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

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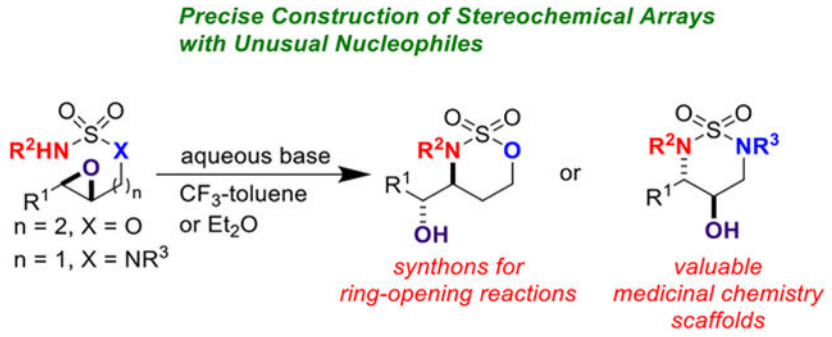
Abstract

We describe the development of the first ring opening of epoxides using pendant sulfamates and sulfamides. These reactions are promoted by a 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.

Graphical Abstract



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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00053.

Experimental procedures, reasoning for structural assignments, NMR spectra, and crystallographic information (PDF)

Accession Codes

CCDC 2231586–2231588 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

The precise construction of polyfunctional molecules remains a topic of great interest.[1,2] Many targets of value are densely functionalized and comprise 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 transient[8–13] 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*-butylsilanol 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 approach (Scheme 1C). While a synthetic step must be expended to attach the tether, the subsequent cyclization is often highly regioselective and diastereoselective. To our surprise, cleaving epoxides with covalently tethered *N*-nucleophiles has not been extensively investigated. Sporadic reports exist with carbamate[30–37] 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 conditions[39] 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]

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 and 2) or with 10-CSA, a strong Bronsted acid (Table 1, entry 3), was met with unproductive substrate decomposition. With 0.3 equiv of NaOH (as a 1 M aqueous solution) in CH_2Cl_2, we were pleased to observe 54% of desired oxathiazinane **B** (Table 1, entry 4). Switching solvents from CH_2Cl_2 to Et_2O increased the yield to 60% (Table 1, entry 5); we hypothesize that the increased miscibility of $Et_2O$with H_2O contributes to this positive effect. A further increase in yield came from using a full equivalent of NaOH (1 M aqueous solution) in Et_2O (Table 1, entry 6). Using KOH orLiOH in place of NaOH did not help the reaction performance (Table 1, entries 7 and 8), but product formation was excellent with Bu_4NOH in a biphasic solvent mixture of CF_3-toluene and H_2O (Table 1, entry 9). Interestingly, there was no reaction when sulfamate **A** was stirred with 1 equiv of KO^{t}Bu in THF (Table 1, entry 10).

We were next interested in exploring the effects of various *N*-substituents on reaction performance (Scheme 3). Our optimized protocol of 1 equiv of Bu_4NOH in a biphasic

solvent mixture of CF_3-toluene/H_2O worked nicely with NH_2-sulfamate **1** and *N*-Me-sulfamate **3** (Scheme 3, entries 1 and 2). With *N*-Et-sulfamate **5**, the reaction time had to be extended to 48 h for full consumption of the starting material (Scheme 3, entry 3). Bulkier substituents on the sulfamate nitrogen (Scheme 3, entries 4 and 5) required us to abandon NBu_4OH in favor of 1 M aqueous NaOH. With *N*-Bn-sulfamate **7**, an extended reaction time of 48 h was required for optimal product formation using 1 M aqueous NaOH in Et_2O (Scheme 3, entry 4). With *N*-*p*-methoxyphenyl-sulfamate **9**, optimal product formation occurred with 1 M aqueous NaOH in CF_3-toluene at an elevated reaction 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 Bu_4NOH to NaOH is required, and elevating the reaction temperature is beneficial in some cases.

Our optimized biphasic protocol (1 equiv of Bu_4NOH, CF_3-toluene/H_2O, 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 generally comprises 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 six-membered rings were preferred in most cases, through judicious choice of the epoxide, five-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 allowed us to confidently assign product identity and relative stereochemistry (see Supporting Information for full crystallographic details and additional structural proof).

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 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 activated[41]

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).

