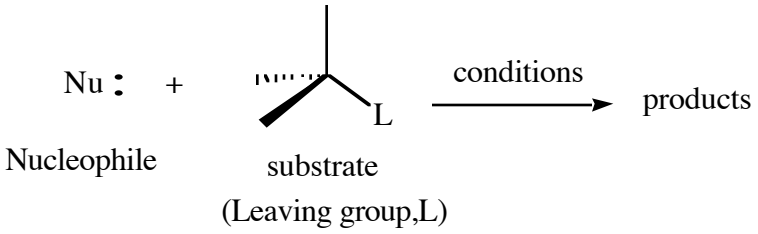
Aliphatic Nucleophilic Substitution



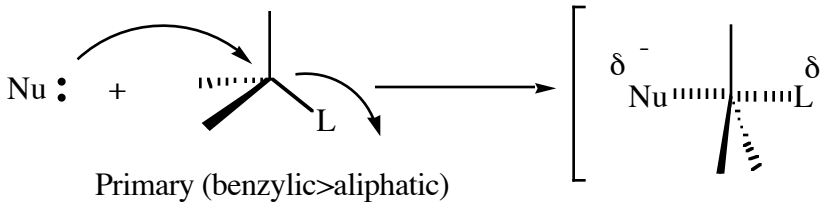
Nucleophiles are chemical species that react with centers of positive ionic character. When the center is an aliphatic carbon, the process is called aliphatic nucleophilic substitution. Chemical reactions of this type are extremely important for the synthesis of new compounds and for understanding the mechanisms in organic chemistry .

All nucleophilic substitution reactions may take several reaction courses, but all have similar appearances at the outset.

All reactions have an attacking species, a **nucleophile** (Nu) that bears a pair of electrons either as an anion or as a neutral compound. The organic compound known as the **substrate** has a structure that greatly influences the outcome of the reaction and it contains the **leaving group** (L) that is lost in the reaction. The **conditions** of the reaction, especially solvent and temperature, are also important contributors to the process.

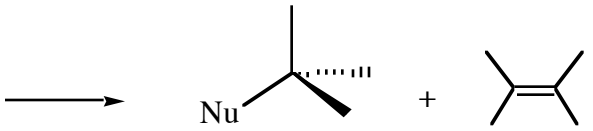
In order to understand the products of the reaction and how they are formed, the reaction is studied from a mechanistic point of view.

The Nucleophilic Substitution Second-Order reaction (SN2)



Primary (benzylic>aliphatic)
>secondary X tertirary

transition state



S_N2 E2

Inversion of
configuration

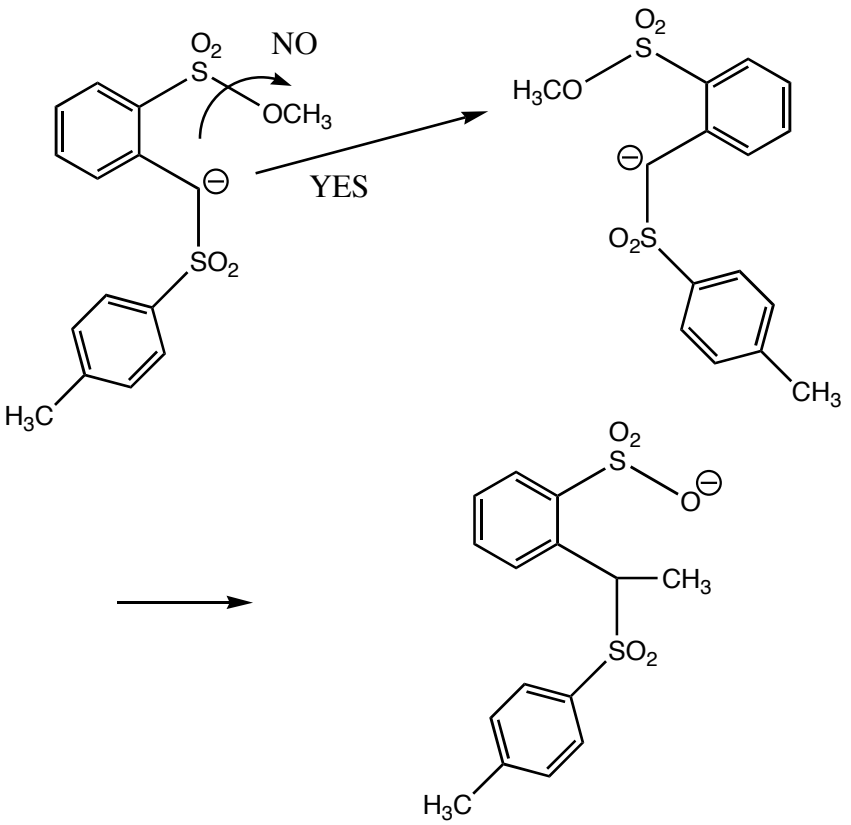
reaction rate $= k\,[Nu][Substrate\}$

The SN2 reaction occurs when a Nucleophile attack a primary substrate and sometimes a secondary substrate. The reaction of a secondary substrate depends on the nucleophile and the leaving group. Tertiary substrates do not undergo reactions by the SN2 mechanism. The overall rate of the reaction depends of the concentration of the nucleophile and the concentration of the substrate, thus it is called second-order.

The mechanism requires that the nucleophile attack the substrate from the backside of the leaving group to give a pentavalent transition state (*). The organic substituents reverse their configuration (an S enantiomer would change into an R enantiomer) The process is sometimes called Walden inversion. Sometimes when the nucleophile has strongly basic characteristics, such as alkoxides, and alkene is formed also. This product is formed in a reaction known as the E2 reaction (Elimination Second-order).

The transition state must be linear as shown from the reactions below. The carbanion must attach a methyl from another molecule (not internally) because a linear attack is not possible internally.

