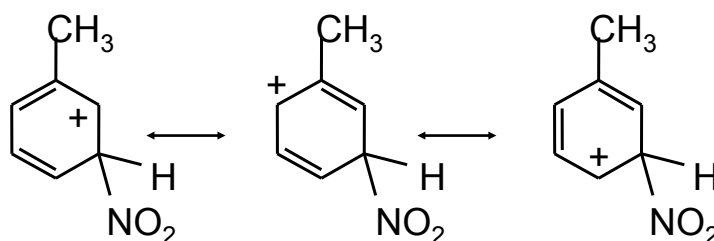


Lecture 12

More EAS

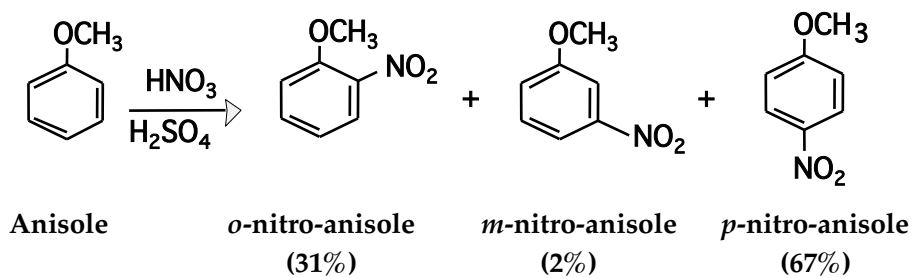


February 25, 2016

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Di- and Polysubstitution

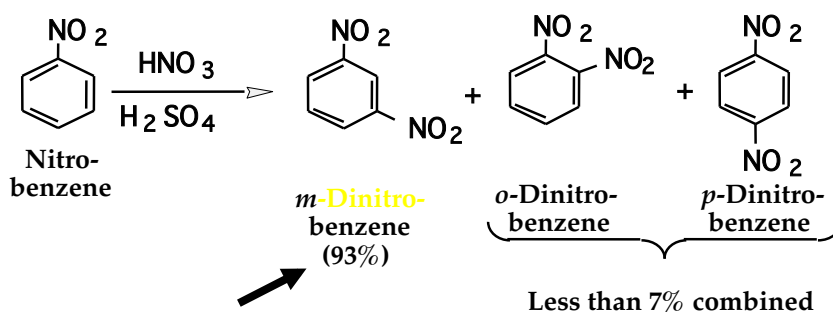


- -OCH₃ is ortho-para directing and activating

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Di- and Polysubstitution



- $-\text{NO}_2$ is meta directing and deactivating!

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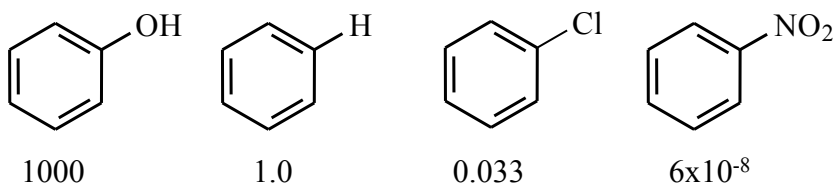
Di- and Polysubstitution

- Existing groups on a benzene ring influence further substitution in both orientation and rate
- Orientation:
 - certain substituents direct preferentially to ortho & para positions; others direct preferentially to meta positions
 - substituents are classified as either Ortho/para directing..... or meta directing
- Rate:
 - substituents are classified as
 - Activating – More reactive to further substitution
 - Deactivating – Less reactive to further substitution

