JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Catalytic Asymmetric Bromoetherification and Desymmetrization of Olefinic 1,3-Diols with C_2-Symmetric Sulfides

Zhihai Ke,[†] Chong Kiat Tan,[†] Feng Chen, and Ying-Yeung Yeung*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

Supporting Information

ABSTRACT: An enantioselective and highly diastereoselective bromoetherification and desymmetrization of olefinic 1,3-diols has been developed using a C_2-symmetric cyclic sulfide catalyst. This methodology has been successfully applied to the synthesis of the key intermediate of an orally active antifungal drug posaconazole (Noxafil).

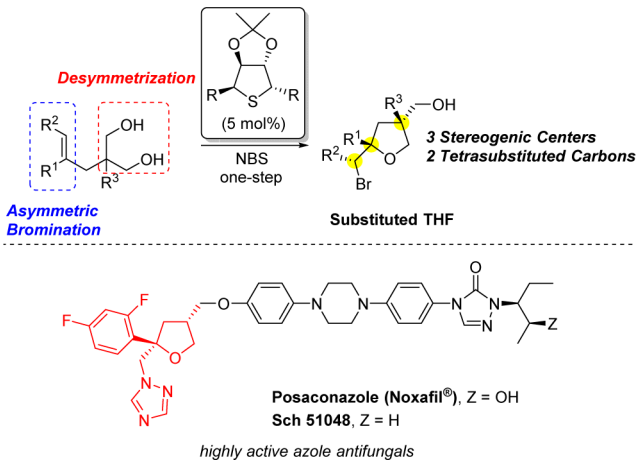
The asymmetric halofunctionalization of olefins is a field with renewed interest.[1] After remarkable endeavors by pioneers,[2,3] torrents of novel solutions to this problem have emerged in recent years. A number of catalytic halolactonization reactions have been reported. In contrast, suitable methods for haloetherification[4] remain elusive.[1,5]

Among the efforts devoted to halo-*O*-cyclization of olefins, the involvement of desymmetrization is a tempting element as it can convert remote, prostereogenic centers to stereogenic centers, although such examples are not that common. Several elegant examples including the use of diolefinic carbonyl,[6a−e] diolefinic carboxylic acid,[6f,g] and dialkynyl carboxylic acid[5h] substrates in the asymmetric halogenation−desymmetrization process have been documented. Nonetheless, the desymmetrization of dinucleophile olefinic substrates is rare. Recently, cyclization of oct-4-ene-1,8-diol using chiral BINOL-derived phosphoric acid catalyst has been reported.[6i]

Herein we disclose the asymmetric bromoetherification and desymmetrization of trisubstituted alkenoic 1,3-diols using a monofunctional C_2-symmetric cyclic sulfide as the catalyst (Scheme 1). It is noteworthy that monofunctional dialkyl sulfides have been reported to be useful in promoting the halogenation process. However, the asymmetric catalytic variant remains unknown.[7,8] This report represents the first case of monofunctional Lewis basic sulfide-catalyzed enantioselective bromocyclization reaction. Our methodology is also the catalytic version (*using substoichiometric amount of catalyst*) of asymmetric desymmetrization of olefinic 1,3-diols, which is an important transformation.[9] The resulting substituted tetrahydrofuran products contain up to three new stereogenic centers, of which two are tetrasubstituted carbons. These compounds resemble the core of the broad-spectrum, orally active azole antifungals posaconazole (Noxafil)[10] and Sch 51048.[11]

The inspiration for this work came from our recent success with the asymmetric bromoaminocyclization of trisubstituted olefinic amides with C_2-symmetric cyclic selenide catalysts.[12] The success with cyclic selenide catalyst is a departure from our recent development on the bifunctional amino-thiocarbamate catalysts.[13] Initial experiments began with alkenoic diol **1a**. NBS was used as the brominating agent, and the reaction was conducted in CH_2Cl_2 at −78 °C. Without catalyst and additive, **2a** was obtained in 57% yield and 84:16 dr after 2 days (Table 1, entry 1). With bases such as K_2CO_3 or triethylamine, which are known to be effective in promoting halocyclization reactions, low diastereoselectivity of **2a** was obtained (entries 2, 3). No desired product was observed when cyclic selenide catalyst **3a** was used (entry 6). Interestingly, 29% yield of **2a** was isolated with high diastereoselectivity and moderate enantioselectivity when 1 equiv of MsOH was added as an additive (entry 6 vs 7).[14] An improved er of 83:17 was observed when cyclic selenide **3b** was used (entry 8).

Scheme 1. Asymmetric Bromoetherification and Desymmetrization of Diols

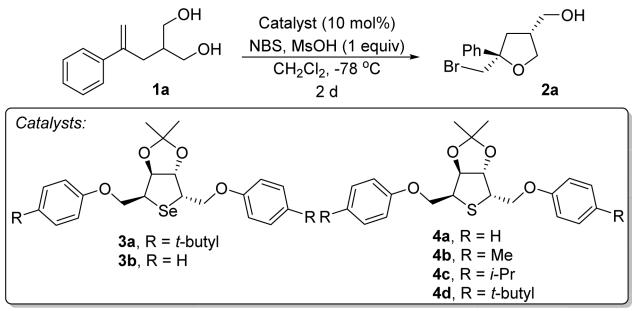


To try to boost the diastereoselectivity and enantioselectivity, we continued to search for different catalysts.[15] Cyclic sulfide catalyst **4a**, an analogue of cyclic selenide **3**, showed improved diastereoselectivity without sacrificing reaction yield (Table 1, entry 9). Reaction yields were reduced when *p*-tolyl catalyst **4b** and *p*-isopropylphenyl catalyst **4c** were used (entries 10, 11). Surprisingly, the best result was obtained with the bulkier *tert*-butyl substituted catalyst **4d**, and 80% yield of the desired product was isolated with dr 92:8 and enantioselectivity 85.5:14.5 (entry 13). Although MsOH itself could promote the reaction (entry 4), addition of **4d** (10 mol %) further accelerated the reaction and improved the dr (entry 4 vs 12). Similar to the reaction with cyclic selenide catalysts **3**, MsOH was necessary in

Received: March 22, 2014
Published: April 3, 2014

   dx.doi.org/10.1021/ja5029155 | J. Am. Chem. Soc. 2014, 136, 5627−5630

Table 1. Asymmetric Bromoetherification and Desymmetrization of Alkenoic Diols[a]



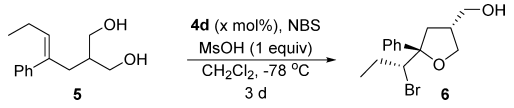
entry	catalyst	yield (%)[b]	dr[c]	er
1[d]		57	84:16	
2[d,e]	K_2CO_3	51	64:36	
3[d,e]	Et_3N	53	68:32	
4[f]		35	88:12	
5		72	88:12	
6[d,g]	**3a**	trace		
7[g]	**3a**	29	92:8	65.5:34.5
8	**3b**	99	88:12	83:17
9	**4a**	73	93:7	82.5:17.5
10[g]	**4b**	55	93:7	82:18
11[g]	**4c**	59	92:8	82:18
12[f]	**4d**	81	92:8	85.5:14.5
13	**4d**	80	92:8	85.5:14.5
14[d,g]	**4d**	61	86:14	52:48

[a]Reactions were carried out with alkenoic diol **1a** (0.05 mmol), catalyst (0.005 mmol), methanesulfonic acid (0.05 mmol), and NBS (0.06 mmol) in CH_2Cl_2 (1.5 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Reaction without MsOH. [e]0.05 mmol of catalyst was used. [f]Reaction was quenched at 12 h. [g]Starting material was consumed, and significant amount of inseparable side products was observed.

obtaining high dr and er (entry 14) (vide infra). Thus, **4d** was selected in the later studies. Other acids were also examined, and MsOH was found to be superior.[16]

Next, we focused on asymmetric cyclization of the trisubstituted olefinic diol **5** and examined the catalyst loading. Substituted tetrahydrofuran **6**, which contains three stereogenic centers, was obtained in excellent dr and yield, and good er when using 10 mol % of catalyst **4d** (Table 2, entry 1). Similar dr and er were observed when 5 mol % of **4d** was used (entry 2). Notably, only a slight er erosion was detected when the catalyst loading was reduced to 2 mol % (entry 3).

Table 2. Effect of Catalyst Loading on the Asymmetric Bromoetherification and Desymmetrization of 5[a]

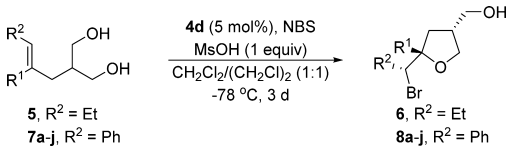


entry[a]	**4d** (mol %)	yield (%)[b]	dr[c]	er
1	10	88	>99:1	90:10
2	5	97	>99:1	90:10
3	2	92	94:6	86.5:13.5

[a]Reactions were carried out with alkenoic diol **5** (0.05 mmol), catalyst **4d**, methanesulfonic acid (0.05 mmol), and NBS (0.06 mmol) in CH_2Cl_2 (1.5 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR.

With the groundwork established, trisubstituted olefinic substrates were then subjected to the study. After a brief screening, mixed solvent systems were found to be superior reaction media which offered better er and dr.[16] As shown in Table 3, the diastereoselectivities obtained with catalyst **4d** were

Table 3. Asymmetric Bromoetherification and Desymmetrization of Trisubstituted Alkenoic Diols[a]



entry	diol, R^1, R^2	yield (%)[b]	dr[c]	er
1	**5**, Ph, Et	99	>99:1	90.5:9.5
2	**7a**, Ph, Ph	99	>99:1	96.5:3.5
3	**7b**, 2-Me-C_6H_4, Ph	95	>99:1	55:45
4	**7c**, 4-Et-C_6H_4, Ph	99	>99:1	96:4
5	**7d**, 3,5-Me_2-C_6H_3, Ph	99	>99:1	95:5
6	**7e**, 3-MeO-C_6H_4, Ph	98	>99:1	86:14
7	**7f**, 4-Ph-C_6H_4, Ph	96	92:8	73:27
8	**7g**, 4-F-C_6H_4, Ph	92	>99:1	97.5:2.5
9	**7h**, 4-CF_3O-C_6H_4, Ph	91	95:5	67:33
10	**7i**, 4-*i*Pr-C_6H_4, Ph	99	>99:1	97:3
11[d]	**7a**, Ph, Ph	94	>99:1	96:4
12[e]	**7a**, Ph, Ph	96	>99:1	96:4

[a]Reactions were carried out with alkenoic diol **5** or **7** (0.05 mmol), catalyst **4d** (0.0025 mmol), methanesulfonic acid (0.05 mmol), and NBS (0.06 mmol) in CH_2Cl_2/$ClCH_2CH_2Cl$ (0.75/0.75 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]1.0 mmol scale. [e]2.0 mmol scale.

generally in excess of 99:1. For the relatively lower dr entries, only a pair of diastereomeric isomers were identified in these reactions, suggesting that the bromonium ring opening was highly regio- and stereoselective. The enantioselectivities were also good in which bromoether **6** was obtained with 90.5:9.5 er and **8a** with 96.5:3.5 er (Table 3, entries 1, 2).

The substituent effect on the trisubstituted alkenoic diol **7** was then studied (Table 3). Generally, higher enantioselectivities were obtained for substrates with alkyl-substituted aryl groups in the R^1 position (Table 3, entries 4, 5, 10). Other substrates with 3-methoxyphenyl and 4-biphenyl substitutions also returned with good er (entries 6, 7). The substrate containing 4-fluorophenyl substituent was also able to achieve a high enantioselectivity of 97.5:2.5 er (entry 8), whereas the other electron withdrawing substrates with 4-trifluoromethoxy phenyl (**7h**) recorded much diminished enantioselectivity (entry 9). Ortho substitution was found to affect the enantioselectivity adversely (entry 3).[17] The reaction was also readily scalable (entries 11, 12). The absolute configuration of **8** was assigned based on an X-ray crystallographic study on the 3,5-dinitrobenzoyl ester derivative of **8a**.[16]

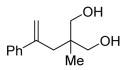
Also it was found that substrates **9** and **11** with an additional benzyl substituent at the C(2) position are also amenable to this protocol and yielded products that contain two tetrasubstituted carbon stereogenic centers (Table 4). For the cyclization of diols **9**, the enantioselectivity was not significantly affected by the R^1 substituent. Good enantioselectivities were recorded for electron-rich (Table 4, entries 1−3) and electron-deficient (entries 4−6) olefinic substrates. Cyclization of trisubstituted diols **11** catalyzed by **4d** could also afford the desired substituted

dx.doi.org/10.1021/ja5029155 | J. Am. Chem. Soc. 2014, 136, 5627−5630

Table 4. Asymmetric Bromoetherification and Desymmetrization of 9, 11, 13, and 15[a]

9a-f, R^2 = H
11a-e, R^2 = Ph
13, R^1 = Ph, R^2 = Et

10a-f, R^2 = H
12a-e, R^2 = Ph
14, R^1 = Ph, R^2 = Et

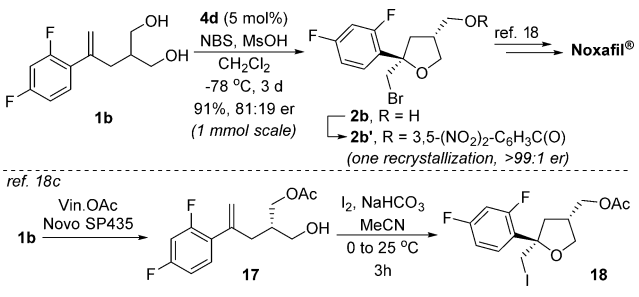
entry	diol, R^1, R^2	yield (%)[b]	dr[c]	er
1	**9a**, Ph, H	92	93:7	93.5:6.5
2	**9b**, 4-Me-C_6H_4, H	96	>99:1	90:10
3	**9c**, 2-Naphthyl, H	97	92:8	82:18
4	**9d**, 4-F-C_6H_4, H	91	95:5	93:7
5	**9e**, 4-CF_3O-C_6H_4, H	93	85:15	80:20
6	**9f**, 4-Cl-C_6H_4, H	86	89:11	94:6
7	**11a**, 4-Et-C_6H_4, Ph	96	92:8	95:5
8	**11b**, 3-MeO-C_6H_4, Ph	99	71:29	97.5:2.5
9	**11c**, 4-Ph-C_6H_4, Ph	98	91:9	96:4
10	**11d**, 4-F-C_6H_4, Ph	94	>99:1	91:9
11	**11e**, 4-CF_3O-C_6H_4, Ph	93	>99:1	92:8
12	**13**, Ph, Et	99	>99:1	92.5:7.5
13[d]	**9a**, Ph, H	91	93:7	93:7
14	 **15**	73	75:25	91:9

[a]Reactions were carried out with alkenoic diol (0.05 mmol), catalyst **4d** (0.0025 mmol), methanesulfonic acid (0.05 mmol), and NBS (0.06 mmol) in CH_2Cl_2 (1.5 mL) in the absence of light. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]1.0 mmol scale.

tetrahydrofurans **12** in excellent yields and enantioselectivities. Results from Table 4 suggest that the enantioselectivity was not significantly affected by the electronic nature of the substituents (Table 4, entries 7−11). High er was also obtained for substrate **13** (R^1 = Ph, R^2 = Et). Similar to the cyclization of **5** and **7**, excellent diastereoselectivities were obtained in the asymmetric bromocyclization−desymmetrization of **9** and **11**. Cyclization of **15**, a substrate with methyl in place of benzyl group in **9a**, also gave the desired product **16** in 73% yield and 91:9 er (entry 14). An X-ray study on a single crystal of **12c** confirmed the absolute configuration.[16]

This type of reaction is applicable in the synthesis of useful drug molecules. As indicated in Scheme 2, our cyclized product **2** resembles the core structure of the highly active antifungal drug candidates posaconazole (Noxafil) and Sch 51048. A reported efficient synthetic route involves the enzymatic desymmetrization of diol **1b** by selectively acetylating one of the hydroxyl groups. Subsequent iodoetherification of **17** afforded **18**.[18] With

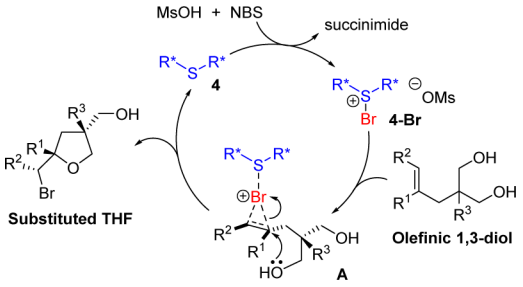
Scheme 2. Single Step Asymmetric Bromoetherification and Desymmetrization Leading to Intermediate of Posaconazaole and Sch 51048



our protocol, enantiopure **2b** that is the synthetic equivalent intermediate of **18** could readily be furnished.[19]

Regarding the reaction mechanism, we believe that the chiral cyclic sulfide catalyst **4** may activate NBS to give active species **4-Br** through a Lewis base activated Lewis acid mechanism.[20] **4-Br** might then deliver the Br asymmetrically to the olefin to give **A** (Scheme 3).[7,8,12] For MsOH, we speculate that its role is to

Scheme 3. A Plausible Mechanism of the Asymmetric Bromocyclization−Desymmetrization Process



facilitate the formation of the cyclic sulfide−Br complex **4-Br** through the protonation of the succinimide and enhance the turnover as described in Denmark's proposal.[21] However, the overall mechanism and the role of MsOH remain unclear and are subjected to further investigation.[22]

In summary, we have developed a facile, efficient, and highly enantio- and diastereoselective bromocyclization−desymmetrization of olefinic 1,3-diols using a cyclic sulfide catalyst. The process allows for the construction of substituted THFs with up to three stereogenic centers with two tetrasubstituted carbons. This methodology is applicable to the synthesis of a key intermediate of the orally active antifungal drug posaconazole (Noxafil).

■ ASSOCIATED CONTENT

Supporting Information

Experimental detail, CIF files, and spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

chmyyy@nus.edu.sg

Author Contributions

†Z.K. and C.K.T. gave equal contributions to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National University of Singapore (Grant No. 143-000-509-112), GSK-EDB (Grant No. 143-000-564-592), ASTAR-Public Sector Funding (Grant No. 143-000-536-305), and NEA-ETRP (Grant No. 143-000-547-490) for financial support. We acknowledge the receipt of President's Graduate Fellowship (to C.K.T.). Special thanks to Prof. Scott E. Denmark (University of Illinois) for the valuable discussion.

■ REFERENCES

(1) For recent reviews, see: (a) Chen, G. F.; Ma, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8306. (b) Castellanos, A.; Fletcher, S. P. *Chem.—Eur. J.* **2011**, *17*, 5766. (c) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Synlett* **2011**,

dx.doi.org/10.1021/ja5029155 | *J. Am. Chem. Soc.* 2014, 136, 5627−5630

1335. (d) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichimica Acta* **2011**, *44*, 27. (e) Hennecke, U. *Chem.—Asian J.* **2012**, *7*, 456. (f) Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10938. (g) Murai, K.; Fujioka, H. *Heterocycles* **2013**, *87*, 763. (h) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985.

(2) For some early advances, see: (a) Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233. (b) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297. (c) Haas, J.; Bissmire, S.; Wirth, T. *Chem.—Eur. J.* **2005**, *11*, 5777. (d) Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748. (e) Kwon, H. Y.; Park, C. M.; Lee, S. B.; Youn, J. H.; Kang, S. H. *Chem.—Eur. J.* **2008**, *14*, 1023. (f) Wang, M.; Gao, L. X.; Mai, W. P.; Xia, A. X.; Wang, F.; Zhang, S. B. *J. Org. Chem.* **2004**, *69*, 2874. (g) Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900. (h) Ning, Z.; Jin, R.; Ding, J.; Gao, L. *Synlett* **2009**, 2291. (i) Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *J. Am. Chem. Soc.* **2010**, *132*, 3298. (j) Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *J. Am. Chem. Soc.* **2010**, *132*, 3664. (k) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332. (l) Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9174. (m) Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 15474.

(3) For an understanding of the mechanistic aspects of this reaction, see: (a) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448. (b) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962. (c) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131. (d) Denmark, S. E.; Burk, M. T.; Hoover, A. J. *J. Am. Chem. Soc.* **2010**, *132*, 1232.

(4) (a) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (b) Denmark, S. E.; Burk, M. T. *Org. Lett.* **2012**, *14*, 256.

(5) For selected recent examples, see: (a) Huang, D.; Liu, X.; Li, L.; Cai, Y.; Liu, W.; Shi, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8101. (b) Zeng, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Chem. Commun.* **2013**, *49*, 2418. (c) Jaganathan, A.; Staples, R. J.; Borhan, B. *J. Am. Chem. Soc.* **2013**, *135*, 14806. (d) Wolstenhulme, J. R.; Rosenqvist, J.; Lozano, O.; Ilupeju, J.; Wurz, N.; Engle, K. M.; Pidgeon, G. W.; Moore, P. R.; Sandford, G.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 9796. (e) Romanov-Michailidis, F.; Guénée, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9266. (f) Tripathi, C. B.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 8450. (g) Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. *Chem. Sci.* **2013**, *4*, 2100. (h) Zhang, W.; Liu, N.; Schienebeck, C. M.; Zhou, X.; Izhar, I. I.; Guzei, I. A.; Tang, W. *Chem. Sci.* **2013**, *4*, 2652. (i) Hu, D. X.; Shibuya, G. M.; Burns, N. Z. *J. Am. Chem. Soc.* **2013**, *135*, 12960. (j) Zhang, Y.; Xing, H.; Xie, W.; Wan, X.; Lai, Y.; Ma, D. *Adv. Syn. Catal.* **2013**, *355*, 68. (k) Yin, Q.; You, S.-L. *Org. Lett.* **2013**, *15*, 4266. (l) Mori, K.; Ichikawa, Y.; Kobayashi, M.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 3964.

(6) (a) Fuji, K.; Node, M.; Naniwa, Y.; Kawabata, T. *Tetrahedron Lett.* **1990**, *31*, 3175. (b) Yokomatsu, T.; lwasawa, H.; Shibuya, S. *Chem. Commun.* **1992**, 728. (c) Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1005. (d) Inoue, T.; Kitagawa, O.; Saito, A.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7384. (e) Kitagawa, O.; Momose, S.; Fushimi, Y.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 8827. (f) Paull, D. H.; Fang, C.; Donald, J. R.; Pansick, A. D.; Martin, S. F. *J. Am. Chem. Soc.* **2012**, *134*, 11128. (g) Ikeuchi, K.; Ido, S.; Yoshimura, S.; Asakawa, T.; Inai, M.; Hamashima, Y.; Kan, T. *Org. Lett.* **2012**, *14*, 6016. (h) Wilking, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Hennecke, U. *J. Am. Chem. Soc.* **2013**, *135*, 8133. (i) Hennecke, U.; Müller, C. H.; Fröhlich, R. *Org. Lett.* **2011**, *13*, 860.

(7) For examples of using stoichiometric chiral cyclic sulfide promotors in the asymmtric dichlorination of olefins, see: (a) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *J. Am. Chem. Soc.* **2010**, *132*, 14303. For related studies on the halocyclization reactions using Lewis basic sulfur as the catalyst/promotor, see: (b) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P.; Sattler, W. *J. Am. Chem. Soc.* **2011**, *133*, 15898. (d) Snyder, S. A.; Treitler, D. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7899.

(8) For related studies using Lewis basic selenium as the catalyst in halolactonization, see: (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801. (c) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752. (d) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979. (e) Balkrishna, S. J.; Prasad, C. D.; Panini, P.; Detty, M. R.; Chopra, D.; Kumar, S. *J. Org. Chem.* **2012**, *77*, 9541.

(9) In 1992, Taguchi et al. reported the first example of asymmetric iodocyclization of olefinic 1,3-diol using stoichiometric amount of chiral titanium complex promoter, which gave the corresponding substituted THF in 36% ee. For details, see ref 6c.

