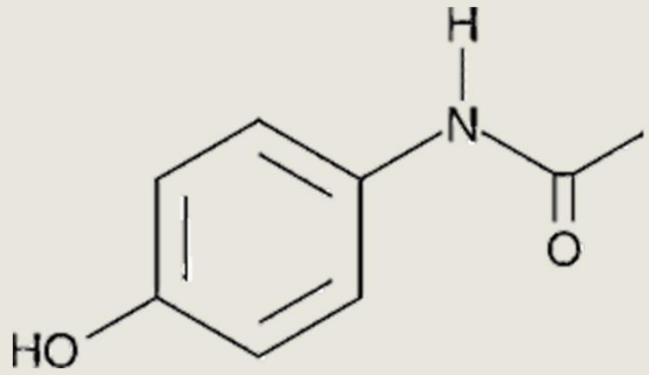
Synthesis of Acetaminophen Process Research

유기화학특강 1조

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1. Introduction: Green chemistry and Process chemistry
2. Synthesis 1: DDQ catalyzed process
3. Synthesis 2: Ar-X process
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1. Introduction: Green chemistry and Process chemistry



As members of pharmaceutical company, we are about to come up with new synthesis of **acetaminophen with low cost, and eco-friendly.**

Green Chemistry **&** **Process Chemistry**

We have to recall these concepts

1. Introduction: Green chemistry and Process chemistry

Green Chemistry

is an area of chemistry and chemical engineering focused on the design of products and processes **that minimize or eliminate the use and generation of hazardous substances.**

출처: https://en.wikipedia.org/wiki/Green_chemistry

1. Introduction: Green chemistry and Process chemistry

Process Chemistry is the arm of pharmaceutical chemistry about the **development and optimization of a synthetic scheme** to manufacture compounds for the drug development phase.

Material Cost

Conversion Cost

Ecoscale

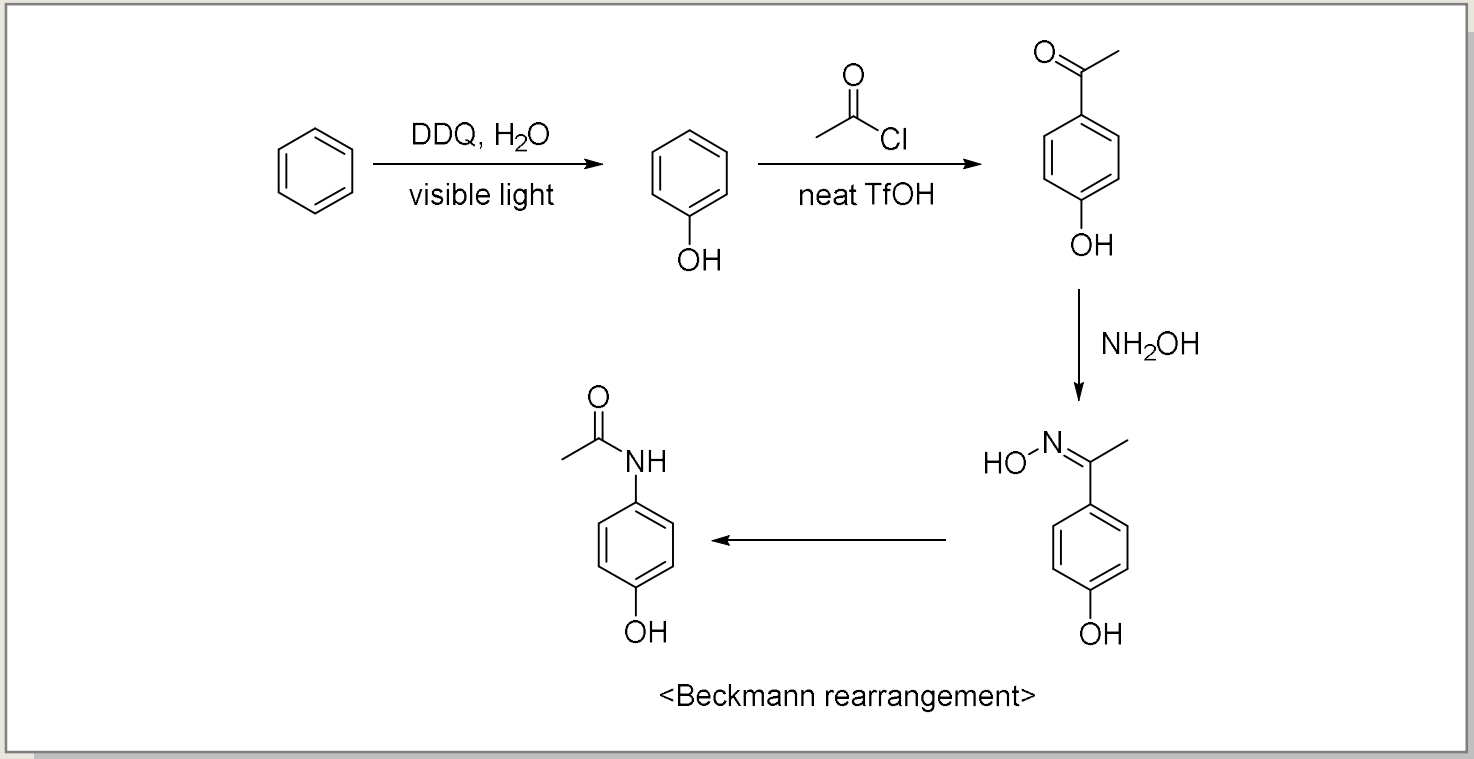
출처: https://en.wikipedia.org/wiki/Process_chemistry

Synthesis1. DDQ catalyzed process

Synthesis 1. DDQ catalyzed process

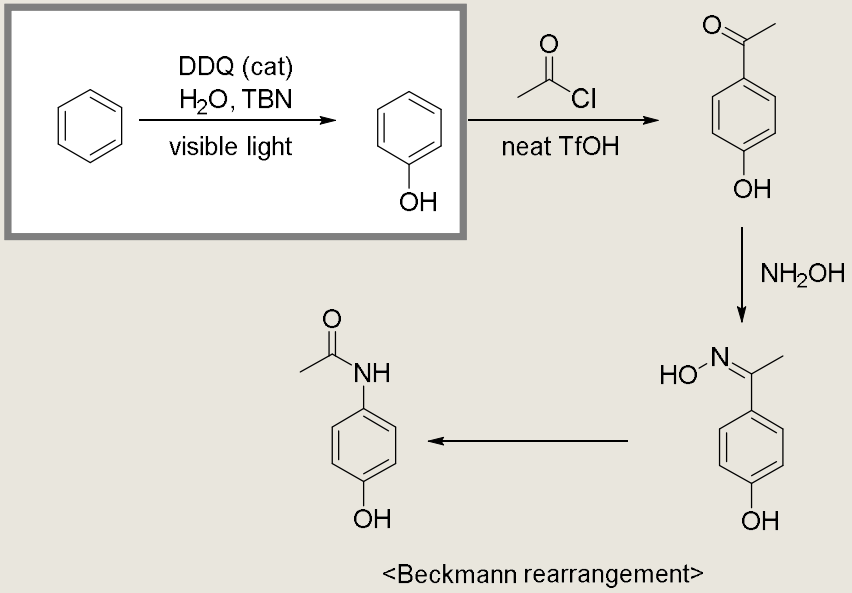
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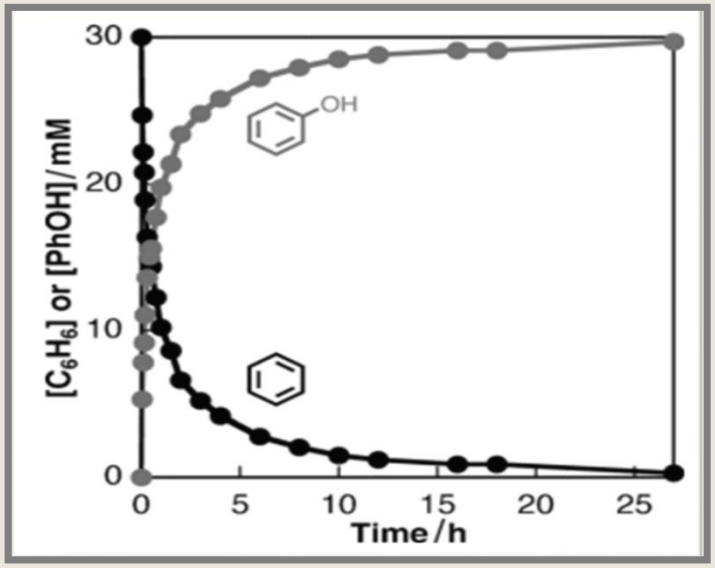


