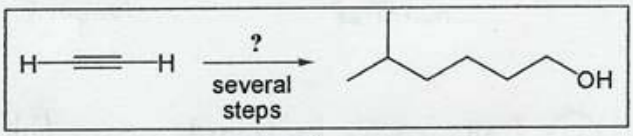
SYNTHESIS - SUMMARY OF GENERAL STRATEGIES

Imagine you have been asked to synthesize the 1° alcohol shown here, starting from acetylene and any other reagents you need. It will take a sequence of several steps (*i.e.*, several reactions done via separate reagents/procedures in lab).



Note: this is not the same as writing a multi-step mechanism for one reaction (which would be several elementary steps resulting from mixing a single set of reagents).

The strategy for designing a synthesis (outlined below) starts with thoroughly comparing the starting material (SM) and the target product. Then, find reactions to build forwards from SM, backwards from target, & finally fill in the gaps in between.

↳ especially useful for more complex examples (see Bruice 6.12 & 9.11) RETROSYNTHETIC ANALYSIS ↳ not used in this example

1. **Connectivity:** Count Cs, compare skeleton/rings, identify functional gps (LGs in SM?) & positions
2. **Changes:** How do skeleton and functional groups change?
3. **Dissect:** Locate SM's C atoms inside target ⇨ which bonds must be broken/formed? ⇨ dissect target into "pieces" to build from
4. **Build bonds:** Nu + E+ → new bond... ⇨ convert "pieces" into reagents by adding LG or Nu group
5. **Precursor:** Now look at target: what type of compound would yield target in final step? what reagents would give desired regio- & stereochemistry?
6. **Combine:** Can you now see a sequence of rxns leading from SM to target? ...if not: analyze precursor structure from step 5 (apply questions 4 & 5 to it)
7. **Synthesize!** Write sequence: draw SM, arrow/reagents, major product...next arrow/reagents...

starting material → target

① H−C≡C−H → 6C chain + CH_3 on C 5 to OH on C 1

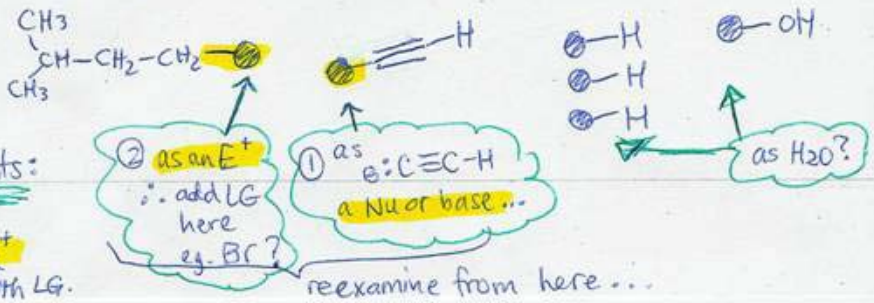
2 C's, no LG's

② triple bond eventually disappears (E^+ addition?) → must connect these 2C's to a longer chain somehow... then functionalize (add OH)... perhaps using the π-bonds?

③ Dissect target... versus starting material

green bonds must be FORMED
pink atoms/bonds are from starting material

This reveals the following "pieces": which we need to turn into reagents next...

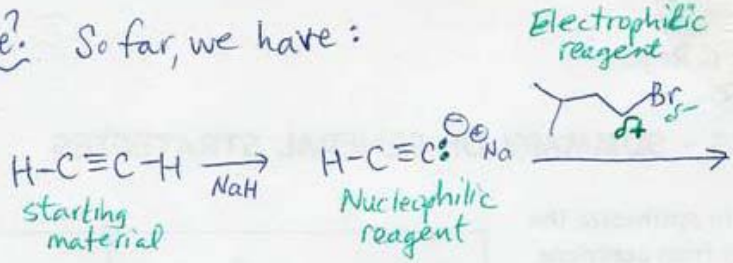


④ Convert into reagents:

to make bonds, need a Nu + an E^+ with LG.

reexamine from here...

Where are we? So far, we have:



Ⓐ our new starting material

⑤ try working backwards now + meet in middle?

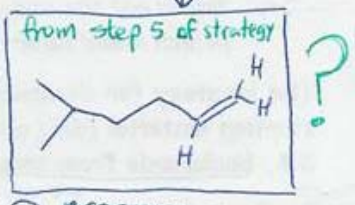
fwd • from Ⓐ : alkynes do E^+-philic additions... eg H_2

backwd • from Ⓣ : make alcohols from SN1/SN2 via R-X

or via E^+-philic addition to alkene

Ⓧ acid-cat. hydration (wrong regio!)

Ⓓ hydroboration (antiMarkovnikov!)



Ⓟ precursor

⑥ How to make this precursor Ⓟ?

? step 6 of strategy

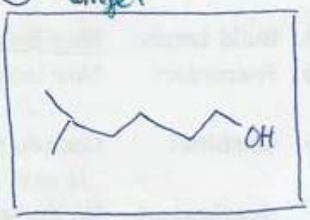
Ⓣ target

alkyne

$R-C\equiv C-R$ $\xrightarrow[\text{Lindlar's catalyst}]{H_2}$ cis alkene

ours is terminal, so either is fine

or $\xrightarrow[NH_3(\ell)]{Na}$ trans alkene.



⑦ Put it all together in a SYNTHETIC PATHWAY: