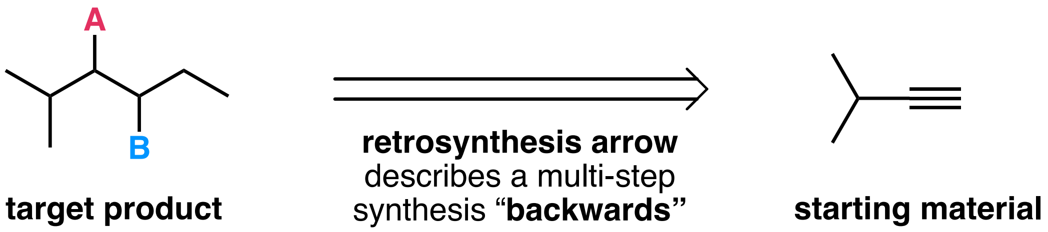
Retrosynthesis in Organic Chemistry 1

What is Retrosynthesis?

Retrosynthesis is a way of “deconstructing” a target molecule into starting materials by thinking backwards. Retrosynthesis questions provide the **target product on the left** and often provide a single **starting material on the right**.



target product

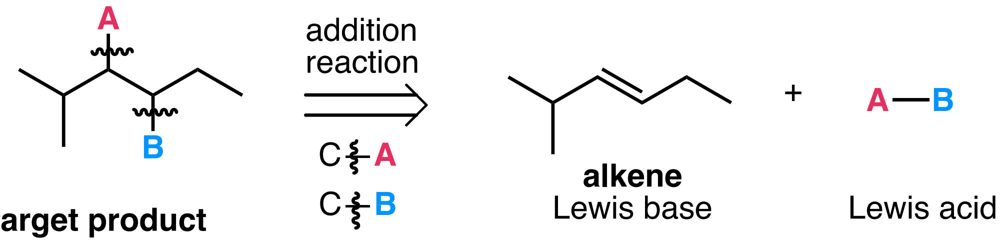
retrosynthesis arrow describes a multi-step synthesis “**backwards**”

starting material

Deconstructing a Molecule Using Strategic Disconnections

Strategic disconnections allow us to deconstruct a molecule based on plausible reactions we have learned. We often deconstruct a covalent bond in the target into polar reactants (e.g. a Lewis acid and a Lewis base).

For example, imagine would could deconstruct the target molecule into an alkene and fragments **A** and **B** (disconnection: C—**A** and C—**B** bonds).



target product

alkene
Lewis base

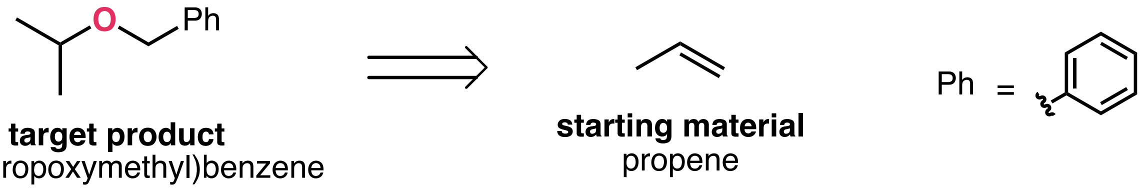
Lewis acid

We would then need to continue to deconstruct the alkene above all the way to the starting material provided. We could then use our retrosynthetic strategy to inform us about a multi-step process to synthesize the target molecule.

> **Note**: Sometimes, we cannot immediately see a bond to strategically break. In these cases, it can help to consider what **functional group interconversions** (**FGI**s) you know and if any of them could be helpful. We will apply this principle in Example 2.

Example 1 - Strategic Disconnections

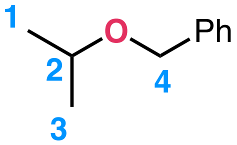
Consider the retrosynthesis of the target molecule below provided propene as a starting material



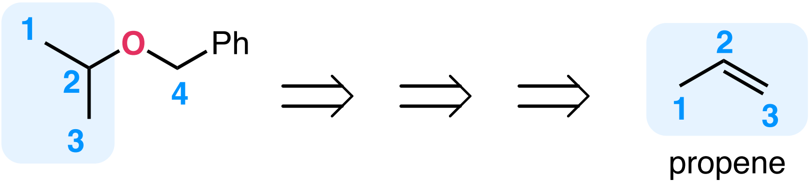
target product
(isopropoxymethyl)benzene

starting material
propene

1 Label your carbon atoms for organization (you do not need to use IUPAC numbering)



2 Identify which carbons in the product came from the provided starting material and any key bonds/functional groups that need to be formed