In summary, we have developed of the first ring opening of epoxides using pendant sulfamates and sulfamides.[42] These reactions are promoted by a 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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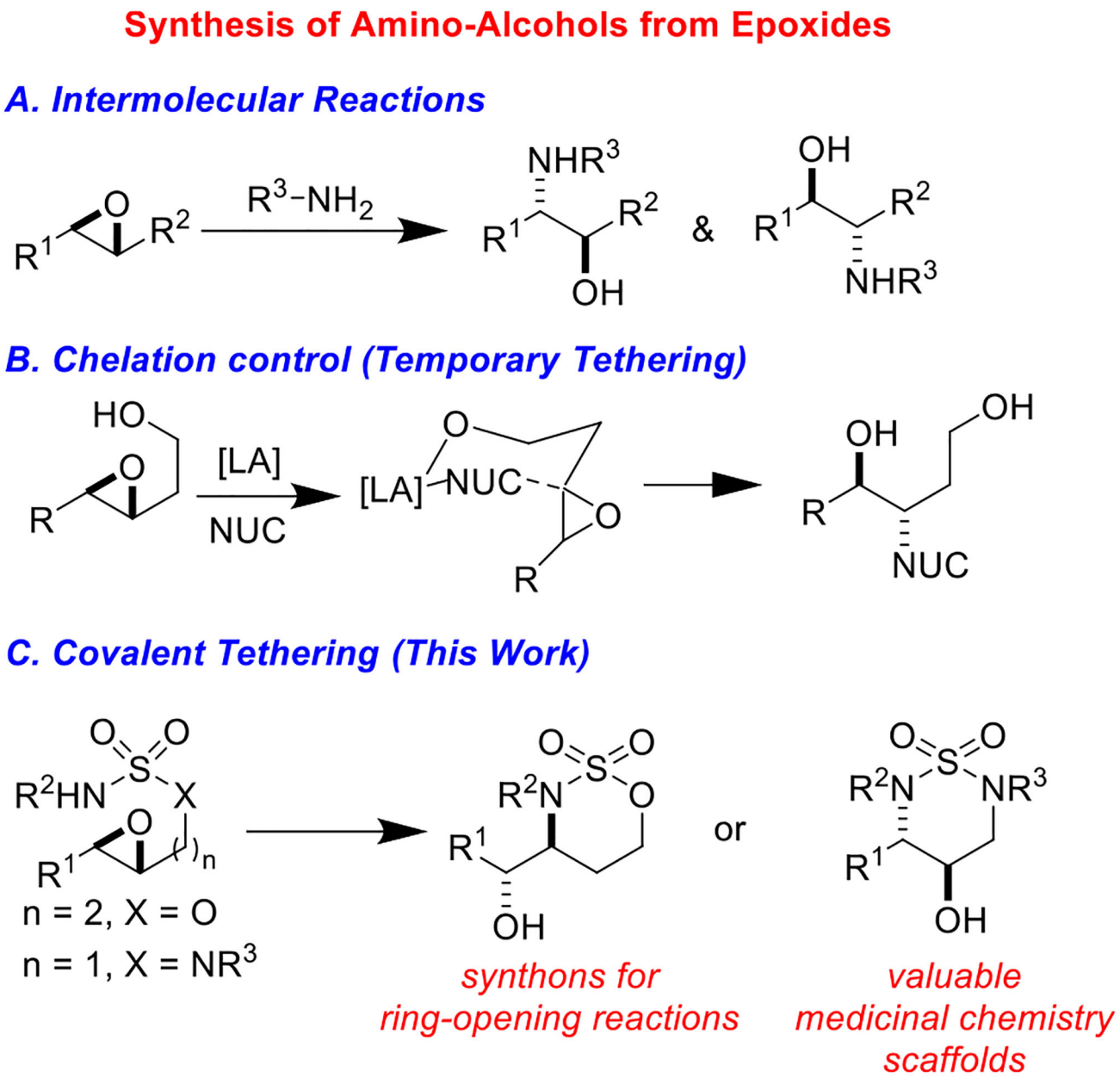
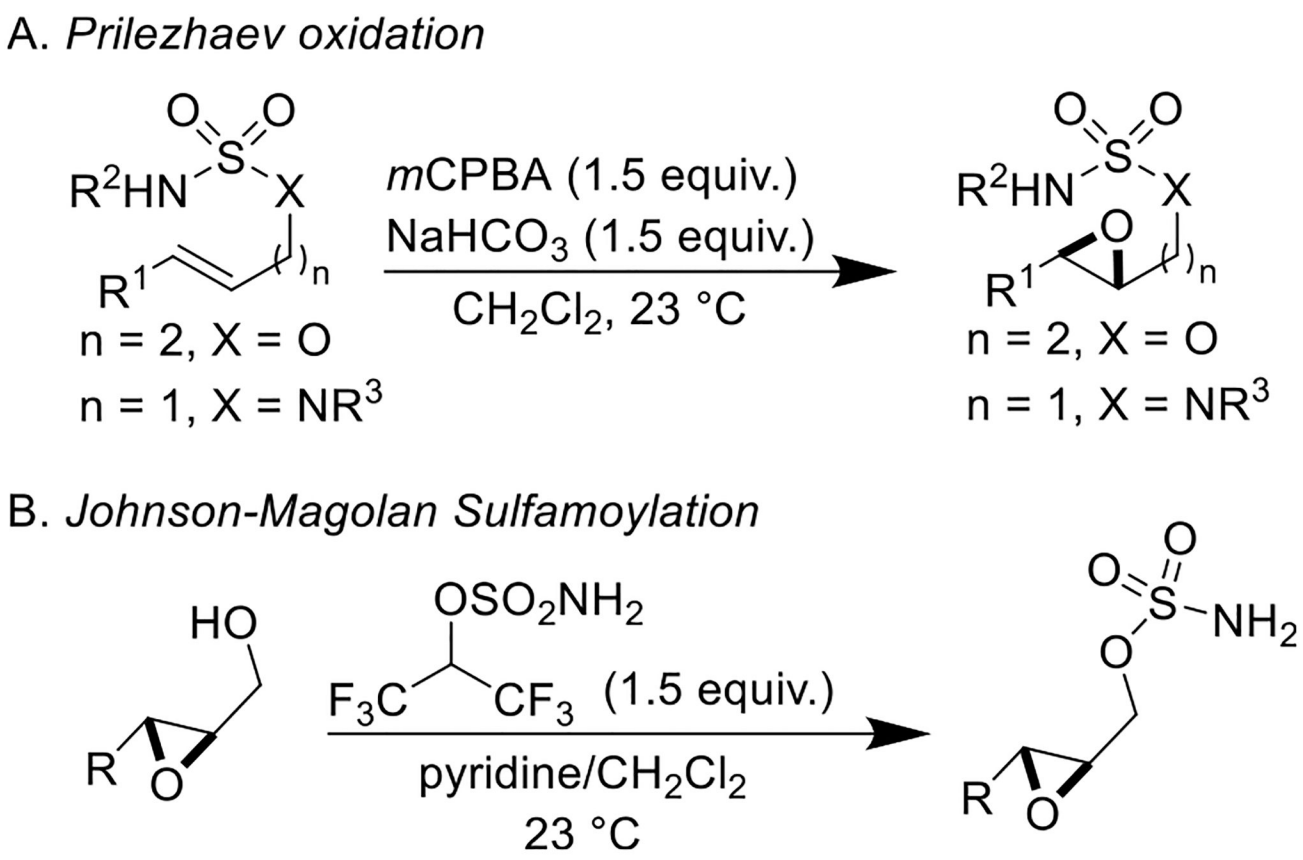
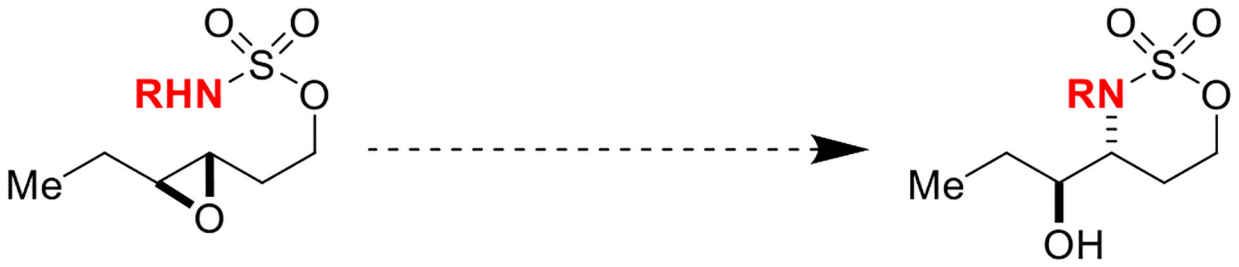
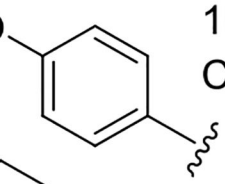
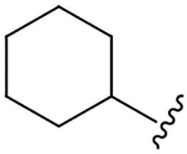


