Lecture 20
Organic Chemistry 1

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March 18, 2010

Self-Test Question

Capnellene (**4**) is a marine natural product that was isolated from coral reef. It has been shown to be cytotoxic to various tumor cell lines. What starting organic fragments (**1** and **2**) could be used to construct the terminal alkyne **3**?

Squirellock says. . .

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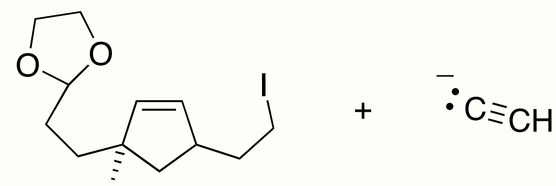

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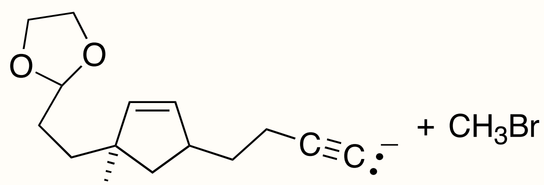

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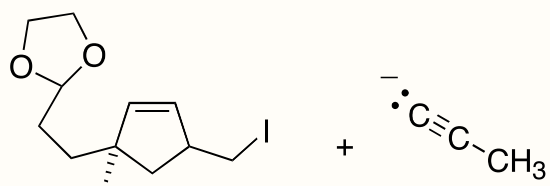

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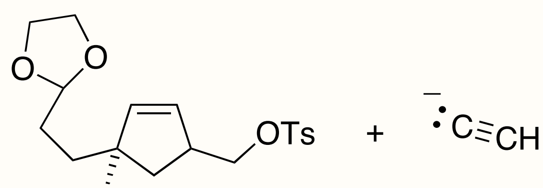
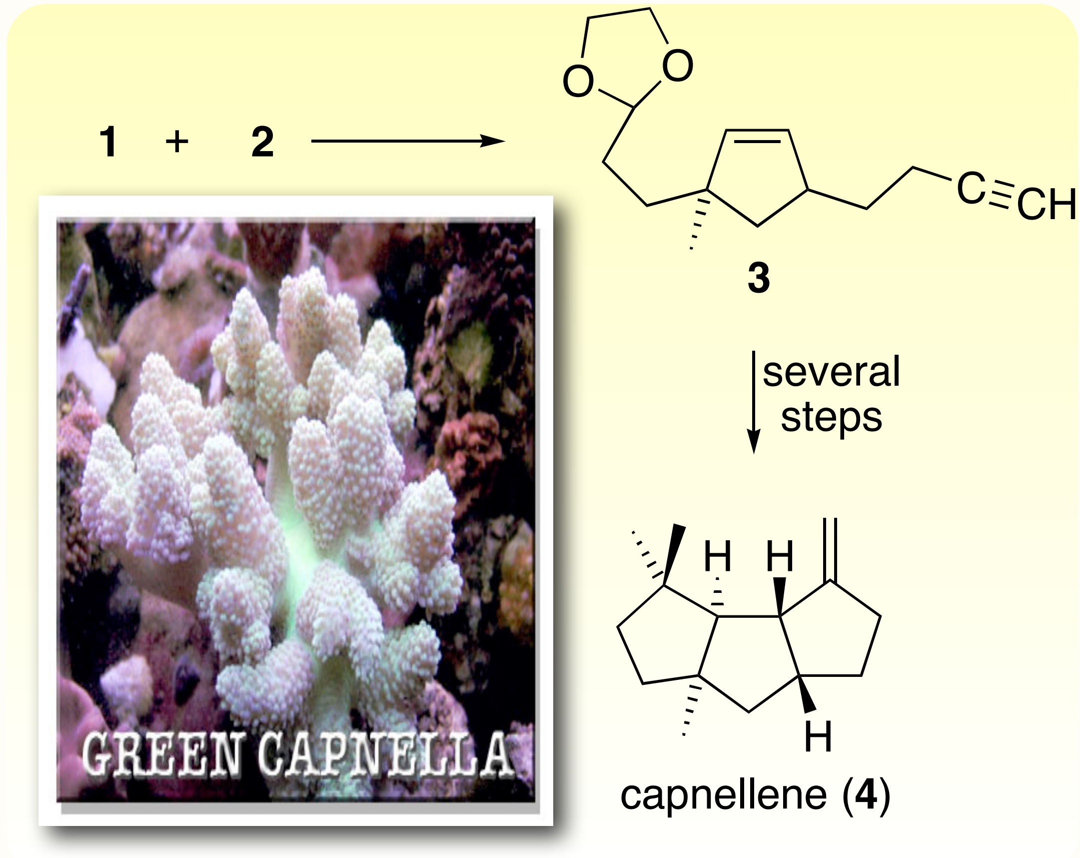
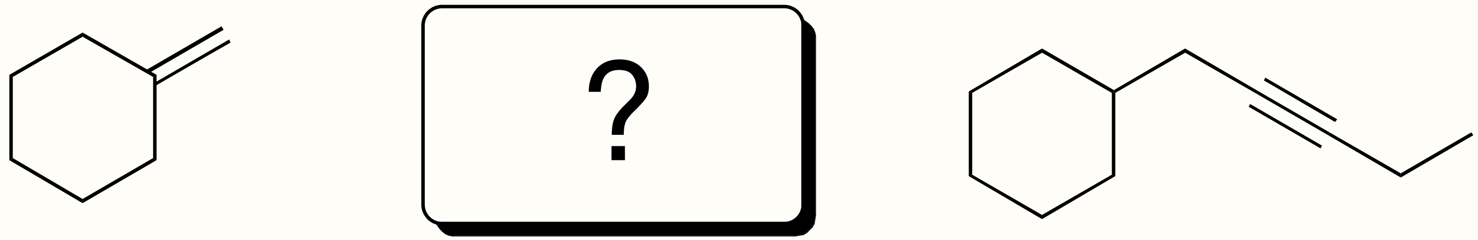




Which set of reagents would most likely cause the transformation below?



A

1. HCl
2. NaC≡CH
3. LDA
4. methyl bromide

B

1. H_2SO_4, H_2O
2. TsCl, pyridine
3. NaC≡CH
4. $NaNH_2$, NH_3
5. iodopropane

C

1. B_2H_6
2. H_2O_2/NaOH
3. MsCl, pyrindine
4. NaC≡CH
5. $NaNH_2$, NH_3
6. ethanol

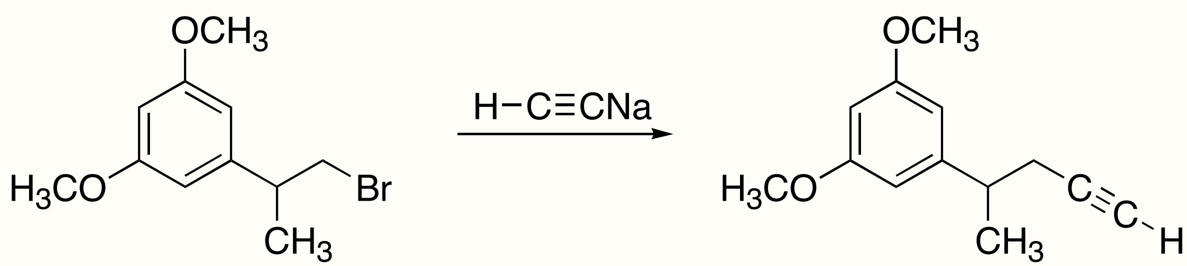
D

1. HBr, ROOH
2. NaC≡CH
3. NaNH2, NH3
4. iodoethane

Preparation of Alkynes

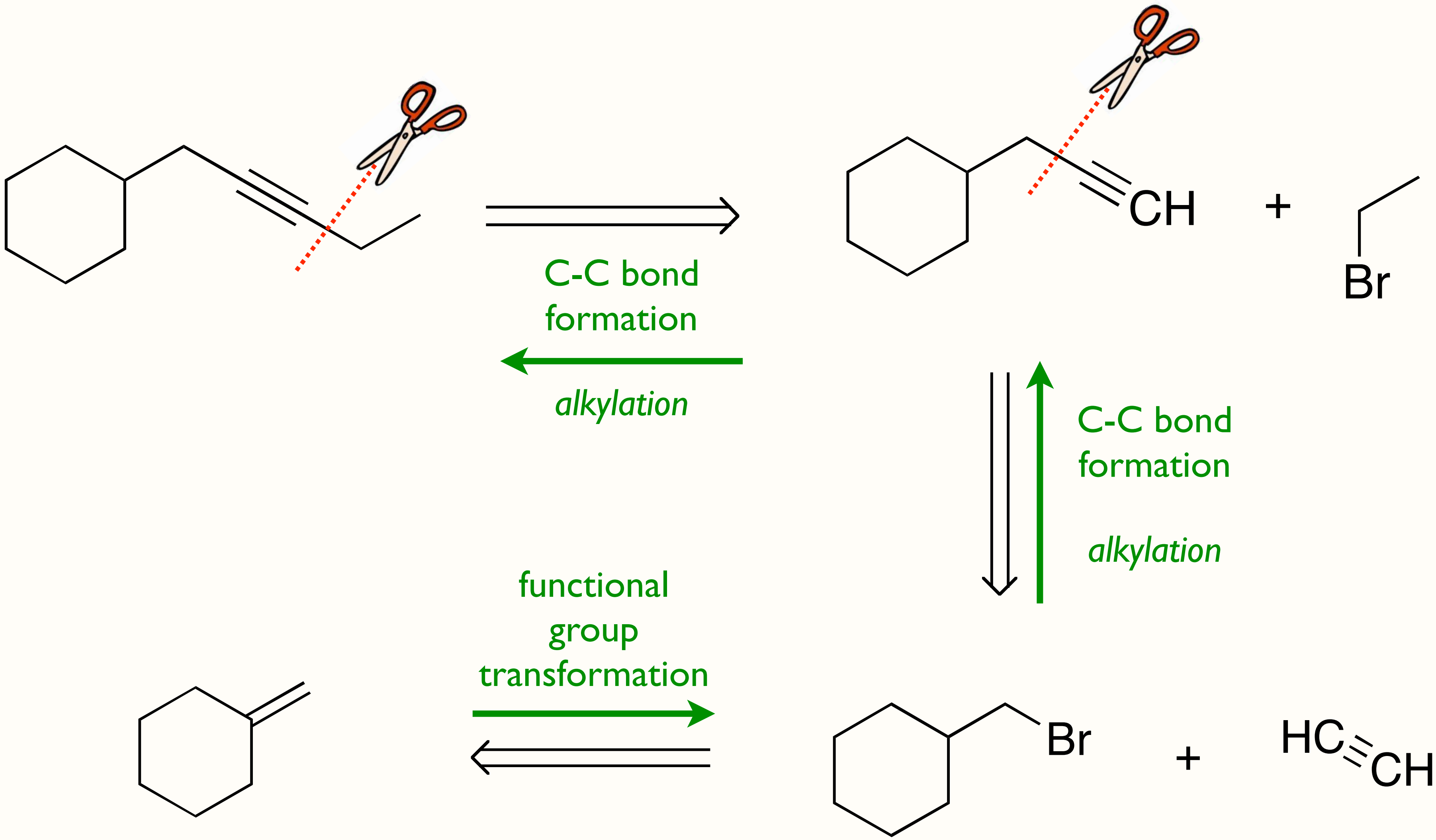
There are two main methods for the preparation of alkynes:

