Organic Letters

Letter

pubs.acs.org/OrgLett

# Tungsten-, Molybdenum-, and Cerium-Promoted Regioselective and Stereospecific Halogenation of 2,3-Epoxy Alcohols and 2,3-Epoxy Sulfonamides

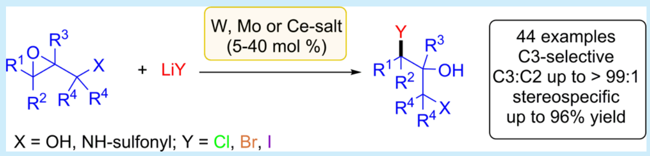
Chuan Wang[†] and Hisashi Yamamoto*[,†,‡]

[†]Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, United States

[‡]Molecular Catalyst Research Center, Chubu University, 1200 Matsumoto, Kasugai, Aichi 487-8501, Japan

*Supporting Information*

**ABSTRACT:** The first catalytic regioselective and stereospecific halogenation of 2,3-epoxy alcohols and 2,3-epoxy sulfonamides has been developed. Under the catalysis of commercially available W- or Mo-salts, complemented by the method using cerium halides, the C-3 selective ring opening of structurally diverse epoxides with Cl-, Br-, and I-nucleophiles afforded various halohydrins in good yields and high regioselectivities.




Since a plethora of methods for asymmetric epoxidation of allylic alcohols have been developed over the last decades, regioselective and enantiospecific ring opening of readily available enantioenriched 2,3-epoxy alcohols provides diverse chiral building blocks for the synthesis of biologically active compounds.[1−3] Recently, our group developed an enantioselective epoxidation of sulfonamides[4] providing a possibility to access various optically active polyfunctionalized compounds through nucleophilic ring opening of 2,3-epoxy sulfonamides. Hitherto, regioselective ring opening of 2,3-epxoy alcohols with halides as nucleophiles are only accomplished employing stoichiometric promoters with limited substrate scope,[5−7] whereas the regioselective halogenations of 2,3-epoxy sulfonamides remain elusive. More recently, our group discovered that W-salts are capable of catalyzing C-3 selective cleavage of 2,3-epoxy alcohols and 2,3-epoxy sulfonamides with various *N*- and *O*-nucleophiles.[8] As a continuation of our research in this area, herein we report a W-, Mo-, and Ce-mediated C-3 selective, stereospecific halogenations of structurally diverse 2,3-epoxy alcohols and 2,3-epoxy sulfonamides.

For optimization of the reaction conditions, we used racemic *trans*-2,3-epoxy cinnamyl alcohol (**1a**) as standard substrate and lithium chloride as the Cl-source. After careful screening of solvents and W- or Mo-salts, the best yield was achieved when the reaction was carried out in monoglyme employing $WO_2Cl_2$ as catalyst.[9]

After the optimum conditions were established, we started to evaluate the substrate scope of this chlorination reaction. First, we varied the structure of the 2,3-epoxy alcohols, and the results are summarized in Scheme 1. In the cases of *trans* aromatic epoxides **1a−d** with primary alcohol as directing group, the reactions proceeded with complete regioselectivities, while the reaction employing the aromatic epoxide **1e** with tertiary alcohol-moiety gave the product **2e** with relatively low regiocontrol. For the terminal epoxides **1f−l** all the reactions afforded only one regioisomer as the product. Notably, the sterically hindering 2,3-epoxy farnesol **1m** was also successfully used as precursor for the chlorination reaction furnishing the product **2m** bearing two quaternary and tertiary stereocenters in complete regioselectivity. When aliphatic 2,3-disbustituted epoxides were employed as substrate, only low regioselectivities could be achieved.

Furthermore, the substrate spectrum of the regioselective chlorination of 2,3-epoxy sulfonamides **3** was investigated (Scheme 2). In the cases of trans-, terminal-, and trisubstituted epoxides **3a−j** complete regioselectivities were obtained, while the reaction using *cis*-epoxide **3k** as precursor gave the product with relatively low regiocontrol.

