Laboratory Course OACP I (2020)

(Praktikum Organische & Anorganische Chemie I)

Protocols

Student Manual

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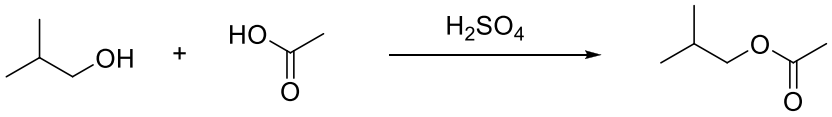
Week 1: Esterification / Distillation

1a) **Isobutyl acetate *(cherry, raspberry, strawberry flavor)***



Preparation: 2-Methylpropan-1-ol (250 mmol) and acetic acid (2.4 equiv) are combined in a 250 ml flask equipped with a stirring bar. Sulfuric acid (5 ml) is carefully added drop wise while stirring is continued. A reflux condenser is placed on the flask, the cooling water is turned on, and the reaction mixture is heated to reflux (temperature?).
After 2-3 hours the reaction is complete and the mixture is cooled to RT. The mixture is poured in a separator funnel and the flask is rinsed with a bit of water. Then, add as much water until the water phase has twice the volume of the organic phase. The two phases are separated, the organic phase is kept in an Erlenmeyer flask, and the water phase is extracted with dichloromethane of equal volume. The combined organic layers are washed with saturated sodium hydrogen carbonate (**careful:** CO_2 evolution) and dried over magnesium sulfate, followed by filtration and concentration on the rotary evaporator.

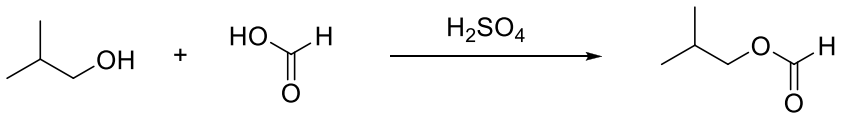
Purification: The residue is distilled at atmospheric pressure.

Analysis: Odor, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
2-Methylpropan-1-ol		1.00	250 mmol			
Acetic acid		2.40				
Sulfuric acid					5.0 ml	
Product	**MW**	**Yield**	**Moles**	**Mass**	**BP**	
					115-117 °C	

1b)* Isobutyl formate *(raspberry flavor)



Preparation: 2-Methylpropan-1-ol (300 mmol) and formic acid (2.00 equiv) are combined in a 250 ml flask equipped with a stirring bar. Sulfuric acid (5 ml) is carefully added drop wise while stirring is continued. A reflux condenser is placed on the flask, the cooling water is turned on, and the reaction mixture is heated to reflux (temperature?).
After 2-3 hours the reaction is complete and the mixture is cooled to RT. The mixture is poured in a separatory funnel and the flask is rinsed with a bit of water. Then, add as much water until the water phase has twice the volume of the organic phase. The two phases are separated, the organic phase is kept in an Erlenmeyer flask, and the water phase is extracted with dichloromethane of equal volume. The combined organic layers are washed with saturated sodium hydrogen carbonate (**careful:** CO_2 evolution) and dried over magnesium sulfate, followed by filtration and concentration on the rotary evaporator.

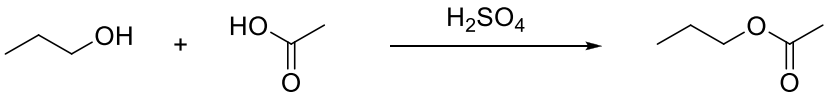
Purification: The residue is distilled at atmospheric pressure.

Analysis: Odor, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
2-Methylpropan-1-ol		1.00	300 mmol			
Formic acid		2.00				
Sulfuric acid					5.0 ml	
Product	**MW**	**Yield**	**Moles**	**Mass**	**BP**	
					98 °C	

1c)* Propyl acetate *(pear flavor)



Preparation: Propanol (200 mmol) and acetic acid (2.50 equiv) are combined in a 250 ml flask equipped with a stirring bar. Sulfuric acid (5 ml) is carefully added drop wise while stirring is continued. A reflux condenser is placed on the flask, the cooling water is turned on, and the reaction mixture is heated to reflux (temperature?).
After 2-3 hours the reaction is complete and the mixture is cooled to RT. The mixture is poured in a separatory funnel and the flask is rinsed with a bit of water. Then, add as much water until the water phase has twice the volume of the organic phase. The two phases are separated, the organic phase is kept in an Erlenmeyer flask, and the water phase is extracted with dichloromethane of equal volume. The combined organic layers are washed with saturated sodium hydrogen carbonate (**careful:** CO_2 evolution) and dried over magnesium sulfate, followed by filtration and concentration on the rotary evaporator.

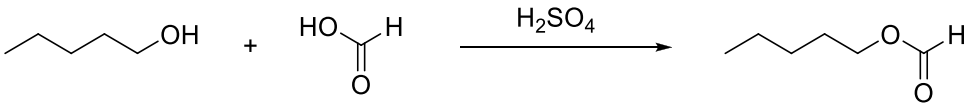
Purification: The residue is distilled at atmospheric pressure.

Analysis: Odor, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Propanol		1.00	200 mmol			
Acetic acid		2.50				
Sulfuric acid					5.0 ml	
Product	**MW**	**Yield**	**Moles**	**Mass**	**BP**	
					102 °C	

1d)* Pentyl formate *(banana flavor)



Preparation: Pentanol (200 mmol) and formic acid (2.50 equiv) are combined in a 250 ml flask equipped with a stirring bar. Sulfuric acid (5 ml) is carefully added drop wise while stirring is continued. A reflux condenser is placed on the flask, the cooling water is turned on, and the reaction mixture is heated to reflux (temperature?).
After 2-3 hours the reaction is complete and the mixture is cooled to RT. The mixture is poured in a separatory funnel and the flask is rinsed with a bit of water. Then, add as much water until the water phase has twice the volume of the organic phase. The two phases are separated, the organic phase is kept in an Erlenmeyer flask, and the water phase is extracted with dichloromethane of equal volume. The combined organic layers are washed with saturated sodium hydrogen carbonate (**careful:** CO_2 evolution) and dried over magnesium sulfate, followed by filtration and concentration on the rotary evaporator.

Purification: The residue is distilled at atmospheric pressure.

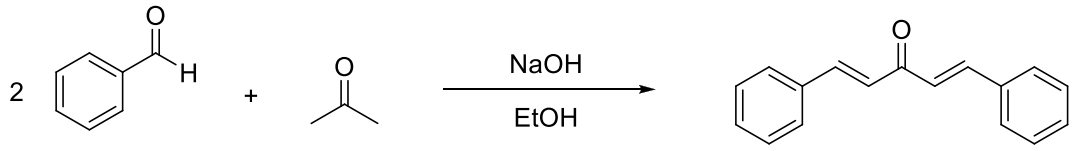
Analysis: Odor, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Pentanol		1.00	200 mmol			
Formic acid		2.50				
Sulfuric acid					5.0 ml	
Product	**MW**	**Yield**	**Moles**	**Mass**	**BP**	
					132 °C	

Week 2: Aldol Condensation / Recrystallization

***2a)* (*E*,*E*)-Dibenzylideneacetone**



Preparation: To a 500 ml one-necked flask equipped with a stirring bar is added a NaOH solution (5 equiv) in 50 ml H_2O. Then, ethanol (33 ml) is added with stirring, and the mixture is cooled to 0 °C. Benzaldehyde (47 mmol, 2.05 equiv) and acetone (1 equiv) are added to the reaction mixture slowly during 15 min. After the addition the reaction mixture is stirred for 1 h at RT. The mixture is filtered, and the solid is washed with water (3 × 50 ml).

