INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

Fundamentals of Medicinal and Pharmaceutical Chemistry

FUNCHEM.19 Alkynes: Structures, properties and reactions. Alkyne-based drugs.

Professor Dan Wu

DATE: 20 November 2024

Learning outcomes

At the end of this lecture, the learner will be able to

- Recall and describe the general structure and bonding in alkynes.
- Recall and apply the rules of IUPAC method of nomenclature to name and identify alkynes.
- Identify internal and external alkynes and explain their reactivities.
- Recall and explain the products and mechanism of hydrogenation reactions of alkynes.
- Recall and explain the products and mechanism of halogenation, hydrohalogenation and hydration reactions of alkynes.
- Recall and explain production and reactions of alkynide anions.

Recommended reading

- Organic chemistry with biological application (John McMurry)
- Chapter 7 and Chapter 8

Introduction

General formula (non cyclic): C_nH_{2n-2}

Functional group: $R_1—C\equiv C—R_2$

carbon-carbon triple bond

Unsaturated hydrocarbons: each carbon is attached to only 2 atoms.

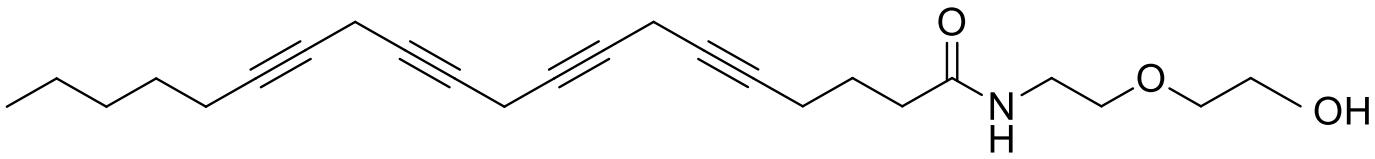
Alkynes exhibit chemical properties similar to that of alkenes (electrophilic addition reactions), but there are also significant differences.

Nomenclature

Names end in *–yne*

ethyne (acetylene)

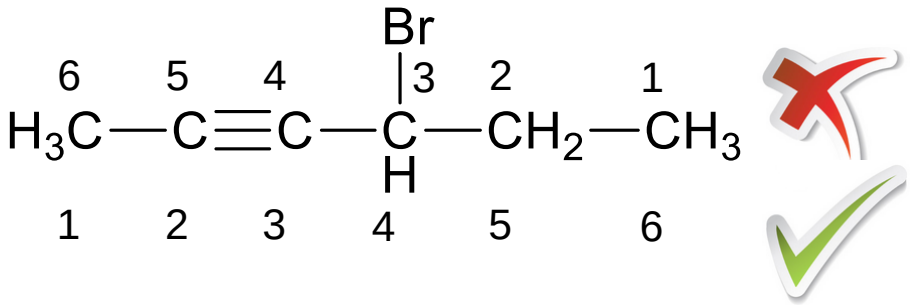
Hydrocarbons with two triple bonds are called *diynes*, with 3 triple bonds are called *triynes*, etc.



tetrayne derivative used as anti-acne drug candidate

Nomenclature

For alkyne chains, C chain is numbered so that the (first) C of the triple bond has the lowest number.



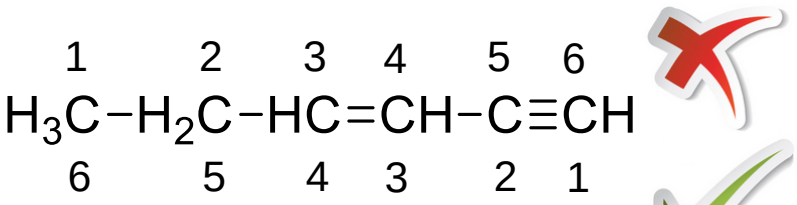
4-bromo-2-hexyne

Nomenclature

Hydrocarbons containing one C=C and one C≡C

are called *enynes*;

numbering of the chain starts from the end nearer the first multiple bond (double or triple).



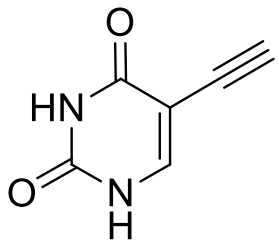
3-hexen-1-yne

Carbon-Carbon Triple Bond

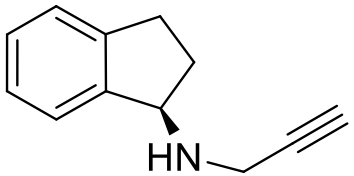
⇨ there are 2 possible types of carbon-carbon triple bonds.

$$R-C\equiv C-H$$

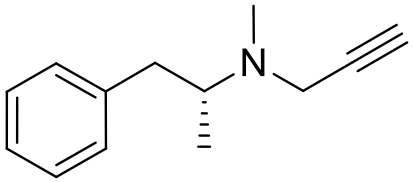
Terminal alkynes



Eniluracil
(anti-neoplastic
enhancer)



Rasagiline
(anti-parkinsonian)



Selegiline
(anti-parkinsonian)

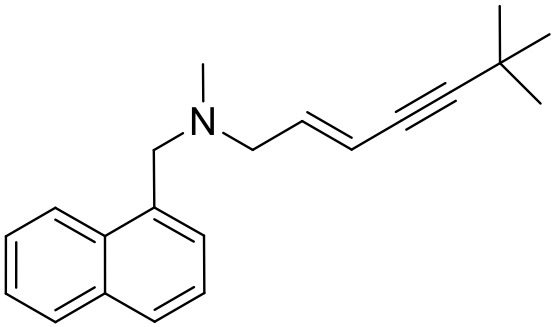
Note: Structures & names of drugs for information only.