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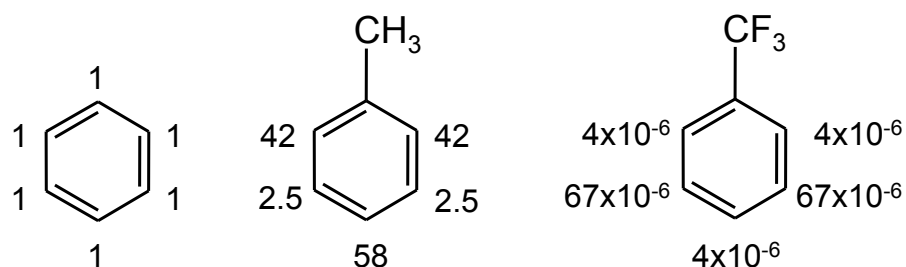
Relative rates of nitration



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Nitration: Partial Rate Factors





- All ring positions in toluene are more reactive than any position of benzene.
- Steric hindrance by the methyl group makes each ortho position slightly less reactive than para.
- All ring positions in trifluoromethylbenzene are less reactive than any position in benzene

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Effects of substitution on further electrophilic aromatic substitution

Ortho-Para Directing	Strongly activating	$-\ddot{\text{N}}\text{H}_2$	$-\ddot{\text{N}}\text{HR}$	$-\ddot{\text{N}}\text{R}_2$	$-\ddot{\text{O}}\text{H}$		Real Fast
	Moderately activating	$-\ddot{\text{N}}\text{HCR}$	$-\ddot{\text{N}}\text{HCAr}$	$-\ddot{\text{O}}\text{R}$	$-\ddot{\text{O}}\text{CR}$	$-\ddot{\text{O}}\text{CAr}$	Pretty fast
	Weakly activating	$-\text{R}$					Kinda slow
	Weakly deactivating	$-\ddot{\text{F}}:$	$-\ddot{\text{Cl}}:$	$-\ddot{\text{Br}}:$	$-\ddot{\text{I}}:$		
Meta Directing	Moderately deactivating	$-\overset{\text{O}}{\parallel}\text{CH}$	$-\overset{\text{O}}{\parallel}\text{CR}$	$-\overset{\text{O}}{\parallel}\text{COH}$	$-\overset{\text{O}}{\parallel}\text{COR}$	$-\overset{\text{O}}{\parallel}\text{CNH}_2$	Slow
	Strongly deactivating	$-\text{NO}_2$	$-\text{NH}_3^+$	$-\text{CF}_3$	$-\text{CCl}_3$	$-\overset{\text{O}}{\parallel}\text{SOH}$ $-\text{C}\equiv\text{N}$	Real Slow

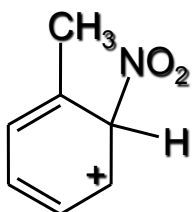
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Effect on Regioselectivity

- *Ortho-para directors* direct an incoming electrophile to positions ortho and/or para to themselves.
- *Meta directors* direct an incoming electrophile to positions meta to themselves.
- *All meta directors* are deactivating
- *All ortho-para directors* are activating except halogen
- For EAS, the rate-limiting step is attack of E^+ on the aromatic ring to form a resonance-stabilized cation intermediate



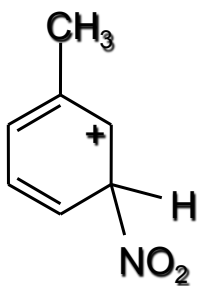
ortho Nitration of Toluene



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meta Nitration of Toluene

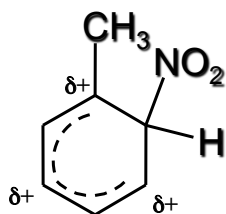


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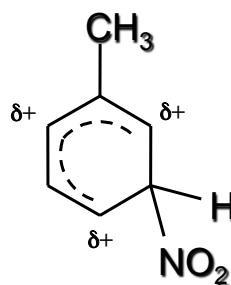


Comparison Ortho/Meta

Which is more stable?



ortho-



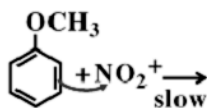
meta-

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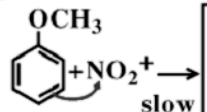


