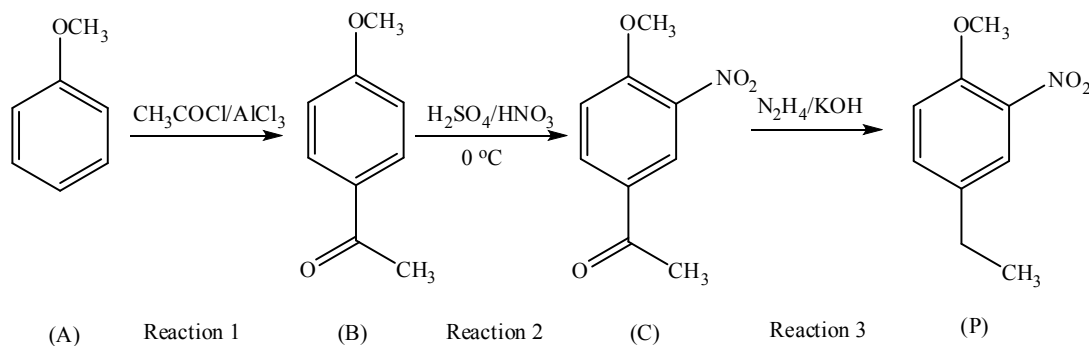
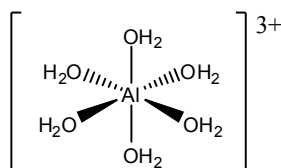


1. a. The first reaction is a Friedel-Crafts Acylation (FCA), where the major product is the para-isomer (60% isolated yield). The second reaction is a nitration, where the incoming electrophile (nitronium ion) is directed to the ortho position of the methoxy group. The last reaction is a Wolff-Kishner reduction that converts the acetyl group into an ethyl group. The nitro group does not react under these conditions.



b. The best solvent for the FC-acylation is dichloromethane. Tetrahydrofuran is a fairly strong Lewis base, which would react and deactivate the AlCl_3 catalyst. Ethanol would also react with AlCl_3 and form alcoholates, which are inactive at FCA catalyst. Dichloromethane is polar enough to dissolve all three compounds but does not form adducts with AlCl_3 . Thus, aluminum chloride maintains its Lewis acidity.

c. As discussed in lecture, $\text{AlCl}_3 \cdot 6 \text{H}_2\text{O}$ is not suitable as catalyst because the Al^{3+} is not a strong Lewis acid anymore. In addition, larger amounts of water would destroy the acetyl chloride as well ($\text{CH}_3\text{COCl} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{HCl}$). Consequently, the reaction would not proceed in the desired fashion.



d. In order to determine the yield, one has to calculate the number of moles of the reactant and the product.

$$n_{\text{A}} = 1.90 \text{ mL} \cdot 0.996 \text{ g/mL} / 108.14 \text{ g/mol} = 17.5 \text{ mmol}$$

$$n_{\text{CH}_3\text{COCl}} = 2.49 \text{ mL} \cdot 1.104 \text{ g/mL} / 78.5 \text{ g/mol} = 35.0 \text{ mmol}$$

$$n_{\text{AlCl}_3} = 4.67 \text{ g} / 133.5 \text{ g/mol} = 35.0 \text{ mmol}$$

Compound (A) is the limiting reagent. The student can expect to isolate 17.5 mmol of compound (B).

$$n_{\text{B}} = 1.50 \text{ g} / 150.17 \text{ g/mol} = 10.0 \text{ mmol}$$

Thus, the yield is

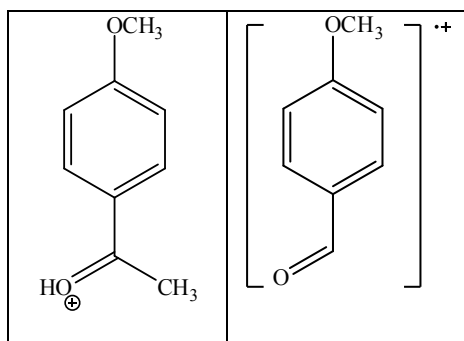
$$X = n_{\text{B}} / n_{\text{A}} \cdot 100 \% = 10.0 \text{ mmol} / 17.5 \text{ mmol} \cdot 100 \% = \mathbf{57.1 \%}$$

e. The nitration reaction itself is very exothermic. Compound (B) is a fairly good nucleophile due to the presence of the methoxy group, which means that the reaction will proceed fairly quickly. The reaction mixture has to be cooled to 0 °C to reduce the chance of dinitration.

f. Like in the lab, compound (B) is not polar enough to dissolve in the nitration mixture directly. Consequently, concentrated sulfuric acid could be used here as well since it is able to protonate the carbonyl group (structure on the left below) and therefore makes it soluble in sulfuric acid. The addition of the nitration mixture does not cause a phase separation afterwards, which makes it easier to control the reaction in the desired fashion.

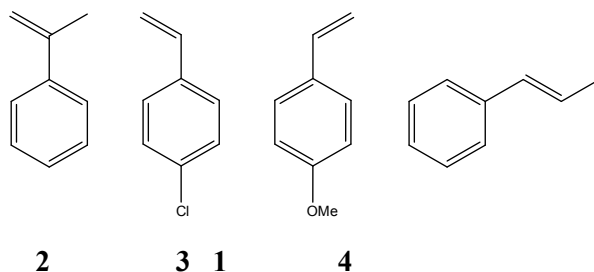
g. Compound (C) will have the lowest R_f -value, while compound (A) will exhibit the highest R_f -value. Compound (A) is an aromatic ether (=anisole), which are usually fairly weakly polar (after all it is a liquid at room temperature). Compound (C) possesses two polar groups (acetyl and nitro group), which both can bind strongly to the polar stationary phase via hydrogen bonding.

h. Extra Credit: The peak at $m/z=135$ is due to a very stable fragment. While the molecule can lose two different methyl groups, the one on the acetyl group is more likely to be the one leaving since a resulting radical cation is better resonance stabilized (structure on the right).



2.a. Bleach is used as oxidant in the epoxidation reaction in this lab. The advantages of this oxidant are that it is fairly cheap. The side products are mostly water soluble and the reaction can be carried out at room temperature. Disadvantages are that it is a two-phase reaction which slows the reaction down. The chemical selectivity is generally lower as compared to low-temperature reactions due to side reactions and the reaction is often less stereoselective under these conditions as well.

b.



The reactivity in this reaction is a result of the configuration of the alkene and the nucleophilicity of the alkene. Thus, the last compound (trans-β-methylstyrene) is the least reactive in the reaction because Jacobsen's catalyst does not work well with trans alkenes. On the other side, the third compound is most reactive because of the electron-donating effect of the methoxy group.

c. Hexane is a very poor choice as solvent for the epoxidation because the catalyst would not dissolve, which makes the reaction heterogeneous. The epoxidation would proceed extremely slowly if at all.

d. NaH_2PO_4 is the wrong buffer for the reaction. The pH-value would be too low, causing the formation of hypochlorous acid causing a chlorination of the alkene. In addition, the low pH-value would promote the hydrolysis of the catalyst and the epoxide as well. The proper buffer for this reaction is Na_2HPO_4 (pH~11).

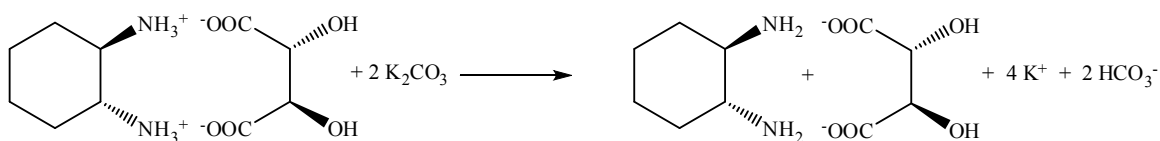
e. This is not the good way to carry out the reaction. The main problem is that the epoxide slowly hydrolyzes even if the reaction conditions are properly adjusted. Fortunately, under these conditions, the epoxidation is faster than the hydrolysis. However, if no more epoxide is formed, the hydrolysis step takes over and the previously synthesized epoxide is converted into a diol that dissolves in the aqueous layer. The student would isolate very little or no product in the end.

f. The best choice here would be the neutral form of alumina because epoxides are sensitive towards acids and bases. Both can cause rearrangement and ring opening reactions. The use of neutral alumina would minimize this possibility.

g. If the stationary phase is changed the R_f -values change as well since it is very sensitive towards many parameters. Unfortunately, it is very difficult to predict how much they change and if the separation is still satisfactory since it highly depends on the activity of the alumina. The solvent mixture as determined on silica is not useful anymore. The student has to obtain TLC plates coated with the same form of alumina and redo these solvent optimization tests.

h. First off, the fact that the TLC plate showed a blue spot upon ceric staining only indicates that there was a compound present that contained a heteroatom. This applies to the epoxide, but also to the aldehyde. The fact that only one peak is observed in the GC spectrum (using a chiral GC-column) allows the conclusion that the isolated product is the achiral aldehyde. If the chiral epoxide was isolated here, there should be two peaks in an approximate ratio of 3:1.

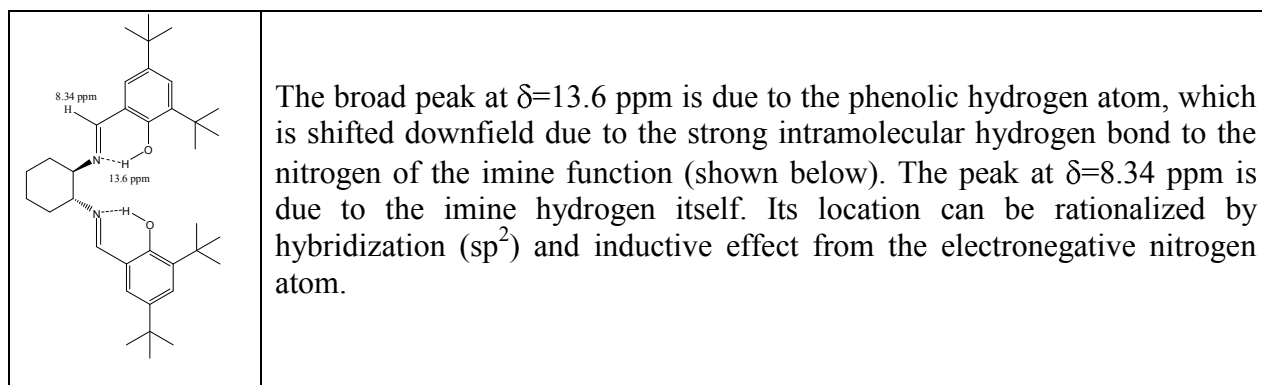
3.a. The initial reaction of the Jacobsen ligand synthesis is the release of the 1,2-diaminocyclohexane from the tartrate salt using potassium carbonate as a base. The reaction is carried out in water because the tartrate salt and potassium carbonate are ionic. Note that there are two equivalents of base required because hydrogen carbonate is too weak of a base to deprotonate the ammonium salt.



b. The student has to add more than two equivalents of the aldehyde to ensure that both amine groups are converted to the respective imine function. Under normal circumstances, a bright yellow precipitate is formed fairly quickly since the ligand does not dissolve well in ethanol.

c. The water is added before the reaction mixture is allowed to cool down. The addition of water increases the solvent polarity which lowers the solubility of the fairly non-polar Jacobsen ligand. By doing so while the solution is hot, the solubility drops more gradually than a sudden change in polarity which can cause the ligand to separate in form of an oil.

d.



e. In order to find the proper concentration, the largest peak is used for calibration. In this case, the peak at $\lambda=258$ nm has a molar extinction coefficient of $\epsilon=32000$. Since nothing else is stated here, $l=1$ cm and the maximum absorbance is $A_{\max}=1$

$$C_{\max} = A_{\max}/\epsilon \cdot l = 1/32000 \cdot 1 = \mathbf{3.125 \cdot 10^{-5} \text{ M}}$$

Using this concentration, the peak at $\lambda=325$ nm would exhibit an absorbance of

$$A_{325} = 3.125 \cdot 10^{-5} \text{ M} \cdot 7200 = \mathbf{0.225}$$

which is well with the limits of $0.1 < A < 1.0$.

f. In order to assess the optical purity, the specific optical rotation of the sample is compared with the literature data.

$$\text{Sample: } [\alpha] = -15.2^\circ / (0.150 \text{ g/3 mL}) * 1 \text{ dm} = -304^\circ$$

$$\text{Reference: } [\alpha] = -315^\circ$$

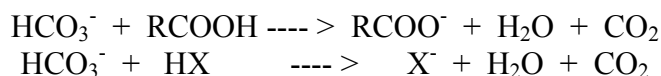
$$\text{Optical purity: } -304^\circ / -315^\circ * 100\% = \mathbf{96.5\%}$$

The optical purity is lower than described in the literature (>99%). This can be explained by improper preparation of the solution for the actual measurement, the fact that the sample might still be wet or poor resolution of the tartrate salt.

g. Extra Credit: The error message is caused by insufficient light at the detector. The improper filling of the polarimeter cell causes this most of the times. An air bubble gets trapped inside, and the light it diffracted of it, which results in a very low transparency of the sample.

4.a. Most the compounds that are synthesized in this lab course are medium in polarity. As a result, they do not dissolve well in water. On the other side, polar compounds like ionics and polar solvents like methanol, dimethyl sulfoxide, etc dissolve in the aqueous layer. The crude organic compounds are either isolated by filtration, or are redissolved in a fairly low polarity solvent i.e. dichloromethane to be further purified by extraction.

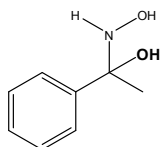
b. The extraction with sodium bicarbonate serves the purpose of neutralizing acids in the organic layer according to



The extraction is completed when the carbon dioxide formation ceased, which means that no more gas bubbles are observed in the extraction (and/or no more pressure is build up during the shaking of the centrifuge tube). The experimenter has to vent the extraction vessel more frequently to release the pressure build-up caused by the carbon dioxide formation.

c. Anhydrous sodium sulfate has a very capacity. It absorbs ten moles of water. In most cases, too much of the drying agent is added which poses a problem because other polar compounds are absorbed on it as well. If the student added enough drying agent, the solution is translucent and some of the drying agent is free floating in the mixture. The drying agent has to be removed because the drying process itself is reversible at elevated temperatures (entropy increases significantly!).

d. The formation of oximes requires a pH-value of 5-7 because the intermediate formed (shown below) has to lose a hydroxy group (the one in bold) in order to be able to form the C=N bond. This can only happen if there are sufficient protons in the solution.

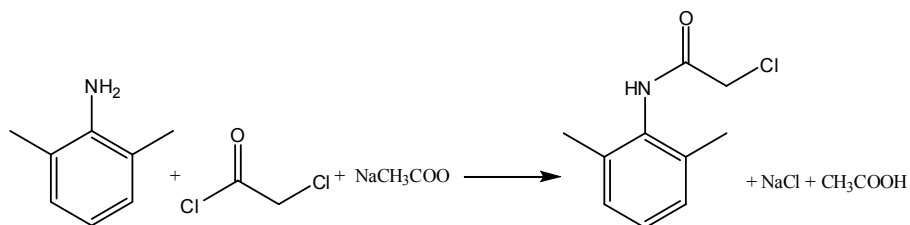


e. All reagent bottles should be kept closed if not needed. This prevents mishaps if something gets tipped over and also maintains the quality of the reagent. In case of the anhydrous magnesium sulfate, the compound would readily absorb moisture, which renders it useless as drying agent. ☹

f. Since it is virtually impossible to prepare a KBr pellet using a viscous oil, the best protocol would be to use a concentrated solution in dichloromethane. One or two drops are applied to the AgCl plate. The solvent is allowed to evaporate off completely leaving behind a very thin film of the oil. If this sample does not provide a satisfactory peak size, the procedure can be repeated to increase the thickness of the film, and therefore the quality of the spectrum.

g. Extra Credit: The abbreviation “ATR” stands for attenuated total reflection.

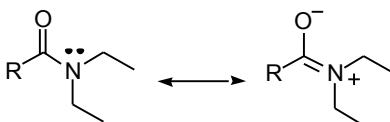
5.a. In the second step of the lidocaine synthesis, 2,6-xylidine is reacted with α -chloroacetyl chloride.



b. Glacial acetic acid is 100% acetic acid that does not contain water. This is necessary because α -chloroacetyl chloride is very sensitive towards water. The solution is usually more or less purplish in the beginning and changes to a lighter purple or reddish through the reaction. After addition of sodium acetate solution the anilide precipitates as a white solid.

c. The sodium acetate acts as a base which deprotonates the protonated form of the amide, while the unreacted 2,6-xylidine remains in solution as xylidium salt.

d. The C=O stretching frequency is fairly low because the amide is resonance stabilized by the amide resonance, which means that the molecule is more stable but the C=O bond is weaker.



The C=O stretching frequency for the amide is found at 1648 cm^{-1} .

6.a. The purpose of the TLC for the crude product is to evaluate how well the reaction progressed and how many other compounds are in the crude. If only the benzylic alcohol was present at this point, the student could skip the recrystallization step. In most cases, the crude contains more or less of the starting phenol and also the salicylic aldehyde. If the corresponding spots are large and very intense, this could help to explain a lower yield for this step.

b. This TLC is a purity check. Ideally, only one spot should appear here if the recrystallization was successful. If more than one spot is observed at this point, the TLC could be used to pinpoint the impurity that causes a melting depression and broadening.

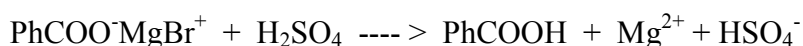
c. The tailing is a result of too much sample being applied to the TLC plate (overloading). The uneven spots are often observed if the sample from the solution is not sufficiently diluted. The DMSO in the sample absorbs strongly to the TLC plate and the other compounds get “washed” to the outside of the spot resulting in crescent shaped and strange looking spots.

d. The solvent mixture is too non-polar to cause significant movement of the compounds. The polarity of the solvent has to be increased to increase the R_f -values of the compounds on the TLC, and subsequently make the solvent mixture suitable for flash chromatography as well.

7.a. Water is a problem in the Grignard reaction because phenylmagnesium bromide is a very strong base, which reacts readily with compounds that possess acidic protons. Water is excluded from the reaction by heating the glassware with a heat gun prior use. In addition, a drying tube with CaCl_2 is placed on top of the reflux condenser, the joint are lubricated and the solvent used is anhydrous!

b. If the reaction initiates, the mixture turned cloudy, and then greenish. The solution starts to boil on its own because the formation of the Grignard reagent itself is exothermic. The remaining bromobenzene solution is added at the rate that the reaction remains boiling on its own.

c. The ice is meant to stabilize the temperature in the system. The sulfuric acid is used to convert the magnesium benzoate into benzoic acid and water-soluble Mg^{2+} salts. Since this is an acid-base reaction, a significant amount of heat is produced, which would cause the diethyl ether to boil off.



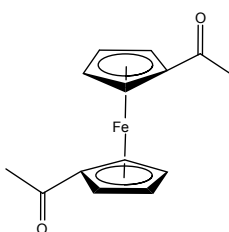
d. The extraction of the organic layer with sodium hydroxide transfers the benzoic acid as benzoate into the aqueous layer while unreacted bromobenzene, biphenyl and benzene remain in the organic layer. The benzoic acid can be recovered from the aqueous layer after addition of hydrochloric acid.



8.a. Hydrocarbons like cyclopentane exhibit $pK_a \sim 50$. This implies that very strong bases are required to deprotonate them efficiently. In case of cyclopentadiene, the acidity is greatly enhanced ($pK_a \sim 16$), because the formed cyclopentadienide ion is aromatic in nature and therefore very stable. A relatively weak base such as potassium hydroxide is strong enough to deprotonate CpH.

b. Dimethyl sulfoxide is polar enough to dissolve sodium cyclopentadienide and iron(II) chloride. On the other side, ferrocene is fairly non-polar and therefore precipitates from the solution as an orange solid while potassium chloride remains in solution.

c. The acylation reagent is fairly selective, because it is only present in low concentration. However, it is virtually impossible to prevent diacylation entirely because ferrocene is a very good nucleophile even after the first acylation.



The second acylation occurs at the unsubstituted ring because this ring is more electron-rich (=better nucleophile).

9.a. The degree of unsaturation is

$$\text{D.B.U.} = (2 * \text{C} + 2 - \text{H} - \text{Hal}) / 2 = (2 * 9 + 2 - 9 - 1) / 2 = 5$$

indicating the presence of a phenyl ring and one additional double bond or ring.

b. The IR spectrum shows peaks at $3001\text{-}3062\text{ cm}^{-1}$ ($\text{sp}^2\text{-CH}$), $2878\text{-}2978\text{ cm}^{-1}$ ($\text{sp}^3\text{-CH}$), 1596 , 1493 cm^{-1} ($\text{C}=\text{C}$, aromatic), 1250 , 1034 cm^{-1} (C-O , ether), 828 cm^{-1} (oop, para-substituted arene).

c. The $^1\text{H-NMR}$ spectrum exhibits signals at $\delta=7.23\text{ ppm}$ (d, 2H), 6.85 ppm (d, 2H), 4.21 (dd, 1H) , 3.89 ppm (dd, 1H), 3.34 ppm (m, 1H), 2.90 ppm (dd, 1H) and 2.74 ppm (dd, 1H). The two doublets in the aromatic range allow the conclusion that the benzene ring is para-substituted. The fact that there are a lot of “dd” signals allows the conclusion that there is most likely a stereocenter and/or ring involved that generates many diastereotopic protons.

d. The $^{13}\text{C-NMR}$ spectrum exhibits signals at $\delta=44.5\text{ ppm}$ (CH_2), 50.0 ppm (CH), 69.1 ppm (CH_2), all most likely somewhat close to an oxygen atom. In addition, there are four signals in the aromatic range (116.0 (CH) , 126.1 (-C-) , 129.4 (CH) and 157.1 (-C-)), which are indicative of a para-substituted ring system. There are seven carbon signals for nine carbon atoms, which means that the basic carbon framework contains some equivalent carbons.

e. Based on the discussion above, compound **Z** is **p-chlorophenyl-2,3-epoxypropyl ether**.