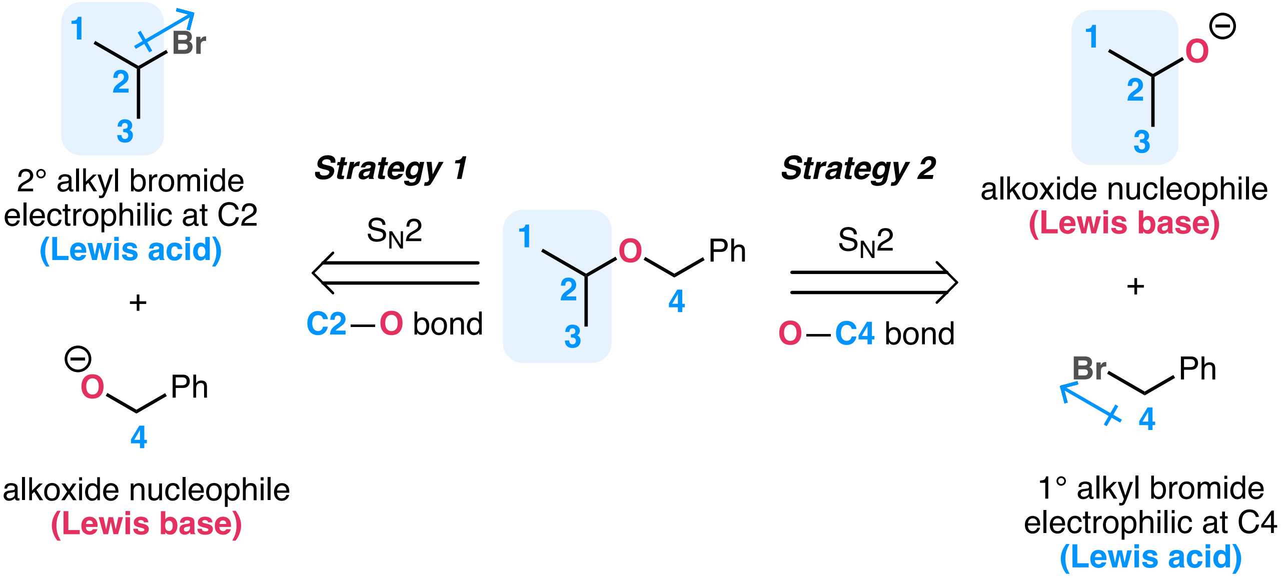


While many steps may be required, it is apparent that **C1-C3** come from propene

Therefore, we need to form the **C2—O** bond as well as incorporate the benzyl fragment (**C4** and benzene ring)

3 Propose strategic disconnections based on the reactivity of the starting materials, as well as the bonds and functional groups you know how to make. **However**, there are often multiple options

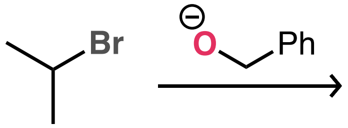
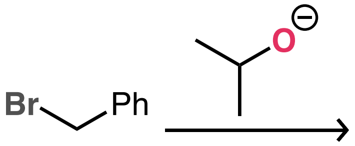
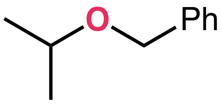
We can disconnect the **C2—O** or the **O—C4** bond since we know that alkoxides (**Lewis base**) can be nucleophiles in S_N2 reactions with alkyl bromide electrophiles (**Lewis acid**). These two strategic disconnections are shown below with the proposed starting materials:



We have proposed two strategies and need to assess if one strategy is clearly better than the other

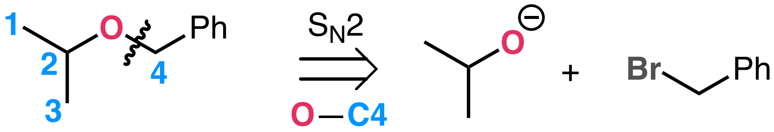
4 Compare the potential strategies

Although S_N2 reactions are possible using alkoxide nucleophiles, remember that E2 reactions compete with this process if the electrophile contains β—H atoms

Strategy	**Desired S_N2 Reaction**	**E2 reaction competes?**	**Likely product**
1		**yes** 2° R—Br + strong base	 (from an unintended E2)
2		**no** no β—H in R—Br	 (from the desired S_N2)

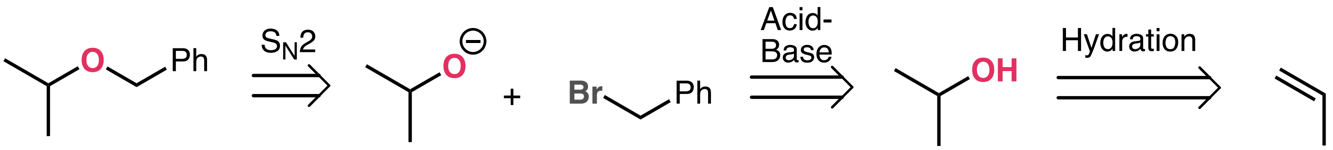
Strategy 1: Since the electrophile in **strategy 1** contains β-H atoms, an E2 elimination reaction would likely compete with the desired S_N2 reaction.