<Beckmann rearrangement>

Synthesis 1. DDQ catalyzed process



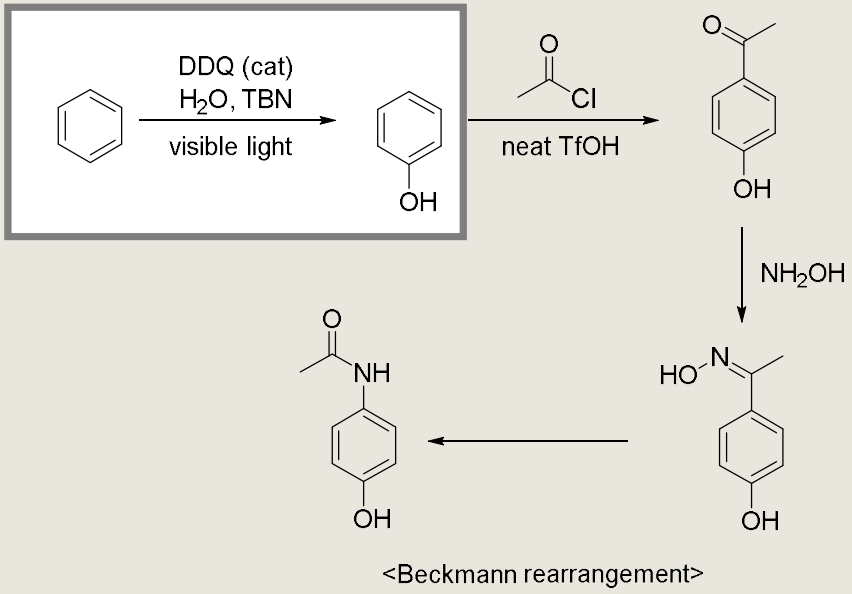
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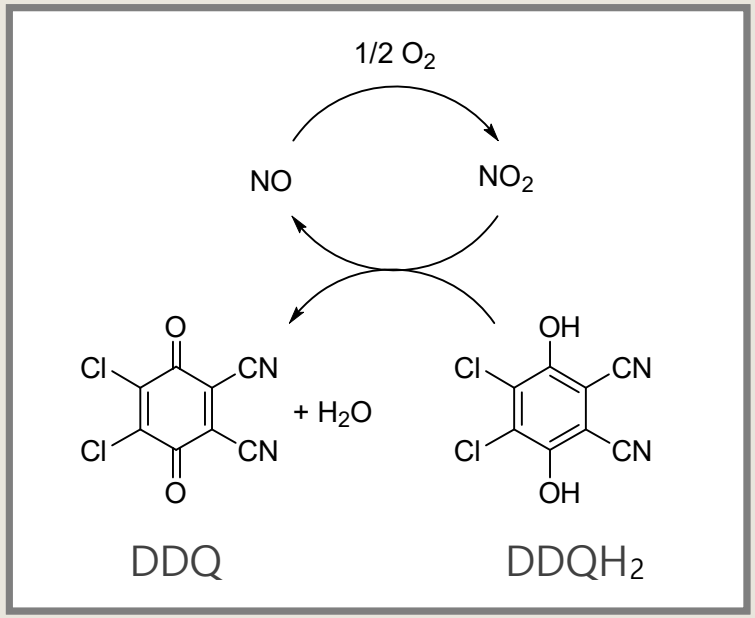
- Conversion of benzene : 98%
- Yield of phenol : 93%

Fukuzumi, S., & Ohkubo, K. (2015). One-Step Selective Hydroxylation of Benzene to Phenol. *Asian Journal of Organic Chemistry*, *4*(9), 836-845.

Synthesis 1. DDQ catalyzed process

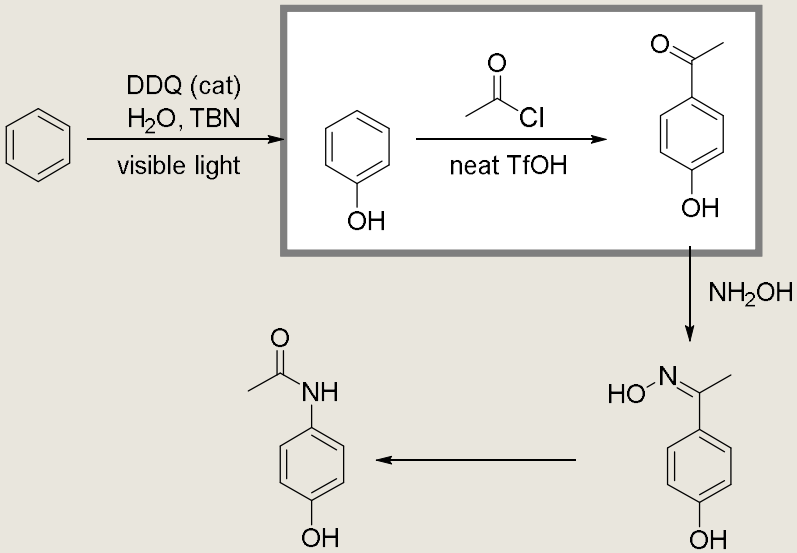


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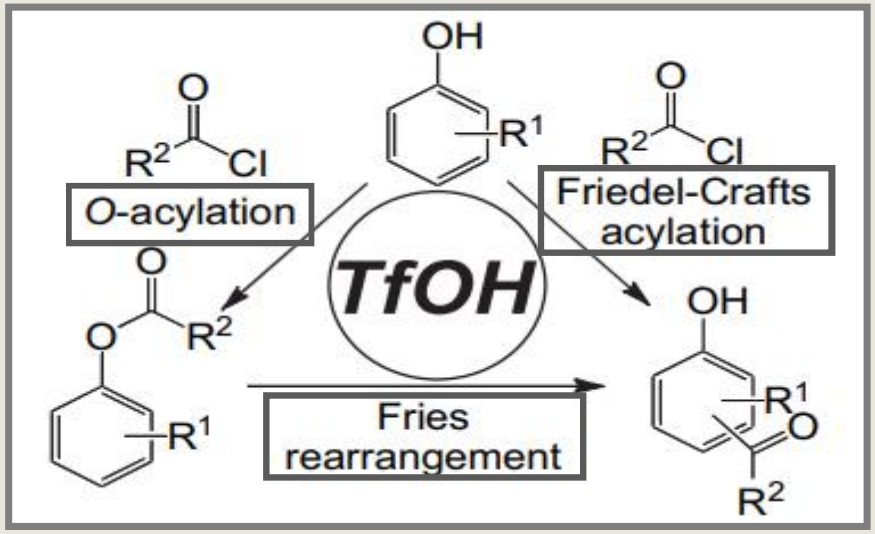


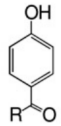
Fukuzumi, S., & Ohkubo, K. (2015). One-Step Selective Hydroxylation of Benzene to Phenol. *Asian Journal of Organic Chemistry*, *4*(9), 836-845.

Synthesis 1. DDQ catalyzed process



<Beckmann rearrangement>

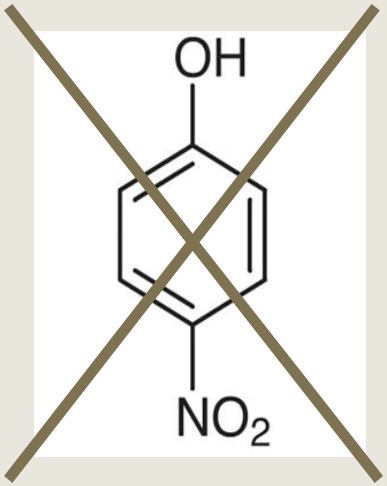


Phenol	RCOCl R=	Time (h)	Product	Yields (%)
Entry 1	CH_3	1		99
	C_2H_5	1		99
	n-C_3H_7	1		98
	n-C_4H_9	1		98
	n-C_5H_{11}	1		97
	n-C_6H_{13}	1		96
	n-C_9H_{19}	1		97
	C_6H_5	1		96

- yield : 99%

https://asset-pdf.scinapse.io/prod/1980862751/1980862751.pdf

Synthesis 1. DDQ catalyzed process





Advantages

- No p-Nitrophenol & No Metal
- Recyclable catalyst 'DDQ'
- High yield & conversion

Disadvantages

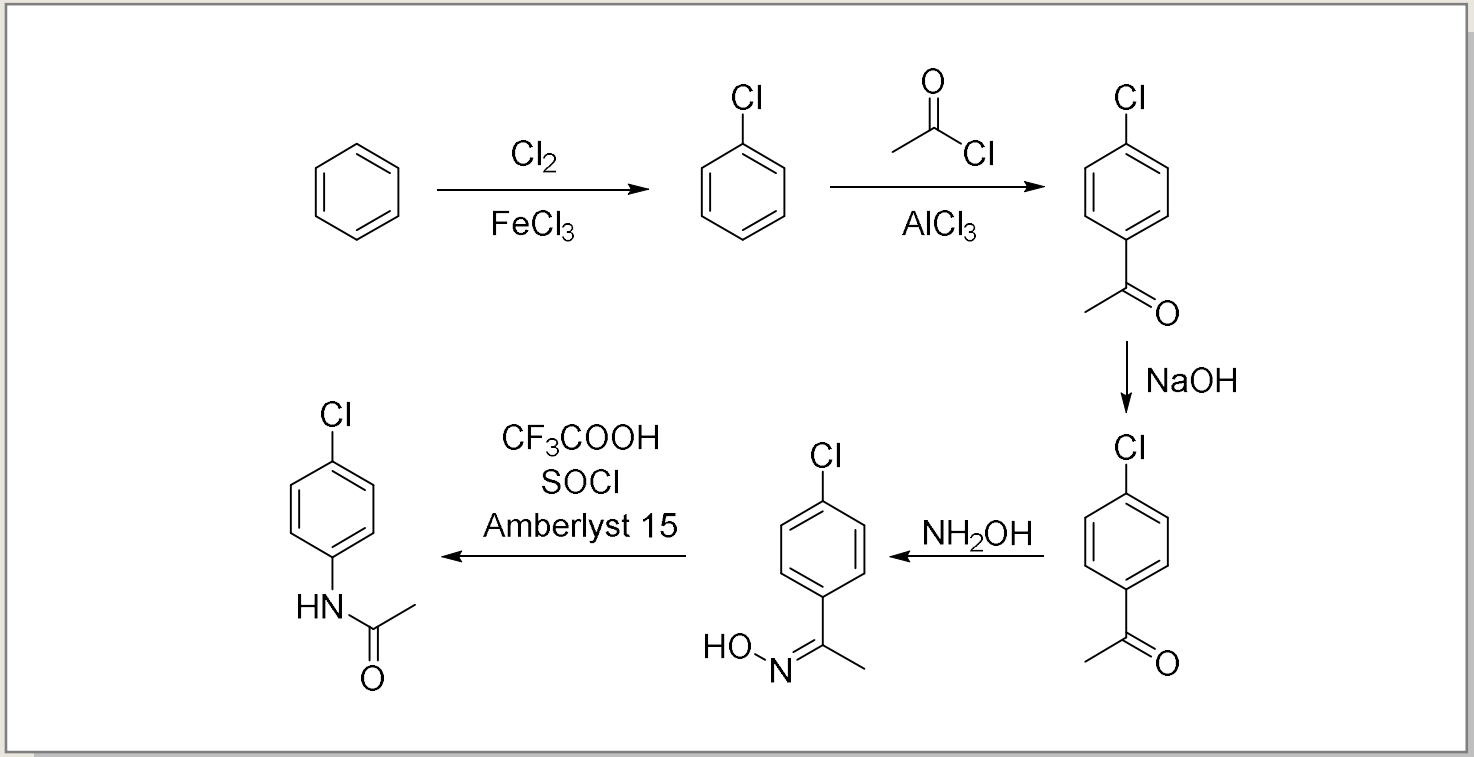
- DDQ : Benzene = almost 1 : 1
- DDQ 200,000₩ per 25g
- Excess of TfOH solvent

Synthesis2. Ar-X process

Synthesis 2. Ar-X process

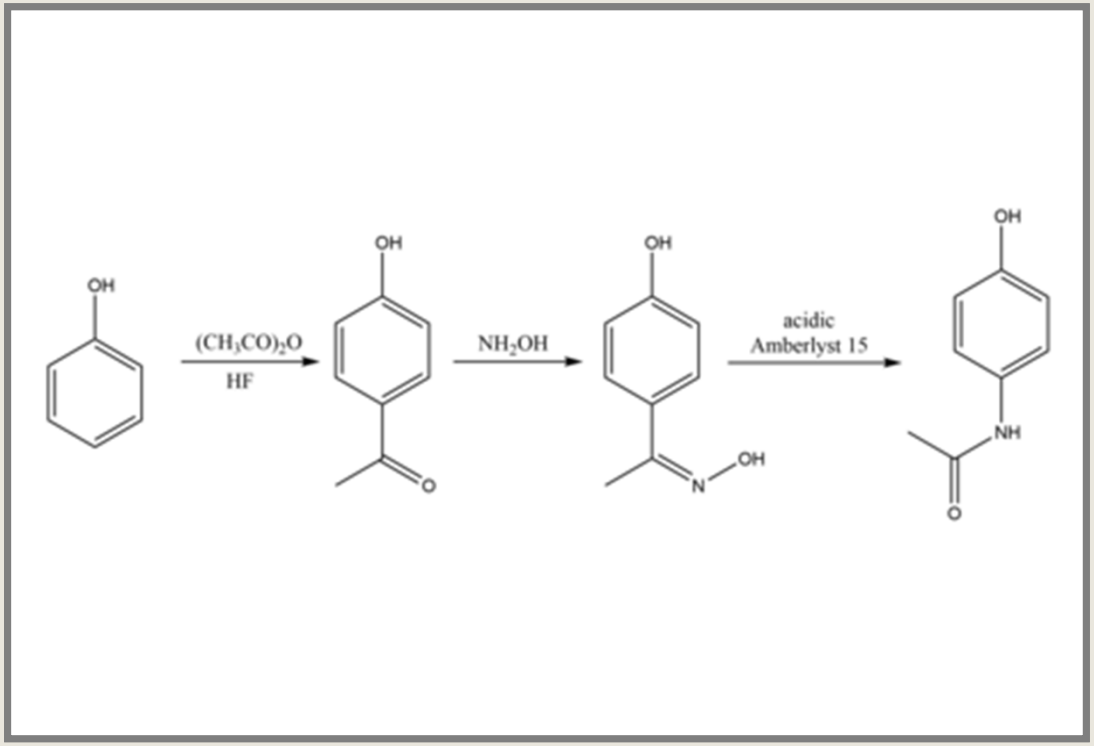
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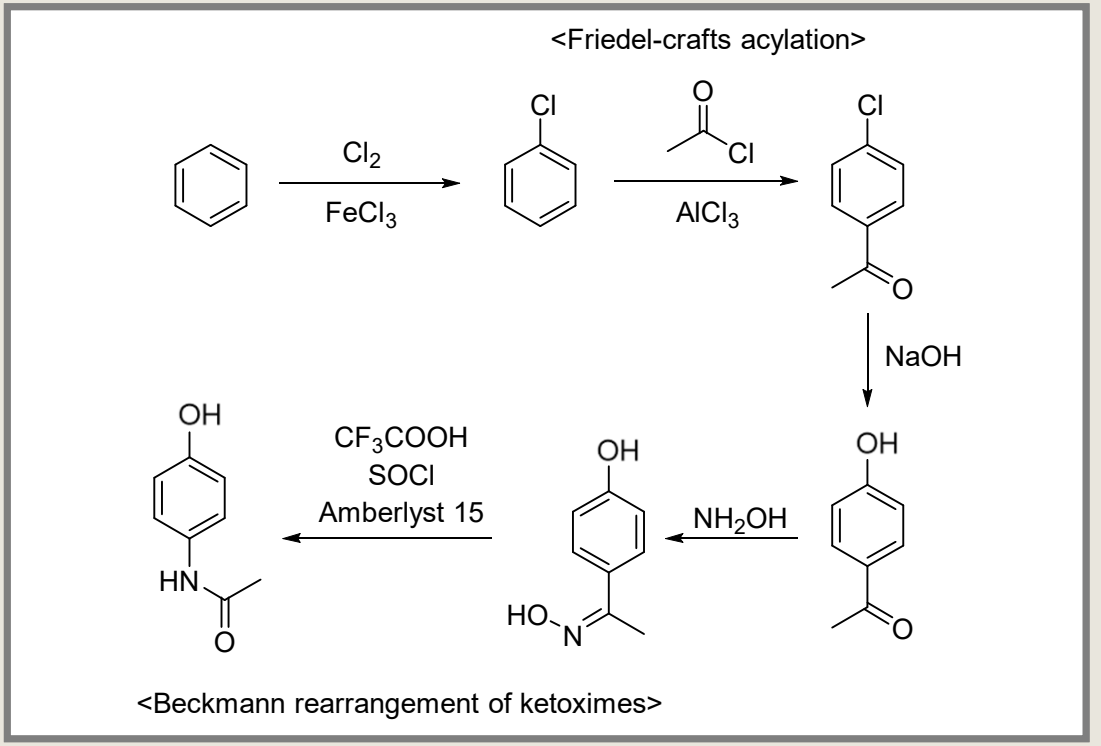