Linear Transition State (Crossover experiments)



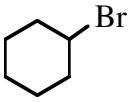
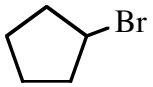
Now for some of the characteristics of substrates, nucleophiles and leaving groups.

The SN2 mechanism **requires** a backside attack. The reaction is very sensitive to the presence of groups that hinder the backside attack. Thus primary substrates are the best because they have the least hinderance to the backside attack by the nucleophile. Neopentyl bromide with a relative rate of 10-7 is a primary substrate with low reactivity because the one substituent is a bulky tert-butyl group

Substrate Reactivity

1^o-benzylic $> CH_3 >$ 1^0-aliphatic $>> 2^0$ not at all 3^0
1^o-allylic

relative reactivity of several aliphatic bromides

CH_3Br	1		.001
CH_3CH_2Br	.01		
$CH_3CHBrCH_3$	.001		.01
$CH_3C(CH_3)_2Br$	10^{-5}	$CH_2=CHCH_2Br$	2.3
		$PhCH_2Br$	4.0
$CH_3C(CH_3)_2-CH_2Br$	10^{-7}		

Some properties of nucleophiles are give by the Swain-Scott equation.

Nucleophiles

$$n_{CH_3I} = \log(k_{nu} / k_{CH_3OH})$$

n = nucleophilicity constant. Compares nucleophiles in with methyl iodide. The standard nucleophile is water.

	n	pKa
CH_3COO^-	4.3	4.8
N_3^-	5.8	4.7
CH_3O^-	6.3	16
NH_2OH	6.6	5.8
^-CN	6.7	9.3
t-BuO^-	4.0	20
Ph_3P	8.7	8.7
H_2O	0.0	7

$$RS^- > ArS^- > S_2O_3^- > I^- > CN^- > SCN^- > OH^- > N_3^- > ArO^-$$

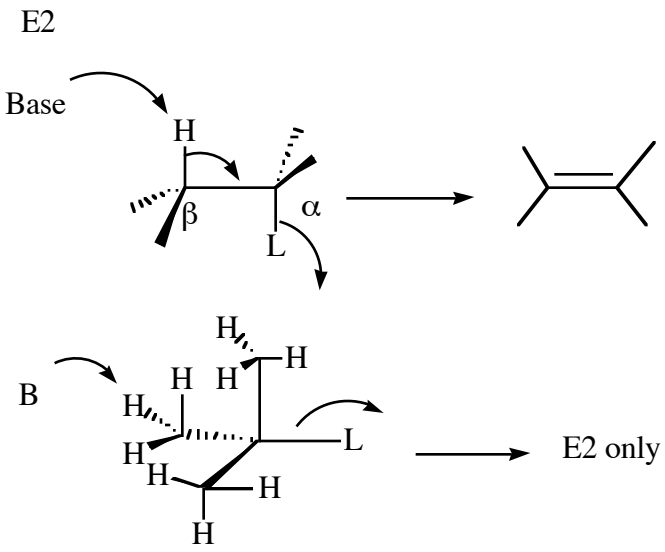
Leaving groups are very important in the SN2 process. Some of the very best leaving groups are not halogens, but instead are esters of sulfonic acids that are easily prepared from alcohols and sulfonyl anhydrides or sulfonyl chlorides. The use of a triflate or tosylate with a secondary substrate is effective for increasing the amount of SN2 reaction when other reactions are compete.

Leaving Groups

L	relative rate
$CF_3SO_3^-$ (Tf, triflate)	10^8
$CH_3PhSO_3^-$ (Ts, tosylate)	10^5
$CH_3SO_3^-$ (Ms, mesylate)	10^4
I^-	91
Br^-	14
CF_3COO^-	2
Cl^-	1
F^-	10^{-6}
CH_3COO^-	10^{-6}

The Elimination Reaction

The formation of an alkene can occur as a competing reaction with the S_N2 process. The proportion of elimination, E2, depends also on the substrate, the basicity of the nucleophile, the leaving group and the temperature. The E2 reaction rate depends on the concentration of the nucleophile (base in this case) and the concentration of the substrate and is therefore second-order. The elimination requires hydrogens in the beta position and the hydrogen eliminates best when it is anti-perplaner to the leaving group.



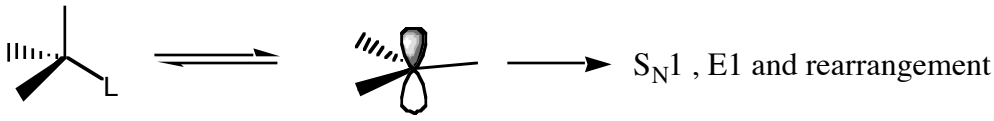
Good bases for the reaction are alkoxides and nitrogen anions. The presence of more beta hydrogens causes more elimination product, thus elimination increases with secondary substrates and is the only product of a tertiary substrate with a base. Carbon-hydrogen bonds are stronger than carbon-leaving group bonds, thus higher temperatures aid the elimination process.

Substitution Nucleophilic First-order (S_N1)

Another reaction of organic substrates with leaving groups is a first-order reaction. This means that the rate of the reaction does not depend on the nucleophile concentration, but depends only on the concentration of the substrate. The final outcome of the reaction may be substitution but elimination and rearrangement are often present.

rate = k [S]

The mechanism for the reaction is shown below. In this process the leaving group departs because of the substrate structure and its interaction with the solvent to form an intermediate called a carbocation. The carbocation is a real-life species with a finite liftime and thus is not just a transition state.



a carbocation

Only substrates that can produce a carbocation with reasonable stability can participate in the S_N1 process. This leaves out methyl and primary substrates as their cations are just too high energy, unless there is some adjacent stabilizing group (such as phenyl or CH_3O). Thus the secondary and expecially tertiary substrates are the best. A list of carbocation stability is shown below.

benzylic
allylic $>$ 3^o $>$ 2^o $>$ Ph^+ $>$ $C{=}C^+$ $>$ 1^o

S_N1 reactions are sometimes referred to as solvolysis reactions, meaning reaction induced by the solvent. Most solvents are polar to interact with the ionic leaving group and to stabilize the polar carbocation intermediate. The study of the S_N1 process centers around the chemistry of carbocations and factors that influence their stability.

