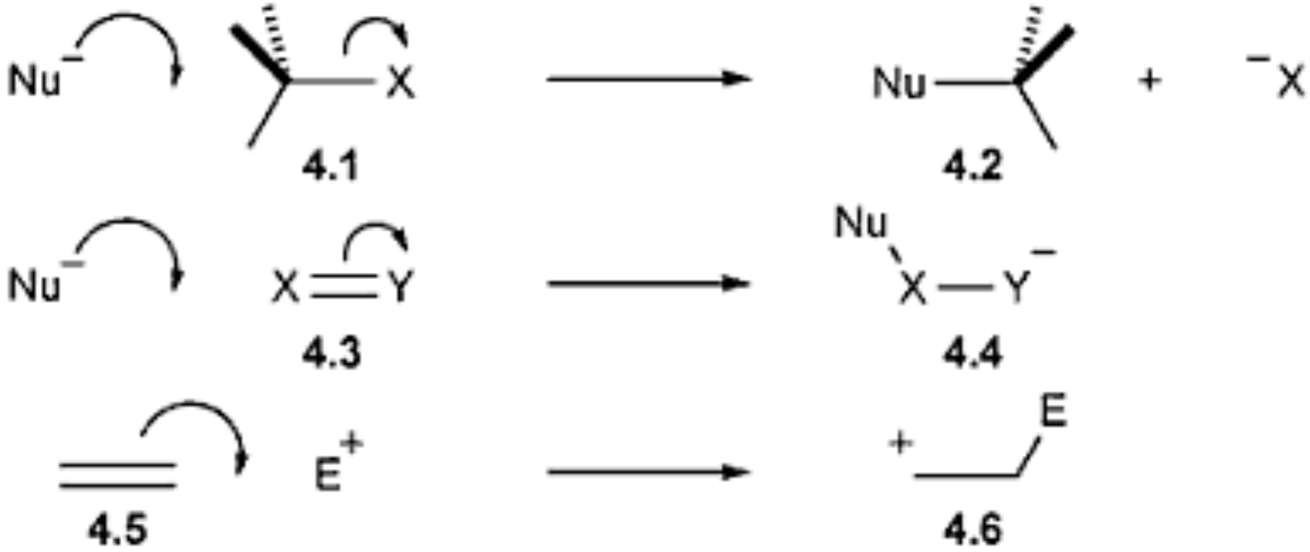
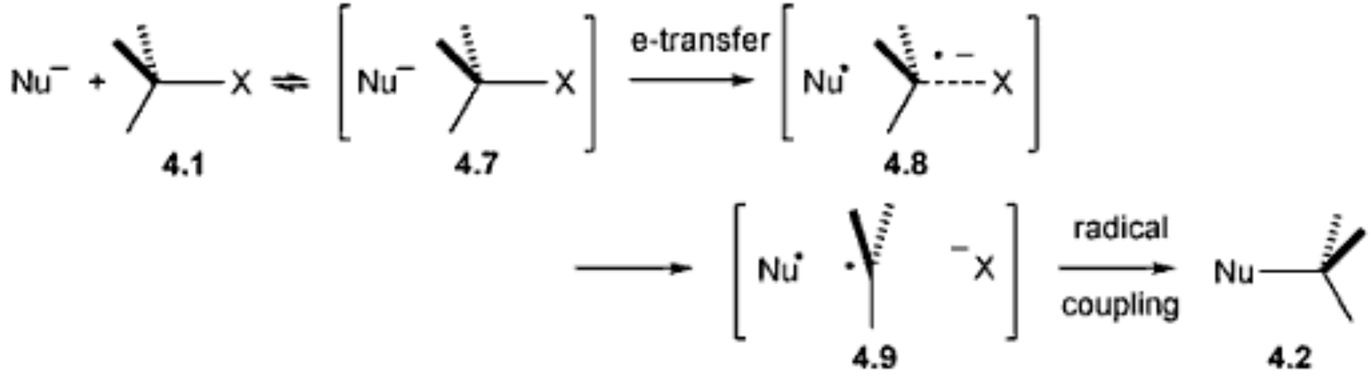
Substituição Nucleofílica

Tipos

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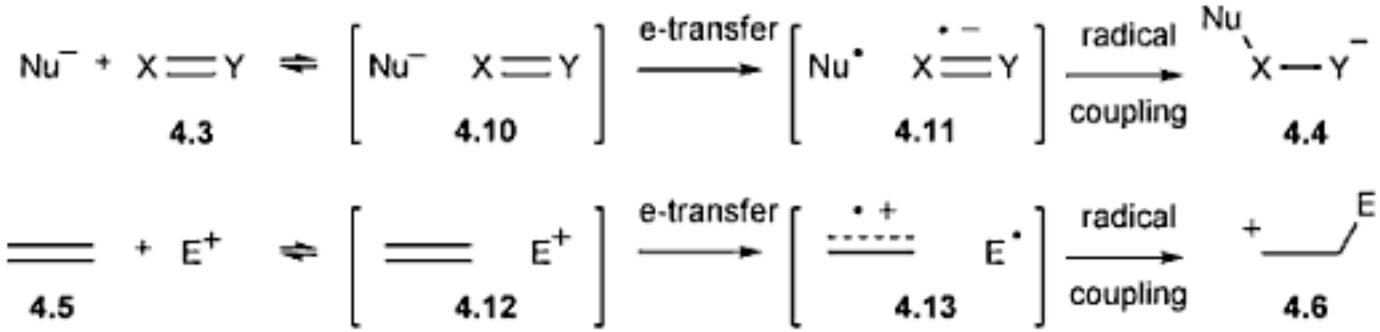
4.1
Nu⁻
X
4.7
e-transfer
Nu•
X
4.8
Nu•
⁻X
4.9
radical
coupling
Nu
4.2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Y
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E•
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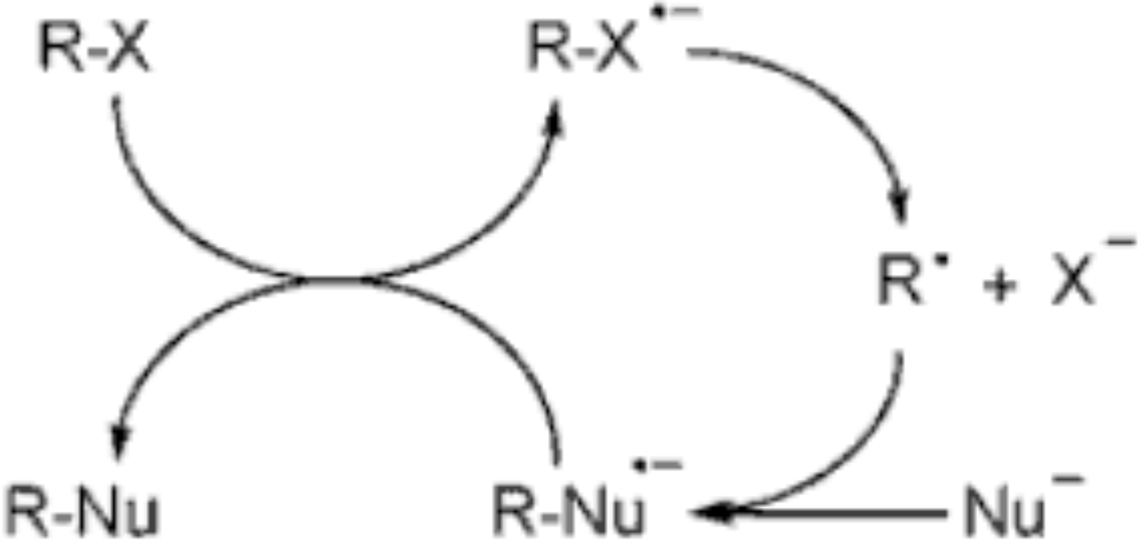
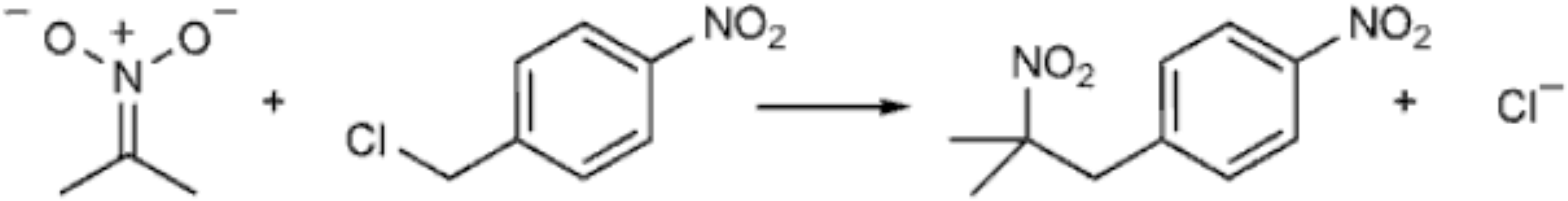
radical
coupling
E
4.6

