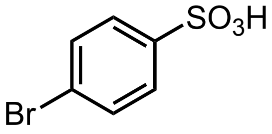
Retrosynthesis of Benzene Derivatives

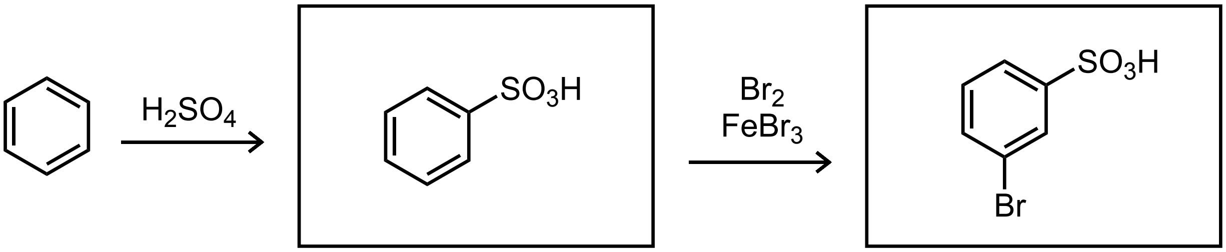
1. Only one of the strategies below is successful in creating the target final product.



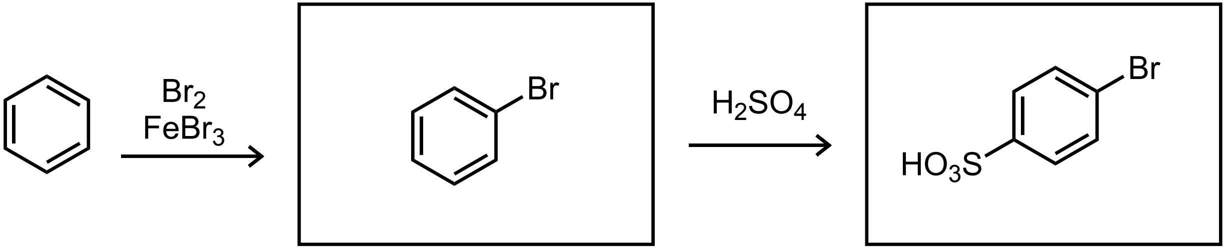
target product

A. **Provide the products** in each scheme below.

Strategy 1



Strategy 2



B. **Which strategy** forms the desired product?

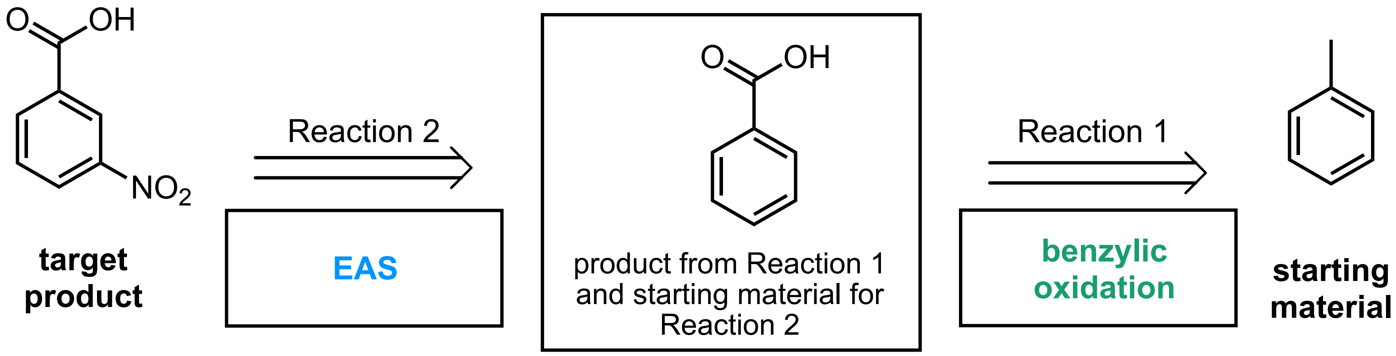
Only **strategy 2** forms the desired product

C. In words, **why does the other scheme not work** for forming our desired product?

In Strategy 1, sulfonation is perfomed first. However, the sulfonate group is a meta director. This causes the bromine to be installed at the incorrect position in the second reaction.

