5.10 Organic Synthesis

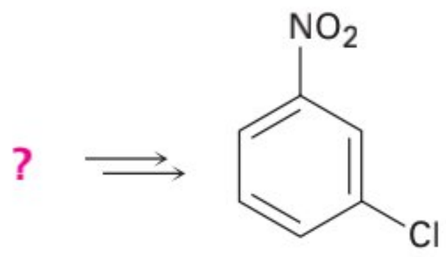
The laboratory synthesis of organic molecules from simple precursors might be carried out for many reasons. In the pharmaceutical industry, new organic molecules are often designed and synthesized for evaluation as medicines. In the chemical industry, syntheses are often undertaken to devise more economical routes to known compounds. In this book, too, we'll sometimes devise syntheses of complex molecules from simpler precursors, but the purpose here is simply to help you learn organic chemistry. Devising a route for the synthesis of an organic molecule requires that you approach chemical problems in a logical way, draw on your knowledge of organic reactivity, and organize that knowledge into a workable plan.

The only trick to devising an organic synthesis is to *work backward*. Look at the product and ask yourself, "What is the immediate precursor of that product?" Having found an immediate precursor, work backward again, one step at a time, until a suitable starting material is found. Let's try some examples.

Worked Example 5.5 Synthesizing a Substituted Aromatic Compound

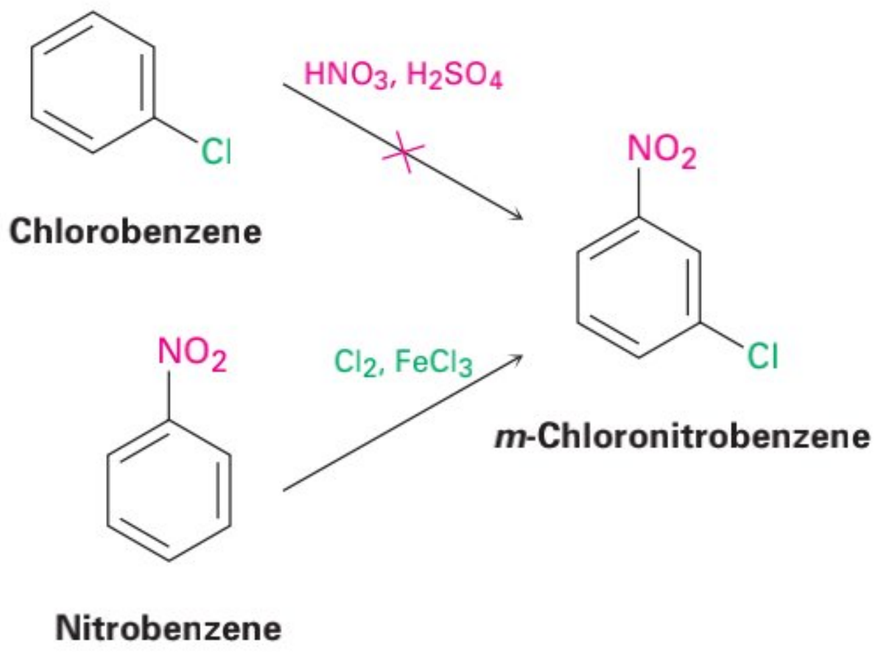
Synthesize *m*-chloronitrobenzene starting from benzene.

Strategy Work backward by first asking, "What is an immediate precursor of *m*-chloronitrobenzene?"



***m*-Chloronitrobenzene**

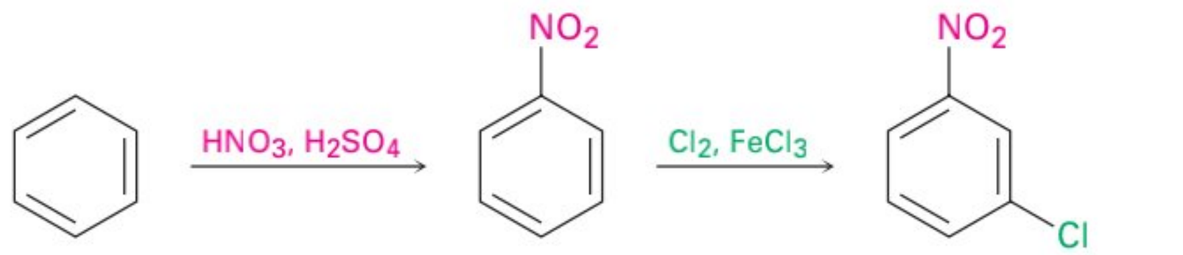
There are two substituents on the ring, a –Cl group, which is ortho- and para-directing, and an $-NO_2$ group, which is meta-directing. We can't nitrate chlorobenzene because the wrong isomers (*o*- and *p*-chloronitrobenzenes) would result, but chlorination of nitrobenzene should give the desired product.