Synthesis 2. Ar-X process

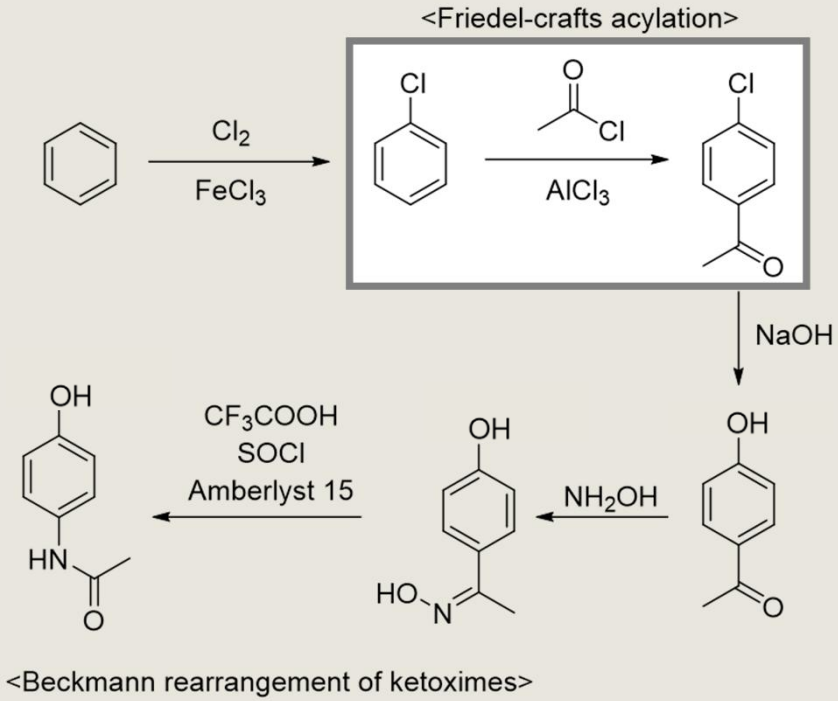
- Celanese synthesis

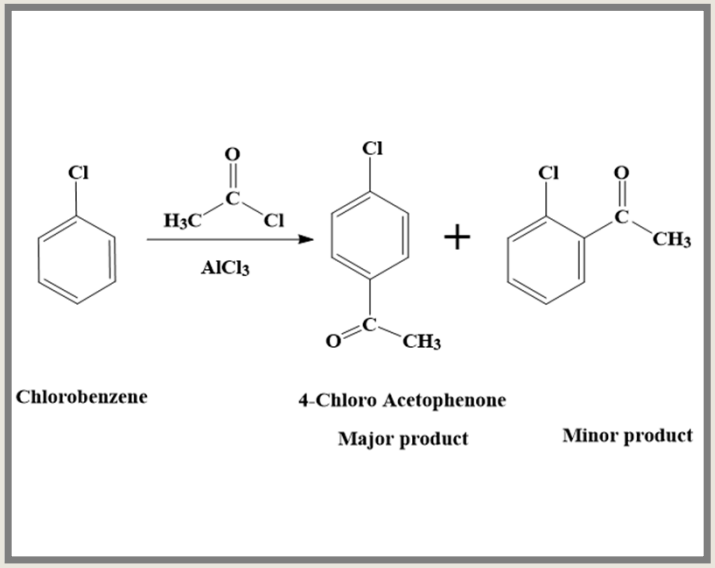


- Ar-X process



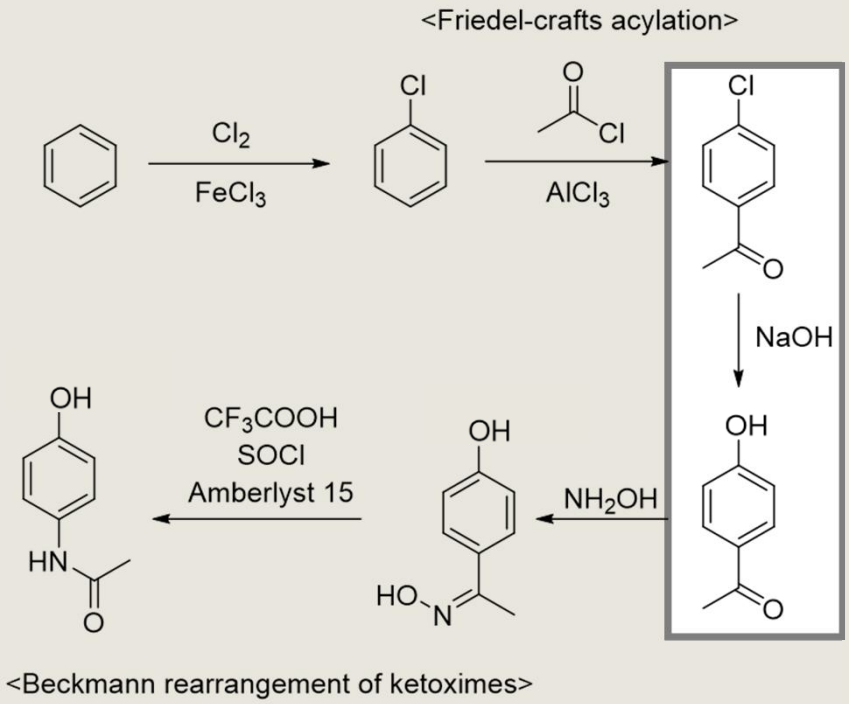
Synthesis 2. Ar-X process

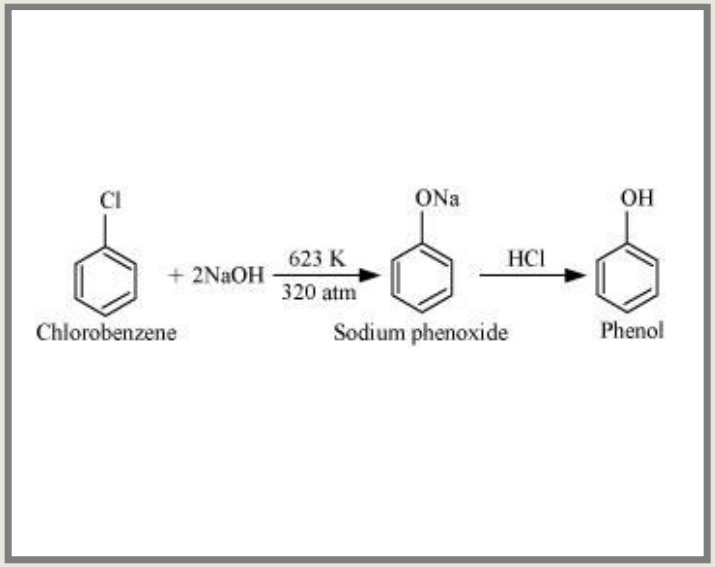




- Major product: p-Chloroacetophenone
- Minor product: o-Chloroacetophenone

Synthesis 2. Ar-X process





- Convert chloro benzene to phenol.

Synthesis 2. Ar-X process

Advantages

- Use well known synthesis
- Use the different substrates

Disadvantages

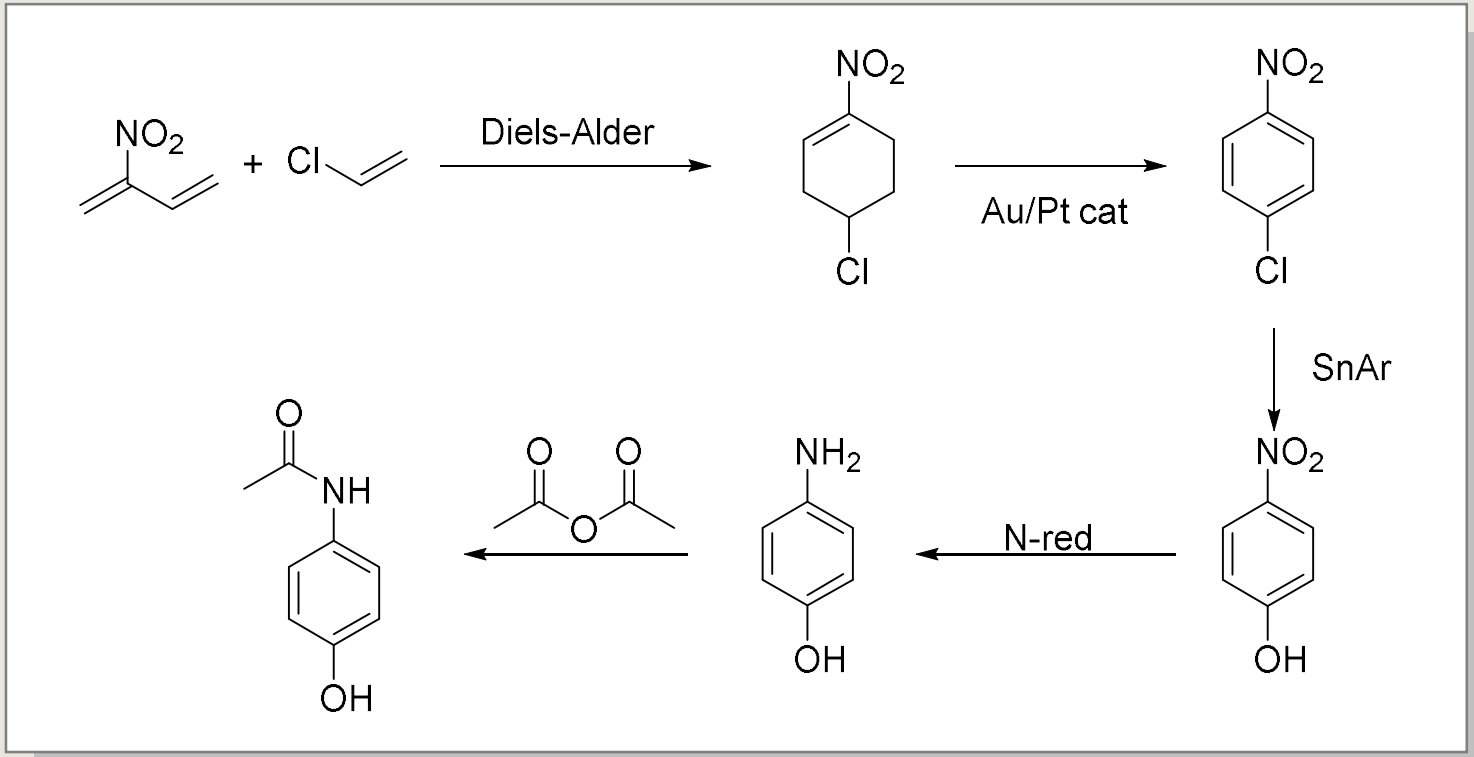
- High temperature and pressure
- By-product's problems (ex. HCl)