Note: Depending on the resource referenced, the sulfonation reaction conditions may be listed as any of the following:
H_2SO_4
SO_3 and H_2SO_4
Fuming sulfuric acid

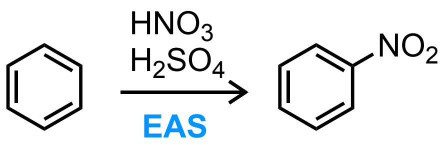
2. **Perform a retrosynthetic analysis** on the target product using the template and guiding questions, labeled as parts A-E.

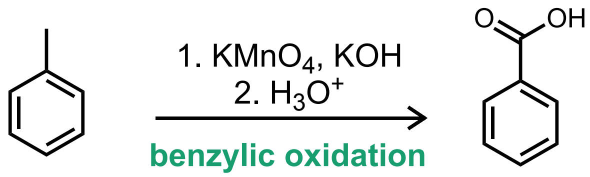


A. What **new functional groups** are present?
B. What is the **relationship** of the new groups (*ortho, meta,* or *para*)?
C. What are the **directing effects** of the new groups (*o*/*p*-director or *m*-director)?

If we consider our first three questions, we see that (A) we have a **carboxylic acid** and a **nitro** group; (B) the two new groups are **meta** to each other; and (C) **both** are *m*-directors.

D. **What types of reactions** (e.g. EAS, NAS, benzylic reactions, oxidation, reduction) could introduce those functional groups?

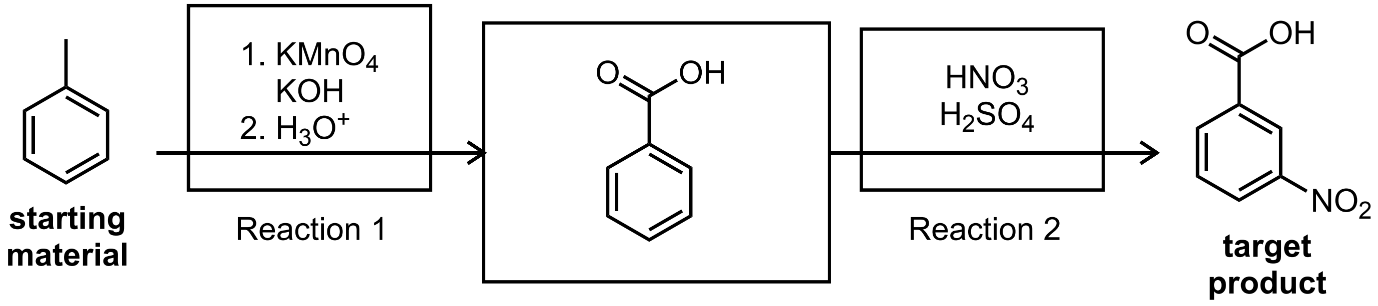




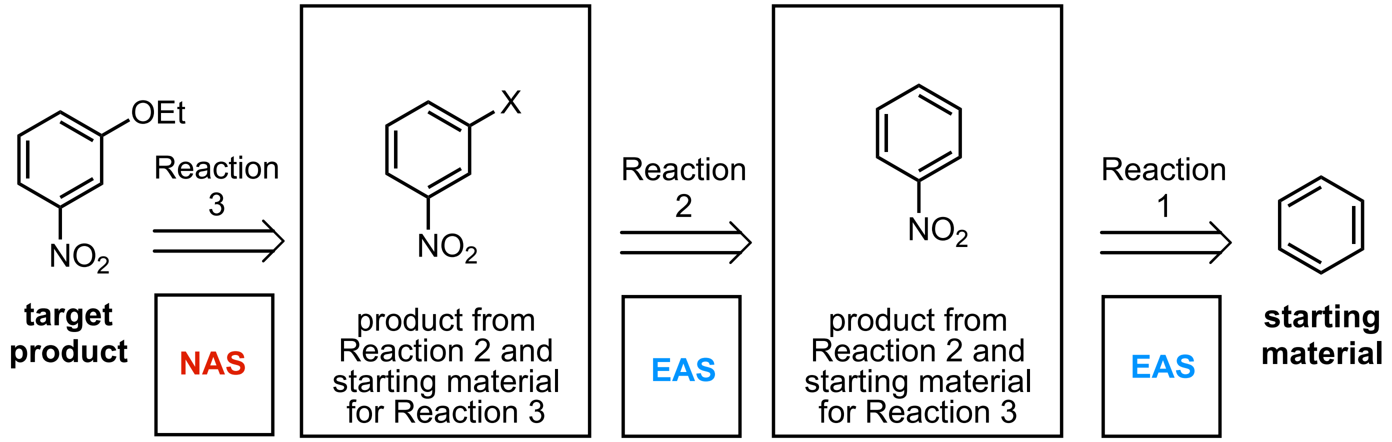
E. Finally, what order of these reactions is needed to achieve the desired relationship?