Chlorobenzene **Nitrobenzene** ***m*-Chloronitrobenzene**

"What is an immediate precursor of nitrobenzene?" Benzene, which can be nitrated.

Solution We've solved the problem in two steps:

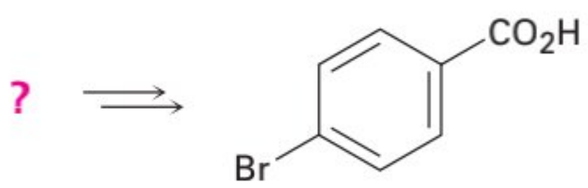


Benzene **Nitrobenzene** ***m*-Chloronitrobenzene**

Worked Example 5.6 Synthesizing a Substituted Aromatic Compound

Synthesize *p*-bromobenzoic acid starting from benzene.

Strategy Work backward by first asking, "What is an immediate precursor of *p*-bromobenzoic acid?"

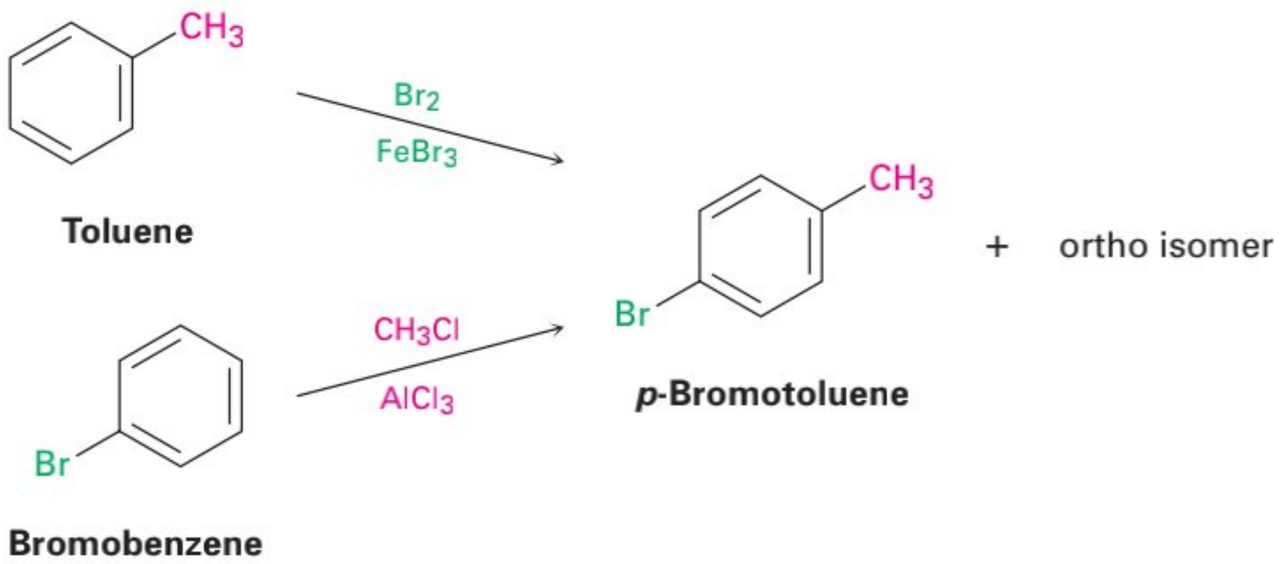


***p*-Bromobenzoic acid**

There are two substituents on the ring, a $-CO_2H$ group, which is meta-directing, and a –Br atom, which is ortho- and para-directing. We can't brominate benzoic acid because the wrong isomer (*m*-bromobenzoic acid) would be formed. We've seen, however, that oxidation of alkylbenzene side chains yields benzoic acids. An immediate precursor of our target molecule might therefore be *p*-bromotoluene.

