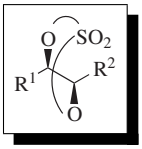
1,3,2-Dioxathiolane 2,2-Dioxide[1]

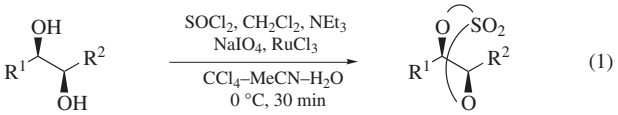


($R^1 = R^2 = H$)
[1072-53-3] $C_2H_4O_4S$ (MW 124.13)
InChI = 1/C2H4O4S/c3-7(4)5-1-2-6-7/h1-2H2
InChIKey = ZPFAVCIQZKRBGF-UHFFFAOYAP
($R^1 = R^2 = n$-Bu)
[127901-92-3] $C_{10}H_{20}O_4S$ (MW 236.37)
InChI = 1/C10H20O4S/c1-3-5-7-9-10(8-6-4-2)14-15(11,12)13-9/h9-10H,3-8H2,1-2H3/t9-,10-/s2
InChIKey = UNBCRBGPJKMSKH-WSYQHHSTBA

(display epoxide-like reactivity;[2,3] nucleophilic displacement of both oxygen functions is feasible[4–6])

Alternate Names: ethylene glycol cyclic sulfate; ethylene sulfate; 1,2-ethylene sulfate; cyclic sulfates.

Preparative Methods: cyclic sulfates of 1,2-diols (1,3,2-dioxathiolane 2,2-dioxides) are most easily prepared in a two-step procedure (eq 1).[2] Reaction of a 1,2-diol with ***Thionyl Chloride*** leads to a cyclic sulfite which is then oxidized to the corresponding cyclic sulfate (**1**). Direct conversion of a 1,2-diol to a cyclic sulfate using ***Sulfuryl Chloride*** is generally less efficient.[2,3] However, with the cyclic sulfates bearing functionalities that are easily subjected to RuO_4-catalyzed oxidation, the direct conversion of diols to cyclic sulfates with ***Sulfuryl Chloride*** is favored.[14]



(1)

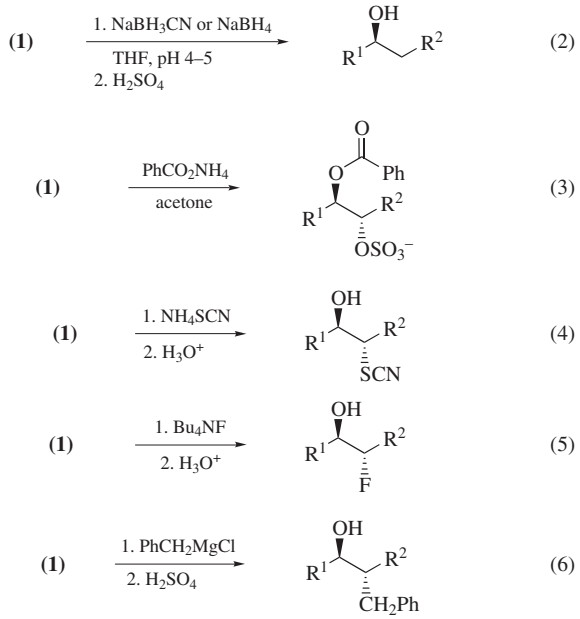
(1)

Handling, Storage, and Precautions: the structural similarity between cyclic sulfates and ***Dimethyl Sulfate*** must be recognized. Dimethyl sulfate, and to a lesser extent ethylene sulfate, are carcinogenic and potent alkylating agents that are toxic by inhalation and ingestion.[1] Cyclic sulfates must, as a result, be treated with extreme care.

