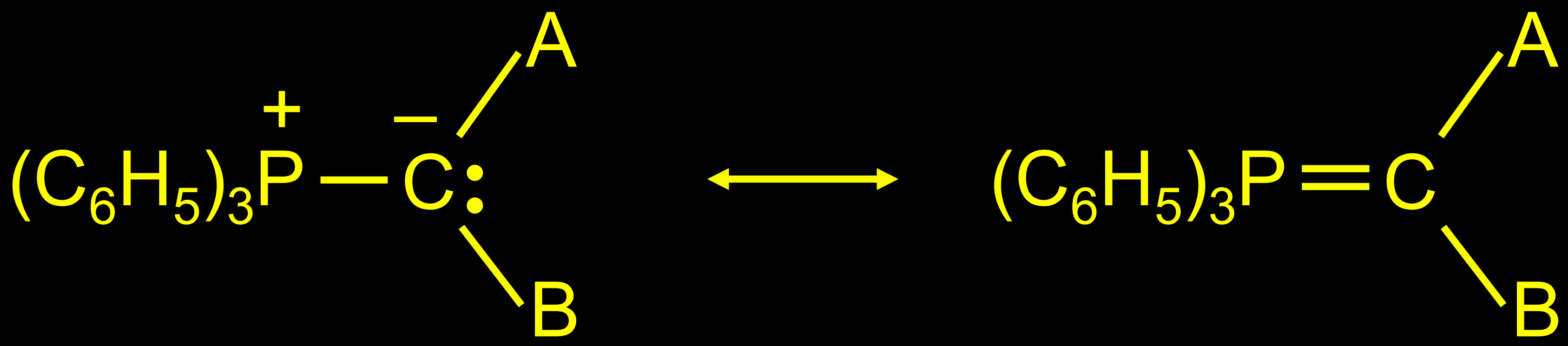
The Wittig Reaction

The Wittig Reaction

Synthetic method for preparing alkenes.

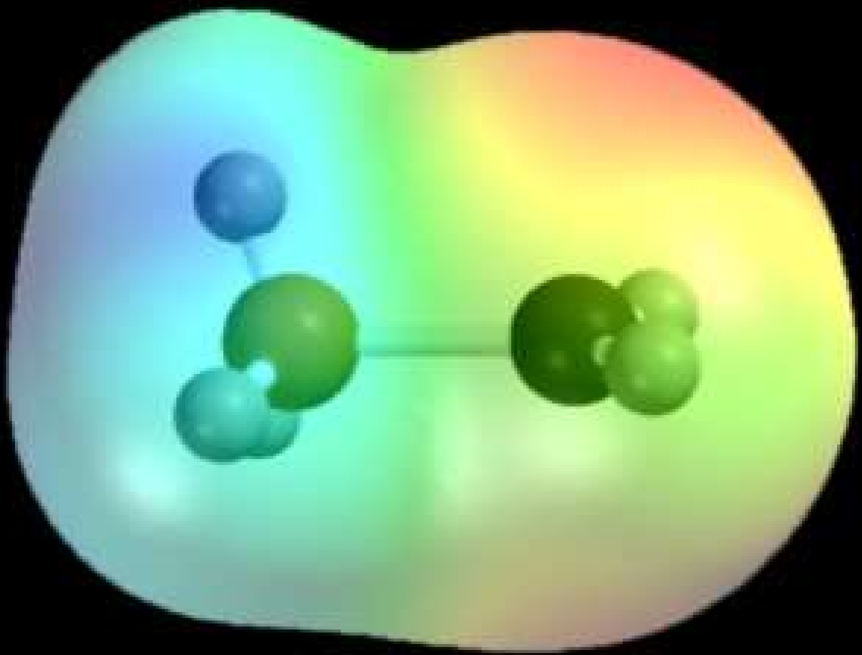
One of the reactants is an aldehyde or ketone.

The other reactant is a phosphorus ylide.

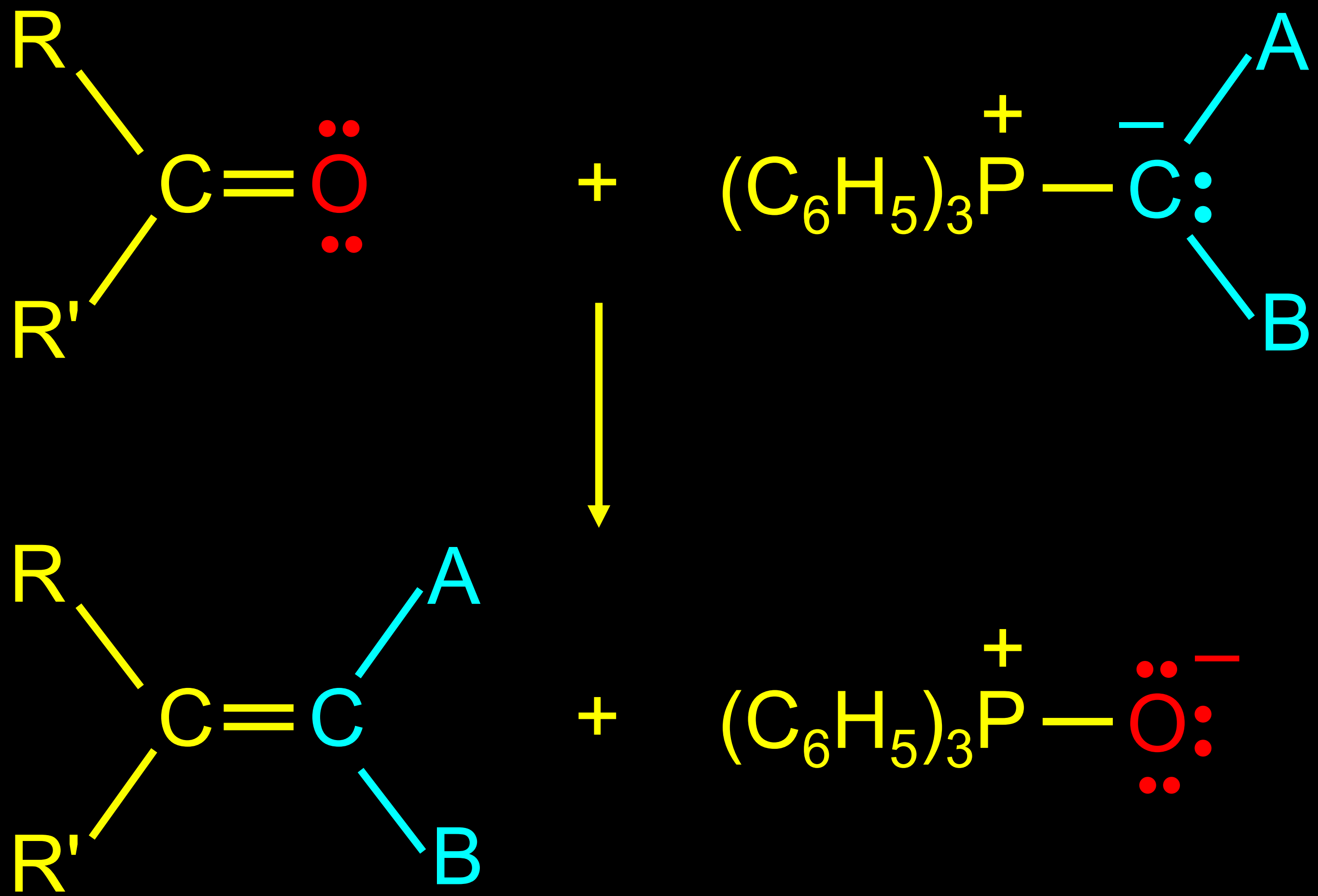


A key property of ylides is that they have a negatively polarized carbon and are nucleophilic.

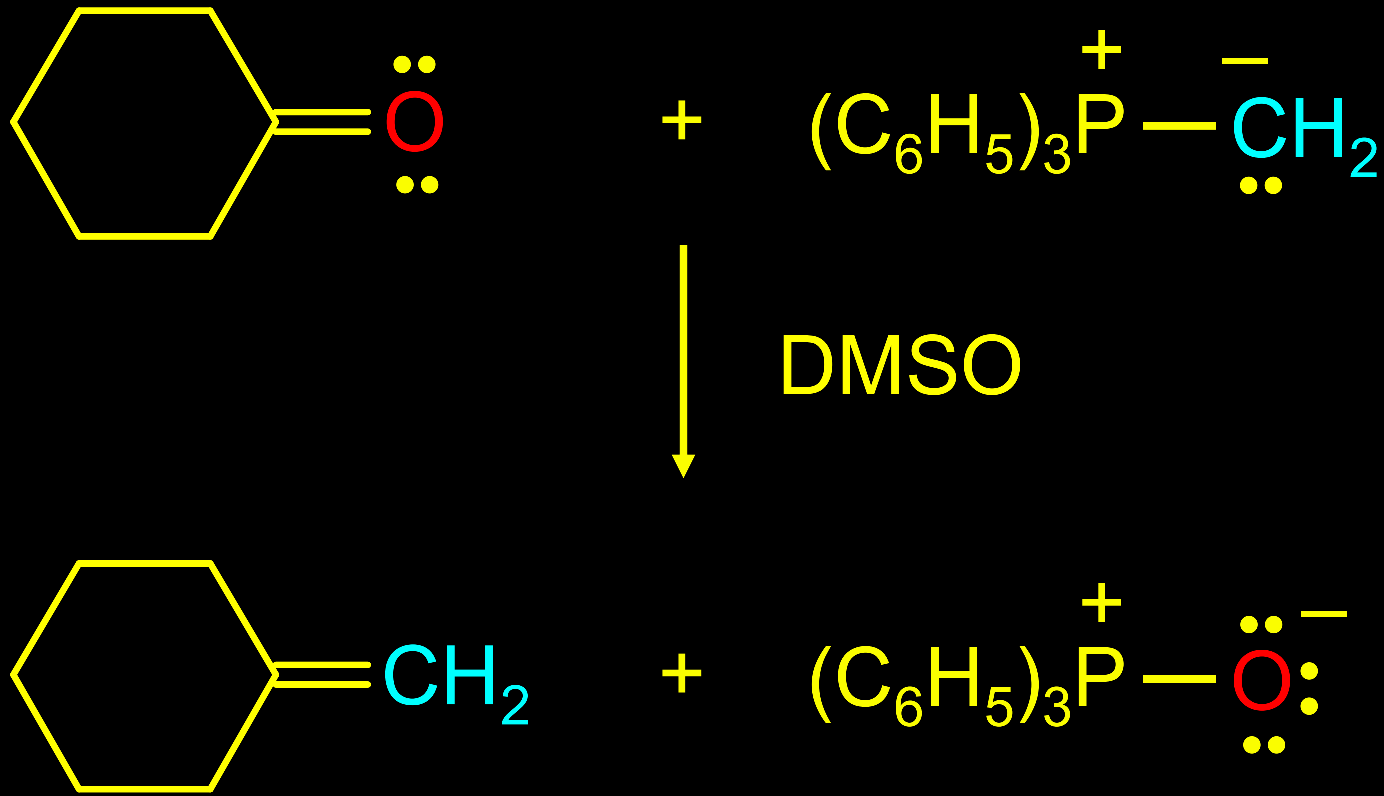
Figure 17.12 Charge distribution in a ylide



The Wittig Reaction



Example

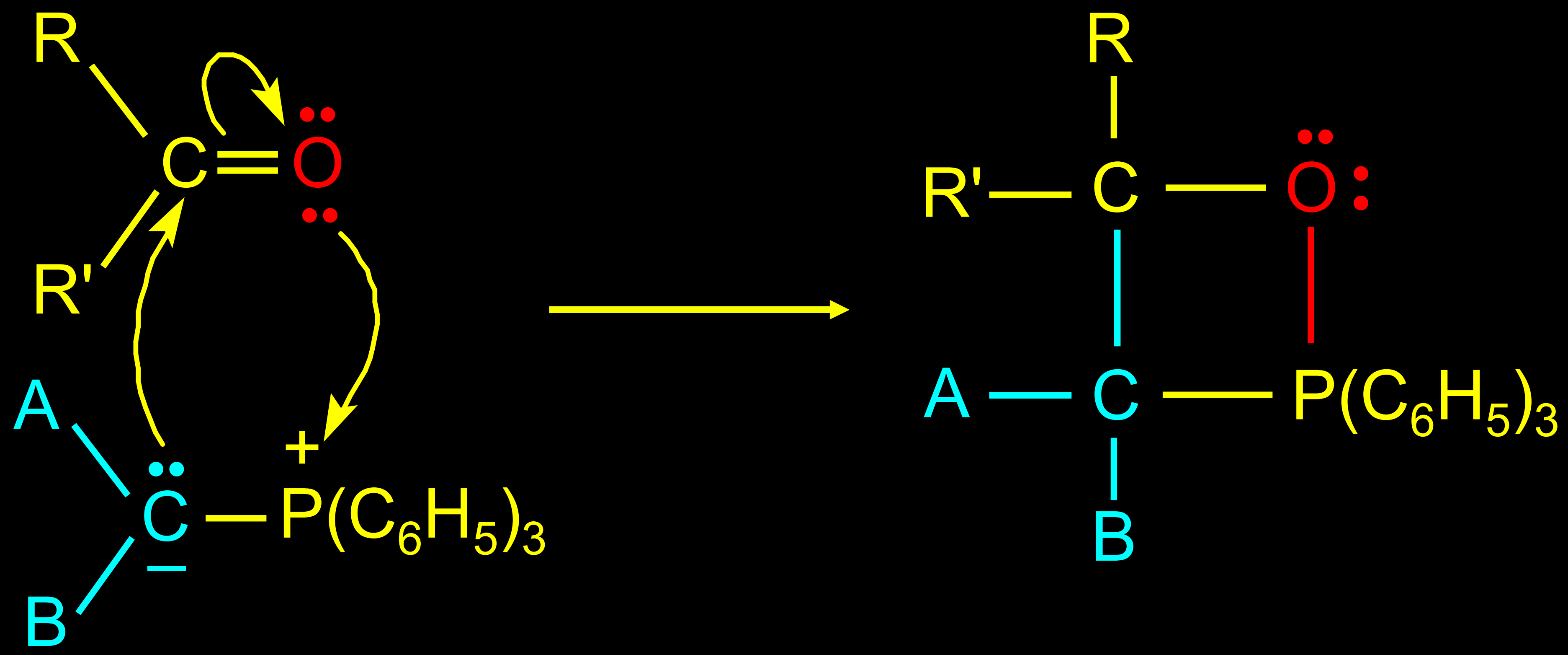


(86%)

dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF) is the customary solvent

