# Instituto de Química – USP
# Fundamentos

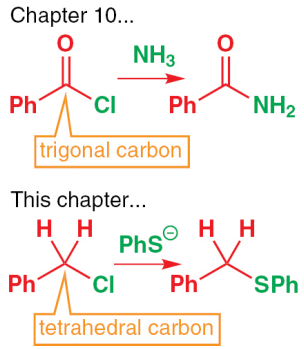
## Aula 3. Substituição Nucleofílica Alifática (SN1 e SN2)

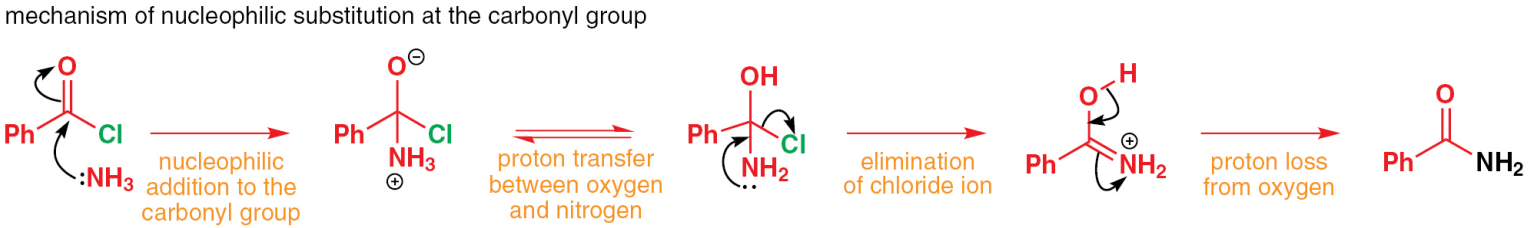
# Literatura

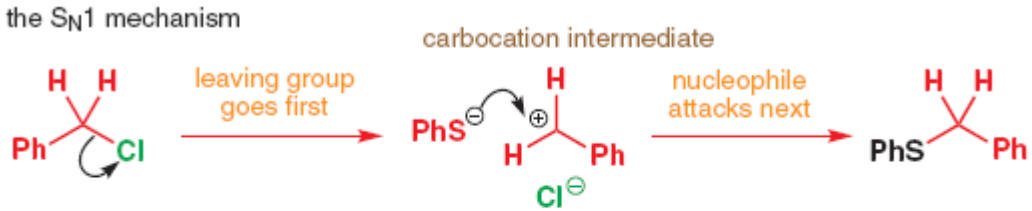
**Leitura recomendada.** Clayden, Greeves, Warren, Wothers, 2ª edição, cap. 15, 16

## Substituição acílica e alifática

- Reações substituição ocorrem em derivados de ácido carboxílico e em compostos alifáticos com grupos abandonares.

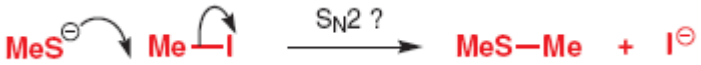


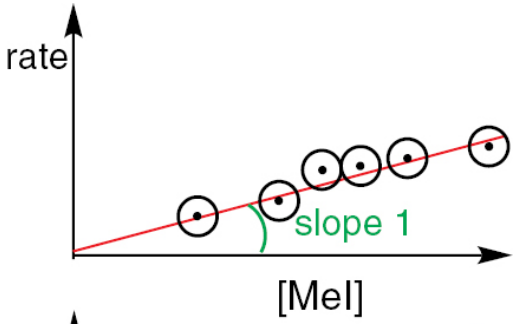




## Substituição Nucleofílica

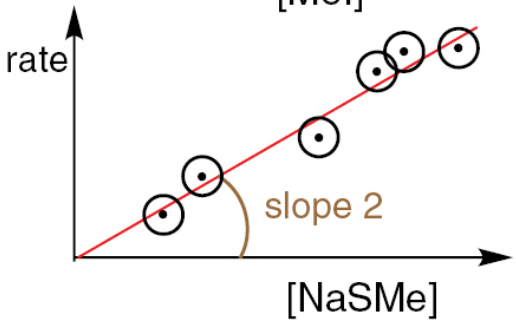
- Há dois tipos de substituição nucleofílica ao carbono saturado, a de primeira ordem ($S_N1$) e a de segunda ordem ($S_N2$).
- Na reação $S_N2$ a velocidade da reação depende da concentração do substrato e do nucleófilo.




v = k[NaSMe][MeI]



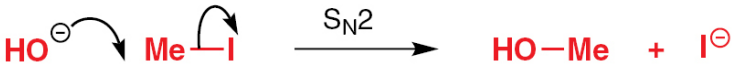

v = k'[MeI]
[NaSMe]>>[MeI]




v = k''[NaSMe]
[MeI]>>[NaSMe]

## $S_N2$ | Evidências experimentais

- A velocidade da reação depende da natureza do grupo abandonador.




rate = $k_2$ [NaOH] [MeI]

| Halide X in MeX | p$K_a$ of conjugate acid HX | Rate of reaction with NaOH |
|---|---|---|
| F | +3 | very slow indeed |
| Cl | –7 | moderate |
| Br | –9 | fast |
| I | –10 | very fast |

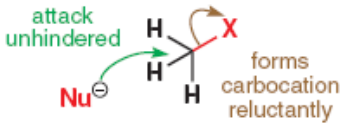
- A velocidade da reação depende da natureza do nucleófilo.

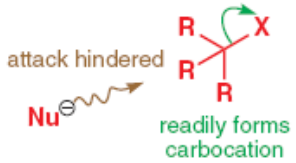
| Oxygen nucleophile | p$K_a$ of conjugate acid[a] | Rate in $S_N2$ reaction |
|---|---|---|
| $HO^-$ | 15.7 ($H_2O$) | fast |
| $RCO_2^-$ | about 5 ($RCO_2H$) | reasonable |
| $H_2O$ | –1.7 ($H_3O^+$) | slow |
| $RSO_2O^-$ | 0 ($RSO_2OH$) | slow |

## $S_N2$ | Evidências experimentais

- A velocidade da reação depende da natureza do substrato.

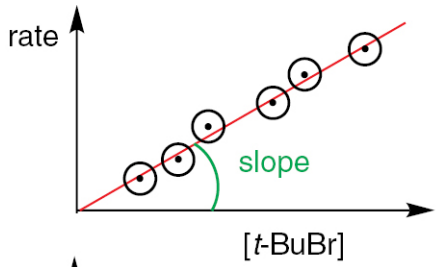
| Structure | Me—X | R, X, H, H | R, X, H, R | R, X, R, R |
|---|---|---|---|---|
| type | methyl | primary | secondary | tertiary |
| $S_N1$ reaction? | no | no | moderate | excellent |
| $S_N2$ reaction? | good | good | moderate | no |

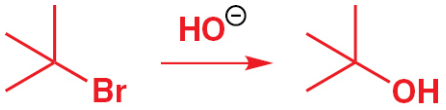


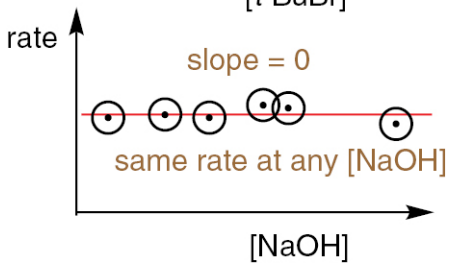
## $S_N1$ | Evidências experimentais

- A velocidade da reação depende da natureza do substrato, mas não do nucleófilo.




$v = k[t\text{-BuBr}]$

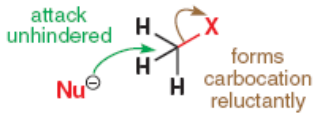


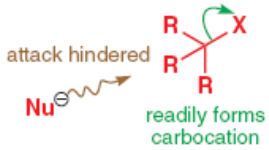

the $S_N1$ mechanism: reaction of *t*-BuBr with hydroxide ion


stage 1: formation of the carbocation


stage 2: reaction of the carbocation

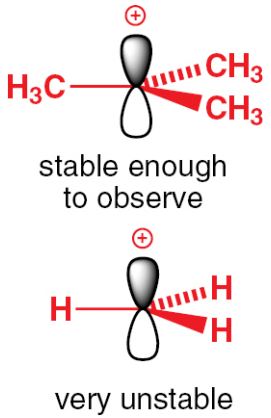
| Structure | Me—X | R X H H | R X H R | R X R R |
|---|---|---|---|---|
| type | methyl | primary | secondary | tertiary |
| $S_N1$ reaction? | no | no | moderate | excellent |
| $S_N2$ reaction? | good | good | moderate | no |