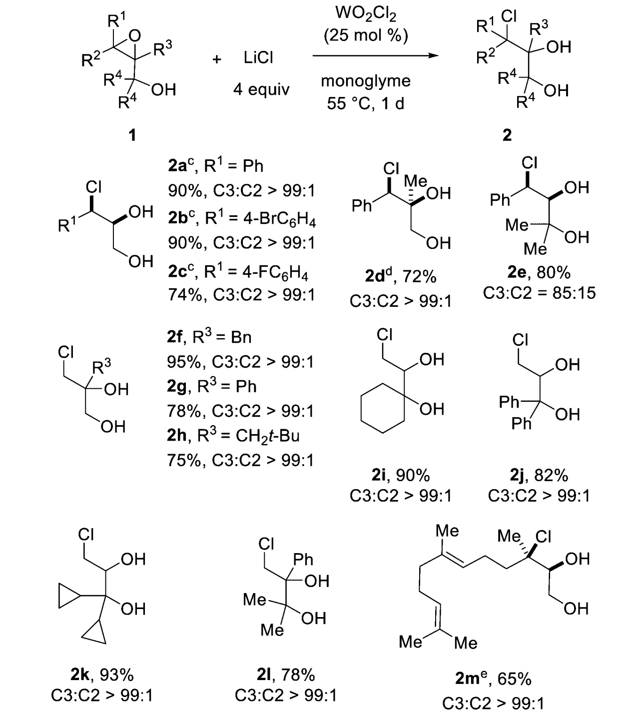
Moreover, we studied the use of LiBr and LiI as nucleophiles for the ring opening reaction. In this case $WO_2Cl_2$ turned out to be unsuitable since Br−Cl and I−Cl exchange between the catalyst and the lithium salts was observed, which resulted in a mixture of chlorohydrin and bromohydrin or chlorohydrin and iodohydrin as products. A brief screening of chlorine-free W- and Mo-salts revealed that the best outcome was achieved when $MoO_2(acac)_2$ was used as catalyst. Under the optimum conditions terminal 2,3-epoxy alcohols and 2,3-epoxy sulfonamides were successfully employed as precursors for the ring opening reaction furnishing the products **5a−i** in high yields and complete regioselectivities (Scheme 3). Unfortunately, this method was not applicable to epoxides of other substitution patterns, which led to low regioselectivities.

As mentioned above the W- and Mo-catalyzed halogenation of 2,3-epoxy alcohols and 2,3-epoxy sulfonamides was not applicable to aliphatic 2,3-disbustitued epoxides. In order to expand the substrate scope of the ring opening reaction we screened some other metal chlorides as nucleophiles. Interestingly, cerium(III) halides turned out to be able to

**Received:** October 22, 2014
**Published:** November 10, 2014

**Scheme 1. W-Catalyzed Regioselective Chlorination of 2,3-Epoxy Alcohols[a,b10]**



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 2,3-epoxy alcohols **1** using 4.0 equiv of LiCl and 25 mol % $WO_2Cl_2$ at 55 °C in 2.5 mL of monoglyme for 1 d. [b]All regiomeric ratios were determined by $^1$H-NMR-spectroscopy. [c]Fifteen mol % $WO_2Cl_2$ was used. [d]MeCN was employed as solvent. [e]Thirty mol % $WO_2Cl_2$ was used.

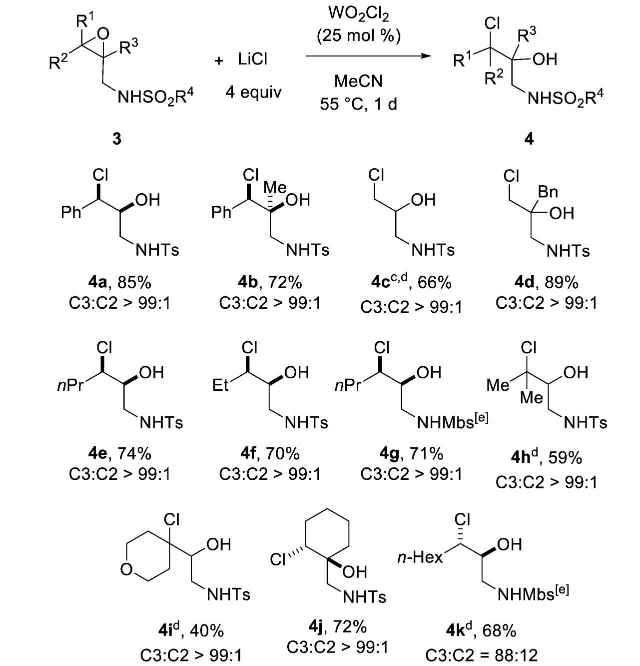
mediate the ring opening reaction of aliphatic 2,3-disubstituted 2,3-epoxy alcohols and 2,3-epoxy sulfonamides smoothly at room temperature under catalyst-free conditions, furnishing the products in high to complete regioselectivities (Scheme 4). Notably, only a substoichiometric amount of cerium halide (0.4 equiv) was necessary to achieve complete conversion of the ring-opening reaction.