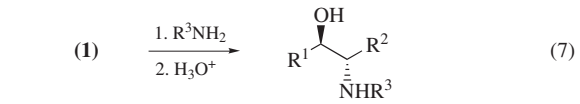
Original Commentary

Nicholas J. Lynch
University of Bristol, Bristol, UK

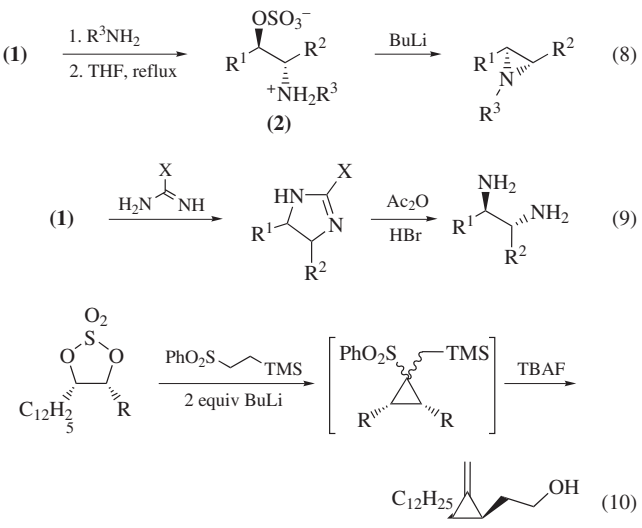
Cyclic sulfates of 1,2-diols are an important group of reagents and recent advances in the asymmetric dihydroxylation of alkenes (see ***Osmium Tetroxide***) will serve to increase further their synthetic potential.[7] Cyclic sulfates display reactivity towards nucleophiles that is closely related to that of epoxides and react in a regioselective fashion with hydride (eq 2)[2] and a wide range of heteroatoms (eqs 3–5)[2,3,8,9] and carbon-based nucleophiles (eq 6).[2–6]



The reactivity of nitrogen nucleophiles towards cyclic sulfates has attracted considerable interest and provides an efficient entry into 1,2-amino alcohols (eq 7).[4,10]

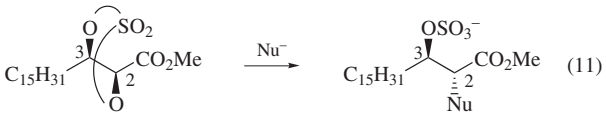


It is, however, important to appreciate the additional scope offered by cyclic sulfates over epoxides as electrophilic components in displacement processes. Following nucleophilic ring-opening, the intermediate β-sulfate, e.g. (**2**), functions as a leaving group and can undergo a second displacement.[2] This provides a direct access to aziridines (including *N*-unsubstituted variants) (eq 8),[4,10] to 1,2-diamines (eq 9),[11] and, with activated carbon nucleophiles, to cyclopropanes (eq 10).[5,6]



In cyclic sulfates derived from α,β-unsaturated esters, regioselective nucleophilic attack has been observed (eq 11);[2] the

corresponding epoxide undergoes ring opening with a lower level of regioselectivity.



(11)

Cyclic sulfates are stable towards L-selectride (***Lithium Tri-sec-butylborohydride***)[12] and are also compatible with acid (and the sulfate cleaved in the presence of acid-labile protecting groups, e.g. OTBDMS, acetonide).[13]

First Update

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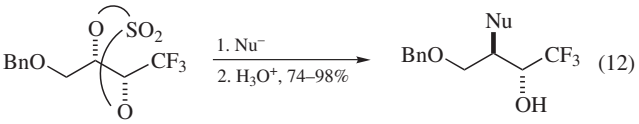
Shanghai Institute of Organic Chemistry, Shanghai, China

Cyclic sulfates of 1,2-diols represent a versatile class of functionalized and often enantiomerically pure electrophiles,[15] and their application in organic synthesis has been widely studied, especially since the development of osmium-catalyzed asymmetric dihydroxylation and aminohydroxylation reactions by Sharpless and coworkers.[16]