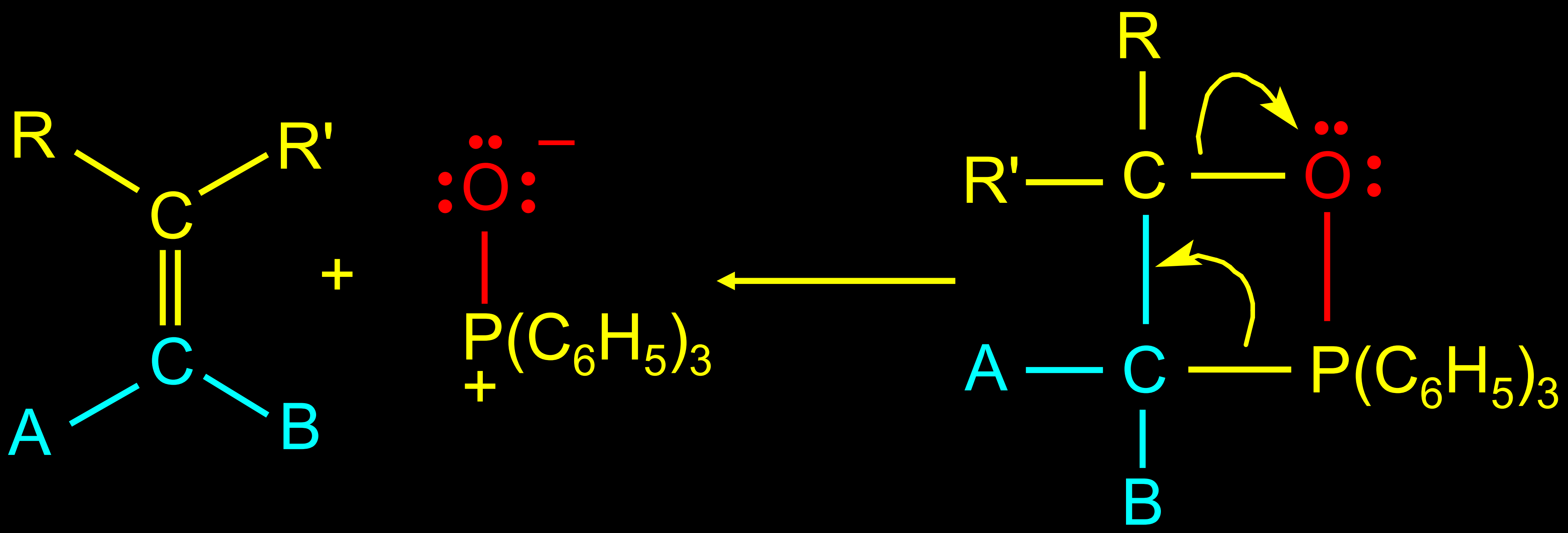
Mechanism

Step 1



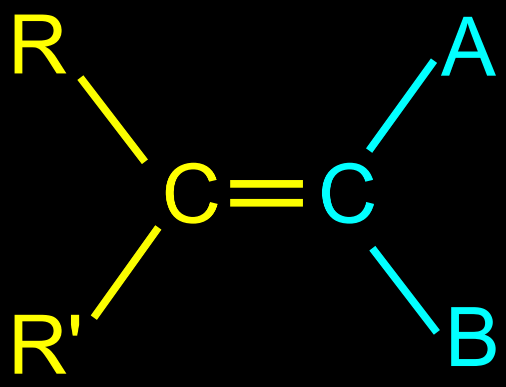
Mechanism

Step 2



Planning an Alkene Synthesis via the Wittig Reaction

Retrosynthetic Analysis

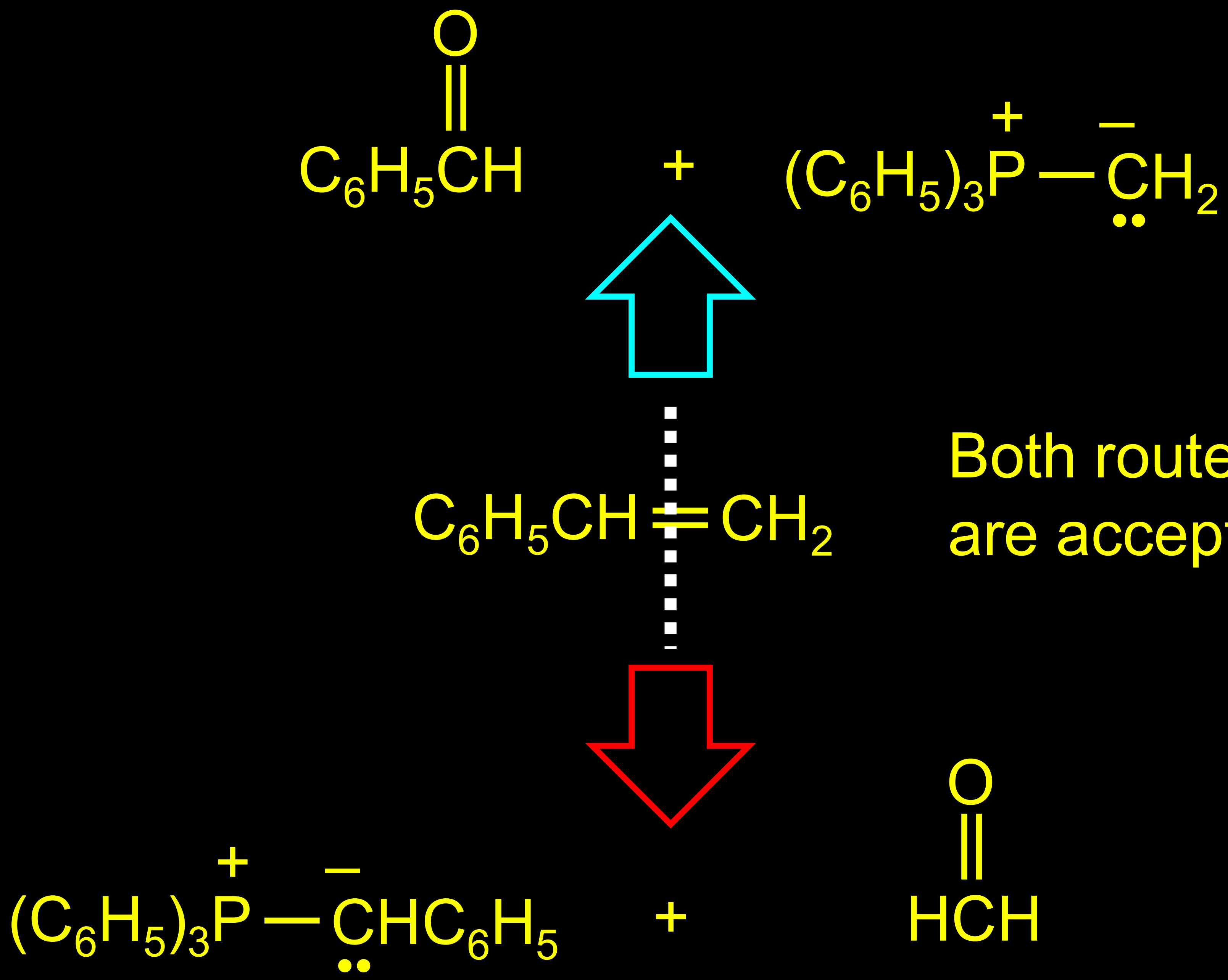


There will be two possible Wittig routes to an alkene.

Analyze the structure retrosynthetically.

Disconnect the doubly bonded carbons. One will come from the aldehyde or ketone, the other from the ylide.

Retrosynthetic Analysis of Styrene

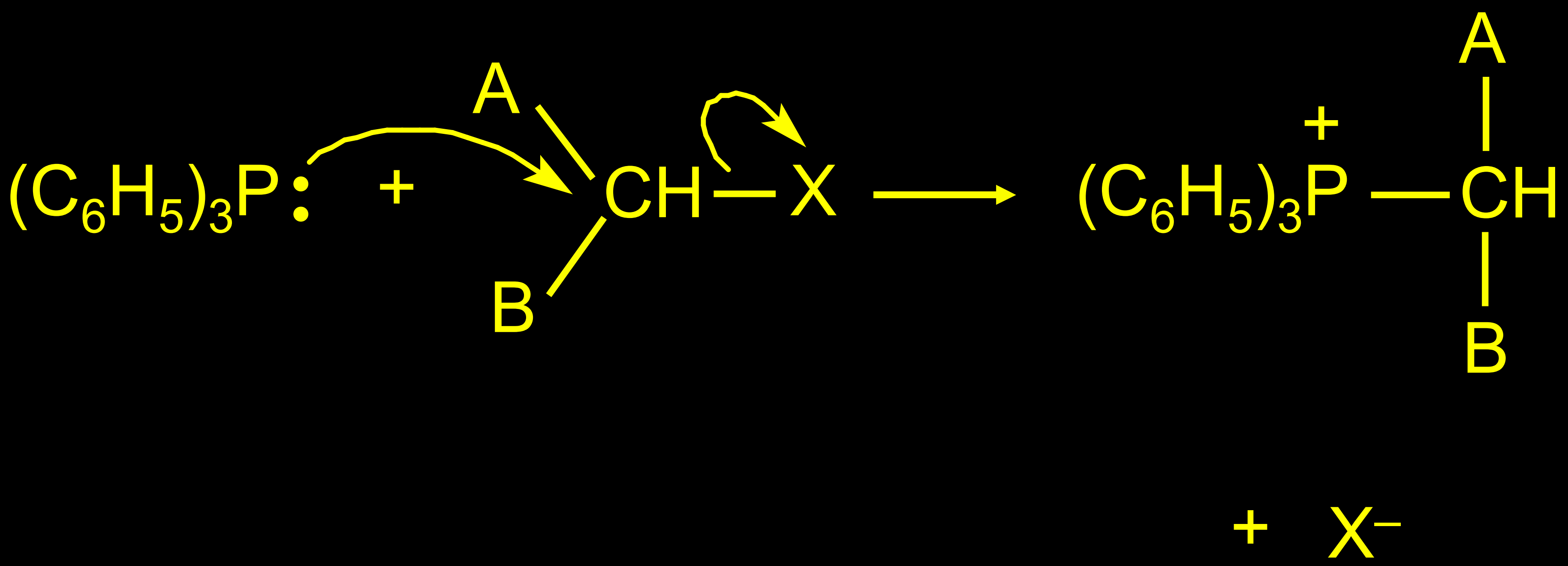


Both routes are acceptable.

Preparation of Ylides

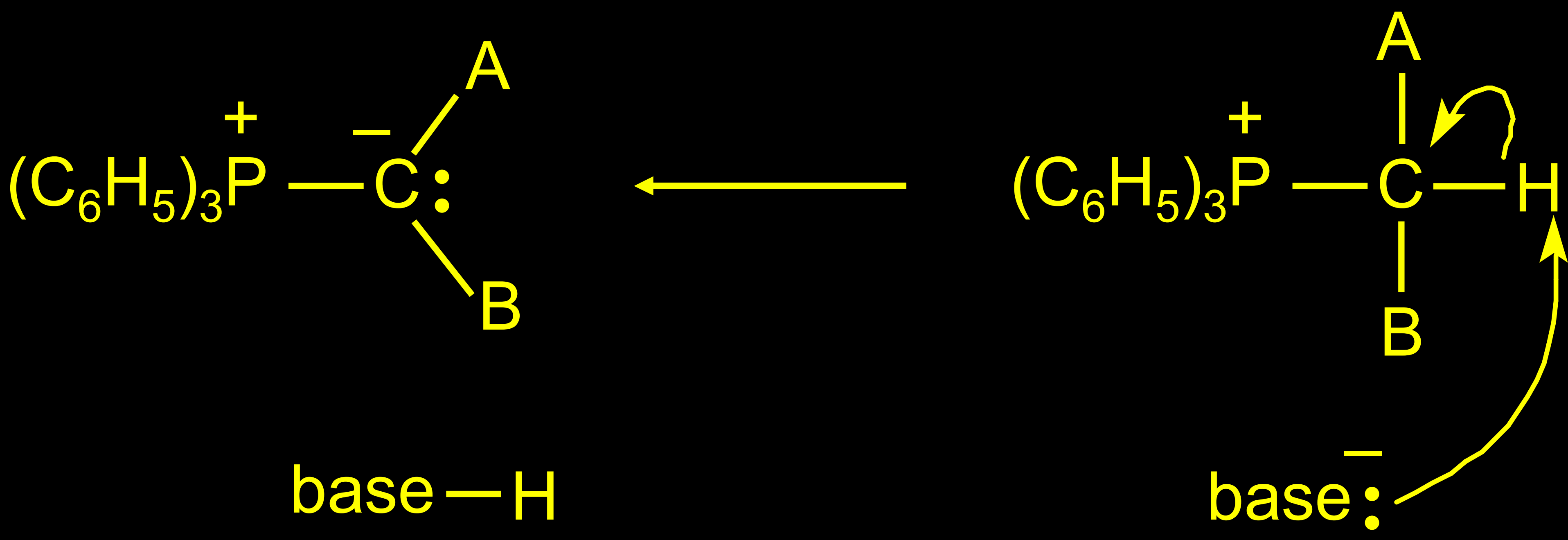
Ylides are prepared from alkyl halides by a two-stage process.

The first step is a nucleophilic substitution. Triphenylphosphine is the nucleophile.



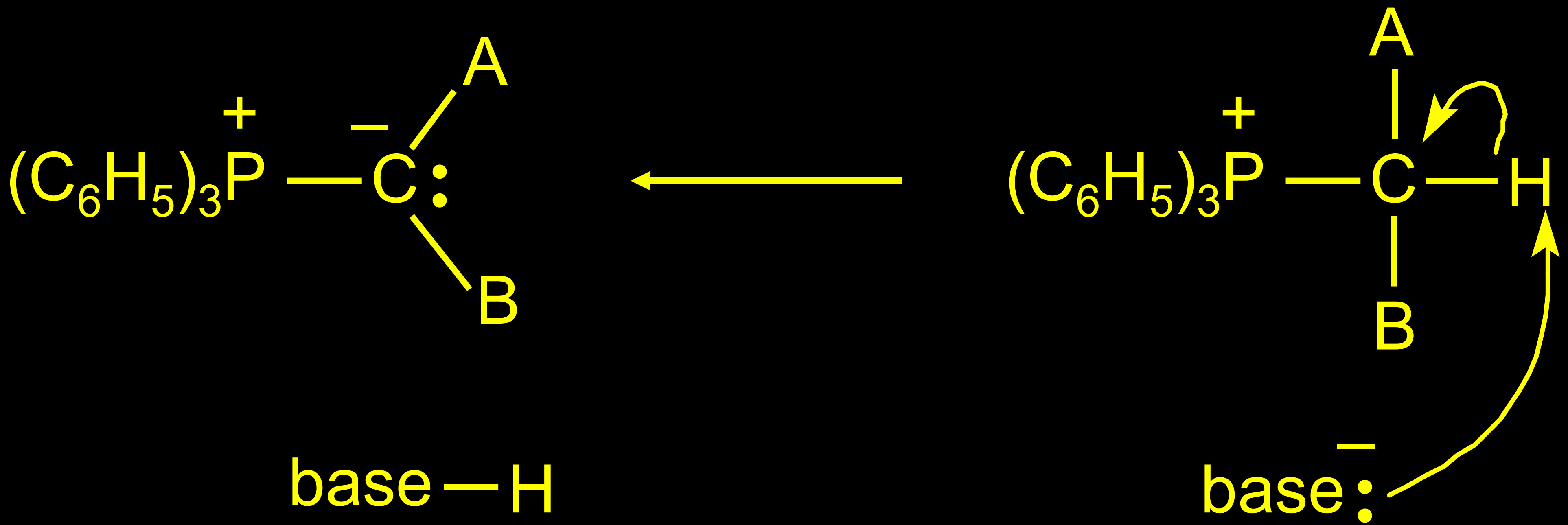
Preparation of Ylides

In the second step, the phosphonium salt is treated with a strong base in order to remove a proton from the carbon bonded to phosphorus.