Strategy 2: Since **strategy 2** only undergoes the desired S_N2 reaction, we determine the appropriate disconnection the **O—C4** bond, and the **last** step of our synthetic route is:



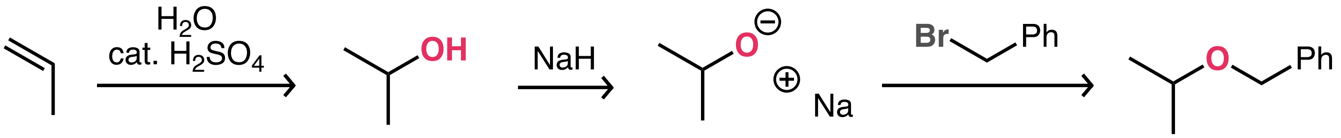
We could obtain the 2° alkoxide above from the propene starting material using a hydration reaction with Markovnikov regioselectivity (NaH to deprotonate the alcohol and form the alkoxide)

The Full Retrosynthesis



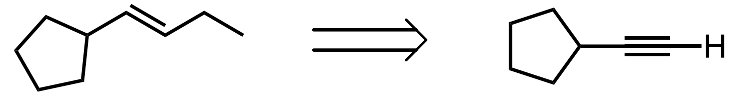
The Forward Synthesis

Includes all reagents for each step and the product of each step



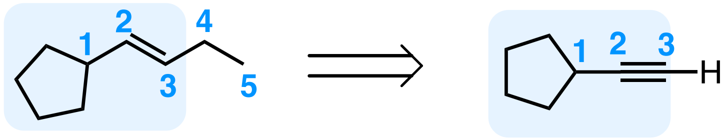
Example 2 - Functional Group Interconversions

As a second example, let's consider if we wanted to synthesize the alkene below from the terminal alkyne.



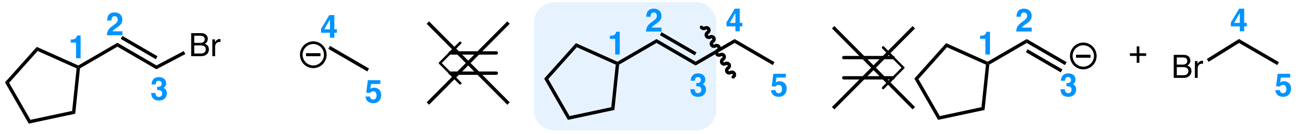
target product starting material

By numbering our carbon atoms, we can see that the cyclopentane ring (**C1**), and **C2** and **C3** come from our alkyne



Thus, we need to form the **C3—C4** bond and incorporate the **C4-C5** fragment of the molecule.

However, when considering potential S_N2 reactions to form the **C3—C4** bond in the target molecule we see that the alkyl and alkenyl nucleophiles are not typical in organic chemistry 1. **This is a case where a FGI could be useful.**



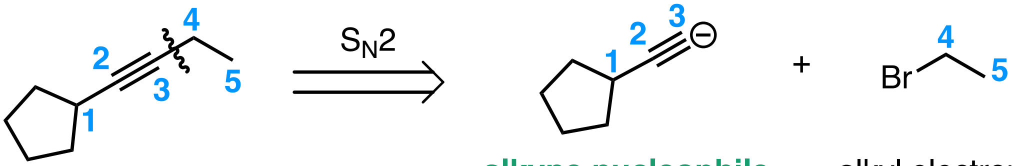
alkenyl halide electrophile **not common**

alkyl anion "nucleophile" **not common**

alkene anion "nucleophile" **not common**

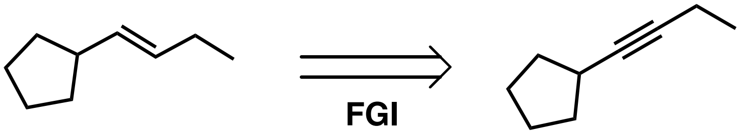
alkyl halide electrophile **common**

However, we know that we could form the **C3—C4** bond using an **alkyne nucleophile** and an alkyl electrophile, as shown below:



alkyne nucleophile alkyl electrophile

and the **last** step of our synthetic route is to convert the alkyne to the desired alkene product:



alkene alkyne

The Forward Synthesis