(10) Posaconazole is a triazole antifungal drug marketed by Merck under the trade name Noxafil.

(11) For the discovery of posaconazole and related triazole antifungal drugs, see: (a) Kauffman, C. A.; Malani, A. N.; Easley, C.; Kirkpatrick, P. *Nat. Rev. Drug Discovery* **2007**, *6*, 183. For the biologically studies on the triazole antifungal drugs, see: (b) Munayyer, H. K.; Mann, P. A.; Chau, A. S.; Yarosh-Tomaine, T.; Greene, J. R.; Hare, R. S.; Heimark, L.; Palermo, R. E.; Loebenberg, D.; McNicholas, P. M. *Antimicrob. Agents Chemother.* **2004**, *48*, 3690. (c) Sugar, A. M.; Picard, M. *Antimicrob. Agents Chemother.* **1995**, *39*, 996. (d) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Desai, J. A.; Pike, R. E.; Jao, E.; Wang, H.; Ganguly, A. K.; Loebenberg, D.; Hare, R. S.; Cacciapuoti, A.; Parmegiani, R. M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 127. (e) FDA labeling information [online], http://www.fda.gov/cder/foi/label/2006/022003lbl.pdf (2006).

(12) Chen, F.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1232.

(13) (a) Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Org. Lett.* **2011**, *13*, 2738. (b) Zhou, L.; Chen, J.; Tan, C. K.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 9164. (c) Jiang, X.; Tan, C. K.; Zhou, L.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7771. (d) Cheng, Y. A.; Chen, T.; Tan, C. K.; Heng, J. J.; Yeung, Y.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 16492. (e) Zhou, L.; Tay, D. W.; Chen, J.; Leung, G. Y. C.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 4412. (f) Zhao, Y.; Jiang, X.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 8597.

(14) Starting materials were consumed for entries 6 and 7, and significant amounts of inseparable side products were observed. It has been reported that Lewis basic chalcogen catalysts could promote oxidation of alcohol in the presence of NBS, and we suspected that the side products might be a result of oxidation. For related references, see: (a) Tripathi, C. B.; Mukherjee, S. *J. Org. Chem.* **2012**, *77*, 1592. (b) Rong, Z.-Q.; Pan, H.-J.; Yan, H.-L.; Zhao, Y. *Org. Lett.* **2014**, *16*, 208.

(15) We also attempted to search for suitable cyclic selenide catalysts. However, the results were not satisfactory. For details, see SI Table S2.

(16) For details, see SI.

(17) Substrate **7** with R^1 = Me was also examined. Good yield and dr were obtained, while the er was low. For details, see SI.

(18) (a) Morgan, B.; Stockwell, B. R.; Dodds, D. R.; Andrews, D. R.; Sudhakar, A. R.; Nielsen, C. M.; Mergelsberg, I.; Zumbach, A. *J. Am. Oil Chem. Soc.* **1997**, *74*, 1361. (b) Morgan, B.; Dodds, D. R.; Zaks, A.; Andrews, D. R.; Klesse, R. *J. Org. Chem.* **1997**, *62*, 7736. (c) Saksena, A. K.; Girijavallabhan, V. M.; Lovey, R. G.; Pike, R. E.; Wang, H.; Ganguly, A. K.; Morgan, B.; Zaks, A.; Puar, M. S. *Tetrahedron Lett.* **1995**, *36*, 1787. (d) Saksena, A. K.; Girijavallabhan, V. M.; Wang, H.; Liu, Y.-T.; Pike, R. E.; Ganguly, A. K. *Tetrahedron Lett.* **1996**, *37*, 5657.

(19) **2b** was converted into the corresponding 3,5-dinitrobenzoyl ester **2b′** followed by recrystallization to obtain an enantiopure sample.

(20) To support the existence of **4-Br**, NMR studies on a mixture of tetrahydrothiophene/NBS/MsOH were performed. For details, see SI Figure S3.

(21) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T. *J. Am. Chem. Soc.* **2011**, *133*, 15308.

(22) We have also examined some acid additives other than MsOH, and it was found that the enantioselectivity varied with different acids. We speculated that the counteranions of the acids might participate in the enantiodetermining step. For details, see SI Table S1.