Aula 2

Nucleophilic Substitution Reactions at the Saturated C Atom

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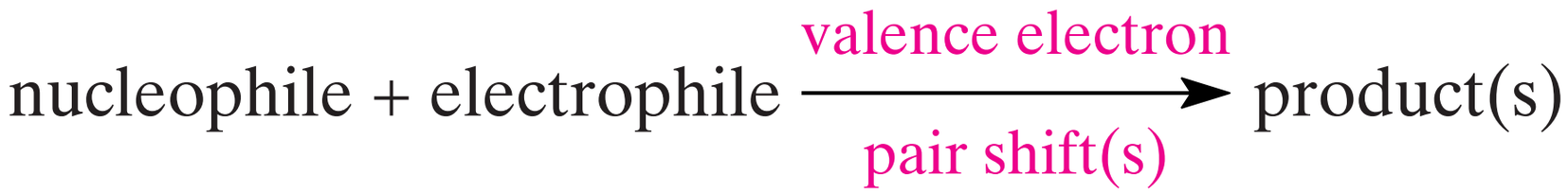
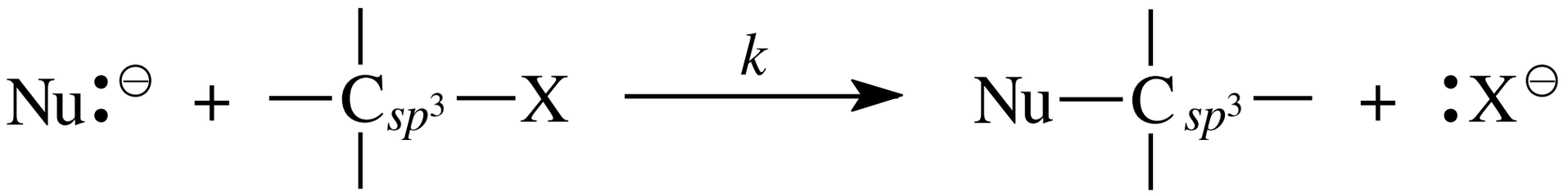
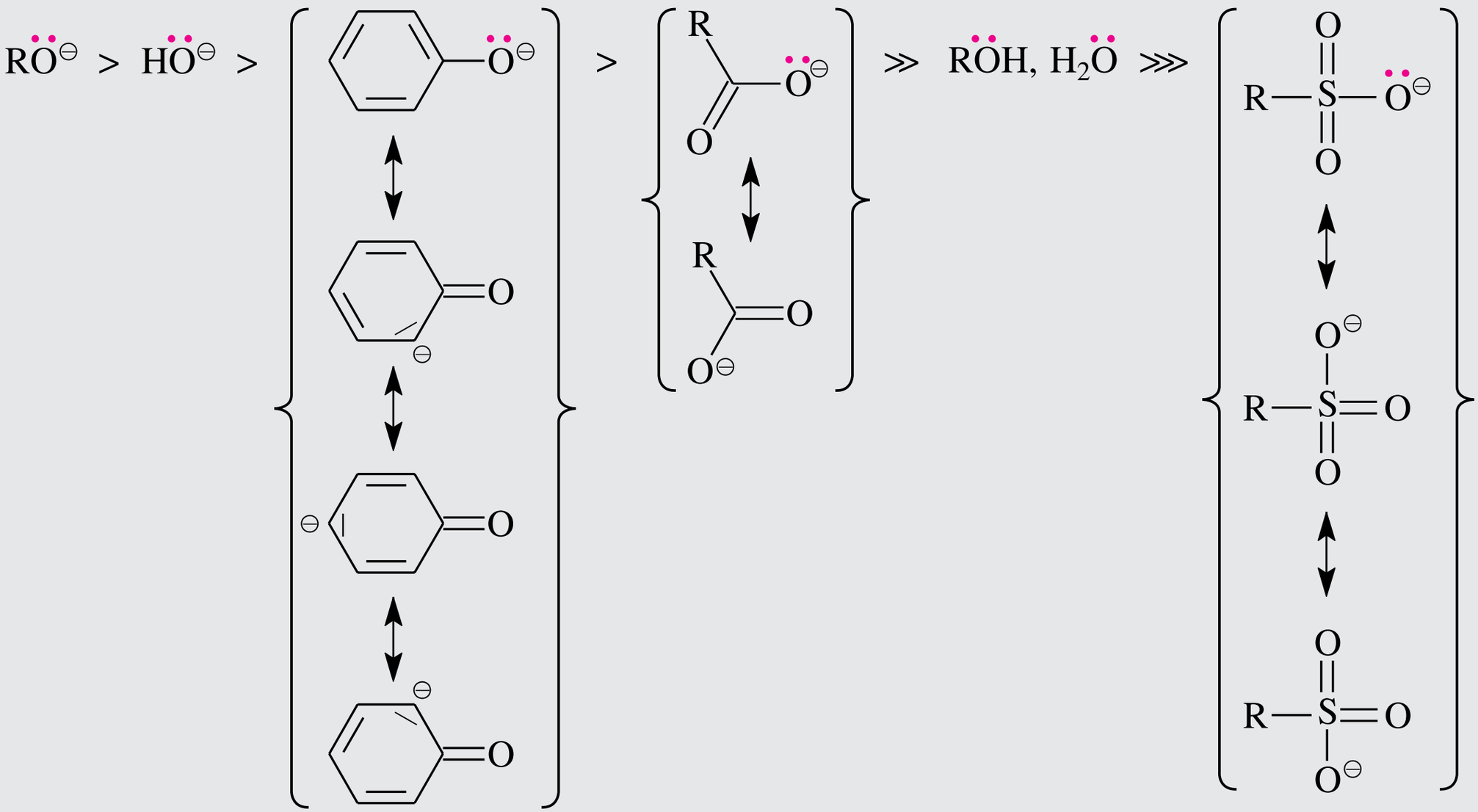

nucleophile + electrophile
valence electron
pair shift(s)
product(s)


Nu:⊖ + E⊕
Nu—E
(+ by-products)


Nu:⊖ + —C sp3 —X
k
Nu—C sp3 — + :X⊖

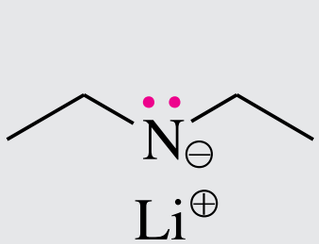
Nucleófilos

- Within a group of nucleophiles that attack at the electrophile with the same atom, the nucleophilicity decreases with *decreasing basicity of the nucleophile* (Figure



Nucleófilos

- This parallel between nucleophilicity and basicity can be reversed by steric effects. Less basic but sterically unhindered nucleophiles therefore have a higher nucleophilicity than strongly basic but sterically hindered nucleophiles (Figure



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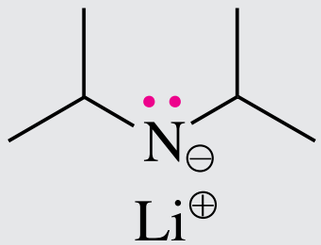

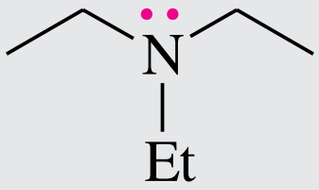

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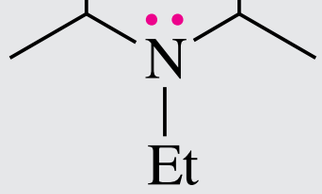

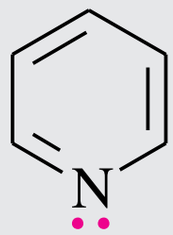

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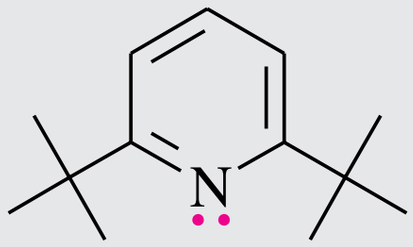
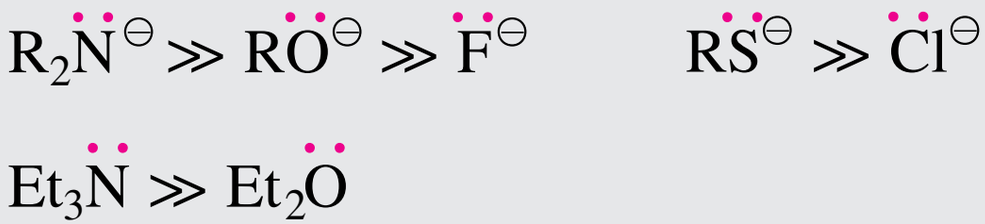
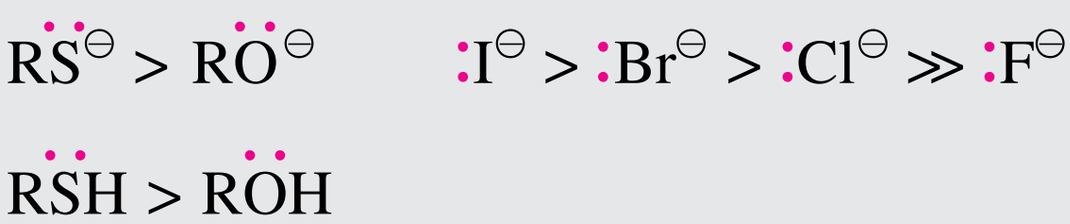


Nucleófilos

- *Nucleophilicity decreases with increasing electronegativity of the attacking atom.* This is true both in comparisons of atomic centers that belong to the same *period* of the periodic table of the elements

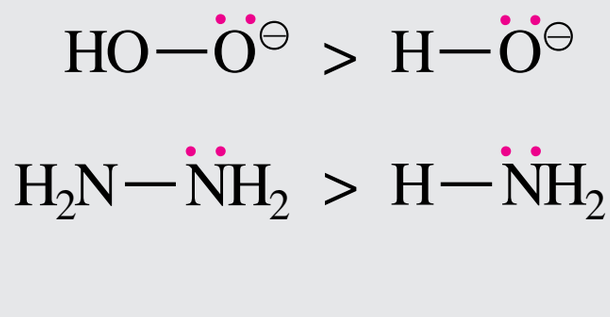


- and in comparisons of atomic centers from the same *group* of the periodic table:



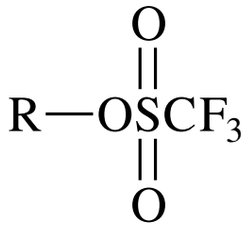
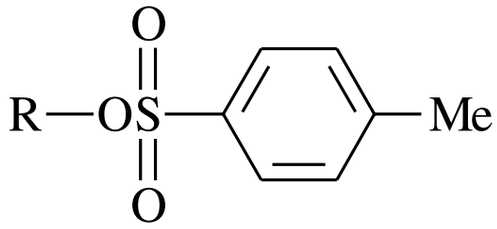
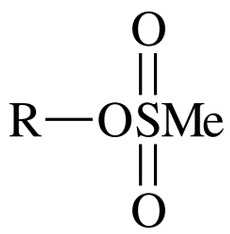
Nucleófilos

- The nucleophilicity of a given nucleophilic center is increased by attached heteroatoms that possess free electron pairs (α-effect):



The reason for this is the unavoidable overlap of the orbitals that accommodate the free electron pairs at the nucleophilic center and its neighboring atom.

Grupo de partida

-  ≡ R—OTf Alkyl triflate
  (Record holder; for R = allyl or benzyl ionic mechanism)
-  ≡ R—OTs Alkyl tosylate
-  ≡ R—OMs Alkyl mesylate
- R—I, R—Br
- R—Cl
- 

Good leaving groups: RHal and epoxides can be further activated with Lewis acids

- $R_{sec\ or\ tert}-OCR'$ (O)

a leaving group
in solvolyses

- $R_{tert}-OCR'$ (O) $\rightleftharpoons$ $R_{tert}-OCR'$ ($\oplus$OH)
- $R-OH \longrightarrow R-\overset{\oplus}{O}=PPh_3$
  $R-\overset{\oplus}{O}H_H$
- $R-OR' \rightleftharpoons R-\overset{\oplus}{O}R'_H$
  $R-\overset{\oplus}{O}R'$ (with $LA^{\ominus}$)

in situ activation of
the leaving group necessary

- $R-F$

$R-SR'(H)$, $R-S(=O)R'$, $R-S(=O)_2R'$, $R-\overset{\oplus}{S}R'_2$

$R-NR'_2(H_2)$, $R-NO_2$, $R-\overset{\oplus}{N}R_3(H_3)$

$R-P(=O)(OR')_2$, $R-P(=O)Ph_2$, $R-\overset{\oplus}{P}Ph_3$

$R-CN$

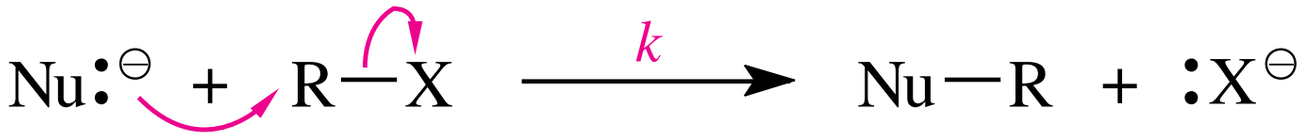
very poor leaving group or
not a leaving group