Synthesis 3. Diels-alder process

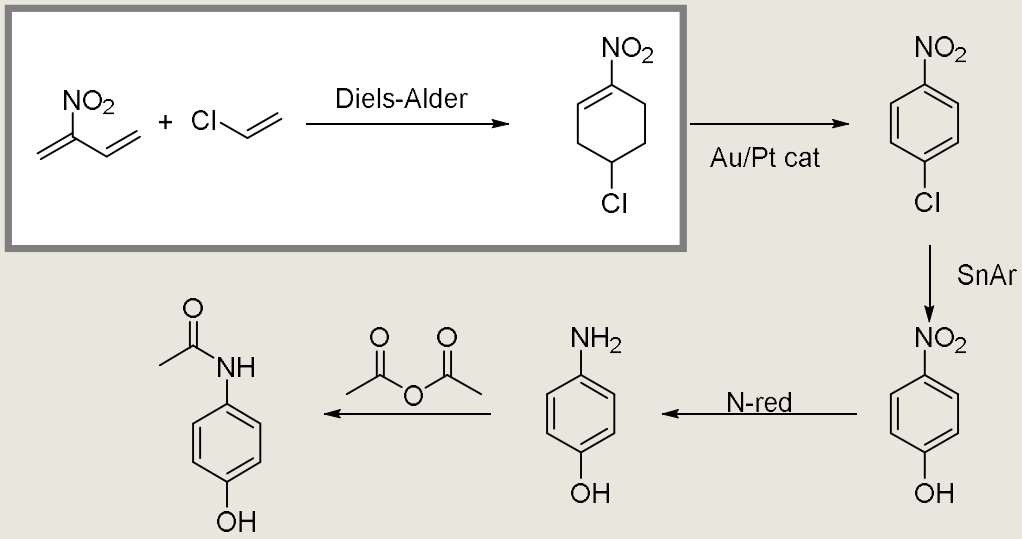
Synthesis 3. Diels-alder process

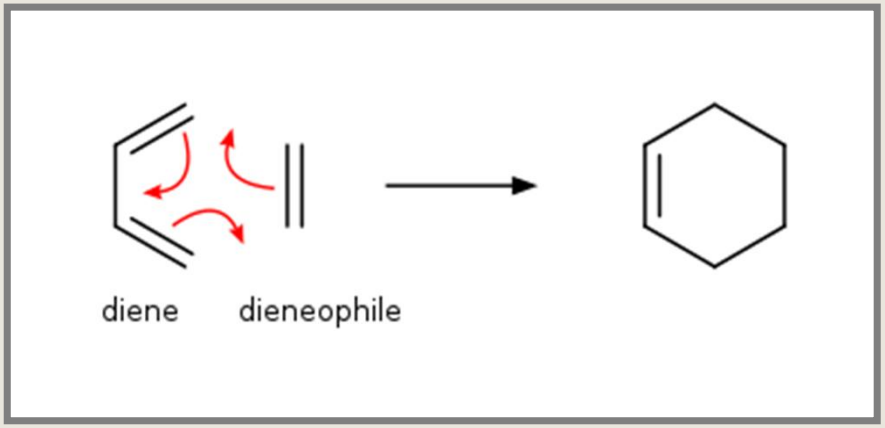
Introduction

Reaction path



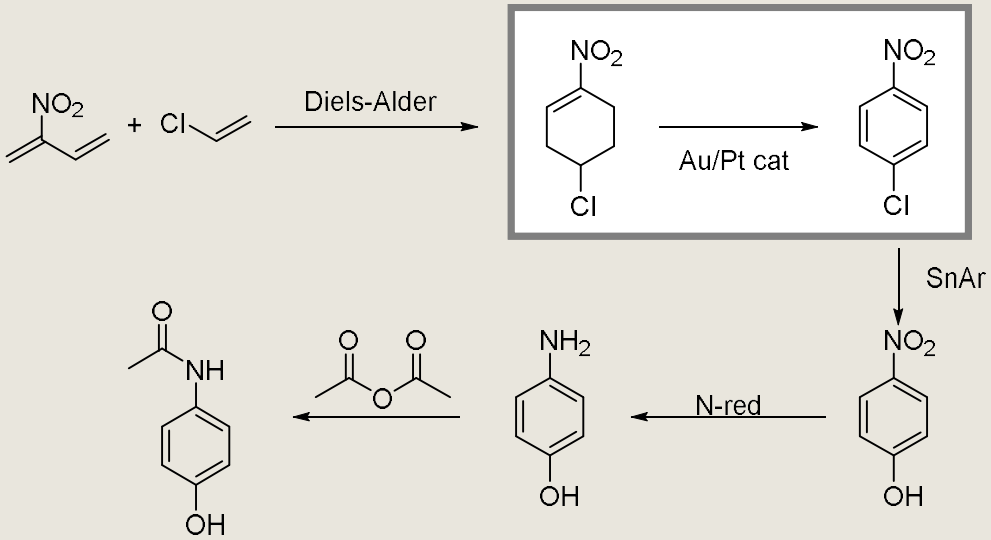
Synthesis 3. Diels-alder process

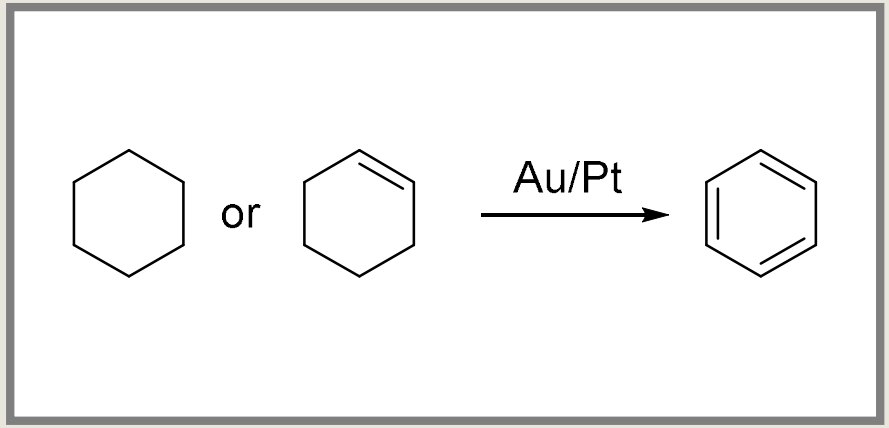




- Diels-alder reaction
- This step can make byproduct

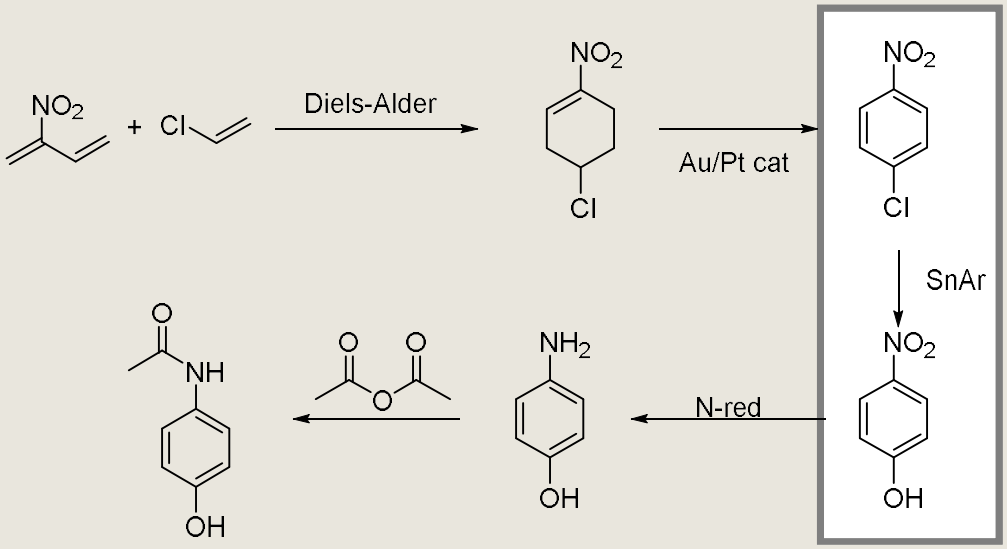
Synthesis 3. Diels-alder process

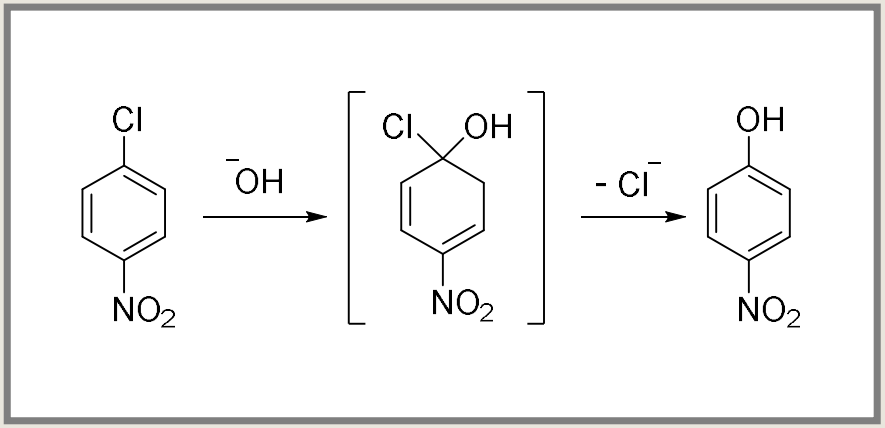




- Au/Pt bimetallic catalyzed dehydrogenation

Synthesis 3. Diels-alder process





- SnAr reaction

Synthesis 3. Diels-alder process

Advantages

- No benzene at first step
- Use the different substrates

Disadvantages

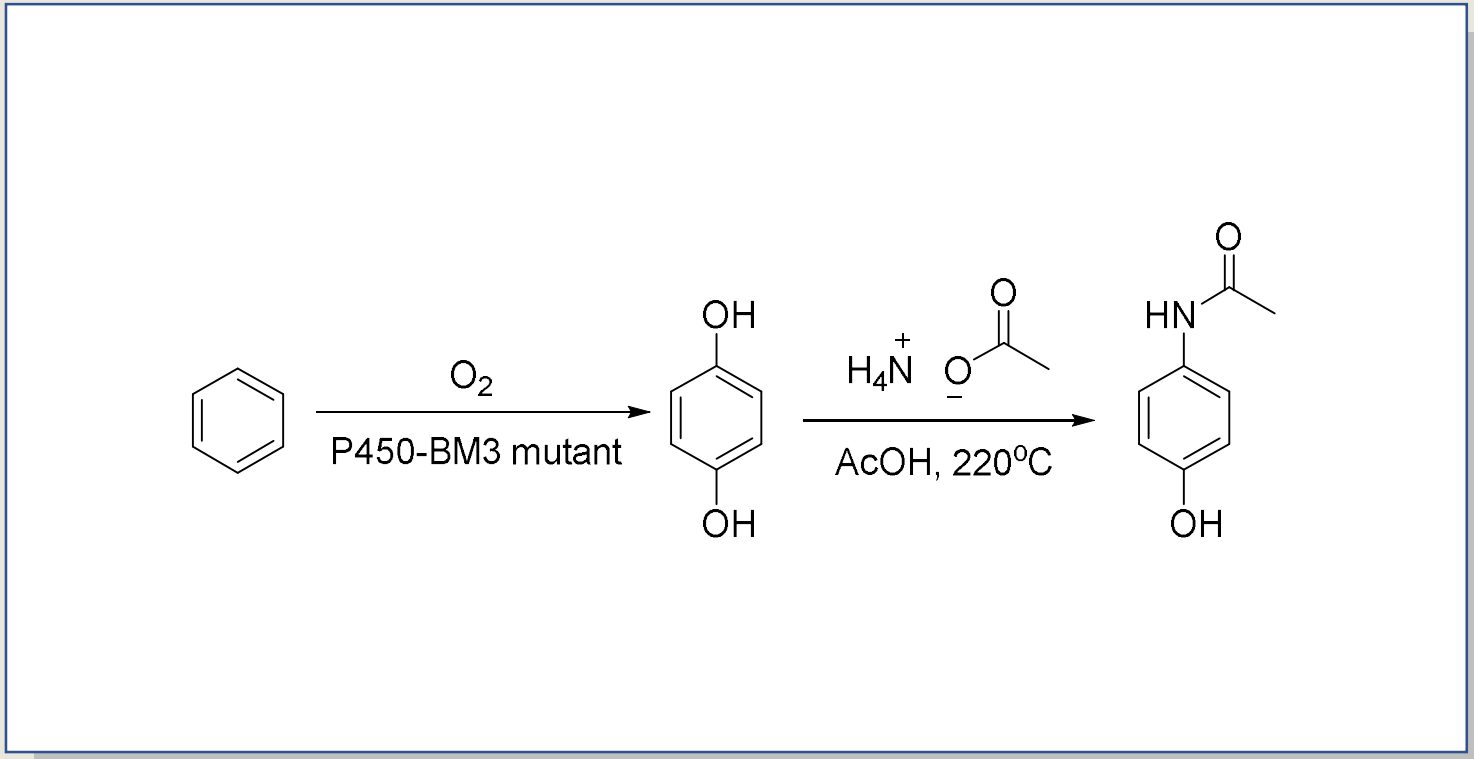
- Low selectivity
- Multi-substitution byproduct

Synthesis 4. Bio catalyzed process

Synthesis 4. Bio catalyzed process

Introduction

Reaction path



Synthesis 4. Bio catalyzed process

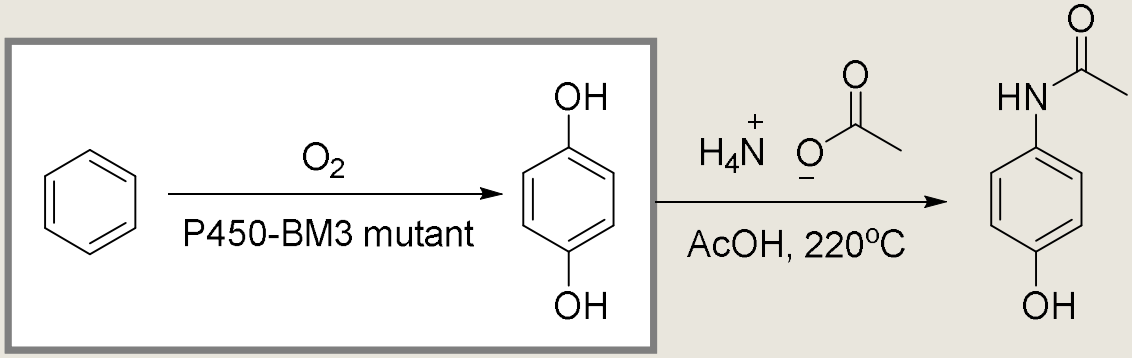


