Synthetic Methods

International Edition: DOI: 10.1002/anie.201501729
German Edition: DOI: 10.1002/ange.201501729

Hydroxy-Directed, Fluoride-Catalyzed Epoxide Hydrosilylation for the Synthesis of 1,4-Diols**

*Yong-Qiang Zhang, Nico Funken, Peter Winterscheid, and Andreas Gansäuer**

Dedicated to Prof. Reinhard Brückner on the occasion of his 60th birthday

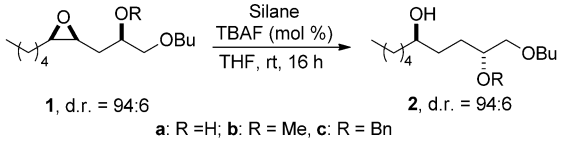
Abstract: *A novel highly regioselective, fluoride-catalyzed hydrosilylation of β-hydroxy epoxides has been developed. The reaction is modular and applicable to the synthesis of a broad range of 1,4-diols. Fluoride is crucial for two reasons: First, it promotes the formation of a silyl ether (which contains a Si-H bond) and, second, it enables ring opening by an intramolecular S_N2 reaction through activation of the silane. The reaction can be performed under air.*

1,4-Diol units are important structural motifs in many natural products and biologically active substances, such as amphotericin B,[1] pladienolide B,[2] the feigresolides,[3] and the schulzeines.[4] Therefore, a number of methods have been devised for the synthesis of 1,4-diols.[5] The highest stereoselectivities were obtained for the rearrangement of 1,2-disubstituted cyclobutenes to *anti*-1,4-diols,[6] the synthesis of *syn*-(*E*)-1,4-diol-2-enes using allyl boronates,[7] and the preparation of *syn*- and *anti*-(*E*)-1,4-diol-2-enes by a Cu-catalyzed boration of an allylic epoxide.[8]

Here, we report a complementary synthetic approach to 1,4-diols that is based on an unprecedented highly regioselective and hydroxy-directed silane reduction of β-hydroxy epoxides. Thermodynamically, epoxide opening through silane reduction is an attractive reaction because ring strain is released and strong C–H and Si–O bonds are formed. However, such reactions have remained virtually unexplored.[9] To the best of our knowledge, the only catalytic reduction of epoxides involving silanes as terminal reductants is a titanocene(III)-catalyzed process.[10,11] It features epoxide-derived radicals and titanocene(III) hydrides as key intermediates.

Our initial investigations on the synthesis of 1,4-diols are summarized in Table 1. It is clear that $PhSiH_3$ and Ph_2SiH_2 alone are not appropriate reagents for opening epoxide **1a**. Therefore, activation of the silane by a catalyst is necessary. Fluoride salts are attractive in this respect because they have been shown to induce the reduction of ketones by silanes.[12]

Table 1: Initial optimization of the silane reduction.



1, d.r. = 94:6 **2**, d.r. = 94:6

a: R =H; **b**: R = Me, **c**: R = Bn

Substrate	Silane	TBAF [mol%]	Conversion [%]	Yield [%][a,b]
1a	$PhSiH_3$	–	0	**2a**, 0
1a	Ph_2SiH_2	–	0	**2a**, 0
1a	$PhSiH_3$	10	84	**2a**, 71
1a	$PhSiH_3$	20	100	**2a**, 82
1a	$PhSiH_3$	20	100	**2a**, 94[c] 91[d]
1a	Ph_2SiH_2	20	100	**2a**, 78
1a	$(EtO)_3SiH$	20	<5	**2a**, 0
1a	PMHS	20	<5	**2a**, 0
1b	$PhSiH_3$	20	<5	**2b**, 0
1c	$PhSiH_3$	20	<5	**2c**, 0

[a] Reaction conditions: substrate 0.5 mmol in THF (2.0 mL), TBAF added as a 1.0 M solution in THF, room temperature, 16 h. [b] Yield of isolated product. [c] Reaction carried out on a 14.8 mmol scale with enantiomerically pure substrate. [d] Reaction carried out on a 10 mmol scale in an open flask under air.

Gratifyingly, the addition of tetrabutylammonium fluoride (TBAF) induced a dramatic change. The reaction proceeds to completion in 16 h with 20 mol% TBAF, and the desired 1,4-diols can be obtained in good yield. No 1,3-diol could be detected or isolated. $PhSiH_3$ is superior to Ph_2SiH_2 in terms of product purification. Other silanes, such as polymethylhydrosiloxane (PMHS) or triethoxysilane [$(EtO)_3SiH$] gave very low conversion into products ($<5\%$). Even higher yields were obtained (94%) when the reaction was carried out on a gram scale (3.6 g of enantiomerically pure **1a**, 14.8 mmol). Furthermore, the reaction has also been performed under air (2.2 g of racemic **1a**, 10.0 mmol) in an open flask with an almost identical yield (91%).

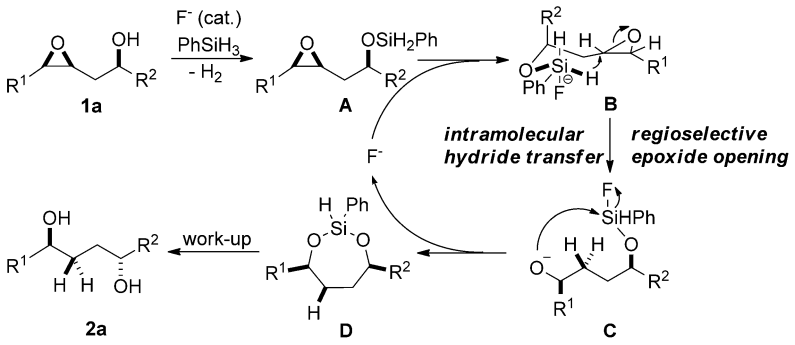
The addition of TBAF to the solution of **1a** and $PhSiH_3$ or Ph_2SiH_2 results in a violent evolution of gas. This is not the case with the *O*-methylated and *O*-benzylated **1b** and **1c** or without TBAF. This finding suggests that the formation of a silyl ether is mandatory for epoxide opening.

Based on these results, a plausible mechanism for the fluoride-catalyzed hydroxy-directed epoxide opening was developed (Scheme 1). Silylation of **1a** with $PhSiH_3$ in the presence of TBAF gives the silyl ether **A**,[13] along with evolution of H_2. Ensuing binding of fluoride leads to the formation of a pentavalent Si species **B**, which subsequently

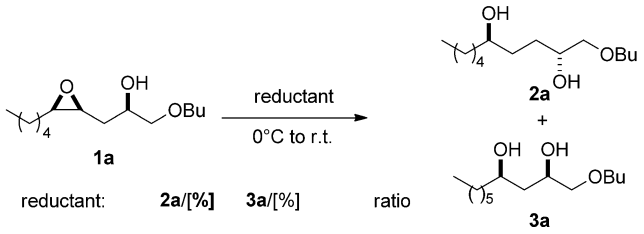
[*] Dr. Y.-Q. Zhang, N. Funken, P. Winterscheid, Prof. Dr. A. Gansäuer
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard Domagk Strasse 1, 53121 Bonn (Germany)
E-mail: andreas.gansaeuer@uni-bonn.de

[**] We gratefully acknowledge support by the Alexander von Humboldt-Stiftung (research fellowship for Y.-Q.Z.) and the DFG (SFB 813 "Chemistry at Spin Centers").

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501729.



Scheme 1. Tentative mechanism of the fluoride-catalyzed epoxide opening.



reductant:	2a/[%]	3a/[%]	ratio
$LiAlH_4$:	59	24	71:29
Dibal-H:	-	-	complex mixture
Red-Al:	51	17	79:21

Scheme 2. Reduction of **1a** with hydride reagents (at −78 °C less than 5% conversion to products was observed).

undergoes the pivotal intramolecular hydride transfer that opens the epoxide. The catalytic cycle is closed by formation of **D** and release of fluoride. The 1,4-diol **2a** is generated through hydrolytic work-up.

