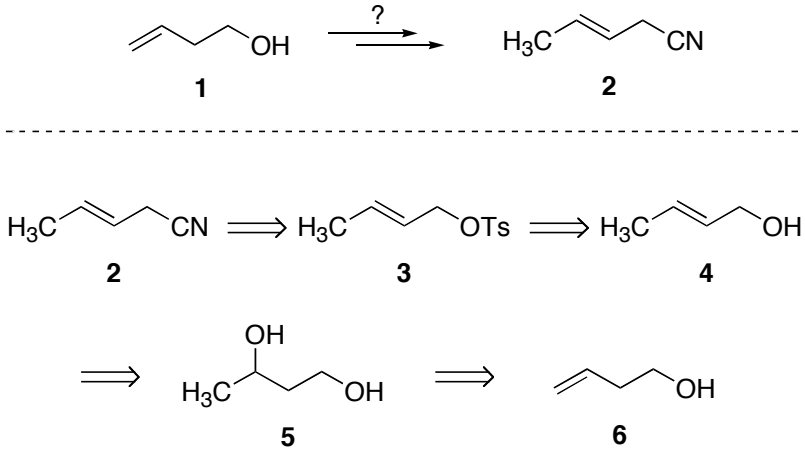
Synthesis Problem Set 2

CHM 223 • Prof. Chad Landrie

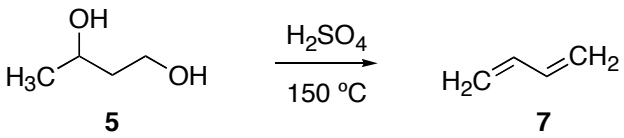
Introduction

Several new synthetic strategies were encountered in Chapters 14-16 that allow us to construct fairly complex molecules in relatively few steps. As we learn new reactions, however, several routes to a target may be possible. Our challenge then becomes not to find any route, but to devise the best route. A common pitfall at this stage is to get stuck in a rut using familiar, comfortable reactions such as Markovnikov additions and dehydrations encountered early in the course. While these transformations certainly have their place, and will undoubtedly be used in the syntheses below, they are not always the best choice when another method can prepare the same molecule in fewer steps or with a higher degree of selectivity.

Let's take, for example, the synthesis of the *trans*-3-pentenenitrile (**2**) from 3-butene-1-ol (**1**). A first approach might consider introduction of the nitrile (CN) group separately from the apparent isomerization of the alkene. Thus, in the retrosynthetic analysis, **2** could be formed by S_N2 substitution of a tosylate (OTs) by cyanide (CN^-). The tosylate **3** could in turn be prepared from the alcohol **4**. So far, everything seems to be falling into place since our requisite starting material **1** does in fact contain an alcohol in the same position as **4**. The next challenge is to develop a method to isomerize the monsubstituted alkene in **1** to the *trans*-disubstituted alkene in **2**. Picking up where we left off, we could image that alkene **4** could be prepared by dehydration of alcohol **5**, which could be prepared by hydration of **6** with H_2SO_4/H_2O. Looks good, right?

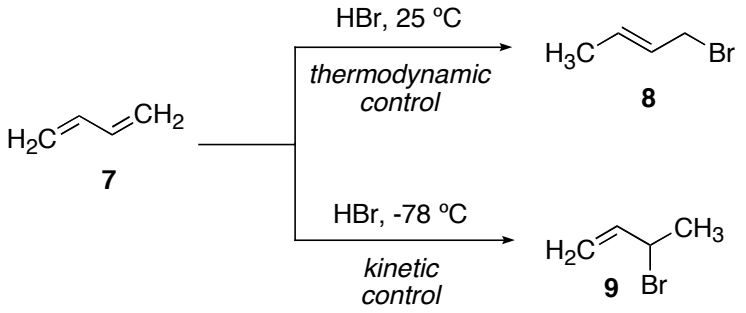


While reasonable, the synthesis above suffers from two drawbacks. First, a shorter route is available. Shorter syntheses are usually more advantageous since overall yields decrease with increasing steps. Second, the isomerization strategy to transform **6** → **4** would likely provide mixtures of products. For example, the conditions required to cause the dehydration of the secondary alcohol in **5** → **4** (H_2SO_4, >150 ºC) may cause dehydration of the primary alcohol instead. Since conjugated dienes are stable and dehydration is a reversible process, the most likely product when **5** is treated with H_2SO_4 is dehydration of both alcohols to form diene **7**.