1. Alkylation of acetylide anions (C-C bond formation)



2. Functional group transformations (Today's topic)

Another Retrosynthesis Example

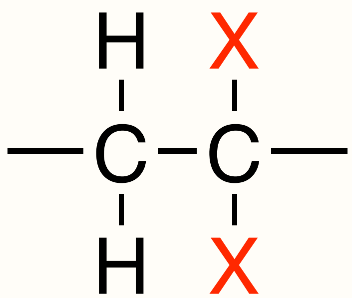


Chapter 9
Preparation of Alkynes
Double Dehydrohalogenation

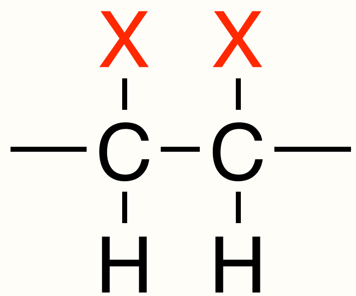
Sections 9.1 - 9.6

Dihalides in “Double Dehyrohalogenation”

geminal and vicinal dihalides are most frequently used in the preparation of terminal alkynes



geminal dihalide

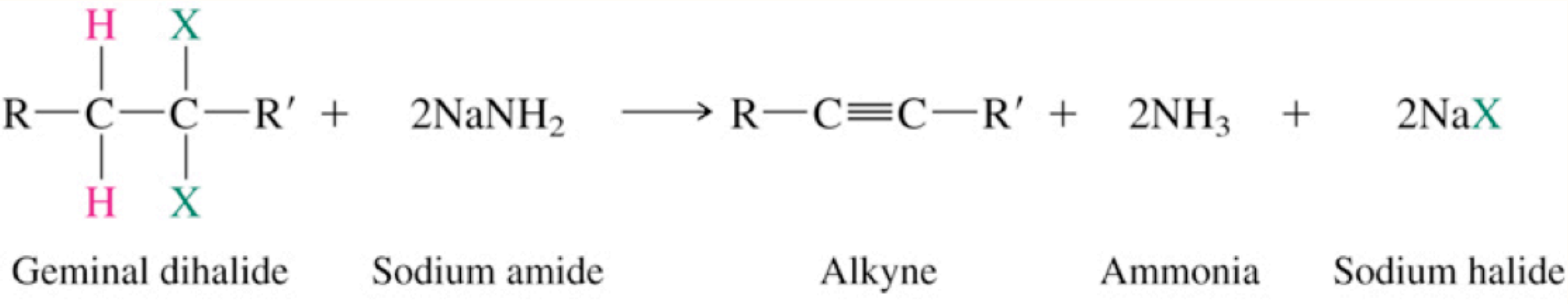


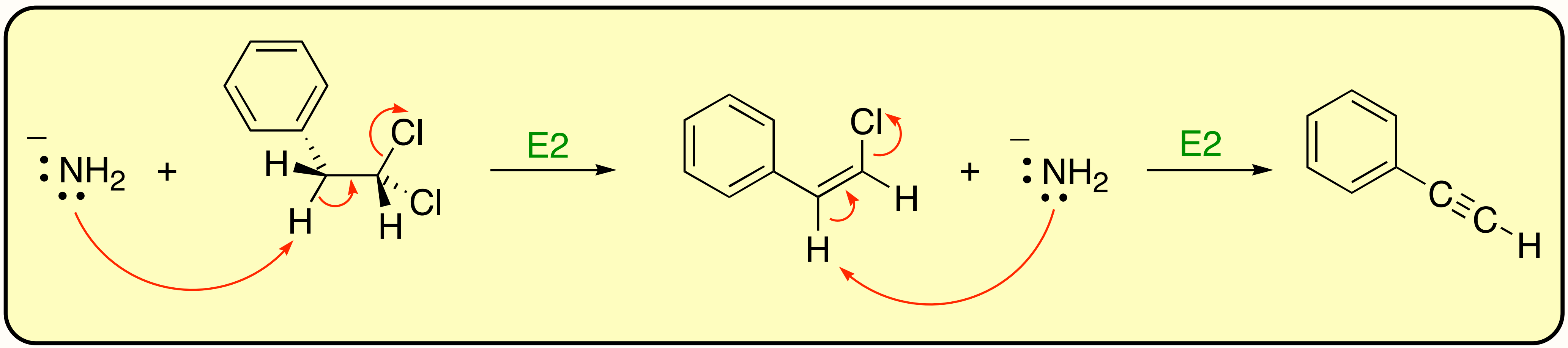
vicinal dihalide

geminal: separated by two bonds (same carbon)
vicinal: separated by three bonds (adjacent carbons)