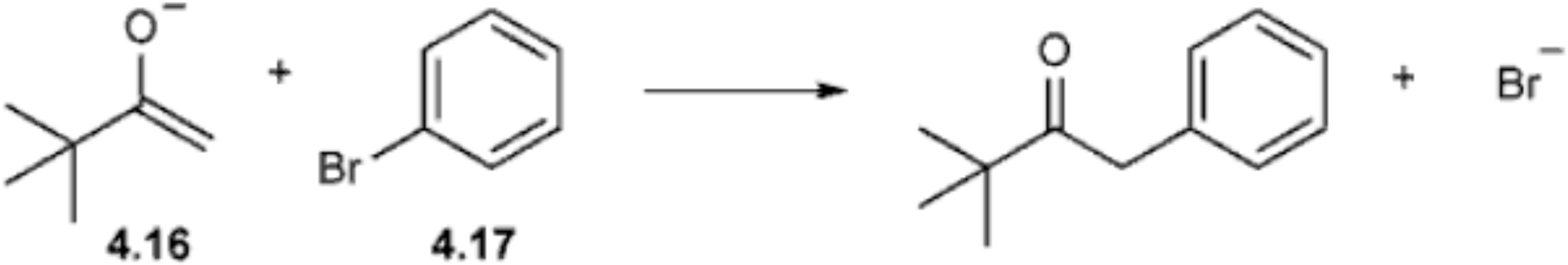
$S_{RN}1$



The $S_{RN}1$ reaction

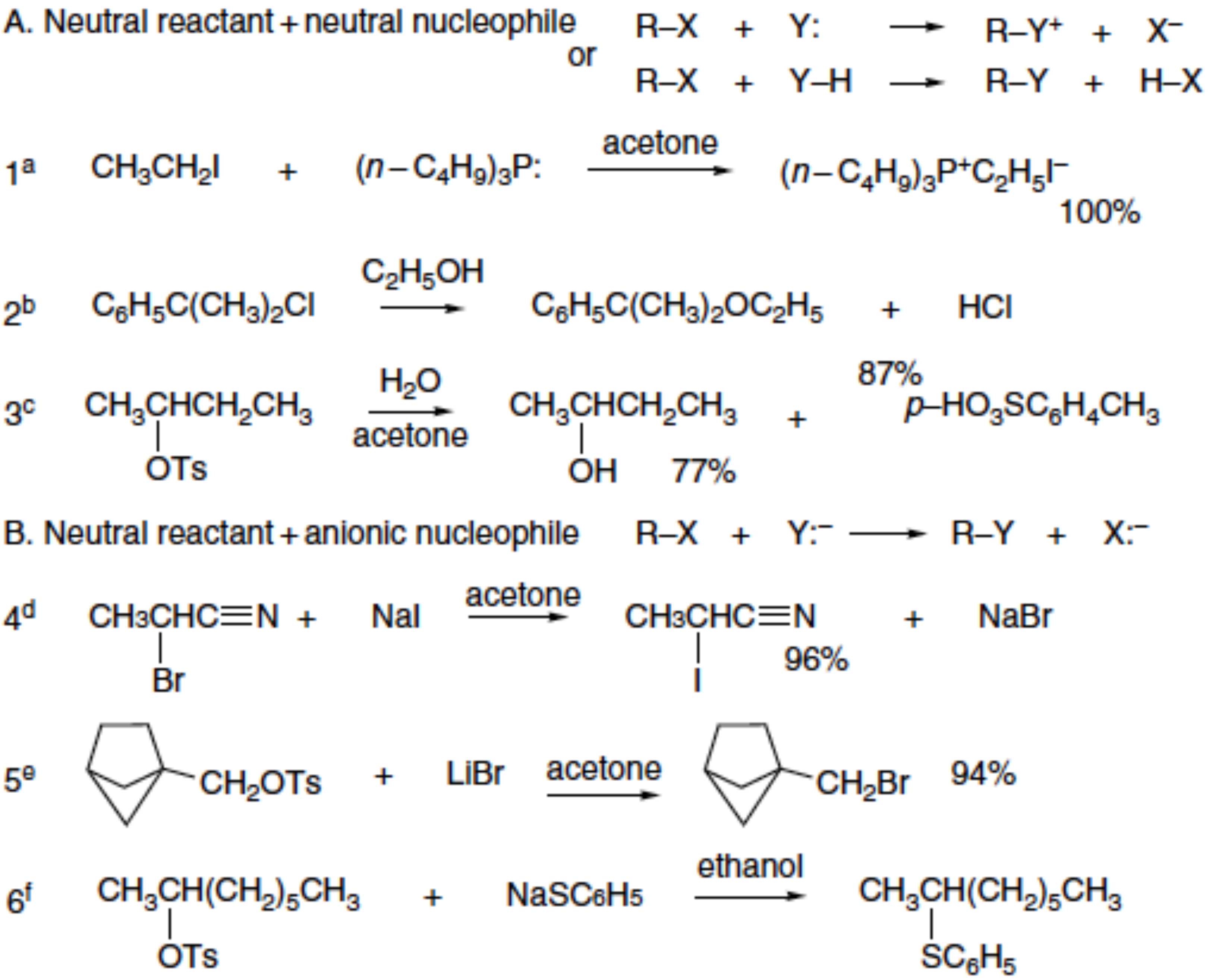


4.14 **4.15**



4.16 **4.17**

Scheme 4.1. Representative Nucleophilic Substitution Reactions



A. Neutral reactant + neutral nucleophile

$$R\text{–}X + Y\!: \longrightarrow R\text{–}Y^+ + X^-$$

or

$$R\text{–}X + Y\text{–}H \longrightarrow R\text{–}Y + H\text{–}X$$

1[a] $CH_3CH_2I + (n\text{–}C_4H_9)_3P\!: \xrightarrow{\text{acetone}} (n\text{–}C_4H_9)_3P^+C_2H_5I^-$ 100%

2[b] $C_6H_5C(CH_3)_2Cl \xrightarrow{C_2H_5OH} C_6H_5C(CH_3)_2OC_2H_5 + HCl$ 87%

3[c] $CH_3\underset{\underset{OTs}{|}}{C}HCH_2CH_3 \xrightarrow[\text{acetone}]{H_2O} CH_3\underset{\underset{OH}{|}}{C}HCH_2CH_3$ 77% $+\ p\text{–}HO_3SC_6H_4CH_3$

B. Neutral reactant + anionic nucleophile

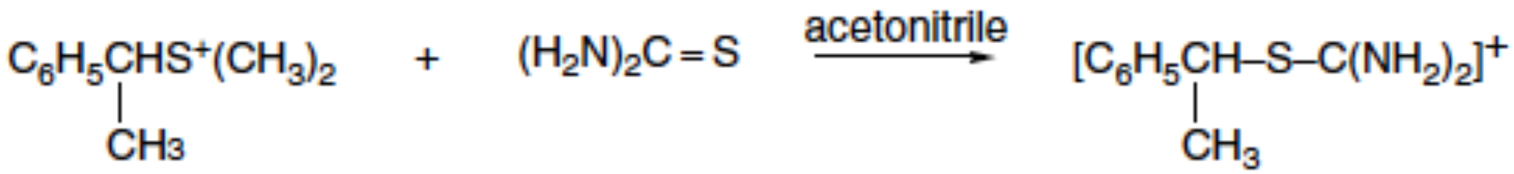
$$R\text{–}X + Y\!:^- \longrightarrow R\text{–}Y + X\!:^-$$

4[d] $CH_3\underset{\underset{Br}{|}}{C}HC{\equiv}N + NaI \xrightarrow{\text{acetone}} CH_3\underset{\underset{I}{|}}{C}HC{\equiv}N$ 96% $+\ NaBr$

5[e]

6[f] $CH_3\underset{\underset{OTs}{|}}{C}H(CH_2)_5CH_3 + NaSC_6H_5 \xrightarrow{\text{ethanol}} CH_3\underset{\underset{SC_6H_5}{|}}{C}H(CH_2)_5CH_3$

C. Cationic reactant and neutral nucleophile $R{-}X^+ + Y: \longrightarrow R{-}Y^+ + X$

7[g] 

$C_6H_5\underset{|\atop CH_3}{CH}S^+(CH_3)_2 + (H_2N)_2C{=}S \xrightarrow{\text{acetonitrile}} [C_6H_5\underset{|\atop CH_3}{CH}{-}S{-}C(NH_2)_2]^+$

8[h] $(C_6H_5)_2C{=}N^+{=}N^- + TsOH \longrightarrow (C_6H_5)_2CH{-}N^+{\equiv}N \xrightarrow{C_2H_5OH} (C_6H_5)_2CHOC_2H_5 + N_2$

D. Cationic reactant and anionic nucleophile $R-X^+ + Y: \longrightarrow R-Y + X:$

9[i] $(C_2H_5)_3O^{+\,-}BF_4 + Na^{+\,-}O_2CC(CH_3)_3 \longrightarrow \underset{90\%}{(CH_3)_3CCO_2C_2H_5} + O(C_2H_5)_2$

10[j] $CH_2{=}CHCH_2CH_2S^+(CH_3)C_6H_5 \xrightarrow[\text{DMF}]{\text{NaI}} \underset{52\%}{CH_2{=}CHCH_2CH_2I} + CH_3SC_6H_5$