Carbon-Carbon Triple Bond

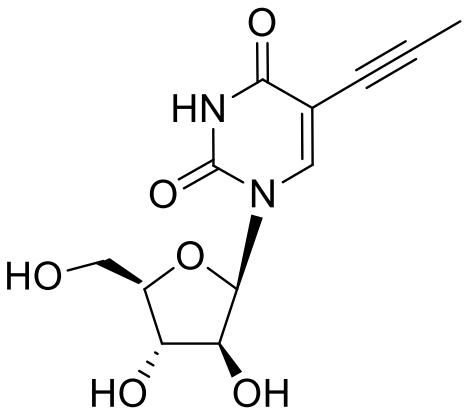
$$R-C\equiv C-R'$$

R, R’ ≠ H

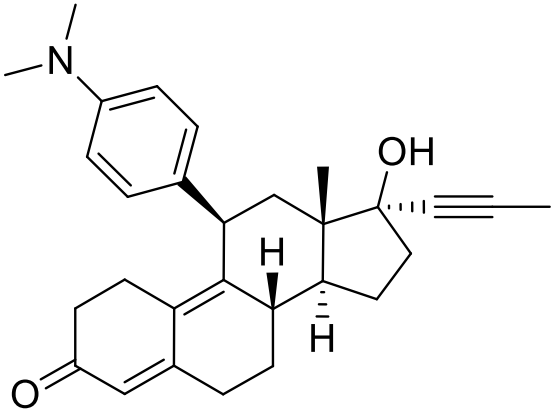
Internal alkynes



Terbinafine
(anti-fungal)



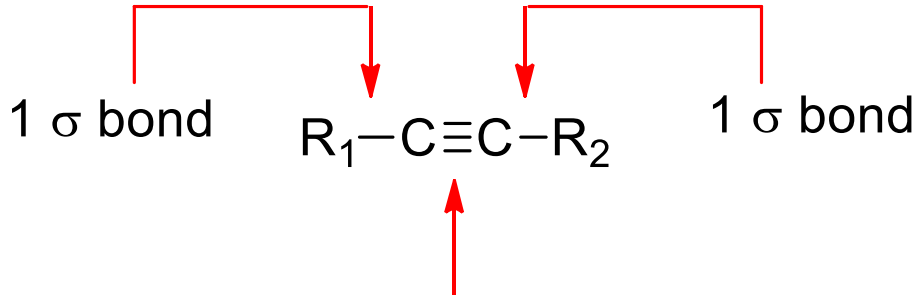
Netivudine
(anti-viral)



Mifepristone
(anti-depressant)

Note: Structures & names of drugs for information only.

Geometry of Carbon-Carbon Triple Bond



each carbon has *sp* hybridisation.

Linear geometry, 180 °

R_1, C, C and R_2 are in a straight line.