Solvents in Solvolysis

The reactions in this section take place because the substrate forms a relatively stable carbocation in the presence of the solvent. Thus solvolysis means reaction with the solvent,

and the term implies a carbocation mechanism. The rate of a solvolysis reactio, an Sn1 reaction, does not depend on the concentration of any nucleophile and thus the term first order, first order in substrate. rate (solvolysis) = k [RX].

Many studies of these reactions in different solvents have led to important determinations of solvent character, or the ability of a solvent to cause a substrate to form a carbocation. An early scale, and still in use, was developed by Grunwald and Winstein in 1940. The defined a value Y as the ionizing power of a solvent from the equation below. Experimentally the rate constant for ionization of t-butyl chloride in 80% ethanol-20% water is determined. Then the rate constant for the ionization of t-butyl chloride in other solvents in determined and the results are substituted in the equation.

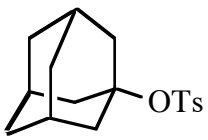
$$Y = \ln\left(\frac{k(\text{solvent})}{k(80\%\ \text{EtOH-}20\%\ \text{water})}\right)$$

for t-butyl chloride as substrate

Some values of Y for several solvents are listed below. Thus formation of carbocations by solvolysis occurs better in solvents with higher Y values.

Solvent	Y
CF_3COOH	1.84
H_2O	3.49
80% EtOH	0.0
HCOOH	2.05
20% EtOH	3.05
EtOH	-2.03

The Y scale was refined to a Y (OTs) scale with the use of another substrate, adamantyl tosylate. The new substrate did not permit any backside attack by the solvent on the cation site and thus is a better measure of pure ionizing ability .

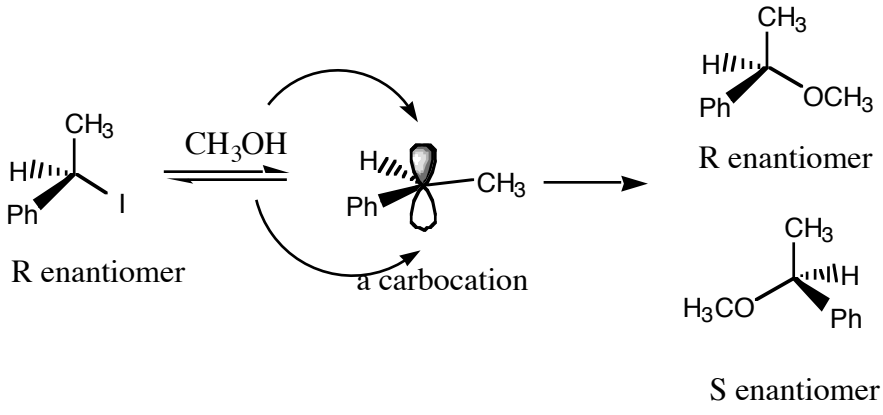


Some new Y values are for CF_3COOH (4.57) and CF_3CH_2OH (1.8). The higher value of trifluoroacetic acid with the adamantyl system shows that some backside assistance occures when t-buty chloride is the substrate.

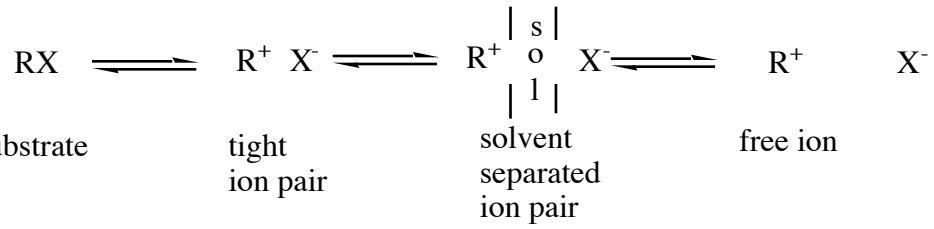
Bently and Schleyer in 1972 founded a method to determine the nucleoplicity (N) of a solvent. The N for several solvents is listed: CF_3COOH (-5.6), HCOOH (-3.0), H_2O (-.41), 20%EtOH (-.09). Larger values indicate more solvent nucleophilicity. Here 20% EtOH is the greatest.

Stereochemistry and Ion Pairs

The carbocation intermediate is a flat sp^2 hybrid with a vacant p orbital. Nucleophiles could be expected to attact the p orbial equaly from the top or bottom. If a chiral substrate were used, the expected product would be racemic as shown below. The example shows a secondary substrate with R configuration giving a planar carbocation that is attacked by the solvent to give the R and S product mixture (after loss of a proton).



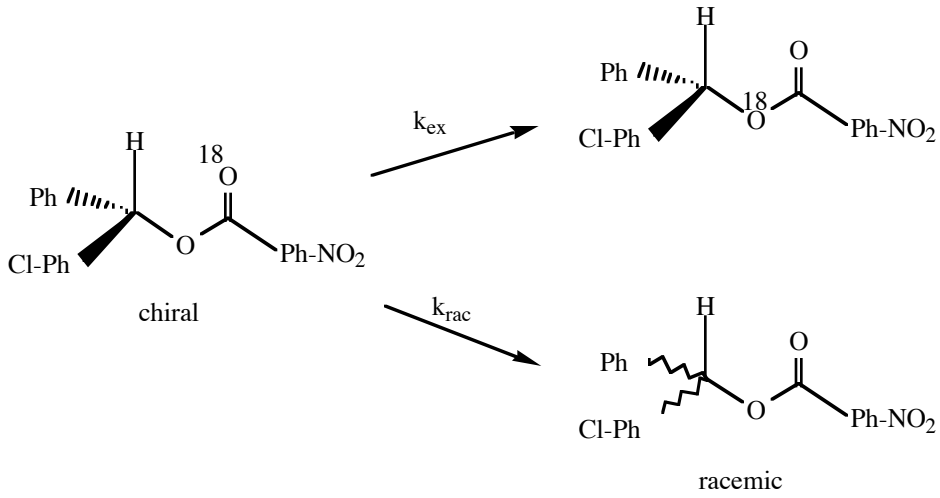
The example above is often presented as the final story in undergraduate organic chemistry. But, many carbocation reactions with chiral substrates give products that show some of inversion of configureation and sometimes retention of configuration during the process. These observations give rise to a more detailed description of the carbocation intermediate as existing as a series of ion pairs. The substrate first solvates into tight ion pairs, then to solvated ion pairs, and finally to the free carbocation. It is only the free carbocation (shown above) that gives the racemization reaction. The ion pairs require different stereochemical outsomes depending on the reaction condition, and many S_N1 reactions occur from the ion pairs before the free ion is formed.



Some experimental evidence for the ion-pair scheme follows.

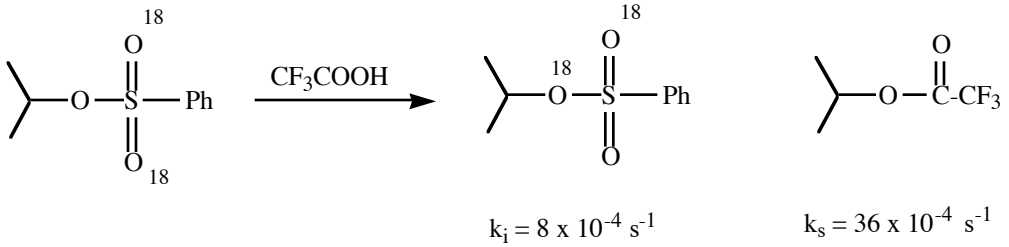
1. $LiCLO_4$ added to the reaction increases the rate. This happens because the perchlorate is a poor nucleophile and slows substitution and at the same time it gets into the solvent separated ion and stabilizes it by polar interaction.

2. The substrate below gives starting product from internal return. The O-18 exchanges occurs in the tight ion-pair to give the rearranged product with retained configuration, while the racemization occurs in the free ion.



3. The addition of NaN_3 give an azide product with inverted configuration. This occurs from backside attack on the solvent separated ion-pair.

The secondary isopropyl substrate below in the highly ionizing solvent trifluoroacetic acid give products from both solvolysis and internal return. The internal return occurs within the tight ion pair while the trifluoroacetate occurs from the free or solvent separated ion.



$k_i = 8 \times 10^{-4}\ s^{-1}$ $k_s = 36 \times 10^{-4}\ s^{-1}$

$k_s / k_i = 4.5$

The Chemistry of Carbocations

Reactions that proceed by S_N1 or E1 mechanisms are reactions that involve carbocation intermediates. The study of carbocation intermediates involves learning about the factors that influence the stability (or instability) of the intermediate. In some cases this becomes interesting from the academic view of learning about reaction mechanisms and in some cases practical synthetic procedures result.

Substituent Effects on Carbocations

The cationic charge is stabilized by substituents that can donate electrons to help reduce the localized charge. Thus any substituent or function that contains non-bonding p electrons or contains pi electrons can stabilize a carbocation. The structures below show how different functions can stabilize a carbocation.

A fluorine atom alpha to a carbocation center is stabilizing. The 6 non-bonding electrons on the F are in 2p orbitals that are of the correct size to overlap with the 2p cationic site. The stabilizing effect is more noted as a directing effect than as a rate enhancing effect. Fluorine atoms beta to a carbocation center are strongly destabilizing and simple beta fluoroalkyl carbocations are unknown. Fluorne atoms more remote from the cationic center, especially in the beta position are very destabilizing.Thus fluorine atoms destabilze the tripheny cation system and slow the solvolysis of benzylic tosylates as shown below. But examples are alpha stablization are well know and are used to control some carbocation reactions as is also shown below. (Banks, Smart, Tatlow, Organofluorine Chem. 1994).

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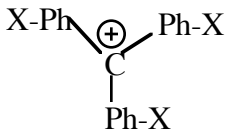
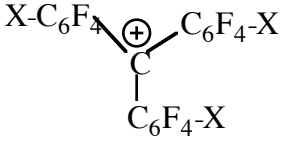


X	pK_R
H	-6.6
CH_3	-3.6
NO_2	-16.2
OCH_3	+0.8
$(CH_3)_2N$	+9.4
$PhCH_2^{\oplus}$	-20
$Ph_2CH^{\oplus}$	-13.3
F	-17.7
CF_3	-26

larger positive pK_R is more stable cation



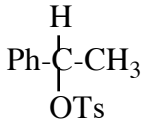
benzylic
allylic $> 3^0 > 2^0 >$ $Ph^{\oplus}$ $C{=}C^{\oplus}$ XX $1^0 >$ $CH_3^{\oplus}$

$NH_2 > CH_3O > OH > Ph > CH_3 >> F$; $CN > C{=}O >> NO_2$

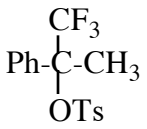
$CH_3\overset{\oplus}{O}\text{-}CH_2 \longleftrightarrow CH_3O{=}\overset{\oplus}{C}H_2$

$CH_3\overset{\oplus}{C}H\text{-}F \longleftrightarrow CH_3CH{=}\overset{\oplus}{F}$

Fluorine alpha to a carbocation stabilized the carbocation in a manner similar to oxygen stabilization.



