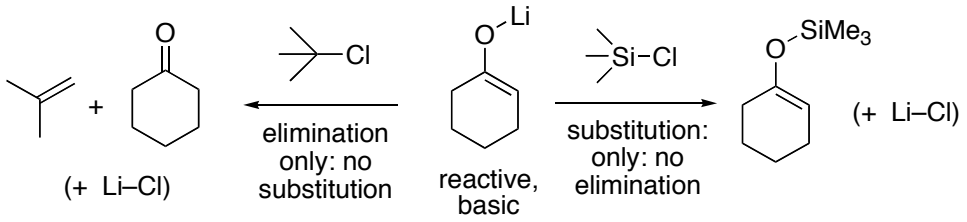
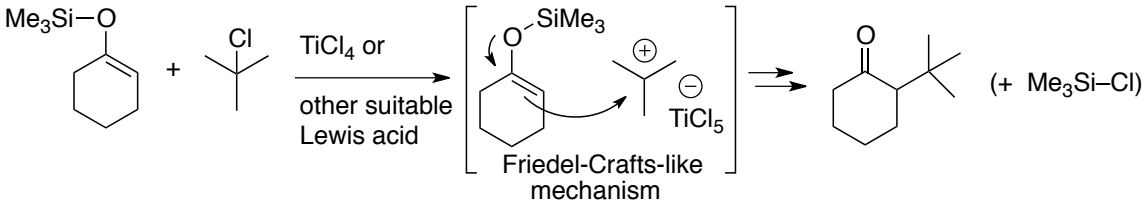
CHEM 330

Topics Discussed on Oct 7

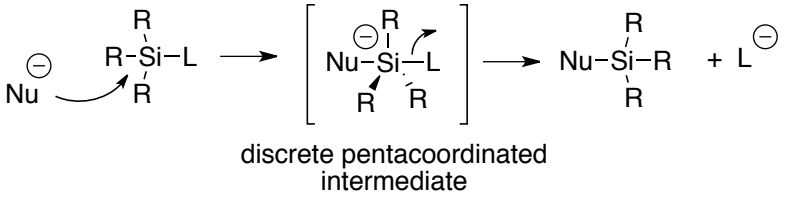
Mechanistic dichotomy in the reactivity of tertiary alkyl halides vs. trialkylsilyl halides:



Interesting feature of silyl enol ethers: possibility of effecting C-alkylation with tertiary alkyl halides (impossible with true metal enolates), e.g.:

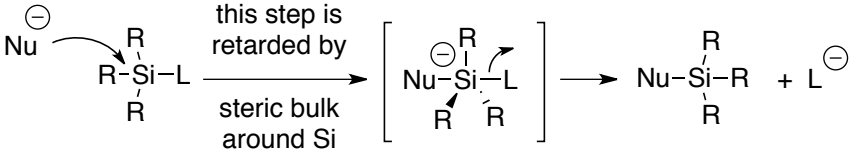


Probable associative mechanism involved in substitution at a Si center [intervention of d orbitals (?), formation of a discrete pentacoordinated Si intermediate ("siliconate"), etc.]:

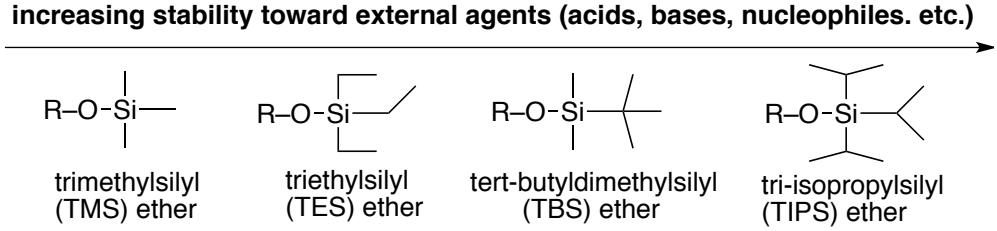


Nu	may be an enolate, alcohol, alkoxide, fluoride ion ....
L	is a generic leaving group; e.g., Cl, OR

Principle: increasing steric bulk around the silicon atom retards the rate of nucleophilic substitution by retarding the rate of formation of the (presumed) siliconate intermediate

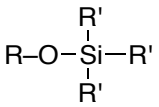


Silyl groups of common use in modern synthetic chemistry:



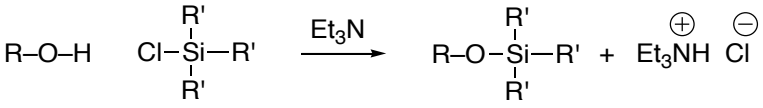
note: because increasing steric bulk around the Si atom retards the rate of nucleophilic substitution (by retarding the rate of formation of the presumed siliconate intermediate), silyl ethers / enol ethers become progressively more resistant to the action of external agents as the steric bulk around the silicon atom increases

Silicon-centered protecting groups for alcohols: silyl ethers

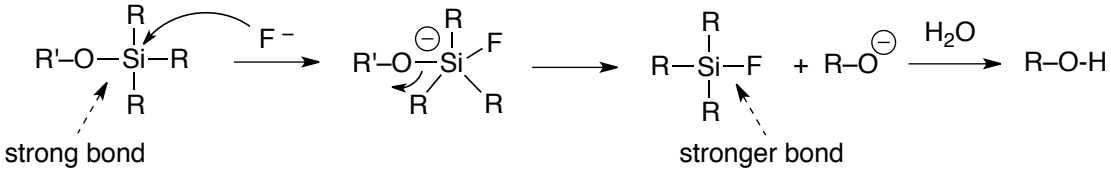


a generic silyl ether

Preparation of silyl ether derivatives of alcohols by reaction of R–OH with a trialkylsilyl chloride in the presence of a base, e.g., Et_3N (often in the presence of a catalyst such as imidazole):



Cleavage of silyl ethers with F^- ion through formation of a very strong Si–F bond



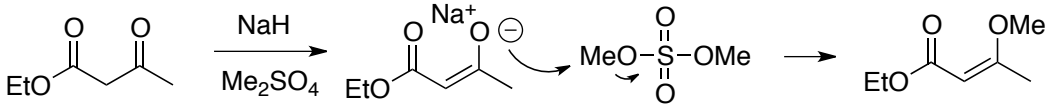
Tetrabutylammonium fluoride ($Bu_4N^+ F^-$, "TBAF") as a convenient source of fluoride ion (soluble in common organic solvents)

Regarding the O-alkylation of enolates (i.e., the reaction of carbon-based electrophiles at the O-terminus of enolates):

i. Generally speaking, the O-alkylation of enolates is not a technologically significant process — or certainly not as significant as the C-alkylation.

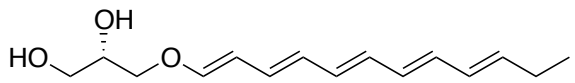
ii. A possible exception is the O-alkylation of enolates of active methylene compounds, which leads to building blocks for the preparation of heterocyclic compounds and other synthetically useful materials

O-alkylation of active methylene compounds with dialkyl sulfates as an avenue to synthetically useful intermediates, e.g.:



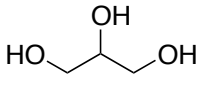
Application of the O-alkyation of the enolate of an active methylene compound in the synthesis of fecaenes:

a typical fecaene

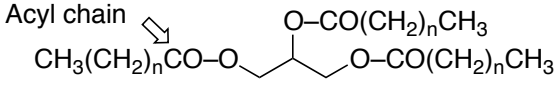


Fecaenes: highly mutagenic, and probably carcinogenic, metabolites of fats (= lipids). They are found in human feces and are associated with the incidence of colon cancer in subjects who consume a high-fat diet

Fats (= lipids): triesters of glycerol and long-chain acids, therefore also described as "triacylglycerols." Each type of fat incorporates a specific permutation of acyl groups:



glycerol

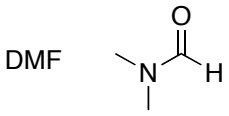


n ≥ 12

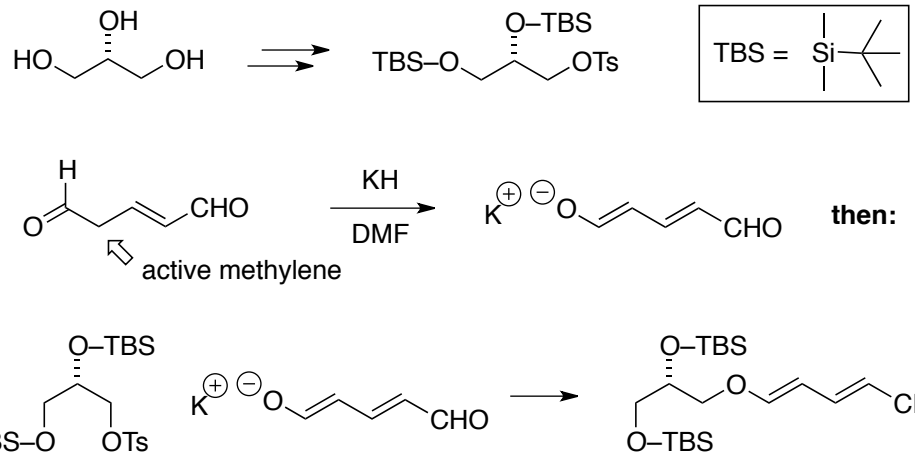
General structure of saturated fats (=lipids)

note • unsaturated fats (lipids) incorporate one or more *cis*-C=C bonds in the acyl chains
• *trans*-fats incorporate *trans*--C=C bonds in the acyl chains

Dimethylformamide (DMF): a polar, aprotic solvent with properties similar to those of DMSO:



Synthesis of fecaenes:



notice how the alkylation step is carried out: the electrophile is a tosylate (tends to react with enolates at O), the enolate counterion is K^+ (the potassium counterion favors O-alkylation), and the reaction is carried out in DMF (a strong donor solvent with properties similar to those of DMSO. This type of solvent favors O-alkylation)