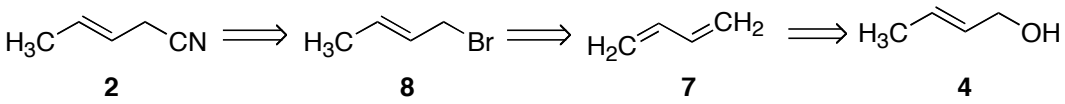


This apparent complication—formation of diene **7**—can be used to our advantage in a revised synthesis. First, we have to recognize that conjugated dienes can react with HBr under kinetic control (irreversible conditions: low temperatures) to provide monosubstituted alkenes such as **9** or under thermodynamic control (reversible conditions: elevated temperature) to provide disubstituted alkenes such as **9**. By performing the addition of HBr under

thermodynamic control, we can install a good leaving group (Br) for a future S_N2 of cyanide and form the disubstituted alkene we require at the same time.



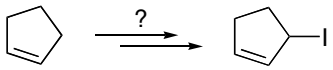
In summary, our revised retrosynthesis only requires four synthetic steps. In addition, each transformation will likely only provide a single product, not a complex mixture. The regioisomer formed by Markovnikov addition of HBr to **7** depends on the conditions chosen. Here, simply performing the reaction at room temperature (25 ºC) will give the thermodynamic product required, **8**. Recognizing these types of strategies requires practice, lots of it. It would be a mistake to *memorize* the *structure* of **8** for future syntheses problems. Rather, recognize that allylic functional groups, such as the allylic nitrile in **2**, can usually be prepared from allylic bromides. Allylic bromides can, in turn, be prepared directly from conjugated dienes. Say these words aloud as you think about the structural units they describe. Then, devise your own synthetic problems that would require a similar strategy, except replace nitrile with another functional group that could be introduced by S_N2. Also, chose a target that would require a conjugated diene different from **7**. By making your own problems, you will reinforce the patterns that make a series of synthetic steps a strategy rather than just a series of steps. This is the same process I will use to create the synthesis questions on the final exam. The strategies required for functional groups transformations will be the same, but the structures will different. Therefore, you want to learn strategies not memorize individual structures.

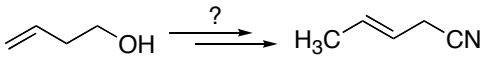


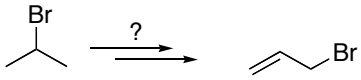
** Do not use dehydrogenation (>750 ºC) of alkanes to form alkenes unless only *one* alkene is possible (e.g. ethane to ethylene). If other isomers can be formed–even if less stable–they will be. Also, this method should never be used when other functional groups are present. It should only be applied to saturated hydrocarbons. You will not receive points for this method if used improperly.

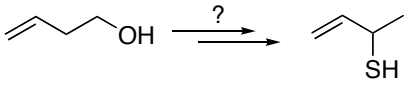
1. Syntheses Utilizing Conjugated Systems

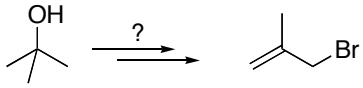
For each synthetic problem below, first write out a retrosynthetic analysis. Then, write the forward synthesis including all necessary reaction conditions and reagents for each transformation. All of the syntheses below utilize preparations of conjugated compounds or reactions of alkenes that proceed through conjugated intermediates (e.g., allylic radical halogenation, benzylic radical halogenation, Diels-Alder, kinetic and thermodynamic addition to dienes, oxidation of benzylic carbons).