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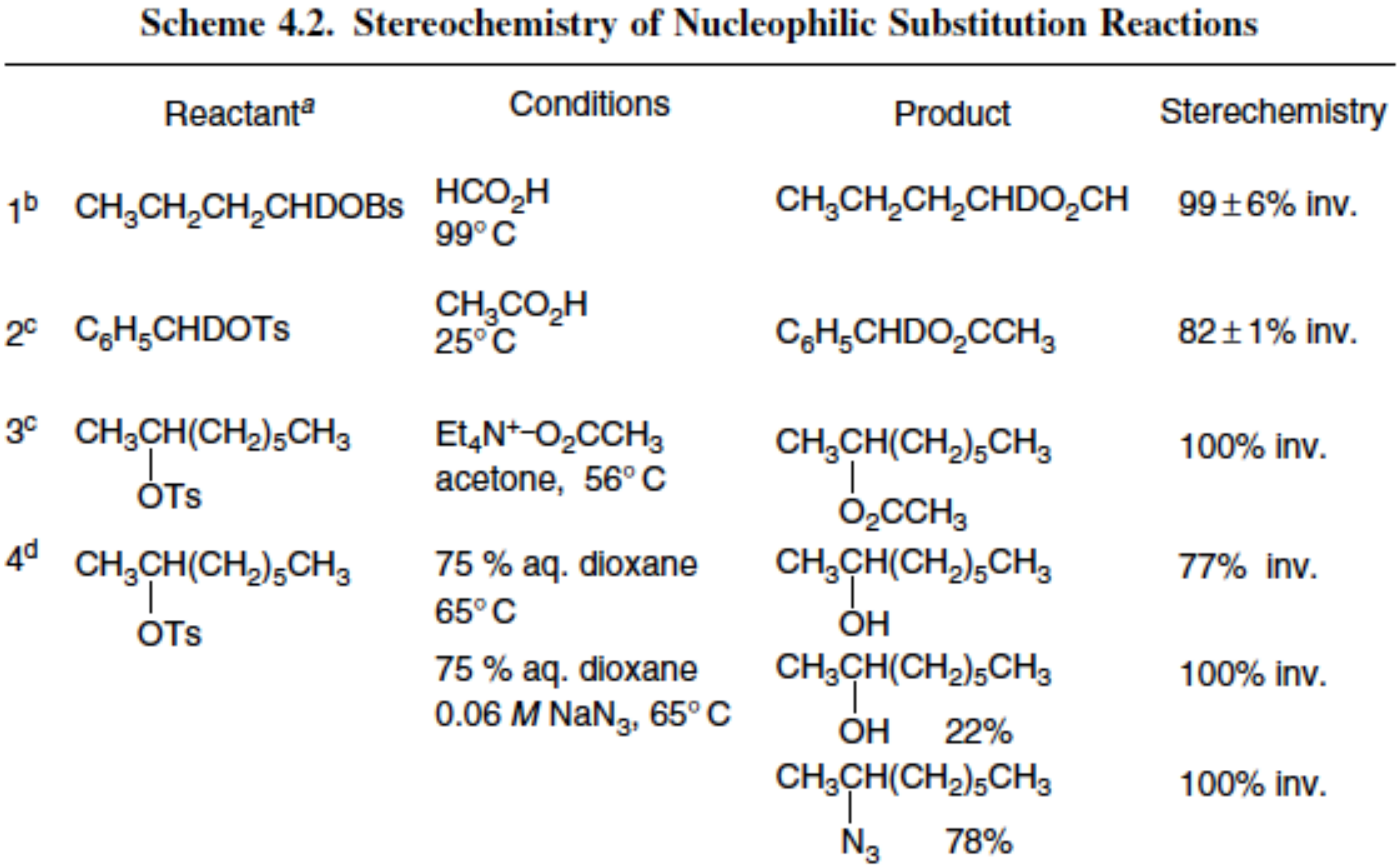
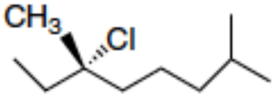
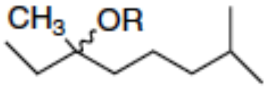
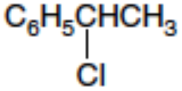
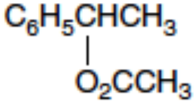
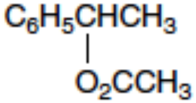
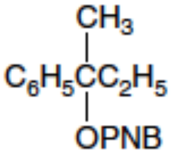
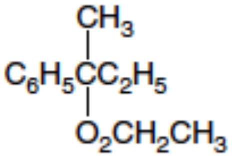
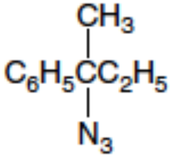
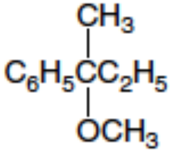
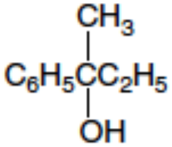
a. S. A. Buckler and W. A. Henderson, *J. Am. Chem. Soc.*, **82**, 5795 (1960).
b. R. L. Buckson and S. G. Smith, *J. Org. Chem.*, **32**, 634 (1967).
c. J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, *J. Am. Chem. Soc.*, **74**, 4283 (1952).
d. M. S. Newman and R. D. Closson, *J. Am. Chem. Soc.*, **66**, 1553 (1944).
e. K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963).
f. H. L. Goering, D. L. Towns, and B. Dittmar, *J. Org. Chem.*, **27**, 736 (1962).
g. H. M. R. Hoffmann and E. D. Hughes, *J. Chem. Soc.*, 1259 (1964).
h. J. D. Roberts and W. Watanabe, *J. Am. Chem. Soc.*, **72**, 4869 (1950).
i. D. J. Raber and P. Gariano, *Tetrahedron Lett.*, 4741 (1971).
j. E. J. Corey and M. Jautelat, *Tetrahedron Lett.*, 5787 (1968).

Estereoquímica



Scheme 4.2. Stereochemistry of Nucleophilic Substitution Reactions

	Reactant[a]	Conditions	Product	Sterechemistry
1[b]	$CH_3CH_2CH_2CHDOBs$	HCO_2H 99° C	$CH_3CH_2CH_2CHDO_2CH$	99 ± 6% inv.
2[c]	$C_6H_5CHDOTs$	CH_3CO_2H 25° C	$C_6H_5CHDO_2CCH_3$	82 ± 1% inv.
3[c]	$CH_3\underset{OTs}{CH}(CH_2)_5CH_3$	$Et_4N^+{}^-O_2CCH_3$ acetone, 56° C	$CH_3\underset{O_2CCH_3}{CH}(CH_2)_5CH_3$	100% inv.
4[d]	$CH_3\underset{OTs}{CH}(CH_2)_5CH_3$	75 % aq. dioxane 65° C	$CH_3\underset{OH}{CH}(CH_2)_5CH_3$	77% inv.
		75 % aq. dioxane 0.06 *M* NaN_3, 65° C	$CH_3\underset{OH}{CH}(CH_2)_5CH_3$ 22%	100% inv.
			$CH_3\underset{N_3}{CH}(CH_2)_5CH_3$ 78%	100% inv.

5[g]				
			CH_3OH, DTBP, 25° C	78% inv.
			C_2H_5OH, DTBP, 40° C	55% inv.
			HCO_2H, DTBP, 0° C	42% inv.
			CF_3CH_2OH, DTBP, 25° C	13% ret.
			t-BuOH, 20% H_2O, 25° C	49% inv.
			dioxane, 20% H_2O, 25° C	98% inv.
6[f]	 $C_6H_5\underset{\displaystyle Cl}{\underset{\mid}{C}}HCH_3$	$K^+{}^-O_2CCH_3$, CH_3CO_2H, 50° C	 $C_6H_5\underset{\displaystyle O_2CCH_3}{\underset{\mid}{C}}HCH_3$	15% inv.
		$Et_4N^+{}^-O_2CCH_3$ 50% acetone	 $C_6H_5\underset{\displaystyle O_2CCH_3}{\underset{\mid}{C}}HCH_3$	65% inv.
7[f]	 $C_6H_5\overset{\displaystyle CH_3}{\overset{\mid}{\underset{\displaystyle OPNB}{\underset{\mid}{C}}}}C_2H_5$	$K^+{}^-O_2CCH_3$, CH_3CO_2H, 23° C	 $C_6H_5\overset{\displaystyle CH_3}{\overset{\mid}{\underset{\displaystyle O_2CH_2CH_3}{\underset{\mid}{C}}}}C_2H_5$	5 ± 2% inv.
		NaN_3 in CH_3OH, 65° C	 $C_6H_5\overset{\displaystyle CH_3}{\overset{\mid}{\underset{\displaystyle N_3}{\underset{\mid}{C}}}}C_2H_5$	56 ± 1% inv.
			 $C_6H_5\overset{\displaystyle CH_3}{\overset{\mid}{\underset{\displaystyle OCH_3}{\underset{\mid}{C}}}}C_2H_5$	14% inv.
		90% aq, acetone	 $C_6H_5\overset{\displaystyle CH_3}{\overset{\mid}{\underset{\displaystyle OH}{\underset{\mid}{C}}}}C_2H_5$	38% ret.

Mecanismos Casos Limitantes: S_N2

$$R\text{–}X + Y{:}^- \xrightarrow{k} R\text{–}Y + X{:}^-$$

$$\text{rate} = \frac{-d[R\text{–}X]}{dt} = \frac{-d[Y{:}^-]}{dt} = k[R\text{–}X][Y{:}^-]$$

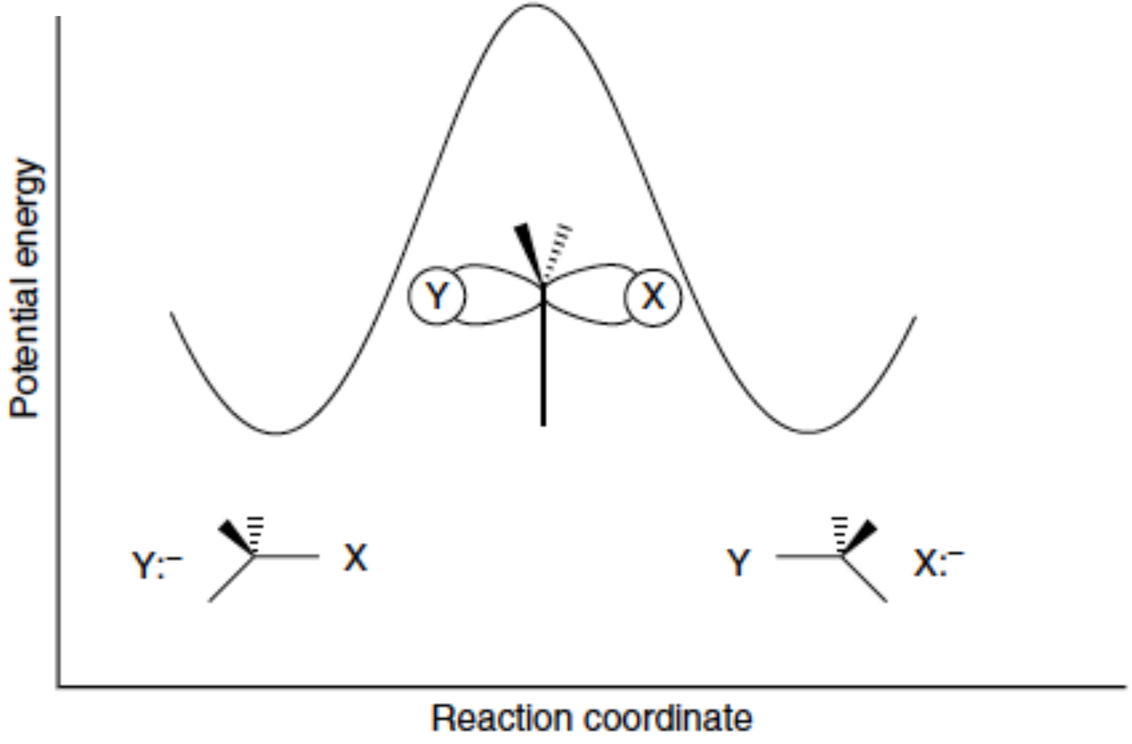
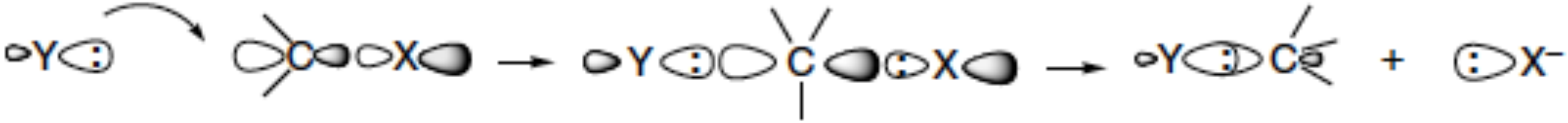
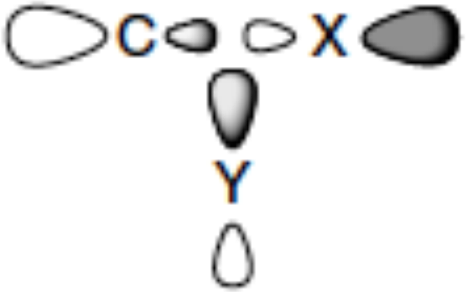


Fig. 4.3. Reaction energy profile for nucleophilic substitution by the direct displacement (S_N2) mechanism.

- Favorecido



- Desfavorecido



(a) Inversion of configuration

(b) Retention of configuration

Fig. 5.1 Frontier orbitals for the S_E2 reaction

Mecanismos Casos Limitantes: S_N1

$$R\text{–}X \xrightarrow[\text{slow}]{k_1} R^+ + X^-$$

$$R^+ + Y^- \xrightarrow[\text{fast}]{k_2} R\text{–}Y$$

$$\text{rate} = k_1[R\text{–}X]$$

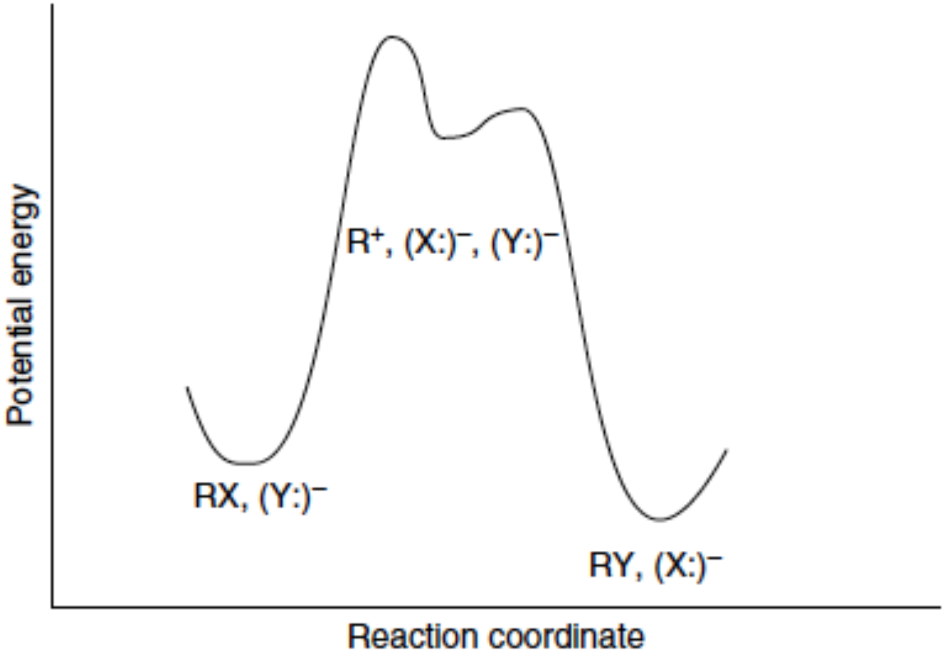
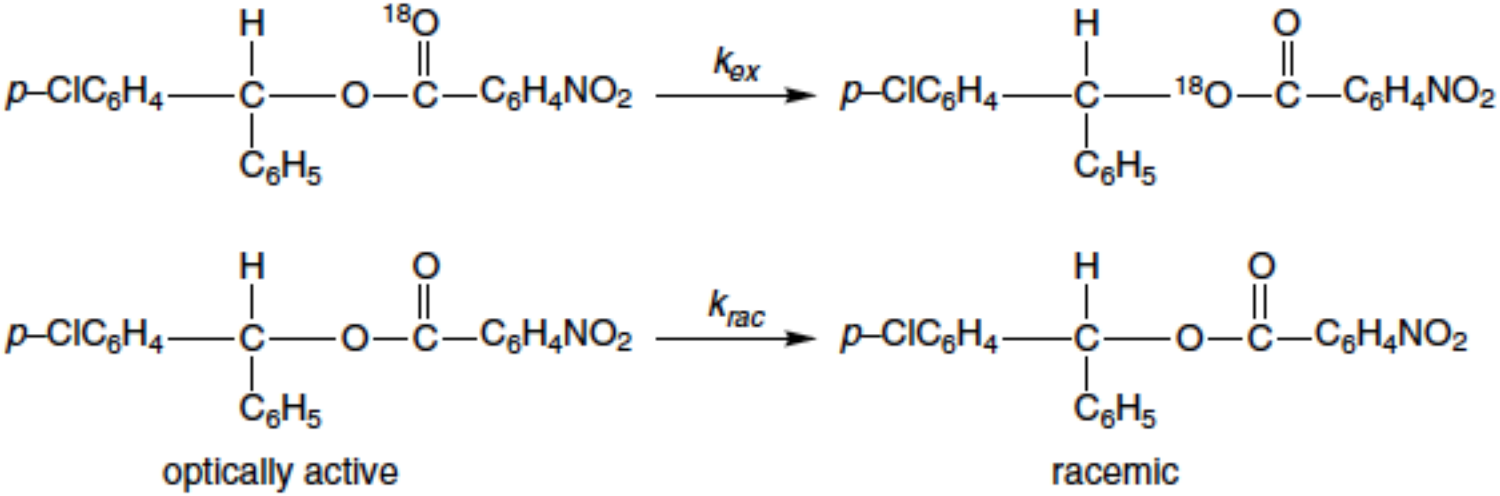


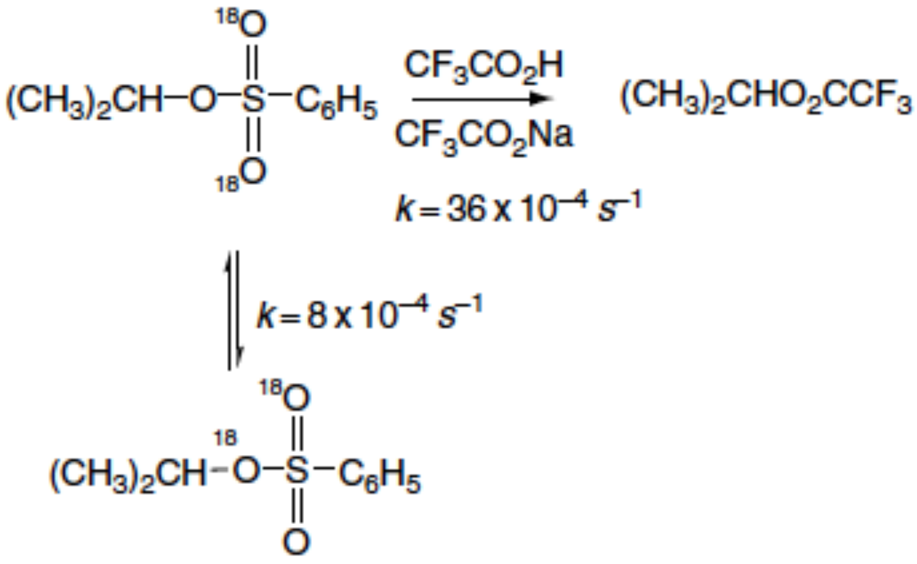
Fig. 4.1. Reaction energy profile for nucleophilic substitution by the ionization (S_N1) mechanism.

Retorno interno



$k_{ex}/k_{rac} = 2.3$

H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.,* ***86, 120 (1964).***


$(CH_3)_2CH-O-S(=^{18}O)_2-C_6H_5$
CF_3CO_2H
CF_3CO_2Na
$(CH_3)_2CHO_2CCF_3$
$k = 36 \times 10^{-4}\ s^{-1}$
$k = 8 \times 10^{-4}\ s^{-1}$
$(CH_3)_2CH-^{18}O-S(=^{18}O)(=O)-C_6H_5$

$$R{-}X \overset{\text{ionization}}{\rightleftharpoons} \underset{\substack{\text{contact}\\ \text{ion pair}}}{R^+X^-} \rightleftharpoons \underset{\substack{\text{solvent-}\\ \text{separated}\\ \text{ion pair}}}{R^+\|X^-} \overset{\text{dissociation}}{\rightleftharpoons} R^+ \quad + \quad X^-$$

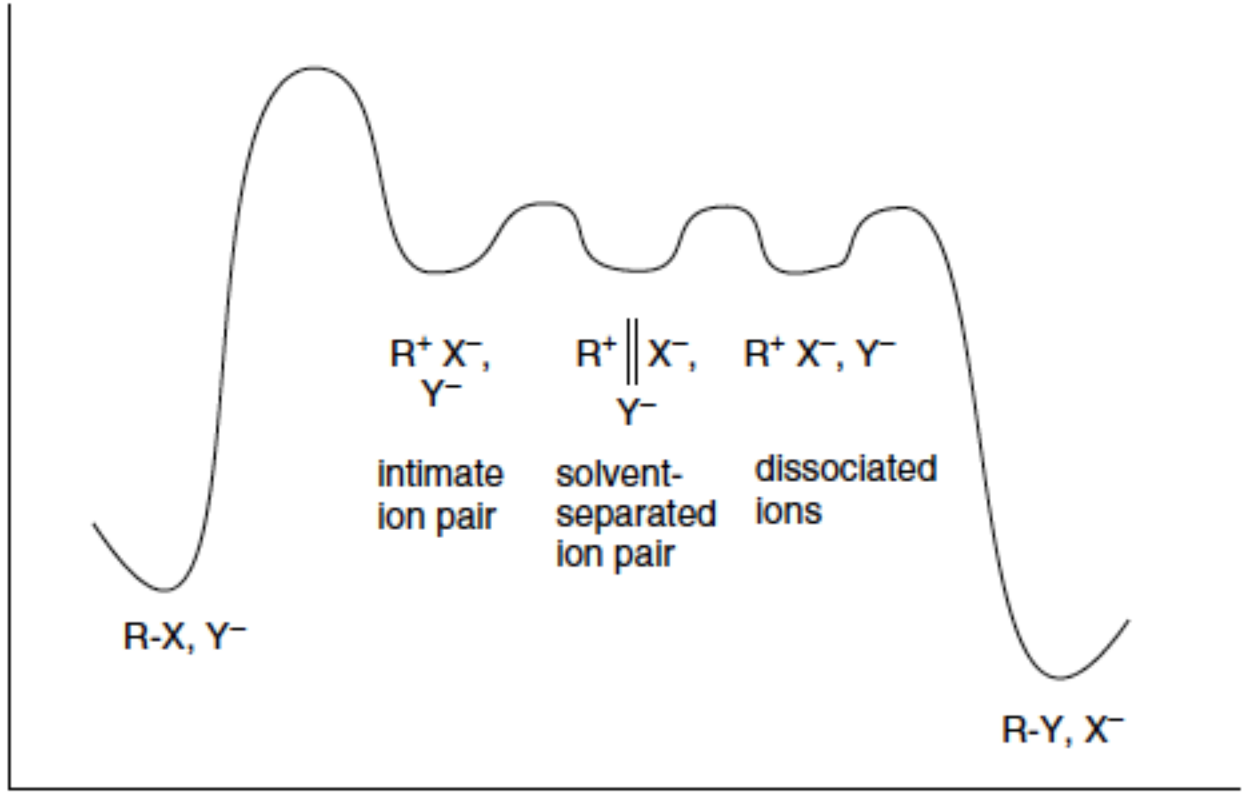


Fig. 4.4. Schematic relationship between reactants, ion pairs, and products in substitution proceeding through ion pairs.

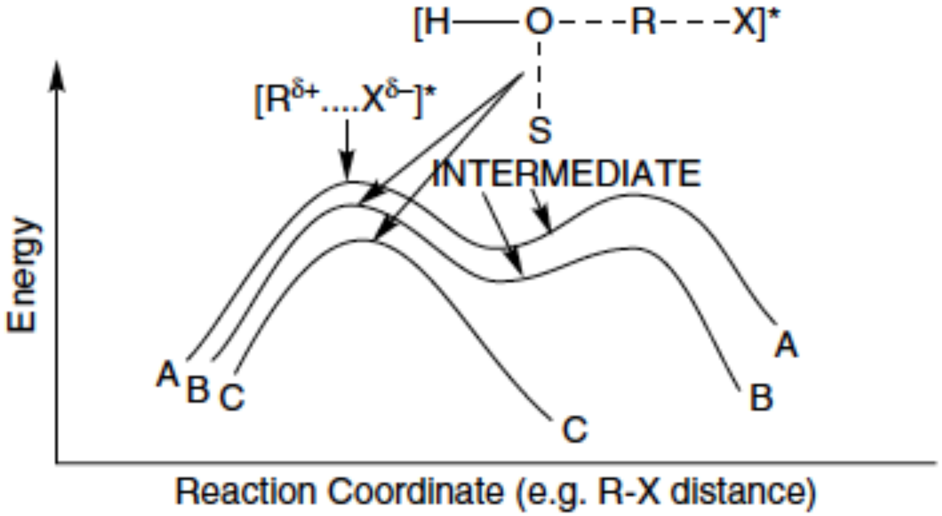


Fig. 4.5. Reaction energy profiles for substitution mechanisms. A is the S_N1 mechanism. B is the S_N2 mechanism with an intermediate ion pair or pentacoordinate species. C is the classical S_N2 mechanism. Reproduced from T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.*, **14,** 1 (1977), by permission of Academic Press.

Gráficos de O’Ferrall-Jencks

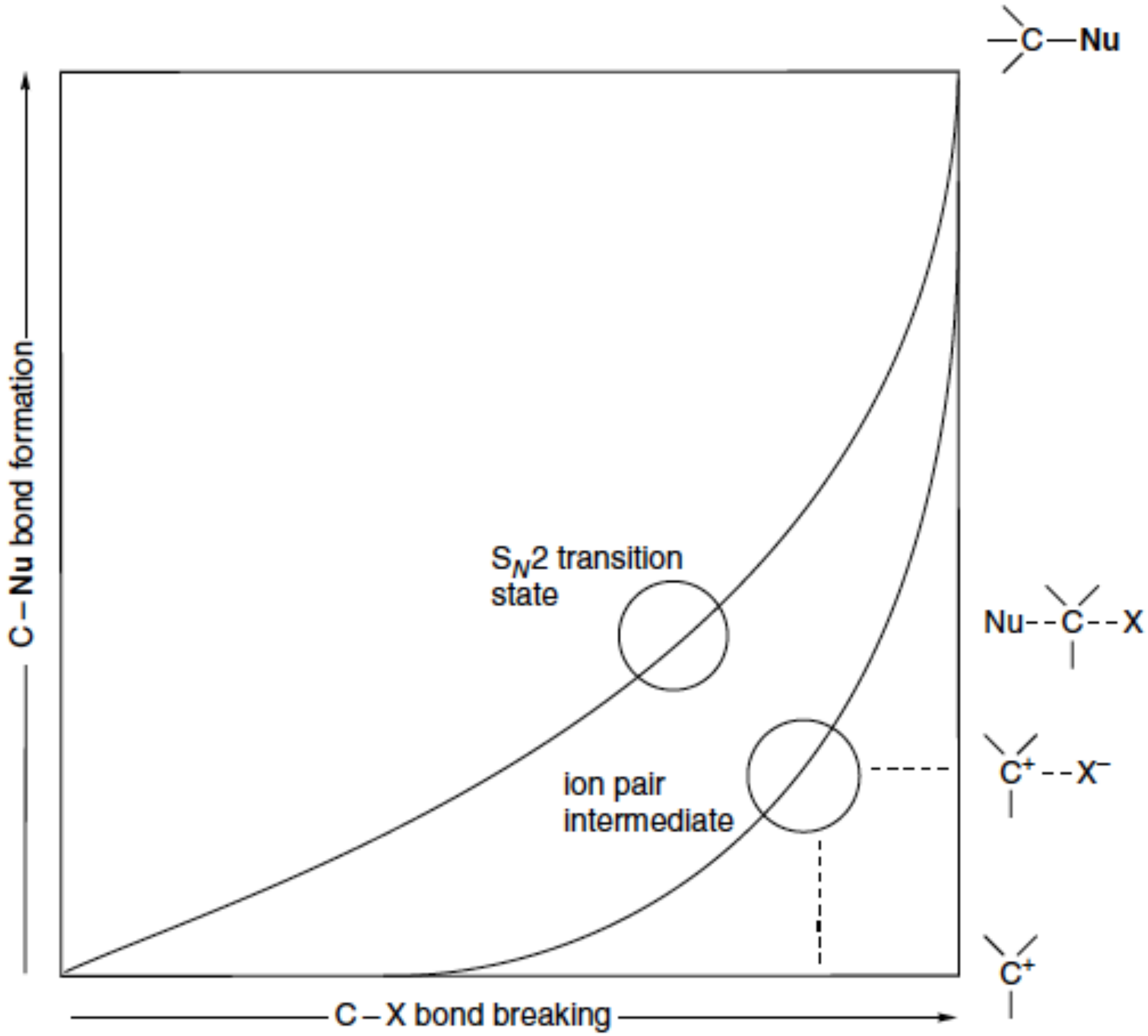


Fig. 4.7. Two-dimensional reaction energy diagram showing concerted, ion pair intermediate, and stepwise mechanisms for nucleophilic substitution.