Alkynes - Physical Properties

Bond length: C≡C : 1.18 Å

C=C : 1.32 Å

C−C : 1.53 Å

⇨ shortest carbon-carbon bond

Bond strength: C≡C : ~835 kJ/mol

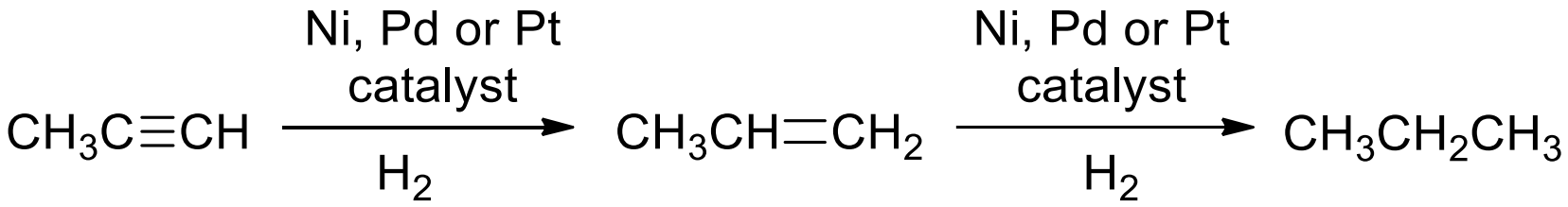
C=C : ~620 kJ/mol

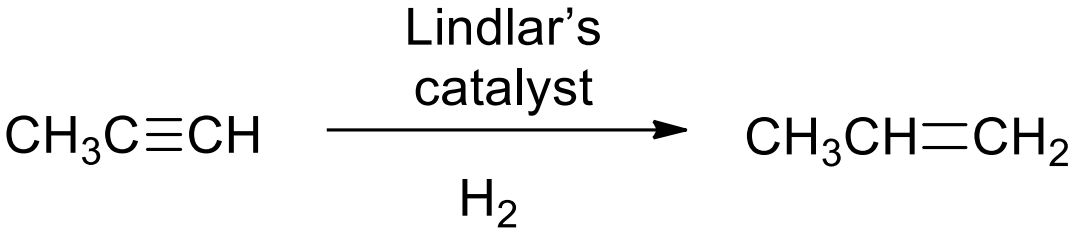
C−C : ~350 kJ/mol

⇨ strongest carbon-carbon bond

Reactions of Alkynes

Hydrogenation





Lindlar's catalyst: palladium metal precipitated

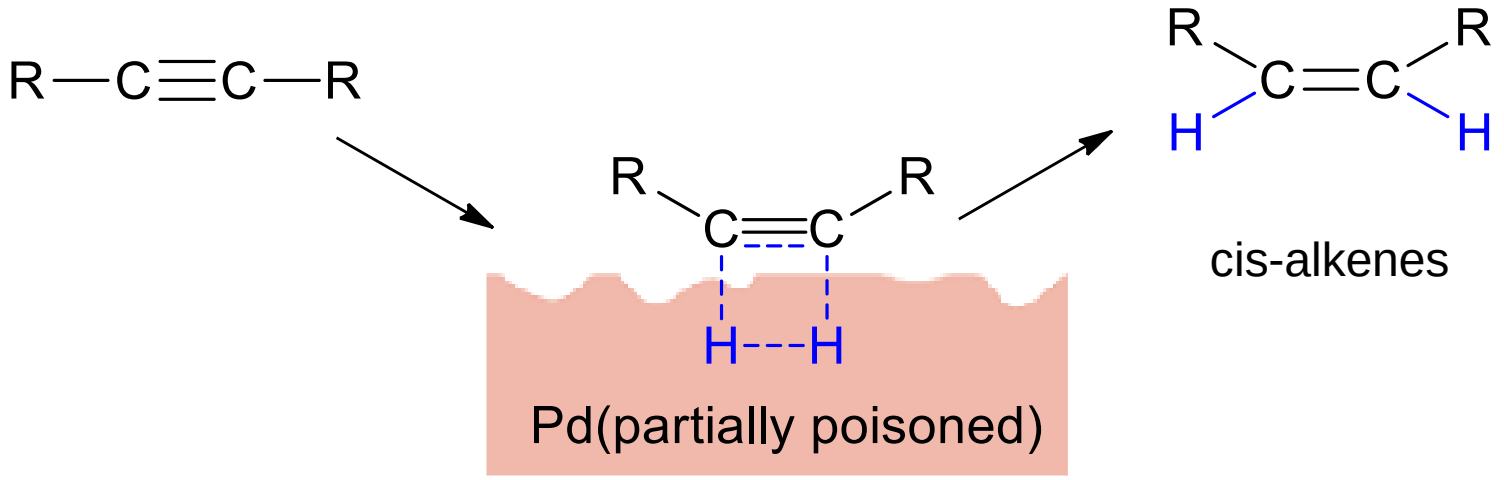
onto a calcium carbonate support and then

deactivated by treatment with lead acetate and quinoline.

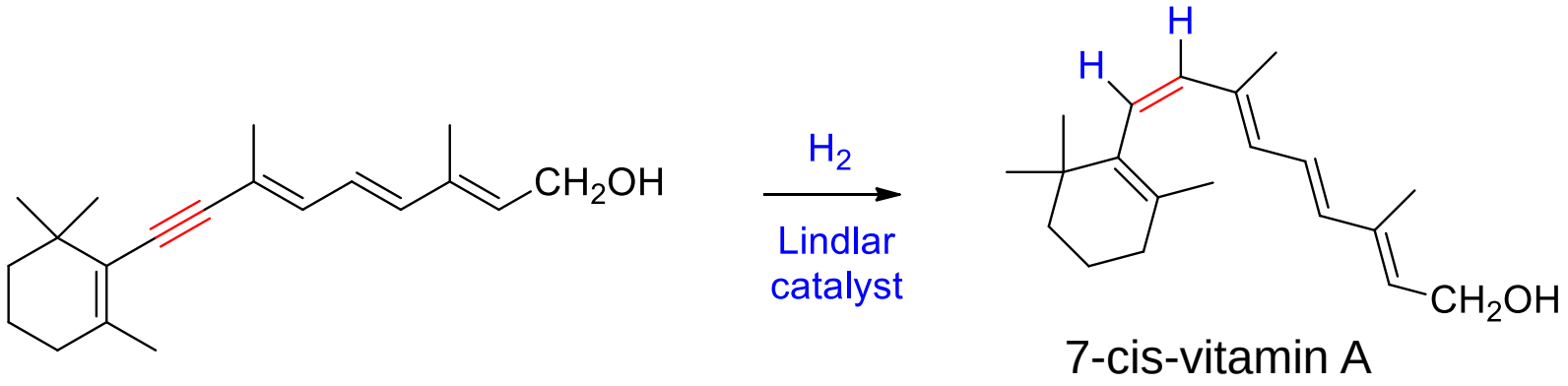
⇨ "poisoned catalyst": hydrogenation stops at alkenes

(no hydrogenation to alkanes).

Internal Alkynes with H_2 in the Presence of Lindlar's Catalyst only Cis-alkenes Obtained

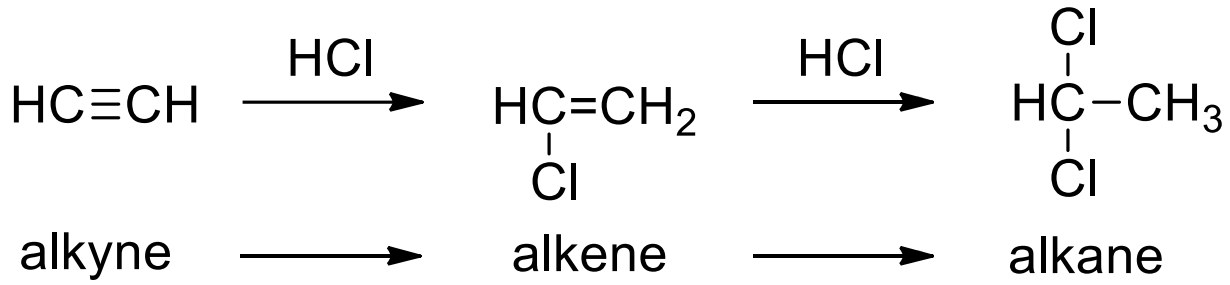


e.g. Synthesis of vitamin A precursor by pharmaceutical company Hoffmann-LaRoche.



Alkyne Reactions: Electrophilic Addition (e.g. HCl)