Table 1. Chemo- and regioselective dihydroxylation of benzene with almost exclusive formation of HQ using the respective P450-BM3-containing *E. coli* resting cells.

Catalysts	Conv. [%] [a]	Product Distribution [%] [b]		
		HQ (5)	Phenol (12)	Catechol
WT	- [c]	- [c]	- [c]	- [c]
A82F	87	86	10	4
A82F/A328F	97	93	6	1
V78F/A82F/A328F	92	93	4	3

- P450 catalyzed reaction can gain90% yeild

Synthesis 4. Bio catalyzed process

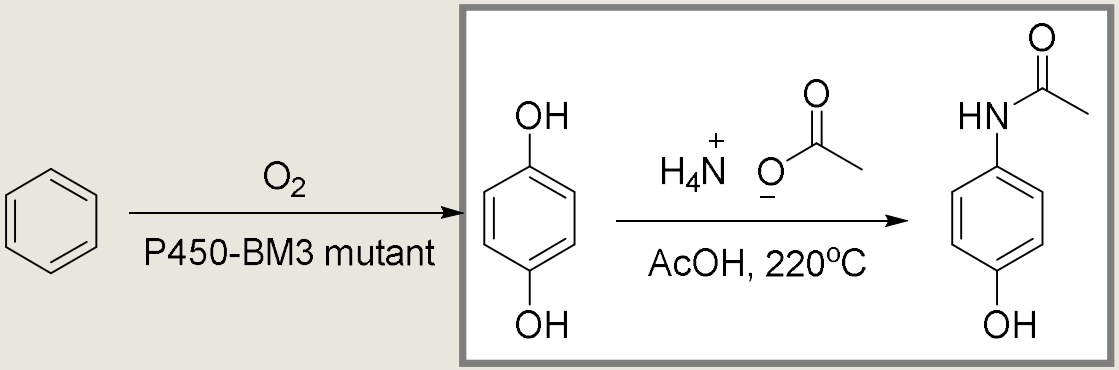
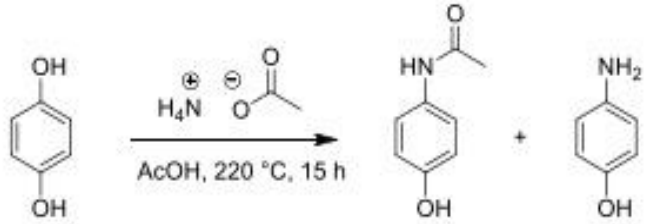


Table 2. Amidation of hydroquinone in acetic acid.[a]



HQ **APAP** **PAP**

Entry	$AcONH_4$ (equiv.)	AcOH (equiv.)	Conv. HQ[b] (%)	Selec.[b] APAP+PAP (%)	APAP/PAP[b] (mol. ratio)
1	10	5	96	> 95	100 / 0
2	2	5	85	> 95	100 / 0
3	1.2	5	76	> 95	100 / 0
4[c]	2	1	32	> 95	99 / 1

[a] Reaction conditions: Hydroquinone (20-100 mmol), $AcONH_4$, 220 °C, 15 hours. [b] Determined by HPLC. [c] Reaction performed at 180 °C for 15 hours.

