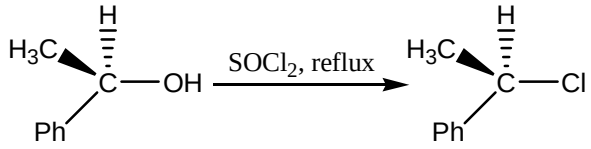
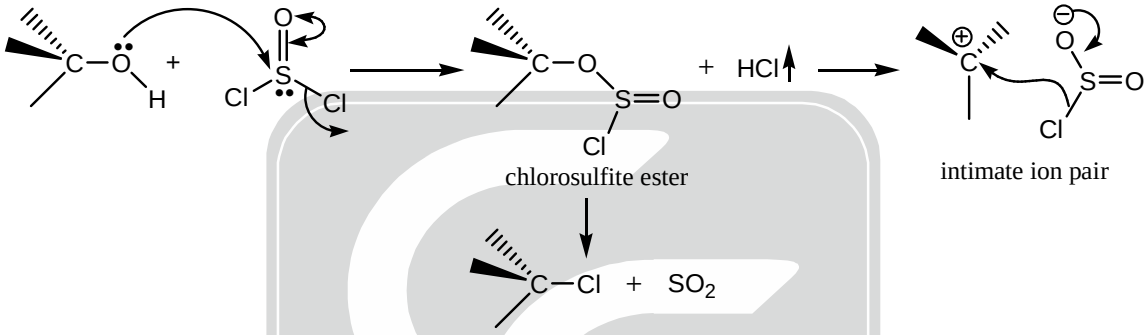
Thionyl Chloride Reaction on Alcohol: S_N1 Mechanism: Retention in Configuration

In the previous discussion regarding the stereochemical outcome of nucleophilic substitution reactions we have seen that these reactions may proceed with either inversion of configuration, to racemiztion, or to a mixture of both. However, few cases are known where substitution proceeds with complete retention of configuration. For example, the chlorination of alcohols with thionyl chloride is very important from stereochemical point of view. When a chiral alcohol is treated with thionyl chloride only, we get the product with retention of configuration.



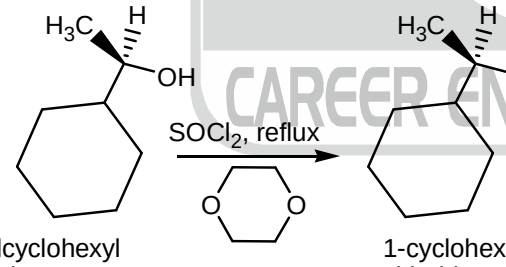
α-phenylethanol α-phenylethyl chloride

The reaction has been shown to follow a second order rate equation, rate = k[ROH][$SOCl_2$]. The reaction is believed to proceed via the S_Ni (Substitution Nucleophilic internal) pathway as shown below via the intermediate formation of alkyl chlorosulfite:



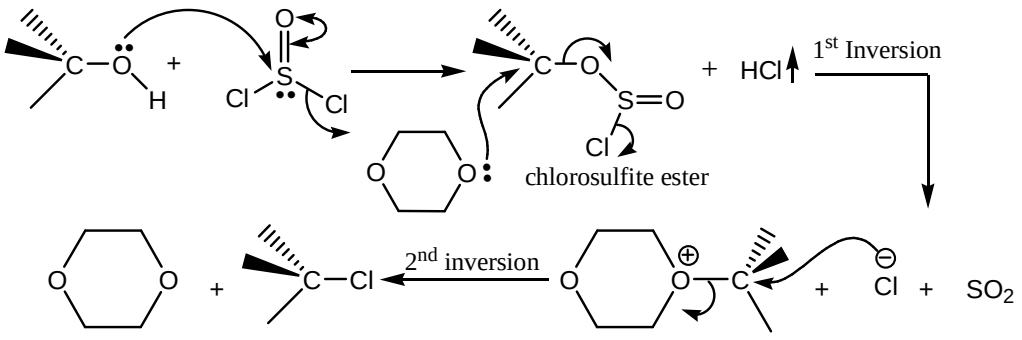
Here alkyl chlorosulfite breaks down to the product directly through a nucleophilic attack of chloride ion on the same side of alkyl group from where the leaving group departs. An alternative description involves the formation of an ion pair from the alkyl chlorosulfite, which then collapses to product through a nucleophilic attack of chloride ion from the same side as before.

Similar retention of configuration is also observed when the reaction is carried out is dioxane solvent.

