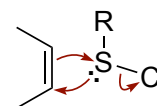
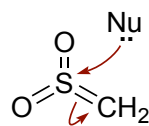
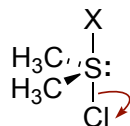
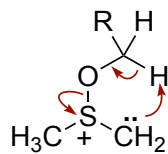


Topic 19: Sulfur Chemistry

B	C	N	O	F
2.0	2.5	3.0	3.5	4.0
Al	Si	P	S	Cl
1.6	1.9	2.2	2.5	3.0

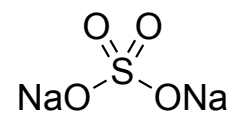


Read:

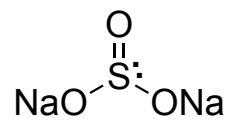
Gordon W. Whitham *Organosulfur Chemistry*. Oxford Science.

Nomenclature

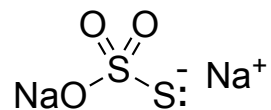
common
inorganic
sulfur
reagents



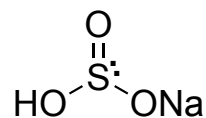
sodium **sulfate**



sodium **sulfite**

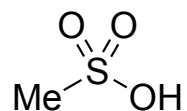


sodium **thiosulfate**

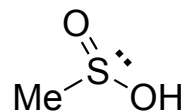


sodium **bisulfite**

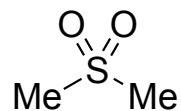
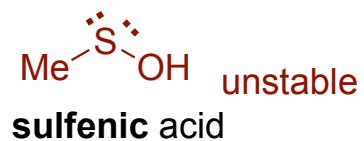
common
sulfur
functional
groups



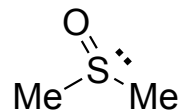
sulfonic acid



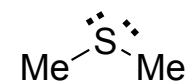
sulfinic acid



sulfone



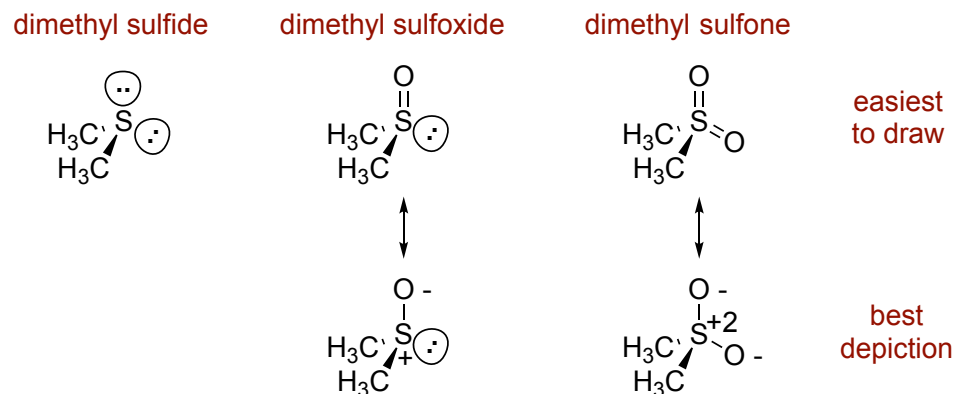
sulfoxide



sulfide

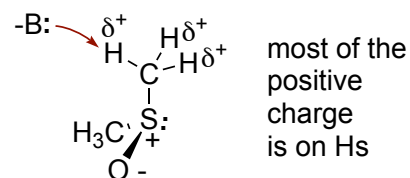
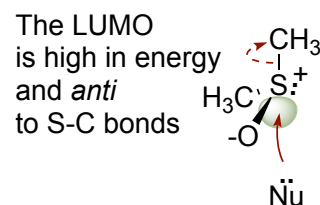
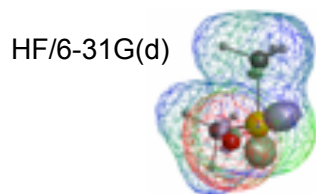
Sulfoxides and Sulfones

■ The 3p orbitals are too large to overlap effectively with 2p orbitals on oxygen or carbon. There is little pi character in the S-O bonds of dimethylsulfoxide and dimethylsulfone. It is common to draw S=O bonds in organosulfur compounds, particularly for sulfones, which look odd with a +2 charge on sulfur. The best depiction should place a single bond between oxygen and sulfur and a negative charge on the oxygens.



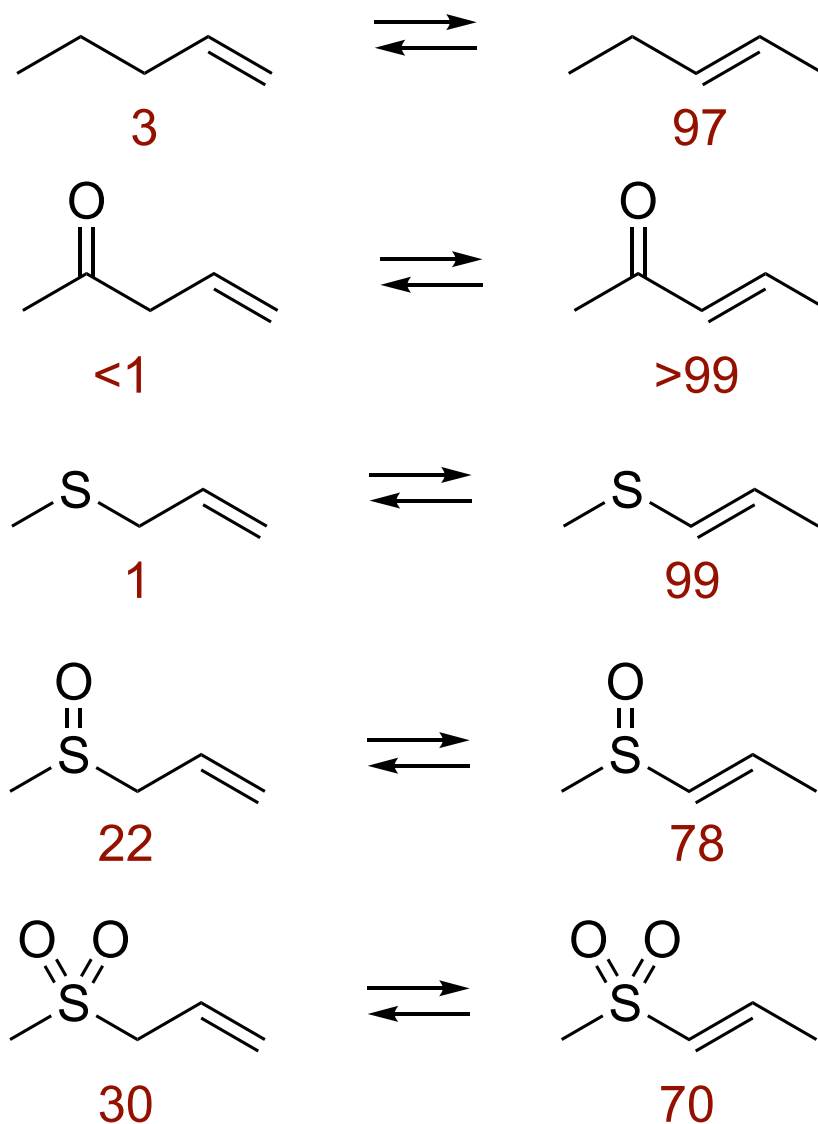
Clark, T.; Murray, J.; Lane, P.; Politzer, P.
J. Mol. Model. **2008**, 14, 689.

■ **Ignore the positive charge on sulfur.** A sulfoxide is *nothing* like a carbocation; the LUMO resembles σ_{s-c}^* .



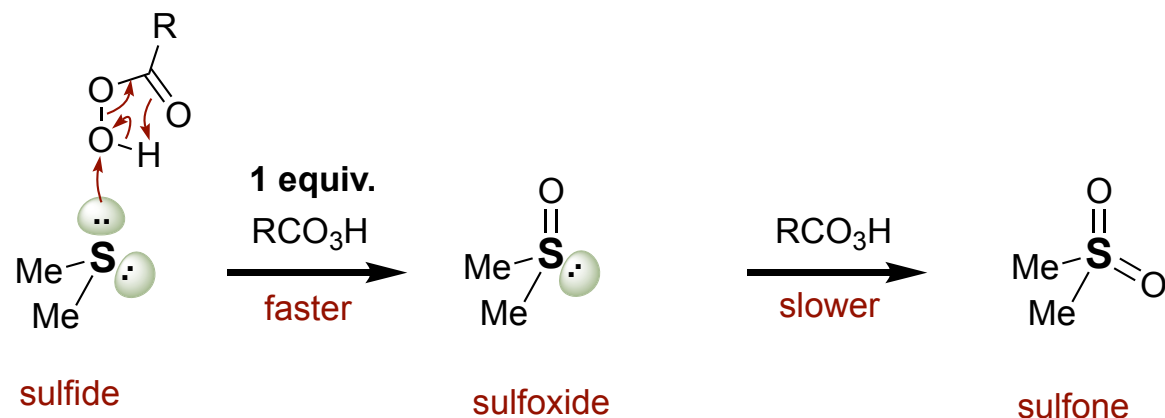
Is "S=O" just like C=O?

■ The fact that there is very little pi character in the S-O bonds of sulfoxides and sulfones should suggest that there will be very little pi character between sulfur and carbon. While enones, ethers, and thioethers want to be conjugated, sulfoxides and sulfones do not.

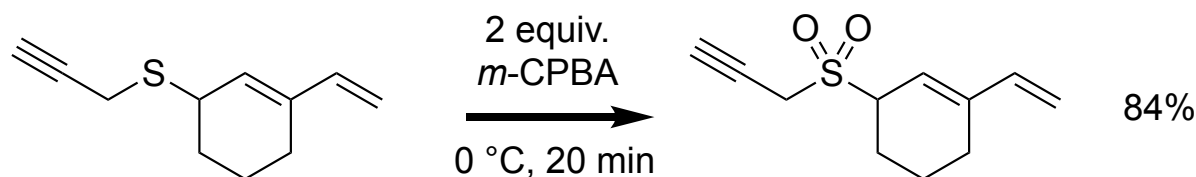


Sulfur L.P. as Nucleophiles: Oxidation of Sulfur

■ Sulfur lone pairs on thioethers (RSR) are more nucleophilic than sulfur lone pairs on sulfoxides (RSOR). That means you can stop oxidation of sulfides at sulfoxides without over-oxidizing to sulfones.



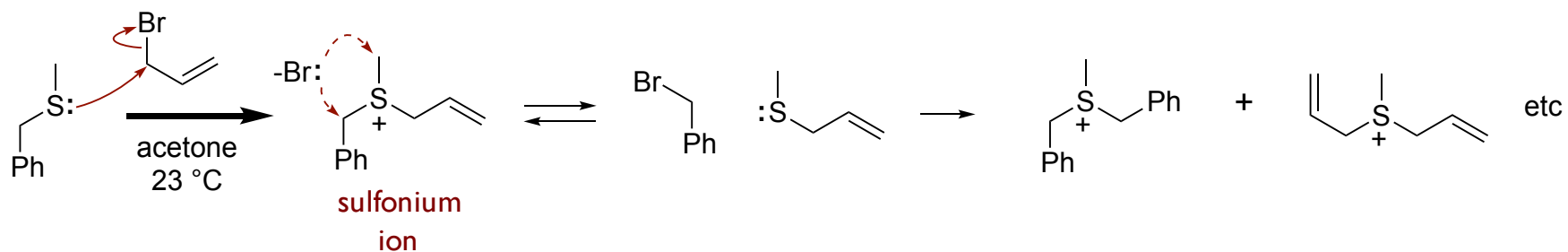
■ Thioether oxidation is faster than epoxidation



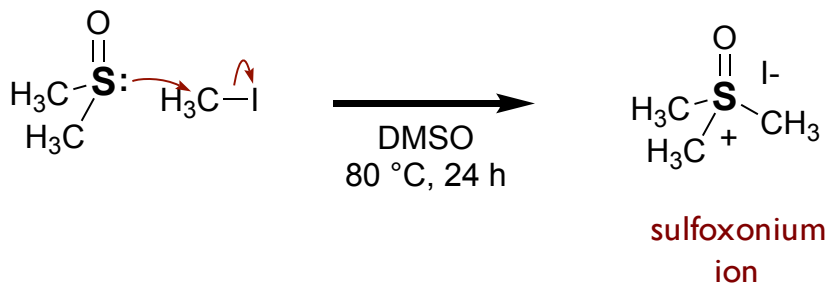
Yeo, S.-K.; Motoo, S.; Kanematsu, K.
JOC **1994**, 59, 1621.

