Reduction of a ketone using sodium borohydride. Control of a reaction by TLC

Supplementary Material

This work is intended to first year chemistry students and uses the easily performed reduction of benzophenone to diphenylmethanol in the presence of sodium borohydride as a starting point to introduce the control of a reaction by TLC. It also includes a recrystallization in an organic solvent that is suitable to increase the skills of students that had limited contact with recrystallization techniques. In the final part the students perform a melting point of the product and compare the IR of the product with the IR of the reagent.

The students perform the reaction in an ice bath to reduce its rate in order to follow it easily by TLC which is made at 0, 5, 10, 15 minutes or every five minutes until the reaction is complete. The results are obtained rapidly because TLC plates are developed as the reaction is taking place and the spots are easily visualized under UV light. The end of the reaction is easily monitored by the disappearance of the substrate and the formation of the product as they have very different Rf. The spot of benzophenone is more suitable to follow the reaction than the diphenylmethanol spot because this last one is usually "tailed". However since the standard of diphenylmethanol is also applied in the plates the students are able to see the disappearance of the benzophenone spot and the appearance of a spot that corresponds to diphenylmethanol.

The spot of the diphenylmethanol can be improved by taking a small aliquot of the reaction mixture with a Pasteur pipette, transferring it to a test tube containing 0.5 ml of water and 0.5 ml of ethyl acetate, shaking the tube and applying a sample from the top layer to a TLC plate. However we found that applying a spot directly from the reaction mixture is a lot easier and is suitable for the objective. Moreover the extraction process takes some time and dilutes the sample, making it more difficult for the students to perform the TLC in real time.

It is very important that students validate the TLC procedure before starting the reaction. Even in an ice bath the reaction is usually complete in less than 10 minutes, so students must be at ease with this TLC procedure in order to follow the reaction appropriately. We propose that they start the experiment by making the solution of benzophenone in methanol and then (before adding the sodium borohydride) use the solution to run a TLC against the standards of benzophenone and diphenylmethanol. This allows the students to practice the TLC technique before doing the control of

the reaction. We advise the instructor to briefly discuss with the students the results of this first TLC. This will rapidly show if they (i) are able to perform the technique in real time and (ii) identify the spots appropriately.

Regarding TLC, benzophenone has a Rf of *ca* 0.6 and diphenylmethanol has a Rf of *ca* 0.3 in the suggested eluent. The intensity of the spots can be visualized before the run by observing the spots under the UV lamp after application. This saves time in the class as allows the application of more sample if needed or even the disposal of the plate if too much sample was applied.

It is important that the students perform the TLC appropriately and are able to identify the spots as the interpretation of the TLC plates will be fundamental to follow the reaction. The objective is that they are able to decide for themselves when the reaction is complete.
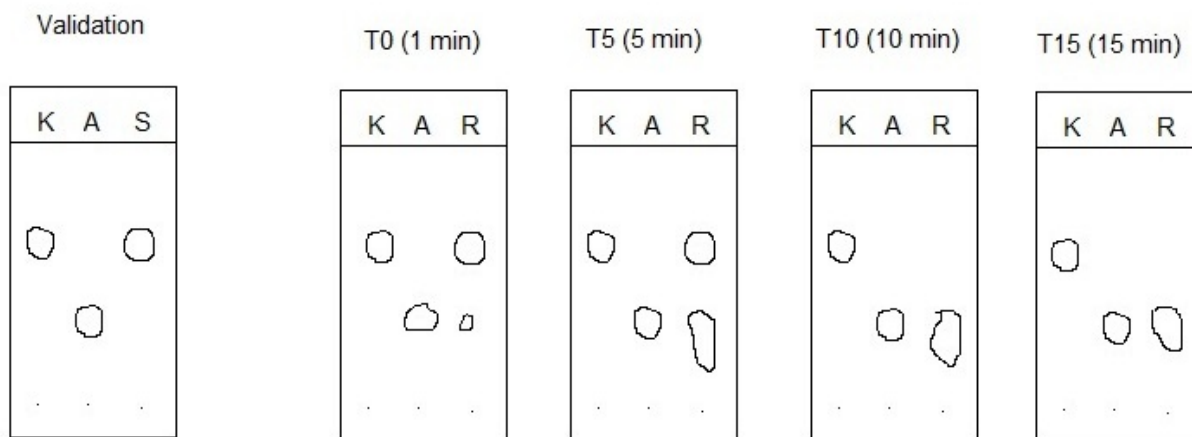
Figure SM 13.1.1. Schematic TLC results obtained in the validation and in the reaction runs. K - benzophenone standard, A – diphenylmethanol standard, S – benzophenone solution, R – reaction.

The reaction is usually finished in 5-10 minutes. The end of the reaction is confirmed after two TLC plates demonstrate the presence of diphenylmethanol and the absence of the ketone. Evidently this can be done after the first TLC, but the confirmation with a second time point does not take long and gives more confidence to the results. If the reaction is not finished after 15 minutes at room

temperature the reason is usually because the students have added an insufficient amount of sodium borohydride. An extra amount can be added to solve the problem

After the reaction finished the product is precipitated and a recrystallization is done. The technique is performed in petroleum ether and is appropriate to increase the skills of students that have only executed a recrystallization using a less volatile solvent (e.g. water).

The crystals must be fairly dry before the dissolution in petroleum ether can be done because the product contains water. Usually it is sufficient to let the crystals in the Buchner funnel with the vacuum on for 3 minutes and then drying the crystals between two filter papers, but if needed the material can be dried in the drying oven. It is important that the temperature of the oven is set bellow the melting point of the product (65 – 67 ºC). In case the crystals are not properly dried a water phase may form below the petroleum ether phase during the dissolution of the crystals. In this case the water can be removed carefully using a Pasteur pipette.

It is important to draw the attention of the students that the solvent is volatile and that it keeps evaporating while they are trying to dissolve the crystals. It is advisable to add hot solvent to the crystals. One way of reducing the evaporation of the solvent is to dissolve the crystals in an Erlenmeyer with a glass funnel on top performing as a condenser. A water bath should be used as a source of heat. Heating should not be performed directly over a hot plate. Flash point of petroleum ether 40-60 is c.a. -20ºC and its auto-ignition temperature is c.a. 290ºC.

Usually the crystals have no insoluble or colored impurities and treatment with charcoal and/or hot filtration is not needed.

This reaction has been used in our lab for many years always with very good results. The yield after recrystallization is typically 60-70% and the product give a very sharp melting point that can be determined during the class as the crystals are easily dried. Spectroscopic IR data can also be obtained and discussed during the class. The ideal time for this session is 4 hours however the experiment can be performed in a 3 hour session if the IR are not done by the students and part of the discussion around the work is done in writing as a homework assignment.

Regarding IR, figure **SM 13.1.**2 below shows a spectrum of benzophenone and a spectrum of diphenylmethanol. Attention can be drawn to the disappearance of the C=O band at 1659 cm^{-1} and the appearance of the OH broad band with a maximum at 3321 cm^{-1}. The instructor can also note that

benzophenone is an aromatic ketone and its carbonyl stretching band has a lower wave number than an aliphatic ketone.

Benzophenone
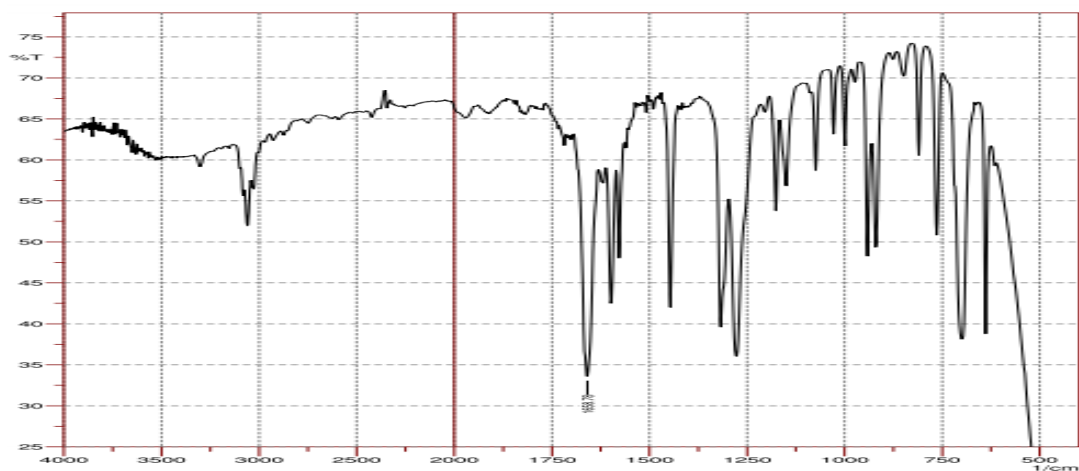
DIphenylmethanol
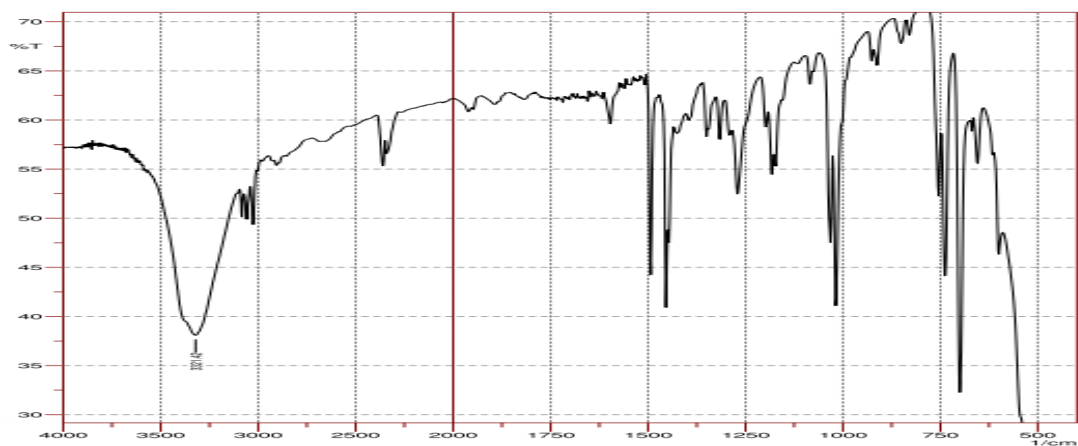
Figure SM 13.1.2. IR spectra of benzophenone and diphenylmethanol. Note the disappearance of the C=O band at 1659 cm^{-1} and the appearance of the OH broad band at 3321 cm^{-1}.

Results interpretation and additional questions:

1. Identify the bands correspondent to the ketone in the starting material and the alcohol in the product.

See IR figure and text above

2. Discuss the results and the purity of the product (use IR and m.p. data).

The yield after recrystallization is typically 60-70% and the product give a very sharp melting point. Spectroscopic IR data can also be obtained and discussed during the class.

3. How many moles of benzophenone can be reduced with one mole of sodium borohydride?

In theory 4 moles of benzophenone can be reduced with one mole of sodium borohydride. In practice some of the borohydride is consume in reaction with the solvent and excess of NaBH$_4$ is always used

4. Could you perform the same reaction with lithium aluminium hydride as a reducing agent? What would you do differently in this case?

Lithium aluminium hydride is a stronger reducing agent but it also reduces ketones. This reducing agent must be used in aprotic solvents like anhydrous diethyl ether or tetrahydrofuran. Following reduction, a separate hydrolysis step, by the addition of water or acid, is required to liberate the alcohol.

5. If sodium borohydride was added to benzoic acid what product would you expect? What if the reducing agent was lithium aluminium hydride?

When sodium borohydride is added to benzoic acid no reaction will occur. Sodium borohydride is not a potent hydride donor and so does not reduce carboxylic acids which are exceedingly difficult to reduce. With lithium aluminium hydride, a stronger reducing agent, benzoic acid will be reduced to benzyl alcohol (phenylmethanol).

Regioselective catalytic transfer hydrogenation of citral
Supplementary Material

The goal of this experiment is the demonstration of a hydrogenation reaction performed under reaction conditions that are compatible with the teaching environment – without using hydrogen gas. The protocol is based on the reports of Heck and co-workers.[1] The student body is students of first year of MSc in the course of organic chemistry, in which the concepts of alkenes hydrogenation were learned. This experience was performed twice in a teaching environment. We would like to emphasize that the reaction mixture must be allow to cool down to room temperature before opening the system to perform the TLC analysis or work-up. For the TLC analysis it is necessary to perform a work-up of an aliquot of the reaction mixture in a small vial according to the general work up protocol described in the manuscript. The yield of the crude product is 80 to 85%. The common filtration through celite of the reaction mixture containing Pd/C is not performed in this experiment to simplify the protocol. This fact does not affect the work-up or analysis of the crude product. Modification of the protocol was not performed but filtration through celite and column chromatography purification can be performed.

For a recent review on citral hydrogenation please see the review reported by Stolle *et al.*[2] In the context of transfer hydrogenation, Bose and co-workers in 1999 demonstrated that microwave irradiation accelerates the reaction (< 5min reaction time), however this was not tested by students.[3]

The importance of the chiral citronellal in total synthesis can be further discussed with the students based on the provided references.[4]

Commercial available citral (3,7-dimethyl-2,6-octadienal; CAS number 5392-40-5) is a mixture of the isomers geranial and neral (geranial is usually the major isomer). The ^{1}H NMR of the starting material is present in figures **Scheme SM 13.2.**1-3. The students are encouraged to analyze the spectrum of the starting material and to determine the ratio of the isomers based on the distinct signals of the aldehyde.

Theoretically several other products can be formed by hydrogenation of citral, namely the hydrogenation of the other double bond, and the carbonyl reduction. Furthermore it is also known that under acid catalysis menthol derivatives can be formed.[2] Regarding the mechanism of the hydrogenation is believed that the hydrogen is transferred from the organic source (triethylammonium formate) to the metal catalyst surface (Pd on carbon) forming metal hydrogen bonds. In a sequential

[1] N. A. Cortese, R. F. Heck, *J. Org. Chem.* 1978, **43***, 3985.

[2] Achim Stolle, Thomas Gallert, Christine Schmöger and Bernd Ondruschka, *RSC Adv.*, 2013, **3**, 2112

[3] B. K. Banik, k. J. Barakat, D. R. Wagle, M. S. Manhas, A. K. Bose, *J. Org. Chem.* 1999, **64***, 5746.

[4] For a review see: Eder J. Lenardão, Giancarlo V. Botteselle, Francisco de Azambuja, Gelson Perin and Raquel G. Jacob, *Tetrahedron*, 2007, **63**, 6671. For very recent examples on the use of citronellal in total synthesis see Karre Nagaraju, Prathama S. Mainkar, Srivari Chandrasekhar, *Tetrahedron Letters*, 2015, **56**, 404

manner, two hydrogen atoms are then transferred to the electron-deficient alkenes, which is also absorbed onto the metal catalyst surface, forming new C-H bonds. Due to the physical arrangement of the alkene and the hydrogens on a flat metal catalyst surface, the two hydrogens must add to the same face of the double bond, resulting in *syn* addition.[5]
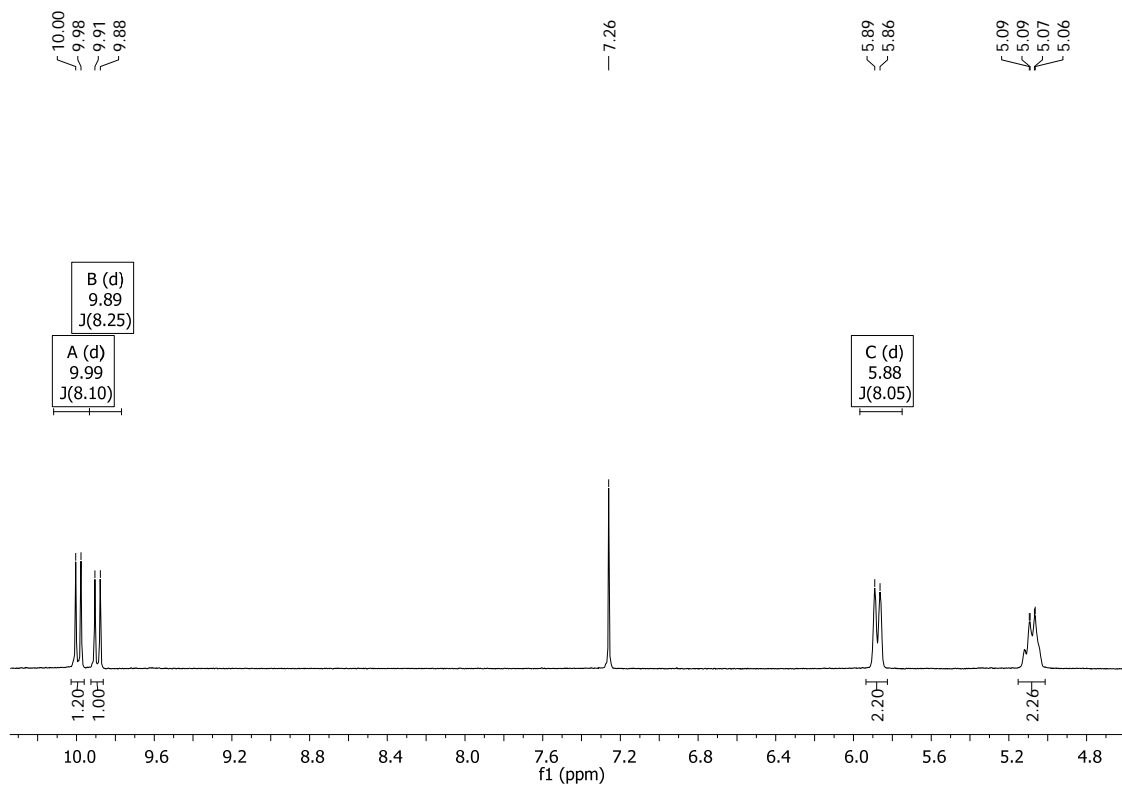
E, citral A, geranial
major isomer
55%

Z, citral B, neral
45%
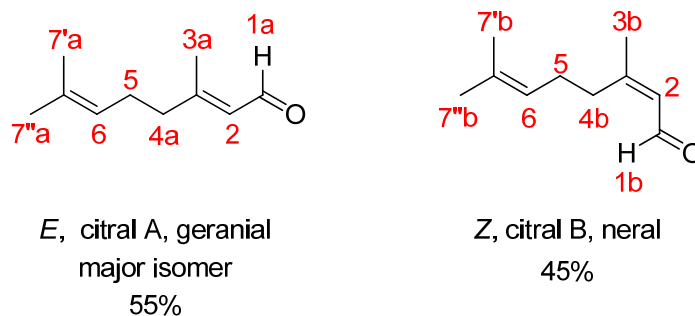
Citral ¹H NMR (300 MHz, CDCl₃) δ 9.99 (d, *J* = 8.10 Hz, 1H, 1a), 9.89 (d, *J* = 8.25 Hz, 1H, 1b), 5.88 (d, *J* = 8.05 Hz, 2H, 2), 5.88 (m, 2H, 6), 2.58 (t, *J* = 7.47 Hz, 2H, 4b), 2.24-2.18 (m, 6H, 5+4a), 2.16 (d, J = 0.82 Hz, 3H, 3a), 1.98 (d, J = 1.07 Hz, 3H, 3b), 1.68-1.59 (various s, 12H, 7).
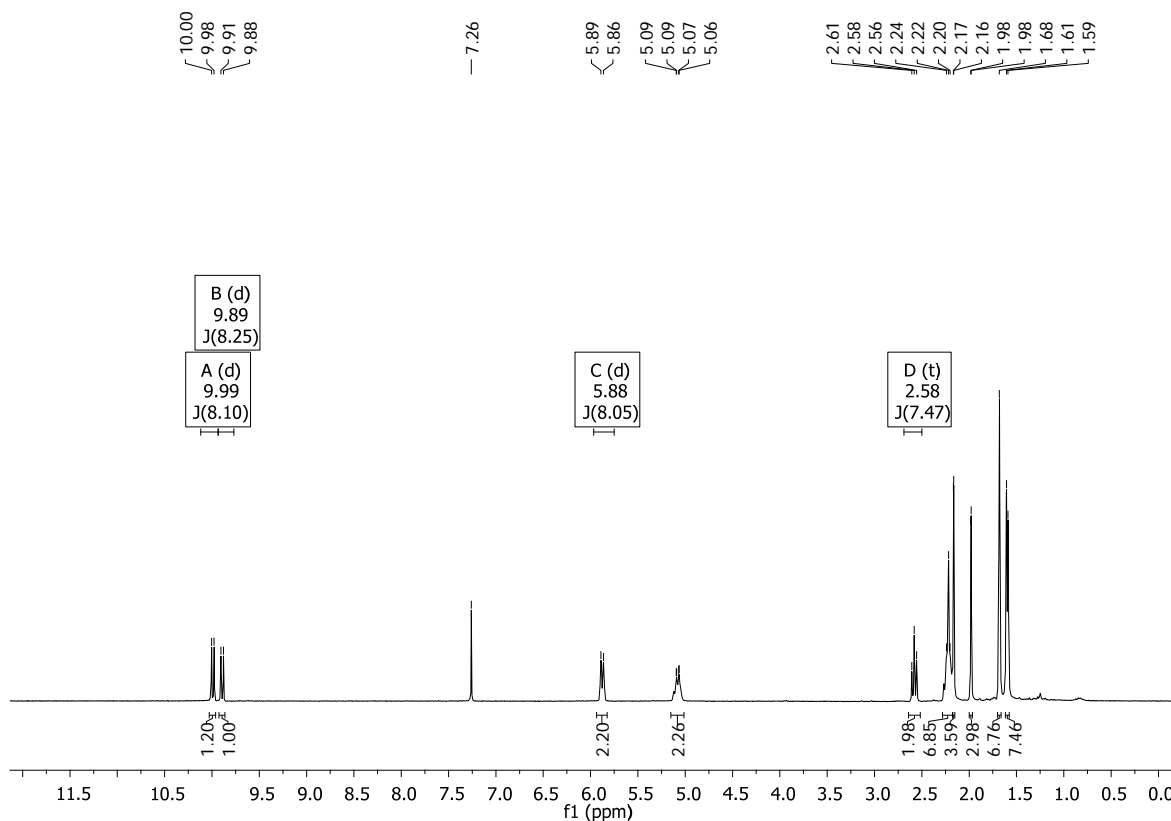
Scheme SM 13.2.1. ¹H NMR (300 MHz) spectrum of starting material citral in CDCl₃

[5] Gottfried Brieger and Terry J. Nestrick, *Chem. Rev.*, 1974, **74**, 567.

Scheme SM 13.2.2. Expansion of ^{1}H NMR (300 MHz) spectrum of starting material citral in CDCl$_3$ (4.8 to 10.2 ppm)
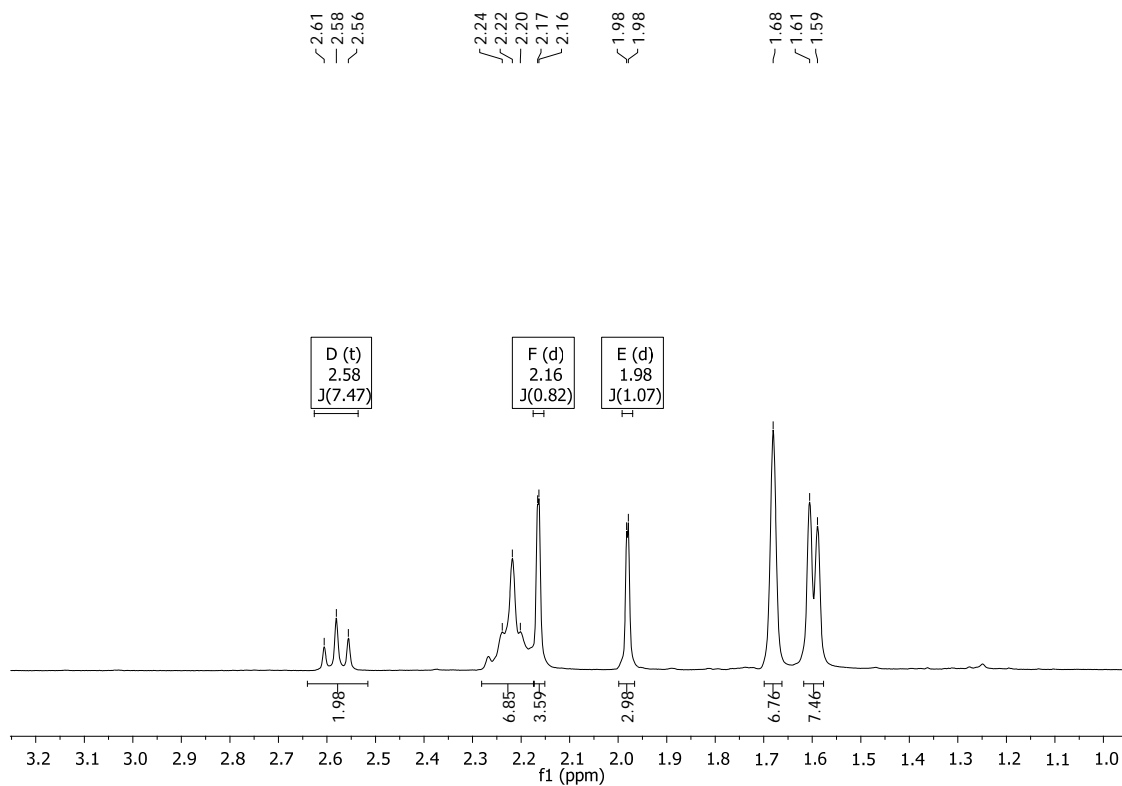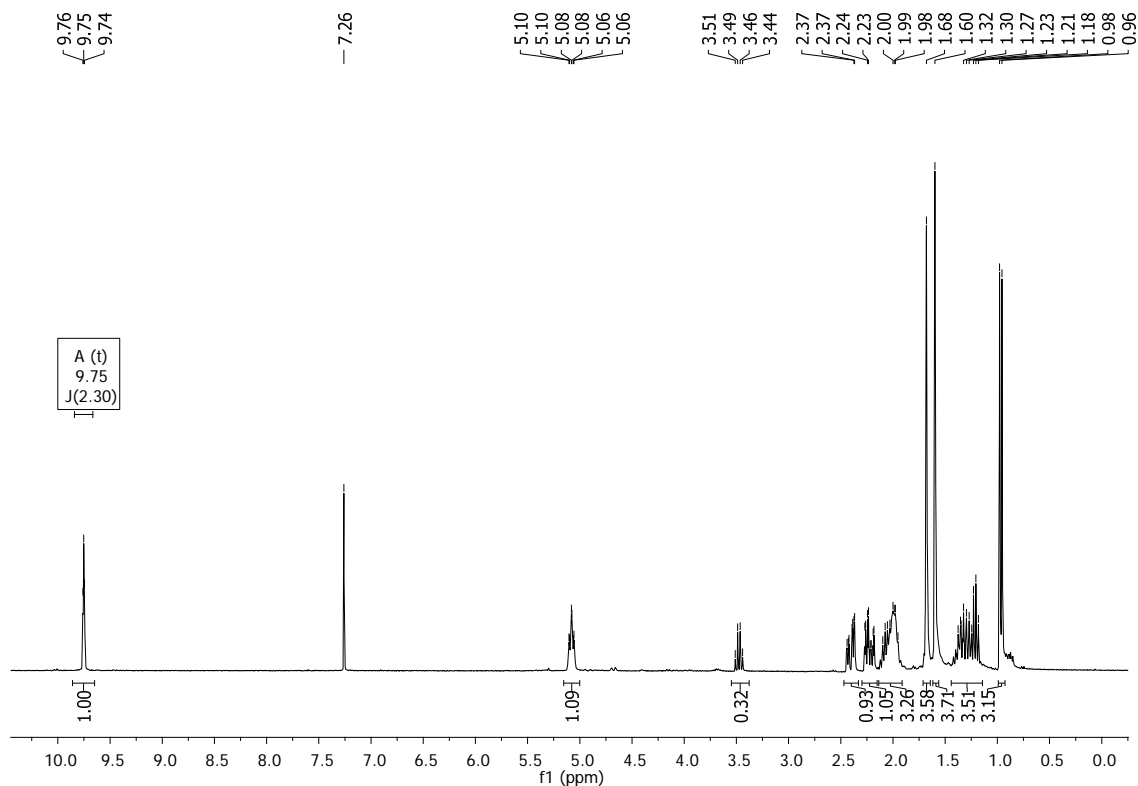
Scheme SM 13.2.3. Expansion of ^{1}H NMR (300 MHz) spectrum of starting material citral in CDCl$_3$ (1.0 to 3.2 ppm)

There is a big concern regarding the reaction time and product storage due to stability issues. The reaction time should not be more than 1 day, because the NMR starts to be messy, without being possible to identify the products. Furthermore, the isolated product should be stored in the freezer since long storage in the bench result in very messy ^{1}H NMR (signal at 5 ppm does not fit to 1 H as should be, see figure **Scheme SM 13.2.**4).
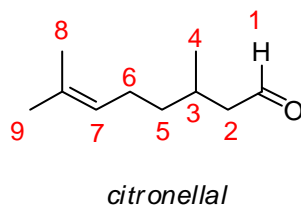
citronellal

Citronellal (isolated a colorless oil). **^{1}H NMR (300 MHz, CDCl$_3$) δ** 9.75 (t, J = 2.30 Hz, 1H, **1**), 5.08 (m, 1H, **7**), 2.43-2.18 (m, 2H, **2**), 2.10-1.95 (m, 2H, **3** and **6**), 2.10-1.95 (m, 2H, **3** and **6**), 1.68 and 1.60 (2 × s, 2 × 3H, **8** and **9**), 1.38-1.18 (m, 2H, **5**), 0.97 (d, J = 6.64 Hz, 3H, **4**). The extra signal at 1.21 and 3.48 ppm corresponds to diethyl ether traces.

Scheme SM 13.2.4. ^{1}H NMR (300 MHz) spectrum of the crude isolated by the students CDCl$_3$.
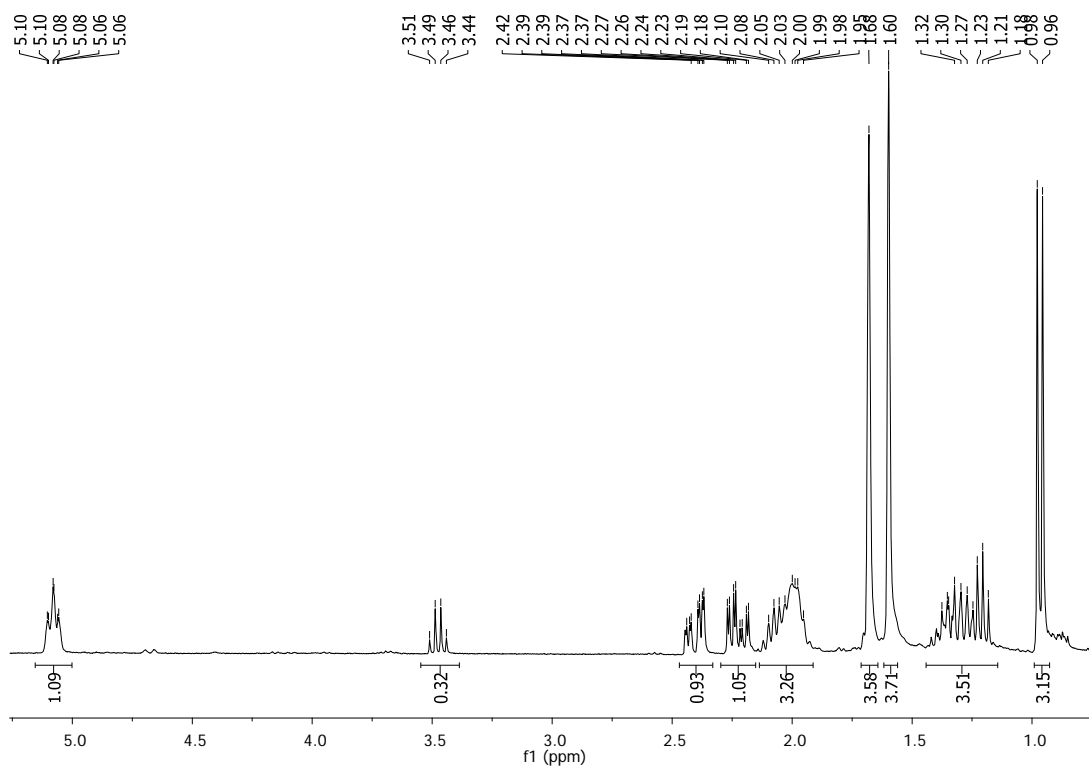
Scheme SM 13.2.4. Expansion of ^{1}H NMR (300 MHz) spectrum of the crude isolated by the students CDCl$_3$ (0.5 to 5.5 ppm).
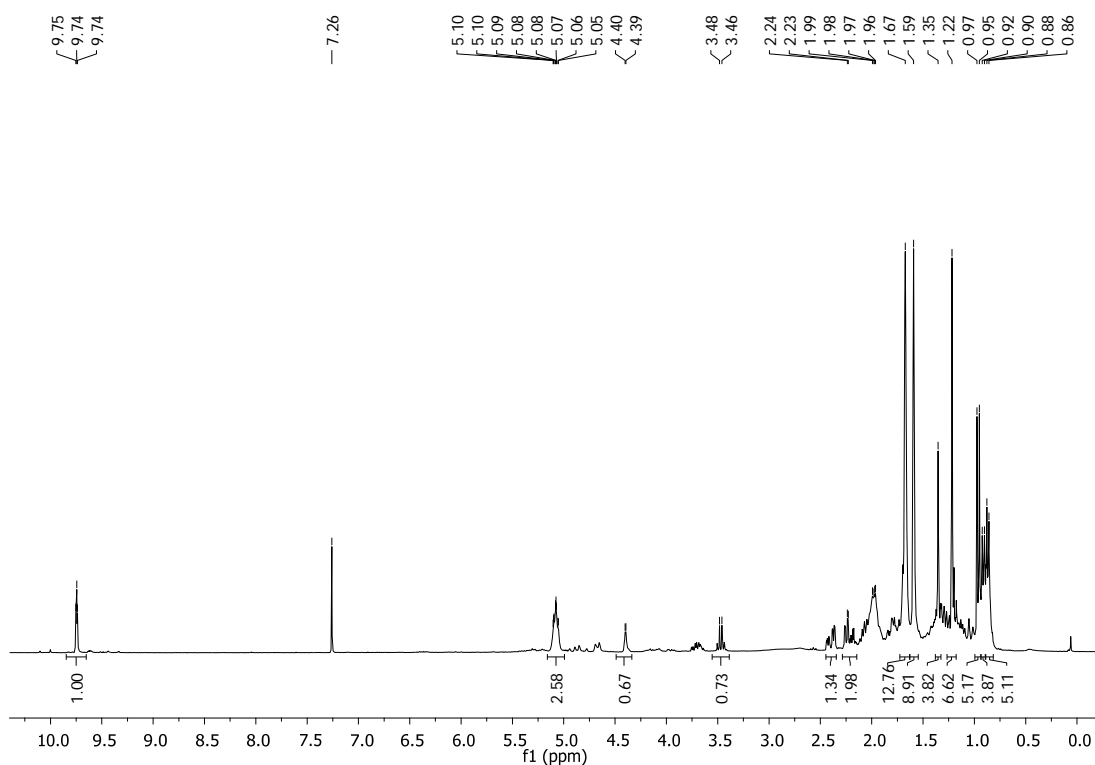
Scheme SM 13.2.5. ^{1}H NMR (300 MHz) spectrum of the crude isolated by the students CDCl$_3$ after 1 week on the bench.

Regarding IR analysis the characteristic band of C=O stretching is at 1726 cm^{-1} for the isolated citronellal. This topic can also be further explored with the students. The C=O band of the starting material citral appears at 1676 cm^{-1} due to conjugation with the double bond.
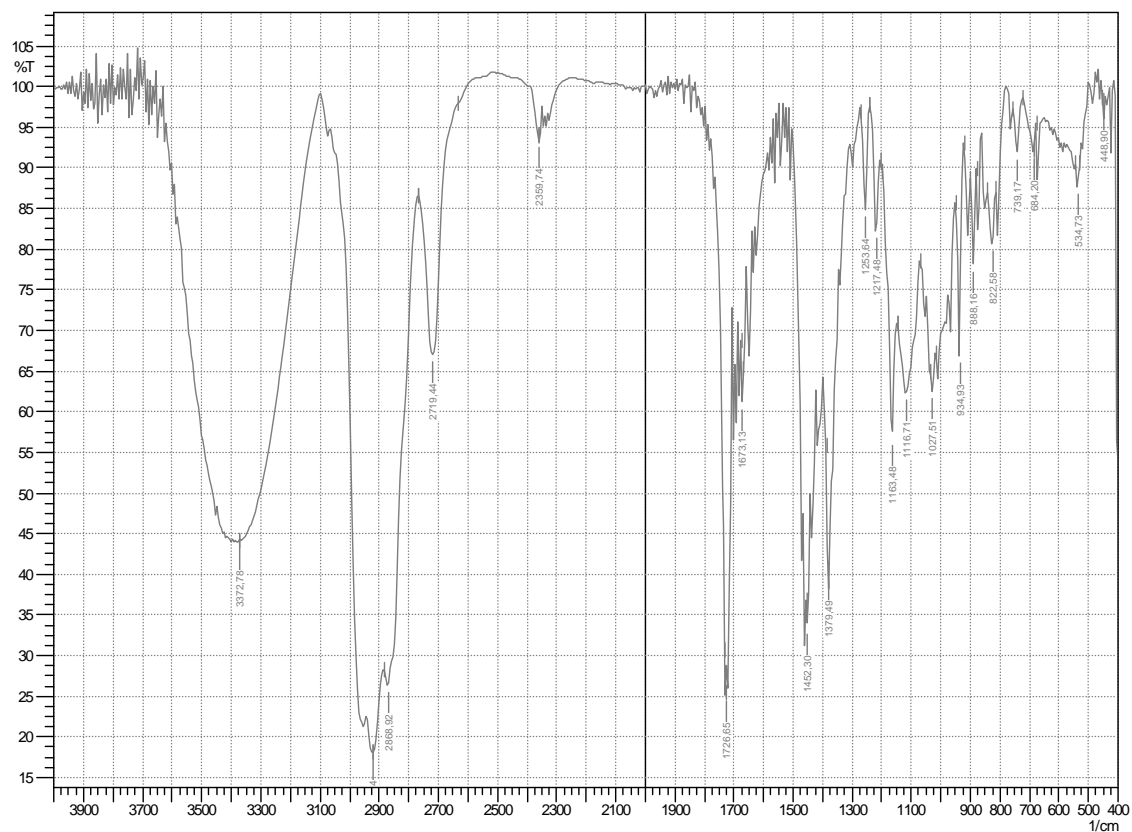
Scheme SM 13.2.6. IR spectrum of the crude isolated by the students after 1 week in the bench.

Scheme SM 13.2.7. Experimental apparatus and behavior of the reaction mixture.

Regioselective 1,2-reduction of an α,β-unsaturated ketone. A green experiment

Supplementary Material

This experiment aims the synthesis of an allylic alcohol, (*E*)-4-phenylbut-3-en-2-ol, from the corresponding unsaturated ketone, (*E*)-4-phenylbut-3-en-2-one, by reduction by sodium borohydride in PEG400 and water. This is a green alternative to the traditional reduction of unsaturated ketones by lithium aluminum hydride in diethyl ether.[1] As reduction by sodium borohydride in PEG400/water occurs in a heterogeneous medium, it is of pivotal importance warm the reaction mixture to solubilize the ketone to get a homogeneous mixture prior to sodium borohydride addition. As refer by Cao[1] using the phase transfer catalyst PEG400/water as reaction medium allows to perform the reduction under mild conditions. The small amount of water may accelerate the reaction by providing protons and hydrolyzing the boric acid ester formed in the transformation. Otherwise, the use of a mixture of PEG400 and water as reaction medium avoid the use of volatile organic compounds (VOCs),diethyl ether or tetrahydrofuran, as solvents.

TLC in silica gel 60 F_{254} (Merck, ref 05554, aluminum sheets 20x20cm) and spraying with a 2,4-dinitrophenylhydrazine solution (0,4% solution of 2,4-dinitrophenylhydrazine in 2N hydrochloric acid) were used to identify the starting material, the ketone and follow its disappearance.

After total disappearance of unsaturated ketone (after approximated 40 minutes) from reaction mixture added 10 mL of water to destruct boron esters and any excess of sodium borohydride. Extract the resulting aqueous solution with 3 x 10 mL of diethyl ether. Wash the collected organic layers with 5 mL of brine and dry the organic solution with anhydrous sodium sulfate. After, filter the dried organic phase though a filter paper. Wash the sodium sulfate with 5 mL of pure diethyl ether to remove traces of product and collect it in the same flask. Distill the organic solvent under reduced pressure in a rotavapor to yield an yellow oil. Weigh the flask and calculate the crude yield.

To purify the crude use 1:70 ratio (sample:silica gel, w/w) of silica gel 60 for column chromatography. Elute with hexane/ethyl acetate (8:2, v/v) and collect fractions of 2 mL in sample tubes.

Although the lead compound is the allylic alcohol the saturated alcohol resulting from the reduction of both the ketone and the double bound groups is observed. Saturated alcohol co-elutes with the allylic alcohol. In the ^{1}H NMR spectrum of the purified desired unsaturated alcohol the presence of 20% of the saturated alcohol can be observed.

The sustainability of the experimental procedure should be emphasized.[2] In the context of green chemistry there are several issues which influence the choice of solvent. It should be relatively nontoxic and relatively nonhazardous, e.g. not inflammable or corrosive. The solvent should also be contained, that is it should not be released to the environment. [2, 3]

The students should recognize that contrarily to diethyl ether, tetrahydrofuran or methanol, PEG400 is a low toxic and safer solvent that minimizes the potential for chemical accidents like fires and explosions and due to low vapor pressure is contained. PEG follows the three of the twelve principals of green chemistry that promotes the use of less hazardous chemical syntheses, the use of safer solvents and auxiliaries and the inherently safer chemistry for accident prevention.[4]

One group of two students of 1st year Bioorganic Chemistry M. Sc. student from Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa did the experiment during ordinary classes affording the results and yields presented in this experiment, where 0.556g of (*E*)-4-phenylbut-3-en-2-ol contaminated with 20% of the side product 4-phenylbutan-2-ol yield was synthesized in 74.8% yield. In this experiment the student can use the ^{1}H NMR spectroscopy to characterize mixtures and IR spectroscopy to follow the consumption of the reagent, the α,β unsaturated ketone, along the time in the reaction mixture. At the end of the reaction and after product purification no C=O band will be observed in IR spectrum.

The same procedure can be used to reduce the (*E*)-chalcone to the correspondent allylic alcohol in analogous yield.[1]

Others less green procedures can be used to prepare the same allylic alcohols from the corresponding α,β-unsaturated ketones in experimental laboratory classes. Reduction of α,β-unsaturated ketones by sodium borohydride in THF and in the presence of charcoal[5] or reduction by lithium aluminium hydride in anhydrous diethyl ether[1] were used.

IR, ^{1}H and ^{13}C NMR spectra
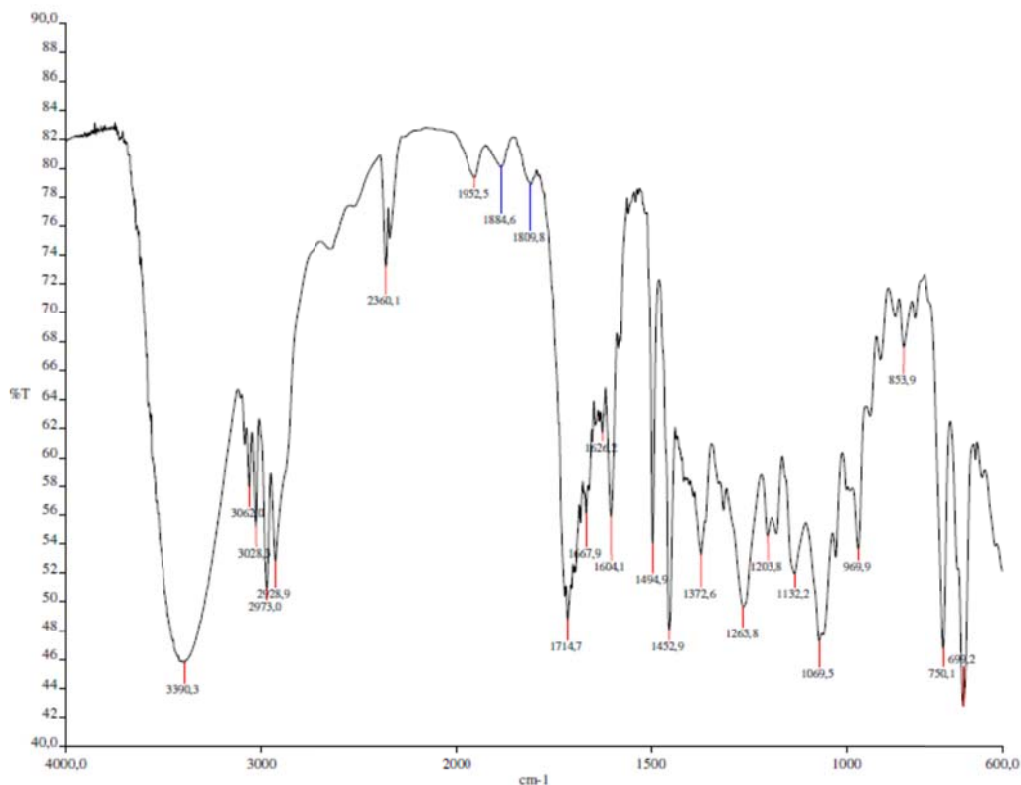
Figure SM.13.3. 1 – IR spectrum of the purified product (*E*)-4-phenylbut-3-en-2-ol (AA) contaminated with 20% of the side product 4-phenylbutan-2-ol (SA) (film in NaCl).

The ^{1}H NMR spectrum (fig. **SM.13.3.** 2) discloses a mixture of two compounds, the allylic alcohol and the corresponding saturated one. By analyzing the spectrum the ratio of the two compounds is obtained. The ^{1}H NMR shows two sets of peaks, the major component, (E)-4-phenylbut-3-en-2-ol (AA) and the minor 4-phenylbutan-2-ol (SA). As you might expect, the minor component shows smaller peaks in the spectrum. In this case, you should make two completely separate sets of data for analysis, one for each compound and keep the integration analysis completely separate. [1]H in one set will not be the same size integral as ^{1}H in the other set unless the concentrations of the two compounds in the sample are the same. Comparing the ratio of two integrals for two different compounds can give you the ratio of the two compounds in solution.
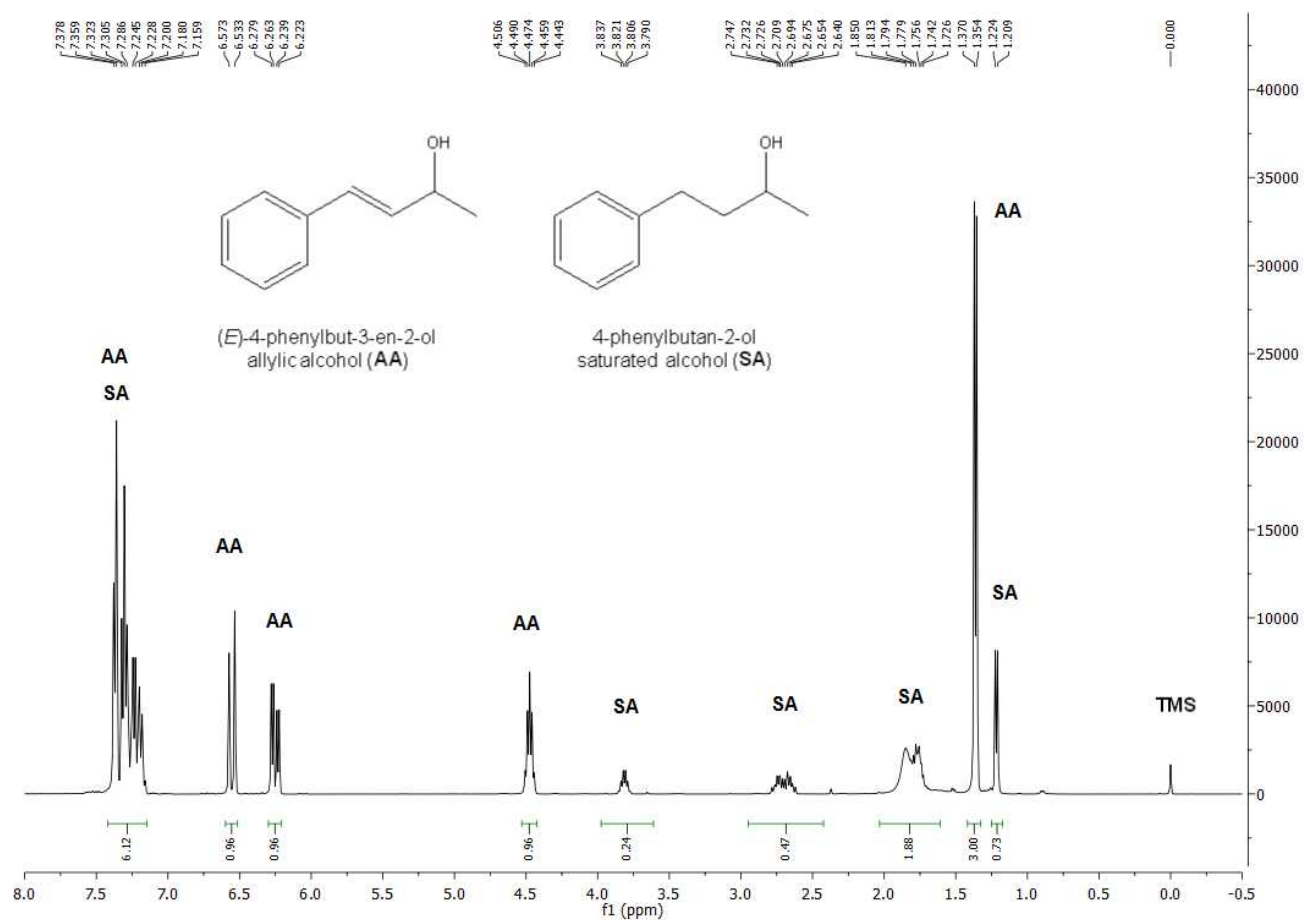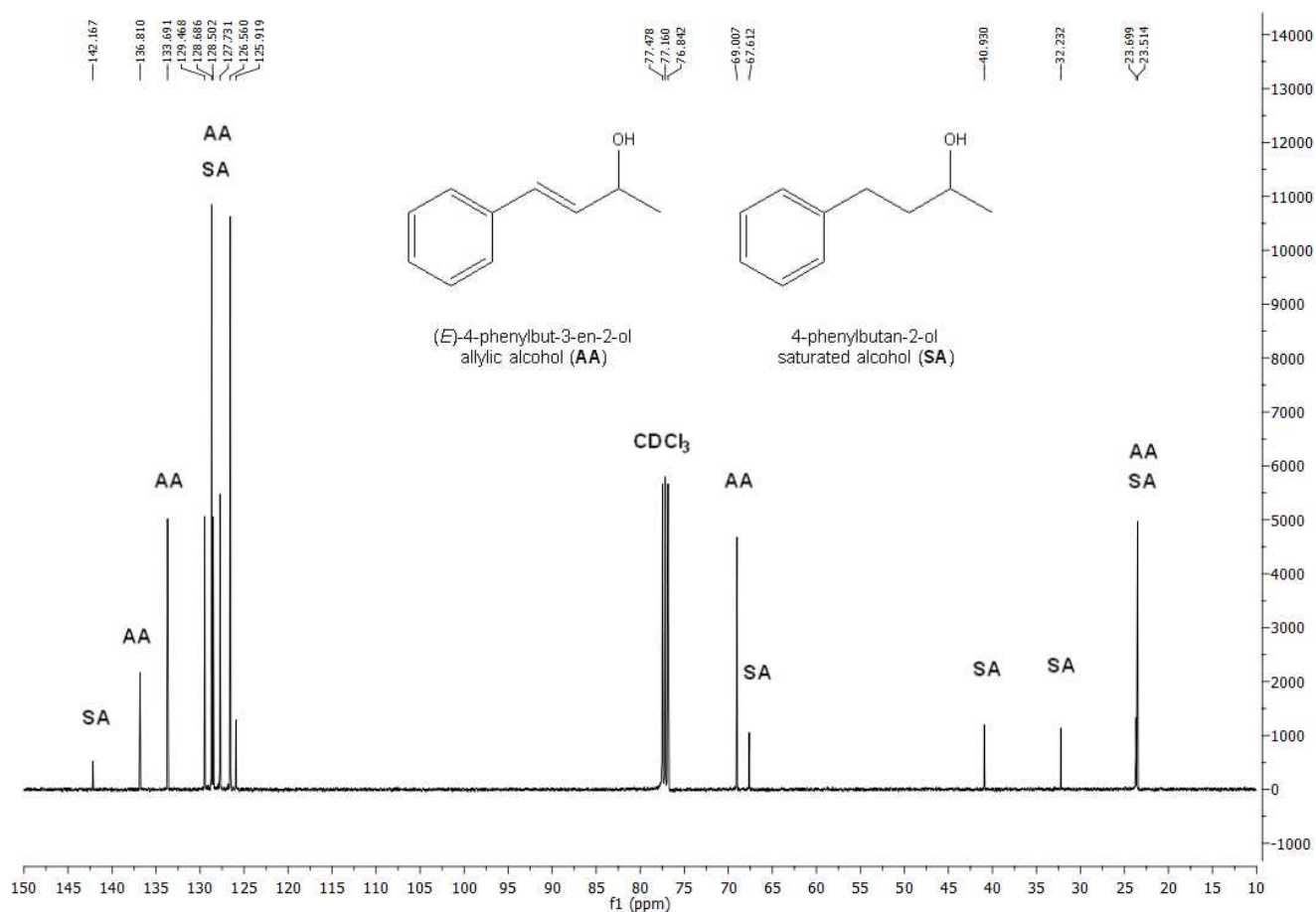
Figure SM.13.3. 2 – ^{1}H NMR spectrum (400MHz, CDCl$_3$) of the purified product with tetramethylsilane (TMS) as internal standard. (*E*)-4-phenylbut-3-en-2-ol (AA) contaminated with 20% of the side product 4-phenylbutan-2-ol (SA).

One way to approach this kind of problem is to:

1. choose one peak from each of the two compounds you want to compare. 1.21 (from SA) and 1.36 (from AA) corresponding to the CH$_3$ group are chosen

2. decide how many hydrogens each peak is supposed to represent in a molecule. It is supposed to be a CH3, representing three hydrogen atoms in (E)-4-phenylbut-3-en-2-ol (AA) and in 4-phenylbutan-2-ol (SA).

3. divide the integral value for that peak by that number of hydrogens it is supposed to represent in a molecule. 3.00/3 = 1 for (E)-4-phenylbut-3-en-2-ol (AA) and 0.73/3=0.24 for 4-phenylbutan-2-ol (SA).

In conclusion the ratio of those two answers is the ratio of the two compounds in the sample (1/0.24). So there is four times as much (E)-4-phenylbut-3-en-2-ol (AA) as 4-phenylbutan-2-ol (SA) in the mixture. In terms of these two compounds alone, there is 80% (E)-4-phenylbut-3-en-2-ol (AA) and 20% side product 4-phenylbutan-2-ol (SA). That is (3/(0.73+3))x100% for the (E)-4-phenylbut-3-en-2-ol (AA), and (0.73/(0.73+1))x100% for the 4-phenylbutan-2-ol (SA). That calculation just represents the amount of individual component divided by the total of the components to be compared.

Figure SM.13.3. 3 – ^{13}C NMR spectrum (100MHz, CDCl$_3$) of the purified product. (*E*)-4-phenylbut-3-en-2-ol (AA) contaminated with 20% of the side product 4-phenylbutan-2-ol (SA).

1.   Y. Q. Cao, Z. Dai, B. H. Chen and R. Liu, *J. Chem. Technol. Biotechnol.*, 2005, **80**, 834.
2.   P. T. Anastas, *Aldrichimica Acta*, 2015, **48**, 3.
3.   R. A. Sheldon, *Green Chem.*, 2005, **7**, 267.

4.   P. T. Anastas and T. C. Williamson, *Frontiers in Green Chemistry. In Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*, ed. P. T. Anastas and T. C. Williamson, Oxford University Press, USA, 1998, 1.

5.   D. Setamdideh and B. Zeynizadeh, *Z.Naturforsch.(B)*, 2006, **61**, 1275.

Reduction of diphenyl sulfoxide catalyzed by the dioxo-molybdenumcomplex MoO$_2$Cl$_2$(H$_2$O)$_2$

Supplementary Material

1. Experiment Notes

1.1 Preparation of catalyst:

Chemical needed: Sodium molybdate dihydrate (Na$_2$MO$_4$·2H$_2$O), concentrated hydrochloric acid, sodium chloride, diethyl ether, anhydrous magnesium sulphate

Apparatus needed: 100 mL round-bottomed flask, 25 mL round-bottomed flask, 100 mL volumetric balloon, 50 mL graduated cylinder, 20 mL pipette,100 mL liquid-liquid extraction apparatus, 200 mL erlenmeyer flask, funnel, filter paper, magnetic stir bar, magnetic stirring apparatus, rotary evaporator.

Previous Laboratory session (30 min) - *Preparation of the diethyl ether solution of MoO$_2$Cl$_2$(H$_2$O)$_2$*[1]

1. In a fume hood prepare a solution with 4.84 g (0.020 mol) of Na$_2$MO$_4$·2H$_2$O in 8 mL of H$_2$O using a 100 mL round-bottomed flask.

2. Add 14 mL of concentrated hydrochloric acid.

3. Stir the mixture at room temperature for 10-15 min to obtain a light yellow/colourless solution along with a significant amount of NaCl crystallized.

4. Add 30 mL of diethyl ether, while stirring it vigorously for 2 min.

5. Transfer the mixture to a separatory funnel and allow the layers to separate. Keep the diethyl ether layer (upper layer) and extract the aqueous layer with 2 x 20 mL of diethyl ether.

6. Combine all the ether layers in an erlenmeyer, add 4 g of anhydrous magnesium sulphate and stir the mixture for 4 min.

7. Filter the mixture and wash the magnesium sulphate with 3 x 3 mL of diethyl ether.

8. Join the filtrate and the washings into a 100 mL volumetric flask and complete the volume with diethyl ether. This light yellow solution contains approximately 90-98% of $MoO_2Cl_2(H_2O)_2$ (Figure SM 13.4.1).

9. Calculate the exact concentration of the diethyl ether solution of $MoO_2Cl_2(H_2O)_2$ (*Crucial step!*). Measure 2 mL of the diethyl ether solution previously prepared. Add it to a tared 25 mL round-bottomed flask. Remove the solvent using a rotary evaporator until you get a dry yellow powder. Weigh the solid and calculate the molarity of the diethyl ether solution of $MoO_2Cl_2(H_2O)_2$. Then, you can calculate the volume of the solution that contains 0.01 mol (10 mol%) of catalyst requested to reduce the diphenyl sulfoxide (~0.4 mL). (Note: *This step is very important, since the addition of less amount of catalyst will increase the reaction time. For example, when the reduction of diphenyl sulfoxide is carried out with only 6 mol% of $MoO_2Cl_2(H_2O)_2$, using phenylsilane as reducing agent, the reaction required 1h30 min to convert all the substrate, instead of 30 min in the presence of 10 mol% of $MoO_2Cl_2(H_2O)_2$).* In order to maintain the concentration of diethyl ether solution of $MoO_2Cl_2(H_2O)_2$, keep the volumetric balloon closed. The instructor should provide to the students the exact value of the concentration of this solution.

Figure SM 13.4.**1** – Diethyl ether solution of $MoO_2Cl_2(H_2O)_2$.

1.2 Photo of reaction apparatus
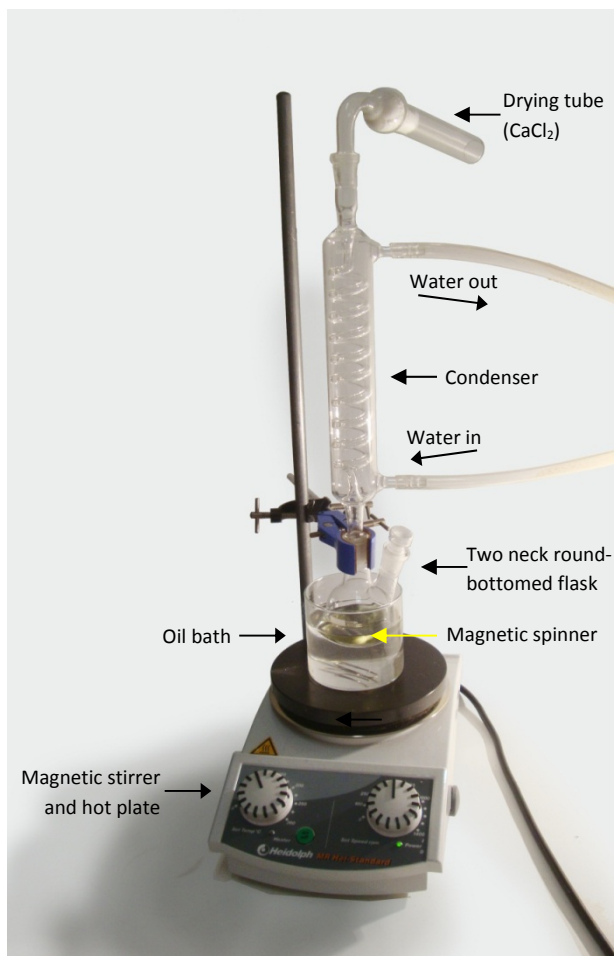
**Figure** SM 13.4.**2 –** Photo of reaction apparatus

1.3 Monitor the course of the reaction by thin-layer chromatography (TLC):

The reduction of diphenyl sulfoxide using the method A will take approximately 1 hour. We propose to monitor the course of the reaction by thin-layer chromatography (TLC) at approximately 20 min intervals using the mixture of ethyl acetate:*n*-hexane (1:3) as eluent. Under the line of the TLC, lightly mark three spots with enough space between the samples so that they will not run together: one with diphenyl sulfoxide (A), the second with triphenylphosphine (B) and the last one with the reaction mixture (C). The analysis of the TLC plates (see Figure SM 13.4.3) shows that the spot corresponding to the substrate disappears after 1 hour in the reaction mixture (point C), indicating that the reduction is complete.
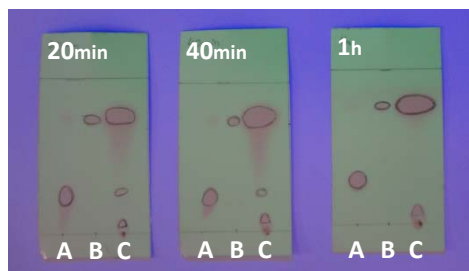
Figure SM 13.4.**3 –** Monitor the course of the reaction by TLC using ethyl acetate:*n*-hexane (1:3) as eluent (A: diphenyl sulfoxide, B: triphenylphosphine, C: reaction mixture). R_f (diphenyl sulfoxide) = 0.31 R_f (diphenyl sulfide) = 0.83.

The reduction of diphenyl sulfoxide using the method B will take 30 min. For this method, we propose to follow the reaction evolution with approximately 10 min intervals using the mixture of ethyl acetate:*n*-hexane (1:3) as eluent. Mark two spots in each TLC plate, for diphenyl sulfoxide and for the reaction mixture. After 30 min the spot corresponding to the diphenyl sulfoxide is not visible in the application point B, indicating that all the sulfoxide was completely reduced (Figure SM 13.4.4).
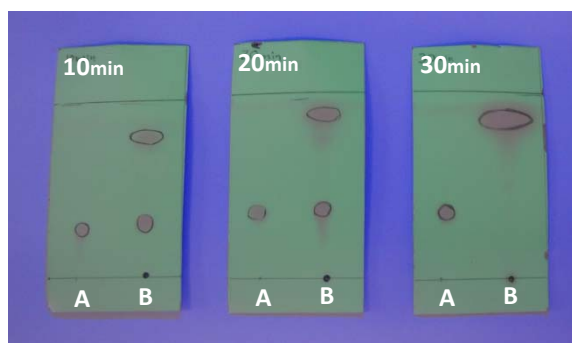
Figure SM 13.4.**4 –** Monitor the course of the reaction by TLC using ethyl acetate:*n*-hexane (1:3) as eluent (A: diphenyl sulfoxide, B: reaction mixture).

1.4 Purification of the product by column chromatography

The purification of the product, obtained using the method A, by column chromatography (Figure SM 13.4.5) should be performed with *n*-hexane as eluent. As we can see in TLC plates developed in
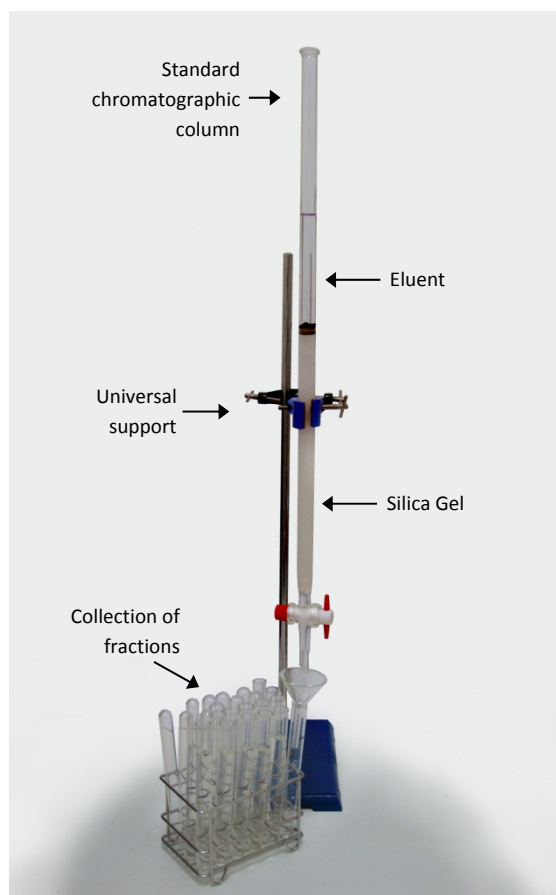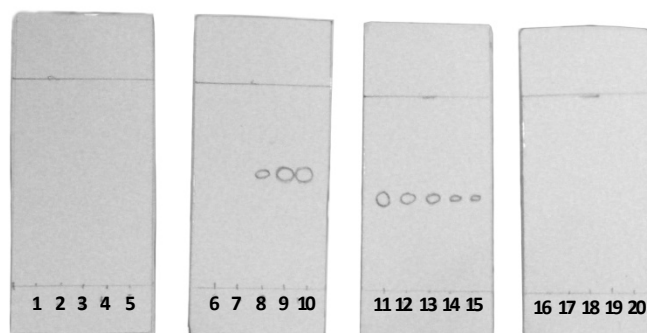
Figure SM 13.4.**5 –** Column chromatography apparatus.

ethyl acetate:*n*-hexane (1:3) (Figure SM 13.4.3), the triphenylphosphine and the product have the same retention time (R_f). With this eluent is not possible to separate the excess of the triphenylphosphine and the product will be contaminated with this reagent. However, using *n*-hexane as eluent, it is possible to separate the two spots corresponding to the diphenyl sulfide and the triphenylphosphine (Figure SM 13.4.6).

Figure SM 13.4.**6 –** TLC using *n*-hexane as eluent (A: diphenyl sulfoxide,
B: triphenylphosphine, C: reaction mixture) at 1 hour of reaction.

Mark the volume of 20 mL in 4 assay tubes and the volume of 10 mL in 16 assay tubes. Elute the column with *n*-hexane and collect the first 4 fractions with 20 mL and the others 16 fractions with 10 mL.

Prepare several TLC plates with 5 application points each and analyse all the collected fractions. The Figure SM 13.4.7 shows the TLC plates obtained for the purification of the product using *n*-hexane as eluent. The purified product started to elute at fraction 8 and ended at fraction 15. Yields = 91-96%.

Figure SM 13.4.**7 –** TLC plates of all collected fractions using *n*-hexane as eluent.

The purification of the product, obtained using the method B, by column chromatography should be performed with ethyl acetate:*n*-hexane (1:3) as eluent.

Mark the volume of 10 mL in 10 assay tubes. Collect 10 fractions with 10 mL of eluent and then analyse all the collected fractions by TLC. The figure SM 13.4.8 shows that the product started to elute at fraction 3 and ended at fraction 6.
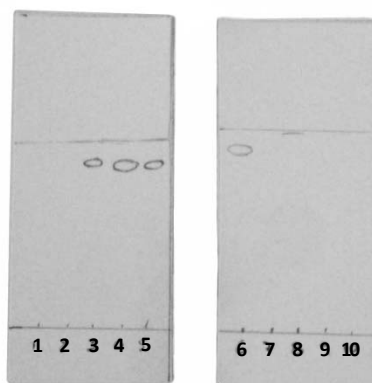
Figure SM 13.4.**8 –** TLC plates of all collected fractions using ethyl acetate:*n*-hexane (1:3) as eluent. Yields: 90-97%

2. Characterization of compounds

2.1 Physical properties of compounds

Table SM 13.4.**1** – Physical properties of compounds

Compounds	Molecular Weight (g mol^{-1})	Boiling point (ºC)	Melting point (Cº)	Density	Appearance (Colour)
Diphenyl sulfoxide	202.27	206-208°C/13 mmHg	69-71	–	White Solid
Diphenyl sulfide	186.27	296 °C	−40	1.113 g/mL at 20 °C	Colorless Liquid
Triphenylphosphine	262.29	377 °C	79-81	–	White Solid
Phenylsilane	108.21	120 °C	–	0.877 g/mL at 25 °C	Colorless Liquid

2.2. Characterization of the compounds by Infrared and NMR spectroscopy

All the characterization data presented in this session were obtained by the authors. IR spectra were recorded with a JASCO FT/IR 4100 spectrometer instrument in the range 400-4000 cm^{-1}. NMR spectra were performed with a Bruker Avance II^{+} Spectrometer (400 MHz) and the chemical shifts (δ/ppm) are referred to tetramethylsilane (δ = 0 ppm, ^{1}H and ^{13}C).

IR spectrum:
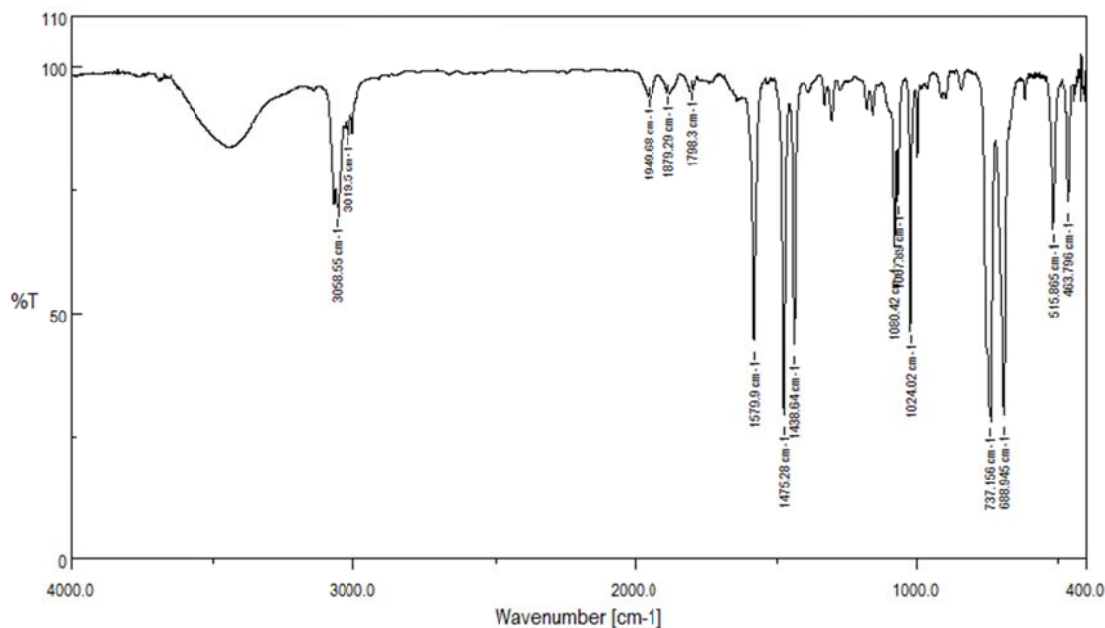
Figure SM 13.4.**9** – Infrared spectrum of diphenyl sulfide.

The streching vibrations assigned to the C-S linkage occur in the region of 700-600 cm^{-1}.[2] Characterization of diphenyl sulfide by IR (KBr, cm^{-1}): ν 3059 (m), 1949 (w), 1878 (w), 1798 (w), 1580 (s), 1475 (s), 1439 (s), 1080 (s), 1068 (s), 1024 (s), 737 (s), 689 (s), 516 (m), 464 (m).
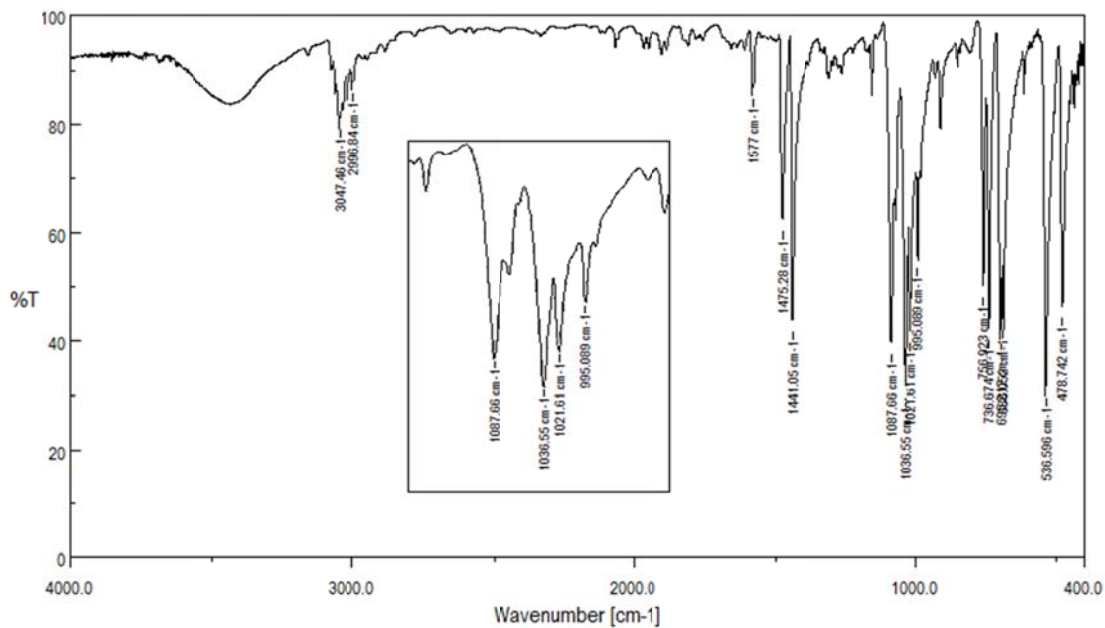
Figure SM 13.4.**10** – Infrared spectrum of diphenyl sulfoxide with emphasis in the range of 1150-950 cm^{-1}.

Aryl sulfoxides show strong absorption in the 1090-1020 cm^{-1} region. The sulfoxide group is susceptible to hydrogen bonding and its absorption can shift to slightly lower frequencies when diluted solutions are used. The frequency of S=O absorption is increased by electronegative substitution.[2]

Characterization of diphenyl sulfoxide by Infrared (KBr, cm^{-1}): ν 3047 (m), 1577 (m), 1475 (s), 1441 (s), 1156 (w), 1088 (s), 1037 (s), 1022 (s), 995 (s), 757 (s), 737 (s), 695 (s), 693 (s), 537 (s), 478 (s).

^{1}H NMR spectra
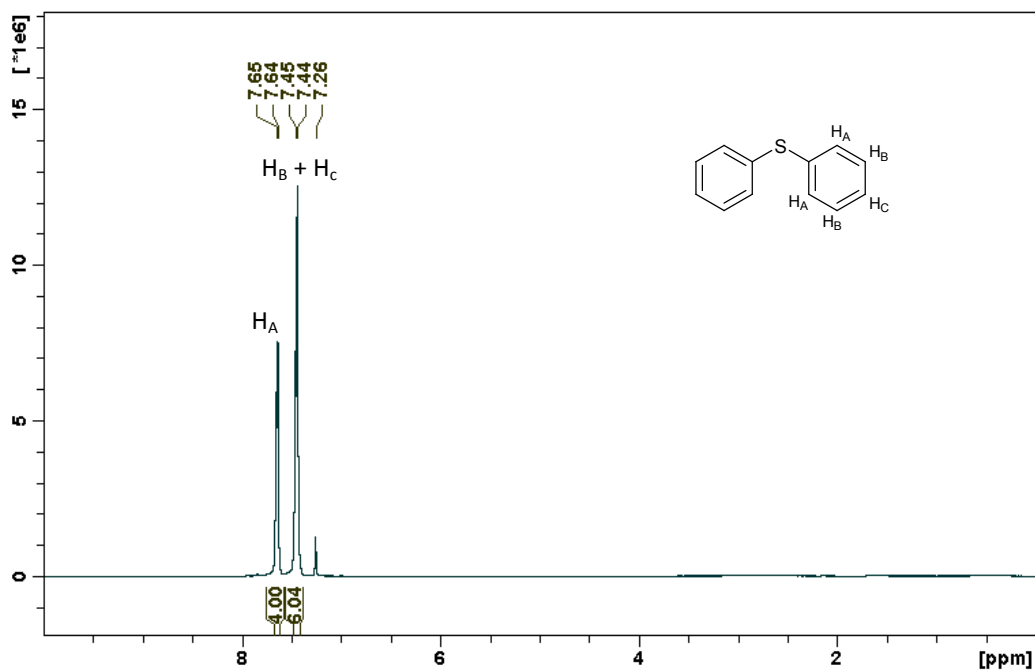
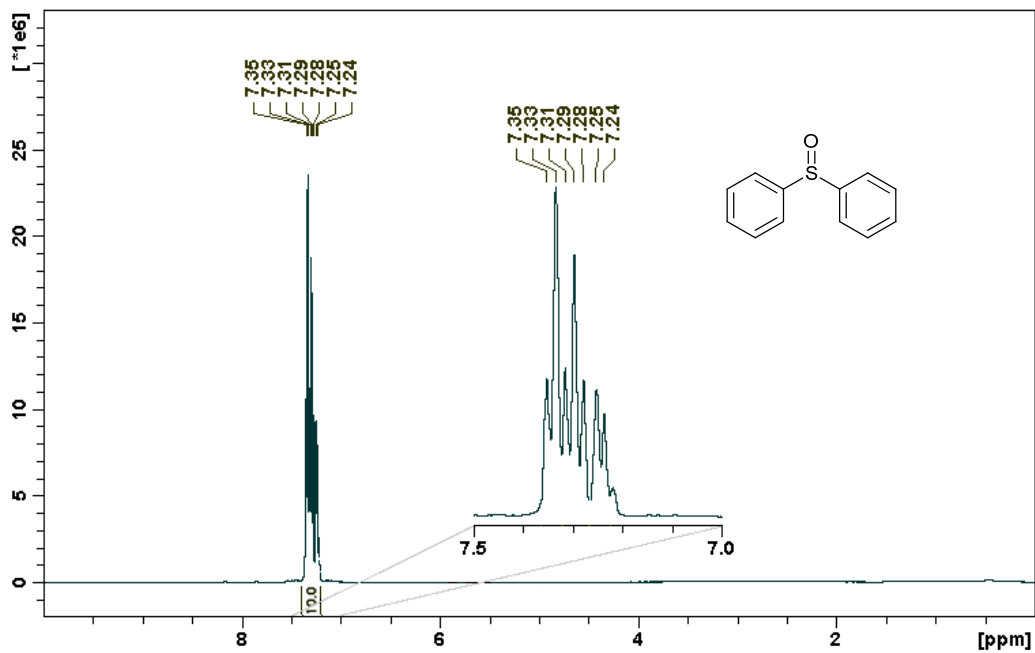**Figure** SM 13.4.**11** – ^{1}H NMR spectrum of diphenyl sulfide (CDCl$_3$, 400 MHz).

Figure SM 13.4.**12** – ^{1}H NMR spectrum of diphenyl sulfoxide (CDCl$_3$, 400 MHz).
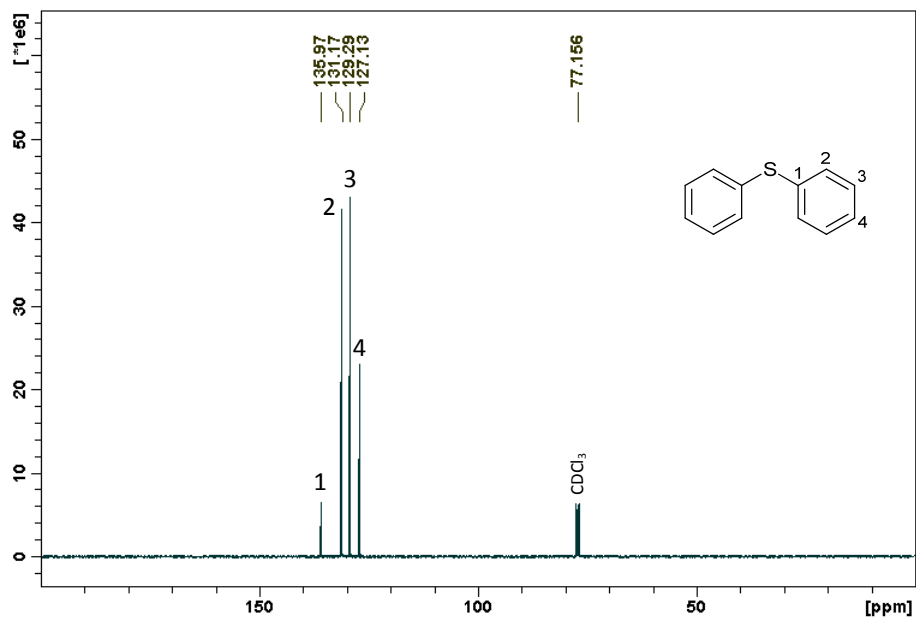
^{13}C NMR

Figure SM 13.4.**13 –** ^{13}C NMR spectrum of diphenyl sulfide (CDCl$_3$, 100 MHz).
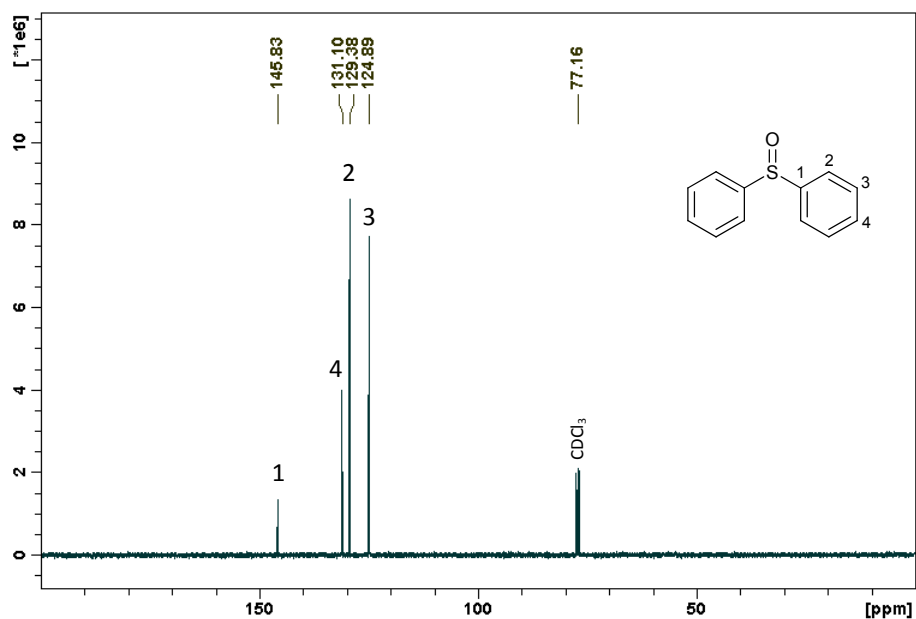
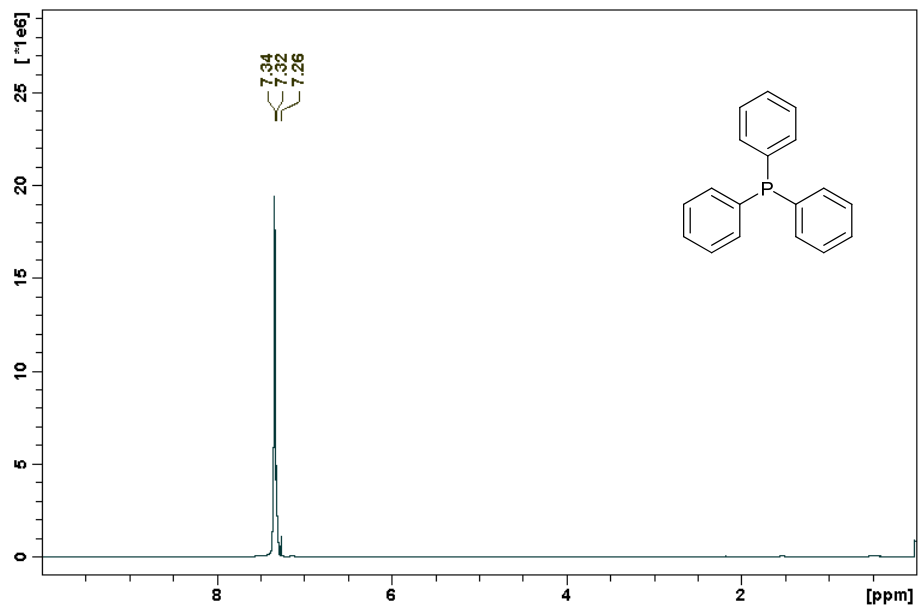**Figure** SM 13.4.**14 –** ^{13}C NMR spectrum of diphenyl sulfoxide (CDCl$_3$, 100 MHz).

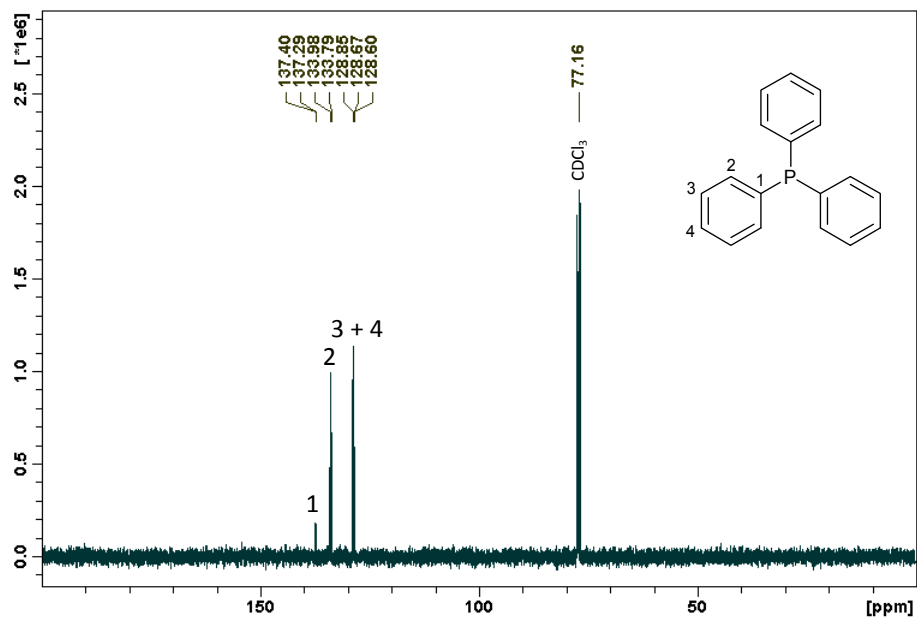**Figure** SM 13.4.**15** – ^{1}H NMR spectrum of triphenylphosphine (CDCl$_3$, 400 MHz).

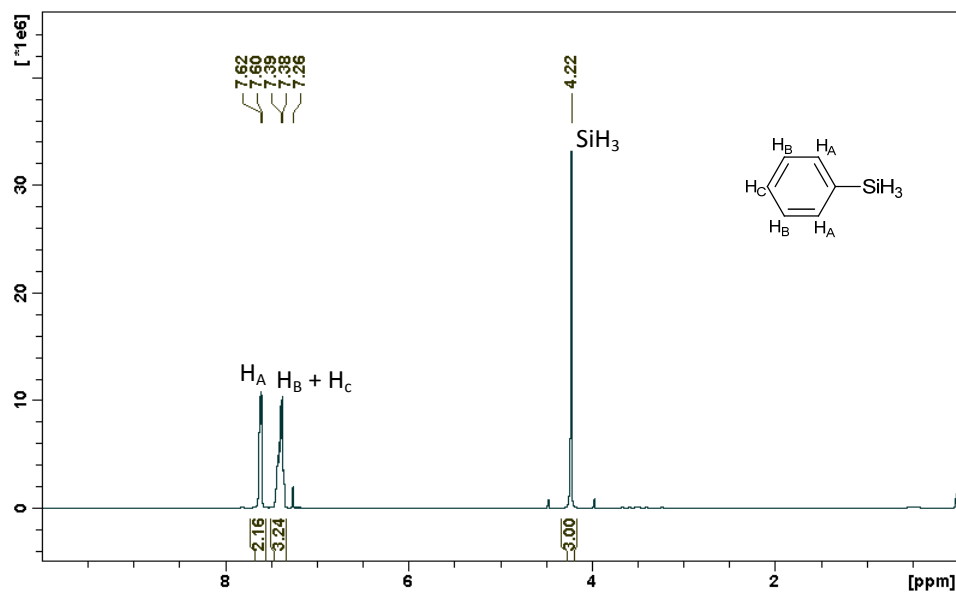**Figure** SM 13.4.**16** – ^{13}C NMR spectrum of triphenylphosphine(CDCl$_3$,100 MHz).

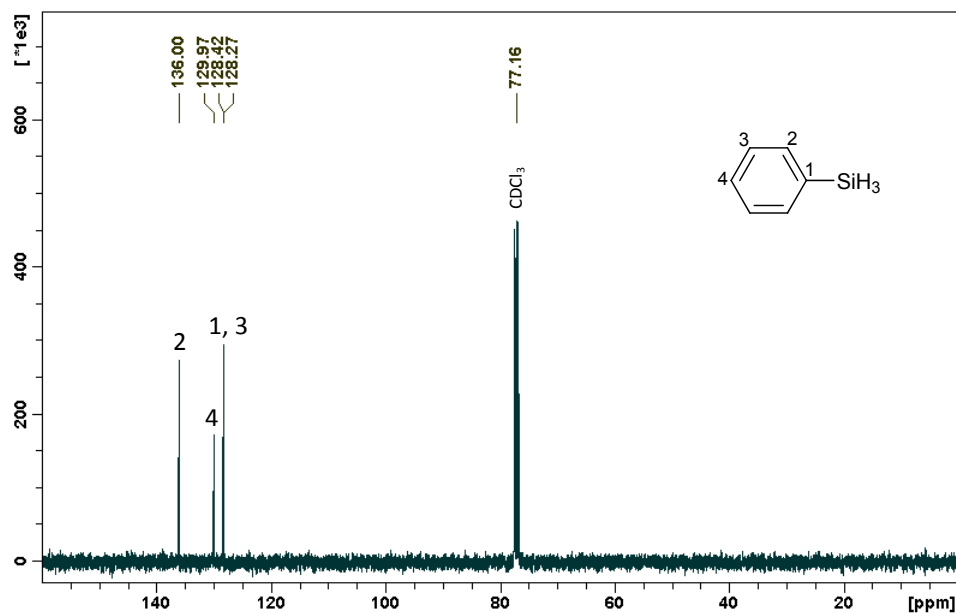**Figure** SM 13.4.**17** – ^{1}H NMR spectrum of phenylsilane (CDCl$_3$, 400 MHz).

Figure SM 13.4.**18** – ^{13}C NMR spectrum of phenylsilane (CDCl$_3$, 100 MHz).

Summary of NMR data:

Diphenyl sulfide: ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.65-7.64 (m, 4H, Ph), 7.45-7.44 (m, 6H, Ph). ^{13}C NMR (CDCl$_3$, 100 MHz): 145.8, 131.1, 129.4, 124.9.

Diphenyl sulfoxide: ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.35-7.24 (m, 10H, Ph). ^{13}C NMR (CDCl$_3$, 100 MHz): 136.0, 131.2, 129.3, 127.1.

Triphenylphosphine: ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.34-7.32 (m, 10H, Ph). ^{13}C NMR (CDCl$_3$, 100 MHz): 137.4, 137.3, 134.0, 133.8, 128.9, 128.7, 128.6.

Phenylsilane: ^{1}H NMR (CDCl$_3$, 400 MHz): 7.61 (d, 2H, Ph, J = 8.0 Hz), 7.39-7.38 (m, 3H, Ph), 4.22 (s, 3H).^{13}C NMR (CDCl$_3$, 100 MHz): 136.0, 130.0, 128.4, 128.3.

3. Results obtained by the students

The reproducibility of the experiment was assessed by its repetitive execution (Tables SM 13.4.2 and SM 13.4.3) by Chemistry M.Sc. students from Technical Superior Institute (Lisbon).
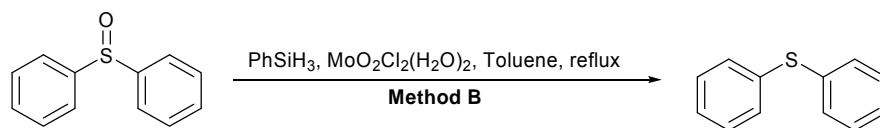
Method A:

PPh$_3$, MoO$_2$Cl$_2$(H$_2$O)$_2$, Toluene, reflux
Method A
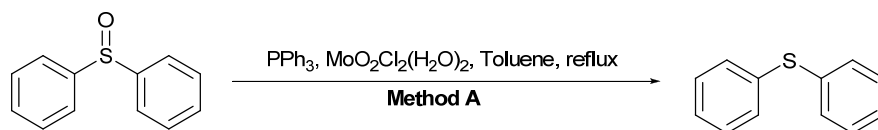
Table SM 13.4.**2** – Experiments were carried out with 1.0 mmol of diphenyl sulfoxide, 10 mol% of the diethyl ether solution of MoO$_2$Cl$_2$(H$_2$O)$_2$ and 1.20 mmol of triphenylphosphine in 5 mL of toluene at reflux temperature.

Entry	Time (min)	Isolated Yield (%)
1	60	96
2	60	94
3	65	93
4	65	94
5	70	80
6	75	91

Method B:

PhSiH$_3$, MoO$_2$Cl$_2$(H$_2$O)$_2$, Toluene, reflux

Method B

Table SM 13.4.**3** – Experiments were carried out with 1.0 mmol of diphenyl sulfoxide, 10 mol% of the diethyl ether solution of MoO$_2$Cl$_2$(H$_2$O)$_2$ and 1.20 mmol of phenylsilane in 5 mL of toluene at reflux temperature.

Entry	Time (min)	Isolated Yield (%)
1	30	97
2	30	94
3	35	95
4	40	90
5	40	91
6	45	83

Table SM 13.4.**4** – Values of R$_f$ for diphenyl sulfoxide and for diphenyl sulfide using the eluent ethyl acetate: *n*-hexane (1:3)

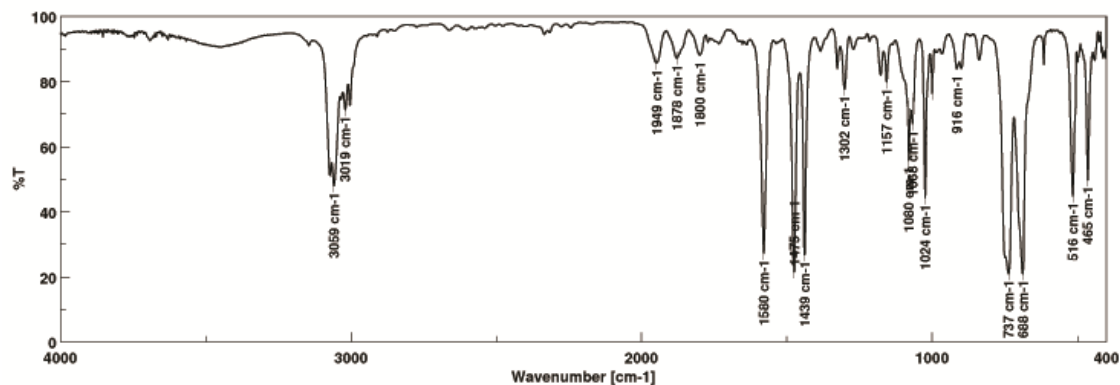| Entry	Method A		Method B	
	R$_f$ (sulfoxide)	R$_f$ (sulfide)	R$_f$ (sulfoxide)	R$_f$ (sulfide)
1	0.30	0.81	0.33	0.83
2	0.31	0.83	0.30	0.81
3	0.33	0.84	0.31	0.81
4	0.30	0.80	0.31	0.82
5	0.31	0.83	0.34	0.79
6	0.29	0.82	0.32	0.83

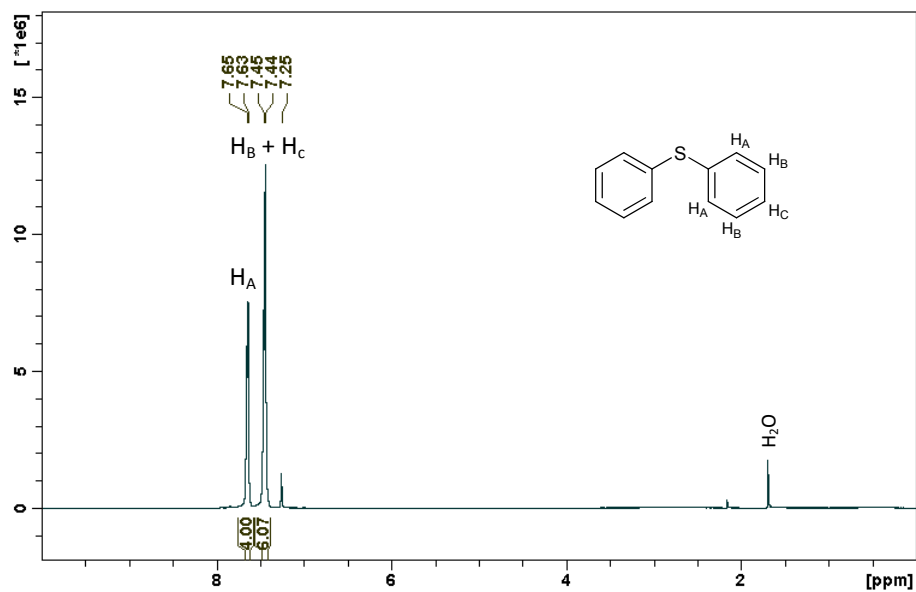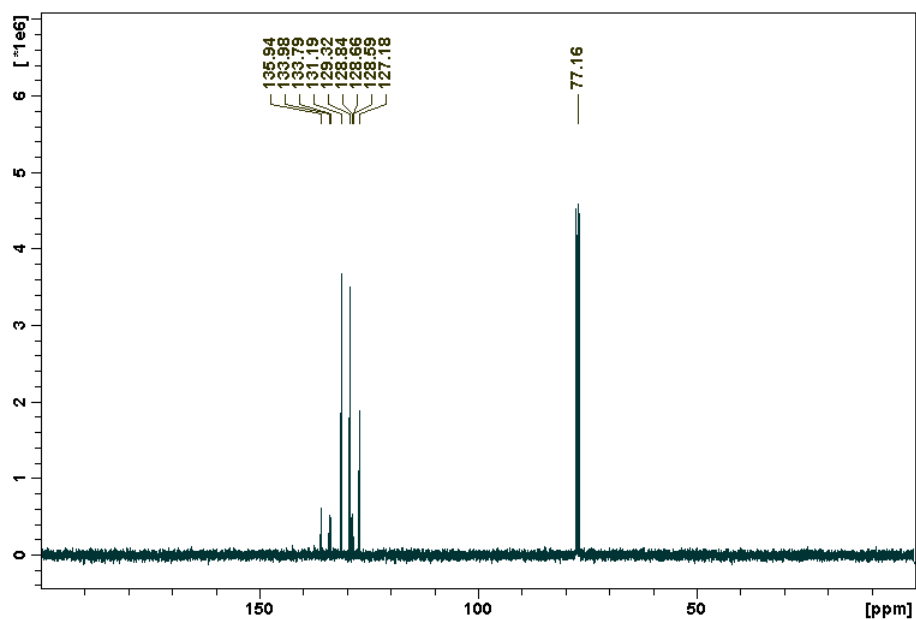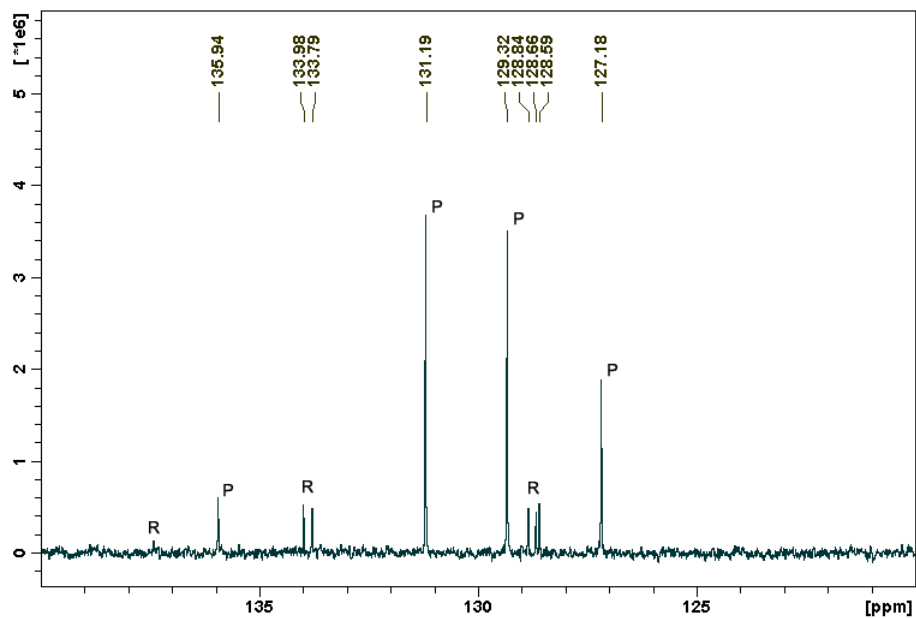**Figure** SM 13.4.**19** – Infrared spectrum of diphenyl sulfide obtained by the students.

Figure SM 13.4.**20** – ^{1}H NMR spectrum of diphenyl sulfide obtained by the students (CDCl$_3$, 400 MHz).

Figure SM 13.4.**21** – ^{13}C NMR spectrum of diphenyl sulfide obtained by the students with a small amount of triphenylphosphine (CDCl$_3$, 100 MHz).

Figure SM 13.4.**22** – Details of ^{13}C NMR spectrum of product (P) obtained by the students with a small amount of triphenylphosphine (R) (CDCl3, 100 MHz).

4. Results interpretation and additional questions

1. Determine the mass of the product and calculate the percent yield.

$$\text{Percent yield} = \frac{moles\ of\ the\ sulfide\ obtained}{moles\ of\ the\ sulfoxide\ used}\ x\ 100\%$$

2. Calculate the R_f values of the sulfoxide and the product using ethyl acetate:*n*-hexane (1:3) as eluent.

The R_f (ratio to the front) is defined as the ratio of the distance traveled by the compound and the distance traveled by developing solvent front.

$$R_f = \frac{distance\ of\ traveled\ by\ compound}{distance\ \ traveled\ by\ developing\ solvent\ front}$$
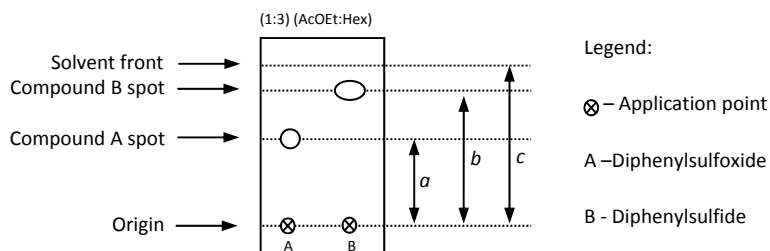
$$R_f\ of\ A = \frac{a}{c}$$

$$R_f\ of\ B = \frac{b}{c}$$

The table SM 13.4.4 contains the values of R_f of sulfoxide and sulfide determined by the students. The values of R_f obtained by the authors are reported in Figure SM 13.4.3.

3. Identify the main difference between the infrared spectra of the diphenyl sulfoxide and the product.
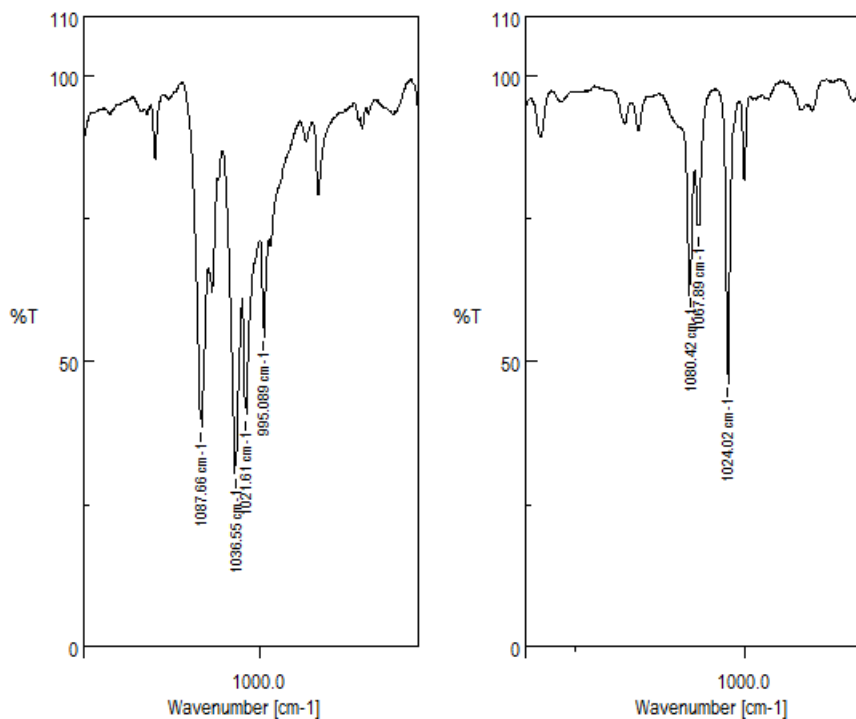
Figure SM 13.4.**23** – Infrared spectra of sulfoxide (left) and of sulfide (right)

Aryl sulfoxides show strong absorption in the 1090-1020 cm^{-1} region. The main difference between the infrared spectra of sulfoxide (left) and sulfide (right) is the absence of the strong bands at 1039 cm^{-1} and 1088 cm^{-1} in the spectrum of the sulfide, confirming the reduction of the group S=O.

4. Analysis the purity of the product based on the ^{1}H and ^{13}C NMR spectra of the product under supervision of your instructor.

Comparing the ^{1}H NMR spectrum of sulfide obtained by the students (Figure SM 13.4.20) with the spectrum reported by the authors (Figure SM 13.4.11), the product isolated by the students seems pure. However, this product contains a small amount of the reducing agent

(triphenylphosphine), but the signals of triphenylphosphine are not visible in the ^{1}H NMR spectrum because they are overlapped by the signal corresponding to the Hb + Hc protons of the sulfide.

In the ^{13}C NMR spectra of the product obtained by the students (Figures SM 13.4.21 and SM 13.4.22) it is possible to observe the signals corresponding to the product (P) and the signals belonging to the triphenylphosphine (R), confirming that the product is not completely pure.

5. Describe the role of triphenylphospine or phenylsilane in the reaction.

Triphenylphosphine and phenylsilane act in this reaction as reducing agents. For example, in the scheme SM 13.4.1 is exemplified the catalytic cycle proposed for the reduction of sulfoxides catalyzed by the dioxomolybdenum complex $MoO_2Cl_2(DMF)_2$ using triphenylphosphite as reducing agent.[3] Based on ^{1}H NMR and ^{13}P NMR studies, the authors proposed that the mechanism for the deoxygenation of sulfoxides (Scheme SM 13.4.1) involves the initial reduction of $MoO_2Cl_2(DMF)_2$ by the reducing agent triphenylphosphite with the formation of monooxo-complex $MoOCl_2(DMF)_2$ and the subsequent deoxygenation of sulfoxides to give the corresponding sulfides.
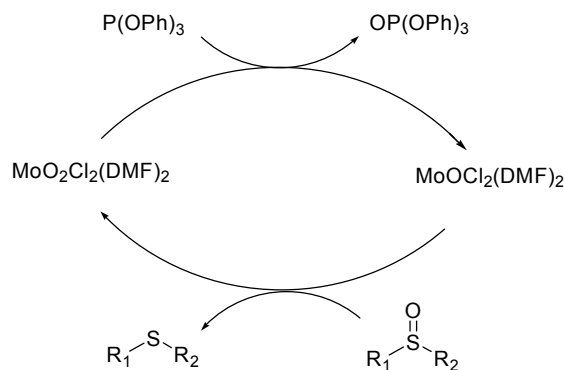
Scheme SM 13.4.**1.** Proposed catalytic cycle for the deoxygenation of sulfoxides with the system $P(OPh)_3/MoO_2Cl_2(DMF)_2$

5.Recommended references

1 F. J. Arnáiz, R. Agudo, M. R. Pedrosa and A. De Cian, *Inorg. Chim. Acta,* 2003, **347**, 33.

2 R. M. Silverstein, G. C. Bassler, T. C. Morrill, Spectrometric Identification of Organic Compounds, John Wiley & Sons, New York, 5th Edition, 1991, chapter 3, 129.

3 R. Sanz, J. Escribano, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synthesis*, 2004, **10**, 1629

Synthesis of allylic esters by reduction of fructone followed by Wittig olefination

Supplementary Material

Thomas A. Logothetis

<u>Experiment notes</u>

Drying of apparatus

The requirement to set up a dry apparatus can be fulfilled by either drying the readily assembled apparatus or by using oven-dried (>100 °C ideally) glassware. Flame-drying or drying with a heat-gun is possible, with the former method providing a visible check due to misting up of the cold glassware (outside, from water-vapour of combustion) and subsequent disappearance of the condensation on hot – internally dry – glassware. Ideally, the sealed apparatus cools down to room temperature under positive pressure of an inert gas.

The outcome of this reaction is not diminished greatly if glassware was dried at ~80 °C overnight and assembled slowly, *i.e.* while cooling down partly in ambient atmosphere. This describes a typical setting and occurrence encountered with (some) students.

Inert gas atmosphere and transfers

The reagents are predominantly moisture sensitive and the reaction should be conducted using either dry nitrogen or argon (not tested). Stock solutions are best kept under nitrogen or argon. Transfers are possible using cannula techniques with pressure form the inert gas reservoir, or by utilising balloons filled with inert gas to protect stock solutions, and easy-going syringes (glass or disposable plastic) with needles (disposable or recyclable). In our labs the balloon option and reusable plastic syringes and needles have been successfully employed.

Solvents and temperature

The solvent (dichloromethane) and temperatures for reduction and olefination were deliberately chosen to produce a mixture of *cis* and *trans* isomers, which would then be separated and isolated by chromatography. In our year 2 undergraduate cohort this is a new purification technique and afflicted with most losses. If so desired, a more selective outcome can be achieved using ethers as solvents (*e.g.* THF, Et$_2$O) and by lowering the temperatures.

In the context of this experiment – planning for a mixture of isomers – it is not critical to maintain the stated temperatures accurately. Sometimes a too fast addition of DIBAL causes the temperature to rise above the recommended value and subsequent strong cooling a temperature lower than recommended for the Wittig reaction (up to 15 °C difference in each case is tolerated). The outcome typically is yields at the lower end of the spectrum and a more prominent selectivity in the olefination step.

Work-up and chromatography[a]

The removal of aluminium is achieved by chelation with Rochelle's salt (Seignette salt, sodium potassium tartrate) followed by extraction into the aqueous phase. In principle, this could be substituted with citrates (not tested). An alkaline workup would hydrolyse the ester whereas acid would deprotect the ketone and both conditions should thus be avoided.

Figure SM 13.5.1: Summary TLC

A summary of typical TLC analyses obtained from various stages of the reaction is depicted in Figure SM 13.5.1. All spots are UV-positive, and all bar the bottom one are stained by permanganate. Any fractions containing substances with a higher retention factor (impurities and less polar by-products – spot A) than the two stereoisomeric products (spots B, mixed fraction C and spot D) are discarded, as are fractions with a lower retention factor (triphenylphosphine oxide residues not removed during trituration – nor-
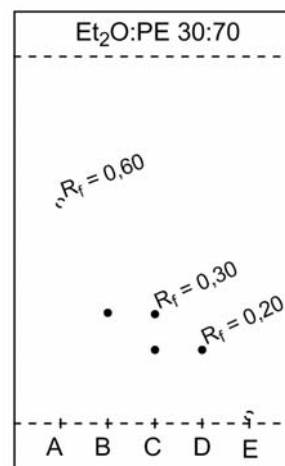
mally very faint to non-observable, intensities are an indication of trituration proficiency – spot E). TLC samples can be taken at any stage (*e.g.* intermediate aldehyde, before and after trituration, monitoring chromatography) and this has been a feature in the past. However in this practical TLC analysis is used only to determine the contents of the fractions, more precisely to monitor the separation of the desired stereoisomers.

The loading of the column is facilitated by using a solution of crude product in light petroleum ether, in which none of the contents penetrate the silica of the packed column. The elution starts once the more polar eluent is applied. Bellows are used to apply pressure; however, alternative means would work equally well.

Typically, circa 50 fractions (~ 10 mL) are collected. Product-containing fractions are then combined to isolate the two pure stereoisomers. Both stereoisomers are colourless, viscous liquids. Depending on skill 1-5 mixed fractions are also obtained.

Yields

In our experience over the years the yields of pure isomers after chromatography is in the range of 5-25% of *cis*-isomer and 15-50% of *trans*-isomer. Neither the intermediate aldehyde nor the by-product, triphenylphosphine oxide, were isolated. The *cis:trans*-ratio averages 1:3.

Optional features

The reaction conditions and choice of solvents can be adapted as described above to increase the yield and to afford greater selectivity in the synthesis. The intermediate aldehyde could be isolated and analysed spectroscopically. Triphenylphosphine oxide[b] could be purified, *e.g.* by recrystallisation, its mass determined and analysed spectroscopically. NMR spectra for the crude oxide obtained after trituration are in the spectra section (*vide infra*).
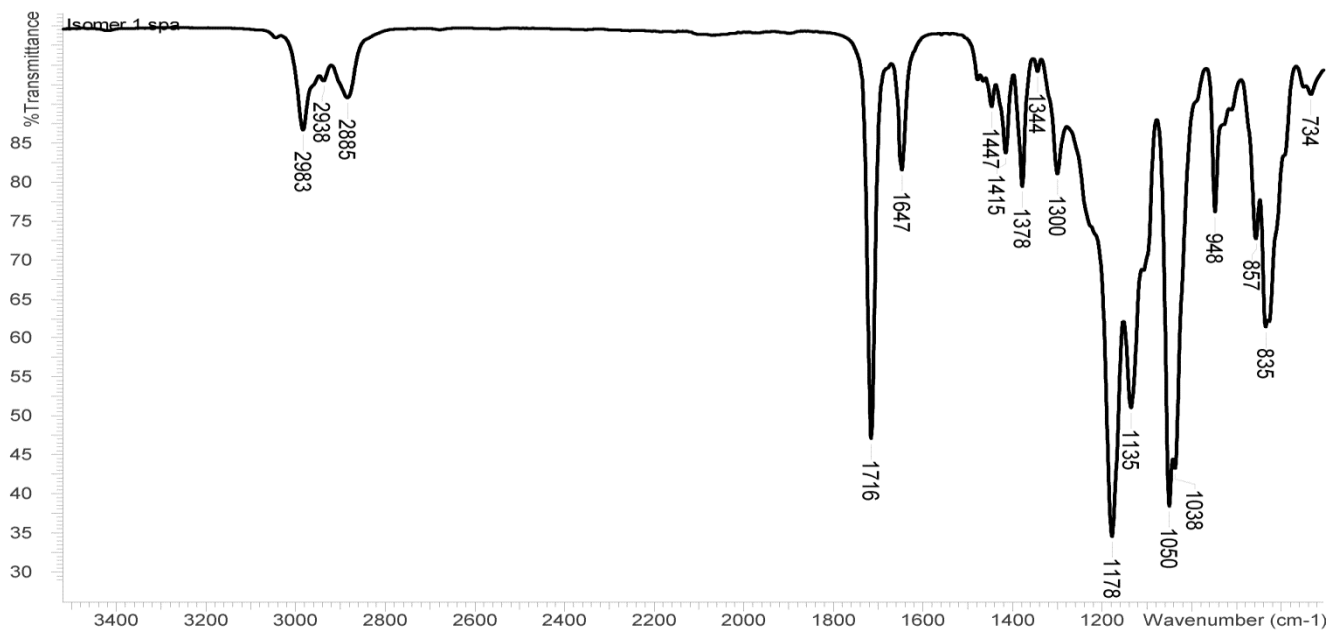
Spectra

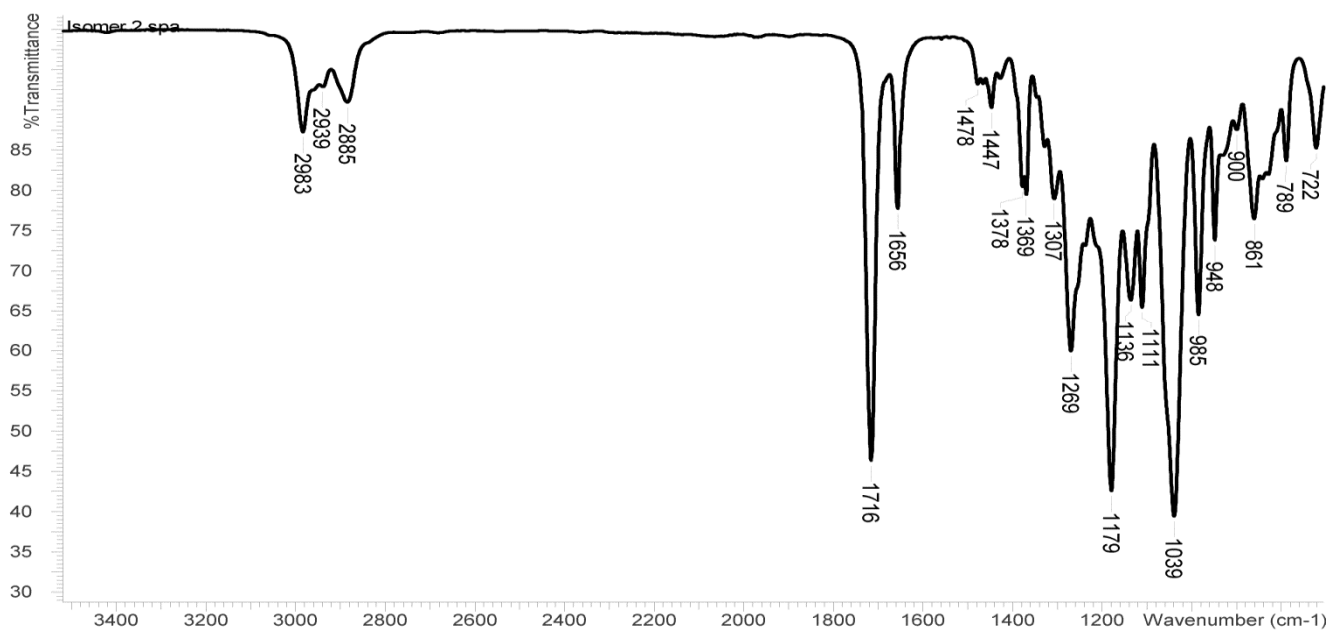**Figure SM 13.5.2: IR (ATR) of ethyl *(Z)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate**

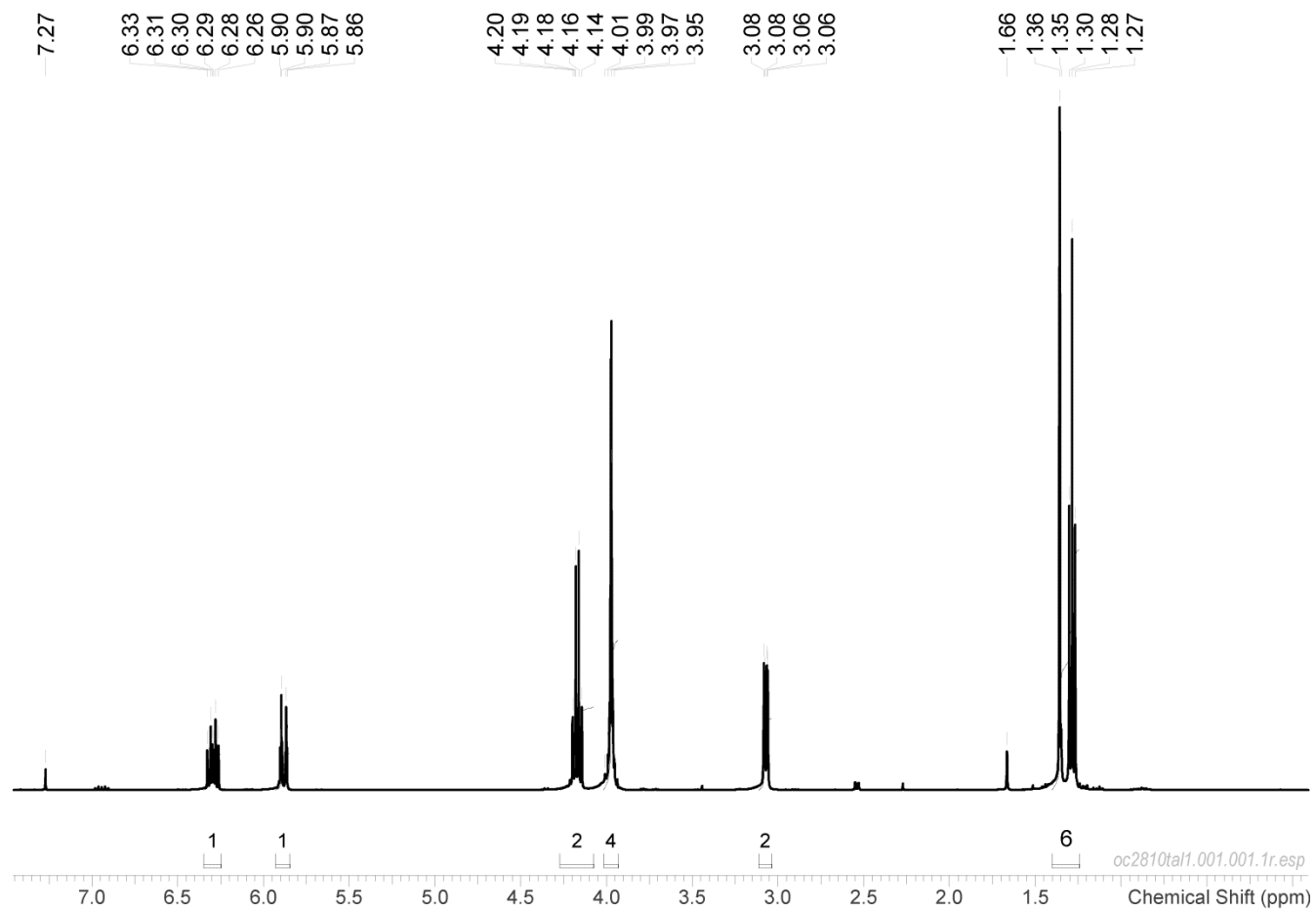**Figure SM 13.5.3: IR (ATR) of ethyl *(E)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate**

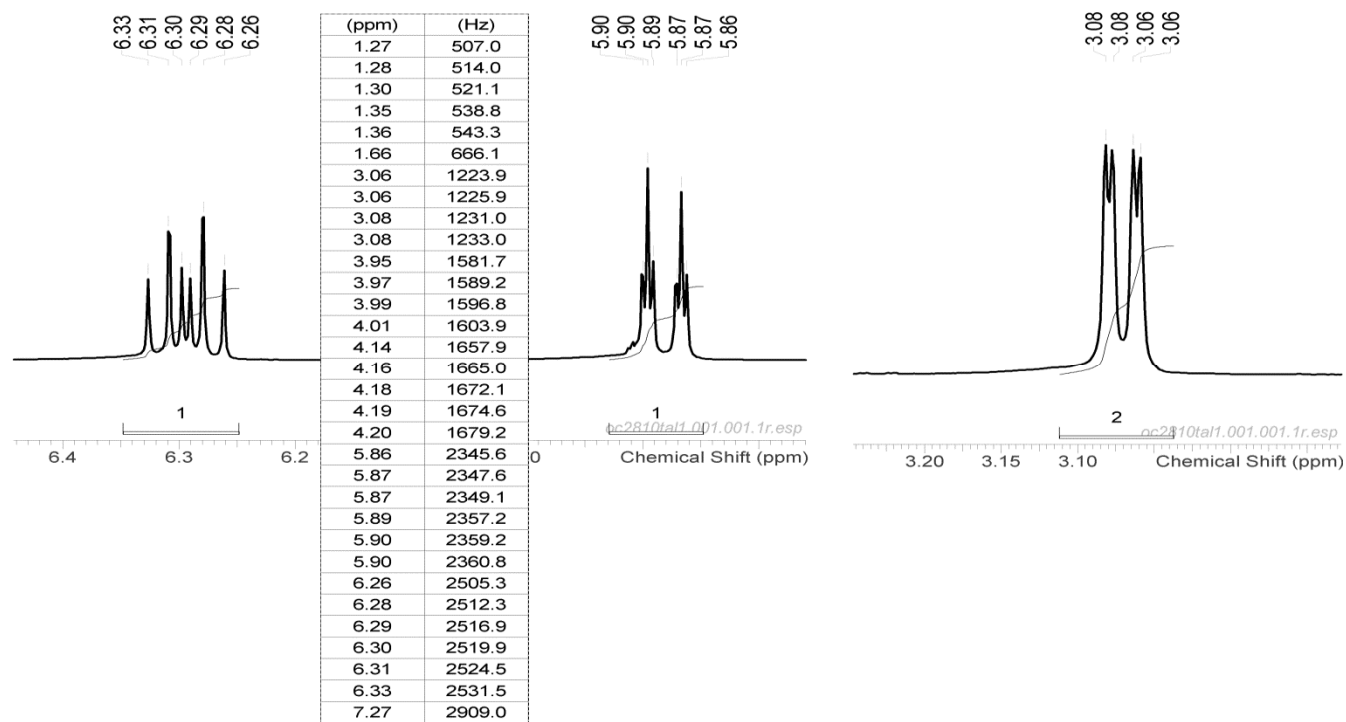**Figure SM 13.5.4:** ^{1}H NMR (400 MHz, CDCl₃) of ethyl *(Z)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate

(ppm)	(Hz)
1.27	507.0
1.28	514.0
1.30	521.1
1.35	538.8
1.36	543.3
1.66	666.1
3.06	1223.9
3.06	1225.9
3.08	1231.0
3.08	1233.0
3.95	1581.7
3.97	1589.2
3.99	1596.8
4.01	1603.9
4.14	1657.9
4.16	1665.0
4.18	1672.1
4.19	1674.6
4.20	1679.2
5.86	2345.6
5.87	2347.6
5.87	2349.1
5.89	2357.2
5.90	2359.2
5.90	2360.8
6.26	2505.3
6.28	2512.3
6.29	2516.9
6.30	2519.9
6.31	2524.5
6.33	2531.5
7.27	2909.0

Figure SM 13.5.5: Expansion of ^{1}H NMR (400 MHz, CDCl$_3$) of ethyl *(Z)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate
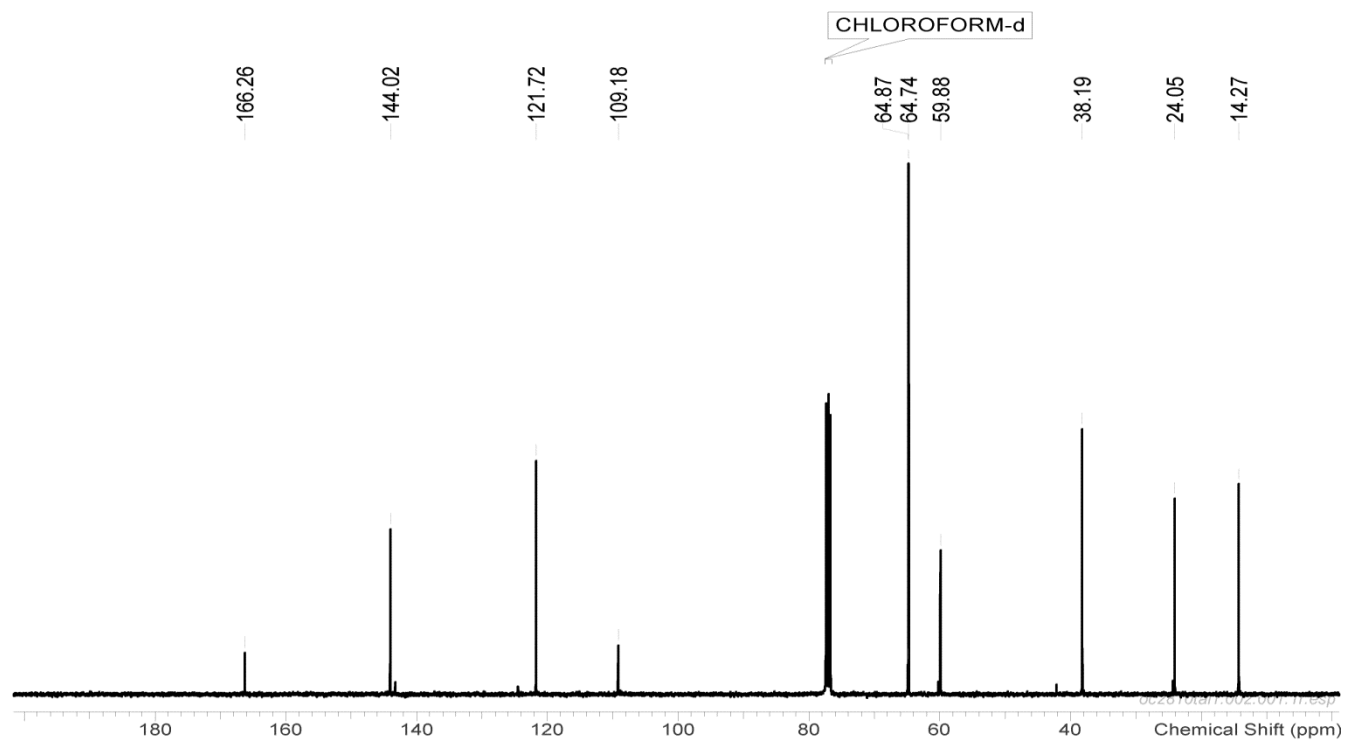

Figure SM 13.5.6: ^{13}C NMR (100 MHz, CDCl$_3$) of ethyl *(Z)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate
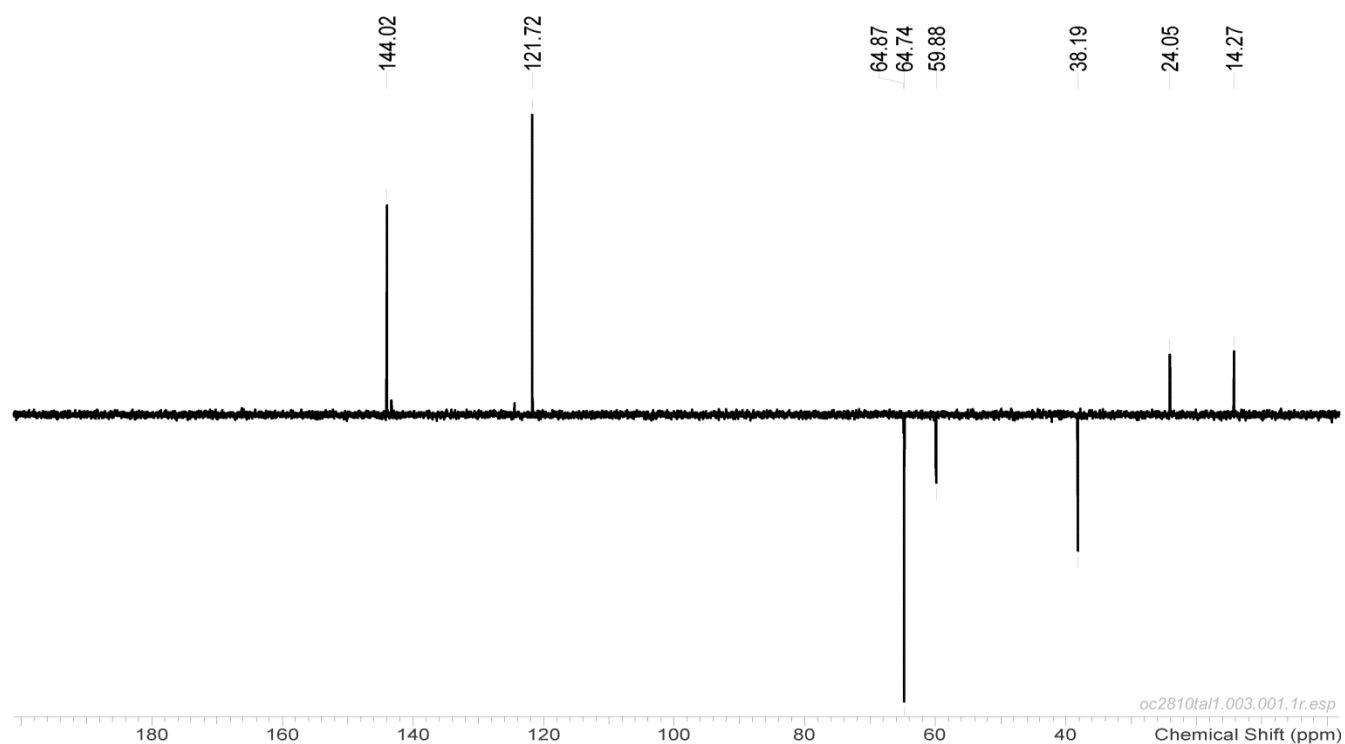
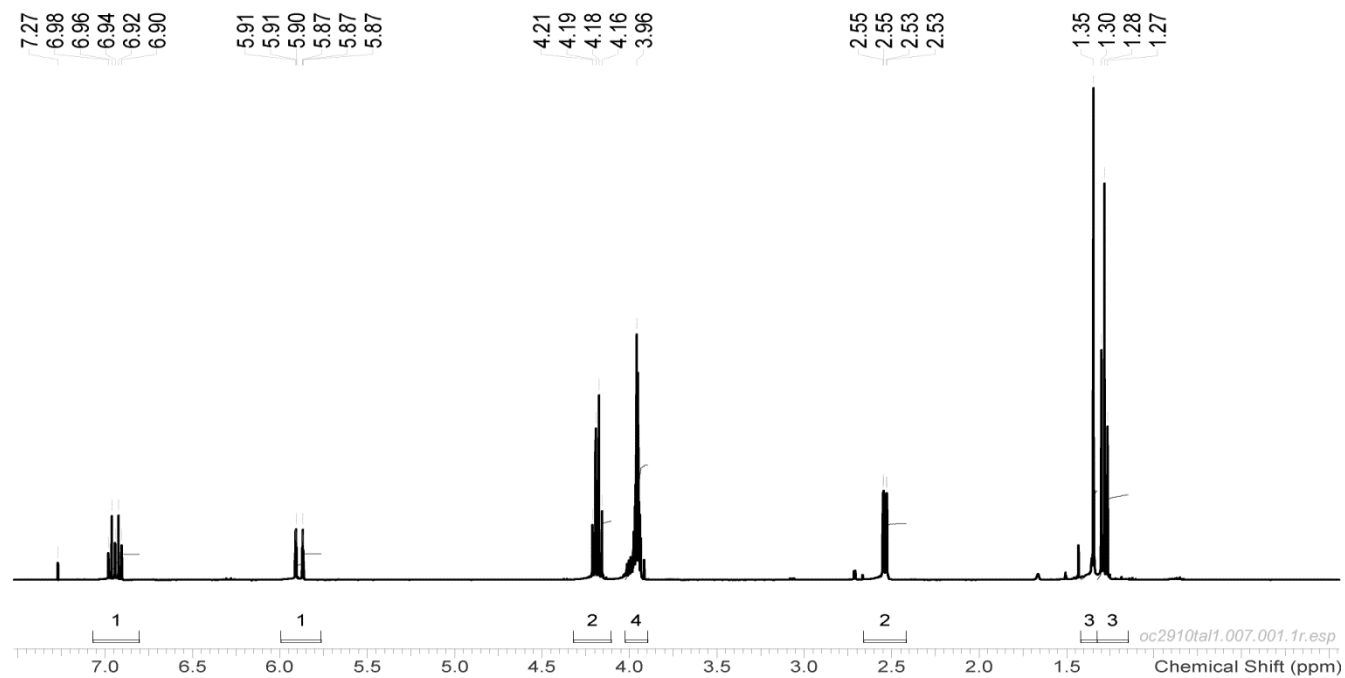**Figure SM 13.5.7: DEPT-135 (100 MHz, CDCl₃) of ethyl *(Z)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate**

Figure SM 13.5.8: ¹H NMR (400 MHz, CDCl₃) of ethyl *(E)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate
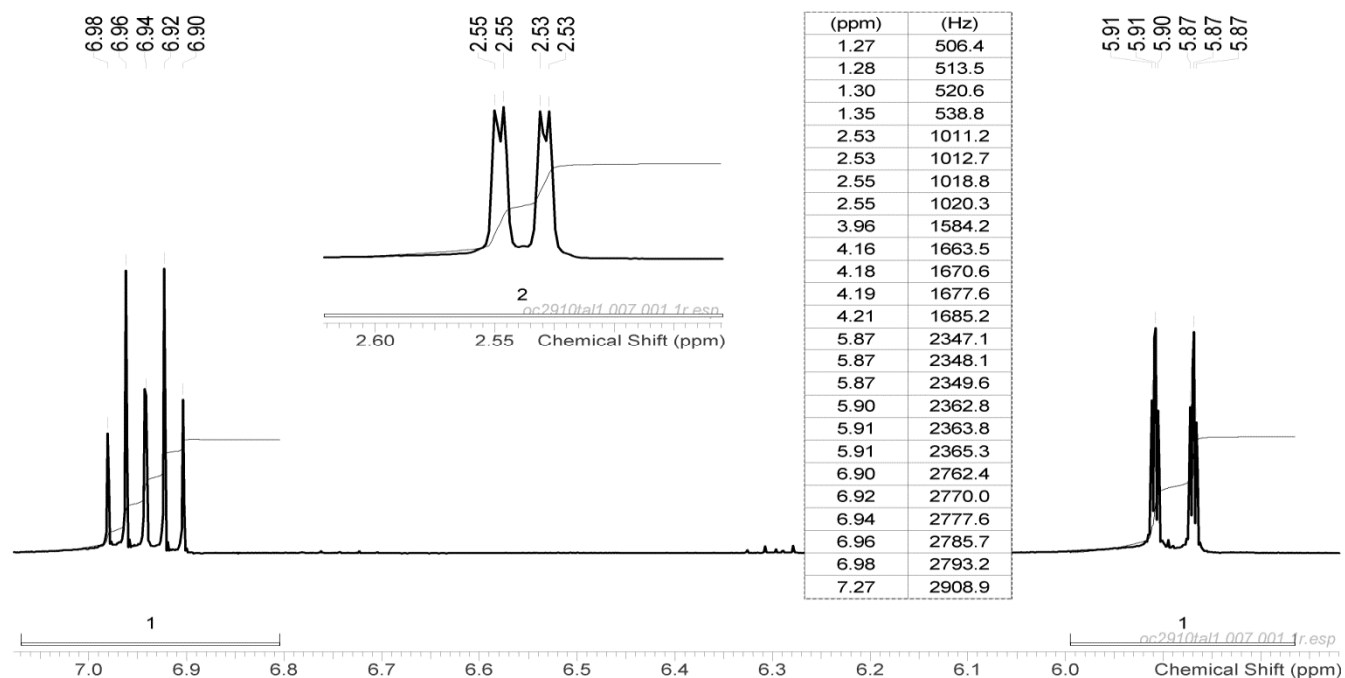
(ppm)	(Hz)
1.27	506.4
1.28	513.5
1.30	520.6
1.35	538.8
2.53	1011.2
2.53	1012.7
2.55	1018.8
2.55	1020.3
3.96	1584.2
4.16	1663.5
4.18	1670.6
4.19	1677.6
4.21	1685.2
5.87	2347.1
5.87	2348.1
5.87	2349.6
5.90	2362.8
5.91	2363.8
5.91	2365.3
6.90	2762.4
6.92	2770.0
6.94	2777.6
6.96	2785.7
6.98	2793.2
7.27	2908.9

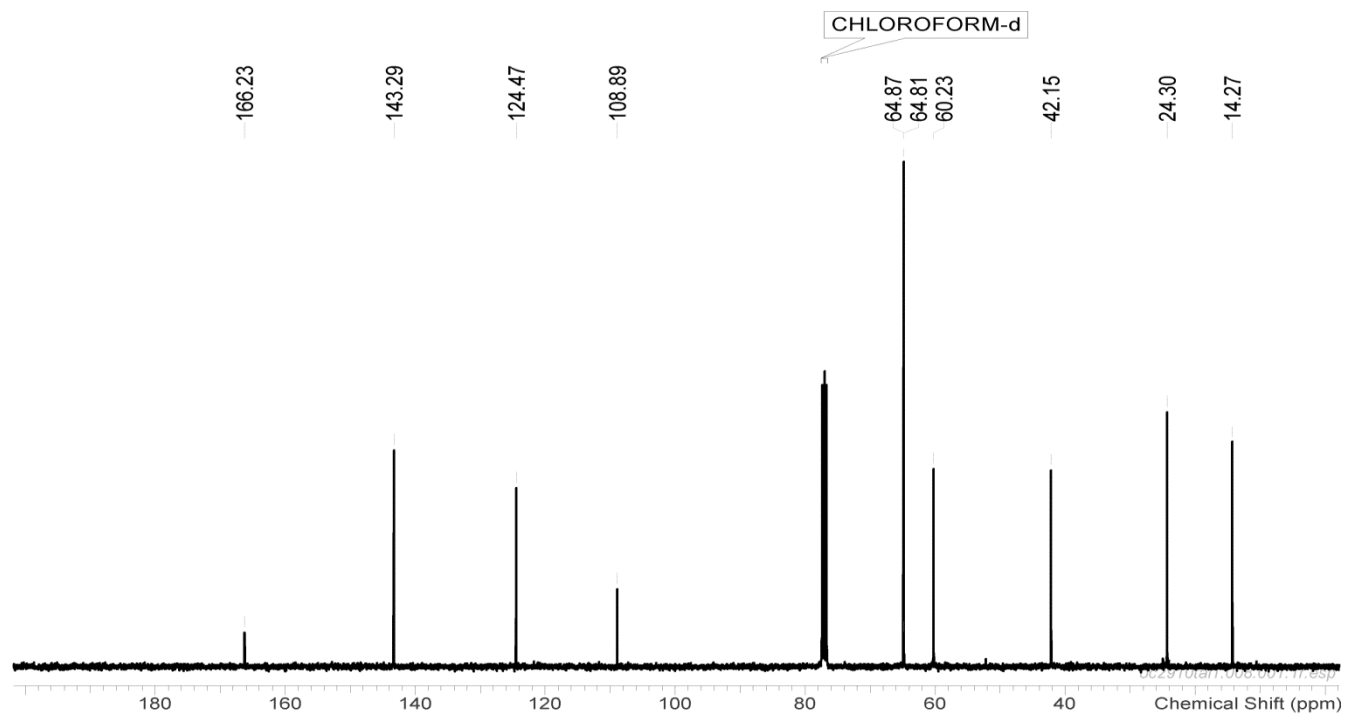**Figure SM 13.5.9: Expansion of ^{1}H NMR (400 MHz, CDCl$_3$) of ethyl *(E)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate**

Figure SM 13.5.10: ^{13}C NMR (100 MHz, CDCl$_3$) of ethyl *(E)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate
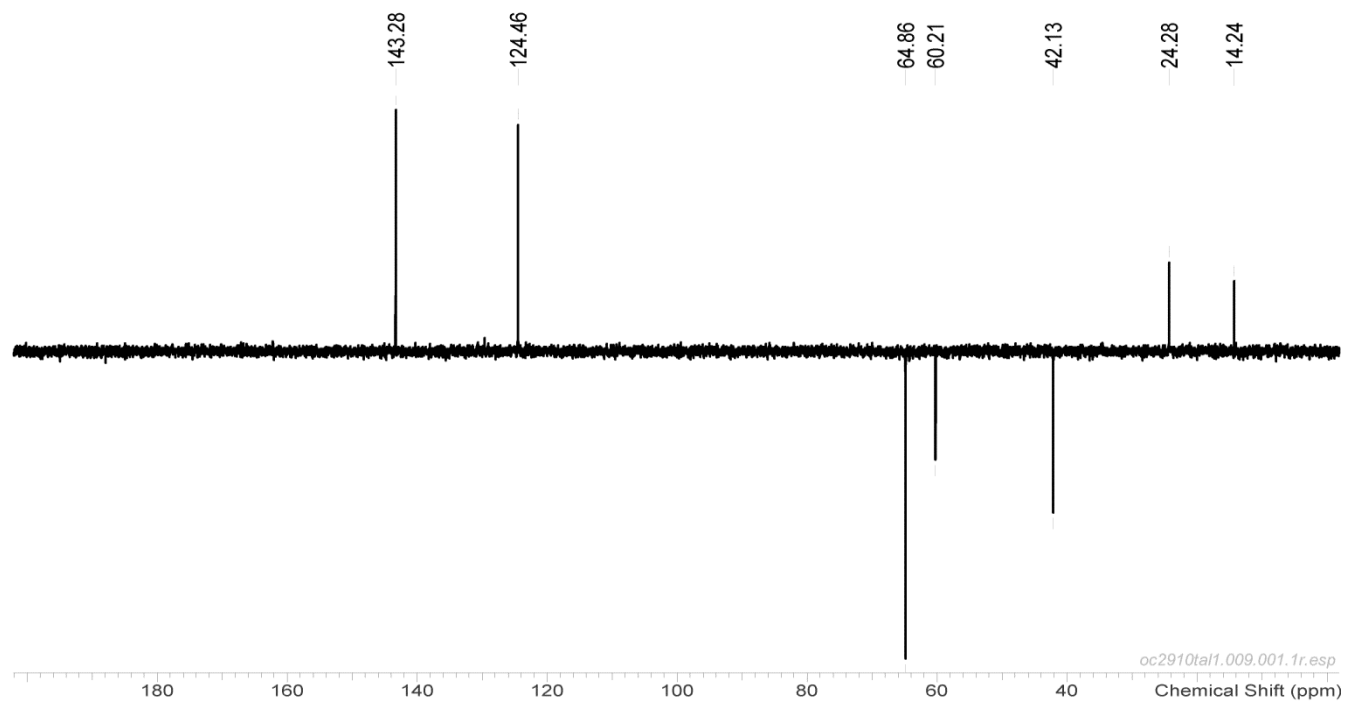
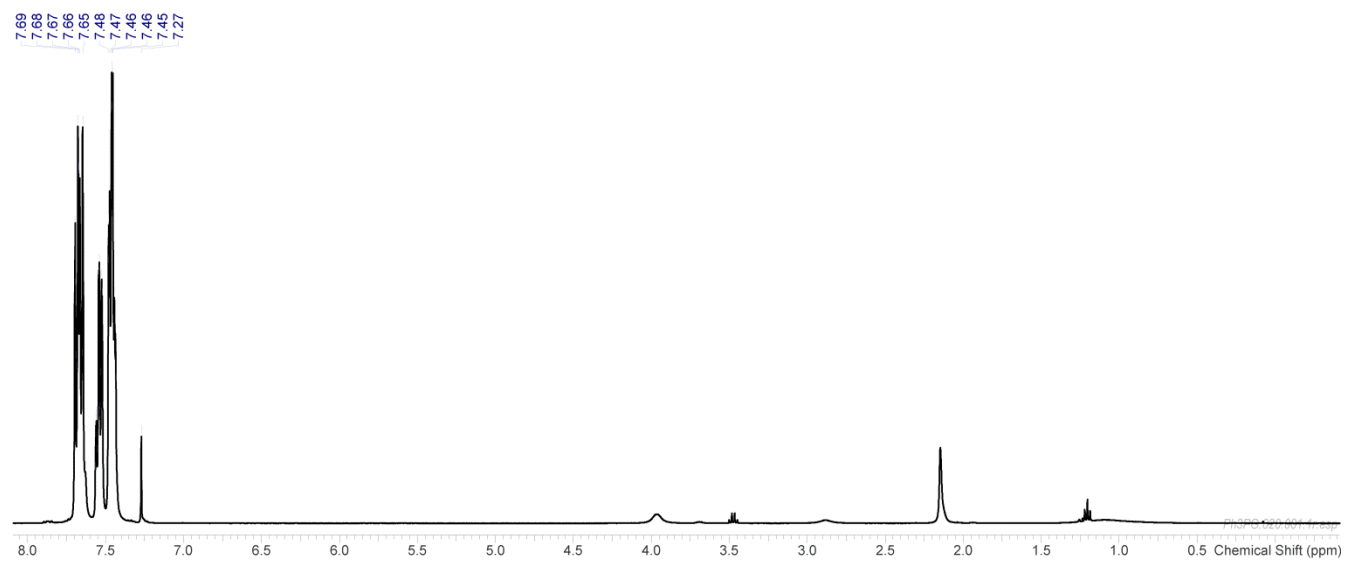**Figure SM 13.5.11: DEPT-135 (100 MHz, CDCl₃) of ethyl *(E)*-4-(2-methyl-1,3-dioxolan-2-yl)but-2-enoate**

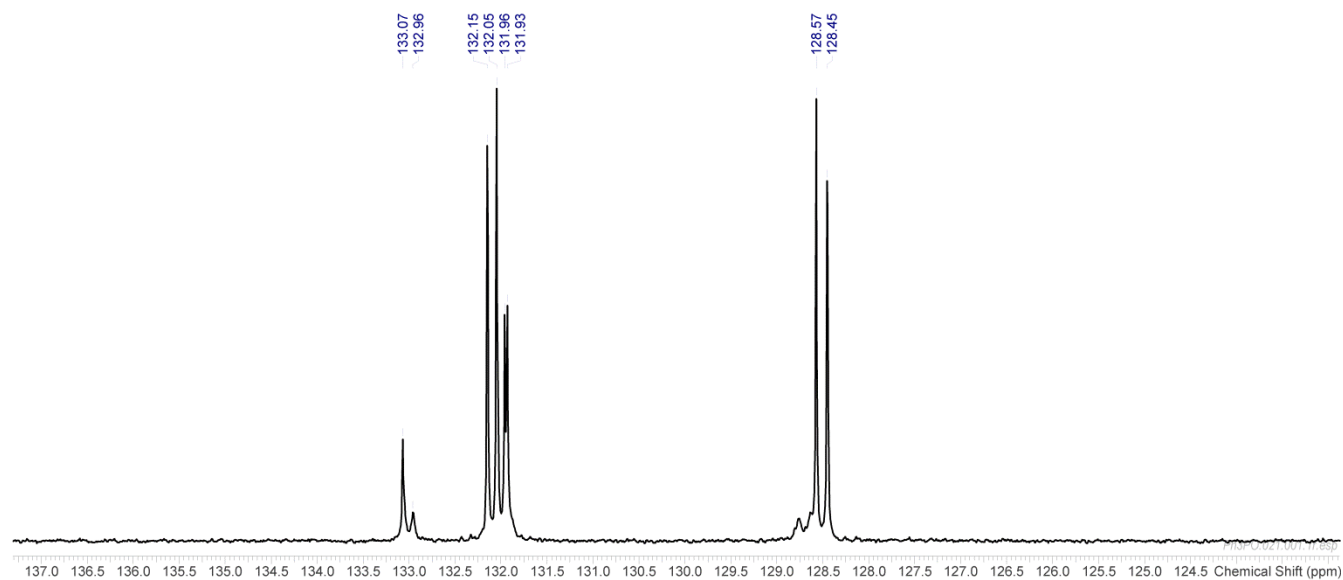**Figure SM 13.5.12: ¹H NMR (400 MHz, CDCl₃) of crude by-product obtained by trituration (chiefly Ph₃P=O)**

Figure SM 13.5.13: Expansion of ^{13}C NMR (100 MHz, CDCl$_3$) of crude by-product obtained by trituration (chiefly Ph$_3$P=O)
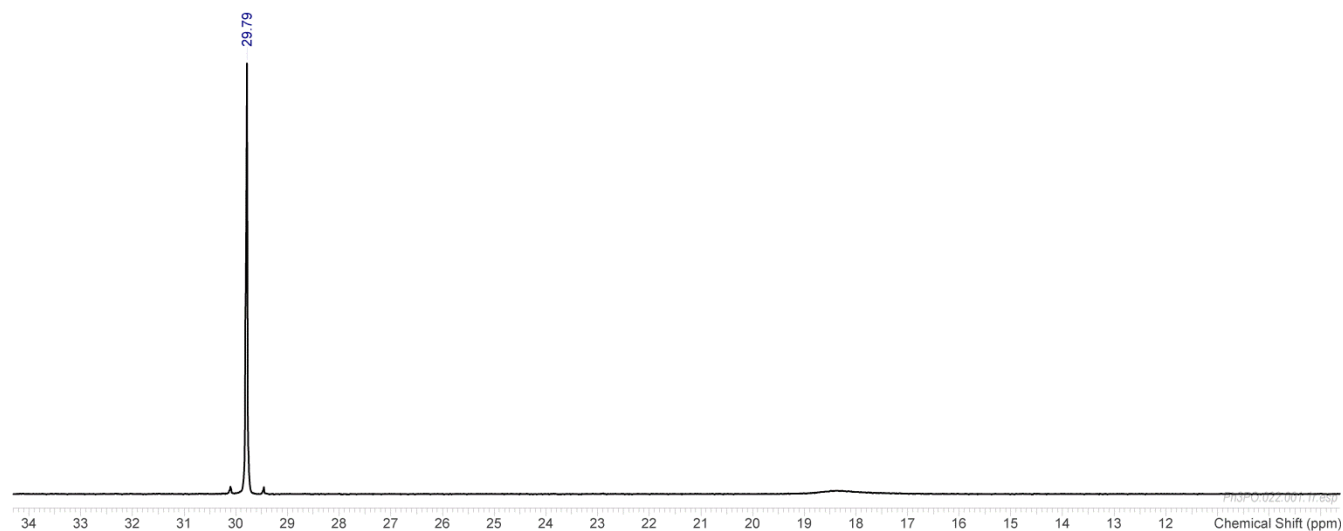
Figure SM 13.5.14: ^{31}P{^{1}H} NMR (162 MHz, CDCl$_3$) of crude by-product obtained by trituration (chiefly Ph$_3$P=O)

Photos of the experiment

Figure SM 13.5.15: Drawing of DIBAL under inert gas protection

Figure SM 13.5.17: Setup after removal of cooling bath

Figure SM 13.5.16: Setup in Dewar, addition of reagent

Figure SM 13.5.18: Packed column with bellows

References

[a] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.*, 1978, **43(14),** 2923.

[b] F.-H. Hu, L.-S. Wang, S.-F. Cai, *J. Chem. Eng. Data*, 2009, **54**, 1382-1384.

Preparation of a thia-tetraaza macrocyclic compound through a dual-step synthesis

Supplementary Material

Background

A macrocyclic compound is a cyclic molecule with three or more potential donor atoms (as example, N, S or O) in a ring of at least nine atoms.[1] Macrocyclic chemistry has expanded phenomenally since the 1960s and still remains a focus of scientific attention.[2-4] In fact, this class of compounds continue to be actively sought and developed due to a myriad of potential applications, namely in medicine as radiopharmaceuticals, MRI contrast agents, SOD mimetics and chelating agents for the removal of metal ions from the organism.[5,6] As a result of these innumerous applications, these compounds, as well as their complexes, are frequently discussed as an integral part of any course on bioinorganic chemistry or medicinal chemistry. However, comparatively, practical courses in basic and advanced organic chemistry usually involve little or no macrocyclic chemistry, once the reported laboratory procedures are typically time-consuming and complex. To overcome this situation and to improve the knowledge of the synthetic methods involving this important class of compounds, we propose in this laboratory project a preparation of a thia-tetraaza macrocyclic compound.

The objective of this work is to synthetize the macrocycle 1-thia-4,7,10,13-tetraazacyclopentadecane ([15]aneN$_4$S) and to properly characterize it by ^{1}H NMR and IR spectroscopies, as well as its cyclic diamide precursor 1-thia-4,7,10,13-tetraazacyclopentadecane-

3,14-dione (dioxo-[15]aneN$_4$S). The full project is designed to be carried out conveniently by a group of two students in two laboratory sessions of four hours each.

For the synthesis of macrocyclic compounds, the most common synthetic methodologies used in the cyclization process are based on three major procedures: template synthesis, high dilution technique and the method of Richman and Atkins.[3,7] However, the cyclization method reported in this work is not included in the above procedures, but it is an adaptation from the methodology published in the literature by Tabushi *et al.*[8] and Steenland *et al.*,[9] in which the macrocyclic ring closure is performed via aminolysis of the dimethyl ester of an α,ω-dicarboxylic acid with a commercially available polyethylenepolyamine. The modifications that we have introduced, such as controlled reaction temperature, dry methanol in a larger volume and nitrogen atmosphere[10] allowed to obtain the pure compound with a higher yield. The obtained cyclic diamide is posteriorly reduced following a similar methodology established by Kimura *et al.*[11]

To prepare the macrocycle [15]aneN$_4$S, firstly it is necessary to obtain the dioxo-[15]aneN$_4$S macrocyclic precursor, by adding the dimethylic ester of tiodiglycolic acid (previously synthetized by the instructor according to a reported procedure[12]) to triethylenetetramine, in dry methanol. The progress of this reaction can be checked by using TLC. In this step, occur two addition-elimination reactions – a first intermolecular one, between the starting reagents, that will lead to the second reaction, intramolecular, wherein the ring is formed (*cf.* Figure **SM 13.6.**1).[12] The purification of dioxo-[15]aneN$_4$S is performed by column chromatography, wherein the third eluate by using a mixture of dichloromethane/methanol (4:1) as eluent. The expected reaction yield for this first step is about 50%. Dioxo-[15]aneN$_4$S is then reduced to the desired product by using a large excess of borane in dry tetrahydrofuran. In this second step, the secondary amide groups are reduced to secondary amines according to the proposed mechanism depicted in Figure **SM 13.6.**2.[13] The choice of this reduction agent is preferable to the common ones, such as lithium aluminium hydride, once the tendency for C-N bond cleavage to yield an alcohol is completely absent.[13] [15]aneN$_4$S is then purified by column chromatography, wherein the pure compound is obtained in the third eluate by using methanol as eluent. The expected reaction yield for this second step is about 40%.

Both dioxo-[15]aneN$_4$S and [15]aneN$_4$S should be properly characterized by ^{1}H NMR (*cf.* Figures **SM 13.6.**3 and **SM 13.6.**4 and Table **SM 13.6.**1) and IR spectroscopies (*cf.* Figures **SM 13.6.**5 and **SM 13.6.**6 and Table **SM 13.6.**2). The first technique will allow the students to verify if the synthetized compound corresponds to the desired pure product for each step of the reaction, while by analysing the IR spectra students may confirm if the reduction step was appropriately executed (there is an absence of the C=O characteristic band in the reduced product).

This experiment will provide the students some knowledge of the fundamentals of the organic chemistry involved in preparation of macrocyclic compounds, giving them a useful practical experience in synthetic chemistry, spectroscopic analysis and team work.
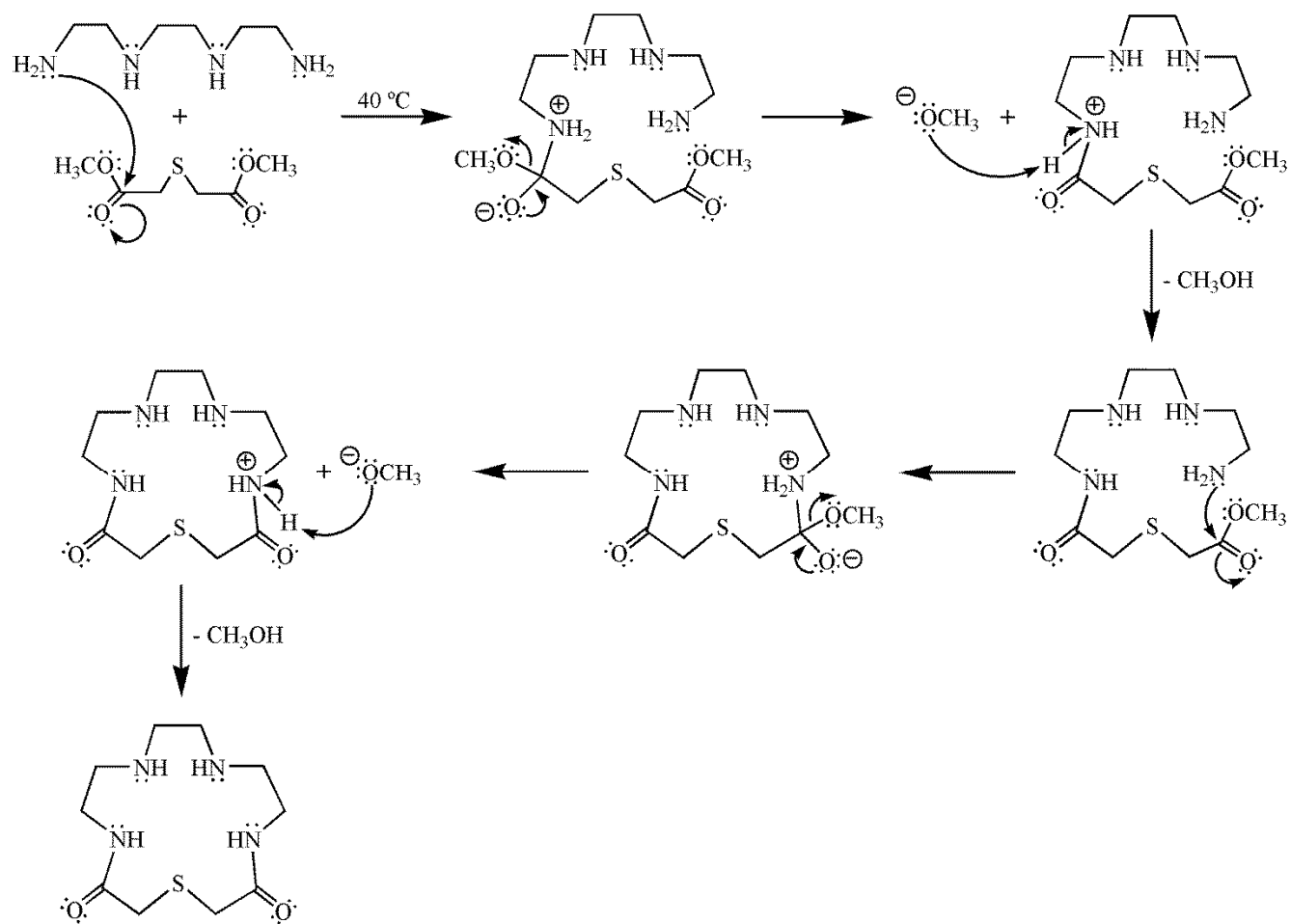
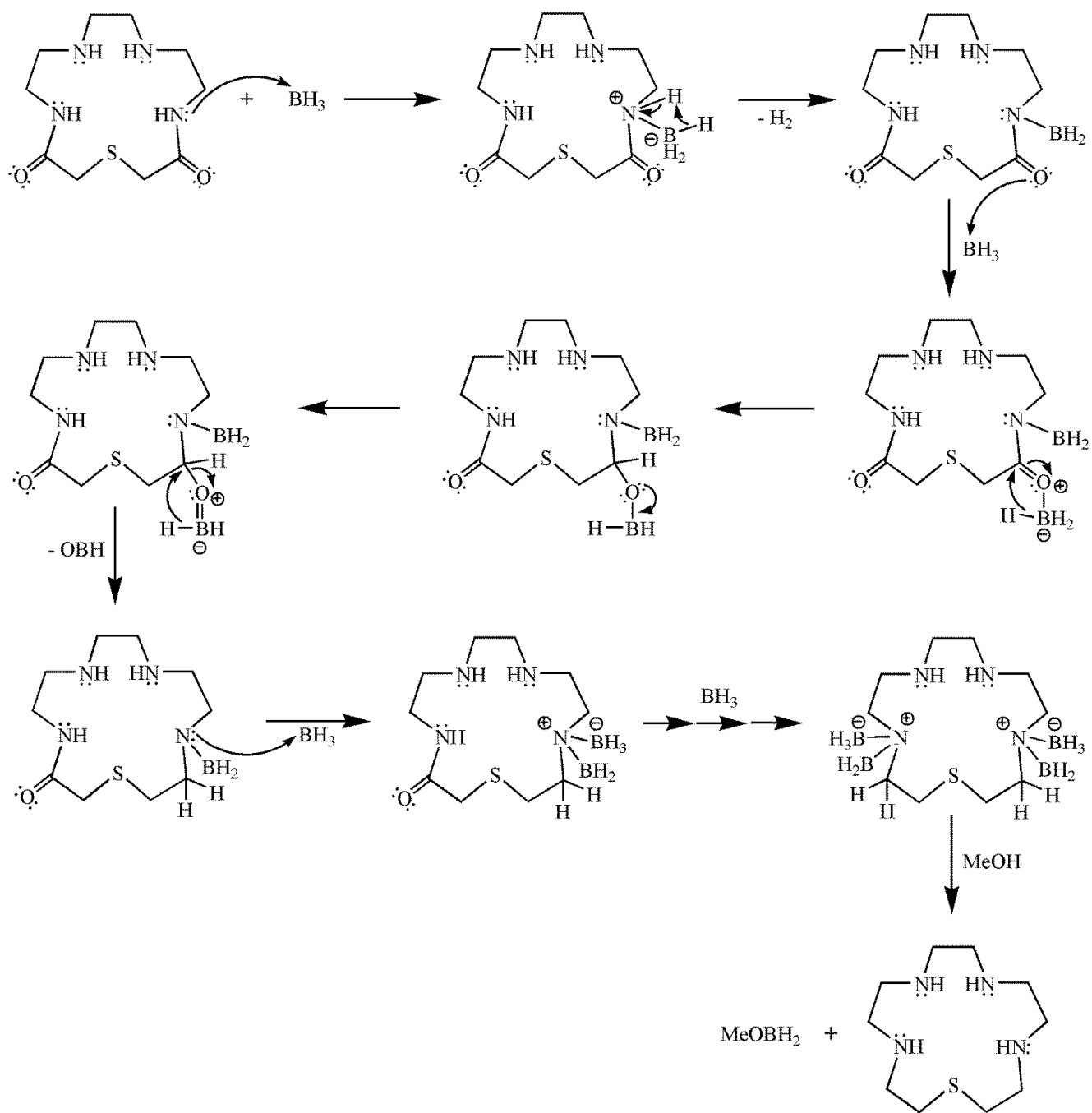**Figure SM 13.6.1** – Proposed detailed mechanism for step 1 reaction.

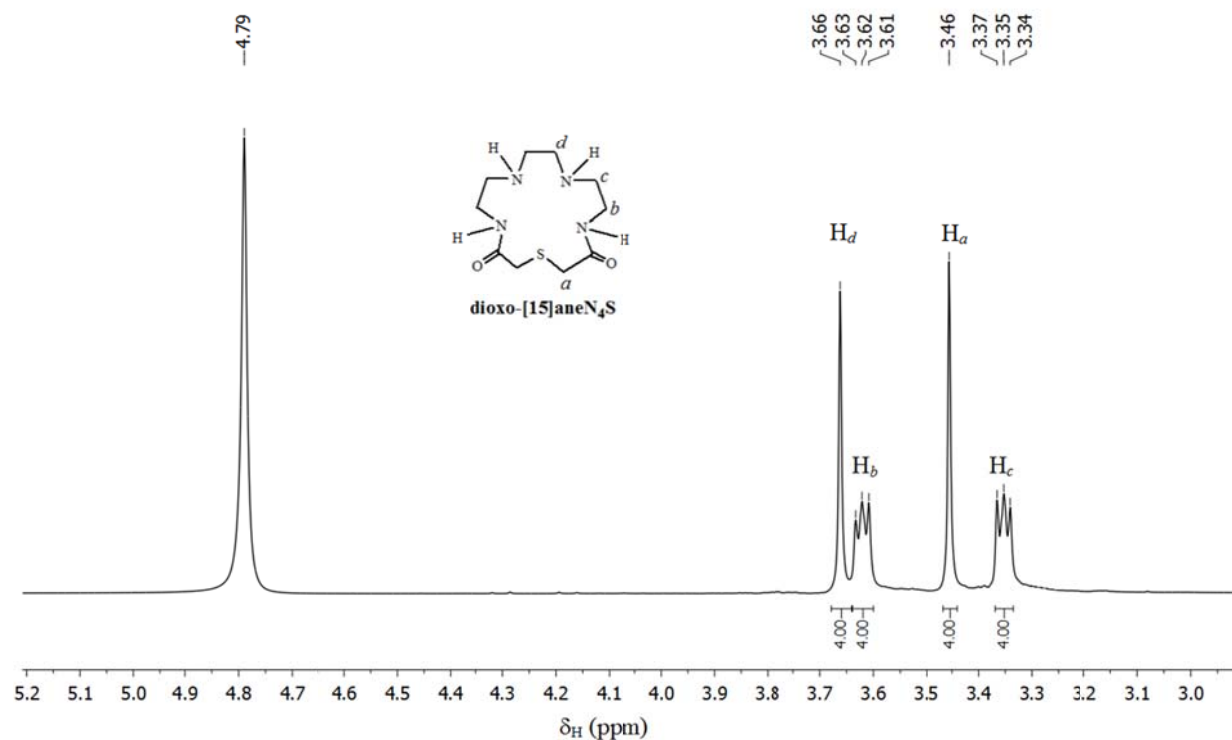**Figure SM 13.6.2** – Proposed detailed mechanism for step 2 reaction.

Figure SM 13.6.3 – ^{1}H NMR spectrum (400.13 MHz) of dioxo-[15]aneN$_4$S in D$_2$O, pH ≈ 4.
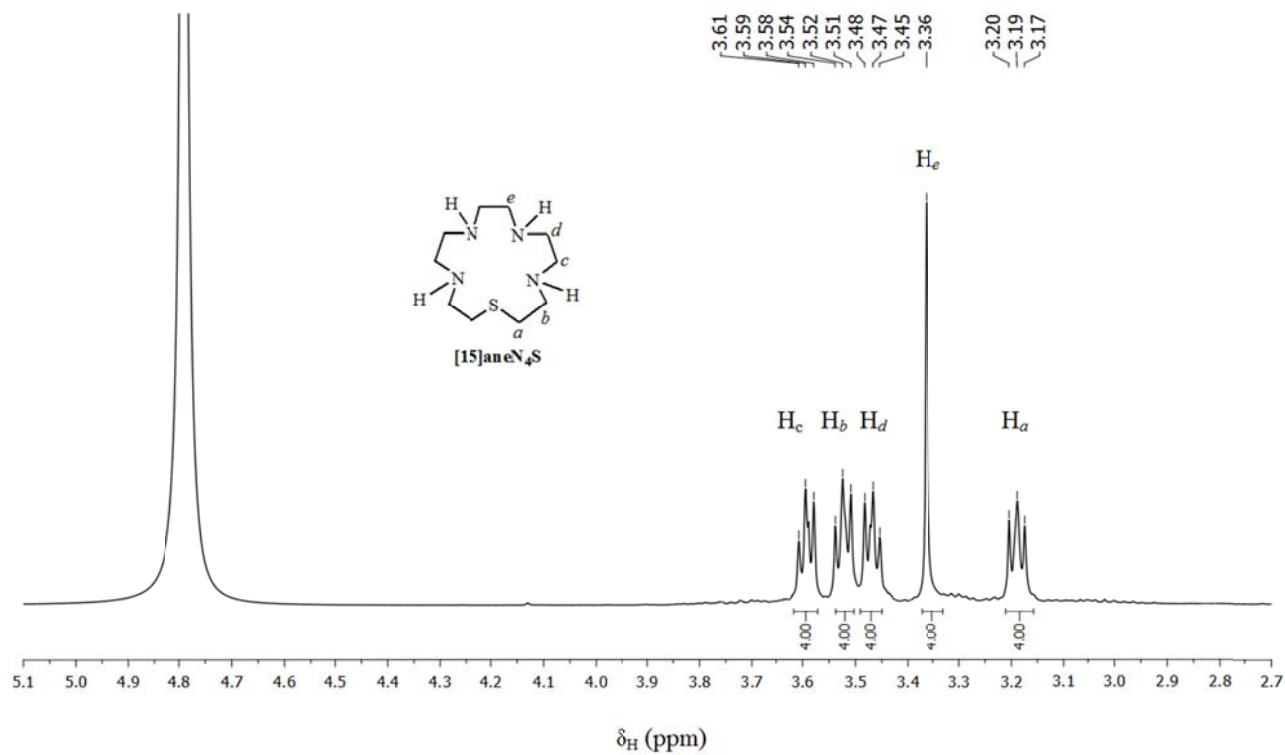

Figure SM 13.6.4 – ^{1}H NMR spectrum (400.13 MHz) of [15]aneN$_4$S in D$_2$O, pH ≈ 1.
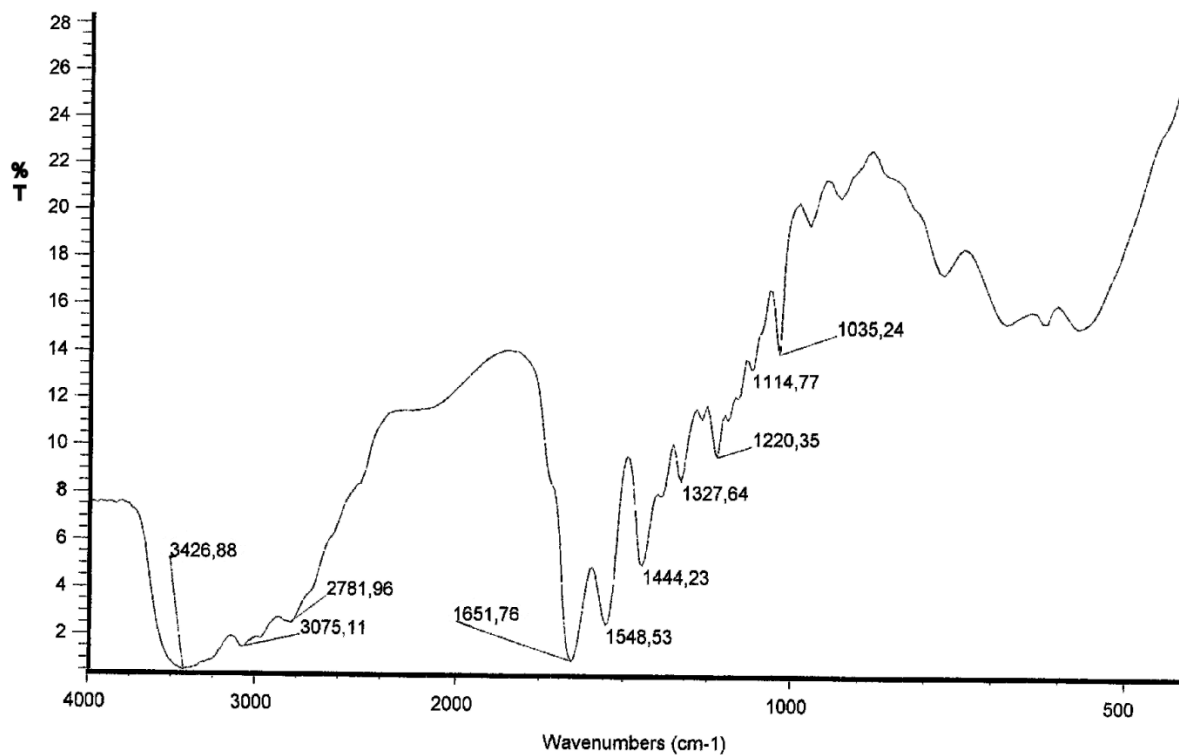
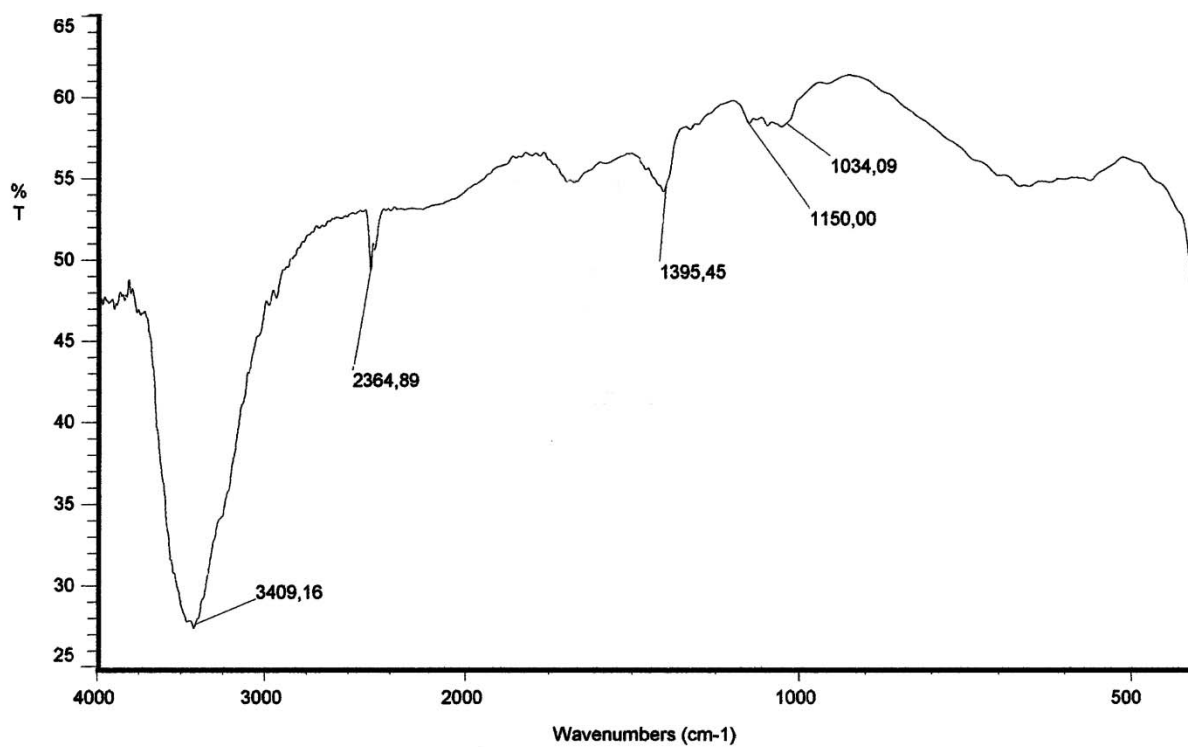**Figure SM 13.6.5** – IR spectrum of dioxo-[15]aneN$_4$S in KBr pellet.

Figure SM 13.6.6 – IR spectrum of [15]aneN$_4$S in KBr pellet.

Table SM 13.6.1 – ^{1}H NMR data (400.13 MHz) for dioxo-[15]aneN$_4$S (D$_2$O, pH ≈ 4) and [15]aneN$_4$S (D$_2$O, pH ≈ 1).

Assignment	Chemical shift (ppm)	
	dioxo-[15]aneN$_4$S	[15]aneN$_4$S
a	3.46 (4H, s)	3.19 (4H, t)
b	3.62 (4H, t)	3.52 (4H, t)
c	3.35 (4H, t)	3.59 (4H, t)
d	3.66 (4H, s)	3.47 (4H, t)
e	–	3.36 (4H, s)

Table SM 13.6.2 – IR data (in KBr pellets) for dioxo-[15]aneN$_4$S and [15]aneN$_4$S.

Assignment	Wavenumbers (cm^{-1})	
	dioxo-[15]aneN$_4$S	[15]aneN$_4$S
-N–H	3426.88	3409.16
-C=O	1651.76	-

Full detailed material/equipment list

All-glass syringe with a needle-lock luer (10 mL)

Analytical balance

Chromatographic column

Double-necked round-bottomed flasks (50 mL)

Electric oven

Filter funnel

Filter paper

Flasks (50 mL)

Fume hood

Gas line adaptor

Glass stopper

Graduated cylinders

^{1}H NMR spectroscopy equipment

Ice-salt bath

IR spectroscopy equipment

Magnetic hot plate

Magnetic stirrer bar   Source of dry nitrogen

Oil bath   Take-off

pH indicator strips   Thermometer

Pipet bulb   Utility clamps

Ring stand base   Volumetric pipets

Rotary evaporator   Watch glass

Sleeve septum stopper   Water-cooled reflux condenser
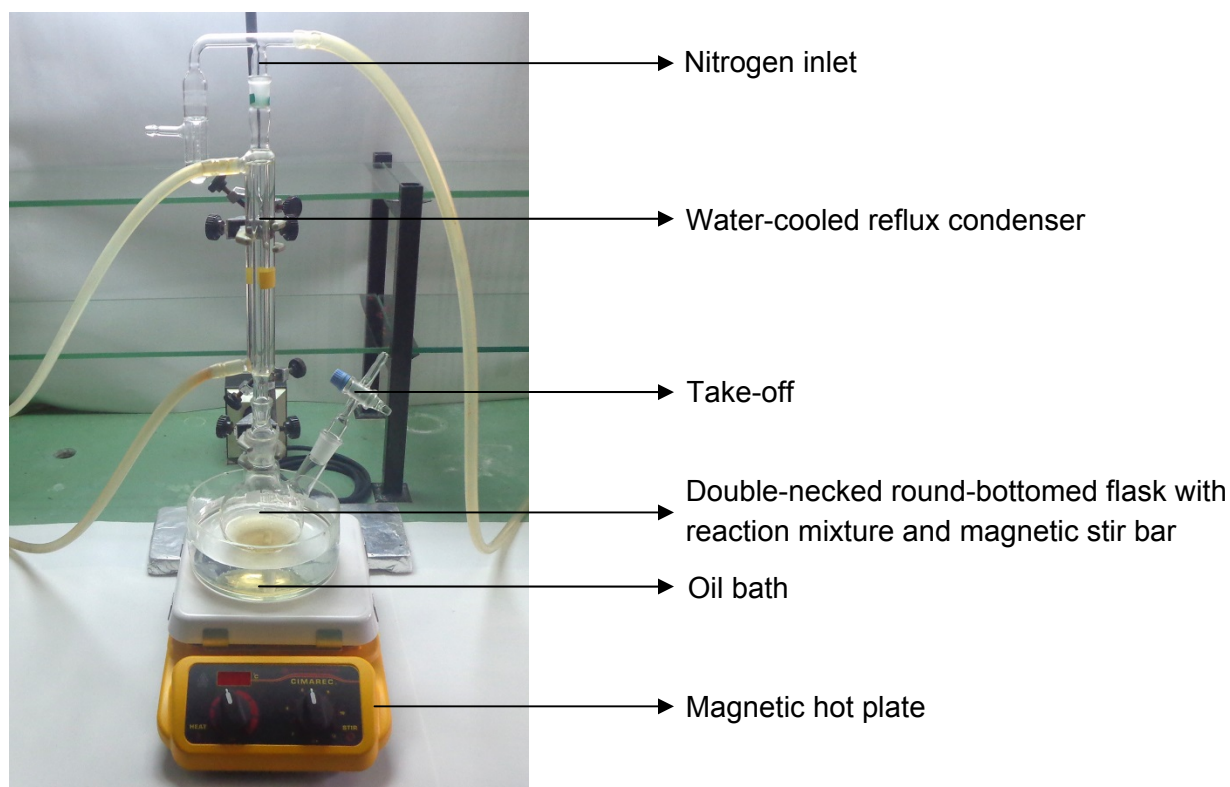
Figure SM 13.6.7 – Apparatus for step 1 reaction.

Column for chromatography with aluminium oxide slurried in dichloromethane (crude mixture already loaded)

Collecting flask for the eluate
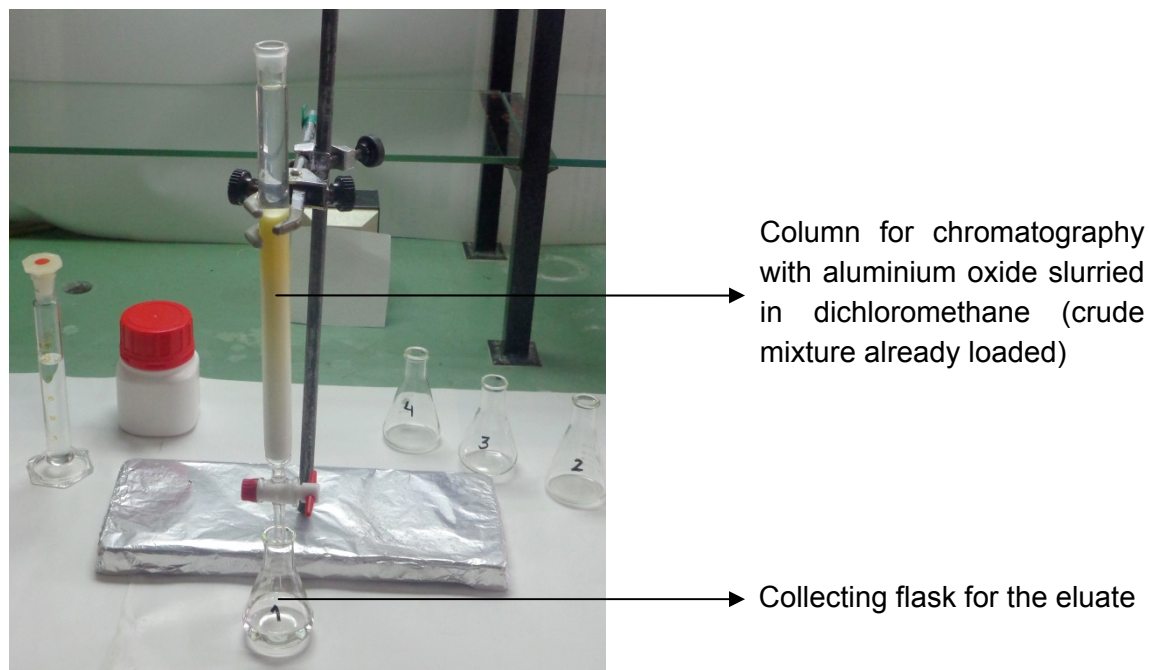
Figure SM 13.6.8 – Apparatus for column chromatography.

Nitrogen inlet

Water-cooled reflux condenser

Syring

Sleeve septum stopper

Double-necked round-bottomed flask with reaction mixture and magnetic stir bar

Oil bath

Magnetic hot plate
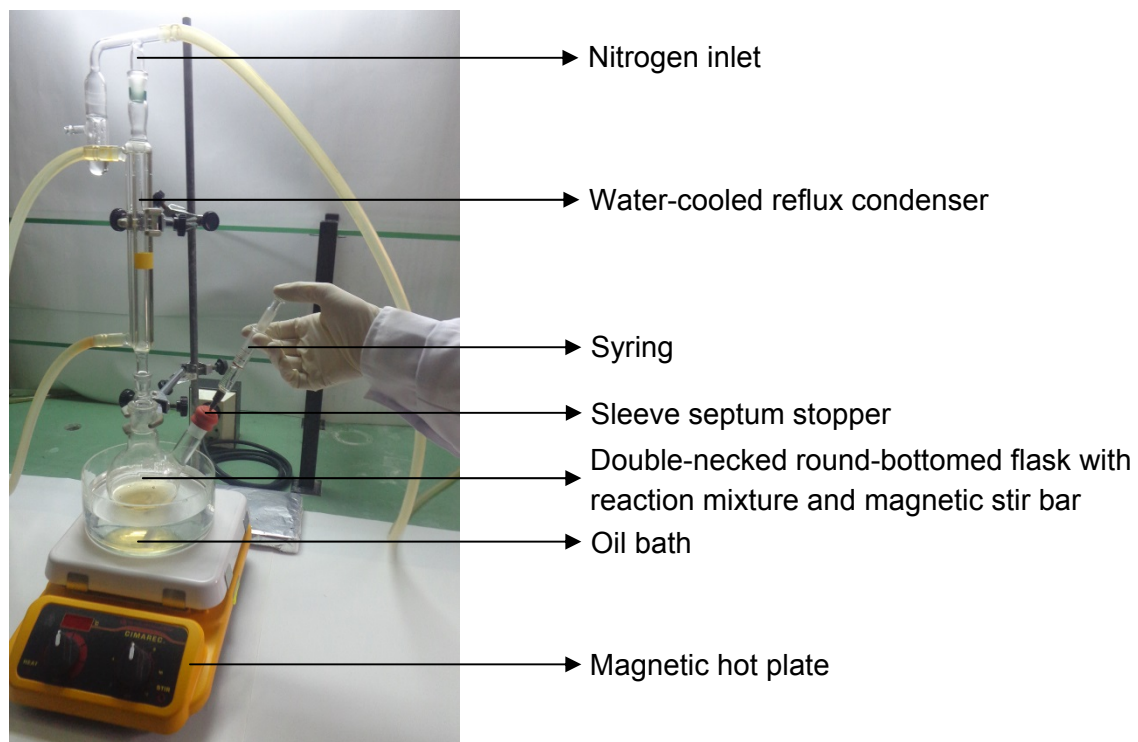
Figure SM 13.6.9 – Apparatus for step 2 reaction.

Alternative purification technique

The purification of dioxo-[15]aneN$_4$S and ~~of~~ [15]aneN$_4$S by column chromatography may also be performed resorting to a different set of stationary and mobile phases, in order to increase the overall yield of each step (about 75% and 65%, respectively):

For dioxo-[15]aneN$_4$S, a column of silica gel 60 is eluted with [1] chloroform, [2] a mixture of chloroform/methanol (1:4), and [3] methanol;

For [15]aneN$_4$S, a column of silica gel 60 is eluted with [1] a mixture of chloroform/methanol (1:4), [2] methanol, and [3] a mixture of methanol/hydrochloric acid 1 M (9:1).

In this case, it is expected to obtain both the pure compounds in the second eluate collected, by using a mixture of chloroform/methanol (1:4) as eluent (for dioxo-[15]aneN$_4$S), or by using methanol as eluent (for [15]aneN$_4$S).

Although this alternative purification technique leads to higher yields the use of the highly toxic chloroform solvent is a crucial drawback.

Notes for the instructor

For the preparation of step 1 reaction (*cf.* Experimental Procedure), the instructor has to synthesize in advance the dimethyl thiodiglycolate according to a reported procedure in literature[12] and methanol has to be dried according to literature[14].

For the preparation of step 2 reaction (*cf.* Experimental Procedure), tetrahydrofuran has to be previously dried according to literature[14] by the instructor and some of the material (such as double-necked round-bottomed flask and syringe) should be previously dried in an electric oven for 1 h at 110 ºC.

A convenient method for preparing the methanolic solutions of hydrochloric acid consists of using commercial aqueous concentrated hydrochloric acid diluted with methanol until concentrations 0.1 M and 3 M

The methanolic solutions of hydrochloric acid (0.1 M and 3 M), as well as the solution of potassium hydroxide in methanol (1 M), should be prepared in advance by the instructor or a student.

To perform the NMR analyses, it is necessary to previously adjust the samples to a range of pH values in which each NMR resonance is completely separate and easily understandable (pH ≤ 4 for both compounds), by using an appropriate acid solution (such as a methanolic solution of

hydrochloric acid) *cf.* Experimental Procedure. Due to this acidification step, dioxo-[15]aneN$_4$S and [15]aneN$_4$S are obtained as dihydrochloride and trihydrochloride salts, respectively.

The NMR spectra are collected using D$_2$O as solvent, so the N-H resonances for both compounds are not detectable, as a result of fast exchange of acidic protons by deuterium.

Students' results

This experiment was executed by students from the 4th and 5th year of the integrated master's degree in Pharmaceutical Sciences from the Faculty of Pharmacy, University of Lisbon. The compounds purification was performed both resorting to the described and to the alternative techniques. The obtained results are listed in Tables **SM 13.6.**3 and **SM 13.6.**4.

Table SM 13.6.3 – Student's results (regular purification technique).

Experiment number	1st step yield (%)	2nd step yield (%)
1	42.9	34.1
2	63.6	50.5

Table SM 13.6.4 – Student's results (alternative purification technique).

Experiment number	1st step yield (%)	2nd step yield (%)
1	74.0	68.0
2	72.9	67.3
3	76.5	62.0

[1] E. C. Constable, *Coordination Chemistry of Macrocyclic Compounds*, ed. Oxford University Press, New York, 1999, vol. 72, p. 1.

[2] G. A. Melson, *Coordination Chemistry of Macrocyclic Compounds*, ed. G. A. Melson, Plenum Press, New York, 1st ed., 1979, p. 2.

[3] L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, ed. Cambridge University Press, Cambridge, 1st ed., 1989, p. 1.

[4] S. Kim, L. F. Lindoy and S. S. Lee, *Coord. Chem. Rev.,* 2014, **280**, 176.

[5] B. P. Burke and S. J. Archibald*, Annu. Rep. Prog. Chem., Sect. A: Inorg. Chem.*, 2013, **109**, 232.

[6] R. E. Mewis and S. J. Archibald, *Coord. Chem. Rev.* 2010, **254**, 1686.

[7] J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, *Aza-Crown Macrocycles*, ed. John Wiley & Sons Inc, New York, 1st ed., 1993, p. 123.

[8] I. Tabushi, H. Okino and Y. Kuroda, *Tetrahedron Lett*. 1976, **17**, 4339.

[9] M. W. A. Steenland, P. Westbroek, I. Dierck, G. G. Herman, W. Lippens, E. Temmerman and A. M. Goeminne, *Polyhedron* 1999, **18**, 3417.

[10] N. Torres, S. Gonçalves, A. S. Fernandes, J. Franco Machado, M. J. Villa Brito, N. G. Oliveira, M. Castro, J. Costa and M. F. Cabral, *Molecules* 2014, **19**, 550.

[11] M. Kodama, T. Koike, N. Hoshiga, R. Machida and E. Kimura, *Dalton Trans*. 1984, 673-678.

[12] P. Vollhardt and N. Schore*, Organic Chemistry: Structure and Function*, ed. W. F. Freeman and Co., New York, 6th ed., 2011, p. 939.

[13] H. C. Brown and P. Heim, *J. Org. Chem*., 1973, **38**, 912.

[14] A. I. Vogel, B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. R. Tatchell. *Vogel' s Textbook of Practical Organic Chemistry*, ed. Longman Scientific & Technical, England, 5th ed., 1989, p. 165.

Asymmetric reduction of acetophenone with borane catalyzed

by *B*-methoxy-oxazaborolidine

Supplementary Material

The purpose of this experiment is to obtain an optically active 1-phenylethanol by the enantioselective reduction of acetophenone with borane catalyzed by chiral oxazaborolidine. The second objective is to acquaint the student with the work under anhydrous conditions and in an inert gas atmosphere. In this procedure oxazaborolidine is obtained directly in the reaction flask prior to the reduction of the ketone from 1,1-diphenylprolinol and trimethyl borate. This way of preparing an oxazaborolidine is easy and lacking the inconvenience of secreting the water as in the reaction of the amino alcohol with boronic acids (the presence of water in the reaction mixture significantly decreases enantiomeric excesses of obtained alcohols). The reducing agent is borane in tetrahydrofuran. Since borane tetrahydrofuran complex is not very stable compound, the key issue is to have a freshly purchased reagent.[1] This problem can also be solved by using adduct of borane with dimethyl sulfide, which is stable and stoichiometric complex of borane (10M borane adduct (BMS) is commercially available). It would be needed 0.2 mL of 10M BMS for this experiment instead of 2mL of 1M borane-THF solution. The only problem is a very unpleasant odor of dimethyl sulfide, but a small amount of the adduct and carrying out an experiment in a fume hood should solve this difficulty. The amount of catalyst in this experiment is 5 mol. %, but 10 mol. % can also be used to give better enantiomeric excesses of product 1-phenylethanol, as it has been shown in the following chromatograms. (*S*)-1,1-Diphenylprolinol is the primary precursor of oxazaborolidines, but the other chiral 1,2-amino alcohols, for example (1*S*,2*R*)-1-amino-2-indanol[2], may be used as starting materials for the synthesis of oxazaborolidines, but the enantioselectivities of the reductions can be lower.

The usual yield of the reduction is in the range of 80–95%. The yield of the reaction was confirmed by multiple repetition of the experiment by the author, as well as by 1st year Chemistry M. Sc. students within the Laboratory of Advanced Organic Synthesis. The described reaction is very fast and if the borane solution used is of good quality, then the reaction should be completed within the described time. 1-Phenylethanol is purified (separated from the amino alcohol) on silica gel eluting with hexane / ethyl acetate 80/20. In the case of not complete reduction of acetophenone (Figure SM **13.7.**9 and SM **13.7.**10), 1-phenylethanol can be separated from the substrate by chromatography on silica gel eluting with hexane / ethyl acetate 90/10.

The addition of methanol to quench the reaction should be done very carefully – see the following photos of the experiment – because of the violent reaction of unreacted borane with methanol with the hydrogen evolution and foaming of the ethereal solution.

Racemic 1-phenylethanol can be purchased from commercial source, or can be synthesized by the students or the instructor. The procedure utilizes standard methodology of the reduction of acetophenone with sodium borohydride.

(±)-1-Phenylethanol – Acetophenone (0.120 g, 1 mmol) and methanol (5 ml) are added to an one-neck flask (25 ml) equipped with a magnetic stirrer. Next, sodium borohydride (0.074 g, 2 mmol) is added portion-wise at room temperature with vigorous stirring. The solution is stirred for 0.5 h, heated at reflux for 10 minutes and the methanol is removed on a rotary evaporator. 1 M Aqueous solution of NaOH (5 mL) is added to the residue. The mixture is stirred for 5 minutes and extracted with diethyl ether (3x10 ml). The combined extracts are washed with brine (10 ml), dried over anhydrous $MgSO_4$ and after removing the ether by rotary evaporation the crude product is purified in an analogous manner as in the synthesis of optically active 1-phenylethanol.
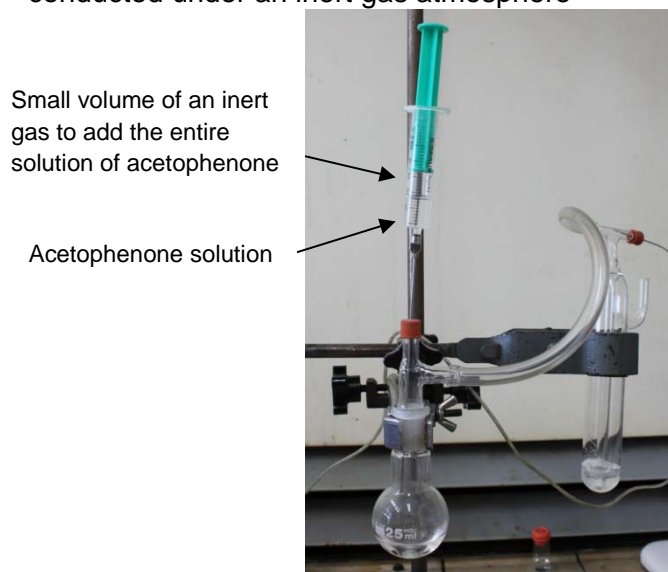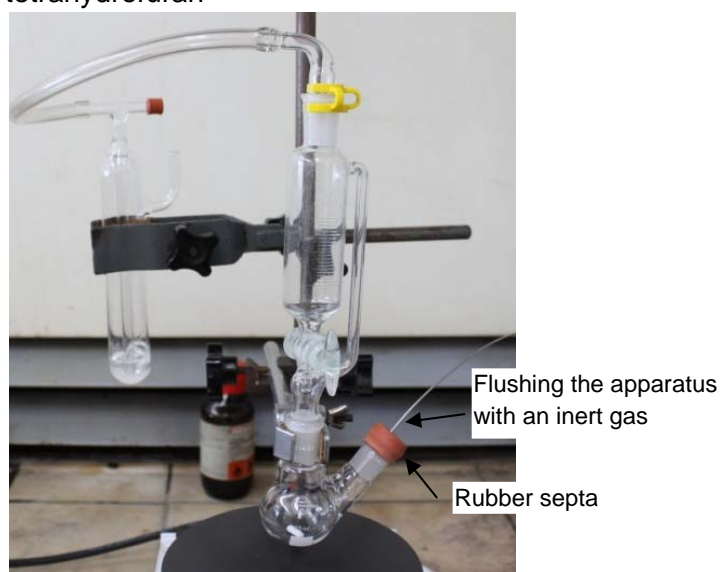
Photos of the experiment

Flushing the apparatus with an inert gas
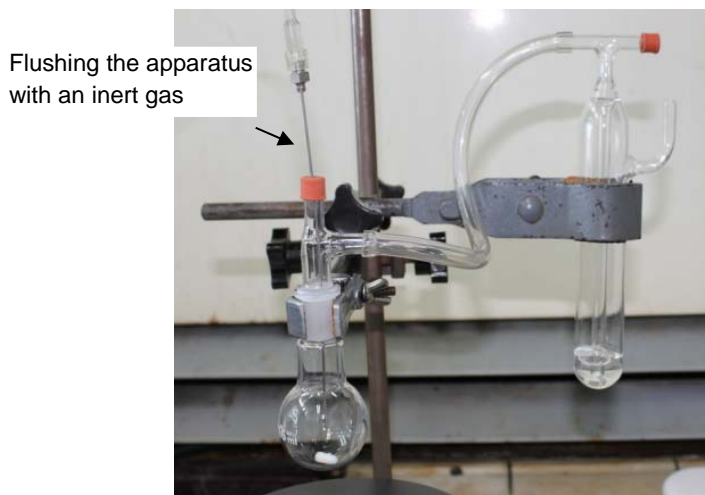
Figure SM 13.7.1 – An apparatus for the reaction conducted under an inert gas atmosphere

THF

The slow flow of an inert gas during the experiment is recommended
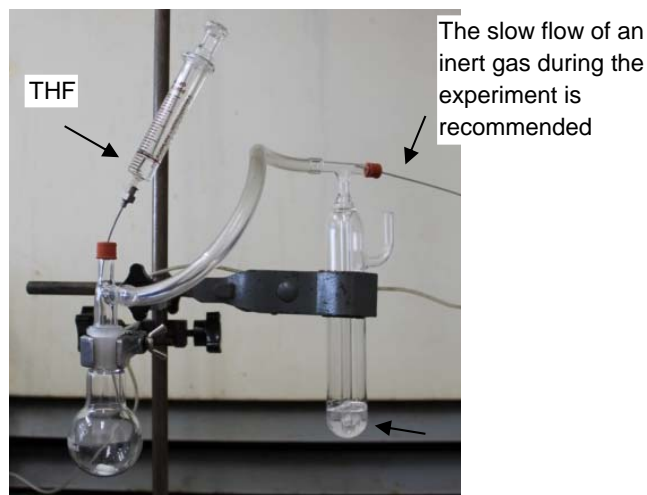
Figure SM 13.7.2 – The addition of anhydrous tetrahydrofuran

Small volume of an inert gas to add the entire solution of acetophenone

Acetophenone solution

Figure SM 13.7.3 – Slow dropwise addition of an acetophenone solution

Flushing the apparatus with an inert gas

Rubber septa

Figure SM 13.7.4 – An apparatus that uses a two-neck flask and a dropping funnel

Figure SM 13.7.5 – Slow dropwise addition of an acetophenone solution using a dropping funnel

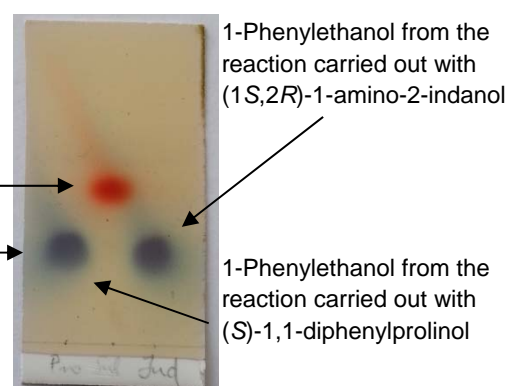First drops of methanol should be added carefully
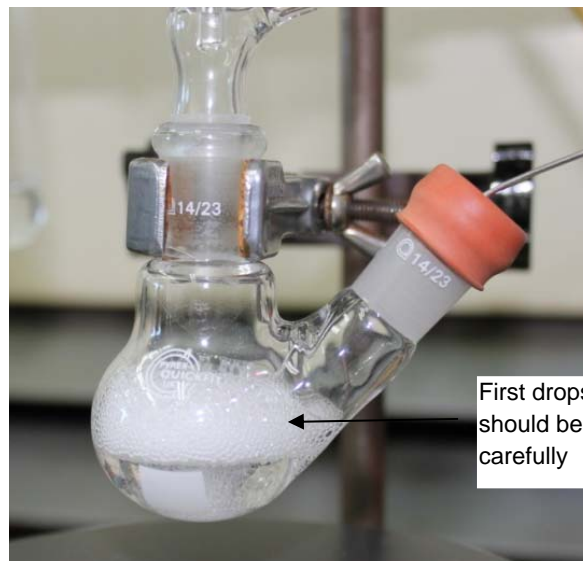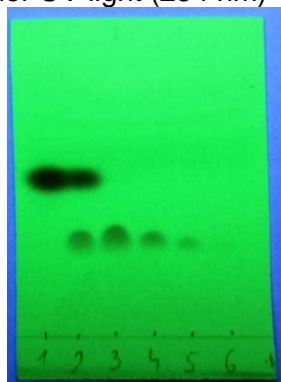
Figure SM 13.7.6 – Quenching the reaction by the addition of methanol

**TLC analysis** (Silica gel (60A) TLC plates with fluorescent indicator 254 nm; eluent: hexane/ethyl acetate (80/20)

$Rf_s = 21/45 = 0.47$

$Rf_p = 13/45 = 0.29$

45 mm

Acetophenone

1-Phenylethanol

21 mm

13 mm
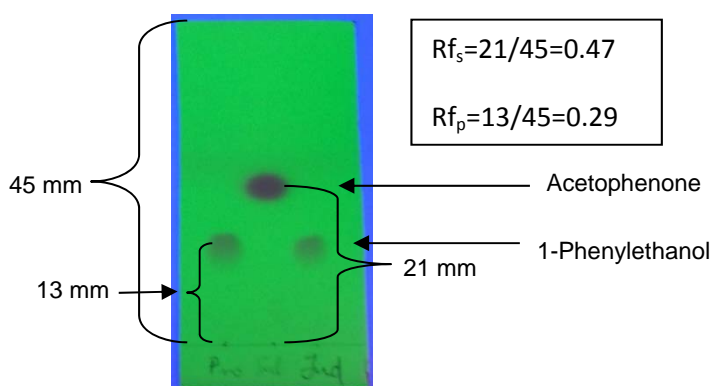
Figure SM 13.7.7 – The TLC plate was visualized under UV light (254 nm)

1-Phenylethanol from the reaction carried out with (1S,2R)-1-amino-2-indanol

1-Phenylethanol from the reaction carried out with (S)-1,1-diphenylprolinol

Figure SM 13.7.8 – The TLC plate was visualized using vanillin solution

Figure SM 13.7.9 – TLC analysis of fractions obtained from the separation of the reaction mixture with incompletely reduced acetophenone (the quality/molarity of borane was not good)
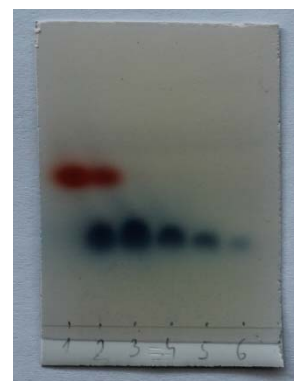
Figure SM 13.7.10 – The same TLC plate visualized using vanillin solution

HPLC analysis of 1-phenylethanol (column: Daicel Chiralcel OD-H; eluent: hexane/*i*-PrOH (95/5), 0.7 mL/min.; detector: 225 nm)
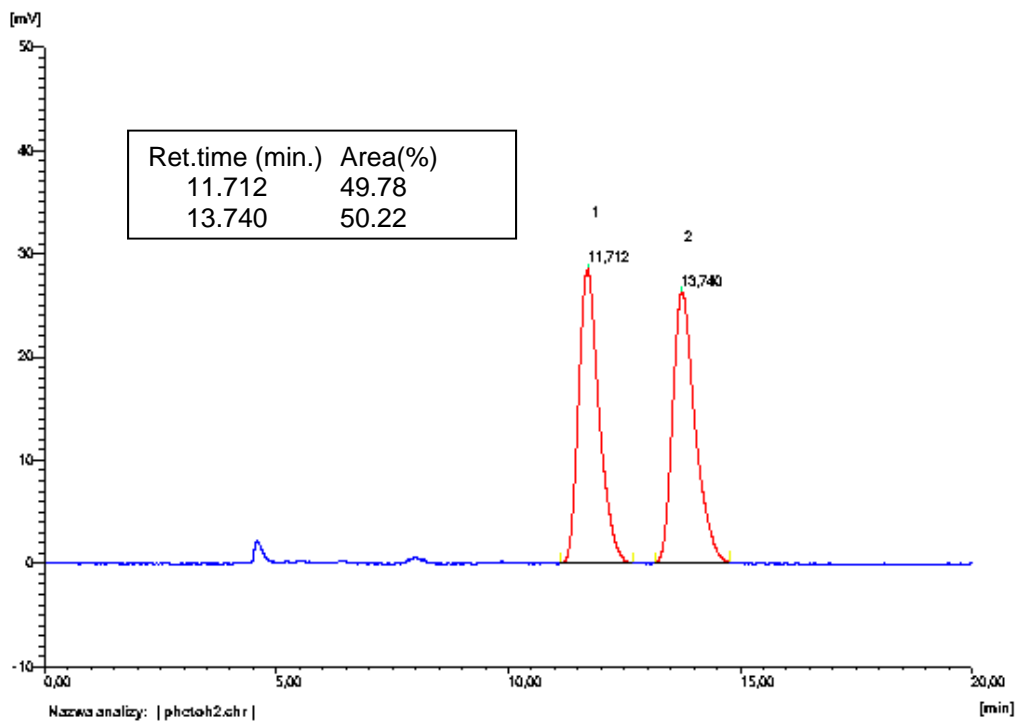

Ret.time (min.)	Area(%)
11.712	49.78
13.740	50.22

Figure SM 13.7.11 – HPLC chromatogram of racemic 1-phenylethanol

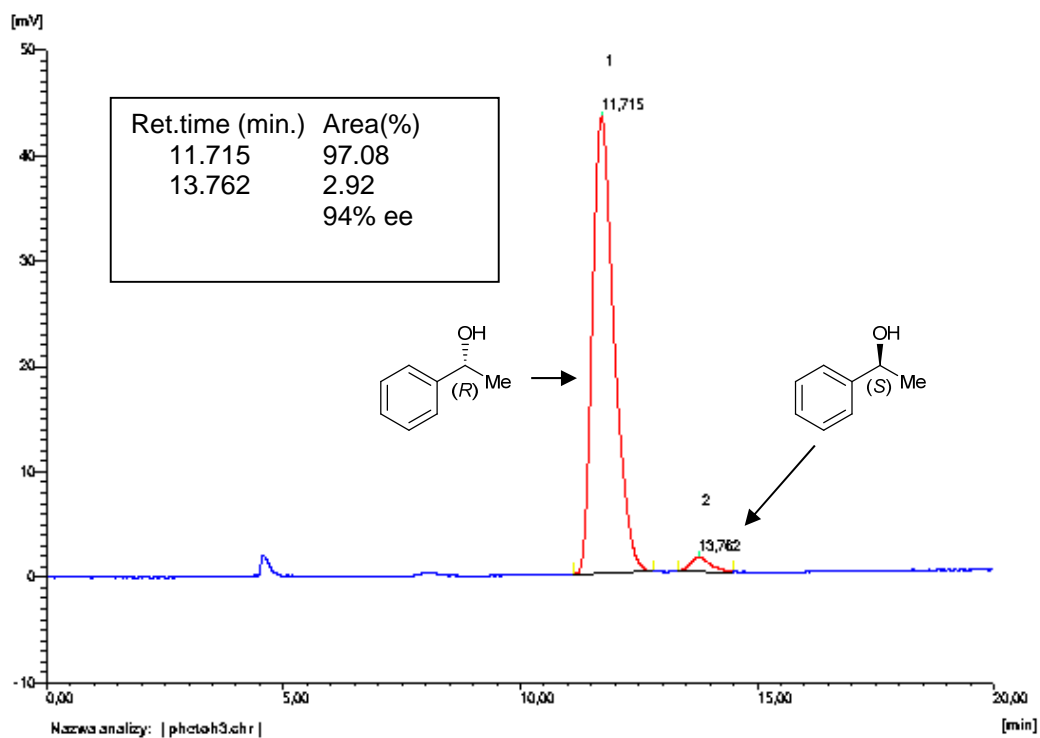| Ret.time (min.)	Area(%)
11.715	97.08
13.762	2.92
	94% ee

Figure SM 13.7.12 – Product of reaction carried out with 5 mol % of (*S*)-1,1-diphenylprolinol
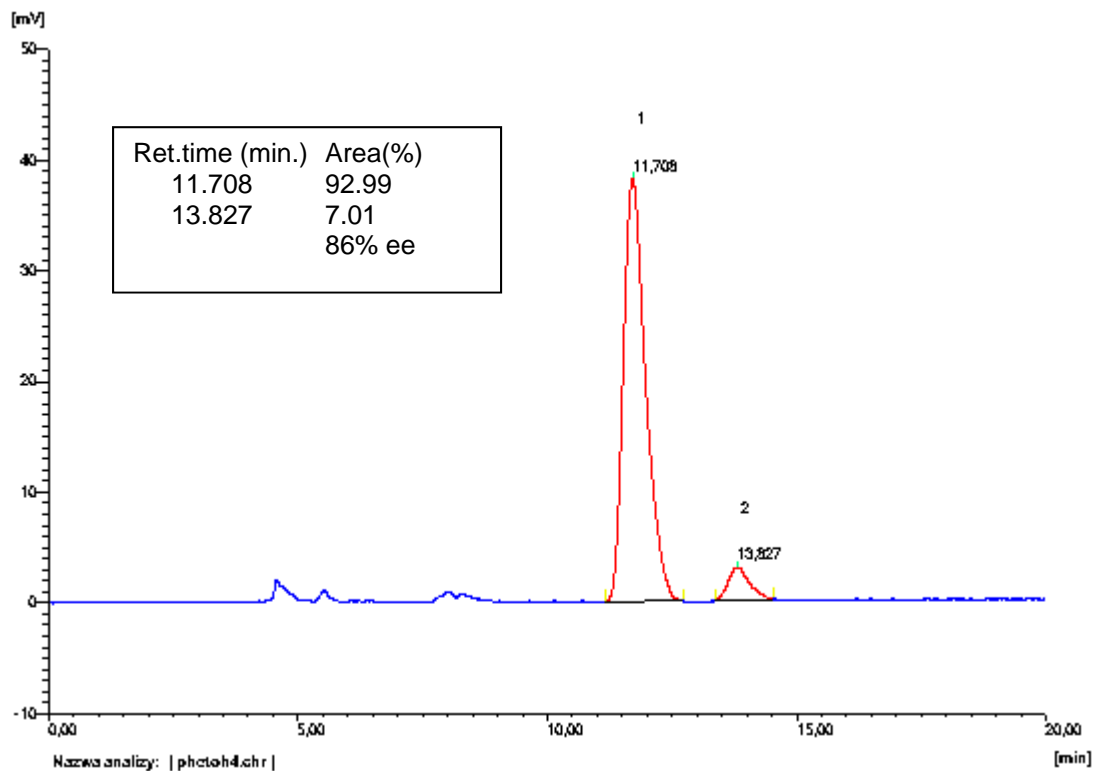
Figure SM 13.7.13 – Product of reaction carried out with 5 mol % of (1*S*,2*R*)-1-amino-2-indanol
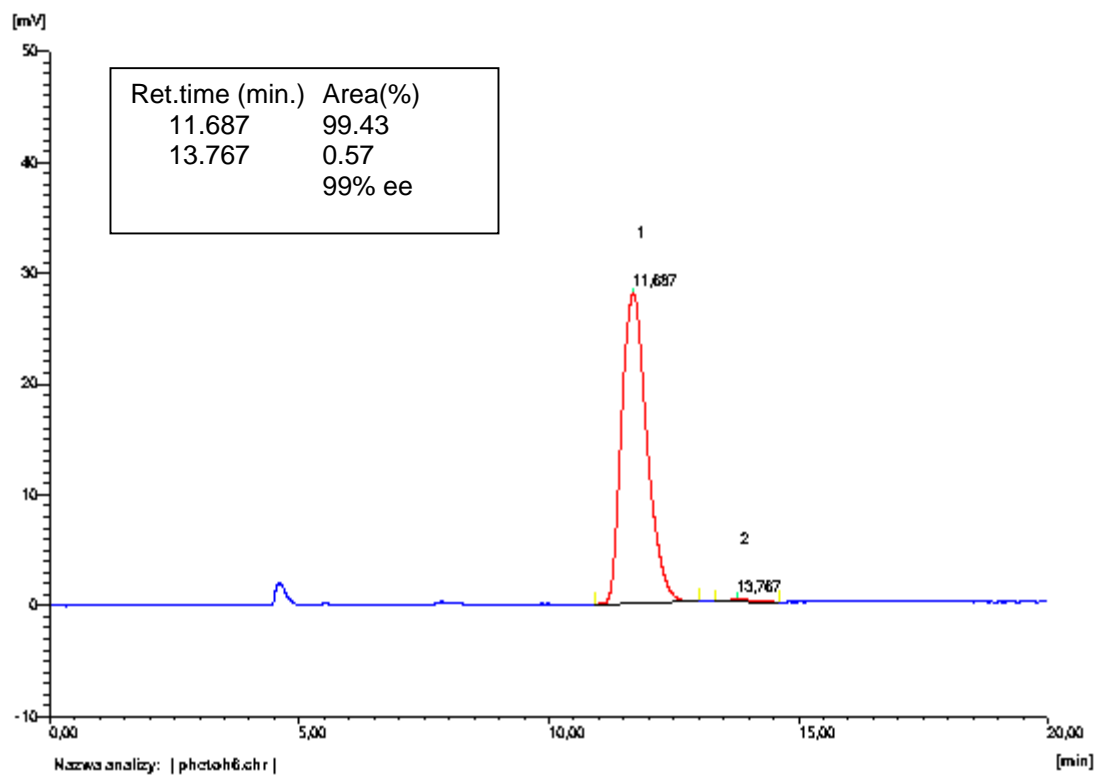

Figure SM 13.7.14 – Product of reaction carried out with 10 mol % of (*S*)-1,1-diphenylprolinol
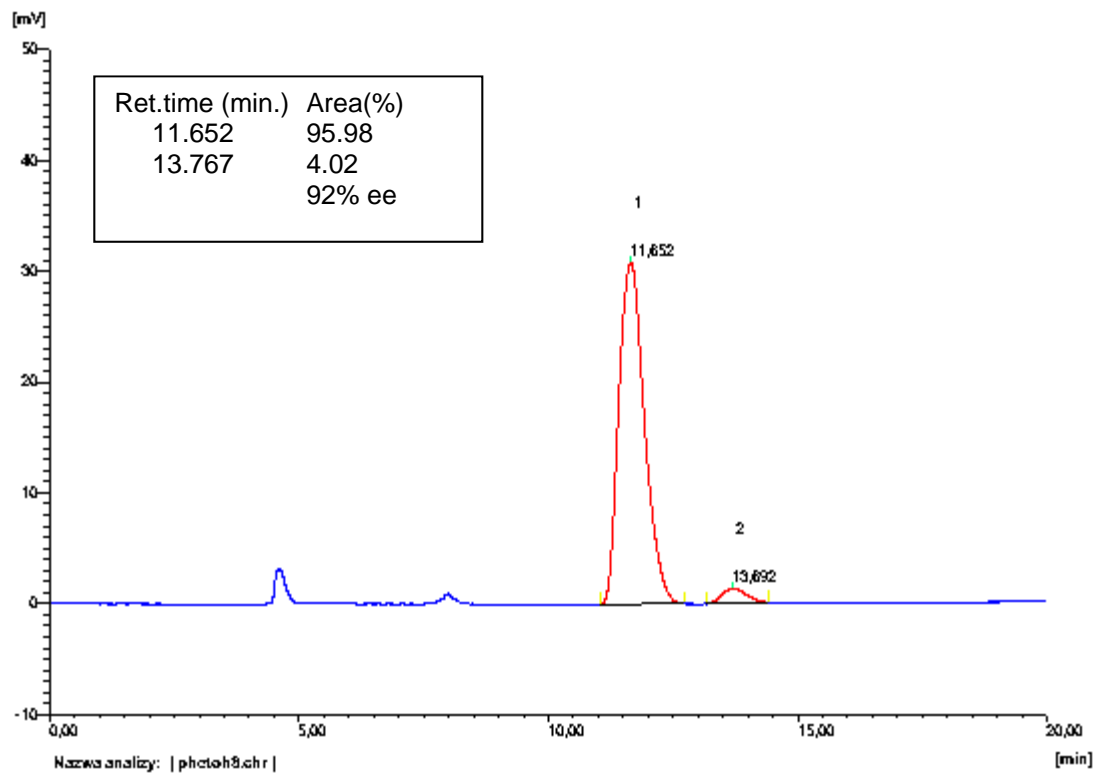
Figure SM 13.7.15 – Product of reaction carried out with 10 mol % of (1*S*,2*R*)-1-amino-2-indanol

¹H and ¹³C NMR spectra
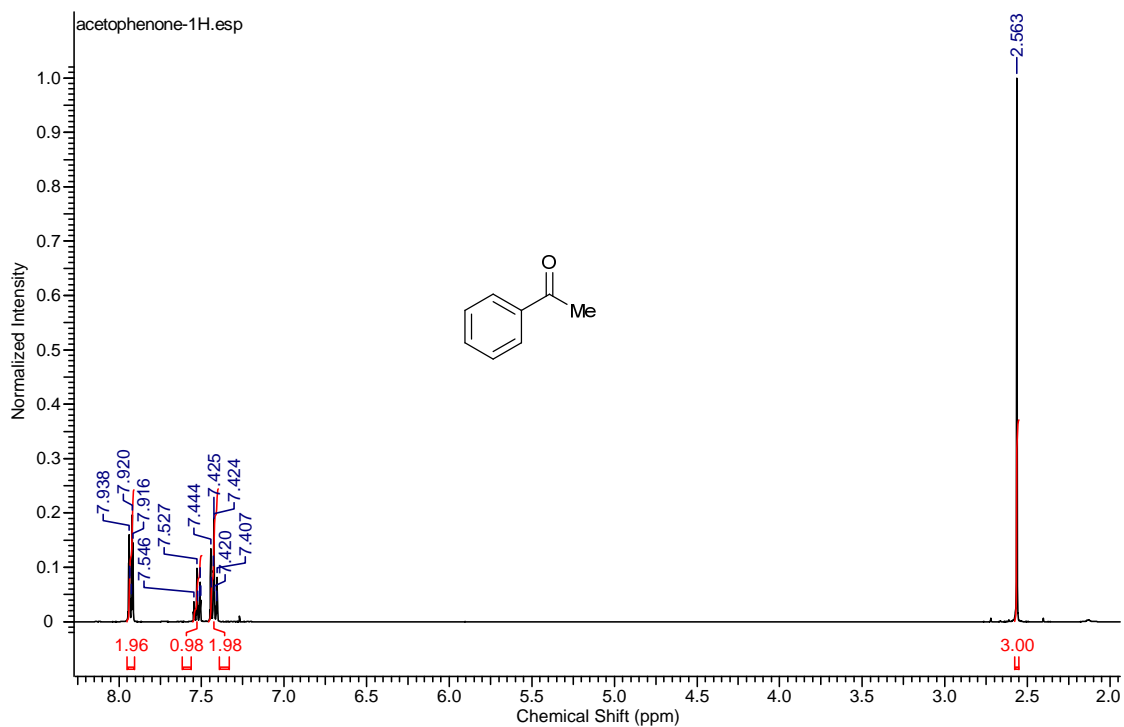

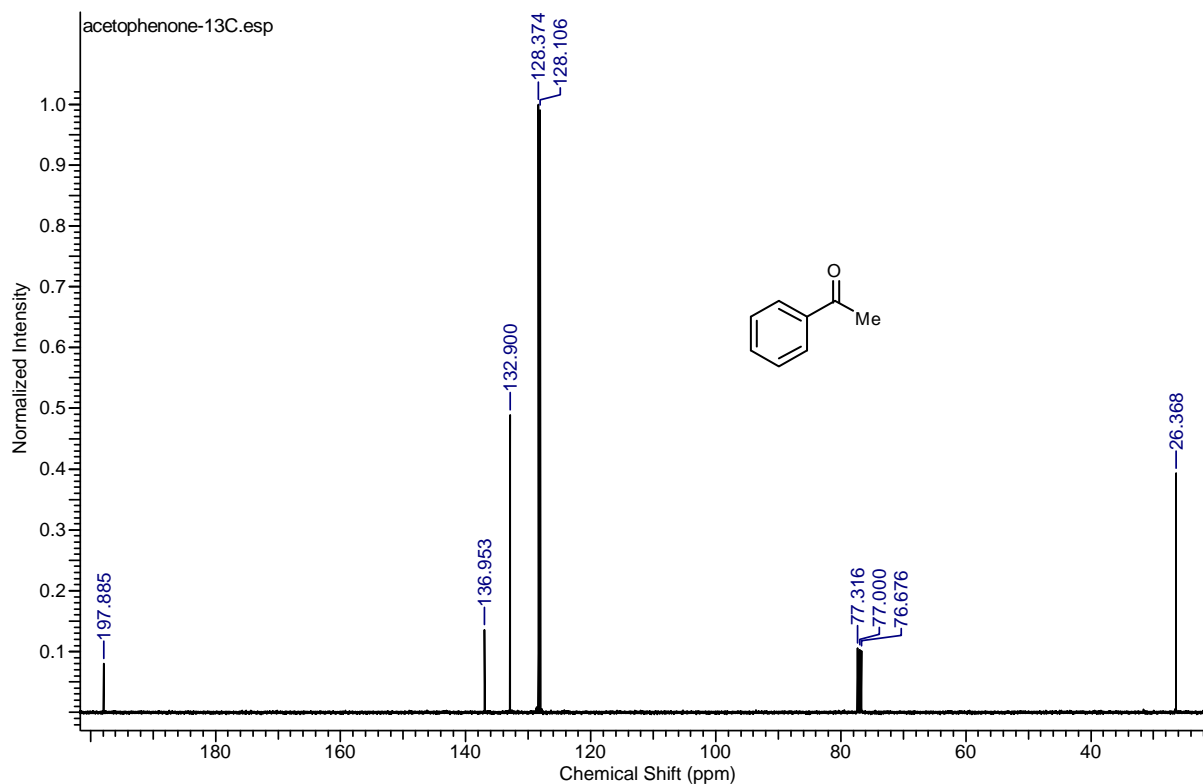**Figure SM 13.7.16** – ¹H NMR spectrum (400 MHz, CDCl₃) of acetophenone

Figure SM 13.7.17 – ^{13}C NMR spectrum (100 MHz, CDCl$_3$) of acetophenone

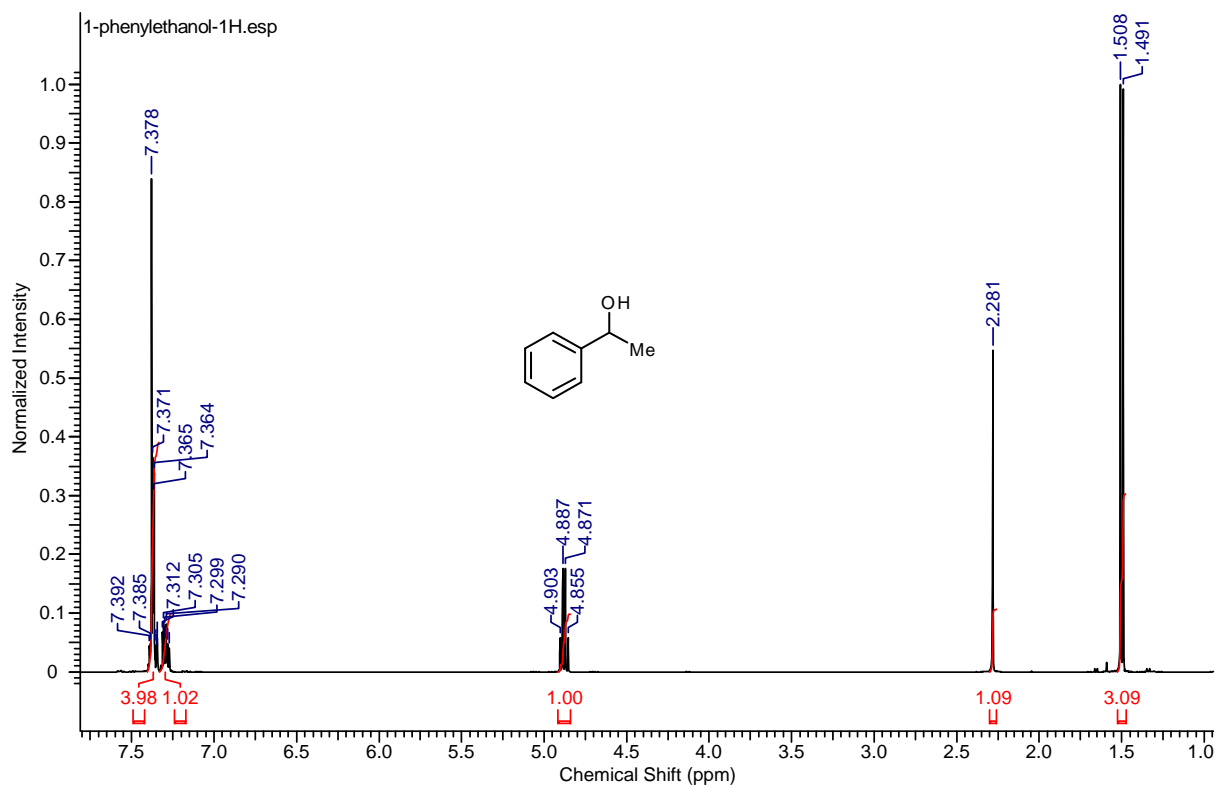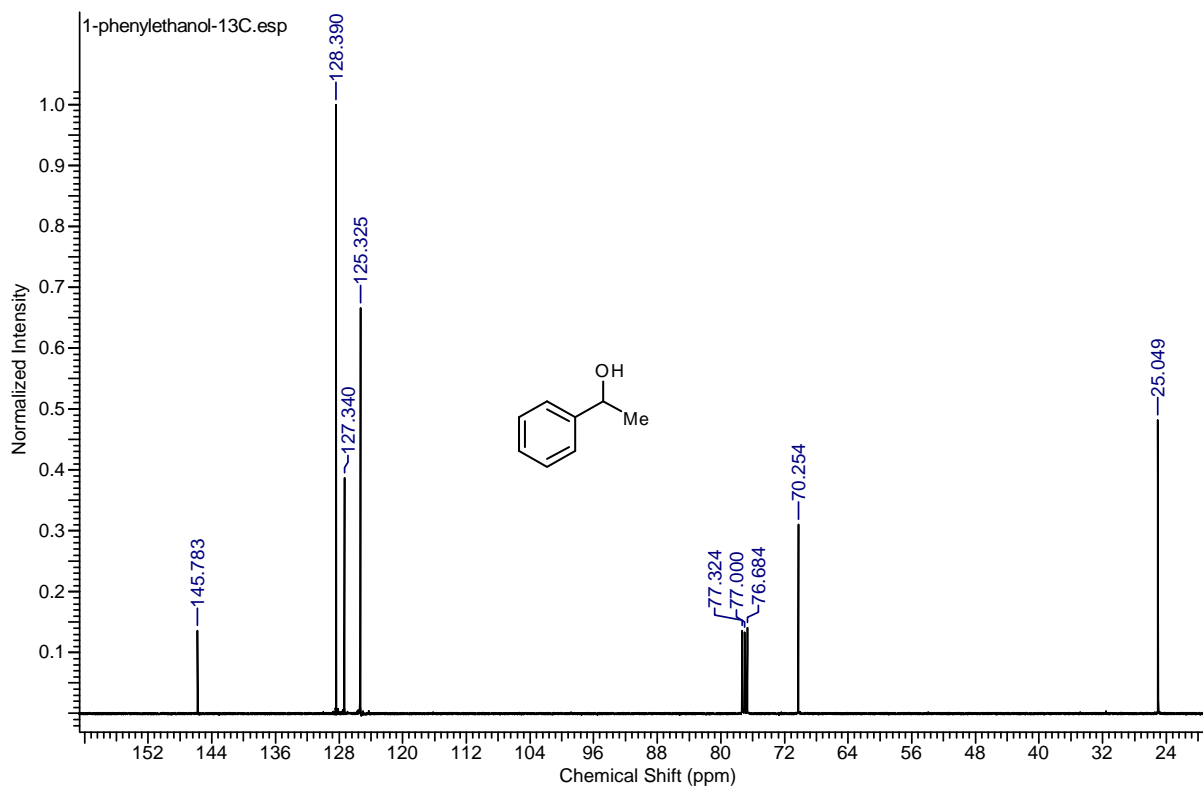**Figure SM 13.7.18** – ^1H NMR spectrum (400 MHz, CDCl$_3$) of 1-phenylethanol

Figure SM 13.7.19 – ^{13}C NMR spectrum (100 MHz, CDCl$_3$) of 1-phenylethanol

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[1] The work with borane and under inert gas atmosphere is perfectly described in: H. C. Brown, *Organic Syntheses via Boranes*, J. Wiley, New York, 1975.

[2] N. J. Gilmore, S. Jones, M. P. Muldowney, *Org. Lett.* 2004, **6**, 2805-2808.

Synthesis of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione
Supplementary Material

The compound obtained in this experiment was prepared by the principal author during his research work and used as a precursor in the synthesis of the electron donor "ET". It was later adapted for students of advanced Chemistry as a short project involving bibliographic research and experimental work. The utilization of hazardous chemicals requires careful during all experiment. No more than 8 students working in pairs have done this work in the same classroom. Sessions 1, 2 and 4 need 6hours to accomplish. Sessions 3, 5 and 6 can be completed in 2/3 hours. The 2 steps require long stirring periods but without need of surveillance until next session. The main purpose of this work is study different chemical transformations involving carbonyl group and organosulfur compounds illustrating easy and inexpensive access to 4,5-dithio-1,3-dithiole-2-thione system. The students can also learn how metal complexation can be used as product isolation method. In addition, this experiment exposes the student cohort to a wide range of laboratory skills like handling inert gas atmosphere, water sensitive reagents, dry solvents, temperature control, recrystallization, vacuum filtration and complexation reactions as a purification method.

Additional notes on the preparation of tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate:

To avoid water condensation on the surfaces, nitrogen or argon should be allowed to flow through the apparatus while the glassware is still hot (Figure **SM 13.8.1**). HPLC-grade carbon disulfide achieved better overall yields. After the complete addition of DMF the reaction mixture should be left stirring overnight under inert atmosphere. At this point the gas inlet can be substituted by a latex balloon filled with argon or nitrogen, closing the system tightly to avoid gas leaks. Students can monitor the reaction and plan the filtration steps according to their timetables. Typically there will not be any sodium metal left, but sometimes small pieces may have adhered to the glass above liquid level and should be

destroyed with methanol. In this case, gas evolution is observed and the reaction mixture is left for one hour with stirring and cooling.

Figure SM 13.8.1 – Reaction set-up apparatus for tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate

The yield interval range of the zinc complex is 70-80% and the melting point measured is the same as in the literature (206-208ºC)[1]. If desired, the zinc complex can be recrystallized by dissolving 20 g in warm acetone (300 mL) with 0.5 g of activated charcoal, refluxed for 10 minutes and filtered while it is hot. The filtered solution is concentrated to half volume in a rotary evaporator before adding 100 mL of isopropyl alcohol. The precipitate formed is then filtered under vacuum and washed with ethyl ether (yield 70-80%).

Additional notes on the preparation of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione:

Acetone should be previously dried using commercial acetone pre-dried with $CaCl_2$, stirred for one hour, filtered to a 500 mL round-bottom flask and fractionally distilled.

The addition of benzoyl chloride (Figure **SM 13.8.2**) to the red solution of zinc complex gradually precipitates a yellow solid. Students can plan the filtration steps according to their timetables. Washing the product with water during filtration hydrolyzes any benzoyl chloride in excess, which will precipitate benzoic acid in the filtering flask.

Figure SM 13.8.2 – Reaction set-up apparatus for 4,5-bis(benzoylthio)-1,3-dithiole-2-thione

Reflux set-up for recrystallization of crude material is shown in Figure **SM 13.8.3**.