To gain more insight into the directing effect of the OH- and NH-sulfonyl moiety, we performed a control reaction using Ac-protected epoxy alcohols and Boc-protected sulfonamide as substrates (Scheme 5). The results obtained indicated that the ring opening of terminal epoxides **9a** and **9b** could proceed with complete regioselectivities even in the absence of OH-moiety. In contrast, the regioselectivity of the *trans*-aromatic epoxide **7** diminished when OH was protected. In both cases mentioned above the reactions proceeded with significantly lower efficiency. Furthermore, protecting the NHTs-moiety still allowed the ring-opening to proceed with complete regiocontrol suggesting that the sulfonyl-group, instead of the amide nitrogen, plays a crucial role as the directing group.

In addition, we have also studied the stereospecificity of this ring opening reaction by employing enantioenriched epoxides as starting materials. To our delight, all the reactions afforded the products **2a**, **4c**, **4g**, and **6b** with identical enantiomeric excesses in comparison to their epoxide precursors.[11]

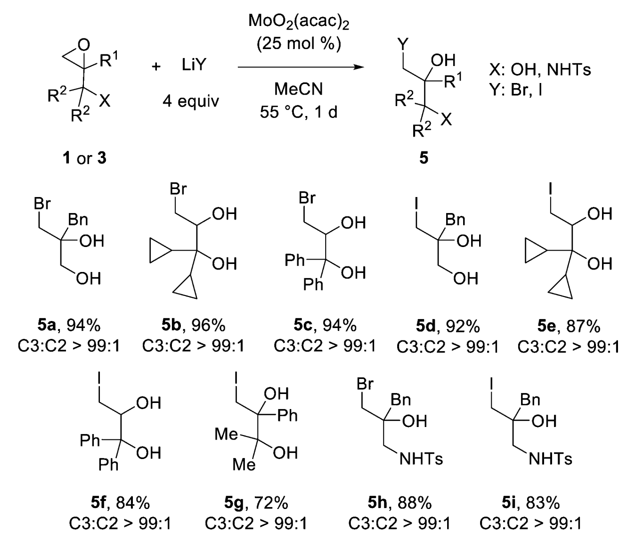
In conclusion we have developed the first catalytic regioselective and stereospecific halogenations of 2,3-epoxy alcohols and 2,3-epoxy sulfonamides. This process was efficiently promoted by commercially available W- and Mo-

**Scheme 2. W-Catalyzed Regioselective Chlorination of 2,3-Epoxy Sulfonamides[a,b10]**



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 2,3-epoxy sulfonamides **3** using 4.0 equiv of LiCl and 25 mol % $WO_2Cl_2$ at 55 °C in 2.5 mL of monoglyme for 1 d. [b]All regiomeric ratios were determined by $^1$H-NMR-spectroscopy. [c]Reaction was performed with 5 mol % $WO_2Cl_2$ at room temperature. Reaction time: 7 h. [d]Monoglyme was used as solvent. [e]Mbs: 4-methoxybenzenesulfonyl.

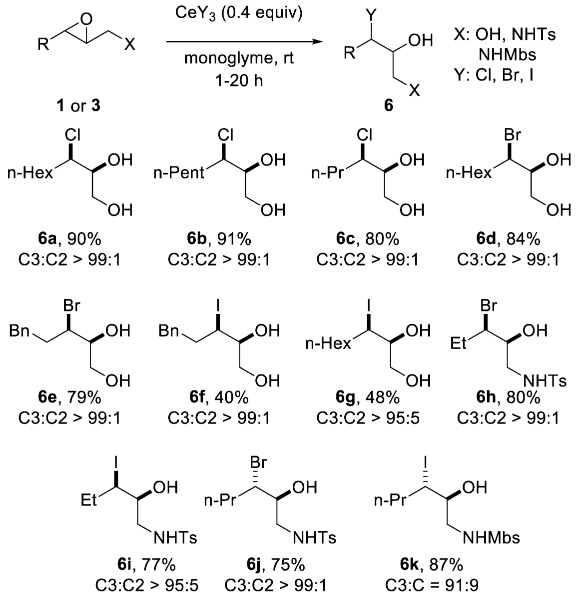
**Scheme 3. Mo-Catalyzed Regioselective Bromination and Iodination of Terminal 2,3-Epoxy Alcohols and 2,3-Epoxy Sulfonamides[a,b10]**



[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 2,3-epoxy alcohols **1** or 2,3-epoxy sulfonamides **3** using 4.0 equiv of LiBr or LiI and 25 mol % $MoO_2(acac)_2$ at 55 °C in 2.5 mL of monoglyme for 1 d. [b]All regiomeric ratios were determined by $^1$H-NMR-spectroscopy.