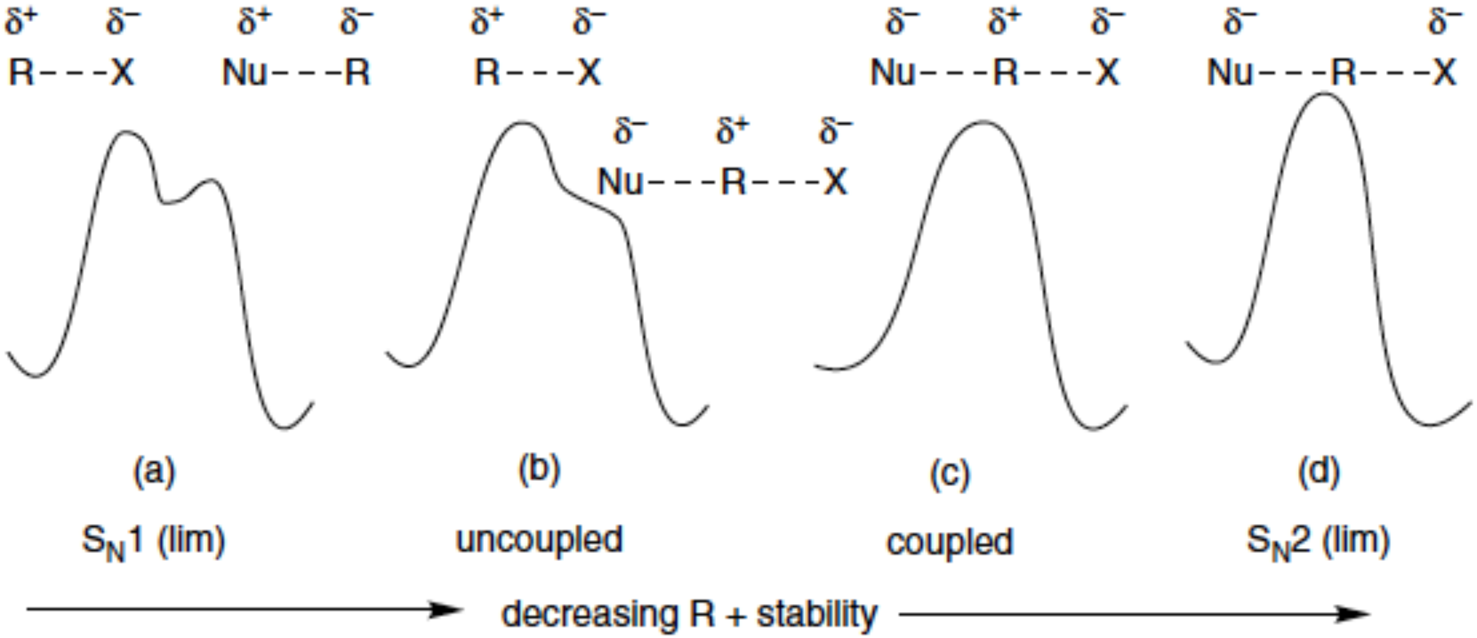
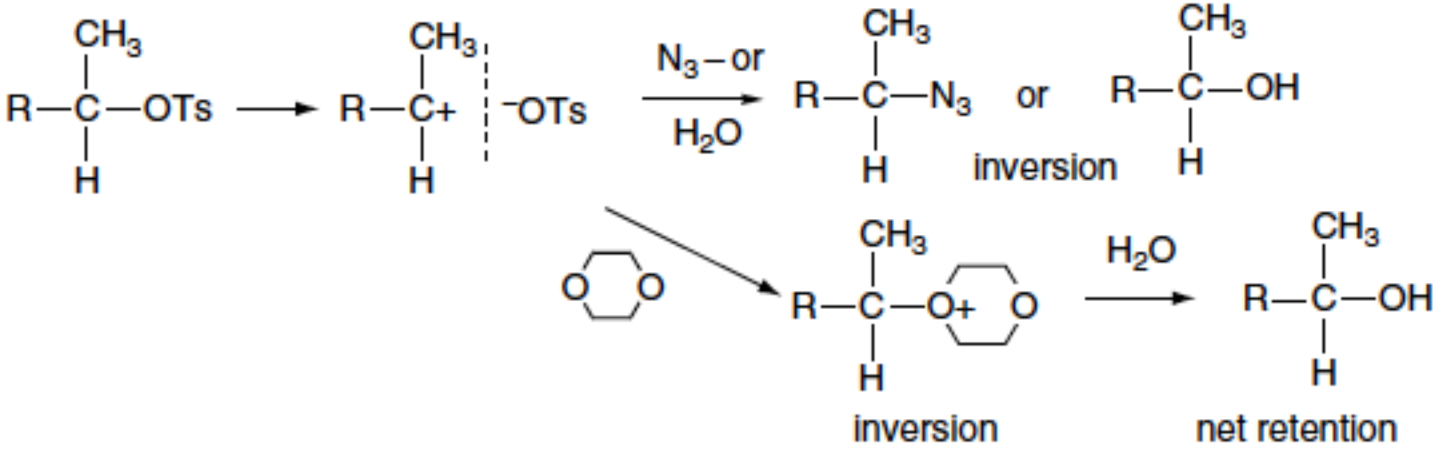


Fig. 4.6. Reaction energy profiles showing decreasing carbocation stability in change from S_N1(lim) to S_N2(lim) mechanisms.

Estereoquímica: Explicação



Escalas de nucleofilicidade

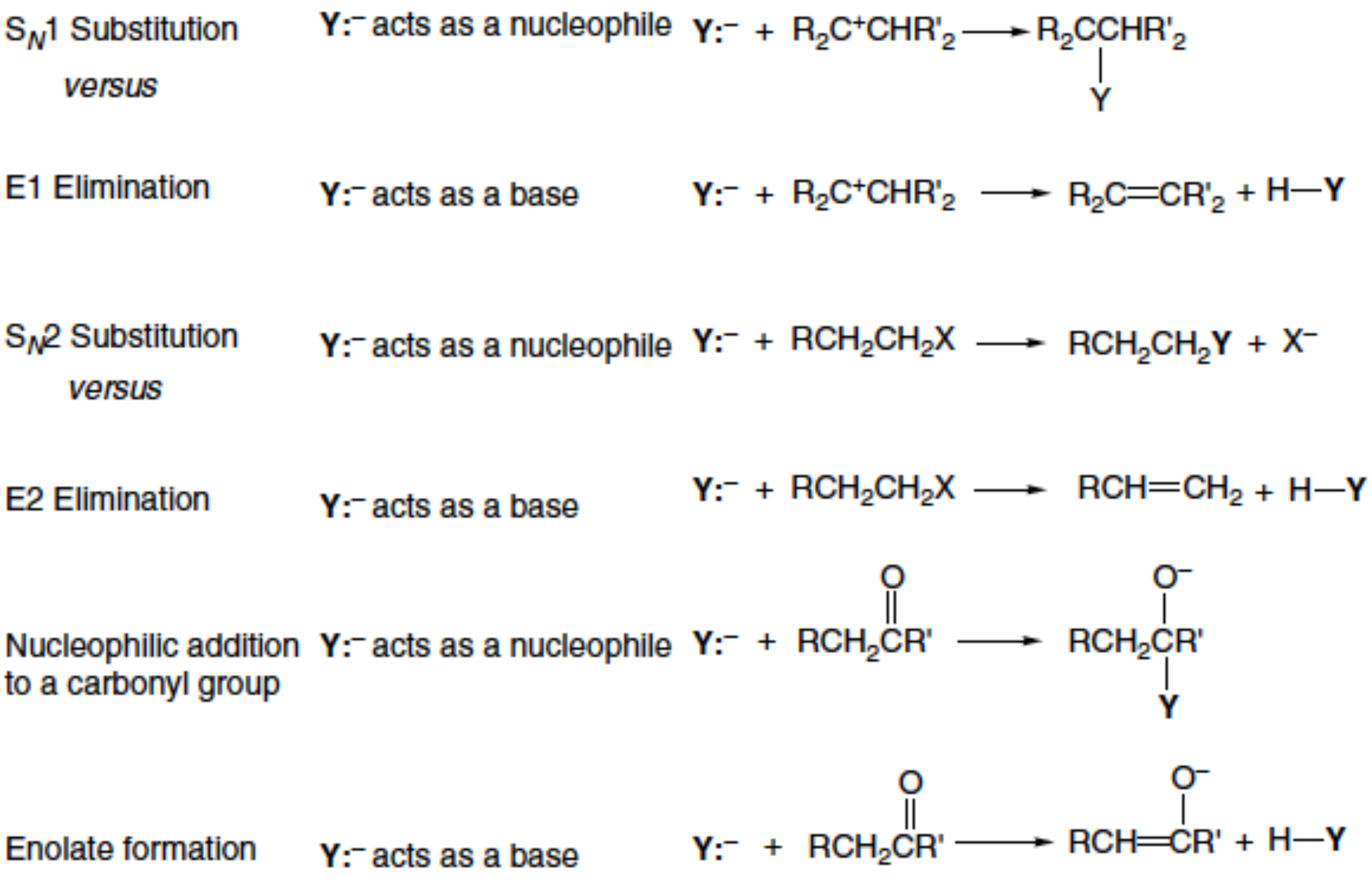
- Swain-Scott $n_{CH_3I} = \log(k_{nucl}/k_{CH_3OH})$ in CH_3OH, 25 °C

Table 4.3. Nucleophilicity Constants for Various Nucleophiles[a]

Nucleophile	n_{CH_3I}	Conjugate acid pK_a
CH_3OH	0.0	−1.7
NO_3^-	1.5	−1.3
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	−5.7
$(CH_3)_2S$	5.3	
NH_3	5.5	9.25
N_3^-	5.8	4.74
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	−7.7
CH_3O^-	6.3	15.7
HO^-	6.5	15.7
NH_2OH	6.6	5.8
NH_2NH_2	6.6	7.9
$(CH_3CH_2)_3N$	6.7	10.7
CN^-	6.7	9.3
$(CH_3CH_2)_3As$	7.1	
I^-	7.4	−10.7
HO_2^-	7.8	
$(CH_3CH_2)_3P$	8.7	8.7
$C_6H_5S^-$	9.9	6.5
$C_6H_5Se^-$	10.7	
$(C_6H_5)_3Sn^-$	11.5	

a. Data from R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.*, **89**, 1827 (1967); R. G. Pearson, H. Sobel, and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968); P. L. Bock and G. M Whitesides, *J. Am. Chem. Soc.*, **96**, 2826 (1974).