Sulfur L.P. as a Nucleophile: Sulfonium and Sulfoxonium Ions

■ Formation of sulfonium ions

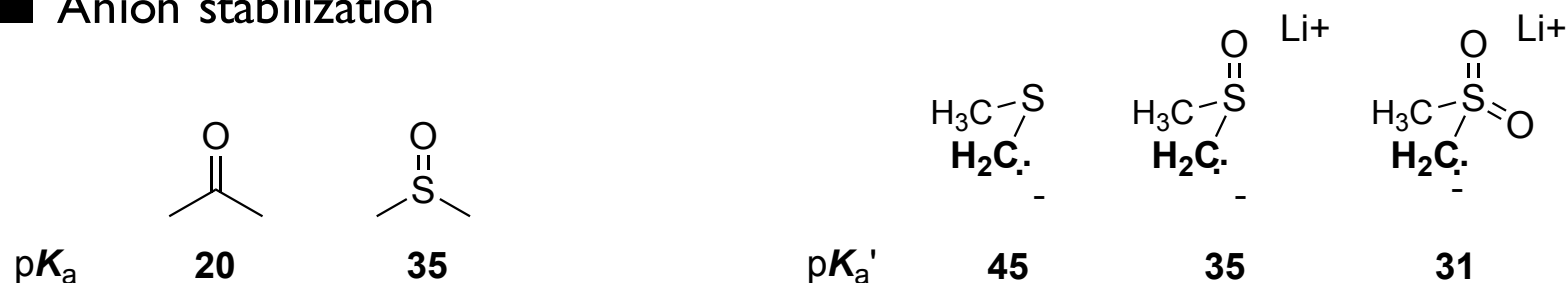


■ Sulfoxide l.p. aren't as nucleophilic. Note the higher temperature.



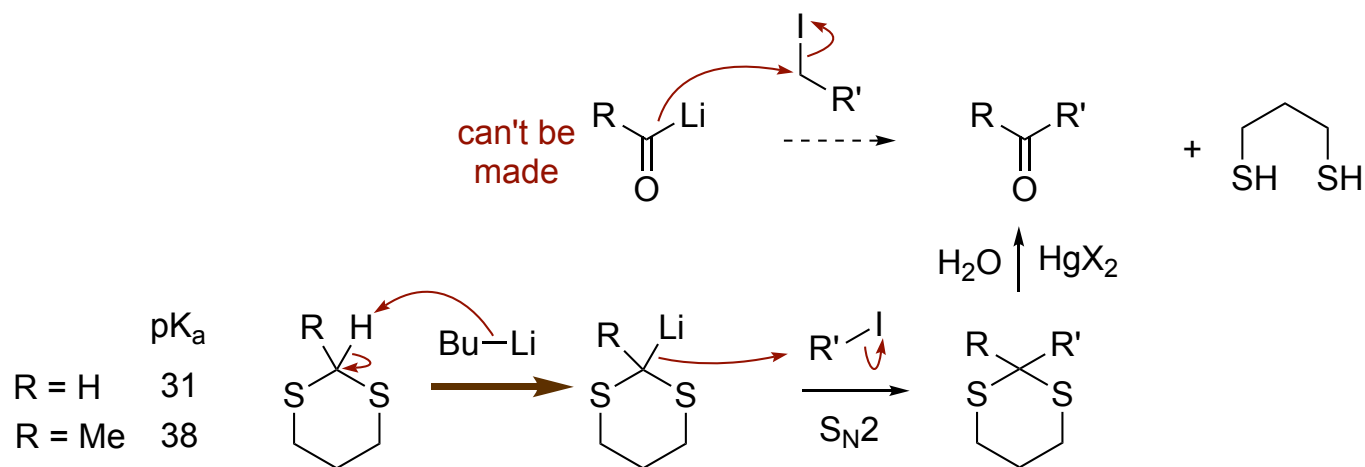
Anion Stabilization By Sulfur Groups

■ Anion stabilization



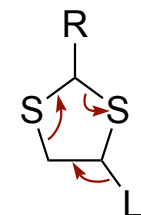
G. Boche p. 353 "The Chemistry of sulphur-containing functional groups" Eds. S. Patai; Z. Rappoport. Wiley, 1993.

■ Dithiane anions can be used as "acyl anion" equivalents.



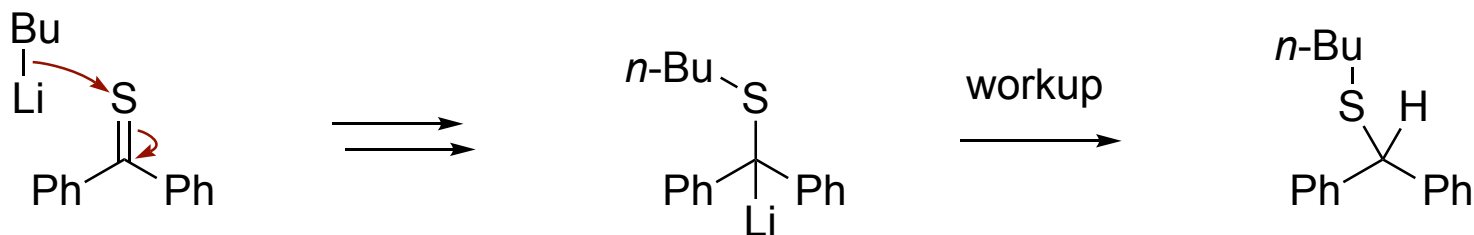
■ The corresponding 5-membered dithiolane anions can't be made efficiently.

Wilson, S. R.; et al. *JACS* **1980**, *102*, 3577.