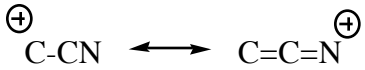
rel rate 10^5

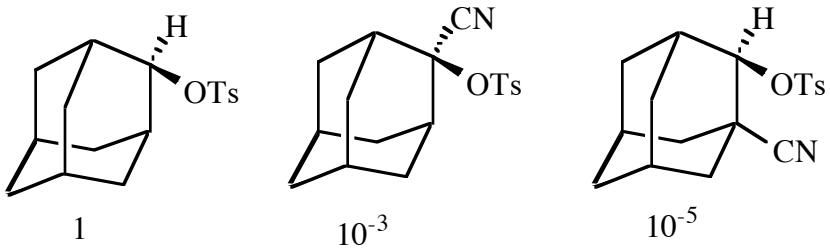


rel rate 1

unfavorable β influence of fluorine atoms

$\overset{\oplus}{C}H\text{-}C{=}O \longleftrightarrow CH{=}C\text{-}O^{+}$ not good

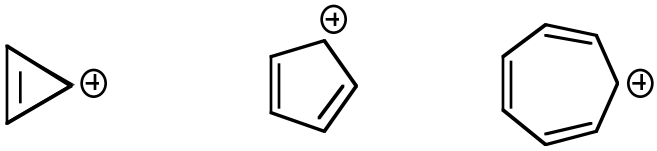




1 10^{-3} 10^{-5}

CN destabilizes cation but offers some assistance when alpha by resonance.

Aromatic cations (4N + 2)

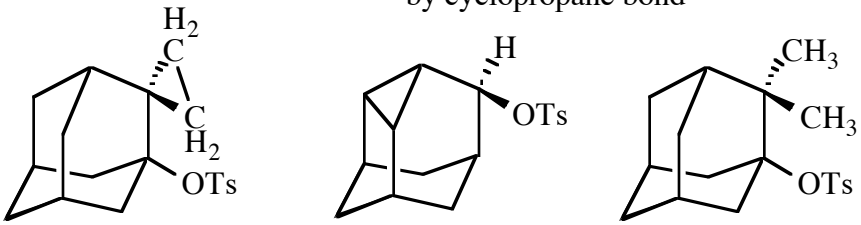


2e (aromatic) 4e 6e (aromatic)

Cyclopropyl Carbinyl Cation

perpindicular bisected

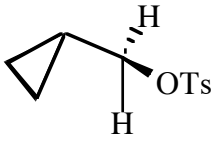
good overlap and stabilization by cyclopropane bond



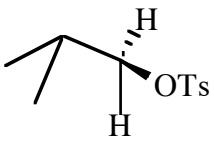
1 10^5 300

The effect of fluorine on the cyclopropyl carbinyl system is shown below. The cyclopropyl carbinyl system was frequently studied during the early days of studies of classical versus non-classical carbocations. Recently studies of a difluoro derivative show

some interesting results. The relative rates of solvolysis of the parent system, the isobutyl system and the difluoro system show that the two fluorine atoms on the cyclopropane ring slow the rate of solvolysis.



10^5



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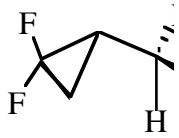
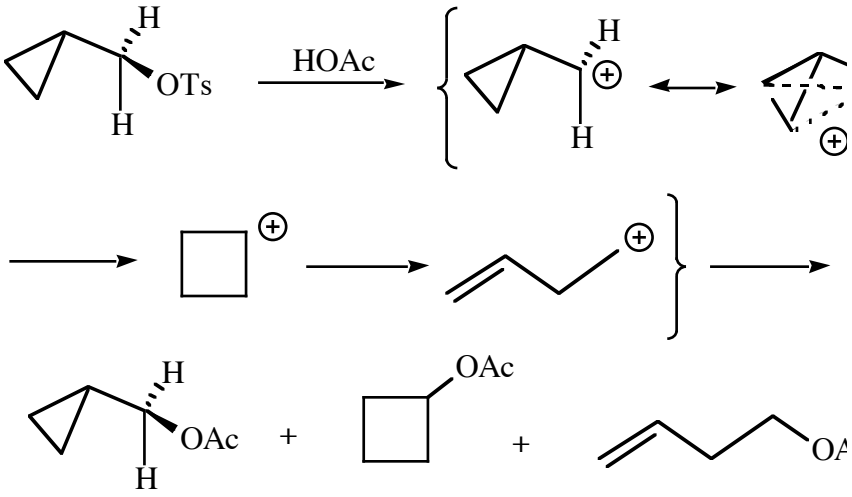
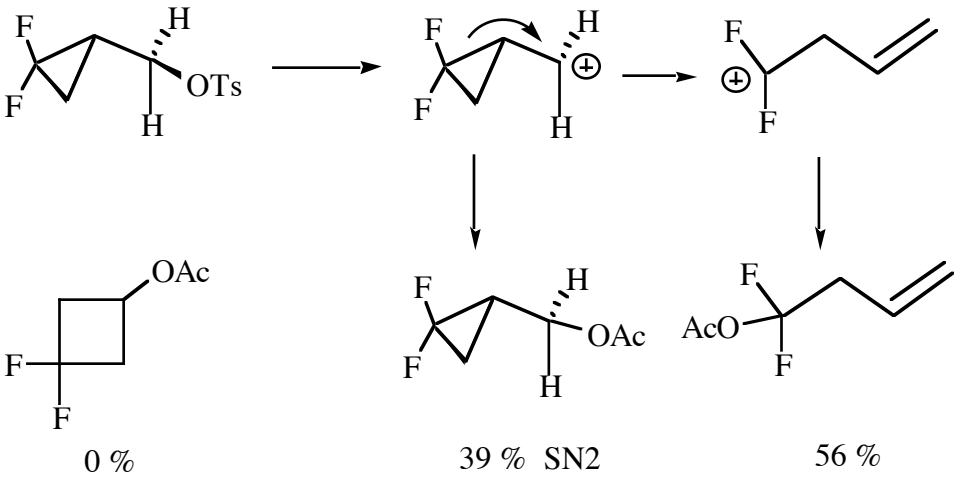


