Ring-Opening of Epoxides by Pendant Silanols

Someshwar Nagamalla,[a] Joel T. Mague,[b] and Shyam Sathyamoorthi[,a]*

AUTHOR ADDRESS

[a]Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas,

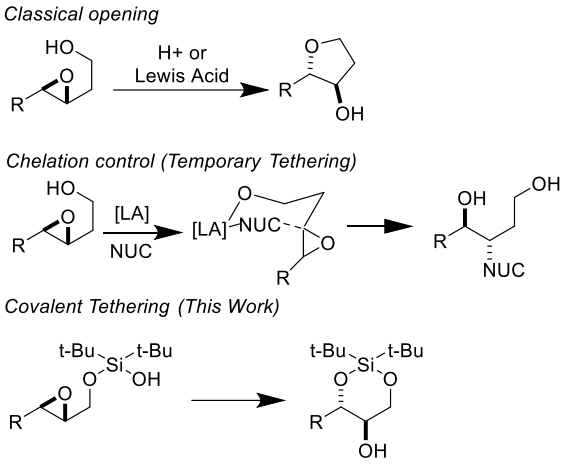
66047, USA.

[b]Department of Chemistry, Tulane University, New Orleans, Louisiana, 70118, USA.

KEYWORDS Synthetic organic chemistry, Lewis acid catalysis, Bronsted acid catalysis, epoxide ring-opening

ABSTRACT

We present a new ring-opening reaction of epoxides by pendant silanols, catalyzed by either $Ph_3C^+BF_4^-$ or BINOL-phosphoric acid. In all cases examined, the reaction is perfectly regioselective and diastereoselective. Silanol epoxides derived from *trans*-allylic alcohols, *cis*-allylic alcohols, *trans*-homoallylic alcohols, and *cis*-homoallylic alcohols were all compatible and gave products from either *endo*- or *exo*-ring opening. With silanol epoxides derived from 4-alkenyl silanols, an unusual rearrangement to tetrahydrofuran products was observed, which is likely the result of tandem nucleophilic attacks. The utility of this methodology was demonstrated in a short preparation of protected D-arabitol.



Scheme 1. Previous efforts with ring cleavage of epoxides inspire our silanoxy-tethered ring-opening approach.

Epoxides are one of the most versatile functional groups in synthetic chemistry, and their cleavage has been investigated in a variety of contexts (**Scheme 1**).[1-4] Nucleophilic opening of epoxides can be broadly characterized as either intermolecular or intramolecular. Intramolecular opening of epoxides by pendant alcohols is a known route to a variety of oxygen heterocycles, including furans, pyrans, and medium-sized rings,[5, 6] and this strategy has been applied on numerous occasions in natural products synthesis.[7-10] Several laboratories have established that "temporary tethering" is an effective strategy for regiocontrol in intermolecular ring-opening reactions of epoxides.[11-16] In such reactions, a Lewis acid or organocatalyst non-covalently binds to both the substrate and the nucleophile and templates attack at a single site of the epoxide. In contrast to these two areas, the use of covalent tethers for epoxide opening is much less established, and most explorations have focused on carbonates,[17-20] carbamates,[21-23] and trichloroacetamidates.[24] Of these tethers, only carbonates cleave epoxides with a masked hydroxy group.