A double addition takes place

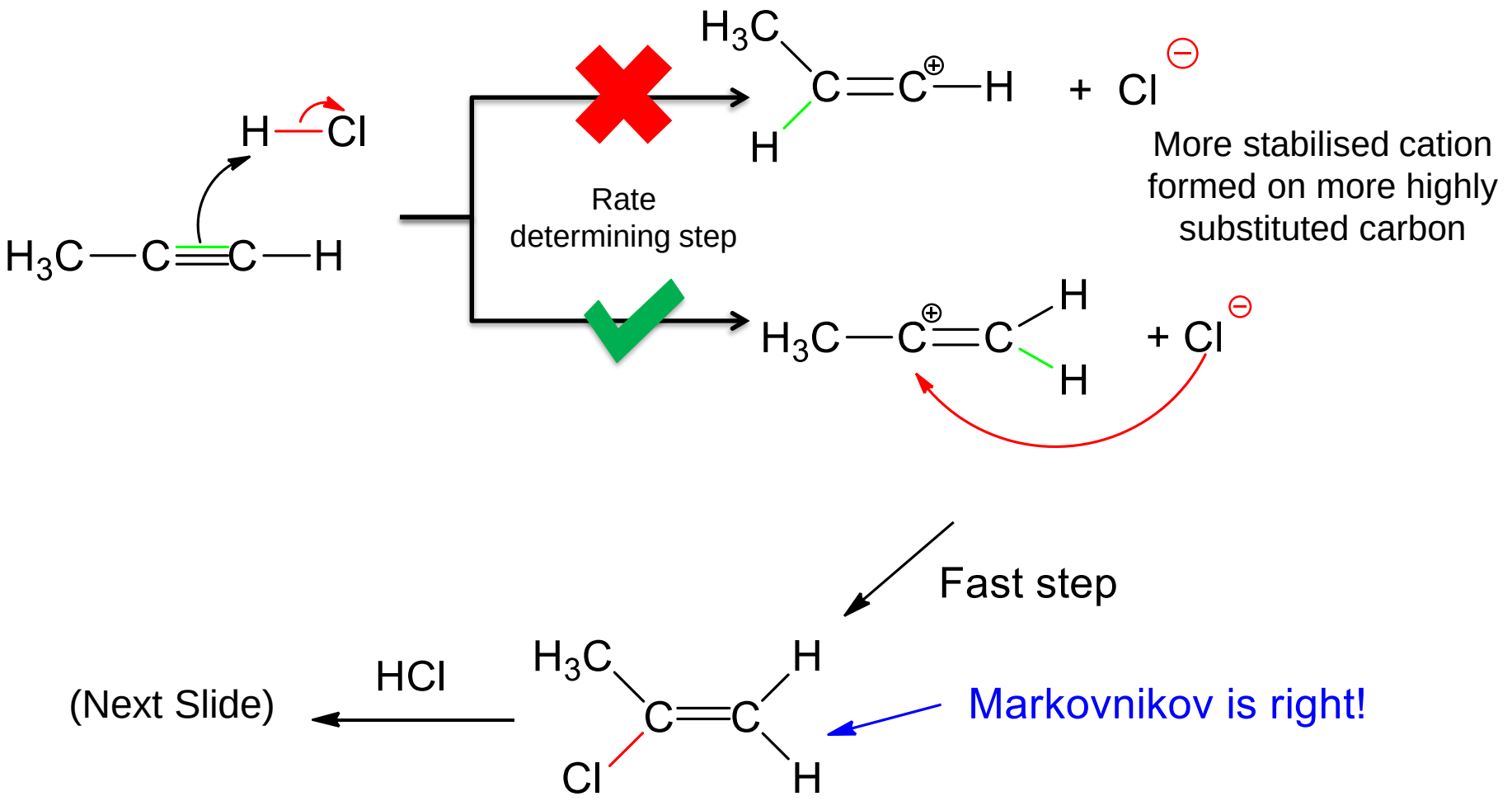


Both additions follow Markovnikov rule:
H will add to the carbon with the greater number of hydrogens.

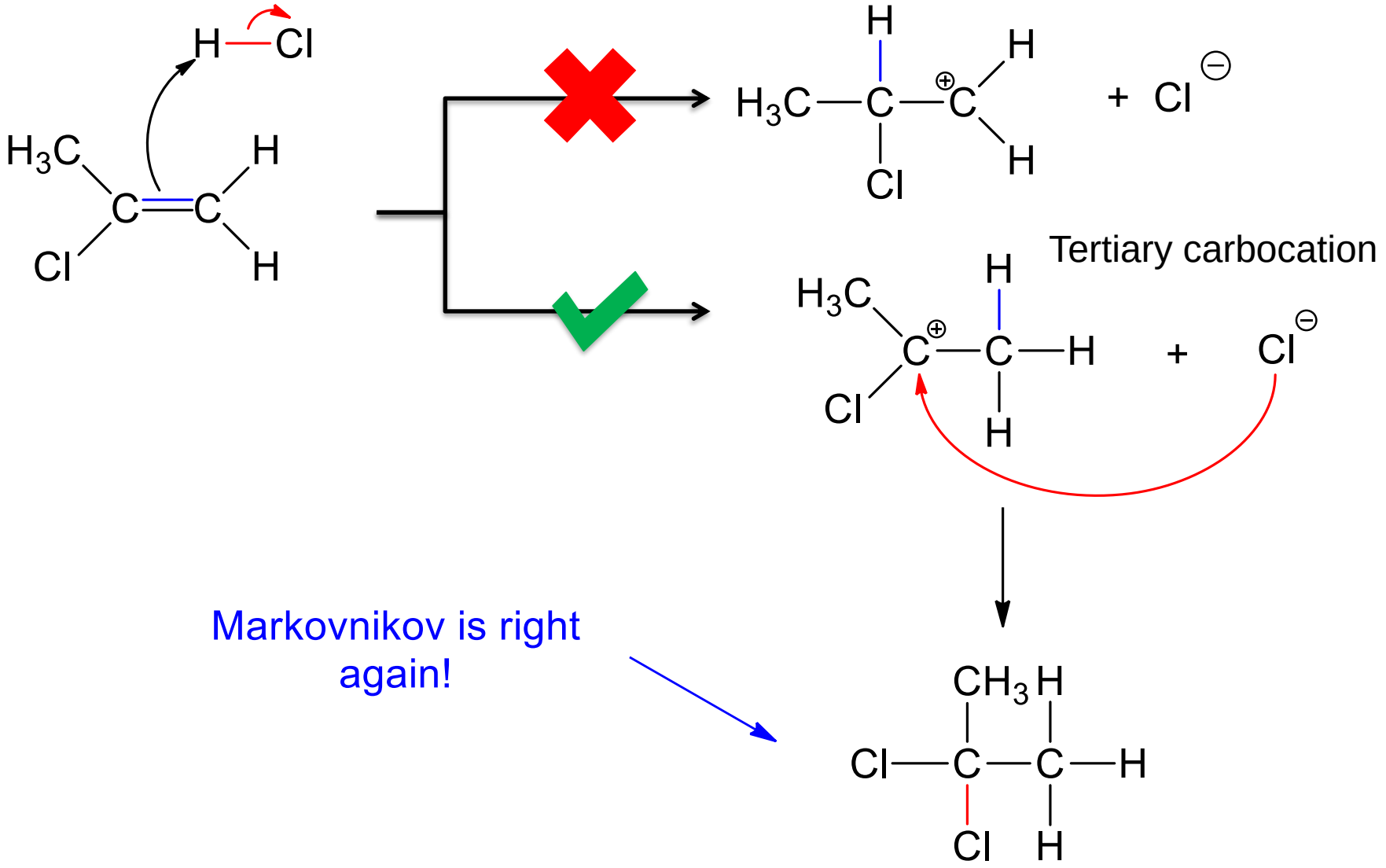
Both hydrogens added on the same carbon,

Both halogens added on the other carbon.

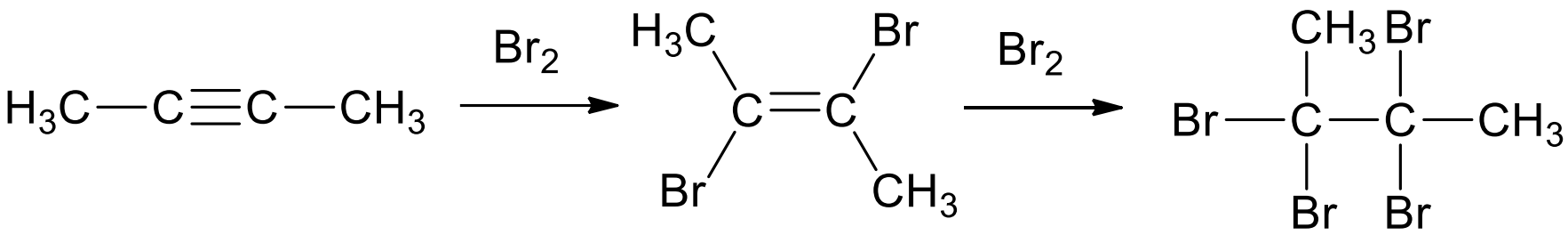
Electrophilic Additions



Electrophilic Additions



Halogenation of Alkynes



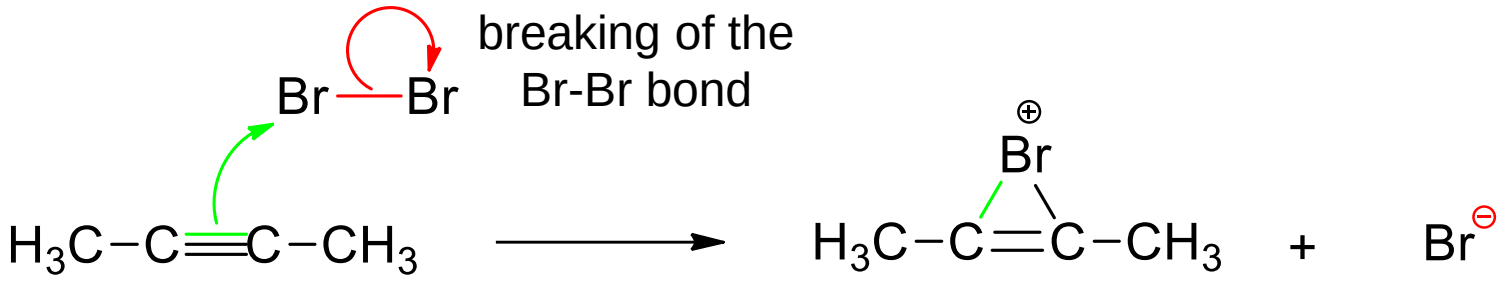
mainly trans di-bromo isomer

Once one Br is attached the other

Br is likely to approach from the opposite side (trans).