1.8

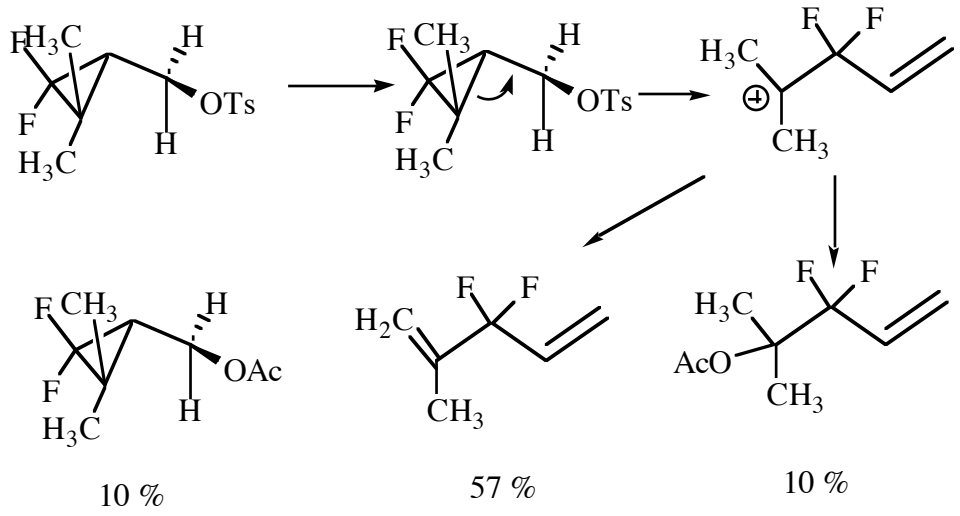
In the parent system usually three products are observed as shown below.



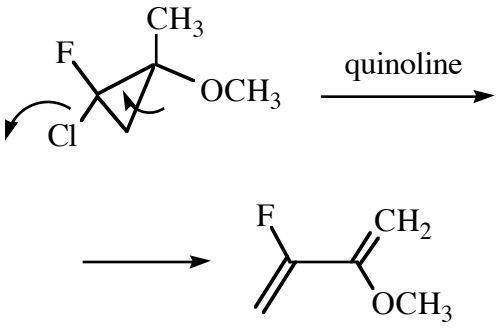
In the difluoro system only two products are observed and the one with the cyclopropane ring intact occurs mainly from SN2 attack on the primary carbon. The difluoro alkene shows the strong directing effect of the fluorine atom on the carbocation, but the first order rate constant for solvolysis is about 2 x 10^{-5} sec^{-1}, which is about10^5 smaller than the parent hydrogen system. The absence of the cyclobutyl product shows the strong destabilization of the fluoine atoms on the beta or gamma carbocation.



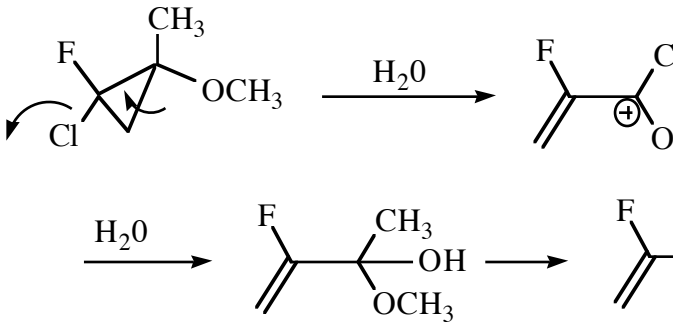
As methyl groups are added adjacent to the difluoro function, solvolytic ring opening shows competition between formation of the difluoro cation and the alkyl cation. With two methyl groups the tertiary alkyl cation system dominated the ring opening. But still no cyclobutyl cations are observed. (Dolbier, CR, 2003)



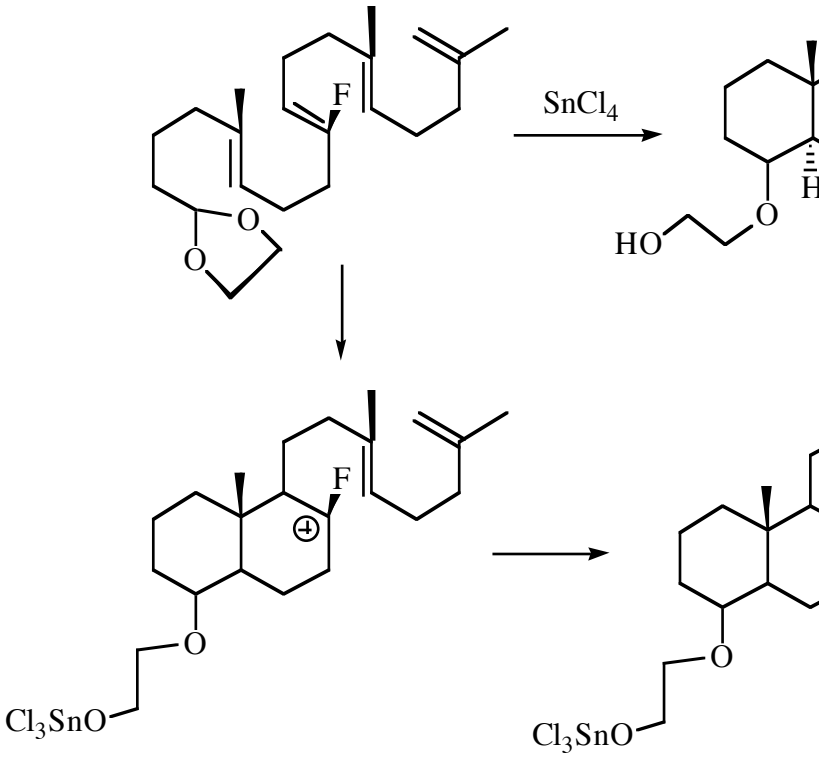
Ionization of the chlorofluoro cyclopropane produces the fluoroallylic cation that elimiantes a proton to give a diene. The fluorine atom is beta to the cationic site in this case but apparently it influence is minimal as proton loss is fast.



When the ionization is performed in aqueous medium the cation is trapped by the water to give an alpha, beta unsaturated fluoro ketone.

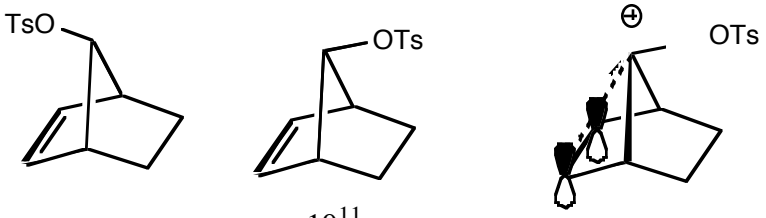


Placement of a fluorine atom at a strategic position in the t
allows acid-catalyzed cyclization to proceed to the final product ir
Without the fluorine atom only low yields of tetracyclic product a
fluorine atom directs the positive charge to the position shown be
fluorine stabilization, and the cyclization proceeds very well. (Joh
1999).



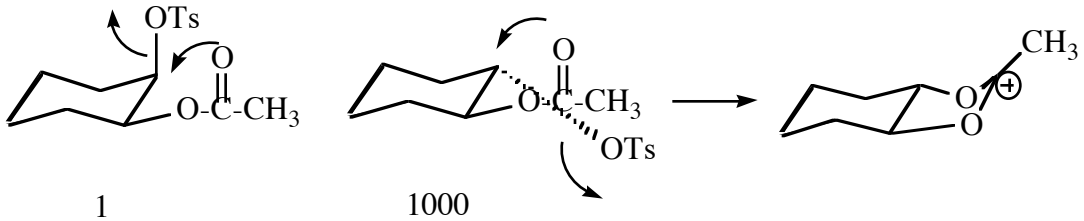
Neighboring groups and Rearrangements

Case 1. The exo bicyclic tosylate undergoes solvolysis 10^{11} times faster than the endo isomer. The happens because the pi bond assists the formation of the carbocation. The assistance is much better from the backside of the tosyl group.



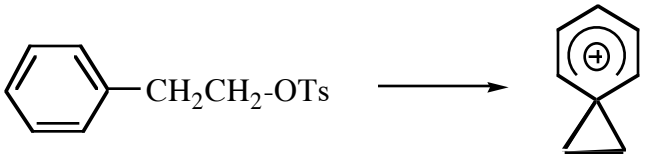
1 10^{11}

Case 2. The trans tosylate undergoes solvolysis 1000 times faster than the cis isomer. the non bonding electrons of the carbonyl group assist the formation of the developing charge, and again the assistance is much better from the backside of the leaving group.

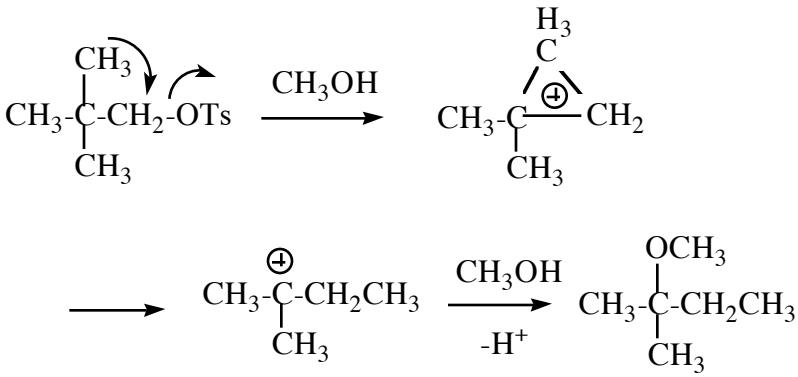


1 1000

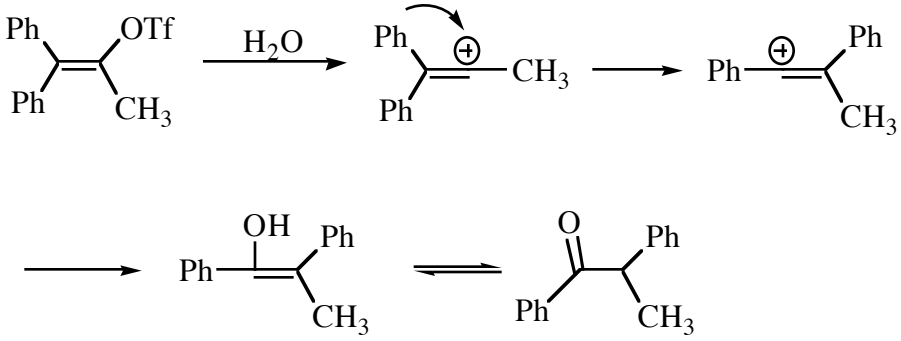
Case 3. Although primary cations are not formed in solvolysis reactions, neighboring groups can assist the solvolysis of a primary substrate in a synchronous step to form a stable carbocation. Rearrangement occurs in beta pheny substrates because the phenyl group donates electrons, from the backside, to give a stable cyclic phenonium ion.



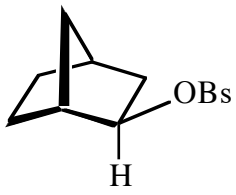
Case 4. The neopentyl system , another primary substrate, rearranges rapidly to give the product shown. The methyl group assists the formation of a charge in a cyclic ion to give the more stable tertiary carbocation.



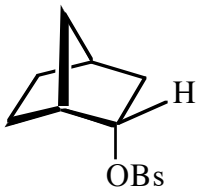
Case 5. Thus shows the uncommon case of a vinyl cation that can be formed by solvolysis because ot the good leaving group triflate. The phenyl group migrates to give a more stable benzylic-type ion.