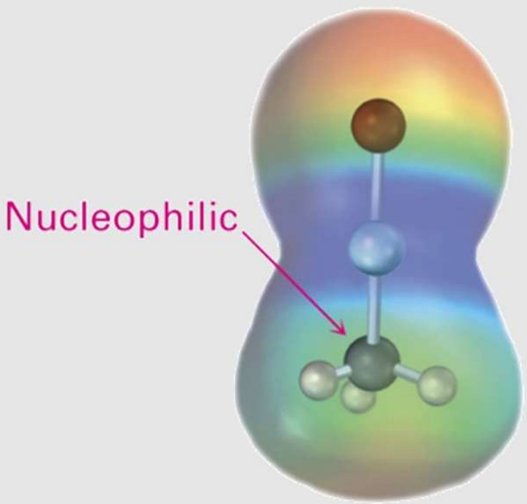
Preparation of Ylides

Typical strong bases include organolithium reagents (RLi), and the conjugate base of dimethyl sulfoxide as its sodium salt [$NaCH_2S(O)CH_3$].



Nucleophilic Addition of Grignard Reagents and Hydride Reagents: Alcohol Formation

- Treatment of aldehydes or ketones with Grignard reagents yields an alcohol
  - Nucleophilic addition of the equivalent of a *carbon* anion, or **carbanion**. A carbon–magnesium bond is strongly polarized, so a Grignard reagent reacts for all practical purposes as R**:** $^{-}$ MgX^{+}.



Methylmagnesium chloride

$$R{-}X + Mg \rightarrow R{-}X^{\bullet -} + Mg^{\bullet +}$$
$$R{-}X^{\bullet -} \rightarrow R^{\bullet} + X^{-}$$
$$R^{\bullet} + Mg^{\bullet +} \rightarrow RMg^{+}$$
$$RMg^{+} + X^{-} \rightarrow RMgX$$

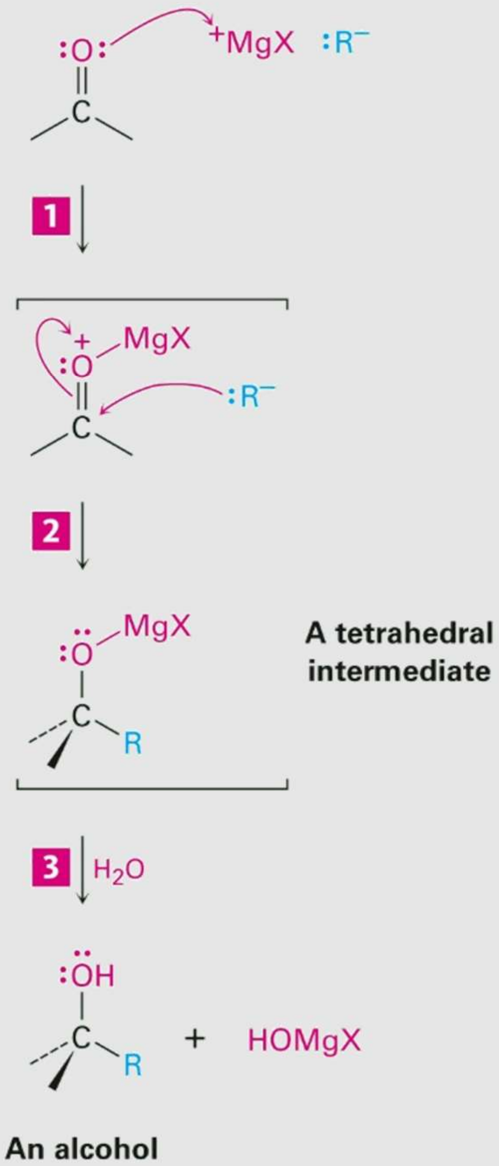
Mechanism of Addition of Grignard Reagents

- Complexation of C=O by Mg^{2+}, Nucleophilic addition of R: $^{-}$, protonation by dilute acid yields the neutral alcohol
- Grignard additions are irreversible because a carbanion is not a leaving group

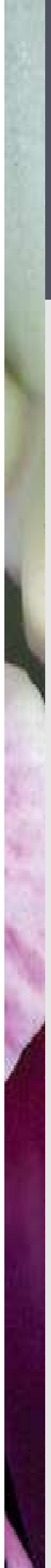
1 The Lewis acid Mg^{2+} first forms an acid–base complex with the basic oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better acceptor.

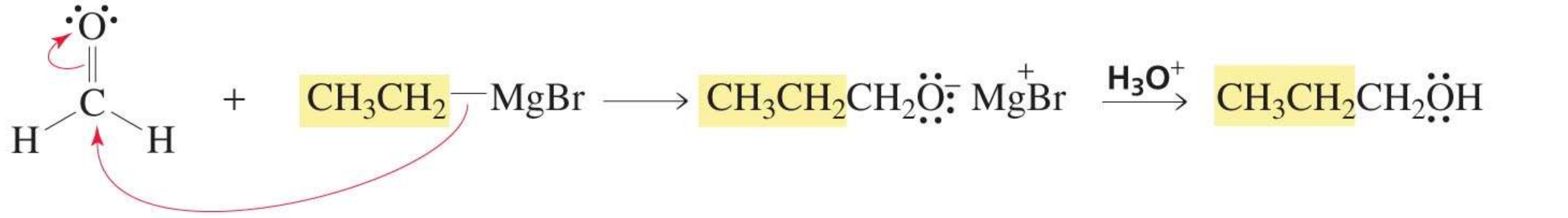
2 Nucleophilic addition of an alkyl group :R^{-} to the aldehyde or ketone produces a tetrahedral magnesium alkoxide intermediate . . .

3 . . . which undergoes hydrolysis when water is added in a separate step. The final product is a neutral alcohol.

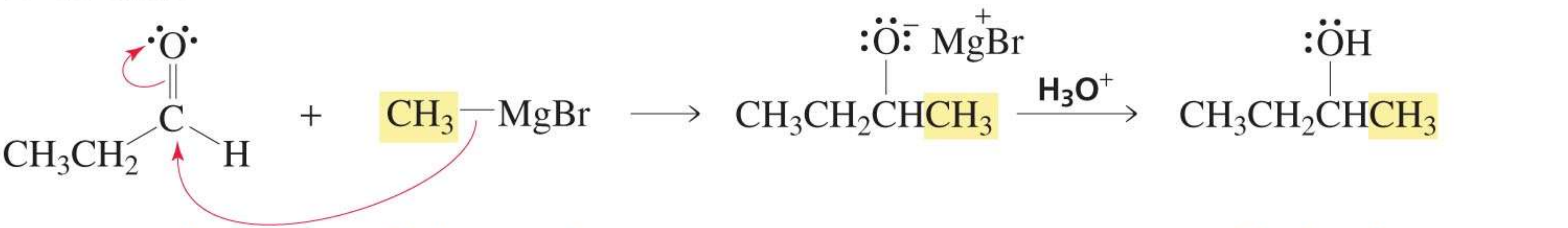


Grignard reagents are used to prepare alcohols:

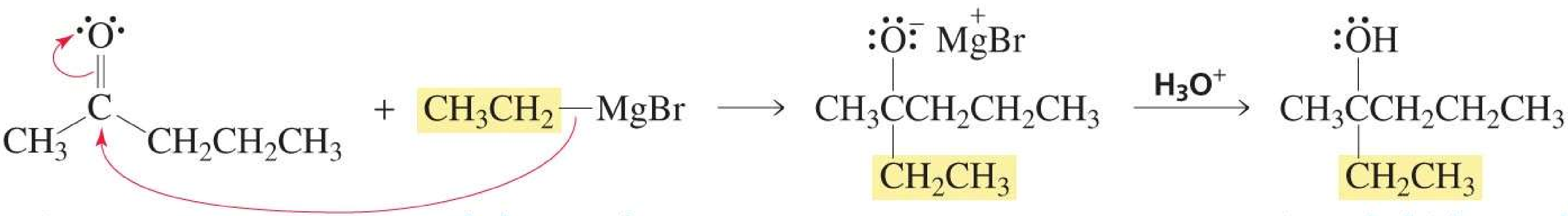




formaldehyde | ethylmagnesium bromide | an alkoxide ion | 1-propanol, a primary alcohol



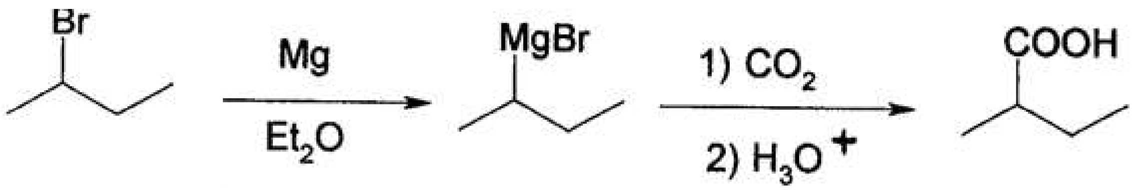
propanal | methylmagnesium bromide | 2-butanol, a secondary alcohol



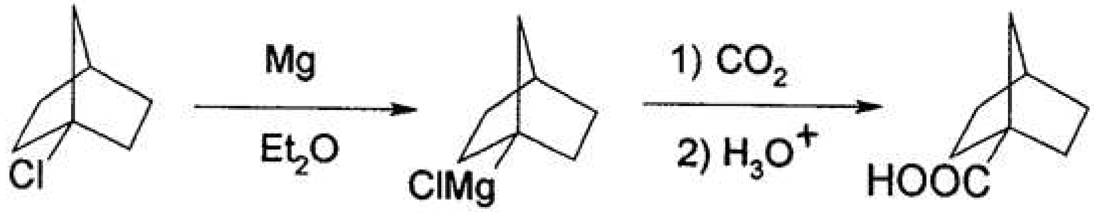
2-pentanone | ethylmagnesium bromide | 3-methyl-3-hexanol, a tertiary alcohol

A.6. ADIÇÃO DE COMPOSTOS ORGANOMETÁLICOS A CARBONÍLICOS

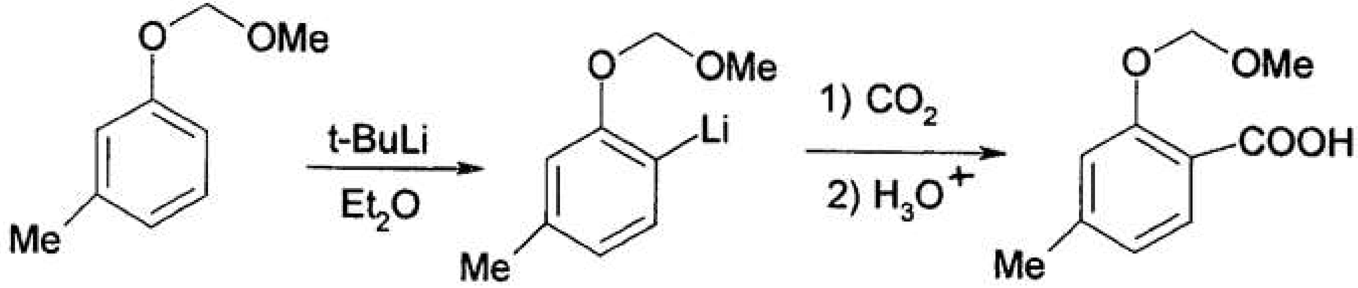
PREPARANDO ÁCIDOS CARBOXÍLICOS



86%



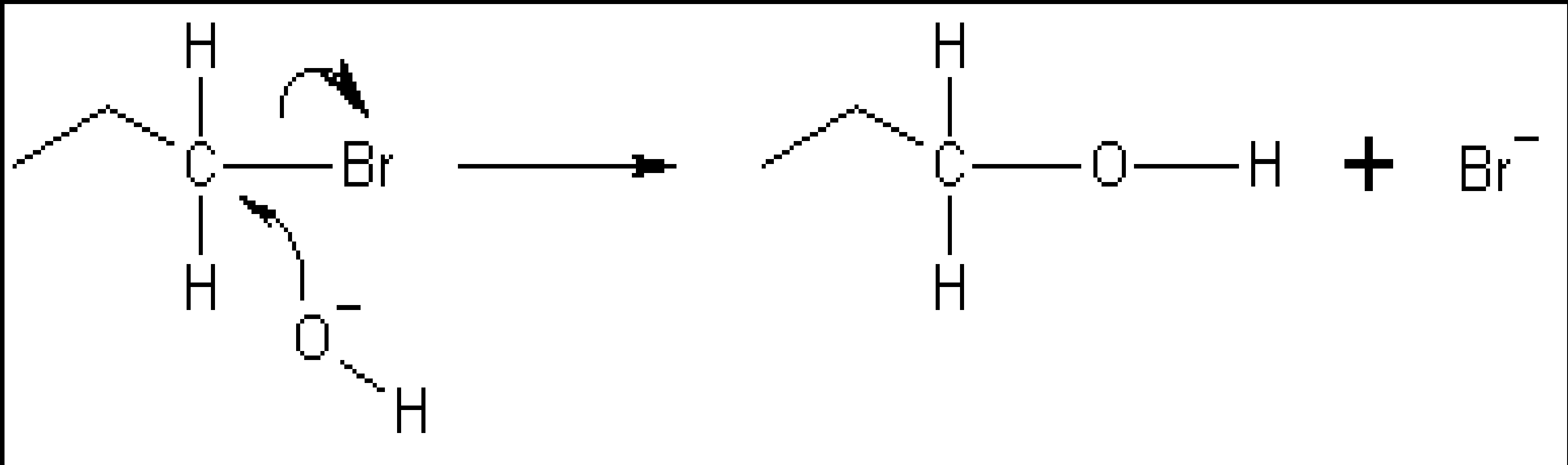
70%



90 %

NUCLEÓFILO

- ✓doa par de elétrons para um eletrófilo para formar uma ligação
- ✓moléculas ou íons com um par de elétrons livre ou com uma ligação π
- ✓são bases de Lewis