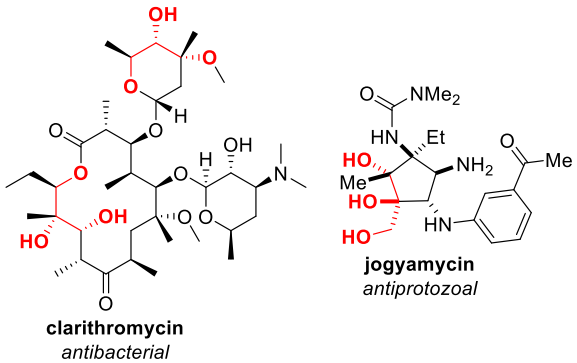
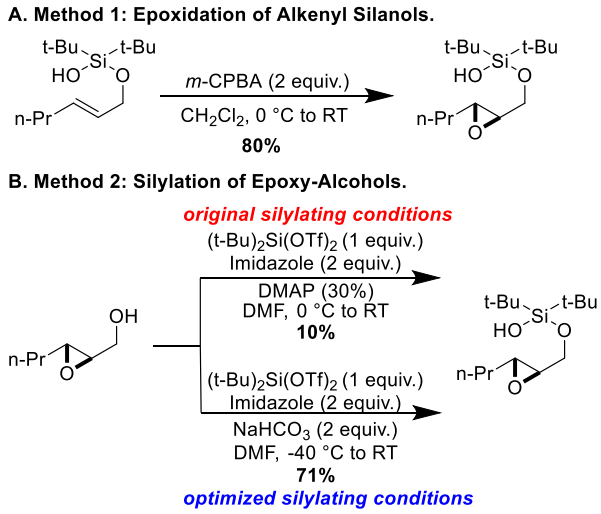


Figure 1. The triol motif is prevalent in natural products with potent biological activity.

Our laboratory is deeply invested in exploring di-*tert*-butylsilanols as covalent tethers for the intramolecular installation of hydroxy groups.[25-28] The triol motif is prevalent in a variety of carbohydrate and polyketide natural products with attractive biological activity (**Figure 1**). We envisioned a ring opening reaction of epoxides

by pendant di-*tert*-butylsilanols, which would form a variety of protected triols. Due to geometric constraints on the transition states of these intramolecular reactions, we reasoned that such openings were likely to be highly regioselective and diastereoselective. Here, we describe our efforts to reduce this concept to practice.



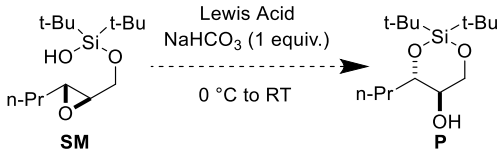
Scheme 2. Two methods to synthesize silanol epoxides.

The substrate silanol epoxides could be conveniently prepared using one of two methods (**Scheme 2**). *m*-CPBA oxidation of the alkenyl silanol[26] delivered the silanol epoxide in good yields, and, in our hands, this proved to be a very general procedure (**Scheme 2A**). As there is much technology[29-31] for the stereocontrolled synthesis of epoxides from alkenyl alcohols, we reasoned that developing a method to attach the silanol auxiliary directly to epoxy-alcohols would be particularly impactful. Our standard silylating conditions[26] failed to deliver product in reasonable yields with these particularly delicate substrates (**Scheme 2B**). We found that replacing DMAP with two equivalents of $NaHCO_3$ and dropping the initial reaction temperature to -40 °C allowed for silanol epoxide formation reproducibly and in much better yields (**Scheme 2B**).

With two protocols allowing reliable access to silanol epoxides, we began optimizing our envisioned ring-opening reaction. Treatment of di-*tert*-butyl(3-propyloxiran-2-yl)(methoxy)silanol with 5 mol% of $Sc(OTf)_3$ and 1 equivalent of $NaHCO_3$ in CH_2Cl_2 for 3 hours gave 20% of the desired product (**Table 1, Entry 1**). Increasing the reaction time to 14 hours led to complete consumption of starting material with 65% of product formation (**Table 1**,

Entry 2). In both cases, a major side product was di-*tert*-butylsilanediol, suggesting that starting material was fragmenting unproductively in the presence of $Sc(OTf)_3$. Switching solvents to benzene, dichloroethane, chloroform, or ethyl acetate (**Table 1, Entries 3-6**) was markedly deleterious. We thus decided to try different Lewis acids with the goal of reducing di-*tert*-butylsilanediol formation. While triflate salts of zinc, indium, and ytterbium (**Table 1**, **Entries 7-9**) did not help reaction performance, with 10 mol% of the unusual Lewis acid triphenylcarbenium tetrafluoroborate[32] (**Table 1**, **Entry 10**), product formation was excellent with no discernible starting material fragmentation.

Table 1. Optimization of epoxide opening by pendant silanols.

