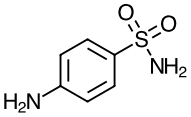
Objective 8. Understand electrophilic aromatic substitution reactions (EAS) of disubstituted and polysubstituted aromatics
Practice Problem solutions

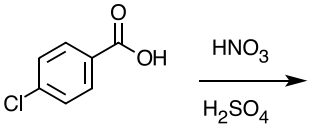
Key ideas: Some groups activate ring, others deactivate ring. Draw resonance structures of carbocation intermediate to ID most stable to determine product.

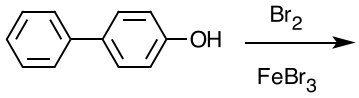
0. Aromatic compounds with multiple substituents undergo EAS reactions. The ***more activating*** group directs the position of substitution.
Rank the groups from most to least activating: Cl, OCH_3, COOH, $COCH_3$, $OCOCH_3$, NH_2, NO_2.
Most activating: NH_2 > OCH_3 = $OCOCH_3$ > Cl > COOH = $COCH_3$ > NO_2 (least activating)
1. a. Sulfanilamide is an antibiotic. Which group directs EAS?



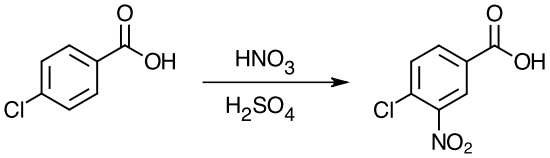
Answer: NH_2

b. For each reaction, identify the group that directs EAS. Then, predict the product.

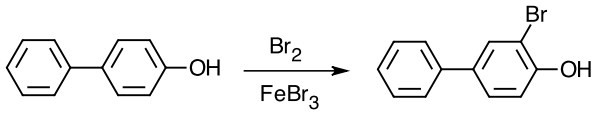




Answer:

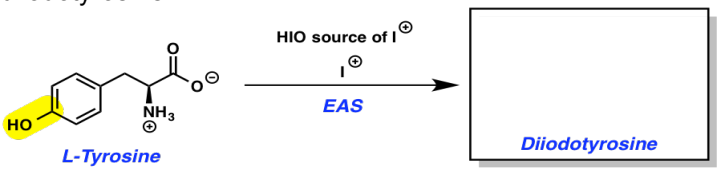


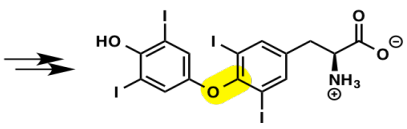
Cl is stronger activating group than COOH. Cl is a o, p director.



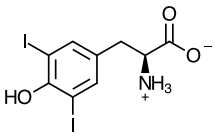
The ring of the right is where EAS occurs because the strongly activating OH group makes the pi electrons more Nu:$^-$. OH is stronger activating group than C_6H_5. OH is a o, p director.

c. From LearnBacon.com: Iodine is an essential nutrient. Iodine deficiency leads to goiter, which occurs because thyroxine (thyroid hormone) cannot be generated without iodine. Which group directs EAS? Draw the structure of diiodotyrosine.



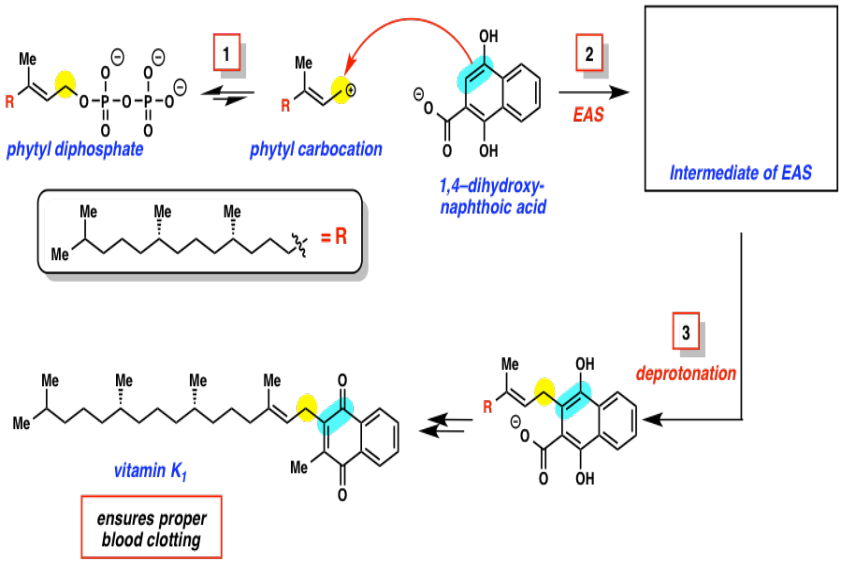


Answer: OH directs EAS because it is a stronger activating group than the $CH_2CH(NH_3^+)COO^-$ group. OH is a o,p director.

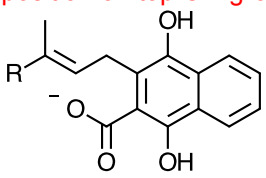


diiodotyrosine

d. From LearnBacon.com: biosynthesis of Vitamin K. Which group directs EAS? Draw the structure of Intermediate.

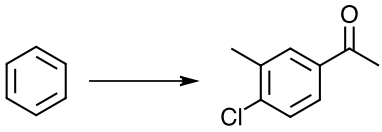


Answer: The strongly activating OH group directs EAS in the o,p positions. There are two OH groups but only one ortho position on top OH group where EAS occurs.