Basicidade vs nucleofilicidade

Basicidade é uma propriedade termodinâmica:

$$A^- + H_2O \overset{K}{\rightleftharpoons} HA + HO^-$$

K = constante de equilíbrio

Nucleofilicidade: conceito cinético

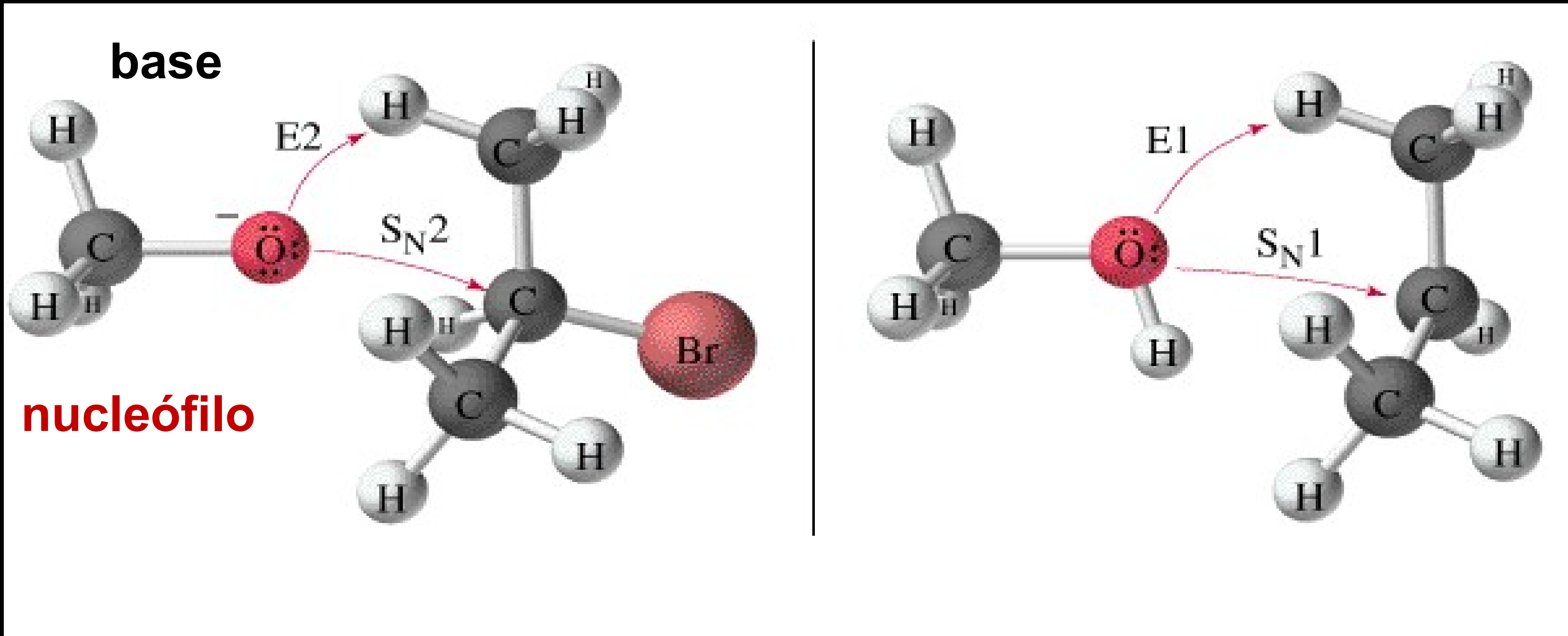
$$Nu^- + R\text{-}X \xrightarrow{k} Nu\text{-}R + X^-$$

k = constante de velocidade

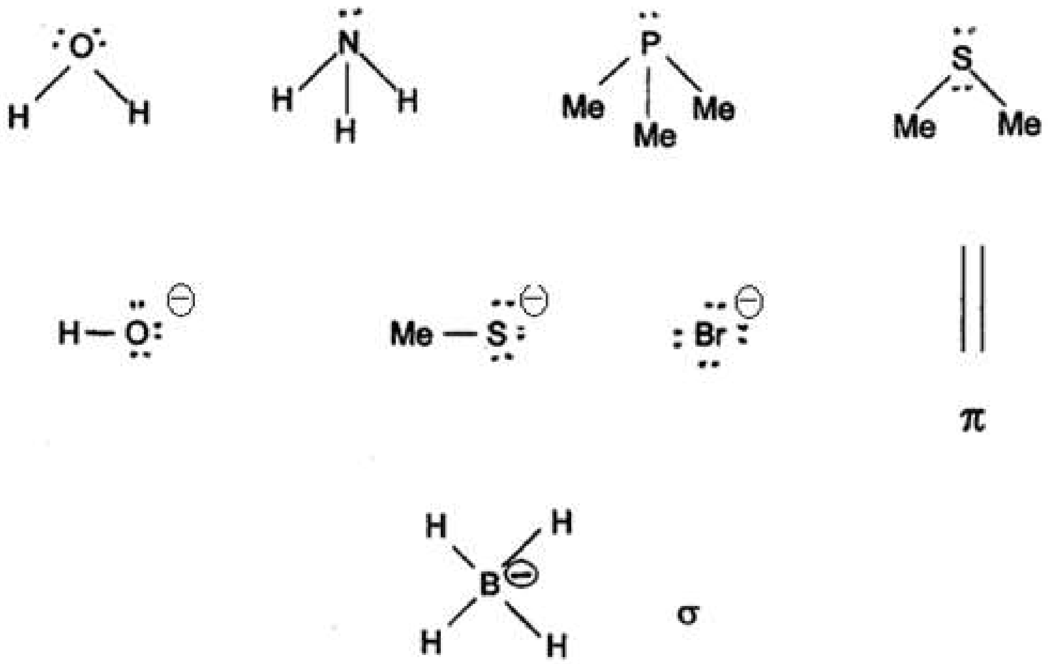
Bases fortes são tipicamente bons nucleófilos

NUCLEÓFILOS VS BASES

Misturas de produtos são comuns

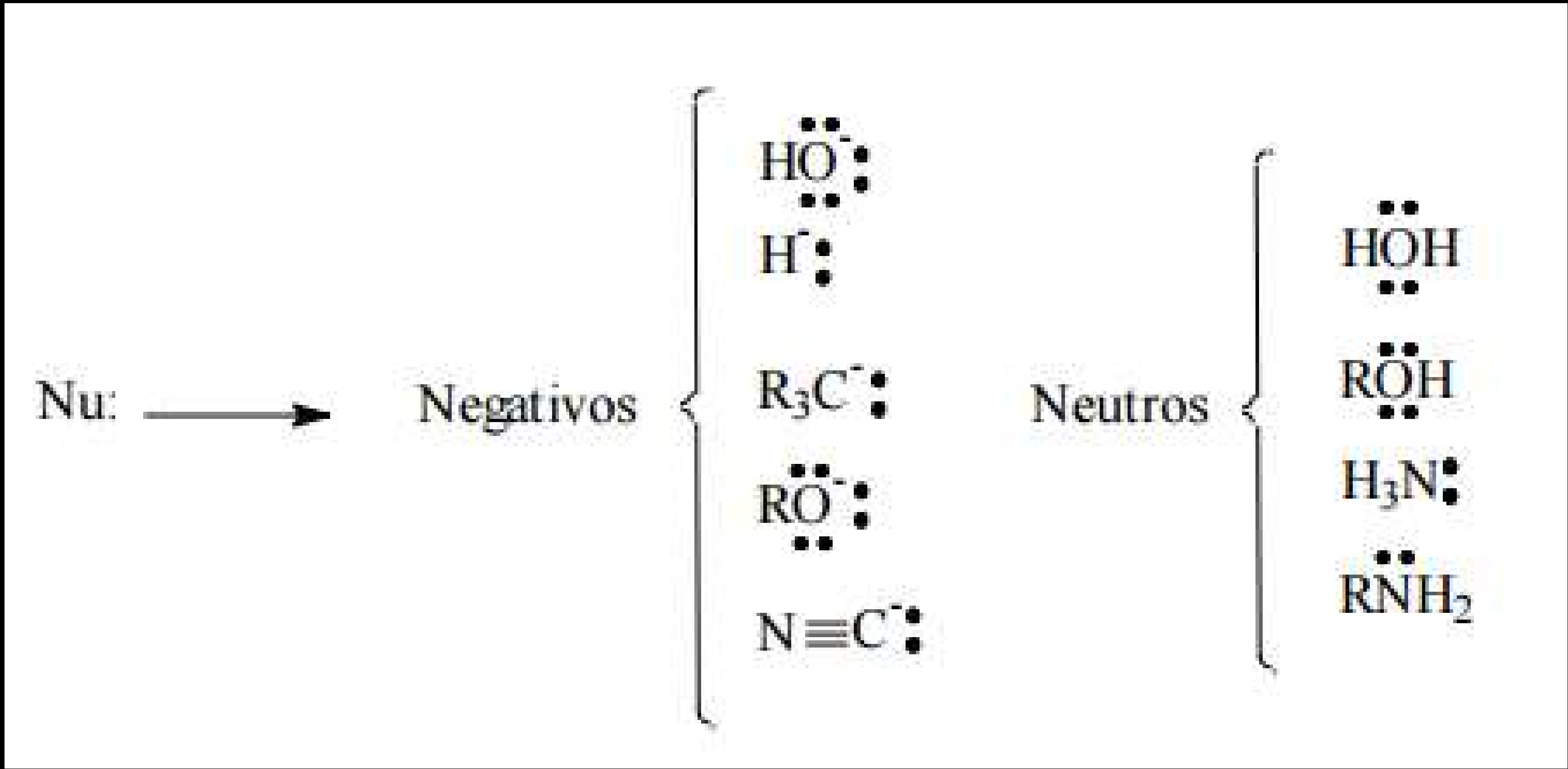


ESPÉCIES NEUTRAS OU CARREGADAS NEGATIVAMENTE QUE POSSUAM PAR ELETRÔNICO EM ORBITAL DE ALTA ENERGIA



Adição nucleofílica a aldeídos e cetonas

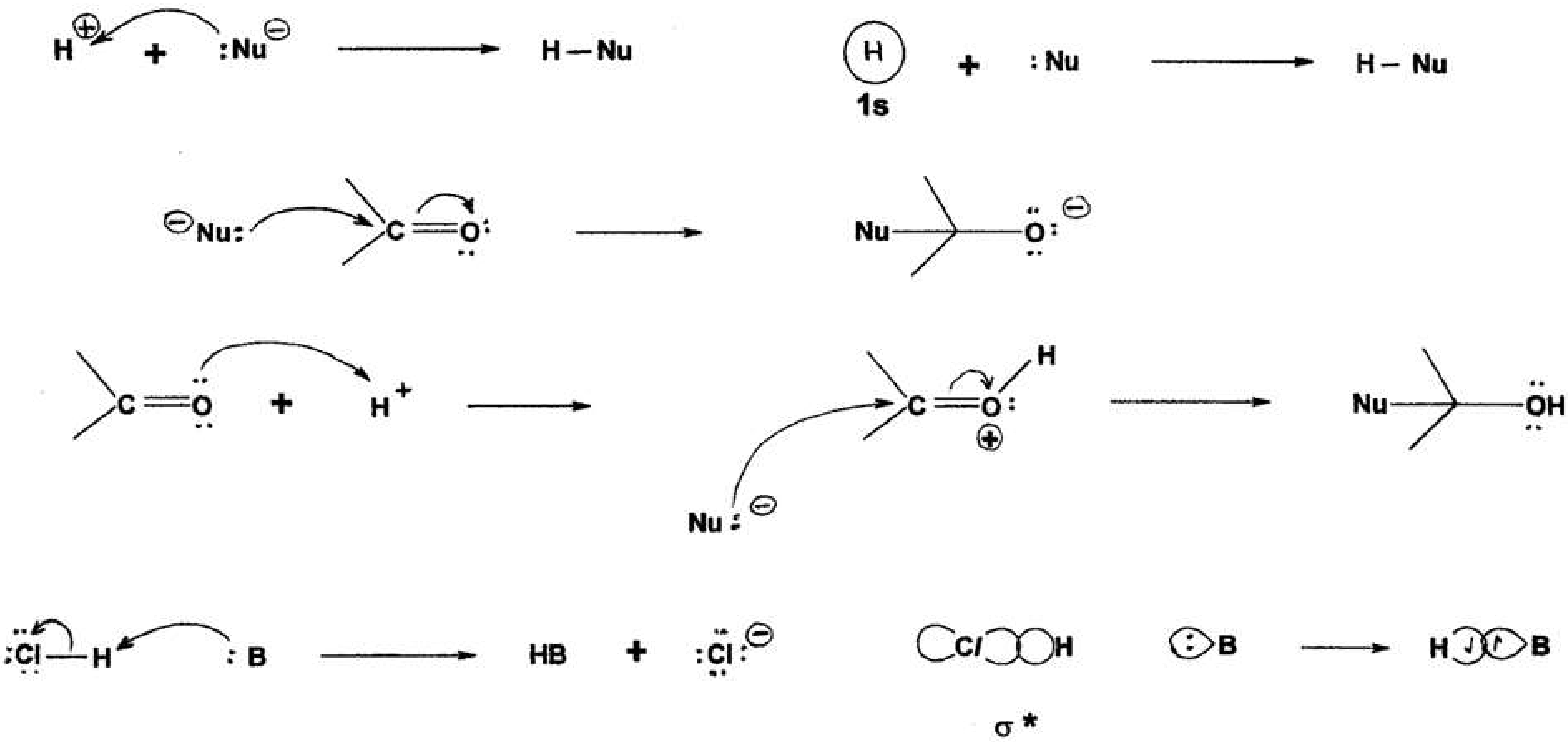
Exemplos de nucleófilos:



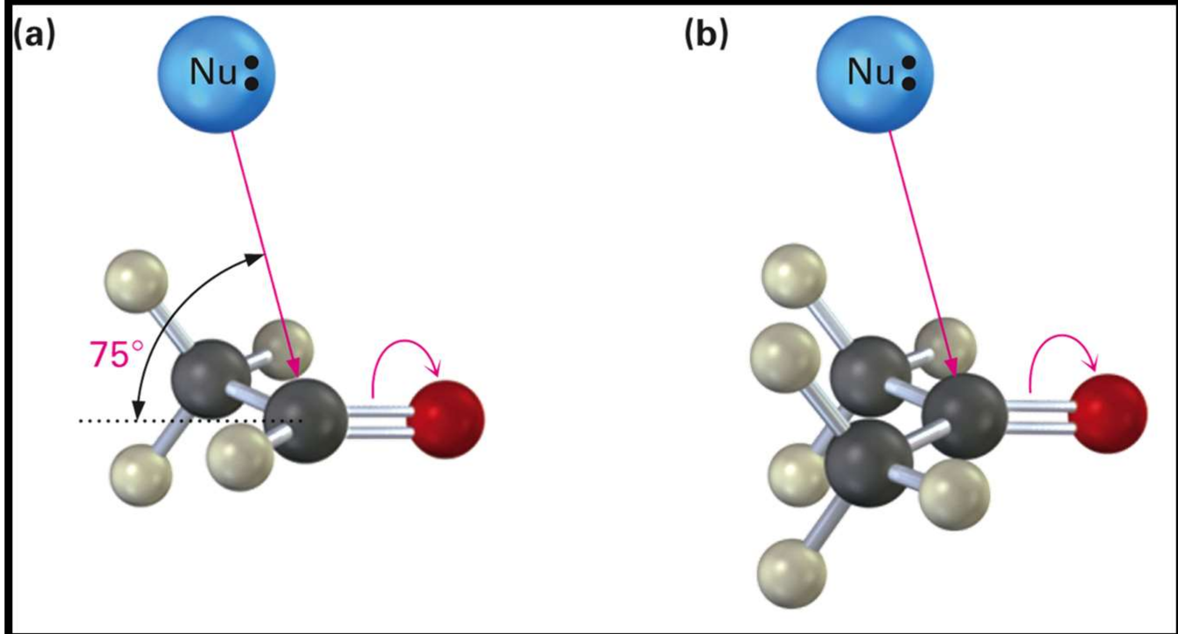
ESPÉCIES NEUTRAS OU CARREGADAS POSITIVAMENTE

