

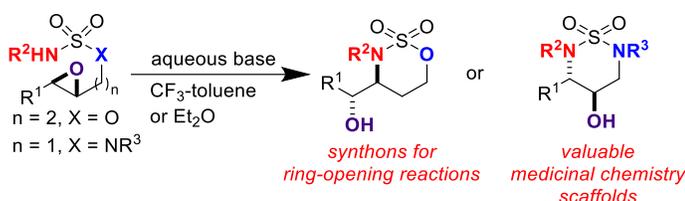
Unusual Covalent Tethers for Precise Amino-Alcohol Syntheses: Ring Opening of Epoxides by Pendant Sulfamates and Sulfamides

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Supporting Information Placeholder

Precise Construction of Stereochemical Arrays
with Unusual Nucleophiles



ABSTRACT: We describe the development of the first ring-opening of epoxides using pendant sulfamates and sulfamides. These reactions are promoted by base and proceed under mild conditions to afford oxathiazinanes and cyclic sulfamides with excellent diastereoselectivity and regiocontrol. The reactions scale well, and the products serve as synthons for ring-opening reactions.

The precise construction of polyfunctional molecules remains a topic of great interest.^{1, 2} Many targets of value are densely functionalized and are comprised of several contiguous stereocenters. The ring-opening of epoxides is an attractive method for the assembly of alcohol-containing stereoarrays.³⁻⁷ Our laboratory has a programmatic focus on the use of unusual nucleophiles for the ring-opening of both transient⁸⁻¹³ and stable electrophiles.^{14, 15} As part of this line of inquiry, it occurred to us that a ring-opening of epoxides by pendant sulfamates and sulfamides would offer predictable access to vicinal amino-alcohols and would complement our previous efforts with intramolecular cleavage of aziridines by di-*tert*-butyl-silanol auxiliaries.¹⁴

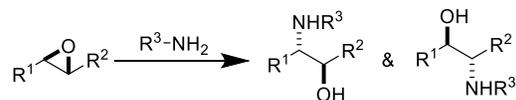
There is no shortage of interesting amino-alcohols, and new methods for their construction are valuable.¹⁶⁻²⁰ Unfortunately, a simple intermolecular aminolysis of epoxides often leads to intractable mixtures of regioisomeric products (**Scheme 1A**).²¹⁻²⁴ Many creative investigators have developed “temporary tethering” approaches for the regioselective opening of epoxides with *N*-nucleophiles (**Scheme 1B**).²⁵⁻²⁹ Nevertheless, even with chelating Lewis acids, depending

on the substrate, a mixture of regioisomers can still result. Covalent tethering offers a complementary

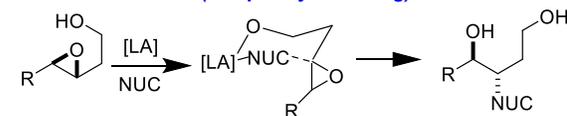
Scheme 1. Previous efforts with aminolysis of epoxides inspire our tethered ring-opening approach.

Synthesis of Amino-Alcohols from Epoxides

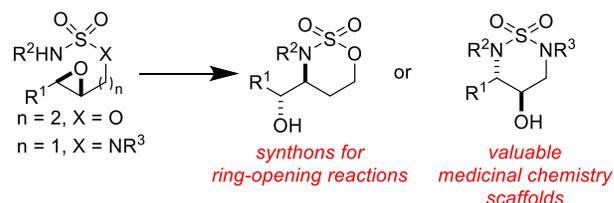
A. Intermolecular Reactions



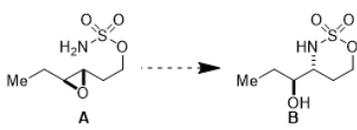
B. Chelation control (Temporary Tethering)



C. Covalent Tethering (This Work)



approach (**Scheme 1C**). While a synthetic step must be expended to attach the tether, the subsequent cyclization is often highly regioselective and

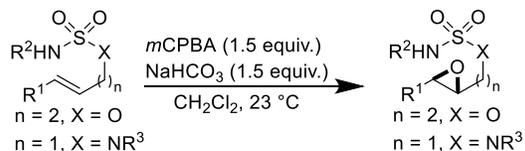
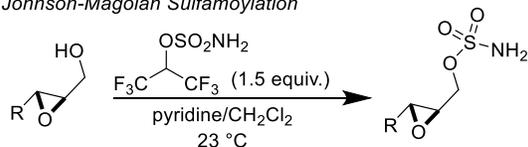
Table 1. Optimization of epoxide opening by a pendant sulfamate.