Double Dehydrohalogenation

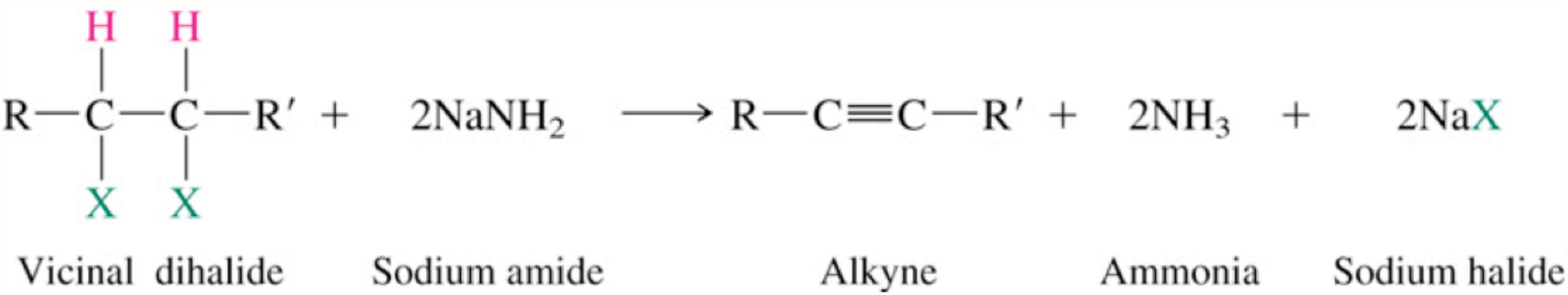
Geminal Dihalide

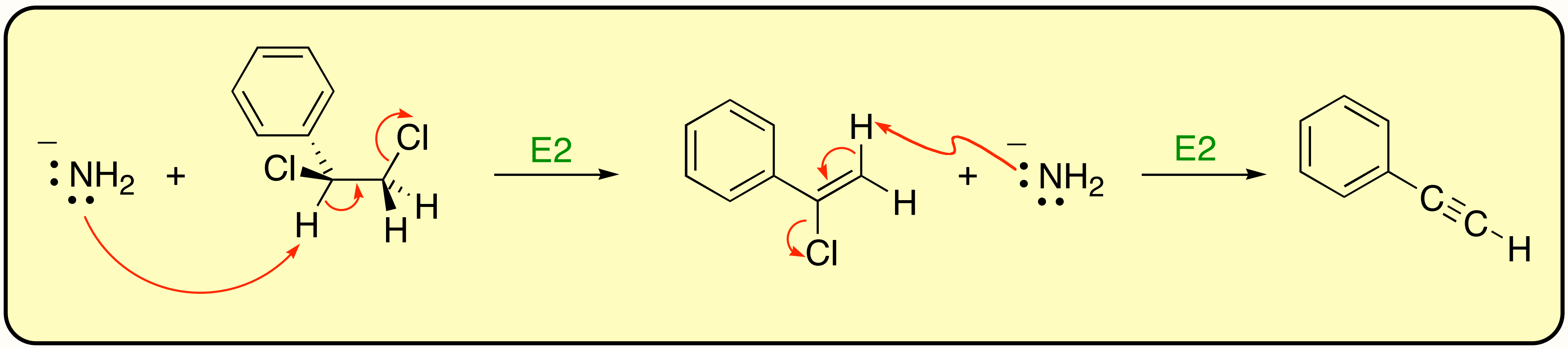




Double Dehydrohalogenation

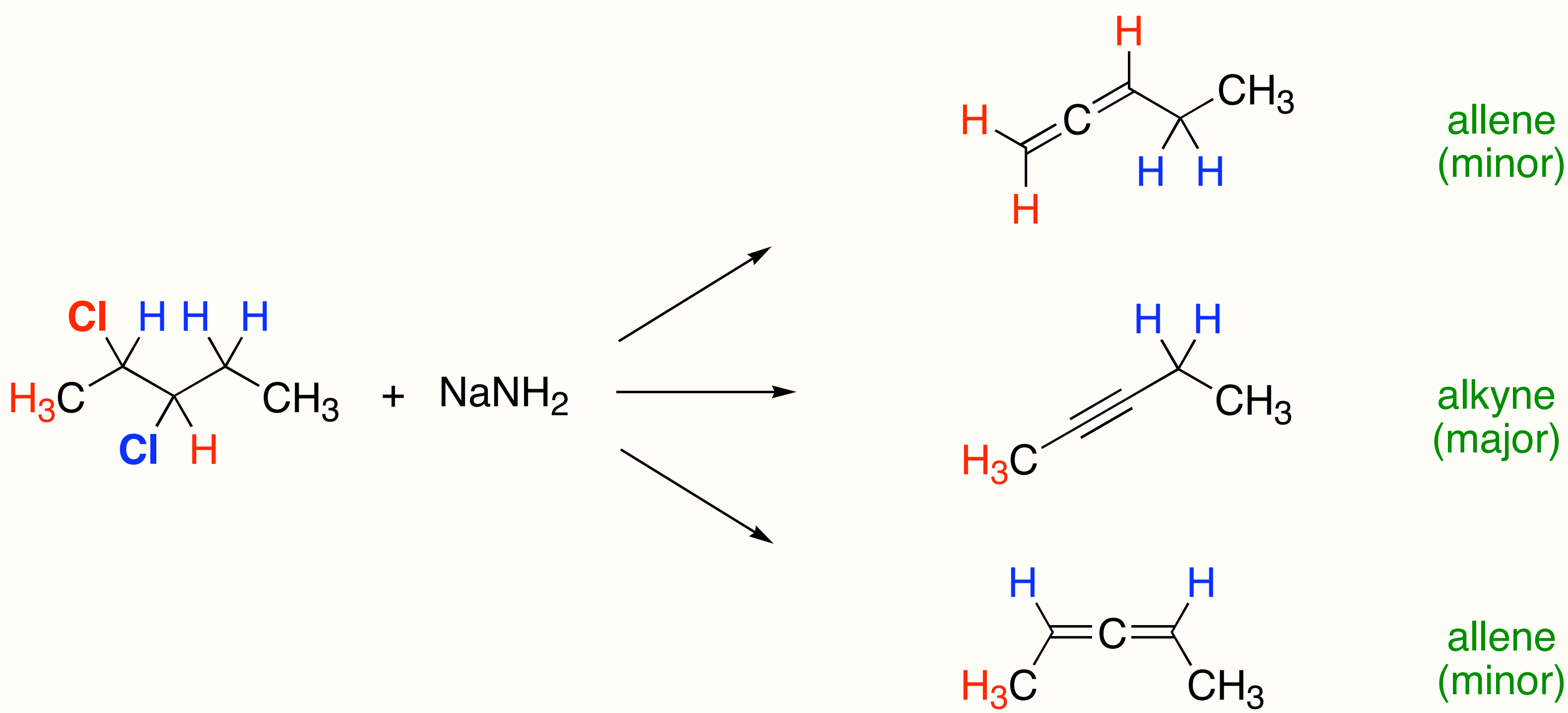
Vicinal Dihalide





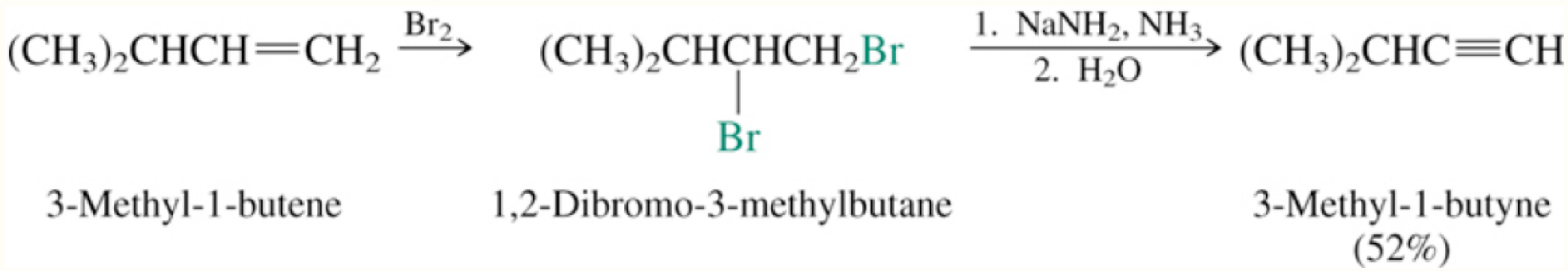
Double Dehydrohalogenation

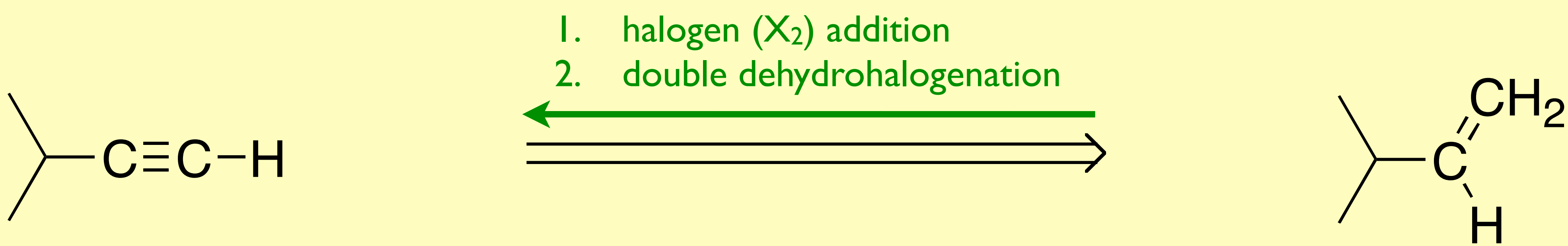
Allenes are formed as *minor* products from double dehydrohalogenation when there is more than one set of β-hydrogen atoms. Since allenes are less stable (higher energy) than alkynes, they are only minor.



Double Dehydrohalogenation in Synthesis

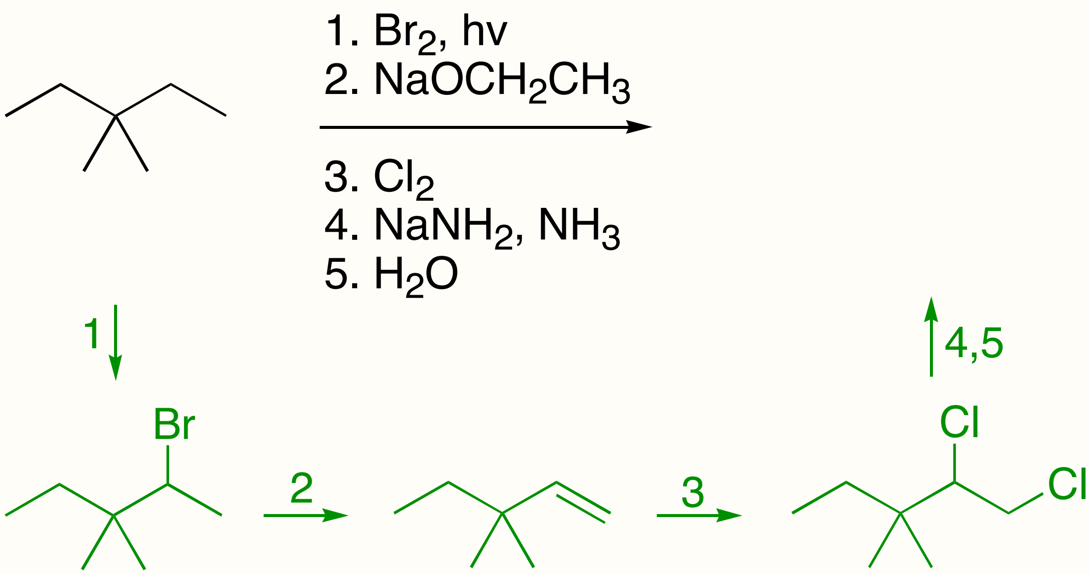
Addition of halogens across double bonds followed by double dehydrohalogenation is a convenient method for preparing terminal alkynes from terminal alkenes.

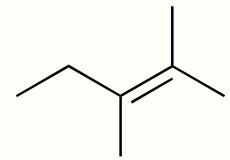


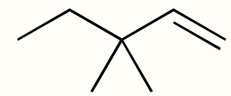


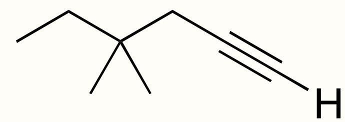
Self-Test Question

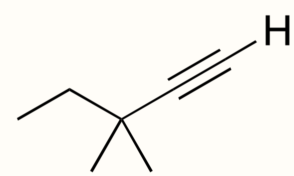
Predict the Product.

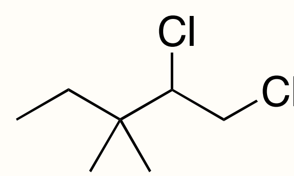


A 

B 

C 

D 

E 

Functional Group Interconversions (FGI) of Alkynes

Sections: 9.8-9.13

You are responsible for section 9.13 & 9.14.

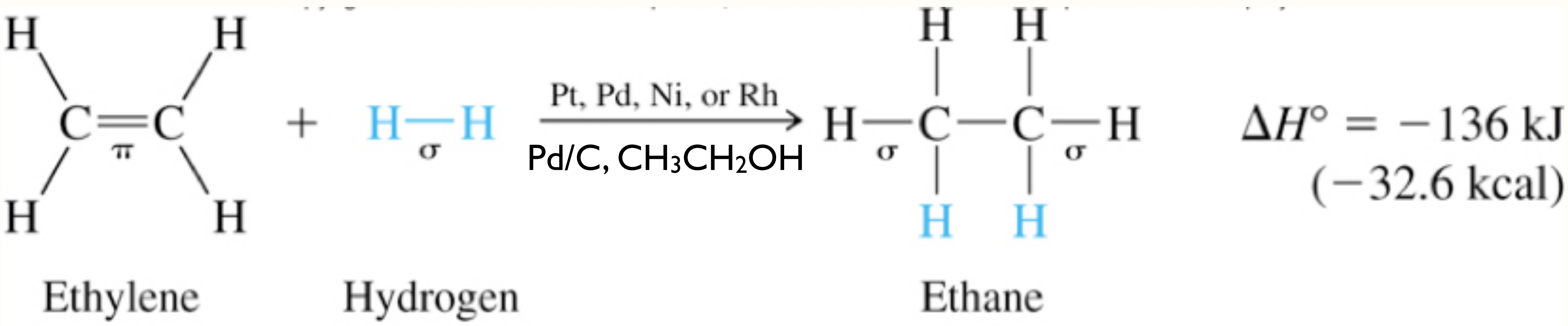
Reactions of Alkynes

- ☑ Acid/base reactions
- ☑ Alkylation
- ☐ Hydrogenation
- ☐ Metal-Ammonia Reduction
- ☐ Addition of Hydrogen Halides
- ☐ Hydration
- ☐ Addition of Halogens
- ☐ Ozonolysis

Functional Group Transformations

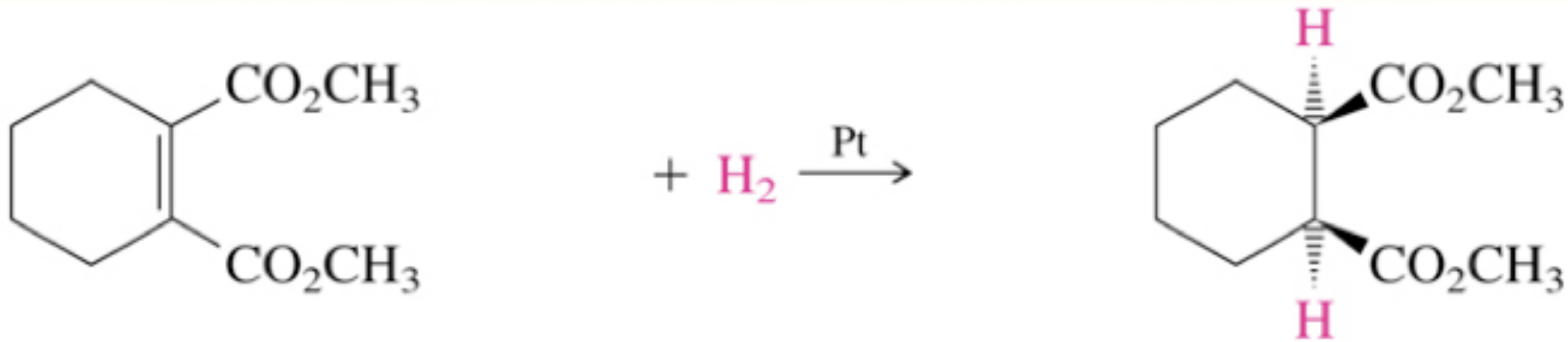
Alkynes
↓
Other FGs

Review: Hydrogenation of Alkenes



- requires transition metal catalyst (fine powder)
- solvent is typically an alcohol (e.g. ethanol, CH_3CH_2OH)
- metals are insoluble (heterogeneous mixture)
- exothermic reaction ($-\Delta H°$)
- heat of hydrogenation (ΔH_{hydrog}) = $-\Delta H°$

Review: Hydrogenation of Alkenes

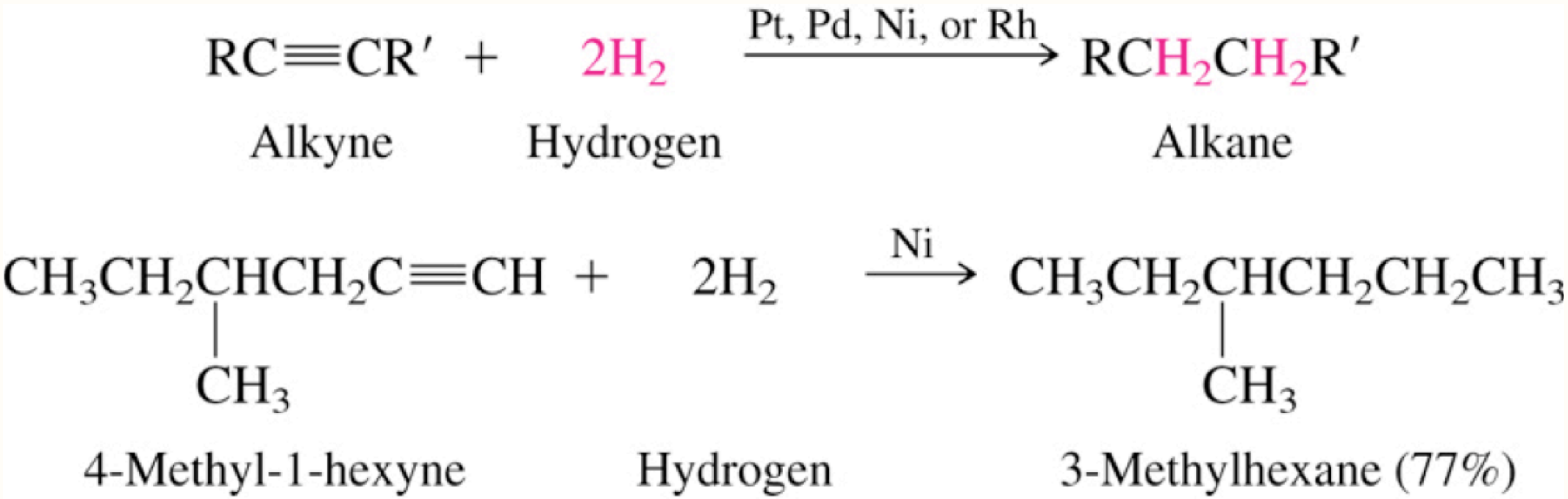


Dimethyl cyclohexene-1,2-dicarboxylate

Dimethyl cyclohexane-*cis*-1,2-dicarboxylate (100%)