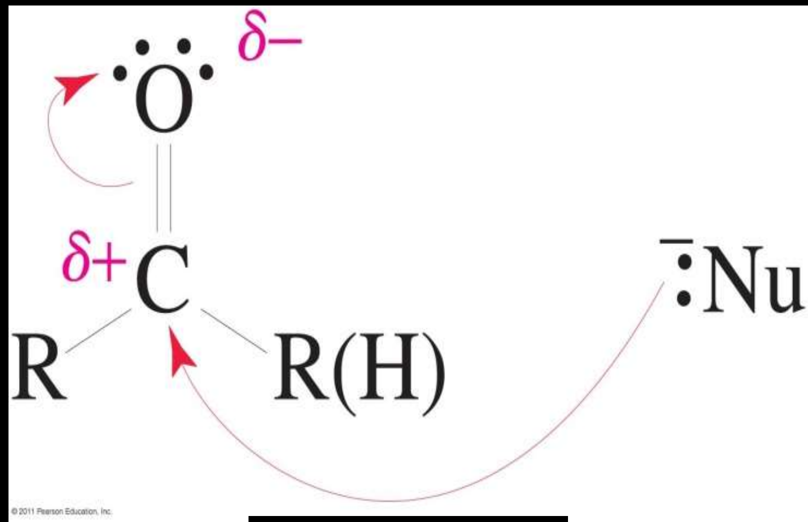
COM UM ORBITAL VAZIO OU COM UM

ORBITAL ANTI-LIGANTE DE BAIXA ENERGIA



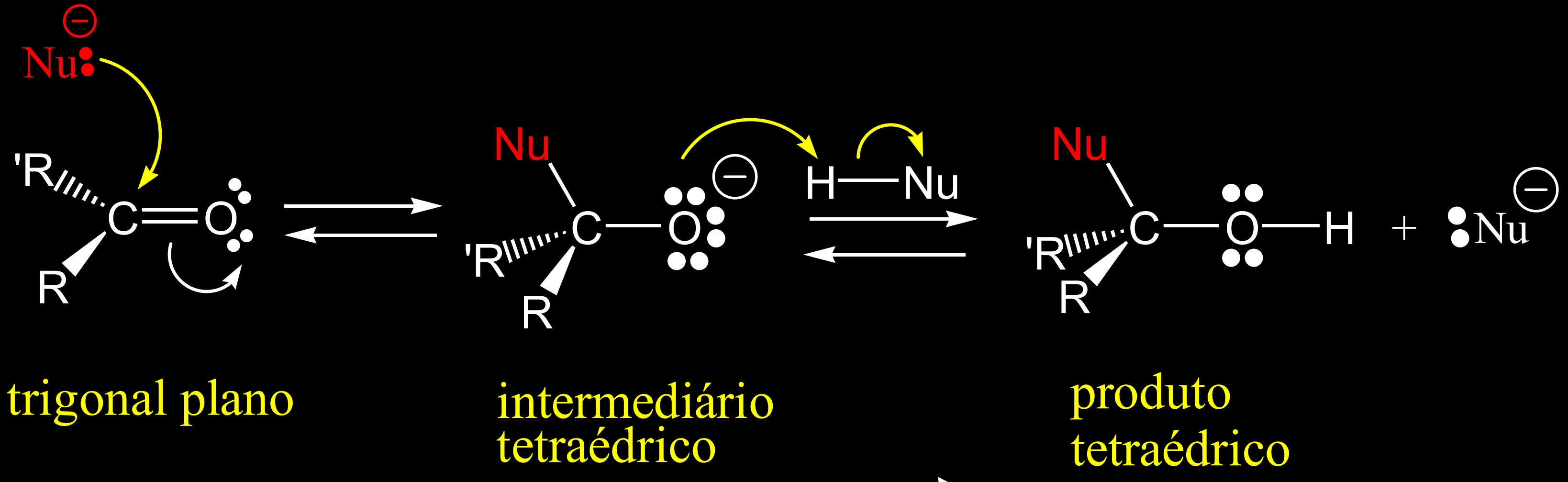
Adição nucleofílica a aldeídos e cetonas



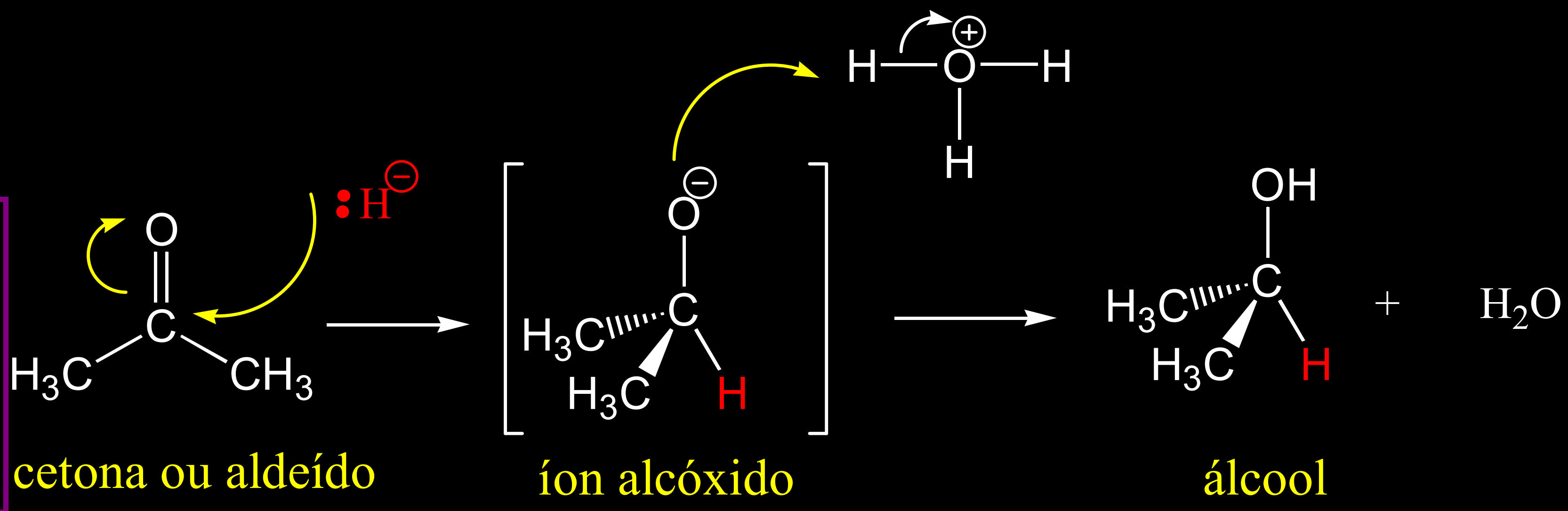


Adição nucleofílica a aldeídos e cetonas

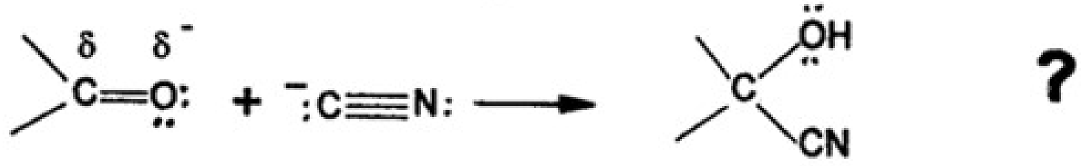
Esquema genérico



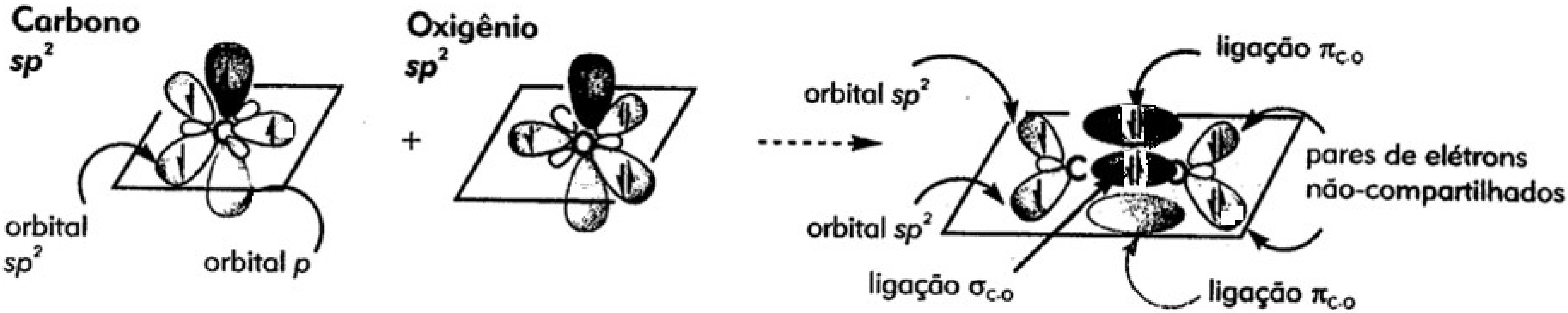
Exemplo: Reação com Hidreto



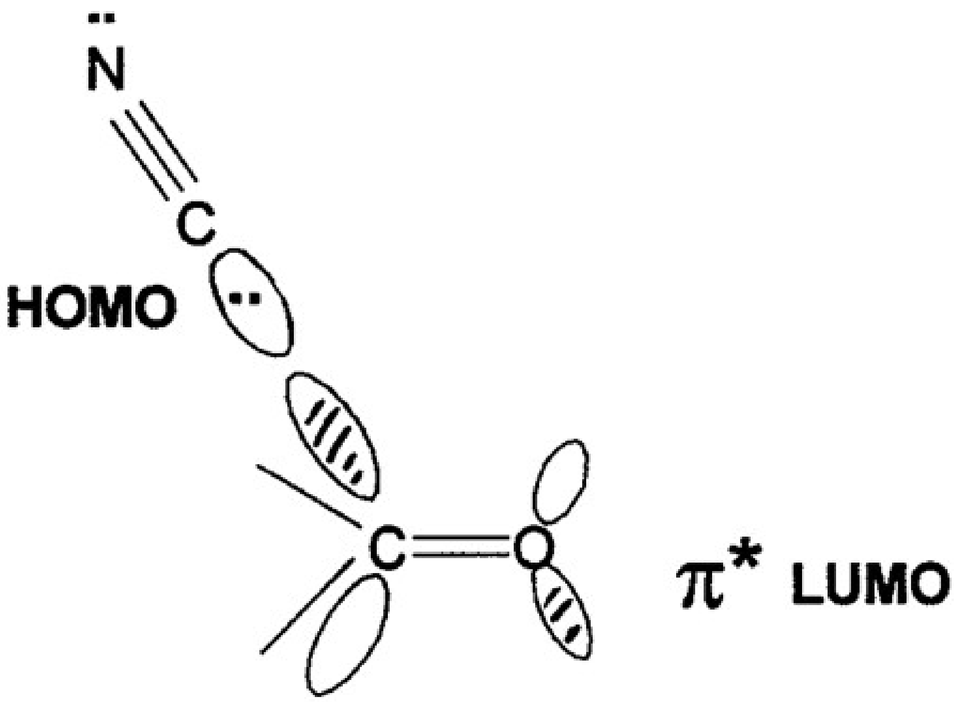
QUAL O MECANISMO DA REAÇÃO ?



