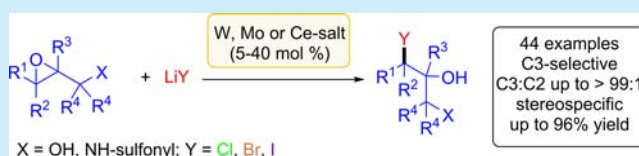


Tungsten-, Molybdenum-, and Cerium-Promoted Regioselective and Stereospecific Halogenation of 2,3-Epoxy Alcohols and 2,3-Epoxy Sulfonamides

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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 sulfonamides⁴ 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-epoxy 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 WO₂Cl₂ 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-disubstituted epoxides were employed as substrate, only low regioselectivities could be achieved.

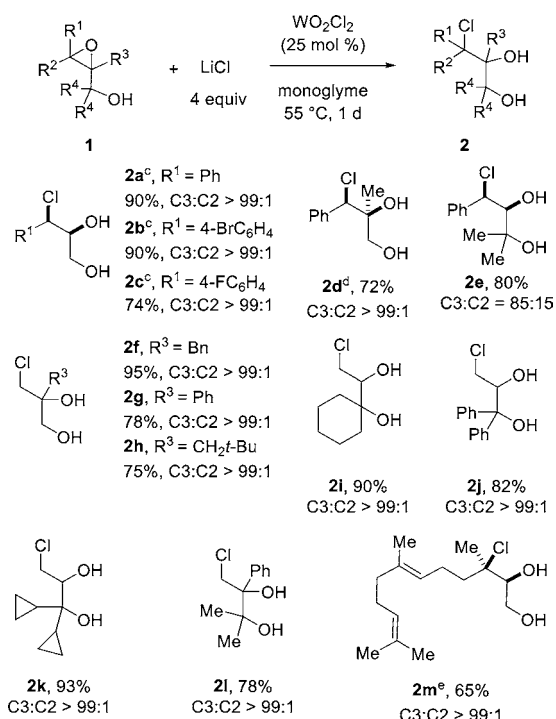
Furthermore, the substrate spectrum of the regioselective chlorination of 2,3-epoxy sulfonamides **3** was investigated (Scheme 2). In the cases of *trans*-, terminal-, and trisubstituted epoxides **3a–j** complete regioselectivities were obtained, while the reaction using *cis*-epoxide **3k** as precursor 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 WO₂Cl₂ 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 MoO₂(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-disubstituted 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

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Scheme 1. W-Catalyzed Regioselective Chlorination of 2,3-Epoxy Alcohols^{a,b,10}

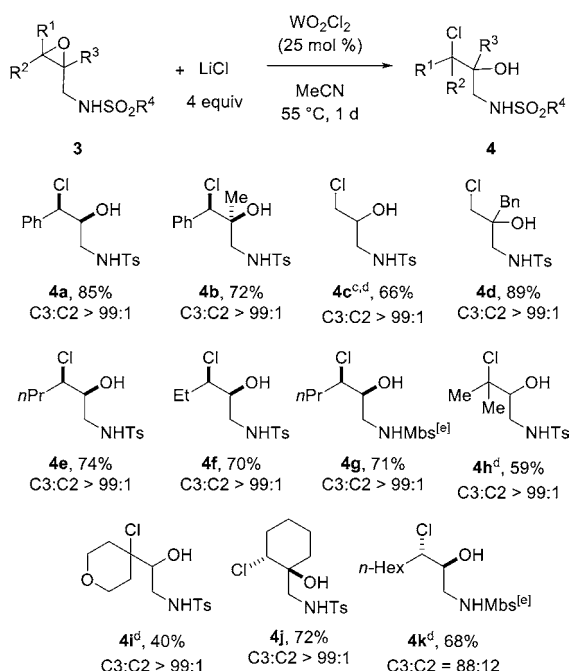
^aUnless otherwise specified, reactions were performed on a 0.25 mmol scale of racemic 2,3-epoxy alcohols **1** using 4.0 equiv of LiCl and 25 mol % WO₂Cl₂ at 55 °C in 2.5 mL of monoglyme for 1 d. ^bAll regiomer ratios were determined by ¹H-NMR-spectroscopy. ^cFifteen mol % WO₂Cl₂ was used. ^dMeCN was employed as solvent. ^eThirty mol % WO₂Cl₂ 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.