	Reagents	Solvent, °C	Time	B/A ^a
1	Ph ₃ C ⁺ BF ₄ ⁻ (15%) NaHCO ₃ (1 equiv.)	CH ₂ Cl ₂ 23 °C	21 h	Decomp.
2	Sc(OTf) ₃ (10%) NaHCO ₃ (1 equiv.)	CH ₂ Cl ₂ 0 °C to 23 °C	2 h	0/50%
3	10-CSA (10%)	CH ₂ Cl ₂ 23 °C	21 h	0/50%
4	1M aq. NaOH (0.3 equiv.)	CH ₂ Cl ₂ 23 °C	18 h	54%/2%
5	1M aq. NaOH (0.3 equiv.)	Et ₂ O, 23 °C	18 h	60%/9%
6	1M aq. NaOH (1 equiv.)	Et ₂ O, 23 °C	18 h	72%/0
7	1M aq. KOH (1 equiv.)	Et ₂ O, 23 °C	18 h	67%/4%
8	1M aq. LiOH (1 equiv.)	Et ₂ O, 23 °C	18 h	65%/3%
9	Bu ₄ NOH (1 equiv.)	CF ₃ - toluene/H ₂ O, 23 °C	18 h	82%/0%
10	KOBu (1 equiv.)	THF	18 h	0/50%

^aYield estimated from ¹H NMR integration with 4-nitrotoluene as an internal standard.

diastereoselective. To our surprise, cleaving epoxides with covalently tethered *N*-nucleophiles has not been extensively investigated. Sporadic reports exist with carbamate³⁰⁻³⁷ and acetamidate nucleophiles.³⁸ Here, we detail our efforts to develop the first cleavage of epoxides by pendant sulfamates and sulfamides.

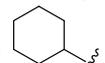
A methodology campaign cannot continue without access to the requisite test substrates. Fortunately, for homoallylic sulfamates, allylic sulfamides, and homoallylic sulfamides, standard Prilezhaev oxidation conditions³⁹ allowed for reliable access to the desired epoxides (**Scheme 2A**). Allylic sulfamates are not stable to synthesis and isolation. Thus, allylic alcohols were first converted into the corresponding epoxides, and the sulfamate auxiliary was subsequently appended using the Johnson-Magolan protocol (**Scheme 2B**).⁴⁰

Scheme 2. Synthesis of epoxide substrates.**A. Prilezhaev oxidation****B. Johnson-Magolan Sulfamoylation**

Our first attempts at tethered ring-opening with a pendant sulfamate were informed by our previous work with di-*tert*-butylsilanol auxiliaries.^{14, 15} In sharp contrast to our past experience, treatment of

sulfamate **A** with either Lewis acids (**Table 1, Entries 1–2**) or with 10-CSA, a strong Bronsted acid, (**Table 1, Entry 3**) was met with unproductive substrate decomposition. With 0.3 equivalents of NaOH (as a 1M aqueous solution) in CH₂Cl₂, we were pleased to observe 54% of desired oxathiazinane **B** (**Table 1, Entry 4**). Switching solvents from CH₂Cl₂ to Et₂O increased the yield to 60% (**Table 1, Entry 5**); we hypothesize that the increased miscibility of Et₂O with H₂O contributes to this positive effect. A further increase in yield came from using a full equivalent of NaOH (1M aqueous solution) in Et₂O (**Table 1, Entry 6**). Using KOH or LiOH in place of NaOH did not help reaction performance (**Table 1, Entries 7–8**), but product formation was excellent with Bu₄NOH in a biphasic solvent mixture of CF₃-toluene and H₂O (**Table 1, Entry 9**). Interestingly, there was no reaction when sulfamate **A** was stirred with 1 equivalent of KO^tBu in THF (**Table 1, Entry 10**).

Scheme 3. Structure-Reactivity Relationship with Various Sulfamate Esters.