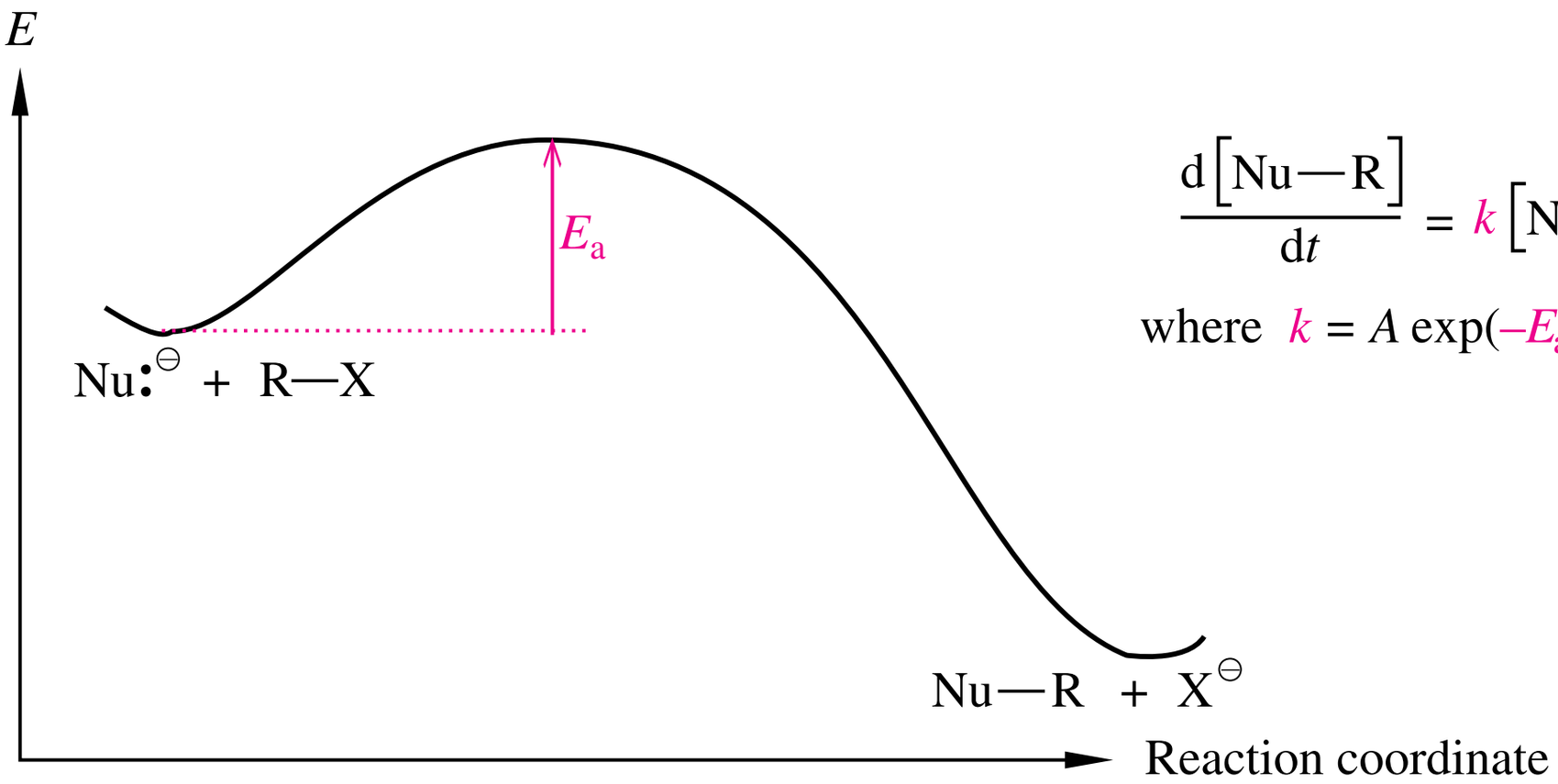
Para a próxima aula

- O **postulado de Hammond** implica que o grupo de partida é uma espécie estabilizada, não uma espécie de alta energia. Explique.
- Depois, baseado no texto acima explique:
- $I^- > Br^- > Cl^- > F^-$
- $F_3C\text{-}SO_3^- > Me\text{-}C_6H_4\text{-}SO_3^-$

Substituição Nucleofílica Bimolecular, S_N2

An S_N2 reaction refers to an S_N reaction

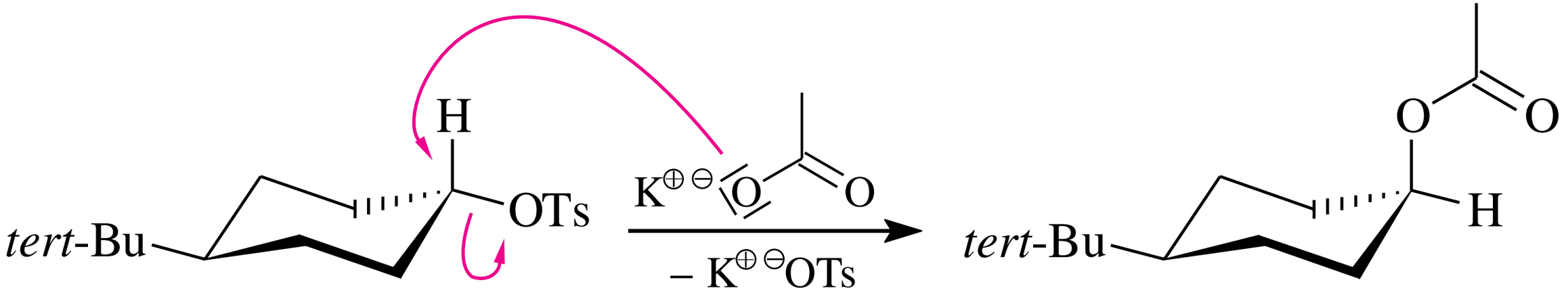




$$\frac{d[Nu{-}R]}{dt} = k[Nu{:}^{\ominus}][R{-}X] \qquad (2.1)$$

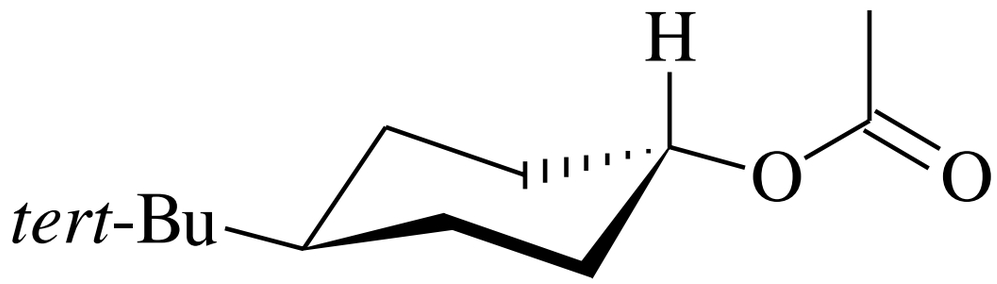
where $k = A\exp(-E_a/RT)$ (2.2)

Estereoseletividade em reações S_N2



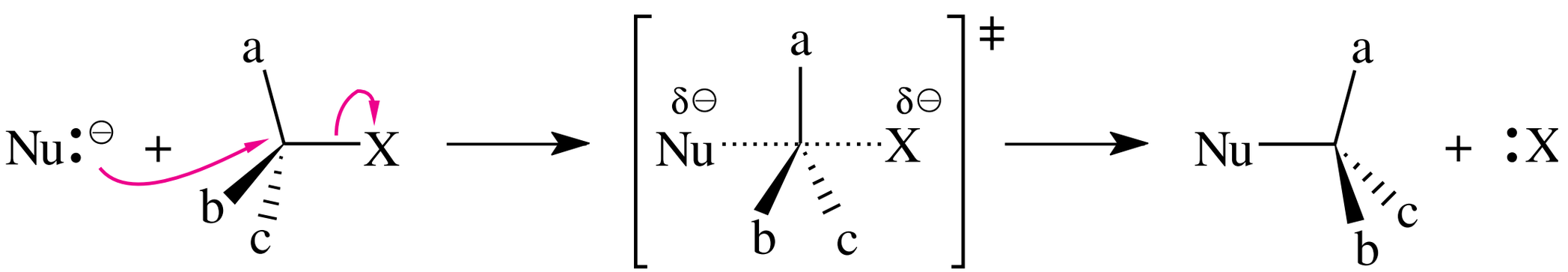
trans-**A** *cis*-**B**

but no



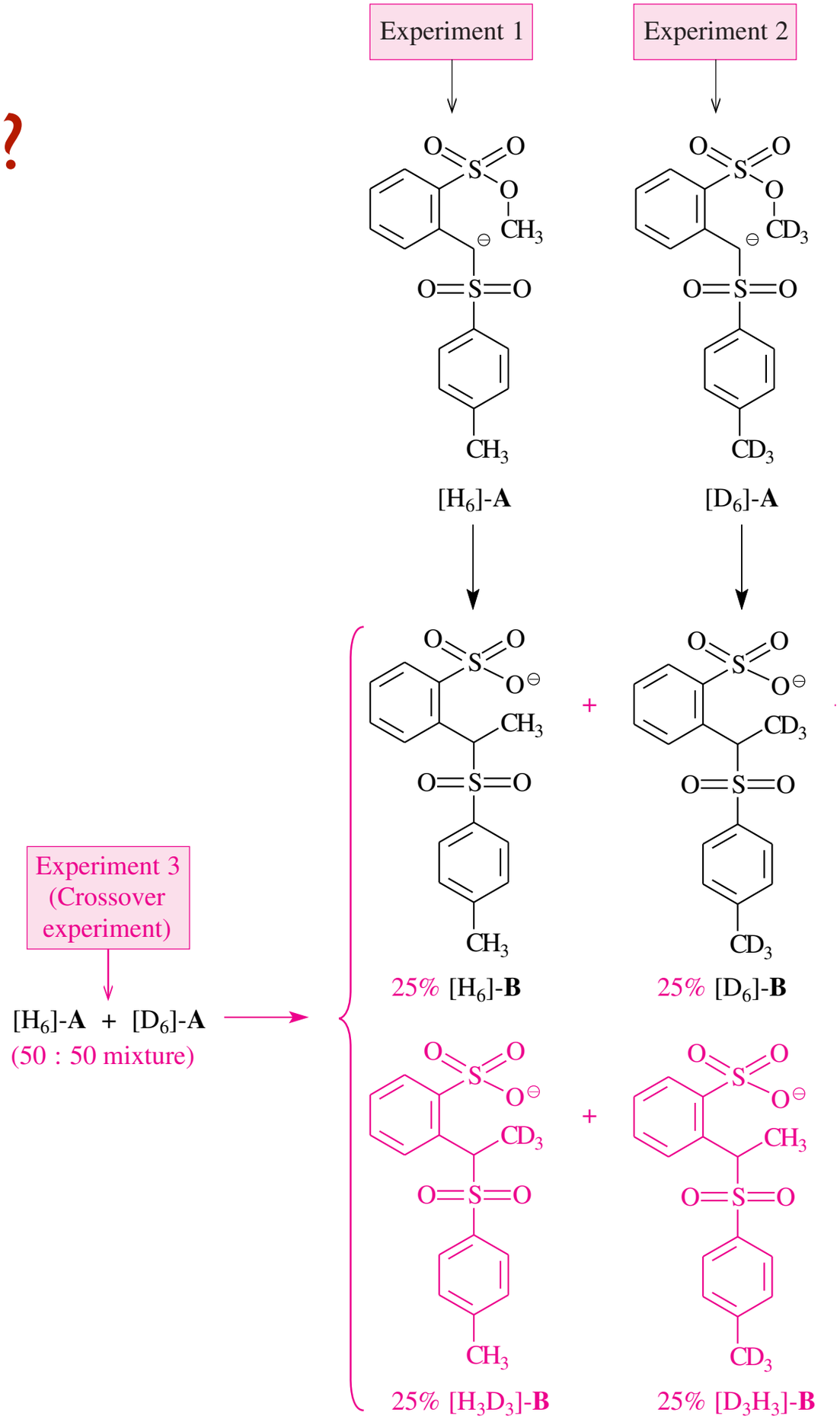
trans-**B**

S_N2



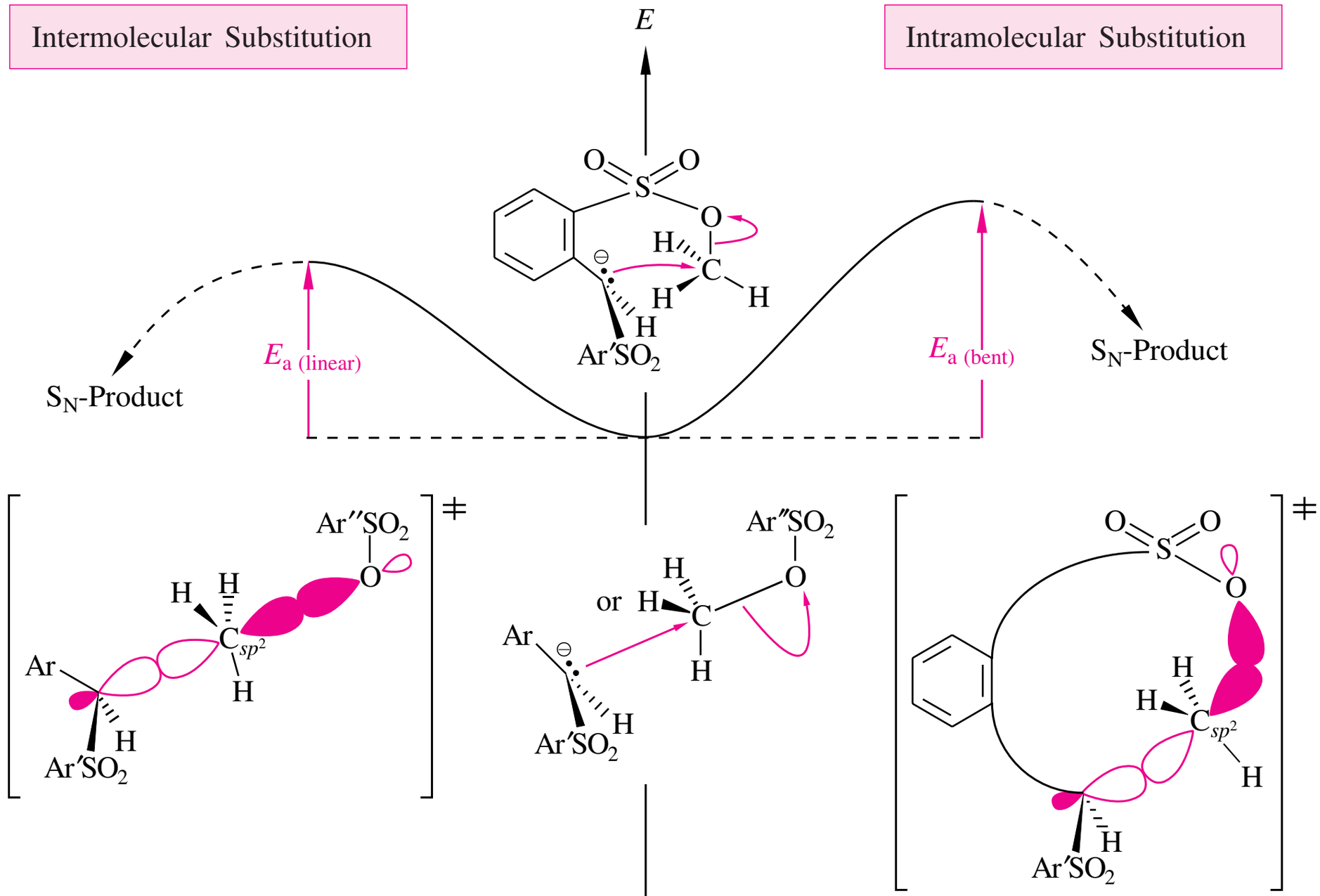
Mecanismo “guarda-chuva”

Why?????