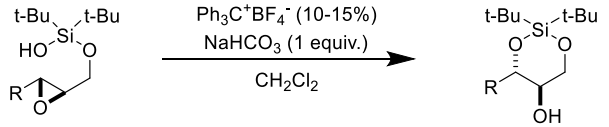


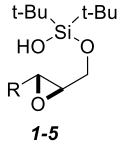
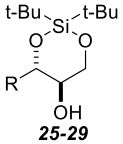
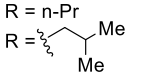
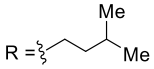
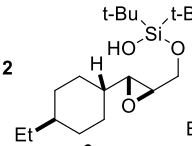
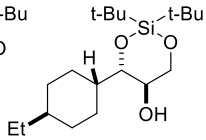
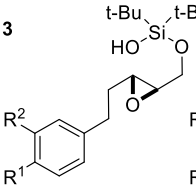
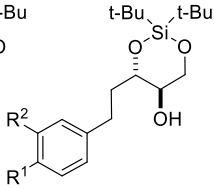
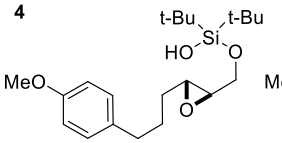
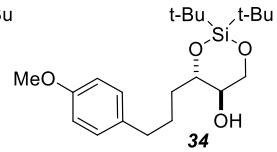
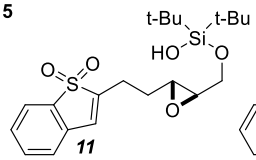
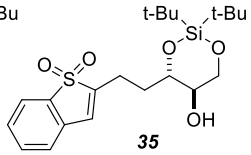
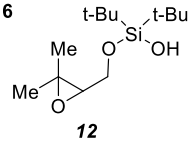
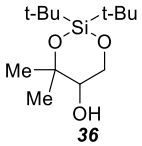
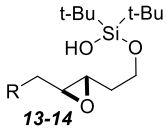
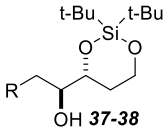
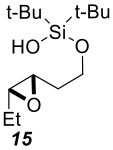
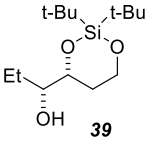
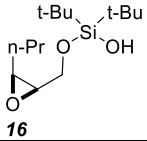
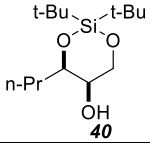
	Lewis Acid (equiv.)	Solvent	Time	P/SM[a]
1	$Sc(OTf)_3$ (5%)	CH_2Cl_2	3h	20/65
2	$Sc(OTf)_3$ (5%)	CH_2Cl_2	14h	65/0
3	$Sc(OTf)_3$ (5%)	C_6H_6	14h	0/100
4	$Sc(OTf)_3$ (5%)	$C_2H_4Cl_2$	14h	27/49
5	$Sc(OTf)_3$ (5%)	$CHCl_3$	14h	10/84
6	$Sc(OTf)_3$ (5%)	EtOAc	14h	0/100
7	$Zn(OTf)_3$ (5%)	CH_2Cl_2	14h	0/100
8	$In(OTf)_3$ (5%)	CH_2Cl_2	14h	45/25
9	$Yb(OTf)_3$ (5%)	CH_2Cl_2	14h	0/100
10	**$Ph_3C^+ BF_4^-$ (10%)**	**CH_2Cl_2**	**2h**	**80/0**

[a]Yield estimated from ^1H NMR integration with 4-nitrotoluene as an internal standard.

Encouraged by this very positive result, we next began the substrate scope exploration (**Scheme 3**). Our optimized conditions proved general for a variety of silanol epoxides, including those with branched alkyl chains (**Scheme 3, Entries 1-2**), substituted aryl rings (**Scheme 3**, **Entries 3-4**), and heteroaryl rings (**Scheme 3**, **Entry 5**). Importantly, we were not limited to di-substituted *trans*-epoxides derived from allylic silanols. Epoxides prepared from tri-substituted allylic silanols (**Scheme 3, Entry 6**), *trans*-homoallylic silanols (**Scheme 3**, **Entry 7**), and *cis*-

Scheme 3. Substrate scope with alkyl epoxides.