Entry	Substrate	Protocol	Isolated Yield
1	R = H (#1, #2 ^a)	Bu ₄ NOH (1 equiv.) CF ₃ -toluene/H ₂ O 24 h, 23 °C	78%
2	R = Me (#3, #4)	Bu ₄ NOH (1 equiv.) CF ₃ -toluene/H ₂ O 24 h, 23 °C	83%
3	R = Et (#5, #6)	Bu ₄ NOH (1 equiv.) CF ₃ -toluene/H ₂ O 48 h, 23 °C	70%
4	R = Bn (#7, #8)	1M aq. NaOH (1 equiv.) Et ₂ O, 48 h, 23 °C	76%
5	R = MeO (#9, #10)	1M aq. NaOH (1 equiv.) CF ₃ -toluene, 18 h, 45 °C	55%
6	R =  (#11)	various attempts	0%

^a(Substrate Number, Product Number); Note: only relative stereochemistry is depicted.

We were next interested in exploring the effects of various *N*-substituents on reaction performance (**Scheme 3**). Our optimized protocol of 1 equivalent of Bu₄NOH in a biphasic solvent mixture of CF₃-toluene/H₂O worked nicely with NH₂-sulfamate **1** and *N*-Me-sulfamate **3** (**Scheme 3, Entries 1–2**). With *N*-Et-sulfamate **5**, the reaction time had to be extended to 48 hours for full consumption of the starting material (**Scheme 3, Entry 3**). Bulkier substituents on the sulfamate nitrogen (**Scheme 3, Entries 4–5**), required us to abandon NBu₄OH in favor of 1M aqueous NaOH. With *N*-Bn-sulfamate **7**, an extended reaction time of 48 hours was required for optimal product formation

using 1M aqueous NaOH in Et₂O (**Scheme 3, Entry 4**). With *N*-*p*-methoxyphenyl-sulfamate **9**, optimal product formation occurred with 1M aqueous NaOH in CF₃-toluene at an elevated reaction

Scheme 4. Substrate Scope with Sulfamates and Sulfamides.

Entry	Substrate	Product	Isolated Yield ^a
1			#12, #13 ^b 75% [x-ray]
			#14, #15 80%
			#16, #17 75%
			#18, #19 90%
2			#20, #21 80%
3			#22, #23 64%
4			#24, #25 63%
5			#26, #27 70% [x-ray]
6			#28, #29 78%
7			#30, #31 90% [x-ray]
8			#32, #33 89%
9			#34, #35 95%

^a Reaction conditions: Bu₄NOH (1 equiv.), CF₃-toluene/H₂O, 23 °C, 24 to 48 h.

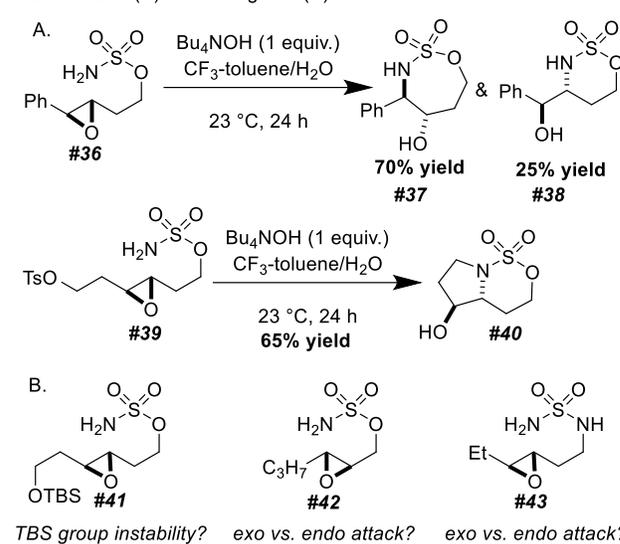
^b Substrate number, product number.

Note: Only relative stereochemistry is depicted.

temperature of 45 °C. Finally, the reaction invariably failed with *N*-cyclohexyl-sulfamate **11** over a range of conditions. From this series of experiments, we conclude that the cyclization is quite sensitive to substituents on the sulfamate nitrogen. In addition, as the steric bulk increases, switching from Bu₄NOH to NaOH is required, and elevating the reaction temperature is beneficial in some cases.

