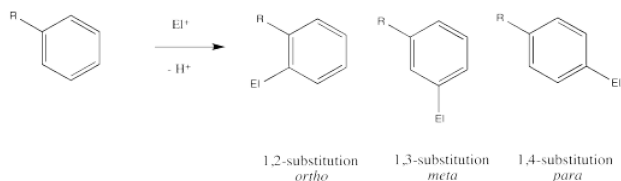


7.5: Directing Effects

In addition to exerting an effect on the speed of reaction, substituents on the benzene ring also influence the regiochemistry of the reaction. That is, they control *where* the new substituent appears in the product.

Remember, there are three different position on the benzene ring where a new substituent can attach, relative to the original substituent. Substitution could actually occur on five positions around the ring, but two pairs are related by symmetry. Isomerism in disubstituted benzenes can be described by numbering the substituents (1,2- etc) or by the relationships *ortho*-, *meta*- and *para*-. There are two positions *ortho*- to the initial substituent and two positions *meta*- to it.



Ingold and colleagues investigated the question of regiochemistry in nitration. They reported the following observations:

Substitution patterns during nitration of benzene derivatives			
R in C ₆ H ₅ R	% <i>o</i> - product	% <i>m</i> - product	% <i>p</i> - product
CH ₃	56	3	41
F	10	0	90
Cl	30	0	70
Br	38	0	62
OH	10	0	90
CHO	19	72	9
CO ₂ Et	28	68	3
CN	17	81	2
NO ₂	6	94	0

In looking at the table, you might see that there are two groups of substituents. One group reacts to make mixtures of *ortho*- and *para*- products. There may be different ratios of *ortho*- to *para*- and there may be small amounts of *meta*-, but don't get bogged down in the details right now. Focus on the bigger picture. Some groups are "*ortho*-/*para*-directors".

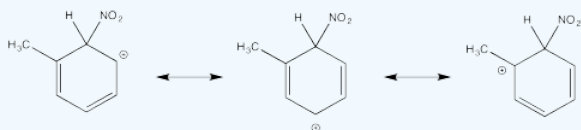
The other group reacts to make mostly *meta*-substituted products. There may be small amounts of *ortho*- and *para*- products, but don't worry about that. Focus on the bigger picture. Some groups are "*meta*-directors".

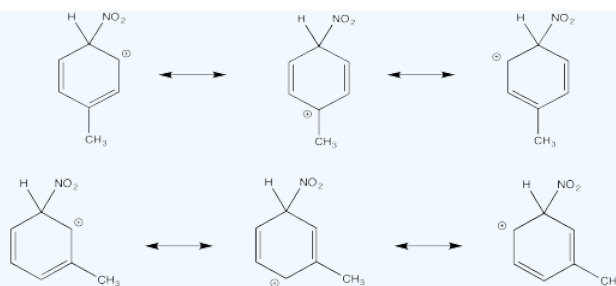
These regiochemical effects are very closely related to the activating and directing effects we have already seen. If we want to understand this data, we need to think about things like π -donation, π -acceptance, inductive effects and cation stability.

? Exercise 7.5.1

Show resonance structures for the cationic intermediate that results during nitration of toluene (methylbenzene). Explain why a mixture of *ortho*- and *para*- substitution results.

Answer



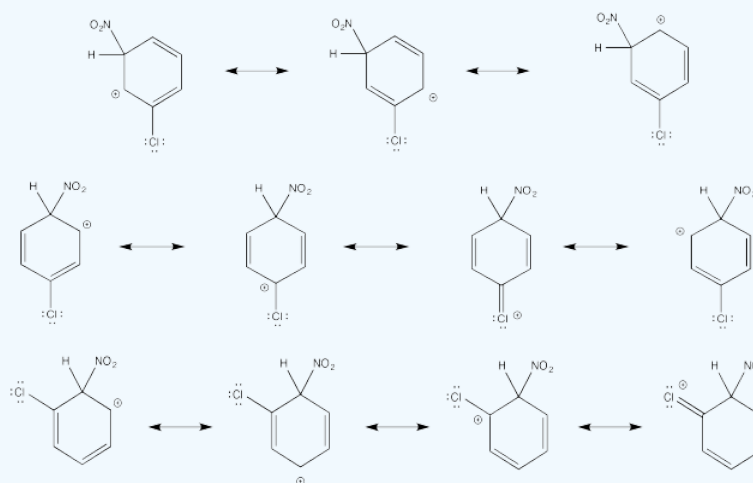


The tertiary cations that result during *ortho*- and *meta*- substitution offer extra stability, leading to preferential formation of these cations.

? Exercise 7.5.2

Show resonance structures for the cationic intermediate that results during nitration of chlorobenzene. Explain why a mixture of *ortho*- and *para*- substitution results.

Answer

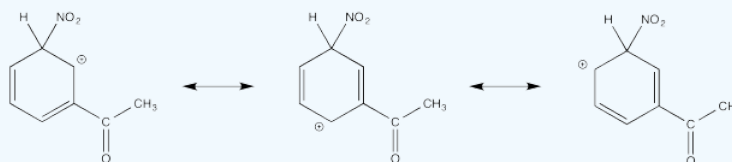


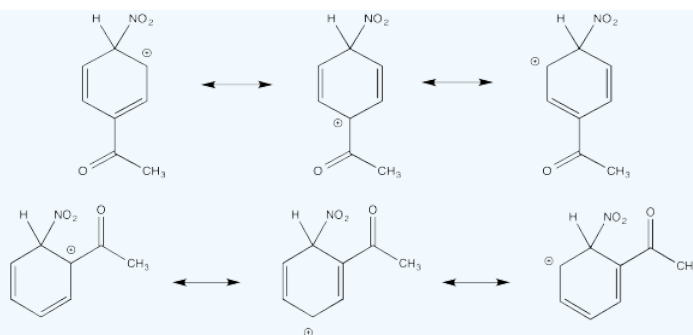
The π -donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

? Exercise 7.5.3

Show resonance structures for the cationic intermediate that results during nitration of acetophenone ($\text{C}_6\text{H}_5\text{COCH}_3$). Explain why mostly *meta*- substitution results.

Answer



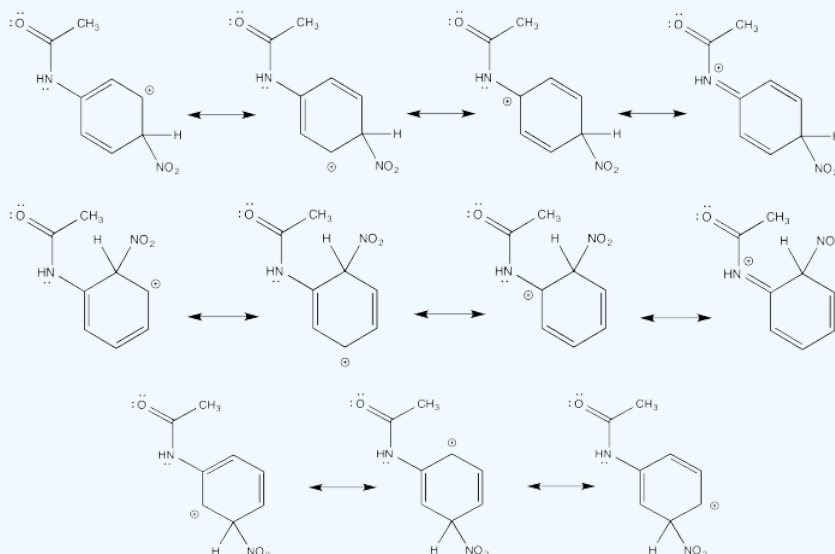


The cation directly adjacent to the carbonyl is destabilized by the electron withdrawing effect of the ketone. By default, the other intermediate is preferentially formed.

? Exercise 7.5.4

Show resonance structures for the cationic intermediate that results during nitration of acetanilide ($\text{C}_6\text{H}_5\text{NH}(\text{CO})\text{CH}_3$). Explain why a mixture of *ortho*- and *para*- substitution results.