The regioselectivity in the ring opening of both cyclic sulfates and epoxides is controlled simultaneously by the steric interaction between the substrates and nucleophiles and by the electronic distribution of the substrates. α,β-Dihydroxy ester cyclic sulfate **2** undergoes nucleophilic attack at the α-position almost exclusively (eq 11),[2] which shows the electronic distribution of the substrate or the transition state instead of steric hindrance was the predominating factor controlling the regioselectivity of the reaction. In the case of trifluoromethylated cyclic sulfate **3**, ring-opening reaction occurred exclusively at C-2 position with clean inversion of chirality (eq 12).[17] This regioselectivity may be due to the steric effect of the trifluoromethyl group.

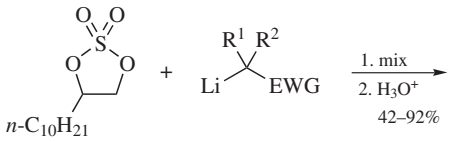


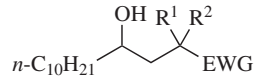
(12)

(**3**) (Nu = N_3^-, BzO^-, $PhthN^-$, H^-) (**4**)

Reactions with Carbon Nucleophiles. The carbon nucleophiles such as phenyllithium,[18] alkynyllithium,[19] cyanide,[20] cuprate reagents,[2,20] malonate,[2] α-dithiaaryl carboxylate anions,[21] 2-dithianyllithium species,[21] 2-(phenylthio) -2-dihydropyranyllithium species,[22] and di(phenylseleno) methyllithium species[14] have been used. Enolates of esters and amides as well as α-cyano-, α-phosphonyl-, and α-sulfonyl-substituted anions can also react with 1,2-cyclic sulfates to give hydroxylated products (eq 13).[23] However, the ketone enolate reacted with 1,2-cyclic sulfates, affording *O*-alkylated product, which was converted to the starting ketone and 1,2-diol after acid hydrolysis.[23]

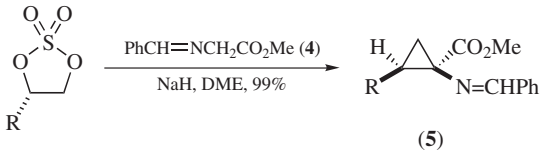
Double displacement of the 1,2-cyclic sulfates can provide cyclopropane derivatives as the corresponding products. Condensation of 1,2-cyclic sulfates with methyl benzylidene glycinate **4** gives the alkylated imine **5** in nearly quantitative yield (eq 14). This reaction is diastereospecific and gives the *Z* isomer, and no *E* isomer can be observed in the crude product.[24]





(13)

(EWG = CN, CO_2R, SO_2Ph, $CONR_2$, $P(O)(OMe)_2$; R^1, R^2 = H, alkyl)

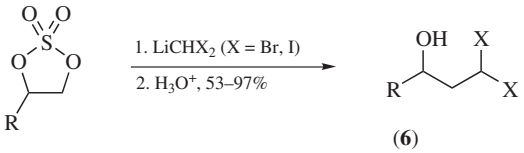


(14)

(**5**)

(R = CH_3 and $ClCH_2CH_2CH_2$)

Due to the instability of halomethyllithiums, the direct opening of an epoxide with these species always results in low yield of the desired products.[25] High yields of β-halomethylated alcohols **6** could be obtained by reaction of dibromomethyllithium[14] or diiodomethyllithium[14] with the more reactive cyclic sulfates (eq 15).