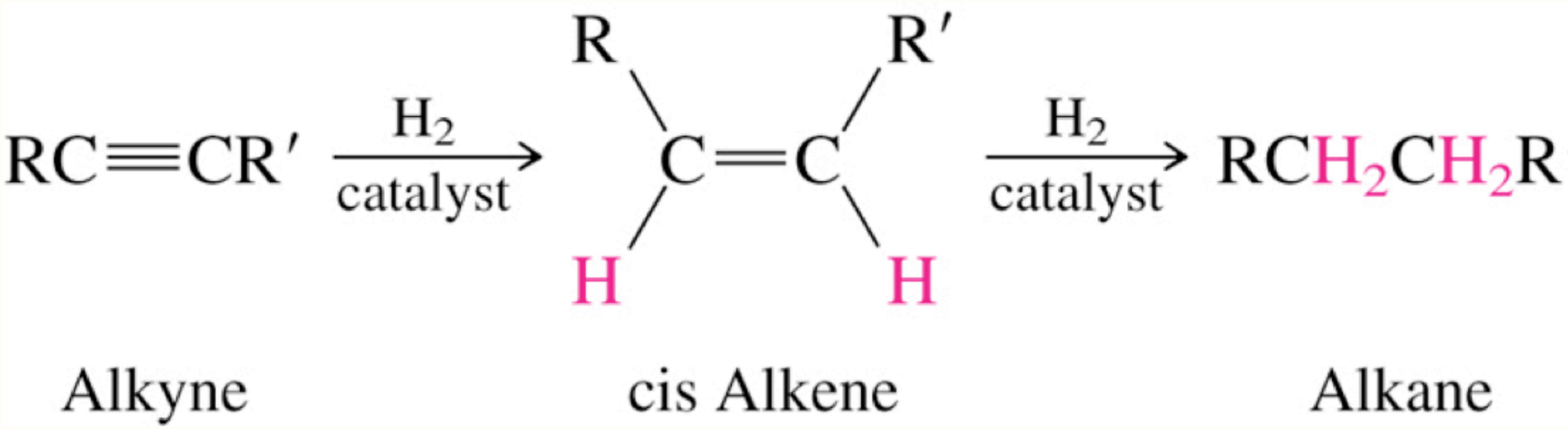
as a consequence of mechanism, both hydrogens are added to the same face of the π-bond: *syn* addition no *anti*-addition prodcuts are formed (addition of hydrogen to opposite faces)

Hydrogenation of Alkynes



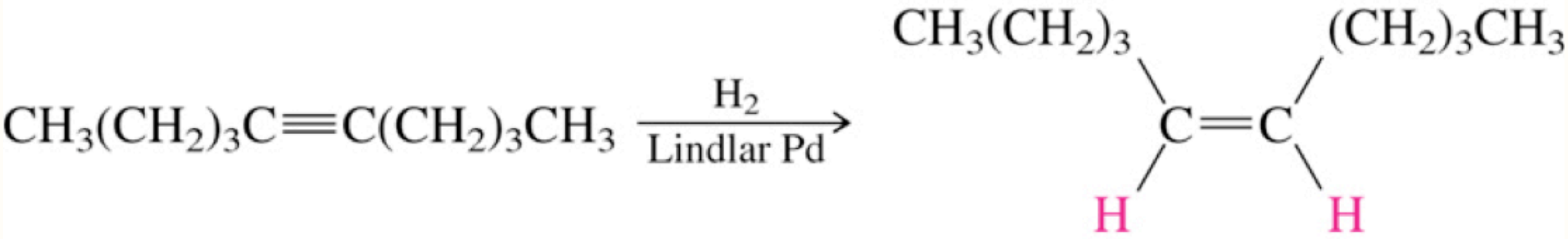
- Alkynes are reduced completely to alkanes under standard conditions (metal catalyst + H_2)
- Alkene is an intermediate, but is subsequently also reduced.

Hydrogenation of Alkynes



- Alkynes are reduced completely to alkanes under standard conditions (metal catalyst + H_2)
- Alkene is an intermediate, but is subsequently also reduced.

Lindlar's Catalyst

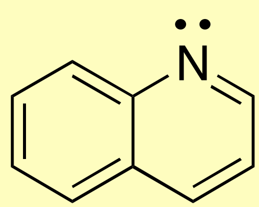


5-Decyne

cis-5-Decene (87%)

Lindlar's catalyst (Lindlar Pd)

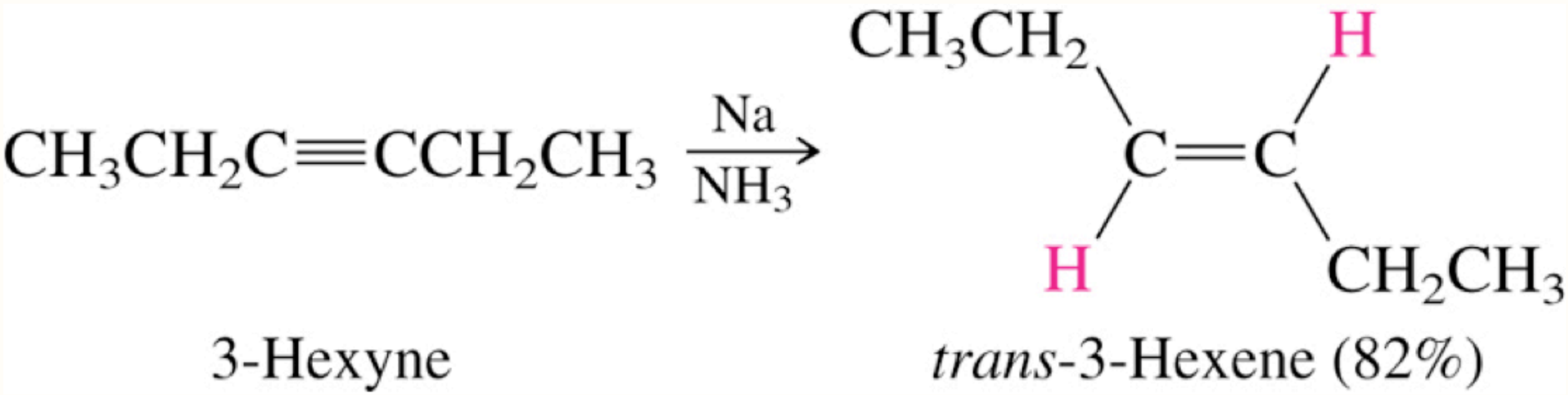
$Pd/CaCO_3$
lead (IV) acetate
quinoline



quinoline

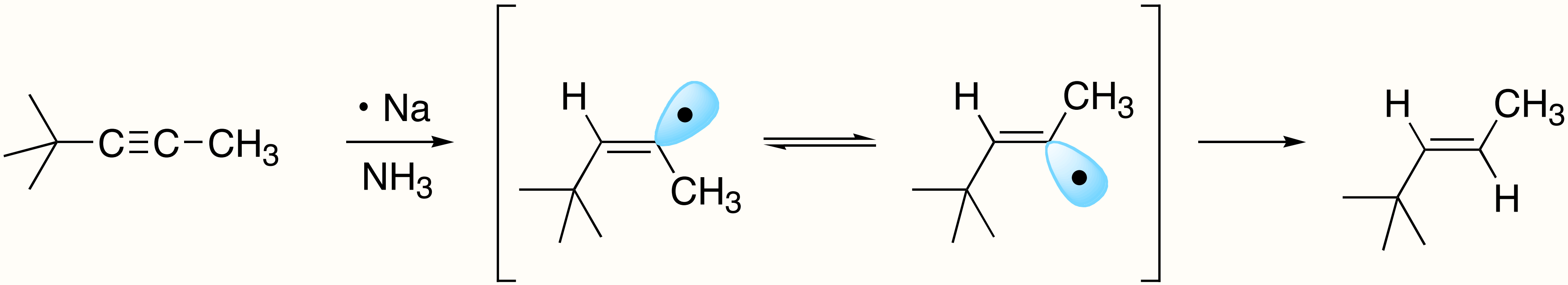
- lead (Pb) and quinoline "poison" the Pd catalyst =
- reduces reactivity of catalyst
- alkynes are more reactive than alkenes
- Lindlar Pd only active enough to reduce alkyne

Metal-Ammonia Reduction



- also known as dissolving metal reduction
- requires group I metal (Li, Na, K)
- provides *trans*-alkenes
- solvent = ammonia (NH_3)

Metal-Ammonia Reduction



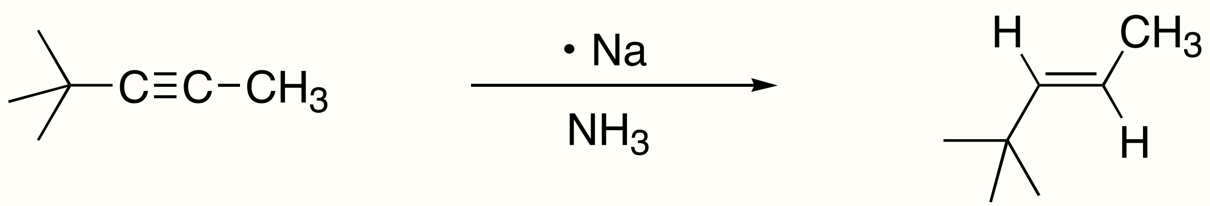
(Z)-alkenyl radical
(less stable)

(E)-alkenyl radical
(more stable)

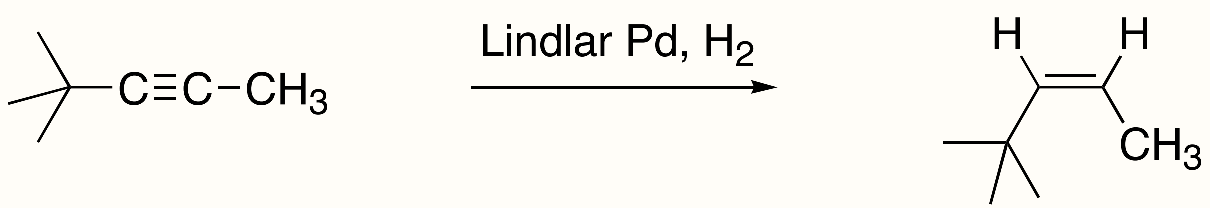
- *(Z)*-alkenyl radical can interconvert with *(E)*-alkenyl radical
- *(E)*-alkenyl radical less sterically hindered = more stable
- *(E)*-alkenyl radical undergoes protonation to give a *trans* alkene
- *I will not ask you to know the mechanism for this reaction; however, you should at least be able to draw the (E) and (Z)-alkenyl radical intermediates.*