Answer



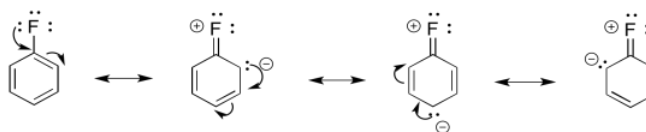
The π -donation that occurs in the cations arising from *ortho*- and *meta*- substitution results in extra stability, leading to preferential formation of these cations.

In general, we can divide these substituents into three groups:

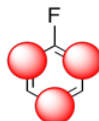
- π -acceptors are *meta*- directors.
- π -donors are *ortho*-/*para*- directors.
- alkyls are *ortho*-/*para*- directors.

Note that, once again, we may have two competing effects in one substituent, such as a halogen. In halogens, although the net effect may be to slow the reaction down, that weak π -donation is still enough to tilt the balance of products in favor of *ortho*- and *para*- substitution.

For example, fluorine has a lone pair. It can be a π -donor.

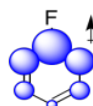


We could illustrate the effects with the following cartoon. It shows negative charge buildup, illustrated in red, on three of the carbons on the benzene ring.

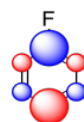


Fluorine is also very electronegative. It can be an electron withdrawing group. Because it withdraws electrons through its sigma bond rather than through resonance effects, we think of it as "inductively" electron withdrawing. Nonetheless, a considerable amount of electron density from the benzene is attracted to the fluorine.

Again, we could illustrate the effects with a cartoon. It shows positive charge buildup, illustrated in blue, on the carbons that are closest to the fluorine. Remember, electrostatic interactions decrease rapidly with distance, so the farther the carbons are from the fluorine, the lower the effect that they will experience.



The sum of these effects can be illustrated in a composite cartoon that shows different amounts of positive or negative charge built up on different carbons.

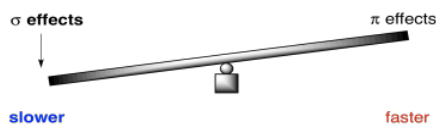


Thus, although fluorine is generally an electronegative and deactivating group, it may still manage to place some extraelectron density on particular carbons.

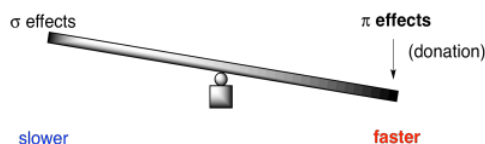
Whether something is overall activating or deactivating depends on a similar balance of factors. In general, we can think about competing effects in terms of a see saw.



For an electronegative π -donor like fluorine or another halogen, the stronger those σ -withdrawing effects, the slower the reaction. It pulls more electron density away from the benzene than it puts back. As a result, the benzene is less nucleophilic than it would be if the halogen were not there.

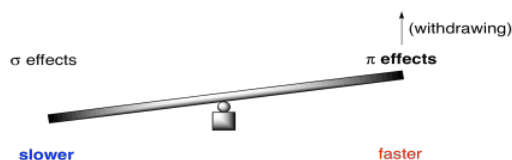


On the other hand, the better the π -donation, the faster the reaction. Good π -donors include oxygen and nitrogen. They are just the right size to lend a lone pair to a neighbouring carbon in the benzene ring. Halogens, on the other hand, are relatively clumsy donors. Either they are just a little too electronegative to be useful, like fluorine, or else they are a little too big to share with carbon. That's the case with chlorine, bromine and iodine.



Remember, the same arguments are true in carbonyl chemistry. The general reactivity of carboxylic acid derivatives depends on a similar balance between donating and withdrawing effects. As a result, esters and amides are relatively stable and unreactive, whereas chlorides are very reactive.

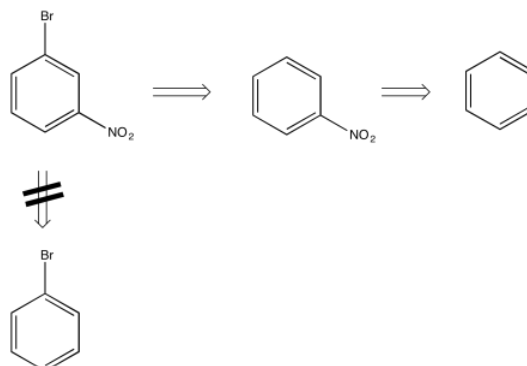
Of course, a π -acceptor would work in the opposite way. That would be true if the atom attached to the benzene is multiply bonded to another atom, especially if that other atom is something electronegative (an oxygen or a nitrogen).



Retrosynthetic Planning

Sometimes in synthetic work it is useful to look at a compound and imagine what it might be made from. This practice is used in industrial chemistry, when a researcher might be trying to decide on the most economical route to make a particular compound. There may be readily available materials that a useful pharmaceutical can be made from. By working backwards one step at a time, the researcher may more easily see different possibilities for starting materials. In a similar way, a biological chemist might be able to identify what biological precursors could lead to the formation of a particular compound in biology.

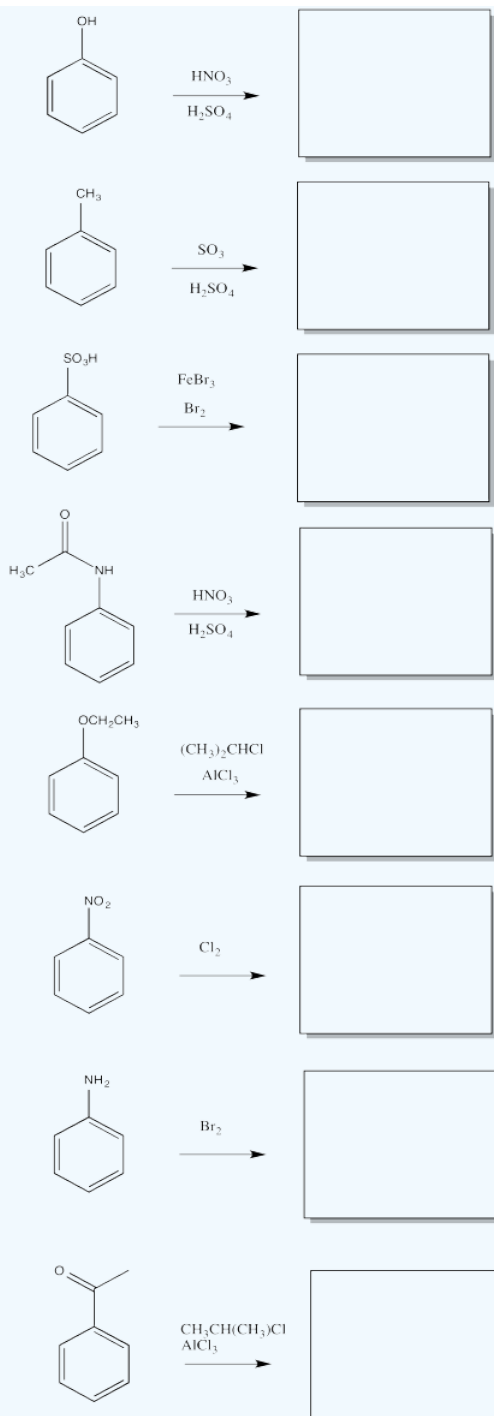
For example, by looking at the structure of *m*-bromonitrobenzene, you could imagine that the compound could be made by the bromination of nitrobenzene, but not by the nitration of bromobenzene. That's because nitro groups are *meta*-directors, but bromo-groups are *ortho*-, *para*-directors.



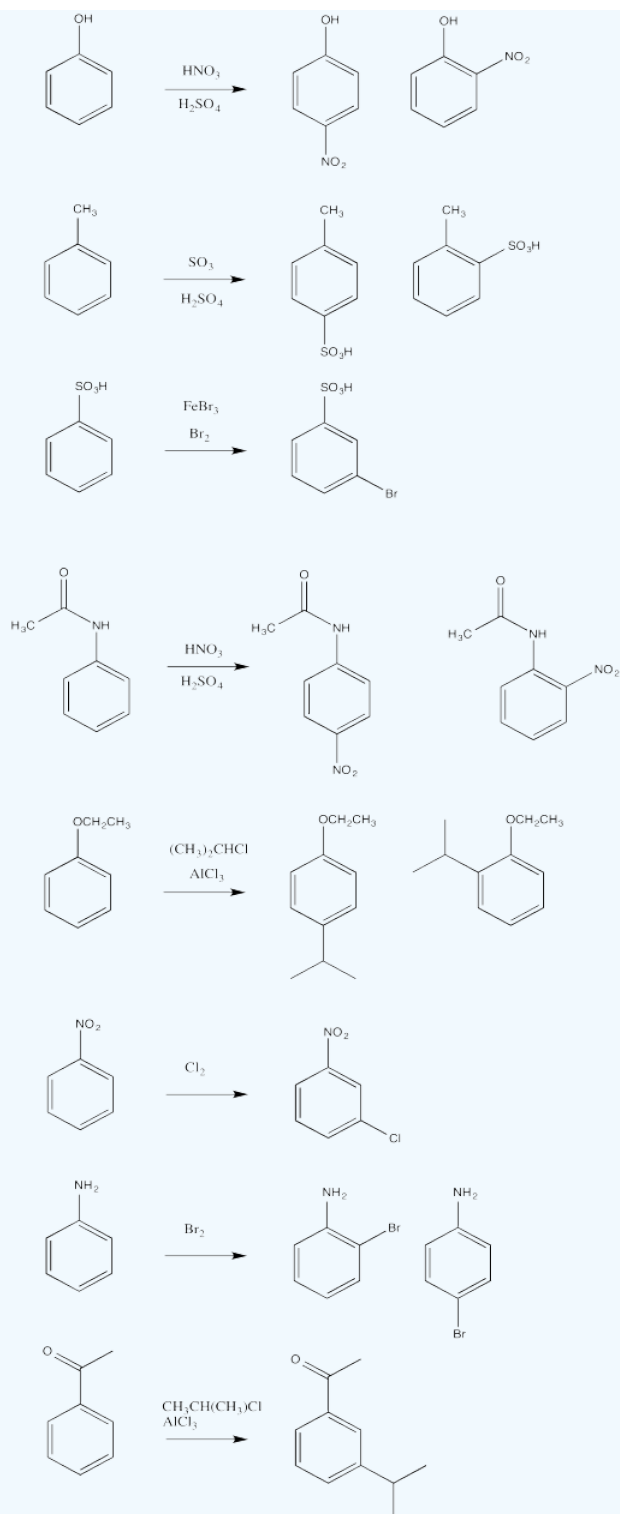
This method of working backward from the target compound is called "retrosynthetic analysis". By making a retrosynthetic plan, we can more efficiently arrive at the possible ways to make a specific compound.

? Exercise 7.5.5

Fill in the major organic products of the following reactions.

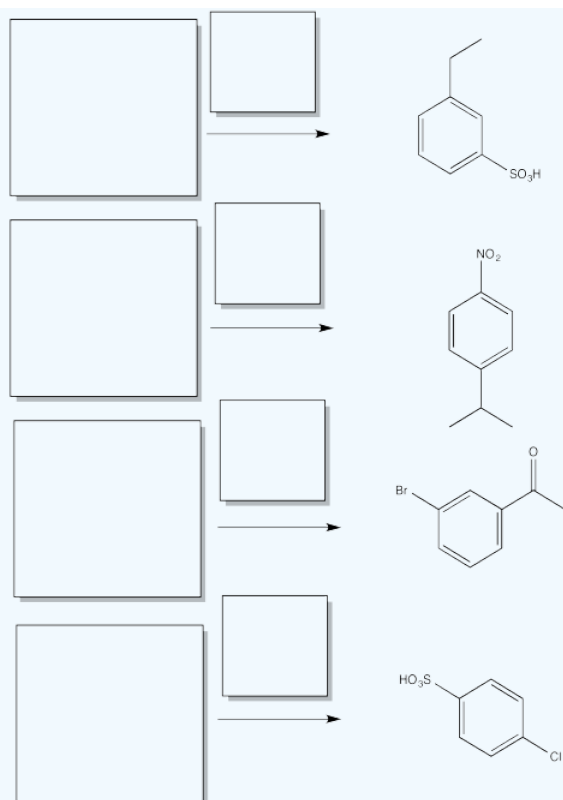


Answer

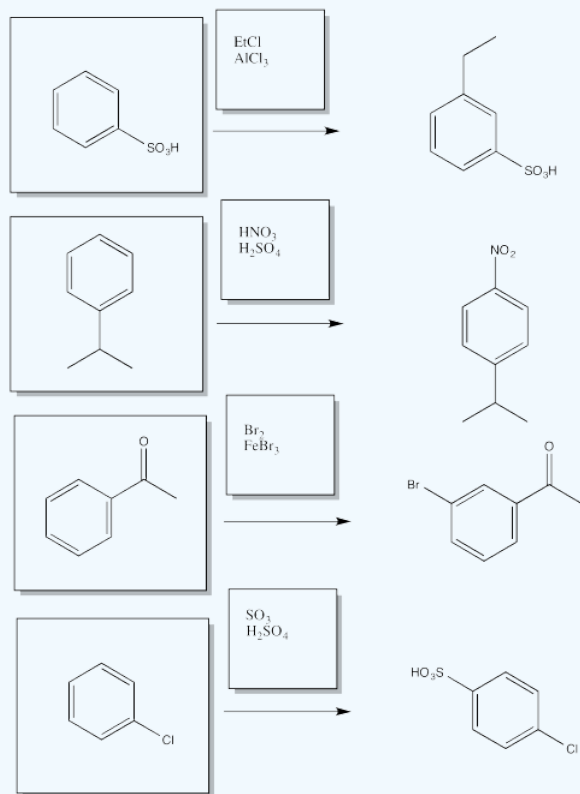


? Exercise 7.5.6

Fill in the starting materials and reagents needed to obtain the major product shown via electrophilic aromatic substitution.