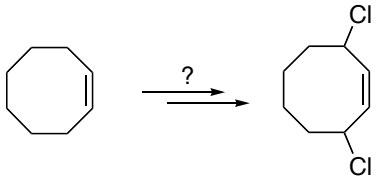


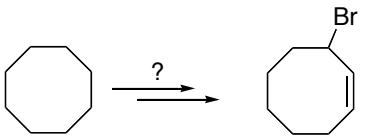


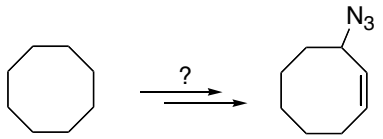


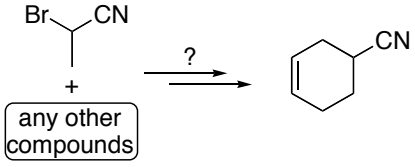


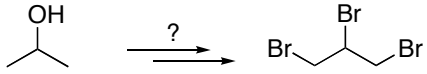


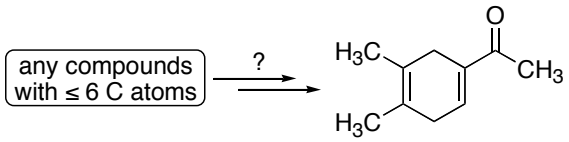


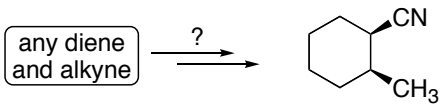


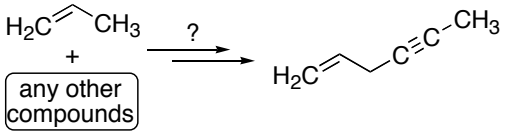


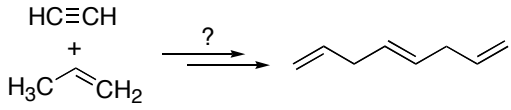


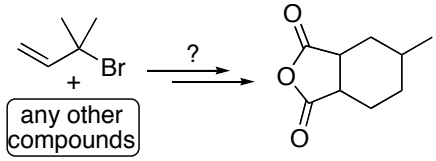


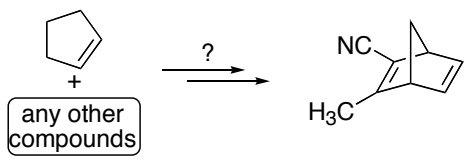


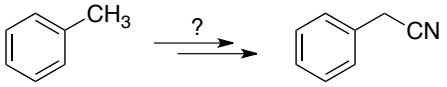


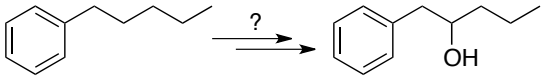


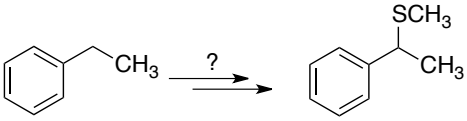


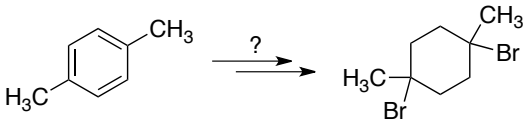


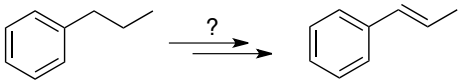


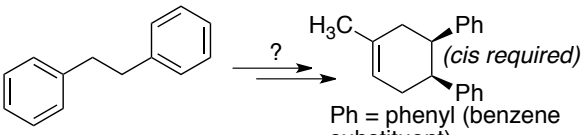




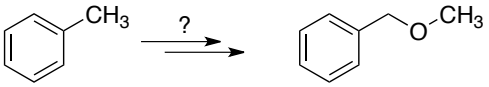


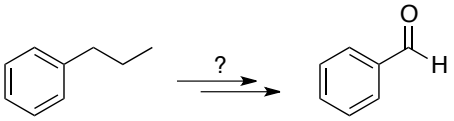


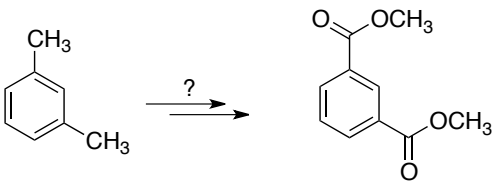


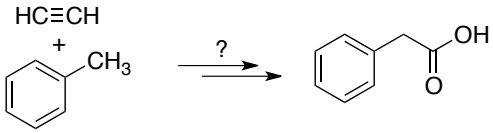


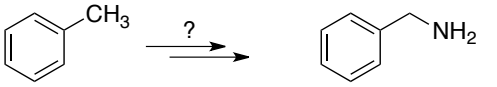
Ph = phenyl (benzene substituent)

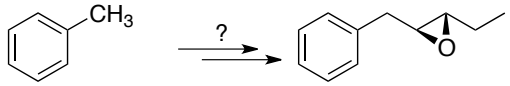


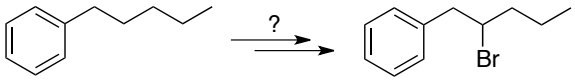


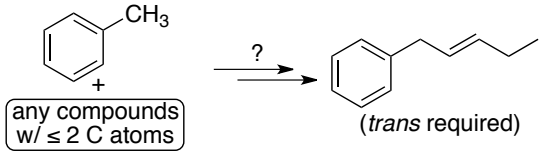












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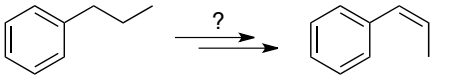