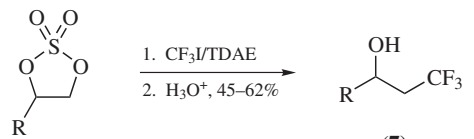


(15)

(**6**)

(R = alkyl)

For the polyfluorinated carbanions, the fluorine substitution on the carbanion center dramatically decreases the thermal stability and nucleophilicity of these carbanions. As a result, these fluorinated carbanions usually are not effective in reaction with epoxides. By using the more electrophilic epoxide equivalents, 1,2-cyclic sulfates, the reaction was found to be general and highly regioselective, with the fluorinated carbanion attacking at the less hindered carbon atom of the cyclic sulfates to provide the secondary alcohols. Trifluoromethylation of 1,2-cyclic sulfates with CF_3I/TDAE (TDAE = tetrakis(dimethylamino)ethylene) gives β-trifluoromethyl alcohols **7** in moderate yields (eq 16).[26] Difluoromethylation of 1,2-cyclic sulfates with $PhSO_2CF_2Li$ (generated in situ from $PhSO_2CF_2H$/LHMDS, LHMDS = lithium hexamethyldisilazide) gives β-difluoromethyl alcohols **8** in good to excellent yields (eq 17).[27]

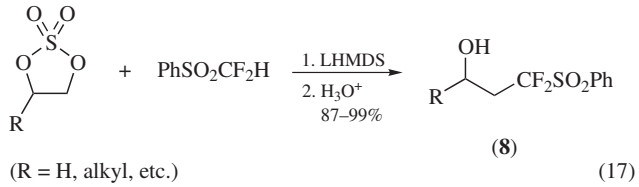


(16)

(**7**)

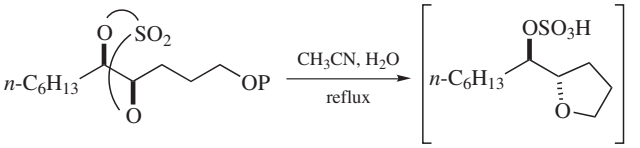
(R = H, alkyl)

Reactions with Oxygen Nucleophiles. Polyepoxide cascade cyclization is a useful method for the synthesis of oligo(tetrahydrofurans), which are common substructures within many polyether ionophore natural products. After solvolysis of the cyclic sulfates **9**, the free alcohol **11** rather than the expected sulfate ester **10** was formed through a 5-*exo-tet* cyclization process (eq 18). The most interesting feature of these reactions is that sulfate ester **10** was hydrolyzed by the acid produced during the reaction in an autocatalytic process.[28] To prove the cascade cyclization, tris(sulfate) **12** was subjected to solvolysis, and tris(tetrahydrofuran) **13** was obtained in 93% yield (eq 19).[28]



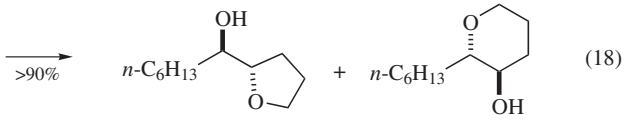
(**8**)

(R = H, alkyl, etc.) (17)

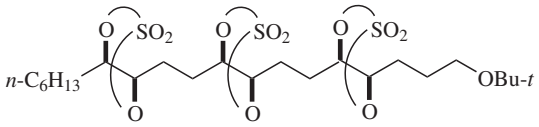


(**9**) (**10**)

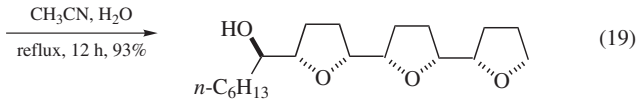
(P = Bn, MOM, TBS, *tert*-butyl)



(**11**) (18)



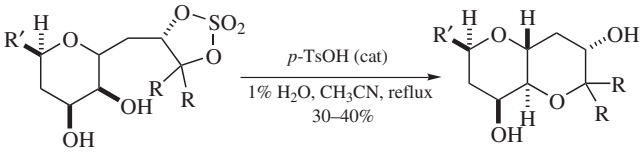
(**12**)



(**13**) (19)

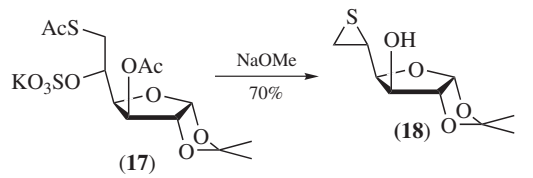
Although hydroxy-epoxide *endo*-cyclizations are generally disfavored by the early transition state associated with opening of the strained oxirane ring, the relatively unstrained cyclic sulfate electrophile **14** permits *endo*-cyclization to afford exclusively or predominantly regioisomer **15** (eq 20).[29]

Reactions with Sulfur Nucleophiles. The reaction of terminal cyclic sulfate **16** with potassium thioacetate or potassium thiocyanate gave β-acetylthio or β-thiocyanate sulfate salts **17** by regiospecific attack at the less hindered primary position.[30] Treatment of the potassium salt **17** with NaOMe–MeOH generated the sodium thiolate, which was converted to the episulfide **18** via intramolecular displacement of the β-sulfate groups (eq 21). Opening of the nonterminal cyclic sulfate **20** with potassium thioacetate did not take place even when the experimental conditions (temperature and solvent) were varied. However, the reaction with sodium sulfide in boiling methanol furnished the desired episulfide **21** in moderate yield (eq 22). An attempt to prepare episulfides from a terminal cyclic sulfate using sodium sulfide gave dimeric sulfide **19** (eq 21).[30] The different behavior of terminal and nonterminal cyclic sulfates implied that intramolecular attack is favored when the cyclic sulfate is sterically hindered. With the less hindered terminal cyclic sulfate, intermolecular displacement was favored.

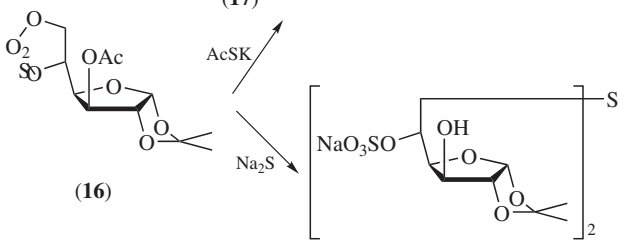


(**14**) (**15**)

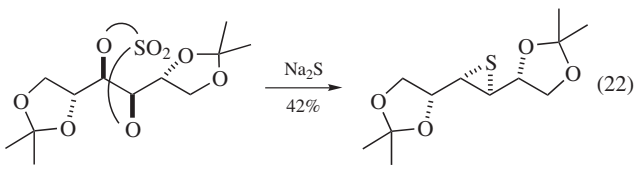
(R, R′ = H, alkyl, etc.) (20)



(**17**) (**18**)



(**16**) (**19**) (90%) (21)



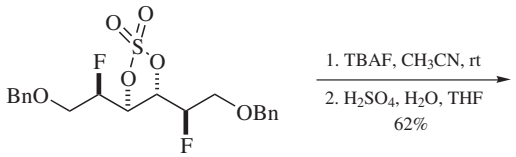
(**20**) (**21**) (22)

Reactions with Halogen Nucleophiles. The incorporation of fluorine atoms is a powerful method for modulating the properties of organic compounds.[31] Ring opening of cyclic sulfate **22** with tetrabutylammonium fluoride (TBAF) gave the trifluoro derivative **23** in good yield, which was ultimately converted to an enantiomerically pure all-*syn* four vicinal fluorine motif **24** (eq 23).[32]

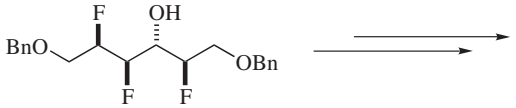
Ring opening of cyclic sulfates **25** with bromide ion has also been utilized in the stereospecific conversion of a diol to the corresponding epoxide **27** (eq 24).[33] Since bromide serves as a leaving group in the base-induced epoxidation step, and a double inversion of the reaction center is involved, both regioisomers **26a** and **26b** lead to the same chiral product.