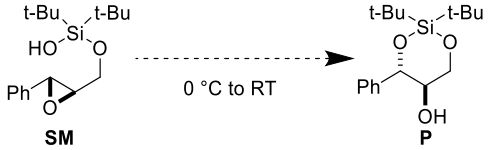
entry	substrate	product	isolated yield
1			R = n-Pr 80% R =  74% R =  83% R = i-Pr 71% R =  52%
	1-5	25-29	
2			71%
	6	30	
3			R1 = F, R2 = H 72% R1 = Br, R2 = H 70% R1 = H, R2 = CF3 87%
	7-9	31-33	
4			70%
	10	34	
5			81%
	11	35	
6			74%
	12	36	
7			R = Me 65% R = c-Hex 50%
	13-14	OH 37-38	
8			60%
	15	39	
9			40%
	16	40	

homoallylic silanols (**Scheme 3**, **Entry 8**) were all compatible with our optimized conditions. Epoxides derived from *cis*-allylic silanols were particularly problematic, likely due to unfavorable 1,3-allylic strain[33] during the cyclization event. However, we were pleased to find that maintaining the reaction temperature at -10 °C delivered desired cyclized product in a respectable 40% yield (**Scheme 3, Entry 9**).

When treated with $Ph_3C^+BF_4^-$, epoxides derived from aryl alkenes failed to cyclize cleanly and, in all cases examined, gave intractable mixtures of products (**Table 2, Entry 1**). Use of $Bi(OTf)_3$ as a Lewis acid (**Table 2, Entry 2**) or HFIP as the solvent (**Table 2, Entry 3**) did little to improve reaction performance, but a more positive result came with treatment of 10-CSA[5, 6] (**Table 2, Entries 4-5**). We hypothesized that a milder Bronsted acid would lead to a cleaner reaction and were pleased to see that with BINOL-phosphoric acid, cyclization

proceeded smoothly and with no discernible side products (**Table 2, Entry 6**).

Table 2. Optimization of aryl epoxide opening by pendant silanols.



	Additive	Solvent	Time	P/SM[a]
1	$Ph_3C^+ BF_4^-$ (10%) $NaHCO_3$ (1 equiv.)	CH_2Cl_2	2h	40/0[b]
2	$Bi(OTf)_3$ (5%) $NaHCO_3$ (1 equiv.)	CH_2Cl_2	2h	30/0[b]
3	None	HFIP	6h	0/40[b]
4	10-CSA (1 equiv.)	CH_2Cl_2	1h	50/0[b]
5	10-CSA (0.25 equiv.)	CH_2Cl_2	1h	50/0[b]
6	**BINOL-Phosphoric Acid (30%)[c]**	**CH_2Cl_2**	**14h**	**80/0**

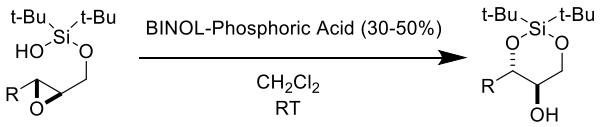
[a]Yield estimated from ^{1}H NMR integration with 4-nitrotoluene as an internal standard.

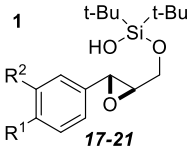
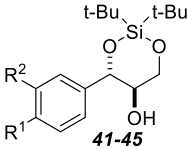
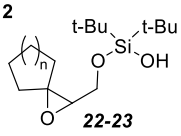
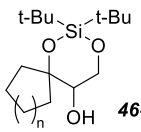
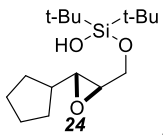
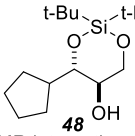
[b]mixture of side products.

[c](R)-(−)-1,1′-Binaphthyl-2,2′-diyl hydrogenphosphate, arbitrarily chosen

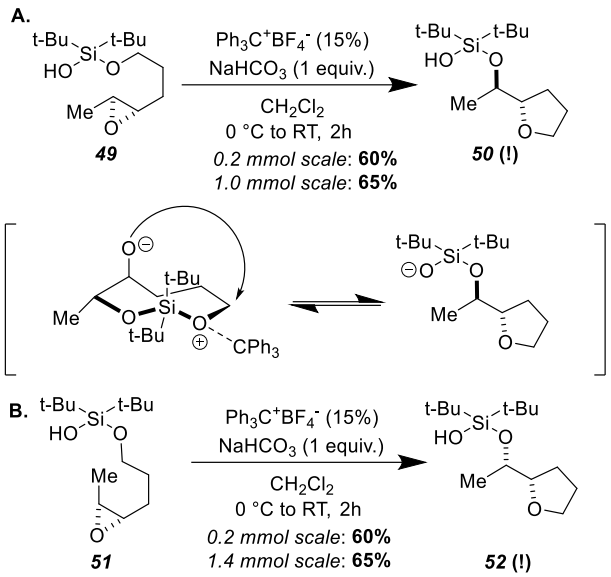
These conditions proved to be excellent for cyclization of aryl epoxide substrates and a variety of substitution patterns on the aromatic ring were well tolerated (**Scheme 4**, **Entry 1**). Furthermore, several substrates which failed to cyclize with $Ph_3C^+BF_4^-/NaHCO_3$ reacted cleanly under these alternate conditions (**Scheme 4**, **Entries 2-3**). In all cases (**Schemes 3-4**), the cyclization reactions were perfectly regioselective and diastereoselective, attesting to the utility of our protocols. A

Scheme 4. Substrate scope with BINOL-phosphoric acid conditions.

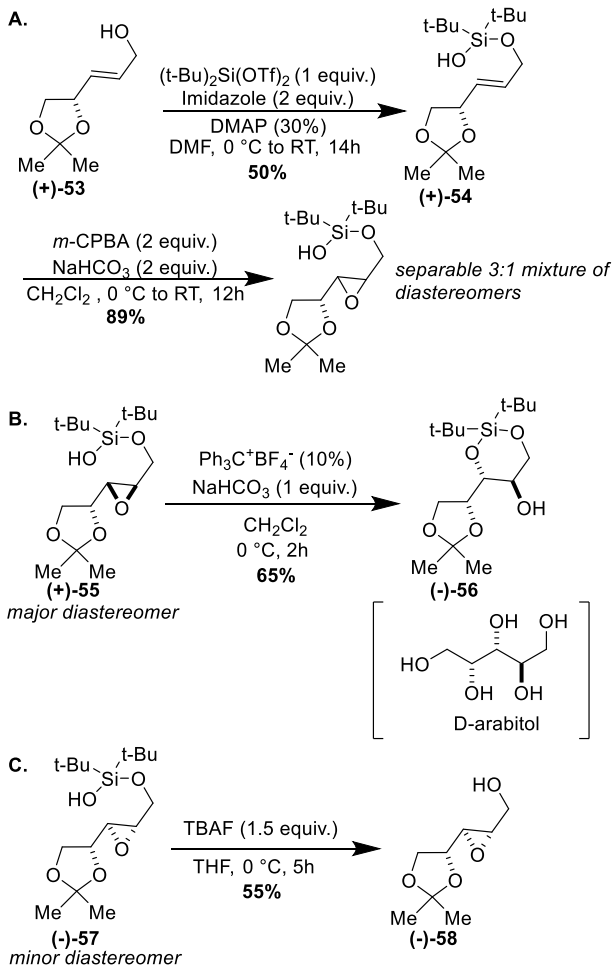


entry	substrate	product		isolated yield
1			R^1 = H, R^2 = H	**80%**
			R^1 = F, R^2 = H	**63%**
			R^1 = Br, R^2 = H	**85%**
			R^1 = Cl, R^2 = H	**82%**
			R^1 = H, R^2 = Br	**85%**
	17-21	***41-45***		
2			n = 1	**54%**
			n= 2	**60%**
	22-23	***46-47***		
3			with 10-CSA	**43%**
			with BINOL-PA	**50%[a]**
	24	***48***		

[a]Yield estimated by ^{1}H NMR integration against an internal standard; 30% recovered starting material also noted.