Useful Synthetic Tools for the Stereoselective Preparation of Alkenes

Both reactions are stereoselective



metal-ammonia reduction
(*trans*-alkenes)

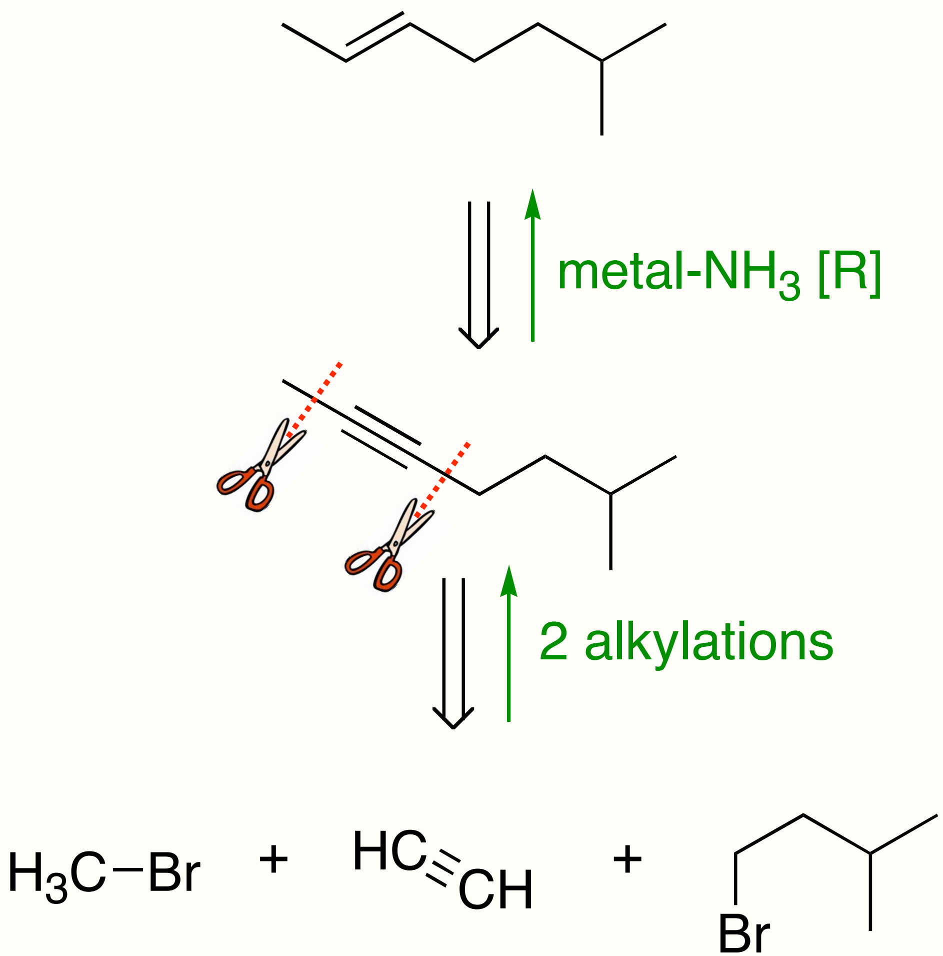


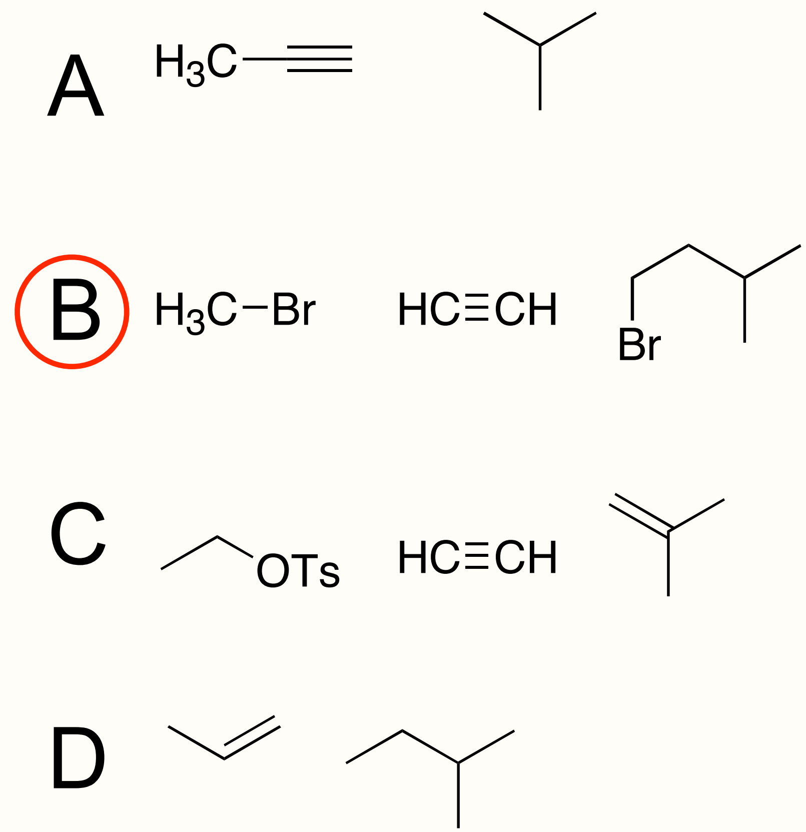
hydrogenation with
Lindlar Pd
(*cis*-alkenes)

Neither of these reactions is stereospecific. Why?

Self-Test Question

What organic molecules could be used to construct the alkene below?





Reactions of Alkynes

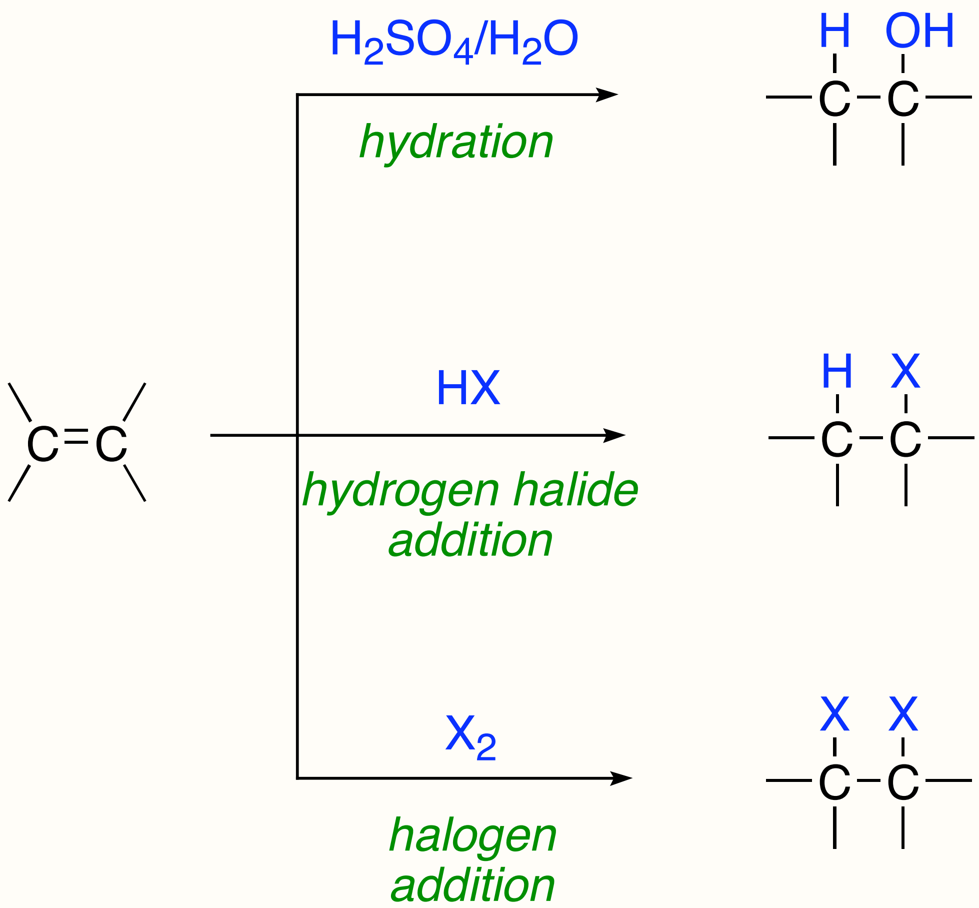
- [x] Acid/base reactions
- [x] Alkylation
- [x] Hydrogenation
- [x] Metal-Ammonia Reduction
- [ ] Addition of Hydrogen Halides
- [ ] Hydration
- [ ] Addition of Halogens
- [ ] Ozonolysis