Experiment 1
Experiment 2
[H6]-A
[D6]-A
Experiment 3
(Crossover
experiment)
[H6]-A + [D6]-A
(50 : 50 mixture)
25% [H6]-B
25% [D6]-B
25% [H3D3]-B
25% [D3H3]-B

Intermolecular Substitution

Intramolecular Substitution



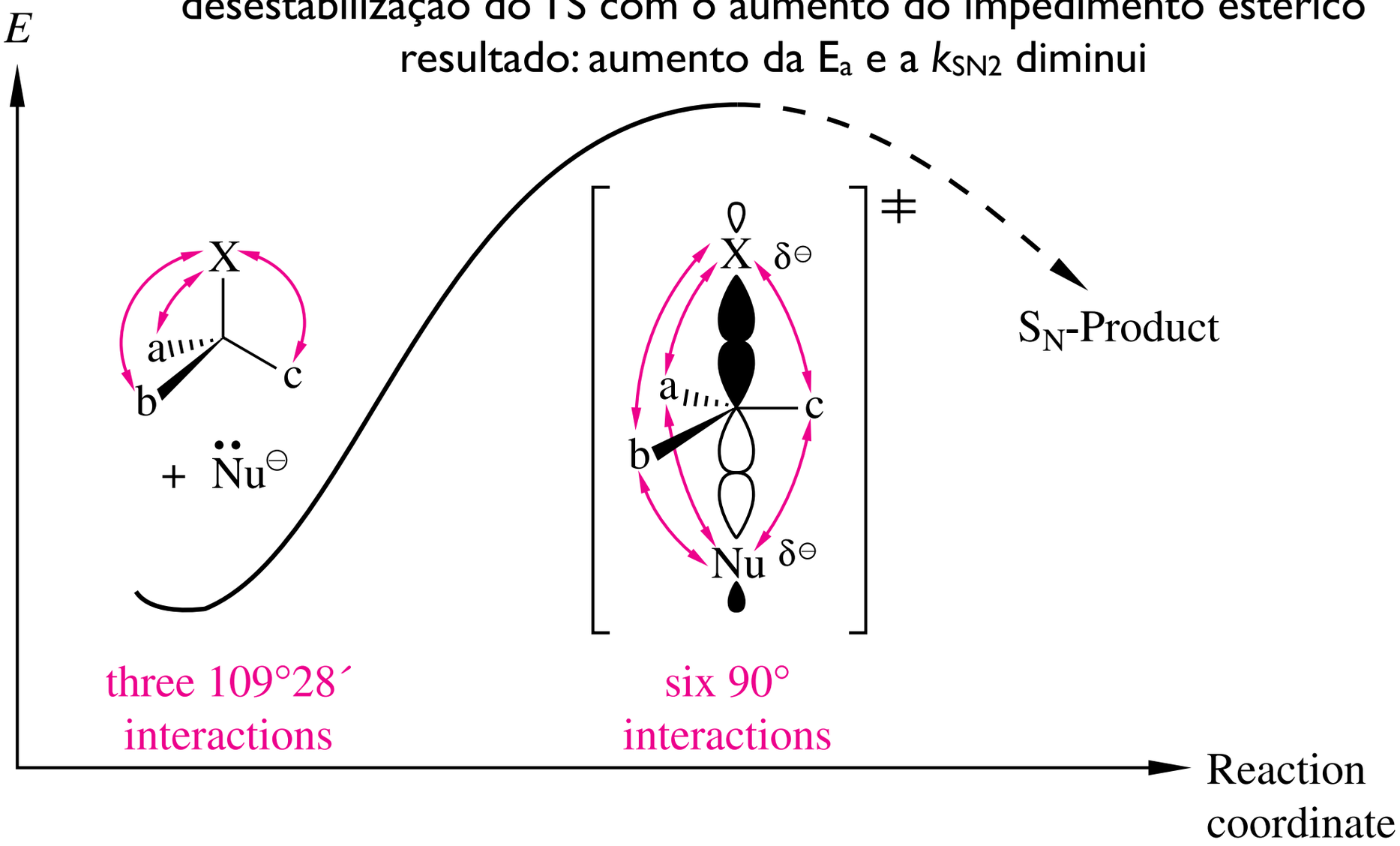
Linear transition state possible

Bent transition state enforced

Reaction coordinate intermolecular

Reaction coordinate intramolecular

Efeito estérico



Efeito estérico: Tendências e regras

- The S_N2 reactivity of an alkylating agent decreases with an increasing **number** of the alkyl substituents at the attacked C atom. In other words, α branching at the C atom of the alkylating agent reduces its S_N2 reactivity. This reduces the reactivity so much that tertiary C atoms can no longer be attacked according to an S_N2 mechanism at all:

$Nu^{\ominus}$ +	Me — X	Et — X	*i*Pr — X	*tert*-Bu — X
$k_{S_N2,\,rel}$ =	30	1	0.025	tiny

Generally stated, for S_N2 reactivity we have $k(\text{Me—X}) > k(\text{R}_{prim}\text{—X}) >> k(\text{R}_{sec}\text{—X})$; $k(\text{R}_{tert}\text{—X}) \approx 0$ (unit: 1 $\text{mol}^{-1}\ \text{s}^{-1}$).

Efeito estérico: Tendências e regras

- The S_N2 reactivity of an alkylating agent decreases with an increase in size of the alkyl substituents at the attacked C atom. In other words, β branching in the alkylating agent reduces its S_N2 reactivity. This reduces the reactivity so much that a C atom with a tertiary C atom in the β position can no longer be attacked at all according to an S_N2 mechanism:

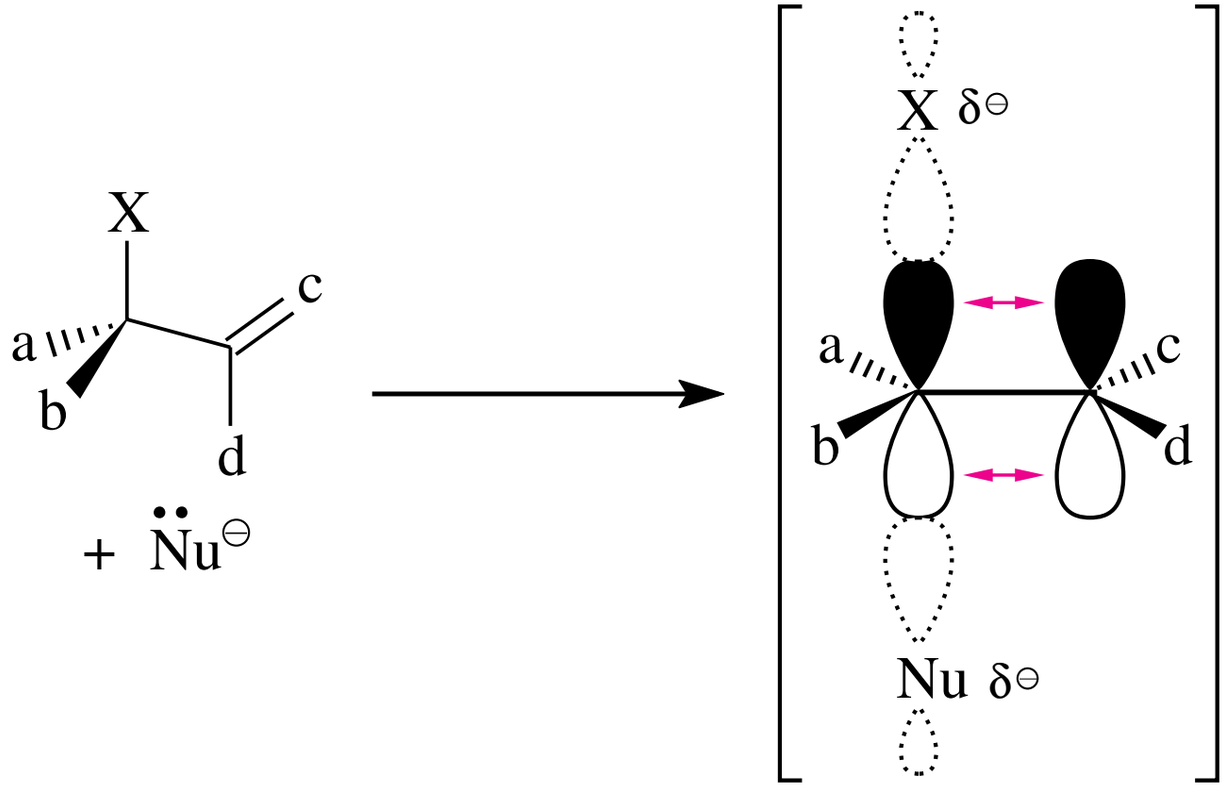
$Nu^{\ominus}$ +	$MeCH_2-X$		$EtCH_2-X$	$iPrCH_2-X$	*tert*-$BuCH_2-X$
$k_{S_N2,\,rel}$ =	1		0.4	0.03	tiny

Generally stated, for S_N2 reactivity we have $k(MeCH_2{-}X) > k(R_{prim}CH_2{-}X) >> k(R_{sec}CH_2{-}X)$; $k(R_{tert}CH_2{-}X) \approx 0$ (unit: 1 mol^{-1} s^{-1}).

Efeitos eletrônicos na reatividade: Estabilização conjugativa

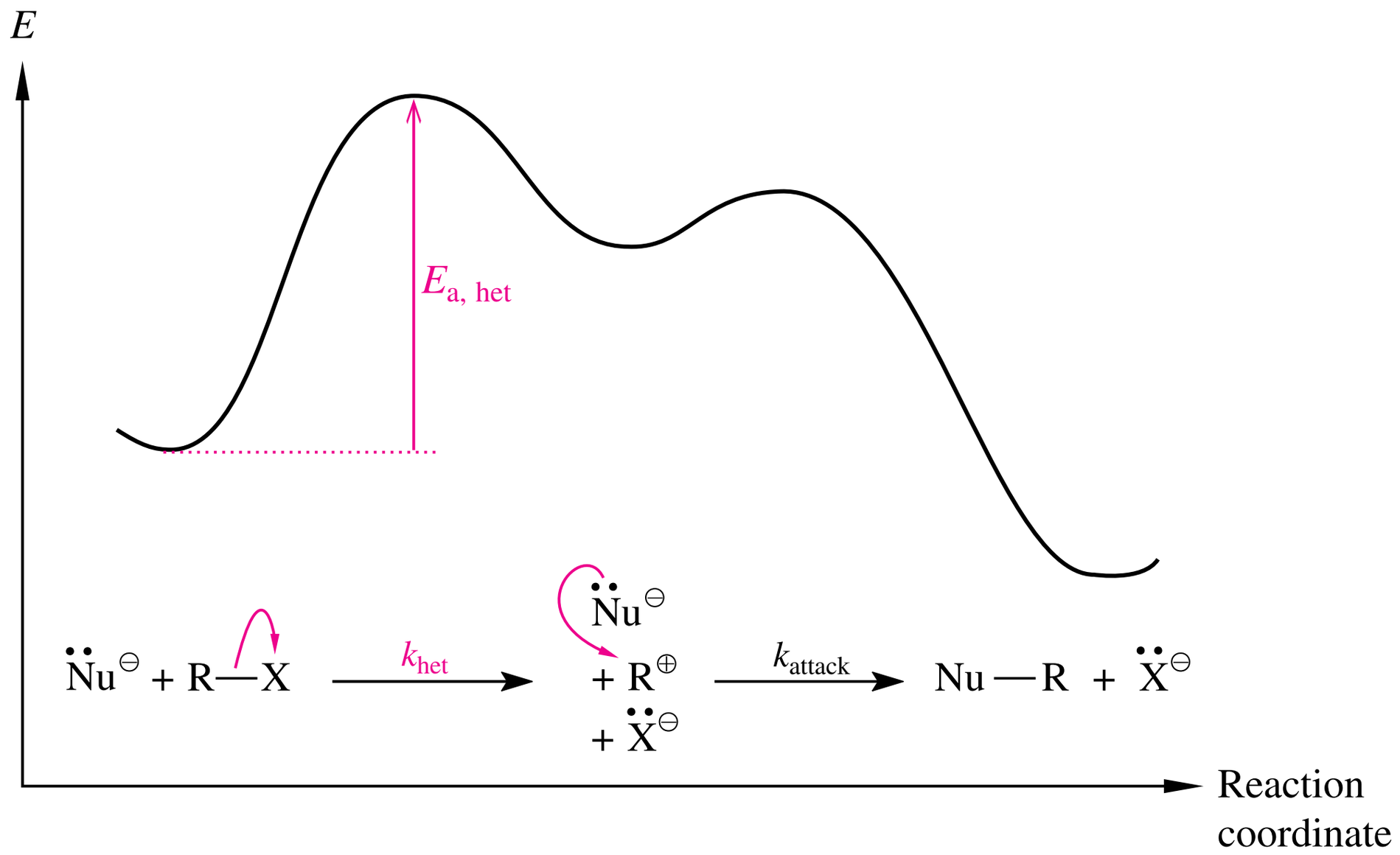
$Nu^{\ominus}$ +	$MeCH_2-X$	$vinylCH_2-X$	$PhCH_2-X$
$k_{S_N2,\,rel}$ =	1	40	120

Because of the substituent effect just described, allyl and benzyl halides generally react with nucleophiles according to an S_N2 mechanism. This occurs even though the S_N1 reactivity of allyl and benzyl halides is *higher* than that of nonconjugated alkylating agents



⇒ conjugative stabilization by overlap with the parallel antibonding MO of the π system

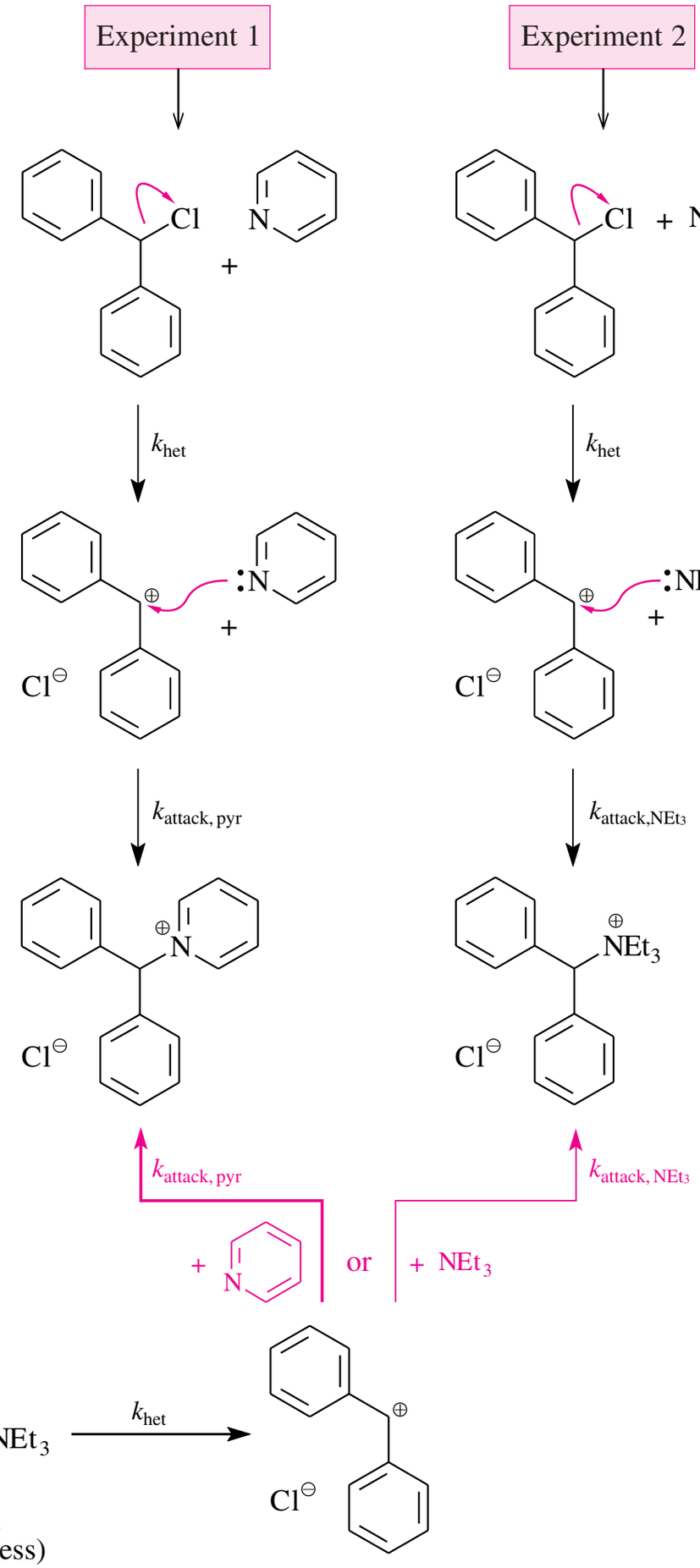
Substituição Nucleofílica Unimolecular, S_N1

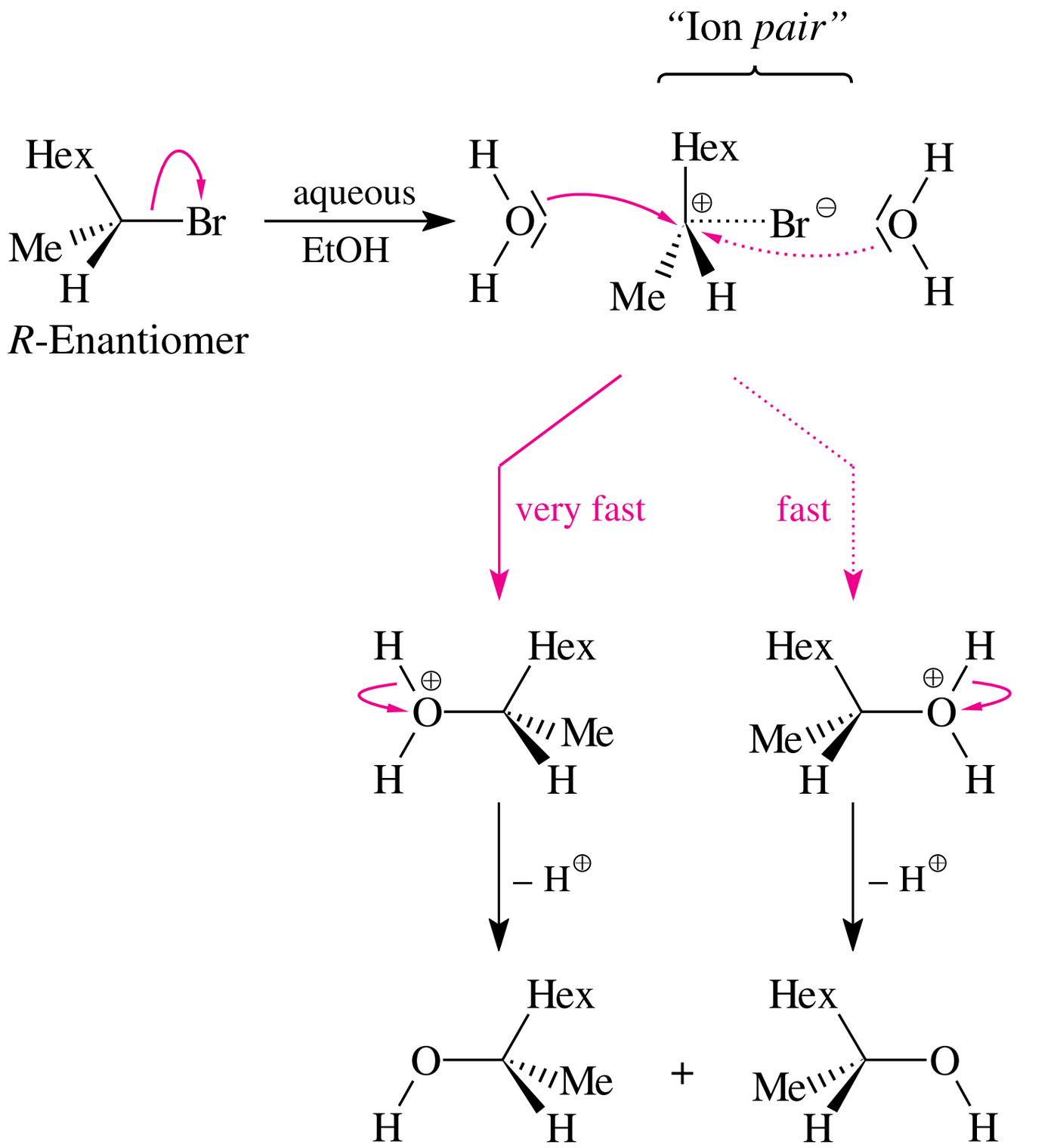


Para próxima aula:

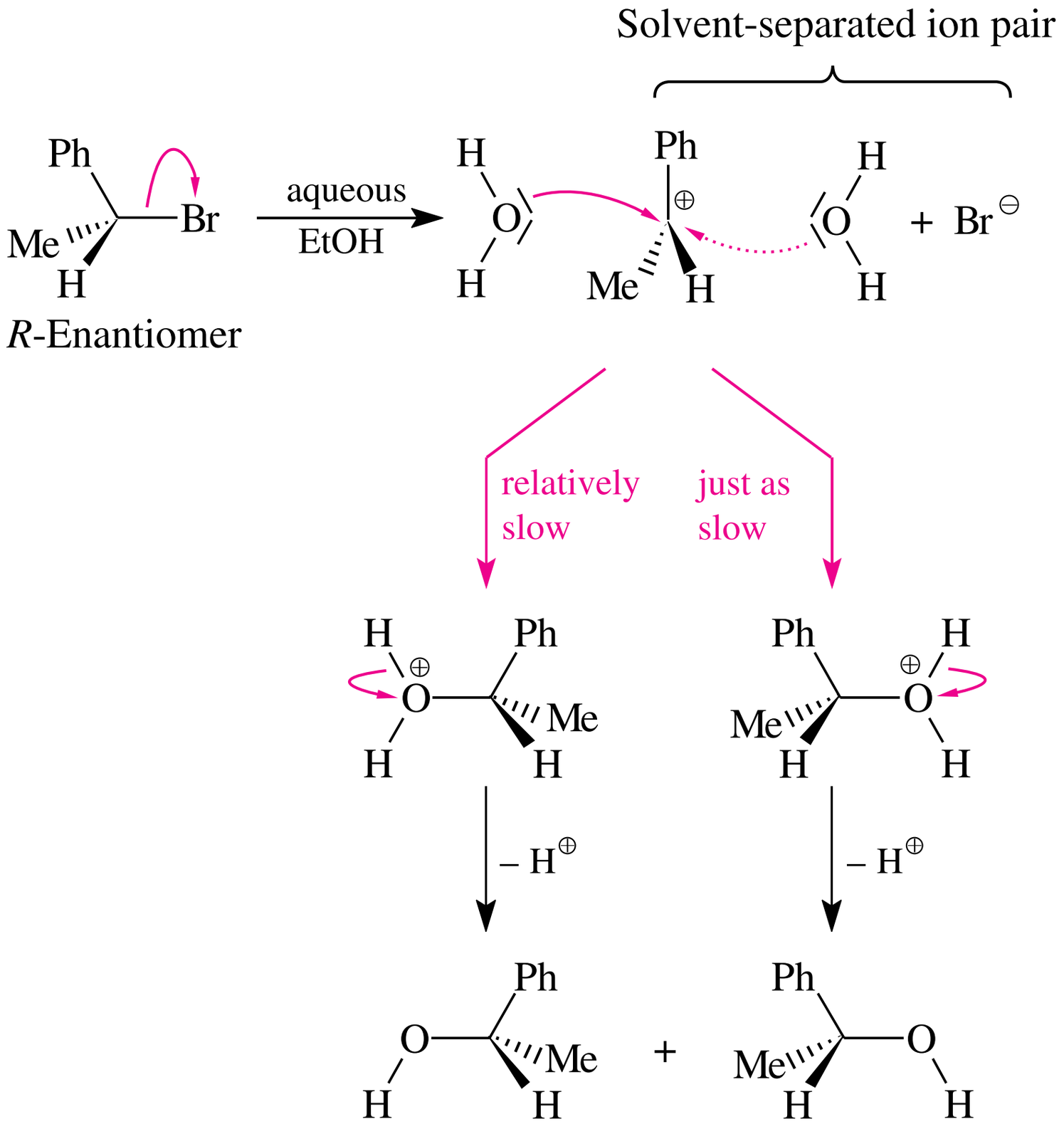
Quem é o melhor nucleófilo? Py ou EtN?

pK_{aH}=5,21 pK_{aH}=10,78





83% *S*-Enantiomer + 17% *R*-Enantiomer, or:
66% *S*-Enantiomer + 34% Racemic mixture
inversão racemização



R-Enantiomer

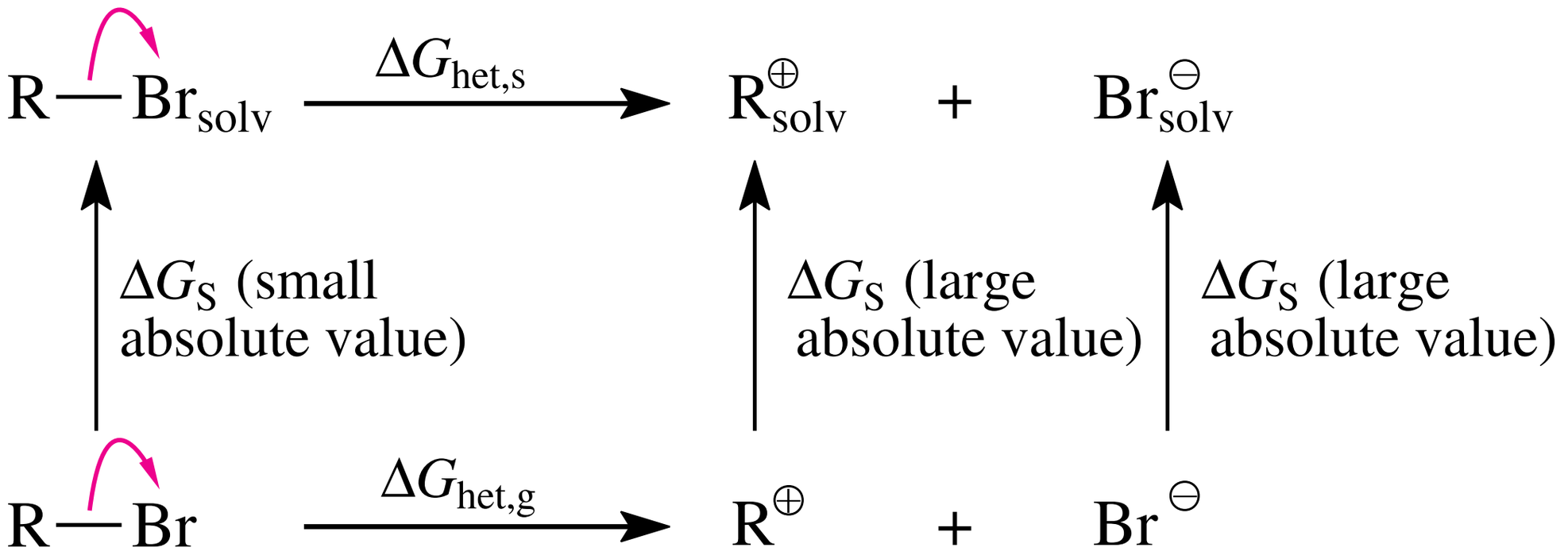
50% *S*-Enantiomer + 50% *R*-Enantiomer, thus:
0% *S*-Enantiomer + 100% Racemic mixture

Table 2.1. Free Energy Values from Gas Phase Studies (Lines 1–3). Free Energies of Heterolysis in Water (Line 4) Calculated Therefrom According to Figure 2.15*

heterórise, *het* R—Br ⟶ $R^{\oplus}$ + $\ddot{B}r^{\ominus}$	Me	Et	*i*Pr	*tert*-Bu	$PhCH_2$
gás — $\frac{\Delta G_{het,\,g}}{kcal/mol}$	+214	+179	+157	+140	+141
gás — $\frac{\Delta G_{hyd\ (R^{\oplus})}}{kcal/mol}$	–96	–78	–59	–54	–59
gás — $\frac{\Delta G_{hyd\ (Br^{\ominus})}}{kcal/mol}$	–72	–72	–72	–72	–72
H_2O ⟶ $\frac{\Delta G_{het,\ H_2O}}{kcal/mol}$	+47	+30	+27	+14	+11
H_2O ⟶ $\left(\text{cf. } \frac{\Delta H_{hom,\ any\ medium}}{kcal/mol}\right)$	(+71)	(+68)	(+69)	(+63)	(+51)
H_2O ⟶ $\tau_{1/2,\ het,\ 298\ K}$	$\geq 10^{16}$ yr	$\geq 10^{5}$ yr	≥ 220 yr	≥ 0.7 s	≥ 0.007 s

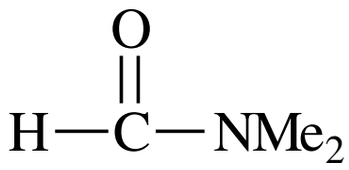
*From these energies and using the Eyring equation (Equation 1.1), one can calculate minimum half-lives for the pertinent heterolyses in water (line 6). These are minimum values because the $\Delta G_{het,H_2O}$ values were used for $\Delta G^{\ddagger}$ in the Eyring equation, whereas actually $\Delta G^{\ddagger} > * \Delta G_{het,\,H_2O}$. ΔG_{hyd} = free energy of hydration, ΔG_{het} = free energy of heterolysis, and ΔH_{hom} = enthalpy of homolysis.

S_N1: Efeito da polaridade do solvente

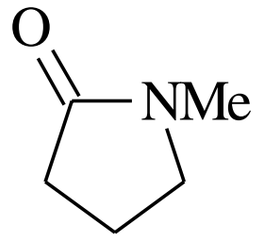


Solventes

DMF = **D**i**m**ethyl**f**ormamide:

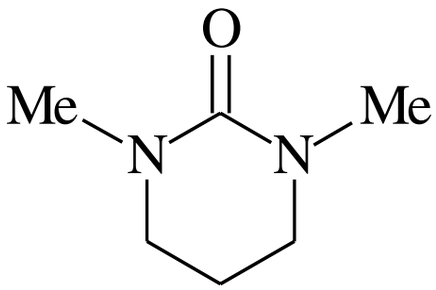


NMP = ***N***-**M**ethyl**p**yrrolidone:

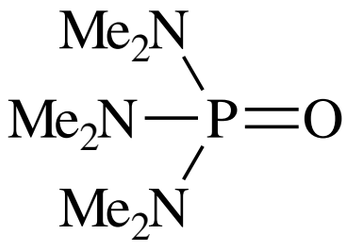


DMSO = **D**i**m**ethyl**s**ulf**o**xide:

DMPU = *N*,*N*´-**D**i**m**ethyl-*N*,*N*´-**p**ropylene **u**rea:



HMPA = **H**exa**m**ethyl **p**hosphoric acid tri**a**mide:



Efeitos de substituintes, VB Theory

Table 2.2. Stabilization of a Trivalent Carbenium Ion Center by Conjugating Substituents: Experimental Findings and Their Explanation by Means of Resonance Theory

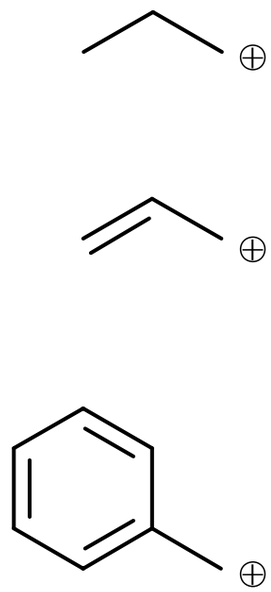
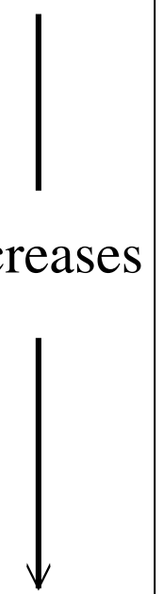
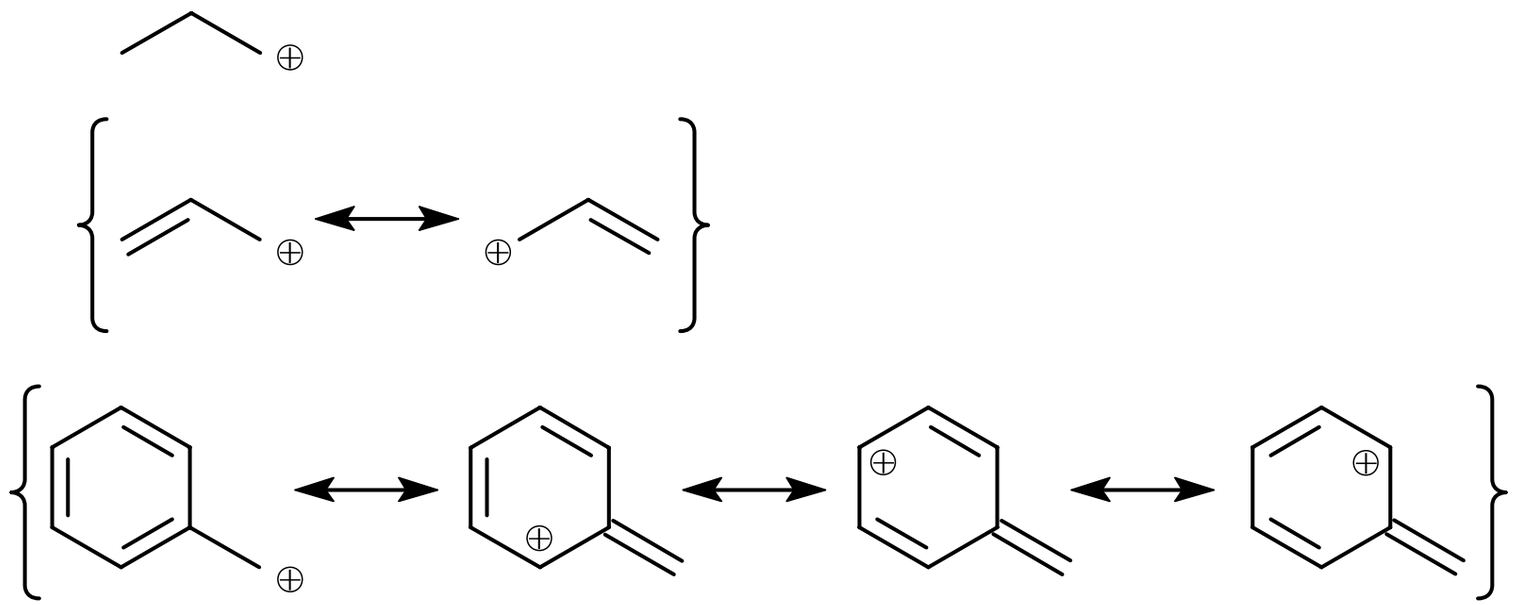
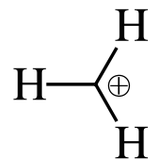
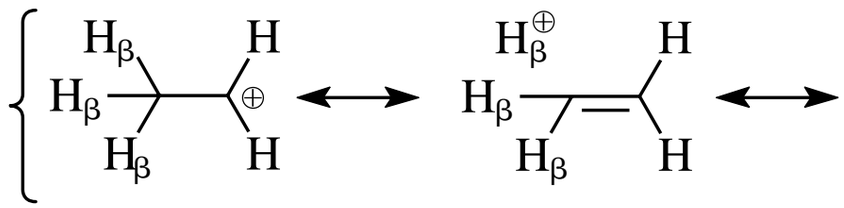
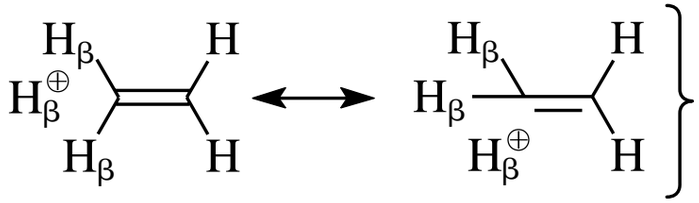
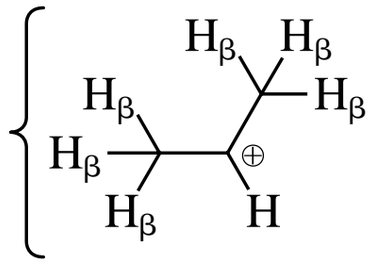
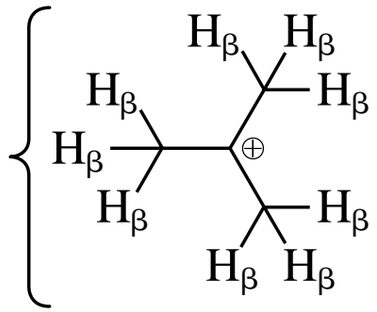
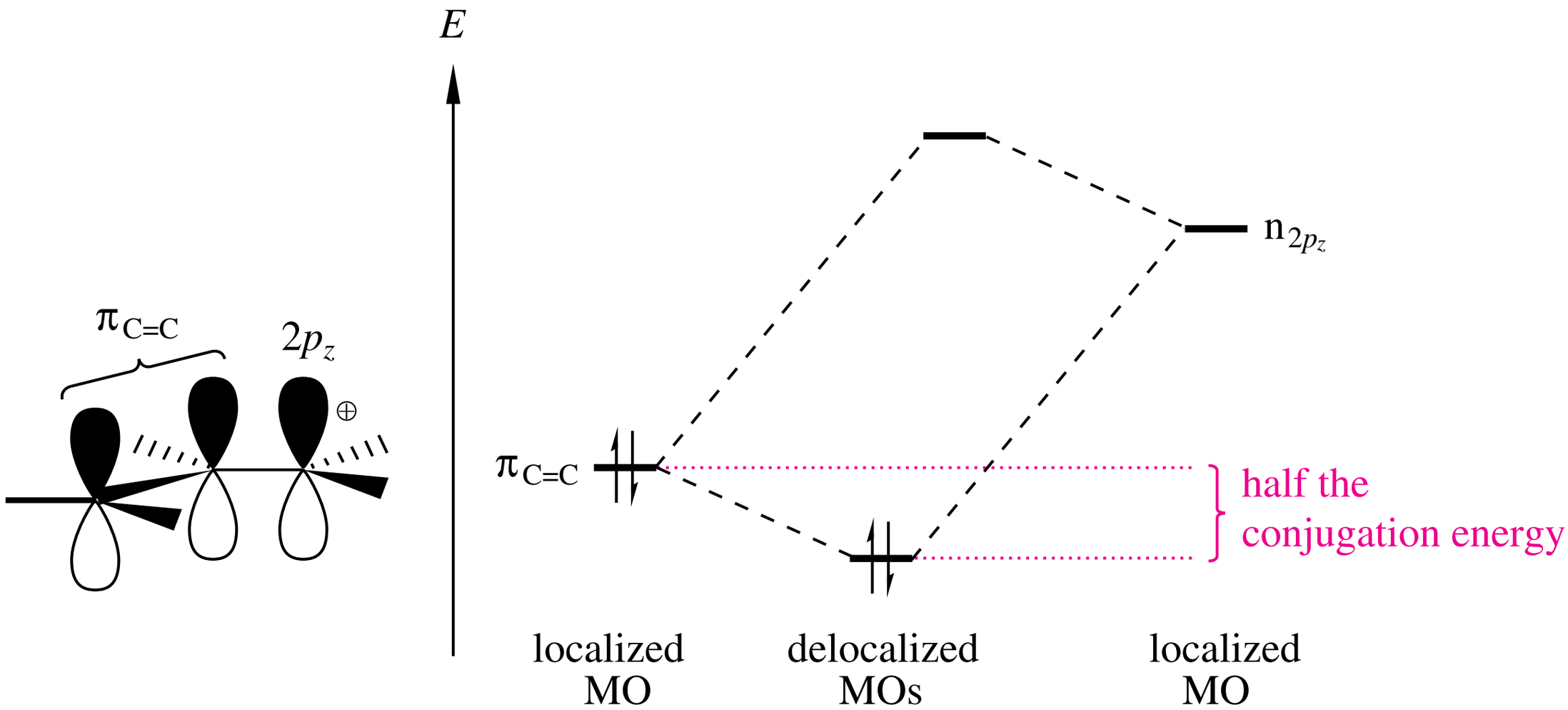
	Stabilization of ⊕	VB formulation
		

Table 2.3. Stabilization of Trivalent Carbenium Ion Centers by Methyl Substituents: Experimental Findings and Their Explanation by Means of Resonance Theory

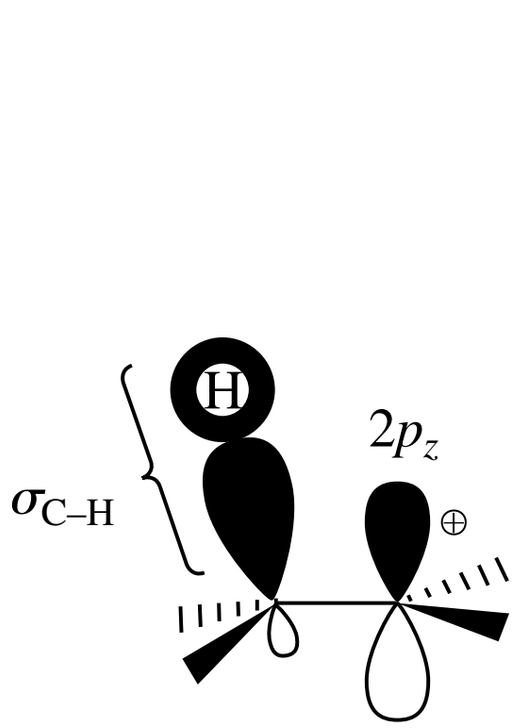
	Stabilization of $\oplus$	VB formulation
$H_3C^{\oplus}$	increases	
$H_3C{-}H_2C^{\oplus}$		  i.e., 1 no-bond resonance form per H_β
$(H_3C)_2HC^{\oplus}$		 6 no-bond resonance forms
$(H_3C)_3C^{\oplus}$		 9 no-bond resonance forms

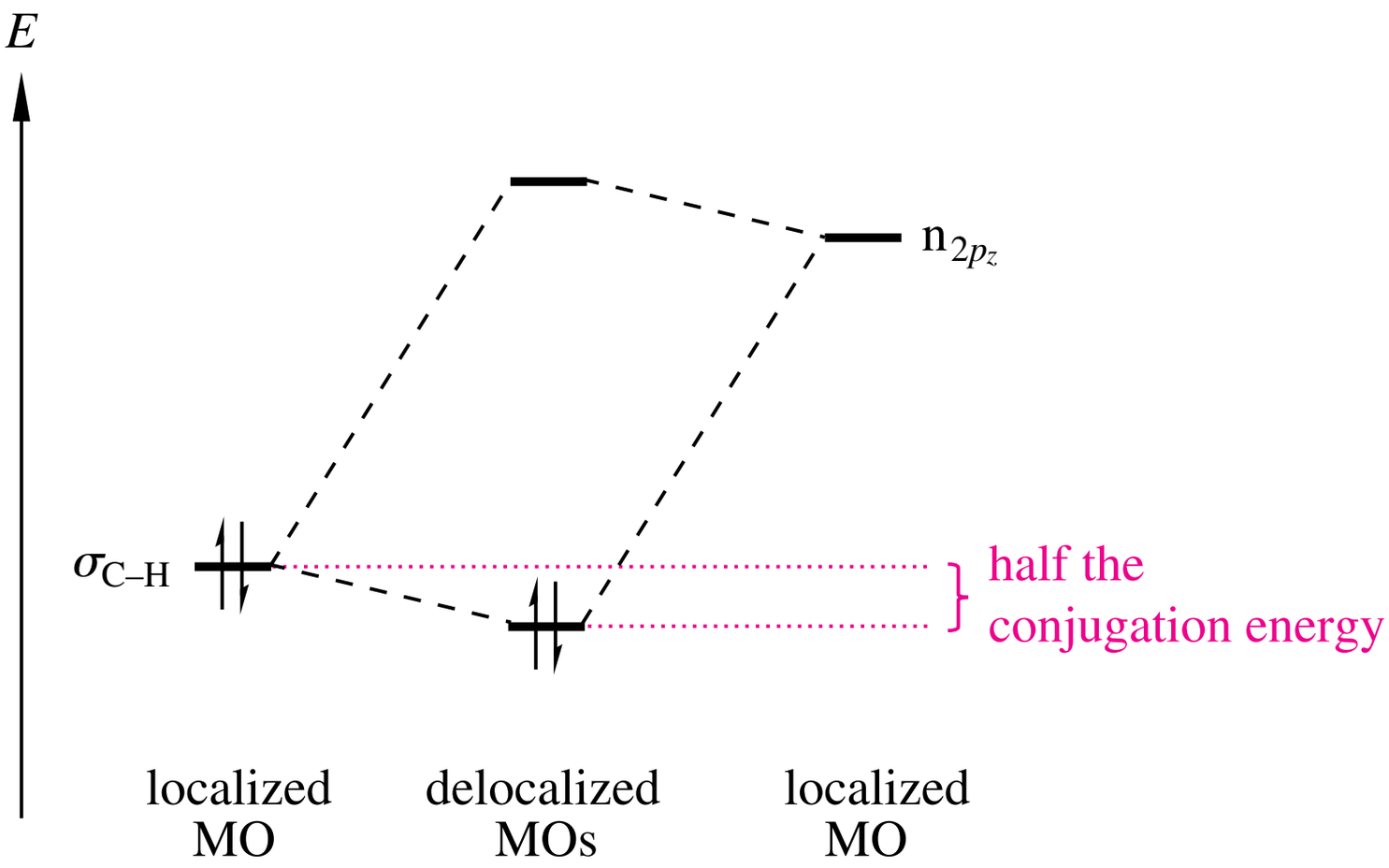
Efeitos de substituintes, MO Theory

	$PhCH_2-X$	Ph_2CH-X	Ph_3C-X
$k_{S_N1,\,rel}$	1	1000	10^8



Efeitos de substituintes, MO Theory





SN1 vs. SN2

S_N1 reactions are observed

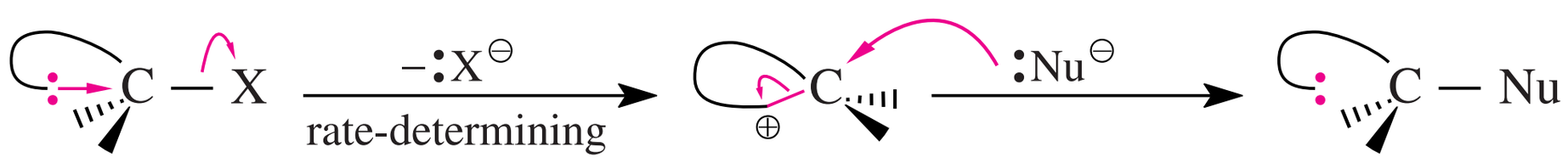
- always in substitutions on R_{tert}—X, Ar_2HC—X, and Ar_3C—X;
- always in substitutions on substituted and unsubstituted benzyl and allyl triflates;
- in substitutions on R_{sec}—X when poor nucleophiles are used (e.g., in solvolyses);
- in substitutions on R_{sec}—X that are carried out in the presence of strong Lewis acids such as in the substitution by aromatics ("Friedel–Crafts alkylation;" Figure 5.21);
- almost never in substitutions on R_{prim}—X (exception: R_{prim}—$N^+{\equiv}N$).