Scheme 1.
Previous Efforts with Aminolysis of Epoxides Inspire Our Tethered Ring-Opening Approach



Scheme 2.
Synthesis of Epoxide Substrates

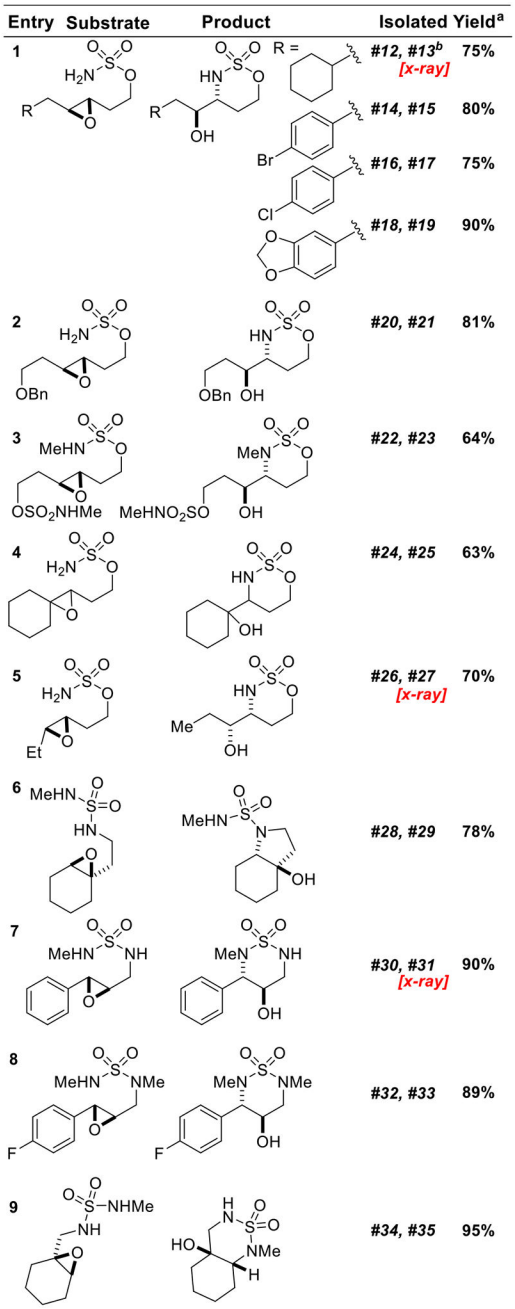


Entry	Substrate	Protocol	Isolated Yield
1	R = H (#1, #2[a])	$Bu_4NOH•30H_2O$ (1 equiv.) CF_3-toluene/H_2O 24 h, 23 °C	77%
2	R = Me (#3, #4)	$Bu_4NOH•30H_2O$ (1 equiv.) CF_3-toluene/H_2O 24 h, 23 °C	83%
3	R = Et (#5, #6)	$Bu_4NOH•30H_2O$ (1 equiv.) CF_3-toluene/H_2O 48 h, 23 °C	70%
4	R = Bn (#7, #8)	1M aq. NaOH (1 equiv.) Et_2O, 48 h, 23 °C	76%
5	R =  (#9, #10)	1M aq. NaOH (1 equiv.) CF_3-toluene, 18 h, 45 °C	55%
6	R =  (#11)	various attempts	0%

Scheme 3.

Structure–Reactivity Relationship with Various Sulfamate Esters

[a]Numbers in parenthesis indicate (substrate number, product number). Note: only relative stereochemistry is depicted.