To achieve the meta relationship, oxidation at the benzylic position must take place prior to the nitration.

Finally, use the answers to the questions above to **propose the full forward synthesis** associated with your proposed retrosynthesis.



3. Perform a retrosynthetic analysis on the target final product using the template and guiding questions, labeled as parts a-e.



A. What **new functional groups** are present?
B. What is the **relationship** of the new groups (*ortho, meta,* or *para*)?
C. What are the **directing effects** of the new groups (*o*/*p*-director or *m*-director)?

If we consider our first three questions, we see that (A) we have an ethoxy group (ether) and a **nitro** group; (B) the two new groups are **meta** to each other; and (C) the **ethoxy group is an *o/p*-director** whereas the **nitro gorup is a *m*-director.**

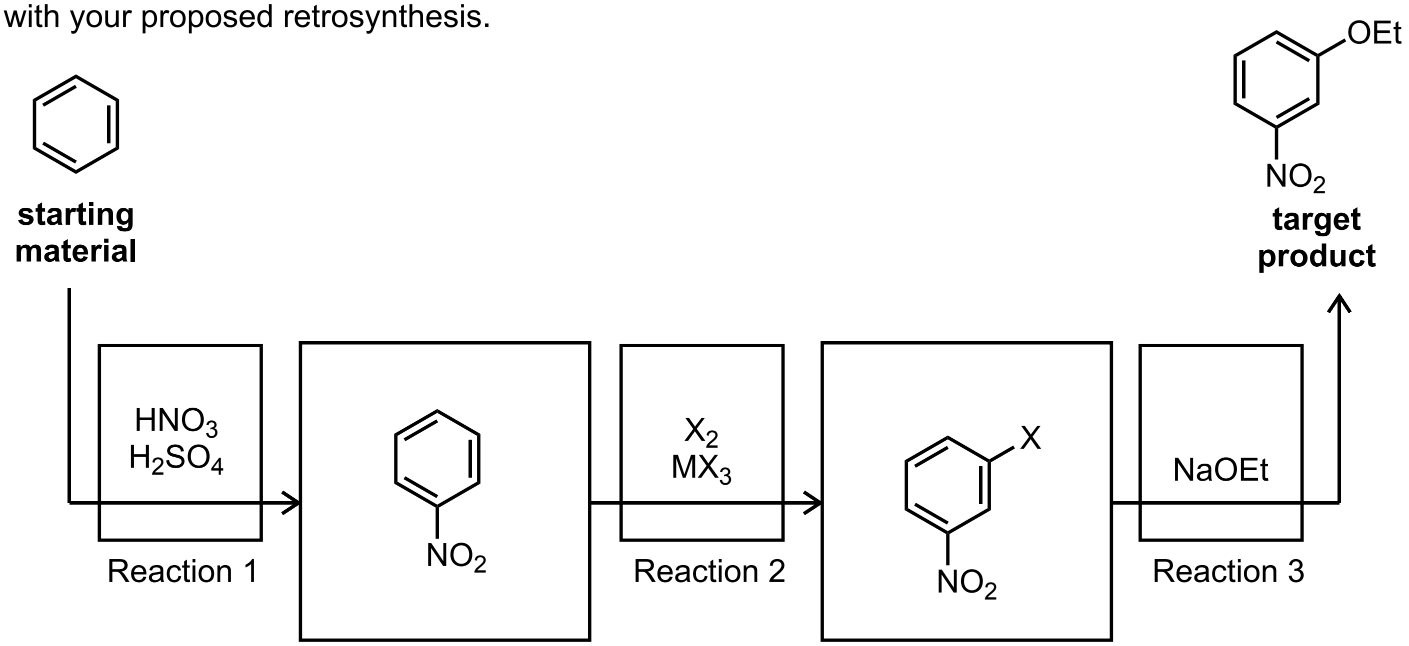
D. **What types of reactions** (e.g. EAS, NAS, benzylic reactions, oxidation, reduction) could introduce those functional groups?