Scheme 4.3. Examples of Competition between Nucleophilicity and Basicity



S_N1 Substitution *versus*	**Y:**$^-$ acts as a nucleophile	$\mathbf{Y}:^- + R_2C^+CHR'_2 \longrightarrow R_2\underset{\underset{Y}{\vert}}{C}CHR'_2$
E1 Elimination	**Y:**$^-$ acts as a base	$\mathbf{Y}:^- + R_2C^+CHR'_2 \longrightarrow R_2C{=}CR'_2 + H{-}\mathbf{Y}$
S_N2 Substitution *versus*	**Y:**$^-$ acts as a nucleophile	$\mathbf{Y}:^- + RCH_2CH_2X \longrightarrow RCH_2CH_2\mathbf{Y} + X^-$
E2 Elimination	**Y:**$^-$ acts as a base	$\mathbf{Y}:^- + RCH_2CH_2X \longrightarrow RCH{=}CH_2 + H{-}\mathbf{Y}$
Nucleophilic addition to a carbonyl group	**Y:**$^-$ acts as a nucleophile	$\mathbf{Y}:^- + RCH_2\overset{\overset{O}{\Vert}}{C}R' \longrightarrow RCH_2\overset{\overset{O^-}{\vert}}{\underset{\underset{\mathbf{Y}}{\vert}}{C}}R'$
Enolate formation	**Y:**$^-$ acts as a base	$\mathbf{Y}:^- + RCH_2\overset{\overset{O}{\Vert}}{C}R' \longrightarrow RCH{=}\overset{\overset{O^-}{\vert}}{C}R' + H{-}\mathbf{Y}$

Table 4.4. Hardness and Softness of Some Common Ions and Molecules

	Bases (Nucleophiles)	Acids (Electrophiles)
Soft	RSH, RS^-, I^-, R_3P $^-C\equiv N$, $^-{:}C\equiv O^+$, $RCH{=}CHR$ benzene	I_2, Br_2, $RS{-}X$, $RSe{-}X$, $RCH_2{-}X$ Cu(I), Ag(I), Pd(II), Pt(II), Hg(II) zero-valent metal complexes
Intermediate	Br^-, N_3^-, $ArNH_2$ pyridine	Cu(II), Zn (II), Sn,(II) R_3C^+, R_3B
Hard	NH_3, RNH_2 H_2O, HO^-, ROH, RO^-, RCO_2^-, Cl^- F^-, NO_3^-	$H{-}X$, Li^+, Na^+, $R_3Si{-}X$ Mg(II), Ca(II), Al(III), Sn(IV), Ti(IV) H^+

- Winstein-Grunwald

$$\mathrm{Log}(k/k_0) = lN + mY$$

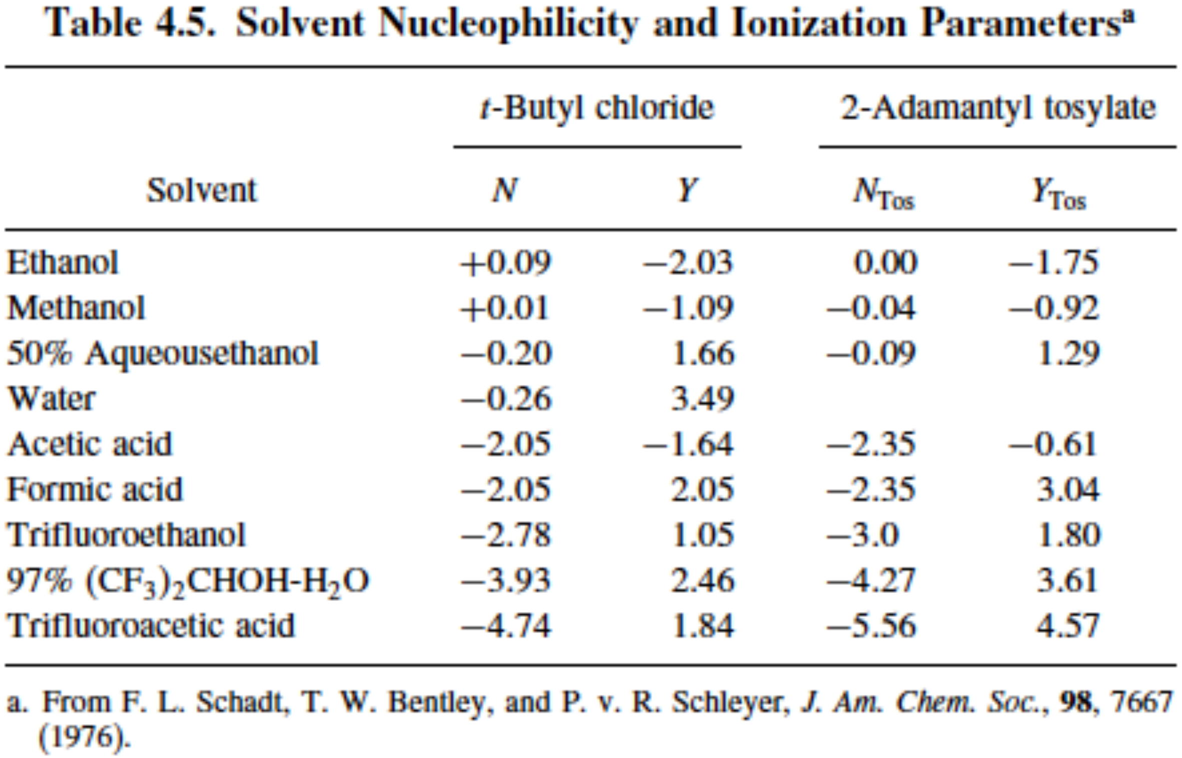
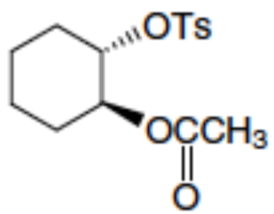


Table 4.5. Solvent Nucleophilicity and Ionization Parameters[a]

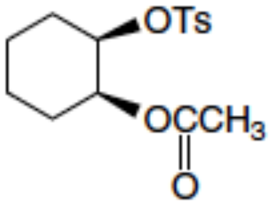
Solvent	*t*-Butyl chloride		2-Adamantyl tosylate	
	N	Y	N_{Tos}	Y_{Tos}
Ethanol	+0.09	−2.03	0.00	−1.75
Methanol	+0.01	−1.09	−0.04	−0.92
50% Aqueousethanol	−0.20	1.66	−0.09	1.29
Water	−0.26	3.49		
Acetic acid	−2.05	−1.64	−2.35	−0.61
Formic acid	−2.05	2.05	−2.35	3.04
Trifluoroethanol	−2.78	1.05	−3.0	1.80
97% $(CF_3)_2CHOH$-H_2O	−3.93	2.46	−4.27	3.61
Trifluoroacetic acid	−4.74	1.84	−5.56	4.57

a. From F. L. Schadt, T. W. Bentley, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **98**, 7667 (1976).

Ajuda Anquimérica



$k = 1.9 \times 10^{-4} s^{-1}$ (100° C)



$k = 2.9 \times 10^{-7} s^{-1}$ (100° C)

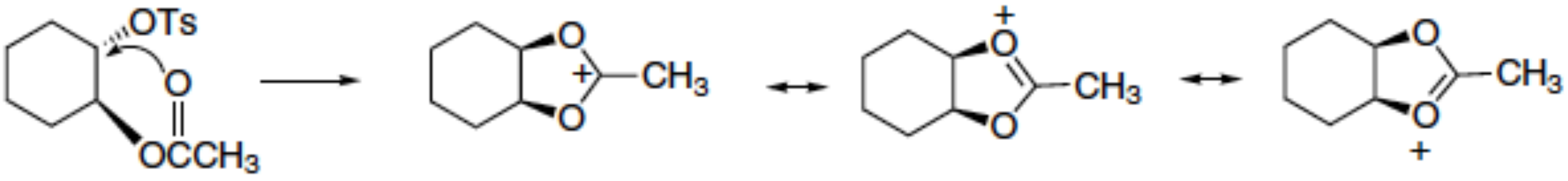


Table 4.11. Solvolysis Rates of ω-Chloro Alcohols[a]

ω-Chloro alcohol	Approximate relative rate
$Cl(CH_2)_2OH$	2000
$Cl(CH_2)_3OH$	1
$Cl(CH_2)_4OH$	5700
$Cl(CH_2)_5OH$	20

[a] B. Capon, *Q. Rev. Chem. Soc.*, **18**, 45 (1964); W. H. Richardson, C. M. Golino, R. H. Wachs, and M. B. Yelvington, *J. Org. Chem.*, **36**, 943 (1971).

Table 4.13. Relative Rates of Cyclization as a Function of Ring Size

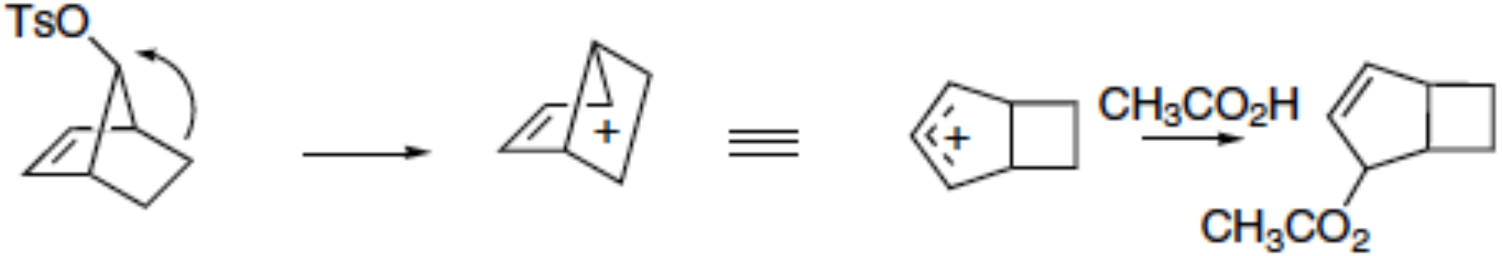
Ring size	Lactonization of ω-bromo carboxylates[a]	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (eu)	Cyclization of ω-bromoalkylmalonates[b]
3	8.2×10^{-4}	22.0	−2.5	
4	0.92	17.7	−5.0	0.58
5	108	15.9	−5.5	833
6	1.00	17.2	−4.1	1.00
7	3.7×10^{-3}	17.4	−13.5	8.7×10^{-3}
8	3.8×10^{-5}	21.7	−9.2	1.5×10^{-4}
9	4.3×10^{-5}	20.3	−14.0	1.7×10^{-5}
10	1.3×10^{-4}	17.3	−20.7	1.4×10^{-6}
11	3.3×10^{-4}	16.4	−22.3	2.9×10^{-6}
12	4.1×10^{-4}	17.6	−18.0	4.0×10^{-4}
13	1.2×10^{-3}	15.3	−23.0	7.4×10^{-4}
17				2.9×10^{-3}
18	2.0×10^{-3}	15.2	−21.8	
21				4.3×10^{-3}
23	2.3×10^{-3}	14.5	−22.3	