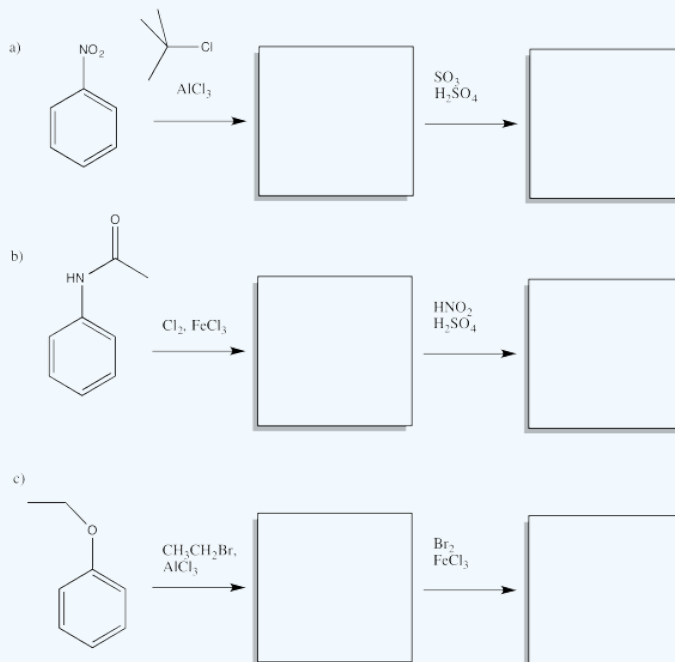


Answer



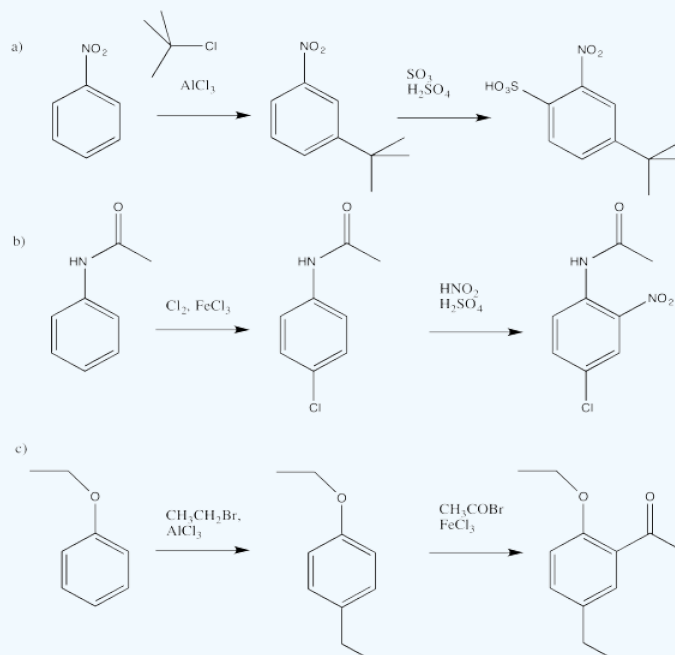
? Exercise 7.5.7

Given two different substituents on a benzene, there can sometimes be a conflict in predicting which substitution pattern will result. Generally, the group with the stronger activating effect wins out. Predict the major products of the following reactions.



Answer

In cases leading to mixtures of *ortho* and *para* products, only one product was chosen, based on minimal steric interactions.

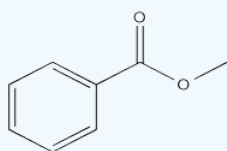


? Exercise 7.5.8

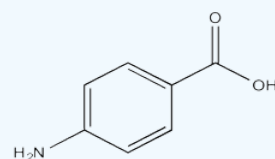
Problem AR5.8

Starting from benzene and any monofunctional group compound, propose a synthesis for the following.

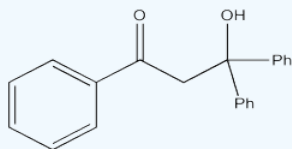
A)



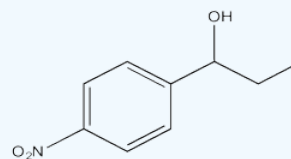
B)



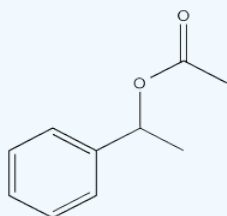
C)



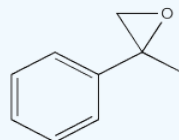
D)



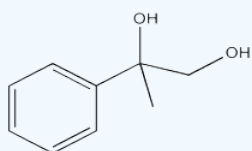
E)



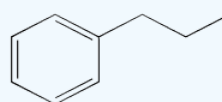
F)



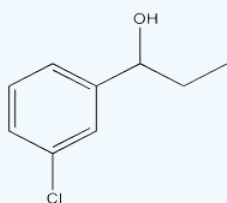
G)



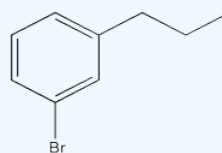
H)



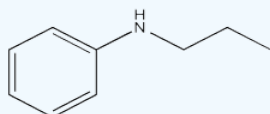
I)



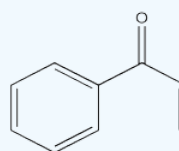
J)



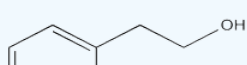
K)



L)

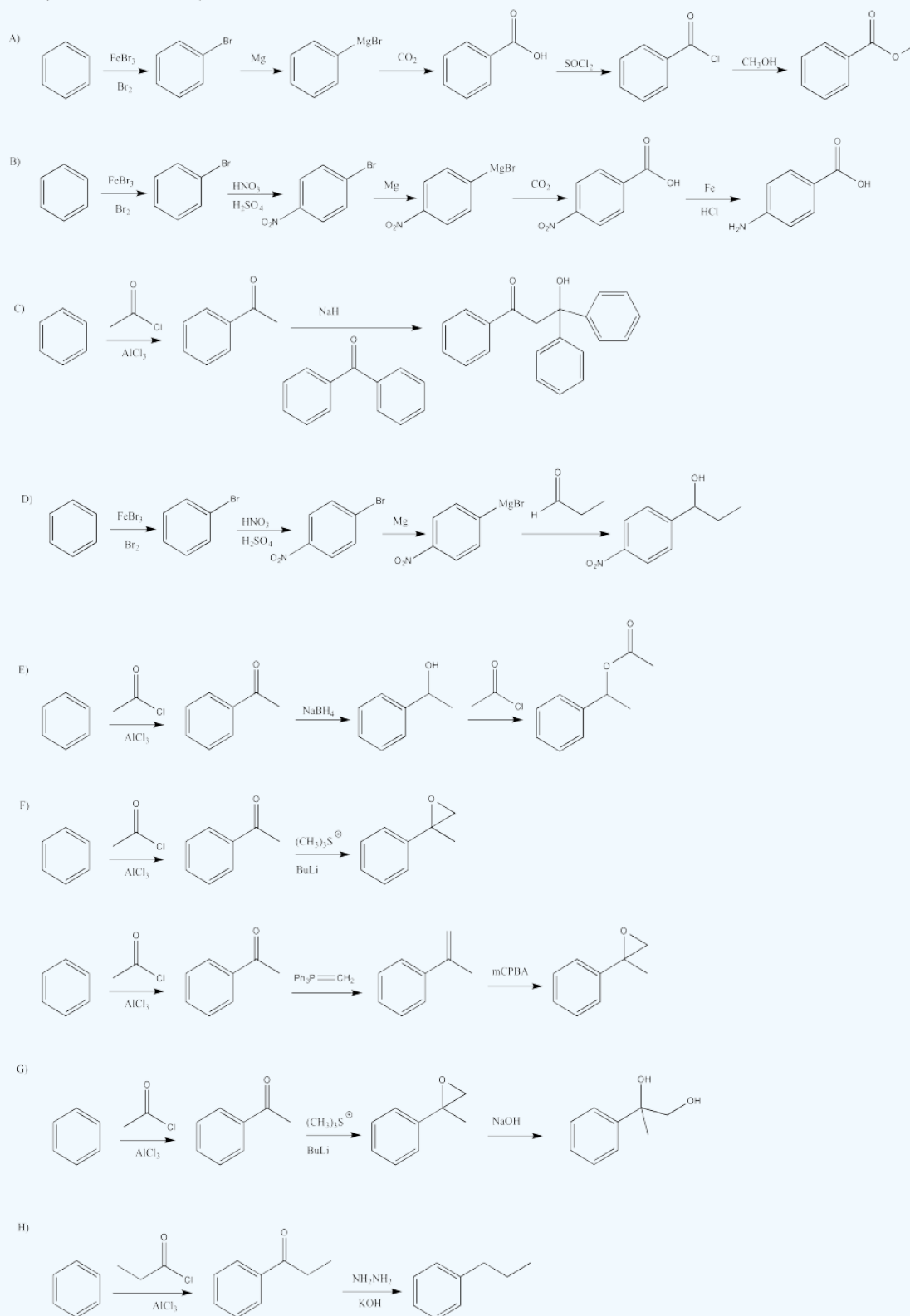


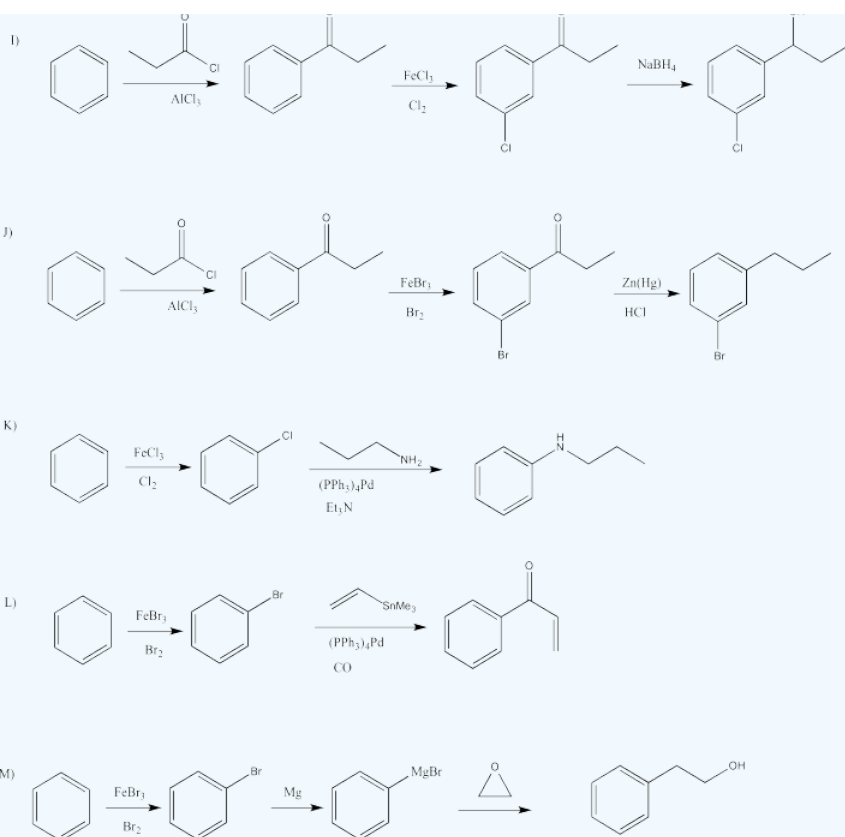
M)



Answer

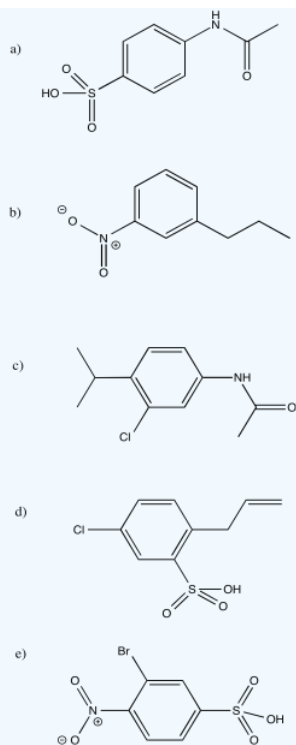
Starting from benzene and any monofunctional group compound, propose a synthesis for the following.
There may be more than one answer than is presented here.



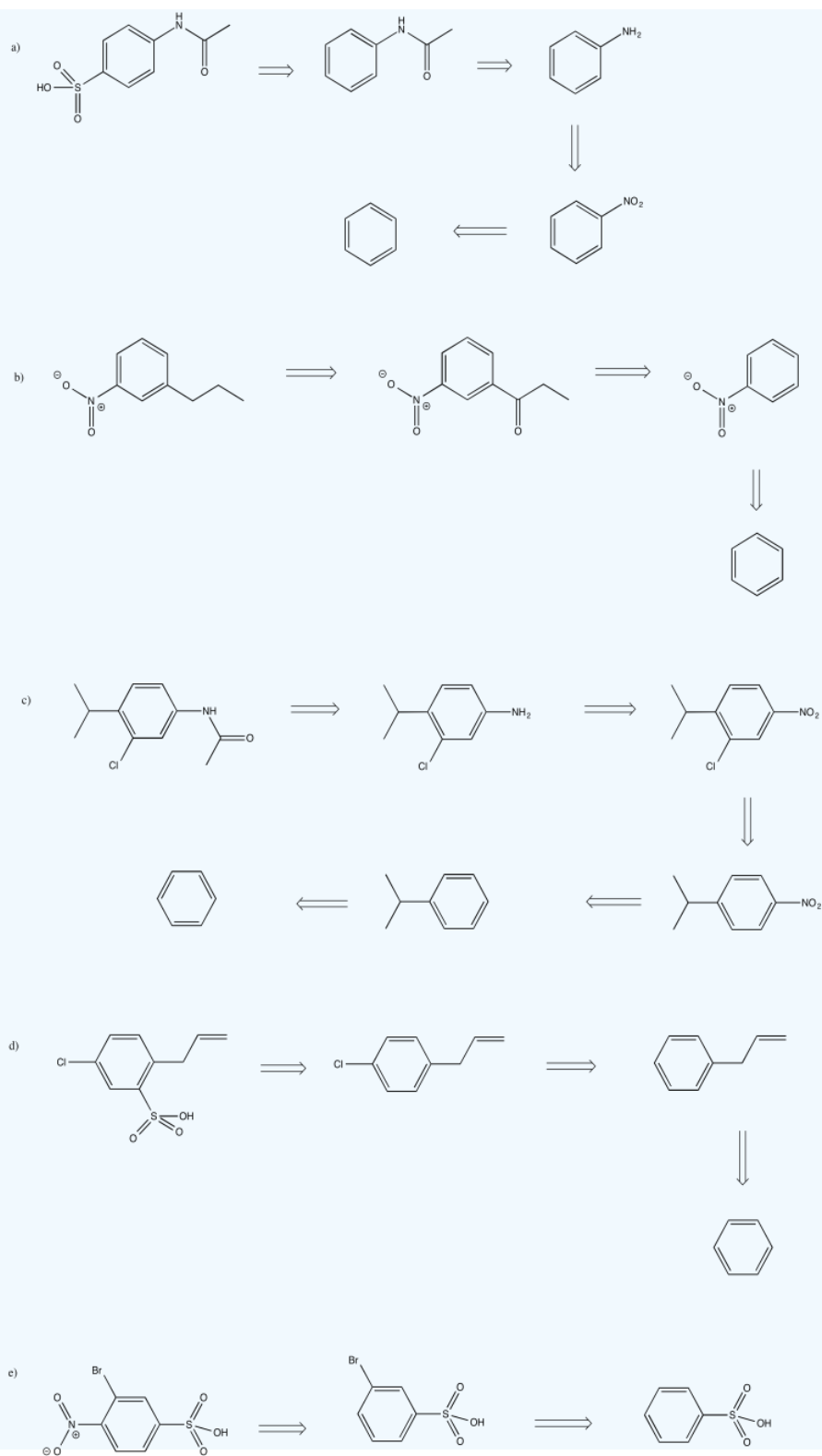


? Exercise 7.5.9

Provide a retrosynthetic plan for each of the following compounds, going back to benzene.