Adding a Second Substituent

meta attack



para attack

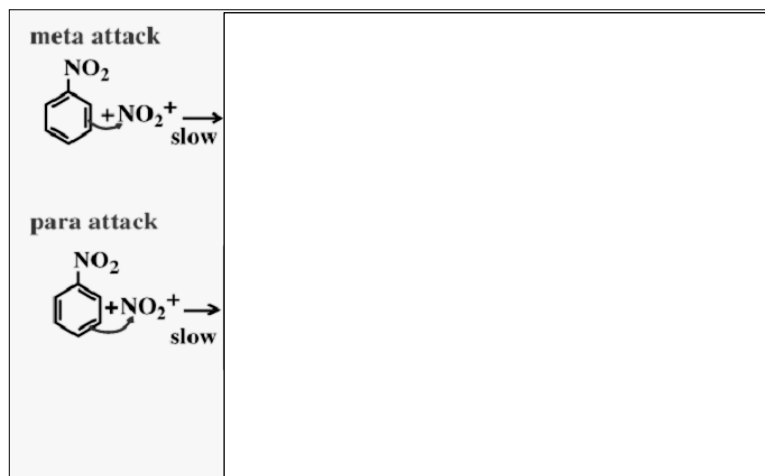


Methoxy is therefore an "o-p director"

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Adding a Second Substituent



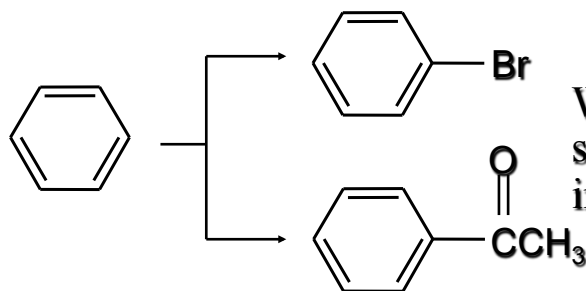
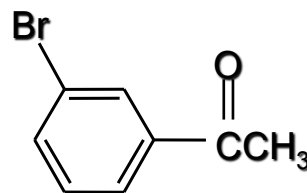
Nitro is therefore a "meta director"

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Synthesis of *m*-Bromoacetophenone

Order of introduction of substituents must be carefully designed to ensure correct orientation

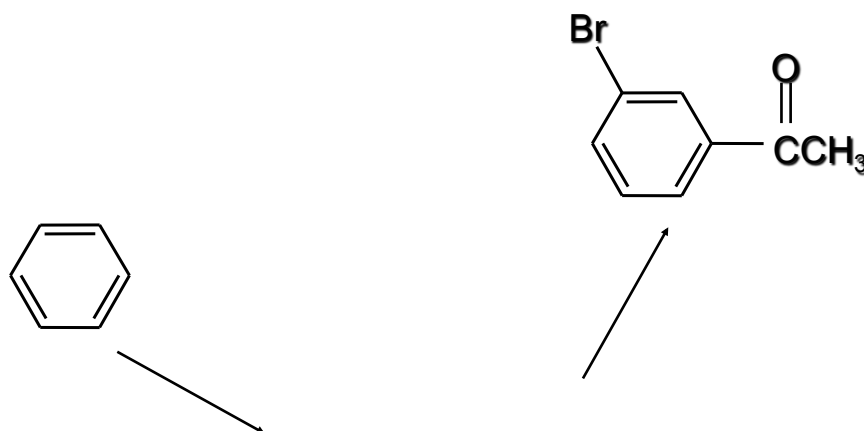


Which substituent should be introduced first?

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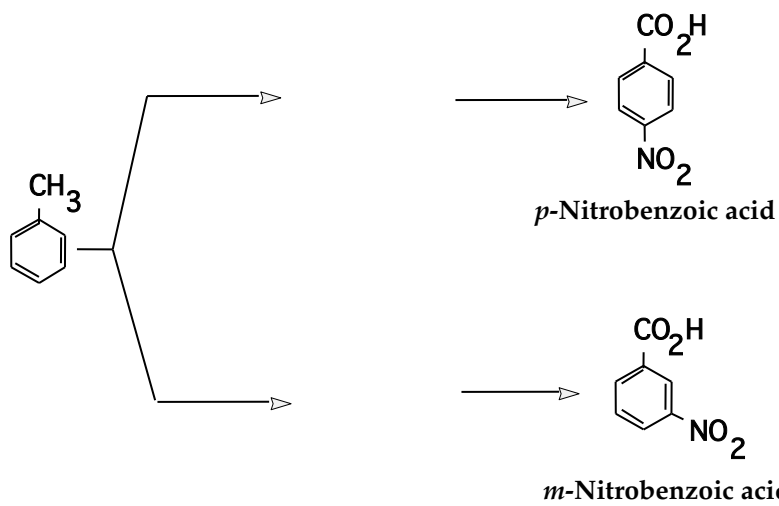
Synthesis of *m*-Bromoacetophenone



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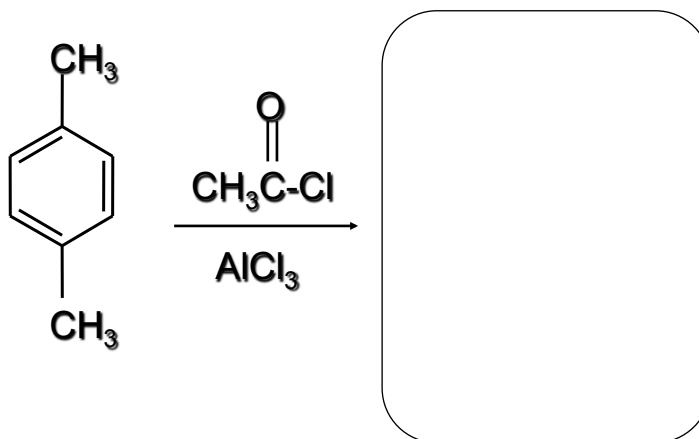
Di- and Polysubstitution



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*Multiple Substitution Effects:
The Simplest Case*

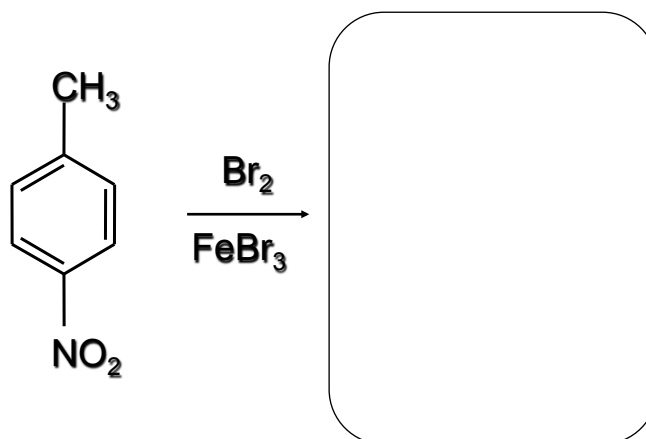


All possible EAS sites may be equivalent.

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Another Straightforward Case

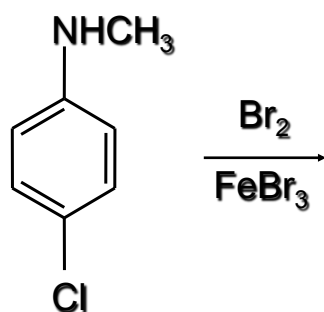


Directing effects of substituents reinforce each other.

