Facile One-Pot Epoxidation–Nucleophilic Opening Sequence for Vicinal Diols

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Received September 22, 1995

The nucleophilic opening of epoxides derived from vicinal diols is a common and useful method for carbon–carbon bond formation and the stereoselective generation of secondary or tertiary alcohols. This synthetic approach has been made particularly attractive in view of the reliable methods available for the direct enantioselective production of 1,2-diols from alkenes.[1] In practice, vicinal diols are often converted into epoxides[2] or 1,2-cyclic sulfates[3–6] as a prelude to nucleophilic opening. Thus, the overall transformation of 1,2-diols into alkylation products generally spans several discrete laboratory operations. We have found that these common multistep sequences may be simplified by effecting both the conversion of vicinal diols into epoxides and nucleophilic epoxide opening in a simple and efficient one-pot operation. This procedure compliments catalytic asymmetric dihydroxylation protocols to provide a powerful two-step conversion of terminal alkenes into a wide variety of enantiomerically enriched carbinols.

Our interest in developing a simplified method for the functionalization of vicinal diols was prompted by the desire to avoid multistep protecting group manipulations and the isolation, purification, and handling of volatile, low molecular weight intermediates. Electrophilic activation of vicinal diols towards the addition of carbon nucleophiles may be accomplished without protecting group manipulations by direct conversion into 1,2-cyclic sulfates or epoxides. However, several discrete steps, as well as the isolation of intermediates, are required for the formation, nucleophilic opening, and hydrolysis of sulfates.[3–5] Sharpless has also shown that 1,2-diols may be converted stereospecifically into epoxides without isolation of halohydrin ester intermediates,[2] but the conditions required are not ideally suited to the in situ nucleophilic opening of epoxides. The one-pot, stereoselective epoxidations of vicinal diols using NaH and *N*-(*p*-toluenesulfonyl)imidazole (*N*-TsIm)[7–9] or *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (*N*-TrisIm)[10] suggested a more convenient approach. These latter epoxidations involve selective monoarylsulfonylation followed by in situ arylsulfonate displacement by the adjacent alkoxide.

We reasoned that the byproducts of one-pot epoxide formation in THF under these conditions (sodium arylsulfonate and sodium imidazolide) would not interfere with the nucleophilic addition of carbanions to the in situ formed epoxide. Therefore, a sequential one-pot epoxide formation–nucleophilic opening process using the primary, secondary vicinal diol (*S*)-4-(phenylmethoxy)-1,2-butanediol (**1**) and several organometallic species that are commonly used for epoxide opening was examined. These include 2-lithio-1,3-dithiane,[11] vinylmagnesium bromide/catalytic CuI,[12,13] and lithium acetylide/BF_3·OEt_2.[14] Sequential addition of NaH (2.5 molar equiv) and *N*-TsIm (1.0 equiv) to a 0 °C THF solution of **1** gave epoxide **2**[15] in 88% isolated yield. Addition of a THF solution of 2-lithio-1,3-dithiane (1.8 equiv) to the in situ prepared epoxide gave **3** in 86% yield from **1** on a 1 mmol scale (Table 1). Similarly, addition of vinylmagnesium bromide/CuI[12] or lithium acetylide/BF_3·OEt_2 to the epoxidation reaction mixture provided the corresponding products **4**[16] and **5**. No attempt was made to optimize the conditions in terms of minimizing the number of equivalents of the various nucleophiles used. Thus, the one-pot epoxidation of **1** using *N*-TsIm and NaH allows for direct and efficient addition of a variety of nucleophiles and in only about 3 h total reaction time.

The scope of this one-pot epoxidation–nucleophilic opening sequence was surveyed with several additional vicinal diols. As shown in Table 1, good yields (82%-90%) of products were obtained using a variety of substrates. Entry 6 illustrates that the one-pot epoxidation–nucleophilic opening of a primary, tertiary vicinal diol (**10**) can also be accomplished efficiently (88% yield) under these conditions. Even a vicinal secondary, secondary diol, *trans* 1,2-cyclohexanediol (**12**, entry 7), was epoxidized and opened in a one-pot fashion to give **13**[14] in a comparable overall yield. However, the reaction time required for the epoxide formation step was substantially longer. Analysis of the Mosher esters derived from products **3–5**, **7**, and **9** indicated that vicinal diols **1**, **6**, and **9** underwent 6–10% configurational inversion using *N*-TsIm and NaH in the epoxidation–nucleophilic opening process (Table 1). Replacing *N*-TrisIm for *N*-TsIm in the conversion of **1** into **4** enhanced both the degree of stereochemical retention and yield (entry 2, Table 1). Similarly, substituting *N*-TrisIm for *N*-TsIm in the conversion of **6** into **7** gave significantly improved yield,