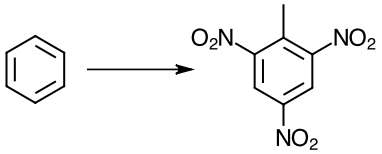
2. Synthesis: The order in which substituents are introduced onto a benzene ring requires **planning** due to o, p or m directing effects.

a. Propose a synthesis:



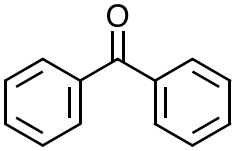
Answer: Most activating group: CH_3 (o,p director) > Cl (o,p director) > $COCH_3$ (m director)
If CH_3 group is substituted first, the ketone group will not substitute in the m position.
If ketone group is substituted first, the Cl group will not substitute in the p position.
So Cl first (Cl_2 /$AlCl_3$), followed by ketone (CH_3COCl/ $AlCl_3$) [Cl still directs EAS], followed by R group (CH_3Cl/ $AlCl_3$).
If So Cl first (Cl_2 /$AlCl_3$), followed by R group, the R group directs EAS, and the ketone group will substitute ortho or para to the R group.

b. Propose a synthesis of TNT (explosive):

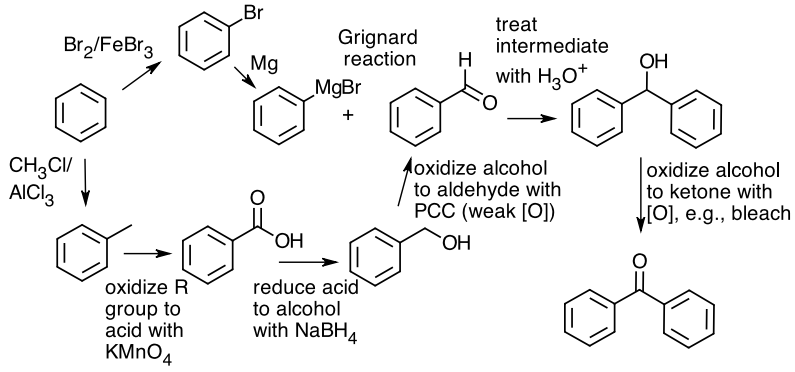


Answer: R group is more activating group than NO_2 group. Each NO_2 group is ortho and para to R group.
So R group (CH_3Cl/ $AlCl_3$) first followed by NO_2 group (HNO_3/H_2SO_4 in excess).

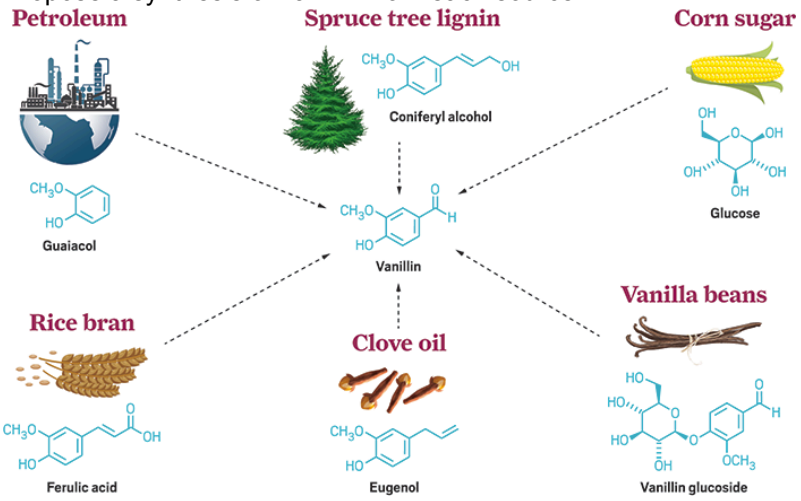
c. Benzophenone (shown below) is added to plastic packaging as a UV blocker to prevent photo-degradation of the plastic polymer. Propose a synthesis of benzophenone from benzene. Hint: make bromobenzene and benzyl alcohol.



Answer: Have to make a C-C bond so use Grignard reaction (RMgX + aldehyde/ketone) or acetylide ion ($HCC:^-$).



d. Vanilla is used in many foods from ice cream to cookies. There is a vanilla shortage! (http://cen.acs.org/articles/94/i36/problem-vanilla.html)
Propose a synthesis of vanillin from each source.



Answer: You can choose one of these reactions, except for guaicol to vanillan, for your Biology/Industrial Reactions project.
Guaicol --> vanillan: OH directs EAS. 1. Substitute R group ($CH_3Cl/ AlCl_3$) para to OH. 2. Oxidize R group to acid ($KMnO_4$). 3. Reduce acid to alcohol ($NaBH_4$). 4. Oxidize alcohol to aldehyde with PCC (weak [O] agent).
Here is a few possible steps for Coniferyl alcohol ---> vanillan: convert side chain to aldehyde group. 1. Convert C=C bond to C-C with H_2/Pd catalyst. The C=C bonds in ring are more stable and won't react with H_2 under these conditions. 2. Substitute OH in side chain for Br with HBr. 3. Br is good LG so do an elimination reaction to form C=C bond. 4.Convert C=C bond to ____. 5. Convert alkyl group to ____.
Ferulic acid --> vanillan:
eugenol ---> vanillan:
vanillan glucoside ---> vanillan:
glucose ---> vanillan. Convert glucose to vanillan glucoside.