Ethoxy can be added through NAS with a halide leaving group. Nitro can be added through EAS.

E. Finally, what order of these reactions is needed to achieve the desired relationship?

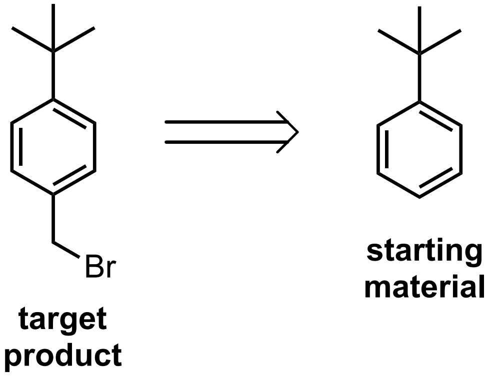
To obtain the meta relationship, we must first nitrate the ring, then do a halogenation. Following this, an NAS reaction will provide the desired product.

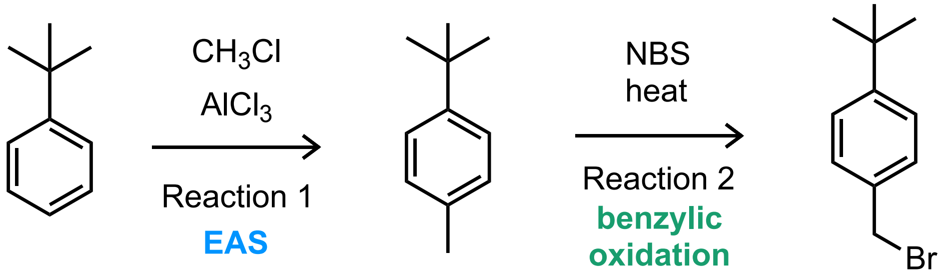
Finally, use the answers to the questions above to **propose the full forward synthesis** associated with your proposed retrosynthesis.



4. Propose a successful forward synthetic route for the formation of the shown target final product from the shown initial starting material.

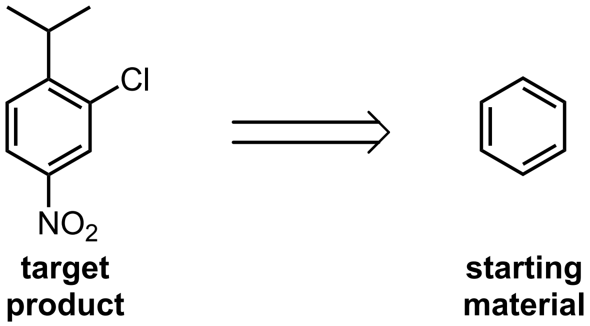
Hint: You **cannot** install the bromine through a Friedel-Crafts reaction. Instead, you must use a benzylic reaction!