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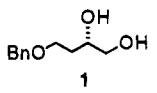
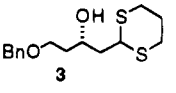
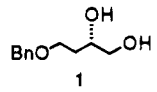
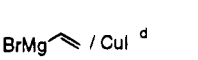
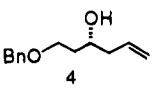
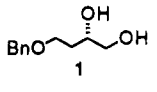
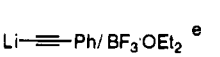
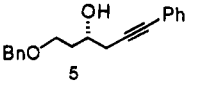
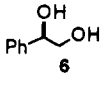
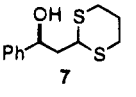
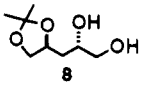
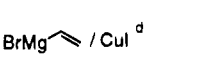
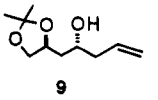
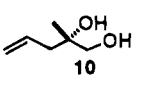
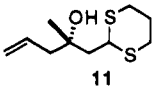
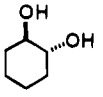
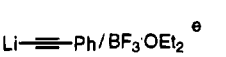
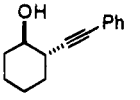
0022-3263/95/1960-8122$09.00/0

Table 1. One-Pot Vicinal Diol Epoxidation–Nucleophilic Opening[a]

Entry	1,2-Diol	1) NaH / $ArSO_2$-Im / THF 2) Nucleophile: R^3	Product	*N*-TsIm % Yield[b] (% Retention)[c]	*N*-TrisIm % Yield[b] (% Retention)[c]
(1)	 **1**		 **3**	86 (92)	—
(2)	 **1**	 [d]	 **4**	85 (92)	89 (96)
(3)	 **1**	 [e]	 **5**	82 (92)	—
(4)	 **6**		 **7**	83 (90)	93 (92)
(5)	 **8**	 [d]	 **9**	90 (94)	92 (96)
(6)	 **10**		 **11**	88 (nd)	—
(7)[f]	 **12**	 [e]	 **13**	82 (na)	—

[a] Full experimental procedures and compound characterization data are given in the supporting information. [b] Isolated yields for chromatographically homogeneous products. [c] For **3**–**7**, the degree of stereochemical retention of the original secondary carbinol was determined by Mosher ester derivatization and analysis and by GC analysis for **9**. [d] CuI (0.2 equiv) was added to the in situ formed epoxide, followed by vinylmagnesium bromide (3.0 equiv). [e] A THF solution of the acetylide followed by $BF_3{\cdot}OEt_2$ (4.0 equiv) were added to the in situ prepared epoxide. [f] Longer reaction times were required.

but afforded only a slight increase in stereoselectivity (entry 4). Modest improvements in yield and stereoselectivity were obtained in the conversion of diol **8** into homoallylic alcohol **9** using *N*-TrisIm and NaH (entry 5).

In summary, a new one-pot reaction sequence for the in situ conversion of vicinal diols into epoxides and nucleophilic epoxide opening has been developed. In the first step, epoxidation is effected by treating the diol with NaH and an (arylsulfonyl)imidazole in THF. Subsequent addition of preformed carbon nucleophiles to the epoxide reaction mixture results in clean and efficient epoxide opening to regenerate secondary and tertiary carbinols with good to excellent stereoselectivity. This procedure provides a convenient and efficient alternative to the standard multistep sequences that are commonly used to convert vicinal diols into electrophilic coupling partners and their subsequent functionalization. In particular, it obviates the necessity for the isolation and purification of activated intermediates derived from vicinal diols, and the total operation can be accomplished in only a few hours. Accordingly, it should find considerable use in preparative organic chemistry.

Acknowledgment. We acknowledge assistance from the research funds of the Graduate School of the University of Minnesota (Grant-In-Aid award 16163), a University of Minnesota McKnight Land-Grant Professorship (C.J.F.), and the National Institutes of Health (CA 62195-02) for partial support of this research. We also thank the 3M Co. and Medtronic, Inc., for the donation of laboratory equipment.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**–**5**, **7**, **9**, **11**, and **13** (9 pages).

JO951731Y