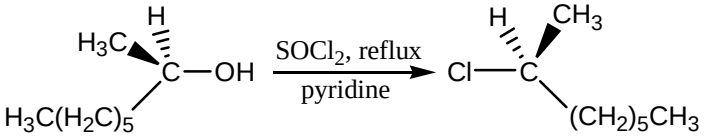


methylcyclohexyl carbinol 1-cyclohexylethyl chloride

The reaction is belived to proceed via a double inversion via participation of the solvent in the following ways:

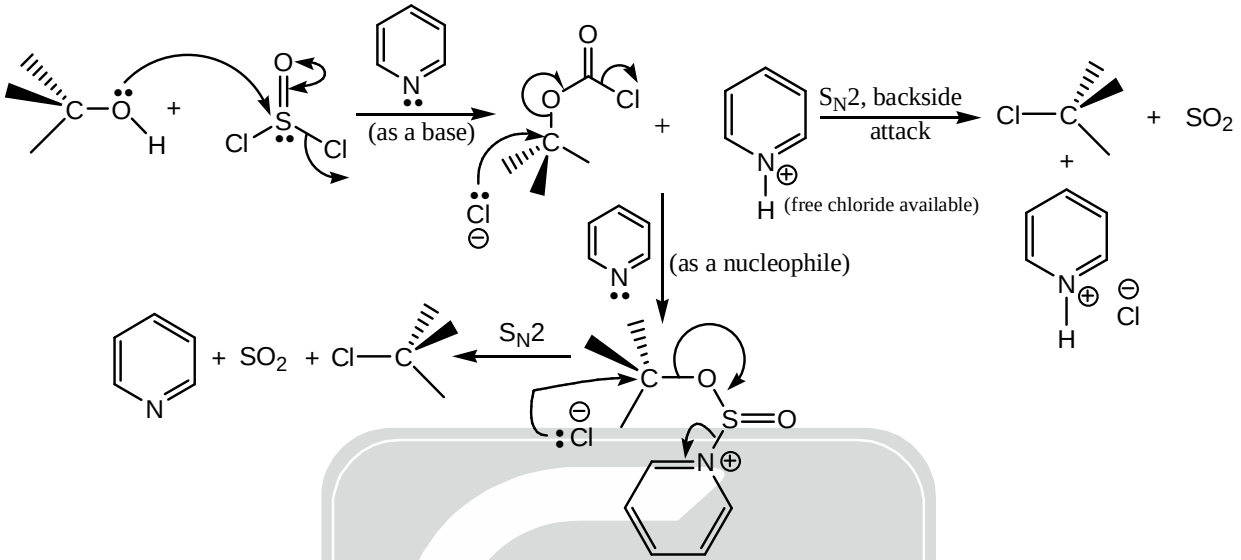


However, when the reaction is carried out in presence of pyridine, we get the product with inversion of configuration; for example:



2-octanol 2-octyl chloride

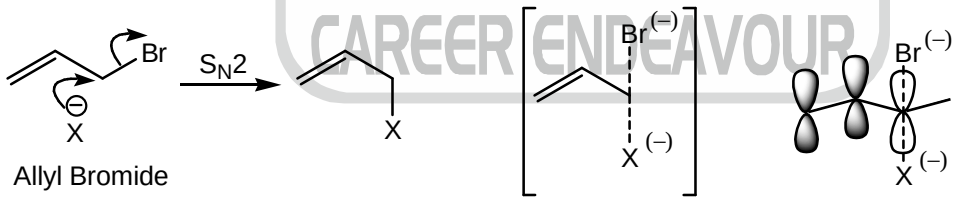
The following S_N2 pathway has been proposed where pyridine may act as a base as well as nucleophile:



Nucleophilic attack on allylic compounds:

The allylic bromides that can be made by these radical reactions display interesting regioselectivity. The allyl bromide is about 100 times more reactive towards simple S_N2 reactions that is propyl bromide or other saturated alkyl halides.

The double bond stabilizes the S_N2 transition state by conjugation with the p-orbital at the carbon atom under attack. This full p-orbital (shown in orange in the diagram below) forms a partial bond with the nucleophile and with the leaving group in the transition state. Any stabilization of the transition state will, of course, accelerate the reaction by lowering energy barrier.