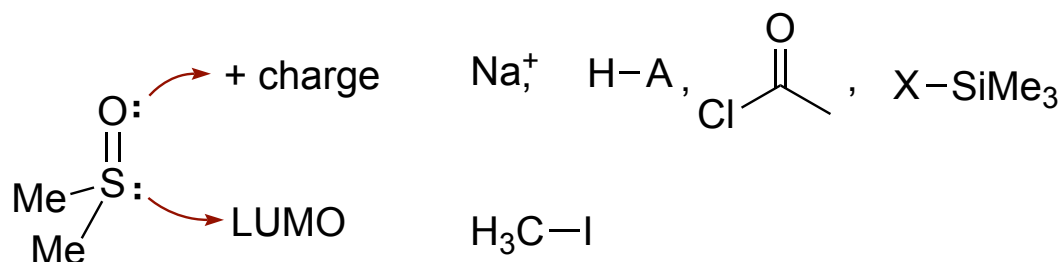
Anion Stabilization By Sulfur Groups

■ C=S isn't highly polarized. With two phenyl substituents on the thioketone the nucleophile adds to sulfur, not carbon, to generate a carbanion.



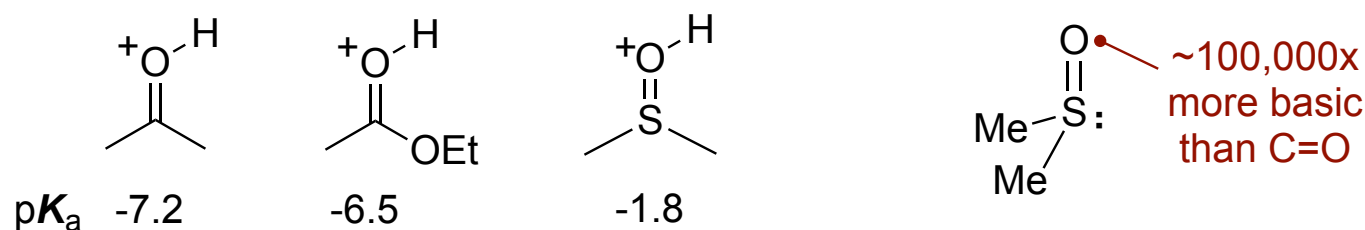
Reaction of Sulfoxide Oxygens

■ Contrast the nucleophilicity of sulfur and oxygen in a sulfoxide. The oxygen has a lot of negative charge and reacts more rapidly than sulfur with “hard” electropositive electrophiles. The HOMO is larger on sulfur. “Soft” electrophiles with low-lying LUMOs and little positive charge react fastest on sulfur.



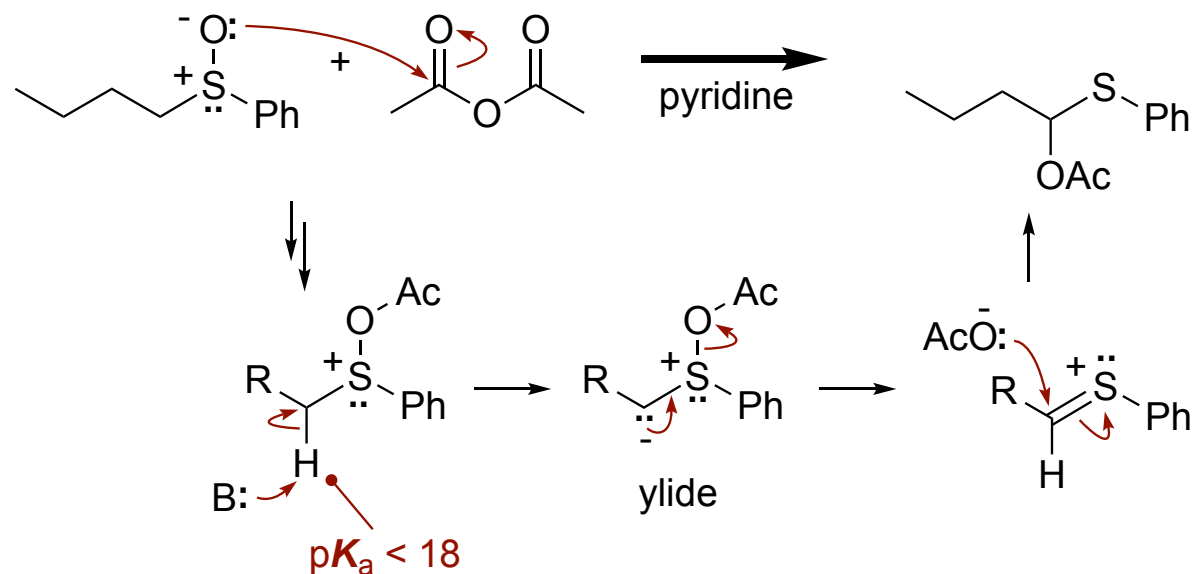
Scorrano, G.
Acc. Chem. Res. **1973**, 6, 132