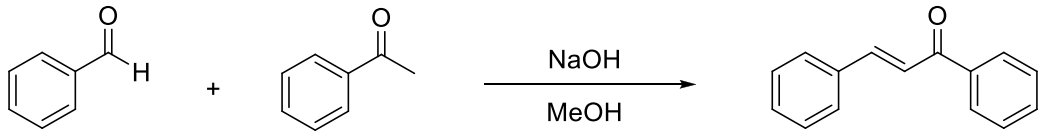
Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Acetone		1.00				
Benzaldehyde		2.05	47 mmol			
Sodium hydroxide		5.00				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

***2b)* (*E*)-Chalcone**



Preparation: A solution of acetophenone (50 mmol), benzaldehyde (50 mmol) and NaOH (1.00 equiv) in 50 ml anhydrous methanol is stirred at RT for 24 h. The reaction mixture turns yellow. After cooling to 0 °C using an ice bath, the product crystallizes (if necessary seed to initiate crystallization). Filter the solid and wash carefully with ice-cold ethanol. Concentration of the filtrate will provide a second portion of product.

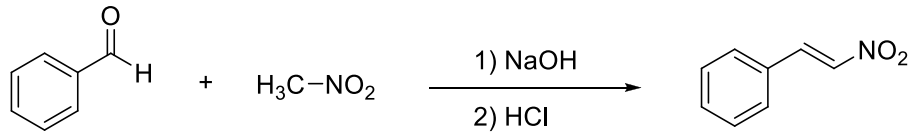
Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Acetophenone		1.00	50 mmol			
Benzaldehyde		1.00	50 mmol			
Sodium hydroxide		1.00				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

***2c)* (*E*)-(2-Nitrovinyl)benzene**



Preparation: To a solution of nitromethane (55 mmol) in MeOH (10 ml) is added benzaldehyde (50 mmol). The mixture is cooled to 0 °C, and an aqueous solution of NaOH (2 M; 1.10 equiv) is added over a period of 30 min. Stirring is continued for another 30 min at 0-5 °C. The mixture is diluted with H_2O (25 ml) and poured onto crushed ice containing 8 ml of concentrated HCl. The formed yellow precipitate is filtered and briefly dried *in vacuo*.

Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

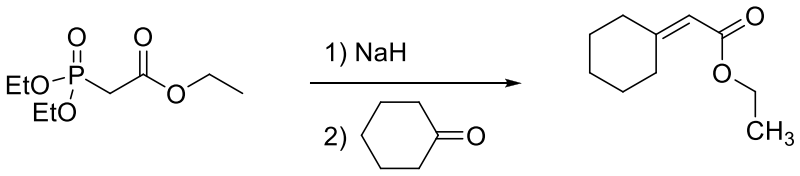
Analysis: TLC, melting point, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Nitromethane		1.10	55 mmol			
Benzaldehyde		1.00	50 mmol			
Sodium hydroxide		1.10				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Week 3: The Wittig (& HWE) Reaction / Column Chromatography

3a) **Ethyl 2-cyclohexylideneacetate**



Preparation: NaH (60% in oil; 480 mg, 12 mmol) under nitrogen atmosphere is suspended in dry THF (8 ml), and the mixture is cooled to 0 °C. Triethyl phosphonoacetate (3.0 ml, 15 mmol) is added dropwise, and the mixture is stirred for 30 min at RT. Then it is cooled to 0 °C and a solution of cyclohexanone (1.0 g, 10 mmol) in THF (2 ml) is added dropwise. The resulting reaction mixture is stirred at RT for 20 h. Then, saturated aqueous NH_4Cl solution is added, and the mixture is extracted with Et_2O (2 x 20 ml). The combined organic layers are washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

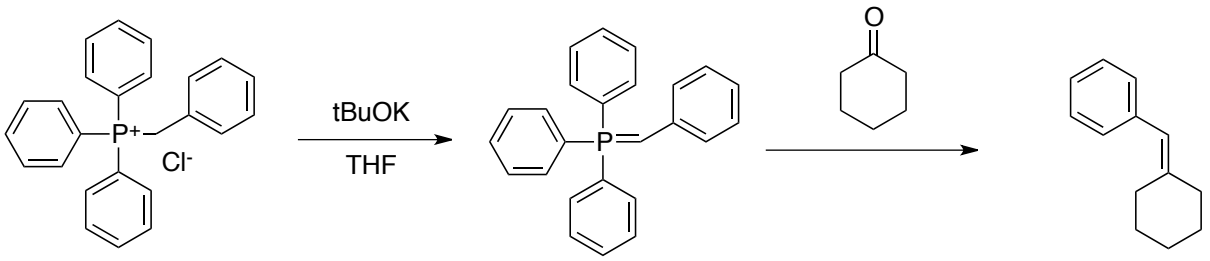
Purification: The residue is purified by flash column chromatography.

Analysis: TLC, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Cyclohexanone		1.00	10 mmol	1.00 g		
Triethylphosphonoacetate			15 mmol		2.98 ml	
Sodium hydride			12 mmol	0.48 g	-	60%
Product	**MW**	**Yield**	**Moles**	**Mass**		

***3b)* (Cyclohexylidenemethyl)benzene**



Preparation: Benzyltriphenylphosphonium chloride (15 mmol) is added to a round bottom flask under nitrogen atmosphere and suspended in dry THF (19 mL). At room temperature add a 12% solution of tBuOK (15 mmol) in THF dropwise. The mixture will turn bright red and is stirred for 30 minutes. Cyclohexanone (10 mmol) in THF (3 mL) is added dropwise and the mixture is stirred overnight. The reaction is quenched with 1M HCl and most THF removed *in vacuo*. To the residue is added water and extracted with MTBE (2x 30 mL). The combined organic layers are dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

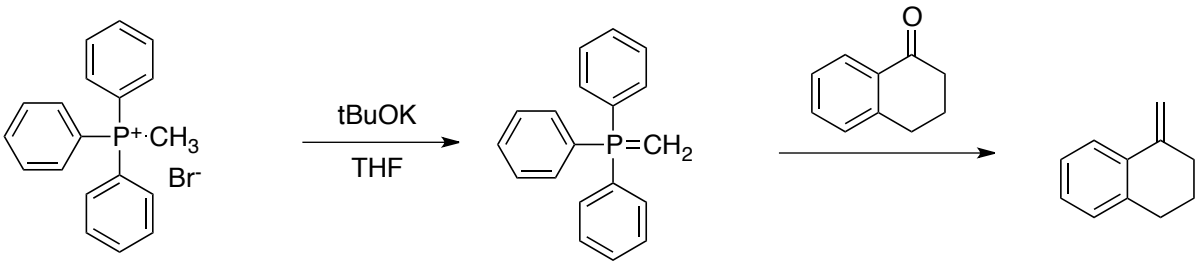
Purification: The residue is purified by flash column chromatography

Analysis: TLC, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Cyclohexanone		1.00	10 mmol			
Benzyltriphenylphosphonium chloride			15 mmol			
12% tBuOK in THF			15 mmol		14.0 mL	12%
Product	**MW**	**Yield**	**Moles**	**Mass**		

3c) 1-Methylene-1,2,3,4-tetrahydronaphthalene



Preparation: Methyltriphenylphosphonium bromide (15 mmol) is added to a round bottom flask under nitrogen atmosphere and suspended in dry THF (19 mL). At room temperature add a 12% solution of tBuOK (15 mmol) in THF dropwise. The mixture will turn yellow and is stirred for 30 minutes. -tetralone (10 mmol) in THF (3 mL) is added dropwise and the mixture is stirred overnight. The reaction is quenched with 1M HCl and most THF removed *in vacuo*. To the residue add water and extract with MTBE (2x 30 mL). The combined organic layers are dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Purification: The residue is purified by flash column chromatography

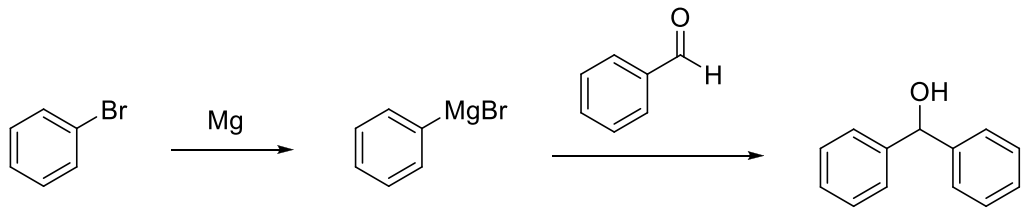
Analysis: TLC, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
α-Tetralone		1.00	10 mmol			
Methyltriphenylphosphonium bromide			15 mmol			
12% tBuOK in THF			15 mmol		14 mL	12%
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Week 4: Grignard Reaction

4a) **Diphenylmethanol**



Preparation: Magnesium turnings (2.0 g) are suspended in Et_2O (15 ml) in a three-necked flask equipped with a stir bar, dropping funnel, and reflux condenser. About $^1/_{20}$ of bromobenzene (50 mmol) is added. To ensure formation of the Grignard reagent (turbidity), the mixture can be heated gently with a warm water bath and/or a few crystals of I_2 can be added. Once the formation of the reagent has started, the rest of the bromobenzene is dissolved in Et_2O (20 ml) and then slowly added to the reaction mixture (ether should be boiling gently; takes ca. 30 min). The mixture is heated to reflux for 30 min. Then it is cooled to 0 °C, and a solution of benzaldehyde (37 mmol) in Et_2O (5 ml) is added. Stirring is continued at RT for 1 h.
Then the mixture is poured into ice-cold saturated aqueous NH_4Cl (20 ml). The phases are separated, and the aqueous phase extracted with Et_2O (2 x 10 ml). The combined organic phases are washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, then dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

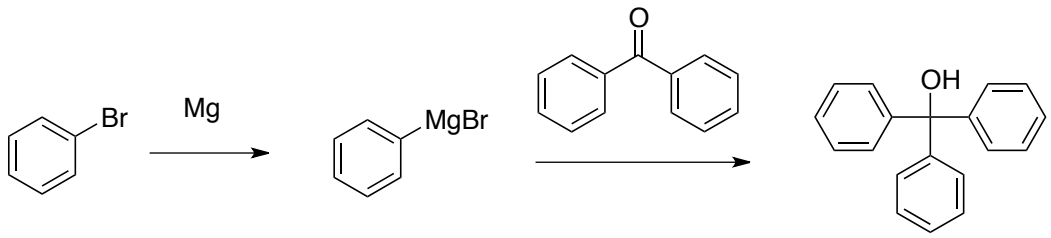
Purification: The residue is purified by flash column chromatography. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Benzaldehyde		1.00	37 mmol			
Bromobenzene			50 mmol			
Magnesium				2.00 g		
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

***4b)* Triphenylmethanol**



Preparation: Magnesium turnings (1.0 g) are suspended in Et_2O (15 ml) in a three-necked flask equipped with a stir bar, dropping funnel, and reflux condenser. About $^1/_{20}$ of bromobenzene (41 mmol) is added. To ensure formation of the Grignard reagent (turbidity), the mixture can be heated gently with a warm water bath and/or a few crystals of I_2 can be added. Once the formation of the reagent has started, the rest of the bromobenzene is dissolved in Et_2O (20 ml) and then slowly added to the reaction mixture (ether should be boiling gently; takes ca. 30 min). The mixture is heated to reflux for 30 min. Then it is cooled to 0 °C, and a solution of benzophenone (32 mmol) in Et_2O (30 ml) is added. After addition the solution is heated to reflux for 20 minutes.
After cooling to RT, add 10 g of crushed ice followed by 10 mL half-concentrated HCl. The mixture is stirred until the phases separate and is then extracted with Et_2O (2 x 30 ml). The combined organic phases are washed with saturated aqueous $NaHCO_3$ and water, then dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

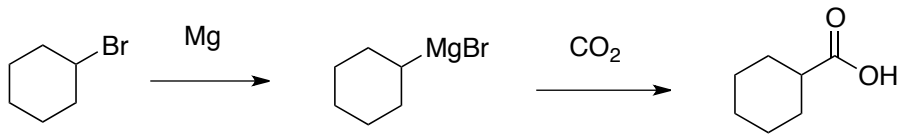
Purification: The residue is purified by flash column chromatography. In case of a high yield not all crude product needs to be purified. Find the proper solvent or solvent mixture!

Analysis: TLC, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Benzophenone		1.00	32 mmol			
Bromobenzene			41 mmol			
Magnesium				1.00 g		
Product	**MW**	**Yield**	**Moles**	**Mass**		

***4c)* Cyclohexanecarboxylic acid**



Preparation: Magnesium turnings (2.0 g) are suspended in Et_2O (15 ml) in a three-necked flask equipped with a stir bar, dropping funnel, and reflux condenser. About $^1/_{20}$ of bromocyclohexane (50 mmol) is added. To ensure formation of the Grignard reagent (turbidity), the mixture can be heated gently with a warm water bath and/or a few crystals of I_2 can be added. Once the formation of the reagent has started, the rest of the bromocyclohexane is dissolved in Et_2O (30 mL) and then slowly added to the reaction mixture (ether should be boiling gently). After the addition is complete the mixture is heated to reflux for 15 min. Then it is cooled to room temperature and diluted with 50 mL of dry Et_2O.

Wrap approximately 500 mmol of dry ice in a cloth and crush it with a hammer, being careful to keep the ice inside the towel to minimize moisture. The crushed dry ice should be put into a 500 mL beaker and the Grignard solution immediately carefully poured over it. Allow the reaction to stand until the carbon dioxide has completely evaporated and add 2 M HCl (35 mL). The phases are separated, and the aqueous phase extracted with Et_2O (2 x 20 ml). The combined organic phases are dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Purification: The residue is purified by flash column chromatography. Find the proper solvent or solvent mixture! Stain TLC with $KMnO_4$ stain in order to see the product.

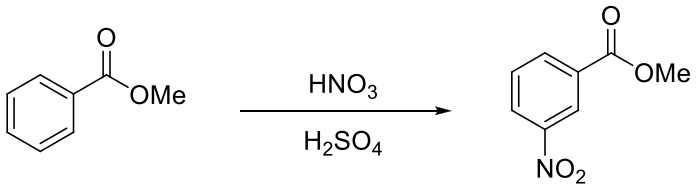
Analysis: TLC, IR.

Fill in this table before you begin:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Bromocyclohexane		1.00	50 mmol			
Carbon Dioxide						
Magnesium				2.00 g		
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Week 5: Electrophilic Aromatic Substitution

5a) **Methyl *m*-nitrobenzoate**



Preparation: Into a round-bottomed flask fitted with a stir bar are placed concentrated sulfuric acid (20 ml) cooled to 0 °C and methyl benzoate (75 mmol). The mixture is cooled to 0-10 °C and then, while stirring, there is added gradually, by means of a dropping funnel, a mixture of concentrated nitric acid (1.30 equiv) and concentrated sulfuric acid (1.56 equiv). During the addition of the nitrating acid, which requires about one hour, the temperature of the reaction mixture should be kept within the range 5-15 °C.
After the nitric acid has been added, stirring is continued for 15 min; the mixture is then poured upon crushed ice (ca. 60 g). The crude methyl *m*-nitrobenzoate separates as a solid and is filtered off by means of suction and washed with water. The product is placed in a flask and stirred in ice-cold methanol (10 ml) in order to remove a small amount of *o*-nitrobenzoic ester and other impurities that are present. The cooled mixture is then filtered by means of suction, washed with another portion of cold methyl alcohol (5 ml), and the solid dried.

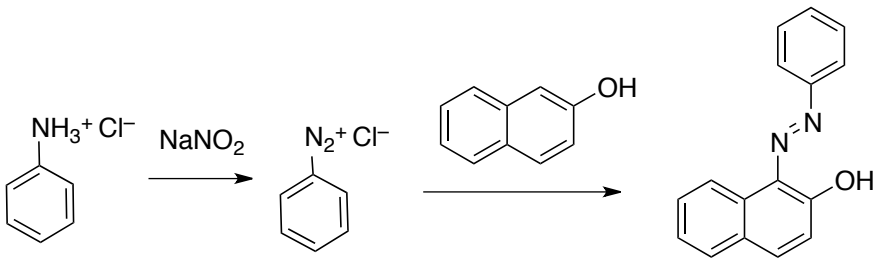
Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Methyl benzoate		1.00	75 mmol			
Nitric acid		1.30				70%
Sulfuric acid		1.56				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

5b) **(E)-1-(phenyldiazenyl)naphthalen-2-ol**



Preparation: To a 100 mL Erlenmeyer flask equipped with a thermometer and a magnetic stir bar, add 13 g ice, 5 mL water and 2.5 mL conc. HCl. To this aniline hydrochloride (11 mmol) is added and then cooled to 0 °C. A solution of $NaNO_2$ (11 mmol) in water (3 mL) is added dropwise, while stirring vigorously. Important: The temperature should not exceed 5 °C.

Charge a separate 250 mL Erlenmeyer flask with 2-Napthol (10 mmol) in 40 mL of 1 M NaOH
While stirring and cooling, add the previously prepared diazonium salt solution portionwise. After the addition stir the reaction for 5 minutes and isolate the orange product by suction filtration.

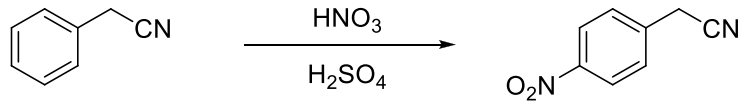
Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Aniline Hydrochloride		1.10	11 mmol			
Sodium Nitrite		1.10	11 mmol			
2-Napthol		1.00	10 mmol			
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

***5c)* (4-Nitrophenyl)acetonitrile**



Preparation: A mixture of concentrated sulfuric acid (14 ml) and concentrated nitric acid (14 ml) is cooled to 10 °C. Within one hour benzyl cyanide (43 mmol) is added dropwise in such a way that the internal temperature does not exceed 20 °C. After the addition is completed the mixture is stirred for 1 h at RT. Then the mixture is poured onto crushed ice (60 g), filtered, and dried *in vacuo*.

Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

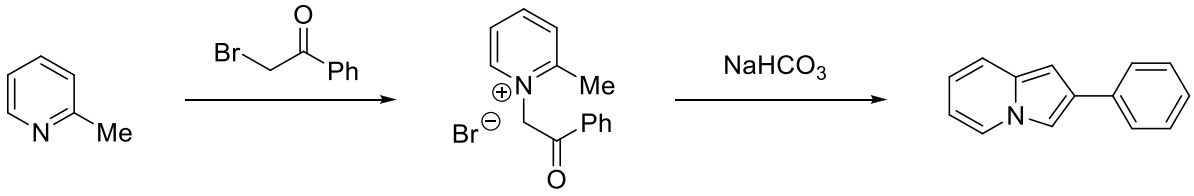
Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Benzyl cyanide		1.00	43 mmol			
Nitric acid					13.8 ml	70%
Sulfuric acid					13.8 ml	
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Note: Benzyl cyanide = Phenylacetonitrile

Week 6: Aromatic & Heteroaromatic Chemistry

***6a)* 2-Phenylindolizine**



Preparation:
a) Pyridinium salt: To a boiling solution of 2-methylpyridine (3.6 g) in toluene (7 ml) is added a solution of 2-bromoacetophenone (1.01 equiv) in toluene (16 ml). After a few minutes the crystallization of the pyridinium salt initiates and refluxing is continued for 3.5 h. After cooling to RT, the colorless solid is filtered, washed with toluene (2 x 15 ml), and dried *in vacuo*.
b) Indolizine: To a vigorously stirred, warm (80 °C) solution of the pyridinium salt (24 mmol) in H_2O (60 ml) is added in small portions sodium hydrogencarbonate (3.66 equiv). An intense yellow color is formed, and after about 1 min a yellowish solid starts crushing out. Stirring is continued for 30 min at 80 °C. After cooling to RT, the solid is filtered, washed with H_2O (3 x 30 ml), and dried *in vacuo*.

Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

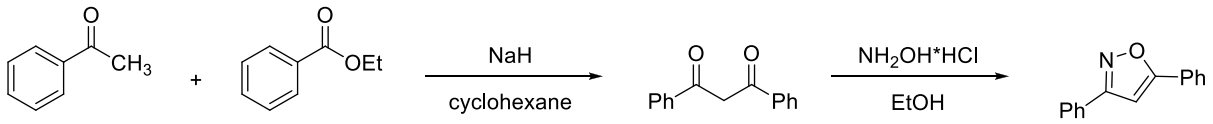
Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
2-Methylpyridine		1.00		3.60 g		
Bromoacetophenone		1.01				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Note: 2-Methylpyridine = 2-Picoline

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Pyridinium salt		1.00	24 mmol			
Sodium bicarbonate		3.66				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

6b) 3,5-Diphenylisoxazole



Preparation:
a) Diketone: To a boiling suspension of sodium hydride (60% in mineral oil; 1.5 equiv) in anhydrous cyclohexane (33 ml) is dropwise added a solution of acetophenone (25 mmol) and ethyl benzoate (2.00 equiv) in cyclohexane (5 ml). Time of addition should be chosen in a way such that the suspension is boiling without external heating (ca. 30 min). After the addition is complete, heating to reflux is continued until gas formation has ceased (ca. 1 h). After cooling to RT a mixture of glacial acetic acid (2.5 ml) and H_2O (12.5 ml) is slowly added, and the mixture is poured into ice-cold water (12.5 ml) and the phases are separated. The aqueous phase is extracted with ether (2 x 25 ml), and the combined organic layers are washed with H_2O (25 ml), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. To the remaining orange oil is added pentane to initiate crystallization. The crude solid is recrystallized from MeOH to afford colorless crystals.
b) Isoxazole: To a solution of the diketone (10 mmol) in EtOH (20 ml) is added a solution of hydroxylamine hydrochloride (2 equiv) in water (3 ml), and 2 drops of concentrated NaOH is added. The mixture is heated to reflux for 1 h. After cooling to RT, the formed crystals are collected by filtration.

Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

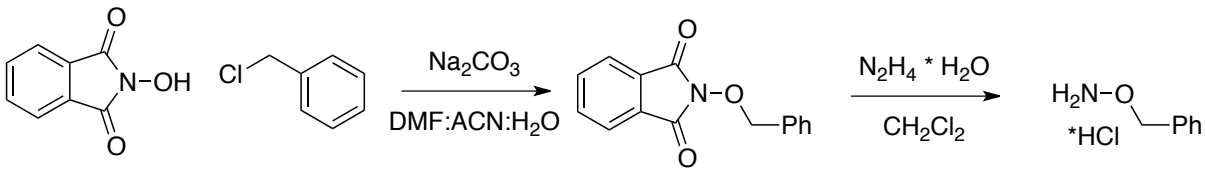
Analysis: TLC, melting point, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Acetophenone		1.00	25 mmol			
Ethyl benzoate		2.00				
Sodium hydride		1.50				60%
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Diketone		1.00	10 mmol			
$NH_2OH{\cdot}HCl$		2.00				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

6c) O-benzylhydroxylamine



Preparation

a) N-(benzyloxy)phthalimide: N-Hydroxyphthalimide (50 mmol) and Na_2CO_3 (1.00 equiv) were dissolved in a mixture of DMF (67 mL), acetonitrile (12 mL) and water (67 mL). To the red solution Benzyl chloride (1.06 equiv) was added and the mixture stirred at room temperature for 5 hours (or longer for the praktikum), during which time the solution lightens from a red colour to orange or yellow. A solid precipitates out, which should be filtered, washed with water (3 x 30 mL), -20°C cold methanol (2 x 22 mL) and dried *in vacuo* to yield the N-(benzyloxy)phthalimide as a white powder.

b) *O*-Benzylhydroxylamin: N-(benzyloxy)phthalimide (1.00 equiv) is dissolved in CH_2CL_2 (0.3M) and heated to ca. 35°C. Hydrazin monohydrate (2.00 equiv) is added and the mixture stirred for 2.5 hours. The resulting suspension is cooled to room temperature and filtered. (Important: <u>The product is NOT the solid</u>) The <u>filtrate</u> is washed successively with 2M NaOH and brine. It is dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Purification: The crude product (oil) is dissolved in EtOH (30 mL) and heated 70 °C. HCl conc. is added (1.00 equiv, ~4 mL) and the mixture cooled to room temperature. The product will crystallize and is collected by filtration. The product was washed with cold iso-propanol.

Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

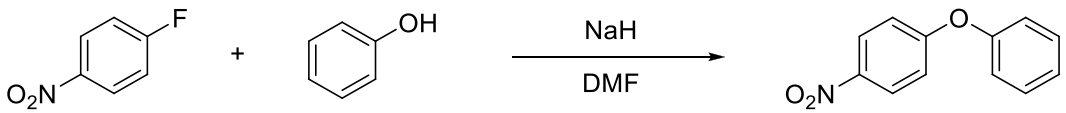
Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
N-Hydroxyphthalimide		1.00	50 mmol			
Na_2CO_3		1.00				
Benzyl chloride		1.06				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
N-(benzyloxy)phthalimide		1.00				-
Hydrazine monohydrate		2.00				-
HCl conc.		1.00				-
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Please submit the final product to your teaching assistant!

Week 7: Nucleophilic Aromatic Substitution

***7a)* 1-Nitro-4-phenoxybenzene**



Preparation: In a three-necked round-bottomed flask, equipped with an addition funnel, a magnetic stir bar, and a condenser, NaH (60% in mineral oil; 1.6 equiv) suspended in DMF (20 ml). Stirring is started and a solution of phenol (1.5 equiv) in DMF (20 ml) is added dropwise at RT. The mixture is stirred for 1 h at RT before 4-fluoronitrobenzene (10 mmol) in DMF (4 ml) is added dropwise. The reaction mixture might become warm and turn dark brown in color. The reaction is stirred at RT for 1 h, then at 50 °C for 12 h. Then it is poured into saturated aqueous NH_4Cl and extracted with MTBE (3 ×). The combined ether layers are washed with 0.2 M NaOH (until aqueous washes remain colorless), 1 M HCl, and saturated aqueous NaCl, then dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

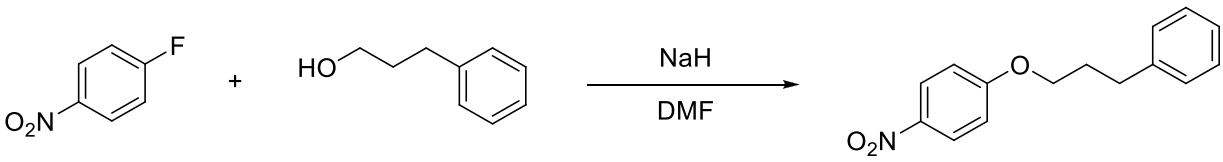
Purification: The residue is purified by flash column chromatography or recrystallization.

Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Fluoronitrobenzene		1.00	10 mmol			
Phenol		1.50				
Sodium hydride		1.60				60%
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

***7b)* 1-Nitro-4-(3-phenylpropoxy)benzene**



Preparation: In a three-necked round-bottomed flask, equipped with an addition funnel, a magnetic stir bar, and a condenser, NaH (60% in mineral oil; 1.6 equiv) suspended in DMF (20 ml). Stirring is started and a solution of 3-phenylpropanol (1.5 equiv) in DMF (20 ml) is added dropwise at RT. The mixture is stirred for 1 h at RT before 4-fluoronitrobenzene (10 mmol) in DMF (4 ml) is added dropwise. The reaction mixture might become warm and turn dark brown in color. The reaction is stirred at RT for 1 h, then at 50 °C for 12 h. Then it is poured into saturated aqueous NH_4Cl and extracted with MTBE (3 ×). The combined ether layers are washed with 1 M HCl, and saturated aqueous NaCl, then dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

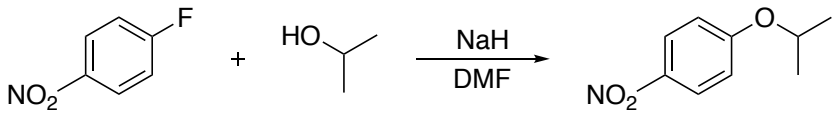
Purification: The residue is purified by flash column chromatography or recrystallization.

Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Fluoronitrobenzene		1.00	10 mmol			
3-Phenylpropanol		1.50				
Sodium hydride		1.60				60%
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

7c) 4-Nitro-1-(1-methylethoxy)benzene



Preparation: In a three-necked round-bottomed flask, equipped with an addition funnel, a magnetic stir bar, and a condenser, NaH (60% in mineral oil; 1.6 equiv) is suspended in DMF (20 ml). Stirring is started and a solution of 2-propanol (1.5 equiv) in DMF (20 ml) is added dropwise at RT. The mixture is stirred for 1 h at RT before 4-fluoronitrobenzene (10 mmol) in DMF (4 ml) is added dropwise. The reaction mixture might become warm and turn dark brown in color. The reaction is stirred at RT for 1 h, then at 50 °C for 12 h. Then it is poured into saturated aqueous NH_4Cl and extracted with MTBE (3 ×). The combined ether layers are washed with 1 M HCl, and saturated aqueous NaCl, then dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

Purification: The residue is purified by flash column chromatography.

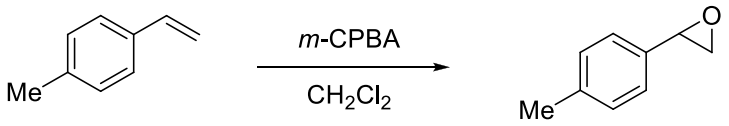
Analysis: TLC, melting point, IR.