***p*-Bromotoluene** ***p*-Bromobenzoic acid**

"What is an immediate precursor of *p*-bromotoluene?" Perhaps toluene, because the methyl group would direct bromination to the ortho and para positions, and we could then separate isomers. Alternatively, bromobenzene might be an immediate precursor because we could carry out a Friedel–Crafts alkylation and obtain the para product. Both methods are satisfactory.



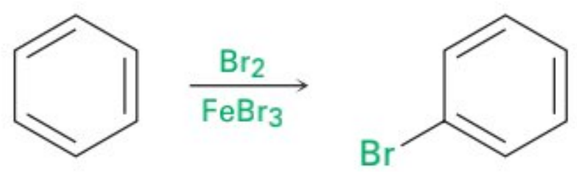
Toluene ***p*-Bromotoluene**

Bromobenzene

"What is an immediate precursor of toluene?" Benzene, which can be methylated in a Friedel–Crafts reaction.

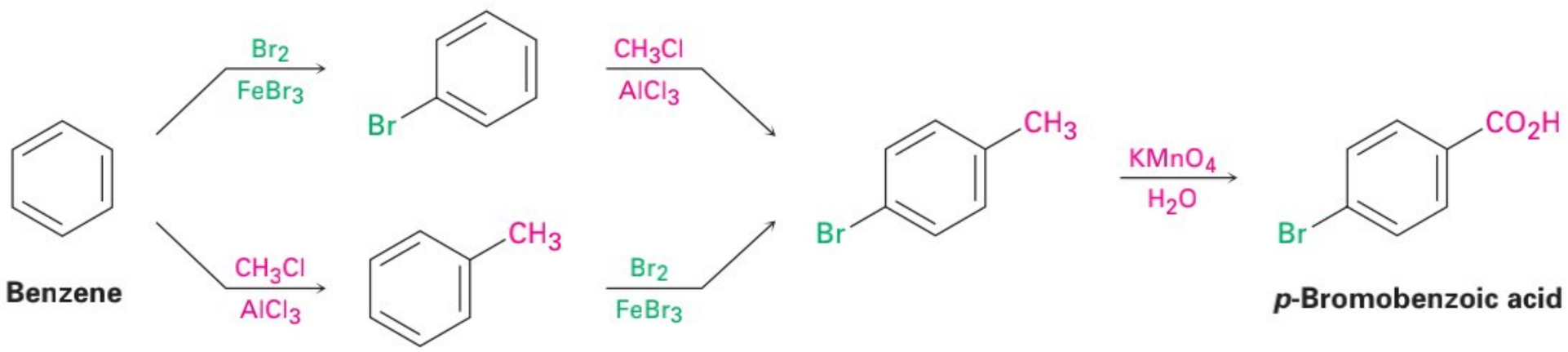
Benzene **Toluene**

"Alternatively, what is an immediate precursor of bromobenzene?" Benzene, which can be brominated.

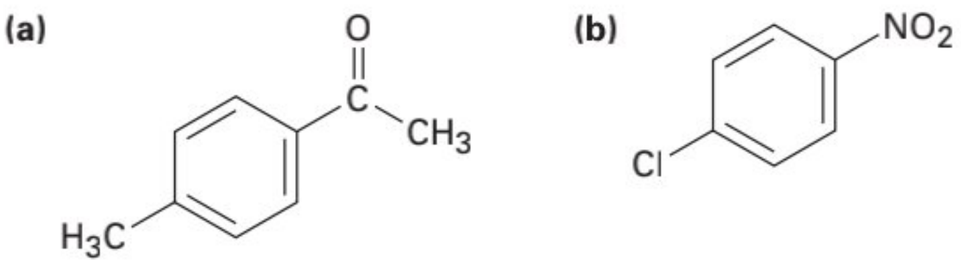


Benzene **Bromobenzene**

Solution Our backward synthetic (*retrosynthetic*) analysis has provided two workable routes from benzene to *p*-bromobenzoic acid.



Problem 5.18 Propose syntheses of the following substances starting from benzene:



Problem 5.19 Synthesize the following substances from benzene:

(a) *o*-Bromotoluene **(b)** 2-Bromo-1,4-dimethylbenzene

Problem 5.20 How would you prepare the following substance from benzene? (Yellow-green = Cl.)