■ Sulfoxide S=O is much more basic than a ketone C=O

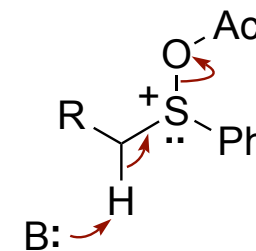


Reaction of Sulfoxide Oxygens

■ Pummerer reaction

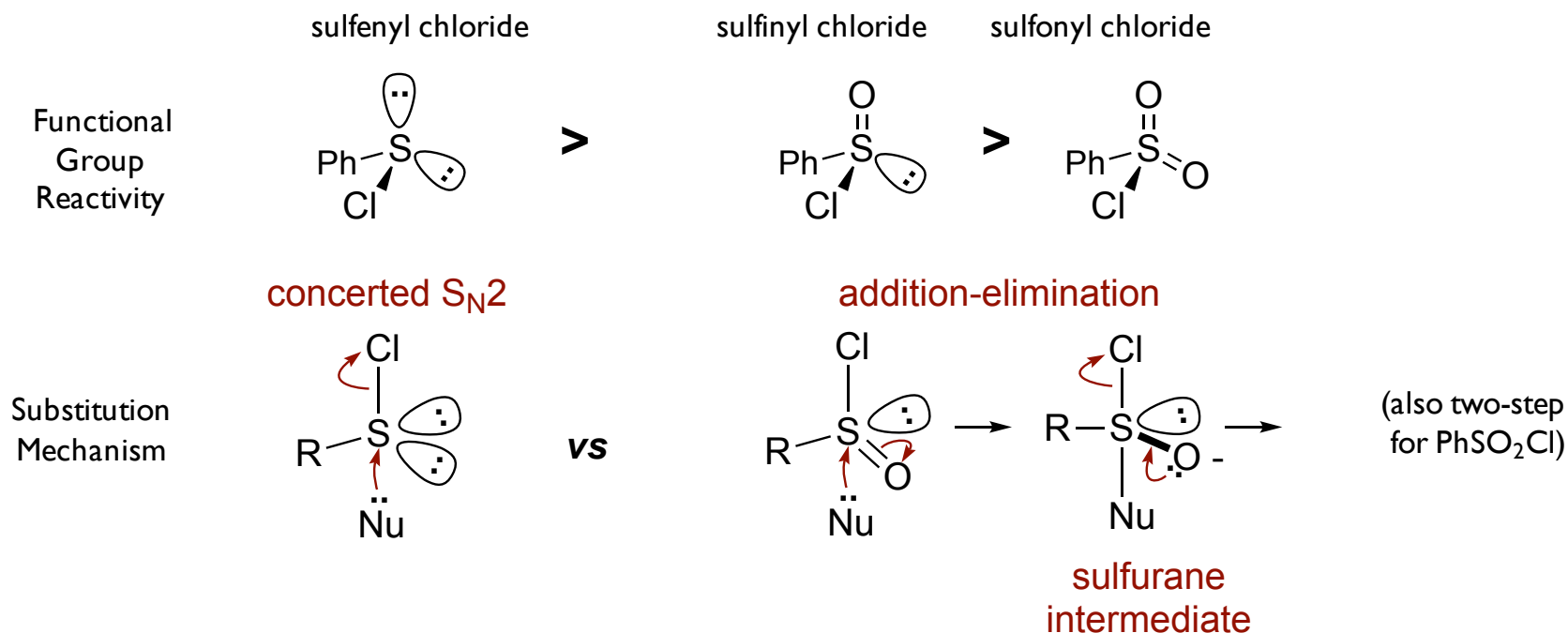


■ The elimination step is often depicted as a concerted E2 process. There is no mechanistic evidence, but I would accept it.



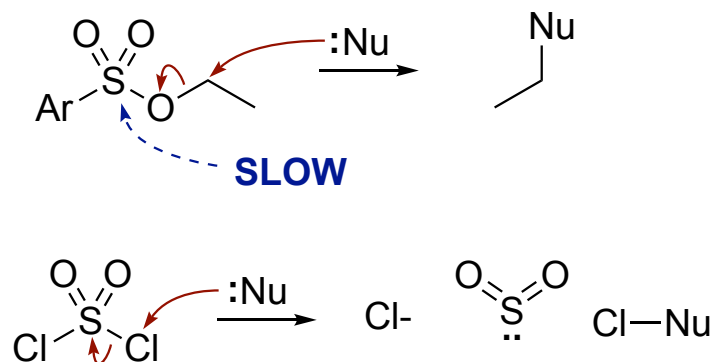
Substitution of Sulfur Substituents: Attack at Sulfonyl Groups

- Contrast the electrophilicity and mechanisms for substitution



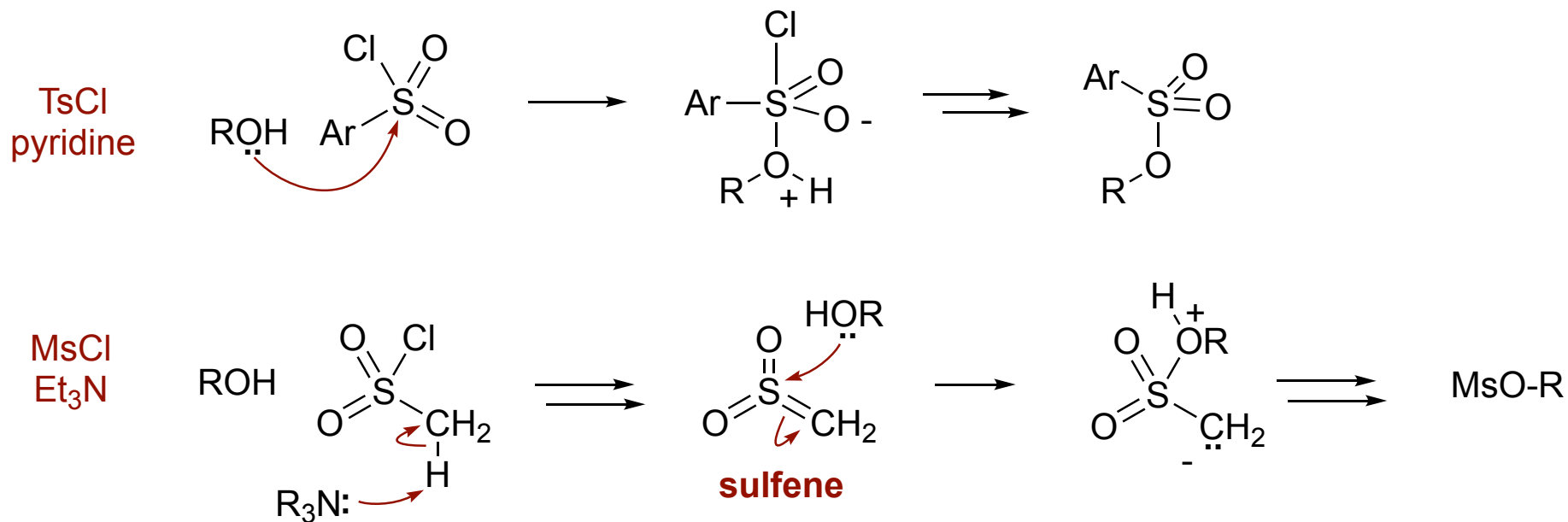
- SLOW** attack at RSO₂X sulfur: that's why tosylate and mesylate are good L.G. for S_N2.