Answer

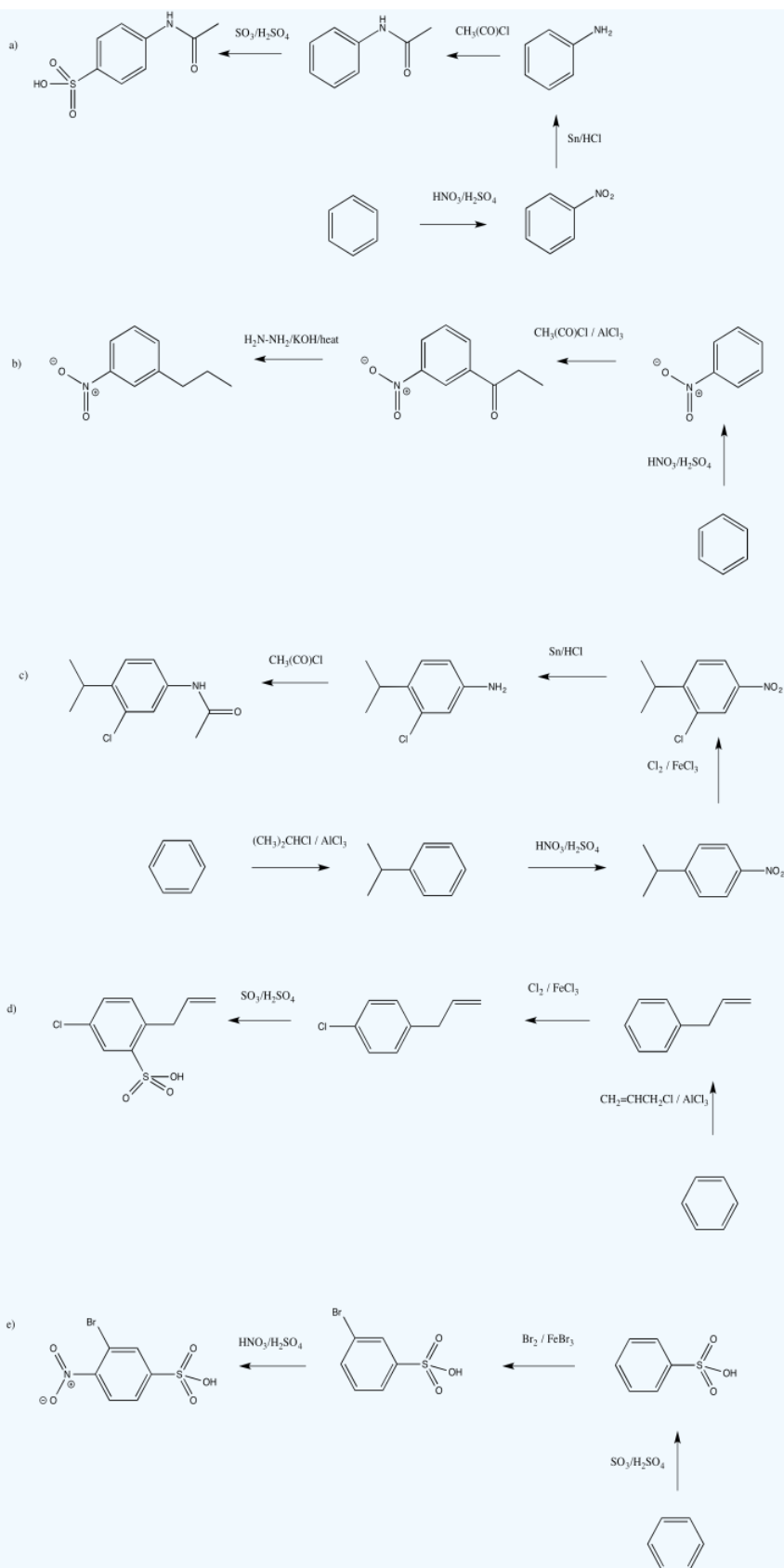


? Exercise 7.5.10

Turn the retrosynthetic plans from the previous problem into syntheses.

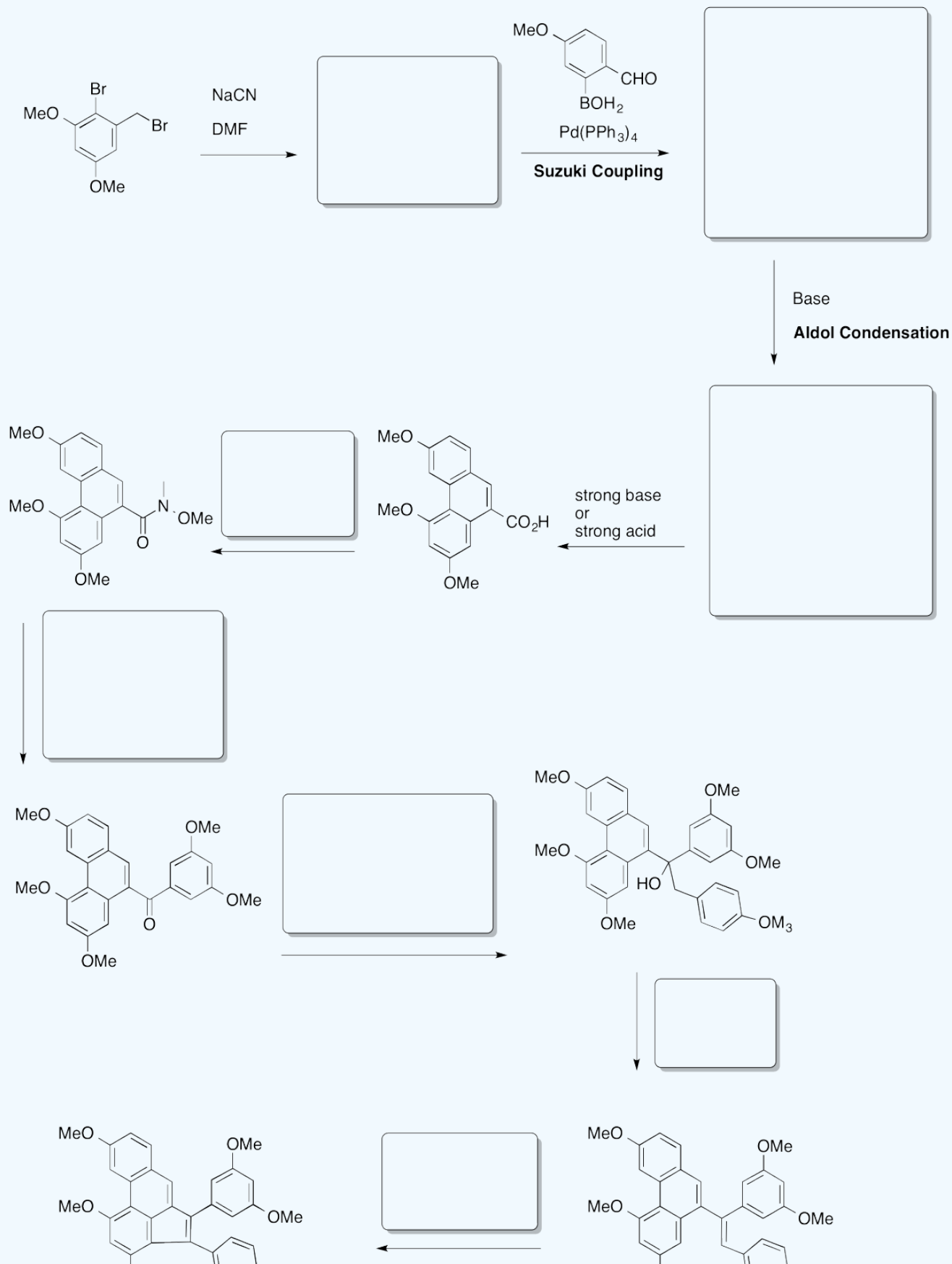
Answer

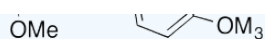




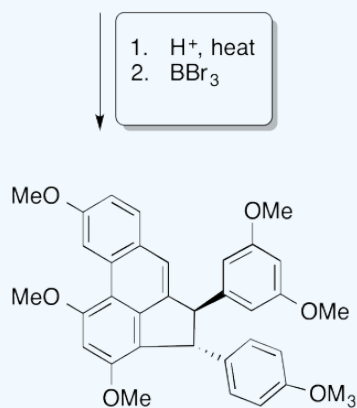
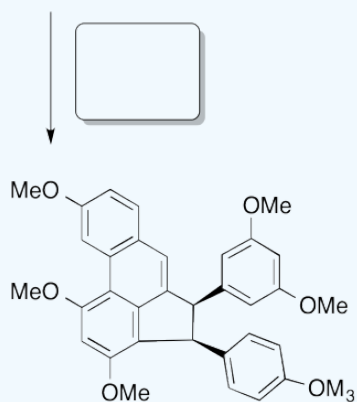
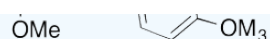
? Exercise 7.5.11

Choi, Kim and Heo, Total Synthesis of Laetevirenol A, *J. Org. Chem.*, **2012**, 77, 8762-8767.