Synthesis 4. Bio catalyzed process

Advantages

- Metal-Free
- Additive Free
- High Yield and Selectivity
- High Atom Economy
- Multigram-Scale

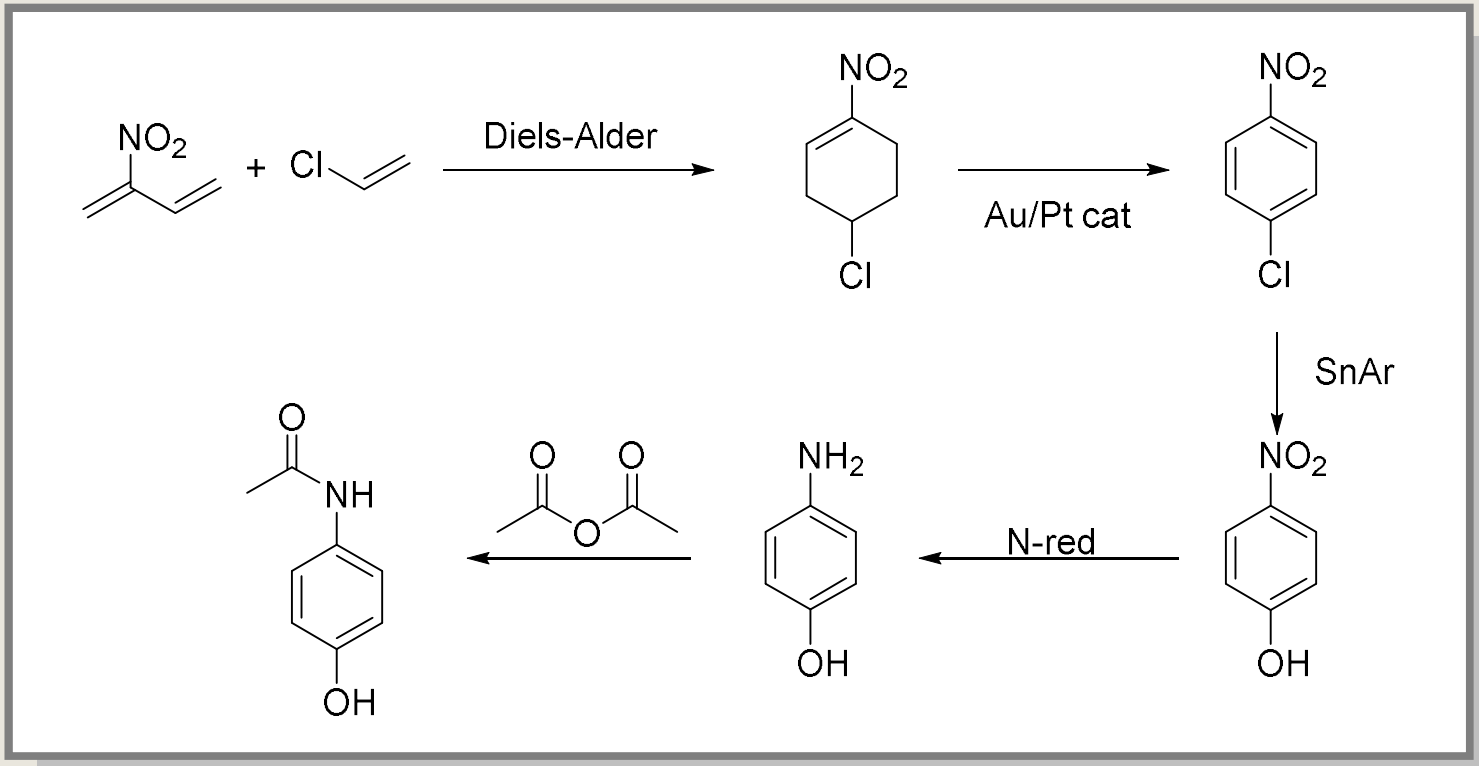
Disadvantages

- P450-BM3 is expensive
- More than 15H

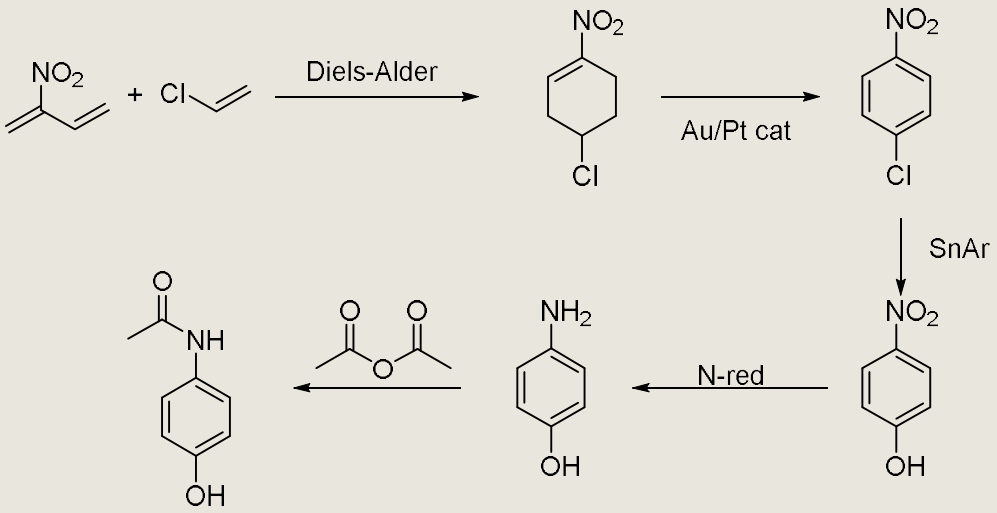
Process choice

Short term perspective

Short term



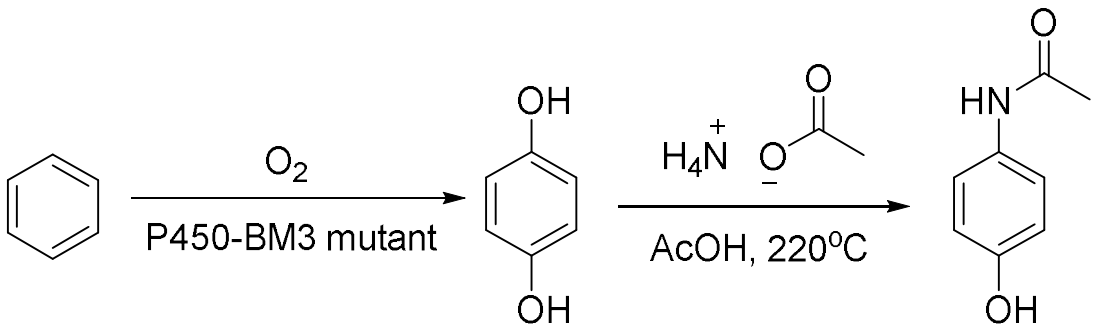
Short term perspective



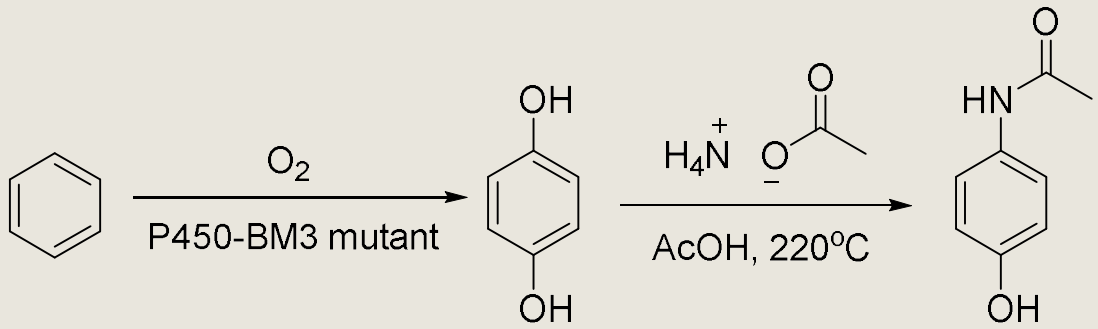
- No benzene at first step
- Use the different substrates

Long term perspective

Long term



Long term perspective



- Metal-Free
- Additive Free
- High Yield and Selectivity
- High Atom Economy
- Multigram-Scale

Thank you!