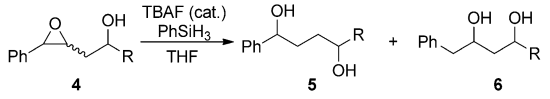
The high regioselectivity of the ring opening is a unique feature of our system. Mixtures of 1,3- and 1,4-diols were obtained with classic hydride reductants (Scheme 2).[14] Further examples addressing the stereochemical issues of the intramolecular S_N2 reaction are summarized in Table 2.

Phenyl substitution was chosen to probe the importance of the six-membered transition state for epoxide opening. Nucleophilic substitution at a benzylic center usually results in a substantial acceleration compared to alkyl-substituted substrates.

In our case, however, benzylic ring opening to the 1,3-diol requires a seven-membered transition state. The 1,4-diols were still formed with excellent regioselectivity (95:5 or 96:4) from all the *cis*-β-hydroxy epoxides (Table 2, entries 2, 3, and 4). However, the regioselectivity of the ring opening of the *trans*-epoxide (entry 1) was significantly lower (76:24), thus indicating a substantial competition of ring opening via a seven-membered transition state.

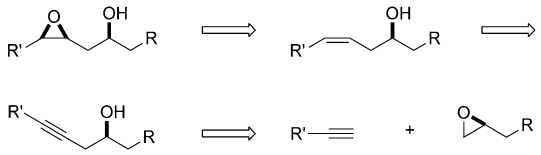
Some representative examples of the novel 1,4-diol synthesis are summarized in Table 3. The examples show that our method can be employed for the synthesis of 1,4-diols with a wide range of substitution patterns, including *syn*- and *anti*-1,4-diols. 1,4-Diols containing primary and tertiary alcohols can be readily prepared. Notably, ring opening was regiospecific in all the cases examined: only 1,4-diols were detected or isolated. The opening of the monosubstituted epoxide **15** occurs with complete regioselectivity at the more hindered position, in agreement with our mechanistic proposal. Furthermore, sensitive functional groups, such as acetals of aldehydes and ketones, are readily tolerated (**19**, **21**). The hydrosilylation of **17** with $PhSiD_3$ affords the 1,4-diol **18D** stereospecifically, with a deuterium incorporation of >98% (entry 7). The configuration was tentatively assigned by assuming an intramolecular ring opening. An additional stereocenter, as in **23**, is readily tolerated.

Table 2: Regioselectivity of the epoxide opening of phenyl-substituted substrates.



Entry	Substrate	Products		Ratio 5/6	Yield [%]
1	*trans*-**4a**	**5a**	**6a**	76:24	74[a]
2	*cis*-**4a**	**5a**	**6a**	95:5	72[b]
3	**4b**	**5b**	**6b**	96:4	68[a]
4	**4c**	**5c**	**6c**	96:4	82[a]

[a] Reaction conditions: substrate 0.5 mmol in THF (2.0 mL), $PhSiH_3$ (2.0 mmol), TBAF added as a 1.0 M solution in THF (0.1 mmol), room temperature, 16 h. [b] TBAF (0.125 mmol) used, reflux, 24 h.