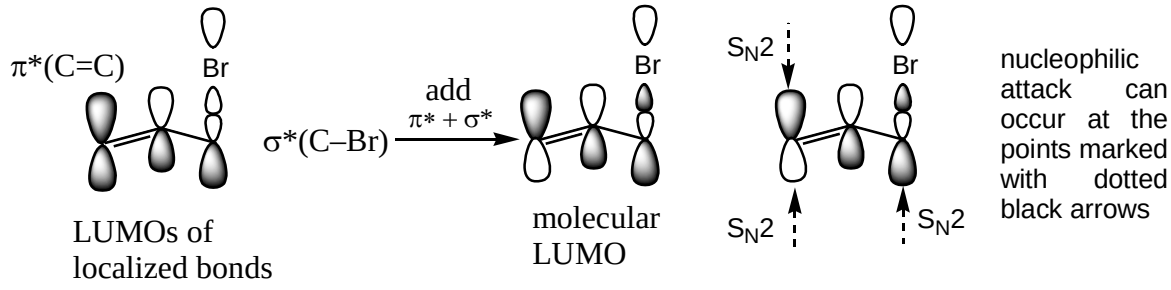


There is an alternative mechanism for this reaction that involves nucleophilic attack on the alkene instead of on the saturated carbon atom. This mechanism leads to the same produc and is often called the S_N2 (pronounced 'S-N-two-prime') mechanism.

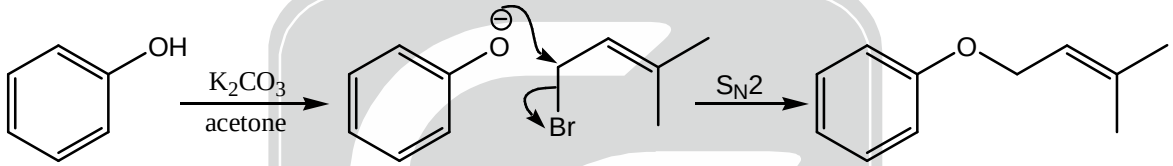
We can explain both mechanism in a unified way if we look at the frontier orbitals involved. The nucleophilic must attack an empty orbital (the LUMO), which we might expect to be simply σ^* (C–Br) for the S_N2 reaction. But this ignores the alkene. The interaction between π^* (C=C) and the adjacent σ^*

(C–Br) will as usual produce two new orbitals, one higher and one lower in energy. The lower-energy orbital, $\pi^* + \sigma^*$, will now be the LUMO. To construct this orbital we must put all the atomic orbitals parallel and make the contact between $\pi^* + \sigma^*$ a bonding interaction.

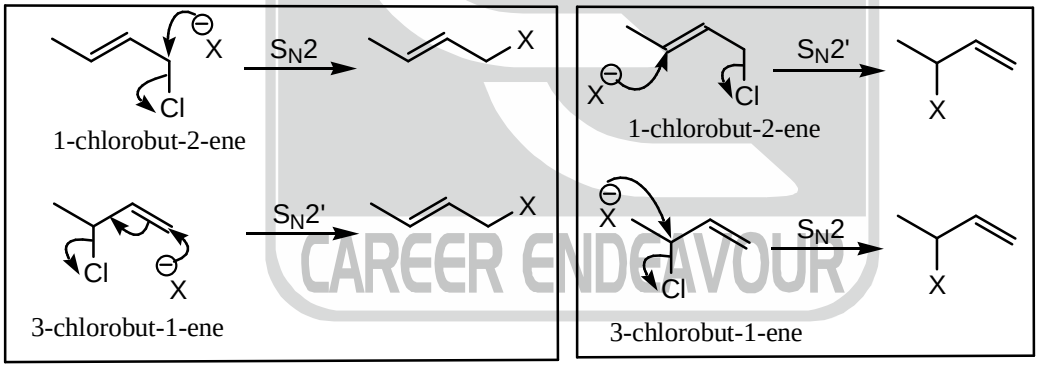
LUMO constructed from π* + σ*



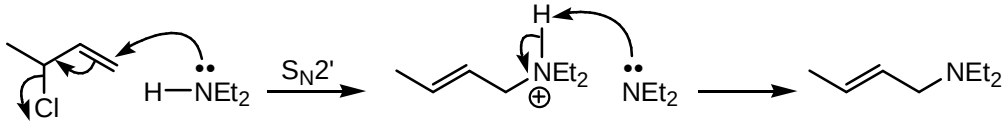
An important example is the reaction of prenyl bromide with phenols. This is simply carried out with K_2CO_3 in acetone as phenols are acidic enough (pK_a ~ 10) to be substantially deprotonated by carbonate. The product is almost entirely from the S_N2 route, and is used in the Claisen rearrangement.



If we make the two ends of the allyl system more similar, say one end primary and one end secondary, things are more equal. We could consider the two isomeric butenyl chlorides.



All routes look reasonable, although we might again expect faster attack at the primary carbon. The reactions in the left-hand box are preferred to those in the right hand box. But there is no special preference for the S_N2 over the S_N2' mechanism or vice versa – the individual case decides. If we react the secondary butenyl chloride with an amine we get the S_N2' mechanism entirely.



If the primary chloride is used, once again we get nucleophilic attack at the primary centre. The more stable product with the more highly substituted alkene is formed this time by the S_N2 reaction. Here is a slightly more advanced example: