1. a. The first reaction is a Claisen-Schmidt condensation between an aldehyde and a ketone, leading to an α,β-unsaturated ketone (C), which subsequently undergoes epoxidation to form an epoxide (D). The treatment with acid leads to a rearrangement product, a 1,2-diketone (P). The stereochemistry on the alkene is trans, while the stereochemistry on the epoxide is difficult to predict.

b. The first step here is to identify the limiting reagent.

Compound (A): \( n_A = \frac{2.00 \text{ mL} \times 1.045 \text{ g/mL}}{106.12 \text{ g/mol}} = 19.7 \text{ mmol} \)

Compound (B): \( n_B = \frac{2.0 \text{ g}}{100.16 \text{ g/mol}} = 20.0 \text{ mmol} \)

Compound (A) is the limiting reagent here, which means that 19.7 mmol of compound (C) should be formed in the reaction if the reaction would run in 100% yield. Since the yield is only 90%, the yield is 17.7 mmol or 3.34 g.

c. The solvent has to be fairly polar in order to ensure that the potassium hydroxide dissolves. In addition, it should not interfere with the reaction. Like in the lab a solvent like absolute ethanol or methanol would work well for reaction 1.

d. An excess of compound (B) has to be avoided in order to minimize the self condensation reaction after the aldehyde is consumed.

This reaction is usually less favorable because the reaction of ketones is less exothermic and therefore only occurs at a reasonable rates if there is no other electrophile present in the reaction.

e. The major product of reaction 1 is a trans alkene, which are generally poor substrates for epoxidation reactions using Jacobsen’s catalyst. In addition, the C=C double bond is connected to an electron-withdrawing group (COCH₃), which makes it an electron-poor alkene, and
therefore a weaker nucleophile. Both of these features make the alkene a poor substrate for the epoxidation \((reaction\ 2)\).

f. Since the alkene and the catalyst are relatively non-polar, and sodium hypochlorite (=bleach) is ionic, a two-phase system should be used here. Like in the lab, dichloromethane can be used as organic layer and a buffered bleach solution as aqueous layer.

g. The easiest way to carry out the reaction is to pour the crude epoxide onto a silica or acidic alumina column without pre-treating it with a base like triethylamine. This would cause the epoxide to rearrange to form the 1,2-diketone, which would be eluted in the end.

h. Extra Credit: The large peak at \(m/z=57\) is due to a fragment \([C_4H_9]^+\), also called tert-butyl, which is a fairly stable cation as well.

\[
[H_3C\overset{\bullet\bullet}{\underset{CH_3}{\text{C}}}CH_3]^+
\]
2. a. The esterification reaction is an equilibrium reaction with a low $K_{eq}$, and water is one of the products as can be seen from the equation below.

\[
\text{PhCOOH} + \text{CH}_3\text{OH} \rightleftharpoons \text{PhCOOCH}_3 + \text{H}_2\text{O}
\]

As such, the use of “wet” benzoic acid would force the reaction to equilibrate at a lower concentration of the ester according to the Le Châtelier Principle. This ultimately results in a lower yield for the ester.

b. The equation above is based on moles and not on weight or volume of reactants. In addition, methanol serves a two-fold purpose here. It is a reactant and also serves as solvent for the solid benzoic acid. The excess of methanol used in the reaction also “pushes” the equilibrium to the right side (Le Châtelier Principle).

c. The concentrated sulfuric acid acts as a catalyst in the reaction. The carboxylic acid is a fairly weak electrophile and the alcohol a fairly weak nucleophile. Ultimately, the carbonyl oxygen of the acid is protonated which increases the electrophilic character of the acid since the carbon atoms carries more of a positive charge then.

d. The addition of water causes a phase separation (aqueous: alcohol, sulfuric acid, organic: ester, unreacted benzoic acid as major components). The diethyl ether allows extracting the ester droplets from the aqueous layer. However, 5% sodium hydroxide is the wrong reagent to remove the unreacted benzoic acid and the sulfuric acid from the organic layer because it also reacts with the ester (saponification).

The resulting benzoate dissolves in the aqueous layer, which means that very little ester will remain in the end. ⊗ The proper reagent to remove the unreacted benzoic acid and the sulfuric acid catalyst would be sodium bicarbonate which is a weaker base and weaker nucleophile.
3. a. Potassium carbonate is used as a base to deprotonate the diammonium salt. Two equivalents of the base are required because the bicarbonate ion formed after the first reaction is not strong enough of a base in order to deprotonate the other ammonium function.

\[
\text{NH}_3^+ + \text{NH}_3^+ + 2 \text{CO}_3^{2-} \rightarrow \text{NH}_2\text{NH}_2^+ + 2 \text{HCO}_3^-.
\]

b. Potassium carbonate and the diammonium salt are both ionic, thus very polar. This means that a polar solvent like water has to be used to dissolve them. If ethanol was used in this step, the deprotonation step would take much more time due to the heterogeneous nature of the reaction mixture. The addition of ethanol later on serves the purpose of increasing the solubility of the salicylic aldehyde in the solution.

c. In order to determine the optical purity, the specific optical rotation for the sample has to be determined and then compared with the optical rotation of the pure sample.

Concentration of the solution: \( c = 0.250 \text{ g/10 mL} = 0.025 \text{ g/mL or 2.5\%} \)

Specific optical rotation for sample: \( \alpha = \frac{\omega}{(c*l)} = -7.7^\circ/(0.025 * 1) = -308^\circ \)

Optical purity = \( \frac{-308^\circ}{-315^\circ} * 100\% = 97.8\% \)

Even though the optical purity is less than 99\% as ideally desired, it will provide a pure enough template to be able to prove that the catalyst is stereoselective.

d. The signal at \( \delta = 13.6 \text{ ppm} \) in the \(^1\text{H}-\text{NMR}\) spectrum is due to the phenolic hydrogen atom that is shifted downfield significantly due to the intramolecular hydrogen bond formed with the imine nitrogen atom.
The large shift of the phenolic hydrogen atoms is indirectly an indication for a very strong interaction.

e. In order to determine the proper concentrations Beer’s Law is used. Assuming a 1 cm cuvette and a maximum absorbance of A=1, one obtains the maximum concentration to be

\[ c = \frac{A_{258}}{(\varepsilon \times l)} = \frac{1}{(32000 \times 1)} = 3.125 \times 10^{-5} \text{ M} \]

The second peak exhibits an absorption of

\[ A_{328} = 3.125 \times 10^{-5} \text{ M} \times 7200 \times 1 = 0.225 \]

which is within the desirable range of 0.1 < A < 1.0.

f. The peak at \( \nu = 1631 \text{ cm}^{-1} \) is due to the stretching of the C=N bond of the imine function, while the peak at \( \nu = 2962 \text{ cm}^{-1} \) is due to the C-H(sp\(^3\)) of the tert.-butyl groups.

g. As discussed above already, the ligand exhibits a very strong intramolecular hydrogen bond. This shows in various spectra and also in its physical properties i.e. solubility. Since the hydroxyl groups are not available for interaction with the solvent and the rest of the molecule is fairly non-polar as well, the solubility in a polar solvent like ethanol is very limited. On the other side, the ligand dissolves fairly well in medium and non-polar solvents like dichloromethane and hexane. Considering the intramolecular hydrogen bond, the “like-dissolves-like” rule still holds.
4. a. The addition of water to the reaction mixture causes often time the organic compounds that have a low polarity to precipitate as a solid or oil. This way, the polar solvents like alcohols and dimethyl sulfoxide are removed in addition to ionic compounds like sodium salts or acids. The organic compounds are subsequently extracted into an organic solvent like dichloromethane, diethyl ether or hexane.

b. Most reagents used in the lab are either sensitive towards oxygen or water. For example, a drying agent like magnesium sulfate loses its activity quickly because it absorbs moisture. Many anhydrous solvents like diethyl ether or ethanol also absorb moisture and therefore are not anhydrous anymore, which causes serious problems in many reactions i.e. Grignard reaction.

c. The procedure has to be downscaled by a factor of fifty. As a result, the procedure should read something like this:

“…5 g of compound G and 2.4 g of compound H are dissolved in 20 mL of methanol and then refluxed for two hours. The mixture is then cooled in an ice-bath and the precipitate isolated by vacuum filtration. The filter cake is washed twice with 2 mL of ice-cold methanol. The final yield is expected to be approximately 5 g…..”

The information in bold is the important information that has to be adjusted properly. Note that the reaction time remains the same.

d. Even though the wetting of the column is usually recommended prior to applying the sample, it should be done with a non- or weakly polar solvent if a polar stationary phase is used for chromatography. This holds especially true if relatively weakly polar compounds are to be separated. In this case, 10% ethyl acetate in petroleum ether is enough to cause the mono-acylation product to move. Applying pure ethyl acetate to the column prior to applying the crude would block out the majority of the surface side for the acylation products, which means that they would basically just flushed through the column without being separated. 😊

e. Saturated sodium chloride solution is used to remove very polar impurities and most of all water from the organic layer. Often times, solvents like alcohols, etc are used that increase the solubility of water in the organic layer. In essence, the extraction with saturated sodium chloride solution is a pre-drying step, which reduces the need for other drying agents like sodium sulfate, etc.

f. The use of CH₃OH would be a poor choice because the NMR spectrometer would have a very difficult time to lock the magnetic field. As a result the obtained data would probably be rather meaningless. In addition, the student would see a very large signal for the methanol itself in the
\(^1\)H-NMR spectrum, which would make it very difficult to detect the actual compound signals as well.

g. The ground glass joints do not fit perfectly together even though they possess a standard size. In order to improve the seal and also to ensure that they can be separated later on, high-vacuum grease is used. However, the grease should be used lightly on the top third of the joint only in order to avoid the contamination of the product and grease to be all over the glassware on the outside.

h. *Extra credit:* In the beginning, the \(\tau\)-scale was frequently used for NMR spectroscopy. The \(\tau\)-scale starts at \(\delta=10\) ppm and increases towards the right side in the spectrum (thus upfield!). As a result, \(\tau=7.5\) ppm correlates to \(\delta=2.5\) ppm.
5. a. The electrophile in the nitration reaction is the nitronium ion. In the lab it is obtained by reaction of concentrated nitric acid and concentrated sulfuric acid.

\[
\text{HNO}_3 + \text{H}_2\text{SO}_4 \rightleftharpoons \text{NO}_2^+ + \text{HSO}_4^- + \text{H}_2\text{O}
\]

Nitric acid acts as a base in this reaction while sulfuric acids acts as the acid.

b. Since the nitronium ion is a very strong electrophile, it was crucial to control the temperature well during the nitration of the methyl benzoate. This was accomplished by placing the reaction mixture in an ice-bath and by adding the nitration mixture very slowly in order to allow the system to dissipate the heat. This way the dinitration can be kept to a minimum because this step has a slightly higher activation energy compared to the first nitration. However, the dinitration product is thermodynamically more stable than the mononitration product.

c. The main difference between the acylation and the alkylation is that the first one deactivates the aromatic system because an acceptor group is attached to the ring, while the second one causes activation because alkyl groups are weakly activating. As a result, the first acylation prevents any further acylation, while the product from the alkylation is actually more reactive than the original arene itself.

\[
\begin{align*}
\text{CH}_3 \text{H} & \text{OC} \text{CH}_3 \\
\text{Decreasing activity towards electrophiles}
\end{align*}
\]

d. The problem here is that the amine is a strong Brønsted and Lewis base. Later one reacts with the strong Lewis acid, AlCl₃, and forms an adduct.

\[
\begin{align*}
\text{NH}_2 + \text{AlCl}_3 & \rightarrow \text{NH}_2 \text{AlCl}_3 \\
\end{align*}
\]

The formerly activating and ortho/para-directing amine group is converted into a strongly deactivating and meta-directing group. This reaction can be prevented by converting the amine into an amide which is still weakly activating and ortho/para-directing as well.
6. a. Sodium acetate is used as the base to deprotonate the hydroxylamine hydrochloride.

\[
\text{NH}_3\text{OH}^+ + \text{OAc}^- \rightarrow "\text{NH}_2\text{OH}" + \text{HOAc}
\]

The hydroxylamine is generated \textit{in-situ} and consumed in the reaction with the ketone immediately.

b. The reaction profile shows that the reaction proceeds slowly at low and high pH-values. A low pH-values, not enough hydroxylamine is formed (see above), while at high pH-values the protons are missing to remove the hydroxyl group highlighted in the intermediate below.

![Intermediate Diagram]

The optimal pH-value for reaction as indicated in the diagram above is pH=4-5, at which enough hydroxylamine is formed and also the acidity is high enough to promote the dehydration of the intermediate.

c. Compounds (J) and compound (K) are diastereomers of each other. Generally, the anti-isomer (compound (K)) would be the major product for ketones because it exhibits less steric hinderance. A Spartan calculation (AM1) reveals that the anti-isomer is about 1.9 kcal/mol more stable than the syn-isomer.
7. a. Compound (M) has a larger dipole moment than compound (N). The intermolecular forces are stronger in the case of compound (M) resulting in an increased melting point. The mass difference between these two compounds cannot really account for the higher melting point of compound (M).

b. Compound (O) is much more reactive towards water since it is an acyl chloride because the chloride ion is a better leaving group than the methoxide. As a result, the hydrolysis of the acyl chloride occurs relatively rapidly, while the hydrolysis of the ester is fairly slow (at room temperature). In both reactions the compound would be converted into the corresponding carboxylic acid.

c. Compound (O) would exhibit a lower R_f-value because it is much more polar due to the presence of the nitro group. The nitro group exhibits a dipolar character (positive charge on the nitrogen atom and negative charge on the oxygen atoms), which allows for a strong interaction with polar stationary phases. Aside of that depending how much water is in the system, the acyl chloride would probably hydrolyze anyway (see c.).

d. Hexane would be the best solvent for recrystallization for Compound (N) since it is the least polar. Compound (O) and compound (M) is are too polar due to the nitro groups, which means that they would exhibit a very limited solubility even at higher temperature.
8. a. Cyclopentadiene tends to dimerize relatively quickly at room temperature. As a result, it has to be prepared fresh from dicyclopentadiene by a cracking process.

\[ \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \xrightarrow{\sim 180 ^\circ C} \quad \text{H} \quad \text{H} \quad + \quad \text{H} \quad \text{H} \]

This process can be understood as a Retro-Diels-Alder reaction. The obtained monomer should be kept at low temperatures (T~78°C) until needed in order to avoid redimerization.

b. The main difference between cyclopentene and cyclopentadiene is that the resulting anions are very different in stability. While the anion formed from cyclopentene is fairly unstable, the anion formed from cyclopentadiene is very stable since it is aromatic (6π-electron). As a result a relative weak base like potassium hydroxide is sufficient to deprotonate the diene.

c. The use of the hexamine complex provides an additional driving force for the reaction.

\[ [\text{Co(NH}_3\text{)}_6]\text{Cl}_2 + 2 \text{NaCp} \rightarrow \text{THF} \rightarrow \text{CoCp}_2 + 2 \text{NaCl} + 6 \text{NH}_3 \]

Aside of the desired cobaltocene, ammonia is formed that leaves the system as a gas, which results in a large entropy increase. Using THF as solvent here causes the sodium chloride to precipitate in addition, which also shifts the equilibrium.

d. The difference between these two compounds is that ferrocene has a full valence shell (18 VE), while cobaltocene has 19 VE, which makes it very susceptible towards oxidation. Cobaltocenium (CoCp\(_2^+\)) on the other hand are very stable and commonly used as counter ions for large anions.
9. a. The degree of unsaturation is \[ \text{D.B.E.} = \frac{2 \times 11 + 2 - 13 + 1}{2} = 6 \]

b. The most important peaks in the infrared spectrum are (in cm\(^{-1}\)): 3294 (\(\nu(\text{NH})\)), 3004-3099 (\(\nu(\text{CH}, \text{sp}^2)\)), 2873-2959 (\(\nu(\text{CH}, \text{sp}^3)\)), 1714 (C=O, ketone), 1668 (C=O, amide), 1514, 1607 (C=C, aromatic), 818 (oop, para-subst.).

c. The proton spectrum shows six signals as shown in the table below.

<table>
<thead>
<tr>
<th>(\delta) (ppm)</th>
<th>Multiplet</th>
<th>Integration</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.10</td>
<td>s, br</td>
<td>1</td>
</tr>
<tr>
<td>7.41</td>
<td>d</td>
<td>2</td>
</tr>
<tr>
<td>7.11</td>
<td>d</td>
<td>2</td>
</tr>
<tr>
<td>3.54</td>
<td>s</td>
<td>2</td>
</tr>
<tr>
<td>2.30</td>
<td>s</td>
<td>3</td>
</tr>
<tr>
<td>2.29</td>
<td>s</td>
<td>3</td>
</tr>
</tbody>
</table>

The signal at \(\delta=9.1\) ppm is due to an amide proton, while the two doublets at \(\delta=7.11\) and 7.41 ppm are indicative of a para-substituted benzene ring. The singlet at \(\delta=3.54\) ppm is due to a methylene group next two weakly deshielding groups. Finally, the two singlets around \(\delta=2.3\) ppm are due to methyl groups on a benzene ring or a carbonyl function.

d. The \(^{13}\text{C-NMR}\) shows nine signals for eleven carbons total, which means that there is some kind of symmetry in the molecule. The signals at \(\delta=204\) and 164 ppm are due to a ketone and an amide, respectively (both are quaternary carbons). The signals at \(\delta=134\) and 135 ppm are quaternary carbon atoms and the signals at \(\delta=120\) and 129 ppm indicate a disubstitution on the ring. The signal at \(\delta=51\) ppm is a result of a methylene function, while the remaining two signals are due to methyl groups.

e. Based on the discussion above, the compound \(Z\) is N-(p-tolyl)acetoacetamide.