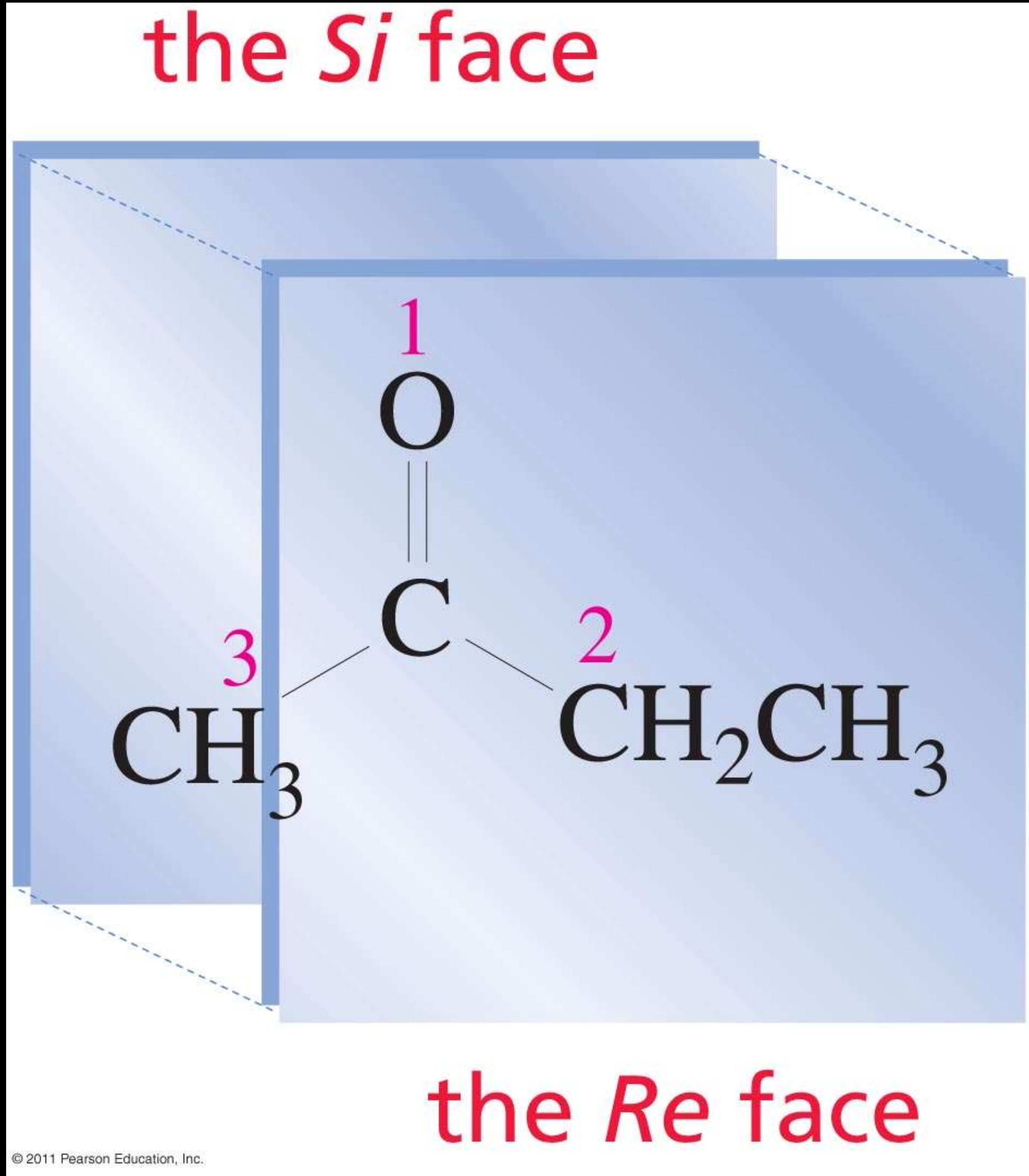
CONSIDEREMOS A ESTRUTURA ELETRÔNICA DO GRUPO CARBONILA



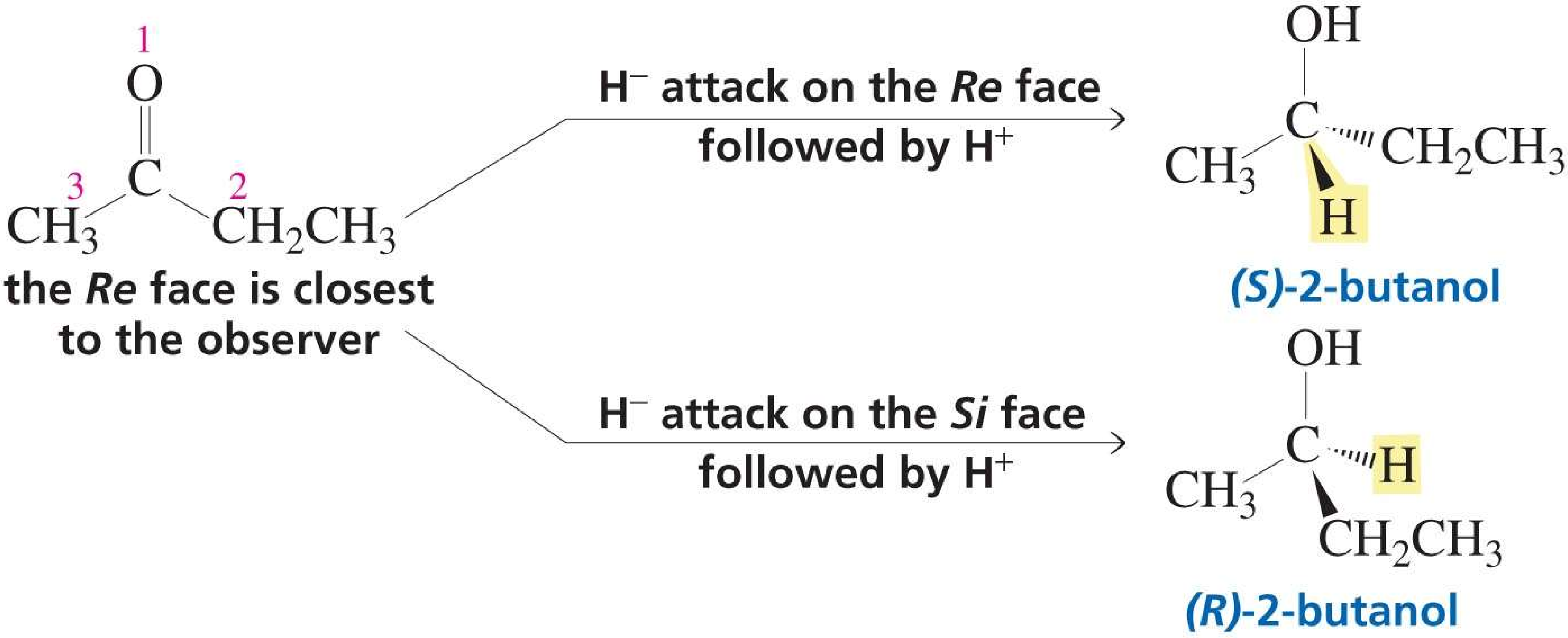
INTERAÇÃO ENTRE O ELETRÓFILO E O NUCLEÓFILO



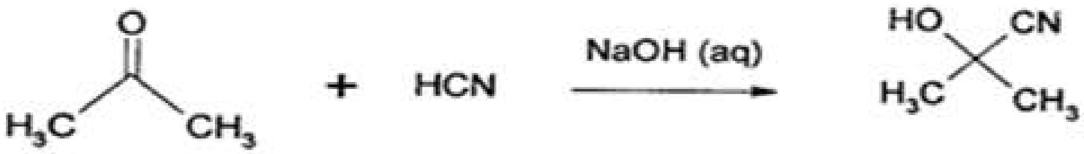
Estereoquímica da Reação de Adição Nucleofílica



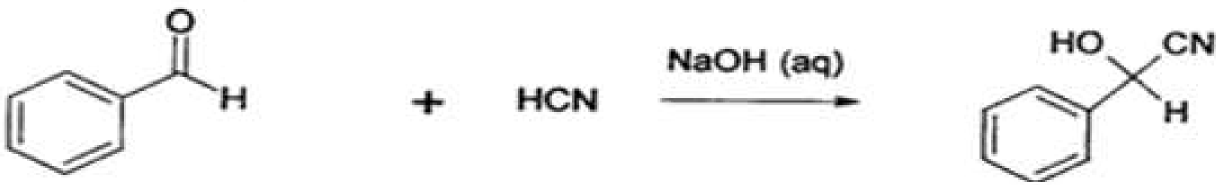
Estereoquímica da Reação de Adição Nucleofílica