- Note the peculiar reactivity of **sulfuryl chloride** (SO₂Cl₂) which is not at all like thionyl chloride (SOCl₂).



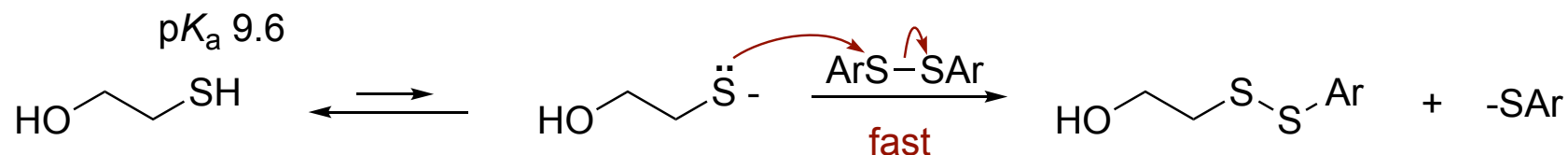
Substitution of Sulfur Substituents: Attack at Sulfonyl Groups

■ Contrast the differing mechanisms for sulfonylation under the two most typical conditions: TsCl/pyridine vs. MsCl/Et₃N

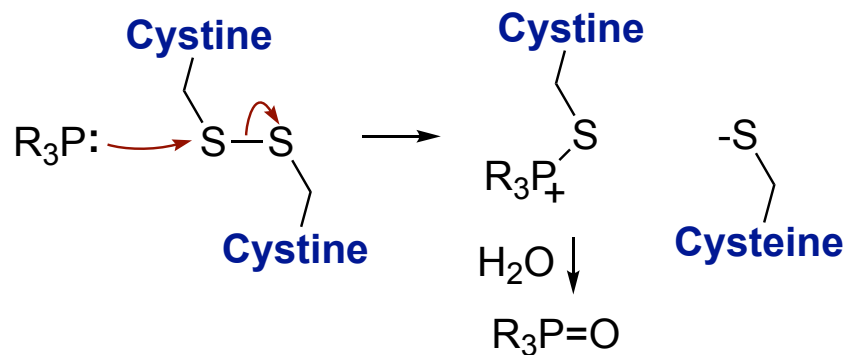


Substitution of Sulfur Substituents: Fast Attack at Divalent Sulfur

- Disulfides exchange very rapidly through S_N2 -like under physiological conditions.



- Phosphines also rapidly attack disulfides through S_N2 reactions. Note the difference in names: cystine disulfide vs cysteine thiol



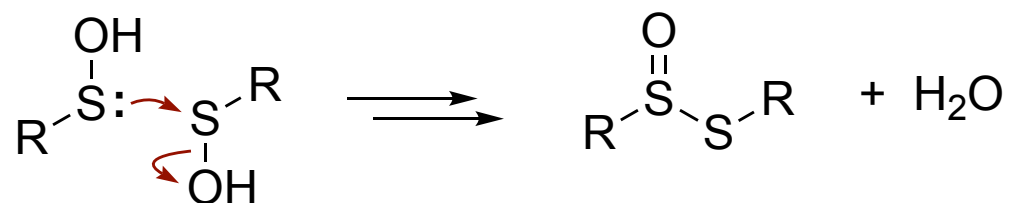
Whitesides, G. M.; Lilburn, J. E.; Szajewski, R. P. *JOC* **1977**, 332

Overman, L. E.; Matzinger, D.; O'Connor, E. M.; Overman, J.D. *JACS* **1974**, 96, 6081. Propose S_N2 mechanism.

Bachrach, S. M.; Gailbreath, B. D. *JOC* **2001**, 66, 2005.

Substitution of Sulfur Substituents: Fast Attack at Divalent Sulfur

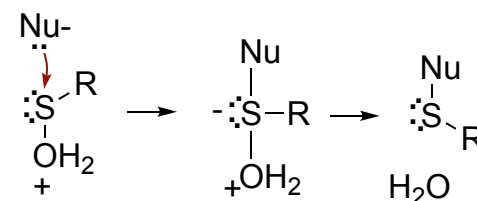
- Sulfenic acids are unstable and react with each other. Note that S_N2 -like reactions at divalent sulfur are so fast that you don't even need a good leaving group.



- Two-step substitution via sulfenic acids has been proposed.

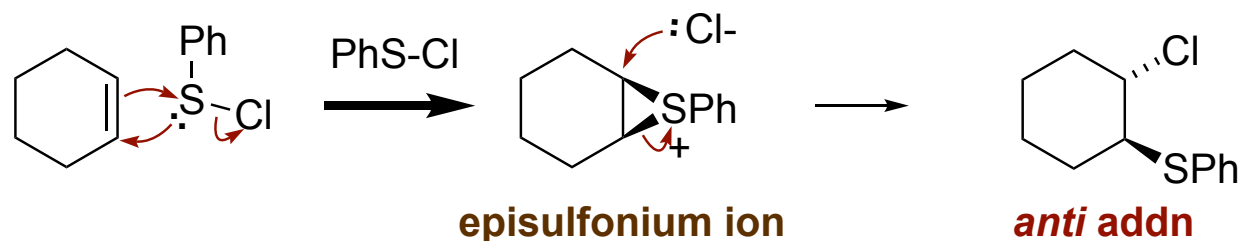
Okuyama, T.; Nakamura, T.; Fueno, T. *J. Am. Chem. Soc.* **1971**, 93, 4327.

Okuyama, T.; Nakamura, T.; Fueno, T. *Chem. Lett.* **1990**, 19, 1133.