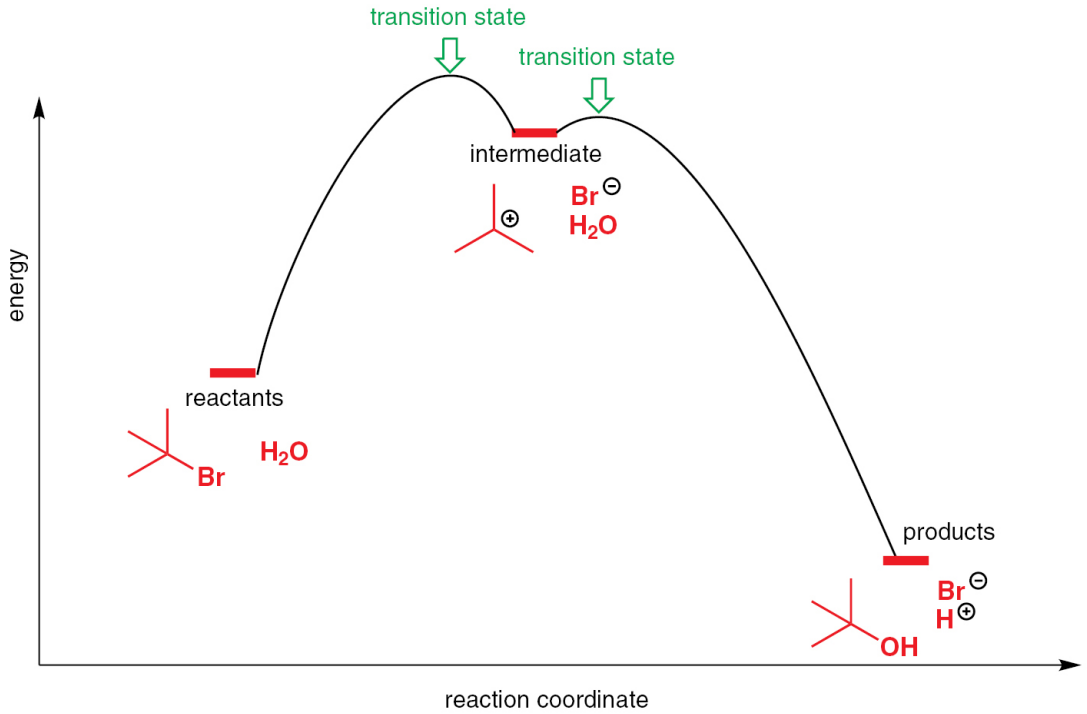


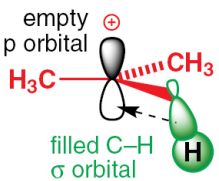



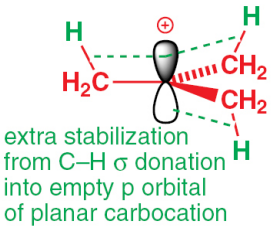
## $S_N1$ | Mecanismo

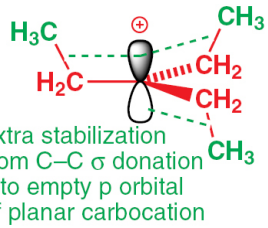
- Quanto mais estável o carbocátion formado, mais rápida a reação $S_N1$.
- Quanto mais substituído o carbocátion, mais estável: hiperconjugação.

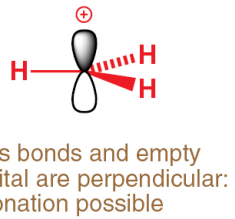


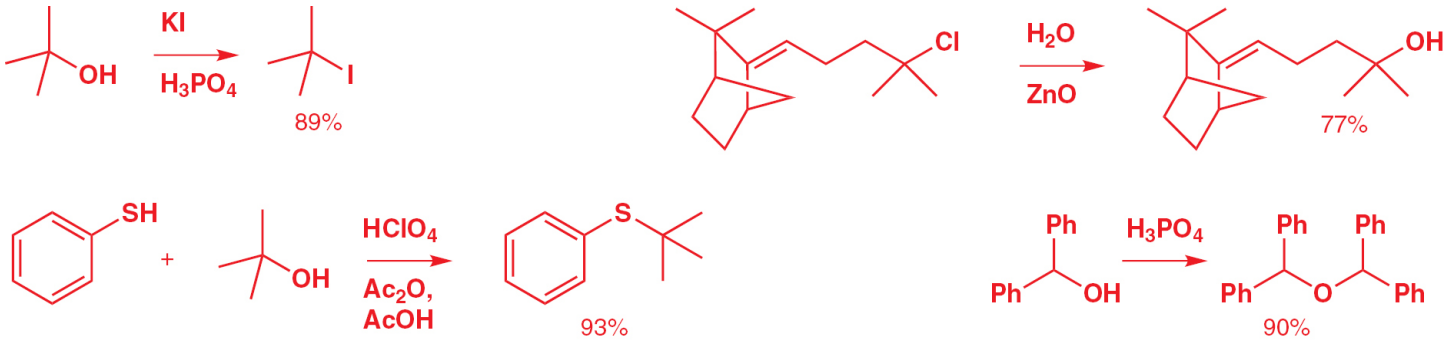



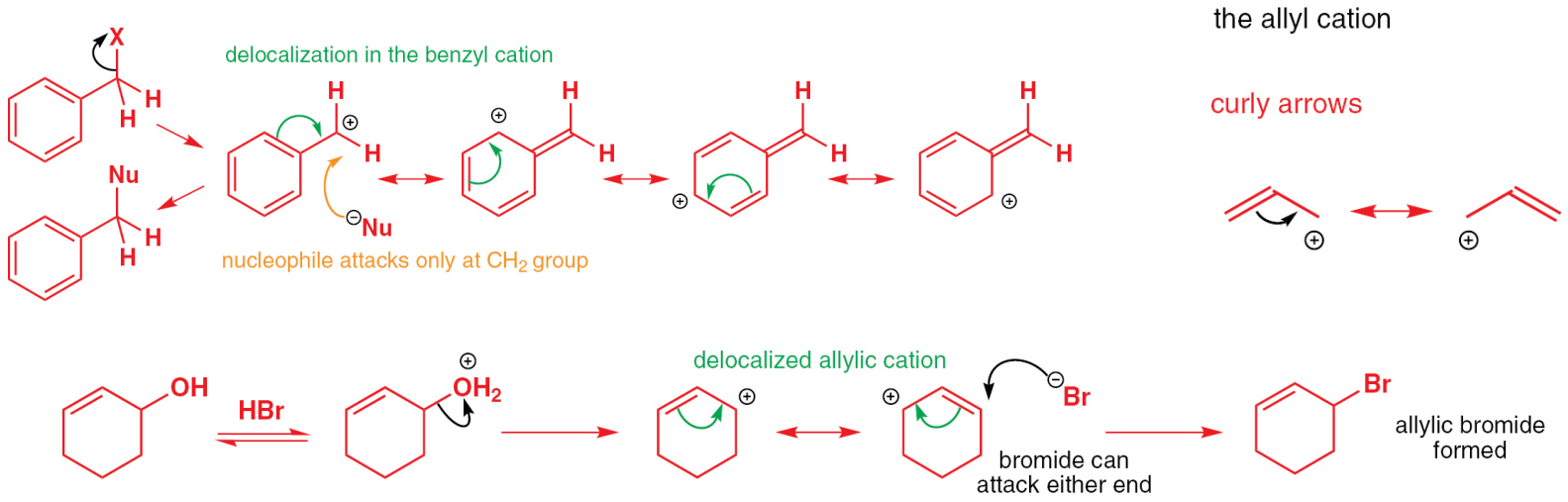



## $S_N1$ | Mecanismo

- Alguns exemplos de reações $S_N1$.

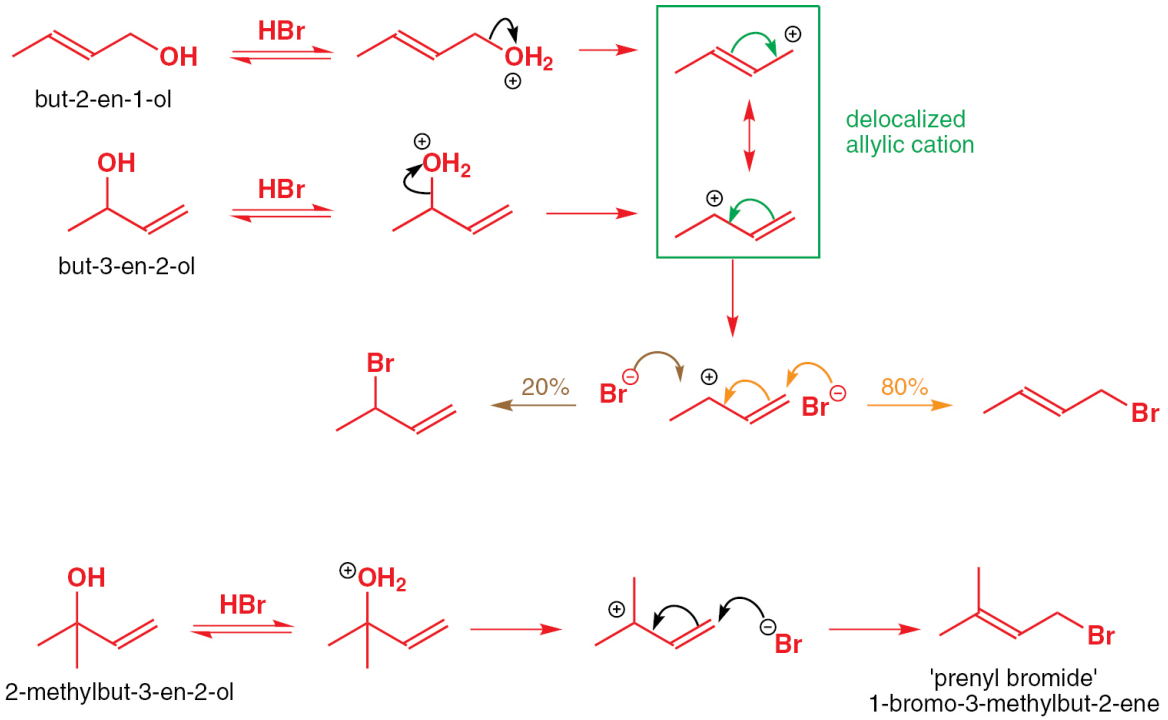



- Carbocátions podem ser estabilizados por ressonância.