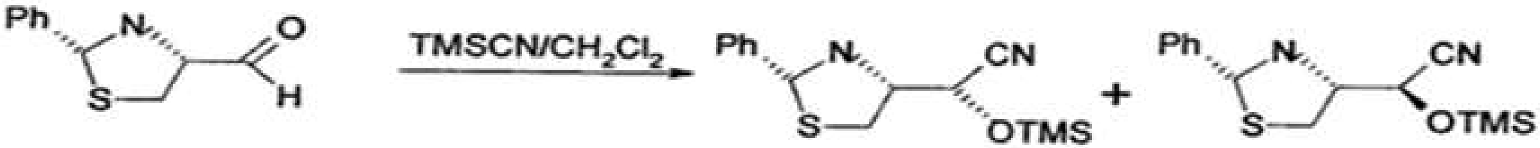
FATOS EXPERIMENTAIS



NÃO HÁ CENTRO ESTEREOGÊNICO



MISTURA RACÊMICA

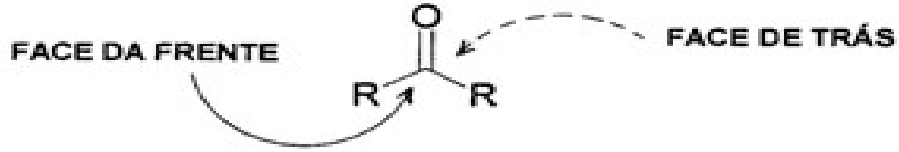


92

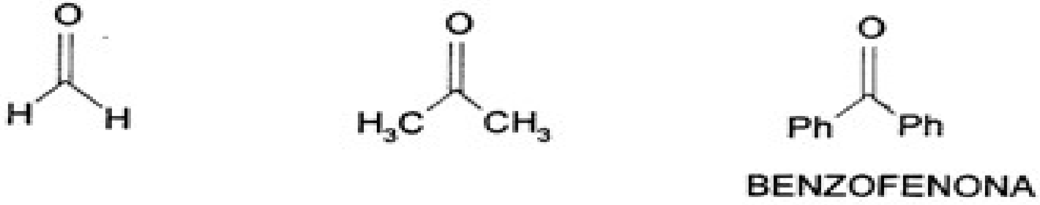
8

MISTURA DE DIASTEREOISÔMEROS

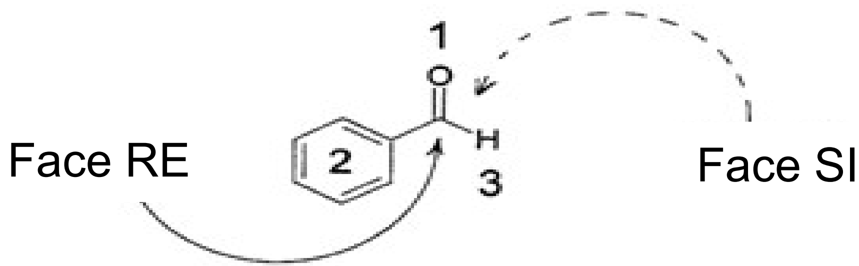
SÍNTESE ESTEREOSSELETIVA - PRINCÍPIOS



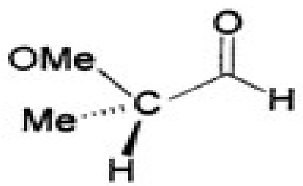
FACES HOMOTÓPICAS

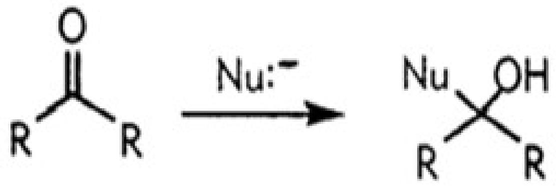


FACES ENANTIOTÓPICAS

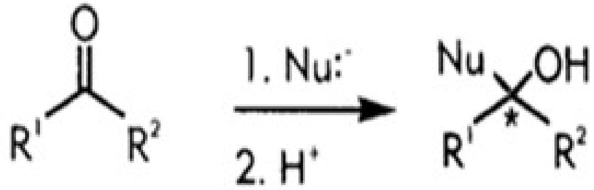


FACES DIASTEREOTÓPICAS

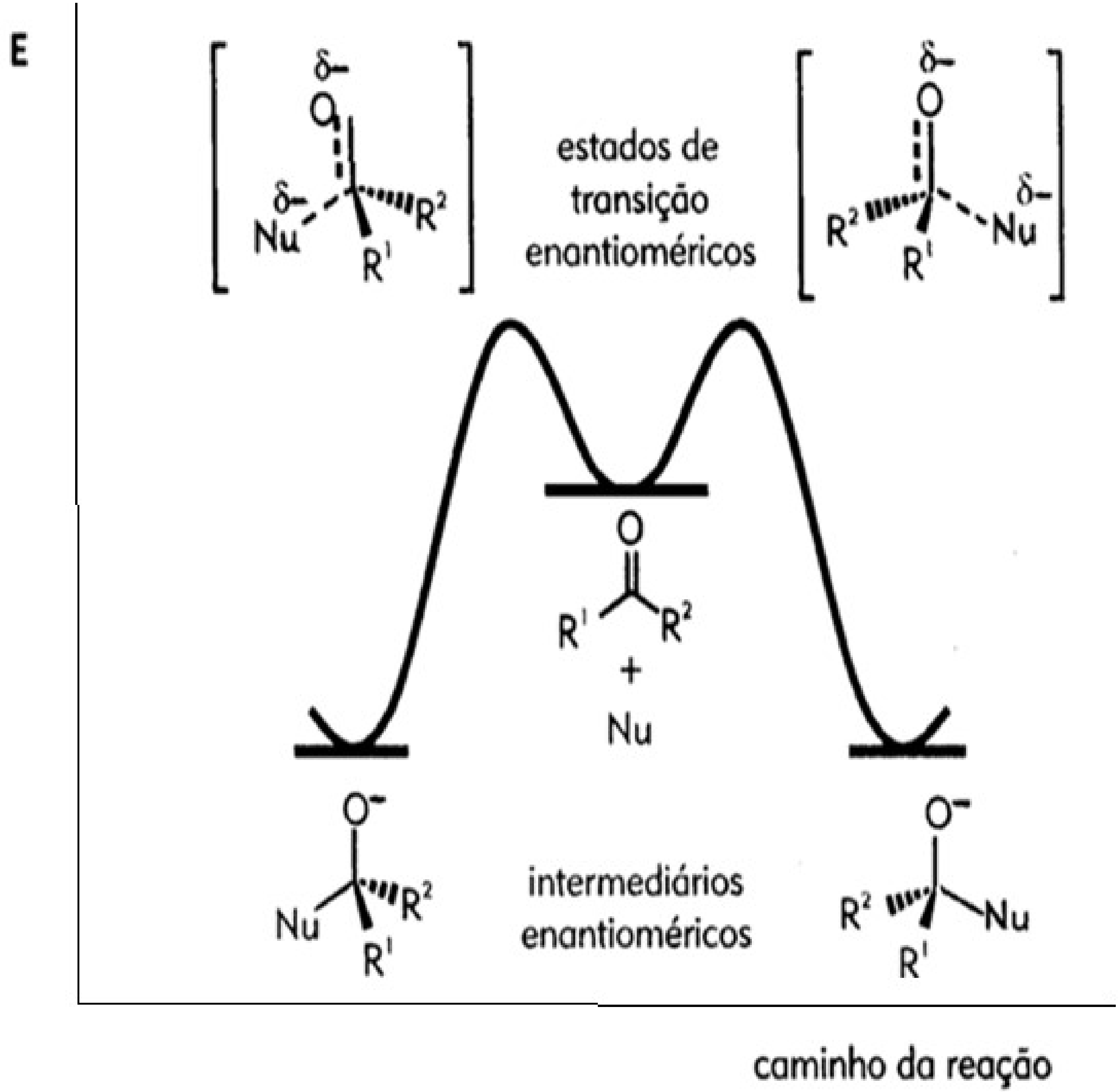


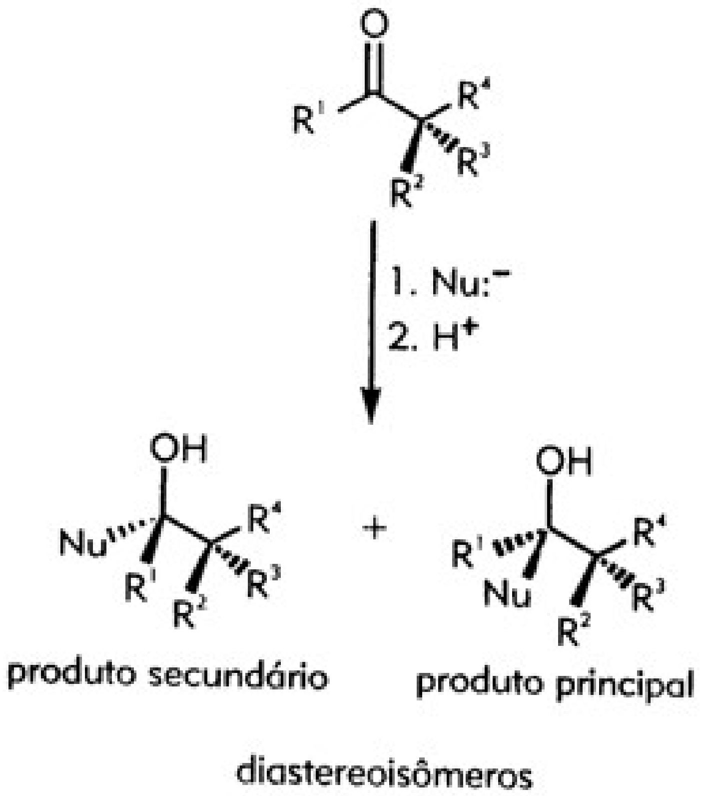


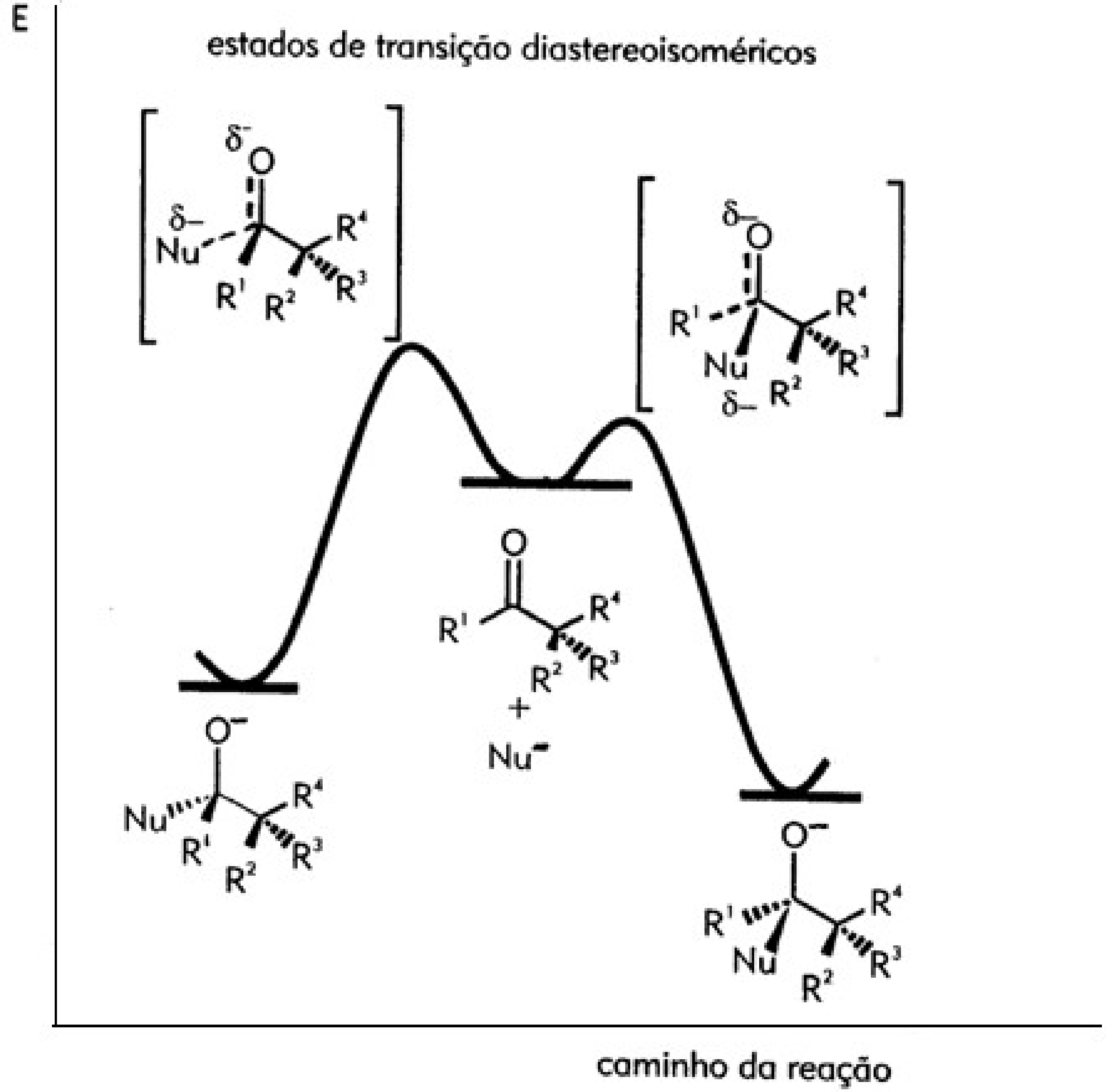
faces homotópicas
não há formação de centro estereogênico



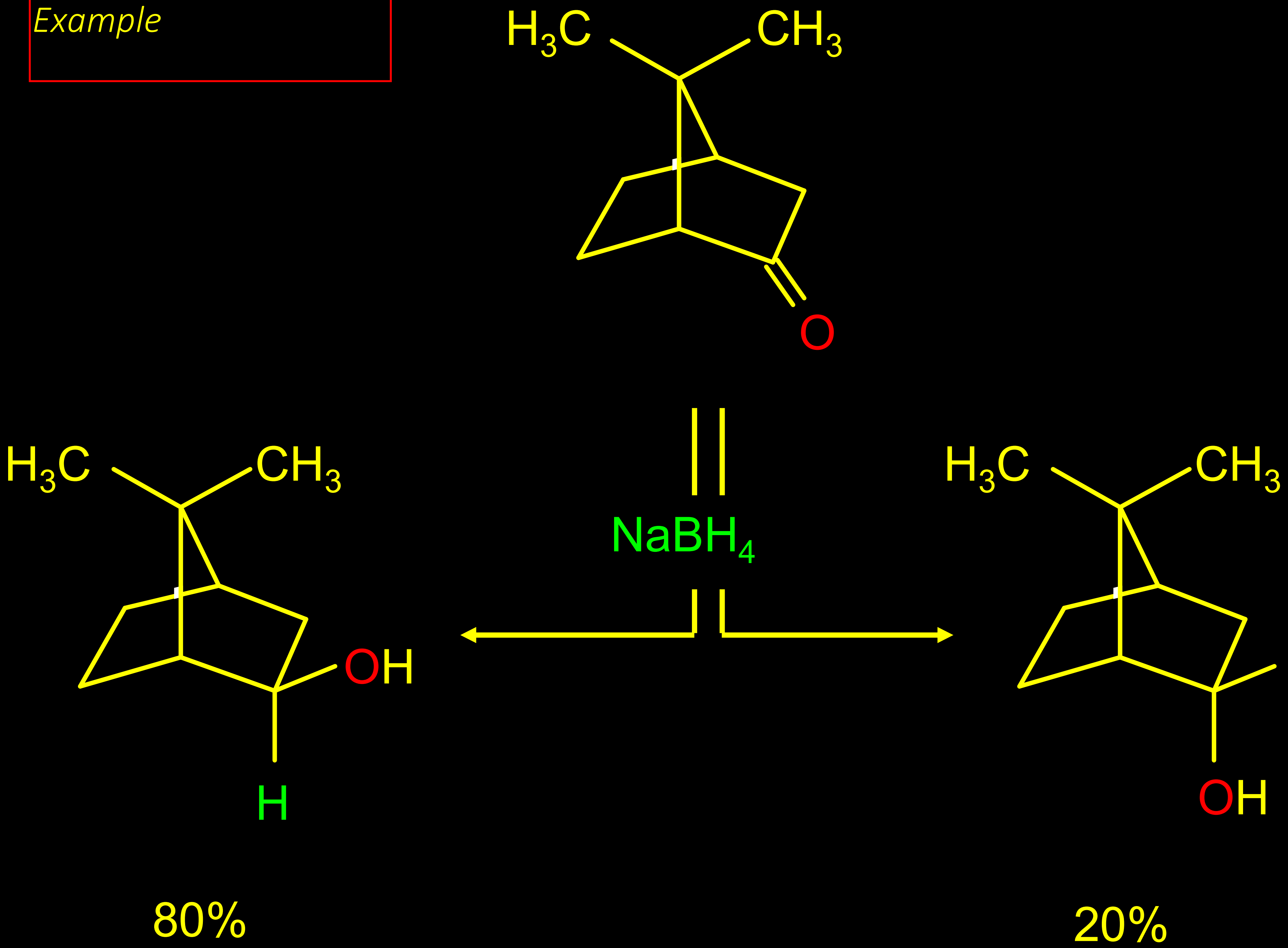
faces proquirais enantiotópicas
há formação de uma mistura racêmica



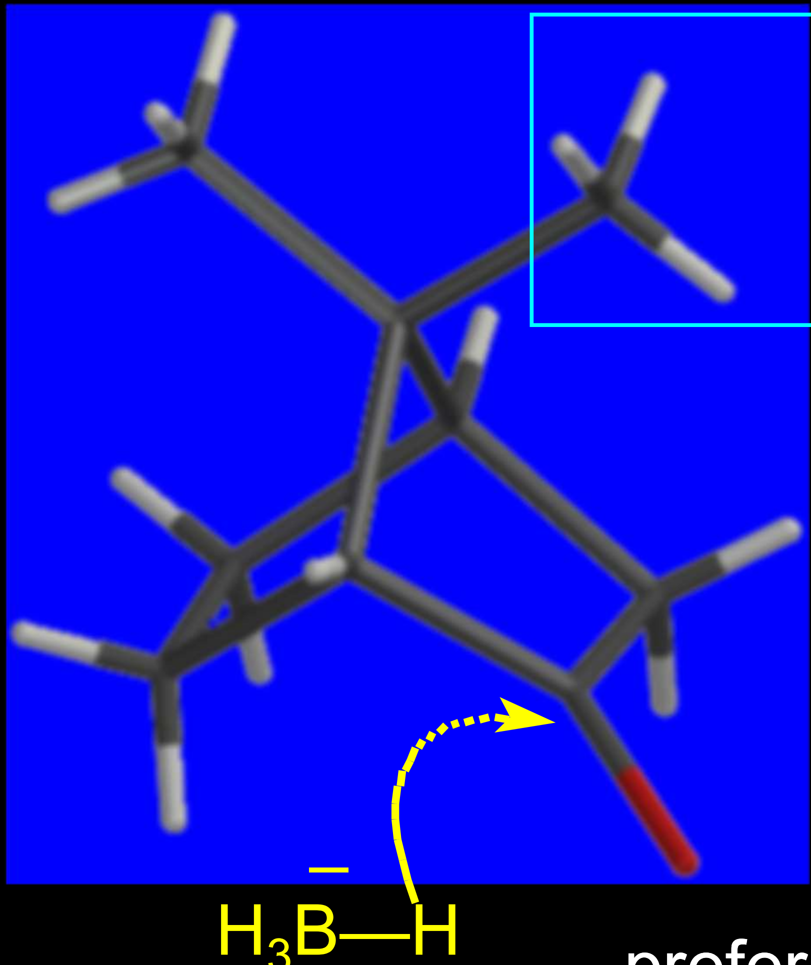

O
R1
R4
R3
R2
1. Nu:⁻
2. H⁺
OH
Nu
R1
R4
R3
R2
+
OH
R1
Nu
R4
R3
R2
produto secundário
produto principal
diastereoisômeros


E
estados de transição diastereoisoméricos
δ⁻
O
δ–
Nu
R1
R2
R4
R3
δ⁻
O
R1
Nu
δ–
R2
R4
R3
O
R1
R4
R2
R3
+
Nu⁻
O⁻
Nu
R1
R2
R4
R3
O⁻
R1
Nu
R2
R4
R3
caminho da reação

Example



Steric Hindrance to Approach of Reagent

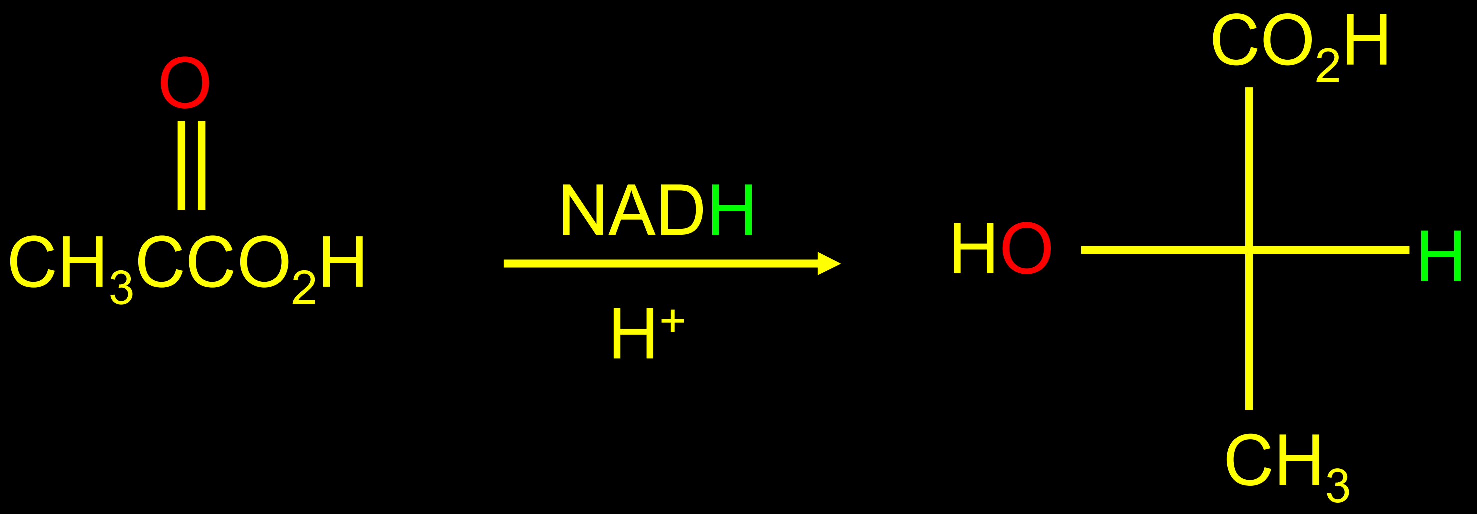


this methyl group hinders approach of nucleophile from top

preferred direction of approach is to less hindered (bottom) face of carbonyl group

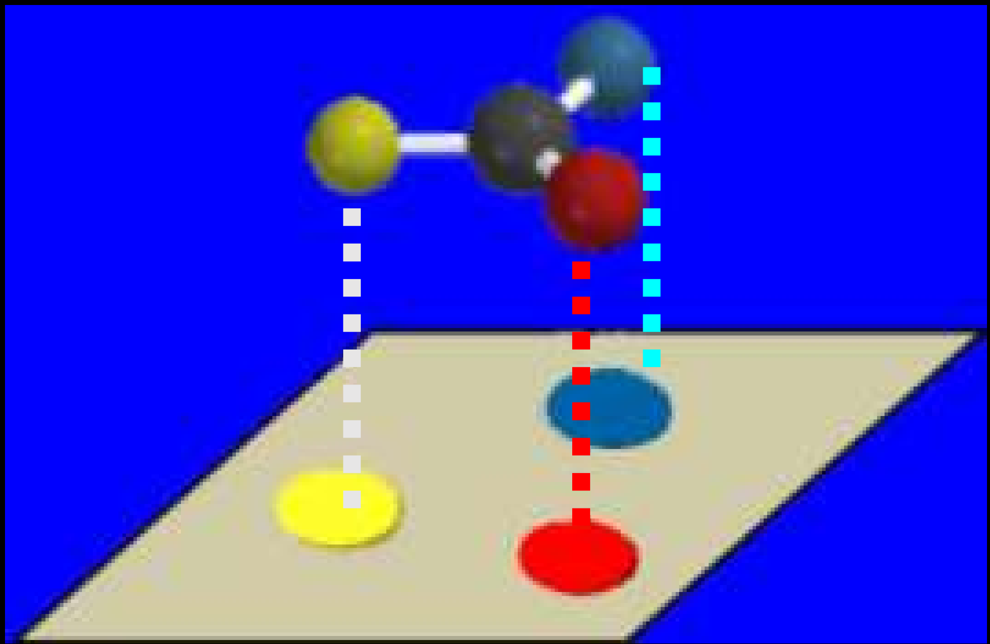
Biological reductions are highly stereoselective