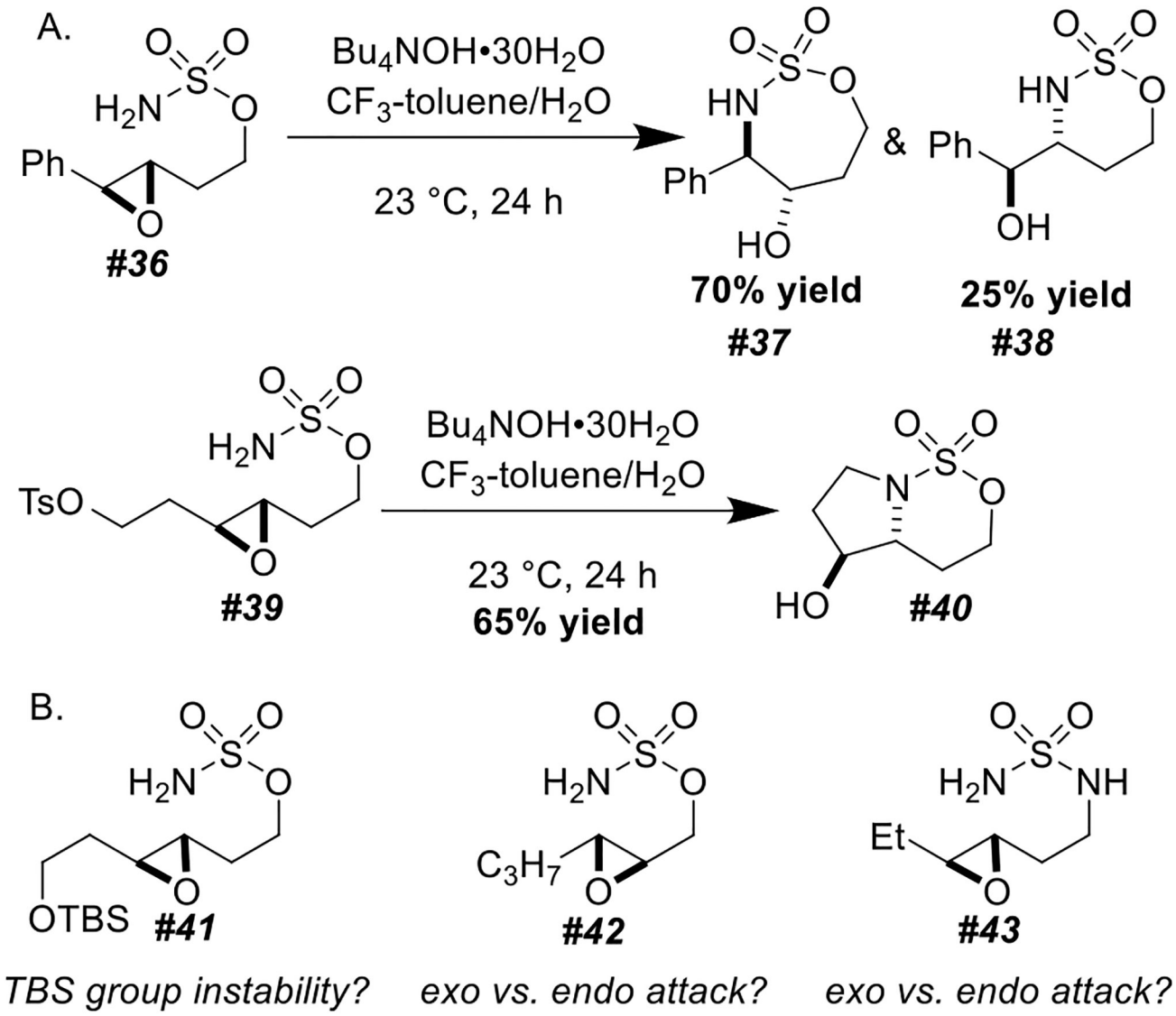


Scheme 4.

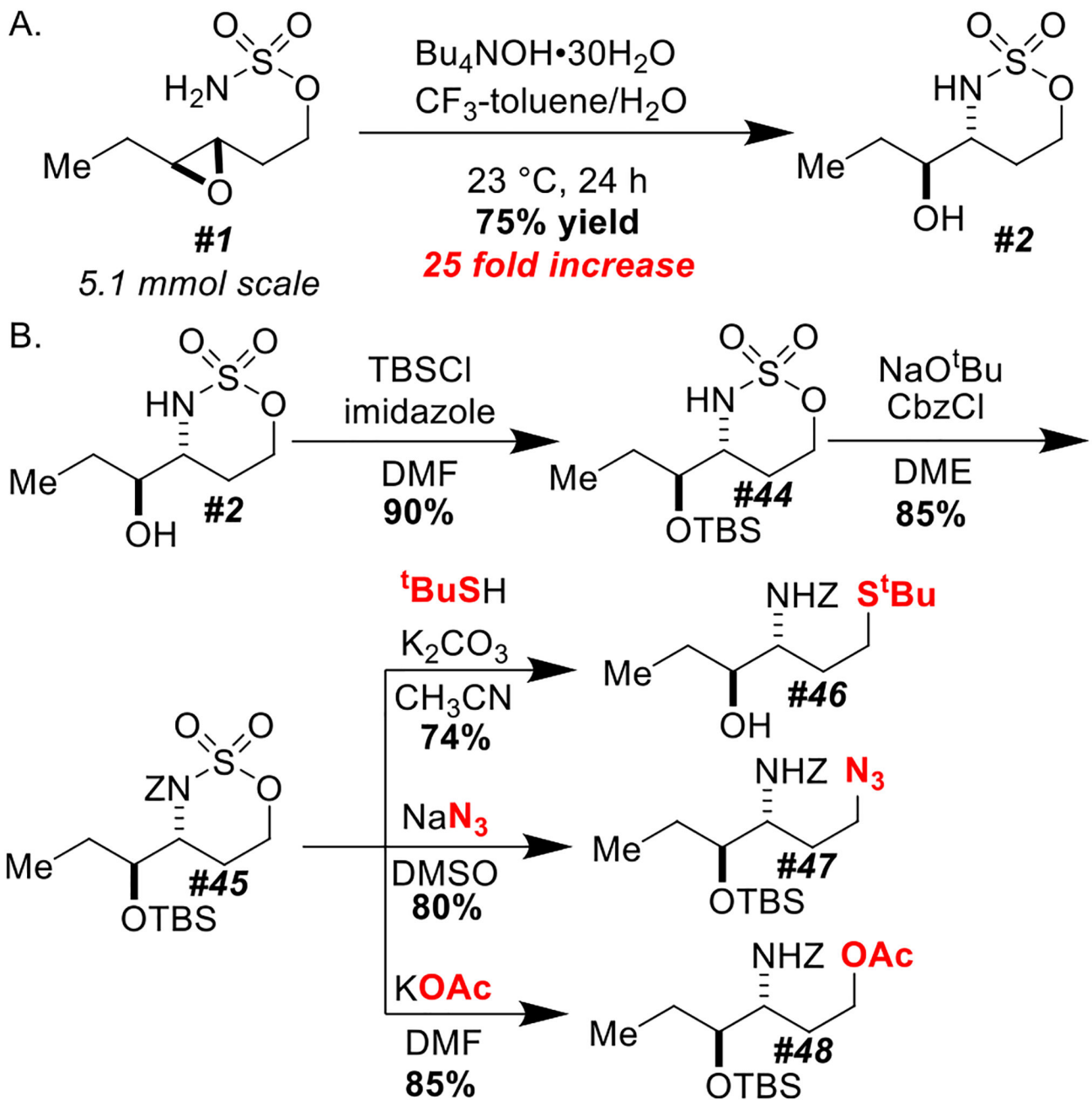
Substrate Scope with Sulfamates and Sulfamides

[a]Reaction conditions: $Bu_4NOH{\cdot}30H_2O$ (1 equiv), CF_3-toluene/H_2O, 23 °C, 24–48 h.

[b]Substrate number, product number. Note: only relative stereochemistry is depicted.



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



Scheme 6.

(A) Ring Opening Scales Successfully and (B) Some Fun with the Product

Table 1.

Optimization of Epoxide Opening by a Pendent Sulfamate

	Reagents	Solvent, °C	Time	B/A[a]
1	$Ph_3C^+BF_4^-$ (15%) $NaHCO_3$ (1 equiv.)	CH_2Cl_2, 23 °C	21 h	Decomp.
2	$Sc(OTf)_3$ (10%) $NaHCO_3$ (1 equiv.)	CH_2Cl_2, 0 °C to 23 °C	2 h	0/50%
3	10-CSA (10%)	CH_2Cl_2, 23 °C	21 h	0/50%
4	1M aq. NaOH (0.3 equiv.)	CH_2Cl_2, 23 °C	18 h	54%/2%
5	1M aq. NaOH (0.3 equiv.)	Et_2O, 23 °C	18 h	60%/9%
6	1M aq. NaOH (1 equiv.)	Et_2O, 23 °C	18 h	72%/0
7	1M aq. KOH (1 equiv.)	Et_2O, 23 °C	18 h	67%/4%
8	1M aq. LiOH (1 equiv.)	Et_2O, 23 °C	18 h	65%/3%
9	$Bu_4NOH•30H_2O$ (1 equiv.)	CF_s-toluene/H_2O, 23 °C	18 h	82%/0%
10	KO^tBu (1 equiv.)	THF	18 h	0/50%

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