Functional Group Transformations

Alkynes
↓
Other FGs

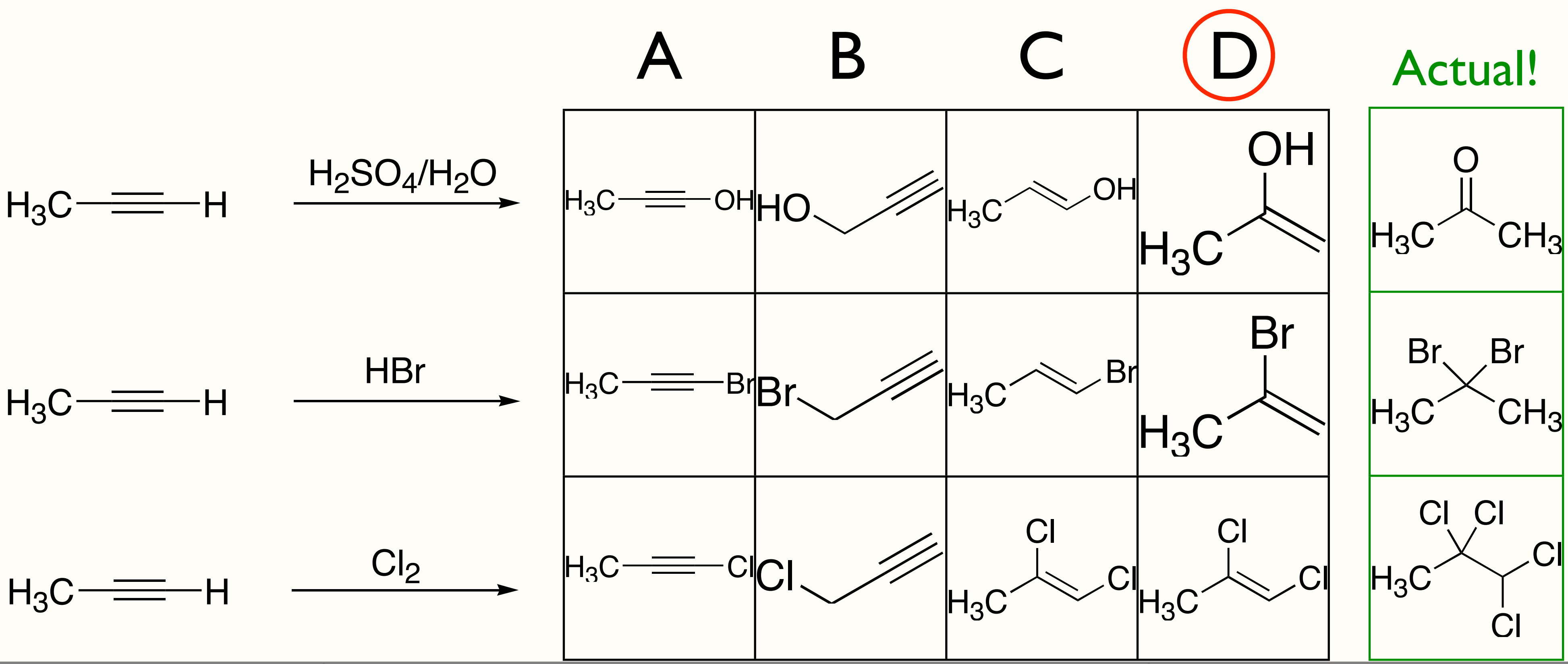
Review: Addition to Alkenes

Alkynes undergo addition reactions similar to alkenes

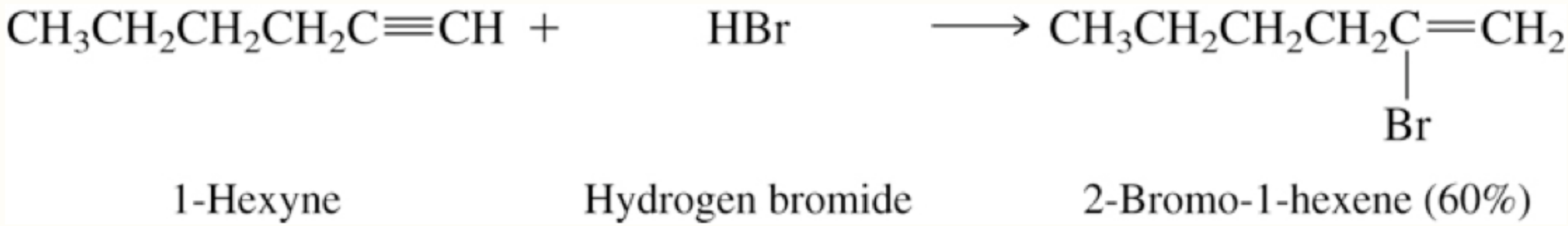


Self-Test Question

Presuming alkynes react similarly to alkenes, chose the column containing the correct set of products.

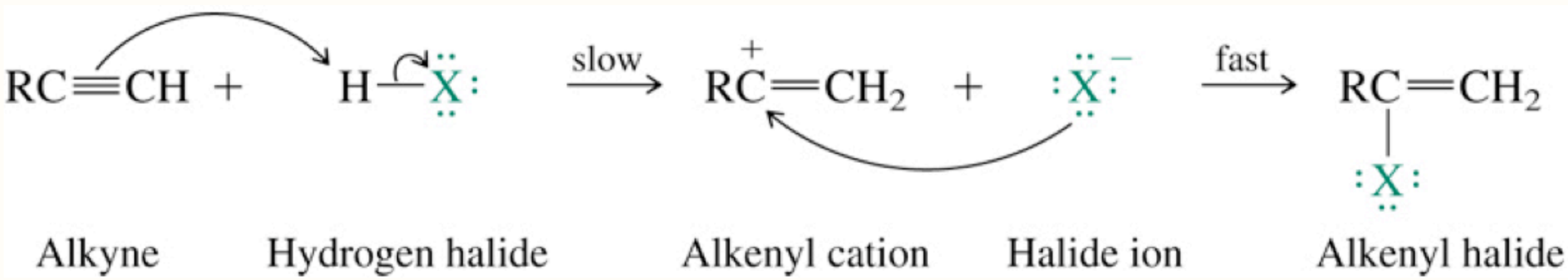


Markovnikov Addition of HX to Alkynes

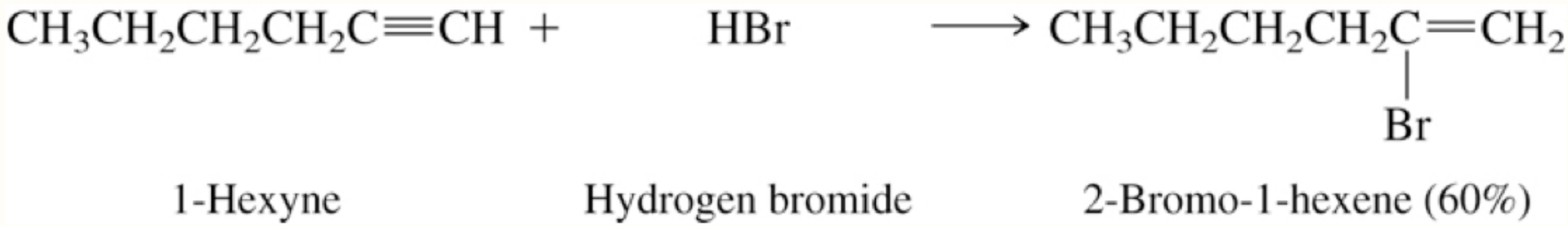


Unlikely Mechanism

- alkenyl cation = sp hybridized =
- more electronegative = high energy
- experimental evidence: 3rd order reaction



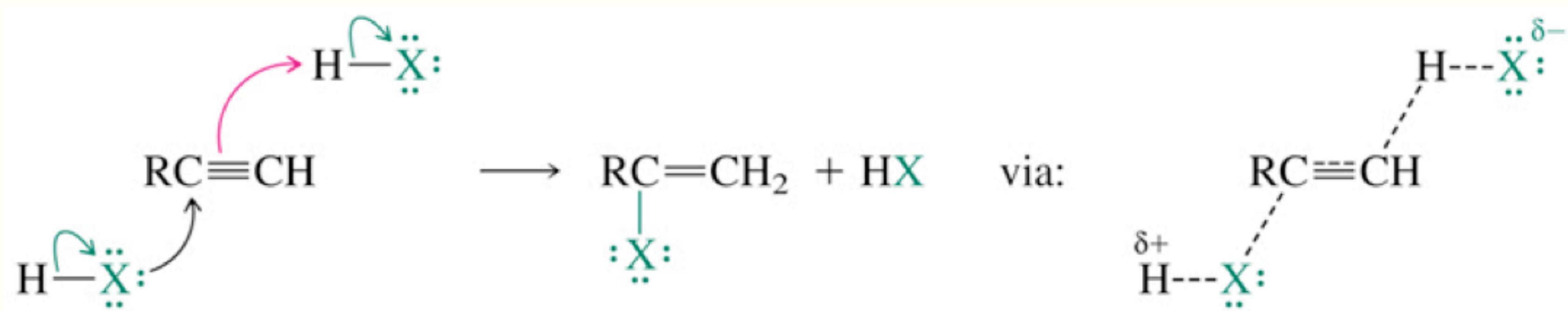
Markovnikov Addition of HX to Alkynes



(vinyl halide)

Better Mechanism

- 3rd oder (termolecular):
- rate=k[alkyne][HX]^2
- transition state = no δ+ on alkyne carbons

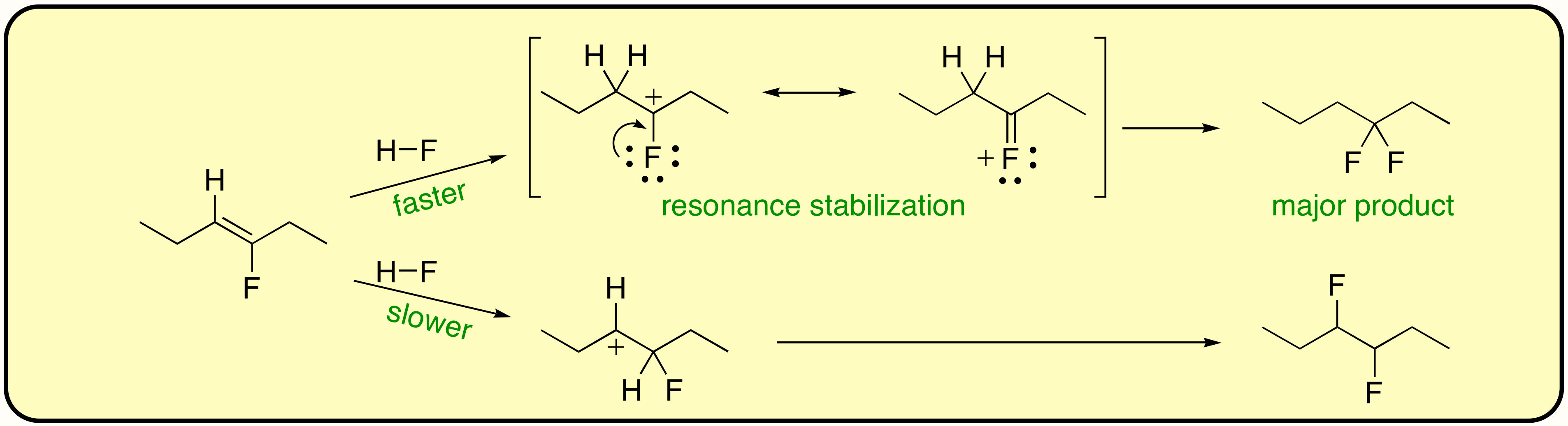


Markovnikov Addition of HX to Alkynes

When excess HX is added, two equivalents are added across the alkyne to provide the geminal dihalide

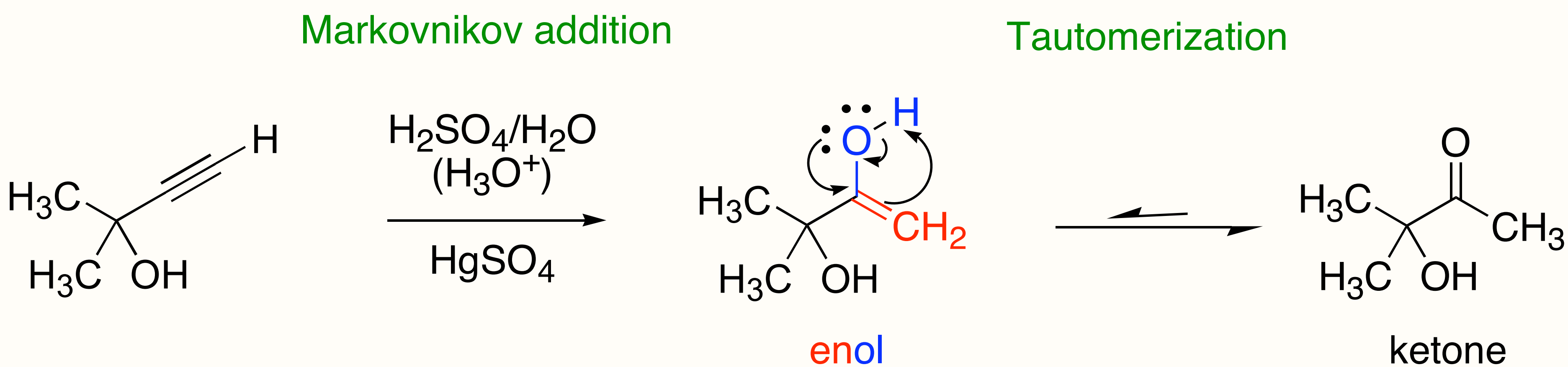
$$CH_3CH_2C{\equiv}CCH_2CH_3 \; + \; 2HF \longrightarrow CH_3CH_2CH_2CF_2CH_2CH_3$$

3-Hexyne — Hydrogen fluoride — 3,3-Difluorohexane (76%)