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The "Best Man Wins"

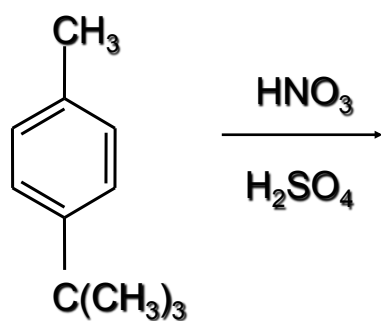


Regioselectivity is controlled by the most activating substituent

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When activating effects are similar...

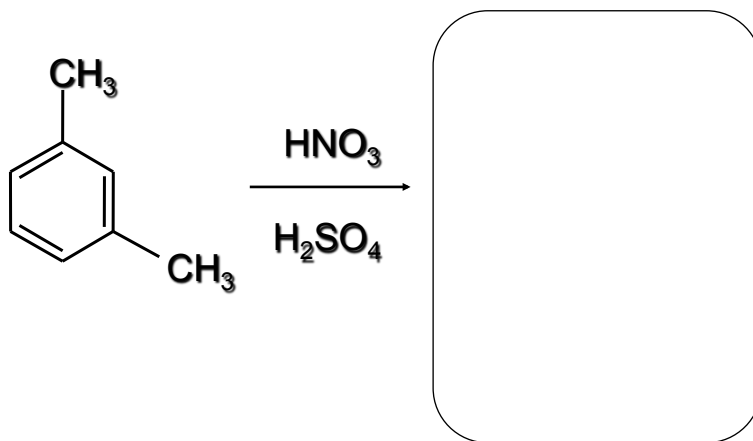


Sterics dominates when activating effects are similar

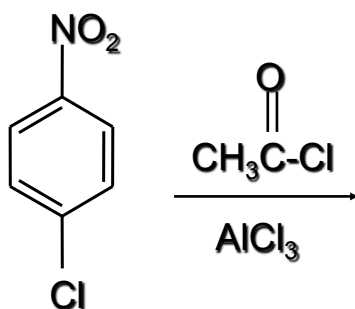
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Steric effects control regioselectivity when electronic effects are similar



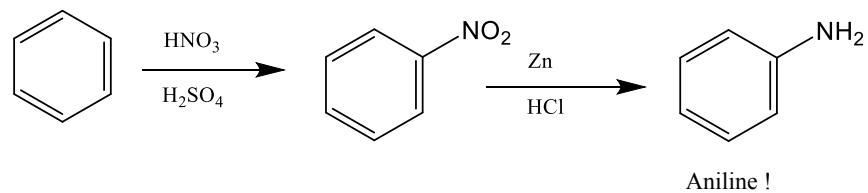
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Reduction of the Nitro Group

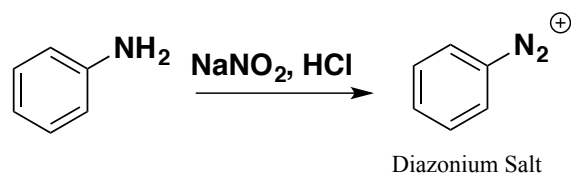


The Nitro group is easily reduced. Many reducing agents can be employed for this transformation including Sn or Fe in HCl, H_2 with Pd/C, etc

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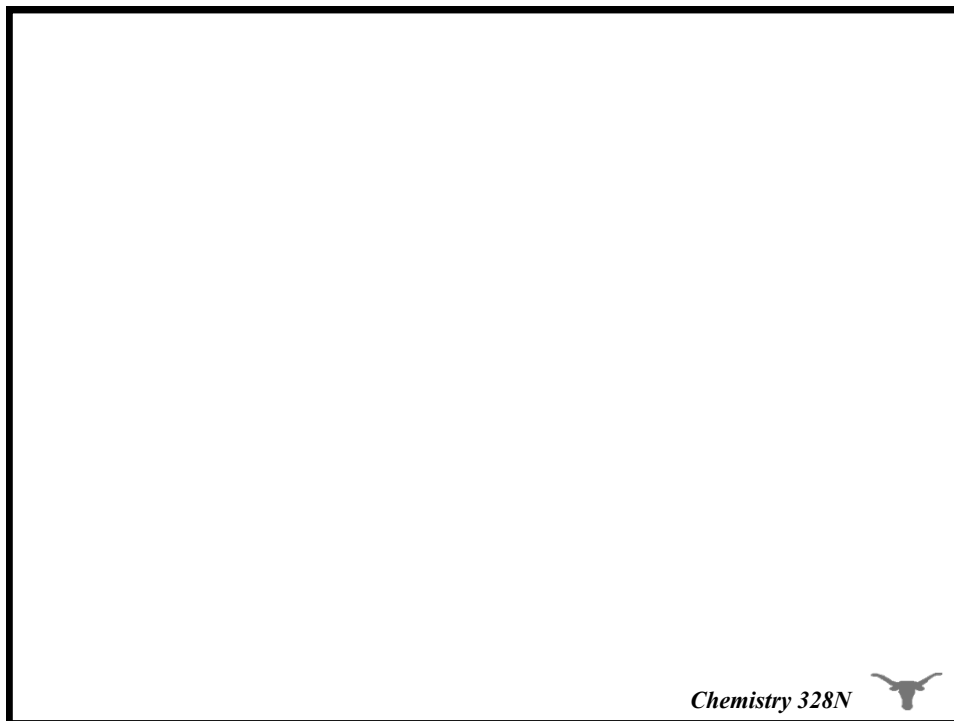


Diazonium Salts



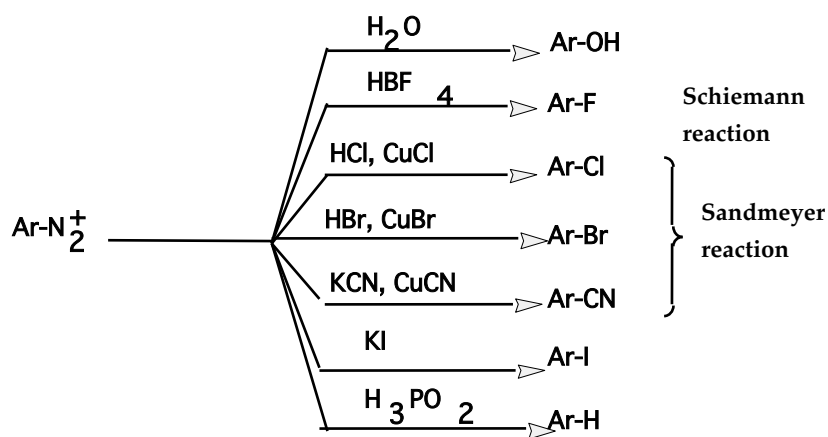
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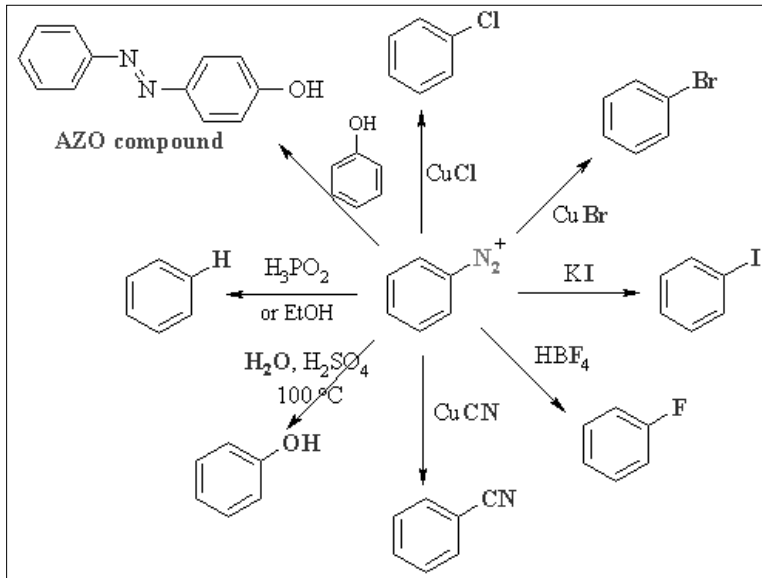