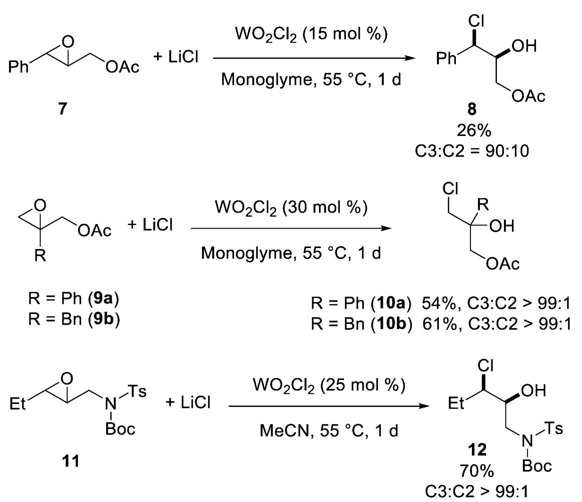
salts using simple lithium halide as nucleophiles and applicable to a variety of epoxides furnishing various halohydrins in good

**Scheme 4. Ce-Mediated Regioselective Halogenation of 2,3-Epoxy Alcohols and 2,3-Epoxy Sulfonamides**[a,b10]




[a]Unless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 2,3-epoxy alcohols **1** or 2,3-epoxy sulfonamides **3** using 0.4 equiv of cerium(III) halide at rt in 2.5 mL of monoglyme. [b]All regiomeric ratios were determined by $^1$H-NMR-spectroscopy.

**Scheme 5. W-Catalyzed Chlorination of 2,3-Epoxy Acetates and Boc-Protected 2,3-Epoxy Sulfonamide**




to high yields and in most cases with excellent regiocontrol. Especially, the successful use of challenging trisubstituted epoxides allows the construction of two consecutive quaternary and tertiary centers. Furthermore, being complementary to the W- and Mo-catalyzed halogenation, cerium(III) halides are capable of mediating the highly regioselective ring-opening of aliphatic 2,3-disubstituted 2,3-epoxy alcohols and 2,3-epoxy sulfonamides.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Representative experimental procedures and necessary characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: yamamoto@uchicago.edu.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Japan Society for the Promotion of Science (JSP-ACT-C) is greatly appreciated for providing financial support. C.W. thanks the Alexander von Humboldt Foundation for his postdoctoral fellowship.

## ■ REFERENCES

(1) For recent selected general reviews on asymmetric epoxidation, see: (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Katsuki, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, p621. (c) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563. (d) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. (e) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(2) For selected examples on asymmetric epoxidation of allylic alcohols: (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4463. (c) Egami, H.; Ogama, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 5886. (d) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2013**, *135*, 3411. (e) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222.

(3) For reviews on regioselective ring-opening of 2,3-epoxy alcohols, see: (a) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437. (b) Pena, P. C. A.; Roberts, S. M. *Curr. Org. Chem.* **2003**, *7*, 555.

(4) Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440.

(5) For a review on regioselective ring-opening of epoxides with halides as nucleophiles, see: Bonini, C.; Righi, G. *Synthesis* **1994**, *16*, 225.

(6) For examples on regioselective ring-opening of 2,3-epoxy alcohols with halide-nucleophiles, see: (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (b) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 117. (c) Gao, L.-X.; Murai, A. *Chem. Lett.* **1989**, *18*, 357. (d) Gao, L.-X.; Murai, A. *Chem. Lett.* **1991**, *20*, 1503. (e) Alvarez, E.; Nuñez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 3429. (f) Gao, L.-X.; Saitoh, H.; Feng, F.; Murai, A. *Chem. Lett.* **1991**, *20*, 1787. (g) Bonini, C.; Righi, G.; Sotgiu, G. *J. Org. Chem.* **1991**, *55*, 6206. (h) Reifeld, Y. E.; Nikitenko, A. A.; Arshava, B. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1083. (i) Bovicelli, P.; Mincione, E.; Ortaggi, G. *Tetrahedron Lett.* **1992**, *33*, 6181. (j) Shimizu, M.; Yoshida, A.; Fujisawa, T. *Synlett* **1992**, 204. (k) Tomata, Y.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2003**, *44*, 8975.

(7) For an example on stereospecific chlorinolysis of 2,3-epoxy alcohol in complex molecule, see: Nilewski, C.; Deprez, N. R.; Fessard, T. C.; Li, D. B.; Geisser, R. W.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7940.

(8) Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 6888.

(9) For details, see Supporting Information, Page 3.

(10) The ring-opening products were assigned by analogy assuming a common SN-2-type reaction pathway.

(11) For details, see Supporting Information, Page 20.