Hydration of Alkynes

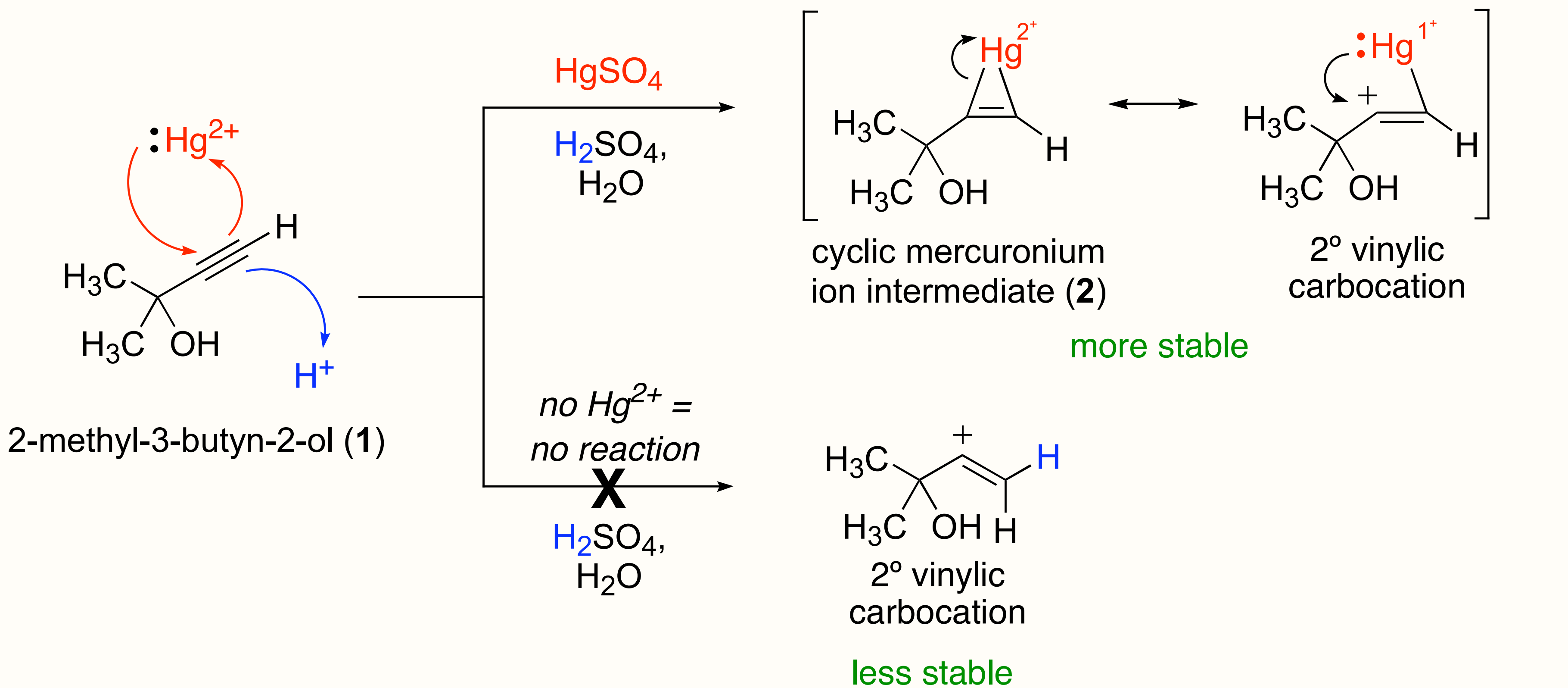
Hydration of alkynes proceeds through a two-step process: Markovnikov addition to provide an enol followed by tautormerization



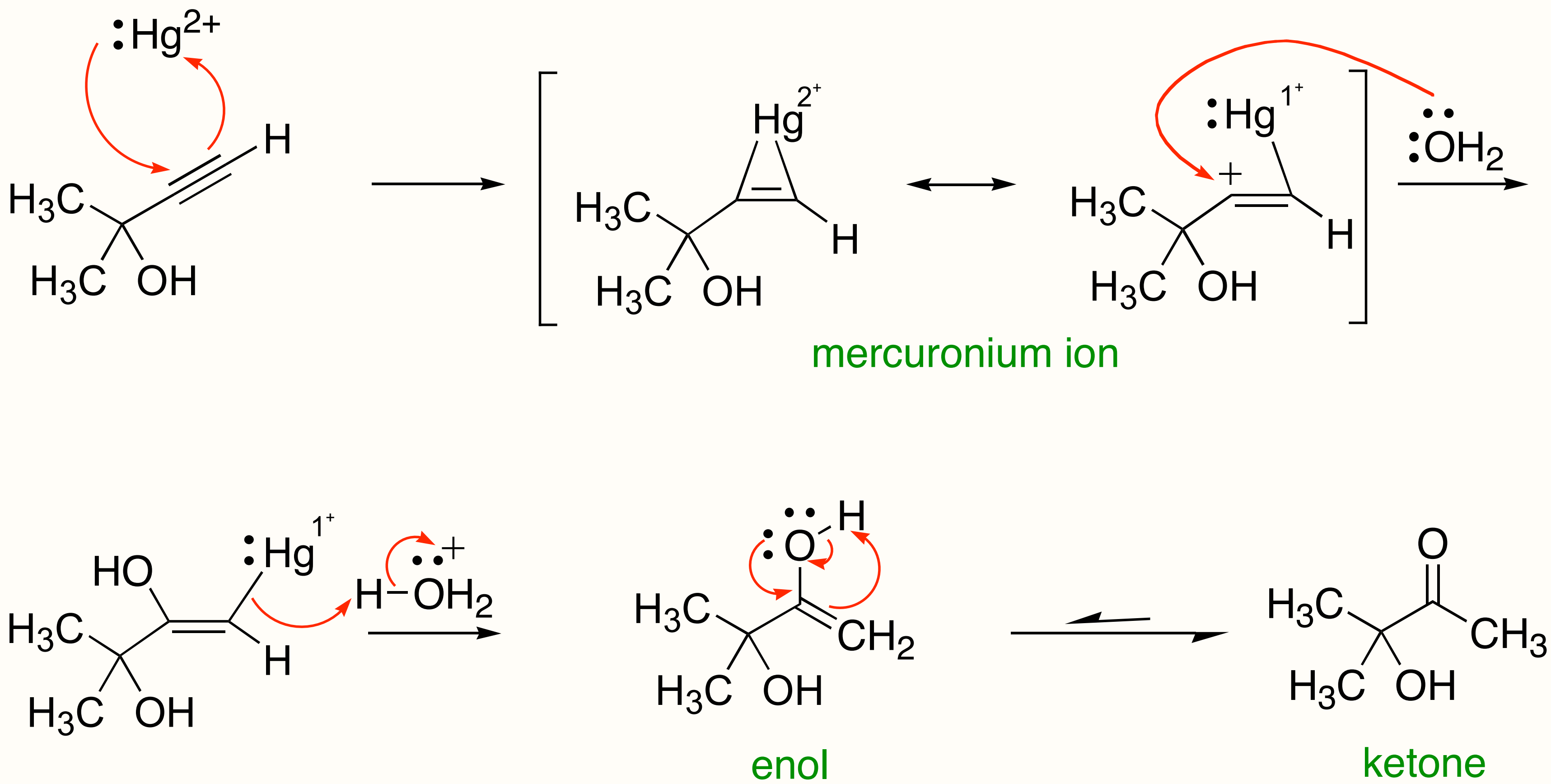
tautomers: rapidly equilibrating constitutional isomers
carbonyl/enol: equilibrium lies toward carbonyl

Why is Hg^{2+} Catalyst Needed?

- Hg^{2+} forms a more <u>stable</u> (low energy) mercuronium intermediate
- Without Hg^{2+}, the alkyne would have to be protonated to give a 2° vinylic carbocation. Unstabilized vinylic carbocations are high energy species and thus unlikely intermediates.



Complete Mechanism



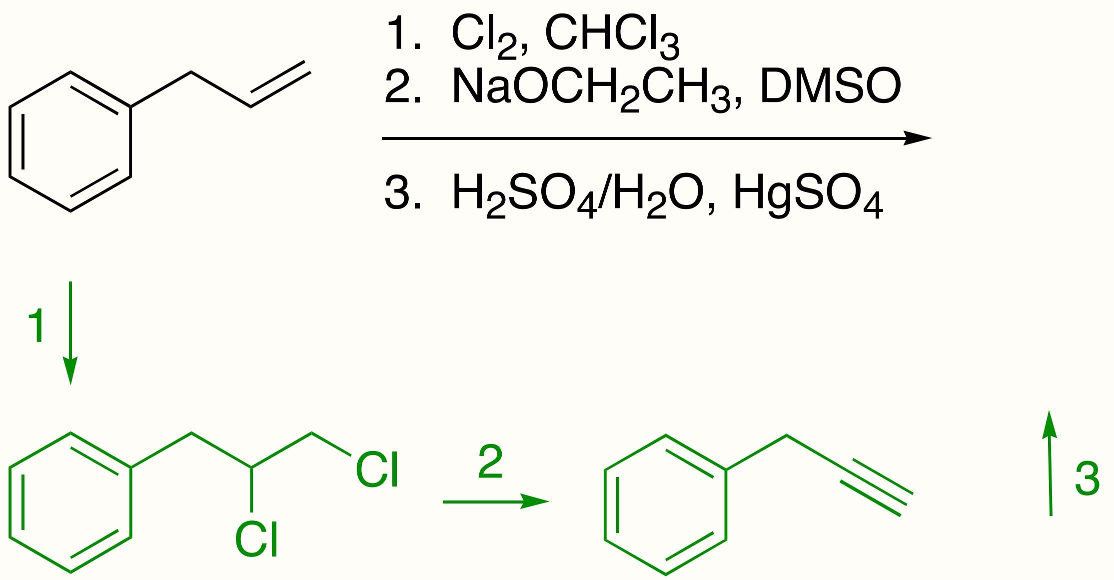
- Note: water adds to the most substituted carbon of mercuronium ion since it is most partially positively charged =
- Only ketones are possible products for alkyne hydration (except acetylene)

Summary of Reactions of Alkynes

Reaction	**Products**
☑ Acid/base reactions	
☑ Alkylation	C-C bond formation
☑ Hydrogenation	alkane or *cis*-alkene
☑ Metal-Ammonia Reduction	*trans*-alkene
☑ Addition of Hydrogen Halides	vinyl halide or vicinal dihalide
☑ Hydration	ketone
☐ Addition of Halogens	tetrahaloalkane
☐ Ozonolysis	carboxylic acid

i>Clicker Question

Predict the product.