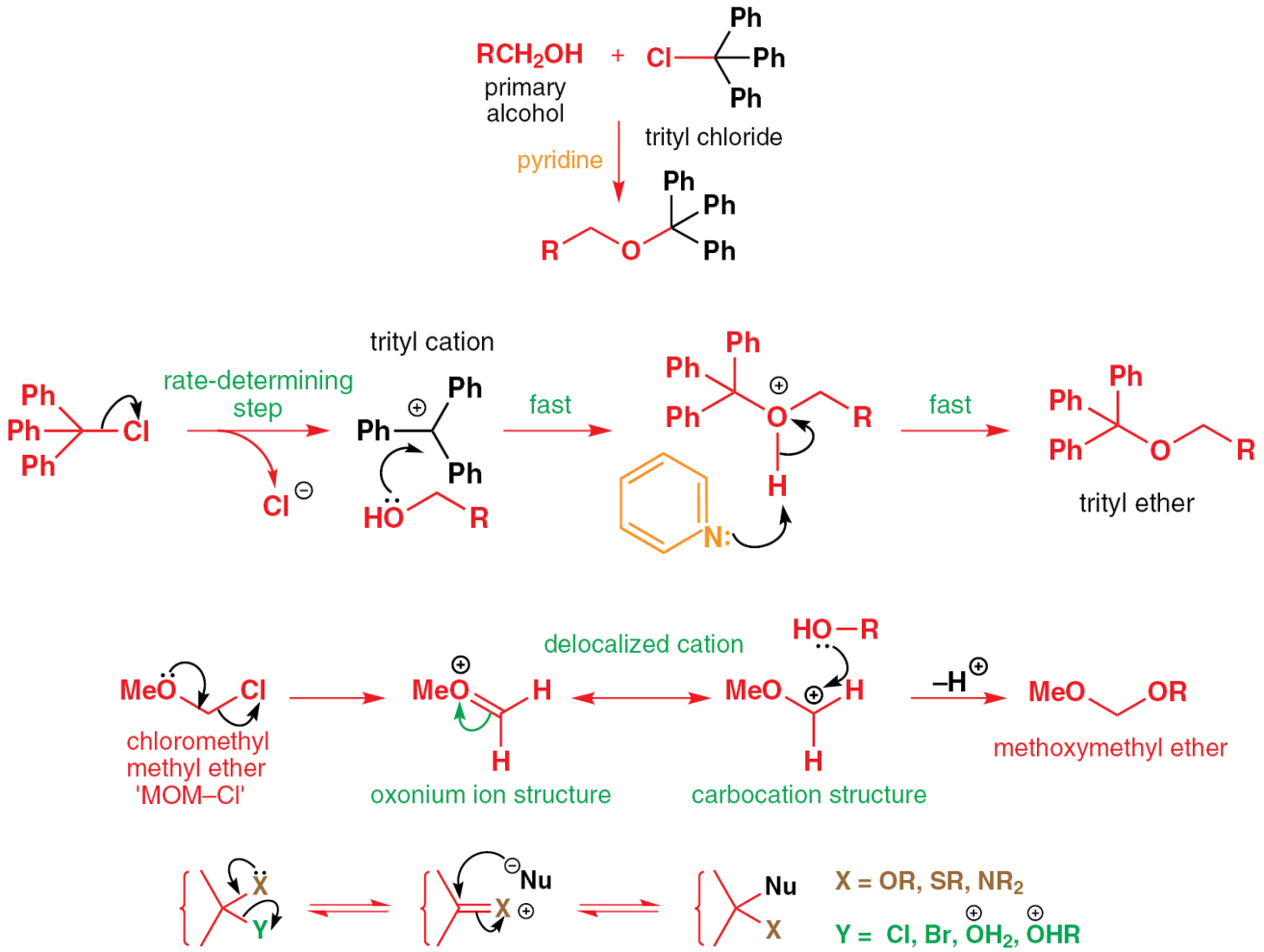
## $S_N1$ | Mecanismo

- Mais alguns exemplos de reações $S_N1$.



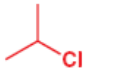
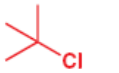
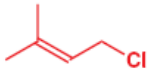
## $S_N1$ | Mecanismo

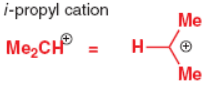
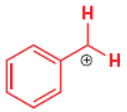
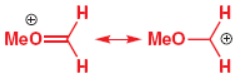
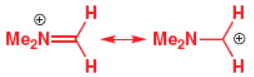
- Mais alguns exemplos de reações $S_N1$.



## $S_N1$ | Mecanismo

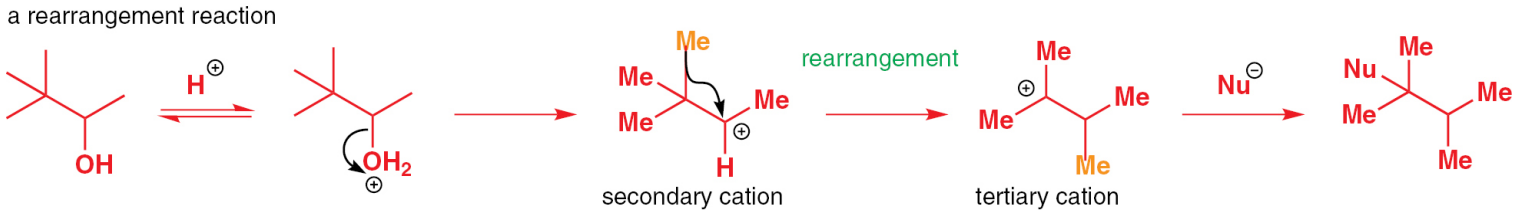
- Influência do substrato.

| Compound | Relative rate | Comments |
|---|---|---|
|  | 0.07 | primary chloride: probably all $S_N2$ |
|  | 0.12 | secondary chloride: can do $S_N1$ but not very well |
|  | 2100 | tertiary chloride: very good at $S_N1$ |
|  | 1.0 | primary but allylic: $S_N1$ all right |
|  | 91 | allylic cation is secondary at one end |
|  | 130000 | allylic cation is tertiary at one end: compare with 2100 for simple tertiary |
|  | 7700 | primary but allylic and benzylic |

| Type of cations | Example 1 | Example 2 |
|---|---|---|
| simple alkyl | tertiary (good)<br>*t*-butyl cation<br>  | secondary (not so good)<br>*i*-propyl cation<br>  |
| conjugated | allylic<br>  | benzylic<br>  |
| heteroatom-stabilized | oxygen-stabilized (oxonium ions)<br>  | nitrogen-stabilized (iminium ions)<br>  |

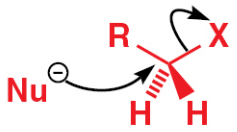
## $S_N1$ | Rearranjo

- Não se esqueça de que carbocátions podem sofrer rearranjo.

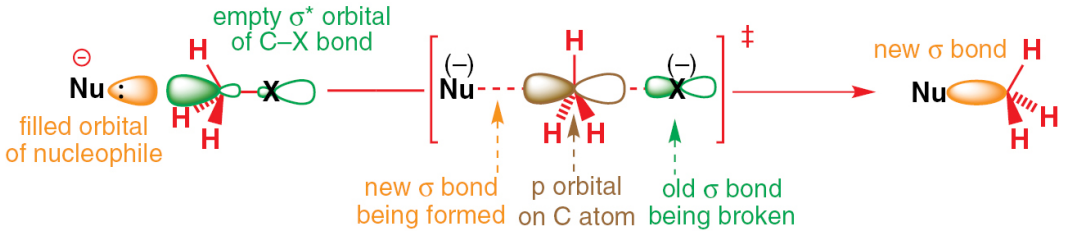


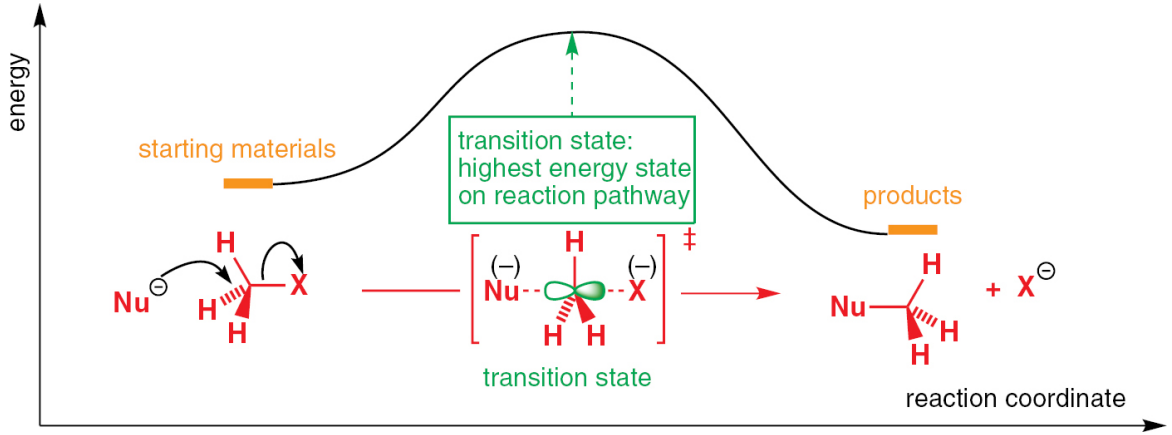
## $S_N2$ | Mecanismo

- Em uma reação SN2 o nucleófilo ataca o orbital LUMO da ligação C-X pelo lado oposto.