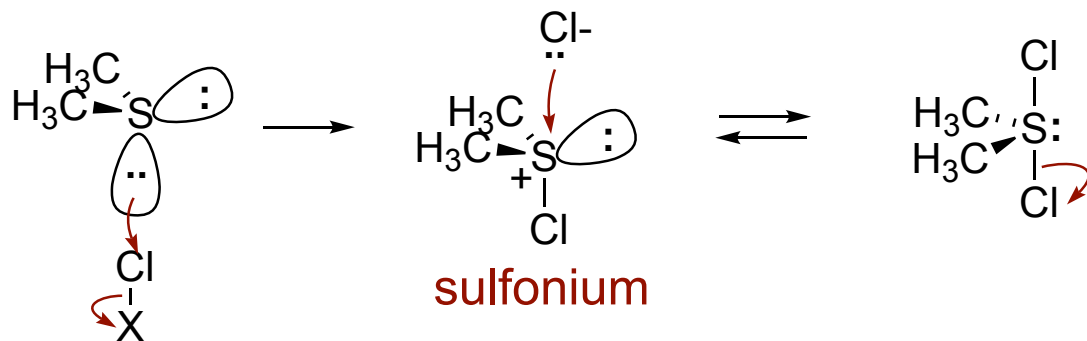
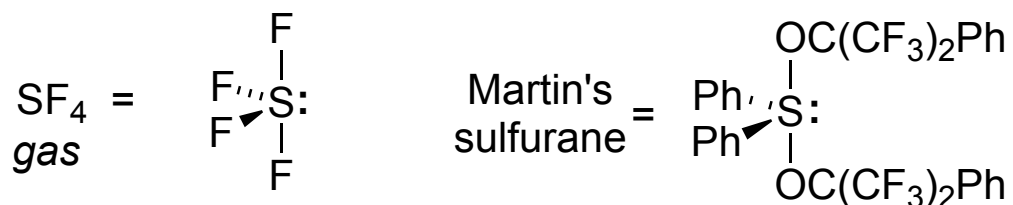
- Sulfonylating reagents lead to episulfonium ion intermediates. Heat reverses the reaction.

$RSOCl$ and RSO_2Cl don't react with alkenes.



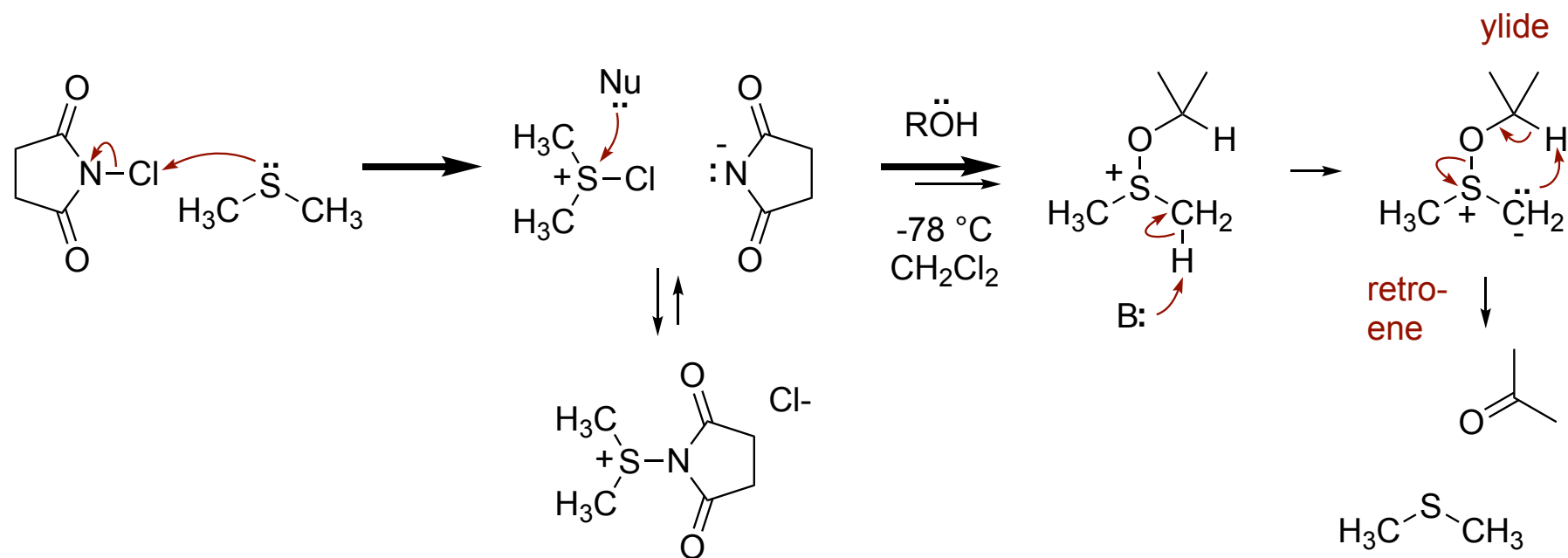
Substitution of Sulfur Substituents: Exchange via Sulfuranes

■ Think of SF_4 as a model for all S(IV) sulfurane intermediates; it's trigonal bipyramidal. Sulfuranes undergo substitution through a dissociative $\text{S}_{\text{N}}1$ substitution mechanism via sulfonium intermediates.