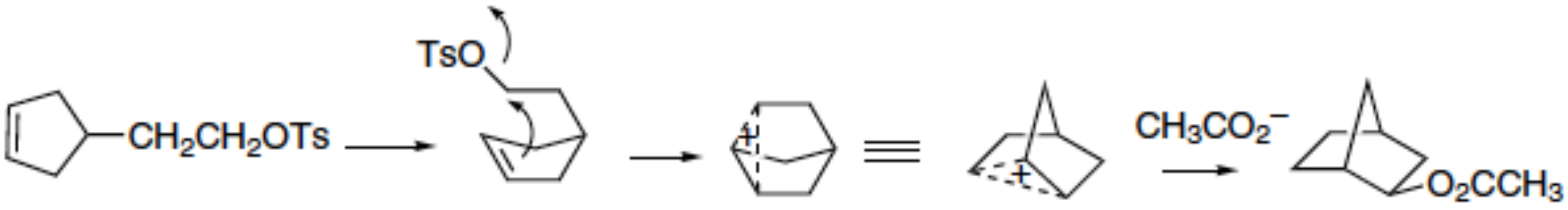
a. C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*, **99**, 2591 (1977); L. Mandolini, *J. Am. Chem. Soc.*, **100**, 550 (1978).

b. M. A. Casadei, C. Galli, and L. Mandolini, *J. Am. Chem. Soc.*, **106**, 1051 (1984).

Solvólise da 7-tosilnorbornenila *anti* é 10^7 vezes mais rápido do que o *syn*

3

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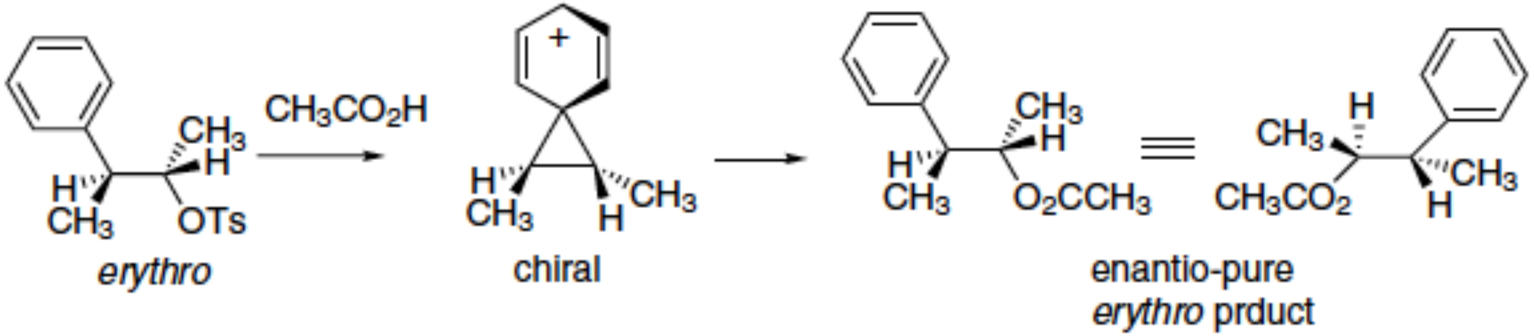
TsO
≡
CH3CO2−
O2CCH3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H
H
CH3
OTs
erythro
CH3CO2H
+
H
CH3
CH3
H
chiral
CH3
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CH3
O2CCH3
≡
H
CH3
CH3CO2
CH3
H
enantio-pure
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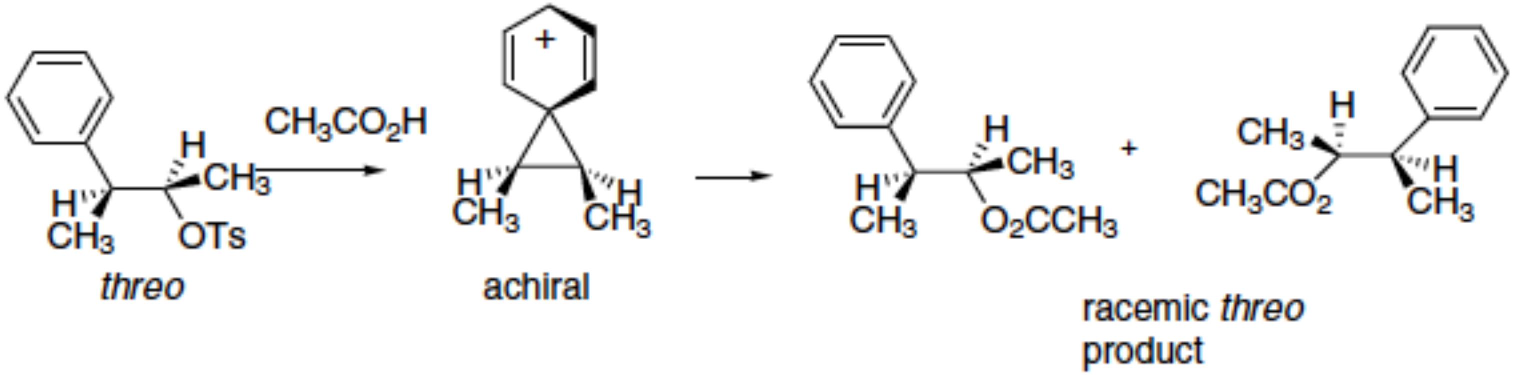
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+
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product

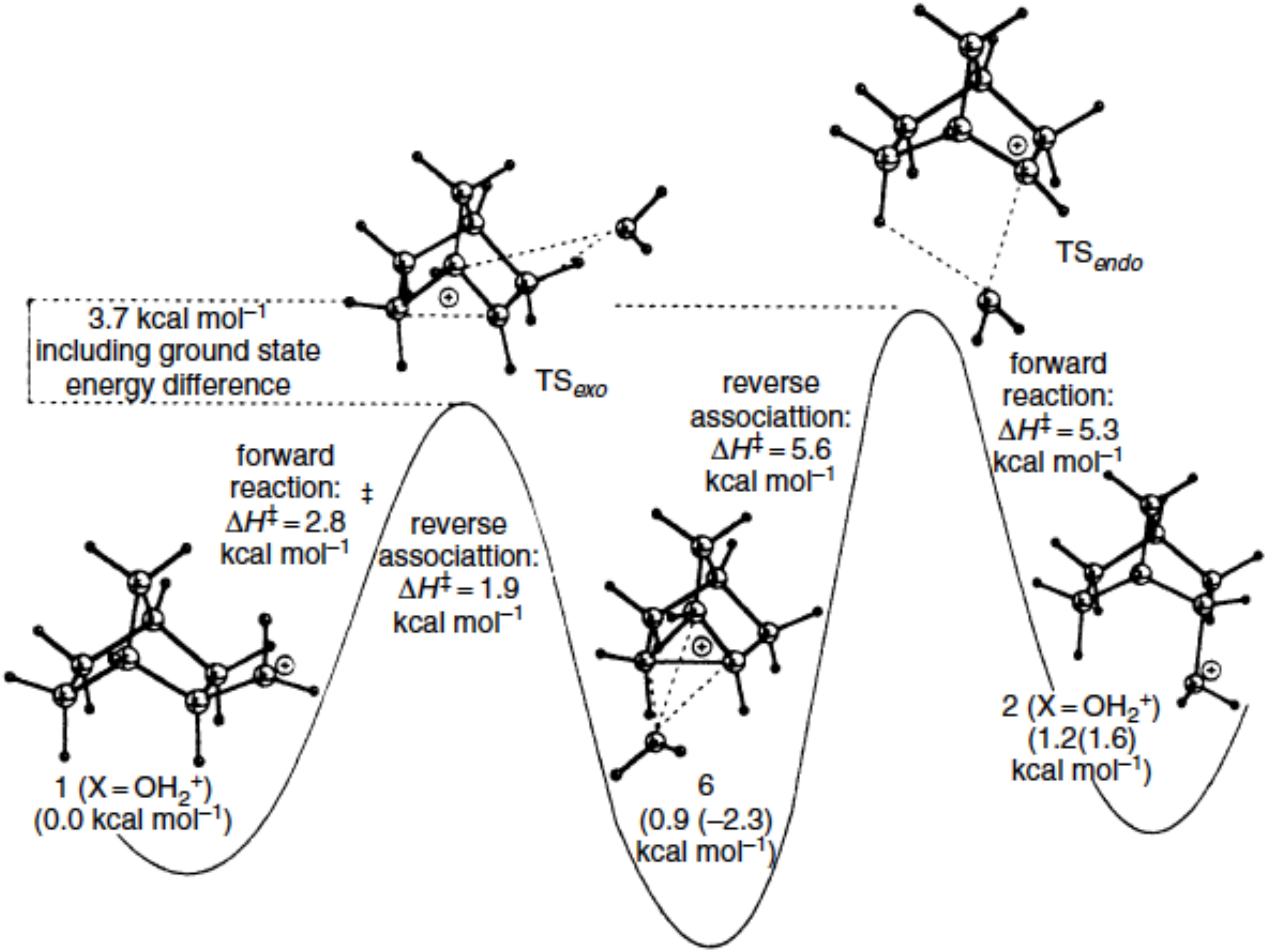

Fig. 4.14. Computational energy diagram (B3LYP)/6-311+G*) for intermediates and transition states in ionization and rearrangement of protonated 2-norbornanol. Reproduced from *J. Org. Chem.*, **62**, 4216 (1997), by permission of the American Chemical Society.