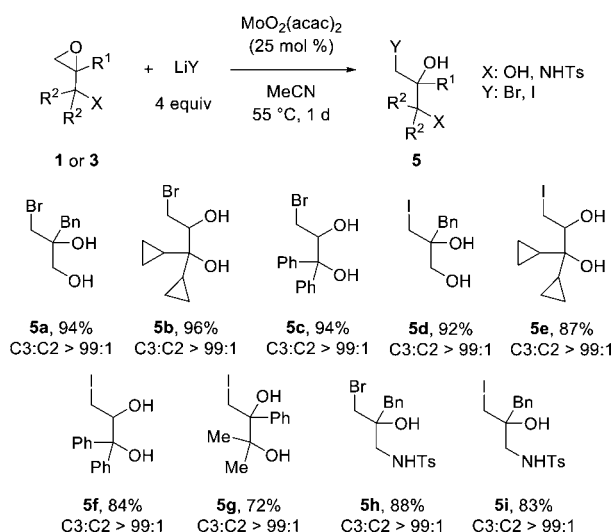
To gain more insight into the directing effect of the OH- and NH-sulfonyl moiety, we performed a control reaction using Ac-protected epoxy alcohols and Boc-protected sulfonamide as substrates (Scheme 5). The results obtained indicated that the ring opening of terminal epoxides **9a** and **9b** could 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-

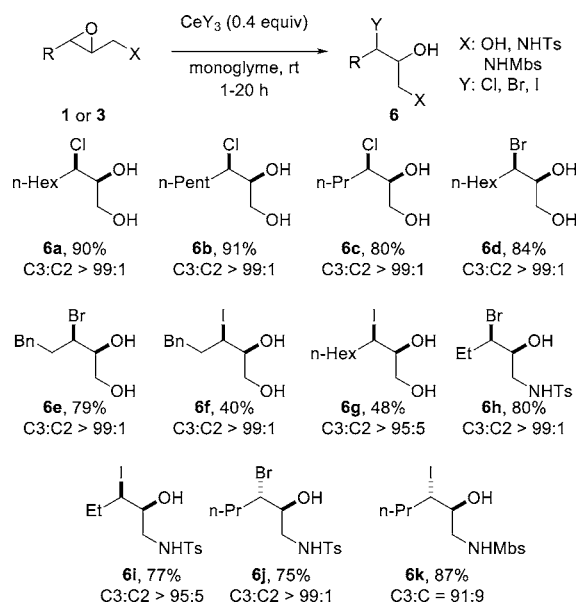
Scheme 2. W-Catalyzed Regioselective Chlorination of 2,3-Epoxy Sulfonamides^{a,b,10}

^aUnless 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 % WO₂Cl₂ at 55 °C in 2.5 mL of monoglyme for 1 d. ^bAll regiomer ratios were determined by ¹H-NMR-spectroscopy. ^cReaction was performed with 5 mol % WO₂Cl₂ at room temperature. Reaction time: 7 h. ^dMonoglyme was used as solvent. ^eMbs: 4-methoxybenzenesulfonyl.

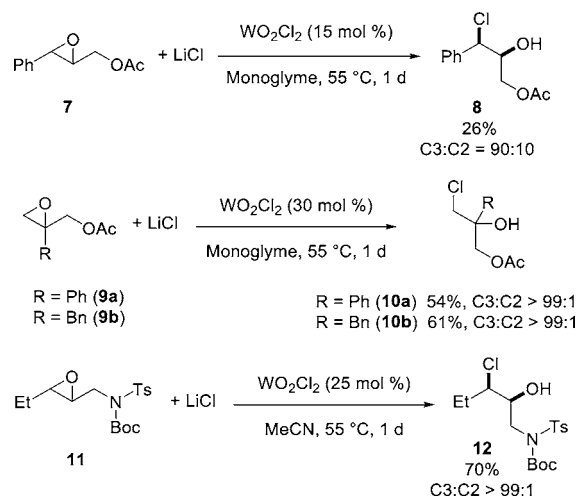
Scheme 3. Mo-Catalyzed Regioselective Bromination and Iodination of Terminal 2,3-Epoxy Alcohols and 2,3-Epoxy Sulfonamides^{a,b,10}

^aUnless 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 % MoO₂(acac)₂ at 55 °C in 2.5 mL of monoglyme for 1 d. ^bAll regiomer ratios were determined by ¹H-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}


^aUnless 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. ^bAll regiomer ratios were determined by ¹H-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>.

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Notes

The authors declare no competing financial interest.

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- (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.