-epoxides, see: (a) Denmark, S. E.; Barsanti, P. A.; Beutner, G. L.; Wilson, T. W. *Adv. Synth. Catal.* **2007**, *349*, 567; (b) Kotani, S.; Nakajima, M. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier, 2012; Vol. 6, p 506.
4. Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747.
5. (a) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246; (b) Roy, C. D.; Brown, H. C. *Tetrahedron: Asymmetry* **2006**, *17*, 1931.
6. Chiral Lewis acid-catalyzed enantioselective ring-opening of *meso*-epoxides were developed, as described in: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139; (b) Bruns, S.; Haufe, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1563; (c) Bruns, S.; Haufe, G. *J. Fluorine Chem.* **2000**, *104*, 247; (d) Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55; (e) Haufe, G.; Bruns, S. *Adv. Synth. Catal.* **2002**, *344*, 165.
7. For reviews of Lewis base catalysis reactions, see: (a) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391; (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29; (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem.* **2008**, *120*, 1584 *Angew. Chem., Int. Ed.* **2008**, *47*, 1560; (d) Benaglia, M.; Guizzetti, S.; Pignataro, L. *Coord. Chem. Rev.* **2008**, *252*, 492; (e) Benaglia, M.; Rossi, S. *Org. Biomol. Chem.* **2010**, *8*, 3824.
8. Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.
9. Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353.
10. Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 8827.
11. For the preliminary communication, see: Tokuoka, E.; Kotani, S.; Matsunaga, H.; Ishizuka, T.; Hashimoto, S.; Nakajima, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2391.
12. Simonini, V.; Benaglia, M.; Benincori, T. *Adv. Synth. Catal.* **2008**, *350*, 561.
13. Chen, J.; Takenaka, N. *Chem.—Eur. J.* **2009**, *15*, 7268.
14. Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574.
15. Pu, X.; Qi, X.; Ready, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 10364.
16. Malkov, A. V.; Gordon, M. R.; Stončius, S.; Hussain, J.; Kočovský, P. *Org. Lett.* **2009**, *11*, 5390.
17. $SiCl_4$ promoted ring-opening under the reaction condition even in the absence of phosphine oxide catalyst, to give the product in 52% yield.
18. Ohmaru, Y.; Sato, N.; Mizutani, M.; Kotani, S.; Sugiura, M.; Nakajima, M. *Org. Biomol. Chem.* **2012**, *10*, 4562.
19. Chauvet, F.; Heumann, A.; Waegell, B. *J. Org. Chem.* **1987**, *52*, 1916.
20. For a recent review of one-pot reactions, see: Albrecht, Ł.; Jiang, H.; Jųrgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8492.
21. (a) Bentley, P. A.; Du, M. J. *Tetrahedron Lett.* **2008**, *49*, 1425; (b) Zhang, J.; Wang, J.; Qiu, Z.; Wang, Y. *Tetrahedron* **2011**, *67*, 6859.
22. *m*CPBA was purified by washing with satd $NaHCO_3$ and brine, follows by drying with $MgSO_4$ prior to use.
23. Chlorohydrin **2i** was decomposed by quenching with 10% aq $Na_2S_2O_3$ leading to a decrease in the yield. The procedure is described in detail in Experimental Section 4.6.
24. Fukuzawa, T.; Shimoji, Y.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1649.
25. Traynham, J. G.; Schneller, J. *J. Am. Chem. Soc.* **1965**, *87*, 2398.