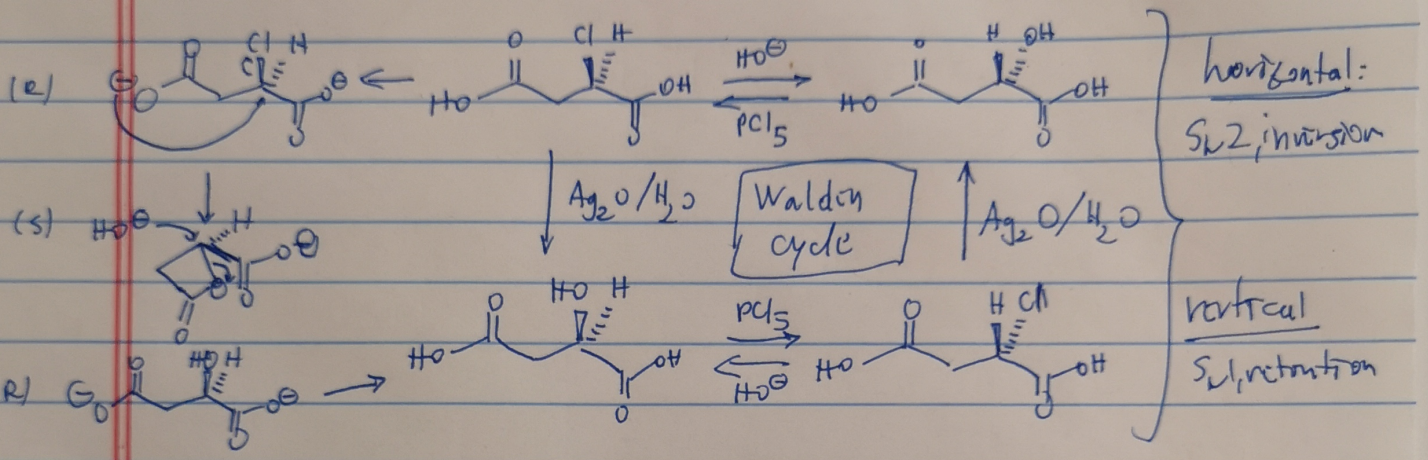
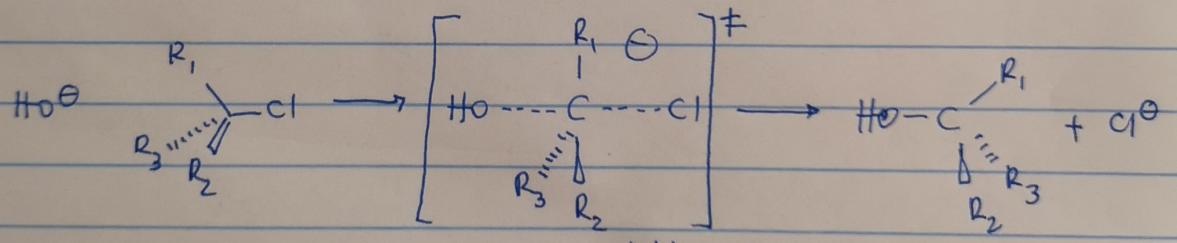
Lecture XXVIII: Stereochemistry of Substitution Reactions

04-10-2020

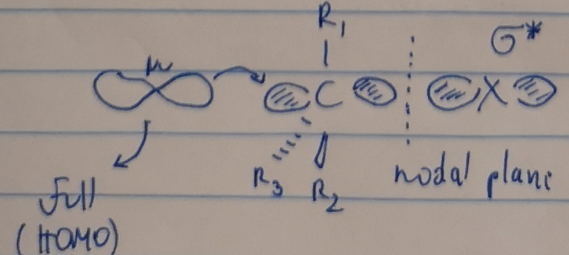
Some of the first reactions to be stereochemically characterized, by Walden in 1896 (Chem Ber 1896, 29, 133):



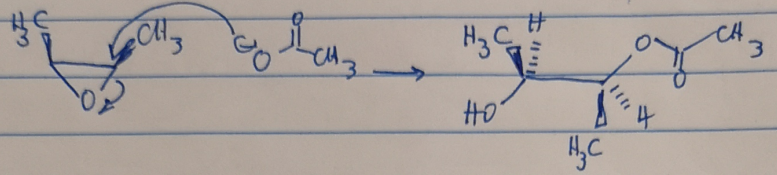
SN2 reaction proceeds with an inversion of configuration on the chiral center:



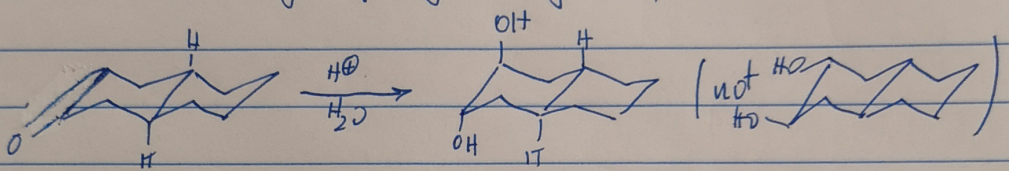
Nucleophile's HOMO will align best with the LUMO (σ^*) of the C–LG bond:



S_N2 reaction is essential in other reactions, such as e.g. opening of epoxides or bromonium ions:

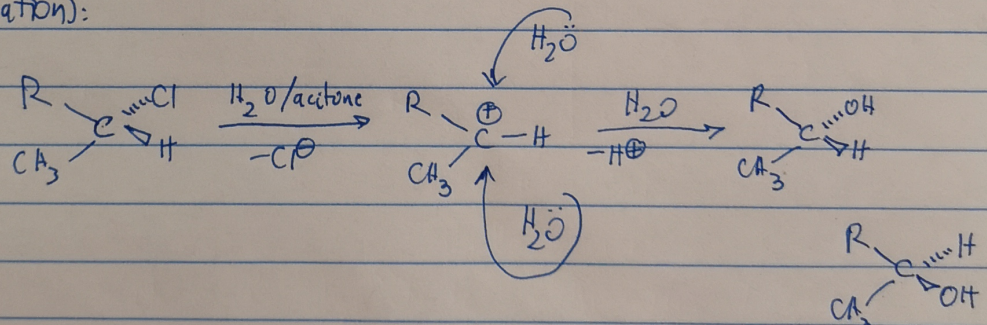


In cyclic systems, ring opening is generally diaxial:

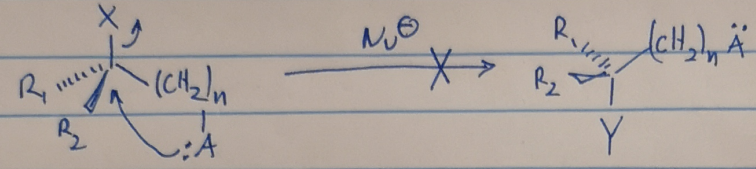


However, if the intermediate cation is stabilized by geminal groups, then this stereoselectivity is lost: mixture of diaxial and diequatorial products.

<u>S_N1 reaction</u> generally proceeds with racemization: loss of stereochemical information):

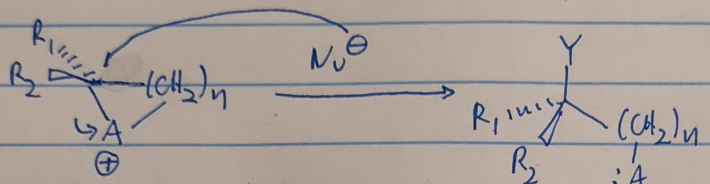


However, some nucleophilic reactions can proceed with a <u>retention</u> of stereochemical configuration. Retention very often suggests <u>neighboring group participation</u> (NGP). NGP also often speeds up the corresponding reactions.