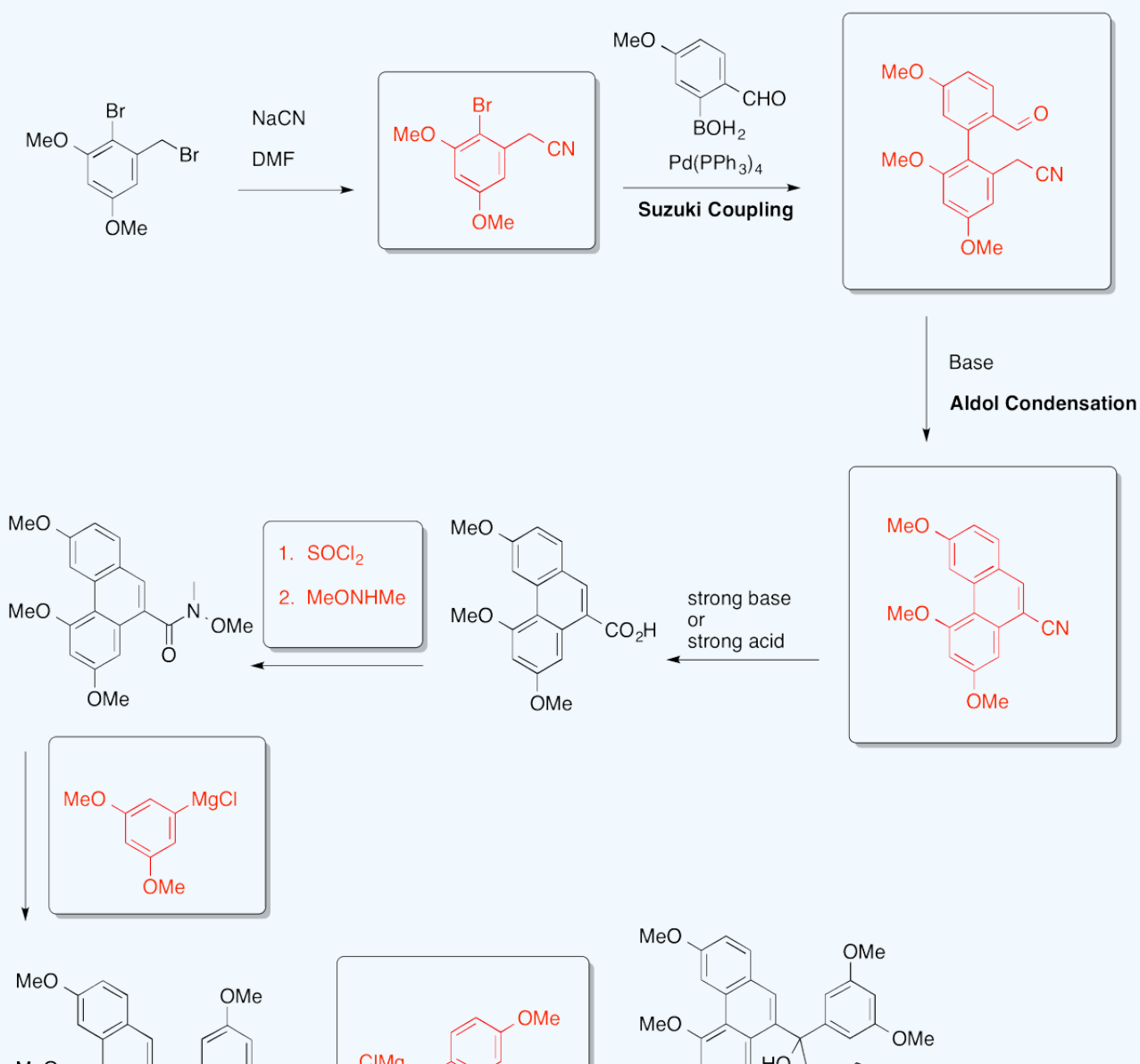


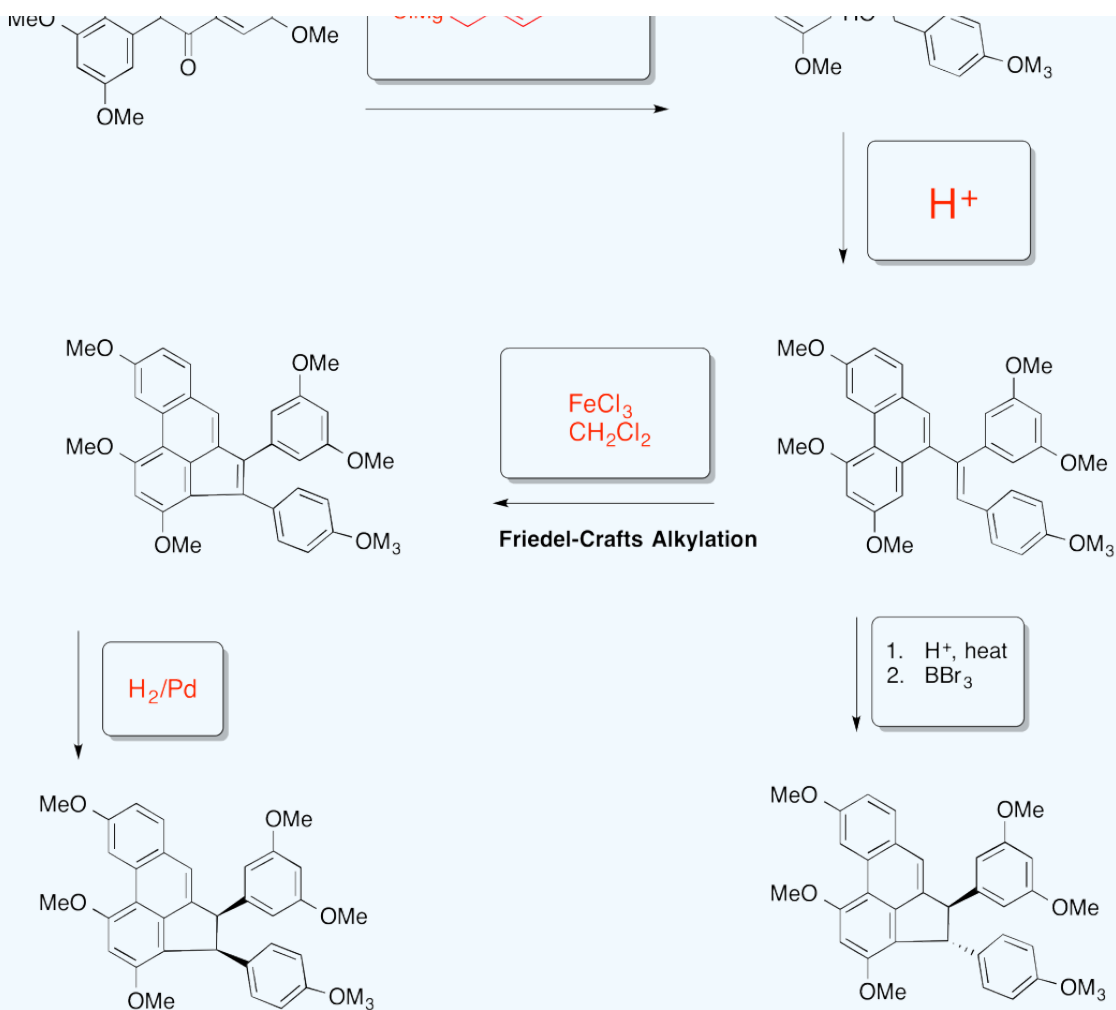
Friedel-Crafts Alkylation



Answer

Choi, Kim and Heo, Total Synthesis of Laetevirenol A, *J. Org. Chem.*, **2012**, 77, 8762-8767.