Fill in this table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Fluoronitrobenzene		1.00	10 mmol			-
2-Propanol		1.50				-
Sodium hydride		1.60			-	60%
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

Week 8: Electrophilic Additions to Alkenes

***8a)* 2-*p*-Tolyloxirane**



Preparation: 4-Methylstyrene (10 mmol) is dissolved in CH_2Cl_2 (50 ml) and mixed with an equal amount of water containing $NaHCO_3$ (5 g). To this solution is carefully added *m*-CPBA (1.1 equiv), and the reaction mixture is stirred at RT until completion (follow reaction by TLC, ~2.5h). Then it is treated with aqueous Na_2SO_3 (6.5 g in 50 ml) for 20 min. The phases are then separated, and the aqueous phase is extracted with CH_2Cl_2 (2 × 50 ml). The combined organic phases are washed with aqueous $NaHCO_3$ (2 × 100 ml) and water, then dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

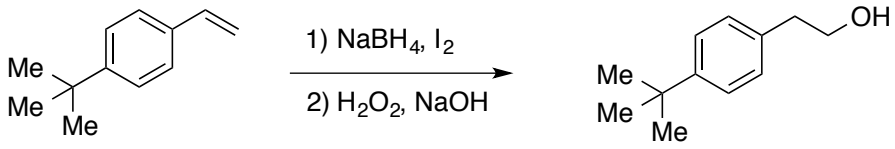
Purification: If necessary (TLC analysis), the residue is purified by flash column chromatography.

Analysis: TLC, IR.

Fill in the table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Methylstyrene		1.00	10 mmol			
m-CPBA		1.10				77%
Product	**MW**	**Yield**	**Moles**	**Mass**		

***8b)* 2-(4-*tert*-Butylphenyl)ethanol**



Preparation: To a three-necked round-bottomed flask, equipped with an addition funnel, a magnetic stir bar, and a thermometer, dry THF (20 mL) is added followed by $NaBH_4$ (0.46 equiv). The mixture is stirred until a suspension is formed and cooled to -5 to 0 °C (NaCl/ice mixture). A solution of Iodine (0.19 equiv) in dry THF (10 mL) is added dropwise as such, so that the brown color of the iodine disappears right after each drop. Afterwards a solution of the alkene (3.21 g, 20.0 mmol, 1.00 equiv) in dry THF (10 mL) is added as such, so that the internal temperature does not exceed 30 °C. The mixture is allowed to stir for another 2 h at room temperature and cooled to 0 °C. Water (2.6 mL) is added carefully followed by THF (25 mL) and a 3M NaOH solution (40 mL). While stirring a 30% solution of H_2O_2 (2.00 equiv) is added dropwise as such, so that the internal temperature does not exceed 30 °C. The mixture is stirred for another 20 min and poured in a separatory funnel and the flask rinsed with MTBE (10 mL). The aqueous phase is saturated with NaCl (15-20 g), the phases are separated and the aqueous phase extracted with MTBE (3 x 10 mL). The combined organic phases are washed with brine (2 x 10 mL), dried (K_2CO_3), filtered and concentrated *in vacuo*.

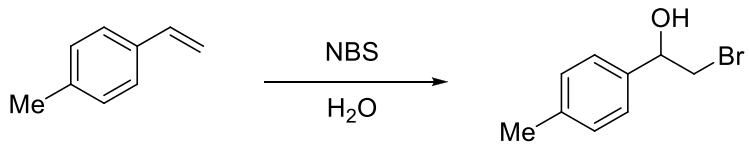
Purification: The residue is purified by flash column chromatography (EtOAc/hexanes = 1/5).

Analysis: TLC, IR.

Fill in the table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-*tert*-Butylstyrene		1.00	20.0 mmol			
Sodium borohydride			9.2 mmol			
Iodine (I_2)			3.8 mmol			
Hydrogen peroxide						30%
Product	**MW**	**Yield**	**Moles**	**Mass**		

***8c)* 2-Bromo-1-*p*-tolylethanol**



Preparation: To a solution of 4-methylstyrene (15 mmol) in THF (30 ml) is added water (6 ml) and NBS (1.5 equiv) at RT and the mixture is stirred until completion of the reaction (follow reaction by TLC, ~30 min). After completion of the reaction, THF is evaporated and the residue is extracted twice with CH_2Cl_2 (15 ml). The combined organic layers are washed with a dilute aqueous solution of sodium hypochlorite (Javelwasser), and then with saturated aqueous NaCl, afterwards dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Purification: The residue is purified by flash column chromatography.

Analysis: TLC, IR.

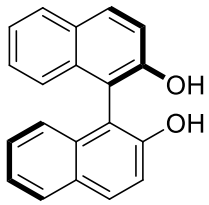
Fill in the table before you begin the experiment:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Methylstyrene		1.00	15.0 mmol			
N-Bromosuccinimid		1.50				
Product	**MW**	**Yield**	**Moles**	**Mass**		

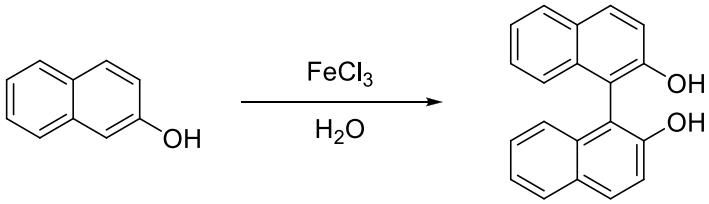
Weeks 9-11: Multi-Step Synthesis of Ligands

***9a)* (*R*)-1,1'-Binaphthyl-2,2'-diol (BINOL)**

[*Tet. Asymm.* **2003**, *14*, 2763.]



1. Preparation of racemic BINOL



Please submit the final product to your teaching assistant!

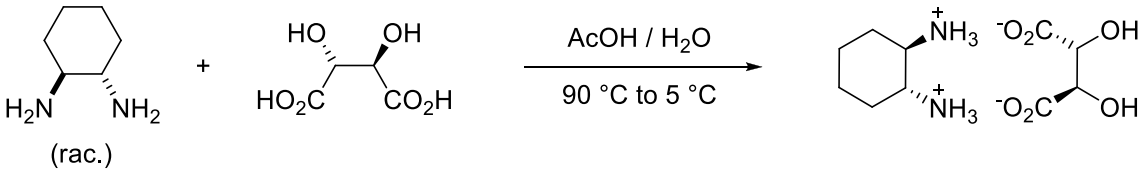
Day 1:

2-Naphthol (15.00 g, 104 mmol) and water (600 ml) are heated under reflux in a 1-l round-bottomed flask equipped with a reflux condenser. A solution of $FeCl_3 \cdot 6\,H_2O$ (30.00 g, 111 mmol) in water (60 ml) is added dropwise with vigorous stirring through the condenser and the mixture is heated under reflux for another 30 min after completion of the addition. Racemic 2,2'-dihydroxy-1,1'-binaphthyl precipitates during the procedure and the hot slurry is filtered through a preheated Buchner funnel. After washing with boiling water until the filtrate becomes colorless, the brownish residue is dried by sucking air through the funnel for 2 minutes. The solid is spread on a sheet of aluminum foil and dried overnight on the air.

Day 2:

Two recrystallization procedures are performed from refluxing toluene (180 ml) with cooling to RT in an ice-/ water bath and filtration through a filtration funnel. The mother liquors are combined, the solvent removed and the residue recrystallized twice in the same fashion from toluene (2×80 ml). Both sets of crystals are combined and dried under vacuum in the desiccator (16 h at 20 mbar). The product is obtained as colorless needles (11.81 g, 41.11 mmol, 79%; mp: 219°C, lit 218°C).

2. Resolution of diaminocyclohexane



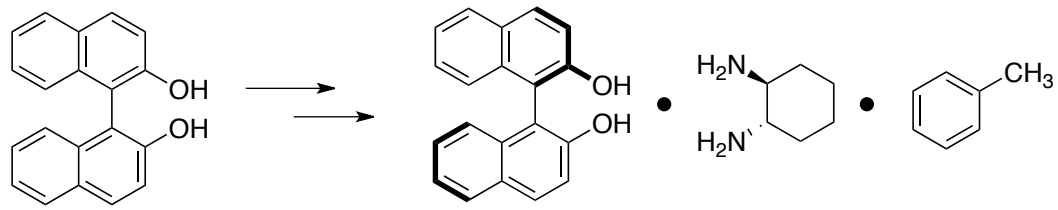
Day 3:

In a 500 ml two-necked round-bottomed flask equipped with reflux condenser, dropping funnel and a big magnetic stir bar, racemic cyclohexanediamine (11.4 g, 100 mmol) is dissolved in a solvent mixture of water (20 ml) and methanol (160 ml). Then glacial acetic acid (7.5 ml, 7.8 g, 130 mmol) is added dropwise with stirring. A solution of L-(+)-tartaric acid (7.51 g, 50.0 mmol) in methanol (30 ml) is added dropwise and the dropping funnel was rinsed with methanol (10 ml). The overall proportion of methanol to water is therefore 10:1. The solution is refluxed for 24 h.

Day 4:

After cooling to room temperature, the slurry is filtered. The precipitate is washed with methanol (3×20 ml) and oven-dried (12 h at 80 °C). Thereby (*R*,*R*)-cyclohexanediammonium tartrate is obtained as an enantiomerically pure, crystalline powder (12.80 g, 48.5 mmol, 49% yield, >99.8% *ee* [HPLC]). To this solid is added 250 ml 4 M NaOH. The mixture is extracted 2 x 200 ml CH_2Cl_2. Drying over $MgSO_4$ and concentration will provide the free amine (*R*,*R*)-cyclohexanediamine**.**

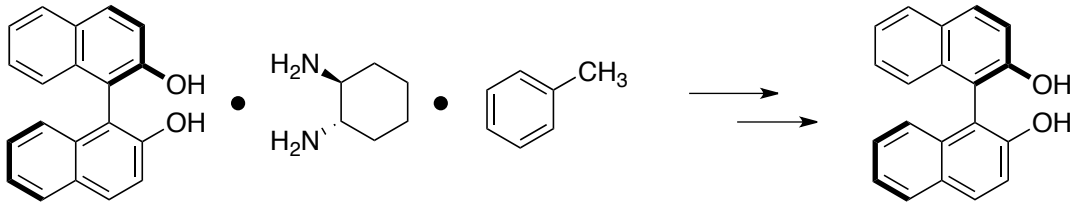
3. Resolution of racemic BINOL



Day 5: *Formation of (*R*)-BINOL-(*R,R*)-cyclohexanediamine ·toluene inclusion complex*

Racemic BINOL (5.73 g, 20.03 mmol) is added to a solution of (*R*,*R*)-cyclohexanediamine (2.514 g, 22.05 mmol, 2.2 equiv.) in toluene (60 ml) and the solution is stirred for 30 min at room temperature, heated to 100 °C for 10 min and then slowly cooled to room temperature. A precipitate will form which is filtered and washed with cold toluene (2×10 ml). Recrystallization of the precipitate from hot toluene (20 ml) affords enantiomerically pure (*R*)-BINOL·(*R*,*R*)-cyclohexanediamine·toluene (4.47 g, 9.06 mmol, 45%, 99.8% ee) as colorless needles which are dried in the desiccator under vacuum (16 h at 20 mbar).

4. Liberation of (*R*)-BINOL



Day 6:

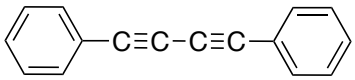
The inclusion complex (*R*)-BINOL·(*R*,*R*)-cyclohexanediamine·toluene (4.47 g, 9.06 mmol) is dissolved in a mixture of water (9 ml) and methanol (80 ml) and L-(+)-tartaric acid (1.496 g, 9.97 mmol, 1.1 equiv.) is added in one portion. The reaction is heated under reflux for 16 h.

Day 7:

After cooling the precipitated (*R*,*R*)-cyclohexanediammonium (+)-tartrate is removed by filtration, and discarded. Water (30 ml) is added to the filtrate and the methanol is removed under reduced pressure affording the precipitation of the (*R*)-BINOL. The precipitate is filtered, washed with water (5×20 ml) and transferred into a separatory funnel charged with CH_2Cl_2 (50 ml) and saturated aqueous Na_2CO_3 solution (20 ml). After vigorous shaking, the organic layer is separated, dried over $MgSO_4$ and after solvent removal under reduced pressure (*R*)-BINOL (2.43 g, 8.50 mmol, 94%, >99.8% *ee*) is obtained in enantiomerically pure form.

Please submit the final product to your teaching assistant!

***9b)* Diphenylbutadiyne**



1. 1,2-dibromo-1-phenylethane

Day 1

Preparation: To a 250 mL round bottom flask, equipped with a dropping funnel and magnetic stir bar, is added 100 mmol styrene in 100 mL cyclohexane. The mixture is stirred for 10 min while cooling with a cold water bath (8 – 10 °C). Afterwards a solution of 100 mmol bromine in 50 mL cyclohexane is added dropwise (check dropping funnel for leaking before adding bromine). (The speed of addition should be as such, so that the red color of the bromine disappears right after each drop). After complete addition the mixture is stirred for 15 min at room temperature.

The precipitated product is filtered. The filtrate is washed with aqueous sodium thiosulfate solution, dried over sodium sulfate and concentrated *in vacuo* to yield a second product fraction. The combined crude product is dried *in vacuo*.

Day 2:

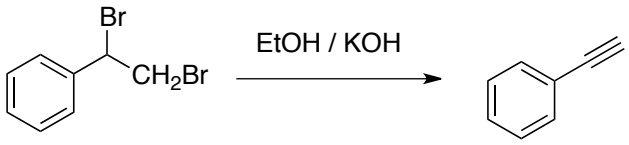
Purification: The solid is recrystallized. Find the proper solvent or solvent mixture!

Analysis: TLC, melting point, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
Styrene		1.00	100 mmol			
Bromine		1.00				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

2. Phenylacetylene



Preparation: A 250 mL round bottom flask is charged with 75 mmol 1,2-dibromo-1-phenylethane and mixed with 350 mmol (powdered!) KOH. The flask is equipped with a reflux condenser and 24 mL EtOH are slowly added through the condenser. An intense reaction will start and the flask is gently shaken from time to time until the reaction has ceased. Afterwards the mixture is heated to reflux for one hour.

The mixture is allowed to cool to room temperature and 100 mL water is added. The mixture is extracted twice with *tert*-Butylmethylether. The combined organic phases are dried ($NaSO_4$), filtered, and concentrated *in vacuo*.

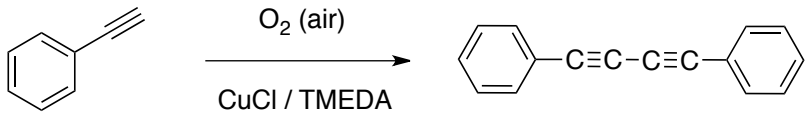
Purification: The residue is fractionally distilled under reduced pressure (bp: 142 – 144 °C/1000hPa; 40 – 45 °C/17hPa). The receiving flasks are cooled with an ice bath.

Analysis: TLC, boiling point, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
1,2-dibromo-1-phenylethane		1.00	75 mmol			
KOH		4.60				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

3. Diphenylbutadiyne



Preparation: A 200 mL round bottom flask equipped with a large stir bar is charged with 2.5 mmol CuCl, 40 mL acetone and 2.0 mmol TMEDA. 50 mmoL phenylacetylene are added via syringe dropwise within five minutes while stirring. Afterwards the reaction is stirred vigorously for two more hours.

The solution is filtered via filter paper and the filtrate is concentrated *in vacuo* to about 15 mL. After cooling the product crystallizes and 30 mL water is added. The mixture is filtered and washed with water until the washing water is not blue anymore.

The crude product is dried and dissolved in 50 mL cyclohexane. The solution is filtered again via filter paper to remove solid impurities and the solvent removed under reduced pressure.

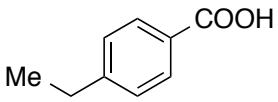
Purification: The solid is recrystallized. Find a proper Ethanol/H_2O mixture!

Analysis: TLC, melting point, IR.

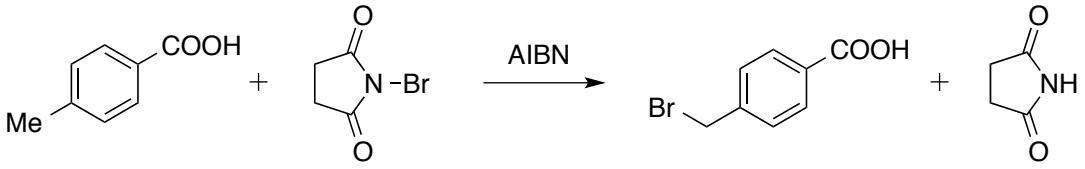
Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
CuCl		0.05	2.5 mmol			
TMEDA		0.04	2.0 mmol			
Phenylacetylene		1.00	50 mmol			
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

9c) 4-Ethylbenzoic acid



1. 4-(Bromomethyl)benzoic acid



Preparation: A 250 mL round-bottom flask under nitrogen atmosphere is fitted with a magnetic stirbar and a reflux condenser. The flask is charged with dry Cyclohexane (75 mL), 4-Methylbenzoic acid (60.0 mmol, 1.00 equiv) and NBS (1.00 equiv). To the solution a spatula tip of AIBN (~50 mg; **no metal** spatula!) is added and the mixture slowly heated to reflux. Refluxing is continued for 1 h and cooled down to 0 °C for 1 h. The precipitate is collected by filtration and washed with Cyclohexane (3 x 35 mL).

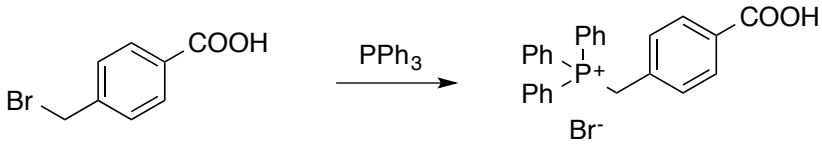
Purification: To the solid 150 mL water is added and the mixture stirred for 10 min. The non-dissolved residues are collected by filtration, washed with ice-water (50 mL) and dried in a vacuum desiccator over silica.

Analysis: TLC, melting point, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Methylbenzoic acid		1.00	60 mmol			
N-Bromosuccinimide		1.00				
AIBN		0.005				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

2. (4-carboxybenzyl)triphenylphosphonium bromide



Preparation: A 250 mL round-bottom flask under nitrogen atmosphere is fitted with a magnetic stirbar and a reflux condenser. The flask is charged with dry Acetone (150 mL), 4-(Bromomethyl)benzoic acid (20.0 mmol, 1.00 equiv) and PPh_3 (1.00 equiv). The mixture is heated to reflux for 1 h and allowed to cool down. The reaction mixture is further cooled in an ice bath and the precipitate collected by filtration. The filtrate is concentrated to 50 mL and cooled in an ice bath for 30 min. Another batch of product can be collected by filtration. The combined solids are washed with MTBE (2 x 25 mL) and dried.

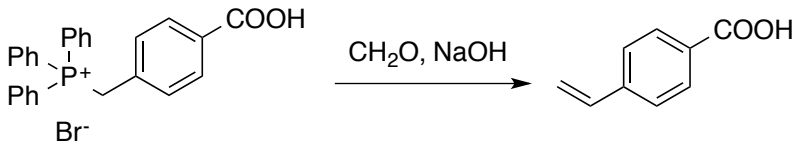
Purification: The phosphonium salt can be used without further purification.

Analysis: TLC, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-(Bromomethyl)benzoic acid		1.00	20 mmol			
Triphenylphospine		1.00				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

3. 4-Vinylbenzoic acid



Preparation: A 100 mL round-bottom flask is fitted with a magnetic stirbar and a dropping funnel. (4-carboxybenzyl)triphenylphosphonium bromide (10 mmol, 1.00 equiv) is suspended in water (15 mL) and 37% aq Formaldehyde solution (50 mL) is added. The dropping funnel is charged with a 5M NaOH solution (8.00 equiv) (check dropping funnel for leaking before adding base), which is added over 30 min with vigorous stirring at room temperature. The mixture is stirred for 1 h at room temperature. The precipitate is filtered and washed with water (3 x 25 mL). The filtrate (not the solid!) is acidified to pH 1 by dropwise addition of half concentrated HCl. The precipitate is collected by filtration, washed with ice-water (3 x 5 mL) and dried in a desiccator over phosphorous pentoxide.

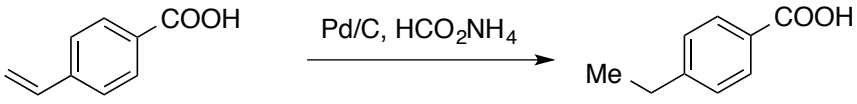
Purification: The product can be used without further purification.

Analysis: TLC, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
(4-carboxybenzyl) triphenylphosphonium bromide		1.00	10 mmol			
Formaldehyde					50 mL	37%
NaOH		8.00			-	-
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	

4. 4-Ethylbenzoic acid



Preparation: A 100 mL round-bottom flask fitted with a magnetic stirbar and a reflux condenser is charged with 4-Vinylbenzoic acid (5.0 mmol, 1.00 equiv) and dissolved in EtOH (50 mL). Ammonium formate (10.0 equiv) is added followed by Pd/C (10 wt% of substrate). The mixture is heated carefully to reflux for 1 h. After cooling to room temperature the mixture is fitered through a small plug of Celite, which is washed with EtOH. The solvent is removed and water (40 mL) is added. The aqueous phase is extracted with MTBE (3 x 30 mL). The combined organic layers are dried (Na_2SO_4), filtered, and concentrated *in vacuo*.

Purification: The solid is recrystallized. Find a proper Ethanol/H_2O mixture!

Analysis: TLC, IR.

Fill in these tables before you begin the experiments:

Reactant	**MW**	**Equiv**	**Moles**	**Mass**	**Volume**	**Purity**
4-Vinylbenzoic acid		1.00	5.0 mmol			
Pd/C 10%		-	-	74 mg	-	10%
Ammonium formate		10.0				
Product	**MW**	**Yield**	**Moles**	**Mass**	**MP**	