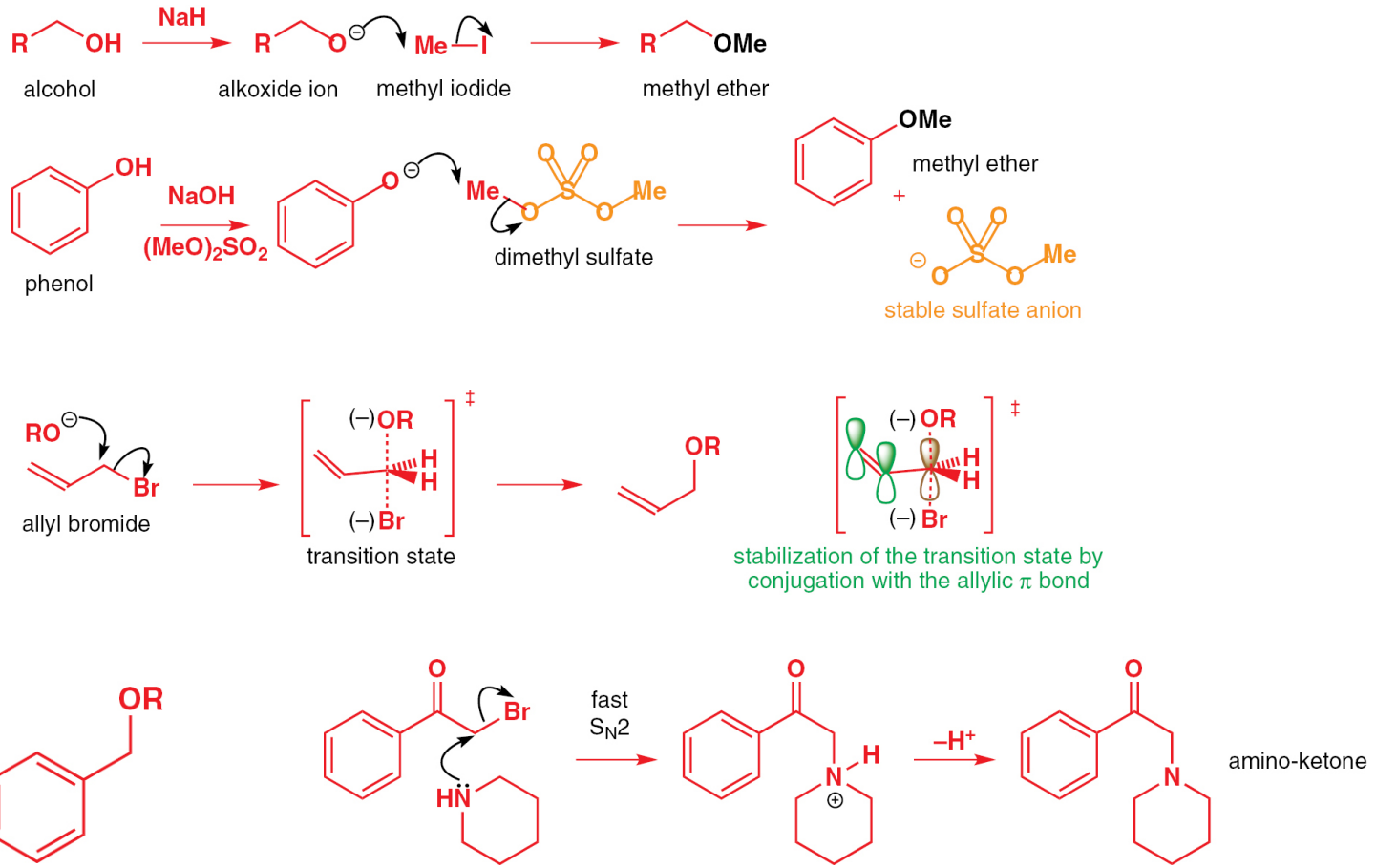



uncluttered approach of nucleophile in $S_N2$ reactions of methyl compounds (R=H) and primary alkyl compounds (R=alkyl)



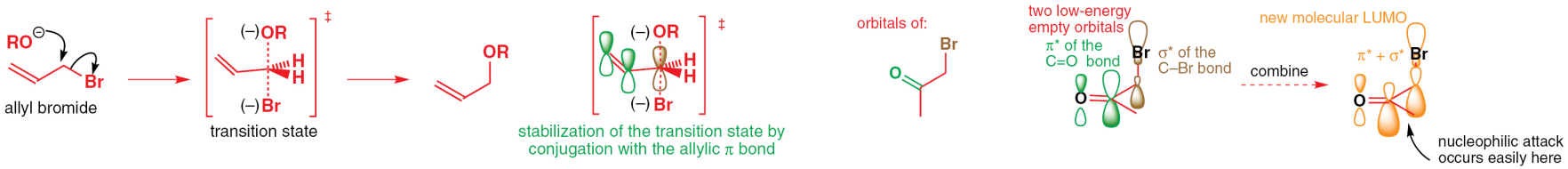



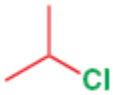
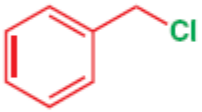
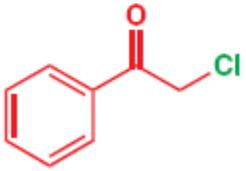
## $S_N2$ | Exemplos



## $S_N2$ | Mecanismo

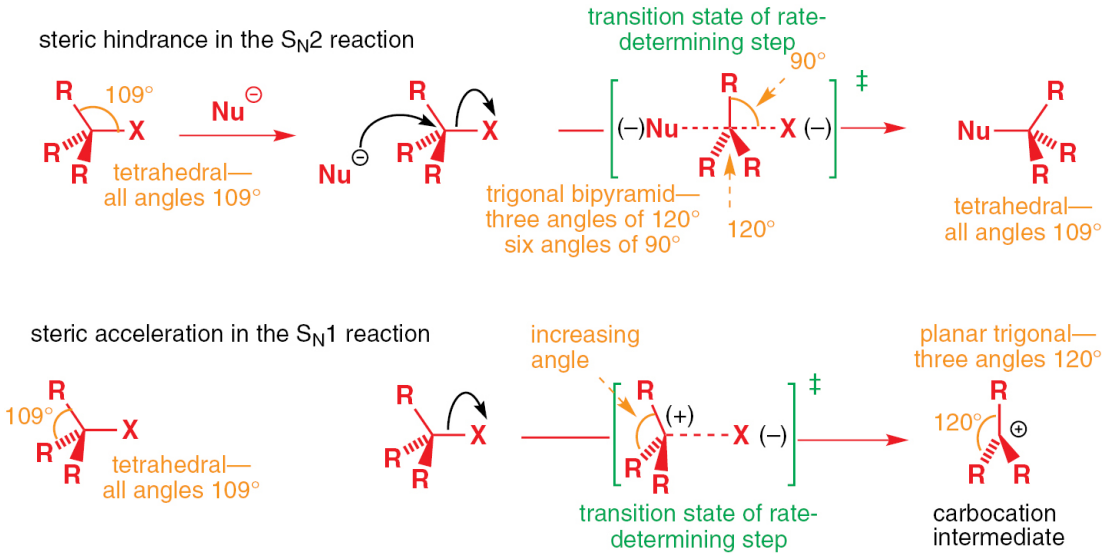
- Influência do substrato.




| Alkyl chloride | Relative rate | Comments |
|---|---|---|
| Me—Cl | 200 | least hindered alkyl chloride |
|  | 0.02 | secondary alkyl chloride; slow because of steric hindrance |
|  | 79 | allyl chloride accelerated by π conjugation in transition state |
|  | 200 | benzyl chloride a bit more reactive than allyl: benzene ring slightly better at π conjugation than isolated double bond |
|  | 920 | conjugation with oxygen lone pair accelerates reaction (this is an $S_N1$ reaction) |
|  | 100,000 | conjugation with carbonyl group much more effective than with simple alkene or benzene ring; these α-halo carbonyl compounds are the most reactive of all |

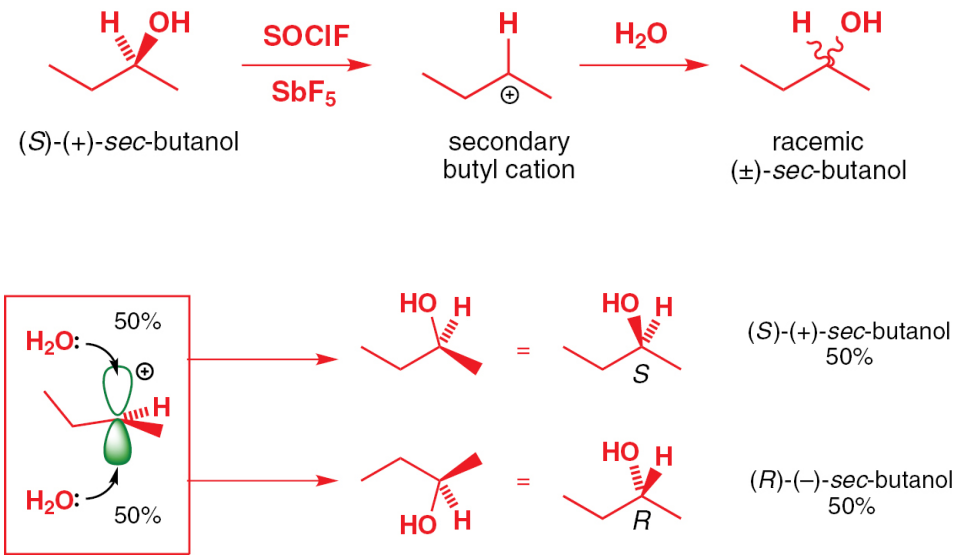
## $S_N1$ vs. $S_N2$ | Substrato

- Impedimento estérico aumenta a energia de ativação da reação.
- Este fator explica a variação de mecanismo com a mudança do substrato.



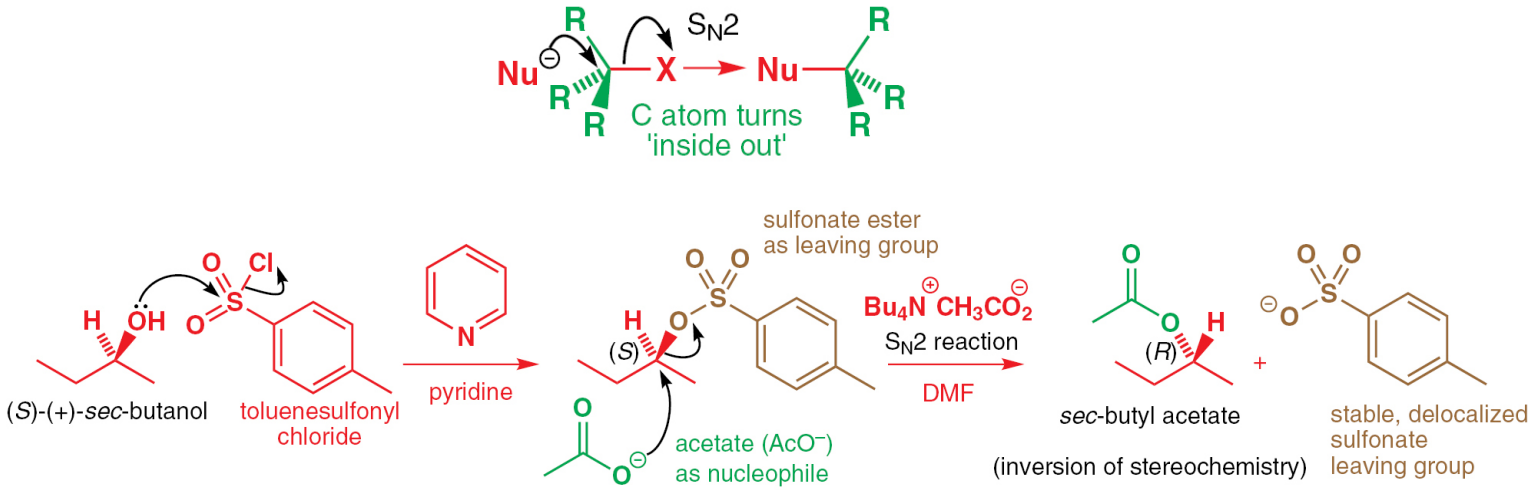
## $S_N1$ vs. $S_N2$ | Estereoquímica

- $S_N1$ ocorre com racemização.



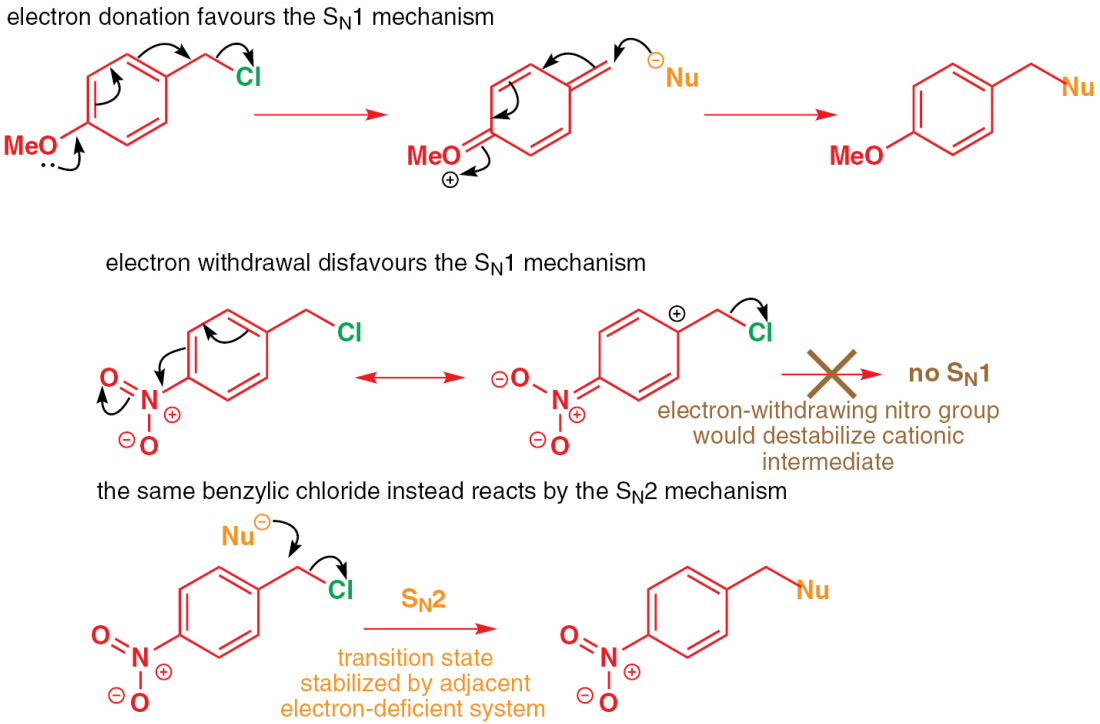
## $S_N1$ vs. $S_N2$ | Estereoquímica

- $S_N2$ ocorre com inversão de configuração.

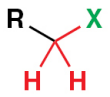


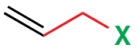
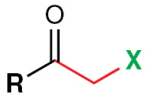
## $S_N1$ vs. $S_N2$ | Efeito eletrônico

- Grupos doadores de elétrons favorecem $S_N1$, grupos sacadores, $S_N2$.



## $S_N1$ vs. $S_N2$ | Resumo da influência do substrato

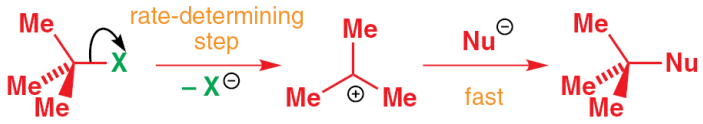
| Electrophile |  |  |  |  |
|---|---|---|---|---|
| | methyl | primary | secondary | tertiary |
| $S_N1$ mechanism? | bad | bad | poor | excellent |
| $S_N2$ mechanism? | excellent | good | poor | bad |

| Electrophile |  |  |  |  |
|---|---|---|---|---|
| | allylic | benzylic | α-alkoxy (adj. lone pair) | α-carbonyl |
| $S_N1$ mechanism? | good | good | good | bad |
| $S_N2$ mechanism? | good | good | okay but $S_N1$ better | excellent |

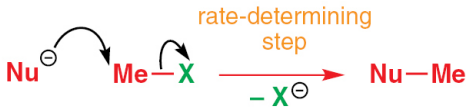
## $S_N1$ vs. $S_N2$ | Grupo abandonador

- Para ambas as reações, a saída do grupo abandonador é a etapa lenta.
- Quanto mais fraca a base, melhor o grupo abandonador.

The leaving group in the $S_N1$ reaction




The leaving group in the $S_N2$ reaction

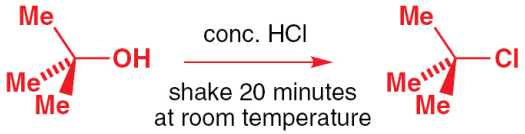



| Halide (X) | Strength of C–X bond,[1] kJ mol⁻ | p$K_a$ of HX |
|---|---|---|
| fluorine | 118 | +3 |
| chlorine | 81 | –7 |
| bromine | 67 | –9 |
| iodine | 54 | –10 |

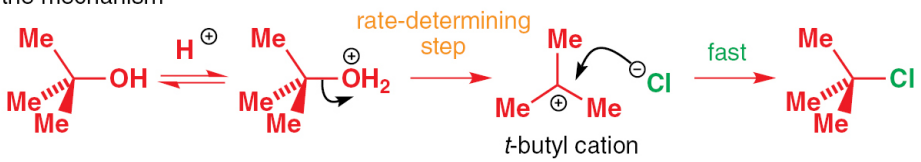
$S_N2$ displacement of hydroxide never happens...


*If* the nucleophile reacts, it attacks the *proton* instead

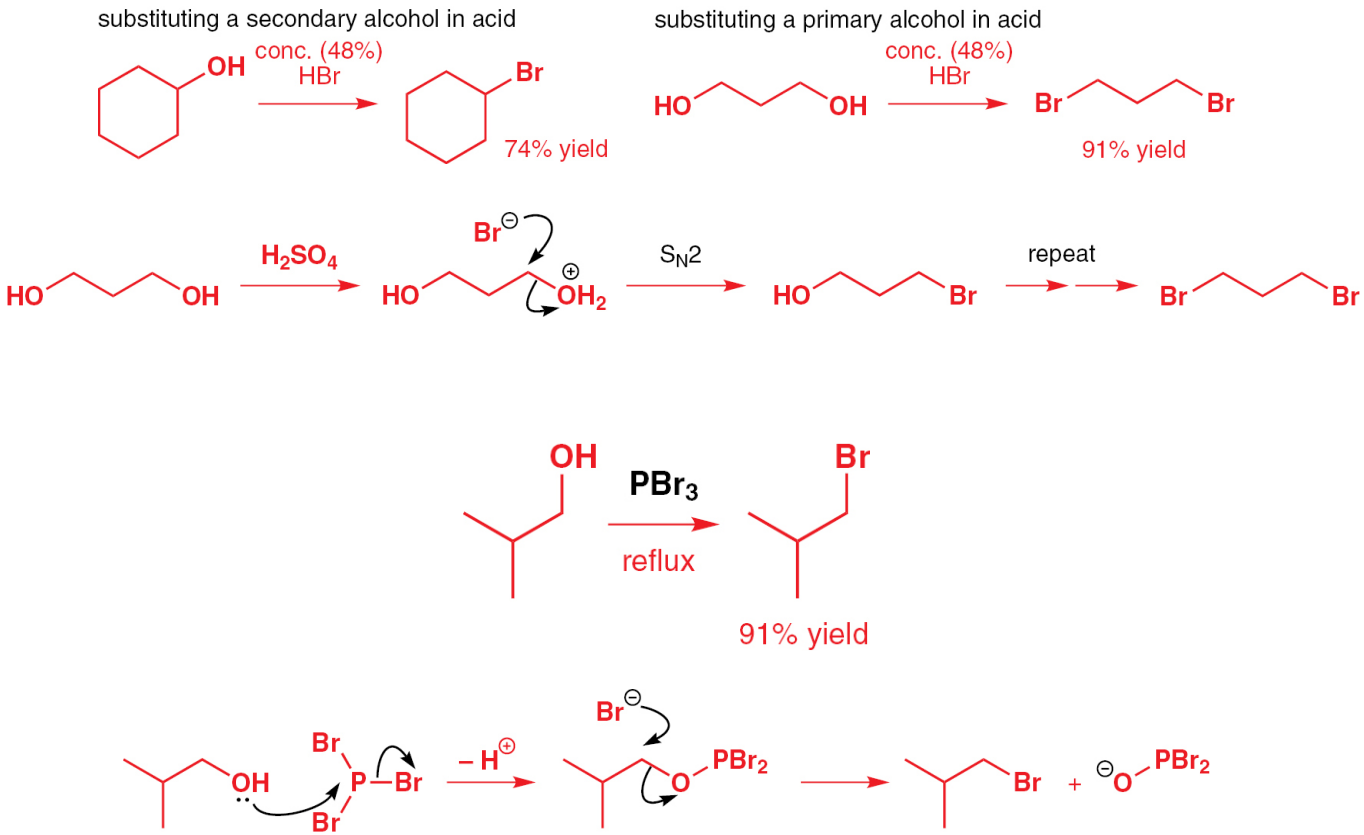

*t*-butyl chloride from *t*-butanol




the mechanism

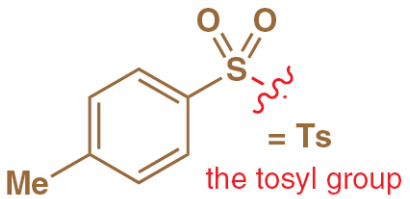


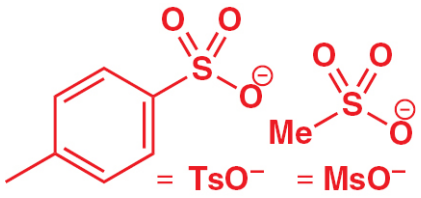
## Haletos de alquila



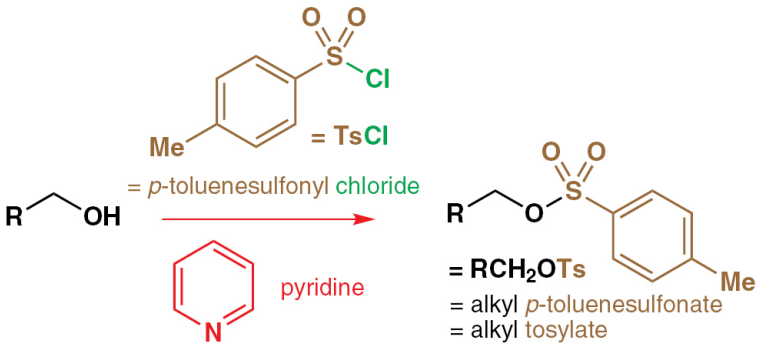
## Outros grupos abandonadores

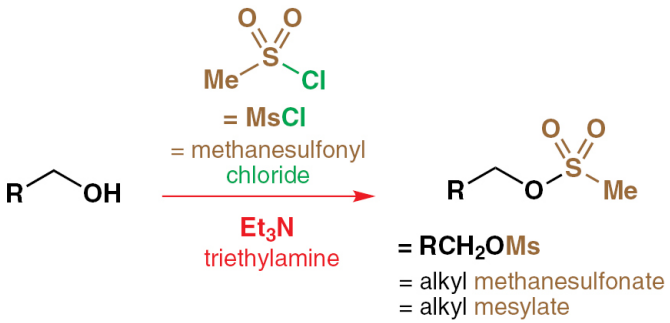
- O grupo tosila (Ts) e mesila (Ms) são grupos abandonadores excelentes.



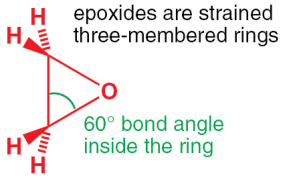

tosylate and mesylate:
excellent leaving groups

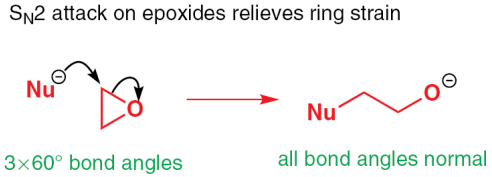


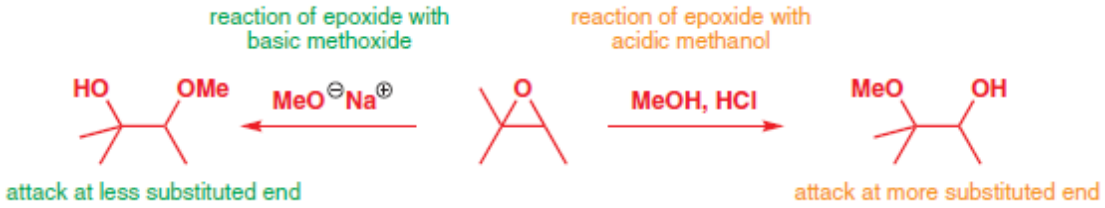



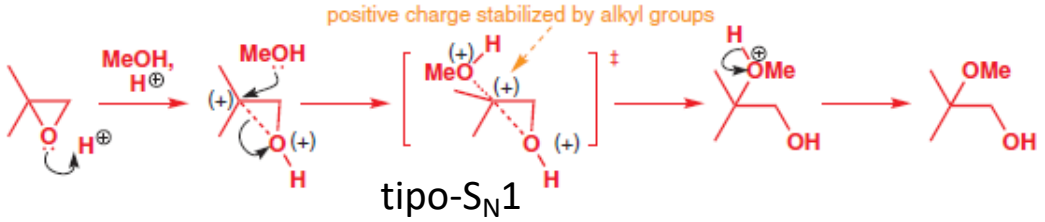
## Outros grupos abandonadores

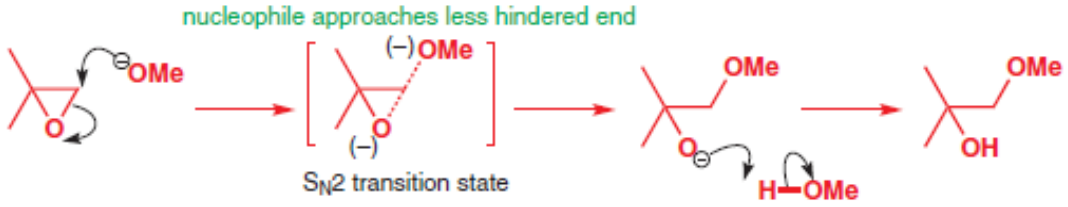
- Epóxidos.



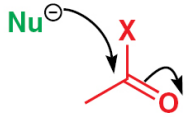



## $S_N2$ | Nucleófilo

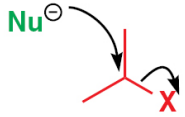
- Geralmente, quanto mais básico o nucleófilo, mais nucleofílico. Isso é verdade quando se comparam nucleófilos do mesmo período da tabela periódica.
- Na família, quanto mais mole e polarizável o nucleófilo, mais nucleofílico.

p$K_a$ of HNu is a good guide to the rate of this sort of reaction




nucleophilic attack on C=O

but the story with this sort of reaction is more complicated

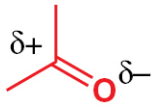



nucleophilic substitution at saturated C

| Nucleophile X | p$K_a$ of HX | Relative rate |
|---|---|---|
| $HO^-$ | 15.7 | $1.2 \times 10^4$ |
| $PhO^-$ | 10.0 | $2.0 \times 10^3$ |
| $AcO^-$ | 4.8 | $9 \times 10^2$ |
| $H_2O$ | −1.7 | 1.0 |
| $ClO_4^-$ | −10 | 0 |

Electronegativities:

C: 2.55 I: 2.66 Br: 2.96 O: 3.44




considerable polarization in the C=O group


much less polarization in the C–Br bond

| Nucleophile X | p$K_a$ of HX | Relative rate |
|---|---|---|
| $PhS^-$ | 6.4 | $5.0 \times 10^7$ |
| $PhO^-$ | 10.0 | $2.0 \times 10^3$ |

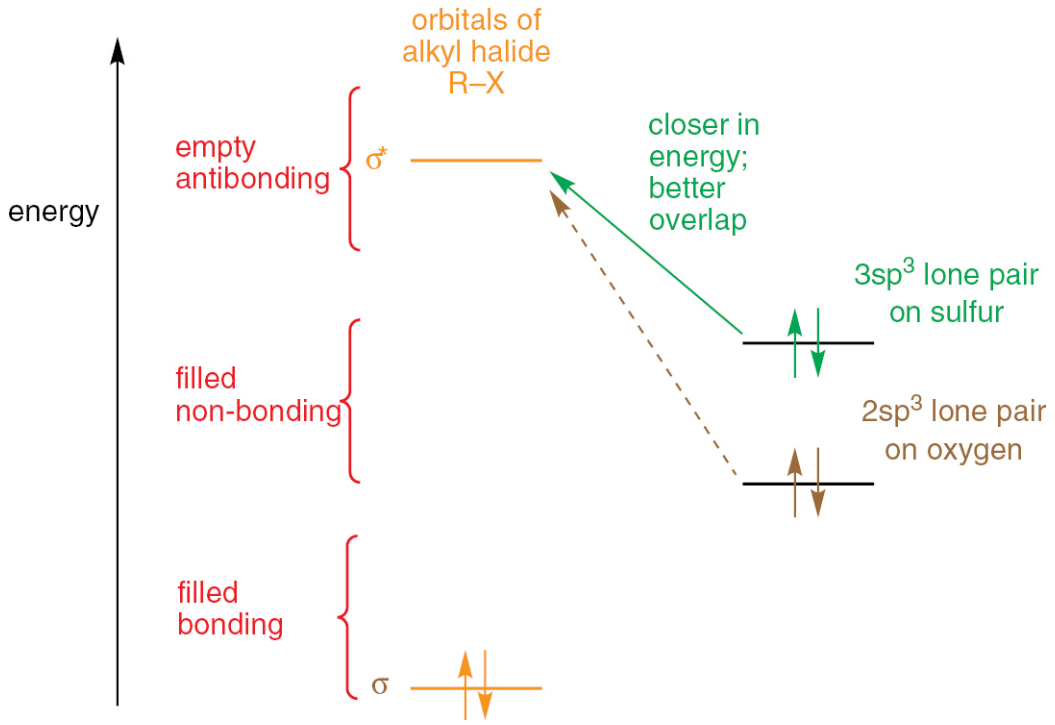
$I^- > Br^- > Cl^- > F^-$

$RSe^- > RS^- > RO^-$

$R_3P: > R_3N:$

## $S_N2$ | Nucleófilo

- Nucleófilos maiores tem energia do HOMO mais próximo do orbital LUMO σ* do substrato.



## $S_N1$ vs. $S_N2$ | Efeito do solvente

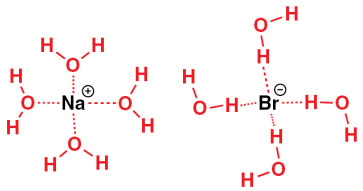
- O solvente afeta as reações de substituição de duas formas:
  a) devido a polaridade e b) devido a solvatação.
- Como o estado de transição de uma $S_N2$ tem carga pouco pronunciada, **solventes menos polares tornam a reação mais rápida**, pois estabilizam o ET.
- **Solventes mais polares estabilizam o ET de reações $S_N1$**, pois a carga é mais pronunciada, **aumentando a velocidade destas reações**.
- O segundo efeito é sobre a solvatação. Solventes polares apróticos (DMSO, acetona, DMF, etc.) não solvatam bem nucleófilos, aumentando, assim a nucleofilicidade.

**Table 10.7 The Dielectric Constants of Some Common Solvents**

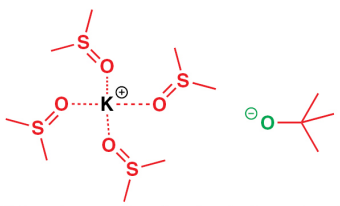
| Solvent | Structure | Abbreviation | Dielectric constant (ε, at 25 °C) | Boiling point (°C) |
|---|---|---|---|---|
| *Protic solvents* | | | | |
| Water | $H_2O$ | — | 79 | 100 |
| Formic acid | HCOOH | — | 59 | 100.6 |
| Methanol | $CH_3OH$ | MeOH | 33 | 64.7 |
| Ethanol | $CH_3CH_2OH$ | EtOH | 25 | 78.3 |
| *tert*-Butyl alcohol | $(CH_3)_3COH$ | *tert*-BuOH | 11 | 82.3 |
| Acetic acid | $CH_3COOH$ | HOAc | 6 | 117.9 |
| *Aprotic solvents* | | | | |
| Dimethyl sulfoxide | $(CH_3)_2SO$ | DMSO | 47 | 189 |
| Acetonitrile | $CH_3CN$ | MeCN | 38 | 81.6 |
| Dimethylformamide | $(CH_3)_2NCHO$ | DMF | 37 | 153 |
| Hexamethylphosphoric acid triamide | $[(CH_3)_2N]_3PO$ | HMPA | 30 | 233 |
| Acetone | $(CH_3)_2CO$ | $Me_2CO$ | 21 | 56.3 |
| Dichloromethane | $CH_2Cl_2$ | — | 9.1 | 40 |
| Tetrahydrofuran |  | THF | 7.6 | 66 |
| Ethyl acetate | $CH_3COOCH_2CH_3$ | EtOAc | 6 | 77.1 |
| Diethyl ether | $CH_3CH_2OCH_2CH_3$ | $Et_2O$ | 4.3 | 34.6 |
| Benzene |  | — | 2.3 | 80.1 |
| Hexane | $CH_3(CH_2)_4CH_3$ | — | 1.9 | 68.7 |

**Table 10.8 The Effect of the Polarity of the Solvent on the Rate of Reaction of *tert*-Butyl Bromide in an $S_N1$ Reaction**

| Solvent | Relative rate |
|---|---|
| 100% water | 1200 |
| 80% water / 20% ethanol | 400 |
| 50% water / 50% ethanol | 60 |
| 20% water / 80% ethanol | 10 |
| 100% ethanol | 1 |



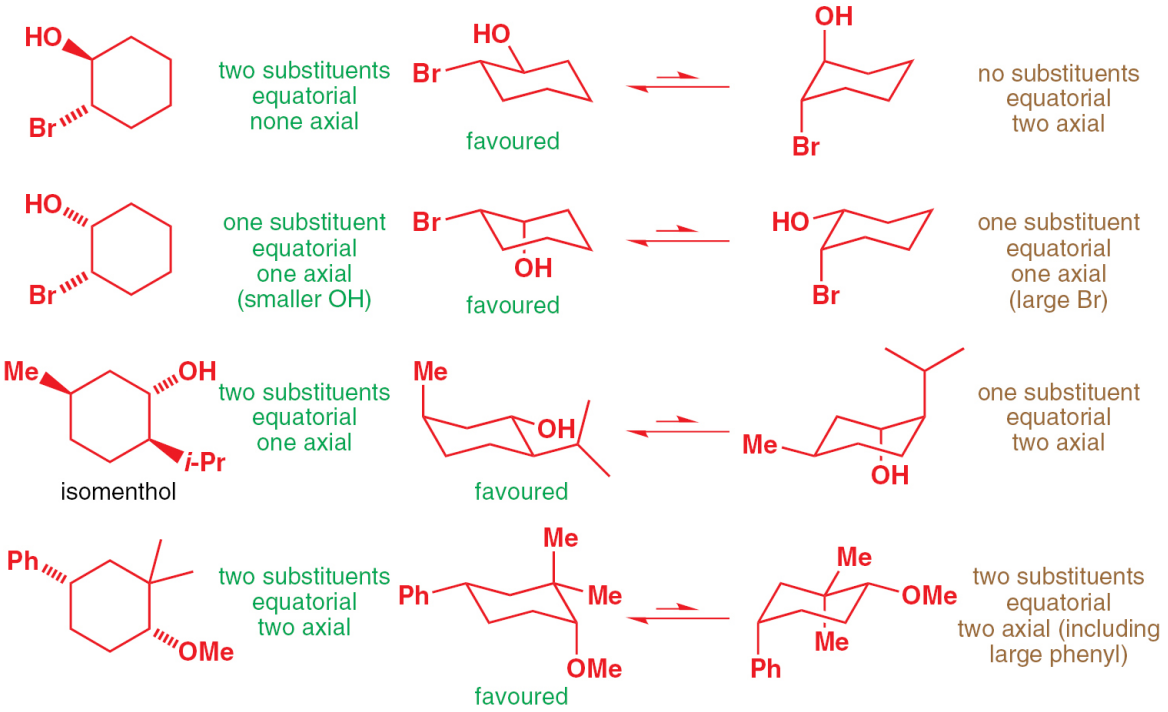
Water solvates cations and anions

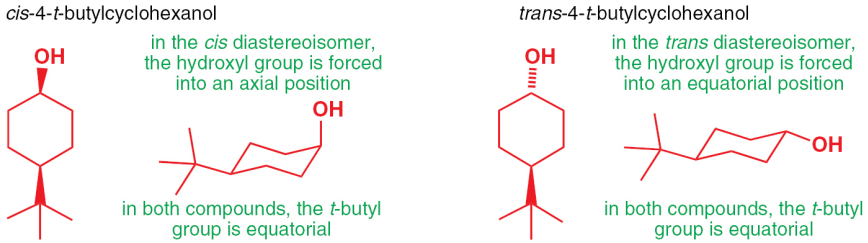


DMSO (a polar aprotic solvent) solvates only cations

## $S_N1$ vs. $S_N2$ | Cicloexano

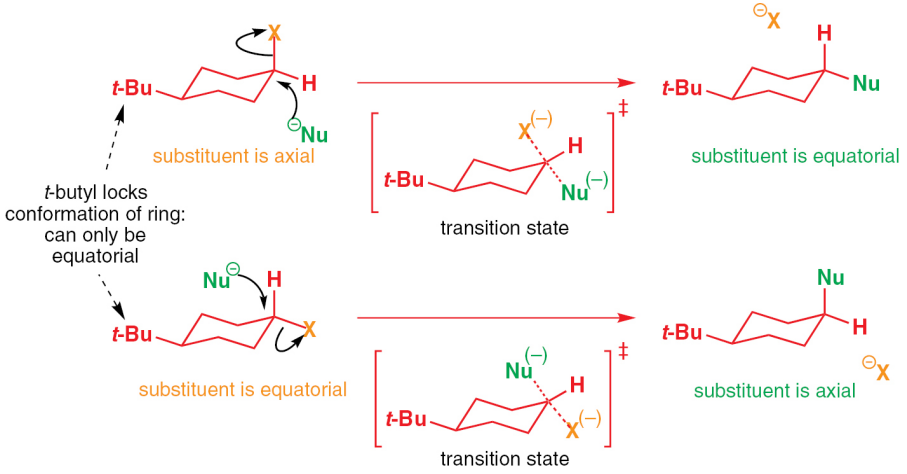
- Lembrando...



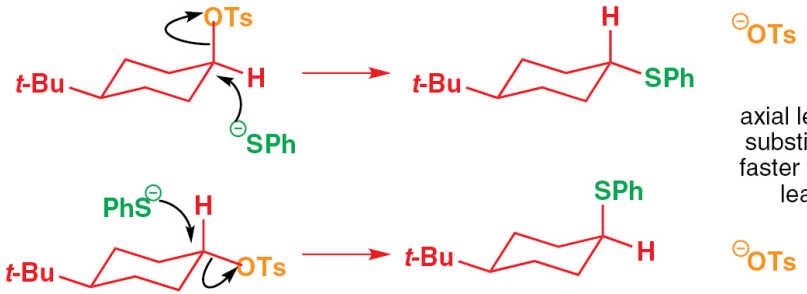



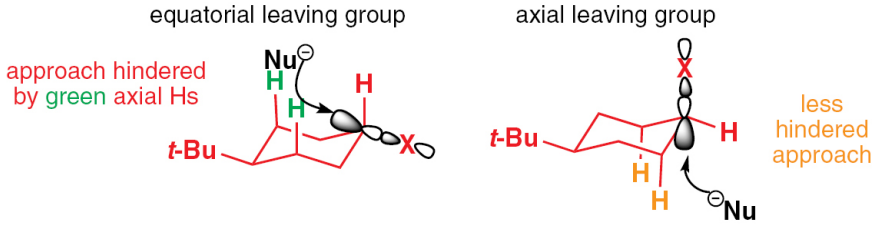
## $S_N1$ vs. $S_N2$ | Cicloexano

- Carbono secundário não reage geralmente bem via $S_N1$ ou $S_N2$.




- Uma $S_N2$ é favorecida quando se tem um bom grupo abandonador e na posição axial.

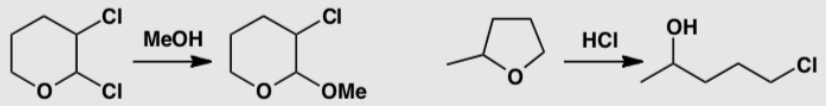


# Problemas

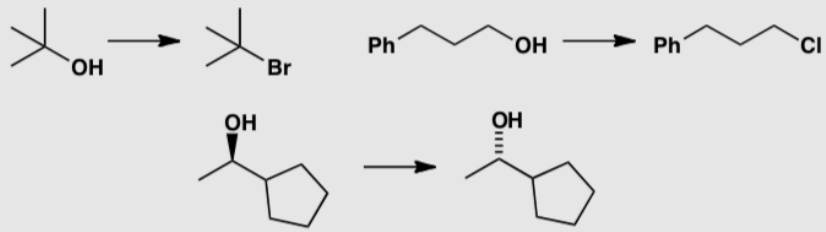
**PROBLEM 3**

Draw mechanisms for these reactions, explaining why these particular products are formed.



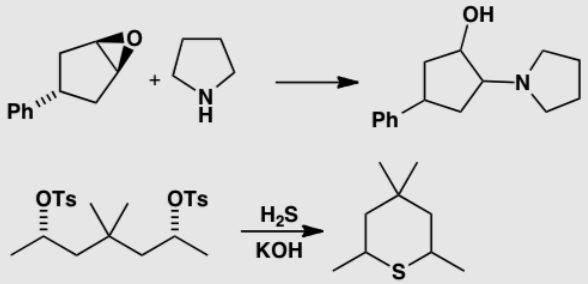

**PROBLEM 4**

Suggest how to carry out the following transformations.



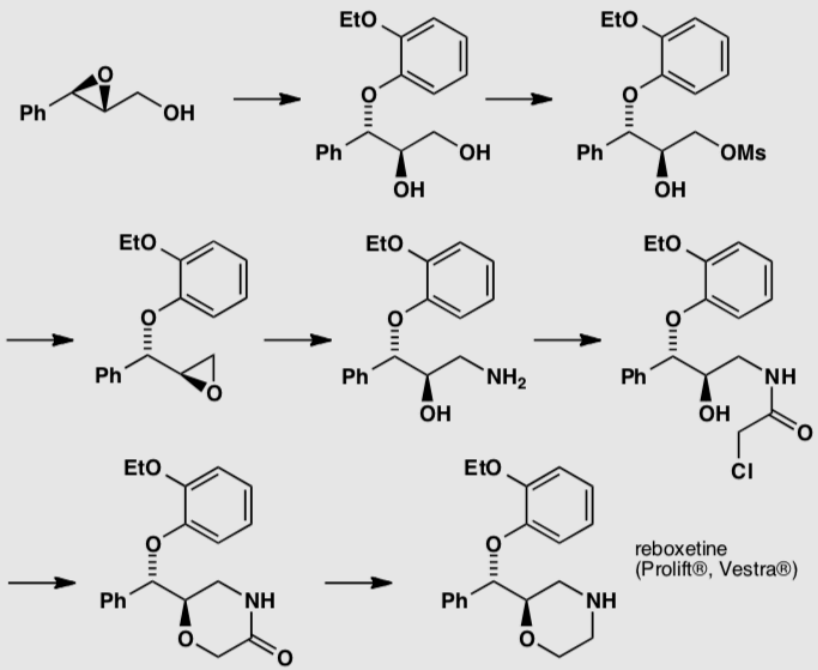

**PROBLEM 7**

Predict the stereochemistry of these products. Are they diastereoisomers, enantiomers, racemic or what?




**PROBLEM 11**

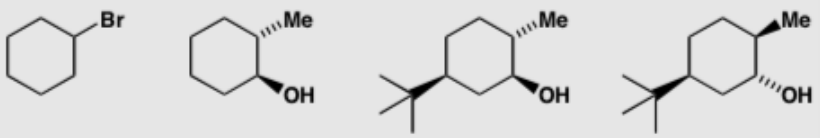
The pharmaceutical company Pfizer made the antidepressant reboxetine by the following sequence of reactions. Suggest a reagent for each step, commenting on aspects of stereochemistry or reactivity.



## Problemas

**PROBLEM 2**

Draw clear conformational drawings of these molecules, labelling each substituent as axial or equatorial.




**4.** Why is it difficult for cyclohexyl bromide to undergo an E2 reaction? When it is treated with base, it does undergo an E2 reaction to give cyclohexene. What conformational changes must occur during this reaction?