Diazonium Salts

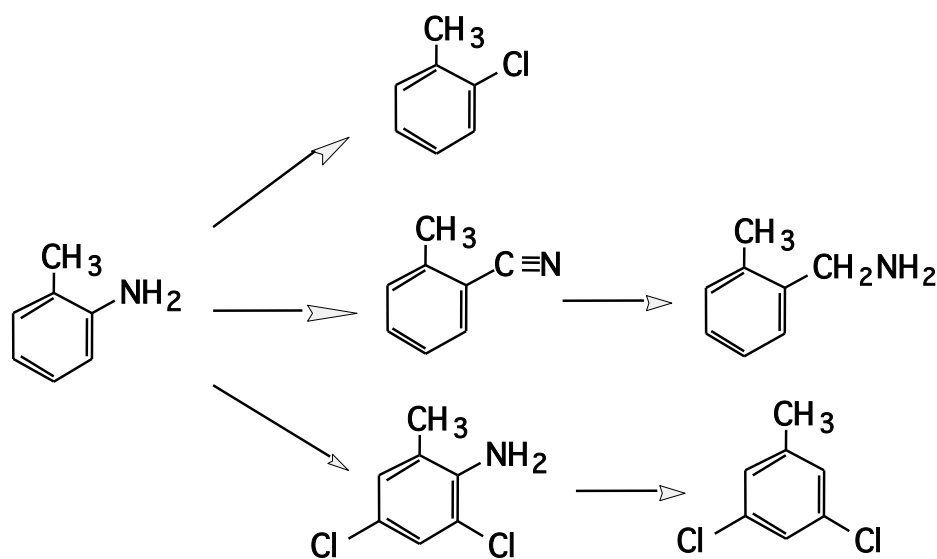
- The $-\text{N}_2^+$ group of an arenediazonium salt can be replaced in a regioselective manner by these groups



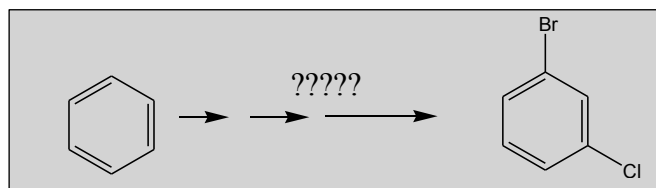
Reactions of Diazonium Salts




Practice Problems

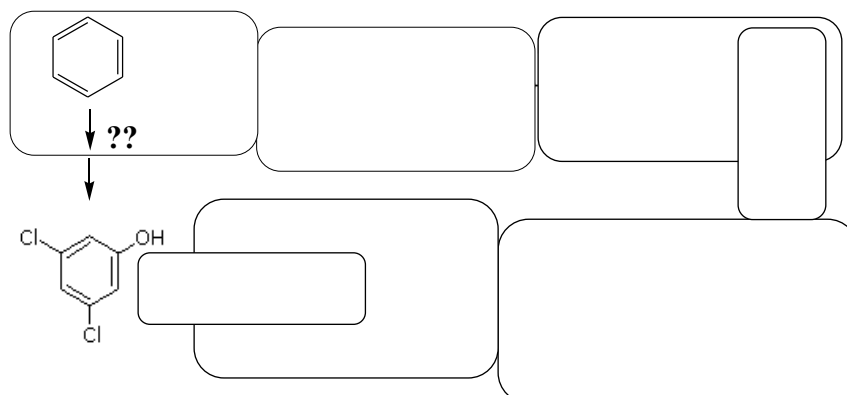


Practice...work backwards



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Synthesis Strategy



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