Scheme 5. An unexpected rearrangement with silanol epoxides derived from 4-alkenyl silanols.



Scheme 6. A short preparation of protected D-arabitol.

crystal structure of **41** (CCDC: 2126173) enabled us to unambiguously establish its relative stereochemistry, and we have assigned the stereochemistry of other products by analogy.

Our success with both allylic and homoallylic silanols prompted us to test our reaction with more remote silanol epoxides (**Scheme 5**). We simply expected the product of either 7-*exo* or 8-*endo* cyclization. What we found, however, was very unexpected and much more interesting. When *trans*-epoxide **49** was treated with our optimized protocol of $Ph_3C^+BF_4^-$ (15 mol%) and $NaHCO_3$ (1 equiv.) in CH_2Cl_2, tetrahydrofuran **50** formed in a 60% yield (**Scheme 5A**)! We hypothesize that two tandem cyclizations took place. The first was the expected 8-*endo* cyclization, which was followed by an unexpected 5-*exo* ring opening. We were pleased to find that with *cis*-epoxide **51**, diastereomeric tetrahydrofuran **52** formed in similar yields (**Scheme 5B**). These reactions were scaled 5 to 7-fold, with no degradation in

yield or selectivity.

We envisioned a short preparation of protected D-arabitol utilizing our ring-opening reaction as a key step (**Scheme 6**). With our laboratory's standard silylating conditions,[26] enantiopure silanol **(+)-54** was prepared from known chiron **(+)-53**.[34] *m*-CPBA epoxidation of **(+)-53** proceeded in excellent yield to give a separable mixture of **(+)-55** and **(-)-57** (**Scheme 6A**). When major diastereomer **(+)-55** was treated with $Ph_3C^+BF_4^-$ (10 mol%) and $NaHCO_3$ (1 equiv.), cyclized product **(-)-56** (protected D-arabitol) formed in a 65% yield (**Scheme 6B**). Minor diastereomer **(-)-57** was de-silylated using TBAF (1.5 equivalents) in THF to yield known alcohol **(-)-58**,[34, 35] allowing us to assign the absolute stereochemistry of diastereomers **(+)-55** and **(-)-57** (**Scheme 6C**).

In summary, we present a new ring-opening reaction of epoxides by pendant silanols. In all cases examined, the reaction is perfectly regioselective and diastereoselective. Silanol epoxides derived from *trans*-allylic alcohols, *cis*-allylic alcohols, *trans*-homoallylic alcohols, and *cis*-homoallylic alcohols were all compatible and gave products from either *endo*- or *exo*-ring opening. With silanol epoxides derived from 4-alkenyl silanols, an unusual rearrangement to tetrahydrofuran products was observed, which is likely the result of tandem nucleophilic attacks. The utility of this reaction was demonstrated in a short preparation of protected D-arabitol. We are optimistic that this methodology will enjoy much use in the pursuit of complex, polyhydroxylated molecules.

ASSOCIATED CONTENT

Supporting Information. Experimental Procedures, Reasoning for Structural Assignments, NMR Spectra, and Crystallographic Information

AUTHOR INFORMATION

Corresponding Author

*E-mail: ssathyam@ku.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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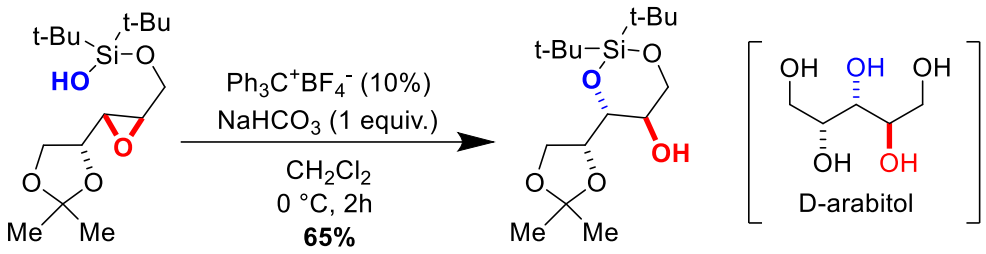

>20:1 regioselectivity and diastereoselectivity in all cases examined!