S_N2 reactions take place

- almost always in substitutions in sterically unhindered benzyl and allyl positions (exception: benzyl and allyl triflates react according to S_N1);
- always in substitutions in MeX and R_{prim}—X;
- in substitutions in R_{sec}—X, provided a reasonably good nucleophile is used;
- never in substitutions in substrates of the type R_{tert}—X or R_{tert}—C—X.

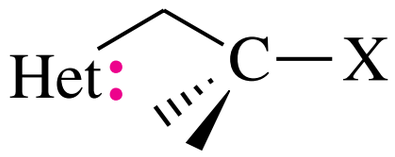
Participação do grupo vizinho

Because of this neighboring group participation, a cyclic and possibly strained (depending on the ring size) intermediate **A** is formed from the alkylating agent:

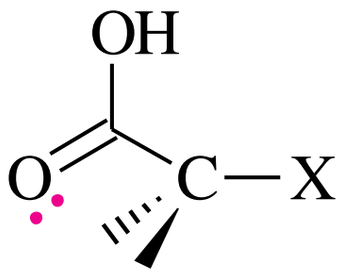


S_N2 / S_Ni **A** (three- or five-membered) **B** S_N1

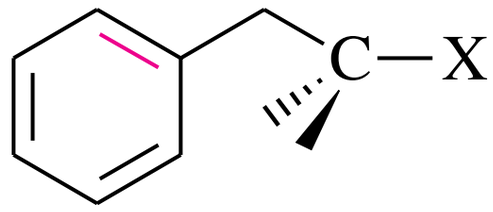
Participação do grupo vizinho



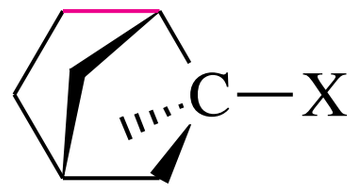
n_{sp^3}



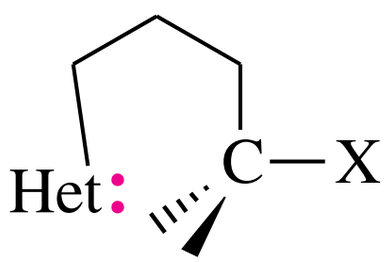
n_{sp^2}

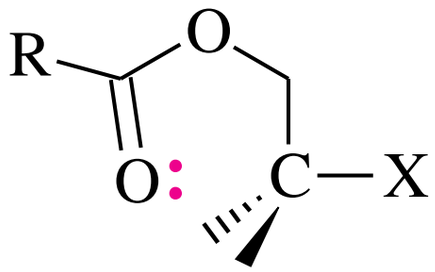


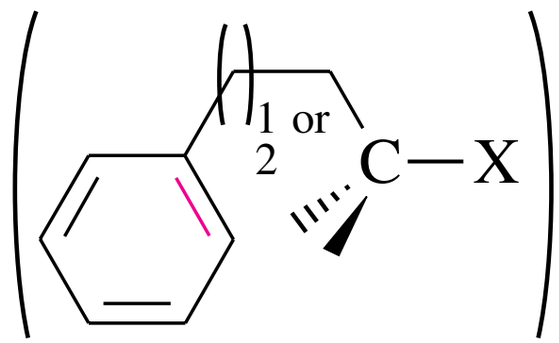
π



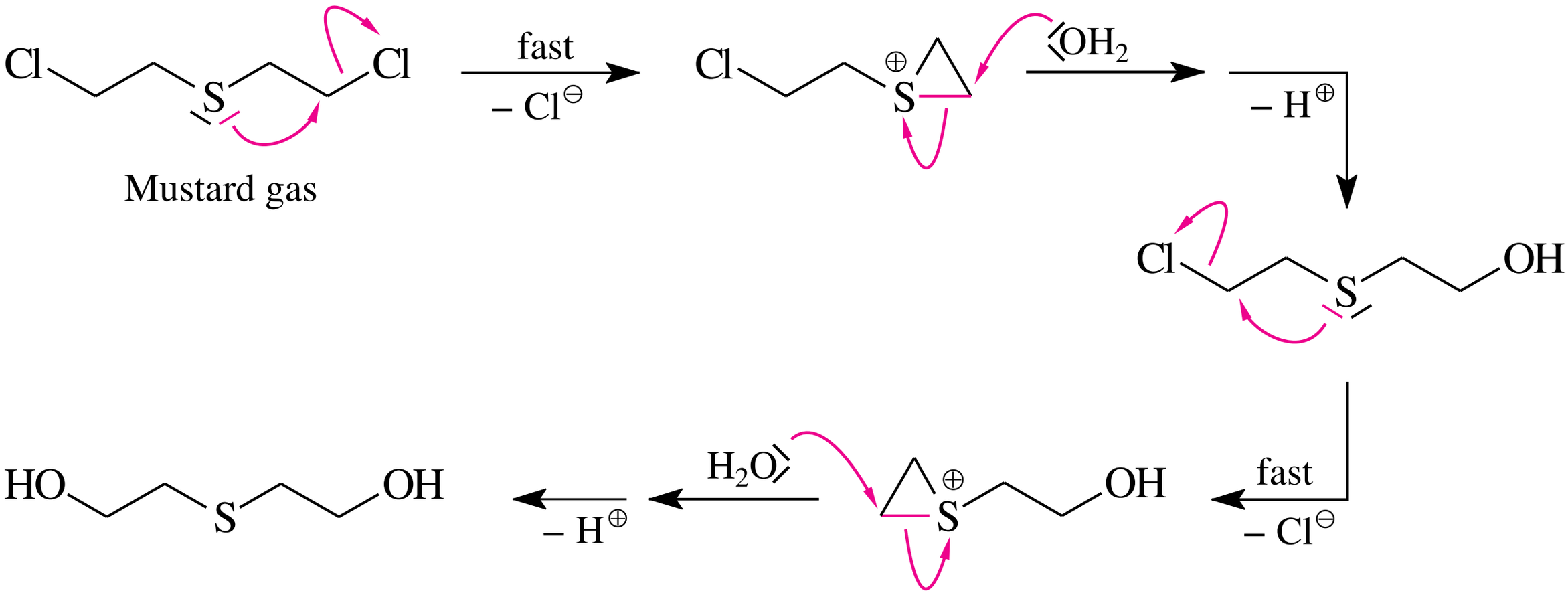
σ



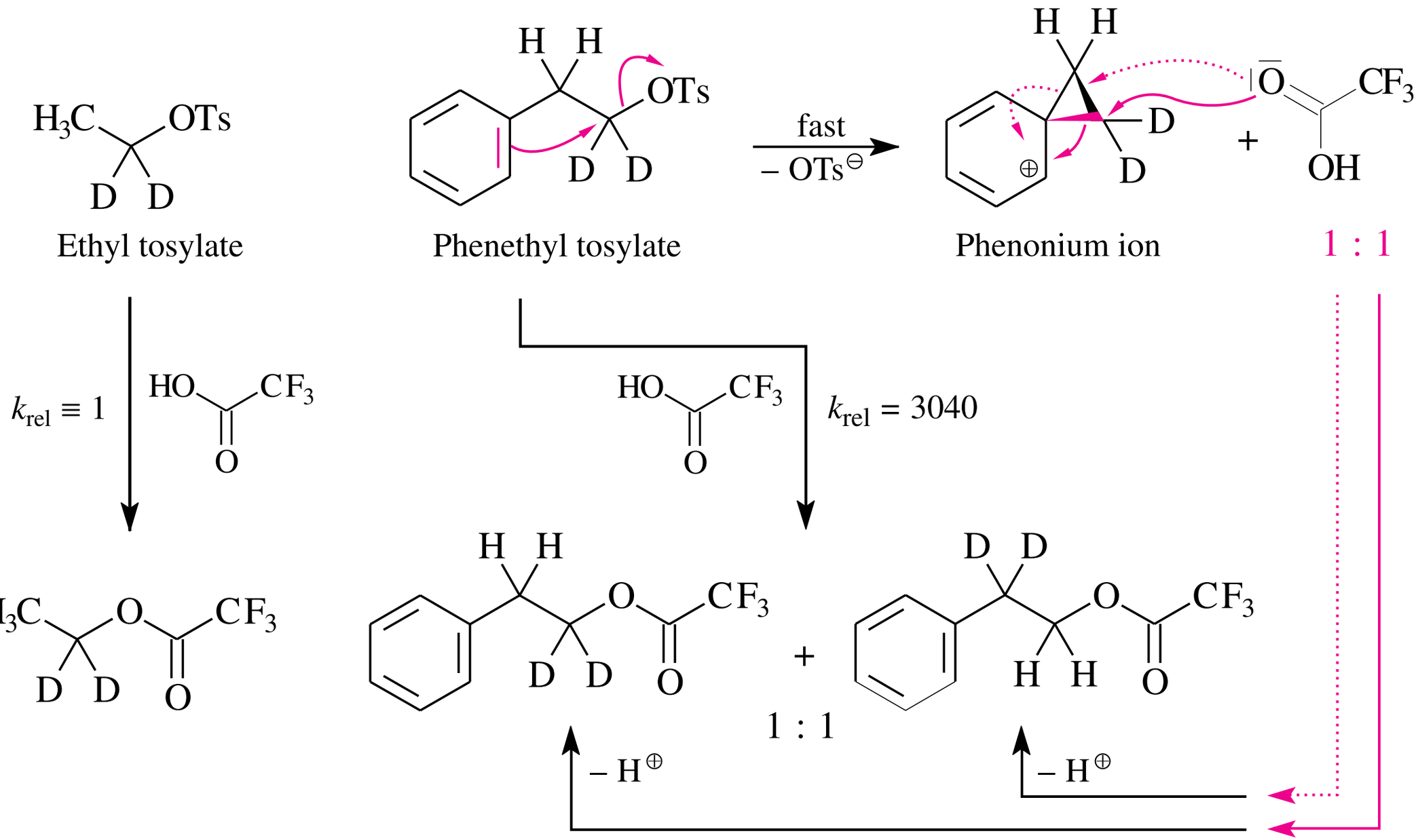




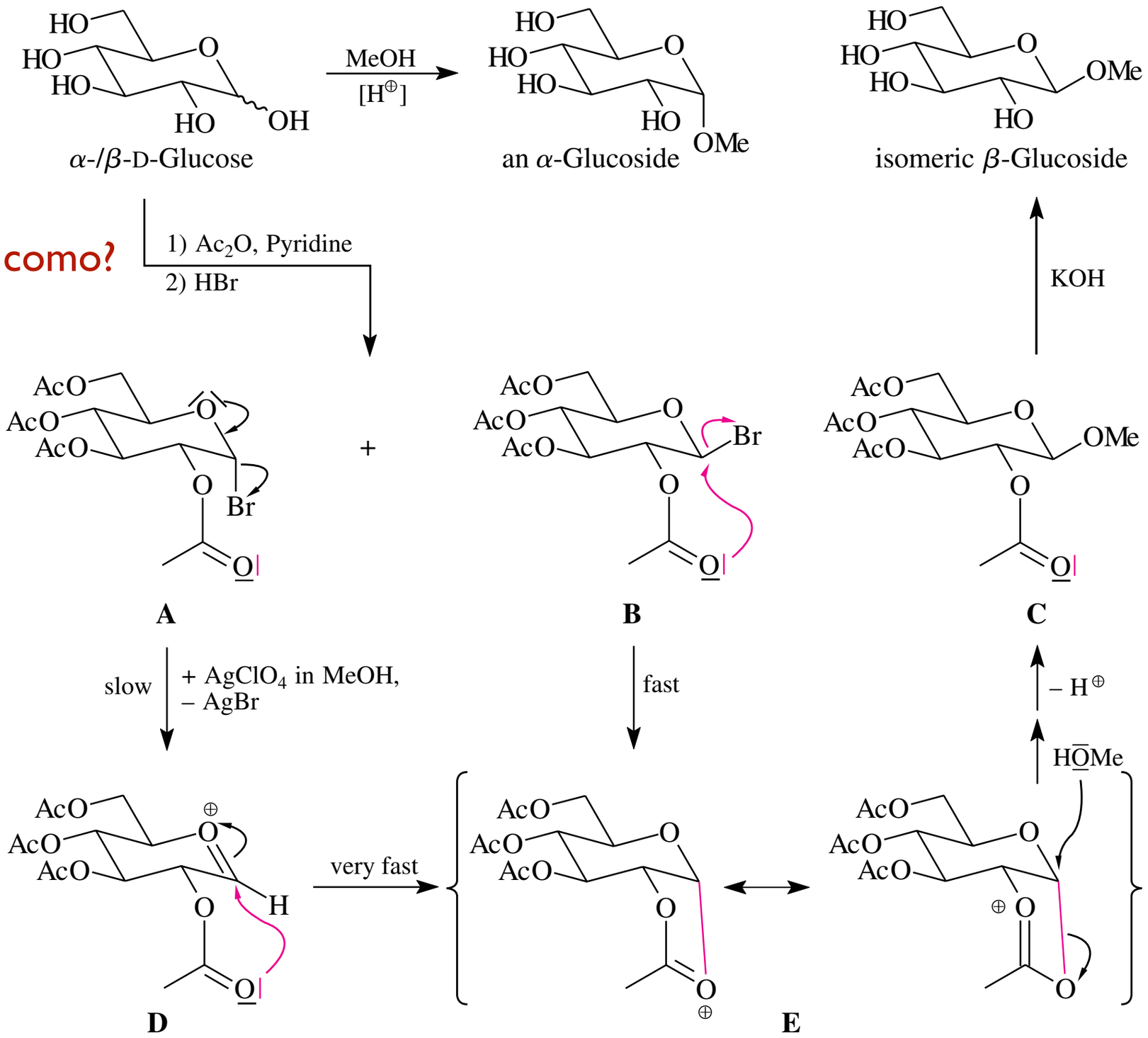
Exemplo


Cl
S
Cl
Mustard gas
fast
– Cl⊖
Cl
S⊕
OH2
– H⊕
Cl
S
OH
fast
– Cl⊖
OH
S⊕
H2O
– H⊕
HO
S
OH

Aumento da velocidade com a participação do grupo vizinho

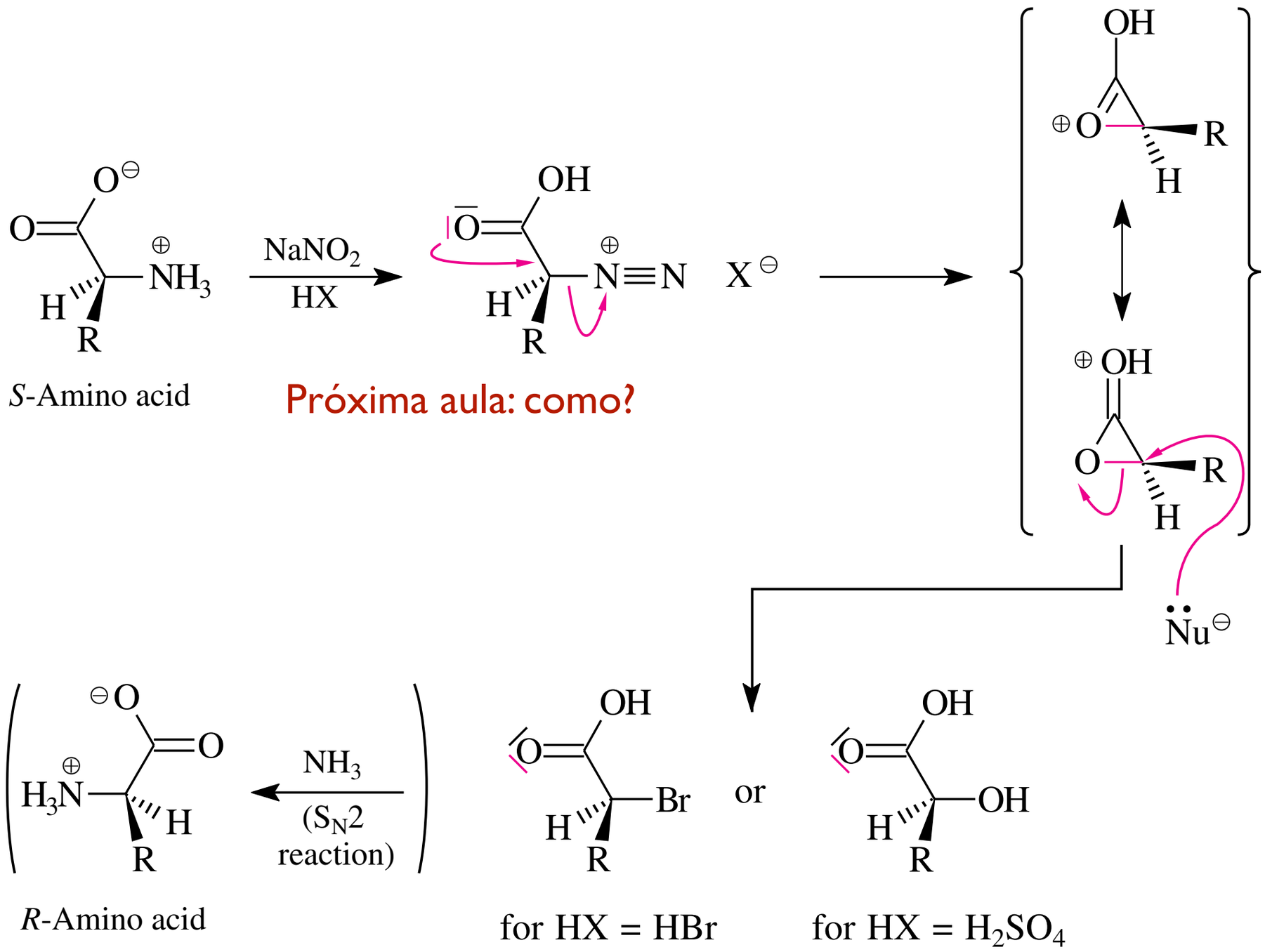


Estereoseletividade como efeito do grupo vizinho



Próxima aula: como?

Estereoseletividade devido à participação do grupo vizinho



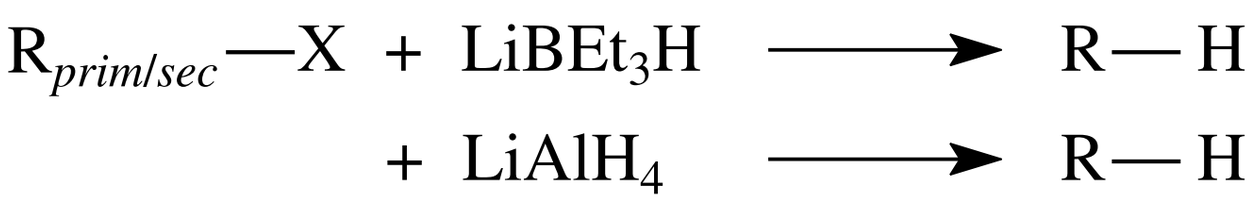
S-Amino acid

Próxima aula: como?