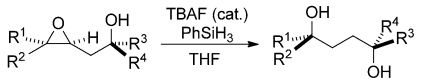


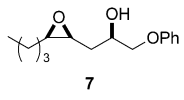
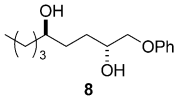
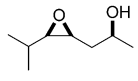
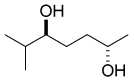
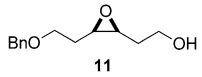
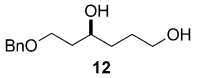
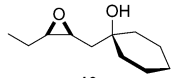
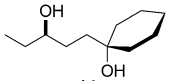
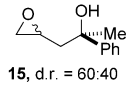
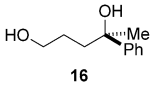
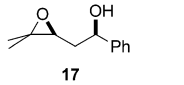
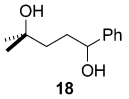
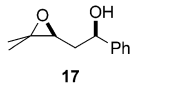
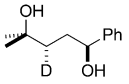
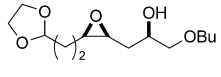
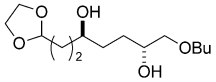
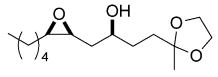
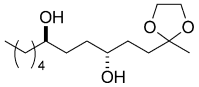
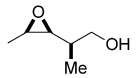
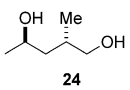
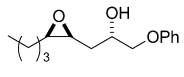
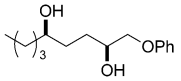
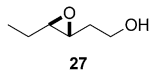
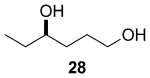
Scheme 3. Modular approach to *syn*-β-hydroxy epoxides.

The *syn*- and *anti*-β-hydroxy *cis*-epoxides can be prepared in a convergent and highly modular manner (Scheme 3). The $[VO(acac)_2]$-catalyzed epoxidation of (*Z*)-homoallylic alcohols provides the *syn*-epoxides with high diastereoselectivity.[15a] The *anti*-epoxides can be obtained from these compounds through Mitsunobu inversion.[16]

The homoallylic alcohols are easily synthesized by the addition of alkynes to epoxides and a chemoselective and *Z*-

Table 3: Epoxide opening for the synthesis of 1,4-diols.



Entry	Substrate	Product	Yield [%]
1	 **7**	 **8**	81,[a] 83[a,d]
2	 **9**, d.r. = 92:8	 **10**, d.r. = 92:8	72[b]
3	 **11**	 **12**	91[b]
4	 **13**	 **14**	63[b]
5	 **15**, d.r. = 60:40	 **16**	78[a]
6	 **17**	 **18**	81[b]
7	 **17**	 **18D**	72[b,c]
8	 **19**, d.r. = 93:7	 **20**, d.r. = 93:7	81[a]
9	 **21**	 **22**	94[a]
10	 **23**	 **24**	70[b]
11	 **25**	 **26**	85,[b] 79[b,d]
12	 **27**	 **28**	76[a]

[a] Reaction conditions: substrate 0.5 mmol in THF (2.0 mL), $PhSiH_3$ (2.0 mmol), TBAF added as a 1.0 M solution in THF, room temperature, 16 h. [b] TBAF (0.125 mmol) used, reflux, 24 h. [c] $PhSiD_3$ (2.0 mmol) used, >98% D incorporation. [d] Reaction carried out under air.

selective hydrogenation of the homopropargylic alcohols. Since enantiomerically pure terminal epoxides and alkynes are readily available on a large scale, a large variety of 1,4-diols is accessible from *syn*- and *anti*-β-hydroxy *cis*-epoxides by our novel method.

The 1,4-diol **28** was also obtained as the sole product from the *n*-alkyl-substituted *trans*-epoxide **27**. This suggests that alkyl-substituted *trans*-substituted β-hydroxy epoxides are also interesting substrates for the synthesis of 1,4-diols. However, since the $[VO(acac)_2]$-catalyzed epoxidation of secondary (*E*)-homoallylic alcohols proceeds with very low diastereoselectivity,[15a] the necessary substrates for the 1,4-diol synthesis cannot be easily prepared.

In conclusion, we have developed an unprecedented fluoride-catalyzed, hydroxy-directed hydrosilylation of β-hydroxy epoxides. The intramolecular ring opening through hydride transfer occurs with very high regioselectivity and, therefore, 1,4-diols are obtained exclusively or with very high selectivity. The reaction can be performed on a gram scale in an open flask under air without a significant effect on the yield. Since the hydrosilylation tolerates a wide range of functionality and the substrates can be prepared in a convergent and modular manner, our novel method is broad in scope and will be useful for the synthesis of diol and polyol targets.