Reactions with Phosphorus Nucleophiles. Phosphines can also be alkylated by the cyclic sulfates.[34] When lithium diphenyl-

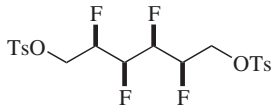
phosphide ($LiPPh_2$) was used as the nucleophile, water-soluble mono tertiary phosphine ligand **28** can be synthesized (eq 25).[34a]



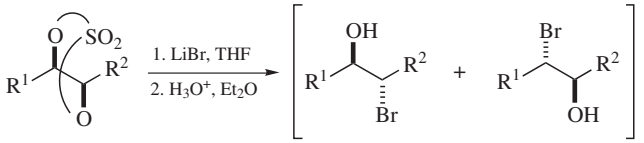
(**22**)



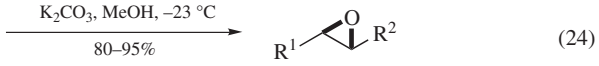
(**23**)



(**24**) (23)

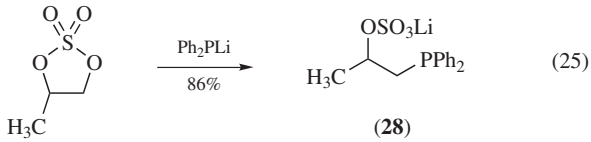


(**25**) (**26a**) (**26b**)



(**27**) (24)

(R^1, R^2 = H, alkyl, CO_2R', etc.)

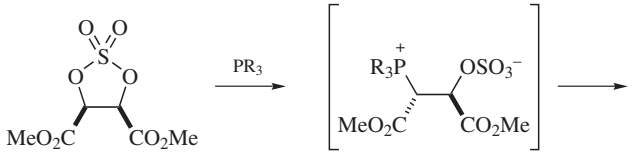


(**28**) (25)

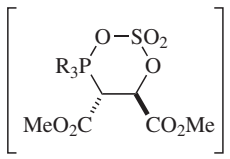
Olefination through deoxygenation of diols is an important transformation in organic synthesis. Reaction of dimethyl *meso*-tartrate cyclic sulfate **29** with PPh_3 at 110 °C in xylene gave *trans*-olefin **32** in 45% yield (eq 26).[35] The first step is the nucleophilic displacement of the cyclic sulfate by a tertiary phosphine. When PMe_3 was used instead of PPh_3, the zwitterionic compound **30** was isolated in good yield.[35]

Reactions with Selenium Nucleophiles. Regioselective opening of the cyclic sulfate **33** with selenide anion followed by acid hydrolysis formed the *trans*-diaxial seleno-alcohol **34** as the sole product.[36] Oxidative elimination of **34** via the selenoxide occurred regiospecifically away from the hydroxy group, leading to the allylic alcohol **35**. The latter compound was ultimately transformed into cyclophellitol **36**, which is a potent inhibitor of β-D-glucosidase (eq 27).[36]

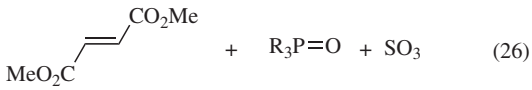
When potassium selenocyanate (KSeCN) is used as nucleophile instead of potassium thioacetate (KSAc), β-selenocyanato-sulfate **37** can be transformed into the corresponding selenirane **38** by treatment with sodium borohydride ($NaBH_4$). However, selenirane **38** is unstable and expels the selenium atom giving alkene **39** (eq 28).[30]



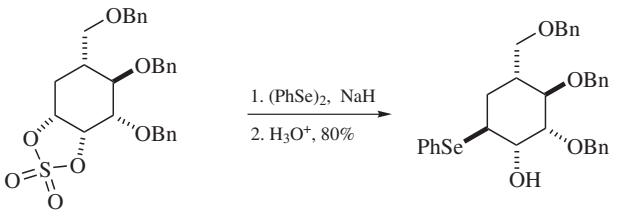
(**29**) (**30**)



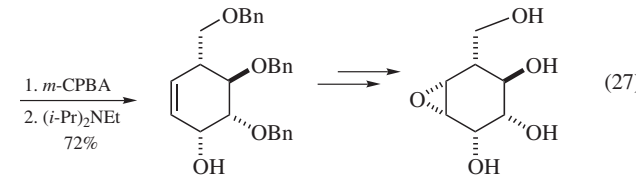
(**31**)



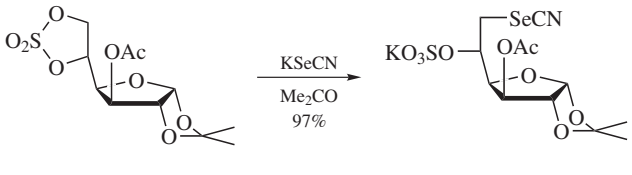
(**32**) (45%) (26)



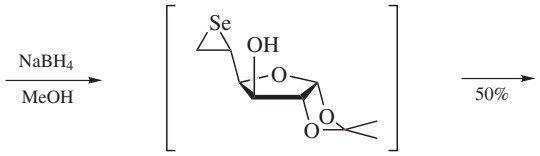
(**33**) (**34**)



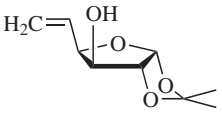
(**35**) (**36**) (27)



(**16**) (**37**)

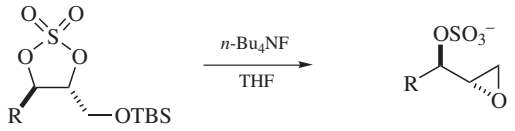


(**38**)



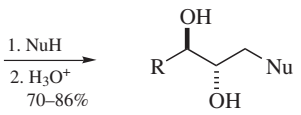
(**39**) (28)

Rearrangement Reactions. Treatment of 1-*O*-*tert*-butyldimethylsilyltriol 2,3-cyclic sulfate **40** with *n*-Bu_4NF (TBAF) furnished a 1,2-epoxy-3-sulfate **41**, which can react with various nucleophiles exclusively at C-1 position (eq 29).[37] This process is analogous to the Payne rearrangement of 2,3-epoxy-1-ol. The difference between the two rearrangements is that the sulfate method is an irreversible process because the 3-hydroxy group in **41** is protected in situ as a sulfate ester.



(**40**) (**41**)

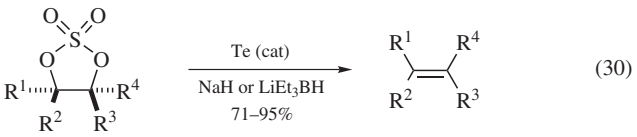
(R = H, alkyl, aryl, etc.)



(29)

(**42**)

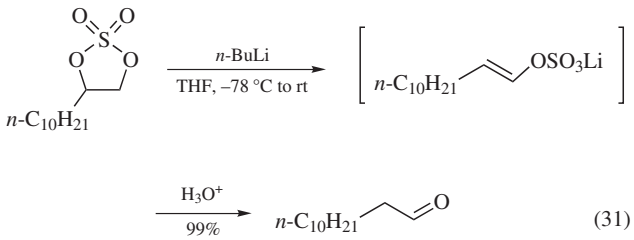
Elimination Reactions. Stereospecific conversion of cyclic sulfate to olefin was achieved by using telluride ion (Te^{2-}) generated in situ (eq 30).[38] Since Te(0) was regenerated during the reaction, the conversion can be achieved by using a catalytic amount of tellurium metal.



(30)

(R^1, R^2, R^3, R^4 = H, alkyl, aryl, etc.)

Reaction of *n*-butyllithium with terminal cyclic sulfates failed to generate a new C–C bond. Instead, the aldehydes were isolated in high yield (eq 31).[23] This presumably arises from an eliminative opening that produces an enol sulfate salt.



(31)

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