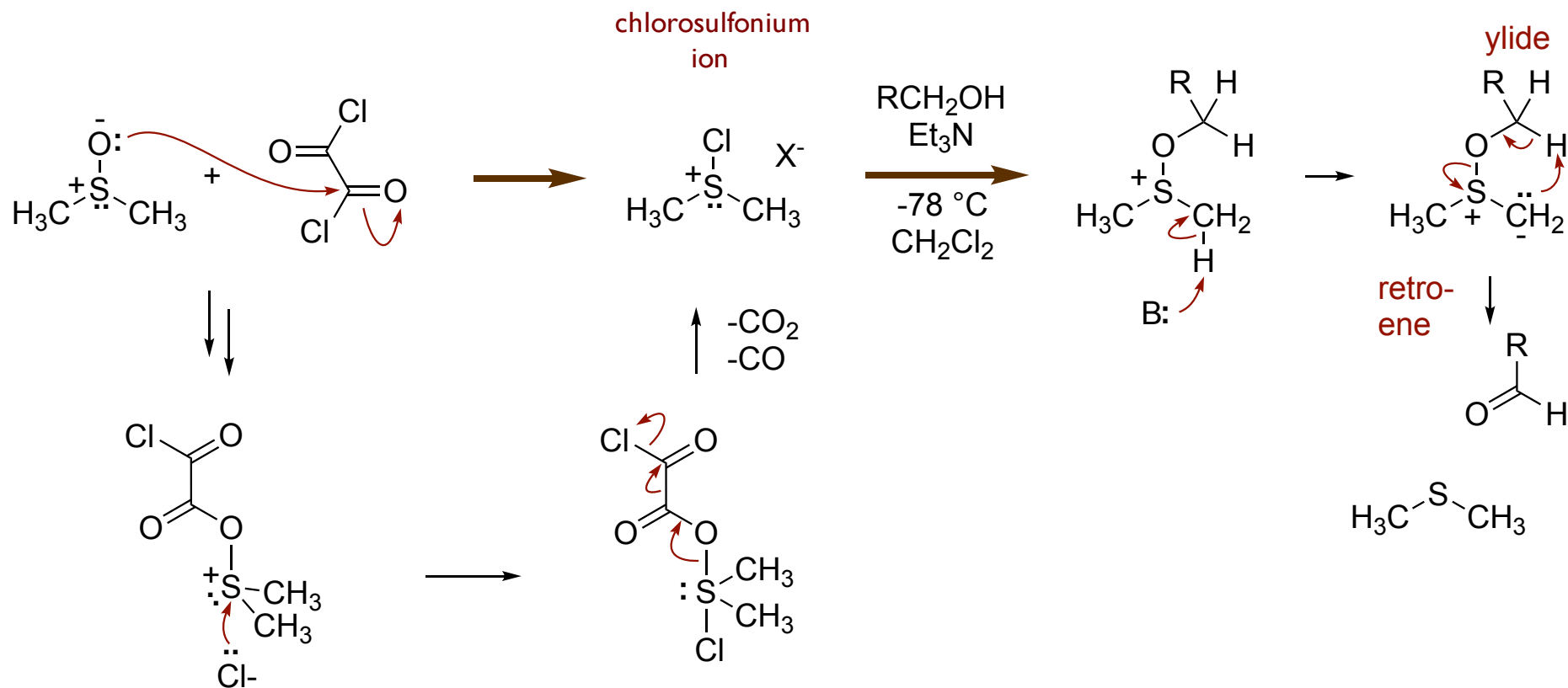
Elimination from Sulfonium Ylides

- The Corey-Kim oxidation is not a common procedure, but it helps one to understand more common oxidation recipes like the Swern oxidation.



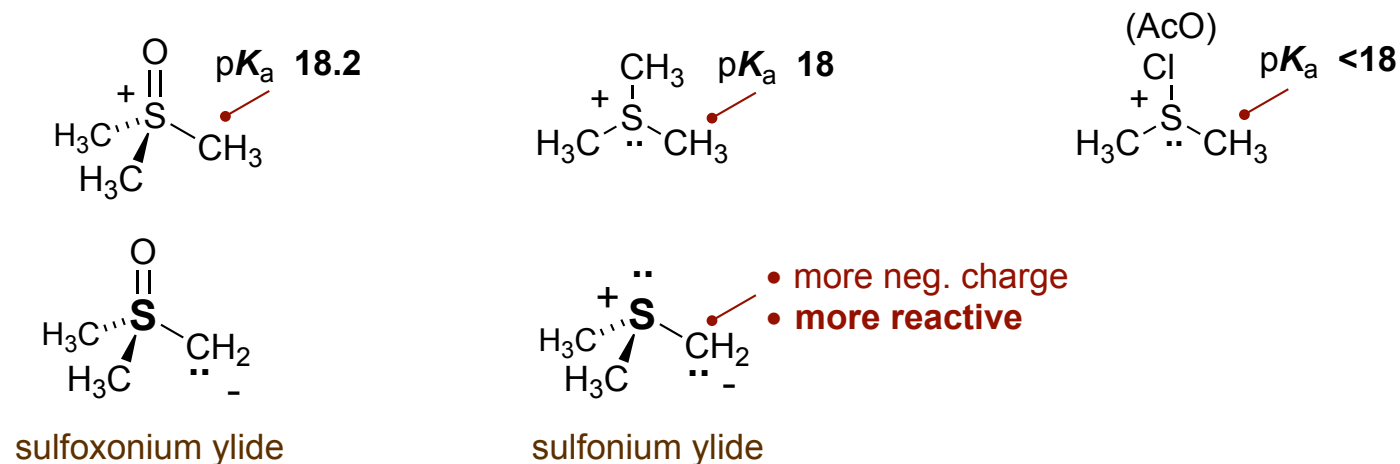
Swern Oxidation: Mild Access to Chlorosulfonium

■ The Swern oxidation generates the same type of chlorosulfonium intermediate used as the Corey-Kim oxidation, but starts from readily available DMSO.

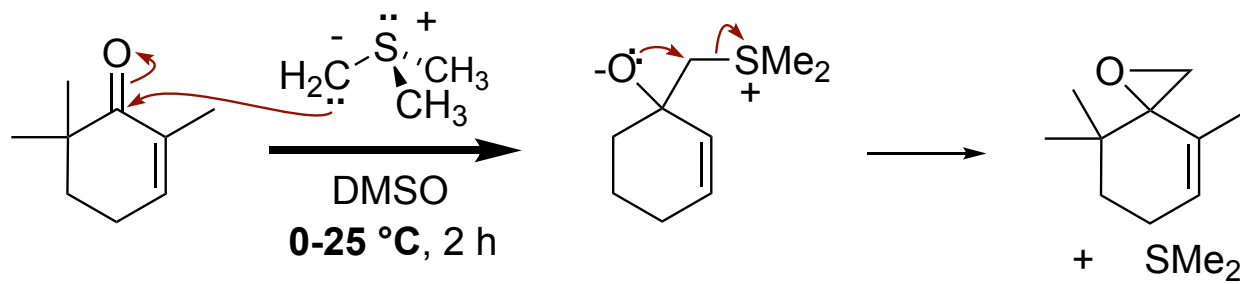


Sulfonium Ylides Make Epoxides

- Sulfoxonium ions and sulfonium ions are easily deprotonated.



- Sulfonium ylides react with aldehydes and ketones to give epoxides.



Rosenberger, M.; et al.
Helv. Chim. Acta **1980**, 63, 1665.

Sulfoxonium Ylides

■ Sulfoxonium ylides add *reversibly* to the C=O of enones. Eventually, you get 1,4 addition to form cyclopropanes.