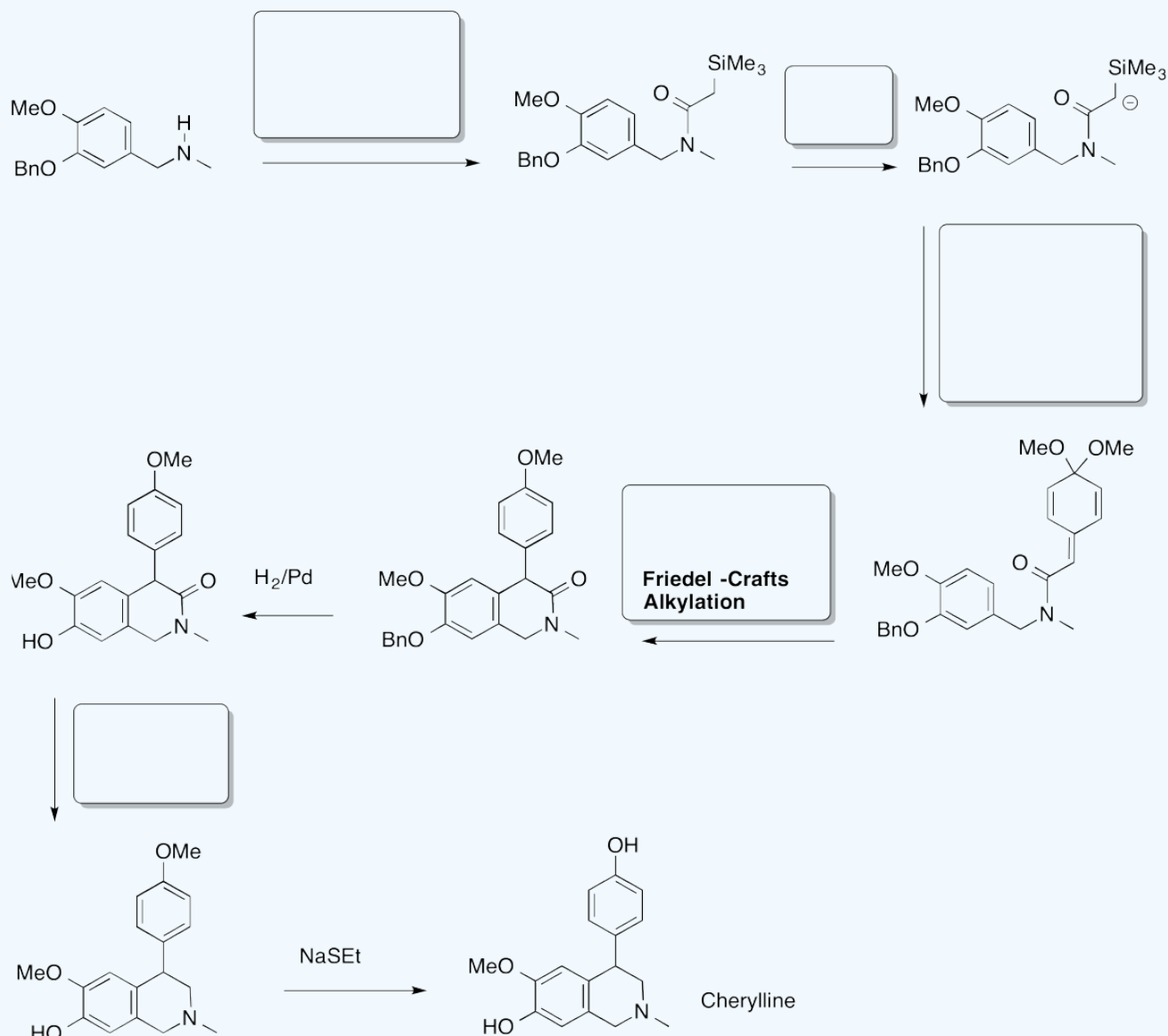




? Exercise 7.5.12

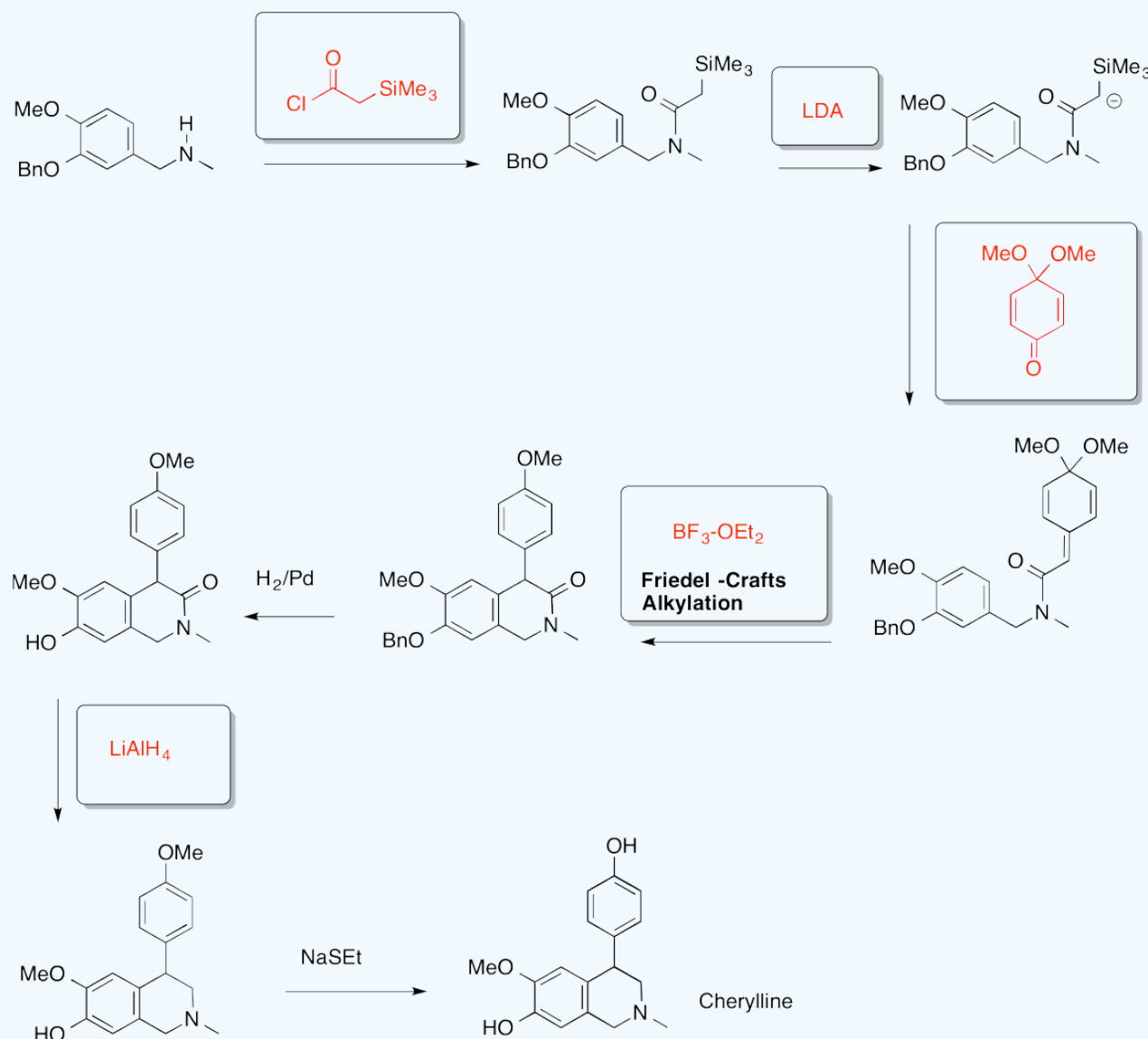
Problem AR5.12.

Hart, Cain, Evans, Approaches to the synthesis of masked p-quinone methides. Applications to the total synthesis of cherylline, *J. Am. Chem. Soc.*, **1978**, *100* (5), 1548-1557.



Answer

Hart, Cain, Evans, Approaches to the synthesis of masked p-quinone methides. Applications to the total synthesis of cherylline, *J. Am. Chem. Soc.*, **1978**, *100* (5), 1548-1557.



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