rate-determining $-X^{\ominus}$

two inversions = retention

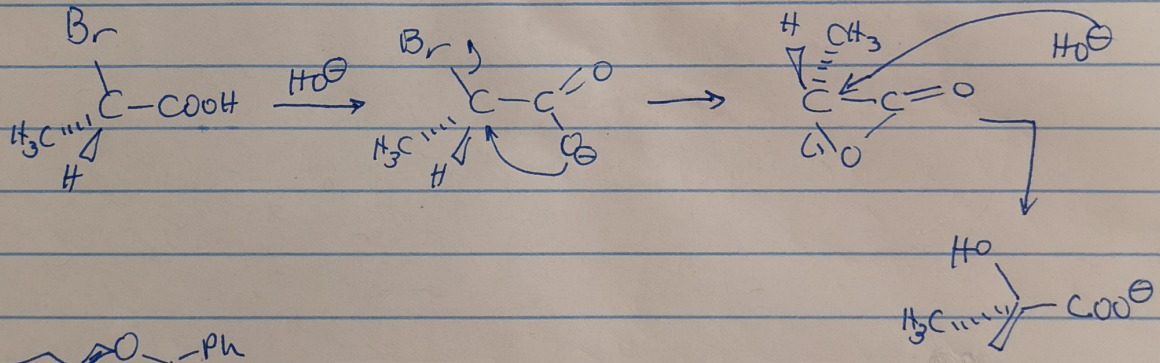


$A = COO^{\ominus}, Br, OH, OCH_3, NR_2$
$SR, S^{\ominus}, O^{\ominus}, COOR$

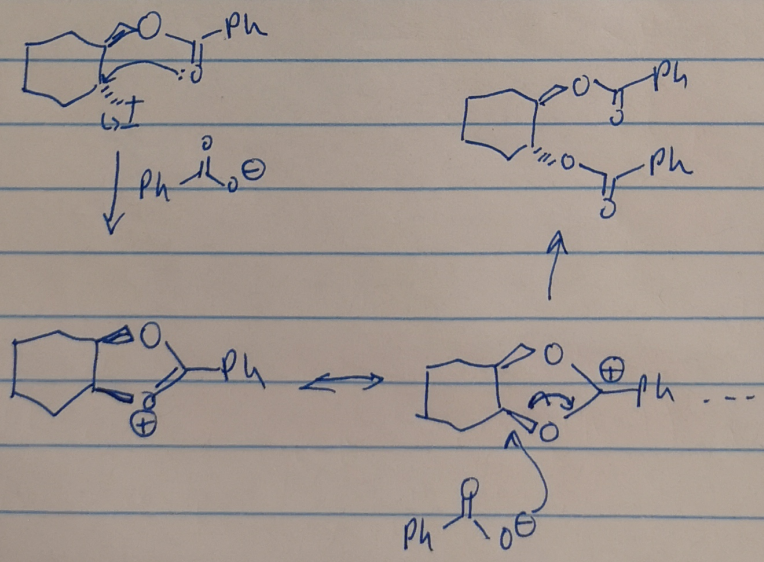
Cyclic intermediate

NGP is particularly pronounced in cases when 3-, 5-, or 6-membered ring can be formed:

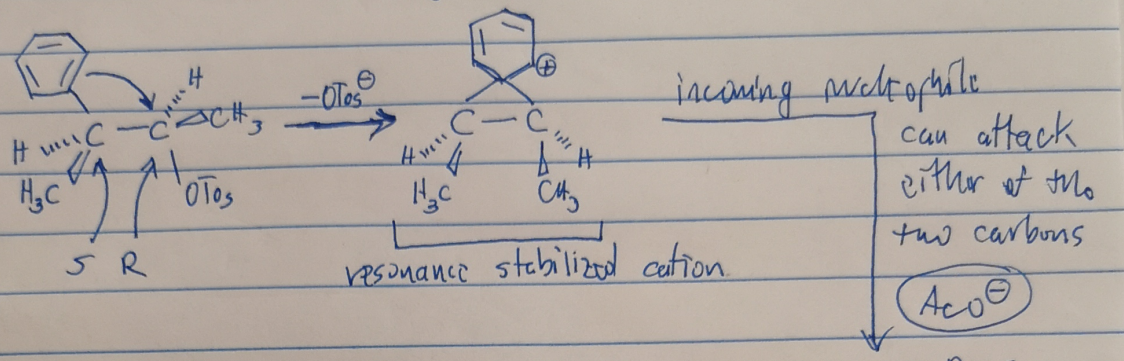
three-membered



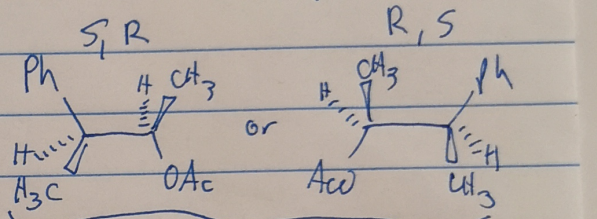
five-membered

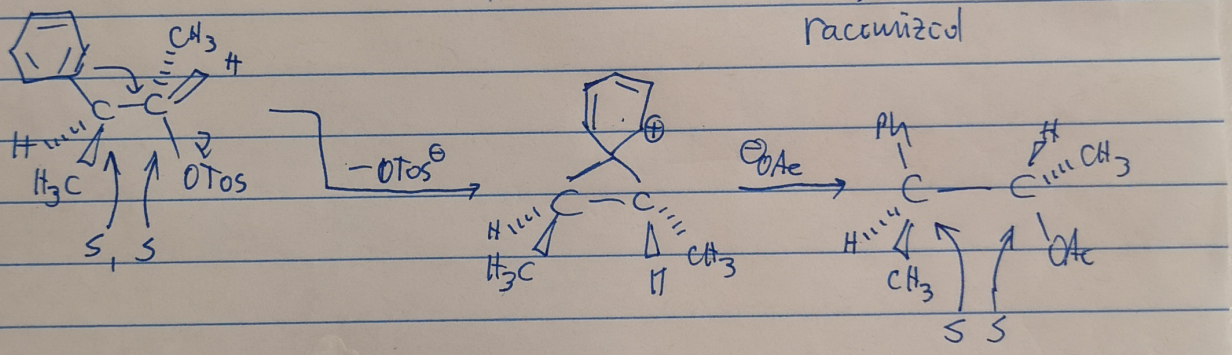


Double bonds or aromatic rings can also participate as neighboring groups:

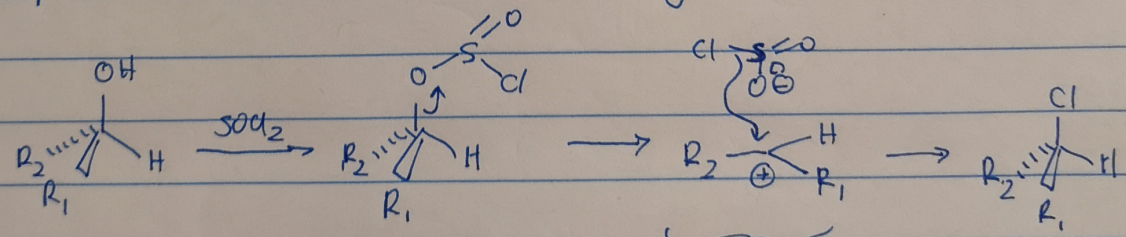


In the S,S-diastereomer, the reaction will proceed with the retention of configuration:



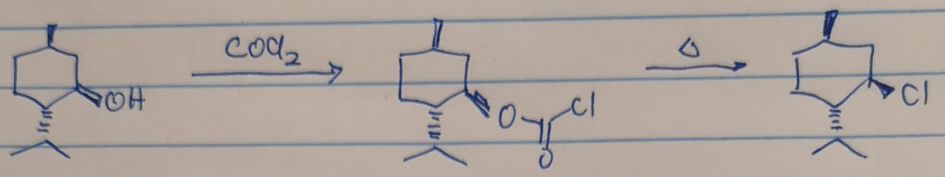


<u>S_Ni reaction</u> is a rare intramolecular nucleophilic substitution, which proceeds with a retention of configuration:

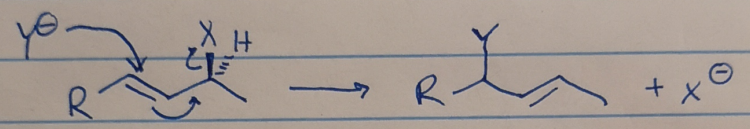


NGP and S_Ni reactions are a lot more common in carbohydrate chemistry, bc of extensive functionalization of sugar molecules

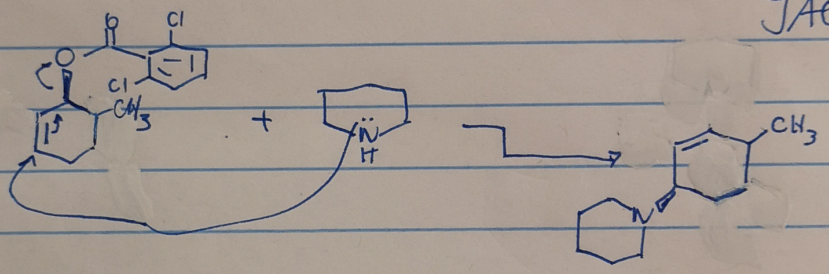
Another example:



<u>S_N2' reactions</u> happen when the leaving group is β to a double bond:



Gilbert Stork
JAcs 1956, 78, 4609



syn – overall substitution

In S_N2' reactions with 1,3 and 1,7 – syn geometry
1,5 " 1,9 double bonds = anti geometry

These are in fact pericyclic reactions, but are commonly analyzed with other substitutions.