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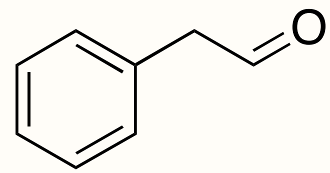

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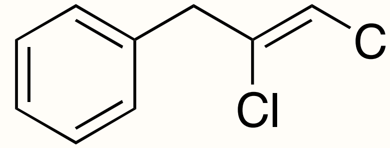

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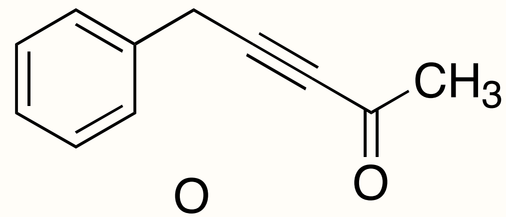

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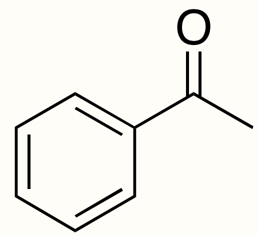

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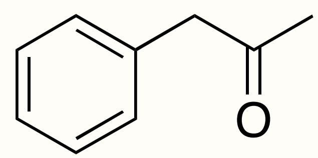
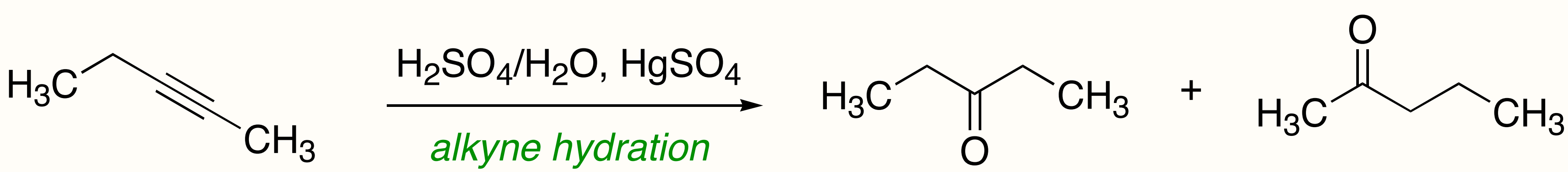
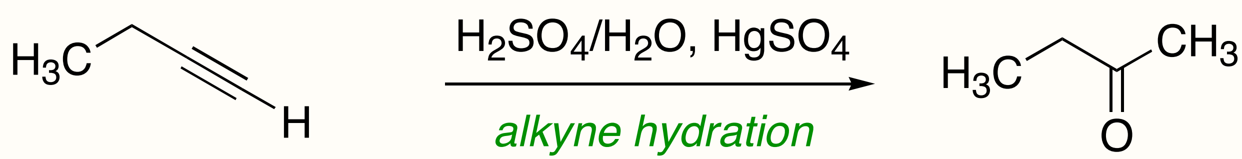


Alkyne Hydration of Terminal Alkynes

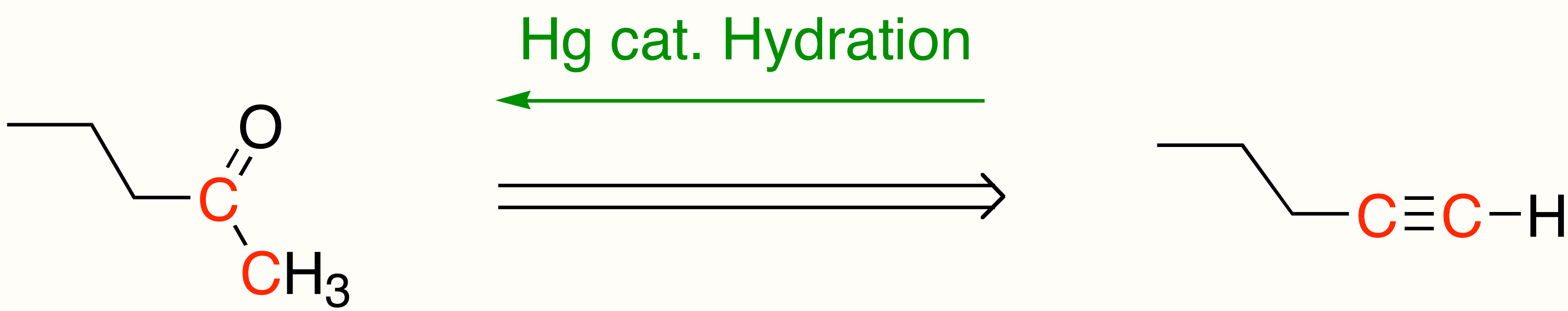
Alkyne hydration is best for the preparation of methyl ketones from terminal alkynes. Hydration of internal alkynes gives mixtures of products.

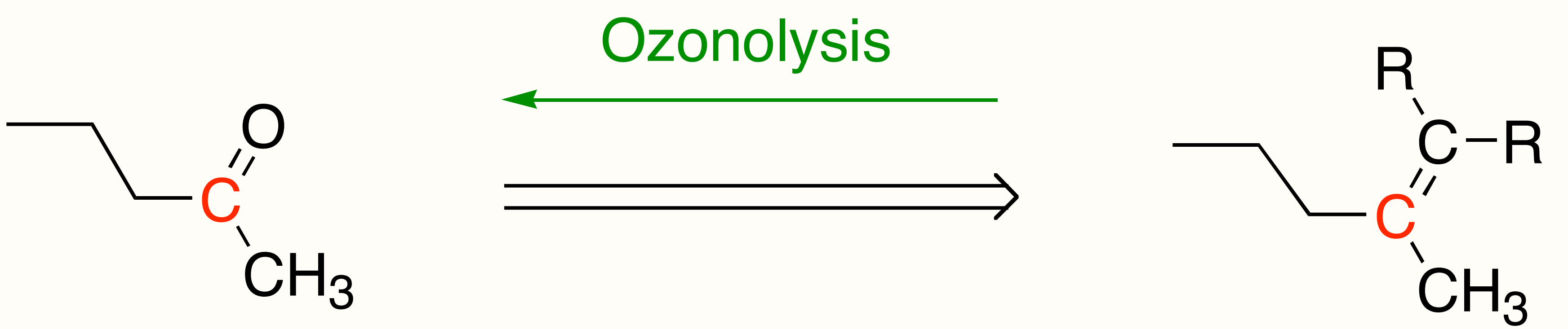




More Synthetic Strategies. . .

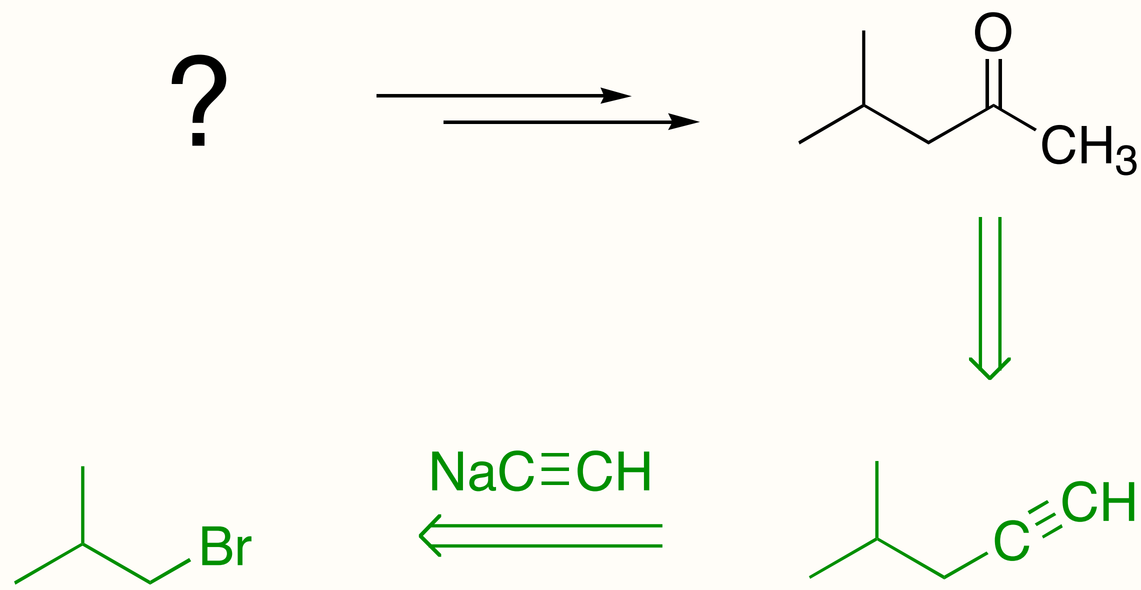
You now know two methods for preparing ketones: ozonolysis of alkenes and hydration of terminal alkynes

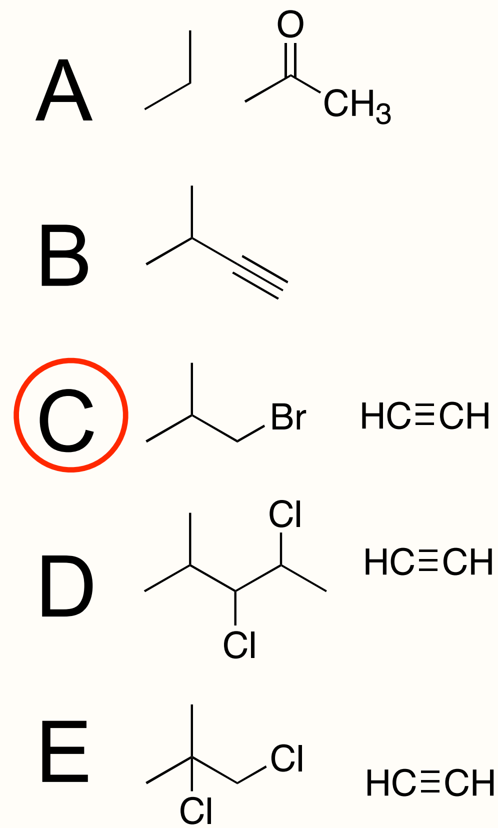




Self-Test Question

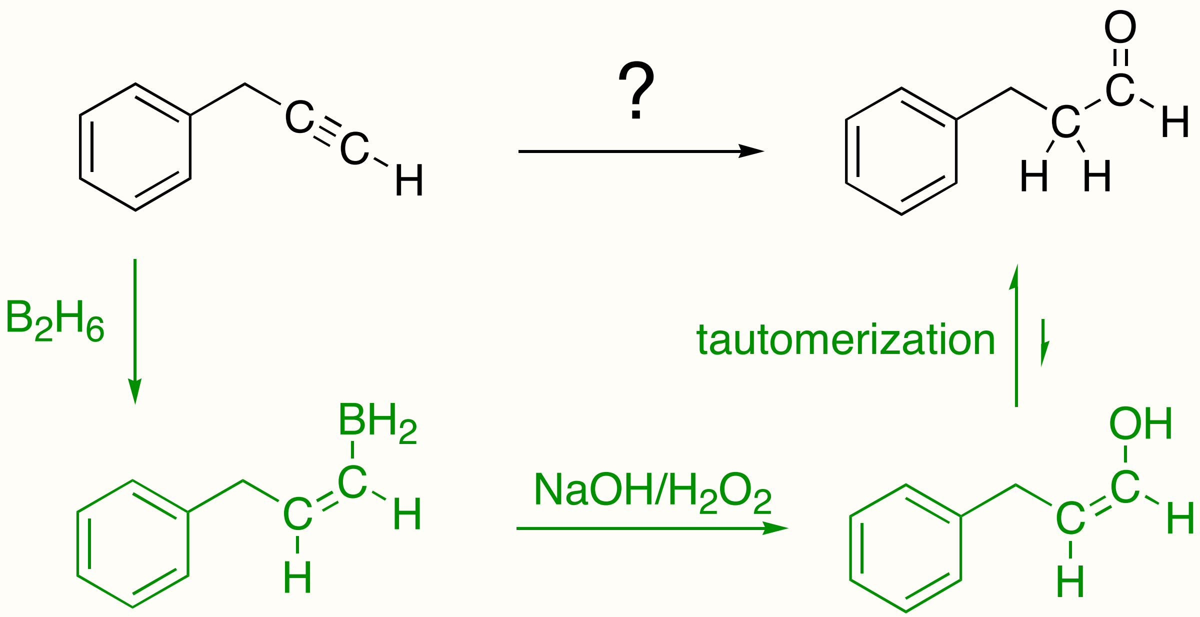
Synthesis: Which compounds could be used to prepare the ketone below? *Hint: Perform a retrosynthetic analysis.*





Self-Test Question

Aldehydes can be made from terminal alkynes by forming the least substituted enol instead. This can be accomplished using a method we've already encountered for the preparation of the least subsituted alcohols from alkenes. What are the conditions?



A. HBr, peroxides

B. Cl_2, hv

C. B_2H_6 then $NaOH/H_2O_2$

D. $NaOCH_2CH_3$

E. HBr

Next Lecture...
After Spring Break!

Chapter 9: Sections 10.1 - 10.7

1st Quiz after S.B....

Synthesis Problems