Mechanism of Alkyne Halogenation

Stage 1



attack of π electrons of triple bond on Br-Br

formation of the bromonium ion

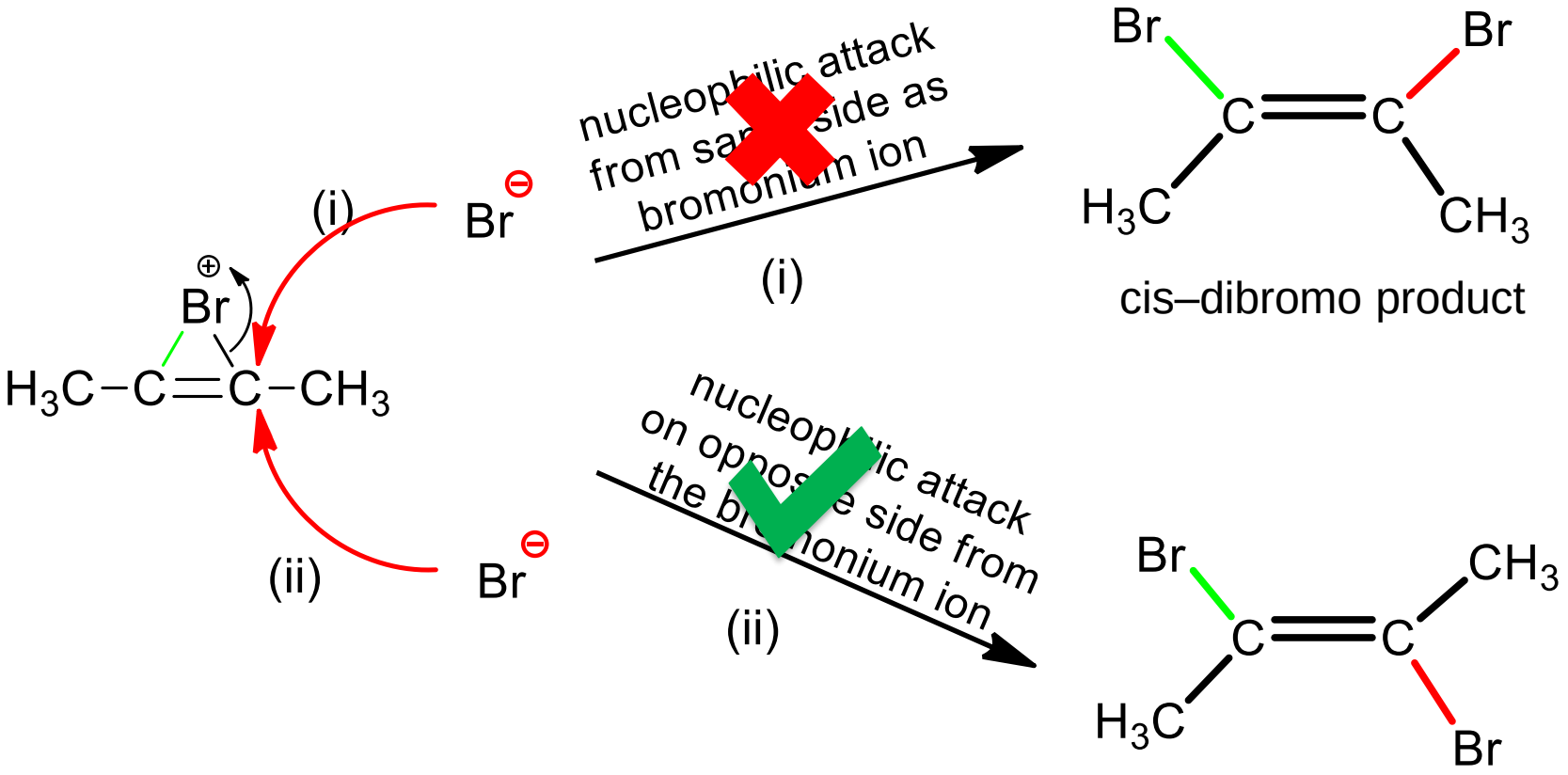
nucleophilic $Br^{\ominus}$ ion formed

(Next Slide)

Note: Mechanism similar to alkene bromination in previous lecture.

Mechanism of Alkyne Halogenation

Stage 2

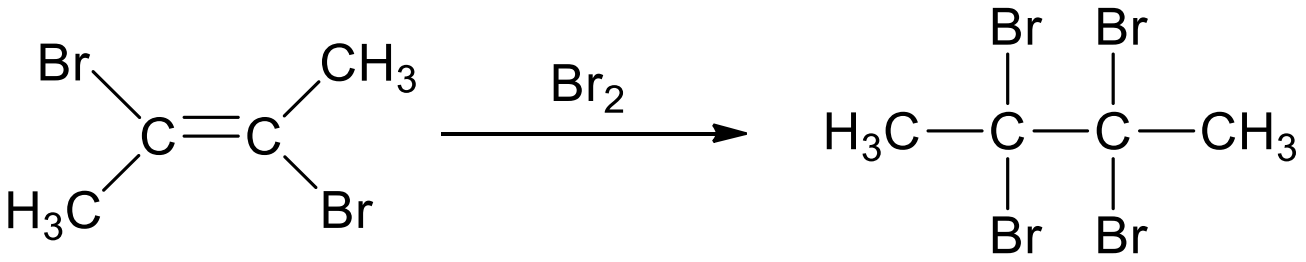


The *trans* di-bromo product is favoured as it is more sterically favourable for nucleophile to attack the face opposite from the bromonium ion.

Mechanism of Alkyne Halogenation

Stage 3

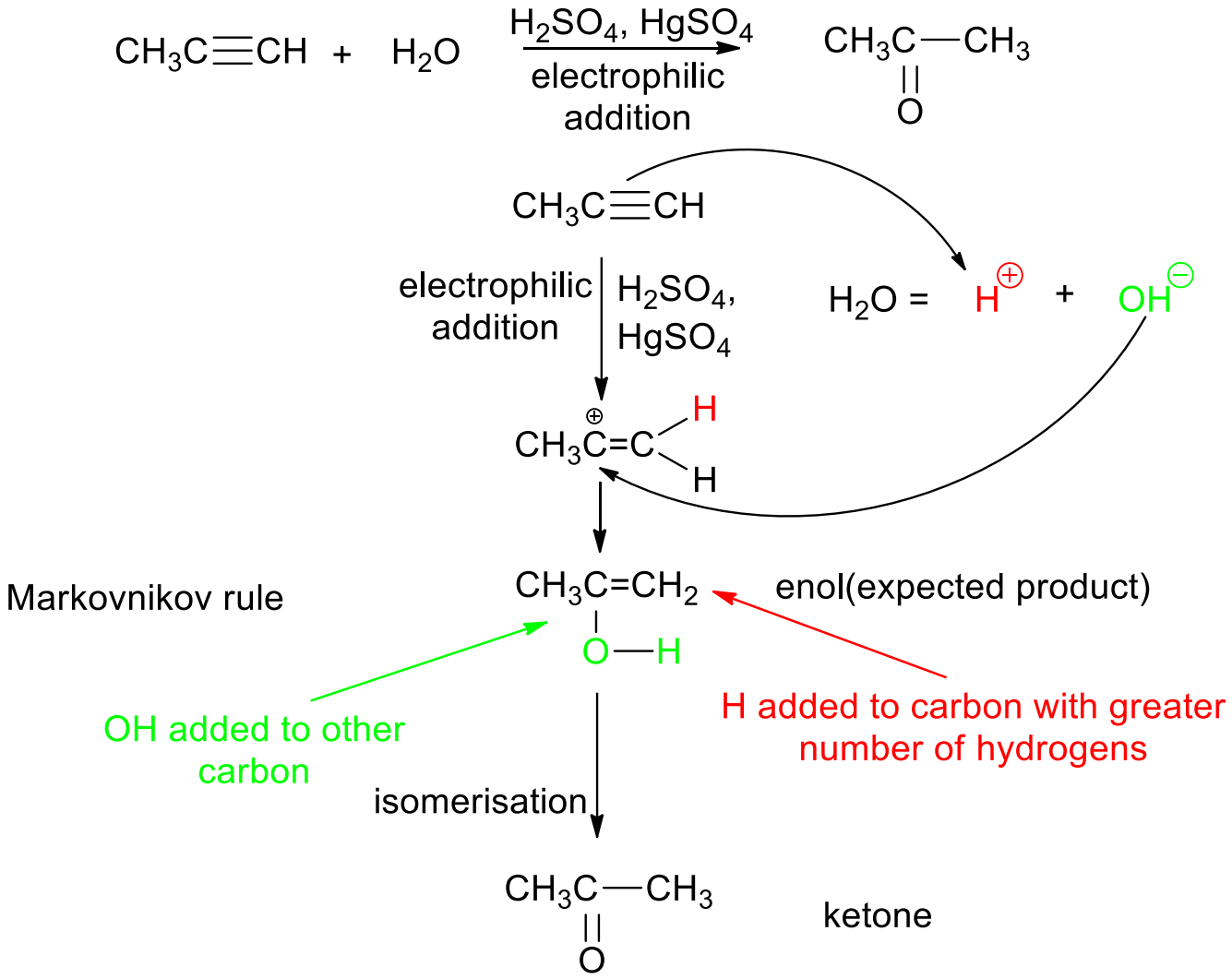
A second bromination now takes place on the alkene formed