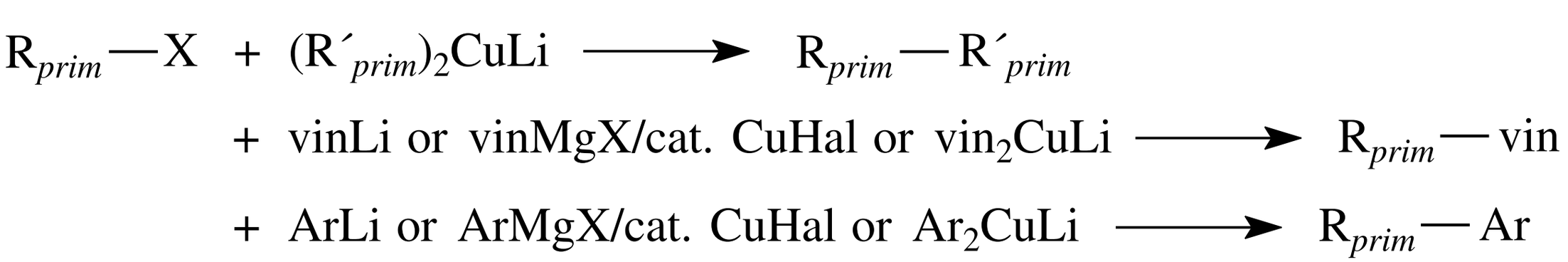
R-Amino acid

Aplicação de reações SN em síntese

Hydride nucleophiles

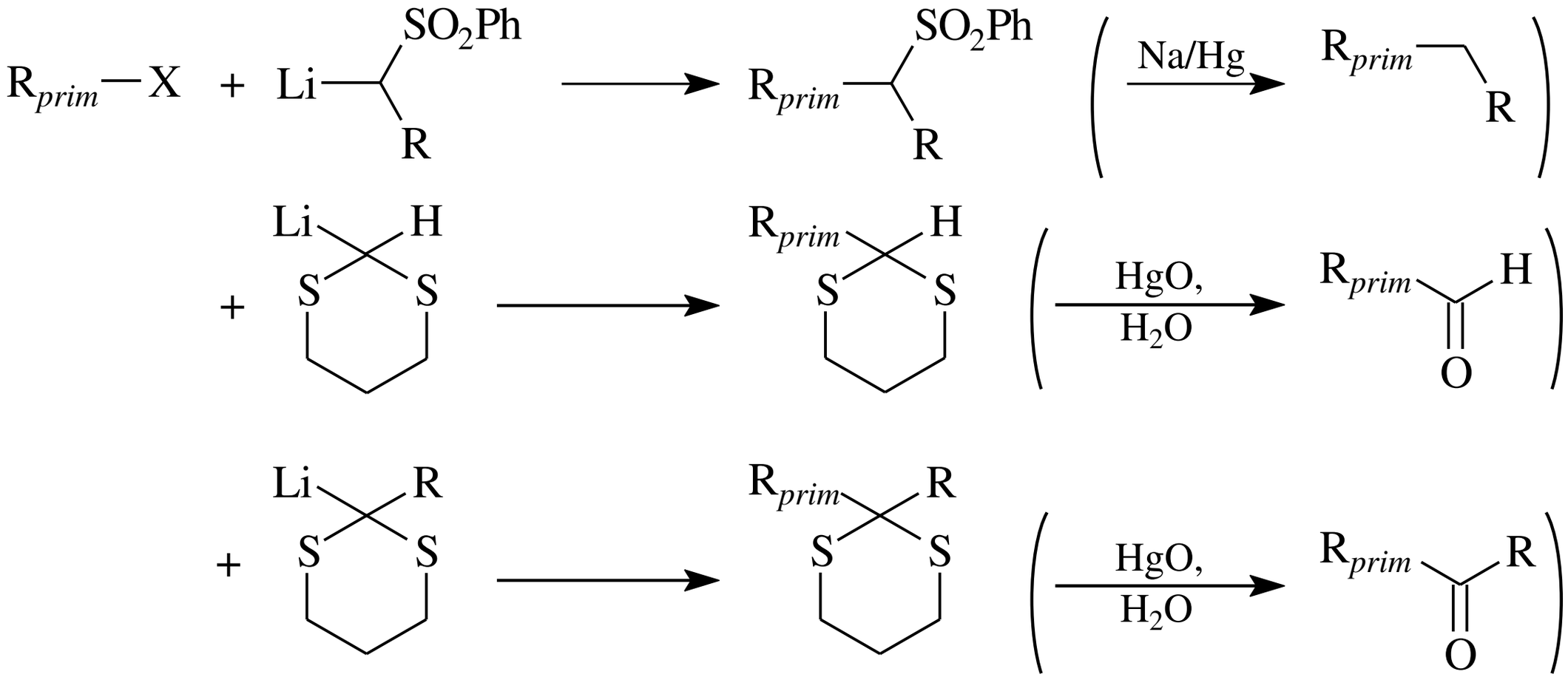


Organometallic compounds



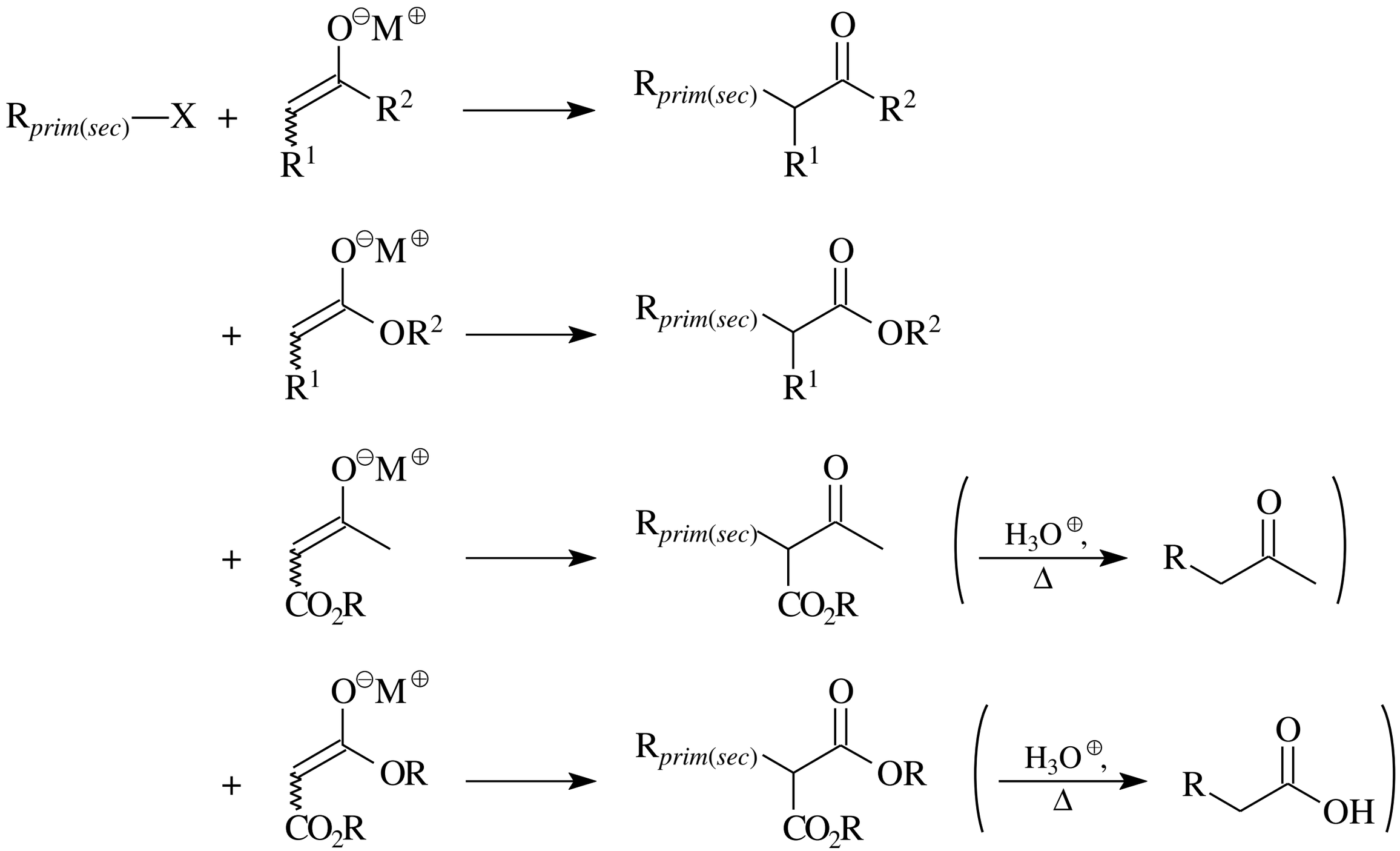
Aplicação de reações SN em síntese

Heteroatom-stabilized organolithium compounds



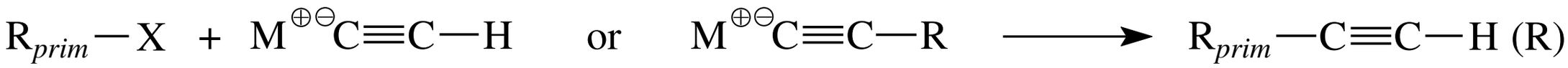
Aplicação de reações SN em síntese

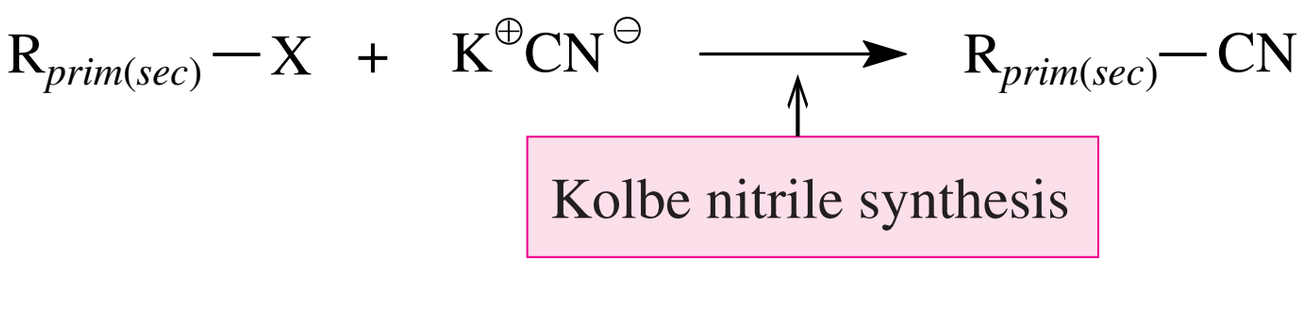
Enolates

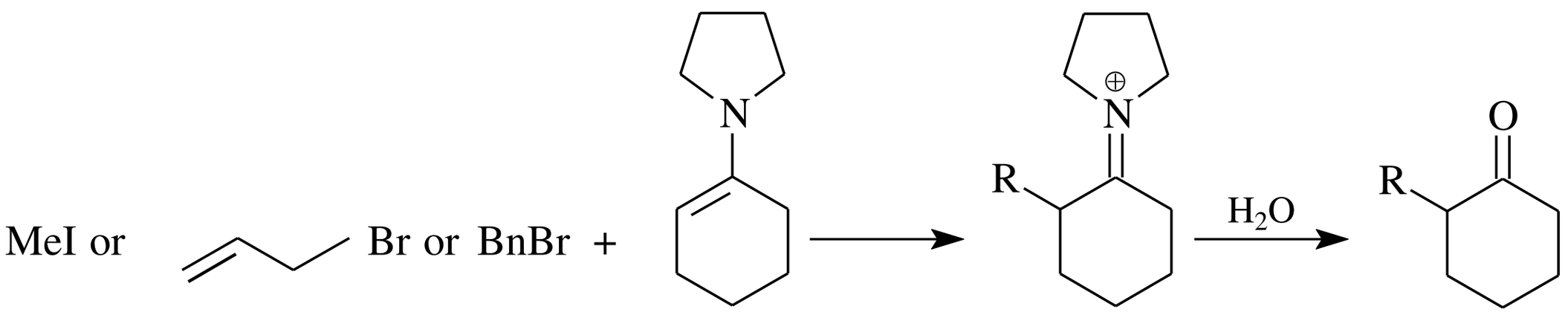


Aplicação de reações SN em síntese

Further C-nucleophiles

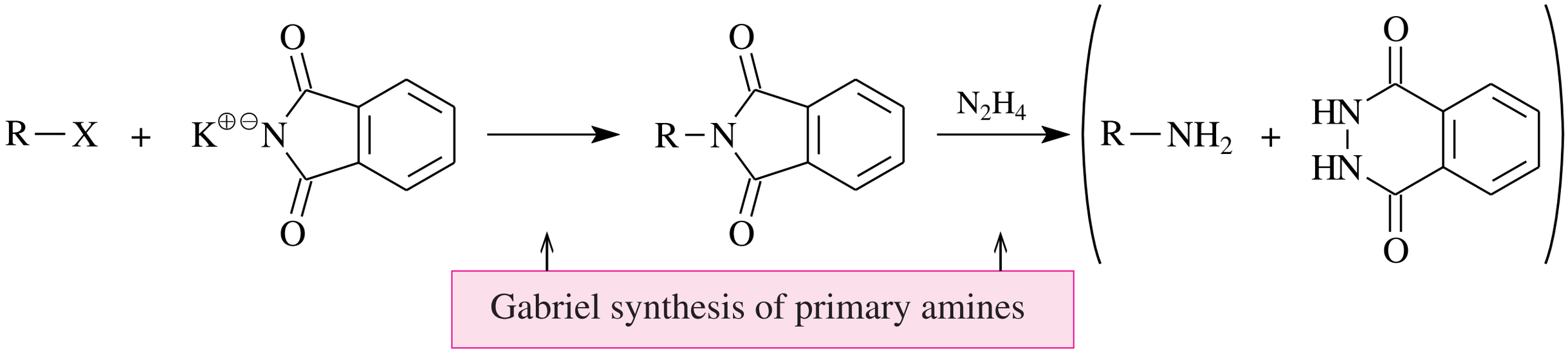


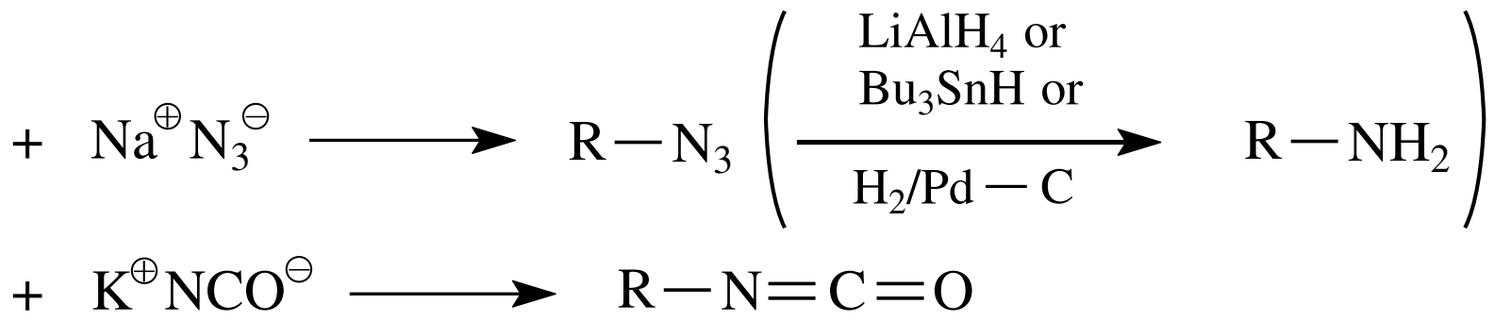




Aplicação de reações SN em síntese

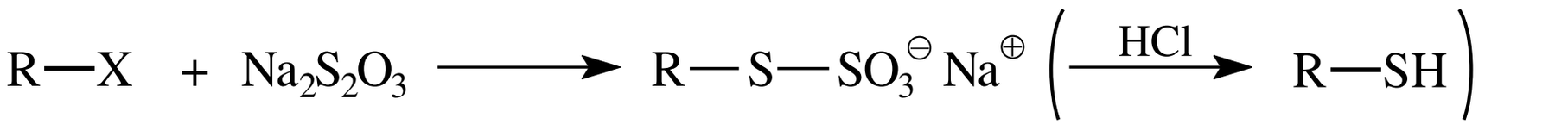
N-nucleophiles

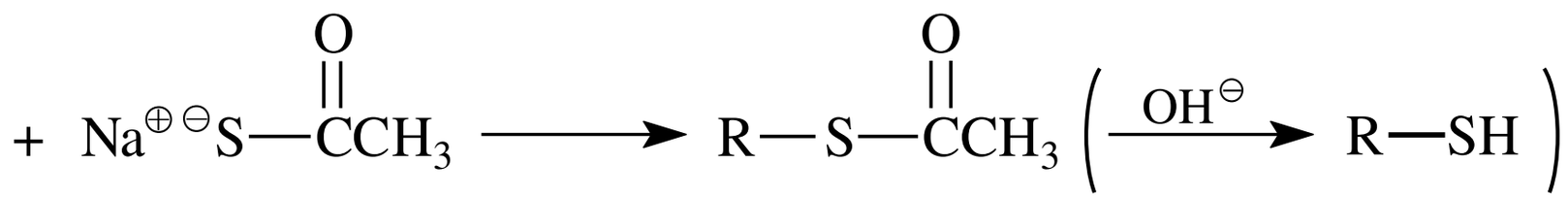


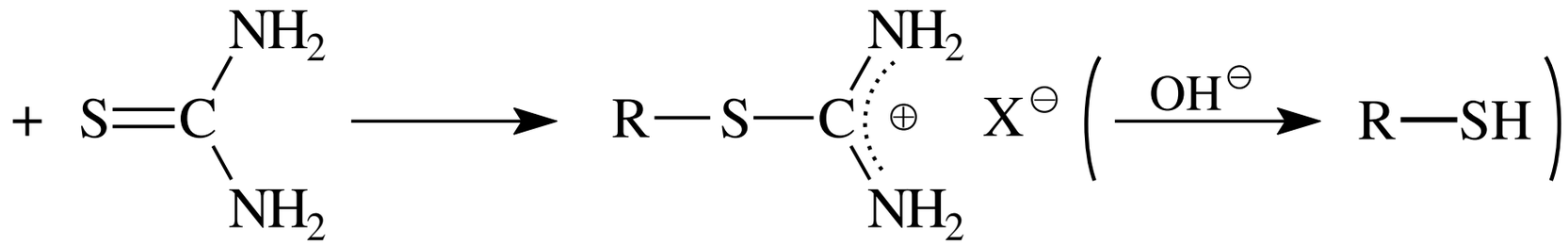


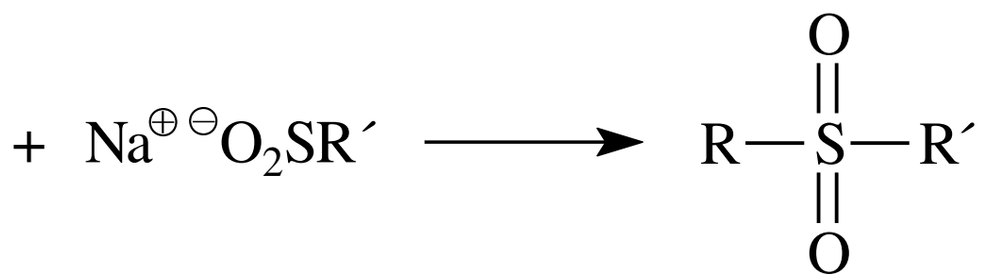
Aplicação de reações SN em síntese

S-nucleophiles



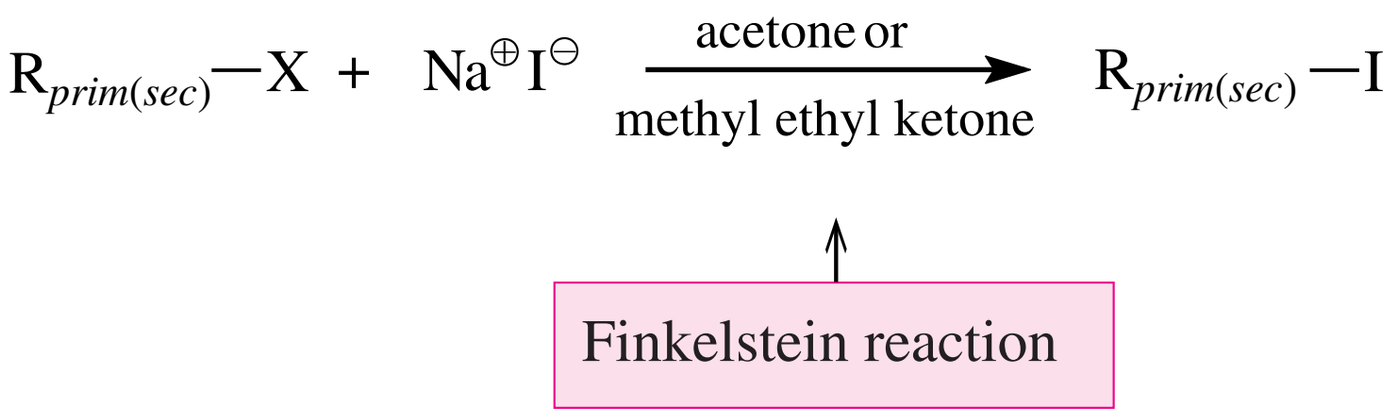




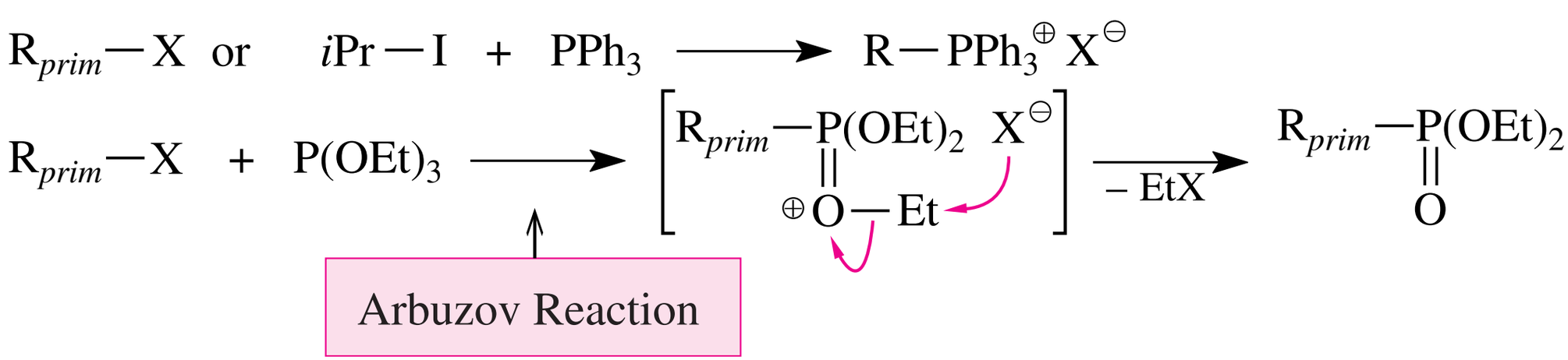


Aplicação de reações SN em síntese

Hal-nucleophiles



P-nucleophiles (→ precursors for the Wittig or Korner–Wadsworth–Emmons reaction)



Aplicação de reações SN em síntese

O-nucleophiles

$$R_{prim}{-}X + Na^{\oplus}\,{}^{\ominus}OR \longrightarrow R_{prim}{-}OR \quad \text{or}$$

Williamson ether synthesis

$$R_{prim(sec)}{-}X + Na^{\oplus}\,{}^{\ominus}OAr \longrightarrow R_{prim(sec)}{-}OAr$$

$$+ Cs^{\oplus}\,{}^{\ominus}OAc \longrightarrow R_{prim(sec)}{-}OAc$$