Our optimized biphasic protocol (1 equiv. Bu₄NOH, CF₃-toluene/H₂O, 23 °C) worked well with a range of sulfamate and sulfamide epoxide substrates (**Scheme 4**). In general, substrates cyclize cleanly and without observable side products. The mass balance of the reactions is good and is generally comprised of product and small amounts of unreacted starting material. Several functional groups are compatible with the reaction conditions, including aryl halides (**Scheme 4, Entries 1 and 8**), aryl ethers (**Scheme 4, Entry 1**), benzyl ethers (**Scheme 4, Entry 2**), and pendant sulfamates (**Scheme 4, Entry 3**). Both *trans* and *cis* sulfamate epoxides (**Scheme 4, Entry 5**) cyclized efficiently. While 6-membered rings were preferred in most cases, through judicious choice of the epoxide, 5-membered heterocycles could be forced to form (**Scheme 4, Entry 6**). Products **13** (CCDC: 2231586), **27** (CCDC: 2231587), and **31** (CCDC: 2231588) were crystalline solids, and their x-ray structures have allowed us to confidently assign product identity and relative stereochemistry (See Supporting Information for full crystallographic details and additional structural proof).

Scheme 5. (A) Interesting and (B) Problematic Substrates.



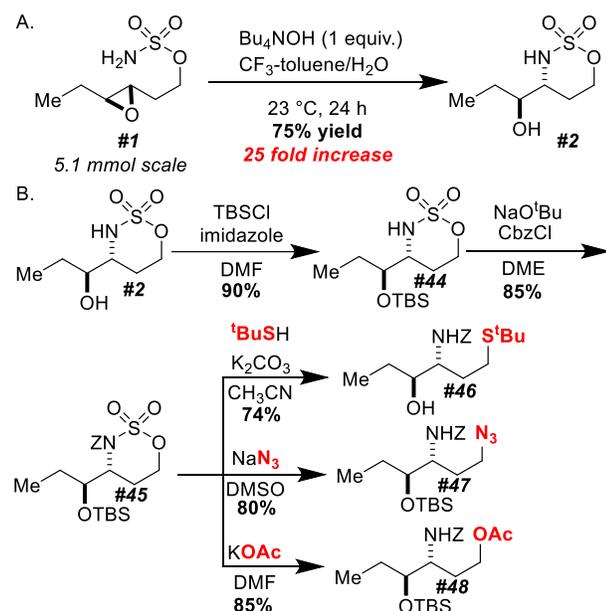
Over the course of our survey, certain substrates behaved a bit differently than expected (**Scheme 5A**). With sulfamate epoxide **36**, seven-membered ring **37** was the major product, forming in a 70% isolated yield. Here, the epoxide carbon attached to the aryl ring is highly activated for S_N2 attack, and this

likely underlies the formation of an unusual seven-membered ring in good yield. With tosylate substrate **39**, tandem nucleophilic attacks took place to form pyrrolidine **40** in a single transformation.

No method is compatible with all substrates (**Scheme 5B**). Subjecting *tert*-butyldimethylsilyl ether substrate **41** to our reaction conditions was met with unproductive decomposition. We hypothesize that the instability of the TBS group to the strongly basic reaction conditions led to substrate failure. Substrates **42** and **43** also failed to provide product cleanly. In both cases, unproductive competition between *exo* and *endo* modes of nucleophilic attack likely led to substrate decomposition.

We were able to scale the cyclization reaction with sulfamate epoxide **1** from 0.2 mmol to 5.1 mmol without loss of yield or selectivity (**Scheme 6A**). The hydroxy group of **2** was converted into the corresponding TBS ether and the oxathiazinane ring was activated⁴¹ by appending a Cbz group (**Scheme 6B**). **45** served as a very effective synthon for oxathiazinane ring opening by sulfur, nitrogen, and oxygen nucleophiles (**Scheme 6B**).

Scheme 6. (A) Ring-opening Scales Successfully. (B) Some Fun with the Product.



In summary, we have developed of the first ring-opening of epoxides using pendant sulfamates and sulfamides. These reactions are promoted by base and proceed under mild conditions to afford oxathiazinanes and cyclic sulfamides with excellent diastereoselectivity and regiocontrol. The reactions scale well, and the products serve as synthons for ring-opening reactions. Given the ubiquity of stereochemical arrays in targets of value, we expect that this technology will be

valuable to both academic and industrial organic chemists.

ASSOCIATED CONTENT

Supporting Information

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

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