pyruvic acid → *S*-(+)-lactic acid



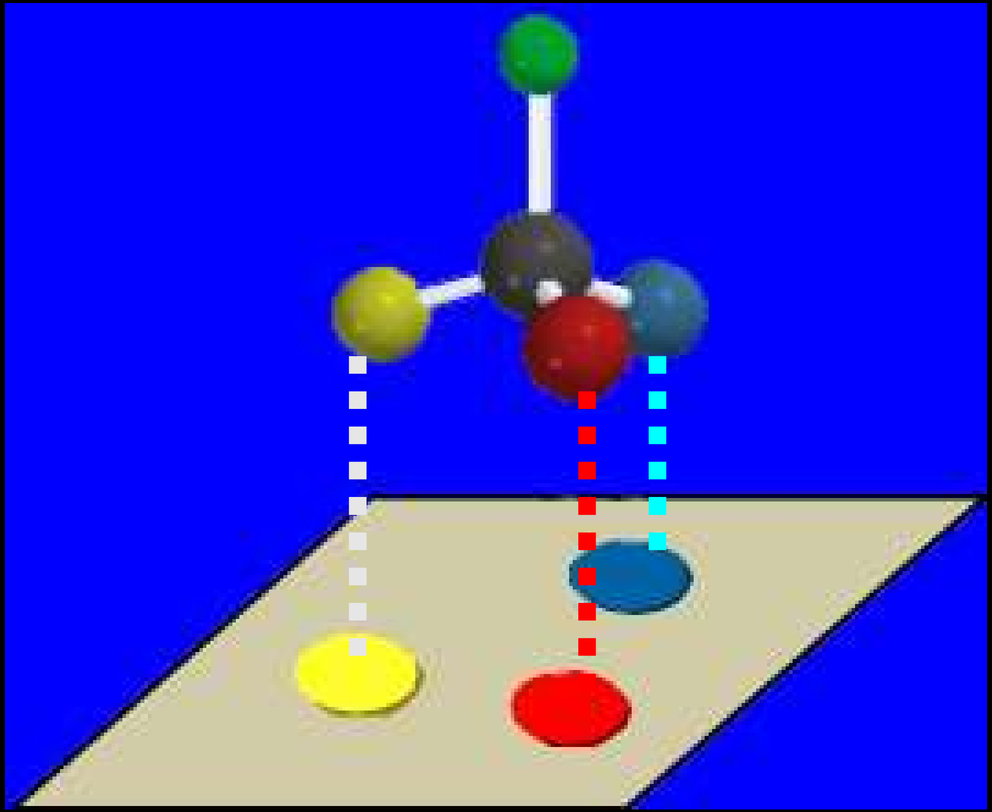
enzyme is *lactate dehydrogenase*

Figure 17.14



One face of the substrate can bind to the enzyme better than the other.

Figure 17.14



Change in geometry from trigonal to tetrahedral is stereoselective. Bond formation occurs preferentially from one side rather than the other.

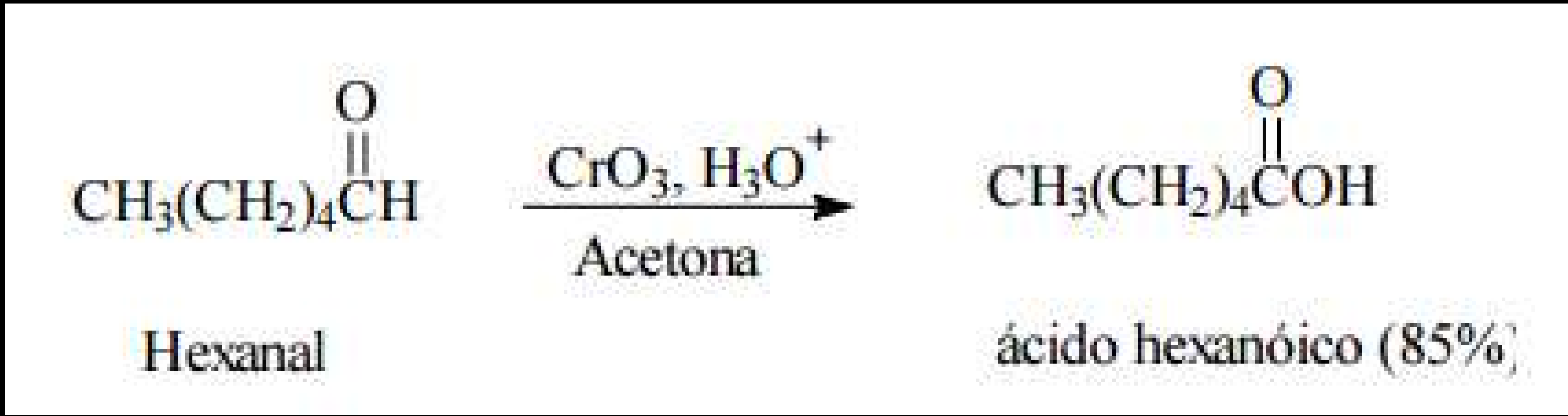
Oxidação de aldeídos e cetonas

Aldeídos: facilmente oxidados para produzir os ácidos carboxílicos

Cetonas: normalmente inertes à oxidação

Diferença: aldeídos têm um hidrogênio (–CHO) que pode ser abstraído como próton durante a oxidação, mas a cetona não

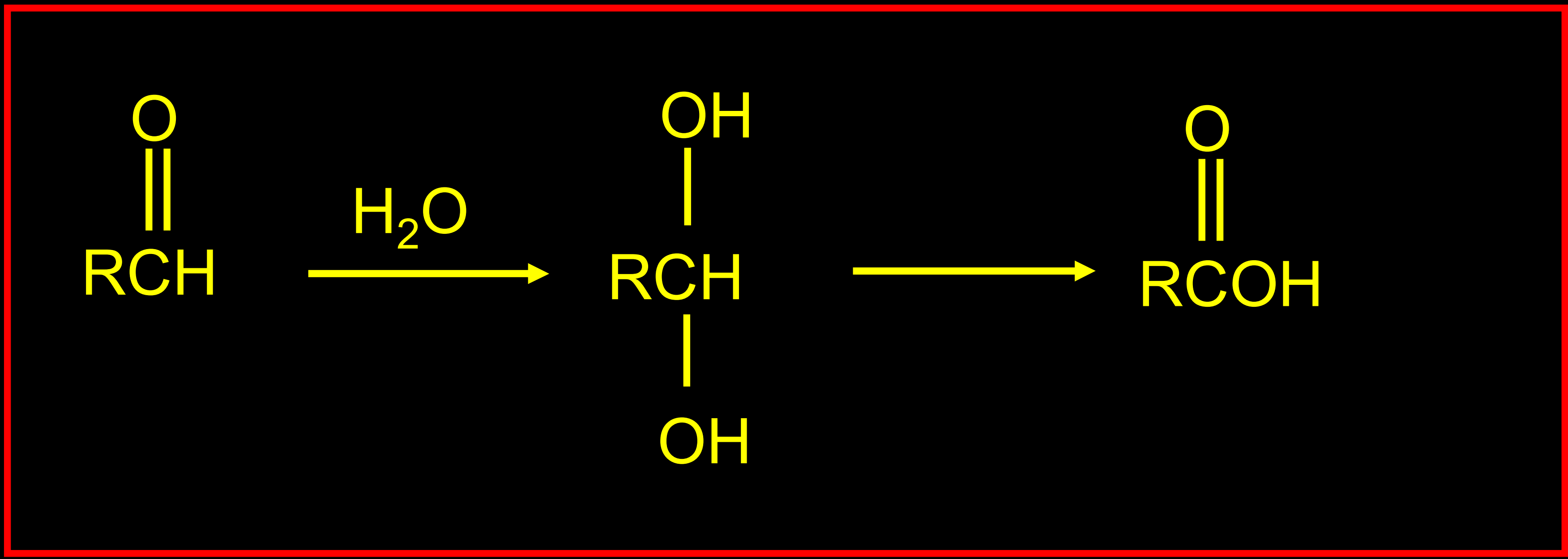
Oxidação de aldeídos e cetonas



CrO_3 em ácido aquoso: oxidação rápida, à temperatura ambiente e com bom rendimento.

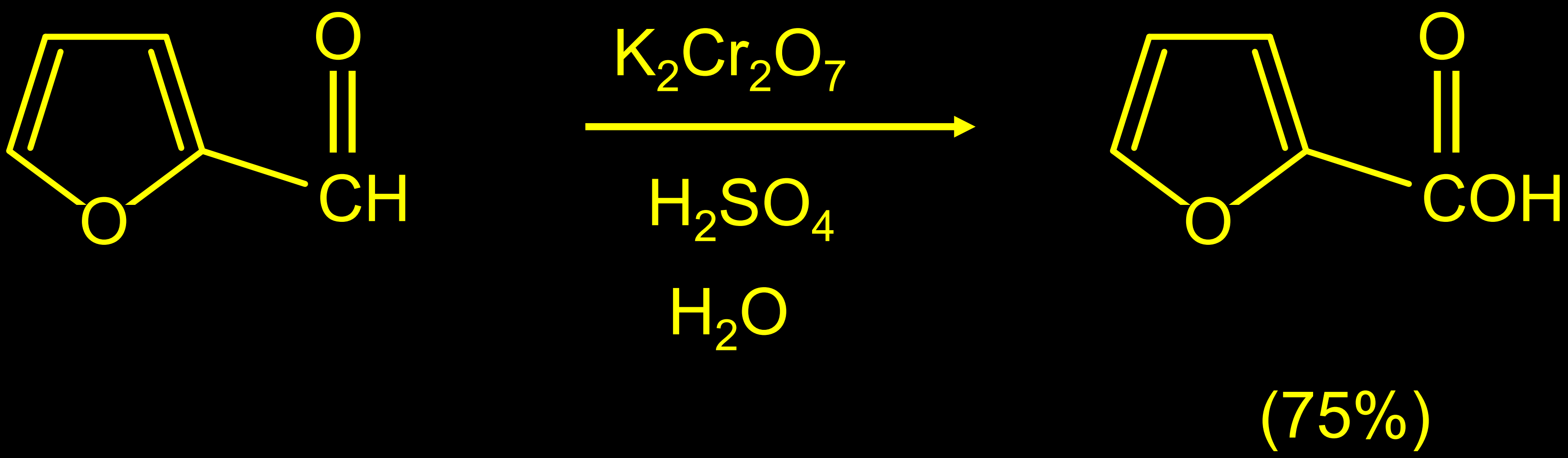
Outros agentes oxidantes: $KMnO_4$, HNO_3 a quente

Oxidation of Aldehydes

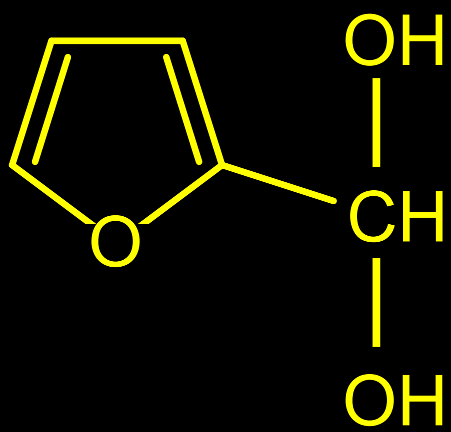


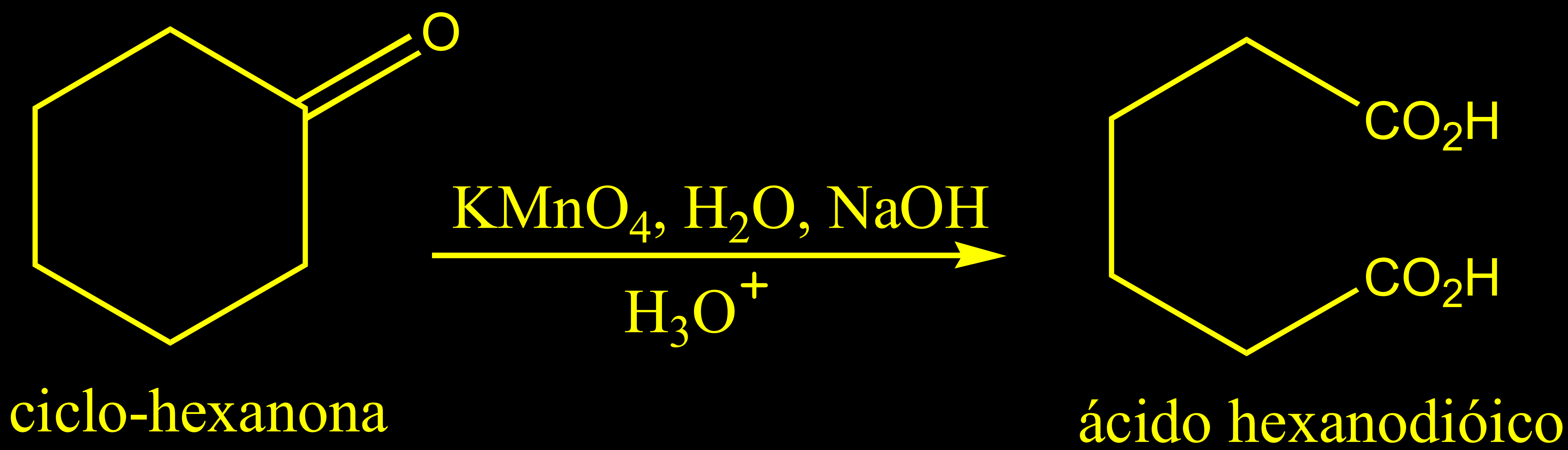
in aqueous solution

Example



via



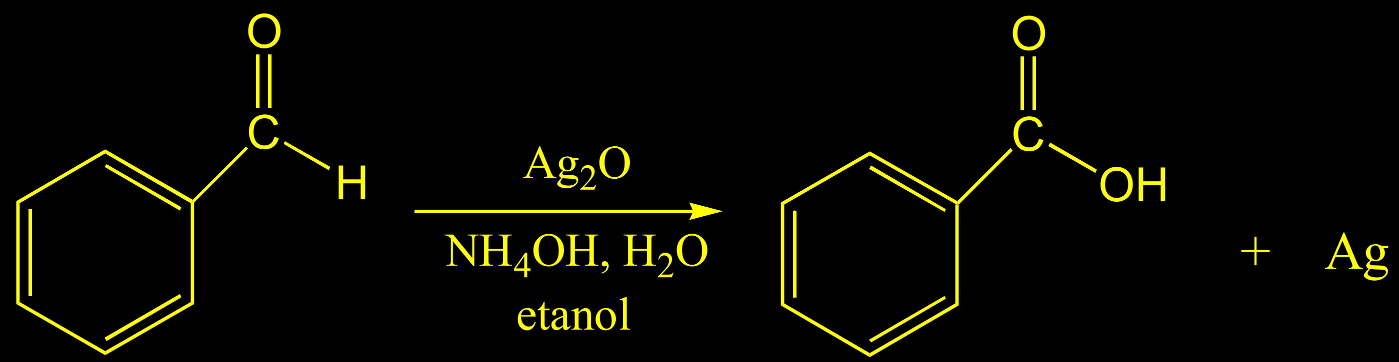


Fonte:
http://www.esalq.usp.br/departamentos/lce/arquivos/aulas/2016/LCE0118/quimica_organica.pdf

Oxidação de aldeídos e cetonas

Desvantagens da oxidação com CrO_3: condições ácidas, podem ocorrer reações laterais.

Alternativa: óxido de prata, Ag_2O, em amônia aquosa = reagente de Tollens.



benzaldeído

ácido benzóico

Espelho de prata