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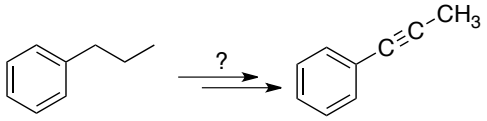
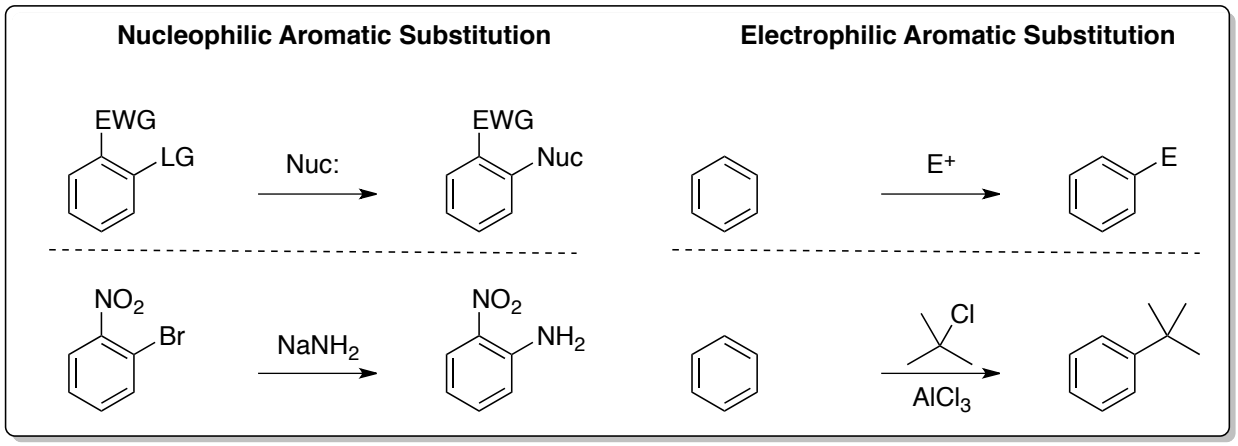
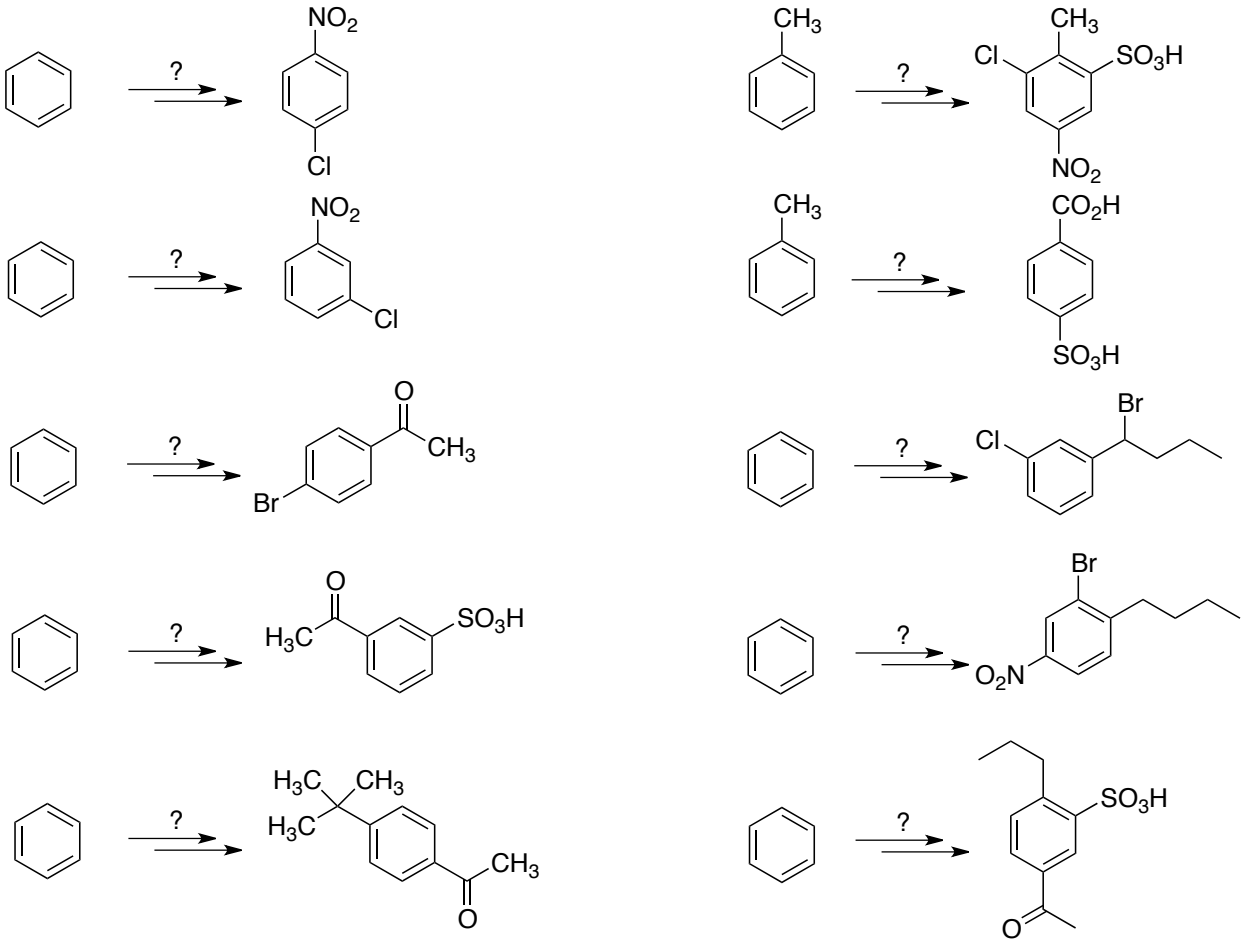
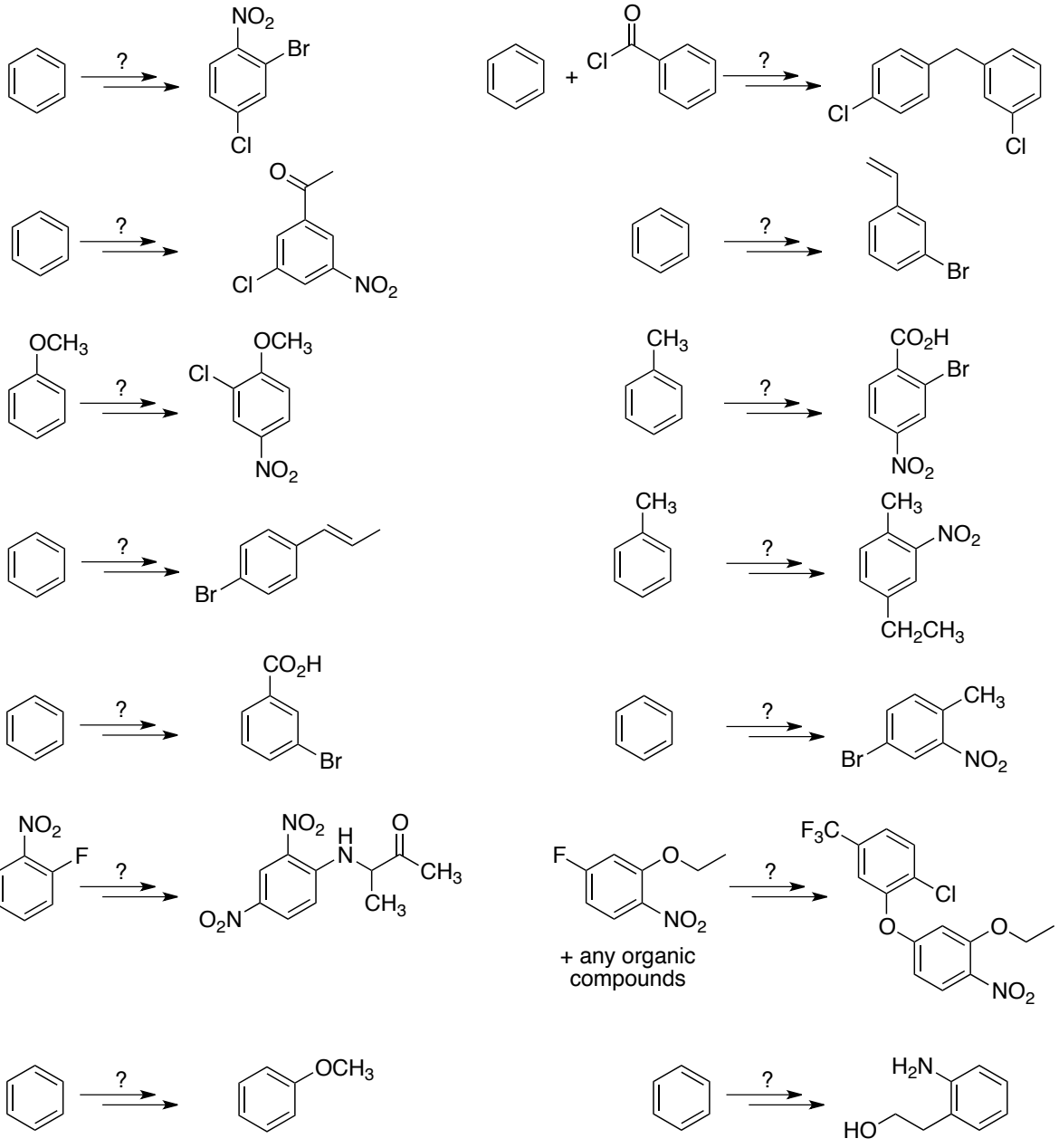


2. Syntheses Utilizing Aromatic Substitution (Nucleophilic and Electrophilic).

For each synthetic problem below, first write out a retrosynthetic analysis. Then, write the forward synthesis including all necessary reaction conditions and reagents for each transformation. All of the syntheses below utilize either electrophilic aromatic substitution or nucleophilic aromatic substitution.



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+
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NO2
Br
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NO2
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NO2
F
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H
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O
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CH3
O2N
F
O
NO2
+ any organic
compounds
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H2N
HO