Experimental Section

1a (2.24 g, 10 mmol, 1.0 equiv) as a 94:6 mixture of *syn* and *anti* isomers, THF (20 mL), and $PhSiH_3$ (4.9 mL, 40 mmol, 4.0 equiv) were added to a 50 mL round bottom flask under air. TBAF (2.0 mL, 1.0 M in THF, 0.2 equiv) was then added dropwise over 40 min. During that time, gas was evolved. The resulting mixture was stirred at room temperature for 16 h and then diluted with THF (20 mL). Subsequently, NaOH solution (2.0 M in H_2O, 10 mL) was added dropwise over 10 min. After stirring the mixture for 3 h at room temperature, it was diluted with H_2O (10 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic solutions were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography (SiO_2, cyclohexane/ethyl acetate 60:40) gave 2.04 g (9.1 mmol, 91%) of **2a** as a 94:6 mixture of the *anti* and *syn* isomers.

Keywords: 1,4-diols · epoxide opening · fluoride catalysis · hydrosilylation · regioselectivity

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 6931–6934
Angew. Chem. **2015**, *127*, 7035–7038

[1] J. Vandeputte, J. L. Watchtel, E. T. Stiller, *Antibiot. Annu.* **1956**, 587.
[2] Y. Kotake, K. Sagane, T. Owa, Y. Mimori-Kiyosue, H. Shimizu, M. Uesuqi, Y. Ishihama, M. Iwata, Y. Mizui, *Nat. Chem. Biol.* **2007**, *3*, 570–575.
[3] Y.-Q. Tang, I. Sattler, R. Thiericke, S. Grabley, *J. Antibiot.* **2000**, *53*, 934–943.
[4] K. Takada, T. Uehara, Y. Nakao, S. Matsunaga, R. W. M. Van Soest, N. Fusetani, *J. Am. Chem. Soc.* **2004**, *126*, 187–193.
[5] For selected examples of 1,4-diol synthesis, see a) M. Amador, X. Ariza, J. Garcia, J. Ortiz, *Tetrahedron Lett.* **2002**, *43*, 2691–2694; b) J.-E. Bäckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619–4631; c) X. Ariza, J. Bach, R. Berenguer, J. Farràs, M. Fontes, J. Garcia, M. López, J. Ortiz, *J. Org. Chem.* **2004**, *69*, 5307–5313; d) D. M. Hodgson, C. D. Bray, N. D. Kindon, *Org. Lett.* **2005**, *7*, 2305–2308; e) D. E. Williams, C. M. Sturgeon, M. Roberge, R. J. Andersen, *J. Am. Chem.*

Soc. **2007**, *129*, 5822 – 5823; f) T. Diyabalanage, C. D. Amsler, J. B. McClintock, B. J. Baker, *J. Am. Chem. Soc.* **2006**, *128*, 5630 – 5631; g) R. Ballini, L. Barboni, G. Giarlo, *J. Org. Chem.* **2003**, *68*, 9173 – 9176; h) G. Guanti, L. Banfi, V. Merlo, E. Narisano, *Tetrahedron* **1994**, *50*, 2219 – 2230; i) N. Ghavtadze, F. S. Melkonyan, A. V. Gulevich, C. Huang, V. Gevorgyan, *Nat. Chem.* **2014**, *6*, 122 – 125; j) R. Fernández de la Pradilla, I. Colomer, M. Ureña, A. Viso, *Org. Lett.* **2011**, *13*, 2468 – 2471; k) T. Hashimoto, D. Hirose, T. Taniguchi, *Angew. Chem. Int. Ed.* **2014**, *53*, 2730 – 2734; *Angew. Chem.* **2014**, *126*, 2768 – 2772; l) S. Vettel, P. Knochel, *Tetrahedron Lett.* **1994**, *35*, 5849 – 5852; m) W. R. Roush, P. T. Grover, *Tetrahedron* **1992**, *48*, 1981 – 1998; n) A. Gansäuer, P. Karbaum, D. Schmauch, M. Einig, L. Shi, A. Anoop, F. Neese, *Chem. Asian J.* **2014**, *9*, 2289 – 2294.