Could you write the mechanism for this reaction ???

Addition of H_2O: Hydration of Alkynes

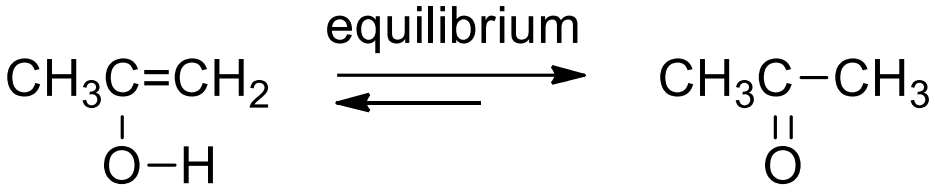
(in the presence of H_2SO_4 and $HgSO_4$ as catalysts)



Enol and ketone are tautomers of each other

Tautomerism

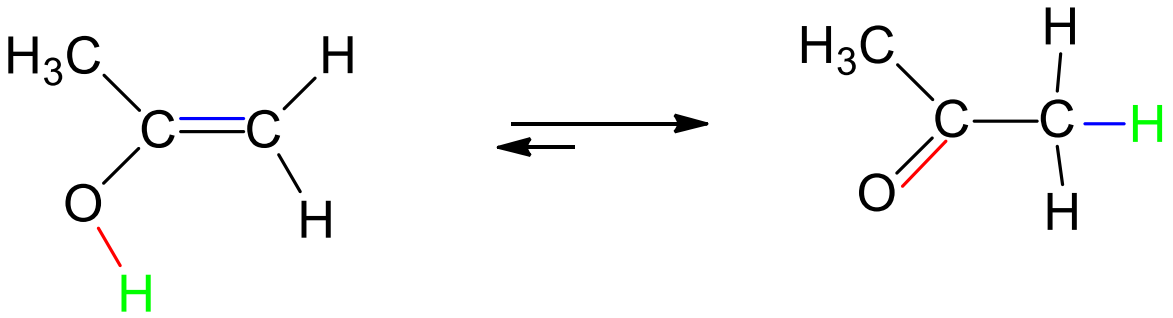
Tautomers are isomers which differ in the positions of H atoms and double bonds.



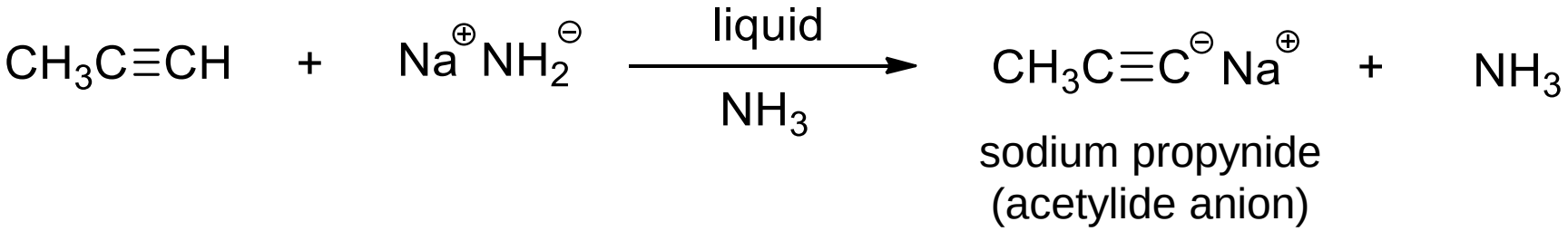
enol ketone

The enol and keto form are in equilibrium with each other with the equilibrium lying strongly towards the ketone form.

Enols are less stable than ketones so the proton from the alcohol shifts to the neighbouring carbon and a double bond is formed between the carbon and the oxygen.

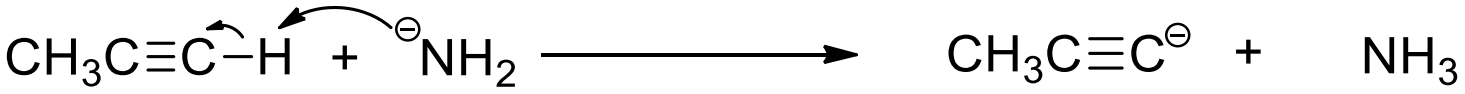


Terminal Alkynes are Weak Acids – Proton can be Removed by a Strong Base



$NaNH_2$ in liquid ammonia is a very strong base.