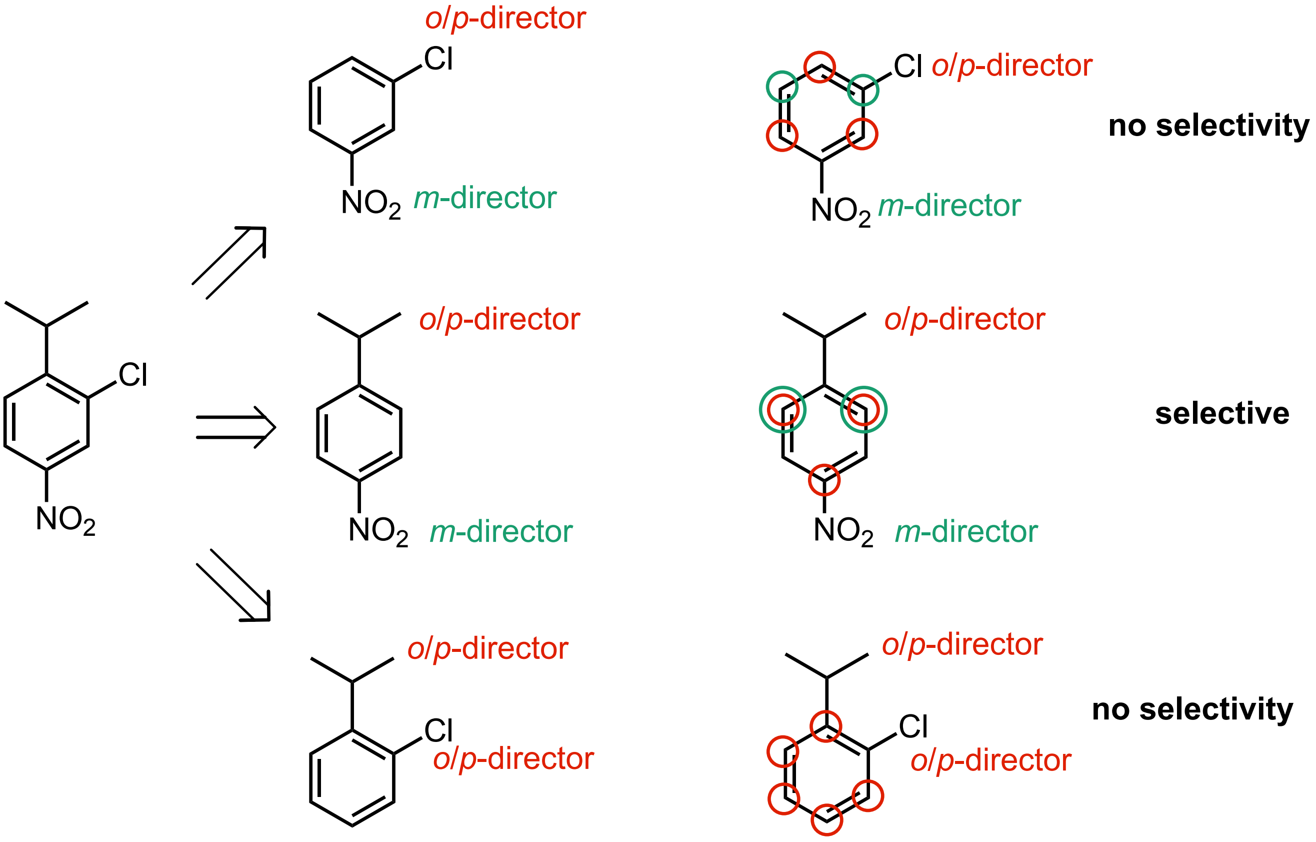
5. Propose a successful forward synthetic route for the formation of the shown target final product from the shown initial starting material.

Hint: This is a more complex tri-substituted product. Utilizing a retrosynthetic analysis of thinking "backwards", consider this question: **Which functional group had to be incorporated last?**

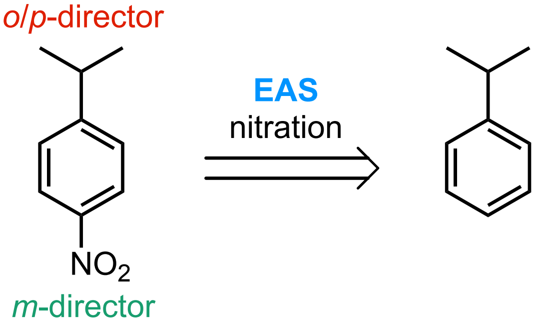


There are three possible options that could be considered for the last reaction of the sequence.

Where would these groups direct the last EAS reaction?



Then,



Therefore,