[6] K. M. Knapp, B. Goldfuss, P. Knochel, *Chem. Eur. J.* **2003**, *9*, 5259 – 5265.

[7] a) M. Binanzer, G. Y. Fang, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 4264 – 4268; *Angew. Chem.* **2010**, *122*, 4360 – 4364; b) A. Robinson, V. K. Aggarwal, *Org. Biomol. Chem.* **2012**, *10*, 1795 – 1801; c) D. Leonori, V. K. Aggarwal, *Acc. Chem. Res.* **2014**, *47*, 3174 – 3183.

[8] a) M. Tortosa, *Angew. Chem. Int. Ed.* **2011**, *50*, 3950 – 3953; *Angew. Chem.* **2011**, *123*, 4036 – 4039; b) R. Alfaro, A. Parra, J. Alemán, M. Tortosa, *Synlett* **2013**, 804 – 812.

[9] For reviews on silane reductions and hydrosilylations, see a) Y. Nagal, *Org. Prep. Proced. Int.* **1980**, *12*, 13 – 48; b) C. Chatgilialoglu, *Acc. Chem. Res.* **1992**, *25*, 188 – 194; c) B. Marciniec, *Hydrosilylation: A Comprehensive Review on Recent Advances*, Springer, Heidelberg, **2009**.

[10] A. Gansäuer, M. Klatte, G. M. Brändle, J. Friedrich, *Angew. Chem. Int. Ed.* **2012**, *51*, 8891 – 8894; *Angew. Chem.* **2012**, *124*, 9021 – 9024.

[11] For a formal iridium-catalyzed epoxide reduction with silane, in which epoxides are isomerized to ketones prior to hydrosilylation, see S. Park, M. Brookhart, *Chem. Commun.* **2011**, *47*, 3643 – 3645.

[12] a) M. Fujita, T. Hiyama, *J. Am. Chem. Soc.* **1985**, *107*, 8294 – 8296; b) M. Fujita, T. Hiyama, *J. Org. Chem.* **1988**, *53*, 5405 – 5415; c) Y. Kobayashi, E. Takahisa, M. Nakano, K. Watatani, *Tetrahedron* **1997**, *53*, 1627 – 1634.

[13] a) H. Gilman, G. E. Dunn, H. Hartzfeld, A. G. Smith, *J. Am. Chem. Soc.* **1954**, *76*, 1287 – 1288; b) J. M. Blackwell, K. L. Foster, V. H. Beck, W. E. Piers, *J. Org. Chem.* **1999**, *64*, 4887 – 4892; c) Y. Gunji, Y. Yamashita, T. Ikeno, T. Yamada, *Chem. Lett.* **2006**, *35*, 714 – 715.

[14] For a classic hydride reagent only resulting in high regioselectivity ($>85:<15$ to $>95:<5$) for β-hydroxy epoxides containing a primary hydroxy group, see a) B. E. Rossiter, K. B. Sharpless, *J. Org. Chem.* **1984**, *49*, 3707 – 3711; b) D. Tanner, T. Groth, *Tetrahedron* **1997**, *53*, 16139 – 16146; c) J. M. Finan, Y. Kishi, *Tetrahedron Lett.* **1982**, *23*, 2719 – 2722.

[15] a) E. D. Mihelich, K. Daniels, D. J. Eickhoff, *J. Am. Chem. Soc.* **1981**, *103*, 7690 – 7692; b) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286 – 287; c) R. R. Rodríguez-Berríos, G. Torres, J. A. Prieto, *Tetrahedron* **2011**, *67*, 830 – 836.

[16] a) K. C. Swamy, N. N. Kumar, E. Balaraman, K. V. Kumar, *Chem. Rev.* **2009**, *109*, 2551 – 2651; b) C. L. Pereira, Y.-H. Chen, F. E. McDonald, *J. Am. Chem. Soc.* **2009**, *131*, 6066 – 6067.

Received: February 23, 2015
Revised: March 16, 2015
Published online: April 20, 2015