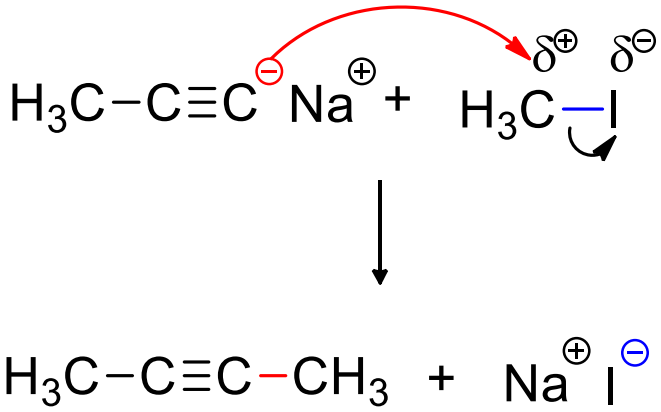
Mechanism



The strong base attack the acidic alkyne proton resulting in the breaking of the C-H bond producing acetylide anion and ammonia (sodium left out for clarity).

Alkynide Anions are Carbon Nucleophiles

(reaction with methyl iodide)



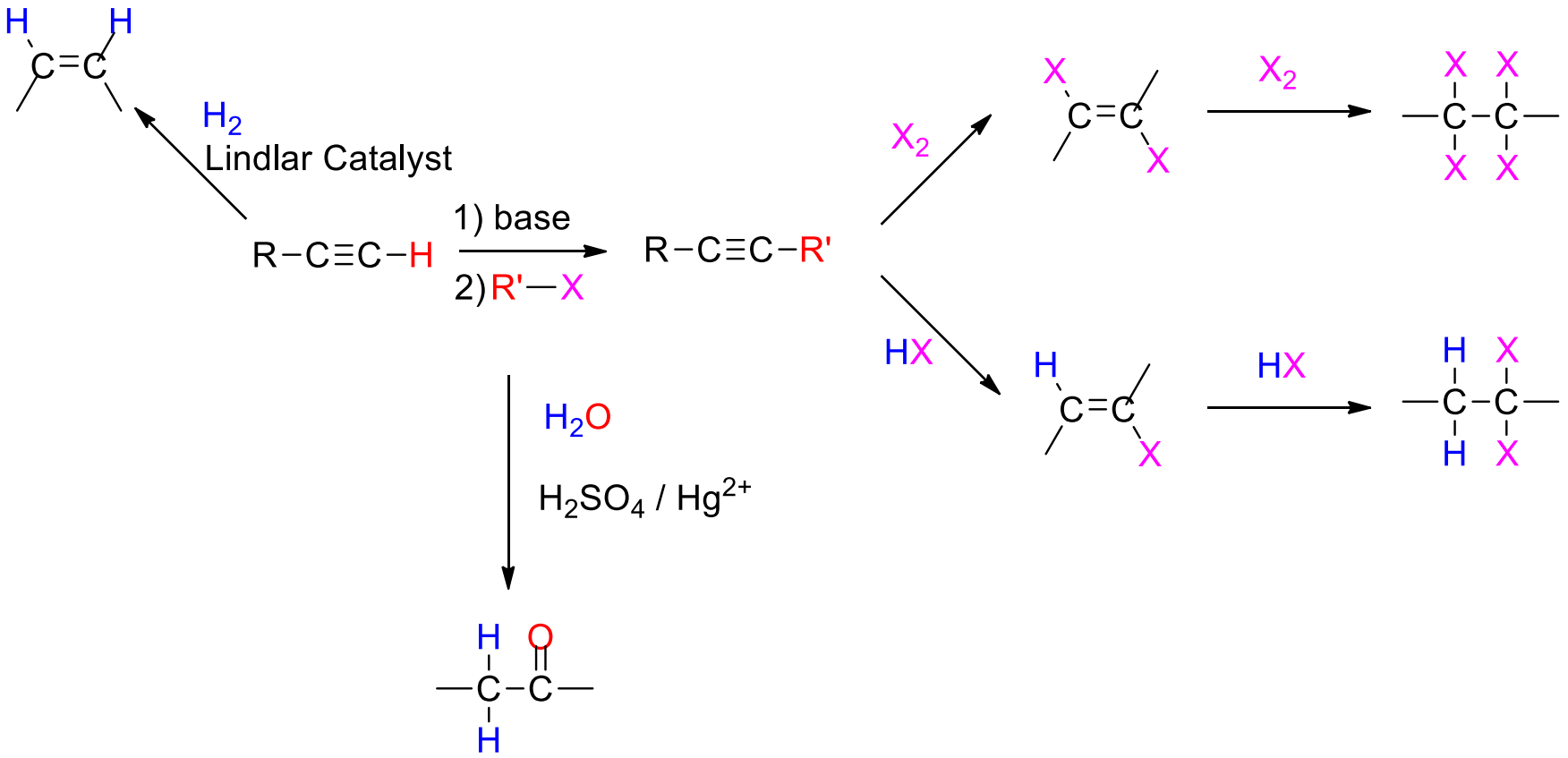
Bond polarisation due to electronegativity difference between C and I

The carbon nucleophile attacks the δ⊕ charged carbon of methyl iodide resulting in the formation of a carbon to carbon bond and breaking of the carbon iodine bond.

This is an S_N2 nucleophilic substitution reaction.

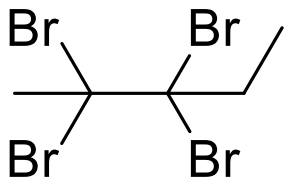
Note: More on S_N2 nucleophilic substitution reactions next semester.

Summary of Alkyne Reactivity



Practice Example

Reaction of alkyne A with 2 equivalents of bromine gave 2,2,3,3-tetrabromopentane as the product.



2,2,3,3-tetrabromopentane

i) Give the structure of alkyne A.
ii) Give the structure of the intermediate product formed after the reaction of alkyne A with one equivalent of bromine.
iii) Give the mechanism for the reaction of the first equivalent of bromine with alkyne A .

Learning outcomes

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- Recall and explain production and reactions of alkynide anions.

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