Figure SM 13.8.3 – Reflux set-up apparatus

Hot filtration (Figure **SM 13.8.4**) is carry out in a copper funnel previously heated by flame. Students should be warned that, as usual, no flames must be present during filtration!

Figure SM 13.8.4 – Copper funnel (previously heated by flame) for hot filtration

The yield interval range of this compound is 60-70% and the melting point recorded is 142-143ºC (literature: 143-144ºC[1]).

IR spectra:

IR spectroscopic data is available in literature[1] for tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate: IR (KBr) cm^{-1}: 1460, 1410, 1165, 1050, 986, 878, 775, 450. IV spectrum is also available in SDBS (No. 18108)[2]. Students easily identify in the Figure **SM 13.8.5** a strong band at 1058 cm^{-1} due to the C=S group. For 4,5-bis(benzoylthio)-1,3-dithiole-2-thione IR spectroscopic data can be also found in the same reference[1]: IR (CHCl$_3$) cm^{-1}: 3001, 1695, 1601, 1586, 1450, 1200, 1179, 1068, 880, 660, 637; The strong band of C=S group is visible at 1058 cm^{-1} as well at 1637 cm^{-1} due to the C=O group.
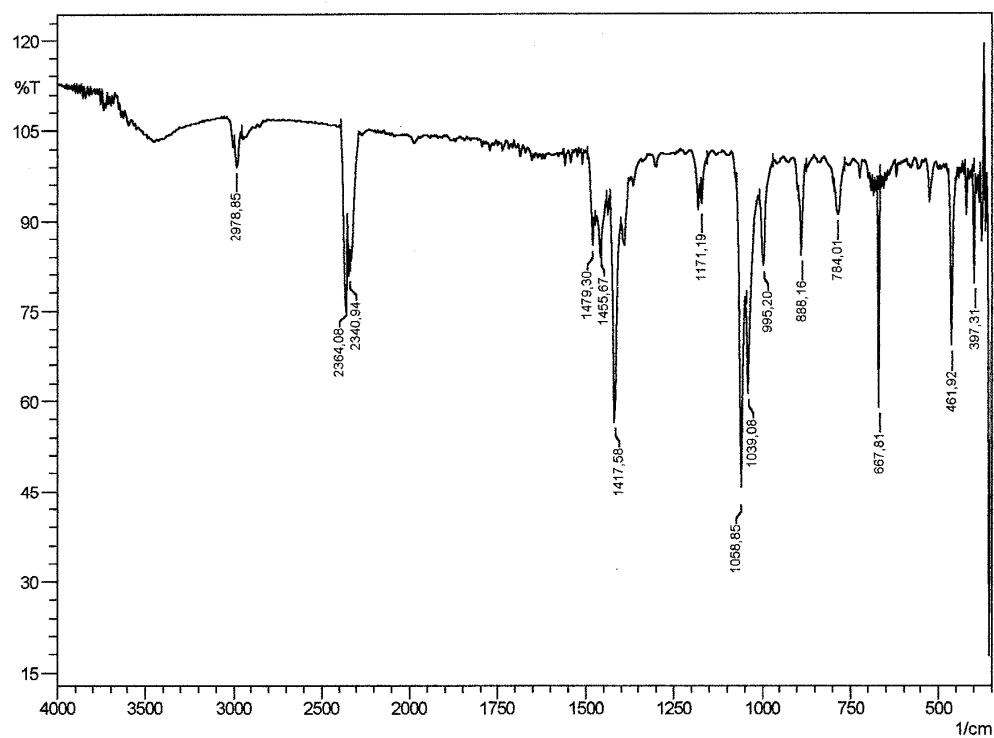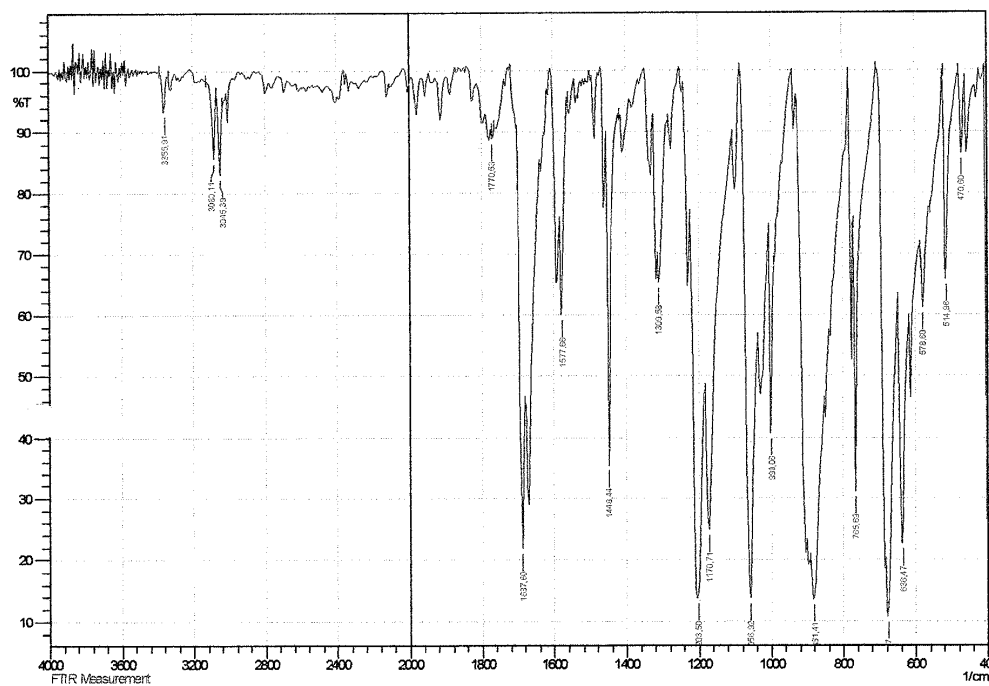
Figure SM 13.8.5 - IR (KBr) of tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate

Figure SM 13.8.6 - IR (KBr) of 4,5-bis(benzoylthio)-1,3-dithiole-2-thione

NMR spectra:

In this experiment NMR spectra were not recorded because does not show relevant information in the structure characterization, nevertheless NMR spectroscopic data can be found in literature[1] for both products: tetraethylammonium bis(1,3-dithiole-2-thione-4,5-dithiol) zincate ^{13}C NMR (125 MHz, CDCl$_3$) δ: 7.9, 53.2, 136.3, 209.5. For 4,5-bis(benzoylthio)-1,3-dithiole-2-thione: ^{13}C NMR (62.9 MHz, CDCl$_3$) δ: 127.8, 129.0, 133.5, 134.6, 134.8, 185.2, 212.1. ^{1}H RMN (CDCl$_3$) is also available in SDBS (No. 18108)[2].

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[1] T. K. Hansen; J. Becher; T. Jergensen; K. S. Varma; H. Khedekar; M. Cava, *Organic Synthesis, Coll.,* 1996, **73**, 270.

[2] http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_search.cgi, accessed in October 2015.

Organocatalytic Asymmetric Reduction of (1*E*)-*N*,1-Diphenyl-1-propanimine to (*S*)-*N*-(1-Phenylpropyl)aniline with Trichlorosilane

Supplementary Material

1.   Experimental Notes

In this experiment (1*E*)-*N*,1-diphenyl-1-propanimine is prepared from propiophenone and aniline, and then transformed in a highly enantioselective fashion to the target product using trichlorosilane and the cinchona-picolinamide organocatalyst, i.e. (+)-*N*-(9-deoxy-epi-cinchonin-9-yl)picolinamide.   Using the generic conditions presented in this experiment, one can obtain chiral amines with yields of up to 99% and enantioselectivities of 90% ee.[1] In this particular experiment under the conditions applied the product is obtained in an overall average yield of 44% for two steps and 80%ee starting from propiophenone.

The reproducibility of both experiments was assessed by repetitive execution by co-author Pedro Barrulas, with average yields for the first step - synthesis of (1*E*)-*N*,1-diphenyl-1-propanimine in the range 50-60%, and for the product amine (*S*)-*N*-(1-phenylpropyl)aniline obtained in the second step, of 57-77%. In the case of the synthesis of (1*E*)-*N*,1-diphenyl-1-propanimine, it is better to employ microdistillation as the method of choice for the purification of the product, as this imine is sensitive to acid. The ketimine is obtained as an aromatic smelling yellow oil (4.33 g, 57%) after microdistillation (b.p = 120-130 °C @ 1mmHg). The unreacted propiophenone with a boiling point of 218°C (atmpspheric pressure) will distill first at about (b.p = 50-60 °C @ 1mmHg), and then by carefully increasing the temperature to (b.p = 120-130 °C @ 1mmHg) the *title compound* will distill.   However, the method of microdistallation is not without limitations and the NMR spectra will exhibit the peaks of (1*Z*)-*N*,1-diphenyl-1-propanimine, which is a side-product in these reactions (This is in accordance with literature reports[2,3]). Their proportions can be estimated from the integrals in the ¹H NMR

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[1] P.C. Barrulas, A.Genoni, M. Benaglia, A.J. Burke, *Eur. J. Org. Chem.* 2014, 7339

[2] M. Bonsignore, M. Benaglia, L. Raimondi, M. Orlandi, G. Celentano, *Beilstein J. Org. Chem.* 2013, **9**, 633.

spectrum, and will be about 10:1.[3] We believe that the presence of this isomer lowers the reaction enantioselectivity somewhat.

In the case of the organocatalytic second step, we have found that through optimization studies conducted with other organocatalysts,[4,5] that lower loadings of both the chlorosilane reagent (down to 1.5 equivalents) and the organocatalyst (down to 1 mol%) can be successfully used.[4,5] So it is highly likely that the catalyst loading used for this particular experiment can be lowered to 1-5 mol% to achieve comparable results with the original loading conditions. These organocatalysts can also be immobilized to solid supports, like nano-silica, MCM-41, and magnetic nanoparticles.[3]

This experiment will be an ideal opportunity to explain to the students the concept of facial selectivity in enantioselective reactions. The students will also use NMR as an analytical tool to confirm the presence and purity of their compounds, and use HPLC to determine the enantiopurity of their compounds. The problems associated with purification of sensitive compounds will also be observed. As mentioned above, it should be noted that in the NMR spectra for the (1*E*)-*N*,1-diphenyl-1-propanimine there are traces of the isomer (1*Z*)-*N*,1-diphenyl-1-propanimine. Figure **SM 13.9.**1, also shows how sensitive these ketimines are to acid catalyzed hydrolysis. This is presumable formed due to an ketimine isomerization process induced by heating during the distillation.[6]

2. NMR spectra

(1*E*)-*N*,1-diphenyl-1-propanimine

^{1}H-NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.96 (m, 2H, Ph), 7.47 (m, 3H, Ph), 7.37 (t, 2H, *J*=8 Hz, Ph), 7.10 (t, 1H, *J*=8 Hz, Ph), 6.82 (d, 2H, *J*=8 Hz, Ph), 2.69 (q, *J*= 8 Hz, 2H, CH2), 1.10 (t, 3H, *J*=8 Hz, CH3).

(1*Z*)-*N*,1-diphenyl-1-propanimine shows the following key non-superimposed signals: 2.80 (q, *J*=7.4 Hz, 2H, CH2), 1.26 (t, 3H, *J*=7.4 Hz, CH3).

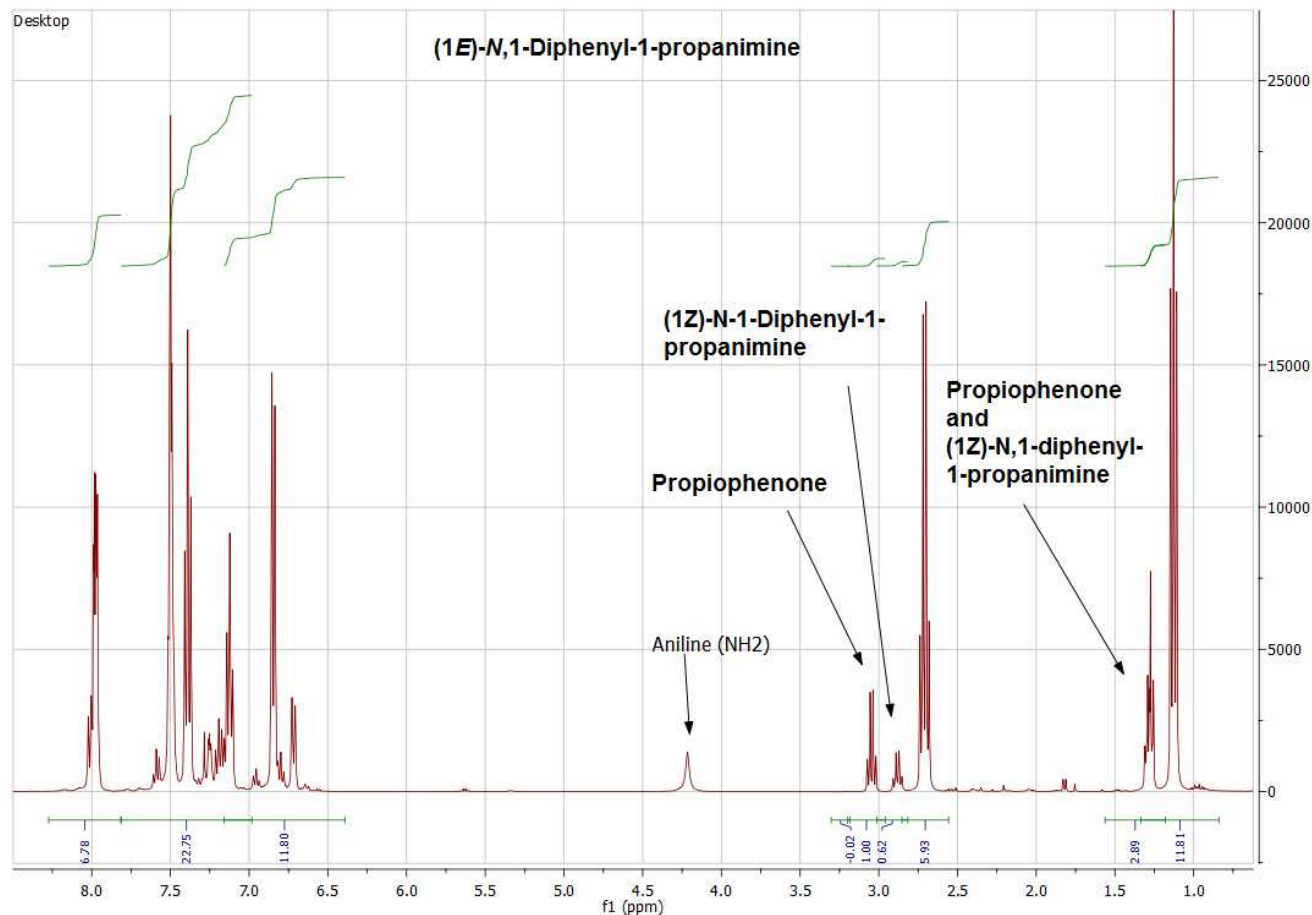[3] J.S.M. Samec, J-E. Bäckvall, *Chem. Eur. J.* 2002, **8**, 2955.

[4] P.C. Barrulas, *PhD Dissertation*, University of Evora, **2014**.

[5] P.C. Barrulas, A.J. Burke, Novel *N*-Alkylated Picolinamide-*Cinchona* Organocatalysts and Derivatives: Homogeneous and Heterogeneous Catalysis, PCT/IB2014/065128. 8-10-2013

[6] W.B. Jennings, S. Al-Showiman, M. S. Tolley, D.R. Boyd, *J. Chem. Soc. Perkin II,* 1975, 1535.

Figure SM 13.9.1 – ^{1}H NMR (400 MHz, CDCl$_3$) spectra of (1*E*)-*N*,1-diphenyl-1-propanimine. (Note, the presence of propiophenone in this case was the result of hydrolysis of the *N*,1-diphenyl-1-propanimines in the CDCl$_3$ solvent upon standing too long, for this reason the NMR spectra should be taken immediately after sample preparation).

^{13}C-NMR (100 MHz, CDCl$_3$): δ (ppm) = 170.9 (C=N), 151.6 (Ph), 138.1 (Ph), 130.5 (Ph), 129.1 (2CPh), 128.6 (2C-Ph), 127.7 (2C-Ph), 123.1 (Ph), 119.2 (2C-Ph), 23.6 (CH2), 13.0 (CH3).
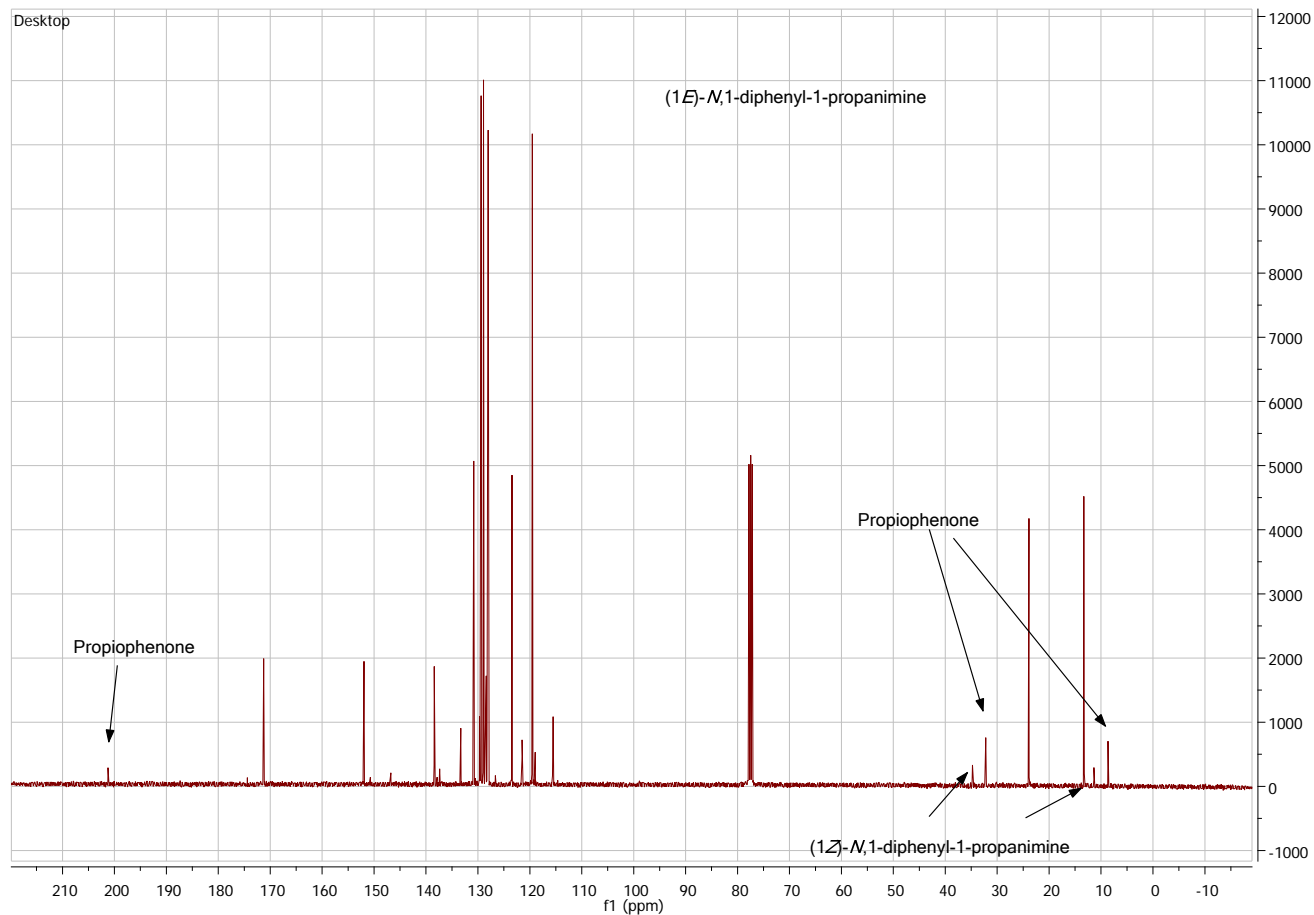
Figure SM 13.9.2 – ^{13}C NMR (400 MHz, CDCl$_3$) spectra of (1*E*)-*N*,1-diphenyl-1-propanimine.

N-(1-Phenylpropyl)aniline
¹H-RMN (400 MHz, CDCl₃): δ (ppm) = 7.42-7.35 (m, 4H, Ph), 7.30-7.26 (m, 1H, Ph), 7.14 (t, 2H, *J*=8 Hz, Ph), 6.69 (t, 1H, *J*=4 Hz, Ph), 6.58 (d, 2H, *J*=8 Hz, Ph), 4.29 (t, 1H, *J*=8 Hz, CH), 4.13 (bs, 1H, NH), 1.95-1.83 (m, 2H, CH₂), 1.02 (t, 3H, *J*=8 Hz, CH₃).
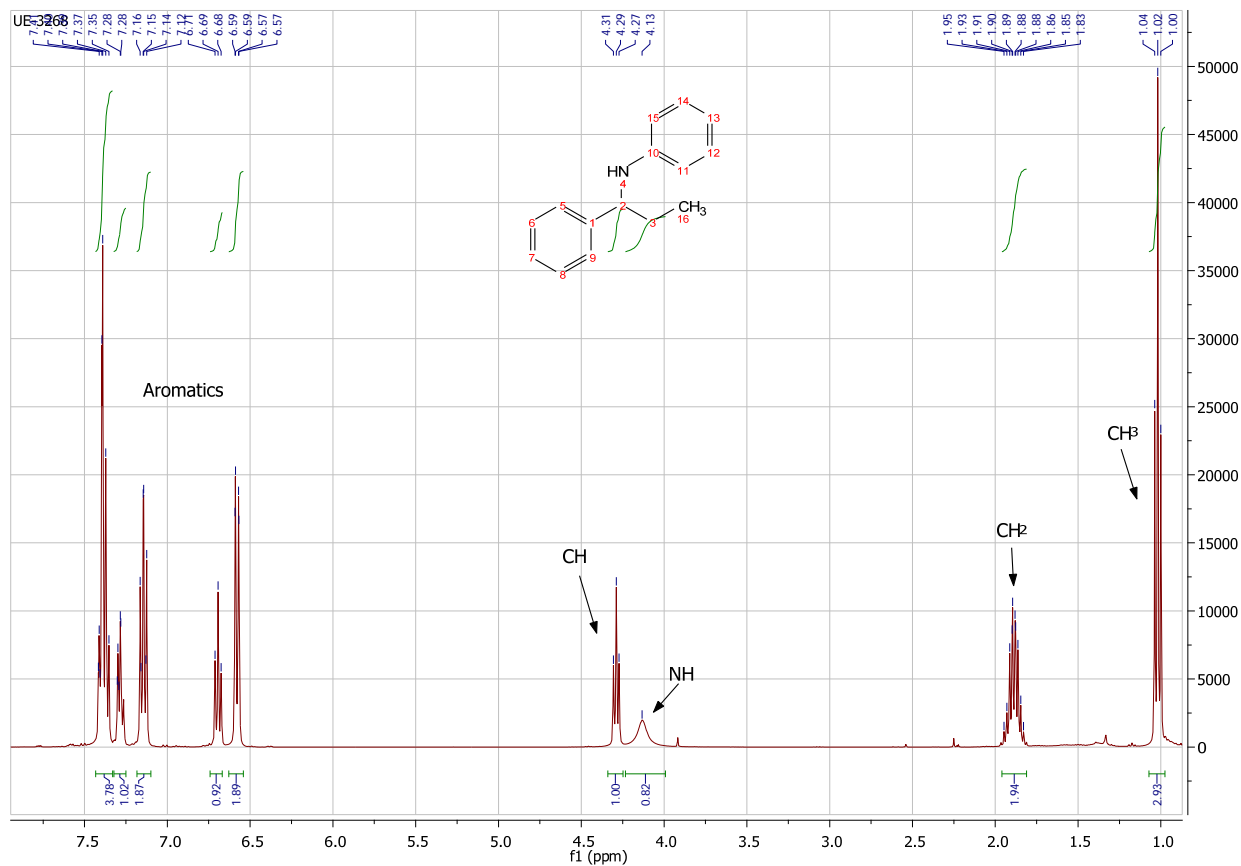
Figure SM 13.9.3 – ^{1}H NMR (400 MHz, CDCl$_3$) spectra of (*S*)-*N*-(1-phenylpropyl)aniline.

^{13}**C-NMR (100 MHz, CDCl$_3$):** δ (ppm) = 147.6 (Ph), 144.0 (Ph), 129.2 (2C-Ph), 128.6 (2C-Ph), 127.0 (Ph), 126.6 (2C-Ph), 117.2 (Ph), 113.4 (2C-Ph), 59.8 (CH), 31.8 (CH$_2$), 10.9 (CH$_3$).
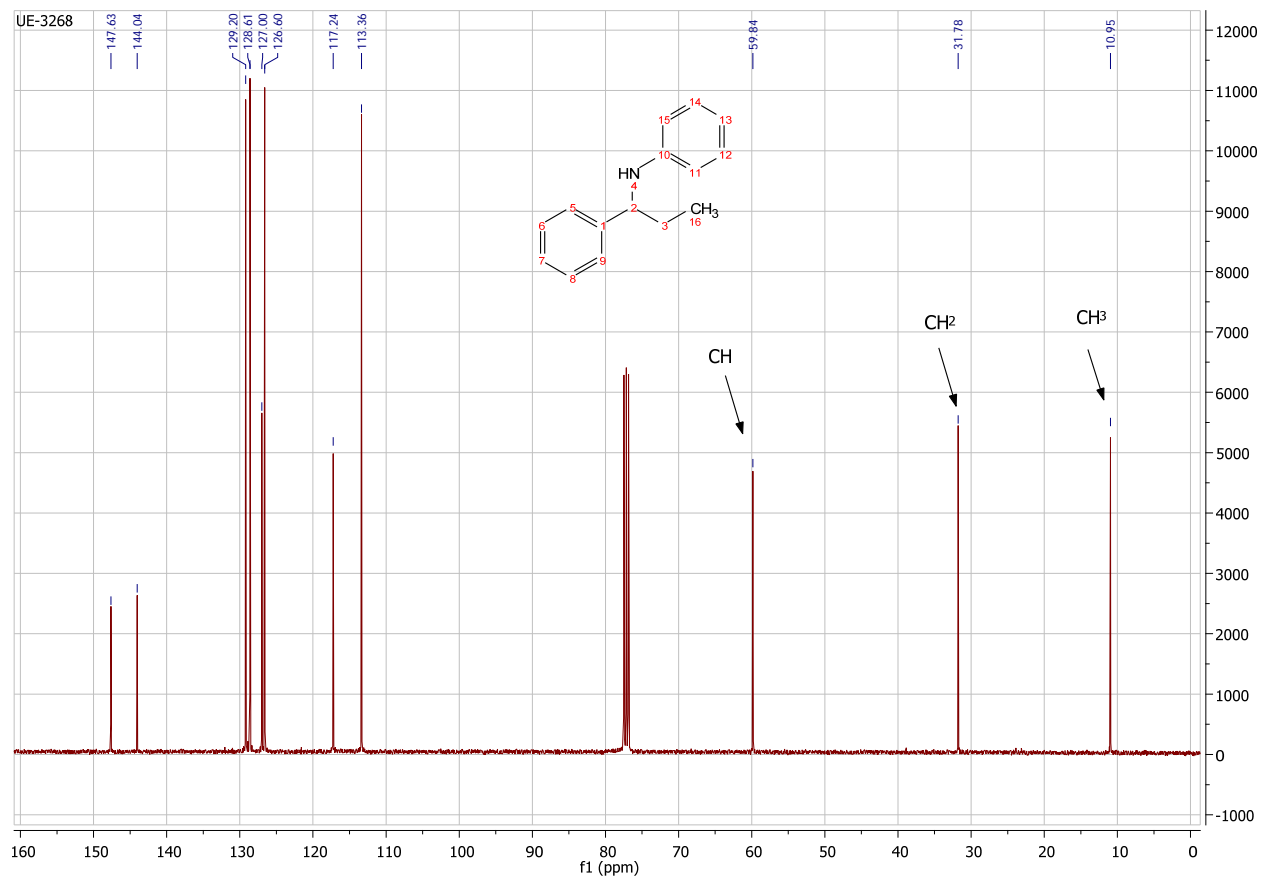
Figure SM 13.9.4 – ^{13}C NMR (100 MHz, CDCl$_3$) spectra of (*S*)-*N*-(1-phenylpropyl)aniline.
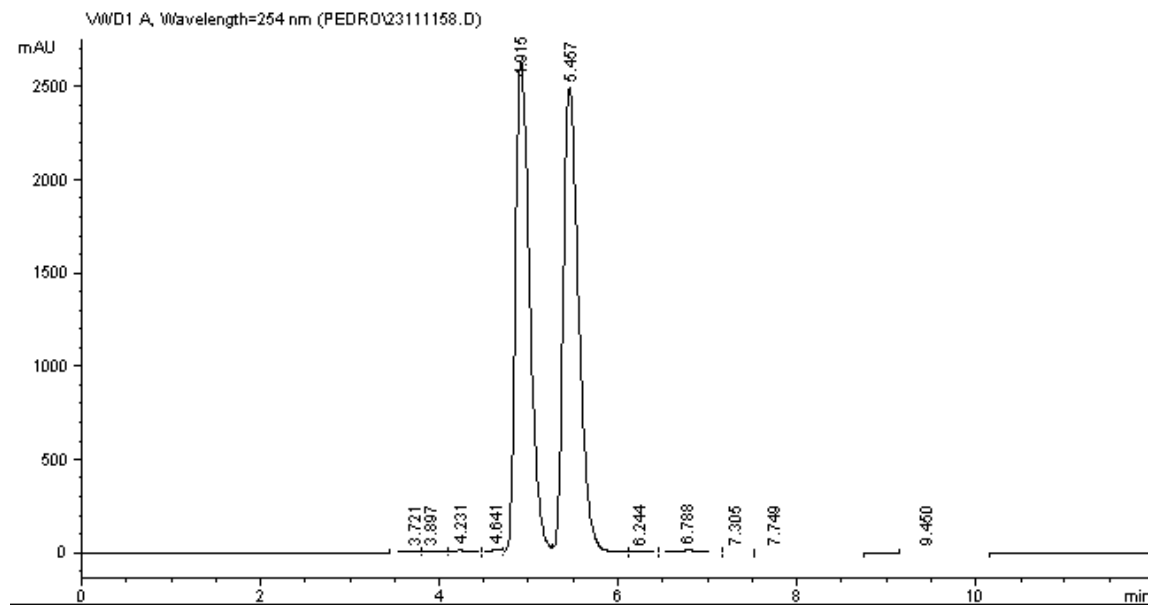
3.   Chromatograms

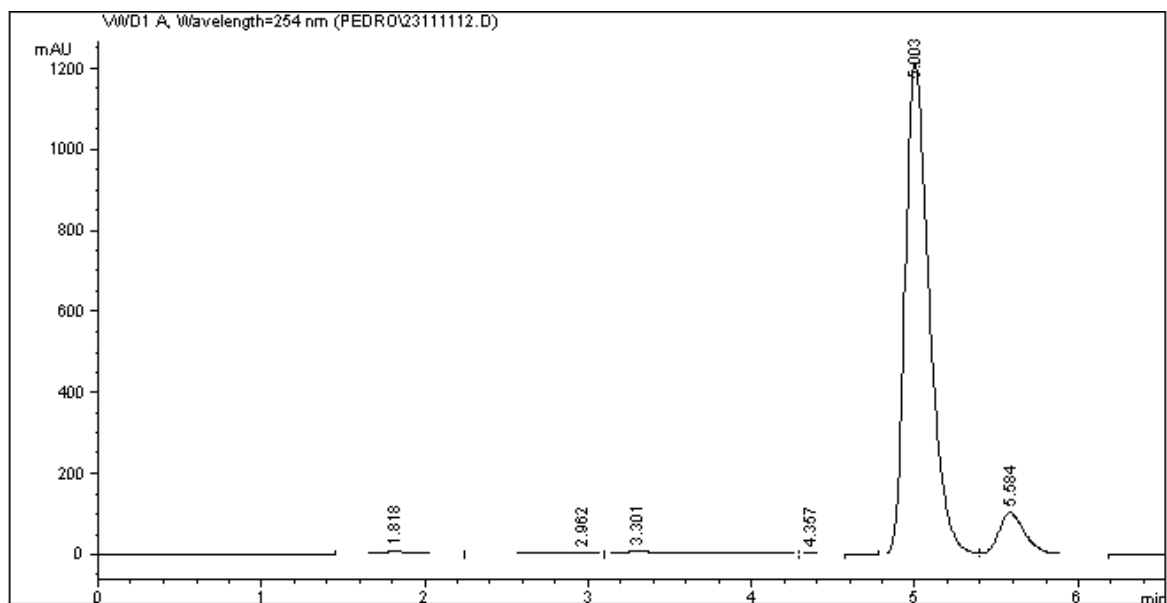**Figure SM 13.9.5** – Racemic *N*-(1-phenylpropyl)aniline.

Figure SM 13.9.6 – HPLC chromatogram of the chiral *N*-(1-phenylpropyl)aniline product (the (*S*)-enantiomer is the main isomer.

```
Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area        Height     Height
 #   [min]         [min]  mAU   *s     [mAU    ]      %
----|-------|----|-------|----------|----------|--------|
  1   1.818 PV   0.2724  150.39621     8.42192   0.6276
  2   2.962 VV   0.4071  182.54608     7.55633   0.5631
  3   3.301 VV   0.5636  361.96286     8.35661   0.6228
  4   4.357 VV   0.1744   30.28482     2.53386   0.1888
  5   5.003 VV   0.1573 1.23931e4  1210.67273  90.2231
  6   5.584 VP   0.1692 1174.30896  104.32400   7.7745

Totals :                  1.42926e4  1341.86546

 Results obtained with enhanced integrator!
=====================================================================
                      Summed Peaks Report
=====================================================================

Signal 1: VWD1 A, Wavelength=254 nm
=====================================================================
                   Final Summed Peaks Report
=====================================================================
```

Figure SM 13.9.7 – HPLC report on *N*-(1-phenylpropyl)aniline enantioselectivity.