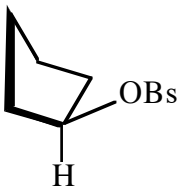
Norbornyl Systems



350 exo

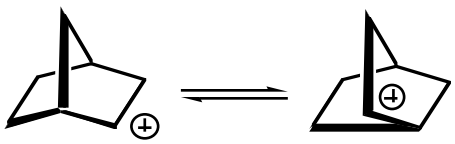


1 endo

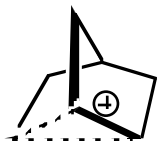


0.3

Only exo products are obtained on solvolysis.

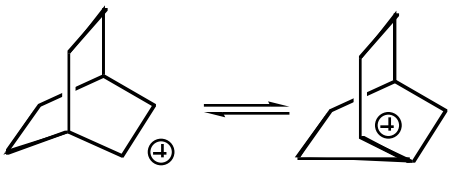


classical



non-classical

Observed by C NMR

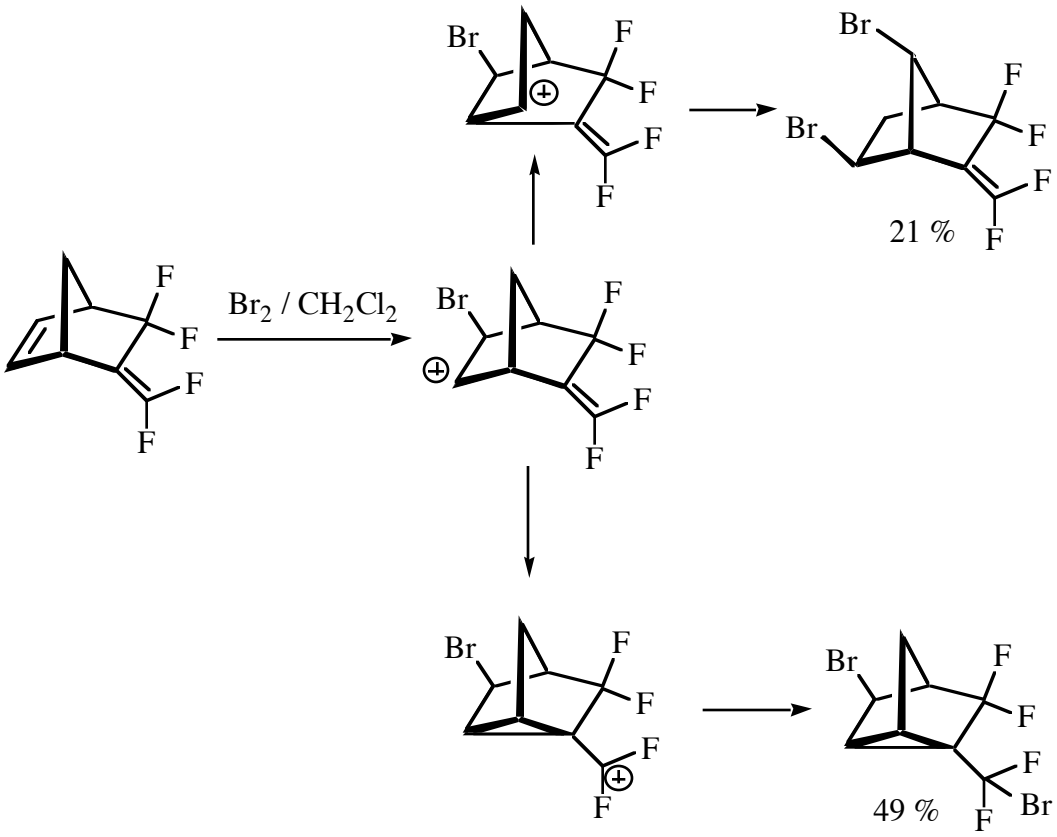


chiral

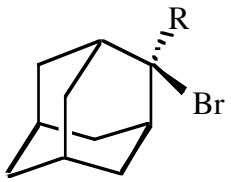
achiral

Chiral substrate give achiral product.

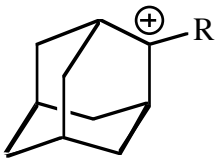
The fluorinated norbornyl system shown below undergoes rearrangement on treatment with Br_2 under ionic conditions. The product produced in 49% yield shows the influence of the fluorine atoms of the exocyclicdifluoro ethylene function by donating the pi electrons in order to achieve a fluorine stabilized carbocation that reacts with bromide ion. (Smart, JOC, 831, 1974).


Br
F
F
F
F
Br
F
F
F
F
21 %
F
Br2 / CH2Cl2
F
F
F
F
Br
F
F
F
F
Br
F
F
F
F
Br
F
F
F
F
Br
49 %
F
Br

Steric Effects

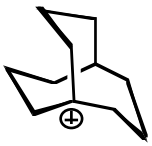
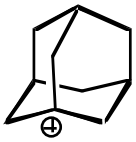
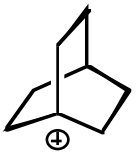
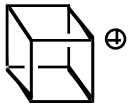


R	k_R / k_H	$k_{CH3} / k_H = 10^8$
CH_3-	1	
CH_3CH_2-	7	
$CH_3-C(CH_3)_2-CH_2$-	10	
$CH_3-CH(CH_3)-CH_2$-	33	
$CH_3-C(CH_3)_2$-	2×10^5	



Demonstrates relief of back strain to become flat ion.

Bridgehead Cations

	ΔG kcal/mol (hydride transfer)	k solvolysis Ms^{-1}
	11 kcal/mol	
	5	OTs 10^{-3}
	-10	OTs 10^{-7}
	-18	OTf 10^{-4} JACS, 1990, 112, 3225
	-26	OTs 10^{-13} OTf 10^{-11}
	-35	

JOC, 1999, 64, 6401